Using computational modelling to combat sudden cardiac death
Dr Martin J. Bishop, Drapers' Company JRF, St Anne's College

Introduction
Sudden cardiac death, resulting from an abrupt loss of heart function, is the biggest killer in Western society. For example, in the year 2002, death as a direct result of cardiac-related illness was responsible for over 39% of all non-accidental deaths in the UK, totally just over 238,000 individuals (source: www.bhf.org). Aside from mortality, treating and caring for people with heart-related illnesses imposes a huge financial burden on the UK health service of over £1.7 billion each year.

As a result, there exists a large and very important area of research, both academic and in the medical and pharmaceutical industries, motivated directly towards gaining a better understanding of how the heart functions, and more importantly, how and why it fails when it does. Gaining such an understanding is currently leading the way in the clinical development of better preventative measures, and more effective therapies, against such potentially lethal heart conditions.

One of the leading causes of sudden cardiac death is due to cardiac arrhythmia. Cardiac arrhythmias occur when the heart’s normal rhythmic electrical activation sequence which stimulates it to beat and contract is disrupted into chaotic and highly unsynchronised patterns of electrical activation. These highly disorganised electrical activation sequences cause isolated regions of the heart to independently contract, causing the heart to flutter, or fibrillate. These arrhythmic contractions severely limit the heart’s ability to pump blood around the body and, if intervention is not sought, death rapidly ensues. The only effective therapy against ventricular fibrillation (the most lethal type of arrhythmia affecting the heart’s major pumping chambers, the ventricles) is via a strong electrical defibrillation shock, applied either via paddles on the torso, or from an internally implanted cardioverter defibrillation unit. However, despite the importance of arrhythmias in society, the specific mechanisms by which they are initiated, maintained and potentially terminated, still remain poorly understood, which compromises the development of effective therapies.

Use of Computational Modelling
In recent years, ‘traditional’ experimental physiological investigations have been combined with highly detailed mathematical and computational simulations which model the electrical behaviour within realistic whole heart models, to more successfully and accurately elucidate the mechanisms responsible for cardiac arrhythmias. Such models accurately represent the structure and anatomy of the heart, and include detailed information regarding the electrical behaviour of individual cardiac cells which make up the model.

The simulations provide a wealth of information about individual ion currents/concentrations in every cell throughout the 3D volume of the tissue, which cannot be provided by experiments alone. For example, the widely used optical mapping experimental technique uses fluorescent electrically-sensitive dyes to measure changes in the electrical state of cardiac tissue. However, such a technique is restricted to measuring a single parameter (in this case transmembrane voltage across cardiac cells) from a narrow field-of-view from the surface of the heart. In contrast, simulations can provide information regarding multiple parameters throughout the entire volume of the tissue, which can complement the experimentally obtained data. Simulations thus act not only as an important means of
elucidating more information from an experimental protocol, but also as vitally important predictive tools which can guide further experimental investigation.

**Requirement for More Detailed Computational Models**

The current state-of-the-art computational model of the rabbit ventricles is shown in Figure 1. The model has been used with great success in numerous computational modelling studies in the past decade or so to help further insight into arrhythmia and defibrillation mechanisms. As can be seen, the model faithfully represents the overall structural geometry of the ventricles and, in addition, contains a representation of the preferential alignment of cardiac cells (commonly referred to as cardiac ‘fibre orientation’) which ‘guide’ conduction of electrical wavefronts throughout the volume of the ventricles. Other models of a similar complexity also exist for the other species, notably the pig and dog.

![Figure 1 – Current state-of-the-art computational model of the rabbit ventricles showing the unstructured finite element grid (left), incorporation of realistic cardiac ‘fibre orientation’ (centre-left) and snap-shots of a simulation of electrical wavefront propagation throughout the ventricular model (right), (Bishop, 2008)](image-url)

Although these models have proved sufficiently realistic to answer important general questions regarding the relationship between global cardiac structure and function, they share a number of limitations. Firstly, they follow a ‘one heart fits all’ approach, lacking representation of intra-population variations in structure and anatomy, which will have important implications when comparing experimental measurements from a particular preparation with computational simulation results from a model constructed from an entirely different sample. Secondly, these models are highly simplified, limited in the level of anatomical complexity, by-and-large lacking the presence of fine-scale structural details such as blood vessels, papillary muscles, coronary valves, endocardial trabeculations, etc. The inclusion of such individualised detail is essential both in providing an accurate like-for-like comparison between simulations and experiments, as well as providing an improved understanding of the role played by these fine-scale anatomical heterogeneities in cardiac function.

