ANALYSIS OF AXONAL RESPONSE TO SINUSOIDAL STIMULATION BASED ON SQUID GIANT AXON

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ABSTRACT

In this study, compartmental model of squid giant axon is constructed, and axonal response to sinusoidal stimulation is examined based on the squid giant axon. Axonal membrane potentials are obtained for a stimulus frequency range and spike counts are estimated. Then sodium ionic channels that cause membrane depolarization in the model are blocked by application tetrodotoxin(TTX), so magnitude of axonal membrane potential oscillations are investigated.

I. INTRODUCTION

Modeling of neuronal structure is an important tool for neuroscientists on understanding of neuronal functions. In this context methods of neuronal excitability have been significantly influenced by Hodgkin and Huxley [1]. Hodgkin and Huxley derived mathematical equations that describe two types of voltage-dependent conductances in squid giant axon [2]. Squid axon has a simple neural structure in terms of voltage-dependent ionic channel number. It contains a fast Na^+ current, a delayed rectifier K^+ current, and a leak current. Fast Na^+ current and delayed rectifier K^+ current are voltage-dependent. Hodgkin-Huxley's mathematical formalism is still used to describe behaviour of voltage-gated ionic channels [3-7]. Therefore new studies are reported on simulating biological systems and neuronal excitability based on squid giant axon as a basis for modeling of neuronal structures include more than two voltage-dependent ionic channels [8,9].

II. HODGKIN-HUXLEY FORMALISM OF AN IONIC CURRENT

In Hodgkin-Huxley mathematical formalism, an ionic current channel is assumed to have gates which are in one of two states, i.e. open or closed state [10]. Conductance of an ionic channel is defined with Hodgkin-Huxley as follows [2]:

$$G_X(v,t) = g_X m^p(v,t) h^q(v,t) \qquad (1)$$

where m and h show voltage-dependent probability of being open state for activation and inactivation gates respectively, g_x is maximal conductance of ionic channel, p is the number of activation gates and q is the number of inactivation gates.

Transitions between open and closed states are modelled with first order differential equations as follows:

$$\frac{dm}{dt} = \alpha_m(v)(1-m) - \beta_m(v)m = \frac{m_\infty(v) - m}{\tau_m(v)} \qquad (2)$$

$$\frac{dh}{dt} = \alpha_h(v)(1-h) - \beta_h(v)h = \frac{h_\infty(v) - h}{\tau_m(v)} \qquad (3)$$

where $\alpha(v)$ and $\beta(v)$ are voltage-dependent rate functions which determine rate of transitions from one state to the other within the ion gates. $m_\infty(v)$ and $h_\infty(v)$ are steady-state activation(i.e. steady-state open gate fraction for activation) and inactivation(i.e. staedy-state open gate fraction for inactivation) respectively; $\tau_m(v)$ and $\tau_h(v)$ show voltage-dependent activation and inactivation time constants which are the times taken to reach a steady-state values for a given potential respectively, and may be written as

$$m_\infty(v) = \frac{\alpha_m(v)}{\alpha_m(v) + \beta_m(v)} \; ; h_\infty(v) = \frac{\alpha_h(v)}{\alpha_h(v) + \beta_h(v)} \qquad (4)$$

$$\tau_m(v) = \frac{1}{\alpha_m(v) + \beta_m(v)} \; ; \tau_h(v) = \frac{1}{\alpha_h(v) + \beta_h(v)} \qquad (5)$$

III. VOLTAGE-DEPENDENT IONIC CHANNELS OF SQUID GIANT AXON

Squid giant axon contains a fast Na^+ current which causes membrane depolarization, a delayed rectifier K^+ current which causes membrane repolarization, and a leak current which determines resting membrane potential.

Conductance of fast Na^+ channel is given by

$$G_{Na} = g_{Na} m^3 h \quad (6)$$

where g_{Na} is 120 mS/cm^2. Rate functions of fast Na^+ channel are as follows:

$$\alpha_m(v) = \frac{0.1(40+v)}{1-e^{-(v+40)/10}} ; \beta_m(v) = 0.108e^{-v/18} \quad (7)$$

$$\alpha_h(v) = 0.0027e^{-v/20} ; \beta_h(v) = \frac{1}{1+e^{-(v+35)/10}} \quad (8)$$

Conductance of delayed rectifier K^+ channel is given by

$$G_K = g_K n^4 \quad (9)$$

where g_K is 36 mS/cm^2. Rate functions of delayed rectifier K^+ channel are as follows:

$$\alpha_n(v) = \frac{0.01(v+55)}{1-e^{-(v+55)/10}} ; \beta_n(v) = 0.0555e^{-v/80} \quad (10)$$

IV. COMPARTMENTAL MODEL OF SQUID GIANT AXON

Squid giant axon model is constructed by using compartmental modeling approach. . Compartmental modeling in which a neuron is divided into small parts called as compartment is derived from linear cable theory [11]. Equivalent electric circuit for squid giant axon compartment is shown in Figure 1. Specific membrane capacitance, CM is taken as 1 μF/cm^2, leak conductance as 0.3 mS/cm^2, resting potential as –65 mV, and reversal potentials E_{Na} as 50 mV, E_K as –77 mV and E_L as –59.4 mV.

