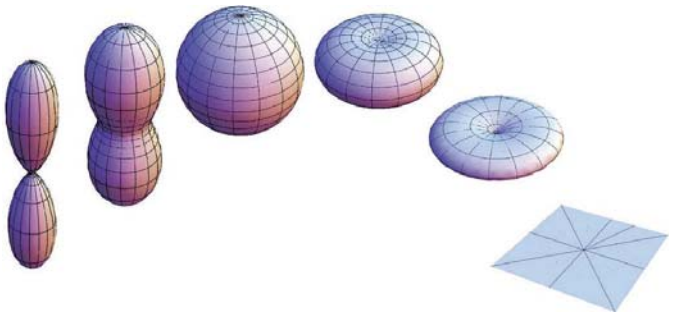
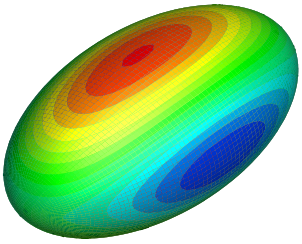
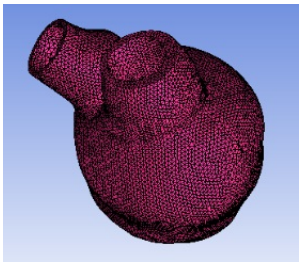
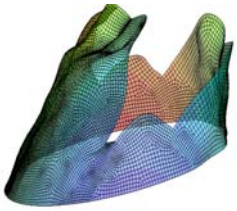
University of Glasgow









Workshop on Soft Tissue Modelling

March 14-16, 2012, Glasgow, UK

Organising Committee:

Xiaoyu Luo

Wenguang Li

Nicholas Hill

School of Mathematics and Statistics

University of Glasgow

Glasgow, G12 8QW

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Welcome

Welcome to Glasgow and to the Soft Tissue Modelling Workshop. One of the greatest challenges in mechanical modelling is to extend its success to fields outside traditional engineering, in particular to biology, biomedical sciences, and medicine. This workshop will provide an opportunity for modelling specialists and medical experts to present and exchange opinions on current developments and challenges in the field of soft tissue modelling, with particular applications (though not exclusively) to human biliary and circulation systems.

Funding:

The workshop is part of a joint project between the University of Glasgow and the University of Sheffield funded by the EPSRC (Grant no. EP/G015651 and EP/G028257). Additional sponsorships are kindly provided by the Glasgow Mathematical Journal Trust Fund, the Centre of Mathematics Applied to the Life Sciences (CMALS), and the Simpleware Ltd.

Acknowledgement:

We thank Susan Chrisie, Dawn Cunningham, and Beverley Dixon for their secretarial assistance. We also thank Nicholas MacDonald for help to setting up the workshop website: www.gla.ac.uk/schools/mathematicsstatistics/softtissuemodelling.

Lunches, reception and the workshop dinner:

Tea/coffee/lunches, posters the cheese and wine session, will be in the Level 5 Meeting Room where the workshop is held. The Workshop Dinner on 15 March will be at The Brasserie, Òran Mór, Junction of Byres Road and the Great Western Road, opposite to the Hilton Grosvenor Hotel, which is just 3 minutes walk up the Byres Road from the venue.

Computers and internet:

There is a free wireless internet at the venue via eduroam (www.eduroam.org). You should use your existing eduroam account automatically. Some of you (if requested) may use the temporary guest accounts that our IT support have set up for you (maths-stats-itsupport@gla.ac.uk). If you don't have your own laptop, we have a School laptop which you can use to check your email. Please ask at the helpdesk.

Programme

(All talks incl. 5 min question/transition time)

Wednesday 14 March

9.00-9.50 Registration

9.55-10.00 Workshop opening - Prof. Xiaoyu Luo

Morning Session-1 Chair: Prof. Nicholas Hill

10.00-11.00 Prof. Raymond Ogden, FRS "A constitutive model for F-actin and other networks"

11.00-11.30 Coffee break

Morning Session-2 Chair: Prof. Rene De Borst

11.30-12.00 Dr. James Going "Understanding tissues: two dimensions are not enough"

12.00-12.30 Dr. Xavier Pelorson " Fluid-structure interactions in the larynx during phonation"

12.30-1.00: **Dr. Paul Watton** "Modelling Evolution of Vascular Disease"

1.00-2.00 Lunch

Afternoon Session-1 Chair: Prof. Francesco Migliavacca

2.00-2.30 Prof. Bingmei Fu "Transport of nanoparticles across the blood-brain barrier"

2.30-2.50 Dr. Hao Gao "Structure-based finite strain modelling of human left ventricle in diastole"

2.50-3.10 Dr Ross Cotton "Image-based meshing and modelling of soft tissues"

3.10-3.40 Coffee break

Afternoon Session-2 Chair: Prof. Boyce Griffith

3.40-4.00 Prof. Godfrey Smith "The electrophysiological basis of the electrocardiograph"

4.00-4.20 Mr. Julien Vignollet "A biphasic swelling model of the intervertebral disc "

4.20-4.40 Prof. Nicholas Hill " Mathematical and numerical modelling of aortic dissection"

Poster-session Chair: Prof. Bingmei Fu

4.40-6.30 Poster-presentations/poster session, cheese and wine reception (All poster presenters will give a 2-min introduction)

Thursday 15 March

Morning Session-1 Chair: Prof. Gerhard Holzapfel

9.00-9.30 Prof. Francesco Migliavacca "Stenting in Coronary Bifurcations: From Solid Mechanics to Drug Transport"

9.30-9.50 Dr. Yufei Zhu "Nonlinear large deformation of a thick-walled tube"

9.50-10.10 Dr. Nigel Bird "Physiology and Pharmacology of Human Gallbladder Muscle"

10.10-10.40 Coffee break

Morning Session-2 Chair: Dr. Nigel Bird

10.40-11.10 Dr. Donghua Liao "Mechanical modelling analysis in gastrointestinal tract: from in vitro to in vivo"

11.10-11.30 Dr. Ali Majeed " Hypochondriacs"

11.30-11.50 Mrs. Anne Smyth "Pain Characteristics in Acalculous Gallbladder Disease"

12.00-1.00 Lunch

12.30-1.00 Optional Antonine Wall and Hunterian Museum Tour (Free)

1.00-1.30 Optional Campus tour (Free, weather permitting)

Afternoon Session-1 Chair: Prof. Donghua Liao

2.00-2.20 Prof. Xiaoyu Luo "Modelling gallbladder pain and inverse identification of gallbladder tissue properties"

2.20-2.40 Mr. Jonathan E. Hiorns "Active and passive forcing of an asthmatic airway"

2.40-3.00 Dr. Tiina Roose "Capillaries in Tumours"

3.00-3.30 Coffee break

Afternoon Session-2 Chair: Prof. Chris Pearce

3.30-4.00 Prof. Rene De Borst "A multiscale approach to fracture in porous media"

4.00-4.20 Dr. Simon Pearce "Bifurcation of elastic tubes as a simple model for aneurysm formation"

4.20-4.40 Dr. Devinder Singh Pathania "Biomechanical analysis of the aortic root: Initial experience with single- and multi-layered models"

7pm Workshop Dinner at The Brasserie, Òran Mór, Junction of Byres Road and the Great Western Road.

