ANALYSIS OF TIME-COURSE OF THE RECOVERY FROM INACTIVATION FOR THE MOLLUSCAN IONIC CURRENTS*

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Abstract– In this study, the time-course of the recovery from inactivation of molluscan ionic currents is examined. Molluscan voltage-gated ionic currents are described in Hodgkin-Huxley-like equations. The peak value function of the recovering conductance is derived from the mathematical equivalent of an experimental procedure of the recovery process in a general form by including the number of inactivation gates. Then the curves of the recovery and its approximation for the molluscan ionic currents are obtained. It is shown that recovering conductance of molluscan ionic currents is asymptotically exponential.

Keywords– Recovery, inactivation, ionic currents, peak value function, molluscan

1. INTRODUCTION

Computer simulations of neuronal structures are powerful tools for neuroscientists in understanding nervous system physiology and its function [1]. Experimental studies are taken as a basis for constructing neuronal models. Furthermore, the simulations based on neuronal models are used to investigate features of neurones that are experimentally inaccessible or not easily controlled [2].

Ionic channels are of great importance in the transfer of ions between the outer and the inner surface of cell membranes. Voltage-gated ionic channels that form an important class of such channels are involved in the generation and propagation of electrical signals in the excitable cell membranes. Many different types of voltage-gated ionic channels are found in neurones [3-6]. Voltage-gated ionic currents have great importance in integrating the information received by the neurones [7]. Spike activity of a neurone is determined by the interaction between voltage-gated ionic currents and inputs, which may have a synaptic or current form. These channels in nerve cells are responsible for generating and propagating the action potentials. Therefore, dynamical behaviour of voltage-gated ionic currents is crucial in understanding how these currents determine membrane responses [2]. In this context, recent theoretical and experimental considerations argued that intrinsic gating mechanisms of voltage-gated ion channels, and slow changes in the availability of the channels for activation might contribute significantly to long lasting modulations in excitable membranes [8]. Lowen et al. [9] examined the effects of fractal ion-channel activity in modifications of two classical neuronal models, Fitzhugh-Nagumo and Hodgkin-Huxley, and concluded that fractal ion-channel gating activity was sufficient to account for fractal-rate firing behavior. At the biophysical level, the magnitude of subthreshold voltage noise that may contribute to variability in spike timing is determined by ion channel kinetics [10]. In a recent study, it has been shown how slowly-inactivating potassium current with specific channel kinetics, along with Hodgkin-Huxley currents and persistent sodium current can generate a robust bursting pattern in a model interneuron [11].

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Determining kinetics of ionic currents and understanding their dynamical behaviors are of great importance. There are several experimental procedures for determining kinetics of ionic currents [12]. Reconstruction of the recovery process is one of them and is used for estimating the inactivation time-constant [13].

In the present paper we obtain the peak value function of recovering conductance derived from the mathematical equivalent of an experimental procedure of the recovery process by including the number of inactivation gates, \( q \), as a variable, and give its explicit expression to be used in other applications. Then, the time-course of the recovery from inactivation of molluscan ionic currents is examined. It is shown that recovering conductance of the molluscan ionic currents is asymptotically exponential.

2. MATHEMATICAL MODEL OF A VOLTAGE-GATED IONIC CURRENTS

Molluscan ionic currents are described in Hodgkin-Huxley-like equations [14]. Hodgkin and Huxley derived mathematical equations that describe two types of voltage-dependent conductance in squid giant axons, and based the equations on a conducting channel model which consists of activation and inactivation gates [15]. In that formalism, an ionic current channel is assumed to have gates which are in one of two states, i.e. open or closed state [16]. Conductance of an ionic channel is defined with Hodgkin-Huxley as follows [15]:

\[
G_X(v,t) = g_X m^p(v,t) h^q(v,t)
\]

where \( m \) and \( h \) show voltage-dependent probability of being open state for activation and inactivation gates, respectively, and \( g_X \) is the maximal conductance of ionic channel, i.e. conductance of an ionic channel when all of the gates were open, \( p \) is the number of activation gates and \( q \) is the number of inactivation gates.

