MATLAB Implementation of Action Potential Generation

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***Abstract*—Biological characteristics of excitable cell are quite complex and interesting. Understanding these characteristics are fundamental to study on cell structure and its properties. Therefore, it was always an important issue to interpret and simulate excitable cell behavior. Hodgkin Huxley mathematical model is an accurate and easy to understand model which gives insights about behavior of excitable cell. In this documentation a simulation of Hodgkin Huxley mathematical model is presented. Main goal was to observe action potential generation phenomena however, reader might use the simulation to explore other characteristics of cell membrane. Using the simulation, responses to different stimuli is observed and action potential properties such as accommodation, temporal summation are verified. Such simulations of excitable cell may be used for research much earlier than clinical trials.**

Keywords—excitable cell, Hodgkin Huxley model, action potential generation, stimuli, MATLAB, accommodation, temporal summation,

I. Introduction

Quantitative modeling of cell membrane was always a great interest of researchers historically. Because once cell membrane is modeled mathematically, it would be possible to observe and give meaning to various characteristics of cell behavior. However, due to remarkable complex structure of cell and its size limitations, it was not possible to develop accurate models since 1953. In 1953, Alan Hodgkin and Andrew Huxley described the model of squid giant axon which allowed them to receive 1963 Nobel Prize in Physiology or Medicine[1]. On contrary to Goldman Hodgkin Katz and parallel conductance equations, Hodgkin Huxley model was able to differentiate ionic current components not only peak and rest, but during all the time instants. Development of such model was possible using quite intelligent technique, Voltage Clamp technique where transmembrane potential is held constant. It should be noted that, detailed behavior of cell membrane is not complete and still great area of interest since macroscopic to microscopic transition is not fully completed.

In this documentation implementation of Hodgkin Huxley model is described, supported with mathematical background information. After the implementation reaction of the cell to different stimuli is presented revealing some key concepts and properties of action potential generation. Reader may find it useful to have simulation of excitable cell to do research or explore cell characteristics.

II. Theory and Algorithm

In this section, mathematical equations and implementation process will be presented. Mathematical model is based purely on Hodgkin Huxley Model and all equations derived from the book Bioelectricity A Quantitative Approach. Required equation will be presented whenever necessary during description of algorithm.

Fundamental approach while developing the algorithm was to use very small time intervals for variable calculation. For each interval variables were calculated from previous time interval. Finding each variable was quite straightforward since only mathematical description was to be coded.

1. Determining Membrane Current

Spatial uniformity ensures that there is no transmembrane current, therefore total membrane current is equal to stimulus current applied. Assuming stimulus current is applied for T duration,

$$\begin{array}{ll} I_m = 0 & t < 0 \\ I_m = I_s & 0 \le t < T \\ I_m = 0 & T \le t \end{array} \tag{1}$$

When more than one stimulus is applied, of course, membrane current is also not equal to zero. In implemented simulation code, it is possible to change duration of stimulus signal, T, and amplitude of this current signal.

2. Estimating Membrane Voltage Change

According to Hodgkin Huxley Model and well known capacitor voltage equation, differential change in membrane voltage can be estimated as follows

$$\frac{dV_m}{dt} \approx \frac{\Delta V_m}{\Delta t} \tag{2}$$

$$\Delta V_m = \Delta t(I_m - I_K - I_{Na} - I_L)/C_m \tag{3}$$

where

$$\begin{array}{c} I_K = g_K(V_m - E_K) \\ I_{Na} = g_{Na}(V_m - E_{Na}) \\ I_L = g_L(V_m - E_L) \end{array} \tag{4}$$

where the conductivities are

$$\begin{array}{c} g_K = g_{K,max} n^4 \\ g_{Na} = g_{Na,max} m^3 h \\ g_L = g_{L,max} \end{array} \tag{5}$$

Here, initial values of n, m, and h are found using

$$n_0 = a_n/(a_n + b_n)$$
$$m_0 = a_m/(a_m + b_m)$$
$$h_0 = a_h/(a_h + b_h) \quad (6)$$

The values of a and b for all n, m, and h can be found in the book Bioelectricity A Quantitative Approach. It is crucial here to note that, all above values are calculated for time instant i. These time instants correspond to small time intervals, 1 usec for this implementation, and calculated million times for 1 sec of simulation.

3. Estimating Changes in n, m, and h

In this step, changes in n, m, and h are calculated. These calculations are done using current values of a and b. For each cycle a and b values are recalculated using the equations from the book Bioelectricity A Quantitative Approach. While changes are calculating, similar estimation to (2) is utilized.

$$\Delta n = \Delta t(a_n(1-n) - b_n n)$$
$$\Delta m = \Delta t(a_m(1-m) - b_m m)$$
$$\Delta h = \Delta t(a_h(1-h) - b_h h) \quad (7)$$

4. Advancing Through Time

After calculating the changes, next step is to calculate new values for all variables. To do this, changes are added to previous values for n, m, h, and V_m. According to new values, v_m and all a and b values are recalculated.

