MATHEMATICAL MODELING

of

ELECTRICALLY ACTIVE CELLS

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A dissertation submitted for the partial fulfillment of BS-MS dual degree in Science

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April, 2014

Certificate of Examination

This is to certify that the dissertation titled "Mathematical Modeling of Electrically Active Cells" submitted by Ms. Kanwal Puneet Kaur (Reg. No. MS09068) for the partial fulfillment of BS-MS dual degree programme of the Institute, has been examined by the thesis committee duly appointed by the Institute. The committee finds the work done by the candidate satisfactory and recommends that the report be accepted.

Dr. Kavita Babu **Dr. Shashi Bhushan Pandit** **Dr. Somdatta Sinha**
(Supervisor)

Dated: April 25, 2014

Declaration

The work presented in this dissertation has been carried out by me under the guidance of Prof. Somdatta Sinha at the Indian Institute of Science Education and Research Mohali.
This work has not been submitted in part or in full for a degree, a diploma, or a fellowship to any other university or institute. Whenever contributions of others are involved, every effort is made to indicate this clearly, with due acknowledgement of collaborative research and discussions. This thesis is a bonafide record of original work done by me and all sources listed within have been detailed in the bibliography.

Kanwal Puneet Kaur

Dated: April 25, 2014 (MS09068)

In my capacity as the supervisor of the candidate's project work, I certify that the above statements by the candidate are true to the best of my knowledge.

Prof. Somdatta Sinha

(Supervisor)

Acknowledgement

Since the very beginning when I started working in Computational Biology lab, I feel privileged to be working with some of the most knowledgeable and professional people in the field. Being very new to the field of Computational Biology, I feel I have gained a lot during my one year work in modeling of cellular activities.

My sincerest and deepest thanks to Prof. Somdatta Sinha who mentored and guided me all through the project. I find her an excellent teacher and guide who inspired me to excel academically. Not just that, her trait of providing personal attention to all her students despite the busy schedule has helped me a lot. Her support, motivation and care throughout the project work has kept me excited in the work. She is the best guide one could have to work with in the field.

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Finally I thank my parents and friends for always having my back in whatever I do in life and supporting me. Without them, this could not have been accomplished.

Kanwal Puneet Kaur

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ABSTRACT

Electrical activity in humans has various functional roles starting from neuronal communication in the brain to pumping of blood in the heart. The idea of being able to relate this activity to certain mathematical and physical systems seems quite intelligent in itself. The next step is to model the entire biological system to be able to study it and incorporate the required changes through change in parameters and variables.

In my thesis, I studied the existing model of the neuron – the Hodgkin-Huxley model, and two models of the pancreatic beta cells – the Chay Keizer model and the Phantom Burster model. I simulated the mathematical models using the mathematical software MATLAB, and standardized the programmes by repeating simulation results obtained in the original studies. To experiment with the models, the values of various parameters and variables were then changed and the relevant results were compared with existing real wet lab experiments wherever possible.

Chapter 1

INTRODUCTION

Electrical activity involving charged particles and their movement within the body plays an important role in terms of the various body functions. There are many organs and tissues within the body like Heart, Brain and islets of Langerhans in the Pancreas, whose functions are regulated by the electrical activity of the cells that make them up.

Human brain cells fire electrical impulses to communicate with one another. Ion channels in the cell membranes work together to deliver messages throughout the brain. Electroencephalography (EEG) is used to study the electrical activity in the brain. In the heart, electrical impulses control the muscles that create the pumping motion. The electrical signals travel across the heart, causing muscles to contract and pump blood throughout the body. Electrocardiography (ECG) is used to study electrical activity in the heart. Besides, electrical activity contributes to various functions like hormonal secretion in different organs. An important example is the secretion of insulin by the beta cells of pancreas – malfunction of which can lead to Diabetes.

1.1 Electrically-Active Cells

Electrically active cells are those cells whose functions are based on reception or generation of electrical signals in terms of current or voltage change. The reason for the electrical activity lies in the presence of different charged ions and their selective permeability across the cell membrane.

Examples of electrically active cells in humans are the neurons, cardiac cells and the pancreatic beta cells. Neurons are the epitomes of electrical activity as the basic neuronal function, i.e. signal conduction, is based on electric properties of the neurons. Cardiac muscle cells and beta cells of the pancreas exhibit electrical activity similar to the neurons but different in many aspects. Electrical activity of any type requires current to be flowing in

some direction and this requires a driving force. In case of cells, this driving force is provided by the electrochemical gradient, which is present due to the unequal distribution of ions on both sides of the membrane and the semi-permeability of the membrane. The semi-permeability of the membrane is essentially due to the presence of ion channels which are selectively permeable depending on the types of ions. Table 1 shows the concentration of various ions on the inside and outside of the membrane of neurons from different organisms. It is clear from the Table that intracellular concentration of potassium ions is much higher than its extracellular and the state is opposite for sodium and chloride ions. Also these concentrations vary considerably within organisms [1].

Table 1: Ionic concentration across membranes

Ion	Intracellular conc.(mM)	Extracellular conc.(mM)
Squid neuron		
Potassium	400	20
Sodium	50	440
Chloride	40--150	560
Calcium	0.0001	10
Mammalian neuron		
Potassium	140	5
Sodium	5--15	145
Chloride	4--30	110
Calcium	0.0001	1--2

Channel Proteins are the proteins that form hydrophilic pores across the membranes (Fig. 1). There are two types of such pores - *gap junctions* and *ion channels.*

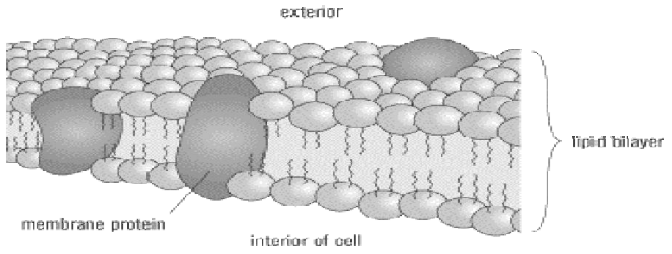


Fig1: Cartoon representation of cell membrane [2]

Gap junctions are the proteins connecting the cytoplasm of two adjacent cells, the plasma membrane of each cell contributing equally to the formation of the junction. Six proteins known as *connexins* form a connexons or hemichannels, two of which make up the *gap junctions*.

Ion channels are the proteins that connect the cytosol to the cell exterior. The arrangement of the different proteins is such that the change in their conformation leads to the opening and closing of the channels and hence semi permeability of the membrane, which has an important role to play in voltage oscillations of the membrane. Different types of ion-specific and non-specific channels - such as, sodium, potassium and calcium channels – are known to exist in electrically active cells.

1.2 The Mathematical Models

Mathematical modeling of any activity of the living system helps in studying the system in its simple form and then experimenting with it virtually before conducting the real experiments. Mathematical models have been used in many electrophysiological systems, such as in neurophysiology, cardiac physiology, etc. for a long time. They have been important in understanding the normal function of cells/tissues and the causes of malfunction in physiological disorders, such as epilepsy and cardiac arrhythmias [3].