Friday 16 March

Morning Session-1 Chair: Prof. Godfrey Smith

9.00-9.30 Prof. Boyce Griffith "Cardiac fluid-structure and electro-mechanical interaction"

9.30-9.50 Miss Joyce Ma "Modelling mitral valve using the immersed boundary methods"

9.50-10.10 Dr Simone Rossi "An Orthotropic Active Strain Formulation in Cardiac Biomechanics"

10.10-10.30 Prof. Colin Berry "Role of MRI for modelling the human heart"

10.30-11.00 Coffee break

Morning Session-2 Chair: Prof. Raymond Ogden, FRS

11.00-12.00 Prof. Gerhard Holzapfel "Aortic Dissection: a Mixed Numerical/Experimental Technique"

12.00-1.00 Workshop Close and Lunch

Abstracts

(In alphabet order using the first author's surnames)

An evolving role for cardiac MRI: potential clinical utility of computed heart modelling

Colin Berry

Institute of Cardiovascular and Medical Sciences
University of Glasgow, UK

Heart disease leads to reductions in exercise capacity, quality of life and longevity. Cardiac imaging has a crucial role for diagnosis and risk assessment since imaging the heart can provide information on structure, function and scar, and all of this information can be important for treatment.

Cardiac magnetic resonance imaging (CMR) represents the gold standard clinical method for imaging the heart. Although echocardiography is cheaper and easier to perform, the information provided by CMR is much more reproducible. Furthermore, unlike computed tomography, CMR does not involve ionising radiation and so can be serially repeated.
A single CMR study involves serial image scans which are usually viewed separately. Computed heart modelling of CMR data has potential to create patient-specific heart models, which could facilitate and enhance the diagnostic and clinical utility of CMR in clinical practice. Computed modelling has potential value as a research tool in a wide range of areas including basic cardiac pathophysiology, biomechanics and drug development.

Physiology and pharmacology of human gallbladder muscle

Nigel Bird, Anne Smythe and Ali Majeed

Liver Research Group, Sheffield University, Sheffield, England

Abstract

The gallbladder is a pear-shaped organ attached to the underside of the liver, in the groove separating the right and left sides. It is responsible for collecting, storing, concentrating and expelling bile into the digestive tract. In the UK today about 10% of adults have gallstones, but most have no symptoms and it is generally agreed that these people should not be operated on, despite the fact that many will go on to develop symptoms eventually. The commonest symptom of gallbladder dysfunction is pain in the right upper quadrant of the abdomen. This can vary in its severity, duration and causative triggers. The commonest clinical association of this pain is with gallbladder stones and the currently prevailing theory (and one that makes most sense) is that a gallstone obstructs the neck of the gallbladder, which responds by a strong contraction, which is perceived as pain. Studies examining the relief of symptoms after gallbladder removal suggest that approximately one quarter of patients undergoing surgery will not experience relief of symptoms, with descriptive studies indicating that dyspeptic symptoms are least likely to be cured by cholecystectomy. In addition to this, there is a significant minority of patients who have typical symptoms of gallstones disease without having gallstones; these patients represent the most difficult group to treat.

Our research is focussed on defining more clearly the nature of gallbladder contraction, in an attempt to understand the origin of gallbladder pain and how gallstones form. We have used strips of tissue cut from the wall of gallbladders removed at operation to measure the rate and strength of contraction of the muscle after stimulation with various agents.

Image-based meshing and modelling of soft tissues

Ross Cotton

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There has been increasing interest in the generation of models appropriate for computational modelling from imaging modalities such as MRI and CT. Although a wide range of mesh generation techniques are available, these on the whole have not been developed for meshing from 3D imaging data. The paper will focus on techniques specific to image-based meshing, and will also discuss new tools improving the interface with commercial CAD, FEA and CFD packages. A number of examples that cover different applications within soft tissue applications will be presented.

The 'image-based approach' presented by the authors are tailored to meshing from 3D imaging data, and do not decouple the surface creation from the volume meshing stage. Meshes can be generated automatically and exhibit image-based accuracy with domain boundaries of the finite element model lying exactly on the iso-surfaces, taking into account partial volume effects and providing sub-voxel accuracy. The presented technique is also topology and volume preserving, avoiding loss or gain of volume. In addition tools are also available to optimise the refinement of the mesh. This can be either automatically to features or by setting user defined zones.

A multiscale approach to fracture in porous media

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In this contribution, we will develop a general numerical model for flow in progressively fracturing porous media, with applications ranging from cracking in the intervertebral disc to hydraulic fracturing. The theory includes flow inside stationary and propagating cracks. The flow inside the evolving crack can be in the tangential direction. This is achieved by a priori adopting a two-scale approach. At the fine scale the flow in the cavity created by the (possibly cohesive) crack is modelled using a sub-grid scale model. Since the cross-sectional dimension of the cavity is small compared to its length, the flow equations can be averaged over the width of the cavity. The resulting equations provide the momentum and mass couplings to the standard equations for a porous medium, which are assumed to hold on the macroscopic scale. The two-scale model which ensues, imposes some requirements on the interpolation of the displacement and pressure fields near the discontinuity. The displacement field must be discontinuous across the cavity. Furthermore, the micro-mechanics of the flow within the cavity require that the flow normal to the cavity is discontinuous, and in conformity with Darcy's relation which is assumed to hold for the surrounding porous medium, the normal derivative of the fluid pressure field must also be discontinuous from one face of the cavity to the other. For arbitrary discretizations, these requirements can be satisfied by exploiting the partition-of-unity property of finite element shape functions.

