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An Audit of Uncertainty in Multi-scale Cardiac Electrophysiology Models

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Abstract

Models of electrical activation and recovery in cardiac cells and tissue have become valuable research tools, and are beginning to be used in safety critical applications including guidance for clinical procedures and for drug safety assessment. As a consequence there is an urgent need for a more detailed and quantitative understanding of the ways that uncertainty and variability influence model predictions. In this paper we review the sources of uncertainty in these models at different spatial scales, discuss how uncertainties are communicated across scales, and begin to assess their relative importance. We conclude by highlighting important challenges that continue to face the cardiac modelling community, identifying open questions, and making recommendations for future studies.

1 Introduction

Mechanical contraction of the heart is initiated and synchronised by a wave of electrical activation that originates in the natural pacemaker in the right atrium and propagates through the atria and into the ventricles. An abnormal sequence of electrical activation and recovery in the heart results in a cardiac arrhythmia, which may require urgent medical intervention. Understanding the mechanisms that initiate and sustain cardiac arrhythmias is a central question in cardiac electrophysiology because there are implications for the design and guidance of clinical interventions as well as for understanding the mechanisms of drug action.

Mathematical and computational models of the heart can provide a detailed and quantitative description of the electrical activation and recovery of cells and tissue, as well as the associated changes in intracellular Ca^{2+} concentration that initiate contraction [1]. These models have been widely used as research tools, but there is a direction of travel towards safety critical applications that include drug safety testing [2] and guidance for clinical interventions [3].

Multi-scale electrophysiology models integrate models at the cell, tissue, and whole organ scale. There are exciting opportunities for the adoption of multi-scale cardiac models in a predictive capacity, but these will require a much more rigorous assessment of model credibility and confidence in predictions [4] as part of a regulatory process that takes into account validation, verification and uncertainty quantification of biomedical models [5].

This paper contributes to this process by undertaking an audit of the sources of uncertainty in multi-scale and personalised models of cardiac electrophysiology. Our aims are to document the uncertainties associated with cardiac models at different scales, to assess their relative importance, and to make recommendations for best practice. We concentrate on models of electrophysiology in order to keep the analysis tractable, but we have included references to relevant and related work on uncertainty quantification in models of cardiac mechanics and cardiovascular flow. Our main focus is on the effects of experimental errors, uncertainties, and natural variability on model calibration; discrepancies between model and reality arising from modelling assumptions and simplifications; uncertainties arising from the choice of modelling framework; and the challenges presented by the clinical setting.

2 Background

2.1 Cardiac electrophysiology models at different scales

During each normal heart beat cardiac cells undergo an action potential, which is a sequence of electrical activation and recovery. In the resting state, the cell membrane is electrically polarised. There is a potential difference of around $-90\ mV$ across the cell membrane, with intracellular space maintained at a lower potential than extracellular space by differences in ion concentrations.

During activation, the potential difference depolarises to around $+30\ mV$ as a result of conventional current carried by Na^+ and Ca^{2+} ions that flow into the cell. The cell then repolarises back to $-90\ mV$ as a result of currents that flow out of the cell, mainly carried by K^+ ions. Following activation, the cell remains in a refractory state until recovery is complete.

Inward and outward currents flow through ion channels, pumps, and exchangers in the cell membrane. Their behaviour can be represented in mathematical models, where ionic currents are described as a set of coupled and nonlinear ordinary differential equations (ODEs) [6]. Biophysically detailed cell models can also represent the storage, sequestration, release and uptake of intracellular Ca^+ as an additional set of ODEs.

Cardiac cells (myocytes) are typically rod-shaped, and tend to be aligned with their neighbours to form fibres and sheets [7]. Myocytes are electrically coupled through gap junctions located predominantly at their ends, and so action potential propagation is faster along fibres than across fibres, with an intermediate propagation speed within sheets. At the cell scale, propagation of the action potential from one cell to its neighbours is a discrete process [8], but at the macroscopic scale normal cardiac tissue behaves as a continuum. The bidomain model of cardiac tissue represents tissue as a continuum composed of intracellular and extracellular domains, and a generalisation of Ohm's law leads to a system of partial differential equations (PDEs) with the cell model included as a reaction term [9]. The bidomain model incorporates anisotropic propagation along fibres as conductivity tensors in both intracellular and extracellular domains. If the conductivity tensors for both domains are proportional, which corresponds to identical anistropy ratios, then the bidomain equations can be simplified to the monodomain equation, which is a single reaction-diffusion PDE.

Cardiac tissue models are typically solved on a computational mesh using finite difference, finite element, or finite volume methods. The mesh may be an idealised geometry, such as a 2D sheet, or an anatomically detailed model obtained from medical images. These solutions will involve choices of model parameters, such as tissue conductivities, as well as solver parameters, such as times steps and space steps [10].

2.2 Features of interest

Cardiac cell and tissue model outputs include features that not only depend on model parameters and structure, but also influence model behaviour. These are illustrated in Figure 1 and include:

- **Action potential shape and duration.** The action potential upstroke determines propagation speed in tissue, and action potential duration (APD) is related to the refractory period, which determines the rate at which the cell can be repeatedly activated.
- **Spontaneous activity.** Some cells are able to generate spontaneous action potentials. This is essential for cells in the heart's natural pacemaker

where the rate of spontaneous depolarisation is an important feature, but in other regions of the heart spontaneous early or delayed afterdepolarisations (EADs and DADs) can result in arrhythmias.

