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Variability in cardiac electrophysiology: Using experimentally-calibrated populations of models to move beyond the single virtual physiological human paradigm

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ABSTRACT

Physiological variability manifests itself via differences in physiological function between individuals of the same species, and has crucial implications in disease progression and treatment. Despite its importance, physiological variability has traditionally been ignored in experimental and computational investigations due to averaging over samples from multiple individuals. Recently, modelling frameworks have been devised for studying mechanisms underlying physiological variability in cardiac electrophysiology and pro-arrhythmic risk under a variety of conditions and for several animal species as well as human. One such methodology exploits populations of cardiac cell models constrained with experimental data, or experimentally-calibrated populations of models. In this review, we outline the considerations behind constructing an experimentally-calibrated population of models and review the studies that have employed this approach to investigate variability in cardiac electrophysiology in physiological and pathological conditions, as well as under drug action. We also describe the methodology and compare it with alternative approaches for studying variability in cardiac electrophysiology, including cell-specific modelling approaches, sensitivity-analysis based methods, and populations-of-models frameworks that do not consider the experimental calibration step. We conclude with an outlook for the future, predicting the potential of new methodologies for patient-specific modelling extending beyond the single virtual physiological human paradigm.

1. Introduction

Physiological variability manifests itself through differences in physiological function between individuals of the same species (Britton et al., 2013; Marder and Taylor, 2011; Sarkar et al., 2012). In cardiac electrophysiology, there are significant inter-subject and intra-subject differences in the electrical activity of cardiac tissue from the same region of the heart (Feng et al., 1998; Walmsley et al., 2015). At the level of isolated cardiac cells (cardiomyocytes), variability becomes apparent via differences in the morphology and duration of their electrical signal – the action potential (AP).

One cause of variability is the biophysical processes responsible for the flow of ionic currents across the cellular membrane. Multiple proteins regulate the sarcolemmal flow of ionic species vital for electrophysiological function, including sodium, calcium, and potassium ions, and an alteration in the balance of these ionic currents would give rise to differences in the AP. Crucially, these currents are affected by processes such as protein expression (Schulz et al., 2006), cell environment (Severi et al., 2009; Vincenti

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et al., 2014), and circadian rhythms (Jeyaraj et al., 2012; Ko et al., 2009). Therefore, even for a specific cell, the balance of ionic currents will change in time or under drug action and following the onset of disease.

Physiological variability has significant implications for treating and managing heart diseases. For instance, drugs that are designed to have anti-arrhythmic properties in a diseased tissue, at certain heart rates, and with a particular acid-base balance, can become pro-arrhythmic at different heart rates or in less diseased tissue (Savelieva and Camm, 2008). Likewise, susceptibility to pathological conditions such as arrhythmias can also differ from individual to individual or depending on the condition of the patient (Severi et al., 2009; Vincenti et al., 2014). By studying variability, we can explore and improve our understanding of the mechanisms that lead to differences in outcomes when different individuals have the same condition or are given the same treatment.

Physiological variability is difficult to investigate with experimental methods alone (Carusi et al., 2012; Sarkar et al., 2012) due to the need to average data to control experimental error. Recently, a body of research (Britton et al., 2013; Groenendaal et al., 2015; Sarkar et al., 2012) has shown the power of computer models for investigations into the sources and modulators of biological variability. Specifically, populations of models – also referred to as ensembles of models – have proven useful in investigations of cardiac electrophysiological variability as reviewed by (Sarkar et al., 2012). Recent studies have furthered the methodology by explicitly incorporating experimental data into the construction of populations of models, thus yielding *experimentally-calibrated populations of models* (Britton et al., 2014, 2013; Muszkiewicz et al., 2014; Passini et al., 2015; Sánchez et al., 2014; Zhou et al., 2013).

The main aim of this paper is to review recent insights into variability in cardiac electrophysiology obtained through experimentally-calibrated populations of models in a variety of cell types and species. We discuss the ability of the experimentally-calibrated population-of-models methodology to provide new insights into sources and implications of variability in cardiac electrophysiology in physiological and pathological conditions, and following pharmacological interventions. The paper presents a description of the methodology and its comparison with alternative approaches for studying variability in cardiac electrophysiology, including cell-specific modelling (Davies et al., 2012; Groenendaal et al., 2015; Syed et al., 2005), sensitivity-analysis-based methods (Pueyo et al., 2010; Romero et al., 2009; Sobie and Sarkar, 2011; Sobie, 2009), and population-of-models methods without experimental calibration (Cummins et al., 2014; Devenyi and Sobie, 2015; Sarkar et al., 2012; Walmsley et al., 2013; Yang and Clancy, 2012). We conclude with an outlook for the future, predicting the potential of new methodologies for patient-specific modelling beyond the single virtual physiological human paradigm. This paper is part of the special issue on Recent Developments in Biophysics & Molecular Biology of Heart Rhythm.