III. Results

Here results to various stimulus amplitude and duration combinations are presented. The word results mean action potential generation and action potential properties. In technical terms, membrane potential, total membrane current, ion currents, leakage current, and channel conductances are observed with respect to time.

Two main properties of the stimulus signal are crucial while observing outputs of the cell. These are amplitude of the stimulus current and duration of the stimulus current.

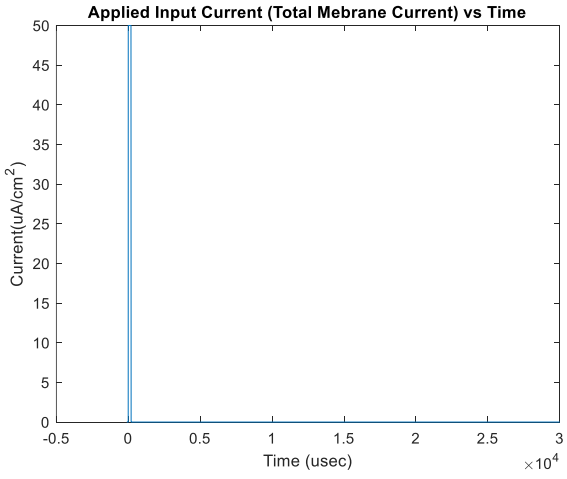

Figure 1: Input Current with duration 200 usec and amplitude 50 uA/cm^2

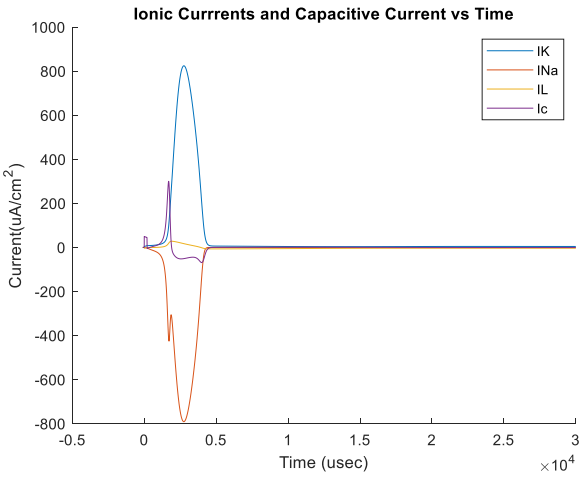

Figure 2: Ionic currents and capacitive current for input in Fig. 1

Typical action potential generation is achieved by and impulse above threshold values shown in Fig. 1. Resultant ionic and capacitive currents are shown in Fig. 2. In this figure it is noteworthy to that I_K and I_{Na} have almost the same shape but opposite polarity. Indeed, for further discharge of the cell such current graph is expected. Also, leakage current is barely varying and capacitive current follows such impulsive path.

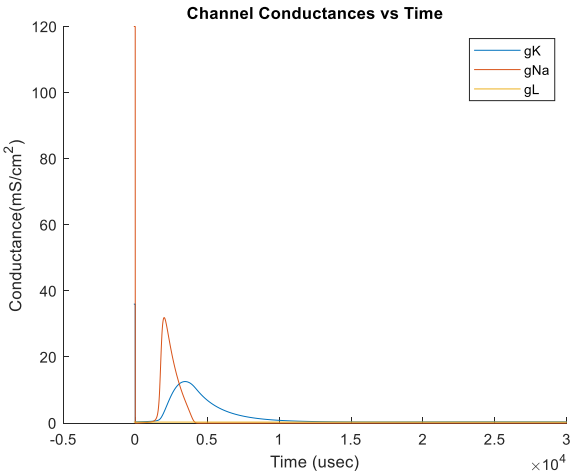

Figure 3: Channel conductances for input in Fig. 1

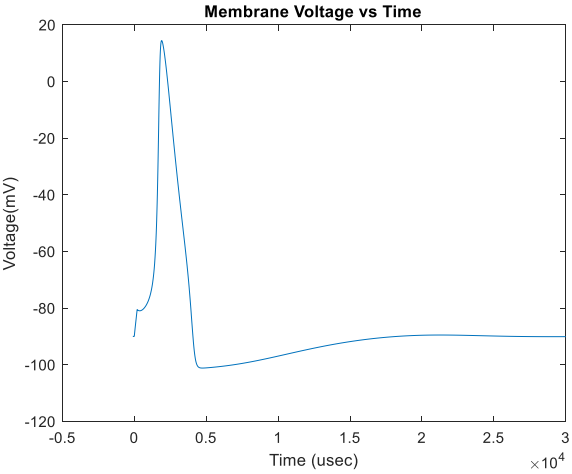

Figure 4: Membrane voltage for input in Fig. 1

Typical action potential shape can be seen in Fig. 4. Due to small time interval dedicated for resting potential it is not clear in the Fig. 4 but for t smaller than zero resting potential is -90 mV and after proper impulse an instant peak is observed. Later, due to remarkable action potential generation, depolarization is further improved by cell membrane itself. Here it is also possible to see the correlation between I_C and V_m since capacitive current is the one discharging the cell.

