Journal of Molecular and Cellular Cardiology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology

journal homepage: www.elsevier.com/locate/yjmcc

# Uncertainty and variability in models of the cardiac action potential: Can we build trustworthy models?

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ARTICLE INFO

*Article history:*
Received 31 May 2015
Received in revised form 13 October 2015
Accepted 17 November 2015
Available online xxxx

*Keywords:*
Uncertainty quantification
Cardiac electrophysiology
Mathematical model
Probability

ABSTRACT

Cardiac electrophysiology models have been developed for over 50 years, and now include detailed descriptions of individual ion currents and sub-cellular calcium handling. It is commonly accepted that there are many uncertainties in these systems, with quantities such as ion channel kinetics or expression levels being difficult to measure or variable between samples. Until recently, the original approach of describing model parameters using single values has been retained, and consequently the majority of mathematical models in use today provide point predictions, with no associated uncertainty.

In recent years, statistical techniques have been developed and applied in many scientific areas to capture uncertainties in the quantities that determine model behaviour, and to provide a distribution of predictions which accounts for this uncertainty. In this paper we discuss this concept, which is termed uncertainty quantification, and consider how it might be applied to cardiac electrophysiology models.

We present two case studies in which probability distributions, instead of individual numbers, are inferred from data to describe quantities such as maximal current densities. Then we show how these probabilistic representations of model parameters enable probabilities to be placed on predicted behaviours. We demonstrate how changes in these probability distributions across data sets offer insight into which currents cause beat-to-beat variability in canine APs. We conclude with a discussion of the challenges that this approach entails, and how it provides opportunities to improve our understanding of electrophysiology.



## 1. Introduction

Models of the cardiac action potential (AP) are established, valuable, and important research tools because they integrate biophysical mechanisms quantitatively, and so have explanatory and predictive power. Since the publication of the first cardiac AP model over 50 years ago [31] these models have become more detailed as our knowledge of the function of ion channels, pumps, and exchangers in cardiac myocytes has increased [11]. Contemporary models are sufficiently detailed to allow the effects of ion channel gene mutations, pharmaceuticals, and disease to be examined in mechanistic detail [41], [28]. However, while the present generation of models are powerful tools, model parameters are generally assigned a fixed value, which means that the models produce a fixed prediction.

In contrast, the experimental APs recorded from real cardiac cells are variable, with changes from beat-to-beat in a single cell (termed intrinsic variability), and from one cell to another (extrinsic variability). Intrinsic variability may be caused by random processes such as stochastic ion channel gating, non-linear dynamics such as alternans of action potential duration (APD), or more complex behaviour. Extrinsic variability is considered to be caused by quantities that genuinely vary from cell to cell, e.g. cell size or ion channel expression. In practice it can be difficult to distinguish these sources of variability; in what follows we model variability as extrinsic only, although some of our data may also capture intrinsic variability. In addition, variability can be compounded by measurement errors when data from experiments are used to generate parameters for use in AP models.

*Abbreviations:* AP[D], Action Potential [Duration]; CMA–ES, Covariance Matrix Adaptation–Evolution Strategy; GP, Gaussian Process; MCMC, Markov Chain Monte Carlo; NLME, Non-Linear Mixed Effects; TP06, the ten Tusscher *et al.* (2006) [45] action potential model; UQ, Uncertainty Quantification; $V_m$, trans-membrane Voltage; VVUQ, Verification, Validation & Uncertainty Quantification.

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http://dx.doi.org/10.1016/j.yjmcc.2015.11.018

Problems related to uncertainty and variability are not unique to cardiac electrophysiology, and new approaches are beginning to emerge from areas as diverse as models of the atmosphere [24] and galaxy formation [47]. In this paper we describe how these approaches might be applied to cardiac AP models.

### 1.1. Uncertainty quantification and cardiac action potential models

There are several potential sources of uncertainty in a computational model of a real system; these include, at least, the following [47]:

- *Observational uncertainty* is uncertainty or measurement errors in experimental data. For example, uncertainty represented by error bars in measurements of the current–voltage profile for a particular ion channel used to assign model parameters, or error bars in measurements of APD restitution used to evaluate model performance. Note that this uncertainty can encapsulate both intrinsic and extrinsic variability.
- *Parameter uncertainty* refers to uncertainty in model parameters, which may be a consequence of observational uncertainty as well as variability, or simply lack of information. It may be advantageous to express a model parameter (such as a maximal conductance) as a random variable with a distribution, rather than a fixed value.
- *Condition uncertainty* describes our uncertainty about the initial conditions and boundary conditions. For a cardiac AP model the initial conditions are typically set by running the model until it has reached a steady state, but this will not capture the constantly varying environment of temperature, ion concentrations, and metabolism in which a real cell operates.
- *Structural uncertainty* accounts for the differences between a model and the real system that it represents. For example, a model of an ion channel will not be an exact representation of the biophysical dynamics of a population of proteins in the membrane, and structural uncertainty aims to quantify this difference.
- *Simulator uncertainty* addresses the uncertainty introduced when using an approximation to the true solution of the equations of the mathematical model when we perform a simulation. This includes any uncertainty introduced by using discretisation in numerical methods (numerical error), or uncertainty when a fast-running surrogate model (e.g. an emulator) is used approximate the outputs of a computational model that is expensive to solve.

