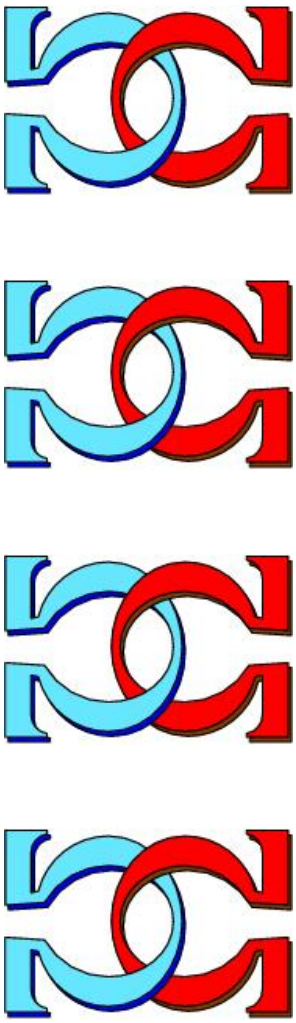

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Exploring Cardiac Arrhythmia as a Communication Failure in Cardiomyocyte Networks

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ORAL PRESENTATION

A human heart consists of a network of approximately five billion cardiomyocytes, connected by a lattice-like structure of low-resistance cell-to-cell gap junctions. The behaviors of individual cardiomyocytes on this network are orchestrated by electrical conduction between adjacent cells through these gap junctions. When the heart is functioning properly this cell-to-cell electrical propagation results in the heart beating normally. However, this process can break down during a phenomenon known as cardiac arrhythmia (abnormal heart rhythm)---a leading cause of sudden death in the world today.

Understanding when and why this electrical-transmission process breaks down is vitally important in developing actionable and effective treatment protocols. However, conventional electrocardiographic metrics simply measure the sequence of electrical excitations in small local regions of the heart, and effectively ignore cell-to-cell interactions. This means that traditional measures cannot quantify how arrhythmia impacts cell-to-cell wave propagation and the breakdown thereof, making it a real challenge to properly diagnose and treat cardiac arrhythmia.

In this talk, we propose a novel approach to this problem: viewing the heart as a communication system in which electrical wave propagation allows information to transmit across this network of cardiomyocytes[1]. Under this paradigm, heart rhythm disorders can be viewed as the result of abnormal production or transmission of information. Processes that, we propose, are quantifiable using information-theoretic measures, such as Shannon entropy, mutual information and transfer entropy, and ignored by traditional electrocardiographic metrics. To this end, we developed a framework to quantify cardiac electrical communication during action potential propagation in normal *and* abnormal heart rhythms. We will show that this paradigm allows for a deeper understanding of the electrical communication process present in the heart; in particular, when this communication system fails. Results will be presented from both *in silic*o experiments and *in vivo* observations. *In silico* experiments were performed with the FitzHugh-Nagumo model, a reaction-diffusion equation traditionally used to model cardiac activity. The *in vivo* observations were collected with a 64-lead basket catheter placed inside of patients' left and right atria during episodes of cardiac arrhythmia.

As we will show in this talk, information theory can be utilized to quantitatively assess electrical communication processes among cardiomyocytes during normal heartbeat and complex arrhythmias beyond electrocardiographic measures. Such information-theoretic metrics may find clinical application in the identification of rhythm-specific treatments which are currently unmet by traditional electrocardiographic techniques. We believe that this new paradigm provides a novel set of tools for practitioners and theorists to analyze the heart as a cellular information-processing unit.

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PEG nanoparticles decorated with Rabies Virus Glycoprotein cross the BBB

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A major impediment in the treatment of neurological diseases is the presence of the blood–brain barrier, which precludes the entry of therapeutic molecules from blood to brain. Here we show that a short peptide derived from rabies virus glycoprotein (RVG) enables the transvascular delivery of micellar nanoparticles (NPs) based on linear polyethylene glycol (PEG)-block-dendritic cholic acids (CA) copolymers (telodendrimers), for the targeted delivery of drugs in the treatment of brain infection and inflammation. The micellar NPs have been decorated with (RVG) peptide which facilitated the (NPs) Trojan-horsing the BBB. "Click chemistry" was used to conjugate alkyne group on (RVG) peptide to the azide group at the distal terminus of the PEG chain at a molar ratio of 1:2 (RVG:PEG). The delivery was demonstrated in vivo biodistribution study after intravenous injection into mice.

Therefore, telodendrimers decorated with (RVG) peptide have great potential as a new therapeutic approach for patients with brain infection or inflammation. This 29-amino-acid peptide specifically binds to the acetylcholine receptor expressed by neuronal cells and transduce the (NPs) to neuronal cells. Controversially, the naked (NPs) could not pass through the BBB. Thus, RVG provides a safe and noninvasive approach for the delivery of (NPs) and potentially other therapeutic molecules across the blood–brain barrier.