In addition to action potential generation repolarization overshoot can be observed especially for t bigger than 5 msec. This overshoot than normalizes and membrane potential gets back to its resting value.

It is crucial to have true depolarization configuration for generation of action potential. In Fig. 5 hyperpolarizing stimulus current is applied. As it can be observed from Fig. 6, hyperpolarizing stimulant did not cause activation and action potential generation.

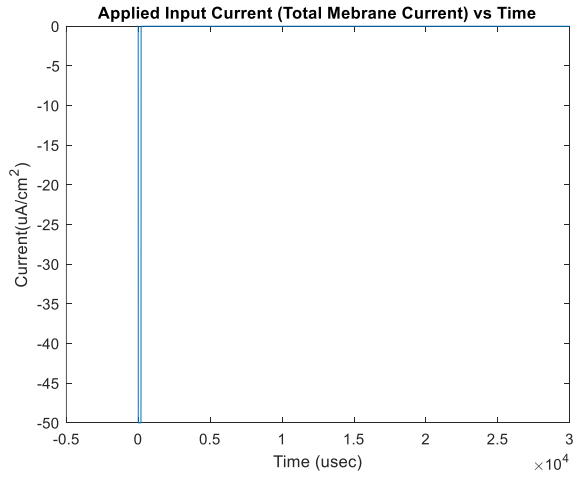

Figure 5: Input Current with duration 200 usec and amplitude -50 uA/cm^2

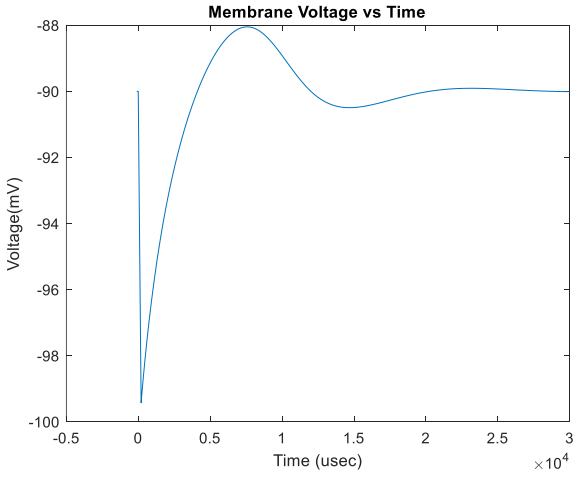

Figure 6: Membrane voltage for input in Fig. 5

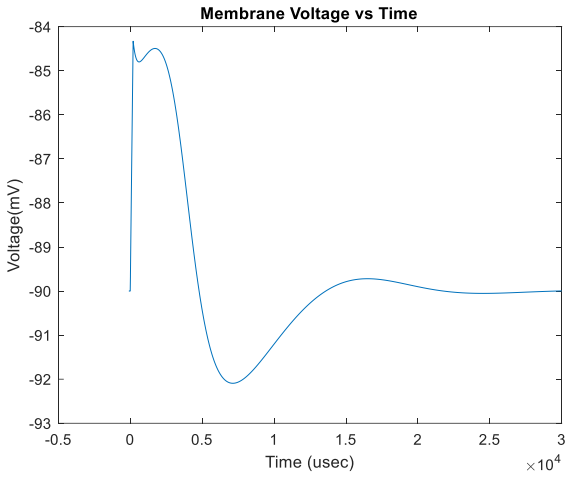

Figure 7: Membrane voltage for input current with duration 200 usec and amplitude 30 uA/cm^2

In Fig. 7 membrane potential for 30 uA/cm^2 input stimulant is shown. Despite true polarization and duration of the stimulant, it did not cause action potential generation.

