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Parameter Fitting using Multiple Datasets in Cardiac Action Potential Modeling

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***Abstract*—A multiple dataset model fitting approach for improving parameter reliability in action potential modeling is presented. A robust generic cardiac ionic model employing membrane currents based on two-gate Hodgkin-Huxley kinetics is described. Its generic nature allows it to accurately reproduce action potential waveforms in heterogeneous cardiac tissue by optimizing parameters governing ion channel kinetics and magnitudes. The model allows a user-defined number of voltage and time-dependent ion currents to be incorporated, in order to reproduce and predict multiple action potential waveforms recorded in intact cardiac myocyte. In total $12N_c+2$ parameters were optimized using a curvilinear gradient method, where N_c is the user-specified number of time-dependent currents. Given appropriate experimental datasets, many of the known physiological membrane currents could be effectively reconstructed. Also, the optimized models were able to predict additional experimental action potential recordings that were not used in the optimization process.**

I. Introduction

A variety of cardiac action potentials (AP) and ionic currents from heterogeneous cardiac myocytes have been studied quantitatively using whole-cell current and voltage-clamp techniques. Such data provide essential information concerning the electric activity of cardiac tissue. At the same time, mathematical representations are required to provide a quantitatively deeper understanding of the underlying mechanisms of cardiac electric activity.

Ionic models are, in general, able to accurately reproduce physiological ionic mechanisms only under the experimental conditions they were based on, limiting the predictive utility of these models [1]. Also important is that parameter fits to AP waveforms may not be necessarily unique. That is, model parameters may not be well-determined even if the model-generated AP perfectly matches the experimental waveform. Many studies have demonstrated that significantly different sets of parameter values can reproduce nearly identical model AP outputs [2-6].

It is therefore desirable to develop computationally simple, robust parameter optimization approaches along with corresponding generic ionic models, which can accurately simulate or predict APs as well as other underlying physiological mechanisms in a variety of cardiac myocytes.

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The model structure should be flexible and modular. By optimizing the appropriate model parameters, the model should be able to fit APs recorded from different myocytes under different experimental conditions. With desired experimental designs, such a model should be able to reproduce complex behavior such as the change in AP morphology due to ionic channel blockage by drugs, or paced high-frequency stimulation.

In this study, a multiple dataset model fitting approach for improving parameter reliability is presented. The importance of parameter estimation using multiple sets of experimental recordings under variable pacing conditions is also discussed.

II. Methodology

A. Generic Model of Cell Electric Activity

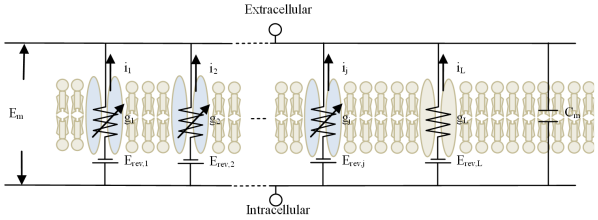

Fig. 1. Equivalent circuit representation of generic ionic model. The cell membrane is represented by a capacitance in parallel with several conductances denoting a variety of ionic currents.

The generic single cell model used in this study consists of N_c membrane currents and one leakage current i_L, acting in parallel across a capacitive cell membrane (Fig. 1). The transmembrane potential E_m is given by

$$\frac{dE_m}{dt} = -\frac{1}{C_m}\left(i_L + \sum_{j=1}^{N_c} i_j\right) \quad (1)$$

where i_j denotes the j^{th} time-dependent ionic current, and N_c is the user-specified total number of time-dependent currents present. Details of the generic model, including equations for the gating variables, can be found in Guo et al. [7].

B. Parameter Estimation with Multiple datasets

Parameter optimization involved the systematic modification of parameter values of the generic model in order to minimize the disparity between the model-generated

APs and experimental data. Each experimental dataset used for optimization constituted a series of 3-4 consecutive APs. A custom curvilinear gradient-based optimization method [8, 9] was performed on a standard desktop PC using Matlab (The Mathworks Inc., USA).

