Simulation of Cardiac Action Potentials
Background Information

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February 7, 2011

1 Introduction

The goal of assignments related to this document is to experiment with a numerical simulation of the cardiac action potential. The form of this simulation is just as described in class, using the Hodgkin-Huxley formalism and differential equations to reproduce the currents responsible for the action potential. To simulate the cardiac action potential, it is necessary to expand the number of channels from the simple squid giant axon case, and also to alter the dynamic of these currents compared with the original work of Hodgkin and Huxley.

This background section and the Matlab code that you will use is primarily the work of Quan Ni, a former Bioengineering graduate student and now engineer at Guidant Corporation.

2 Derivation

In this section we describe the derivation and additional material you need to know in order to simulate cardiac ventricular membranes. This assumes you have already studied the text and/or read the notes from the lecture on this material, the notes from which are also available on the class website.

The basic equation is the familiar one describing all the currents that travel across the cell membrane of any excitable cell:

$$I = I_{ion} + C_m \frac{dV}{dt} \tag{1}$$

where I_{ion} is the sum of all the ionic currents and $C_m \frac{dV}{dt}$ is the current that arises from the membrane capacitance.

There are six major (and many minor) ionic currents present in cardiac ventricular cell membranes: I_{Na}, a fast sodium current; I_{si}, a slow inward (largely) calcium current; I_K, a time-dependent potassium current; I_{K1}, a second time-independent potassium current; I_{Kp}, a plateau potassium current; and I_b, a time-independent background current. Thus we can write I_{ion} from Equation 1 as

$$I_{ion} = I_{Na} + I_{si} + I_K + I_{K1} + I_{Kp} + I_b \tag{2}$$

We can assume that the *instantaneous* voltage-current relation is linear, *i.e.,* the ionic current for any ion species x, $I_x(t)$, is related to the voltage across the membrane, V_m, by Ohm's law

$$I_x(t) = g_x(t, V)(V_m - V_{eq}^x) \tag{3}$$

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where g_x is the conductance of the particular ionic channel and V_{eq}^x is its Nernst or equilibrium potential. The behavior of a cell membrane for most ion channels is not totally ohmic but instead shows some degree of rectification. The use of Ohm's law is best justified by past simulation results that have successfully reconstructed membrane potential [1], however, one has to be skeptical about the linear assumption under certain conditions, such as large and fast changes in calcium concentration [2].

The conductance of an ionic channel is determined by the maximal conductance, $\overline{g}$, and the fraction of channels that are open. The fraction of channels open is given by some combination of that Hodgkin and Huxley proposed as hypothetical activation variables. For the sodium channel, they assumed two gating variables, "m", representing activation and "h", representing inactivation, both raised to some integral power such that the resulting simulation matches measured values for membrane voltage and current.

$$g_{Na}(t, V) = \overline{g} \cdot m(t, V)^i \cdot h(t, V)^j \tag{4}$$

where i and j are positive integers. They further assumed m and h to obey first-order kinetics of the form

$$\frac{dy}{dt} = \frac{y_\infty - y(t, V)}{\tau_y(V)}, \tag{5}$$

where y represents any gating variable, y_∞ is the steady-state value of y, and τ_y is its time constant. To adapt this formalism to a particular care, one has to determine the rate constants y_∞ and τ_y, as well as the powers, i and j, experimentally.

3   Numerical Simulations

The individual components of ionic currents in the cardiac membrane simulations described here are formulated in terms of Hodgkin-Huxley type equations[1]. The formulae for gating variables follow those of Beeler and Reuter[3], Ebihara and Johnson[4], and Luo and Rudy models[5, 6, 7], all of which are based on cardiac ventricular cells.

The primary goal of the simulation is to approximate the electrical behavior of a single piece of membrane that consists of a membrane capacity with six ionic currents. To represent the ionic currents, we use a coupled system of eight first order, ordinary differential equations. At each step in time, an algorithm establishes a set of values for the variables involved and then we integrate them based on initial conditions and simulation parameters. To determine the membrane potential, we sum the individual ionic currents together with any externally applied current to arrive at the charging current for the membrane capacitance, which then determines the derivative of the membrane potential. Finally, the Equation 1 contains all the necessary values and an integration steps yields $V_m(t)$.

