Dynamics of HH Model for Excitable Neuron with Added Voltage Gated Calcium Channel

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ABSTRACT
Hodgkin and Huxley conducted Voltage Clamped experiments to study mechanism for generation of action potential in giant Axon of Squid and proposed a simple mathematical model. Their model remains basis for understanding electrical activities in excitable neurons even today. Looking back at their work after six decades certain inadequacies are observed in the proposed model. One of limitation was that whole mechanism was expressed using only Na and K ions, role of other ions like Ca, Mg and Cl were not considered. Calcium is the most common ion available in all most all cells, behaviour of which was not understood by then. However with information available now we proposed a simple extended model which includes calcium current in HH model. The extended model is used to study affects of calcium current on action potential and at the same time also to prove that HH model remains stable and can generate self-sustaining regenerative action potential spikes even with added Ca current.

General Terms
Hodgkin Huxley model, Excitable neurons.

Keywords
Voltage clamp, Axon, Action potential, Mathematical model, Calcium current.

1. INTRODUCTION

1.1 Neural Communication and Action Potentials
In order to communicate neuron need to transmit information both within the neuron and from one neuron to the other. This process utilizes both electrical signals and chemical messengers. The dendrites of neurons receive information from sensory receptors or other neurons in the body. This information is then passed to the cell body and on to the axon. Once the information has arrived at the axon, it travels down the length of the axon in the form of an electrical signal known as action potential.

An action potential is an explosion of depolarizing current which travels along the cell. For an action potential to occur, the depolarization must cause a minimum threshold voltage. Action potentials are generated only as an 'all-or-none' response. This means that action potentials do not vary in size and will not occur if threshold voltage is not reached. Action potential is a short-lasting event where the electrical membrane potential of a cell rapidly rises and falls, following a consistent trajectory.A neuron that emits an action potential is said to "fire". Once an electrical impulse has reached the end of the axon, the information must be transmitted across the synaptic gap to the dendrites of the adjoining neuron. In some cases, the electrical signal can instantaneously bridge the gap between the neurons and continue along its path. In other cases, neurotransmitters are needed to send the information from one neuron to the next. Neurotransmitters are known as chemical messengers that are released from the axon terminals to cross the synaptic gap and reach the receptor sites of other neurons. In a process known as reuptake, these neurotransmitters attach to the receptor site and are reabsorbed by the neurons to be reused.

1.2 Historical Perspective
The conception that information is conveyed by sequences of action potentials (spike trains) has resulted from more than 100 years of neurophysiologic investigation. It involves both the relation of action potentials to behavior, and an explicit, detailed understanding of how action potential works. The latter is the triumph of the Hodgkin-Huxley model. Some of the findings on time line are as follows-

Signals are transmitted from one neuron to another across synapses (Sherrington, 1897).

Action potentials are not graded in intensity; they are "all or nothing" (Adrian, 1926).

Substantial information is contained in the neuronal firing rate (Adrian, 1926; Hubel and Wiesel, 1962; Evarts, 1966).

Action potentials result from the flow of ions across excitable membranes. Membranes can be electrically excitable (Bernstein, 1902; based on Nernst, 1888).

Ion channels gate the flow of ions across membranes (Cole and Curtis, 1939).

Sodium ions (in addition to potassium ions) are involved in action potential generation (Hodgkin and Katz, 1949).

Action potential generation may be described quantitatively using voltage-current-capacitance relationships, and voltage-dependent conductance of distinct ions (Hodgkin and Huxley 1952).

Successes of Hodgkin Huxley model can be manifested as, 150-year-old problem of "animal electricity" solved, correct predictions of conductance, form of action potential, including "undershoot"

Their model, which was developed well before the advent of electron microscopes or computer simulations, was able to give scientists a basic understanding of how nerve cells work without having a detailed understanding of how the membrane of a nerve cell looked like on the micro scale. They even did not know about the details of ion channels and ion pumps in the membrane.