The cell membrane of any living cell is essentially comprised of a lipid bilayer and membrane proteins (ion channels and cell receptors). The lipid bilayer is highly hydrophobic on the inside with hydrophilic ends on the cytoplasmic and the extracellular sides (Fig. 1). In that case the two ends of the bilayer act as charged regions (due to the presence of ions) with the inside being completely uncharged. The entire setup can be compared to a parallel plate capacitor. Also the ion channels within the membrane allow different ions to flow from one side of the membrane to the other offering some amount of resistance in terms of conformational and structural changes in the ion channels just like resistors in an RC circuit as shown in Fig. 2**.**

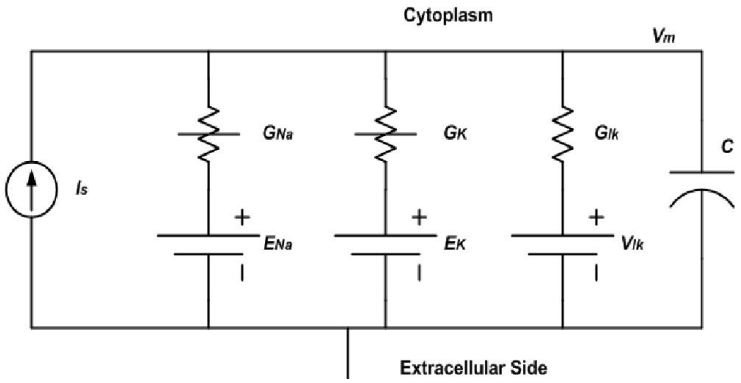


Fig 2: Cell membrane compared to an RC circuit [4]

The mathematical models describe the electrical cells using an RC circuit. In these models, the plasma membrane of the cells is compared to an RC circuit, where the lipid bilayer is considered analogous to a parallel plate capacitor and the ion channels to the resistors with different resistances. Going by this analogy, mathematical models of the electrically active cells are developed and studied using the various laws of electric circuitry like ***Ohm's law*** and ***Kirchoff's law***.

Ohm's Law states that the current through a conductor between two points is directly proportional to the potential difference across the two points.

I = V/R

where, *I = current, V = potential difference, and R= resistance*

Kirchoff's law is based on the principle of conservation of electric charge, and it states that the algebraic sum of currents in a network of conductors meeting at a point is zero.

$$\sum_{k=1}^{k=n} \boldsymbol{I(k) = 0}$$

where *n is total number of branches in the network.*

1.3 Objectives and Organization of Work

Mathematical modeling of biological systems is an interdisciplinary activity. It requires biological knowledge to understand the system/process to be modelled, and mathematical and computational expertise to analyse and simulate the model. The mathematical and

computational results then need to be understood in terms of biology for their relevance and application. The primary objective of my MS thesis was two-fold –

1) to learn the concepts and methods/techniques of mathematical modeling of electro-physiological systems; and

2) to study two specific systems – models of Neurons and Pancreatic Beta cells – having different ionic processes, and carry out various numerical experiments with them by changing the parameters and values in the models. The results of these virtual experiments were compared with available real experiments wherever possible.

In this thesis, I present my studies with the Hodgkin-Huxley model for the neuron [4,5] and Chay-Keizer model [6] and Phantom Burster model [7] for the beta-cell. I have studied the development of the models from the underlying biological processes, learnt the relevant mathematical software for developing the programmes for coding the mathematical models, performed simulation experiments, and arrived at biologically relevant conclusions.

In Chapter 2, I describe the details of the theoretical and computational methods used for modeling and simulation. A detailed description of the mathematical models for the two physiological systems is also given here.

In Chapter 3, I present the simulation experiment results for the models of the two physiological systems, namely the Hodgkin-Huxley model for the neuron, and the Chay-Keizer and Phantom Burster model for the beta cells.

Chapter 4 concludes the thesis by summarizing all results and indicating future studies necessary to understand tissue level functions of these physiological systems.

Chapter 2

MODELS AND METHODS

2.1 Models

Model of Neuron:

Hodgkin Huxley Model [4,5] is a mathematical model named after two scientists Sir Andrew Huxley and Sir Alan Hodgkin who in 1952 published a series of five articles [4,10,11,12,13] on modelling the electrical activity of the squid giant axon. In 1963, they were awarded the Nobel prize in Physiology and Medicine for their work.

The first time direct measurements were made in the membrane potential of the squid axon were in 1939 [8], where a capillary tube filled with sea water was carefully pushed down the axon, which served as an electrode to measure potential difference across membrane. Time course was indicated by 500 Hz sine wave on oscilloscope screen (Fig. 3).

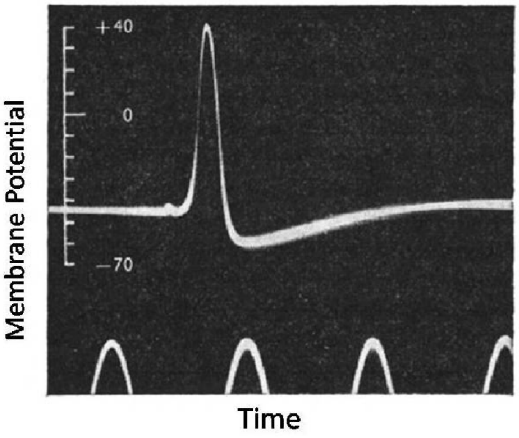


Fig 3: Action potential measured in squid giant axon for the first time in 1939 [8]

As mentioned earlier, sodium and potassium ion channels play an important role in the electrical activity in the neurons.

As is clear from the Table 1, sodium and potassium ion concentrations show great variation across the plasma membrane of the neurons both in squid and humans.

Semi permeability of the ion channels and the concentration gradient of the ions across the membrane lead to something known as the *resting membrane potential*. It is the potential of the inside of the cell with respect to the outside when there is no external stimulus or stimuli from the neighboring cells. For nerve cells of the squid, it is approximately -70mV.

With the external stimulus, the neuronal membrane shows a deviation from the resting membrane potential depending on the direction of the current. Negative current seems to hyperpolarize the membrane and positive current depolarizes it. There is a threshold current associated with the depolarization such that after that current, we have something known as *action potential.* It is the phenomenon of rapid change in the potential of the membrane in the form of spikes. Higher is the magnitude of the external current, more is the frequency of the spikes.

