Mechanisms of Arrhythmia Triggers Predicted by a Novel Computational Model of Rat Cardiac Physiology

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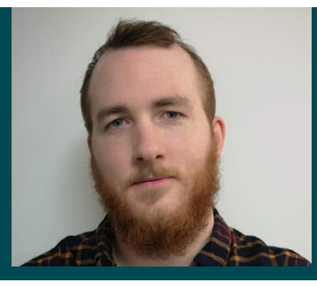
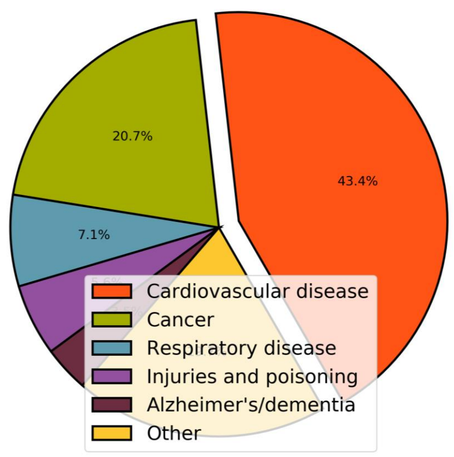


Background

- Cardiovascular disease (CVD) has been the **leading cause of mortality** since 1980 and is only increasing in prevalence in the developed world due to ageing populations.
- It is estimated **up to 1.5% of the UK population live with heart failure** (HF), a subset of CVD.
- A hallmark of HF is the development of **cardiac arrhythmias** – disturbances to normal heart rhythm which are at worst lethal, and at best result in significant morbidity and socioeconomic cost.



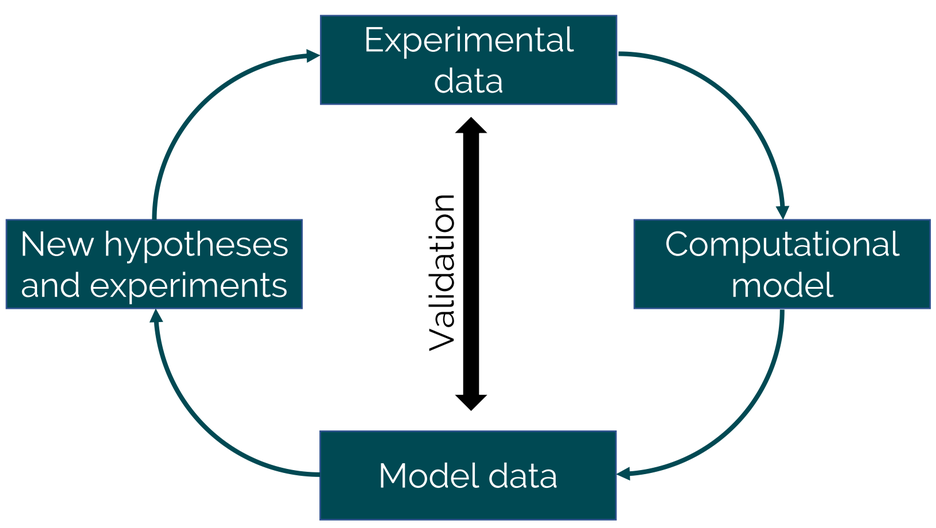
The Problem

- The heart is made up of **billions of individual cells**, which contract synchronously to generate a heart beat.
- Sub-cellular events determine cell-level behaviour, which determines organ-level behaviour.
- Sub-cellular events occur over **milliseconds** yet arrhythmias manifest over **months to years**, but can be triggered by **split-second** events – this presents a huge challenge to understanding the mechanisms via traditional experimental approaches.