2. HH MODEL
The Journal of physiology in 1952 presented a series of papers that would forever change the relationship between mathematics and physiology. Alan Lloyd Hodgkin and Andrew Huxley authored a series of five papers describing the nonlinear ordinary differential equations that model how action potentials can be initiated and propagated through an axon. Nobel Prize for physiology and medicine was awarded

to Hodgkin and Huxley in 1963, for their ground-breaking research on the squid giant axon. The Hodgkin Huxley model for the generation of the nerve action potential is regarded as one of the most successful mathematical models of a complex biological process that has ever been formulated till date. The basic concepts expressed in the model have proved a valid approach to the study of bio-electrical activity from the most primitive single-celled organisms such as Paramecium, to the neurons within our own brain.

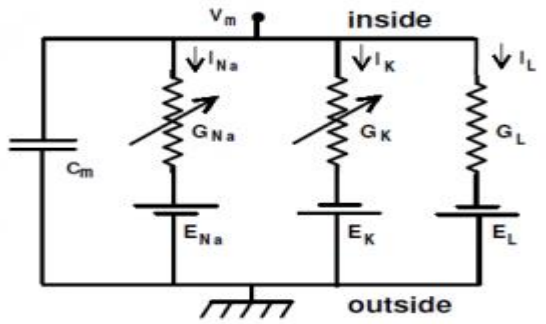


Figure 1. Equivalent electrical circuit of HH Model

The starting point of the HH model is the equivalent electrical circuit of a cellular compartment as shown in Figure 1. There were three types of ionic currents in the circuit, a sodium current, INa, a potassium current, IK, and a current that Hodgkin and Huxley described as the leak current, IL, which is mostly made up of chloride ions. The sodium and potassium conductance are variable depend on voltage. Since their properties change with the voltage across them, they are treated as active rather than passive elements. The voltage-dependence of ionic conductance is incorporated into the HH model by assuming that the probability for an individual gate to be in the permissive or non-permissive state depends on the value of the membrane voltage.

The equation that corresponds to the equivalent electrical circuit is

$$I = Ic + Ii = Cm\ dV/dt + Ii$$

The total ionic current Ii is the sum of sodium, potassium and leak currents

$$Ii = INa + IK + IL$$

The magnitude of each type of ionic current is calculated from the product of the ion's driving force (the difference between the membrane potential and the equilibrium potential of that ion, i.e. the sodium driving force is V – ENa) and the membrane conductance for that ion.

$$INa = gNa\ (V - ENa)$$

$$IK = gK\ (V - EK)$$

$$IL = gL\ (V - EL)$$

where the sodium, potassium and leak conductance are gNa, gK and gL respectively and ENa, EK and EL are the corresponding equilibrium potentials. In the final paper of the series, Hodgkin and Huxley inserted their expressions for the three ionic currents into the membrane equation to give a description of how the membrane potential in a small region of squid giant axon changes over time.

$$Cm\ dV/dt = -GL\ (V - EL) - GNa\ m^3h\ (V - ENa) - GK\ n^4\ (V - EK) + I$$

where Iis the local circuit current and Gl, GNa and GK are maximum conductance for the specific ions. When this equation is put together with the differential equations for the gating variables m, nand hand the expressions for the rate coefficients, the resulting set of four ordinary differential equations forms the HH model.

Complete Hodgkin–Huxley model is described by following equation for the membrane current by summing up the various currents in the membrane, including spatial spread of current from local circuits.

$$Cm\ \partial V/\partial t = -GL\ (V - EL) - GNa\ m3h\ (V - ENa) - GK\ n4\ (V - EK) + d/4Ra * \partial^2 V/\partial x^2$$