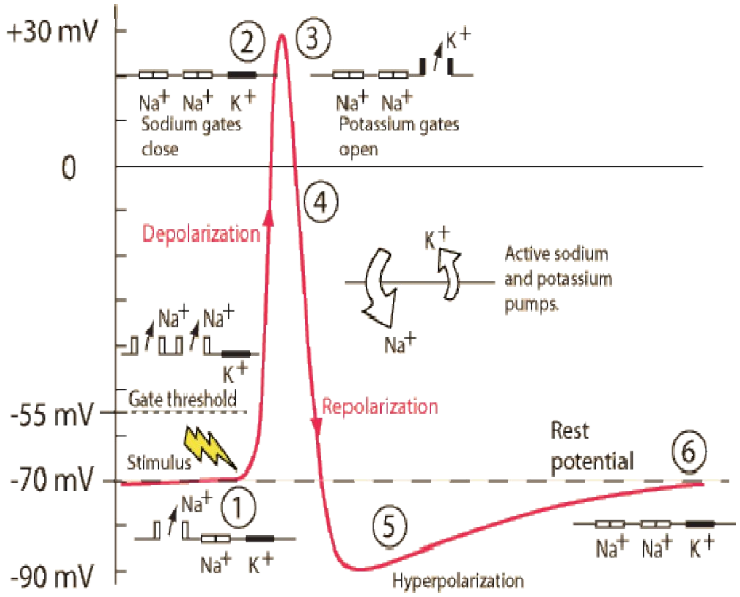


Fig 4: Action potential as a 6 step process. 1-Na (fast) channels open, 2- Na channels close, 3- K (slow) channels open, 4- Na-K pumps activate, 5- Excess K flows out, 6- Resting membrane potential restored [9]

Considering the RC circuit of the neuron, the following equations of the Hodgkin Huxley model were developed.

$$I = C_M \frac{dV}{dt} + I_i,$$ {Kirchoff's law}

$$I_{Na} = g_{Na}(V - V_{Na}),$$
$$I_K = g_K(V - V_K),$$
$$I_l = \bar{g}_l(V - V_l),$$ {Ohm's law}

$$\boxed{I_i = I_{Na} + I_K + I_l.}$$

$$g_{Na} = m^3 h \bar{g}_{Na},$$
$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m,$$
$$\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h,$$

$$g_K = \bar{g}_K n^4,$$
$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n,$$

Where,

I - current

V - potential difference across membrane

C_M - capacitance of the membrane

g_X - conductance of 'X' ion channel

n,m,h are probabilities (1 when fully permeable to ions, and 0 for fully non-permeable). Product of the variables yield the percentage of conducting channels.

n ∝ No. of open K channels

m ∝ No. of activated Na channels.

h ∝ No. of deactivated Na channels.

The Full model [10,11,12] is:

$$I = C_M \cdot \frac{dV}{dt} + \bar{g}_K \cdot n^4 (V - V_K) + \bar{g}_{Na} \cdot m^3 \cdot h \cdot (V - V_{Na}) + \bar{g}_L \cdot (V - V_L)$$

$$\frac{dm}{dt} = \alpha_m \cdot (1 - m) - \beta_m m$$

$$\frac{dn}{dt} = \alpha_n \cdot (1 - n) - \beta_n n$$

$$\frac{dh}{dt} = \alpha_h \cdot (1 - h) - \beta_h h$$

Where, the values of all the parameters are as given below:

$C_M = 1.0 \mu F / cm^2$

$V_{Na} = -115 mV$

$V_K = +12 mV$

$V_L = 10.613 mV$

$\bar{g}_{Na} = 120 m \cdot mho / cm^2$

$\bar{g}_K = 36 m \cdot mho / cm^2$

$\bar{g}_L = 0.3 m \cdot mho / cm^2$

$\alpha_n = 0.01 \cdot (V + 10) / \{\exp[1 + (0.1 \cdot V)] - 1\}$

$\beta_n = 0.125 \cdot \exp(V / 80.0)$

$\alpha_m = 0.1 \cdot (V + 25.0) / \{\exp[(0.1 \cdot V) + 2.5] - 1.0\}$

$\beta_m = 4.0 \cdot \exp(V / 18.0)$

$\alpha_h = 0.07 \cdot \exp(V / 20.0)$

$\beta_h = 1.0 / \{\exp[3.0 + (0.1 \cdot V)] + 1\}$

Models of Beta cell:

a. Chay Keizer model [14,15,16]**:** It is one of the basic β-cell models which is based on the Hodgkin Huxley paradigm. Unlike the voltage oscillations in neurons, oscillations in beta cells are characterized by silent and active phases with spiking behavior.

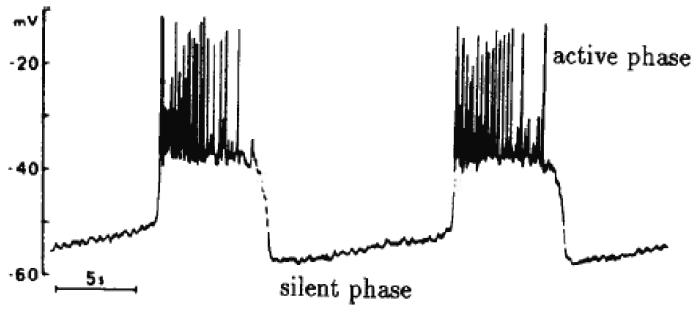


Fig 5: Voltage oscillations in the cell membrane of beta cells [17]

Pancreatic β-cells secrete insulin, which regulates the concentration of plasma glucose. Schematic representation of the model is given below:

There are 4 types of ion channels that have important roles to play in beta cell electrical activities:

- **ATP-gated potassium channels:** Close when ATP binds to them.
- **Voltage-gated calcium channels:** Open when membrane potential is decreased.
- **Voltage-gated potassium channels:** Open when membrane potential is decreased.
- **Calcium-gated potassium channels:** Open when calcium ions bind to the channel.

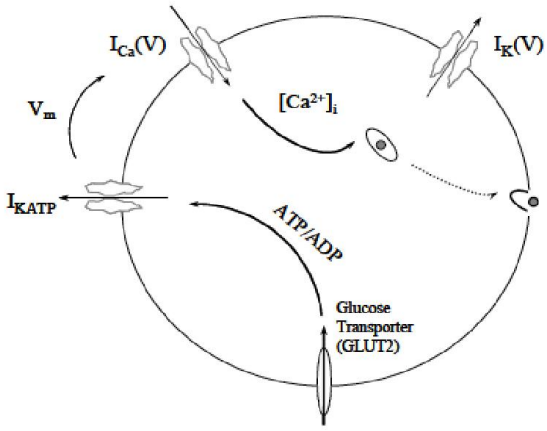


Fig 6: Schematic representation of Chay Keizer model [18]

With the intake of glucose, it enters the beta cells via the glucose transporters (Fig 6). The breakdown of glucose then releases ATP which closes ATP gated potassium ion channels. This leads to slight depolarization of the membrane which triggers the opening of the voltage gated calcium ion channels and hence causes further depolarization of the membrane. Then open the voltage gated potassium ion channels whose activity interacts with calcium ion channels which is responsible for the spiking behavior. A particular minimum amount of calcium in the cytosol leads to insulin release and opening of calcium gated potassium ion channels which leads to restoration of the resting membrane potential, completing the cycle.