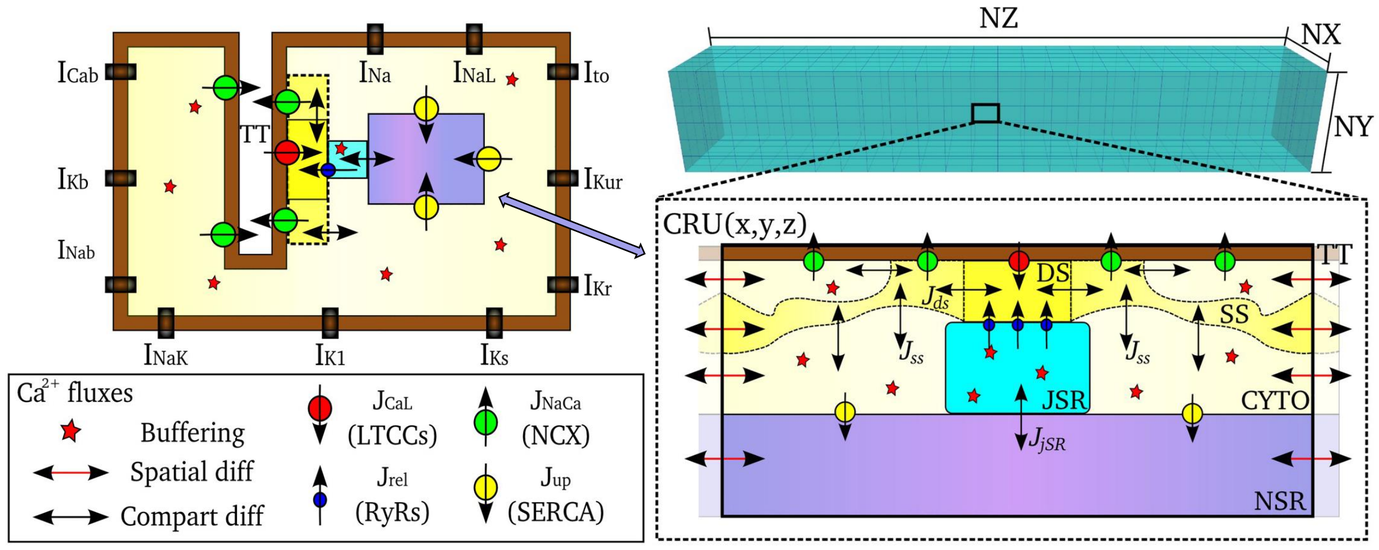
AIM: To develop a method of investigating the complex mechanisms underlying arrhythmia development in HF.

The Solution: Computational Modelling

- Computational modelling is the **interface of biology, physics, mathematics and computer science**.
- Computational models of cardiac physiology simulate the electrical activity and structure of heart muscle cells, and reproduce the complex sequences of events from signal (an **action potential**) to response (contraction, caused by **calcium, Ca^{2+}**).



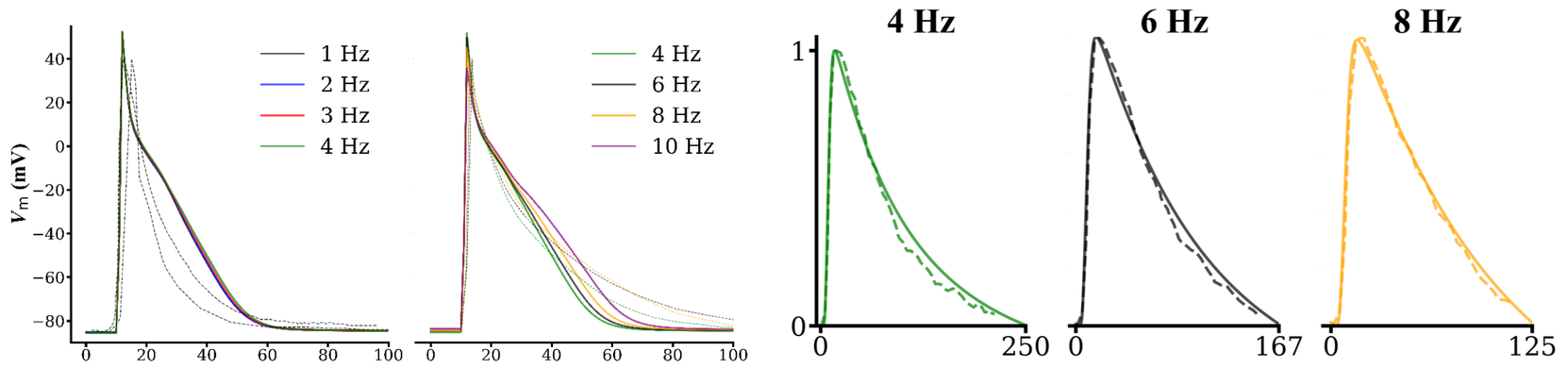
- An action potential causes Ca^{2+} to be released from intracellular stores (the **sarcoplasmic reticulum, SR**), and the binding of Ca^{2+} to muscle filaments leads to contraction.
- This is a tightly regulated process that occurs in a beautifully coordinated matter in billions of individual muscle cells to cause the heart to beat. **Disturbances to these processes are common in diseases** like HF, and can trigger arrhythmias.



