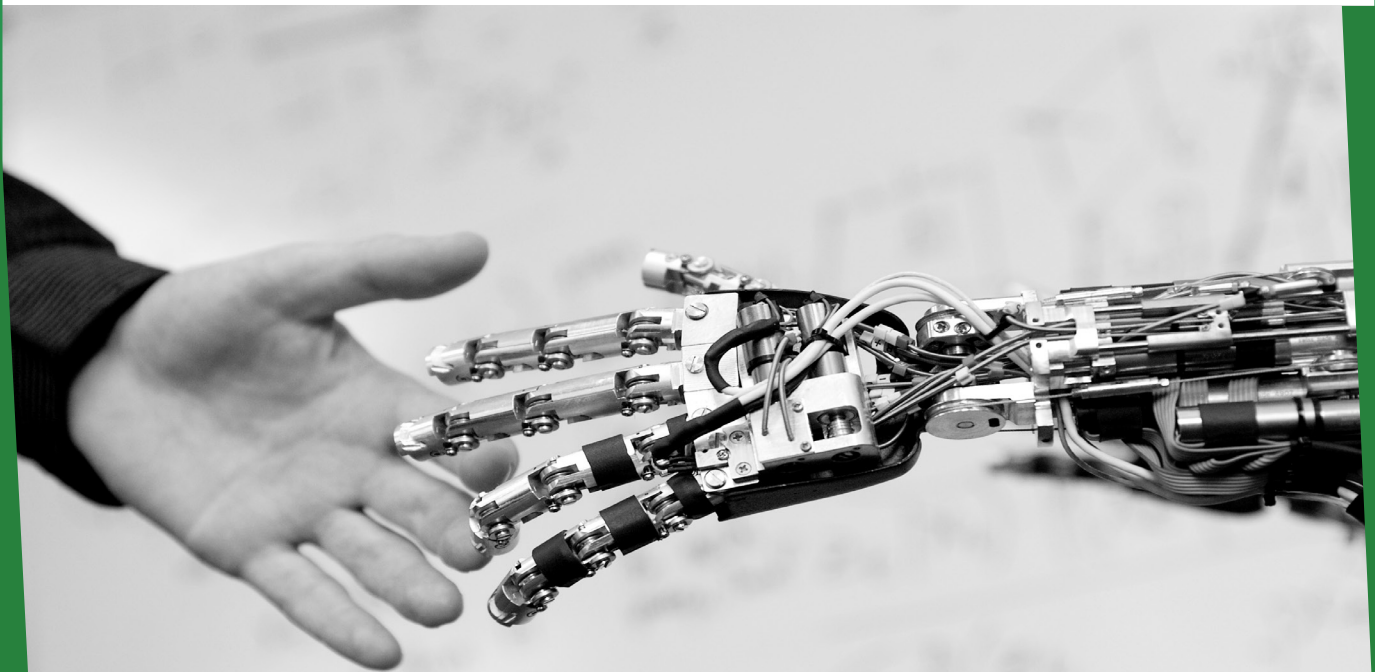


BioMedEng18

The UK's largest gathering of Biomedical Engineers
Medical Engineers and Bioengineers



6–7 September 2018 • Imperial College London

EPSRC
Engineering and Physical Sciences
Research Council



Medical Engineering Initiative

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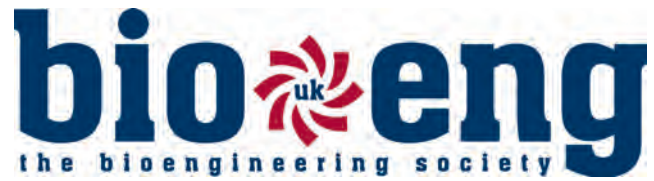
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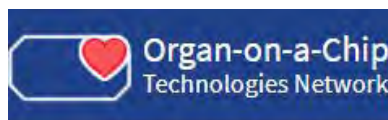
Engineering and Physical Sciences
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Medical Engineering Initiative



Partnering Organisations



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Foreword from the Conference Chair

Peter Weinberg
Professor of Cardiovascular Mechanics,
Imperial College London



Dear Delegate

A warm welcome to BioMedEng18! Under a variety of similar names, starting with Bioengineering08, this meeting has been held annually for more than a decade, and has become the foremost such gathering in the UK. It was held at Imperial College London in 2008 and 2014, and returns here for 2018.

The name change reflects our desire to be as inclusive as possible. We hoped that the re-badged meeting would be attractive to researchers who consider themselves Biomedical Engineers, Bioengineers and Medical Engineers and the response has been overwhelming: the largest meeting hitherto – in 2014 – received 255 abstract submissions but for 2018 that number has risen to over 400.

That number is a testament to the phenomenal growth of bioengineering and cognate subjects in the UK. But it also reflects the dedication and hard work of our Steering and Programme Committees, the collaborations with leaders of Networks and Centres described elsewhere in this booklet, and the unstinting efforts of those who have organised workshops. I am grateful to all these contributors for the major part they have played in nurturing the meeting, and I am proud to be a member of a nascent discipline that is demonstrating such collegiality and community of purpose.

I also wish to say a huge personal “Thank you” to my co-members of the BioMedEng18 Organising Committee – Conference Director Dr Gifty Tetteh and Communications Manager Miss Kemi Aofolaju – who have put in countless hours of hard work to make the meeting a success; it is certainly true that there would have been no meeting without them. And we are grateful to Professor Anthony Bull, Head of the Department of Bioengineering at Imperial, for his tremendous moral, practical and financial support.

Finally, we thank the Wellcome and EPSRC for the support, the British Heart Foundation and Arthritis Research UK for providing bursaries for early career researchers and students, and the University of Strathclyde Centre for Doctoral Training in Medical Devices & Health Technologies.

Thank you for joining us to present your work and to share the excitement of the research adventure that is our discipline. I wish you a productive and enjoyable meeting.

A handwritten signature in black ink that reads "P.D. Weinberg". The signature is written in a cursive, slightly slanted style.

Professor Peter Weinberg

Chair, BioMedEng18

BioMedEng18 Organising Committee

Professor Peter Weinberg
Conference Chair



Peter Weinberg won a scholarship to Cambridge, where he read Natural Sciences. He then obtained a DIC, MSc and PhD from Imperial College, the latter being obtained in the Physiological Flow Studies Unit under the supervision of Colin Caro.

After being awarded a Lady Davis Fellowship in the Department of Bioengineering at the Technion, Israel, and further postdoctoral studies in the Physiological Flow Studies Unit, he was appointed Lecturer and then Reader in the School of Animal and Microbial Sciences, University of Reading. In 2004, he returned to Imperial College as a Reader in the Department of Bioengineering, and was appointed Professor of Cardiovascular Mechanics there in 2007.

Professor Weinberg's research is chiefly concerned with elucidating mechanisms involved in the development of atherosclerosis. He has developed a new theory relating the anatomically patchy distribution of atherosclerosis to variation in blood flow and uptake of plasma macromolecules by the arterial wall. He is also developing methods of pulse wave analysis for assessing heart failure non-invasively.

Dr Gifty Tetteh
Conference Director



Gifty Tetteh is the Musculoskeletal Medical Engineering (MSkMEC) Centre Manager at Imperial College London. In addition to organising BioMedEng18, she manages and promotes activities of the MSkMEC and contributes to cross-college research grant proposals and funding bids. She joined Imperial College from Sweatcoin, a digital currency-based tech start-up, where she managed relationships with key executives of health & wellbeing companies. Prior to Sweatcoin, she worked at Smith & Nephew as a Technology Analyst within the Research and Innovation-New Product Development team.

Gifty is passionate about S.T.E.M. outreach and has volunteered for several events in the United Kingdom and Africa. She received the Sir Harry Kroto Family Science Award in 2014 for her Labs2Africa programme as 'The researcher who has made the most worthwhile contribution, in a particular year, to science education of young people locally, nationally or globally'. Gifty completed a PhD in Bioengineering at the University of Sheffield and has experience in teaching various biological and medical courses to students at the undergraduate and postgraduate level.

Miss Kemi Aofolaju
Communications Manager



Kemi Aofolaju joined the Department of Bioengineering in 2016 as Departmental Secretary before moving on to take over the department's social media, printed media and key events administration as Communications and Events Officer in 2017.

Message from the Head of the Department of Bioengineering Imperial College London



On behalf of Imperial College London I am delighted to welcome you to BioMedEng18, the third time we have hosted this meeting.

I have had the privilege of attending all but one of these since we inaugurated the annual meeting in 2008, and have seen the growth in depth and breadth of the discipline in the UK through the leadership demonstrated by our universities in growing the number and type of taught courses in the discipline, through industry's pull for graduates and research interactions and through funding support by research councils and major charities.

It is on the back of this that the overwhelming support for BioMedEng18 is not a surprise - it is a reflection of the vibrancy and strength of our disciplinary community.

I invite you to participate fully in all that this meeting has to offer, attending the many excellent sessions, listening to our fantastic keynote speakers, and, most importantly, spending time with other members of this community, developing your network, socialising, and forging new collaborations and friendships.

As a coming together of Biomedical Engineers, Bioengineers and Medical Engineers from across the UK, many people have contributed to this meeting through organising sessions and stimulating scientific contributions and I thank you all. However, my greatest thanks go to Peter Weinberg; much of the credit for the undoubted success of this meeting goes to Peter who, in starting the series of meetings in 2008 and chairing the meeting this year has put in a shift for our community that goes above and beyond the call of duty.

I look forward to meeting as many of you as I can over the next few days and wish you a fruitful and enjoyable meeting.

Professor Anthony Bull, FEng
Head, Department of Bioengineering,
Imperial College London

Useful Information

BioMedEng18 Proceedings

The full BioMedEng18 conference proceedings containing both oral and poster abstracts is available on the conference website. It is also available on USB sticks which can be collected from the registration desk. The conference proceedings will be published with ISBN 978-1-9996465-0-9 and a copy will be deposited in the British Library

Conference Rooms

The BioMedEng18 conference will be taking place in seven (7) different rooms across Imperial College. The Great Hall, Queens Tower Rooms, Read and Pippard lecture theatres are in the Sherfield building (#20 on the map). Clore and Huxley 308 lecture theatres are in the Huxley Building (#13 on the map) and RSM 3.01 C, D & E is in the Royal School of Mines building (#9 on the map with an entrance through the Bessemer Building-#11 *pink staircase roof*).

Parallel Sessions

Delegates are able to move between parallel sessions if they wish. Please do not disrupt sessions if you are moving between them. To ensure sessions run in parallel, all presenters will be kept **STRICTLY** to time.

WiFi

Free WiFi is available for all delegates. If you do not have automatic access to WiFi through Eduroam, free WiFi is available throughout the college via Sky WiFi. To connect to 'The Cloud' from the available network list, open a browser and follow the instructions to register. Instructions on how to connect to the WiFi are also listed behind your BioMedEng18 name badge.

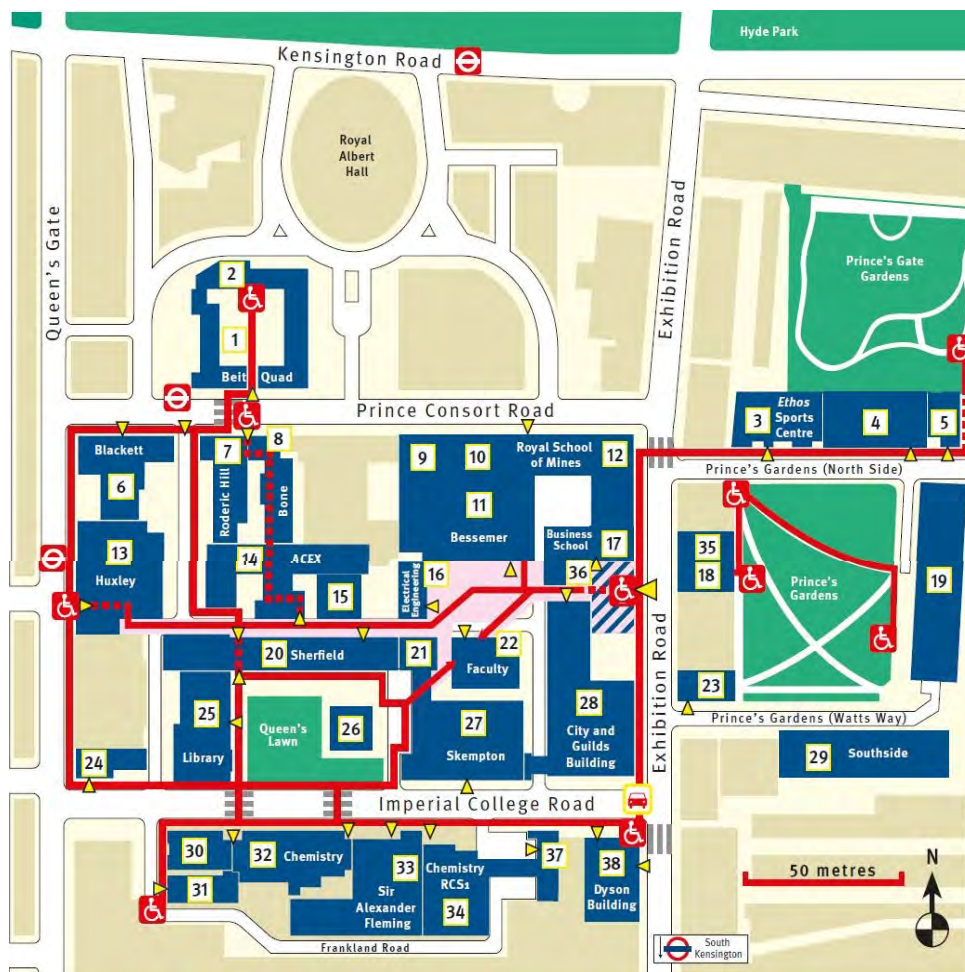
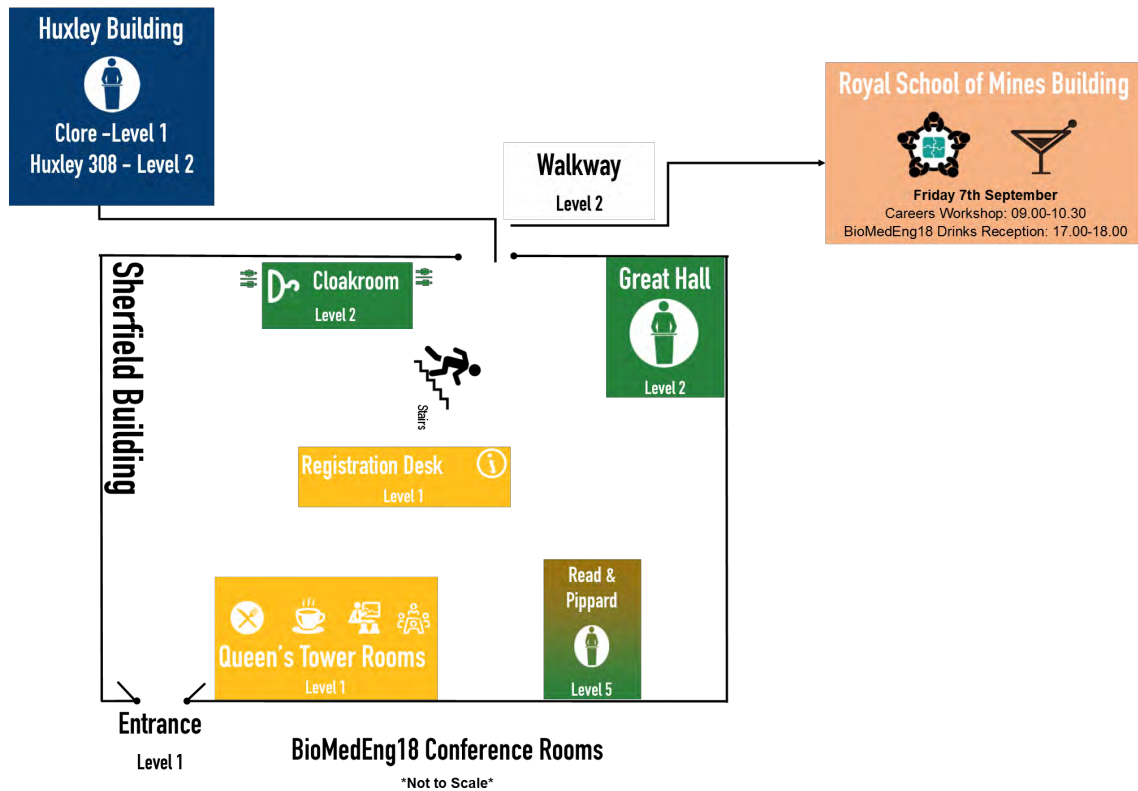
Cloakroom

There is a cloakroom located on Level 2 of the Sherfield building, next to the Great Hall. The cloakroom will be manned during the hours of the conference.

BioMedEng18 Volunteers

There are several BioMedEng18 volunteers wearing branded green and yellow t-shirts who will be happy to help and assist with any queries you may have during the conference. Please reach out to them as your first point of call.

Conference Locations & Imperial College Map



Conference Buildings

Huxley - #13, Sheffield - #20, Royal School of Mines - #10 (Entrance through Bessemer - #11)

BioMedEng18 Summary Schedule: Day 1

08:30	Conference Registration			
09:30	Welcome Ceremony - Professor Nick Jennings CB, FREng - (Great Hall)			
09:45	Plenary Session 1 (OATech+) - Professor Kyriacos Athanasiou - (Great Hall)			
10:35	Rapid Fire Presentations - (Great Hall)			
10:55	Poster Session + Tea & Coffee Break - (Queens Tower Rooms)			
11:15	OATech+ Network (Great Hall)	Medical Devices & Diagnostics (Clore)	Mechanics of Tissues & Organs (Read)	Motor Neuron Interfacing & Biomedical Applications Workshop (Pippard)
12:45	Lunch, Posters & Networking - (Queens Tower Rooms)			
13:45	Mechanobiology (Great Hall)	BioMedEng18 Phenomenal Women in Innovation Workshop (Clore)		Recent advances in Mechanical Circulatory Support Workshop (Read)
				Synthetic Biology and Engineering Biology (Pippard)
15:00	Poster Session + Tea & Coffee Break - (Queens Tower Rooms)			
15:30	Cardiovascular I & Lymphatic Bioengineering (Great Hall)	Organ on a chip Network (Clore)	Personalised Medicine & Modelling Biological Systems (Read)	Biomedical Imaging (Pippard)
17.00 -18.00	Plenary Session 2 (Organ on a Chip) - Dr Geraldine Hamilton - (Great Hall)			
18.45	Dinner Arrival & Seating - (Queens Tower Rooms)			
19.00 -23.00	BioMedEng18 Dinner with After Dinner Speaker - Prof Sophie Scott			

Colour Bands	Keys
	Opening/ Closing Ceremony
	Poster, Networking Breaks & Lunch
	Plenary Session
	Conference Registration
	Workshop
	Rapid Fire Session
	Dinner / Drinks Reception

BioMedEng18 Summary Schedule: Day 2

08:30	Conference Registration				
09:00	Musculoskeletal Biomechanics, Gait Analysis & Human Movement (Great Hall)	Neurotechnology, Rehabilitation Engineering & Robotics (Clore)	Haemodynamics Workshop: "Reduced-order modelling and pulse wave analysis" (Read)	Cancer Engineering, Drug & Gene Delivery (Pippard)	BioMedEng18 Careers Workshop (RSM 3.01 C, D&E)
10:30	Poster Session + Tea & Coffee Break - (Queens Tower Rooms)				
11:00	Plenary Session 3 - Professor Jonathan Cooper, FREng, FRSE - (Great Hall)				
12:00	Lunch, Posters & Networking - (Queens Tower Rooms)				
13:00	Biomaterials (Great Hall)	Biosensors, Biomedical Signal Processing & Bioelectronics (Clore)	IMPRESS:"Engineering for Continence Care – Innovation for the Stigmatised" (Read)	Cardiovascular Bioengineering II & Biofluids (Pippard)	BioMedEng18 Bioengineering Education Workshop (Huxley 308)
14:15	Poster Session + Tea & Coffee Break - (Queens Tower Rooms)				
14:35	Artificial Intelligence & Machine Learning (Great Hall)	Trauma, Surgery, Orthopaedics & Prosthetics (Clore)	Tissue Engineering & Regenerative Medicine (Read)	Biomimetics: "From Biology to Engineering & Back Again" (Pippard)	
15:50	Plenary Session 4 - Professor Hanjoong Jo - (Great Hall)				
16:35	BioMedEng18 Awards & Closing Ceremony - (Great Hall)				
17:00	Drinks Reception & Networking - (RSM 3.01 C, D & E)				
-18:00					

Colour Bands	Keys
	Opening/ Closing Ceremony
	Poster, Networking Breaks & Lunch
	Plenary Session
	Conference Registration
	Workshop
	Rapid Fire Session
	Dinner / Drinks Reception

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10:55	Poster Session + Tea & Coffee Break - (Queens Tower Rooms)
	OATech+ Network - (Great Hall) Chairs - Prof Cathy Holt & Dr Jonathan Jeffers
11:15	Gwenllian Tawy, University of Manchester, - 'The Efficiency of a Clinical Motion Capture System for Quantifying Knee Function'
11:28	Sheetal Inamdar, Queen Mary University of London, - 'Multi-scale in-situ Cartilage Mechanics using Small Angle X-ray Diffraction'
11:40	Lindsay Millar, University of Strathclyde, - 'Robotic Assisted Unicompartmental Knee Arthroplasty Leads to Improvements in Knee Flexion at Five-Year follow-up in Comparison to Conventional Methods'
11:52	Geoffrey Ng, Imperial College London, - 'Hip Joint Mechanics Before and After Cam FAI'
12:05	Jessica Mansfield, University of Exeter - 'Tracking Collagen Fibre Reorganisation under Load in Articular Cartilage using Polarization Sensitive SHG Microscopy'
12:17	Oliver Morgan, Anglia Ruskin University - 'Pre-Clinical Investigation of an Extra-Capsular Knee Joint Unloading Implant'
12:30	Nimrah Munir, University of Edinburgh - 'Multizone Scaffolds as Cell Free Platforms for Cartilage Tissue Engineering'
	Medical Devices & Diagnostics - (Clare)
	Chairs - Dr Silvia Schievano
11:15	Caleb Gambrah, University of Strathclyde - 'The Development and Hydrodynamic Assessment of a Tri-leaflet Polyurethane Heart Valve Prosthesis'
11:28	Selim Bozkurt, UCL Great Ormond Street Institute of Child Health, - 'Towards a Novel Device for Treatment of Unicoronal Craniosynostosis'
11:40	Yuetao Li, University of Southampton, - 'Rapid Detection of β -lactam Resistant Bacteria via an Integrated Microfluidic System'
11:52	Yousuf Makki, University College London, - 'Real-time Imaging of Radio-Frequency Ablation Using All-Optical Ultrasound'
12:05	Syed Anas Imtiaz, Imperial College London, - 'A Low-power System for Automatic Sleep Monitoring and Diagnosis'
12:17	Momen M. Osman, Imperial College London, - 'Behind-the-Ear Wireless Micro-instrument for Traumatic Brain Injury Neuroelectrochemical Monitoring'
12:30	Adrian Nightingale, University of Southampton, - 'Wearable Droplet Microfluidics for Real-time Continuous Monitoring of Tissue Chemistry'
	Mechanics of Tissues & Organs - (Read)
	Chairs - Dr Nuria Gavara & Dr Joseph Sherwood
11:15	Sherif Elsharkawy, Queen Mary University of London, - 'Highly-ordered Mineralised Structures for Dental applications'
11:28	Joseph Sherwood, Imperial College London, - 'Characterising Mechanical Forces in the Outflow Pathway of the Eye'
11:40	Darryl R. Overby, Imperial College London, - 'Mechanoregulation of Intraocular Pressure by Nitric Oxide'
11:52	Colin Boyle, Imperial College London, - 'Hacking the Skin's ability to bear Load'
12:05	Alastair Gregory, University of Cambridge - 'A Physical Mechanism for Wheezing in Lungs'
12:17	Richard Pangonis, Imperial College London, - 'A Novel Mechanical Testing Apparatus for Brain Tissue'
12:30	Hari Arora, Swansea University - 'Synchrotron imaging of the lung: dynamic mechanical characterisation of the micro-architecture'
	Motor Neuron Interfacing & Biomedical Applications Workshop - (Pippard)
	Chairs - Dr Silvia Muceli & Dr Ivan Vujaklija
11:15	Keynote Speaker: Professor Simon Gandevia, Neuroscience Research Australia, - 'Motor Neurons: some unexpected messages'
11:40	Mario Bracklein, Imperial College London - 'Decorrelation of Common Input to a Muscle's Motor Neuron Pool'
11:52	Gonthicha Puttaraksa, Imperial College London - 'Common and independent synaptic input to motor neurons in essential tremor patients'
12:05	Michael Rotherham, Keele University - 'Remote control of cell signalling with magnetic particles for neuronal cell differentiation- emerging therapies for Parkinsons disease'
12:17	Nathan Steadman, John Radcliffe Hospital, Headington, Oxford - 'A Robotic System to Automate Parameter Tuning for Deep Brain Stimulators'
12:30	Dr Alessandro Del Vecchio, Imperial College London - 'You are as fast as your motor neurons: Early recruitment and maximal discharge of motor neurons determine the maximal rate of force development in humans'
12:45	Lunch, Posters & Networking - (Queens Tower Rooms)
	BioMedEng18 Phenomenal Women in Innovation Workshop - (Clare)
	Chairs - Dr Gifty Tetteh & Prof Ipsita Roy
13:45	Professor Alison Noble OBE FREng FRS, University of Oxford, - 'TBC '
13:55	Dr Kath Mackay, Innovate UK - 'TBC '
14:05	Professor Alison McGregor, Imperial College London, - 'The Accidental Innovator'
14:15	Dr Katerina Spranger, OxfordHeartbeat, - 'From STEM Student to a MedTech Entrepreneur: a Personal Perspective'
14:25	Prof Ipsita Roy, University of Westminster, 'My Exciting Scientific Journey: from Chemistry to Biochemistry to Biomaterials'
14:35	Dr Susannah Clarke MBE, Embody Orthopaedic, - 'The Long Road to 'First in Man''
14:45	Panel Discussion
	Mechanobiology - (Great Hall)
	Chairs - Dr Christina Warboys & Dr Darryl Overby
13:45	Christina Warboys, Imperial College London, - 'The role of Wnt/ β -catenin signalling pathways in endothelial mechanotransduction under disturbed and undisturbed flow'
13:58	Ryan Petrie, Drexel University, - 'Myosin II governs Intracellular Pressure and Traction by Distinct Mechanisms'
14:10	Mean Ghim, Imperial College London, - 'Segmentation of Endothelial Cell Growth in a Swirling Well Plate allows Investigation of the Shear-Dependent Release of Soluble Mediators'
14:22	David Barrett, Queen Mary University of London, - 'Mechanotransduction Mechanisms leading to Fetal Membrane Weakening and Tissue Damage'
14:34	Josefin Jansson-Edqvist, Imperial College London, - 'Engineering in vitro Blood Vessels for Studying Endothelial Cell Function'
14:46	Derek Warren, University of East Anglia, - 'Vascular Smooth Muscle Cell Contractile Response is altered by Matrix Stiffness'

Recent advances in Mechanical Circulatory Support Workshop - (Read) Chairs - Dr Katharine Fraser & Prof Ashraf Khir	
13:45	Keynote Speaker: Dr Christopher Bowles, Harefield Hospital, - 'What do clinicians want from new MCS devices?'
14:10	Keynote Speaker: Professor Cathy Thornton, Swansea University, - 'Measurement of Blood Damage due to Fluid Stresses and Biomaterials'
14:34	S. McConchie, Calon Cardio-Technology Ltd. - 'A UK VAD: from Engineering to Clinical Trials'
14:46	Dr K. H. Fraser, University of Bath - 'Pulsatile Flow in Ventricular Assist Devices: CFD Analysis of Velocity Fields around the Pressure-Flow Loop'
Synthetic Biology and Engineering Biology - (Pippard) Chairs - Dr Thomas Ouldrige & Dr Rodrigo Ledesma-Amaro	
13:45	Ismael Mullor Ruiz, Imperial College London, - 'Design and Development of DNA-based Push-pull Networks'
13:58	Rodrigo Ledesma-Amaro, Imperial College London, - 'Affordable microbial bio-manufacturing by Multilevel Strain Engineering'
14:10	Govind Menon, Imperial College London, - 'Modelling and Systems Analysis for Elucidating and Engineering Compartmentalisation in Synthetic and Natural Biochemical Pathways'
14:22	Alexander Ohmann, University of Cambridge, - 'A Synthetic DNA-built Enzyme flips 10 ⁷ lipids per second in Biological Membranes'
14:34	James Hindley, Imperial College London, - 'Engineering Molecular Machines that can Sense and Respond to their Environment'
14:46	Yuval Elani, Imperial College London, - 'A Toolkit for the Construction of Vesicle-based Artificial Cells: Microfluidics, Optics, and Biomembrane Engineering'
15:00	Poster Session + Tea & Coffee Break - (Queens Tower Rooms)
Cardiovascular I & Lymphatic Bioengineering - (Great Hall) Chairs - Dr Chris Cantwell & Dr Sam Au	
15:30	Ethan Rowland, Imperial College, London – 'A New Method for Non-Invasive Measurement of Arterial Wave Speed, Intensity and Reflection'
15:43	Anastasia Nasopoulou, King's College, London, - 'Can we estimate myocardial material parameters from reduced 2D imaging data?'
15:55	Konstantinos Tzortzis, Imperial College London, - 'Simultaneous optical mapping of transmembrane potential and electrogram recordings in human heart slices'
16:08	Shuo Wang, University of Cambridge, - 'Bayesian Inference-based Estimation of Normal Aortic, Aneurysmal and Atherosclerotic Tissue Mechanical Properties: from Material Testing, Modelling to Histology'
16:20	Daniel Watson, Swansea University, - 'Limb-Scale Modelling of the Lymphatic System'
16:32	Maximilian Balmus, King's College London - 'An overlapping domain method for hemodynamics based on weighted sums'
16:44	Max Falkenberg McGillivray, Imperial College London, - 'Unified Mechanism of Atrial Fibrillation in a Simple Model'
Organ on a chip - (Clare) Chairs - Prof Martin Knight & Dr Malcolm Haddrick	
15:30	Liliang Ouyang, Imperial College London, - 'Development of Perfusable Vascular Platform by Using 3D Bioprinting'
15:43	Arianna Rech, Imperial College London, - 'Engineering a Pulmonary Epithelium-on-a-Chip device to Investigate the Mechanobiology of Lung Disease'
15:55	Elisabetta Bottaro, University of Southampton, - 'Vein-on-a-chip platforms for evaluating the performance of sclerosing agents'
16:08	Samantha Peel, AstraZeneca, - 'High-Content Confocal Imaging of Organ-Chips: A Robust and High-Throughput Workflow Enables Evaluation of Drug Candidates in a Liver-Chip model'
16:20	Lydia Baldwin, University of Hull, - 'Development of a gut-on-a-chip model for the study of inflammatory bowel diseases'
16:32	Nikki-Maria Koudis, University of Manchester, - 'Cell sheet engineering for kidney-on-a-chip applications'
16:44	Cyril Deroy, University of Oxford, - 'Microfluidics accessible to cell biology: a network of fluid-constrained channels and droplets'
Personalised Medicine & Modelling Biological Systems - (Pippard) Chairs - Prof Perumal Nithiarasu & Dr Nick Linton	
15:30	Wan Mohd Radzi Rusli, Imperial College London, - 'Importance of dimension reduction in quantifying shape variability in a population'
15:43	Massimo Capoccia, University of Strathclyde, - 'A Simulation Approach to Guide Therapeutic Intervention in Advanced Heart Failure'
15:55	Jorge Aramburu, Universidad de Navarra, - 'Numerical modelling of the Fontan circulation'
16:08	Julio Ortega, Tecnun - University of Navarra, 'Analysis of the influence of the hepatic artery geometry on microsphere and radiation distributions during radioembolization'
16:20	Anastasia Giannari, Imperial College London, - 'Optimisation of Proactive Therapy for Atopic Eczema by Model Predictive Control'
16:32	Paolo Gargiulo, University of Reykjavik, - 'Aging Health Behind an Image: Quantifying Sarcopenia and Associated Risk Factors from Advanced CT Analysis'
16:44	Emilie Sauvage, University College London, - 'Aorta remodelling in babies born with hypoplastic left heart syndrome'
Biomedical Imaging - (Read) Chairs - Dr Amanda Foust & Prof. Adam Gibson	
15:30	Hubin Zhao, University College London, - 'A wearable, modular, high-density diffuse optical tomography system'
15:43	Hendrik Pauw, University College London, - 'A Scalable and Versatile Method for Fabricating Highly-Directional Optical Ultrasound Sources for Minimally Invasive Imaging'
15:55	Istvan Huszar, University of Oxford, - 'Registration of Histological Images to Post-Mortem MRI'
16:08	Matthieu Toulemonde, Imperial College London, - 'Locally activated nanodroplets and high frame rate imaging for real-time flow visualization – preliminary in-vivo demonstration'
16:20	Bob-Dan Lechner, Exeter University, - 'Microdomain Structure and Mechanical Properties of Lipid Monolayers Mimicking Red Blood Cell Membranes'
16:32	Antonio De Grazia, University of Southampton, - 'High-throughput microfluidic arraying and imaging of individual skeletal stem cells from human bone marrow isolates'
16:44	Robert Robinson, Imperial College London, - 'Subject-level Prediction of Segmentation Failure using Real-Time Convolutional Neural Nets'
17:00	Plenary Session 2 (Organ on a Chip) - Dr Geraldine Hamilton - (Great Hall)
18:45	Arrival & Seating - BioMedEng18 Dinner - (Queens Tower Rooms)
19:00-22:00	BioMedEng18 Dinner with After Dinner Speaker - Prof Sophie Scott

BioMedEng18 Conference Schedule: Day 2

08:30	Conference Registration
	Musculoskeletal Biomechanics, Gait Analysis & Human Movement - (Great Hall) Chairs - Dr Angela Kedgley & Dr Tom Shearer
09:00	Muhammad Qasim, Anglia Ruskin University, - 'The effect of including initial strain in the ligaments on the predictive accuracy of the finite element model of the knee joint'
09:13	Christian Klemt, Imperial College London, - 'Analysis of shoulder muscle forces during functional daily activities'
09:25	Marta Da Conceicao Godinho, Queen Mary University of London, - 'Regional Specific Effect of Elastin Depletion on the Mechanical Properties of Tendon'
09:38	Neil Evans, University of Warwick, - 'A Novel Methodology for Analysis of Lower-Limb Loading with Applications for Implant Testing'
09:50	Louise Jennings, University of Leeds, - 'Development of pre-clinical test methods for assessing functional performance of osteochondral grafts in the tibiofemoral and patellofemoral joints'
10:02	Gwenllian Tawy, University of Manchester - 'Functional outcome of the Medacta GMK-Sphere total knee arthroplasty as quantified by a clinical motion capture system'
10:15	Nicola Omo-Dare, Imperial College London, 'The Effect of Aging on Kinematic Strategy Following Forward Perturbation'
	Neurotechnology, Rehabilitation Engineering & Robotics - (Clare) Chairs - Prof Ferdinando Rodriguez y Baena & Dr Rebecca Shipley
09:00	Edward Chadwick, Keele University, - 'Control of a Robotic Hand with an EMG-driven, Real-time Biomechanical Computer Model'
09:13	Felix Russell, Imperial College London, - 'A compliant bicondylar knee for prosthetics, exoskeletons and walking robots.'
09:25	Yazi Aljobori, University College London, 'Frequency Dependant Facilitation of Motor Evoked Potentials with Transcutaneous Spinal Stimulation'
09:38	Myriam Bontonou, Imperial College London, - 'Lossless compression and entropy estimation of neural spike trains'
09:50	Navjeevan Soor, Imperial College London, - 'All-optical crosstalk-free manipulation and readout of Chronos- expressing neurons'
10:02	Mikolaj Kegler, Imperial College London, - 'Navjeevan Soor, Imperial College London, - 'All-optical crosstalk-free manipulation and readout of Chronos- expressing neurons'
10:15	Georgios Zafeiropoulos, Imperial College London, - 'PANACEA 2.0: A Wireless, High-Performance Multi-instrument for (Bio)Signals Recording'
	Haemodynamics Workshop: "Reduced-order modelling and pulse wave analysis" - (Read) Chairs - Prof Ashraf Khir & Dr Jordi Alastruey
09:00	Keynote Speaker: Professor Kim Parker, Imperial College London, - 'Wave Speed on the Arteries'
09:20	Keynote Speaker: Professor Perumal Nithiarasu, Swansea University, - 'Active and Passive Human Digital Twins Based on Reduced Cardiovascular Flow Models'
09:40	Prof A. Hughes, University College London - 'Arterial waves in the pulmonary circulation'
09:52	Dr G. Biglino, University of Bristol - 'Wave intensity analysis from MRI data: linking wave dynamics with vessel morphology?'
10:04	Dr P. Charlton, King's College London - 'A Database for the Development of Pulse Wave Analysis Algorithms'
10:16	Dr M. Negoita, University of Brunel - 'Non-invasive Measurement of Local Wave Speed in Human Ascending Aorta'
	Cancer Engineering, Drug & Gene Delivery - (Pippard) Chairs - Dr Umber Cheema & Dr Darryl Overby
09:00	Ewelina Wajs, University of Cambridge, - 'Film bulk acoustic resonator (FBAR) based biosensor for early detection of aggressive prostate cancer'
09:13	Judith Pape, University College London, - 'Investigating Cancer Invasiveness and Vasculature with a Biomimetic 3D Model and Patient-Specific Cancer Associated Fibroblasts'
09:25	Maria Vias, University of Cambridge, - 'Human primary high grade serous ovarian carcinoma organoid cultures for disease modelling and drug screening'
09:38	Sophie Morse, Imperial College London, - 'Drug delivery to the Brain using a Rapid Short-Pulse Ultrasound Sequence and Microbubbles'
09:50	Gareth LuTheryn, University of Southampton, - 'Ultrasound responsive microbubbles enhance the activity of sub-inhibitory concentrations of gentamicin in the treatment of Pseudomonas aeruginosa biofilms'
10:02	Hemmel Amrania, Imperial College London, - 'Digistain' mid-IR based Chemical Imaging for Breast Cancer Diagnosis'
10:15	Matthew Dibble, Queen Mary University of London, - 'Developing an Ovarian Cancer Model on-a-Chip'
	BioMedEng18 Careers Workshop - (RSM 3.01 C, D & E) Chairs - Dr Gifty Tetteh & Ms Katie Dallison
	IBM - Imogen Hanson, IBM UK Early Professional Attraction & Engagement Events Coordinator
	Arthritis Research UK - Shereen Sabbah, Research Programme Manager
	Cambridge Bio-Augmentation - Oliver Armitage, Director
09:00 - 10:30	Open Accelerator - Giovanni Rizzo, Chief of Innovation Division
	Teach First - Pip Saran, Experienced Hires Team Leader
	Entrepreneur First - Olivia Stamp, Associate
	AA Thornton - Christopher Burnett, Associate Patent Attorney
10:30	Poster Session + Tea & Coffee Break - (Queens Tower Rooms)
11:00	Plenary Session 3 - Professor Jonathan Cooper, FEng, FRSE - (Great Hall)
12:00	Lunch, Posters & Networking - (Queens Tower Rooms)
	Biomaterials - (Great Hall) Chairs - Dr Helena Azevedo & Prof Michael Sutcliffe
13:00	Gaston Primo, Queen Mary University of London - 'Creating functional and high complexity hydrogels with electric fields'
13:12	Julien Gautrot, Queen Mary University of London, - 'Protein self-assembly at oil-water interfaces controls nanoscale mechanics, cell adhesion and stem cell fate decision'
13:25	Cristina Martins, INEB /i3S, - 'Lipid-based nanoparticles that counteract gastric infection without affecting gut microbiota'

- 13:38 Ipsita Roy, University of Westminster, - 'Natural Polymers of Bacterial Origin for Cardiac Regeneration'
- 13:50 Lihui Peng, Queen Mary University of London, - 'Stem cell culture on nanosheets assembled at the surface of liquid microcarriers for applications in regenerative medicine'
- 14:03 Rami Mhanna, American University of Beirut, - 'The sulfation of biomimetic glycosaminoglycans controls growth factor binding and subsequent cell proliferation and differentiation'

Biosensors, Biomedical Signal Processing & Bioelectronics - (Clare)

Chair - Prof. Andrew Flewitt

- 13:00 Fabrizio Siracusa, University of Southampton, - 'High speed electro-mechanical single cell analysis'
- 13:12 Peter Charlton, King's College London, - 'A Signal Quality Index for the Impedance Respiratory Signal'
- 13:25 Carl Henning Lubba, Imperial College London, - 'Efficient peripheral nerve decoding through massive feature extraction'
- 13:38 Gareth Evans, University of Southampton, - 'Droplet microfluidics for continuous chemical sensing of cortisol'
- 13:50 Biswajoy Bagchi, University College London, - 'Flexible and Biocompatible Piezoelectric Nanocomposites for Physiological Pressure Sensing'
- 14:03 Manousos Klados, Aston University, - 'Personality Computing: Automatic Recognition of Personality Using EEG Functional Connectivity'

IMPRESS Workshop: "Engineering for Continence Care – Innovation for the Stigmatised" - (Read)

Chairs - Dr Peter Culmer & Dr Thelma Lovick

- 13:00 Keynote Speaker: Professor Jenny Southgate, University of York, - 'Tissue Engineering for Better Bladders'
- 13:25 Dr John Young, University of Portsmouth, - 'Developing a non-invasive biosensor to fingerprint Overactive Bladder'
- 13:38 Dr Nicola Irwin, Queen's University Belfast, - 'Anti-Blocking Catheter Coatings; from lab to commercial reality'
- 13:50 Dr Bhavik Patel, University of Brighton, - 'Faecal sensor to understand physiological signalling and muscle dynamics with incontinence'
- 14:03 Dr Thelma Lovick, University of Bristol, - 'Pelvic Nerve Stimulation for urinary urge incontinence (UUI)'

BioMedEng18 - Biomedical Engineering Education - (Huxley 308)

Chairs - Prof Martyn Boutelle & Prof Julia Shelton

- 13:00 Prof Jimmy Moore – Entrepreneurship in Bioengineering - The BioDesign approach
- 13:10 Panel Discussion with Danny Green, Entrepreneur-in-residence & Ben Lakey, MRes student
- 13:30 Prof Adam Gibson – Comparison of Students' Performance in Examinations compared to Group Coursework
- 13:40 Dr Ian Radcliffe - Group Design Projects / Sports Innovation Challenge
- 13:50 Dr Tina Chowdhury - Use of the Virtual Lab - Improving Outcomes in Tissue Engineering
- 14:00 General Panel Discussion - Biomedical Engineering Teaching - Future Directions

Cardiovascular Bioengineering II & Biofluids - (Pippard)

Chair - Dr Zhongzhao Teng

- 13:00 Wesleigh Dawsmith, Queen Mary University of London, - 'Monitoring Dehydration with Osmolality in Whole-Blood Specimens Collected from Cycling Athletes'
- 13:12 Cristian Soitu, University of Oxford, - 'Cell biology in mini-chambers with fluid walls'
- 13:25 Kim Parker, Imperial College London, - 'A Functional Model of the Small Arteries'
- 13:38 Marta Dazzi, Imperial College London, - '3D imaging of arterial permeability in the intact brachiocephalic artery using confocal microscopy'
- 13:50 Charles Houston, Imperial College London, - 'Electrical waves rotate around a stable core in monolayers of cardiac cells without functional or structural inhomogeneity'
- 14:03 David Pitcher, Imperial College London, - 'Human Langendorff: Building an ex vivo whole heart perfusion system for high fidelity controlled electrophysiological assessment'

14:15

Poster Session + Tea & Coffee Break - (Queens Tower Rooms)

Artificial Intelligence & Machine Learning - (Great Hall)

Chair - Dr Anil Bharath

- 14:35 Gareth Jones, Swansea University, - 'A proof of concept for machine learning application to stenosis detection'
- 14:47 Girmaw Abebe Tadesse, University of Oxford, - 'Personalised Diagnostic Tool for Infectious Disease'
- 15:00 David Narganes, University of Leeds, - 'Girmaw Abebe Tadesse, University of Oxford, - 'Personalised Diagnostic Tool for Infectious Disease'
- 15:12 Lance Rane, Imperial College London, - 'Extracting robust controllers from motion data using computed muscle control and imitation learning'
- 15:25 Guillem Hurault, Imperial College London, - 'Bayesian Machine Learning to Predict Short-term Course of Eczema Severity'
- 15:37 Ansab Fazili, Kings College London, - 'Automatic Shadow Detection in Fetal Ultrasound Images'

Trauma, Surgery, Orthopaedics & Prosthetics - (Clare)

Chairs - 'TBC'

- 14:35 Michael Ward, University of Liverpool, - 'Assessing the Mechanical Suitability of 3D Printable Polymers, for Use in Maxillofacial Prosthetics'
- 14:47 Ugur Tanriverdi, Imperial College London, - 'Development of a soft robotics liner for prosthetics'
- 15:00 Antonia Pontiki, Kings College London, - 'Chest Wall Reconstruction Using Patient Specific 3D Printing and its Motion Analysis'
- 15:12 Raelene Cowie, University of Leeds, - 'Pre-clinical Experimental Wear Simulation of an All-Polymer Total Knee Replacement'
- 15:25 Trang Nguyen, University of Leeds, - 'Biomechanically Controlled Simulation of Traumatic Spinal Cord Injury In Vitro Using a 3D Hydrogel Model'
- 15:37 Fady Abayazid, Imperial College London, - 'Computational Design of a Dummy Neck for Head-First Impacts'

Tissue Engineering & Regenerative Medicine - (Read)

Chairs - Dr Tina Chowdhury & Prof Alicia El Haj

- 14:35 Clara Hedegaard, Queen Mary University of London, - 'Hierarchical biofabrication: Integrating bioprinting with molecular self-assembly'
- 14:47 Xinqing Pang, Queen Mary University of London, - 'Engineering the endothelial glycocalyx through defined patterns of peptide self-assembled monolayers'
- 15:00 Ciro Chiappini, King's College London, - 'Modulating Neural Cell Differentiation with Electrically Active Nanoneedles'
- 15:12 Oluwadamilola Agbabiaka, University of Bradford, - 'Fabrication and Characterisation of PCL and PLGA for Vascular Tissue Engineering'
- 15:25 Iria Echevarria, ISTM (Keele University), - 'Magnetic nanoparticle mediated activation for chondrogenic differentiation of MSCs'
- 15:37 James S. Bell, Cardiff University, - 'A subfibrillar deformation mechanism in corneal collagen that affords flexibility'

Biomimetics Workshop: "From Biology to Engineering & Back Again" - (Pippard) Chairs - Prof Holger G Krapp & Dr Huai-Ti Lin	
14:35	Keynote Speaker: Professor Richard Bomphrey, Royal Veterinary College, 'Aerodynamic imaging: implementing a mosquito-inspired sense-and-avoid device on a drone'
15:05	Dr H. Lin, Imperial College London - 'The role of active vision in dragonfly visual guidance'
15:20	Dr D. Labonte, Imperial College London - 'How to stick but not get stuck – climbing with adhesive pads'
15:35	Prof H. G. Krapp, Imperial College London, - 'A Fly(brain)-Robot-Interface to study multisensory integration.'
15:50	Plenary Session 4 - Professor Hanjoong Jo - (Great Hall)
16:35	BioMedEng18 Awards & Closing Ceremony - (Great Hall)
17:00-18:00	Drinks Reception & Networking - (RSM 3.01 C, D & E)

BioMedEng18 Poster Presentation: Day One

Mechanics of Tissues & Organs

- 1 - Ignacio Medina Fernandez*, Imperial College London – 'Gelatin Methacryloyl – Bioceramic Scaffolds for Dentine-Pulp Complex Regeneration'
- 2 - Edward Cozens*, Queen Mary, University of London, 'Development of Novel Methods for Adhesion of Implants to Soft Tissue and a Next Generation of Dental/Bio Adhesives'
- 3 - Bob-Dan Lechner*, Exeter University – 'De- and Remineralisation of Human Teeth Induced by Food Stuffs'
- 4 - Minh Tran*, Oxford University – 'The Inspired Sinewave Technique: Assessment of an Index of Lung Inhomogeneity using a Two-compartment Lung Simulation'
- 5 - Charlotte McIntyre*, Imperial College – 'Thresholding the Large Airways for Computational Fluid Dynamics'
- 6 - Francesco Menduni*, Aston University – 'Optimisation of Porcine Eyeball Storage for Ophthalmic Research Applications'
- 7 - Yichen Yuan*, Queen Mary University of London – 'Supramolecular Peptide-Hyaluronan Hydrogels for Ocular Applications'
- 8 - Jacques Bertrand*, Imperial College London – 'Investigating the Mechanism of Long-Term Intraocular Pressure Reduction by PGN9856i in Mice'
- 9 - Salahudeen Mohamed*, University of Naples Parthenope – 'A Finite Element Study on the Modelling of Keratoplasty'
- 10 - Ahmed Kazaili*, University of Liverpool - 'An Experimental Model to Understand Corneal Degradation in Keratoconus'
- 11 - Ester Reina-Torres*, Imperial College London – 'The Effect of Temperature on Aqueous Humour Outflow in Enucleated Mouse Eyes'
- 12 - Joseph Sherwood*, Imperial College London – 'Modulation of Outflow Facility by the Ocular Pulse'
- 13 - Alberto Coccarelli*, Swansea University – 'Towards a Comprehensive Active-Structural Model for the Arterial Wall'
- 14 - Aziz Tokgoz*, University of Cambridge – 'Microstructure-mechanics Relationship of Human Aortic Aneurysms'
- 15 - Debao Guan*, University of Glasgow – 'Studying the General Holzapfel-Ogden Model on Fitting Various Experimental Myocardial Data and its Reduction'
- 16 - Jessica Prior*, Imperial College London – 'Internal Deformations in Human Intervertebral Discs: a 9.4T MRI Study'

Special Session: Neurotechnology CDT

- 17 - Kyle Edmunds*, Reykjavik University – 'Cortical Recruitment in Postural Control Adaptation and Habituation During Vibratory Proprioceptive Stimulation'
- 18 - Seigfred Prado*, Imperial College London – 'NeuroSEE: An Automated Neuronal Source Extraction and Exploration Toolbox for Calcium Imaging Data Analysis'
- 19 - Konstantinos Petkos*, Imperial College London – 'A Wireless Monitoring Instrument for Recording Tissue Biopotential and Sensing Metabolites During Surgery: Proof-of-concept Realisation and Preliminary Results'
- 20 - Amadeus Maes*, Imperial College London – 'Encoding Input Correlations into the Weight Matrix of a Recurrent Spiking Network with Structure'
- 21 - James Tyrrell*, Imperial College London – 'Organic Electrochemical Transistors for Measuring Neural Activity'
- 22 - Peter Quicke*, Imperial College London – 'Multifocal Two-Photon Imaging of a Genetically Encoded Voltage Indicator'
- 23 - Hristo Dimitrov*, Imperial College London – 'Simultaneous and Proportional EMG Control of Ankle Joint Movement and Stiffness for Below-Knee Prostheses'
- 24 - Sam Podmore*, Imperial College London – 'Investigating Grey Matter Lesion Distribution in Multiple Sclerosis Using Second Generation Radioligand [11C]-PBR28'
- Claire Baker*, Imperial College London – 'AutoTRIAGE: A Multidisciplinary Approach towards Modelling, Diagnosing and Predicting Traumatic Brain Injury Severity in Road Traffic Collisions'
- Jean-Charles Mariani*, Imperial College London – 'Structural changes in brain circuitry in healthy ageing'
- Gillian Koehl*, Imperial College London – 'Topographically Patterned Hydrogels for Spinal Cord Regeneration'

Medical Devices & Diagnostics

- 25 - Stephen O'Connor*, City University of London – 'Advances in Cardiac Implantable Devices: Defibrillators'
- 26 - Daniil Nikitichev*, University College London – 'Gel Wax 3D Printing Technology'
- 27 - Duncan Finlayson*, Strathclyde University – 'Facilitating the Translation of ATR-FTIR to the Clinical Setting'
- 28 - Baboo D. Goordyal*, University of Leeds – 'Engineering Safety in Vacuum Assisted Delivery Devices'
- 29 - Aleksandra Vuckovic*, University of Glasgow – 'Home-based Neurofeedback Treatment of Neuropathic Pain'
- 30 - Jugal M. Dave*, Bournemouth University – 'VibraScan: A Smart Device to Replace Neurothesiometer for measuring Diabetic Vibration Perception Threshold'
- 31 - Chia-Hung Li*, University College London – 'Monitoring of Nasal Blockage Treatment Using an Acoustic Method'
- 32 - Robert Dickinson*, Imperial College London – 'Orthogonal Electric Field-based Catheter Alignment'
- 33 - Jennifer Frattolin*, Imperial College London – 'Effect of Corrosion on the Mechanical Properties of an Fe-316L Amalgamate for Biodegradable Stent Application'
- 34 - Suraj Pathak*, University Hospitals of Leicester – 'Short and Medium Term Outcomes Following Endobronchial Therapy with Nd:YAG Lasers for Central Airway Obstruction'
- 35 - Alessandro Borghi*, UCL Great Ormond Street Institute of Child Health – 'Population-derived Material Properties for Craniosynostosis Patients Improve Outcome Predictions in Craniofacial Surgery'
- 36 - Hanna Burton*, Cardiff Metropolitan University – 'Utilising Surface Roughness in the Design of Cranio-implants'
- 38 - Thomas Watts*, Imperial College London – 'Modelling Deformable Structures for Multi-Segment Needle Steering'
- 40 - Ho Shu Chan*, Imperial College London – 'Design and Implementation of a Transcranial Alternating Current Stimulation (tACS) Device'
- 41 - Saja Aabith*, University College London – 'High-resolution Capacitive Pressure Sensing for Health'

Special Session: Medical Devices and Health Technology CDT

- 42 - Aiden Hannah*, University of Strathclyde – 'Identification of Pathogenic Bacteria Using Disposable Screen-Printed Sensors and Electrochemical Impedance Spectroscopy'
- 43 - Sean Donnelly*, University of Strathclyde – 'Cystic Fibrosis Patient Monitor'
- 44 - Vincent Vezza*, University of Strathclyde – 'Rapid Electrochemical Detection of Sepsis Causing Bacteria'
- 45 - Mark Governo*, University of Strathclyde – 'Lipids in Cancer – Advanced Nanospectroscopic Profiling and Assessment of Non-Conventional Drugs for Cancer Therapy'
- 46 - Jacob Melnyk*, University of Strathclyde – 'Lipid Imaging of Cancerous Cells on a Teflon-Based Microfluidic Device'
- 47 - Ross Collins*, University of Strathclyde – 'User Requirements for an Upper Limb Weight Support Device for Stroke Rehabilitation'
- 48 - Ian Coghill*, University of Strathclyde – '3D Reconstruction of the Fundus of a Phantom Eye Through Stereo Matching of Slit Lamp Images'
- 49 - Pretheepan Radhakrishnan*, University of Strathclyde – 'Developing a Microfluidic Blood Preparation Device for Infrared Spectroscopic Diagnostics'
- 50 - Zanib Panni*, University of Strathclyde – 'Using ATR-FTIR for Investigating Cardiovascular Diseases and Dementia'
- 51 - Bukola Omolaiye*, University of Strathclyde – 'The Development of an Electrochemical Sensor for Measuring and Detecting Circulating Tumour DNA in Human Fluids'
- 52 - Christopher Rinaldi*, University of Strathclyde – 'Fusing Infrared & Electrochemical Analysis for Accurate and Sensitive Clinical Measurements'
- 53 - Jonathan Failes*, University of Strathclyde – 'A Soft Wearable Robotic Exoskeleton for Rehabilitation of the Frozen Shoulder'
- 54 - Abbey Sturrock*, University of Strathclyde – 'Nicotine Sensor for Electronic Cigarettes'
- 55 - Jake Bagwell*, University of Strathclyde – 'Hall Effect for Proximity Sensing in Medical Devices'
- 56 - Myndert Claassen*, University of Strathclyde – 'Combining a Microfluidic Platform with LC-MS for Metabolic Profiling for Preclinical Toxicity Screening'
- 57 - Scott Gilmarin*, University of Strathclyde – 'Development of a Microfluidic Platform for High Throughput Screening of Anti-Cancer Drugs in Prostate Cancer Spheroids'
- 58 - Francesca Farrell*, University of Strathclyde – 'Wearable LED-based Device for Phototherapy Applications'
- 59 - Joshua Paulinus*, University of Strathclyde – 'Biomarkers of Leakage After Anastomotic Dehiscence Evolution (BLADE) study'
- 60 - Ruairidh Winstanley*, University of Strathclyde – 'Development of a Multimodal Neuromodulation System for Investigation of Neural Circuitry'
- 61 - Jack Logan*, University of Strathclyde – '3D Bioprinting of ADSCs for Tissue Repair'
- 62 - Ross McWilliam*, University of Strathclyde – '3D Bioprinting of Resorbable Scaffolds for Bone Tissue Engineering in Maxillofacial Surgery'

OATech+ Network

- 63 - James Taylor*, Queen Mary University of London – 'CNP with TGFβ Enhanced Chondrogenic Differentiation of Human Amniotic Fluid Stem Cells Cultured in Agarose Constructs'
- 64 - Elze Porte*, Imperial College London – 'Moving Smoothly: Lubrication of Hydrogel Cartilage Mimics'
- 65 - Axel Moore*, Imperial College London – 'Recapitulating the Solid-Fluid Interactions in a Cartilage Mimic'
- 66 - Hannah Heywood*, SEMS, Queen Mary University of London – 'Small Molecule Sirtuin Activators Enhance In Vitro Cartilage Regeneration'
- 67 - Humaira Mahmood*, University of Birmingham – 'Alterations in the Underlying Material Density on the Surface Damage of Bovine Articular Cartilage'
- 68 - Federico Sanna*, Imperial College London – '3D Scanner for Monitoring Hand Osteoarthritis'

Mechanobiology

- 69 - Aban Shuaib*, University of Sheffield – 'Identifying Signalling Loci Involved in The Emergence of Mechanical Memory in Osteoblasts'

- 70 - Clare Thompson*, Queen Mary University of London – 'Polycystins in Ciliary-mediated Chondrocyte Mechanotransduction'
- 71 - Ahmad Zuheir bin Zaidon*, University of Cambridge – 'Assessing the Usability of the Micropipette Aspiration Technique to Determine Cell Tribology'
- 72 - Stephen Thorpe*, Queen Mary University of London – 'Fibrochondrogenic Differentiation Alters Mechanosensitive YAP Signalling in Mscs'
- 73 - Mehwish Arshad*, Imperial College London – 'Validation of CFD Method used to Model Flow in Cell Culture Dishes on an Orbital Shaker'
- 74 - Kristina Slogeryte*, Queen Mary University of London – 'Vimentin Filaments Play a Crucial Role in Cell Aging by Regulating Cell Migration'
- 75 - Wenjian Yang*, Newcastle University – 'Effect of Tip Size and Geometry on the Measured Elastic Moduli of Cells During Nanoindentation Tests'
- 76 - Beth McGill*, University of Exeter – 'Red Cell Mechanical Properties and Biochemical Signalling'
- 77 - Marie Lang*, Imperial College London – 'The Role of Methotrexate in Endothelial Cells Under Shear Stress'

Synthetic Biology and Engineering Biology

- 78 - Javier Cabello-Garcia*, Imperial College London – 'Catalytic DNA Sequence-copying through Handhold-Mediated Strand Displacement'
- 79 - Wooli Bae*, Imperial College London – 'Autonomous Generation of Multi-Stranded RNA Complexes for Synthetic Molecular Circuits'
- 80 - Diana Sobota*, University of Cambridge – 'Microfluidic Lab-on-a-chip Device for Studying Synthetic Enzymes Based on DNA Nanotechnology'
- 81 - Ignacio Gispert*, Imperial College London – 'Light-responsive Vesicles to Control Protein Expression'

Cardiovascular I & Lymphatic Bioengineering

- 82 - Ilunga Tshimanga*, University of South Africa – 'Development of 3D Printed Models for Arterial Disease Investigation'
- 83 - Willy Bonneuil*, Imperial College London – 'Microfluidic Devices for Quantifying Lymphatic-Derived Chemokine Gradients'
- 84 - Yumnah Mohamied*, Imperial College London – 'Determinants of Pro-atherogenic Shear Stress Patterns in the Aorta'
- 85 - Jason Carson*, Swansea University – 'A Benchmark Study for Non-Invasive Fractional Flow Reserve'
- 86 - Ya Hua Chim*, University of Liverpool – 'The Role of Elastin Microstructure in the Micromechanical Properties of Ascending Aortic Aneurysms'
- 87 - Amisha Desai*, University of Leeds – 'In vitro Real Time Fatigue Testing of Cellular and Decellularised Porcine Aortic Heart Valve Roots'
- 88 - Christopher Morris*, Imperial College London – 'Multiscale Modelling of Lymphatic Muscle'
- 89 - Peter Mortensen*, University of Glasgow – 'Numerical Simulations of Action Potential Propagation In Cardiac Tissues With Myocardial Infarction Scars'
- 90 - Sarah Johnson*, Imperial College London – 'Modelling the effects of Lymph Node Hypertrophy on the T Cell Mediated Response'
- 91 - Phakakorn Panpho*, University of Liverpool – 'Regional Variations in the Micromechanical and Biochemical Properties of the Ovine Aorta'
- 92 - Maria Boumpoulis*, University of Strathclyde – 'Computation of Blood Flow in the Pulmonary Bifurcation: Towards a More Effective Treatment for Adults with Congenital Heart Disease'
- 93 - Shima Abdulateef*, Brunel University London – 'Effect of Tapering on the Measured Pressure in the Inlet of a Single Artery'
- 94 - Ataollah Taj*, King's College London – 'Computational Modelling of Atrial Fibrillation: Mechanisms Based on the Generation of Transmural Rotors'
- 95 - Charles Houston*, Imperial College London – 'Investigating Uncertainty in Parameter Choices for Cardiac Cell Action Potential Models Using Statistical Inference'
- 96 - Mengke Zhuang*, Imperial college London – 'The Study of Microcirculation and Oxygen Uptake in the Liver in Cirrhosis'
- 97 - Massimo Capoccia*, University of Strathclyde – 'Computational Fluid Dynamics Analysis of the Interactions Between Heartmate II Axial Flow Pump and the Cardiovascular System: Potential for Patient-specific Modelling in Advanced Heart Failure'

Organ on a chip

- 98 - Carlos Matellan*, Imperial College London – 'Accessible Microfluidics: Rapid Prototyping of Thermoplastic Devices'
- 99 - Elisa Budyn*, ENS Cachan – 'Human Bones-on-chip Self-assembly to Form New Bone'
- 100 - John Wilkinson*, Kirkstall Ltd – 'A Roadmap for How Organ-on-a-Chip Technology Might Replace Animal Tests for Drug Safety'
- 101 - Beth Middleton, University of Warwick – 'Low-cost Injection Moulding Strategies for the Fabrication of Organ on a Chip devices'
- 102 - Virginia Pensabene*, University of Leeds – 'Investigating the Correlation Between Infection and Preterm Birth in a Human Organ-on-a-chip Model of the Human Endometrium'
- 103 - Malcolm Haddrick*, Medicines Discovery Catapult – 'Medicines Discovery Catapult – At the Heart of Drug Discovery'
- 104 - Pranav V. Bathrinathan*, Aston University – 'Employing an In-vitro Differentiated Co-culture Model of Human Bronchial Epithelium to Study Cytotoxicity of E-Cigarette Aerosols'
- 105 - Sandrine Willaime-Morawek*, University of Southampton – 'Alzheimer's Patients Induced Pluripotent Stem Cells Form 3D Mature Neural Cultures to Model Biochemical Aspects of the Disease Pathology'
- 106 - Nikita Karra*, University of Southampton – 'Recapitulation of Human Airways through the Development of a Novel In Vitro 'Lung on Chip''
- 107 - Tomasz Kostrzewski*, CN Bio Innovations Ltd – 'Analysing the Effects of the PNPLA3 I148M Variant in Hepatic Stellate Cells Using an Organ-on-Chip Model of Non-alcoholic Steatohepatitis'

Personalised Medicine & Modelling Biological Systems

- 108 - Selene Pirola*, Imperial College London – 'Comparison of Aortic Hemodynamics Between Surgical Aortic Valve Replacement (SAVR) and TAVI'
- 109 - Gemma Stiles*, King's College London – 'Statistical Shape Modelling of the Pregnant Abdomen'

Biomedical Imaging

- 111 - Daniil Nikitichev*, University College London – 'Patient-Specific Pituitary Phantoms for Ultrasound Imaging: Development and Early Validation'
- 112 - Aleksandra Vuckovic*, University of Glasgow – 'fMRI Neurofeedback for Treatment of Phantom Pain'
- 113 - Manousos Klados*, Aston University – 'Classifying Cognitive Recovery after Stroke'
- 114 - Richard Caulfield*, University College London – '3D Printed Probes with Optically-Generated Ultrasound for High-Resolution Imaging during Minimally Invasive Procedures'
- 115 - Muhammad Zubair*, Imperial College London – 'Synthetic Aperture Imaging and Therapy with Random Phased Arrays'
- 116 - Jonathan Williams*, University of Strathclyde – 'Site-specific Changes in Bone in a Rat Model of Spinal Cord Injury'
- 117 - Gustave Ronteix*, University of Cambridge – 'Extracting Features from Confluent Cellular Sheets'
- 118 - Kai Riemer*, Imperial College London – 'Measuring Blood Flow and Wall Shear Stress In Vivo Using Ultrasound Imaging Velocimetry with Native Blood Speckle or Microbubble Contrast Agents'
- 119 - Ge Zhang*, Imperial College London – 'Ultrasound and Microscopic Imaging of Nanodroplet Adhesion to Endothelial Cells under Atheroprone Flow Conditions'
- 120 - Xiaowei Zhou*, Imperial College London – 'Out-of-plane In-vitro Flow Velocity Investigation for Measuring Cardiac Output with High-Frame-Rate Microbubble-Enhanced Ultrasound'
- 121 - Cornelia Schmitz*, King's College London – 'Design and Development of Mechanically Powered Multimodal Imaging Phantoms'
- 122 - Pei-Jung Wu*, Imperial College London – 'Brillouin Microscopy: A Tool to Access the Water Content in Hydrated Materials'
- 123 - Dawn Gillies*, University of Edinburgh – 'Real-time and Non-invasive Measurements of Cell Mechanical Behaviour Using Optical Coherence Phase Microscopy'
- 124 - Hasan Koruk*, MEF University – 'Displacement of A Bubble Along Fluid-Tissue Interface'
- 125 - Hannah Perry*, Imperial College London – 'Multifunctional Nanoparticles for Targeted MRI and Therapy'
- 126 - William S. Hart *, Imperial College London – 'Nano-imaging in the Mid-IR for Intra-cellular Drug Localisation'

BioMedEng18 Poster Presentation: Day Two

Musculoskeletal Biomechanics, Gait Analysis & Human Movement

- 1 - Gwenllian Tawy*, University of Manchester – 'Motor Control and Gait Variability of Patients with the Medacta GMK Sphere Total Knee Arthroplasty'
- 3 - Isotta Rigoni*, Aston University – 'Acute Effects of Whole Body Vibration on Postural Stability'
- 4 - Suzanne Shanel*, Imperial College London – 'Using Whole Body Kinematics to Predict Ground Reaction Forces During Military Load Carriage'
- 5 - Caryn Urbanczyk*, Imperial College London – 'Facilitating Compatibility across Motion Tracking Systems in Sports Biomechanics'
- 6 - Richard Ademefun*, Imperial College London – 'Improving Gait Measurements for the Kinematic Movement of the Knee Joint'
- 7 - Samuel Smith* - Imperial College London – 'A Change in Muscle Recruitment Strategy Could Explain Difficulties in Elderly Sit-to-stand Movements'
- 8 - Robert Cooper*, University of Leeds – 'Three-dimensional Severity Measures and Rapid Model Generation for Cam Type Femoral Geometries'
- 9 - Yuming Huang*, Imperial College London – 'Effects of Abnormal Fetal Movements on Rib Cage Development'
- 10 - Letizia Gionfrida*, Imperial College London – 'Markerless and Marker-based Solution to Estimate Kinematics'
- 11 - David Wallace*, University of Strathclyde – 'Wavelet Analysis in the Diagnosis of Knee Instability – Early Results from a Novel Assessment Method'
- 12 - Daniel Nolte*, Imperial College London – 'Improving Statistical Shape Model Predictions from Partial Femur Bones Using Prior Knowledge of Mineral Density in the Residual Bone'
- 13 - Chia-Han Yeh*, Imperial College – 'Why is a Lower Limb Musculoskeletal Model Most Sensitive to Where Muscles Insert on the Foot? An Explanation Using Lagrangian Multipliers'
- 14 - Ziyun Ding*, Imperial College London – 'Improving Musculoskeletal Model Scaling Using Gender and Anthropometric Similarity'
- 16 - Dominik Sobczak*, Imperial College London – 'The 'Imperial Spine Cluster Model' as a Simplified Approach of Evaluating Spinal Kinematics in Patients'
- 17 - Dan Terracina*, Imperial College London – 'Monitoring Back Muscle Fatigue During Activities of Daily Living'
- 18 - Christian Klemf*, Imperial College London – 'The Effect of Rotator Cuff Tears on Anterior Shoulder Instability'
- 19 - Dasen Xu*, Northwestern Polytechnical University – 'Study on the Mechanism of Fluid Percussion Injuries on Immune Cells'
- 20 - Jun Liu*, Northwestern Polytechnical University – 'Investigations on Passive Mechanical Properties of Porcine Myocardium Under Compression'

Neurotechnology, Rehabilitation Engineering & Robotics

- 21 - Chen Wang*, Imperial College London – 'Vision-based Automatic Control of a Simulated Schunk 5-Finger Robotic Hand for Activities of Daily Living'
- 22 - Nuria Pena Perez*, Imperial College London – 'Does Visual Feedback Improve the Soft Mechanisms of Interaction?'
- 23 - Taegyun Jeong*, King's College London – 'New Shape Sensing Approach for Flexible Manipulator used in MIS'
- 24 - Cameron Higgins*, Oxford Centre for Human Brain Activity – 'Decoding the Features of Neural Replay Through Dynamic Logistic Regression'
- 25 - Katie Timms*, University of Leeds – 'Developing Experimental Models of Non-Traumatic Spinal Cord Injury'
- 26 - Finda Putri*, University of Glasgow – 'Brain Functional Network During Resting vs Active State: an EEG Study'
- 27 - Fabio Barollo*, University of Reykjavik – 'Effects of Anxiety on Cognitive Neurodynamics Among University Students: Preliminary Data'
- 28 - Jiewon Kang*, Imperial College London – 'Dissociating Frontoparietal Networks Based on Functional Connectivity States'
- 29 - Alexander Davidson*, Imperial College London – 'Non-invasive Neurostimulation to Modulate Frontoparietal Synchronisation and Accelerate Learning'
- 30 - Sarah J. Massey*, University College London – 'The Effects of Neuromodulation on Central Excitability of the Upper Limb in Healthy, Able-bodied Adults'
- 30 - Aleksandra Vuckovic*, University of Glasgow – 'Effect of Neurofeedback Training on Laterality During Leg Motor Imagery'
- 32 - Suyi Zhang*, University of Cambridge – 'Endogenous Control of Closed-Loop Brain-Machine Interfaces for Pain'
- 33 - Richard Daws*, Imperial College London – 'Working Harder Together': Surges in Global Activity & Synchrony during Cognitive State Transitions'
- 34 - Solomia Boretska*, Imperial College London – 'Integrating Neurodata Without Borders (NWB) into NeuroSEE, the Automated Neuronal Source Extraction and Exploration toolbox'
- 36 - Rejin Varghese*, Hamlyn Centre for Robotic Surgery – 'Modelling Tremor for Virtual Prototyping of Exo-Glove'

Pulse Wave Analysis

- 37 - Jorge Mariscal Harana*, King's College London – 'Reduced-Order Computational Models for Central Blood Pressure Estimation: Two Clinical Scenarios'
- 38 - Samuel Vennin*, King's College London – 'Tracking Variations in Cardiac Output from Pressure and Pulse Wave Velocity Measurements: A Proof-of-Concept Study'
- 39 - Alessandro Giudici*, Brunel University London – 'The Effect of the Mach Number on the Reflection Coefficient Estimated by Wave Intensity Analysis'
- 40 - Weiwei Jin*, King's College London – 'A Computational Based Analysis of Flow Mediated Dilation: Towards Improved Endothelial Function Assessment'
- 41 - Igor Sazonov*, Swansea University – 'Aortic Aneurysm Detection by Waveform Analysis'
- 42 - Peter Charlton*, King's College London – 'A Database for the Development of Pulse Wave Analysis Algorithms'
- 44 - Riaz Akhtar*, University of Liverpool – 'Altered Adventitial Collagen Fibril Mechanics and Morphology in Patients with High Pulse Wave Velocity'
- 45 - Wisam Hacham*, Brunel University London – 'Wave Speed Estimated by Using PU-loop Technique in the Presence of Continuous Flow'

Cancer Engineering, Drug & Gene Delivery

- 46 - Yu Huang*, Imperial College London – 'A Multiphysics Model for Focused Ultrasound-Mediated Thermosensitive Liposome Drug Delivery to Tumour'
- 47 - Nathan Sjoquist*, University of Cambridge – 'Semi-Automatic Detection and Visualization of Metastatic Bone Disease'
- 48 - Patricia Pascual Vargas*, Institute of Cancer Research – 'Combining New Imaging and Bioengineering Technologies to Study How Rhogefs Drive Triple Negative Breast Cancer Cell Invasion'
- 52 - Stewart Smith*, The University of Edinburgh – 'Development of an Implantable Microsystem for In Vivo Measurement of Oxygen in a Large Animal Model of Cancer'
- 53 - Marco Fiorito*, King's College London – 'Impact of Nonlinear Tissue Mechanics on Solid Tumour Surrounding Soft Tissue: A Phantom and In Silico Investigation'
- 54 - Elena Tsolaki*, University College London – 'Ultrastructural Characterization of Breast Cancer Tissue Reveals Distinct Micro and Nano Apoptosis and Whitlockite'
- 55 - Andrew Riley*, University of Hull – 'A Precision Cut Tumour Slice (PCTS) Culture Model Capable of Maintaining Ex Vivo Thyroid Carcinoma Specimens'
- 56 - Maryam Parhizkar*, University College London – 'Nanoparticle Drug Delivery Systems for Synergistic Effect of Cisplatin and Decitabine'
- 57 - Yueyun Zhang*, Imperial College London – 'Fast and Efficient Light-Controlled CRISPR/Cas9 Gene Editing'
- 58 - Justine Fraser*, University of Strathclyde – 'A Local Drug Delivery Technology to Prevent Implant Infections'
- 59 - Elnaz Jamili*, University College London – 'Model Based Optimal Control of Gene Delivery'
- 60 - Shami Shrivastava*, University of Oxford – 'Designing Acoustically Responsive Lipid Nanoparticles for Intracellular Macrodug Delivery'
- 61 - Ioanna Marina Syntouka*, University of Strathclyde – 'Flow simulation of a Collagen Solution in Syringes with Different Geometries'
- 62 - Wenbo Zhan*, Imperial College London – 'Numerical Simulation of Convection Enhanced Delivery of Nano Drug Carriers into Brain Tumour'

Biomaterials

- 63 - Corinne Morfill*, Imperial College London – 'Peptide-targeted Gold Nanostars for Treatment of Parkinson's disease'
- 64 - Arturo Mendoza-Meinhardt*, Queen Mary University of London – 'Peptide Amphiphiles as Manipulators of Protein Conformation'
- 65 - Moutaz Hamdan*, University of Strathclyde – 'Investigation of the use of Electroactive Polymer for Cardiovascular Applications'
- 66 - Anna Majkowska*, Queen Mary University of London – 'Functionalisation Of A Protein/Peptide System Towards a More Complex and Functional Biomaterial'
- 67 - James Reid*, The University of Edinburgh – 'Novel Extracellular Matrix Scaffolds in a Hypoxic Environment'
- 68 - Elham Radvar*, Queen Mary University of London – 'Fabrication of Aligned Nano-fibrous Membranes Through Supramolecular and Magnetic Forces'
- 69 - Gareth Menagh*, Ulster University – 'The Effect of Increasing Dosage of Atmospheric Dielectric Barrier Plasma Discharge (DBD) on Electrospun PLCL/PANI Biomaterials'
- 70 - linke Wu*, Queen Mary, University of London – 'Thiol-Ene Clickable Gelatine Hydrogel for Tissue Engineering'
- 71 - Farshad Oveissi*, The University of Sydney – 'Soft, Robust, and Bioactive Hydrogels with Tuneable Mechanical Properties and Rapid Load Recovery'
- 72 - Amy Smith*, University of Leeds – 'On-Demand Activation of Antimicrobial Biomaterials for Oral Soft Tissue Regeneration'
- 73 - Anthony Callanan*, The University of Edinburgh – 'Production of Synthetically Derived Extracellular Matrix as a Controlled Platform for Liver Bioengineering'
- 74 - Nazia Mehrban*, University College London – 'Engineering Soft Tissues: Learning From Nature'
- 75 - Ji Eun Hong*, Sogang University – 'Uptake of Radioactive Cesium by Alginate Immobilized Microalgae'
- 76 - Alessandra Lo Fiego*, Imperial College London – 'Designing Organic Electronic Materials for Biology'
- 77 - Philipp Seib*, University of Strathclyde – 'Reverse-engineered Silk Hydrogels as a Stem Cell Delivery Matrix for Stroke'

Biosensors, Biomedical Signal Processing & Bioelectronics

- 78 - Bahareh Hosseini*, Kumamoto University – 'Antibacterial effects of *Perilla frutescens* var. *crispa* fo. *viridis* Makino extracted by nanosecond pulse electric shock waves'
- 79 - Amparo Güemes *, Imperial College London – 'A Glucose Controller for Type I Diabetes Using Insulin Sensitivity Modulation'
- 80 - Anastasios Polygras*, University of Cambridge – 'Noise in Organic Electrochemical Transistors'
- 81 - Kylie de Jager*, University College London – 'A Multi-channel Multiplexed EMG Recording System to Study Electrode Array Configuration'
- 82 - Aleksandra Vuckovic*, University of Glasgow – 'Event Related Potentials and Event Related Perturbations During Movement Imagination Depending on Muscle Activations'
- 83 - Jetsada Amin*, University of Strathclyde – 'Implementation and Evaluation of Different Time and Frequency Domain Feature Extraction Methods for a Two Class Motor Imagery BCI Applications: A Performance Comparison Between GPU and CPU'
- 84 - Oluwalogbon Akinnola*, Imperial College London – 'Recommending a Protocol for Normalisation of Forearm Electromyography (EMG)'
- 85 - Hattan Ballaji*, University of Nottingham – 'An Optical Sensor Probe for Measuring Blood Volume and Skin Contact Pressure'
- 86 - Anitha Devadoss*, Swansea University – 'Graphene Biosensors for Early Detection of Dementia Biomarkers'
- 87 - Rowan Nicholls*, University of Oxford – 'Quantification of Advanced Glycation End-Products in a Streptozotocin Rat Model of Diabetes'
- 89 - De-Shaine Murray*, Imperial College London – 'A Microfabricated Probe for the Non-Invasive Monitoring of the Injured Brain'

Cardiovascular Bioengineering II & Biofluids

- 90 - Ali Mosayyebi*, University of Southampton – 'Study of the Flow Field in In-vitro & In-silico Stented Ureter Models'
- 91 - Gianluca Marcelli*, University of Kent – 'Simulation of the Thermal Fluctuations of Red Blood Cells with the Inclusion of Hydrodynamic Interactions'
- 92 - Froso Sophocleous*, University of Bristol – 'Shape Variability in Bicuspid Aortic Valve Patients: An Insight into the Effect of Coarctation on Arch Morphology'
- 93 - Waruj Akaraworatikamporn*, Imperial College London – 'Mathematical Method to Investigate Effect of Hypertension on Mass Transport in Arterial Walls'
- 94 - Mikaela Webster*, University of Bristol – 'The Potential of Director Theory for Modelling Blood Flow in the Cardiovascular System'
- 95 - Genevieve Pounds*, University of Leeds – 'Design for a Housing for an Aortic Root to attach to a ViVtiro Real-Time Wear Tester'
- 96 - Parthasarathi Mandal*, University of Manchester – 'Investigating the Influence of Precision of the Reconstructed AAA Geometries on Hemodynamic Parameters of Abdominal Aortic Aneurysm Employing Fluid-Structure Interaction Analysis'
- 97 - Lauren Johnston*, University of Strathclyde – 'Blood Flow in an Intracranial Aneurysmal Artery with a Dual-layer Stent'
- 98 - Ian Mann*, Imperial College London – 'Atrial Fibrillation is Chaotic but Not Random'
- 99 - Benjamin Owen*, University of Manchester – 'Many-core Acceleration of a Discrete Fluid-structure Interaction Method and Potential as a Clinical Decision-support Tool'
- 100 - Wenbo Zhou*, University College London – 'In-Vitro Modelling of Mitral Valve Therapies'
- 101 - Alberto Gambaruto*, University of Bristol – 'Three-dimensional Simulations of Idealised Lymphangion'
- 102 - Manuela Ratnayake*, University of Strathclyde – 'Complex Interactions of Excitatory Stimuli in the Vascular Endothelium'

Artificial Intelligence & Machine Learning

- 103 - Lucrezia Lorenzon*, Politecnico di Milano – 'Using Convolutional Neural Networks to Identify Functional Mutations in the Human Genome Through Patterns of Natural Selection'
- 104 - Daniel Toth*, King's College London and Siemens Healthineers, UK – 'AI-based Registration for Cardiac Interventions'
- 105 - Syed Ghufuran Khalid*, Anglia Ruskin University – 'Cuffless Blood Pressure Estimation Using Support Vector Machine Algorithm'
- 106 - Konstantinos Tzortzis*, Imperial College London – 'Supervised Machine Learning Predicts Fibrosis in Ex Vivo Human Cardiac Slices Using Electrogram Morphology'
- 107 - Stef Garasto*, Imperial College London – 'Learning Representations for Physical Systems: An Application to a Two-dimensional Diffusion Model'

Trauma, Surgery, Orthopaedics & Prosthetics

- 108 - Alix Chadwell*, University of Salford – 'Clinical Functionality of Prosthesis Users Compared Against Actual Prosthesis Usage in the Real-World'
- 109 - Anna Pace*, University of Salford – 'A New Hydraulic Prosthetic Ankle to improve Amputee Cost of Walking'
- 110 - Shruti Turner*, Imperial College London – 'Visualising Complex 3D Data in a Clinical Environment'
- 111 - Fjodors Tjulkins*, Aspire Create – 'Transcutaneous Feedthrough Enabled Bone Anchor for Attachment and Control of a Smart Upper Limb Prosthesis'
- 112 - Henry Lancashire*, University College London – 'Electrode Configuration Selection for Electromyographic Prostheses'
- 113 - Alex van Heesewijk*, University of Surrey – 'Effect of Prosthetic Liner Properties on Residual Limb Stresses'
- 114 - Joshua Steer*, University of Southampton – 'FEA-driven Surrogate Modelling of the Residuum-Prosthesis Interface'
- 115 - Blake McCall*, Aston University – 'The Influence of Movement on Biofilm Formation to External Fracture Fixation Pins'
- 116 - Eduardo Rebelo*, Imperial College London – 'Protection of the Foot and Ankle in Under-body Blast'
- 117 - Raelene Cowie*, University of Leeds – 'Third Body Wear Simulation of UHMWPE-on-PEEK-OPTIMA™'
- 118 - Hanna Burton*, Cardiff Metropolitan University – 'Engineering Accuracy in Safety Critical Spinal Surgery'
- 119 - Louise Jennings*, University of Leeds – 'Influence of Test Frequency on the Friction of UHMWPE-on-Cobalt Chrome'
- 120 - Warren Macdonald*, Imperial College London – 'Hexapod External Fixator Biomechanics – The Final Link'
- 121 - Muhammad M. Khan*, Aston University – 'Development of a Smart Elbow Prosthesis'
- 122 - Ruben Doyle*, Imperial College London – 'Using the 'Woodpecker' to seat Acetabular Cups during Hip Arthroplasty: Reduce Strain and Increase Fixation'
- 123 - Julius Lipskas*, University of Strathclyde – 'Evaluation of Remote Centre of Motion Mechanism Suitability for Osteochondral Tissue Milling'
- 124 - Dong Wang*, Imperial College London – 'A Multi-station Shoulder Wear Simulator and its First Wear Test Results'

Tissue Engineering & Regenerative Medicine

- 125 - Oluwadamilola Agbabiaka*, University of Bradford – 'Fabrication and Optimisation of Electrospun Scaffolds for Ligament Tissue Engineering'
- 127 - Elisa Tarsitano*, University of Nottingham – 'Encapsulation of Human Hepatocytes in Chemically Modified Alginates'
- 128 - Jessica Bratt*, Keele University – 'Placental Mesenchymal Stem Cells for the Treatment of Neonatal Chronic Lung Disease'
- 129 - Dhanak Gupta*, University of Sheffield – 'Comparison of Fucoidan from Two Different Species of Brown Seaweed for Bone Tissue Engineering'

Biomedical Engineering Education

- 130 - Carolyn Thompson*, University College London – 'Animal Robotic Locomotion: An Interdisciplinary Teaching Programme'
- 131 - Rebecca Yerworth*, University College London – 'Teaching Biomedical Engineering Undergraduates How to Keep a Lab Notebook'
- 132 - Mike Raxworthy*, University of Leeds – 'Introducing Innovation Practices to Medical Engineering Students'

Messages from our Partnering Organisations

The ICR/Imperial Cancer Research Centre of Excellence



Concepts and tools from engineering, the physical sciences and cognate disciplines have improved the understanding, diagnosis and treatment of disease in a number of body systems.

One example is the cardiovascular system, where pressures, flows and electrical activity are studied and routinely monitored using engineering techniques, and where deficiencies are treated with engineered devices such as stents, grafts, defibrillators and pumps. Another example is the musculoskeletal system, and the nervous system is a third area where such technologies are rapidly developing. Equal or greater scientific and clinical impact could be achieved by applying engineering and physical science concepts and tools to understanding, diagnosing and treating cancer.

The Institute of Cancer Research and Imperial College London have come together to establish the Cancer Research Centre of Excellence (CRCE), with the aim of forming a closely integrated and sustainable partnership that eliminates disciplinary barriers by bringing together world-class researchers in engineering, physics, chemistry, data science and basic and applied cancer research to create convergence science-based solutions, driving a paradigm shift in cancer research that will generate inspiring new treatments and technologies to improve the lives of people with cancer.

Innovative approaches will cover prevention, early and improved diagnosis, and novel treatments, including approaches to overcome cancer's ability to adapt and evolve, leading to drug resistance. In addition, the CRCE will attract and recruit new international leaders in convergence science and provide the training for the next generation of non-clinical and clinical multidisciplinary scientists. The CRCE has stimulated submissions to BioMedEng18 from the cancer engineering interface, leading to a session and numerous posters devoted to the subject.

On behalf of Professor Paul Workman and Professor the Lord Darzi of Denham

Organ-on-a-Chip Technologies Network



The newly funded Organ-on-a-Chip Technologies Network is a joint MRC, EPSRC and BBSRC funded Technology Touching Life initiative, designed to capture, inspire and grow UK research activity in the Organ-on-a-Chip research field.

An organ-on-a-chip is an engineered system in which the architecture, functions and surrounding physiochemical environment of a living human organ are recreated, allowing drugs or therapies to be tested on an in vitro system which recapitulates the in vivo one. The development of organ-on-a-chip in vitro models has grown from a nascent idea in 2000 to one of the most promising, fastest growing research areas in the world, predicted to achieve a compound growth rate of 38-57% over the next 5 years to become a multi-billion pound industry.

Our network aims are to:

- a. Develop a vibrant multidisciplinary research community, bringing focus to the varied Organ-on-a-Chip and In Vitro model research activity in the UK;
- b. Facilitate inter-disciplinary and inter-sectoral research collaborations, to develop the next generation of organ-on-a-chip research solutions;
- c. To train, support and inspire the next generation of outstanding leaders in organ-on-a-chip research.

We launch in September 2018 in collaboration with BioMedEng18, facilitating a day of exciting research discussions as we prepare to shape network activities and priorities over the coming years.

We are excited to be part of the UK's largest gathering of Biomedical Engineers, Medical Engineers and Bioengineers, providing an ideal home for initiating our multidisciplinary network activity. We look forward to welcoming biomedical engineers, physical scientists, life scientists and clinicians to our community.

Professor Hazel Screen, Director of the Organ-on-a-Chip Network

Briefs from our Partnering Organisations

The Osteoarthritis Technology Plus Network (OATech+ Network)



Osteoarthritis (OA) affects 8.75 million people in the UK, places a considerable burden upon the economy, and seriously impairs the quality of life of its sufferers. The OATech+ Network is a four-year UK based Engineering and Physical Sciences Research Council (EPSRC) funded project.

The aim of the Network is to utilise the expertise of multidisciplinary network partners to:

- Identify challenges and knowledge gaps
 - Support and drive multidisciplinary collaborations in UK osteoarthritis research
 - Form the basis for high-level grant funding and publications
- and ultimately improve diagnosis, treatment and bring novel therapies to market.

Several research focused and cross cutting themes have been established as the basis on which to identify knowledge gaps in osteoarthritis research. Theme leaders have been appointed to help direct these key areas and drive multidisciplinary working groups.



These groups bring together experts across all fields of OA research, including biomedical engineers, surgeons, rheumatologists, imaging experts, musculoskeletal scientists, modelling experts, biomechanists and biologists, to explore where the technology- based research priorities within each theme lie.

A series of feasibility studies and technology driven activities are now being undertaken to address the knowledge gaps. These outputs will be shared across the Network and disseminated to stakeholders including clinicians, patients and the general public. These outputs will form the building blocks for future research within the field of technology and OA. To promote translation, this will be underpinned by a focused drive towards patient and clinical engagement.

Principle investigator: Prof Catherine Holt

Co-investigators: Prof Anthony Bull, Prof Philip Conaghan, Prof Andrew Pitsillides, and Prof Philip Rowe

Network coordinator: Dr Leanne Sawle

<http://oatechnetwork.org/>

Plenary Speakers

Professor Kyriacos Athanasiou

Lecture Title: Toward Bioengineering Translation



Kyriacos A. Athanasiou is a Distinguished Professor of Biomedical Engineering and the Director of DELTAi (Driving Engineering & Life-science Translational Advances @ Irvine), at the University of California, Irvine.

He obtained his PhD in Bioengineering (Mechanical Engineering) from Columbia University in 1989. He has published 330 peer-reviewed papers, 20 books, and multiple patents. He has also served as president of the Biomedical Engineering Society. Additionally, he is the immediate past Editor-in-Chief of the Annals of Biomedical Engineering, the flagship journal of BMES.

His list of awards includes the Nemitsas Prize (Cyprus' largest award presented by the President of Cyprus), Savio Woo Medal for Translational Biomechanics from the American Society of Mechanical Engineers, Distinguished Service Award from BMES, HR Lissner Medal from ASNE, Wall Street Journal's 2008 Innovation Award, Thomas A. Edison Patent Award from ASME, Hershel Rich Outstanding Invention Award, Marshal Urist Award for Excellence in Tissue Regeneration Research from the Orthopaedic Research Society, and the Van Mow Medal from ASME.

He is a Fellow of BMES, AAAS, AIMBE, and ASME; he was also elected to the National Academy of Inventors. In addition to his academic interests, he has been involved with effecting the translation of devices and instruments into clinical use and commercialization.

Dr Geraldine Hamilton

Lecture Title: Organs-on-Chips Technology: A Platform for Advancing Efficacy and Safety Testing in Drug Discovery and Development



Dr. Hamilton is the President and Chief Scientific Officer of Emulate, Inc. Based on their Organs-on-Chips technology platform, the company is developing a new living human system that combines cell biology within micro-engineered environments - for researchers to accurately understand how different diseases, medicines, chemicals and foods will affect human health.

Hamilton's career spans industry, academia and building entrepreneurial companies. Prior to joining Emulate's founding team, she led the development of the Organs-on-Chips technology within the Wyss Institute for Biologically Inspired Engineering at Harvard University. The work on Organs-on-Chips has been published in high-impact scientific journals, curated into New York's Museum of Modern Art (MoMA) and awarded Product Design of the Year 2015 by London's Design Museum.

Hamilton has more than 11 years experience within the pharmaceutical industry in leadership roles managing drug discovery teams - driving new technologies, applications and product validation. Earlier in her career she was a founding scientist and VP of Scientific Operations for CellzDirect. Hamilton led scientific work and business development to translate the company's innovative technology for cell-based products to broad use across the pharmaceutical industry.

Hamilton earned her Ph.D. in cell biology and toxicology from the University of Hertfordshire (England) in conjunction with GlaxoSmithkline, followed by a post-doctoral research fellowship at the University of North Carolina. Her research career has focused on the development of novel cell-based models and applications for drug safety and efficacy testing. She has co-authored over 40 peer-reviewed publications and numerous patents.

Plenary Speakers

Professor Jonathan Cooper, FREng, FRSE

Lecture Title: Paper Based DNA Diagnostics in Low Resource Under-Served Communities



Professor Jon Cooper holds the Wolfson Chair in Biomedical Engineering at the University of Glasgow and is the Vice Principal leading the University's strategy in Knowledge Exchange and Innovation.

He is an EPSRC Research Fellow and holds a European Research Council Advanced Programme Grant. His major research interests are in medical diagnostics and imaging, with a track record of spin-out and translation of devices into industry and practice. In one example, he is working with colleagues in UCLA on combining ultrasonics with computational photonics to produce ultra-high resolution mobile microscopes for biological imaging, resolving objects at sub-micron resolutions on a phone camera (e.g. differentiating viruses and bacteria).

In a second strand of his current work, rapid, zero-cost multiplexed "origami paper" diagnostics are being trialled in rural East Africa as species-specific DNA sensors to identify the cause of infectious disease and inform treatment amongst under-served rural communities. Further examples of translation of his research include bathroom diagnostics, sold as a bowel cancer test on the high street (e.g. Boots the Chemist), and a new venture-funded product for sexual health testing in the clinic.

He is an elected Fellow of the Royal Academy of Engineering (UK's national academy of engineering) and a Fellow of the Royal Society of Edinburgh (Scotland's national academy of arts, humanities and sciences).

Professor Hanjoong Jo

Lecture Title: Mechanoregulation of MicroRNAs – From Mechanobiology to Translation



Dr. Hanjoong Jo is John and Jan Portman Professor and Associate Chair for Emory BME in the Coulter Department of Biomedical Engineering (BME) at Georgia Tech and Emory University, and Professor of Medicine at Emory University.

Dr. Jo received his BS at Korea University and PhD at Pennsylvania State University. Following postdoctoral training in the Jay McDonald Lab at Washington University in St. Louis and University of Alabama at Birmingham, he became Assistant Professor in Pathology and Biomedical Engineering. Dr. Jo joined the BME Department at Georgia Tech and Emory University in 2000.

He directs the Cardiovascular Mechanobiology and Nanomedicine lab. His lab studies how blood flow regulates genes in endothelial cells, and how they induce or prevent atherosclerosis and aortic valve disease. To this end, his lab uses OMICs approaches to discover novel flow-sensitive coding and non-coding genes, develops novel therapeutics by targeting the flow-sensitive genes, and develops novel nanodelivery methods for targeted therapies to treat the cardiovascular disease.

He has published more than 165 peer-reviewed papers and two books as editor. He is an elected fellow of American Institute of Medical and Biological Engineering, Biomedical Engineering Society, American Heart Association and American Physiological Society. He has also served as a Distinguished Visiting Professor at Ewha Womans University and Chonbuk National University.

After Dinner Speaker



Sophie Scott is a Professor of Cognitive Neuroscience at University College London. She investigates human communication and the human brain, with particular emphasis on the neurobiological basis of vocal communication and how this can go wrong.

She is particularly interested in studying both verbal and non-verbal aspects of vocal communication and has pioneered the study of the human voice as a social signal. She has also recently started to address the ways that non-verbal emotional expressions like laughter are used socially. She was the 2017 Royal Institution Christmas Lecturer.

Keynote Speakers & Workshops

Motor Neuron Interfacing & Biomedical Applications

6th September 2018, 11:15-12:45 (Pippard Lecture Theatre)

Keynote Speaker: Professor Simon Gandevia

Title: "Motor Neurons: some unexpected messages"



Professor Simon Gandevia (PhD, MD, DSc) is Deputy Director of Neuroscience Research Australia in Sydney and an NHMRC Senior Principal Research Fellow. He studied medicine at the University of New South Wales and subsequently conducted research in clinical neurophysiology at the Prince Henry Hospital. In 1992, he established the Prince of Wales Medical Research Institute (now Neuroscience Research Australia). His research on volunteers and patients focuses on four areas: proprioceptive mechanisms, human motor control and muscle fatigue, neural control of breathing, and the passive behavior of muscles. He has published more than a hundred papers in the Journal of Physiology. He has had longstanding editorial roles with the Journal of Physiology and Journal of Applied Physiology and currently heads an NHMRC program in 'Motor Impairment'. He was elected a Fellow of the Australian Academy of Science in 1998 and the Australian Academy of Health and Medical Sciences in 2016.

Other Talks in this Workshop

M. Bräcklein, Imperial College London - 'Decorrelation of Common Input to a Muscle's Motor Neuron Pool'

G. Puttaraksa, Imperial College London - 'Common and independent synaptic input to motor neurons in essential tremor patients'

M. Rotherham, Keele University - 'Remote control of cell signalling with magnetic particles for neuronal cell differentiation- emerging therapies for Parkinsons disease'

N. Steadman, John Radcliffe Hospital, Headington, Oxford - 'A Robotic System to Automate Parameter Tuning for Deep Brain Stimulators'

Dr Alessandro Del Vecchio, Imperial College London - 'You are as fast as your motor neurons: Early recruitment and maximal discharge of motor neurons determine the maximal rate of force development in humans'

Recent advances in Mechanical Circulatory Support

6th September 2018, 13:45-15:00 (Read Lecture Theatre)

First Keynote Speaker: Dr Christopher Bowles

Title: "What do clinician's want from new MCS devices?"



Dr Christopher Bowles is the Clinical Specialist in Mechanical Circulatory Support at Harefield Hospital and has over three decades' experience of mechanical circulatory support. He was instrumental in establishing the circulatory support programme at Harefield Hospital in the late 1980's, the largest programme in the UK and has used 19 different assist devices for patient treatment. Dr Bowles has an active clinical research interest, is author of 60 peer review publications and is an Honorary Research Associate of the Department of Bioengineering, Imperial College London. Current research activities include analysis of the acoustic properties of rotary left ventricular assist devices, the interaction between the left ventricle and the LVAD, and myocardial recovery. Dr Bowles previously chaired a national consortium which has developed guidelines for ambulance clinicians for the management of emergencies in LVAD recipients in the pre-hospital setting.

Other Talks in this Workshop

S. McConchie, Calon Cardio-Technology Ltd. - 'A UK VAD: from Engineering to Clinical Trials'

Dr K. H. Fraser, University of Bath - 'Pulsatile Flow in Ventricular Assist Devices: CFD Analysis of Velocity Fields around the Pressure-Flow Loop' (*Abstract on Page - 65*)

Please see the next page for the Second Keynote Speaker's details

Keynote Speakers & Workshops

Second Keynote Speaker: Professor Cathy Thornton

Title: "Measurement of Blood Damage due to Fluid Stresses and Biomaterials"



After a science degree in Biochemistry and Microbiology/Immunology at the University of Tasmania Cathy undertook a PhD at Flinders University of South Australia. On completion of her PhD she was awarded a CJ Martin Post-doctoral Fellowship from the National Health and Medical Research Council (NH&MRC) Australia. This enabled her to pursue post-doctoral studies at the Universities of Southampton and Western Australia. Cathy has been at Swansea University Medical School for nearly 15 years and is now Professor of Human Immunology studying various aspects of the immunology of pregnancy. Much of this work centres on the study of blood and these skills support research activity in the area of inflammation and blood handling medical devices; this work has been supported by Innovate UK and EPSRC. Cathy is currently a Deputy Head of the Medical School, and oversees the School's flow cytometry facility and human tissue research activity.

BioMedEng18 Phenomenal Women in Innovation

6th September 2018, 13:45-15:00 (Clore Lecture Theatre)

The Phenomenal Women in Innovation workshop will celebrate the achievements of women who have contributed in diverse ways in changing the innovation landscape of Science and Technology in the UK, by illustrating the diversity in their career paths. The workshop will feature a series of talks from women in academia, industry and leading start-ups. It will be an opportunity to showcase their journeys, highlight major achievements and awards they have received, and also present the challenges that strengthened them along their journeys. There will be a panel discussion after the final presentation.

Gifty Tetteh, Conference Director

Speakers

Professor Alison Noble



Alison Noble OBE FREng FRS is the Technikos Professor of Biomedical Engineering and an Associate Head of the Mathematical, Physical and Life Sciences Division at the University of Oxford. She was awarded a PhD in computer vision from Oxford University in 1989. Alison then moved to the USA to work as a scientist at the GE Corporate R&D Center, Schenectady NY, returning to the UK in 1995 to take up a lectureship at the University of Oxford. She became the first woman to hold a Statutory Professorship in Engineering at Oxford University in 2011. Alison's research interests are in ultrasound imaging, computational analysis of images, and the development of decision-support tools for medical professionals. Her research is motivated by clinical unmet needs in western and developing world healthcare settings. She co-founded Intelligent Ultrasound Ltd to commercial research from her laboratory which was acquired by MedaPhor Group Plc in 2017. Professor Noble is a Fellow of the Royal Academy and of the Royal Society, a Trustee of the Institute of

Engineering Technology (IET) and of the Oxford Trust. She received an OBE for services to science and engineering in the Queen's Birthday Honours list in June 2013.

Dr Kath Mackay



Kath Mackay is Deputy Director of Ageing Society, Health & Nutrition at Innovate UK, the UK's innovation agency and prime channel by which the UK Government incentivizes innovation in business. Kath leads a team delivering programmes across high value areas for UK health and biomedical businesses. These include advanced therapies, precision medicine, medicines discovery, digital health, disease prevention & wellbeing, antimicrobial resistance and vaccines, biosciences, the Biomedical Catalyst and Small Business Research Initiative. Kath joined Innovate UK in 2013 to co-manage the Regenerative Medicine & Advanced Therapies Programme. Prior to joining Innovate UK, she held various commercial biotech roles and has over 15 years' experience in business development, commercial operations, and life sciences research, spanning multiple disease areas and technologies across USA and EU markets. Kath has a PhD in Pharmacology where she researched using stem cell models for novel drug discovery applications.

Keynote Speakers & Workshops

Professor Alison McGregor



Alison McGregor is a Professor of Musculoskeletal Biodynamics at Imperial College London. Her research focuses on the musculoskeletal system with respect to mechanisms of injury; effects of injury on function and management. She has investigated injury/disease management using a variety of clinical and biomechanical approaches. Alison was a lead investigator in the Medical Engineering Solutions in Osteoarthritis Centre where she led an initiative into the use of technology to further rehabilitation.

She currently leads the Rehabilitation Theme of Imperial's Centre for Blast Injury Studies and currently supervises work on smart amputee sockets, understanding long term health issues and rehabilitation requirements, and the prevention of osteoporosis in above knee amputees.

Dr Katerina Spranger



Katerina Spranger is the founder of Oxford Heartbeat (www.oxfordheartbeat.com<<http://www.oxfordheartbeat.com/>>) - a start-up company that develops medical device software to make planning for surgeries simpler, faster and more accurate.

Katerina is an Enterprise Fellow at the Royal Academy of Engineering and holds DPhil in Engineering Science from the University of Oxford. She was named "Young Innovator of the Year 2013" at the Falling Walls Berlin - International Conference on Future Breakthrough in Science and Society. Her company successfully attracted funding from the Innovate UK, NIHR, SBRI, EIT Health, etc., and received numerous awards for their innovative technology, including the NHS Innovation Award 2017 from HEE and WIRED "Best Healthcare Startup of 2018".

Professor Ipsita Roy



Ipsita Roy is an expert in Microbial Biotechnology, Biomaterials and Tissue Engineering. She is currently a Professor at the School of Life Sciences, University of Westminster, London. She was awarded the Inlaks Scholarship for her Ph.D. at the University of Cambridge. Her postdoctoral work was at the University of Minnesota, USA. She leads the Applied Biotechnology Research Group at UoW. She has published over 100 papers in high 'Impact Factor' journals. Her group is currently focussed on the production and characterisation of novel polyhydroxyalkanoates, a group of FDA-approved polymers.

She is an editor of JCTB and is on the BBSRC, EPSRC, NSERC, Canada, ERC, NSFC, China panel. Her work has been funded by the EPSRC, EU and DuPont. Ipsita was Scientific Coordinator of REBIOSTENT and HYMEDPOLY and has led the material work in NEURIMP, and POLBIOSKIN. She is also leading an EPSRC project,

within CYCLOPS, that combines AI with Materials. All projects involve the use of PHAs for medical applications, cardiac patches, drug eluting biodegradable stents, nerve guidance conduits, antibacterial polymers and wound healing.

Dr Susannah Clarke



Susannah Clarke is CEO and co-founder of Embody, an orthopaedic spin out company from Imperial College. She has been awarded an MBE and a Silver Medal from the Royal Academy of Engineers in recognition of her work. Embody's flagship product, the H1 implant, is currently undergoing clinical trials.

Keynote Speakers & Workshops

Haemodynamics Workshop: "Reduced-order modelling and pulse wave analysis"

7th September 2018, 09:00 -10:30 (Read Lecture Theatre)

First Keynote Speaker: Professor Kim Parker

Title: "Wave Speed on the Arteries"

Dr. Parker is Professor of Physiological Fluid Mechanics (Emeritus) in the Department of Bioengineering, Imperial College, London. He obtained his PhD in the Aeronautics and Mechanical Engineering Department at Princeton University and spent his early years as a 'rocket scientist', first as a Post-Doc in the Department of Mechanical Engineering at Imperial College and then as an Assistant Professor in the Department of Mechanics at The Johns Hopkins University in Baltimore, Md. He moved back to London in 1970 to join the Physiological Flow Studies Unit at Imperial College. He has remained at Imperial College while the PFSU metamorphosed into the Department of Bioengineering.

His principle interest is in arterial hemodynamics and cardiovascular mechanics. He devised and developed wave intensity analysis of arteries drawing on his background in compressible gas dynamics. He has collaborated widely with cardiologists and vascular surgeons to explore the application of his work to the clinical measurements and diagnosis. Two recent areas of interest are the use of reservoir and excess pressure to characterise arterial dynamics and the development of the instantaneous wave-free ratio (iFR) for the clinical assessment of the functional importance of coronary stenoses. Since retiring in 2006 he has continued his research and has found relief from administrative and teaching duties to be very productive. He has found retirement to be an excellent career move and recommends it to his younger colleagues.

Other Talks in this Workshop

Prof A. Hughes, University College London - 'Arterial waves in the pulmonary circulation'

Dr G. Biglino, University of Bristol - 'Wave intensity analysis from MRI data: linking wave dynamics with vessel morphology?'

Dr P. Charlton, King's College London - 'A Database for the Development of Pulse Wave Analysis Algorithms'

Dr M. Negoita, University of Brunel - 'Non-invasive Measurement of Local Wave Speed in Human Ascending Aorta'

Second Keynote Speaker: Professor Perumal Nithiarasu

Title: "Active and Passive Human Digital Twins Based on Reduced Cardiovascular Flow Models"



Professor P Nithiarasu earned his BE from Madurai Kamaraj University in 1989, MTech from Kerala University in 1992, PhD from IIT Madras in 1997 and DSc from Swansea University in 2007. He moved to Swansea in 1996 to work with Professor O.C. Zienkiewicz in the area of finite element method. He became a lecturer in 2000, Senior Lecturer in 2004, Reader in 2006 and a full Professor in 2008. Currently, he is the Dean for Research Impact at Swansea University; Research Director and Deputy Head of Engineering; and Head of Zienkiewicz Centre for Computational Engineering. His research interests are mainly in the areas of computational healthcare engineering and fluid dynamics.

Professor Nithiarasu received Zienkiewicz Silver Medal of ICE, London in 2002; ECCOMAS Young Investigator award in 2004 and EPSRC Advanced Research Fellowship in 2006. He was appointed as a distinguished foreign scientist twice by

CSIR labs in India. Professor Nithiarasu held Adjunct Professorship at Moscow Institute of Physics and currently holds a visiting professor position at the University of Naples 'Parthenope', Italy and VAJRA Adjunct Professorship at IIT Madras, India.

Professor Nithiarasu is the founding editor of the International Journal for Numerical Methods in Biomedical Engineering and founded now one of the important conferences in biomedical engineering, Computational and Mathematical Biomedical Engineering. He is on the editorial boards of several computational engineering journals and conferences.

Professor Nithiarasu has published nearly 200 peer reviewed articles in journals, books and conferences. He is a co-author of two books in the area of finite element method and fluid dynamics. Professor Nithiarasu is a fellow of IMechE, IPEN and IMA and he has been recently elected to the fellowship of the Learned Society of Wales.

Keynote Speakers & Workshops

BioMedEng18 Careers Workshop

7th September 2018, 09:00-10:30 (RSM 3.01 C, D & E)

The BioMedEng18 careers workshop will be a great opportunity for highly skilled Postdoctoral researchers, PhD, MRes and MSc students, and Undergraduates attending the conference to meet, network and possibly be recruited by a variety of companies. Representatives of companies interested in students and graduates with a biomedical engineering, medical engineering and bioengineering background will discuss the various roles and internships opportunities available at their firm, their recruitment process and expectations, and other useful information.

Gifty Tetteh, Conference Director



"There is no other company like IBM and there is no business professional like the IBMer. We are experts in nearly every technical scientific and business field. We are citizens of, and apply our expertise in, more than 170 countries. Yet we are united by a single purpose: to be essential. We do that by creating the most advanced technology to change how our clients work and run their businesses. And through them, IBMers change how the world works. The world is at a major turning point: technology is enabling entirely new forms of businesses, industries and outcomes.



Arthritis Research UK is committed to building a world-class workforce to continue the fight against arthritis through supporting research careers and ensuring there's sufficient capacity within the UK to translate ideas into benefit for people with arthritis. Our success depends on the quality of the scientists and clinicians involved. We aim to encourage the brightest and most committed researchers, from all relevant disciplines based in the UK and beyond, to become involved in research into musculoskeletal diseases. We support musculoskeletal research careers through dedicated fellowship support for outstanding researchers at different stages of their career, as well as extensive funding of researchers through our other funding schemes such as challenge calls and Centres of Excellence.



CBAS is creating the open standard hardware and software interface between the human nervous system and bionics. Our technology sits between nerves and the healthcare devices of the future. We are solving the complex problems of successfully integrating and communicating with the human body using a combination of applied materials, machine learning and AI, neuroscience, software design, and advanced surgical techniques. Our mission is to create the open standard platform to support high functionality neural & bionic treatments, making it easy for clinicians, engineers

and researchers to develop and deliver superior treatments to patients.



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Keynote Speakers & Workshops

IMPRESS Workshop: "Engineering for Continence Care – Innovation for the Stigmatised"
6th September 2018, 13:00-14:15 (Read Lecture Theatre)

Keynote Speaker: Professor Jenny Southgate

Title: "Tissue Engineering for Better Bladders"



Professor Jenny Southgate began her career at the Imperial Cancer Research Fund (ICRF) in London. She relocated to Leeds in 1989 and led the Biology of Normal and Malignant Epithelial Cells group based at the ICRF Cancer Medicine Research Unit at St James's University Hospital from 1992.

She moved to the University of York in 1999 after she was appointed as the Chair of Molecular Carcinogenesis and Director of the Jack Birch Unit, a research unit supported in part by York Against Cancer. Her research interests encompass the cell/molecular biology of human urothelium in health and disease, and bioengineering approaches for bladder and urinary tract reconstruction with cells and biomaterials.

She is the Director of the John Birch Unit of Molecular Carcinogenesis at the University of York.

Other Talks in this Workshop

Dr John Young, University of Portsmouth, - 'Developing a non-invasive biosensor to fingerprint Overactive Bladder'

Dr Nicola Irwin, Queen's University Belfast, - 'Anti-Blocking Catheter Coatings; from lab to commercial reality'

Dr Bhavik Patel, University of Brighton, - 'Faecal sensor to understand physiological signalling and muscle dynamics with incontinence'

Dr Thelma Lovick, University of Bristol, - 'Pelvic Nerve Stimulation for urinary urge incontinence (UUI)'

BioMedEng18 - Biomedical Engineering Education

6th September 2018, 13:45-15:00 (Huxley 308)

Many of us will remember when the number of UK undergraduate courses in Bioengineering, Biomedical Engineering and cognate subjects could be counted on the fingers of one hand – perhaps with some fingers to spare. Today, over thirty such courses are on offer. This phenomenal expansion mirrors the growth of research in the discipline within UK universities but is also testament to the passion that the new generation of school-leavers has for using engineering to improve quality of life for the injured, the infirm, the aged and the ill.

Students that we welcome onto our courses will go on to develop new technological solutions through university research, through work in industry or through entry into the healthcare system itself. It is incumbent on us to match and develop their passion with high quality teaching, and a workshop at the symposium – the Workshop on Biomedical Engineering Education – aims to examine how best to do that. Chaired by Julia Shelton and Martyn Boutelle, it will include: presentations and a panel discussion on entrepreneurship education, descriptions and appraisals of two innovative and unusual modules, and research on the education process itself, which we hope will be a harbinger of things to come. The session will conclude with a general discussion. I warmly welcome you to the workshop, and to view the associated posters; I hope it will be repeated and enlarged in subsequent years.

Peter Weinberg, Conference Chair

Workshop Programme

Prof Jimmy Moore – Entrepreneurship in Bioengineering - The BioDesign approach

Panel Discussion with Danny Green, Entrepreneur-in-residence & Ben Lakey, MRes student

Prof Adam Gibson – Comparison of Students' Performance in Examinations compared to Group Coursework (*Abstract on Page - 145*)

Dr Ian Radcliffe - Group Design Projects / Sports Innovation Challenge

Dr Tina Chowdhury - Use of the Virtual Lab - Improving Outcomes in Tissue Engineering

General Panel Discussion - Biomedical Engineering Teaching - Future Directions

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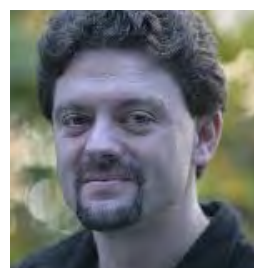
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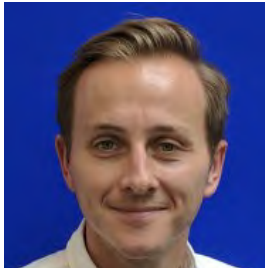


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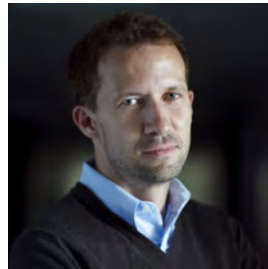
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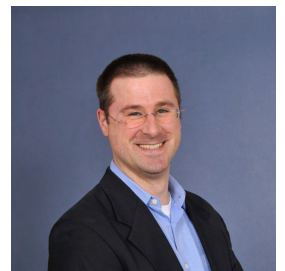
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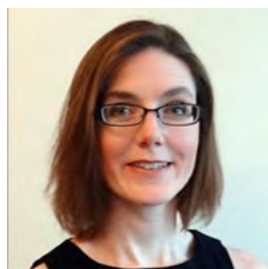
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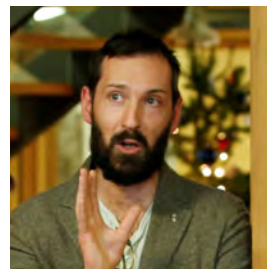
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The BioMedEng18 organising team is grateful to all members of the
Scientific and Programme Committees

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Oral abstracts have been grouped into sessions and follow the presentation order of the detailed conference schedule

The efficiency of a clinical motion capture system for quantifying knee function

G.F. Tawy^{1,2}, L.C. Biant¹, P.J. Rowe²

¹Stopford Building, University of Manchester, Manchester M13 9PG ²Graham Hills Building, University of Strathclyde, Glasgow G4 0NW.

Introduction

The orthopaedic environment lacks a standardised functional outcome measurement protocol for treatments of knee osteoarthritis (OA). As such, clinicians cannot easily identify the patients with poorest knee function, who could benefit from rehabilitation and/or further treatment. The current gold standard method of reporting knee function is 3D motion analysis. This technology is rarely used in clinical environments, as the equipment require large amounts of space. Furthermore, the protocols used to record, analyse and interpret the data are complicated and time consuming¹. This study aimed to develop and use a simplified motion capture system in an orthopaedic environment to report the functional outcome of total knee arthroplasty.

Methods

A small-scale motion capture system was designed for use in a clinical environment. A bespoke cluster-based biomechanical model was developed in D-Flow (Motekforce Link, Amsterdam) to report knee function. To test the efficiency of the system, patients with end-stage knee OA were assessed pre-TKA, then six-weeks and one-year post-TKA. The protocol at each visit involved donning the clusters before anatomical landmarks were calibrated with an instrumented pointer. The patients then carried out tasks to assess bilateral knee ranges of motion and isometric strengths. These were followed by a 2-minute self-paced walking task. The duration of the entire protocol (from donning to doffing clusters) was recorded. The data were analysed statistically ($\alpha = 0.05$).

Results & Discussion

The motion capture system measured 3.5(L) x 2.1(H) x 1.1(W)m. The small scale of the system allowed it to be used successfully within a multifunctional hospital environment. Implementation of the cluster model allowed for automatic labelling, thus eliminating time-consuming labelling and data processing processes. Results could therefore be obtained in real time. On average, the entire protocol took 17.4($\pm$ 2.4) minutes pre-operatively ($n = 63$), 15.7($\pm$ 2.4) minutes six-weeks post-operatively ($n = 57$) and 15.2($\pm$ 2.4) minutes one year post-operatively ($n = 30$). The improvement in efficiency was significant between pre- and post-operative assessments ($p = 0.004$). The longest assessment took 25 minutes.

Conclusion

This system has the potential to be used routinely in a clinical environment. If successful, motion capture technology could be used in future practices to better report functional outcome in orthopaedics.

References

1. Meldrum D et al. Gait & Posture. 2014; 39(1): 265-271.

Acknowledgments

This study was supported by Medacta International as part of a PhD studentship.

Multi-scale *in-situ* cartilage mechanics using small angle x-ray diffraction

S.R. Inamdar¹, N.J. Terrill², M.M. Knight¹, H.S. Gupta¹

¹ Institute of Bioengineering, School of Engineering and Material Sciences, Queen Mary University of London, Mile End, E1 4NS, London.

² Harwell Science and Innovation Campus, Diamond Light Source, Harwell, Didcot OX11 0DE, United Kingdom.

Introduction

Articular cartilage, a soft tissue that lines diarthrodial joints, has a unique depth-dependent structure that enables the tissue to respond to mechanical loading¹. In order to respond accordingly to the repetitively loading, the tissue possesses a complex fibrillar and proteoglycan composition and the interactions between these macromolecules directly impact the tissues functionality². Direct measurement and experimental evidence of these interactions through the spatially graded structure is currently limited³. More specifically, there is little understanding into how the fibrillar network responds dynamically to tissue level loading and how changes in the extracellular matrix as a result of tissue degradation leads to nanoscale level mechanics.

Methods

High brilliance synchrotron microfocus small-angle X-ray diffraction was used to measure the depth-wise structure of the fibrillar architecture whilst performing time-resolved measurements during compressive stress-relaxation of bovine and human cartilage explants. Enzymatic digestion was applied to bovine cartilage explants using Chondroitinase ABC to remove part of the proteoglycan matrix, these were incubated in 0.1U/ml for 24 hours at 37°C prior to being snap frozen. A micro-compression tester was then used in the beamline at I22 Diamond Light Source to perform the *in-situ* measurements.

Results & Discussion

The results show the existence of a depth-dependent fibrillar pre-strain as determined by the axial D-periodicity of the fibrils, estimated at approximately 1-2%, due to osmotic swelling pressure from the proteoglycans. Partial removal of the proteoglycan phase causes a significant reduction in the collagen fibril pre-strain. Under loading, we reveal a rapid reduction and recovery of the reported pre-strain during stress relaxation, which is disrupted in the degraded case. In order to explain these findings, we developed an ultrastructural X-ray scattering model where the key mechanisms driving the reduction and recovery are axial molecular rearrangement and intra-fibrillar disordering. We suggest that the fibrils respond to loading via intra- and inter-fibrillar disordering alongside a transient response that is mediated by changes in hydration.⁴

Conclusion

These are the first studies to highlight previously unknown depth-dependent fibrillar architectural differences alongside transient responses to loading, and are likely to transform our understanding of the role of collagen fibril nano-mechanics in cartilage and other hydrated soft tissues.

References

1. Lu, X. L. & Mow, V. C. *Med. Sci. Sports Exerc.* **40**, 193–9 (2008).
2. Wilson, W., Huyghe, J. M. & Van Donkelaar, C. C. *Biomech. Model. Mechanobiol.* **6**, 43–53 (2006).
3. Moger, C. J. *et al. J. Biomech. Eng.* **131**, 1–9 (2009).
4. Inamdar, S. R. *et al. ACS Nano* **11**, 9728–9737 (2017).

Acknowledgments

We are grateful to the Institute of Bioengineering (QMUL) PhD studentship funding (funded through the EPSRC) and the BBSRC for providing grant funding to continue research in this field (BB/R003610/1). We thank Diamond Light Source (Harwell, UK) for synchrotron beamtime and the team at I22 for their continued support.

Robotic Assisted Unicompartmental Knee Arthroplasty Leads to Improvements in Knee Flexion at Five-Year follow-up in Comparison to Conventional Methods

L.J. Millar¹, M. Banger¹, P.J. Rowe¹, M. Blyth², B. Jones², A. Maclean²

¹ Graham Hills Building, University of Strathclyde, G1 1QE, Glasgow. ²Glasgow Royal Infirmary, G4 0SF

Introduction

The prevalence of unicompartmental knee arthroplasty (UKA) in the UK and US is high [1]; demonstrating good mid-long terms results [2]. Current minimally invasive methods can cause poor alignment; reducing longevity and function [2]. The MAKO RIO robotic surgery system has previously shown improved alignment in comparison to the conventional Oxford method [3]. Therefore, the aim of this study was to determine if the MAKO system also resulted in improved function five-years post-operatively.

Methods

Forty-six patients attended a five-year follow up (25 MAKO/21 Oxford knees). Three-dimensional gait analysis was carried out using a 10 camera Vicon Bonita optical tracking system. Participants performed a number of 10 m walks at a self-selected pace. The primary outcome measure was total excursion of the knee in the sagittal plane during weight acceptance (WA).

Results & Discussion

Figure 1 shows mean knee flexion ($\pm 2SD$) for MAKO and Oxford patients. There was a significant difference in excursion during WA (MAKO: $14.3 \pm 6.4^\circ$, Oxford: $9.9 \pm 4.2^\circ$; $\alpha = 0.05$, $P=0.008$).

These data suggest that the improved alignment offered by the MAKO system may result in improved function of the knee during gait and that use of the MAKO system results in a gait pattern which facilitates the normal function of the knee more closely than the Oxford implant. As this was a short-term follow-up study, outcomes should be investigated longer term (at 10–15 years) to determine the longevity of improved knee flexion in the MAKO group.

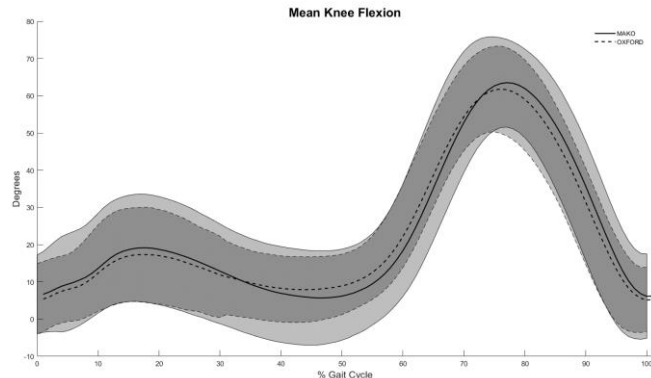


Figure 1. Mean($\pm 2SD$) knee flexion for MAKO (solid) and Oxford (dashed) patients.

References

- [1] The national Joint Registry, National Joint Registry for England, Wales, Northern Ireland and the Isle of Man. Surgical Data to 31 December 2014, 2015.
- [2] H. Xue, *et al.*, Up to twelve year follow-up of the Oxford phase three unicompartmental knee replacement in China: seven hundred and eight knees from an independent centre, *International Orthopaedics (SICOT)*. 41 (2017) 1571–1577. doi:10.1007/s00264-017-3492-4.
- [3] S.W. Bell, *et al.*, Improved accuracy of component positioning with robotic assisted unicompartmental knee arthroplasty: data from a prospective, randomised controlled study, *Journal of Bone and Joint Surgery - British*. 98 (2016) 627–635.

Hip Joint Mechanics Before and After Cam FAI

K. C. Geoffrey Ng¹, Hadi El Daou¹, Marcus J. K. Bankes², Ferdinando Rodriguez y Baena¹, Jonathan R. T. Jeffers¹

¹Department of Mechanical Engineering, Imperial College London, London, SW7 2AZ. ²Department of Orthopaedics, Guy's and St. Thomas' NHS Foundation Trust, London, SE1 9RS.

Introduction

Cam-type femoroacetabular impingement (FAI) is characterized by an enlarged, aspherical femoral head-neck morphology and is associated with early hip joint degeneration [1], limited joint mobility [2], and adverse loading [3]. While surgical management of cam FAI aims to preserve the native hip and restore joint function, it is unclear how the capsulotomy, cam deformity, and capsular repair influence functional mobility. The purpose was to examine the contributions of the capsule and cam deformity to FAI.

Methods

Twelve cadaveric cam hips (n = 12) were skeletonized to the capsule and mounted onto a robotic testing platform. The robot positioned each hip in multiple positions: 1) Extension, 2) Neutral 0°, 3) Flexion 30°, 4) Flexion 90°, 5) FADIR, 6) FABER; and performed internal and external rotations, recording the neutral path of motion until a 5-Nm torque was reached in each direction. Each hip then underwent a series of surgical stages (T-capsulotomy, cam resection, capsular repair) and was retested to reach 5 Nm torque after each stage. In addition, during the capsulotomy and cam resection stages, the initial intact hip's recorded path of motion was replayed to measure changes in resisted torque.

Results

Examining changes in motion, external rotation increased substantially after capsulotomies, but internal rotation only increased at Flexion 90° (change = +32%, p = 0.001) and FADIR (change = +33%, p < 0.001) after cam resections. Capsular repair provided marginal internal rotation restraint, but restrained the external rotation compared to the capsulotomy stage. Examining changes in torque, both internal and external torques decreased after capsulotomy. Cam resection further reduced internal torques during Flexion 90° (change = -45%, p < 0.001) and FADIR (change = -37%, p = 0.003), where the cam deformity accounted for 21% in Flexion 90° and 27% in FADIR of the intact hip's torsional resistance.

Discussion

Although the capsule played a predominant role in joint constraint, the cam deformity provided 25% of the intact hip's resistance to torsional load in flexion and internal rotation. This further contributes to the understanding of the cam morphology and the role of surgical management in joint preservation strategies. These findings are the first to quantify the contribution of the cam deformity to resisting hip joint torsional loads and thus quantify the reduced loading on the chondrolabral complex that can be achieved after cam resection.

References

1. Ganz R, et al. *Clin Orthop Relat Res*. 2003; 417: 112-120.
2. Ng KCG, et al. *Am J Sports Med*. 2018; Accepted: 1-12.
3. Ng KCG, et al. *PLoS One*. 2016; 11: e0147813.

Acknowledgments

We wish to acknowledge the funding contributions from the EPSRC (EP/N006267/1).

Tracking collagen fibre reorganisation under load in articular cartilage using polarization sensitive SHG microscopy

J.C.Mansfield¹, V.Mandalia², A.Toms², **C.P.Winlove¹**, S.Brasselet³

¹ Physics Building, College of Engineering, Mathematics and Physical sciences, University of Exeter, EX4 4QL.

²Princess Elizabeth Orthopaedic Centre, Royal Devon and Exeter Hospital, EX2 5DW, ³Institut Fresnel, 13397 Marseille, France.

Introduction

The mechanical properties of articular cartilage are determined by its proteoglycan content and collagen fibre network. The type II collagen fibres are beneath the diffraction limit for light microscopy and therefore alternative techniques are needed to measure their organisation. We use polarization sensitive second harmonic generation (SHG), exploiting the sensitivity of the SHG signal to the laser excitation polarization angle with respect to the collagen fibre axis. This allows us to determine changes in orientation and degree of fibril alignment with submicron resolution as cartilage samples were exposed to both tensile and compressive loading.

Methods

SHG was excited using the 810nm output from a 100fs Ti:Sapphire laser (MIRA coherent), and imaged using a modified confocal microscope (Olympus, Flouview 300). A series of 10 SHG images were collected while the incident laser polarization was rotated in 18° steps. These images were analysed using a MatLab script to fit the intensity as a function polarization angle (α) at a pixel level to the equations:

$$I(\alpha) = a_0 + a_2 \cos 2\alpha + b_2 \sin 2\alpha + a_4 \cos 4\alpha + b_4 \sin 4\alpha$$

$$I_2 = \frac{\sqrt{a_2^2 + b_2^2}}{a_0} \quad \varphi_2 = 0.5 \tan^{-1} \left(\frac{b_2}{a_2} \right)$$

Where I_2 gives a measure of the molecular order within the pixel ($I_2 = 0$ indicating no molecular order) and φ_2 gives the preferred collagen fibre direction. Overlays of I_2 and φ_2 were used to visualise the collagen fibre arrangement in the images. Cartilage samples were collected from bovine metacarpophalangeal joints and from patients undergoing total knee replacement surgery. Cartilage strips were mounted on a custom built tensile loading rig and polarization sensitive SHG measurements were taken at a series of increasing loads.

Results & Conclusions

Polarization sensitive SHG measurements showed clear differences in collagen fibre organisation in deep and superficial zone cartilage, and between young bovine and osteoarthritic human samples. Additionally it allowed us to visualise the organisation of collagen fibres surrounding the chondrocytes. Under tensile strain changes in φ_2 demonstrated that fibres aligned to the direction of applied strain. In the superficial zone there was also an increase in I_2 at higher strains which was greater in the stiffer samples and indicated an increase of submicron order. In revealing sub-micron scale changes in collagen fibre organisation under mechanical loads polarisation sensitive SHG provides a new tool for investigating the micromechanics of collagen-rich tissues.

Acknowledgments

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BioMedEng18

Pre-Clinical Investigation of an Extra-Capsular Knee Joint Unloading Implant

O.J. Morgan¹, H.J. Hillstrom², A. Ranawat³, S.R. Rozbruch⁴, A.T. Fragomen⁴, R. Hillstrom^{1,2}

¹Medical Engineering Research Group, Anglia Ruskin University, Chelmsford, Essex, UK

²Leon Root Motion Analysis Laboratory, Hospital for Special Surgery, New York, New York, USA

³Sports Medicine and Hip Preservation Centre, Hospital for Special Surgery, New York, New York, USA

⁴Institute for Limb Lengthening and Reconstruction, Hospital for Special Surgery, New York, New York, USA

Introduction

The Atlas™ unicompartmental knee system (Moximed inc. Hayward, CA, USA) is a novel implant for patients with mild to moderate medial knee osteoarthritis (OA). The device is placed subcutaneously upon the medial aspect of the knee joint without violating the natural joint capsule (i.e. extra-capsular). A polycarbonate urethane (PCU) absorber provides an opposing force to reduce a portion of the compressive load in the medial knee. Using a representative “healthy” tibiofemoral-specific finite element (FE) model [1], we have previously shown the Atlas™ may reduce stress in the medial compartment [2]. The purpose of this study was to predict tibiofemoral joint stress pre- and post- Atlas™ using a model simulating (1) no cartilage defect (NCD) and, (2) a grade-III medial tibial cartilage defect (MTCD).

Methods

A computer aided design (CAD) model of the Atlas™ was virtually implanted on the medial aspect of a validated three-dimensional (3D) FE model of a left cadaveric knee. The model was assembled in CATIA V5 (Dassault Systèmes, France), and meshed in Abaqus 6.14-1 (Dassault Systèmes, France). A grade-III MTCD (surface area: 4.69mm²; normalised depth: 66.6%) was generated based on the International Cartilage Repair Society (ICRS) grading system. Forces and moments from gait analysis of an anthropometrically-matched male were used to drive the models at each sagittal knee angle. Multiple quasi-static simulations were used to analyse a range of time-points during stance.

Results & Discussion

The post-Atlas™ MTCD model exhibited reduced peak stress in the medial compartment throughout stance equivalent to the pre-Atlas™ NCD model (Figure 1a). This finding suggests the Atlas™ may restore medial tibiofemoral joint stress to pre-degenerative magnitudes. Limitations of the model include: (1) material properties were not specimen-specific and, (2) loading during gait was acquired from inverse dynamics which did not include muscular forces.

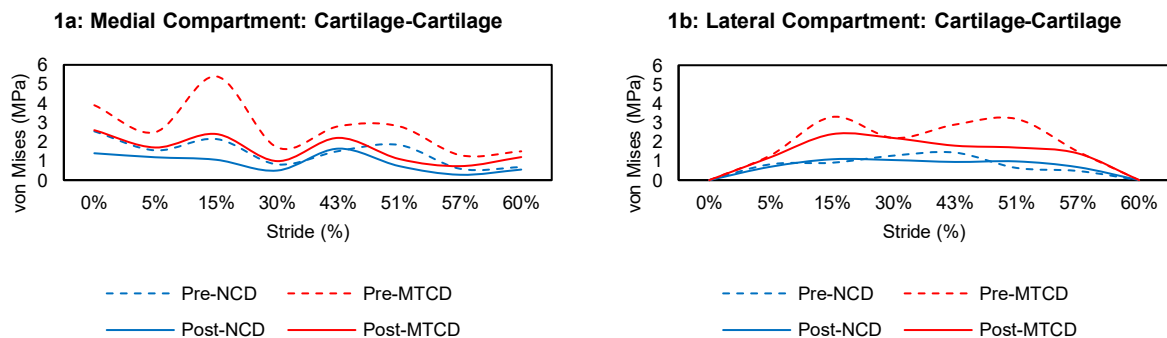


Figure 1a&b. Comparison of pre-Atlas™ (dashed line) and post-Atlas™ (solid line) stress in the (a) medial and (b) lateral tibiofemoral compartments for the NCD model (blue) and MTCD model (red).

Conclusion

The decrement of medial compartment peak stress predicted in this study supports the Atlas™ efficacy for ‘internally’ unloading the medial tibiofemoral joint. Medial compartment unloading was not shown to correlate with a lateral transfer of the net load, suggesting that the Atlas™ works by sharing as opposed to transferring load.

References

1. Mootanah, R., et al. *Comp Method Biomech Biomed Eng.* 2014; 50: 102-109.
2. Morgan, O., et al. *64th Annual ORS Meeting, 2018.* New Orleans, Louisiana, USA.

Acknowledgments

Moximed Inc.

Multizone scaffolds as cell free platforms for cartilage tissue engineering

N.Munir¹, A. Callanan¹

¹Institute for Bioengineering, School of Engineering, University of Edinburgh, EH9 3JL

Introduction

Osteoarthritis is predicted to become the fourth leading cause of disability by 2020¹. Microfracture is considered the gold standard treatment for osteoarthritis. This technique usually results in the formation of fibrocartilage tissue that is biomechanically and biochemically inferior to native hyaline cartilage. This is due to the lack of structural support and guidance of cellular migration, which leads to the dedifferentiation of mesenchymal stem cells (MSC)²⁻³. This preliminary *in vitro* study proposes a multizone scaffold as a platform to support growth and differentiation of MSC.

Methods

Multizone scaffolds consist of three different zones. The bottom helix scaffold was fabricated using cryo-printing, which involves printing of a 8% wt/vol Polycaprolactone (PCL)/1, 4 Dioxane solution directly onto a cold plate set at -40°C. The middle and top electrospun layers are composed of randomly orientated and aligned electrospun fibres, respectively (8% wt/vol PCL and HFIP). Multizone scaffolds were seeded with isolated primary rat MSC for 24 hours, 2 weeks and 4 weeks. Electrospun (ESP) and directionally frozen (D/F) scaffolds were used as controls. Scaffold morphology was assessed using scanning electron microscope (SEM). Mechanical, biochemical quantification and gene expression were performed at all time points.

Results and Discussion

Multizone scaffolds successfully captured the zonal architecture of the native cartilage (Fig 1A). Moreover, these scaffolds supported cell attachment and viability (Fig 1) and expressed improved mechanical properties compared to the directionally frozen control. Trends in the expression of key genes and DNA quantification were also examined.

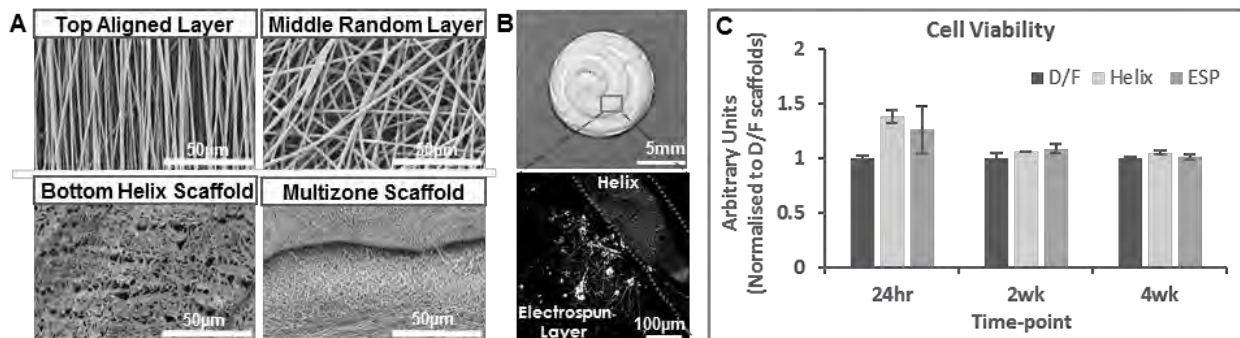


Fig. 1: (A) SEM images of multizone scaffolds layers. (B) Image of multizone scaffold and MSC attached to scaffold. (C) Cell viability of MSC seeded scaffolds, values normalised to D/F controls. Error bars=SE, n= >3.

Conclusion

Multizone scaffolds supported long-term MSC attachment with key gene expression and the production of essential chondrogenic biomolecules, glycosaminoglycans, highlighting their potential as a cell free approach for cartilage tissue engineering.

References

1. Li et al. J Tissue Eng Regen Med. 2009; 3: 1-10.
2. Peck et al. Sci Rep. 2015; 5: 1-14.
3. Makris et al. Nat Rev Rheumatol. 2015; 11: 21-34.

Acknowledgments

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The development and hydrodynamic assessment of a trileaflet polyurethane heart valve prosthesis

C. Gambrah¹, T. Gourlay¹

¹ Graham Hills Building, University of Strathclyde, Glasgow.G11QE

Introduction: Mechanical heart valves, although very durable, tend to exhibit limited bio and haemocompatibility. Bioprosthetic valves, on the other hand, possess good haemodynamic function but limited durability. Polymeric heart valves have the potential of combining the benefits of mechanical and bioprosthetic valves, while eliminating their deficiencies. This study aims at the hydrodynamic testing of polyurethane heart valves under pulsatile flow conditions.

Methods: 22mm internal diameter valves were developed via dip coating in a polyurethane solution and left to dry, a process which forms the valve leaflets. A custom pulse duplicator, capable of producing physiological aortic valve pressure waveforms, was designed and manufactured. Pressure tracings were validated using a HANCOCK II bioprosthetic valve. Valves were tested under 4 different flow rates, between 2 to 7L/min according to ISO 5840 pulsatile flow testing conditions. Valve performance was assessed based on Effective Orifice Area, (EOA) and the Transvalvular Pressure Gradient (TPG).

Results & Discussion: Both polymeric valves and HANCOCK II bioprosthetic valve exhibited good physiological aortic pressure waveforms in accordance to ISO 5840 standards, thus showing the adequate performance of the custom designed pulse duplicator. Polymeric valve exhibited a higher transvalvular pressure gradient, as compared to that of the bioprosthetic valve. Bioprosthetic valve exhibited a higher effective orifice area than the polymeric valves however they both meet the required standards of a replacement heart valve.

Conclusion: Results from hydrodynamic testing show the promising nature of polymeric heart valves. Further tests are however necessary in order to fully assess their potential as an ideal alternative to mechanical and bioprosthetic heart valves.

References:

1. Bezuidenhout D, Williams DF, Zilla, P. *Biomaterials*. 2015; 36: 6–25.
2. De Gaetano, F. et al. *Journal of Mechanics in Medicine and Biology*. 2015; 15: 1540009.
3. Mankad S. *Current Treatment Options in Cardiovascular Medicine*. 2012; 14: 608–21.
4. Taylor CE, Miller GE. *Journal of medical devices*. 2012; 6: 450031–450038.
5. Lanzarone E, Vismara R, Fiore GB. *Artificial Organs*. 2009; 33: 1048–1062.
6. Bonow RO. et al. *Journal of the American College of Cardiology*. 2006; 48: 1-48.
7. De Paulis R. et al. *Journal of Thoracic and Cardiovascular Surgery*. 2005; 130: 1016–1021.
8. Vesey JM, Otto CM. *Curr.Cardiol.Rep*. 2004; 6:106-111.
9. Mackay TG. et al. *Biomaterials* 1996; 17: 1857–1863.
10. Westerhof N, Elzinga G, Sipkema P. *Journal of applied physiology* 1971; 31:776–81.

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Towards a Novel Device for Treatment of Unicoronal Craniosynostosis

S.Bozkurt^{1,2}, A. Borghi^{1,2}, O. Jeelani^{1,2}, G. Burriesci^{3,4}, D. Dunaway^{1,2}, S. Schievano^{1,2}

¹UCL Great Ormond Street Institute of Child Health; ²Great Ormond Street Hospital for Children, ³UCL Mechanical Engineering, Cardiovascular Engineering Laboratory, University College London, UK; ⁴Ri.MED Foundation, Bioengineering Group, Palermo, Italy.

Introduction

Unicoronal craniosynostosis (UC) is the second most common type of nonsyndromic craniosynostosis [1], characterised by ipsilateral forehead and fronto-parietal region flattening with contralateral compensatory bossing. UC is surgically corrected between six and twelve months of age, with the aim of expanding and reshaping the skull [2]. However, surgical outcomes often remain suboptimal, with aesthetic concerns such as flattening of the brow and forehead on the affected side, and noticeable deviation of the nose towards the affected side which may continue to the chin [2]. So, treatment of UC remains a challenge. The aim of this study is to use a parametric finite element (FE) model to determine the optimal osteotomy locations, dimensions, and force requirements applied on UC skulls to develop a new device correcting UC deformities.

Methods

The bony skull and suture geometries from eleven UC patients (mean age: 190days $\pm$ 87days) were reconstructed from computed tomography scans in Simpleware ScanIP. Osteotomies were designed to expand the affected side of the skull using an implantable distractor. The osteotomy on the lateral region was aligned to coronal suture and shifted backwards with 10mm intervals, the osteotomy on the anterior side was aligned to nasion and again shifted upwards and also extended with 10mm intervals in each iteration resulting in 48 different osteotomies on the skull. The bone and sutures were modelled using elastic properties to perform the FE analyses in MSc Marc software using a tetrahedral element mesh and implicit solver. Different force magnitudes and locations were tested to assess bone displacement with different osteotomies.

Results & Discussion

A patient skull reconstruction, two designed osteotomies and the displacement map resulting from 10N point force applied at different points are shown as example in Fig.1. The osteotomy aligned with the coronal suture on the UC side and force applied to the frontal bone provided a better overall correction of the deformity, with larger increase in skull volume and a more symmetrical final shape.

Conclusion

FE models of patient skulls with UC can provide information to support the design of new devices to implant in the skull during the surgery. Parametric simulations allow testing of the effect of different osteotomies, forces and their locations in order to optimise the material and geometry of potential distractors.

References

1. Garza RM, Khosla RK. *Semin Plast Surg*, 2012, 26:53–63.
2. Persing JA. *Plast Reconstr Surg*, 2008, 121:1-11.

Acknowledgments

ESPRC Grant EP/N02124X/1, GOSH Craniofacial Unit.

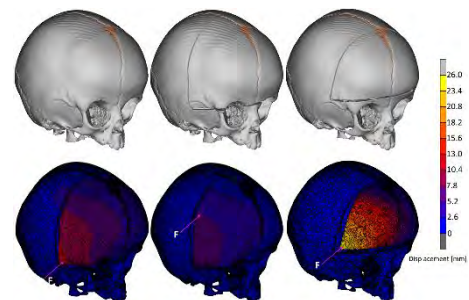


Fig.1 A skull model with different osteotomies and displacements in the skull model under 10N force applied at different points

Rapid Detection of β -lactam Resistant Bacteria via an Integrated Microfluidic System

Yuetao Li¹, Sumit Kalsi¹, Hywel Morgan¹

¹ Centre for Hybrid Biodevices, University of Southampton, SO17 1BJ

Introduction

Antimicrobial resistance (AMR) is becoming one of the biggest threats to health [1]. Misuse of antibiotics may exacerbate the situation, thus there is an urgent need to perform antibiotic susceptibility test (AST) before antibiotic prescription. This project aims to develop a miniaturised microfluidic system to detect antibiotic resistant bacteria from low concentration clinical samples at the point of care.

Methods

The detection system consists of a filter, a dielectrophoresis (DEP) based concentration chamber and an optical signal detection chip. *E. coli* TOP10 with both the CTX-M-15 and TEM gene are used in this assay. In the first stage, a 0.22 μm sterile filter is used to increase bacteria concentration in the sample and also to reduce the medium conductivity. Bacteria are then concentrated using positive-DEP (p-DEP) at 1 MHz in a medium whose conductivity should be less than 100 $\mu\text{S}/\text{cm}$ for significant DEP forces [2]. DEP chips comprise interdigitated Pt electrodes (100 pairs, 20 $\mu\text{m} \times 4.0$ mm electrodes with 20 μm gap) on a glass substrate with PDMS channel on top. The optical detection chip detects a colorimetric change produced due to the hydrolysis of a β -lactam substrate (nitrocefin) by the bacterial proteins. The chip is fabricated in tinted PMMA using micromilling and has eight high-sensitivity absorbance channels (25 mm path length, 4 μL volume) with a 470 nm LED and a photodiode glued on either side. The light from the LED is coupled into the absorbance channel and the transmitted light is collected by the photodiode.

Results & Discussion

Use of 0.22 μm filter not only reduced the medium conductivity from 8.3 mS/cm in LB broth to 33 $\mu\text{S}/\text{cm}$ in water but also helped in increasing the bacteria concentration by 10 folds due to low retrieval volume. The DEP capture efficiency was optimised for different flow rates ranging from 2000 $\mu\text{L}/\text{min}$ to 20 $\mu\text{L}/\text{min}$. A capture efficiency of 95.5% was obtained for a flow rate of 20 $\mu\text{L}/\text{min}$ and this increased the *E. coli* concentration 8 times for a sample containing an initial *E. coli* concentrations of 10^4 CFU/mL. The optical chip has a limit of detection (LoD) of 3.1 milli-AU and can detect *E. coli* CTX-M-15 and *E. coli* TEM within 15 minutes at concentration of 10^5 CFU/mL. Combining the filter, DEP capture and optical chip together, this microfluidic system can determine *E. coli* TOP10 susceptibility against β -lactam antibiotics in 1 hour at a minimum *E. coli* concentration of 10^3 CFU/mL (From sample to result).

Conclusion

A simple system can capture and determine the susceptibility of *E. coli* TOP10 against β -lactam antibiotics down to 10^3 CFU/mL within 1 hour. In the future, urine samples containing bacteria will be tested and a low-cost moulding technology will be used to fabricate the optical chip.

References

1. J. O'Neill, Antimicrobial resistance. London: Review on Antimicrobial Resistance, 2014.
2. H. Morgan and N. Green, AC electrokinetics. Baldock: Research Studies Press, 2003.
3. V. Sieben, C. Floquet, I. Ogilvie, M. Mowlem and H. Morgan, "Microfluidic colourimetric chemical analysis system: Application to nitrite detection", Analytical Methods, vol. 2, no. 5, p. 484, 2010.

Acknowledgments

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Real-time Imaging of Radio-Frequency Ablation Using All-Optical Ultrasound

Y. Makki¹, E. Alles^{1,2}, R. Colchester^{1,2}, S. Noimark^{1,2}, E. Zhang¹, P. Beard^{1,2},
M. Finlay^{1,2,3}, A. Desjardins^{1,2}

¹Department of Medical Physics and Biomedical Engineering, University College London, UK

²Wellcome / EPSRC Centre for Surgical and Interventional Sciences, University College London, U.K.

³William Harvey Cardiovascular Research Institute, Queen Mary University of London and Barts Heart Centre, UK

Introduction

Due to electromagnetic interference, imaging lesion formation during radio-frequency (RF) ablation is difficult using conventional imaging modalities, such as computed tomography or magnetic resonance imaging. In this work we present an all-optical ultrasound system that yields video-rate images and is insensitive to electromagnetic interference, and hence is ideally suited to image RF ablation *ex vivo* in real time.

Methods

Ultrasound is generated via the photoacoustic effect in a composite material comprising carbon nanotubes and polydimethylsiloxane (PDMS) [1], using focused pulsed laser light. The optical focal spot and hence the acoustic source is steered by a set of scanning mirrors, thus synthesising a linear acoustic aperture (width: 13 mm, 200 source positions). Back-scattered ultrasound is detected using a broadband and omni-directional fibre-optic hydrophone [2]. The system achieved a sustained frame rate of 9 Hz at an imaging depth of up to 15 mm, and an isotropic resolution of approximately 100 μm . Fresh organic chicken breast tissue samples were submerged in physiological saline and placed in direct contact with a monopolar RF ablation catheter (maximum power: 30 W, temperature: 65°C, duration: 60 seconds) and simultaneously imaged using the all-optical ultrasound scanner.

Results & Discussion

Imaging of lesions was successfully carried out, despite the presence of an RF field and the increase in temperature due to RF ablation. Isotropic lesion growth (as highlighted by the dashed boxes in Fig.1) could clearly be observed in the images of homogenous chicken breast tissue, up to a penetration depth of 8 mm.