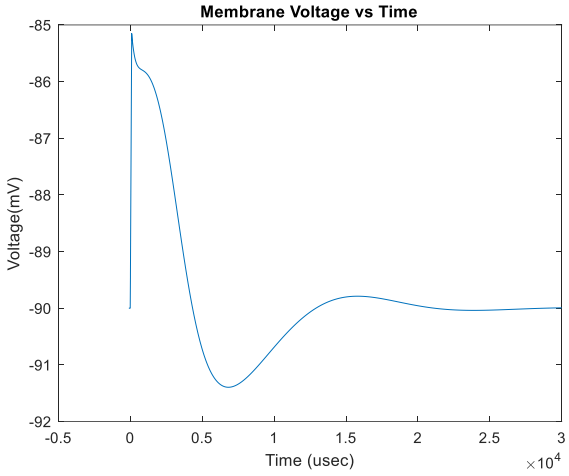

Figure 8: Membrane voltage for input current with duration 100 usec and amplitude 50 uA/cm^2

In Fig. 8 membrane potential for 50 uA/cm^2 input stimulant is shown. Despite true polarization and amplitude of the stimulant, it did not cause action potential generation.

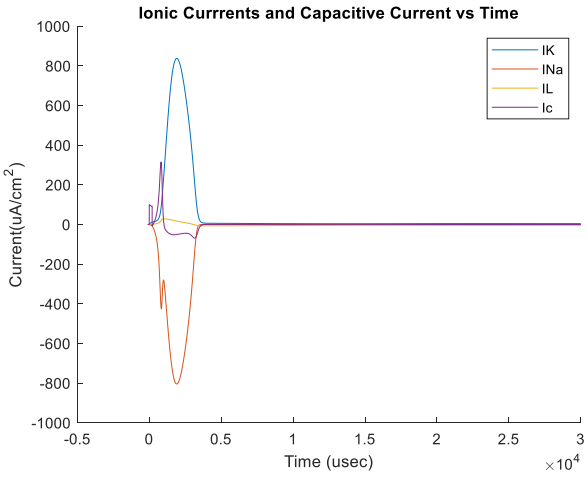

Figure 9: Ionic currents and capacitive current for input current with duration 200 usec and amplitude 100 uA/cm^2

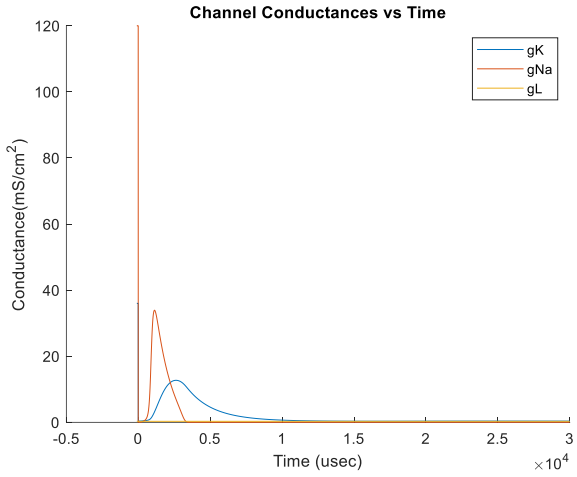

Figure 10: Channel conductances for input current with duration 200 usec and amplitude 100 uA/cm^2

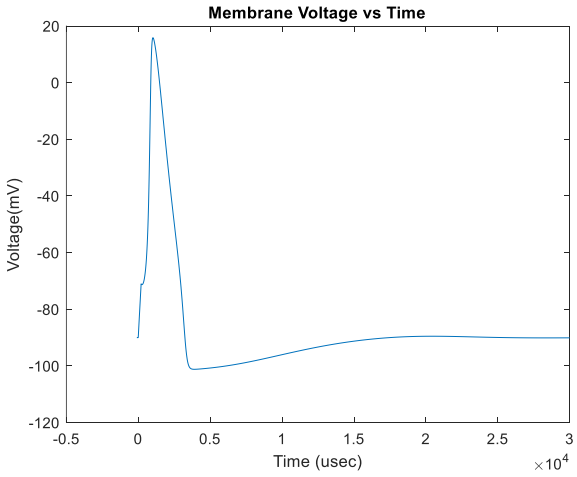

Figure 11: Membrane voltage for input current with duration 200 usec and amplitude 100 uA/cm^2

Comparing Fig. 2 with Fig. 9, Fig. 3 with Fig. 10, and Fig. 4 with Fig. 11 increasing stimulant amplitude does not result in nearly any difference for currents, conductances, and generated action potential.