It is also possible (although outside the scope of this assignment) to fix the membrane potential at a desired value and simulate a voltage-clamp experiment. This then permits the study of the characteristics of gate variable by using a simple exponential expression without the need for integration.

The integration algorithm used to solve the differential equations for gate variables is based on a hybrid method[8]. Briefly, for a sufficiently small change of membrane potential over the corresponding time interval, Δt, the gate variables remain essentially unchanged, and an approximate solution for Equation 5 becomes a simple exponential of the form

$$y(t + \Delta t) = y_\infty - (y_\infty - y(t))e^{-\Delta t/\tau_y}, \tag{6}$$
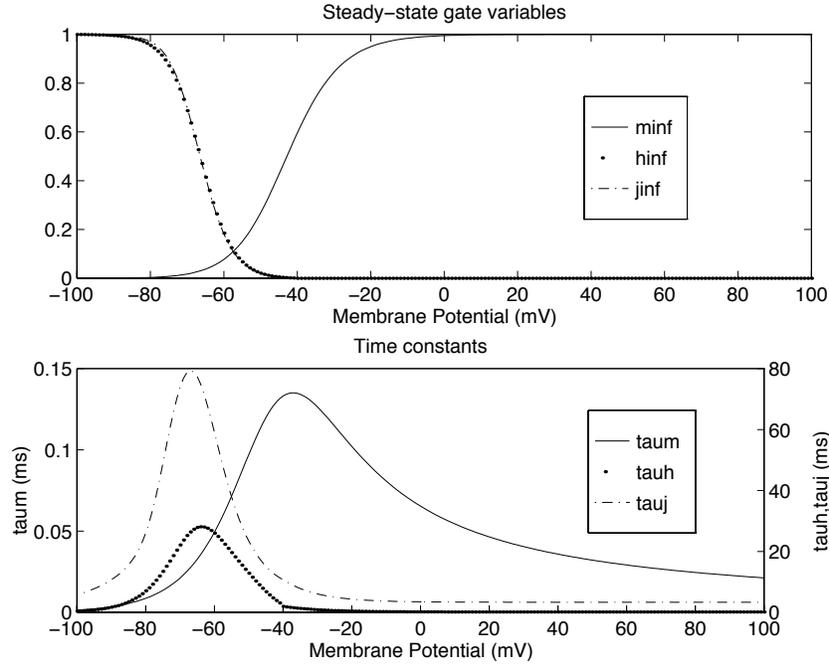
Figure 1: Steady state values and time constants for the activation (m), inactivation (h) and slow inactivation (j) parameters of the fast inward sodium current I_{Na}.

where

$$y_\infty = \frac{\alpha_y}{\alpha_y + \beta_y} \tag{7}$$

and

$$\tau_y = \frac{1}{\alpha_y + \beta_y} \tag{8}$$

are the rate constants. α_y and β_y depend on transmembrane potential V and are determined by fitting data from voltage clamp experiments.

3.1 Ionic Currents

3.1.1 The Fast Inward Sodium Current

The sodium current in this particular model is described by the equation

$$I_{Na} = \bar{g}_{Na} \cdot m^3 \cdot h \cdot j \cdot (V_m - E_{Na}), \tag{9}$$

where $\bar{g}_{Na}$ is the maximum conductance of the sodium channel. m and h are activation and inactivation parameters, respectively; j is a slow inactivation gate for modeling the slow recovery. E_{Na} is the Nernst (equilibrium) potential for sodium (= 54.8 mV). See Fig. 1 for steady state values and time constants for these parameters.

