Fitting Membrane Resistance in Single Cardiac Myocytes reduces Variability in Parameters

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Abstract

Mathematical models of single cardiac myocytes have a valuable role in driving progress in cardiac physiology and in exploring the electrophysiological mechanisms underlying heart function. Most of these models are used to mimic the results of experimentally observed biological phenomena measured in animal models, and can also provide quantitative insights into natural processes. Adjusting parameters in an ionic model to reproduce experimental behaviour is difficult. Mostly, researchers fit the only the net current to reproduce an action potential (AP) shape. However, even with an excellent AP match in the single cell, tissue behaviour can be vastly different. We hypothesize that this uncertainty can be reduced by additionally fitting R_m.

1. Introduction

Mathematical modeling is an important tool in the field of cardiac electrophysiology, providing significant insights into natural processes. The basic modeling unit of cardiac electrophysiological simulations is the single cell ionic model reproducing action potentials (APs). In recent years, various automated algorithms have been devised to optimize the tedious and complex fit of model parameters to experimental observations. For cardiac ionic models, a particular problem is that models that produce a good AP fit in single cell simulations sometimes fail to reproduce the AP in tissue simulations, due to the electrotonic loading present when cells are electrically interconnected. To date, researchers only fit net membrane current to yield proper membrane voltage changes in the single cell scenario.

In this paper, we used a multi objective parallel genetic algorithm to fit ionic model parameters to model-generated data using AP waveforms and membrane resistance (R_m). In recent years, various automated algorithms have been devised to optimise the tedious and difficult fitting. A curvilinear gradient optimization algorithm method [1] was used to fit the Beeler Reuter model [2] to a model-generated ventricular AP [3]. A genetic algorithm (GA) was developed by Syed et al. [4] to fit the Nygren et. al. human atrial model [5] to experimental data [6]. In the present paper, we used a multi-objective parallel algorithm to fit human ventricle model.

We show that fitting R_m along with the AP improves the fit to the desired AP curve while reducing variability in the solutions obtained. This also reduces the variability of the estimated parameters. Furthermore, average error and standard deviation of the parameters was reduced significantly by fitting AP and R_m simultaneously as compared to fitting AP only. Thus, R_m is an important parameter that can provide information regarding ionic currents that is not sufficiently provided by just the shape of the AP.

2. Methods

2.1. R_m measurement

The membrane resistance at a particular point during an AP was defined as the inverse of the slope of the I-V curve around the membrane voltage V_m of the action potential at a particular time. At each indicated time (for instance time point B in Fig. 1), two successive clamp pulses were applied for 30 ms. The voltages of the two pulses were 10 mV above and below the V_m of the AP at that time, respectively (shown by red clamp pulses at point B in Fig. 1). The membrane current measured 5 ms after initiation of the clamp (black elliptical markers in Fig. 1) was used to construct I-V curves. R_m was calculated at three different points A, B and C during the AP at 10, 150 and 250 ms after the AP upstroke. The AP was run for at least 3 s to reach the steady state.

2.2. Single cell and tissue simulations

The Cardiac Arrhythmias Research Package (CARP) was used for all simulations including single cell and tissue.

For tissue simulations, a 1 cm square 2-dimensional grid was discretized into quadrilateral finite element mesh with edge lengths of 100 µm. A monodomain formulation with a time discretization of 25 µs was used. Center point stimulation was applied to tissue with intracellular conductivity in the longitudinal and transverse directions to the fibers set to 0.174 and 0.019 S/m respectively.

2.3. Genetic algorithm approach

Multi-objective optimization involves optimizing a number of objectives simultaneously. Our initialization procedure involved a random creation of solutions. In the context of multi-objective optimization [7], the extremist principle of finding the optimum solution cannot be applied to one objective alone when the rest of the objectives are also important. Different solutions may produce trade-offs (conflicting outcomes among objectives) among different objectives. A solution that is superior with respect to one objective may require a compromise in other objectives. This prohibits one from choosing a solution which is optimal with respect to only one objective. This clearly suggests two ideal goals of multi-objective optimization: (i). Find a set of solutions which lie on the Pareto-optimal front, and (ii) Find a set of solutions which are diverse enough to represent the entire range of the Pareto-optima, i.e., a set of solutions in which it is impossible to make any one individual better off without making at least one individual worse off.