Activation and inactivation gates change their states (open or closed) over time in response to membrane potential with first order differential equations as follows:

\[
\frac{dm}{dt} = a_m(v)(1-m) - \beta_m(v)m = \frac{m_a(v) - m}{\tau_m(v)}
\]

\[
\frac{dh}{dt} = a_h(v)(1-h) - \beta_h(v)h = \frac{h_a(v) - h}{\tau_h(v)}
\]

where \( \alpha(v) \) and \( \beta(v) \) are voltage-dependent rate functions which determine the speed of transitions from one state to the other within the ion gates, and given by

\[
\alpha(v) = \frac{a + bv}{c + e^{(d+e)v}}
\]

where a, b, c, d, and e are constants. These constants are determined by theoretical and empirical considerations [12].

The values of \( m_a(v) \) and \( h_a(v) \) are steady-state activation (i.e. steady-state open gate fraction for activation) and inactivation (i.e. steady-state open gate fraction for inactivation), respectively, since \( m \) and \( h \) will get a value asymptotically close to these values when the membrane voltage is held constant for a sufficient duration; \( \tau_m(v) \) and \( \tau_h(v) \) are voltage-dependent activation and inactivation time constants which are the times taken to reach steady-state values respectively; and may be written as

\[
m_{a\infty}(v) = \frac{\alpha_m(v)}{\alpha_m(v) + \beta_m(v)}
\]

\[
\tau_m(v) = \frac{1}{\alpha_m(v) + \beta_m(v)}
\]
$h_v(v)$ and $\tau_h(v)$ have similar forms. When the voltage is held constant, the solution of Eq. (2) is given by

$$m(t) = m_v(v) - (m_v(v) - m_0)e^{-t/\tau_m(v)}$$

where $m_0$ is the initial value of $m$. Similarly, under the same condition, the solution of Eq. (3) is given by

$$h(t) = h_v(v) - (h_v(v) - h_0)e^{-t/\tau_h(v)}$$

where $h_0$ is initial value of $h$.

### 3. INACTIVATED IONIC CURRENTS IN MOLLUSCAN NEURON

Inward sodium ($\text{Na}^+(v)$) and delayed rectifier ($\text{K}^+(A)$) ionic currents are inactivated voltage-gated ionic currents present in molluscan Somata [14]. A mathematical description of the currents was given by Connor and Stevens [17-19]. De Schutter converted the equations for the molluscan ionic currents given by Connor and Stevens into Hodgkin-Huxley like equations and showed the accuracy of these equations [14]. Kinetics of the ionic currents used in this study are based on the study by De Schutter [14].

Conductance of inward sodium current is given by

$$G_{\text{Na}^+(v)}(v,t) = g_m m^3(v,t)h(v,t)$$

Voltage-dependent rate functions of the inward sodium channel are as follows:

$$\alpha_m(v) = -0.0698(v+7.5) + 0.0726 \frac{e^{v+5.5}/6}{e^{v+5.5}/6 + 1}$$
$$\beta_m(v) = \frac{0.117}{e^{v+25.5}/2 + 1}$$

Voltage (mV)

<table>
<thead>
<tr>
<th>-100</th>
<th>-75</th>
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<th>0</th>
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$$\alpha_h(v) = \frac{0.0117}{e^{v+25.5}/2 + 1}$$
$$\beta_h(v) = \frac{0.289}{e^{v+10.5}/5 + 1}$$

The graphics of steady-state activation and inactivation and of their time constants for the inward sodium current are obtained by using Eqs. (5), (6) and (10) for a voltage range from –100 to 75 mV, and shown in Fig. 1 and Fig. 2, respectively.

