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Research Article

INTERACTION OF LIPIDS AND PROTEINS OF NEURONAL MEMBRANES VIA A MATHEMATICAL MODEL

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Abstract: Biological systems are inherently complex. This paper tries to find a model that simulates various actions and reactions resulting from the permeability of the neural cell membrane by ions through channel proteins. The problem here focuses on multiple channel protein concentration and cell dynamics inside and outside of the membrane. For simplicity we assume only two channel proteins; sodium and potassium and study the interaction effects due to them. Cell dynamics emphasizes on finding how ions actually move across the membranes of excitable cells. A mathematical model measuring the boundary voltage due to the rapid movement of ions inside and outside (the action potential) is discussed. We attempt to solve a partial differential equation derived and then investigate the convergence of its solution.

Keywords: Hodgkin Huxley Model, Voltage Clamped Protocol, Hodgkin-Huxley Sodium and Potassium model, Lipid membranes, Protein models

Introduction

There are specialized cells in most living creatures called neurons which are specific to generate signals, to transmit sensory data and to exert control of movement and cognition through mechanisms we don't fully understand. A neuron is an example of what is called an excitable cell which is a membrane full of many voltage gated sodium and potassium channels (*Segel et al., 2013*).

Qualitative and quantitative description of the mechanism's effect involved in transmission of the sensory data by nerves has been elucidated very early in a paper on mathematical model written by Hodgkin and Huxley (*Hodgkin et al. 1952*), inspired by the electronic aspect of the propagating impulse along the axon of the nerve cell, discovered by L. Galvani and Volta in 1894 and in 1900 respectively. Since, it has assumed that the propagation of the action potential through the neuron was a consequence of the circulation of ions through cell membranes (*Hodgkin, et al., 1949*). A set of differential equations has magnified thoroughly the impact of the ion channels in change of the conductance of the membrane, causing a sudden increase in voltage across the membrane.

It is reported that the membrane of the neural cell is composed of two kinds of molecules: Lipids and proteins. The membrane has a structure of a tiny layer of lipids folded, inside of which proteins are embedded. This membrane is responsible of the selective permeability and transport of Na^+, K^+, Cl^- and Ca^{2+} ions through the membrane from outside or inside the neural cell (*Kandel, et al., 2000*). An important number of proteins in the

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membrane are also called ion channels because they are in charge of the transport of ions.

The channel proteins disseminated in the outer cell membrane have a likely structure of pores through which flow sodium ions inward and potassium ions outward. There are many ions current taking place in a neural cell. However, Hodgkin – Huxley model highlights three kinds of currents of ions responsible of the dynamics effect of the neuronal cells these are sodium current, potassium current and leak current. The last one is due to the effect of other ions among which abound Cl^- ions (*Appali et al., 2014*).

Initially, we assume, under certain circumstances, the rest potential across the membrane can be stimulated to cause a rapid rise in equilibrium potential of the cell, followed by a sudden drop below the equilibrium voltage and then terminated by a slow increase back up to rest potential (*Noble, et al., 2012*). The response curve thus generated is called an action potential and it is a fundamental characteristic of excitable cells.

Speaking of which, the true cause of the action potential in neuron is closely connected to the opening and closing of the ion channel proteins (or gates). The action potential starts when the sodium channels open and switch on a high inward flow of sodium into cell (*Keynes, et al., 2001*); this raises a depolarization of the membrane which on the turn increases the action potential up to its peak. Later on, the potassium channels also open and allow the potassium ions to flow outside of the cell (*Hill, 1992*). This current of potassium ions decreases the depolarization of the cell which results in the decrease of the action potential below the normal resting potential. The process ends when sodium and potassium channels remained closed.

The Underlying dynamics

Our focus is on dynamic processes – nice little phrase to describe the constant movement of ions inside and outside of the membrane. We represent dynamics processes as equations of chemical kinetics and diffusion, membrane as electric circuits and molecule as charges, dipoles and dielectrics. We introduce a voltage clamp to measure the action potential locally across the membrane. As the title suggests the impetus is primarily on the modeling of the excitation effects across the cell! The standard Hodgkin-Huxley model of an excitatory neuron consists of the total membrane current which can be obtained from Ohm's law. It is convenient to measure the membrane voltage, potassium current, sodium current and the leakage current carried by other ions moving passively through the membrane. The equation is derived by modeling the potassium, sodium and leakage currents using a simple electrical circuit model of the membrane. Assume a gate in the membrane as having an intrinsic resistance and the cell membrane itself as having an intrinsic capacitance. The driving electromotive force (EMF) is the difference between the ion equilibrium potential and the voltage across the membrane itself. The next step is to measure the voltage across the space. The voltage is assumed to be both time and space dependent. In the assumed model, the membrane is considered as a parallel circuit with four main branches of current: sodium, potassium, membrane capacitance and leakage current. We endeavor to link the inside current with the outside current through our model. We run a set of simulation experiments describing behavioral patterns in sodium and potassium conductances against time. A general inference about the cell behavior under the assumptions of our model is then deduced. The model is built around the following standard set up of cable model:

1. The cell membrane is a cylindrical boundary separating two conductors of current called the intracellular and extracellular solutions. We assume these solutions are homogeneous and obey Ohm's law;
2. All electrical variables have cylindrical symmetry which means they are independent of the position variable;
3. A circuit theory description of currents and voltages would suffice;
4. Inner and outer currents are axial or longitudinal only and membrane currents are radial;
5. At any position along the cylinder the inner and outer conductors are equi-

potential. Hence, radial potential in the outer and inner are constant.

The important parameters are the rest value of the membrane potential, rest value of the membrane current per length density, rest value of the inner current, rest value of the outer current, rest value of the inner voltage, rest value of the outer voltage, resistance of the inner fluid of the cable, resistance of the outer fluid surrounding the cable, membrane conductance per unit length and membrane capacitance per unit length.