To provide a proper setting, we will first briefly recapitulate the governing equations for a deforming porous medium under quasi-static loading conditions. The strong as well as the weak formulations will be considered, since the latter formulation is crucial for incorporating the micro-mechanical flow model properly. This micro-mechanical flow model will be treated next, and it will be shown how the momentum and mass couplings of the micro-mechanical flow model to the surrounding porous medium can be accomplished in the weak formulation. Time integration and consistent linearization of the resulting equations, which are non-linear due to the coupling terms and because of the cohesive crack model, complete the numerical model. Example calculations are given of a body with stationary cohesionless cracks and with a propagating cohesive crack.

Left ventricle strain and its pattern estimated from cine MRI: validation with DENSE

Hao Gao[1], Andrew Allan[1], Christie McComb[1], Xiaoyu Luo[2], Colin Berry[1]

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2. School of Mathematics and Statistics, University of Glasgow, Glasgow, UK, G12 8QW

Myocardial strain, or deformation is tightly linked with contractility and measurement of local strain provides insight into the biomechanical significance of viable myocardium. We sought to estimate myocardial strain from cine magnetic resonance imaging (MRI) by using deformable image registration method, and validated with in-vivo measurement from displacement encoding with stimulated-echo (DENSE) MRI on both healthy volunteers and patients with acute/chronic myocardial infarction (MI).

Methods: 3 healthy volunteers and 41 patients with either acute or chronic MI were studied at 1.5 Tesla with both cine and DENSE MRI. Regional circumferential and radial myocardial strains were estimated from cine and DENSE MRI. Myocardial strain and its patterns were compared.

In all healthy volunteers, the regional cine MRI estimated circumferential and radial strains are significantly correlated to those from DENSE ($p<0.05$). There is no difference for peak circumferential strain (-0.18±0.04 vs. -0.18±0.03, $p<0.05$) between cine and DENSE, however it overestimates peak radial strain from cine MRI (0.84±0.37 vs. 0.49±0.2). In the patient study, the peak strain patterns predicted by cine MRI are similar as the patterns from DENSE MRI analysis, including the strain evolution related to recovery time, strain patterns related to MI scar extent.

The circumferential and radial myocardial strains estimated from cine MRI are comparable to the values from DENSE for both healthy volunteers and patients with MI, and able to characterize different strain patterns in MI and non-MI regions as DENSE, demonstrating that useful strain information could be obtained from routine MRI to differentiate myocardial functional abnormalities for better diagnosis, management and treatment of heart disease.

The electrophysiological basis of the electrocardiograph

Godfrey Smith

Institute of Cardiovascular and Medical Sciences
University of Glasgow, UK

The ECG is a well established method of non-invasively assessing the electrical behaviour of the heart. Despite approximately 100 years of research, there are still questions over the electrical basis of some aspects of the ECG signal. This talk will describe new experimental data obtained with novel optical techniques that aims to quantify the timing of electrical events within the muscle of the heart.

Understanding tissues: two dimensions are not enough

James Going
Institute of Cancer Sciences, University of Glasgow, UK

Histology *sensu lato* is the scientific study of living tissues. A narrower meaning is the study of tissues in two dimensional sections, often after fixation in formaldehyde and embedding in paraffin wax. Although informative, 2D sections have limitations which serious students have sought to overcome. The development of microtomy by Wilhelm His, Jr was motivated by his desire to study embryos in 3D at different points in their development.

Three dimensional reconstruction from 2D section data remains difficult. Unlike CT, MRI or confocal microscopy image sequences, histological sections are not inherently aligned, and require rotation and translation, as a minimum, to register them. Often, section deformations must also be allowed for. Confocal microscopy avoids these problems only for small tissue volumes. Sequential imaging of cut surfaces, as in episcopic microscopy or in 'visible human' projects overcomes the registration problem, at the cost of tissue destruction. Between these scales an 'imaging gap' is troublesome. Optical projection tomography partly fills this gap, up to a maximum object diameter of about 15mm.

A tissue requiring multiscale 3D visualisation to understand its development, physiological organisation and susceptibility to disease is human breast, which begins during fetal life as a primary ectodermal bud from which multiple duct progenitors ramify into surrounding connective tissue. Full development in women following puberty establishes a complex organ with ~15-30 independent duct trees (lobes) each ramifying from its own central duct in the nipple. The smallest rami terminate in thousands of milk-secreting glandules. Ducts and glandules are lined by the epithelium in which breast cancer usually evolves over a long period prior to becoming fully malignant. Lobes are fields of epithelium at risk and their structure must be understood if one is to understand breast pre-cancer, and has diagnostic and therapeutic possibilities.

Data illustrating studies of the 3D anatomy of human breast will be presented.

Cardiac fluid-structure and electro-mechanical interaction

B. E. Griffith

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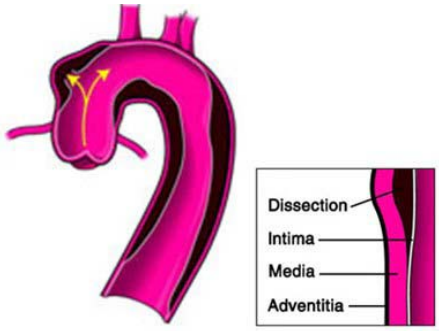
350 First Avenue, 10016 New York, USA

The heart is a coupled electro-fluid-mechanical system. The contractions of the cardiac muscle are stimulated and coordinated by the electrophysiology of the heart; in turn, these contractions affect the electrical function of the heart by altering the macroscopic conductivity of the tissue and by influencing stretch-activated transmembrane ion channels. To develop a unified approach to modeling cardiac electromechanics, we have extended the immersed boundary (IB) method for fluid-structure interaction, which was originally introduced to model cardiac mechanics, to describe cardiac electrophysiology. The IB method for fluid-structure interaction uses Lagrangian variables to describe the elasticity of the structure, and uses Eulerian variables to describe the fluid. Coupling between Lagrangian and Eulerian descriptions is mediated by integral transforms with Dirac delta function kernels. An analogous approach can be developed for the bidomain equations of cardiac electrophysiology. Quantities associated with the cell membrane, like the ion channel gating variables, are tracked along with the intracellular variables in Lagrangian form. Employing an Eulerian description of the extracellular space, on the other hand, makes it straightforward to extend that space beyond the myocardium, into the blood and into the extracardiac tissue, both of which are electrically conducting media that couple directly to the extracellular space of the myocardium. In the electrophysiological immersed method, interaction between Lagrangian and Eulerian variables happens in a manner that is completely analogous to the corresponding coupling between Lagrangian and Eulerian variables in the conventional IB method for fluid-structure interaction.