**Fig. 1. Steady-state activation and inactivation curves for inward sodium current**

**Fig. 2. Time constants of activation and inactivation gates for inward sodium current**

The conductance of a delayed rectifier current is given by

$$G_{\text{K}^+(A)}(v,t) = g_K m^4(v,t)h(v,t)$$

Voltage-dependent rate functions of the delayed rectifier channel are as follows:

$$\alpha_m(v) = -0.00124(v+70) + 0.0418 \frac{e^{v+40}/41}{e^{v+40}/41 + 1}$$

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Graphics of steady-state activation and inactivation and their time constants for the delayed rectifier current are obtained by using Eqs. (5), (6) and (12) for a voltage range from –125 to 125 mV, and shown in Figure 3 and Fig. 4, respectively. Membrane potentials given in the rate functions above are the absolute potentials as a modern sign convention in contrast to the ones used by Hodgkin-Huxley, in which the potentials are expressed as the difference with the resting membrane potential.

\[ a_h(v) = \frac{0.00390}{e^{(v+56)/4}+1} \]
\[ \beta_h(v) = \frac{-0.0001104(v+79)}{e^{(v+79)/3}-1} \]  

(12.b)

4. RECOVERING PROCEDURE

A detailed experimental procedure of recovering is given by Toth and Crunelli [13]. They have also derived a mathematical equivalent of the experimental procedure and have given the peak value function of recovering conductance. But the peak value function of recovering conductance which they have given is not explicit in terms of $C$ (in their Eqs. (9) and (10)), and doesn’t include the number of inactivation gates, $q$, as a variable, which came from the conventional Hodgkin-Huxley mathematical formalism defined in Eq. (1). We obtain the peak value function of recovering conductance in the same manner by Toth and Crunelli [13] with the same symbols by including the number of inactivation gates, $q$, as a variable, and give its explicit expression to be used in other applications.

In the first step, membrane is depolarized for a sufficiently long time, so complete inactivation of the current is provided. Therefore it can be assumed the $m_0=1$, and $h_0=0$ at $V_0$, depolarized potential. Then a voltage step from $V_0$ to $V_1$ is applied for variable time duration ($t_1$) so that the complete removal of inactivation is provided with $m_1=0$ and $h_1=1$. This voltage step hyperpolarizes the membrane. In the hyperpolarized condition, activation and inactivation variables after time $t_1$ are obtained, respectively from Eqs. (7) and (8), respectively, by using the values given above

\[ m_1(t_1) = e^{-t_1/\tau_{m1}(V_1)} \]  
\[ h_1(t_1) = 1 - e^{-t_1/\tau_{h1}(V_1)} \]  

(13)

(14)

In the second step, the membrane is depolarized to $V_0$ potential at $t=t_1$. In the depolarized condition, activation and inactivation variables for $t>t_1$ are obtained, respectively from Eqs. (7) and (8), respectively, by using the initial values given in Eqs. (13) and (14)

\[ m_2(t; t_1) = 1 - (1 - m_1(t_1))e^{-(t-t_1)/\tau_{m0}(V_0)} \]  
\[ h_2(t; t_1) = h_1(t_1)e^{-(t-t_1)/\tau_{h0}(V_0)} \]  

(15)

(16)

Conductance response to the depolarization step is obtained by substituting Eqs. (15) and (16) into Eq. (1).
Analysis of time-course of the recovery from …

\[ G_{X2}(t; t_1) = g_X m_2^p(t; t_1) h_2^q(t; t_1) \]  
(17)

The peak value function of recovering conductance in terms of \( t_1 \) is obtained by differentiating Eq. (17) according to \( t \) as

\[ G_{X2, peak}(t_1) = C \frac{h_2^q(t_1)}{g_{X2} q \tau_{m0} (1 - m_1(t_1)) \tau_{h0}} \]  
(18)

where

\[ C = g_X \left[ 1 - \frac{1}{(1 + \frac{p}{q} \frac{\tau_{h0}}{\tau_{m0}}) \tau_{m0}} \right]^p \frac{1}{(1 + \frac{p}{q} \frac{\tau_{h0}}{\tau_{m0}}) \tau_{h0}} \]  
(19)

The details of the derivation of Eq. (18) are given in Appendix A.