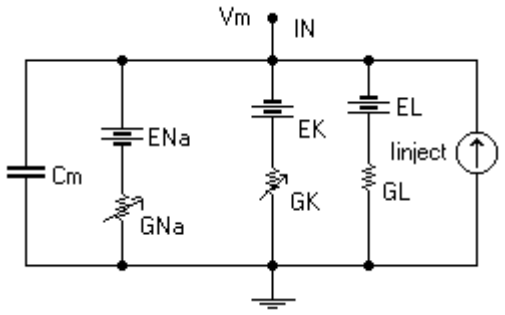

Figure 1. Equivalent electric circuit for the model

In Figure 1, current equation is obtained as

$$C_m \frac{dV_m}{dt} + I_{ion} = I_{inject} \quad (11)$$

where C_m , V_m , I_{ion} , I_{inject} represent membrane capacitance, membrane potential, sum of ionic currents, and injected current respectively. Sum of the ionic currents is given by

$$I_{ion} = \sum G_k (V_m - E_k) = I_{Na} + I_K + I_{leak} \quad (12)$$

So the change in membrane potential is expressed as follows:

$$\frac{dV_m}{dt} = \frac{1}{C_m}\left[I_{inject} - I_{ion}\right] = \frac{I_{total}}{C_m} \quad (13)$$

V. INTEGRATION METHOD

It's necessary to compute *m* and *h* values at each time step before calculating of membrane potential. Eq. (2) and Eq. (3) have a general form as

$$\frac{dy}{dt} = f(t) = A - By \quad (14)$$

where A=α , B=α+β. We use Forward Euler method to obtain the values of *m* and *h* for each time step. Solution of Eq. (14) for time increment Δt is given as follows [1]:

$$y(t+\Delta t) = y(t) + \Delta t f(t) \quad (15)$$

After calculating of *m* and *h* values, it's easy to calculate an ionic current with Eq. (12) . Next step at the integration is to calculate the membrane potential according to Eq. (13). The expression on the right side of Eq. (13) was calculated, so have a constant value. Therefore the integration of membrane potential is done with Forward Euler method [1]:

$$V_m(t+\Delta t) = V_m(t) + \Delta t \frac{I_{total}}{C_m} \quad (16)$$

VI. SIMULATION RESULTS AND DISCUSSION

Simulations were run with fixed time increment of 40 ms same as in [8,9]. Sinusoidal currents with different frequencies were injected into the compartment for several different magnitudes, and membrane potentials were calculated. Then spike counts were estimated over 200 ms simulation duration and a plot of spike count vs. stimulus frequency was obtained as shown in Figure 2. As seen in Figure 2, range of spike activity increases with increasing current magnitude. These ranges were observed as nearly 60 Hz, 110 Hz, 250 Hz, 300 Hz for 2.5, 5, 10 and 15 μA magnitudes respectively. At the same time the total spike count decreases with increasing frequency, but the decrease didn't happen smoothly.

To determine relation between magnitude of axonal membrane potential oscillations and stimulus frequency, sodium channels that causes membrane depolarization are blocked, i.e. their conductance was reset to zero. Then sinusoidal currents with different frequency were injected into the compartment for several different magnitudes, peak depolarization potentials were recorded and a plot of peak depolarization vs. stimulus frequency was obtained as shown in Figure 3. Setting fast sodium channel conductance to zero, spike activity was blocked. Therefore only membrane potential oscillations were allowed. As seen in Figure 3, all curves showed same characteristic. A higher frequency stimulus resulted in a smaller membrane potential oscillations. Magnitude of the peak depolarization increased up to nearly 50 Hz, and then decayed exponentially.