Mathematical Modelling of Aortic Dissection

NA Hill, S Roper, XY Luo, B Li, & L Wang

School of Mathematics & Statistics, University of Glasgow, 15 University Gardens, Glasgow, G12 8QW, U.K.



Aortic dissection is a tear that occurs in the aortic wall, where high pressure penetrates the intima and enters the media layer, and blood enters the media at the point of the tear. The majority of aortic dissections originate with an intimal tear in the ascending aorta and/or aortic arch (65%). The risk of death is high in untreated aortic dissection, especially within the first 24 hours. Although aortic dissection is a frequently occurring phenomenon and a challenging clinical entity, the underlying biomechanics remains largely unclear. There are very few analytical and computational models in the literature that study dissection in human arterial layers from a mechanical point of view (a notable exception being [1]).

We model aortic dissection as a tear in the tissue using fracture mechanics concepts. In linear elastic fracture mechanics (LEFM), the behaviour of the stress and strain fields around a crack tip determines whether, and in which direction, a crack will propagate. Crack propagation can be modelled by considering the cohesive zone, which is a narrow band of vanishing thickness ahead of a crack tip, and is resisted by cohesive tractions. Asymptotic analysis near the tip gives useful information on the strain and stress fields, e.g. in LEFM asymptotic methods predict a square-root singularity in the behaviour of the stress field near the tip. However, in soft tissues, in which the deformations can be large and nonlinear effects are important, there is no similar universal behaviour.

We have studied the linear theory of a tear in a residually and pre-stressed Green elastic material with a realistic physiological strain energy function (see e.g. [2]). We use a cohesive zone approach to resolve the stress singularity at the tear in an axisymmetric fluid-filled arterial configuration. The elastic problem consists of first solving for the finitely deformed equilibrium configuration of an elastic tube and then examining the incremental equations with displacement discontinuities representing the presence of a tear. A hypersingular integral equation relates the crack opening to the traction on the crack faces, in which the kernel captures the geometry and boundary conditions on the elastic solid without the tear. For all but the simplest geometries and boundary conditions, the kernel is difficult to calculate analytically. We have made use of integral transforms, simplified crack geometries and asymptotic results. In particular we have formulated the integral equation for a finite-length axisymmetric crack parallel to the axis of an elastic tube. The equation can be inverted to find the tear opening given any distribution of traction on the crack faces. We have successfully applied this method to study the equilibrium configurations of axisymmetric crack parallel to the axis of an elastic tube. The equation can be inverted to find the tear opening given any distribution of traction on the crack faces. We have successfully applied this method to study the equilibrium configurations of

axisymmetric dissections, and derive conditions under which the tear will propagate. This work is complemented by finite-element numerical studies for large deformations.

Acknowledgement. LB and LW gratefully acknowledge funding from the Chinese Scholarship Council.

References

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Active and passive forcing of an asthmatic airway

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When asthmatics come in contact with agonists (e.g. cold air, chemicals or dust), the smooth muscle in the walls of their lung airways contracts, causing wheezing and other breathing difficulties. Over long periods there is also substantial thickening of the muscular airway wall. Mathematical modelling has significant potential to offer insights into the interactions between the signalling pathways that initiate smooth muscle contraction, the mechanical action of cross-bridges within smooth muscle that leads to contraction of the airway and surrounding tissue, and the longer-term impact of wall remodelling on airway function. Here we address some of the mechanical aspects of this problem by modelling an airway as a two-layer annulus in plane strain. The inner layer, representing the airway wall, is modelled as a nonlinear incompressible fibre-reinforced material. Huxley-Hai-Murphy theory is used to model cross-bridge mechanics, generating contractile forces along the fibres. The outer layer, representing the surrounding parenchyma, is modelled as a nonlinear compressible material. Airway deformations are also induced by imposing external stresses. The model reveals differences in patterns of deformation depending on whether inflation is driven by stresses on the inner or outer boundary (reflecting differences between artificial and natural ventilation). The model also shows significant stress gradients across thickened airway walls.

Aortic dissection: A mixed numerical/experimental technique

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An aortic dissection is a tear of the delicate intima of the aortic wall (inner layer) that spreads into the media (middle layer) or between the media and adventitia (outer layer). In addition to the original aortic channel for blood flow the dissection creates a new flow channel, the 'false' lumen that may cause the artery to narrow and even close off entirely. Simultaneously, the dissection may cause the formation of a thrombus from which fragments embolize. Aortic dissections frequently result from an intimal tear or from a perforation of the intima as, for example, caused by intramural hemorrhage and hematoma formation. Moreover, mechanical traumatization of the intima due to cannulation for catheter-based diagnostic and/or therapeutic interventions have been identified as initiating aortic dissections. These intimal defects can cause concentrations of mechanical stress of the pressurized aorta and may be the trigger for the propagation of the medial dissection.

In this short communication we provide an overview of aortic dissections [1]. We focus on the dissection properties of the media of human abdominal aortas in heath and disease [2,3] and focus particularly on the three-dimensional constitutive and numerical modeling of aortic dissection [4]. By using the finite element method, we analyze a few deformation modes such as the peeling test of a human media and the plaque fissuring and dissection of an atherosclerotic plaque such as is frequently observed in clinical practice.

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Modelling gallbladder pain and inverse identification of gallbladder tissue properties

Li WG[1], Luo XY[1], Hill NA[1], Ogden RW[2,1], Smythe A[3], Majeed AW[3] and Bird N[3]

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Parameter estimation of soft bio-tissues from non-invasive measurements has clinical significance in patient specific modelling and disease diagnoses. In this work, we present two different inverse approaches to estimate the elastic modulii of human gallbladder wall. One is a quasi-nonlinear method, in which the forward approach is built on a linear orthotropic material model and an inverse iteration is carried out to determine the elastic modulii in the circumferential and longitudinal directions between two successive ultrasound images of gallbladder. The other approach models the gallbladder with the nonlinear invariant-based anisotropic strain energy that has been used successfully in arteries (Holzapfel et al. 2000), and tracks the material parameters inversely in the least-square sense. The first approach is fast and stable, but suffers from the linear assumption. The second approach is theoretically sound and has been validated against published arterial work. However, it is time consuming and can be difficult to get converged solutions. The results demonstrate that human gallbladder behaves in an anisotropic manner, and should be modelled with appropriate constitutive models. The elastic modulii estimated are also nonlinear and patient-dependent. Importantly, the peak stress predicted here changes from the earlier estimation using a linear membrane theory (Li et al. 2011a). As the peak stress inside the gallbladder wall has been found to strongly correlate to acalculous gallbladder pain (Li et al. 2011a; Li et al. 2011b), reliable mechanical modelling for the gallbladder tissue is crucial if this information is to be used in clinical diagnosis.