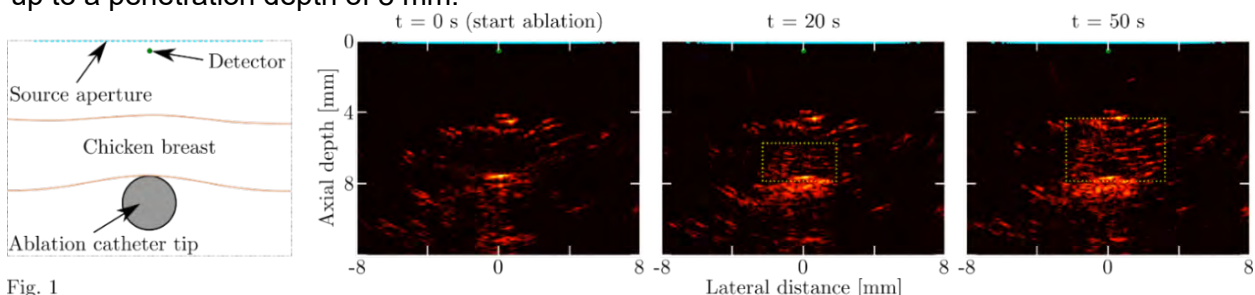


Fig. 1

Conclusion

We present the first real-time, video-rate 2D imaging performed with an all-optical ultrasound system during RF ablation. This imaging technique provides a promising tool for guidance of RF ablation procedures.

References

1. Noimark and Colchester et al., *Adv Funct Mat*, 26(46), 2016.
2. Guggenheim et al., *Nature Phot*, 11(11), 2017

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A low-power system for automatic sleep monitoring and diagnosis

S. A. Imtiaz¹, E. Rodriguez-Villegas¹

¹ *Wearable Technologies Lab, Imperial College, South Kensington, SW7 2AZ, London.*

Introduction

It is estimated that over 5 million people in the United Kingdom suffer from some form of sleep disorder while more than a third of the UK population is reported to have poor sleep quality. Traditional methods of diagnosing sleep disorders suffer from high cost and require multiple electrodes to be used for monitoring sleep at specialised clinics. Intelligent wearable devices need to be designed for in-home monitoring and diagnosis of sleep disorders such that they can automatically detect sleep abnormalities. This requires designing low-complexity algorithms for on-node processing and low-power systems capable of operating for extended periods of time.

Methods

A low-complexity algorithm for automatic sleep staging has been developed [1] specifically for use in embedded and on-chip implementations. It uses data from one (frontal) EEG channel to extract different spectral features that are classified using a set of contextual decision trees that are driven using a state machine based on the current sleep stage. Essentially, the classifier takes into account the current stage and extracts only those features that are relevant for classification. It has also been designed to take the shortest route to classification thereby minimising the number of comparisons and arithmetic operations.

The automatic sleep staging algorithm is implemented on chip [2] using ultra-low power integrated circuits including a state-of-the-art analogue front end to capture EEG signals, a digital processor for feature extraction and a classifier to score the features into one of the five different sleep stages. It also includes a SPI port that is used to interface the chip with a Bluetooth Low Energy transceiver that transmits the result of each classification on to a smartphone or tablet.

Results & Discussion

The sleep staging algorithm developed specifically for low-resource hardware implementation results in classification accuracy of 83% and reduces the number of comparisons for classification needed by 40% compared to a traditional decision tree for similar performance. It uses only a subset of features and trees in each state resulting in better usage of computational resources. The on-chip implementation of the algorithm allows processing of signal on the node requiring only the sleep staging result to be wirelessly transmitted. The entire system weighs only 10g and results in power consumption of 575 μ W, which translates to a continuous battery life of up to 14 days when powered using a hearing aid battery.

Conclusion

A single-channel, ultra-low power, sleep monitoring system makes it possible not only to improve diagnosis of sleep disorders by providing a lot more contextual information over a long period of time but also allows for the possibility of large clinical trials in sleep medicine, which would not be possible with traditional bulky polysomnography systems.

References

1. Imtiaz SA, Rodriguez-Villegas E. "Automatic Sleep Staging Using State Machine-Controlled Decision Trees." *IEEE EMBC*. 2015; 378-381.
2. Imtiaz SA, Jiang Z, Rodriguez-Villegas E. "An Ultralow Power System on Chip for Automatic Sleep Staging". *IEEE JSSC*; 2017: 52(3), 822–833.

Behind-the-Ear Wireless Micro-instrument for Traumatic Brain Injury Neuroelectrochemical Monitoring

M.K. Tageldeen, S.A.N. Gowers, M.G. Boutelle and E.M. Drakakis

Department of Bioengineering, Bessemer Building, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

Traumatic brain injury (TBI) is the collection of observable and non-observable insults that are induced by an external mechanical force. In the UK, 1.4 million patients suffer from TBI yearly. Many require neuroelectrochemical monitoring as 40% of hospital admissions will suffer from a secondary injury [1, 2]. Currently, however, only fully sedated, immobile ICU patients who have undergone craniotomy can be monitored by means of a rather invasive and bulky setup. The monitoring of mobile or mobilised TBI patients calls for the realisation of a new wearable, wireless TBI micro-instrument.

Methods

Our wireless micro-instrument constitutes an aggressive miniaturisation of a previous reduced-size wired TBI instrument of ours [2]. Here, a compact circuit design has been implemented on a flexible Printed Circuit Board (PCB) with a printed antenna for size reduction. The slow dynamics of the relevant neurochemical signals were exploited by multiplexing the chemical channels to enhance performance and footprint efficiency. Bluetooth Low Energy (BLE) was chosen to extend the device operation cycle and the protocol was modified for data streaming. A cloud server is used to store and visualize the human brain's neuroelectrochemical data. To measure chemical activity, LabSmith microfluidic toolkit was used to step-up chemical concentrations of glucose, lactate (0mM to 1mM) and potassium (2.7mM to 30mM) in artificial cerebrospinal fluid (aCSF). A 50µm Pt working electrode was used. For electrocorticography (ECoG) signal acquisition simulation, function generators and ultra-low noise current sources were employed.

Results & Discussion

The device achieves a high sampling rate of 1.25 kSPS (or 385 SPS with UART at 115200 baud rate) for each of 10 channels with 12-bit resolution. Each channel offers programmable gain for adjustment of its dynamic range. Current measurements of less than 10pA were verified. Chemical signals were accurately measured and calibration curves were generated with limit of detection and R-squared of (1.3µM, 0.9 µM, 1.01 mM) and (0.995, 0.998, 0.966) for lactate, glucose and potassium respectively. Finally, ECoG signals recorded from a real patient were passed through the system and the data was reconstructed from the cloud with 29.9dB SNR. The instrument is battery-operated, occupies a volume of 13.5 (4.5 × 3 × 1) cm³, can be borne behind the ear (similarly to the case for hearing aids) and costs £200.

Conclusion

A cost-effective, low-power, wearable system has been developed and shown to accurately sample, wirelessly send, process and store clinical electrochemical measurements in the cloud. The system, coupled with intraparenchymal depth electrodes [1] and in conjunction with an appropriate cranial bolt, enables the real-time monitoring of mobile or mobilised TBI patients.

References

1. Jeffcote T *et al.* Detection of spreading depolarization with intraparenchymal electrodes in the injured human brain. *Neurocritical Care* 2014; 20: 21-31.
2. Papadimitriou, K. I., et al. High-Performance Bioinstrumentation for Real-Time Neuroelectrochemical Traumatic Brain Injury Monitoring. *Frontiers in Human Neuroscience* 2016; 10: 1–15.

Wearable droplet microfluidics for real-time continuous monitoring of tissue chemistry

A. M. Nightingale¹, Chi Leng Leong^{1,2}, Rachel A. Burnish³, Sammer-ul Hassan,¹ Yu Zhang¹, Geraldine F. Clough⁴, Martyn G. Boutelle², David Voegeli⁵, Xize Niu¹

¹Faculty of Engineering and the Environment, University of Southampton, Southampton, U.K. SO17 1BJ

²Department of Bioengineering, Imperial College London, South Kensington, London, U.K. SW7 2AZ ³Critical Care/ Anaesthesia and Perioperative Medicine Research Unit, University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton, U.K. SO16 6YD ⁴Faculty of Medicine, University of Southampton, Southampton, U.K. SO17 1BJ ⁵Faculty of Health Sciences, University of Southampton, Southampton, U.K. SO17 1BJ

Introduction

Continuous real-time measurement of biomolecule levels in tissue offers the potential to monitor metabolic processes in exquisite detail, develop new therapies driven by live biochemical information, and increase our understanding of fundamental physiological and pathological processes.¹ While the use of embedded electrochemical sensors has shown promise, their long-term stability and ability to measure low concentration biomarkers (e.g. hormones, neurotransmitters, proteins and peptides) poses significant challenges to *in situ* measurement.^{2,3} Here we report a different approach, a wearable droplet microfluidic-based sensor that can constantly sample interstitial tissue fluid, analyse *in situ* using a chemical assay, and relay the results.

Methods

The sensor uses a novel screw-driven miniature peristaltic micropump which can sample interstitial fluid *via* a microdialysis probe, can robustly produce nanolitre droplets for analysis of the sample, and can be easily integrated with other components such as liquid reservoirs, optical flow cell and control electronics; all contained within a small (palm-sized) footprint. The use of droplet-flow allows the real-time characterisation of tissue chemical dynamics with excellent temporal resolution, while the use of traditional laboratory assays means the device can be used to measure a range of different biomarkers. To validate the device, we implemented a single-step mix-and-read assay for glucose measurement and a more complex two-step assay for lactate. The device was then used to monitor real-time *in vivo* dermal tissue glucose and lactate levels in healthy volunteers. In each case baseline levels were perturbed, *via* an oral glucose challenge and restriction of blood flow to/from the tissue, for glucose/lactate testing respectively.

Results & Discussion

The sensor constitutes the first time, to our knowledge, that droplet microfluidics has been implemented in a compact wearable unit. When used *in vivo*, the device gave a measurement approximately every three seconds, meaning that glucose/lactate concentrations could be closely tracked in real-time. The sensor results correlated well with values obtained using traditional microdialysis and offline laboratory analysis (a measurement every 2-10 minutes), while the trends were also consistent with those observed in blood levels. Importantly the small size and autonomous operation of the device make it highly practical: During *in vivo* testing the offline blood and traditional microdialysis measurements required near-constant manual operation by a minimum of two people. By contrast, following setup our sensor gave continuous live feedback of the absolute analyte levels and their rate of change, without human interaction.

References

1. Kishida KT et al., PNAS, 2016, 113(1):200-205
2. Anderson JM, Annu. Rev. Mater. Res., 2001, 31(1):81-110
3. Wisniewski N, Moussy F, Reichert MW, Fresenius J. Anal. Chem., 2000, 366(6):611-621

Acknowledgments

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Highly-ordered Mineralized Structures for Dental applications

S. Elsharkawy^{1,2}, A. Mata¹

¹*Institute of Bioengineering, Queen Mary University of London, London E1 4NS, United Kingdom.* ²*Institute of Dentistry, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London E1 4NS, United Kingdom.*

Introduction

There is growing evidence that intrinsically disordered proteins (IDPs) play a fundamental role in mineralisation. IDPs contribute in intermolecular interactions at the protein–mineral interface. Here we report a protein-mediated mineralisation process that takes advantage of disorder-order interplay using elastin-like recombinamers (ELRs) to program organic-inorganic interactions into hierarchically-ordered mineralised structures.

Methods

We exploited recombinant technologies to design a supramolecular matrix that is based on ELR molecules. Membranes were fabricated directly on both etched and rough surfaces of human dentin and mineralized for 8 days.

Results & Discussion

SEM observations confirmed that the hierarchically mineralized membranes grew, adhered, and conformed to the surface of the etched dental tissues. Integration between the hierarchical structures and the dental tissues was observed at the dentin-membrane interface, where the nanocrystals infiltrated and blocked dentinal tubules. Furthermore, to assess the acid resistance of the mineralized coatings, we conducted acid attack experiments, on both mineralized membranes and dental enamel. The mineralized structures exhibited comparable acid resistance to dental enamel after 15 minutes of exposure. It is probable that the acid resistance exhibited by the mineralized structures is related to their intrinsic fluorapatite crystalline phase in comparison to the carbonated hydroxyapatite phase found in enamel. As expected, after 7 days of exposure to acid, the inorganic content of the mineralized membranes and dental enamel were disturbed. Interestingly, the stiffness of ELR membranes after the 7-day acid attack was similar to that of unmineralized membranes, suggesting that the ELR matrix was preserved after the attack. This preservation could potentially enable a remineralization treatment once the acid attack subsides.

Conclusion

Great progress has been made aiming to repair enamel using either wet chemical processes or organic matrices. Our process provides a potential route to control the growth of fluorapatite crystals with tuneable hierarchical order and mechanical properties (1).

Reference:

1) Elsharkawy et al. (2018), Protein disorder-order interplay to guide the growth of hierarchical mineralized structures, *Nature Communications* (accepted).

Acknowledgments

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No conflicts of interests in this section.

Characterising mechanical forces in the outflow pathway of the eye

J.M. Sherwood¹, W.D. Stamer², D.R. Overby¹

¹ Department of Bioengineering, Imperial College London, London, SW7 2BP. ² Duke Eye Center, Duke University, Durham, NC 27710, USA.

Introduction

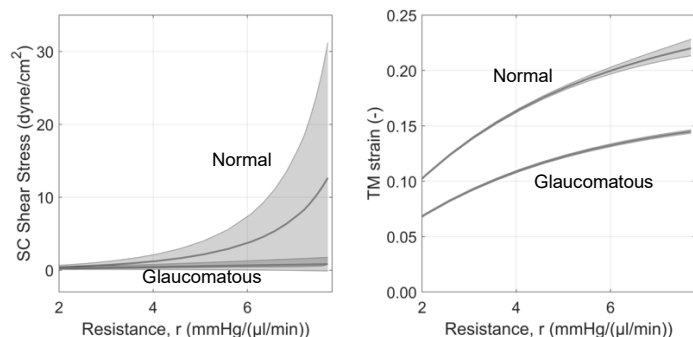
Reduction of intraocular pressure (IOP) is the sole therapeutic aim for glaucoma, a leading cause of irreversible blindness. IOP is generated by the constant flow of aqueous humour across the resistance of the outflow pathway, comprising the trabecular meshwork (TM), Schlemm's canal (SC) and distal vessels. Mechanical forces acting on these tissues have the potential to modulate outflow resistance by stimulating mechanotransduction pathways via shear stress acting on SC endothelial cells and strain on TM cells. However, the dynamics of these forces have not been characterised. We developed a mathematical model to estimate the magnitude of SC shear stress and TM strain and investigate the factors influencing these forces in the presence of the ocular pulse under normal and glaucomatous conditions.

Methods

We built upon the steady-state model of Johnson and Kamm¹ to incorporate the ocular pulse and pressure-dependence of TM stiffness. The model was coupled upstream to a lumped parameter model of the whole globe and downstream to distal vessels, accounting for distal resistance, ocular rigidity, and oscillatory blood flow. To model glaucoma, we assigned elevated TM stiffness and increased outflow resistance, r . Solution of the model used iterative estimation of IOP for a given r , with the constraint that total outflow balanced aqueous humour production.

Results

As r increased from ~2 to 8 mmHg/ μ l/min (spanning normotensive to glaucomatous conditions; IOP=15-28 mmHg), mean shear stress in SC increased more than 30-fold, up to a maximum of 12 dyne/cm² (upper curve in Figure). The oscillatory shear stresses had a maximum peak to peak amplitude (shaded area) of 30 dyne/cm² that increased 57-fold relative



to physiological levels for the highest values of r .

Over the same range of r , TM strain increased approximately two-fold. While the amplitude of the oscillations in TM strain increased with r , the magnitude of oscillatory strain was less than 10% of the steady component. The increased TM stiffness observed in glaucoma² was modelled by a 50% increase in the apparent TM stiffness (lower curves in Figure). This resulted in a moderate damping of the TM strain response, but almost entirely eliminated the shear stress acting on SC inner wall.

Conclusion

Under normal conditions, the oscillatory shear stress within SC is extremely sensitive to outflow resistance, whereas the TM strain is only moderately sensitive. Increased TM stiffness eliminates the shear stress response, but only mildly dampens the TM strain. This implies a possible two-component mechanism to sense IOP that can be disrupted in glaucoma by alteration of TM stiffness.

References

1. Johnson and Kamm, IOVS 24:320-325, 1983.
2. Last et al., IOVS 52(5):2147-2152, 2011.

Mechanoregulation of Intraocular Pressure by Nitric Oxide

D.R. Overby¹, J.Y.H. Chang¹, W.D. Stamer², J.M. Sherwood¹

¹ Dept. of Bioengineering, Imperial College London, London ²Dept. of Ophthalmology, Duke University Medical School, Durham, NC, USA.

Introduction

Elevated intraocular pressure (IOP) is the primary risk factor for glaucoma, but the factors controlling IOP remain largely unknown. Nitric oxide (NO), delivered exogenously into the eye, decreases aqueous humour outflow resistance, the principal determinant of IOP. Endothelial cells lining Schlemm's canal (SC), the primary aqueous humour drainage vessel, express endothelial nitric oxide synthase (eNOS) and release NO in response to hydrodynamic shear stress^{1,2}. SC is a collapsible vessel, such that increasing IOP narrows SC lumen and increases the magnitude of shear stress acting on SC endothelium³. We hypothesize that this mechanism allows mechanoregulation of IOP, whereby elevated IOP results in shear-induced NO production that acts to lower outflow resistance and normalize IOP.

Methods

We used NO-sensitive microbeads that yield a fluorescent readout in response to local NO production⁴. Microbeads were injected into anterior chambers of enucleated mouse eyes, where they become enmeshed in the tissue upstream of Schlemm's canal. *iPerfusion*⁵ was used to perfuse contralateral eyes at 8 or 16 mmHg, representing normal or elevated physiological pressure drop across the outflow pathway. An identical quantity (6.5 μ l) of microbeads was delivered to each eye. Eyes were enucleated from 10 transgenic mice that were engineered to express GFP reporter under the control of the human eNOS promoter. The distribution of microbeads, the intensity of the NO-sensitive readout and eNOS-GFP expression were imaged by confocal microscopy in limbal flat-mounts and sagittal cryosections.

Results & Discussion

eNOS-GFP expression was observed throughout SC and the limbal vessels, delineating an intricate 3-dimensional network for the drainage of aqueous humour. There was a correlation between local microbead accumulation and eNOS expression at both 8 and 16 mmHg ($p < 10^{-4}$). Increasing IOP from 8 to 16 mmHg lead to a 3-fold increase in NO-sensitive microbead fluorescence (0.06 ± 0.04 vs. 0.17 ± 0.11 , mean $\pm$ SD; $p = 0.006$, $n = 10$ each).

Conclusion

Regions of active filtration in the outflow pathway coincide with regions of higher eNOS expression. Elevated IOP leads to increased local NO production, presumably resulting from shear-induced NO expression by SC endothelial cells. These data provide the first evidence of a mechanosensory feedback loop that may act to regulate IOP by NO signalling.

References

1. Ashpole NE, et al. *Invest Ophthalmol Vis Sci*. 2014;55(12):8067–8076.
2. Chang JYH, et al. *AJP: Cell Physiology*. 2015;309(4):C205–C214.
3. Ethier CR, et al. *Biophysical Journal*. 2004;87(4):2828–2837.
4. Chang JYH, et al. *Adv Healthcare Mater*. 2017;6(16):1700383.
5. Sherwood JM, et al. *PLoS ONE*. 2016;11(3):e0150694.

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BioMedEng18

Hacking the skin's ability to bear load

C. J. Boyle¹, S. F. Villata¹, S. Patel¹, M. Plotczyk¹, S. Hettiaratchy², M. A. Masen³, S. Masouros¹, C. A. Higgins¹

¹ Dept. Bioengineering, Imperial College, South Kensington, SW7 2AZ, London. ² St. Mary's Hospital, Praed St., W2 1NY, London ³ Dept. Mechanical Engineering, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

The design of prosthetic lower limbs has improved substantially in recent years. Despite this improvement, 40% of amputees develop skin problems¹. This is because the soft tissue of the residual limb is asked to do a job for which it is not well adapted: to transfer load from the ground to the skeleton. Plantar skin – on the sole of the foot – can tolerate loading that would rapidly lead to degeneration if applied to skin on other body sites. When plantar skin is grafted on load-bearing sites, it appears to be more robust², but this skin is not readily available to an amputee. We test the hypothesis that reprogramming epidermis on residual limbs to be more plantar-like would make the skin more robust under load.

Methods

We use tissue-level mechanical testing to establish the gross mechanical response of human skin to compression and shear. We use AFM indentation to probe the depth-specific properties of skin across all layers. The data from both modes of testing are implemented in a finite element model of the skin. The model geometry is built up from histology images of human plantar and non-plantar skin. These computational models are used to compare the mechanical environments of both plantar and non-plantar skin.

Results & Discussion

Plantar skin is substantially stiffer, both in compression and shear. Creep tests show that plantar skin is more robust under long-term loads. AFM data reveals a more gradual change in stiffness in plantar skin (ranging from 10^5 Pa to 10^3 Pa over 2mm versus a range of 10^4 to 10^3 over 0.7 mm in non-plantar skin). All layers are stiffer in plantar skin. Computational models show that both geometry and material properties influence the plantar skin's ability to bear load.

Conclusion

Plantar skin protects the cells, ECM and microvasculature from excessive deformation. Redirecting non-plantar epidermis to be plantar-like would greatly reduce the deformations experienced in the skin on residual limbs. This work suggests that epidermal reprogramming could be a way to prevent pressure-related skin injuries on residual limbs.

References

1. Dudek, N. L., Marks, M. B., & Marshall, S. C. (2006). Skin problems in an amputee clinic. *American journal of physical medicine & rehabilitation*, 85(5), 424-429.
2. Schwabegger, A. H., Schubert, H. M., Baltaci, M., Djedovic, G., Engelhardt, T. O., & Pierer, G. (2012). Instep split skin grafts on muscle flaps to reconstruct pressure exposed soft tissue parts at the lower extremity. *Archives of orthopaedic and trauma surgery*, 132(10), 1451-1459.

Acknowledgments

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A Physical Mechanism for Wheezing in Lungs

A.L. Gregory¹, A. Agarwal¹, J. Lasenby¹

¹ Dep. Of Engineering, University of Cambridge, Trumpington Street, Cambridge, CB2 1PZ.

Introduction

Wheezing is a high-pitched tonal sound generated by the lung. It can be indicative of several pathologies, including asthma, COPD, and cancer^{1,2}. A quarter of the global population wheeze, but we still do not understand the physical mechanism for the onset of wheezing.

Methods

Wheezing is a result of self-excited oscillations of the airways of the lung, which can be modelled as flexible tubes. We have completed the first set of systematic experiments of direct relevance to the wheezing, in that the length to radius ratio l/a , the tube wall thickness to radius ratio h/a , the axial strain of the tube l/l_0 , and the material properties of the flexible tubes match those of the airways.

Results & Discussion

The onset of oscillations occurs when the tube is almost fully collapsed, ruling out a naive use of linear stability analysis for Poiseuille flow through a cylinder. In fact, it is possible to predict the pressure required for oscillations to start based on the pressure needed for collapse of the tube, as shown in Fig. 1.

We observe that there is a coupling between longitudinal waves along the tube and transverse vibrations of the tube wall at onset, and we believe that a flutter-like interaction between these modes is responsible for the instability. However, we know that the longitudinal waves are not purely elastic, and so we propose that when the wave travels downstream it is driven by an eddy convected with the flow, but upstream the wave is an elastic one. This requires flow separation in order for the flow eddy to be present, and it is the eddy that transfers energy from the fluid to the tube. We call the upstream velocity c and the downstream velocity v . Given this, the modified Strouhal number $f(l/v + l/c)$ should have the value $1/n$, where $n = 1, 2, 3, \dots$, and this is exactly what we observe in our experiments, as indicated in Fig. 2.

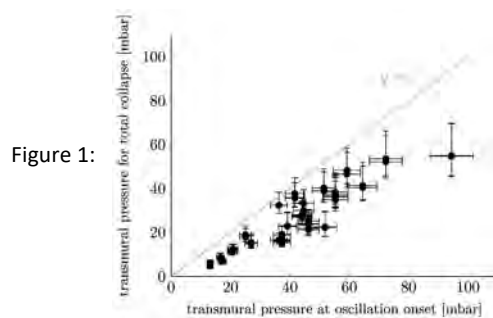


Figure 1:

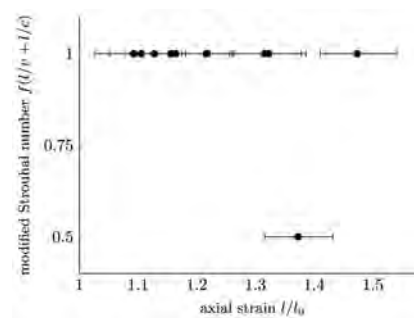


Figure 2:

Conclusion

We provide the first conclusive evidence that wheezing is caused by the coupling of transverse and longitudinal oscillations after flow separation in the tube.

References

1. Meslier et al. *Eur. Respir. J.* 1995; 8: 1942-1948
2. Bohadana et al. *N. Engl. J. Med.* 2014; 370: 744-751

BioMedEng18

A Novel Mechanical Testing Apparatus For Brain Tissue

Richard Pangonis¹, Mazdak Ghajari¹

¹ Dyson School of Design Engineering, Imperial College London, South Kensington, SW7 2AZ

Introduction

In Traumatic Brain Injury (TBI) research, computational modelling is an essential tool in predicting injury. Accurate material properties for brain tissue are of paramount importance to the fidelity of these models. During injury, the brain undergoes a combination of compressive, tensile and shear loading at high rates. However, much of the previous work is at rates significantly lower than those found in blast or impact scenarios, and primarily in compression and shear, rather than tension. This is due primarily to both the inherent difficulty in testing such soft tissue in tension and the lack of suitable apparatus commercially available.

Methods

We designed a custom rig for soft tissue testing at high rate in tension (Figure 1). The apparatus features an electromagnetic linear motor, an encoder for reading displacements and a miniature load cell, integrated onto a small metal base, making it portable. To cut the soft brain tissue accurately, we designed and 3D printed a brain matrix to support the brain.

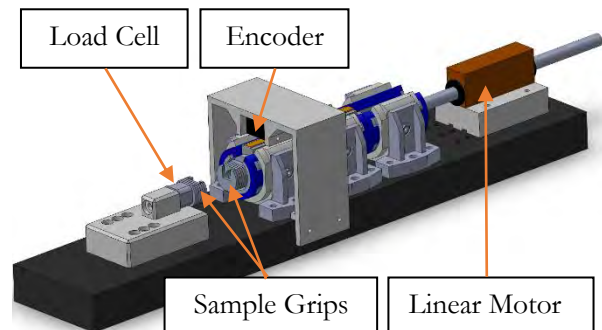


Figure 1: Schematic of the Apparatus

Results & Discussion

The custom rig was prototyped and successfully validated with a variety of tests, see Figure 2. The rig has successfully tested porcine brain tissue at strain rates up to 280 s^{-1} , which represents a substantial increase to the previous work, 90 s^{-1} [1]. The procedure allowed us to successfully and repeatably cut small samples from fresh brain tissue, without resorting to usual methods such as fixing or freezing the tissue that would affect the mechanical properties [2].

Conclusion

The custom rig represents a substantial step forward over existing commercial and custom experimental apparatus for tensile tissue testing, allowing tests to be run on individual brain regions at a higher rate and to a greater accuracy than ever before. It opens new avenues for testing variables like structural anisotropy in the brain at high loading rates.

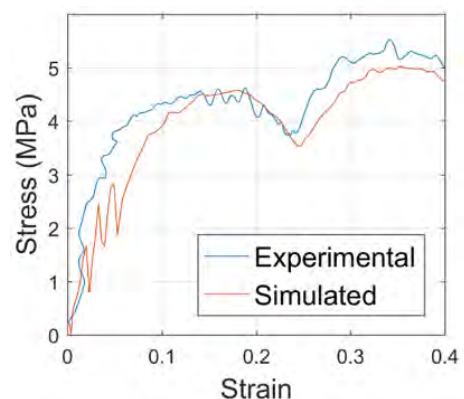


Figure 2: Graph comparing simulated output of the apparatus with actual output

References

- [1] B. Rashid, M. Destrade, and M. D. Gilchrist, *J. Mech. Behav. Biomed. Mater.*, vol. 33, no. 1, pp. 43–54, 2014.
- [2] A. Tamura et al, *J. Biomech. Sci. Eng.*, vol. 3, no. 2, pp. 263–274, 2008.

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Synchrotron imaging of the lung: dynamic mechanical characterisation of the micro-architecture

H. Arora^{1,2}, K. Vitharana², J.M. Sherwood², I.K. Mohammed³, R.L. Mitchell¹, A.J. Bodey⁴, D. Hollis⁵

¹ College of Engineering, Swansea University, Bay Campus, Swansea, SA1 8EN. ² Department of Bioengineering, Imperial College London, South Kensington, London, SW7 2AZ. ³ Department of Mechanical Engineering, Imperial College London, South Kensington, London, SW7 2AZ. ⁴ Diamond Light Source, Didcot, OX11 0DE. ⁵ LaVisionUK Ltd., Oxford, OX26 6QB.

Introduction

Traumatic lung injury in general provides a complex problem to treat. Blast lung injury represents the most extreme form of lung trauma and can range from instantaneous catastrophic rupture of tissue to milder more transient forms of disruption. On the macroscale, these milder forms of injury may be missed by clinical imaging during early-stage assessments. This study focused on microscale architecture of the lung to assess how this can be disrupted and its influence on local lung mechanics [1].

Methods

Shock tube experiments were performed on cadaveric rats to generate our blast injured lung tissue. Mechanical measurements of the initial and post-trauma lung stiffness were collected using a custom-built ventilator. Further pressure measurements were recorded of the incident loading on the specimen. Synchrotron x-ray microtomography experiments were conducted at the Diamond-Manchester Imaging Branchline I13-2 of Diamond Light Source (DLS), UK. Multiple inflation points were imaged to highlight any local defects produced by the blast and their influence on surrounding tissue strain fields obtained via digital volume correlation methods.

Results & Discussion

Results showed that blast injured tissues exhibited significantly different behaviour to the controls. The strain maps extracted from the blast injured samples showed a greater level of strain localisation and a shift in the maximum strains measured. This indicated that even in milder doses of blast, microscale imaging was able to extract and highlight signs of tissue damage. Multiple protocols were performed (excised, *in situ* and enhanced contrast) to highlight at higher resolutions (~1µm) the alveolar network in control/injured lungs. Alveolar volume and shape characteristics were also characterised to deliver statistical analysis alongside visualisations.

Conclusion

Work is ongoing to characterise a range of trauma threats. This study provides a new insight into how tissue damage in any form of injury or disease can be visualised and studied. Tissue strains add a new level of detail alongside visual or morphological analyses. Global measures of tissue stiffness changes post-trauma were linked to local micro-mechanical changes in the tissue.

References

1. Arora H *et al.* *Frontiers in Materials*. 2017; 4 (41): 1-12.

Acknowledgments

This work was conducted under the auspices of the Royal British Legion Centre for Blast Injury Studies at Imperial College London. The authors would like to acknowledge the financial support of the Royal British Legion and the Royal Society (Research Grant Scheme). The authors would like to thank Diamond Light Source for beamtime at I13-2 under proposals MT12864, MT15813 and MT19348 and time at its associated data beamline.

Decorrelation of Common Input to a Muscle's Motor Neuron Pool

M. Bräcklein^{1*}, D. Barsakcioglu ¹, E. Burdet ¹, D. Farina ¹

¹ Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London.

* E-mail: m.bracklein17@imperial.ac.uk

Introduction

Common synaptic input (CI) to a pool of motor neurons was long assumed to be the output of hardwired neural circuitry [1], determining the control of muscles and muscle synergies [2]. It has recently been shown, that subjects provided with a closed-loop biofeedback system, however, can learn to change the input to a muscle conglomerate to decorrelate the output [3, 4]. Whether similar results can be replicated on a more granular level of motor control within one muscle has yet not been investigated. We hypothesize that by providing visual feedback, humans can learn to decorrelate CI given to motor unit (MU) sub-pools of one muscle.

Methods

We used high-density surface electromyography (sEMG) of the tibialis anterior of one subject, and a real-time decomposition technique [5] to decode active MU spiking. In a training phase, the subject was asked to follow a 10% MVC trajectory in a closed-loop feedback task using the visually presented sEMG signal. The data was decomposed. The detected MUs were randomly divided into three subsets of equal size. The filtered cumulative spike train (fcst) of two subsets was visually presented while the subject was asked to follow the trajectory with the real-time fcst of the same two subsets simultaneously recorded. This procedure was repeated for both conditions: fcst of the first and second, and of the second and third subset.

Results & Discussion

The subject was able to follow and react accordingly to the visual feedback. The coherence in theta and alpha band between first/third and second subset after stimulating in both conditions showed dissimilarities towards the training data. The discharge rate of several MUs varied after the visual stimuli were received. However, the mismatch between training and stimulation data only indicates a marginal decorrelation.

Conclusion

The preliminary results show that CI is strongly embedded in the motor control system. However, minor changes observed in both frequency and time domain after stimulation providing evidence for plasticity of CI on MU level which might be amplified by longer learning cycles.

References

1. d'Avella *et al.*, *Nat Neurosci*, vol. 6, no. 3, pp. 300-8, Mar 2003.
2. D. Farina and F. Negro, *Exercise and Sport Sciences Reviews*, vol. 43, no. 1, pp. 23-33, 2015.
3. Radhakrishnan *et al.*, *Journal of Neurophysiology*, 10.1152/jn.90614.2008 vol. 100, no. 4, p. 2397, 2008.
4. Nazarpour *et al.*, *The Journal of Neuroscience*, 10.1523/JNEUROSCI.5481-11.2012 vol. 32, no. 36, p. 12349, 2012.
5. Glaser *et al.*, *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, vol. 21, no. 6, pp. 949-958, 2013.

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Common and independent synaptic input to motor neurons in essential tremor patients

G. Puttaraksa¹, S. Muceli¹, D. Farina¹

¹ Department of Bioengineering, Imperial College London, London, SW7 2AZ.

Introduction

Pathological tremor is a rhythmic oscillation of body parts at frequencies of 3–10 Hz [1]. Although body movements and forces are ultimately controlled by neural commands from the motor cortex [2], the origin and physiology underlying the tremor occurrence are not well understood. Recent research has shown that voluntary activation of muscles is mediated by a relatively large proportion of shared synaptic inputs to motor neurons [3], [4]. With the purpose of investigating sources of common and independent input to motor neurons during essential tremor, we have investigated the characteristics of tremor and the synchronization of motor units (MUs) in multiple muscles. We tested the hypothesis that motor neuron pools innervating pairs of antagonist muscles receive a single common input at the tremor frequency.

Methods

We recorded high-density surface electromyographic (EMG) signals from the forearm extensor and flexor muscles in 15 Essential Tremor (ET) patients during postural tremor. EMG signals were decomposed in the constituent MU spike trains using the CKC decomposition algorithm [5]. The shared synaptic input was accessed by performing coherence and phase difference analysis of MU spike trains within a muscle and between antagonist muscles at the tremor frequency and in the bandwidth of voluntary movements (<2Hz). To study the strength of the common input to muscles, the magnitude of coherence (intramuscular) and cross-coherence (intermuscular) was investigated as a function of the number of MU spike trains used to derive the cumulative spike trains (CSTs).

Results & Discussion

All pairs of MU spike trains within a muscle showed high coherence (mean $\pm$ standard deviation, 0.82 ± 0.27) at the peak tremor frequency (6.03 ± 1.83 Hz). They showed a phase difference of $30.2 \pm 27.3^\circ$. The high coherence values and the small phase difference indicated that the MUs within a muscle received mainly common inputs at the tremor frequency. However, the averaged cross-coherence values between MUs of antagonist muscles (0.48 ± 0.26) were lower compared to the intramuscular coherence and the neural drive to antagonist muscles showed out-of-phase pattern with phase difference of $100.3 \pm 38.5^\circ$. The reduction in common input strength with respect to the total inputs indicated that the pools of motor neurons of antagonist muscles receive not only shared input but also individual inputs, which might be related to Ia and Ib feedback loops.

References

1. K. E. Lyons, R. Pahwa, *Handbook of Essential Tremor and Other Tremor Disorders*. Taylor & Francis Group, 2005.
2. R. Merletti, P. J. Parker, *Electromyography*. A John Wiley & Sons, Inc., 2004.
3. F. Negro, D. Farina, Linear transmission of cortical oscillations to the neural drive to muscles is mediated by common projections to populations of motoneurons in humans, *J. Physiol.*, 589 (3), 629-637, 2011.
4. F. Negro, U. Ş. Yavuz, and D. Farina, *The human motor neuron pools receive a dominant slow-varying common synaptic input*, *J. Physiol.*, 594 (19), 5491-5505, 2016.
5. A. Holobar, D. Zazula, Multichannel Blind Source Separation Using Convolution Kernel Compensation, *IEEE Trans. Signal Process.*, 55 (9), 4487-4496, 2007.

Remote control of cell signalling with magnetic particles for neuronal cell differentiation- emerging therapies for Parkinsons disease

M. Rotherham¹, T. Nahar¹, T. Goodman¹, N.D. Telling¹, M. Gates¹, A.J. El Haj¹

¹*Institute for Science and Technology in Medicine, Keele University, UK*

Introduction

Cell signalling pathways such as the Wnt pathway and Trek channel signalling are important controllers of cell fate and regulators of neuronal development. The development of modulators of these pathways is therefore of clinical relevance for the treatment of neurodegenerative disease. Cell surface receptors that initiate cell signalling and neural progenitor differentiation can be targeted using ligand functionalised magnetic nanoparticles (MNP). This allows remote mechano-stimulation of receptors using externally applied magnetic fields for remote activation of differentiation pathways or induction of directional neurite outgrowth. The aim of this research was to investigate the effects of remote activation of the Wnt receptor Frizzled and the Trek1 potassium channel on neuronal differentiation of neuroprogenitor cells.

Methods

Target receptor expression was assessed in SH-SY5Y and neural progenitor cells using rtPCR. 250nm MNP were coated with peptides or antibodies allowing MNP tagging to Frizzled/Trek receptors. Remote MNP-receptor complex stimulation was performed in 1h-3h sessions using alternating magnetic field gradients provided by a magnetic force bioreactor (MICA Biosystems). Downstream signalling activity was assessed by monitoring β -catenin mobilisation and TCF/LEF responsive gene expression using a TCF/LEF reporters. Neuronal differentiation marker expression was determined both *in vitro* and *ex vivo* embryonic rat brain slices of the nigral-striatal circuit to assess the effects of remote signalling activation on neuronal differentiation of injected progenitor cells.

Results & Discussion

Basal expression of Frizzled1, 2 and Trek1 was confirmed in SH-SY5Y cells and was found to fluctuate during RA/BDNF induced neural differentiation. β -catenin mobilisation and TCF/LEF reporter activity both increased in response to Frizzled targeted MNP and magnetic field stimulation. Short-term fluctuations in expression of stress-response genes NF- κ B and COX2 were observed in response to MNP induced receptor activation. Expression of dopaminergic markers DAT and TH was augmented *in vitro* and maintained in *ex vivo* rat brain slices when SH-SY5Y cells were cultured in neuronal differentiation media and treated with MNP and magnetic stimulation.

Conclusion

Our results demonstrate that remote activation of Wnt signalling pathways can be achieved in neuronal precursor cells using tagged magnetic particles and external magnetic fields. This remote activation approach can then be used to stimulate and augment precursor cell differentiation towards the neuronal lineage. This technique may offer a novel therapeutic strategy for treating neuro-degenerative diseases such as Parkinsons disease.

Acknowledgments

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A Robotic System to Automate Parameter Tuning for Deep Brain Stimulators

N.Steadman¹, R.Vaidyanathan¹, P. Brown², H.Tan²

¹ City and Guilds Building, Imperial College, South Kensington, SW7 2AZ, London. ² West Wing, John Radcliffe Hospital, Headington, OX3 9DU, Oxford

Introduction

Deep Brain Stimulation (DBS) is a procedure involving the implantation of neurostimulators into a patient's brain. It is most commonly used as a treatment for Parkinson's Disease (PD) in situations where a patient's symptoms are particularly severe or drug-resistant^[1]. These stimulators can be parameterised to modulate the frequency, duration and amplitude of the stimulation provided. Currently, alteration of these stimulation parameters involves assessment by a clinician using the Universal Parkinson's Disease Rating Scale (UPDRS)^[2] and manual tweaking of the parameters. Not only does this process require the prolonged input from a trained professional but the lack of precision in tuning and qualitative nature of assessment often results in suboptimal stimulation parameterisation^[3].

Methods

The current system consists of a soft robotic sensor-suit for quantifying upper-body movement and a table-mounted wrist robot used to assess rigidity. The readings from these robotic devices are to be correlated with underlying neural recordings collected through electroencephalography and from the local field potentials at the DBS implantation site. Mapping the relationship between the physical symptoms and neurological patterns will be integral in determining how to alter stimulation parameters.

Conclusion

The research being conducted is in pursuit of a fully closed-loop DBS system - one which does not require the input of a trained clinician and can adjust its parameters automatically to provide optimal stimulation. Such a system would offer substantial benefits in terms of specificity, cost-effectiveness and longevity of DBS implants. The approach taken is novel in its use of robotics in actively guiding patient assessment as opposed to passive measurement during clinician-lead assessment.

References

1. J. Guridi, M. C. Rodriguez-Oroz, and J. A. Obeso, "Deep Brain Stimulation of the Globus Pallidus Pars Interna and Subthalamic Nucleus in Parkinson's Disease: Pros and Cons," in *Deep Brain Stimulation in Neurological and Psychiatric Disorders*, 2008, pp. 277–289.
2. C. G. Goetz *et al.*, "Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results," *Mov. Disord.*, vol. 23, no. 15, pp. 2129–2170, Nov. 2008.
3. C. G. Goetz and G. T. Stebbins, "Assuring interrater reliability for the UPDRS motor section: utility of the UPDRS teaching tape," *Mov. Disord.*, vol. 19, no. 12, pp. 1453–1456, Dec. 2004.

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BioMedEng18

You are as fast as your motor neurons: Speed of recruitment and maximal discharge of motor neurons determine the maximal rate of force development in humans

A. Del Vecchio¹, F. Negro², A. Holobar³, A. Casolo^{1, 4}, J.P. Folland⁵, F. Felici⁴, D. Farina¹

¹ Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London, ² Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy, ³ Faculty of Electrical Engineering and Computer Science, University of Maribor, ⁴ Department of Movement, Human and Health Sciences, University of Rome "Foro Italico", Rome, Italy, ⁵ School of Sport and Exercise Sciences, Loughborough University, Loughborough, UK

Introduction

The central nervous system controls muscle force by recruitment and rate coding of motor units. During maximal-speed feedforward contractions (MFC) motor neurons discharge at high frequencies (up to >200 Hz) and are recruited in a short burst. It has been hypothesized¹ but not proven experimentally that the maximal motor neuron discharge rate determines the human rate of force development. Here we assessed the behaviour of populations of motor neurons during MFC in humans validating a new approach to accurately identify motor neuron activity during fast contractions.

Methods

Twenty men (age 24.9 ± 3.0 years) performed isometric ankle dorsi-flexion contractions at maximal speed and force². The discharge timings of populations of motor units from the tibialis anterior muscle were identified by high-density surface EMG decomposition^{3,4}. The neural parameters extracted by EMG decomposition were studied as a function of the maximal rate of force development and to the impulse (the time-force integral).

Results & Discussion

The maximal motor neuron discharge rate and the estimated neural drive to the muscle (i.e. the average number of discharges per motor unit) were correlated to the impulse and the maximal rate of force development ($P < 0.001$). The peak of strength of the neural drive occurred before force onset and the drive decreased thereafter ($P < 0.001$). The maximal motor neuron discharge rate and the strength of the neural drive to the muscle were associated to the maximal rate of change of force ($R^2 = 0.71 \pm 0.12$, $P < 0.001$). Moreover, the neural drive and force estimates were inversely correlated with the speed of motor unit recruitment ($P < 0.05$).

Conclusion

We showed experimentally the association between the effective neural drive to the muscle and maximal rate of force development. These results indicate that individuals with high rate of force development may have enhanced cortical projections to the motor neuron pool.

References

1. Duchateau J, Baudry S. *Front Hum Neurosc.* 2014; 8: 9-11.
2. Del Vecchio *et al.* *J Appl Physiol.* 2018; doi: 10.1152/jappphysiol.00025.2018. [Epub ahead of print]
3. Holobar A, Zazula D. *IEEE Trans Sign Proc.* 2007; 55: 4487-4496.
4. Del Vecchio *et al.* *J Appl Physiol* 2017; 123: 835-843

Acknowledgments

The authors declare no conflict of interest.

The role of Wnt/ β -catenin signalling pathways in endothelial mechanotransduction under disturbed and undisturbed flow

M. Rickman¹, M. Sureda-Vives¹, A.C. von Huelsen Rocha¹, M. Ghim¹, **C.M. Warboys**¹

¹*Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London.*

Introduction

Atherosclerotic lesions develop preferentially in regions of arteries exposed to multidirectional 'disturbed' flow whilst regions exposed to unidirectional flow are spared. Mechanical forces exerted by flowing blood regulate endothelial cell function and dysfunction; disturbed flow increases inflammatory activation although the signalling mechanisms responsible for these changes are not fully understood. The Wnt/ β -catenin pathway plays an important role in mechanosignalling in non-vascular cells and is known to control vascular development. The aim of this study is to explore the role of Wnt/ β -catenin in endothelial mechanosignalling.

Methods

Human aortic endothelial cells seeded onto fibronectin-coated 6-well plates were exposed to flow for 72h using an orbital shaker (1). Cells were exposed to flow in the presence or absence of different Wnt pathway inhibitors: iCRT5 (50 μ M), DKK-1 (250 ng/ml), IWP2 (5 μ M), sFRP4 (200 ng/ml) or siRNA targeting Fzd4. RNA or protein was isolated from discrete regions at the centre and edge of the well where flow is multidirectional/'disturbed' with low wall shear stress (DF) or unidirectional with high wall shear stress (UF) respectively and analysed by qRT-PCR or Western blot. For analysis of protein expression and localisation by immunofluorescence, cells were seeded onto glass-bottomed 6-well plates and imaged directly in the well by confocal microscopy.

Results & Discussion

The expression of Fzd4, Fzd7 and Wnt5a was increased in endothelial cells exposed to DF as was the activation of GSK3 β and nuclear accumulation and activation of β -catenin. Conversely, the expression of Fzd5, Lrp5 and Lrp6 (associated with the canonical pathway) was increased in endothelial cells exposed to UF. Inhibition of Wnt secretion (using IWP2) or β -catenin transcriptional activity (using iCRT5) reduced the expression of E-selectin and MCP-1 in endothelial cells exposed to DF. This was associated with reduced adhesion of THP-1 monocytes and reduced nuclear localisation of NF- κ B. Preliminary data suggest that knockdown of Fzd4 had a similar effect suggesting the role of a Wnt-Fzd4- β -catenin dependent pathway in DF-induced pro-inflammatory signalling. Inhibition of the canonical Wnt pathway with DKK-1 had no effect on responses to DF suggesting the involvement of a novel non-canonical pathway. Interestingly, DKK-1 did alter endothelial responses to UF; the expression of KLF2 and KLF4 was significantly reduced in cells exposed to UF in the presence of DKK-1 added prior to the onset of flow.

Conclusion

These data suggest that Wnt signalling regulates divergent pathways under different flow conditions. A non-canonical Wnt-Fzd4- β -catenin pathway may be involved in the regulation of pro-inflammatory signalling in response to disturbed flow.

References

1. Warboys CM. *et al.* ATVB. 2014; 34(5): 985-995.

Acknowledgments

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Myosin II governs intracellular pressure and traction by distinct mechanisms

Kimheak Sao¹, Tia M. Jones¹, Andrew M. Doyle², Galina Schevzov³, Peter W. Gunning³ and Ryan J. Petrie¹

¹Department of Biology, Drexel University, Philadelphia, PA, USA, ²National Institute of Dental and Craniofacial Research, NIH, Bethesda, MD, USA, and ³School of Medical Sciences, University of New South Wales, Sydney, Australia.

Introduction

During wound healing by dermal fibroblasts and tissue invasion by metastatic cells, the actin-binding proteins tropomyosin (Tpm) and non-muscle myosin II control the cellular contractile forces that drive cell motility. Classically, two-dimensional (2D) substrate rigidity promotes myosin II activity to increase traction force and enlarge focal adhesions in a process coordinated by Tpm 2.1. We recently discovered actomyosin contractility can also compress the cytoplasm to increase intracellular hydraulic pressure and switch cells from low-pressure lamellipodia to high-pressure lobopodial protrusions during 3D migration (1). It remains unclear whether these myosin II-generated cellular forces are produced simultaneously, and by the same molecular machinery.

Methods

These studies were performed on primary human dermal fibroblasts. Intracellular pressure was directly measured using our established micropressure assay (2). Briefly, a microelectrode was inserted through the plasma membrane and into the cytoplasm of cells moving on 2D glass, or 3D extracellular matrices. Pressure-dependent changes to the resistance of the electrical circuit were monitored by the 900A micropressure system and translated into intracellular pressures. Traction stress was calculated using beam theory by plating cells on flexible microposts and measuring the cell-mediated displacement of posts of known position and stiffness (3).

Results & Discussion

We found adhesion size decreased and intracellular pressure increased on soft 2D material, suggesting traction force and pressure can be controlled independently. We identified Tpm 1.6 as a positive regulator of intracellular pressure and confirmed that Tpm 2.1 is a negative regulator of traction force. Although these Tpm's can independently regulate pressure and traction, both pathways affect adhesion size and the targeting of the mechanosensitive transcription factor YAP/TAZ to the nucleus. While Tpm 2.1 expression is required for efficient migration in non-linearly elastic 3D collagen, rapid migration through linearly elastic cell-derived matrix was dependent on the normal regulation of both intracellular pressure and traction force. While Tpm 1.6 and 2.1 were both associated with actin filaments, Tpm 1.6 uniquely controlled the recruitment of the regulatory myosin light chain to these structures.

Conclusion

Together, our work suggests that actomyosin contractility generates intracellular pressure and traction by distinct mechanisms and these mechanisms can be integrated to control complex cell behaviours on 2D and in 3D environments.

References

1. Petrie RJ, Koo, H, Yamada KY. *Science*. 2014; 345:1062-1065.
2. Petrie RJ, Koo, H. *Curr. Protoc. Cell Biol.* 2014; 63:12.9.1-9.
3. Goedecke, N, et al. *J. Vis. Exp.* 2015; 105.

Segmentation of Endothelial Cell Growth in a Swirling Well Plate allows Investigation of the Shear-Dependent Release of Soluble Mediators

Mean Ghim^{1,#}, Kuin T. Pang^{1,2,#}, Mehwish Arshad¹, Peter D. Weinberg¹

¹Department of Bioengineering, Imperial College London, UK. ²Institute of Molecular and Cell Biology, Agency for Science, Technology and Research (A*STAR), Singapore. #These authors contributed equally

Introduction

Endothelial cells (EC) sense haemodynamic shear stress and the release of soluble mediators is one of their responses¹⁻². The swirling well model can induce complex spatially-varying flow profiles thus gaining increasing attention. However, there is a potential flaw in this model: the release of soluble mediators by EC responding to effects of flow in one region of the well may consequently affect EC in another region. To overcome this, we developed a method that allows culture of EC at only specific regions in a well.

Methods

Flow in a swirling 6-well plate was simulated in STARCCM+ to obtain maps of shear stress. Human Umbilical Vein Endothelial Cells (HUVEC) were grown in a specific region by coating with fibronectin and passivating the remainder of the well with Pluronic. Sheared HUVEC were fixed and stained with DRAQ5 prior to confocal imaging. Cell density and alignment were obtained using MATLAB. Calcein-labelled monocytes were incubated with previously-sheared and TNF- α -treated HUVEC grown on a segmented or full well in static conditions.

Results & Discussion

Centre of wells exhibited Low Magnitude Multidirectional Flow (LMMF) whereas the edge exhibited High Magnitude Uniaxial Flow (HMUF). The alignment and number of HUVEC grown at the edge of the segmented well was unaffected compared to HUVEC grown in the same location of a full well. There was more THP-1 adhesion on HUVEC exposed to LMMF compared to HMUF, both with and without TNF- α treatment. Segmenting the growth of sheared, TNF- α -treated HUVEC resulted in a significant increase in monocyte adhesion at the centre but not at the edge. We interpret this as demonstrating that EC exposed to HMUF release a mediator into the medium that inhibits the pro-inflammatory effects of TNF- α .

Conclusion

We present a simple and effective method to restrict cell growth to a specific region of well plates. This reduces the likelihood of mediators released from cells in response to shear in one region of the well confounding the effect of shear on cells in another region.

References

- [1] Sage H, *et al.* *ATVB*. 1980; 1:427-442
- [2] Tunica DG, *et al.* *Proteomics*. 2009;9:4991-4996.

Acknowledgments

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BioMedEng18

Mechanotransduction mechanisms leading to fetal membrane weakening and tissue damage

D. W. Barrett ¹, A. L. David ², A. Mata ¹, J. A. Deprest ³, C. Thrasivoulou ⁴, **T. T. Chowdhury**¹

¹Institute of Bioengineering, School of Engineering and Materials Science, Queen Mary University of London, E1 4NS. ²Institute for Women's Health, University College London, WC1E 6AU. ³Department of Obstetrics and Gynaecology, University Hospitals Leuven, Belgium. ⁴Department of Cell and Developmental Biology, University College London, WC1E 6XA.

Introduction

Preterm premature rupture of the fetal membrane (PPROM) is a major cause of preterm birth and accounts for 40% of early infant death. The causes of spontaneous PPRM are multifactorial and have been linked to infection, placental abruption and uterine stretch which weaken the membrane, but little is known about the primary signals that initiate the inflammatory process and lead to fetal membrane rupture.

Methods

Human term amniotic membrane (AM, N=32) was collected after written informed consent from women who had undergone elective caesarean section at UCLH. Placental (PAM) and cervical (CAM) amniotic membrane specimens were subjected to intermittent (1 min every 9 min) cyclic tensile strain (CTS, 2%) at 1Hz frequency for 24 hours using an ex-vivo bioreactor system. Second harmonic generation (SHG) imaging microscopy was used to image collagen protein expression. We identified alignment of collagen when AM was dissected parallel to the placental disc (PAM) and perpendicular to the placental disc in the cervical region (CAM). Therefore, throughout CTS experiments, the method of dissection and collagen strain direction remained consistent. After CTS, tissue and media samples were analysed for GAG (DMMB assay), collagen (hydroxyproline assay), elastin (Fastin assay), PGE₂ (ELISA) and MMP activity (fluorogenic peptide substrate assay). Unstrained and strained CAM and PAM specimens were cultured in the presence and absence of Cx43asODNs (10 µM, inhibits Cx43), AKTi (25 µM, selectively inhibits Akt-1/2 kinase), wortmannin (WTM 50 nM, non-specific PI3-kinase inhibitor), and NS-398 (10 µM, selective COX-2 inhibitor).

Results & Discussion

SHG microscopy showed collagen fibre degradation after strain in CAM and PAM specimens. In PAM specimens, strain reduced SHG intensity after 2 hr (p<0.05) and 24 hr (p<0.001). In CAM specimens, strain reduced SHG intensity at 2 and 24 hr (p<0.05). SHG intensity was higher in PAM tissue compared to CAM tissue and decreased in both CAM and PAM tissue over time in response to strain. Strain increased Cx43 and AKT protein expression in term AM after 24 hours and the expression of Cx43 and AKT protein was reduced following incubation with Cx43asODNs and AKTi during strained conditions, respectively. After strain; GAG synthesis increased (CAM and PAM both p<0.001), collagen content decreased (CAM and PAM both p<0.001), elastin content decreased (CAM and PAM both p<0.05), PGE₂ release increased (CAM and PAM both p<0.001) and total MMP activity increased (CAM and PAM both p<0.001). Interestingly, incubation with pharmacological agents reduced repetitive CTS-induced damage to the ECM (collagen and elastin), concomitant with a reduction in PGE₂ release and total MMP activity in CAM and PAM tissue regions.

Conclusion

We observed that downregulation of Cx43 and Akt prevents CTS-induced tissue damage and promotes tissue remodelling in term human AM. We speculate that a combination of inflammatory and mechanical factors disrupt AM biomechanics mediated by abnormal signalling via Cx43. Previous research shows targeted knockdown of Cx43 in chronic skin wounds improves healing, and therefore could be a potential therapeutic option to promote AM healing and treat PPRM.

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Engineering *in vitro* blood vessels for studying endothelial cell function

J. Jansson-Edqvist^{1,2}, J.M. Sherwood², A.M. Randi¹

¹Vascular Sciences, Imperial Centre for Translational and Experimental Medicine, National Heart and Lung Institute, Imperial College London. ²Department of Bioengineering, Faculty of Engineering, Imperial College London.

Introduction

The complex 3D microenvironment that endothelial cells (EC) experience *in vivo* is not well represented by static, 2D monocultures on rigid plastic substrates. However, it is not yet clear specifically how these differences affect *in vitro* biological responses. To be able to better study EC function *in vitro* in order to investigate how the microenvironment affects EC phenotype, we have developed a microfluidic device that incorporates a 3D vessel, based on the approach of creating a vessel by polymerising hydrogel around a needle [1].

Methods

The microfluidic device was designed with 4 inlets; 2 vessel inlets and 2 hydrogel inlets (Figure 1 A), allowing perfusion of the vessel and hydrogel respectively. To create the microfluidic device PDMS was cast in a 3D printed mould and bonded to a glass cover slip. The vessel was created by injecting collagen (4mg/ml) into the device and then inserting a stainless-steel needle between the vessel inlets. The collagen was polymerised around the needle after which the needle was withdrawn to leave a hollow vessel inside the collagen (Figure 1B). The vessel was endothelialised through capillary action using a cell seeding density of 10^6 cells/ml. To obtain homogeneous cell attachment on the vessel wall the construct was rotated during cell seeding. To maintain cell viability in the construct the vessel was perfused at a low flow rate (0.01 dynes/cm^2) using a syringe pump in order to achieve media turnover during cell culture.

Results and Discussion

HUVECs (p3-6) were successfully seeded in a $300\mu\text{m}$ diameter vessel and a monolayer was formed after overnight culture, which was confirmed by CD31 staining of EC junctions (Figure 1 C-E). Permeability assays can be performed by perfusing fluorescently labelled dextran and measuring the diffusion through the vessel wall using live imaging. Mechanical stimuli can be applied to the ECs by flow-induced shear stress. The design of the device supports a wide range of perfusion flow rates and vessel diameters.

Conclusion

We have developed a microfluidic platform of *in vitro* blood vessels for studying EC function under different stimuli and microenvironmental conditions.

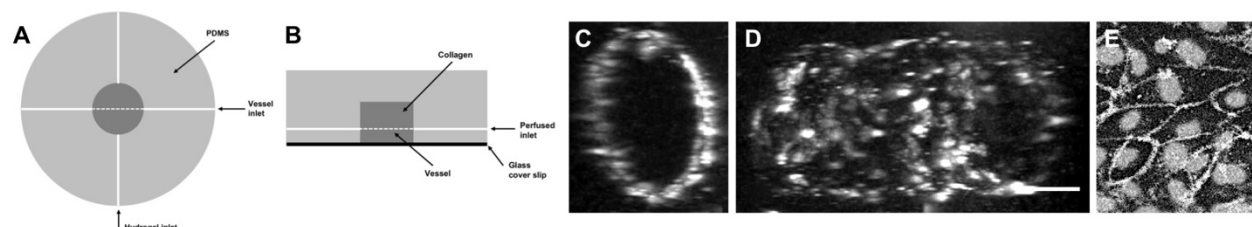


Figure 1: A-B: Top view and cross-sectional view of the microfluidic device showing the vessel in the collagen. D-E: Immunocytochemistry and confocal imaging of the vessel in the microfluidic device. Scale bar= $100\mu\text{m}$. F: Zoomed in image of the vessel wall showing staining of cell nuclei (DAPI) and junctions (CD31), confirming the formation of a EC monolayer after overnight culture.

References

1. Chrobak KM et al., *Microvascular research*. 2006; 71 (3): 185-196.

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Vascular smooth muscle cell contractile response is altered by matrix stiffness

S. Ahmed and D.T. Warren

School of Pharmacy, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ

Introduction

Decreased aortic compliance is associated with ageing and vascular disease, including atherosclerosis and hypertension. Vascular smooth muscle cells (VSMCs) line the blood vessel wall and VSMC contraction regulates vascular tone and contributes to aortic compliance. Mechanical cues derived from the extracellular matrix ECM (ECM) influence VSMC function, yet whether ECM stiffness influences VSMC contraction remains unknown.

Methods

We use an immunofluorescence-based assay to interrogate the impact of matrix stiffness on VSMC contractile response. VSMCs are grown on 12kPa (physiological) and 72kPa (stiff) polyacrylamide hydrogels. Quiescence is induced by serum withdrawal and VSMCs are stimulated with an increasing dose of contractile agonists, including angiotensin II and carbachol. Confocal microscopy is performed to determine VSMC spread area and volume.

Results & Discussion

Contractile agonist stimulation of VSMCs grown at physiological stiffness results in decreased VSMC area. In contrast, contractile agonist stimulation of VSMCs grown on stiff environments resulted in increased spreading. VSMC volume remained unchanged during contraction at physiological stiffness, however, VSMCs displayed increased volume when stimulated with contractile agonists on stiff environments. Traction force microscopy revealed that VSMCs displayed similar levels of actomyosin activity on physiological and stiff substrates, however, increased VSMC spreading observed on stiff environments was reduced by actomyosin inhibition. VSMCs possess mechanical-gated ion channels that normally transiently open during pulsating blood flow. We speculated that these channels open in response actomyosin activity on stiff substrates. Importantly, treatment with a mechanical-gated channel antagonist decreased VSMC spreading in response to contractile agonist stimulation on stiff substrates, confirming that in stiff environments, actomyosin activity triggers opening of mechanical gated channels to increase VSMC volume.

Conclusion

We propose that matrix stiffness enhanced VSMC volume potentially contributes to increased VSMC stiffness and decreased aortic compliance during ageing and vascular disease.

Acknowledgments

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Pulsatile Flow in Ventricular Assist Devices: CFD Analysis of Velocity Fields around the Pressure-Flow Loop

K.H. Fraser¹, D.P.Y. Khoo¹

¹ Department of Mechanical Engineering, University of Bath, Bath, BA2 7AY, UK.

Introduction

Ventricular Assist Devices (VADs) are commonly designed in steady state to give either a specific operating point, or a specific gradient of the pressure-flow curve. However, due to the heartbeat, which is still apparent even with severe heart failure, the flow through a VAD is pulsatile. The pulsatile flow means that over a cardiac cycle the VAD experiences a range of flow rates, and so also the pressure varies. However, due to inertia of the blood the pressure-flow relationship does not follow the steady state curve but rather forms a closed loop. The aim of this study was to investigate the velocity field within the VAD during pulsatile flow.

Methods

Computational Fluid Dynamics was used to calculate the flow within two popular VADs: the HeartMate II and the HVAD. In order to calculate the unsteady flow it was necessary to simulate at least two cardiac cycles and therefore a relatively large timestep was used: 0.001 s. This is too large for studying the rotor-stator interaction and therefore the frozen rotor method was used to approximate the rotation of the impeller.

Results & Discussion

The transient simulation results were in good agreement with published experiments [1]. Large differences in the pressure and velocity fields (fig 1) throughout the cardiac cycle were revealed in the HVAD but smaller variations were found to occur in the HeartMate II. These velocity field differences included variations in the high speed regions (HVAD) and size of recirculation zones (HeartMate II).

Conclusion

These preliminary results suggest that although, with pulsatile flow, any given flow rate has two different pressure heads, depending on whether the flow is accelerating or decelerating, the difference in the velocity field depends on the VAD geometry. This implies steady state calculations may be sufficient for design optimisation of certain types of VAD, but not others. That said, the pulsatile flow calculations are likely to be important for more advanced modelling such as washout or blood damage calculations in all VADs.

References

1. Noor M. R *et al*, Artif Organs, 40(6):549-560,2016.

Acknowledgments

DPYK received funding from the University of Bath Research Studentships.

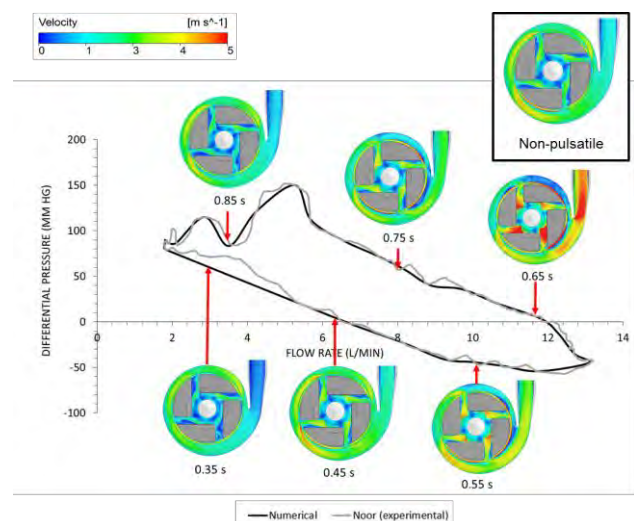


Figure 1: Pulsatile pressure-flow loop for one cardiac cycle for HVAD. Inset: Non-pulsatile (steady) flow condition.

Design and development of DNA-based push-pull networks

Ismael Mullor-Ruiz¹, Wooli Bae ¹, Guy-Bart V. Stan ¹, Thomas E. Ouldridge ¹

¹Imperial College Centre for Synthetic Biology, Imperial College London, South Kensington Campus, SW7 2AZ, U.K.

Introduction

Push-pull networks are out-of-equilibrium biochemical network motifs consisting of a substrate that can be switched between an active and an inactive state by two catalysts. These networks are prominent in protein regulation and ubiquitous in cellular signalling, which features multistep cascades [1]. In these cascades, push-pull networks propagate and process signals related to the relative abundance of the catalysts. Push-pull networks are able to act both as noise filters and signal amplifiers working near the Wiener-Kolmogorov optimal regime [2]. Due to these features, artificial push-pull networks are an area of interest for synthetic biology as programmable and controllable biomolecular systems. In our work, we aim to develop synthetic nucleic acid-based push-pull networks.

Methods

In order to build and test the nucleic acid-based push-pull networks, we design and use 4-way strand displacement reactions as the fundamental functional motif [3]. The proposed design allows us to use DNA duplexes to rationally design systems at the base-pair level, resulting in a high degree of control of the reaction network biophysical parameters. The characterisation of these parameters is performed using different FRET pairs for tracking the different reactions taking place in the system as well as fitting the obtained data to different biophysical models.

Results & Discussion

In the present work, we present results pertaining to the characterisation of the push-pull network elements. These results include deep profiling of the 4-way branch migration process at the free energy and kinetics level and experimental evidence that our designed DNA-based network allows us to achieve the desired catalytic functions. These designed catalytic functions, along with the specificity allowed by the design of DNA domains, permit the coexistence of different catalysts and fuels through which fine tuning of the network dynamics can be achieved.

Conclusion

These results constitute the first proof that analogues for push-pull networks can be built using nucleic acid strands. Potential applications for our devised system range from the exploration of the fundamental thermodynamic costs and trade-offs in signal transduction to the construction of orthogonal, low-burden, programmable control systems for nucleic-acid-based synthetic biology.

References

1. Qu et al. 2009. Effects of cascade length, kinetics, and feedback loops on biological signal transduction dynamics in a simplified cascade model. *Physical Biology*. Vol. 6, no 1, p. 016007.
2. Hinczewski et al. 2014. Cellular signaling networks function as generalized Wiener-Kolmogorov filters to suppress noise. *Physical Review X*, Vol. 4, no. 4, p. 041017.
3. Kotani et al. 2017. Multi-arm junctions for dynamic DNA nanotechnology. *Journal of the American Chemistry Society*. vol. 139, no 18, p. 6363-6368

Acknowledgments

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Affordable microbial bio-manufacturing by Multilevel Strain Engineering

R Ledesma-Amaro¹

¹ Department Bioengineering and Imperial College Centre for Synthetic Biology, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

Moving towards a bioeconomy relies on the viability of bio-based processes costs. Nowadays, thanks to the fast development of research fields like synthetic biology and metabolic engineering, the manipulation of microbes with enhanced capacities to produce pharmaceuticals and materials or to degrade toxic compounds is becoming an easier and more standardize task. However, and despite the vast amount of scientific works engineering microorganisms to synthesize a wide range of products, there are just a few of examples that have reached the market, being the major limitation for this the high cost of the overall process.

Methods

Multilevel Strain Engineering is a combination of metabolic engineering and synthetic biology strategies aimed not only to maximize production yields of compounds of interest but also to diminish the cost of the overall process, including the upstream and downstream parts by engineering microorganisms to confer them with non-native properties.

Results & Discussion

The Multilevel Strain Engineering concept will be illustrated through several recent works from the lab where 1) we improved vitamin B2 production in *A. gossypii* by using a metabolic model an pathway engineering and 2) decreased the overall cost of bio-lipid production in *Y. lipolytica*. This was achieved by A) expanding the substrate range making it able to efficiently degrade inexpensive and preferred lignocellulosic [1,2], B) maximizing lipid production until reaching the theoretical maximum yield [2] and uncoupling biomass and product formation allowing a production of lipids higher than 100% of Cell Dry Weight [3], C) facilitating the recovery of the lipids by engineering the secretion of those to the cultre media [3], and D) producing higher-value lipid-derived compounds such as beta-carotene, a colorant, antioxidant and precursor of Vitamin A, what was produced with the highest titers described so [4].

Conclusion

In order to make bioproduction affordable we now, thanks to the development of synthetic biology and metabolic engineering, have the tools to improve microbial strains in order turn them not only into efficient producers of the compound of interest but also into better in industrial organisms, with beneficial features in upstream and downstream processes.

References

- [1] Niehus, LeCoq, Sandoval, Nicaud, Ledesma-Amaro. Biotech for biofuels 2018
- [2] Ledesma-Amaro et al. Metabolic Engineering 2016a
- [3] Ledesma-Amaro et al. Metabolic Engineering 2016b
- [4] Larroude, Celinska, Thomas, Nicuad, Ledesma-Amaro. Biotech & Bioeng 2017

Acknowledgments

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Modelling and systems analysis for elucidating and engineering compartmentalisation in synthetic and natural biochemical pathways

G. Menon¹, J. Krishnan^{1,2}

¹ Department of Chemical Engineering, Centre for Process Systems Engineering, Imperial College London, SW7 2AZ, London. ² Institute for Systems and Synthetic Biology, Imperial College London, SW7 2AZ, London

Introduction

Compartmentalisation/spatial organisation of biochemical pathways at the intracellular level plays a critical role in many cellular contexts, including signal transduction and the regulation of metabolic processes. Compartmentalisation is also an essential ingredient in bottom-up approaches to building functional pathways in synthetic and chemical biology, and there is significant interest in manipulating the natural compartmentalization within cells, for example to engineer metabolic pathways. We present a dedicated modelling/systems framework, which involves the dissection of basic building blocks of signalling and metabolic pathways, more complex extensions of these, and the effects of compartmentalisation. We evaluate compartmental ODE models as tools for the reliable analysis and design of such systems. We also extend our framework to examine cell-free synthetic nucleic acid based circuits, including transcription-translation systems, and identify basic design principles for spatial organisation in engineering these systems.

Methods

We combine generic models of biochemical pathways from the literature (signalling, metabolic, or gene regulatory) with explicit spatial models (PDE), incorporating compartmentalisation and diffusive transport. We use numerical simulations and bifurcation analysis, backed by analytical results, and make connections to concrete biological contexts as well as experimentally engineered synthetic biochemical circuits.

Results & Discussion

We use our framework to show (i) how compartmentalisation affects the basic building blocks of pathways, such as modification cascades, (ii) how various trade-offs emerge in engineering the compartmentalisation of more complex signalling and metabolic pathways, and (iii) our analysis of compartmental ODE models (by comparison with a detailed PDE model), shows when they are reliable, and where they fall short. We suggest augmentations/better procedures based on our analysis, which make compartmental models more reliable in certain regimes. Our study of compartmentalisation in cell-free synthetic nucleic acid based circuits, yields important insights into the interplay between spatial organisation and network structure, and gives us a unified view of the underlying capabilities, design principles, and trade-offs, across multiple compartmentalised configurations.

Conclusion

Our analysis yields a range of insights into the role of compartmentalisation in natural cellular pathways, the choice of modelling framework for the analysis and design of compartmentalised pathways, and highlights the role of spatial organisation as a key ingredient in the bottom-up engineering of functional biochemical circuits in synthetic cell-free systems.

References

1. Menon G, Okeke C, Krishnan J. *Scientific Reports* 2017; 7.
2. Menon G, Krishnan J. *Paper in preparation* 2018

Acknowledgments

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A synthetic DNA-built enzyme flips 10^7 lipids per second in biological membranes

Alexander Ohmann^{1†}, Chen-Yu Li^{2†}, Christopher Maffeo³, Kareem Al Nahas¹, Kevin N. Baumann¹, Kerstin Göpflich¹, Jejoong Yoo³, Ulrich F. Keyser^{1*}, Aleksei Aksimentiev^{2,3,4*}

¹Cavendish Laboratory, University of Cambridge, UK. ²Center for Biophysics and Computational Biology, University of Illinois at Urbana-Champaign. ³Center for the Physics of Living Cells, University of Illinois at Urbana-Champaign.

⁴Department of Physics and Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign. [†]Contributed equally to the work. *Correspondence to: ufk20@cam.ac.uk, aksiment@illinois.edu

Introduction

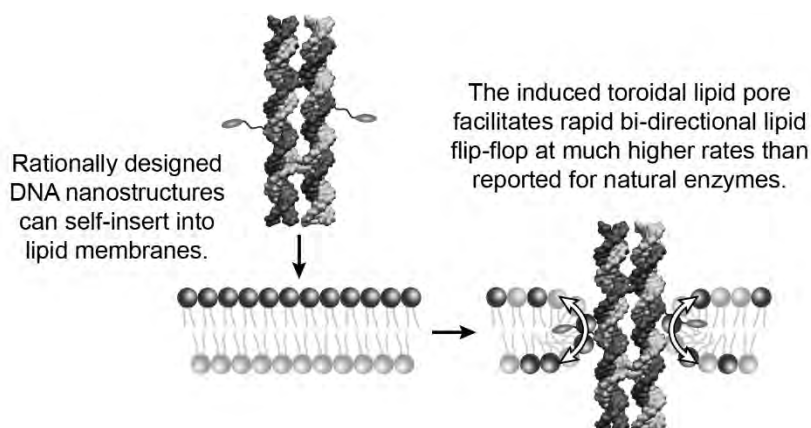
Mimicking enzyme function and increasing performance of naturally evolved proteins is one of the most challenging and intriguing aims of nanoscience. Here, we employ DNA nanotechnology to design a synthetic enzyme that substantially outperforms its biological archetypes [1].

Methods

Through a combination of microscopic simulations and fluorescence microscopy experiments we demonstrate the rapid lipid flipping activity of our membrane-inserting DNA-built nanostructure.

Results & Discussion

Consisting of only eight strands, our DNA nanostructure spontaneously inserts into biological membranes by forming a toroidal pore that connects the membrane's inner and outer leaflets. This DNA-induced pore catalyses spontaneous transport of lipids between the bilayer leaflets, rapidly equilibrating the lipid composition at a rate exceeding 10^7 molecules per second, which is three orders of magnitude higher than the rate of lipid transport catalysed by biological enzymes.



Conclusion

Control over lipid homeostasis by synthetic DNA nanostructures opens up a yet to be explored direction for designing personalized drugs and therapeutics for a variety of health conditions. Ultimately, the ability to outperform naturally evolved proteins allowed for a glimpse at the tremendous opportunities still to be explored in nucleic acid-based nanotechnology.

References

1. Ohmann, A. *et al.* A synthetic enzyme built from DNA flips 10^7 lipids per second in biological membranes. *Nat. Commun.* **9**, 2426 (2018). <https://doi.org/10.1038/s41467-018-04821-5>

Acknowledgments

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Engineering Molecular Machines that can Sense and Respond to their Environment

J.W. Hindley^{1,2}, Y. Elani^{1,2}, S. Ali³, R.V. Law^{1,2}, C.L. Bevan³, O. Ces^{1,2}

¹ Department of Chemistry, Imperial College London, South Kensington, London, SW7 2AZ, UK

² Institute of Chemical Biology, Imperial College London, South Kensington, London, SW7 2AZ, UK

³ Department of Surgery and Cancer, Imperial Centre for Translational & Experimental Medicine, Imperial College London, Shepherd's Bush, London, W12 0UQ, UK

Introduction

The development of soft matter structures that are responsive to specific stimuli is essential for engineering the next generation of drug delivery systems as well as the construction of artificial cells and tissues. This research focuses on the development of a suite of lipid vesicles that utilise chemical functional groups and biomolecules to create nano- and microscale systems that are responsive to light¹, temperature² and enzymatic stimuli³.

Methods

Lipid vesicles are produced from a combination of thin film hydration, extrusion and emulsion-based methods, whilst membrane protein incorporation is carried out through detergent-mediated reconstitution. Vesicle characterisation and function is primarily evaluated through a combination of molecular spectroscopy, microscopy and dynamic light scattering.

Results & Discussion

The first design strategy exploits light-responsive functional groups present in the membrane to generate nanopores under irradiation with ultraviolet light, enabling the construction of hierarchical vesicles capable of light-controlled catalysis (figure 1).¹ A second approach uses ternary lipid formulations as tunable, thermoresponsive content release platforms, creating cell-sized lipid chassis that can interact with their external environment.² Finally, protein channel-containing vesicles can respond to local increases in enzyme concentration by triggering release of contained cargo.

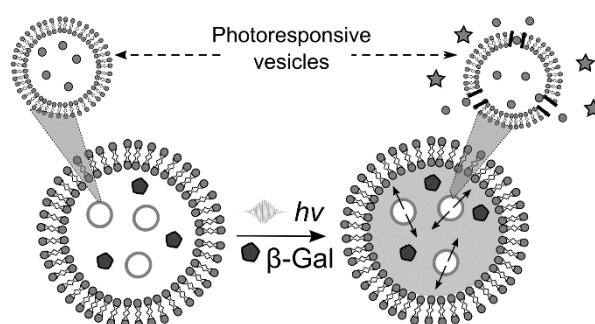


Figure 1. Nested Vesicles for Light-Controlled Catalysis.

Conclusion

The incorporation of different chemical and biological motifs enables the creation of a new generation of responsive vesicles. By combining these functional modules across different length scales, biomolecular machines can be engineered and customised to suit a range of applications across biotechnology and medicine.

References

1. J. W. Hindley *et al.*, *Nat. Commun.*, **2018**, 9, 1093.
2. K. Karamdad *et al.*, *Chem. Sci.*, **2018**, DOI: 10.1039/c7sc04309k.
3. K. Charalambous, *et al.*, *J. Am. Chem. Soc.*, **2012**, 134, 5746–5749.

BioMedEng18

A toolkit for the construction of vesicle-based artificial cells: microfluidics, optics, and biomembrane engineering

Y. Elani^{1*}, M. Friddin¹, O. Ces¹, T. Trantidou¹, G. Bolognesi¹

¹ Department of Chemistry, Imperial College London, SW7 2AZ

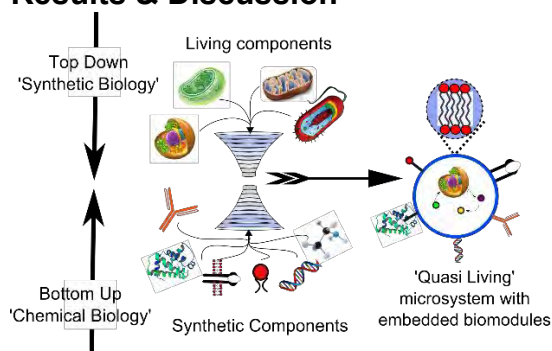
Introduction

One of the ultimate goals of Synthetic Biology is to construct artificial cells from the bottom-up from non-living building blocks.¹ Existing methods do not allow control over size, curvature, compartmentalisation, and spatial organisation of content and function in artificial cells, which is significant bottleneck. Precision engineering of artificial cells requires the development of new technologies to control their architecture, to interface them with biological systems, and to introduce new biotechnologically relevant functionalities for industrial and clinical applications.²

Methods

We use droplet microfluidics to generate artificial cells of user-defined architectures in high throughput, and optical traps to manipulate and sculpt cells of varied morphologies. Biomolecular components derived from cell-lysates and purified membrane-based machinery are used to impart cell-like functionalities.

Results & Discussion



We have developed a suite of technologies for synthetic cell construction and manipulation. We can generate structures that have defined sub-compartments that perform discreet tasks akin to organelles, with signalling cascades mediating communication between subcellular locations. We take advantage of concepts in membrane biophysics to engineer synthetic gap junctions where individual cells can be connected in 3D into proto-tissue structures. These developments now enable us to interface artificial cells with biological

ones, to form hybrid cells composed of living and synthetic components³ (Fig. opposite). This allows us to leverage the power of cellular biology in a synthetic soft-matter microsystem and to bridge the gap between the bottom-up and top-down approaches to synthetic biology; it provides a means of interfacing the richness and versatility of cell biology with artificial cells.

Conclusion

The use of microfluidics, optical trapping, membrane chemical biology, and cell-free synthetic biology allow us to incorporate principles of precision engineering into the field of artificial cells. This conceptual shift is needed for their applications in the clinic and in biotechnology. Our structures can serve as the basis of new generation of soft-matter microdevices with application in smart therapeutics, biosensing, responsive and self-healing materials and micro-scale reactors.

References

1. D. E. Cameron, C. J. Bashor and J. J. Collins, *Nature Reviews Microbiology*, 2014, 12, 381-390.
2. Y. Elani, *Biochemical Society Transactions*, 2016, 44, 723-730.
3. Y. Elani et al. *Scientific Reports*, 2018, 8, 4564.

Acknowledgements

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BioMedEng18

A new method for non-invasive measurement of arterial wave speed, intensity and reflection

E.K. Rowland, K. Riemer, K. Lichtenstein, M-X. Tang and P.D. Weinberg

Department of Bioengineering, Imperial College London, London SW7 2AZ.

Introduction

Ventricular ejection generates a forward-going compression wave in the arterial system. Slowing of ejection leads to a forward-going expansion wave. The waves contain clinically useful information: their magnitude varies with cardiac performance, their speed depends on arterial stiffness, and their reflection is affected by conduit artery tone. These properties can be studied using Wave Intensity Analysis (WIA) [1]. Here we describe and validate a new, non-invasive method for measuring the arterial properties that allow accurate WIA.

Methods

The method employs a novel WIA formulation [2] based on blood flow velocity and arterial diameter. That enables all necessary data to be obtained from the same ultrasound images, using standard techniques for diameter measurement and ultrasound imaging velocimetry ([3]) for velocity measurement. In vitro experiments employed blood driven through a latex tube by a pulsatile pump; capillary tubes and air-filled reservoirs gave appropriate resistance and compliance. In vivo experiments were conducted by imaging the abdominal aorta of 24 rabbits, some of which were administered esmolol to induce ventricular dysfunction. Experiments complied with the Animals (Scientific Procedures) Act 1986 and were approved by Imperial's Animal Welfare and Ethical Review Board. In vitro and in vivo, a Verasonics ultrafast plane-wave imaging system gave kHz frame rates, microbubble contrast agents were used in some experiments, and data were compared with conventional WIA based on pressure and Doppler velocity measurements from an invasive, catheter-based system (Volcano).

Results

In vitro, UIV with contrast agent gave the same velocity waveform as the invasive method. Native blood speckle could be used in place of contrast agent speckle if blood and tissue signals were separated by singular value decomposition. In vivo, flow waveforms obtained by UIV with contrast agent, with native blood speckle and singular value decomposition, and with the invasive method were essentially identical. Changes in peak intensities could be detected after administration of esmolol.

Conclusion

The new method enables wave speeds, intensities and reflections to be obtained simply, reliably and non-invasively at single points in the arterial system using existing ultrasound scanners. It could provide a clinically useful way to detect arterial stiffening, heart failure, and alteration of arterial tone.

References

1. Parker KH. Med Biol Eng Comput. 2009; 47: 175-188
2. Feng J, Khir AW. J Biomech. 2010; 43: 455-462
3. Leow CH, et al. Ultrasound Med Biol. 2015 ;41: 2913-2925

Acknowledgments

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BioMedEng18

An overlapping domain method for hemodynamics based on weighted sums

M. Balmus¹, A. Massing², D.A. Nordsletten¹

¹ St Thomas' Hospital, King's College London, SE1 7EH, London. ² UMIT, Umeå University, 901 87, Umeå.

Introduction

Balancing solution accuracy and computational feasibility remains significant challenge in solving fluid flow problems; particularly in cases where the domain undergoes large deformations. Arguably, the most challenging example in biomedical applications occurs for cardiac valves, which move significantly through the ventricular chambers, as well as pulmonary and aortic roots. Currently, the most widespread approach for this class of problems are the immersion methods. While moving mesh techniques (i.e. ALE) can suffer from large element distortions, in popular immersion methods the mesh is kept fixed, eliminating mesh distortion or the need for re-meshing. This comes at the cost of poor stress and pressure estimations on the boundary surface. Chimera methods aim to combine the advantages of the two approaches. Generally, the setup consists of two overlapping meshes: one global and the other embedded, enveloping the surface of the immersed body. This creates a conforming interface between the fluid and solid, while it diminishes mesh distortions. However, it introduces an artificial non-conforming fluid-fluid interface, resulting in a discontinuous flow solution at the transition between domains.

Methods

In this paper, we introduce an overlapping domains technique where fluid velocity and pressure function spaces are defined as the weighted sum of the functions which can be represented on distinct sub-meshes. Thus, while we retain the main advantages of the chimera method, we introduce greater flexibility on how the fluid-fluid coupling is achieved. Most significantly, C^0 continuity can be obtained at the interface by choosing the embedded function weight to be zero on this surface, irrespective of the resolutions used to represent the domains.

Results

To assess the accuracy of this approach, we consider a series of test cases of increasing complexity. Spatio-temporal convergence is shown to be optimal and comparable with those of boundary fitted and ALE approaches. For transient flows, we demonstrate that the technique can be used to accurately estimate parameters that define the system in the case of the Schäfer-Turek benchmark. Finally, we apply the method to solve a more realistic 3D problem for fluid flow around a moving cardiac valve.

Conclusion

We present a new overlapping domain method which is particularly suited for flow around structures which undergo large deformations, such as cardiac valves. Furthermore, we show that the method is accurate and applicable for a number of 2D and 3D problems.

Acknowledgements

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Simultaneous optical mapping of transmembrane potential and electrogram recordings in human heart slices

K.N. Tzortzis^{1,4}, R.A. Chowdhury^{1,4}, E. Dupont^{1,4}, S. Selvadurai¹, F. Perbellini¹, C.D. Cantwell^{2,4}, F.S. Ng^{1,4}, A.R. Simon³, C.M. Terracciano¹, N.S. Peters^{1,4}

¹ Cardiac Function Section, NHLI, Imperial College London, Hammersmith Campus, W12 0NN, London. ²Department of Aeronautics, Imperial College London, South Kensington, SW7 2AZ, London, ³Department of Cardiothoracic Transplantation & Mechanical Circulatory Support, Royal Brompton and Harefield NHS Foundation Trust, UB9 6JH, London, ⁴ElectroCardioMaths Programme, Imperial Centre for Cardiac Engineering, Imperial College London

Introduction

The contact cardiac electrogram (EGM) and the cellular action potential (AP) are extracellular and transmembrane recordings of the same voltage change, and should change in conjunction with each other during pathologies¹. We report a novel dual modality apparatus for concurrent EGM and AP recording at a single-cell level within multicellular preparations to validate their relationship.

Methods

A custom system was built incorporating microelectrode arrays (MEA) (8x8 electrodes/100µm diameter/700µm spacing) mounted within an optical mapping system with single cell resolution. Concurrent EGM and AP measurements were acquired from 300µm-thick slices of the left ventricle obtained from end stage heart failure patients (n=21). Slices were stimulated from 0.2-1Hz. Ten sec MEA recordings were obtained simultaneously with 5sec optical mapping recordings, both before and after administration of the cellular uncoupler carbenoxolone (CBX).

Results

Direct correlation was observed between APD₉₀ and Field Potential Duration (FPD) ($r^2=0.64$, slope=0.39, $p<0.0001$). An indicator of the effect of gap junction uncoupling by CBX on tissue slices is the conduction velocity reduction from $11.85\pm3\text{cm/s}$ (n=2 slices) to $6.9\pm3.2\text{cm/s}$ (n=2 slices). Gap junction uncoupling modified both AP and EGM morphology. Action potential duration to 90% repolarisation (APD₉₀) decreased with CBX administration (control: 0.2Hz $883.6\pm77\text{ms}$, 1Hz $522.6\pm8\text{ms}$; CBX: 0.2Hz $481.3\pm123\text{ms}$, 1Hz $445.5\pm5\text{ms}$; n=8; $p<0.0001$) and restitution with respect to pacing frequency was observed ($p<0.01$). Field potential duration (FPD) was affected by pacing rate ($p<0.0001$), but not CBX (control: 0.2Hz $603.9\pm33\text{ms}$, 1Hz $522.5\pm135\text{ms}$; CBX: 0.2Hz $622.5\pm46\text{ms}$, 1Hz $455.8\pm45\text{ms}$; n=4).

Conclusion

We demonstrate the utility of a novel system combining optical mapping with MEA recordings for simultaneous recording of AP and EGMs with single cell resolution from the same group of cells². This technique can be used to investigate electrophysiological abnormalities and provide unique insight into cellular mechanisms leading to changes in EGM morphology.

References

1. Himel HD & Knisley SB. *Physiol Meas* 2007; 28:707-19
2. Chowdhury RA, Tzortzis KN, et al. *Scientific Reports* 2018

Acknowledgments

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BioMedEng18

Bayesian Inference-based Estimation of Normal Aortic, Aneurysmal and Atherosclerotic Tissue Mechanical Properties: from Material Testing, Modelling to Histology

S. Wang¹, A. Tokgoz², Y. Huang³, P. Sastry⁴, C. Sun¹, N. Figg³, M.P.F. Sutcliffe², J.H. Gillard¹, **Z. Teng**^{1,2}

¹ Department of Radiology, University of Cambridge, Cambridge, CB2 0QQ. ² Department of Engineering, University of Cambridge, Cambridge, CB2 1AG. ³ EPSRC Centre for Mathematical and Statistical Analysis of Multimodal Clinical Imaging, University of Cambridge, Cambridge, CB3 0WA. ⁴ Department of Medicine, University of Cambridge, Cambridge, CB2 0QQ.

Introduction

Mechanical properties of healthy, aneurysmal and atherosclerotic arterial tissues are essential for assessing the risk of lesion development and rupture¹. Strain energy density function (SEDF) has been widely used to describe these properties, where material constants of the SEDF are determined using the ordinary least square (OLS) method. However, the material constants derived using OLS are usually dependent on initial guesses.

Methods

To avoid such dependencies, Bayesian inference-based estimation was used to fit experimental stress-stretch curves of 312 tissue strips from 8 normal aortas, 19 aortic aneurysms and 21 carotid atherosclerotic plaques to determine the material constants C_1 , D_1 and D_2 of the modified Mooney–Rivlin SEDF.

Results & Discussion

Compared with OLS, material constants varied much less with prior in the Bayesian inference-based estimation. Moreover, fitted material constants differed amongst distinct tissue types. Atherosclerotic tissues associated with the biggest D_2 , an indicator of the rate of increase in stress during stretching, followed by aneurysmal tissues and those from normal aortas. Histological analyses showed that C_1 and D_2 were associated with elastin content and details of the collagen configuration, specifically, waviness and dispersion, in the structure.

This study suggested a robust procedure to determine the material constants in SEDF and demonstrated that the obtained constants can be used to characterise tissues from different types of lesions, while associating with their inherent microstructures.

Conclusion

Bayesian inference-based estimation robustly determines material constants in the modified Mooney–Rivlin SEDF and these constants can reflect the inherent physiological and pathological features of the tissue structure.

Refere

1. Huang Y, et al., *Circ Cardiovasc Imaging*. 2016; 9(11): pii: e004656.
2. Stevens RRF, et al., *PLoS One*. 2017; 12: e0187421.
3. Thondapu V, et al., *Eur Heart J*. 2017; 38: 81-92.

Acknowledgments

This study was support by EPSRC (EP/P021654/1), BHF (PG/18/14/33562) and NIHR Cambridge Biomedical Research Centre. Mr Wang is supported by China Scholarship Council and Mr Tokgoz by an EPSRC Doctoral Training Award at the University of Cambridge.

Limb-Scale Modelling of the Lymphatic System

D. J. Watson¹, K. Karakashian¹, J. Carson¹, C. Pike², R. van Loon¹

¹ Zienkiewicz Centre for Computational Engineering, College of Engineering, Swansea University, Bay Campus, Swansea, UK. ² Lymphoedema Network Wales, Cimla Health & Social Care Centre, Abertawe Bro-Morgannwg University Health Board, Neath, UK.

Introduction

Lymphoedema is characterised by an accumulation of fluid within the tissues. Secondary lymphoedema of the upper-limb can develop as a consequence of the treatment of breast cancer. Modelling lymphoedema at the limb-scale may offer insights into this condition and offer improved methods of diagnosis and treatment. Whilst network-scale models have been proposed with imposed phase differences in contraction cycles [1], the nature of large networks precludes this approach

Methods

3D scans of the upper limbs of lymphoedema patients were subjected to shape analysis to explore the changes associated with lymphoedema [2]. This approach was supplemented with biphasic FEA models. The lymphatics of the upper limb were reconstructed from anatomical drawings as a 3D topology to form a 0D limb-scale model, which was tuned based on existing experimental data [3][4]. A diameter-dependent frequency model was implemented that allowed lymphangions to contract at different frequencies and develop phase differences.

Results & Discussion

Shape analysis of patient limb geometries has identified a novel metric which may impact the diagnosis of lymphoedema. 0D lymphatic models have explored the kinetics of fluid transport within the lymphatic system and can inform understanding of lymphatic insufficiency. Whilst FEA arm models have explored the development of lymphoedema and the consequences of pressure garments. Future work can seek to further integrate these approaches to produce a more holistic understanding of the condition.

Conclusion

A mixture of biphasic FEA, shape analysis and 0D lumped modelling are used to inform the understanding of 3D limb scans taken from lymphoedema clinic patients. Novel metrics of lymphoedema have been identified.

References

1. Jamalian, S. et al. Parameter sensitivity analysis of a lumped-parameter model of a chain of lymphangions in series. *Am. J. Physiol. - Heart Circul. Physiol.* 2013; 305, H1709–H1717.
2. Karakashian, K. et al. Investigation of Shape with Patients Suffering from Unilateral Lymphoedema. *Ann Biomed Eng.* 2017; 1-14
3. Davis, M. J. et al. Determinants of valve gating in collecting lymphatic vessels from rat mesentery. *Am. J. Physiol. - Heart Circul. Physiol.* 2011; 301: 48–60.
3. Bertram, C.D. et al. Development of a model of a multi-lymphangion lymphatic vessel incorporating realistic and measured parameter values. *Biomech. Model. Mechanobiol.* 2013; 13, 401–416.
4. McHale N., Roddie I., The effect of transmural pressure on pumping activity in isolated bovine lymphatic vessels. *J Physiol* 1976; 261:255-69

Acknowledgments

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Can we estimate myocardial material parameters from reduced 2D imaging data?

A. Nasopoulou¹, D.A. Nordsletten ¹, S.A. Niederer ¹, P. Lamata ¹

¹ *Department of Biomedical Engineering, King's College, London.*

Introduction

Central to both the personalization of predictive cardiac biomechanical models and the in vivo estimation of myocardial material stiffness is the process of material parameter estimation from clinical images of the myocardium. Currently this process involves the acquisition of 3D imaging data, which are costly and not widely available bedside - as opposed to the ubiquitous 2D ultrasound images. Aiming to translate recent advances in cardiac modelling into the clinic, we develop in this study a method for myocardial material parameter estimation from 2D images, such as provided by 2D or 3D speckle tracking echocardiography.

Methods

The method relies on previous work, where an energy based cost function (CF) was introduced to address the inability of deformation based CFs to uniquely confine the parameter space [1]. In this work, the 'virtual works' principle (VWP) is used instead of 'energy balance' in the CF, offering the model flexibility to adapt to the limited data. In our analysis the myocardium is assigned transversely isotropic material properties described by a popular model [2]. Using the modified CF in conjunction with the VWP (both expressed at end diastole), our pipeline focuses on recovering the two most inter-correlated parameters, considering the remaining two parameters fixed.

Results & Discussion

To test the accuracy and robustness of the method against model assumptions and data noise, two synthetic data sets were generated from the passive inflation of a truncated prolate spheroid mimicking the availability of pressure recordings and 'long axis images' with either 3D or 2D displacement and deformation information. The parameter estimation pipeline using the 3D deformation data set recovered the ground truth values, while its application on the 2D data set also performed reasonably well (<10% error). The accompanying sensitivity analysis showed that the method was robust to offsets of the imaging plane from the axis of symmetry. Image noise was identified as the most critical factor for accurate estimation, while model assumptions concerning the tissue microstructure were found to be the least crucial.

Conclusion

Based on the results of our study it can be concluded that myocardial material parameters can be accurately estimated from 2D imaging data. Moving forward we apply the pipeline to clinical data from heart failure patients and identify the challenges of the transition from synthetic to real data sets.

References

1. Nasopoulou et al. Improved identifiability of myocardial material parameters by an energy-based cost function. *Biomech Model Mechanobiol* (2017) 16: 971.
2. Guccione et al. Passive material properties of intact ventricular myocardium determined from a cylindrical model. *J Biomech Eng* (1991).

Acknowledgments

This work was supported by the Wellcome/EPSRC Centre for Medical Engineering [g.a. 203148/Z/16/Z]. PL holds a Wellcome Trust Senior Research Fellowship [g.a. 209450/Z/17/Z].

Unified Mechanism of Atrial Fibrillation in a Simple Model

M. Falkenberg McGillivray¹, A. Ford¹, A. Li¹, A. Ciacchi¹, N.S. Peters², K. Christensen^{1,2}

¹ Centre for Complexity Science, Imperial College London, London SW7 2AZ, UK.

² ElectroCardioMaths Programme, Imperial Centre for Cardiac Engineering, Imperial College London, London W12 0NN, UK.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia with an overall lifetime risk of approximately 37%. Despite over 100 years of continuous research, the mechanistic origin of AF is still not fully understood, with evidence for numerous contradictory proposals. Recent work by Hansen and colleagues has given the first evidence for a potential unifying mechanism of AF, based on sustained re-entrant circuits forming in the complex architecture of the human atria [1,2]. In this paper, we present a simple theoretical model for the spontaneous emergence of AF that strongly supports the mechanism proposed by Hansen and colleagues.

Methods

We introduce a simple cellular automata model of AF in 3d. This is an extension of a 2d model we have published previously [3,4]. The model is inspired by the discrete nature of cardiac muscle cells and the complex arrangement of muscle fibres walls of the atrial myocardium. The model is minimal in design with simple activation rules.

Results & Discussion

We demonstrate that AF-like behaviour can emerge spontaneously in the model given two conditions: the increase of structural heterogeneity in the myocardium, and the presence of small regions with the potential for localised conduction block. The model shows sinus rhythm conduction as well as both paroxysmal and persistent AF as structural heterogeneity increases. Additionally, the model demonstrates a diversity of AF conduction patterns on the Epicardial and Endocardial surfaces which are consistent with the mechanism proposed by Hansen and colleagues.

Conclusion

We have presented a simple model of atrial fibrillation that reproduces many of the key results in recent AF literature. Although our model is very basic and on a simplified topology of the atria, the model could be adapted using realistic atrial fibre maps to study the emergence and development of human AF.

References

1. B. Hansen et al., European Heart Journal, Volume 36, Issue 35, 14 September 2015, Pages 2390–2401.
2. S. Nattel et al., Nature Reviews Cardiology, Volume 14, 2017, Pages 509–520.
3. K. Christensen et al., Physical Review Letters, Volume 114, January 2015, Pages 028104.
4. K. Manani et al., Physical Review E, Volume 94, Issue 4, October 2016, Pages 042401.

Acknowledgments

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Development of Perfusable Vascular Platform by Using 3D Bioprinting

L. Ouyang^{1,2,3}, M. M. Stevens^{1,2,3}

¹Department of Materials, ²Department of Bioengineering, ³Institute of Biomedical Engineering, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

Vascular structures are needed in numerous biomedical areas, including fundamental (e.g. angiogenesis, cell-cell interaction, disease model) and application-based studies (e.g. tissue engineering, drug testing). The objective of this work is to develop a hydrogel-based perfusable vascular platform, with the ability to form endothelialized channels and to incorporate additional matrix materials together with cells.

Materials & Methods

Basically, gelatin and gelatin methacryloyl (GelMA, synthesized from gelatin) were used as the sacrificial and matrix bioinks, respectively. A multi-nozzle 3D bioprinter (EnvisionTEC) was used to perform the heterogeneous printing, where dispensing pressure and temperature (both for the nozzle and stage) were well controlled to achieve good printability. The hydrogel vascular platform was fabricated in a layer-by-layer fashion, fitting into a well-defined PDMS chamber with inlet and outlet (Fig1A). After UV treatment for GelMA crosslinking, the whole system was placed at 37°C to dissolve the sacrificial materials and thus to leave out the perfusion channels, followed by optional endothelial seeding and perfusion culture. The vascular structure could be customized to other patterns, allowing the incorporation of additional components along the generated channels (Fig1B).

Results & Discussion

1) The printability of both gelatin and GelMA was optimized in terms of parameters such as concentration (5~10 wt%), temperature (24~28°C), pressure (0.6~1.2 bar), printing speed (3~10 mm/s) etc. It was found that the gelation temperature of GelMA was lower than that of gelatin, which meant that the modification process would compromise the thermo-sensitivity of gelatin. 2) Perfusion of the structure was demonstrated by using a peristaltic pump and the flow rate of up to 2 ml/min can be applied without breaking the hydrogel structure. 3) The connection between the steel needle and the hydrogel channel was well sealed without leaking for weeks. 4) On-going work includes cell seeding into the channels, direct cell printing with sacrificial bioink and incorporating microchannels by using two-photon cleaving technology.

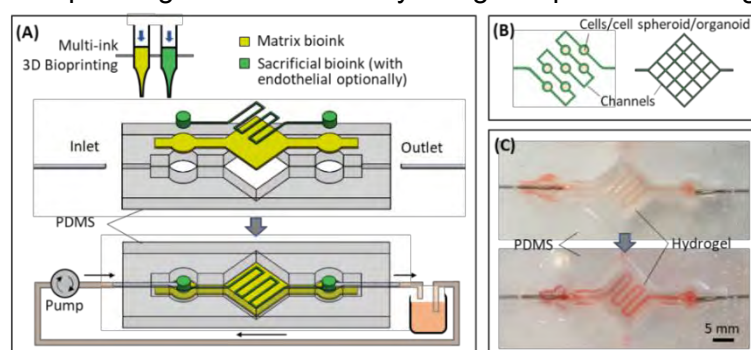


Figure 1. (A) Schematic of the perfusable hydrogel platform fabrication with multi-ink bioprinting and perfusion culture. (B) Isle and grid pattern design of the in-between vascular structure, where cells/cell spheroid/organoid can be incorporated by the vessel. (C) The fabricated hydrogel structure with perfusion demonstration.

Conclusion

A perfusable hydrogel-based biochip system was developed, with the flexibility of customizing the vascular pattern and incorporating additional cells and matrix materials. Such vascular system will act as a platform for numerous cell-based studies, including angiogenesis, cancer invasion, organoid culture and most likely nextgen organ-on-a-chip.

References

1) Ouyang L *et al.* *Biofabrication*. 2016, 8(3):035020. 2) Kolesky DB *et al.* *PNAS*. 2016, 113(12):3179-3184. 3) Lee VK *et al.* *Biomaterials*. 2014, 35(28):8092-8102.

Engineering a Pulmonary Epithelium-on-a-Chip device to Investigate the Mechanobiology of Lung Disease

A. Rech^{1,2}, Franz Puttur², J. M. Sherwood¹, C. M. Lloyd², D. R. Overby¹

¹ Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London. ² Inflammation, Repair & Development Section, National Heart and Lung Institute, Imperial College London, SW7 2AZ, London.

Introduction

During breathing the pulmonary airway epithelium experiences shear stress, which modulates the epithelial barrier¹. Airway shear stress may change in asthma or idiopathic pulmonary fibrosis to affect epithelial barrier function. To investigate these mechanisms *in vitro*, we are developing a pulmonary airway epithelium-on-a-chip, in which primary epithelial cells can be cultured and subjected to physiological airway forces. Our approach builds on the microfluidic device of Benham et al² and incorporates an airflow control system to apply shear stress to the apical surface of epithelial cells.

Methods

The microfluidic device comprises two channels separated by a permeable membrane. The upper channel is seeded with human bronchial epithelial cells, whilst a microfluidic pump is used to perfuse both channels at 1 µl/min to provide media turnover until the cells reach confluency. An air-liquid interface (ALI) is then created to trigger cellular differentiation. Immunofluorescence staining for tight-junctions (ZO-1) is used to assess barrier integrity and viability.

Results & Discussion

Preliminary data show survival and initial tight-junction formation of cell line 16HBE for 6 days, including 4 days with ALI (Fig. 1a). Future work will incorporate primary bronchial epithelial cells. To apply apical shear stress, we used a linear actuator and glass syringes in a custom holder (Fig. 1b) to drive airflow through the upper channel. The system is controlled using LabVIEW to customise the inhalation and exhalation airflow profiles to achieve desired shear stress waveforms. Future experiments will investigate the impact of oscillatory shear stress on epithelial barrier function.

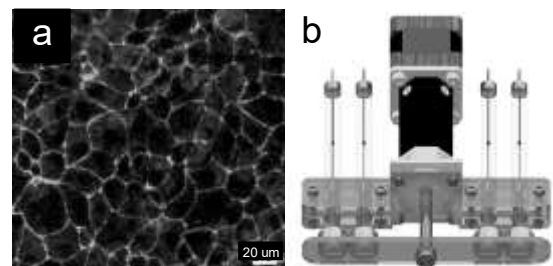


Figure 1 – a) Tight-junction staining (ZO-1), b) Airflow device CAD model

Conclusion

The pulmonary epithelium-on-a-chip device will provide a useful platform for the mechanobiology of airway epithelial cells in controlled microenvironments.

References

1. V. K. Sidhaye *et al.*, “Shear stress regulates aquaporin-5 and airway epithelial barrier function”, PNAS, vol. 105, no. 9, pp. 3345-3350, 2008.
2. K. H. Benam *et al.*, “Small airway-on-a-chip enables analysis of human lung inflammation and drug responses *in vitro*”, Nature Methods, vol. 13, p. 151–157, 2015.

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Vein-on-a-chip platforms for evaluating the performance of sclerosing agents.

Elisabetta Bottaro¹, Jemma Paterson¹, Xunli Zhang^{1,2}, Martyn Hill^{1,2}, Andrew L. Lewis³, Timothy Millar⁴ and Dario Carugo^{1,2}

¹Faculty of Engineering and the Environment, University of Southampton, Southampton, UK, ²Institute for Life Sciences, University of Southampton, Southampton, UK, ³Biocompatibles UK Ltd. A BTG International Group Company, Farnham, UK, ⁴Faculty of Medicine, University of Southampton, Southampton, UK

Introduction

Sclerotherapy is widely employed for treating varicose veins[1]. Pre-clinical studies on sclerosing agents are often performed using *in-vitro* models that do not fully replicate physiological conditions. In this study, vein-on-a-chip (VOC) models were developed as a platform to investigate the mechanical and biological performance of sclerosants, at conditions relevant to their administration *in-vivo*.

Methods

VOCs were fabricated in PDMS using replica moulding. They replicated the venous architecture, and their surfaces were coated with endothelial cells. A blood surrogate was injected into the VOC using a syringe pump (62.5-125.0 ml/h), and a pressure transducer measured blood pressure. Pressure recordings were analyzed using a custom-built computational analysis system. Sclerosing agents investigated were physician compounded foams (PCFs), made using the Double Syringe System (DSS) or Tessari (TSS) methods.

Results & Discussion

A robust experimental platform was developed to evaluate the performance of sclerosing agents, within both physiological and varicose vein architectures. From the analysis of blood pressure recordings, it was possible to determine the expansion (ER) and degradation (DR) rate of sclerosing foams, which were employed as indicators of mechanical cohesiveness. Results showed that, at the lowest blood flow rate, TSS had a lower ER in both straight and varicose models (0.25 ± 0.01 and 0.12 ± 0.08 mmHg/s, respectively) compared to DSS (0.27 ± 0.03 and 0.18 ± 0.08 mmHg/s, respectively). Lower ER values indicate a foam that expands more slowly and thus provides higher contact time with the vein wall upon injection. With respect to foam DR, DSS had lower DR in the straight model (0.26 ± 0.009 mmHg/s) compared to TSS (0.32 ± 0.03 mmHg/s). In the varicose models, all PCF foams had comparable performance.

Conclusion

Vein-on-a-chip models were developed in this study, and employed to evaluate the physical performance of sclerosing agents pre-clinically. Models are currently used in our laboratories to correlate physical performance with biological and therapeutic outcomes.

References

1. J. Alòs, P. Carreño, et al. "Efficacy and Safety of Sclerotherapy Using Polidocanol Foam: A Controlled Clinical Trial," *Eur. J. Vasc. Endovasc. Surg.*, 31(1), pp. 101–107, 2006.

Acknowledgments

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BioMedEng18

High-Content Confocal Imaging of Organ-Chips: A Robust and High-Throughput Workflow Enables Evaluation of Drug Candidates in a Liver-Chip model

Sam Peel¹, Beate Ehrhardt², Adam M Corrigan², Kyung-Jin Jang³, Pedro Pinto⁴, Matt Boeckeler⁵, Beverley Isherwood¹, Jonathan Rubins³, Konstantia Kodella³, Debora B. Petropopolis³, Dominic Williams⁴, Geraldine Hamilton³ and Lorna Ewart⁶

¹Discovery Biology, ²Quantitative Biology, Discovery Sciences, IMED Biotech Unit, AstraZeneca, Cambridge, UK; ³Emulate Inc., Boston, USA; ⁴Safety and ADME Translational Sciences, Drug Safety and Metabolism, IMED Biotech Unit, AstraZeneca, Cambridge, UK; ⁵Sample Management, Discovery Sciences, IMED Biotech Unit, AstraZeneca, Waltham, USA; ⁶Microphysiological Systems Centre of Excellence, Drug Safety and Metabolism, IMED Biotech Unit, AstraZeneca, Cambridge, UK.

Introduction

Organ-Chips are *in vitro* models that aim to recreate the organ microenvironment. Implementation within the pharmaceutical industry aims to improve the probability of success of drugs by generating models that are human and disease relevant. Whilst capturing cellular phenotype via imaging in response to drug exposure is a useful readout in these models, application has been limited due to difficulties in imaging the chips robustly and at scale.

Methods

We have developed an end to end, automated imaging workflow to robustly capture and analyse confocal images of multicellular Organ-Chips to assess detailed cellular phenotype across large batches of chips. We have also established an analysis pipeline to reduce bias and variability and investigate spatial effects.

Results and Discussion

By automating the 3D acquisition and analysis of images, we have reduced user interaction time (from over 2 hours/ Chip to just ~5 mins per 8 Chips), process variability and user bias as well as establishing a framework of statistical best practice for Organ-Chip imaging. We have applied this workflow to design and prosecute studies to evaluate known hepatotoxic compounds as well as active AZ drug candidates in human Liver-Chips illustrating its applicability in drug safety assessment. Finally, use of bespoke, 3D printed adaptors allows this process to be adaptable to different chip formats and we demonstrate this through application to a Kidney-Chip model.

Conclusion

We have developed a novel, automated imaging and analysis pipeline to extract robust data from Organ-Chip models creating the capability of using Organ-Chips in a drug screening context and enhancing the data we can obtain from these models going forward.

References

Ewart, L., et al., Application of Microphysiological Systems to Enhance Safety Assessment in Drug Discovery. *Annu Rev Pharmacol Toxicol*, 2018. 58: p. 65-82.

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Development of a gut-on-a-chip model for the study of inflammatory bowel diseases

L. Baldwin¹, J. Greenman¹, N. Pamme², C.E Dyer¹

¹ Biomedical Sciences, School of Life Sciences, University of Hull, UK ² Chemistry, School of Mathematics and Physical Sciences, University of Hull, UK.

Introduction

Inflammatory bowel disease (IBD) is a chronic condition characterised by inflammation of the gut wall arising from an uncontrolled immune response, leading to damage to the epithelial barrier lining the intestinal wall. IBD is currently not curable and ongoing research aims to provide improved laboratory models of IBD¹, to support further understanding of the disease, including the role of the microbiota in the progression of IBD and its systemic impact, including effects on the nervous system². Here we describe the design and manufacture of an improved dual flow microfluidic chip device that maintains viable cell lines or tissue biopsies, aiming to enhance the understanding of IBD and the development of future treatments.

Methods

A dual chamber chip has been designed, with two independent flow streams separated by a semi-permeable membrane, that allows for the co-culture of cell lines either side of the membrane. Cell monolayer barrier integrity can be analysed using TEER (Trans-Endothelial Electrical Resistance) measurements. The effluent can be analysed for biomarkers of cell viability and function, such as using a cell death assay (Lactate dehydrogenase) and detection of inflammatory mediators (IL-10, IL-8, IL-6, TNF- α).

Results & Discussion

The dual flow device has been used to a) culture gastrointestinal epithelial cell lines (CACO2 or HT29-MTX-E12) to create a **gut chip** and b) co-culture of endothelial (hUVEC) and commonly used brain tumour (U87) cell lines to create a blood-brain-barrier chip. The key results from this are the ability of the chip to keep single and co-cultures of cells alive for at least 72 hours. This has been shown using fluorescein diacetate/propidium iodide live/dead stains and LDH assays to assess cell death. Studies are now underway integrating the gut and blood-brain barrier chips, connected via flow of culture medium, to model the gut-brain axis, allowing for the study of the effects of IBD on wider aspects of the body. Initial results have demonstrated that the 2 chips can be run in sequence while maintaining the cell viability achieved in individual chip set up.

Conclusion

Preliminary work has successfully established a dual channel chip to model the gut-brain axis with focus on the impact of IBD, while allowing for reliability and ease of use. Following initial validation of the chip using cell lines, future work will progress to incorporate full thickness gut tissue biopsies on the chip in place of cell lines to allow for a more clinically relevant model.

References

1. Dawson, A., et al. (2016). A microfluidic chip based model for the study of full thickness human intestinal tissue using dual flow. *Biomicrofluidics* 10(6): 064101.
2. Carding, S. et al. (2015) Dysbiosis of the gut microbiota in disease. *Microb Ecol Health Dis*, 26, 26191.

Acknowledgments

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BioMedEng18

Cell sheet engineering for kidney-on-a-chip applications

W.L.G. Loewenhardt¹, N. Koudis², R. Lennon ², B. Derby¹

¹ School of Materials, University of Manchester, Manchester M13 9PL, UK. ² School of Biological Sciences, University of Manchester, Manchester M13 9PL, UK.

Introduction

Nephrotoxicity causes only 2% of failures during preclinical drug developmental stages, however, during phase III trials, this percentage increases to 19% [1]. In order to improve these statistics, it is paramount to develop an improved *in vitro* model of the kidney. The drug development process can take 8-12 years and 0.8-1.2 billion US\$ to reach market [2]. Therefore, a complex human cell model holds potential to accurately predict drug toxicity, reduce failure rates and cut costs during drug development. The glomerular filtration barrier and the proximal tubule within the kidney are important for blood filtration and selective reabsorption of water and small molecules. We are developing an *in vitro* model of both components using cell sheet engineering and a custom bioreactor designed specifically for this purpose. Cell sheet engineering allows for the supporting membrane in the model to be eliminated, producing a more authentic mimic of the *in vivo* structures.

Methods

Bioreactors were constructed with a Solidscape 3Z PRO wax printer using 3Z model and support materials. Bioreactor inserts were constructed using an OBJET30-Pro 3D printer to print moulds with VeroBlue RGD840 build material. Silicone elastomer (PDMS) was weighed at 10:1 ratio and cast into the bioreactor and insert moulds. Proximal tubular cell line, RPTEC, as well as human glomerular podocytes and endothelial cells, were utilised. Two techniques were performed to harvest cell sheets (1) temperature responsive surfaces using Poly(N-isopropylacrylamide) (PIPAAm) coated UpCell Nunc Multidishes® and (2) high density cell seeding on glass coverslips. Cells were grown to confluence and the cell sheet was harvested. A PDMS insert was coated with either collagen IV or fibronectin overnight, to encourage cell attachment. PDMS inserts were inverted onto the cell sheets to allow attachment for 50 minutes. The PDMS insert, with the cell sheet was flipped to the correct orientation and transferred into the bioreactor for functional assays to be conducted.

Results & Discussion

We successfully harvested proximal tubule and glomerular cell sheets using the two different methods. The cell sheets were transferable to a PDMS insert, which can be transferred into the specifically designed bioreactor. Viability, morphological and functional studies of cell sheets under both static and flow conditions were performed. Further functional and toxicity assays are to be conducted to characterise the model.

Conclusion

Cell sheet formation and suspension onto a PDMS insert is possible with proximal tubular and glomerular cells. Cell sheet engineering has benefits due to the absence of artificial membrane therefore, producing a system which may more closely reflect the cell and extracellular matrix assembly and maintenance that occurs *in vivo*.

References

1. Ge F, He QY. *Expert Opinion on Drug Metabolism and Toxicology*. 2009; 29–37.
2. Grainger DW. *Advanced Drug Delivery Reviews*. 2014; 69-70.

Acknowledgments

We are grateful to the BBSRC and GSK for supporting this project.

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Microfluidics accessible to cell biology: a network of fluid-constrained channels and droplets

Cyril Deroy¹, Agata Rumianek², James Wheeler³, Kevin Foster³, David Greaves², Peter R. Cook², Edmond J. Walsh¹

¹ Department of Engineering Science, University of Oxford, Oxford, OX1 3PJ. ² Dunn School of Pathology, University of Oxford, Oxford, OX1 3RE. ³ Department of Zoology, University of Oxford, Oxford, OX2 6GG. ⁴ iotaSciences, University of Oxford, Oxford, OX1 3RE.

Introduction

Despite the great potential of microfluidics in the field of biomedical research, current microfluidic devices are rarely adopted by the life-science community. This is mainly due to technical complexities such as high failure rates due to gas-bubbles and questionable bio-compatibility of polydimethylsiloxane (PDMS). Here, we have designed and implemented a system that prints microfluidic circuits using only materials commonly used by biologists - standard cell culture dishes and media. Novel devices were fabricated to demonstrate the functionality of this system; we performed passive and active cell migration assays using primary and bacterial cells.

Methods

We print fluidic circuits made from cell media onto conventional petri dishes. These circuits are made by shaping cell media onto a conventional petri dish to form networks of conduits and reservoirs, in much the same way as drawing with pen on paper. Post fabrication, the circuits are overlaid with an immiscible fluorocarbon to limit evaporation and enable the formation of interfacial tension mediated interfaces to external fluid movers. Cells may be added anywhere to the open microfluidic format or flow driven from any point within the circuit by passive or active means using principles of Laplace pressure.

Results & Discussion

Using cell media on a petri dish, fluidic devices consisting of fluid chambers connected by microfluidic conduits were fabricated. Live cells are added to one chamber, to which they adhered to the substrate overnight. Following cell adhesion, different reagents were added to each chamber to create a chemical concentration gradient in the conduit. A strong migration response from the cells was recorded as they migrate across the chemical gradient in both the active and passive devices.

Conclusion

Due to its versatility and biocompatibility, this method has been demonstrated to offer an accessible solution when contrasted to traditional PDMS based microfluidic devices. The simplicity combined with the use of materials familiar to biologists for several decades makes this a unique microfluidic technology to promote utilisation of microfluidics in cell biology.

References

1. Walsh E. J. et al. (2017). "Microfluidics with fluid walls." *Nature Communications* 8(1):816.

Acknowledgments

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Conflicts of Interest

A.F., P.R.C., and E.J.W. each hold equity in iotaSciences Ltd, a company that is exploiting this technology under a licence agreement from Oxford University Innovations. A.F. is an employee of iotaSciences and the company provides a scholarship for C.D.

Importance of dimension reduction in quantifying shape variability in a population

W. M. R. Rusli and A.E. Kedgley

Bioengineering Department, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

Dimension reduction is one of the essential processes in shape analysis. Principal component analysis (PCA) has been used to perform dimension reduction but, because there are a greater number of landmark points (or variables) than samples, this technique suffers from a high dimension low sample size (HDLSS) problem. The aim of this study was to compare two different dimension reduction techniques, namely classical PCA and projection pursuit PCA [1]. The comparison was done on the joint located at the base of the thumb.

Methods

Manual segmentation was done on CT images of 50 specimens (53.53 ± 10.06 years old, 24 right and 26 left hands) to obtain the 3D bone models of the first metacarpal and trapezium. The 3D bone models from the left hand side were mirrored. Alignment and scaling was done using the rigid coherent point drift method (CPD) [2]. Non-rigid registration was done in two stages 1) non-rigid CPD [2] of the down sampled 3D objects based on relevance-based sampling [3] and 2) local optimisation [4]. Projection pursuit PCA [1] was implemented for dimension reduction and compared with classical PCA based on singular value decomposition (SVD). Diagnostic plotting was carried out for all principal components obtained by both types of PCA to determine the effect of the outliers on each of the principal components.

Results & Discussion

Ninety percent of the total variation obtained by both classical and projection pursuit PCA were represented by the first 19 and the first 30 principal components, respectively. As shown in Fig. 1, two of the sample considered as good leverage outliers by classical PCA caused the variance to be increased for the first principal component. The comparison showed that classical PCA was not able to handle outliers in the dataset effectively. This caused the principal components obtained by classical PCA to be dependent. It was difficult, if not impossible, for an HDLSS dataset to pass the assumption of a normal distribution. This is a disadvantage for classical PCA, where each of the principal components are orthogonal. The non-orthogonal properties of the principal components obtained by projection pursuit PCA maximise potential variation.

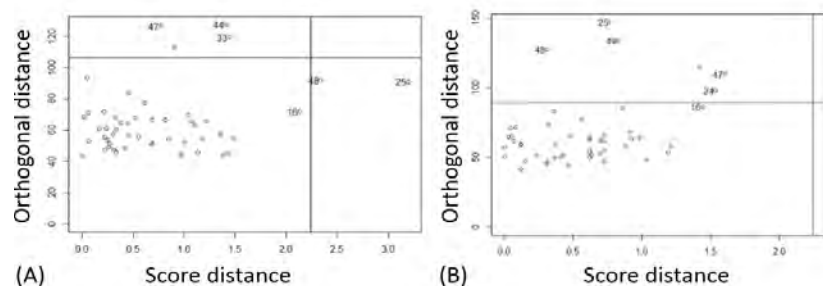


Fig. 1: Diagnostic plot for the 1st principal component for (A) classical and (B) projection pursuit PCA.

Conclusion

Projection pursuit PCA is an alternative dimension reduction technique when performing shape analysis, as it searches for non-orthogonal principal components that can maximise variation.

References

1. Croux C., Filzmoser P. and Oliveira M. R. *Chemom. Intell. Lab. Syst.* 2007; 87(2): 218-225
2. A. Myronenko and X. Song. *IEEE Trans Pattern Anal Mach Intell.* 2010; 32: 102-109.
3. Rodola E et al. *Pattern Recognit Letts.* 2010; 59:41-47
4. Li H., Sumner R.R. and Pauly M. *Computer Graphics Forum.* 2008; 27(5): 1421-1430.

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A Simulation Approach to Guide Therapeutic Intervention in Advanced Heart Failure

M. Capoccia^{1,2}, S. Marconi³, C. De Lazzari^{3,4}

¹Manchester Heart Centre, Manchester University NHS Foundation Trust, UK ²Biomedical Engineering, University of Strathclyde, Glasgow, UK ³National Research Council, Institute of Clinical Physiology, Rome, Italy ⁴National Institute for Cardiovascular Research (I.N.R.C.), Bologna, Italy.

Introduction

Simulation in the context of patient-specific modelling has the potential to become a clinically applicable tool for detailed evaluation of the cardiovascular system and decision-making to guide therapeutic intervention. Models based on pressure-volume relationship and lumped parameter representation of the cardiovascular system may be a suitable choice because of their simplicity and versatility. This approach has great potential for application in advanced heart failure for the selection and optimisation of device-based treatment.

Methods

We sought to investigate the value of simulation in the context of heart failure patients already discussed at a multidisciplinary team meeting with a view to predict or guide further management. CARDIOSIM[®], a software package developed by the Cardiovascular Numerical Modelling Lab based at the Institute of Clinical Physiology and consisting of lumped parameter models, modified time-varying elastance and pressure-volume analysis of ventricular function, was used for this purpose.

Results & Discussion

The outcome of the simulations addressed the value of a more quantitative approach in the clinical decision process with agreement between simulated haemodynamic data and measurements from echocardiography and right heart catheter.

Conclusion

Although previous experience, co-morbidities and the risk of potentially fatal complications play a role in clinical decision-making, patient-specific modelling may become a daily approach for the selection and optimisation of device-based treatment for heart failure patients. Willingness to adopt such a combined approach may be the way forward for further progress.

References

1. Doshi D, Burkhoff D. Cardiovascular Simulation of Heart Failure. Pathophysiology and Therapeutics. *J Card Fail* 2016; 22(4): 303-311.
2. De Lazzari et al. Interactive simulator for e-Learning environments: a teaching software for healthcare professionals. *Biomed Eng OnLine* 2014; 13:172.
3. De Lazzari C, Pirckhalava M (Eds). *Cardiovascular and Pulmonary Artificial Organs: Educational Training Simulators*. Rome, CNR Press, 2017.

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Numerical modelling of the Fontan circulation

J. Aramburu¹, B. Ruijsink², R. Chabiniok^{2,3,4}, K. Pushparajah^{2,5}, J. Alastruey²

¹ Universidad de Navarra, TECNUN Escuela de Ingenieros, Donostia-San Sebastián, Spain. ² School of Biomedical Engineering & Imaging Sciences, King's College London, St Thomas' Hospital, SE1 7EH, London, UK. ³ Inria, Paris-Saclay University, Palaiseau, France. ⁴ LMS, Ecole Polytechnique, CNRS, Paris-Saclay University, Palaiseau, France. ⁵ Department of Congenital Heart Disease, Evelina Children's Hospital, SE1 7EH, London, UK.

Introduction

The Fontan circulation is a surgically created circulation for the management of patients born with a functionally single ventricle. The superior and inferior vena cava are directly connected to the pulmonary arteries in order to ameliorate hypoxemia and prolong survival of patients [1]. The long-term improvement of the outcome of the created Fontan circulation is a challenge, which requests transferring novel methods into cardiology practice [2]. In line with this, the aim of the presented study is to develop a numerical model of blood flow in the Fontan circulation that will be used to study various mechanisms of the failure of this delicate system.

Methods

The reduced-order one-dimensional (1D) and zero-dimensional (0D) forms of the governing equations of haemodynamics are used for the Fontan circulation modelling. The most important large vessels in the Fontan circulation (*i.e.* aorta, superior vena cava, inferior vena cava including the lateral Fontan tunnel, right and left pulmonary arteries) are modelled using 1D models, whereas the rest of the elements of the cardiovascular system are grouped into 0D lumped-parameter models. Initially, the model parameters are taken from the literature [3], and later made patient-specific, with the model parameters being estimated based on pressure and flow measurements taken at various locations across the cardiovascular system using, respectively, cardiac catheterization and cardiovascular magnetic resonance imaging (CMR).

Results & Discussion

Our numerical results show that the shape of pressure and flow pulse waves in the main vessels differ from the waves in the same vessels in the normal circulation. We will present numerical results that show potential mechanisms of Fontan failure (*e.g.* myocardial dysfunction, altered resistance/compliance in the pulmonary or systemic vascular beds, hepatic circulation dysfunction, reduced systemic arterial oxygen content due to pathological shunting, and reduced systemic or pulmonary venous return).

Conclusion

It is of utmost importance to estimate the local properties of cardiovascular system of Fontan patients. This can be achieved by employing a patient-specific haemodynamic model, as was presented in this work. This model could potentially be used for virtually studying the response of the circulation to different actions taken by physicians. The most significant physical parameters, which could be targeted by treatment, and some limitations of our approach, will be further discussed.

References

1. Pundi KN *et al.* *J Am Coll Cardiol.* 2015; 66: 1700-1710.
2. Goldberg DJ. *J Am Coll Cardiol.* 2015; 66: 1711-1713.
3. Mynard JP, Smolich JJ. *Ann Biomed Eng.* 2015; 43: 1443-1460.

Acknowledgements

Authors declare no conflict of interest.

Analysis of the influence of the hepatic artery geometry on microsphere and radiation distributions during radioembolization

J. Ortega¹, R. Antón^{1,2}, J. C. Ramos¹, J. Aramburu¹, A. Bengoechea⁴, A. Rivas¹, G. S. Larraona¹, T. Gómez-Acebo¹, B. Sangro^{2,3}, J. I. Bilbao^{2,3}

¹ Universidad de Navarra, TECNUN - Escuela de Ingenieros, Donostia – San Sebastián, Spain. ² Instituto de Investigación Sanitaria de Navarra (IdiSNA), Pamplona, Spain. ³ Clínica Universidad de Navarra, Pamplona, Spain.

⁴ Tecexsa (Egile), Mendaro, Spain.

Introduction

Radioembolization is a medical treatment for liver cancer [1], and consists of the catheter-based intra-arterial administration of radiation-emitting Y90 microspheres that get lodged in the tumoral area [2]. The purpose of this study is to analyze the influence of the geometry of the hepatic artery (HA) on microsphere and radiation distributions. To do so, numerical simulations of particle–hemodynamics in the HA were performed using two types of commercially available microspheres in two geometries: an idealized HA and a patient-specific HA.

Methods

An Euler–Lagrange coupled approach was used to solve the governing equations of blood flow and microsphere transport in the discretized geometries. The physiologically realistic boundary conditions (BCs) were taken from previous work [3]. The solver Fluent® 17.1 (ANSYS® Inc, Canonsburg, PA) was used for the numerical resolution of the equations.

Results & Discussion

Results show marked differences in the microsphere and radiation distributions for both geometries, therefore suggesting that the HA geometry plays an important role in the microsphere distribution. However, if the effect of the upstream tortuosity is taken into account via tortuosity-simulating BCs, the idealized HA could potentially be a valid surrogate of the patient-specific HA for analyzing the influence of some treatment parameters, on the microsphere and radiation distributions.

Despite the fact that the idealized HA does not represent the full patient-specific HA flow patterns, results show that the idealized HA is a simple, fast, and valuable model to study numerically the influence of the aforementioned parameters on microsphere distribution. Moreover, the influence of the type of microspheres on microsphere distribution will be discussed.

Conclusion

An idealized HA with tortuosity-simulating BCs could be a feasible alternative to the patient-specific HA in evaluating the influence of treatment parameters in the microspheres and radiation distributions in the liver by performing numerical particle–hemodynamics simulations.

References

1. Sangro B *et al.* *Semin Liver Dis* 2014; 34: 435-443.
2. Salem R *et al.* *J Vasc Interv Radiol.* 2006; 17: 1251-1278.
3. Aramburu J *et al.* *Int J Num Method Biomed Eng.* 2017; 33: e02791.

Acknowledgments

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Optimisation of Proactive Therapy for Atopic Eczema by Model Predictive Control

A. G. Giannari, M. D. A. van Logtestijn, P. Christodoulides and R. J. Tanaka
Department of Bioengineering, Imperial College London

Introduction

Atopic Dermatitis (AD), or eczema, is a chronic inflammatory skin disease that affects up to 25% of global paediatric population and bears a high medical and socioeconomic burden. The current mainstay of AD treatment is topical application of corticosteroids and emollients, but lacks consensus regarding their effective usage in terms of potency, duration and frequency. We recently developed a mathematical model of AD pathogenesis [1] that reflects the complex dynamic interplay between environmental stressors, immune responses and skin barrier integrity. We further proposed a computational method to suggest personalised treatment strategies for individual virtual AD patient cohorts, by recursively solving optimal control problems using a differential evolution algorithm [2]. However, the proposed method was computationally expensive due to the hybrid nonlinear nature of the mathematical model of AD pathogenesis.

Methods

We applied Model Predictive Control (MPC) to the mathematical model of AD pathogenesis to design optimal and personalised treatment strategies for AD. We specifically consider designing treatment schedules for a 'proactive therapy' [3] for long-term management of moderate to severe AD symptoms. Proactive therapy aims to first achieve remission (stop inflammation) by continuous application of corticosteroids, and then prevent AD flares (inflammation) while achieving skin barrier stabilisation by intermittent use of low-dose topical corticosteroids. We linearized and discretized the model and used it to design an MPC that determines the optimal schedule for daily application of corticosteroids to achieve remission. The MPC obtains the daily measurement of the disease state from the virtual AD patient (mathematical model of AD), predicts the disease progression using the linear discrete model, and calculates the optimal dose of corticosteroids to be applied that minimizes the cost function. The calculated dose of corticosteroids is then applied to the virtual AD patient, whose disease state is updated.

Results & Discussion

We demonstrated that the MPC controllers designed by our proposed method can suggest optimal treatment strategies of AD at a much lower computational cost than by the previously suggested optimisation method. Effective treatment schedules for proactive therapy can be personalised by adapting the parameters of the model according to the severity of the AD symptoms and responsiveness of each patient to the treatment. We further identified the importance of the appropriate tuning of the controller parameters, reflecting the penalties on the total amount of corticosteroids applied and the duration of treatment. While this work assumed that all the disease states of the virtual patient are measurable and that there are no uncertainties associated with the model, it demonstrates a proof-of-concept for the use of MPC to inform the design of such personalized effective treatment schedules for proactive therapy.

References

1. E. Dominguez-Huttinger et al, "Mathematical modelling of Atopic Dermatitis reveals double switch mechanisms underlying four common disease phenotypes", *Journal of Allergy and Clinical Immunology*, vol. 139, no. 6, pp. 1861-1872e7, 2017.
2. P. Christodoulides et al, "Computational design of treatment strategies for proactive therapy on Atopic Dermatitis using optimal control theory", *Philosophical Transactions of the Royal Society A*, vol. 375, 2017.
3. A. Wollenberg and L. M. Ehmann, "Long term treatment concepts and proactive therapy for atopic eczema", *Annals of Dermatology*, vol. 24, no. 3, pp. 253-260, 2012.

Aging Health Behind an Image: Quantifying Sarcopenia and Associated Risk Factors from Advanced CT Analysis

P. Gargiulo^{1,2}, K. J. Edmunds¹, M. K. Gíslason¹, S. Sigurðsson³, V. Guðnason³

¹Institute for Biomedical & Neural Engineering, Reykjavík University, Reykjavík, Iceland; ²Department of Science, Landspítali, Reykjavík, Iceland; ³Icelandic Heart Association (Hjartavernd), Kopavogur, Iceland

Introduction

Sarcopenic muscular degeneration has been consistently identified as an independent risk factor for mobility loss, falling, disability, and high mortality in aging populations, and despite its increasing prevalence in an ever-aging world, standardized quantitative definitions for the diagnosis and etiology of sarcopenia remain debated. Extant literature has realized the quantitative potential of computed tomography (CT) image analysis to characterize skeletal muscle volume and composition, yet most studies report numerous incongruities in employed methodology. Motivated by this disparity in standardization, we propose a novel tool for quantifying muscle quality named nonlinear trimodal regression analysis (NTRA).

Methods

Defining HU distributions with the NTRA method begins with a modified methodology for nonlinear regression analysis. First, the general equation for each distribution is defined as a quasi-probability density function by summing two skewed and one standard Gaussian probability density functions, (φ) , described by **Equation 1** and **Fig. 1**:

$$\sum_{i=1}^3 \varphi(x, \mu_i, \sigma_i, \alpha_i) = \sum_{i=1}^3 \frac{N_i}{\sigma_i \sqrt{2\pi}} e^{-\frac{(x-\mu_i)^2}{2\sigma_i^2}} \operatorname{erfc}\left(\frac{\alpha_i(x-\mu_i)}{\sigma_i \sqrt{2}}\right) \quad (1)$$

where N is the amplitude, μ is the location, σ is the width, and α is the skewness's of each distribution – all of which are iteratively evaluated at each HU bin, taken as the dependent variable, x . This definition results from the hypothesis that each HU distribution is trimodal, in that they consist of three separate tissue types whose linear attenuation coefficients occupy distinct HU domains: namely, fat [-200 to -10 HU], loose connective tissue and atrophic muscle [-9 to 40], and normal muscle [41 to 200]. Utilizing this definition, a patient-specific distribution function based on 11-parameter is generated [1].

Results & Discussion

We tested the NTRA model with some aging comorbidities and physiological measurements extracted from the AGES-dataset [2] (**Fig. 2**).

Conclusion

Further testing of our method as a new gold standard for quantitative muscle assessment is a crucial step in ultimately proving how aging health can be optimally interrogated and defined.

References

1. Edmunds, K. et al. (2018). Advanced quantitative methods in correlating sarcopenic muscle degeneration with lower extremity function biometrics and comorbidities. PloS One, 13(3), e0193241
2. Lang, T. et al. (2010). Computed tomographic measurements of thigh muscle cross-sectional area and attenuation coefficient predict hip fracture: the health, aging, and body composition study. Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research, 25(3), 513–9

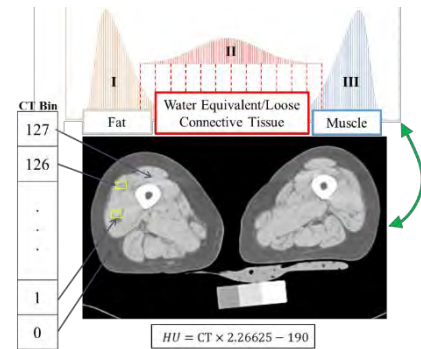


Fig. 1: The three soft tissue components that generate trimodal HU distributions. [1]

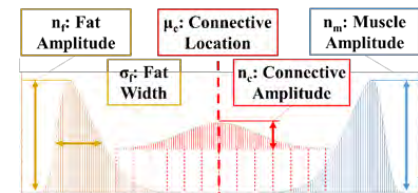


Fig. 2: Example illustrating NTRA parameters with linear sensitivity ($R^2 > 0.85$) to isometric leg strength.

Aorta remodelling in babies born with hypoplastic left heart syndrome

E. Sauvage¹, G. Biglino², T-Y. Hsia¹, A. Taylor¹, S. Schievano¹

¹ University College London, Institute of Cardiovascular Science,

² Bristol Heart Institute, Bristol Medical School, Department of Translational Health Sciences

Introduction

Children born with hypoplastic left heart syndrome (HLHS) require complex surgery of the heart and vessels just after birth to ensure survival. As part of their first surgical intervention, it is often necessary to add a piece of tissue (patch) in order to enlarge the aorta which is too small to be otherwise compatible with life [1,2]. The vessel is remodelled by sewing a patch in order to partially restore the systemic circulation. Such major interventions often involve complications that require regular follow-up of the patient and life-long support, with problems related specifically to the patch itself. It is therefore important to optimise the shape, size and the mechanical properties of the patch.

Methods

The present work is based on patient data retrospectively collected at Great Ormond Street Hospital for Children, London, UK. In order to study the patch mechanics, a patient specific geometry is generated from medical images obtained by a post patch implantation scan. Statistical shape modelling is used to generate an average shape from the geometry cohort. Following this step, two distinct zones are identified: one corresponding to the native aortic wall, and the other to the patch material. The influence of the patch on local blood flow in the aorta is studied in silico via a fluid-structure interaction simulation. Physiological flow boundary conditions are imposed in the region of interest where appropriate.

Results & Discussion

Early fluid structure simulation results have demonstrated a strong influence of the material properties mismatch between the patch and the native aortic tissue on local haemodynamics of HLHS patient aorta. We present data that support this hypothesis and discuss potential paths to obtain an improved patch design.

Conclusion

Patient-specific modelling of aortic patch has the potential to improve the overall quality of surgical procedures in HLHS patients. Statistical shape modelling in combination with fluid-structure interaction analysis preserves the essential geometric features of a set of patient morphologies and allows us to obtain previously inaccessible insight into the patch mechanics.

References

1. Gargiulo G. et al. A new patch for the norwood procedure. *Ann Thor Surg*, 1999.
2. da Silva J.P et al. Hypoplastic left heart syndrome: the influence of surgical strategy on outcomes. *Arquivos brasileiros de cardiologia*, 2007.

Acknowledgments

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The authors listed above declare no conflicts of interests.

A wearable, modular, high-density diffuse optical tomography system H Zhao, D Chitnis, N E Everdell and R J Cooper

Biomedical Optics Research Laboratory, Department of Medical Physics and Biomedical Engineering, UCL, London WC1E 6BT, UK. Email: hubin.zhao@ucl.ac.uk

Introduction

Diffuse optical tomography (DOT) is an extension of near-infrared spectroscopy (NIRS) [1] in which multiple sources and detectors of near-infrared light are arranged so as to provide 3D spatial sampling of the target object [2]. The ability to image human brain function using a wearable device has long been a goal of NIRS and DOT research. However, existing systems are either cumbersome, have limited field of view, or provide insufficient channel density to yield 3D images. Our group recently presented the first ever functional images of the human brain obtained using a fibreless, high-density DOT system [3]. Here, we present an extension of this technology that furthers our goal of unrestricted functional imaging of the human brain.

Methods

We have developed a high-density DOT system consisting of twelve independent, light-weight DOT modules that each contain multiple sources and detectors of NIR light. Each module is based on a $30 \times 30 \text{ mm}^2$ printed circuit board (PCB), on which were mounted two dual-wavelength LED sources and four photodiode detectors. Each module also incorporates a motion sensor (Invensense Inc. USA) that provides 3-axis accelerometry data at a rate of 100 Hz. As a demonstration of the utility of this technology, we arranged the modules in a 2×6 pattern (Fig. 1), which is sufficient to cover the entire adult somatomotor cortex. In the first neuroimaging study of its kind, we applied this wearable system to image the somatomotor cortices of a group of healthy adults during a series of naturalistic movement tasks, including walking and texting.

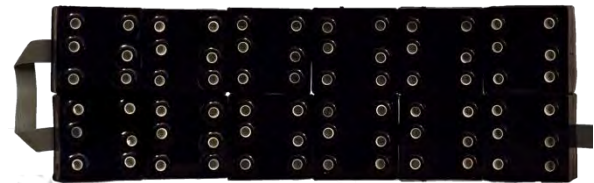


Figure 1. The 12-module high density DOT system

Results & Discussion

In the 2×6 arrangement, the fibreless DOT imaging device provides ~ 700 viable DOT channels, with a spatial density of $\sim 6 \text{ channels/cm}^2$.

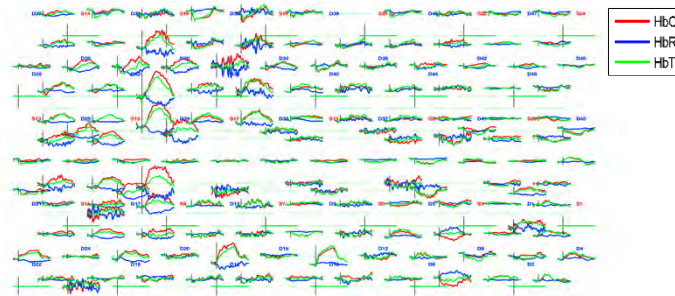


Figure 2. Haemodynamic responses during right unimanual texting and walking. Note the large left-sided (contralateral) functional response.

Preliminary results demonstrate contra-lateral functional responses during unimanual texting. Unimanual texting performed during walking yielded similar contra-lateral functional activation but with additional, distinct activation patterns, thought to be associated with gait. Figure 2 shows the channel-wise functional haemodynamic signals obtained during right unimanual texting and walking.

Conclusion

The advancement of fibreless, wearable, high-density DOT will give researchers across a broad range of fields the ability to produce functional images of the human brain outside of the laboratory environment.

References

1. D. A. Boas *et al.*, *Neuroimage* 85(Pt 1), 1–5 (2014).
2. A. Bluestone *et al.*, *Opt. Express* 9(6), 272–286 (2001).
3. Chitnis *et al.*, *Biomed. Opt. Express* 7(10), 4275–4288 (2016).

A Scalable and Versatile Method for Fabricating Highly-Directional Optical Ultrasound Sources for Minimally Invasive Imaging

H. C. Pauw¹, E. J. Alles^{1,2}, S. Noimark^{1,3}, A. E. Desjardins^{1,2}

¹Department of Medical Physics and Biomedical Engineering, University College London, UK. ²Wellcome / EPSRC Centre for Surgical and Interventional Sciences, University College London, UK. ³Department of Chemistry, University College London, UK

Introduction

Optical ultrasound generation has been demonstrated as a viable alternative to piezoelectric technology. Optical ultrasound sources generate strong, broadband signals and are readily miniaturised [1], and hence are ideally suited to minimally-invasive applications. Here, a simple casting-based fabrication technique is presented that allows for the fabrication of sound generating structures of arbitrary geometry. This is shown through the production of miniature, highly directional optical ultrasound generators. Such directional sources utilise spatial confinement rather than image reconstruction to achieve high lateral imaging resolutions, verified here through imaging of phantoms and *ex vivo* tissue samples.

Methods

Optical sources generate ultrasound *via* the photoacoustic effect: pulsed laser light is absorbed within an optically absorbing structure, and the resulting temperature increase generates a pressure increase due to thermoelastic expansion. Here, composite optical ultrasound sources were fabricated by first coating a ball bearing (radius: 3.4 mm, acting as a negative mould) with an optically absorbing coating. This coating was then integrated into an optically transparent elastomeric host material (polydimethylsiloxane (PDMS), exhibiting a high thermoelastic expansion coefficient) injected into a connected cylindrical mould (diameter: 2 mm). Illuminating the resulting concave structure resulted in the generation of a weakly focussed pressure field that was characterised using a needle hydrophone. In addition, the composite optical ultrasound generator was paired with a fibre-optic ultrasound detector [2] and mechanically translated to obtain all-optical ultrasound images without the need for image reconstruction.

Results & Discussion

The resulting optical ultrasound source generated broadband (2-20 MHz) signals with a peak-to-peak pressure >165 kPa in the geometrical focus. The acoustic beam waist, and hence lateral resolution, was found to be <1 mm for axial distances between 1 and 7 mm, as was confirmed through imaging of the wireframe phantom. Imaging of an *ex vivo* swine carotid sample showed that the fabricated optical ultrasound source could be used to determine clinically relevant parameters, such as vessel wall thickness.

Conclusion

In this work, a scalable fabrication method is presented for the manufacture of millimeter scale, highly directional optical ultrasound sources. Such sources can be integrated into, e.g., steerable catheters to enable novel, minimally-invasive imaging and therapeutic applications of optical ultrasound.

References

1. Noimark and Colchester *et al.*, Adv Funct Mat 28(9), 2018
2. Guggenheim *et al.*, Nature Phot 11(714), 2017

Registration of Histological Images to Post-Mortem MRI

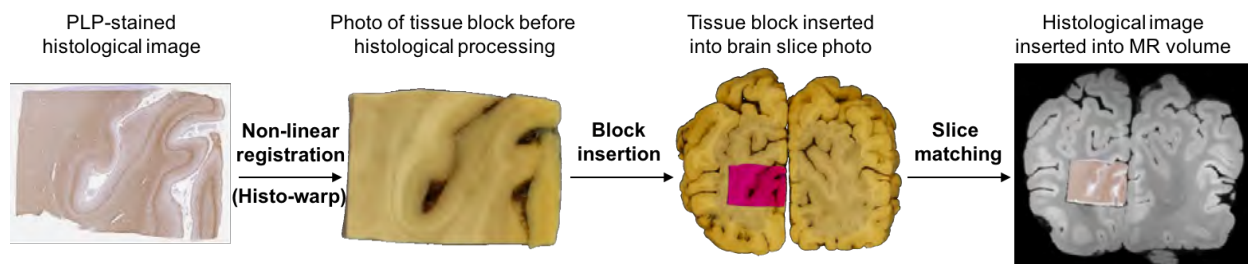
Istvan N. Huszar^{1,2}, Karla L. Miller^{1,2}, Menuka Pallegage-Gamarallage², Olaf Ansorge², Christopher Mirfin³, Mattias P. Heinrich⁴, and Mark Jenkinson^{1,2}

¹Wellcome Centre for Integrative Neuroimaging (WIN), University of Oxford, Oxford, UK, ²Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK, ³Sir Peter Mansfield Imaging Centre, University of Nottingham, Nottingham, UK, ⁴Institute of Medical Informatics, Universität Lübeck, Lübeck, Germany

Introduction

Establishing a clinically useful quantitative mapping between microstructural features and MRI signals requires accurate spatial alignment between MRI and histology. This is hindered by the ill-conditioned problem of slice-to-volume registration, the three-orders-of-magnitude resolution mismatch, the inherent differences in image contrast, and the artefacts related to tissue processing. Here, we present a semi-automated prototype of a fully automated registration pipeline that can accurately align digital histological images with 3-dimensional whole-brain MRI.

Methods



Multi-modal MRI [1] was acquired from post-mortem brains, photographs were taken during dissection of the brains [1], histological sections were digitised using an Aperio® slide scanner, and a novel registration pipeline was implemented using Python 3.6. Deformable registration [2] was used to align histological images with block-face photographs of the corresponding tissue blocks, and to insert the blocks into the brain slice photographs. Slice-to-volume registration was achieved by fitting a polynomial surface to 20 hand-annotated anatomical landmarks in MRI space, then resampling the MR at surface points and performing deformable registration [2] to the slice photo.

Results & Discussion

Five different PLP-stained histological images were registered to a structural MR image from the same subject. A representative result is shown in the rightmost panel of the figure. Registration accuracy was found to be almost exclusively dependent on slice-to-volume registration. The average distance between manual and final alignments of the segmented slices was measured to be 0.84 mm at 100 anatomically identifiable points (20 points per slice).

Conclusion

The proposed method provides a reliable and efficient alternative to existing methods that require full-slice whole-brain histology. Work is in progress to make the pipeline fully automated.

References

1. Pallegage-Gamarallage, M., et al. *BMC Neuroscience*, 2018; 19(1), 11.
2. Heinrich, M.P., et al. *Med Image Anal.* 2012; 16:1423-1435.