Model equations [6]:

$$4\pi r^2 C_m \frac{dV}{dT} = -\left[I_{Ca}(V) + I_K(V) + I_{K,Ca}(V, Ca_i) + I_L(V)\right]$$ {Kirchoff's laws}

$$\begin{aligned} \frac{dm}{dT} &= \frac{m_\infty(V) - m}{\tau_m(V)}, \\ \frac{dh}{dT} &= \frac{h_\infty(V) - h}{\tau_h(V)}, \\ \frac{dn}{dT} &= \frac{n_\infty(V) - n}{\tau_n(V)}. \end{aligned}$$

$$\frac{dCa_i}{dT} = f\left[\frac{-3}{4\pi r^3 F} I_{Ca}(V) - k_{Ca} Ca_i\right]$$ {Rate of removal of Ca^{2+}}

$$\begin{aligned} I_{Ca}(V) &= \bar{g}_{Ca} m^3 h (V - V_{Ca}), \\ I_K(V) &= \bar{g}_K n^4 (V - V_K), \\ I_{K,Ca}(V, Ca_i) &= \bar{g}_{K,Ca} \frac{Ca_i}{K_d + Ca_i} (V - V_K), \\ I_L(V) &= \bar{g}_L (V - V_L), \end{aligned}$$

$$g_K = \bar{g}_K n^4, \qquad g_{Ca} = \bar{g}_{Ca} m^3 h$$

$$g_{K,Ca} = \bar{g}_{K,Ca} \frac{Ca_i / K_d}{1 + Ca_i / K_d}$$

C	capacitance
V	membrane potential
k(Ca)	dissociation constant
g	conductance
n	probability of activation of V-gated K^+ channel.

m	probability of activation of V-gated Ca^{2+} channel.
h	probability of inactivation of V-gated Ca^{2+} channel.
Ca_i	intracellular Ca^{2+} concentration.
K_d	dissociation constant for Ca2+ bound to K channel.
F	Faraday's constant
f	ratio of free to bound intracellular Ca ions.
K(Ca)	glucose dependent rate constant for removal of Ca ions.

b. Phantom Burster Model [7]

Beta cells do not exist or function in isolation. In intact islets of Langerhans, beta cells oscillate with intermediate (10–60s) time periods as opposed to single cells which oscillate with either very small (1-5s) or very large (1-2min) time periods. This can be modeled by combining very small and very large time periods. Intermediate bursting is known as Phantom bursting.

The new element in Phantom burster model that makes it different from original Chay-Keizer model is the essential participation of two distinct slow negative feedback variables, denoted by s_1 and s_2 in the model. In the simulations, $s1$ drives the fast oscillations, with period ,10 seconds; $s2$ drives the slow oscillations, with period .60 s; and the interaction of $s1$ and $s2$ drives the medium oscillations with period between 10 and 60 s.

Model equations:

$$\frac{dV}{dt} = -(I_{Ca} + I_K + I_{s1} + I_{s2} + I_L)/C_m$$

$$\frac{dn}{dt} = (n_\infty(V) - n)/\tau_n$$

$$\frac{ds_1}{dt} = (s_{1\infty}(V) - s_1)/\tau_{s1}$$

$$\frac{ds_2}{dt} = (s_{2\infty}(V) - s_2)/\tau_{s2}$$

$$I_{Ca} = g_{Ca} m_\infty(V)(V - V_{Ca}),\ I_K = g_K n(V - V_K)$$

$$I_{S1} = g_{s1} s_1(V - V_K),\ I_{S2} = g_{s2} s_2(V - V_K)$$

$$I_L = g_L(V - V_L).$$

Where, I_{Ca} - Ca^{2+} current that activates instantaneously

I_K - rapidly activating K^+ current

I_L - a leak current

V – membrane potential

C- capacitance

g_x – conductance

$$m_\infty(V) = \frac{1}{1 + \exp[(-22 - V)/7.5]},$$

$$n_\infty(V) = \frac{1}{1 + \exp[(-9 - V)/10]}$$

$$s_{1\infty}(V) = \frac{1}{1 + \exp[(-40 - V)/0.5]},$$

$$s_{2\infty}(V) = \frac{1}{1 + \exp[(-42 - V)/0.4]}$$

$$\tau_n(V) = \frac{8.3}{1 + \exp[(V + 9)/10]}.$$

Although the slow currents, I_{s1} and I_{s2}, are formulated here as K^+ currents for concreteness, their biophysical identities remain obscure. However, as an illustrative example, one may think of I_{s1} as a K(Ca) current, activated by cytosolic Ca^{2+}, and of I_{s2} as a K(ATP) current, activated by an increase in [ADP] relative to [ATP]. Neither of these currents is voltage-dependent, but K(Ca) responds to the rise in cytosolic [Ca^{2+}] that follows depolarization, and it has been suggested that K(ATP) current might also increase with [Ca^{2+}] as a result of either hindered ATP production or enhanced ATP consumption. For our purpose it is sufficient that I_{s1} and I_{s2} are repolarizing, negative feedback currents that turn on when the cell is depolarized. Indeed, the model works equally well if either or both are depolarizing inward currents that turn off or inactivate when the cell is depolarized.

Where Chay-Keizer model is for single beta cell and, which is rarely the case, as beta cells function in groups, Phantom burster model takes care of the latter scenario and we have a model mimicking the beta cells functioning in a group.

2.2 Methods

For studying the dynamic behavior of the above-mentioned models for neurons and β-cells under different conditions, the scientific software MATLAB [18] was used. The models primarily comprise of coupled differential equations, which can be integrated using the ordinary differential equation (ODE) solvers in MATLAB. There are many ode integrators for different tpes of differential equations. After working with several of them, I used the *ode23* and *ode45*. These solvers use Runge-Kutta method (order 4) for integrating the equations, and are specifically used for stiff equations.

The models were coded in MATLAB script and simulations were run using the above-mentioned differential equation integrators. On obtaining reasonable time course of electrical activity traces from each model, further virtual experiments were carried out.

MATLAB code for Hodgkin-Huxley model:

```
function answer= hhfinal (t,x)
C = 1;
I = 10;
Vk= -12; %original -12
VNa= 115; %original= 115
Vl=10.6; %original = 10.6
gk = 36; %original= 36
gNa= 1000; %original=120
gl = 0.3;
answer(1,1)= (I - gk*((x(2))^4)*(x(1)-Vk) - gNa*((x(3))^3)*x(4)*(x(1)-VNa) - gl*(x(1)-Vl))/C;
answer(2,1)= (.01*(10-x(1))./(exp((10-x(1))/10)-1))*(1-x(2)) - (.125*exp(-x(1)/80))*x(2);
answer(3,1)= (.1*(25-x(1))./(exp((25-x(1))/10)-1))*(1-x(3)) -  (4*exp(-x(1)/18))*x(3);
answer(4,1)= (.07*exp(-x(1)/20))*(1-x(4))- (1/(exp((30-x(1))/10)+1))*x(4);
```