Acknowledgments

The project has been supported by EPSRC through the grants of EP/G015651 and EP/G028257.

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Mechanical modelling analysis in gastrointestinal tract: from *in vitro* to *in vivo*

Donghua Liao[1,2], **Jingbo Zhao**[1,2], **Hans Gregersen**[3]

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The major motor function of the gastrointestinal (GI) tract is to move and absorb the luminal contents. This function is facilitated by changes in the geometry of the GI wall and lumen. Associations between GI mechanical remodelling and disease development have been observed in diseases such as diabetes mellitus, partial intestinal obstruction, and systemic sclerosis. Therefore, the biomechanical properties of the GI tract are important determinants of flow, the stress distribution in the wall, and the remodelling process of the wall under physical environment change. The majority of the research done on estimating mechanical parameters in the GI tract has been done *in vitro* on animals and cadavers. However, assessing the disease or treatment caused tissue remodelling *in vivo* is considerable important for diagnostics and treatment. Exploration of the human body has dramatically improved by the introduction of medical imaging modalities such as Magnetic Resonance Imaging (MRI), ultrasonography and the functional luminal imaging probe (FLIP) system. These techniques have revolutionised the way in which many conditions are diagnosed and treated. The ability to examine in detail structures inside the body, without resorting to surgery, has allowed clinicians to diagnose disease at an early stage. This allows the planning of interventional procedures with a minimum of risk to the patient. In order to continue this exploration, it will be necessary to complement the traditional approach with an integrative approach.
The aim of this review is to describe the biomechanical remodelling by diseases in the GI tract, the imaging techniques based human GI tract simulation models, and new analytic methods and medical devices based *in vivo* tissue remodelling assessment. This will combine observations, theories and predictions across the temporal and dimensional scales, across the scientific disciplines, and across the anatomical subsystems.

Modelling and simulation of a healthy human mitral valve from in-vivo MRI

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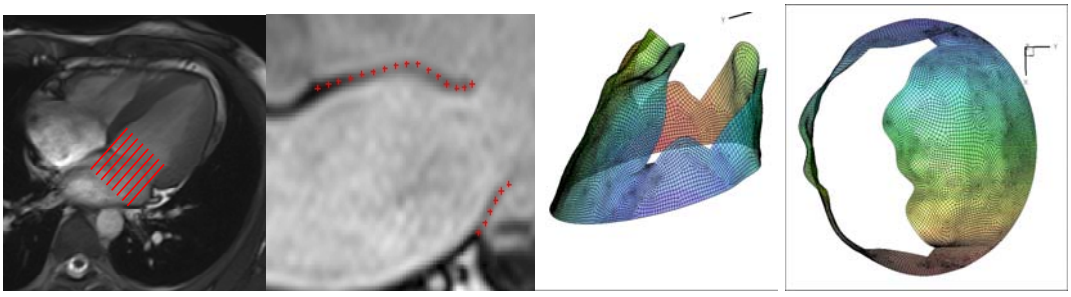
The mitral valve (MV) has pivotal importance for normal heart function. The MV consists of a large antero-medial leaflet and a smaller postero-lateral leaflet, which are both connected to the left ventricular papillary muscles via multiple fibrous chordae tendinae [1]. Computer simulation can provide an efficient means for studying and providing detailed spatial and temporal data that may not be easily obtained experimentally. However, computerised reconstruction of the MV in vivo is challenging because the leaflets and tendinae are small and highly mobile, their overall geometry is complex, and the imaging methods that are available clinically have technical constraints in terms of temporal and/or spatial resolution. Therefore, the objective of our study is to develop an in-vivo human MV model from magnetic resonance imaging (MRI) data, which is a non-invasive. MRI data will be used to simulate interactions between flowing blood and the MV leaflets by using immersed boundary method (IB)[2].

High resolution anatomical imaging was performed on a healthy 28-year-old volunteer using a 3T MRI system (Siemens). A stack of MR images (3-mm slice thickness) were obtained in an apical long-axis 2-chamber view to cover the entire mitral valve, as shown in Figure 1(a). The annulus of the model has been assumed as a circular orifice, and the radius is the mean measurement obtained from 4-Chamber and 2-Chamber views.



(a) (b) (c) (d)

Figure 1, (a), (b): MR images of in-vivo MV; (c), (d) reconstructed MV model

Manual segmentation of the MV was performed on a slice-by-slice basis. An in-house MATLAB program was written to read the coordinates of segmentation landmarks from each slice. Spline curves were used to interpolate the MV as shown in Figure 1(b). The manually segmented MV boundaries were assembled together along the circular annulus, and imported into CUBIT Tool suite for reconstructing the in-vivo 3D MV model and meshing.
Using the Immersed Method(IB) method, we have simulated the dynamics of the MV under realistic left-atrium pressure loading. The results are compared to clinic measurements on patient.

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Effect of Bending Rigidity in a Dynamic Model of a Polyurethane Prosthetic Mitral Valve

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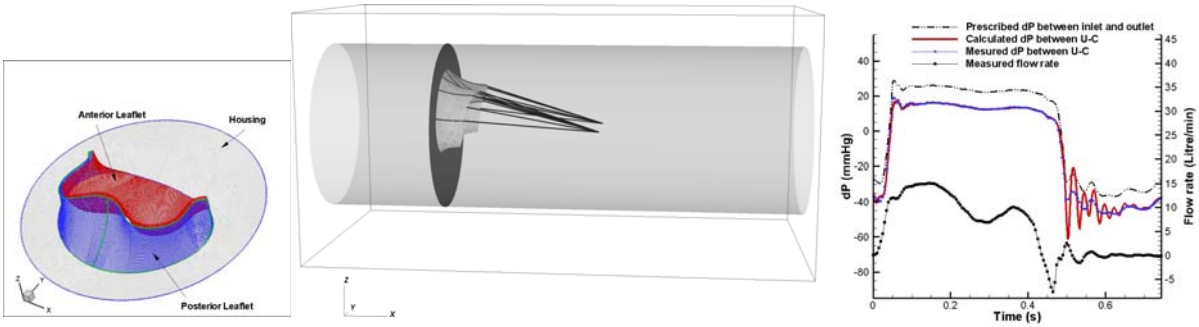
We investigate the behaviour of a dynamic fluid-structure interaction model of a chorded polyurethane mitral valve prosthesis, focusing on the effects on valve dynamics of including descriptions of the bending stiffness of the valve leaflets and artificial chordae tendineae. Each of the chordae is attached at one end to the valve annulus, and at the other to one of two chordal attachment points. These attachment points correspond to the positions where the chords of the real prosthesis would attach to the left-ventricular wall, although in the present study, these attachment points are kept fixed in space to facilitate comparison between our simulations and earlier results obtained from an experimental test rig.