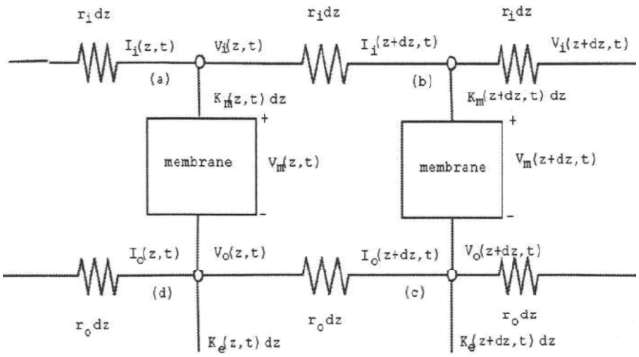

Figure 1: **Equivalent electrical network**

Derivation of the Model

The Basic Hodgkin – Huxley model

The standard Hodgkin-Huxley model of an excitatory neuron satisfies the following partial differential Equation:

$$\frac{\partial^2 V_m}{\partial z^2} = \left(r_i + r_0\right) K_m - r_0 K_e \qquad (1)$$

Where

- V_m^0 is the rest value of the membrane potential;
- K_m^o is the rest value of the membrane current per length density;
- K_e^o is the rest value of the externally applied current per length density;
- r_i is the resistance of the inner fluid of the cable;
- r_o is the resistance of the outer fluid surrounding the cable.

We will create a parallel circuit analog of the above block diagram where the box is a chunk of membrane of width Δz. According to our standard cable model assumptions the membrane has a constant resistance and capacitance. So, in the circuit model, one branch contains a capacitor and the other, the conductance element. Let c_m denote the membrane capacitance density per unit length measured in farad/cm. The value of capacitance should be $c_m \Delta z$ since the box is Δz wide. Similarly, we let g_m be the conductance per unit length measured in $\frac{1}{Ohm \times cm}$ for the membrane. The value of conductance for the box element is thus $g_m \Delta z$.

Figure 2 describes the new membrane model. This is a resistance – capacitance parallel circuit and it is called an RC membrane model.

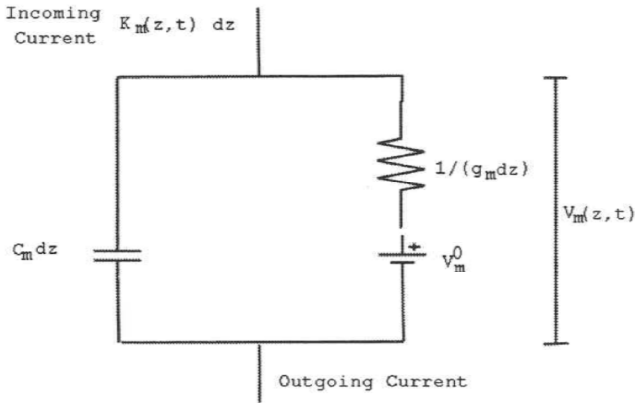

Figure 2: **The RC membrane model**

In Figure 2, the incoming current is $K_m(z,t)\Delta z$ and the rest voltage for the membrane as a battery of value V_m^o. The membrane current, K_m, satisfies Equation (2).

$$K_m(z,t) = g_m V_m(z,t) + c_m \frac{\partial V_m}{\partial t} \qquad (2)$$

If we interpret the equation in terms of membrane current densities, it looks like

$$K_m = K_c + K_{ion} \qquad (3)$$

Where K_m is the membrane current density, K_c is the current through the capacitance element and K_{ion} is the current flowing through the side of the circuit that is modeled by the conductance term, g_m. This model satisfies the following equations:

$$K_c = c_m \frac{\partial V_m}{\partial t} \tag{4}$$

$$K_{ion} = g_m V_m \tag{5}$$

However, there are practical difficulties in implementing this model and coming up with subsequent inferences. It is imperative to know the relationship between different membrane activities and the membrane voltage by adding models of ion flow controlled by gates in the membranes. We are going to study the diffusion processes inside the cell that contribute to ion flow across the membrane. Our work will be based on the Hodgkin and Huxley model. Initially, the membrane model focuses on potassium, sodium and leakage current. The leakage current is thought of as an all purpose current. The gate in the membrane is modeled to have an intrinsic resistance and the cell membrane to have an intrinsic capacitance as shown in Fig. 3.

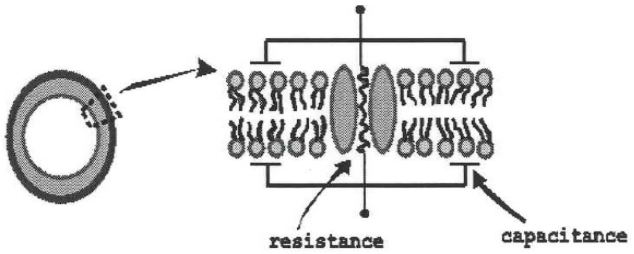

Figure 3: **Membrane and gate circuit model**

Thus, our new model consists of multiple branches – one for each ion flow. There are potassium, K_k current, sodium, K_{Na} current and leakage K_L current. The leakage current takes care of all other sources of ion flow across the membrane and which are not explained by the model. For example, ion pumps; gates for other ions such as Calcium, Chlorine etc are captured by this definition of leakage current. The leakage current is assumed to nullify any excitable neural activity at equilibrium. Here we show an idealized cell with a small portion of the membrane blown up into an idealized circuit. We see a small piece of the lipid membrane with an inserted gate. We think of the gate as having some intrinsic resistance and capacitance. Now for our simple Hodgkin-Huxley model here, we want to model a sodium and potassium gate as the cell capacitance. So we will have a resistance for both the sodium and potassium. In addition, we know that other ions move across membrane due to pumps, other gates and so forth. We will temporarily model this additional ion current as a leakage current with its own resistance. In the standard Hodgkin-Huxley model of an excitatory neuron the new equation for the total membrane current is K_M and it is obtained from Ohm's law:

$$K_m = c_m \frac{\partial V_m}{\partial t} + K_K + K_{Na} + K_L \tag{6}$$

The new equation for the membrane voltage is now

$$\frac{\partial^2 V_m}{\partial z^2} = \left(r_i + r_o\right) K_m - r_o K_e$$

This can be simplified in the form of the following Equation:

$$\frac{\partial^2 V_m}{\partial z^2} = \left(r_i + r_0\right)\frac{\partial V}{\partial t} + \left(r_i + r_0\right) K_K + \left(r_i + r_0\right) K_{Na} + \left(r_i + r_0\right) K_L - r_0 K_e$$

$$\frac{1}{r_i + r_o}\frac{\partial^2 V_m}{\partial z^2} = K_m - \frac{r_o}{r_i + r_o} K_e \tag{7}$$

$$\frac{1}{r_i + r_o}\frac{\partial^2 V_m}{\partial z^2} = c_m \frac{\partial V_m}{\partial t} + K_K + K_{Na} + K_L - \frac{r_o}{r_i + r_o} K_e \tag{8}$$

