Cellular Electrophysiology

Recreation & Exploration of the Hodgkin and Huxley Model

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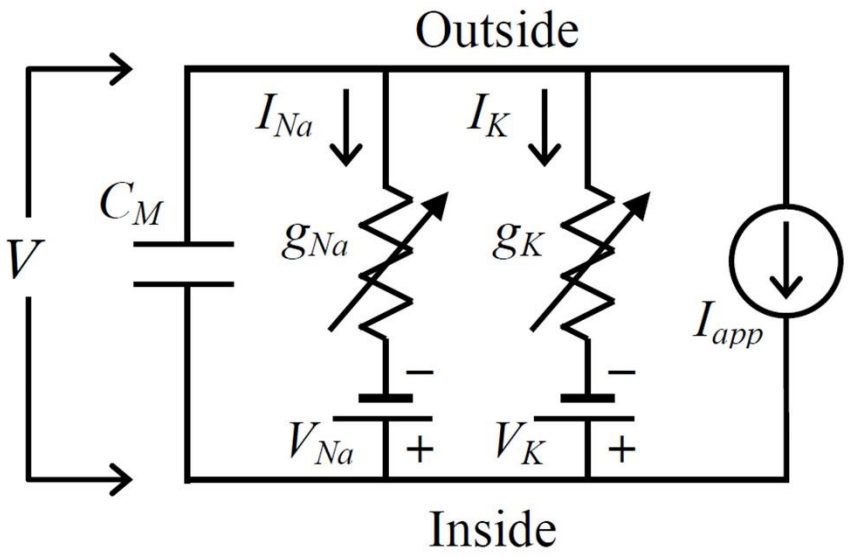
Theory – Understanding the Hodgkin and Huxley Model

In general, the Hodgkin and Huxley model mathematically describes how action potentials are generated and propagated by a neuron. The overall process of an action potential occurs as a rapid positive increase in the membrane potential voltage from the more negative resting potential, ultimately termed depolarization. The depolarization peak will reach a voltage maximum in which the membrane potential voltage rapidly decreases to near its resting membrane potential. Furthermore the neuron enters a refractory period, during which its voltage overshoots its resting potential during which the neuron becomes temporarily non-excitable. Finally given a sufficient period of time the membrane potential will begin to recover and stabiles back to its resting potential, as the membrane potential becomes closer to the resting potential it becomes easier for an input current to cause the generation of a new action potential.

Understanding the Model:



The above diagram shows a representation of a cell membrane. I_app represents the injected current, which can be akin to the presentation of a stimulus. V represents the cell membrane potential measured by the inside potential minus the outside potential. The VNa and Vk batteries represent the Nernst potentials of potassium and sodium ions. The interplay between V and the VNa/Vk batteries is what simulates the concentration gradient driving force. For example consider the interplay with sodium via –(V-VNa), if the membrane potential is at a value near the resting potential of -65mV and the sodium Nernst potential being +50mV one can see the difference between such numbers will be large at +115mV indicating a strong thermodynamic driving force. Therefore as expected if sodium becomes sufficiently permeable to the membrane the large driving force will cause sodium ions to rapidly move inside the cell, due to the concentration outside being higher than the inside, causing the membrane potential to rapidly increase towards sodium's equilibrium potential of +50mV, ultimately causing the depolarization phase of action potential generation. The second driving force is the electrostatic potential across the membrane which is represented by the Cm capacitator in the circuit diagram. Thus fundamentally, the generation of an action potential in this circuit model arises as a consequence of voltage dependent changes in the membrane

permeabilities of sodium and potassium ions. This is represented via gNa and gK, which describe the probabilities of voltage-gated ion channels being open or closed for sodium (fast opening – slow closing) and potassium ions (slow opening and closing). Overall the above dynamics of the circuit model of a cell membrane can be mathematically expressed relative to time by a governing first order differential equation:

$$C_m \frac{dv}{dt} = -g_L(v - v_L) - g_{Na}(v - v_{Na}) - g_K(v - v_K) + I_{app}$$

Whereby g_L represents leakage current such as chlorine ion channels, which in this model always remain open, to allow the membrane potential to recover from an action potential back to its resting membrane potential over time.

Potassium voltage gated ion channel:

The following equation describes the potassium voltage gate ion channel mechanism:

$$g_K = n^4 \bar{g}_K$$

$$\frac{dn}{dt} = a_n(1 - n) - B_n n$$

The above equations overall describe the rate of change of the probability of a potassium ion channel being opened(n), given the rate at which the potassium gate opens (a_n) and closes (B_n) with respect to time. Overall the value of g_k, thus the flow of potassium ions, is expected to increase from 0 to a maximal value $\bar{g}_k$ as the probability of a the potassium ion gate being open increases. Finally, it is expected that the opening rate a_n, thus the speed at which potassium ions will move from the inside to outside of the cell membrane, will increase as voltage of the membrane potential positively increases. Likewise closing rate is also expected to decrease as the voltage of the membrane potential positively increases. Ultimately such a process will occur in response to increasing sodium levels, in order bring the membrane potential of cell back down to near its resting membrane potential and thus hyperpolarizing the already depolarized membrane and ending the current action potential spike.

Sodium voltage gated ion channels:
The following equation describes the Sodium voltage gate ion channel mechanism:

$$g_K = m^3 h \bar{g}_{Na}$$

$$\frac{dm}{dt} = a_m(1 - m) - B_m m$$

$$\frac{dh}{dt} = a_h(1 - h) - B_h h$$

The above equations quantitatively describe the rise and decay behavior of sodium ion during the process of an action potential over time. Like (n) in potassium opening rate , the (m) in sodium gated channels opening rate will increase as the cell membrane becomes increasingly depolarized. Both a_m & B_m have values significantly greater than opening & closing rates for potassium, which ultimately allows sodium to rapidly respond to changes in membrane potential. In disparity to the (m) gate the (h) closing rate (Bh) increases, thus (h) decreases, as membrane depolarization increases. Like wise the values of the rate constants of (h) are set to be much smaller than the rate constants of m, which allows for h to respond more slowly to changes in membrane potential. The sodium gating variable (h) plays an important role1 in the generation of an action potential causes the sodium gated ion channels to switch to an inactivated state when closed. The during a state of inactivation the sodium gated ion channels are unable to open at any membrane potential for a brief amount of time. This is known as the absolute refractory period, one use of such a mechanism is to stop an action potential from travelling back up the axon from whence it originated, such effects without the absolute refractory period would be detrimental for effective neuronal data transmission.