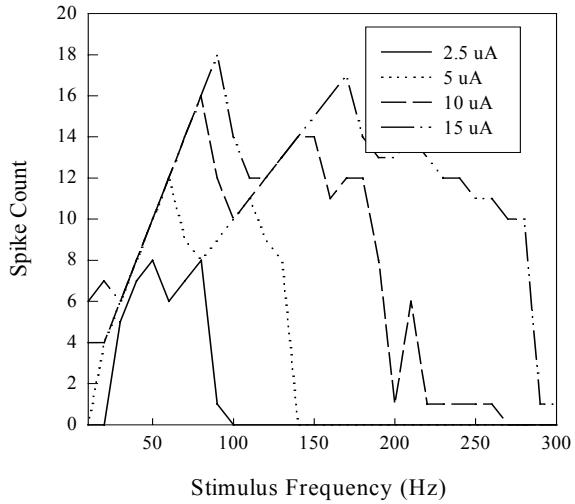

Figure 2. Relation between spike count and stimulus frequency

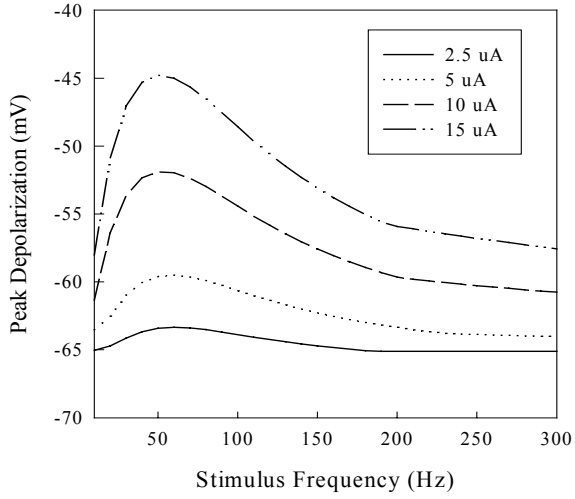

Figure 3. Relation between peak depolarization and stimulus frequency

VII. CONCLUSION

In this study, axonal response to sinusoidal stimulation based on squid giant axon is examined. Compartmental model of squid giant axon is constructed for the aim. Investigation consists of two steps. In the first step, the effect of stimulus frequency on the spike activity is analysed for several different magnitudes. In the second step, magnitude of membrane potential oscillations is taken into consideration. Therefore a fast sodium ionic channel that causes spike activity is blocked, and peak depolarization to stimulus frequency is calculated for the magnitudes. Results show that sinusoidal stimulus with a higher frequency results in the potential oscillations with a smaller magnitude.

REFERENCES

1. J. M. Bower, D. Beeman, The Book of Genesis, Springer, Berlin, pp. 29-34, 1995.
2. A. L. Hodgkin, A. F. Huxley, A Quantitative Description of Membrane Current and its Application to Conduction and Excitation in Nerve, Journal of Physiology (Lond.), Vol. 117, pp. 500-544, 1952.
3. E. De Schutter, Alternative Equations for the Molluscan Ion Currents Described by Connor and Stevens, Brain Research, Vol. 382, pp. 134-138, 1986.
4. O. Belluzzi, O. Sacchi, A Five-Conductance Model of the Action Potential in the Rat Sympathetic Neurone, Prog. Biophys. Molec. Biol., Vol. 55, pp. 1-30, 1991.
5. E. De Schutter , J. M. Bower, An Active Membrane Model of the Cerebellar Purkinje cell: I. Simulation of Current Clamps in Slice ., J. Neurophysiol., Vol. 71, pp. 375-400, 1994.
6. G. L. Yuen, P. E. Hockberger, J. C. Houk, Bistability in Cerebellar Purkinje Cell Dendrites Modelled with High-Threshold Calcium and Delayed-Rectifier Potassium Channels, Biol. Cybern., Vol. 73, pp. 375-388, 1995.
7. O. Sacchi, O. Belluzzi, R. Canella, R. Fesce, A Model of Signal Processing at a Mammalian Sympathetic Neurone, Journal of Neuroscience Methods, Vol. 80, pp. 171-180, 1998.
8. A. M. Brown, A Methodology for Simulating Biological Systems Using Microsoft Excel, Computer Methods and Biomedicine, Vol. 58, pp. 181-190, 1999.
9. A. M. Brown, Simulation of Axonal Excitability Using a Spreadsheet Template Created in Microsoft Excel, Computer Methods and Biomedicine, Vol. 63, pp. 47-54, 2000.
10. D. J. Aidley, P. R. Stanfield, Ion Channels, Cambridge University Press, pp. 161-222, 1996.
11. E. De Schutter, Computer Software for Developments and Simulation of Compartmental Models of Neurons, Comput. Biol. Med., Vol. 19, No. 2, pp. 71-81, 1989.