The voltage clamped protocol

Under certain experimental conditions, we can think of the membrane voltage to be independent of space. That is

$$\frac{\partial^2 V_m}{\partial z^2} = 0$$

Equation (8) assumes to the form as follows:

$$c_m \frac{dV_m}{dt} + K_K + K_{Na} + K_L - \frac{r_o}{r_i + r_o} K_e = 0 \tag{9}$$

Since, in the voltage clamped protocol the membrane voltage is assumed to depend only on time variable t, partial derivatives are replaced with a normal derivative. The above equation can also be interpreted in terms of capacitance, c_m, and currents, I_K, I_{Na}, I_L and an external type current I_e (since c_m is capacitance par unit length). So, the

new equation, in terms of capacitance and sodium, potassium and leakage currents should be written as follows:

$$c_m \frac{dV_m}{dt} + I_K + I_{Na} + I_L - \frac{r_o}{r_i + r_o} I_e = 0 \qquad (10)$$

Finally, if we label as external current, I_E, the term

$$I_E = \frac{r_o}{r_i + r_o} I_e ,$$

The equation to be solved under the voltage clamped protocol becomes is:

$$\frac{dV_m}{dt} = \frac{1}{c_m}\left(I_K + I_{Na} + I_L - I_E\right) \qquad (11)$$

The Hodgkin – Huxley gate model

In our idealized circuit model, the driving electromotive force or **driving emf** is the difference between the ion equilibrium potential and the voltage across the membrane itself. The equilibrium potential of each ion is computed by using Nernst equation. Let E_c be the equilibrium potential due to ion c and V_m be the membrane potential. The driving force is $V_c - V_m$.

Figure 4 summarizes the above proposition. The parallel circuit model with a branch for the sodium and potassium ion, a branch for the leakage current and a branch for the membrane capacitance describes the idea.

The charge q across a capacitor is $q = CE$, where C is the capacitance and E is the voltage across the capacitor. Hence, if the capacitance C is a constant, the current flowing through the capacitor is given by the rate of change of the charge with the time.

$$\frac{dq}{dt} = C\frac{dE}{dt}$$

If the voltage E was also space dependent, then the normal derivative becomes a partial derivative as E is now a function of both time and space variables. The capacitive current would be

$$\frac{dq}{dt} = C\frac{\partial E}{\partial t}$$

Ohm's law tell us that voltage is current times resistance; hence for each ion c,

$$V_c = I_c R_c$$

where we label the voltage, current and resistance due to this ion with the subscript c. This means

$$I_c = \frac{1}{R_c} V_c$$

$$I_c = G_c V_c$$

Where the leakage battery voltage, G_c is the conductance of ion c. This is a general scheme of modeling all the ionic currents using a conductance equation of the form above. The potassium and sodium conductance's are nonlinear functions of the membrane voltage V and time t. This implies that the amount of current that flows through the membrane for these ions is dependent on the voltage differential across the membrane which is also time dependent. The general functional form for an ion c can thus be written as

$$I_c = G_c(V,t)\left(V(t) - E_c(t)\right) \qquad (12)$$

The force driving, $V - E_c$, is the difference between the voltage across the membrane and the equilibrium value for the specific ion, E_c. The ion battery voltage E_c itself might also change in time. Hence, the driving force can also be time dependent. The conductance is modeled as the product of an activation m, and an inactivation h, variable that are nonlinear. The activation and inactivation are functions of V and t also. The conductance functional now looks like

$$G_c(V,t) = G_0 m^p(V,t) h^p(V,t) \qquad (13)$$

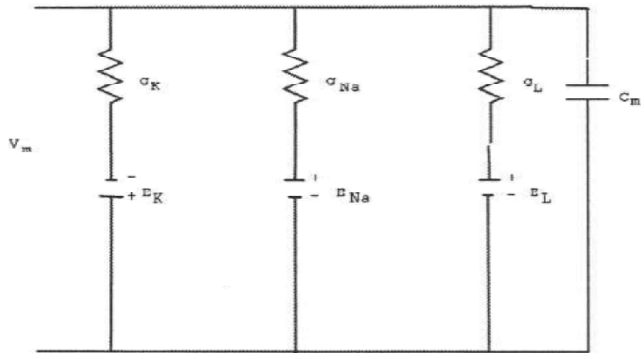

Figure 4: **The simple Hodgkin – Huxley membrane circuit model**

where suitable values of p and q are found to match known data for a given ion conductance. The leakage current, I_L, is expressed as,

$$I_L = g_L\left(V(t) - E_L\right) \tag{14}$$

Where the leakage battery voltage, E_L, and the conductance g_L are constants specific to data. Let g_K, g_{Na} and g_L respectively denote the potassium, sodium and leakage ion conductance's per length.

$$I_K = g_K\left(V - E_K\right) \tag{15}$$

$$I_{Na} = g_{Na}\left(V - E_{Na}\right) \tag{16}$$

$$I_L = g_L\left(V - E_L\right) \tag{17}$$

Rewriting the membrane voltage equation, we obtain:

$$\frac{1}{r_i + r_o}\frac{\partial^2 V_m}{\partial z^2} = c_m\frac{\partial V_m}{\partial t} + g_K\left(V_m - E_K\right) + g_{Na}\left(V_m - E_{Na}\right) + g_L\left(V_m - E_L\right) - \frac{r_o}{r_i + r_o}K_e \tag{18}$$

Activation and inactivation variables

The voltage dependence of the activation and inactivation variables has been fitted from data.

$$\frac{dx(V)}{dt} = \alpha_x(V)(1 - x(V)) - \beta_x(V)x(V) \tag{19}$$

$$x(V,0) = x_o(V) \tag{20}$$

Rewriting:

$$\frac{dx}{dt} = \alpha_x(1 - x) - \beta_x x \qquad x(0) = x_o \tag{21}$$

Equivalently,

$$\frac{1}{\alpha_x + \beta_x}\frac{dx}{dt} = \frac{\alpha_x}{\alpha_x + \beta_x} - x \qquad x(0) = x_o \tag{22}$$