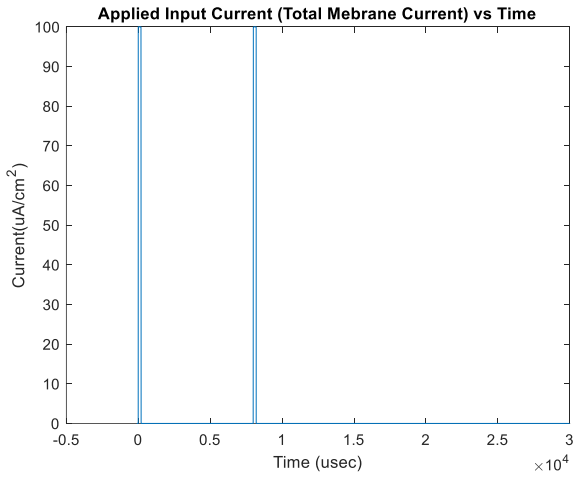

Figure 12: Input Current with duration 200 usec and amplitude 100 uA/cm^2 with 8 msec delay in between

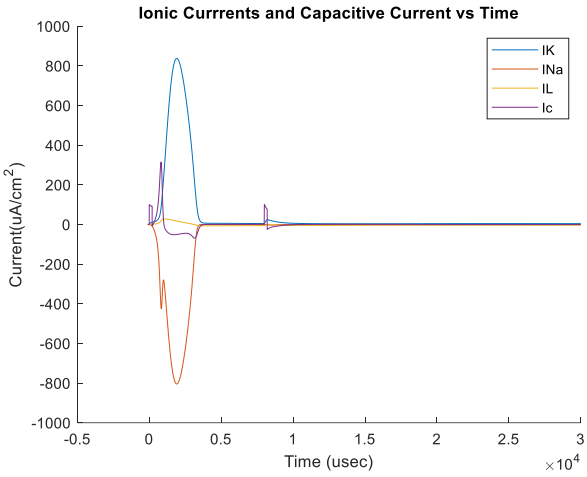

Figure 13: Ionic currents and capacitive current for input in Fig. 12

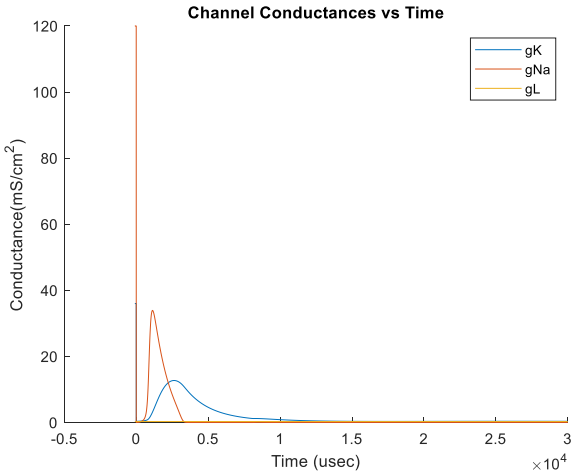

Figure 14: Channel conductances for input in Fig. 12

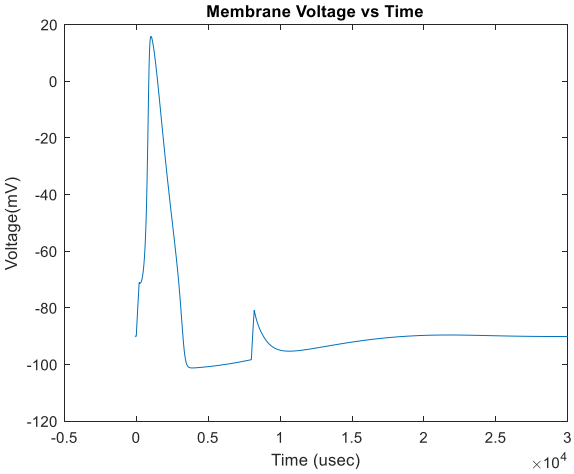

Figure 15: Membrane voltage for input in Fig. 12

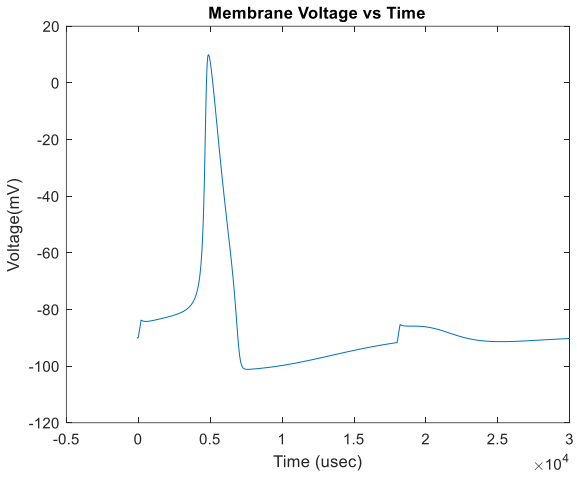

Figure 16: Membrane voltage for two consecutive input currents with duration 200 usec and amplitude 33 uA/cm^2