- **Dynamic behaviour.** APD and propagation speed are rate-dependent properties of cardiac cells and tissue, and under some conditions cells and tissue exhibit alternans, where APD alternates from one beat to the next.
- **Activation and recovery sequence.** A consistent electrical activation sequence from one beat to the next is important for efficient mechanical contraction. Abnormal activation and recovery sequences arising from tissue pathology or EAD/DADs can disrupt contraction, and also indicate heightened vulnerability to arrhythmia.
- **Arrhythmia vulnerability.** Re-entry is a type of arrhythmia where an action potential continually propagates into recovering tissue, and it can be initiated by a premature stimulus (for example from a DAD) with particular strength and timing. Vulnerability can be quantified from the range of stimulus strength and timing that results in re-entry.
- **Arrhythmia stability**. Once initiated, re-entry can remain stable with a single rotating action potential, or may break up into multiple waves of activation.

2.3 Uncertainty and variability

A cardiac or cardiovascular model is a quantitative representation of a real system. Since models embed assumptions and simplifications, they are necessarily an incomplete representation, and so their outputs and behaviours will differ from those of the real system. Additional differences will arise from the functional form of the model, the precision with which model parameters are known, the choice of initial and boundary conditions, and errors arising from the numerical solution scheme that is selected. Physiological systems are inherently variable, for example cardiac action potentials vary from cell to cell and from beat to beat in the same cell [13, 14], and so further differences between the model and the real system will result from natural variability. This may be evident as model parameters that are described by a distribution instead of a single number. Uncertainty quantification (UQ) provides a conceptual framework within which uncertainty and variability can be characterised [15, 16], and the application of these ideas to cardiac models is an area of emerging importance [4, 17, 18, 19, 20]. However, there is sometimes confusion about what is meant by uncertainty, variability, sensitivity and error, and so next we discuss and clarify these terms.

Uncertainty is associated with a lack of information, and uncertainties are often categorised as either epistemic or aleatory. Epistemic uncertainties result from a lack of knowledge about a system, and can in principle be reduced. For

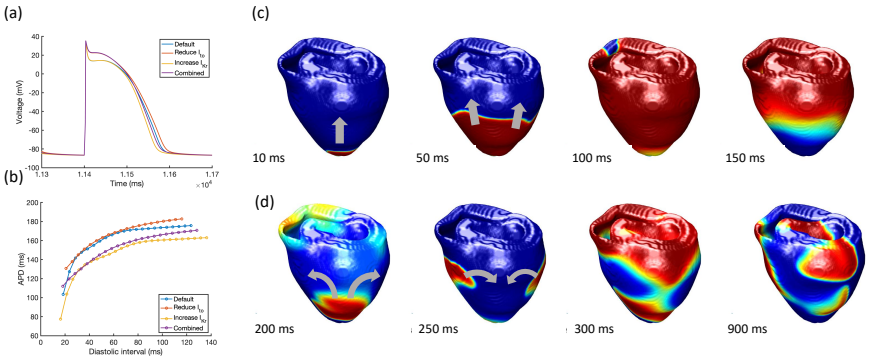

Figure 1: **Cardiac electrophysiology models:** Action potentials (a) and action potential duration restitution (b) produced by a model of rabbit ventricular cell electrophysiology [11] paced at a cycle length of 300 ms, showing the effects of halving the transient outward current I_{to}, and doubling the rapidly inactivating K^+ current I_{Kr}. Snapshots of epicardial electrical potential from simulations in a rabbit ventricle model with a phenomenological cell model [12], showing activation following pacing at the apex (c), followed by unstable reentry initiated by a premature stimulus (d). Red regions are activated, blue regions recovered, and arrows show direction of action potential propagation.

example one type of epistemic uncertainty in a cell model could be discrepancy between the model and real system arising from an ion current that is neglected or incorrectly formulated in the model. This uncertainty could in principle be reduced by performing more experiments and/or developing a better model [21]. Aleatory uncertainties result from random variation in the system, and are considered to be irreducible. In most cases, aleatory uncertainty and variability can be considered interchangeable.

Variability in cardiac models normally refers to the multiple values that a model parameter can have at different locations or times. This natural variability is inherent in biological systems. An example is the intrinsic beat-to-beat fluctuation of action potential duration (APD) in a single cell and extrinsic cell-to-cell differences in APD [13].

Uncertainty analysis and sensitivity analysis are related but distinct ideas [17]. Uncertainty analysis is normally used to investigate how uncertainty in model parameters affects model outputs [22]. Sensitivity analysis naturally follows uncertainty analysis as it gauges how variability in model outputs can be related qualitatively or quantitatively to contributions from changes in model parameters or other inputs [23, 24].

Several techniques have been developed for sampling-based approaches used to perform uncertainty analysis namely, Monte Carlo (MC) and Latin hypercube sampling (LHS) methods [25, 26, 27, 28, 29]. MC methods involve multiple

model evaluations using random numbers to sample from probability distributions of uncertain inputs. Sampling is guided by the specification of a probability density function, depending on *a priori* information. The results of these evaluations can be then used to characterise uncertainties in model responses and perform sensitivity analysis [30, 31, 32]. LHS methods use stratified sampling without replacement, where the random parameter distributions are divided into sub-intervals with equal probability. LHS is a space-filling technique that optimises the coverage of a high dimensional input space. LHS allows for unbiased measure of the average model output, with the advantage that it requires fewer samples when compared with simple random sampling to achieve the same coverage. Several developments that explain how to implement LHS methods in different scientific applications can be found in [33, 34, 35, 27].