MATLAB code for Chay-Keizer model:

```
function answer= ckoriginal (t,x)
kCa=0.02;
Iapp=0;
Cm=5;
gKCa=0.09;
gKHH=12;
gCaHH=6.5;
gL=0.04;
VK=-75;
VCa=100;
```

```
VL=-40;
Vstar=30;
Vplus=50;
Kdiss=1;
r=8.9e-4;
f=0.004;
F=96487;
temp =20;
alphan= 0.01*(10-x(1)-Vstar)/(exp((10-x(1)-Vstar)/10)-1);
betan= 0.125*exp((-x(1)-Vstar)/80);
alpham= 0.1*(25-x(1)-Vplus)/(exp((25-x(1)-Vplus)/10)-1);
betam= 4*exp((-x(1)-Vplus)/18);
alphah=0.07*exp((-x(1)-Vplus)/20) ;
betah= 1/(exp((30-x(1)-Vplus)/10)+1);
phi = 3^((temp-6.3)/10);
g2= gKCa*x(5)/(Kdiss+x(5));
g3= gKHH*(x(2))^4;
g1= g2+g3;
g4= gCaHH*x(3)*x(3)*x(3)*x(4);
answer(1,1)= (g1*(VK-x(1))+ 2*g4*(VCa-x(1)) + gL*(VL-x(1)) + Iapp)/Cm;
answer(2,1)= phi*(alphan*(1-x(2))- betan*x(2));
answer(3,1)= phi*(alpham*(1-x(3))- betam*x(3));
answer(4,1)= phi*(alphah*(1-x(4))- betah*x(4));
answer(5,1)= f*(3*g4*((VCa-x(1))/(r*F))-kCa*x(5));
```

MATLAB code for Phantom Burster model:

```
function answer= phantom (t,x)
lambda= 1.1;
gca= 280;
gk= 1300;
gl= 25;
vs1= -40;
taus1=1000;
vs2= -42;
taus2= 120000;
gs2= 32;
gs1= 12.5;
vl= -40;
vca= 100;
vk= -80;
cm= 4524;
tnbar= 9.09;
vm= -22;
vn= -9;
sm= 7.5;
sn= 10;
ss1=0.5;
```

```
ss2= 0.4;
minf = 1.0/(1.0+exp((vm-x(1))/sm));
ninf = 1.0/(1.0+exp((vn-x(1))/sn));
taun = tnbar/(1.0+exp((x(1)-vn)/sn));
s1inf = 1.0/(1.0+exp((vs1-x(1))/ss1));
s2inf = 1.0/(1.0+exp((vs2-x(1))/ss2));
ica = gca*minf*(x(1)-vca);
ik = gk*x(2)*(x(1)-vk);
il = gl*(x(1)-vl);
is1 = gs1*x(3)*(x(1)-vk);
is2 = gs2*x(4)*(x(1)-vk);
answer(1,1) = -( ica + ik + il + is1 + is2 )/cm;
answer(2,1) = lambda*(ninf - x(2))/taun;
answer(3,1) = (s1inf - x(3))/taus1;
answer(4,1) = (s2inf - x(4))/taus2;
```

The code was run in MATLAB (version) and the graphs were plotted using MS Excel. Parameter values were taken from existing literature.

Chapter 3

RESULTS AND DISCUSSION

The results of the study are given in two sections – for the Neuron and the Beta cells

3.1 Electrical activity of Neuron - Hodgkin Huxley model:

Solution of the model:

The simulation results for the Hodgkin-Huxley model for the given parameters is shown below in Fig 7.

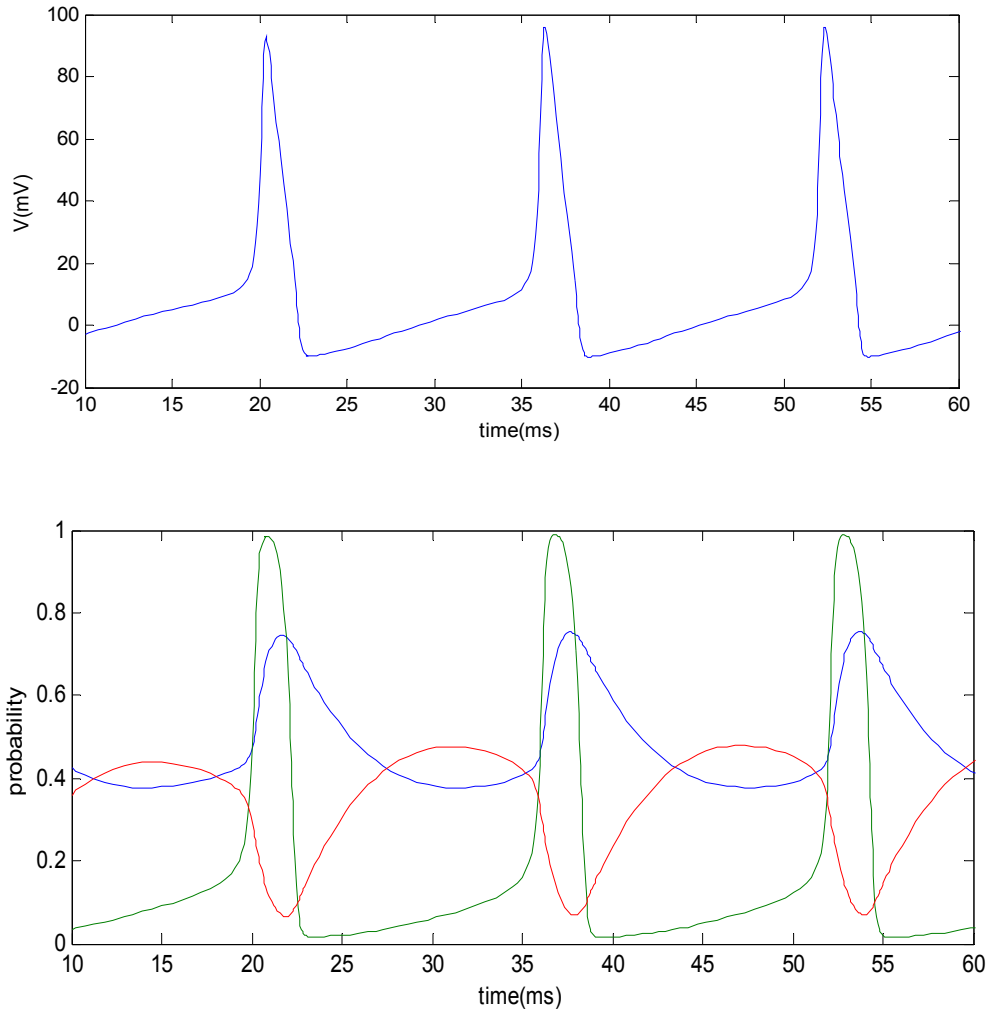


Fig 7: Solution of Hodgkin Huxley model

Where, n ∝ number of open K channels.

m ∝ number of activated Na channels.

