Simulation of Voltage Change Effects in Ion Channels in order to Reproduction of Action Potential by MATLAB Software

Mostafa Mohammadi, Alireza Kashani Nia

Abstract: - In this study, the effects of voltage change in ion channels in order to reproduction of action potential and its simulation by Hodgkin Huxley model have been explored . The simulation has been performed by using the Matlab software . By writing Hodgkin Huxley equations codes and applying the parameters values of it , action potential waveform to obtain. Then by reducing the amount of excitation current, the lowest value that the action potential is placed on the eve of the production will be obtain. The next step is to stabilize the input excitation current to the value obtained and then change the sudiom , potasiom and leakage channels voltage. According to the characteristics of each ion channels and voltage variations on them, action potential will start to reproduce. Thus we have shown, with the decline of the excitation current for reasons such as some illness, we can reproduce the action potential and propagate it inside of axon by changing the ion channels voltage.

Keawords*: *Action potential, Axon, Hodgkin Huxley model, Excitation current, Matlab simulation.

I. INTRODUCTION

Myelin is a substance lipoprotein around the some axons to form a discontinuous covering sheath. On the other hand, the same substance that causes the white color of the brain, spinal nerves and some areas. The myelin sheath is a layer that is formed on the long axons. The main role of the myelin sheath, cause an insulator on the surface of the axons that increases the speed of electrical signals along the axon. In addition to the rapid transfer of myelin nerve impulses along nerve fibers, it also has a duty to protect nerve cells. The areas in axon that lacking of myelin sheath is called Node of Ranvier that the nerve impulses are transmitted by action potentials through these nodes. When the myelin sheath is destroyed as a result of some diseases, the input excitation current is reduced and even in some cases generally disappears. As a result, Action potential can not be released into the axon and transmit nerve impulses, therefore we organs will not be able to execute commands. Hence, we consider the minimum excitation current that the action potential is in eve of the generation and then start to change the ion channels voltage. With this method, the action potential was produced again and propagated inside of axon.

II. ACTION POTENTIAL

When the membranes of neurons is stimulated,a bioelectric change that occurs in the nerve membrane and propagate from the stimulation site to other parts of the nervous fiber. This phenomenon is called action potential. In other word, the action potential occurs on a excitable membranes of nerve cells, over the length of the axon and has the task of messaging .

Each action potential start with suddenly change in negative natural potential (rest mode) to positive potential of memrance and come back with the same speed in the negative mode and ends[1]. To convey a message of nerve, action potential travels along the nerve fibers to reach the nerve endings. The successive stages of the action potential are as follows.

A. Resting stage

This is the resting membrane potential before the action potential begins. The membrane is said to be polarized during this stage because of the –70 millivolts negative membrane potential that is present [2].

B. Depolarization stage

At this time, the membrane suddenly becomes very permeable to sodium ions, allowing tremendous numbers of positively charged sodium ions to diffuse to the interior of the axon. The normal polarized state of –70 millivolts is immediately neutralized by the inflowing positively charged sodium ions, with the potential rising rapidly in the positive direction. This is called *depolarization*. In large nerve fibers, the great excess of positive sodium ions moving to the inside causes the membrane potential to actually overshoot beyond the zero level and to become somewhat positive. In some smaller fibers, as well as in many central nervous system neurons, the potential merely approaches the zero level and does not overshoot to the positive state [2].

C. Repolarization stage

Within a few 10,000ths of a second after the membrane becomes highly permeable to sodium ions, the sodium channels begin to close and the potassium channels open more than normal. Then, rapid diffusion of potassium ions to the exterior re-establishes the normal negative resting membrane potential. This is called *repolarization* of the membrane [2].

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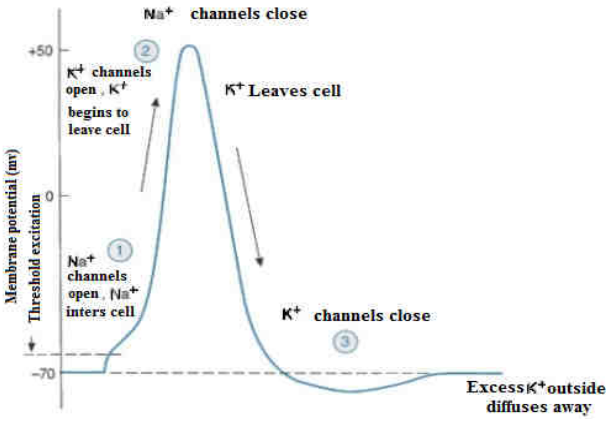

Fig1. Ion Flow in Action Potential [3]

III. HODGKIN HUXLEY MODEL

In 1952 , Hodgkin and Huxley provided a mathematical model to explain how to start and the distribution of the action potential in neurons that includes a set of non-linear ordinary differential equations that approximation the electric properties of excitable cells, such as neurons and cardiac muscle cells . Hodgkin and Huxley by presenting this model, received the nobel prize in physiology and medicine in 1963[4].