Normally, uncertainties are considered to affect the output of a computational model, but they should not be termed errors because they are physical and inherent in the model itself. Errors can be defined as an *a priori* estimate of deficiencies in the models or the algorithms employed to solve them. Errors are mathematical in nature and arise when translating the system physics into approximate numerical algorithms and computational code. Inaccuracies, intrinsic to the discretisation process, are introduced in this step giving rise to numerical errors. These errors can be controlled and reduced to a smaller level if the numerical methods and algorithms used are selected carefully. Acknowledged error is related to the finite precision arithmetic that is used to perform the calculations (round-off) and convergence accuracy. Unacknowledged error is related to coding mistakes during implementation, and can lead to differences between codes that implement identical models [36].

3 Cell scale models

Cardiac electrophysiology models at the cellular scale reconstruct the action potential (AP) and Ca^{2+} transient of cardiac myocytes, facilitate understanding of mechanisms, and are represented typically using a system of non-linear, coupled, and often stiff ODEs [6]. Following the initial work by Noble in 1962 [37], tremendous progress has been made resulting in the development of numerous cell models for different species and different regions of the heart [6, 38, 39]. Depending on the purpose and context of use, these cell models are often constructed using biophysically-detailed, simplified or phenomenological frameworks [6, 38]. Whilst biophysically-detailed cell models integrate explicit descriptions of transmembrane ion channels, transporters and exchangers and intracellular Ca^{2+} handling, simplified models are generated by reducing the number of ODEs in biophysically-detailed models. In simplified models, intracellular Ca^{2+} dynamics are frequently described using a common pool [40], compartmentalized [41] or spatially-detailed representation [42]. On the other hand, phenomenological models are designed for large scale tissue simulations and utilise a minimal number of ODEs to reproduce key aspects of global dynamics of the transmembrane voltage at low computational cost [6], without

accounting for details of ion currents or Ca^{2+} handling.

Transmembrane voltage in cardiac cell models is generally described by a Hodgkin and Huxley type electrical circuit model, in which the gating behaviors of ionic currents are simulated using memory-less Markov chain-type models, and transporters and exchangers are simplified as time-independent processes [6]. Intracellular Ca^{2+} release from the ryanodine receptors (RyR) is modelled by multiple-state Markov models or ODEs. Although each component of these models is calibrated against data from carefully designed experiments, uncertainties can arise from discrepancy between the model and the real system, calibration, and choice of an appropriate model. We discuss each of these sources in turn.

3.1 Model discrepancy, calibration, and identifiability

Biophysically-detailed cell models combine models of subcellular processes and so model discrepancy (sometimes called structural uncertainty) in each component is propagated to the cellular level. This is exemplified by the number and topology of states in a Markov model of ion currents and current models of intracellular Ca^{2+} recycling [4], as well as simplifications to the models of intracellular Ca^{2+} buffers and post-translational modifications. Typically, models are calibrated before being used for predicting unseen scenarios, sometimes referred as the context of use. One aspect of model calibration is the process of tuning model parameters to minimise the difference between observations and model simulations. However even for cell-scale models this is not a trivial task [43]. Model parameters describing channel conductances and flux rates are generally further tuned to simultaneously calibrate the model output often to important electrophysiological biomarkers such as APD, resting membrane potential, upstroke velocity, and systolic and diastolic Ca^{2+} concentrations. These data are obtained from multiple experimental protocols and conditions (e.g., different pacing rates, extracellular ion concentrations).

Identifiability can be an important consideration when calibrating a model. An identifiable model has a unique set of parameters for which the model simulation matches a particular experiment [44]. Non-identifiability can indicate that the model structure is incorrect, or that the experimental observations do not allow the parameters to be identified. The activation and recovery of real cardiac cells is very robust, and is based on many redundant components. This redundancy can make the task of model calibration ill-posed. For instance, in [45] a model of the human ventricular action potential was adjusted to reproduce specific experimental observations. By calibrating only to the shape of the action potential, hundreds of models, each with a different parameter set, could reproduce the data and so the model was not identifiable. Conversely, a wide range of action potentials can be produced by variations in model parameters [46]. Measurements of action potentials alone may therefore be necessary but not sufficient to calibrate a cell model correctly [47, 48]. In [45], it was found that by using both the action potential shape and the transmembrane resistance profile as two different objective functions, the models were forced to solve a

trade-off and the possible candidates that could reproduce both observations decreased to just a few. Assessing whether we have sufficient experimental information that allows us to infer all of the parameters therefore becomes a task of primary importance [49, 21, 48], and recent review discusses these issues in detail [50].

3.2 An abundance of cell models

Cardiac cell models have been developed to represent myocytes from many different species and different parts of the heart. Many of these models have been encoded and curated within the CellML framework (see `https://models.physiomeproject.org/electrophysiology`). In addition, different research groups have independently developed cardiac models that represent the same species and region of the heart, usually based on different experimental data sets [51, 52, 53]. One might expect these models to be similar. However they usually differ in many aspects, and may behave very differently. Selecting an appropriate model for a particular task therefore becomes important, and highlights the limitations of cardiac electrophysiology models. For example Fig. 2 illustrates three models of the human ventricular action potential each with a different time course of action potential and principal currents.

