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Limitations in electrophysiological model development and validation caused by differences between simulations and experimental protocols

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ABSTRACT

Models of ion channel dynamics are usually built by fitting isolated cell experimental values of individual parameters while neglecting the interaction between them. Another shortcoming regards the estimation of ionic current conductances, which is often based on quantification of Action Potential (AP)-derived markers. Although this procedure reduces the uncertainty in the calculation of conductances, many studies evaluate electrophysiological AP-derived markers from single cell simulations, whereas experimental measurements are obtained from tissue preparations. In this work, we explore the limitations of these approaches to estimate ion channel dynamics and maximum current conductances and how they could be overcome by using multiscale simulations of experimental protocols.

Four human ventricular cell models, namely ten Tusscher and Panfilov (2006), Grandi et al. (2010), O'Hara et al. (2011), and Carro et al. (2011), were used. Two problems involving scales from ion channels to tissue were investigated: 1) characterization of L-type calcium voltage-dependent inactivation $I_{Ca,L}$; 2) identification of major ionic conductance contributors to steady-state AP markers, including APD_{90}, APD_{75}, APD_{50}, APD_{25}, *Triangulation* and maximal and minimal values of V and dV/dt during the AP (V_{max}, V_{min}, dV/dt_{max}, dV/dt_{min}).

Our results show that: 1) $I_{Ca,L}$ inactivation characteristics differed significantly when calculated from model equations and from simulations reproducing the experimental protocols. 2) Large differences were found in the ionic currents contributors to APD_{25}, *Triangulation*, V_{max}, dV/dt_{max} and dV/dt_{min} between single cells and 1D-tissue.

When proposing any new model formulation, or evaluating an existing model, consistency between simulated and experimental data should be verified considering all involved effects and scales.

Contents

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1. Introduction

From the earliest mathematical model of an electrical cell's action potential (AP) developed by Hodgkin and Huxley in the fifties, the complexity of current AP models has grown considerably. The advent of new experimental techniques has made large sets of experimental data readily available, which has motivated the development of more complex models to accurately describe cellular electrical activity. Whereas growing in model complexity is a natural consequence of the increased knowledge (Noble et al., 2012), the more complex the model, the more difficult the identification of model parameters tends to be. An AP model involves the sum of different transmembrane ionic currents and the balance between intra- and extra-cellular ionic concentrations. Each ionic current follows a mathematical formulation in which several effects are present, e.g., ion channel activation and inactivation gating or current conductance. For each effect, a number of model parameters are identified based on data from experimental protocols specific for each particular ionic current.

The experimental protocols used to obtain most of the parameters of each ionic current are performed in isolated cells. But, due to the sensitivity of some ionic channels to the cell isolation process used in voltage-clamp experiments (Yue et al., 1996), the conductances of the ionic currents in cardiac models are often not estimated from direct measurements of the current density. Instead, individual channel conductances are adjusted so that measures from model-generated APs closely match experimental AP measurements in tissue such as AP duration (APD) or others. In the Courtemanche-Ramirez-Nattel (CRN) model (Courtemanche et al., 1998), the ionic conductances G_{Na}, G_{K1}, G_{to}, G_{Kr} and G_{Ks} were fitted to obtain a correct input resistance, AP morphology, AP amplitude (APA) and upstroke velocity (dV/dt_{max}). In a late version of the Luo-Rudy (LR) model (Zeng et al., 1995), G_{Ks} was fitted to get the right APD prolongation when the I_{Ks} current was blocked. Taking those models as an example, in the tenTusscher-Noble-Noble-Panfilov (TNNP04) model (ten Tusscher et al., 2004), G_{Ks} was set to obtain physiologically plausible APD values for each cell type (epicardial, midmyocardial and endocardial). In the Grandi-Pascualini-Bers (GPB) model (Grandi et al., 2010), G_{Na} was set so as to reproduce experimental measurements of APA and maximum value of the transmembrane potential (V_{max}). In the O'Hara-Rudy dynamic (ORd) model (O'Hara et al., 2011), the potassium current conductances were fitted to reproduce the experimental effect on the APD when they were blocked. Finally, in the Carro-Rodríguez-Laguna-Pueyo (CRLP) model (Carro et al., 2011), using the sensitivity analysis proposed in Romero et al. (2009), G_{K1}, G_{NaK}, $G_{Ca,L}$, and G_{Na} were fitted to obtain not only APD values within physiological ranges, but also other markers of arrhythmic risk, including time constants of APD rate adaptation or rate dependence of ionic concentrations.

On the contrary, the parameters that model current kinetics (gating parameters) are usually identified from single-cell experiments. The calibration process is usually performed using a nonlinear least square fitting of voltage clamp data by assuming that each parameter's effect is independent from the rest (e.g., the steady-state of an inactivation gate is calibrated against experimental results while considering that the time constant of the gate does not affect such results, which might not be correct). . However, when the complexity of the model increases, the interaction between effects becomes increasingly important. Therefore, assuming independence of the effects when identifying model parameters may be misleading. While other techniques have been proposed in recent years to improve the fitting of the gating parameters (Csercsik et al., 2012; Dokos and Lovell, 2004; Lee et al., 2006; Wang and Beaumont, 2004), none of the models analyzed in the present study have used such techniques.

Once model parameters have been identified, the resulting AP models are validated against experimental measurements commonly obtained also from tissue preparations. Characteristics such as resting membrane potential (V_{min}) and upstroke velocity (dV/dt_{max}) are usually compared between model-generated and experimental APs. In the CRN model, the role of different ionic conductances, the morphology of the AP, and the behavior of the model under different cycle lengths (CLs) were compared with experimental observations. In the updated version of the LR model (Zeng et al., 1995), the theoretical APD restitution curve was compared with an experimental restitution curve obtained by means of optical recordings of cardiac APs. In the TNNP04 model, simulated APD restitution curves (at 90% repolarization, APD_{90}) were evaluated in single cells to validate the model against experimental results measured in tissue preparations. Also in this model, propagation in a homogeneous one-dimensional (1D) tissue was simulated to validate the model in terms of Conduction Velocity (CV). In a subsequent version of the model, the ten Tusscher-Panfilov (TP06) model (ten Tusscher and Panfilov, 2006), simulated APD restitution curves (at 90% and 50% repolarization) in single cells were compared with experimental results. The GPB model was validated by comparing the predicted APD_{90} prolongation caused by blockade of different potassium currents with experimental results. The CRLP model, as the GPB model, was validated by comparing APD_{90} prolongation caused by potassium current blockades with experimental results, but also by comparing a number of computed markers not used in the fitting process.

For the aforementioned reasons, problems appear in the calibration and/or validation of electrophysiological models caused by two related situations: submodel variable interactions and cell-to-cell interactions during the AP propagation. Parameters related to ion channel gating kinetics are commonly obtained by considering each gate of the channel independently. Ionic conductances are adjusted or validated with experimental data obtained from tissue preparations by using single cell computer simulations. In both situations, the differences caused by not considering the corresponding interactions introduce non-negligible cross-effects between parameters that are not considered in the fitting process.