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MODELING CARDIAC ION CHANNEL CONDUCTIVITY: MODEL FITTING VIA SIMULATION

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ABSTRACT

We describe a Markov state model for a cloned potassium channel of the human heart (I_{KvLQT1}). The parameters of the model are determined by a least-squares fit of predicted vs. measured data. The fitting process is achieved by using the "SPSA" optimizer to sequentially choose trial values of the parameters. At each choice of parameter value, a loss function is computed by simulating the action of the channel at that trial parameter value. When the optimizer has converged, the parameter value represents the best fit.

1 INTRODUCTION

Recently, modeling approaches to the understanding of heart action have received increasing attention by researchers, e.g., Romey et al. (1997), Luo and Rudy (1994), Vandenberg and Bezanilla (1991), and Balser, Roden, and Bennett (1990). An important aspect of modeling the action of the human heart is modeling the electrical conductivity of ion channels within the heart. An understanding of cardiac electrical activity can lead to new diagnostic and treatment protocols, as well as facilitating the development of drug treatments for heart disease. In this paper, we describe a model for conductivity of a cardiac potassium channel. The model is based on eight key parameters that determine the transition rates among two closed (non-conducting) states and one open (conducting) state of the channel. We describe a simulation-based method to compute the least squares fit of these parameters to experimental data obtained when various voltages are applied across the channel. In this computation, the parameters are varied in a controlled fashion, and, at each setting of the parameters, a simulation of the conductivity of the channel is performed to obtain predicted output current across the membrane. By iteratively comparing the predicted currents with actual measured current values, the algorithm attempts to converge to the parameter vector that best fits with the measured data.

The next sections describe the model, the simulation-based model fitting methodology, and the results of fitting the model to experimental data.

2 THE CONDUCTIVITY MODEL

The model postulates three modes, designated $C0$, $C1$, and $O2$ of the KvLQT1 potassium channel, $C0$ and $C1$ being closed states and $O2$ being the open state of the channel. It is assumed that the state of the channel can transition between $C1$ and either $C0$ or $O2$, but not between $C0$ and $O2$, and that there are voltage-dependent quantities $K_{ij} = K_{ij}(V)$, where V is membrane potential, representing the transition rates between states, as shown schematically in Figure 1.

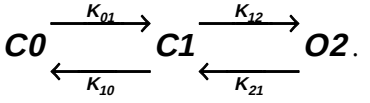

Figure 1. Schematic of Transitions Between States

By the law of mass action, the probabilities C_0, C_1, or O_2 that the channel is in state $C0$, $C1$, or $O2$, respectively, are governed by the three differential equations:

$$\dot{C}_0 = K_{10}C_1 - K_{01}C_0,$$
$$\dot{O}_2 = K_{12}C_1 - K_{21}O_2,$$
$$\dot{C}_1 = K_{01}C_0 + K_{21}O_2 - (K_{10} + K_{12})C_1, \qquad (1)$$

where the derivatives are with respect to time, t, and the probabilities are, of course, functions of time

($C_0 = C_0(t)$, etc.). It is further assumed that the dependence of the rates K_{ij} on voltage is expressed as

$$K_{ij} = \exp(A_{ij} + B_{ij}V), \quad (2)$$

where A_{ij} and B_{ij} are (constant) parameters to be determined. Once these parameters are determined, the action of the channel can be simulated, i.e., the probabilities of the channel's being in the various states can be calculated over time, given the initial conditions and a time sequence of membrane voltages. When the channel is in state $O2$, the current $I_m(t)$ across the membrane at time t is:

$$I_m(t) = G_{KvLQT1} O_2(t)[V(t) - E_K], \quad (3)$$

where G_{KvLQT1} is the (known) maximum conductance of I_{KvLQT1}, and E_K is a known reversal potential.