3.1.2 The Slow Inward Current

The slow inward current (I_{si}) plays a dominant part in the creation of the myocardial action potential plateau. I_{si} is mainly carried by calcium ions[3] and we can write it using the same form
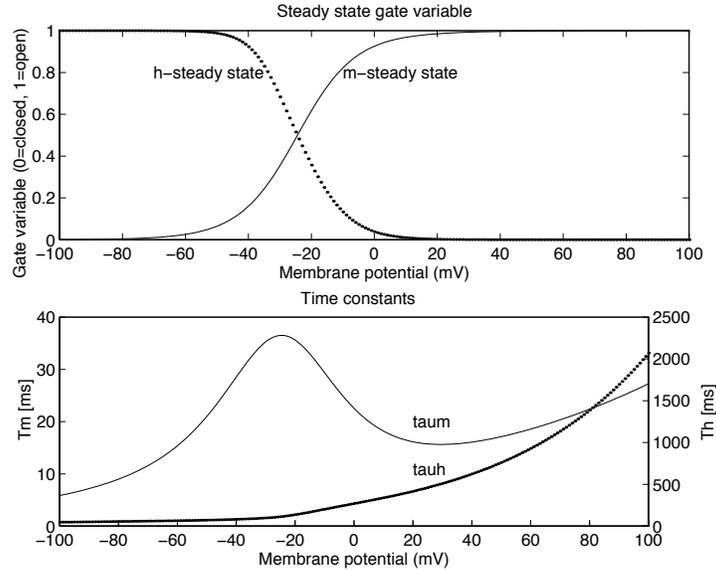
Figure 2: Steady state values and time constants for the activation (m) and inactivation (h) parameters of the slow inward current I_{si}.

as for sodium,

$$I_{si} = g_{si} \cdot m \cdot h \cdot (V_m - E_{si}), \tag{10}$$

where g_{si} is the maximum conductance, m and h are activation and inactivation variables, respectively. Unlike for other ions, we must take into account the change in equilibrium potential that arises with variation in calcium concentration, which we can write as

$$E_{si} = 7.7 - 13.0287 \, ln([Ca]_{in}). \tag{11}$$

We can approximate the change in intracellular calcium concentration caused by the inward current as

$$\frac{d[Ca]_{in}}{dt} = -10^{-4} I_{si} + 0.07(10^{-4} - [Ca]_{in}) \tag{12}$$

See Figure 2 for the steady state values and time constants for the activation (m) and inactivation (h) parameters of the slow inward current. Compared to corresponding values for the Na channels, the time constant of the activation gate is extremely large (slow), indicating that I_{Ca} not only has a delayed onset because of its more positive threshold voltage, but also is slower to develop.

The dynamics of the gating variables for the slow inward current have the same form as for the sodium channel. We can generalize this to an equation of the form

$$\alpha; \beta = \frac{C_1 \, e^{(\frac{Vm - V_0}{C_2})} + C_3(V - V_0)}{1 + C_4 \, e^{(\frac{V - V_0}{C_5})}} \tag{13}$$

where to find the values $C_1 \ldots C_5$ we must carry out voltage clamp experiments on the respective currents.
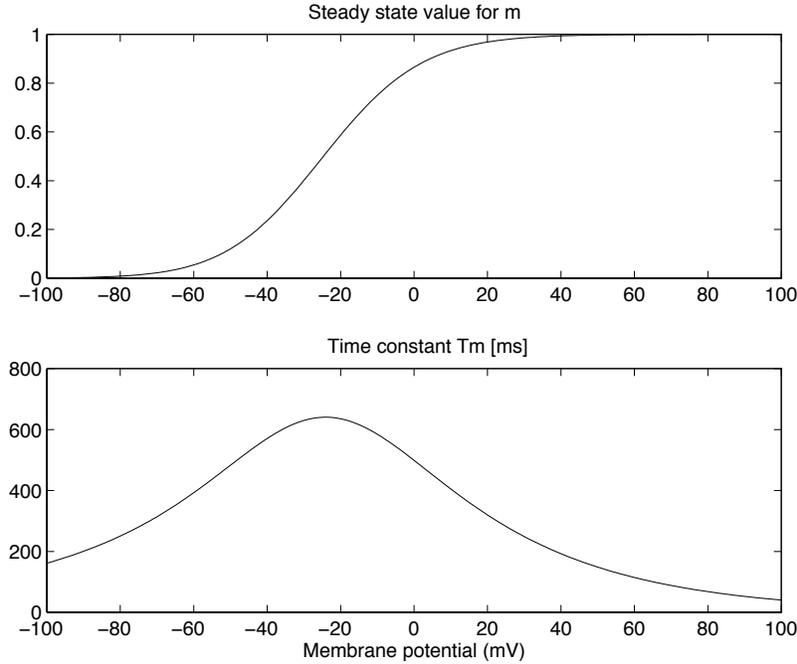
Figure 3: Steady state values and time constants for the activation gate of the time dependent potassium current I_K.

