Creating Multi-Modality Cardiac Digital Twins to Study Conduction System Pacing

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Background: A digital twin is a set of virtual information constructs that mimics the structure, context, and behavior of a natural, engineered, or social system, is dynamically updated with data from its physical twin, has a predictive capability, and informs decisions that realize value. The bidirectional interaction between the virtual and the physical is central to the digital twin. Historically digital twins have been applied in aerospace, manufacturing and environmental systems. However, they are increasingly being applied in healthcare applications.

In cardiology digital twins can be used to improve diagnosis, optimize therapies and forecast patient outcomes. However, creating these models is very expensive and requires multiple manual steps. This PhD will look to develop and test methods for scaling the creation of cardiac digital twins, apply these to patient groups and test if twins can improve outcome prediction.

Task 1 (Year 1): *Create a human heart model with accurate in vivo fiber measurements.*

Background: Heart muscle cells have preferential alignment that can be measured with diffusion tensor MRI. New measurements of fibres in the relaxed and contracted state provide detailed measurements to stimulate cardiac contraction.

Question: What role does fibre orientation play in ventricular contraction?

Data: Diffusion Tensor MRI data for health controls and patients will be available through collaboration with Dudley Penel and Sonia Nielles-Vallespin, through jointly held BHF Programme grant and Chang Zuckerberg Imaging grant.

Study: We will 1) explore the use of our recently published image completion networks applied to sparse DTMRI data to reconstruct higher resolution DTMIR data sets, 2) create the first reference human fibre atlas based on human data, 3) test the use of Gaussian Manifolds to represent uncertain fibre fields, 4) perform simulation studies to quantify the impact of fibre field uncertainty on simulation predictions, 5) combing Gaussian Process Emulators, Monte Carlo-Markov Chain sampling and Bayesian History matching to calibrate orthotropic constitutive laws to the contracted and relaxed states, and 6) test is spatially varying stiffness is required to recover cardiac motion and if varying stiffness maps to information in the DTMRI data sets.

Outcome: Publication on human fibre biomechanics, a reference atlas of human fibres that can be used by other groups and a calibrated orthotropic constitutive law that allows models to recover observed fibre and sheet motion during cardiac contraction, provide an atlas for spatially varying stiffness in the myocardium. We will have novel methods for interpolating DTMRI data, for representing uncertainty in the data and for calibrating multi-scale models.

Task 2 (Year 2): *Create a human heart model with accurate Purkinje Fibre measurements.*

Background: New pacing systems target the conduction system. However, limited information is available to confirm their locations. Electrophysiological mapping systems can detect the endocardial Purkinje system but labelling the signal is laborious.

Data: We will work the Zach Whinnett to collect left ventricle and right ventricle endocardial electrophysiological maps in patients undergoing paroxysmal atrial fibrillation.

Study: We will create a labeled dataset of Purkinje signals and test 1D Convolutional Neural Networks, Residual Networks and Recurrent Neural Networks to identify the presence and label the timing of Purkinje signals. We will project all Purkinje signal maps onto a reference anatomy to test for 1) common locations, 2) common activation timings and 3) if the activation patterns follow a continuous activation or if breakout activation points are observed. We will create a statistical Purkinje Atlas to describe the variability in Purkinje activation, and a reference Purkinje atlas

Outcome: We will create a rule-based Purkinje activation pattern that will provide strong priors for patient specific modelling calibration studies. We will have the first understanding of the variation of endocardial Purkinje activation. We will understand if the Purkinje activities sequentially or if activation jumps ahead, which will dictate future modeling studies.

Task 3 (year 3): *Test the relative contributions myocardia fibre orientation and Purkinje activation patterns on response to conduction system pacing systems*

Background: Conduction system pacing targets activation through the Purkinje system to achieve a return to synchronous activation in dyssynchronous heart failure patients. With new systems, choosing the right system for the right patient and how best to optimize this system becomes and important question. Part of this question is understanding what patient attributes are important in determining their response to therapy.

Question: How do fibre orientation and Purkinje activation pattern interact to impact patient response to conduction system pacing.

Data: We will work the Zach Whinnett to collect MRI images, activation times and hemodynamic responses to conduction system pacing.

Study: We will create patient specific computational models of patients undergoing conduction system pacing. We will calibrate the model to the pre-pacing data. We will validate the model against the predicted change in activation pattern with pacing. We will test the sensitivity of the predicted response of each conduction system pacing option to the uncertainty in Purkinje activation and fibre fields.

Outcome: We will have created a virtual patient cohort that identifies underlying physiology that determines patient outcomes. This information can then be used for informing diagnostic studies in future patients.

Additional Time: There is 6 months contingency for targeted training, theses write up, unexpected delays and personal issues.

Techniques and Methods: The student will be exposed to Neural Network image and signal analysis, Gaussian manifolds, Finite Element Method, Gaussian Process Emulators, Bayesian History Matching and Monte Carlo Markov Chain Sampling.

Method Development: Novel methods to 1) interpolate tensor fields, 2) represent uncertainty in tensor fields, 3) calibrate multi-scale models by combining Monte Carlo Markov Chain Sampling with Bayesian History Matching.

Skills: Presentation, working an interdisciplinary team, public engagement, article writing, problem solving, application writing, interviewing candidates, supervision of students.