The mitral valve prosthesis that we model is the same as that considered by Watton et al. (Watton et al. 2007; Watton et al. 2008) and by Griffith et al. (2009), and is shown in Figure (a). The mitral valve and the housing disc are mounted in a semi-rigid circular tube as shown in Figure (b). These structures are embedded in a $16\ \text{cm} \times 8\ \text{cm} \times 8\ \text{cm}$ fluid box. In our simulations, a pressure gradient measured in this experimental rig drives flow through the model valve during diastole, and provides a realistic pressure load during systole. The pressure drop is estimated from experimental measurement as shown in Figure (c).

In previous modelling studies of this valve prosthesis, the valve presents an unrealistically large orifice at beginning of diastole, and does not close completely at the end of diastole. We show that including a description of the chordal bending stiffness enables the model valve to close properly at the end of the diastole. In addition, valve over-opening is eliminated only by incorporating a description of the bending stiffnesses of the valve leaflets into the model. Thus, bending stiffness plays a significant role in the dynamic behaviour of the polyurethane mitral valve prosthesis.



(a) (b) (c)

Figure1 (a)The mitral valve mesh; (b)The mitral valve and the housing disc, mounted in a semi-rigid circular tube; (c) The pressure gradient determined in experiments.

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Capillaries in Tumors

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Capillaries in tumours are often severely buckled (in a plane perpendicular to the axis) and/or chaotic in their direction. We develop a model of these phe- nomena using nonlinear solid mechanics. Our model focuses on the immediate surrounding of a capillary. The vessel and surrounding tissue are modeled as concentric annuli. The growth is dependent on the concentration of a nutrient (oxygen) diffusing from the vessel into the tumor interstitium. The stress is modeled using a multiplicative decomposition of the deformation gradient F = FeFg. The stress is determined by substituting the elastic deformation gradient Fe (which gives the deformation gradient from the hypothetical configuration to the current configuration) into a hyperelastic constitutive model as per classical solid mechanics. We use a Blatz-Ko model, parameterised using uniaxial compression experiments. We use the entire system is in quasi-static equilibrium, with the divergence of the stress tensor equal to zero. We determine the onset of buckling using a linear stability analysis. We then investigate the postbuckling behaviour by introducing higher order perturbations in the deformation and growth before using the Fredholm Alternative to obtain the magnitude of the buckle. Our results demonstrate that the growth-induced stresses are sufficient for the capillary to buckle in the absence of external loading and/or constraints. Planar buckling usually occurs after 2–5 times the cellular proliferation timescale. Buckles with axial variation almost always go unstable after planar buckles. Buckles of fine wavelength are initially preferred by the system, but over time buckles of large wavelength become energetically more favourable. The tumoural hoop stress $T_{\Theta\Theta}$ is the most invariant(Eulerian) variable at the time of buckling: it is typically of the order of the tumoural Young's Modulus when this occurs.

Hypochondrium

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When the hypochondrium was considered to be the seat of melancholy. Patients with gallbladder disease usually present with pain in the right upper quadrant. Symptomatic cholelithiasis is the commonest indication for cholecystectomy. Unfortunately the symptomatology of gallbladder stone disease has been hard to define despite research spanning decades. The mechanisms of pain production in the gallbladder are unknown. The current explanation of pain arising from the gallbladder is a contraction of the fundus of the gallbladder against a physical or functional obstruction. Functional obstruction is also called 'acalculous' gallbladder disease because the symptoms are identical to patients with gallstones. Cholecystectomy will cure a proportion of patients but patient selection is extremely important to prevent unnecessary surgery. Currently there are no tests that will allow patient selection and the aim of the current research is to develop a predictive tool which will allow us to treat only those patients who have the best chance of a good symptomatic outcome.

Stenting in coronary bifurcations: from solid mechanics to drug transport

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Despite their success, stenting procedures are still associated to some clinical problems like sub-acute thrombosis and in-stent restenosis that seem to be related to a combination of both structural and hemodynamic factors. Numerical models have been widely used to investigate the biomechanical aspects of stenting procedures but always analyzing the phenomenon from a purely structural, fluid dynamic or mass transport point of view. In this presentation the combination of structural, fluid dynamic and mass transport models is outlined by using the realistic geometrical configurations of coronary bifurcation obtained through structural simulations as a fluid domain for the fluid dynamic analyses. This process leads to a more realistic estimate of the local blood flow pattern and drug release and a more accurate investigation of the hemodynamic forces acting on a stented bifurcation.

A constitutive model for F-actin and other networks

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In this talk we aim to develop a constitutive model, based on continuum mechanics, of cross-linked biopolymer networks, such as F-actin, in terms of the mechanical properties of its constituent filaments, their concentration, and the influence of cross-linking proteins (actin binding proteins) and their concentration. First, we review briefly the experimental methods that are used to determine the force extension behaviour of individual biopolymer filaments, and then discuss some of the models that are used in the literature to exhibit this response. We then consider the formation of a network of such filaments that involves cross-linking to form a solid or gel-like material. The nonlinear theory of the elasticity of fibrous materials is then used to model the overall elastic behaviour of the network and the theory is illustrated by considering, in particular, a simple shear test. We how the 'negative normal stress' evident in such networks when subject to simple shear tests can be predicted. This is the opposite of the 'positive normal stress' which is known in rubberlike materials and some other polymeric materials.

A biphasic swelling model of the intervertebral disc

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A biphasic swelling model, inspired by Ehler's work [2], has been derived using mixture theory for soft, hydrated and charged tissues in order to capture all the salient characteristics of the behaviour of the disc. The model fully couples the solid matrix under finite deformations with the ionised interstitial fluid. The nucleus is assumed to behave isotropically while the effects of the collagen fibres in the annulus fibrosus are accounted for with a transversely isotropic model [1].
The electro-chemical response, resulting from the presence of the fixed negative charges of the proteoglycans, is modelled under the simplifying Lanir hypothesis [3], which allows a constitutive relationship between the osmotic effects and the volume change of the mixture.