Hodgkin Huxley model made by electronic components such as resistors and capacitors is shown in the following figure. Each components of a cell irritable with a physical component is shown[5]. Lipid layer is shown as a capacitor. voltage ion channels shown with a resistance that they can be based on a nonlinear conductor, in other word can be said the conductivity depends on the time and voltage, which indirectly through voltage channels gate proteins have relation to the possibility of the opening of each that is proportional to the voltage.

Leakage channels have been shown with a resistance that It can also be indicated by a linear conductivit. Electrochemical gradient that causes a flow of ions with a battery E is also shown. V_m is the membrane potential that the difference between the internal and external potential.

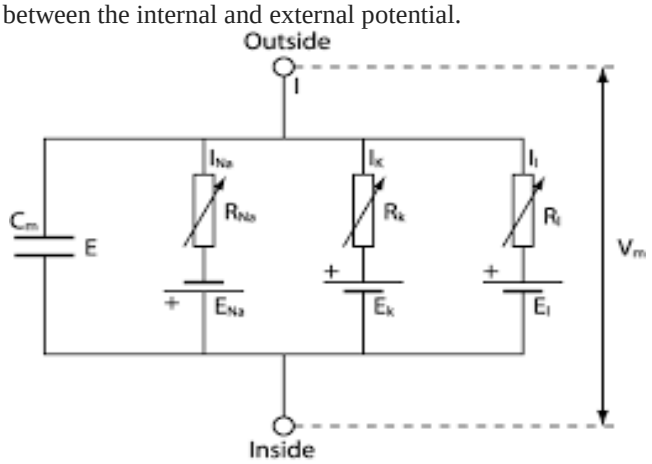

Fig2. Schematic diagram for the Hodgkin-Huxley model [6]

Also they were modeled the currents influences on the production and propagation the action potential. these current is as following [7] :

Sodium channel current (I_{na})

Potassium channel current (I_k)

Leak channel current (I_{leak})

Capacitive current (*Ic*)

According to the Hodgkin and Huxley model, each of these channels acts independently and carries only a specific type of ions. In other words, a sodium channel can only transport sodium ions. A leak channel on the other hand, does not have selective permeability and therefore, different types of ions can move through it. And finally, capacitive current is a current through the phospholipid bilayer of an excitable cell [8]. Ionic potential for sodium, potassium and chloride ions are known Nernst voltages to be obtained through the following equations :

$$V_{Na} = -\frac{RT}{ZF} Ln \frac{Ci,Na}{Co,Na} \quad (1)$$

$$V_K = -\frac{RT}{ZF} Ln \frac{Ci,K}{Co,K} \quad (2)$$

$$V_{Cl} = -\frac{RT}{ZF} Ln \frac{Ci,Cl}{Co,Cl} \quad (3)$$

Ci and Co values respectively in the above equation represent the concentration of ions inside and outside the cell and the value of the parameter Z in sodium and potassium ions is equal to 1 and in the chloride is equal to -1.

Since the channel leakage passage of the small number of ions from the inside to the outside and vice versa , That's why it can be considered constant leakage conductance channel and along the channel voltage leakage can be assumed to be constant. Therefore, the total ion flow at rest is zero. Since the conductivity of the membrane to sodium and potassium is a function of voltage through the membrane , when V_m=V_{Na} ,there is no flow of sodium and sodium flow is equal to zero and when $V_m = V_K$, there is no potassium current and potassium currents is equal to zero . Channel conductance are obtained from the following equation :

$$g_{NA} = \frac{I_{NA}}{V_m - V_{Na}} \quad (4)$$

$$g_K = \frac{I_K}{V_m - V_K} \quad (5)$$

$$g_L = \frac{I_L}{V_m - V_L} \quad (6)$$

In the above equations , the unit is equal to [$\mu A/Cm^2$].