Letting

$$\tau_x = \frac{1}{\alpha_x + \beta_x} \tag{23}$$

$$x_\infty = \frac{\alpha_x}{\alpha_x + \beta_x} \tag{24}$$

The rate equation becomes a first order ordinary differential equation:

$$\tau_x\frac{dx}{dt} = x_\infty - x \qquad x(0) = x_o \tag{25}$$

The solution is:

$$x(t) = (x_o - x_\infty)e^{\frac{-t}{\tau_x}} + x_\infty \tag{26}$$

The Hodgkin – Huxley sodium and potassium model

According to Hodgkin and Huxley the sodium and potassium gates can be modeled as

$$g_{Na}(V,t) = g_o^{Na}m^3(V,t)h(V,t) \tag{27}$$

$$g_K(V,t) = g_o^K n^4(V,t) \tag{28}$$

where the activation variables, m and n, and the inactivation variable satisfy first order kinetics as discussed. Hence, if the parameters τ_m and m_∞ and so forth were constants,

$$m(t) = (m_o - m_\infty)e^{\frac{-t}{\tau_m}} + m_\infty \tag{29}$$

$$h(t) = (h_o - h_\infty)e^{\frac{-t}{\tau_m}} + h \tag{30}$$

$$n(t) = (n_o - n_\infty)e^{\frac{-t}{\tau_m}} + n_\infty \tag{31}$$

with parameters defined as:

$$\tau_m = \frac{1}{\alpha_m + \beta_m} \tag{32}$$

$$m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m} \tag{33}$$

$$\tau_h = \frac{1}{\alpha_h + \beta_h} \tag{34}$$

$$h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h} \tag{35}$$

$$\tau_n = \frac{1}{\alpha_n + \beta_n} \tag{36}$$

$$n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n} \tag{37}$$

However, every coefficient α and β is a function of voltage. These were determined from data fits as:

$$\alpha_m = -0.10 \frac{V + 35.0}{e^{-0.1(V+35.0)} - 1.0} \tag{38}$$

$$\beta_m = 4.0 e^{\frac{-(V+60.0)}{18.0}} \tag{39}$$

$$\alpha_h = 0.07\, e^{-0.5(V+60.0)} \tag{40}$$

$$\beta_h = \frac{1.0}{\left(1.0 + e^{-0.1(V+30.0)}\right)} \tag{41}$$

$$\alpha_n = -0.01 \frac{V + 50.0}{e^{-0.1(V+50.0)} - 1.0} \tag{42}$$

$$\beta_n = 0.125\, e^{-0.0125(V+60.0)} \tag{43}$$

These data fits were obtained at a certain temperature and all the other constants need to have assumed values as well. Those are given in the units below:

Voltage	mV	milli volts	10^{-3} Volts
Current	na	nano amps	10^{-9} Amps
Time	ms	milli second	10^{-3} Seconds
Concentration	mM	milli moles	10^{-3} moles
Conductance	μS	micro Siemens	10^{-6} ohms^{-1}
Capacitance	nF	nano Farads	10^{-9} Farades

The approximate model assumes the differential form:

$$\tau_m \frac{dm}{dt} = m_\infty - m \tag{44}$$

$$\tau_h \frac{dh}{dt} = h_\infty - h \tag{45}$$

$$\tau_n \frac{dn}{dt} = n_\infty - n \tag{46}$$

$$\frac{dV}{dt} = \frac{I_M - I_K - I_{Na} - I_L}{c_M} \tag{47}$$

with initial conditions:

$$\begin{aligned} m(0) &= m_\infty(V_0, 0) \\ h(0) &= h_\infty(V_0, 0) \\ n(0) &= n_\infty(V_0, 0) \\ V(0) &= V_0 \end{aligned} \tag{48}$$

At equilibrium, there is no current across the membrane. Hence, the sodium and potassium currents are zero and the activation and inactivation variables are at their steady state values which would be m_∞, h_∞ and n_∞ computed at the equilibrium membrane potential which is denoted by V_0.

The Hodgkin – Huxley model solution under the voltage clamp protocol

The solution to the equation 11,

$$\frac{dV_m}{dt} = \frac{1}{c_m}\left(I_K + I_{Na} + I_L - I_E\right)$$

Using the equations 15, 16 and 17 yield:

$$\begin{aligned} \frac{dV_m}{dt} = \frac{1}{c_m}[&g_{Na}(V,t)(V_m - E_K) + g_K(V,t)(V_m - E_{Na}) \\ &+ g_L(V,t)(V_m - E_L) - I_E] \end{aligned}$$

And by using equations (27) and (28) the above reduces to

$$\begin{aligned} \frac{dV_m}{dt} = &g_0^{Na} m^3(V,t) h(V,t) + g_0^K n^4(V,t) \\ &+ g_L(V_m - E_L) - I_E \end{aligned} \tag{49}$$

Which has to be solved under the specification of activation / inactivation variables as it is the way by which the cell dynamics is encoded.

We assume a solution to the model in a four dimensional vector form y depending on four independent variables V, m, h and n written as:

$$y = \begin{bmatrix} y[0] = V \\ y[1] = m \\ y[2] = h \\ y[3] = n \end{bmatrix} \tag{50}$$

The form which allows expressing the model in form of a system of ordinary differential equations of the form:

$$\frac{dy}{dt} = f(t, y)$$
$$y(0) = y_0 \quad (51)$$

Where f is the Hodgkin - Huxley dynamics force depending on the time t and y defined by equation (50). For this reason, f is expressed in components as follows:

$$f(t, y) = \begin{bmatrix} f[0] = \frac{I_M - I_T}{c_M} \\ f[1] = \frac{m_\infty - m}{\tau_m} \\ f[2] = \frac{h_\infty - h}{\tau_h} \\ f[3] = \frac{n_\infty - n}{\tau_n} \end{bmatrix}$$

with I_M an the external current to apply to the system.

Introducing the components of the vector y as it is given by the equation (50), we obtain:

$$f(t, y) = \begin{bmatrix} f[0] = \frac{I_M - I_T}{c_M} \\ f[1] = \frac{m_\infty - y[1]}{\tau_m} \\ f[2] = \frac{h_\infty - y[2]}{\tau_h} \\ f[3] = \frac{n_\infty - y[3]}{\tau_n} \end{bmatrix} \quad (51)$$

A scheme to solve the dynamics

The sequential multistep algorithm comprises the following parts:

1) Computation the activation and inactivation variable.

Given the time t and the voltage V, different values of the activation and inactivation variables $\alpha_m, \beta_m, \alpha_h, \beta_h, \alpha_n$ and β_n are computed using the equations (38) up to (43).