Under space clamp conditions, i.e. no axial current:

$$Cm\ dV/dt = -GL\ (V - EL) - GNa\ m3h\ (V - ENa) - GK\ n4\ (V - EK).$$

Sodium activation and inactivation gating variables

$$dm/dt = \alpha_m (1-m) - \beta_m m$$

$$dh/dt = \alpha_h (1-h) - \beta_h h$$

$$\alpha_m = 0.1 * V + 40/\ [1 - \exp\ (-(V + 40)/10)]$$

$$\alpha_h = 0.07\ \exp\ (-(V + 65)/20)$$

$$\beta_m = 4\ \exp\ (-(V + 65)/18)$$

$$\beta_h = 1/\ [\exp\ (-(V + 35)/10) + 1]$$

Potassium activation gating variable

$$dn/dt = \alpha_n (1-n) - \beta_n n$$

$$\alpha_n = 0.01 * V + 55/\ [1 - \exp\ (-(V + 55)/10)]$$

$$\beta_n = 0.125\ \exp(-(V + 65)/80)$$

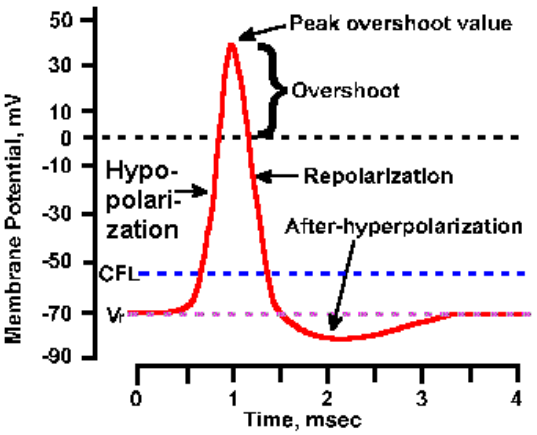


Figure 2. A typical waveform of action potential

3. METHOD AND MATERIAL

In order to predict how the membrane potential changes over time, the complete system of coupled non-linear differential equations comprising the HH model has to be solved. Model representing more complex neurons requires a set of equations which contain more than sodium and potassium conductance. This can be achieved by including in the same equivalent electrical circuit any number of trans-membrane conductance in series with a voltage source for representation of new ionic

currents. The voltage dependence of conductance may be characterized by the Hodgkin Huxley formalism, if the independent gating particle approach is deemed accurate enough.

The overall simulation was performed using MATLAB. A simple model of HH neuron was simulated and tested for generation of action potential. Minimal calcium current, corresponding to conductance of a cell (maximum Ca conductance 0.116 mS cm $^{-2}$) was included in the model and properties of action potential are than compared with the original model. Calcium current increased twenty fold, in stapes of one and all the parameters were studied, with reference to induction as well as increase in calcium current.

4. CALCIUM CHANNELS - TYPE AND BEHAVIOR

Ionized calcium is the most common signal transduction element in all of biology. Calcium is required for survival of cells yet an excess of calcium ions can result in to cell death. Calcium channels allow passage of Ca^{2+} ions into the cytoplasm through selective pores which are opened in response to depolarization of the cell membrane. The calcium flux creates a net inward, depolarizing current and the resulting accumulation of calcium ions in the cytoplasm can act as a chemical trigger for secretion of hormones and neurotransmitters, contraction of muscle and a variety of other calcium sensitive events. Sensing membrane potential changes, calcium channels simultaneously generate an electrical signal while directly creating an intracellular chemical messenger. This dual ability is unique among the family of ion channels and allows the calcium channels to play a variety of roles in excitation-secretion and excitation-contraction coupling. It has now become clear that versatility of function is reflected by diversity of the types of calcium channels on the membrane of individual cells and multiple calcium channel type are common in many cells. In addition to producing the action potential they also evoke increases in intracellular calcium used for intracellular signaling.