The general equation is the sum of the currents flowing through all channels and membrane capacitance is as follows :

$$I = C_m \frac{dV_m}{dt} + g_k (V_m - V_k) + g_{Na} (V_m - V_{Na}) + g_l (V_m - V_l) \quad (7)$$

Table1. Hodgkin Huxley equations parameters and their definition .

Parameters	describtion
I	total current of membrane [$\mu A/Cm^2$]
C_m	Membrane capacitance F/Cm^2
V_m	Membrane voltage[mv]
g_{Na}, g_K, g_l	channels conductance[$mmho/Cm^2$]
V_{Na}, V_K, V_l	nernst voltage[mv]

A. Voltage gated sodium channel

Sodium ions cross the cell membrane via voltage gated sodium channels. Sodium ion equilibrium is achieved when

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the condition $V_m = V_{Na}$ is satisfied. At the sodium equilibrium potential there is no net movement of sodium ions across the cell membrane because for each sodium ion that moves into the cell by diffusion, exactly one sodium ion moves out of the cell due to the electrostatic gradient. Therefore, the net current of sodium during this state is 0 (I_{Na} = 0). Any deviation from this state ($V_m \neq V_{Na}$) will result in a non-zero current in the sodium channel. According to Ohm's Law the current in a sodium channel is equal to [8] :

$$I_{Na} = g_{Na}(V_m - V_{Na}) \quad (8)$$

Hodgkin Huxley model is based on the assumption that sodium channel activation is based on the parameter m can be opened and closed. Parameter m sodium channels has allowed the state when the channel is open and unregulated mode when the channel is closed. The other parameter is called h can be used to disable the channel. In other words, the parameter h represents the active mode and (h-1) idle mode and just have one condition is described.Thus,the relationship between sodium conductivity and parameters m and h are as follows :

$$G_{Na} = g_{Na_{max}} - m^3.h \quad (9)$$

Where , $g_{Na_{max}}$ is maximum conductivity of sodium channels. Activation of sodium channels are expressed as the following equation :

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m \quad (10)$$

Inactivation of sodium channels are expressed as the following equation :

$$\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h \quad (11)$$

Alpha and beta coefficients transmission rate depend on the voltage and independent of time.

B. Voltage Gated Potassium Channel

Potassium ions cross the cell membrane via voltage gated potassium channels. The equilibrium for potassium ions is achieved when $V_m = V_K$. During this state, there is no potassium current going through the cell membrane (I_K= 0). Any deviation from this state ($V_m \neq V_K$) will result in a non-zero current in the potassium channel. According to Ohm's Law, the current in a potassium channel is equal to [8]:

$$I_K = g_K(V_m - V_K) \quad (12)$$

Hodgkin Huxley model is based on the assumption that potassium channel activation is based on the parameter n can be opened and closed. Parameter n potassium channels has allowed the state when the channel is open and unregulated mode when the channel is closed . so, (1-n) indicates the time when the channel is closed. Hodgkin and Huxley for parameter n is assumed that the four conditions for the activation of potassium channels is required to be licensed in each state . Thus, the relationship between the conductivity K and n parameters are as follows:

$$G_K = G_{K_{max}}.n^4 \quad (13)$$

Where, $G_{K_{max}}$ represents the maximum conductance potassium channels. Activation of potassium channels are expressed by the following equation :

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n \quad (14)$$

C. Leak Channel

Different types of ions (e.g. potassium, calcium, sodium) cross the cell membrane via leak channels. Equilibrium in leak channels is achieved when the following condition is satisfied $V_m = V_l$. During this state there is no leak current going through the cell membrane and therefore I_l = 0. Any deviation from this state ($V_m \neq V_l$) will result in a non-zero current in the leak channel. According to Ohm's Law, the current in a leak channel is equal to[8]:

$$I_L = g_L(V_m - V_L) \quad (15)$$

D. Memrane capacitance

Another component that contributes to the total membrane current is the membrane capacitance.

$$I_C = C\frac{dV_c}{dt} \quad (16)$$

IV. SIMULATION

As mentioned, sometimes due to certain diseases and the loss of the myelin sheath, the excitation current to produce an action potential is reduced and isn't longer able to produce action potentials. For this reason, in this section, we first find the least amount of excitation current that the action potential is in eve of the generation. Then By fixing the amount of the excitation current, Changes the voltage of each channel so that the action potential is generated. First, simulate the equations and obtain the general form of the action potential which is as follows:

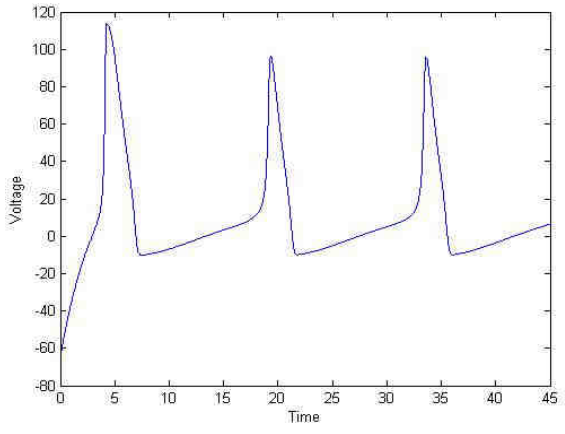

Fig3. Action potential

Now, we examine the excitation current effects and ion channel voltage change to reproduce the action potential.

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A. *The effect of excitation current thrshould*

The excitation cyrrent threshold which is an important factor, in time of the damage to axons is subject to change and to a large extent, its value is close to zero. In this section, with simulation of Hodgkin Huxley equations and change in the amount of excitation current,The action potential waveform is observed.

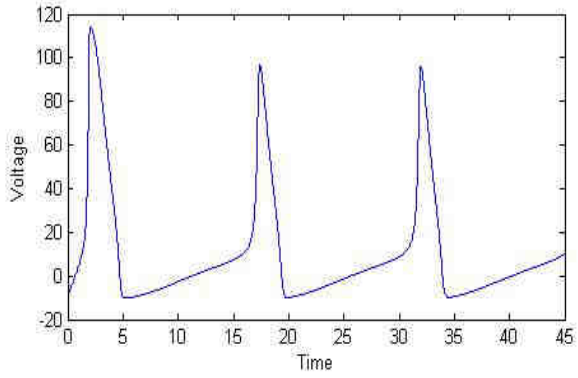

Fig4.action potential with the input excitation current of 10µA

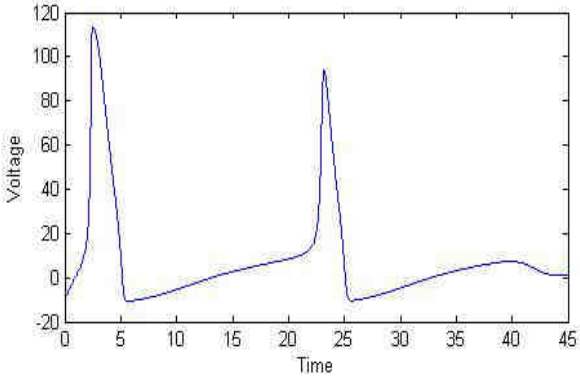

Fig5.action potential with the input excitation current of 5.8µA

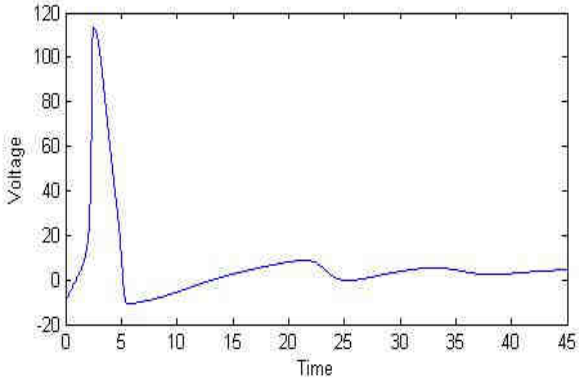

Fig6.action potential with the input excitation current of 5.7µA

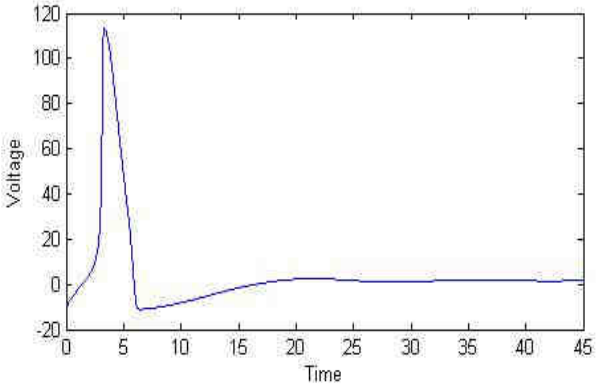

Fig7.action potential with the input excitation current of 2µA

The results show that the excitation current can not be less than 5.7 µA because the waveform will lead to absolute zero. You'll see the waveform in 5.7 µA largely damped but not zero in general and it can be considered as the threshold. So with this amount, nernst voltages can be changed and reproduced action potentials that Our main purpose in this paper. According to the above explanation ,we consider the least of input excitation current is equal to 5.7 µA .