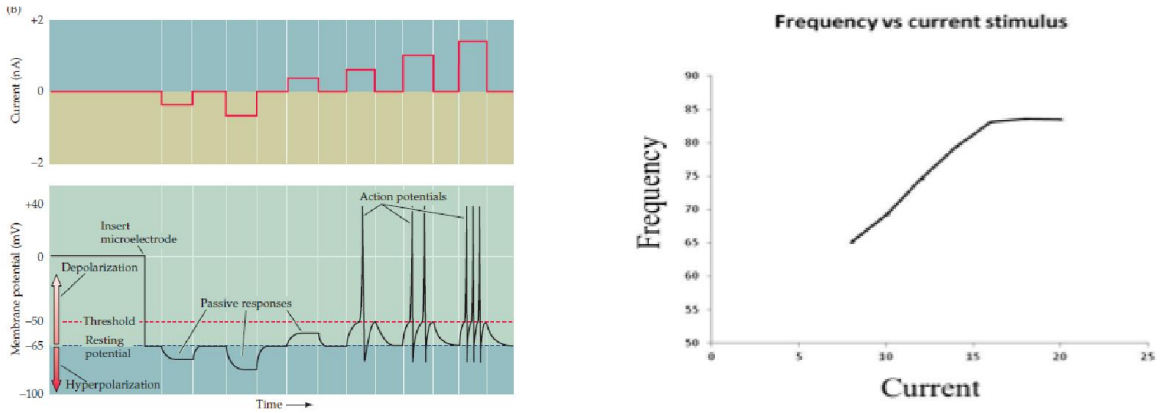
h ∝ number of deactivated Na channels.

Following points were observed from the solution of the model:

- Potassium channels (known as slow channels) take a longer time to open and close as compared to the sodium channels.
- Not all the potassium channels are closed at a time unlike the case with sodium channels.
- When sodium channels are in deactivated stage, there is no action potential.

1. Effect of external current on neurons:

It is known that as the magnitude of external stimulus is increased, the frequency of oscillations of the membrane potential (V) increases (Fig. 8(A)). I have simulated the H-H model for different external currents and have obtained the same trend as shown in Fig 8(B).

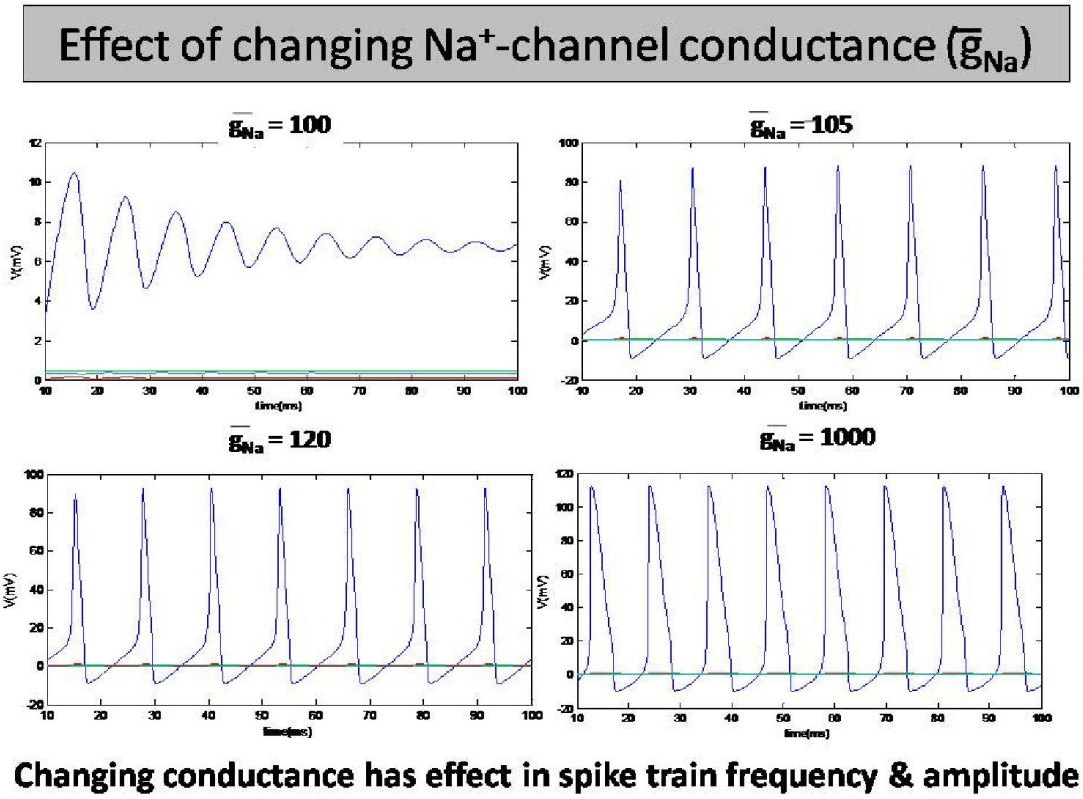


A B

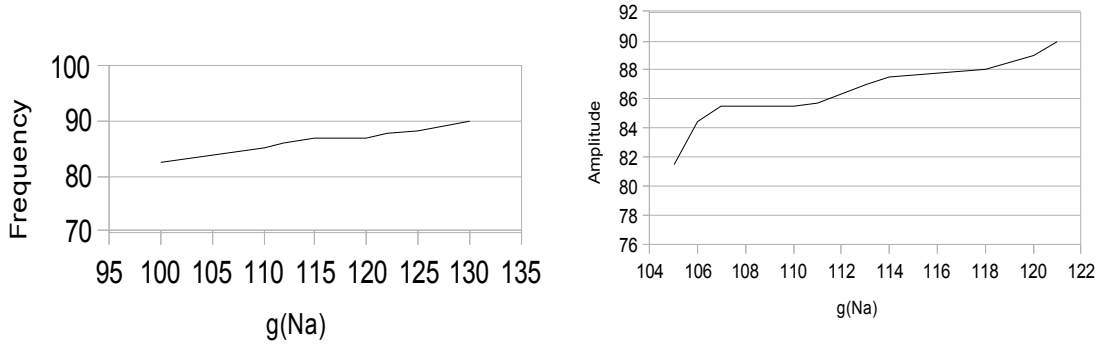
Fig 8: Effect of current magnitude on frequency of oscillations.