Method Used to solve Differentials:

The depicted 4 equations are first order differential equations thus the forward Euler first order approximation method was used. An approximation of the true yet unknown non-linear curvature of an action potential can be calculated using the initial know point of the curve at time = 0. At the initial point the slope of the curve, thus the tangent line for the first time stamp can be calculated, for each of the 4 differential equations. One can then take a small movement across the current tangent line by multiplying the differential result by a small constant value. This constant value represents the sample rate, and has increased accuracy the more samples taken per time stamp E.g. per millisecond. Additionally if the sample is small enough the slope of the new sampling point will not have changed much in comparison to the previous slope, thus the new and current sample point will still be close to the true curve. This process is repeated across the entire timestamp series and overall will generate a polygonal curve, with a smaller sampling rate yielding a closure polygonal approximation of the true curvature of the action potential. Despite the ode45 algorithm being the method of choice I find that its use in MATLAB is not intuitive, many of its control parameters are hidden for the beginner. Euler's method was chosen as it gives myself, the user, more explicit control over the looping mechanism across the timestamp series and sampling accuracy of the model, allowing me greater ability to explore and analysis the model.

Programmatic Implementation:

```
%===simulation time===
TimeSeries = 35; %in milliseconds
SampleRate=.01;
timestep=0:SampleRate:TimeSeries;


%===specif5 the external current I===
changeTimes = [0]; %in milliseconds
startCurrentLevels = [0];%Change this to see effect of different
currents on voltage (Suggested values: 3, 20, 50, 1000)
currentLevels  = [1.9];

% level1 = 0.615;
level0 = -3.2;
level1 = -0.324943; %1.015; %-0.325

% level2 = 2;
% level3 = 2.5;
% level4 = 4;
% level5 = 4.5;

%Set externally applied current across time
IterationWindow(1:500) = level0; IterationWindow(501:1500) = level0
; IterationWindow(1501:2500) = level1;

%System Constants
gbar_K=36;
gbar_Na=120;
g_L=.3;
E_K = -12;
E_Na=115;
E_L=10.6;
C=1;


%Calculate the inital State of the Cell membrane
V=0; %Baseline voltage
An_gate = .01 * ( (10-V) / (exp((10-V)/10)-1) ); %Equation 12
Bn_gate = .125*exp(-V/80); %Equation 13
Am_gate = .1*( (25-V) / (exp((25-V)/10)-1) ); %Equation 20
Bm_gate = 4*exp(-V/18); %Equation 21
Ah_gate = .07*exp(-V/20); %Equation 23
Bh_gate = 1/(exp((30-V)/10)+1); %Equation 24

n(1) = An_gate/(An_gate+Bn_gate); %Equation 9
m(1) = Am_gate/(Am_gate+Bm_gate); %Equation 18
h(1) = Ah_gate/(Ah_gate+Bh_gate); %Equation 18


for i=1:numel(timestep)-1 %Compute coefficients, currents, and
derivates at each time step
```

```
  %Calculate the Rate Constants across the time series -1 for inital
state
  %calc
    An_gate(i) = .01 * ( (10-V(i)) / (exp((10-V(i))/10)-1) );
    Bn_gate(i) = .125*exp(-V(i)/80);

    Am_gate(i) = .1*( (25-V(i)) / (exp((25-V(i))/10)-1) );
    Bm_gate(i) = 4*exp(-V(i)/18);

    Ah_gate(i) = .07*exp(-V(i)/20);
    Bh_gate(i) = 1/(exp((30-V(i))/10)+1);


    %---calculate the currents---%
    Ion_Na = (m(i)^3) * gbar_Na * h(i) * (V(i)-E_Na); %Equations 3
and 14
    Ion_K = (n(i)^4) * gbar_K * (V(i)-E_K); %Equations 4 and 6
    Ion_L = g_L *(V(i)-E_L); %Equation 5
    main_Equ = - I_K - I_Na - I_L +  I(i) ;


    %---calculate the derivatives using Euler first order
approximation---%
    V(i+1) = V(i) + SampleRate*main_Equ/C;
    n(i+1) = n(i) + deltaT*(alpha_n(i) *(1-n(i)) - beta_n(i) *
n(i)); %Equation 7
    m(i+1) = m(i) + deltaT*(alpha_m(i) *(1-m(i)) - beta_m(i) *
m(i)); %Equation 15
    h(i+1) = h(i) + deltaT*(alpha_h(i) *(1-h(i)) - beta_h(i) *
h(i)); %Equation 16

end


V = V-65; %Set resting potential to -70mv

%DATA ANALYSIS
============================================================

%===Voltage Graph===%
figure; plot(t,V,'LineWidth',1.5)
hold on
plot(t, I, 'r','LineWidth',2);
legend({'voltage'}, 'Injected Current (mA)')
ylabel('Voltage (mv)')
xlabel('time (ms)')
title('Voltage over Time in Simulated Neuron')

set(gca, 'XTick', [5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60,
65, 70, 75, 80, 85, 90, 95, 100])
set(gca, 'YTick', [-80, -75, -70, -65, -60, -55, -50, -45, -40, -35,
-30, -25, -20, -15, -10, -5, 0, 5, 10, 15, 20, 25, 30, 35, 40, 45,
50, 55, 60])

 grid on
```

```
% ===Conductance Graph===%
figure
p1 = plot(t,gbar_K*n.^4,'LineWidth',2);
hold on
p2 = plot(t,gbar_Na*(m.^3).*h,'r','LineWidth',2);

legend([p1, p2], 'Conductance for Potassium', 'Conductance for
Sodium')
ylabel('Conductance')
xlabel('time (ms)')
title('Conductance for Potassium and Sodium Ions in Simulated
Neuron')
figure;

%Injected Current Graph
plot(t, I, 'r','LineWidth',2)

set(gca, 'XTick', [5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60,
65, 70, 75, 80, 85, 90, 95, 100])
set(gca, 'YTick', [0,0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9,
1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2,
2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0])
% -3, -2.5, -2.0, -1.5, -1.0, -0.5,
legend({'Current'})
ylabel('Injected Current(mA)')
xlabel('time (ms)')
title('Injected Current over Time in Simulated Neuron')
grid on

figure;

hold on
plot(t, n, 'LineWidth', 1.5)
plot(t, m, 'LineWidth', 1.5)
plot(t, h, 'LineWidth', 1.5)

%Gating Variable Graph
title('Na & K Ion Channel: Gating Variables')
xlabel('Time(ms)')
ylabel('Probability')
legend('n', 'm', 'h')
hold off
set(gca, 'XTick', [5, 10, 15, 20, 25, 30, 35,])

grid on
```