Initial studies have focussed on one-dimensional simulations and the results have been compared to experimental data [5] with good agreement. However, the numerical solution of the three dimensional problem exhibits numerical instabilities, manifesting in the form of non-physical oscillations in the pressure field near boundaries, when loads and free-draining boundary conditions are simultaneously applied. As an alternative to considerable mesh refinement, these spurious instabilities have been extensively addressed in the context of Biot's poro-elasticity using various stabilization techniques. The current work proposes to stabilize the pressure oscillations in the context of the theory of porous media, using a Galerkin Least-Square (GLS) formulation based on [4], which has been extended for finite deformations. The performance and robustness of the GLS framework are demonstrated on a 3D numerical example, modelling a charged soft tissue.

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Bifurcation of elastic tubes as a simple model for aneurysm formation

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When a thin-walled elastic cylinder is inflated by an internal pressure, an axisymmetric localised non-uniform deformation may occur, as may be seen during the inflation of modelling balloons. Modelling the cylinder as an isotropic hyperelastic membrane with a general strain-energy function, we derive conditions on the form of the strain-energy function to produce such a localised bulging or necking. In addition, a 'kinked' solution may also exist, where uniform sections of the tube with different radii are connected by non-uniform transition regions.

The choice of strain-energy function directly affects whether such solutions may exist, showing how the material behaviour is important in determining the response of the tube to the inflation. For instance the simplified one-parameter Gent strain-energy function, with parameter Jm representing the maximum possible value of the invariant J1 = I1-3, has bulged and kinked solutions only when Jm >18.231 for closed tubes, in a realistic range for rubber but not for human arteries. Such critical values of parameters in strain-energy functions for bifurcated solutions to exist, and the corresponding values of the pressure at the bifurcation point, are sensitive to the boundary conditions applied to the tube, imperfections in the tube thickness and how the pressure loading is controlled. We suggest that biological changes in the constitutive components of the artery, leading to changes in the overall stress-strain response, may allow aneurysms to form when they are not a permissible solution to a healthy artery undergoing the same pressure-driven deformation.

Fluid-structure interactions in the larynx during phonation

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The vocal folds are mechanically complex, elastic, structures located inside the larynx. After centuries of controversy, the production of voiced sounds, phonation, is now widely accepted as being the result of a non-linear interaction between an airflow coming from the lungs, the elastic vocal folds and some acoustical resonators (the oral or the nasal tract and the subglottal system). While the advances of signal processing derived methods have been spectacular during the last decades of the twentieth century, there is a growing interest in the physical modeling of the phonation process. The motivation for these studies is to increase our knowledge about the complex mechanisms involved during speech, to improve the quality of speech synthesis using physical models. Concerning voice pathology, physical modeling is intended to provide tools for analysis and diagnostic, for the prediction of surgery events or for the design of vocal folds prosthesis.

In this paper, we will review recent theoretical and experimental advances in the field. Some specific, but widely recognised as crucial, aspects will also be addressed, such as the influence of liquids on the surface of the vocal folds, anatomical anisotropy or asymmetry due, or not, to the presence of growth, from both the fluid mechanical and the biomechanical point of view.

An orthotropic active strain formulation in cardiac biomechanics

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Nonlinear hyperelastic models are needed to describe the complex structure of the cardiac tissue, which is recognized as orthotropic. In this context, the internal forces induced by $[Ca]^{2+}$ within the sarcomeres, the cell contractile units, may be modelled in different ways: active stress and active strain approaches can be used for the computation of the large deformations taking place during a contraction cycle. We found that in the case of linear isotropic materials and for small deformations, the active contraction shows similar behavior for both approaches. Anisotropic laws, though, give different results in terms of deformations and stresses and in particular the active strain shows milder anisotropic response. The active response of the tissue is usually derived from the ionic models considering the cycling of myosin cross-bridge that leads to sliding of myosin filaments relative to actin filaments. We describe this complex behavior with a simplified model to obtain the time evolution of the active strain. Active strain formulation have demonstrated to have important properties which are usually desired for the well-posedness of the problem and to be suitable for electromechanical simulations with isotropic and anisotropic materials.

Biomechanical analysis of the aortic root: Initial experience with single- and multi-layered models

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Construction of computational models describing the biomechanics of the aorta requires extensive knowledge of its mechanical and structural properties, which is often challenging to obtain. Consequently, various assumptions and approximations are made about these properties (Fung, 1993). Quite often, simplified models are constructed based on the constraints imposed by these assumptions. While these models may be qualitatively accurate, prediction of the development of aortic diseases and design of treatments require models that are also quantitatively precise. Relaxing the assumptions upon which the simplified models are based leads to more realistic models, but additional parameters are then required in the governing equations and consequently, the computational complexity of the model increases.

In this preliminary study, structural models of the aortic root and ascending aorta were developed and compared. These included a linearly elastic, mono-layer model and a hyperelastic, mono-layer model. While both models showed similar stress distributions, the elastic model had significantly larger deformations. Similarly, Gao (2006) developed two aortic arch models, one mono-layer, the other multi-layer. It was observed that the stress distribution in the mono-layer model was continuous, while the multi-layer model illustrated a discontinuous distribution between the layers. More specifically, the multi-layer model showed that the stress in the media was the highest.

It has been observed that the development of advanced, realistic models depends on the application of the model and the availability of appropriate structural and mechanical data. The models developed in this project will be used to evaluate an external aortic root support device designed specifically for patients with Marfan syndrome. For this purpose, quantitative accuracy will be important. Hence, careful selection of the structural model with an appropriate level of complexity and relevant mechanical properties is necessary.

Pain characteristics in acalculous gallbladder disease

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Acalculous biliary type pain (ABP) in the abdominal region is a common clinical problem, and its pathophysiology is unclear. Patients with ABP present with symptoms of typical pain due to gallstones but these are not visible on ultrasound or other scanning techniques. ABP has therefore been attributed to factors such as biliary dyskinesia, including sphincter of Oddi dysfunction, gallbladder dyskinesia and irritable bowel syndrome.

Investigations involving gallbladder emptying measurement, after stimulation with either a fatty meal or after more specific hormonal CCK infusion, often provide results leading to poor prediction as to which patients will benefit from gallbladder removal. These patients with APB therefore may have inappropriate and ineffective surgery with an unsatisfactory outcome. Because of this, it is important to understand the pain characteristics of patients with APB, both at baseline level and when the gallbladder pain is reproduced following stimulation.

Pain is very difficult to quantitate but questionnaires have been developed which attempt to evaluate its presence and characteristics. Visual analogue scales, drawings of the body to indicate the spatial distribution of pain and sensory and affective descriptors have been used. The role of these questionnaires will be described both in past trials investigating patients with ABP and also in the current work attempting to link patient pain description with the mechanical properties of the gallbladder.

