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Original article

A web portal for in-silico action potential predictions

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ABSTRACT

Introduction: Multiple cardiac ion channels are prone to block by pharmaceutical compounds, and this can have large implications for cardiac safety. The effect of a compound on individual ion currents can now be measured in automated patch clamp screening assays. In-silico action potential models are proposed as one way of predicting the integrated compound effects on whole-cell electrophysiology, to provide an improved indication of pro-arrhythmic risk.
Methods: We have developed open source software to run cardiac electrophysiology simulations to predict the overall effect of compounds that block I_{Kr}, I_{CaL}, I_{Na}, I_{Ks}, I_{K1} and I_{to} to varying degrees, using a choice of mathematical electrophysiology models. To enable safety pharmacology teams to run and evaluate these simulations easily, we have also developed an open source web portal interface to this simulator.
Results: The web portal can be found at https://chaste.cs.ox.ac.uk/ActionPotential. Users can enter details of compound affinities for ion channels in the form of IC_{50} or pIC_{50} values, run simulations, store the results for later retrieval, view summary graphs of the results, and export data to a spreadsheet format.
Discussion: This web portal provides a simple interface to reference versions of mathematical models, and well-tested state-of-the-art equation solvers. It provides safety teams easy access to the emerging technology of cardiac electrophysiology simulations for use in the drug-discovery process.
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1. Introduction

The heart's pumping action is driven by the flow of electrically charged particles — ions — across the membrane of muscle cells. These ions flow through protein channels in the cell membrane, which change conformation dependent on the voltage (electrical potential due to a difference in charge) across the membrane. The change in conformation makes the ion channels permeable, or not, to the flow of ions between the inside and outside of the cell. If a channel is permeable, then ions passively move through the pore, driven by their concentration gradient and the electrical potential gradient across the membrane. Different ion channels have evolved to be selective to different ionic species (e.g. Na^+, K^+, Ca^{2+}, Cl^-), and to carry these ionic currents with differing time- and voltage-dependence. A number of pumps and exchangers actively move ions back across the membrane to restore intra- and extra-cellular concentrations of ions, enabling sustainable electrical activity.

Ion channels can be blocked by pharmaceutical compounds due to their binding directly to channel pores, or compound binding can lead to conformational changes of the ion channel and also lead to impaired passage of ions. Some cardiac ion channels, such as hERG channels, are particularly prone to block, by a wide variety of pharmaceutical compounds (Mitcheson & Perry, 2003). Blockade of the hERG potassium channel is linked with prolongation of electrical activity at the cell, organ, and body-surface (observed as an increase in the QT interval of the ECG). Both block of hERG and prolongation of QT interval are linked with pro-arrhythmic Torsade-de-Pointes risk (Redfern et al., 2003; Sanguinetti & Tristani-Firouzi, 2006; Pollard et al., 2010). As such, hERG block and human QT intervals are assessed as part of the ICH-S7B and ICH-E14 safety guidelines (ICH, 2005a, 2005b).

Improved predictions of torsadogenic risk have been created using information on a compound's interactions with not simply hERG, but also additional ion channels (Mirams et al., 2011; Kramer et al., 2013). In early drug discovery, compounds are commonly screened for their effect on particular cardiac ion currents using cell lines that over-express certain genes. Table 1 shows common choices for human ventricular targets that routinely feature in pharmaceutical safety screens.

Direct measurements of the overall action of a compound are provided in later safety testing on isolated myocytes, tissue cultures, or ex-vivo cardiac tissue preparations. It would be beneficial to be able to provide these 'integrated' predictions for larger numbers of compounds, earlier in drug discovery, prior to such experiments being performed. One way to do this is to let biophysical mathematical models integrate any multi-channel effects of a compound, based on channel screening data.

The targets shown in Table 1 were chosen as potential inputs for simulations because they (i) are important in controlling cardiac

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Table 1
Assumptions of the cardiac currents that are recorded from cell lines expressing certain genes. Each of these can be given an IC_{50} value in web portal simulations, which is then used to calculate conductance-block in action potential simulations.

Gene	Protein	Current	Current description
hERG or KCNH2	Kv11.1	I_{Kr}	Rapid delayed rectifying potassium current
CACNA1C	Cav1.2	I_{CaL}	L[ong-lasting]-type calcium current
SCN5A	Nav1.5	I_{Na}	[Fast] sodium current
KCNQ1/minK	Kv7.1	I_{Ks}	Slow delayed rectifying potassium current
KCNJ2	Kir2.1	I_{K1}	Inward rectifier potassium current
KCND3	Kv4.3	$I_{to,fast}$	Fast transient outward potassium current

If a model only contains total I_{to} then this is conductance blocked instead of $I_{to,fast}$.

electrical activity, (ii) are prone to blockade by pharmaceutical compounds, and (iii) are possible to screen with automated assays.

Additional ion currents can, of course, also be affected by compounds. The late/persistent sodium current I_{NaL} is of particular interest, as it has been affected by a number of pharmaceutical compounds, and modelling work on block this current has been performed (Noble & Noble, 2006; Moreno et al., 2013). The story is complicated by the fact that late sodium represents just part of the overall sodium current, which may emerge from channel kinetics, or may be carried by voltage-gated sodium channels other than Nav1.5 (Noujaim et al., 2012; Yang et al., 2012). Late sodium does not yet have a standard representation in the mathematical models: sometimes it is a separate current; sometimes late sodium is modelled by preventing inactivation of fast sodium; and sometimes late sodium is represented as a distinct conducting state in a Markov model of the Nav1.5 channel (Irvine, Jafri, & Winslow, 1999). For this reason, introducing late sodium current block into the literature action potential models is not straightforward, and is future work.