Running the Model: Results

Figure 1.a – Action Potential: Voltage

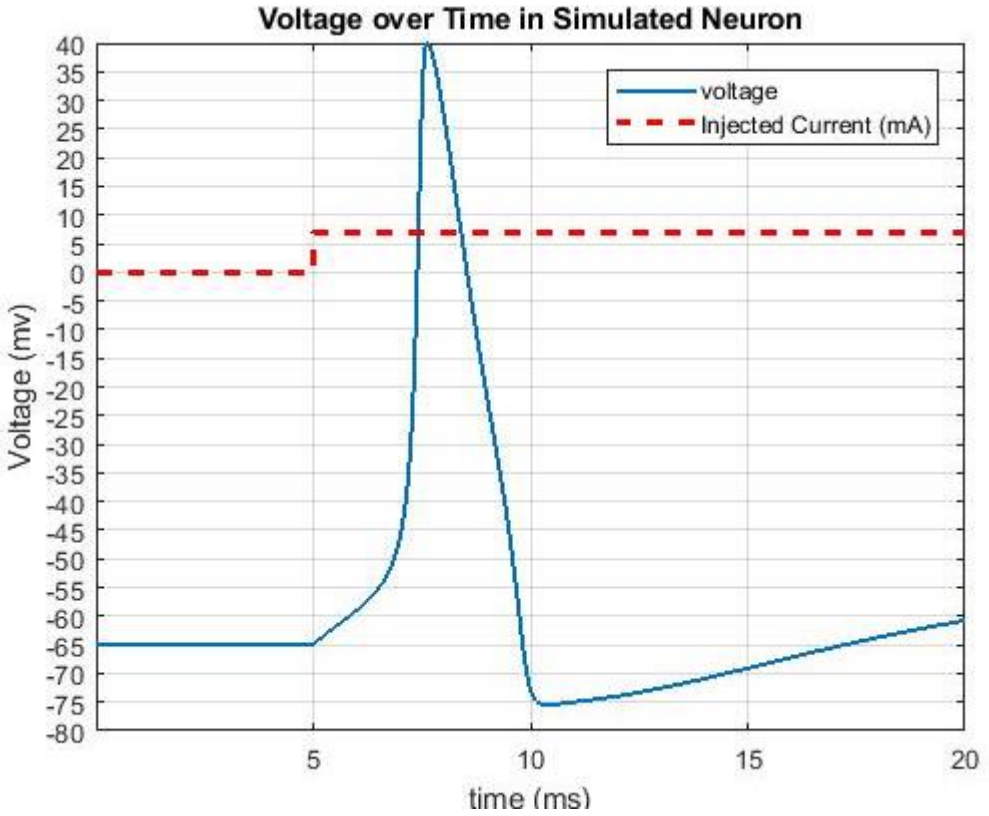


Figure 1.b – Action Potential: Ion Conductance

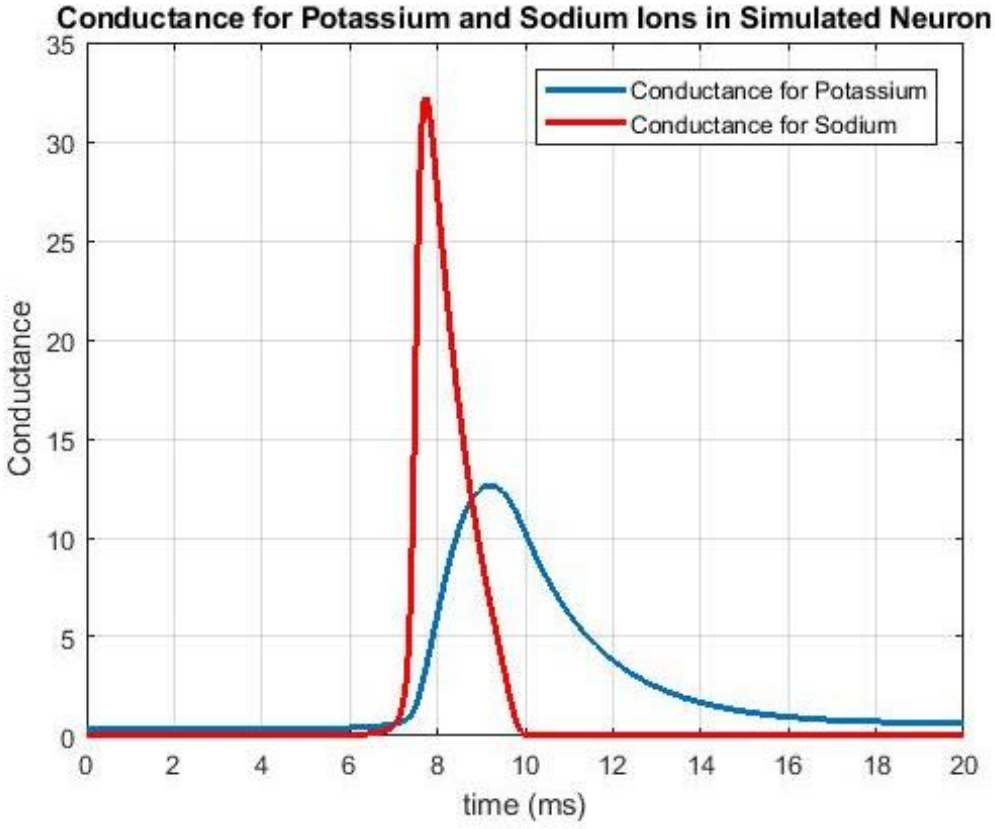


Figure 1.a & 1.b show the results generated when the MATLAB code simulating the Hodgkin and Huxley model is run. An input current = 0 was added for the first 5 milliseconds to show the maintained resting membrane potential of the cell at -65mV. A stepped increase of input current of +7mA was continuously injected at the 5-millisecond mark for the remainder of the timestamp series. As expected when positive current is injected into the circuit it causes the membrane to hyperpolarize enough to cause the sodium ion channels to rapidly open in response to the hyperpolarization. As stated in the above theory section one can see , as expected, that the rapid influx of sodium ions causes a large and rapid positive spike of the membrane potential, that tends towards the Equilibrium potential of sodium at +50mV. Likewise as the conductance of sodium reaches its maxima the sodium gates begin to close, through this rapid spiking of voltage the delayed and slow response of the potassium gated ion channel can be observed as it reaches its maximum conductance of ion flow as the conductance of sodium rapidly decreases. The opening of the potassium ion channels allows the membrane potential to be rapidly reduced to a more negative voltage value that now tends towards potassium's equilibrium potential. As the responsiveness of the opening and closing rates of potassium (a_n & B_n) are slow the flow of potassium ions steadily decreases over the course of 10 milliseconds, allowing the leakage channels of chloride to pull the membrane potential slightly towards its own equilibrium potential of -54.4mV, eventually allowing the voltage to stabilize at its original resting membrane potential of -65mV.