If the kinetics of \( m_1(t_1) \) are much faster than the kinetics of \( h_1(t_1) \), the peak value function of recovery conductance becomes asymptotically exponential as follows:

\[ G_{X2, peak}(t_1) \approx C h_1^q(t_1) \]  
(20)

5. SIMULATION RESULTS

All calculations in the simulations were performed in SigmaPlot 2000 for Windows Version 6.00 on a 350 MHz Pentium II processor. In the simulations, \( V_0 \) voltage was selected so that complete inactivation of the current was provided, i.e. \( m_0=1 \), \( h_0=0 \). \( V_1 \) voltage was selected so that complete removal of inactivation was provided, i.e. \( m_1=0 \) and \( h_1=1 \). Two simulations were carried out.

In the first simulation, \( V_0 \) voltage was determined as 57 mV for inward sodium current (Na⁺) by using Fig. 1. Activation and inactivation time constants were calculated from Eqs. (6) and (10) as \( \tau_{m0}=0.222463 \) ms, \( \tau_{h0}=3.460212 \) ms at that voltage. \( V_1 \) voltage was determined as –99.1 mV in the same manner. Activation and inactivation time constants were calculated from Eqs. (6) and (10) as \( \tau_{m1}=13.774094 \) ms, \( \tau_{h1}=85.470043 \) ms at that voltage. \( C/g_{Na} \) value was calculated from Eq. (19) as 0.731949. The curves of recovery and its approximation are obtained by using Eqs. (18) and (20), respectively, and shown in Fig. 5.

In the second simulation, \( V_0 \) voltage was determined as 120 mV for delayed rectifier current (K⁺) by using Fig. 3. Activation and inactivation time constants were calculated through Eqs. (6) and (12) as \( \tau_{m0}=4.229330 \) ms, \( \tau_{h0}=45.271402 \) ms at that voltage. \( V_1 \) voltage was determined as –123.3 mV in the same manner. Activation and inactivation time constants were calculated through Eqs. (6) and (12) as \( \tau_{m1}=3.133476 \) ms, \( \tau_{h1}=256.410144 \) ms at that voltage. \( C/g_K \) value was calculated from Eq. (19) as 0.640515. The curves of recovery and its approximation are obtained by using Eqs. (18) and (20), respectively, and shown in Fig. 6.
6. CONCLUSIONS

In this paper, the time-course of the recovery from the inactivation of molluscan ionic currents is examined. The peak value function of recovering conductance is obtained from the mathematical equivalent of the experimental procedure of the recovery process in a general form by including the number of inactivation gates as a variable, and given explicitly. It is seen from the curves of recovery and its approximation in Figs. 5 and 6 for the inward sodium and delayed rectifier currents, respectively, that there is no deviation between recovery curves and their exponential curves, and both of the curves coincide. The recovering conductance of the molluscan ionic currents is shown to be asymptotically exponential.

REFERENCES

APPENDIX A. DETAILS OF THE PEAK VALUE FUNCTION OF THE RECOVERING CONDUCTANCE

Differentiating Eq. (17) and setting the derivative to zero gives

\[
\frac{\partial G_{X,2}(t; t_1)}{\partial t} = g_X p \left[ 1 - (1 - m_1(t_1))e^{-(t-t_1)/\tau_{m0}} \right]^{p-1} \left[ \frac{1}{\tau_{m0}} (1 - m_1(t_1))e^{-(t-t_1)/\tau_{m0}} \right] h_1(t_1)e^{-(t-t_1)/\tau_{h0}} q
\]

\[
+ g_X q \left[ - (1 - m_1(t_1))e^{-(t-t_1)/\tau_{m0}} \right] p \left[ h_1(t_1)e^{-(t-t_1)/\tau_{h0}} \right] q^{-1} \left( -\frac{1}{\tau_{h0}} \right) h_1(t_1)e^{-(t-t_1)/\tau_{h0}} = 0
\]