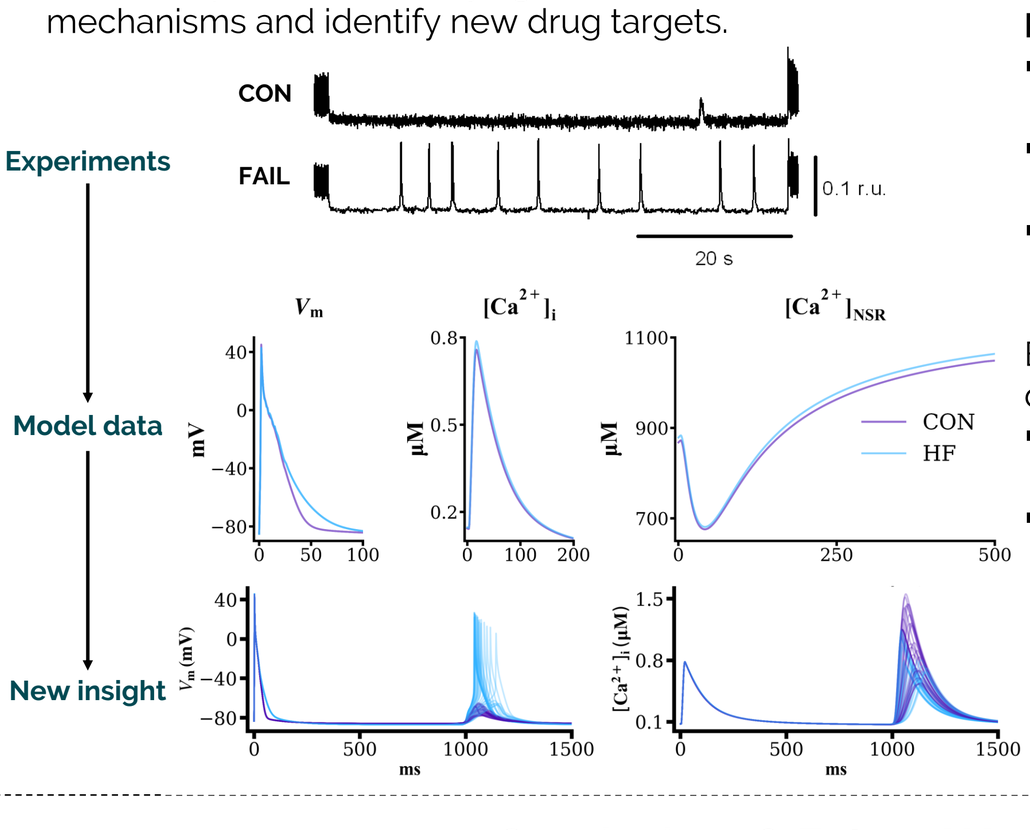
Results

Model Development

- **Previous computational models were unable to capture** the complex dynamics that underpin Ca^{2+} regulation in cardiac muscle cells, which is drastically altered in diseases like HF and so an important target for therapeutic interventions.
- **Our newly-developed model does capture these phenomena** and so can be used to explore the underlying mechanisms and identify new drug targets.



Left: action potentials. **Right:** intracellular Ca^{2+} concentration. Experimental data denoted by dashed lines, model data by solid lines. X-axis shows time in ms.



Pro-arrhythmic Mechanisms

- Using existing data from our lab we then explored how I_{K1} **reduction** results in **greater frequency of spontaneous Ca^{2+} release** in HF compared to control (CON).
- The model showed that the **action potential in HF cells is longer**, leading to higher intracellular and SR Ca^{2+} levels.
- The **threshold for spontaneous Ca^{2+} release is exceeded** in HF, resulting in frequent spontaneous release events (as we saw experimentally)

Even when fixing Ca^{2+} levels for CON and HF to the same value (something that cannot be done experimentally):

- The reduction in I_{K1} is sufficient to destabilise HF cells such that spontaneous Ca^{2+} release events lead to **triggered action potentials**, which can be sufficient to trigger arrhythmias.
- This happens despite the magnitude of spontaneous Ca^{2+} release actually being smaller in HF vs CON – further demonstrating **increased sensitivity to arrhythmia development in HF**.

HF → longer action potential → spontaneous Ca^{2+} release
AND
HF → unstable cell membrane → higher sensitivity to spontaneous Ca^{2+} release

Conclusions & Future Work

Our new model reproduces **previously uncaptured, complex phenomena** and has provided new insight into **mechanisms underlying arrhythmia development**. It can be used to explore new hypotheses, identify anti-arrhythmic targets, and test anti-arrhythmic drugs.

Next steps:

- Explore **other features of HF**, and **other CVDs** in general.
- **Cross-species analyses** – can we predict human mechanisms from a rat model?
- **Multi-scale modelling** – how do subcellular changes influence whole-heart behaviour?

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References

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