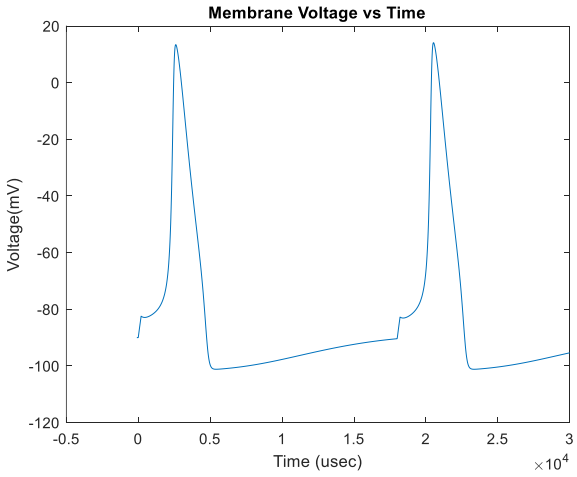

Figure 17: Membrane voltage for two consecutive input currents with duration 200 usec and amplitude 40 uA/cm^2

In Fig. 16 and Fig. 17 two consecutive pulses with different amplitude are given as inputs. For the amplitude just above the threshold second stimuli did not cause action potential generation due to accommodation property of action potential.

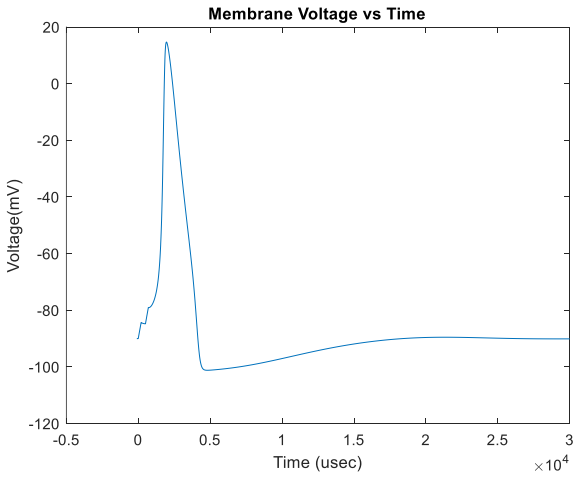

Figure 18: Membrane voltage for two consecutive input currents with duration 200 usec and amplitude 30 uA/cm^2 with small delay in between

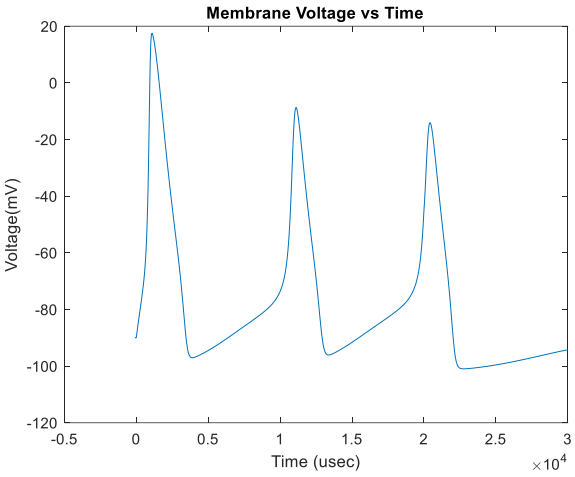

Figure 19: Membrane voltage for step input current with amplitude 40 uA/cm^2

In Fig. 18 although the amplitude of the stimulant is below the threshold value, consecutive impulses resulted in an action potential generation verifying the temporal summation phenomena. In Fig. 19 response of the cell to step input is observed.

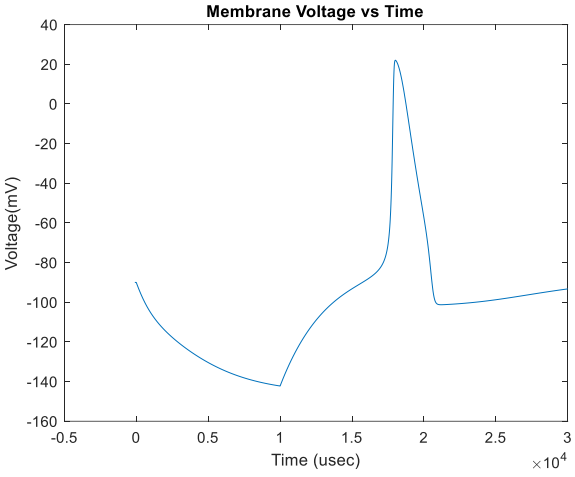

Figure 20: Membrane voltage for rectangular input current with amplitude -20 uA/cm^2