Voltage-gated calcium channels were first identified by Fatt and Katz (1953). All excitable cells express voltage-dependent calcium channels. It was discovered later that there are different channel subtypes in excitable cells and, consequently, voltage-gated calcium channels were classified and named according to various schemes. In general, these calcium channels inactivate very little during a maintained depolarization and close (deactivate) very quickly after repolarization. Voltage-gated calcium channels mediate calcium influx in response to membrane depolarization and regulate intracellular processes such as contraction, secretion, neurotransmission, and gene expression in many different cells. Calcium channel activity is essential to couple electrical signals in the cell surface to physiological events in cells.

4.1 Calcium Currents

Calcium currents recorded in different cell types have diverse physiological and pharmacological properties, and an alphabetical nomenclature has evolved for the distinct classes of calcium currents. There are ten voltage-gated calcium channel families that have been characterized in mammals, and they serve distinct roles in cellular signal transduction. Depending on the functions, calcium channels can broadly be divided in three main groups namely L, T and N type [4].

L-type or long lasting calcium currents was for many years the only known calcium current, require a strong depolarisation for activation. They are the main calcium currents recorded in muscle and endocrine cells, where they initiate contraction and secretion. T-type or transient calcium currents are activated by weak depolarisation. They are expressed in variety of cell types, where they are involved in shaping the action potential and controlling patterns of repetitive firing. This T-like activity would remain inactive at all times except during the after hyper-polarization that follows a burst of action potentials and it is said that this conductance helped control the duration of the inter burst interval. A burst of such spikes is terminated when the accumulation of intracellular calcium sufficiently activates a calcium dependent potassium conductance. The after hyper-polarization caused by the increased potassium conductance would unmask these T-type channels which reprime excitability and help trigger the next burst. Thus, T-type channels would play a crucial electrical role in neuronal coding. N type channels are channels neither L nor T type, serve a neuron-specific function since they have only been demonstrated in nerve.

5. MODELLING Ca CURRENT

Activation mechanism of all type calcium channels is similar to that of sodium channel. Ca channels activate during depolarization phase of action potential and inactivate very little and very slowly thus can essentially be considered "noninactivating," for the duration of action potential. This approximation does not affect the model outcome significantly while retaining simplicity of the model. All type of calcium currents are clubbed together for the purpose of simulation. The data indicate that the gating of calcium channels is based on principles similar to the gating process in sodium channels as described by Hodgkin & Huxley, thus can be modelled using general equation described below.

$$Ica = m^{I} (V,T) h^{j} (V, T) G_{ca} (V_m - E_{ca})$$

Where I and j are integers, can be decided by best fit and G_{ca} being maximum conductance.With added calcium current the HH model equation will become

$$I\ ion = G_{Na} m^3 h (V_m - E_{Na}) + G_K n^4 (V_m - E_K) + G_L (V_m - E_L) + m^{I} (V,T) h^{j} (V, T) G_{ca} (V_m - E_{ca})$$

Assuming channel to be non inactive and opting values of m from 1 to 4 it is found that m = 2 fits best to the experimental results [9]. The sodium time constant are retained for calcium current also. With these simplification the equation becomes

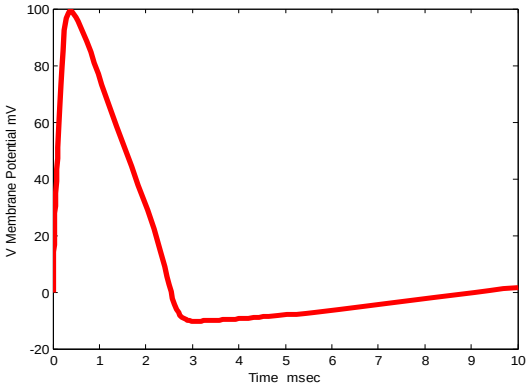
$$I\ ion = G_{Na} m^3 h (V_m - E_{Na}) + G_K n^4 (V_m - E_K) + G_L (V_m - E_L) + G_{ca} m^2 (V_m - E_{ca})$$

6. RESULTS

Simulation was done firstly for simple model using equations of original HH equations and tested for ability to generate action potential and gating behavior. Figure 3 shows the results of simulation. Subsequently simulation was generated for proposed extended model with added calcium current. Various features of action potential were than compared between original and extended model.