In our parameter estimation algorithm, the major difference between single and multiple dataset optimization lay in the calculation of the Jacobian matrix **J**. Assume a single array of $m\times1$ data points **d** is required to be fitted by an ODE system **f**(**p**), whose m outputs are a function of an $n\times1$ parameter vector **p**. The Jacobian matrix is then given by,

$$\mathbf{J} = [\frac{\partial \mathbf{f}(\mathbf{p})}{\partial \mathbf{p}}]^{m\times n} \tag{2}$$

This Jacobian matrix is then used to iteratively define a curvilinear trajectory in parameter space, along which a 1D search is conducted for the minimum least squares objective [7]. The Jacobian given in (2) is used when fitting to a single recording. However, this form of the Jacobian is altered when optimizing a model to multiple AP data recorded from the same electrically-paced cell under multiple frequencies. In this case, it can be assumed that the density and kinetic properties of the ionic channels will not change in individual paced recordings. Hence all parameter values describing the ionic currents are shared across the N multiple datasets. In this case, the form of **J** will be:

$$\mathbf{J} = \begin{bmatrix} \partial \mathbf{f_1}(\mathbf{p})/\partial \mathbf{p} \\ \partial \mathbf{f_2}(\mathbf{p})/\partial \mathbf{p} \\ \vdots \\ \partial \mathbf{f_N}(\mathbf{p})/\partial \mathbf{p} \end{bmatrix}^{N_d m\times n} \tag{3}$$

where N_d is the number of data records, m is the number of data points per record (assumed here to be the same for each record), and n is the number of model parameters.

Compared with single dataset fitting, more computational resources are required for optimization using multiple data due to the larger size of the Jacobian matrix, as well as the fact that more local minima are likely to be involved in the objective parameter space. [10].

C. *Experimental Methods*

Intracellular APs were recorded from intact LA myocytes in an *in vitro* rabbit LA preparation (refer to [11] for details of experimental methods). The sequence of PIs for the random stimulation protocol was generated in Matlab.

III. RESULTS

A. *Uniformly-Paced Left Atrial Data*

A left atrial rabbit tissue preparation was paced using suprathreshold pulses at three different pacing intervals (PIs): 400 ms, 300 ms and 200 ms, and APs were recorded at each PI. A series of steady state APs were selected for each pacing frequency.

The generic model was optimized to simultaneously fit two series of left atrial AP waveforms (PI= 400 and 200 ms), which displayed significant variation in AP waveshape. Optimized parameters across these two datasets were specified to share the same values. A total of five time-dependent ion currents and one leakage current were required to simultaneously reproduce these two sets of experimental data. With decreasing PI, both the model generated AP characteristics and corresponding ionic currents (fig. 2) revealed beat-to-beat waveform variation. The RMS error between the optimized model and corresponding experimental data were 2.01 mV (PI= 400 ms), and 3.22 mV (PI= 200 ms). The optimized model was then used to predict the AP responds to a PI of 300 ms, which was not used in the optimization process. According to the third panel in Fig. 2A, the additional experimental dataset can be accurately predicted (RMS error 2.46 mV) using the parameters obtained from the first two experimental datasets.

B. *Randomly Paced Left Atrial Data*

A left atrial tissue preparation was both uniformly and randomly paced using suprathreshold stimuli, and APs were recorded for each pacing protocol. Random pacing was generated from a normal distribution of PIs, with mean and standard deviation of 275 and 69 ms respectively. A series of APs were selected for each dataset based on its electrophysiological characteristics. Besides the alternans

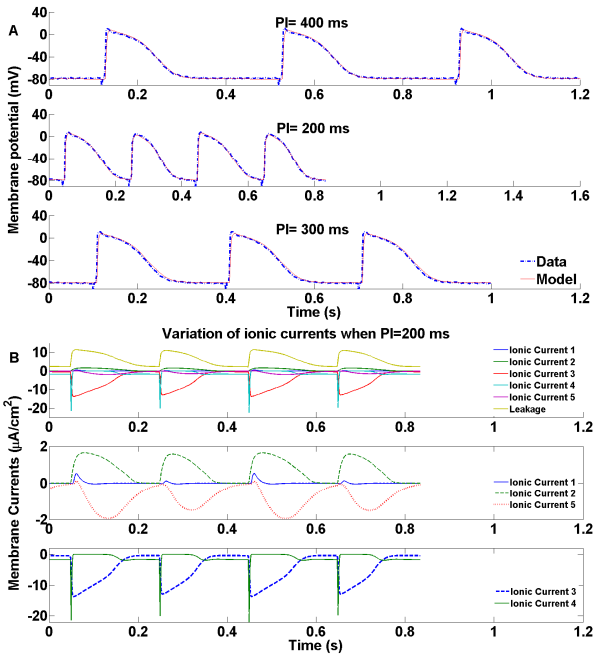

Fig. 2. A: Multiple dataset fitting for left atrial action potentials. From top to bottom: APs with pacing interval (PI) of 400, 200 and 300 ms. The AP traces at PIs of 400 ms and 200 ms were simultaneously fitted, and the AP trace at a PI of 300 ms was predicted using N_c = 5 time-dependent currents and one leakage current. B: Model-generated ionic and leakage currents at a PI of 200 ms.