2) *Computation of the steady state activation and inactivation variables.*

The steady state values of the activation and inactivation variables are based on the equations (32) to (37)

3) *Computation of the sodium and potassium potentials*

These potentials are evaluated by using Nernst's equation and the standard concentrations are temperature dependent. At 6.3 degrees Celsius they are approximately:

$$[Na]_0 = 491.0$$
$$[Na]_i = 50.0$$
$$[K]_0 = 20.11$$
$$[K]_i = 400.0$$

4) *Computation of the sodium and potassium conductances.*

These values are obtained from the equations (27) and (28), the model assume the values g_0^{Na} and g_0^K not time dependent and given by:

$$g_0^{Na} = 120.0$$
$$g_0^K = 36.0$$

5) *Computation of the ionic currents*

The computations are performed using the equations (15), (16) and (17) with data on g_L and E_L are given by: g_L = 0.3 and E_L = –49.0

6) *Computation of the total current*

The total current I_T is obtained from the equation

$$I_T = I_{Na} + I_K + I_L \quad (52)$$

7) *Computation of the dynamics of our system at time t and voltage V:*

$$\frac{dV}{dt} = \frac{I_M - I_T}{c_M} \quad (53)$$

$$\frac{dm}{dt} = \frac{m_\infty - m}{\tau_m} \quad (54)$$

$$\frac{dh}{dt} = \frac{h_\infty - h}{\tau_h} \quad (55)$$

$$\frac{dn}{dt} = \frac{n_\infty - n}{\tau_n} \tag{56}$$

where c_M = 1.0 and I_M being an external current supplied to the system.

Numerical solver for H-H excitable cell models

To guarantee the accuracy in the solution of the IVP of the system (51), we shall use a pair of explicit Runge – Kutta methods of fourth and fifth order, implemented by Fehlberge denoted RKF45. To apply this numerical method, the solution domain is subdivided into a collection of discrete points and by RKF45 an approximate solution in vector form y_n is generated. The process starts with the initial data y_0 at time t_0 = 0 and use an estimation formula to generate a new approximation solution y_i at time $t_i = ih, i = 1, 2, \ldots, n$ for a suitable step size h.

At each step i, two different approximate solutions are generated by RK4 and RK5 and then compared. The approximation is accepted as long as the difference between the two approximate solutions met some specified accuracy, otherwise the step size h is reduced. But, if the two approximate answers agree to more significant digits than required, the step size is increased. Numerical methods being based on approximation, it is very important to denote the following:

1. The usual way to approximate the function f is to use Taylor's series expansion of f around the iteration point at each iteration. This truncation gives rise to an error as expected. The error term can be large or small depending on how amny terms used in the expansion. If h_n denotes the difference between n+1th and n^{th} time step, then a fourth order method gives rise to an error of the form Ch^5 for some constant C. This means that taking a step size of magnitude $\frac{h_n}{2}$ will decrease the error by a factor of 2^5 = 32.
2. For a 5th order Runge-Kutta method, to have a local truncation error of order 5, it requires to carry 4 function evaluations; this error is purely local. This is why the global error can significantly grow as long as the computation is performed over a very large time step. So, the numerical solution to the ordinary differential equation can be 5th order accurate locally but still the issue of the global convergence remains to be solved.
3. Round – off error always occurs. It is for this reason exact precision can never be achieved on computer system.
4. The standard assumption about the model certainly does not match the exact biological phenomena because of the truncation and round-off errors.

Typical numerical algorithm opted for the solution to the mathematical model is of Runge-Kutta-fehlberg 45 (RKF45) characterized by the following specifications:

1. Four functions evaluations are required to perform the fourth order Runge-Kutta method which generates a local error proportional to h^5;
2. One more function evaluation is necessary to achieve the Runge-Kutta method of order 5. The local error generated by this method is obvious of order h^6.

Note that this algorithm uses six function evaluations per time step which really need considerable amount of memory. Any change in the step size h results in a return back to the computation of all solutions. Using this technique for the simulation of the model based on a complex biological system, hampers the computer efficiency.

Calculation of initial conditions

The initial conditions for the activation and inactivation variables for this model should be calculated carefully. When the excitable nerve cell is at equilibrium, with no external current applied, there is no net current flow across the membrane. At this point, the voltage across the membrane should be the applied voltage E_M. This is why I_T = 0

That yields the following equation:

$$I_{Na} + I_K + I_L = 0 \quad (57)$$

$$\bar{g}_{NA}\left(E_M - E_{NA}\right)\left(m^{\infty}\right)^3 h^{\infty} + \bar{g}_K\left(E_M - E_K\right)\left(n^{\infty}\right)^4 + \bar{g}_L\left(E_M - E_L\right) = 0 \quad (58)$$

The two parameters, g_L and E_L are used to compute the leakage ionic currents. Assuming that there is no external pumping of current and knowing there should be no activity at equilibrium in the absence of an external current. Finally, endeavor to solve to the leakage parameters in terms of the rest of the variables. Thus, $\bar{g}_L$ and E_K must be chosen for the solution to the leakage conductance.

Compute the Sodium equilibrium current:

$$I_{NA} = \bar{g}_{NA} * \left(y(1) - E_{NA}\right) * y(2) * y(2) * y(2) * y(3)$$

Compute the Potassium equilibrium current:

$$I_K = \bar{g}_K * \left(y(1) - E_K\right) * y(4) * y(4) * y(4) * y(4)$$

Compute the leakage conductance:

$$I_L = g_L * \left(y(1) - E_L\right);$$

Compute initial variables:

$$y(1) = V_R$$

$$y(2) = m_{NA}^{\infty}$$

$$y(3) = h_{NA}^{\infty}$$

$$y(4) = m_K^{\infty}$$

Generate several conductance inside the function itself and setup a parametric study. The graphics is managed within the main simulation code.

```
g-NA (1) =0;
gnanonminal =120.0;
gnastart =60.0;
gnafreq =9;
gnaloopsize =10;
gnadelta =gnanominal / gnafreq;
g-NA-bar (1)= gnastart;
I-NA(1)=g-NA-bar(1)*(V-R-E-NA)*m-NA-infinity*m-NA-infinity *m-NA-infinity*h-NA-infinity;
h=gnadelta;
  for i=1: gnaloopsize-1
    g-NA-bar(i+1)=g-NA-bar(i)+h;
   I-NA(i+1)=g-NA-bar(i+1)*( V-R-E-NA)* m-NA-infinity*m-NA-infinity *m-NA-infinity*h-NA-infinity;
End
g-K(1)= 0;
gknominal=36.0;
gkstart = 18.0;
gkfreq = 9;
gkloopsize = 10;
gkdelta = gknominal / gkfreq;
g-K-bar (1)= gkstart;
I-K(1)=g-K-bar(1)*(V-R-E-K)*m-K-infinity*m-K-infinity * m-K-infinity*m-K-infinity;
end
     for i= 1: gnaloopsize;
       for j=1: gkloopsize;
          numerator =-I-NA(i)-I-K(j);
          denominator V-R-E-L;
          g-L(i, j)= -(I-NA(i) + I-K(j))/(V-R – E-L);
     end
  end
end
```

For Sodium conductance calculations, the range is set from 60 to 180 with the nominal value being at 120. Then we set up an array having dimensions of the loop- size and we calculate Sodium conductance and Sodium ionic current using the equations. The step-size of our simulation run equals the nominal value of Sodium conductance divided by the frequency of the run which equals the loopsize-1. We thus generate 100 different values of Sodium conductance and Sodium ionic currents.

