INTRODUCTION

Nerve cells can be found in central nervous system which they start and end in the brain and in peripheral nervous system which they start from the brain and can extend to the tip of the finger in the human body. Sensory neurons carry information to the brain while motor neurons carry the response of the brain to the effector organ. This communication is occurred through the synapses and in here, chemical energy turns into electrical energy when there is an action potential which is enough to create an impulse in the neuron[1]. For this, ions should create the action potential by moving through the cell membrane due to the chemical and electrical gradient. When cell is in its resting state, Na^+ gradient is higher in outside. A stimulus causes Na^+ channels to open and inside becomes more positive. This phase is called as depolarization. Then, as a result of inside is being more positive, K^+ channels are opened and outside becomes more positive and this phase is called repolarization. Due to these changes, cell membrane reaches its resting membrane potential again.

Modeling this event in neurons is very important in biomedical engineering to shed light on the causes or cures of various neural diseases or designing prosthetics. To model this, by using Nernst equation, potentials of ions can be reached and these are used to generate the membrane potential. This chemical system can be assumed as electrical system which results as Hodgkin-Huxley model[2]. This model consists of an RC circuit which aims to find the solution of first-order, linear, non-homogeneous differential equation with constant coefficients. Numerical methods such as Matlab/Simulink are useful to solve this equation and they are fast for users.

MATERIALS and METHODS

In the electrical system, the independent variable is charge (q) which is stored by capacitance, effort variable is potential and motion variable is current. From capacitance formula, it is known that $q = VC$. If both sides' derivative is taken, $\dot{q} = \dot{V}C$, since current is equal to the first derivative of the charge, $I = C\dot{V}$(**Equation 1**). As modeling the variations in action potential in a nerve cell, RC circuit is used where resistance represents the dissipation of energy in the form of heat and capacitance represents the storage of any species as potential. Hodgkin-Huxley model's RC circuit includes resistances of Na^+, K^+ and leakage which comes from leak ion channels and it is represented as it is shown in **Figure 1**. Here, from the Kirchoff's current law, the current of action potential which comes from the external is the sum of the membrane current which goes through the capacitance and the current which continues[3]:

$I_{AP} = I_{membrane} + I_{continues}$, where $I_{continues}$ is equal to $I_{Na} + I_K + I_L$ (I_L is the leakage current).

$I_{AP} = I_{membrane} + I_{Na} + I_K + I_L$, here, **Equation 1** can be applied to $I_{membrane}$:

$I_{AP} = C\dot{V_m} + I_{Na} + I_K + I_L \rightarrow c\dot{V_m} = I_{AP} - I_{Na} - I_K - I_L \rightarrow \dot{V_m} = \frac{1}{c}[I_{AP} - I_{Na} - I_K - I_L]$

From Ohm's law, $V = RI \rightarrow R$ is $\frac{1}{g}$ where g is admittance, $V = \frac{1}{g}I \rightarrow I = gV$.

Potential difference of two points is equal to the multiplication of the resistance between them and the current flows through the wire which connects the points. As it is seen in **Figure 1**, I_{Na} can be written as $I_{Na} = g_{Na}(V_m - V_{Na})$. It can be applied for other currents:

$$\dot{V_m} = \frac{1}{C}[I_{AP} - g_{Na}(V_m - V_{Na}) - g_K(V_m - V_K) - g_L(V_m - V_L)]\text{(**Equation 2**)}$$

Hodgkin-Huxley model includes three gating variables (m, n, h) to measure the probability of channels to be opened at any time[4]. So, the equation becomes:

$$\dot{V_m} = \frac{1}{C}[I_{AP} - g_{Na}m^3h(V_m - V_{Na}) - g_K n^4(V_m - V_K) - g_L(V_m - V_L)]\textbf{(Equation 3)}$$