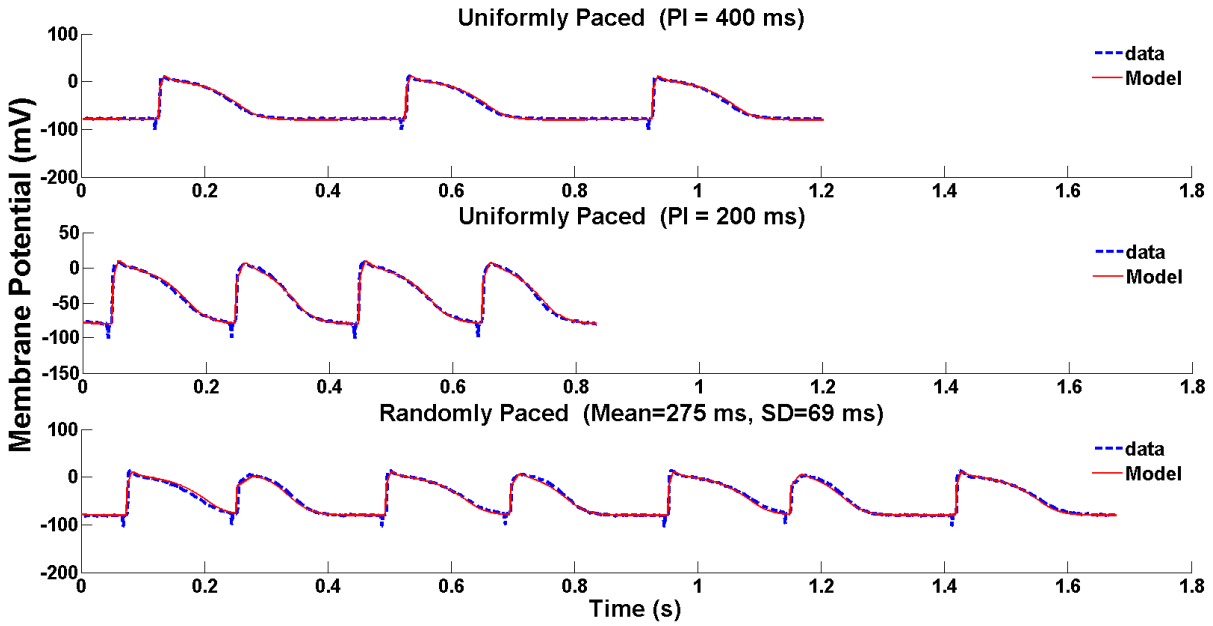

Fig. 3. Multiple simultaneous dataset fitting for uniformly and randomly paced left atrial action potentials. From top to bottom: APs with pacing interval (PI) of 400, 200 ms and randomly-paced. Each AP trace was fitted using N_c=7 time-dependent currents and one leakage current.

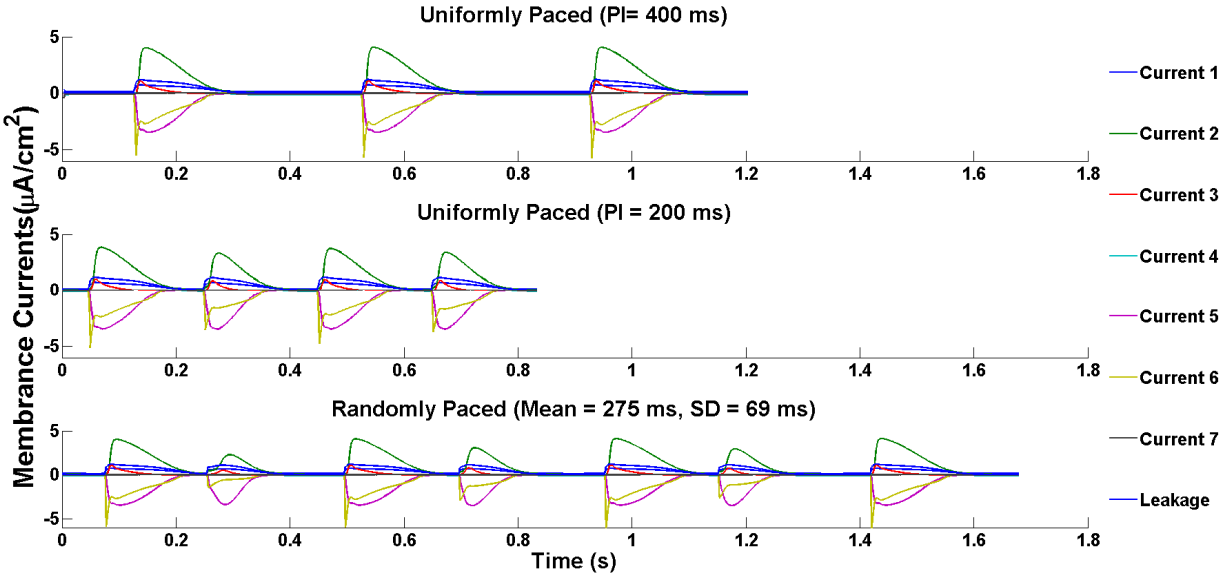

Fig. 4. Model-generated ionic and leakage currents of the left atrial AP fits shown in figure 3.