Techniques for uncertainty quantification (UQ) provide a means to deal with these different sources of uncertainty. In this paper we concentrate on UQ methods that address parameter and condition uncertainty, which will also concern observation and simulator uncertainty. Statistical methods for structural uncertainty can be complex and are outside the scope of this paper. Such techniques attempt to statistically quantify the 'model bias', the difference between model and experiment; the interested reader may refer to [22].

There are two stages to UQ related to parameter/condition uncertainty (for clarity we only refer to parameters below, but the same ideas apply to initial or boundary conditions, though these may be more difficult to measure):

1. *Uncertainty characterisation* regards uncertainty in model *inputs*. In this stage uncertainty in parameters is characterised by assigning probability distributions to input parameters instead of single values, although sometimes simple statistics (i.e. means and variances) are used. If the input is a parameter that is directly measurable, this is a purely experimental task because the probability distribution is informed by the experimental observations. On the other hand, if the input is a parameter that is indirectly inferred from other data, statistical methods may be required to estimate the parameter uncertainty (examples will be provided in this paper).
2. *Uncertainty propagation* (or *uncertainty analysis*) regards uncertainty in model *outputs*. Here the aim is to establish the uncertainty in model outputs due to the uncertainty in inputs, again as probability distributions or simple statistics. Generally, this stage is very computationally-demanding, since a large number of simulations are needed to generate outputs for the different combinations of inputs that are possible. Sophisticated methods have been developed to mitigate such difficulties, as will be illustrated in this paper

Interest in UQ has grown as part of a drive for rigorous and formal approaches to assess the credibility of computational models. The heavy use of computational models for safety-critical applications in the automotive, aerospace, nuclear and structural engineering industries in particular motivated the development of 'Verification, Validation and Uncertainty Quantification' (VVUQ), which forms a set of methodologies, frameworks and best practises for improved assessment of the reliability and robustness of model predictions [30], [33]. In this context, *verification* is defined as the process of confirming that a computational model (software) correctly implements an underlying mathematical model, and validation compares a model's predictions with reality. Although UQ forms part of the overall VVUQ process, each of the stages are intertwined, and in particular UQ improves the ability to perform validation, since understanding the uncertainty in model predictions facilitates comparison with experimental results.

Until recently, VVUQ has not been a priority for cardiac modelling, because this type of model has not been widely used in high-risk or safety-critical applications. However, the present generation of cardiac AP models are sufficiently detailed that there is the prospect that they could be used as both as part of clinical applications and also for drug safety assessment. Both of these applications are safety critical. For clinical applications the model output could be guidance for ablation in clinical procedures, and the inputs would include personalised measures of tissue conductivity and anatomy [46]. For safety testing in drug development, the output could be a measure of action potential prolongation, and the inputs would include a quantification of the reduction of different ion currents as a function of compound concentration [27]. In both types of application it will be important to express a measure of confidence in the model outputs, given uncertainties and errors in the inputs. As a result, there has been growing interest and application of (VV)UQ in cardiac modelling [14], [10], [36], [37], [38].

In [38] Pathmanathan *et al.* quantified the natural variability in the steady-state inactivation of the canine fast sodium channel using a statistical framework known as Non-Linear Mixed Effects (NLME) modelling. The authors examined the consequences of this uncertainty at the cellular and tissue scales, in perhaps the first application of uncertainty quantification to multi-scale cardiac modelling. In Fig. 1 we present a summary of this study, as it provides an excellent introduction to the concept of uncertainty quantification applied to this field.

We have also included a short extension to this work in Supplementary Material A, where we examine how the same technique can be applied to investigate both intra- and inter-animal variability in cellular recordings.

### 1.2. Aim and scope

The pipeline shown in Fig. 1 concentrates on a single component of $I_{Na}$ channel behaviour, and examines how observation uncertainty can be expressed as parameter uncertainty, and how UQ can be used to establish how these uncertainties influence the model output.

The aim of this paper is apply a statistical UQ approach to cardiac AP models, and so gain mechanistic insight into the models as well as cardiac myocytes. We present two complementary case studies. In the first case study we show how the maximal conductances of ion channels can be inferred from noisy experimental recordings as distributions that express uncertainty about the estimates. The second case study then uses a statistical model (an *emulator*, surrogate model or metamodel) of a cardiac AP model to examine how uncertainties in maximal ion channel conductances influence uncertainty in model outputs, such as APD.

Please cite this article as: R.H. Johnstone, et al., Uncertainty and variability in models of the cardiac action potential: Can we build trustworthy models?, J Mol Cell Cardiol (2015), http://dx.doi.org/10.1016/j.yjmcc.2015.11.018