Acknowledgments

Tissue was provided by the Oxford Brain Bank. Funding was provided by EPSRC, MRC [EP/L016052/1] and Wellcome Trust.

BioMedEng18

Locally activated nanodroplets and high frame rate imaging for real-time flow visualization – preliminary in-vivo demonstration

M. Toulemonde¹, G. Zhang¹, K. Riemer¹, P.D. Weinberg¹, M.X. Tang¹

¹Department of Bioengineering, Imperial College London, London, UK, SW7 2AZ, United Kingdom

Introduction

Blood flow visualisation and quantification with microbubble (MB) contrast agents using High-Frame-Rate (HFR) ultrasound has been investigated but the real-time feedback is limited because of the high computational cost. Nanodroplets have been investigated as an alternative to MB, due to their smaller size and longer half-life. However, their potential use as a flow indicator has not been fully explored. The aim of this work is to demonstrate the feasibility of real-time flow pattern visualization *in-vivo* using HFR ultrasound acquisition and locally activated nanodroplets.

Methods

The *in-vivo* acquisitions have been acquired on a New Zealand White (NZW) rabbit with an intravenous bolus injection (0.1ml) of decafluorobutane (DFB) nanodroplets (10^{10} droplets/mL). The nanodroplets were activated with focused waves (10-cycle, 4MHz) at 15mm near an arterial bifurcation and imaged with a HFR diverging transmission (3 angles, 1-cycle, 8MHz, 4000Hz). Standard deviation (STD) of 51 consecutive images was performed before log compression. All experiments complied with the Animals (Scientific Procedures) Act 1986 and were approved by the Local Ethical Review Process Committee of Imperial College London.

Results & Discussion

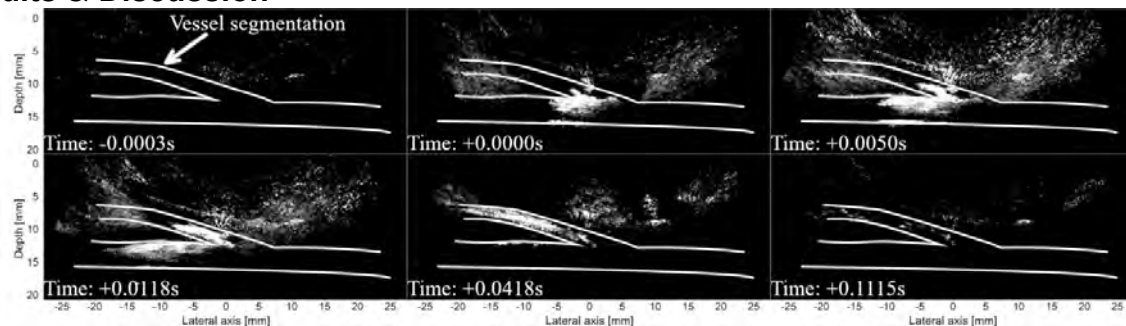


Figure: HFR B-Mode acquisition before and after nanodroplets activation in a New Zealand White rabbit.

The figure shows STD frames before and after activation of nanodroplets with a manual segmentation of a bifurcation vessel. The activated nanodroplets highlight the flow in the bifurcation which is slower than in the aorta. After 0.1s, most of the activated nanodroplets have been washout and the activation and acquisition processes can be simply repeated in real-time. Side lobes artefacts are visible on images due to the insufficient compounding angles and artefacts can be reduced by some further processing.

Conclusion

In this work, we showed that locally activated DFB nanodroplets present an opportunity to introduce indicator into flow non-invasively with a high temporal resolution. Results will be further processed and compared to speckle blood flow analysis for further flow analysis.

Acknowledgments

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Microdomain Structure and Mechanical Properties of Lipid Monolayers Mimicking Red Blood Cell Membranes

B.-D. Lechner¹, C.P. Winlove ¹, P.G. Petrov ¹

¹ School of Physics, University of Exeter, EX4 4QL Exeter

Introduction

Red blood cells (RBCs) have remarkable mechanical properties that are major determinants of blood flow. This is made possible by the unique structure of the erythrocytes. The lipid membrane accounts for the bending rigidity of RBCs whereas the membrane skeleton, made up of a network of spectrin dimers sparsely anchored to the lipid membrane, regulates the area and shear elasticity.[1] Deformation of RBC is a key property to ensure efficient passage through the microcirculation. A number of diseases such as diabetes are related to changes in the RBC's deformability and their physical properties caused by oxidative stress.[2] To reduce the complexity of the system, model membranes and lipid monolayers have been used to determine membrane properties.[3]

Methods

We investigate the microdomain structure of synthetic lipid monolayers mimicking the composition of the inner or outer leaflet of erythrocyte plasma membranes by means of the Langmuir trough technique coupled with fluorescence microscopy, grazing incidence X-ray diffraction and X-ray reflectivity (GIXD) to study domain structures. Surface relaxation (dilatational rheology) is used to quantify the dynamic interfacial rheological properties of the lipid film.

Results & Discussion

We show that a replacement of cholesterol by 7-ketocholesterol as a main oxidation product leads to a significant stiffening of the monolayer at surface pressures above ≈ 20 mN/m (Figure1), in the range of the bilayer equivalence surface pressure ($\pi \approx 30$ mN/m). Fluorescence imaging was used to reveal crystallite-like microdomain structures of the monomolecular layers containing 7-ketocholesterol whereas the monolayer with non-oxidized cholesterol features more circular domain shapes. We also report differences in the monolayer organisation as detected by GIXD and x-ray reflectivity.

Conclusion

Oxidative stress could modulate the structure and mechanical properties of lipid monolayers. Removal of cholesterol from RBC inner leaflet does not change the elasticity significantly, but oxidation to 7-ketoChol leads to a drastic stiffening of the monolayer especially at high surface pressures.

References

1. H.W.G. Lim M. Wortis, R. Mukhopadhyay *PNAS* 99, 2002 16766.
2. F.C. Mokken M. et al. *Annals Hematol.* 64 1992 113.
3. H. Brockman, *Curr. Opin. Struct. Biol.* 9, 1999, 438-443.

Acknowledgments

We thank Kibron Inc. for helpful discussions on dilatational rheology and data analysis. This work was supported by the EPSRC under project EP/N007700/1: "Red Cell Physical Properties in Health and Disease"

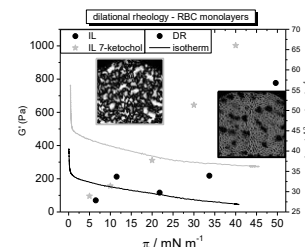


Figure1. Langmuir monolayer compression isotherms, storage moduli from dilatational rheology experiments and fluorescence micrographs at 25 mNm⁻¹ for the RBC inner leaflet mixture with cholesterol (grey) or 7-ketocholesterol (black).

High-throughput microfluidic arraying and imaging of individual skeletal stem cells from human bone marrow isolates

A. De Grazia^{1,2}, N.D. Evans², M.R.R. de Planque¹

¹ Electronics and Computer Science, University of Southampton, Southampton, SO17 1BJ. ² Centre for Human Development, Stem Cells and Regenerative Medicine, University of Southampton, Southampton, SO16 6YD.

Introduction

Human cell populations exhibit a significant extent of functional heterogeneity, which can only be investigated with single-cell methodologies. Flow cytometry is the prominent high-throughput single-cell characterisation technique, detecting the presence, but not the cellular localisation, of fluorescent labels for each cell of the sample. Intracellular localisation is functionally relevant but sub-cellular fluorescence microscopy is very low throughput. We therefore aimed to develop a scalable optical imaging platform for high-throughput microscopy.

Methods

We fabricated an optically accessible two-height microfluidic device consisting of eight chambers, each with a serpentine main flow channel of 25 µm height. Parallel segments of the main channel are connected by cross-channels of 5 µm height. The hydrodynamic flow guides cells from the main channel to the entrance of these height-restricted channels, where cells are retained in binding pockets, presenting an array of up to 1,500 cells per chamber (Fig.1-A).

Results & Discussion

We arrayed samples of human bone marrow mononuclear cells, fluorescently labelling the rare sub-population of skeletal stem cells (SSCs) (Fig.1-B). The fraction of SSCs was in agreement with flow cytometry studies. Arrayed SSCs were imaged with a high-NA objective, revealing a distinct size and morphology as well as clustering of antibody markers at the cell membrane (Fig.1-C). The pattern of staining results different from common erythroid progenitors (EP) with a continuous membrane staining, and putative skeletal stem cells with a punctuated form.

Conclusion

Our microfluidic platform is scalable and combined with automated microscopy will enable fluorescence microscopy characterisation of thousands of individual cells of a heterogeneous population with sub-cellular resolution. We seek to apply this technology to the optimisation of nanoparticle delivery of Wnt signal pathway modulators to SSCs, influencing stem cell differentiation for regenerative medicine applications.

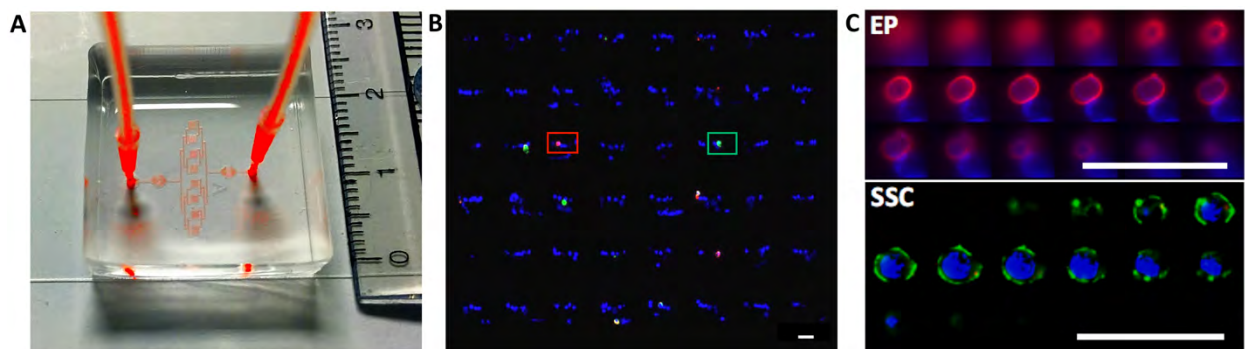


Figure 1 – A. Device; B. Arraying of bone marrow cells; C. Z-stacks of arrayed cells. Bars: 30 µm.

Subject-level Prediction of Segmentation Failure using Real-Time Convolutional Neural Nets

R. Robinson¹, O. Oktay¹, W. Bai¹, V. V. Valindria¹, M. M. Sanghvi^{3,4}, N. Aung^{3,4}, J. M. Paiva³, F. Zemrak^{3,4}, K. Fung^{3,4}, E. Lukaschuk⁵, A. M. Lee^{3,4}, V. Carapella⁵, Y. J. Kim^{5,6}, B. Kainz¹, S. K. Piechnik⁵, S. Neubauer⁵, S. E. Petersen^{3,4}, C. Page², D. Rueckert¹, and B. Glocker¹

¹Biomedical Image Analysis Group, Imperial College London, London, UK. ²Research & Development, GlaxoSmithKline, UK. ³William Harvey Research Institute, NIHR Barts Biomedical Research Centre, Queen Mary University London, UK. ⁴Barts Heart Centre, Barts Health NHS Trust, London, UK. ⁵Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, UK. ⁶Department of Radiology, Severance Hospital, Yonsei University College of Medicine, South Korea

Introduction

Image-analysis pipelines usually require a segmentation step which informs subsequent analyses or diagnoses. It is therefore imperative that such segmentations are of high-quality and we must quickly identify cases where they may have, or are likely to, fail. In a deployed algorithm, where there is no comparable ground truth (GT), this is a challenging task.

Methods

We present a deep-learning methodology which predicts segmentation quality from a 3D (224, 224, 8) cardiac MR image and segmentations of its right-ventricular (RV) and left-ventricular (LV) cavities and LV myocardium. We report Dice Similarity Coefficient (DSC) as a measure of quality. First we train with manual GT DSC from [1] and second, with predicted DSC from reverse classification accuracy [2], which is more realistic as labelled data is often unavailable.

Results & Discussion

We report low mean absolute error (MAE) of 0.03 (SD = 0.04) and MAE = 0.14 (SD = 0.09) on DSC from experiments 1 and 2 respectively. We show excellent true and false positive rates and 97% and 91% binary classification accuracies of 'good' and 'poor' segmentations for the respective experiments on a DSC threshold of 0.70. This is better than in [3]. We note 72% of data with MAE less than 0.05 and only 6% of data forming outliers (DSC $\geq$ 0.12).

Conclusion

We demonstrate a methodology to provide accurate, real-time automated quality control of medical image segmentations in the absence of GT. When paired with an automated segmentation method, it would be possible to provide real-time feedback during image-acquisition indicating if the image is of sufficient quality for the downstream segmentation task.

References

1. Petersen SE *et al.* *JCMR*. 2017; 19(1):18
2. Valindria VV *et al.* *IEEE Trans Med Imaging*. 2017; 36(8):1597-1606
3. Robinson R *et al.* *LNCS. MICCAI 2017*. 2017; 720-727

Acknowledgments

RR is funded by EPSRC CDT in Medical Imaging (EP/L015226/1) and GSK. Work made possible through UK Biobank Application 2964 and associated support: Oxford NIHR Biomedical Research Centre, Oxford BHF Centre of Research Excellence, MRC eMedLab Medical Bioinformatics infrastructure (MRC grant MR/L016311/1) and the BHF (PG/14/89/31194). SEP provides consultancy to Circle Cardiovascular Imaging Inc. (Calgary, Alberta, Canada). BG receives research funding from HeartFlow Inc. (Redwood City, CA, USA).

The effect of including initial strain in the ligaments on the predictive accuracy of the finite element model of the knee joint

M. Qasim¹, H. Hillstrom^{1, 2}, R. Hillstrom^{1, 2}

¹Engineering and Built Environment, Anglia Ruskin University, UK. ²Hospital for Special Surgery, USA

Introduction

Osteoarthritis (OA) is a disease affecting all of the tissues within the diarthrodial joint, that impacts individuals world-wide, and is among the leading causes of disability. Finite element (FE) models of the knee joint have been developed to investigate the initiation, progression and treatment of OA. Three-dimensional continuum representation of the knee ligaments have been shown to predict knee joint kinematics and contact mechanics better than the one dimensional spring elements. The combined effect of collagen fibers stiffness, initial strain, and alignment in the ligaments on the knee joint kinematics was recently reported [1]. Collagen fibers orientation and strain have been shown to vary among different ligaments and cadaveric specimens [2]. The aim of this study is to investigate the role of initial strain and fibers alignment in knee ligaments upon knee joint mechanics using a subject-specific knee FE model.

Methods

A previously validated FE model of a cadaveric knee that included anterior/posterior cruciate ligaments (ACL & PCL) and medial/lateral collateral ligaments (MCL & LCL) was modified for the current study [3]. The Holzapfel-Gesser-Ogden (HGO) hyperelastic material model was implemented to represent ligaments, whereby the ground substance was defined using Neo Hookean (C10 & D), collagen fibers stiffness (k_1 & k_2), and fibers alignment (K) parameters. K varies between 0 and 1/3 where 0 represent perfect alignment while 1/3 represent randomly arranged fibers. K values of 0 and 0.1 were used since the fibers are aligned longitudinally within the knee ligaments. Thermal loading, in conjunction with the expansion coefficient, was used to simulate uniform initial strain in the knee ligaments. Initial strain values of 0% and 10% were simulated in all four ligaments. Passive flexion of the knee joint from 0° to 65° deg was simulated. The corresponding internal/external and varus/valgus rotations were calculated to investigate the effect of initial strain and fibers alignment on knee joint kinematics.

Results

Preliminary analysis showed that inclusion of 10% initial ligament strain altered the corresponding internal/external and varus/valgus rotation by 3% and 4%, respectively. The change in K from 0 to 0.1 did not have a substantial effect upon knee joint kinematics, with the corresponding rotations changing < 0.25%.

Discussion

The current study demonstrates the importance of including initial strain in the FE model to correctly simulate knee joint kinematics. This will be further evaluated by introducing ligament specific initial strains as different ligaments are known to be under varied strains *in situ*. The effect of non-uniform initial strain over different regions of the ligament will also be investigated. This work will improve the subject-specific FE modelling of the knee joint and thus help understanding the biomechanics of OA.

References

1. Hamid NB et al. *J Biomech.* 2017; 65: 1-11
2. Jon OW et al. *J Bone Joint Surg.* 2016; 98(19): 1656-1664
3. Rajshree M et al. *Comp Meth Biomech Biomed Eng.* 2014;17(13):1502-17

Acknowledgements

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BioMedEng18

Analysis of shoulder muscle forces during functional daily activities

C. Klemt¹, D. Toderita ¹, P. Reilly ¹, A.M.J. Bull ¹

¹Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London.

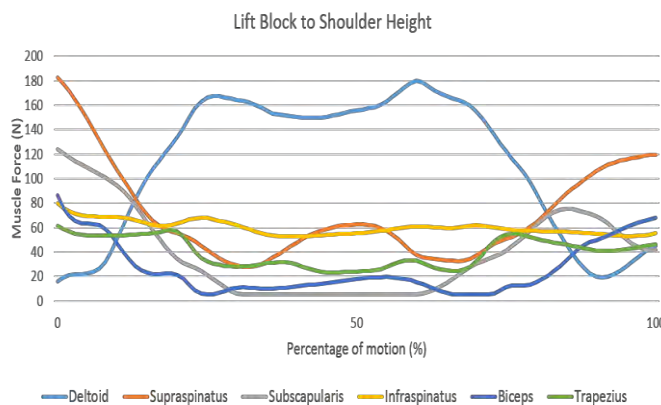
Introduction

The stability of the shoulder in the mid-range of motion is achieved through compression of the humeral head into the glenoid labral concavity through rotator cuff muscle contraction. Therefore, the precise knowledge of shoulder muscle loading during functional daily activities (ADLs) is essential for rehabilitation planning to avoid overloading of surgically repaired tissues. As there is very little knowledge of muscle forces during functional daily activities, with computational studies only focusing on individual tasks and muscles [1], this study aims to analyse shoulder muscle loading during essential functional daily activities to aid rehabilitation planning.

Methods

Shoulder kinematics of 35 participants was recorded using a 10-camera optical motion tracking system. 28 functional daily activities were measured, including tasks of personal hygiene, feeding, dressing, mobility and lifting everyday objects. The motion data served as input into the UK National Shoulder Model (UK NSM), with anthropometric scaling of ten subject-specific shoulder models allowing the accurate prediction of muscle loading during these tasks [2].

Results & Discussion



42% of the ADLs (12/28) are associated with a rotator cuff muscle loading of at least 150 N. The maximum muscle force during functional daily activities was obtained during the lifting block to head height activity, with a supraspinatus load of 268N. As the failure strength of rotator cuff muscle repairs ranges between 200 N and 325 N [3], the data presented in this study suggest that rotator cuff muscles may be loaded beyond their repair strength during functional daily activities.

Conclusion

This study provides comprehensive insight into shoulder muscle loading during functional daily activities in order to aid rehabilitation planning.

References

1. Pandis P, Prinold JAI, Bull AMJ. *Clin Biomech.* 2015; 30: 839-846.
2. Charlton IW, Johnson GR. *Proc Inst Mech Eng.* 2006; 220: 801-812.
3. Smith et al. *J Bone Joint Surg.* 2006;88:2425-2431.

Acknowledgments

This work was supported by the EPSRC through an industrial case PhD studentship with JRI Orthopaedics under Grant EP/M507878/1. The authors declare no conflict of interest with the content of this study.

Regional Specific Effect of Elastin Depletion on the Mechanical Properties of Tendon

M.S.C. Godinho¹, S.E. Greenwald ², H.R.C. Screen ¹

¹ Institute of Bioengineering, Queen Mary University of London, London, E1 4NS, United Kingdom. ² Blizzard Institute, Barts and London School of Medicine and Dentistry, Turner Street, London, E1 1BB, United Kingdom

Introduction

Previous studies have identified functional specialisations in energy storing (ES) tendons, facilitating extensible, elastic mechanical behaviour¹. Of particular note, the matrix between fascicles (interfascicular matrix; IFM) is load bearing and elastic in ES tendons, enabling fascicles to slide when tendon is loaded, for efficient extension and recoil without collagen overload². We recently demonstrated that elastin is localised to the IFM and is more abundant in ES tendons, but is also reduced with ageing³. Together, findings indicate that localisation of elastin to the IFM may be crucial for ES tendon function, and alterations in elastin contribute to the previously observed stiffening and reduced resilience of aged tendons. In this study, we investigate how elastin depletion affects the mechanical properties of IFM and fascicle samples from the ES equine superficial digital flexor tendon (SDFT) and how these relationships are affected by age.

Methods

Five young (3-7 years) and five old (16-19 years) SDFTs were dissected from the forelimbs of horses euthanized for unrelated reasons. 12 groups of 2 intact fascicles (bounded by IFM) and 12 individual fascicles were dissected from each tendon, and divided into three test groups: Fresh, Control and Elastase (4 samples/treatment). Elastase treated samples were incubated in 2units/ml elastase in buffer (15 ml PBS, 0.1 mg/ml soybean trypsin inhibitor) for 18 hours to digest elastin, whilst controls were incubated for the same period in buffer alone. Grouped fascicles were prepared for IFM tests by cutting the opposing end of each fascicle to test 10 mm of IFM in shear. Fascicle and IFM samples were preconditioned with 10 loading cycles and pulled to failure, recording hysteresis during preconditioning, then failure properties.

Results & Discussion

Fascicles showed no significant differences between treatment or age groups. However, IFM samples showed a significant decrease in failure load and maximum stiffness with elastase treatment in both age groups. Data also showed a significant increase in IFM hysteresis, when elastin is removed in both age groups (significant differences between treatments (*) and age groups (a) are highlighted in the table).

	Age Group	Treatment	Failure Load (N)	Failure Extension (mm)	Max Stiffness (N/mm)	Hysteresis (%) Cycle 1	Hysteresis (%) Cycle 10
IFM	Young	Fresh	1.661 ± 0.686	1.991 ± 0.547	1.298 ± 0.361	31.575 ± 5.529	12.626 ± 3.406
		Control	1.473 ± 0.560	2.091 ± 0.595	1.176 ± 0.290	31.565 ± 3.805	13.051 ± 2.421
		Elastase	0.951 ± 0.389 *	1.865 ± 0.587	0.912 ± 0.234 *	39.196 ± 7.172 *	17.283 ± 6.632 *
	Old	Fresh	1.632 ± 0.602	1.728 ± 0.478	1.462 ± 0.409	30.641 ± 5.671	14.471 ± 4.819
		Control	1.489 ± 0.589	1.746 ± 0.454 a	1.282 ± 0.319	33.080 ± 7.065	16.108 ± 6.973
		Elastase	0.855 ± 0.370 *	1.482 ± 0.449 a	0.909 ± 0.242 *	35.292 ± 6.490 *	18.435 ± 12.554

Conclusion

Elastase treatment affected IFM mechanics specifically, suggesting a loss of structural integrity after removal of elastin. The increase in hysteresis matches additional data from our group demonstrating reduced capacity for fascicle recoil in elastin depleted tendons, and points to an important role of elastin in ensuring appropriate local mechanics in tendon.

References

1.Thorpe, C. et al. *Acta Biomater.* 2013; **9**: 7948–7956. 2.Thorpe, C. et al. *J. R. Soc. Interface.* 2012, **9**: 3108–17. 3.Godinho, M. S. C. et al. *Sci. Rep.* 2017; **7**:9713.

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BioMedEng18

A Novel Methodology for Analysis of Lower-Limb Loading with Applications for Implant Testing

J. Gaskell¹, A. Doru¹, D. Harrold¹, E. Tam¹, R. Groves¹, T. Enaigbe¹, M.J. Chappell¹, P. Upadhyay², N.D. Evans¹

¹*School of Engineering, University of Warwick, Coventry, CV4 7AL.* ²*University Hospitals Coventry and Warwickshire (UHCW), .Clifford Bridge Road, Coventry CV2 2DX*

Introduction

The tibia is the most common site of long-bone fractures in adults with approximately 12 for every 10,000 people per year in the UK [1] and a third of these are treated surgically, often using intramedullary (IM) nailing. Failure of the nail or its locating screws can prevent union from occurring: a retrospective analysis [2] found that 2% of 340 tibial IM nails failed, with a total failure rate of 7% when including screws. ASTM F1264-16E1 prescribes mechanical testing regimes for intramedullary fixation devices (IMFDs) recognised by the FDA. This approach permits torsional and bending moment testing, with no axial forces applied to implants. Previous research has examined the failure of IMFDs, applying axial [3, 4] and torsional loads [3], but no empirical justification exists for any loading case currently used.

Methods

Kinematic and kinetic data were collected for healthy volunteer subjects in a Vicon-based gait laboratory during normal walking. Data were exported into OpenSim (Stanford) to calculate muscle forces in the lower leg in order to provide bone-on-bone forces at joints and hence loading patterns in the tibia during normal walking. Muscle forces were then used as inputs to a forward simulation of a simple ankle model to validate against Vicon net ankle moments. CT scans of IMFDs with screws were converted to 3D models for Finite Element Analysis (FEA) using SimpleWare, with loading patterns then investigated using the FEA tool ABAQUS.

Results & Discussion

Significant axial and lateral forces were found, with the axial load having a larger magnitude at the knee than at the ankle. Load in the lateral direction was up to three times bodyweight. Despite intra- and inter-subject variability there was good repeatability and consistency across subjects. Peak stress was observed where the screws meet the nail at approximately 75% of the yield of Ti-6Al-4V. The stresses induced in the screws are sufficient for a potential failure over the order of 10^5 gait cycles. Peak stress in the nail was observed at the ends and the distribution of stress indicates that the most proximal screw is the most likely point of failure.

Conclusion

The results generated suggest that the testing procedures described in F1264-16E1 do not accurately represent the forces that an IM nail may be subject to when implanted in the tibia. However, the FEA geometry currently treats screws and nail as being a homogeneous component and more complex geometries need to be included.

References

1. Curtis *et al.* *Bone*. 2016; 87: 19-26.
2. Ruiz Al, Kealey WDC, McCoy GF. *Injury*. 2000; 31: 359-362.
3. Gaebler *et al.* *Injury*. 2001; 32: 708-712.
4. Knoth *et al.* *Injury*. 2000; 31: 617-626.

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BioMedEng18

Development of pre-clinical test methods for assessing functional performance of osteochondral grafts in the tibiofemoral and patellofemoral joints

L.M.Jennings¹, R.M.Cowie¹, P.Bowland¹, E.Ingham¹, J.Fisher¹

¹ Institute of Medical and Biological Engineering, University of Leeds, UK.

Introduction

There is considerable investment in the development of scaffolds for tissue repair and regeneration in the natural knee and patella, as they have the potential to delay total joint replacement. There is a clinical need both for improved interventions, and for stratified pre-clinical simulation methods to assess the intervention before being offered to the patient. There is currently no capability in the world to pre-clinically simulate and evaluate the biomechanical or tribological function of regenerative interventions in the natural tibiofemoral joint (TFJ) or patellofemoral joint (PFJ), prior to animal studies or clinical trials. In this study standardised pre-clinical simulation methods to assess the functional performance of osteochondral grafts in the TFJ and PFJ have been developed and applied.

Methods

Separate methods were developed for the TFJ and PFJ, using porcine knee joints, which were mounted in a six axis single station knee simulator [1]. Kinematic input profiles were adapted from artificial TFJ and PFJ simulation and scaled for use with porcine tissue. Three experimental groups were investigated; negative control (no intervention), positive control (stainless steel graft 1mm proud) and osteochondral allograft; minimum n=4 per group. All grafts were 6mm in diameter. The graft was inserted into the medial femoral condyle (TFJ) or medial side of the patella (PFJ) and the experimental simulation run for 2 to 3 hours at 1Hz with a lubricant of PBS + 25% (v/v) newborn calf serum. The wear/deformation/damage of the surface of the medial meniscus (TFJ) and opposing cartilage (PFJ) was visually assessed and quantified.

Results & Discussion

For the negative controls, no deformation, damage or wear was visible on the medial meniscus (TFJ) or opposing cartilage (PFJ). For the positive controls, there was substantial damage on the medial meniscus (TFJ) and the femur (PFJ), as well as evidence of graft subsidence. For the osteochondral allografts, there was no visible deformation, damage or wear on the surface of the medial meniscus (TFJ) or opposing femoral cartilage (PFJ) at the end of testing.

Conclusion

Pre-clinical test methods have been developed for the biomechanical and tribological evaluation of osteochondral grafts in physiologically relevant TFJ and PFJ simulation models of osteochondral defect repair. The use of such methods can potentially reduce risk to industry investors, the health service and also patients during introduction of new technology.

References

1. Liu *et al.* *J Biomech.* 2015; 48:3004–3011.

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Functional outcome of the Medacta GMK-Sphere total knee arthroplasty as quantified by a clinical motion capture system

G.F. Tawy^{1,2}, L.C. Biant¹, P.J. Rowe²

¹Stopford Building, University of Manchester, Manchester M13 9PG ²Graham Hills Building, University of Strathclyde, Glasgow G4 0NW.

Introduction

One of the most important outcomes following total knee arthroplasty (TKA) is improvement in joint function. New implants and technologies aim to provide patients with optimum knee biomechanics post-operatively. However, many implants fail to reach patients' expectations, leaving up to 20% of individuals dissatisfied with the outcome of the surgery. The Medacta GMK-Sphere total knee arthroplasty (TKA) is designed to mimic the movements and stability of a natural knee for optimal post-operative function and mobility. However, its functional outcome is yet to be quantified biomechanically.

Methods

A small-scale motion capture system was designed for use in a clinical environment. The system consists of a treadmill and two frames, onto which infra-red cameras and a load cell are mounted. Custom-written software controls the treadmill, and calculates and records biomechanical data. A bespoke cluster-based biomechanical model was developed for use with this system. Patients due to undergo TKA to treat end-stage osteoarthritis were recruited into this study. Functional tests of knee ROM, isometric strengths, and gait kinematics were carried out pre-operatively, six-weeks post-operatively and 1-year post-operatively at routine clinics using the clinical motion capture system. Statistical analyses were carried out on the results ($\alpha = 0.05$).

Results & Discussion

63 patients underwent pre-operative assessments; 30 of whom returned 1-year post-operatively. The operative knee was found to have poorer ROM than the contralateral knee pre-operatively ($100.6 \pm 21.8^\circ$ vs $110.3 \pm 19.2^\circ$; $p < 0.05$). The strengths of the flexors and extensors of the knee were also poorer on the operative side (Flexors: $49.2 \pm 11.7\text{Nm}$ vs $53.9 \pm 18.9\text{Nm}$; $p = 0.026$ & Extensors: $45.2 \pm 10.7\text{Nm}$ vs $47.1 \pm 10.1\text{Nm}$; $p = 0.039$). Gait kinematics were pathological pre-operatively in sagittal, frontal and transverse planes. Post-operatively, knee ROM significantly improved to a mean of 115.1 ± 24.0 in the operative knee. Differences between knees were no longer statistically significant ($p = 0.312$). Gait kinematics also improved, especially in the frontal plane, but some pathological traits remained in the sagittal plane (Figure 1). Despite these improvements, knee strength decreased bilaterally post-operatively (Flexors: $44.3 \pm 3.7\text{Nm}$ vs $45.8 \pm 4.5\text{Nm}$; $p = 0.941$ & Extensors: $44.3 \pm 7.6\text{Nm}$ vs $44.6 \pm 6.7\text{Nm}$; $p = 0.803$).

Conclusion

The Medacta GMK-Sphere TKA improves knee kinematics enough within the first year to allow patients to carry out most activities of daily living ($>110^\circ$ knee flexion¹), but continued poor knee strength may limit their abilities to complete tasks which are more biomechanically demanding than walking, such as stair negotiation. Patients may therefore benefit from strength training of the quadriceps and hamstrings in order to optimise overall functional outcome.

References

1. Rowe P J *et al. Gait & Posture*; 12(2): 143-155.

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The Effect of Aging on Kinematic Strategy Following Forward Perturbation

N.A. Omo-Dare¹, J.A. Deane ¹, E. Papi ^{1,2}, A.H. McGregor ¹

¹ Department of Surgery and Cancer, Imperial College London, Fulham, W6 8RF, London.

² Department of Bioengineering, Imperial College London

Introduction

Falls are the leading cause of injury-related deaths within the growing aging U.K. population. The balance perturbation paradigm is increasingly being used to examine kinematic strategy relating to falls. This paradigm involves the delivery of balance disturbances using a mechanical perturbation and resultant kinematic strategies are assessed. As we age, this kinematic strategy may change, predisposing us to falls. The aim was to investigate if kinematic differences are present between younger (≤ 30 s) and older adults. (> 30 s).

Methods

Forty-six healthy volunteers divided into two groups; ≤ 30 s and > 30 s, stood on a platform which moved forwards at unexpected time intervals. A 3-D optical tracking system measured the kinematics of the ankle, knee, hip, pelvic and thoracic and lumbar spinal segments. The joint angles were calculated using the Joint Co-ordinate System convention. Three perturbation trials were averaged and analysed for differences in joint range-of-motion and variability in the timing of movement within a "perturbation cycle".

Results & Discussion

A general trend of decreased range-of-motion with increased age was observed in all leg joints. There was a significant reduction in right ankle range-of-motion (by 2.58° ; $p < 0.05$) and in maximum ankle flexion (by 6.29° ; $p < 0.01$) in the > 30 s. Significant reduction was also seen in older individuals right knee maximum/minimum flexion (by 5.90° ; $p < 0.01$ and 8.59° ; $p < 0.01$). Maximum knee flexion occurred at a significantly different time throughout the perturbation cycle (≤ 30 s: 93% ($\pm 5\%$), > 30 s: 66% ($\pm 24\%$)). Greater variability in the timing of maximum ankle and knee flexion within the older cohort was also evident. This variability illustrates a diversity in ankle-strategy that is not observed within the younger cohort.

Conclusion

There are significant differences in joint range-of-motion and timing of strategy between ≤ 30 s and > 30 s. This indicates that aging changes kinematic strategy and needs to be a consideration within perturbation studies used to investigate pathology.

References

1. De Freitas P, Knight C, Barela J. Postural reactions following forward platform perturbation in young, middle-age, and old adults. *Journal of Electromyography and Kinesiology*. 2010;20(4):693-700.
2. Tsai Y, Hsieh L, Yang S. Age-related changes in posture response under a continuous and unexpected perturbation. *Journal of Biomechanics*. 2014;47(2):482-490.
3. Grood E, Suntay W. A Joint Coordinate System for the Clinical Description of Three-Dimensional Motions: Application to the Knee. *Journal of Biomechanical Engineering*. 1983;105(2):136.

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BioMedEng18

Control of a Robotic Hand with an EMG-driven, Real-time Biomechanical Computer Model

E.K. Chadwick¹, D. Blana¹, A. Krasoulis², K. Nazarpour²

¹*Institute for Science and Technology in Medicine, Keele University, Stoke-on-Trent, ST4 7QB, UK* ²*School of Engineering, Newcastle University, Newcastle upon Tyne, NE1 7RU, UK.*

Introduction

Current prosthetic hands have the same number of joints as human hands, and are capable of performing complex movements involving individual finger motions. However, a user's ability to control the hand is limited by the availability of information on what they are trying to achieve. Our aim is to enable natural control of prosthetic hands by feeding electrical signals from residual muscles through a biomechanical computer model of the hand to interpret the desired action. We have previously demonstrated that our computer model runs faster than real time [1]. Here we drive the model with EMG and test how well the model movement matches the intended movement. Moreover, we connect the model to a physical robotic hand, and test whether the combination of model and hardware is fast enough for prosthesis control.

Methods

The robotic hand used in this study was a Prensilia IH2 Azzurra. The computer model of the hand presented in [1] was simplified to match the robotic hand: the wrist was fixed, and all abduction/adduction degrees of freedom were removed, as well as all muscles that cross only the wrist. Four surface electromyography (EMG) sensors recorded the activity of flexor and extensor muscles in the forearm. Following [2], the EMG signals were rectified and processed through an exponential moving average filter. Participants were asked to move their hand to a number of postures, and their EMG signals were used to drive the model. In a separate experiment, we connected the model to the robotic hand, and quantified the time required for all processing steps.

Results

Preliminary data from one participant show that the model achieved the correct posture with 93% accuracy. When the robotic hand was included, its position was updated every 100ms, and within that time: (a) EMG was recorded and processed, which took an average of 1.6ms. (b) The model was simulated for 25 timesteps of 4ms. The CPU time required for each step was 0.49ms, thus the simulation speed was 9.3 times faster than real time. The 25 steps took an average of 12.3ms. (c) The model position was sent to the robotic hand, which took an average of 2.3ms. The overall time required was 16.2ms out of 100ms.

Discussion

We have demonstrated that our model interprets the desired action with high accuracy, and combined with real hardware, it runs fast enough for prosthesis control. In fact, the combination of all processing steps leaves 83.8ms out of 100ms free, which could be used to incorporate force feedback from fingertip sensors to enable control of grip.

References

1. Blana, D., Chadwick, E. K., van den Bogert, A. J., & Murray, W. M. (2017). Comput Methods Biomech Biomed Engin, 20(5), 540–549.
2. Blana, D., Kyriacou, T., Lambrecht, J. M., & Chadwick, E. K. (2016). J Electromyogr Kinesiol, 29, 21–27.

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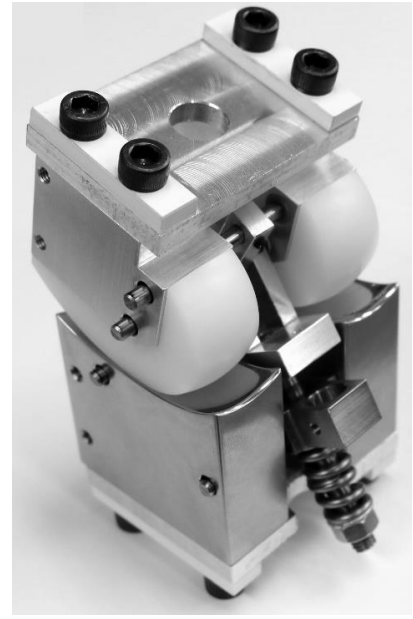
A compliant bicondylar knee for prosthetics, exoskeletons and walking robots:

F. Russell¹, W. Hey¹, R. Vaidyanathan¹, P. Ellison^{3,2,1}

¹ Biomechatronics lab, Imperial College, South Kensington, SW7 2AZ, London ² Dept. of Clinical Medicine, University of Bergen, Norway; ³ Dept. of Orthopaedic Surgery, Haukeland University Hospital, Norway;

Introduction

Bioinspiration in walking robots is typically achieved by adding compliance to the drive train in order to replicate the overall dynamics of human motion [1]. However, those robots that do achieve similar levels of efficiency of gait are often incapable of performing high load tasks [2]. Differently from this, we have focused instead on the specific mechanical properties and geometry of the human knee. In humans the peak knee moments required to perform high load tasks are found to be in the midrange of motion which matches the location of the maximum moment arm. Therefore, we hypothesise that by replicating the human joint design the actuator sizes required for high load tasks such as stair ascent can be reduced.



Methods

Our joint has been designed and manufactured with two smooth curved surfaces (condyles) that slide and roll over each other as the joint rotates; two ligament-like springs hold the joint surfaces together; Actuators drive the joint via cables to represent tendons. As a result, the moment arm the actuators can impart changes as a function of joint angle with the locations of the cable attachment points affecting the shape of this curve. We have then selected these attachment points so that the absolute difference between moment arm of our joint and human moment arm curve is minimised.

Results & Discussion

In the configuration with lowest fitting error the maximum moment arm is 50.4 mm achieved at 44.8° flexion, compared to 51.8 mm at 43.9° found in the human knee [3]. The mean absolute difference between the two is 3.36 mm.

In a computer model we have shown that by using our joint the minimum actuator volume for stair ascent may be reduced by 12% compared to a joint with a constant moment arm.

Conclusion

The bicondylar joint described here is, to the best of our knowledge, the first of its kind to be designed with rolling, sliding, compliant and actuation mechanisms inspired by the human knee. The current results could be significant in future designs of robotic knees for exoskeletons, prostheses and walking where minimum actuator sizes for high load tasks may be reduced.

References

1. S. Seok *et al.* IEEE Int. Conf. In Robotics and Automation (ICRA) 2013; 3307–3312.
2. P. A. Bhounsule, J. Cortell, and A. Ruina. Proc. CLAWAR 2012; 441–448
3. J. Krevolin, M. G. Pandy, and J. Pearce. *J Biomech.* 2004; 37(5): 785–788

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Frequency Dependant Facilitation of Motor Evoked Potentials with Transcutaneous Spinal Stimulation

Al'joboori Y.D^{1,2}, Massey S.J², N Donaldson¹, L.D. Duffell^{1,2}.

¹Department of Medical Physics & Biomedical Engineering, University College London, Malet Place Engineering Building, London, UK. ²Aspire Centre for Rehabilitation Engineering and Assistive Technology, UCL Institute of Orthopaedics and Musculoskeletal Sciences, Royal National Orthopaedic Hospital (RNOH), London, UK.

Introduction

Spinal cord injury results in chronic disability, the majority of lesions are discomplete as some neurons in the spinal cord remain intact while descending control is lost. Electrical stimulation over the spinal cord to encourages spinal circuits to produce leg movements¹ and restore some voluntary movement in motor complete SCI²; with similar effects between epidural or transcutaneous delivery. We recently demonstrated that transcutaneous spinal stimulation (tSS) increased corticospinal excitability, which may in part explain these findings. SS applied transcutaneously additionally activates back muscles, causing discomfort at greater amplitudes. It has been suggested that different stimulation patterns may reduce discomfort with tSS. Specifically, the application of tSS in high-frequency (HF) bursts is associated with reduced discomfort compared to the application of conventional stimulation (Conv)³. In this study we will investigate the effects of different tSS patterns/configurations on corticospinal activity and sensation in 20 non-spinally injured subjects.

Methods

Reflex responses in the lower limb were established using tSS at vertebral levels T11/12 in the supine position. Reflex responses to three waveforms were assessed: Single pulse Conv-Monophasic (Conv; 1 ms pulse width), HF-monophasic (HF-Mono; 1 ms burst of ~10kHz), and HF-biphasic (HF-Bi; 1 ms burst of ~10kHz) with a current limit of 200 mA. Focal TMS was administered over the M1 area of the cortex to establish motor evoked potentials (MEPs) in relevant muscle (recorded by EMG). TMS pulses were delivered 50 ms after trains of 20 single pulses/bursts of Conv or HF SS and motor evoked potential (MEP) amplitudes were measured in the relevant muscle amplitude was assessed. Discomfort was assessed using a visual analogue scale.

Results & Discussion

Single bursts of HF-Bi-SS lacked PRRs at the 200 mA limit. One PRR was attained with HF-Mono-SS at ~3x the current required to elicit a PRR with Conv-SS. Trains of Conv-SS showed facilitation of MEPs whereas, trains of HF-SS indicate a much smaller facilitation.

Conclusion

These early findings suggest that the HF-SS is more comfortable than Conv-SS, however HF-SS is lacking a substantial facilitation of descending drive observed with Conv-SS. Further investigation of HF-SS acting on alternative spinal pathways is required.

References

- 1 Dimitrijevic, M. R., Gerasimenko, Y. & Pinter, M. M. Evidence for a spinal central pattern generator in humans. *Ann N Y Acad Sci* **860**, 360-376 (1998).
- 2 Angeli, C. A., Edgerton, V. R., Gerasimenko, Y. P. & Harkema, S. J. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. *Brain* **137**, 1394-1409, doi:10.1093/brain/awu038 (2014).
- 3 Gerasimenko, Y. *et al.* Initiation and modulation of locomotor circuitry output with multisite transcutaneous electrical stimulation of the spinal cord in noninjured humans. *J Neurophysiol* **113**, 834-842, doi:10.1152/jn.00609.2014 (2015).

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Lossless compression and entropy estimation of neural spike trains

M. Bontonou¹, S. R. Schultz¹

¹*Department of Bioengineering and Centre for Neurotechnology, Imperial College, South Kensington, SW7 2AZ, London.*

Introduction

Neurons propagate information by generating sequences of action potentials (also known as “spike trains”), which can be monitored using electrophysiological (microelectrode) or fluorescence imaging techniques. Spike trains as binary time series, without losing substantial information, provided that digitisation occurs on a timescale comparable to the temporal precision of action potential firing. New developments in large-scale, wireless Brain-Machine Interfaces motivate the development of compression algorithms optimized for such spike trains, in order to transmit these binary time series fast enough, and to store them efficiently. Taking into account redundancies in both time and space, we should be able to compress them without removing any crucial information. We therefore have investigated the use of two lossless compression algorithms, the Context-Tree Weighting (CTW)^[1] and the Burrows-Wheeler transform (BWT)^[2]. Both approaches allow subsequent entropy estimation, to estimate the best achievable compression rates, as well as measuring the complexity of brain dynamics.

Methods

Lossless compression uses a modelling algorithm, such as CTW or BWT, to attribute a probability table to the next symbol according to the previous context. Their efficiency depends on the inherent properties of the data. We chose these two modelling algorithms on the basis of previous studies (CTW has already proven its efficiency on spike trains^[3] and BWT has been used to compress binary time series^[2]). The entropy rate can then be estimated through the computed probability table. Research has already been conducted on entropy estimation of spike trains with CTW^[3]. We applied these techniques to simulated data (“homogeneous Poisson”, Markov Chains, Hidden Markov Models) enabling comparison with the results of other studies^[3], as well as allowing the effect of finite sampling to be assessed. This is a precursor to application of the algorithms to real neurophysiological datasets (electrophysiological and calcium imaging data recorded from the mouse nervous system).

Results & Discussion

We have demonstrated consistent results on simulated data with the CTW algorithm. We are currently applying our approach to real data, and working on comparison of the CTW algorithm with the BWT algorithm, with respect to accuracy on simulated data, and compression efficiency on real data.

Conclusion

This class of algorithms should provide a viable approach both for information estimation for spike train data and for on-the-fly compression of brain-recordings for BMI applications.

References

1. Willems, F. M. J., Shtarkov, Y. M., & Tjalkens, T. J. (1995). The context-tree weighting method: Basic properties. *IEEE Transactions on Information Theory*, 41(3), 653-664.
2. Haixiao Cai, Kulkarni, S. R., & Verdu, S. (2004). Universal entropy estimation via block sorting. *IEEE Transactions on Information Theory*, 50(7), 1551-1561.
3. Gao, Y., Kontoyiannis, I., & Bienenstock, E. (2008). Estimating the entropy of binary time series: Methodology, some theory and a simulation study. *Entropy*, 10(2), 71-99.

All-optical crosstalk-free manipulation and readout of Chronos-expressing neurons

N. S. Soor^{1,2}, K. Pang², P. Quicke^{1,2}, S. Schultz^{1,2}, A. J. Foust^{1,2}

¹Centre for Neurotechnology, Imperial College London

²Department of Bioengineering, Imperial College London

Introduction

All-optical manipulation and readout of neuronal activity has the potential to revolutionise our understanding of neural network structure and function¹. Neurons can be made to express opsins and fluorophores for photoactivation and activity readout respectively. However, the wavelengths used to excite most readout fluorophores cause inadvertent depolarisation of opsin-expressing neurons, thus spuriously influencing network activity. Here we propose the first crosstalk-free activity readout of the fast opsin Chronos² using the deep-red calcium indicator CaSiR-1³.

Methods

Chinese Hamster Ovary (CHO) cells were transfected with Chronos and photostimulated with a blue Light-Emitting Diode (LED, 470nm) and deep-red LEDs (630nm and 660nm) suited for CaSiR-1 calcium imaging. We then observed and compared photocurrents induced by each light source with whole-cell voltage clamp. As a demonstration of crosstalk-free all-optical stimulation and readout, we loaded CaSiR-1 AM into transgenic brain slices expressing Chronos in layer 2/3 cortical neurons to observe calcium transients from photostimulated neurons.

Results & Discussion

Experiments in Chronos-expressing CHO cells demonstrated an absence of photocurrents, and thus optical crosstalk, when illuminating the cells with a red light source suitable for CaSiR-1 calcium imaging. Furthermore, increasing the illumination power and duration had no effect on membrane potential, whilst in control experiments, a 470nm light source suited for Chronos activation induced photocurrents of hundreds of picoamps in the same cells. We therefore expect calcium transients in photostimulated Chronos expressing neurons to arise from blue light illumination, without spurious contribution from red imaging wavelengths.

Conclusion

Previous studies aimed to minimise crosstalk between imaging and photostimulation channels by modulating illumination power or wavelengths, though none fully removed crosstalk. Our strategy eliminates crosstalk with a deep-red indicator spectrally separate from Chronos' absorption. Moreover, the deep-red imaging wavelength penetrates deeper into scattering brain tissue than light from green- or orange-emitting fluorophores previously used for reading out the activity of optically stimulated neural circuits, enhancing applicability to *in vivo* imaging conditions.

References

1. Ronzitti, E. *et al.* Recent advances in patterned photostimulation for optogenetics. *J. Opt. (United Kingdom)* **19**, 113001 (2017).
2. Klapoetke, N. C. *et al.* Independent optical excitation of distinct neural populations. *Nat. Methods* **11**, 338–46 (2014).
3. Egawa, T. *et al.* Development of a far-red to near-infrared fluorescence probe for calcium ion and its application to multicolor neuronal imaging. *J. Am. Chem. Soc.* **133**, 14157–14159 (2011).

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Computational model for the modulation of speech-in-noise comprehension through transcranial electrical stimulation

M.A. Kegler^{1,2}, T. Reichenbach^{1,2}

¹ Department of Bioengineering ² EPSRC Centre for Neurotechnology,
Imperial College, South Kensington, SW7 2AZ, London.

Introduction

Transcranial electrical stimulation (TES) can non-invasively modulate neuronal activity in humans. Recent studies have shown that TES with an alternating current that follows the envelope of a speech signal can increase the comprehension of this voice in background noise [1]. However, how exactly TES influences cortical activity and improves speech comprehension remains poorly understood [2]. Here we present a computational model for speech coding in a spiking neural network and employ it to investigate the effects of TES on the coding of speech in noise.

Methods

We constructed a computational model of a spiking neuronal network that encodes natural speech through entraining network oscillations in the theta and gamma frequency range. We attempted to use the network's output to classify simple acoustic stimuli as well as speech in different levels of background noise. We then simulated the effect of different external currents on the network dynamics as well as on the neural output and the associated speech coding. Finally, we analysed the behaviour of the computational model and its speech classification performance in different conditions to optimize the stimulation paradigm for enhancement of natural speech processing.

Results

The computational model generated coupled oscillations in theta and gamma frequency ranges. In agreement with experimental results the slower theta oscillations reliably predicted the onsets of syllables and provided a temporal reference frame for the faster activity in the gamma band that encoded phonemes [3]. Simulating the effect of simultaneous external current with a range of different temporal patterns we were able to identify the optimal setup that increased neuronal synchrony and improved the neural coding of speech in noise.

Conclusion

The developed model provides an insight into the neural mechanisms through which TES can enhance speech processing. Moreover, our computational model allows to optimize the TES temporal pattern for improving speech-in-noise comprehension.

References

1. Wilsch, A., Neuling, T., Obleser, J., & Herrmann, C. S. (2018). Transcranial alternating current stimulation with speech envelopes modulates speech comprehension. *NeuroImage*, 172, 766-774.
2. Zoefel, B., & Davis, M. H. (2017). Transcranial electric stimulation for the investigation of speech perception and comprehension. *Language, Cognition and Neuroscience*, 32(7), 910-923.
3. Giraud, A. L., & Poeppel, D. (2012). Cortical oscillations and speech processing: emerging computational principles and operations. *Nature Neuroscience*, 15(4), 511.

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PANACEA 2.0: A Wireless, High-Performance Multi-instrument for (Bio)Signals Recording

G.C. Zafeiropoulos^{1,2}, D. O'Hare¹, E.M. Drakakis¹

¹ Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London. ² Centre for Doctoral Training in Neurotechnology, Imperial College, South Kensington, SW7 2AZ, London

Introduction

Accurate and in real-time recording of various (bio)signals has become a necessity in today's clinical/research world [1]. Subsequently, the design of a single instrument that is portable, low-power, high-performance, able to provide multiple types of recordings and their transmission simultaneously, may be considered nowadays as a "sine qua non" modality. This abstract presents PANACEA 2.0, an instrument satisfying each of the aforementioned requirements. It constitutes a recent version of the Panacea instrumentation [2] and an aggressive miniaturisation of a bioinstrument we proposed in the past [3].

Methods

Panacea 2.0 comprised of two "sub-instruments". The first serves as a front-end (FE) device ($115 \times 80 \text{ mm}^2$), which is responsible for the accurate, low-noise data acquisition and their transmission (wired and/or wirelessly) to the second "sub-instrument", serving as a base station, which is responsible for data collection/processing and for providing the necessary signals for voltammetry methods. The FE device is split into two main autonomous sections, potentiometric and amperometric. Both sections are equipped with dedicated 2Mbps ZigBee radio transceivers for wireless data transmission and are designed around a powerful off-the-shelf analog-to-digital converter, offering eight low-power, simultaneous conversion, and 24-bit resolution recording channels with built-in programmable gain amplifiers. Eight potentiometry channels are offered, while only four transimpedance amperometry (TIA) channels are available, supported by a set of dedicated potentiostats. The FE device can be operated independently from the "base station". Finally, both "sub-instruments" are controlled by a small area embedded FPGA module.

Results & Discussion

Preliminary tests confirm the versatility of our poly-instrument. Successfully recorded results include: i) Potentiometry: ECoG signals, EMG, ECG, pH, and several other biopotentials. ii) TIA Amperometry: nA to 10uA recording range. It has been also confirmed that the 16-bit digital-to-analog converters (DACs), provided by the base station, enable the delivery of squarewave and staircase voltammetry. No wireless connection "drop-off" was ever observed.

Conclusion

A novel, highly versatile, battery operated (front-end only) bioinstrument has been presented and its various capabilities have been discussed.

References

1. E. S. Berner (Ed.), *Clinical Decision Support Systems*, Health Informatics, Springer International Publishing, Cham, 2016.
2. Zafeiropoulos GC, Papadimitriou KI, Drakakis EM., *Performance ANd ACcuracy in Electrical BioActivity Recordings (PANACEA): A High-Performance, Wireless, Multi-instrument for Potentiometric and Amperometric Recording of Biosignals*, Measurement; <https://doi.org/10.1016/j.measurement.2018.05.115>
3. Papadimitriou et al. *High-Performance Bioinstrumentation for Real-Time Neuroelectrochemical Traumatic Brain Injury Monitoring*, *Frontiers in Human Neuroscience*. 2016; 10: 1-15.

Acknowledgments

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BioMedEng18

A Database for the Development of Pulse Wave Analysis Algorithms

P. H. Charlton¹, J. Mariscal Harana ¹, S. Vennin ^{1,2}, P. Chowienzyk ², J. Alastruey ¹

¹ Department of Biomedical Engineering, King's College London, King's Health Partners, London, SE1 7EH.

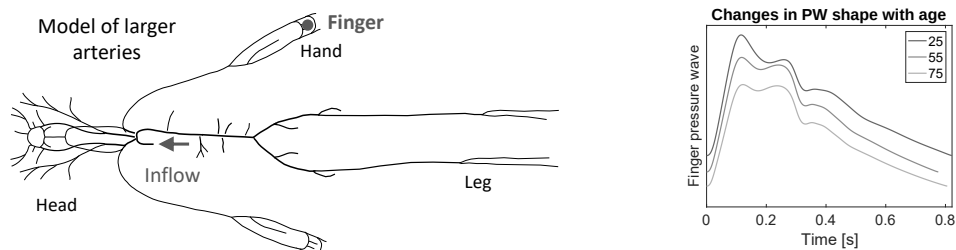
²Department of Clinical Pharmacology, King's College London, King's Health Partners, London, SE1 7EH.

Introduction

The shape of the arterial pulse wave (PW) is a rich source of information on cardiovascular (CV) health, since it is influenced by both the heart and the vasculature. Consequently, many algorithms have been proposed to estimate clinical parameters from PWs. However, it is difficult and costly to acquire comprehensive datasets with which to assess their performance. Our aim was to create a database of simulated PWs under a range of CV conditions, representative of a healthy population.

Methods

Baseline PWs were simulated using 1D computational modelling [1]. CV model parameters were varied across normal healthy ranges to simulate a sample of subjects for each age decade from 25 to 75 years. The model was extended to simulate photoplethysmographic PWs at common measurement sites, in addition to the pressure, flow and diameter PWs produced by the model.



Results & Discussion

The database was verified by comparing simulated PWs with in vivo PWs. Good agreement was observed, with age-related changes in blood pressure and wave morphology well reproduced. The utility of the database was demonstrated by applying algorithms to estimate arterial stiffness, cardiac output and left ventricular ejection time to PWs. The relative performances of several algorithms were compared, and CV factors which reduced algorithm performance were identified.

Conclusion

The database is a valuable resource for development and pre-clinical assessment of PW analysis algorithms [2, 3]. It is particularly useful because it contains several types of PWs at multiple measurement sites, and the exact CV conditions which generated each PW are known.

References

1. Mynard JP, Smolich JJ. *Ann Biomed Eng.* 2015; 43(6): 1443-1460.
2. Vennin S *et al. Hypertension.* 2017; 70(6): 1176-1182.
3. Li Y *et al. Hypertension.* 2017; 69(2): 375-381.

Acknowledgments

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BioMedEng18

Noninvasive Measurement of Wave Speed in Human Ascending Aorta

M Negoita¹, C Manisty², A D Hughes², K H Parker³, A W Khir¹

¹*Brunel Institute of Bioengineering, Brunel University London, UK;* ²*Institute of Cardiovascular Science, University College London, UK;* ³*Department of Bioengineering, Imperial College London, UK*

Introduction

Wave speed, commonly known as Pulse Wave Velocity (PWV) is a measure of arterial stiffness and considered as an independent predictor of cardiovascular risk. Recently, it has been shown that local PWV can be measured by means of ultrasound through successive recordings of diameter and velocity [1]. The aim of this study was to determine PWV in adult ascending aorta, non-invasively, and compare the results of ultrasound and MRI.

Methods

PWV was determined in 20 adults (12 male) from ultrasound images of diameter (long axis view, M-mode) and flow velocity (Apical 5 Chamber, Pulsed Doppler) in the ascending aorta. The Dicom images were recorded using an ultrasound scanner (GE Vivid-E95) and phased array probe 1.5 – 4.5 MHz. The luminal walls were traced by grey-scale thresholding, from which diameter waveform was extracted. Doppler ultrasound was traced using thresholding to extract the velocity waveform. Recordings were taken for 20s and 6 consecutive representative waveforms for each run and In(D)U-loop method was used for all diameter and velocity waveforms [2] to determine the mean value of PWV per participant.

The results obtained from ultrasound measurements were compared with the gold-standard MRI measurements, which were taken using Siemens MAGNETOM Aera 1.5T. The images were analyzed with validated software [3].

Results & Discussion

The mean PWV across all participants using the ultrasound was 3.8 ± 1.1 m/s. The measurements were compared with MRI results showing an average of 4.0 ± 1.7 m/s.

The maximum diameters recorded showed an average of 3.0 ± 0.4 cm using ultrasound while for MRI it was 3.1 ± 0.3 cm. The average of maximum velocity was 1.1 ± 0.2 m/s for ultrasound and for MRI 0.8 ± 0.2 m/s. The measurements and results of ultrasound were similar to those obtained using MRI.

Conclusions

A method for determining PWV in human ascending aorta was developed based on non-invasive ultrasound measurements. The close agreement between the ultrasound and MRI results suggest that the new technique could potentially be used as a screening tool.

Acknowledgements

The authors would like to thank the British Heart Foundation (grant no PG/15/75/31748) for financial support.

References:

1. Madalina Negoita, Alun D Hughes, Kim H Parker, Ashraf W Khir, 'Non-invasive Technique for Determining Local Pulse Wave Velocity in Humans Ascending Aorta', *Computing in Cardiology* 2017, Volume 44:1-4.
2. J Feng and AW Khir. 'Determination of wave speed and wave separation in the arteries using diameter and velocity'. *Journal of Biomechanics*, 2010, 43(3):455-462.
3. A. De Cesare, A. Redheuil, A. Dogui, O. Jolivet, A. Lalande, F. Frouin, E. Mousseaux, A. Herment, 'ART-FUN: an Integrated Software for Functional Analysis of the Aorta', *Journal of Cardiovascular Magnetic Resonance*, 2009, 11(Suppl 1): P182

BioMedEng18

Film bulk acoustic resonator (FBAR) based biosensor for early detection of aggressive prostate cancer.

E. Wajs¹, G. Rughoobur², V. Gnanapragasam³, A. Flewitt¹

¹Electrical Engineering, University of Cambridge, 9 JJ Thomson Avenue, Cambridge, CB3 0FA, UK. ²Microsystems Technology Laboratories, Massachusetts Institute of Technology, 60 Vassar Street, Cambridge, MA02139, USA

³Academic Urology Group, Department of Surgery & Oncology, University of Cambridge, Box 193, CUTRACT office, Cambridge Biomedical Campus Cambridge CB2 0QQ, UK.

Introduction

Prostate Specific Antigen (PSA) remains the most important serum marker currently available for the detection of prostate cancer. Assays available for PSA detection are processed on large analysers at dedicated testing sites, which require samples to be sent away for testing. This leads to delays in patient management and increased administration costs. Thus, the need for point-of-care patient management has led to the development of novel biosensor detection strategies that are suitable for the miniaturization of assays for rapid and accurate PSA detection.

Methods

The thiol molecules were used for the coating of the gold surface (active area) of the FBAR sensor and serve as the attachment points for the monoclonal anti-tPSA antibody. The gold surface coverage with subsequent biological layers was characterised by using atomic force microscopy. The fabricated FBARs were characterized on a coplanar probe station by measuring the electrical admittance (Y) in the frequency range from 0.5 GHz to 3.0 GHz using 150 μm pitch ground-signal-ground radio-frequency (RF) probes connected to a vector network analyzer. For each antigen concentration, 25 devices were tested, and average results were calculated.

Results & Discussion

Here we present a label-free biosensor on a film bulk acoustic resonator (FBAR) for early detection of aggressive prostate cancer. The operation of this sensor is based on the shift that its resonant frequency suffers when a mass is attached to its surface. It is consisted of a thin piezoelectric film (ZnO) deposited between two metallic electrodes and works in the GHz frequency range. The piezoelectric layer transforms the electric signal applied through the electrodes into a mechanical deformation and vice-versa, producing a resonance when a standing wave forms in the structure. The position of the resonance in the electrical domain depends mainly on the thickness of the piezoelectric layer and it shifts towards lower values whenever a mass is firmly attached to its active area.

Conclusion

Experimental results demonstrate that the FBAR biosensor can detect PSA antigen successfully from PBS – buffered samples and serum samples from the hospital without chemical or fluorescent labelling. The proposed FBAR biosensor shows very high sensitivity and selectivity, without the interference of a non-specific binding. The advantages of this sensors are their high sensitivities, small size and low power, which makes them well suited to mobile sensing applications, such as point-of-care medical diagnostics.

Acknowledgments

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Investigating Cancer Invasiveness and Vasculature with a Biomimetic 3D Model and Patient-Specific Cancer Associated Fibroblasts

J. Pape¹, M. Emberton², U. Cheema¹

¹*Division of Surgery and Interventional Science, UCL, HA7 4LP London, UK.* ²*Faculty of Medical Sciences, UCL, W1T 7DN London, UK*

INTRODUCTION: 3D models of cancer (“tumouroids”) are increasingly being used as a platform to demonstrate all crucial aspects of the tumour microenvironment and therefore study disease pathways¹. In this study, we utilized a tissue-engineered biomimetic colorectal cancer model, which recapitulates the solid tumour surroundings including matrix composition, cell spatial configuration and a primitive vascular network to study invasion, matrix remodelling and vasculogenesis.

METHODS: HT29 and HCT116 immortalised colorectal cancer cell lines and CCD841 CoN normal colon cells were used to generate artificial cancer masses (ACM) utilising monomeric rat-tail type 1 collagen (FirstLink, UK) and plastic compression with RAFT™ absorbers (Lonza, Switzerland). These were then nested into a stromal compartment, acellular or containing either HDF or patient-derived cancer associated fibroblast (CAF) samples and HUVEC cells additionally to mouse laminin (Corning, UK) at 50 µg/mL. The resulting tumouroids were analysed, formalin fixed, media samples were taken and extracted for RNA at temporal time points (n=3).

RESULTS: The “invasion” of cancer cells into the stromal compartment within the model was distinctive when compared to the non-cancerous colon normal cells. Phenotypically, the formation of spheroids within the original cancer mass and the outgrowth as cell clusters is a cancer exclusive observation, which was supported by the statistically significant upregulation of invasive markers *MACC1*, *MMP7* and *HSPE* within the cancer type models. CCD841 CoN colon normal cells migrated as single cells and did not form budding cell clusters detaching from the original mass. The addition of CAFs into the stromal compartment increased invasion significantly (>10 fold) but decreased or diminished the development of endothelial networks within the tumouroid models. CAF samples were therefore added to a day 21 established endothelial network and a disruption of the networks could be observed. This was further investigated for molecular pathways responsible.

DISCUSSION & CONCLUSIONS: The results indicate that the tissue-engineered colorectal tumouroid model can be utilized as a novel platform to study cancer invasion patterns and vasculogenesis by comparing to healthy colon cells and looking at specific invasive angiogenic disease markers. Making the model more biomimetic by adding patient-specific CAF samples, allows studying the exact molecular pathways involved in the effect on invasiveness and vasculogenesis. This indicates that CAFs play an essential role not only in invasiveness but also the remodelling of local blood vessels.

REFERENCES: ¹Magdeldin T. Scientific Reports. (7) 44045, 2017.

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BioMedEng18

Human primary high grade serous ovarian carcinoma organoid cultures for disease modelling and drug screening.

Maria Vias¹, Debbie Sanders¹, Filipe Correia-Martins¹, Anna Piskorz¹, James D. Brenton¹

¹ CRUK-Cambridge Institute, University of Cambridge, Cambridge, CB2 0RE

Introduction

High grade serous ovarian cancer (HGSOC) is the commonest histotype of ovarian cancer and is characterised by extreme genomic complexity and dysregulation of DNA damage repair pathways. Overall survival for women with HGSOC has not improved in the last two decades and five-year survival is less than 30%. The majority of the continuous cell lines used as models of this disease are not HGSOC [1]. There is an urgent need for clinically relevant *in vitro* models that could be used to identify therapeutic vulnerabilities.

Organoid culture allows the propagation of normal primary human fallopian secretory and ciliated cells for long-term expansion [2]. As HGSOC originates from the secretory cell of the fallopian tube, we established same culture conditions to the propagation of cancer organoids. We considered an organoid line as successfully established when it had been serially passaged >5 times and been cryopreserved/thawed allowing for their long-term storage [3]

Methods

We have used sWGS, Tagged amplicon sequencing and immunohistochemistry to characterised the organoid lines and the originating tumours. High-throughput drug sensitivity assays were also performed.

Results & Discussion

Success for serial passage success was dependent on the originating primary sample: solid tumour (n=1/10), ascites (n=16/43) or established patient-derived xenografts (n=5/15). Survival rates after cryopreservation was also a limiting factor. We generated 13 HGSOC organoid lines from 10 unique patients and for three patients we have organoids at different time points during patient treatment. Cancer organoid cultures retain the histological architecture and genomic landscape of the original tumour. Direct comparison between primary patient-derived HGSOC spheroids and derived cancer organoids showed highly similar response in *in vitro* drug sensitivity assays.

Conclusion

HGSOC cancer organoids can be derived at reasonable efficiency and accurately recapitulate genomic and response characteristics of patients.

References

1. Domcke et al. Nature communications (2013)
2. Kessler et al. Nature Communications (2015)
3. Lee SH et al. Cell (2018)

Drug Delivery to the Brain using a Rapid Short-Pulse Ultrasound Sequence and Microbubbles

S.V. Morse¹, T.G. Chan², M.J. Copping¹, A.N. Pouliopoulos¹, N.J. Long², J.J. Choi¹

¹ Department of Bioengineering, ²Department of Chemistry, Imperial College London, SW7 2AZ, London.

Introduction

Patients suffering from diseases such as Alzheimer's and glioblastoma currently have no effective treatment available to them because drugs cannot cross the blood-brain barrier (BBB). Focused ultrasound and microbubbles can non-invasively and locally enhance the permeability of the BBB, allowing drugs into the brain.¹ This technology has recently progressed to clinical trials, but concerns with efficacy and safety remain, such as a poor drug distribution and the release of red blood cells and albumin (neurotoxic) into the brain.²⁻⁴ We hypothesised that these adverse effects are caused by the sequence of ultrasound pulses that were emitted into the brain. We have developed a new Rapid Short-Pulse (RaSP) sequence⁵ to improve the efficacy and safety of drug delivery to the brain in vivo.

Methods

A RaSP ultrasound sequence is composed of short μ s pulses emitted at a kHz rate. Ultrasound (1 MHz) was focused at 350 kPa on the left hippocampus of mice using RaSP ($n = 5$, pulse length (PL): 5 cycles; pulse repetition frequency: 1.25 kHz; burst length: 10 ms) or long pulse sequences ($n = 5$; PL: 10,000 cycles; repetition frequency: 0.5 Hz). A Texas Red 3 kDa dextran was administered systemically followed by SonoVue[®] microbubbles. Drug delivery and distribution was assessed from fluorescence microscopy images of frozen brain sections, while safety was evaluated with an anti-albumin antibody staining for albumin extravasation and H&E staining for red blood cell extravasation and morphological damage.

Results & Discussion

Despite emitting 150 times less acoustic energy, the RaSP sequence delivered a similar drug dose and a better drug distribution (statistically significant) compared to the long pulse sequence. The drug was delivered more homogeneously within the brain parenchyma with high levels of neuronal uptake while the long pulses resulted in high drug concentrations near blood vessels and in some glial cells and neurons. RaSP also reduced the amount of endogenous albumin released into the brain by 3.7 times compared to the long pulse sequence and no signs of red blood cell extravasation or morphological changes were found.

Conclusion

RaSP sequences deliver a homogeneous drug distribution, a higher dose to the parenchyma and neurons, and release less albumin into the brain. These results suggest that RaSP sequences improve both the efficacy and safety of focused ultrasound-mediated drug delivery to the brain.

References

1. Hynynen K et al. *Radiology*. 2001; 220: 640-6.
2. Baseri B et al. *Ultrasound Med Biol*. 2010; 36(9): 1445-59.
3. Choi JJ et al. *Ultrasound Med Biol*. 2007; 33(1): 95-104.
4. Kovacs ZI et al. *PNAS*. 2017, 114(1): 75-84.
5. Pouliopoulos AN et al. *J Acoust Soc Am*. 2016; 140(4): 2469-80.

Acknowledgments

We thank the Michael Uren Foundation, Alzheimer's Research UK, and the EPSRC CDT in Medical Imaging for their support.

Ultrasound responsive microbubbles enhance the activity of sub-inhibitory concentrations of gentamicin in the treatment of *Pseudomonas aeruginosa* biofilms

Gareth LuTheryn^{1,*}, Filip Plazonic^{1,*}, Charlotte Hind², Melanie Clifford², Peter Glynne-Jones¹, Martyn Hill^{1,4}, Jeremy S Webb^{3,4}, J. Mark Sutton², Dario Carugo^{1,4}

¹ Faculty of Engineering and the Environment, University of Southampton, Southampton, UK. ² Public Health England, Porton Down, Salisbury, Wiltshire, UK. ³ Centre for Biological Sciences, University of Southampton, Southampton, UK. ⁴ Institute for Life Sciences, University of Southampton, Southampton, UK.

* Authors have equally contributed to the work in this study.

Introduction

The propensity of *P. aeruginosa* to both form a biofilm and readily select multi-drug resistant (MDR) mutants, augments its ability to survive conventional treatment¹. Ultrasound (US) responsive gas microbubbles (MBs) provide a novel method of treating biofilms in chronic wound infections^{2,3}. Microbubbles undergo volumetric oscillations or collapse upon exposure to an ultrasound field⁴; this makes them a powerful tool for the penetration of loose solids, such as a biofilm⁵.

Methods

Gas microbubbles with a mean diameter of 1.8 μm and stabilised by a phospholipid layer, (composed of DSPC:PEG40s, in a 9:1 molar ratio) were generated by sonication. An antibiotic-microbubble suspension (AMS) was applied to a *P. aeruginosa* biofilm, grown on a polypropylene coupon in a CDC bioreactor. In all experiments, the US frequency was 1 MHz and a sub-inhibitory concentration for biofilm eradication ($<10 \mu\text{g/ml}$) of the aminoglycoside gentamicin was used.

Results

The application of gentamicin in combination with MBs and US achieved a 73% greater quantitative reduction in *P. aeruginosa* biofilm, than gentamicin administered alone. At a lower concentration of 1.2×10^7 MB/ml, a biofilm reduction of 99% was observed compared to gentamicin alone; this is significantly greater than the reduction achieved in treatments that used higher MB concentrations (6×10^7 MB/ml).

Discussion

This research has shown that the application of MB and US as adjuvants, allow ordinarily sub-inhibitory concentrations of antibiotic to kill *P. aeruginosa* biofilms. Building upon this study, ongoing research is focusing on understanding the mechanisms of the MB-biofilm interaction, investigating the effect of this treatment on polymicrobial biofilms, and developing alternative microbubble formulations.

References & Acknowledgements

We would like to thank EPSRC and the University of Southampton for the funding for this project, and our collaborators at PHE. Presenting author: Gareth LuTheryn - G.LuTheryn@soton.ac.uk

1. Morita Y, Tomida J, Kawamura Y. Responses of *Pseudomonas aeruginosa* to antimicrobials. *Front Microbiol.* 2014;4:422. doi:10.3389/fmicb.2013.00422.
2. Dong Y, Xu Y, Li P, Wang C, Cao Y, Yu J. Antibiofilm effect of ultrasound combined with microbubbles against *Staphylococcus epidermidis* biofilm. *Int J Med Microbiol.* 2017;307(6):321-328. doi:10.1016/j.ijmm.2017.06.001.
3. Sirsi S, Borden M. Microbubble Compositions, Properties and Biomedical Applications. *Bubble Sci Eng Technol.* 2009;1(1-2):3-17. doi:10.1179/175889709X446507.
4. Seol SH, Lindner JR. A primer on the methods and applications for contrast echocardiography in clinical imaging. *J Cardiovasc Ultrasound.* 2014;22(3):101-110. doi:10.4250/jcu.2014.22.3.101.
5. Birkin PR, Offen DG, Leighton TG. An activated fluid stream "â€" New techniques for cold water cleaning. 2016. doi:10.1016/j.ultsonch.2015.10.001.

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“Digistain” mid-IR based Chemical Imaging for Breast Cancer Diagnosis.

H. Amrania¹, L. Woodley-Barker⁴, K. Goddard², B. Rosales², S. Shousha⁴, G. Thomas⁴, T. McFarlane⁴, M. Sroya⁴, C. Wilhelm-Benartzi⁵, K. Cocks³, R.C. Coombes^{2*}, and C.C. Phillips¹.

1 Physics Dept., Imperial College London, Prince Consort Rd., London, SW7 2BW, UK.

2 Department of Cancer and Surgery, Faculty of Medicine, Imperial College London, Du Cane Road, London W12 0NN, UK.

3 KCStats Consultancy, Leeds, UK

4 Dept. of Surgery and Cancer, Faculty of Medicine, Imperial College London, Charing Cross Hospital, Fulham Palace Rd., London W6 8RF, UK.

5 Centre for Trials Research, College of Biomedical & Life Sciences, Cardiff University, 6th Floor, Neuadd Meirionnydd, Heath Park, Cardiff, CF14 4YS

Introduction

The majority of cancers are diagnosed using “H+E” grading of excised biopsy specimens. The grading is done by eye and concordance rates between practitioners are typically only ~70%. Our new ‘Digistain’ technology, uses mid-infrared imaging to map the fractional concentration of nucleic acids, i.e. the nuclear-to-cytoplasmic chemical ratio (NCR), across an unstained biopsy section¹. It delivers a quantitative “Digistain index” (DI) score based on the NCR, that is extracted from an objective and reproducible physical measurement of a cancer. We find it correlates with breast H+E grade at a very high significance level ($p=0.0007$).

Methods

Two adjacent slices were taken from 75 breast cancer FFPE blocks; one was graded with the standard H+E protocol, and also used to define a “Region of Interest” (RoI). Digistain was then used to acquire a DI value averaged over the corresponding RoI on the other (unstained) slice and the results were statistically analysed.

Results & Discussion

The NCR is elevated by increased mitotic activity because cells divide when they are younger and, on average, become smaller as the disease progresses. Also, extra DNA and RNA is generated as the nuclear transcription machinery goes awry and nuclear pleomorphism occurs. Both effects make the NCR a recognized biomarker for a wide range of tumors, so we expect Digistain will find application in a very wide range of cancers.

Conclusion

We believe Digistain can significantly reduce, or even eliminate, the subjective element in cancer biopsy grading.

References

1. Amrania H, et al. Digistain: A Digital Staining Instrument for Histopathology. *Optics Express* **201**;, 20 (7) 7290-7299
2. H. Amrania¹, et al.. “Mid-Infrared Imaging in Breast Cancer Tissue: An Objective Measure of Grading Breast Cancer Biopsies.” 2018 Conver. Sci. Phys. Oncol. 4 025001 <https://doi.org/10.1088/2057-1739/aaabc3>.

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Developing an Ovarian Cancer Model on-a-Chip

M. Dibble¹, F. Balkwill², J.E. Gautrot¹

¹ School of Engineering and Materials Science, Queen Mary, University of London, London, E1 4NS. ² John Vane Science Centre, Barts Cancer Institute, London, EC1M 6BQ.

Introduction

Ovarian cancer is responsible for 5% of all female cancer deaths in the UK (4,277 in 2016) [1], with 70-80% of these deaths being attributable to high-grade serous ovarian cancer (HGSOC). Despite this, very little is known about the role the vasculature plays in HGSOC progression. Organ-on-a-chip technology is a rapidly expanding field due to these platforms ability to recreate complex tissue structure and function, directly leading to the development of various cancer-on-a-chip platforms, i.e. breast cancer [2]. Here I report on the development of an ovarian cancer model on-a-chip, providing a novel platform for studies into the role the vasculature and tumour microenvironment has on ovarian cancer progression, and concurrently the impact ovarian cancer has on the vasculature.

Methods

Devices were created using standard photo- and soft lithography techniques. A three-channelled device is used for mono-culture studies, whereas a four-channelled device is used for coculture experiments. Cells seeded within the device were first embedded within a fibrinogen/collagen gel before injection. Fixed samples were imaged using a Leica TCS SP2 confocal and Multiphoton microscope, live imaging was conducted using a Lumascope 720 microscope.

Results

This project initially focused upon developing a reproducible, vasculogenesis model on-a-chip. Following this we investigated the ability of difference stromal cells to promote vessel formation. It was shown that pericytes, normal human lung fibroblasts and cancer cells were all able to significantly promote vasculogenesis. In turn, we have investigated the role the vasculature plays in cancer cell proliferation and phenotypic transitions. Furthermore, we have demonstrated this model can be adapted to investigate cancer metastasis.

Discussion and Conclusions

This study has developed a novel, HGSOC model, and demonstrated the ability of ovarian cancer cells to directly induce vascularisation *in vitro*. However, we are still to investigate through which mechanisms this occurs, with a plethora of growth factors and cytokines associated with vasculogenesis it is likely to be through dynamic signalling networks.

References

1. Cancer Research UK, <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer#heading-One>, Accessed 16/05/18
2. Bersini, S., et al., *Biomaterials*, 2014. **35**(8): p. 2454-2461.

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Creating functional and high complexity hydrogels with electric fields

G.A. Primo¹, M. Lipka¹, J. P. Aguilar², A. Mata¹

¹ Institute of Bioengineering, School of Engineering and Materials Science, Queen Mary University of London, Mile End, E1 4NS, London. ² Tecnológico de Monterrey, Campus Guadalajara, Zapopan, Mexico.

Introduction

The human body and its parts are complex, anisotropic, hierarchical, and three dimensional. The challenge is to fabricate materials¹, scaffolds, and environments² with specific molecular and chemical composition³ and to do it with spatial control. We have developed a novel 3D-Electrophoresis-Assisted-Lithography (3DEAL) platform to create patterns of multiple functional molecules, and subsequently complex anisotropic environments, within readily available hydrogels.

Methods

The key feature of the 3DEAL is the use of an electric field to precisely localize functional molecules into hydrogels by means of a templating mask. Readily available hydrogels and a broad spectrum of proteins can be used with the 3DEAL technology. For this work, polyacrylamide (PA) 6 and 3% hydrogels, and fluorescently labelled IgG [blue (b-), green (g-) and red(r-)], as patterned molecules, were used.

Results & Discussion

The 3DEAL enables to create complex patterns of functional molecules (**Figure 1A**) within 3-dimensional hydrogels. The technique has the capability to create chemically complex and anisotropic (**Figures 1B-C**) environments within hydrogels in an easy manner and with high spatial resolution.

Conclusion

An affordable, easily tuneable, and versatile device and fabrication process designed to print multiple types of functional molecules within different kinds of hydrogels with high precision has been developed. The printing platform offers a simple, accessible, and practical molecular printing method with potential widespread applications in cell studies, in vitro models, drug screening, and tissue engineering due to its specific spatio-temporal location of proteins to recreate anisotropic environments.

References

1. McCracken et al. *Adv. Healthcare Mater.* 2016; 5:1025-1039.
2. Tam et al. *Acc. Chem. Res.* 2017; 50:703-713.
3. Colosi et al. *Adv. Mater.* 2017; 28:677-684.

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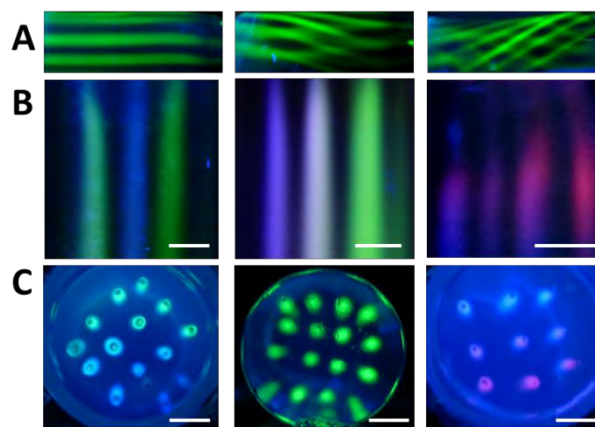


Figure 1. 3DEAL versatility. B, PA 3% printed with glgG. The mechanical properties of the hydrogel allow the moulding of the scaffold to form helicoidal structures without losing the patterns definition (*from left to right*). Different chemical gradients produced with the 3DEAL of either one, two or three proteins (g-, b- and r-IgG), B, in z and, C, x-y directions. Scale bar: 2 mm.

Protein self-assembly at oil-water interfaces controls nanoscale mechanics, cell adhesion and stem cell fate decision

D. Kong^{1,2}, L. Peng^{1,2}, W. Megone^{1,2} and **J.E. Gautrot^{1,2}**

¹Institute of Bioengineering and ²School of Engineering and Materials Science, Queen Mary, University of London, Mile End Road, London, E1 4NS, UK.

<http://biointerfaces.qmul.ac.uk/> j.gautrot@qmul.ac.uk

Introduction

The mechanical behaviour of the extracellular matrix has an important impact on cell phenotype. It has been shown to regulate cell adhesion and spreading, cell motility, proliferation and differentiation in a wide range of cells, stem cells as well as cancer cells¹. Recently, we reported that keratinocytes and mesenchymal stem cells do not seem to respond to the bulk mechanical properties of silicone materials, in contrast to their behaviour on acrylamide hydrogels². We now show that HaCaT, primary keratinocytes and mesenchymal stem cells can adhere, spread and proliferate at the surface of non-viscous liquids containing surfactant molecules and promoting the assembly of protein nanosheets^{3,4}.

Methods

We characterised cell proliferation and adhesion via fluorescence microscopy and scanning ion conductance microscopy. We used AFM and interfacial rheology to study the nanoscale mechanical properties of protein nanosheet assemblies generated at liquid-liquid interfaces. We used AFM and SEM to characterise the morphology and thickness of deposited protein nanosheets.

Results & Discussion

We show that the cell behaviour observed (spreading and proliferation on non-viscous liquids) is directly correlated with the assembly of protein nanosheets at the oil-water interface, mediated by pro-surfactants. This is supported by interfacial rheology data and XPS experiments. We identify that protein self-assembly at the oil-water interface is the main driver of this behaviour. We show that the type and concentration of surfactant as well as the proteins self-assembled control the nanoscale mechanical properties of the resulting interfaces and associated cell behaviour, despite the absence of bulk elasticity in the low viscosity oils used. We show that cell spreading at such liquid interfaces is mediated by integrin ligation, focal adhesion formation and acto-myosin contractility. In addition, we show that this behaviour depends on the interfacial mechanical properties of the protein layer assembled. We show that keratinocyte differentiation is not initiated by spreading at the surface of liquids, despite the absence of bulk mechanical properties. Finally, we apply these interfaces for the culture of cells in emulsions (Fig. 1).

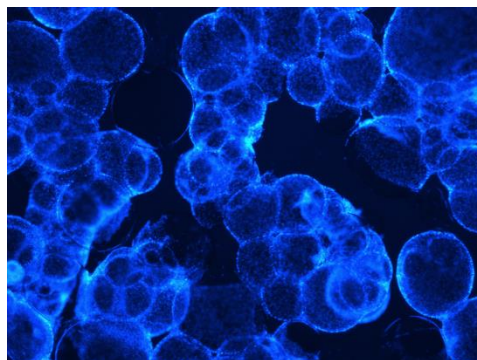


Figure 1. MSCs cultured on emulsions.

Conclusion

Our results suggest that nanoscale mechanical properties of biomaterials may dominate over bulk physical properties. This concept has important implications for the design of biomaterials in the field of regenerative medicine.

References 1. Guilak, F. et al. Cell Stem Cell 2009, 5:17-26. 2. Trappmann, B. et al., Nat. Mater. 2012, 11:642-649. 3. Kong, D. et al. Nano Lett. 2018, 18: 1946. 4. Kong, D. Faraday Discuss. 2017, 204: 367.

Lipid-based nanoparticles that counteract gastric infection without affecting gut microbiota

C.L. Seabra^{1,2,3}, C. Nunes⁵, P. Parreira^{1,2}, P. Henriques^{1,2}, C. Monteiro^{1,2}, J. Gomes^{1,3}, C.A. Reis^{1,3,4,6}, I.C. Gonçalves^{1,2}, S. Reis⁵, **M.C.L. Martins**^{1,2,3}

¹Instituto de Investigação e Inovação em Saúde, Universidade do Porto (UP), Portugal. ²INEB - Instituto de Engenharia Biomédica, Portugal. ³IPATIMUP – Instituto de Patologia e Imunologia Molecular UP, Portugal. ⁴ICBAS- Instituto de Ciências Biomédicas Abel Salazar, UP, Portugal. ⁵REQUIMTE, Laboratório de Química Aplicada, Faculdade de Farmácia, UP, Portugal. ⁶Faculdade de Medicina, UP, Portugal

Introduction

Helicobacter pylori infection is one of the major risk factors for gastric cancer development¹. Available antibiotic treatments not only fail in around 20% of patients but also have a severe negative impact on gut microbiota. Docosahexaenoic acid (DHA) is a polyunsaturated fatty acid with bactericidal activity against *H. pylori*². However, we demonstrated that DHA loaded lipid nanoparticles (NPs) improve DHA bactericidal effect since DHA-NPs inhibited *H. pylori* growth at much lower concentrations (25 μ M) than free DHA (>100 μ M)³. This work aims to evaluate the efficacy of DHA-NPs in the treatment of gastric infection, using an infection mice model, and to clarify if their bactericidal effect is specific to *H. pylori* without affecting gut microbiota.

Methods

DHA-NPs were synthesized by hot homogenization and ultrasonication using a mixture of solid lipid/liquid lipid/stabilizer (3). DHA-NPs were characterized in terms of morphology, size and charge, entrapment, stability in the simulated gastric fluid. *In vitro* efficiency was assessed using *H. pylori* J99, SS1, *L. casei* and *E. coli* by colony forming units (CFU) counting (24h). Bacteria morphology was evaluated by SEM and TEM. Cytocompatibility was evaluated in MKN45 gastric cells by metabolic activity (MTT assay) and cytotoxicity (LDH assay). *In vivo* efficacy was evaluated in SS1 *H. pylori*-infected C57BL/6 mice. After 4 weeks, DHA-NPs were administered by oral gavage for 14 days. Stomachs were collected to assess *H. pylori* infection by CFU counting. Toxicity was evaluated by histological analysis of mice liver/stomach.

Results & Discussion

Homogenous DHA-NPs with a size ~300 nm, stable in the simulated gastric fluid, were able to release 40% of DHA after 3h in bacteria media. DHA-NPs was bactericidal against *H. pylori* due to their ability to adhere and disrupt *H. pylori* membranes. This effect was specific to *H. pylori*. At bactericidal concentration, DHA-NPs are cytocompatible to human gastric cells. *In vivo* efficacy assays further confirmed that DHA-NPs was able to kill *H. pylori* reducing 91% of mice infection. Toxicity assays demonstrated that DHA-NPs was biocompatible and well-tolerated by mice.

Conclusion

Our findings suggest that DHA-NPs should be envisaged as an antibacterial nanotherapeutic or an adjuvant agent in *H. pylori* infection treatment.

References (examples – use “First author *et al.*” if more than 3 authors, minimum font size 9pt)

1. O'Connor et al, Nature, 14:230-240, 2017
2. Correia et al, PloS One, 7:e35072, 2012
3. Seabra et al, Int J Pharmaceutics, 519: 128-137, 2017

Acknowledgments

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Natural Polymers of Bacterial Origin for Cardiac Regeneration

Prachi Dubey¹, Eleanor Humphrey², Molly M. Stevens³, Cesare Terracciano²,
Sian E. Harding², Ipsita Roy^{1,2}

¹Faculty of Science and Technology, University of Westminster, London, UK; ²National Heart and Lung Institute, Faculty of Medicine, Imperial College London; ³Department of Bioengineering, Department of Materials, Institute for Biomedical Engineering, Faculty of Engineering, Imperial College London, UK

Introduction

Polyhydroxyalkanoates (PHAs), are a family of natural polymers of bacterial origin that are biodegradable and biocompatible, with a range of material properties and degradation rates. They are known to be cardio-regenerative in nature^{1,2,3}. Myocardial infarction results in the generation of scar tissue with limited or no regeneration, due to the modest nature of intrinsic myocardial regenerative capability. The concept of a cardiac patch is tailored to meet the unmet medical need of cardiac regeneration. Medium chain length PHAs (MCL-PHAs) with monomer chain length between C₆-C₁₆ are highly elastomeric in nature^{1,2} and have been shown to be excellent substrates for the growth and function of neonatal cardiomyocytes³. This work describes an in-depth study of the potential of MCL-PHAs for the development of cardiac patches laden with hiPSC-CMs, providing mechanical support and cell based therapy.

Methods

Two MCL-PHAs, P(3HO) and P(3HN-co-3HHP) were produced using batch fermentation of *Pseudomonas mendocina* CH50 and their chemical structure determined. Neat and blend 2D scaffolds were prepared by solvent casting and electrospinning, and characterized with respect to their material properties. *In vitro* biocompatibility and cardio-regenerative properties were analysed by growing hiPSC-CMs on the scaffolds followed by live/dead assays, beat-rate and calcium transience measurements. Confocal microscopy was used to observe and evaluate hiPSC-CM growth and maturation.

Results & Discussion

The hiPSC-CMs grew extremely well on the MCL-PHA scaffolds, and growth was comparable to that on gelatin, a substrate with known biocompatibility with cardiomyocytes. The beat rates were normal and comparable to that measured on gelatin, a remarkable unprecedented result for a biomaterial of bacterial origin. Immunohistochemical analysis showed that the hiPSC-CMs exhibited all expected phenotypic characteristics of mature, adult cardiomyocytes with the required sarcomere length. Calcium transients were within required values, confirming that the MCL-PHAs supported the calcium exchange within the cell tubules and promoted contractions, thus establishing their cardio-regenerative nature. Random and aligned electrospun fibres of the neat and blend polymers were assessed as potential components of a cardiac patch. The aligned fibres induced a high degree of aligned anisotropic growth of the hiPSc-CMs as compared to the control, a feature essential for cardiac regeneration.

Conclusion

This work established that MCL-PHAs are highly cardio-regenerative in nature and hiPSC-CMs readily attach, grow and exhibit all associated functionality on them. Electrospun aligned fibres of the MCL-PHAs induced anisotropy, mimicking native cardiac tissue.

References

1. Rai *et al.*, *Biomac.* 12:2126-2136, 2011;
2. Rai *et al.*, *Mat. Sci. Eng (Reviews)* 72(3): 29-47, 2010;
3. Bagdadi *et al.*, *JTERM* doi:10.1002/term.2318

Acknowledgments

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Stem cell culture on nanosheets assembled at the surface of liquid microcarriers for applications in regenerative medicine

L. Peng¹, D. Kong¹, K.D.Q. Nguyen¹, J.E. Gautrot¹

¹ Engineering Building, Queen Mary, University of London, Mile End, E1 4NS, London.

Introduction

Adherent cell culture is typically thought to require cell spreading on rigid substrate. However, it was proposed that cells may be able to sense nanoscale physical and mechanical properties rather than directly bulk mechanics¹. In fact, several reports indicate that cell adhesion and culture may be possible at the surface of liquids^{2,3}. Here, we show that mesenchymal stem cells (MSCs) can be cultured at the surface of liquids and demonstrate that this behavior is regulated by protein self-assembly at the liquid-liquid interface and associated nanoscale mechanical properties.

Methods

The formation of poly(L-lysine) (PLL) nanosheets at liquid-liquid interface were studied by X-ray photoelectron spectroscopy (XPS), fourier-transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM) and atomic force microscopy (AFM) and their mechanical properties were characterised by interfacial rheology. Fluorescence microscopy was used to study the spreading and proliferation of MSCs on oil substrates.

Results & Discussion

Interfacial rheology demonstrated the assembly of PLL and fibronectin nanosheets, with mechanical properties controlled by protein concentration, pH and the presence of surfactants. Interfacial shear moduli ranged over several orders of magnitude (from 10^{-4} to 10 N/m). We propose that such variation results from variations in the surfactant functionalization level of PLL, as indicated by XPS. Immunostaining shows stable focal adhesion formation and F-actin assembly, despite the absence of bulk mechanics of oil

substrates used. MSCs expansion was also observed (Figure 1) and their proliferation profile was correlated to the nanoscale mechanical properties of the interfaces they were cultured on.

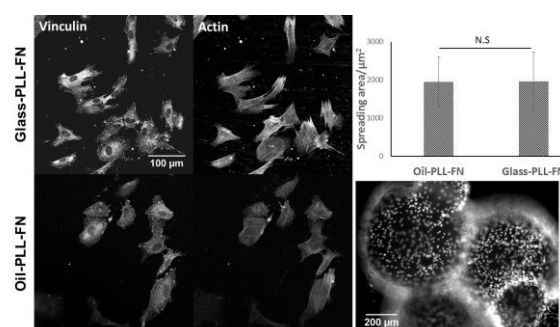


Figure 1. Cell spreading at liquid-liquid interfaces

Conclusion

Cell adhesion and proliferation is regulated by nanoscale mechanical properties of protein interfaces assembled on oils, rather than their bulk mechanical properties. The interfacial mechanics can be optimized for cell culture by controlling nanosheet chemistry and self-assembly. Such platform can be applied to the design of emulsion-based 3D bioreactors allowing stem cell expansion.

References

1. Trappmann B. *et al. Nat. Mater.* **11**, 742–742 (2012).
2. Giaever I, Keese CR. *Proc. Natl. Acad. Sci. U. S. A.* **80**, 219–222 (1983).
3. Kong D. *et al. Nano Lett.* **18**, 1946–1951 (2018).

Acknowledgments

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The sulfation of biomimetic glycosaminoglycans controls growth factor binding and subsequent cell proliferation and differentiation

D. El Hajj ¹, W. Malaeb ¹, H. Bahmad ², W. Abou Kheir ², R. Mhanna ¹

¹ Biomedical Engineering Program, Faculty of Engineering and Architecture, American University of Beirut, Beirut 1107 2020, Lebanon

² Department of Physiology, Faculty of Medicine, American University of Beirut, Beirut 1107 2020, Lebanon.

Introduction

Glycosaminoglycans (GAGs) are major components of the extracellular matrix that possess structural and functional roles in many tissues. The sulfation arrangements of GAGs have been tightly correlated with biological events including morphogenesis, tissue repair and aging. However, it is not clear how such events are affected by sulfation. Elucidating the mode of action of sulfated GAGs will enable the synthesis of biomimetic 2D and 3D substrates that can be used in the treatment of diseases and injuries.

Methods

Alginate was sulfated at different sulfation degrees and then biotinylated in an end-on fashion. The biotinylated sulfated alginates were then used to modify gold or polystyrene substrates. Binding of growth factors including fibroblast growth factor (FGF), epidermal growth factor (EGF) and nerve growth factor (NGF) to the substrates was assessed quantitatively using quartz crystal microbalance with dissipation monitoring (QCM-D) and enzyme-linked immunosorbent assay (ELISA) and validated qualitatively with immunostaining. Finally, the morphology and growth of cells including normal and tumour breast epithelial, neuroblastoma and lung cancer cells was evaluated via ImageJ, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and 5-bromo-2'-deoxyuridine (BrdU) assays.

Results & Discussion

Sulfated GAG modified substrates with different degrees of sulfation were constructed and assessed using QCM-D. Growth factor binding was found to increase with increased sulfation of GAGs. These findings were confirmed with ELISA and immunostaining. Cell proliferation was typically hindered when sulfated materials were added in solution. However, when neuroblastoma cells were cultured on sulfated substrates, they exhibited more stem cell spheres on the more sulfated substrates.

Conclusion

The ability to prepare sulfated substrates with controlled sulfation levels has strong implications in the biomedical field. Sulfated substrates can be used to induce different levels of growth factor binding, and to increase or inhibit cell proliferation which has major implications in tissue engineering and cancer therapy.

References

1. Gama CI, Hsieh-Wilson LC. *Curr Opin Chem Biol.* 2005; 9: 609-619.
2. Linhardt RL, Toida T. *Acc. Chem. Res.* 2004; 37: 431-438.
3. R. Mhanna et al., *Adv Biosyst.* 2017; 1: 1-7

Acknowledgments

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High speed electro-mechanical single cell analysis

F. Siracusa¹, H. Morgan¹, D. C. Spencer¹

¹ School of Electronics and Computing Science, University of Southampton, Highfield, Southampton, UK

Introduction

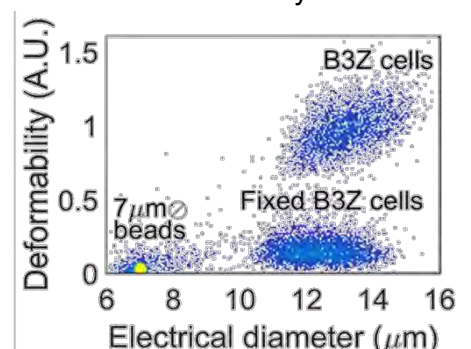
The biophysical properties of cells are important markers of a cell's physiological state and understanding these changes can contribute to new approaches to the diagnosis and treatment of human diseases. For example, the mechanical behaviour of cancer cells can be used as a measure of metastatic potential¹ and similarly, the electrical phenotype of a cell can be used as a biomarker for sepsis². Mechanical properties play also a role in processes such as cell differentiation³ and drug response⁴. Traditional single-cell mechanical measurement techniques, such as atomic force microscopy, micropipette aspiration and optical stretching have very limited throughput and cannot be applied to rare-cell analysis. Inertial effects and hydrodynamic forces have been used to deform cells in microfluidic devices coupled with high-speed cameras^{5,6}, but their complex setup and the use of optics limits their implementation for Point-Of-Care applications. We have developed a microchip to profile the electro-mechanical properties of single cells at high speed to provide new insights into cell biophysical analysis.

Methods

Cells cultured following standard culturing protocols are resuspended in phosphate buffered saline (PBS) solution before each experiment. Cells are fixed with glutaraldehyde (GA) 0.1% for 30 minutes. Fixed and non-fixed cell suspensions are then mixed with methylcellulose solution in PBS to a final concentration of 0.5%. The suspension is pumped through a microchannel where cells are deformed by the shear stress caused by the high viscosity methylcellulose medium. Sets of microelectrodes at different orientations measure the impedance at different directions to evaluate the electrical shape before deformation (wide section of the channel) and after deformation (narrow section) and the ratios calculated. Optical verification is enabled by a custom dark field setup illuminated by a pulsed high-power LED.

Results & Discussion

The setup was first tested with fixed vs. non-fixed cells. For B3Z cells Fig. 1 shows the difference in deformation. While this represents extreme case, there is substantial separation in populations. We are now studying the effects of cytoskeletal drugs on cell deformability and investigating the possibility to identify fibroblast differentiation.



Conclusion

A novel high-throughput microfluidic cytometer has been presented, capable to measure mechanical and electrical properties of cells simultaneously and to distinguish between fixed and non-fixed cells. This device can be used to measure intrinsic biophysical markers related to disease, cell differentiation and drug response.

References

1. Lekka M *et al.* *Eur. Biophys. J.*, 1999; 50 (4): 312–316.
2. Prieto JL *et al.* *Lab Chip*. 2016; Nov 1; 16(22): 4333–4340.
3. Bongiorno T *et al.* *J Biomech* 2014; 47: 2197–2204.
4. Rotsch C and Radmacher M *Biophys J.* 2000; Jan; 78(1): 520–535.
5. Gossett DR *et al.* *Proc Natl Acad Sci USA*. 2012 May 15;109(20):7630-5.
6. Otto O *et al.* *Nature Methods*, 2015; 12 (3): 199-202.

Acknowledgments

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A Signal Quality Index for the Impedance Respiratory Signal

P. H. Charlton¹², T. Bonnici³, L. Tarassenko², P. J. Watkinson⁴, R. Beale³, D. A. Clifton², J. Alastruey¹

¹Department of Biomedical Engineering, King's College London, King's Health Partners, London, SE1 7EH

²Department of Engineering Science, University of Oxford, Oxford OX3 7DQ

³Department of Asthma, Allergy and Lung Biology, King's College London, King's Health Partners, London, SE1 7EH

⁴Kadoorie Centre for Critical Care Research and Education, Oxford University Hospitals NHS FT, Oxford, OX3 9DU

Introduction

Respiratory rate (RR) is an important physiological marker, often increasing prior to acute clinical deteriorations such as cardiac arrests. Consequently, RR is often monitored using thoracic impedance pneumography (IP), since the IP signal can be easily acquired with ECG electrodes. However, IP is highly susceptible to motion artifact, reducing signal quality and resulting in inaccurate RRs. Our aim was to design a signal quality index (SQI) to discriminate between low and high quality periods of IP, and to estimate RR accurately from high quality periods.

Methods

We designed an SQI to quality assess segments of IP of 32 seconds, based on [1]. It consists of: (i) filtering the IP signal to eliminate non-respiratory frequencies; (ii) detecting individual breaths; (iii) assessing the plausibility of breath-to-breath timings; and (iv) assessing the similarity of breath morphologies using template matching. Performance was assessed using IP signals from 59 hospital patients recovering from cardiac surgery, each of one hour duration. Each segment was manually annotated as high or low quality, and individual breaths were annotated. Performance was compared to an existing SQI [2], and the RRs provided by the clinical monitor.

Results & Discussion

See table. The novel SQI had improved discriminatory performance compared to a technique from the literature [2]. RRs had a lower mean absolute error, more accurate estimates (error < 2 bpm), and fewer inaccurate estimates (error > 5 bpm), than this technique or the clinical monitor.

Performance metric	Novel SQI	Technique from literature	Monitor
SQI Sensitivity [%]	76.7	45.0	-
SQI Specificity [%]	84.9	77.4	-
Mean absolute error of RRs [bpm]	0.20	1.34	1.27
Proportion RR error < 2 bpm [%]	97.8	79.5	83.0
Proportion RR error > 5 bpm [%]	0.0	4.7	4.7

Conclusion

The novel SQI can be used to improve the accuracy of RRs estimated from IP. It has applications in both tethered and wearable monitors, and in hospital and home settings.

References

1. Orphanidou C *et al.* *IEEE J Biomed Health Inform.* 2015; 19(3): 832-8.
2. Pimentel M A F, Charlton P H, Clifton D A. in *Wearable Electronics Sensors*. 2015; 15: 241-62

Acknowledgments

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Efficient peripheral nerve decoding through massive feature extraction

C.H. Lubba^{1,2}, B.D. Fulcher⁵, N.S. Jones^{3,4}, S.R. Schultz^{1,2}

¹Department of Bioengineering, ²Center for Neurotechnology, ³Department of Mathematics, ⁴Center for Mathematics of Precision Healthcare, Imperial College London, London, United Kingdom. ⁵School of Physics, Faculty of Science, University of Sydney, Sydney, New South Wales, Australia.

Introduction

Bioelectronic Medicines aim at treating diseases via implanted devices that interact with the peripheral nervous system. Today's devices mostly act in an open-loop fashion and don't analyse the existing activity on the nerve. Closed-loop systems that diagnose nerve activity and adapt nerve stimulation or block accordingly have the potential of being more efficient and effective. Closing the loop is challenging, however, as the signal processing needs to be energy-efficient and at the same time robust against noise. We here investigate the possibility of an efficient feature-based characterisation of peripheral nerve activity.

Methods

Our work is based on the Highly Comparative Time Series Analysis (HCTSA) framework [1] which enables the computation of ~8000 time series features. We calculated those features on simulated datasets obtained from the peripheral nerve simulator PyPNS [2]. Each dataset consisted of 100 to 1000 individual recordings over 400ms from a nerve of length 5cm containing 500 axons. Between single recordings, the underlying simulation parameters were varied continuously (myelination ratio, firing rate, burstiness). By applying dimensionality reduction (PCA, Isomap) in the high-dimensional feature space, we detected and quantified signal characteristics following those parameter changes and identified single, efficiently implementable features as estimators for those characteristics/ parameters.

Results & Discussion

For each dataset, N varying parameters could be reconstructed linearly from the first N main dimensions obtained from dimensionality reduction with an unexplained variance below 0.4 per parameter – even after reducing the signal to noise ratio to 6dB. We were therefore able to identify relevant signal characteristics in an unsupervised manner. By selecting features with high correlation to the main dimensions, single estimators could be obtained.

Conclusion

Our method enables investigators to identify main varying characteristics of peripheral nerve recordings and proposes single efficient estimators.

References

- [1] B.D. Fulcher, M.A. Little, N.S. Jones Highly comparative time-series analysis: the empirical structure of time series and their methods. J. Roy. Soc. Interface 10, 83 (2013).
- [2] C. Lubba, Y. Le Guen, S. Jarvis, N. Jones, S., A. Eftekhari, S.R. Schultz Multiscale simulation of peripheral neural signalling. bioRxiv 196451

Droplet microfluidics for continuous chemical sensing of cortisol

Gareth Evans¹, Wahida Bhuiyan¹, Sammer-UI Hassan², Brett Warren² Sharon Coleman² and Xize Niu^{1*}

¹ Faculty of Engineering and the Environment, University of Southampton, Southampton, U.K. SO17 1BJ

² SouthWestSensor Limited, 2 Venture Road, Chilworth, Southampton, U.K. SO16 7NP

Introduction

Droplet microfluidics has proven to be a powerful tool for bio-chemical analysis using small sample volumes [1]. Many 'mix-and-read' assays have been demonstrated in droplets however, multiple step reactions are more challenging. In 2016, Ferraro *et al.* demonstrated a method with obvious potential for integrating many 'gold standard' ELISA assays for biochemical analysis into droplet microfluidic platforms [2]. However, their approach relies on large instrumentation and complex operation of pumps and valves for droplet generation, not suitable for field applications.

Methods

Here we show a new point-of-care monitoring technique performing heterogeneous assays continuously in micro droplets. Our small and low power system makes use of droplet microfluidics, magnetic beads and optical detection. We have chosen to demonstrate a competitive assay for cortisol (a stress related steroid hormone), however this platform may be tailored for a wide variety of target analytes. Our all-in one integrated device shown in Fig.1a contains a peristaltic micropump and microfluidic chip for continuously generating repeated sequences of droplets by our group's novel pulsed method [3], automated magnetic traps for transferring magnetic beads between droplets to carry out assay steps and a miniaturized in-line spectrophotometer for the final measurement [4].

Results & Discussion

Figure 1b shows an example (50ng/ml) of the raw readout (light intensity) data from the miniaturized inline spectrophotometer used for final detection and Fig1c. shows a promising early calibration of the assay carried out in droplets with expected trend.

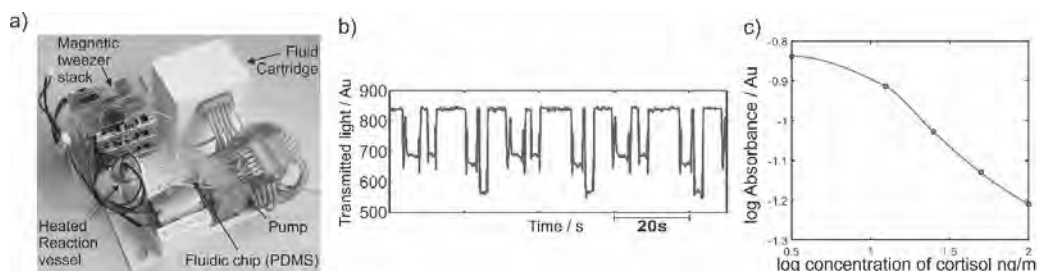


Figure 1a) Photograph of the device b) Example raw data from inline spectrophotometer (50ng/ml) c) Early calibration data of Cortisol assay

Conclusion

Our device can collect samples directly from the sampling site (e.g. body fluids), making it possible to perform complex assays continuously at the point-of-care. The continuous nature of this method combined with the small-footprint of the experimental setup promises to revolutionize chemical monitoring in the medical field and offers exciting research opportunities for studying the biochemistry of short term events and long-term trends.

References

1. WL.Chou et al., Micromachines, 6, 9, 1249-1271. (2015)
2. D. Ferraro et al., Scientific Reports, 6, 25540 (2016)
3. A.M. Nightingale et al, Lab on a Chip, 17, 6 (2017)
4. S. Hassan et. al, Analyst, 141, 11 (2016)

Acknowledgments

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Flexible and Biocompatible Piezoelectric Nanocomposites for Physiological Pressure Sensing

B. Bagchi^{1,2}, M. K. Tiwari,^{1,2}

¹Wellcome/EPSCRC Centre for Interventional and Surgical Sciences (WEISS), UCL, London W1W 7TS, UK
²Nanoengineered Systems Laboratory, UCL Mechanical Engineering, London WC1E 7JE, UK
 *E-mail: m.tiwari@ucl.ac.uk

Introduction

Continuous multimodal physiological pressure monitoring is a crucial step toward effective diagnosis and prevention of several endovascular and cardiovascular abnormalities which may develop into life threatening conditions. In this context, piezoelectric polymers have tremendous potential due to their dynamic pressure sensing capabilities along with all the desirable attributes of an implantable biomaterial. The present work aims to fabricate a flexible biomedical sensor element based on piezoelectric Molybdenum disulphide-polyvinylidene difluoride (MoS₂-PVDF) nanocomposite films and determine their performance in sensing normal human activities like tactile response, fluid/blood pressure, pulse etc.

Methods

Polymer nanocomposite films were synthesized by incorporating hydrothermally synthesized MoS₂ (10 wt%) nanoflowers (Nfs) in PVDF matrix. The flexible films were characterized by infrared spectroscopy (FTIR), electron microscopy (SEM), and X-ray diffraction techniques (XRD). Piezoresponse against dynamic pressure (as imparted by light human finger tapping and ultrasonic vibration) were recorded by digital scanning oscilloscope (DSO).

Results & Discussion

FTIR and XRD analyses confirm formation of piezoelectric β crystals in the MoS₂ doped PVDF, (Figure 1a and b). SEM image in Figure 1c shows MoS₂ Nfs and PVDF β spherulite (Figure 1d). The dynamic piezoresponse obtained using the DSO confirms high sensitivity of the film to finger tapping (~2-10Hz) (Figure 2a) and ultrasonic vibration (40 kHz) (Figure 2b).

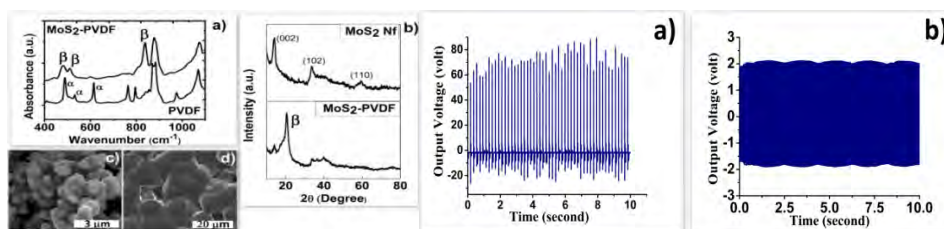


Figure 1: FTIR, XRD and SEM of the nanocomposite. Figure 2: Piezoresponse from the nanocomposite film.

Conclusion

Flexible piezoelectric sensors were successfully fabricated and tested against finger tapping. Future work includes monitoring dynamic fluid pressures, mimicking endovascular flow.

References

Yoon S, Sim J K, Cho Y H. *Sci Rep.* 2016;6:23468-23479.

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Personality Computing: Automatic Recognition of Personality Using EEG Functional Connectivity

P. Konstantinidi¹, M. Zervakis ¹, A. Fratini ², M. A. Klados ²

¹ School of Electrical and Computer Engineering, Technical University of Crete, Greece. ² Department of Biomedical Engineering, School of Life and Health Sciences, Aston University, Birmingham, UK

Introduction

This project is an extensive research based on the concept of Personality Computing. The purpose of this work is the automatic detection of personality traits using electroencephalographic (EEG) signals processing and functional connectivity through emotional processing for the first time, having in mind that this would not be accomplished in case of resting-state EEG.

Methods

Our work is based on an open dataset [1], which includes Big-Five personality traits and the already pre-processed EEG signals (14 channels according to the 10-20 system, sampling frequency of 128 Hz and 14 bit resolution) as they recorded by a low cost Emotiv EPOC Neuroheadset. The recordings took place during a short-videos experiment, where participants observed video clips with pleasant and unpleasant content. For classification purposes each one of the five dimensions was binarised (low and high scoring) using k-means clustering, while around 25000 features were extracted by the brain networks, computed using the imaginary part of coherence. Feature selection is performed using ReliefF algorithm which results in the *10 best features* firstly for the pleasant and unpleasant videos respectively and later for the fusion of them. For the classification purposes, different algorithms were used and optimised by the classification learner of the Matlab environment, aiming to generate effective and accurate personality prediction models. Support Vector Machines (SVMs) with Gaussian kernel, Linear Discriminant Analysis, *k*-Nearest Neighbors and ensemble methods are used in the classification procedure, while our evaluation was performed using 5-fold cross validation scheme.

Results & Discussion

Our results (Table 1) suggest that 4 out of 5 dimensions, namely Extroversion, Neuroticism, Agreeableness and Conscientiousness appeared to be accurately detected (> 80%) while Openness was the dimension with the lowest but not insignificant accuracy (75.7%).

Dimension/Trait	Pleasant Videos	Unpleasant Videos	Both
Extroversion	83.8%	59.5%	85.5%
Openness	73%	73%	75.7%
Neuroticism	73%	67.6%	83.8%
Agreeableness	75.7%	73%	86.5%
Conscientiousness	86.5%	70.3%	81.1%

Table 1 – Accuracy results obtained by the features extracted for the pleasant and unpleasant videos as well as for their fusion.

It's the first time that a study tackles automatic personality recognition with so high accuracy results, and our success was solely based in the selection of brain network features extracted during emotional processing.

References

1. Miranda-Correa, J. A., Abadi, M. K., Sebe, N., & Patras, I. (2017). AMIGOS: A dataset for Mood, personality and affect research on Individuals and GrOuPS. *arXiv preprint arXiv:1702.02510*.

An RNA-Aptamer Biosensor for Detection of a Key Component of a Biomarker Fingerprint for Overactive Bladder

S. Firouzmand¹, A.J. Callaghan², J.S.Young¹

¹ School of Pharmacy & Biomedical Sciences, University of Portsmouth, UK. PO1 2DT. ² School of Biological Sciences, University of Portsmouth, UK. PO1 2DY.

Introduction

Affecting 1 in 5 adults, one of the most common causes of urinary incontinence is a disease called overactive bladder (OAB). OAB is the focus of our study because current methods for diagnosing this disease are inaccurate, highly invasive and very expensive. We have recently discovered five chemicals, contained within urine, that together provide a novel biomarker 'fingerprint' of OAB. Developing our OAB fingerprint into a simple-to-use diagnostic tool requires the simultaneous detection of five chemicals. These five biomarkers are a mixture of immunogenic and nonimmunogenic molecules; as such, a single platform capable of detection of both is required. Here we unite our proven OAB biomarker fingerprint with our RNA aptamer platform technology to develop a biosensor to detect a key component of the OAB biomarker fingerprint, molecule 'A'; a component that is nonimmunogenic and relatively difficult to quantify. This proof-of-concept will be a key step towards developing our discovery into an easy-to-use, point-of-care OAB diagnostic tool.

Methods

The structure of our RNA aptamer biosensor is comprised of three elements (each being single-stranded RNA aptamers); acting as detector, transducer and signaller elements. Sequences for each of these aptamers are known; the project required the elements to be first tethered and then their efficacy, as a biosensor, to be documented. Methods used included generating DNA templates from overlapping primers using standard PCR; visualisation (and thus confirmation of desired) amplified PCR product by gel electrophoresis; synthesis of the RNA aptamers by *in vitro* transcription; visualisation (and thus confirmation of desired) RNA aptamers on denaturing urea polyacrylamide gel; assessment of biosensor functionality by measures of signal generated of the aptamer biosensor in the presence of the target molecule (molecule A) or an analogue (molecule B).

Results & Discussion

Sensitivity of the RNA aptamer biosensor was confirmed by the observation that the fluorescent signal observed following incubation with the target molecule (molecule A) is detectable and relatively stable over a 45-minute period. Specificity of the biosensor was confirmed by the observation of a negligible fluorescent signal following incubation with an analogue (molecule B).

Conclusion

Our RNA aptamer biosensor can detect a key component of the OAB biomarker fingerprint, with high sensitivity and specificity.

Acknowledgments

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Lubricious Catheter Coating Technology Towards the Prevention of Catheter Encrustation

N.J. Irwin¹, M. Bryant², C.P. McCoy¹, J. Trotter¹

¹School of Pharmacy, Queen's University Belfast, BT9 7BL, Northern Ireland. ²School of Mechanical Engineering, University of Leeds, LS2 9JT, Leeds.

Introduction

Urinary catheters are among the most commonly employed medical devices.¹ Repeated catheterisation with poorly lubricated catheters can, however, lead to urethral tissue trauma, pain and infection.² In addition, recurrent episodes of catheter encrustation and blockage are experienced by up to 50% of all chronically-catheterised patients as a result of infection by urease-producing pathogens including *Proteus mirabilis*.³ We herein describe the development of an exciting and transformational new lubricious anti-blocking coating technology for urinary catheters.

Methods

PVC substrates were dip-coated with developmental hydrogel formulations. Following UV curing and incubation in *P. mirabilis*-infected artificial urine, *in vitro* resistance of the coated surfaces to bacterial adherence and encrustation was assessed by viable bacterial counts, pH measurements and SEM imaging. Surface coefficient of friction (COF) values were measured using *in vitro* tissue erosion models against polymeric and tissue counterprobes.

Results & Discussion

Following 24 h incubation with *P. mirabilis*, visible encrustation was observed on uncoated control surfaces and urinary pH elevated to values up to pH 9. In contrast, the pH of wells containing samples coated with developmental formulations was maintained at values <pH 6 for periods exceeding 72 h incubation, and no crystalline deposits were observed on coated surfaces after 24 h. Furthermore, logarithmic reductions in bacterial adherence of up to 2.54 were demonstrated on developmental coated-surfaces relative to uncoated controls after 24 h incubation. Respective COF values for coated and uncoated surfaces against a PDMS probe following 30 sec hydration were 0.007 and 2.03. Importantly, coatings were also highly durable, with these significantly lower COF values maintained for >200 repeated cycles of applied force.

Conclusion

This multifunctional lubricious coating technology exhibits promising potential for preventing catheter blockages, tissue trauma and associated infections, with resultant benefits to patient health and dignity anticipated.

References

1. Loveday HP *et al.* *J Hosp Infect.* 2014; 86S1: 1-70.
2. Wilde M *et al.* *J Clin Nurs.* 2017; 26: 2558-2571.
3. Li L *et al.* *Arch Phys Med Rehabil.* 2013; 94: 782-787.

Acknowledgments

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Ano-rectum sensor probe for assessment of bowel incontinence

O. Keattch¹, H.H. Hamzah², M.S. Yeoman^{2,3}, D. Covill¹, **B.A. Patel**^{2,3}

¹School of Computing, Engineering and Mathematics, ²School of Pharmacy and Biomolecular Sciences and ³Centre of Stress and Age-Related Diseases, University of Brighton, BN2 4GJ, Brighton.

Introduction

Bowel incontinence is highly prevalent in the elderly and associated with significant social stigma and psychological distress. Although there are some studies in bowel incontinence, there is a significant lack of knowledge regarding normal and abnormal changes of anorectal function and the biological changes associated with ageing. To date studies in humans have shown the pathophysiology of bowel incontinence is multifactorial, making assessment and management difficult ¹⁻³. Our findings strongly suggest that epithelium signalling plays a key role in the regulation of ano-rectal muscle patterns and this is altered with age ⁴, therefore making such markers useful in assessment of incontinence.

Methods

Sensors were made using 3D printing, where a 4.5 mm radius hollow cone was printed using conductive ABS/carbon black filament. This was connected to a 3D printed cap to develop the shape of the ano-rectum sensor probe. The sensors were assessed for sensitivity, stability and ability to measure changes in muscle contraction using electrochemical techniques. The sensors were validated for by conducting measurements in the ano-rectum of the guinea pig bowel in the presence of pharmacological agents.

Results & Discussion

The printed ABS/carbon black probe showed good electrochemical behaviour in physiological concentrations of serotonin, which is the main transmitter released from the mucosa. The sensitivity of the developed probe was 134 nM μM^{-1} and the limit of detection of the probe was 1 μM . Real-time measurements in the ano-rectum were conducted where serotonin transporter fluoxetine was added. This led to an increase in serotonin overflow detected on the probe and a reduction in contractions. From multiple measurements the increase in serotonin overflow correlated with a reduction in the amount and strength of contractions.

Conclusion

We fabricated a sensor using that can be inserted into the ano-rectum of the bowel for measurement of luminal signalling transmitter. The sensor was able to monitor serotonin in physiological concentrations, showed the ability to record stable responses *in vitro*. This sensor provides pharmacological and physiological insight into mucosal signalling patterns in the ano-rectum and can provide useful knowledge in identifying the onset of functional bowel disorders.

References

- 1 Rao, S. S. C. *Gastroenterology* **126**, S14-S22 (2004).
- 2 Rao, S. S. C. *American Journal Of Gastroenterology* **99**, 1585, (2004).
- 3 Yu, S. W. B. & Rao, S. S. C. *Clinics in Geriatric Medicine* **30**, 95-106, (2014).
- 4 Wang, C. *et al. Neurogastroenterology & Motility* **25**, e469-e477, doi:10.1111/nmo.12144 (2013).

Acknowledgments

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Pelvic Nerve Stimulation for Urinary Urge Incontinence.

Thelma Lovick, University of Bristol, UK

Introduction

Neuromodulation: “the alteration of nerve activity through targeted delivery of a stimulus to specific neurological sites in the body” is a clinically effective intervention for treating a number of urinary and bowel dysfunctions that are refractory to conservative management. Stimulation of the sacral nerve roots at low frequency (10-15Hz) is the most commonly used procedure and whilst effective in many cases, adverse effects such as pain and the requirement for re-intervention remain problematic. Moreover, current stimulation paradigms may not be optimal for all cases. For the patient with urinary urge incontinence for example, for whom the need is intermittent, the requirement would be for temporary suppression of unwanted voiding operated ‘on demand’ by the patient when urge occurs, in order to buy time for the individual to reach a suitable and socially acceptable environment to void.

Experimental approach

With the above proviso in mind we developed an animal model of conditional nerve stimulation in which we were able to suppress imminent voids on demand by high frequency (1-3kHz) stimulation of the pelvic nerve. In conscious rats with a miniature cuff electrode implanted unilaterally on the pelvic nerve, stimulation initiated at the onset of the bladder contraction signalling an imminent void was able to suppress the void and maintain urinary continence during the 60s stimulation period. The effect was rapid in onset, reproducible over weeks and readily reversible. Importantly, the stimulation did not evoke any sign of discomfort or other adverse side effects (Brouillard et al, 2018).

These studies provided proof-of-concept for conditional stimulation of the pelvic nerve at high frequency to control urinary continence ‘on demand’. However, a limitation of the translational potential of this approach is the need for an invasive laparotomy to access the preganglionic pelvic nerve bundle within the abdominal cavity. As an alternative we are now investigating the effectiveness stimulating the pelvic nerve fibres outside the abdominal cavity as they approach the spinal cord within the S1 sacral nerve root. Initial studies in anaesthetised rats show that high frequency (1-3kHz, 1mA for 60s) stimulation at the S1 sacral foramen is effective in suppressing imminent voids, in a rapid onset, readily reversible and reproducible manner.

Conclusions.

The results provide proof-of-concept for developing high frequency stimulation of sacral nerve roots as an ‘on demand’ patient-operated means to suppress imminent urinary voids on-demand in humans with urinary urge incontinence.

References

Brouillard CBJ et al , *Front Physiol.* 2018; 9: 437. doi: 10.3389/fphys.2018.00437.

Acknowledgements

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Monitoring Dehydration with Osmolality in Whole-Blood Specimens Collected from Cycling Athletes

W. Dawsmith¹, R. Donnan³, N. Ohtani, R. Dudley² and T. T. Chowdhury¹

¹ Institute of Bioengineering, School of Engineering and Material Science, Queen Mary University of London, London, E1 4NS. ²National Physical Laboratory, Teddington, TW11 0LW, ³ School of Electrical Engineering and Computer Science, Queen Mary University of London, E1 4NS.

Introduction

There are currently no real-time, non-invasive devices to monitor hydration levels for sports and healthcare applications. NPL and QMUL have been working together, to develop technology for a hydration monitor device. This study tests a new method of measuring dehydration using whole blood osmolality taken from healthy cycling athletes who exercised intensely.

Methods

Four healthy cycling athletes consented to take part in the study. The volunteers cycled intermittently for 40 min at 35°C and 40% humidity environment. The intensity rate of the exercise was considered difficult (17/20) on the Borg RPE scale. The nude mass was measured before, during and after intermittent cycling exercise. Whole blood specimens were collected before and after intermittent cycling and osmolality measured in whole blood specimens within 10 min. Glucose (mmoles/L) and oxygen (%) levels were measured using ISO standards.

Results & Discussion

The present study showed a 4.8% increase in osmolality with values ranging from 287 to 301 mOsm/Kg before and after intermittent cycling exercise (Fig. 1). Body weight significantly reduced by 3% after intermittent cycling exercise with % change values for each volunteer ranging from 1.6 to 3%. This response was associated with a parallel increase in values for osmolality (R value = 0.95). Our findings are in agreement with previous studies which showed plasma osmolality changes ranging from 288 to 297 mOsm/Kg [1-2].

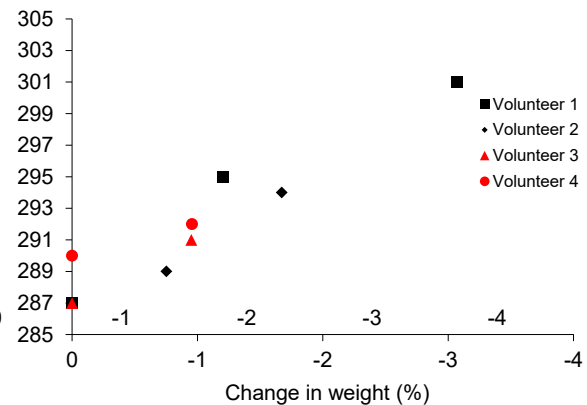


Fig. 1. Correlation between changes in body weight (dehydration) and osmolality in whole blood specimens (n=4).

Conclusion

The present study demonstrates a positive correlation of osmolality with dehydration, suggesting the technique has the potential to monitor hydration in sports people.

References

1. Fortes M, Diment BC, Di Felice U, Gunn AE, Kendall JL, Esmaeelpour M, Walsh NP. *Med Sci Sports Exerc.* 2016;43:1590-7.
2. Morgan RM, Patterson MJ, Nimmo MA. *Acta Physiol Scand.* 2004;182:37-43.

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BioMedEng18

Cell biology in mini-chambers with fluid walls

Cristian Soitu¹, Alexander Feuerborn², Ann Na Tan², Henry Walker², Pat A. Wals³, Alfonso Castrejon-Pita¹, Peter R. Cook⁴, Edmond J. Walsh¹

¹Department of Engineering Science, University of Oxford, Parks Road, Oxford, OX1 3PJ, ²Iota Sciences Ltd., Begbroke Science Park, Begbroke, Oxfordshire OX5 1PF, ³Department of Civil Engineering, University of Limerick, Castletroy, Limerick, Ireland, ⁴The Sir William Dunn School of Pathology, University of Oxford, South Parks Road, Oxford OX1 3RE, UK

Introduction

A high variety of microfluidic platforms that aim to miniaturize and automate biochemical assays have been developed in the last two decades but for the majority of these there is no progression beyond the proof-of-concept experiments due to the complexity of fabricating and operating them. We introduce a novel method for creating arrays of fluidic-walled sessile droplets, the equivalent of conventional microtiter plates, using only standard dishes and fluids.

Methods

The method consists in displacing a continuous fluid layer into a pattern of isolated chambers overlaid with an immiscible liquid to prevent evaporation. This liquid plays an additional role acting as a physical barrier, making the system contamination resilient. The resulting chambers have a rectangular footprint and use the maximum surface available. Pliant, self-healing fluid walls confine volumes as small as 10 nL. The technique is not restricted to arrays but allows for quick and flexible prototyping of a high range of microfluidic circuits with irregular patterns.

Results & Discussion

A basic set of capabilities is demonstrated by accommodating cell and organism-based assays: biocompatibility, ways of introducing samples and reagents in the system, and methods that allow the retrieval of samples for subsequent analysis. The scalability of the system facilitates assays at both population and single-specimen level. Time-efficient means of manipulating fluids have been implemented to accommodate high-throughput experiments. Fluidic-walled chambers offer good optical clarity making them ideal for imaging the samples contained within.

Conclusion

The simplicity of the technique eliminates the need for expensive machinery or equipment. It is all incorporated in a bench-top system that can produce and access arrays of hundreds of fluidic chambers within minutes.

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Oxford University Innovation - the technology transfer company of The University of Oxford - has filed provisional patent applications on behalf of C.S., A.F., P.R.C., and E.J.W. partly based on this study. A.F., H.W., P.R.C., and E.J.W. each hold equity, or rights to equity, in IotaSciences Ltd, a company that is exploiting this technology. IotaSciences Ltd. provides a scholarship for C.S., and partially funds salaries and research of A.F., A.N.T., H.W., and P.A.W.

BioMedEng18

A Functional Model of the Small Arteries

K.H. Parker¹

¹ *Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London.*

Introduction

Most models of the systemic arteries can be described as empirical models based on experimental measurements and/or models based on the minimum work principle, introduced in 1922 by Murray. The empirical models exhibit large variance in the model parameters and there is considerable doubt about the applicability of the principle of minimum work to biological systems. For background and extensive references, see the excellent review [1].

Our model eliminates a major source of variation by considering only the small arteries and not the larger, conduit arteries. We assume the simplest, idealistic morphology of a uniform scalable bifurcating tree including the arterioles. The architecture of the capillaries is accommodated by defining a 'microvascular unit' which is perfused by an arteriole.

Methods

The size of the tree (number of generations) is determined by the estimated number of capillaries in the organ or tissue of interest and the number of capillaries perfused by each arteriole.

The lengths of the vessels in generation n scale as $L_n = \lambda L_{n-1}$, but the angles between each daughter vessel and the parent vessel are assumed to be independent uniformly distributed random variables $0 < \theta < \pi/2$. The mean square end-to-end length is calculated and the positions of the arterioles at the end of each of the branches is assumed to be a Brownian path. The density of arterioles is calculated from the number of arterioles and the volume of the complex hull of a Brownian path. The density and the length of the arterioles determine λ .

The diameters of the vessels in generation n scale as $D_n = \delta D_{n-1}$. Given the average volume flow rate in the tree, the pressure drop is calculated by assuming steady Poiseuille flow. We assume that the maximum flow rate is attained when the resistance through the arterial tree is negligible. The enhanced flow ratio and the diameter of the arterioles determine δ .

Most speculatively, we assume that the wave speeds in generation n scale as $c_n = \sigma c_{n-1}$. With this assumption, we can calculate the effective reflection and transmission coefficients at each bifurcation. Since the travel times of wave fronts in each branch are identical, it is possible to use traditional discrete wave front analysis to describe the dynamic behaviour of the whole tree. The observed attenuation of the pulse pressure through the small arteries determines the wave speed scale factor σ .

Results and Conclusions

Initial results suggest that this model may provide a useful tool for increasing our knowledge about the function of the small arteries, a frequently neglected part of the cardiovascular system. Examples are given of the model applied to the superficial calf muscles, the heart, the brain and to a single finger.

References

1. Hughes AD, *Artery Res.* 2015; 10: 1-10.

3D imaging of arterial permeability in the intact brachiocephalic artery using confocal microscopy

M.Dazzi¹, E.M. Rowland¹, P.D. Weinberg¹

¹ Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

The focal distribution of atherosclerosis has been attributed to the influence of biomechanical forces, in particular wall shear stress, on the endothelium [1]. Shear stress may trigger lesions by increasing endothelial permeability to macromolecules. Correlating maps of permeability, disease and wall shear stress can provide an insight into atherogenesis. Existing optical techniques for imaging arterial macromolecule uptake are limited by depth penetration. Therefore, imaging is most commonly performed on straight segments of the aorta where the vessel can be cut longitudinally and mounted *en face* [2]. Imaging areas of high curvature would be more relevant in understanding disease progression. We propose a novel technique which quantifies uptake of rhodamine-albumin into the artery wall by extended 3-D imaging of intact, optically cleared arteries.

Methods

Male Sprague-Dawley rats (250-280 g) were anaesthetised and rhodamine-labelled albumin tracer (150 mg/kg *iv*) administered. Animals were sacrificed after 30 mins with sodium pentobarbital (*iv*) and perfusion fixed. The aortic arch and daughter vessels were collected, dehydrated in a graded ethanol series and cleared in Benzyl Alcohol:Benzyl Benzoate (BABB). 3D image volumes were obtained of the intact aorta-brachiocephalic junction using a confocal microscope with low powered objective. Images were post-processed using VMTK [3] and VTK [4] to generate a 3D surface mesh of the arterial geometry, onto which tracer uptake was mapped.

Results & Discussion

Despite a vessel diameter >800 µm, fluorescence was still detectable on the posterior wall; the drop-off in intensity with depth was corrected for. Macromolecule permeability was readily mapped in the intact junction where the highest uptake occurred on the flow divider. Control experiments where tracer was omitted produced a uniform mesh of low signal intensity.

Conclusion

Extended-depth 3D imaging of rhodamine-albumin uptake in the intact brachiocephalic artery was achieved for the first time. It obviates the need for labour-intensive sample preparation associated with standard *en face* mounting/imaging. More importantly it preserves arterial geometry, facilitating co-localisation with maps of biomechanical factors which typically exist on 3D surface meshes. This technique will allow us to correlate wall shear stress with macromolecule permeability more accurately in regions of high curvature in the vasculature, in particular the coronary arteries.

References

1. Peiffer V et al., *Cardiovasc Res.* 2013; 99: 242-250.
2. Bailey EL et al. *PLoS One*, 2015; 10:1-20.
3. Antiga L et al. *Med Biol Eng Comput.* 2008; 46: 1097-112.
4. Schroeder W et al. *The Visualization Toolkit* (4th Ed.), 2006, Kitware, ISBN 978-1-930934-19-1

Acknowledgments

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Electrical waves rotate around a stable core in monolayers of cardiac cells without functional or structural inhomogeneity.

C. Houston¹, K.N. Tzortzis¹, D.S. Pitcher¹, R.A. Chowdhury¹, F.S. Ng¹,
C.D. Cantwell¹, N.S. Peters¹, E. Dupont¹

¹ *ElectroCardioMaths Program of the Imperial Centre for Cardiac Engineering, National Heart & Lung Institute, Imperial College, London, W12 0NN.*

Introduction

Cardiac fibrillation may be driven by self-sustaining waves of electrical propagation that form rotating circuits. Due to the challenge of capturing and interpreting this activity in complex in-vivo models, it is often studied in simplified in-vitro preparations. However, single-cell resolution optical mapping of these preparations using conventional cardiac cell types pushes modern imaging technology to its limit. The reduced conduction velocity of HL1-6 myocytes [1] allows recording at high frame-rate and single-cell resolution, while the functional homogeneity allows the dynamics of the propagation to be studied in the absence of structural obstacles.

Methods

Rotational waves of propagation were initiated by natural automaticity in small colonies of the atrial-derived HL1-6 cell line (areas 3-10mm²) and visualised on a 10x lens at 100FPS. Ca²⁺ transients and action potentials were recorded using Fluo-4 and BeRST. Stability of the rotational activity was tested by checking for reappearance at the same location after either depolarisation (with KCl) or electrical uncoupling (with Heptanol) of the monolayer. The cores of the stable rotating waves were characterised using a novel algorithm which generates a heatmap of fixed features computed from differences in activation times between individual cells.

Results & Discussion

All rotational activity (n=27) remained in the same location for the recording duration (10-30s) and time to locate cores (several minutes). The activity never returned to the same location after depolarisation or uncoupling despite initiating sites (i.e. pacemaking cells) remaining fixed. Our processing algorithm revealed cores were composed of thin lines of conduction slowing (lengths: ~0.3-1.5mm) connecting small groups of cells, suggesting this rotational activity is not regulated by an equilibrium between wavefront curvature and source-sink mismatch. Cells in the core area exhibited either no periodicity or activated at double the frequency of the rotating wave.

Conclusion

We studied the core and stability of self-sustaining rotational waves at single-cell resolution in a functionally homogeneous in-vitro preparation. Our results show that stable rotational activity can appear and perpetuate in a simplified biological model and in the absence of more complex structural (e.g. fibrosis) or functional inhomogeneity (e.g. differing cell types), and suggest this characteristic feature of cardiac fibrillation may instead be determined by microscopic mechanisms between individual cells.

References

- [1] Dias P et al. Characterisation of connexin expression and electrophysiological properties in stable clones of the HL-1 myocyte cell line. PLoS ONE 2014;9:e90266. doi:10.1371/journal.pone.0090266.

Acknowledgments

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BioMedEng18

Human Langendorff: Building an ex vivo whole heart perfusion system for high fidelity controlled electrophysiological assessment

DS Pitcher, B Handa, M Kim, R Jabbour, C Cantwell, S Harding, FS Ng, NS Peters, RA Chowdhury

ElectroCardioMaths Programme, Imperial Centre for Cardiac Engineering, Imperial College London, Hammersmith Campus, W12 0NN, London.

Introduction

A major barrier to translational research, particularly in the cardiovascular field, is the inability to translate bench and animal research to the bedside, with many laboratory findings failing to translate to the clinic. Explanted intact human hearts provide the ideal middle ground to bridge this translational gap. Technologies based on the Langendorff preparation have long existed for intact whole organ preparations, for probing *ex vivo* hearts in a controlled and high fidelity manner not possible *in vivo*. However, for the most part these apparatus are in routine use in rodent animal models, with few large animal, and even fewer human studies being carried out. We describe our build of a Langendorff perfusion system suitable for use with *ex vivo* intact human hearts.

Methods

The challenges of performing the Langendorff preparation with human hearts lies in its size, which adds complexity due to the large volumes of perfusate required to be circulated and due to its weight and size requiring appropriate cannulation and support. We built human Langendorff system with a custom cannula appropriate to support the human aortic size. The system includes a high pressure pump and appropriate tubing size to incorporate the flow rates suitable for sustaining human hearts. The system also incorporates ECG, temperature, pressure, pH and lactate monitoring, to assess stability of the preparation. Preliminary calibration was carried out using porcine hearts, followed by validation of the technique using a human donor heart rejected for transplantation.

Results & Discussion

We have successfully sustained an *ex vivo* human heart for live recordings for up to three hours for high fidelity controlled electrophysiological assessment. During this time we recorded contact electrograms using endocardial and epicardial research and clinical electrode arrays, for assessment of electrophysiology using clinically accessible tools. We also carried out voltage optical mapping for probing of action potential changes. Pacing protocols allowed for sustained regular activation, and arrhythmogenic pacing protocols induced both atrial fibrillation and ventricular fibrillation for assessment of mechanisms of arrhythmia induction and perpetuation.

Conclusion

This unique apparatus provides a platform for investigations of *ex vivo* intact human hearts for high fidelity controlled electrophysiological assessment to validate that any findings from small animal models holds true in intact human myocardium.

Acknowledgments

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BioMedEng18

Comparison of students' performance in examinations compared to group coursework

A P Gibson¹, J A Griffiths², I Direito³

¹ Medical Physics and Biomedical Engineering, UCL London WC1E 6BT. Arena Centre for Research-Based Education, UCL London WC1E 7HB ³Centre for Engineering Education, UCL London WC1E 6BT.

Introduction

Some reports suggest that traditional examinations favour male students while coursework favours women, while others disagree¹⁻³. It can be difficult to test this in engineering subjects due to the uneven gender balance. We have examined results from a biomedical engineering module which attracts approximately 50/50 male/female students and which is assessed by 60% exam and 40% group-based open ended problem solving coursework.

Methods

Exam board results from eight years of a final year module on Treatment with Ionising Radiation were analysed. In total, 226 students took the module. 90 were female and 126 male. The difference between exam score and coursework score was calculated for each student and the distributions plotted. Similar analysis was performed for nationality (using fee status as a proxy for UK/overseas students) and programme type (the module attracts approximately even numbers of intercalating medical students and students from physics and engineering programmes).

Results & Discussion

On average, students scored 5.8% higher on coursework than exams. However, the difference between coursework and exam score for men was not statistically significantly different ($p < 0.05$) than that for women. Similarly, there was no statistically significant difference between the scores for home and overseas students.

Physics and engineering students were awarded 9.9% higher marks on coursework than exam compared to intercalating medical students who received 1.1% higher on coursework than exam. This result is statistically significant and is entirely due to the medical students' improved performance in the examination

Conclusion

There is no evidence to support the hypothesis that women are more suited to assessment by coursework and men are more suited to examination. Similarly, home and overseas students perform equally well. It does seem that students' prior experience on their programme may equip them more for some types of assessment than others.

References

1. Woodfield R, Earl-Novell S, Solomon L. Gender and mode of assessment at university: should we assume female students are better suited to coursework and males to unseen examinations? *Assess Eval High Educ.* 2005 Feb 1;30(1):35–50.
2. Richardson JTE. Coursework versus examinations in end-of-module assessment: a literature review. *Assess Eval High Educ.* 2015 Apr 3;40(3):439–55.
3. Donnelly RCA. Gender differences in undergraduate students' performance, perception and participation in physics. PhD Thesis, University of Edinburgh. 2014.

A proof of concept for machine learning application to stenosis detection

G. Jones¹, J. Parr², P. Nithiarasu¹, S. Pant¹

¹ College of engineering, Swansea university, SA1 8EN, ²McLaren technology centre, Woking, GU2 14YH.

Introduction

Current methods for detecting stenosis involve either invasive procedures or expensive imaging techniques. Using a combination of 1D pulse wave propagation and machine learning techniques, a proof of concept is developed to detect stenosis from easily obtainable peripheral measurements. A virtual patient database is created, where each patient has randomised network parameters. A total of 10,000 patients have been generated, with 50% of the patients given healthy parameters. The other 50% of the virtual population represents unhealthy patients, i.e. a stenosis is present. This complete database is used to train a binary classifier and a regressor, to predict the presence of stenosis and the severity respectively.

Methods

The network used to test the proof of concept is created to represent an aortic bifurcation, with the abdominal aorta and two common iliac arteries included. For each virtual patient the following parameters are randomised: three geometric parameters (length, reference area, wall thickness), one material property (the Young's modulus), and the boundary conditions (the volumetric inflow into the system and the terminal boundary conditions, modelled as a Windkessel system). For unhealthy patients, the location of the stenosis within the system and the severity are also randomised. A pre-existing 1D pulse wave propagation arterial model [1] is used to solve the pressures and flow-rates across the network for each patient. Two machine learning algorithms (a binary classifier and a logistic regressor) have been trained from this database. For the proof of concept, the classifier has been given the input of a combination of pressure and flow rates at different locations in the network, and the output is either 1 or 0 representing diseased and healthy patients, respectively. The regressor then predicts the severity of stenosis, represented as percentage reduction in area.

Results and discussion

Two different approaches have been taken to train the classifier. The first is to use measurements of pressure and flow without enforcing any restrictions on their geometric locations. By using both pressure and flow-rates at 7 locations (the three boundaries, the bifurcation, and at the centre of each vessel) an average classification accuracy of over 85% has been achieved. The second approach restricts the inputs to the algorithm to only boundary measurements. In this case, a classification accuracy of approximately 65% is obtained.

Conclusion

While the classifiers show promising results, the accuracy of the restricted classifier needs improvement by exploring advanced parameter optimization algorithms and weighted cost measures to minimise false negatives.

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References: [1] Boileau, E., Pant, S., Roobottom, C., Sazonov, I., Deng, J., Xie, X. and Nithiarasu, P., *International journal for numerical methods in biomedical engineering*, **34**:e2908. (2018).

BioMedEng18

Personalised Diagnostic Tools for Infectious Diseases

G. Abebe Tadesse¹, T. Zhu¹, H. Duong², L. Thwaites², D.A. Clifton¹

¹ Institute of Biomedical Engineering, Department of Engineering Science, University of Oxford, Oxford, UK.

² Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam.

Introduction

Infectious diseases, such as tetanus, still pose life-threatening risks in low and middle income countries (LMICs), particularly for unvaccinated individuals [1]. The WHO estimated that 34,019 newborns died from neonatal tetanus alone in 2015 (the latest year for which estimates are available) [2]. Autonomic nervous system dysfunction (ANS) is the main cause of death by infectious diseases. Early detection of ANSD, using low-cost wearable sensors in conjunction with intelligent algorithms, may allow more efficient use of (often scarce) hospital resources and improve the care to patients.

Methods

We propose using novel features encoding the temporal variation (in time and frequency domains) of physiological data to classify the severity of ANSD in tetanus patients. Time domain features include gradient pooling (i.e., the count and sum of the positive and negative gradients once a first-order temporal derivative is applied), along with a set of summary statistics of the time-series [3]. Low-frequency components were also found to be discriminative additional features for this application. Furthermore, the amplitude response is also quantised into a number of frequency bands to encode whole-spectrum characteristics. A prototype dataset of 10 patients (4 mild and 6 severe tetanus cases) was considered for our proof-of-principle study. Each patient had approximately 24 hours recording of vital signs, such as heart rate (HR) and oxygen saturation (SpO2). In addition, the electrocardiogram (ECG), photoplethmogram (PPG), and impedance plethysmography (IP) waveforms were collected. The data from each patient was partitioned into training (50%) and testing (50%) sets randomly. A kernel machine was used for classifying the severity of each patient using our proposed features. Accuracy was used to validate classification performance on the held-out data.

Results & Discussion

We obtained accuracy of using each data source independently: HR (87%), SpO2 (73%), ECG (95%), PPG (94%) and IP (94%). The results show that the predicted accuracies using vital signs are inferior to those using waveforms because the latter exhibit periodic variations that can be exploited by frequency-domain features. The concatenation of features into a multivariate model (i.e., HR+SpO2+ECG+PPG+IP) is also shown to improve the performance further to 96%.

Conclusion

Tetanus is an infectious disease that represents a serious threat to health in the developing world. Early diagnosis of its severity using low-cost and unobtrusive devices, in conjunction with machine learning algorithms, could be used for timely intervention. Our results show that features extracted from an (inexpensive, easy-to-use) pulse oximeter achieve competitive performance when compared to (a more costly, difficult-to-use) ECG.

References

1. D. B. Thuy *et al.* Tetanus in Southern Vietnam: Current Situation, *Am J Trop Med Hyg*, 2017; 96(1): 93–96.
2. http://www.who.int/immunization/diseases/MNTE_initiative/en/
3. G. Abebe and A. Cavallaro, Hierarchical modeling for first-person vision activity recognition, *Neurocomputing*, 2017; 267: 362-377

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Identification of Clinical Factors Associated with Poor Surgical Outcomes in a Large Primary Care Dataset

D. Narganes¹, L. McMenamin^{2,3}, D.J.Drayton^{2,3}, C. Bates⁴, A. Kotze³, S.J. Howell^{2,3}, D. Wong¹

¹Leeds Institute for Data Analytics, University of Leeds, UK; ²Leeds Institute of Biomedical and Clinical Sciences, University of Leeds, UK; ³Department of Anaesthesia, Leeds Teaching Hospitals NHS Trust, UK; ⁴TPP, Leeds

Introduction

There are 310 million surgeries worldwide per year, there is a 1-5% short-term mortality and 20% post-surgical complications rate. Aims: (i) to statistically infer clinical factors associated with poor surgery outcomes and (ii) to overcome the limitations of missing data.

Methods

ResearchOne is a longitudinal, anonymised primary care dataset from TPP. A subsample of 860,649 individual surgeries performed from Jan 2011 to Dec 2016 was used. We predicted mortality (1, 3, 6 months), length of survival (LoS), and 12 months increase in electronic frailty index² (ΔeFI_{12}) using a general linear model with Elastic Net regularisation and iterative fitting along a regularisation path. Confidence intervals were derived via bootstrap sampling ($n=100$).

Age; gender; use of antihypertensives (AH); eFI at surgery; mean, slope, and count of both systolic (SBP) and diastolic (DBP) BP 12 months prior to surgery; socioeconomic status (IMDR 2011); counts of GP visits (GPV) 12 months prior to surgery; and latent variables for missing data were the assumed independent variables. In sensitivity analysis, all missing data was imputed with MICE ($n=30$) apart from preoperative BP, which was imputed in 39% of cases based on population-level centiles adjusted for age, gender, and AH³.