To investigate the implication of R_m, a genetic algorithm approach was developed incorporating R_m data calculated at a few points during the AP, in addition to AP morphology.

The following objective functions were minimized:

(i) Normalized mean square error difference in the AP.

(ii) Normalized absolute difference in R_m at three different time points during the AP as indicated in Fig. 1. by the three vertical arrows corresponding to three time points A to C.

Fits were performed and the optimal parameter sets were compared. A human ventricular cardiac myocyte ionic model was fit [8] to an alternate human ventricle model. Performance was compared using a genetic algorithm either incorporating only AP morphology data or incorporating both AP and R_m data in the fit. Mean square error (MSE) was used as the objective function for AP fit and was normalized to squared difference of peak voltage and resting level voltage. The MSE was calculated from upstroke to final repolarization, not including the diastolic interval. Absolute difference between actual value and calculated value of R_m normalized to the actual value was used as the objective function for R_m fit at each point.

3. Results

Two different sets of parameters for the TNNP ventricle model [8] produce similar AP in single cell as demonstrated by Sobie at al. [9]. We determined whether those two parameter sets have similar AP in tissue as well. This was not the case; for one parameter set the result was similar to the single cell AP, whereas for the second parameter set action potential duration (APD) decreased significantly. R_m was evaluated in the single cell model at a few different time points. R_m changed substantially during the time course of the AP, and, moreover, R_m values for the two parameter sets were very different. In particular, R_m for parameter set 1 at time point C (150 ms after the upstroke of AP, during the repolarization phase) is approximately ten-fold higher than for parameter set 2. This demonstrates that R_m contains information independent of AP shape. In tissue, the cells are connected by gap junctions that are responsible for charge transfer between cardiomyocytes. R_m provides information about how sensitive the AP waveform is to current flow among adjacent cardiomyocytes. In the single cell, a large efflux cancelling a large influx, or a small efflux cancelling a small influx, may yield the same net current and, thus, the same AP. However, these two scenarios will likely have different R_m and could be distinguished by taking R_m into account.

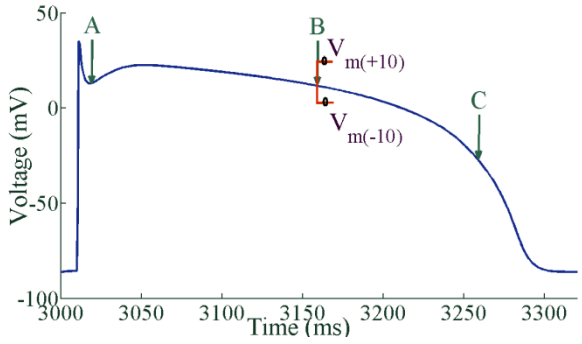

Fig. 1. AP of TNNP human ventricle model. Rm was measured at point A, B and C.

Membrane resistance R_1, R_2 and R_3were calculated at points A, B, C, i.e., at time points at 10, 150 and 250 ms after the upstroke of. Membrane resistance was measured 5 ms after applying the clamp pulse. In the genetic algorithm we attempted to fit AP as well as R_1, R_2, R_3. Parallel Multiple Objective Algorithm was implemented in MATLAB.