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Towards a Computational Model of Regulatory Networks Dictating Cardiac Morphogenesis.

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Background: The heart is the first organ to form and function during early development in vertebrates. Heart development consists of sequential events including the formation of the cardiac crescent followed by linear heart tube formation. The heart tube then undergoes a ventral bending prior to a helical torsion to form a looped heart, leading to proper alignment of the future cardiac chambers and tracts.

During the looping phase the heart tube gradually develops distinct regions with characteristic myocardial cells that show differential gene expression, growth, and functional features. The presence of positional signals within the heart tube along the anteroposterior and dorsoventral axes is proposed to regulate this regionalization. Key gene regulatory networks and signaling pathways are also identified playing primary roles in regionalization and myocardial specification during looping.

Despite the wealth of experimental data, the underlying mechanisms controlling the looping phase are unclear. Indeed, the signals and regulatory networks through which these signals coordinate cells' localized morphological and functional properties during looping are unknown.

Aim: We aim to study how the bending configuration of the looping phase (tissue level) emerges from coordinated and localized cell proliferation and growth (cellular level) in response to positional signals and their downstream signaling pathways and gene regulatory networks (subcellular level).

Method: We use open source platforms, CellML and FieldML, for computational modeling. Data are collected from a comprehensive review of the literature and our own experimental results. Regional growth rate within the heart tube simulates configurational changes during bending phase. CellML models of signaling and gene regulatory networks control expression of specific cardiac genes in response to spatial signals. These cardiac genes directly or indirectly control myocardial cell proliferation and growth. CellML models will then be linked to the tissue remodeling model through a growth function to study how temporal and spatial expressions of specific cardiac genes contribute to bending morphology.

Results: We show how differential regionalized growth within the heart tube could result in a bending configuration. We also show how cellular growth could be driven by models of subcellular regulatory networks and in turn affect tissue structure.

Keywords: cardiac development, regulatory network, signaling, growth, multi-scale modeling.

Preferred type of presentation: oral presentation

Computational and Experimental Modelling of Alveolar Epithelial Fluid Transport

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The alveolar epithelium secretes and regulates a surface-lining liquid layer which facilitates gas exchange and immune defence. The composition and thickness of the layer is controlled by active and passive transport of ions and water. It is important to understand the mechanisms behind the control, as abnormal regulation can lead to pulmonary disease. Here we report on the development of computational and human cell culture models of fluid transport in Type II alveolar epithelial cells (ATII).

We have formulated a quantitative mathematical model to aid our understanding of transport in ATII cells. The model includes the key cellular components facilitating transport of water, sodium, potassium, and chloride via transcellular and paracellular pathways. We solved for the steady-state intracellular ion concentrations, membrane potentials and cell volume using model parameters for alveolar epithelial cells derived from the literature.

Model results showed that the absorption of sodium through the epithelial sodium channel (ENaC) was a major driver for fluid transport. The model also predicted that the chloride current through the cystic fibrosis transmembrane conductance regulator (CFTR) is small under baseline conditions.

It has recently been found that the ENaC and CFTR channels interact and influence one another's activity, though the mechanism of interaction is unclear[1]. Different modes of interactions have been modelled, with model results compared against experimental data.

A cell culture model of ATII cells was developed using the human pulmonary epithelial cell line NCI-H441. Gene and protein expression in the cell line were similar to cultures of primary human ATII cells[2]. Cultures developed a transepithelial potential difference (basolateral minus apical) of approximately 10 mV under baseline conditions. Treatment wih the ENaC inhibitor amiloride reduced the potential difference by 85% while inhibitors of CFTR and other chloride channels had negligible impact. These results lend support to the computational model.

In conclusion, we have established computational and cell culture models of ATII cells that are well suited for the study of alveolar fluid transport.

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Modelling endothelial cell force transmission of flow-induced shear stress

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Endothelial cells detect and respond to blood flow-induced shear stresses acting on the vessel wall. A number of sub-cellular features within endothelial cells have been shown to be stress-sensitive including: cell-cell junctions, integrins, the primary cilium, the cytoskeleton (through tensegrity) and focal adhesions. The endothelial decentralised model states that the overall cell response to shear stress is not controlled by any one of these possible transducers, but is instead determined by the aggregate response of the all transducers located at different locations throughout the cell.[1] The molecular signalling of these transducers can lead to disease-protective or disease-susceptible cell states, depending on the internal stresses acting on the transducers. Studies have demonstrated that endothelial cells adapt their morphology in response to changes in flow-induced shear stress.[2] It has been postulated that these adaptions minimise the change in intracellular stress/strain acting on the transducers thus maintaining a healthy internal force homeostasis. This study aims to quantify endothelial internal stress distribution in response to different flow-induced shear stresses. Furthermore, we aim to understand how changing cellular morphology affects this stress distribution.