Results & Discussion

Age, preoperative eFI, and AH were the best predictors for the outcomes ΔeFI_{12} (95% CI standardised β coefs (βC): 0.94-1.06, 0.73-0.86, 0.33-0.37, respectively); and LoS (95% CI S βC : 1.00-1.00, 0.88-0.89, 0.26-0.27, respectively). Low DBP was a predictor for LoS, mortality, and ΔeFI_{12} . After missing data imputation, no reduction was observed in βC for features with no missing data. However, there was a >80% reduction in βC (for all outcomes) for low DBP. In a subsequent analysis, patients with missing BP were found to be a selective subsample: AH, age, eFI, and LoS and ΔeFI_{12} were predictors of missing BP (95% CI βC : (-1.43, -1.43), (-0.55, -0.54), (-0.42, -0.42), (-0.07, -0.07), (-0.06, -0.06), respectively). Because BP were not missing at random, the association between BP and outcomes is likely to be spurious.

Conclusion

While the relationship between post-operative survival and BP requires further clarification, the eFI may warrant further investigation for inclusion in risk assessment measures.

References

1. Pearce, R. M., Holt, P. J. E. & Grocott, M. P. W. BMJ 343, d5759 (2011).
2. Clegg, A. *et al.* Age Ageing 45, 353-360 (2016).
3. Wright, J. D., Hughes, J. P., Ostchega, Y., Yoon, S. S. & Nwankwo, T. Natl Heal. Stat Rep. 1-22,24 (2011).

Acknowledgments

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Extracting robust controllers from motion data using computed muscle control and imitation learning

L. Rane¹, A.H. McGregor², A.M.J. Bull¹

¹ Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London. ²Department of Surgery and Cancer, Imperial College, South Kensington, SW7 2AZ, London

Introduction

There is growing interest in neurorehabilitation routines that account for subject-specific differences in control strategy. Motion data promises a window into the workings of the motor system. Standard tools of biomechanical analysis may be used to derive trajectories of muscle activations consistent with observed kinematics but in many cases we require a policy – a function mapping from states to actions – for reasons of generalisability and robustness. Imitation learning may be used to obtain such a policy.

Methods

Laboratory-captured kinematic data were used to create a computational simulation of level-walking in a torque-actuated humanoid model. By application of computed muscle control (CMC [1]) torque trajectories were derived which, when applied during a forward dynamic simulation, drove the model through the observed kinematics. These torques and the time-matched trajectories of input joint angles and speeds were used to train a feedforward neural network by minimisation of mean squared error between predictions of the torque vector and target values. To combat distributional mismatch between training states and those encountered at test time due to accumulated errors, dataset aggregation (DAgger [2]) was performed using CMC to label actual states visited by the model with actions required to drive its return to the desired trajectory. Iterations of DAgger and network re-training were run consecutively until convergence.

Results & Discussion

Given an initial state, trained policies were able to drive humanoid models through a gait cycle that accurately matched experimentally measured kinematics.

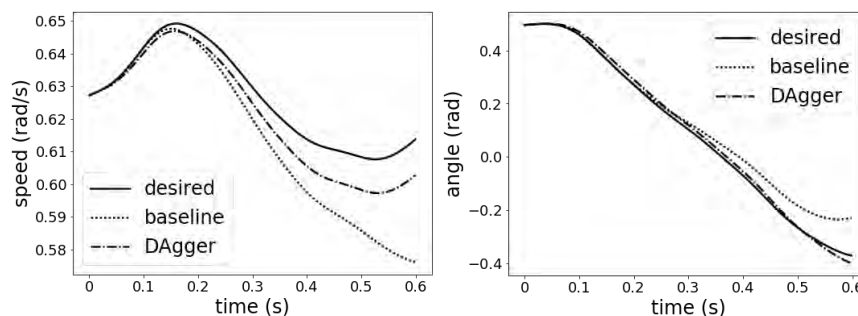


Fig: Desired/ actual trajectories for two selected kinematic trajectories, before and after a single iteration of DAgger

Conclusion

Robust policies represent subject-specific models of motor control. By optimisation with respect to biomechanical variables, using reinforcement learning for example, personalised insights may be gained into potentially beneficial rehabilitation strategies.

References

1. Thelen DG, Anderson FC, Delp SL. *J Biomech.* 2003; 36(3):321-8.
2. Ross S, Gordon GJ, Bagnell A, *arXiv.* 2010; 1011.0686v3.

BioMedEng18

Bayesian Machine Learning to Predict Short-term Course of Eczema Severity

G. Hurault, R.J Tanaka

Department of Bioengineering, Imperial College London, London, UK.

Introduction

Atopic dermatitis (AD), or eczema, is a most common chronic skin disease characterised by a dry and itchy skin. The disease pathogenesis is governed by a dynamic interplay between skin barrier, immune responses, and environmental stressors. Given a large variation in the disease severity and responses to treatments from one individual to another, it is of high clinical relevance to design personalized treatment strategies for AD, rather than the “one-fits-all” treatments. Better prognoses of the course of AD severity could help to choose appropriate treatments for each patient. In this study, we aim to develop a statistical model that can predict the short-term course of the eczema severity by fitting clinical data using Bayesian Machine Learning to a mechanistic model of AD pathogenesis (“double-switch model”) that we previously developed [1].

Methods

We used the data from an already published longitudinal clinical study [2] on 60 AD children under a topical corticosteroid therapy. The data included daily self-assessment of two eczema severity scores and environmental exposures, for up to 9 months. We modelled the evolution of eczema severity based on the double-switch model, performed inference using the Hamiltonian Monte-Carlo algorithm and validated the predictions in an online learning setting.

Results & Discussion

We developed a statistical model to predict the short-term course of eczema severity. The Brier score for all patients decreased from 0.91 (random guess) to 0.74, confirming that the model learns AD dynamics as more data becomes available. We also estimated patient-dependent parameters, such as the recovery rate and the flare occurrence. The latter could be used to determine whether AD flares (exacerbation) are more likely to occur in the coming week and patients need proactive treatments. We further observed a wide difference in predictability of the model across patients. This information could be useful for patient stratification.

Conclusion

We developed and internally validated a statistical model to predict the short-term course of eczema severities. Similar models could be developed to assess the effects of different treatments on the dynamic course of eczema severities. The method used here will be tested with another patient population data, as the data used in this study was from a relatively small number of patients who might not be representative of the general population.

References

- [1] E. Domínguez-Hüttinger et al., “Mathematical modeling of atopic dermatitis reveals ‘double-switch’ mechanisms underlying 4 common disease phenotypes”, *Journal of Allergy and Clinical Immunology*, vol. 139, no. 6, pp. 1861-1872.e7, Jun. 2017.
- [2] S. M. Langan, P. Silcocks, and H. C. Williams, “What causes flares of eczema in children?”, *British Journal of Dermatology*, vol. 161, no. 3, pp. 640–646, Sep. 2009.

Acknowledgments

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Automatic Shadow Detection in Fetal Ultrasound Images

G. Kaur ¹, A. Fazili ¹, K. Wynter ¹, A. Gomez ¹, K. Rhode ¹, J. Housden ¹

¹ School of Biomedical Engineering and Imaging Sciences, King's College London, UK.

Introduction

Ultrasound is the primary modality used in fetal anomaly screening as part of the national Fetal Anomaly Screening Programme (FASP) [1]. The purpose of this scan is to detect abnormalities early enough to allow the conditions to be appropriately managed. Currently only about half of fetal abnormalities are detected in this process, with success depending largely on the skill of the sonographer in acquiring correct and complete images. This is partly because of the presence of ultrasound shadow artefacts [2]. which can hide the required anatomy.

Methods

Images of the standard head (HC, TCD) and abdomen (AC) views were acquired from fetal anomaly scans of 52 patients comprising 983 images. Images of ultrasound beam lines were extracted, and shadows manually segmented using custom software, and the shadow masks saved as images. The images were processed to extract features at each pixel likely to indicate a shadow, including normalised intensity, average intensity below the pixel, standard deviation below the pixel, and standard deviation of lateral gradient below the pixel. The individual pixels of the original images and mask images were used to train a decision tree classifier to detect shadows, using the four features as input. 40 of the patient cases were randomly selected as training data, and 10 were reserved for testing. The trained model was applied to the images from the 10 testing cases and compared to the manual segmentation as ground truth for shadow.

Results

The classification accuracy per pixel, in terms of true and false positive rate (TPR, FPR) and true and false negative rate (TNR, FNR) is shown in Table 1, for different combinations of training and testing data. Example results are shown in Figure 1.

Table 1: classification accuracy

Training	Testing	TPR	FNR	TNR	FPR
TCD	TCD	0.57	0.43	0.92	0.08
TCD	AC	0.70	0.30	0.83	0.17

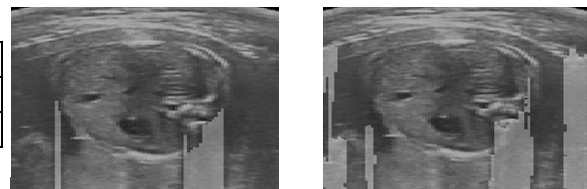


Figure 1: Example manual (left); automatic (right) detection

Discussion & Conclusion

Both the numerical and visual results show that shadows can be reliably detected using this method. In some cases, the automatic segmentation detects valid shadows that are not present in the manual segmentation. The visual results are therefore very encouraging, as is the fact that the results are maintained when training and testing on different types of images.

References

1. Fetal Anomaly screening programme (Online, Accessed 10/04/18) – Available at <https://www.gov.uk/government/publications/fetal-anomaly-screening-programme-handbook>.
2. Abu-Zidan FM, Hefny AF, Corr P. Clinical ultrasound physics. Journal of Emergencies, Trauma and Shock. 2011;4(4):501.

Acknowledgments

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BioMedEng18

Assessing the Mechanical Suitability of 3D Printable Polymers, for Use in Maxillofacial Prosthetics

M. C. Ward¹, J. Yates², R. Judge³, S. Wuerger⁴, R. Akhtar¹

¹ Department of Mechanical, Materials and Aerospace Engineering, University of Liverpool, Liverpool, L69 3BX, ² School of Dentistry, University of Manchester, Manchester, M13 9PL, ³ Department of Civil Engineering and Industrial Design, University of Liverpool, Liverpool, L69 3GH, ⁴ Institute of Psychology, Health and Society, University of Liverpool, Liverpool, L69 7ZA

Introduction

Facial prosthetics are currently dominated by hand produced, labour-and-time-intensive, silicone-based designs. However, there has been an increased interest in recent years towards using additive manufacturing as an alternative to conventional methods. This study investigates the mechanical properties of an elastomeric photopolymer, Agilus30 Clear, used in a commercial 3D printer; the J750 (Stratasys, Ltd. Eden Prairie, Minnesota, United States), with a comparison against a widely used, medical grade, platinum based silicone, VST 50, produced by Factor II (White Mountain Avenue, Lakeside, AZ, USA). In order to further progress the digital development of maxillofacial prosthetics, the study has looked at incorporating skin-mimicking biomechanical properties, within the sub-structure of the additively manufactured polymer.

Methods

The Agilus30 test specimens were designed in PTC Creo. The VST 50 was cast in custom machined, aluminium moulds, under accelerated heat curing (170°C for 5 minutes). Five types of test were carried out, with the parameters and specimen dimensions based on the following standards, in line with those currently used in industry; Tensile Strength: ASTM D-412 Type C, Tear Strength: ASTM D-624 Type C, Compressive Strength and Indentation: ASTM D-575 Test A 40% Compression, Shore A Hardness: BS ISO 7619-1. All but the latter were carried out on an Instron uniaxial testing machine (Norwood, Massachusetts, United States). The Shore A testing was carried out using a Shore Durometer (The Shore Instrument & MFG. Co., NY, USA). A minimum of five samples were tested for each standard.

Results & Discussion

The tensile test showed the Agilus30 to have an UTS of 2.7MPa and elongation at break of 270%, although finite element analysis indicates that the true UTS is approximately 6.1MPa. The VST 50 had a UTS of >3.5MPa and >500% elongation at break. Tear strength of the Agilus 30 averaged at 5.46 Kg/cm, whereas it was difficult in determining the same value for the VST 50, due to nonlinear tearing. Full compressive strain of 40% produced stresses of 0.78MPa and 0.68MPa for Agilus30 and VST 50, respectively, although the silicone portrayed a lower strain energy per unit volume. Indentation results showed expected parallels in relation to the full compression results. The Shore A hardness results came in at 25.7±0.4 for Agilus30 and 21.3±0.3 for VST50, both lower than expected.

Conclusion

In conclusion, close similarities between the two materials were noted in both full compressive tests and indentation tests. Tensile tests varied significantly, but within the range required for routine use of maxillofacial prosthetics, Agilus30 was still deemed to be a viable alternative. A necessary follow up study is required to assess the biocompatibility of commercial additive manufacturing polymers.

Acknowledgments

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Development of a soft robotic liner (SRL) for prosthetics

U. Tanriverdi¹, F. Guder¹

¹Royal School of Mines Building, 4.23, Imperial College London, South Kensington, SW7 2BP, London.

Introduction

This abstract presents the suspension characterisation and performance of a novel robotic prosthetic technology employing soft actuators (Figure 1). Soft Robotic Liner (SRL) is a close-ended elastomeric sleeve with pneumatic chambers, and combines the conforming feature of the soft robotics with an existing limb fitting technique, *prosthetic liners*, (i) to improve the fitting by compensating the volume and geometry changes in the residual leg, (ii) to enhance the weight-bearing feature of the prosthetic sockets, and (iii) to reduce the medical complications (i.e. blisters and ulcers) caused by poor limb fitting.

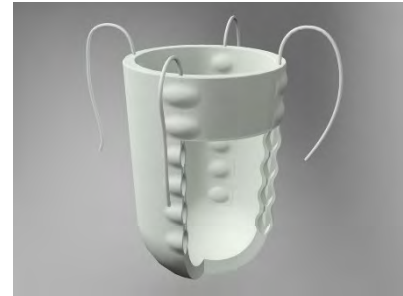
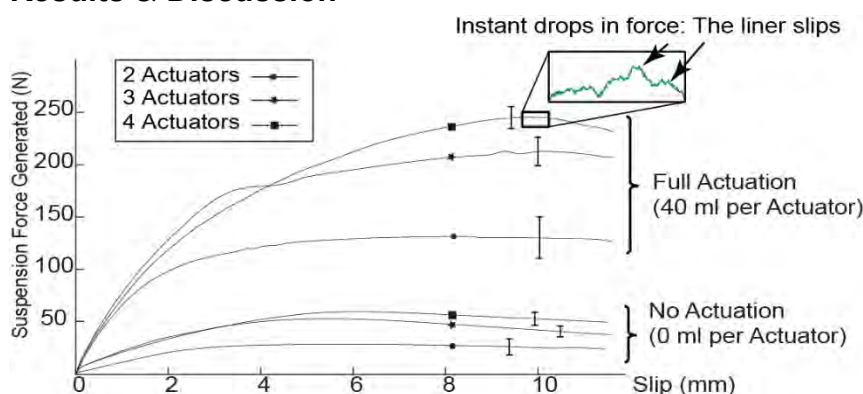


Figure 1: The cross-section of SRL with 4-serial actuators¹.

Methods

We validated the preliminary SRL design by experimenting the correlation between weightbearing and actuation parameters such as *pneumatic pressure, force and actuation volume*. To demonstrate the effects of these parameters on weight-bearing and fitting performance, we fabricated nine liners with actuators ranging from two to four serial actuators. The force-displacement data of each liner was recorded over three repeats while SRL was actuated between a 3D printed socket and stump.

Results & Discussion



"No actuation" represents the suspension behaviour of a regular prosthetic liner. Injecting 40 ml air per actuator (full actuation) generates approx. 250N weightbearing force and creates a pneumatic pressure of approx. 21 psi, which is the safety limit of the preliminary design. The

pneumatic actuation of SRL results in the alteration of the wall thickness and surface geometry which are crucial fitting factors involved between the residual leg and prosthetic socket.

Conclusion

The instant and pneumatic customisation of SRL's geometry demonstrates opportunities to reduce the geometric significance of hand-made sockets, which could lead to a cost-effective and time saving prosthetic fitting process.

References

1. Tanriverdi, U, Guder F. *J Soft Robotics*. 2018; (Submitted)

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BioMedEng18

Pre-clinical Experimental Wear Simulation of an All-Polymer Total Knee Replacement

R. M. Cowie¹, A. Briscoe², J. Fisher¹, L. M. Jennings¹

¹ Institute of Medical and Biological Engineering, University of Leeds, UK. ² Invibio Ltd, Thornton Cleveleys, UK

Introduction

PEEK has been considered as an arthroplasty bearing material due to its favourable mechanical properties, biocompatibility and clearance for clinical use¹. In this study, PEEK-OPTIMA™ has been investigated as an alternative to cobalt chrome in the femoral component of a total knee replacement. This would give a non-metallic implant of lower weight and would potentially reduce stress shielding². A series of experimental studies of both the patellofemoral and tibiofemoral³ joints were carried out to investigate the wear performance of this implant.

Methods

Experimental wear simulation of both the tibiofemoral and patellofemoral joints was carried out using a 6-station Pro-sim knee simulator with input profiles to replicate a walking gait cycle. For all tests, the all-polymer knee replacement (collaboration partners Maxx Orthopedics Inc., Plymouth Meeting, PA, USA and Invibio Knee Ltd, Thornton-Cleveleys, UK) was investigated in parallel with a conventional metal-on-polyethylene implant (MAXX Orthopaedics Inc.) of similar initial surface topography and geometry. Conventional UHMWPE components were used throughout, all components were EO sterile. Minimum n=3 and 5 million cycles was carried out for each study. 25% bovine serum supplemented with 0.03% sodium azide was used as a lubricant and the wear of UHMWPE was assessed by gravimetric analysis.

Results & Discussion

The wear of UHMWPE in both the tibiofemoral and patellofemoral joints was low, <5mm³/MC and <1mm³/MC respectively. There was no significant difference in the wear performance of the UHMWPE tibial components when articulating against the different femoral component materials, p=0.27 and p=0.38 for the tibiofemoral and patellofemoral joints respectively. Scratching was observed on the surface of the PEEK implants however, this did not influence the wear rate which remained linear over the duration of the study.

Conclusion

Experimental wear simulation of both tibiofemoral and patellofemoral joints showed an equivalent rate of wear of UHMWPE against PEEK-OPTIMA™ and cobalt chrome femoral components. The scratches on the surface of the PEEK implants was not of sufficient magnitude to influence the wear of UHMWPE. These studies show PEEK-OPTIMA™ to have promise as an alternative to cobalt chrome in the femoral component of total knee replacements.

References

1. Kurtz S, Devine J. *Biomaterials*. 2007; 28(32):4845-4869.
2. de Ruiter *et al.* *Proc Inst Mech Eng H*. 2017; 231(12):1204-1212.
3. Cowie RM *et al.* *Proc Inst Mech Eng H*. 2016; 230(11): 1008-1015.

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Biomechanically Controlled Simulation of Traumatic Spinal Cord Injury *In Vitro* Using a 3D Hydrogel Model.

T.K. Nguyen¹, J.C.F. Kwok², J.B. Phillips³, R.M. Hall¹, J.L. Tipper⁴

¹ Institute of Medical and Biological Engineering, University of Leeds, LS2 9JT. ² School of Biomedical Sciences, University of Leeds, LS2 9JT. ³ Department of Pharmacology, UCL School of Pharmacy, University College London, WC1N 1AX. ⁴ Faculty of Engineering and IT, University of Technology Sydney, NSW 2007.

Introduction

Traumatic injuries to the spinal cord lead to a microenvironment in which regeneration is poor. Replicating the biomechanics of injury has increasingly been shown to be important in understanding the heterogeneity of pathophysiological events¹. The aim of this work was to determine the feasibility of using an adapted materials testing machine, to investigate the interactions between injury biomechanics and neural cellular responses, in a simple 3D hydrogel.

Methods

Characterisation of the BOSE Electroforce BioDynamic 5110 was performed, in air, to determine whether it was suitable for simulating contusion injuries *in vitro*. The waveform setup was as follows: 10 ms dwell, 1000 mm.s⁻¹ acceleration to 25, 50, or 75% gel height, 100 ms dwell, 1000 mm.s⁻¹ deceleration to 0%. 3D primary rat astrocyte seeded collagen gels were prepared in 48-well plates (300 µl). A contusion regime was then implemented, as described. Astrocyte reactivity was measured over a 14-day period, using glial fibrillary acidic protein (GFAP) as a marker.

Results & Discussion

Manual tuning improved concordance between the theoretical and experimental displacement profiles; increasing the working distance from 0 mm (gel surface) to 8 mm allowed for acceleration up to 1000 mm.s⁻¹. An increase in load with increasing displacement was observed, likely due to the viscous response of the gel. Work done was calculated, with values which can be compared with literature². Contusion in seeded gels resulted in a greater mean volume of GFAP, compared to control gels. This suggests an increase in astrocyte reactivity after simulated injury, which has been widely reported in other *in vitro* and *in vivo* models³.

Conclusion

Characterisation of the BOSE determined that it is an apparatus capable of simulating defined biomechanical inputs in a controlled and repeatable manner. There is also potential for the development of additional common injury mechanisms, such as distraction and dislocation. The collagen hydrogel served as an appropriate physiological substrate for astrocytes to survive. This allows the progression into using additional neural cells types, such as neurons, and in various combinations thus increasing the biological complexity of the model.

References

1. S. Mattuci et al. *Clinical Biomechanics*. 2018; 18: [Epub ahead of print].
2. C.J. Lam et al. *Journal of Neurotrauma*. 2014; 14: 1985-97.
3. Okada. S et al. *Neuroscience Research*. 2018; 126: 39-43.

Acknowledgments

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Chest Wall Reconstruction using Patient Specific 3D Printing and its Motion Analysis

S. Natarajan¹, A.A.Pontiki¹, A. Bille², K. Rhode¹

¹ Department of Biomedical Engineering, King's College London, SE1 7EH, London. ²Department of Thoracic Surgery, Guy's and St. Thomas' NHS Foundation Trust, SE1 9RT, London.

Introduction

Patients with early stage lung cancer undergo en-bloc resection surgery. Accurate reconstruction of the chest wall should provide protection, reduce post-operative complications and allow for proper respiratory motion of the chest wall. This study aimed to create a novel method to produce patient-specific rib-like prosthesis and device a system to evaluate the effect of reconstruction on chest wall mechanics.

Methods

The preoperative CT scan of a patient was used to create and 3D print a model of their ribs using image segmentation techniques. The model was then used to produce a silicone mould. The mould was filled with Methyl methacrylate cement to create the rib prosthesis. An Optical tracking system, Optotrak, was used to collect chest wall motion data from healthy volunteers. Chest wall reconstruction was simulated by taping the left arm to the side of the body to limit the range of motion on the left hand side. Principal component analysis (PCA) was used to identify the first two modes of variation and the values were plotted in scatter graphs for evaluation.

Results & Discussion

Based on the 3D chest wall reconstruction from the patient's CT scans, a mould was produced that can be sterilised and used to create sterile, exact replicas of the patient's ribs while maintaining the low procedure cost. This technique has been approved by the Clinical Governance and it is ready to be used in patients. Chest wall markers moving in similar patterns clustered together. Therefore, data from volunteers under healthy conditions showed three clusters representing the upper, middle and lower row markers. They also demonstrated symmetrical chest wall motion. Data obtained with the left arm taped showed asymmetrical chest wall motion. These findings have validated that this system is capable of identifying any asymmetries in the chest wall.

Conclusion

A practical and cost-effective method for the creation of patient specific rib-like prosthesis is feasible. The mechanical structure of the resulting rib prosthesis is accurate and when implanted in the chest wall should provide chest wall stability, good cosmetic results, and satisfactory respiratory movement. Chest wall motion analysis using Optotrak and PCA shows potential to be used to analyse reconstruction and its effect on chest wall kinetics. Different reconstructive techniques and their effect can be studied to further advance reconstruction procedures. Application of the proposed patient-specific prosthesis is the next step. This will be evaluated against current techniques using Optotrak.

Acknowledgments

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COMPUTATIONAL DESIGN OF A DUMMY NECK FOR HEAD-FIRST IMPACTS

Fady F. Abayazid¹, Mazdak Ghajari¹

¹ Dyson School of Engineering, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

Current surrogate necks are not biofidelic under axial loading, e.g. in head-first impacts in sporting collisions¹. For instance, the HIII neck is four times stiffer than the human neck under axial loading¹. We have designed a new 3D printable human surrogate neck that can accurately represent the response of the cervical spine under head-first impacts.

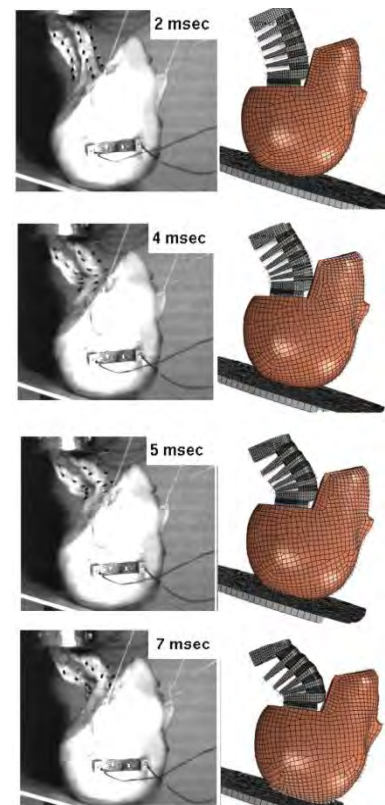
Methods

We used anthropometric data to develop a CAD model of the surrogate neck, which incorporates the same number of vertebrae and normalised mass distribution as the human neck. Curvature was implemented by means of a Bezier spline². We characterised 3D printable rubbers using Dynamic Mechanical Analysis and incorporated these properties in a finite element (FE) model of the surrogate neck. We then simulated vertical impact cadaveric experiments of Nightingale et al.³ A Hybrid III FEA model was also created and tested.

Results & Discussion

Figure 1 shows that the new neck can mimic the 1st and 2nd buckling modes of the human neck, the mechanisms that assist in energy absorption. Peak FEA surrogate neck C7-T1 force was 7kN, which had a significantly improved performance compared to cadaveric peak force (3.7kN³) than Hybrid III (22kN). The higher peak force is partly due to the rigidity of the head-form used. The average dynamic stiffness of the surrogate neck was 0.43kN/mm, which was in reasonable agreement with the cadaver data (0.55kN/mm)⁴.

Figure 1 - Comparison between cadaveric drop test³ and the surrogate neck.



Conclusion

The new neck better predicts the key feature of the response of the human in head-first impacts, e.g. buckling modes. It can be 3D printed with dual-materials, which makes it cheaper and more flexible than current ATD necks currently on the market.

References

1. F. A. Pintar et al., "Biodynamics of the total human cadaveric cervical spine," Soc. Automot. Eng. Pap. No. 902309, pp. 55–72, 1990.
2. K. D. Clinich, S. M. Ebert, and M. P. Reed, "Quantifying Cervical-Spine Curvature Using Bézier Splines," J. Biomech. Eng., vol. 134, no. 11, pp. 114503–114503, 2012.
3. R. W. Nightingale et al. "The dynamic responses of the cervical spine" buckling, end conditions, and tolerance in compressive impacts," 41st Stapp Car Crash Conf., no. 973344, pp. 451–471, 1997.
4. F. A. Pintar, N. Yoganandan et al. "Dynamic characteristics of the human cervical spine," Stapp Car Crash Conf. Proc., no. P-299, pp. 195–202, 1995.

Hierarchical biofabrication: Integrating bioprinting with molecular self-assembly

C.L. Hedegaard¹, E.C. Collin¹, C. Redondo-Gómez¹, L.T.H. Nguyen², K.W. Ng², A.A. Castrejón-Pita³, J.R. Castrejón-Pita¹ and A. Mata¹

¹ School of Engineering and Materials Science, Queen Mary University of London, E1 4NS, London. ² School of Materials Science & Engineering, Nanyang Technological University, 639798, Singapore. ³ Department of Engineering, University of Oxford, OX1 2JD, Oxford.

Introduction

In tissue engineering bioprinting is used to build precise tissue-like architectures, however the technique is limited in the choice of bioinks due to stringent printing requirements¹. Conversely, self-assembling biomaterials can be molecularly designed to better mimic the extracellular matrix², but often lack macroscale precision. The objective of this study was to develop a biofabrication method that integrates the benefits of bioprinting with molecular self-assembly.

Methods

An in-house designed acoustic based print-head was used to generate droplets-on-demand (DoD). Different peptide amphiphile (PA) sequences were co-assembled with a range of macromolecules (keratin, collagen, fibronectin and hyaluronan), by jetting one into the other. All solutions were prepared using a cell friendly buffer.

Results & Discussion

The 'droplet into liquid' bioprinting method allowed interfacial liquid forces to be used to guide the self-assembling process into gels with specific shape and topography³. We show that the gels can be individualised by changing the macromolecule/PA, integrating biological signals and/or aligning the nanofibers. As such, one fabrication set-up can be tuned according to the target tissue without the need to redesign the print-head. We show that individual gels can be assembled into larger structures. The printing method can be carried out in presence of cells (viability >80%). We demonstrate spatial control of cell positioning as well as co-culture, by encapsulating cells in the PA or macromolecular solution.

Conclusion

By combining self-assembling materials with DoD based printing we create a biofabrication method with a hierarchical approach to control. The method enables for the first time the possibility to bioprint whilst controlling biomolecular and structural elements of the printed scaffold³.

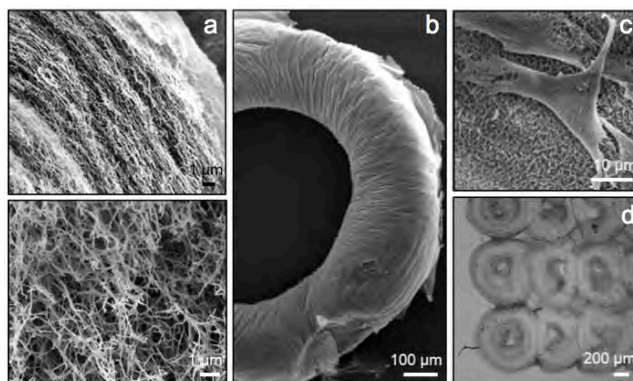


Figure 1| Hierarchical biofabrication; a) aligned and disordered nanofibers in printed gels, b) gel structure determined by fluid dynamics, c) cell attachment and d) example of an assembled structure.

References

1. Hospodiuk M. *et al. Biotechnol. Adv.* 2017; 35: 217-239.
2. Mendes A.C. *et al. WIREs Nanomed. Nanobiotechnol.* 2013; 5:582-612.
3. Hedegaard C.L. *et al. Adv. Funct. Mater.* 2018; 1703716: 1-14.

Acknowledgments

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Engineering the endothelial glycocalyx through defined patterns of peptide self-assembled monolayers

XQ Pang, WQ Li, W Wang, H S Azevedo

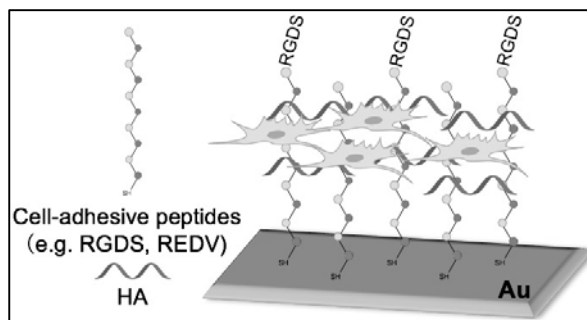
School of Engineering and Materials Science, Queen Mary University of London, Mile End Road, E1 4NS, London.

Introduction

The extracellular matrix (ECM) provides cells with a physical and chemical microenvironment that determines their proliferation, migration or differentiation.¹ The glycocalyx is the immediate pericellular matrix that surrounds many cell types, including endothelial cells (ECs), and is typically composed of glycans (glycosaminoglycans, proteoglycans, glycoproteins). The glycocalyx of endothelial cells (ECs) is rich in hyaluronan (HA), which influences the assembly of other proteins in the ECM and plays an important role in maintaining the vascular integrity.² We are interested in investigating how HA contributes for the regulation of the endothelial function. Towards this goal, we are developing model surfaces using self-assembled monolayers (SAMs) for the co-presentation of adhesive ligands and HA as surrogates of the endothelial glycocalyx.

Methods

Peptides bearing different functionalities and a terminal thiol group were synthesized by solid phase methods and purified by reverse-phase HPLC. They were then immobilized on 2D gold (Au) surfaces using SAMs method. Cell adhesive sequences (e.g. Arg-Gly-Asp-Ser (RGDS)) and ECM-binding peptides were used to form patterned SAMs. Functionalized surfaces were first characterized by contact angle and the interactions between immobilized peptides and HA with different molecular weights was studied by quartz crystal microbalance with dissipation (QCM-D). Human umbilical vein endothelial cells (HUVECs) were then cultured on the patterned surfaces and analysed by scanning electron and fluorescence microscopy.



Results & Discussion

Contact angle measurements demonstrate that functionalization of Au surfaces with peptides and HA leads to more hydrophilic surfaces and QCM-D results indicate the formation of stable SAMs. Different peptides can be patterned on Au surfaces allowing the co-presentation of multiple ligands for studying the behavior of endothelial cells.

Conclusion

SAMs using HA-binding peptides enabled spatial control over HA localization. The results of these studies will then be applied to develop new HA-based biomaterials as potential therapeutic solutions for vascular diseases.

References

1. Frantz, C., Stewart, K. and Weaver, V. The extracellular matrix at a glance. *Journal of Cell Science* 2010, 123(24), pp.4195-4200.
2. Lennon FE, Singleton PA, Hyaluronan regulation of vascular integrity, *Am J Cardiovasc Dis* 2011, 1(3): 200-213.

Acknowledgments

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Modulating neural cell differentiation with electrically active nanoneedles

C Chiappini¹, A. Serio², E. Makila³, S. Aliko¹, M. Okseola¹, J. Salonen³

¹Centre for Craniofacial and Regenerative Biology, King's College London, United Kingdom

²Division of Tissue Engineering and Biophotonics, King's College London, United Kingdom

³Department of Physics and Astronomy, University of Turku, Finland

Introduction

Vertical arrays of nanostructures have emerged as an efficient platform to interface with cells in order to deliver drugs, genes and nanoparticles, to sense their intracellular conditions and to manipulate cell behavior through biophysical stimuli. In particular, porous silicon nanoneedles have emerged as the first platform to interface efficiently with living organisms and human tissue, to mediate localized in-situ gene therapy¹ and biomarker-based molecular diagnostics². Electrical stimulation is an important component in the interaction with excitable cells such as neurons and cardiomyocytes. Several nanowire arrays have been developed to tightly interface with cells and stimulate or record electrical activity³. Enabling porous silicon nanoneedles to modulate the electrical interaction with cells, would provide a much-needed further layer of direction over cell interaction and fate.

Methods

We microfabricated porous silicon nanoneedles chips (2µm pitch, 3.2µm height, 50nm tip)¹. The nanoneedles were functionalized by plasma oxidation (OX) followed by aminosilation (APTES), or they were thermally treated in acetylene furnace to obtain thermally carbonized (TC) and thermally hydrocarbonized (THC) nanoneedles⁴ and functionalized to obtain carboxylic acid (UnTHC) and amine (APTC) surfaces. We determined the biodegradation of these structures in PBS by SEM and ICP-MS. We tested their long-term cytocompatibility with iPSC-derived neural progenitors. We evaluated the specific capacitance of the by cyclic voltammetry. We devised a custom-made chamber to stimulate neural progenitors continuously for 10 days through the nanoneedles with a 100mV pulse for 100ms every 1s.

Results & Discussion

Oxidized and APTES nanoneedles degraded within the course of few days in PBS, while TC and THC nanoneedles lasted for over 21 days, with minimal degradation. The APTC and UnTHC nanoneedles exhibited an intermediate behavior, slowly degrading within the course of a week. Neural progenitors survived for seven days in culture over TC, THC and UnTHC nanoneedles, and displayed a morphology similar to that exhibited when cultured on flat silicon. The cells did not survive on OX, APTES or APTC. Cyclic voltammetry indicated that both TC and THC nanoneedles displayed a far superior specific capacitance than OX ones, with minimal faradaic coupling. Nanoneedle-mediated stimulation influenced the arrangement of the neural progenitors reducing their ability to form rosettes, and promoted their maturation towards neural cells.

Conclusion

We have developed a nanoelectrode platform with the suitable characteristics to interface with excitable cells. This platform is cytocompatible, provides electrical stimulation and supports the survival and maturation of human neural progenitors derived from induced pluripotent stem cells.

References

1. Chiappini, C. et al. . Nat. Mater. 14, 532–539 (2015).
2. Chiappini, C. et al. Adv. Mater. 27, 5147–5152 (2015).
3. Abbott, J. et al.. Nat. Nanotechnol. 110, 609 (2017).
4. Salonen, J., Makila, E. Adv Mater epub ahead of print doi: 10.1002/adma.201703819.

Acknowledgments

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BioMedEng18

Fabrication and Characterisation of PCL and PLGA for Vascular Tissue Engineering

N. Khan, M. Bazgir, O.A. Agbabiaka, M. Youseffi, F. Sefat

Medical Engineering Department, University of Bradford, Bradford, West Yorkshire, BD7 1DP, UK

Introduction

Electrospinning has recently emerged as a leading technique for generating biometric scaffolds fabricated of synthetic and natural polymers for tissue engineering applications. Electrospinning allows the integration of various biomaterials to be effectively tailored to create constructs that provide the essential characteristics. Fabricating vascular grafts aims to regenerate and mimic the extracellular matrix structure abundant in the walls of the inherent vessels. Prior to implantation, the investigation of scaffold characteristics such as degradation and solid surface tension are vital in ensuring appropriate and effective function.

Methods

Polycaprolactone (PCL) and Poly (lactic co-glycolic acid) (PLGA) 85:15 are biopolymers that were selected for this investigation due to their outstanding properties such as biocompatibility, degradability and cost effectiveness. Furthermore, previous literature has also highlighted the benefits of each synthetic polymer [1-2]. For this project, a total of six scaffolds were fabricated of which three were of PCL 15% (W/V) and three PLGA 10% (W/V). Spin time varied with periods of 30, 60 and 90 minutes. Once fabricated, the scaffolds were cut and weighted prior to the initiation of the 12-week experiment. The degradability was assessed via scaffold weight-loss and the change in fibre diameter. Scaffold topography was evaluated using scanning electron microscopy (SEM) which, highlighted the morphology, structure and physical characteristics including fibre diameter occurring over the 12-week period. Furthermore, the wettability of the scaffold was determined using various solutions alongside scaffold handling were examined. Additionally, this experiment also looked at scaffold behaviour under controlled conditions thus, the fabricated constructs were exposed to a controlled temperature of 37°C for a duration of four weeks. Again, six scaffolds were removed weekly to be assessed under the SEM to assess the degradation.

Results & Discussion

Overall both PCL and PLGA scaffolds displayed exceptional fibre structure and excellent degradability over the course of the experiment. The fibre diameter gradually increased thus, exemplifying gradual degradation. The percentage weight-loss of the scaffold increased and so, indicated the degradability of the scaffold. Although, both PCL and PLGA degraded, the results represented significant degradation in PLGA compared to PCL. As expected, this was also significant in the scaffolds observed under controlled conditions.

Conclusion

The conclusions drawn from this project are that both PCL and PLGA coupled with the correct testing provide great promise for future endeavours within vascular tissue engineering. However, for future work we are aiming to fabricate more complex architecture including coaxial electrospinning to provide a better scaffold for vascular tissue engineering.

References

1. Deshpande, P., et al. (2013) "Simplifying corneal surface regeneration using a biodegradable synthetic membrane and limbal tissue explants" *Biomaterials*, 34(21):5088-106.
2. Mahjour, S.B, et al. (2016) Improved cell infiltration of electrospun nanofiber mats for layered tissue constructs. *J Biomed Mater Res Part A*, 104(6):1479-88.

BioMedEng18

Magnetic nanoparticle mediated activation for chondrogenic differentiation of MSCs

I. Echevarria¹, A. El Haj¹, H. Markides¹

¹ ISTM, Guy Hilton research centre. Keele University, Stoke-on-Trent

Introduction

The absence of a long term treatment for osteoarthritis (OA) has led to the development of new approaches which can be used for early intervention¹. Mechanical regulators are known to play a key role in OA and present some key targets for modulation. The mechanotransductive potential of stem cells introduces the possibility of using external mechanical stimuli to promote cell differentiation and provides cues for tissue maturation². For this purpose, our group has developed a new technology based on remote magnetic activation of MSCs. The magnetic nanoparticles (MNPs) are targeted and bound to specific mechano-transductive ion channels or receptors on the MSCs membrane which then allows remote forces to be delivered directly to the channels or mechano-receptive parts of the cells membrane. This effect is translated downstream into the activation of specific chondrogenic signaling pathways.

Methods

Equine MSCs were cultured as pellets (4x10⁵ cells) and micromass cultures (5x 10⁴ cells). Cells were previously transfected with GFP dye linked to collagen type 2 expression. For this experiment, the cells were labelled with a MNP, Nanomag (250 nm) with carboxylic coating and linked to the specific antibody for each group: TRPV4, TREK1 and RGD. The cells were cultured for 21 days under the relevant media, chondrogenic media (DMEM, 10% FBS, 1% L-Glutamine, 1% Antibiotics, 1% Non-essential aminoacids, 50 mg/ml ITS, 10 ng/ml TGF- β 3, 50 μ g/ml Ascorbic acid, 0.1 mM Dexamethasone), chondrogenic media without TGF- β 3 (key for differentiation) and basal media. The 3 different media were tested for all groups. The cells were submitted to 1h daily stimulation using the changing magnetic field generated using the MICA bioreactor (MICA Biosystems Ltd). Samples belonging to all the groups were also grown and cultured under the same conditions lacking the magnetic stimulation.

Results

Collagen 2 expression was increased in all the chondrogenic groups cultured in chondrogenic media when compared to the cells cultured in basal media for all groups. In response to the mechano-activation with MNP, we observed an increase in collagen 2 production in the TRPV4 group, especially for the micromass cultured in chondrogenic media. Additional histological analysis demonstrated a similar pattern for collagen and aggrecan upregulation. A higher production of both markers was observed for all MNPs tagged cells in both chondrogenic and incomplete chondrogenic media. The cells labelled with MNPs showed enhanced production of collagen without the addition of TGF- β 3.

Conclusion & Discussion

The development of injectable solutions for early OA therapy could provide solutions which would improve motility with ageing. MICA approaches using MNP tagged to mechano-responsive receptor targets has the potential to generate these new therapeutic approaches. The use of ion channels such as TRPV4 as targets for enhancing chondrogenesis is being explored further.

Acknowledgments

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BioMedEng18

A subfibrillar deformation mechanism in corneal collagen that affords flexibility

J.S. Bell¹, S. Hayes¹, C. Whitford², J. Sanchez-Weatherby³, O. Shebanova³, C. Vergari⁴, C.P. Winlove⁴, N. Terrill³, T. Sorensen³, A. Elsheikh², K.M.Meek¹

¹ Structural Biophysics Group, Optometry and Vision Sciences, Cardiff University, CF24 4HQ. ² School of Engineering, University of Liverpool, The Quadrangle, Brownlow Hill, Liverpool L69 3GH ³ Diamond Light Source Ltd, Diamond House, Harwell Science & Innovation Campus, Didcot, Oxfordshire OX11 0DE

⁴ Department of Physics and Astronomy, University of Exeter, Stocker Road, Exeter EX4 4QL

Introduction

Collagen is a ubiquitous structural protein with the primary role of providing structural support to the extracellular matrix of connective tissue. The range of loads and strains experienced by connective tissue throughout the animal body is vast, and collagen caters for these varying mechanical environments by varying its hierarchical structure and its interactions with other matrix proteins, glycosaminoglycans and water. In this study we aim to elucidate the hierarchical mechanical architecture of collagen in the human cornea, where the precise shape and arrangement of collagen fibrils are essential for transparency. Of particular interest was the tropocollagen supramolecular helical tilt relative to the fibril axis, which is significant in the cornea and has been previously postulated to be a potential source of compliance.

Methods

Extensometry of human donor corneal specimens was carried out on X-ray scattering beamlines. Small and wide angle scatter patterns were acquired at rest, and during static and cyclic loading protocols. Scatter patterns were analysed to extract structural data that included collagen fibrillar and molecular spacing, orientation, coherence and D-period. Supramolecular tilt was calculated by comparing azimuthal distributions of fibrils and molecules via a scattering model.

Results & Discussion

Measurements of hierarchical structure were acquired at static strain increments of 0%, 1.4%, 2.8% and 5%, and the average supramolecular tilt at these strains was calculated to be 16°, 14°, 12° and 11°. The tilt in the rest configuration matches observations from electron microscopy studies, and the changes under load imply fibrillar elongations of 0%, 0.9%, 1.8%, 2.1%. The D-period for fibrils aligned approximately parallel to the applied strain increased under strain, while those aligned orthogonally exhibited a decrease in D-period. In the cyclic loading protocol, the supramolecular tilt reduced as the sample was loaded and increased again as tension was released. The largest change in tilt was during the first cycle, suggesting the tilt mechanism has a smaller time constant than other, larger-scale mechanisms.

Conclusion

The calculated change in supramolecular tilt supports the hypothesis that there is a significant subfibrillar deformation mechanism in corneal collagen, which can be approximated as being “spring-like”. This mechanism would appear to be the primary deformation mechanism at small strains, meaning it likely plays an important role in vivo. Its apparently small time constant may also suggest it is energetically efficient. As well as cornea, tissues such as skin, blood vessels and tendon sheath contain collagen with high supramolecular tilt, and it remains to be seen whether this mechanism plays a role in these tissues.

Acknowledgments

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BioMedEng18

The role of active vision in dragonfly visual guidance

H-T. Lin

Bessemer Building, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

How simple animals such as insects utilize limited spatial resolution to perform complex **visual guidance** has fascinated generations of naturalists. Insect eyes have only hundreds of “pixels” and fixed optics, yet they implement better visuomotor control than most modern machine vision systems with millions of pixels and adaptable lenses. A key element is the efficient coordination of vision and motor systems (i.e. **active vision**). One main research stream in my lab focuses on how **directed gaze control** in insects shapes visual input in the context of visual guidance (e.g. prey interception or conspecific aerial interactions).

Methods

The dragonfly is believed to be the first animal to fly on earth and remains one of the best aerial acrobats today. Together with its amazing flight behaviours, excellent vision, sufficient size, and electrophysiological access, the dragonfly is an attractive insect model for studying vision in flight. To capture the flight behaviours and relevant visual neural signals, we developed an insect motion capture technique and an ultralight neural telemetry system. The accurate 3D head kinematics measurement allows us to reconstruct the visual input to a hunting dragonfly [1].

Results & Discussion

Detailed 3D kinematics data show that the dragonfly actively steers the head to centre the prey in the visual fovea before take-off and maintain such foveation throughout the prey interception flight. By isolating different components of head rotations in-flight, we found active head movements that cancel the expected prey drift with zero delay [1]. This strongly suggests the use of internal models for predictive control. In addition, we identified a set of visual criteria that determine the dragonfly’s prey selection, take-off timing and decision to give up the prey pursuit [2]. Manipulating these simple visual heuristics induces the expected behaviours.

Conclusion

Unlike most engineered visually guided systems, dragonflies rely heavily on predictions to intercept prey instead of fast reactions [1]. The flying targets were visually tracked for ~300ms prior to take-off. During this time, the dragonfly measures several prey movement parameters and assess the likelihood of capture. This series of pre-flight visuomotor behaviour generates a prey prediction which initializes and guides the interception flight [2]. Ongoing research aims to dissect the guidance strategies implemented through directed gaze control and sparse neural signalling. We will explore such active vision in dynamic aerial interactions such as conspecific chases [3]. This research has direct implications for visual guidance in autonomous systems, and will lead to a new active vision paradigm for efficient machine vision.

References

1. Mischianti* M & Lin* H-T *et al. Nature*. 2015; 517: 333-338.
2. Lin H-T, Leonardo A. *Curr Biology*. 2017; 27: 1124-1137.
3. Bompfrey RJ *et al. Flight of the dragonflies and damselflies. Phil. Trans. Roy. Soc. B*. 2016; (DOI: 10.1098/rstb.2015.0389)

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BioMedEng18

How to stick but not get stuck - climbing with adhesive pads

D Labonte¹

¹ Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ.

Introduction

The ability to climb on plants and in the canopy of trees conveys significant ecological advantages, and is widespread in the animal kingdom. Smaller vertebrates and arthropods climb using specialised attachment structures such as adhesive pads. In order to allow small climbing animals to forage efficiently and to escape rapidly from predators, these pads must meet contradictory demands: attachment forces must be strong and reliable, but voluntary detachment should be rapid and effortless. Indeed, some insects can withstand detachment forces of over 100 times their own body weight while running upside down on smooth surfaces. In this talk, I will illustrate some principles of reversible and dynamic attachment in animals climbing with adhesive pads, with a focus on how climbing animals maintain attachment performance as they change in size – a major unresolved question for the design of useful bio-inspired adhesives.

Methods

I studied the scaling of (i) contact area across the entire size-range of climbing animals, and (ii) the attachment performance within different-sized stick insects (*Carausius morosus*). I quantified both whole-body performance with a centrifuge, and single-pad forces with custom-built fibre-optics force transducers.

Results & Discussion

Data on pad area of climbing animals covering seven orders of magnitude in body weight suggest that pad area indeed grows much faster than expected from geometric similarity across different lineages. In sharp contrast, pad area is approximately isometric *within* closely related taxa, suggesting that heavier representatives of a given species possess smaller safety factors. However, measurements of pad area and adhesion in insect and tree frog species suggested that the peak adhesive force per unit pad area can increase with body size so that attachment performance is approximately size-independent, despite the decrease in pad area per body weight. More detailed measurements within stick insects revealed that this increase in pad efficiency is caused by linking pad adhesion to shear forces: Adhesion for single-pad perpendicular pull-offs without shear forces scaled with mass^{0.34}, but the scaling coefficient increased dramatically to 0.87 when shear forces equivalent to one body weight were applied before pull-off. The link between adhesion and friction is hence key to both the controllability and scalability of biological adhesives, and understanding the detailed mechanics of this coupling is hence crucial for the design of bio-inspired adhesives: Shear forces can be used to dynamically switch between length-scaling (easy detachment), and above area-scaling (strong attachment), allowing to maintain and control performance across pad sizes. I demonstrate that this switch can be explained by pad sliding, which increases the stress levels required for detachment. Sliding is more likely to occur for pads of heavy animals, thus ensuring that small animals can detach their pads effortlessly, while large animals can attach safely. In combination, my results shed light on how climbing animals achieve size-independent safety factors, and hence how nature's climbers maintain attachment performance across almost seven orders of magnitude in weight.

Acknowledgments

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BioMedEng18

A Fly(brain)-Robot Interface to Study Multisensory Integration

Y. Wei, J.V. Huang, H.G. Krapp

Department of Bioengineering, Imperial College London, South Kensington, SW7 2AZ, London

Introduction

Biomimetics is mostly associated with the translation of biological design principles into technical applications. But the joint venture between biological research and engineering also enables us to apply engineering methodologies to study functional mechanisms in biology.

We are designing an experimental platform to study the integration of sensory information flies use for gaze and locomotor control. It consists of a small 2-wheeled robot steered by the electrical activity of an identified motion-sensitive neuron, the H1-cell¹, in the fly visual system. This Fly-Robot-Interface (FRI) will be configured to avoid collisions with potential obstacles while moving autonomously in an experimental arena².

Methods

A female blowflies (*Calliphora vicina*) is mounted on the robot with its rear head capsule opened to access the animal's optic lobes. Electrical spiking activity of the H1-cell induced by rotational self-motions of the robot is monitored using extracellular recorded techniques and converted into a time-continuous signal. This signal controls the pulse-width-modulated turning velocity of the two robot wheels. When neuronal activity exceeds a given threshold level indicating close proximity to a wall, the robot is programmed to initiate a collision avoidance manoeuvre. We performed open- and closed loop experiments to determine the most robust sensorimotor control strategy that enables collision-free self-motions of the robot.

Results & Discussion

The FRI has been tested mainly in a tunnel-like experimental area the walls of which feature vertically oriented visual gratings. Movements of the robot induces horizontal visual motion across the fly's eyes, where back-to-front and front-to-back motion increase and decrease the spiking activity in the H1-cell, respectively. By implementing an active oscillatory trajectory of a known turning radius we induce an alternating pattern of increased and decreased spiking activity that can be interpreted as a function of distance and enables the FRI to follow but not crash into the area walls³. The next step will be to record from both H1-cells in either half of the animal's brain and allow the FRI to autonomously move within arbitrary environments.

Conclusion

Our results reflect the significance of "*active sensing*" where known locomotor activity helps to derive meaningful steering commands from otherwise ambiguous sensory signals. They also underline the value of hardware implementations as proof of concept studies when identifying and characterizing functional principles of biological sensorimotor control.

References

1. Krapp H.G., Hengstenberg R, Egelhaaf M. *Journal of Neurophysiology* 2001, 85(2):724-734.
2. Huang J.V., Wei Y., and Krapp H.G.: Active collision free closed-loop control of a biohybrid fly-robot interface. In: *Biomimetic and Biohybrid Systems*, 2018, Living Machines, Springer (accepted).
3. Huang J.V., Krapp H.G.: Neuronal distance estimation by a fly-robotic interface. In: *Biomimetic and Biohybrid Systems*, 2017, Living Machines, Springer, pp. 204-215

Acknowledgments

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Gelatine Methacryloyl – Bioceramic Scaffolds for Dentine-Pulp Complex Regeneration

I. Medina Fernández, A. D. Celiz

Department of Bioengineering, Imperial College London, South Kensington, SW7 2AZ, London.

Introduction

Dental decay and poor long-term outcomes of traditional endodontic treatments have led the search for new dental tissue regeneration strategies. There is a lack of biomaterial-approaches that harness the native dental pulp stem cells (DPSCs), which constitute the main agent responsible for the intrinsic regenerative capabilities of the pulp. To achieve this, a gradient, bioactive scaffold is proposed, so odontogenic differentiation of cells and thus mineralisation may occur preferentially at the dentine/pulp. Bioceramic particles will be used as the bioactive moiety within a macroporous gelatine methacryloyl (GelMA) scaffold.

Methods

Biphasic calcium phosphate (BCP), a mixture of hydroxyapatite (HA) and tricalcium phosphate (TCP), and bredigite ($\text{Ca}_7\text{Mg}(\text{SiO}_4)_4$) bioceramics have been prepared through wet precipitation and a sol-gel process (respectively). GelMA has been prepared via the direct reaction of porcine skin gelatine with methacrylic anhydride.

X-ray diffraction (XRD) has been used to assess the crystallinity of the bioceramics, while nuclear magnetic resonance (NMR) and a ninhydrin fluorescence assay were used to provide qualitative and quantitative confirmation, respectively, of the degree of gelatine functionalisation. GelMA cryogels were prepared using a solution of GelMA in water at 1% w/v. The mass of the hydrated and dried scaffolds was measured to infer the interconnected porosity of the resulting cryogels ¹.

Results & Discussion

XRD spectra confirmed the formation of biphasic calcium phosphate, with a high β -TCP/HA ratio, and bredigite after calcination. A more prevalent TCP phase is considered desirable as BCPs with higher β -TCP/HA ratios have been described to be more odontogenic, presumably due to the higher bioresorbability of β -TCP².

NMR and fluorescence assays confirmed the modification of Gelatine with MA. This information may be of use for future adjustment of the parameters during synthesis to obtain GelMA with different degrees of functionalisation. After cryogelation, a consistent GelMA cryogel was obtained, with an interconnected porosity of $69 \pm 0.05\%$.

Conclusion and future work

In this work, preparation and characterisation of the main components of a scaffold for dentine-pulp regeneration have been carried out. The effects of the bioceramics on the proliferation and odontogenic differentiation *in vitro* of DPSCs will be assessed next. This will be followed by the selection, further modification and incorporation of the bioceramics into a gradient GelMA scaffold.

References

1. Koshy et al. *Biomaterials*. 2014; 35: 2477-2487.
2. Abdulqader et al. *Materials Science and Engineering C*. 2015; 49: 225-233.

BioMedEng18

Development of Novel Methods for Adhesion of Implants to Soft Tissue and a Next Generation of Dental/Bio Adhesives

E. J. Cozens¹, N. Roohpour², J.E. Gautrot¹

¹ School of Engineering and Materials Science, Queen Mary University of London, London, E1 4NS, UK ² Consumer Healthcare R&D, GlaxoSmithKlein, St George's Ave, Weybridge, KT13 0DE, UK.

Introduction

Interfaces between tissues and implants are playing an important role in the design of scaffolds for tissue engineering and other healthcare applications, such as dental or bio-adhesives. The mechanical properties of the implants and devices are important, but the bonding between an implant and the surrounding tissue should also be engineered to ensure optimal mechanical coupling. This is essential when the adhesive should sustain mechanical loads, but also to avoid detachment of the implant and formation of fibrotic or necrotic tissue. This project explores novel methods and materials for optimizing bonding between implants and soft tissues and protocols to characterise this adhesive interface.

Methods

Bioadhesives based on functionalised Poly(Acrylic acid) were developed. A variety of functionalisation strategies, such as DCC/DMAP and DMTMM coupling¹, were used to conjugate various biomolecules to the polymer. In order to enable multi-scale characterisation of the properties of the PAA-based adhesives, two strategies were developed: functionalisation of free polymers allows the bulk properties of the materials to be characterised, whereas synthesis of polymer brush layers² enables the interaction between individual polymer chains and biomolecules to be probed via colloidal probe AFM.

Results & Discussion

PAA was functionalised with tyramine and boronic acid residues and the functionalisation levels confirmed through ¹H NMR, ellipsometry, XPS, and FTIR. Adhesion to self-assembled monolayers, cells (primary keratinocyte and HACAT), and soft tissue samples (porcine gingiva and epicardium) was studied on the microscale and macroscale. AFM adhesion tests between these surfaces and the functionalised polymer brush layers indicate that molecular interactions with the cell glycocalyx dominate adhesion to cells and tissues.

Conclusion

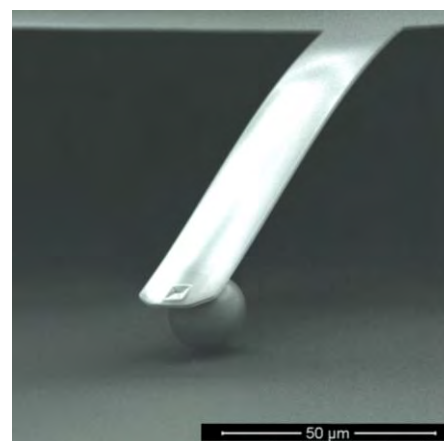
This study has identified how an understanding of interactions across different length scales enables a more effective and rational design of bioadhesives.

References

1. Loebel C. et al., Carbohydr. Polym. 115: 325-333, 2015.
2. Lego B. et al., Macromolecules. 43: 4384-4393, 2010.

Acknowledgments

I would like to acknowledge the EPSRC (grant EP/M507532/1).



Colloidal probe AFM technique characterising the interaction between a polymer brush-functionalised probe and a functionalised silicon substrate

De- and Remineralisation of Human Teeth Induced by Food Stuffs

C. Weber ¹, B. Fricke ¹, J. Messerschmidt ² **B.-D. Lechner^{1, 3}**

¹ Martin-Luther-Universität-Halle-Wittenberg, D-06120 Halle, Germany. ²Labor für Strukturanalyse, D-06246 Bad Lauchstädt, Germany ³School of Physics, University of Exeter, EX4 4QL, Exeter.

Introduction

Human teeth are always exposed to the interplay of food-induced demineralisation (DEM) and remineralisation (REM) generated by saliva or milk products as external source for calcium and phosphate ions. In the past 50 years nutrition habits have changed immensely and DEM of enamel and dentine has become a serious problem.[1] Alimentation with mainly fast food or even with mainly fruit as well as the consumption of acidic or fruit drinks of natural origin cause a high degree of DEM.[2] Thus, it is necessary to find and study ways that REM can keep teeth healthy. Here we monitor the nanoscale surface morphology and chemical structure at the dentin-enamel junction during demineralization upon impact of acidic beverages and subsequent remineralisation with a repair paste[3] or milk products.

Methods

The surface alteration in terms of loss or gain of roughness and change in surface morphology was followed by atomic force microscopy (AFM). The chemical changes at the tooth surface are studied using attenuated total reflection Fourier transform infrared spectroscopy (ATR-FTIR). Studies were carried out *in vitro* using polished, caries-free human tooth slices.

Results & Discussion

In mineralisation studies we show that a stepwise treatment of the tooth with DEM or REM agents followed with repeated AFM imaging of the same place allows us to draw detailed conclusions regarding the specific mechanism of the demineralization and the subsequent remineralisation process. DEM induces a significant shift of the phosphate band $\tilde{\nu}(\text{PO}_4)$ to higher wavenumbers in the IR spectrum. This process is reverse by the impact of REM agents and saliva, leading to a red shift of the band. The comparison of the different REM agents reveals that calcium containing food stuff promotes REM as efficient as commercial repair pastes.

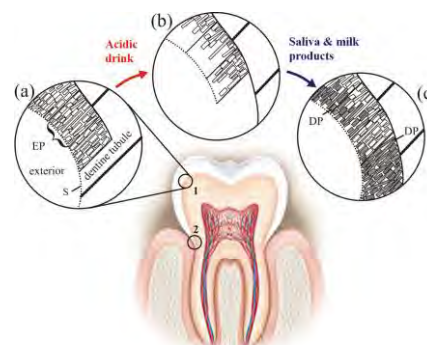


Figure1. Scheme for DEM by acidic drinks and REM by saliva and milk products.

Conclusion

Our experiments model the de- and remineralisation process of teeth occurring in everyday life. Successive AFM imaging reveals how the dentine-enamel junction is gradually eroded over time by acids and how mineral nanoparticles are deposited by the commercial REM agent or casein containing food stuff (Fig1). ATR-FTIR is an easy mean of quantifying the DEM/REM impact.

References

1. R. A. Lussi, M. Schaffner, T. Jaeggi, *Zahnmedizin* 2007, 3, 38.
2. (a) G. W. Marshall Jr., et al. *J. Biomed. Mat. Res. A* 1998, 42, 500;
(b) F. Lippert, D. M. Parker, K. D. Jandt, *Caries res.* 2004, 38, 465.
3. (a) C. Poggio, et al. *J. Dent.* 2009, 37, 949; (b) G. M. Giovanna, et al. *J. Dent.* 2008, 36, 565.

Acknowledgments

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The Inspired Sinewave Technique: assessment of an index of lung inhomogeneity using a two-compartment lung simulation.

M.C. Tran^{1,2}, A.P. Phan¹, S.J. Payne², A. Farmery¹

¹ Nuffield Department of Clinical Neurosciences, Level 6, West Wing, John Radcliffe Hospital, Oxford OX3 9DU

² Institute of Biomedical Engineering, University of Oxford, Old Road Campus, Oxford, OX3 7DQ,

Introduction

Mathematical lung simulations have provided better understanding of the principles and behaviours of the lung, particularly in diseased states where ventilation is spatially inhomogeneous. The Inspired Sinewave Technique (IST) is a non-invasive method to investigate the pulmonary system [1] in which sinusoidally varying concentrations of a tracer gas are fed into the inspired gas. In this paper, we use a tidal ventilation model to simulate an inhomogeneously ventilated lung. We then observe how the simulation handles forced inspired oscillations in nitrous oxide (N₂O) at two different frequencies, and from these observations aim to infer the degree of ventilatory inhomogeneity.

Methods

A set of mathematical equations describing gas flux in inspiration and expiration during tidal ventilation generates our lung simulation model. The model contains a deadspace compartment, two lung compartments and body compartments [2], [3]. The ‘input’ is the inhaled sinusoidal N₂O signal at the mouth. After passing through all compartments, the ‘output’ appears in the exhaled gas. Finally, the output signal is analysed by IST.

Lung inhomogeneity was simulated by changing the fraction of perfusion and ventilation of the two-compartment in the simulation model. Simulated sinewave test data was analysed by the IST to estimate the lung parameters, including an index of inhomogeneity. By changing the level of lung inhomogeneity set in the model, we could determine how effectively the IST ‘inhomogeneity index’ can detect true inhomogeneity.

Results & Discussion

The results showed that the inhomogeneity index was less influenced by inhomogeneity of perfusion than ventilation. When the degree of simulated inhomogeneity increased, the recovered IST inhomogeneity index also increased (non-linearly). Changing the ratio fraction of ventilation and alveolar volume, three scenarios of a human lung can be observed intuitively: homogeneous lung, inhomogeneous lung and a partially collapsed lung with a smaller apparently homogeneous counterpart (the so-called “baby lung”).

The results also suggested that in IST, 180s period may better identify inhomogeneity than 60s period. This model is a universal lung simulation, and so can also use for other applications such as the single and multiple breath nitrogen washout tests. However, a limitation of this study is that measurement noise has not yet been included in the model.

Conclusion

The lung inhomogeneity index can be captured by IST. The tidal lung simulation can be utilized as a tool for education and to investigate the behaviour of the lung in a number of different clinical scenarios.

References

- [1] P. A. Phan, A. Farmery, and C. Hahn, “Method and apparatus for measurement of cardiopulmonary function,” WO2015145115, 13-Apr-2015.
- [2] A. B. Baker and A. D. Farmery, “Inert gas transport in blood and tissues,” *Compr. Physiol.*, vol. 1, no. 2, pp. 569–592, 2011.
- [3] C. E. W. Hahn and A. D. Farmery, “Gas exchange modelling: No more gills, please,” *Br. J. Anaesth.*, vol. 91, no. 1, pp. 2–15, 2003.

Thresholding the Large Airways for Computational Fluid Dynamics

C.J.MCINTYRE^{1,3}, Q. Xiao¹, J. Rose¹, N. Tolley³, R. Schroter², D. Doorly¹
¹Aeronautics, ²Bioengineering, ³Medicine & Surgery; Imperial College, SW7 2AZ, London.

Introduction

A common reason for performing thyroid surgery is breathlessness due to extrinsic compression on the trachea by a goitre. An accurate clinical tool, predicting any benefit from surgery, does not presently exist. Surgery based on a 35% reduction in tracheal diameter is commonly used as guidance. Such a simple algorithm fails to take into consideration the geometrical complexity and its impact on the work of breathing.

Computational fluid dynamics (CFD) offers a tool to determine the significance of both tracheal compression and tracheal deviation on tracheal losses, and therefore the work of breathing.

CFD estimates tracheal power loss by using CT images with an accurate 3D reconstructed surface mesh of each patient trachea. Anonymised CT scans in DICOM (Digital imaging communication in medicine) format were used. Segmentation of images forming a 3D surface geometry is imported into a CFD pre-processor for meshing. Once the mesh is prepared, flow simulations are run using CFD.

Segmentation locates structures of interest in an image by separating them from background. Thresholding is used as the basis for segmentation processing. After selection of a threshold interval, all voxels with grey levels within that interval are used for 3D-reconstruction of the 3D model. An accepted threshold for segmenting the large airways does not exist and most studies use a fixed threshold varying between literature studies.

This research critically appraises the significance of using different fixed thresholds on CFD in the trachea and inter and intra variability of thresholding between ENT surgeons.

Methods

A series of healthy and pathological tracheas were segmented using incremental fixed thresholds. Pathological tracheas had been compressed and deviated by retrosternal goitres. A geometric analysis was performed to calculate the volume and smallest cross-sectional area. CFD was performed and the power loss calculated. The significance of incremental changes in threshold levels was analysed. ENT surgeons independently determined the threshold for each of the tracheas they deemed to be the correct threshold to accurately select the large airways.

Results & Discussion

There is a significant difference in both geometric analysis and power loss when comparing the same tracheas segmented at different thresholds with increments of 100 HU. This difference had an impact on the interpretation of CFD of the large airways and makes cross-study analysis difficult due to the lack of international consensus of an accepted threshold.

Conclusion

The threshold used for CFD studies of the large airway has significant implications on the interpretation of airflow.

The findings support the need for an internationally agreed threshold standard.

Optimisation of porcine eyeball storage for ophthalmic research applications

F. Menduni¹, V. Franklin², F. Lydon², T. Ipek¹, A. Fratini¹, B. Tighe², J.S. Wolffsohn¹

¹Ophthalmic Research Group, School of Life and Health Sciences, Aston University, B4 7ET, Birmingham.

²Biomaterials Research Unit, Department of Chemical Engineering & Applied Chemistry (CEAC), School of Engineering & Applied Science, Aston University, B7 4ET, Birmingham.

Introduction

The role of ex vivo models is becoming increasingly important in the applied ophthalmic research¹. Porcine eyeballs represent a useful and cost effective model of the anterior segment due to their similar morphology to the human eye². However, the “translation” of the scientific findings is very dependent on the eyeball storage conditions. This study aimed to optimise the preservation technique of porcine eyes to maximise corneal transparency and minimise tissue deterioration.

Methods

Ten porcine eyeballs were enucleated at a local abattoir within 4 hours of death and transferred to the laboratory at 4°C. Either air or supplemented Dulbecco's Modified Eagle's Medium (DMEM) were used during the transport as preservation solutions. Central corneal thickness was obtained using ultrasound pachymetry, while corneal and crystalline lens transparency were quantified using spectrophotometry. Dynamic mechanical properties of the tissue were also assessed. All measurements were obtained within 24-hour after enucleation.

Results & Discussion

The corneal tissue transparency was influenced by both the freshness of the eyeball and the storage conditions. Using supplemented DMEM reduced corneal turgidity thereby maintaining corneal thickness and transparency during storage. Crystalline lenses were less influenced by the storage conditions due to the protection of the eyeball. The use of spectral transmission enabled assessment of the intactness of the lens capsule. This study showed that dynamic mechanical testing can also be used as a tool to assess tissue properties, which will be beneficial in future studies linked to the dry and ageing eye.

Conclusion

These findings provide baseline information on the influence of storage conditions that may help increase the reproducibility of published values derived from ex vivo eye models. Additionally, it highlights the need for fresh tissue and contributes to reducing slaughterhouse waste in powerful alternative assays in line with animal experimentation rules.

References

1. Shafaie, S., et al. "In Vitro Cell Models for Ophthalmic Drug Development Applications." *Biores Open Access* 5.1 (2016): 94-108.
2. Menduni, F., et al. "Characterisation of the Porcine Eyeball as an in-Vitro Model for Dry Eye." *Contact Lens and Anterior Eye* (2017).

Acknowledgments

The authors gratefully acknowledge the abattoir C.H. Rowley Ltd. for the consistent supply of porcine eyes.

Supramolecular Peptide-Hyaluronan Hydrogels for Ocular Applications

Y.Yuan¹, J. Banerjee¹, H.S. Azevedo¹

¹ School of Engineering and Materials Science, Queen Mary University of London, London E1 4NS, UK

Introduction

Posterior segment diseases constitute a great portion of treatable ocular disorders. However, delivery of drugs to the posterior of the eye is challenging owing to anatomical and physiological constraints of the eye [1]. Drugs for vitreoretinal diseases are typically injected into the vitreous of the eye, located between the lens and the retina, but their distribution is not fully understood. Therefore, there is an increasing demand for developing novel methods to test the diffusion of drugs in the vitreous. Current vitreous substitutes only satisfy biomechanical aspects of the natural vitreous, with the ability to serve as retinal tamponades [2]. Hydrogels are promising for recreating the natural vitreous, not only as vitreous substitutes but also as a synthetic platform to perform *in vitro* studies. In this work, we present a novel supramolecular hydrogel as an artificial vitreous model where drugs can be tested in systematic and reproducible way, essential to optimize drug dosages and ultimately patient's outcomes.

Methods

Hydrogels were formed by self-assembly by mixing aqueous solutions of hyaluronic acid and rationally designed peptides. The micro- nanostructure of the gels was examined by scanning electron microscopy (SEM) and their mechanical properties evaluated by rheology.

Results & Discussion

Gels with different levels of transparency were obtained. SEM images showed entangled nanofibers forming a dense network. Rheology measurements showed a significantly higher elastic modulus G' compared to the viscous modulus G'' , which is representative of a gel state. Diffusion experiments also showed that the gels are permeable to proteins.

Conclusion

The biomimetic composition and structure of our gels, tunable mechanical properties and permeability, indicate their potential as an *in vitro* model of the vitreous for testing more accurately the delivery of drugs for vitreoretinal pathologies.

References

1. Thrimawithana TR, et al. *Drug delivery to the posterior segment of the eye*. Drug discovery today, 2011, 6: 270-277.
2. Kleinberg TT, et al. *Vitreous Substitutes: A Comprehensive Review*. Survey of ophthalmology, 2011, 56: 300-323.

Acknowledgments

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Investigating the mechanism of long-term intraocular pressure reduction by PGN9856i in mice

J.A. Bertrand¹, J.M. Sherwood¹, R.A. Coleman², D.F. Woodward¹, D.R. Overby¹

¹ Dept. of Bioengineering, Imperial College, South Kensington, SW7 2AZ. ² Private Consultant, Falmouth

Introduction

Existing pharmacological modalities for the treatment of glaucoma require daily dosing to manage intraocular pressure (IOP) and preserve vision. In a previous study (led by DFW), a single dose of PGN9856 isopropyl ester (PGN9856i), a putative prostaglandin EP₂ receptor agonist, lowered IOP in glaucomatous monkeys for up to 5 days. To determine the mechanism of this long-term IOP reduction, we measured outflow facility, a determinant of IOP, and IOP itself in response to PGN9856i in mice with steroid-induced ocular hypertension. We also examined the effect of PGN9856i in mice that were genetically deficient in the EP₂ receptor (*Ptger2*^{-/-}).

Methods

Ocular hypertension in C57BL/6 mice was induced by either subcutaneous osmotic mini-pumps loaded with dexamethasone or bilateral periocular injection of dexamethasone-eluting nanoparticles, over a period of 1 or 2 wks, respectively. Nanoparticle treated mice received either a single topical dose of PGN9856i (0.01%, 10µl) (n=9) or the prototypical EP₂ agonist butaprost (0.01%, 10µl) (n=9) administered to both eyes. Mini-pump treated mice received either PGN9856i (n=9) or vehicle (n=9) to both eyes. Rebound tonometry was used to measure IOP immediately before dosing and at regular intervals thereafter. Outflow facility was measured using the *iPerfusion* system¹ in eyes enucleated 3 or 7 days after a single topical dose of PGN9856i. IOP experiments were repeated in *Ptger2*^{-/-} mice without steroid treatment. Additional experiments examined the acute effect of de-esterified PGN9856i (100 nM) perfused directly into enucleated eyes from C57BL/6 mice without steroid treatment.

Results

Dexamethasone-eluting nanoparticles increased IOP by 4.2 [3.5, 4.9] mmHg (mean [95% CI]) over baseline after 2 wks. Butaprost reduced IOP by 2.6 [0.9, 4.3] mmHg p<0.001, an effect undetectable after 2 days. A single topical dose of PGN9856i significantly reduced IOP by 2.8 [1.7, 3.9] mmHg (p<0.001, n=9), for up to 6 days. Similar effects were observed with dexamethasone-eluting mini-pumps. Outflow facility measured 3 days after unilateral PGN9856i was no different from contralateral eyes treated with vehicle (relative difference of 18% [-7, 50%], n=9 pairs). PGN9856 had no effect on outflow facility relative to contralateral eyes perfused with vehicle (-3% [-22, 20%], n=7 pairs), suggesting a mechanism other than pressure-dependent outflow. In *Ptger2*^{-/-} mice, a single topical dose of 0.01% PGN9856i or butaprost had no apparent effect on IOP.

Discussion & Conclusion

A single topical dose of PGN9856i achieves long-term IOP reduction, for up to 1 week, in mice with steroid-induced ocular hypertension. The reduction in IOP requires the EP₂ receptor, but the duration of IOP reduction is significantly longer than a prototypical EP₂ agonist. This suggests that PGN9856 achieves long-lasting IOP reduction by a novel pharmacological mechanism involving EP₂ that may be exploited for glaucoma therapy.

References

1. Sherwood, J. M., Reina-Torres, E., Bertrand, J. A., Rowe, B. & Overby, D. R. Measurement of Outflow Facility Using iPerfusion. *PLoS One* **11**, e0150694 (2016).

Acknowledgments

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No conflicts of interest.

A finite element study on the modelling of keratoplasty.

Salahudeen M¹, Coccarelli, A²., Mauro, A¹., Massarotti, N¹., Romano, MR³., Romano, V^{4,5} and Nithiarasu, P²

¹Dipartimento di Ingegneria, Università degli Studi di Napoli "Parthenope", Isola C4, Centro Direzionale di Napoli, 80143 Napoli, Italy, UB8 3PH. ²Zienkiewicz Centre for Computational Engineering, College of Engineering, Swansea University, Swansea SA2 8PP, UK. ³Department of Biomedical Sciences, Humanitas University, Via A. Manzoni 113, 20089, Rozzano (Milano), Italy. ⁴Department of Eye and Vision Science, Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, UK. ⁵Moorfields Eye Hospital, London EC1V 2PD, UK.

Introduction

Keratoplasty is a corneal transplantation surgical method in which the damaged corneal tissues are replaced with a healthy donor corneal tissue[1,2].

The aim of the present study is to numerically investigate the stress intensity at host corneal tissue and donor corneal graft in the post-operative conditions, based on the air bubble pressure exerted at the host donor corneal graft to attach with the host corneal tissue.

Methods

The present problem is solved by means of a non-linear finite element method.

The three dimensional model consist of host cornea and donor corneal graft. The materials of the ocular tissue are treated as hyper-elastic.

Results & Discussion

Different air bubble pressures are modelled at the donor corneal graft in order to attach the graft to host corneal tissue..

The stress and strain intensity at the attachment site are studied so that the threshold limit of the air bubble pressure, at which the graft attaches, can be predicted

Conclusion

The current numerical study models keratoplasty and provides a physical insight into the structural parameters, such as stress and strain intensity, at the attachment site depending on air bubble pressure.

References

1. Vito Romano et al. *J Cataract Refract Surg.* 2017; 43: 12-15.
2. Vito Romano et al. *Br. J. Ophthalmol.* 2018; 102: 549-555.

Acknowledgments

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An experimental model to understand corneal degradation in keratoconus

Ahmed Kazaili^{1,2}, Riaz Akhtar¹

¹ Department of Mechanical, Material and Aerospace Engineering, School of Engineering, University of Liverpool, Liverpool, UK; ² Department of Biomedical Engineering, School of Engineering, University of Babylon, Babylon, Iraq.

Introduction

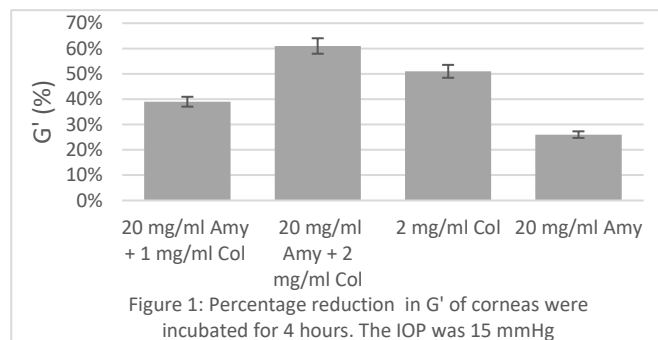
Keratoconus (KC) is associated with a degradation of the collagen network in the cornea and a detrimental change in the viscoelastic properties.¹ Alpha-amylase (Amy) or collagenase (Col) can degrade the collagenous structure of the cornea.² This study aims to develop an *in vitro* keratoconic model using enzymatic degradation to degrade the corneal microstructure and to determine how that affects its micromechanical properties.

Methods

One hundred and twelve porcine corneas were obtained from a local abattoir. They were grouped into a control group (8 corneas) and 13 groups (8 corneas each) incubated for different periods (1, 2, 3, 4, 24, 48 hours) in varying amylase (10, 20 mg/ml) and collagenase (1, 2 mg/ml) concentrations. The epithelium layer was peeled off before incubation. Nanoindentation was carried out with a G200 system using a DCM-II head (KLA-Tencor, USA). The shear storage (G') and loss modulus (G'') were measured.³ The corneas were fixed in a holder to mimic the *in-vivo* conditions and internally pressurised (IOP) from 0 – 60 mmHg during the indentation.

Results & Discussion

The G' and G'' were decreased in the corneas as the concentration of either amylase or collagenase and incubation time increase. Figure 1 shows G' -results from 4 groups which all were incubated for 4 hours. The maximum reduction in G' (61%) was observed when the corneas were incubated in a solution containing both amylase and collagenase for 4 hours. Non-linear behaviour in treated corneas was seen in high IOP.



Conclusion

Amylase and collagenase treatment decrease the viscoelastic properties, affected the collagenous structure of the cornea, and can be a potential model for a subset of human KC.

References

1. Ambekar *et al.* Journal of the Mechanical Behavior of Biomedical Materials; (2011).
2. Jayes, *et al.* American Journal of Obstetrics & Gynecology; 2016: 596.e1-596.e8.
3. Akhtar, *et al.* Journal of Materials Research; In Press (2018).

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The Effect of Temperature on Aqueous Humour Outflow in Enucleated Mouse Eyes

E. Reina-Torres¹, J.M. Sherwood ¹, D.R. Overby ¹

¹Department of Bioengineering, Imperial College London, South Kensington, SW7 2AZ, London.

Introduction

Elevated intraocular pressure (IOP) is the main risk factor for glaucoma, and IOP is determined by the aqueous humour (AH) outflow resistance. Understanding the physiology of AH drainage is thus important for developing better glaucoma therapies. Classic studies argued that AH resistance is insensitive to both temperature¹ and metabolic inhibitors², leading to the conventional view that the TM functions largely as a passive conduit. We recently challenged this view by showing that outflow resistance is indeed temperature-dependent between 20°C and 35°C³. We hypothesise that temperature reduction suppresses outflow function. To test this hypothesis, we measured outflow resistance in response to either increasing or decreasing temperature perturbations within individual mouse eyes.

Methods

We measured outflow facility (C , 1/resistance) in enucleated eyes from C57BL/6 male mice (9-14 weeks old) using *iPerfusion*⁴. We considered three experimental sets. Firstly, we measured C in contralateral eyes perfused at either 22°C or 35°C using an established pressure-stepping protocol⁴. Secondly, at a constant pressure of 8 mmHg, one eye was perfused initially at 35°C, followed by 22°C. Thirdly, also at 8 mmHg, one eye was perfused initially at 22°C followed by 35°C. Paired t tests were used to compare facility measured between the two temperatures.

Results

In the first set, C was 283% [125, 551] (geometric mean [95% CI]) higher in eyes at 35°C versus 22°C ($n=10$ pairs, $p=0.0003$). This difference was larger than the predicted 33%⁵ increase due to temperature-dependent changes in AH viscosity. In the second set, reducing temperature from 35°C to 22°C decreased outflow facility by 25% [10, 38], ($n=9$ eyes, $p=0.021$), which can be fully attributed to viscosity increases. In the third set, increasing temperature from 22°C to 35°C increased C by 297% [146, 541] ($n=9$ eyes, $p=0.003$), which was comparable to the facility difference observed in the first set.

Discussion and Conclusion

After death and enucleation, eye temperature should rapidly decrease, and maintaining sub-physiological temperatures suppresses outflow function. Returning the eye to physiological temperature restores outflow function and increases facility. However, once restored, reducing temperature only minimally perturbs outflow via effects on AH viscosity. The AH outflow pathway is thus temperature sensitive, and must be returned to physiological temperature after death to restore function. This suggests that yet unidentified active cellular processes may be involved in outflow regulation.

References

1. VanBuskirk EM, Grant WM. *Am J Ophthalmol*. 1974
2. Bárány EH. *Acta Soc Med Upsal*. 1954
3. Boussommier-Calleja A et al. *IOVS*. 2015
4. Sherwood JM et al. *PLoS One*. 2016
5. Wagner W, Kretzschmar HJ. *Springer Berlin Heidelberg*. 2008

Acknowledgments

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Modulation of Outflow Facility by the Ocular Pulse

J.M. Sherwood¹, M. Madekurozwa¹, W. D. Stamer², D.R. Overby¹

¹ Department of Bioengineering, Imperial College London, SW7 2AZ.

²Department of Ophthalmology, Duke University, NC 27705, United States

Introduction

Intraocular pressure (IOP) is determined by the product of the net flow of aqueous humour and the hydraulic conductance or 'facility' of the outflow tissues. IOP is not static, but rather oscillates by 2-3 mmHg due to cardiac pulsations in ocular blood volume known as the *ocular pulse*. Modelling predicts that the ocular pulse induces oscillatory shear stress along Schlemm's canal (SC) endothelium (amplitude up to 30 dyne/cm²). SC endothelial cells release signalling factors, such as nitric oxide, in response to shear stress, which may affect outflow facility. We hypothesise that the ocular pulse modulates outflow facility by stimulating shear-induced production of nitric oxide from SC cells. We test this hypothesis by examining the effect of IOP oscillations on outflow facility.

Methods

Using *iPerfusion*, we measured outflow facility whilst imposing 2-3 mmHg oscillations in IOP at 10 Hz to mimic the murine heart rate. We used post-mortem cadaveric C57BL/6 mice (13-14 weeks, N=5) with the eyes retained *in situ* and body temperature regulated at 35°C. Oscillations were generated using a custom-built module, *iPulse*, calibrated and tuned using a 50µm diameter glass capillary and flexible tubing as an '*in vitro* eye'. Signal decomposition was used to isolate and measure the steady component of the dynamic flow rate entering the eye during oscillations. For experiments, one eye was cannulated and acclimated under steady conditions at 8 mmHg for 2 hours using PBS + 5.5 mM glucose as a perfusate, followed by five or six 30 minute periods of alternating oscillatory or steady pressure.

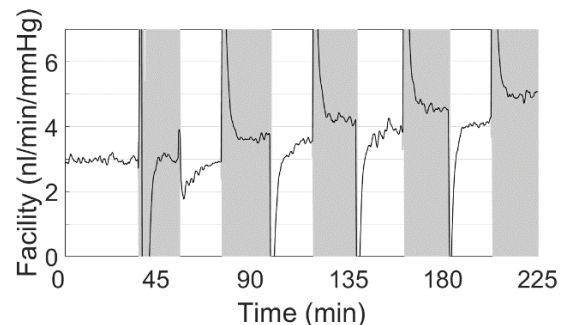


Figure: Outflow facility increases during the period of oscillations on (shaded) relative to periods of oscillations off.

Results and Discussion

We validated that *iPulse* can generate 10 Hz pressure oscillations of 2-3 mmHg whilst accurately measuring the resistance of a glass capillary that matched the resistance of a mouse eye. During acclimation at 8 mmHg, the baseline outflow facility (flow/pressure) was 2.6 [1.9,3.5] nl/min/mmHg (mean [95% CI]). During oscillatory periods, the average facility increased on average by 12 [4, 20] % ($p < 0.01$) relative to the facility measured during the surrounding steady periods. The effect was reversible and disappeared soon after oscillations ceased (Figure).

Conclusion

The ocular pulse causes a rapid increase in outflow facility in mice. These studies reveal a dynamic component to outflow function that responds instantly to the ocular pulse and may be important for outflow regulation and IOP homeostasis. Future studies will examine the role of nitric oxide in the oscillatory response.

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BioMedEng18

Towards a comprehensive active-structural model for the arterial wall

A. Coccarelli¹, D. Parthimos ², P. Nithiarasu ¹

¹ Biomedical Engineering Group, Zienkiewicz Centre for Computational Engineering, College of Engineering, Swansea University, UK ²Division of Cancer and Genetics, School of Medicine, Cardiff University.

Introduction

In the last couple of decades several modeling methodologies have been proposed in order to characterize the structural response of the arterial wall. Among these studies, only few of them have focused on the modelling of the active layer of the wall, the media, and its fundamental sub-units, called contractile units [1]. These components are extremely relevant in muscular arteries and arterioles, since it is responsible for the lumen modulation and thus of the blood and nutrients transport. Coccarelli et al. [2] have developed an experimentally-validated multiscale model able to reproduce the structural response of the arterial muscle layer induced by specific drug interventions. This study has allowed to quantify the effects of the biochemical cellular dynamics over the resultant/global tissue behavior. However, such methodology is still far from being comprehensive since it does not account for the regulatory action of endothelial layer, which plays a key role as interface between blood flow and contractile media layer. In addition to this, there is still the need to elucidate the ionic transport between cells, which may induce to cellular synchronization phenomena. This can be done by simulating how the calcium ion is transported within an array of cells for different coupling conditions. A complete modelling methodology, supported by experimental evidence, may shed light on the control mechanism of the vascular wall system.

Methods

With the current study, a strategy for integrating all the wall layers/sub-systems within the same computational framework is proposed. The dynamics occurring at cellular level for both endothelium and media are governed by set of ordinary differential equations, whilst the structural mechanics calculations are carried out by means of finite element discretization [2].

Results, Discussion

At this research stage we want to define the role of cellular coupling on the Ca^{2+} diffusion within an array of cells. Simulations with different cellular coupling conditions are carried out. For coupling coefficients equal to zero (no communication between cells) each cellular oscillates independently, whilst by increasing the coupling the intracellular Ca^{2+} fluctuations start synchronizing. It is worth noticing that for intermedium level of coupling the Ca^{2+} variations present chaotic patterns.

Conclusion

This study represents a key step towards the definition of the pathways governing the arterial wall contractile machinery.

References

1. Murtada S.-I. and Holzapfel G. Investigating the role of smooth muscle cells in large elastic arteries: a finite element analysis. J Theor Biol: 358, 1-10. 2014.
2. Coccarelli, A. and Edwards, D.H. and Aggarwal et al. A multiscale active structural model of the arterial wall accounting for smooth muscle dynamics. Journal of the Royal Society Interface 15. 2018.

Microstructure-mechanics relationship of human aortic aneurysms

Aziz Tokgoz¹, Shuo Wang², Priya Sastry³, Chang Sun², Nichola Figg³, Yuan Huang^{2,4}, Martin R. Bennett³, Sanjay Sinha³, Jonathan H. Gillard², Michael P. F. Sutcliffe^{1*}, Zhongzhao Teng^{1,2*}

¹ Department of Engineering, University of Cambridge, Trumpington Street, Cambridge CB2 1PZ

² Department of Radiology, University of Cambridge, School of Clinical Medicine, Box 218

Cambridge Biomedical Campus, Cambridge CB2 0QQ ³ Division of Cardiovascular Medicine, Department of Medicine, University of Cambridge ⁴ Centre for Mathematical and Statistical Analysis of Multimodal Clinical Imaging, University of Cambridge

Introduction

Aortic aneurysms are amongst the leading vascular diseases that claim millions of lives every year. They cause dilatation of aorta, leading pathological changes in its microstructure and resulting in ruptures and fatal clinical events. Although mechanical properties of the diseased aorta have been studied[1], literature on its microstructure-mechanics relationship does not exist. This study is aimed at exploring the disease driven microstructural changes of aortic aneurysms and influence of the microstructural changes on the tissue mechanical behaviour.

Methods

Aortic regions affected by aneurysm were collected from eight patients and stored in liquid nitrogen. Tissue pieces were thawed prior to testing and tissue strips were cut from their intima, media and adventitia layers, along both the circumferential and the axial artery directions. Uniaxial tensile tests were performed on all tissue strips and force versus tissue displacement data were collected. Immunohistochemical analysis was used to quantify microstructural components of each tissue.

Results & Discussion

Immunohistochemical analysis showed that the intima layer of aneurysmal aorta tissues has significantly lower collagen content than their media ($p < 0.05$) and the adventitia ($p < 0.001$) layers. On the other hand, the glycosaminoglycan content was found to be significantly larger in the intima ($p < 0.001$) and the media ($p < 0.0001$) layers, compared to the adventitia. Moreover, a marginal correlation ($r^2 = 0.132$, $p < 0.05$) between the increase in collagen content and a corresponding decrease in glycosaminoglycan content of all arterial layers was observed. The uniaxial tensile test results revealed that the ultimate tensile strength of circumferential tissue strips was significantly higher ($p < 0.05$) than that of the axial tissue strips for the media and adventitia layers, while the difference between circumferential and axial intima layer tissue strips were found to be insignificant. In addition, significant ($p < 0.05$) microstructure-mechanics relationships were identified for the intima layer. The increase in collagen content was found to correlate positively with axial ultimate tensile strength ($r^2 = 0.70$), axial tangential modulus at 50kPa ($r^2 = 0.84$) and axial tangential modulus at 200kPa ($r^2 = 0.86$) of the intima layer. Significant ($p < 0.05$) negative correlation between the glycosaminoglycan content and axial tangential modulus at 50kPa ($r^2 = 0.59$), as well as a negative correlation between the macrophage cell content and axial tangential modulus at 200kPa ($r^2 = 0.879$) of the intima layer were found.

Conclusion

Majority of the pathological processes that lead to development of aortic aneurysms takes place in the intima. Consequently, its microstructure undergoes the highest level of pathological change. This leads to corresponding changes in its mechanical properties, which are reflected by the outcomes of this study.

References

1. Teng Z., et al. *Annals of Biomedical Engineering*. 2015; 43(11): 2745-59.

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Studying the general Holzapfel-Ogden model on fitting various experimental myocardial data and its reduction

DB. Guan¹, F. Ahmad², P. Theobald², S. Soe², H. Gao¹, XY. Luo¹

¹ School of Mathematics and Statistics, University of Glasgow, UK. ²School of Engineering, Cardiff University, UK.

Introduction It has been shown that bi-axial test data with different loading protocols and simple shear test data at different loading directions are required to adequately capture the direction-dependent nonlinear material response of myocardium[1]. In this work, we estimated myocardial property using the general Holzapfel-Ogden(HO) model from two sets of experimental data: Sommer[2] and Ahmad[3], respectively. Furthermore, the Akaike Information Criterion (AIC) was used to simplify the general HO model.

Methods The strain energy function(SEF) of the general HO model for myocardium[1] is

$$\Psi = \frac{a}{2b} \exp[b(I_1 - 3)] + \sum_{i=f,s,n} \frac{a_i}{2b_i} \{ \exp[b_i(I_{4i} - 1)^2] - 1 \} + \sum_{i=fs,fn,sn} \frac{a_{ij}}{2b_{ij}} [\exp(b_{ij}I_{ij}^2) - 1],$$

in which I_{4f} , I_{4s} and I_{4n} are the invariants associated with each direction; I_{8fs} , I_{8fn} and I_{8sn} are the coupling invariants between two different directions; a , b , a_i , b_i , a_{ij} , b_{ij} are unknown material parameters and are denoted as set $\mathbf{a}$.

The importance of each term in the above SEF can be assessed by analysing the AIC, defined as $AIC = N \ln[f(\mathbf{a})/N] + 2K$, where K is the number of unknown parameters and N is the total number of data points. If by reducing one term, the AIC value is not changed much compared with that of the general HO model, then the term can be dropped.

Results & Discussion For Sommer's data[2], according to the AIC in Fig.1 (a), I_{4s} , I_{8fs} and I_{8sn} can be excluded and the reduced HO model is

$$\Psi = \frac{a}{2b} \exp[b(I_1 - 3)] + \frac{a_f}{2b_f} \{ \exp[b_f(I_{4f} - 1)^2] - 1 \} + \frac{a_n}{2b_n} \{ \exp[b_n(I_{4n} - 1)^2] - 1 \} + \frac{a_{fs}}{2b_{fs}} [\exp(b_{fs}I_{fs}^2) - 1].$$

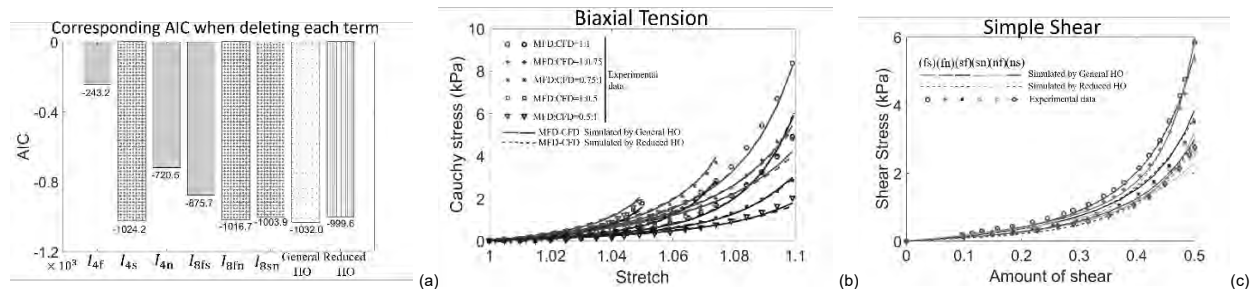


Figure 1: (a) shows the AIC values when individually removing the corresponding part from the general HO model. (b) and (c) describe the goodness-of-fit comparison between the general HO and the reduced HO, and the difference is negligible.

Conclusion Our study showed that different reduced HO models may be needed to fit to different types of myocardium. The AIC analysis can be used to reduce general HO model without losing accuracy.

References

1. Holzapfel GA, Ogden RW. Philos. Trans. Royal Soc. A. 2009 Sep 13;367(1902):3445-75.
2. Sommer G *et al.* Acta biomaterialia. 2015 15;24:172-92.
3. Faizan A *et al.* Journal of the Mechanical Behavior of Biomedical Materials, in revision

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Internal deformations in human intervertebral discs: a 9.4T MRI study

J. Prior¹, S. Tavana², N. Baxan³, U. Hansen², S. D. Masouros¹, N. Newell¹

¹ Dept. Bioengineering, Imperial College London, SW7 2AZ. ² Dept. of Mechanical Engineering, Imperial College London, SW7 2AZ. ³ Biomedical Imaging Centre, Dept. of Medicine, Imperial College London, W12 0NN

Introduction

Back pain will be experienced by 70-85% of all people at some point in their lives [1]. Although low back pain is linked with intervertebral disc (IVD) degeneration [2], there are few studies that have attempted to quantify changes in the internal deformations within IVDs as they degenerate. Recent advances in MRI technology provide the opportunity to observe 3D deformations within intact IVDs in unprecedented detail. The aim of this study was to quantify deformations within human IVDs under pure axial compression using images captured with a 9.4 T MRI scanner.

Methods

Four human vertebral body – IVD – vertebral body specimens (L4-L5) were used for this study. Two were classed as degenerate (age = 55.5 ± 3.5 years (average $\pm$ SD), Pfirrmann rank = 3.5 ± 0.4 [3]) and two were classed as non-degenerate (age = 24.0 ± 2.8 years, Pfirrmann rank = 2.0 ± 0.3). Specimens were aligned such that the transverse plane of the disc was parallel to the base of the mounting pots of a custom made compression rig, and fixed in place using polymethyl methacrylate (PMMA). MR Images were acquired before, and after 2 mm of compression using a T₂-weighted RARE sequence (coronal plane, resolution = $(90 \times 90) \mu\text{m}^2$, slice thickness = 800 μm , 17 min scan time – Fig 1). Vertical IVD heights were measured at 1.4 mm intervals on the unloaded and loaded images (ImageJ, National Institutes of Health, USA), to calculate axial strain in the nucleus pulposus (NP), and the annulus fibrosus (AF).

Results & Discussion

The axial strain in both the NP and AF of the degenerate specimens was significantly higher (two tailed, unpaired t-test, $p < 0.05$) compared to the non-degenerate specimens (11.2 vs 7.4%, and 12.6 vs 9.4%, respectively). This could be due in part to the shorter initial disc heights in the degenerate specimens (9.6 ± 0.9 vs 11.3 ± 1.0 mm, respectively). High lateral strains were seen in the AF regions of the non-degenerate discs, while high lateral strains were seen in both the AF and the NP of the degenerate discs. Future work will involve quantifying 3D internal deformations, and investigating other physiological motions.



Fig 1 – T₂ weighted MRI of (left) a non-degenerate, and (right) a degenerate human IVD specimen under 2 mm of compression.

Conclusion

This is the first study to use high field MRI to obtain images with in plane resolution as high as $(90 \times 90) \mu\text{m}^2$ to investigate internal deformations within degenerate and non-degenerate human discs. The insight afforded by these high resolution images will enable developments to improve the effectiveness of spinal implant designs, and other clinical interventions to reduce the discomfort to low back pain patients.

References

- [1] Andersson GB. Lancet 1999;354:581–5.
- [2] Luoma K et al. Spine (Phila Pa 1976) 2000;25:487–92.
- [3] Pfirrmann C et al. Spine (Phila Pa 1976) 2001;26:1873–8.

“Cortical recruitment in postural control adaptation and habituation during vibratory proprioceptive stimulation”

K. J. Edmunds¹, H. Petersen², R. Friðriksdóttir¹, M. K. Gíslason¹, A. Fratini³, and P. Gargiulo^{1,4}

¹Institute for Biomedical and Neural Engineering, Reykjavík University, Reykjavík, Iceland. ²Department of Anatomy, University of Iceland, Reykjavík, Iceland. ³School of Life and Health Sciences, Aston University, Birmingham, UK. ⁴Department of Science, Landspítali, Reykjavík, Iceland

Introduction

Maintaining normative posture is a complex task governed by the integration of afferent sensorimotor information with compensatory neuromuscular reactions, and the compensation for unpredictable perturbations in balance is essential to retaining stability and avoiding injury from falling. The cerebral cortex and central nervous system (CNS) play integral roles in adapting to transient balance perturbation, incorporating information from visual, somatosensory, and vestibular systems to carry out the corrective motions needed to maintain balance. However, the specific nature of adaptive and habitual cortical involvement during postural control in this regard is still unclear. In the present work, we outline two primary objectives: 1) to describe the properties of the postural control responses evoked by the proprioceptive stimulation, and 2) to study cortical habituation processes during prolonged perturbation.

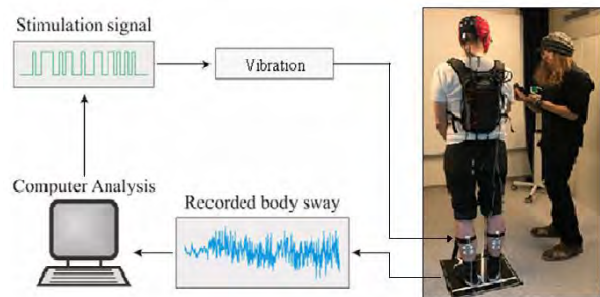


Figure 1. Schematic illustration of the experimental setup

Methods

Ten healthy subjects were instructed to maintain upright stance. Balance perturbations were evoked by applying vibratory stimuli simultaneously to the calf muscles of both legs. EEG data were recorded continuously from 64 channels in bipolar configuration during two distinct experimental phases: before applying vibratory stimuli (baseline), and during vibratory stimulation. Trials were performed both with open eyes (OE) and closed eyes (CE), and after acquisition, each vibratory stimulation phase was divided into four segments, Q1-Q2-Q3-Q4, each with 16 stimuli. EEG raw data were filtered and pre-processed in ASA (ANT Neuro, Enschede Netherlands). Finally, spectral power was determined by fast Fourier transformation (FFT) into six frequency bands (delta, theta, alpha, beta, low gamma, and high gamma).

Results & Discussion

Comparing the initial OE baseline to OE-Q1 elicited significant correlation in delta, theta, beta, and low gamma spectral density topology, whereas only the high gamma band yielded correlation during the CE trials. This could be due to the nature of primary exposure to sudden balance perturbation without the aid of vision, wherein the employment of cortical processes becomes requisite. This notion was further evidenced by the subjects' benefitting from the use of vision in the OE trials, wherein postural perturbation may have been manageable with only subcortical processes, such as fast medullary, brainstem, and/or subcortical reflexes.

Conclusion

This study extends previous research on human postural control perturbation when exposed to proprioceptive stimulation by introducing the investigation of adaptive cortical response. Furthermore, the present work provides evidence for the importance of vision and visual referencing in postural control. Nonetheless, these findings would be further aided by utilizing more metrics of balance performance, such as posturography or EMG to gauge postural sway.

NeuroSEE: An automated Neuronal Source Extraction and Exploration toolbox for calcium imaging data analysis

S.V. Prado^{1,2,3}, M.A. Go², S. Boretska^{1,2}, S.R. Schultz^{1,2}

¹Centre of Excellence in Neurotechnology, Imperial College London, South Kensington, SW7 2AZ, London.

²Department of Bioengineering, Imperial College London, South Kensington, SW7 2AZ, London.

³Department of Electronics Engineering, University of Santo Tomas, Manila, 1008, Philippines.

Introduction

Two-photon calcium imaging, coupled with the use of genetically encoded calcium indicators (GECIs), is widely used in monitoring large targeted neuronal populations because of its capability to provide single-cell spatial resolution recording in deep brain structures. However, there are still several issues that need to be addressed to accurately infer neural activity from raw calcium imaging data. Among these, movement artefacts induced during *in vivo* imaging of animal models pose problems for the automatic detection and segmentation of neuronal signal sources. In this study, we present a toolbox that is capable of automatically detecting and segmenting neuronal cells and extracting their activity information for the analysis of either *in vitro* or *in vivo* calcium imaging data.

Methods

To address the problem imposed by the movement of behaving animals during *in vivo* imaging, a line-by-line Hidden Markov Model-based motion artefact correction^[1] and frame-wise translational registration were employed to rectify frames in reference with a selected image from the resting state. For the segmentation, we integrated both activity-based and morphology-based approaches in initialising the multiple coupled active contours as candidate ROIs. These contours are evolved using the level set method to approximate the final cell boundaries^[2]. Upon segmentation, neuropil decontamination was performed prior to the extraction of the calcium signals. To quantify the performance of the toolbox, we tested it on our *in vivo* imaging datasets that were generated using GCaMP6s and mRuby GECIs from awake behaving Alzheimer's mice models.

Results & Discussion

We have addressed the problem of motion artefacts in *in vivo* imaging data using our proposed algorithm. Using a hybrid motion correction approach and neuropil decontamination, we have shown a significant improvement in the performance of cell segmentation and an increase in signal-to-noise ratio of the extracted calcium transients.

Conclusion

Our proposed toolbox has shown promising results in automatically detecting, segmenting and extracting neural activity information from *in vivo* calcium imaging data. Without prior correction, motion and neuropil contamination artefacts can severely affect the evolution of the active contours during activity-based segmentation that can lead to inaccurate extraction of neural activity information. In the future, we aim to use this tool to investigate how the spatiotemporal dynamics of neural cortical circuits during memory encoding and recall are affected by Alzheimer's disease.

References

1. Dombeck, Daniel A., et al. "Imaging large-scale neural activity with cellular resolution in awake, mobile mice." *Neuron* 56.1 (2007): 43-57.
2. Reynolds, Stephanie, et al. "ABLE: An Activity-Based Level Set Segmentation Algorithm for Two-Photon Calcium Imaging Data." *eNeuro* 4.5 (2017): ENEURO-0012.

BioMedEng18

A wireless monitoring instrument for recording tissue biopotential and sensing metabolites during surgery: proof-of-concept realisation and preliminary results

K. Petkos^{1,2}, P. Lizunkova ¹, P. Cunnea ³, C. Fotopoulou ³,
M.G. Boutelle ¹, E.M. Drakakis ¹

¹ Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London.

²Centre for Doctoral Training in Neurotechnology, Imperial College, South Kensington, SW7 2AZ, London.

³Institute of Reproductive and Developmental Biology, Imperial College, Hammersmith, W12 0NN, London.

Introduction

Surveys indicate that approximately 1,000 people die in the UK each month at hospitals as a result of medical errors caused by wrong diagnostics and subsequent treatment methods [1]. Such errors may be partly attributed to the fact that the current technology does not offer personalized treatment. In the case of epithelial ovarian cancer (EOC) 25% of patients do not benefit from ultra-radical surgery. This paper presents a low area profile portable instrument with wireless capabilities which enables the simultaneous and real-time tissue biopotential recording and metabolite sensing, potentially facilitating the identification and stratification of EOC patients who would not benefit from ultra-radical surgery.

Methods

The proposed design is based on a three-channel topology. The first channel records biopotential from cancerous/healthy omental tissues using a specific two-electrode setup [2]. The second channel enables the recording of signals stemming from potentiometric biosensors. The third channel interfaces with amperometric biosensors.

Results & Discussion

Preliminary results show that the biopotential recording channel can successfully interface with our two-electrode tissue monitoring setup [2], record signals from ex-vivo omental tissues and wirelessly transmit them to a computer. The potentiometric channel can handle hundreds of μV to tens of mV voltage signals while the amperometric channel can sense current changes as small as 10 pA.

Conclusion

The recording capabilities of the instrument enable the determination of EOC tissue parameters detectable by means of tissue biopotential measurements and metal or ion-selective electrodes. The device aspires to facilitate the currently lacking pre- or intra-operative identification and stratification of EOC patients who would not benefit from ultra-radical EOC surgery [3].

References

1. Hogan H *et al.* *Learning from preventable deaths: exploring case record reviewers' narratives using change analysis.* *Journal of the Royal Society of Medicine*; 2014.
2. Wu W *et al.* *A method for voltage measurements of cancerous vs non-cancerous omentum*; 2015.
3. National Institute for Health and Care Excellence. *Ultra-radical (extensive) surgery for advanced ovarian cancer: Interventional procedures guidance*; 2013.

Acknowledgments

This work was supported by the UK Engineering and Physical Sciences Research Council (EPSRC) [grant number EP/L016737/1] for the Imperial College London Centre for Doctoral Training, the Centre for Neurotechnology.

Encoding input correlations into the weight matrix of a recurrent spiking network with structure

Amadeus Maes¹, Mauricio Barahona ², Claudia Clopath ¹

¹ Department of Bioengineering, ² Department of Mathematics
Imperial College, South Kensington, SW7 2AZ, London.

Introduction

Increasingly large numbers of neurons can be simultaneously recorded. Recorded neuron pairs show correlations in their trial-to-trial activity. A network with a simple diagonal connectivity structure captures this experimental observation. Such structure can be learned in a recurrent network from input correlations by a combination of plasticity rules. Furthermore the structure is also stabilized in a regime of spontaneous activity. This study investigates whether structures can be learned and stabilized from input correlations and what the possible dynamics are that can arise from such structured networks.

Methods

A recurrent network model is constructed by connecting excitatory and inhibitory neurons sparsely. The excitatory neurons are adaptive exponential integrate-and-fire neurons and the inhibitory neurons are standard integrate-and-fire neurons. An external excitatory input in the form of Poisson spike trains is given to all the neurons in the network. Increasing the rate of the external input to a group of neurons makes them cluster by using a combination of voltage-based STDP and a homeostatic inhibitory plasticity rule. L1 normalization is used to introduce synaptic competition [1]. The diagonal connectivity structure that arises creates an eigenvalue gap and a resulting separation of time scales [2]. Clusters are active for tens of ms to hundreds of ms and their activity is randomly switched on and off.

Results & Discussion

External input correlated in time is generated by sampling from a transition matrix. Using this procedure it is possible to create off-diagonal structure in the weight matrix and obtain some interesting dynamics as a result. A feed-forward chain and a hierarchical structure are learned and remain stable over longer time periods. Studying a tridiagonal weight matrix shows that while the weights on the upper and lower diagonal change linearly, the dynamics samples in a non-linear fashion. More research is needed to study how random transition matrices are encoded and what possible functional applications there are to such flexible networks.

Conclusion

Several non-trivial structures can be encoded by applying a certain structured input to a recurrent network. Different structures give rise to different dynamics. It is an open question how this structure and resulting dynamics can be used functionally to make computations.

References

1. Litwin-Kumar A, Doiron B. *Nature Communications*. 2014; 5: 1-12.
2. Schaub MT et al. *Plos Computational Biology*. 2015; 11.7: 1-28.

Acknowledgments

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BioMedEng18

Organic Electrochemical Transistors for Measuring Neural Activity

J.E. Tyrrell¹, M.G. Boutelle ¹, A.J. Campbell ²

¹Department of Bioengineering, Imperial College London, London, SW7 2AZ ²Department of Physics, Imperial College London, Blackett Laboratory, South Kensington Campus, London SW7 2AZ

Introduction

It has been previously shown that organic electrochemical transistors (OECTs) are superior to electrodes in recording neurological activity whilst maintaining biocompatibility [1]. Here is demonstrated the fabrication of OECT arrays using photolithographic methods with their output and transfer characteristics.

Methods

OECTs were fabricated on glass substrates using photolithography to pattern the electrode, active semiconductor and encapsulation layers. The source and drain electrodes were gold. The active semiconductor layer consisted primarily of PEDOT:PSS – a biocompatible conducting polymer. The OECTs had p-type channels and operated in depletion mode. The semiconductor channel has a width of 2 mm, length of 10 μm and a thickness of 100 nm. The electrolyte used was phosphate buffered saline. The output characteristics and transfer curves of the OECTs were found using an Agilent 4156C semiconductor parameter analyser. This showed how the devices responded to a variety of voltages applied to their drain and gate electrodes.

Results & Discussion

Output characteristics show clear linear and saturation regions. As gate voltage increases, the drain current decreases. For gate voltages $> 0.6\text{ V}$, the OECT ‘turns off’. The transfer curve shows that there is no effect on drain current with negative gate voltages. For positive gate voltages, the drain current decreases. Around zero gate voltage, an increase by 1 mV results in a change in drain current by approximately 1 μA . This change in current is detectable, therefore neural signals of this magnitude can be identified. Transconductance measures the ability to amplify signals. The peak transconductance was 1.76 mS at a gate voltage of 0.132 V – similar to the best-performing OECTs [2].

Conclusion

The OECT fabrication using biocompatible materials and photolithographic methods resulted in devices with expected characteristics and high transconductance values. These devices are capable of measuring neural signals and have a wide range of applications.

References (examples – use “First author *et al.*” if more than 3 authors, minimum font size 9pt)

- [1]: D. Khodagholy *et al.*, “In vivo recordings of brain activity using organic transistors,” Nature Communications, vol. 4, pp. 1575 EP –, Mar 2013. Article.
- [2]: D. Khodagholy *et al.*, “High transconductance organic electrochemical transistors,” Nature Communications, vol. 4, pp. 2133 EP –, Jul 2013. Article.

Acknowledgments

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Multifocal two-photon imaging of a genetically encoded voltage indicator

P. Quicke^{1,4}, N. S. Soor^{1,4}, C. L. Howe^{1,4}, M. Neil^{2,4}, T. Knöpfel^{3,4}, A. Foust^{1,4} and S. R. Schultz^{1,4}

¹ Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London. ²Department of Physics, Imperial College, South Kensington, SW7 2AZ, London. ³Department of Medicine, Imperial College, South Kensington, SW7 2AZ, London. ⁴Centre for Neurotechnology, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

Functional imaging of genetically encoded voltage indicators (GEVIs) allows simultaneous monitoring of the membrane potential dynamics of genetically specified cell type populations. Due to the small fluorescence changes induced by membrane activity, GEVI imaging has been largely restricted to one-photon (1P) imaging due to its high signal-to-noise ratio (SNR). Two-photon (2P) imaging offers advantages due to optical sectioning but has been limited in its application to voltage imaging due to its low fluorescence excitation bandwidth. We present results showing multifocal two-photon microscopy enables improved 2P GEVI imaging and show single-shot GEVI transients at frame rates up to 100 Hz.

Methods

We prepared an acute brain slice preparation from CamK2a-tTA; chimeric VSFP Butterfly mice [1], which express a genetically encoded voltage indicator in pyramidal neurons. We imaged the brain slice preparation using our recently described multifocal two-photon microscope [2] whilst stimulating the cortex with a concentric bipolar electrode. We characterised the signals arising from two-photon and one-photon excitation in order to assess this technique's viability.

Results & Discussion

We compare the size of functional signals evoked at different 2P excitation wavelengths and compare this to a model based on published 2P excitation spectra [3]. We show that multifocal 2P imaging at 945 nm resolves voltage transients of up to 1.2% and compare this to transients imaged with 1P excitation on the same microscope. We show that our multifocal 2P system can resolve voltage transients at up to 100 Hz in a single trial.

Conclusion

We have presented the first images of GEVI transients from a multifocal two-photon microscope, maintaining SNR at the higher frame rates required to capture rapid voltage transients. The combination of improved voltage indicators and microscope technologies will enable previously inaccessible experimental paradigms.

References

1. Song C, *et al. Int. J. Mol. Sci.* 2017; 18: 1461
2. Quicke P, *et al. Biomed. Opt. Express.* 2018; in press.
3. Drobizhev M, *et al. Nat. Methods.* 2011; 8: 393-399

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Simultaneous and Proportional EMG Control of Ankle Joint Movement and Stiffness for Below-Knee Prostheses

H. Dimitrov¹, A. Bull¹, D. Farina¹

¹Dept. Bioengineering, Imperial College London, South Kensington, SW7 2AZ, London

Introduction

Transfemoral is the most frequent amputation level [1] and as the amputation rate has been growing [1] so has the demand for better prosthesis. In transfemoral amputees, the energy expenditure requirements during walking cannot be met by passive or semi-active prostheses [2]. Therefore, there is a need for reliable and robust powered/active foot prostheses, which require an interface with the user that can be obtained using EMG signals in remnant muscles above the amputation. This study proposes and preliminary tests a myoelectric interface for simultaneous and proportional control of two degrees-of-freedom (DoFs) as well as ankle stiffness.

Methods

Two able-bodied men (age 26 and 30 years) and one unilateral transfemoral male amputee (age 33 years) participated in the study. During the short training phase, subjects were seated comfortably and instructed to follow a visual circular cue on a screen by performing motions of their (phantom) foot. The vertical movement of the cue represented ankle dorsi/plantar flexion, while the horizontal referred to eversion/inversion of the foot. After training, DoF-wise factorization [3] was performed addressing direction and magnitude of the movements based on the recorded high-density monopolar lower leg EMG signal (192 electrodes). Gains for each DoF were heuristically adjusted to aid the subject in covering the full range of motion. An additional control signal for modulating stiffness was obtained using the estimation for the antagonist muscle activity of the dominant direction during each movement. After training, the subjects were in control of a circular cursor and were instructed to match a set of 20 random targets. An additional task was also devised to investigate simultaneous movement and stiffness control.

Results & Discussion

Currently, only the target matching in the able-bodied subjects was considered. The results indicated that the myoelectric interface provided a robust proportional and simultaneous control of the 2 DoFs with 90% mean success rate and mean completion time of 8.06s. The additional channel for stiffness consistently allowed modulation of stiffness during each motor task. The experiment conducted on the amputee subject showed that the patient could control the direction and magnitude of the cursor reliably in two directions (left and up) and their combination, whereas the control to the right was jittery. This impairment in control was due the observed atrophy of the tibialis anterior muscle (mainly responsible for dorsiflexion).

Conclusion

This pilot study has demonstrated the feasibility of simultaneous and proportional control of 2 DoF of the foot via EMG, with promising results in both able-bodied individuals and an amputee patient. An additional signal for stiffness is also extracted reliably and, while the control of all control estimates requires further improvement, it has potential for a clinical implementation.

References

1. K. Ziegler-Graham et al. *Archives of Physical Medicine and Rehabilitation*. 2008; 89(3): 422-429.
2. Grimmer M, Sayfarth A. In: *Neuro-robotics*. Berlin: Springer; 2014.
3. Andrea Serino et al. *Brain*. 2017; 140(11): 1993-3011.
4. Jiang, N et al. *IEEE Trans Neural Syst Rehabil Eng*. 2014, 22(3): 501-510.

Acknowledgments

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BioMedEng18

Investigating grey matter lesion distribution in Multiple Sclerosis using second generation radioligand [^{11}C]-PBR28

S. Podmore¹, Prof. P. Matthews²

¹ Imperial College, South Kensington, SW7 2AZ, London

² Imperial College, Hammersmith Hospital, W12 0NN, London

Introduction

[^{11}C]-PBR28 is a widely used second generation radio ligand in positron emission tomography (PET) due to its high specificity for the 18 kDa translocator protein (TSPO). In this study, we used [^{11}C]-PBR28 to quantitatively assess reactive astrocytes and activated microglia, pathophysiological markers of neuroinflammation in patients with relapsing-remitting multiple sclerosis (RRMS) and secondary progressive multiple sclerosis (SPMS).

Methods

In this study 22 Healthy controls and 28 MS patients (22 RRMS / 6 SPMS) underwent [^{11}C]-PBR28 PET with MR imaging [1]. Subjects were separated into two cohorts; high affinity binding and mixed affinity binding based on TSPO genotype to reduce heterogeneity arising from gene expression. Images were registered to MNI space to account for motion blur and PET data was corrected with 3D Poisson ordered subset expectation maximisation to account for scatter, attenuation and sensitivity. Subjects' SUV underwent pharmacokinetic simplified reference tissue modelling (SRTM) with pseudo-reference to generate estimate non-displaceable binding potential (BP_{ND}) map [2].

Results & Discussion

Stability and biological meaningfulness of pseudo-reference regions was assessed by selecting reference regions which minimised SSE between stable BP_{ND} and approximate BP_{ND} and were small enough to minimise the risk of selecting voxels with microstructural damages not representative of normal appearing white matter. Significant differences in BP_{ND} were detected in deep grey matter clusters at $p < 0.05$.

Conclusion

The optimal anatomically defined pseudo-reference to maximise grey matter heterogeneity was identified as mean plus half the standard deviation of the SUV present in healthy controls independently for mixed and high affinity binders. Though it is shown to be sufficient, the approach is still limited in its analysis of neocortical inflammation by partial volume effects, inter-subject differences in gene expression and by restricted by the spatial resolution of the PET imaging.

References

1. Datta, G., Violante, I., Scott, G., Zimmerman, K., Santos-Ribeiro, A., Rabiner, E., . . . Matthews, P. (2017). Translocator Position-Emission Tomography and Magnetic Resonance Spectroscopic Imaging of Brain Glial Cell Activation in Multiple Sclerosis. *Multiple Sclerosis Journal*, 1469-1478.
2. Herranz, E., Gianni, C., Louapre, C., Treaba, C. A., Govindarajan, S. T., Ouellette, R., . . . Mainero, C. (2016). Neuroinflammatory Component of Gray Matter Pathology in Multiple Sclerosis. *Annals of Neurology*, 776-790.

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BioMedEng18

AutoTRIAGE: A Multidisciplinary Approach towards Modelling, Diagnosing and Predicting Traumatic Brain Injury Severity in Road Traffic Collisions

C Baker¹, M. Ghajari¹, P. Martin², D. Sharp¹, M. Wilson¹

¹ Imperial College, South Kensington, SW7 2AZ, London. ² Transport Research Laboratory, Crowthorne House, Nine Mile Ride, Wokingham, Berks, UK, RG40 3GA

Introduction

Traumatic brain injuries (TBI) are a leading cause of death and serious injury during road traffic collisions (RTC), with serious cases requiring substantial emergency medical service (EMS) resources. The rapid and accurate diagnosis of TBI severity during collisions, through the use of embedded on-board sensors, provides an opportunity for the automotive sector to better direct EMS resources, reduce response times and, ultimately, improve patient outcomes. The AutoTRIAGE project aims to investigate the feasibility of using crash characteristics, such as those collected by on-board vehicle sensors, recorded via Event Data Recorders (EDRs), to model, diagnose and predict the severity of TBIs experienced during RTCs. Change in velocity has been shown to be a promising indicator of injury severity.

Methods

We will utilise the wealth of information available about UK collisions from the Department for Transport's RAIDS database to reconstruct collisions involving i) vulnerable road users, who are most susceptible to TBI and ii) vehicles with EDR data, as these give us directly from the vehicle information about its movement characteristics. By using physical evidence from physical examination of the scene itself and vehicles involved, and EDR data or CCTV where available, we reconstruct collisions in PC Crash 11.0 using multibody simulation.

By extracting lateral and rotational accelerations on the head in the x, y, z lateral and rotational directions, the head and brain's physical response to the collision stimulus can be modelled. These acceleration curves are used as an input to our TBI model, which is run using LS DYNA before results are post processed and then visualised using VisIt. The strain rates in different regions of the brain are used as an indicator of TBI severity.

References

1. M Peden and LL Sminkey. *World health organization dedicates world health day to road safety*. Injury prevention, 10(2):67–67, 2004.
2. Douglas W Kononen, Carol AC Flannagan, and Stewart C Wang. *Identification and validation of a logistic regression model for predicting serious injuries associated with motor vehicle crashes*. Accident Analysis & Prevention, 43(1):112–122, 2011.
3. Douglas J Gabauer and Hampton Clay Gabler. *Comparison of delta-v and occupant impact velocity crash severity metrics using event data recorders*. In Annual Proceedings/Association for the Advancement of Automotive Medicine, volume 50, page 57. Association for the Advancement of Automotive Medicine, 2006

Acknowledgments

We are grateful to the Department for Transport for granting the AutoTRIAGE project access to the Road Accident In Depth Study database, without which detailed analysis of both the collision and resulting injury would not be possible. The Transport Research Laboratory (TRL) provides a wealth of knowledge and support as a world leading institution, and this research output has been enhanced by the partnership and support (financial and otherwise) that TRL provides. We would also like to thank the EPSRC support of this project through Imperial College London's Centre for Doctoral Training in Neurotechnology.

BioMedEng18

Structural changes in brain circuitry in healthy ageing

JC. Mariani¹, S. Brickley¹, P. Chadderton¹

¹ Imperial College, South Kensington, SW7 2AZ, London.

Introduction

The ageing population has been targeted as one of the main challenge for the following century by authorities. This project wants to better understand physiological mechanisms at the origin of age related cognitive decline. Counter-intuitively, hemispheric asymmetry reduction in older adults (HAROLD) model suggests that prefrontal cortex (PFC) activity is increased for elderlies. More precisely it seems that this region of the brain shows symmetrical activity where only one lobe is usually activated for younger individuals. To our knowledge, no fundamental clues at the neural circuit scale have been demonstrated so far. We use electrophysiology in order to observe both physically and functionally how connectivity evolve between both PFC.

Methods

Local properties of neurons as well as synaptic weight between the two lobes is being investigated. On one hand, dynamic current clamp is used in order to observe different features of the cell such as action potential (AP) characteristics but also dynamic properties. On the other hand some mice have been transfected with AAV-Flex-ChR2-GFP using optogenetically induced signal properties, the synaptic weight between both sides is evaluated.

Results & Discussion

Our results so far tend to show a non-linear evolution of neurons features with age. If static properties such as threshold potential or AP amplitude seem unaltered during ageing, dynamic of the AP appear to evolve significantly.

Conclusion

PFC neuron properties seem to be influenced by age. Those properties still have to be linked with PFC to PFC connectivity in order to provide or not a support to the HAROLD theory. Such results will be compared with behavioural assessment to correlate the alteration with age related impairment.

References

1. UN 2017, Population Division Report.
2. Cabeza R, 2002, PMID: 1931290
3. Park and Leuter Lorentz 2009, DOI: 10.1146/annurev.psych.59.103006.093656
4. Song 2018, Cell reports in press.

Acknowledgments

Andy Li, Ann Go, Diana Lucaci, Dominica Niedzwiezka, Florian Zirpel, Gerald Moore, Rushdie Abuhamdah, Wei Ba

Topographically Patterned Hydrogels for Spinal Cord Regeneration

G.E. Koehl¹, R.Green ¹, S. Di Giovanni ³

¹Department of Bioengineering, South Kensington Campus, Imperial College London. ³Department of Medicine, Hammersmith Hospital, Imperial College London

Introduction

Spinal Cord Regeneration is a complex clinical challenge. Despite evidence that rehabilitation, electrical stimulation and cell transplant approaches can partially improve spinal nerve regrowth, no isolated solution has significant patient outcomes for large spinal cord defects. As a first step towards the design of a bionic spinal cord bridge, a biomimetic device is designed to include topographical cues to help guide axonal growth. In this study, topographical patterning of hydrogels is investigated as a tool to guide axonal growth in 2D and 3D structures *in vitro*. This is tested with a PVA-tyramine system that is expected to reduce fibrous encapsulation and can be bio-functionalized to contain polypeptides and proteins to provide support for cell adhesion and migration.

Methods

A 3D model for a bionic spinal cord bridge was designed, from which simplified models can be derived in order to test the influence of topography on 2D and 3D cell-material interactions *in vitro*.

Subsequently, a patterning technique for hydrogels is developed using PDMS casting of patterned silicon wafer. Square tracks of 5 and 10 μm feature size were assessed.

Finally, this system is tested with a PVA-tyramine system. Patterned and un-patterned hydrogels are cultured in 2D with PC12 (murine pheochromocytoma) cells to explore the effect of micro-topography on cell attachment and neurite outgrowth. For this, cell viability and cytotoxicity assays are performed along with cell adhesion studies and 96-hour cell differentiation assays.

Designs

To mimic the structure of the spinal cord, a cylindrical implant consisting of a hydrogel core surrounded by wrapped topographically patterned layers to promote axonal growth is designed. This is shown in figure 1 (a). In order to test the viability of this design with PVA-tyramine hydrogels, 2D and 3D models for the outer layers are designed and subsequently tested with PC12s. These models are shown in figure 1 (b) and (c).

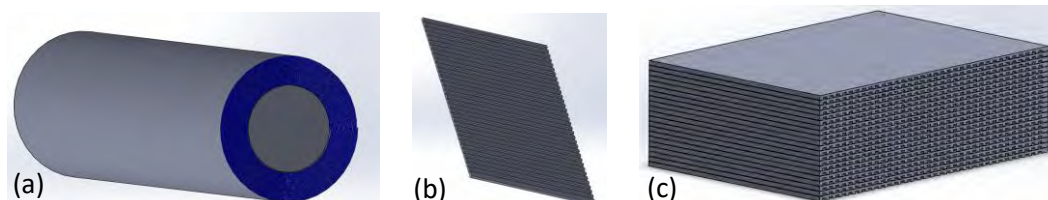


Figure 1 (a) Biomimetic Design of Hydrogel Implant (b) 2D model for experimental investigation of neurite outgrowth with PC12 (c) 3D model for experimental investigation of neurite outgrowth with PC12

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BioMedEng18

Advances in implantable cardioverter defibrillators

Stephen A. O'Connor¹ and Benedetta Sabiu²

¹City, University of London, Northampton Square, London EC1V 0HB and ²Strathclyde University, 50 George St., Glasgow G1 1QE

The first implantable cardioverter defibrillator, ICD, implanted in 1980, following the pioneering work of Mirowski and Mower¹, was non-programmable, shocking above 170 bpm, with a short battery life and peri-operative mortality, p-op, of 9.7%, increasing with concomitant surgery.

Transvenous leads were developed with a reduction in p-op to <0.5%, with programmable ICDs able to deliver anti-tachy, ATP, and brady pacing, ATP during charge with reconfirmation before shock. This has become the gold standard to prevent sudden cardiac death. Patients started to outlive their leads² highlighting the Achilles' heel of the system, the lead itself, with up to 30% of shocks being inappropriate leading to some cardiac patients requiring psychiatric referrals.

The totally subcutaneous ICD, S-ICD, was developed³, with no leads either on or in the heart, comprising an electrode with two sensing and one shocking elements and pulse generator, PG, for sensing as well as a shocking. The electrode is implanted left parasternally with the PG on mid-axillary line at the level of the 5-6th intercostal space. The S-ICD preserves the vasculature and is therefore of particular use in young patients. There have been no lead failures but pocket complications surprisingly increased restricting the uptake⁴. An intermuscular technique⁵ for PG placement, between serratus anterior and latissimus dorsi, has found favour, reducing the intra-operative complications compared with truly subcutaneous PG placement. There are >50k S-ICD implants worldwide for both primary and secondary prevention.

A further advance is the 44 F, 14.6mm, 'string defibrillator'⁶, implanted subcutaneously, high right parasternal to left dorsal positions in an arc, caudally. The battery is integral to the string and therefore does not require a pocket. Advantages appear to be the absence of pocket complications and a 1-year battery longevity with the ability to recharge over 1 hour at a planned outpatient follow-up. The first-in-man study was performed in 22 patients with defibrillation thresholds of 20 / 30 / 50 Joules in 7 / 4 / 7 patients respectively. Results in 4 (18%) were ignored as the lead was not correctly placed disproving claims of fluoroscopy free implants and ability to implant in an outpatient environment. Claims of patient comfort from acute implants cannot be justified.

The most recent advances include a totally leadless cardiac resynchronisation system for heart failure⁷ as well as an electrode for extra-pericardial defibrillation, yet to be published.

The area of implantable cardiac devices continues to move rapidly and once proven will improve patient outcomes.

References

1. Mirowski M et al. N Engl J Med 1980; 303(6): 322-324.
2. Kleeman T et al. Circulation 2007; 115: 2474-80.
3. Bardy G et al. N Engl J Med. 2010; 363: 36-44.
4. Brouwer T et al. J Am Coll Cardiol 2015; 2: 89-96.
5. Winter J et al. Europace 2017; 19(12): 2036-2041.
6. Neuzil P. HRS Late breakers, 2017.
7. Reddy V. et al., J Am Coll Cardiol 2017; 69: 2119-29.

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Gel Wax 3D printing technology.

D.I. Nikitichev¹, C. Mosse¹, J. C. Hebden¹.

¹ Medical Physics and Biomedical Engineering Department, University College London, London, WC1E 6BT

Introduction

Medical phantoms with precise and accurate tissue-mimicking properties and anatomical structures are vital for evaluation of imaging system performance and for training of clinical staff in techniques such as ultrasonography. Novel hybrid imaging technologies such as photoacoustic imaging require phantoms with suitable both optical and acoustic properties. Agar/gelatin and polyvinyl alcohol (PVA) can be used for phantoms [1]. However, the resulting phantoms are fragile and exhibit instability due to dehydration. There is an on-going need for novel tissue-mimicking materials and phantom fabrication methods to validate new advances in optical and acoustic imaging technology. Recently, 3D printing technology has developed rapidly, enabling the manufacture of highly complex structures [2-4]. However, commercially available 3D printing materials don't routinely provide the physical properties required for tissue-mimicking phantom. Recently, optical phantoms were developed by adding dye into the 3D printer resin [5]. In this work, we developed a novel 3D printing technology directly printing tissue-mimicking material known as Gel Wax.

Methods

Conventional 3D printers employ various methods, such as pushing a rigid filament into a heated nozzle so that molten material is extruded, or using a focussed spot of light to cure an epoxy, or using heat to sinter metal powder. However, these methods cannot be used with gel wax or other gels as they are not strong enough to form a filament and cannot be photo-cured or sintered. We adapted Fused Deposition Modeling 3D printing technology to deliver hot gel wax into the conventional printing head using a syringe and peristaltic pumps. Moreover, it allows two gel waxes with different properties to be mixed together in a single phantom.

Results & Discussion

In this work we present the first gel wax hippocampus and brain models that were 3D printed using our technology. Ultrasound images of the models show that gel wax is a very promising material due to its optical and acoustical transparency. Moreover, gel wax material does not dehydrate, and has good temporal stability.

Conclusion

The demonstrated technology holds a great promise for fabricating patient-specific medical phantoms at low cost for emerging optical and acoustic imaging. It is also highly energy efficient, using more than 90% of the material.

References

- [1] Pogue BW, Patterson MS, *J. Biomed Opt.*, 2006; 11:041102-16
- [2] Nikitichev DI, *et al. J. Ultrasound Med.* 2016; 35: 1333-1339.
- [3] Mitsouras D, *et al. RadioGraphics*, 2015; 35: 1965-1988.
- [4] Bucking TM, *et al. Plos One.* 2017; 12: e0178540.
- [5] Dempsey LA, *et al. Biomed Opt Express.* 2017; 8: 1754–1762.

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BioMedEng18

Facilitating the Translation of ATR-FTIR to the Clinical Setting.

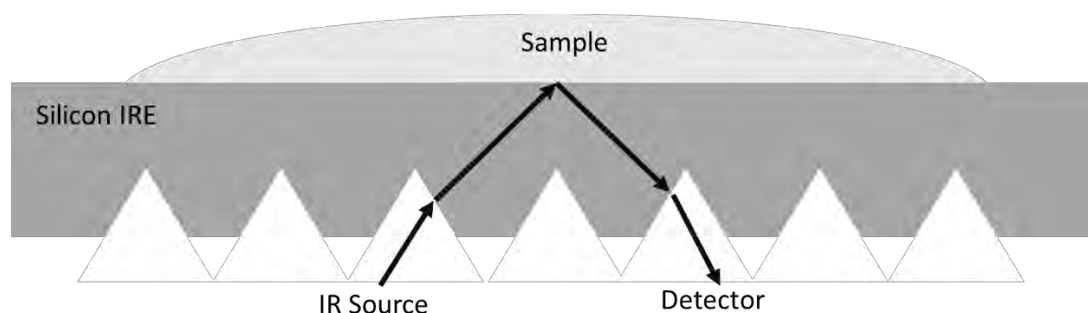
D. Finlayson^{1,2}, H.J. Butler^{1,3}, M. Hegarty³, T. Gourlay², M.J. Baker^{1,3}

¹ Department of Pure and Applied Chemistry, The Technology and Innovation Centre, University of Strathclyde, Glasgow, Lanarkshire, G1 1RD. ² Department of Biomedical Engineering, Wolfson Centre, University of Strathclyde, 106 Rottenrow, Glasgow, G4 0NW. ³ Clinspec Diagnostics Limited, The Technology and Innovation Centre, University of Strathclyde, Glasgow, Lanarkshire, G1 1RD.

Introduction

Attenuated total reflection – Fourier transform infrared (ATR-FTIR) spectroscopy has demonstrable potential as a tool for serum diagnostics [1]. It is a non-destructive analytical technique that uses infrared light to characterise the specific biochemical profile of a sample without the use of reagents. It has previously been shown that ATR-FTIR can discern the presence and severity of brain cancers using only serum with high specificity and sensitivities (91.5% and 83% respectively) [2]. Brain cancers are commonly asymptomatic and current diagnostic modalities, such as MRI or CT scans, are in high demand and expense. ATR-FTIR in the form of a triage tool can provide clinical significant evidence, but currently does not possess the throughput capabilities to be practically implemented into a clinical environment. ATR-FTIR relies on a fixed and expensive component called the Internal Reflection Element (IRE) whereupon the sample is located during analysis. Presented are novel and disposable Silicon IREs which are cheap, easy to manufacture and can equip ATR-FTIR spectrometers with high throughput capabilities.

Current Silicon IREs are limited in the spectral information that can be obtained from them. This is due to the propensity of Silicon to absorb certain wavelengths of infrared light [3]. Various design parameters of Silicon IREs were modulated to successfully circumvent this limitation. Designs were assessed on Signal to Noise Ratio (SNR) and structural integrity. Clinically relevant biosamples (human pooled serum) were also used to determine which designs were most able to analyse biological samples. Designs were created with scaled manufacturability in mind, and as a result multi-sample Silicon IREs are far cheaper and more functional than similar commercially available devices, especially for use in the clinical setting. A basic schematic of a single compartment on the multi-sample Silicon IRE is shown below:



The ability for high-throughput ATR-FTIR spectroscopic analysis has been realised through these cheap, multi-sample, disposable Silicon IREs. This in turn will facilitate the successful translation of ATR-FTIR spectroscopy into the clinical environment as a powerful serum diagnostics tool.

References & Acknowledgements

1. Baker MJ *et al.* *Nat. Protoc.* 2014; 9: 1771–1791.
2. Hands JR *et al.* *J. Biophotonics.* 2017; 7: 25640-25649.
3. Merdernach JW. *Handbook of Vibrational Spectroscopy*, John Wiley & Sons, Hoboken; 2006.

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Engineering Safety in Vacuum Assisted Delivery Devices

B.D Goordyal¹, A.Alazmani ¹, P.R Culmer ¹

¹ Surgical Technologies Research Group, School of Mechanical Engineering, University of Leeds, LS9 2JT, Leeds.

Introduction

Vacuum-Assisted Delivery (VAD) is an obstetric practice used to assist child birth during the second stage of labour. During the procedure, the obstetric professional attaches the VAD device to the scalp of the foetus through suction and tractive force is then applied alongside maternal contractions to assist the baby's passage through the delivery channel. VAD is more prevalent than obstetric forceps due to its ease of use, lower maternal morbidity and improved cosmetic outcome for her baby. However, safety concerns such as unintentional cup detachment or high vacuum, can lead to induced trauma to the foetus [1, 2]. Since its original inception, there have been limited effort to evaluate the safety of VAD devices or optimise their design and operation. Here, an engineering approach to assess the devices' failure modes is proposed to inform training, best obstetric practice and improved VAD design.

Methods

An instrumented experimental recreation of VAD has been developed to achieve a comprehensive understanding of the mechanics of VAD devices and the associated trauma. It features a commercially available VAD device (the Kiwi® Omnicup) connected to a tensile testing machine to simulate obstetric traction onto a head scalp model (fabricated using textile reinforced silicone). A pneumatic control system provides an actively controlled vacuum to the instrumented device. Optical markers, placed onto the scalp model, combined with a high-speed camera system provide tracking of scalp deformation during mechanical simulation of obstetric traction. Experiments have been devised to investigate the clinical impact of system variables including the applied force rate, magnitude of vacuum imposed and geometry of the VAD cup.

Results & Discussion

Our results show that a simulated obstetric VAD traction produces a characteristic response from which a number of key clinically relevant metrics can be determined. The phenomena of undesirable cup detachment is strongly linked to the magnitude and stability of applied vacuum, but is less dependent on load rate. Image analysis shows that loss of vacuum is strongly affected by the geometry and physical properties of the VAD device during its interaction with the scalp.

Conclusion

Our instrumented VAD simulation has provided valuable insight into this critical area of healthcare. Results indicate important clinical aspects and understanding of the mechanics of the system during use. The outcomes from the research provides a quantifiable approach for assessing the performance of VAD devices and improving their design, and usage, in the future.

References

1. Awon, M.P. The vacuum extractor-extractor-experimental demonstration of distortion of the foetal skull. *BJOG: An International Journal of Obstetrics & Gynaecology*. 1964, 71(4), pp.634-636.
2. Pettersson, K. et al. Traction force during vacuum extraction: a prospective observational study. *BJOG*. 2015, 122(13), pp.1809-16.

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Home-based Neurofeedback Treatment of Neuropathic Pain

M.K.H. Altaieb^{1,2}, M. Purcell³, M. Fraser³, A.Vuckovic¹

¹ School of Engineering, James Watt (South) building, University of Glasgow, G12 8QQ, Glasgow ² College of Engineering, Wasit University, Wasit, Iraq, ³Queen Elizabeth National Spinal Injuries Unit, Queen Elizabeth University Hospital, G51 4TF Glasgow, .

Introduction

Central neuropathic pain (CNP) has a prevalence of 50% in spinal cord injured (SCI) patients.¹ Pharmacological treatments of CNP have limited efficiency and multiple side effect. Neurofeedback (NF) is a neuromodulatory approach used to reduce CNP.² In this study we present results of electroencephalography (EEG) based NF treatment self-managed by SCI patients at their homes. The system was based on Brain Computer Interface (BCI) technology.

Methods

Participants: Twenty complete and incomplete SCI patients with chronic CNP (age 50±14, 4F, 16 M) and their caregivers, were trained to use BCI system consisting of 14 channel wireless EEG (Epoch, Emotiv, USA) and a computer tablet under Windows, with custom made NF software developed in C++. The NF protocol consisted of increasing the alpha band power while decreasing theta and higher beta (20-30 Hz) power from electrode location C4.² Patients used NF to treat CNP up to three months at their home, with occasional support from the researchers.. The custom made NF software consisted of main screen for NF training, electronic pain diary and EEG setup screen. EEG signal was recorded during NF for post-hock analysis.

Results & Discussion

All 20 participants learned how to use BCI to practice NF. On average 2-4 training sessions at the hospital was required. Three patients with complete tetraplegia had caregivers who setup the system for them. Fifteen patients reported some reduction of pain and in 40% patients it was clinically significant (larger than 30%). Average setup time was 5-15min and NF was practiced minimum once a week. On average 80-90% recorded EEG was of a good quality.

Conclusion

People of average technical literacy can learn to operate BCI in their own to practice NF, The efficacy of NF of 40% is comparable to efficacy of well recognised CNP medications such as gabapentine.³ Future work should explore infrastructure required for introducing BCI NF as a customer service.

References

1. Siddall PJ et al. . *Pain*. 2003;103:249–257
2. Hassan et al. *Clin Neurophysiol*. 2016;127:3118-3127.
3. Wiffen P.J. et al. *Cochrane Database Syst Rev*. 2017;6:CD007938

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VibraScan: A smart device to replace Neurothesiometer for measuring diabetic vibration perception threshold

J.M. Dave¹, V.N. Dubey¹, D.V. Coppini², J. Beavis¹

¹Faculty of Science and Technology, Bournemouth University, Bournemouth, UK,

²Department of Diabetes, Poole Hospital NHS Foundation Trust, Poole, UK

Introduction

There are about 3.7 million people diagnosed with diabetes in the UK (Diabetes UK). Diabetic neuropathy is one of the serious complications of diabetes which needs constant monitoring to track its progression. The common method employed is based on measuring vibration perception threshold (VPT) on the at-risk foot. Considering the limitations of Biothesiometer/Neurothesiometer [1] as the principal tool for diagnosing diabetic neuropathy, an innovative device VibraScan [2] has been developed that offers many advanced features. A preliminary result using this device is reported here.

Methods

Using Neurothesiometer, VPT is obtained by pressing the vibration probe to the touch site which is manual and operator dependent, whereas in VibraScan, VPT is measured by automatic operation of the device by simply placing the feet over the plate. The voltage range in both devices is similar (0-50 V) with further flexibility of changing the amplitude and frequency of vibration. These are programmable in the device and pressure at the foot is continuously monitored for consistency of the test.

Results & Discussion

A preliminary study has been made with 20 healthy subjects using each device to show that the results are comparable. The mean VPT measured for left and right foot using Neurothesiometer are 4.53 ± 0.65 V and 4.97 ± 0.57 V compared to 4.76 ± 0.60 V and 5.22 ± 0.67 V using VibraScan. The correlation between individual values for each device is described as $r = 0.816$, $p < 0.01$ for left foot and $r = 0.893$, $p < 0.01$ for right foot. There is not much difference in the readings of the measured VPT using both the devices although the method of conducting the test is completely different. It also shows agreement with using Bland-Altman method [3].

Conclusion

A smart diabetic screening device has been developed that automatically interprets and displays the results on a graphical user interface and due to the close correlation between the measured VPTs, VibraScan can be used as an alternative to Neurothesiometer in the clinical setting providing consistent results with many advanced features as described above.

References

1. Young MJ, Every N, Boulton AJM. A comparison of the neurothesiometer and biothesiometer for measuring vibration perception in diabetic patients. Diabetes research and clinical practice: 1993 20(2), pp.129-131.
2. JM Dave et al. A 'smarter' way of diagnosing the at-risk foot: Development of a novel tool based on vibratory measurements in subjects with diabetes. Diabetes UK conference: 2018.
3. Bland JM, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. The lancet. 1986 Feb 8;327(8476):307-10.

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Monitoring of Nasal Blockage treatment using an Acoustic Method

C-H. Li¹, C. Tan ¹, S. Hope ², I. McCutcheon ², G. Smith ², P. Andrews ³, T.S. Leung ¹

¹ Department of Medical Physics and Biomedical Engineering, University College London, United Kingdom.

²Integrated Technologies Limited, Ashford, Kent, United Kingdom. ³Royal National Throat, Nose and Ear Hospital, London, United Kingdom.

Introduction

A simple procedure to assist in diagnosing nasal blockage is to monitor the nasal condition before and after applying medications and observe the changes [1]. Nasal Inspiratory Peak Flow (NIPF) is one of the most commonly used objective methods for such monitoring [1]. This study proposes the concept of an alternative objective method: the Nasal Acoustic Device (NAD), which measures the sound of a subject's nasal breathing.

Methods

11 control subjects clinically assessed to have normal nasal conditions took part in this study. Both NIPF and NAD were measured prior to and after applying decongestant spray to the nose. NAD was measured by placing an acoustic sensor on the nasal ala (external surface of the nose) on each side. NIPF measures nasal air flowrate of both nasal cavities together while NAD measures the acoustic signal power (at a specific frequency range) of nasal inspiratory breathing for each cavity separately and the average of the two was calculated. Results are presented in terms of percentage change in the post-decongestant measurements compared to pre-decongestant measurements.

Results & Discussion

Overall, the control group exhibited a positive change in the measured values for both NIPF and NAD. The positive percentage increase was found to be statically significant ($p < 0.05$) for both NAD ($p = 0.03$) and NIPF ($p = 0.02$).

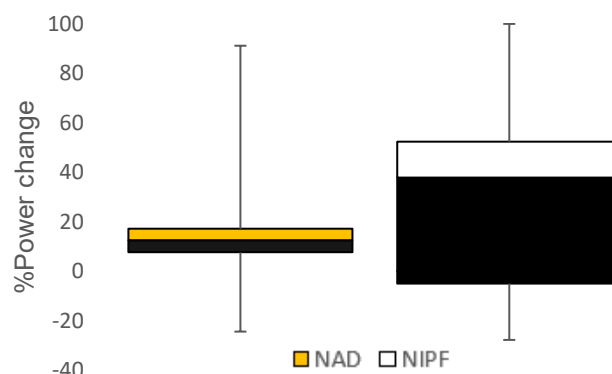


Fig 1. Box plot of percentage changes in NAD and NIPF measurements after decongestant.

Conclusion

The results showed that NAD can monitor nasal treatments, similar to NIPF. While the result for NIPF showed a greater statistical significance, the NAD has the advantage of being able to also measure nasal expirations, simultaneously monitor both sides of the nose separately and requires a much lower effort of breathing from the subject.

References

1. D. Chin, G. Marcells, J. Malek, E. Pratt, R. Sacks, K. Snidvongs, et al., "Nasal peak inspiratory flow (NPIF) as a diagnostic tool for differentiating decongestable from structural nasal obstruction," *Rhinology*, vol. 52, pp. 116-21, Jun 2014.

Acknowledgments

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Orthogonal Electric Field-based Catheter Alignment

M.A.Diallo¹, S.C.Popa², R.J.Dickinson^{1,2}

¹ Department of Bioengineering, Imperial College London, SW7 2AZ, UK, ² Stent Tek Ltd, 1 Square Rigger Row, London SW11 3TZ. UK

Introduction

An innovative vascular access solution has been developed that uses two intravascular catheters to direct a needle to cross between vessels to create a fistula without surgery. A system using a dipole electrode configuration has been previously reported, where locating the maximum electric field indicates alignment. A more accurate technique has now been developed in which two perpendicular asymmetric electrical fields are generated and detected by a catheter in the target vessel to give an estimate of the angle of alignment.

Methods

The new system uses four electrodes positioned around the circumference of a catheter as shown in Figure 1. The electrodes are connected in pairs to create dipole in the front and back configuration, where the signal is a maximum at alignment, or a dipole in the left-right configuration, where the signal is a zero at alignment. The amplitude of both signals have a sinusoidal relationship to the alignment angle θ as in Figure 1. By rapidly switching the signal between the two electrode configurations using analogue switches, both configurations can be sampled as an interleaved signal. The signals are digitised and processed to give a display of the angle in real-time as in Figure 2.