For Potassium conductance calculations, the range is set from 18 to 54 with the nominal value being at 36. Then we set up an array having dimensions of the loop-size and we calculate

Potassium conductance and Potassium ionic current using equations. The step-size of our simulation run equals the nominal value of Potassium conductance divided by the frequency of the run which equals the loopsize-1. We thus generate 100 different values of Potassium conductance and Potassium ionic currents.

Once the values of Sodium and Potassium conductance are computed, leakage conductance values are computed using the equation mentioned earlier and are stored in an array having the size of our simulation. We obtain 100 different values and they are all reasonably low.

Setting up the parametric study

In rest calculation: parameters are

g-leak-bar = 0.0306363.

Initial activation and inactivation are

m- NA(0) = 0.0258481

h-NA(0) = 0.777813

m-K1(0) = 0.232349

E-NA =55.54

E-K = -72.7004

E-M = -65.9

E-L = -49

g-leak-bar = 0.0306363

//we use the nominal leakage conductance

//of 0.0306, then recalculate the leakage conductance

//with a call to the rest function.

//the other numbers are the battery voltages.

//we then recalculate the leakage conductance

//to be

g-leak-bar = 0.0153182

//we find the initial values for the state vector

Initial activation and inactivations are

m-NA(0) = 0.0258481

h-NA(0) = 0.777813

m-K1(0) = 0.232349

//this gives us the initial state

yinit = -65.9 0.258481 0.777813 0.232349

//we now print out some of simulation results

Tspan= 25

NUMBER-PLOT-POINTS= 1000

The rest of the parameters are set inside the rest.m function

Options=odeset ('RelTol', 1.0e-6)

T = 6.3000

E-NA= 54.9850

E-K = -71.9739

m-NA-infinity = 0.0258

h-NA-infinity = 0.7778

m-K-infinity = 0.2323

entery y0: [-65.9, 0.0258481, 0.777813, 0.232349]

Leakage conductance =

Columns 1		through 5		
0.0131	0.0173	0.0215	0.0257	0.0298
0.0118	0.0160	0.0202	0.0244	0.0286
0.0105	0.0147	0.0189	0.0231	0.0273
0.0092	0.0134	0.0176	0.0218	0.0260
0.0080	0.0122	0.0163	0.0205	0.0247
0.0067	0.0109	0.0151	0.0193	0.0234
0.0054	0.0096	0.0138	0.0180	0.0222
0.0041	0.0083	0.0125	0.0167	0.0209
0.0028	0.0070	0.0112	0.0154	0.0192
0.0016	0.0057	0.0099	0.0141	0.0183

Columns 6		through 10		
0.0340	0.0382	0.0424	0.0466	0.0508
0.0328	0.0369	0.0411	0.0453	0.0495
0.0315	0.0357	0.0399	0.0440	0.0482
0.0302	0.0344	0.0386	0.0428	0.0470
0.0289	0.0331	0.0373	0.0415	0.0457
0.0276	0.0318	0.0360	0.0402	0.0444
0.0264	0.0305	0.0347	0.0389	0.0431
0.0251	0.0293	0.0335	0.0376	0.0418
0.0238	0.0280	0.0322	0.0364	0.0405
0.0225	0.0267	0.0309	0.0351	0.0393

// Different values of leakage conductance are obtained

// from different choice of maxim sodium and potassium

// conductance such that at equilibrium potential there is no

// flow of current across the membrane.

Setting up a parametric study which computes 100 different data runs for different values of the maximum sodium and potassium conductance. For each of these last values, a new value of the leakage conductance is computed to ensure that there will be no current across the membrane at equilibrium potential. These values are listed above in the array. All of these are handled by the ***rest.m code***. The graphical results are organized in a series of arrays. The injection current is simulated in the simple ***HH.m code***.

Matlab session

```
    //set the path as U: /working directory/working folder
    //set variables
%   voltage          mV
%   current          na
%   time             ms
%   concentration    mM
%   conductance      micro Siemens
%   capacitance      nF
%   Rydberg's        Constant
    R = 8.31;
%   Kelvin Temperature; use 6.3 degrees celcius
    T = 6.3;
%   Faraday's Constant
      F = 9.649e+4;
%   Reference Voltage
      V-R = -65.9;
%   Leakage Voltage
      E-L = -49.0;
% Sodium Parameters; inside and outside concentrations
%
      NA-0 = 491.0;
      NA-I = 50.0;
      E-NA = Nernst(1 , T , NA-I , NA-0 )
%
% Potassium Parameters; inside and outside concentrations
%
    K-0 = 20.11;
    K-1 = 400.0;
    E-K = Nernst(1, T , K-I , K-0);
//run the simulation
Run the main simulation code rest .m……
% y1 = input ('enter y0: ');
% y0=y1;
% enter y0: [-65.9, 0.0258481, 0.777813, 0.232349]; correct values of
% Reference Voltage , m-NA-infinity, g-L and m-K infinity.
```

Runtime results: Discussion

Figure 5 shows that voltage dynamics are being nicely clustered in time steps.

The action potentials were generated for potassium and sodium conductance in the ranges from 60 to 180 and 18 to 54, respectively. In the first 10 times steps between 0 to 5 milliseconds, the voltage response of the cell model grows and then stops down. Further, between 5 to 15 milliseconds, the response kind of "flattens out".

In figure 7, we observe the trend of the sodium currents with to tspan which is 25 milliseconds. Due to insufficient cell membrane depolarization sodium conductance parameter does not generate response within the time frame of 10 to 15 milliseconds.

Figure 6 illustrates the leakage conductance and the steadily increasing pattern that is generated.