We cultured, stained and imaged human-microvascular endothelial cells (n=15) using a combination of immunofluorescence and confocal microscopy. These images were used to form the spatial domain of our finite-element mechanical analysis of a single cell. The following subcellular components were imaged and included in the model: nucleus, actin and tubulin components of the cytoskeleton, the primary cilium and focal adhesions. Physiological flow (shear stress <6.5 Pa) was simulated in our model. The greatest stresses were found at the interface of the nucleus and cytoplasm. We found that the inclusion of the primary cilium increased the magnitude of stress two-fold over a non-ciliated cell (with the same geometry). Since the primary cilium is typically expressed on endothelial cells in low shear stress regions, our study suggests that the primary cilium may represent an adaptive response to restore internal force homeostasis.

We are in the process of extending our study to consider the effect of cytoskeletal remodelling: components of the cytoskeleton have been shown to realign in the direction of flow. We propose using images taken from live cells under flow to extend our model, and incorporating tensegrity principles to model cytoskeletal mechanics. In future, it would be useful to consider diseased or mutant endothelial cells, as it has been suggested that pathogenesis is caused by the lack of ability to fully maintain force homeostasis in response to changes in blood flow-induced shear stress.

Keywords: Endothelium, mechanotransduction, mechanotransmission, decentralised model, tensegrity, mechanical modelling

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Effect of oxygen and shear stress on human placental vascular cells

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Background: The normal development of placenta is important to sustain a healthy baby as this organ supplies the oxygen and nutrients required for fetal growth. The placental vasculature first forms around 21 days of pregnancy (vasculogenesis) and the vessels continue to elongate and branch throughout the pregnancy by angiogenesis [1]. These processes are crucial for pregnancy success, as inadequate placental vascularisation is associated with fetal growth restriction [2]. Both mesenchymal stem cells and endothelial cells are thought to play important roles in placental vasculogenesis and angiogenesis [1] . Shear stress and oxygen have been shown to affect the differentiation, migration and proliferation of mesenchymal stem cells [3, 4]. However, we have a poor understanding of how these factors regulate placental vascular development during pregnancy.

Objectives: This study aims to use a combination of in vitro experiments and computational modelling to understand how oxygen and shear stress affect the differentiation, proliferation and migration of cells involved in placental vascular development.

Methods: In order to understand how shear stress affects the growth of the vasculature, endothelial cells (HMEC-1 microvascular cell line) and first trimester mesenchymal stem cells will be subjected to physiologically relevant shear stress using the BioFlux200 system. The proliferation and migration of the cells will be determined by quantitative time-lapse microscopy over a 48hr period. In order to understand how changes in oxygen distribution seen in early pregnancy affect placental vascular development, the same cell types will be cultured in 1% or 8% oxygen, their proliferation quantified by determining the expression of the proliferation marker Ki67, and their production of angiogenic growth factors quantified by ELISA. We will assess continuum and discrete analysis strategies to analyse cell data of this type and explore the capabilities of agent based computational models in predicting cell behaviour in the Bioflux system.

Conclusion/Implication: We have conducted an assessment of continuum and individual cell based methods to assess cell migration and interactions in vitro and concurrently we have developed methods of translating these data into agent based computational models of cell behaviour. Developing computational models of the placental vasculature that are informed by experimental cellular data will allow us to study how predictions of placental oxygenation and shear stress during pregnancy affect the development of the placental vascular tree, and how aberrations in these processes may contribute to pregnancy disorders such as Fetal Growth Restriction.

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Chaos Fuzzy Genetic Algorithm

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***Abstract*—**The genetic algorithms have been very successful in handling difficult optimization problems. The fundamental problem in genetic algorithms is premature convergence. This paper, present a new fuzzy genetic algorithm based on chaotic values instead of the random values in genetic algorithm processes. In this algorithm, for initial population is used chaotic sequences and then a new sexual selection proposed for selection mechanism. In this technique, the population is divided such that the male and female would be selected in an alternate way. The layout of the male and female chromosomes in each generation is different. A female chromosome is selected by tournament selection size from the female group. Then, the male chromosome is selected, in order of preference based on the maximum Hamming distance between the male chromosome and the female chromosome or The highest fitness value of male chromosome (if more than one male chromosome is having the maximum Hamming distance existed), or Random selection. The selections of crossover and mutation operators are achieved by running the fuzzy logic controllers and the crossover and mutation probabilities are varied on the basis of the phenotype and genotype characteristics of the chromosome population. Computational experiments are conducted on the proposed techniques and the results are compared with some other operators, heuristic and local search algorithms commonly used for solving p-median problems published in the literature.

***Keywords*—**Fuzzy system, genetic algorithm, chaos, sexual selection.