Eight variables: G_{CaL} (maximum L type calcium current), G_{Kr} (maximum rapid delay rectifier

conductance), G_{to} (maximum transient outward

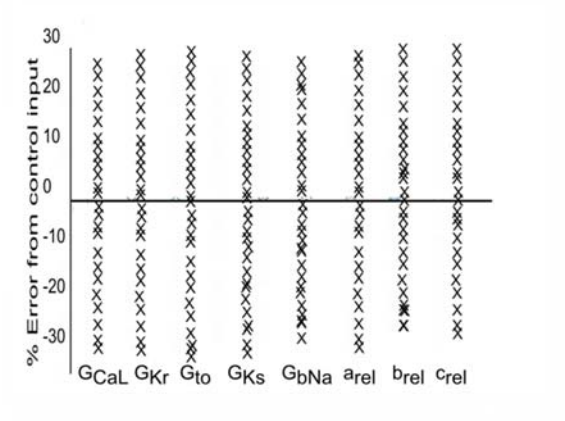

Fig. 2. AP only fit for different R_m values. X axis shows parameters G_{CaL}, G_{Kr}, G_{to}, G_{Ks}, G_{bNa}, a_{rel} , b_{rel}, $c_{rel.}$ Y axis shows the % of error from the control values. Different markers show the result for 50 different paretos.

conductance), G_{Ks} (maximum slow delay rectifier conductance), G_{bNa} (maximum background sodium current conductance), a_{rel} (maximum calcium sarcoplasmic reticulum calcium content (CaSR) - dependent I_{rel}) , b_{rel} (CaSR half-saturation constant of I_{rel}), c_{rel} (maximum sarcoplasmic reticulum calcium content-independent I_{rel}) were varied in the TNNP human ventricle model. The genetic algorithm was used to attempt to find parameter sets to fit the AP produced by an alternative human ventricle model developed by Iyer et. al. [10]. The variability in the estimated parameter values is reduced significantly in case of AP + R_m fit (Fig. 3) as compared to AP only fit (Fig. 2), by at least 1.5-fold for $G_{CaL,}$ $G_{to,}$ $G_{ks,}$ $G_{Na,}$ a_{rel} , $b_{rel,}$ $c_{rel.}$ The parameters are from the range ±30% for AP only fit (Fig. 2) whereas it has been narrowed down in Fig. 3 by fitting AP as well along with R_m. Also the number of pareto solutions obtained was decreased from 50 to 6 by adding R_m fitting at three points during the AP.

It was noticed that the variability in G_{Kr} (Fig. 3) was quite high even in case of AP + R_m fit (ranging from +15 to -24%. In an attempt to improve this, we increased the number of iterations of the algorithm, such that the GA maintained a population of 100 potential solutions instead of 50 as used earlier. The average and standard deviation (SD) of the resulting parameter estimates is plotted in Fig. 4, where blue error bars are for SD for AP only fit and red error bars are for AP+R_m fit. As shown in Fig. 4 although the averages are not significantly changed, the variation of parameters is significantly reduced including the variability of G_{Kr}. Thus, it is clear that increasing number of iterations decreases the parameter variability.

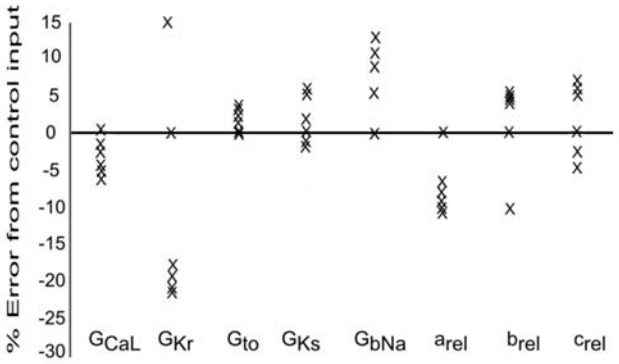

Fig. 3: AP + R_m fit for different R_m values. X axis shows parameters G_{CaL}, G_{Kr}, G_{to}, G_{Ks}, Gb_{Na}, a_{rel} , b_{rel}, $c_{rel.}$ Y axis shows the % of error from the control values. Markers show the result for 6 different paretos.

In Fig. 4, for parameters G_{CaL}, G_{K1}, G_{Kr}, G_{to}, G_{Ks}, G_{Na} the variation is reduced at least 2.5-fold whereas in case of a_{rel}, b_{rel}, c_{rel} it is reduced approximately 2-fold by adding R_m as an additional parameter for fitting along with AP shape.