In figure 8, we see the trend of the sodium currents with respect to tspan which is 25 milliseconds. Due to insufficient cell membrane depolarization sodium conductance parameter does not generate response within the time frame of 10 to 15 milliseconds.

The above descriptions have a very important underlying lesson. We have to be careful about the leakage values. In all of the above described pictures a secondary pulse is observed which is due to the fact that leakage values are not set right i.e.; the way leakage conductance was computed was wrong. Setting things straight, we observe the expected pattern- the insufficient cell membrane depolarization effect. The response dies out after a certain amount of time.

Figure 9, Figure 10, Figure 11, Figure 12, all bear testimony to this simple but crucial fact of setting leakage values right. We don't see any secondary pulse here because the low values of the leakage conductance don't allow them to trigger.

The cell dynamics inside of the neuron results from the rise in differential potential between the two sides of the lipid membranes and current starts to flow through as it is happening in electrical circuit. This arose current, resultant of the three types of currents mentioned in this

paper (Na^+, K^+ and Cl^-) is voltage-time dependent and it is largely regulated by the conditions of the state in which the lipids and ion channel proteins are. The concentration in Na+ ,in K+ and in Cl- ions changes according to the nature of the ion within time for a specific a voltage differential across the membrane. This model brings forth an interaction relationship between lipid membranes and protein membranes in case of transmission of information to the brain via nerves.