A. Experimental data [1] B. Simulation results

2. Effects of changed Na^+ conductance on neural oscillations:



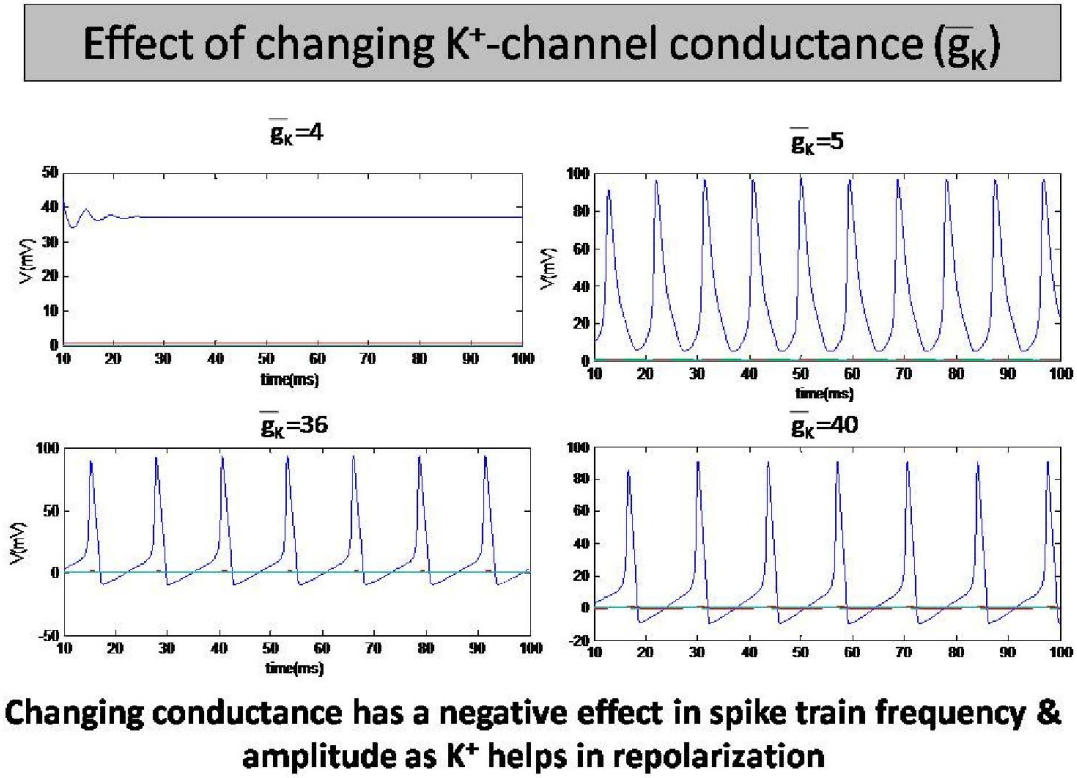
As Na^+ conductance in the beta cells increases, the simulation results show that both the frequency and amplitude of the action potentials increase (as summarized in Fig.9).

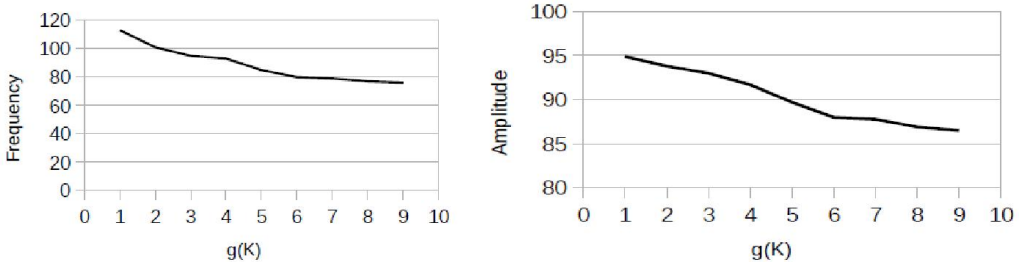


A **B**

Fig 9: Both frequency (A) and amplitude (B) of oscillations increase with increase in sodium conductance

3. Effects of changed K^+ conductance on neural oscillations:





A **B**

Fig 10: Both frequency (A) and amplitude (B) of oscillations decrease with an increase of potassium conductance

The above mentioned simulation results can be explained in terms of the difference in time scales of the ion channel opening/closing in the neurons.

3.2 Electrical activity of Beta cells:

a. Chay-Keizer Model

Solution of the model:

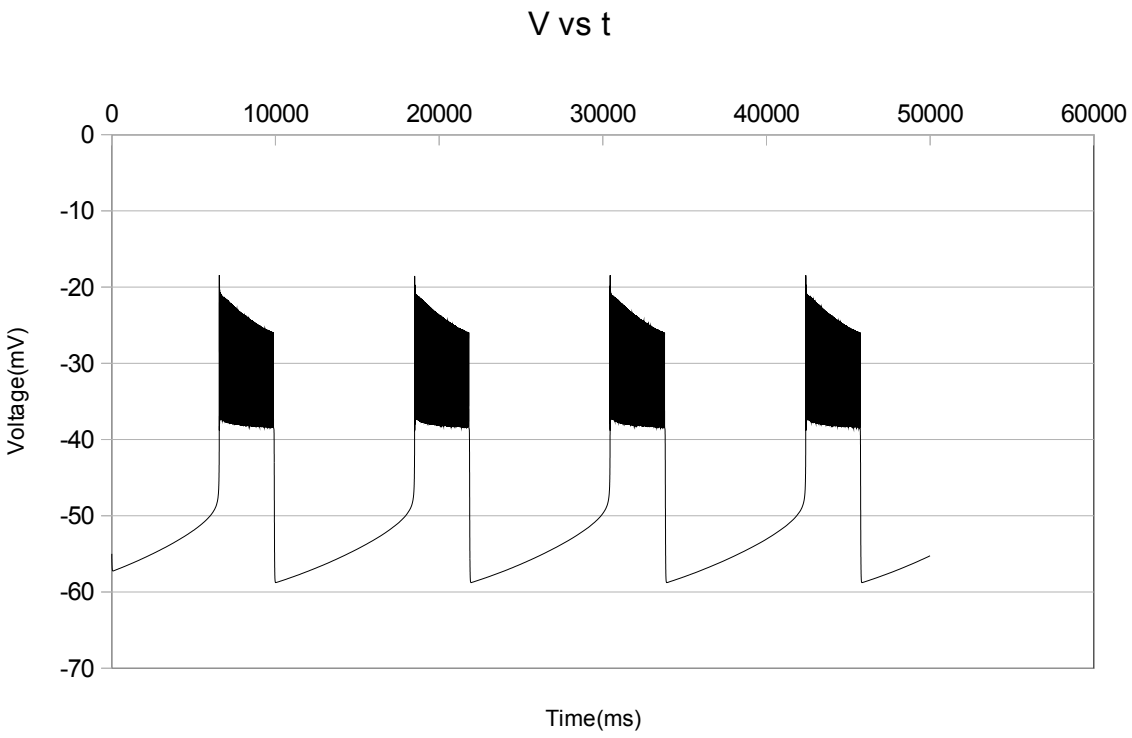
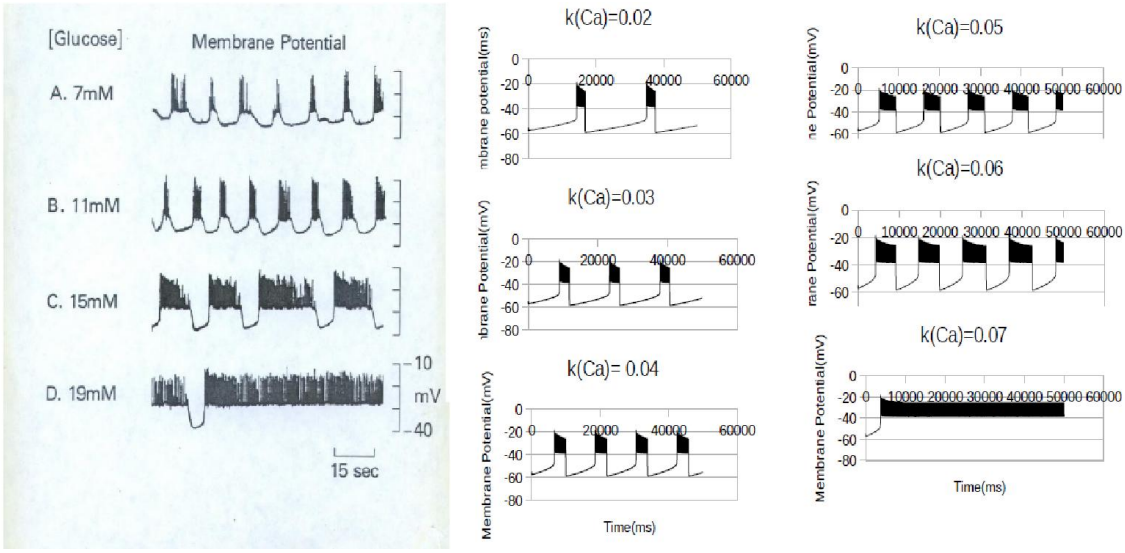


