Ischemia Alters Sensitivity of Action Potential to the Sodium-Potassium Pump

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Abstract

Ischemia increases extracellular concentration of potassium, $[K^+]_o$, reduces the cytosolic ATP concentrations, and reduces cytosolic pH. The sodium-potassium pump, I_{NaK}, is an ATPase that maintains the ionic gradients across the cell membrane required to drive the action potential (AP) and depends on these parameters. The suitability of biophysically detailed mathematical models to study pathophysiological conditions is in their capability to produce physiological responses to parameter alterations. This study evaluated the sensitivity of I_{NaK} parameters and of $[K^+]_o$ to AP in a human ventricle cell model using forward sensitivity analysis.

The derivative based forward sensitivity of the O'Hara et al. model AP to $[K^+]_o$, ATP, and pH was estimated using difference quotient algorithms. The FSA was verified by computing I_{NaK}-concentration curves for each of the three parameters. AP alterations under small and large alterations of the parameters were also computed.

The model's AP has sensitivity to the ischemic parameters in agreement with experimental data. The sensitivity of the AP to pH, however, was found to be small. This could be improved by further developing the I_{NaK} formulation. FSA is a straightforward method serving as a first port of call to evaluate model suitability.

1. Introduction

There is an increasing number of mathematical models of cardiac electrophysiology [1-3] and other cardiac processes described by intricately coupled ordinary differential equations. This mathematical modelling of the intricate biological processes allows for the interpretation of the extensive amounts of data produced by modern experiments and assigning of a quantitative understanding to the experimental findings and hypotheses.

Systems biology provides increasingly powerful tools for the simulation of complex biological processes [4, 5]. In particular cardiac cell models consist of ordinary algebraic-differential equations (DAEs) describing cell membrane and intracellular electrophysiology [1]. Cardiac cell models are composite constructions of ion current and intracellular dynamics components. Although the models are validated extensively with experimental data, it is not always obvious as to the applicability of the cell models in the study of a specific disease. In a previous study [6], we have demonstrated the significantly different ionic processes that regulate cardiac electrical properties where the models considered were constructed to reproduce the electrical activity from the same tissue type and same animal species. The application of a mathematical model in studying physiopathological processes requires it to be sufficiently detailed and consist of functional processes that are capable of simulating the physiopathology. An easy to implement methodology is proposed that will allow a straightforward evaluation of the function of model components in the simulation of the cardiac cell dysfunction.

Parameter sensitivity analysis is an increasing trend among cardiac modelling community [7-9], but has yet found limited applicability systematically and routinely. In our previous study [6], we implemented a global sensitivity index that correlated overall cell function to underlying regulatory parameters. Other developments are the application of regression based indices [10] and uncertainty analysis [11, 12]. Such approaches are computationally intensive as well as involve substantial post-processing of the data. The deployment of resources may be justified if a model is being constructed *de novo*, or when there are no alternatives. In contrast, there is a spectrum of cardiac mathematical cell models that permit the simulation of human ventricle action potential (AP) based on validated electrophysiological processes.

In this study, we tested the feasibility of using a straightforward derivative based forward sensitivity analysis (FSA) to assess suitability of a recent model of human ventricular electrophysiology to simulate ischemia as a case. The FSA was confirmed by simulating the parametric dependence of the sodium-potassium pump (I_{NaK}) and AP on I_{NaK} parameters. I_{NaK} was chosen as it

may be a significant contributor to ischemic physiopathology [13]. The FSA calculations were computationally validated by additional simulations. This study highlights the necessity of quantitatively evaluating model suitability for purpose prior to being used in numerical simulations.

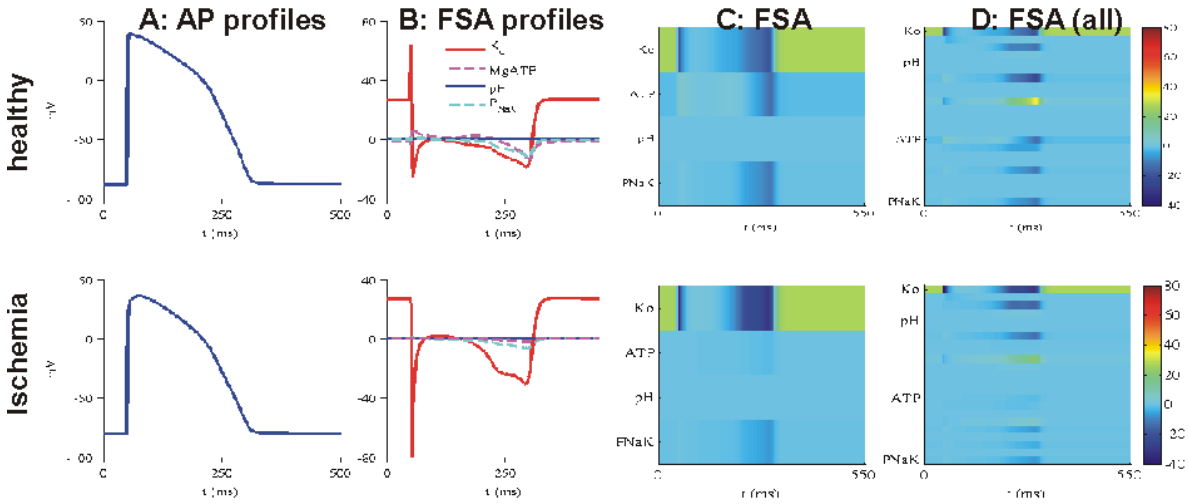

Figure 1. AP profiles. AP profiles (Column A), FSA coefficients of ischemia related parameters (Column B), time-parameter plots of data from Column B, and FSA coefficients of all I_{NaK} parameters (Column D). The colour bar applies to Columns C and D.