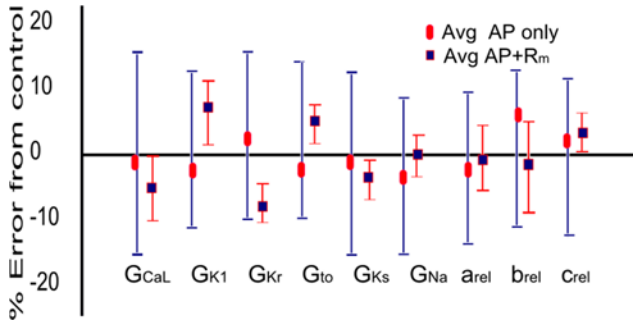

Fig. 4: Average and standard deviation plot for $G_{CaL,}$ $G_{K1,}$ $G_{to,}$ $G_{ks,}$ $G_{Na,}$ a_{rel} , $b_{rel,}$ $c_{rel.}$ Blue error bars are for standard deviation for AP only fit and red error bars are for AP + R_m fit.

4. Discussion

This paper presents a method for enhancing fitting of APs in single cell models. We propose adding R_m as an objective, beyond just AP morphology, and demonstrate that it leads to less variability in the parameters values obtained.

In the tissue, cells are interconnected through gap junctions and interact electrically with neighboring cells. For instance, if two single cells are connected to each

other, cell 1 (source) is more depolarized than cell 2, so it will try to depolarize cell 2 whereas the sink has opposite effect on the source (repolarizing influence). The membrane resistance, R_m, relates the change in membrane voltage to the current by these source-sink interactions. If R_m is high, a small current produces a large change in voltage. If R_m is low, a large current produces a small change in voltage. In tissue, cells are interconnected through gap junctions and interact electrically with neighboring cells.

Take the current flow of ion X through a channel represented by a Hodgkin-Huxley formulation,

$$\frac{\partial \mathrm{I_x}}{\partial \mathrm{V_m}} = g_\mathrm{x} + \frac{\partial g_x}{\partial V_m}(V_m - E_x),$$

where first term, is the chord conductance, and the second term is a function of the driving force and the rate of change of the chord conductance, and can be negative. Whether first or second term dominates depends on many factors which change during the AP. Pumps and exchangers also have nonlinear conductances. The total cell conductance is, then, the summation of a set of nonlinear conductances.

When a particular channel is more active during a certain phase and contributes a large portion of the membrane conductance, which provides more information to the GA to help fit its absolute magnitude. For the calculation of I_m for the single cell simulations 5 ms was chosen to measure the current as a trade off so that most of the currents are stabilized and also very fast transients have decayed. In particular, we avoid the sodium current transient. For the theoretical R_m calculation, capacitive transients did not need to be dealt with so 5 ms was a reasonable choice. However, experimental measurements may require a longer time to allow capacitive transients to decay. If we wait too long, the state evolves too much and it is more a function of the clamp voltage.

Fig. 4 compares the average and standard deviation of the normalized parameter adjustments obtained for the two different fitting protocols over 50 and 6 fits for AP only and AP + R_m fit respectively. The variability in the majority of estimated parameter values was significantly reduced by considering R_m.

5. Limitations

For the results presented here, we chose different time points A, B, and C, as shown in Fig. 1 for computing R_m. There is a possibility that we could get multiple samples from the plateau which would be very similar. If the two cells had very different APs, we might end up sampling very different states and R_m comparisons might not be as meaningful as they could be. To reduce the error, we need to adjust the algorithm to the particular APD to ensure proper sampling of all states. A better approach may be to calculate and fit the membrane resistances at particular voltage points instead of time points to make are sure to get different distributions of conducting ionic channels. When a particular channel is more active during a certain phase and contributes a large portion of the membrane conductance, this provides more information to the GA to help fit its absolute magnitude.

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