In [51], six different models of human ventricular myocytes were compared. They were all based on systems of ODEs, but ranged from a phenomenological model with only four state variables, to a biophysically detailed model with 67 state variables. The differences in complexity reflect the intended context of use of these models. A more detailed context of use will usually require a more detailed model, but complexity often has to be tensioned against computational cost. For example, a model used to investigate the whole-cell consequences of a gene mutation or drug action will require a detailed Markov chain description of ion channel states, which may be computationally intensive when embedded in a tissue scale model. On the other hand, cell models that use the Hodgkin-Huxley (HH) formalism to describe ion channel kinetics would be appropriate for a study of arrhythmia dynamics, and would be less computationally intensive. We could think of a hierarchy of models, where detailed models should be able to reproduce some basic phenomena as precisely as the most simple model developed for this task. However this is not currently the case [51]. There are many possible reasons for this observation, and we describe three of them below.

First, the different models compared in [51] were developed using different experimental datasets, which partially explains the reason for their lack of consistency. Second, in [52], a comparison was carried out between two human atrial models that were based on the same set of experimental data available at the time. The models have similar complexity, were both based on the HH formalism, and yet behave differently. After a careful analysis, the lack of consistency was attributed to different structure in the models of intracellular Ca^{2+} storage and release. In the absence of Ca^{2+} data for human atrial cells, two different and previously developed mammalian models of Ca^{2+} handling were incorporated into the cell models. These modulate transmembrane ion currents

in different ways, resulting in uncertainty arising from different model discrepancies. A third source of inconsistency between models of the same species and the same region of the heart is natural variability. It is well known that neighbouring cells can behave similarly when diffusively coupled in tissue, but differently when isolated, which is due to electrotonic effects [54]. In addition, cells used in experiments can come from different hearts, of different ages, gender, and health condition, with different genotype and phenotype. However, most of the models in cardiac electrophysiology today do not take account of natural variability, which is often partially reported in experimental work using basic statistical measures such as mean and variance.

Uncertainties, variability, and errors in experimental observations can also come from experimental design, instrumentation, experimental conditions, experimental protocols, and can even be influenced by the experimentalist in charge of the experiment. Therefore, methods such as history matching (HM) and MCMC are promising for model calibration because they take explicit account of uncertainty and variability in observations. For instance, HM can define feasible regions of the model parameters that produce results within the experimental variability [55]. MCMC methods search for probability distributions for all the parameters that again can produce results within the experimental variability, but are more computationally demanding [56]. Therefore, instead of adjusting a single model to the experimental data, MCMC and HM can generate a population of models, where each model can reproduce the experiments within a margin given by the total variability.

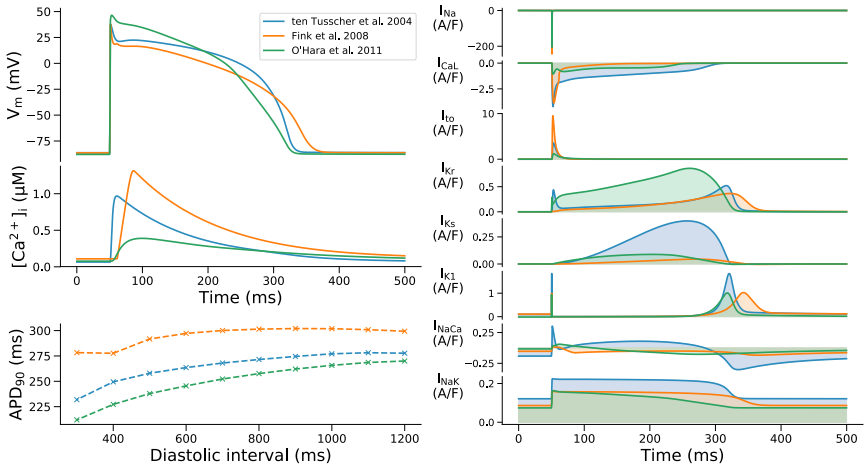

Figure 2: **Uncertainties in cell scale models arising from model choice** showing different action potential shapes, calcium transients, APD restitution, and time course of principal ionic currents produced by different human models for ventricular myocytes.

3.3 Uncertainty in cell scale models

Developing accurate mathematical models of cardiac cell electrophysiology requires integration of multiple data sets from various *in-vivo/vitro* sources into a reliable biophysical computational platform. Although this methodology is routinely applied, as demonstrated by the increasing number of studies which use or extend previously developed cardiac cellular models [57, 58], there are major challenges in increasing the prediction capabilities. A meta-analysis of two human ventricular cell models has shown that although both models aim to represent the same physiological system, the sources of parameter values from different species and cell types, as well as the function of equivalent components were significantly different [59]. Experimental measurements may be made at room temperature, and although model parameters are sometimes adjusted to compensate for temperature differences, these adjustments might lead to further uncertainty [60].

All of these uncertainties can affect features of interest in cardiac electrophysiology models. Uncertainty and variability in model parameters influence the shape and duration of both the action potential and the Ca^{2+} transient, as well as rate-dependent dynamical behaviours including APD restitution and the presence of alternans [52]. Even in a single cell model, wide variations in parameters can produce enormous variation in the action potential [46]. Certain regions in parameter space can also produce spontaneous depolarisation of cell models [61, 62]. The choice of cell model for a particular application is an important source of uncertainty, and discrepancy between the model and the real system may make the greatest contribution to output uncertainty (Fig 2). In the following section we consider how these cell-scale uncertainties combine with uncertainties associated with tissue scale models.

4 Generic tissue scale models

Models of action potential propagation in cardiac tissue reconstruct the electrical coupling of individual myocytes through gap junctions. Generic tissue models implement models of action potential propagation, where the tissue geometry is configured to answer a specific research question rather than to represent a particular individual. The main context of use for generic tissue models is as research tools for understanding integrative physiological mechanisms. Personalised models aim to reconstruct electrical activation in an individual, and we cover these in section 5. Uncertainty in generic tissue models arise from the choice of tissue geometry, modelling framework, initial conditions, and boundary conditions. We consider these in turn below.