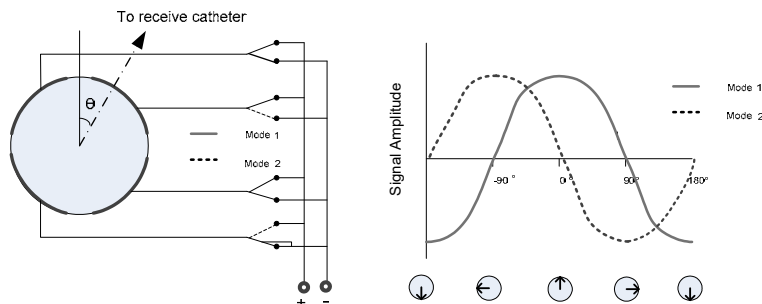


Figure 1 : Switching between 2 modes to give orthogonal signals angle

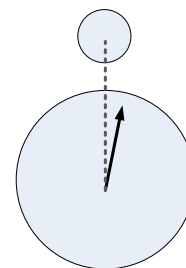


Figure 2 : Display of alignment

Results & Discussion

The system gave a real-time angle dependent signal that directly shows the angle of alignment with greater accuracy than the previous maximum amplitude method.

Conclusion

A four electrode configuration on the catheter gives two orthogonal alignment signals that can be processed to display the actual angle of the device away from alignment.

References

1. Diallo M A, Popa S, Dickinson R J *Catheter Alignment System for Vascular Access* - MPEC 2017

Acknowledgments

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BioMedEng18

Effect of corrosion on the mechanical properties of an Fe-316L amalgamate for biodegradable stent application

J. Frattolin^{1,2}, S. Yue³, O.F. Bertrand^{2,4}, R. Mongrain^{2,5}

¹Department of Bioengineering, Imperial College, South Kensington, London. ²Department of Mechanical Engineering, McGill University, Montreal, Canada. ³Department of Mining and Materials Engineering, McGill University, Montreal, Canada. ⁴Interventional Cardiology Laboratories, Quebec Heart and Lung Institute, Laval University, Quebec City, Canada. ⁵Montreal Heart Institute, Montreal, Canada.

Introduction

Bioresorbable stents have promise to revolutionize coronary artery disease treatment. A novel cold-sprayed material, composed of 80% iron and 20% stainless steel 316L, has been proposed to address the limitations of current generation biodegradable stents.¹ This investigation assesses the effect of degradation on the mechanical properties of Fe-316L, which is a critical study for the potential implementation of Fe-316L stents in a clinical setting.

Methods

Dogbone samples were manufactured from 1-mm thick sheets of cold-sprayed Fe-316L. Samples were corroded in a static environment for 24, 48, 96, and 168 hours in buffered Hanks' Balanced Salt Solution, maintained at $37 \pm 1^\circ\text{C}$. Uniaxial tensile tests were then conducted to failure. All tests were completed in triplicate, and statistical significance testing was conducted.

Results & Discussion

Tensile tests of uncorroded samples indicated an ultimate tensile strength (UTS) of Fe-316L of 300 MPa, with a resulting decrease in UTS of only 6.3% after 168 hours of degradation. It was found that that corrosion only had a statistically significant effect on the mechanical performance of Fe-316L after 168 hours of corrosion, $p < 0.05$. Prior to this timestep, any reported decrease was not significantly less than that of bulk Fe-316L. This was determined for all properties analysed, including UTS, yield strength, elongation at fracture, and toughness.

Galvin *et al.* found that the UTS of corroded magnesium alloy WE43 specimens decreased by approximately 50% after only 10 days of static immersion in SBF.² In contrast, it was extrapolated from the experimental data that it would require 54 days of corrosion time for a 50% drop in UTS to occur for Fe-316L. From a clinical perspective, this suggests that Fe-316L may be a more suitable material for biodegradable stent application as its mechanical integrity can be maintained long-term due to its reduced corrosion rate in comparison to other magnesium alloys.

Conclusion

This investigation demonstrated the potential of Fe-316L for biodegradable stent application as corrosion had a limited effect on the mechanical performance of the amalgamate.

References

1. Frattolin J *et al.* *Ann Biomed Eng.* 2016; 44: 404-418.
2. Galvin E *et al.* *Acta Biomater.* 2017; 55: 505-517.

Acknowledgments

We are grateful to the Wellcome Trust and EPSRC Medical Engineering Initiative and the Bioengineering Society for supporting this conference. We also acknowledge funding support from the Natural Sciences and Engineering Research Council of Canada and MEDA.

Short and Medium Term Outcomes Following Endobronchial Therapy with Nd:YAG Lasers for Central Airway Obstruction.

S Pathak¹; E J Caruana¹; A G Dawson¹; S Rathinam¹; A Nakas¹.

¹ University Hospitals of Leicester, UK.

Introduction

Central airway obstruction is distressing and may prove life-threatening ^[1]. Rigid bronchoscopy with endobronchial laser therapy is one of a spectrum of interventions that may benefit this patient group ^[2]. Previous studies have shown endobronchial therapy with Nd:YAG lasers to improve both symptoms and survival ^[3]. We conducted a retrospective observational study to report on the perioperative to medium-term outcomes following endobronchial laser therapy at a single thoracic centre in the East Midlands.

Methods

This study included all patients who received endobronchial laser therapy at a single institution in the East Midlands, between January 2012 and December 2014. Patients were identified through operative databases. Data was collected retrospectively from case notes and electronic records. Statistical analysis was performed using Matlab and the Analyze-it® package in Microsoft Excel. P values less than 0.05 were considered statistically significant.

Results & Discussion

We collected data on 84 endobronchial laser (Nd:YAG) procedures which were performed in 52 patients over 23 months. 64% of the study population were male with a mean age of 64±13 years (SD) and a median Charlson comorbidity index of 6 (range: 0 to 11) at first presentation. 79% of all cases were malignant, of which 54% constituted primary lung cancer. Tracheal involvement was demonstrated in 37% of all patients. Average laser energy usage was 1510±1621 Joules; with a median length of stay of 2 (range 0 to 55) days. There were no immediate perioperative deaths. Overall mortality was 10% (n = 5) at 30-days, and 65% (n = 34) at 2-years following the initial procedure. Median survival in the malignant group was 10 (range: 0 to 43) months. No statistically significant difference in 30-day survival was noted when comparing subgroups of patients with: tracheal versus bronchial disease (p = 0.87), benign versus malignant disease (p=0.22), as well as primary versus metastatic (secondary) lung disease (p = 0.36).

Conclusion

Our results demonstrated that there were no statistically significant differences in short term mortality post-endobronchial laser therapy between any of our subgroups. We were able to demonstrate that laser therapy can be used safely in a wide variety of patients with a low perioperative morbidity and mortality, despite the high-risk nature of the procedure and patient group.

References

1. Han CC, Prasetyo D, Wright GM. Endobronchial palliation using Nd:YAG laser is associated with improved survival when combined with multimodal adjuvant treatments. J Thorac Oncol [Internet]. 2007;2(1):59–64. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17410011>
2. Khemasuwan D, Mehta AC, Wang KP. Past, present, and future of endobronchial laser photoresection. J Thorac Dis. 2015;7(2):S380–8.
3. Koerner DJRZMSK. Survival characteristics after neodymium: YAG laser photoresection in advanced stage lung cancer. Chest. 98(3):581–5

Population-derived material properties for craniosynostosis patients improve outcome predictions in craniofacial surgery

Alessandro Borghi^{1,2}, Naiara Rodriguez Florez³, Owase Jeelani^{1,2},
David Dunaway^{1,2}, Silvia Schievano^{1,2}

¹UCL Great Ormond Street Institute of Child Health; ²Great Ormond Street Hospital for Children,
³Department of Biomedical Engineering, Mondragon Unibertsitatea

Introduction

Sagittal craniosynostosis consists of premature fusion (ossification) of the sagittal suture during infancy, which causes head deformity and brain growth restriction. Spring assisted cranioplasty (SAC) entails skull incisions to free the fused suture and insertion of springs (metallic distractors, one anteriorly and one posteriorly) to promote cranial reshaping. Although safe and effective, this operation's outcomes are still uncertain due to an incomplete understanding of the skull-distractor interaction. We aimed hereby to retrieve and validate a skull material model for SAC outcome prediction.

Methods

Pre-SAC computed tomography (CT) images, spring models and spring expansion measurements on-table (OP_{IO}^M) and at follow-up (OP_{FU}^M on day 1) were retrieved from 10 SAC patients (age = 5.5 ± 1.2 months). 3D models of each patient calvarium (skull and sutures) were created and discretized using SCANIP®. ANSYS® was used for simulation of spring expansion. A viscoelastic material model was used to model skull reshaping due skull-spring interaction. Data relative to bone elastic [1] and viscoelastic properties [2] were initialized to literature values and reference values (OP_{IO}^R , OP_{FU}^R) were retrieved in this configuration. Design of Experiment was used to assess the parametric correlation between simulated expansion and input material parameters. A two-stage optimization process was performed: firstly, the skull Young's modulus (E_B) was varied between 100 and 600 MPa and optimized against OP_{IO}^M ; secondly, the total relaxation (G_{TOT}) was varied between 83% and 99% and optimized against OP_{FU}^M . Population values for E_B and G_{TOT} were calculated as average values. A final simulation was run to estimate the value of spring opening after material optimization (OP_{IO}^{OPT} , OP_{FU}^{OPT}) and compared with the baseline values and measurements (mean opening between anterior and posterior spring was used for comparison).

Results & Discussion

The use of the population model improved the prediction of average spring opening at insertion ($OP_{IO}^R = 34.8 \pm 2.7$ mm, $OP_{IO}^{OPT} = 37.0 \pm 4.3$ mm, $OP_{IO}^M = 37.9 \pm 4.0$ mm) and at FU ($OP_{FU}^R = 43.6 \pm 3.5$ mm, $OP_{FU}^{OPT} = 46.5 \pm 2.8$ mm, $OP_{FU}^M = 48.3 \pm 3.6$ mm). The estimation error was reduced both at insertion ($-7.5 \pm 8.4\%$ vs $-2.1 \pm 8.9\%$, $p=0.0098$) and at FU ($-9.5 \pm 6.7\%$ vs $-3.4 \pm 6.8\%$, $p=0.002$).

Conclusion

Surgical planning by means of computer simulations requires reliable tissue mechanics models. This work shows that a population derived material model can help improve numerical prediction of spring dynamics in SAC.

References

- 1) Li et al. CMPB 2013
- 2) Yan et al. CMBBE 2011

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BioMedEng18

Utilising surface roughness in the design of cranio-implants

H.E. Burton, D. Eggbeer

Surgical & Prosthetic Design, PDR, Cardiff Metropolitan University, Cardiff, CF5 2YB

Introduction

Cranioplasty is a common procedure across the world, including within the UK National Health Service (NHS). Patient-specific cranioplasty implants are used to replace absent portions of cranium, usually following the removal of diseased anatomy [1]. These implants are formed either through time-consuming, fully or semi-traditional pressing methods, or more recently through automated additive manufacture (AM) [2]. AM-produced plates have a rougher surface finish than pressed sheet, therefore post-production finishing techniques may be employed. Current research concentrates on the osseointegrative properties of implants, but little research investigates the requirements of implant-tissue interfaces. This study quantifies the surface roughness of cranioplasty implants produced using AM and sheet titanium forming, then discusses the potential clinical implications.

Methods

Traditionally pressed and AM cranio-implants were produced for this study. Optical imaging of plates was performed using an Alicona microscope (G5 InfiniteFocus, Alicona UK) at 10 × magnification. The mean and standard deviation values of the arithmetic average roughness (R_a) was evaluated over five profile lengths of 10 mm for each plate.

Results & Discussion

The average R_a of traditionally formed plates was $0.52 \pm 0.14 \mu\text{m}$, whereas for AM plates R_a was significantly rougher at $9.96 \pm 1.57 \mu\text{m}$ ($p < 0.05$). Early soft tissue integration may be desirable to prevent liquid capsule formation and decrease infection risk by minimising implant movement. However, a gliding motion may be preferred for cases such as orbital floor reconstruction, where a liquid capsule may be beneficial to prevent soft tissue connecting to an implant [3]. There is currently no evidence-based consensus on what constitutes an acceptable surface finish and roughness for cranioplasty plates. Traditionally, pressed titanium plates are polished to a subjectively reflective finish, with the anecdotal justification that it makes them easier to clean and prevents overlaying soft tissue adhesion. AM-produced implants can also be highly polished, but given the current lack of evidence that supports the need for a polished finish, the extra time and potential to increase contamination levels through the introduction of polishing compounds and tools, it is currently deemed unnecessary. An automated polishing process sometimes applied for AM implants employs a tumbling machine, where a mask can be applied to protect the edge of implants but which could be applied to designate areas of surface finish.

Conclusion

This study assessed existing surface finishes of clinical cranio-plates, to aid in improving current design processes. Future work will aim to improved cranio-plate design by applying designating areas of varying surface roughness to encourage: osseointegration at the bone-implant borders for increased implant stability; soft tissue-implant integration for decreased infection risk; and non-adhering fibrous capsule formation at gliding interfaces.

References

1. Moreira-Gonzalez A, Jackson IT, Miyawaki T et al. *J Craniofac Surg*. 2003; 14(2): 144-153.
2. Bibb R, Eggbeer D, Paterson A. *Medical modelling*. Woodhead Publishing. 2014.
3. Richards RG. *AODialogue*. 2007; 1(07): 20-24

Modelling deformable structures for multi-segment needle steering

T. E. Watts¹, R. S. Secoli¹, F. M. Rodriguez y Baena¹

¹ *Mechatronics in Medicine Laboratory, Mechanical Engineering, Imperial College London, South Kensington, SW7 2AZ, London.*

Introduction

Steerable needles are a promising technology, developed to provide greater targeting accuracy and access to clinical targets which are currently unreachable via rigid instruments [1]. In previous work, a deformable multi-segment needle has been shown to steer through soft tissue [2]. Control is achieved through modifying the shape of the tip, via relative axial motion of the segments. In this work we present a Finite Element deflection study for 3 and 4-segment designs, considering the deflection of the tip under different configurations. We hope this will shed light on the potential steering behaviour of each design and inform future design choices.

Methods

In order to compare the two designs, a 20mm section of each segment design was meshed. The segments were configured as shown in Fig. 1, with axial displacements described by the segment offsets o_i .

The segments of the structure were meshed with linear hexahedral elements of type C3D8R. The loading at the tip of each segment is provided by a uniform pressure, with 'encastre' boundary condition ensuring zero rotation and deflection 20mm from the tip. The analysis was performed with Abaqus explicit and deflection was measured at the tip node of the furthestmost extended segment.

Results & Discussion

Both needle designs show the greatest deflection with a single segment extended, with the next largest deflection exhibited with two leading segments. Combinations of two extended segments had comparatively lower deflection. The deflection magnitude of the 4-segment design was more consistent across tip configurations than for the 3-segment case.

Conclusion

This study shows that needle deflection is greatest in certain principal directions, attributable to the multi-segment geometry. The greater consistency of deflection magnitude for the 4-segment needle suggests this design should be easier to control than its 3-segment counterpart.

References

1. N.J. van de Berg, D.J. van Gerwen, J. Dankelman, and J.J. van den Dobbela. Design choices in needle steering 2014; a review. *Mechatronics, IEEE/ASME Transactions on*, PP(99):1–12, 2014.
2. Secoli, R. & Rodriguez y Baena, F., 2016. Adaptive path-following control for bio-inspired steerable needles. In 2016 6th IEEE BioRob. pp. 87–93.

Acknowledgments

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Tip configuration (mm) $\{o_1, o_2, o_3, o_4\}$	Deflection	Tip configuration (mm) $\{o_1, o_2, o_3\}$	Deflection
A4: $\{20, 20, 10, 10\}$		A3: $\{20, 20, 10\}$	
B4: $\{20, 18, 10, 10\}$		B3: $\{20, 18, 10\}$	
C4: $\{20, 16, 10, 10\}$		C3: $\{20, 16, 10\}$	
D4: $\{20, 14, 10, 10\}$		D3: $\{20, 14, 10\}$	
E4: $\{20, 12, 10, 10\}$		E3: $\{20, 12, 10\}$	
F4: $\{20, 10, 10, 10\}$		F3: $\{20, 10, 10\}$	
G4: $\{20, 10, 10, 12\}$		G3: $\{20, 10, 12\}$	
H4: $\{20, 10, 10, 14\}$		H3: $\{20, 10, 14\}$	
I4: $\{20, 10, 10, 16\}$		I3: $\{20, 10, 16\}$	
J4: $\{20, 10, 10, 18\}$		J3: $\{20, 10, 18\}$	
K4: $\{20, 10, 10, 20\}$		K3: $\{20, 10, 20\}$	

Design and Implementation of a Transcranial Alternating Current Stimulation (tACS) Device

H. Chan¹ and E.M. Drakakis¹

¹ Department of Bioengineering, Imperial College London, South Kensington Campus, SW7 2AZ, London-UK

Introduction

Transcranial alternating current stimulations (tACS) have the ability to non-invasively provide insight into neuronal activity patterns and brain structures, as well as neurological disorders [1–3]. Stimulation frequencies span from near DC to 5kHz for plasticity studies and reach 200kHz for tumour treatment [4]. Here, a novel tAC stimulator realisation is presented, which covers this frequency range and offers customisable current stimulation waveforms with tuneable amplitudes up to 2mA.

Methods

To achieve such versatility, waveforms are produced through Direct Digital Synthesis (DDS) and converted into stimulation currents using Operational Transconductance Amplifiers (OTAs). More specifically, the architecture of our customised PCB-based tACS instrument comprises three key off-shelf components: the AD9834CRUZ arbitrary waveform generator chip is SPI-programmed to generate the desired stimulation profile in voltage-mode by means of DDS; the desired DDS-dictated voltage profile is appropriately amplified by AD8014ARZ and is subsequently converted to the intended current stimulation profile by means of a pair of NE5517DG dual OTAs. The design benefits from safety considerations-induced digital isolation and occupies an area of 11.5 cm x 5.8 cm. The instrument's functionality has been confirmed through passive equivalent electronic circuit models and using tissue-based tests to verify the delivery of the desired current stimuli for tACS.

Results & Discussion

Results from appropriate electrical models demonstrate the ability of the device to generate and deliver sinusoidal and triangular waves/stimulation currents from 0-200kHz, with a granularity of 0.28Hz and 0.02mA in frequency and amplitude respectively. Moreover, it was further confirmed that customised waveform stimulations along with random noise (tRNS) and direct current (tDCS) stimulation profiles can also be produced.

Conclusion

Tests confirmed the functionality, programmability and practicality of the device and shows its prospective competitiveness compared to prior art. Its flexibility and potential in offering additional features to existing instruments should allow researchers to efficiently explore the effects of varying different tACS stimulation parameters and offer the possibility of providing insights into and treatment for brain associated ailments.

References

- [1] N. Jaušovec, K. Jaušovec, and A. Pahor, *The influence of theta transcranial alternating current stimulation (tACS) on working memory storage and processing functions. Acta Psychol. (Amst).*, vol. 146, pp. 1–6, Feb. 2014.
- [2] J.-S. Brittain et al., *Tremor suppression by rhythmic transcranial current stimulation. Curr. Biol.*, vol. 23, no. 5, pp. 436–40, Mar. 2013.
- [3] H. Chan, *Final Year Report: Transcranial Alternating Current Stimulation*. London, 2017.
- [4] A. Antal and W. Paulus, *Transcranial alternating current stimulation (tACS). Front. Hum. Neurosci.*, vol. 7, p. 317, 2013.

High-resolution capacitive pressure sensing for health

Saja Aabith^{1,2}, Shervanthi Homer-Vanniasinkam^{1,2} and Manish K. Tiwari^{1,2*}

¹ Nanoengineered Systems Laboratory, UCL Mechanical Engineering, London WC1E 7JE, UK

² Wellcome/EPSCRC Centre for Interventional and Surgical Sciences (WEISS), UCL, London W1W 7TS, UK

*E-mail: m.tiwari@ucl.ac.uk

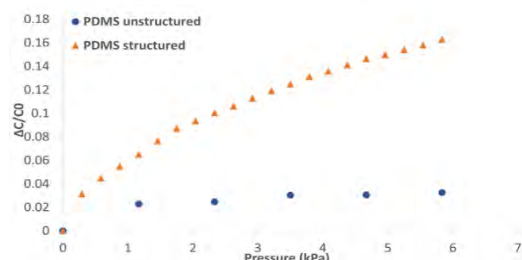
Introduction

High-resolution manufacturing techniques have erupted in many sectors including optics, microfluidics, microelectronics, healthcare, etc. Of these techniques, additive manufacturing (3D printing) and in particular the direct-write assembly approach is a promising candidate for miniaturised device manufacturing and rapid prototyping [1]. However, each printable ink requires extensive fine tuning of viscosity, evaporation rate, storage modulus to form self-standing structures [1]. Miniaturised medical devices and in particular miniaturised flexible capacitive pressure sensors have gained much attention recently with personalised medical devices contending with wireless extensions for convenient diagnostic monitoring, etc. Structuring the dielectric medium of such capacitive pressure sensors into pyramidal structures have been reported to increase sensor sensitivity up to 30-fold [2]. So far the structuring has been achieved with photolithography [2] or similar subtractive approaches [3] or inkjet printing [4].

Methods

Here we demonstrate a high-resolution 3D printing as a new approach for rapid microscale prototyping using simple water based inks to print micro moulds for fabricating structured dielectric mediums. The moulds are filled with otherwise difficult to print inks such as elastomers like polydimethylsiloxane (PDMS) – having low storage modulus and thus struggling to form self-standing structures – to be micro moulded. This opens up unprecedented control on structuring the dielectric medium in open air away from the clean room; fabricating specific structures directly onto delicate devices such as catheters, etc.

Results & Discussions



Capacitive pressure sensors few milli meters in size with structured dielectric mediums were made with the developed technique giving expected enhancements in sensitivity due to structuring (pyramid structure) in contrast to unstructured (film) dielectric medium.

Conclusion

The developed fabrication technique been tested on various substrates including copper, aluminium, stainless steel, glass and Kapton. This shows much potential in fabricating novel miniaturised and personalised devices directly onto several substrates including existing medical devices and surgical tools.

References

1. Fang F, Aabith S, Homer-Vanniasinkam S, Tiwari MK. High-resolution 3D printing for healthcare underpinned by small-scale fluidics, 3D Printing in Medicine, 2017, p167-206
2. Mannsfeld SCB, Tee BC-K, Stoltenberg RM, Chen CVH-H, Barman S, Muir BVO, et al. Highly sensitive flexible pressure sensors with microstructured rubber dielectric layers. Nature Materials, 2010
3. Shuai X, Zhu P, Zeng W, Hu Y, Liang X, Zhang Y, et al. Highly Sensitive Flexible Pressure Sensor Based on Silver Nanowires- Embedded Polydimethylsiloxane Electrode with Microarray Structure. 2017
4. Zhuo B, Chen S, Zhao M, Guo X. High Sensitivity Flexible Capacitive Pressure Sensor using Polydimethylsiloxane Elastomer Dielectric Layer Micro-structured by Three-Dimensional Printed Mold. IEEE J Electron Devices Soc. 2017

Acknowledgments

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Identification of Pathogenic Bacteria Using Disposable Screen Printed Sensors and Electrochemical Impedance Spectroscopy

A.J. Hannah¹, A.C. Ward¹, P. Connolly¹

¹ Department of Biomedical Engineering, University of Strathclyde, Glasgow, G1 1RD.

Introduction

Current clinical gold-standard bacterial detection methods are time consuming; emerging rapid techniques can be expensive to employ and are not optimised for point of care use. Electrochemical impedance spectroscopy (EIS) may provide a cost effective and rapid alternative (Figure 1). Obtaining characteristic impedance signatures for key pathogens is vital to the development of a real-time infection monitoring device with applications such as *in-situ* wound monitoring.

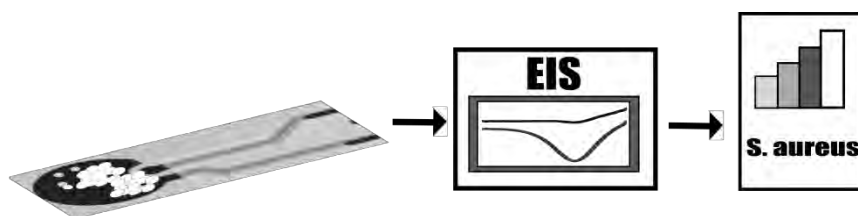


Figure 1. Identification of bacterial growth on a screen printed electrode using EIS.

Methods

In this study, both carbon screen printed electrodes and silver- silver chloride screen printed electrodes were used independently to detect the growth of *Staphylococcus aureus* and *Pseudomonas aeruginosa*, species commonly isolated from infections. The impedance of liquid media, inoculated with overnight culture media forming a 1% solution, was measured over AC frequencies between 1 MHz and 0.1 Hz to create spectra. Using a novel normalisation approach, changes in these spectra over time were linked to the presence of the bacteria.

Results & Discussion

Significant differences in normalised impedance spectra were evident for both *S. aureus* and *P. aeruginosa* using the two different electrode types (2 sample t-test, $p < 0.05$). With the Ag-AgCl sensors, changes were most pronounced at frequencies below 100 Hz. Investigation of the spectra obtained with carbon sensors highlighted that a number of different electrochemical processes were influential. For example, characteristic 1 kHz phase differences that were observed after 30 minutes of *S. aureus* growth were linked to changes in the media composition, whereas cell settlement on the electrode surface resulted in concentration dependant resistance peak formation at 10 Hz for cell concentrations above 3.6×10^6 CFU/ml.

Conclusion

Therefore, this study demonstrates the rapid detection of *S. aureus* and *P. aeruginosa* using a low cost EIS-based sensor. This technology could have important applications for the real-time identification of infections in clinically relevant contexts.

Acknowledgments

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BioMedEng18

Cystic Fibrosis Patient Monitor

S. Donnelly¹, A.C. Ward¹, G. MacGregor², P. Connolly¹

¹ Department of Biomedical Engineering, University of Strathclyde, G1 1RD, ² Department of Respiratory Medicine, Queen Elizabeth University Hospital, 1345 Govan Road, Glasgow

Introduction

Elevated sweat chloride concentration is the biomarker used to diagnose Cystic Fibrosis (CF) and one of the main indicators in gauging the efficacy of emerging treatments. The gold standard of CF diagnosis is the sweat test, but this is time-consuming and unsuitable for the frequent measurements required to gauge the success of new treatments. Therefore, there is a need for a wearable device to non-invasively monitor sweat chloride levels.

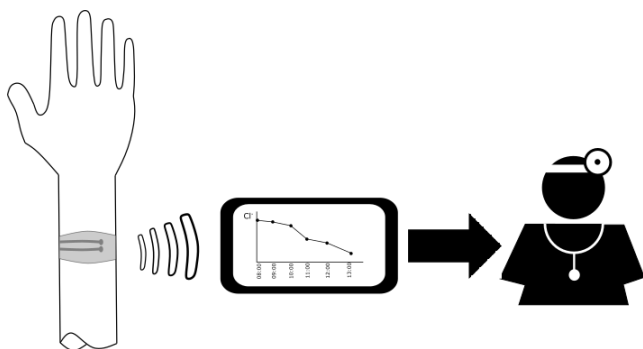


Figure 1. Illustration of wearable sensor to enable health professionals to monitor sweat Cl^- concentrations in CF patients.

Methods

Potentiometric devices were manufactured by printing Ag/AgCl working and reference electrodes onto flexible substrates. A range of biogel mixtures, made following published protocols, were deposited upon the reference electrodes and treated in a 3M KCl solution to provide a stable Cl^- concentration above the electrode surfaces.

Results & Discussion

The device sensitivity to Cl^- ions were evaluated by measuring their open circuit potentiometric response to KCl solutions of concentration range 1 mM – 1M. This encompasses the Cl^- concentrations used to diagnose CF in a sweat test: where <40 mM results in a negative diagnosis and >60 mM is consistent with CF.

One device was found to possess a sensitivity of 28.5 mV/decade over the concentration range ($R^2 = 0.97$). Other electrodes made using the same protocol have displayed similar sensitivities. The Nernstian value for such a sensor is 59 mV/decade.

Conclusion

The biogel electrodes display encouraging results and have the potential to form part of a wearable Cl^- sensor. The focus going forward in this investigation is on improving the sensitivity of the sensors as well as integrating it with a wireless transceiver onto a wearable patch. Such a device would be a vital tool in monitoring the efficacy of new CF treatments and could be used to aid in the diagnosis of the disease.

Acknowledgments

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Rapid Electrochemical Detection of Sepsis Causing Bacteria

V.Vezza¹, D.Corrigan ¹, P.Hoskisson ², D.Alcorn ³

¹ Department of Biomedical Engineering, University of Strathclyde, Glasgow, G1 1RD. ²Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, G4 0RE ³Royal Alexandra Hospital, Paisley, PA2 9PN.

Introduction

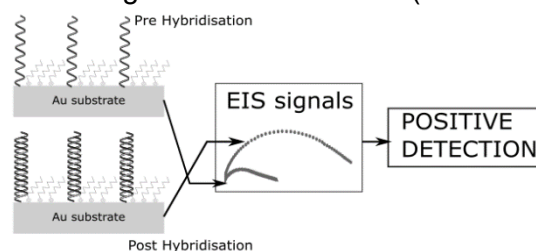
Sepsis is a medical emergency with high mortality rates. Bacterial detection times can take as long as 72 hours. Every hour sepsis is untreated mortality raises by 10%. Sepsis affects 260,000 people per year in the UK and kills 44,000. Current bacterial detection methods are expensive, lengthy and complex. Electrochemical sensors allow for cheap, quick and simple detection of sepsis causing bacteria.

Methods

Specific thiolated single stranded bacterial DNA (ssDNA) sequences and alkanethiols were attached to 25 μm diameter gold microelectrode surfaces via incubation in solution, generating a sensing layer on the electrode surface. Target DNA sequences (tDNA) complementary to the ssDNA were then added, resulting in the ssDNA and tDNA becoming hybridised on the surface. Differential pulse voltammetry (DPV) and Electrochemical impedance spectroscopy (EIS) measurements with frequency range from 100 KHz – 0.1 Hz were taken pre and post hybridisation.

Results & Discussion

Differences in electrode behaviour between pre and post hybridisation stages were evident in both DPV and EIS measurements. DPV revealed the difference in current response due to mass transport of redox agent to the electrode surface to be in the nano Amp range. EIS measurements give sensitive information about the surface properties. Charge transfer resistance (resistance of electron transfer from redox agent to surface) is of particular interest and showed differences between the two stages (Figure 1). These measurements are in agreement with the theory that bacterial DNA can be detected readily due to the ssDNA hybridising with specific complementary tDNA sequences, modifying the surface properties, leading to changes in signal. These differences are evident after 30 mins of complementary tDNA addition.



(Figure 1) EIS measurements pre and post hybridisation. Significant signal differences confirm bacterial DNA detection.

Conclusion

Sepsis is one of the leading causes of death worldwide, slow bacterial detection times of current methods compound this problem. By modifying electrochemical sensors with specific DNA sequences for sepsis causing bacteria and measuring target binding it will allow detection within 30 minutes.

Acknowledgments

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Lipids in Cancer – Advanced nanospectroscopic profiling and assessment of non-conventional drugs for cancer therapy.

M. Governo¹, D. Graham ², P. Murray³, L. Jamieson ⁴

^{1,2,3} TIC Building, Strathclyde University, Glasgow, G1 1RD. ⁴ Royal College, Strathclyde University, Glasgow, G1 1RD,

Introduction

This study aims to utilise Raman spectroscopy and its variants to assess the efficacy of non-conventional drugs in treating prostate cancer. In particular, drug treatments that target the lipid metabolism of cancerous cells will be the focus of our work. Expanding on research such as that conducted by Wright *et al.* (2017), drugs such as Orlistat commonly used for anti-obesity therapy will be used alongside other non-conventional treatments.

Methods

Cancerous human prostate endothelial cells of the cell line PC3 were treated with selected drugs and fixed to CaF₂ plates. The cell line PNT2 was also used in the same manner to provide a non-cancerous prostate endothelial standard to which the PC3 cells could be compared.

After treatment, each of the cell samples underwent intensity mapping, in triplicate, using a Renishaw Raman spectrometer with a 532nm laser. To ascertain the extent of the drug treatment effects an examination of the extracted Raman spectra and corresponding image analysis was carried out using a combination of the spectrometer's companion software WiRE and Matlab.

Results & Discussion

The spectral peaks within the extracted data each pertain to a particular biomolecule. In this case the peak at 1449cm⁻¹ corresponds to the cell lipid molecule content. By comparing the intensity maps of PC3 and PNT2 cells at 1449cm⁻¹ there was a clear difference in the images, confirming the expected changes in lipid metabolism between cancerous and non-cancerous cells. A similar change was also observed between drug treated and untreated PC3 cells indicating the treatments had carried out their desired effects.

These tests have provided a set of foundational results establishing the ability of Raman spectroscopy to detect changes in biomolecules within drug treated cells. Further investigation will look to expand upon the use of image processing as a means of determining drug efficacy.

Conclusion

To date, we have used Raman to image PC3 and PNT2 cells treated with Orlistat and Methotrexate and successfully observed the expected changes to their target biomolecules. Future work will aim to test other non-conventional drugs for potential anti-cancer properties whilst also seeking to improve pre-processing and analysis of spectral data by amalgamating the functions within WiRE and Matlab.

References

1. C. Wright, A. Iyer, V. Kaushik, N. Azad. *J Biomech.* 2017; 118 (11), 3834-3845

Acknowledgments

Professor Hing Leung at the Beatson Laboratories for providing the necessary tissue samples. Funding provided by EPSRC grant number, EP/L015595/1. **There are no conflicts of interest.**

BioMedEng18

Lipid Imaging of Cancerous Cells on a Teflon-Based Microfluidic Device.

J. Melnyk¹, M. Zagnoni², D. Graham³

¹ Centre for Doctoral Training in Medical Devices & Health Technologies, Biomedical Engineering, University of Strathclyde, Glasgow. ² Centre for Microsystems & Photonics, Electronic & Electrical Engineering, University of Strathclyde, Glasgow. ³ Centre for Bionanotechnology, Pure & Applied Chemistry, University of Strathclyde, Glasgow.

Introduction

Cancerous cells are known to have an upregulation of de novo lipid synthesis¹. It has been shown that drugs inhibiting the lipid synthesis pathway can have an anti-cancer effect² & that the lipid content of a cell can be measured using label-free Raman spectroscopy³. A microfluidic device has been developed that can trap live cancerous cells so they can be imaged with Raman spectroscopy as they are being treated with multiple concentrations of drugs targeting lipid metabolism.

Methods

Microfluidic devices are created by hot embossing fluorinated ethylene propylene (FEP) sheets on polydimethylsiloxane (PDMS) stamps. Cancerous PC3 cells or non-cancerous PNT2 cells are loaded into the device by pipetting 15µl of cell suspension at 1x10⁶cells/ml into the inlet wells. The cells enter traps within the device channels & the drugs Orlistat and CAY10566 are then added. Raman spectroscopy is used to measure high wavenumber peaks at 2850cm⁻¹ & 2930cm⁻¹ attributed to the lipids & proteins within the cells. The lipid content of the cells is then estimated by the ratio of the protein to lipid peak heights.

Results & Discussion

PDMS, a common material for microfluidics, was found to be unsuitable for this device as it produced a very high background, totally obscuring the Raman signal from the cells. FEP, a form of Teflon, was chosen instead as a material for the device. The process for creating FEP microfluidic devices was developed & optimised. PC3 & PNT2 cells loaded into the device were shown to remain viable after 24 hours. Raman spectra from cells within the device clearly show the lipid & protein peaks. Changes in the ratio of these peaks have been investigated when the cells were treated with the drugs Orlistat and CAY10566.

Conclusion

The microfluidic device has been successful in trapping cells & changes to the lipid composition of cancerous & non-cancerous cells have been observed following treatment with lipid metabolism altering drugs. This demonstrates the device's potential for screening new drugs that target metabolic transformations within cancerous cells.

References

1. MENENDEZ, J. A. & LUPU, R. 2007. Fatty acid synthase & the lipogenic phenotype in cancer pathogenesis. *Nature Reviews Cancer*, 7, 763-777.
2. KRIDEL, S. J. et al. 2004. Orlistat is a novel inhibitor of fatty acid synthase with antitumor activity. *Cancer Research*, 64, 2070-2075.
3. ABRAMCZYK, H. et al. 2015. The role of lipid droplets & adipocytes in cancer. Raman imaging of cell cultures: MCF10A, MCF7, & MDA-MB-231 compared to adipocytes in cancerous human breast tissue. *Analyst*, 140, 2224-2235.

Acknowledgments

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BioMedEng18

User Requirements for an Upper Limb Weight Support Device for Stroke Rehabilitation

R. Collins¹, A. Kerr ¹, A. Thomson²

¹Graham Hills Building, University of Strathclyde, G1 1XQ Glasgow. ²James Weir Building, University of Strathclyde, G1 1XJ, Glasgow.

Introduction

Upper limb function after stroke can be improved with repetitive, task specific movement^[1]. Achieving high practice intensity necessitates independent activity, outwith routine therapy. Weight support devices (WSDs) can help stroke survivors (SS) perform upper limb exercises by unloading the weight of their arm, providing more opportunity for rehabilitation activities^[2]. However, current commercial WSDs are expensive, creating a barrier to adoption by users. The purpose of this work was to interview SS and therapists to obtain the necessary user requirements for an upper limb WSD.

Methods

Concepts for a WSD were created through brainstorming sessions with engineers and physiotherapists. A controlled convergence method was employed to evaluate and improve these concepts, utilizing the device's performance criteria from a design specification created through research of literature and existing devices. The best concepts were chosen and presented to two focus groups of SS (n=3) and therapists (n=6) respectively. Feedback on the designs were recorded focusing on desirable attributes.

Results & Discussion

Desirable attributes recorded were a device that was portable, comfortable, with supports for both the upper arm and forearm. Incorporation of feedback on movement and completion of functional tasks was also desired. Therapists recommended a design that would help facilitate functional tasks without pain or difficulty. The SS group also highlighted their lack of awareness of WSDs.

Conclusion

An upper limb weight support device is a desirable tool for rehabilitation. Participant feedback suggests designing a device that is comfortable, has two points of support, and is portable to enable independent home use. A prototype is currently in development.

References

1. French, B. et al., 2016. Repetitive task training for improving functional ability after stroke (Review). *Cochrane database of systematic reviews*, (11).
2. Mehrholz, J. et al., 2015. Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke (Review). *Cochrane database of systematic reviews*, (11).

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3D reconstruction of the fundus of a phantom eye through stereo matching of slit lamp images

I. Coghill¹, K.C. Jordan ¹, R.A. Black ¹, I.A.T. Livingstone ², M.E. Giardini ¹

¹ Biomedical Engineering, University of Strathclyde, Glasgow, G1 1XQ. ²Ophthalmology, NHS Forth Valley, Falkirk Community Hospital, FK1 5QE, Falkirk.

Introduction

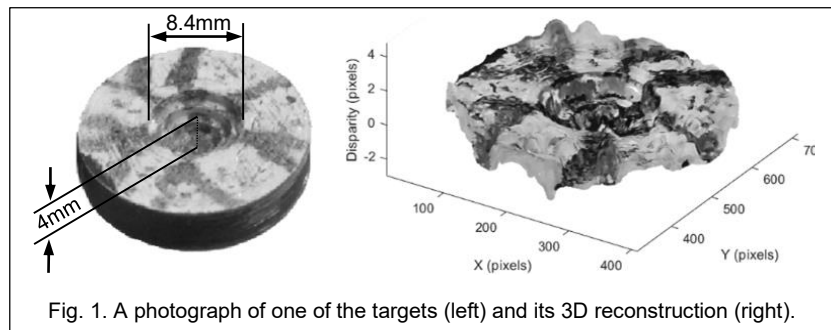
In the detection of glaucoma, the second leading cause of blindness worldwide¹, the alteration of the optic disc's morphology is a key clinical indicator. The current gold standard test, stereo funduscopy using stereo fundus cameras, is subjective². Quantitative devices exist but are prohibitively expensive. Work carried out elsewhere has demonstrated quantitative results from stereo matching fundus camera images³. Building on this idea, the slit lamp microscope (a mainstay of eye diagnostics, present in practically all ophthalmology and optometry practices) has the potential to be used as a quantitative device. This study explored the feasibility of uncalibrated 3D reconstructions of retinal structures of a phantom eye's fundus using a slit lamp.

Methods

A Zeiss 30 SL-M slit lamp was mounted with 720p cameras to its eyepieces and a funduscopy lens in front of its objective. A scaled up eye phantom comprising a 14D lens and interchangeable 3D printed retinal targets with cylindrical step/depression structures was built and imaged using the device. A 3D map was reconstructed from the stereo images through matching via fundamental matrix estimation using RANSAC, rectification and Semi-Global Block Matching.

Results

The stereo matching algorithm yielded a 3D reconstruction of the targets. As an example, Figure 1 shows one of the retinal targets and its corresponding 3D reconstruction.



Discussion & Conclusion

The fundus structures were detected and an overall 3D structure was recovered for all targets. The reconstructions are consistent with the targets. However, at this stage of the research, they are uncalibrated and performance in vivo is also yet to be assessed. The findings warrant further work to assess the potential of the slit lamp being used for quantitative measurements in vivo.

References

1. Kingman S. *Bull World Health Organ.* 2004; 82(11): 887-888.
2. Stone et al. *Invest Ophthalmol Vis Sci.* 2010; 51(11): 5667-5674.
3. Bansal et al. *Conf Proc IEEE Eng Med Biol Soc.* 2013; 2013: 5877-5882.

Acknowledgments

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Developing a microfluidic blood preparation device for infrared spectroscopic diagnostics

P. Radhakrishnan¹, N.J. Mottram², M.S.N. Oliveira³, C. Jenkins⁴, M.J. Baker⁴

¹Medical Devices and Healthcare Technologies CDT, University of Strathclyde, Glasgow, G1 1RD. ²Dept of Maths & Stats, University of Strathclyde, Glasgow, G1 1XH. ³Dept of Mechanical and Aerospace Engineering, University of Strathclyde, Glasgow, G1 1XJ. ⁴WestChem, Dept of Pure and Applied Chemistry, University of Strathclyde, Glasgow, G1 1RD.

Introduction

Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy is a potentially portable diagnostic tool for variety of diseases such as cancer^[1]. In order to make this a viable point of care technique a portable sample preparation device needs to be developed. The main samples that have been analysed using ATR-FTIR are serum, plasma, infected red blood cell, white blood cells and circulating tumour cells. This work presents a conceptualised multi-step device to produce the components described above from a single blood sample.

The two aims of this work are first to create a model to help optimise a microfluidic separation device based on the Fahraeus-Lindqvist effect. The second is to use ATR-FTIR to determine suitability of the components as outputs for the device.

Methods

A one-dimensional phenomenological model was developed in COMSOL Multiphysics with Matlab to simulate the formation of the cell free layer (CFL). This work is based on the continuum effective medium (CEM) model developed by Ley & Bruus^[2] but with the migration force being a function of shear. Horse red blood cells (TCS biosciences) flowing through straight microfluidic channels were imaged using an Olympus inverted microscope IX70. The CFL was measured for a range of haematocrit levels (10%, 20% and 40%) and flow rates (10µl/min, 40µl/min and 100µl/min) to validate the model.

To identify the spectroscopic difference between plasma and serum; first paired frozen samples of plasma and serum from 15 cancer and 15 non-cancer donors (Brain Tumour North West Biobank, with full ethical approval) were measured using a Spectrum 2 FTIR Spectrometer (Perkin Elmer) fitted with an ATR accessory, then the same technique was used to analyse fresh and frozen samples from local volunteers (with full ethical approval). The spectra underwent pre-processing and principal component discriminant functional analysis (PC-DFA) using Matlab.

Results & Discussion

A mathematical model has been successfully developed and appropriate parameters of the CEM model were determined based on validation from experiments.

Results of the PC-DFA of plasma and serum indicate that ATR-FTIR is unable to differentiate between the two. Freezing caused greater variation in plasma samples compared to fresh whereas serum remained consistent. This indicates that serum is a better sample to store but plasma is a suitable sample for point of care analysis.

References

1. Baker M. J., Hussain, S. R., Lovergne, L., Untereiner, V., Hughes, C., Lukaszewski, R. A., Thieffin, G. and Sockalingum, G. D. *Chemical Society Reviews*, 2016, 45: 1803–1818.
2. Ley M.W.H. & Bruus H, 2016. *Lab Chip*. 2016, 16: 1178–1188.

Acknowledgments

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USING ATR-FTIR FOR INVESTIGATING CARDIOVASCULAR DISEASES AND DEMENTIA

Zanib Panni¹, Dr William J McGeown², Dr Matthew J Baker³, Cerys Jenkins³, Dr Jane A Cannon⁴, Professor John JV McMurray⁴, Dr Terry J Quinn⁴, Dr John Sharp⁵

¹Department of Biomedical Engineering, Graham Hills Building, University of Strathclyde, 40 George Street, Glasgow, UK, G1 1QE, ²Department of Psychological Sciences and Health, 6th floor, Graham Hills Building, University of Strathclyde, 40 George Street, Glasgow, UK, G1 1QE, ³Department of Pure and Applied Chemistry, Level 7, Technology and Innovation Centre, University of Strathclyde, 99 George Street, Glasgow, UK, G1 1XL, ⁴BHF Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow, G12 8TA, ⁵Consultant Clinical Psychologist, Scottish National Advanced Heart Failure Service, Golden Jubilee National Hospital, Glasgow

With improvements in health care extending overall life expectancy, a greater proportion of the population is reaching old age and suffering from age-related disorders like dementia and cardiovascular diseases (CVD). Both disorders are considered among the most socially and economically burdensome conditions in UK, costing a combined total of £36.3 billion per year to UK economy [1,2]. Research and epidemiological studies suggest associations between CVD and dementia, in addition to CVD playing a causal role in dementia development. This study aims to investigate the potential for serum analysis using Attenuated Total Reflection Fourier-transform Infrared spectroscopy (ATR-FTIR) in combination with multivariate analysis, to discriminate patients with CVD, who have various levels of cognitive impairment, from controls.

Serum samples and associated neuropsychological test data have been donated by the Glasgow Cardiovascular Research Centre. Serum samples from 147 healthy controls and 253 patients with CVDs have been analysed. The disease group includes patients with i) Coronary Artery Disease and ii) Heart Failure which further categorised into i) Atrial Fibrillation, ii) Non-Ischemic Cardiomyopathy, and iii) Ischemic Cardiomyopathy.

Using random forest analysis, sensitivity and specificity values of 76% and 83%, respectively, were achieved for differentiating healthy controls from CVD patients. The major spectral features and hence biochemical components responsible for the classification have also been identified during the analysis; with most features responsible for classification found in the fingerprint region. Upon categorising disease group into subgroups, the sensitivity of a test for differentiating control from patients decreased while specificity remained the same.

ATR-FTIR when combined with pre-processing and random forest analysis especially for control vs disease analysis performed similarly well as reported in literature [3]. The study is ongoing and in September the updated results will be presented.

References

- [1] Alz.co.uk. (2016). World Alzheimer Report 2015: The Global Impact of Dementia | Alzheimer's Disease International. Available at: <https://www.alz.co.uk/research/worldalzheimerreport2015summary.pdf>
- [2] BHF CVD Statistics Factsheet - UK. (2017). Available at: <https://www.bhf.org.uk/research/heart-statistics>
- [3] Petrich, W., et al. (2009). Potential of mid-infrared spectroscopy to aid the triage of patients with acute chest pain. The Analyst, 134(6), p.1092.

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The development of an Electrochemical Sensor for measuring and detecting circulating tumour DNA in human fluids

B. A O Attoye¹, D. Corrigan ², Centre for Doctoral Training Medical Devices ³

¹ LT730 Livingstone Tower Building, University of Strathclyde, Glasgow, G1 1XQ. ² Biomedical Engineering Department, Level 8. Graham Hills Building, 16 Scotland Rd Richmond Street G11XQ ³ Technology & Innovation Centre, University of Strathclyde, 99 George Street Glasgow G1 1RD.

Introduction

Cancer arises from small insertions or deletions of nucleotides, polymorphic alterations in the human genome and mutation-originated sequence variations which all play important precursor roles in its development of cancer. Activated KRAS mutations are very common and take place in approximately 90% of pancreatic cancers, 30% of lung, 60% of thyroid and 43% of colorectal carcinomas. This project aims to develop a nano-sensor that can accurately detect circulating tumour DNA using electrochemical methods.

Methods

The simplicity and affordability of carbon electrodes has made them suitable for characterizing processes in electrochemistry. Carbon electrodes are chemically inert at negative potential ranges in all media giving them an advantage over metal electrodes. Voltammetry and electrochemical impedance spectroscopy were used to analyse the electrochemical activity of unmodified and DNA modified electrodes. Redox agents' were compared to decide on what was most suitable for measuring DNA hybridization. An isothermal PCR reaction for ctDNA was developed to amplify DNA from patients negative and positive for the KRAS G12D mutation. DNA hybridization measurements were carried out to determine whether differential binding could be determined from such samples.

Results & Conclusion

An electrochemical measurement protocol and a suitable redox media was established for measuring electron transfer using screen printed carbon electrodes. The desired number of expected amplicons were obtained after amplification of clinical samples and an increase in charge transfer resistance was observed between the matched analytes and targets. Simultaneous detection of the common KRAS mutations in synthetic oligonucleotides reflected a similar detection in clinical samples.

Acknowledgments

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References

1. Earl, Julie et al. "Circulating Tumor Cells (CTC) and KRAS Mutant Circulating Free DNA (cfDNA) Detection in Peripheral Blood as Biomarkers in Patients Diagnosed with Exocrine Pancreatic Cancer." *BMC Cancer* 15 (2015): 797. *PMC*. Web. 13 Apr. 2018.
2. Shoaie, Nahid et al. "Highly Sensitive Electrochemical Biosensor Based on Polyaniline and Gold Nanoparticles for DNA Detection." *IEEE SENSORS JOURNAL*, VOL. 18, No. 5, 01 Mar. 2018

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Fusing Infrared & Electrochemical Analysis for Accurate & Sensitive Clinical Measurements

C. Rinaldi¹, L. Dennany², M.J Baker³

¹Dept. of Biomedical Engineering, University of Strathclyde, Wolfson Centre, 106 Rottenrow, Glasgow, G4 0NW, UK.

^{2,3} Dept. of Pure and Applied Chemistry, University of Strathclyde, Technology and Innovation Centre, 99 George Street, Glasgow, G1 1RD, UK.

Introduction

The emergence of point-of-care testing promises to redefine the landscape of healthcare in both the developed and developing world and provides a new model of the relationship between patient and clinician. The practicalities of delivering health care in the developed world require change amidst growing realisation that the escalating cost of health care is unsustainable in times of fiscal uncertainty, increased prevalence of chronic disease and changing demographics. Point-of-care testing, whilst in its infancy, currently provides identification of biomarkers for rapid detection of disease states enabling health care professionals to make timely clinical decisions and better utilise healthcare resources. However, single biomarkers are often elusive on investigation of heterogeneous diseases, which require a panel of biomarkers or fingerprint of the sample to provide sufficient diagnostic information. The development of a point-of-care device, which performs both attenuated total reflection-Fourier transform infrared spectroscopy (ATR-FTIR) and either cyclic voltammetry (CV) or electrochemical impedance spectroscopy (EIS), would circumvent such challenges enabling simultaneous identification of the molecular bonding environment of sample constituents and detection of biologically relevant molecules.

Methods

Our device transports pooled/spiked human serum samples and model complexes through microfluidic channels to multiple detection reservoirs, where our novel silicon and gold components perform ATR-FTIR and CV/EIS measurements respectively.

Results

Preliminary ATR-FTIR results indicate suitability of our silicon component for the molecular classification of pooled human serum samples, where characteristic changes in pertinent diagnostic peaks including amide I and amide II bands may be employed to diagnose diseased states. Preliminary CV results indicate suitability of our gold component for detection of redox-active biological molecules, where characteristic redox peaks may be employed for the quantitative detection of certain diagnostic biomarkers. Preliminary EIS results indicate suitability of the gold component for identifying the attachment of biological molecules to the surface of functionalised electrodes, where the increase in charge transfer resistance upon binding to self-assembled monolayers permits quantitative detection of certain prognostic biomarkers.

Conclusion

Preliminary evidence suggests suitability of our device for qualitative and quantitative detection of biological molecules in heterogeneous samples, which we anticipate could facilitate the development of a rapid, non-invasive diagnostic platform for a myriad of medical conditions with capabilities of providing personalised therapeutic intervention.

Acknowledgments

We are grateful to the Wellcome Trust and EPSRC Medical Engineering Initiative and the Bioengineering Society for supporting this conference. I would also like to acknowledge the Medical Devices CDT at University of Strathclyde and EPSRC for continued guidance and funding of this project, grant reference number EP/L015595/1.

BioMedEng18

A Soft Wearable Robotic Exoskeleton for Rehabilitation of the Frozen Shoulder

J.F. Failes¹, H. Lakany¹, B. Conway¹

¹ *Graham Hills Building, University of Strathclyde, Glasgow, G1 1QE*

Introduction

Adhesive capsulitis (or “frozen shoulder”), is a joint condition resulting in pain and reduction to range of motion (ROM). Contemporary treatments can be effective but currently suffer from a number of drawbacks, including: high cost, lengthy treatment; lack of specificity to each patient; and lack of consistent, repetitive treatment between clinics and therapists [1]. Researchers are thus working to combat these drawbacks by developing rehabilitation exoskeletons. Traditional exoskeletons however aren’t always suitable, being rigid and heavy. Soft robotics may be suitable to overcome all of the above problems, combining the best of robotics (consistency, specificity) while being affordable and wearable through lightweight, compliant materials and design.

Methods

A literature review on the current state of both soft robotics and the robotic rehabilitation field has been conducted. Important features and current capabilities of soft robots have been identified through comparison with traditional exoskeletons. This data will be used to choose both the methods of actuation and the control system (plus informing other design considerations) to be taken forward into a novel soft robotic design, the realisation of which will form the remainder of the project.

Results & Discussion

While electric actuated rigid exoskeletons were the most prominent of the previous generation due to their high power-to-weight ratio, their weight and noise makes them unsuitable for soft robotics. Pneumatic systems on the other hand forgo heavy motors and utilise compliant compression chambers, matching with the lightweight, wearable characteristics of soft robotics, as shown through O’Neill’s shoulder device [2]. Shape memory alloy (SMA) also looks promising [3], but requires further development by the field to be viable. Control systems have benefitted from the switch to soft robotics, allowing the development of sensing suits and lightweight sensors, with inertial measurement units (IMUs) receiving a lot of focus due to their affordability and adaptability.

Conclusion

A direction for the project has been presented, focusing on a pneumatic-based shoulder rehabilitation device, using IMUs as a primary sensor for feedback and control. There will be further detailed research into pneumatics, followed by CAD development to determine an appropriate and effective design. A prototype will be completed by the end of 2018.

References

1. Kelley MJ *et al.* *J Orthop Sports Phys Ther.* 2009; 39: 135-148
2. O’Neill CT *et al.* *IEEE Int Conf Rehabil Robot.* 2017:1672-1678
3. Copaci D *et al.* *Applied Bionics and Biomechanics.* 2017; 2017: 1605101

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Development of a nicotine sensor to monitor e-cigarette use

A. Sturrock¹, A. Ward ¹, G. MacGregor¹, P. Connolly¹

¹ University of Strathclyde, 99 George St, Glasgow G1 1RD, UK

Introduction

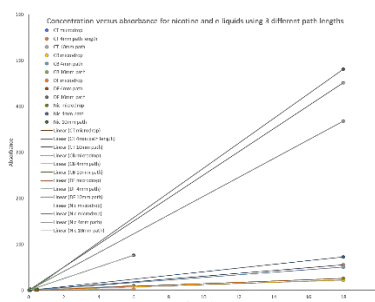
The overall aim of this project is to develop a sensor for e-cigarettes to help users monitor and reduce their nicotine intake. The experiments performed this year have been focused around the detection of nicotine and cotinine, and the subsequent determination of concentration and creation of calibration curves.

Methods

Several methods have therefore been explored and compared in order to determine which is the most suitable for our purpose. The methods chosen were: electrochemistry with a carbon screen printed electrode, ultraviolet (UV) spectrophotometry, and high performance liquid chromatography (HPLC) coupled with UV detection. Further experiments were performed to examine the effect of path length on the absorbance measured using UV spectrophotometry.

Results & Discussion

The key results of these experiments include corroborating literature values of the redox potential of nicotine (0.95V), the wavelength of the nicotine and cotinine peaks (260nm), and the formation of calibration curves through testing increasing concentrations of nicotine or cotinine solutions, in order to compare the measured concentration of three e-liquids to the labelled value. The measured concentrations were consistently lower than the label value for all methods tested. The Beer-Lambert law states that absorbance is proportional to concentration and path length. Proportionality constant was generally consistent for the 4mm and 10mm path lengths at low concentrations .



Conclusion

The best method of those tested is UV spectroscopy at a path length of 10mm, and so there are further experiments planned to utilise UV spectroscopy in analysing e-cigarette vapour.

Acknowledgments

Many thanks to the EPSRC and the CDT (grant reference number EP/L015595/1)

References

1. Alecrima, M.F. *et al* (2016) "Electrochemical behavior of the cotinine at a boron-doped diamond electrode and its determination in saliva by multiple-pulse amperometry in an FIA system". *Electrochimica Acta*, 222, 331–337.
2. Cheng T. (2014) "Chemical evaluation of electronic cigarettes". *Tobacco Control*, 23:ii11–ii17.
3. Kassa, H., A. Geto and S. Admassie (2013). "Voltammetric Determination Of Nicotine In Cigarette Tobacco At Electrochemically Activated Glassy Carbon Electrode". *Bull. Chem. Soc. Ethiop* 27.3, pp. 321 – 328.
4. Clayton P.M. (2013) "Spectroscopic Studies on Nicotine and Nor nicotine in the UV Region" *Chirality*, 25(5): 288–293.

Hall Effect for Proximity Sensing in Medical Devices

J. Bagwell¹, A. Buis ¹, M. Giardini¹

¹ Department of Biomedical Engineering, University of Strathclyde, Glasgow, G1 1XN.

Introduction

Hall effect sensing is commonly used in mechanical applications where measurement of distance and or orientation is required. With the development of soft robotics and wearable technologies, similar problems are becoming more prevalent in the medical device industry. Demonstrated in robotic skin simulants, Tomo et al have highlighted the possibilities for touch sensing in robotic solutions, particularly useful in such as grip strength control and feedback and potentially displacement feedback in areas such as stroke rehabilitation. Where small developments in body mechanics can be accurately measured and displayed for the user. Holding advantages in terms of accuracy, repeatability and compatibility over its light and sound based equivalents, Hall Effect sensors produce a regular and repeatable output voltage in response to the density of a magnetic field passing through the sensor. Meaning the displacement of a magnet positioned on the target surface can be monitored with less than millimetre precision over a calibrated range.

The study was designed to establish how differences in magnet size and orientation could influence the range and repeatability of the induced voltage from a Hall Effect sensor. Information that could prove useful in future studies involving the development of robotic and other wearable devices. With the sensors being capable of measuring the unpredictable nature of human movement whilst producing an input value that could be used in adaptive feedback systems.

Methods

The rate and range of detection of a ratiometric Hall Effect sensor was established in response to neodymium magnets. With both magnet size and orientation (creating perpendicular or parallel magnetic field lines at the sensors surface) evaluated to determine how stable and repeatable a signal could be detected, using an Arduino Uno microcontroller, at different distances.

Results & Discussion

Experimental studies demonstrated the increase in sensed range when magnet orientations resulted in perpendicular magnetic field lines at the sensors surface. Whilst a magnet measuring 12.5mm diameter x 3mm had a functional range of approximately 50mm although at slightly reduced sensitivity to a smaller magnet (3mm diameter x 1mm) with a functional range of 10mm. Some hysteresis was detected reaching a peak value of 5.7% at a sampling rate of 50Hz.

Conclusion

The results indicated that Hall Effect sensors can provide a very accurate displacement measurement over small ranges, whilst also being very easy and cheap to integrate with microcontrollers to produce a feedback system. Providing an adaptable, small but effective alternative to the light and sound based displacement sensors often used.

References

1. Tito Pradhono Tomo et al. *Design and Characterisation of a Three-Axis Hall Effect-Based Soft Skin Sensor*. 2016. *Sensors*, 16, 491, 1-11.

Acknowledgments

With thanks to the Engineering and Physical Sciences Research Council (EPSRC) for providing the support and funding required to make this research possible (EP/L015595/1). With further thanks to the Centre of Doctoral Training (CDT) for their excellent service and encouragement throughout the project. The authors whose names are listed above report they have no conflicts of interest.

BioMedEng18

Combining a microfluidic platform with LC-MS for metabolic profiling for preclinical toxicity screening

M.P. Claassen¹, M.H. Grant¹, M. Zagnoni²

¹ Department of biomedical engineering, Graham Hills building, University of Strathclyde, G1 1XN, Glasgow.

² Department of electronic and electrical engineering, TIC building, University of Strathclyde, G1 1RD, Glasgow.

Introduction

Development of a new drug entities (NDEs) can take up to 15 years and cost in the millions of pounds, with the majority failing in the later stages of development due to hepatotoxicity¹. Microfluidics is increasingly being used in biological assays as it can provide high-throughput data, uses minimal resources and allows control over the fluidic microenvironment. Mass spectroscopy (MS) is commonly used to identify compounds at minute concentrations and when combined with liquid chromatography (LC), that facilitates separation of complex samples, can be used with microfluidics to generate high throughput and sensitive readouts useful to improve NDEs processes.

Methods

HepG2 cells and primary rat hepatocytes (PRH) were cultured in 3D, as spheroids, within a microfluidic platform, alongside collagen sandwich cultures (CSC), as a comparison. Cultures were then exposed to different concentrations of a known hepatotoxin and stained to assess viability. Subsequently, cells and the supernatant, were collected for LC-MS analysis to identify drug effects and produced metabolites.

Results & Discussion

HepG2 cells in the microfluidic platform formed compact spheroids within 3 days and remained viable for up to 11 days (> 70%), while those in the CSC developed distinct borders, suggesting the establishment of bile canaliculi². LC₅₀ values for CSC HepG2 (762 ± 179 µM) calculated by assessing viability post fall within the range indicated by literature for similar conditions³; no significant difference between CSC and microfluidic devices were obtained. PRH declined in viability from seeding (85%) to less than 40% after day 3 in the microfluidic platform, indicating a need to improve the culture environment. A new device layout allowing medium perfusion is currently under validation. Only material from HepG2 cultures were used for LC-MS analysis, with the parent drug being detected, but no significant readouts from metabolites were obtained.

Conclusion

The developed microfluidic platform can maintain HepG2 cultures as spheroids for up to two weeks. However, this cell line lacks the necessary metabolic capabilities to accurately mimic in vivo conditions. Current work is refining the microfluidic platform for sustaining viable PRH spheroid cultures for hepatotoxicity testing.

References

1. Khetani et al. "Microengineered liver tissues for drug testing", J. Lab. Autom. 20(3), pp 216 – 250, 2015.
2. LeCluyse E. L et al. "Formation of extensive canalicular networks by rat hepatocytes cultured in collagen-sandwich configuration", Am. J. Physiol. Cell Physiol. 266(6), pp 1764 – 1774, 1994.
3. Fey S, Wrzesinski K. "Determination of drug toxicity using 3D spheroids constructed from an immortal human hepatocyte cell line", Toxicol. Sci. 127(2), pp 403 – 411, 2012.

Acknowledgments

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BioMedEng18

Development of a Microfluidic Platform for High Throughput Screening of Anti-Cancer Drugs in Prostate Cancer Spheroids

S. Gilmartin¹, G. Burley² and M. Zagnoni³

¹ Centre for Doctoral Training in Medical Devices & Health Technologies, Biomedical Engineering, University of Strathclyde, Glasgow. ²Organic Chemistry, Pure & Applied Chemistry, University of Strathclyde, Glasgow.. ³ Centre for Microsystems & Photonics, Electronic & Electrical Engineering, University of Strathclyde, Glasgow

Introduction

Prostate cancer is one of the most common causes of cancer deaths for males in the UK, with thousands of deaths being attributed to the condition each year, and an ever increasing number of cases being reported. For this reason the development of new technologies that can aid or streamline the process of producing drugs to combat prostate cancer and its more aggressive forms are urgently required. This work presents the development of a high-throughput microfluidic device that can be used to screen the effects of emerging anti-cancer drugs on prostate cancer spheroids efficiently and accurately. To this end, the device is being used to test a novel Cell Penetrating Peptide (CPP) based drug, and compare its efficacy to a series of standards used for prostate cancer.

Methods

This work investigates LNCaP and PC3 prostate cancer cells in the form of 3D cell aggregates, known as spheroids, and the response of these spheroids to various standard anti-cancer drugs inside the microfluidic device. Thousands of spheroids were formed from single-cell suspensions within a single device across several fluidic channels. In each channel, a different concentration of a particular drug was added. Quantitative results were obtained through image analysis of both the circularity of the spheroids (an indicator of viability) and the relative intensities from live/deadstain.

Results & Discussion

Spheroids consistently formed inside the device 48-72 hours after seeding, and remained viable in the device for up to 24 days. Dose response curves for standard anti-cancer drugs, such as Enzalutamide and Docetaxel, were obtained. from spheroids inside the device, comparing responses from LNCaP and LNCaP AI and PC3. Preliminary tests with novel CPP based drug is currently ongoing.

Conclusion

A high-throughput microfluidic platform has been developed and tested for performing anticancer drug testing of 3D cancer models, comparing CCP-based drugs to standard of care drugs. Further work is investigating development of the platform for specific spheroid retrieval.

Acknowledgments

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Wearable LED-based device for phototherapy applications

F. Farrell¹, B. Guilhabert¹, A-M. Haughey², P. Connolly³, M. D. Dawson¹, N. Laurand¹

¹Institute of Photonics, Department of Physics, SUPA, University of Strathclyde, 99 George St, Glasgow G1 1RD, UK. ²Fraunhofer Centre for Applied Photonics, 99 George St, Glasgow G1 1RD, UK. ³Department of Biomedical Engineering, University of Strathclyde, 106 Rottenrow, Glasgow, G4 0NW, UK.

Introduction

Phototherapy with UV or visible wavelengths is used to treat skin disorders such as psoriasis, eczema and vitiligo. Traditionally, phototherapy is carried out in a clinical environment and utilises large fluorescent lamps. These are now being replaced with more efficient light-emitting diodes (LEDs), a trend that is set to continue thanks to the progress of LED technology. LEDs are also facilitating the emergence of at-home devices to improve patient convenience and decrease demand on the healthcare system [1]. Current at-home devices consist of rigid LED arrays, which limits their conformability and produces non-uniform light distribution over the treatment area, in turn limiting their efficacy and wearability [2]. As a solution to this problem, we are engineering a flexible light therapy device that combines LEDs and a sub-mm-thick polydimethylsiloxane (PDMS) light sheet in an edge-lit configuration.

Methods

PDMS has previously been shown as an effective flexible light guide [3]; its high transparency from 290 nm upwards and its biocompatibility make it an ideal substrate for a wearable phototherapy device. The PDMS sheet acts as a waveguide and the light diffused through the top surface is measured as irradiance ($\mu\text{W}/\text{cm}^2$) with a spectrally calibrated imaging/detection system. The change in irradiance by embedding scattering titanium dioxide nanospheres has been demonstrated utilising a blue LED (450 nm) with an optical power of 30 mW.

Results & Discussion

This approach produces a uniform emission of $130 \mu\text{W}/\text{cm}^2$ ($\pm 4\%$) over a treatment area of 2.25 cm^2 , an increase from $3 \mu\text{W}/\text{cm}^2$ without the nanospheres. Optical modelling shows that when coupling a commercially available “macro-LED” to the PDMS light sheet only 33% of the LED light is coupled. When modelling a custom-shape micro-size LED array, 90% of the LED output is coupled; this should produce a higher irradiance over the treatment area whilst ensuring the small footprint, and mechanical flexibility, of the device.

Conclusion

Uniform irradiance of $130 \mu\text{W}/\text{cm}^2$ over a 2.25 cm^2 area was achieved by adding scattering particles to an edge-lit PDMS light sheet. Utilising a custom-shape LED array we are planning to develop a flexible light therapy device with an irradiance value of at least $1 \text{ mW}/\text{cm}^2$.

References

1. R. Hung et al. *CED*, 2015, 40, 827-833.
2. C. Cochrane et al, *Mater Sci Eng C Mater Biol Appl*, 2013, 33, 1170-1175.
3. J-H. Lee et al, *Journal of the SID*, 2008, 16, 329-335.

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Biomarkers of Leakage after Anastomotic Dehiscence Evolution (BLADE) study

J.A. Paulinus¹, S. Moug², R. Anderson², N. McLaughlin², R. Hawkins², P. Connolly¹

¹ CDT in Medical Devices and Healthcare Technologies, University of Strathclyde, Glasgow, G1 1RD. ²Royal Alexandria Hospital, PA2 9PN, Paisley

Introduction

Colorectal cancer is a globally prevalent disease with over 40,000 new cases occurring in the UK¹. One effective treatment is the surgical resection of the cancer, where the tumorous section of the colon is removed and the remaining ends of the colon are then reattached to form what is known as an anastomosis. However, there is a risk of patients undergoing this type of treatment to develop a complication known as anastomotic leakage where the reattachment site of the colon starts to break down leading to the contents of the colon leaking into the peritoneal cavity². Currently, there is no universally acknowledged test for diagnosing anastomotic leakage and often doctors will only consider diagnosing only after the patient starts exhibiting symptoms. Delays in treatment have been shown to increase the likelihood of patients dying³. Therefore, the aim of this work is to determine biomarkers that can be used to determine anastomotic leak at an early stage so a patient can be given appropriate treatment.

Methods

Ethics was sought after and approved from the NHS Greater Glasgow & Clyde Biorepository (Ref No. 300) to collect peritoneal fluid from patient who had undergone colorectal resection in which an anastomosis was formed. Fluid was collected from patients daily for up to 3 days post-op and tested the same day for various biomarkers including lactate, pH and several electrochemical parameters to determine any trends between patients with and without anastomotic leakage. The data produced was then analysed using Matlab to determine any significant trends between patients and to develop electrochemical models.

Results & Discussion

An electrochemical model, consisting of various electrical components, was established from the electrochemical results and fitted using least squares in Matlab. Initial results with lactate and pH have shown large variability between patients and further work is required to determine sound conclusions.

References

1. Cancer Research UK. Bowel cancer incidence statistics | Cancer Research UK. (2015). at <<http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence#heading-Zero>>
2. Komen, N. *et al.* Anastomotic leakage, the search for a reliable biomarker. A review of the literature. *Color. Dis.* **10**, 109–115 (2008).
3. den Dulk, M. *et al.* Improved diagnosis and treatment of anastomotic leakage after colorectal surgery. *Eur. J. Surg. Oncol.* **35**, 420–426 (2009).

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BioMedEng18

Development of a multimodal neuromodulation system for investigation of neural circuitry.

R. Winstanley¹, A. Boudet¹, Y. Cheng¹, G. Varkonyi¹, N. McAlinden¹, R. Scharf², K. Mathieson¹

¹ Institute of Photonics, University of Strathclyde, Glasgow, G1 1RD.

² The University of Utah, Salt Lake City, United States

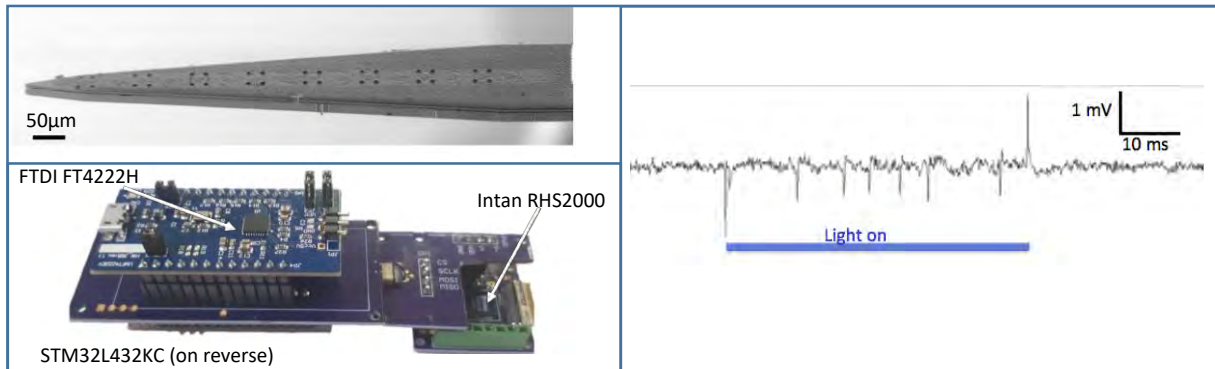
Introduction

Micron-scale neural probes are an established tool in neuroscience for furthering the understanding of processing in brain circuits. Recent developments in optogenetics have allowed precise control of neurons through activation of light-sensitive membrane channels/pumps¹. Here we report on the development of a neural probe that has multiple independent light sources (microLEDs), coupled with microelectrodes, that facilitates optical and electrical stimulation and combines them with electrical recording capabilities. This multi-modal approach allows specific perturbation of neural circuits, with genetic targeting, enhancing our ability to understand neural circuits and the role they play in degenerative neural conditions. The device has the potential to optimise stimulation protocols for diseases such as Parkinson's and epilepsy and can be operated in closed-loop configuration.

Methods

Optogenetic neural probes were produced from Gallium Nitride on silicon semiconductor materials using standard microfabrication techniques. Electronic control was facilitated through an Intan RHS2000 to provide amplification and digitisation of potentials and also stimulation currents for both optical and electrical neuromodulation. Digital instructions were provided by an Arm Cortex-M4 microcontroller, and results were transferred to a computer for further processing. The system features close loop capabilities, with spike/LFP thresholding and microsecond precision timing of the microLED light sources.

Results & Discussion



Left: Upper, Electron micrograph of neural probe tip, featuring 25µm diameter LEDs and electrodes. **Lower**, Control system prototype. **Right**, *In Vivo* optically induced neuronal spiking.

Conclusion

The work describes the development of a multimodal neuromodulation system, with the ability to provide optical control of genetically targeted neurons, while monitoring the subsequent neural activity.

References

1. Boyden E. *et al. Nature Neuroscience*. 2005; 8: 1263-1268.

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BioMedEng18

3D Bioprinting of ADSCs for Tissue Repair

J.W. Logan¹, S.E. Thomson², D-J. Cornelissen¹, M. Riehle², W.Shu¹

¹ Department of Biomedical Engineering, Graham Hills Building, University of Strathclyde, Glasgow, G1 1XQ.

² Centre for Cell Engineering, Joseph Black Building, University of Glasgow, Glasgow, G12 8QQ.

Introduction

A customised 3D bioprinting platform has been developed with the ability to create adipose-derived stem cell (ADSC) microfibres using hydrogel scaffolds. This platform has the potential for a number of tissue engineering and regenerative medicine applications, including fibrous and cylindrical tissue fabrication as an autologous therapy. This system also allows fine tuning of scaffold porosity, degradation time and the ability to incorporate cells and growth factors. The bioprinted scaffolds have shown excellent biocompatibility with ADSCs and aggregation into a fibre has been exhibited with this cell type.

Methods

A custom-built 3D bioprinting platform was used to bioprint ADSCs encapsulated in extracellular matrix solution in the lumen of hollow cylindrical hydrogel scaffolds with internal diameter of approximately 760 μm . Live/dead imaging was used to analyse cell viability and aggregation.

Results & Discussion

Cells were able to aggregate within the lumen of the bioprinted constructs, to produce fibre-like structures over the course of 28 days. This indicates that the hydrogel scaffolds have the potential to facilitate tissue fibre formation.

Conclusion

It has been shown that ADSCs are biocompatible in our tubular hydrogel scaffolds and that these cells are capable of aggregating into a fibre-like structure. Further work will investigate hydrogel compatibility with other cell types and growth factors. Also, more biomaterial studies will be undertaken to optimise hydrogel tuneable properties such as porosity and degradation time.

Acknowledgments

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BioMedEng18

3D Bioprinting of resorbable scaffolds for bone tissue engineering in maxillofacial surgery

R. McWilliam¹, X. Luo ¹, R.Black ¹, W. Shu ¹

¹Graham Hills, 40 George St, Glasgow G1 1QE

Introduction

To investigate the use of 3D bioprinting techniques and tissue engineering in order to manufacture bespoke resorbable bone implants for cases of patients with maxillofacial injury. Injuries to the Maxillofacial bones can come from a wide range of afflictions, including: tumour resection; airbag crash trauma; sports injuries or as a result of assault or GBH. These types of injury are difficult to treat, with bone autografting or metal implants being preferred; however, these can come with the problems of not being sufficient aesthetically (difficult to recreate the complex structure of the face) or a lack of supply of autologous bone¹. One way to improve treatment would be to use additive manufacturing (3D printing), in tandem with patient stem cells in order to produce bespoke grafts (made from synthetic or natural polymer) that would degrade as the cells produce mineralised ECM, thus leaving entirely new bone in the desired shape. This shape would be derived from CAD files obtained from CT scans of the patient's injury, with 3D printing being perfect for bringing these shapes 'to life'.

Methods

Creating this implant involves research into pulling together several different ideas and components. Deciding which polymers to use, which morphology is most suitable and how best to arrange it is imperative to a successful implant. Are there any micro- or nano-changes to topology and morphology that can improve the polymer somehow? Deciding which stem cells to use and how they are integrated and differentiated is also very important to the success of the implant.

Results & Discussion

So far a range of materials in different morphologies have been tested with regards to their interactions with hMSCs. PCL and PLGA scaffolds have been fabricated and 3D printed with success, and preliminary data shows that hMSCs are viable on these scaffolds.

Conclusion

Even with no results as yet, the promising work done so far is helping to build up the idea of using 3D bioprinting in the application of manufacturing bespoke bone grafts for cases of maxillofacial injury.

References

1. Gassner, R. *J Cranio-Maxillofacial Surgery*. 2003; 31 (1): 51-61.

Acknowledgments

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CNP with TGF β enhanced chondrogenic differentiation of human amniotic fluid stem cells cultured in agarose constructs

J.R.M.Taylor¹, A.J. Hobbs², A.L. David³, P. De Coppi⁴, T.T. Chowdhury¹

¹Institute of Bioengineering, School of Engineering and Material Science, Queen Mary University of London.

²William Harvey Research Institute, School of Medicine and Dentistry, Queen Mary University of London.

³Institute for Women's Health, UCL. ⁴Institute of Child Health, UCL.

Introduction

C-type natriuretic peptide (CNP) has previously been demonstrated in human and mouse models to enhance cell proliferation, matrix synthesis and induce mesenchymal stem cell differentiation into chondrocytes [1]. However, the effect of CNP on fetal stem cell differentiation using human amniotic fluid derived stem cells (AFSCs) is not known. The present study examined the effect of CNP and/or TGF β on matrix synthesis in AFSCs cultured in agarose constructs.

Methods

AFSCs were obtained with informed consent and ethical approval during the second trimester of pregnancy. C-kit positive AFSCs/agarose constructs (3%, 4×10^6 cells/ml) were cultured in the presence and absence of CNP (100nm) and/or TGF β 1 (10ng/ml), TGF β 3 (10ng/ml) or dexamethasone (100nm) for up to 21 days. GAG, DNA and hydroxyproline content were quantified by biochemical assay.

Results & Discussion

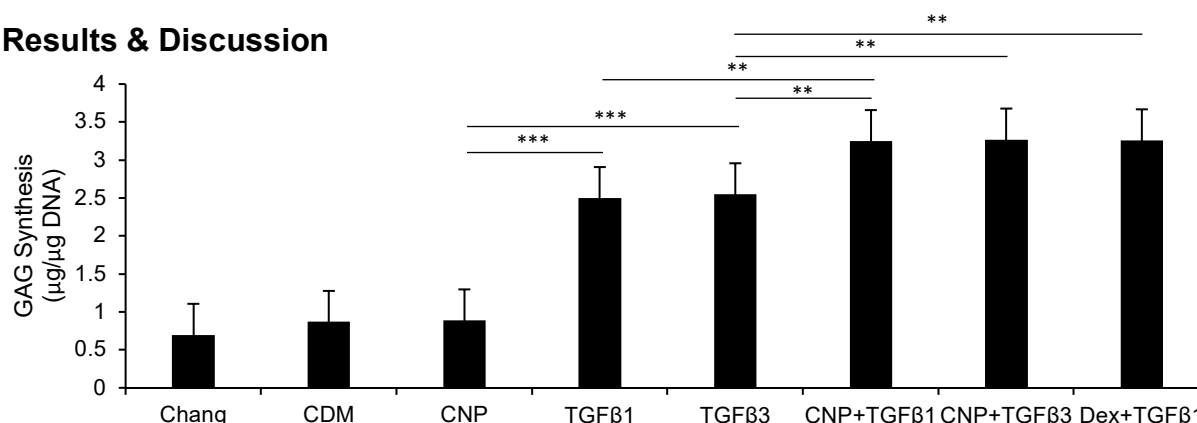


Fig.1 - The effect of CNP and/or TGF β 1 or 3 on GAG synthesis in AFSC/agarose constructs cultured up to 21 days. Controls: stem cell medium (Chang) and chondrogenic medium without growth factor supplementation (CDM), where (p<0.05). ** = 0.01<p<0.05, *** = p<0.01.

The present study demonstrates that CNP alone did not significantly influence the values for GAG synthesis when compared to control constructs (Fig.1). The presence of CNP in combination with TGF β 1 or 3 significantly increased GAG synthesis when compared to constructs cultured with or without CNP (all p<0.01).

Conclusion

The present study shows that CNP in conjunction with members of the TGF family is a potential differentiation agent for AFSCs cultured in agarose constructs.

References

1. Tezcan, B. *J Mol Histol.* 2010;41:247-58.

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Moving smoothly: lubrication of hydrogel cartilage mimics

E.M. Porte¹, P.M. Cann¹, M.A. Masen¹

¹ Tribology Group, Mechanical Engineering Department, Imperial College London, SW7 2AZ, London.

Introduction

Hydrogels are under consideration for use as a replacement material for damaged articular cartilage in the treatment of ailments such as osteoarthritis as well as sports injury. Although much work has been done to develop hydrogels with appropriate mechanical properties, little is known about the basic lubrication and load-carrying mechanisms of this type of materials in sliding motion. The current work aims to study the friction behaviour of hydrogels with respect to the formation of a lubricating film under simulated articular joint conditions.

Methods

Friction tests were performed on a BioTribometer (PCS Instruments, UK) while recording the lubricant film thickness in the contact using a fluorescent imaging technique (Fig. 1). A transparent poly(vinyl-alcohol) hydrogel sample is rubbed against a glass lens at a controlled normal load, while the resulting friction force is measured. The sliding motion is varied between 2 and 10 mm to study a physiologically relevant range of joint movement regimes. The applied lubricant is a solution of fluorescein (0.0025%w/w) in deionised water, enabling the fluorescent intensity to be measured using a fluorescence microscope (SMZ1270 with GFP-L filter, Nikon, Japan) that is mounted above the test setup. This setup allows the lubricant film distribution in the contact to be measured.

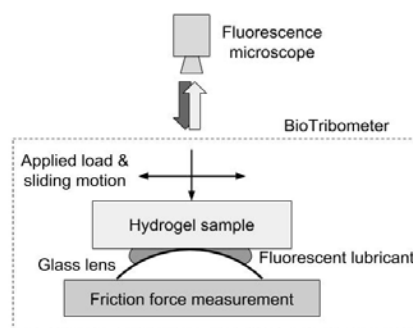


Fig.1: BioTribometer with fluorescent setup

Results & Discussion

The results show that the friction and lubrication behaviour closely relate to the motion characteristics of the contact, with the size of the contact patch between the hydrogel and the glass acting as a threshold. The lubricating film is not replenished for relatively small contact movements (< 6 mm), resulting in high friction. Low friction forces were measured for longer sliding paths (> 6 mm), with the fluorescence measurements showing a fully flooded contact. More specifically, when the motion amplitude is smaller than the size of the contact patch, part of the contact is continuously loaded which prevents replenishment of the lubricant (see Fig. 2). The obtained results illustrate the importance of providing a sufficient amount of lubricant in the contact to ensure continued low friction.

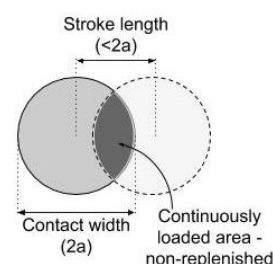


Fig. 2: Schematic illustration of the contact

Conclusion

This study shows that the replenishment of the lubricant in the contact is essential to ensure the optimum sliding performance of PVA hydrogels and that effective replenishment is strongly dependent on the contact conditions. This finding is an important step towards a better understanding of the lubrication mechanisms of soft tissue mimics like hydrogels, where contact areas can be relatively large compared to their sliding path.

Acknowledgments

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BioMedEng18

Recapitulating the Solid-Fluid Interactions in a Cartilage Mimic

A.C. Moore¹, M.M. Stevens¹

¹*Department of Bioengineering and Department of Materials, Imperial College, South Kensington, SW7 2AZ, London.*

Introduction

Articular cartilage is the load bearing and lubricating material of synovial joints. Healthy articular cartilage is unrivalled in its functional performance; it boasts a physiological friction coefficient of ~0.02 and a load bearing capacity ~1000X greater than the hardest bearing steels. Cartilage achieves this superior function through the pressurization of internal fluid, which effectively stiffens the matrix and lubricates the contact [1]. Experimental and theoretical models have shown that this internal fluid pressure is strongly dependent on the solid-fluid interactions between the fibrous and hydrated polymeric network [2,3].

To date there has been little effort to directly mimic these features in engineered scaffolds for cartilage repair [4]. In this work we take a direct approach toward recapitulating the load bearing and lubricating performance of articular cartilage by designing a fibre reinforced hydrated construct.

Methods

Scaffolds were formed by dissolving polyhydroxyalkanoate, a bacterial derived polymer, in organic solvent. The solution was then frozen at -20°C using a bench top chiller, followed by solvent extraction on a low vacuum Schlenk line. The resulting structure was an open network foam with high tensile strength. A second polymer phase (chitosan) was permeated through the matrix to increase solid-fluid interactions and osmotic stress.

Constructs were evaluated using unconfined compression to determine the flow dependent properties, while scanning electron microscopy was used to study the internal structure of the multiphasic constructs.

Results & Discussion

Our preliminary results are consistent with theoretical predictions about solid-fluid interactions and their ability to create internal fluid pressure following deformation. Our current efforts are aimed at optimizing these constructs to reach cartilage like stiffnesses (10 MPa). Future work will aim to characterize the tribological performance and biocompatibility of these engineered constructs.

Conclusion

This work takes a first step at designing scaffolds that mimic the functional performance of articular cartilage.

References

1. McCutchen CW. *Wear*, 1962
2. Soltz MA, Ateshian GA, *J Biomech Eng*, 2000
3. Moore AC, Burris DL. *J Biomechanics*, 2014
4. Butler DL, Goldstein SA, Guilak F. *J Biomech Eng*, 2000

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Small molecule sirtuin activators enhance in vitro cartilage regeneration

H.K. Heywood¹, S.D Thorpe¹, D.A. Lee¹

¹ School of Engineering and Materials Science, Queen Mary University London, UK. E1 4NS.

Introduction

Sirtuins are a family of seven enzymes (SIRT1-7) that are established to play a key role regulating cartilage homeostasis^{1,2} and body of evidence supports an important role of the sirtuins in the development and progression of OA^{3,4}. However, the importance of sirtuins to the success of cell therapy approaches to cartilage repair, which use non-arthritic chondrocytes, is not known. This study examines for the first time the importance of sirtuin activity during monolayer culture for subsequent cartilage regeneration by cultured cells.

Methods

Primary bovine chondrocytes were seeded in monolayer and cultured for 4 population doublings in the presence or absence of the sirtuin inhibitor, 10 mM NAM or two different activators of sirtuin activity; the NAD precursor, 100 μ M NMN or the selective SIRT1 activator, 100 nM SRT1720. The cells were prepared as 3D pellets by centrifugation at 380g and cultured for an additional 2 weeks in control media only before the subsequent neo-cartilage development was assessed by wet weight and biochemical assessment of extracellular matrix.

Results & Discussion

qPCR data shows that SIRT1 expression rapidly declines during monolayer culture. The presence of the sirtuin inhibitor NAM in monolayer culture further reduced the capacity of the chondrocytes to regenerate cartilage tissue in subsequent 3D culture, with 50% lower wet weight, collagen and glycosaminoglycan content compared to untreated cells, determined by dimethylmethylene blue and hydroxyproline assay, respectively. By contrast, supplementing monolayer cultures with sirtuin activators NMN and SRT1720 resulted in 34-60% increased wet weight and significantly greater ($p < 0.05$, ANOVA) collagen content of subsequent 3D cell pellet cultures. Unexpectedly, this study found that the direct application of sirtuin activators, NMN and SRT120 to freshly isolated chondrocytes in a 3D pellet inhibited tissue regeneration, particularly decreasing collagen content by 59% and 25% respectively.

Conclusion

This study demonstrates the importance of maintaining sirtuin activity during the in vitro culture of chondrocytes, in order to retain their regenerative potential, with relevance to the clinical success of cartilage repair procedures. Increases in the regenerated tissue mass, cell survival and collagen content were achieved by supplementing monolayer expansion media with small molecule sirtuin activators during monolayer culture. Importantly, however, the in situ application of these small molecule sirtuin activators may be contraindicated due to their adverse effects on matrix synthesis in differentiated cells.

References

1. Dvir-Ginzberg, M. et al. J Biol Chem 283, 36300-36310 (2008).
2. Gabay, O. et al. Arthritis Rheum 65, 159-166 (2013).
3. Matsuzaki, T. et al. Ann Rheum Dis 73, 1397-1404 (2014).
4. Li, Y. et al. J Orthop Surg Res 11, 144 (2016).

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Alterations in the underlying material density on the surface damage of bovine articular cartilage

H. Mahmood, D.E.T. Shepherd, D.M Espino

Department of Mechanical Engineering, School of Engineering, University of Birmingham, B15 2TT, Birmingham.

Introduction

The condition of Osteoarthritis is related to alterations of the cartilage tissue, including the manipulation of its structure through depletion¹. Further, the density of the underlying subchondral bone experiences modification as a result of Osteoarthritis. The aim of this study was to explore the variation in an underlying material of a controlled density, mimicking bone mineral density, on the respective surface failure of bovine articular cartilage.

Methods

Sawbones substrates were used as a bone mimicking material above which bovine articular cartilage cores were placed. The substrate densities were assessed at 0.1556, 0.3222, 0.5667 and 0.6000 g/cm³. A sinusoidal load of 5-50 N was applied to the specimens. Frequency was investigated at normal-gait; 1 Hz, and above-normal; 10 and 50 Hz, as a combined factor with the material density. The surface damage at each cartilage specimen was analysed with Image analysis software, with a specific focus on the resulting crack length.

Results & Discussion

The damage in the form of total crack length was observed at its peak with 10 Hz of applied frequency, reaching a maximum of 24.4 mm. Crack length was found to reduce at 50 Hz to a maximum of 18.0 mm, with a further reduction at 1 Hz to a maximum crack length at 8.8 mm. Linear regression analysis between substrate density and crack length at 10 Hz displayed a statistical significance ($p < 0.05$), whilst frequencies at 1 and 50 Hz failed to show a statistically significant trend.

The density of the underlying substrate in combination with 10 Hz of applied frequency at loading, is required to implement significant cartilage surface failure. There are several factors that contribute to the damage to the cartilage tissue, notably obesity, trauma and injuries². The findings from this study highlight the importance of considering cartilage damage inducing factors as combined parameters for significant results.

Conclusion

The effect of substrate density on the resulting cartilage surface failure should also be considered with an above-normal gait frequency, precisely that at 10 Hz. This specific combination results in the trend of statistically significant cartilage damage.

References

1. Hunter DJ *et al.* *Osteoarthr Cartil.* 2013; 21: 1170-1178
2. Chaganti RK, Lane NE. *Curr Rev Musculoskelet Med.* 2011; 4: 99-104

Acknowledgments

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3D Scanner for Monitoring Hand Osteoarthritis

F. Sanna¹, Q. Renault¹, D. Toderita¹, M. Teal¹, A. Peirs¹, A. Wright¹, A. Kedgley¹

¹Bioengineering Department, Imperial College London, South Kensington, SW7 2AZ, London.

Introduction

Osteoarthritis (OA) is the most common form of joint disease, affecting at least 8 million people in the UK.¹ Most commonly hand OA affects the distal interphalangeal (DIP) joints of the fingers.² Early detection and monitoring are essential to provide effective treatment. Quantitative and low-cost approaches for tracking the progression of hand OA are not yet available in most clinics. Commercially available surface scanners with the required accuracy are prohibitively expensive. This study introduces a low-cost three-dimensional (3D) scanning system to reconstruct the morphological features of individual fingers and assess the progression of hand OA.

Methods

The scanner is comprised of 8 cameras attached to a semi-circular ring that acquire pictures of a finger from different angles. An outline of the finger is obtained from each view through edge detection and these data are combined using custom-written MATLAB code to generate a 3D model of the finger. The reconstruction algorithm is novel and proved to be more efficient than other widely used 3D reconstruction techniques when scanning convex and cylindrical-like objects. Key physiological parameters, such as the ratio between the diameter of the DIP joint and the intermediate phalanx, as well as the angle between the phalanges were evaluated.

Results & Discussion

The time required to scan a finger was 10.3s and the points on the surface of the finger were mapped with an accuracy of 0.1mm. The right index finger of 6 people was scanned 10 times with 2 minute intervals between measurements; for each person we obtained a coefficient of variation of less than 1.3%. We achieved the same consistency when testing on a finger simulating the characteristics of OA. The 3D representations obtained accurately represented the fingers, and the results were consistent and repeatable (Fig. 1).

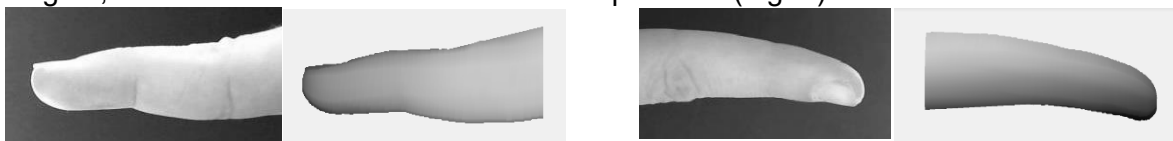


Fig. 1: Two sample fingers and their 3D reconstruction rendered using custom-written code in MATLAB

Conclusion

3D scanning through edge detection can be achieved using equipment costing less than £275 and may be an effective and inexpensive way to quantify OA progression. This could be used to deliver more personalised treatment for this common joint pathology.

References

1. Arthritis – NHS. 2016. Available at: <https://www.nhs.uk/conditions/arthritis/> [Accessed:16/11/2017].
2. Wilder et al. (2006) Osteoarthritis Cartilage 14:953-7

Identifying Signalling Loci Involved in The Emergence of Mechanical Memory in Osteoblasts

A. Shuaib^{1,2}, G. Ascolani^{1,2}, P. Bhattacharya^{2,3}, Y. Beladaci³, TM. Skerry¹, D. Lacroix^{2,3}

¹ Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK. ²Insigneo Institute of In Silico Medicine, University of Sheffield, Sheffield, UK. ³Department of Mechanical Engineering, University of Sheffield, Sheffield, UK

Introduction

Mechanical stimulation induces changes in bone mechanical properties and morphology through bone remodelling. At the cellular and molecular scales, these effects are thought to be linked to memory-like events which record previous mechanical excitations. How information of previous mechanical events is stored within cells is not yet fully elucidated [1, 2]. In order to address this question, conditions associated with mechanical memory were examined using a mechanical model combined with the agent-based modelling (ABM) paradigm, which simulated an osteoblast exposed to dynamic mechanical events.

Methods

ABM-mechanical model simulated an osteoblast in bone tissue exposed to various mechanical regimens with mechanotransduction downstream of integrin mechanoreceptors leading to osteogenic extracellular matrix proteins (ECMps) synthesis. ECMps modulated the surrounding ECM elasticity, and updated mechanical forces transferred to the integrins. All molecules were modelled as autonomous agents. The ABM simulated mechanotransduction via an integrin population that was heterogeneous with respect to mechanosensitivity. Time series analysis was generated from molecule-agents in bound, active and inactive state. Signals were transformed by removing the average trend (of the curve) and filtered via the moving standard deviation as a threshold to detect genuine peaks. The transformed time series were analysed in terms of Waiting Time Distribution (WTD).

Results & Discussion

The results point to mechanisms responsible for mechanical memory emergence. Further analysis identified FAK, Ras, MEK and ERK proteins as potential loci for regulating the process. Sensitivity analyses suggest that ERK and MEK feedback loops play an important role in the emergence of mechanical memory. Yang et al., [2] demonstrated that mechanical memory is related to induction of YAP-TAZ, which is linked upstream to FAK and Src proteins. YAP-TAZ induced mechanical memory through interaction with the transcription factor Runx2, which is directly modified by ERK. The model does not integrate cytoskeletal element of mechanotransduction which is a limitation of the model.

Conclusion

In addition to identifying loci involved in the emergence of mechanical memory, our results demonstrate two cascades which mediate YAP-TAZ dependent mechanical memory. Thus, they may explain time-dependent tissue adaptation to dynamic mechanical stimuli.

References

1. Skerry T. Neurotransmitters in bone. Introduction. *J Musculoskelet Neuronal Interact.* 2002;2(5):401-3.
2. Yang, C., et al. 2014. Mechanical memory and dosing influence stem cell fate. *Nature Materials*, 13, 645. Mohammed Y, Sherwin SJ, Weinberg PD. *J Biomech.* 2017; 50: 102-109.

Acknowledgments

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Polycystins in ciliary-mediated chondrocyte mechanotransduction

C. L. Thompson¹, HM Mitchison², PL Beales², M Ramachandran¹, JP Chapple³,
M.M. Knight¹

¹ Institute of Bioengineering, Queen Mary University of London, London, UK. ² Genetics and Genomic Medicine, UCL Institute of Child Health, London, UK. ³ William Harvey Research Institute, Barts and the London School of Medicine, Queen Mary University of London, London, UK

The primary cilium, a singular microtubule-based organelle, functions as a signalling nexus for numerous cellular pathways such as wnt, hedgehog and PDGF and is required for chondrocyte mechanotransduction (for review see [1]). Cilia disruption through hypomorphic mutation of IFT88 renders chondrocytes insensitive to mechanosensitive ATP release and disrupts the mechanical regulation of cartilage matrix genes [2, 3]. Disruption of the cilia-associated ion channel complex polycystin-1 (PC-1)/polycystin-2 (PC-2) has been identified in mutant cells, this complex is essential for cilia-mediated mechanotransduction in kidney epithelial cells [4]. Therefore this study aims to investigate the role of PC-1/PC-2 in chondrocyte mechanotransduction.

PC-1 and PC-2 expression were modulated in conditionally immortalised murine wild-type chondrocytes. Cells were subjected to 10% cyclic tensile strain (CTS) or the addition of 100µM ATP. Ca²⁺ signalling was examined using the Ca²⁺ sensitive dye Fluor-4. Gene expression was quantified by qRT-PCR. Localisation of PC-1 and PC-2 was quantified by confocal and super resolution microscopy.

CTS upregulated the expression of the matrix genes ACAN and COL2A, this was inhibited by PC-1 and PC-2 knockdown. In response to exogenous ATP, approximately 50% of cells exhibited Ca²⁺ transients, this was not significantly influenced by PC-1 or PC-2 knockdown. PC-1 did not localise to chondrocyte cilia under basal conditions whereas PC-2 was present in 50% of cilia at varying levels along the length of the axoneme. Cilia localisation of PC-2 was increased in cells subjected to CTS, this response was inhibited by the addition of suramin (P2 channel blocker) or apyrase (ATP hydrolase) prior to loading. PC-2 ciliary accumulation was also observed in response to exogenous ATP indicating this response is dependent upon mechanosensitive ATP release.

In conclusion, our data support a role for PC-1 and PC-2 in chondrocyte mechanotransduction, and suggest a novel polycystin-dependent mechanosignalling pathway exists that is different from that previously reported for kidney epithelia. Understanding PC-1/PC-2 function in chondrocyte mechanotransduction may provide novel ciliotherapy targets for treatment of osteoarthritis.

References

1. Pala, R., N. Alomari, and S.M. Nauli, *Int J Mol Sci*, 2017. 18(11). 2. Wann, A.K., N. Zuo, C.J. Haycraft, et al., *FASEB J*, 2012. 26(4): p. 1663-71. 3. He, Z., D.J. Leong, Z. Zhuo, et al., *Osteoarthritis Cartilage*, 2016. 24(5): p. 892-901. 4. Praetorius, H.A., J. Frokiaer, S. Nielsen, et al., *J Membr Biol*, 2003. 191(3): p. 193-200.

Acknowledgments

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BioMedEng18

Assessing the usability of the micropipette-aspiration technique to measure cell tribology

A Z bin Zaidon¹

¹ Department of Engineering, University of Cambridge, Cambridge, CB2 1PZ.

Introduction

Friction is vital to the functioning of a normal cell. Activities such as cellular adhesion and migration that leads to processes such as extravasation and morphogenesis requires the ability of a cell to interact with its surface thereby, creating friction. A technique called the micropipette-aspiration technique was developed previously [1] that is able to measure force within nanonewton range but its potential in measuring tangential friction is relatively unexplored. In this project, we planned to construct a device based on this widely documented technique and assess the reliability of this method to measure and characterize sliding dynamics at micro-sized level particles. From there, we proposed to expand the usage of this device to test the sliding properties of several cells in various biologically-relevant situations.

Methods

A 15µm hard, polystyrene bead was immobilized at the end of a micropipette and was slid across a glass substrate under controlled velocity. The deflection of the pipette as a result was recorded on a high-speed camera and visualised as tangential force versus distance curve. The stiffness of the micropipette was determined through calibration [2] and the deflection of the pipette was translated into force on the force-distance curve. The normal force was measured by analysing the projection of the deflection onto a circular curve. From the tangential and normal force, the coefficient of friction of the sliding bead was determined and compared to classical values.

Results & Discussion

Preliminary result showed typical kinetic profile associated with the sliding motion of a glass bead against a smooth surface. The coefficient of friction was determined to be 0.05, well within the range of the coefficient of friction of polystyrene against a glass [3]. Nevertheless, temporal and spatial resolution can still be improved to better capture the motion of the micropipette.

Conclusion

The micropipette apparatus has a huge potential in understanding cell tribology. By optimizing the sensitivity of the apparatus to the deflection movement of the micropipette we can expect the device to be able to capture kinetic profiles of various cells in different biologically-relevant situations.

References (examples – use “First author *et al.*” if more than 3 authors, **minimum font size 9pt**)

- [1] E. A. Evans, “Analysis of adhesion of large vesicles to surfaces,” *Biophys. J.*, vol. 31, no. 3, pp. 425–431, 1980.
- [2] M.A. Goulet, M.-J. Colbert, and K. Dalnoki-Veress, “Friction Measurements on Living Cells,” *La Phys. Au Canada*, vol. 64, no. 3, pp. 129–131, 2008.
- [3] B. Bhushan and B. K. Gupta, *Handbook of Tribology*. New York: McGraw-Hill, 1997.

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Fibrochondrogenic differentiation alters mechanosensitive YAP signalling in MSCs

S.D. Thorpe¹, K. Panesar¹, A. Deen¹, D.A. Lee¹

¹ Institute of Bioengineering, School of Engineering and Materials Science, Queen Mary University of London, E1 4NS, London, UK.

Introduction

Forces transmitted through the cytoskeleton to the nucleus are important for mechanosensing, including the activation of the Yes-associated protein (YAP)/transcriptional co-activator with PDZ-binding motif (TAZ) pathway which plays a role in the regulation of fibrochondrogenic differentiation [1]. Nuclear shape, mechanics, and architecture also change with differentiation state [2], and differentiation associated increases in the nucleoskeleton component lamin A/C, have been associated with increased levels of nuclear YAP [3]. The aim of this study is to test the hypothesis that differentiation induced changes in nuclear architecture and nucleocytoplasmic connectivity alter YAP signalling in MSCs.

Methods

MSCs undergoing chondrogenic differentiation with or without the addition of transforming growth factor- β 3 on silicone substrates were exposed to 3% uniaxial dynamic tensile strain at 1 Hz for up to 6 hours/day for up to 3 days.

Results & Discussion

Nuclei in MSCs which had been subjected to intermittent strain for 3 days exhibited increased cell and nuclear spread area, and f-actin intensity, indicative of an increased state of contractility and nuclear flattening. Nuclei in undifferentiated MSCs demonstrated significant elongation post strain while chondrogenic MSC nuclei did not exhibit nuclear elongation, suggesting that chondrogenic differentiation alters either nuclear stiffness, or strain transfer to the nucleus via the LINC complex. Indeed, strain application reduced levels of LINC complex component SUN2. Reductions in SUN2 were associated with an increase in H3K27me3, a histone mark associated with gene silencing. Nuclear YAP localisation was upregulated in response to strain in control MSCs, while chondrogenic differentiation suppressed overall YAP activity and the response to strain.

Conclusions

Our data suggests that chondrogenic differentiation leads to alterations in both nuclear mechanics and strain transfer to the nucleus via the LINC complex which is required for YAP activation [4].

References

1. Zhong W, *et al. Stem Cells Dev* 2013; 22(14): 2083-2093.
2. Heo S-J, *et al. Elife* 2016; 5: e18207.
3. Swift J, *et al. Science* 2013; 341(6149): 1240104.
4. Driscoll TP, *et al. Biophys J* 2015 108(12): 2783-2793.

Acknowledgments

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Validation of CFD method used to model flow in cell culture dishes on an orbital shaker

M. Arshad^{1,2}, E.M.Rowland¹, K. Riemer¹, E. McDonnell³ and P.D. Weinberg¹

Departments of ¹Biomedical Engineering and ²Aeronautics, Imperial College London, London, UK and ³Trinity College, Dublin, Ireland

Introduction

The non-uniform distribution of atherosclerosis within the arterial tree has been attributed to low wall shear stress (WSS) and to highly multidirectional flow, amongst other mechanical factors. Effects of shear on cultured endothelial cells are being investigated by swirling the culture dishes on an orbital shaker. Computational fluid dynamics (CFD) can be used to simulate the wave and compute shear on the base of the well [1], but the model has not been validated experimentally. Here we use particle image velocimetry (PIV) to characterise the flow behaviour in a 2D plane. Due to the 3D nature of the problem, the accuracy of the post processing PIV algorithm is tested using synthetic datasets derived from the CFD model.

Methods

For the PIV, glass spheres suspended in the fluid were illuminated using a laser sheet aligned parallel to the base of the well. Image pairs were acquired using a high frame rate camera affixed to the shaker and an angled mirror. From a CFD model of the swirling well (Star CCM+ software; CD-Adapco), synthetic PIV image pairs were produced to match the experimental setup using Synthetic Image Generator [2]. The experimental and synthetic PIV image pairs were post-processed using PIVlab [3] to produce 2D velocity maps. These were quantitatively compared with CFD velocity maps.

Results & Discussion

Due to the thickness of the laser sheet and out-of-plane fluid motion, out-of-focus particles were apparent in the PIV images, so 2D velocity maps represented an average of a 3D fluid domain. When the CFD data were averaged perpendicular to the base of the well, the peak velocity magnitude was 0.1 m/s; the experimental value was 0.2 m/s. Magnitude and vector direction discrepancies could not be attributed to errors in post processing since there was excellent agreement between CFD and synthetic PIV velocity maps, but rather due to errors in the experimental PIV set-up and the idealized CFD model not capturing the experimental model accurately. For example, tests have shown a fluctuating rotation of the shaker as appose to a smooth rotation assumed by the CFD model.

Conclusion

The experimental PIV set-up needs to be further optimized and the CFD model improved to validate shear stress patterns at the base of the well, before they can be rigorously compared to cell behaviour under different flow conditions.

References

1. Mohamied, Y., et al.. Ann Biomed Eng, 2015 43(1):16-25
2. Lecordier, B., & Westerweel, J., 2004. The EUROPIV Synthetic Image Generator (S.I.G.):145-161.
3. Thielicke, W. & Stamhuis, E.J. J Open Res Soft 2014. 2(1):e30

Acknowledgments

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Vimentin filaments play a crucial role in cell aging by regulating cell migration

K. Sliogeryte, N. Gavara

Queen Mary University of London, Mile End Road, E1 4NS, London.

Introduction

Delayed wound healing in aging of individuals and the overall aging phenotype of cells is the result of a complex interaction of biological, physical and biochemical processes that cause damage and changes to molecules, cellular and extracellular function. Changes in biomechanical properties are an essential characteristics of the aging process of human dermal skin. Previous studies indicated that changes in cell stiffness was correlated with an increase of F-actin in old cells. Nevertheless, it is not clear how intermediate filaments and microtubules contribute to cell mechanics in relation to cell aging.

Results & Discussion

This study examined the influence of cell aging on single cell viscoelastic properties and morphometric parameters of cytoskeleton, microtubules and intermediate filaments. Atomic force microscopy was used to quantify the viscoelastic properties of individual human dermal fibroblast cells from donors at different age. The cell stiffness increased from 1.58 kPa in neonatal human dermal fibroblast cells to 3.85 kPa for adult human dermal fibroblast cells, but there was no significant changes in viscosity. In addition, the immunostaining analysis of three cytoskeletons indicated a 2-fold increase cell area of adult cells. The adult cells also exhibited 2-fold increase in F-actin organization, with thinner and less curved fibres, reduced radial spread as well as increased 2 folds in nuclear stiffness. Vimentin assembly increased 3-fold with reduced stellar factor in adult cells. The microtubule organization was increased in adult cells with reduced fibre length. Also, we examined the dynamic properties of three cytoskeletons and cell migration during cell reattachment experiment. The migration experiment demonstrated that cell velocity increased 2-folds for neonatal cells, which agreed with previous studies on wound healing assay. The fibre formation was observed during reattachment experiments, which allows to monitor the fibre growth and dynamics through the process of cell spreading. The findings indicated no significant changes in F-actin and tubulin fibre amount and formation speed for neonatal and adult cells. Surprisingly, the formation of vimentin fibre was slower with longer and denser fibres for neonatal cells.

Conclusion

This findings suggest, that cell aging of human dermal fibroblasts are regulated by dynamics of intermediate filaments. This leads to increased cell mobility of young cells which in turn maybe regulate other fundamental aspects of cell function including mechanotransduction.

Acknowledgments

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Effect of tip size and geometry on the measured elastic moduli of cells during nanoindentation tests

W Yang¹, D. Lacroix ², J. Chen¹

¹ School of Engineering, Newcastle University, NE1 7RU. ²Department of Mechanical Engineering, The University of Sheffield, S10 2TN

Introduction

Nano-indentation has proven effective to characterize the mechanical properties of cells. However, various indentation studies have demonstrated contradictory results while probing the same type of cells with different indenter geometries [1]. There is a lack of comprehensive mechanisms for discrepancy of the same type of cells measured by different experimental protocols. Therefore, this study aims to reveal how different test protocols affect the apparent elastic properties of cells determined by indentation tests.

Methods

A previously validated finite element model as described in [2] was employed to account for the cytoskeletal structure in cells. Pre-stress inside the actin stress fibres were applied to take the active cell contraction into account. Microtubules were modelled as star shape emanating from a point near the nucleus. All the cellular components were assumed to be linear elastic. Spherical indenters with different radius (1-5 μm) and conical indenters with various semi-included angles (15° to 75°) were adopted for nanoindentation tests of a spreading cell (with length of 19 μm , width and thickness of 4 μm). The indenters were displaced from the receptor site to study the variations of measured moduli due to structural heterogeneity. The maximum penetration is up to 0.5 μm . Hertz model were applied to analyse the measured apparent moduli.

Results & Discussion

Indentation study shows a negative correlation between spherical indenter size and measured modulus. The modulus slightly decrease while increasing the spherical indenter radius from 1 to 5 μm . However, the measured modulus dramatically drops by nearly an order of magnitude while increasing the semi-included angle of the cone. Large indenters tend to measure the whole cell properties while small ones tend to sense the local stiffness of the cell. The measured moduli by conical indenters are significantly higher than the results yields by spherical indenters. By offsetting the indenters, the moduli changes significantly when measured with smaller size indenters. However, indentations with large indenters are not sensitive to indentation penetration.

Conclusion

Indentations with large indenters enable quantifying the whole cell properties while those with small indenters tend to sense the local stiffness of the cell. The cell structure heterogeneity can lead to significant variations of measured moduli. The key findings of this work can guide the design of nanoindentation testing protocols for cells and subcellular structures.

References

1. Chen. Interface Focus 2014, 4(2), 20130055
2. Barreto et al. Biomaterials. 2013. 34(26):6119-6126.

Acknowledgments

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Red Cell Mechanical Properties and Biochemical Signalling

B. McGill¹, B-D Lechner¹, C.P. Winlove¹, P.G. Petrov¹

¹ School of Physics, University of Exeter, EX4 4QL.

Introduction

Red blood cells (RBCs) are highly specialised for transporting oxygen around the body. Structurally the unique composite membrane (lipid bilayer and membrane skeleton) provides the elasticity required to maintain shape and withstand deformation throughout the microcirculation. RBCs also play an active role in matching oxygen supply to local demand, acting as both sensor and response officiators, by releasing the vasodilatory signalling agent ATP under increased mechanical stress [1]. Many diseases, such as diabetes mellitus, are related to an alteration of the RBC membrane mechanical properties due to high oxidative stress and this may compromise ATP-dependent signalling pathways. Here we investigate how alteration of membrane mechanical properties affects deformation-induced ATP release from RBCs.

Methods

We investigate RBC bending and shear elasticity using thermal fluctuation spectroscopy [2]. Chemical treatments are used to mimic high oxidative stress and selectively alter the mechanical properties of membrane components. To induce ATP release, cells (whole blood diluted to 1% haematocrit) are perfused through a tubular shearing device, mimicking the physiological shear stress RBCs experience in capillaries of the microcirculatory system. Concentration of released ATP is measured pre- and post-shearing using a luciferin-luciferase chemiluminescence assay and a luminometer [3].

Results & Discussion

The mechanical properties of the RBC membranes are altered significantly when the RBCs are incubated with oxidizing agents, leading to a stiffening of the membranes as seen from the thermal fluctuation studies. The concentration of released ATP from RBCs in whole blood, induced by shearing with a shear stress of 5 Pa, is in the low-end nanomolar range. We show that the amount of released ATP is decreased for samples treated with oxidizing agents (Fig.1).

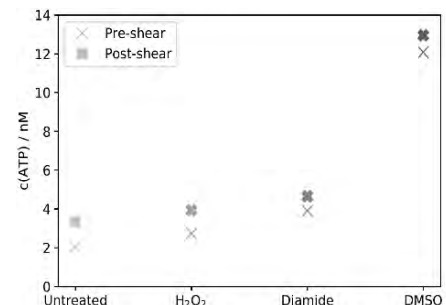


Fig. 1. ATP release of RBCs induced by shearing ($\tau = 5$ Pa): comparison of untreated blood and blood after chemical treatment.

Conclusion

We investigate the role of the RBC as an effective regulator of vascular tone, by its ability to release the vasodilator ATP when subjected to external mechanical stress. Treatment with oxidizing agents which mimic the effects of disease leads to changes in the RBC membrane mechanical properties, accompanied by decreased ATP-release after shearing. This suggests that high oxidative stress in disease may lead to a decreased ability of RBCs to release ATP.

References

1. Forsyth A et al. *P. Natl Acad.* 2011; 108: 10986-10991.
2. Hale J et al. *Biophysical Journal.* 2011; 101: 1921 -1929.
3. Lyman GE, and DeVincenzo JP. *Analytical Biochemistry.* 1967; 21: 453-443.

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The role of methotrexate in endothelial cells under shear stress

M. Lang¹, C. Pericleous¹, C. Warboys², A. Kiprianos¹, J. Mason¹

¹ Department of Vascular Sciences, NHLI, Imperial College London, Hammersmith Campus, W12 0NN, London.

² Department of Bioengineering, Imperial College London, South Kensington, SW7 2AZ, London.

Introduction

Anti-inflammatory therapy has been recently validated as a treatment option for patients with cardiovascular disease (CVD) [1]. Methotrexate (MTX) is one of the candidate anti-inflammatory drugs currently being evaluated for its efficacy in reducing recurrent cardiovascular events in patients with CVD in a clinical trial [2]. MTX has been found to reduce cardiovascular risk in patients with systemic inflammatory rheumatic diseases [3]; possibly by improving endothelial function [4]. However, the molecular basis of the drug's anti-inflammatory and anti-atherogenic effects on the vasculature is not well described. Therefore, our goal is to characterize the effects of MTX on vascular endothelial cells (EC), with a special focus on cell signaling and the effects of shear stress.

Methods

Human aortic endothelial cells (HAEC) were subjected to high laminar (LSS, 20dyn/cm²), low LSS (5dyn/cm²) or oscillatory shear stress (OSS, +/- 5dyn/cm², 2Hz) using a parallel plate system. After pre-conditioning for 48h, HAEC were treated with low-dose MTX (100nM) under shear stress for a further 48h. Alternatively, EC were exposed to shear stress using an orbital shaker or a y-shaped slide, which allows different shear rates within the same slide. EC were analyzed by quantitative real-time PCR (qRT-PCR), immunoblotting or immunofluorescence.

Results and Discussion

All shear stress models were characterized by analyzing cellular morphology and phenotype. Validation included analysis of flow-inducible genes such as Krüppel-like factor (KLF)-2. As expected, OSS enhanced endothelial expression of the vascular cell adhesion molecule (VCAM)-1. MTX reduced Akt phosphorylation in EC subjected to LSS and OSS using the parallel plate model. Moreover, our preliminary data suggest that MTX may prevent OSS-induced VCAM1 mRNA expression in EC. These findings are currently being investigated further, also in other models of shear stress using the orbital shaker and y-shaped slide. Additional experiments will look for MTX-induced changes in the expression of other pro- and anti-inflammatory molecules.

Conclusion

Preliminary data suggest low-dose MTX may influence the behavior of vascular EC under shear stress. Further experiments are required to understand the functional importance of these findings and how these might contribute to the clinical cardiovascular benefits of MTX.

References

1. Ridker, P.M., et al., *Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease*. N Engl J Med, 2017. **377**(12): p. 1119-1131.
2. Everett, B.M., et al., *Rationale and design of the Cardiovascular Inflammation Reduction Trial: a test of the inflammatory hypothesis of atherothrombosis*. Am Heart J, 2013. **166**(2): p. 199-207 e15.
3. Micha, R., et al., *Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease*. Am J Cardiol, 2011. **108**(9): p. 1362-70.
4. Guin, A., et al., *Effects of disease modifying anti-rheumatic drugs on subclinical atherosclerosis and endothelial dysfunction which has been detected in early rheumatoid arthritis: 1-year follow-up study*. Semin Arthritis Rheum, 2013. **43**(1): p. 48-54.

Catalytic DNA sequence-copying through handhold-mediated strand displacement

Javier Cabello-Garcia^{1,2}, Wooli Bae^{1,2}, Guy-Bart V. Stan^{1,2}, Thomas E. Ouldridge^{1,2}

¹ Imperial College Centre for Synthetic Biology, Imperial College London, South Kensington Campus, SW7 2AZ, U.K.

² Department of Bioengineering, Imperial College London, South Kensington Campus, SW7 2AZ, U.K.

Introduction

Strand displacement reactions are the spontaneous replacement of one RNA or DNA strand, in a duplex, by other strand with more base-pairs exchanged. These reactions introduce sequence-complementarity-driven dynamics inside nucleic acids systems, opening the door to the design of multi-stepped, out-of-equilibrium processes [1]. Our goal is to harness these reactions to design synthetic analogues of natural polymer sequence-copying processes, like transcription, translation and replication. In the same vein as natural polymer sequence-copying processes, current synthetic analogues, such as PCR, depend on highly-evolved enzymes and/or periodic influxes of heat to overcome the energetic barriers that copy creation and separation from the template entails [2]. In this work, we aim to construct a DNA sequence-copying mechanism that relies solely on rationally designed DNA-based reactions, without the use of enzymes or temperature control. To do so, we develop a new geometry for strand displacement reactions: “handhold-mediated strand displacement”. Here we present and characterise this new geometry and its implementation in a sequence-specific copying system.

Methods

We design a DNA strand displacement geometry that introduce sequence complementarity between the replaced strand, which acts as a template, and the free-in-solution invader strand. This mechanism allows two or more strands to bind to the template, via sequence complementarity, and subsequently attach each other. The resulting duplex eventually detaches from the template without external manipulation. The system’s strand sequences are rationally designed with the software NUPACK considering the predicted free energy profile [3]. Characterisation of the reaction and analysis of the designed systems is performed with FRET pairs to track the relative position of the strands inside the system.

Results & Discussion

The fluorescence variations in the system are measured for handholds of different lengths and compared with those of identical invader strands without any handhold-complementarity. Comparison shows a significant correlation between the strand displacement reaction rate and handhold’s length. The competition of several species of monomers is used to demonstrate the sequence-specific copying of catalyst dimers via this mechanism.

Conclusion

Here we demonstrate the feasibility of an autonomous, rationally designed DNA-based catalytic copying system. Additionally, we introduce “handhold-mediated strand displacement”, a new strand displacement reaction that increases the catalogue of DNA nanotechnology tools.

References

1. Zhang, DY and Seelig G. *Nature Chemistry*, 2011; 3(2): 103-113.
2. Ouldridge, T and Rein ten Wolde, P. *Physical Review Letters*, 2017; 118(15). 158103-158107
3. Zadeh, J. et al. *Journal of Computational Chemistry*, 2010; 32(1), 170-173.

Autonomous generation of multi-stranded RNA complexes for synthetic molecular circuits

Wooli Bae,¹ Thomas E. Ouldrige¹, Guy-Bart V. Stan¹

¹ Imperial College Centre for Synthetic Biology, Imperial College London, South Kensington Campus, SW7 2AZ, U.K.

Introduction

Synthetic molecular circuits using DNA Oligonucleotides can perform complex functions including logic-gate operation¹ and molecular computing². Multi-stranded DNA oligonucleotides complexes with specific sequences are the essential components for such circuits. However, components for DNA circuits are usually synthesised by chemical methods because nucleic acid synthesis enzymes mainly produce simple double-stranded DNA strands. In contrast, RNA molecules are mainly synthesised as single strands in living organisms which have potential to form multi-strand components for such circuits. The drawback here is that the RNA transcription reaction can only produce one type of single-stranded RNA from one type of DNA template. Therefore, it cannot produce multiple components at the same time. Here we utilise naturally occurring ribozymes to digest one long single-stranded RNA into multiple strands that forms multi-stranded complexes ready to perform strand displacement reactions.

Methods

DNA templates for RNA transcription are designed with the Benchling software and synthesised from IDT. Single-stranded RNA molecules were transcribed from DNA template with T7 RNA polymerase and then analysed in native and denaturing PAGE gel. Strand-displacement reactions were observed with a fluorescence plate reader.

Results & Discussion

Digestion of RNA strands by two different hammerhead ribozyme variants was observed using 20% denaturing PAGE gel. The cleavage yield was close to 90% which is similar to previously reported yields. We also demonstrate both ribozymes work well even when they are connected. The digested RNA strands are released from each construct to displace pre-hybridised Cy3-quencher DNA strand pair. After 12 hours of incubation, we observed complete recovery of the fluorescence signal. We also demonstrate real-time displacement reaction while RNA strands are being transcribed from DNA templates. This demonstrates the possibility of autonomous displacement reaction.

Conclusion

In the present work, we show that the hammerhead ribozyme (HHR) can be used to generate in one transcription reaction short RNA fragments that forms multi-stranded complexes to be used for strand displacement reactions. Our basic module consists of two connected HHR variants can release partially double-stranded RNA. We will develop this basic module to perform more complex strand displacement reaction in different conditions like living cells.

References

- (1) Qian, L.; Winfree, E. *Science* (80-.). **2011**, 332 (6034), 1196–1201.
- (2) Benenson, Y.; Paz-Elizur, T.; Adar, R.; Keinan, E.; Livneh, Z.; Shapiro, E. *Nature* **2001**, 414 (6862), 430–434.

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BioMedEng18

Microfluidic lab-on-a-chip device for studying synthetic enzymes based on DNA nanotechnology

Diana Sobota¹, Kareem Al Nahas¹, Alexander Ohmann¹, Michael Schaich¹, Jehangir Cama¹, Ulrich F. Keyser¹

¹ Cavendish Laboratory, University of Cambridge, Cambridge

Introduction

A fundamental understanding of the mechanisms controlling the composition of biological membranes is highly desirable in both therapeutic and diagnostic aspects of medicine. One of the molecular machines responsible for these processes are transmembrane proteins that control cell's interactions with the environment, as well as the composition of the bilayer itself. Studying properties of these structures is of great interest to researchers. However, insertion rate of both natural proteins and artificial channels is a recurring issue, as it is known to be low, but no precise studies has ever been performed.

Methods

DNA nanoengineering was used to form artificial transmembrane structures, and microfluidic device was developed to study their properties. Our device enables highly controlled GUV formation using octanol-based liposome assembly [1], with the GUVs immobilised downstream in parallel arrays of physical traps. After GUV immobilisation, we perfuse the DNA structures using controlled microfluidic flows, thereby enabling their incorporation within the GUV membranes.

Results & Discussion

In this work, we develop a microfluidic platform that integrates all the experiments required for the reliable characterisation of artificial transmembrane structures like ion channels [2] or scramblases [3].

Conclusion

In our lab-on-a-chip system, we can perform a variety of assays in parallel to study transmembrane structures and quantify their properties.

References

- [1] S. Deshpande et al. "**Octanol-assisted liposome assembly on chip.**" *Nature Communications* 7, 10447 (2016).
- [2] K. Göpfrich et al. "Ion Channels Made from a Single Membrane-Spanning DNA Duplex." *Nano Letters* 16, 7(2016)
- [3] A. Ohmann et al. "**Outperforming nature: synthetic enzyme built from DNA flips lipids of biological membranes at record rates.**" *Nature Communications* 9, 2426 (2017).

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Light-responsive vesicles to control protein expression

I. Gispert^{1,2}, J.W. Hindley^{1,2}, Y. Elani^{1,2}, O. Ces^{1,2}

¹ Department of Chemistry, Imperial College London, South Kensington, London, SW7 2AZ, UK

² Institute of Chemical Biology, Imperial College London, South Kensington, London, SW7 2AZ, UK

Introduction

Lipid vesicles have been extensively used in a wide range of applications, from drug delivery to cosmetics. Of particular interest is the use of lipid vesicles in bottom-up synthetic biology¹, where individual functional units are arranged together to create soft matter assemblies with cell like properties and behaviour. These systems, often called 'artificial cells', have been engineered to establish artificial cell-cell communication networks with many possible applications², from biomedicine to the development of biosensors. In a step forward to gain greater control of these processes, artificial cells have been designed to respond upon specific stimuli, e.g. temperature, pH or light. This research focuses on using light-controllable artificial cells to achieve protein expression in *E. coli*.

Methods

Light-responsive vesicles are created using thin film hydration, freeze-thaw cycles and extrusion techniques. Before being employed, the obtained vesicles need to be purified through a gel-filtration chromatography column. To assess their performance, spectroscopic methods are combined with dynamic light scattering and liquid chromatography.

Results & Discussion

Through precise design of lipid vesicles, it is possible to create a light responsive system which delivers its cargo in a controllable manner. Artificial cell-cell communication is controlled through light, enabling spatiotemporal control of biological processes. This efficiency of the system is quantified using a combination of fluorescent enzymatic assays, mass spectrometry and fluorescence microscopy. We assess both the send and receiving ends of the synthetic cell-cell signalling cascade. Using light gives us a handle with which to tune the extent of communication by varying parameters such as exposure time.

Conclusion

These straightforward systems, in addition to other stimuli-responsive biosystems, allow us to remotely control cell behaviour. Moreover, by using light as a trigger, the artificial cell-cell communication can be regulated with high spatiotemporal control on demand.

References

1. Trantidou, T *et al.*, *ACS Nano*, 2017, **11**, 6549–6565.
2. Hennig, S., Rödel, G. and Ostermann, K, *Journal of Biological Engineering*, 2015, **9**.

Acknowledgments

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Development of 3D Printed Models for Arterial Disease Investigation

I.J. Tshimanga ¹, W.H. Ho ¹, M. Ngoepe ² M. C. Jermy ³, **P.H. Geoghegan** ⁴

¹ University of South Africa, Johannesburg, South Africa ²University of Cape Town, South Africa ³ University of Canterbury, Christchurch, New Zealand ⁴ Aston University, Birmingham.

Introduction

Cardiovascular disease (CVD) is a leading cause of death. CVD haemodynamics are still poorly understood. Numerical simulation applied to CVD requires validation and presents limitations modelling complex flow dynamics. *In-vivo* study is the preferred alternative, however, observing CVD phenomena is extremely challenging. *In-vitro* tools can be utilised for validation and provide faithful flow dynamics. Particle Image Velocimetry (PIV), an *in-vitro* quantitative laser based optical technique, obtains non-intrusive, flow measurements in transparent artery models. The current method of model construction employs investment casting transparent silicone in 2-part moulds [1]. Recent advances in 3D printing in material range and resolution have made it possible to directly print *in-vitro* models [2], reducing error propagation caused by the multipart production process of investment casting and significantly reducing manufacture time. One of the challenges of this is matching the Refractive index (RI) required for optical access, due to the high RI of current polymers compared to possible blood mimicking fluids. In this study, a cheaper alternative for use in direct printing models of arteries utilising Stereolithography (SLA) is investigated.

Methods

The model was printed on a Form Labs Form 2 SLA printer using clear photopolymer resin FLGPCL02. An idealised geometry representing a curved artery with a sphere added to simulate an aneurysm was used. A 3D Design of the model in CAD generates a .stl printer file. Printing was performed at the finest resolution achievable (50µm). Once printed, the phantom was cleaned in isopropyl alcohol removing uncured resin from the print surfaces. It was sanded, and sprayed with a clear lacquer, to improve clarity (Fig 1).



Figure 1 Printed Phantom

Results & Discussion

To match RI a fluid of 66% ammonium thiocyanate and 34% water at room temperature was used [1]. Visual inspection of any distortion due to mismatch of RI was performed with a checked grid placed behind the model (Fig 2). It can be observed that the phantom/solution combination caused minimal distortion, providing the level of optical access required for PIV analysis.



Figure 2 Refractive matched

Conclusion

The SLA printed FLGPCL02 photopolymer resin produced a model acceptable for PIV analysis. At the conference, surface roughness measurements and PIV analysis will be presented, where we expect to present the usability of these directly printed models.

References

1. Geoghegan, P.H., et al., *Fabrication of rigid and flexible refractive-index-matched flow phantoms for flow visualisation and optical flow measurements*. Experiments in Fluids, 2012. **52**(5): p. 1331-1347.
2. Aycok, K.I., P. Hariharan, and B.A. Craven, *Particle image velocimetry measurements in an anatomical vascular model fabricated using inkjet 3D printing*. Experiments in Fluids, 2017. **58**(11): p. 154.

Acknowledgments

We are grateful to the NRF South Africa for funding (KIC171023270560). No conflicts of interest.

Microfluidic devices for quantifying lymphatic-derived chemokine gradients

W.V. Bonneuil¹, L.T. Edgar¹, B.S. Brook², R.J.B. Nibbs³, J.E. Moore Jr¹

¹ Imperial College London, Department of Bioengineering, London SW7 2BP, United Kingdom

² University of Nottingham, School of Mathematical Sciences, Nottingham NG7 2RD, United Kingdom

³ University of Glasgow, Institute of Infection, Immunity & Inflammation, Glasgow G12 8TA, United Kingdom

Introduction

All immune and inflammatory responses require leukocyte migration. The interstitial localisation and migration of leukocytes is guided by concentration gradients of a class of chemo-attractant cytokines, the chemokines. In healthy and diseased tissues, chemokine gradients are formed through diffusion, advection, binding kinetics, and cellular uptake. Little is known quantitatively about how chemokine gradients are produced *in vivo*, and how their characteristics affect leukocyte behaviour. We are therefore developing microfluidic chips in which the factors leading to chemokine gradient formation can be isolated and quantified.

Methods

The microfluidic chips consist of polydimethylsiloxane (PDMS) channels bound to a glass coverslip. Two arrays of trapezoidal posts encapsulate a hydrogel region, where well-defined extracellular matrix (ECM) formulations are injected¹. On either side of that region are two fluid channels where fluorescent chemokines or a saline buffer are injected. Gradients of fluorescent chemokine form across the hydrogel and are visualized by fluorescent microscopy. An advection control strategy was designed from electrical-analogy modelling of Poiseuille and Darcy flows in the chip. Least-squares estimators are employed to estimate the gradient formation parameters from simulation of a partial differential equation (PDE) model².

Results & Discussion

We visualized and quantified the diffusivity of dextran, a chemokine surrogate, from a physiologic source concentration of 10 nM³ into a collagen I hydrogel. The diffusivity of 1×10^{-10} m²/s corresponds to Stokes' theory. Flow is controlled across the hydrogel by varying the relative hydrodynamic resistances of the open outlets. This method enables a cross-gel advection that is physiologic (0.5-10 μ m/s) and uniform along the device. Pressure-actuated valves at the source inlet enable chemokine pulse supplies of different durations to measure binding and unbinding rates to ECM components.

References

1. Farahat, WA et al. PLoS One 7.5 (2012), e37333.
2. Jafarnejad, M et al. J Immunol 199 (2017), pp. 2291-2304
3. Luther, SA et al. J Immunol 169 (2002), pp. 424-433.

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Determinants of pro-atherogenic shear stress patterns in the aorta

Y. Mohamied^{1,2}, S.J. Sherwin², P.D. Weinberg¹

¹Department of Bioengineering and ²Department of Aeronautics, Imperial College London, London SW7 2AZ.

Introduction

The focal distribution of atherosclerosis within the arterial tree has been attributed to anatomical variation in characteristics of haemodynamic wall shear stress (WSS). The current consensus is that the disease is associated with low time-average [1] and oscillatory [2] WSS. A heterodox suggestion is that WSS acting across the long axis of endothelial cells triggers the disease [3]. Such “transverse WSS” upregulates proinflammatory pathways and downregulates homeostatic ones [4,5]. It also increases paracellular permeability [6] and simulations indicate that it tensions adherens junctions [7]. Transverse WSS, like lesions and permeability, can show age-related patterns around rabbit intercostal branch ostia. However, there are many exceptions at individual branches. The current study investigates the causes of this variation.

Methods

Numerical simulations were conducted as previously described [3], with minor modifications. WSS patterns and branch position were categorised by ten observers blinded to rabbit age.

Results

Patterns of time-averaged WSS and oscillatory shear index around branch ostia showed little change with age. Equivalent patterns of transverse WSS were also similar between ages but variability was higher. Two distinct patterns could be seen; they were categorised as “immature” or “mature” (resembling triangles downstream of the branch mouth or lobes at its lateral margins, respectively), based on established lesion patterns. 87% of branches showing the immature pattern lay within two longitudinal streaks of high transverse WSS that propagate from the arch to the distal thoracic aorta and 100% of branches showing the mature pattern were outside of the streaks, regardless of age. Patterns were not much affected by aortic flow waveform or by setting branch outflow to zero. They were altered by changing the Womersley number, which determines the character of the streaks [8].

Conclusion

The pattern of transverse WSS around intercostal branch ostia depends on the location of the ostia relative to two longitudinal streaks of high transverse WSS that lie within the descending thoracic aorta. Models need high geometric accuracy to give physiologically relevant results.

References

1. Caro CG, Fitz-Gerald JM, Schroter RC. Proc R Soc Lond B Biol Sci. 1971; 177: 109-159
2. Ku DN, Giddens DP, Zarins CK, Glagov S. Arteriosclerosis. 1985; 5: 293-302.
3. Peiffer V, Sherwin SJ, Weinberg PD. J Biomech. 2013; 46: 2651-2658.
4. Wang C, et al. Arterioscler Thromb Vasc Biol. 2013; 33: 2130-2136
5. Potter CM, et al. PLoS One. 2012; 7: e31228
6. Ghim M, et al. Am J Physiol. 2017; 313: H959-H973
7. Dabagh M, et al. J R Soc Interface. 2017; 14pii: 20170185
8. Mohamied Y, Sherwin SJ, Weinberg PD. J Biomech. 2017; 50: 102-109

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BioMedEng18

A Benchmark Study for Non-Invasive Fractional Flow Reserve

J.M.Carson¹, S.Pant¹, C.Roobottom², R.Alcock², P.J.Blanco³, C.A.Bulant³,
Y.Vassilevski⁴, F.Liang⁵, P.Nithiarasu¹

¹ ZCCE, College of Engineering, Swansea University, UK.

² Derriford Hospital, Plymouth, UK. ³ National Laboratory for Scientific Computing, Brazil.

⁴ The Institute of Numerical Mathematics of the Russian Academy of Sciences, Russia.

⁵ Shanghai Jiao Tong University, China

Introduction

Fractional Flow Reserve (FFR) is the current gold standard of care for estimating the severity of coronary obstructive lesions. The procedure is performed during the invasive coronary angiogram and under hyperaemic conditions, leading to a significant expense, which is unaffordable in many countries. Thus, there is room to develop non-invasive techniques to determine the FFR. One such technique involves the use of coronary computed tomography angiography (CCTA), often in conjunction with computational models (often called computed FFR or FFR_c). This study involves an international collaboration, with an aim to provide benchmark problems for the non-invasive assessment of FFR_c.

Methods

The study involves blind testing different techniques to determine FFR and compared simulated results with clinical measurements, which are performed during coronary angiogram. Each research group was provided with the same 10 CT scans and basic patient information. Each group employed their own novel techniques, from image segmentation to computational analysis. The results are to be compared with the clinically measured FFR from coronary angiogram.

Results & Discussion

At the end of the project the benchmark problems will be made available as supplementary material to a paper. Surface meshes for the 10 patients will be provided, allowing other groups to test their own methodologies.



Figure 1: Surface Mesh Example

Conclusion

It is expected that benchmark problems for computed FFR will provide a valuable tool for future research, especially for groups comparing non-invasive FFR models with clinical measurements.

References

(examples – use “First author *et al.*” if more than 3 authors, minimum font size 9pt)

1. Boileau E *et al.* Estimating the accuracy of a reduced-order model for the calculation of fractional flow reserve. IJNMBE. 2017, 34(1).

Acknowledgments

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The role of elastin microstructure in the micromechanical properties of ascending aortic aneurysms

Y.H. Chim¹, H. Davies², F.A Diaz De la O³, M. Field⁴, J. Madine², R. Akhtar¹

¹ Department of Mechanical, Materials and Aerospace Engineering, University of Liverpool, L69 3GH, Liverpool.

² Institute of Integrative Biology, University of Liverpool, L69 7ZB, Liverpool. ³ Institute of Risk and Uncertainty, University of Liverpool, L69 7ZF, Liverpool. ⁴ Liverpool Heart and Chest Hospital, L14 3PE, Liverpool.

Introduction

Elastin microstructure is an important factor in aortic aneurysms [1]. However, it is unclear whether elastin microstructure varies in different ascending aneurysm aetiologies, and how this may be related to its micromechanical properties. Here, we measured the micromechanical properties, and the elastin properties within the aortic tissue of two specific groups; bicuspid aortic valve with associated aneurysm (BAV) and idiopathic degenerative aneurysm (DA).

Methods

Aortic tissue was collected from 30 patients undergoing either BAV or DA aneurysmal repair. Oscillatory nanoindentation with a 100 μm flat punch [2] was used to characterise the medial layer. The same tissues were subsequently chemically digested and measured for elastin content using fastin elastin kit. Fixed tissue samples were stained for elastin, and images were captured across the tissue; the number of elastic fragments and their lengths were measured using custom image analysis methods.

Results & Discussion

The micromechanical properties of BAV tissue was found to be significantly higher than DA tissue (Figure 1; $p < 0.001$). Although there was no significant difference in elastin content within the tissue groups, it was noted that more elastic fragments were present in BAV tissue compared to DA tissue, and these fragments were longer than in the DA tissue ($p < 0.001$).

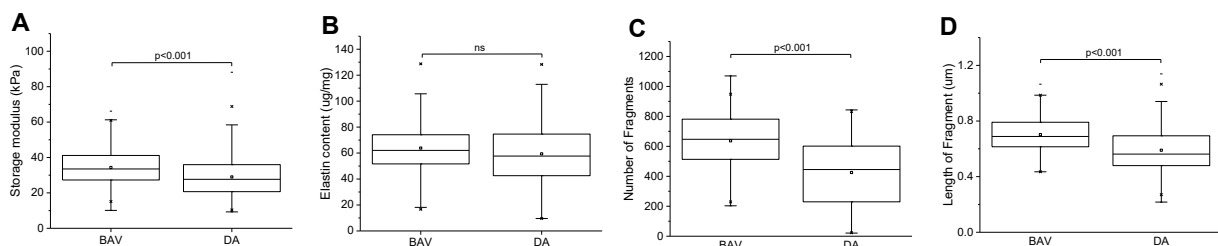


Figure 1: Comparison between the (A) storage modulus, (B) elastin content, (C) number of and (D) length of elastic fragments within the aortic tissue from BAV and DA patients; displaying median and interquartile ranges.

Conclusion

BAV tissue was significantly different to DA tissue, having higher tissue stiffness and an increase amount of longer elastic fragments. Interestingly, micromechanical properties and elastin characteristics could be used as tools to distinguish the type of aneurysm. These initial observations provide new insight in to the aetiology ascending aortic aneurysms.

References

1. Tsamis A, Krawiec JT, Vorp DA. *J R Soc. Interface*. 2013; 10: 20121004.
2. Akhtar et al., *J. Mat. Res.* 2018; *In Press*.

Acknowledgments

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***In vitro* Real Time Fatigue Testing of Cellular and Decellularised Porcine Aortic Heart Valve Roots**

A Desai¹, T Munsey¹, H E Berry¹, E Ingham¹, J Fisher¹, L M Jennings¹

¹ *Institute of Medical & Biological Engineering, University of Leeds, Leeds, UK, LS2 9JT*

Introduction

Accelerated fatigue testers are widely used to estimate the expected durability of prosthetic heart valves in the human body. At accelerated rates, the valve leaflets experience non-physiological loads [1]. The time dependent viscoelastic behavior of biological heart valve roots (HVR) such as allografts and biological scaffolds for tissue regeneration requires testing under more physiological frequencies and pressures. The aim of this study was to develop an *in vitro* real time fatigue testing method for biological HVR and compare the real time fatigue of cellular and decellularised porcine aortic HVR.

Methods

A six station real time wear tester (RWT; Vivitro Systems Inc, Victoria BC, Canada) was modified to accommodate HVRs and to control physiological pressures in the heart valve roots. Cellular and decellularised porcine aortic HVRs (n=6 each) were tested in the RWT at a physiological frequency of 2 Hz for a maximum of 1.2 million cycles to assess real time fatigue. Physiological pressure in the aorta and the transvalvular pressure across the valves (100 ± 20 mmHg) was controlled for at least 95 % of the test cycles. The real time fatigue of leaflets was assessed by high speed camera imaging of the HVR leaflet dynamics, and through qualitative visual assessment at the end of testing.

Results & Discussion

Eight HVRs showed no sign of mechanical damage after 1.2 million cycles of testing. Two cellular and two decellularised leaflets in different HVRs showed a small tear in the belly region. The site of fatigue on the decellularised leaflets was identical to the cellular leaflets.

Conclusion

A method has been developed to experimentally assess real time fatigue of biological heart valve roots under physiological test conditions. This is the first report of preclinical fatigue testing of decellularised heart valve roots under physiological real time conditions. There was no difference in fatigue properties between the cellular and decellularised HVRs in this study. Discussion of the test method and data from this study will help in the development of the next generation of replacement biological HVRs, such as decellularised HVRs. Future work will investigate the extension of the duration of real time testing.

References

1. D'Souza, S.S., et al.,(2003). J Heart Valve Dis, 12(1): p. 110-9

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Multiscale modelling of lymphatic muscle

C. Morris¹, J.E. Moore Jr.¹

¹ Royal School of Mines, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

Lymphatic vessels form a converging network parallel to the venous system and return interstitial fluid to the blood. Insufficient transport of interstitial fluid leads to lymphoedema, a poorly understood condition. The lymphatic vasculature lacks a central pump, so muscle lining the vessel walls exhibits phasic contractions like cardiac muscle for flow generation and tonic contractions like vascular smooth muscle for flow regulation. At the molecular level, these functions can be related to the presence of both smooth and cardiac myosin isoforms. This research aims to develop a multi-scale chemo-mechanical model of lymphatic muscle to investigate the interaction between contraction types and the effect on lymph transport.

Methods

Force generation at the molecular level from both myosin isoforms and the effects of this force at cell and tissue scales are modelled. In the tissue model, a wall-force balance is used to relate the muscle forces to pressure within the lymphangion. This pressure is used for coupling to a previously published^{1,2} fluid-structure-interaction (FSI) model of lymph flow.

The cell model is based on the work of Brook and Jensen³ and consists of rows actomyosin elements with a parallel viscoelastic element. Each actomyosin element is either of two models based on the work of A.F. Huxley⁴, resulting in a combination of contraction types. In the Huxley-based models, myosin heads are modelled as springs, and Hooke's law is used to calculate force based each head's displacement from its equilibrium. The cardiac isoform is assumed to exist in two states (attached or detached) whilst the smooth muscle isoform can additionally be phosphorylated or de-phosphorylated, resulting in four states. Attached heads can change in state or displacement, displacement being dependent on the relative sliding velocity between actin and myosin filaments. Coupling with the FSI model requires changes in diameter to be passed down for calculation of the actomyosin sliding velocity. This sliding velocity is used to calculate the displacement-distribution of heads and generated force.

Results & Discussion

A simulation was run in which a muscle cell with only the smooth isoform contracted isometrically before sinusoidal length oscillations were imposed, reproducing the published results of Brook and Jensen³. Variations in cytoskeletal stiffness change the transmitted force dynamics significantly, sometimes swamping the non-linearity of molecular force generation. The time-averaged dimensionless cell force for an oscillation cycle (normalized to maximum isometric), however, showed low sensitivity to cell viscosity, varying by 0.43% in response to a two order of magnitude change in cell viscosity.

Conclusion

A multiscale model is developed for the capture of the unique combination of contractile properties exhibited by lymphatic muscle. Preliminary results indicate the importance of accurately representing the cell stiffness in generating realistic models of lymphatic muscle cell contractile forces.

References

1. Jamalian S, et al. *Am J Physiol Heart Circ Physiol*. 2013; 305: H1709-H1717
2. Jamalian S, et al. *Plos ONE*. 2016; 11: e0148384
3. Brook BS, Jensen OE. *Math Med Biol*. 2014; 31: 99-124
4. Huxley AF. *Prog Biophys Biophys Chem*. 1957; 7: 255-318

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Numerical Simulations of Action Potential Propagation in Cardiac Tissues with Myocardial Infarction Scars

P. Mortensen¹, R. Simitev², H. Gao², C. Berry¹, G. Smith¹

¹ *Institute of Cardiovascular and Medical Sciences, G12 8QQ, Glasgow*

² *Mathematics and Statistics Building, G12 8QQ, Glasgow*

Introduction

The heart beats with a particular pattern. Starting at the Sino-Atrial node in the right atrium, an electrical wave passes across the atria, past the Atrioventricular node, down the septum and around the outside of the ventricles. This wave causes blood to be pumped through with maximum efficiency. However, when a myocardial infarction damages the muscle tissue, this pattern is interrupted, leading to heart failure.

Methods

We use finite element methods to simulate and explore the propagation of electrical excitation waves in cardiac tissues in 2D and 3D slabs as well as in more realistic geometries of the left ventricle. We include regions with reduced conductivity to model tissue that has been affected by myocardial infarction. The simulations are compared to experiments on rabbit hearts, performed on sections of the left ventricle and on whole hearts, by R. Myles et al [1] and A. Allan [2], respectively.

Results & Discussion

Currently, the single-cell electrophysiology models being used are for human ventricles (by Tusscher-Panfilov et al. [3]) and for rabbit ventricles (by Mahajan et al. [4]). Both models are upscaled to monodomain tissue models and the simulations produce contour plots for key properties such as activation times, calcium concentration and action potential duration. Future work will include using parameter estimation with data from rabbit left ventricles and coupling with models of muscle contraction.

Acknowledgements

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References

1. R. C. Myles et al, Am J Physiol Heart Circ Physiol, 199, 1812 - 1822, (2010).
2. Andrew Allan, University of Glasgow, (2015).
3. K. H. W. J. ten Tusscher et al, Am J Physiol Heart Circ Physiol, 286, 1573 - 1589, (2003).
4. A. Mahajan et al, Biophys J, 94, 392 - 410, (2008).

Modelling the effects of Lymph Node hypertrophy on T cell transit and interactions during the cell mediated response.

S.C. Johnson¹, L. T. Edgar ², J.E. Moore Jr. ^{2, 3}

³*Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London.*

Introduction

The cell mediated response (CMR) initiates within the lymph node (LN) paracortex where migrating T cells interact with antigen presenting dendritic cells (DCs). Macroscopic LN hypertrophy during this event is a hallmark of the adaptive immune response, but the cause and effect between LN hypertrophy and the carefully coordinated T cell response is poorly understood. Increased lymphocyte recruitment is known to accompany a CMR, in part mediated by vasculature increase within the LN^{1,2}. Our aim was to better understand how LN hypertrophy and geometric change of recruitment and egress areas affects T cell transit and interaction mechanisms. Implications include enhanced vaccine design and a better understanding of disease cases with chronic LN enlargement.

Methods

LN swelling during a CMR was stimulated using a 3D agent based model of a murine LN paracortex, realistically describing T cell migration, DC entry and resulting interactions that lead to activation, proliferation, and differentiation of T helper and Cytotoxic T cells. As our focus was on cell transit, Sphingosine-1-Phosphate receptor 1 regulation, which plays a critical role in retention of activated cells, was included. Increased T cell recruitment was modelled to include rate increase due to early innate signalling, and a rate increase proportional to increased vasculature during LN enlargement. LN volume change during swelling was described using a sigmoid function of T cells present, with the maximum fold volume increase and inflection point varying between different simulations. Different models of entry area (vasculature growth) and exit area alteration, proportional to overall size change, were also simulated.

Results & Discussion

Initial activation of T cells is aided by LN hypertrophy in most circumstances but not when S1Pr₁ mediated retention is inhibited and is unrelated to the number of interactions with DCs. Effector cell production is aided by LN hypertrophy in some cases but is highly sensitive to egress area alteration. Above a 3 fold LN volume increase, T cell exit rate rises beyond physiological levels, thus dampening the increased effector response. The increased vascular surface area and relative increase in recruitment rate that accompanies enlargement is needed to drive further change; increased rate of recruitment due to innate signals alone is insufficient.