6.1 Shape, Pattern and Peak Amplitude

Comparison of result indicates that action potential in depolarization and repolarisation phase remains identical indicating that added calcium current does not affect the shape. model rise faster than that of original model indicating short inter spike interval and earlier readiness of neuron to generate next action potential. Peak amplitude of spikes also reduces marginally.



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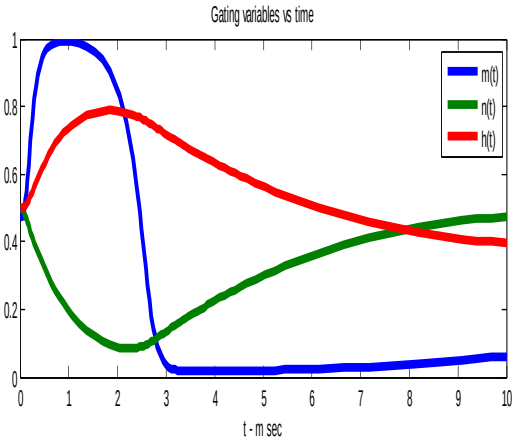

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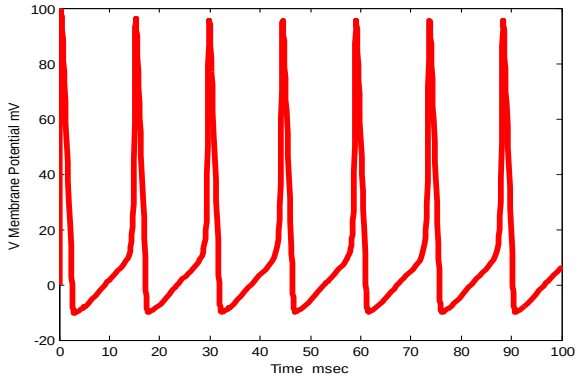


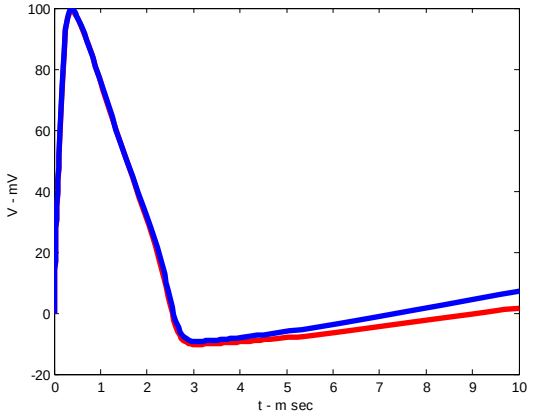
(c)

Figure 3. Simulation of original HH model (A) Action potential (B) Gating particle behavior and (C) Spike train.

This reduction vanishes and peak amplitude becomes identical with that of original model when calcium current is increased. Figure 4 illustrates the comparison of simulations.

6.2 Gating Behavior

Figure 5 shows gating behavior of extended model. Comparison with Fig. 3 (B) reveled that though the general behavior of extended as well as original model remain same, behavior of gating variable m remain unchanged whereas n & h gating particles attain their steady state value slower in extended model.



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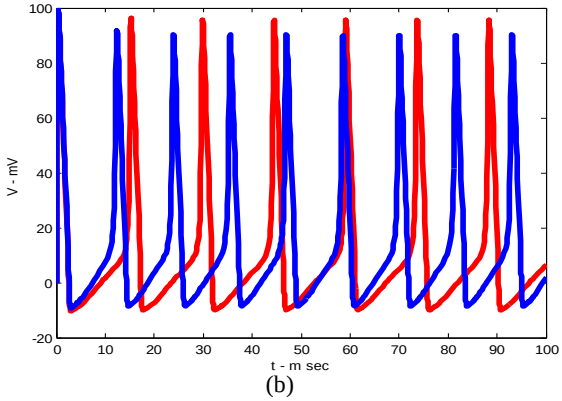