B. *Survey the effect of sodium channel voltage change*

Now with keeping the excitation current amount to 5.7 µA , we see that by changing the sodium channel voltage and to what extent and accuracy can be reproduced action potentials. So we start by changing the sodium voltage .

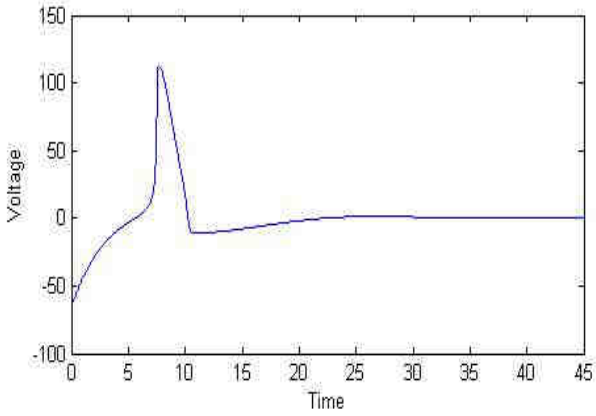

Fig8.action potential when V_{Na} = 50mv

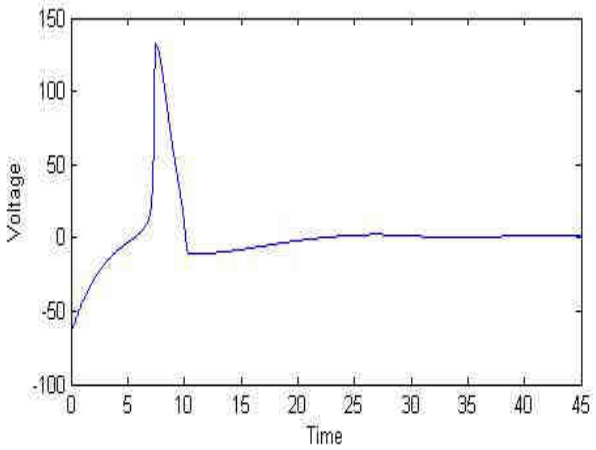

Fig9.action potential when V_{Na} = 70mv

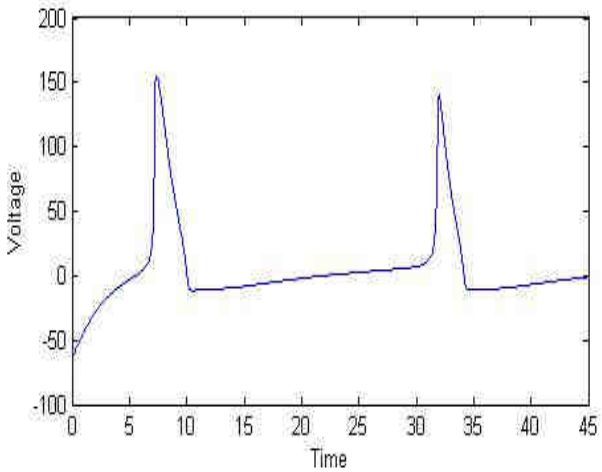

Fig10.action potential when V_{Na} = 93mv

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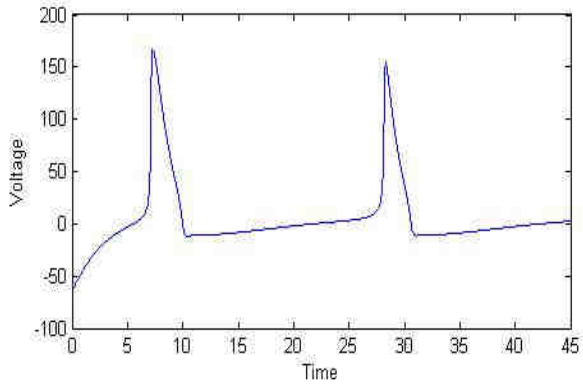

Fig11.action potential when V_{Na} =115mv

The results show that by increasing the sodium voltage from 55mv to 93mv in 5.7µA stimulation current, action potentials begin to produce.