**Development of the Next Generation of Cardiac Computational Models**

In order to be able to probe the specific role of fine-scale anatomical structures, such as the coronary vasculature or endocardial structures, in cardiac function, it is first necessary to include a matching level of structural detail in computational cardiac models. Recently, efforts have been focussed towards developing techniques to construct 3D computational cardiac models directly from magnetic resonance (MR) data, due to the non-destructive nature of that technique. In the last few years, the advent of stronger magnets and refined scanning protocols has significantly increased the resolution of anatomical MR scans, such that smaller mammalian hearts now can have MR voxel dimensions of 20-25 µm.
MR data acquired at such an exceptional high resolution has been the focus of a large inter-departmental collaborative project (funded by the BBSRC) held between teams in the Computing Laboratory (led by Prof. David Gavaghan), the Department of Physiology, Anatomy and Genetics (led by Dr Peter Kohl) and the Department of Cardiovascular Medicine (led by Dr Jürgen Schneider). Figure 2 (left) shows MR data obtained from a fixed and embedded rabbit heart, scanned on an 11.7 T anatomical MR scanner obtained through the Oxford 3D Heart Project. As can be seen in the image, the exceptionally high resolution of the data-set (26.5 x 26.5 x 24.5 μm) allows a wealth of anatomical detail to be elucidated. One of the main goals of the Oxford 3D Heart Project has been concerned with developing the technological pipeline to facilitate the generation of fine-scale structure-function computational models directly from high resolution MR data containing an unprecedented level of anatomical detail. The computational pipeline for generating these ‘next generation’ of cardiac models is summarised in Figure 2 and described below.

![Computational MR-to-model pipeline](image)

Figure 2 – Computational MR-to-model pipeline to translate high resolution MR data (~25 μm resolution) into an unstructured finite element computational ventricular model over which cardiac electrical activation dynamics can be simulated (Burton et al., 2006; Plank et al., 2009).

Briefly, the model generation pipeline involves the processes of segmentation of the MR data set, finite element mesh generation of the segmented voxel image stack, incorporation of functional electrical properties (anisotropic conduction) into the model, and finally simulation of electrical activation. The processes of segmentation and mesh generation convert the grey-scale geometrical information contained within the MR images into an anatomically detailed computational model. The finite element computational model allows the governing equations which represent the electrical activation of cardiac tissue to be solved numerically to simulate the propagation of electrical waves throughout the heart.

Information regarding cardiac fibre orientation (which results in anisotropic conduction within the heart) is most reliably obtained from either histological analysis, where the heart is sectioned, stained and imaged in a microscope, or diffusion-tensor MR imaging (DTMRI), where measurement of the preferential direction of water molecule diffusion can be related to the underlying fibre architecture of the sample. However, in certain instances where such data sets are unavailable for a particular heart preparation, fibre architecture can be embellished into the model through the use of rule-based approaches using a priori knowledge regarding cardiac fibre structure within the heart of a particular species (see Figure 3, next page).
Finally, mathematical equations which represent the electrical behaviour of individual cardiac cells within the heart, as well as equations which model the electrical coupling between cells, can be solved numerically over the high resolution computational finite element cardiac model using specialised cardiac simulation software. Figure 4 shows snap-shots of the spread of electrical activation throughout the model following stimulation close to the apex. Here we compare the differences between incorporating an accurate representation of cardiac fibre architecture within the model: anisotropic conduction (bottom), and isotropic conduction (top).
Conclusions
Use of this next generation of computational cardiac models, of which groups in Oxford are leading the way in the development, are currently facilitating the investigation of how fine-scale anatomical structures and heterogeneity affect the functioning of the heart during normal and pathological conditions. It is hoped that acquiring such insight will not only bring a new level of understanding to our knowledge of cardiac arrhythmia mechanisms and their treatment through electrical-shock therapies, but more importantly, will lead to more effective and patient-specific diagnoses and intervention-planning.

Dr Martin Bishop’s research, the combination of advanced computational simulations alongside experimental measurements, will provide a new level of insight into how differences in cardiac structure and anatomical heterogeneity, both between and within individuals, affect the basic dynamics of electrical propagation and electromechanical interaction during arrhythmogenesis, resulting in pro- or anti-arrhythmic tendencies.

References