\[
g_X p \left[ - (1 - m_1(t_1))e^{-(t-t_1)/\tau_{m0}} \right]^{p-1} \left[ \frac{1}{\tau_{m0}} (1 - m_1(t_1))e^{-(t-t_1)/\tau_{m0}} \right] h_1(t_1)e^{-(t-t_1)/\tau_{h0}} q
\]

\[
p \left[ - (1 - m_1(t_1))e^{-(t-t_1)/\tau_{m0}} \right]^{q-1} \left[ \frac{1}{\tau_{m0}} (1 - m_1(t_1))e^{-(t-t_1)/\tau_{m0}} \right] = \frac{q}{\tau_{h0}}
\]

\[
\frac{p \frac{\tau_{h0}}{q \tau_{m0}} (1 - m_1(t_1))e^{-(t-t_1)/\tau_{m0}}}{1 - (1 - m_1(t_1))e^{-(t-t_1)/\tau_{m0}}} = 1 \Rightarrow \frac{p \frac{\tau_{h0}}{q \tau_{m0}}}{q \frac{\tau_{m0}}{\tau_{m0}}} (1 - m_1(t_1))e^{-(t-t_1)/\tau_{m0}} = 1
\]

\[
e^{-t/\tau_{m0}} = \frac{e^{-t/\tau_{m0}}}{1 - m_1(t_1)(1 + p \frac{\tau_{h0}}{q \tau_{m0}})} \Rightarrow e^{-t} = \left[ \frac{e^{-t/\tau_{m0}}}{1 - m_1(t_1)(1 + p \frac{\tau_{h0}}{q \tau_{m0}})} \right] \tau_{m0}
\]

(A.1)

Rearranging Eq. (17) with (A.1) gives

\[
G_{X,2,peak} (t_1) = g_X \left[ 1 - (1 - m_1(t_1))e^{h_1/\tau_{m0}} \right] \frac{e^{h_1/\tau_{m0}}}{(1 - m_1(t_1))(1 + p \frac{\tau_{h0}}{q \tau_{m0}})} \left[ \frac{e^{-h_1/\tau_{m0}}}{(1 - m_1(t_1))(1 + p \frac{\tau_{h0}}{q \tau_{m0}})} \right]^{q}
\]

\[
x \left[ h_1(t_1)e^{h_1/\tau_{h0}} \right] \frac{e^{-h_1/\tau_{h0}}}{(1 - m_1(t_1))(1 + p \frac{\tau_{h0}}{q \tau_{m0}})} \left[ \frac{e^{-h_1/\tau_{h0}}}{(1 - m_1(t_1))(1 + p \frac{\tau_{h0}}{q \tau_{m0}})} \right]^{q}
\]

\[
G_{X,2,peak} (t_1) = g_X \left[ 1 - \frac{1}{(1 + p \frac{\tau_{h0}}{q \tau_{m0}})} \right] \left[ \frac{h_1(t_1)}{(1 - m_1(t_1))^{\tau_{m0}/\tau_{h0}} (1 + p \frac{\tau_{h0}}{q \tau_{m0}})^{\tau_{m0}/\tau_{h0}}} \right]^{q}
\]
\[ G_{X, \text{peak}}(t_1) = g_X \left[ 1 - \frac{1}{1 + p \left( \frac{\tau_{h0}}{q \tau_{m0}} \right)} \right]^p \frac{h^q(t_1)}{q \tau_{m0} (1 - m(t_1)) \tau_{m0}} \]

(A.2)

\[ = g_X \left[ 1 - \frac{1}{1 + p \left( \frac{\tau_{h0}}{q \tau_{m0}} \right)} \right]^p \frac{1}{(1 + \frac{p \tau_{h0}}{q \tau_{m0}}) \tau_{m0}} \frac{h^q(t_1)}{q \tau_{m0} (1 - m(t_1)) \tau_{m0}} = C \frac{h^q(t_1)}{q \tau_{m0} (1 - m(t_1)) \tau_{m0}} \]

(A.3)