2. Methods

The human ventricle model by O'Hara et al. (ORD) [1] model of human ventricle electrophysiology was adopted in this study. The extracellular potassium, $[K^+]_o$, plays an important role in all the potassium currents as well as the sodium-calcium exchanger and the I_{NaK}. On the other hand, MgATP and H^+ are parameters that occur only in the I_{NaK} formulation. The I_{Nak} formulation in the ORD model has been adopted from the King-Altman method [14] scheme that was further developed by Smith and Crampin [15]. The model was implemented in MATLAB as well as C programming languages to: a) ensure that multiple FSA tools may be used; b) MATLAB was used for fast prototyping whereas C programming implemented a computationally efficient version of the MATLAB code; and c) MATLAB offers ready to use graph plotting functions at run time allowing the runtime monitoring of the simulations. The results from the C based code are presented in this work.

The basal ORD cell model has several hundred independent parameters, several of which are regulators of I_{NaK}. To illustrate the FSA, we established the influence of the I_{NaK} parameters on the main output of the model, i.e. action potential. Under ischemic conditions, there are extensive ion channel and intra-cellular alterations [16, 17]. We focused on parameters as the most significant in ischemia: $[K^+]_o$, ATP, pH, and the conductance of I_{NaK}, i.e. P_{NaK}. We considered the I_{NaK} conductance, P_{Nak}, as a control parameter that regulates overall I_{NaK}. I_{NaK} is an ATPase and consumes ATP to form ADP, and a conservation law was implemented.

Derivative based SA have been introduced by Nygren [9]. In brief, the sensitivity coefficient ε_p of voltage, V, to a model parameter p is defined as,

$$\varepsilon_p = p\frac{\partial V}{\partial p} \qquad \text{Eq. (1)}$$

which gave time profiles of FSA coefficients during dynamical simulations. The FSA coefficients are computed using a difference quotient algorithm implemented in the two programming paradigms found in an established C library [18]. The FSA coefficients were interpreted to be significant if at any time instant, they were comparable to the variable itself, voltage V in our case.

The cell model was paced at 1 Hz and the ultimate excitation analysed for results. Using the definition of FSA (i.e. Eq 1), the sensitivity of voltage to the ischemia related parameters, $[K^+]_o$, ATP, P_{NaK}, and pH, was computed under healthy and ischemic conditions. Under healthy conditions, the values of $[K^+]_o$ = 5.4mM, ATP = 9.8 mM, pH = 7, and P_{NaK} = 30 were taken. Under ischemic conditions, the values of K_o = 7 mM, ATP = 4 mM, pH = 6.5, and P_{NaK} = 20 were taken. The FSA coefficients of all I_{NaK} parameters were also computed to ascertain if other I_{NaK} based parametric regulators of AP could be identified. The FSA was confirmed by simulating parameter variations and their effects on the system. The parameters were varied in a ± 200% range of their basal values. To achieve this, we first estimated I_{Nak} in resting condition (no stimulus). We then simulated AP features such as resting potential, up stroke velocity, peak

potential, and APD_{90} as functions of individual parameters in a large range of their values.

3. Results

AP profiles under healthy and ischemic conditions are illustrated in Figure 1, A. As defined, the ischemia elevated the resting potential by 10 mV, significantly reduced upstroke velocity by 50%, and reduced the peak potential by 5 mV. The FSA coefficients (Figure 1, B) revealed that [K+]o is the most significant regulator among the four ischemia related parameters. It sustains the resting potential, and takes significant part in the repolarization. The ATP and P_{NaK} parameters were not found to affect resting potential, but do contribute to repolarization. Interestingly, the AP was found to be insensitive to pH (or H^+ concentration). The same data were visualized in time-parameter plots as shown in Figure 1, C. Such a representation allowed simultaneous examination of the data without the time profiles intersecting each other. It was especially true when the FSA coefficients of all I_{NaK} parameters were examined (Figure 1, D). Among the I_{NaK} parameters, there are a significant number of parameters to which the AP has negligible sensitivity, but there are also parameters that are sensitive and whose physiological role should be investigated further. Ischemic conditions affected the AP as described above. The FSA coefficients were also altered (Figure 1, B). With an elevated $[K^+]_o$, it was observed that the APs sensitivity to $[K^+]_o$ is augmented. Interestingly, the AP was found to be insensitive to pH under healthy and ischemic conditions.