4.1 Tissue geometry

Individual myocytes are rod-shaped, and tend to be aligned in fibres. Propagation in cardiac tissue is typically anisotropic because action potential propagation is faster along fibres than transverse to them. In ventricular tissue

the fibre structure can be well characterised [63], although this approach does not explicitly consider fibre branching. Furthermore, fibres are also arranged in sheets, and the orthotropic behaviour arising from preferential propagation within sheet planes is less well understood [64].

Generic cardiac tissue models can be configured as a 1D fibre, a 2D sheet, a 2D sheet with anatomical detail such as a short axis slice through the ventricles, a 2D surface representing generic atrial anatomy, a 3D tissue block with or without anisotropy/orthotropy (See for example Figure 3), a 3D ellipsoid or idealised biventricular model, or a 3D atrial or ventricular model based on generic anatomy. Fibre and sheet fields can be incorporated into anatomical models using rule-based methods that are grounded in experimental observations [63, 65, 66].

Simplified geometries enable mechanisms to be simulated and investigated without the confounding effects of anatomical detail, but there is associated model discrepancy because these geometries may not represent the fine detail of real tissue. For example there is a tendency for re-entrant drivers in AF to anchor in regions characterised by a large atrial wall thickness gradient [67, 68], and this is an observation that would be missed by simplified 2D atrial geometries. The importance of model discrepancy in this context depends on the research question, and so a simplified geometry should be chosen with consideration of the assumptions and limitations, and these should be carefully documented.

4.2 Modelling framework

A homogenisation approach to models of coupled cells leads to a set of one or more partial differential equations (PDEs) that describe action potential propagation, where the cell models described above appear as a reaction term [69, 9]. This is a convenient simplification that enables efficient numerical solutions on a mesh.

Cardiac tissue can be represented as a bidomain or a monodomain. For anisotropic tissue, if the ratio of longitudinal and transverse conductivity is the same for intracellular and extracellular space, and provided no current is injected into the extracellular space, the differences between bidomain and monodomain simulations are minimal [70, 71]. However, use of the bidomain model is essential for the correct modelling of the response to defibrillation [72]. Errors arising from numerical solutions of both monodomain and bidomain models are relatively small, provided care is taken to ensure numerical convergence [59, 73, 74].

The homogenisation inherent in both bidomain and monodomain models assumes that tissue can be treated as a functional syncytium. However, cardiac tissue microstructure affects activation and recovery in real tissue, and this is a source of model discrepancy. Important features include heterogeneity of cell type [54], fibre and sheet architecture [64], the presence of fibrosis and small lines of block [75, 76], and the role of the conduction system [77]. Some of these effects are blurred by diffusive coupling in bulk tissue, but may be exposed under pathological conditions such as the presence of fibrosis. For example, small scale features can be important for simulating mechanisms of atrial fibrillation [78],

and alternative approaches that preserve microstructure have been proposed [79, 80, 81].

Fibrosis is an important aspect of microstructure. Several recent studies have addressed the problem of representing the presence of fibroblasts, macrophages, and their coupling [82, 83, 84, 85], but there is no consensus on the most suitable approach. The spatial scale of patchy fibrosis varies, and different configurations of fibrosis influence vulnerability to arrhythmias [86, 87]. Although it is known that there are regional differences in the response of the ventricles to autonomic stimulation [88], the distribution of nerve terminals is not well established [89]. All of these can be considered to be sources of epistemic uncertainty in generic tissue models.

4.3 Parameter selection

A significant component of the modelling framework is the choice of model parameters including tissue conductivities, surface to volume ratio, and membrane capacitance. Tuning these parameters enables a tissue model to be calibrated so that it is representative of real tissue. However, these parameters depend on the choice of cell model [9], are very difficult to measure directly [64], may vary spatially, and estimates can vary as much as five-fold [9]. A pragmatic approach to calibration is to adjust these parameters to reconstruct the conduction velocity or activation pattern observed in real tissue. For anisotropic and orthotropic simulations, a further choice is the ratio of conductivities. Fig. 3 illustrates how the ratio of longitudinal and transverse conductivity, as well as the presence of curved fibres, can influence activation, recovery, and APD in a small tissue block. Detailed models of tissue microstructure are being used to characterise the distributions of these parameters in normal and diseased tissue [90], but parameter selection and choice of cell model should be considered an important source of uncertainty in generic tissue models.

4.4 Boundary and initial conditions

For monodomain simulations, typical boundary conditions are that the gradient of transmembrane potential difference normal to the edge or surface is zero. For bidomain simulations, different types of boundary condition can be imposed that can take into account the leakage of current into surrounding non-myocardial tissue [9]. The effects of changing boundary conditions on arrhythmia stability are small [71], but are important for detailed modelling of the response to pacing or defibrillation shocks [72]. On the other hand initial conditions can be important because of the nonlinear nature of behaviours such as VF mechanisms, where small perturbations to initial conditions can influence the activation sequence [4].

