Chapter - III

Hodgkin - Huxley Equations - Numerical Simulation
In this chapter, simulation of Hodgkin-Huxley (H-H) equations is presented. Squid axon data is adopted and the effects of step, sine and triangular current stimuli are studied. Functional dependency of activation variables on voltage is computed and plotted.

3.1 MATHEMATICAL AND NUMERICAL SOLUTION METHODS

Solution methods may be categorised in general as analytic or numerical. An analytic solution is one that can be expressed in terms of known functions. Usually such closed-form solutions can be found only for simple geometries and fairly simple models. However, they are useful for studying trends and exhibiting the influence of various parameters. They should always be attempted and studied because they may give valuable insight[1].

Numerical solutions are generally obtained by discretizing the governing equations, as in finite difference or finite element methods of approximating partial differential equations. These numerical methods allow treatment of complex geometries as well as variable, nonlinear material properties and nonlinear governing equations.

The capacity of modern computers is such that realistic complex problems can be solved numerically which can't be approached by analytic methods effectively. Moreover, the technology of numerical methods and computer capabilities is advancing so rapidly that such modeling is a speciality of its own.
3.2 MEMBRANES AND MEMBRANE POTENTIALS

3.21 What Membranes Are

A membrane is a non-covalent assembly of lipid and protein. Often these major components also have carbohydrate residues attached to them. It is arranged as bilayered sheet, with each layer being termed a "leaflet". Because interactions among components are non-covalent, each leaflet is fluid in that individual molecules are free to move within the place of the leaflet. A membrane also is asymmetric in that one leaflet is different from the other, and many directional functions are carried out by the membrane[2].

3.22 What Membranes Do

✦ Permeability barrier

A membrane forms the boundary between a cell and its environment, and also forms compartments within a cell. But a membrane is highly selective in what it allows to pass through it. Some molecules cross a membrane easily; others hardly at all, or only with the aid of a transport mechanism. The presence of transport mechanisms enables a membrane to selectively regulate what ions and molecules may pass through it.

✦ Create and maintain gradients

Membranes not only regulate what may diffuse through, but also contain energy-dependent devices for creation of specific gradients, and for maintenance of different concentrations of a substance on each side.
Regulate flow of information

A membrane can have receptors on one side which are specific for a particular informational entity such as a hormone. Binding of the hormone leads to transmission of a signal across the membrane, with diverse physiological effects.

Convert energy

A membrane often has structural elements which convert one form of chemical energy to another. Examples: Use of ATP energy to produce a gradient (as in active transport); use of a gradient to generate ATP (as in oxidative phosphorylation).

3.3 HODGKIN - HUXLEY (H-H) EQUATIONS

3.31 Assumptions

Six assumptions were made in the derivation of the H - H equations [4].

* The ionic current is carried entirely by the ions moving down their respective electrochemical gradients. This assumption required either that the Na⁺ - K⁺ pump should be electrically neutral or that the current which it generates should be negligibly small.

* Na⁺ and K⁺ ions flow through separate channels in the membrane and there is no direct interaction between them. The flow through any channel is expressed as the product of the ionic conductance of the channel and the electrochemical force driving ions through the channel.

* Each kind of channel can be in one of two states, open or closed. Only in open state ions can pass through the channel.
* Each channel is controlled by one or more independent gates. The gates consist of charged groups of the proteins or phospholipids which open or close, depending on the electric field.

* The condition for a channel to be in the closed state is that at least one of the gates is closed. The condition for a channel to be open is that all of the gates are open.

* Each gate obeys a first order reaction with voltage-dependent rate coefficient. This reaction is a change in the orientation of the charged group.

### 3.32 H - H Equations

The H-H model consists of

- four first order differential equations describing the state variable equations (3.1.1 - 3.1.4)

- five identities defining causal relationships among these state variable equations (3.1.a - 3.1.e)

- six expressions relating the parameters of the model to the membrane potential (3.1.i - 3.1.vi)

The relationship between the membrane potential and the membrane capacitance is given by

\[
\frac{dV_m}{dt} = \frac{1}{C_m} (I_L + I_K + I_{Na}) 
\]

\...(3.1.1)
The three currents are given by the following identities.

\[ I_L = G_L (V_c - V_m) \]  \hspace{1cm} ...(3.1.a)

\[ I_K = G_K (V_K - V_m) \]  \hspace{1cm} ...(3.1.b)

\[ I_{Na} = G_{Na} (V_{Na} - V_m) \]  \hspace{1cm} ...(3.1.c)

Where

\[ I_L \] : Leakage current due to all ions other than potassium and sodium.

\[ G_L \] : Equivalent conductance of the membrane to these ions

\[ I_K, I_{Na} \] : Potassium and sodium ionic currents

\[ G_K, G_{Na} \] : Equivalent transmembrane conductances to Na\(^+\) and K\(^+\) ions

Hodgkin - Huxley estimated that \(C_m\) and \(G_L\) are each essentially constant. Explicit mathematical expressions are needed to describe the two other parameters \(G_K\) and \(G_{Na}\).