2. Description of the experimentally-calibrated population-of-models methodology

Fig. 1 illustrates the process of developing and analysing an experimentally-calibrated population of models, described in more detail in the following sections.

2.1. The research question and the baseline model of cellular electrophysiology

The research question (and corresponding hypotheses) will inform both the choice of experimental data and the modelling process. These will be the two corner stones for the construction of

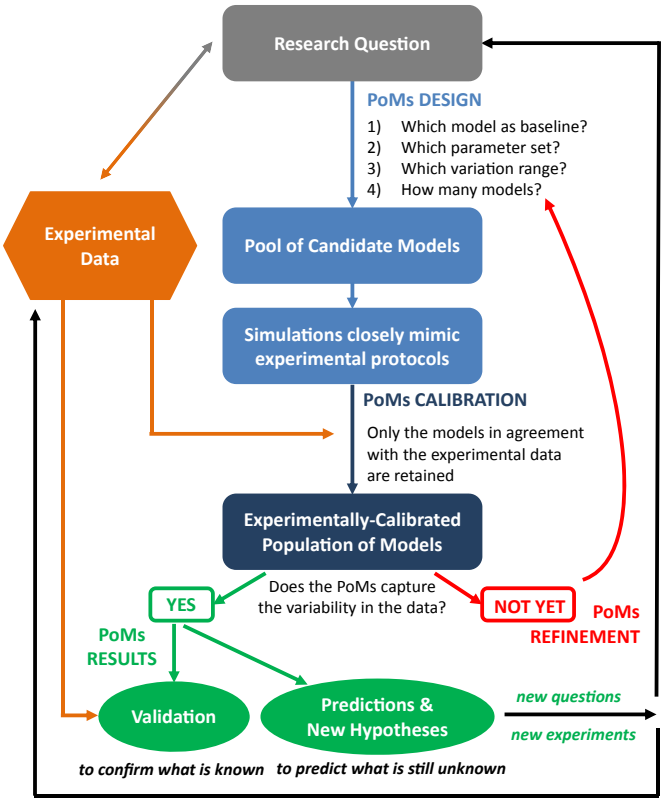

Fig. 1. Flowchart illustrating the process behind constructing an experimentally-calibrated population of models (abbreviated as PoMs).

the experimentally-calibrated population of models. A common assumption is that inter-individual variability affects electrophysiology at the level of ionic current properties (such as the ionic current conductances, time constants of channels opening/closing, and other parameters characterising the currents), and not at the level of ion channel structure (which is represented in the models through equations describing each modelled channel's transitions between gating states) (Britton et al., 2013; Groenendaal et al., 2015; Sarkar et al., 2012). Therefore, at the initial stage of modelling, one selects an appropriate cardiac cell model whose model equations are used as a 'scaffold', whilst the baseline model parameters are varied to represent variability in ionic current properties.

Aside from the research question, additional factors that may play a critical role in selecting the baseline model to use as the scaffold are model complexity and unique model characteristics, particularly if multiple models of a particular cell type exist. For instance, there are six published biophysically-detailed models of human atrial electrophysiology (Colman et al., 2013; Courtemanche et al., 1998; Grandi et al., 2011; Koivumäki et al., 2011; Maleckar et al., 2009; Nygren et al., 1998). The Colman et al., Courtemanche et al. and Grandi et al. models produce a spike-and-dome AP; however, the latter model includes a formulation for chloride current that is missing in the former. In comparison, the models of Nygren et al., Maleckar et al. and Koivumäki et al. generate more triangular APs. At the same time, the Maleckar et al. model is the only one able to incorporate the effects of vagal stimulation on the AP due to the inclusion of acetylcholine-activated potassium current, while the Koivumäki et al. model contains a much more detailed description of the intracellular calcium transient compared to the remaining models. The assumptions made in a particular study, together with key features of experimental data to be