The FDA, Cardiac Safety Research Consortium, Health and Environmental Sciences Institute and Safety Pharmacology Society are working on a new Comprehensive in-Vitro Pro-arrhythmia Assay (CiPA). The CiPA initiative intends to use mathematical (in-silico) action potential models to integrate multiple ion channel screening data and to make predictions about pro-arrhythmic risk, to be compared with stem-cell derived myocyte assays (Sager, Gintant, Turner, Pettit, & Stockbridge, 2014). As suggested by some commentaries, the computational models need thorough testing, standardisation and wide availability for such uses (Gintant, 2012; Kleiman, Shah, & Morganroth, 2014; Cavero & Holzgrefe, 2014). To this end, this article introduces a publicly accessible open-source web portal we call 'AP predict online'. The portal has been developed to enable electrophysiology simulations to be performed by safety teams, to evaluate the performance of different models and to define suitable contexts of use.

2. Methods

2.1. Mathematical electrophysiology models

Mathematical models of cardiac electrophysiology offer a way to integrate the effect of blocking individual types of cardiac ion current, in order to predict effects at the whole-cell level, and higher. The models are designed to describe the evolution of the cell's electrical activity due to the interaction of the different ionic currents. The electrical activity is most commonly described by the *action potential* — the activation and recovery (known as de- and re-polarisation) of transmembrane voltage.

The models therefore describe the evolution of membrane voltage through time by modelling the membrane as simply a capacitor, and saying "the change in voltage is proportional to the sum of the ionic currents across the membrane". This is expressed quantitatively as an ordinary differential equation:

$$\frac{dV}{dt} = -\frac{1}{C_m}\left(\sum_{channels j} I_j + I_{stim}\right). \quad (1)$$

Here V is the transmembrane voltage, t is time, C_m is the capacitance of the membrane, I_j represents each type of ionic current j, and I_{stim} is any stimulus current applied to the cell. This can become a complicated system of nonlinear equations when we consider that the ionic currents I_j are themselves nonlinear functions of both voltage and time.

This forms a nonlinear system where intuition often fails us, and so quantitative models have allowed much progress, beginning with the Nobel prize winning work of Hodgkin and Huxley (1952), and its application to cardiac cells by Noble (1960). Many of the large advances since — discoveries of new currents, and uncovering of the roles of ionic currents in arrhythmia mechanisms — have been enabled by these mathematical modelling efforts (Noble & Rudy, 1783). Modern mathematical models now include all of the major cardiac ion channels, pumps and exchangers, as well as a detailed description of the calcium subsystem, and the concentration of ions in different cellular compartments. As an example of a modern model, the currents that are modelled in the Shannon, Wang, Puglisi, Weber, and Bers (2004) rabbit ventricle model, available for AP-predict simulations, are shown in Fig. 1.

The AP-predict web portal provides an interface to a simulation tool that attempts to predict changes to the cellular action potential, given the data we have already obtained from cardiac ion channel screens in Table 1. At present the following models are available from the web portal: rabbit — Shannon et al. (2004), Mahajan et al. (2008); human — Ten Tusscher and Panfilov (2006), Grandi, Pasqualini, and Bers (2010), O'Hara, Virág, Varró, and Rudy (2011); and human stem-cell derived myocyte (Paci, Hyttinen, Aalto-Setälä, & Severi, 2013). These models have been chosen to represent the assays that are commonly performed and of safety interest, and to include some of the models that have been used to simulate pharmaceutical compound block in the literature (discussed in Section 3). Any further models that are in the Physiome Model Repository could be added easily to future versions of the portal, and the authors will be pleased to assist with this.

2.2. Data for model input

AP-predict uses simple concentration–response curves to determine the degree of reduction to be applied to each channel's maximal conductance, for any given concentration. The simulations integrate the concentration–effect curves from multiple ion channel screens (for any channel listed in Table 1), to predict the effect on the whole cell level, as shown in Fig. 2.

A concentration–response (or concentration–effect) curve is commonly defined as:

$$\%\ \text{current}\quad \text{remaining} = \frac{100\%}{1 + \left(\frac{[\text{Conc.}]}{[IC_{50}]}\right)^{\text{Hill}}}. \quad (2)$$

Eq. (2), plotted in Fig. 3A, provides a very accurate description of (peak) ion-current blockade for most compounds. In the (Elkins et al., 2013) study, we found large variability was associated with Hill coefficient measurements from high-throughput screens. We believe this variability is likely to be a larger source of error than simply saying that "the Hill coefficient is equal to one" in most cases (as from first principles, Hill = 1 occurs when one compound interacts with one ion channel and a channel can be fully blocked by a single molecule of the compound).

Our concentration–response curve is therefore fully defined by a single IC_{50} value — that is, the concentration of the compound that would inhibit the maximum current by 50%. The web portal should be provided with IC_{50} (or pIC_{50}) values that result from data fitted to this curve, as shown in Fig. 3B. Where an IC_{50} is not directly observed (e.g. you only know that $IC_{50} < 30$ μM, since at 30 μM 50% block was not achieved), you should still input the 'extrapolated' IC_{50} that parameterises the concentration–response curve fitted through the

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