3.1.3   The Time-dependent Potassium Current

In this model, we include four different potassium channels, each with different voltage and time dependencies. Note that this is still a small fraction of the K^+ channels that experimentalists have characterized, but these four replicate the overall behavior of most of them.

The time-dependent potassium current (I_K) is controlled by a time-dependent activation gate (m) and a time-independent inactivation gate (h).

$$I_K = \overline{g}_K \cdot m^2 \cdot h \cdot (V_m - E_K) \tag{14}$$

See Fig. 3 for the steady state values and time constants for the activation parameters of the time dependent potassium current.

3.1.4   Time-independent Potassium Current, I_{K1}

The time-independent potassium current, I_{K1}, only consists of an single inactivation gate (h). Furthermore, the time constant of this gate is small ($\tau_h = 0.06$ at V=-50 mV, see Fig. 4), so it can be approximated by its steady state value, h_∞

$$I_{K1} = \overline{g}_{K1} \cdot h_\infty \cdot (V_m - E_{K1}) \tag{15}$$

See Figure 5 for the current-voltage curve of I_{K1} for different values of external K^+ concentration. Note the strong difference between the behavior at positive membrane voltages (right half of the curve) and that at negative membrane voltages (left half of curve). In this case, current flows much more easily in the inward direction at negative potentials, a behavior known as *inward rectification*.
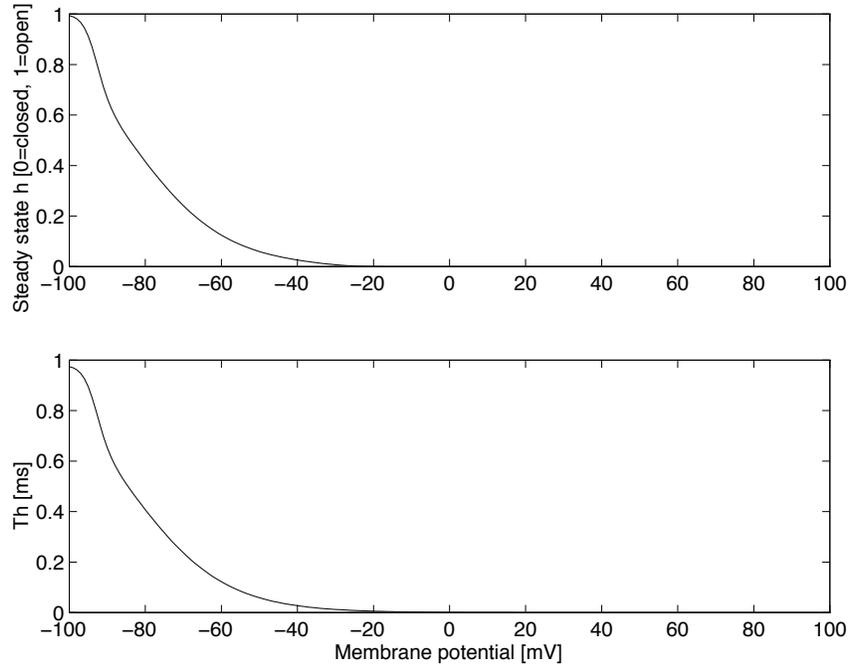
Figure 4: Steady state values and time constants for the inactivation gate (h) of the time dependent potassium current I_{K1}. Note the small time constant.

I_{K1} plays a major role in stabilizing the ventricular cells at rest. These channels are normally absent from pacemaker cells such as sinoatrial (SA) and atrioventricular (AV) cells. If we hyperpolarize a cell from its equilibrium point, there will be an influx of K^+; once hyperpolarized voltage stops, this inward K^+ current will bring the cell to equilibrium again. On the other hand, if we depolarize a cell, it will result in an efflux of K^+ and as depolarization stops, the efflux current will bring the cell back to equilibrium.