evident at a PI of 200 ms, more significant beat-beat variations were demonstrated in the random-paced dataset. Compared with uniformly-paced data (PI = 200 ms), random paced AP or APD alternans were more obvious and less consistent. Fig. 3 illustrates multiple dataset fits to left atrial APs, in which experimental data from the same cell was generated by applying two uniform and one random pacing protocol. The RMS error between the optimized model and corresponding experimental data were 2.94 mV (PI = 400 ms), 3.51 mV (PI = 200 ms) and 3.91 mV (randomly paced).

The generic model was used to simultaneously fit all three datasets. Optimized parameters across these multiple datasets shared the same value. A total of seven time-dependent ion currents and one leakage current were required to reproduce the multiset data. With decreasing PI, the model was able to generate AP characteristics and corresponding ionic currents consistent with accurate waveform fidelity, especially for randomly-paced results. From the results shown in Figs. 3 and 4, at a high pacing frequency, a second AP is activated soon after the previous one. In this case, the corresponding APD is shorter due to the not fully-recovered model currents.

IV. Discussion and Conclusion

In this study, a series of experimentally-recorded APs were used to optimize generic ionic models of cardiac electrical

activity. Ionic mechanisms underlying APs in atrial myocytes can be reconstructed by using such a generic model, whose complexity lies somewhere between simple phenomenological models and biophysically-accurate models. A major improvement over existing modeling approaches is that model parameters have here been adjusted to accurately reproduce AP waveforms recorded under multiple experimental conditions, reconstructing AP characteristics in the heart operating over a range of conditions. Given more degrees of freedom, the generic model was able to simultaneously fit a large variety of complex AP records.

Our experience from this study suggests that any additional data used for multiple dataset fitting must include additional information not present in the original dataset, or the predictability and usefulness of the model will decline. Numerically, introducing such additional data will introduce more local minima on the least square objective surface, confounding the search for a global optimum. Thus for multiple data optimization, it was much more time-consuming to fit the model to all datasets simultaneously, particularly if there were stringent constraints on each parameter, and these parameter values were shared between different datasets. Nonetheless, once the model had been optimized, the underlying currents were found to follow physiologically reasonable waveforms consistent with known behaviors of existing membrane currents. This indicates that the additional information provided by the multiple data can lead to accurate reconstructions of membrane currents. This was, in general, not easy to achieve with single datasets, even though the AP record itself could be well-fitted (results of single dataset fits are not shown here).

With multiple datasets, the global minimum may be harder to locate due to the more complex objective surface with larger numbers of local minima introduced by the additional data. However, this multiple data provides a greater opportunity of successfully searching for 'better' local minima, since each local minimum will be now shallower compared to the global one. This is due to the additive effects of multiple data on the objective, akin to an 'ensemble' averaging procedure reducing the 'noise' of local minima whilst enhancing the global minimum signal, It should be noted that when fitting to a single dataset, we have found that there exist more than one combination of membrane current waveshapes that are able to reproduce the single AP waveform but these will generally fail to simultaneously reproduce multiple data.

Besides reproducing accurate AP waveshapes, our model can also reconstruct reliable ionic current waveforms, which are also important in simulating realistic cardiac dynamics. In addition, any number of user-defined ionic currents can be incorporated into the model structure, giving the model added flexibility to reproduce even more complex electrophysiological behaviors. The number of ionic currents included depends on matching between the model and corresponding data. Because of the uniform structure of each ionic current, many currents can be conveniently combined if they are found to follow similar behaviors during the optimization, making the process of model reduction easier. Although the generic model's utility in higher dimensional simulation is still not clear, we believe that it could be a promising model for tissue or whole-heart simulations due to its simplified nature, and therefore, computational efficiency.

Future refinements of this study should focus on experimental designs for more physiologically-meaningful multiple dataset optimization, continuously improving the model's predictive ability and utility. Cardiac arrhythmia is a multi-cellular property of the whole heart, suggesting that higher dimensional simulations and optimizations will be more useful. Therefore, an effective approach of modeling electronic coupling currents between neighboring cells in whole-tissue simulation will be an important issue in our future work.

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