4.5 Uncertainty in generic tissue scale models

Cardiac tissue models inherit all sources of uncertainty in cell scale models, since their behaviour depends on the choice of cell model and the cell model parameters. For example, the action potential upstroke in a cell model influences conduction velocity in tissue, which goes on to affect the activation sequence. Both APD and APD restitution at cell scale affect the recovery sequence in tissue. Spontaneous depolarisation at the cell scale may be produced by variability in model parameters, and can result in arrhythmias in tissue [91]. Diffusive coupling in tissue tends to suppress the effect of both intrinsic and extrinsic variability in action potential shape and duration in cell scale models [14]. Nevertheless, selection of cell model parameters can affect the behaviour of simulated arrhythmias[92]. In particular, a cell-scale APD restitution curve that is either steep or shows alternans can increase vulnerability to re-entry in tissue, as well as influencing stability or re-entry [53, 52]. However, despite the generally accepted understanding that the cell model and its parameters influence simulated electrical activation in tissue, there is not yet a comprehensive and quantitative description of uncertainty propagation from cell to tissue scale.

A further issue is that although electrical activation in the heart acts to initialise and synchronise mechanical contraction, the effects of mechanics are often neglected in electrophysiology simulations and this is an important source of model disrepancy. Mechanical contraction not only deforms the tissue, but also changes repolarization via electrotonic effects, results in local changes in stretch activated ion channels, and promotes wavebreak and arrhythmia in disease conditions [93, 94, 95].

5 Personalised tissue models

Personalised computational tissue models of action potential propagation differ from generic tissue models in that the physical parameters and tissue geometry of the system are calibrated to simulate the behaviour of one or more chambers in the heart of a specific patient or animal. A personalised model can be thought of as a special case of a generic model. The objective or context of use for personalised electrophysiology modelling is to aid disease diagnosis, support treatment planning or as part of a broader cohort study seeking mechanistic insight by studying *individuals*. For example, one might seek to use personalised modelling to diagnose the origin or mechanism by which an arrhythmia is triggered or maintained in a particular individual, or to minimise destruction of myocardium by testing a range of potential ablation strategies [96].

In developing personalised models, care must be given to the choice of model as well as the assumptions and simplifications made. A personalised model of cardiac electrophysiology will use a similar modelling framework to generic tissue models. However, constructing personalised models also involves calibration using specific experimental or clinical measurements. These observations are typically noisy, sparsely collected, or incomplete due to practical or ethical

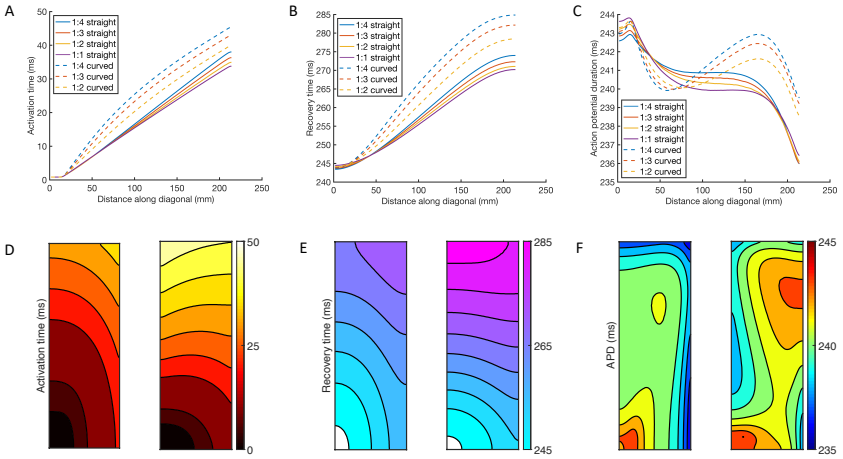

Figure 3: **Effect of anistropy ratio and curved fibres in a tissue model** Plots of (a) activation time, (b) recovery time, and (c) APD in simulations of action potential propagation along the diagonal of a $x = 20.0 \times y = 7.0 \times z = 3.0$ mm tissue block, with straight fibres aligned along the x-axis, as described in a benchmark study [59], or fibres that curve so that they are aligned with the x-axis at $x = 0$ and are aligned with the y axis at $x = 20$ mm. These measurements are shown for longitudinal:transverse anisotropy ratios of 1:4, 1:3, 1:2, and 1:1. Cell electrophysiology was described by the Ten Tusscher 2006 model, with a stimulus applied at one corner of the block. The lower panel shows (a) activation time, (b) recovery time, and (c) APD for simulations with anisotropy ratio of 1:3. Left panels show output for straight fibres and right panels show output for curved fibres.

considerations, which lead to sources of epistemic uncertainty [97].

5.1 Data acquisition for personalised models

Observations may be incorporated from a range of imaging modalities, electrical measurements or patient records. Imaging modalities include various forms of magnetic resonance imaging (MRI), particularly delayed gadolinium enhancement for quantifying and co-localising fibrosis and scar. Electrical observations can be used to calibrate tissue properties [98, 99], and are recorded either from the body surface or directly from the myocardium. The body surface electrocardiogram (ECG) is the most common electrical measurement because it is non-invasive. However ECGs provide only low-resolution information about the gross electrical activity of the heart. More recently electrocardiographic imaging (ECGi) offers a higher-resolution alternative and can localise information about activation and recovery times [100]. Intra-cardiac electrical signals (electrograms) are obtained from direct contact between a multi-polar diagnostic catheter and the myocardium at or close to the endocardial surface. These are more costly and necessarily invasive, but provide detailed and localised electrophysiological measurements as well as positional information that can be used to generate an endocardial mesh. Epicardial electrograms may also be obtained, for example during open-heart surgery [101].