3.1.5   Plateau Potassium Current

The potassium current at plateau potentials results from a time-independent channel defined by

$$I_{Kp} = \overline{g}_{Kp} \cdot m \cdot (V_m - E_{Kp}). \tag{16}$$

3.1.6   Background Current

We can formulate the background potassium current as

$$I_b = \overline{g}_b \cdot (V_m - E_b). \tag{17}$$

See Figure 6 for the current-voltage curves of total time-independent potassium current ($I_{K1} + I_{Kp} + I_b$), which are very similar to those for the I_{K1} component.

3.2   Action Potential

With all the currents computed, it is now a relatively simple matter to integrate Equation 1 at each time instant and derive the voltage signal for the action potential. By varying some of the
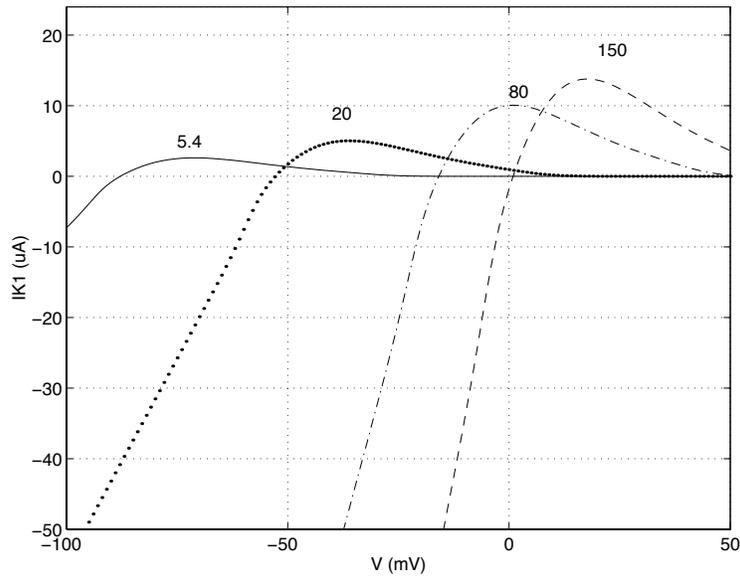
Figure 5: Current-voltage curve of I_{K1} for different values of $[K]_o$. Note the strong inward rectification, indicated by the large inward currents at negative potentials.
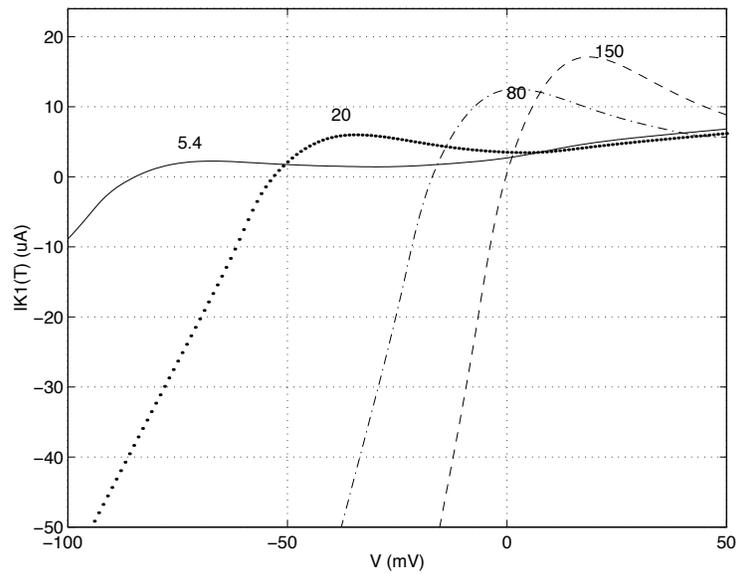

Figure 6: Current-voltage curve of the *total* time-independent current $I_{K1} + I_{Kp} + I_b$ for different values of $[K]_o$.

conditions of the simulation, it is possible to alter the course of the action potential, and also observe the underlying currents that are responsible.

References

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