Fig 11:Solution of Chay-Keizer model

The simulation results of the Chay-Keizer model gives the above solution with default parameters. The frequency of the bursting pattern matches with the experimental values as given in their paper.

1. Effect of changed glucose concentration on ß-cell oscillations:

Addition of glucose leads to release of insulin. It was experimentally found that more is the amount of glucose added, more is the k(Ca) [glucose dependent rate constant for the removal of calcium ions from cytosol]. Therefore, in the simulations increased value of k(Ca) signifies increased addition of glucose experimentally.



A B

Fig 12: Increased glucose concentration increases insulin release.

A- Experimental results [20] B- Simulation results

2. Effect of addition of quinine on beta cell oscillations:

Quinine blocks calcium gated potassium channels. Theoretically, this should lead to a hindrance restoring the hyperpolarized stage during membrane oscillations. This prolongs the period of active phase and hence insulin release. Also, some experimental studies [21] have found out that addition of quinine leads to an increase in plasma insulin levels and decrease in plasma glucose levels.

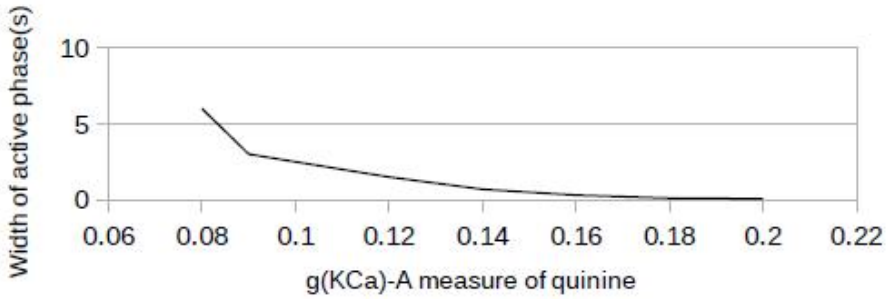


Fig 13: Addition of quinine increases insulin release (simulation results)

3. Effect of addition of TEA(tetraethyl ammonium ions) on beta cell oscillations:

TEA blocks voltage gated potassium channels. Experimentally [22], it has been found out that addition of TEA leads to an increased plasma insulin levels.

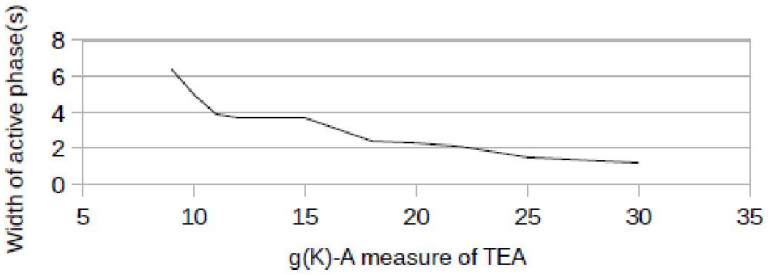


Fig 14: Addition of TEA increases insulin release (simulation results)

b. Phantom Burster model:

Beta cells do not exist or function in isolation. In intact islets of Langerhans, beta cells oscillate with intermediate (10–60s) time periods as opposed to single cells which oscillate with either very small (1-5s) or very large (1-2min) time periods. This can be modeled by combining very small and very large time periods. Intermediate bursting is known as Phantom bursting.

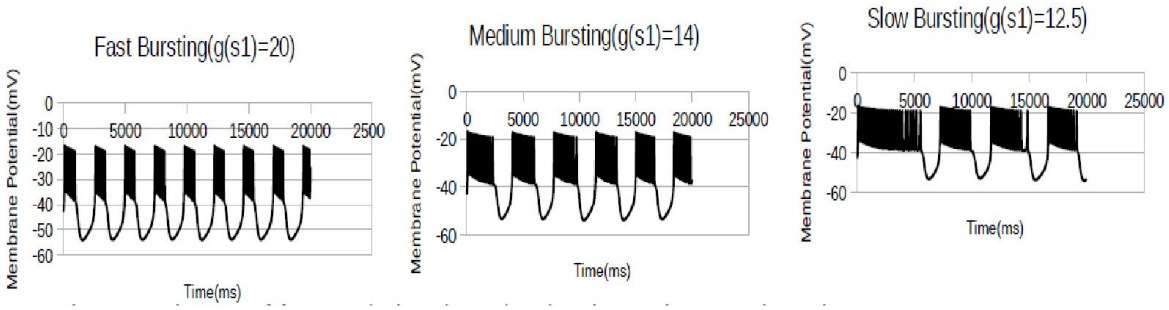


Fig 15: A mixture of fast and slow bursting leads to phantom bursting.

Chapter 4

CONCLUSION:

Modeling the electrical activity in the cells helps in studying the impact of various external chemicals and stimulations(like current) on the normal/diseased cells and the same can be mimicked in in-vitro systems as well. Impact of change of various internal conditions like conductance of cell membrane , etc which might depend on external conditions like pharmacological agents and drugs can be studied. Further deep diving & closely analyzing the dependence of changing internal conditions on various external conditions provide useful insights on practical implementation in medical science.

The results of the project work are summarized as follows:

- In case of neurons, the increase in external stimulation (current) leads to an increase in frequency of oscillations of action potential in the cell membrane.
- With the increase in sodium channel conductance, there is an increase in both the frequency as well as the amplitude of oscillations of action potential in neuronal cell membranes.
- With the increase in potassium channel conductance, there is a decrease in both the frequency as well as the amplitude of action potential oscillations of neuronal cell membranes.
- The amount of insulin secretion from beta cells increases with the increase in the amount of plasma glucose levels.
- Addition of drugs like TEA and quinine increases the secretion of insulin from beta cells.

The already existing models that I studied did not take into account all the parameters that are present in a living cell. So there is always a scope for improvement to make the models more realistic. For example: in the beta cells, the source of calcium ions in the Chay Keizer models was just the extracellular, but that is practically not true. There are many other sources of calcium ions like ER, mitochondria, etc. within the cell. The more recent models do take care of some of these parameters.

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