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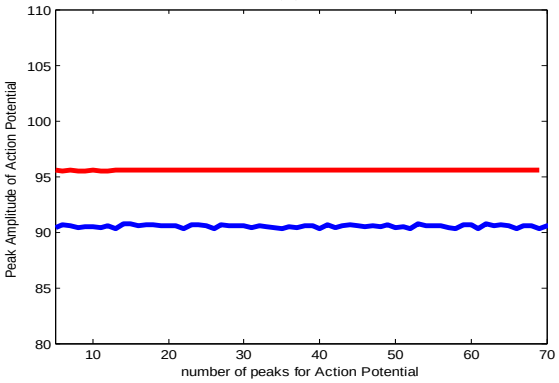

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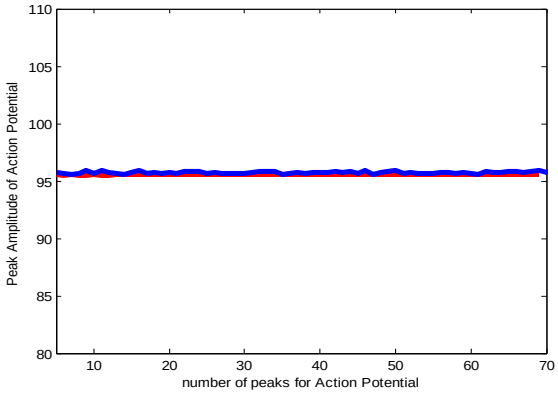

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Figure 4. Comparison of original and extended HH model simulations. (A) Shape (B) Pattern (C) Peak amplitude (D) Peak amplitude with increased calcium current

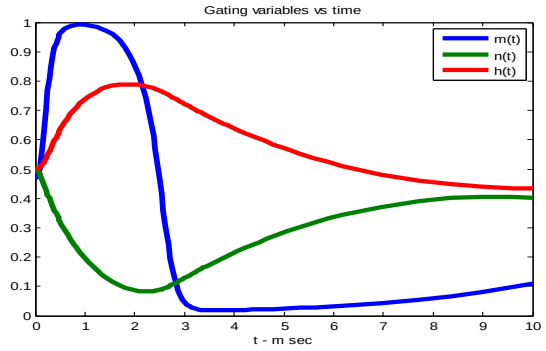
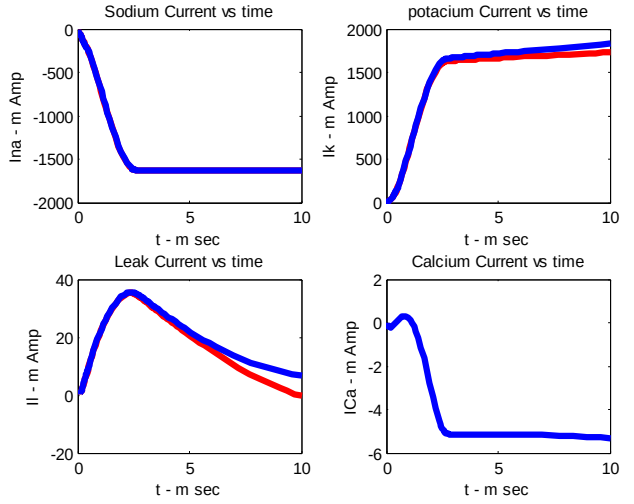


Figure 5. Gating behavior of extended model

6.3 Current Dynamics

Analysis of results obtained through simulation indicates that sodium current does not get affected by induction of calcium current. However potassium and leak currents increased marginally with added calcium current and the margin increases with increase in calcium current. Similar effects were observed when currents were plotted against membrane potential as shown in Figure 6. .