Simulink can be used to create the model as in **Figure 2**. The three subsystems in **Figure 3** represent each current and their equations. Here, since $\dot{V_m}$ is a first-order differential equation, it can be thought as $\dot{V_m} = -aV_m + b$. To solve this equation in Simulink, an “integrator” block can be used. Since V_m is used for the calculation of each current, it should be fed into the subsystems but subsystems’ outputs should be summed (three of them should be subtracted), which gives the differentiation of V_m. This is fed into the “integrator” block to get the membrane potential. Two additional parameters (α and β) of each current can be generated to solve the gating variables’ equations[5]:

$$\dot{m} = \alpha_m(1-m) - \beta_m m \rightarrow \dot{m} = \alpha_m - \alpha_m m - \beta_m m = -(\alpha_m + \beta_m)m + \alpha_m \textbf{(Equation 4)}$$

$$\dot{n} = \alpha_n(1-n) - \beta_n n \rightarrow \dot{n} = \alpha_n - \alpha_n n - \beta_n n = -(\alpha_n + \beta_n)n + \alpha_n \textbf{(Equation 5)}$$

$$\dot{h} = \alpha_h(1-h) - \beta_h h \rightarrow \dot{h} = \alpha_h - \alpha_h h - \beta_h h = -(\alpha_h + \beta_h)h + \alpha_h \textbf{(Equation 6)}$$

$\alpha_m = 0.1\frac{25-E}{e^{\frac{25-E}{10}}-1}$ and $\beta_m = 4e^{-\frac{E}{18}}$, $\alpha_n = 0.01\frac{10-E}{e^{\frac{10-E}{10}}-1}$ and $\beta_n = 0.125e^{-\frac{E}{80}}$, $\alpha_h = 0.07e^{-\frac{E}{20}}$ and $\beta_h = \frac{1}{1+e^{\frac{30-E}{10}}}$. Here, $E = V_m - V_{rest}$.

In Simulink, same approach as in solving V_m with “integrator” block can be applied to find the gating variables by using **Equation 4, 5** and **6**. Membrane potentials of Na^+, K^+ and leakage can be found by using the Nernst equation[6] which is $V_m = \frac{RT}{zF}\ln\frac{[ion]_{out}}{[ion]_{in}}$. z is equal to “1” for both ions and V_m of each depends on approximately $60(\ln\frac{[ion]_{out}}{[ion]_{in}})$.

RESULTS

Membrane potentials are given as $V_{rest} = -60mV$, $V_{Na} = 50mV$, $V_K = -77mV$, $V_L = -54mV$ according to an experimental data which is generally used for HH model[7]. Also, constants are given as $g_{Na} = 120\frac{mmho}{cm^2}$, $g_K = 36\frac{mmho}{cm^2}$, $g_L = 0.3\frac{mmho}{cm^2}$, and capacitance is given as $C = 1$.

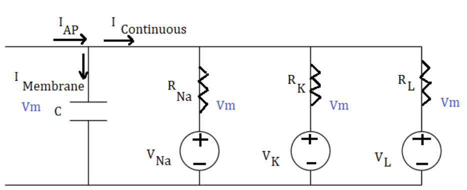

Figure 1. RC circuit for HH model (By me)