Figure 1.c – Action Potential: Gating Variables

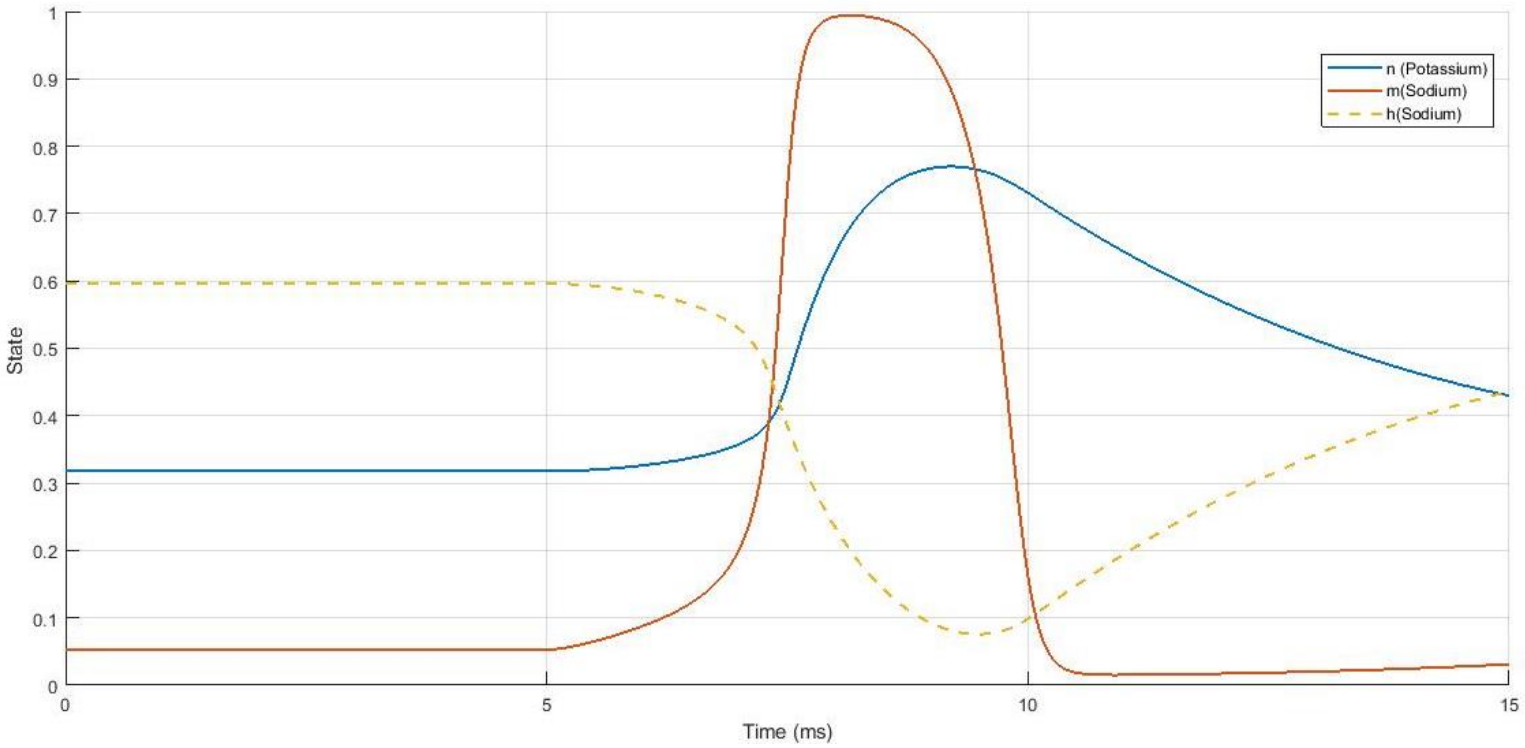


Figure 1.c shows a detailed depiction of the behavior of the gating variables over time. As expected we see the probability of the sodium ion channel being open n(blue line) increase steadily as the membrane potential reaches the threshold limit, once passed such limit its probability exponentially increases towards 1, thus certainty. Additionally as shown in figure 1.b the slow responsive behavior of the potassium ion gate opening and closing mechanism (m) can be evidence in-response to the rapid reduction of sodium and hyperpolarization of the membrane potential. Finally and more interestingly figure 1.c shows the behavior of the

sodium's (h) variable, as the action potential begins to conclude via hyperpolarization we see the a significant decrease in the value of (h) which ultimately causes the sodium gated channels to move into a state of inactivation. Again the (h) gate control variable slowly increases on a trajectory and time course associated with the recovery of the membrane potential back to the stable resting membrane potential, which ultimately simulates the refractory period of the neuron.