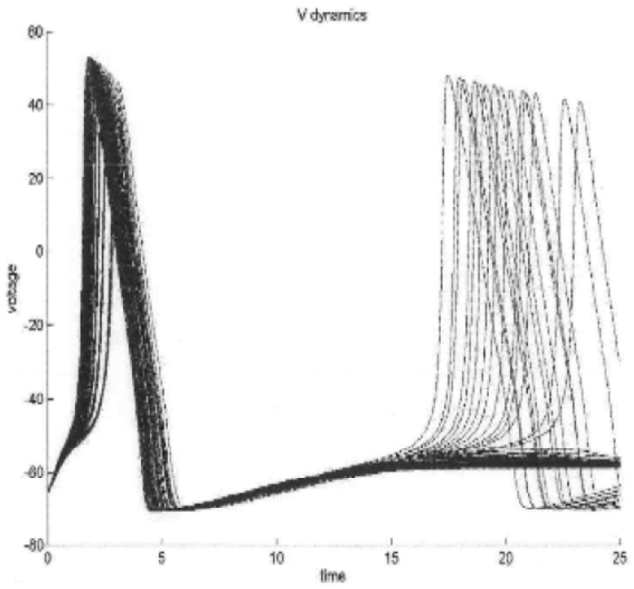

Figure 5: **Voltage dynamics with time; faulty values of leakage**

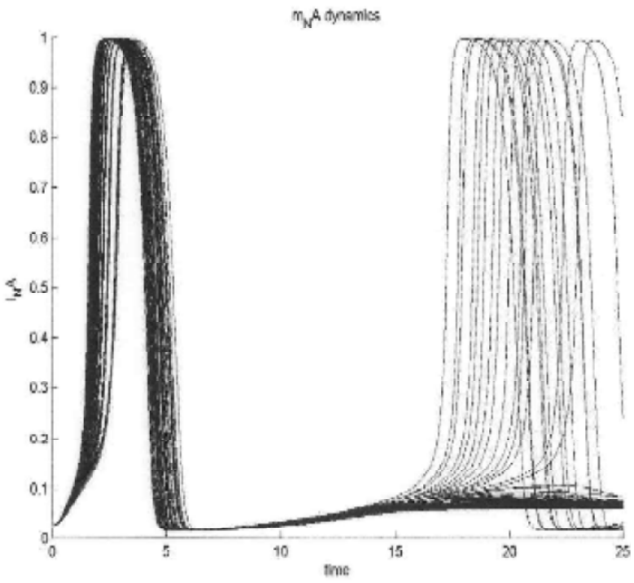

Figure 6: **Sodium conductance with time; faulty values of leakage**

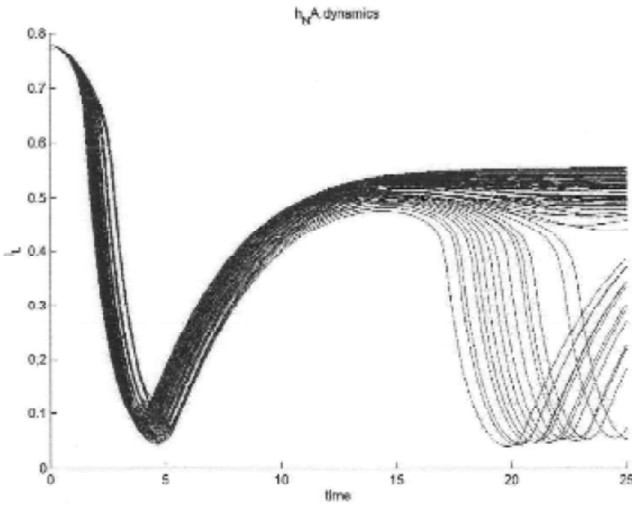

Figure7: **Leakage conductance variance with time; faulty values of leakage**

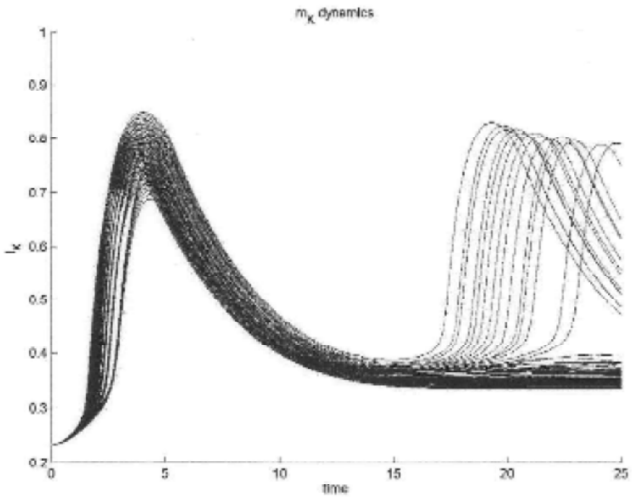

Figure 8: **Potassium conductance variance with time; faulty values of leakage**

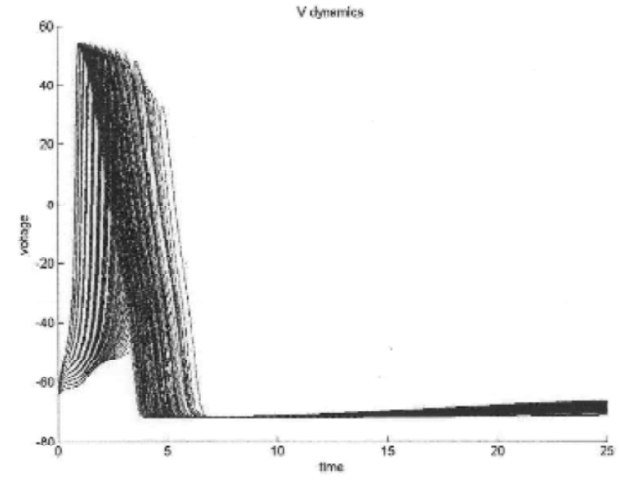

Figure 9: **Voltage dynamics with time**

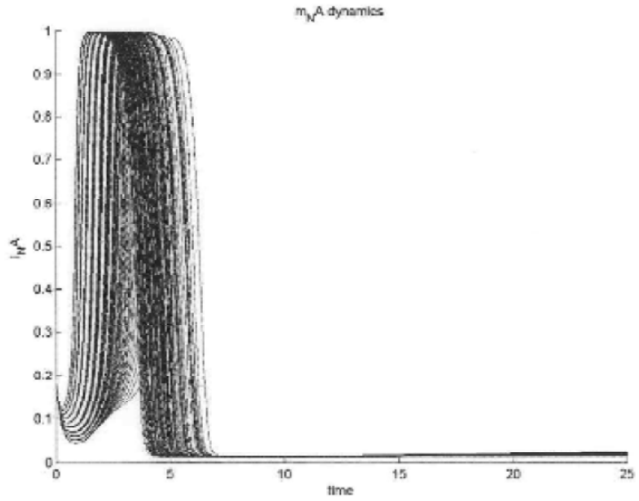

Figure 10: **Sodium Conductance variance with time**

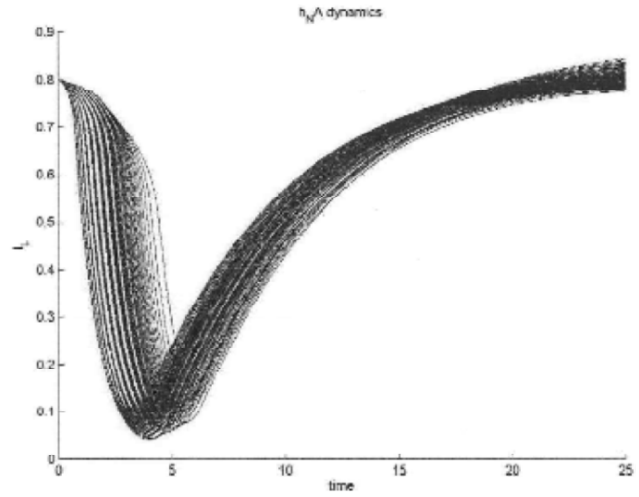

Figure 11: **Leakage conductance variance with time**

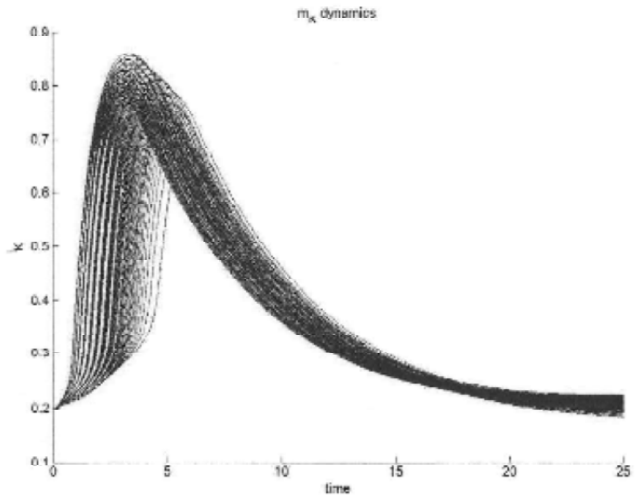

Figure 12: **Potassium conductance variance with time**

References

Appali, R., Rienen, U. V. and Heimburg, T., (2012). Acomparison of the Hodgkin – Huxley Model and the Soliton Theory for the Action Potential in Nerves. Advances in Planar Lipid Bilayers and Liposomes 16, 275 – 299.

Chan, X.J, Cox, C.L, Rienzel, J., and Sherman, S.M., (1999) Current clamp and modeling studies of low-threshold calcium spikes in cells of the cat's lateral geniculate nucleus. J. Neurophysiol. 81, 2360.

Ermentrout, G.B., and Terman, D.H., (2010). The Hodgkin – Huxley Equations. Mathematical Foundations of Neuroscience, Interdisciplinary Applied Mathematics 35, 1 – 28.

Hill, B., (1992). Ionic Channels of Excitable Membranes, Sinauer Associates Inc.

Hodgkin A. L. and Huxley A.F, (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol 117, 500 -544)

Hodgkin, A. L. and Katz, B., (1949). The effect of sodium ions on the electrical activity of the giant axon of the squid, J Physiol. 108, 37 – 77.

Johnston, D and S. Miao – Sin, (1995). Foundations of Cellular Neurophysiology, MIT Press.

Kandel, E.R, Schwartz, J.H, and Jessell, TM, eds (2000). Principles of Neural Science, 4th ed., McGraw-Hill.

Kynes, R.D, Aidley, D.J, and Huary, C.L – H, (2001). Nerve and Muscle, 4th ed., Cambridge University Press.

Koch, C. and I. Segev. Editors, (1992). Methods in Neuronal Modeling, A Bradford Book. MIT Press.

Noble, D., Gerny, A. and Noble P. J, (2012). How the Hodgkin – Huxley equations inspired the Cardiac Physiome Project. JPhysiol 590:11, 2613 – 2628.

Segel, Lee A., Leah Edelstein – Keshet, (2013). A Primer on Mathematical Models in Biology. USA.

Varghese, A., (2000). "Membrane Models", in The Biomedical Engineering Handbook 2nd Ed. Boca Raton: CRC Press LLC.

Weiss, T., (1996). Cellular Biophysics: Vol. 1, Transport. MIT Press.

Weiss, T., (1996). Cellular Biophysics : Vol. 2, Electrical Properties, MIT Press.