C. Survey the effect of potassium channel voltage change

In this section we consider the effect of potassium channel voltage change in order to reproduce the action potential .

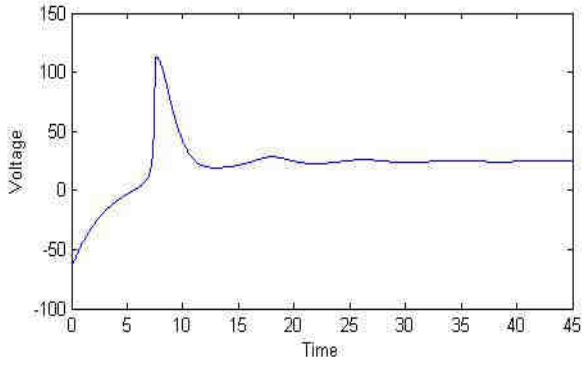

Fig12.Action potential when V_k= - 49mv

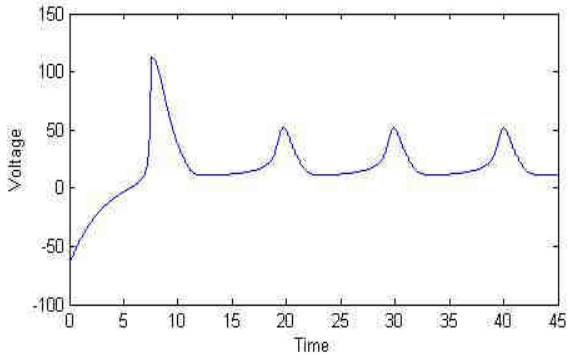

Fig13.Action potential when V_k= - 55mv

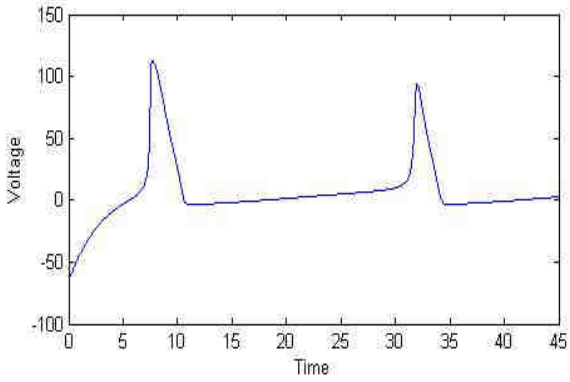

Fig14.Action potential when V_k= - 69mv

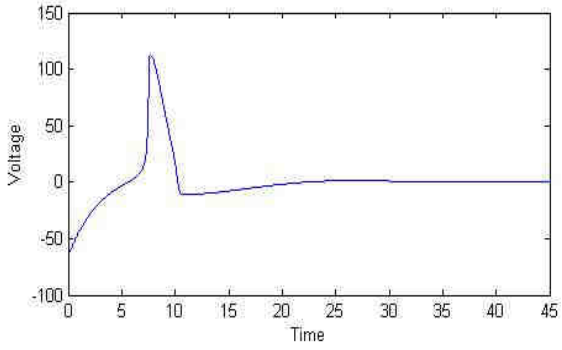

Fig15.Action potential when V_k= - 77mv

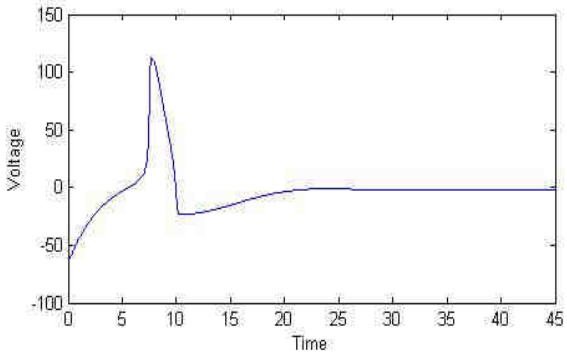

Fig16.Action potential when V_k= - 90mv

The results show that by increasing the potassiom voltage from -77mv to -69mv in 5.7µA stimulation current, action potentials begin to produce.