3 FITTING THE MODEL

The channel conductivity modeling task is completed by determining the parameters A_{ij} and B_{ij}. This can be accomplished by fitting the "best" values of these constants to experimental data. We use a least-squares criterion, defined below, to define the best fit. For the data, we use electric current values, measured (over time) across the channel membrane in a laboratory setting where the membrane voltages are controlled to remain at known fixed levels over fixed time periods (a "voltage clamp" sequence). Given the data and the time history of voltage settings, we fit the model by simulating the action of the channel as follows:

1. Determine starting values of the eight parameters A_{ij} and B_{ij}. A method for this is described below in Section 4.
2. Determine initial conditions for the probabilities C_0, C_1, and O_2. This step can be aided by engineering judgment, or can be arbitrary, except that the three probabilities should add up to unity:
   $$C_0 + C_1 + O_2 = 1. \quad (4)$$
   In our study (see Section 4 below), the voltage regime used in the experiment allowed a good guess of these initial values.
3. Based on the present values of A_{ij} and B_{ij}, the initial conditions and the voltage clamp history, use equations (1) and (2) to simulate the probabilities C_0, C_1, and O_2 over time. As part of this process, equation (4) should be used to eliminate one of the equations in (1), in order to assure that the constraint in equation (4) is satisfied. This also serves to simplify the computations somewhat. To simulate the differential equations (1), we used a simple Runge-Kutta method available in Matlab. Use equation (3) to compute the resulting (predicted) time history of output current.
4. Compute a loss function $L(\Theta)$, for $\Theta \equiv (A_{01}, A_{10}, A_{12}, A_{21}, B_{01}, B_{10}, B_{12}, B_{21})$, equal to the sum of squared differences between the predicted and actual output current values over the time history. Actually, for the final fit, this loss function was modified slightly, as described below in Section 4, to compensate for differences in noise levels in the data.
5. Using an optimization procedure, update the value of Θ, and cycle back to step 3 above, iterating to find the value of Θ that minimizes the loss function $L(\Theta)$.

The final value of Θ defines the best-fitted values of the A_{ij} and B_{ij} terms, in the least squares sense. For the optimization procedure, we plan to use a relatively new methodology, called Simultaneous Perturbation Stochastic Approximation (SPSA), introduced in Spall (1992). This algorithm is especially well adapted to cases like this one, where the parameter is a multivariate (vector) quantity (Θ has 8 states here) and the derivative of the loss function with respect to the parameter to be fitted is difficult or impossible to obtain. This algorithm is also suited to cases where the observations of the loss function are corrupted by noise (which may be the case if we implement the simulation using stochastic sampling based on the probability values described above). Studies of SPSA in comparison to the popular optimization method of simulated annealing have shown a marked advantage for SPSA in certain applications, e.g., Chin (1998).

4 NUMERICAL STUDY

We start with a description of the experiments that generated the data. Cloned cells were treated in the laboratory to express the KvLQT1 gene. These cells acted as cardiac cells having potassium ion channels affected by this gene. After preparation of the cells, the cell culture was subject to 11 experiments. In each experiment, three voltage potentials were applied across the cell culture during three contiguous time periods. In the first time period, a constant voltage of –80 mV was applied for several seconds. In the second time period, one of 11 different voltages (one per experiment) ranging from –40 mV to 60 mV (in 10 mV increments) was applied and held constant for 2000 milliseconds (ms). In the third time period, a voltage of –40 mV was applied for 2000 ms. For 50 ms during period 1, and for the duration of time periods 2 and 3, current flow across the culture was measured and recorded at one-ms time intervals, obtaining about 2000 data points in each of periods 2 and 3.

The value of the reversal potential, E_k, was obtained from the Nernst-Plank equation $E_k = (RT/zF)\log(K_0/K_i)$, where K_0 and K_i are the external and internal potassium concentrations (4 and 140, respectively), T is the temperature (22 degrees Celsius) and R, z, and F are the usual physical constants. The result is that E_k is –88mV. The maximum conductance, G_{KvLQT1}, was obtained using equation (3) at the highest current level measured during the experiments (i.e., near the end of the experiment where the time-period 2 voltage level was 60 mV), and assuming that O_2=1 at that time. From our data, G_{KvLQT1} = 12.0 nS. Under the voltage regime used in these experiments, it is reasonable to assume (as we did) that the initial values of C_0, C_1, and O_2 were 1, 0, and 0, respectively.

Next, we describe how to obtain initial guesses of the desired parameters A_{ij} and B_{ij}. The first step of this was accomplished by using the algorithm described in Section 3 with three simplifications, as follows:

1. We used only data from time period 2.
2. We used only data at one of the 11 voltage settings.
3. We estimated the four transition rates, K_{ij}, rather than the eight parameters A_{ij} and B_{ij}.