The time and voltage dependencies of the potassium are described by making \(G_K\) directly proportional to the fourth order of a newly defined state variable \(n\) which obeys a first order differential equation with time as independent variable.

\[ G_K = I_K n^4 \]  \hspace{1cm} ...(3.1.d)

where \(I_K\) is a constant and

\[ \frac{dn}{dt} = \alpha_n (1-n) - \beta_n \]  \hspace{1cm} ...(3.1.2)
Similarly, the time and voltage dependencies of the sodium conductance are described by

\[ G_{Na} = g_{Na} m^3 h \]  

(3.1.e)

where \( I_{Na} \) is constant and

\[ \frac{dm}{dt} = \alpha_m (1-m) - \beta_m m \]  

...(3.1.3)

\[ \frac{dh}{dt} = \alpha_h (1-h) - \beta_h h \]  

...(3.1.4)

The following set of six equations describe the voltage dependencies of the rate constants (\( \alpha \)'s and \( \beta \)'s) as determined by the data:

\[ \alpha_n = \frac{0.01(10-V)}{\{\exp(10-V/10) - 1 \}} \]  

...(3.1.i)

\[ \beta_n = 0.125 \exp (-V/80) \]  

...(3.1.ii)

\[ \alpha_m = 0.1 (25-V) \]  

...(3.1.iii)

\[ \beta_m = 4.0 \exp (V/18) \]  

...(3.1.iv)

\[ \alpha_h = 0.07 \exp (-V/20) \]  

...(3.1.v)

\[ \beta_h = \frac{1}{\{\exp(30-V)/10 + 1 \}} \]  

...(3.1.vi)
Where the units are in m/sec. Equations (i) to (vi) give the rate constants measured at a temperature of 6.3°C. For other temperatures they should be multiplied by the factor $\phi$ where

$$\phi = \exp \left( \frac{T - 6.3}{10} \right)$$ ...

### 3.33 Activation Variables

Hodgkin and Huxley described the change in activation variables such as $m$ in terms of rate constants $\alpha$ for opening and $\beta$ for closing a gate. The fraction of open gates follow a first order equation:

$$\frac{dm}{dt} = \alpha - (\alpha + \beta)m$$ ...

Rearranging and Integrating yields

$$m = m_\infty - (m_\infty - m_0) e^{-\frac{\alpha m}{\tau_m}}$$ ...

Where

$m_0$ is the value of $m$ at $t = 0$

$$m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m}, \text{ is the steady-state value of } m$$

$$\tau_m = \frac{1}{\alpha_m + \beta_m}, \text{ is the time constant with which } m \text{ approaches the steady-state value.}$$
Similarly,

\[ n = n_0 - (n_w - n_0) e^{-t/m} \]  
\[ h = h_w - (h_w - h_0) e^{-t/m} \]

...(3.5) \hspace{1cm} ...(3.6)

Where

\[ n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n} ; \quad \tau_n = \frac{1}{\alpha_n + \beta_n} \]

\[ h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h} ; \quad \tau_h = \frac{1}{\alpha_h + \beta_h} \]

...(3.7)

3.4 SOFTWARE SIMULATION

3.41 Squid Axon Data

To study in detail the bioelectric processes that occur during activity in a single nerve fiber, it is necessary to isolate a single axon, and to insert the tip of a microelectrode into that axon so the effect of stimulating and other experimental procedures can be analyzed. Typically, single mammalian nerve fibers are quite small (less than 30 \( \mu \)m) and many of these elements are bound tightly into compact bundles (nerve trunks) by connective tissue.

The largest axons are found in the mantle of the squid (Loligo). Axons isolated from these marine molusks range up to 1000 \( \mu \)m in diameter. Thus, they provide an ideal biologic model system for study of the bioelectric properties of nerve cells. There are no major differences between the bioelectric phenomena observed in
the squid axon and those in mammalian nerve fibers. Hence, the squid axon data is adopted [4] for simulation (refer table 2.1):

\[
\begin{align*}
G_k &= 36 \text{ mmho/cm}^2 \\
V_k &= -77 \text{ mV} \\
G_{Na} &= 120 \text{ mmho/cm}^2 \\
V_{Na} &= 50 \text{ mV} \\
G_L &= 0.3 \text{ mmho/cm}^2 \\
V_L &= 54.4 \text{ mV}
\end{align*}
\]

The initial values are taken as

\[
V_{\text{rest}} = -65 \text{ mV}; \quad C_{\text{memb}} = 1\mu F/\text{cm}^2; \quad t_{\text{max}} = 5\text{ms}; \quad t_{\text{step}} = 0.1\text{ms}; \quad \delta t = 1\mu\text{s}.
\]

3.42 Functional Dependency of Activation Variables

Functional dependency of phenomenological or activation variables is computed in the following way:

* Equations 3.3 to 3.7 are used
* Using initial values, rate constants (\(\alpha\)'s and \(\beta\)'s) are calculated
* Values of activation variables are determined
* Voltage is incremented in steps of 10 mV and at each point the above values are computed.
* Voltage is varied in the range -100 mV to +100 mV and the values are computed

3.43 Response of Axon to Constant Current Stimulation

* Squid axon data is adopted
* Current stimuli of step, sine and triangular waveforms of 0.1 mA amplitude are applied for a duration of 2.5ms and the response is computed
* Current is applied from 0.5 ms to 3 ms in steps of 1 \(\mu\)s
3.5 RESULTS AND OBSERVATIONS

Functional Dependency of Activation Variables

- The functional dependency curves of $m$ and $\tau_m$, $n$ and $\tau_n$, $h$ and $\tau_h$ are presented in Fig. 3.1(a), 3.1(b) and 3.1(c) respectively.

- With increasing voltage, $m$ and $n$ reach a steady-state value which is high and $h$ attains a value which is low.

- At different voltages, the time constants $\tau_m$, $\tau_n$ and $\tau_h$ attain peak values.

- Peak value of $\tau_h$ is higher than the other two time constants.

Response of Axon to Constant Current Stimulation

In this section, using H - H equations, the effects of step, sinusoidal (50Hz, 400Hz, 1000Hz) and triangular (50Hz, 400Hz, 1000Hz) stimuli are studied.

** Variation of Voltage **

- The Voltage response curves are plotted in Fig. 3.2.

- In case of voltage response, step, sine and triangular stimuli are applied for a duration of 2.5 ms.

- For step excitation, the voltage response reached a peak value of 44.79 mV in 0.7 ms after applying the stimulus.
Fig. 3.1(a) Functional dependency of $m$ and $\tau_m$ on voltage $V$. 

Voltage, $V$
Fig. 3.7(b) Functional dependency of $n$ and $\tau_n$ on voltage $V$
Fig. 3.1(c) Functional dependency of $h$ and $\tau_h$ on voltage $V$
(a) Response to step stimulus

(b) Response to sinusoidal stimulus

(c) Response to triangular stimulus

Fig. 3.2 Variation of voltage for step, sine (50 Hz, 400 Hz, 1000 Hz) and triangular (50 Hz, 400 Hz, 1000 Hz) stimuli
In case of sinusoidal excitation, the voltage response reached peak values 42.55 mV, 43.44 mV and 43.78 mV in 1.7 ms, 1.0 ms and 0.9 ms for 50Hz, 400Hz and 1000Hz frequencies respectively, after applying the stimulus.

In case of triangular excitation, the voltage response reached peak values of 40.94 mV, 44.09 mV and 41.9 mV in 2.5 ms, 1.3 ms and 1.0 ms for 50 Hz, 400 Hz and 1000 Hz frequencies respectively, after applying the stimulus.

Above results reveal that the step response has a higher peak value than the other two responses and it attains the peak value quickly.

The shape of voltage response curve, is nearly similar for the three stimuli.

It can be observed that the response is improved by increasing the frequency.

□ Variation of Current Components

- The response curves of current components for step, sine and triangular stimuli are presented in Fig. 3.3 (i, ii and iii).

- The response has same shape for the three types of stimuli but it will be delayed for sine and triangular stimuli at low frequencies.

- The membrane current is affected by step stimulus in 0.5ms after the application of the stimulus.

- For sine and triangular stimuli, the membrane current is affected after 1.1 ms after the application of the stimuli.

- The potassium and sodium currents are nearly similar for three types of stimuli.
Fig. 3. Variation of current components for step, sine (50 Hz) and triangular (50 Hz) stimuli.
(a) Response to sinusoidal stimulus

(b) Response to triangular stimulus

Fig S2(iii) Variation of current components at 400 Hz
Fig. 33(iii) Variation of current components at 1000 Hz
Variation of Conductances

- The response curves of conductances for step, sine and triangular stimuli are presented in Fig. 3.4 (i, ii and iii).

- For step excitation, the sodium conductance reached its peak value linearly with time and it decreased exponentially to initial value.

- Similar response is observed for sinusoidal and triangular stimuli, but it is delayed at low frequencies.

- The potassium conductance gets affected delayed than sodium conductance because the voltage is not constant.

50 Hz stimulus contributes to a reduction in excitability since it will not reach peak magnitude within the period that the stimulation is applied.
(a) Response to step stimulus

(b) Response to sinusoidal stimulus

(c) Response to triangular stimulus

Fig. 3. Variation of conductances for step, sine (50Hz) and triangular (50 Hz) stimulus
(a) Response to sinusoidal stimulus

(b) Response to triangular stimulus

Fig. 3.4(ii) Variation of conductances at 400 Hz
(a) Response to sinusoidal stimulus

(b) Response to triangular stimulus

Fig. 3.4(iii) Variation of conductances at 1000Hz.
REFERENCES