Conclusion

LN swelling influences the resulting cell mediated response, although aiding or ameliorating effector cell production is dependent on the ability to maintain a T cell density rather than number of specific cognate T cell-DC interactions. All parameters regarding exit area appear highly sensitive, yet the way in which exit areas alter is unknown. Our simulations suggest which scenarios are more likely than others and highlights the requirement of increased recruitment through blood vessel growth that accompanies swelling for an effective response.

References

1. Soderberg KA *et al. Natl Acad Sci U S A.* 2005; 102(45): 16315-20.
2. Kumar V *et al. Frontiers in immunology.* 2012; 3(282);

Regional variations in the micromechanical and biochemical properties of the ovine aorta.

P. Panpho¹, M. Field ², J. Madine³, R. Akhtar ¹

¹School of Engineering, University of Liverpool, UK. ² Department of Cardiac Surgery, Liverpool Heart and Chest Hospital, UK. ³ Institute of Integrative Biology, University of Liverpool, UK

Introduction

Investigation of the mechanical properties of the aorta is important for better understanding of aortic diseases such as aortic aneurysms and aortic dissection. While there have been previous studies examining regional differences in the structure and biomechanical properties of the aorta, little is known about how these properties vary across its entire length [1, 2]. The aim of this study was to map the biomechanical properties and biochemical changes of the ovine aortic wall along its entire length.

Methods

Three fresh ovine aortas were obtained from the local slaughterhouse. They were split into nine sections and they were separated by 2 cm intervals between the aortic root and the celiac artery region. For each section, three biopsies were cut out using a 5 mm biopsy punch (a total of 81 biopsies). A dynamic nanoindentation method using a KLA-Tencor Nanoindenter G200 with a DCM-II head was employed to measure the mechanical properties of aortic tissue. A 100 μ m cylindrical flat punch and 16 oscillatory indentations were applied to the surface of the tissue. The shear storage modulus (G'), the shear loss modulus (G'') were determined using the method reported elsewhere [3]. Subsequently, the same samples were used to determine elastin, collagen and glycosaminoglycan (GAG) levels using established biochemical assays.

Results & Discussion

Overall, the shear storage modulus and the shear loss modulus increased by 175.2% and 140.7%, respectively from the ascending to the abdominal region. The collagen level was lowest at the first point of the ascending region and steadily increased with distance whereas elastin level and GAG decreased along its length. Our results were consistent with previous studies [1, 4], which also showed that the mechanical properties of the aortic tissue increased from proximal to distal locations of the aorta. Our findings also agreeable with a previous study that found the collagen content in canine aortic tissue increased from the carotid to abdominal aorta, while the elastin content decreased [2].

Conclusion

In conclusion, there is a significant correlation between an increase in G' and collagen ($P=0.01$) with distance from the aortic root whilst elastin ($P=0.05$) and GAG ($P=0.05$) levels were significantly decreased.

References

1. Haskett, Darren, et al., *J Biomech.Mechano*. 2010;9(6):725-736.
2. Harkness et al. The Royal.Soc,London. 1957;146(925):541.
3. Akhtar et al., *J Mat Res*;2018; 33(8): 873-883.
4. Peña, Juan A., et al., *J Biomech*;2018; 77: 434-445.

Computation of blood flow in the pulmonary bifurcation: towards a more effective treatment for adults with congenital heart disease

M.Boumpouli¹, M. Danton ^{1,2}, T. Gourlay ¹, A. Kazakidi ¹

¹ Department of Biomedical Engineering, University of Strathclyde, G4 0NW, Glasgow.

²Scottish Adult Congenital Cardiac Service, Golden Jubilee National Hospital, Clydebank, G81 4DY, Glasgow.

Introduction

Adults with congenital heart disease represent an increasing population of patients that require repeated surgical interventions, most commonly for pulmonary valve replacement (PVR) and stenting [1]. Currently, the decision for treatment relies on symptoms, including arrhythmias and abnormal right ventricular volume and function [2], however the optimal timing for surgery remains unclear [3]. The aim of this work is to investigate the altered haemodynamic environment of the pulmonary bifurcation in adults with repaired tetralogy of Fallot, before and after pulmonary valve replacement. The overall objective is to derive a computational fluid dynamic metric to determine the optimal time for surgery. In this preliminary study, we present results in simplified geometries of the pulmonary trunk, focusing on the effects of geometry and flow conditions.

Methods

Blood flow simulations were performed in simplified models of the pulmonary bifurcation using a finite volume method solution. Physiological vessel dimensions and boundary conditions were used in the models, and blood flow was assumed steady, incompressible, and governed by the Newtonian Navier-Stokes equations. The effect of the bifurcation angle between the main pulmonary artery and its branches were studied and different Reynolds numbers were tested, representing healthy and diseased conditions.

Results & Discussion

Blood flow in the pulmonary bifurcation is strongly dependent on local geometric characteristics and haemodynamic conditions. Flow separation increases when the bifurcation angle and Reynolds number increase. In addition, the geometry has a significant effect on velocities and shear stresses developed on the vessel wall. Evaluation of these parameters can provide an insight into the underlying flow mechanisms of more complex 3D patient-specific geometries. Future work will involve time-dependent effects and anatomically-correct geometries, reconstructed from CT and MRI image data of adult patients with repaired tetralogy of Fallot that have or are about to undergo pulmonary valve replacement or stenting. Pre- and post- operative haemodynamic analysis is expected to establish new reliable metrics for a more accurate and timely assessment for PVR treatment in this particular group of patients and contribute towards better medical care.

References

1. Gatzoulis M.A., Webb G.D., Daubeney P.E.F. *Diagnosis and Management of Adult Congenital Heart Disease (Elsevier)*. 2017; 474-488.
2. Buechel, E.R.V., et al. *European Heart Journal*. 2005; 26: 2721-2727.
3. Geva T. *Circulation*. 2013; 128: 1855-1857.

Acknowledgments

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Effect of Tapering on the Measured Pressure in the Inlet of a Single Artery

S. Abdullateef¹, J. Mariscal-Harana ², J. Alastruey ², A.W Khir ¹

¹College of Engineering, Design, and Physical Sciences, Brunel University London, Middlesex, UK, UB8 3PH.

²School of Biomedical Engineering and Imaging Sciences, King's College London, SE1 7EU, London.

Introduction The pressure in the ascending aorta carries valuable information about the pumping heart and the response of the arterial tree. However, extracting useful information about the arterial tree is challenging due to the occurrence of many physical phenomena, such as reflections resulting from the effect of tapering, bifurcations and the pumping heart. Whilst reflections from bifurcations, stenosis and aneurisms have received enough attention, the effect of tapering on reflected waves has not been adequately studied. Therefore, the aim of this work is to investigate the effect of tapering on reflected waves using simplified computational 1-D models.

Methods In order to analyse the effect of tapering on wave reflections, a standard tapered tube (**Fig.1b**) is simplified into a series of staggered segments connected with reduction of cross-sectional area (**Fig.1a**). The segments are 5 metres long initially and then their length is reduced to 0.3125m. The results are compared to those obtained from the tapered tube. We tested both systems using half-sinusoidal inputs with different time periods, and with both 5 and 0.3125m segments. The boundary condition at the end of the final segment is a complete absorption of any incoming pulse wave.

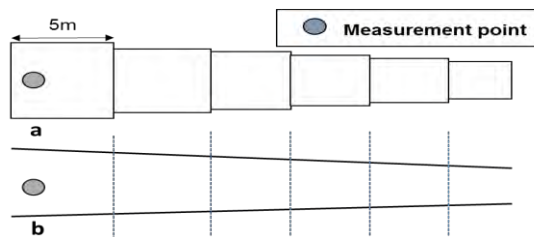


Figure 1. Imposing the tapering with systematic reduction of cross-sectional area

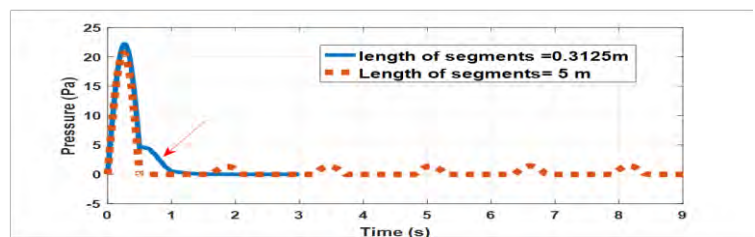


Figure 2. Measured pressure in the inlet of staggered structure with 5 m (dashed line) and 0.3125 m (straight line) long segments

Results & Discussion Both systems produced a similar response to the half-sinusoid inputs. There are reflected waves arriving to inlet of the structure with the same timings?, which are originated from the junctions of segments. However, the magnitude of the reflected waves in the staggered structure is higher than those in the standard tapered tube because of the higher difference in the cross-sectional areas of the junction. In addition, when the segments' length is reduced to 0.3125 m the reflections from each junction are overlapped and amalgamate (**Fig 2**).

Conclusion In this study we used segments of 5 meters, which allowed the reflected waves to be distinguishable. The staggered structure of the tubes imposed the effect of tapering with sudden alteration of area and caused reflection waves travelling backward to the inlet. Since the length of human arterial segments is much smaller than 5m, the gradual tapering will cause small reflections which we anticipate to amalgamate producing a smooth reflected waveform as observed *in vivo* and straight line of **Fig 2**.

References

1. Khir AW, Parker KH. Jof Biomech 2002;35:775-783.
2. Segers P, *et al.* Artery Res. 2017;18:75-80
3. Alastruey J *et al.* J Eng Math. 2009;64:331-351

Computational Modelling of Atrial Fibrillation: Mechanisms Based on the Generation of Transmural Rotors

A. Tajabadi, A. Roy, M. Varela, O.V. Aslanidi

*School of Biomedical Engineering & Imaging Sciences, King's College London,
St Thomas' Hospital, London, SE1 7EH, United Kingdom*

Introduction

Atrial fibrillation (AF) is a cardiac arrhythmia characterized by rapid and irregular beating of the atria, which affects 33.5 million people worldwide. Currently the understanding of AF mechanisms, as well as the success of its treatments, remain limited. Various phenomena, including periodic re-entrant waves, 'rotors', and focal 'breakthroughs' that emerge from a small area, have been observed experimentally and proposed as the main drivers sustaining AF. However, relations between such controversial mechanisms are unclear. This work aims to elucidate the mechanistic links between rotors and breakthroughs by considering 3D transmural rotors that propagate within the atria via pectinate muscles.

Methods

A computational model of atrial electrical activity was created using a canine 3D atrial geometry combined with Varela et al. ¹ atrial cell models. The model included ionic and structural heterogeneities in the atria, and specifically between the right atrium (RA) and pectinate muscles (PM). Sustained AF was generated by ectopic rapid pacing in the pulmonary veins (PVs). Results were visualized with 3D atrial membrane voltage maps (VM), along with 2D isochronal (IM) and wave (WM) maps based on electrogram recordings from the endocardium and epicardium. IM recorded epi- and endocardial activation times over a given period, and WM segmented individual wavefronts that appeared within this period of time. In the IM and WM, waves that appeared from focal locations within the atria were defined as breakthroughs, while periodic re-entrant activation patterns were considered as rotors. The effects of anti-arrhythmic drugs on AF termination were also studied: 10 μ M Amiodarone was introduced after 5 seconds of AF, which was modelled by blocking the appropriate ionic channels based on experimental data.

Results

Following pacing in the PVs, AF was initiated in the entire 3D atria and maintained by several epicardial rotors in the PVs and RA, as well as an additional transmural rotor propagating through the PMs and emerging at the RA epicardium. Therefore, IM and WM electrogram maps showed multiple breakthroughs in the RA, which were due to the re-entrant transmural activations emerging to the epicardium from various insertions of the underlying network of PMs. The applications of amiodarone resulted in the termination of both the transmural rotor and epicardial rotors in the RA, leaving a single rotor in the PVs. The effect was due to amiodarone increasing the wavelength and preventing re-entry.

Conclusion

The 3D atrial simulations showed that complex AF patterns can be explained interactions of epicardial rotors with transmural waves propagating through the depth of 3D atrial tissue, and appearing as rotors in the PMs or breakthroughs on the RA surface. These results can unify apparently controversial viewpoints on AF mechanisms and potentially improve mechanism-based AF treatments.

References

1. Varela M, Colman MA, Hancox JC & Aslanidi OV. Atrial Heterogeneity Generates Re-entrant Substrate during Atrial Fibrillation and Anti-arrhythmic Drug Action: Mechanistic Insights from Canine Atrial Models. *PLoS Comput. Biol.* 2016; 12: 1–22.

Investigating uncertainty in parameter choices for cardiac cell action potential models using statistical inference.

C. Houston¹, R.A. Chowdhury¹, F.S. Ng¹, E. Dupont¹, N.S. Peters¹, C.D. Cantwell¹

¹ *ElectroCardioMaths Program of the Imperial Centre for Cardiac Engineering, National Heart & Lung Institute, Imperial College, London, W12 0NN.*

Introduction

Simulations of electrical activity in patients' hearts are built from mathematical models for the action potential in single cardiac cells. These models include hundreds of parameters to fit the dynamics of each ion channel present in the cell. The parameters are typically chosen by fitting to data from biological experiments using traditional methods, such as least squares regression. These methods give single point estimates and do not consider the uncertainty introduced by the fitting process, i.e. different parameter choices able to give similar output. Approximate Bayesian Computation (ABC) is a modern statistical method which can be applied in a Monte Carlo algorithm to fit parameter *distributions*, and thus provide more visibility of model uncertainty [1].

Methods

Published patch-clamp data for eight channels of the HL-1 atrial-derived cell line were used as input to the ABC algorithm to fit parameters in the cell model. The ability to constrain parameters based on this data was studied in the shape of resulting fit distributions. Uncertainty in the output of the full model at a macro-level, e.g. transmembrane voltage, was assessed by running multiple simulations with parameters set by random draws from their ABC distributions. The model was validated by comparing simulated action potentials to biological measurements of optical action potentials in HL-1 monolayers.

Results & Discussion

Simulated experiments on ion channels fit by ABC showed close agreement with the corresponding biological data, with generally small uncertainty in the output. When interrogated further, the ABC distributions showed the data well constrained steady-state parameters but struggled to constrain temporal parameters. This suggests that available experimental protocols and data may be insufficient to characterise specific temporal dynamics of the ion channels. Resting potential, action potential amplitude, action potential duration and Ca^{2+} transient decay agree well between simulations and experimental observations.

Conclusion

This study applies a statistical inference approach as a fitting method for action potential models that is informative of uncertainty in the fitting process itself. The work represents a further step towards uncertainty quantification in more complex tissue- and organ-scale models, which is critical to ensure their credibility and confidence in clinical decision-making informed by computer simulations. It is suggested that alternative patch-clamp experimental protocols could be investigated in an effort to better constrain the temporal parameters in these models.

References

- [1] Daly AC et al. Hodgkin-Huxley revisited: reparametrization and identifiability analysis of the classic action potential model with approximate Bayesian methods. *R Soc Open Sci* 2015;2:150499. doi:10.1098/rsos.150499.

Acknowledgments

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BioMedEng18

The study of microcirculation and oxygen uptake in the liver in cirrhosis

M. Zhuang¹, J. H. Tweedy², J. E. Moore Jr.³

Affiliation: ¹Department of Bioengineering, Imperial College London, London SW7 2AZ, UK

Introduction

Liver disease is the fifth biggest cause of death in England and Wales and is the only major cause of death that is increasing year on year. Cirrhosis is one of the most prevalent types of disease, and one of its characteristic features is an altered liver architecture, due to the development of fibrosis. The effect on the haemodynamics of the microcirculation is not fully understood. To investigate this, we develop a mathematical model to predict the effect of cirrhosis on the blood flow and oxygen uptake.

Methods

Following Bonfiglio et al (2010), we consider a functional unit of liver tissue called a lobule, with a poroelastic tissue model, treating the solid tissue as an elastic solid and the blood flow using Darcy's law. The development of fibrosis is modelled by including a region with anisotropic elastic properties, and the uptake of oxygen is included via a model developed by Lettmann and Hardtke-Wollenski (2014).

Results & Discussion

The pressure is highest at the portal tract and drops towards the central vein, meaning the blood flows from portal tracts to central vein, with the highest fluid velocities obtained near the portal tract and central vein. We also investigate the behaviour of the poroelastic solid under an increasing portal tract pressure, finding that the largest deformation occurs at the outer boundary. The oxygen concentration is rich near the outer boundary and drops towards the central vein, with the highest uptake rates near the portal tracts.

Conclusion

We have developed a poroelastic model that reproduces aspects of blood flow and oxygen uptake in liver lobules. The approach will allow us to investigate perfusion and mass transport under different pathological conditions via changing the governing parameters.

References (examples – use “First author *et al.*” if more than 3 authors, **minimum font size 9pt**)

1. Karsten Alexander Lettmann, M. Hardtke-Wolenski. The importance of liver microcirculation in promoting autoimmune hepatitis via maintaining an inflammatory cytokine milieu – a mathematical model study. *J. Theor. Biol.*, 348:33–46, 2013.
2. Andrea Bonfiglio, K. Leungchavaphongse, R. Repetto and J. H. Siggers. Mathematical modeling of the circulation in the liver lobule. *J Biomech Eng*, 132(11):111011, 2010.

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Computational fluid dynamics analysis of the interactions between HeartMate II axial flow pump and the cardiovascular system: potential for patient-specific modelling in advanced heart failure

M. Capoccia^{1,2}, T. Scanlon³, T. Gourlay²

¹Manchester Heart Centre, Manchester University NHS Foundation Trust ²Biomedical Engineering, University of Strathclyde, Glasgow ³Mechanical and Aerospace Engineering, University of Strathclyde, Glasgow.

Introduction

Technological development from pulsatile to continuous-flow ventricular assist devices has improved advanced heart failure treatment with significant increased patients' survival on prolonged circulatory support. Reduced arterial pulsatility may be responsible for complications like pump thrombosis, aortic regurgitation, gastro-intestinal bleeding and arterio-venous malformations. A pre-operative strategy aimed at the reduction of complications and patient-device suitability may be appropriate.

Methods

3D reconstruction from CT-scan of patients with continuous-flow pumps. Computational fluid dynamic analysis using Ansys Fluent 17.1. Mimics Materialise or 3D Slicer for anatomical reconstruction. Blood as either Newtonian fluid or Non-Newtonian using Carreau-Yasuda model. Simulations at steady state with laminar flow and turbulent flow using k- ω SST or k- ϵ models. Boundary conditions set at a specific steady velocity profile (inlet) and at a fixed steady pressure (outlet). Rotational speed at 9500 rpm for the HeartMate II device.

Results & Discussion

Flow behaviour analysis: velocity magnitude, pressure contour, shear stress, strain rate and exposure time. Convergence was observed for laminar flow and k- ω SST model. Laminar flow may be suitable as a preliminary analysis of the problem; a turbulent model may add more accuracy despite current controversy in relation to its use for rotary blood pumps.

Conclusion

Patient-specific modelling as a preoperative planning strategy seems a feasible and attractive option. It is time to focus on the complications to achieve the full potential and selling-point of this technology for the treatment of the increasing heart failure patient population.

References

1. Bazilevs Y et al. Patient-specific isogeometric fluid-structure interaction analysis of thoracic aortic blood flow due to implantation of the Jarvik 2000 left ventricular assist device. *Comput Methods Appl Mech Eng* 2009; 198: 3534-3550.
2. Fraser KH et al. The use of computational fluid dynamics in the development of ventricular assist devices. *Med Eng Phys* 2011; 33: 263-280.
3. Sheriff J et al. Evaluation of Shear-Induced Platelet Activation Models Under Constant and Dynamic Shear Stress Loading Conditions Relevant to Devices. *Ann Biomed Eng* 2013; 41(6): 1279-1296.

Acknowledgments

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Accessible Microfluidics: Rapid prototyping of thermoplastic devices

C. Matellan¹, A. E. del Río Hernández¹

¹ Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

Despite the potential of microfluidic technologies, their adoption is limited by the requirement for specialised equipment and the difficulty in translating conventional manufacturing to the industry. Here we present a “mask-less” rapid prototyping method for thermoplastic microfluidics with readily available equipment and reagents that enables cost-effective design iteration.

Methods

A proof-of-concept h-filter was fabricated in poly methylmethacrylate (PMMA) via laser ablation with a CO₂ laser cutter. Channels were treated with acetone vapour and annealed below the normal glass transition temperature of PMMA. Bonding was accomplished by injecting an epoxy adhesive into the interstitial space between the chips and a glass substrate. Size separation in the device was demonstrated with a sample containing brilliant blue dye (0.1% w/v) and 20 µm polystyrene beads.

Results & Discussion

Laser ablation enabled flexible fabrication of microfluidic chips without a photomask or a microfabricated mold. The solvent-assisted thermal annealing accomplished a reduction in the surface roughness caused by the ablation process without affecting the bulk of the device¹, while adhesive bonding readily allowed room-temperature PMMA-Glass bonding as opposed to conventional thermal bonding. The H-filter² demonstrated microfluidic diffusion-based separation between a dye (high diffusion) and beads (low diffusion) at low flow rates

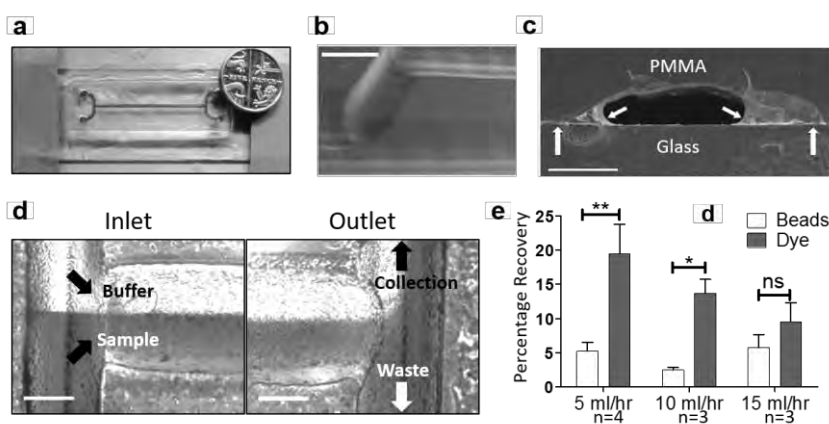


Figure 1. Proof of concept fabrication. (a) A microfluidic PMMA H-filter. (b) Surface of the channels after solvent-assisted annealing. Scale bar: 1 mm. (c) Cross-section of a microfluidic device bonded to glass showing accumulation of adhesive at the interface (arrows). Scale bar: 500 µm. (d) Diffusion of the dye in the sample stream to the buffer stream. Scale bar: 500 µm (e) Percentage recovery of dye and beads in the collection outlet at different flow rates (mean ± s.e.m, two-way ANOVA, ** p<0.01, * p<0.05)

Conclusion

The method presented here enables manufacturing of common microfluidic devices in a flexible and accessible manner that facilitates the translation of microfluidics from concept to prototype.

References

1. Ogilvie IRG, et al. J. Micromechanics Microengineering. 2010; 20: 065016
2. Brody JP, Yager P. Sens. Actuator A-Phys. 1997; 58: 13-18

*A complete version of this work has been submitted to *Scientific Reports*

Human bones-on-chip self-assembly to form new bone

E. Budyn¹, N. Gaci¹, S. Sanders¹, M. Bensidhoum², E. Schmidt³, B. Cinquin⁴, P. Tauc⁴, H. Petite²

¹LMT CNRS UMR 8535, Ecole Normale Supérieure Cachan, 94235 Cachan, France. ²B2OA CNRS UMR 7052, University Paris-Diderot, 75010 Paris, France. ³MIE Dept., ERF Building, University of Illinois at Chicago, 60607 Chicago IL, USA. ⁴LBPA CNRS UMR 8113, Ecole Normale Supérieure Cachan, 94235 Cachan, France.

Introduction

Large bone defects after a massive trauma or a cancer resection will not repaired on its own. Successful techniques of tissue regeneration of such defects are challenging and require the addition of functional materials. Bone microstructure results from the continuous remodeling where microdamage are mechanical stimuli that initiate tissue resorption by osteoclasts before tubular osteons are formed by osteoblasts that derive from Mesenchymal Stem Cells (MSCs) and further differentiate into osteocytes that are able to sense mechanical stimulations produced by microdamage and loop the remodeling cycle. Osteocytes regulate healthy bone turnover. It is essential to quantify the evolution of the *in situ* mechanical stimuli during differentiation and the matrix formation in order to design successful regenerative medicine.

Methods

Multiple human bone samples were cellularised with human MSCs to be co-cultured in bones-on-chip. MSCs, osteoblasts and stem cell derived osteocytes have been shown to reseed on such bone systems [1,2]. In systems composed of multiple bones, the movements of the bone samples were tracked by sequential imaging during the self-assembly. The cellularised bone systems composed of a single or multiple bones were subjected to controlled mechanical stimulations for up to 26 months. The cells calcium response to mechanical stimuli was measured. The mechanical stress field was measured around and within the cells by 3D multi-scale image-based FEM simulations. The effect of the progressive mineralization of the collagenous matrix and its fibre orientation was studied on the cell stimulation.

Results & Discussion

The cellularised bones assembled through matrix contraction at 5 weeks leading to large displacement. The organisation of the assembled bones depended on the orientation of the osteons in the samples. A large amount of matrix was formed at 4 months. The numerical models measured the stress field at the tissue and cell scales as the tissue mineralised and concurrently to the *in situ* calcium cell response.

Conclusion

These bones-on-chips showed osteocyte *in situ* mechanotransduction and produced large amount of new mineralised ECM from 1 to 26.5 months. The mineralisation was function of the mechanical load. The systems were osteoconductive, osteoinductive and osteogenic.

References (examples – use “First author *et al.*” if more than 3 authors, minimum font size 9pt)

1. Budyn E, Gaci N, Sanders S et al. *MRS Advances*. 2018; doi.org/10.1557/adv.2018.278.
2. Budyn E, Bensidhoum, Gaci N et al. European Cells and Materials Conferences, TCES 2016. 2016; 32(supp. 4):32

Acknowledgments

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A Roadmap for how Organ-on-a-Chip Technology might replace Animal Tests for Drug Safety

J. M. Wilkinson¹, B. Singh¹

¹ Kirkstall Ltd., Unit 3 Aspen Court, Centurion Business Park, Rotherham, S60 1FB.

Introduction

This presentation looks at the current use of animals in research, and explores the technical and other challenges to be overcome to produce better data by alternative methods including the emerging organ on a chip models

Background

There is currently great interest in applying microfluidics technology to the construction of complex in vitro models with the eventual goal of simulating the behaviour of an organ or even a whole organism. The current enthusiasm for microtechnology is based on the success of the microelectronics industry in producing incredibly complex devices in high volume. Scaling biological processes does not follow the same laws. The gold standard for clinical response is the human body, which incorporates functional units that require larger scale. It is widely recognised that 3D cell cultures are more representative of human physiology than 2D monolayers of cells growing on a flat surface. Correct organ function also requires gradients of oxygen and metabolites and removal of waste material, as well as co-culture of multiple cell types- hence advanced and accurate models also require flow of media.

Discussion

Any technology which aims to replace animal based methods for safety and toxicity testing will have to meet the following requirements:

- Systemic models (connected organs or organoids)
- Long term culture for disease study or and repeat dose drug exposure
- Ability to maintain homeostasis (before insult)
- Good disease models.

The current status of the proprietary Quasi Vivo® technology will be presented in comparison with other leading Organ-on-a-Chip approaches. Cells cultured under optimum flow conditions are more metabolically competent than those cultured using traditional static techniques, and it appears that cells in interconnected chambers can create homeostatic conditions. Technical challenges include the selection of a common media and flow conditions to suit multiple connected cell types.

Conclusion

It is believed that the currently available meso-scale Quasi Vivo® technology can lead the way towards relevant and easy-to-use in vitro techniques for animal replacement. Ease of use, robustness of the protocols and scalability are key factors that are necessary for widespread adoption.

References

1. Ahluwalia A, *Nature Scientific Reports* 2017; 7:42113 | DOI: 10.1038/srep42113

Low-cost injection moulding strategies for the fabrication of Organ on a Chip devices

B. J. Middleton¹, V. Goodship¹, R. Dallmann², J. Charmet¹

¹ Warwick Manufacturing Group (WMG), University of Warwick, CV4 7AL, Coventry

² Warwick Medical School, University of Warwick, CV4 7AL, Coventry

Introduction

Polydimethylsiloxane (PDMS) based devices are commonly used for Organ on a Chip applications, despite serious material property limitations [1,2]. Besides, the soft-lithography approach [3,4] used to fabricate such devices is not well suited for medium to large scale manufacturing, which limits the potential translational impact of such devices. Injection moulding, which is compatible with a wide range of polymers, addresses these issues. However, the high cost associated with the microfabricated moulds is currently hindering the development of microfluidics devices for research applications [5]. Here we describe three routes to develop a flexible approach suitable for low-cost prototyping of microfluidic devices.

Methods

We used conventional injection moulding bolster plates with a cavity to accommodate mould inserts fabricated using photolithography, 3D printing or conventional micromachining. A range of polymers compatible with injection moulding were investigated for their low gas permeability (PET), transparency (PC), opacity (PA6) and solvent resistance (PP, COC).

Results & Discussion

Using these approaches, we were able to mould complex channels with features sizes ranging from 20 μm to a few millimetres. Figure 1 shows an injection moulded microfluidic device in PP showing features obtained by photolithography on a positive master mould. We are currently investigating the fidelity of the moulding for the different materials and the wear of the moulds to define the limits of the processes. We will validate the concept by fabricating a high-throughput platform to study cellular circadian clocks using real-time bioluminescence and fluorescence reporters.

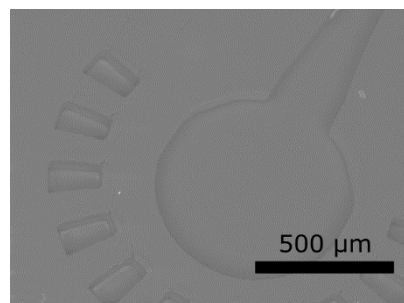


Figure 1: SEM micrographs of injection-moulded devices (PP) based on photolithographic master mould.

Conclusion

The flexible and low-cost injection moulding process proposed herein opens up opportunities for the fabrication of Organ on a Chip devices; in terms of material choice and translational impact.

References

1. Moore, T.A., Brodersen, P., Young, E.W.K., Anal. Chem. 2017; 89, 11391
2. M.W. Toepke, D.J. Beebe, Lab Chip 2006; 6, 1484.
3. Y. Xia, G.M. Whitesides. Annu. Rev. Mater. Sci. 1998; 28, 153–184
4. P.K. Challa, T. Kartanas, J. Charmet, T.P.J. Knowles, Biomicrofluidics 2017; 11, 014113
5. H. Becker, C. Gärtner, Anal. Bioanal. Chem. 2008; 390, 89.

Acknowledgments

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Investigating the correlation between infection and preterm birth in a human organ-on-a-chip model of the human endometrium

V. Mancini¹, V. Pensabene¹

¹University of Leeds, School of Electronic and Electrical Engineering, Leeds, United Kingdom.

Introduction

Our main goal is to develop new models of the female reproductive organs to clarify aspects of fertility and pregnancy complications. Specifically we developed an organ on a chip model of the endometrial microvascular system¹ for investigating the interaction between intrauterine infection and the onset of premature labour. Preterm birth (PTB) corresponds to spontaneous preterm rupture of the foetal membranes and can be caused by multiple pathologic processes, among which microbial-induced intrauterine infections. It is known that during bacterial infection specific signalling pathways determine the secretion of pro-inflammatory cytokines (eg IL-8 and TNF- α)², involved in neutrophil activation, and strictly correlated with metalloprotease activation and cervix dilatation.

Methods

The study consists in the examination of the response of primary endometrial stromal (T-HESCs) and human umbilical vein endothelial cells (HUVECs) to infection in a dynamically perfused microfluidic device ($\sim 6\mu\text{L}$)¹. The microfluidic device allows to culture cells for up to 4 weeks that enables 1) to develop confluent cell culture of T-HESCs and HUVECs under controlled shear stress, 2) to measure the cytokines secretion (IL-8) after exposure to lipopolysaccharides (LPS) for 24 hours, using enzyme-linked immunosorbent assay (ELISA). Cell morphology of stimulated cells was visualized by ActinGreenTM and Hoechst-nuclei staining.

Results & Discussion

The microfluidic device allows to directly visualize morphological changes during cell growth and potential effects of infection. From the comparison with conventional cell culture 96-well plates, no significant difference was observed in terms of cell morphology and vitality. LPS stimulation did not affect cell morphology and proliferation. THESCs shown a tenfold increase in IL-8 secretion ($2433.54 \pm 281 \text{ pg/ml}$) at 24 hours after LPS stimulation. Following the same stimulation with LPS, HUVECs produced slightly less IL-8 ($1314.07 \pm 206.54 \text{ pg/ml}$) than THESCs, exhibiting a threefold increase secretion with respect to the control. Further experiments involving different cytokines and larger sample size are needed for confirming the findings of this study.

Conclusion

Our results demonstrated the use of a microfluidic device for analysis of cytokines expression after bacterial stimulation. Novel platforms, such as microfluidic microphysiological system and life-on-a-chip models, provide novel insight to a comprehensive understanding about paracrine signalling and infection mechanisms that can trigger the initiation of Pre Term Birth³.

References

1. Gnecco JS, Pensabene V., Li DJ, et al. *Ann Biomed Eng*, 2017; 45: 1758
2. Peltier MR, *Reprod Biol Endocrinol*. 2003; 1: 122.
3. Gnecco JS, Anders AP, Cliffler D, Pensabene V, et al. *Curr Pharm Des* 2017; 23(40):6115-6124.

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Medicines Discovery Catapult – At the Heart of Drug Discovery

M. Haddrick¹, S. Price ¹, P. Simpson ¹

¹ *Medicines Discovery Catapult, Block 35, Alderley Park, Cheshire, SK10 4TG.*

Introduction

Drug discovery may take up to 10-15 years to deliver a drug to market with an estimated cost of £1.2bn. Despite unprecedented development and access to innovative technologies, traditional Pharma-based drug discovery success and productivity rates continue to decline (1).

The Medicines Discovery Catapult (MDC), funded by Innovate UK, is a newly-established national centre with a remit to work in the pre-clinical and pre-competitive medicines discovery space, to help drive cross-sectoral collaborations of charitable, public and private sector organisations to discover and prove new medicines more effectively. Through collaborative programmes of R&D we are aiming to tackle the most challenging issues in drug discovery, addressing systemic problems and bottlenecks, and using innovative technologies to enable “fast-to-patient” medicines discovery.

MDC is particularly interested in novel human-based cell models and associated technological breakthroughs that might radically transform the drug discovery process and improve clinical success. The MDC is committed to co-develop predictive, representative humanised model systems exploiting the latest in stem cells, co-cultures and primary cells in 3D configurations with and without scaffold supports. In addition to isolated cell models, we have established organ on a chip technology within our laboratories. This enables multi-organ microphysiological systems approach for target validation, drug efficacy, drug delivery or toxicity studies. In parallel, MDC has invested in leading edge detection technologies that are accessible to the community to exhaustively characterise cell systems and support drug projects. Mass spectrometry and mass spec imaging, Nanostring, digital droplet PCR and the capability to identify novel biomarkers are operational in our laboratories alongside support from expert scientists

Conclusion

At the MDC we aim to help UK SME biotechs, academics and innovators have access to the laboratory facilities, knowledge, data, technologies and networks they need to be able to progress their programmes of medicines research and development. Our objective is to work collaboratively as part of a patient centric disease syndicates to bring new proven therapies to patients faster and more cost-effectively.

References

1. State of the nation report. MDC and BioIndustry Association.
<https://md.catapult.org.uk/report-state-of-the-discovery-nation-2018>
 #SODNReport18

BioMedEng18

Employing an *in-vitro* differentiated co-culture model of human bronchial epithelium to study cytotoxicity of e-cigarette aerosols

Pranav Vasanthi Bathrinarayanan¹, James E.P Brown^{2,3}, Lindsay J Marshall⁴, Laura J Leslie¹

¹ Aston Institute of Materials Research, School of Engineering and Applied Science, Aston University, Birmingham. B4 7ET. ² School of Life and Health Sciences, Aston University, Birmingham. B4 7ET. ³ Aston Medical Research Institute, Aston University, Birmingham. B4 7ET. ⁴ Research and Toxicology Department, Humane Society International, 5, Underwood Street, London. N1 7JQ.

Introduction

Although ECs have been widely promoted as a safer alternative to tobacco cigarettes, limited scientific data is currently available on their potential health effects. One possible reason for this is the lack of a standardised testing method which leads to conflicting experimental data. Factors such as the chosen cell model and EC exposure methodology determine the physiological relevance and potentially the outcome of any EC study. The current study aims to investigate the effects of EC aerosols delivered using a novel aerosol delivery system to a physiologically relevant *in-vitro* 3D differentiated co-culture model of human bronchial epithelium.

Methods

Human bronchial epithelial cell line CALU 3 and human pulmonary fibroblasts cell line MRC-5 were co-cultured together at air-liquid interface on permeable membranes for 11-14 days. Additionally, a bespoke, automated smoking machine was designed and built in-house in order to deliver whole cigarette smoke (WCS) or EC vapour (ECV) to the co-culture model in a controlled fashion mimicking the human smoking behaviour as per the ISO:3308 standard smoking regime. WCS and ECV effects were initially investigated for 7 min although ECV was further investigated at extended exposure times (1 h – 6 h) considering the prolonged vaping habits of EC users. 24 h post exposure, cell viability, pro-inflammatory IL-6/IL-8 mediators' release, oxidative stress and caspase 3/7 activity were analysed.

Results & Discussion

XTT assay results showed that while WCS caused a significant reduction in cell viability post 7 min exposure, neither air nor ECV demonstrated any effect compared to the untreated cells. During extended exposure, results revealed that ≥ 3 h ECV exposure caused a significant increase in oxidative stress and elevated IL-6/IL-8 production, both of which are hallmark characteristics of airway inflammatory conditions like COPD. Further, although a significant reduction in cell viability was observed, ECV exposure had no impact on caspase 3/7 release, thus suggesting that ECV induced cell death could ensue in a caspase in-dependent fashion.

Conclusion

Overall, results from the current study suggest that ECs have the potential to cause substantial airways damage and as yet, cannot be regarded as safe alternatives to tobacco cigarettes. In order to test ECs more robustly, a standardised test method must be established.

Acknowledgments

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Alzheimer's patients induced pluripotent stem cells form 3D mature neural cultures to model biochemical aspects of the disease pathology

E.J. Siney¹, P. Prasannan^{1*}, S. Chatterjee^{2*}, K. Kurbatskaya²,
A. Mudher², **S. Willaime-Morawek¹**

¹Faculty of Medicine, University of Southampton.UK, ²Centre for Biological Sciences, University of Southampton.UK,
*Authors contributed equally

Introduction

Alzheimer's Disease (AD) is the leading cause of dementia and with a population of increasing longevity is set to become a major burden on health services. Currently human tissue from AD cases is only available for research from post mortem brain but we can now utilise iPSC technology to obtain neural stem cells from AD patients with the aim to produce mature neurons with the same genetic signature of AD patients.

Methods

Using induced Pluripotent Stem Cells (iPSCs) from early onset AD patients containing Presenilin-1 mutations or from healthy aged-matched controls, we have created a 3D human neural culture system for the study of some early onset Alzheimer's disease mechanisms. Using immunofluorescence, western blotting and electrophysiology we have characterised neuronal function, morphology and maturity and disease-protein profiles.

Results & Discussion

Neural progenitors derived from AD iPSCs (Axol Biosciences) were plated in matrigel and self-organised into 3D structures by week 3. These cultures contained a heterogeneous cell population expressing differentiation markers for neurons (MAP2) and astrocytes (GFAP) and importantly AD-associated proteins, amyloid precursor protein/Abeta and tau. These 3D cultures were maintained *in vitro* for 18+ weeks. 3R-foetal tau isoforms were expressed at 6 weeks while 4R-adult tau isoforms were seen at 18 weeks. Abeta oligomers were present in the cultures by week 6 and neurons exhibited repetitive firing by week 12. Together these results suggest the presence of astrocytes and mature neurons within these cultures and the expression of pathology-associated proteins.

Conclusion

We have created 3D mature neural cultures derived from AD patients to study mechanisms of the disease pathology in a human cell model. This is a viable new *in vitro* 3D neural model for the study of neuropathology, which can serve as a powerful new translational tool in this area of research.

Acknowledgments

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Recapitulation of human airways through the development of a novel *in vitro* 'lung on chip'

J. Fernandes¹, N. Karra¹, J. James², R. Reale¹, D. Davies², E. Swindle², H. Morgan¹

¹ Electronics and Computer Science, Faculty of Physical Sciences and Engineering, University of Southampton. ² Academic Unit of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, UK.

Introduction

Respiratory diseases account for approx. 1 million deaths per annum worldwide with mortality rates predicted to remain constant for another decade¹. Producing successful respiratory disease treatments is both costly and lengthy due to the current models used to mimic human specific diseases such as Asthma. Failure in late preclinical to clinical trials is mostly due to a lack of efficacy and safety, inhibiting progress to market². To replace animal models and more accurately recapitulate the human *in-vivo* lung, we have developed a new 'Lung on Chip' technology based on a prototype system which uniquely enables measurement of trans-epithelial electrical resistance (TEER)³ and high resolution temporal analysis of mediator release⁴ from one side (liquid). The aim is to develop a microfluidic device integrating a "Plug and Play" biochip array.

Methods

The 'Lung on Chip' platform consists of two main components: the biochip and the microfluidic manifold. The biochip contains human bronchial epithelial cells (BECs) grown at air liquid interface (ALI) on a high porosity support membrane, with medium flowing below recapitulating interstitial flow, allowing long-term culture. TEER measurements are taken periodically to assess epithelial barrier formation and disruption after apical or basolateral challenges.

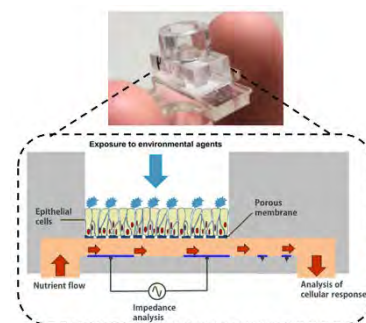


Figure 1: Lung on Chip

Results & Discussion

Human BECs grown at ALI in the 'Lung on Chip' microfluidic platform were polarised and showed a response to viral infection in a manner comparable to conventional static cultures. The integrated TEER capability has been used to monitor epithelial barrier formation and disruption after challenge. The device enables long-term culture BEC culture, apical and basolateral surface experimental challenges and analysis of key physiological, biochemical and phenotypic outputs.

Conclusion

The 'Lung on Chip' platform has the potential to improve and replace conventional static culture models and the ability to better recapitulate the *in vivo* human microenvironment. Ongoing research includes incorporation of additional real-time sensing modalities and the use of electrospun, biodegradable membranes and provides a scalable platform for compound screening and target discovery.

References

1. European Lung White Book (2013). *The burden of lung disease - ERS*. [online] Erswhitebook.org.
2. Barnes *et al.*, (2015). Barriers to new drug development in respiratory disease. *ERJ*. 45. 1197-207.
3. Tao *et al.*, (2010). On-chip epithelial barrier function assays using electrical impedance spectroscopy. *Lab on a Chip*. 10: 1611-1617
4. Blume *et al.*, (2016). Temporal monitoring of differentiated human AECs using microfluidics. *PLoSOne*. e0139872

Acknowledgments

This work is supported by EPSRC, BBSRC, GlaxoSmithKline Research and Development Ltd. and Innovate UK.

Analysing the Effects of the PNPLA3 I148M Variant in Hepatic Stellate Cells Using an Organ-on-Chip Model of Non-alcoholic Steatohepatitis

T.M. Kostrzewski¹, P. Maraver¹, A. Bray¹, K. Smith¹, K. Rombouts², D.J. Hughes¹

¹ CN Bio Innovations Ltd, Welwyn Garden City, Hertfordshire, AL6 9PU. ² University College London, Institute for Liver and Digestive Health, Royal Free Hospital, London, NW3 2QG.

Introduction

The single nucleotide polymorphism I148M in the gene encoding patatin-like phospholipase domain-containing 3 (PNPLA3), is strongly associated with adverse outcomes for patients with Non-alcoholic Steatohepatitis (NASH). PNPLA3 I148M has been associated with increased hepatic inflammation, steatosis and enhanced development and severity of liver fibrosis. The mutation has been shown to directly affect hepatocytes and their propensity to become steatotic and more recently PNPLA3 I148M has been shown to affect the fibrogenic phenotype of hepatic stellate cells (HSCs). HSC are the key players in extra cellular matrix deposition in the liver and primary I148M HSCs have been found to produce more inflammatory mediators and have a higher lipid droplet content.

Methods

The effects of this mutation in HSC have only been explored in isolation and are yet to be explored in a disease model of NASH. Using a fully human Organ-on-Chip NASH model, which comprises primary human hepatocytes (PHH), Kupffer (HK) and HSCs, we investigated how PNPLA3 I148M in HSCs influenced the development of NASH.

Results

PHH and HK were co-cultured in a 3D perfused platform with wild-type (WT) or I148M mutant HSCs. All cultures were performed in high fat steatotic conditions to induce a NASH phenotype. Inflammation in the model was analysed by Luminex cytokine arrays and gene expression RT profiler arrays and I148M HSCs were found to induce significantly increase production of key cytokines including IL-6. Soluble fibrotic markers (pro-collagen 1, YKL-40 and TIMP-1) and pro-fibrotic gene expression profiles were analysed and a pro-fibrotic phenotype was observed in all conditions, but it was highest in cultures with I148M HSCs (e.g. smooth muscle actin increased up to 3-fold).

Discussion

This study further validates the effect the I148M polymorphism on HSC and for the first time directly demonstrates how the NASH disease phenotype can be directly affected by the enhanced activity of I148M HSCs. It also shows how advanced Organ-on-Chip models are well suited for analysing the molecular mechanism that underly human diseases and for creating disease models with specific genetic backgrounds.

Acknowledgments

This work was supported by a grant from Innovate UK (Technology Strategy Board), Ref: 131720; for the development and adoption of non-animal technologies.

Comparison of Aortic Hemodynamics between Surgical Aortic Valve Replacement (SAVR) and TAVI

S. Pirola¹, O.A. Jarral², M.Y. Salmasi², Z. Cheng¹, D.P. O'Regan³, T. Athanasiou², X.Y. Xu¹

¹Department of Chemical Engineering, Imperial College, SW7 2AZ, London. ²Department of Surgery and Cancer, St. Mary's Hospital, W2 1NY, London. ³Royal Brompton and Harefield NHS Foundation Trust, SW3 6NP, London.

Introduction

The treatment of aortic valve (AV) disease with SAVR and transcatheter AV implantation (TAVI) have proven prognostic and survival benefits. However, studies show that normal native valve haemodynamics are often not restored. The aim of this study was to investigate and compare the effect of different AV replacement procedures on the aortic haemodynamics by means of computational fluid dynamics (CFD).

Methods

Magnetic resonance images of a healthy subject (HV) and of four patients (P1-P4) presenting prosthetic AVs were used to reconstruct patient-specific 3D aortic geometries. P1-P2 had their AVs surgically replaced with mechanical and biological valves, respectively; P3 underwent mechanical valve and graft-conduit implantation, while P4 had a TAVI. 3D patient-specific time-varying velocity profiles were imposed at the model inlet, whilst Windkessel models were used at the outlets.

Results & Discussion

In comparison with pre-operative data, our results showed that SAVR and TAVI improve aortic haemodynamics, with lower velocities and wall shear stress (WSS). Despite this, we found higher velocity and WSS values in P1-P3 compared to HV, while TAVI well compared with HV's haemodynamics (Fig. 1). Further flow-specific features were strongly dependent on the implanted valve, as will be discussed.

Conclusions

Although SAVR and TAVI could lead to better aortic haemodynamics, this is still different to that of healthy native valves. Larger group studies will ascertain the clinical implications of these differences.

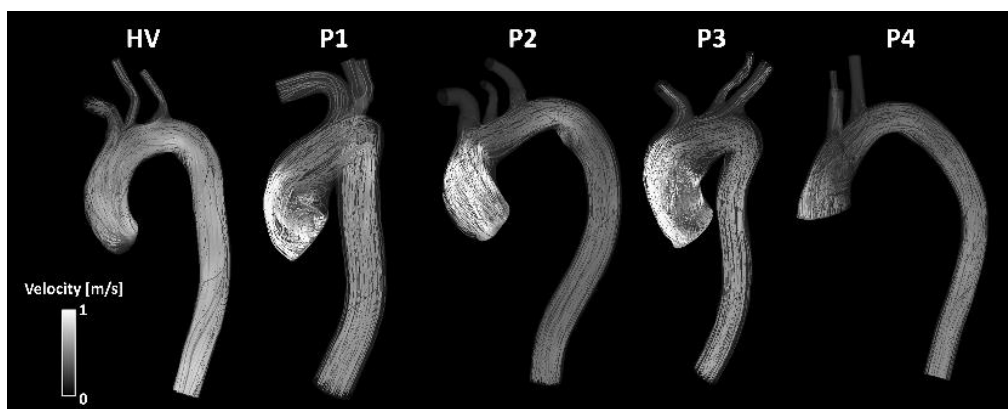


Figure 1: Comparison of flow patterns among all studied subjects

Acknowledgments

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Statistical Shape Modelling of the Pregnant Abdomen

G.L. Stiles¹, C. Knight², J. Matthew³, A. Gomez¹, Y. Noh¹, K. Rhode, J. Housden¹

¹ School of Biomedical Engineering and Imaging Sciences, King's College London, UK. ² Division of Women's Health, King's College London, Fetal Medicine Unit, Guy's & St Thomas' NHS Foundation Trust, Women's Health Academic Centre, King's Health Partners, London, UK. ³ Women's Ultrasound, Guy's & St Thomas' NHS Foundation Trust, London, UK.

Introduction

Statistical shape modelling of human organs is valuable for determining average shape and patterns of variation among subjects [1]. Here, we aim to model the shape variations of the abdomens of pregnant women encountered during fetal anomaly ultrasound scans [2], with the aim of developing more automatic patient-specific scanning.

Methods

Surface shape data of 52 patients were acquired using an NDI Aurora tracking device attached to an ultrasound probe during fetal anomaly scanning. An ellipsoid was fitted to the tracked data and cropped to the region of the measured surface. Statistical shape modelling produced the mean shape and the modes of variation. 43 of the patients had data for height, weight, body mass index, gestational age and girth at time of scan. Pearson's correlation coefficients were calculated between each variable and each of the 4 most significant modes of variation.

Results & Discussion

The main modes of variation are shown in Figure 1. The shape model indicates that the primary mode of variation is simply the height of the scanned surface above the bed, while the second most significant variation is the abdominal width. Individual modes had only small correlations with most of the surrogate parameters; the largest values of correlation coefficient were found to be -0.4860 for patient girth and -0.4097 for patient BMI both with the 4th mode of variation.

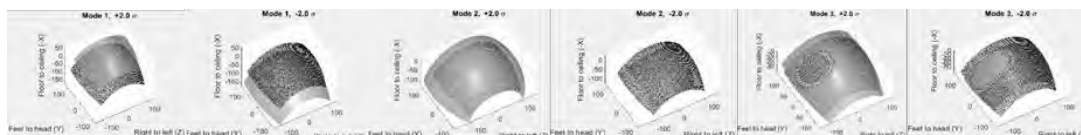


Figure 1 First three modes of variation at +/- 2SD

Conclusion

We have produced a statistical description of the shape of the scanned regions of pregnant abdomens encountered during fetal ultrasound scans. This model may be useful for developing automated scanning techniques specific to individual patients. However, the low correlations with simply measured parameters suggest that these cannot be used to directly predict the shape.

References

1. Heimann T, Meinzer H. Statistical Shape Models for 3D medical image segmentation: A review. *Medical Image Analysis*. 2009;13(4): 543-563.
2. Morris J ed. *Congenital Anomaly Statistics 2012, England and Wales*. British Isles Network of Congenital Anomaly Register (BINOCAR). Report number: 4, 2014.

Acknowledgments

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Patient-specific pituitary phantoms for ultrasound imaging: Development and early validation

D. I. Nikitichev¹, S. Mendes ¹, R. Delaunay ¹, S. Ourselin ², N. L. Dorward ³,
H. J. Marcus ³, T. Vercauteren ¹

¹ Medical Physics and Biomedical Engineering Department, University College London, WC1E 6BT, London. ²National The School of Biomedical Engineering and Imaging Sciences, King's College London, WC2R 2LS, London. ³National Hospital for Neurology and Neurosurgery, Queen Square, WC1N 3BG, London.

Introduction

Pituitary adenomas are among the most common brain tumours. In most cases, transsphenoidal surgery is the treatment of choice, in which the brain is accessed through the nose. Although technological innovations such endoscopy have improved outcomes, some pituitary adenomas remain difficult to cure, and approximately a third of patients will have an incomplete resection. The clinical corollary is that imaging techniques that improve intraoperative visualisation and identification of tumour tissue and related neurovascular structures will further improve the effectiveness and safety of surgery. Intraoperative ultrasound has been proposed as a relatively inexpensive and simple imaging technique that provides important structural information in real time [1, 2]. In order to better evaluate ultrasound devices designed for pituitary surgery, and to allow for training of surgeons using such devices, we have developed a patient-specific pituitary phantom for ultrasound imaging.

Methods

The phantom consisted of a skull and important soft tissues including the pituitary gland, carotid arteries, and optic chiasm. The skull was developed from segmented CT images using several freely available 3D-modelling software programs including Seg3D, MeshLab and MeshMixer. The model was created using an extruded thermo-plastic polymer 3D printer (Ultimaker) with a layer height of 0.12 mm and a shell, bottom, and top thickness of 0.8 with a nozzle size of 0.4 mm. The material used for printing was polylactic acid (PLA). Soft tissues were developed from segmented MRI images and 3D printed using recently developed technology using tissue-mimicking Gel Wax material that was mixed with glass microspheres to change its acoustic properties. Early validation of the phantom was by a neurosurgeon using a prototype ultrasound device specifically designed for pituitary surgery.

Results

A patient-specific pituitary phantom for ultrasound imaging was feasible using segmented CT and MRI images. Early validation demonstrated that the phantom had face and content validity.

Conclusion

The development of a pituitary phantom using patient imaging allowed for anatomically accuracy, and the use of gel wax for soft tissues allowed for realistic properties for ultrasound imaging. Moreover, in future different sizes and types of pituitary adenoma to be printed, thus allowing for phantom optimisation and customizability.

References

1. Freudenrich CC. How Ultrasound Works. 2017
2. Marcus HJ et al. World Neurosurgery, 106:680-685 2017

Acknowledgments

The work was supported by Wellcome/EPSRC [203145Z/16/Z; NS/A000050/1; EP/L016478/1; EP/R511638/1; EP/M020533/1, EP/L016478/1].

fMRI Neurofeedback for Treatment of Phantom Pain

S.M.H. Al-Wasity^{1,2}, **A.Vuckovic**¹, F. Pollick

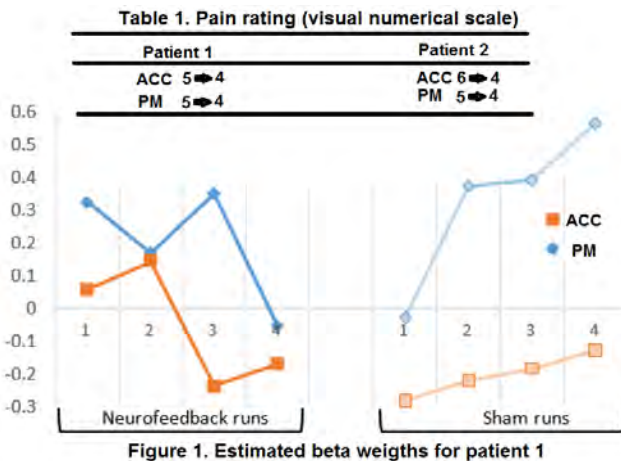
¹ School of Engineering, James Watt (South) building, University of Glasgow, G12 8QQ, Glasgow ² College of Engineering, Wasit University, Wasit, Iraq, ³ School of Psychology, Hillhead Street, G12 8QB University of Glasgow,

Introduction

Phantom pain is related to the reorganisation of the sensory-motor cortex following amputation¹. fMRI neurofeedback (NF) is a technique that enables voluntary control of brain activity, and has previously been used to treat chronic pain of mixed aetiology². In this study we test feasibility of fMRI for reduction of phantom limb pain.

Methods

Participants: Two male right arm amputee (age 50 and 55) with intermittent shooting phantom pain took part in two daily sessions. Each session consisted of training from a pain related region of interest (ROI) and sham training from the left auditory cortex ROI. On the first session the pain related ROI was premotor cortex (PM) identified by imagined phantom limb movement and ROI at rACC, taken from the literature². **Experimental setup:** Data from 3T Siemens Tim Trio MRI scanner were collected by hosted software PC and sent it to another PC for real time analysis in Turbo-Brain Voyager (Brain Innovation, the Netherlands) and NF visualisation in BrainStim software. Each daily session consisted of 9 downregulating blocks (30s each) from a pre-selected ROI, interleaved by 10 blocks of rest (16s each) for NF and sham training each.



Results & Discussion

A linear regression of beta weights over training sub-sessions (Fig 1) indicated that patients successfully learned to downregulate brain activity during NF but not during sham sessions. Table 1 shows slight reduction of pain after NF from PM and ACC ROI.

Conclusion

People can learn to downregulate PM and rACC during one training session but more patients with pain present at the time of NF are needed to make conclusions about the efficacy of the treatment.

References

1. Flor H, Nikolajsen L, Staehelin Jensen T. *Nat Rev Neurosci.* 2006; 7:873-81
2. deCharms RC, et al. *Proc Natl Acad Sci U S A.* 2005; 102:18626-31..

Acknowledgments

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Classifying Cognitive Recovery after Stroke

Rosalía Dacosta-Aguayo¹, Tibor Auer², Christian Stephan-Otto³ and Manousos A. Klados⁴

¹Department of Clinical Psychology and Psychobiology, University Barcelona. ²Department of Psychology, Royal Holloway University of London, UK. ³Institut de Recerca Sant Joan de Deu, Esplugues de Llobregat ⁴Department of Biomedical Engineering, School of Life and Health Sciences, Aston University, Birmingham, B4 7ET.

Introduction

Acute ischemic stroke is the second most common cause of death worldwide and a major cause of disability in older adults [1]. However, the mechanisms related to a better or a worse cognitive recovery are still not fully understood. The main objective of this study is to examine whether structural connectivity combined with neurophysiological assessment can be used as a tool to classify cognitive recovery after stroke.

Methods

We performed a longitudinal study of 25 consecutive subjects that had suffered a first ischemic stroke. Stroke patients received neuropsychological assessment both within 72 hours after admission (baseline) and at three months. MRI acquisition including diffusion-weighted imaging was performed at three months post-stroke. Patients were grouped into two groups: the stroke group with good (SG, n=12) and with poor (SP, n=13) cognitive recovery. Labelling was based on an improvement of at least 1.5 SD in at least three cognitive tests at three months in comparison to the corresponding baseline scores. Probabilistic tractography was performed using FSL's probtrackx (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT/UserGuide>) [2]. Diffusion connectome was estimated based on the Automated Anatomical Labeling (AAL) [3]. Two matrices with equal number of rows (25; one row per subject) were formed. The first matrix had size 25×380 (connections), while the second matrix had size 25×23 (neuropsychological tests), with each column as a feature. After applying a feature selection algorithm, using the Best-First search method, the selected features were imported to Auto-WEKA [4]. Validation was performed by 5-folds cross validation.

Results & Discussion

At three months after stroke, there was no significant difference between the two groups either in demographic or in clinical characteristics, highlighting that the progress of their cognitive recovery was independent from the aforementioned characteristics. We were able to classify cognitive recovery with 85.18% of accuracy, having 100% sensitivity, 78% specificity and 66% precision based on the diffusion connectome features. The feature that drove the classification was a single distinguishing connection (difference in the probability of connectivity) between the left Superior Parietal Gyrus (SPG) and the left Angular Gyrus (AG), which we also saw in our previous study [5].

Conclusion

Classification of cognitive recovery in stroke is a research area of increasing interest. Finding an accurate model for the classification of cognitive recovery allows us an early detection of the patients that will need cognitive rehabilitation at early stages of stroke.

Limitations and future directions

Due to the small sample size and the fact that we only had MRI at three months (post-hoc design), we can only state that the brains are different between the two groups after three months of recovery. Further studies are required to confirm whether the difference is an innate predictor of good recovery or rather indicate areas more affected by stroke recovery. Our plan is to fuse the two aforementioned feature sets, using PCA or Latent Variable models in order to elaborate the model describing the stroke recovery and potentially increase the classification performance.

References (examples – use “First author *et al.*” if more than 3 authors, minimum font size 9pt)

1. P. B. Gorelick et al., “Vascular Contributions to Cognitive Impairment and Dementia A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association,” *Stroke*, vol. 42, no. 9, pp. 2672–2713, 2011.
2. Behrens TE, et al., Probabilistic diffusion tractography with multiple fibre orientations: what can we gain? *Neuroimage* 34:144 –155, 2007.
3. N. Tzourio-Mazoyer et al., “Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain.” *Neuroimage*, vol. 15, no. 1, pp. 273–289, 2002.
4. Eibe Frank, Mark A. Hall, and Ian H. Witten. The WEKA Workbench. Online Appendix for “Data Mining: Practical Machine Learning Tools and Techniques”, Morgan Kaufmann, Fourth Edition, 2016
5. Dacosta-Aguayo, R., Stephan-Otto, C., Auer, T., et. al (2017). Predicting Cognitive Recovery of Stroke Patients from the Structural MRI Connectome Using a Naïve Bayesian Tree Classifier. In 2017 IEEE 30th International Symposium on Computer-Based Medical Systems (CBMS) (pp. 413–418). IE

BioMedEng18

3D printed probes with optically-generated ultrasound for high-resolution imaging during minimally invasive procedures

R. Caulfield^{1,2}, S. Aabith¹, R. Colchester², S. Noimark², A.L. David³, I. Papakonstantinou⁴, A. Desjardins^{2,5}, M.K. Tiwari^{1,5}

¹Nanoengineered Systems Laboratory, UCL Mechanical Engineering, Roberts Building, WC1E 7JE, London. ²UCL Medical Physics and Biomedical Engineering, Malet Place, WC1E 6BT, London. ³UCL EGA Institute for Women's Health, Medical School Building, WC1E 6AU, London. ⁴UCL Electronic and Electrical Engineering, Roberts Building, WC1E 7JE, London. ⁵Wellcome/EPSCRC Centre for Interventional and Surgical Sciences, University College London, Charles Bell House, W1W 7TS, London.

Introduction

Despite the many benefits and advances of minimally invasive fetal surgeries there is still an associated risk of iatrogenic preterm premature rupture of membranes (iPPROM) leading to preterm births. The risk of iPPROM is related to the size and number of operating ports^[1]. It is proposed that by creating miniaturised ultrasound imaging probes the diameter and amount of operating ports required can be reduced, and thus improve neonatal outcome after fetal surgery.

Methods

To construct miniaturised ultrasound imaging probes, the photoacoustic effect is used to create laser generated ultrasound^[2]. By generating ultrasound optically, the constraints traditionally associated with constructing miniaturised ultrasound transducers are avoided (eg. cross talk and cutting micron sized piezoelectric elements). In this work high-resolution 3D printing is utilised to deposit photoacoustic material on the end face of optical fibres. High-resolution 3D printing allows the material to be deposited in patterns to give lens-like structures capable of focusing the generated ultrasound beam and enabling higher resolution ultrasound images.

Results & Discussion

Printable photoacoustic materials have been developed and used to print microstructures on the tips of optical fibres. Acoustic hologram designs^[3] have been used to create lens-like structures capable of focusing ultrasound. Nanocomposites of gold nanoparticles and polydimethylsiloxane (PDMS)^[4] have been exploited to create selectively absorbing microstructures. By employing selective absorption, probes with both imaging and therapeutic capabilities can be designed. At resonant wavelength absorption is high and ultrasound can be generated but away from resonance light is transmitted and can be used therapeutically.

Conclusion

The demonstrated control in the deposition and structuring of photoacoustic materials on the tips of optical fibres opens the door to truly miniaturised ultrasound imaging probes. The use of lens-like structures would enable focused ultrasound and higher resolution images intra-operatively. Selectively absorbing microstructures also allow for multi-capability probes to be developed.

References

1. Beck et al. *Fetal Diagnosis and Therapy*, 2012; 31:1–9.
2. Colchester et al. *Biomedical Optics Express*, 2015, Vol. 6, No. 4, 1502-1511.
3. Brown et al. *IEEE International Ultrasonics Symposium*, 2014, pp.1037–1040.
4. Noimark et al. *Advanced Functional Materials*, 2018, 28, 1704919.

Acknowledgments

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Synthetic Aperture Imaging and Therapy with Random Phased Arrays

Muhammad Zubair, Robert J. Dickinson

Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

Randomized phased arrays have been used for generating and steering single focus and multiple foci with low levels of grating lobes due to the breakage of periodicity of the elements and are considered as useful source of HIFU. However, the reliance of HIFU on MRI for real time visualization of the targeted tissue is a major constraint in its clinical use due to the high cost of MRI and its low temporal resolution. There is a need to study the imaging capabilities of a therapeutic random phased array transducer for guiding the treatment process.

Methods

Dual mode random phased arrays would have the advantage of using the same array for both therapy and imaging due to the inherent registration between imaging and therapeutic frames of reference. Since strong scattering objects in path of HIFU beam are also in path of imaging beam, such scattering objects can be detected in real time and the HIFU beam can be adjusted accordingly. In our HIFU system the elements are randomly distributed with inter-element spacing much more than the required half a wavelength for reduced side lobes (Hand et. al. 2009), thus the spatial resolution of this system is poor. However, we use synthetic aperture imaging technique which has the potential to improve the spatial resolution of the random phased array. The simulations were carried out in MATLAB. The numerical and experimental results were performed for a 1 MHz 256-element random phased array, made by Acublate Ltd, London, UK and Verasonics system. Simultaneous foci were generated in simulations as well as experimentally based on the theory described by Gavrilov and Hand (2000a).

Results & Discussion

Four simultaneous foci were generated at the geometric focus of the array as shown in fig.1. In fig.2, grey scale simulated image of a wire target array is shown. The array was integrated with the verasonics system to acquire raw data. Three metallic balls of diameter 7mm immersed in water bath with lateral and axial spacing of 10 mm were imaged with only 50 active elements from one of the four quadrants of the array and is shown in fig. 3. Initial results suggest that Synthetic Aperture Imaging has the potential to acquire images with a therapeutic phased array.

Conclusion

Simulation and experimental results show that with synthetic aperture imaging algorithms we can do both imaging and therapy simultaneously using the same random phased array.

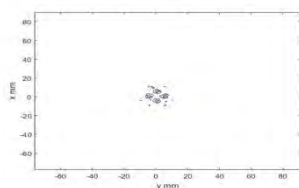


Fig 1: Multiple simultaneous foci

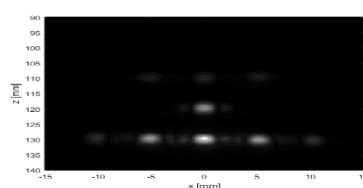


Fig 2: Simulated image of wire phantom



Fig 3: Experimental image of ball targets

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Site-specific changes in bone in a rat model of spinal cord injury

J.A. Williams¹, J.F.C. Windmill², K.E. Tanner³, J.S.Riddell⁴ & S.Coupaud¹

¹ Dept. Biomedical Engineering, Wolfson Building, University of Strathclyde (UoS), Glasgow, G4 0NW. ² Dept. Electronic & Electrical Engineering, Royal College, UoS, G1 1XW. ³ Dept. Biomedical Engineering, James Watt South, University of Glasgow (UoG), G12 8QQ. ⁴ Institute of Neuroscience and Psychology, School of Life Sciences, UoG, G12 8QQ.

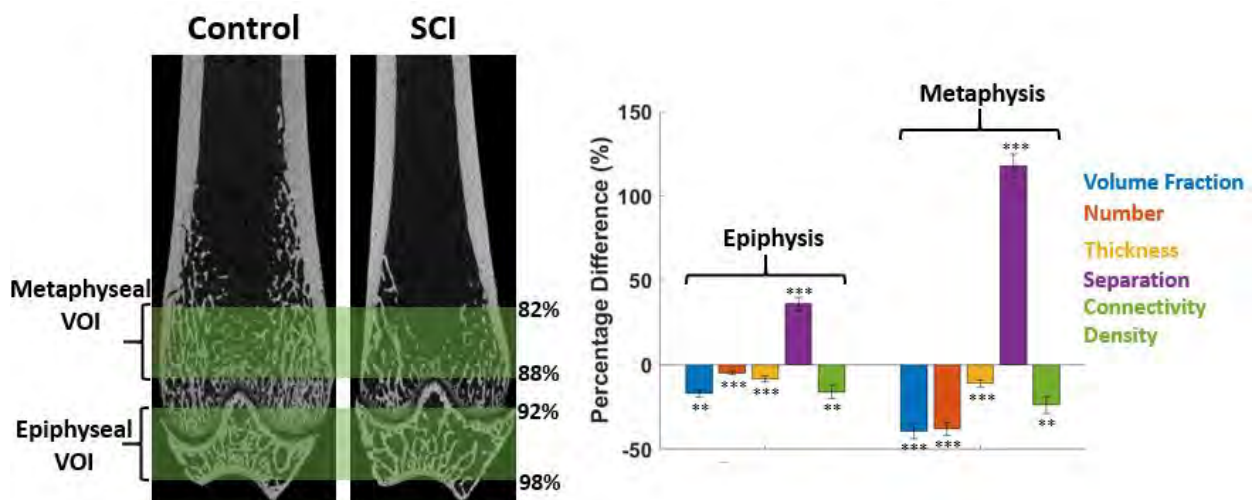
Introduction

The trabecular-rich distal femur and proximal tibia (knee area) are highly vulnerable to fracture post spinal cord injury (SCI)¹. This study describes the site-specific micro-architectural changes that occur within two trabecular bone compartments (epiphysis and metaphysis) within the distal femur of a rat model of SCI-related disuse osteoporosis. Studying this model will improve or understanding of bone loss in patients with SCI, which arises from the removal of muscle-driven bone stimulation.

Methods

Twelve ten-week old male Wistar rats were randomly assigned in to two groups. One group was given a transection of the spinal cord at thoracic level T9 (n=6), the other group were sham-operated (n=6). ten weeks post-surgery the right distal femurs were micro-Computed Tomography scanned *ex vivo* at 6.89 μm . The trabecular morphometric parameters analysed were the average trabecular bone volume fraction, number, thickness, separation, and connectivity density.

Results



Conclusion

SCI compromises trabecular bone quantity and quality throughout the distal femur in a site-specific manner. Techniques developed here could be translated into image analysis protocols in patients and may assist in identifying regions of long bones that are structurally weaker, to inform design of targeted interventions.

References

1. Cirnigliaro CM., et al. *Osteoporosis International*, 2017; 28(3): 747 - 765.

Acknowledgments

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Extracting Features From Confluent Cellular Sheets

G. Ronteix, T. Savin

Engineering Department, Cambridge University, Cambridge, CB2 1PZ.

Introduction

Collective cell motion is an important component of organogenesis, but also of other processes such as wound healing or cancer. This complex behavior calls for understanding the influence of inter-cellular interactions as well as the intrinsic properties of cell movement. Thus, being able to follow cells in confluent cellular sheets undergoing collective motion is of great interest.

Methods

The image analysis method rests upon two consecutive steps that are a segmentation procedure we developed and then a cleaning process in order to sort out the features detected in the main image.

The first step revolves around the “watershed algorithm” to recognize cells. We then sort out results in order to improve the accuracy and eliminate false positives. We then link cells detected in different frames together using methods borrowed from the Crocker and Grier algorithm [1] and the Gale Shapley algorithm.

Results & Discussion

Automatically extracting cell trajectories has been done before [2], but our new methods allows us to access new variables such as cell size, shape and orientation, even in confluent cellular sheets. These insights enable us to better understand the collective cell dynamics involved.

Our initial work focuses on the collective behavior of gliomablastoma cells. Thanks to the information gathered by our technique, we offer additional and complimentary insights to the results obtained in previous studies [3].

Conclusion

New image treatment techniques open up numerous opportunities to better understand complex behaviors such as collective cell movement. Thanks to the algorithm developed we can link purely dynamical variables such as cell velocity with qualitative ones such as cell shape.

References

1. Crocker, John C., and David G. Grier. "Methods of digital video microscopy for colloidal studies." *Journal of Colloid and Interface Science* 179: 298-310 (1996).
2. Meijering, Erik, Oleh Dzyubachyk, and Ihor Smal. "Methods for cell and particle tracking." *Methods in Enzymology*. Vol. 504: 183-200 Academic Press, 2012.
3. Hegedüs, Balás, et al. "Locomotion and proliferation of glioblastoma cells in vitro: statistical evaluation of videomicroscopic observations." *Journal of Neurosurgery* 92: 428-434 (2000).

Acknowledgments

We thank Agavi Stavropoulou-Tatla and Athina Markaki for providing us with the images of the gliomablastoma cells.

Measuring blood flow and wall shear stress in vivo using ultrasound imaging velocimetry with native blood speckle or microbubble contrast agents

K Riemer, E M Rowland, C H Leow, M-X Tang, P D Weinberg

Department of Bioengineering, Imperial College London, London SW7 2AZ, U.K

Introduction

A wide range of cardiovascular diseases manifest themselves with, or develop as a result of, abnormalities in blood flow and wall shear stress (WSS) [1]. Contrast-enhanced ultrasound (CEUS) imaging velocimetry can be used to assess the spatiotemporally varying magnitude of near wall flow and WSS *in vitro* [2]. However, the need for contrast agent might restrict the use of ultrasound imaging velocimetry (UIV) for general health screening due to constraints on time, cost and discomfort. The efficacy of non-contrast UIV using the speckle pattern of blood-mimicking Orgasol has been demonstrated in vitro [3]. This study compares the near-wall tracking of microbubble contrast agent (CEUS) or native blood speckle (NBS) for the assessment of blood flow and wall shear stress in the rabbit abdominal aorta.

Methods

A Verasonics Vantage 64 LE research ultrasound system with a L11-4v broadband probe was used to image the abdominal aorta of a male New Zealand White rabbit. Images were acquired with either a B-Mode or a Pulse Inversion (PI) transmit sequence with a pulse repetition frequency between 1500-7500Hz. Up to five plane waves with angles spanning 12° were transmitted. The transmit frequency was between 3-5MHz or 6-10MHz for PI and B-Mode respectively; MI was between 0.05-0.15. Post-acquisition, the blood signal was extracted from the radiofrequency data through spatial similarity thresholding of an adaptive SVD clutter filter [4]. In addition, microbubble contrast agent (6-25µl/kg) was injected as a bolus via the marginal ear vein. Vessel tracking was semi-automated using a simple cross-correlation method. NBS measurements were performed before CEUS. Experiments complied with Animals (Scientific Procedures) Act 1986 and were approved by the Animal Welfare and Ethical Review Body of Imperial College London.

Results & Discussion

Tracking of NBS or contrast agent delivered similar results for velocity and shear rate but NBS gave significantly lower SNR ratios. Semi-automated vessel tracking is more robust for B-Mode acquisitions than for PI but equally accurate for CEUS and NBS. Differences between CEUS and NBS can be attributed to initial uncertainties in wall location and to out-of-plane motion.

Conclusion

We demonstrated that both CEUS or NBS can be used for shear rate measurements in the simple geometry of the rabbit abdominal aorta. More complex flow regions will be examined in the future.

References

- [1] D. De Wilde, B. Trachet, G. R. Y. De Meyer, and P. Segers, "Shear Stress Metrics and Their Relation to Atherosclerosis: An In Vivo Follow-up Study in Atherosclerotic Mice," *Ann. Biomed. Eng.*, vol. 44, no. 8, pp. 2327–2338, 2016.
- [2] C. H. Leow and M. X. Tang, "Spatio-Temporal Flow and Wall Shear Stress Mapping Based on Incoherent Ensemble-Correlation of Ultrafast Contrast Enhanced Ultrasound Images," *Ultrasound Med. Biol.*, no. i, 2017.
- [3] J. Voornveld *et al.*, "Native blood speckle vs ultrasound contrast agent for particle image velocimetry with ultrafast ultrasound - in vitro experiments," *IEEE Int. Ultrason. Symp. IUS*, vol. 2016–Novem, no. Imd, pp. 3–6, 2016.
- [4] J. Baranger, B. Arnal, F. Perren, O. Baud, M. Tanter, and C. Demene, "Adaptive spatiotemporal SVD clutter filtering for Ultrafast Doppler Imaging using similarity of spatial singular vectors," *IEEE Trans. Med. Imaging*, vol. 62, no. c, 2018.

Acknowledgments

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Ultrasound and Microscopic Imaging of Nanodroplet Adhesion to Endothelial Cells under Atheroprone Flow Conditions

Ge Zhang^{1,*}, Kuin T. Pang^{1,2,*}, Mean Ghim¹, Peter D. Weinberg¹, Meng-Xing Tang¹

¹Department of Bioengineering, Imperial College London, London, UK, SW7 2AZ, United Kingdom

²Institute of Molecular and Cell Biology, Agency for Science, Technology and Research (A*STAR), Singapore

* These authors contributed equally to this work

Introduction

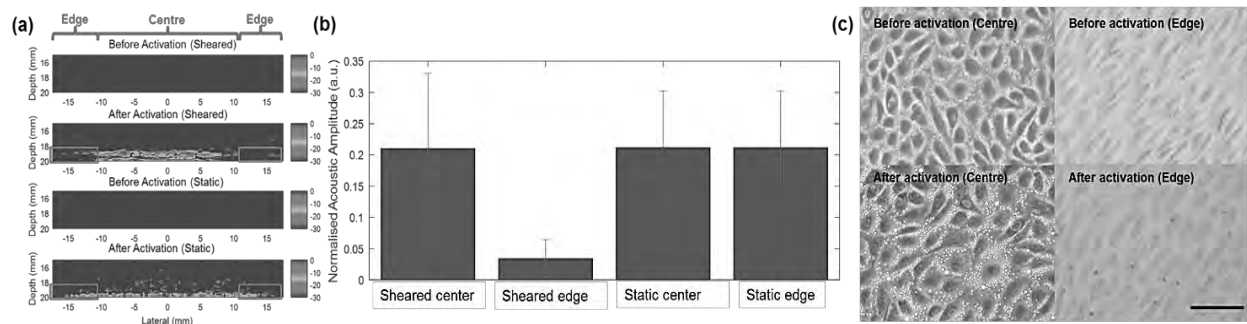
Ultrasound molecular imaging, using microbubbles targeted to the activated endothelium that is involved in the initiation and progression of atherosclerosis, could improve risk stratification for atherosclerotic complications. Nanodroplets, may have advantages over microbubbles as they have smaller dimensions, a longer in vivo circulation time, and activation that can be controlled in both space and time. In this study, we investigate the passive adherence of perfluorocarbon nanodroplets to endothelial cells exposed to atheroprotective versus pro-atherogenic flow conditions in vitro.

Methods

Porcine Aortic Endothelial Cells (PAEC) were seeded in 6 well-plates and cultured until confluent. The plates were placed on an orbital shaker in the incubator to allow cells to experience low magnitude multidirectional (pro-atherogenic) flow and high magnitude uniaxial (atheroprotective) flow in the centre or at the edge of the swirling well, respectively, or were static. After 3 days, nanodroplets were added into the wells for 30 mins in the absence of flow, followed by three washes before the ultrasonic exposure. A Verasonics 128 research platform equipped with a L11-4v probe was used to activate and subsequently image the nanodroplets. A custom 'Imaging-Activation-Imaging' Matlab script was used to transmit 8MHz, 2-cycle focus pulses (MI=1.5) to activate the nanodroplets and to perform plane wave (MI=0.1) imaging at 4MHz.

Results & Discussion

Figure (a) shows that, the signals from activated nanodroplets were predominantly located at the centre of the swirled well while the signals were uniformly distributed in the static well. Figure (b) shows the normalised acoustic amplitude at the centre and edge of sheared and static wells respectively. Figure (c) shows microscopic images of activated nanodroplets on cells at the centre and edge of the well. A large number of activated nanodroplets adhered to PAEC sheared with pro-atherogenic flow at the centre of the swirled well.



Conclusion

This study showed that nanodroplets adhered to cells sheared with pro-atherogenic flow, but not to the cells sheared with atheroprotective flow, even without a receptor targeting mechanism. This finding could be developed further to develop a novel technique to non-invasively detect the early development and progression of atherosclerosis, without the need for receptor conjugation to the agents.

Acknowledgments

Authors are grateful to the BHF grant for supporting cell culture work and Kuin T. Pang would like to acknowledge the PhD funding from A*-STAR Singapore.

Out-of-plane in-vitro flow velocity investigation for measuring cardiac output with high-frame-rate microbubble-enhanced ultrasound

X. Zhou¹, CH. Leow¹, M. Toulemonde¹, MX. Tang¹

¹ Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

Cardiac output is an important indicator and measuring it is of great value in guiding therapy. Currently it is still a challenge to measure the volumetric flow with a conventional 1D-array ultrasound probe which can only estimate in-plane flow velocities. This study proposed to measure the volume flow by placing the ultrasound probe to obtain the cross-sectional view of the blood vessel and estimating 2D flow velocity normal to the imaging plane using speckle decorrelation ^[1]. A flow phantom was used to test the feasibility of this method.

Methods

A straight-tube flow phantom (C-flex tube, diameter: 6.4mm) was used to generate a developed steady flow (600 ml/min) where the fluid is water mixed with microbubble contrast agent. Ultrasound diverging wave B-mode images (6000 fps) of the tube's transverse view (lumen area is shown in Fig.1a with a white cycle) were collected by a cardiac probe (P4-1 at 2.5Mhz) connected with a Verasonics Vantage system. Decorrelation analysis of the B-mode speckle pattern within the lumen was employed to estimate the out-of-plane velocity which was then integrated to estimate volume flow. Parabolic velocity profile was used as a velocity reference and timed-collection method as a flow rate reference to evaluate the proposed SDC method.

Results & Discussion

Fig. 1 shows the B-mode images, the 2D velocity profile (Fig.1b) and velocity curve (Fig.1c) along the white line in Fig.1a. The estimated flow rate is 704 ml/min with a 17% overestimation (true flow rate is 600 ml/min). The overestimation from the SDC method could be caused by the tube wall which can distort the ultrasound transmission or by the bubble destruction. Further investigation is necessary to diminish this overestimation.

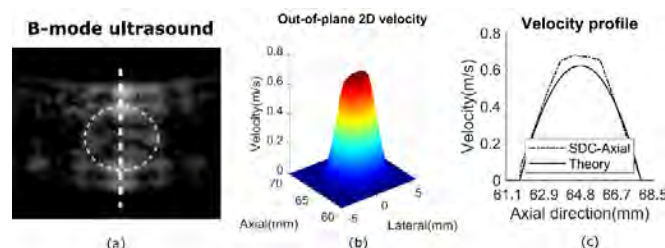


Fig. 1. Ultrasound B-mode images for SDC method and the estimated velocity results.

Conclusion

The proposed SDC is capable of measuring volume flow and has a potential for measuring the cardiac output for clinical applications. Further work needs to be done to improve the accuracy.

References

1. Rubin JM, Tuthill TA, Fowlkes JB. *Volume flow measurement using Doppler and grey-scale decorrelation. Ultrasound Med. Biol* 2001; 27(1):101–109.

Acknowledgments

We are grateful to British Heart Foundation (PG/16/95/32350), EPSRC (EP/M011933/1) and NVIDIA Corporation (donation of the Titan Xp GPU used in this study).

Design and Development of Mechanically Powered Multimodal Imaging Phantoms

C.K. Schmitz¹, J. Housden¹, Y. Noh¹, M. Hennigsson¹, A. Gomez¹

¹ School of Biomedical Engineering and Imaging Sciences, King's College London, UK.

Introduction

Motion imaging phantoms are useful for validating motion correction algorithms to quantify and correct organ and fluid motion in the body [1]. Such phantoms usually require complex experimental setups and external energy sources [2]; hence, we propose two self-contained phantoms: a 3D printed model with a wind-up spring and a LEGO model with elastic bands.

Methods

Both designs were validated using ultrasound (US) and MRI to evaluate their performance across imaging modalities. Each phantom was placed in a water-filled container and imaged 5 times per modality upon release of the wound-up mechanism. The imaging data were analysed using Laplacian eigenmapping and manifold learning to extract the angular velocity (AV) of each phantom. The similarities between the AVs within and across modalities were measured by calculating the RMS differences for each phantom.

Results & Discussion

The extracted AVs are shown in Figure 1. Within modalities, the median RMS differences were between 11.2-13.7% of the mean AV for both phantoms. Across modalities, the 3D printed phantom performed better with a median RMS difference value of 13.0% of the mean AV, compared to 24.1% for the LEGO model. Overall, the MRI datasets showed less variability than the US datasets and the LEGO phantom produced a narrower range of RMS differences than the 3D printed model (10.8-16.1% vs. 6.7-15.6% of mean AV respectively for MRI).

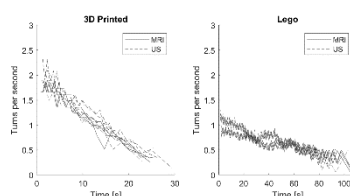


Figure 1: Angular velocity over time for each phantom and modality

Conclusion

We have created two phantoms which successfully address the issue of complex and expensive motion phantoms. The motion patterns may not be reproducible enough at this stage, both within and across modalities. However, further iteration of the designs could lead to a phantom with a more consistent motion pattern.

References

1. Huang C et al. *MR-based motion correction for PET imaging using wired active MR microcoils in simultaneous PET-MR: phantom study*. Medical Physics, 41(4), 041910; 2014.
2. Günther M, Feinberg DA. *Ultrasound-guided MRI: Preliminary results using a motion phantom*. Magnetic Resonance in Medicine, 52(1):27–32; 2004.

Acknowledgments

This work was supported by the Wellcome/EPSRC Centre for Medical Engineering [WT203148/Z/16/Z].

Brillouin microcopy measures water content in hydrated materials

Pei-Jung Wu¹, Irina Kabakova¹, Jeffrey Ruberti², Joseph M. Sherwood¹, Iain E. Dunlop¹, Carl Paterson¹, Peter Török¹, Darryl R. Overby¹

¹ Imperial College, South Kensington, London UK. ² Northeastern University, Boston, MA USA.

Introduction

Brillouin microscopy is an optical method to map the longitudinal modulus M of materials at confocal resolution. Hydrated materials are network structures containing a large quantity of water, and thus the elastic properties of hydrated materials are strongly influenced by water content $\varepsilon = V_f/V$, where V_f and V are the water volume and total hydrogel volume, respectively. Based on prior elastodynamic models of hydrogels¹, we propose a biphasic model that describes M as:

$$\frac{1}{M} = \frac{\varepsilon}{M_f} + \frac{1-\varepsilon}{M_s}$$

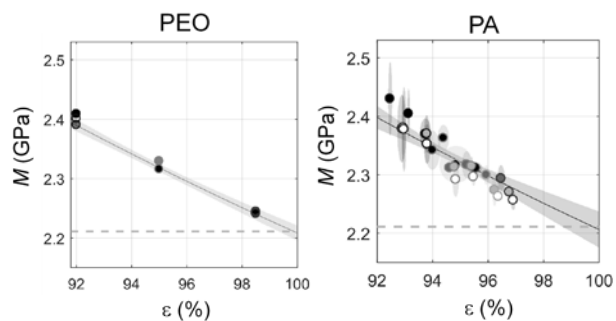
where M_f and M_s are the longitudinal elastic moduli of the fluid and the solid, respectively. This study examined the relationship between ε and M in two different hydrogels, polyethylene oxide (PEO) and polyacrylamide (PA).

Methods

PEO hydrogels were prepared in water with an average molecular weight of 1, 4 or 8 MDa and ε of 0.985, 0.95 or 0.92. PA hydrogels were prepared in water with 10% acrylamide and 0.03–0.30% N-methylene-bis-acrylamide. PA hydrogels were allowed to swell, and M , ε and ρ were measured throughout swelling. ε and ρ were calculated based on hydrogel mass. n was measured with a refractometer. M was measured with a custom² Brillouin microscope.

Results & Discussion

Regardless of molecular weight or swelling time, all values of M for both PEO and PA hydrogels collapsed onto a single relationship that depended only on ε and agreed with predictions from the biphasic model (Figure).



Conclusion

Brillouin microscopy is strongly influenced by the water content of hydrated materials. Studies that use Brillouin microscopy to measure other mechanical properties, such as stiffness, must account for the influence of water content.

References

1. Johnson, D. L. *J. Chem. Phys.*, 1982, **77**, 1531-1539.
2. Lepert G et al. *Faraday Discussions*, 2016, **187**:415-428.

Acknowledgments

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BioMedEng18

Real-time and non-invasive measurements of cell mechanical behaviour using optical coherence phase microscopy

D. Gillies¹, W. Gamal¹, A. Downes², Y. Reinwald³, Y. Yang³, A. J. El Haj³, P. O. Bagnaninchi¹

¹ MRC Centre for Regenerative medicine, The University of Edinburgh, Edinburgh, UK. ²Institute for Bioengineering, School of Engineering, University of Edinburgh, Edinburgh, UK. ³Institute for Science and Technology in Medicine, Keele University, Keele, UK.

Introduction

There is an unmet need in tissue engineering for non-invasive, label-free monitoring of cell mechanical behaviour in their physiological environment. Here, we describe a novel optical coherence phase microscopy (OCPM) set-up which can map relative cell mechanical behaviour in monolayers and 3D systems non-invasively, and in real-time [1].

Methods

The human fibroblast cell line (3T3) and the human breast cancer cell line (MCF-7) were investigated using the novel OCPM set-up. Their phase response to varying cycles of hydrostatic pressure was recorded, allowing us to compare their qualitative mechanical response. MCF-7 cells were also exposed to cytochalasin-D, a drug known to break down the cytoskeleton of cells.

Results & Discussion

MCF-7 demonstrated an increased response to hydrostatic stimulus indicating it being softer than the 3T3 cells investigated. After exposure to cytochalasin-D, MCF-7 cells showed an increased response, indicating that the cells had become softer after exposure.

Conclusion

We have demonstrated the ability of OCPM to provide qualitative data on cell mechanical behaviour.

References

1. D. Gillies *et al.* Methods 136 (2018) 126-133.

Acknowledgments

The authors are grateful to the research group of Dr Anthony Callanan in the Institute for BioEngineering, University of Edinburgh, Edinburgh, UK for facilitating use of the Cell Scale Microsquisher® system.

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Displacement of A Bubble Along Fluid–Tissue Interface

H. Koruk¹, J.J. Choi²

¹ Mechanical Engineering Department, MEF University, Istanbul 34396, Turkey.

² Department of Bioengineering, Imperial College London, London SW7 2AZ, United Kingdom.

Introduction

Imaging techniques based on the application of ultrasound and monitoring of the response have been used to determine tissue properties such as the elasticity modulus [1]. The use of microbubbles was proposed to improve the contrast and spatial resolution of elasticity imaging [2]. However, the mechanisms of deformation and the dependence of deformation dynamic on bubble and ultrasound parameters remain unknown. It would be useful to be able to predict the deformation and stress applied to tissue for different microbubble and ultrasound parameters.

Methods

A mathematical model is proposed for the displacement of a bubble into fluid–tissue interface and the tissue deformation in response to the primary Bjerknes force. The technique is based on the approach used for the displacement of a spherical object embedded in a bulk material [3-4]. Equations coupling the applied force, displacement and shear modulus of the medium are derived to evaluate the displacement of a bubble along fluid–tissue interface.

Results & Discussion

Results show that a bubble into fluid–material interface is both displaced by the applied force and changes its shape (Fig. 1). The bubble remains almost spherical for forces producing a displacement of up to half the bubble radius.

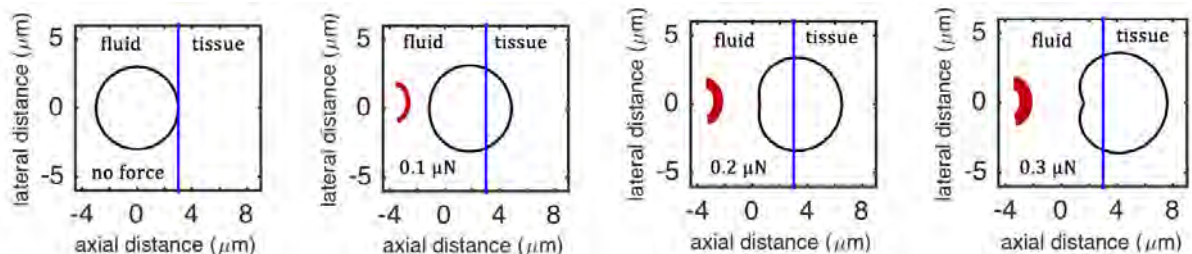


Fig. 1. Bubble displacement for a radius of $3\ \mu\text{m}$, medium shear modulus of $3\ \text{kPa}$ and different force values.

For an impulsive force, the steady-state amplitude changes nonlinearly with the applied force. The displacement and the time required for the steady-state response decreases as medium shear modulus increases.

Conclusion

The proposed model can be used for predicting the displacement of a bubble into fluid–tissue interface and tissue deformation. Hence, the model can be exploited in biomedical ultrasound applications, including the design of experiments and material characterization.

References

1. Nightingale KR et al. *J. Acoust. Soc. Am.* 2001; 110: 625–634.
2. Koruk H et al. *Appl. Phys. Lett.* 2015; 107: 223701.
3. Ilinskii YA et al. *J. Acoust. Soc. Am.* 2005; 117: 2338–2346.
4. Koruk H, Choi JJ. *J. Acoust. Soc. Am.* 2018; 143: 2535–2540.

Acknowledgments

There are no conflicts of interests.

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Multifunctional nanoparticles for targeted MRI and therapy

Nicolas Chabloz,¹ Margot Wenzel,¹ Hannah Perry^{1,2} and James Wilton-Ely¹

¹ Imperial College, South Kensington, SW7 2AZ, London, ² King's College, St Thomas' Hospital, SE1 7EH, London.

Introduction

Magnetic Resonance Imaging (MRI) is a non-invasive imaging technique that allows visualisation of soft tissue with a resolution in the millimetre range. Contrast agents based on paramagnetic gadolinium are often employed to improve differentiation between tissue types. The performance of a contrast agent can be enhanced by decreasing its rotational correlation time, which can be achieved simply by tethering the gadolinium unit to a large structure, such as a nanoparticle.^{1,2} Furthermore, unlike current clinically-approved gadolinium contrast agents, a nanoparticle-based design enables imaging, targeting and therapeutic units to be incorporated into the same structure.

Methods

Gold nanoparticles (3-5 nm in diameter) were synthesised using the Brust-Schiffrin method³ and functionalised with gadolinium chelates (for contrast enhancement), polyethylene glycol (for stability), thioglucose (for uptake and solubility) and folic acid (for targeting). The relaxivities of the functionalised nanoparticles were tested on a relaxometer (0.25 mT – 0.25 T) and a clinical MRI scanner (1.5 T). Uptake and viability studies were performed on HeLa cells for 24 hours.

Results & Discussion

The relaxivities of our nanoparticle-bound gadolinium chelates were up to five-fold greater than that of a molecular gadolinium contrast agent at 1.5 T. These high relaxivity values mean that, with our nanoparticles, an improved contrast enhancement could be achieved, even whilst delivering a reduced dose of gadolinium to the patient. The nanoparticles also displayed good uptake in cells and were found to be non-toxic.

Conclusion

Our multifunctional nanoparticles have displayed exceptional relaxivities, particularly at a clinical magnetic field. We have also shown that they are able to accumulate in cells and are non-toxic. Current work is focused on developing the therapeutic element of the nanoparticle assembly. We are investigating porphyrins for use in photodynamic therapy and gold nanorods/nanostars for use in photothermal therapy.

References

1. Caravan P. *Chem. Soc. Rev.* 2006, 35, 512-523
2. Roux S et al. *J. Am. Chem. Soc.* 2008, 130, 5908-5915
3. Brust M et al. *J. Chem. Soc. Chem. Commun.* 1994, 801-802
4. Wilton-Ely JDET et al., *submitted*

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Nano-imaging in the mid-IR for Intra-cellular Drug Localisation.

William S. Hart^{1,*}, Hemmel Amrania¹, Alice Beckley², Jochen R. Brandt³, Sandeep Sundriyal^{3,4}, Ainoa Rueda-Zubiaurre³, Alexandra E. Porter⁵, Eric O. Aboagye², Matthew J. Fuchter³, and Chris C. Phillips¹.

¹ Experimental Solid State Group, Department of Physics, Imperial College London, London, SW7 2AZ, UK

² Department of Surgery and Cancer, Imperial College London, London, UK

³ Department of Chemistry, Imperial College London, London, SW7 2AZ, UK

⁴ Department of Pharmacy, BITS Pilani, Pilani Campus, 333031, Rajasthan, India.

⁵ Department of Bioengineering, Royal School of Mines, Imperial College London, London, SW7 2AZ, UK.

Introduction

Optical microscopies offer diffraction limited resolution, of the order of an $\sim 0.5 \mu\text{m}$ optical wavelength. Fluorescence-based approaches have beaten this in the last few decades, giving $\sim 10 \text{ nm}$ resolution, but they rely on specialised labelling that can perturbing the biology and limits them to so-called “discovery” applications. The alternative, Electron microscopy (EM), requires complex, potentially disruptive and time-consuming sample preparation. Recently infrared light-based scanning probe techniques have demonstrated a capability for $\sim 1 \text{ nm}$ spatial resolution in Solid state physics experiments, but they have not been applied to biological specimens. We show here how these probe-based techniques can be adapted for biomedical imaging for the first time. The technology allows for “Mid-infrared Chemical Nano-imaging” (MICHNI) that delivers chemical analysis at a $\sim 10 \text{ nm}$ spatial resolution, suitable for studying cellular ultrastructure.

Methods

A culture of RPMI-8226 myeloma cells was dosed with the anti-cancer drug Bortezomib (BTZ), spun down, FFPE embedded and sectioned in a manner similar to that used for standard H+E biopsy processing. The sections were mounted on glass slides, dewaxed, and imaged with a novel “scattering-type scanning near-field optical microscope” (s-SNOM) that uses a sharp conducting probe to focus light to give a spatial resolution of , in this instance $\sim 10 \text{ nm}$. Uniquely, the s-SNOM was equipped with quantum cascade lasers (QCL's) that could be tuned ($5 \mu\text{m} < \lambda < 12 \mu\text{m}$) through the B-C absorption peak of the BTZ, allowing us to image its binding sites.

Results & Discussion

The s-SNOM images contained a wealth of “ultrastructure “ morphological information that has never before been seen optically. Regions of elevated BZT concentration were clearly isolated and had absorption spectra that matched those of BZT test reference samples.

Conclusion

We demonstrate that s-SNOM can be used to obtain $\sim 10 \text{ nm}$ resolution optical images of single cells. The sample preparation is quick cheap and simple (compared with EM). We believe the MICHNI technique will find wide application across the whole of life sciences.

References

1. Edward Yoxall et al. “Widely tuneable scattering-type scanning near-field optical microscopy using pulsed quantum cascade lasers” **Appl. Phys. Letts.** 103, 213110 (2013).

Acknowledgments

CCP, WH and HA acknowledge financial support from EPSRC (EP/K503733/1, EP/K029398) MF acknowledges support from EPSRC (EP/L014580/1, EP/R00188X/1) and Cancer Research UK (C33325/A19435). AR-Z acknowledges fellowship support from the Alfonso Martin Escudero Foundation. EA and AB acknowledge support from Cancer Research UK, C2536/A16584.

Motor control and gait variability of patients with the Medacta GMK Sphere total knee arthroplasty

G.F. Tawy^{1,2}, L.C. Biant¹, P.J. Rowe²

¹Stopford Building, University of Manchester, Manchester M13 9PG ²Graham Hills Building, University of Strathclyde, Glasgow G4 0NW.

Introduction

Gait instability is a common complaint following total knee replacement. The Medacta GMK Sphere total knee replacement is specifically designed to provide patients with a functionally stable knee. The gait stability of patients implanted with this device remains unknown, however. Reduced gait stability can be quantified in terms of increased gait variability. The Uncontrolled Manifold (UCM) method has recently been used to quantify gait variability in patients with knee osteoarthritis². The UCM method calculates combinations of elemental variables (joint degrees of freedom) that successfully stabilise ('good variance') or compromise ('bad variance') the stability of the centre of mass (COM). Successful COM stability is said to have been achieved when the 'good variance' outweighs the 'bad variance'. This suggests that the adoption of variable combinations of hip, knee and ankle kinematics is beneficial for stabilising the COM whilst walking. This is known as kinematic synergy. Improving our knowledge of the relationship between gait variability and COM stability in TKA may enable us to investigate the possibility of using the UCM method as a biomarker for gait instability.

Methods

Patients with end-stage osteoarthritis meriting TKA were implanted with the Medacta GMK Sphere. The patients walked on a self-paced treadmill for two minutes six-weeks and one-year post-operatively. A motion capture system and bespoke cluster-based biomechanical model recorded and calculated lower limb kinematics. The kinematic variability of gait over 50 consecutive gait cycles was analysed using the UCM method with a custom-written MATLAB program. Balanced ratios of 'good' to 'bad' variances were calculated. Ratios > 0 suggest that the task in question (COM stabilisation) was successful.

Results & Discussion

The patients were able to maintain a stable COM whilst walking, as shown by the outweighing of the 'bad variance' by the 'good variance' throughout the gait cycle in both planes. The balanced ratios were also >0 in both planes at each percentage of the gait cycle. Thus, it can be said that kinematic synergy was used by the patients to stabilise the COM during gait.

Conclusion

The presence of kinematic synergy following TKA suggests that the implant was successful at providing patients with a stable and functional knee. This investigation has also alluded to the fact that employment of this technique may allow specific personalised prescription for prehabilitation and rehabilitation.

References

1. Freeman M A R *Journal of Biomechanics* 2005; 38(2): 197-208.
2. Tawy, G F *Gait & Posture* 2018; 59: 272-277.

Acknowledgments

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Acute effects of whole body vibration on postural stability

I. Rigoni¹, T. Bonci ¹, W. Högler², A. Fratini ¹

¹*School of Life and Health Sciences, Aston University, Aston Triangle, B4 7ET, Birmingham.*

²*Birmingham Women's and Children's Hospital, B4 6NH, Birmingham*

Introduction

Whole body vibration (WBV) is a popular complement to training and rehabilitation programmes. Although positive impact on postural outcomes have been shown in long-term stimulation [1], short-term studies are still limited. To this aim, this study analyses the acute effect of WBV on postural control to highlight short-term outcomes on healthy subjects.

Methods

Fourteen healthy participants (age: 25-42 yrs; height: 155-188 cm; weight: 38.5-90 kg) took part in the study. A Galileo® Med vibrating platform was used to deliver the WBVs. Participants were familiarised with the procedure and asked to keep a squat posture (100° flexion/extension knee angle) on the platform during stimulations, with feet placed 16.5 cm apart from the centre. Three minutes WBV stimulation at 10 and 25 Hz were administered. Centre of pressure (COP) trajectories were recorded (AMTI OR-6-7 force platform, 1000 Hz) before and immediately after WBVs with open (OE) and closed-eyes (CE). Six COP time histories were acquired for 90 s. COP trajectories were filtered (fourth-order zero phase Butterworth low-pass filter with a 5 Hz cut-off frequency), and then used to calculate mean velocity [mm/s], RMS distance (RMSD) [mm], mean frequency [Hz] and frequency dispersion [2]. To evaluate the effect of vibration on postural control, a repeated measures ANOVA test was used to compare the above-mentioned parameters. A LSD post hoc test was run when significant differences were observed.

Results & Discussion

WBV affects COP RMSD and mean velocity with CE and OE, respectively (Fig. 1). The reduction of the distance travelled by the COP may indicate a higher stability achieved with closed eyes after the WBV at 25 Hz. The increase of the COP mean velocity, since not unanimously recognised as a reduction of the postural stability, could indeed represent a bigger engagement of the postural control muscles and, in turn, a higher postural control capability. The frequency domain analyses did not show any significant change. Further analyses with a bigger sample size are planned to increase the reliability of the obtained measures. A simple randomization of the order of the applied stimulation would also eliminate the potential contribution of any associated muscle fatigue.

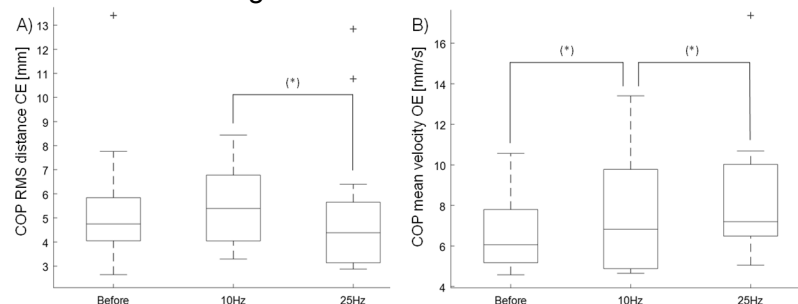


Figure 1. Box-plots of CE RMSD (A) and OE mean velocity (B) values (n=14) computed for COP trajectories recorded before, and after 10 Hz and 25 Hz WBVs. Asterisks (*) indicate a difference statistically significant ($p < 0.05$). Outliers are also depicted.

Conclusion

Even a single session of vibration can positively affect postural stability, especially at higher frequencies (25Hz). This is a crucial factor for treatment and research studies design.

References

- [1] R. Ritzmann *et al.* *PLOS One*. 2014; 9: e89905.
- [2] T. E. Prieto *et al.* *IEEE Trans. Biomed. Eng.* 1996; 43: 956–966.

Using whole body kinematics to predict ground reaction forces during military load carriage

S. Shanel¹, D. Terracina¹, A.H. McGregor², A.M.J. Bull¹

¹ Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London. ² Department of Surgery and Cancer, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

Ground Reaction Forces (GRFs) can be calculated using only kinematic data for walking (1) and other daily activities (2) using Newton Euler mechanics. These approaches allow for kinetic analysis of motion where the use of force plates may not be suitable or even possible. This study assesses the potential to predict GRFs during military load carriage tasks by adapting an inverse dynamics based model (3).

Methods

One male subject (mass, BW, 72kg, height 177cm, age 29 years) wearing a military rucksack and boots walked and ran at a self-selected pace carrying (a) no load, (b) 25% BW (c) 35% BW. Whole body kinematic data were captured using optical motion tracking hardware (Vicon Motion Systems). Force plate data (Kistler) recorded simultaneously was used for validation. Three dimensional GRFs were calculated using the captured motion data and by adapting the model described in (3). In the model, equations of motion for each body segment were solved to obtain force vectors, applied at the centre of mass (COM) of the segment. The rucksack was added as an additional body segment. The GRFs were assumed to be the sum of these segment forces. During double stance, GRFs were distributed between the feet based on the distance from each foot to the Zero Moment Point, the point on the ground at which the sum of the horizontal moment components of the segment loads were zero (1).

Results & Discussion

Vertical GRF was predicted with excellent Pearson correlation ($p > 0.9$) for all load conditions. Antero-posterior GRF was predicted with strong Pearson correlation ($0.67 < p < 0.9$) for all load conditions. Medio-lateral GRF showed moderate correlation ($0.35 < p < 0.67$), likely due to the small magnitude of this force relative to BW, and the relatively small change in the COM position of the body in this direction. Additional errors occurred due to approximations made in the model, including estimation of body segment parameters and the distribution of GRFs between the left and right feet during the double stance phase of walking.

Conclusion

This study has shown that whole body kinematic data can be used to accurately estimate GRFs for military load carriage tasks. Addition of the military rucksack and boots did not affect the accuracy of the model for walking. During running, the accuracy of the model was slightly reduced with increasing load. Further trials should be completed using additional subjects and load conditions to further validate the adapted model.

References

1. Dijkstra, E.J., Gutierrez-Farewik, E.M., 2015. J. Biomech. 48, 3776–3781.
2. Fluit, R. et al, 2014. J. Biomech. 47, 2321–2329.
3. Terracina, D., Bull, A.M.J., 2018 Under review.

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Facilitating compatibility across motion tracking systems in sports biomechanics

C.A. Urbanczyk¹, A. Bonfiglio¹, A.H. McGregor², A.M.J. Bull¹

¹ Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London.

² Department of Surgery & Cancer, Imperial College, Hammersmith, W6 8RF, London.

Introduction

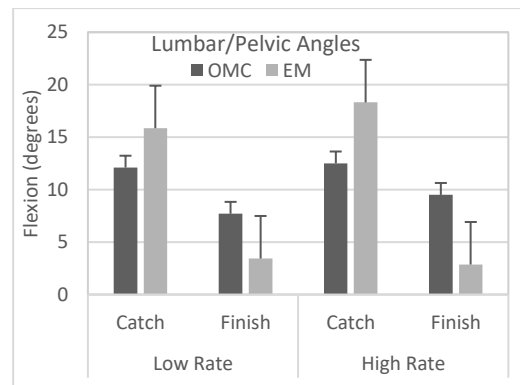
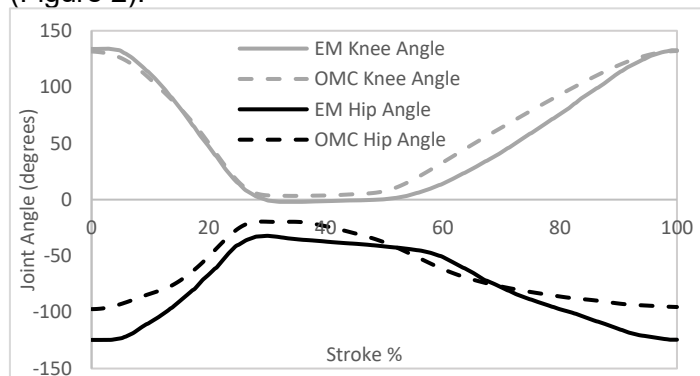
Collaboration between Imperial College and British Rowing has produced biomechanics research on elite rowers - offering a framework to describe proper execution of rowing technique and provide quantitative feedback to help athletes improve performance and reduce injury risk. Researchers have used an electromagnetic (EM) tracking system to quantify kinematics of the right leg and pelvis. However, hardware limitations and a desire for broader dynamic data have necessitated a technological shift. Optical motion capture (OMC) is well equipped to image whole body dynamics of rowing while providing resolution to detect subtle movements. The purpose of this study was to establish standard operating procedures for an OMC method and to compare accuracy of ergometer rowing kinematics between OMC and EM systems.

Methods

Reflective markers (Vicon, UK) and EM sensors (Ascension Technologies, USA) were attached to three volunteer rowers. Each was recorded moving through known ranges of motion for system calibration, then performed a series of rowing trials at low, middle, and high speeds, on an instrumented ergometer [1]. Kinematic data were collected simultaneously using both tracking systems. Pearson correlation and RMSE were used to quantify curve similarity.

Results & Discussion

Estimates of knee and hip joint angles were similar between the EM and OMC systems (99%, 95% correlation) with average differences not exceeding 8.9° and 14.7°, respectively (Figure 1). Comparing average lumbar-pelvic angle to previously published results calculated from EM tracking [1], OMC under-estimates flexion at the catch and over-estimates flexion at the finish (Figure 2).



Conclusion

Measurements obtained from either system can be related provided that appropriate scaling and biomechanical models are used to obtain joint centre positions. This backward compatibility validates comparisons of new OMC data with previously acquired EM data, which is important for ensuring continuity of athlete training progression.

References

1. Buckeridge et al. *Medicine & Science in Sports & Exercise*. 2012; 44(11):2147-53.

Acknowledgments

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A change in muscle recruitment strategy could explain difficulties in elderly sit-to-stand movements

S.H.L. Smith¹, P. Reilly^{1,2}, A.M.J. Bull¹

¹ Department of Bioengineering, Imperial College London, Kensington, London, SW7 2AZ. ² Department of Orthopaedics, Imperial College NHS Trust, Praed St, London, W2 1NY.

Introduction

Developments in modern medicine, promotion of well-being in the elderly, and a greater understanding of healthy lifestyles have given rise to an 'ageing population'. It is predicted that by 2050 the population of over 65s will be 20% of the general population¹, which will have repercussions for both the economy and healthcare systems. However, current age-related research fails to address the consequences of many physiological changes. Our bodies are not designed to perform at high levels of activity into old age. Muscle mass begins to decline around the 5th decade² with diminishing internal systems, making activities which were easier at a younger age more strenuous on the body. This research aimed to quantify the difficulties of the older population in performing everyday activities.

Methods

The movements of 95 eighteen to ninety-five-year-old males were observed during a sit-to-stand task and analysed using musculoskeletal modelling. Scenarios both with and without the use of arm rest support were included.

Results & Discussion

The young (aged 18 to 35 years) were found to use short, tetanic contraction of the quadriceps to lift the body when not using arm rests, whereas the elderly (aged 65 years and older) used prolonged activity of multiple muscle groups to stand. The elderly subjects had significantly lower quadriceps forces, thus lowering the forces on the knee, and compensated by increasing activity of the hamstring and calf muscles – a result of different movement strategies. The elderly's tendency to use prolonged activity of multiple muscle groups makes simple, everyday activities more strenuous on the body. More importantly it makes the movements of the elderly more susceptible to functional decline with age. Alternatively, using arm rests dramatically increased elderly joint forces in the shoulder when compared with the young.

Conclusion

A premature reduction in lower limb strength with age places more reliance on the upper limb muscles to complete everyday activities, resulting in further lower limb atrophy through disuse. The eventual decline of upper limb strength leaves the elderly with a lack of reserve body strength to complete the activities, leading to increased vulnerability, dependence on others and risk of institutionalisation.

References

1. World Health Organisation, Q&A site, 2011. Available at: <http://www.who.int/features/qa/42/en/> [Accessed February 27, 2017]
2. Lexell, J., Taylor, C.C. & Sjöström, M., *J. Neurol. Sci.*, 84, 275–294, 1988

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This research was achieved through collaboration with the Royal Hospital Chelsea. This work was funded by the Engineering and Physical Sciences Research Council through a PhD studentship.

Three-dimensional severity measures and rapid model generation for cam type femoral geometries

R.J. Cooper¹, S. Williams¹, M. Mengoni¹, A.C. Jones¹

¹ Institute of Medical and Biological Engineering, University of Leeds, LS2 9JT, UK.

Introduction

In the hip joint, variations in shape of the femoral neck and head can give rise to abnormal contact with the acetabular rim, resulting in cartilage and labral damage. There is a requirement for quantification and modelling of these geometric differences, for both clinical assessment and classification of research subjects. This work demonstrates the utility of a three-dimensional parametrisation for cam type femoral geometries, both for severity assessment and rapid model generation.

Methods

Parametric femoral surfaces were defined by a spherical proximal head and ellipse sections through the neck/cam region. This method produced surfaces that were well fitted to bone geometry segmented from CT scans of cam patients, and capable of producing trends in results similar to those found using segmented models^[1]. A simplified spherical representation of the labrum and acetabular cartilage was used. Models were generated for two cam sizes and two positions (anterior and superior), which fell within previous clinically measured bounds^[2]. Alpha angles of these parametric femurs were measured in two views (Fig 1).

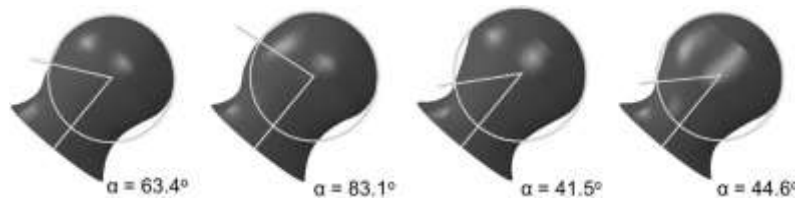


Fig 1: Cam femoral models, representing bounds of a clinical group and rapidly generated using shape parameters. Alpha angle measurement in the anterior-posterior view are shown.

Results

Potential for tissue damage, indicated through local strain, was not predicted by measured alpha angle, but resulted from cam extent and position as defined by the three-dimensional parameters.

Discussion & Conclusion

Although it is well established that clinical alpha angle is a crude tool for assessment of femoral bone shape, the clinical and research communities currently lack a strong alternative. This work demonstrates the potential of a parametric system to capture the extent and position of the cam in three-dimensions and differentiate in terms of finite element damage measures.

References

1. Cooper et al. *Int J Numer Method Biomed Engng.* 2017; 33(11), e2867.
2. Cooper et al. *Clin. Biomech.* 2018; 54, p62-70.

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Effects of Abnormal Fetal Movements on Rib Cage Development

Y. Huang¹, A. Levillain¹, N.C. Nowlan¹

¹Department of Bioengineering, Imperial College, London SW7 2AZ, UK.

Introduction

Spine and rib development is influenced by mechanical forces due to fetal movement [1], but the effects of abnormal movements on rib development has not been described in detail, a deficit which we address in this study. With a genetically modified mouse model, we assess the effects of abnormal hypaxial muscle on rib development, while using the immobilised chick embryo model system, we assess the most critical timepoints for fetal movements for rib formation and growth.

Methods

Embryonic mice from a genetically modified line in which *Pax3* was modified were harvested between Theiler stage (TS) TS22 to TS27. *Pax3* mutation leads to abnormal development of the hypaxial muscles which contribute to rib cage formation [2]. For the chick work, experimental embryos were immobilised with Decamethonium bromide (DMB), a neuromuscular blocking agent that induces rigid paralysis to simulate no muscle contractions [3]. Two types of immobilisation regimens were designed: (1) paralysis on single embryonic days (E) (3 to 6) and harvest on embryonic day 9 (E9) for the study of critical timings of movement; (2) immobilisation on E4 and harvest daily until E9, for the study of the effects of immobilisation on rib development.

Dissected samples were stained with Alcian Blue for cartilage and Alizarin Red for mineralised tissue, and scanned with Optical Projection Tomography (OPT) to acquire 3D structures. Control and mutant groups were compared at different stages in terms of rib lengths, tortuosity (representing curvature) and extent of mineralisation in ribs and sternum using Mimics, and Paraview. Statistical analyses (t-tests and ANOVA) were performed using SPSS.

Results & Discussion

In the mouse model, a delay in rib mineralisation was observed. Rib fusion occurred around the sternum, likely due to reduction in the spinotrapezius muscle [2]. Ongoing work is investigating the proportion of mineralised ribs at different stages and how the sternum is affected. In the chick study, paralysis on embryonic day 5 was found to have the most severe effects on rib development, leading to the shortest ribs at E9. E8 was the most affected stage with the most different rib features from control.

Conclusion

Muscle contraction and absence of hypaxial muscles have a crucial impact on rib cage development, specifically on the timing of mineralisation, rib length and tortuosity and possibly sternum formation. Findings from this study will contribute to early diagnosis and treatment of congenital rib deformities, which are often concomitant with congenital scoliosis.

Acknowledgments

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References

1. Rolfe, R.A., et al., J Orthop Res, 2017. **35**(10): p. 2135-2144.
2. Tremblay, P., et al., Dev Biol, 1998. **203**(1): p. 49-61.
3. Osborne, A.C., et al., J Musculoskelet Neuronal Interact, 2002. **2**(5): p. 448-56.

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Markerless and Marker-Based Solution to Estimate Kinematics

L. Gionfrida^{1,3}, S. Yuan², T.K. Kim², A. Williamon³, A.A Bharath¹, A.E. Kedgley¹

¹ Department of Bioengineering, Imperial College London, Royal School of Mines Building, London SW7 2AZ, UK.

² Department of Electrical and Electronic Engineering, Imperial College London, London SW7 2AZ, UK.

³ Centre for Performance Science, Royal College of Music, London SW7 2BS, UK.

Introduction

Despite the fact that marker-based motion capture is widely used in laboratory studies of hand kinematics, its application outside the laboratory setting is challenging. To address this, computer vision techniques are being explored for hand pose estimation, including estimating inverse kinematics; for instance, a number of approaches have made use of depth-image sensors and associated processing techniques [1]. However, few approaches have attempted to use images from a single RGB camera for hand pose estimation. Moreover, the estimated inverse kinematics usually rely on synthetic data for validation. In this study we want to estimate hand kinematics using i) a marker-based optical tracking system, and ii) a markerless, vision-based, solution from one RGB camera. The latter will be implemented with a convolutional neural network (CNN) that predicts hand kinematics after being trained from RGB images annotated with the ground truth of the joint locations. The cost function will be measured as the distance between the ground truth locations of the joints and the estimated locations of the CNN model.

Methods

The continuous motions of the joints of a hand and wrist were captured over two minutes with an optical motion capture system (Qualisys AB, Sweden) at 100 Hz. Semi-spherical, 4mm diameter markers were attached to the first through fifth proximal and distal phalanges and the second through fifth intermediate phalanges. During the trial, the participant performed three seconds of pinching between each of the fingers and the thumb. To allow better learning of long-term dependencies, the neural network included long short term memory (LSTM) neurons. Network performance was assessed by making use of the ground truth from the optical tracking using a series of error distance measures for each joint.

Discussion

This approach aims to overcome the lack of large-scale annotated datasets to provide ground truth for kinematic estimation. Ultimately, our aim is to train a vision system to infer kinematics directly from a single RGB camera. A key outcome of this study is to determine network architecture, such as the depth of the network, objective functions and learning rates, and the levels of performance accuracy that can be achieved. The way in which data are pre-processed and the inclusion of markers will potentially introduce spatial distortions that limit accuracy. However, the ability to train a network that can estimate kinematic parameters will broaden the possibility of estimating kinematics outside lab-based settings, potentially allowing wider applications of marker-free hand pose estimation in the biomechanics community.

References

1. Yuan S, et al. *CVPR, IEEE Conference 2017*: 2605-2613.
2. Pham TH, et al. *IEEE Transactions on Pattern Analysis and Machine Intelligence 2017*.
3. Goisard De Monsabert et al. *Ann Biomed Eng.* 2017: 71-85.

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Wavelet analysis in the diagnosis of knee instability – Early results from a novel assessment method

D.T. Wallace^{1,2}, J.V. Clarke², P.E. Riches¹

¹ Graham Hills Building, University of Strathclyde, 40 George Street, Glasgow, G1 1QE. ² Department of Orthopaedics, Golden Jubilee National Hospital, Agamemnon Street, Clydebank, G81 4DY

Introduction

Instability in the knee following total knee arthroplasty (TKA) is a leading cause for dissatisfaction, often requiring revision surgery¹. However, instability remains a symptom with no corresponding objective measure. The purpose of this study was to identify quantifiable differences in frontal plane accelerations at the knee between subjectively “stable” and “unstable” TKA patients.

Methods

Post-operative TKA patients with symptomatic instability were recruited from a national orthopaedic centre, along with asymptomatic post-operative TKA patients, and healthy controls. Frontal plane knee accelerations were measured using an accelerometer mounted on the lateral aspect of the proximal lower leg. Individual strides were extracted, and continuous wavelet transform (CWT) of the accelerations were performed, with the absolute value of the CWT coefficient examined for differences between groups.

Results & Discussion

10 controls, 9 “stable”, and 7 “unstable” participants were tested. Increased CWT coefficients were found between 50% and 80% of stride (heel strike to heel strike), and between 4 and 8 Hz, in the “unstable” TKA group in comparison with the “stable” and control groups. This corresponds to increased oscillation at the proximal tibia frontal plane during early swing phase, consistent with reduced stiffness and increased contact point movement in subjectively unstable osteoarthritic knees^{2,3}.

Conclusion

Accelerations in the frontal plane of the knee during swing phase corresponds to subjective instability in the TKA. This portable and inexpensive technology has potential for use in clinics to quantify instability in the unhappy TKA.

References

1. Sharkey PF *et al.* Why are total knee arthroplasties failing today-has anything changed after 10 years? *J Arthroplasty*. 2013;29(9):1774-1778. doi:10.1016/j.arth.2013.07.024.
2. Creaby MW *et al.* Self-reported knee joint instability is related to passive mechanical stiffness in medial knee osteoarthritis. *BMC Musculoskelet Disord*. 2013;14:326. doi:10.1186/1471-2474-14-326.
3. Gustafson JA *et al.* Knee motion variability in patients with knee osteoarthritis: The effect of self-reported instability. *Clin Biomech*. 2015;30(5):475-480. doi:10.1016/j.clinbiomech.2015.03.007.

Acknowledgments

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Improving statistical shape model predictions from partial femur bones using prior knowledge of mineral density in the residual bone

D. Nolte¹, A.M.J. Bull¹

¹ Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

In clinical practice, the shape of long bones for the treatment of large bone defects due to trauma and complex arthroplasty is typically predicted using the contralateral side. However, this method is not suitable in cases of bilateral pathologies and asymmetries. Statistical shape models have been used to predict the bone shape from partial bones with reasonable accuracy [1], but prediction of material properties and shape has not been studied to a great extent. Recently, we have shown that statistical shape and appearance models (SSAMs) describing shape and grey scale values (GSV) of computed tomography (CT) scans can be used to predict shape and material properties from surface geometries of partial bones only. This study compares the accuracy of reconstructions from geometry data alone to reconstructions using geometry data and GSV of the residual limb.

Methods

An SSAM representing the shape and GSV were created from right and mirrored left femur bones from CT scans of 40 female cadaveric specimens of the Digital Korean dataset. Shapes were aligned using the method described in [2], and the shape and appearance model was created following the method described in [3]. Bone defects were simulated by cutting the segmented bone models at levels of 50%, 75%, 80% and 90% of the full length. Intact bones were predicted from the SSAM using three different methods: (i) minimising the landmark-to-surface distance; (ii) minimising a weighted average of landmark-to-surface distance and GSV difference of model and residual bone; (iii) minimising GSV differences of model and residual bone and superimposing the GSV on a shape created with method (i). The accuracy of the reconstructions was evaluated by measuring discrepancies in surface distance, stress, strain and deformation during a gait cycle compared to a model obtained from the intact CT image.

Results & Discussion

Predictions of the superimposition (iii) significantly decreased the average error of strain and deformation by 2% and 4%, but increased the error in stress by 2% compared to the reconstructions method (i). Method (ii) significantly decreased the average error of strain, stress and deformation by 4%, 8% and 10%, respectively, compared to method (i). The average root mean squared error increased by 0.2 mm for the models created using objective functions (ii) compared to models created with (i) and (iii), but the difference was not significant.

Conclusion

This study showed that predictions of the material properties for reconstructions of bones can be significantly improved by using information of material properties of the residual limb.

References

1. Plessers, L. et al. *J Shoulder and Elbow Surgery*. 2017; 27 (1): 160-166.
2. Zhang, K.Y. et al. *Plos One*. 2014; 7(4): 34619.
3. Bryan, R. et al. *Med Eng & Physics*. 2010; 32 (1): 57-65.

Acknowledgments

Study: Beit Fellowship for Scientific Research; data: Digital Korean dataset by KISTI.

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Why is a lower limb musculoskeletal model most sensitive to where muscles insert on the foot? An explanation using Lagrangian Multipliers

C. H. Yeh¹, A. M. J. Bull¹, A.E. Kedgley¹

¹ Department of Bioengineering, Imperial College London, South Kensington, SW7 2AZ, London.

Introduction

Lower limb musculoskeletal models are most sensitive to the muscles that insert to the foot.¹ A mathematical approach to understand this phenomenon is to investigate the Lagrangian multipliers used in solving the optimization process used within these models.

Methods

Subject-specific musculoskeletal models of eight participants, based on lower limb MRI data, were constructed using 'FreeBody'² and used to predict muscle forces and Lagrangian terms during walking. The cost function was set to minimise the sum of muscle activations cubed. The model had twenty-two kinematic constraints, including the force and moment equilibrium of the foot, shank, and thigh segments, and force equilibrium of the patella. The 22 Lagrangian multipliers were shared in prediction of all 163 muscle elements in the optimal condition.

Results & Discussion

The Lagrange terms reached their maximum/minimum at the middle of the cycle (median: 50%, Interquartile Range (IQR) = 4%) (Fig. 1). The maximal absolute value of the Lagrangian terms for the ankle moment equilibriums are the largest among other constraints (median: 1.76; IQR: 3.92) and significantly different from those of thigh force equilibrium (median 7.8×10^{-7} , IQR: 2.1×10^{-7}). ($p=0.00039$).

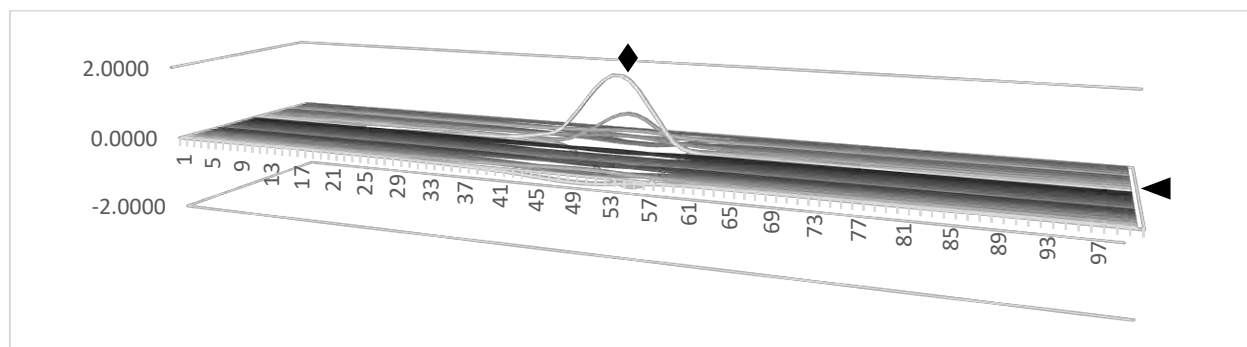


Figure.1 Lagrangian terms in a gait cycle. The change of Lagrangian terms for a gait cycle, from heel strike to heel strike. Noticed that the Lagrangian term for the ankle moment equilibrium is the largest (diamond) and almost zero (triangle) for the hip force equilibrium.

Conclusion

The large magnitude of the foot moment Lagrangian terms suggests that changing the moment arms of muscles that affect the foot will make a large impact on the force prediction of other muscles. The Lagrangian terms related to the hip force equilibrium were close to zero, suggesting that violating the force equilibrium of the hip doesn't affect the cost function much. This supports the inverted pendulum model of human gait, which suggests that no active force is needed in the thigh during the stance phase.

References

1. Carbone et al. J Biomech 2012;45:2476-80
2. Ding et al. J Biomech Eng 2016;138:021018-1-021018-9

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Improving musculoskeletal model scaling using gender and anthropometric similarity

Z.Y. Ding, D. Nolte, A.E. Kedgley, A.M.J. Bull

¹ *Department of Bioengineering, Imperial College London, South Kensington, SW7 2AZ, London*

Introduction

Linear scaling of a generic musculoskeletal model was long considered as the most time and cost efficient manner to represent any individual's musculoskeletal anatomical geometry [1]. However, the generic models do not enable gender and inter-individual anatomical variations to be accounted for, leading to substantial errors in model predictions [2]. The hypothesis of this study is that linear scaling to a musculoskeletal model with gender and anthropometric similarity to the individual subject reduces errors when compared to scaling to a single, generic model. This hypothesis is tested through: first, developing a lower limb musculoskeletal anatomical database, or atlas, consisting of datasets derived from magnetic resonance imaging (MRI) and the generic dataset from the literature [3]; secondly, quantifying the errors from scaled models where the outputs from the subject-specific musculoskeletal model are considered the gold standard; and finally, establishing any relationship between errors of scaled models and the discrepancies of the underlying anatomical datasets when compared to the subject-specific models, which allows a definition of the most appropriate use of the atlas.

Methods

MRI of ten healthy subjects (five males and five females, age 32 ± 9 yrs, height 172 ± 12 cm, mass 69.5 ± 14.5 kg) was acquired. MRI segmentation and digitisation were performed to create ten MR-based anatomical datasets. Gait were measured in a motion lab with a 10-camera optical motion capture system and two force plates and simulated using a lower limb musculoskeletal model FreeBody V2.1 [4]. Eleven lower limb musculoskeletal models were created for each individual: one using the subject-specific MR-based dataset and the others through linear scaling of the generic and the remaining nine MR-based datasets.

Results & Discussion

Significant correlations were found between the errors from the scaled musculoskeletal models and the discrepancies in gender and anthropometric measurements of the underlying anatomical datasets when compared to a subject-specific model. Our hypothesis was supported: the errors from scaling of a generic model can be reduced significantly when scaling through a model with same gender and similar anthropometry to the individual.

Conclusion

The publically available lower limb musculoskeletal anatomical atlas can improve the outcomes from the musculoskeletal models and accelerate the development of subject-specific musculoskeletal modelling.

References

1. S. L. Delp, et al., *IEEE Trans. Biomed. Eng.*, 1990; 37(8), 757–67.
2. T. A. Correa, et al., *J Biomech.* 2011; 44 (11): 2096-2105.
3. M. D. Klein Horsman, et al., *Clin. Biomech.* 2007, 22 (2), 239–247.
4. D. J. Cleather, and A. M. J. Bull, *R.Soc.open sci.*, 2015, 2:140449.

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BioMedEng18

The 'Imperial Spine cluster model' as a simplified approach of evaluating spinal kinematics in patients

D. Sobczak¹, E. Papi ^{1 2}, J. Deane ¹, A. McGregor ¹

¹Department of Surgery and Cancer, Imperial College London, W6 8RP, London. ²Department of Bioengineering, Imperial College London

Introduction

The 'Imperial spine model' (1) has been developed as a reliable 3 rigid segment spine model for the examination of upper thoracic (UT), lower thoracic (LT) and lumbar kinematics during functional tasks. In order to simplify the approach, the 'Imperial cluster model' has been designed as a step towards reducing the marker application and post processing time.

Aim

To compare the 'Imperial cluster model' with the 'Imperial spine model' as a reliable method of analysing spinal kinematics during different functional tasks.

Methods

To compare the models, both spine and cluster markers were applied to 45 individuals. A 10-camera 3DMC system was used to track retro-reflective markers as they performed gait and sit-to-stand (STS) tasks three times. The average spine segment angles were calculated using the Joint Coordinate System (2) and a paired t-test was used to determine significance differences between the models.

Results

There was no significant difference between the cluster and spine model for the LT segment, except for rotation during 30% of the gait cycle. There was no significant difference in the UT segment in terms of rotation for both tasks and in flexion for gait. In terms of ab/adduction for both tasks and STS flexion, there was a significant difference ($p < 0.05$) between the two models. The lumbar segment showed significant difference ($p < 0.05$) in ab/adduction and flexion for both gait and STS. There was no difference in terms of rotation.

Conclusion

The 'Imperial cluster model' has potential to be used as a reliable way to examine spinal kinematics for the UT and LT segment. However, a new cluster model for the lumbar region may be necessary to provide more reliable kinematic data.

References

1. Jeane D, et al. The design and development of the 'Imperial spinal model': a holistic and reliable approach to assessing kinematics using 3d motion technology. Orthop Proc. 2018;99–B(SUPP_10):18–18.
2. Grood ES, Suntay WJ. A Joint Coordinate System for the Clinical Description of Three-Dimensional Motions: Application to the Knee. J Biomech Eng. 1983;105(2):136.

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No conflicts of interest.

BioMedEng18

Monitoring back muscle fatigue during activities of daily living

D. Terracina^{1,2}, P. Georgiou¹, P. Strutton²

¹ Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London. ² Department of Surgery and Cancer, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

Low Back Pain (LBP) affects 4 out of 5 people at some point in their lives. There is evidence that back muscle fatigue weakens trunk muscles, which can lead to an injury of the back and therefore LBP [1]. Very few studies have evaluated the evolution of back muscle fatigue for a prolonged time while the subject is performing activities of daily living, such as walking.

Methods

One male subject performing 3 Maximum Voluntary Contraction (MVC) of the trunk, followed by 5 forward bending of the trunk, 30 minutes walk, 5 forward bending and 3 MVC. The muscles monitored with surface electromyography (sEMG) are the latissimus dorsi, the multifidus, the iliocostalis and the longissimus. Each muscle activity is bilaterally. The data gathered is band pass filtered (cut-off frequencies at 10 and 500 Hz) and then the Short Time Fourier Transform (STFT) is applied to extract the following muscle fatigue parameters: the mean and median frequency, and the Root Means Square (RMS).

Results & Discussion

During the 30 minutes walk the subject experienced an increase in muscle fatigue in the 8 different muscles, represented by a decrease in median and mean frequency (from 36.2 to 16.4 Hz and 46.7 to 30.1 Hz respectively). Likewise, the progression of fatigue was not linear. A 5th order model was elaborated to illustrate this evolution. The model's order was chosen according to the adjusted R-square and RMSE values. We obtained a mean adjusted R-square of 0.70 and a mean RMSE of 0.09. There was also an increase in muscle activation due to fatigue for the 8 muscles. The latter was observed by an increase in the RMS over time. It is worth pointing out that the muscle fatigue experienced while performing the walking activity affected the trunk's ability to carry out the forward bending. Indeed, for the 8 muscles considered the median frequency of the forward bending activity before and after having undergone the 30 minutes walk was smaller.

Conclusion

Back muscle fatigue can be observed in activities of daily living such as walking. Muscle fatigue starts as soon as the activity begins and the back muscles are activated. Further studies should be completed in order to determine the muscle fatigue threshold, after which the subject decreases his performance in a dynamic activity. The variation in median frequency for the forward bending exercise indicates that the muscles accomplishing this task have modified their activation strategy in order to perform the same task.

References

1. C. C. Hung, T. W. Shen, C. C. Liang and W. T. Wu, "Using surface electromyography (SEMG) to classify low back pain based on lifting capacity evaluation with principal component analysis neural network method," *2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, Chicago, IL, 2014, pp. 18-21.

Acknowledgments

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The effect of rotator cuff tears on anterior shoulder instability

D. Toderita¹, C. Klemm¹, P. Reilly¹, A.M.J. Bull¹

¹Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London.

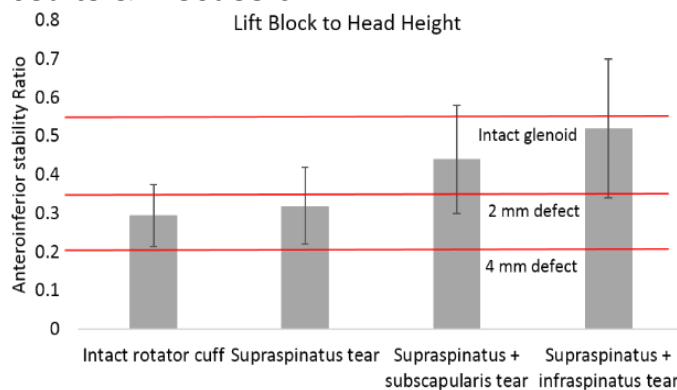
Introduction

Shoulder stability in the mid-range of motion is achieved through compression of the humeral head into the glenoid concavity through rotator cuff muscle contraction. This stability is reduced in patients with anterior shoulder dislocations due to anteroinferior glenoid osseous defects. Previous work quantified the critical lesion size of an anteroinferior glenoid defect that necessitates bone-grafting to restore joint stability to be of width 4 mm. However, these prior works did not consider rotator cuff pathology that frequently occurs concomitantly. The aim of this study is to investigate the effect of rotator cuff pathology on anterior shoulder stability to aid surgical decision-making.

Methods

Shoulder kinematics of 35 participants performing 26 functional daily activities was recorded using a 10-camera optical motion tracking system. The motion data served as input into the UK National Shoulder Model [1], with anthropometric scaling of ten subject-specific shoulder models allowing the accurate prediction of joint loading. The stability of the shoulder for each activity was assessed using the stability ratio [2]. The stability ratios were computed for 6 different combinations of rotator cuff tears and compared to literature data of dislocation forces of the glenoid with different osseous defect sizes to quantify the critical lesion size.

Results & Discussion



Isolated tears of the supraspinatus did not significantly decrease anterior shoulder stability. Combined tears of supraspinatus and either subscapularis or infraspinatus resulted in a significant loss in anterior shoulder stability ($p < 0.01$), reducing the critical lesion size of an anteroinferior glenoid osseous defect from 4 mm to 2 mm for an activity involving lifting a 2kg block to head height.

Conclusion

This study demonstrates the effect of rotator cuff tears on anterior shoulder instability and shows that the critical lesion size of an anteroinferior glenoid defect decreases with rotator cuff tears.

References

1. Charlton IW, Johnson GR. *Proc Inst Mech Eng Part H*. 2006; 220: 801-812.
2. Fukuda K. *Orthopaedics*. 1988; 11:141-149.

Acknowledgments

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Study on the Mechanism of Fluid Percussion Injuries on Immune Cells

Dasen Xu^{1,2}, Nu Zhang^{1,2}, Hui Yang^{1,2,3,*}

1 Center of Special Environmental Biomechanics & Biomedical Engineering, Northwestern Polytechnical University

2 School of Life Sciences, Northwestern Polytechnical University, Youyi West Road 127 #, Xi'an, China

3. Medical Research Institute, Northwestern Polytechnical University, Youyi West Road 127#, Xi'an, China

** Kittyyh@nwpu.edu.cn*

Introduction

In vitro models of traumatic injury are helping elucidate the pathobiological mechanisms responsible for dysfunction and delayed cell functional variation after mechanical stimulation of the single waveform pressure. It is likely that injury outcome is related to the biomechanical parameters of the traumatic event such as amplitudes and durations. However, the influence of impulsive pressure on endothelial function has not yet been fully studied in vitro. In this study, we developed a pressure loading device that produced positive by modifying an in vitro fluid percussion model and examined the effects of the pressures on macrophages' basic functions.^{[1][2]}

Methods

To model variations in the biomechanical injury parameters and simplify the experiment, single-use syringe was chosen to be the cell container and a drop hammer driven fluid percussion injury system (FPI) was designed and built to generate a single waveform with adjustable peak pressure and durations. Mice macrophage cells (Raw 264.7) were subjected to three types of the single positive pressure (120KPa, 550KPa and 1100KPa). Every 12 hours we detected its basic functions (including phagocytosis and proliferative capacity) during the following 48 hours, also the immediate cell death.

Results & Discussion

This single waveform pressure loading device could produce positive pressure with amplitudes of 70-1200KPa. After the pressure loading, there is no significant differences between the control cells and experiment cells. However, it does have a notable effect on its basic functions. The results showed that its phagocytosis and proliferative capacity were getting increasing with a peak value on 36 h and suddenly decreasing on 48 h. Moreover, these 4 regular curves are in proportion to the pressure.

Conclusion

Those results indicate that single waveform pressure have a main effect on cell's biological functions, not on cell death. And these effects on functions did have a regular functional relationship. To explore more regular curves and the mechanism, we need more experiments such as genomics technical.

References

1. Hiromichi Nakadate^{1*}, et al. Effect of amplitude and duration of impulsive pressure on endothelial permeability in in vitro fluid percussion trauma. BioMedical Engineering OnLine 2014, 13:44.
2. Radia Abdul Wahab¹, et al. Fluid percussion injury device for the precise control of injury parameters. Journal of Neuroscience Methods 248 (2015) 16–26

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BioMedEng18

Investigations on passive mechanical properties of porcine myocardium under compression

Jun Liu, Yulong Li, Yaxi Li

College of Aeronautics, Northwestern Polytechnical University, 710072 Xi'an, People's Republic of China

Introduction

The objective of the present work is to test the compressive mechanical properties of pig heart muscle under different loading rate, and try to explain the strain rate effects.

Methods

Firstly, the medium layer in left ventricle of the pig heart was cut out and then it was used to machine test samples in two directions, namely, cross muscle fibers and parallel along the fibers. Then quasi-static test was performed by using Instron5848. A modified SHPB experiment with PMMA pressure bars was set up. Samples and loading waves were designed to reduce radial inertia effects and the time for stress equilibration. To assess the extent of the stress equilibration in samples, PVDF films were used.

Results & Discussion

After propagation correction for polymer bars, the dynamic compressive response of the samples under different loading rate was tested as shown in Fig.1. Sequence picture of the deformation process were obtained by high-speed camera deformation mechanics of fibers indicated that strain rate effects is very different between static and dynamic loading conditions

Conclusion

Some conclusions were obtained from the study as follows: (1) Strength along the cross-fiber direction showed much stiffer than the other one under compression; (2) Heart muscle appears to be visco-hyperelastic under compressive loading at different strain rates; (3) Strong strain-rate sensitivity exists in both along and perpendicular to muscle fiber directions in heart muscle; (4) The difference in strain-rate sensitivity between along and perpendicular to muscle fibers is less significant than skeleton muscle; (5) Different deformation mechanics exist under static and dynamic loadings, muscle fibers showed to buckle and get separated easier in static than impact experiments; this is a possible reason for the strain-rate sensitivity in heart muscle; (6) Similarity between microstructures of long-section and cross-section in heart muscle is likely to be a reason for the less obvious strain-rate sensitivity behavior in heart muscle.

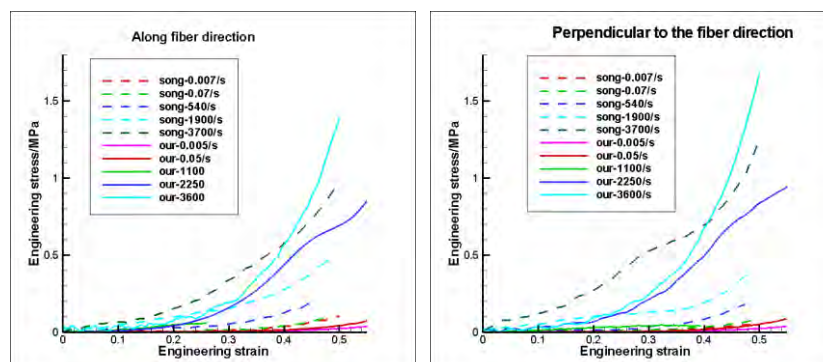


Fig.1 Stress-strain curves in the direction of cross muscle fiber

Vision-based Automatic Control of a Simulated Schunk 5-Finger Robotic Hand for Activities of Daily Living

C. Wang¹, D. Freer¹, J. Liu¹, G.Z. Yang¹

¹ Hamlyn Centre, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

Assistive robotic manipulators (ARMs) have been developed for people with upper-limb disabilities and the elderly to assist them in fulfilling activities of daily living (ADLs). However, as objects in ADLs differ in size, shape and handling constraints, most two or three finger end-effectors of ARMs have trouble robustly interacting with different object types¹. Because the world is developed for human hands, we proposed vision-based control of a 5-fingered hand (Schunk SVH), allowing it to automatically change its shape based on object classification using computer vision and deep learning.

Methods

As our study is task-oriented, following the classification of limb activities suggested by the International Classification of Functioning, Disability, and Health (ICF),² we have chosen five of most common ADLs: pressing a button, twisting a door handle, and grasping spherical, cylindrical and long and thin objects. In order to achieve automatic real-time object recognition and localization, we used a computationally light-weight version of ResNet³. This network was trained via transfer learning on our own customized object dataset. The robotic hand gestures were achieved with a V-REP simulator in real-time after object classification.

Results & Discussion

The following pictures are three examples of daily object detection and the corresponding robotic hand gesture on a simulator that would be used to interact with the object. We believe the detection accuracy and robustness can be improved with a larger dataset of daily objects.



Fig.1. Robotic Hand gestures of twisting a door handle, pressing a button and grasping long and thin objects

Conclusion

This result validates that deep learning is effective in daily object recognition in unstructured environment and can be designed to change the shape of a robotic end-effector for customized object interaction and manipulation. The next stage of our study is to attach the hand to an ARM and test whether these hand poses give any practical improvement for task completion.

References

1. Ruehl, S.W. et al., 2014. Experimental evaluation of the schunk 5-Finger gripping hand for grasping tasks. Robotics and Biomimetics (ROBIO), 2014 IEEE International Conference on, pp.2465–2470.
2. Chung, C.-S. et al., 2017. Task-Oriented Performance Evaluation for Assistive Robotic Manipulators: A Pilot Study. 96(6), pp.395–407.
3. He, K. et al., 2016. Deep residual learning for image recognition. Proceedings of the IEEE Computer Society Conference on Computer Vision and Pattern Recognition, 2016, pp.770–778.

Does visual feedback improve the soft mechanisms of interaction?

N. Peña Pérez¹, S. Abdul Motalib¹, E. Burdet¹

¹Department of Bioengineering, Imperial College London, South Kensington, SW7 2AZ, London.

Introduction

Haptic communication allows individuals to understand their partner's movement intention when collaboratively manipulating an object (e.g. carrying a table or mattress). However, it has been shown that the pair's performance deteriorates with a decrease in coupling strength when the interaction is informed through haptic sensing only [1]. Can additional visual feedback of the partner's activity modify the relationship between performance and coupling strength?

Methods

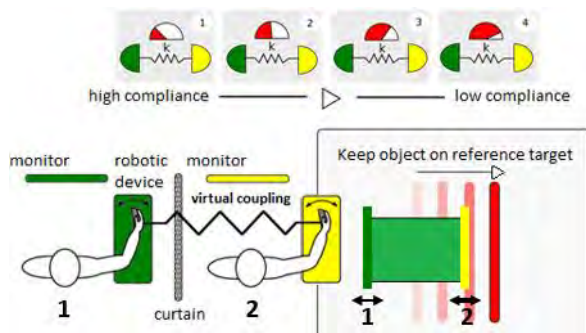


Fig. 1: Object has 4 levels of stiffness per round. Each subject controls a cursor to hold the object.

A one-degree of freedom, dual robotic interface (Hi5) was used [2]. 14 subjects were recruited in 7 dyads for the study. Each subject controlled a cursor on the screen with their wrist flexion/extension. Each dyad had to collaborate to lift an object and move it along a 25 second pseudorandom reference trajectory without dropping it (Fig. 1). The experiment consisted of 12 rounds of 4 trials of different object stiffness. Subjects were not allowed to communicate verbally during the experiment.

Results & Discussion

All dyads were able to complete the experiment with an average success rate of 0.91 ± 0.08 . Root-mean squared (RMS) tracking error was measured between the target and the object's centre trajectories. Each subject could understand the movement intention of their partner. However, performance decreases as stiffness decreases (Fig. 2).

Conclusion

Soft interaction modes deteriorate sensory information, hindering performance even with visual feedback of the partner's intention. Future work will incorporate the effect of the additional visual feedback to the neuromechanical goal sharing model [1].

References

1. Takagi, A. et al. (2018). *PLoS Computational Biology*, 14(3), 1–17.
2. Melendez-Calderon, A. et al. (2011). *Proc. IEEE International Conference on Intelligent Robots and Systems*, 2578–2583.