5.2 Mesh generation

Electroanatomical mapping data or MRI are frequently used for generating a mesh representing the geometry of the personalised model. Fibre orientation is not easy to characterise *in-vivo* and so algorithmic methods are typically used to generate local fibre angles in personalised models [63]. The difference between algorithmic fibre orientation and the actual fibre orientation in an individual is likely to have a small effect on the electrical activation sequence, but could introduce a much greater discrepancy in models that include cardiac mechanics. Electroanatomical mapping uses catheter sensors to locate the interior surface of a chamber and build a corresponding mesh, however uncertainties may arise from observational uncertainty in electrode locations [97], missing regions of the chamber and the combined motion of the thoracic cavity and heart. If MRI is used t create a mesh, uncertainty may arise due to poor resolution of the imaging modality and errors in the segmentation process [102]. As an example of how mesh uncertainty affects model behaviour, Fig. 4 illustrates the effect of uncertainty in a left atrial mesh on simulated electrical activation times [102].

Minimally-invasive cardiac MRI also contributes to observational uncertainty in personalised modelling when delayed enhancement protocols are used to identify likely regions of scar or fibrosis based on the signal intensity. In particular challenges in the normalisation of MR signal intensity may lead to differences in the level of intensity used to identify scar and therefore poor intra-patient reproducibility and inter-patient consistency [103, 104].

5.3 Model selection and parameter fitting

For personalised tissue models to be used in the clinical setting, a simplified cell model is often used to reduce computation time [98, 105], and so model discrepancy associated with this choice can be an important consideration. Parameter uncertainty arises directly in tissue conductivities due to our limited understanding of how MRI intensity relates to the electroarchitecture of the imaged substrate [106, 107, 108, 104]. This may be further compounded by uncertainties due to co-registration of data from different imaging modalities. Parameter uncertainty also arises due to heterogeneity of cell types, which is challenging to measure *in-vivo*. This might be accounted for in the calibration process [109].

Where electrograms are used for parameter fitting, observational uncertainty may include errors in the electrode location which is often determined due to a magnetic or impedance based localisation system. This will affect both the electroanatomic geometry generated by the mapping process as well as the relative position of specific recordings [97, 110]. Electrode movement during signal acquisition will also generate uncertainty. Processing of the signals used for calibration will also be subject to observational uncertainty. For example, local activation times (LATs) are regularly computed clinically and the consistent identification of these timings is often unclear [97]. This may be due to noise in the signal arising from poor contact or changes in impedance due to the movement of blood around the electrode.

Model discrepancy may also become more significant for personalised modelling where the pathological substrate is poorly characterised and represented in the mathematical model. For example, the nature of conduction across diffuse fibrosis in the atrium is poorly understood and there are outstanding challenges in constructing the most appropriate representation in mathematical models [82]. There are also residual uncertainties due to physical processes which are often not accounted for, such as the lack of an explicit Purkinje network in a ventricular model.

5.4 Uncertainty in personalised models

Personalised models inherit uncertainties from cell scale and generic tissue scale models. The increase in model complexity in personalised tissue models leads to a corresponding increase in the complexity and sensitivity of the output to uncertainty and variability in the model and its parameters. Consequently robust UQ becomes more important, particularly when the context of use requires identifying bifurcations in the solution space; for instance, when determining if a particular treatment will terminate an arrhythmia, or not.

A key challenge is to balance the effect of uncertainties arising from these sources against the benefits of a personalised approach. Some of the unique considerations for UQ in personalised models in the clinical setting include effective model calibration given time constraints and limited data, how uncertainties propagate across scales, and communicating uncertainties effectively so

that model outputs can be used as part of the decision making process. A further challenge is to develop or adapt methods to generate consistent samples from uncertain anatomical and functional measurements. For example an anatomical model sampled from a statistical shape model [102] should have tissue conductivities that are sampled such that the activation sequence is consistent with observations. Samples that also represent microstructure are an additional challenge, although methods developed for geostatistical modelling may prove to be of benefit in the future [111].

Initial condition and boundary condition uncertainties are particularly significant for personalised modelling and are closely related to the observational uncertainties described above. In particular, pacing locations may be uncertain (due to observational error) but also the current amplitude injected, duration and stimulus and contact area of pacing electrode are may not be known precisely. More subtle effects may result from the way that a re-entrant arrhythmia is initiated. For example atrial fibrillation can be initiated by simulating burst pacing [96, 112] or by seeding phase singularities [113], and an arrhythmia may be simulated in a model tuned to sinus rhythm [105]. The relative importance of these uncertainties remains an open question.For models that link to mechanics and the cardiovascular system then the idea of a physiological envelope of plausible initial and boundary conditions becomes important.

The relative importance of these uncertainties is not well characterised. Initial studies indicate that uncertainty arising from geometry and the fibrotic substrate may be more important than uncertainties or variability in cell and tissue electrophysiology, and this observation was consistent for both atrial and ventricular models [114, 115, 116]. Further studies should investigate the individual and combined effects of the factors listed above on patient specific predictions. Understanding the way that uncertainties in mesh generation combine with model discrepancy to influence model credibility is an important and as yet unanswered question.