Figure 1.d – Action Potential: Refractory period – Voltage

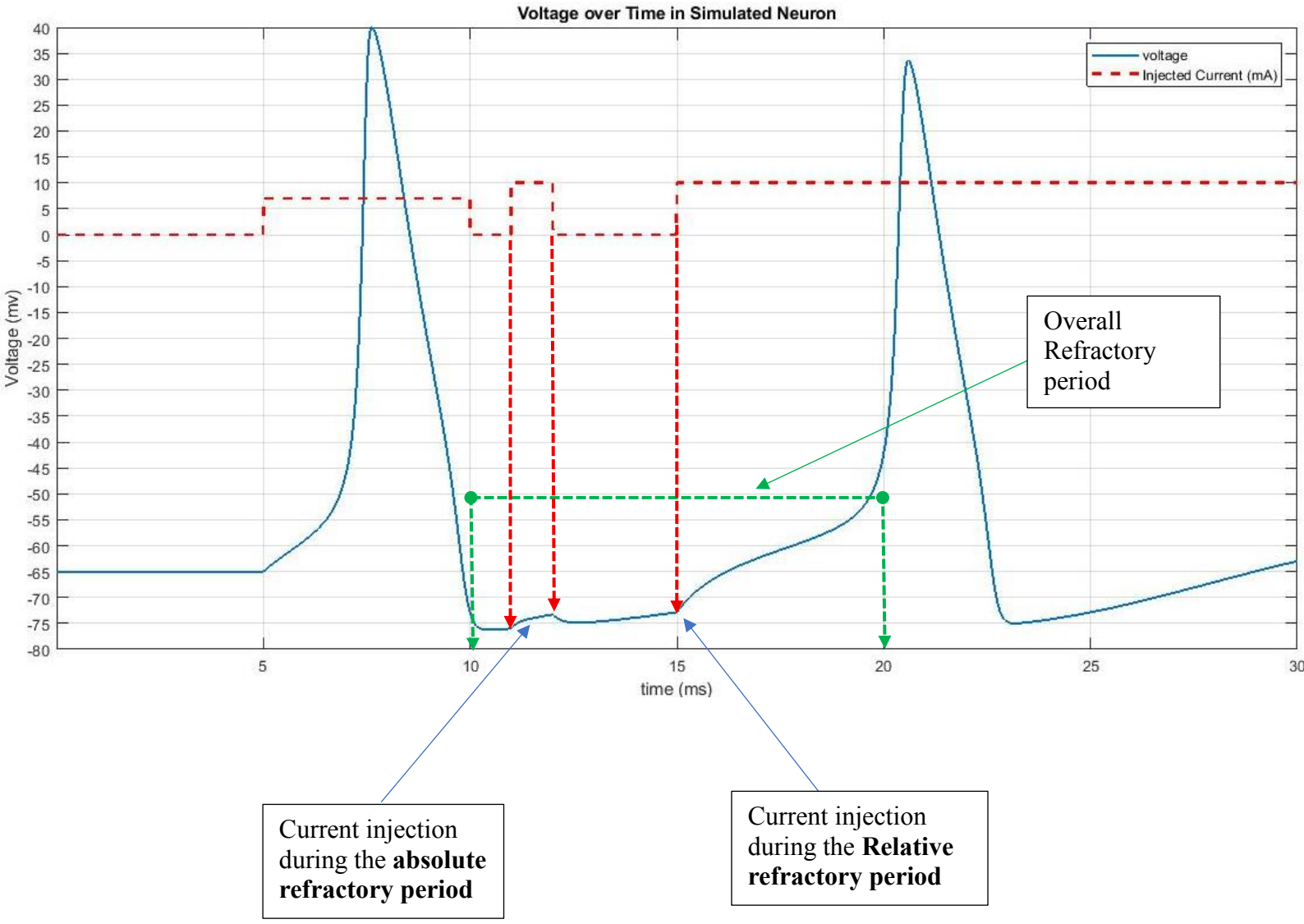
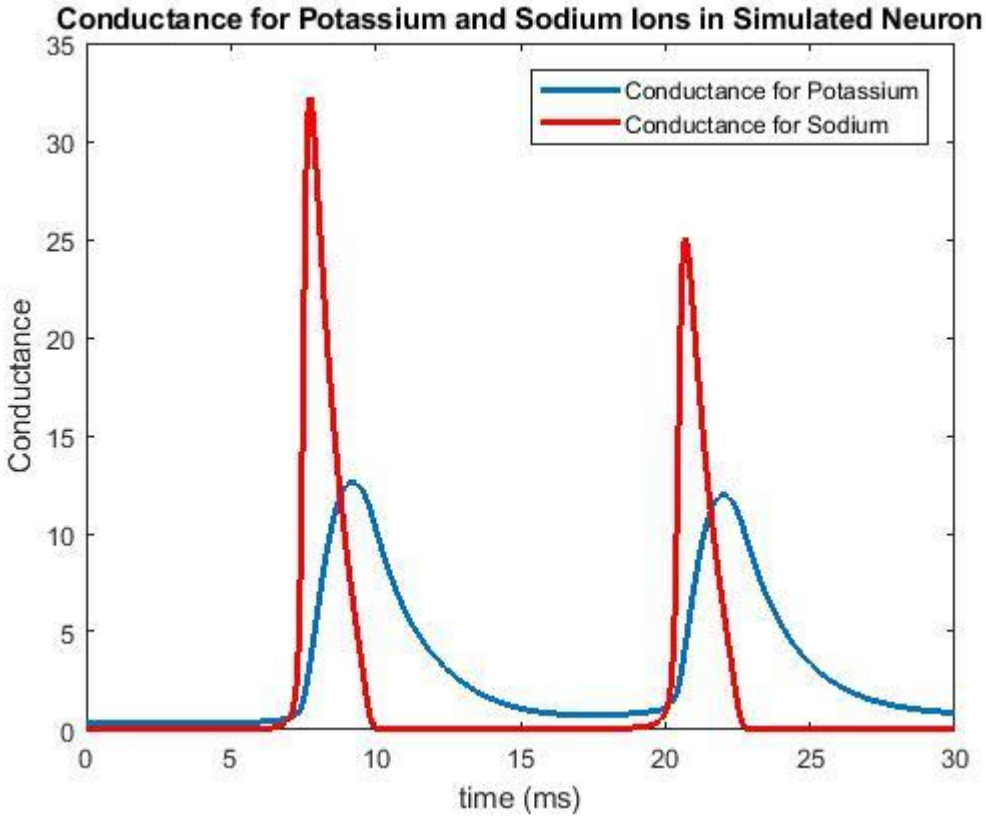