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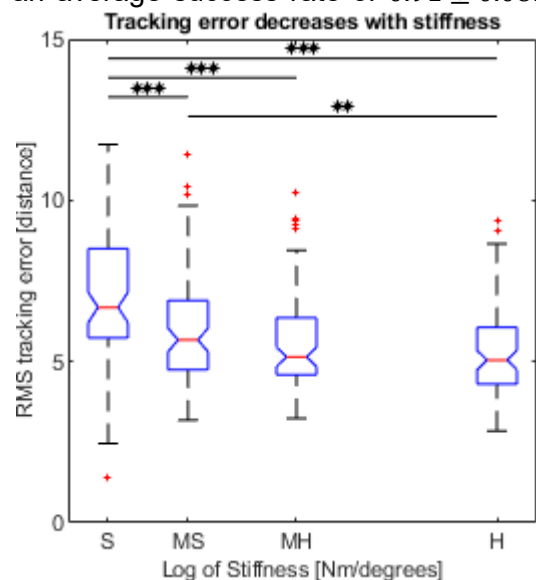


Fig. 2: Tracking error versus stiffness condition. S: Soft, MS: Medium-Soft, MH: Medium-Hard, H: Hard (**p<0.001, **p<0.01, *p<0.05).

New shape sensing approach for flexible manipulator used in MIS

T. Jeong¹, S. Han², K. Rhode¹, Y. Noh¹

¹) Department of Biomedical Engineering, King's College London, UK

²) Department of Electrical and Computer Engineering Texas A & M University, USA

(Corresponding Author : yohan.noh@kcl.ac.uk)

Introduction

There are two popular shape sensing methods in practice for flexible manipulators used in medical applications such as Minimally Invasive Surgery (MIS) (1). One uses imagers to sense shape visually, while the other approach utilises Fibre Bragg Grating (FBG) (2). However, the vision-based approach cannot guarantee persistent performance since obstacles such as organs and blood disintegrate its shape sensing quality. FBG based approach requires high-end fabrication and calibration processes, and also needs high-cost interrogators. Therefore, we propose an alternative low-cost shape sensing method using optoelectronic sensors and Inertial Measurement Unit (IMU), where the calibration process is simplified while maintaining a good accuracy.

Methods

The flexible manipulator comprised multiple, identical and independent units designed using Solidworks and printed with a 3D printer. Three optoelectronic sensors were embedded in each unit providing voltage outputs, where the linearity of the outputs vary with two resistances connected to the sensor. Hence, optimal resistances were determined to obtain the most linear voltage output. A program was developed to read and synchronise voltage outputs from the optoelectronics sensors and the Euler angle outputs (Roll and Pitch) from the IMU sensor (LPMSB, LP-RESEARCH, Japan). Linear regression method was then applied to voltage outputs and real Euler angles to compute the orientation matrix.

Results & Discussion

Estimated Euler angle values between the units were collected to compare with the ground truth Euler angles. (See figure 1 below). The maximum error was 2.5 degrees, therefore the product of the orientation matrix and any arbitrary set of voltage outputs could provide an accurate orientation angles of the unit.

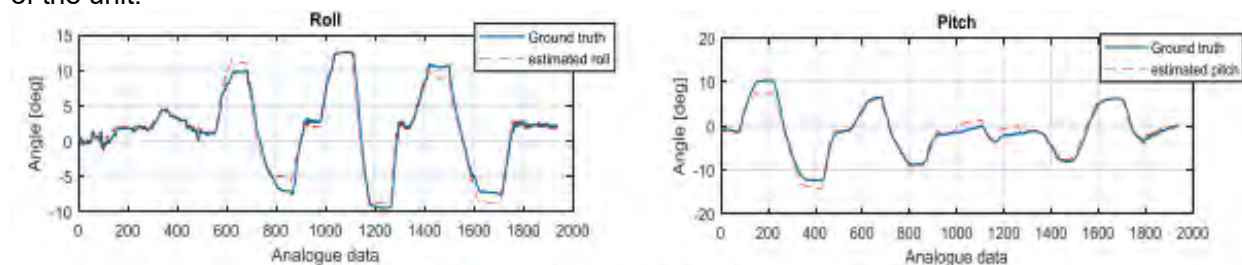


Figure 1 : Graph comparing estimated and ground truth angles

Conclusion

Multiple units can be joined to compose a complete manipulator, and the orientations of each units can be concatenated into a single orientation by using a rigid link model. It can be further improved by applying non-linear regression method, to minimise the error as the voltage output from an optoelectronic sensor is not completely linear.

References

1. D. Marchese, D. Rus, "Design, kinematics, and control of a soft spatial fluidic elastomer manipulator, "The International Journal of Robotics Research, Vol. 35(7), pp. 840–869, 2016.
2. A. Taghipour et al. "Comparative study between LPFG- and FBG-based bending sensors, " Optics Communications, Vol. 312, pp. 99-105, Feb 2014.

BioMedEng18

Decoding the Features of Neural Replay through Dynamic Logistic Regression

C. Higgins^{1,2,3}, Y. Liu⁴, D. Vidaurre^{1,2}, T.E.J. Behrens^{1,3}, M. Woolrich^{1,2}

¹ Wellcome Trust Centre for Integrative Neuroimaging, Oxford. ²Oxford Centre for Human Brain Activity (OHBA), Oxford ³Oxford Centre for Functional Magnetic resonance Imaging of the Brain (FMRIB), Oxford. ⁴Max Planck UCL Centre for Computational Psychiatry and Ageing Research, London.

Introduction

The recent discovery of cortical replay in human MEG studies, whereby neural representations of task-specific content are reactivated during rest periods in rapid sweeps, represents a novel paradigm with significant potential for computational psychiatry research and practice. It is analogous to rodent hippocampal replay, a well-studied phenomenon with strong functional links to memory encoding and retrieval – key brain functions that break down in certain types of dementia – however the exact relationship between hippocampal and cortical replay remains unknown.

The spontaneous nature of cortical replay in the resting brain poses a challenge to existing decoding methods, which generally rely on synchronous temporal alignment over trials. Consequent limitations in decoding accuracy have thus far been a hurdle to fully exploring these replay events. We have developed specialised methods that relax the assumption of temporal synchrony to achieve greater decoding accuracy over the spontaneous resting state patterns.

Methods

We outline a dynamic logistic regression model, which infers a dynamic state sequence through time and corresponding logistic regression parameters from the training data. This is achieved by introducing a Markov state variable over the regression parameters and performing variational Bayesian inference over the parameter space.

Results & Discussion

This model demonstrates enhanced decoding accuracy on held-out test data against the existing standard (mean accuracy of 65.3%, with std of 1.9% on binary classification tests using hold one out cross validation, vs mean accuracy of 62.1% and std of 2.3% for support vector machine classification), and achieves this with fewer parameters.

Furthermore when fitted to resting data the state description allows more robust inference of spatiotemporal dynamics of replay itself, with each state presenting coherent patterns of activation over sensor topographies and regular transition features through state space.

Conclusion

We introduce a new technique that demonstrates improvements on the existing decoding standard by relaxing the assumption of temporal synchrony, allowing for a richer characterisation of the dynamics of neural replay. The method generalises well across time and is broadly applicable to neural decoding problems involving dynamic or non-synchronous data.

References

1. Kurth-Nelson Z et al. *Neuron* 2016; 91: 194-204.
2. Vidaurre D et al 12 February 2018 *BioRxiv* doi:260943

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Developing experimental models of non-traumatic spinal cord injury

K. V. Timms^{1,2}, J. L. Tipper³, R. M. Ichiyama¹, J.B. Phillips⁴, J.C.F. Kwok¹, R.M. Hall²

¹ Faculty of Biological Sciences, University of Leeds, Leeds, LS2 9JT. ² Faculty of Engineering, University of Leeds, Leeds, LS2 9JT. ³ Faculty of Engineering, University of Technology Sydney, Ultimo, NSW 2007, Australia. ⁴ Centre for Nerve Engineering, University College London, Gower Street, London, WC1E 6BT

Introduction

Non-traumatic spinal cord injury (NT-SCI) is spinal cord stenosis which increases over months to years; as opposed to the millisecond duration of traumatic spinal cord injuries. NT-SCI affects up to 150000 people in the UK¹. The pathological process of NT-SCI is poorly understood and requires further investigation². The progressive and prolonged nature of NT-SCI allows neural cells to respond to changes in the mechanical environment. This is exemplified by the fact that clinically the radiological degree of stenosis does not correlate with symptoms³. This research aims to develop experimental models of NT-SCI in order to better understand the neural cell response to low-velocity mechanical insults. Ultimately, an *in-vitro* and *in-vivo* model will be established. Initial aims for the *in-vitro* model included developing a 3D environment where primary astrocytes expressed a relevant phenotype. Further, cellular responses to TGF-beta treatment, a known chemical stimulant inducing spinal cord injury-like phenotypes, were established as a positive control.

Methods

Primary rat astrocytes were isolated from pre-weaner rats. The population was validated using glial fibrillary acidic protein (GFAP) expression. Subsequently, primary rat astrocytes were seeded into rat collagen I hydrogels (1.6 mg.mL⁻¹) at a cell density of 1x10⁶ cells per mL of gel. Half of the samples were treated with 10 ng.mL⁻¹ TGF-beta and the others remained untreated. Over 14 days, cell viability was determined using ethidium homodimer and Hoechst staining; and reactivity was determined via GFAP expression. Image analysis was undertaken using FIJI.

Results & Discussion

A total of 89.7 ± 3.5% (mean ± S.E.M.) of primary glial cells were positive for GFAP. Thus, based on previous studies, the population could be described as astrocytes^{4,5,6}. These cells remained viable in collagen hydrogels, with viability increasing by 18% over 14 days in treated and untreated conditions (p<0.05 day 1 vs 14). GFAP expression did not change over time in untreated samples. In TGF-beta treated samples, GFAP-stained area increased by 2.27 fold (p<0.05 day 1 vs 14); indicating a more reactive phenotype as seen in previous studies^{4,7}.

Conclusion

Primary astrocytes were compatible with a collagen hydrogel system. The cells expressed relevant physiological and chemical-induced reactivity phenotypes which have been previously characterised in the literature. Further steps will be to use the BOSE Electroforce 5110 Biodynamic to apply controlled mechanical insults to the seeded hydrogels. Further, the *in-vivo* model is yet to be established.

References

1. New, P. W., Marshall, R. *Spinal Cord*. 2014, 52: 123-32.
2. Karadimas, S. K., Yu, W.R., Fehlings, M. *Neurobio of Disease*. 2013, 54: 43-58.
3. Nakashima, H. et al. *Eur Spine J*. 2016, 25: 2149-54
4. East, E., Golding, J.P., and Phillips, J.B. *J Tissue Eng Regen Med*. 2009, 3:634-46
5. Kerstetter, A.E. and Miller, R.H. *Methods Mol. Biol.* 2012, 814:93-104
6. Smith, J. *PhD Thesis: University of Leeds*. 2016
7. Cullen, D. K., Simon, C. M., Laplaca, M.C.. *J Neurotrauma*. 2007, 1158:103-115

Acknowledgments

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Brain Functional Network During Resting vs Active State: an EEG Study

F.Putri¹, A. Vuckovic¹

Biomedical Engineering, James Watt building, University of Glasgow, G12 8QQ, Glasgow

Introduction

EEG Resting state activity reflects the basal activity of the brain when there is no higher cognitive processes involved. In this ongoing study, comparison between baseline (B) and two different cognitive tasks (neurofeedback [NF] and mental arithmetic [MA]) were performed to give better understanding in EEG characteristics during resting state and during active state.

Methods

Five healthy able-bodied adults participated in EEG experiments, consisted of three tasks for each experiment: baseline state, alpha NF training, and MA task. Each subject performed three EEG daily sessions, first two serving as training for NF task in third session. EEG was recorded with 32 channels and linked ear reference. During NF, participants upregulated 8-12 Hz power for 30 min at Pz while MA consisted of subtraction from 100 in steps of 7. Spatial distribution of

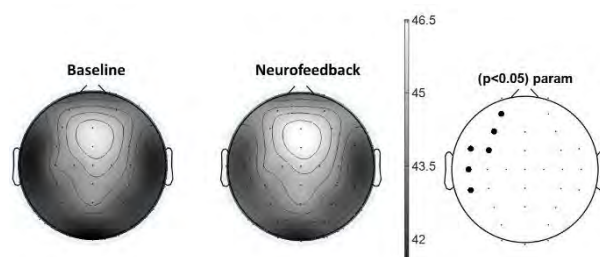


Figure 1. Spatial power distribution of theta (4-7 Hz) between B and NF show significant difference in fronto-central area. Black dots show stat. significant differences

power spectral was analysed in: 4-7 Hz (theta), 7-10 Hz (lower alpha), 10-13 Hz (upper alpha), and 13-16 Hz (lower beta). Paired t-test was performed to compare the spatial distribution of power spectra B vs NF and B vs. MA in all frequency bands. Source paired t-test analysis was performed by Low Resolution Electromagnetic Tomography (sLORETA) to analyse significant difference between B-NF and B-MA.

Results & Discussion

Power spectra analysis showed significantly stronger theta band power during B for B vs. NF comparison in left frontal and left fronto-central area (Figure 1) and no difference for other frequency bands and conditions. sLORETA analysis for the same band revealed significantly stronger left precentral gyrus (Brodmann area 4) activity in B compared to NF task, confirming significant difference found in the power spectral analysis. Theta is known for largely active in fronto-central area of the brain [1]. This result may suggest the spatially selective changes of EEG power spectra during resting and task-evoked state.

Conclusion

Results from this ongoing study provide information on the relevance of theta band for the brain during resting state and during active state. Experiments on larger number of participants are required to understand the source of differences and whether they exist in other frequency bands.

References

1. Chen, A.C., et al., Neuroimage, 2008. 41(2): p. 561-74.

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Effects of anxiety on cognitive neurodynamics among university students: preliminary data

F. Barollo^{1,4}, K. Edmunds¹, C. Ramon², I. D. Sigfúsdóttir³, A. Fratini⁴, M.K. Gislasson¹ and P. Gargiulo^{1,5}

¹Institute for Biomedical and Neural Engineering, Reykjavik University, Reykjavik, Iceland. ²Departments of Electrical Engineering and Neurology, University of Washington, Seattle, WA, USA. ³Department of Psychology, School of Business, Reykjavik University, Reykjavik, Iceland. ⁴School of Life and Health Sciences, Aston University, Birmingham, UK. ⁵Department of Science, Landspítali, Reykjavik, Iceland.

Introduction

Anxiety is a common emotion, but when experienced beyond a certain threshold, it may symptomatically compromise cognitive and functional performance. EEG is a useful tool that may be employed to investigate differences in cortical responses to tasks eliciting varying cognitive loads, implicating quantitative definitions for levels of anxiety. The *LIFECOURSE ERC* project establishes a multilevel developmental framework utilizing EEG in this context to examine the influence of stress on diverse physiological, emotional, and behavioural outcomes among adolescents. In the present pilot investigation, we outline the assessment of individuals with disparate anxiety indices to examine the potential interplay between anxiety and cognitive neurodynamics defined by EEG.

Methods

University students between the ages of 22 and 29 years (n=27) underwent anxiety assessment defined by emotive and semantic feedback in a designed psychological questionnaire. EEG was acquired, using a 32-channel wet electrode cap, over the duration of four visuospatial and/or verbal neurocognitive tasks: object naming, mental rotation, antonym generation, and spatial frequency assessment. A Matlab Graphical User Interface (GUI) was developed in order to perform statistical assessment of event-related potential (ERP) and power spectral analyses, defined by fast fourier transformation (FFT) into delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), beta (12.5-30 Hz), gamma (30-80 Hz) and ripple (80-150 Hz) bandwidths. The GUI allowed for comparative assessment within a single subject, between different subjects, or against the entire cohort.

Results & Discussion

Differences in task-related regional hemispheric power spectral density (PSD) asymmetry patterns were found between subjects with the highest and lowest anxiety levels. Within high-frequency bands (beta, gamma, ripple), this was most evident in left and right temporal electrodes during the mental rotation task (see Figure 1). Likewise, changes in left frontal delta and theta frequencies, along with occipital alpha frequencies, were identified during the object-naming task.

Conclusion

Altogether, these changes suggest the impact of anxiety on language, motor, and somatosensory cortical activity when engaged in visuospatial and/or verbal cognitive tasks. These results present a first look at understanding the effects of anxiety on cognitive neurodynamics and highlight the need for continued assessment in this regard with larger subject cohorts.

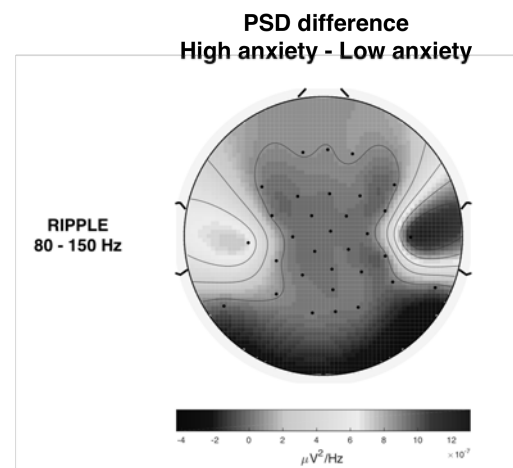


Figure 1. Example PSD results: PSD difference in the ripple frequency band (80 – 150 Hz) between high-anxiety subjects and low-anxiety subjects during the Mental Rotation task.

Dissociating frontoparietal networks based on functional connectivity states

J. Kang¹, I. Violante², R. Monti³, E. Soreq¹, R. Leech⁴, A. Hampshire¹, & R. Lorenz¹

¹ Imperial College London; ² University of Surrey; ³ University College London; ⁴ King's College London

Introduction

Non-invasive brain imaging such as functional magnetic resonance imaging (fMRI) has shown that a set of frontoparietal networks (FPNs) plays a particular prominent role in high-level cognition [1]. However, understanding how these FPNs differ in their exact functional role remains poorly understood as these FPNs co-activate for many different cognitive tasks. To overcome this challenge, in our previous study [2] we searched through a large battery of cognitive tasks using neuroadaptive Bayesian optimisation (NaBO) - an approach combining real-time analysis of fMRI and machine learning (**Fig. 1a**). We showed that NaBO can efficiently identify a set of cognitive tasks that dissociate these FPNs in terms of brain activation [2]. However, functional connectivity (FC) is more sensitive to capture brain network function. Therefore, in the present study, we revisit this data to investigate if we can reliably identify cognitive tasks that dissociate these FPNs in terms of their FC state.

Methods

20 healthy volunteers (10 each in 2 studies, 2 runs per subject) originally participated in our NaBO study [2]. In the present offline analysis, 12 regions of interest (ROIs) from two different FPNs were extracted (**Fig. 1b/c**). We

used psychophysiological interaction analysis to obtain FC estimates between each pair of ROIs. We then computed different graph-theoretical metrics on these FC estimates and identified the reliability of these metrics using spatial correlation (Spearman's Rho) between the group-level task spaces of the two independent studies.

Results & Discussion

When comparing within network connectivity strength difference for the two studies, we found high reliability ($r=.64$). Ranking nodes based on connection degree and comparing connection strength of nodes between two FPNs yielded moderate reliability ($r=.52$). Another metric computed ranks of degrees for within network connection ($r=.46$). Consistently across both studies and for all three metrics the "Counting/Calculation" task corresponded to higher metric values (i.e. optimum). Interestingly, these results are not in line with the identified optimal cognitive task in our original study [2] and may reveal a differential functional role underlying these networks when looking at FC. Other metrics that summarise strength of inter-network connections and contrast of within and between network coupling yielded unsatisfactory reliability. Next, we will investigate subject-level reliability of the most promising metrics.

Conclusion

Our results show that it is possible to dissociate FPNs based on FC states. These results will be used to inform our upcoming NaBO study in healthy controls. As a striking range of psychiatric and neurological disorders shows disruptions in FPNs, our work has the potential to lead to a novel branch of study on network dysfunction in patients.

References

1. Duncan J. & Owen A. M. *Trends Neurosci.* 2000; [https://doi.org/10.1016/S0166-2236\(00\)01633-7](https://doi.org/10.1016/S0166-2236(00)01633-7)
2. Lorenz R et al. *Nature Communications.* 2018; doi:10.1038/s41467-018-03657-3

Non-invasive neurostimulation to modulate frontoparietal synchronisation and accelerate learning

A.Davidson¹, R.Leech¹, I. Violante¹, A.Hampshire¹

¹ Imperial College, South Kensington, SW7 2AZ, London.

Introduction

A crucial part of cognitive function is the ability to assimilate information and make value based decisions. The role that particular neuronal oscillatory rhythms play in facilitating these processes was largely unknown until the development of non-invasive neurostimulation techniques, such as transcranial alternating current stimulation (tACS)⁽¹⁾. From such advances, there has been a much greater understanding of the how the brain uses distinct rhythmic frequencies for specific tasks⁽²⁾. Stimulation with tACS, can have a profound effect on the behavioural markers of learning, particularly in theta and gamma rhythms. Furthermore, these effects have been shown as especially crucial in modulating frontoparietal synchronisation and have shown to act in a phase dependent manner⁽³⁾. This study investigated the effects of tACS stimulation on the behavioural markers of learning.

Methods

This study investigated the effects of tACS stimulation with 4 different stimulation conditions that varied in frequency and phase, with one condition acting as a control. 12 participants underwent stimulation while performing a deductive reasoning task in this pseudo-randomised single blinded, cross design study. The task performed during stimulation was an “odd one out” task which evidence has shown is particularly dependent on frontoparietal communication⁽⁴⁾. Due to heterogeneity in task performance between individuals an initial “staircase” was used before undergoing the 4 types of stimulation. This is an important aspect since the beneficial effects of stimulation on cognition are seen when difficulty is high⁽⁵⁾. Response performance was recorded as accuracy and reaction time.

Results & Discussion

No significant effect was found of stimulation type on accuracy or reaction time. The order of stimulation condition was found to have a significant effect on accuracy. The effect of order of stimulation has no significant effect on reaction time.

Conclusion

Our findings may reflect a lack of therapeutic potential of tACS for modulating the neural systems involved in this task; alternatively, it may be the result of limitations with the current study, and provides direction for future studies using non-invasive stimulation to consider. The importance of testing participants at difficulty levels that are appropriate for each individual, as well as the need for personalisation of stimulation parameters

References

1. Antal A, et al. Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. *Brain Stimul* 2008 Apr;1(2):97-105.
2. Rangel A, Camerer C, Montague PR. A framework for studying the neurobiology of value-based decision making. *Nat Rev Neurosci* 2008 Jul;9(7):545-556.
3. Polania R, et al. The precision of value-based choices depends causally on fronto-parietal phase coupling. *Nat Commun* 2015 Aug 20;6:8090.
4. Lorenz R, et al. Dissociating frontoparietal brain networks with neuroadaptive Bayesian optimization. *Nature communications*. 2018; 9 (1): 3.
5. Violante IR, et al. Externally induced frontoparietal synchronization modulates network dynamics and enhances working memory performance. *Elife* 2017 Mar 14;6:10.7554/eLife.22001.

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The Effects of Neuromodulation on Central Excitability of the Upper Limb in Healthy, Able-bodied Adults

S.J. Massey¹, Y.D. Al'joboori ^{1, 2}, A. Vanhoostenberghe ^{1, 2}, L.D. Duffell ^{1, 2}

¹Aspire Centre for Rehabilitation Engineering and Assistive Technology, Royal National Orthopaedic Hospital, University College London, HA7 4LP, London. ²Department of Medical Physics and Biomedical Engineering, University College London, WC1E 7JE, London.

Introduction

Transcutaneous electrical nerve stimulation (TENS) has been shown to alter cortico-spinal mechanisms known to be involved in spasticity at frequencies >90 Hz (Mima et al., 2004; Koyama et al., 2016). Transcutaneous spinal cord stimulation (tSCS) at 50 Hz is also used in the treatment of spasticity (Hofstoetter et al., 2014). However, 49-71% of people experience paresthesia (Leonardo and Adnan, 2018). High-frequency tSCS (HF-tSCS), up to 10 kHz, may be an effective treatment, without paresthesia (Van Buyten et al., 2013). This study investigated the effects of HF-tSCS and TENS in the upper limb on motor-evoked potential (MEP) and H-reflex amplitude.

Methods

MEPs were triggered in the flexor carpi radialis (FCR) and extensor carpi radialis longus (ECRL) in two participants and FCR H-reflex was triggered in one. This was followed by 30 minutes of TENS (150 Hz, 100 μ s pulse width) and HF-tSCS (30 Hz, 9090 Hz carrier frequency, 50 μ s pulse width) in separate sessions. Interventions were delivered in 2 second bursts following 2 seconds of no stimulation. MEP and H-reflex amplitude was then measured immediately following intervention and for 15 minutes thereafter, up to 60 minutes.

Results & Discussion

ECRL MEP amplitude decreased for 60-mins following TENS. However, this increased following HF-tSCS. The effects of both therapies on FCR MEP amplitude were inconclusive, however H-reflex amplitude decreased immediately after both. These preliminary results suggest that HF-tSCS may not be as effective as TENS for spasticity management.

Conclusion

These results indicate that TENS intervention has triggered reciprocal inhibition in the ECRL, and has had an excitatory effect on the FCR. Conversely, HF-tSCS facilitated ECRL MEP amplitude. Further investigation will confirm the effectiveness of HF-tSCS compared with TENS intervention for the management of upper limb spasticity.

References

1. Mima T, Oga T, Rothwell J, Satow T, Yamamoto J, Toma K, Fukuyama H, Shibasaki H, Nagamine T. *Neuroscience Letters*. 2004;355(1-2): 85-88.
2. Koyama S, Tanabe S, Takeda K, Sakurai H, Kanada Y. *Somatosensory & Motor Research*. 2016; 33(1): 8-15.
3. Hofstoetter U, McKay W, Tansey K, Mayr W, Kern H, Minassian K. *The Journal of Spinal Cord Medicine*. 2014; 37(2): 202-211.
4. Leonardo K, Adnan A. In: 2nd ed. *Ten Kilohertz (10 kHz) High-Frequency Spinal Cord Stimulation*. Elsevier Ltd. 2018: 693-699.
5. Van Buyten J, Al-Kaisy A, Smet I, Palmisani S, Smith T. *Neuromodulation: Technology at the Neural Interface*. 2013; 16(1): 59-66.

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Effect of Neurofeedback Training on Laterality During Leg Motor Imagery

A. Zulauf-Czaja, A. Vuckovic, A. Fatih

James Watt Building, University of Glasgow, G12 8QQ, Glasgow, UK

Introduction

Laterality index (LI) [1] provides a quantitative measure of the involvement of each brain hemisphere during a particular task. Here an attempt is made to calculate LI during leg motor imagery (MI) condition using data obtained via electroencephalography (EEG). Since brain areas involved in leg MI are deeper than the cortical surface and in the central longitudinal fissure, therefore not easily accessed via EEG, sLORETA is used to calculate active voxels of the brain during this task to calculate LI.

Methods

The EEG of three healthy subjects was recorded using 44 channels during two separate sessions at least a week apart. During both sessions the tasks were performed in 20s alternating intervals of the task (e.g. MI) and relaxed state. The first session was a control consisting mostly of MI of the right leg. During the second session the subject was shown nearly real time neurofeedback (FB) in the form of a 3D model of the brain with projection of their brain activity in the subject's specific dominant frequency band (determined after control session), and asked to upregulate the activity of the right leg M1 and SMA area. Later weighted LI was calculated as $LI = (v_L - v_R) / (v_L + v_R)$ where v_L and v_R represent the number of active voxels in BA 4 and 6 of the left and right hemispheres during MI with FB as compared to resting state.

Results & Discussion

Figure 1 presents cortical projections of MI with FB compared to resting state at each subject's frequency band used for the FB. Both S1 and S2 present left hemispheric dominance, while S3 a more central pattern. This is reflected in the LI values listed below each cortex – left dominance ($LI > 0.2$) was found for S1 and S2, while bilaterality ($LI < |0.2|$) for S3 [1].

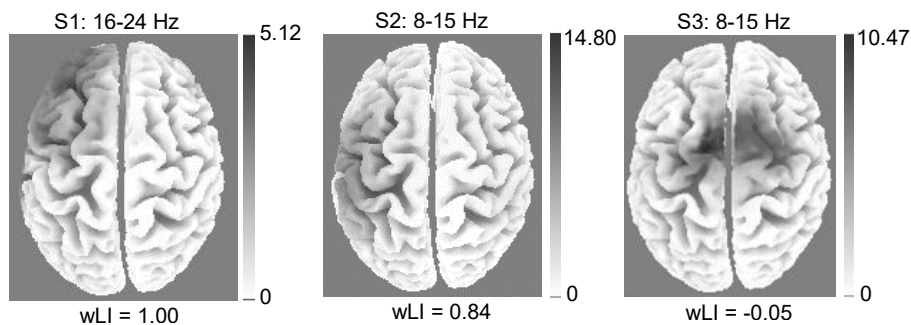


Figure 1. Images of cortical projections of MI with FB compared to resting state for each subject in the frequency band used for FB. The bar graph represents the r-value at each voxel for each subject – darker colour means more activity in MI than in resting state. The LI index is listed below each cortical image.

Conclusion

Initial volumetric analysis of laterality shows more activity in the left hemisphere in two cases, and bilateral activity in one. The dominant frequency band varies between subjects.

References

- [1] M. L. Seghier, "Laterality index in functional MRI: methodological issues," *Magn. Reson. Imaging*, vol. 26, no. 5, pp. 594–601, 2008.

Acknowledgments

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Remote control of cell signalling with magnetic particles for neuronal cell differentiation- emerging therapies for Parkinsons disease

M. Rotherham¹, T. Nahar¹, T. Goodman¹, N.D. Telling¹, M. Gates¹, A.J. El Haj¹

¹*Institute for Science and Technology in Medicine, Keele University, UK*

Introduction

Cell signalling pathways such as the Wnt pathway and Trek channel signalling are important controllers of cell fate and regulators of neuronal development. The development of modulators of these pathways is therefore of clinical relevance for the treatment of neurodegenerative disease. Cell surface receptors that initiate cell signalling and neural progenitor differentiation can be targeted using ligand functionalised magnetic nanoparticles (MNP). This allows remote mechano-stimulation of receptors using externally applied magnetic fields for remote activation of differentiation pathways or induction of directional neurite outgrowth. The aim of this research was to investigate the effects of remote activation of the Wnt receptor Frizzled and the Trek1 potassium channel on neuronal differentiation of neuroprogenitor cells.

Methods

Target receptor expression was assessed in SH-SY5Y and neural progenitor cells using rtPCR. 250nm MNP were coated with peptides or antibodies allowing MNP tagging to Frizzled/Trek receptors. Remote MNP-receptor complex stimulation was performed in 1h-3h sessions using alternating magnetic field gradients provided by a magnetic force bioreactor (MICA Biosystems). Downstream signalling activity was assessed by monitoring β -catenin mobilisation and TCF/LEF responsive gene expression using a TCF/LEF reporters. Neuronal differentiation marker expression was determined both *in vitro* and *ex vivo* embryonic rat brain slices of the nigral-striatal circuit to assess the effects of remote signalling activation on neuronal differentiation of injected progenitor cells.

Results & Discussion

Basal expression of Frizzled1, 2 and Trek1 was confirmed in SH-SY5Y cells and was found to fluctuate during RA/BDNF induced neural differentiation. β -catenin mobilisation and TCF/LEF reporter activity both increased in response to Frizzled targeted MNP and magnetic field stimulation. Short-term fluctuations in expression of stress-response genes NF- κ B and COX2 were observed in response to MNP induced receptor activation. Expression of dopaminergic markers DAT and TH was augmented *in vitro* and maintained in *ex vivo* rat brain slices when SH-SY5Y cells were cultured in neuronal differentiation media and treated with MNP and magnetic stimulation.

Conclusion

Our results demonstrate that remote activation of Wnt signalling pathways can be achieved in neuronal precursor cells using tagged magnetic particles and external magnetic fields. This remote activation approach can then be used to stimulate and augment precursor cell differentiation towards the neuronal lineage. This technique may offer a novel therapeutic strategy for treating neuro-degenerative diseases such as Parkinsons disease.

Acknowledgments

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Endogenous control of closed-loop brain-machine interfaces for pain.

S. Zhang^{1,2}, W. Yoshida², H. Mano³, T. Yanagisawa⁴, K. Shibata⁵, M Kawato², B. Seymour^{1,2,3}

¹ Computational and Biological Learning Laboratory, Department of Engineering, University of Cambridge, Cambridge CB2 1PZ, UK ² Brain Information Communication Research Laboratory Group, Advanced Telecommunications Research Institute International, Kyoto, Japan ³ Center for Information and Neural Networks, Osaka, Japan ⁴ Endowed Research Department of Clinical Neuroengineering, Osaka University, Japan ⁵ Department of Cognitive and Psychological Sciences, Nagoya University, Japan

Introduction

The aim of closed-loop brain-machine systems for pain is to automatically adjust the ongoing level of intervention to pain-related neural activity. However pain is highly susceptible to endogenous modulation, raising the possibility that active or passive changes in neural activity provoked by the operation of the system could interfere with the signals upon which it is based.

Methods

We studied 19 healthy human participants in real-time fMRI-based closed-loop pain control.

Day 1: Participants received sequences of high/low intensity pain stimuli, and their functional brain images were used to train multi-voxel pattern decoder for pain levels classification.

Day 2: Trained decoders were used to predict participant's pain intensity from real-time fMRI, and a reinforcement learning algorithm learned to control the level of upcoming pain stimuli using the decoded pain levels as feedback, with the objective to learn to deliver less painful stimuli.

Results & Discussion

We showed that the closed-loop pain control system could learn to deliver less pain to participants. We also identified that the system engaged two types of endogenous processes in the brain. First, despite the inherent incentive for participants to enhance the neural decodability of pain, decodability was either reduced or unchanged in classic pain-processing regions, but increased in an endogenous pain modulatory region - the pregenual anterior cingulate cortex (pgACC). Second, we found that pain perception itself was modulated by an endogenous computational uncertainty signal as participants learned the success rate of the closed-loop system in reducing pain - an effect also correlated with pgACC responses.

Conclusion

Our results illustrate how regionally and computationally specific co-adaptive brain-machine learning influences the efficacy of closed-loop systems for pain, and shows that pgACC acts as a key hub in the endogenous controllability of pain.

References

1. Zhang S and Seymour B, *Current Biology*. 2014; 24(18):R930–R935
2. Shibata, K. *et al. Science*, 2011; 334(6061):1413–1415

Acknowledgments

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BioMedEng18

‘Working harder together’: Surges in global activity & synchrony during cognitive state transitions

Richard E. Daws¹, Eyal Soreq¹, Robert Leech², Peter Hellyer² & Adam Hampshire¹

¹The Computational Cognitive & Clinical Neuroimaging Lab (C³NL), Imperial College London, UK. ²The Centre for Neuroimaging Sciences (CNS), King’s College London, UK.

Introduction

A recognised issue in cognitive neuroscience is the “one-to-many” & “many-to-one” mappings problem[1]. Multiple Demands Cortex (MDC)[2], is a set of regions that co-activate for distinct cognitive processes[3]. This suggests that it is the way that brain regions communicate that allows for a set of regions to perform differing processes. Questions remain around how the brain self-organises dynamic network states & transitions between them. Previous work has identified frontal polar cortices as ‘switching modules’[4]. Here, we use functional Magnetic Resonance Imaging (fMRI) & a Self-Ordered Switching (SOS) paradigm to examine neural regional activity and dynamic Functional Connectivity (dFC) during transitions between cognitive states.

Methods

SOS fMRI recordings were collected from 16 controls (mean Age=25 years, SD=7, F=10/25) on a Siemens 3T Trim Trio & modelled in SPM12. Activity was predicted voxelwise in a General Linear Model (GLM) using the individuals psychological (10 predictors: Switch & Trial Events) & motion timecourses. Group-level activation maps were segmented into Regions of Interest (ROIs) using a watershed algorithm. ROI dFC was estimated pairwise with Psychophysiological Interactions (PPI) [6] & between multiple ROIs with phase synchrony [7,8,9].

Results & Discussion

Task switches were associated with costs to reaction time (Main effect: $F(2,47)=10.05$, $p<0.001$) & global increases in activation ($F(2,47)=119.229$, $p<0.001$) & phase synchrony ($F(2,47)=4.350$, $p=0.022$). Moreover, we see distinct multivariate patterns of PPI dFC for task states & switches between them.

Conclusion

In contrast to previous findings of the frontal poles acting as ‘switching modules’, we see *widespread* increases in activation associated with task switching. Switch related performance costs may reflect learning effects as the system (increasing in activation & synchrony) optimizes toward the incoming task state.

References

1. Lorenz, R., et al. 2017. *TICS*, 21(3), pp.155-167.
2. Fedorenko, E., et al., 2013. *PNAS*, 110(41), pp.16616-16621.
3. Hampshire, A., et al. 2012. *Neuron*, 76(6), pp.1225-1237.
4. Ramnani, N. & Owen, A. M. 2004. *Nat Rev Neurosci*, 5(5), 184-94.
5. Friston, K.J. et al. 1996. *MR in medicine*, 35: pp. 346-55.
6. McLaren, D. G., et al. 2012. *Neuroimage*, 61: 1277-86.
7. Hellyer, P. J., et al. 2014. *J Neurosci*, 34: 451-61.
8. Kuramoto, Y. . 1984. Springer: New York .
9. Laird, A. R., et al. 2002. *Hum Brain Mapp*, 16: 71-80.
10. Ward Jr, J.H., 1963. *Journal of the American statistical association*, 58(301), pp.236-244.
11. Langs, G. et al. 2016. *Cerebral Cortex*, 26(10), pp.4004-4014.
12. Crittenden, et al., 2015. *Elife*, 4.

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BioMedEng18

Integrating Neurodata Without Borders (NWB) into NeuroSEE, the automated Neuronal Source Extraction and Exploration toolbox

S. Boretska^{1,2}, S.V.Prado^{1,2,3}, M.A. Go², S.R. Schultz^{1,2}

¹ Centre for Neurotechnology, Imperial College London, South Kensington, SW7 2AZ.

²Department of Bioengineering, Imperial College London, South Kensington, SW7 2AZ.

³Department of Electronics Engineering, University of Santo Tomas, Manila, 1008, Philippines.

Introduction

Due to the increasing sizes of neuroscientific data sets, considerable efforts have been made to establish a format across these and to automate data handling procedures that help reduce human error and time consuming pre-processing. The NeuroSEE Toolbox aims to overcome these issues through the automation of extraction, with the integration of the Neurodata Without Border (NWB) format, supporting the exploration of two-photon imaging data for place field analysis [1].

Methods

The pipeline workflow consists of the captured raw two-photon movies and behavioural .mp4 files, which are run through extraction algorithms, resulting in two MATLAB files holding the behavioural tracking data and timeseries data. The NWB File formatting module was built to be run after data capture using the Python programming language, storing the intermediate outputs from the processing algorithms, rather than the raw video files. This avoids the handling of large processor heavy files and removes data dependencies when using the NWB Files for analysis.

Results & Discussion

The formatting module integrates the stages of Timeseries Extraction and Behavioural Tracking Extraction from the workflow. Whilst also mapping these to metadata using an ontological vocabulary, resulting in files which are built through an automated pre-processing, extraction and data labelling process [2].

Conclusion

With this integration of processes, exploring and visualising the data after experimentation is streamlined, and results are stored in a single file structure, allowing for users to gain an insight to the quality of the captured data. The next step in this module, is making it accessible to other groups and experiments, allowing users to define the data they are providing, whilst making sure it is meeting the minimum information required for the formatting and extraction modules [3].

References (examples – use “First author *et al.*” if more than 3 authors, **minimum font size 9pt**)

1. Teeters, J.L., *et al.* (2015) Neurodata without borders: creating a common data format for neurophysiology. *Neuron*, 88(4), pp.629-634
2. Stevens, R., Goble, C.A. and Bechhofer, S. (2000) Ontology-based knowledge representation for bioinformatics. *Briefings in Bioinformatics*, 1(4), pp.398-414.
3. Gibson, F., *et al.* (2009) Minimum information about a neuroscience investigation (MINI): electrophysiology. *Nature Precedings* [online]. Available at: <http://hdl.handle.net/10101/npre.2008.1720.1>

Acknowledgments

We are grateful to the Wellcome Trust and EPSRC Medical Engineering Initiative and the Bioengineering Society for supporting this conference. **Please declare all possible conflicts of interests in this section.** No conflicts of interest to declare

BioMedEng18

Modelling Tremor for Virtual Prototyping of Exo-Glove

R. J. Varghese¹, C. Romanczyk¹, J. Liu¹, G-Z. Yang¹

¹The Hamlyn Centre, Department of Computing, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

The rapid prototyping lifecycle - design, development and optimization of assistive devices for tremor suppression gets delayed as access to patients during initial prototyping stages is limited. Additionally, the manifestations of tremor vary significantly from one patient to another [1]. To expedite the development of assistive devices for tremor suppression, it therefore becomes important to develop virtual design and prototyping methods.

Methods

In this work, the open-source musculoskeletal modelling software, OpenSim [2] was used. The primary frequency in tremor ranges between 4-8Hz, with multiple secondary frequencies (<10% amplitude of primary tremor) in the range 5-20Hz [1]. A random neural signal with the aforementioned characteristics was generated in MATLAB®. The signal was then divided into activations for the agonist (wrist flexion-FCR, FCU) and antagonist muscles (wrist extension – ECRL, ECRB) in a wrist model developed by Gonzalez et al. [3]. Forward dynamics simulations were run based on the muscle controller made up of these activations.

Results & Discussion

The results are summarized in the figure following underneath. Even though activations were applied only to the flexion/extension muscles, tremor in both flexion and deviation angles is observed. Activation and tremor signals have been shown in both time and frequency domains.

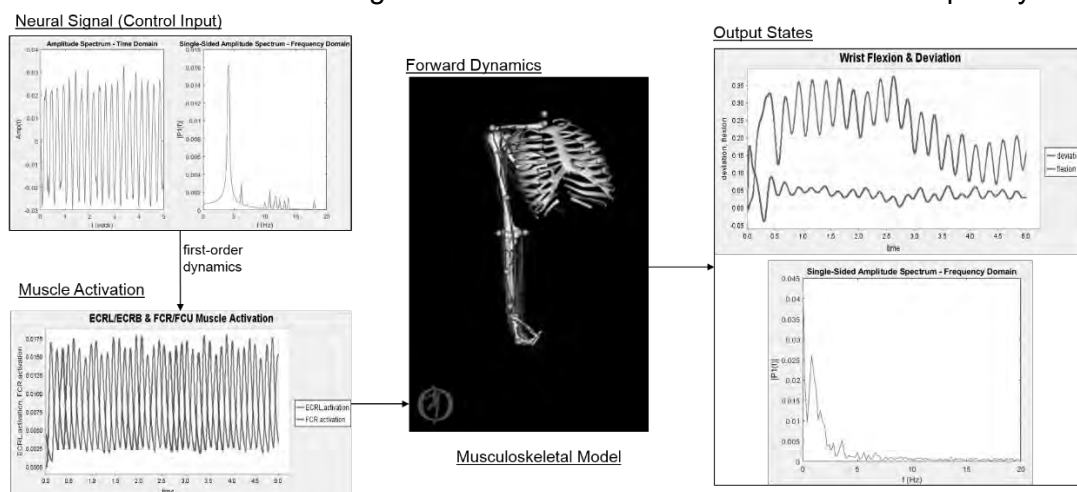


Fig. 1 Overview of method and results for simulating tremor in wrist (using MATLAB® & OpenSim)

Conclusion

Though access to patients with tremor is challenging, we have presented an alternative simulation based solution for virtual prototyping of tremor suppression exo-gloves.

References

1. Rahimi F., et al. "Tremor suppression orthoses for parkinson's patients: a frequency range perspective." In Engineering in Medicine and Biology Society, 2009. EMBC 2009. Annual International Conference of the IEEE, pp. 1565-1568. IEEE, 2009.
2. Delp, S.L., et al. OpenSim: open-source software to create and analyze dynamic simulations of movement. IEEE Transactions on Biomedical Engineering 54(11):1940–1950, 2007
3. Gonzalez, R. V., Buchanan, T. S., Delp, S. L. How muscle architecture and moment arms affect wrist flexion-extension moments, Journal of Biomechanics Vol. 30, pp. 705-712. (1997)

Reduced-Order Computational Models for Central Blood Pressure Estimation: Two Clinical Scenarios

Jorge Mariscal-Harana¹, Peter Charlton¹, Spencer Sherwin², Jordi Alastruey¹

¹ School of Biomedical Engineering and Imaging Sciences, King's College London, SE1 7EU, London.

² City and Guilds Building, South Kensington Campus, Imperial College London, SW7 2AZ, London.

Introduction

Central blood pressure (CBP) is a better cardiovascular risk indicator than brachial pressure [1]. The current gold standard for the assessment of CBP is a catheter, which is invasive. We propose a new method to assess CBP from aortic blood flow and peripheral blood pressure, which can be measured non-invasively. This clinical data is used to generate reduced-order (0-D or 1-D) computational models which provide accurate CBP estimates. Our analysis is based on basic haemodynamic principles and on phenomena occurring directly in the ascending aorta. The aims of this study are twofold: to compare reduced-order CBP estimation models; and to find optimum parameter estimation methods for two common clinical scenarios.

Methods

Two 0-D models, namely the two-element and three-element Windkessel models, and one 1-D model of the aorta were studied. A population of 'virtual' (computed) healthy subjects was generated using a 1-D model of the systemic arteries based on [2]. Using each subject's unique pressure and flow waveforms as reference data, parameter estimation methods were developed. The optimal method was identified based on the errors between reference and estimated systolic (SBP) and pulse (PP) pressure values. Two common clinical scenarios were considered: (i) a pressure waveform is available, and (ii) only diastolic (DBP) and mean (MBP) blood pressure values are available. These optimum methods were applied to two clinical cohorts: hypertensives and normotensives.

Results & Discussion

For scenario (i), average relative errors in SBP and PP were <3% and <8%, respectively, across both clinical cohorts. Average relative errors in SBP and PP for scenario (ii) were <6% and <17%. In both scenarios, average SBP and PP errors were higher for the hypertensive cohort.

Conclusion

Parameter estimation methods which account for two different clinical scenarios were developed and compared. All three models performed similarly when estimating landmark values of blood pressure. However, the 1-D model was superior at reproducing space-dependent features of the pressure waveform.

References

1. McEniery *et al.* *European Heart Journal*. 2014; 35(26): 1719-1725.
2. Willemet, M., Chowienczyk, P., & Alastruey, J. *American Journal of Physiology – Heart and Circulatory Physiology*. 2015; 309(4): H663-H675.

Acknowledgments

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Tracking variations in cardiac output from pressure and pulse wave velocity measurements: a proof-of-concept study

S. Vennin^{1,2}, P. Charlton ², F. Vallée ³, J. Alastruey ², P. Chowienczyk¹

¹ Dept of Clinical Pharmacology, King's College London, SE7 1EH, London ²Dept of Biomedical Engineering, King's College London, SE1 7EU, London ³ Dept of Anesthesiology, Hôpitaux Universitaires St-Louis-Lariboisière, Paris

Introduction

Cardiac output (CO), the volume of blood ejected by the heart per minute, is of critical importance in delivering oxygen and nutrients to vital organs [1]. A fall in CO is one of the main reasons of death in intensive care units and for complications during/after major surgery. For this reason, it is routinely monitored to guide management, but accurate measurements of CO require specialist equipment and invasive access. Non-invasive alternatives that could transform critical care outside of the intensive care unit, if they were sufficiently accurate, perform poorly when tracking within-patient changes in CO that are used to inform patient management. We present an algorithm based on physical principles that show great promise in overcoming these limitations.

Methods

The algorithm first extracts the key pressures of a measure pressure waveform. A corresponding blood flow waveform is generated through an iterative algorithm to minimise errors between the measured pressure features and those generated from a validated simplified model of the arterial tree linking pressure to flow [3]. We tested the algorithm with invasive data obtained in 29 patients (19 men, age 45 ± 15 years old, BP $117 \pm 18/63 \pm 12$ mmHg, mean $\pm$ SD) during general anaesthesia. We also compared the performance of the algorithm against 11 other algorithms previously published – some used by existing commercial devices - to 1) estimate single CO measurements (n=106) and 2) track within-subject variations in CO (n=29).

Results & Discussion

The estimates yielded by the algorithm were highly correlated with reference measures (Pearson coefficient, $r=0.93$) with a small deviation after calibration (SD=0.42 L/min). Comparatively, the second-best algorithm had a Pearson coefficient $r=0.77$ and a standard deviation twice as high (SD=0.83 L/min). Importantly, our algorithm was the only one to accurately track within-subject variations in CO (Pearson coefficient, $r=0.85$), despite variations over a relatively small range. By contrast, many existing methods showed no or little correlation with the “gold-standard” measure which is in accordance with the findings of other studies [3].

Conclusion

Our algorithm provided the most accurate estimates and trends of all the algorithms tested. We now need to test it prospectively on wider ranges of variation.

References

1. Vlachopoulos C, O'Rourke M, Nichols WW. *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles*. CRC Press; 2011.
2. Vennin et al. Identifying Hemodynamic Determinants of Pulse Pressure. *Hypertension*, 70(6), 1176-1182; 2017
3. Caillard et al. *Comparison of cardiac output measured by oesophageal Doppler ultrasonography or pulse pressure contour wave analysis*. *British Journal of Anaesthesia*, 114(6), 893-900; 2015.

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The Effect of the Mach Number on the Reflection Coefficient Estimated by Wave Intensity Analysis

A. Giudici¹, W. Hacham^{1,2}, A. W. Khir¹

¹ Brunel Institute for Bioengineering, Brunel University, Middlesex, UK. ² University of Baghdad, Iraq

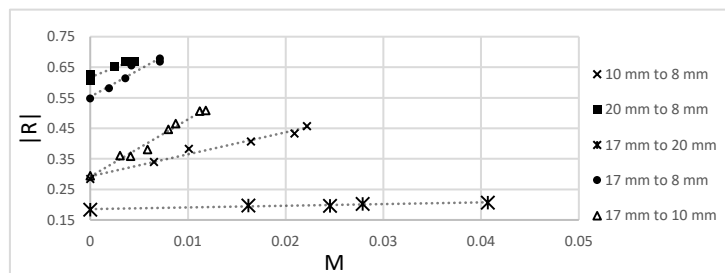
Introduction

The standard formulation of Wave Intensity Analysis (WIA) assumes that the flow velocity (U) in the conduit is negligible with respect to the velocity of propagation of waves (c) in the system; $U \ll c$, where Mach number ($M = U/c$) is ≈ 0 . This assumption holds true in most regions of the arterial tree, however, in large conduit arteries U is relatively high due to ventricular contraction and c is relatively low due to the high compliance; thus, M is significantly greater than 0. Therefore, the aim of this study is to identify experimentally the relationship between M and the reflection coefficient in vitro.

Methods

Combinations of flexible tubes, of 2 m in length with circular cross sectional area, isotropic and uniform material properties along their longitudinal axes of internal diameter of (8, 10, 17 and 20 mm) and wall thickness of (1, 1.5, 2 mm) were used to present a mother connected to a daughter tube. An approximately semi-sinusoidal pulse was generated at the inlet of each tube using a syringe pump, first the waves speed was determined using the foot to foot and PU-loops methods in the condition of unperturbed velocity ($U_0=0$). The theoretical reflection coefficient (R_0) for $M=0$ has been calculated as $R_0 = (1-Y)/(1+Y)$, where $Y = 1/Z_0$; Z_0 is the characteristic impedance $= \rho A/c$, where ρ is the density and A is the cross sectional area. Then, superimposing steady flow using constant DC motor over the pulse waveform generated by a syringe pump, we recorded simultaneously pressure and velocity in the mother tube at a sampling rate of 500 Hz to identify the relationship between M and R . WIA was used to separate the pressure waveforms and the experimental reflection coefficients (R) at $M>0$ were determined as $dP-/dP+$, where $dP+/-$ are the changes in pressure in the forward and backward directions.

Results & Discussion



In the present experiments of pulsatile flow in long flexible tubes R increased significantly with small value of M (order of 10^{-2}). In the range of $M=0$ to 0.005, R increases by 4% to 36%. Further, R changes significantly with the geometrical and mechanical features of the connected tubes.

Conclusion

In pulsatile flow of flexible tubes where M is not negligible, the reflection coefficient provided by standard WIA is significantly altered by M . The reflection coefficient is not determined solely by geometrical and mechanical properties of flexible tubes but also by their relative value.

Acknowledgments

The authors have no conflict of interest to report.

A computational based analysis of flow mediated dilation: Towards improved endothelial function assessment

W. Jin¹, P. Chowienczyk², J. Alastruey¹

¹Department of Biomedical Engineering, King's College London, St Thomas' Hospital, SE1 7EH, London.

²Department of Clinical Pharmacology, King's College London, St Thomas' Hospital, SE1 7EH, London.

Introduction

Endothelial function (the effective working of cells lining blood vessels) is a crucial diagnostic biomarker for assessing cardiovascular function¹. Flow mediated dilation (FMD) is a standard test for the non-invasive assessment of endothelium function. It measures the increase in arterial diameter in response to an increase in wall shear stress (WSS) produced by a surge in blood flow generated by deflation of a sphygmomanometer cuff around the forearm². Current FMD assumes that total vasodilation is attributed to the increase in WSS, which triggers the release of the vasodilator nitric oxide (NO) by the endothelial cells². Whereas, recent studies showed that the initial pressure drop due to the surge in flow velocity, as well as the stiffness of the vascular system, have a considerable effect on the amount of vasodilation measured during FMD³. This study aims to investigate and quantify the effect on FMD of pressure drop and arterial stiffness.

Methods

Arterial diameter, blood flow velocity, and blood pressure in the larger arteries of the arm were simulated during FMD using a one-dimensional solver of blood flow in compliant vessels⁴. The simulation involved evolution functions for arterial stiffness and peripheral resistance which were generated based on haemodynamic data measured in 8 subjects. The model was run under different scenarios of changing arterial stiffness and peripheral resistance.

Results & Discussion

Our computational results showed that the initial pressure drop after cuff deflation is due to a decrease in peripheral resistance, physiologically caused by the tissue-starvation-induced dilation of distal vessels. Maintaining peripheral resistance constant leads to a zero pressure drop and an increase in FMD for about 1% (Normal range: $8.9 \pm 3.1\%$ ⁵). These results suggest that the pressure-drop-induced vasoconstriction should be eliminated from current FMD measurement to quantify endothelial function more accurately. Moreover, FMD was considerably affected by the stiffness of the whole artery system. Doubling the stiffness decreased the FMD by about 2%. This indicates that the patient's age needs to be considered when interpreting FMD readings.

Conclusion

Our novel computational model allows us to investigate and quantify the amount of vasoconstriction due to the initial pressure drop after cuff deflation, and the amount of vasodilation due to the increase of WSS for a given arterial stiffness value. They should both be taken into account when measuring FMD.

References

1. Brunner, H. *et al. J. Hypertens.* 2005; 23: 233–246.
2. Thijssen, D. H. J. *et al. AJP Hear. Circ. Physiol.* 2011; 300: H2–H12.
3. Jiang, B. *et al. Hypertension* 2011; 57: 1145–1150.
4. Alastruey, J., Parker, K. H. & Sherwin, S. J. *BHR Gr. - 11th Int. Conf. Press. Surges* 2012; 401–442.
5. Adams, M. R. *et al. J. Vasc. Investig.* 1996; 2: 146–150.

Acknowledgments

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Aortic Aneurysm Detection by Waveform Analysis

I. Sazonov¹, A.W. Khir², P. Nithiarasu¹

¹ Swansea University, Bay Campus, Fabian Way, SA1 8EN. ² Brunel University London, Uxbridge B8 3PH

Introduction

An aortic aneurysm is a progressively growing dilation of the aorta with a risk of potentially lethal rupture. Successful treatment of an aneurysm depends on how early it has been detected. To detect an aneurysm on time, a continuous and expensive screening programme is necessary. Ultrasound (US) echography is mainly used in AAA (abdominal aortic aneurysm) screening programmes but it has limitations due to fact that aorta is buried deep in human body. It is also inapplicable for the thoracic aortic aneurysm (TAA) detection. Other methods like 3D CT, MRI are expensive and are mainly applied at the latter stages of the aneurysm evolution.

Methods

A novel non-invasive method of AAA/TAA detecting and monitoring is proposed here which comprises measuring of the blood pressure/velocity waveforms in accessible parts of a human body followed by analysis the waveforms by means of special algorithms for solving the inverse problem. Development of the aneurysm detecting algorithms is based on 1D modelling of systemic circulation and approximation of an aneurysm by a lumped (0D) model. A new numerical scheme is proposed which combines the perturbation method and the fast Fourier transform (FFT) method. Its effectiveness is shown for the 1D numerical modelling of cardiovascular systems with aneurysms.

Results & Discussion

It is shown that the parameters of wave pulse reflected from the aneurysm are determined mainly by the aneurysm integral parameter which we call the aneurysm compliance. This parameter grows proportional to the cube of the aneurysm diameter and inversely proportional to the vessel wall stiffness, therefore, it can be considered as an aneurysm severity indicator: it can be large for an aneurysm of a larger diameter with relatively stiff vessel walls and for a smaller aneurysm with 'softer' walls, i.e. one which poses a higher rupture risk despite its small size.

The study shows the potential of determining this aneurysm severity parameter and the aneurysm location on an aorta via the waveforms analysis (i) experimentally in a simplified network with aneurysms of different diameter, (ii) numerically by the 1D modelling of this experimental network and (iii) for an in silico human arterial network with AAA of different size.

Conclusion

The proposed method allows determination of aneurysm location on aorta and its severity parameter which incorporates the aneurysm size and mechanical properties of its wall. The method is justified experimentally in the simplified arterial network and in the numerical modelling of the human arterial network. The method can provide clinicians with a non-expensive, easily accessible tool for aneurysm screening, monitoring and the intervention time estimating.

References

1. Sazonov I *et al.* A novel method for non-invasively detecting the severity and location of aortic aneurysms., *Biomech Model Mechanobiol*, 2017; 16:1225–1242

BioMedEng18

A Database for the Development of Pulse Wave Analysis Algorithms

P. H. Charlton¹, J. Mariscal Harana ¹, S. Vennin ^{1,2}, P. Chowienczyk ², J. Alastruey ¹

¹ Department of Biomedical Engineering, King's College London, King's Health Partners, London, SE1 7EH.

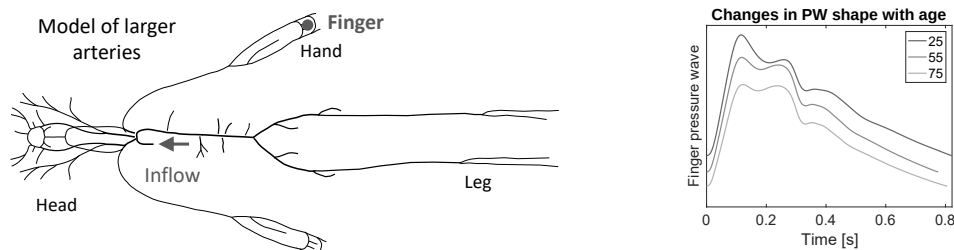
²Department of Clinical Pharmacology, King's College London, King's Health Partners, London, SE1 7EH.

Introduction

The shape of the arterial pulse wave (PW) is a rich source of information on cardiovascular (CV) health, since it is influenced by both the heart and the vasculature. Consequently, many algorithms have been proposed to estimate clinical parameters from PWs. However, it is difficult and costly to acquire comprehensive datasets with which to assess their performance. Our aim was to create a database of simulated PWs under a range of CV conditions, representative of a healthy population.

Methods

Baseline PWs were simulated using 1D computational modelling [1]. CV model parameters were varied across normal healthy ranges to simulate a sample of subjects for each age decade from 25 to 75 years. The model was extended to simulate photoplethysmographic PWs at common measurement sites, in addition to the pressure, flow and diameter PWs produced by the model.



Results & Discussion

The database was verified by comparing simulated PWs with in vivo PWs. Good agreement was observed, with age-related changes in blood pressure and wave morphology well reproduced. The utility of the database was demonstrated by applying algorithms to estimate arterial stiffness, cardiac output and left ventricular ejection time to PWs. The relative performances of several algorithms were compared, and CV factors which reduced algorithm performance were identified.

Conclusion

The database is a valuable resource for development and pre-clinical assessment of PW analysis algorithms [2, 3]. It is particularly useful because it contains several types of PWs at multiple measurement sites, and the exact CV conditions which generated each PW are known.

References

1. Mynard JP, Smolich JJ. *Ann Biomed Eng.* 2015; 43(6): 1443-1460.
2. Vennin S *et al. Hypertension.* 2017; 70(6): 1176-1182.
3. Li Y *et al. Hypertension.* 2017; 69(2): 375-381.

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Altered adventitial collagen fibril mechanics and morphology in patients with high pulse wave velocity

Z. Chang¹, Maria Lyck Hansen^{2,3}, Paolo Paoletti¹, Y-H Chim¹, Lars Melholt Rasmussen³ and R. Akhtar¹

¹ Department of Mechanical Materials and Aerospace Engineering, School of Engineering, University of Liverpool, Liverpool, L69 3GH UK

² Department of Cardiothoracic and Vascular Surgery, Odense University Hospital, Denmark;

³ Department of Clinical Biochemistry and Pharmacology, Centre of Individualized Medicine In Arterial Diseases (CIMA), Centre for Clinical Proteomics, Odense University Hospital, Odense, Denmark

Introduction

The collagen-rich adventitia is the outermost arterial layer and plays an important role in the biomechanical and physiological properties of arteries. Adventitial mechanical properties are attributed to the collagen fibrils which exhibit high tensile strength when an axial load is placed on the vessel. However, little is known about how localised changes in the adventitia contributes to arterial stiffening that occurs as part of the natural ageing process. The objective of this study was to determine the relationship between the adventitial collagen fibril properties in the human internal mammary artery (IMA) and carotid-femoral pulse wave velocity (PWV). The IMA has already been established as a suitable vessel for exploring the systemic effects of arterial stiffening [1].

Methods

16 patients were split into high PWV ($13.6 \pm 1.1 \text{ ms}^{-1}$) and low ($8.5 \pm 0.3 \text{ ms}^{-1}$) PWV groups (t-test, $P < 0.001$) based on carotid-femoral PWV measurements obtained in vivo using a Sphygmocor system. IMAs which were collected during coronary artery bypass grafting (CABG) and were used to nano-scale characterisation of the tissue with atomic force microscopy (AFM) using Peakforce Quantitative Nanomechanical Mapping (PFQNM). PFQNM was used to determine nanomechanical properties and collagen fibril morphology. Data were compared with quantitative proteomics data on small leucine-rich proteoglycans (SLRPs) [1], and clinical data using principle component analysis (PCA).

Results & Discussion

Abundant, highly oriented collagen fibrils were observed in the adventitial layer in both groups. The adventitia had high elastic modulus values in the high PWV group (Low PWV = $2159.3 \pm 282.5 \text{ MPa}$; High PWV = $2895.2 \pm 414.4 \text{ MPa}$, Adjusted p-value = 0.003). The collagen fibril diameters followed an altered distribution in the high PWV group with a greater number of large fibril diameters and a reduction in lower fibril diameters. The collagen D-Periods were also more variable in the high PWV group. PCA analysis showed that elastic modulus in the adventitia and PWV measurements were closely related. SLRP expression was reduced in patients with high nanomechanical stiffness in the adventitia.

Conclusion

Nanomechanical properties and collagen fibril morphology in arterial tissue was found to be associated with carotid-femoral PWV. Nano-scale changes in the IMA adventitia are therefore indicative of systematic changes in arterial stiffness in the vasculature.

References

1. Hansen, M.L., et al. *Arterioscler Thromb Vasc Biol*;2015;35: 896-1903

Wave Speed Estimated by Using PU-loop Technique in the Presence of Continuous Flow

W. S. Hacham^{1,2}, A. Giudici¹, A. W. Khir¹

¹ Brunel University London, Uxbridge UB8 3PH, United Kingdom. ² University of Baghdad, Baghdad, Iraq

Background

The PU-loop is a technique widely used for the estimation of the wave speed (c) in arteries and flexible vessels. As the technique relies on the wave free period in early systole, the starting flow velocity (U)=0. The impact of varying u on the determination of c using the PU-loop has not been investigated before, and investigating which is the main objective of this work.

Methods

We connected inline a respective flexible mother tube to pump operated by a brushless DC motor which generated flow with velocity (U_c). The mother tube was also connected in parallel at the inlet to a piston-pump that generated approximately a single semi-sinusoidal forward pulse-wave, with velocity of (U_p). Pressure (p) and u_m were measured simultaneously 20cm downstream the inlet of the respective mother tube, where $U_m = U_p + U_c$. Pressure was also measured at the end of the tube approximately 170cm downstream inlet of the tube. c was measured in the tube using the PU-loop (C_{PU}) and the foot-to-foot (C_{f-t-f}) techniques; the latter was used to verify the results.

Results

c increased with increasing of the flow velocity when estimated using the foot-to-foot and the PU-loop techniques. When $u=0$, c was measured as (20 ± 0.34) m/s and (20 ± 0.25) m/s using the, f-t-f and PU-loop techniques respectively. Varying $u= 0.16, 0.33, 0.49, 0.64$ and 0.75 m/s induced changes in the results of the f-t-f and PU-loop techniques as shown in Table 1. Increasing u induced an increase in the maximum pressure, also reported in Table 1.

U_c (m/s)	U_m (m/s)	C_{f-t-f} (m/s)	C_{PU} (m/s)	P_{Max} Pa (mmHg)
0	0.09	20 ± 0.34	20 ± 0.25	3205 (24.03)
0.16	0.29	29 ± 0.32	29 ± 0.20	6028 (45.21)
0.33	0.47	30 ± 0.18	30 ± 0.10	8808 (66.06)
0.49	0.65	32 ± 0.09	32 ± 0.20	12660 (94.95)
0.64	0.85	33 ± 0.39	33 ± 0.35	18110 (135.82)
0.75	0.92	34 ± 0.18	34 ± 0.12	21370 (160.27)

Table 1. U_c = Continuous flow velocity; U_m = Maximum measured velocity; P_{max} = peak pressure.

Conclusions

Wave speed increased with the increase of maximum measured flow velocity. The results of the PU-loop and foot-to-foot techniques are in good agreement; the PU-loop is a reliable technique for determining local c when pressure and velocity vary within the physiological range.

A multiphysics model for focused ultrasound activated thermosensitive liposome drug delivery to tumour

Yu Huang, Wenbo Zhan, Cong Liu, Xiao Yun Xu⁺

Department of Chemical Engineering, Imperial College London, South Kensington Campus, London SW7 2AZ, UK

Introduction:

With the development of cancerology, various new drugs have been developed to treat cancer. However, efficient transport of drugs into the interior of a solid tumour is still very challenging due to the unfavourable tumour microenvironment. In addition, serious side effects associated with chemotherapy have always been a major concern. Liposome-mediated drug delivery may offer a potential solution to these problems.

Methods:

An *in silico* model has been developed to facilitate our understanding of the multiple transport processes and reactions involved in thermosensitive liposome (TSL) encapsulated chemotherapy drug delivery to a targeted tumour, with detailed information on spatio-temporal drug distribution. The model couples a continuum-based drug transport model described by the convection-diffusion-reaction equation in a porous domain with bioheat transfer equations where the heating effect induced by focused ultrasound is simulated using the fast near-field method. The model also incorporates multiple compartments in the tumour and normal tissues. The integrated model has been used to examine doxorubicin (DOX)-loaded TSL transport in an idealised tumour where the release of DOX is triggered by locally applied focused ultrasound (FUS).

Results & Discussion:

Our numerical results show that: (1) the distribution of free DOX in tumour extracellular space is strongly dependent on the temperature profile, (2) the drug release rate of TSL has a significant impact on drug distribution in all compartments, (3) a uniform temperature profile can be achieved by applying multi-focal heating, and (4) DOX concentration in normal tissue is greatly reduced compared with conventional delivery method.

Conclusion:

By integrating a multi-compartmental model, a spatially resolved transport model, and a bioheat transfer model incorporating the heating effect of FUS, the mechanistic *in silico* model presented here is capable of providing clear-cut understandings of the transport mechanisms involved and shedding light on strategies to improve efficacy of TSL-DOX therapy. Once fully validated, the models can be used to determine the effects of drug dosage on anticancer efficacy for a specific tumour.

Semi-Automatic Detection and Visualization of Metastatic Bone Disease

N.S. Sjoquist¹, D. Thurtle³, V.J. Gnanapragasam³, T. Barrett ², G.M. Treece¹

Uni. Cambridge ¹Dept. Engineering, Cambridge CB2 1PZ, UK. ²Dept. Radiology, School of Clinical Medicine, Cambridge CB2 0QQ, UK and ³Urology, Dept. Surgery, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK.

Introduction

Metastatic bone disease is a common secondary feature of prostate, breast, and many other malignancies. Bone scintigraphy is the usual imaging detection technique but has limitations in detecting changes over time and is only 2-dimensional. With improvements in bone-targeting therapies, better evaluation of therapeutic response is now a Europe-wide research priority. Positron-emission tomography is promising, but the expense and inaccessibility means computed tomography (CT) is increasingly used for serial assessment. This requires time-consuming reviews of many CT cross-sectional images looking for small and diffuse bony changes - the summary of which is difficult to demonstrate in a multidisciplinary review setting.

Methods

We are developing a new visualisation algorithm which interprets raw CT data consisting of chest, abdomen, pelvic and upper femur regions of the body. The bone regions (individual ribs, vertebral column, bony pelvis, upper femurs) are semi-automatically segmented and the trabecular bone densities are accurately measured using Stradwin software [1,2]. Each segmentation is paired with a symmetric region by mirroring one to match the other (i.e. left femur matched to right femur). In the case of a bone region without a corresponding symmetry match (vertebral column and pelvis), the region is matched with an x-axis inverted copy of itself. Locally adaptive rigid registration is used to register each pair of symmetric regions using wxRegSurf software [3]. A specialized viewer then visualizes the results by displaying a polygonal mesh of the skeleton. Each vertex is uniquely coloured based on the difference in trabecular bone density of registered polygons. Local differences in bone may be the result of osteolytic or osteoblastic metastases due to cancer, both of which can change the bone material and structure.

Results & Discussion

This technique was used on ten pathological CT datasets and compared to metastatic scoring by radiologists from conventional CT review. Areas marked as malignant and suspicious on the scoring sheets successfully showed up as areas of high colour contrast in the viewer in all cases. There were also results which varied from the scoring sheets due to errors in the segmentation, registration and marking sheets. Further investigation is needed to reduce these problems.

Conclusion

We have introduced a new algorithm which demonstrates potential to semi-automatically detect and display metastasized cancer in bones.

References

1. G.M. Treece *et al.* High resolution cortical thickness measurement from clinical CT data. Medical Image Analysis, Vol. 14, No. 3, pp. 276-290, June 2010
2. Stradwin is available from <http://mi.eng.cam.ac.uk/~rwp/stradwin/>
3. wxRegsurf is available from <http://mi.eng.cam.ac.uk/~ahg/wxRegSurf/>

Acknowledgments

We are grateful to the W. D. Armstrong Trust Fund for funding this research.

BioMedEng18

Combining new imaging and bioengineering technologies to study how RhoGEFs drive triple negative breast cancer cell invasion.

P. Pascual-Vargas¹, M. Arias-Garcia¹, C. Bakal¹.

¹ Institute of Cancer Research, 237 Fulham Road, SW3 6JB, London.

Introduction

Changes in cell shape are essential for triple negative breast cancer (TNBC) metastasis. In all eukaryotic cells, shape is determined by the actions of Rho Guanine Nucleotide Exchange Factors (RhoGEFs). RhoGEFs integrate mechanical and informational cues from the microenvironment, and in turn, dictate the spatiotemporal activity of Rho GTPases that control the organisation of the cytoskeleton, adhesions, and cell membrane. Due to their key role in regulating cell shape and druggable nature, RhoGEFs represent attractive targets for therapeutic interventions aimed at inhibiting metastasis.

The transcriptional coactivators YAP/TAZ are key effectors of RhoGEF-Rho signalling, which regulate the transcription of genes underpinning tumour cell invasion. Given that components of RhoGEF-Rho-TAZ signalling pathways are upregulated in the mesenchymal subtype of TNBC, we hypothesise that specific RhoGEFs are driving TNBC invasion through the activation of YAP/TAZ (1). However, the mechanism by which RhoGEFs couple tumour microenvironment information to YAP/TAZ transcriptional activity, and which RhoGEFs are altering YAP/TAZ activity, remains unclear.

Methods & Results

To identify RhoGEFs driving TNBC invasion via YAP/TAZ signalling, we performed 2D RNAi screens on the TNBC cell line MDA-MB-231 and its highly metastatic derivative LM2 (2). From these screens we identified nine RhoGEFs whose knockdown causes significant changes in cell shape and/or localisation of YAP/TAZ in LM2s. To study how RhoGEFs identified in our screens promote YAP/TAZ dependent invasion, we are using novel bioengineering approaches to create materials and experimental conditions that more closely resemble the 3D environments TNBC cells invade into, *in vivo*.

Discussion & Conclusion

We found that depletion of the RhoGEF *DOCK5* decreases YAP/TAZ activity in 2D, and invasion in novel 3D matrices, suggesting *DOCK5* regulates invasion through the activation of YAP/TAZ. We will validate our 3D findings *in vivo*, with the goal of demonstrating that the *DOCK5*-Rho-YAP/TAZ signalling axis is a new point for therapeutic intervention in TNBC.

References

1. Lehmann B.D, et al. *JCI*. 2011; **121** (7), 2750-2767
2. Pascual-Vargas P, et al. *Scientific Data*. 2017; **4**, 170018

Acknowledgements

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Development of an Implantable Microsystem for *In Vivo* Measurement of Oxygen in a Large Animal Model of Cancer.

S. Smith¹, J.R.K. Marland¹, E.O. Blair¹, Eva González-Fernández², P. Sullivan¹, A. Tsiamis¹, C. Dunare¹, M.E. Gray³, S.N. Greenhalgh³, R. Gregson³, R.E. Clutton³, C. Ward³, A.J. Walton¹ & A.F. Murray¹

¹*School of Engineering, The University of Edinburgh, SMC, Alexander Crum Brown Road, Edinburgh, EH9 3FF*

²*School of Chemistry, The University of Edinburgh;*

³*College of Medicine and Veterinary Medicine, The University of Edinburgh*

Introduction

The IMPACT project (Implantable Microsystems for Personalised Anti-Cancer Therapy) is developing silicon based implantable chemical and biochemical sensors for use in cancer treatment. The aim is to improve the delivery of radiotherapy and other treatments through real-time measurement of the tumour microenvironment. The key sensor technology is a microfabricated electrochemical oxygen sensor based on the well-known Clark electrode. Producing such a sensor with technologies that are capable of integration with silicon electronics has required significant interdisciplinary research including inputs from engineers, chemists and biological and clinical researchers. The implantable devices have now been tested in a large animal model, namely sheep with ovine pulmonary adenocarcinoma viral lung tumours.

Methods

The fabrication of a microminiaturised sensor which can be integrated with electronic instrumentation is challenging. This has involved the development of processes to make a robust Ag/AgCl reference electrode by developing methods for thin film deposition and patterning of the ionic transport membrane material, Nafion [1]. The completed three-electrode sensors then require packaging on a flexible printed circuit board "cable" with insulation that protects the electrical connections from the environment during dissolved oxygen measurement [2]. Finally, instrumentation based on a commercial portable wireless potentiostat was used to create a wearable system for continuous *in vivo* testing (Fig 1).



Figure 1.

Results & Discussion

Figure 2 shows exemplar results showing the recorded current from the Clark oxygen sensor in 0 and 21% O₂ concentration in saline solution. This demonstrates the sensors capability to measure oxygen in solution.

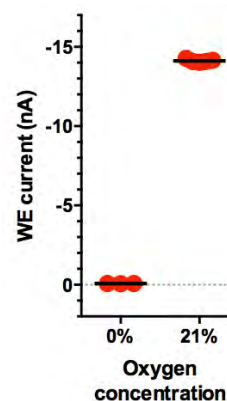


Figure 2.

References

1. J. R. K. Marland *et al.*, "Test structures for optimizing polymer electrolyte performance..." ICMTS 2017. doi: 10.1109/ICMTS.2017.7954280
2. E. O. Blair *et al.*, "Test structures for the characterisation of sensor packaging technology," ICMTS 2017. doi: 10.1109/ICMTS.2017.7954279

Acknowledgments

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Impact of Nonlinear Tissue Mechanics on Solid Tumour Surrounding Soft Tissue: a Phantom and *in silico* Investigation

M. Fiorito¹, A. Capilnasiu¹, D. Nordsletten¹, R. Sinkus^{1,2}, J. Lee¹

¹ School of Biomedical Engineering and Imaging Sciences, King's College London, London, United Kingdom

² U1148, INSERM, Hôpital Bichat, Paris, France

Introduction

Solid tumour growth is often associated to the accumulation of mechanical stresses acting on the surrounding host tissue¹. These forces alter the biomechanics of the adjacent tissue, which can be probed with propagating shear waves and quantified through MR-Elastography (MRE)². The reconstructed tangent stiffness in the peri-tumoural region inherits a signature from the tumour expansion which depends on multiple factors, including the soft tissue constitutive law, stress/strain states in the ensemble and the wave propagation vector $\mathbf{K}$. Here we have used theoretical, simulation and experimental means based on a simple setup of the tissue-tumour ensemble to investigate the shifts in tangent stiffness as a way to bridge to *in vivo* tissue.

Methods

Due to tissue nonlinearity, the shear modulus of the tumour environment will change according to the local deformation created by the tumour forces, increasing when undergoing stretch and decreasing when compressed. A shear wave can sense the apparent stiffness along its propagation direction, hence probing a negative change (compared to the background modulus) at the leading edge of the inflated object and a positive variation along the lateral area³. We have reproduced the tissue-tumour ensemble by inflating a Foley catheter inserted inside a cuboidal phantom made of a tissue-mimicking material. The probed tangent stiffness has been reconstructed at different inflations from the MRE data, while T2W images of the various states have been registered to estimate the associated deformation. The radial stress σ_r has also been measured at the interface between the balloon and the phantom through a pressure sensor. Finally, a pure-stretch rheometric investigation of the chosen material has been carried out to identify a constitutive law that characterises the hyper-elastic behaviour of the phantom under compression.

Results & Discussion

We have used a suitable PVC-based hyper-elastic material (plastisol)⁴ to investigate the signature pattern generated during the inflation experiments and have identified a Mooney-Rivlin law to model its nonlinear behaviour when exposed to micro-oscillations superimposed to macro-deformations. The choice of the constitutive law is confirmed by the agreement between the radial stress σ_r measured at the different inflation states and the stress-strain curves obtained analytically and through numerical simulation. The stiffness variation estimated from the MRE data matches the expected pattern associated to the deformation sensed by the probing shear waves. Furthermore, the intensity of the pattern correlates with the magnitude of the deformation and is consistent with the nonlinear response of the selected material for strains above 15–20 %.

Conclusion

We have demonstrated that MRE, in combination with non-linear mechanics, is capable to predict the alteration of tangent stiffness of soft tissue generated by tumour expansion. More experiments are currently underway to further extend this investigation to real tissue.

References

1. Stylianopoulos, T. J. *Biomech. Eng.* 139, 021004 (2017).
2. Sinkus, R. *et al. Magn. Reson. Imaging* 23, 159–65 (2005).
3. Fovargue, D. *et al. ISMRM* #0973 (2017).
4. Leclerc, G. E. *et al. J. Biomech.* 45, 952–957 (2012).

Ultrastructural characterization of breast cancer tissue reveals distinct micro and nano apatite and whitlockite

E. Tsolaki¹, W. Doran¹, A. Rodríguez Meira², J. Overbeck^{3,4}, A. Olivo¹, I. K. Herrmann⁵, L. Magnani², S. Bertazzo^{1*}

¹Department of Medical Physics & Biomedical Engineering, University College London, London WC1E 6BT, UK, ²Department of Surgery and Cancer, Imperial College London, Du Cane Road, London W12 0NN, UK, ³Department Materials Meet Life, Swiss Federal Laboratories for Materials Science and Technology, Überlandstrasse 129, CH-8600, Duebendorf, Switzerland, ⁴Swiss Nanoscience Institute, Switzerland, ⁵Department Materials Meet Life, Swiss Federal Laboratories for Materials Science and Technology, Lerchenfeldstrasse 5, CH-9014, St. Gallen, Switzerland.

Introduction

Breast calcification contributes to the diagnosis of 50% of non-palpable breast cancers. Attempts at a physicochemical characterization of these structures suggest that calcium oxalate, hydroxyapatite and whitlockite minerals exist in the soft tissue. However, the mechanisms of their formation remain unknown, preventing a complete understanding of the diseased breast tissue microenvironment and, as a result, of breast cancer itself. In this work, using advanced nano-analytical methods, we provide a physicochemical characterisation and detailed analysis of the spatial distribution of the minerals found in malignant, benign and healthy breast tissue, aiming to give fundamental insights into tissue microenvironment in the context of different diseases, and revealing unique properties that trigger the formation of different minerals.

Methods

66 histological slides of breast tissue from healthy, benign and malignant cases were deparaffinised, carbon coated, and silver painted prior to any analysis. The characterisation included Scanning Electron Microscopy with Energy Dispersive X-ray Spectroscopy, Focused Ion Beam, Transmission Electron Microscopy, Immunohistochemistry and Raman spectroscopy.

Results & Discussion

Our analyses show that there is whitlockite and apatite in breast tissue, and further demonstrate that whitlockite appears in the form of spherical particles, with diameters ranging between 100nm and 500nm, diffracting as single crystals, while apatite is present as a poorly crystalline mineral with no specific morphology or dimensions. Immunochemical and spatial distribution analysis indicate that the apatite crystals were in the stroma and ducts of healthy, benign and malignant cases, while the whitlockite particles were mostly present either on or in close proximity to the vascular tissue of malignant cases. The physicochemical differences between the apatite mineral and the whitlockite particles are indications that the mechanisms of formation of the two minerals are completely independent. Moreover, the lack of both collagen and bone-like architecture in either of the two minerals identified indicate that neither follows a formation mechanism similar to bone or any other known osteogenic process. The lack of a specific morphology of the apatite mineral and its low crystallinity, are indications of an unmediated and potentially noncellular mineralization process. The clear association between the calcific particles and the vasculature of malignant invasive tumours, on the other hand suggests that the malignant tissue microenvironment exhibits properties which promote the involvement of vascular cells and vesicles in the mineralization mechanisms of formation of the particles.

Conclusion

Our results provide unprecedented information on breast calcifications, giving new insights into the biochemical processes leading to their formation and breast tissue microenvironment in the context of different diseases. Furthermore, the association of whitlockite particles to the vasculature of malignant tissue suggests a microenvironment with unique properties promoting distinct mineralisation processes.

A precision cut tumour slice (PCTS) culture model capable of maintaining ex vivo thyroid carcinoma specimens.

Andrew Riley¹, Vicky Green¹, Laszlo Karsai², James England², John Greenman¹.

¹ School of Life Sciences, University of Hull, UK ²Hull and East Yorkshire Hospitals NHS trust, UK.

Introduction: Management of differentiated thyroid carcinoma (DTC) involves treatment using radioactive iodine (RAIT), to ablate residual and metastatic tumour foci. Phenotypic dedifferentiation occurs during the natural progression of DTC in approximately 5% cases [1] causing loss of expression of the sodium iodide symporter (NIS). This negates treatment using RAIT, causing an 80% reduction in 10-year survival [2]. Identification of this cohort of patients would allow their stratification onto alternative treatment pathways. Microfluidic (MF) technology offers a biomimetic environment for the maintenance of *ex vivo* tumour tissue, suitable as a vehicle to test tissue response to a range of therapeutic regimens.

Methods: Live *ex vivo* thyroid tissue (LREC: 15/NE/0412) was either live-sliced (500µm) and integrated into the MF culture device (continual medium perfusion [2µl min⁻¹], 37°C, 96h), immobilised in Tissue Tek™, or dispersed for analysis by flow cytometry. Fixed tissue was sectioned (8µm) prior to morphological and immunohistochemical (IHC) analysis (Ki67, γH2aX, BrdU). Cellular suspensions were analysed by trypan blue (TB) and propidium iodide (PI) exclusion to assess viability, and lactate dehydrogenase (LDH) and dead-cell protease (DCP) were measured in culture effluent. Differentiation was assessed by expression of thyroid transcription factor 1 (TTF-1) using IHC; sodium iodide symporter (NIS) expression was detected by western blotting of fresh and post-culture tissue lysates. The on-chip functionality of thyroid material was assessed by enzyme linked immunosorbent assay (ELISA) of thyroxine (T4) in culture effluent. Fresh and post-culture tissue samples were compared to validate the MF culture system for maintaining *ex vivo* thyroid tissue.

Results & Discussion: Tissue morphology was maintained following MF culture as measured by H&E staining; no discernible difference in gross architecture was evident, confirmed by a consultant histopathologist (LK). Levels of proliferation (Ki67, BrdU) and DNA damage (γH2aX) were concordant in both fresh and post-culture tissue samples. In addition, no significant difference in viability was observed between fresh and post-culture thyroid explants using TB and PI analysis by flow cytometry. LDH and DCP release profiles suggest that some tissue damage occurs during initial processing, illustrated by a raised level of LDH/ DCP release, before stabilisation after ~24h. Deliberate lysis of on-chip tissue after 96h by addition of 10% [v/v] lysis buffer reliably led to a significant increase in LDH/ DCP, suggesting that viable cells remained at that time point. Expression of TTF-1 and NIS (differentiation) was not altered during culture. On-chip thyroid tissue continued to release T4 throughout the 96-hour period; benign thyroid tissue appeared to produce a higher quantity of hormone than malignant tissue at all time points, in agreement with the notion that T4 production is less efficient in malignant thyroid tissue [3].

Conclusion: The culture system described was successful in maintaining thyroid explants for 96h. Future work will involve using the system as a vehicle to treat thyroid explants with RAIT and characterise response.

References:

- [1] A. Antonelli et al. Biomedicine & Pharmacotherapy, vol. 62, pp. 559-563, 2008.
- [2] F. Worden. Therapeutic Advances in Medical Oncology, vol. 6, pp. 267-279, 2014.
- [3] R. Robbins et al. Journal of nuclear medicine, vol. 46, pp. 28S-37S, 2005.

Nanoparticle Drug Delivery Systems for Synergistic Effect of Cisplatin and Decitabine

M. Parhizkar^{1,5}, P. J. T. Reardon², R. J. Browning³, E. Stride³, R. B. Pedley⁴, M. Edirisinghe¹, J. C. Knowles²

^{1,5}Mechanical Engineering, University College London, London, United Kingdom; ²Division of Biomaterials and Tissue Engineering, UCL Eastman Dental Institute, University College London, London, United Kingdom; ³Institute of Biomedical Engineering, Department of Engineering Science, University of Oxford, Oxford, United Kingdom; ⁴UCL Cancer Institute, Department of Oncology, University College London, London, United Kingdom; ⁵ Mechanical Engineering, University of East London, London, United Kingdom.

Introduction

Treatment of multifunctional disease such as cancer cannot be achieved by therapeutic agents that inhibit a single target ¹. Combination therapy, on the other hand, is attracting a considerable amount of interest due to the synergistic anticancer effects, reduction in individual drug-related toxicity and suppression of multi-drug resistance through different mechanisms of action². Polymeric nanoparticles with compartmentalised structures have emerged as an effective strategy for successful delivery of anticancer drugs ³. Herein, coaxial electrohydrodynamic (EHD) technology was utilised to develop a nanoparticulate platform for co-delivery of a chemotherapeutic agent, cisplatin, and chemosensitizing agent, decitabine, to tumour cells.

Methods

The core-shell (CS) structured nanoparticles (NPs) were formed through electrohydrodynamic encapsulation of decitabine and cisplatin in Poly (lactic-co-glycolic acid) (PLGA) copolymer. Drug distribution and release profile of each drug were tuned by altering the encapsulation of Decitabine in different layers of the NPs. In vitro release of cisplatin encapsulated in PLGA nanoparticles was observed in PBS at physiological temperature (37°C) and pH (7.4). Cisplatin encapsulation was confirmed via TEM/EDX. In vitro cytotoxicity of dual drug loaded NPs against two different types of human ovarian carcinoma cell lines (non-resistant and resistant A2780 cells) were tested.

Results & Discussion

Measurement of the release rate showed a more sustained release for the coaxial EHD NPs. However, decitabine had a higher burst release for the coaxial EHD NPs compared with uniform NPs.

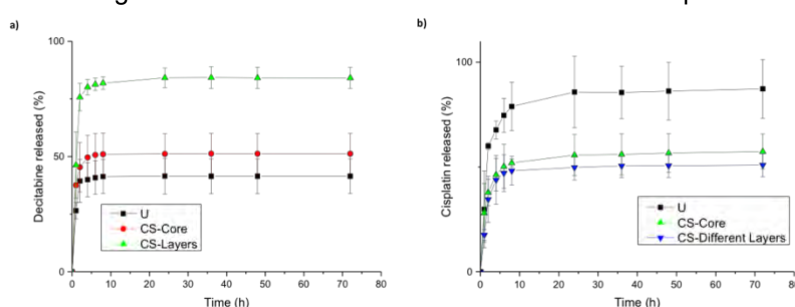


Figure 1: Structure dependent a) decitabine and b) cisplatin release.

Conclusion

The drug distribution within NPs potentially plays an important role in controlling delivery. This work suggests that NPs containing decitabine enhance the sensitivity of non-resistant cells to cisplatin.

References

1. Holohan C et al. *Nat. Rev. Cancer*. 2013; 13: 714–726.
2. Hu C-M J, Aryal S, Zhang L. *Therapeutic Delivery*. 2010; 1(2): 323-334.
3. Pina M F et al. *Nanoscale*. 2017; 9 (18): 5975-5985.

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Fast and Efficient Light-Controlled CRISPR/Cas9 Gene Editing

E. Moroz^{1,2}, **Y. Zhang¹**, **Z. Liu¹**, I. Sunyovszki¹, C. Grigsby², M. M. Stevens^{1,2}

¹Imperial College, South Kensington, SW7 2AZ, London, ²Karolinska Institute, SE-171 77 Stockholm, Sweden.

Introduction

CRISPR/Cas9 system has emerged as a facile and efficient genome editing platform that holds great potential for development of novel therapeutics for gene therapy. The greatest challenge lies in safe and efficient delivery of CRISPR/Cas9 to target cells in human body. We have developed a cationic biodegradable polymer-based ribonucleoprotein (gRNA and Cas9 complex) delivery system to achieve higher editing efficacy. To realise precise spatiotemporal control over CRISPR functions, we have developed a light-activatable CRISPR gene editing method through modifying the gRNA of CRISPR system with photocaging groups.

Methods

Polymer-based ribonucleoprotein delivery system

To optimize the polyplex formulation and release, we performed PAGE gel retardation assays at various RNP/polymer weight ratios necessary for complete condensation of RNP and to verify reduction-triggered degradation of polyplex by adding 2.5 mM DTT. Cytotoxicity of the polymer was analysed by AlamarBlue® assay. The gene editing efficacy of the polyplex formulation was compared to the one of commercial transfection reagent using Guide-It mutation detection kit. To enhance the efficiency of our delivery system, we introduced a reporter mRNA in the polyplex allowing for sorting of successfully transfected cells.

Light-activatable CRISPR gene editing system

To test whether photocaging is efficient in preventing target cleavage and whether the gene cutting activity can be restored upon light irradiation, we performed in vitro DNA cleavage assay. The mixture containing photocaged CRISPR and the DNA template was irradiated by 365 nm UV light followed by agarose gel electrophoresis to determine gene cutting efficiency. To test gene editing efficacy in genome, same experiments were conducted in HEK Cas9 cells and HEK Cas9 iGFP cells. Cells transfected with photocaged CRISPR were irradiated with or without 365 nm UV light (300 s). Indel mutation frequency was determined using Guide-It mutation detection kit.

Conclusion

The developed delivery system has achieved higher efficacy than commercial transfection reagents with minimal cytotoxicity effects in HEK293, HEK293-ZsGreen and hMSC cells. The light-activatable gene editing method achieved temporal control over gene editing by exposing cells to light at a self-design time point and spatial control by exposing cells to light through a photomask. Our gene editing system has great potential for photoactivation and multiplexing of different targets enabling the use of this strategy in 3D matrices for tissue engineering applications.

Acknowledgments

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A Local Drug Delivery Technology To Prevent Implant Infections

J. Fraser^{1,2}, F. Cameron¹, M. Maclean^{1,2}, C. McCormick¹

¹ Department of Biomedical Engineering, University of Strathclyde, Glasgow, G1 1QE, UK; ² The Robertson Trust Laboratory for Electronic Sterilisation Technologies, University of Strathclyde, Glasgow, G1 1XW, UK.

Introduction

Medical implant associated infection is an ongoing problem, which can be particularly problematic when infection pathogenesis involves formation of bacterial biofilms¹. Biodegradable polymer drug delivery technology may be of use in some devices as a means of delivering a high local dose of antimicrobial drug. In this study the broad-spectrum antibiotic rifampicin was formulated with the polymer PLGA (Poly(D,L-lactic-co-glycolic acid (65:35)) and the *in vitro* drug release and activity analysed.

Methods

PLGA (65:35) and rifampicin were dissolved in chloroform to produce 10% w/v solutions and combined to produce polymer:rifampicin volume ratios (50:50; 60:40). 20µl solution was pipetted onto 13mm Ø glass cover slips and left to dry. These were then immersed in PBS and agitated (37°C; 120 rpm) and drug release measured over 4 weeks. Periodically, coverslips were removed and their antimicrobial activity against *Staphylococcus aureus* analysed by a disk diffusion test. Preliminary evaluation of biofilm formation was also performed.

Results & Discussion

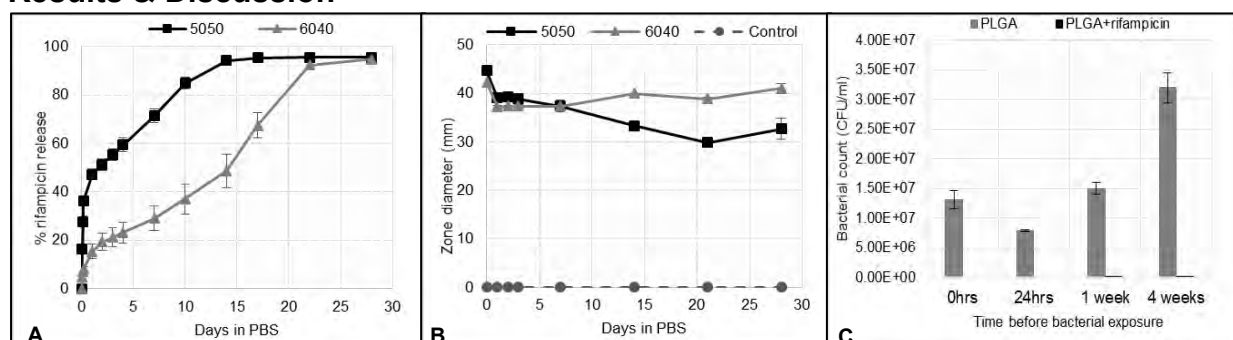


Figure 1: **A** shows percentage of loaded rifampicin released into PBS from PLGA formulations over 4 weeks incubation at 37°C/120rpm (analysed by UV spectrophotometry using absorbance peak 334nm). **B** shows diameter of zones of inhibition produced by the same formulations against *S. aureus* in a disk diffusion test at progressing times during release. **C** shows inhibition of *S. aureus* biofilm formation on coverslips coated in 60:40 formulation of PLGA:rifampicin (for all data $n=3 \pm \text{SEM}$).

After 4 weeks both formulations had released more than 95% of their rifampicin load (Fig.1A). Furthermore, both formulations continued to produce large zones of inhibition against *S. aureus* for the duration tested (Fig. 1B), and were able to inhibit biofilm formation (Fig. 1C)

Conclusion

The PLGA:Rifampicin formulations provided controlled drug release and activity against *S. aureus* for at least 4 weeks. The drug release profile can be tuned by adjusting the ratio of PLGA to rifampicin. Biodegradable polymers therefore represent a promising material for local antimicrobial delivery to help prevent infection in implanted medical devices.

References

1. Khardori, N., Yassien, M. *J. Industrial Microbiology*. 1995; 15: 141-147

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BioMedEng18

Model Based Optimal Control of Gene Delivery

E. Jamili and V. Dua

*Department of Chemical Engineering, Centre for Process Systems Engineering, University College London,
Torrington Place, London, WC1E 7JE, United Kingdom.*

Introduction

Gene therapy is a promising technique for treating a wide range of serious incurable diseases such as genetic disorders and cancer. The key to success of gene-based therapy is to develop a delivery system for safe and efficient *in vivo* gene transfer, allowing the transition of discoveries to the clinical arena [1, 2]. This work presents an innovative approach based on the optimal control strategy aims at describing the dynamics of the gene delivery process while simultaneously considering the key pharmacological issues.

Methods

In this work, an integrated pharmacokinetic/pharmacodynamic (PK/PD) model-based control algorithm was developed for non-viral siRNA delivery to take into account the main multi-objective optimisation issues such as efficacy and toxicity, as well as the effect of uncertainty in cell division time. The methodology developed in this study provides an effective model-based tool for making decisions under uncertainty, which is lacking for gene delivery systems.

Results & Discussion

The proposed modelling and control platform allows for the computation of an optimal siRNA delivery profile in the presence of different practical constraints that is applicable for *in vivo* conditions. A constrained multi-objective optimisation problem was formulated and solved to achieve maximum gene silencing activity while simultaneously preserving cell viability at desirable levels. Effect of variations in cell doubling time was also explored during the modelling process by incorporating time constraints into the optimisation problem to improve the pharmacological effects before cell division occurs. The results obtained from the work show that an optimal continuous infusion is superior to a bolus injection for achieving maximum therapeutic effects with minimal toxicity. The analysis successfully provides quantitative predictions of non-viral siRNA activity paving the path for further experimental work to probe more efficient delivery systems.

Conclusion

A promising platform for gene delivery systems is provided by model-based optimal control technology, which can further assist in the optimisation of the process. Solving the gene delivery optimal control problem has provided very interesting insights on what siRNA delivery profile might look like in a clinical setting.

References

1. Ibraheem D, Elaissari A, Fessi H. *Int J Pharm.* 2014; 459: 70-83.
2. Kumar SRP, et al. *Mol Ther Methods Clin Dev.* 2016; 3: 16034.

Conflicts of Interest

The authors have no conflict of interest to declare.

Designing acoustically responsive lipid nanoparticles for intracellular macrodrug delivery

S. Shrivastava¹, J. Zhang ², T. H. Rabbitts ², R.O. Cleveland ¹

¹ Institute of Biomedical Engineering, University of Oxford, Oxford, OX3 7DQ. ²Weatherall Institute of Molecular Medicine, John Radcliff Hospital, Oxford OX3 9DS

Introduction

Intracellular delivery of therapeutic genetic material remains a major challenge in translating the advances of genetic therapies to clinical use. Unlike small molecule drugs that can enter the cell passively, cell membranes are impermeable to therapeutic macromolecules such as mRNA, DNA or proteins. Therefore, such macromolecules are typically delivered by fusogenic lipid nanoparticles (LNPs) that can carry the macromolecules into the cell [1]. Here, we show that the physical and chemical state of a LNP can be controlled via shock waves, based on real time measurement of their thermodynamic properties in response to a shock wave. A mRNA was developed which interfered with cell function and also had a colour indicator to confirm delivery.

Methods

LNPs were prepared using a rotary evaporator followed by extrusion through polycarbonate filter. The changes in the thermodynamic properties of the lipid membranes during shock wave were observed by time-resolved (sub-microsecond) measurements of the fluorescence spectra of lipid-state sensitive dyes [2]. The phase state of lipid nanoparticles was characterised based on infra-red spectroscopy. A bicistronic mRNA was developed, coding for an inhibitory intracellular antibody fragment [3] together with a reporter green fluorescent protein (GFP), which would form a complex with the LNP. Differential light scattering was used for sizing and zeta potential measurements for quantifying and optimising the mRNA-LNP ratio. Different cancer cell lines were exposed *in vitro* to the mRNA-LNP complex, followed by exposure to shock waves. Transfection efficiency was monitored at different times compared to Lipofectamine 2000, by quantifying GFP expression by flow cytometry.

Results & Discussion

The mRNA-LNP complex was able to successfully deliver our bicistronic mRNA to several different cancer cell types *in vitro* and showed enhancement of delivery in the presence of shock waves. The shock waves resulted in an increase in the number of transfected cells and not an increase of transfection to already permeable cells. The transfection efficiency was found to depend strongly on the cell type for our LNP formulation. This suggests further understanding of cellular biophysics will be needed in order to design LNPs that are tuned to target cell types.

Conclusion

Using knowledge of the thermodynamic state of lipid membranes a mRNA-LNP complex was developed that can selectively enter and transfect cancer cells. The delivery was enhanced when insonified by shock waves, which provides a path for focal non-invasive triggering.

References

- [1] R. Koyanova and B. Tenchov, *Soft Matter* **5**, 3187 (2009).
- [2] S. Shrivastava, R. O. Cleveland, and M. F. Schneider, *ArXiv E-Prints* **1612.06709**, 1 (2016)
- [3] Tanaka, T., Williams, R., & Rabbitts T.H. *EMBO J.* **26**, 3250 (2007) .

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Flow simulation of a collagen solution in syringes with different geometries

I.M. Syntouka^{1,2}, P. Riches¹, G. Busby², A. Kazakidi¹

¹ Department of Biomedical Engineering, University of Strathclyde, G4 0NW, Glasgow.

² Collagen Solutions Plc, G33 1AP, Glasgow.

Introduction

In recent years, cell therapy has emerged as a promising therapeutic strategy for many diseases, including Parkinson's disease [1]. To increase cell viability, biomaterials are often used as scaffolds to facilitate cell deposition, through injection, to the site of interest. However, fluid forces acting on the cells during injection may lead to cell disruption or death [2]. This study aims to develop a novel device for the delivery of a cell-embedded collagen hydrogel, forming *in situ*. Here, we discuss computational results on constricted channels representing the connection between the syringe barrel and the needle to gain insight into the effect of syringe geometry.

Methods

Straight needles emanating co-axially from syringes of various geometries were modelled computationally in the two-dimensional space. A low dead space syringe design was modelled first (Geometry 1) and was compared with sudden and tapered contraction designs (Geometries 2 and 3). Within the finite volume method framework, the flow of a viscous collagen solution was considered almost incompressible, with non-Newtonian fluid constitutive behaviour, and constant inlet velocity that corresponds to a maximum delivery volume.

Results & Discussion

The effects of the syringe geometry on velocity and shear stress were examined at the syringe-needle connection. Simulation results demonstrated 10% lower velocity magnitude in Geometry 2 compared to Geometries 1 and 3. Wall shear stress calculations indicated a greater influence of Geometries 1 and 3 on the collagen solution; values at the entrance of the needle were found 40% higher in these two geometries than in Geometry 2.

Conclusion

This study highlights the importance of syringe geometry on the design of new cell delivery devices. As therapeutic cells pass from the syringe barrel to the needle, the pressure drop and the increased velocity could damage them. Further analysis is required including the simulation of cells during injection and understanding of their deformation.

References

1. Gunay MS., Ozer AY., Chalon S. *Curr Neuropharmacol.* 2016; 14(4): 376–391.
2. Aguado BA *et al.* *Tissue Eng. Part A* 2012; 18: 806–815.

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Numerical Simulation of Convection Enhanced Delivery of Nano Drug Carriers into Brain Tumour

W. Zhan, F. Rodriguez Y Baena

Department of Mechanical Engineering, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

Convection enhanced delivery (CED) is a promising alternative to systemic administration for bypassing the blood brain barrier, because of which most anticancer drugs are blocked in the blood circulatory system instead of concentrating in the targeted tumour tissue. As drugs are injected directly into the tumour extracellular space during CED treatment, fast drug elimination due to physical degradation and metabolism significantly hinders effective drug penetration into large tumours, which represents one of the main limitations of CED. If drugs are encapsulated within nanoparticles which are harder for the body to eliminate, drugs can be released in a more controllable manner over time, thereby improving the potential for treatment. The present study aims to examine the impact of tumour and nanoparticle transport properties on the delivery outcomes, with the aim to optimise this drug delivery system.

Methods

A multiphysics model is applied to a 3-D brain tumour volumetric mesh, which is reconstructed from an anonymised human MR dataset. The brain tumour and surrounding tissue are treated as porous media where Darcy's law is applied. The Convection-Diffusion-Reaction equation is introduced to describe the key processes in drug transport and accumulation for CED, including migration via the interstitial fluid flow, drug release from nanoparticles, drug binding with proteins, elimination due to physical degradation, metabolism and capillary drainage, as well as cell uptake. The treatment efficacy is evaluated by the effective therapeutic volume, wherein the drug concentration is sufficient to eliminate 90% of the tumour cells, as tested in *in vitro* experiments.

Results & Discussion

Modelling results show that CED injection is effective in enhancing the bulk movement of interstitial fluid flow so as to improve the drug penetration. As compared to the direct infusion of free drugs, nanoparticle mediated CED results in more homogeneous drug distribution and a larger effective therapeutic volume. Simulations further demonstrate that the delivery outcome is less correlated with nanoparticle diffusivity as the movement by convection is dominant. Infusing nanoparticles into the tumour with sparse capillaries leads to improved drug accumulation because of the reduced capillary drainage, although the interstitial fluid flow in these tumours is relatively slow. Drug release rate can thus be optimised through a larger therapeutic volume by achieving a suitable trade-off between free drug supply and penetration depth.

Conclusion

The delivery of nanoparticle encapsulated drugs by intracranial infusion is largely dependent on the properties of both the tumour and the chemotherapeutic agents. Results obtained in this study can serve as a guide to optimise nanoparticle design and CED treatment regimens.

Acknowledgments

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Peptide-targeted gold nanostars for treatment of Parkinson's disease

C. Morfill¹, D. Kiryushko¹, F. Xie¹, A. Porter¹

¹ Royal School of Mines, Department of Materials and London Centre for Nanotechnology, Imperial College London Exhibition Road London SW7 2AZ.

Introduction

Nanoparticles (NPs) are commonly used as drug delivery systems and have been shown to cross the blood-brain barrier. Therefore, the use of these particles to carry therapeutic materials to the brain could lead the way to treating neurological diseases. The aim of our study is to design and produce gold NPs of varying geometries conjugated with neuroprotective peptides and to investigate their interaction with and biological effects in neurons and dopaminergic neuronal cell line (N27). In particular, we sought to determine whether peptide-conjugated NPs can promote neurite extension from cultured neurons and protect them against oxidative stress-induced neurotoxicity, a common cause of cell death in several neurological diseases.

Methods

Gold NPs (spherical and star-shaped) were synthesised via Turkevich reduction method and the peptides were synthesized as tetramers composed of four monomers coupled to a lysine backbone (Schafer-N, Denmark). Hippocampal neurons were isolated from rat embryos at E18-E19, plated on either Thermanox coverslips (NP-neurons interaction studies) or LabTek chambers (neurite outgrowth and neuroprotection studies). Neurons/N27's were stimulated with varying concentrations of the peptide conjugated NPs. For neurite outgrowth studies, neurons were fixed after 24 h in culture and stained with Coomassie Blue. Neurite length was determined using ProcessLength software package (University of Copenhagen). For cell survival studies, cells were pre-treated with peptide-conjugated NPs for 1h followed by 24h exposure to the oxidative stress inducer H₂O₂ (neurons) or neurotoxin reproducing major hallmarks of Parkinson's disease 6-OHDA (N27's). Cell viability was evaluated using Hoechst 33258 staining for nuclear condensation. NP interaction with neurons (5 days in culture) was studied using TEM.

Results & Discussion

Our data shows the successful conjugation of the peptides to both nanospheres and nanostars. We demonstrate that upon interaction with neurons, both star-shaped and spherical peptide conjugated NPs stimulate neurite outgrowth and protect against oxidative stress-induced neuronal death.

Conclusion

Our data can be used as a step forward for a potential therapy for neurodegenerative disorders and also provide a benchmark for further neurological drug designs.

References

1. Dmytriyeva, O., *et al* (2012). The Metastasis – promoting S100A4 protein confers neuroprotection in brain injury. *Nature Communications*. **3** article 1197
2. Moldovan, M., *et al* (2013). Peptide mimetic of the S100A4 protein modulates peripheral nerve regeneration and attenuates the progression of neuropathy in myelin protein P₀ null mice. *Molecular Medicine*. **19** 43-53

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Peptide Amphiphiles as Manipulators of Protein Conformation

A. Mendoza-Meinhardt¹, S. Trujillo-Muñoz ², M. Salmeron-Sanchez ², A. Mata ¹

¹ Institute of Bioengineering, School of Engineering and Materials Science, Queen Mary University of London, E1 4NS, London. ² School of Engineering, Rankine Building, University of Glasgow, G12 8LT, Glasgow.

Introduction

Protein-based materials are ubiquitous in nature and widely used in bioengineering due to the versatility of proteins as building blocks for biomaterials ^[1]. This versatility results from the complexity of the structure of proteins and the close relationship between their structure and bioactive properties. Our group recently identified ^[2] that when elastin-like-proteins (ELPs) and peptide amphiphiles (PAs) interact in solution, the conformations of the ELPs change. At the same time, the PAs co-assemble with the proteins to form hierarchically structured materials that mimic the extracellular matrix, and for which the type of microstructure formed depends on the conformational change. The potential for PAs to be predictably used as modulators of protein conformation in co-assembled materials may enable the design of novel materials, the bioactive properties and microstructure of which are tailored by bottom-up design of the initial protein-peptide interaction. In this work, we investigate the role of the structural properties of proteins and PAs in the co-assembly interaction and the resultant conformational change.

Methods:

A set of rationally designed ELPs with systematic variations in structural properties were co-assembled with PAs of varied charge. The resulting conformational change in the proteins was estimated by small angle x-ray scattering and Fourier transform infrared spectroscopy (amide III band deconvolution). The microstructure of the co-assembled materials was characterized by scanning electron microscopy. The interaction of human fibronectin with PAs of varying charge was also investigated, for which change in exposure of the cell-binding and heparin-binding domains of fibronectin was quantified via enzyme-linked immunosorbent assays.

Results & Discussion:

Our results suggest that PA charge has the largest effect on the protein conformational change. We also observe trends in microstructure and secondary structure changes that correlate to variations in protein hydrophobicity, charge distribution, and molecular weight. Finally, the exposures of the heparin-binding and cell-binding domains of fibronectin were significantly oppositely altered by interaction with the tested PAs, as the exposure of the heparin-binding domain increased, and that of the cell-binding domain decreased. The magnitude of these exposure changes followed a trend with PA charge that was reproduced in both domains.

Conclusion

Our results suggest that PAs may be used as molecular manipulators of protein conformation in co-assembled materials. Future work will focus on providing a mechanistic understanding of the conformational modulation and on constructing a predictive library of protein-PA interactions.

References

1. Gagner, J. E.; Kim, W.; Chaikof, E. L. *Acta Biomaterialia*. 2014; 10: 1542-1557.
2. Inostroza-Brito, K. E. *et al. Nature Chemistry*. 2015; 7: 897-904.

Acknowledgments

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BioMedEng18

Investigation of the use of Electroactive Polymer for Cardiovascular Applications

Moutaz Hamdan¹, Terence Gourlay ¹

¹ Department of Biomedical Engineering, University of Strathclyde, Glasgow, G1 1QE.

Introduction

Heart failure is one of the principal causes of death and disability. The causes of heart failure are many, and a number of technologies have been developed to address this issue by providing support to the failing heart, both as a permanent solution and as a bridge to recovery. These options are called Mechanical Circulatory Support Devices, a particular branch of these devices is the Ventricular Assist Devices, which have been under intense development over the recent years offering a promising solution for this major problem. However, these devices are still bulky, and heavy designed to support failing hearts in the adult population. On the other hand, little has been done in recent times on the development of implantable solutions for heart failure or insufficiency in children. There are many reasons for this, but primarily the relatively small number of children requiring these procedures, the challenges associated with growth, and the lack of physical space for such implantable circulatory support technologies in children are fundamental limitations to the development and deployment of these technologies.

Methods

The primary purpose of this project was to investigate the development of a new miniaturised self-power VAD that is suitable for paediatrics implantation. This project suggested the use of the newly developed Artificial Muscles to create a mesh that envelops the heart and works as an external assisting circulation mechanism. The same materials could be used to generate electricity when deformed, which can be used to power the proposed device. Critically, the project was to focus on optimising the materials with regard to their operating efficiency to ascertain whether they represent a viable option for VAD production.

A full review of the current available Artificial Muscles was performed to choose the most suitable type for this project. Then different fabrication protocols were developed to make IPMC Artificial Muscles using platinum and palladium coatings. A series of characterization tests were conducted on the fabricated Ionic Polymeric Metal Composites (IPMC) to ensure their quality. Finally, the mechanical and electrical properties were tested and compared with the proposed device requirements.

Results & Discussion

The review of Artificial Muscles showed that IPMC would be the best candidate to use in this application. The characterisation tests showed as well that the produced IPMC Artificial Muscles were fabricated to the same standards as those commercially available, and the reported by other investigators. However, these materials showed very low mechanical output with high electrical power consumption, which made them far from practical and not suitable for the proposed application. On the other hand, IPMCs showed promising results as an option to generate electricity to power low consumption implantable devices.

References

1. Bar-Cohen, Y. (2004). Electroactive polymer (EAP) actuators as artificial muscles: reality, potential, and challenges, SPIE press.
2. Roche et al(2017). "Soft robotic sleeve supports heart function." Science Translational Medicine 9(373).

BioMedEng18

Functionalisation of a protein/peptide system towards a more complex and functional biomaterial

A.M. Majkowska¹, K.E. Inostroza-Brito¹, E. Collin¹, A. Mata¹

¹*School of Engineering and Materials Science, Queen Mary University of London, London*

Introduction

The use of protein and peptides to build functional materials is of great interest in the field of tissue engineering (TE) and regenerative medicine (RM). While great work has been done^{1,2}, there is still a need for more complex systems mimicking the micro-environments of the ECM. We had explored the self-assembling capabilities of elastin-like-polypeptides (ELPs) and peptide amphiphiles (PAs) in order to develop a complex and bioactive membrane showing a hierarchical architecture and dynamic properties³. This system offers an attractive platform for TE and RM applications because of the capacity to engineer with molecular control while creating controlled macroscopic scaffolds. In this work we aim to include bioactive PA molecules to enhance cell adhesion and the ECM biomolecule heparan sulphate (HS) to increase complexity and delivery of growth factors⁴.

Methods

Cell attachment study was conducted. ELISA immunosorbent assay was used to quantify growth factor's retention and release rates. Student t-test was used to analyse data ($n = 6$). Significant differences between the groups were looked for at $p < 0.05$ and at $p < 0.005$.

Results & Discussion

We have shown the successful incorporation of HS within the ELP/PA membrane without disturbing its stability or hierarchical structure. By conducting an ELISA assay we were able to demonstrate that the membrane can retain and release a growth factor (VEGF). In order to tune membranes' cell adhesion properties, a bioactive peptide was incorporated. Figure 1C shows morphology of membranes formed with non-bioactive ELP and bioactive peptide PA-RGDS. There is a significant increase in cell adhesion between the conditions (0%, 5% and 10% RGDS).

Conclusion

In this study, we were able to improve the functionality of ELP/PA membranes by using a PA with a cell adhesive epitope and by incorporating a third biomolecule (HS) which enabled retention and release of VEGF overtime. This work demonstrates the possibility to engineer complex scaffolds for TE and RM that can be fabricated with multiple functional biomolecules.

References

- ¹Saxena et al. *Drug Deliv.* 22, 156–167, 2015
- ²Mendes et al. *Nanomed Nanobiotechnol.* 5(6):582–612, 2013
- ³Inostroza-Brito et al. *Nat. Chem.* (11) 897-904, 2015
- ⁴Xu et al. *J. Biol. Chem.* 286, 737–745, 2011

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Novel Extracellular Matrix Scaffolds in a Hypoxic Environment

J.A. Reid¹, A. Callanan¹

¹ Institute for Bioengineering, School of Engineering, The University of Edinburgh, EH9 3JL, Edinburgh, UK.

Introduction

Oxygen deficiency (hypoxia) has been shown to lead to several vascular pathologies in endothelial cells¹. Alongside this, the addition of decellularized extracellular matrix to a polymer scaffold has been shown to drastically alter cellular gene expression². In this study, we propose combining the effects of hypoxia with that of vascular based ECM/PCL bioscaffold to see how the performance of human umbilical vein endothelial cells (HUVECs) is affected.

Methods

Briefly, pieces of bovine aorta were perfusion decellularized (0.5% sodium dodecyl sulfate), lyophilized and milled into powder. The resulting ECM powder was added at a concentration of 0.25% w/v to an 8% w/v PCL/HFIP solution. The solution was electrospun into randomly orientated fibres. Electrospun PCL was used as a control. Scaffolds were punched out (diameter = 10mm) and seeded with HUVECs at 110,000 cells/cm². All scaffolds were left in normoxic conditions (18.6% O₂)³ for 2h to allow cells to bind to the scaffold. After 2h, half of the scaffolds were moved into hypoxic conditions (2% O₂), and the other half were left in normoxic conditions. Various biochemical quantification methods were performed at time points of 12h, 24h and 48h, including DNA quantification, PCR and cell viability. Scanning electron microscopy was performed on unseeded scaffolds, 12h scaffolds and 48h scaffolds.

Results

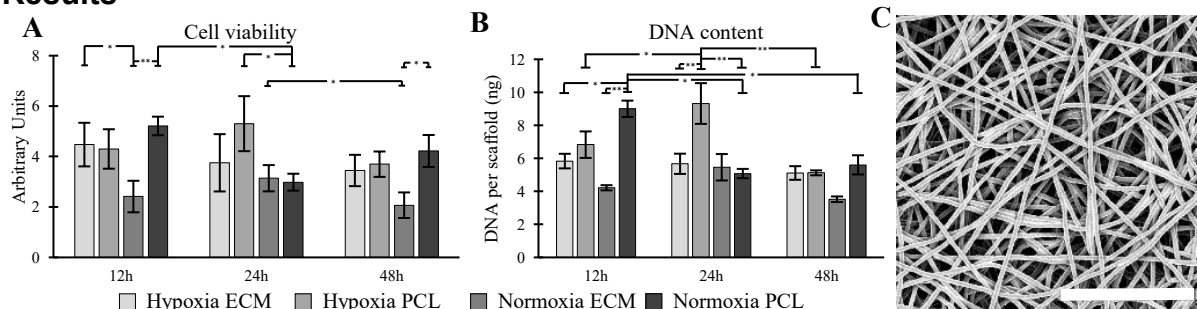


Figure 1: (A) Cell viability of scaffolds. **(B)** DNA content of scaffolds. **(C)** Representative Scanning Electron Microscopy image of electrospun scaffold. Scale bar = 50µm. n=4, errors bars = Standard error of mean, one-way ANOVA with Fishers' post hoc *p<0.05, **p<0.01.

Discussion & Conclusion

This systematic study has shown that aorta ECM bioscaffolds are capable of accommodating the attachment and growth of HUVECs under hypoxic and normoxic conditions. Results show the great potential of the scaffolds and their possible applications in tissue engineering and/or drug testing platforms.

References

1. Michiels C, Arnould T, Remacle J. *Biochimica et Biophysica Acta*. 2000; 1-10.
2. Grant R, Hay DC, Callanan A. *Tissue Eng: Part A*. 2017; 23(13-14): 650-662.
3. Wenger RH, et al. *Hypoxia*. 2015; 3: 35-43.

Acknowledgments

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Fabrication of aligned nano-fibrous membranes through supramolecular and magnetic forces

E. Radvar, Y. Shi, S. Grasso, M. J. Reece and H. S. Azevedo

Institute of Bioengineering, School of Engineering and Materials Science, Queen Mary University of London

Introduction

Supramolecular self-assembly of biomaterials has generated great interest as it allows their fabrication with nanoscale precision. However, it is difficult to extend this level of organization across length scales. Externally applied fields can be used to direct the self-assembly process and control orientation over the micro and macroscale. In addition, external fields can be switched on/off allowing the fabrication of biomaterials with complex patterned structures¹. Our group has been interested in generating self-assembling biomaterials by combining the natural polymer hyaluronic acid (HA) with rationally designed peptides^{2,3}, but never exploited the use of external fields to guide their co-assembly. Here we tested the ability of magnetic field to direct the supramolecular self-assembly of newly designed peptides in presence of HA and promote nanofibre alignment in these biomaterials.

Methods

Peptides with the generic $K_aX_nF_b$ sequence were synthesized to investigate the effect of the primary structure on their self-assembly behaviour. Peptides were then combined with HA to trigger their self-assembly. To direct the alignment of the peptide nanofibres, the co-assembly of peptides and HA was also conducted under magnetic field (12 T, www.magnetat.uk). The self-assembled biomaterials were analyzed by scanning electron microscopy and tensile test to assess the effect of magnetic field on nanofiber orientation and mechanical properties.

Results & Discussion

Peptides were designed with distinct blocks. Lysine residues at the N-terminal allow interaction with negative charges of HA, whereas the phenylalanines at the C-terminal enable π - π interactions. Our results show that the linker block (X_n) controls the peptide secondary structure (α -helix or β -sheet) and depending on the linker length soft hydrogels or membranes can be obtained. Peptide/HA co-assembly under magnetic field resulted in membranes with highly aligned nanofibres.

Conclusion

The aligned nano-fibrous membranes obtained under magnetic field resemble the hierarchical structure of many human tissues (e.g. tendons, ligaments) and provide a biomimetic physical environment for tissue engineering and regeneration.

References

1. Mendes, et al. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, 2013. 5(6), pp.582-612.
2. Ribeiro, et al. *Nanoscale*, 2017. 9(36), pp.13670-13682.
3. Ferreira, et al. *Biomaterials Science*, 2013. 1(9), pp.952-964.

Acknowledgments

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The effect of increasing dosage of atmospheric dielectric barrier plasma discharge (DBD) on electrospun PLCL/PANI biomaterials

G.C. Menagh¹, D. Dixon¹, G. Burke¹

¹ NIBEC, Ulster University, Belfast, Northern Ireland.

Introduction:

Plasma surface treatments such as DBD are routinely used to enhance cellular attachment and differentiation in tissue engineering.¹⁻² Electrically conductive polymers have become increasingly important as a method of promoting cellular response and monitoring real time cell culture in vitro.³ Here we investigate the effects of increasing DBD plasma processing on the surface physical, mechanical and chemical properties of electrospun PLCL/PANi an electrically conductive polymer.

Methods:

Electrically conductive PLCL/PANi (4:1) composite polymer was manufactured from 10% w/w PLCL and 0.3% w/w PANi in chloroform/DMF solvent. Polymers were electrospun at 12 cm distance and 20kV to produce a randomly aligned 50µm disc. This was exposed to increasing dosages of DBD plasma up to 20 J/cm² under atmospheric conditions. After a 48-hour resting period, the samples were characterised using wettability analysis, SEM, Tensile Testing AFM, FTiR and XPS.

Results and Discussion

Randomly aligned, electroconductive electrospun PLCL/PANi matrices 50µm of thickness, with an average fibre diameter of 1.75µm were manufactured. The effect of the increasing DBD treatment caused a dose-dependent statistically significant enhancement in their wettability until the point where surface melting was observed. SEM revealed a dose-dependent beneficial change in fibre morphology and topography at low DBD dosages up to 10 J/cm². However, higher dosages above this caused polymer fibre fractures and surface melting changes to be observed. FTiR analysis following DBD plasma treatment showed no chemical changes to the bulk properties of the polymer. AFM showed alterations in the topography of the individual surface fibres. Chemical XPS analysis showed an increase in surface oxygenation in plasma treated samples a desirable quality in a cell culture biomaterial. Tensile testing was used to assess the effect of adding PANi to PLCL and the effect of increasing DBD dosage on PLCL/PANi. Adding PANi causes a significant increase in Young's modulus and strength ($P < 0.05$) with no significant difference between the maximum load potentials between the two groups. A significant decrease Young's modulus and strength was noted on all DBD treated samples ($P < 0.05$).

Conclusions:

Electrically conductive polymers have many applications in tissue engineering. The problems associated with synthetic medical polymers are their inherent hydrophobicity and poor surface chemistry. The research presented here clearly shows that atmospheric DBD plasma treatment alters the surface topography to improve surface wettability. The addition of PANi to PLCL leads to the formation of stronger, stiffer fibre scaffolds with a similar maximum load potential. Despite DBD being a cold plasma technology thermal damage to the individual fibres was observed at higher DBD dosages. 10 J/cm² DBD treatment is the optimal DBD dosage to surface modify electrospun PLCL/PANi matrices balancing the need for improved surface wettability against polymer thermal degradation.

References

1. Sorkio A, Porter PJ et al (2015) Tissue Engineering Part A 21:2301-14.
- 2 Wang M, Favi P, Cheng X, et al (2016) Acta Biomater 46:256-65.
- 3 Balint R, Cartmell SH. (2014). Acta Biomater 10:2341-53.

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Thiol-Ene Clickable Gelatine hydrogel for Tissue Engineering

Linke Wu¹, Burcu Colak¹, Julien E Gautrot^{1*}

¹ Engineering Building, Queen Mary, University of London, Mile End, E1 4NS, London

Introduction

The click chemistry is wide in scope, gives quantitative yields, generates inoffensive byproducts that are easily removed by non-chromatographic methods and is stereospecific [1].

Gelatine is a natural derived material for tissue engineering and it could become physical hydrogel under room temperature. The physical gel is not stable at physiological temperature [2]. In this project, gelatine was modified with norbornene and the properties of thiol-ene cross-linking with the favorable biological properties of gelatine was synergized.

Methods

Norbornene modified gelatine was studied by Nuclear magnetic resonance (NMR) and Fourier-transform infrared spectroscopy (FTIR). The thiol-ene crosslinked gelatine hydrogel were studied by photo rheology, Thermogravimetric Analysis (TGA) and Atomic force microscopy (AFM).

Results & Discussion

Photo rheology shows that storage modulus of hydrogels were varied by crosslinkers. We assumed that the chain length of crosslinkers could vary the pore size of hydrogels, it could lead different property of hydrogel including mechanical property (figure 1) and swelling property.

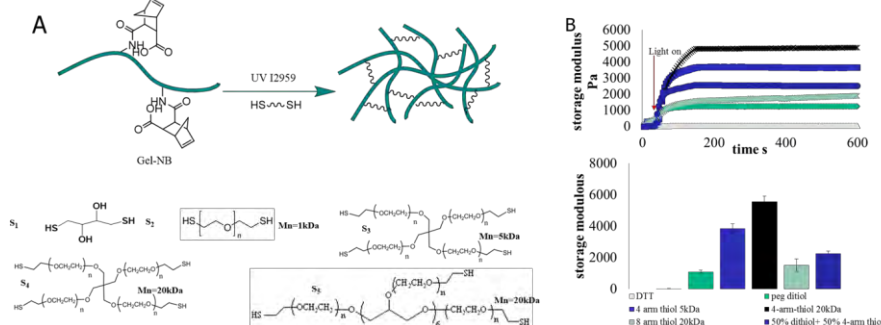


Figure 1. (A) Scheme of the free radical polymerization of Gel-NB in comparison of different crosslinkers (S1-S5). (B) Rheological profiles showing hydrogel formation by UV light induced photopolymerization of Gel-NB (5% (w/v)) with the photosensitizers I2959 and different crosslinkers.

Conclusion

Thiol-ene clickable gelatine was fabricated and the mechanical property of hydrogels with different crosslinkers were characterised. The final mechanical property of hydrogels primarily depends on the cross-linking degree of the network. Recent studies have shown that matrix stiffness would influence cell growth and morphogenesis in 3D and tunable mechanical property is essential for the universality of the platform used in different cell types.

References

1. B. Lowe, et *Polym. Chem.* vol. 1, pp. 17–36, 2010
2. Bertlein, Sarah, et al *Adv. Mat.* 2017

Acknowledgments

The authors are grateful Dr Halena's guide and advice for this project. The authors gratefully acknowledge the financial support from China Scholarship Council.

Soft, robust, and bioactive hydrogels with tuneable mechanical properties and rapid load recovery

F. Oveissi, S. Naficy, T.Y.L. Le, F. Dehghani

School of Chemical and Biomolecular Engineering, The University of Sydney, Sydney, NSW, Australia 2006.

Introduction

There is great interest in fabricating materials that resemble the mechanical properties of biological soft tissues. These naturally occurring materials are soft, tough, and possessing rapid load recovery; properties which have been challenging to reproduce in synthetic materials [1]. Recently, polyether-based polyurethanes (PEO-PU) have been introduced as a class of tough hydrogels with rapid load recovery [2]. In this study, we provided more degree of freedom over tunability of PEO-PU hydrogels, and its conjugation to proteins and growth-factors, by integrating a second copolymer network within the network of PEO-PU hydrogel.

Methods

Hydrogel films were made via random polymerisation of three co-monomers within the PEO-PU network. The co-monomers were selected to provide load recovery and robustness, protein conjugation, and controlled hydrophilicity. The effect of each component on physical and mechanical properties of hydrogels including swelling ratio, gelation, compression and tensile properties, cyclic mechanical behaviour and fracture energy were investigated. The release of protein and cell proliferation was also studied.

Results & Discussion

Our results demonstrated that a double-network hydrogel was formed through interpenetrating two crosslinked networks of copolymer and PEO-PU. The fully swollen hydrogel films had stiffness ranged from 20 to 500 kPa, and elongation of 150 up to 900% tuned via various ratios of polymeric units. *In-vitro* cell proliferation and cell viability tests confirmed the biocompatibility of the materials. The overlapping of more than 10 continues load/unload cycles indicated the elastic behaviour of the hydrogel. The fracture energy for one tough formulation was 1000 J/m² which is considerably higher than conventional hydrogels (~10 J/m²).

Conclusion

We made a library of various formulations of double-network hydrogels with tuneable softness, toughness, elasticity and robustness. These biocompatible materials can bond to proteins and growth factors thanks to the protein affine units on one of the networks. Such properties make these hydrogels suitable candidates for a variety of applications including tissue engineering, soft robotics and potentially soft electrodes.

References

1. O. Bas *et al.*, *ACS Applied Materials and Interfaces*, 2017; 9: 29430-29437.
2. S. Naficy *et al.*, *Macromolecular Materials and Engineering*, 2017; 302: 1600212.

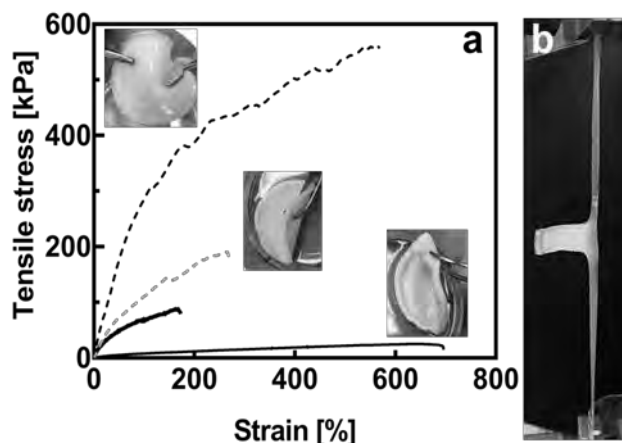


Figure 1 (a) Tensile stress-strain curves of several formulations of the double network hydrogels, (b) toughness of material during trouser tear test.

On-Demand Activation of Antimicrobial Biomaterials for Oral Soft Tissue Regeneration

A.L. Smith^{1,2,3}, S.R. Wood¹, M.J. Raxworthy^{3,4}, G. Tronci^{1,2}

¹ School of Dentistry, ²School of Design, ³Institute of Medical and Biological Engineering, University of Leeds, Leeds, LS2 9JT. ⁴Neotherix Ltd. The Hiscox Building, Peasholme Green, York YO1 7PR

Introduction

Oral soft tissue can be lost through disease, accidents and congenital defects¹. Advanced biomaterials can be used to aid regeneration of oral soft tissue whilst treating localised bacterial infections. Use of antibiotic-free treatments minimises the spread of antimicrobial resistance (AMR)². Our strategy is to use a bioresorbable electrospun polymer scaffold equipped with antimicrobial photodynamic therapy (aPDT) capability to support oral soft tissue regeneration. To enable aPDT, a photosensitiser (PS) dye is polymer-encapsulated in its inert form and then the antimicrobial function activated on-demand via a light source³.

Methods

Two polyesters (Poly(ϵ -caprolactone) (PCL) and 75:25 Poly-DL-lactide/glycolide (PLGA) were selected as fibre-forming polymers as they are approved by the FDA for drug delivery and suture applications. Each polymer was dissolved in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) solvent at 6% w/w and 12% w/w respectively. Either Methylene Blue (MB) or Erythrosine B (ER) PS dyes were added to the electrospinning solutions at a concentration of 2.2mM. Polymer solutions were electrospun and resulting scaffolds analysed using porometry and SEM. Scaffolds were then incubated in PBS to determine the scaffold degradability and dye release capability.

Results & Discussion

There was a significant reduction in fibre diameter upon incorporation of either MB or ER dye (54% and 49% for PCL, 51% and 69% for PLGA respectively). This is likely due to the charge of the PS dye causing increased charge density on the jet surface during electrospinning⁴. Similar trends were observed in the mean flow pore diameter. This can be rationalised because an increase of fibre density per unit of scaffold volume ultimately results in a decreased average pore size in the scaffold. Both MB and ER dye was released more readily from the PCL scaffolds than from the PLGA scaffolds. The burst release observed is commonly seen with fibrous scaffolds used in drug delivery applications⁵. A macroscopic shrinkage of the PLGA scaffolds could be contributing to the reduced dye release observed from these scaffolds.

Conclusion

This study has shown that incorporation of PS-dye significantly alters the structure of the electrospun scaffolds. PLGA scaffolds with incorporated ER or MB was concluded to not be suitable for use in oral or moist regenerative medicine applications due to shrinkage upon contact with water. Future work will include tuning the release of the dyes from the PCL scaffolds to avoid burst release (e.g. with multilayer structure) or the use of a different polymer as a carrier for the PS dye.

References

1. Sculean, A., et al.; J Clin Periodontol; 2014; 41; S6–S22.
2. Wainwright, M. et al.; Lancet Infect. Dis.; 2017; 17; e49–e55.
3. Pérez-Laguna, V. et al.; Photodiagnosis Photodyn. Ther.; 2017; 19; 98–102.
4. Wood, S., et al.; J. Antimicrob. Chemother.; 2006; 57; 680–684.
5. Nirmala, R. et al.; Colloids Surf B Biointerfaces.; 2013; 104; 262–267.
6. Chou, S. et al.; J. Control. Release.; 2015; 220; 584–591.

Acknowledgments

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Production of Synthetically Derived Extracellular Matrix as a Controlled Platform for Liver Bioengineering

R. Grant¹, A. Callanan¹

¹ Institute for Bioengineering, School of Engineering, University of Edinburgh, EH9 3JL, Edinburgh, UK.

Introduction

Increasing incidence of liver disease and a shortage of organs available for transplant¹ has led to a push for lab grown liver 'organoids'². Part of the challenge of developing such an organoid lies in the creation of 3D environments for hepatocytes. Biofunctionalization of electrospun polymer scaffolds with cell-derived extracellular matrix [ECM] has been shown to influence hepatocyte function³. We selected a single ECM protein; Fibronectin, and selectively biofunctionalized an electrospun polylactic acid [PLA] scaffold with a fibronectin-rich cell-derived 'synthetic' ECM.

Methods

A fibronectin vector [Protein Structure Initiative:Biological Material Repository] was transfected into confluent 5637 bladder epithelials, seeded on electrospun PLA scaffolds and cultured for 7 days before decellularization. The resulting synthetically derived ECM-PLA scaffolds were re-seeded with HepG2s, and cultured for 3/5 days before scanning electron microscopy [SEM], mechanical and biochemical quantification, histology, and gene expression analysis were performed.

Results

SEM and immunohistochemistry demonstrated retention of both native and synthetically derived ECM proteins. Gene expression and albumin production was significantly altered between conditions. Cellular growth and survival can be seen in Figure 1; with Live/Dead staining demonstrating low levels of cell death. Furthermore, differences in mechanical properties confirmed the presence of an altered ECM on the vector treated constructs.

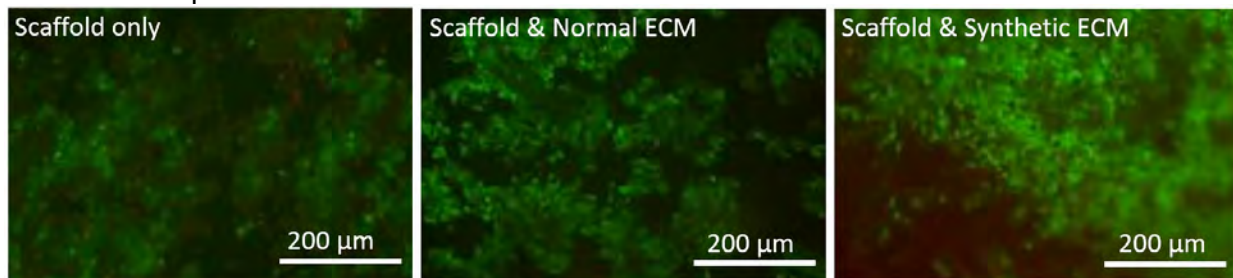


Figure 1: Live/Dead imaging demonstrating the living functional HepG2 layer present with minimal cell death on polymer only electrospun scaffolds, decellularised normal and decellularised fibronectin-rich synthetic ECM.

Discussion & Conclusion

Transfected cells can be harnessed to produce customized ECMs for liver bioengineering. These results demonstrate that synthetically derived ECMs represent a viable method of producing customized ECM's and biofunctionalizing electrospun polymer scaffolds.

References

1. Williams, R. et al. Lancet 384, 1953-1997, 2014.
2. Takebe, T. et al. Cell Stem Cell 16, 556-565, 2015.
3. Grant, R et al. Tissue Eng. Part A, 2017.

Acknowledgments

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BioMedEng18

Engineering soft tissues: learning from nature

N. Mehrban¹, D.N. Woolfson², S.F. Badylak³, M.A. Birchall¹

¹ UCL Ear Institute, University College London, WC1X 8EE, London. ²School of Chemistry, University of Bristol, BS8 1TS, Bristol ³McGowan Institute for Regenerative Medicine, University of Pittsburgh, PA 15219-3110.

Introduction

Surgical repair of damaged tissue can impact overall functionality while tissue engineering allows full functional restoration. Using nature to design smart scaffolds we can support and guide cell behaviour while integrating with surrounding healthy tissue at the wound site.

Methods

De novo peptides were synthesised and functionalised to produce hydrogels which were physically and biologically characterised (neural stem cells, adipocytes and tenocytes). Porcine bladder was decellularised before being lyophilised, milled and reconstituted as a pH-neutralised hydrogel. Cell viability was assessed using 3T3 fibroblasts and C2C12 myoblasts.^{3,4}

Results

Soft tissue scaffolds were formed via peptide synthesis (Figure 1A and 1B) or through decellularisation methods (Figure 1C and 1D). All scaffolds supported cell attachment, migration, proliferation and some functional differentiation. Some of these materials can also be 3D printed.

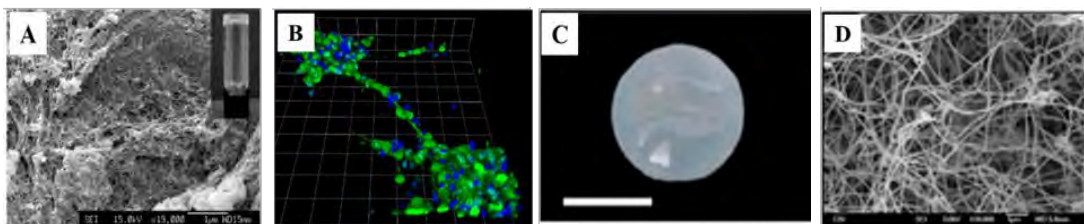


Fig. 1: Fibrous scaffolds to support cell proliferation were formed through peptide synthesis (A and B) or through decellularisation techniques (C and D). All images taken from previously published text²⁻⁵.

Discussion & Conclusion

Here *de novo* peptide-based materials which can be chemically and physically tuned to match tissue type^{1,2} and, decellularised materials that can be modified to suit patient-specific geometries.^{3,4} are presented towards soft tissue engineering. Both materials are based on exploiting nature's designs. The resulting scaffolds allow better control of overall geometry, cell attachment, migration and differentiation⁵ as well as scaffold stiffness⁶ for better integration with healthy native tissue and towards full functional restoration.

References

¹Banwell EF, Abelardo ES, Adams DJ et al. *Nat. Mat.* 2009; 8:596-600. ²Mehrban N, Abelardo E, Wasmuth A et al. *Adv. Health. Mat.* 2014; 3:1387-91. ³Crapo PM, Gilbert TW, Badylak SF. *Biomater.* 2011; 32:3233-43. ⁴Wolf MT, Daly KA, Brennan-Pierce EP et al. *Biomater.* 2012; 33:7028-38. ⁵Mehrban N, Zhu B, Tamagnini F et al. *ACS Biomater. Sci. Eng.* 2015; 1:431-39. ⁶Discher DE, Mooney DJ, Zandstra PW. *Science* 2009; 324:1673-7.

Acknowledgments

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Uptake of Radioactive Cesium by Alginate Immobilized Microalgae

Ji Eun Hong¹, Hara Ku¹, Sang-Hyo Lee¹, Tae Yoon Kim¹, Seung-Yop Lee^{1,2}

¹ Department of Biomedical Engineering, Sogang University, 35 Baekbeom-ro, Mapo-gu, Seoul 04107, Korea.

² Department of Mechanical Engineering, Sogang University, 35 Baekbeom-ro, Mapo-gu, Seoul 04107, Korea.

Chlorella vulgaris is a green microalga known for a potential source of food or bioenergy. We have shown that this species has a great potential to remove radionuclides, particularly radioactive strontium (^{90}Sr), through a bio-mineralization process [1] (Fig. 1). Also, the uptake properties of radioactive cesium (^{137}Cs) by microalga *Haematococcus pluvialis* were evaluated with different cell conditions, and its cesium-uptake rate was compared with results by other microalga *Chlorella vulgaris* [2]. Alginate, a naturally occurring biopolymer extracted from brown algae, has several unique properties that have enabled it to be used as a matrix for the entrapment and/or delivery of a variety of biological agents. Alginate can be ionically cross-linked by the addition of divalent cations in aqueous solution. However, monovalent cations do not induce alginate gel formation [3]. Using the properties of biosorption of microalgae and cell encapsulation of alginates, we aim to develop the removal technology of radioactive materials in order to apply to practical nuclear incidents (Fig. 2).

C. vulgaris and *H. pluvialis* were cultivated on BG11 and modified C medium, respectively. Each strain was collected by centrifugation and washed 3 times with 3mM of NaHCO_3 to remove residual media and trace elements for following Sr^{2+} and Cs^+ uptake experiments. ICP-OES was used to quantify the removal rate of each strontium and cesium ion. 1% (w/v) alginate solution and 1% (w/v) calcium chloride solution were used to prepare the microalga cell encapsulated beads (2-5mm).

Uptake of Sr^{2+} and Cs^+ by specific alginate encapsulated microalga was observed with time in the solution of $\text{Sr}(\text{NO}_3)_2$ and CsCl , and maximum removals of Sr^{2+} by *C. vulgaris* and of Cs^+ by *H. pluvialis* were 68% and 73.5% of the total Sr^{2+} and Cs^+ , respectively. These results demonstrate that each microalga species has its own capability to remove different radioactive elements effectively. Also, immobilization of microalga cells inside the pores of alginate polymers were conducted removal of radioactive materials and post processing system.

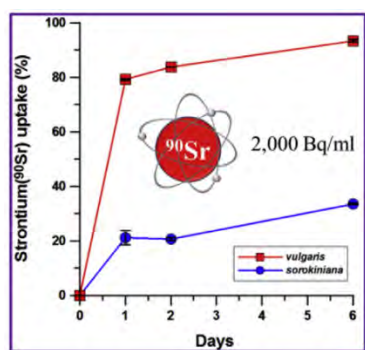


Fig. 1 Radioactive strontium removal by *Chlorella vulgaris* [1]

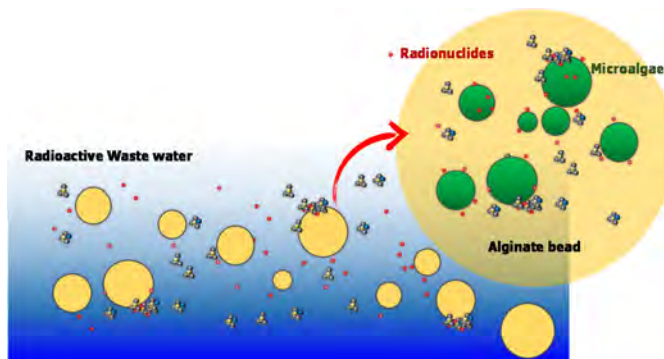


Fig. 2 Principle of removal of radionuclides in water using microalgae-containing alginate beads

References

1. Lee S-Y, et al. *Bioresour Technol* 2014; 172: 449-452.
2. Lee K-Y, et al. *J Environ Radioact* 2018 in press.
3. Chen, KL, Mylon SE, Elimelech M. *Langmuir* 2007; 23.11: 5920-5928.

Acknowledgments

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BioMedEng18

Designing organic electronic materials for biology

A. Lo Fiego^{1,2,3}, S.G. Higgins^{1,2,4}, A. Creamer^{1,2,3}, D. Boland^{1,2,3}, M. Heeney⁴, M.M. Stevens^{1,2,3}

¹ Department of Bioengineering, Imperial College London, London, SW7 2AZ, UK ² Department of Materials, Imperial College London, London, SW7 2AZ, UK ³ Institute of Biomedical Engineering, Imperial College London, London, SW7 2AZ

⁴ Department of Chemistry, Imperial College London, London, SW7 2AZ, UK

Introduction

Neurodegenerative conditions often have complex pathogenetic mechanisms involving physico-chemical, molecular and electrical alterations. Understanding how these factors interact with each other will be the key for the development of more effective therapeutic strategies.¹ High-aspect-ratio nanostructures can intimately contact cells in a minimally invasive, uniform and controlled way², while organic transistors are an ideal tool for interfacing biological systems in physiological conditions as a means of biosensing, electrical stimulation and recording.³ Combining nanostructured surfaces with novel organic electronic materials will allow the development of new neural-interfacing technologies for the longitudinal multi-parametric monitoring of in vitro models of neurodegenerative conditions.

Methods

New semiconducting organic polymers are generated through the method demonstrated by Creamer, Wood et al.⁴ Their electrical performance is characterized using an Organic Field-Effect Transistor (OFET) platform, and their 3D patterning will be achieved through Nanoimprint Lithography (NIL) and other microfabrication techniques.

Results & Discussion

The exploited synthetic pathway allows for the generation of a versatile library of functionalised DT-BT based polymers with promising electrical properties. Polymeric high-aspect-ratio nanostructures, fabricated via NIL, show high potential as cell interfacing system.

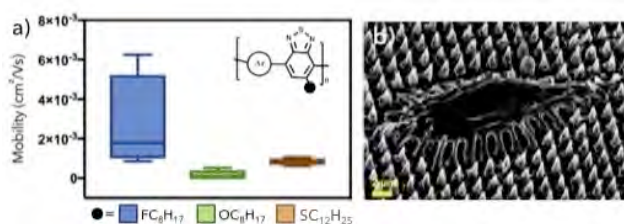


Fig. 1. a) Charge carrier mobility in thin film Organic Field Effect Transistor fabricated with differently functionalised IDT-BT based polymers. b) SEM micrograph of a cell seeded on a polymeric nanoneedle array.

Conclusion

Our preliminary data demonstrate new organic semiconducting materials with good electrical properties and capability for patterning. This paves the way for the fabrication of integrated multifunctional organic electronic devices as a means of in vitro model interrogation.

References

1. Eric R. Kandel et al. Principles of neural science, 5th ed. Mc Graw Hill Education (2013).
2. C. Chiappini et al. Biodegradable Nanoneedles for Localized Delivery of Nanoparticles in vivo: Exploring the Biointerface. ACS Nano 9, 5500–5509 (2015).
3. L. Torsi et al. Organic field-effect transistor sensors: a tutorial review. Chem Soc Review 42, 8612 (2013).
4. A. Creamer, C.S. Wood et al. Quantitative post-polymerisation functionalisation of conjugated polymer backbones and its application in multifunctionalised semiconducting polymer nanoparticles. Nature Communications, accepted (2018).

Reverse-engineered silk hydrogels as a stem cell delivery matrix for stroke

Natalia Gorenkova¹, Osama Ibrahim¹, Hilary V.O. Carswell¹, F. Philipp Seib^{1,2}

¹Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, UK

²Leibniz Institute of Polymer Research Dresden, Germany.

Introduction

Advanced cell therapies require robust delivery strategies¹; one promising contender is the biopolymer silk.² Silk already has a long clinical track record for load bearing applications and can be assembled into a range of material formats, including hydrogels.³ The aim of this study was to (i) assess the biocompatibility of self-assembling silk hydrogels in the stroked brain and (ii) optimise self-assembling silk hydrogels as a mesenchymal stem cell (MSC)-support matrix.

Methods

B. mori silk was reverse engineered as described previously.⁴ Sonication energy was used to control silk self-assembly. The resulting hydrogels were characterised using FTIR, CD, rheology and SEM. During the solution-gel transition MSCs were embedded and cytocompatibility was assessed; analogous studies were performed to examine the impact of injection on cell viability. Next, stroke studies were performed. Sprague Dawley rats underwent transient middle cerebral artery occlusion 2 weeks before random assignment to treatment groups including stereotaxic injection of self-assembling silk hydrogels into the stroke cavity. Space conformity, GFAP glial scar manifestation, CD11b microglia/macrophage localisation and Ki67 cell proliferation were examined 1 and 7 weeks later.

Results & Discussion

We used sonication energy to programme the transition of the silk secondary structure from a random coil to a stable β -sheets configuration. It was thus possible to fine tune self-assembling silk hydrogels to achieve space conformity in the absence of any silk hydrogel swelling and to support uniform cell distribution as well as cell viability. Embedded cells showed significant cell proliferation over 14 days but 2% w/v hydrogels supported proliferation best. When injected through a 30G needle, MSC viability was significantly better when hydrogels were in the pre-gelled state versus post-gelled state. Silk hydrogels with matched physical characteristics of brain tissue were able to show good space conformity after stereotaxic injection into an ischaemic stroke lesion. Self-assembling silk hydrogels filled the stroke cavity with excellent space conformity and presented no overt microglial/macrophage response.

Conclusion

Overall, this study demonstrates that self-assembling silk hydrogels are emerging as a promising cell delivery platform for CNS diseases, especially stroke.