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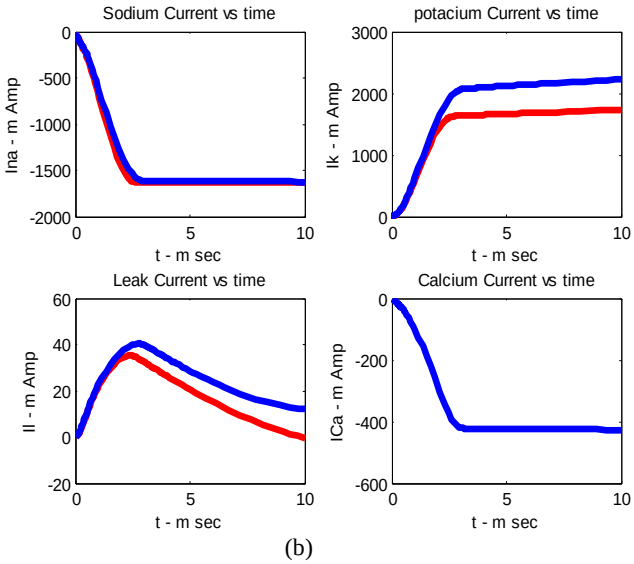

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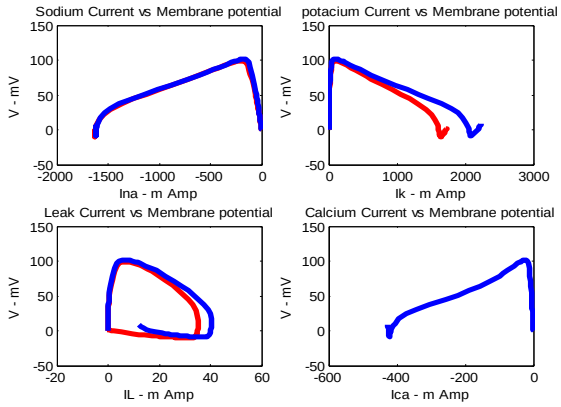

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Figure 6. Comparison of currents of original model with extended model (A) With minimum calcium current (B) With increased calcium current (C) Variation of currents with membrane potential

6.4 Frequency & Enter Spike Interval of Action Potential

Frequency of action potential is compared in Figure. 7. It is evident that with added calcium current in extended model frequency increases and inters pike interval reduces. The increase in frequency is proportional to increase in calcium current. Thus it can be said that calcium current can be responsible for controlling frequency of action potential in excitable neurons.

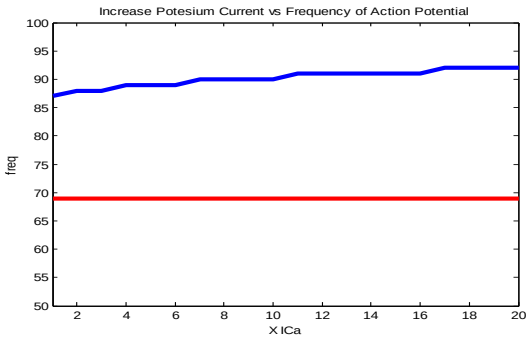

Figure 7. Comparison of action potential frequency in original and extended models, with increasing calcium current

7. CONCLUSION

Calcium currents during action potentials have important roles in determining action potential shapes and firing patterns or frequency. Calcium currents generally make little contribution to the rising phase of action potentials because of their activation kinetics. Calcium channels typically begin to be activated near the peak of the action potential and calcium currents are largest during the falling phase, typically greatest in the later stages of the repolarization and results in a broadening of the action potential. HH model proved to be stable and robust, overall stability and ability to generate sustained action potential spikes is not affected with added calcium current. Nominal calcium current has no significant change in the generation of action potential. However increase in calcium current reduces the inter spike interval thus increasing the frequency of action potential. Results of our simulation suggest that HH model can be successfully used to model neurons with more currents than voltage gated sodium and potassium channels.

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