SEMS: RESEARCH PROJECT DESCRIPTION

1. Project Background and Description

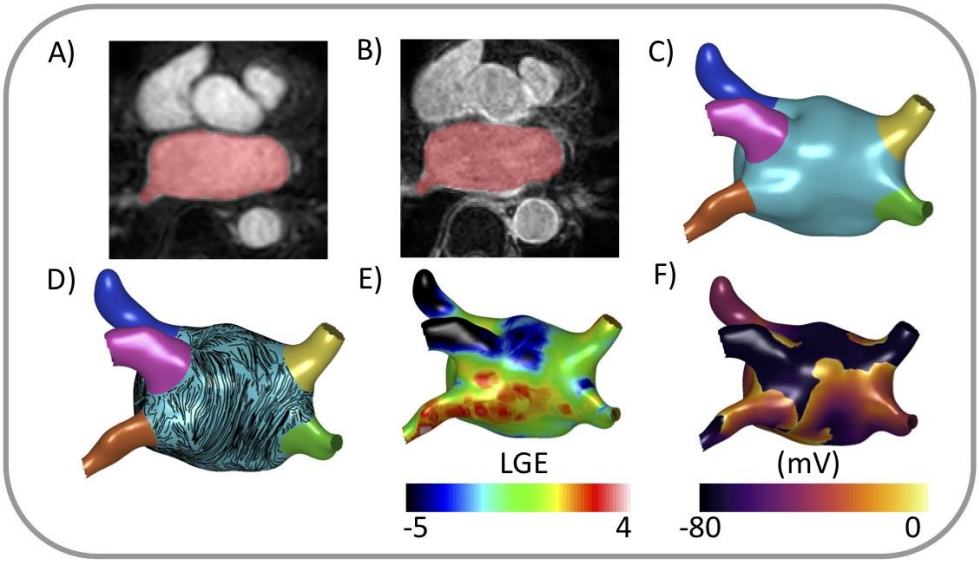
Multi-scale electromechanical cardiac digital twins: from genetics to organ scale predictions

Biophysical simulations of cardiac electromechanics may be used for guiding therapy, diagnosing disease, and developing devices. We recently performed a large atrial fibrillation virtual cohort study to demonstrate the potential of combining personalized biophysical simulations with machine learning approaches to predict therapy outcome. However, we did not include information on the patients' genetics in our digital twin modelling pipeline. Understanding the changes in cardiomyocyte mechanosensing, electrophysiology and mechanics associated with genetic mutations is important for improving personalized therapy guidance. This research aims to develop a framework for incorporating the effects of genetics on stress, mechanics, and excitability in personalised cardiac electromechanical digital twins.

This PhD will first develop and test the framework on iPSC cardiomyocytes with mutations in the dystrophin or fukutin-related protein gene, which leads to dilated cardiomyopathy. Specifically, the project aims to:

- Calibrate cellular electrophysiology, calcium, and mechanics models to recordings from iPSC cardiomyocytes with muscular dystrophy mutations (mechanical sensing, optical mapping, and multi-electrode array data).
- Investigate the effects of these changes in electrical and mechanical function at the organ level across a cohort of four chamber biophysical models with a range of anatomies; augmented with anatomies from a statistical shape model.
- Determine the separate and combined effects of anatomy, electrophysiological changes and mechanical changes on arrhythmia susceptibility and mechanical function.
- Collaborate with the electrogenomics research group to determine how to extend this approach to other genetic mutations using biobank data.

A key outcome of the PhD project will be a framework for creating electromechanical four-chamber models that include the effects of genetic mutations. This would enable future virtual clinical trials to utilize genetic information from the UK biobank dataset. The student will gain training in experimental protocols (Dr Thomas Iskratsch, SEMS & Prof Andy Tinker, William Harvey Institute), machine learning and biophysical simulation (Dr Caroline Roney, SEMS).



Modelling pipeline: (A) MRA segmentation, (B) LGE-MRI imaging data used to determine fibrosis distribution, (C) Simulation mesh with labelled atrial regions, (D) DTMRI fibres, (E) Regions of remodelling, (F) Simulated arrhythmia.

References:

https://pubmed.ncbi.nlm.nih.gov/35089057/
https://pubmed.ncbi.nlm.nih.gov/29396114/
https://pubmed.ncbi.nlm.nih.gov/31291141/
https://pubmed.ncbi.nlm.nih.gov/33041850/
https://pubmed.ncbi.nlm.nih.gov/32458222/

2. Project Scope

The project objectives are:

1. To calibrate cellular electrophysiology, calcium, and mechanics computational models to experimental recordings from iPSC cardiomyocytes with muscular dystrophy mutations (mechanical sensing, optical mapping, and multi-electrode array data from William Harvey Research Institute and SEMS).
2. To develop an open-source framework for creating electromechanical four-chamber models that capture the effects of genetic mutations.
3. To simulate the effects of anatomy, electrophysiological changes and mechanical changes on arrhythmia susceptibility and mechanical function across a virtual cohort of patients with and without genetic mutations.

3. Desired Skills from the Student

Undergraduate in biomedical engineering, mechanical engineering, mathematics, computer science, biology etc. Motivation to work in an interdisciplinary environment, with computational researchers, experimental researchers, and clinicians.

4. Supervisory Team

Primary: Dr Caroline Roney (https://www.sems.qmul.ac.uk/staff/c.roney)

Secondary: Dr Thomas Iskratsch (https://www.sems.qmul.ac.uk/staff/t.iskratsch)

Additional: Prof Andy Tinker (William Harvey Research Institute, https://www.qmul.ac.uk/whri/people/academic-staff/items/tinkerandrew.html)