References

1. Tam et al. *Neuropsychopharmacology* 2014; 39: 169-188.
2. Seib *Therapeutic Delivery* 2018; 9: 469-487.
3. Seib Chapter 3. *In: Self-assembling Biomaterials. Molecular Design, Characterization and Application in Biology and Medicine.* Eds. Azevedo, da Silva. Woodhead Publishing 2018.
4. Seib, Pritchard, Kaplan *Advanced Functional Materials* 2013; 23: 58-65.

Acknowledgments

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Antibacterial effects of *Perilla.frutescence* var. *crispa* fo. *viridis* Makino extracted by nanosecond pulse electric shock waves

B. Hosseini¹, A. Guionet², H. Hosano^{1, 2}

¹Graduate School of Science and Technology, Kumamoto University, Japan

²Bioelectronics Department, Institute of Pulsed Power Science, Kumamoto University, Japan

Introduction

Recently, non-thermal food preservation methods has gained considerable attention as they are able to preserve the fresh-like quality of foods, nutritional values, and sensory properties. Non-thermal inactivation of microorganisms, in order to prevent foodborne diseases and extend the shelf life, compare favorably to thermal food preservation methods; as thermal process reduces nutritional values (Rabie et al. 2015; Lund 1988; Leizerson and Shimoni 2005).

Methods

In this study, a nanosecond pulse electric discharge shock wave generator was used for applying shockwaves as a hurdle method of food pasteurization for orange juice. Orange juice contained E.coli JM109 (as a target bacteria with 10^9 CFU/ml concentration) and *Perilla.frutescence* (green shiso) leaf was exposed to underwater shock waves. Leaf and extract samples were observed under a microscopic. The concentration of bacteria was evaluated by counting colony CFU/ml during 120 h. Quality of *Perilla.frutescence* extraction were examined by LC/MS (Liquid chromatography mass spectrophotometry).

Results & Discussion

The concentration of bacteria according to CFU/ml was evaluated. The concentration of E.coli reached to less than $<10^2$ after 96 h, 8 log reduction in treated samples containing *Perilla.frutescence*. A complete eradication in full concentration was observed after 120 h; indicating and referring to the antibacterial molecules extracted from the shiso leaves. The quality of *Perilla.frutescence* extracts were examined by LC/MS (Liquid chromatography mass spectrophotometry) and the antibacterial components of the extract were obtained.

Conclusion

The results suggest an efficient non-thermal food preservation method. This technique consumes less energy and uses natural compounds like *P.frutescens* to preserve the nutritional values and organoleptic properties. The strong antibacterial activity of the extract make it of considerable interest for further use in biomedical engineering and medicine.

References

1. Leizerson S, Shimoni E. Stability and sensory shelf life of orange juice pasteurized by continuous ohmic heating. Journal of agricultural and food chemistry. 2005 May 18; 53(10):4012-8.
2. Lund D. Effects of heat processing on nutrients. In: Effects of heat processing on nutrients. 2nd ed. Springer, Dordrecht; 1988. p. 319–54.
3. Rabie MA, Soliman AZ, Diaconeasa ZS, Constantin B. Effect of Pasteurization and Shelf Life on the Physicochemical Properties of Physalis (Physalis peruvianaL.) Juice. J Food Process Preserv. 2015;39(6):1051–60.

BioMedEng18

A Glucose Controller for Type I Diabetes using Insulin Sensitivity modulation

A. Güemes¹, P. Herrero ¹, B. Hernandez ¹, P. Georgiou ¹

¹Centre for Bio-Inspired Technology, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

Diabetes is a disease caused by a breakdown in the glucose metabolic process resulting in abnormal blood glucose fluctuations. The World Health Organization estimates that it affects over 422 million people worldwide and will be the 7th leading cause of death in 2030. Existing therapies for type 1 diabetes (T1D) implement closed-loop controllers to calculate the delivered dosage of insulin and glucagon to manage blood glucose fluctuations. However, glucose control is still suboptimal and requires user intervention, such as meal announcements.

Methods

The insulin sensitivity (SI) of the patient defines the effectiveness of the injected insulin action in the tissues. In this study, we propose to extend existing closed-loop systems by including SI as an additional control variable. Hence, two standard proportional-derivative (sPD) controllers were designed to specify the insulin dose and the desired SI from continuous blood glucose measurements. The tuning of the parameters of the resulting hybrid (Insulin-Insulin Sensitivity Glucose, ISIG) controller and a comparison in performance with the existing sPD¹ and bioinspired bi-hormonal (BiAP)² controllers were carried out on a virtual population of subjects with T1D (n=20, with 10 adults and 10 adolescents). The statistical significance of the differences between controllers was determined using the parametric student paired t-test ($\alpha = 0.01$).

Results & Discussion

The proposed controller significantly increased ($p < 0.01$) the percentage of time glucose levels were within target (70-180 md/dL) to $98.5 \pm 2.5\%$ in adults (sPD: $92.9 \pm 7.1\%$, BiAP: $96.1 \pm 3.9\%$) and to $91.7 \pm 5.8\%$ in adolescents (sPD: $83.7 \pm 11.2\%$ BiAP: $81.1 \pm 12.5\%$). In addition, the total risk index significantly decreased ($p < 0.01$) to 1.24 ± 0.35 in adults (sPD: 2.25 ± 1.66 , BiAP: 1.44 ± 0.60) and to 2.13 ± 1.05 in adolescents (sPD: 4.1 ± 3.2 , BiAP: 3.78 ± 2.23). Using the ISIG controller, the insulin meal bolus was not required for meals with less than 60g of carbohydrates. This suggests that modulation of SI in patients with T1D using the proposed controller allows partial suppression of meal announcements without hindering the safeness and efficacy of glucose control.

Conclusion

The presented new generation of closed-loop glucose controllers demonstrates enhanced glucose control in terms of safety and efficacy by modulating SI and moves one step ahead towards the development of fully automated systems for diabetes treatment. Moreover, these findings serve as motivation to design technology to non-invasively adjust the insulin sensitivity of the patient for diabetes management.

References

1. Mahmud F, et al. AIP Conf. Proc. 2017; 1788: 030072-1–030072-7
2. Herrero P, et al. J Diabetes Sci Technol, 2013; 7: 941–51

Acknowledgments

The authors would like to acknowledge the Rafael del Pino Foundation for supporting A. Güemes during this work. We are grateful to the Wellcome Trust, EPSRC Medical Engineering Initiative and the Bioengineering Society for supporting this conference. No conflicts of interest to declare.

Noise in Organic Electrochemical Transistors

A.G. Polyravas¹, V.F. Curto¹, G.G. Malliaras¹

¹ *Electrical Engineering Division, Department of Engineering, University of Cambridge, Cambridge CB3 0FA, UK.*

Introduction

A great deal of contemporary research focuses on organic electronic devices and their use in recording and stimulating the brain in order to diagnose and treat neurological disorders¹. These bioelectronic devices must be biocompatible and able to efficiently record and stimulate neuronal activity. The organic electrochemical transistor (OECT) fits these requirements: It can be developed from biocompatible materials and has been shown to provide high signal-to-noise ratio recordings² and localised electrical stimulation³. However, the noise characteristics of this device remain unexplored. In this work, we characterise noise in OECTs.

Methods

Fabrication of the OECTs took place using lithographic techniques as discussed in previous publications^{2,4,5}. Electrical characteristics and noise was measured using a Keysight B1500 parameter analyser.

Results & Discussion

We designed transistors with different architectures, varying the source-drain distance, the channel thickness, the placement of the gate electrode, the electrolyte, etc. We measured the output and transfer curves and characterised the frequency response of the transconductance. We then applied white noise to the gate and measured the response of the drain current. The results show that noise depends on device architecture in a way that is sensitive to the contacts. In a practical recording situation, it is the signal-to-noise ratio that needs to be optimised. Our results show how to tune device architecture in order to optimise this important figure-of-merit.

Conclusion

Although the basic principles of operation of OECTs are understood reasonably well, our study shows how to optimise the signal-to-noise ratio in practical recording situations.

References

1. Rivnay J, Owens RM, Malliaras GG. *Chem. Mater.* **26**, 679–685 (2014).
2. Khodagholy D, *et al.* *Nat. Commun.* **4**, 1575 (2013).
3. Williamson A, *et al.* *Adv. Mater.* **27**, 4405–4410 (2015).
4. Khodagholy D, *et al.* *Appl. Phys. Lett.* **99**, 163304 (2011).
5. Sessolo M, *et al.* *Adv. Mater.* **25**, 2135–2139 (2013).

Acknowledgments

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BioMedEng18

A multi-channel multiplexed EMG recording system to study electrode array configuration

K. de Jager¹, M. Mentink^{1,2}, F. Tjulkens¹, H. Lancashire¹, S. Taylor¹,
A. Vanhoostenberghe¹

¹ Aspire CREATE, UCL, London, UK. ² UREST Ltd., Basingstoke, UK.

Introduction

Choice of EMG recording electrode configuration (monopolar, bipolar, tripolar) determines the electrode pick-up area [1], affecting the amount of cross-talk detected from adjacent muscles and the signal-to-noise ratio (SNR) [2]. Al-Ajam et al. [3] proposed that incorporating multiplexer functionality in an implantable EMG recording device [4] would provide the necessary versatility for optimising electrode configurations, limiting cross-talk and increasing SNR in vivo.

Methods

The implantable EMG recorder (figure 1) uses an ADS1298 analogue front end (6 channels, 16-bit resolution, 2 kHz sampling rate, 12x gain, 500 Hz bandwidth) with a balanced analogue band-pass filter (30-800 Hz). ADG2188 multiplexers facilitate user-defined electrode configurations from 5-electrode arrays for each ADC channel individually (2 channels per electrode array). Raw EMG data is sent to an external Bluetooth hub via SPI, or the envelope (sampled at 31.25 Hz), via a bidirectional “1-wire” bus (baud rate 38400 bps). The 1-wire also provides system power, rendering it fully implantable when used with a feedthrough-enabled bone fixation device [5]. The raw EMG data will be used in animal studies on optimal electrode configurations.

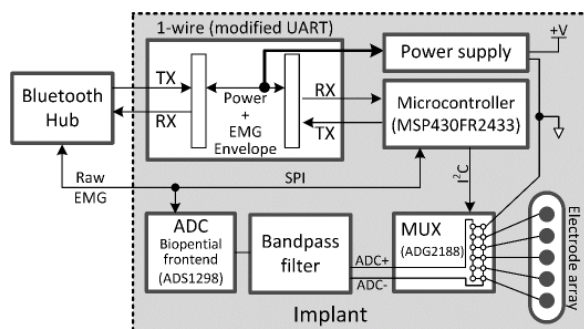


Figure 1: EMG recording system block diagram of the implant and Bluetooth hub: TX and RX forms a modified 1-wire bus; multiplexer system shown for 1 of 6 ADC channels.

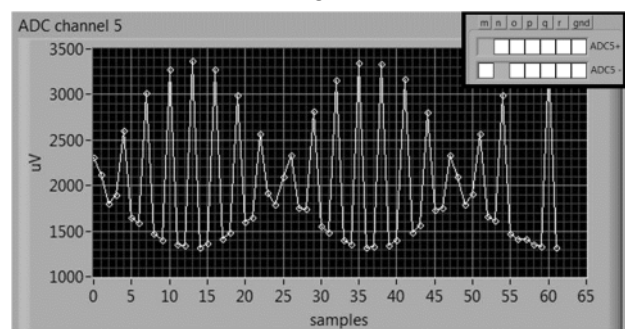


Figure 2: Bipolar electrode configuration selected for ADC channel 5 (top right inset) and the enveloped signal measured via 1-wire in response to a 20 Hz sinewave test signal.

Results & Discussion

Electrode array configurations are selected using a LabVIEW GUI which also displays the EMG signal in real-time (figure 2); recordings are saved as a csv file.

Conclusion

The multiplexers allow the realisation of monopolar, bipolar and quasi-tripolar electrode configurations of varying inter-electrode spacing in vivo.

References

1. Koh TJ, Grabiner MD. *J Biomech*, 1993; 26: 151-157.
2. van Vugt JPP, van Dijk, JG. *Clin Neurophysiol*, 2001; 112(4): 583-592.
3. Al-Ajam Y et al. *IEEE T Bio-Med Eng*, 2013; 60(6): 1654-1659.
4. Mentink MJA, Taylor SJG, Vanhoostenberghe A. In: *21st IFESS Annual Conf. Proc.*, 2017.
5. Tjulkens F et al. In: *BioMedEng18*; 2018.

Acknowledgments

Thanks to the Restoration & Function Trust (RAFT, UK) for financial support; no conflicts of interest exist.

Event related potentials and event related perturbations during movement imagination depending on muscle activations

A. Vuckovic¹, A. Sosnowska¹, H. Gollee¹

¹ Department of Biomedical Engineering, University of Glasgow, G12 8QQ, Glasgow

Introduction

Motor imagination (MI) paradigms used in BCI studies on healthy people rely on the assumption that there is no muscle activity which is controlled with electromyography (EMG). EMG is prone to noise, thus ultrasound imaging (USI) was used to detect muscle twitches and establish percentage of truly imagined movements during MI. It was analysed whether presence of muscle twitches was reflected in differences in event related potentials (ERPs) and event related spectral perturbations (ERSPs).

Methods

16 able-bodied volunteers performed cue based motor imagery of ankle plantar flexion with ultrasound videos and EMG recorded from the gastrocnemius medialis muscle. EEG was recorded with 27 self-adhesive Ag/AgCl scalp electrodes. 200 repetitions of task were performed by each participant. Ultrasound videos were analysed using image segmentation and tracking of features to detect muscle contractions and twitches [1]. EEG data was cleaned and epoched separating trials with no muscle activations and detection of twitches with USI.

Results & Discussion

Among whole group 21.53% of trials resulted in muscle twitch detected with USI, but not seen on EMG recording. 55.72% showed pure imagination, while the rest resulted in real muscle contraction. Comparing trials with twitches and pure imagination, we observed the largest differences in ERS in centro-parietal area (Fig.1a), covering motor cortex, in period 0.5-2s post cue. It indicates that there is no big difference in motor planning (frontal region) whether muscle activation occurs or not. Similarly ERP has largest difference in parieto-occipital region with reafferentation potential (sensory component) being larger in case when there is no twitches (Fig1b). Results indicate that larger mental effort is required to control imagination without proprioceptive feedback (no muscle activation), as is also seen in people with complete sensory loss and paraplegia when sensory component of ERP is larger than in able bodied. [2]

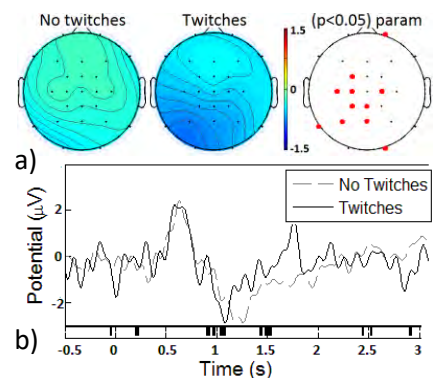


Fig. 1 a) Scalp maps of ERS (0.5-2s post cue, 7-15Hz), and b) ERP at Pz electrode showing trials without and with muscle twitch. Statistical difference is marked.

Conclusion

Muscle twitches are present during MI and USI can automatically detect them during BCI training. The difference in ERP and ERS when muscle twitches were present were most pronounced in parietal area of the brain. Detailed control over muscle activity is necessary to reliably transfer motor imagination BCI paradigms based on healthy population to paralysed individuals.

References

1. Darby J, Hodson-Tole EF, Costen N, Loram ID, *J. Appl. Physiol.*, 2012; 112: 313–327.
2. Xu R *et al*, *Front. Neuroeng.*, 2014; 7: pp. 1–9.

Acknowledgments

This project was founded by ESPRC. **Authors declare that there is no conflict of interest.**

BioMedEng18

Implementation and Evaluation of Different Time and Frequency Domain Feature Extraction Methods for a Two Class Motor Imagery BCI Applications: A Performance Comparison between GPU and CPU

J. Arnin¹, D. Kahani ¹, B.A. Conway ¹

¹ Centre of Excellence in Rehabilitation Engineering, Department of Biomedical Engineering, University of Strathclyde, Glasgow, G1 1QE, United Kingdom.

Introduction

OpenCL platform is widely used in high-performance computing such as multicore CPUs, GPUs, or other accelerators [1] which employed heterogeneous computing concept resulting in execution acceleration. As the advantages of parallel computing, it has been applied to brain-computer interface (BCI) applications especially speeding up signal processing pipelines such as feature selection [2]. In this study, we used OpenCL to implement some feature extraction methods on a IEEE open-access dataset [3] which provides 2-class motor imagery EEG recordings.

Methods

Different feature extraction methods including template matching, statistical moments, selective bandpower and fast Fourier transform power spectrum were selected to evaluate their computational performance on both CPU and GPU using OpenCL. This study used an open-access dataset that contains data presenting a 2-class motor imagery tasks. The dataset used to compare the performance of proposed feature extraction approaches in terms of accuracy and computation time. The study processed following a standard signal processing pipeline including pre-processing for artifact rejection, feature extraction, and classification.

Results & Discussion

The preliminary results show that running feature extraction methods on GPU yields a computing speed up at least to five times compared to CPU. In addition, amending parameters of parallel computing such as the number of work-items or work-groups could reduce computing time more.

Conclusion

The complexity of the proposed algorithm can be assessed by the heterogeneous computing concept. Fine-tuning the parameters of parallel computing and system optimization could increase the performance.

References

1. J. E. Stone, D. Gohara, and G. Shi, "OpenCL: A parallel programming standard for heterogeneous computing systems," *Computing in science & engineering*, vol. 12, no. 3, pp. 66-73, 2010.
2. J. J. Escobar, J. Ortega, J. González, and M. Damas, "Assessing parallel heterogeneous computer architectures for multiobjective feature selection on EEG classification," in *International Conference on Bioinformatics and Biomedical Engineering*, 2016, pp. 277-289: Springer.
3. R. Leeb, C. Brunner, G. Müller-Putz, A. Schlögl, and G. Pfurtscheller, "BCI Competition 2008–Graz data set B," *Graz University of Technology*, Austria, 2008.

Acknowledgments

We gratefully acknowledge the support of Scottish Government Health Directorates and the Royal Thai Government scholarship. The authors do not have any conflicts of interest to declare.

Recommending a protocol for normalisation of forearm electromyography (EMG)

O.O Akinola¹, V. Vardakastani¹, A.E. Kedgley¹

¹ Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

Electromyography (EMG) is an important tool used in diagnosis of neuromuscular disease, muscular rehabilitation, and input for some prostheses. However, for EMG data to be useful it needs to be normalised; this accounts for sensor position, and individual variations in muscle use. Raw signals are normalised with a maximum voluntary contraction (MVC) task. Ngo and Wells recommended using resisted moment tasks to obtain MVCs, but found no one task would illicit MVCs for all muscles of the forearm [1]. This study seeks to build on their work and suggest a protocol to achieve MVCs for seven prime mover muscles in the forearm.

Methods

23 subjects performed nine resisted moment tasks. The muscle activity of the flexor digitorum superficialis (FDS), flexor carpi ulnaris (FCU), flexor carpi radialis (FCR), pronator teres (PT), extensor digitorum communis (EDC), extensor carpi ulnaris (ECU), and extensor carpi radialis (ECR) were monitored by a surface EMG system (Delsys, Natick, MA, USA). The activation for each muscle was recorded in every task and the task that produced the highest activation was noted.

Results & Discussion

Figure 1 shows, for each muscle, how many people produced their MVC when performing each task. The task most likely to produce the MVC for a muscle can be inferred from this graph; for example, the ECR is most likely to achieve MVC during the pull task. From this, a protocol likely to ensure MVCs are recorded for the seven prime mover muscles of the forearm can be recommended.

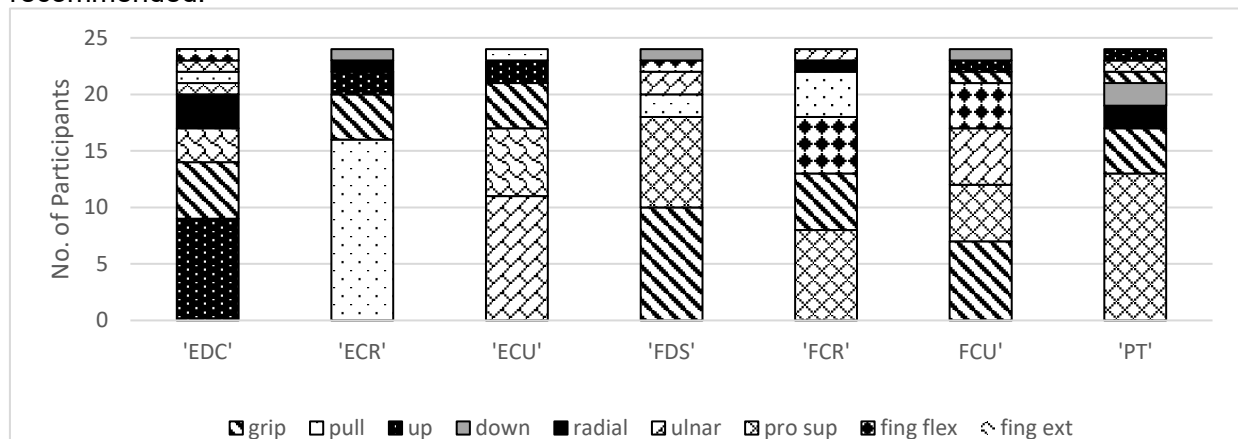


Figure 1 The MVC tasks ranked in descending order of number of participants that achieved MVC in that task.

Conclusion

From the data collected it is recommended that an MVC protocol for the forearm containing pull, pull up, pronation-supination, grip, and pull ulnar tasks will ensure MVCs for all the forearm muscles are collected for the majority of people.

References

- [1] B. P. T. Ngo and R. P. Wells, *J. Electromyogr. Kinesiol.*, 2016: 66–72.

BioMedEng18

An optical sensor probe measuring blood volume and skin contact pressure

H.K. Ballaji, C. Liu, S.P. Morgan, S. Korposh, R. Correia, B.R. Hayes-Gill
Optics and Photonics Research Group, Faculty of Engineering, University of Nottingham, UK, Nottingham.

Introduction

Photoplethysmography (PPG) is used extensively in clinical care. It provides information about blood volume changes while also monitoring the oxygen saturation (SpO_2) levels. This technology is a non-invasive way to measure the oxygen saturation of arterial blood [1]. However it is known that contact pressure of the probe affects the SpO_2 value [2] and so a probe that could measure both contact pressure and SpO_2 would be beneficial. The aim of this project is to develop an optical fibre measurement system for detecting of the PPG from two different wavelengths in order to calculate the oxygen saturation of the human body. In addition, the pressure applied by the SpO_2 sensor during operation is measured using a fibre Bragg grating (FBG) technique.

Methods

Two different wavelengths: red LED (660 nm) and infrared LED (850 nm) are used to monitor SpO_2 in reflection mode by using Plastic Optic Fiber (POF). The Time Division Multiple Access (TDMA) technique is applied on the signals that are received from the body to determine both red and IR PPG Signals. AC and DC components of both wavelengths are used to estimate SpO_2 [3] using the equations: $R = (\text{Red}_{\text{AC}}/\text{Red}_{\text{DC}}) / (\text{IR}_{\text{AC}}/\text{IR}_{\text{DC}}) \dots (1)$ % $\text{SpO}_2 = 110 - 25 R \dots (2)$. To enable contact pressure measuring three FBGs sensors are fabricated on a single mode silica fibre. FBG1 acts as the temperature reference, FBG2 is used to measure the pressure and FBG3, measures the strain. FBGs 1 and 2 along with the SpO_2 measuring POFs are embedded in an epoxy patch to form a single probe. The combined (pressure and SpO_2) sensor is placed on finger then covered by a cuff to apply pressure and is compared with a commercial pulse oximeter place on another finger.

Results & Discussion

The effect of pressure on Red and IR PPG is investigated. PPG signals were lost when the wavelength peak change of FBG is 37 pm, which is approximately equal to 20 kPa. In addition, SpO_2 deviated from that measured from the commercial pulse oximeter when the pressure rose above 12 kPa [2].

Conclusion

The combination of POF for SpO_2 and FBG for pressure sensors on one patch makes them more comfortable for long-term monitoring, convenient and suitable for use in textile-based sensors. Ultimately, this sensor patch has potential in reflectance oximetry and textile-based sensor devices, in something such as a shirt or a sock. A limitation of this sensor lies in the need to adjust it multiple times on the body in order to receive the desired signals. Therefore, finding a way to optimize the signal by using signal quality scoring would be paramount.

References

1. I. Yoshiya, Y. Shimada, and K. Tanaka, (1980). Spectrophotometric monitoring of arterial oxygen saturation in the fingertip. *Medical and Biological Engineering and Computing*, 18(1), 27-32.
2. Drescher, R. P., & Mendelson, Y. (2006, August). Reflectance forehead pulse oximetry: Effects of contact pressure during walking. In *Engineering in Medicine and Biology Society, 2006. EMBS'06. 28th Annual International Conference of the IEEE* (pp. 3529-3532). IEEE.
3. Ti.com. (2016). [online] Available at: <http://www.ti.com/lit/an/slaa655/slaa655.pdf> [Accessed 18 Jul. 2017].

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BioMedEng18

Graphene Biosensors for early detection of dementia biomarkers

Ryan Bigham¹, Hina Abbasi¹, Zari Tehrani¹, Ehsaneh Dagahmadi¹, Jacob Mitchell¹,
Anitha Devadoss^{1*}, Owen J. Guy^{1,2*}

¹ Centre for NanoHealth, College of Engineering, Swansea University, Singleton Park, SA2 8PP, Swansea.

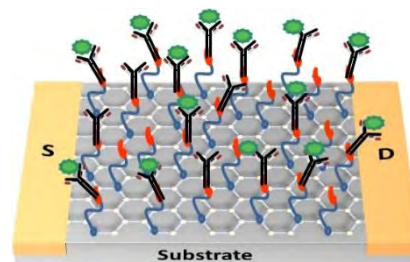
²Department of Chemistry, Swansea University, Singleton Park, SA2 8PP, Swansea.

Introduction

Rapid detection of low concentration of specific analytes in small sample volumes is critical in early point-of-care dementia diagnosis as it results in progressive degeneration and/or death of nerve cells in the brain, causing problems with mental functioning.^{1, 2} The most advanced diagnosis routes (MRI scan and CSF protein assay) to date in Alzheimer's disease (AD) – the commonest cause of dementia, are expensive, invasive and time-consuming, which limits the practicality of large screening programs. There is a huge demand for the development of a simple and sensitive biosensor technology for the detection of blood-based biomarkers at the point-of-care (POC). Graphene biosensors are promising for early POC diagnosis owing to their exceptional electron transport properties, flexible surface chemistry and large scale manufacture possibilities.^{3, 4} This talk details the development of devices for monitoring levels of Clusterin - an Extracellular Amyloid Chaperone Protein - as a potential tool for the detection of severity, and progression of dementia at an early stage.

Results & Discussion

Graphene field-effect-transistors (G-FET) were fabricated using a multi-step semiconductor device fabrication processes that is followed by the selective chemical functionalisation using 1,5-diaminonaphthalene (DAN) *via* pi-stacking resulting in amine terminated G-FETs. XPS analysis confirms the existence of amine groups upon DAN functionalisation. The anti-clusterin antibodies were immobilised onto the amine terminated G-FETs using EDC-NHS coupling. Systematic transport measurements were performed to study the effect of surface functionalization on the charge transport characteristics of graphene. The G-FET devices showed high sensitivity detection of Clusterin. Furthermore, the real-time measurement of antibody-antigen binding gives new insights into the development of rapid diagnostic graphene sensors.



Conclusion

Graphene field effect transistors devices were fabricated. The novel chemical functionalisation route was developed for the effective immobilisation of dementia biomarkers. Our G-FETs shows high sensitivity and lower limits of detection for the early detection of clusterin protein from micro-litre buffer samples.

References

1. Walsh, D. M.; Selkoe, D. J. *Journal of Neurochemistry* 2007, 101, (5), 1172-1184.
2. Kasai, T. *et.al* . *Neuroscience Letters* 2013, 551, 17-22.
3. Geim, A. K.; Novoselov, K. S. *Nat Mater* 2007, 6, (3), 183-191.
4. Tehrani, Z. *et.al* . *2D Materials* 2014, 1, (2), 025004.

Acknowledgments

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BioMedEng18

Quantification of advanced glycation end-products in a streptozotocin rat model of diabetes

R.C. Nicholls¹, N.J. Gardiner², M.S. Thompson¹

¹ Institute of Biomedical Engineering, Department of Engineering Science, University of Oxford, Parks Road, Oxford, OX1 3PJ, UK. ² Division of Diabetes, Endocrinology and Gastroenterology, School of Medical Science, Faculty of Biology, Medicine and Health, University of Manchester, Oxford Road, Manchester, M13 9PT, UK

Introduction

Previous work on damage accumulation in tendons¹ showed a significant, order of magnitude decrease in damage susceptibility of rat tail tendon fascicles from a streptozotocin (STZ) model of diabetes compared with controls. While it has been speculated that this change is due to the presence of advanced glycation end-products (AGEs) in the structure, this has not been verified. As 25% of the adult population will experience tendon injury at some point², a risk which is exacerbated if the patient is diabetic³, a clear clinical need for the elucidation of the mechanisms behind tendon damage and diabetic tendinopathy exists.

Methods

AGEs were quantified in tail tendons from STZ-treated rats and from healthy controls using spectrofluorimetry to measure collagen-associated fluorescence in the tissue⁴. This was performed according to an established protocol⁵. A concentration standard curve was also generated, which served as evidence of the validity of the assay.

Results & Discussion

The results showed no significant difference between the groups ($p=0.15$). The previously-measured effects of this model on this material might thus not be due to these crosslinks. Alternatively, they may indeed be due to the AGEs but merely take a longer timescale to manifest.

Following this experiment, the exact mechanisms behind the effects of STZ and diabetes remain unknown and in need of elucidation if a greater understanding of tendon damage - and the prevention and treatment thereof - is to be developed.

Conclusion

The presence of advanced glycation end-products has been quantified, using spectrofluorimetry, and found to not be significantly different in tail tendons from an STZ rat model of diabetes compared to controls.

References

1. Nicholls RC, Gardiner NJ, Thompson MS. *ME/BioEng Conference*. 2017
2. Walden G *et al.* *Tissue Engineering*. 2017; 23(1):44-58
3. Abate M, Schiavone C, Salini V. *BMC Musculoskeletal Disorders*. 2010; 11(1):278-284
4. Reiser KM. *Journal of Gerontology: Biomedical Sciences*. 1994; 49(2):71-79
5. Li Y *et al.* *Matrix Biology*. 2013; 32(3):169-177

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BioMedEng18

Non-Invasive Monitoring of the injured brain using biocompatible, flexible materials

D.R.K Murray¹, M.G Boutelle ¹, M. Wilson ²

¹ Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London, ²St Mary's Hospital, Paddington

Introduction

Spreading Depolarisations (SDs) and Depressions are electrical markers of brain injury and occur in 50-60 percent of severe TBI cases. They have characteristic shapes, are often coupled and are the main mechanism by which secondary injury occurs. As the neurotrauma surgeon works to offset the initial damage, they must also be aware of the movement of these electrical signals which propagate across the cortex between 1.7-9.2 mm/min.¹ Successfully managing intensive care patients after severe injury needs real-time electrical monitoring of such phenomena to help clinicians improve a patient's outcome. Ultimately, the aim is to help the clinician make more informed decisions when protecting against further cortical degradation.

Methods

Photolithographic methods will be combined to fabricate flexible, biocompatible arrays which can conform to the surface of the cortex, made of gold and parylene C. These arrays will then be modified with PEDOT:PSS using potentiodynamic (PD) methods of electrodeposition under a nitrogen atmosphere. Verification of successful deposition would be confirmed by cyclic voltammetry and optical techniques.

Results & Discussion

Here, we show the design of a 9-contact microelectrode array currently being fabricated. Sample electrodes made of the same materials have been tested and modified with PEDOT:PSS to reduce impedance.² The array is of a comparable geometry to the current clinical standard, so that it can be used in interventional surgery such as a craniotomy or craniectomy and has a grid structure in order to track SDs in 2 dimensions.

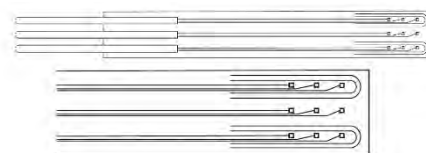


Figure 1: Design of 9 contact MEA

Conclusion

Overall, the beginning of the development of a multimodal probe has been demonstrated. This array needs to be tested in viable tissue before valid conclusions can be drawn but the aim will be to add chemical monitoring via microdialysis, followed by temperature, pressure and blood flow sensing in order to give the clinician a full picture of the extent of the secondary damage to the brain.

References

1. Dreier, J. P. et al, J. Cereb. Blood Flow Metab. 37, 1595–1625 (2017)
2. Ganji et al, Adv Funct Mater, 1700232 (2017)

Acknowledgments

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Study of the flow field in *In-vitro* & *in-silico* stented ureter models

A. Mosayyebi¹, X. Zhang ¹, C. Manes ², D. Carugo ¹

¹ University of Southampton, Faculty of Engineering and the Environment, Southampton, UK

² Politecnico di Torino, Department of Environment, Land and Infrastructure Engineering, Turin, Italy

Introduction

A ureteral stent is a flexible tube with side-holes, which is deployed by clinicians to restore urine drainage when this is impaired by intrinsic or extrinsic occlusions of the ureter lumen. However, over 80% of stents fail because of complications, such as deposition of encrusting crystals and formation of bacterial biofilms. These complications can compromise the performance of a stent and lead to antibiotic-resistant urinary tract infections (UTI), with a significant impact on patients' quality of life and costs for healthcare providers [1]. Despite efforts have been devoted to develop novel materials and stent coatings, encrustation still remains a major complication [2]. In this study, we investigate the role of fluid dynamics on the formation and growth of encrusting and bacterial deposits, using full-scale computational and experimental models of ureteric stents.

Methods

A computational model of the stented ureter was designed. The ureter model was reconstructed from pig ureters [3], and the stent replicated the commercial Universa® (Cook®, USA). Computational fluid dynamic (CFD) simulations were performed in Fluent® (Ansys, USA) to characterise the flow field within the model, and identify relevant flow metrics that could play a role in the deposition of particles. Spatial contours of wall shear stress (WSS) over the stent were determined, including over the inner surfaces of each individual side-hole. A physical replica of the computational model was employed to evaluate encrustation *in-vitro*; artificial urine (pH 6.8, temperature 37°C) was injected in the model for 8 hrs. Images were acquired using a EOS 600D camera (Canon®, Japan) and analysed using ImageJ (NIH, USA) to quantify the mean % coverage area (MCA) covered by encrustation, at specific regions of interest within the model.

Results & Discussion

Results demonstrated an inverse correlation between the amount of encrusting deposits and the WSS magnitude. Regions of the stent suffering from low-WSS were characterised by higher MCA, and these included the pigtail ends of the stent and side-holes that were not interested by fluid exchange (referred to as 'inactive' side-holes). Numerical mean WSS values in side-holes ranged between 0.002 and 0.114 Pa (from proximal to distal), whilst the MCA reduced from 91.50 to 1.15 %. Additionally, results indicated that the large majority (>~60%) of side-holes suffer from encrustation, with only a limited number of active side-holes maintaining their functional role.

Conclusion

Numerical and experimental models presented in this study revealed that the majority of side-holes in a stent experience low-WSS levels, favouring deposition of encrusting crystals.

References

1. Lange, D., et al., *Ureteral stent-associated complications [mdash] where we are and where we are going*. Nature Reviews Urology, 2015. **12**(1): p.17-25.
2. Mosayyebi, A., et al., *Advances in Ureteral Stent Design and Materials*. Current Urology Reports, 2018. **19**(5):35.
3. Clavica, F., et al., *Investigating the flow dynamics in the obstructed and stented ureter by means of a biomimetic artificial model*. PloS one, 2014. **9**(2): p. e87433.

Acknowledgments

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BioMedEng18

Simulation of the thermal fluctuations of red blood cells with the inclusion of hydrodynamic interactions.

T.A. Hunt ¹, B. McGill ³, G. Marcelli ¹, C.D. Lorenz ², C.P. Winlove ³, P.G. Petrov ³

¹ School of Engineering and Digital Arts, University of Kent, Canterbury, Kent, CT2 7NT. ² Biological Physics & Soft Matter Group, Department of Physics, King's College London, WC2R 2LS, ³ College of Engineering, Mathematics and Physical Sciences, University of Exeter, Exeter, EX4 4QL

Introduction

The mechanical properties of the red blood cell (RBC) membrane are of considerable significance to blood flow. This is especially so in the case of microcirculation where the cell must deform to pass through the narrow capillaries. One experimental technique for determining the mechanical properties of the membrane involves observing the fluctuations of the equatorial contour of the cell via phase-contrast microscopy. In this work we further extend a previous analysis, which used molecular dynamics simulation.

Methods

Following our previous coarse-grained molecular dynamics simulations^{1,2} and extending them with dissipative particle dynamics simulations³ (DPD) we analyse the fluctuations of the RBC in the equatorial contour to infer the mechanical properties of the cell. The advantage of using DPD is that we are able to calculate both the time correlation functions of fluctuations of the RBC as well as the equilibrium average of the amplitudes of the modes. The time correlation function allows us to determine the cytoplasmic viscosity, which can be affected in diseased cells.

Results & Discussion

Comparison between experimental and computational spectra of the fluctuations allow the determination of the bending and shear moduli of the membrane, which are in the range of values reported in the literature.

Conclusion

Through simulation, we present analysis of the fluctuation of the contour of RBCs and subsequent determination of the mechanical properties of the cell membrane. Measurements of the cytoplasmic viscosity as well as the membrane elastic properties will give an indication of the importance of the cell environment on the physical properties of the cell.

References

1. Hale JP *et al.*, Red blood cell thermal fluctuations: comparison between experiment and molecular dynamics simulations, *Soft Matter*, 2009, 5, 3603–3606
2. Marcelli G, Parker KH and Winlove CP, Thermal Fluctuations of Red Blood Cell Membrane via a Constant-Area Particle-Dynamics Model, *Biophysical Journal*, 2005, 89, 2473–2480
3. Fedosov DA, Caswell B, Karniadakis GE, A Multiscale Red Blood Cell Model with Accurate Mechanics, Rheology, and Dynamics, *Biophysical Journal*, 2010, 98, 2215–2225

Shape Variability in Bicuspid Aortic Valve Patients: An insight into the effect of coarctation on arch morphology

F. Sophocleous¹, B. Biffi², E.G. Milano^{1,3}, J. Bruse⁴, M. Caputo¹, C. Rajakaruna¹,
S. Schievano², C. Bucciarelli-Ducci¹, G. Biglino¹

¹Bristol Heart Institute, University of Bristol, BS2 8HW, ²Institute of Cardiovascular Science, University College of London, WC1E 6DD, ³University of Verona, 37129 Verona, Italy, ⁴Vicomtech, 20009 San Sebastián, Spain.

Introduction

Single-centre retrospective study, aimed to explore aortic morphology and any potential effects on functionality within BAV patient—sub-groups, i.e. with repaired, unrepaired and without CoA.

Methods

Native BAV patients were studied (n=525); those with a 3D MRI dataset were included for shape analysis (n=108, 64% males, 38±16.5 years). MRI-derived 3D aortic reconstructions were analysed using a statistical shape modelling framework [1]. A mean aortic shape ('template') and shape deformations ('shape modes') were computed for the whole population and correlated with demographic, volumetric and functional data within the three sub-groups, as well as with 2D measurements. Sub-group analysis was also performed specifically for repaired CoA.

Results & Discussion

A comparison of the three sub-groups revealed that absence of CoA was significantly associated with decreased curvature ($p<0.001$) and increased width ($p=0.001$), suggesting a less angulated aorta. This group also had the highest degree of proximal ascending aortic dilation ($p<0.001$),

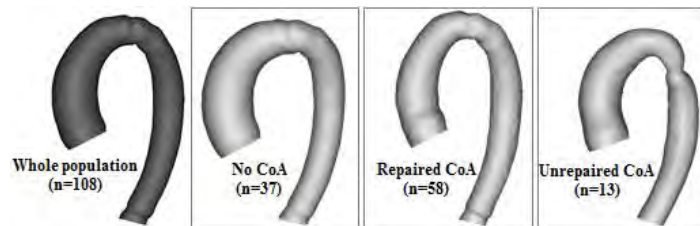


Figure 1: Templates of the whole population and of the sub-groups.

as confirmed visually by the computed 3D shape results and measured diameters. Unrepaired CoA was significantly associated with increased height-to-width ratio ($p=0.005$) and smaller isthmus ($p=0.05$), suggesting the presence of gothicity and confirming the presence CoA. This group also had higher left ventricular mass ($p=0.04$) and the smallest percentage of functionally normal aortic valves whereas the sub-group of repaired CoA had the highest percentage (23% vs. 52%, $p=0.01$). The three sub-groups showed significant differences for shape modes 1 ($p=0.007$), 2 ($p=0.02$), 3 ($p<0.001$), 4 ($p=0.002$), 6 ($p=0.03$) and 8 ($p=0.02$). Sub-group analysis of patients with repaired CoA interestingly revealed that mode 6, which displays dimensional changes and angulation, was significantly associated with left ventricular ejection fraction ($p=0.01$) and end-diastolic volume ($p=0.02$), and with the presence/absence of re-CoA ($p=0.05$).

Conclusion

The clinical impact of our approach has been demonstrated by its potential to characterise patient sub-groups unearthing nuanced differences in arch morphology that would otherwise not be captured by gross dimensional or functional data.

References

1. Bruse JL et al. *BMC Med Imaging* 2016; 16(1): 40.

Acknowledgments

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Mathematical Method to Investigate Effect of Hypertension on Mass Transport in Arterial Walls

W. Akaraworatikamporn¹, J.H. Tweedy ¹, C.G. Caro¹, K. H. Parker¹

¹ Department of Bioengineering, Imperial College London, South Kensington Campus, SW7 2AZ, London.

Introduction

The relationship between hypertension and atherosclerosis has been at the forefront of cardiovascular disease research, and mass transport is found to be reduced in patients with hypertension and in arteries with an implanted stent. It has been hypothesised that an expansion of the arterial wall leads to a reduction in mass transport as a result of two main mechanisms: (1) reduces the gaps between tightly packed cells; and (2) deforms the vasa vasorum (blood vessels embedded within the arterial wall). To investigate this, a mathematical model is developed to predict mass transport in arterial wall in patients with elevated blood pressure and in arteries with an implanted stent.

Methods

The arterial wall is treated as a homogeneous poroelastic medium, with the flow governed by Darcy's law with plasma assumed to be Newtonian, and small solid deformation assumed. We assume that the arterial wall is axisymmetric and independent of the axial coordinate and there is no deformation in the axial direction, and thus the dynamics can be conveniently reduced to a one-dimensional problem in terms of the radial coordinate. To include the vasa vasorum, we extended to a 2D model, treating the vasa vasorum as a circular pressurised lacuna in the tissue.

Results and Discussion

Under hypertensive conditions, the flow grows with the increased pressure due to the fact that the permeability increases when the arterial wall expands. The wall deformation due to abnormally high arterial pressures caused the initially circular vasa vasorum to take an approximately elliptical shape, and for sufficiently high pressures there was enough stretching to cause an increase in hydraulic resistance and thus a decrease in blood supply, although for lower pressures the resistance was reduced.

Conclusion

The model of arterial wall and vasa vasorum presented in this study contradicts hypothesis (1) and provides support for hypothesis (2) at sufficiently elevated arterial pressures. Thus, at slightly elevated pressures other mechanisms must be involved in the observed increased morbidity. In current research we are adding a model of the network of vessels in the vasa vasorum to reflect their actual physiological structure as this would enable us to calculate the total wall perfusion. In addition, the nonlinear elastic property of the wall and the effect of arterial wave propagation could also be added to the model at later stage. By implementing these improvements, the transport phenomena in the arterial wall could be further investigated as they are important keys to understand the development of atherosclerosis.

References

1. Bonfiglio A, Leungchavaphongse K, Repetto R, Siggers JH. Mathematical Modeling of the Circulation in the Liver Lobule. J Biomech Eng. 2010 ;132(11):11011.

The Potential of Director Theory for Modelling Blood Flow in the Cardiovascular System

M.J. Webster¹, A.M. Gambaruto¹, A.R. Champneys²

¹ Department of Mechanical Engineering, University of Bristol, Bristol, BS8 1TH. ² Department of Engineering Maths, University of Bristol, Bristol, BS8 1TH, UK

Introduction

We are looking at using director theory (also known as Cosserat theory) as an alternative to classical 1D models for arterial modelling of the human cardiovascular system with the intent of balancing accuracy with low computational cost.

Methods

The director theory is a hierarchical, theory where the velocity is approximated by a series of vectors that depend only on the co-axial direction and time, multiplied by shape functions that depend only on the cross-section. Director theory can retain more of the structure of complex geometries than classical 1D modelling. Preliminary discussion and comparison of director theory to classical 1D models are outlined in Robertson and Sequeira [1].

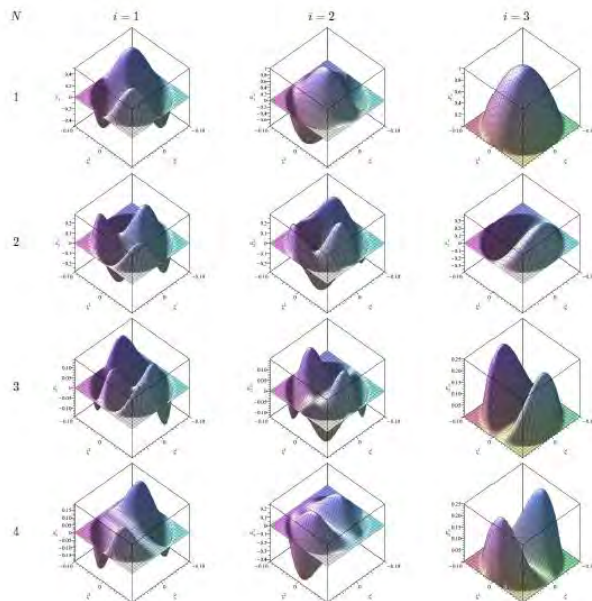


Fig 1: Plots of the shape functions $\lambda_N(\zeta^1, \zeta^2)$ for order $N=1,2,3,4$ and basis vector component $i=1,2,3$, with ζ^1 along the bottom right axis, ζ^2 along the bottom left axis and λ_N along the vertical axis.

Results & Discussion

The first results we obtained by applying director theory to fluid, following the approach of Caulk and Naghdi [2], were for Poiseuille flow and steady swirling flow in a straight pipe of constant radius.

We now begin to look at curvature, following the approach of Green *et al* [3]. Fig 1 shows plots of the shape functions for a toroidally curved pipe of circular cross-section.

Conclusion

We show in this abstract the potential for director theory for modelling the cardiovascular system without resorting to the over simplification required by classical 1D modelling.

References

1. Robertson AM, Sequeira A. A director theory approach for modeling blood ow in the arterial system: An alternative to classical 1D models. *Mathematical Models and Methods in Applied Sciences*. Vol 15, No.6 871-906, 2005.
2. Caulk DA, Naghdi PM. Axisymmetric motion of a viscous fluid inside a slender surface of revolution. *Journal of Applied Mechanics*. Vol 54, 190-196, 1993.
3. Green AE, Naghdi PM, Stallard MJ. A direct theory of viscous fluid flow in pipes II. Flow of incompressible viscous fluid in curved pipes. *Philosophical Transactions of the Royal Society of London A: Mathematical, Physical and Engineering Sciences*. 1993.

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Design for a Housing for an Aortic Root to attach to a ViVitro Real-Time Wear Tester

G.A. Pounds¹, A. Desai¹, L. M. Jennings¹

¹ *The Institute of Medical and Biological Engineering, University of Leeds, Leeds, LS2 9JT.*

Introduction

In-vitro testing of the durability of tissue-derived aortic heart valves at physiological pressures and frequencies (real-time), both reduces in-vivo animal sacrifice and improves clinical application¹. In-vitro real time wear tester (RWT, Vivitro Systems Inc, Victoria BC, Canada) is designed to hold mechanical or bioprosthetic valve replacements which is not suitable for the shape or viscoelastic behaviour of tissue-derived aortic roots^{1,2}. Therefore, this project presents a novel design for an aortic root housing which can be attached to a RWT to assess the fatigue of porcine aortic roots.

Methods

Five conceptual designs were compared with a design specification, which outlined the requirements of the housing to function in the RWT. The chosen design was manufactured and a 500,000-cycle test was carried out with a dissected porcine aortic root. The root was sutured to the housing using a modified simple interrupted technique on the myocardium side and a cross-stitch method on the aorta side (Figure 1). The coronary arteries were also tied. RWT testing was carried out at 120bpm (2Hz) and 50.4% gain to maintain transvalvular pressures for at least 95 % of the test cycles. A high-speed camera was set up to record leaflet dynamics at 500 frames per second.



Figure 1: Porcine aortic root sutured to the housing.

Results & Discussion

The housing design was able to withstand the mechanical function of the RWT and allowed for appropriate axial movement, radial distension of the aorta and leaflet dynamics of the valve. However, the percentage of cycles reaching the targeted transvalvular pressure dropped from 100% to 65% in 24 hours. This was due to the suturing technique on the myocardium side and insufficient closure of the right coronary artery which resulted in reduced movement of the right coronary leaflet. Further tests to include optimisation of suturing technique and careful preparation in order to maintain pressures in the test.

Conclusion

The design was appropriate to attach to the RWT and withstand the test. Future tests of 1 million cycles to be carried out provided sutures are properly tightened and preparation checks made.

References

1. D'Souza, S., Butterfield, M. and Fisher, J. *J heart valve disease*. 2003. 12(1), pp.110-119.
2. Schleicher et al. *Annals of Biomedical Engineering*. 2010. 38(5), pp.1919-1927.

Investigating the influence of precision of the reconstructed AAA geometries on hemodynamic parameters of abdominal aortic aneurysm employing Fluid-structure interaction analysis.

Wisam Al-Obaidi^{1,2}, Alistair Revell¹, Parthasarathi Mandal¹

¹ School of Mechanical, Aerospace and Civil Engineering, University of Manchester, Manchester, M13 9PL, UK.

² Department of Mechanical Engineering, College of Engineering, University of Al Qadisiyah, Al-Diwaniyah, Qadisiyah, Iraq.

Introduction

Abdominal aortic aneurysm (AAA) is a silent killer disease owing to the continuing dilation of the abdominal aorta and its eventual rupture. Nowadays, Patient-specific geometries of AAA can be obtained easily from medical images such as CT, MRI and 3D Ultrasound, which in turn significantly contribute to predict the rupture site by evaluating the hemodynamic parameters of AAA by employing the transient interaction between the wall and blood flow. In this work, the impact of precision of the constructed AAA geometries on predicting the hemodynamic parameters and stress distribution in abdominal aortic aneurysm wall (AAA) is investigated.

Methods

A default idealised aneurysm model recommended by experts in AAA anatomy ⁽¹⁾ (lumen) and two others were created by increasing and decreasing the dimensions of the default aneurysm with %10. A uniform wall thickness of 2 mm was generated by expanding the lumen surface outwards. Then, the lumen and wall parts were imported and meshed in Star ccm+ and Abaqus using polyhedral and tetrahedral elements respectively, in order to run a coupled fluid-structure analysis under transient flow conditions. Wall shear stress profiles, time average wall shear stress, oscillatory shear index, relative time residence and wall stress were then compared for the three geometries by assuming the default AAA geometry as the reference.

Results & Discussion

The results show measurable predictions of wall shear stress patterns, hemodynamic parameters (TAWSS, OSI and RRT) for a small change in the AAA geometry. Varying (+%10) of the AAA dimensions decrease the TAWSS, however, increase the peak wall stress, OSI and RRT because the regions on the vessel wall subjected to highly oscillating WSS values during the cardiac cycle and associated with splitting flows and vortex creation. The contrast was observed when varying (-%10) of the geometry.

Conclusion

It is concluded that the TAWSS, OSI, RRT, wall stress and wall shear stress of AAA are highly sensitive to small changes in the AAA geometry. The findings of this work suggest that any variations to the exact AAA geometry will have implications on subsequent analyses. Therefore, it is vital to use good-quality geometry for rupture-risk assessment of AAA using computational methods.

References

1. C. A. Meyer, E.B., O. Boiron, and V. Deplano, *Stereoscopically observed deformations of a compliant abdominal aortic aneurysm model*. Journal of biomechanical engineering, 2011. **133**(11).

Blood flow in an intracranial aneurysmal artery with a dual-layer stent

L. Johnston¹, V. Flamini², A. Kazakidi¹

¹ Department of Biomedical Engineering, University of Strathclyde, Glasgow, UK

² Tandon School of Engineering, New York University, New York, USA

Intracranial aneurysms are focal dilatations of arteries in the cerebral vasculature that require surgical intervention once detected. Dual-layer flow-diverting stents are the latest innovation intended for the endovascular treatment of intracranial aneurysms. A fine-mesh device, comprised of a low porosity inner stent and a high porosity outer stent, is implanted within the parent artery bearing the aneurysm. The inner layer is designed to alter the haemodynamics of both the aneurysm and parent vessel, and is therefore the active flow-diverting element, while the outer layer ensures the patency of nearby perforating arteries^{1,2}. The FRED (Flow-Redirection Endoluminal Device) stent is the first device of its kind, with clinical approval in European and international markets. Several studies investigating the efficacy of the FRED stent have found its design to be safe and effective in the treatment of difficult-to-treat or otherwise untreatable intracranial aneurysms^{2,3}. However, clinical radiological post-procedural data is limited. As of January 2018, only 370 patients across ten studies reported the efficacy of the FRED device, with primarily saccular and small aneurysms being treated. This work is the first detailed computational fluid dynamic analysis of blood flow in a section of an intracranial aneurysmal artery after treatment with a dual-layer stent. In particular, two-dimensional computational models implemented a virtual bench test to investigate local haemodynamic changes in part of the treated vessel. Preliminary results consider steady flow conditions, based on a parabolic inlet profile, for the solution of the incompressible Newtonian Navier-Stokes equations. Computational fluid dynamic analysis focussed on the variance of flow parameters, including velocity, pressure, vorticity, and wall shear stress, for three dual-layer stent models: a baseline model with the same number of total wires as the FRED stent on both layers; an alternative model with half the number of wires in the outer layer; and a second alternative model with half the number of wires in the inner layer⁴. The most favourable flow behaviour in the aneurysmal artery was observed for the design in which the outer layer has half the number of wires than the inner layer. For all designs, the radial clearance between the two layers was seen to reduce the velocity of the surrounding blood flow to 98% of the blood flowing at the vessel centre. This research provides an aid to quantitatively estimate the flow of blood in a dual-layer treated vessel and will facilitate the optimisation of such devices.

References

1. Diaz O. *et al.*, *Journal of NeuroInterventional Surgery* 2014; 6(8): 614 - 617.
2. Kocer N. *et al.*, *Journal of Neurosurgery* 2014; 120(5): 1158 - 1171.
3. Mahboobani N.R. *et al.*, *Neurointervention* 2017; 12(1): 11 - 19.
4. Alherz A.I., Tanweer O., Flamini V., *Journal of Biomechanics* 2016; 49(1): 2420 - 2427

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Atrial Fibrillation is Chaotic but Not Random

I. Mann, C. Coyle, P. Kanagaratnam, N. Linton
Imperial College London, UK

Introduction

Atrial fibrillation (AF) is the most commonly encountered clinical arrhythmia with a prevalence of around 1%. However, mechanistic insight into the maintenance of persistent AF remains poorly understood: this has hampered the improvement of ablation treatments. Patterns of activation during AF are regarded as multiple electrical wavelets with randomly disordered propagation across the atria.¹ We hypothesise that while these AF wavefronts show chaotic activation patterns, they are not random. Furthermore, they may provide insight into the underlying mechanism of AF. In order to test this hypothesis, we have developed a custom algorithm to track activation patterns during persistent AF.

Methods

4 patients with persistent AF, undergoing invasive cardiac ablation procedures, underwent mapping of the left atrial roof, floor, anterior and posterior walls using a 20-pole double loop spiral catheter (AFocusII). Bipolar electrograms were recorded for 30 seconds in each location, both before and also after ablation (pulmonary vein isolation). Bipolar electrograms and electrode locations were exported for offline processing with a custom algorithm. A histogram displaying the distribution of electrical wavefront direction for each data segment was produced.

Results & Discussion

68 data segments were analysed pre and post PVI. On manual analysis of activation patterns, periods of organised activation were observed in all locations, interspersed with disorganised activation patterns. The overall number of locations with one dominant direction increased from 18 pre PVI to 30 post PVI, and two dominant directions increased from 1 location pre PVI to 3 post PVI. 49 locations had no dominant direction before PVI, decreasing to 35 locations post PVI. PVI resulted in a reduction in Shannon entropy ($p < 0.05$).

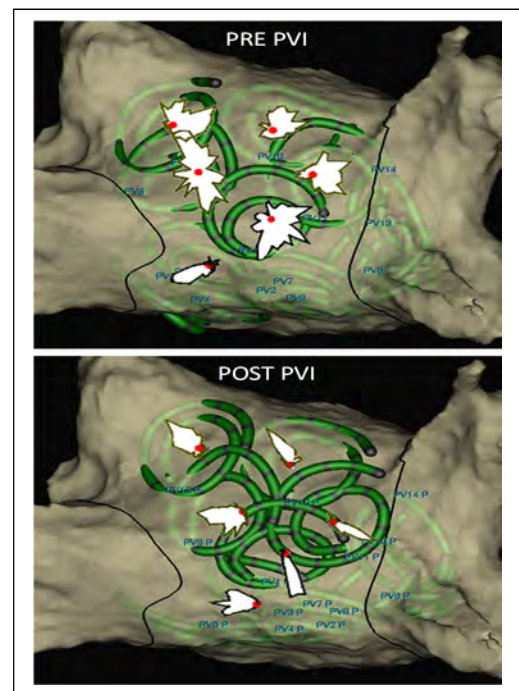
If activation patterns during psAF are random, one would not expect to see dominant directions of activation. PVI is known to prevent persistent AF in many patients. These data demonstrate that PVI results in greater organisation of activation and a reduced number of dominant activation directions.

Conclusion

Activation patterns during persistent AF display distinct periods of organisation, with wavefronts in non-random directions. Ablation with PVI reduces the dispersion of wavefront directions during AF.

References

1. Moe GK. On the multiple wavelet hypothesis of atrial fibrillation. *Arch Int Pharmacodyn Ther.* 1962;140:183–188.



Many-core acceleration of a discrete fluid-structure interaction method and potential as a clinical decision-support tool

B. Owen¹, A. Harwood¹, N. Bojdo¹, B. Keavney², A. Revell¹

¹ School of Mechanical, Aerospace and Civil Engineering, University of Manchester, Manchester, M1 3BB.

² Division of Cardiovascular Sciences, University of Manchester, Manchester, M13 9PL.

Introduction

The interaction between blood and vascular structures is known to play a role in the pathogenesis of many cardiovascular diseases. To date, the majority of fluid-structure interaction (FSI) methods have been developed using continuum methods, which have grown increasingly sophisticated and incorporated patient-specific data via various medical imaging modalities. However, an inherent disadvantage of the continuum hypothesis is an inability to easily incorporate meso-scale effects such as local material inhomogeneity. Discrete methods are more readily able to include these effects but have traditionally been restricted to smaller scales due to high computational expense. In this regard, 'coarse graining' and increasing access to high performance computing have the combined effect of relaxing these restrictions.

Methods

The Vector-based discrete element method, also known as the V-model, is a recently proposed variant of the discrete element method [1]. In previous studies it has been coupled to a lattice Boltzmann fluid solver via immersed boundary on CPU architecture, and used to investigate cardiovascular applications. The intrinsically local and explicit nature of this approach, along with linearity of governing equations, renders it particularly suitable to many-core computer technology such as graphical processing units (GPU)s. This feature facilitates significant performance gains and the potential opportunity to provide fast, low-cost, computational support at the bedside rather than an off-site high performance computing facility.

Results & Discussion

Here an FSI solver, coupling lattice Boltzmann and V-model via immersed boundary and implemented on GPU architecture, is validated and compared against its implementation on CPU. The potential for the V-model to handle non-linear phenomena such as aggregation and remodeling, is also demonstrated. Finally, the FSI method is applied to flow through an idealized, two-dimensional deep leg venous valve to demonstrate the capabilities of the method in cardiovascular applications. A detailed assessment of predictive-accuracy and speed is provided, in the context of using these tools in a clinical decision-support framework.

References

1. Kuzkin V, Azanov I, *Phys. Rev. E*, 2012; 86: 051301.

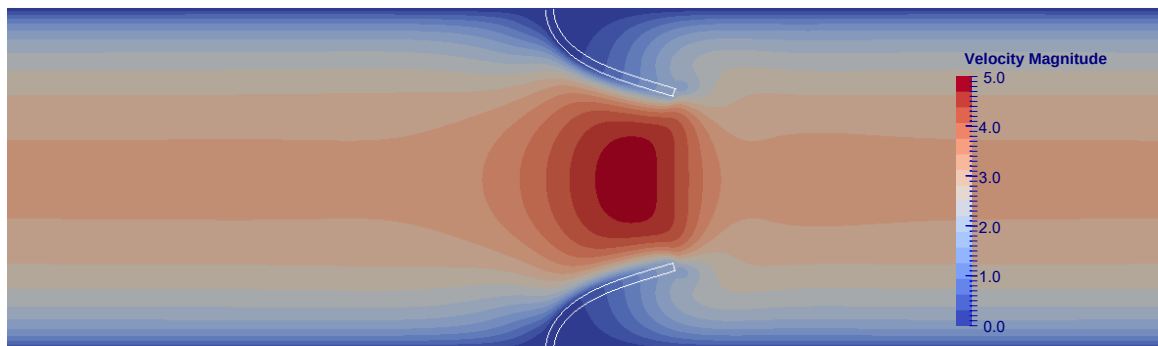


Figure 1: Example cardiovascular application - 2D idealised venous valve.

IN-VITRO MODELLING OF MITRAL VALVE THERAPIES

W. Zhou¹, S. Bozkurt^{2,3}, M.H. Cheang⁴, S. Schievano^{2,3}, G. Burriesci^{1,5}

¹ UCL Mechanical Engineering, Cardiovascular Engineering Laboratory, University College London, UK. ² UCL Great Ormond Street Institute of Child Health. ³ Great Ormond Street Hospital for Children. ⁴ Barts Health NHS Trust, University College London Hospital, London, UK. ⁵ Ri.MED Foundation, Bioengineering Group, Palermo, Italy.

Introduction

Mitral regurgitation (MR), the reverse blood flow through the mitral valve (MV), is the most common valvular heart disease. Various repair and replacement treatments are available to restore the function of the valve, but it is often difficult to evaluate and compare the risks and results of these alternative approaches, due to the great anatomical heterogeneity of mitral pathologies.

Patient-specific *in vitro* simulation of MV function could provide an essential benchmark for potential treatments and to help predict post-surgical outcomes, thus assisting clinical pre-operation decision-making to increase the success rate of surgeries. However, this solution requires patient-specific anatomical heart chambers and the ability to finely control the anatomical parameters that monitor the MV functions, such as the position of the papillary muscle (PM) and the mitral annulus shape.

Methods

In this study, a novel test rig is developed to incorporate and test MV functions into a cardiovascular hydrodynamic testing system (ViVitro System, ViVitro Labs, Inc., Canada), available at the Cardiovascular Engineering Laboratory, UCL Mechanical Engineering. The implemented system enables the accurate positioning of each PM to be adjusted in 3 dimensions, while replicating the ventricular shape with a silicone sack.

Results & Discussion

The test rig has been successfully used to replicate the function of a porcine MV, evaluating the effect of the positions of the PMs on MV performances. Results were consistent with data from *in vivo* observations (1) from swine models. Further study investigated the impact of cardiac output and PM positions on MV performance.

The system has been employed to test a novel prosthetic valve concept and a number of percutaneous repair implants. These *in vitro* implants have enlightened potential problems which are difficult to predict in numerical studies, providing a substantial support in the design optimisation of the therapeutic solutions and in their assessments. The test rig can also be employed as a useful tool for surgeons training on new treatments.

Conclusion

The developed test rig has been used as a physiological model, demonstrating its ability not only to evaluate existing therapies but also to support the development of new solutions.

References

1. Jensen H et al. 2010. J Thorac Cardiovasc Surg 140: 1312-8

Acknowledgments

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Three-dimensional Simulations of Idealised Lymphangion

A.M. Gambaruto¹, R. van Loon²

¹ Queen's Building, University of Bristol, BS8 1TR, Bristol. ² Bay Campus, Swansea University, SA1 8EN, Swansea.

Introduction

The lymphatic system is responsible for collecting fluid leaked from blood vessels, returning it to the blood system to maintain overall fluid balance. Lymphatic vessels also fulfill important immune functions by transporting leukocytes and antigens [1,2,3]. The functional units of collecting lymphatic vessels are called the lymphangions [2,4]. Some experimental and computational studies exist, however much still needs learnt about the transport mechanisms.

Methods

An idealised geometry of a lymphangion unit is considered. This consists of a deforming cylinder with valves at either end. The flow is considered to be periodic. The Moving Particle Semi-implicit (MPS) method is employed, since this has been shown to be effective in simulation of micro-circulation [5]. Periodic boundary conditions are employed in order to investigate time integrated measures.

Results & Discussion

A parametric study is carried out, varying geometry of the lymphangion and the pulsatility of the lymph. We study the redistribution of particles as they traverse the valve constriction, looking at the forces imposed on cells and the transport properties.

References

1. Moore Jr JE, Bertram CD. Lymphatic System Flows. *Annual Review of Fluid Mechanics*. 2018; 50:459-482.
2. Margaris KN, Black RA. Modelling the lymphatic system: challenges and opportunities. *Journal of the Royal Society Interface*. 2012; 9(69):601-612.
3. Bazigou E, Wilson JT, Moore Jr JE. Primary and secondary lymphatic valve development: molecular, functional and mechanical insights. *Microvascular research*. 2014; 96:38-45.
4. Russo E, Nitschké M, Halin C. Dendritic cell interactions with lymphatic endothelium. *Lymphatic research and biology*. 2013; 11(3):172-182.
5. Gambaruto AM. Computational haemodynamics of small vessels using the moving particle semi-implicit (MPS) method. *Journal of Computational Physics*. 2015;302:68-96.

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Complex Interactions of excitatory stimuli in the vascular endothelium

Manuela Ratnayake^{1, 3}, Calum Wilson¹, Chris D Saunter², John M Girkin², John G McCarron¹

¹ Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 16 Richmond St, Glasgow G1 1XQ, ² Department of Physics, Durham University, DH1 3HP, ³ Biomedical Engineering Department, University of Strathclyde, 16 Richmond St, Glasgow G1 1XQ

Introduction

The endothelium is the single, innermost, layer of cells in blood vessels and it controls almost all cardiovascular functions. The endothelium regulates immune responses, blood coagulation, angiogenesis, vessel repair, and vascular permeability. To regulate function, the endothelium continuously monitors multiple chemicals that are circulating in the blood or derived from nearby cells (e.g. endocrine, paracrine, autocrine or neurotransmitter signals). These chemicals each provide cues to physiological status. The chemicals are detected and processed selectively by the endothelium to direct resources that adjust physiological function. Some chemicals provide conflicting signals to the endothelium such as those which promote or inhibit vascular tone. How conflicting signals are detected and managed by the endothelium is not understood.

Methods

The present study was undertaken to determine how the endothelium selectively processes conflicting information. To monitor the behaviour of the endothelium, changes in cytosolic Ca^{2+} concentration were measured simultaneously in ~200 endothelial cells in small mesenteric arteries using the indicator Cal-520 and high-resolution imaging. The calcium traces from each cell were then extracted and analysed using software written in python. Changes in cytosolic Ca^{2+} concentration underlay virtually all endothelial functions and so provide a useful measure of endothelial activity.

Results & Discussion

The vasodilator substance acetylcholine (ACh) evoked Ca^{2+} increases that initiated in small clusters of cells. As the concentration of acetylcholine increased, the amplitude of the Ca^{2+} rise in each activated cell and the number of activated cells increased. To examine the interaction of excitatory and inhibitory inputs, acetylcholine (as an excitatory input) at an EC_{75} (15nM) was used. In the first series of experiments the vasoconstrictor U-46619 (thromboxane A_2) was used. U-46619 (1 μM) did not itself evoke any detectable Ca^{2+} signals in the endothelium. However, U-46619 increased the amplitude of the response in each activated cell and the number of cells activated in response to ACh. The vasoconstrictor agonist angiotensin (10 μM) did not evoke Ca^{2+} increases when applied by itself. However, angiotensin increased the amplitude of the Ca^{2+} response to acetylcholine in each activated cell. The number of cells activated did not change.

Conclusion

This effect of angiotensin and U-46619 on the endothelium may serve to limit a vasoconstrictor response. Together these data reveal complex interactions occur between excitatory and inhibitory stimuli acting on the endothelium.

Acknowledgments

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Using Convolutional Neural Networks to identify functional mutations in the human genome through patterns of natural selection

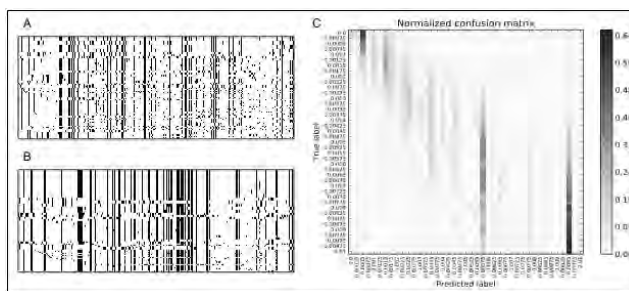
L. Lorenzon^{1,2}, L. Pattini², S. Mathieson³, M. Fumagalli¹

¹ Department of Life Sciences, Imperial College London, UK. ² Department of Electronics, Information and Bioengineering, Politecnico di Milano, Milan, Italy. ³ Department of Computer Science, Swarthmore College, Swarthmore, PA, USA.

Introduction

The genetic basis of complex diseases, such as cardiovascular and neurological disorders, is still largely unknown due to the polygenic nature of the disorder and the small effect each associated mutation contributes to the onset of the disease. A valid alternative to classic association studies is by using an evolutionary approach. As sites targeted by natural selection are likely to harbour important functionalities for the carrier, the identification of selection signatures in the genome has the potential to unveil the genetic mechanisms underpinning human phenotypes, including susceptibility to complex disorders. Commonly used strategies to detect such signals rely on compressing the genomic information into summary statistics with an inevitable loss of information. Here we explore the use of deep learning to make full use of population genomics data into an evolutionary-epidemiology context.

Methods



The information of genomes from multiple individuals is translated into abstract images, representing the variation at each position for each sample. Specifically, each population image is created by stacking aligned genetic data and encoding derived and ancestral alleles as black and white pixels, respectively. Lines are then ordered by increasing frequency of occurrence (Figure 1 A and B).

Figure 1: Images of genome variation under neutrality (A) or positive selection (B). (C) Confusion matrix for the estimate of the selection coefficient.

To detect signatures of positive selection, we implemented a Convolutional Neural Network that recognises patterns of selection, in the form of less genetic variation than expected under neutral evolution. We trained the network using extensive simulations.

Results & Discussion

In the simplest scenario of binary classification of a genomic region experiencing neutral evolution (Figure 1A) or positive selection (Figure 1B), our method perfectly distinguishes among them with a prediction accuracy over 99%. We also found that our network is able to accurately estimate the selection coefficient with an average error of 0.0016 (Figure 1C). We finally apply this tool to detect positive selection in genes associated to several cardiovascular disorders.

Conclusion

While the use of deep learning in evolutionary genomics is at its infancy, here we show its potential to detect informative patterns from large-scale genomic data. When information of evolutionary history of mutations is coupled with functional data, these inferences will facilitate mapping studies and provide novel insights on the molecular mechanisms leading to disorders.

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AI-based Registration for Cardiac Interventions

D. Toth^{1,2}, S. Miao³, T. Kurzendorfer⁴, C.A. Rinaldi^{2,5}, R. Liao³, T. Mansi³,
K. Rhode², P. Mountney³

¹Siemens Healthineers, Frimley, UK. ²School of Biomedical Engineering & Imaging Sciences, King's College London, UK. ³Siemens Healthineers, Medical Imaging Technologies, Princeton, NJ, USA. ⁴Siemens Healthineers, Forchheim, Germany. ⁵Dept. of Cardiology, Guys and St. Thomas Hospitals NHS Foundation Trust, London, UK

Introduction

Minimally invasive X-ray guided cardiac interventions, such as cardiac resynchronization therapy, can greatly benefit from overlay of preoperative information [1,2]. To have a useful overlay, a robust and accurate registration is required.

Methods

In this paper, a registration approach for preoperative MR and intraoperative X-ray fluoroscopy is presented. The MR images are automatically segmented to extract cardiac chambers [3]. An artificial intelligence-based (AI-based) registration framework is trained to predict motions of the segmented models to iteratively transform them towards the optimal registration.

Results & Discussion

Since no ground truth registration between the MR and X-ray fluoroscopy images can be acquired, evaluation was performed qualitatively. Overlay images of the MR derived models and the X-ray images were inspected. The overlays show good alignment between the registered preoperative models and the heart shadow in the intraoperative X-ray images.

To prove robustness against different initial transformations, the registration was performed with different starting positions (perturbations) repeatedly, resulting in the same alignment.

Conclusion

An AI-based registration approach was proposed that is able to register preoperative MR to intraoperative X-rays for interventional guidance. Accuracy and robustness were shown. This suggests that the method could be employed in minimally invasive cardiac interventions.

References

1. Mountney, P et al.: *A Planning and Guidance Platform for Cardiac Resynchronization Therapy*. IEEE TMI 36(11), 2366-2375; 2017.
2. Jolly, MP et al.: *Automatic Segmentation of the Myocardium in Cine MR Images Using Deformable Registration*. In: STACOM – Imaging and Modelling Challenges, vol. 8896, pp. 105-113. Springer, Berlin, Heidelberg; 2011.

Acknowledgments

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Cuffless Blood Pressure Estimation Using Support Vector Machine Algorithm

Syed Ghufuran Khalid¹, Jufen Zhang ², Dingchang Zheng ³

^{1 3} Sawyers Building, Anglia Ruskin University, Chelmsford, CM11SQ. ² Salmon Building, Anglia Ruskin University, Chelmsford, CM11SQ

Introduction

Blood pressure (BP) is an important factor to measure as increased number of population affected by the cardiovascular diseases. Present cuff-based BP measurement provides inconvenience and discomfort to the users for long-term usage in their daily routine. Researchers have attempted various technologies including pulse transit time (PTT) to estimate cuffless BP parameters (systolic & diastolic). However, these technologies face frequent calibrations and wearability issues. Therefore, there is a high need for the development of new technology which is only based on a finger photoplethysmograph (PPG) sensor with precisely designed machine learning model to achieve accurate cuffless BP measurement.

Methods

In this study, PPG waveforms and intermittent Non-invasive Blood Pressure (NIBP) data were obtained from the University of Queensland database. It consists of thirty-two patients from whom 8133 signal segments with the duration of 5-seconds were extracted. Three significant PPG signal features (Total Pulse Area, Crest Time and Pulse Width 25%) and their corresponding NIBP levels were used for training and testing machine learning model. The support vector machine (SVM) based machine learning algorithm trained with 50% of signal segment features while remaining 50% data used to test model performance. The model further evaluated in three different BP categories (Normotensive, Hypertensive and Hypotensive). The results presented in terms of mean and standard deviation of difference (mmHg) for SBP and DBP. Bland Altman plot also used to identify the agreement between the reference BP and SVM-based algorithm.

Results

The SVM based machine learning algorithm achieved mean and standard deviation of difference for SBP (-0.06 ± 9.3) mmHg and DBP (1.66 ± 8.5) mmHg. The Bland-Altman plot also showed the agreement between the reference BP and SVM based algorithm with few outliers. The algorithm also showed acceptable accuracy in Normotensive category for SBP (5.6 ± 9.2) mmHg and DBP (2.3 ± 9.6) mmHg.

Conclusion

This study revealed that the SVM based machine learning model have acceptable overall accuracy in terms of mean of difference and it also showed that SVM based model achieved good accuracy in Normotensive BP category.

Acknowledgement

Authors declared no conflicts of interest regarding this research.

Supervised machine learning predicts fibrosis in ex vivo human cardiac slices using electrogram morphology

K.N. Tzortzis^{1,4}, A.R. Simon³, F. Perbellini¹, C.M. Terracciano¹, R.A. Chowdhury^{1,4}, N.S. Peters^{1,4}, C.D. Cantwell^{2,4}

¹ Cardiac Function Section, NHLI, Imperial College London, Hammersmith Campus, W12 0NN, London. ²Department of Aeronautics, Imperial College London, South Kensington, SW7 2AZ, London, ³Department of Cardiothoracic Transplantation & Mechanical Circulatory Support, Royal Brompton and Harefield NHS Foundation Trust, UB9 6JH, London, ⁴ElectroCardioMaths Programme, Imperial Centre for Cardiac Engineering, Imperial College London

Introduction

Clinical studies show that targeting scar regions defined by abnormal EGMs cannot significantly improve the catheter ablation outcomes¹. We investigate the use of supervised machine learning techniques for predicting fibrosis in human heart slices from EGM morphology features as a way to improve the diagnosis of structural abnormalities.

Methods

300µm-thick slices of left ventricular tissue samples were prepared from end-stage heart failure patients (n=10). EGM recordings were collected using microelectrode arrays (8x8 electrodes/100µm diameter/700µm spacing). EGM morphology was analysed against 25 features. Second harmonic generation microscopy was used to quantify collagen coverage. Classification training was carried out using supervised machine learning algorithms on a training dataset of 294 EGMs, characterised by a features sub-group, to classify them according to collagen content. This was followed by validation of prediction models on 71 EGMs.

Results

EGMs were classified using various collagen coverages between 15-22% of tissue slice area. Forward sequential feature selection was applied to isolate the feature sub-group which most effectively correctly partitioned the training dataset. Selected features included Shannon entropy and R-peak width, instead of established clinical scar markers of voltage and fractionation, which changed counter-intuitively with increased amounts of collagen coverage. Ensemble methods exhibited the highest accuracy during training and validation. These were optimised for our training dataset and a model was developed and validated for its ability to accurately predict fibrosis burden.

Conclusion

Supervised machine learning can predict fibrosis from unipolar EGMs obtained from ex vivo human heart slices. Ensemble methods lead to highly accurate predictions by using a relatively small EGM dataset during classification training.

References

1. Kanagaratnam P et al. *PACE* 2008; 31(4): 443-453
2. Hunter RJ et al. *Circ Arrhythm Electrophysiol* 2011; 4(5): 622-629

Acknowledgments

This study was supported by the Cardiovascular Research Centre Biobank at the Royal Brompton and Harefield NHS Foundation Trust, the Facility for Imaging by Light Microscopy and BHF Centre of Research Excellence. **The authors declare no competing interests.**

BioMedEng18

Learning representations for physical systems: an application to a two-dimensional diffusion model

Stef Garasto¹, Chris D. Cantwell,^{2,3} Rasheda A. Chowdhury,³ Jennifer H. Tweedy,¹ Fu S. Ng,^{3,4} Nicholas W.F. Linton,^{3,4} Nicholas S. Peters,^{3,4} Anil A. Bharath¹

¹ Department of Bioengineering, Imperial College, South Kensington, SW7 2AZ, London. ²Department of Aeronautics, Imperial College, South Kensington, SW7 2AZ. ³ElectroCardioMaths Programme, Imperial Centre for Cardiac Engineering, Hammersmith, W12 0NN, London. ⁴Imperial College Healthcare NHS Trust, Imperial College, South Kensington, SW7 2AZ.

Introduction

Modelling a physical system through a set of partial differential equations (PDEs) plays a key role in many fields, including biology, chemistry and engineering. Such models represent our prior knowledge of the system and allow us to predict its future behaviour in many circumstances of interest. However, allowing the model to learn from data, for example to infer the parameters of the system, can still be a challenge [1]. Furthermore, current numerical simulation methods require large computational resources and can be time-consuming.

Methods

Here, we propose to supplement modelling of PDEs with Deep Learning techniques. By learning to predict the future behaviour of a system from a set of initial states [2], it is possible for a deep neural network to build an internal representation of the model that can then be probed to recover hidden parameters of interest. Finally, the forward inference step of a trained network would require less computational time than a numerical simulation, thus allowing for a faster exploration of *what if* scenarios of interest. We apply this approach to a two-dimensional diffusion with a spatially heterogeneous and anisotropic diffusion coefficient, which is a critical component of models of excitable media, such as cardiac tissue. We investigate the amount of training data needed to achieve good generalisation performance and which hyper-parameters of the deep network are conducive to the learning of a robust internal representation.

Results & Conclusion

We show that the network successfully learns to predict the evolution of the system, also extrapolating for more time steps than those used for training. Furthermore, we can extract latent parameters of the model from the internal activity of the network, and better results are obtained when using max pooling instead of strided convolutions. This suggests that the representation learned by the deep architecture contains information about physically relevant quantities.

References

1. Zettinig O, *et al.* *Medical image analysis* 18.8 (2014): 1361-1376.
2. Ehrhardt S, *et al.* *arXiv preprint arXiv:1703.00247*. 2017.

Acknowledgments

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Clinical functionality of prosthesis users compared against actual prosthesis usage in the real-world

A. Chadwell¹, L. Kenney¹, M. Granat¹, S. Thies¹, J. Head¹, A. Galpin²

¹ Brian Blatchford Building, University of Salford, Salford, M6 6PU. ² Allerton Building, University of Salford, Salford, M6 6PU.

Introduction

To date the primary method of evaluating the performance of upper limb prostheses has been through the use of clinical tests of user functionality. To evaluate the use of the prosthesis outside of the clinic, clinicians and researchers are reliant on self-reported feedback from the user. We have previously published the first objective data on prosthesis use recorded using activity monitors worn on the wrists^[1]. Here we report on the relationships between various measures of user functionality with the prosthesis assessed within a clinical environment and the real-world upper limb activity of myoelectric prosthesis users.

Methods

Twenty unilateral trans-radial myoelectric prosthesis users were recruited, from six sites across the UK. Participants completed a multi-stage manual task 10 times. Sensors were worn to allow the recording of task success, task duration, patterns in the opening and closing of the hand during reach-to-grasp, temporal kinematic variability in the acceleration of the forearm between trials, and gaze behaviour.

Participants were then provided with two activity monitors (tri-axial accelerometers) to be worn on the wrists for a period of 7 days. A wear diary was also completed to assist interpretation of the data. Based on the activity monitoring data (converted into activity counts using proprietary algorithms within the Actilife software and grouped into 1-min epochs) the prosthesis wear time was calculated, and two measures of symmetry of upper limb activity^[2] were produced: (1) the median percentage reliance on the anatomical arm, and (2) the ratio of unilateral activity on each arm.

Kendall's Tau-b correlations were used to analyse whether any relationships existed between the measures of functionality and the everyday activity measures.

Results & Discussion

No significant correlations ($p < 0.05$) were found between any of the measures of functionality and the everyday upper limb activity measures. A simple assumption might be that the better a prosthesis user performs on a functional task, the more likely they are to use the prosthesis to perform everyday tasks. Our findings begin to question this assumption and suggest the need for further work to explore how we assess prostheses.

Conclusion

The data presented here suggests that the performance of a prosthesis user within the clinic does not necessarily correspond to how they use the prosthesis outside of the clinic. In future we recommend that further data is collected across a larger cohort; and that everyday activity data is compared to performance on other tests of clinical functionality. We also recommend that the activity measures are expanded to evaluate more aspects of upper limb activity (for example, the active use of the prosthetic hand).

References

1. Chadwell et al. *Frontiers in Neurorobotics*. 2016; 10
2. Chadwell et al. *P&O Int*. 2018; Vol. 42(1) 37–44

A new hydraulic prosthetic ankle to improve amputee cost of walking

A. Pace¹, J.D. Gardiner², L.Kenney¹, D. Howard¹

¹ University of Salford, Salford M5 4WT. ² University of Liverpool, Liverpool, L7 8TX.

Introduction

In an intact ankle, the tendons crossing the joint store energy during the stance phase of walking, when the whole foot is in contact with the ground. Subsequently, the tendons release this energy providing forward propulsion during push-off, as the foot leaves the ground [1]. Most energy storage and return (ESR) prosthetic feet fail to accurately replicate this energy recycling behaviour, because they cannot produce a plantarflexion moment while plantarflexing beyond their neutral ankle angle. Therefore, they fail to provide the required energy during push-off hindering forward propulsion. This results in a higher metabolic cost of walking and slower walking speeds for amputees, as they overcome the lack of prosthetic push-off power [2]. To tackle this problem, a new hydraulic prosthetic ankle is being designed which: a) stores all of the work done during stance prior to push-off; b) releases the stored energy during push-off.

Methods

The concept design comprises a prosthetic ankle joint driving two cams, which in turn drive two miniaturised hydraulic rams. The stance cam-ram system captures the work done during stance prior to push-off, by pumping oil into an accumulator. This hydraulic ram is then isolated using valves and the push-off cam-ram system returns energy to help power push-off. Both cam-ram systems are reset during swing ready for the next cycle. The modelling of the system used a combination of theoretical and empirical models, implemented in Matlab. The design parameters were optimised based on the results of multiple Matlab simulations to minimise energy losses. Finally, the model's performance was assessed to provide justification for physical prototyping.

Results & Discussion

Design optimisation has been completed for the two cam-ram systems during their working phases (stance and push-off respectively). The simulation results show good performance during both phases. The system can store significant energy during stance in the form of oil pumped into the accumulator. Likewise, the push-off ram is able to release energy effectively during push-off. The results show that the main components of the system would be physically realistic and could fit within a typical prosthetic ankle. Preliminary simulation results are promising with low energy losses: less than 2% of the total energy stored during stance; and less than 2% of the total energy returned during push-off.

Conclusion

The performance of the final design – including all components – still needs to be assessed over the full gait cycle. Nevertheless, given the promising results obtained so far, it seems that this new design based on miniature hydraulics may be suitable for physical prototyping. It may eventually help many amputees by making their walking less tiring and faster. Hence, hydraulic energy storage and return is a promising avenue for future research.

References

1. Ishikawa M *et al.* *J Appl Physiol*; 99: 603-608, 2005.
2. Waters RL, Mulroy S. *Gait Posture*; 9:207-231, 1999.

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Visualising complex 3D data in a clinical environment

S. Turner¹, A.H. McGregor ^{1,2},

¹ Centre for Blast Injury Studies, Imperial College London, South Kensington Campus, London SW7 2AZ.

² Musculoskeletal Lab, Level 7 Lab block, Charing Cross Hospital, London W6 8RF.

Introduction

There are approximately 5000 lower limb amputations in the United Kingdom each year [1]. Research has shown a plethora of difficulties and complications arise during the rehabilitation process of amputees, ranging from medical conditions related to the wearing of prostheses to the difficulties in obtaining a good socket fit. A smart socket is being conceived with pressure sensors embedded that are capable of outputting the relative change in pressure over time. The aim of this study is to develop an application that visualises the pressure data in a clear way so that it can be used by amputees and clinical rehabilitation teams to improve prosthetic rehabilitation.

Methods

To create an accurate visualisation, the computational model needs to be accurately created from the physical environment. The socket is scanned to produce a 3D model and a map of the embedded pressure sensors. The data from the sensors is then processed and assigned to the relevant locations on the model, before interpolation techniques are used to create a colour map. Unity3D and the C# programming language are used for the modelling so the application can be compiled for use on a variety of mobile and desktop devices – an important factor to allow it to translate from research into clinical practice.

Results & Discussion

A working proof of concept computational model has been developed. Computational models are advantageous as they are easily reproducible, editable and can be adapted for different patients and purposes. There are various methods that can be used to visualise the data, each with varying advantages and disadvantages: processing time, accuracy, clarity of image – the merits of different data visualisations is on-going. However, the primary issues with all the methods are the accuracy and validation of results. Interpolation is unlikely to give highly accurate results and current work is determining the level of accuracy required for clinical utility.

Conclusion

Whilst it is feasible to create a biofeedback application to relay socket sensor pressure changes, it is important to establish the level of accuracy required to facilitate clinical utility.

References

1. N. Ahmad et al., *Lower limb amputation in England: prevalence, regional variation and relationship with revascularisation, deprivation and risk factors. A retrospective review of hospital data*, Journal of the Royal Society of Medicine, 107(12): 483-489, 2014.

Acknowledgments

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Transcutaneous Feedthrough Enabled Bone Anchor for Attachment and Control of a Smart Upper Limb Prosthesis

F. Tjulkins¹, H. Lancashire¹, K. de Jager¹, **A. Vanhoostenberghe¹**

¹ Aspire CREATE, Institute of Orthopaedics and Musculoskeletal Sciences, University College London, Royal National Orthopedic Hospital HA74LP

Introduction

Prostheses fitted via socket and strap can lead to skin irritation and sores. Direct skeletal fixation, via a permanently inserted bone anchor with soft tissue flange avoids such complications by loading the bone, not skin [1]. In this abstract we report on the mechanical robustness of a bone anchor modified to become a transcutaneous port able to carry EMG signals from implanted electrodes, enabling control of the prosthesis without surface electrodes [2]. The bone anchor must withstand the forces of implantation and loading in everyday use.

Methods

A Ti6Al4V bone anchor for the Humerus was made by additive manufacturing (M280, EOS GmbH, Krailing, Germany). The response to loads experienced during implantation (impact, 600N average, 900N peak) and daily use (bending, 200N) were studied via Finite Element Analysis (SimScale GmbH, Munich, Germany) and experimentally. A Zwick 2kN (Zwick Roell GmbH, Ulma, Germany) machine was used for the bending test. An instrumented hammer with a type 9102a 20kN load cell (Kistler Holding AG, Winterthur, Switzerland) was used for the impact tests.

Results and Discussion

At 200N bending load FEA and experiment deflections were 120 and 110 μm respectively. Stresses in both impact and bending models satisfied the von Mises criterion, no component damage is expected.

Conclusion

The system was shown to be reliable under expected loads. A bone anchor with feedthrough can provide patients with a reliable long-term solution for combined prosthesis attachment and control.

References

1. Pendegrass CJ, Goodship AE, Blunn GW. Biomaterials, vol. 23, no. 26, 2006.
2. Al Ajam Y et al. IEEE Trans Biomed Eng, vol. 60, no. 6, pp. 1654-1659, 2013.

Acknowledgments

The authors thank the Restoration of Appearance and Function Trust (RAFT, UK) for financial support. Authors declare no conflicts of interest.

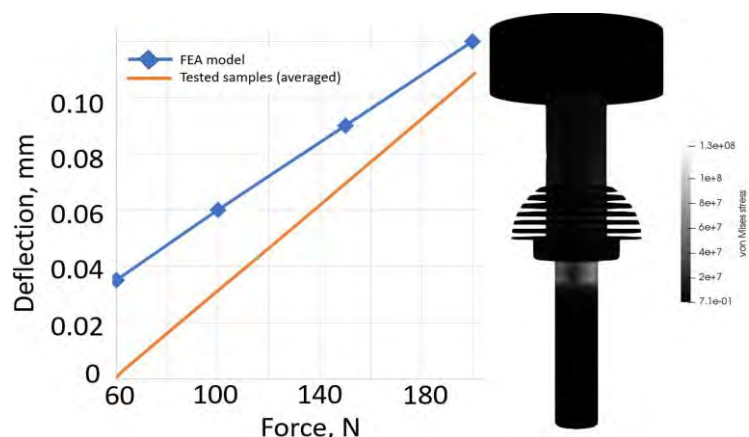


Figure 1: Anchor deflection vs force (left); stress diagram (right).

Electrode configuration selection for electromyographic prostheses

H. Lancashire¹, K. de Jager¹, F. Tjulkens¹, A. Vanhoostenberghe¹

¹ Aspire CREATE, Institute of Orthopaedics and Musculoskeletal Sciences, University College London, Royal National Orthopedic Hospital, HA7 4LP.

Introduction

Myoelectric control of prostheses requires reliable electromyography (EMG) signals. Implanted epimysial electrodes may overcome some limitations with surface EMG: electrode lift-off; impedance changes; and repeatable placement [1]. However electrode configuration and interelectrode distance must be optimised to achieve the greatest selectivity and signal-to-noise ratio (SNR) [2,3]. We have designed passive (tested here) and active [4] switching systems for optimising electrode layout.

Methods

A passive switch system was implemented to select any electrode(s) from a 5-electrode array in monopolar, bipolar, and pseudo-tripolar configuration with controlled interelectrode distance. The switch system was connected to a BIOPAC MP150 with EMG100C bioamplifiers was (BIOPAC Systems UK), 0.1 Hz to 5 kHz bandpass, 1000× gain, 10 kS/s. Common mode rejection ratio (CMRR) was tested using a floating signal source (Steinberg UR22 mkII) and a 1:22 turn ratio transformer. EMG recording was carried out using 6 skin surface electrodes, 5 formed an in-line array above the left extensor digitorum with 3 mm interelectrode distance, and one on the back of the hand was a reference.

Results & Discussion

CMRR using the complete switch system was 124 ± 4 dB, compared with 130 dB measured, and 110 dB specified, for the amplifiers alone. Example EMG recordings are shown in Fig. 1. SNR of EMG using the switch system was: 30.3 ± 4.3 dB for bipolar recordings (Fig 1c); 28.6 ± 2.3 dB for pseudo-tripolar recordings (Fig 1d); and -2.19 ± 0.76 dB for monopolar recordings (Fig 1b). SNR of concurrent bipolar recordings without the switch system was 30.4 ± 5.3 dB (Fig 1a). In this study power line interference was not removed by the bandpass filter, furthermore monopolar configurations are not differential and therefore do not reject the common mode power line interference. For both bipolar and tripolar configurations SNR is largest with 6 mm interelectrode distance centred on the muscle body.

Conclusion

The switch system developed does not appreciably reduce CMRR or SNR for bipolar and pseudo-tripolar EMG recordings. We will use the system in studies to optimise electrode configuration and interelectrode distance with epimysial electrodes.

References

1. Al Ajam Y et al. *IEEE Trans Biomed Eng.* 2013; 60; 6; 1654-1659.
2. van Vugt JP, van Dijk J. *Clinical Neurophys.* 2001; 112; 4; 583-592.
3. De Luca CJ et al. *J. Biomechanics*, 2012; 45; 3; 555-561.
4. de Jager K. et al. In: *BioMedEng18*; 2018.

Acknowledgments

The authors thank the Restoration of Appearance and Function Trust (RAFT, UK) for financial support. No conflicts of interest to declare.

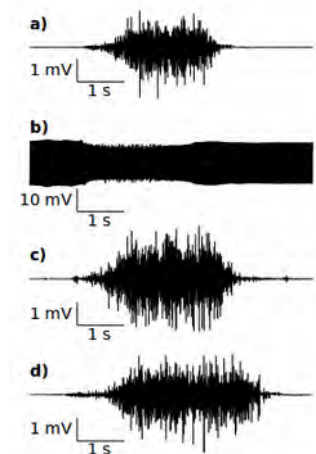


Fig. 1 EMG recordings: a) bipolar without switch system; b) switch system monopolar; c) switch system bipolar; d) switch system pseudo-tripolar.

Effect of prosthetic liner properties on residual limb stresses

A. van Heesewijk¹, A. Crocombe¹, S. Cirovic¹, W. Xu¹

¹ Centre for Biomedical Engineering, University of Surrey, Guildford, Surrey, GU2 7XH

Introduction

Trans-femoral amputees require prosthetic sockets in order to restore their functional mobility. The interface stresses between the residual limb and prosthetic socket greatly affect the amputees' satisfaction and comfort [1]. A prosthetic liner is commonly used to minimise the detrimental interactions between prosthetic socket and residuum. Previously, prosthetic liners have been classified by their friction coefficients [2]. Finite Element Analysis can be used to simulate how the prosthetic liner characteristics alter the interface stresses on the residuum.

Methods

This study looked to simulate the effect of varying coefficient of friction on the trans-femoral amputee interfaces. A 3-D finite element model of a trans-femoral amputee including the residual limb, liner and socket was generated from a computerised tomography scan. The model included nonlinear material properties and frictional contact at the soft tissue-liner and liner-socket interfaces. Medium (0.5) and High (0.8) friction coefficients were applied to the soft tissue-liner interface while Low (0.2) and Medium (0.5) values [2] were applied to the liner-socket interface. Four simulations were performed in total, with a bodyweight load applied to the socket.

Results & Discussion

For all models the peak pressures were found beneath the ischium. Increasing the friction coefficient at either the soft tissue-liner and/or liner-socket interfaces caused an increase in peak contact pressure. The highest contact pressure was reported in the High-Medium model, with the lowest contact pressure in the Medium-Low model.

Table 1. Peak contact pressures on residual limb.

	Soft tissue/Liner interface – Liner-Socket interface			
	High-Low	High-Med	Med-Low	Med-Med
Peak contact pressure	83 kPa	137 kPa	75 kPa	110 kPa

Conclusion

The results of this study can be used to aid the design of a prosthetic liner, however this information should be used in collaboration with experimental data. Whilst a Med-Low model may reduce the pressure on the residuum, the friction coefficients must be high enough as to prevent slip and allow full proprioception for the user.

References

1. Meulenbelt HE et al. Disabil Rehabil. 2006; 30: 603-608
2. Sanders JE et al. J Rehab Res & Dev. 2004; 41: 175-186
3. Restrepo V, Villarraga J, Palacio, JP. J Prosthet Orthot. 2014; 26: 205-211

Acknowledgments

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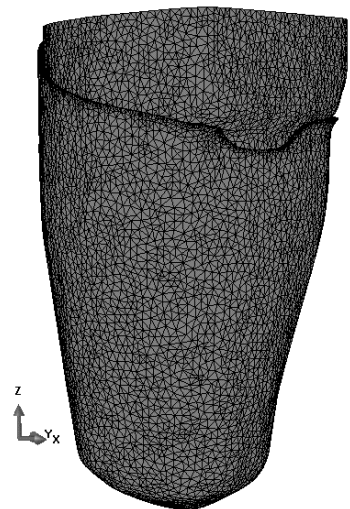


Fig 1. Finite Element mesh of residual limb and socket

FEA-driven surrogate modelling of the residuum-prosthesis interface

J.W. Steer¹, P.R. Worsley², M. Browne¹, A.S. Dickinson¹

¹ Bioengineering Research Group, Faculty of Engineering & Physical Sciences, University of Southampton

² Fundamental Care & Safety Research Group, Faculty of Environmental & Life Sciences, University of Southampton

Introduction

Inadequate fit of the prosthetic socket used by people with lower limb amputations can lead to adverse pressure and shear which contribute to discomfort and soft tissue injury¹. The prosthetic socket is designed by a prosthetist in a manual, iterative process towards an optimal functional prosthesis-skeleton coupling. Finite element analysis (FEA) models have long been proposed to predict the structural interactions at the residuum-socket interface as part of a more informed design process, although clinical translation has not yet been achieved due to lengthy simulation times, lack of input data and the need for model development and analysis expertise².

Methods

A FEA model was developed from MRI scans of a transtibial amputee, using hyperelastic soft tissues and full socket donning followed by stance loading. Six input parameters were used to parameterise the model, corresponding to three socket design variables of proximal, mid and distal geometric reduction, and three anatomical variables of residuum length and soft tissue shape and stiffness. Latin hypercube sampling was used to generate 150 model permutations which were solved to generate predictions of pressure and shear at the interface. These results were constructed into a Kriging surrogate model³, which fitted a continuous function across the discrete data points in the six-dimensional input space. The surrogate was then exploited to solve new data points in real-time (~40 ms) as opposed to requiring a full simulation (~2 hrs) and visualise the relationship between variables.

Results & Discussion

Across all anatomies, an optimal region of socket design between 3-5% socket reduction was found to minimise residuum tip pressure, which is often an area of sensitivity following amputation. Shorter limbs with low soft tissue stiffness were predicted to experience higher predicted residuum tip loading. As such, to minimise the residuum tip pressure, a greater magnitude of socket reduction was required than for longer limbs with a greater soft tissue stiffness. These observations are consistent with socket fitting theory where shear forces around the main body of the residual limb, influenced by socket design and residuum morphology, contribute to off-loading at the residuum tip.

Conclusion

Exploitation of the surrogate model enabled quantification and visualisation of the relationships between anatomical population and socket design variables. Clinical translation of these technologies would give prosthetists access to patient-specific predictions of socket fit, which would be used alongside their skill and experience in a more informed design process to improve outcomes for people with amputations.

References

1. Pezzin *et al.* *Arch.Phys.Med.Rehabil.* 2004; 85: 723-729.
2. Dickinson *et al.* *Med Eng & Phys.* 2017; 43: 1-18
3. Forrester *et al.* *Engineering Design via Surrogate Modelling.* Wiley. 2008

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The Influence of Movement on Biofilm Formation to External Fracture Fixation Pins

B. McCall¹, K. Rana ², T. Worthington ², S. Junaid ²

¹ Biomedical Engineering Research Group, School of Engineering and Applied Science, Aston University, Birmingham. ² School of Life and Health Sciences, Aston University, Birmingham

Introduction:

External fracture fixation is a valuable surgical technique in limb construction for treating both open and closed fractures. However, pin-site infections are common, with infection rates reported in the literature ranging from 4.5% to 100% (1-4). Literature based on clinical research has highlighted a relationship between excessive movement of the pin and skin and an increase in the patient's risk of pin-site infection, however the interplay between pin movement, skin movement, bacterial growth and biofilm formation is not clearly understood and warrants further study. Therefore, the aims of the following study were to develop and validate a protocol for removing and counting high adherent bacteria attached to the surface of the pins, as well as investigating the effect of mechanical movement on the rate bacterial attachment

Methods

Sections of 1.8 mm diameter 316L stainless steel surgical wire were submerged in nutrient broth inoculated with *Staphylococcus Epidermidis* RP62A (*S. Epidermidis*). A positive control (broth without pin) was also included. The samples were incubated at 37 °C with shaking frequencies of 0, 60, 120 and 180 rpm and measurements were taken at 1, 6 and 24 hours. At each time point, the pins were removed from the broth and rinsed to remove all low adherent bacteria, followed by ultrasound sonication to dislodge the high adherent bacteria. Aliquots of the high adherent bacteria solution were then inoculated onto nutrient agar in triplicates and incubated for 24 hours, so that the colony forming units (CFUs) could be counted

Results & Discussion

Both the CFU counts of high adherent bacteria removed from the pin samples, and the concentration of bacteria in the positive control study, showed an increase with increased shaking frequency. Highlighting a correlation between mechanical movement and the rate of bacterial attachment. It is not clear whether is a consequence of increased fluid shearing between the bacterial broth and pin surface or simply due to an increased bacterial growth at higher shaking frequencies and therefore a greater abundance of bacteria available to adhere to the pin surface. This increase in high adherent bacteria on pins subject to mechanical movement highlights the problem of high pin movement, which is likely to lead to a higher risk of pin site infections

Conclusion

We have shown that the rate of bacterial attachment to a stainless steel fixation pin submerged in a bacterial broth containing *Staphylococci Epidermidis* is dependent upon the frequency of shaking during incubation. . The effect of shearing without broth agitation will be investigated to further elucidate the relationship between movement and bacterial attachment. This will help in the development of more effective preventative measures to combat pin site infections.

Protection of the foot and ankle in under-body blast

E Rebelo¹, S. Masouros¹, A. Bull¹, G. Grigoriadis¹, D. Carpanen¹

¹Royal British Legion Centre for Blast Studies, Imperial College, South Kensington, SW7 2AZ, London.

Introduction

When a vehicle is attacked by an improved explosive devices (IED), the explosion causes deformation of the floor of the vehicle and the transmission of a high-rate axial loading to the lower limb of the occupants. This incident often leads to difficult-to-treat fractures in the ankle and foot and partial amputation of the lower limb [1]. The aim of this study was to develop a finite element (FE) model of the lower limb with various mitigation systems able to simulate under-body blast. This model can help to understand the function of mitigation systems, quantify their effect and act as a design tool for developing new combat boots and blast mats.

Methods

The loading scenario was simulated using a non-linear explicit solver MSC.Dytran (v2017, MSC.Software, Santa Ana, CA, USA). The model simulates the impact of a rigid floor to the lower limb as a result of an underbody blast event. The 15 kg rigid floor is driven upwards to reach a maximum speed of 5.2 m/s (time to peak velocity of 10ms) and was restricted to move only in the direction of the impact. The proximal ends of the tibia and fibula were also restricted to move in the direction of the impact, while the rest of the limb was represented by a mass of 12 kg also fixed on the distal end of the bones.

The model allows the user to tune the material properties and dimensions of combat boot layers and assess which set of parameters optimizes the protective ability of the design. The tool also allows the inclusion of honeycomb structures near the heel to maximize the protective ability of the boot.

Results & Discussion

The cadaveric lower limb used for the model development was exposed to loading of 5.2 m/s within 15 ms with and without a combat boot using an anti-vehicular under-body blast injury simulator (AnUBIS) previously developed at Imperial College London [2]. Ten strain gauges were attached on different locations on the tibia and the calcaneus of the specimen. An X-Ray Fluoroscan (Vertec, Reading, United Kingdom) was used to assess whether the specimen had fractured during the tests (with and without protection). The results from this experiment were used to validate the finite element lower limb model without the mitigation systems.

Conclusion

The tool presented in this study allows the design of a blast mitigating boot for under body blast scenarios. By tuning the relevant properties of the components of mitigation systems, its mitigating efficacy can be optimized.

References

1. Ramasamy, A. et al. (2013). From the battlefield to the laboratory: the use of clinical data analysis in developing models of lower limb blast injury. Royal Army Medical Corps.
2. Masouros, S. (2013). Design of a traumatic injury simulator for assessing lower limb response to high loading rates. Ann Biomed Eng

Third Body Wear Simulation of UHMWPE-on-PEEK-OPTIMA™

R. M. Cowie¹, N. M. Pallem¹, A. Briscoe², J. Fisher¹, L. M. Jennings¹

¹ Institute of Medical and Biological Engineering, University of Leeds, UK. ² Invibio Ltd, Thornton Cleveleys, UK

Introduction

PEEK-OPTIMA™ is being considered as an alternative to cobalt chrome in the femoral component of total knee replacements¹. In this study, the influence of third body wear on UHMWPE-on-PEEK was investigated, tests on UHMWPE-on-cobalt chrome (CoCr) were also carried out to compare PEEK to a conventional femoral component material.

Methods

Wear simulation was carried out using a multi-directional pin-on-plate simulator. 5 scratches were created on each PEEK and CoCr plate perpendicular to the direction of the wear test using a diamond stylus to produce scratches with a geometry similar to that observed in retrieved CoCr femoral components. To investigate the influence of scratch lip height on wear, scratches of approximately 1, 2 and 4µm lip height were created. Wear simulation of UHMWPE pins against the plates was carried out for 1 million cycles using 25% bovine serum as a lubricant and the wear factors of pins against scratched plates compared to unscratched controls (0µm lip height).

Results & Discussion

For the control tests (0µm lip height), the wear factor of UHMWPE pins was similar ($p=0.64$) against PEEK and CoCr plates, Figure 1. Against CoCr, with an increasing lip height, an exponential increase in wear factor of UHMWPE pins was observed; for PEEK, with increasing lip height, the wear factor did not show an exponential increase. When articulated against the largest scratches, 4µm, the wear factor of UHMWPE was significantly higher against CoCr than PEEK ($p=0.01$).

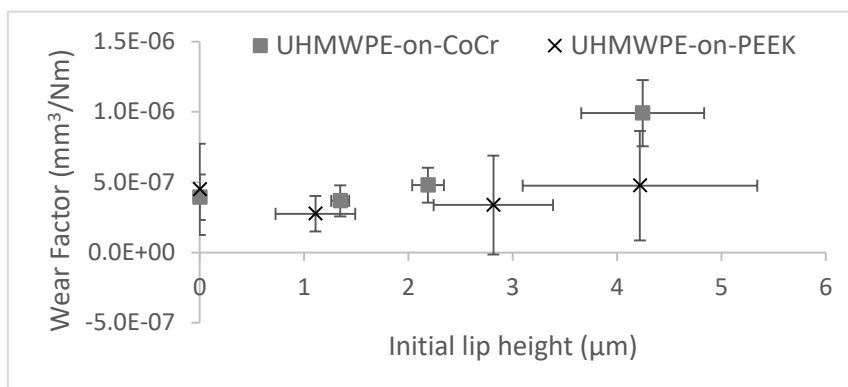


Figure 1: Mean ($\pm 95\%$ CL) wear factor versus initial lip height ($\pm 95\%$ CL) of UHMWPE pins against CoCr and PEEK plates scratched with a diamond stylus, minimum $n=3$ for each.

Conclusion

The trend in the wear of UHMWPE was different when articulating against scratched PEEK and CoCr counterfaces, with a significantly higher wear factor of UHMWPE against CoCr than PEEK at a scratch lip height of 4µm.

References

1. Cowie RM *et al.* Proc Inst Mech Eng H. 2016; 230(11): 1008-1015.

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Engineering accuracy in safety critical spinal surgery

H.E. Burton, C.L.P. Ribolzi, D. Eggbeer

PDR – International Centre for Design & Research, Cardiff Metropolitan University, CF5 2YB, Cardiff.

Introduction

Spinal fusion is a surgical intervention to stop abnormal and painful movement in a patient. Fusion surgeries can take up to 7 hours to complete, and between 2-5% of procedures cause damage releasing cerebrospinal fluid. Patient-specific guides, designed from 3d medical scan data, can help surgeons confidently drill and cut with accuracy based on a computer-plan [1]. Although guides are the latest development in the standard of care for decreasing risks in orthopaedic and maxillofacial surgery [2], the benefits have not yet been realised as standard practice in spinal applications. This study aimed to decrease the risk associated with spinal surgery through the application of guides designed to increase the accuracy of screw trajectory.

Methods

A concept pedicle screw placement guide was developed (Figure 1) based on a review of academic literature and with surgeon feedback. Literature was reviewed to determine current best practice in guide design and to identify specific clinical success criteria. Error in surgical drilling can result in angle deviation from planned trajectory, or displacement from planned exit. A validation study was designed to confirm the accuracy of the concept guide.

This involved creating a surgical training model to perform repeatable studies in physical models, and using CT to measure hole trajectory angles in virtual models.



Figure 1 - pedicle screw insertion guide with innovative design features.

Results & Discussion

There is no standard for best practice when designing these high-risk medical devices. Historically, guides have evolved without rigorous evaluation of design principles. This concept guide was designed to minimise the necessary tissue dissection envelope and increase the accuracy of screw placement through the implementation of design engineering guidelines identified in the literature. Since each guide is unique to both the patient and vertebrae, and the shape was low profile and complex, metal additive manufacture was selected as the intended fabrication method.

Conclusion

This study has developed and tested design and engineering controls for surgical guides intended for metal additive manufacture production. With further pre-clinical validation of the accuracy achieved using these style guides compared to alternative surgical approaches, they could help to improve the safety and efficiency of high-risk spinal surgery. This has the potential to positively impact patient outcomes while reducing surgical time and costs for the NHS. Further validation testing to confirm repeatable accuracy of these guides is underway.

References

1. Fan Y, Du JP, Liu JJ et al. *Scientific Reports*. 2018; 8(1): 890.
2. Peel S, Eggbeer D. *Rapid Prototyp J*. 2016; 22(1): 189-199.

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Influence of Test Frequency on the Friction of UHMWPE-on-Cobalt Chrome

R. M. Cowie, L. M. Jennings

Institute of Medical and Biological Engineering, University of Leeds, UK.

Introduction

Experimental wear simulation of orthopaedic implants is generally carried out at 1Hz to replicate the speed of a walking gait cycle. The aim of this study was to investigate the influence of test frequency on the dynamic coefficient of friction (COF) of UHMWPE-on-cobalt chrome (CoCr).

Methods

The study was carried out using a simple geometrical configuration in a single station pin-on-plate friction simulator. GUR 1020 UHMWPE pins with an 8mm contact face were articulated against polished cobalt chrome plates. A uniaxial test was carried out whereby the pin was statically loaded with 160N and the plate was reciprocated at different frequencies (0.25, 0.5, 0.75 and 1Hz). The dynamic COF was derived from measurements taken using a piezoelectric sensor. The lubricant used throughout was 25% bovine serum and the study was carried out at room temperature for 10 minutes. N=6 was completed each test condition and statistical analysis carried out using ANOVA with significance taken at $p < 0.05$.

Results & Discussion

The dynamic COF of UHMWPE-on-CoCr at different frequencies is shown in Figure 1. There was no significant difference in the measured COF at any of the frequencies assessed ($p=0.35$).

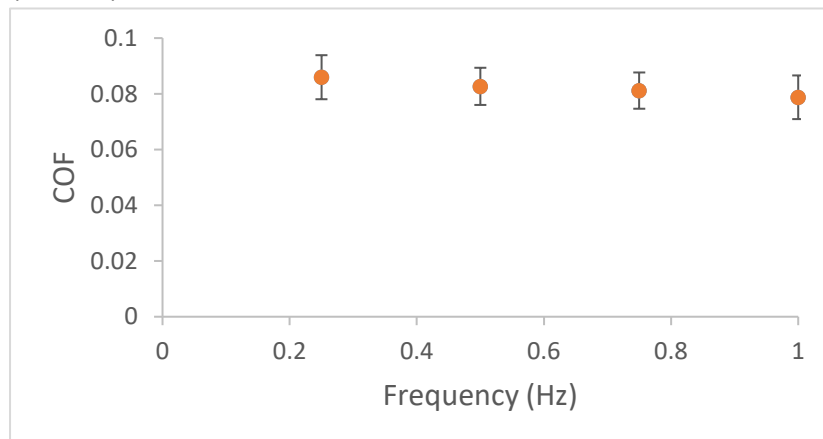


Figure 1: The dynamic COF of UHMWPE-on-CoCr measured at different frequencies.

Conclusion

Between 0.25 and 1Hz, frequency did not influence the dynamic friction of UHMWPE-on-CoCr. The maximum frequency was limited at 1Hz due to a limitation of the rig so it is not known whether at higher frequencies there would be a change in the COF. The tests were short-term therefore, it is not known whether in longer duration tests carried out at higher frequencies there will be enhanced frictional heating and whether this will affect the lubrication regime.

Acknowledgments

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Hexapod External Fixator Biomechanics – The Final Link

W. Macdonald¹, M. T. Yeung¹, J. Farquharson¹, S. Naique²

¹ Department of Bioengineering, Imperial College, London, South Kensington SW7 2AZ, London.. ²Trauma & Orthopaedics, Imperial College Healthcare NHS Trust, St Mary's Hospital, London W2 1NY.

Introduction

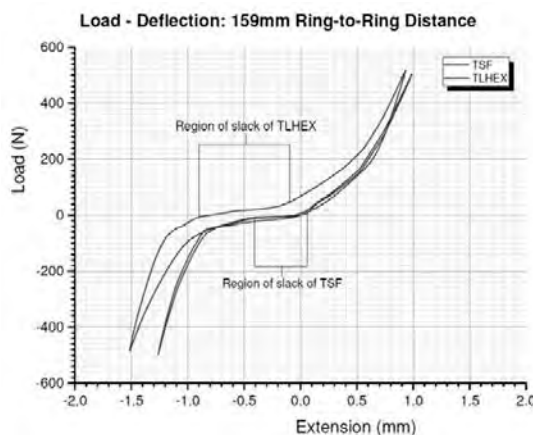
Mechanobiology of fracture healing is now sufficiently well understood that the prediction of optimal biomechanics for fracture fixation is possible (1). External fixators used for the stabilisation of compound, complex or compromised fractures of the long bones have been mechanically characterised in regard to fixator type (planar, ring or hexapod), bone fixation elements, and overall geometry (2-6).

However, hexapod fixators such as the Taylor Spatial Frame (TSF) show complex mechanics dependent on the components used and the geometry adopted; the biomechanics of the newer Truelock Hexapod System™ (TL-HEX) have not previously been reported.

Methods

We performed mechanical tests on the hexapod frames of TSF and TL-HEX systems under a range of conditions and geometries, and also tested fixation constructs of bone analogues (GFRP tubes) supported by paired crossed wires connected to TSF and TL-HEX fixators.

Results & Discussion



The results indicate that both Hexapod fixators demonstrate similar more compliant mechanics than Ilizarov type frames, allowing physiological fracture gap motions.

Conclusion

Hexapod fixators' more compliant biomechanics allow physiological motions in the fracture zone, which can be expected to enhance and support fracture healing.

References

1. Steiner M, Claes L, et al. J Royal Society, Interface. 2013;10(86):20130389.
2. Henderson DJ, et al. Clin Orthop Relat Res. 2017;475(5):1472-82.
3. Nikonovas A. Bristol: Bristol; 2005.
4. Fleming B, et al. Clin Orthop Relat Res. 1989(241):95-105.
5. Antoci V, et al. J Orthop Trauma. 2005;19(3):180-6.
6. Roberts CS, et al. Injury. 2005;36(9):1107-12.

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Development of a Smart Elbow Prosthesis

M. M. Khalid Khan¹, S.C. Deshmukh ^{1, 2}, K. Theivendran ^{1, 2}, L.J. Leslie ¹, S. Junaid ¹

¹ Biomedical Engineering Research Group, School of Engineering and Applied Sciences, Aston University, B7 4ET, Birmingham. ²Sandwell and West Birmingham Hospital, NHS Trust, B71 4HR, Birmingham.

Introduction

Elbow prosthesis are medically implanted device which are surgically inserted into the elbow joint to restore its function affected by rheumatoid arthritis or osteoarthritis. However, the expected lifetime of an elbow prosthesis is only around 5 -10 years, and sometimes even less for younger patients. The prosthesis suffers from higher complication rates and lower survival rates as compared with knee and hip prosthesis and these problems are mainly due to septic (infection) and aseptic (mechanical) loosening. A failed prosthesis requires revision surgery, which is more complex, traumatic and costly than the primary replacement. Currently, the diagnostic methods which are used to assess the performance and detect any complications in the elbow prosthesis involve clinical measurement and imaging techniques which has low sensitivity and specificity [1-3]. Therefore, the aim of this work to develop a diagnostic technique which will have the ability to unobtrusively measure migration of the implant from its original position.

Methods

A magnetic measuring system was used which will have the capability to detect any migration of the implant with respect to its original position. To obtain the correlation between the magnetic field and displacement, an algorithm was made which will first measure the relative distance between the magnetic source and magnetic sensor, and with respect to that find any change. A 2D scanning process was used to calibrate sensor which includes a micro- positioning system with motorised linear stage and a motorised torsion stage (Electro force 3300). One of the motorised linear stage moved in y-axis with a range of 15mm having step size of 0.1mm with frequency of 0.1 Hz while the torsion stage in x-axis with a range of 10 degree in x –axis with a step size of 1 degree with a frequency of 0.1 Hz. The Moving least square method was used to reduce the noise level of the signal and two different types of movement were performed (Static and dynamic).

Results & Discussion

According to the result the resolution of the sensor was calculated as 1mm to 12 mm in z axis and 0.3mm to 10mm in x/y axis linearly while 0.1 to 6.0 degree x/y axis angularly with a radius of 42 mm. The resolution depend upon the operating condition. When operated in calibrated range the maximum detected distance between source and sensor was approximately 10.5mm, while the maximum displaced distance was approximately 6mm linearly and 3.5 degree angularly in x/y axis. The repeatability and stability of the calibrated sensor showed an excellent result (0.05 Standard deviation for 150 cycles).

Conclusion

This study shows that how magnetic measuring system can be used to assess the migration of the implant and has many virtues as low cost, stability, high accuracy, stability durability and robustness. However the current technique has some limitation as well which are: operating at low frequency. The system was only able to detect accurate result when frequency was between 0.1 to 0.5 Hz. Greater than this frequency the sensor sensed the change but could not assessed the accurate distance. Tilting effect: when sensor or source is tilted more than 4 degree the magnetic field changes which cause error to the desired output by introduction another sensor this error can be compensated.

Using the Woodpecker™ to seat Acetabular Cups during Hip Arthroplasty: Reduce Strain and Increase Fixation

R. J. Doyle¹, W. W. Ong¹, G. Desoutter² J. R. T. Jeffers¹

¹ Mechanical Engineering, City and Guilds Building, Imperial College London, sw7 2az, UK

² Desoutter Medical Limited, Halton Brook Business Park, Weston Road, Aston Clinton, Bucks, HP22 5WF, UK

Introduction

Traditionally hammer strikes are used by orthopaedic surgeons to press-fit 'cementless' implants into an appropriately under-reamed cavity in the pelvis during hip arthroplasty. However over-impaction during this process can lead to fracture (if strains are excessive) or aseptic loosening (if poor implant fixation is achieved). This study evaluates the performance of an oscillating pneumatic tool (Woodpecker [1]) as a novel method of seating implants.

Methods

The Woodpecker was fitted to a custom rig and supplied with 6 bar air pressure in 0.5s pulses. CNC milled blocks of bone substitute ('Sawbone', [2]) were used to simulate the acetabular bone cavity. 40N, 60N & 80N axial forces were applied to the Woodpecker (simulating surgeon pressure) while custom titanium implants were seated with 1mm under ream. Dynamic strains around the 'acetabular rim' were measured. Following seating the force required to extract each implant from the acetabular cavity was measured. Traditional mallet strikes were also evaluated with the same methodology across 10 strikes at low (1j), medium (5j), and high (15j) energy.

Results & Discussion

The push-out force of the cups implanted with the woodpecker increased with increasing applied force ($144 \pm 32\text{N}$, $439 \pm 16\text{N}$ and $474 \pm 64\text{N}$ for 40, 60 & 80N respectively). For the hammer strikes peak push-out was achieved with the 5j impact energy ($723 \pm 48\text{N}$). At this energy peak strain was significantly higher than any of the woodpecker strains ($623\mu\epsilon$ versus $352\mu\epsilon$). The desirable ratio of pushout (which should be maximised) over strain (which should be minimized) is found to be 45% higher when implanting using the Woodpecker versus hammer strikes (Fig. 1).

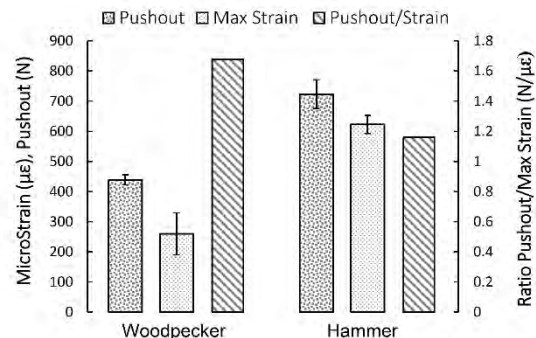


Figure 1: Pushout, max strain and pushout/strain ratio for most effective woodpecker and hammer methods

Conclusion

Having previously only been used to broach the femoral cavity during arthroplasty the Woodpecker shows promise as a viable alternative to implant seating versus the conventional mallet strike approach. Bone strain, and therefore chance of fracture, is reduced. Peak push-out force (therefore fixation) is also reduced, however the desirable ratio of these two values is increased versus traditional mallet strike.

References

IMT, "Woodpecker" [Online]. Available: <http://www.imt-medicalusa.com/products/woodpecker-hip-broaching-system.aspx>
 Sawbone Europe AB, "Sawbones," [Online]. Available: <https://www.sawbones.com/>

Acknowledgments

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Evaluation of Remote Centre of Motion mechanism suitability for osteochondral tissue milling

J. Lipskas¹

¹ *Graham Hills Building, 16 Richmond Street, Glasgow, G1 1XQ.*

Introduction

Current minimally invasive robotic knee arthroplasty still uses relatively large (up to 14cm) incisions¹ and new approaches could be necessary to further reduce invasiveness of this type of surgery. One of the options could be wider application of regenerative medicine approaches, such as autologous chondrocyte transplantation² and autologous collagen-induced cartilage repair techniques³. Such surgery presumably could be performed using a Remote Centre of Motion (RCM) robotic manipulator, traditionally seen in abdominopelvic MIS, for defect preparation by milling and later implantation of biological tissue or synthetic scaffold. To test such mechanism suitability for osteochondral tissue milling, a simple, yet reliable spherical link-based RCM mechanism was built and employed for bovine femur milling.

Methods

A solid tungsten carbide 3mm fluted ball nose and 3mm shank cutter was used as a bone cutting tool (Burr shape D30303-2, Aria Developments Ltd, UK). Cutting tool feed of 3 mm/s, cutting depth of 1mm, rotational speed of 35000 rpm, and cutting width of 2 mm were selected for this experiment. After milling procedure, dimensional accuracy of the milling procedure was evaluated by taking number of measurements in X, Y and Z directions, using digital machinist calliper which has accuracy of 0.02mm (Mitutoyo, Japan). In total, 15 measurements at approximately equal intervals for width and length performed on the straight parts of the cut.

Results & Discussion

Visual naked eye inspection of the created osteochondral defect revealed clean surface of the cut, without visible imperfections which had intended shape and sharp, undamaged corners on the surrounding tissue. Results of this experiment, at maximum dimensional error of 0.29mm are comparable to these, performed using different methods of bone cutting and reported in literature of 0.19-0.80mm^{4,5}.

Conclusion

Overall, the initial RCM manipulator testing can be considered as successful and results may suggest, that this type of manipulator could be used for bone preparation tasks in knee arthroplasty without major negative effects, what in turn could lead to development of new surgery techniques.

References

1. Bonutti et al., Minimally invasive total knee arthroplasty. *J Bone Joint Surg Am*. 2004;26:32.
2. Brittberg et al., Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation, *The New England Journal of Medicine*. 1994;331(14).
3. Shetty et al., Autologous Collagen - induced Chondrogenesis: Single - stage Arthroscopic Cartilage Repair Technique. *Orthopedics*. 2013;36(5):1-18.
4. Macdonald et al., Improved tibial cutting accuracy in knee arthroplasty. *Med Eng Phys*. 2004;26:807-812.
5. Van Ham et al., A semi-active milling procedure in view of preparing implantation beds in robot-assisted orthopaedic surgery. *Proc Inst Mech Eng Part H J Eng Med*. 2005;219(3):163-174.

Acknowledgments

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A Multi-station Shoulder Wear Simulator and its First Wear Test Results

D. Wang¹, A. A. Amis^{1, 2}, J. H. Tay¹

¹Department of Mechanical Engineering, ²Musculoskeletal Surgery Group, Department of Surgery & Cancer, Imperial College London, London, SW7 2AZ, United Kingdom.

Introduction

Osteolysis is one of the biggest problems for the aging population, which made implants needed more and last longer. Wear particle-induced osteolysis plays an important role for glenoid loosening in total shoulder revision. Wear of the glenoid component limits the long-term survivorship for patients [1]. Therefore, it is vital to do the wear measurement of glenoid implants *in vitro* and then to improve their wear performance *in vivo*. A shoulder wear simulator was built to accurately simulate physiological gleno-humeral forces and displacements during activities of daily living. Investigation of wear characteristics through a comprehensive range of motion using the sophisticated shoulder simulator would reveal the durability of the implant material, the performance of the implant design and its safety in the laboratory.

Methods

Imperial shoulder simulator was designed with six articulating stations and one loaded soak control station for anatomical shoulder system wear simulation. It gives an adduction-abduction (AA) range of -15° to 55°, flexion-extension (FE) range of -90° to 90° and internal external rotation (IER) range of 15° to -90°. The rotations are applied simultaneously to the humeral implants by using stepper motors with integral position encoders. Axial and shear loadings to each glenoid implant were applied using pneumatic cylinders. Force controlled translations were recorded using load cells and LVDTs, and a data acquisition system. Pneumatic cylinders were also installed to work to counterbalance weights during the motion of adduction-abduction. All bearing pairs are within isolated and sealed test chambers. Diluted bovine calf serum was employed as a lubricant. The simulator is controlled by LabVIEW program allowing to reproduce shoulder activities of daily living.

A commissioning trial was conducted when commercial shoulder implants were subject to rotational and translational motions and loading to replicate the 'combing' activity of daily living. The motion ranges were typically 5° to 15° in AA, 15° to 80° in FE, and -30° to -20° in IER with applied loads from 60 to 440 N, principally along the medio-lateral direction. The waveform was at frequency of 1 Hz. The activity was loaded at 250,000 cycles around 3 full days, when test and control specimens were cleaned, measured and then re-installed into the simulator. Totally, the shoulder implants were wear tested for 2 million cycles.

Results & Discussion

The results from kinematic and kinetic inputs and outputs were obtained from the trial study to check the performance of the simulator. The volumetric wear results for the glenoid components were calculated from weight losses. A multi-station shoulder wear simulator has been successfully developed to facilitate the wear tests of shoulder implants. By using the simulator, wear performance of the implants can be characterised *in vitro*.

References

1. Cofield RH, Sperling JW. In: 1st ed. *Revision and Complex Shoulder Arthroplasty*. Lippincott Williams & Wilkins, Philadelphia; 2008:90

Fabrication and Optimisation of Electrospun Scaffolds for Ligament Tissue Engineering

O.A. Agbabiaka¹, P. Twigg¹, F Sefat¹

¹*Medical Engineering Department, University of Bradford, Bradford, West Yorkshire, UK*

Introduction

The ligament is a fibrous and dense connective tissue responsible for the stability and movement of the knee joint, whilst connecting bone to bone. Injuries of the ligament are commonly associated with individuals who are athletic or indulge in sporting activities and the elderly population. These injuries limit the mobility and activity of the joint [1]. Ligament damage has also been recorded in motor vehicle accidents. 40% of all knee injuries occur at ligaments, and within these injuries, 49% occur at the anterior cruciate ligament (ACL). Ligaments heal from mild sprains on their own with time but, with proper care such as; elevating the knee, cold compression and rest, the recovery will be sped up [Fu et al. 1999]. A completely lacerated ligament needs orthopaedic surgery to reattach the torn tissue to regain stability and movement functionality [2]. Tissue engineering has become an effective method for the repair and regeneration of some types of lost and damaged tissue, from defects or trauma. Tissue engineering may offer a way of overcoming the issues associated with natural and synthetic ligament repair grafts.

Aim

The aim of this study is to fabricate suitable scaffold using electrospinning technique for the optimization of ligament tissue constructs.

Methodology

The electrospinning process is currently being developed to overcome the challenges of allografts and autografts. Electrospinning has been utilised to mimic the diameter of a native ECM fibres at a nano-scope to microscopic level. In this process, a loaded syringe passes a solution made up of suitable synthetic or natural biomaterials, e.g. a mixture of polylactic-co-glycolic acid (PLGA) and collagen I, through a nozzle of 0.1-0.6mm, which is accelerated by a high voltage (18kV) to a collector plate. For an aligned fibre variant, the collector must rotate at a specific rotation speed e.g. 600 rotations per minute (RPM), whilst for a random fibre variant, the collector plate is static. The parametric considerations of this technique are biomaterial, applied voltage, nozzle size, plate diameter, collector plate distance from syringe, and RPM. These parameters vary the properties of the porous electrospun scaffold. The electrospinning process fabricates fibrous tissue constructs which are flexible with compression and bending forces. Scaffold micro-fibres provide topographic features through mechanical anisotropy, that leads to cell alignment guidance and arranges cells in tissue oriented constructs. Research shows that aligned fibre orientation constructs a higher mechanical tensile property in comparison to random fibre orientation. The electrospinning technique has a unique potential in being a suitable means for creating 3-dimensional tissue scaffolds for the human body and aiding orthopaedic surgery.

References

1. Choudhuri U, Patel J, (2008). "Synopsis of causation – Knee ligament damage", University College Hospital, London, University of Aberdeen.
2. Vunjak-Novakovic G, Altman G, Horan R, and Kaplan DL, (2004). "Tissue engineering of ligaments," Annual Review of Biomedical Engineering, vol. 6, pp. 131–156.

Encapsulation of Human Hepatocytes in chemically modified alginates

E. Tarsitano¹, Nishant Singh², Cameron Alexander², Andrew J. Bennet³, Morgan R. Alexander², Jing Yang¹

¹ School of Pharmacy, University of Nottingham, NG7 2RD. ² Faculty of Science, Nottingham University, NG7 2TQ, ³ School of Life Science, Queens Medical Centre, Nottingham, NG7 2UH.

Introduction

High throughput screening is a powerful tool for evaluating the influence of large libraries of materials on cellular activities such as attachment and proliferation [1]. 3D printing permits spatial patterning of cells and materials to create biomimetic architectures with high reproducibility. The aim of this project is to assess the functionality of primary hepatocytes and progenitor liver cell encapsulated in the in-house modified alginates libraries using a microarray approach. The final aim is to 3D print the most effective form of modified alginate to manufacture an *in vitro* liver model for drug development and toxicity testing.

Methods

Alginate hydrogel synthesis and HepG2 encapsulation

5 types of modified alginate hydrogels (X1, X2, X3, X4, X5) were synthesised through click reaction, appended with triazole rings and different chemical functionalities [2]. Food (FA) and medical grade alginate (MGA) were used as controls. All hydrogels were sterilised and mixed with HepG2 cells which are used for testing viability before use of primary hepatocytes.

Albumin secretion and DNA quantification

DNA content and albumin secretion of the HepG2-laden alginate hydrogels samples were measured by a PicoGreen™ assay and ELISA, respectively.

Results & Discussion

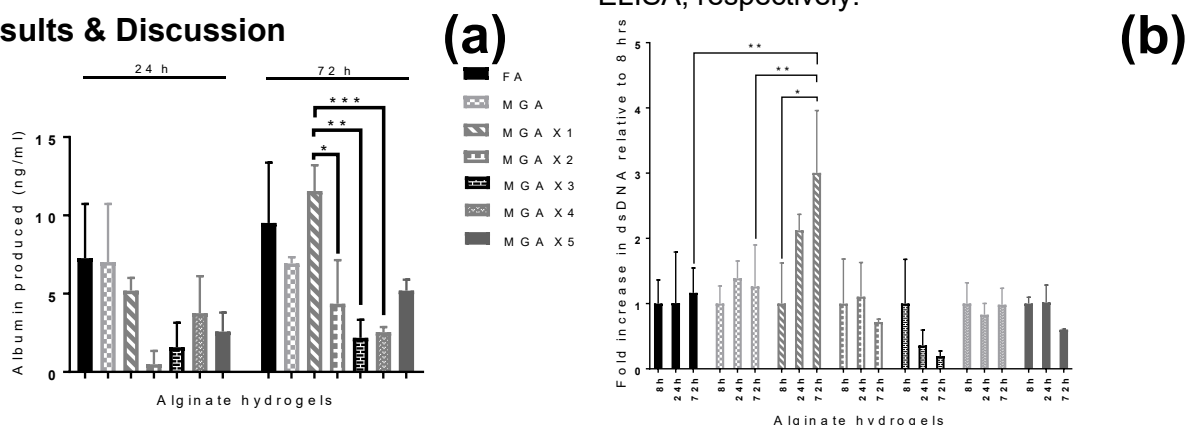


Figure 1. (a) **Albumin productions.** An increase in albumin production was seen over 72h for X1 compared to X2, X3, X4 and X5 as well as controls. (b) **Relative DNA content normalised to 8 h.** A 4-fold increase in DNA content was observed in X1 when compare 8h to 72h, suggesting that the cells proliferate during this time. No significant increase in DNA content was found for the rest of alginates. Interestingly, X1 at 72h outperformed the controls (non-modified alginates). Data are expressed as the means $\pm$ SD from three replicates. $p < 0.05$ was consider significant.

Conclusion

HepG2 cells encapsulated in X1 showed increased Albumin secretion over 72h compare to the other modified alginates. Higher increase in DNA content in X1 was observed suggesting that cells proliferated

more than the controls and other modified alginates tested.

Acknowledgments

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References

1. Hook A.L. *et al.* (2012). Combinatorial discovery of polymers resistant to bacterial attachment. *Nat Biotechnol.* 30, 868–875.
2. Vegas, A. *et al.* (2016). Combinatorial hydrogel library enables identification of materials that mitigate the foreign body response in primates. *Nat Biotechnol.* 34(3):345-352.

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Placental mesenchymal stem cells for the treatment of neonatal chronic lung disease

J. Bratt¹, P. Wu², N. Forsyth¹, A. El Haj¹

¹ISTM, Guy Hilton Research Centre, Keele University, Stoke-on-Trent, UK ²Univeristy Hospital of North Midlands, Stoke-on-Trent, UK

Introduction

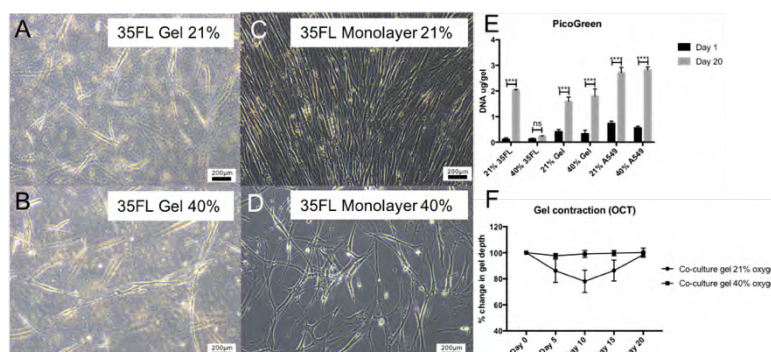
Bronchopulmonary Dysplasia (BPD) is a neonatal condition affecting the lungs of premature infants. The disease interferes with alveolar maturation and vascularisation. There are currently no treatment options but only supportive (oxygen ventilation and surfactant treatment) and prevention measures (Costeloe KL *et al.* 2012). Mesenchymal stem cells (MSCs) are the focus of regenerative medicine and have the potential to offer a promising therapeutic tool for the treatment of BPD (Ahn SY *et al.* 2015) as shown in hyperoxia induced rodent and murine models. Placental derived MSCs (pMSCs) are associated with fewer ethical concerns, easy attainability and a high capacity for differentiation (Pasquinelli G *et al.* 2007). This study currently focuses of developing an *in vitro* model to assess the suitability of pMSCs for the treatment of BPD.

Methods

3.5mg/ml collagen and elastin hydrogel constructs were made using type I rat-tail collagen (BD Bioscience) using a previously described protocol. Human adult lung fibroblasts 35FL were seeded in monolayer or within the gels and human epithelial cell line A549 were seeded on the gel surface. The constructs were incubated for 20 days at either 21% O₂ or 40% O₂. The contraction of hydrogels was measured using optical coherence tomography (OCT). DNA quantification was achieved on day 0 and day 20 using the PicoGreen dsDNA quantification assay (Invitrogen). Gene expression was examined using qPCR. The equivalent experiments were conducted with cells extracted from endotracheal suctioning of neonates on ventilation in the NICU (NL cells).

Results & Discussion

An increase in cell number was observed in all samples except adult lung fibroblasts 35FL cultured at 40% O₂ (figure D and E). NL cell seeded hydrogels did not contract at 40% O₂. 40% oxygen prevented cells contracting hydrogels (figure F)



Conclusion

In this work we have developed an *in vitro* model to represent the human lung alveoli and BPD. The air-liquid interface allows us to model the high O₂ ventilation BPD patients are exposed to. Current results show that culture at 40% O₂ has a significant effect on adult lung fibroblast proliferation, contraction and gene expression. So far, we have not seen the same effect in NL cells.

Acknowledgments

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Comparison of fucoidan from two different species of brown seaweed for bone tissue engineering

D. Gupta^{1,2}, D.C. Martinez¹, V.L. Hearnden¹, M. Silva³, M. A. Puertas-Mejia³, G.C. Reilly^{1,2}

¹ Department of Materials Science and Engineering, University of Sheffield, UK. ² Insigneo Institute for in Silico Medicine, University of Sheffield, Sheffield, UK. ³ Institute of Chemistry, University of Antioquia, Medellín, Colombia.

Introduction

Fucoidan is a polysaccharide derived from several species of brown seaweed [1]. Studies have shown that fucoidan from different species may have different therapeutic effects [2]. Here we explore crude fucoidans extracts from two different brown seaweed species, namely commercially available *Fucus vesiculosus* (Sigma) and locally sourced (from the Caribbean coast of Colombia) *Sargassum* sp., to determine whether they exhibit similar behaviour in bone regeneration applications.

Methods

To assess cell attachment, human embryonic derived mesenchymal progenitor cells (hES-MPs) were seeded in culture medium containing different doses of crude fucoidan from the two sources. After 24 h, a resazurin assay of cell metabolic activity was performed. For long-term experiments hES-MPs were seeded in non-supplemented media, fucoidan was added after 24 h and total DNA quantified at a range of time-points. To assess early osteogenic differentiation, alkaline phosphatase (ALP) activity was assayed at day 7.

Results

Fucoidans from both species inhibited hES-MP attachment in a dose dependent manner (but more severely for *Sargassum* sp) with significant differences at higher doses 25-100 µg/ml compared to 0 µg/ml (control) (Fig. 1a). By Day 3, fucoidan only from *F. vesiculosus* inhibited cell numbers in a dose dependent manner and by Day 7 this inhibition was clearly visible for both fucoidans in a dose dependent manner ($p < 0.001$, Fig. 1b). Interestingly, there was significantly higher ALP activity for hES-MPs treated with 0.1 to 1 µg/ml of fucoidan compared to control ($p < 0.001$, Fig. 1d) for both fucoidans.

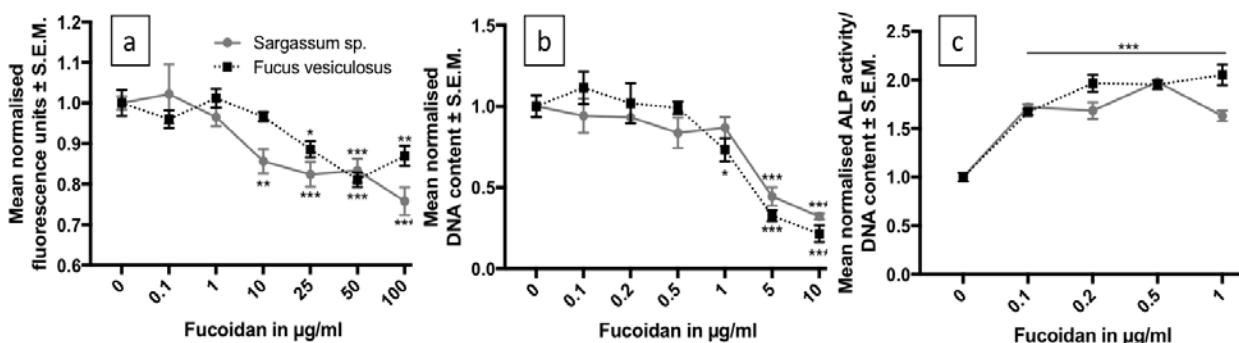


Figure 1: Effect of fucoidans from two different brown seaweed species on cell attachment (a), cell growth (b) and ALP activity (c) on day 7. *, ** and *** indicate $p < 0.05$, 0.01 and 0.001 vs control.

Discussion & Conclusion

The effects of Colombian *Sargassum* derived fucoidan on hES-MPs was examined for the first time, identifying similar effects to commercially available fucoidan, including inhibition of cell attachment and growth at high doses but osteogenic activity at low doses.

References

1. Fitton JH, Stringer DN, Karpiniec SS. Mar Drugs. 2015;13(9):5920–46.
2. Cumashi A, et al. Glycobiology. 2007;17(5):541–52.

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Animal Robotic Locomotion: An Interdisciplinary Teaching Programme

C. Thompson ¹², F. Martins ¹², T. Enchill ³, M. Hussain ³, S. Odufuwa-Bolger ⁴,
S. Mendes ⁵, R. Harbird ⁴, E. Bryant ¹, D.I. Nikitichev ⁵

¹ Culture Department, University College London, London, WC1E 6BT

² Genetics Evolution and Environment, University College London, London, WC1E 6BT

³ Art and Sciences Department, University College London, London, WC1E 6BT

⁴ Computer Science Department, University College London, London, WC1E 6BT

⁵ Medical Physics and Biomedical Engineering Department, University College London, London, WC1E 6BT

Introduction

New disruptive technologies such as Machine Learning and Artificial Intelligence will change the world of work dramatically via automation. The jobs we see today will be swept away and young people need to be prepared for that change. Schools are willing to teach new concepts but often have limited resources available. Our aim is to meet this need: we have developed a cross-curricular programme about animal locomotion with the aim of broadening both young people's vision and skill set. Students learn about programming using microprocessors, animal biology and movement, and the relevance of bioinspired robotics. The programme is taught in a stimulating zoological museum environment, and targets pupils from widening participation backgrounds as a means of inspiring students to study STEM subjects at university level.

Methods

To date, we have run a pilot programme in which six secondary schools participated. We ran two continuing professional development (CPD) sessions for teachers who were able to meet our team, learn about the project, get first-hand experience using the robotic kits, and arrange dates for the students to visit the university campus. The school pupils visited the Grant Museum of Zoology at UCL with their teachers for an Animal Locomotion Workshop where they learned about animal movement using museum objects, handled 3D printed snake vertebrae and discussed the use of robots. Back at school, the teachers with the help of UCL students, helped the pupils learn about coding using the developed caterpillar robots based on the BBC microbit.

Results & Discussion

Over the last six months our team of academics, museum professionals and students have worked with 212 pupils (144 pupils in Key Stage 3, 68 pupils in 6th Form) from six secondary schools pupils in the boroughs of Hackney, Newham, Tower Hamlets and Waltham Forest in London. We have developed and delivered a series of successful Animal Movement Workshops in the UCL Grant Museum of Zoology along with teaching materials to inspire the next generation of scientists and engineers to continue their education in STEM subjects. Based on the feedback we have received, we are looking at different ways to make the workshop more inclusive, improve teaching resources and strengthen our evaluation.

Conclusion

By working together, professionals from different fields including biology, computer science, biomechanics and engineering have developed a highly engaging and rewarding interdisciplinary teaching programme. The schools we have worked with have benefitted from keeping the robotics kit on loan for an extended period (1 term) and our current undergraduate students have played an essential role by acting as ambassadors and role models of support.

Acknowledgments

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Teaching Biomedical Engineering undergraduates how to keep a lab notebook

R.J. Yerworth¹, E. Hatten ¹, A. Vanhoostenberghe ^{2,1}

¹ Dept Medical Physics and Biomedical Engineering, University College London, London, WC1E 6BT. ² Aspire Centre for Rehabilitation Engineering and Assistive Technology, UCL, London, WC1E 6BT.

Introduction

Keeping a lab book is a key skill for biomedical engineers, but teaching on this is often inadequate^[1]. We have tried giving extensive personal feedback, and like others, have found this very time consuming^[2]. This year we trialled a method inspired by a driving instructor's competency chart; combining aspects of rubric and 'live marking'^[3].

Methods

Thirteen key aspects of good lab notebook keeping were identified by the authors, in consultation with colleagues. Each student was given an A4 sheet to stick at the front of their lab book. On one side was a list of the topics with an explanatory sentence for each, and on the other a grid, one row per topic, one column per lab session. During each lab session 2-3 topics were selected and a facilitator inspected each lab notebook, making brief verbal comments, relating to the selected topic (e.g. "clear methods section but you need to write down what you observed, not just the numbers on the oscilloscope"), and scoring that element from 0 (unsatisfactory) to 3 (best practice) in a dated column of the table. Lab notebooks will be collected at the end of the year and compared with those from the previous year.

Lab book keeping					
	04/09/17	11/09/17	18/09/17	25/09/17	02/10/17
Checked on:					
Date	3	3			
Title/aim	2	3			
Strategy/Action plan	0	1	2		
Method		2	2	3	
setup diagrams	3	2	3		

Figure 1 Example of part of completed lab grid

Results & Discussion

Students responded well to the lab grids, and productive conversations were had during the live marking. The load on staff was much less than offline marking of lab books. It proved difficult for a facilitator to get round all the students (~20) in one session, but it was easy to spot which students were not improving and focus more time on them.

Conclusion

Observations show that the method enabled constructive feedback to be given in a timely manner, and shows more promise than other methods tried. It will be used again, with minor refinements, next year.

References

1. Stanley JT, Lewandowski HJ. *Physical Review Physics Education Research*, 2016; 12.
2. Fernandez M *et al.* 7th International Technology, Education and Development Conference (INTED2013). INTED Proceedings, Valencia, SPAIN; 2013:231-238.
3. Hance J *et al.* *European Journal of Cardio-Thoracic Surgery*, 2005; 28: 157-162

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Introducing Innovation Practices to Medical Engineering Students

M.J. Raxworthy^{1,2}

¹Institute of Medical and Biological Engineering, University of Leeds, Leeds LS2 9JT; ²Neotherix Ltd, Hiscox Building, Peasholme Green, York YO1 7PR.

Introduction

We describe work undertaken at the University of Leeds under the Royal Academy of Engineering (RAEng) Visiting Professors scheme to introduce training in innovation practices and translation¹ to medical engineering students. This is consistent with RAEng's stated aim to embed innovation practices in industry and academia².

Methods

We assessed the interest in acquiring skills in innovation and translation through short taster sessions to which engineering students of all levels and subject entry points were invited. Working in small teams, students were required to use brainstorming for idea generation, and idea grouping, ranking and selection.

We used the experience gained to design a "full-line", medical technology (MedTech)-specific innovation and translation module. This became MedTech BEST (Business and Entrepreneurial Skills Training) and provides training on taking research into the marketplace using the Technology Readiness Level model to manage the stages of the new product development process. Students were given the task to develop a MedTech product concept to solve a verified clinical need. Although hypothetical this had to be plausible and grounded in real science to address a real market. Teams first needed to generate ideas for a technology and select their lead idea(s) to take forward. They also needed to "build" a company formed to commercialise their product. Teams received training in building a business and technology case around their idea – elements of this were delivered by external MedTech sector specialists from industry and the supply/support chain. Eight sessions were held over the course of the academic year.

Results & Discussion

Nearly 50 students were involved in MedTech BEST in the past two years. Participants gained a thorough understanding of the new product development process, value proposition and the role of innovation in addressing market and customer needs and had the opportunity to build a compelling business case. Students were encouraged to seek and respond to feedback (peers, experienced mentors, course leaders, external sector experts) to improve their final proposal. Teams pitched against each other to win the award for the development of the best MedTech product and investment opportunity (supported by a business plan) for each year's competition.

Conclusion

Exposure and acquisition of the skills outlined will be of direct value to students considering entry into the world of MedTech start-ups. MedTech BEST was demonstrated to be an effective means of introducing innovation practices and an awareness of the challenges in identifying, developing and introducing new product opportunities to medical engineering students.

References

1. Meyer M, Glod F. "Transferring Technology from Bench to Bedside: Practices, Barriers, Policies," <https://hal-mines-paristech.archives-ouvertes.fr/hal-00676638> 2011.
2. Royal Academy of Engineering, "Educating engineers to drive the innovation economy," Royal Academy of Engineering. ISBN 1-903496-64-0. April 2012.

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Thank you for attending BioMedEng18

We look forward to seeing you at
BioMedEng19

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