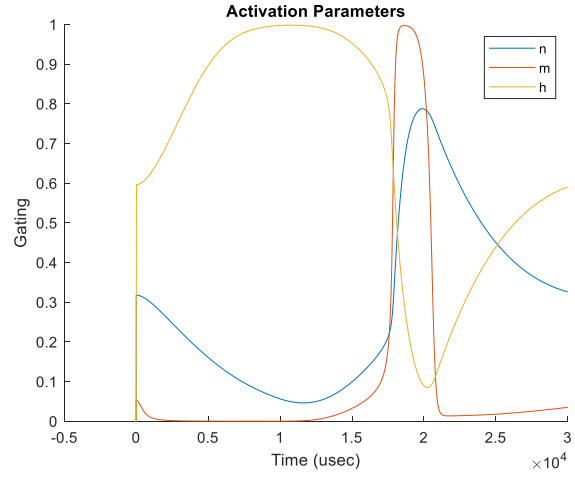

Figure 21: Activation parameters for rectangular input current with amplitude -20 uA/cm^2

IV. Discussion and Conclusion

Quantitative modeling of excitable cell reveals some of the most important characteristics of action potential generation. While single cell simulations yield results for only one cell, because of the interaction between neighbor cells such results give broader perspective. Consequently, one may be able to derive wide range of results both in microscopic and macroscopic scale. In this section, reaction of the cell membrane to various stimuli will be discussed. Furthermore, some specifications of action potential will be presented.

Firstly, basis of action potential generation may be interpreted through observing Fig. 1 to Fig. 11. Action potential is described as all or none meaning if some certain threshold, which depends on numerous factors, is exceeded by stimulant action potential generates. If this threshold is not achieved, action potential does not generate. At this point, this behavior of excitable cell may be appreciated by understanding that this threshold allows living to be insensitive to all stimulants. For example, unless a threshold temperature is exceeded, human does not react to each temperature change. Also, as it can be interpreted from Fig. 9 to Fig. 11, magnitude of the stimulant does not affect the response generated.

To generate action potential, stimulant must have certain properties in addition to exceeding some threshold. Polarization of the stimulant must be correct, depolarizing the cell membrane, not hyperpolarizing. In Fig. 6 membrane voltage response to hyperpolarizing stimulant is shown. There is not any action potential generation for hyperpolarizing stimulant although the amplitude is satisfactory. Moreover, duration of the stimulant must be long enough. In Fig. 8 one may see the unsatisfactory duration of the stimulant did not create action potential despite having true polarization and amplitude. This property may be interpreted as noise reduction system of the excitable cell making it insensitive to too impulsive stimulants.

Besides requirements of stimulant, shape of the action potential is a topic of interest. Observing either figure with proper action potential generation, responses of membrane voltage is quite similar if not the same in. typically, a small voltage increased followed by huge depolarization is observed. This is due to the active behavior of the membrane. Channel conductance changes result in ionic currents which eventually cause this action potential generation. After the peak hyperpolarization, going back to resting state, is observed with an overshoot. This overshoot, namely hyperpolarizing afterpotential, is followed by passive reaction of the membrane and settling in resting condition in time.

Action potential has several properties for different stimulant combinations in addition to a single stimulant. One of them, refractory period, can be seen in Fig. 15. Although second stimulant has all qualification to generate action potential, it does not cause an action potential generation. This is due to previous generation. After some action potential is generated, membrane is insensitive to other stimulants for a period called refractory period. Refractory period can be explained by activation constants especially the parameter h. Analyzing activation parameters carefully, need for time to decrease in n is also available meaning elevated n and decreased h are the reason for failure of new action potential generation[2]. Another interesting property may be observed comparing Fig.16 and Fig. 17. In both figure consecutive stimulants having same amplitude are applied. However, in Fig. 16 stimulant amplitude was set just above threshold. At the end, second stimulant did not cause action potential generation due to increased threshold after the first one. This phenomenon is called accommodation. On the other hand, when two consecutive stimuli with amplitude below threshold is applied with a short delay in between an action potential shown in Fig. 18 is generated. This is because when second stimulant current hits the cell, effect of the first stimulant is not vanished yet. Consequently, positive feedback can be generated with small stimulant and this process is called temporal summation.

Reaction of the excitable cell to long duration pulses are also interesting. In Fig. 19 response of the cell to step input is shown. Consecutive pulses are generated by the cell membrane as response to unit step and it is called pulse frequency modulation. In Fig. 20 anode breakdown excitation can be observed. When hyperpolarizing stimulant is applied for long duration, termination of it cause an action potential generation. This may be explained easily by plotting n, m and h activation parameters as shown in Fig. 21. m regains normal value while n is depressed, and h is elevated just after hyperpolarization. This combination yields sodium current higher than potassium current and initiates an action potential generation.

To sum it all up, remarkable mathematical model of excitable cell from Hodgkin and Huxley reveals important properties of action potential generation. Mathematical implementation is quite straightforward and results are very much relatable with behavior of cell in microscopic scale and behavior of living in macroscopic scale. Simulation of cell membrane may provide accessibility to research even in early stages of work.

References

[1] "The Nobel Prize in Physiology or Medicine 1963", NobelPrize.org, 2020. [Online]. Available: https://www.nobelprize.org/prizes/medicine/1963/summary/. [Accessed: 22- May- 2020].