We repeated steps 2 and 3 for the other 10 voltage settings, each time using the simple $L(\Theta)$ described in Section 3, step #4, thus obtaining values for each K_{ij} at each of the 11 voltage settings. This process was quick and reasonably simple. Then, under our model's assumption that $K_{ij} = \exp(A_{ij} + B_{ij}V)$, we performed, for each of the four relevant (i,j) settings, a linear fit to obtain A_{ij} and B_{ij} that best fit the $\log K_{ij}$ values at the various voltages. These values of A_{ij} and B_{ij} were then used to initialize the value of Θ in the recursion described in Section 3.

Finally, we ran the algorithm described in Section 3, using data for all of the 11 experiments, but only from time period 2. Ordinarily, data from both time periods 2 and 3 would be used (time period 1 was done simply to start all of the experiments from the same polarized initial state). However, some unexplained anomalies in the time period 3 data were evident, which seemed to indicate that the simpler approach, using only the time period 2 data, would be preferable to start with.

Initial attempts to fit the A_{ij} and B_{ij} using this algorithm showed a tendency to over-emphasize loss function data from the noisiest experiment, i.e., where the time period 2 voltage was –40 mV. That is, the algorithm worked hardest to fit this noisy data since the differences between the predicted and observed values were greatest on that one experiment (due to the noise levels). In order to make the algorithm work harder to fit the "better" (less noisy) data from other experiments, we scaled the loss function values derived from each experiment. The scale factor was the inverse of the standard deviation of the set of observed differences between the predicted and measured current values for the experiment, obtained using the per-voltage K_{ij} parameter values. This resulted in much better performance.

The final fit resulted in values of A_{ij} and B_{ij} given in Table 1.

Table 1. Final Fitted Parameters

	j=0	j=1	j=2
i=0		A_{ij} = 3.8 B_{ij} = .028	
i=1	A_{ij} = -4.9 B_{ij} = .008		A_{ij} = 1.0 B_{ij} = .041
i=2		A_{ij} = -.67 B_{ij} = -.06	

A typical plot (in this case, for the time-period-2 voltage = 20 mV) of the simulated probabilities C_0, C_1, and O_2, and the corresponding (good) fit of simulated current values to the measured values are shown in Figures 2 and 3.

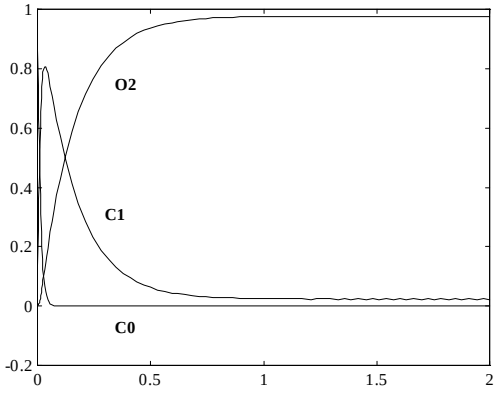

Figure 2. Probabilities Over Time Period 2

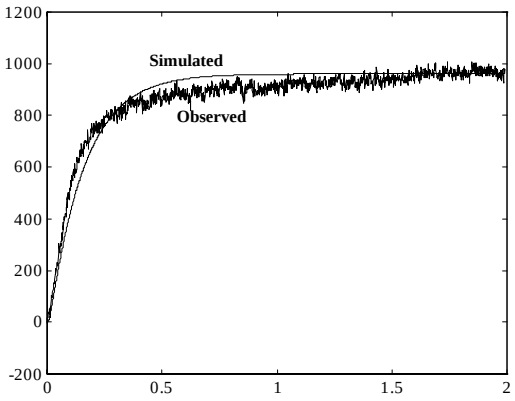

Figure 3. Simulated and Observed Current Over Time Period 2

The algorithm was written in Matlab, and typically ran (not using compilation) in about 20 minutes on a 233-MHz Pentium processor. At this preliminary stage, the good fitting performance and reasonably fast running times are very encouraging. Further work on this data will aim to assess the data quality and how to treat the data from time period 3, which is likely an important step in capturing the best model of the ion channel under a wider range of conditions.

5 SUMMARY

We have described a Markov model for conductivity of a potassium ion channel of the human heart. The parameters of the model are determined by a least-squares fit of predicted vs. measured data. The fitting process is achieved by using the SPSA optimizer to sequentially choose trial values of the parameters. At each choice of parameter value, a loss function is computed by simulating the action of the channel at that trial parameter value. The optimizer converged to parameter values that provided a very good fit to the experimental data in the time period analyzed.

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