Structure-based finite strain modelling of the human left ventricle in diastole

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Finite strain analyses of the left ventricle provide important information on heart function, and have the potential to provide insights into the biomechanics of myocardial contractility in health and disease. Systolic dysfunction is the most common cause of heart failure, and can be treated with evidence-based drug therapies. Abnormalities of diastolic function also contribute to heart failure, however, and are associated with conditions including left ventricular hypertrophy and diabetes. The clinical significance of diastolic abnormalities is less well understood than systolic dysfunction, and specific treatments for diastolic dysfunction are presently lacking. To obtain qualitative and quantitative information on heart function in diastole, we develop an anatomically realistic model of the human left ventricle that uses a structure-based constitutive model along with a rule-based fibre structure. We investigate the sensitivity of this comprehensive model to small changes in the constitutive parameters and to changes in the fibre distribution. We also compare the predictions of this model to similar computational models that employ different constitutive modelling approaches, and to available computational and experimental data on stress and strain distributions in the left ventricle. Our results highlight the need for additional experimental data for both model development and validation.

Modelling the evolution of vascular disease

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In this talk I will present a computational framework which provides the foundations for modeling the evolution of vascular disease. For purposes of illustration, I will focus on modeling intracranial aneurysm (IA) evolution. IAs are a disease of the brain vasculature. They appear as a sac-like out-pouching of a part of the arterial wall, inflated by the pressure of the blood that fills them. They are relatively common and affect up to 5% of the adult population. Most remain asymptomatic; however, there is a small but inherent risk of rupture. If rupture occurs there is a 30% to 50% chance of fatality. Consequently, if an IA is detected, clinical intervention may be deemed appropriate. However, interventional procedures are not without risk to the patient. Given the relatively low risk of rupture it would be desirable to be able to identify those aneurysms most at risk of such an episode. This would assist clinical diagnostic procedures and avoid the potentially undesirable consequences of an unnecessary operation. It is envisaged that computational models of aneurysm evolution will ultimately be of help in achieving this aim.

Watton et al. [1] developed a mathematical model to simulate the adaption of arterial tissue that occurs during the evolution of an abdominal aortic aneurysm. This work introduced micro-structural variables into a realistic constitutive model of the arterial wall so that the evolving structure and composition of the tissue is simulated, i.e. elastin degradation and collagen growth and remodelling (G&R). The model has been adapted to consider IA evolution and extended to explicitly link G&R to the local haemodynamic stimuli [2]. Most recently, it is has been integrated into physiological vasculature geometries with G&R additionally linked to cyclic stretch stimuli [3,4]. In this talk, the computational framework for modeling aneurysm evolution will be presented; model limitations and the direction for future research will be discussed.

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Transport of nanoparticles across the blood-brain barrier

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The blood-brain barrier (BBB) is a dynamic interface between the blood circulation and the central nervous system (CNS). While it serves as a selective barrier to water and solutes to prevent the blood-borne toxins from entering into the brain tissue, it hinders the drug delivery to the CNS for the treatment of brain diseases. Recently, the therapeutic drug-loaded nanoparticles (NPs, 20-100nm) have been widely used to treat CNS disorders such as brain tumors, Alzheimer's disease and Parkinson's disease. To improve brain delivery efficacy of these NPs, it is necessary to quantify their transport parameters across the BBB and understand the underlying transport mechanisms. In this study, we used an *in vitro* BBB model of a cultured cell monolayer from an immortalized mouse cerebral microvascular endothelial cell line, bEnd3. Permeability of the monolayer to three neutral NPs with the representative diameters was measured using an automated fluorometer system. The measured permeability to NPs of diameter 22nm, 48nm and 100nm was 2.58, 2.27 and 2.23 × 10^{-8}cm/s, respectively.

As measured by electron microscopy, the gap distance between adjacent brain microvascular endothelial cells is less than 20 nm, which does not allow the passage of NPs with the above sizes. To explain the *in vitro* BBB permeability to these neutral NPs, and that to NPs with positive charge, which was measured in our previous study (Yuan et al., 2010), we developed a new transcellular transport model. This model incorporates the charge at the luminal (surface glycocalyx) and abluminal (basement membrane) sides of the bEnd3 monolayer, the mechanical property of the cell membrane (modeled as a standard linear solid viscoelastic material), the ion concentrations of the surrounding salt solution and the size and charge of the NPs. Our model indicates that the negative charge of the surface glycocalyx and basement membrane of the BBB plays a pivotal role in the transcelluar transport of NPs of diameters ranging from 20 to100nm, regardless of charged or neutral NPs. The

electrostatic force between the negative charge at the surface glycocalyx and basement membrane of the cell monolayer and the positive charge at NPs further increase the permeability of positively charged NPs greatly. For the bEnd3 cell monolayer, the measured permeability to positively charged (charge number ~3000) NPs of ~100 nm diameter was ~100 times that to their neutral counterparts. The predictions from our transcellular model fitted very well with the measured permeability data for both neutral and charged NPs. In the future study, we will use this model to find the optimal size and charge of the NPs and the optimal charge of the BBB for an optimal drug delivery to the brain.

Three-dimensional nonlinear buckling of thick-walled elastic tubes under pressure

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This research is concerned with numerical simulations of three-dimensional finite deformation of a thick-walled circular elastic tube subject to internal or external pressure and zero displacement on its ends. We formulate the system of equations that can accommodate large strain and displacement for the incompressible isotropic neo-Hookean material. The fully nonlinear governing equations are solved using the C++ based object-oriented finite element library libMesh. A Lagrangian mesh is used to discretize the governing equations, and a weighted residual Galerkin method and Newton iteration solver are used in the numerical scheme. To overcome the sensitivity of the fully nonlinear system to small changes in the iterations, the analytical form of the Jacobian matrix is derived, which ensures a fast and better numerical convergence than using a numerically approximated Jacobian matrix. Results are presented for different parameters in terms of wall thickness/radius ratio, and length/radius ratio, as well as internal/external pressure. Validation of the model is achieved by the excellent agreement with the results obtained using the commercial package Abaqus. Comparison is also made with the previous work on axisymmetric version of the same system (Zhu et al. 2008, 2010), and interesting fully three-dimensional post-buckling deformations are highlighted. The success of the current approach paves the way for fluid-structure interaction studies with potential application to collapsible tube flows and modelling of complex physiological systems.

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