D. Survey the effect of leakage channel voltage change

In this section we consider the effect of leakage channel voltage change in order to reproduce the action potential.

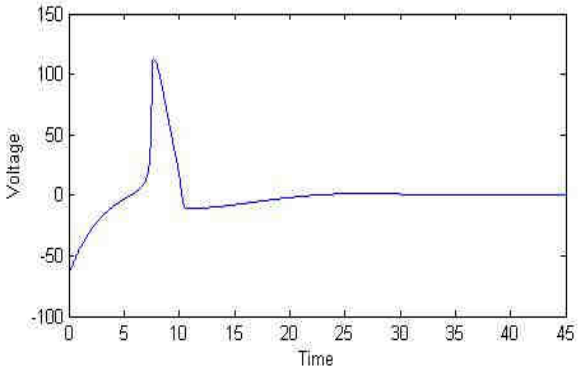

Fig17.Action potential when V_l= - 54.4mv

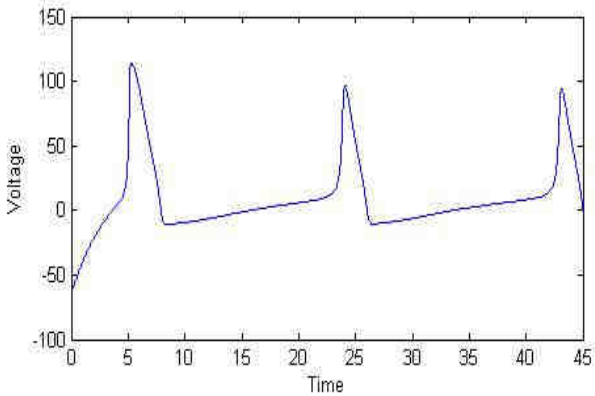

Fig18.Action potential when V_l= - 37mv

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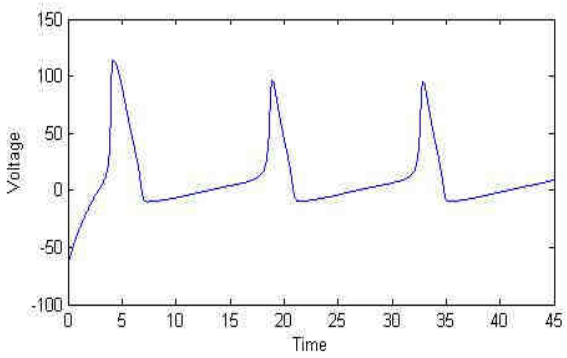

Fig19.Action potential when V_l= - 20mv

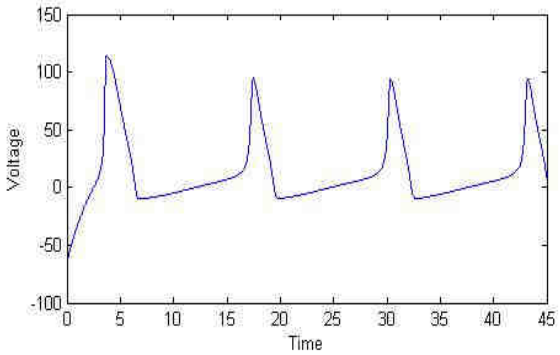

Fig20.Action potential when V_l= - 10mv

The results show that by incrising the leakage voltage from -54.4mv to -37mv in 5.7μA stimulation current, action potential begin to produce.

V. CONCLUSION

In this paper, with simulating of Hodgkin Huxley equations and obtaining a minimum amount of excitation current that may be due to certain diseases is reduced or eliminated, with holding constant the amount of excitation current at the threshold of action potential generation, start to change the voltage of sodium, potassium and leakage ion channels so that we see in what voltages reproduction of action potential is possible. Based on the simulations performed and with voltage change in sodium, potassium and leakage ion channels, respectively at voltage of 93mv, -69mv and -37mv action potential reproduced. Thus in this method , we could reproduce the action potential and propagate it along axon .

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Appendix

Constants for Hodgkin Huxley equations that used in the simulation.

Parameters	Value
V_{Na}	55 mv
V_K	-77 mv
V_L	-54.4 mv
g_{Na}	120 $mmho/Cm^2$
g_k	36 $mmho/Cm^2$
g_L	0.3 $mmho/Cm^2$
C_m	1 F/Cm^2

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