6 Challenges, open questions and recommendations

In this paper we have reviewed the potential sources of uncertainty in multi-scale models of cardiac electrophysiology. The list is a long one, and one response would be that cardiac electrophysiology models are unreliable because of the potential for uncertainties in outputs. On the other hand, the value and effectiveness of multi-scale cardiac models for explaining underlying mechanisms and guiding interventions has been demonstrated in a range of experimental and clinical studies [98, 99, 117, 118]. The importance of the present analysis is therefore to highlight the *potential* impact of uncertainties on model outputs and predictions, and to make recommendations for ways in which these impacts can be mitigated. Some sources of uncertainty and variability, especially at the cell scale, are becoming understood. Others are not well characterised. A quan-

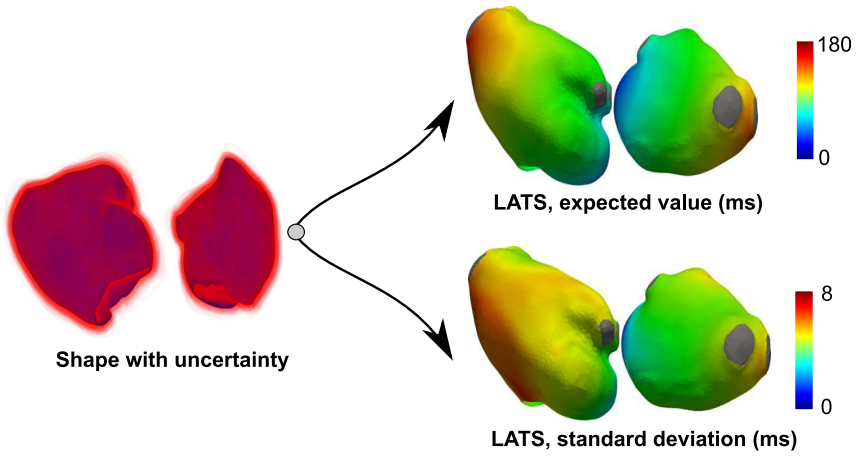

Figure 4: **Impact of shape uncertainty on simulated activation times in the human left atrium.** Left panel shows statistical model of the human left atrium, with the mean shape shown as solid surface and uncertainty shown as blurring. Right hand panel shows expected value (top) and standard deviation (bottom) of local activation time (LAT), following initial activation close to the coronary sinus. For further details see [102].

titative and systematic assessment of their relative importance, and how they are coupled across scales, remains an important challenge. We have highlighted particular open questions below.

- **Cell model calibration and identifiability** remain key concerns for cardiac electrophysiology models. This topic is covered in detail by another paper in this volume [48] and a recent review [50]. Despite some progress, there is a need to reflect on current experimental methods [119, 21], the way that uncertainties in experimental data are taken into account in cell model calibration [43, 120], ways to fit models to data from individual cells and populations [45, 49, 46], the extent to which experimental datasets are available to the research community, and how cell models can be constructed to facilitate uncertainty and sensitivity analysis [18]. The importance of identifiability is yet to be explored in depth; in some situations it may be important to know that a model is uniquely identifiable, but identifiability may be less of a concern for generic tissue models that aim to reconstruct generic behaviours.

- **Selection of an appropriate cell-scale model** to answer a particular research question can be difficult because it may involve choosing among many models, each with associated assumptions, simplifications, and model discrepancy. Recent comparative studies (e.g. [52, 51]) are

helpful in this regard, along with tools that enable comparison of model components [121]. However, cell models are often selected based on personal preference or existing codes, so there is a clear need for guidelines that can be used for rational model choice.

- **Natural variability** has been assessed at the cell scale [49, 46, 39, 13], tissue scale [14] and in population studies of shape [102]. However, there are open questions about how natural variability at these different scales interacts to influence tissue and organ scale behaviours, how natural variability should be accounted for in generic models, how natural variability in generic models should inform the credibility of personalised models, and how prior distributions of model parameters can be constructed to represent natural variability. Methods developed for geostatistics may be promising tools to identify and take account of spatial correlations among model parameters in cardiac tissue [111].

- **Cohort modelling of variability within populations** is important for *in-silico* clinical trials where a model is used to simulate an intervention on a range of patients [5]. Methods and techniques developed for UQ will be relevant for this type of application, but progress is at an early stage.

- **Quantitative comparison of different sources of uncertainty and variability** at different scales has yet to be undertaken in a systematic way. The present manuscript has highlighted potential sources of uncertainty, and the next step is to assess their relative importance quantitatively. This open question will highlight important sources of uncertainty, and will motivate efforts to reduce them. A particular example would be the way that credibility of a personalised model is informed by better understanding of sources in uncertainty in generic tissue models.

- **Coupling of uncertainties across scales** requires tools to couple uncertainties across scales and types of model [92, 116]. This coupling may operate not only from cell to whole organ, but also in the reverse direction. Co-variances among model parameters, especially at different scales, are also an important consideration. A recent study has reviewed sensitivity analysis in many different modelling applications, and has highlighted the fact that many sensitivity analyses are flawed because model input spaces have not been explored thoroughly taking into account co-varying inputs [122].

Cardiac electrophysiology models have become a valuable tool not only for basic science, but also have been proposed for transition into clinical applications [98, 99, 117, 118]. The credibility of model outputs has therefore become an important challenge. Models are necessarily incomplete representations of reality, and so uncertainty and sensitivity analysis should focus on quantifying the extent to which the model outputs are reliable, and the minimisation of uncertainty [122]. For safety-critical applications, these are crucial questions.

The main recommendation from the present analysis is therefore that taking into account uncertainty and variability should be considered a critical aspect of cardiac electrophysiology model development and evaluation. This is a particularly important consideration for models that are to be used in safety-critical applications, where there is a need to assess robustness of outputs, and sensitivity to clinically meaningful biomarkers. Examples of good practice are beginning to emerge, where the robustness of a predictive model to uncertainties in the anatomical mesh and electrophysiology have been assessed [114, 115]. Nevertheless there is an urgent need for end-to-end UQ frameworks that include tools for model calibration, data assimilation, uncertainty propagation using both intrusive and non-intrusive methods, as well as certification and validation.

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