[2] R. Plonsey and R. C. Barr, Bioelectricity: a quantitative approach. New York, NY: Springer, 2014.K. K. Shung, M. Smith, and B. M. W. Tsui, *Principles of Medical Imaging*. Burlington: Elsevier Science, 2012.

APPENDIX A

SIMULATION CODE

```
%Muhammed Saadeddin Kocak 2232346
%EE416 Term Project
t=linspace(-99,30000,30100);%usec
Im(1:100)=0;%uA/sec^2
impulseduration=200;%usec
impulseamplitude=40;%uA/cm^2
numberofconsecutivestimuli=1;
timedelaybetweenstimuli=500;%usec
Cm=1;%uF/cm^2
Vm(1:length(t))=-90;%mV
vm(1:length(t))=0;%Vmembrane-Vrest
gNarest=120;%mS/cm^2
gKrest=36;%mS/cm^2
gLrest=0.3;%mS/cm^2
gK(1:length(t))=gKrest;
gNa(1:length(t))=gNarest;
gL(1:length(t))=gLrest;

VNa=25;%mV
VK=-102;%mV
VL=-79.387;%mV
for i=100:length(t)
   if t(i)>-1 && t(i)<impulseduration
       Im(i)=impulseamplitude;%uA/cm^2
   else
       Im(i)=0;
   end
   %For the second stimuli
   if numberofconsecutivestimuli~=1
   if t(i)>timedelaybetweenstimuli &&
t(i)<timedelaybetweenstimuli+impulseduration
       Im(i)=impulseamplitude;%uA/cm^2
   end
   end
   %
   an(i)=((0.01*(10-vm(i)))/(exp((10-vm(i))/10)-1))/1000;%1/usec
   bn(i)=(0.125*exp((-vm(i))/80))/1000;%1/usec
   am(i)=((0.1*(25-vm(i)))/(exp(0.1*(25-vm(i)))-1))/1000;%1/usec
   bm(i)=(4*exp((-vm(i))/18))/1000;%1/usec
   ah(i)=(0.07*exp((-vm(i))/20))/1000;%1/usec
   bh(i)=(1/(exp((30-vm(i))/10)+1))/1000;%1/usec
   n(100)=an(100)/(an(100)+bn(100));
   m(100)=am(100)/(am(100)+bm(100));
   h(100)=ah(100)/(ah(100)+bh(100));
   gK(i)=gKrest*(n(i).^4);%mS/cm^2
   gNa(i)=gNarest*(m(i).^3)*h(i);%mS/cm^2
```

```
    IK(i)=gK(i)*(Vm(i)-VK);%uA/cm^2
    INa(i)=gNa(i)*(Vm(i)-VNa);%uA/cm^2
    IL(i)=gLrest*(Vm(i)-VL);%uA/cm^2
    Ic(i)=Im(i)-IK(i)-INa(i)-IL(i);
    %Estimating deltan deltam deltah
    deltan(i)=(an(i)*(1-n(i)))-(bn(i)*n(i));
    deltam(i)=(am(i)*(1-m(i)))-(bm(i)*m(i));
    deltah(i)=(ah(i)*(1-h(i)))-(bh(i)*h(i));
    deltaVm(i)=(Im(i)-IK(i)-INa(i)-IL(i))/(Cm*1000);%mV
    %Calculating next variables
    n(i+1)=n(i)+deltan(i);
    m(i+1)=m(i)+deltam(i);
    h(i+1)=h(i)+deltah(i);
    Vm(i+1)=Vm(i)+deltaVm(i);
    vm(i+1)=vm(i)+deltaVm(i);
end
figure
plot(t,Im(1:length(t)));%Both for applied and membrane current
title('Applied Input Current (Total Mebrane Current) vs Time');
xlabel('Time (usec)');
ylabel('Current(uA/cm^2)');
figure
hold on
plot(t,IK(1:length(t)));
plot(t,INa(1:length(t)));
plot(t,IL(1:length(t)));
plot(t,Ic(1:length(t)));
legend({'IK','INa','IL','Ic'});
title('Ionic Currrents and Capacitive Current vs Time');
xlabel('Time (usec)');
ylabel('Current(uA/cm^2)');
hold off
figure
hold on
plot(t,gK(1:length(t)));
plot(t,gNa(1:length(t)));
plot(t,gL(1:length(t)));
legend({'gK','gNa','gL'});
title('Channel Conductances vs Time');
xlabel('Time (usec)');
ylabel('Conductance(mS/cm^2)');
hold off
figure
plot(t,Vm(1:length(t)));
title('Membrane Voltage vs Time');
xlabel('Time (usec)');
ylabel('Voltage(mV)')
```