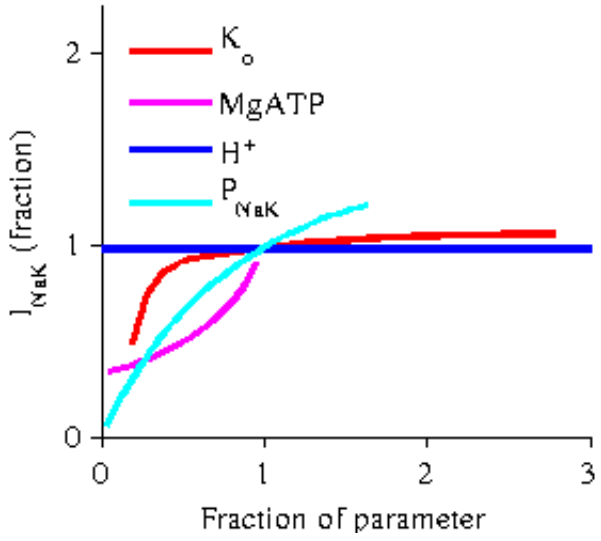

Figure 2. Control of I_{NaK} in ORD model by ischemia related parameters. The parameter values as well as those of I_{NaK} were normalized to basal values to facilitate comparison.

To validate the FSA computations, we performed further simulations to ascertain the control of I_{NaK} and AP by the parameters. Figure 2 illustrates the variation of resting I_{NaK} when the ischemia related parameters were perturbed in a large range of 200% reduction or increase. I_{NaK} has a direct proportionality relationship with all parameters except for pH, to which it was found to be insensitive. Multiple dynamical simulations were also performed where the cell models were paced at 1 Hz for 100 beats and the AP features of the final excitation noted. The ischemia related parameters were perturbed, one at a time in the large range, to ascertain the effects on AP features. As illustrated in Figure 3, resting potential reduced as [K+]o increased. [K+]o also has a significantly large influence on the peak potential. AP duration at 90% repolarization and upstroke velocity were affected by [K+]o, ATP, as well as overall INaK represented by PNaK. The simulations also confirmed that pH does not affect APs in the ORD model.

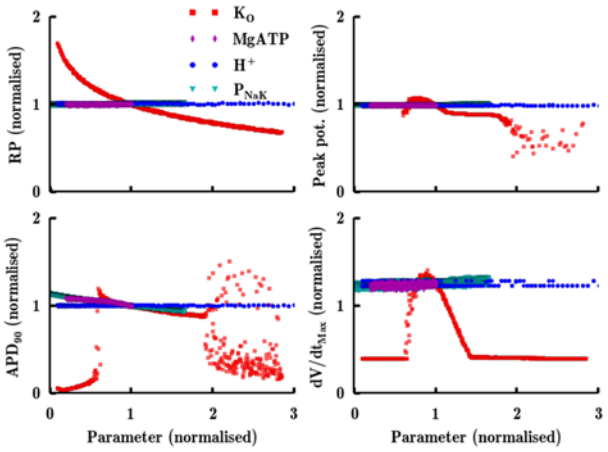

Figure 3. Control of AP features of resting potential (top left), peak potential (top right), APD90 (bottom left), and upstroke velocity (bottom right) by ischemia related parameters. The AP features as well as the parameters are normalized to basal values to facilitate data interpretation.

4. Discussion

An easy to implement method of quantitative assessment of suitability of a cell model for purpose is demonstrated in this study. The ease of implementation comes from the availability of highly optimised sophisticated numerical libraries that are available permitting the difference quotient based calculations. The computation of FSA coefficients may benefit from the use of automatic differentiation tools such as ADOL-C [19] but was found not to be necessary for the ORD model. In comparison to the more in depth methods such as global sensitivity using mutual information,

uncertainty analysis, and multi-variate regression, FSA offers a rapid but quantitative method for model evaluation. Although FSA has these advantages, it may not be applicable in several instances of cardiac cell modelling. Firstly, it provides sensitivity with respect to each parameter at a fixed parameter set. Therefore, it will need to be replaced by the more rigorous methods when exploring model robustness and the effects of multiple parameters being perturbed. Secondly, numerical differentiation is known to be unstable especially in the case of stiff ordinary differential equations, and therefore may provide erroneous results which may not be easily detected. The use of automatic differentiation may provide a solution for such a shortcoming as models become progressively complex and therefore are likely to be very stiff.

This FSA study shows that although most parameters regulating ORD model's AP behaviour are functional, there are a few redundant parameters such as pH. FSA analysis demonstrated that it is a much smaller subset of parameters that influence model behaviour substantially (Figure 1, D). An interesting aspect that FSA revealed was that model response is substantial for all biophysical parameters, and not just channel conductances. Thus, during model development, refinement, and customization, all the biophysics of the electrophysiology must be considered in its entirety.

In conclusion, the FSA scheme to quantify the influence of modelling parameters objectively has been re-introduced. It is robust and easily implementable. It can assist in systematic model construction for purposes of *in silico* investigations of phenomena and disease.

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