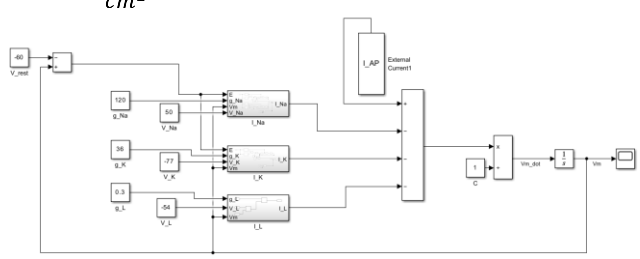

Figure 2. HH model in Simulink

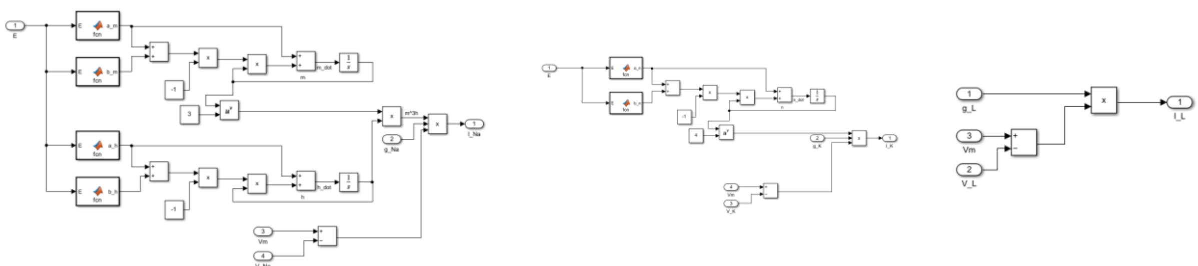

Figure 3. Inside of the subsystems of I_{Na}, I_K, I_L respectively

Current is given with respect to a time which starts from 0 and goes to 250 with increment of "1" and it has a value from 50-250 seconds[8].

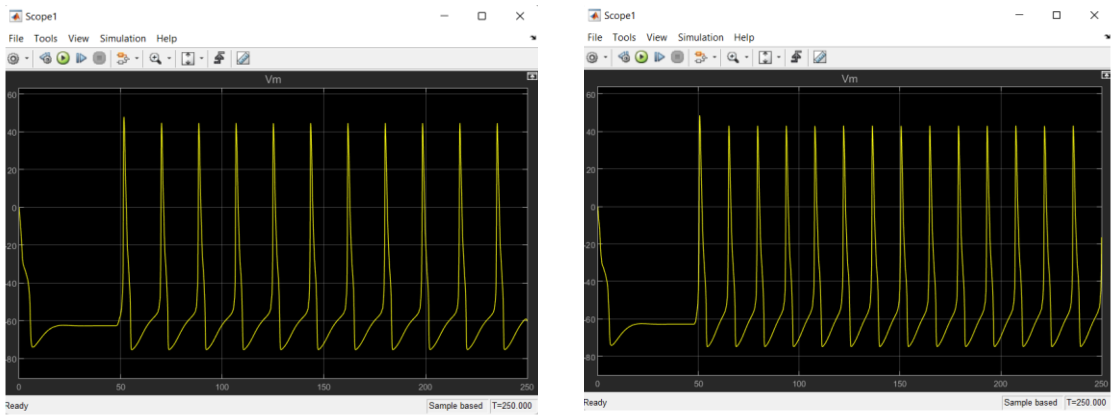

Figure 4. Simulation results of HH model when I_{AP} is given as a multiple of 5 and 10 respectively

DISCUSSION

According to the **Figure 4**, when the resting membrane potential is almost $-60mV$, if a stimulus comes to the cell membrane, the Na^+ channels are opened and transfer of Na^+ ions occurs and depolarization is appeared. This causes concentrations of inside and outside to be changed, so, after a time, K^+ channels are opened and repolarization occurs. If this stimulus is enough to exceed the threshold (it is usually $-55mV$) in the depolarization phase, then action potential is generated. It is reached about $45mV$ as a result of depolarization. At each generation of action potential, the difference between potentials exceeds the resting membrane potential and hyperpolarization occurs. There is no response for any stimulus at that time interval. After some time, it reaches the resting membrane potential again. If the resting membrane potential was given as $-70mV$, the values for potentials of ion channels would be different and membrane potential would be reached to $-70mV$ after repolarization.

As it is seen in **Figure 4**, it can be said that as current value increases, the number of action potential is increased at the same time interval but the magnitude of action potential is not changed. This means, action potential's magnitude is not related to the stimulus, it depends on the frequency information of itself[9]. Giving smaller current values to the model causes no action potential generation since the stimulus with smaller current doesn't have enough effect to start it.

The reason why the first action potential has larger magnitude is that Na^+ channels are faster than K^+ channels. They are rapidly opened and closed and Na^+ ion concentration will be increased in inside until K^+ channels are opened which are slower to effect the membrane potential. Thus, first depolarization occurs in higher magnitude[10].

FitzHugh–Nagumo model is the simplified version of HH model which includes two differential equations to model the action potentials. One of these equations includes a parameter u which is the recovery parameter of neuron to return to its resting state. FHN model is a useful method to express the dynamic behavior of oscillating neurons with parameters[11].

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