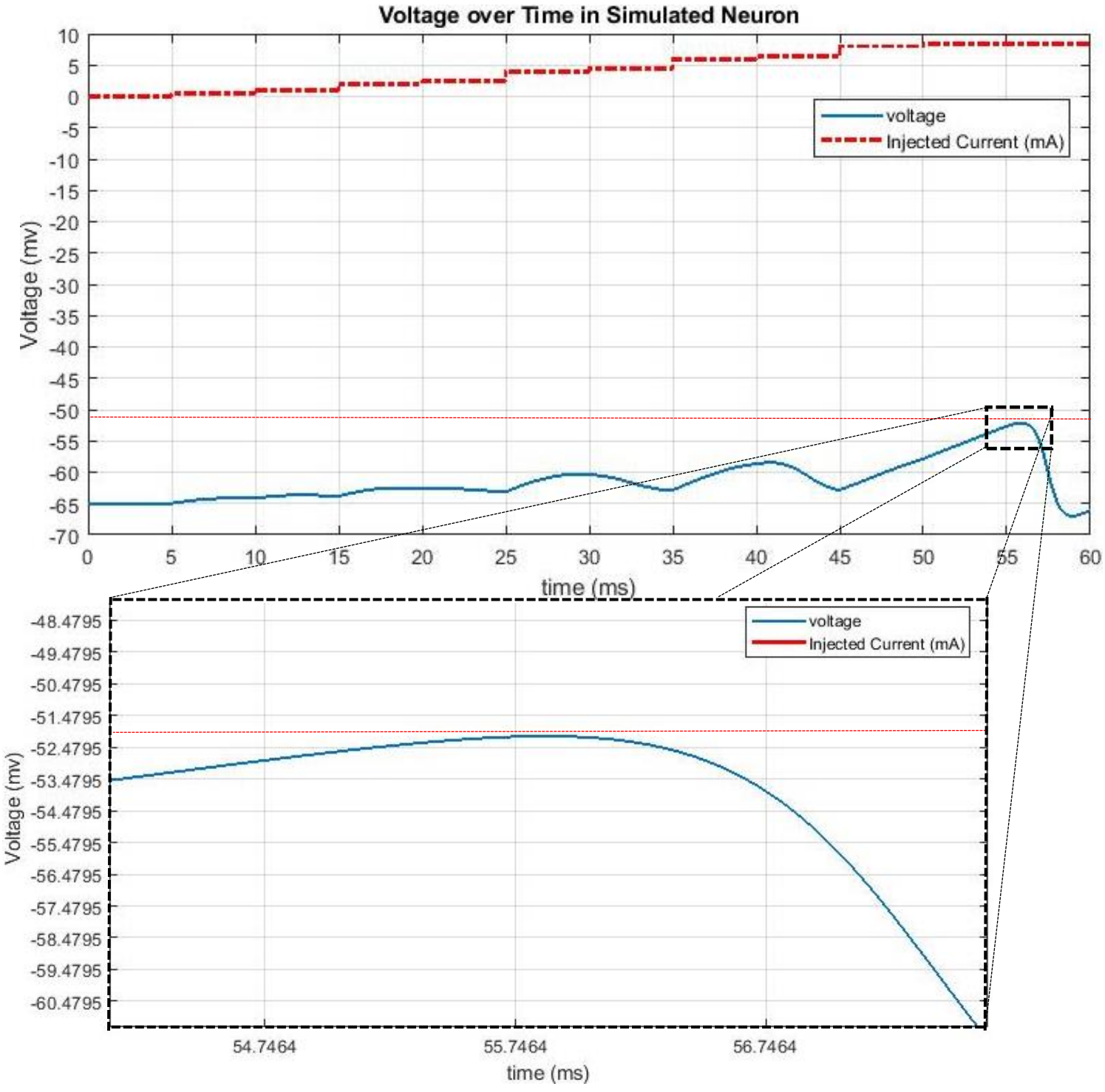
Figure 1.e – Action Potential: Refractory Period - Ion Conductance



Figures 1.d and 1.e evidence the implementation and effects of the refractory period on action potential generation. Recall figure 1.a in which at time = 5ms, 7mA of current was injected into the system to cause an action potential. This current was held constant for the remainder of the timestep series, yet following the model did not produce an action potential immediately after the event of rapid hyperpolarization. This due to the effects of the absolute and relative refractory period. The absolute refractory when the sodium (h) gate variable is lowest causes the sodium ion channels to be in a state of increased inactivation, by which they will not open to any further injections of stimulation for a brief time. This can be evidenced by figure 1.d as an increased amount of current was injected into the membrane immediately after maximal hyperpolarization at time = 11ms. As shown despite the increased amount of applied current of 10mA the voltage of the membrane only fluctuates by a very small amount and we see in figure 1.e that at, time = 11ms, that there is 0 activation of sodium ion conductance, indicating that the sodium gated ion channels are not responding at all to injected stimulation, thus evidencing the absolute refractory period. Moving on when the same amount of current is injected into the cell at a later timestep within the overall refractory period one finds different cellular behavior. Instead it is shown that at time = 15ms an injection of 10mA is enough stimulation to cause the membrane potential to begin depolarizing towards the activation threshold and ultimately allows for the generation of a new action potential. This behavior demonstrates the relative refractory period. The sodium (h) gating variable has increased enough to allow the sodium ion channels to become active, thus responsive to stimulation once more, however a major difference is that this time it requires much more stimulation of 10mA as compared to the previous action potential which only required 7mA. Furthermore, to drive home this point, we see in figure 1.a that 7mA is insufficient to cause depolarization at time = 15mA thus evidencing the effects of the relative refractory period.

Finding the Threshold:

The threshold potential value determines if incoming input stimulation is sufficient to generate an action potential. The threshold is mainly described as a voltage responsive limit whereby spike initiation in neurons based on an all or none response. Therefore it possible approximate the threshold potential of the neuron in Hodgkin and Huxley Model, by slowly incrementing the membrane potential until it reaches a voltage just under the all or nothing spike initiation. This can be shown in the graphs below:



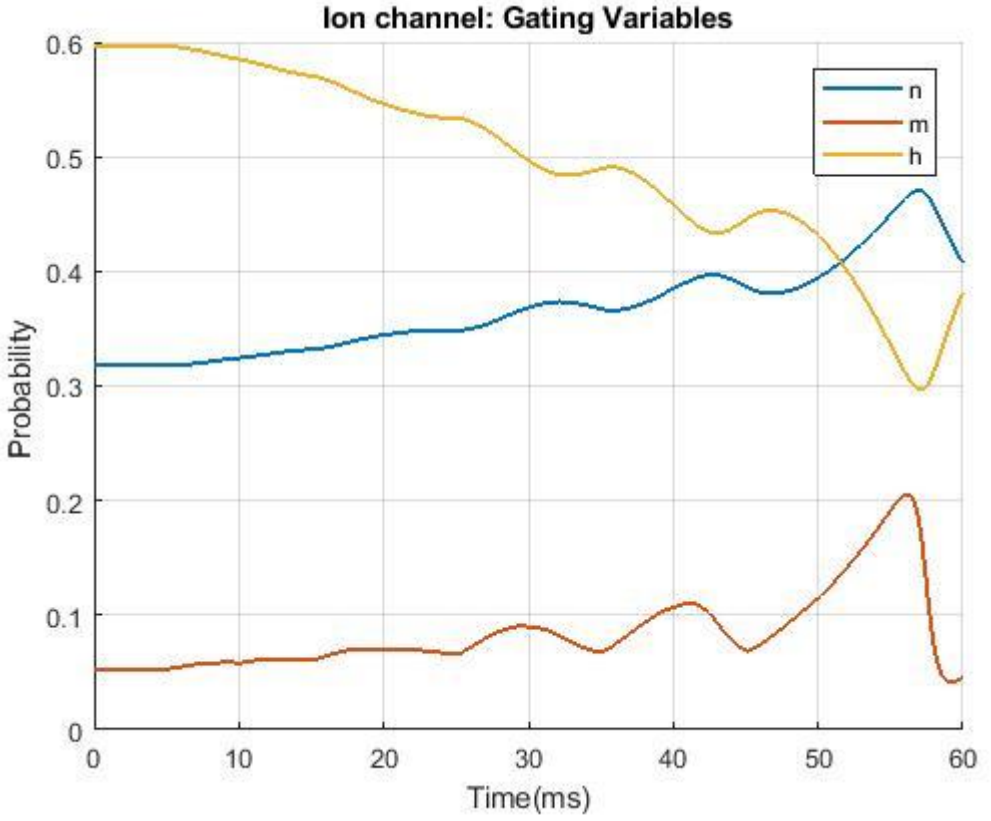
The amount of injected current slowly increased every 5ms over the course of the time series of 60ms. We can see the voltage threshold more precisely using the zoomed in graph ultimately showing that voltage threshold potential is to 4 decimal precision -52.1313mV. This can be evidenced by the below screen shot of the voltage membrane potential matrix for each time sample.

membrane potential matrix:

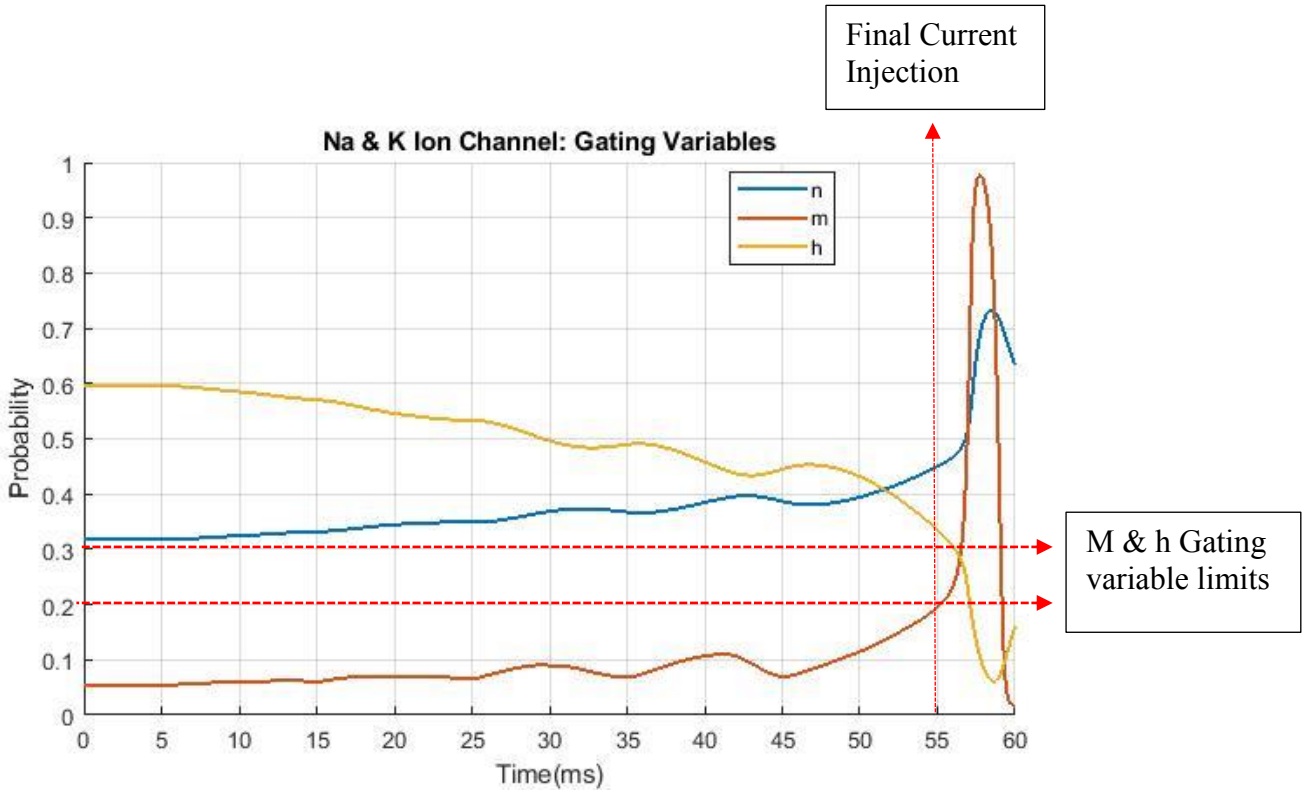
5001 double

5585	5586	5587	5588	5589
-52.1321	-52.1316	-52.1313	-52.1313	-52.1315

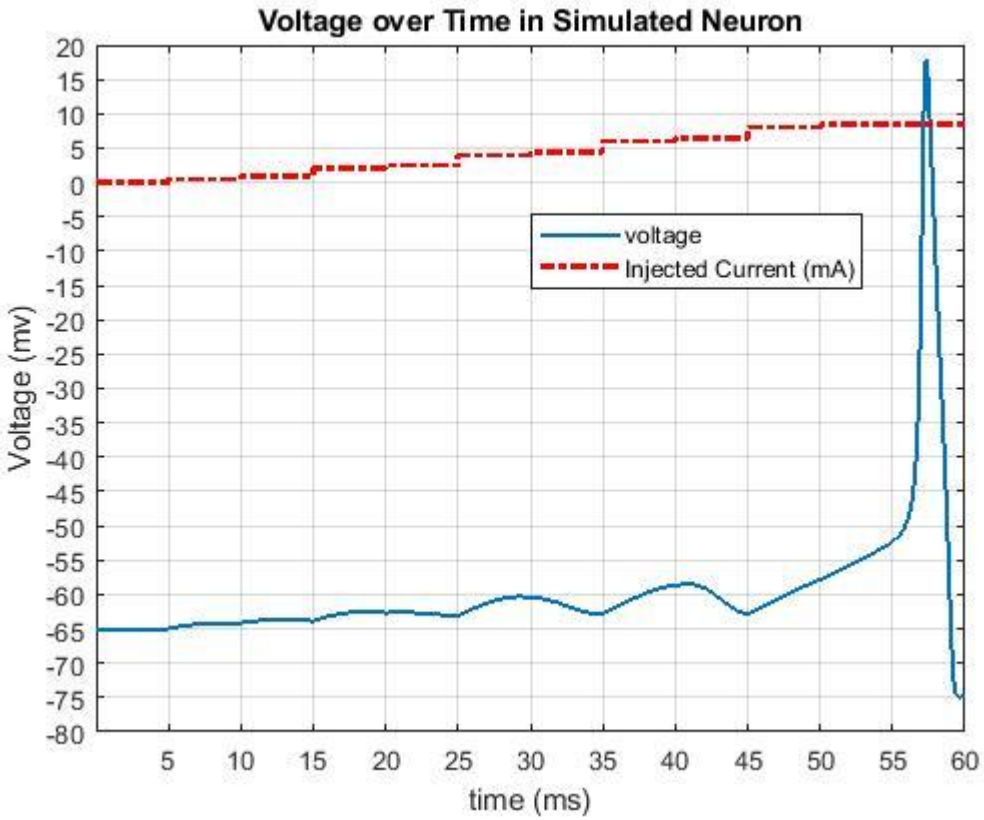
Such a threshold is directly related to the dynamics of the sodium gating variables, as shown below.



Based on the above graph it would seem that for variable (m) the probability of sodium channel gates being open must exceed 20% in order for an action potential to be generated. Likewise the probability of the sodium gates being in a state of inactivation to increases as the probability of sodium ion gates being open decreases via the closing variable (h). There is also a positive difference of 0.1 between (m), and (h) as they both seem to oscillate inversely.

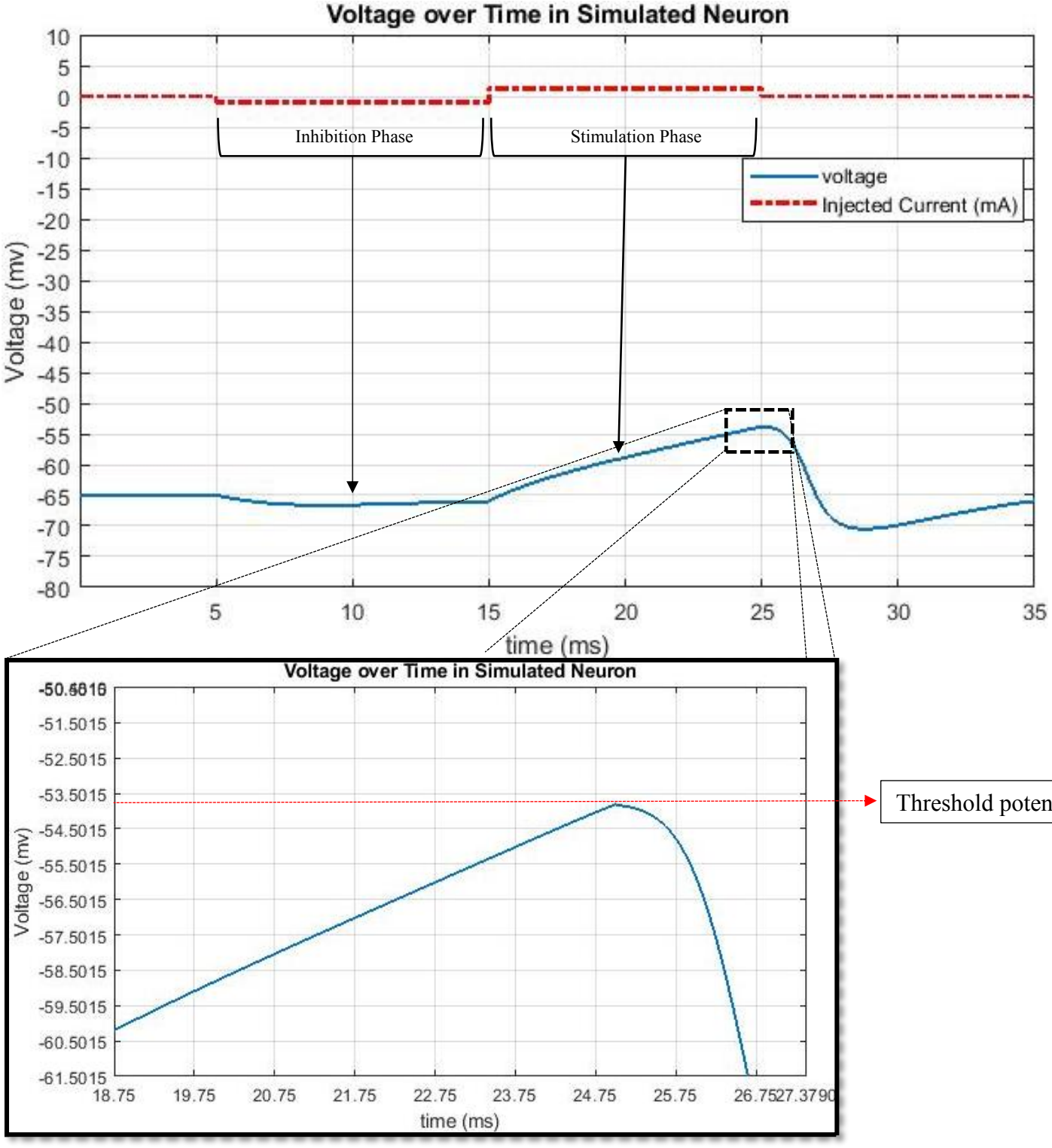


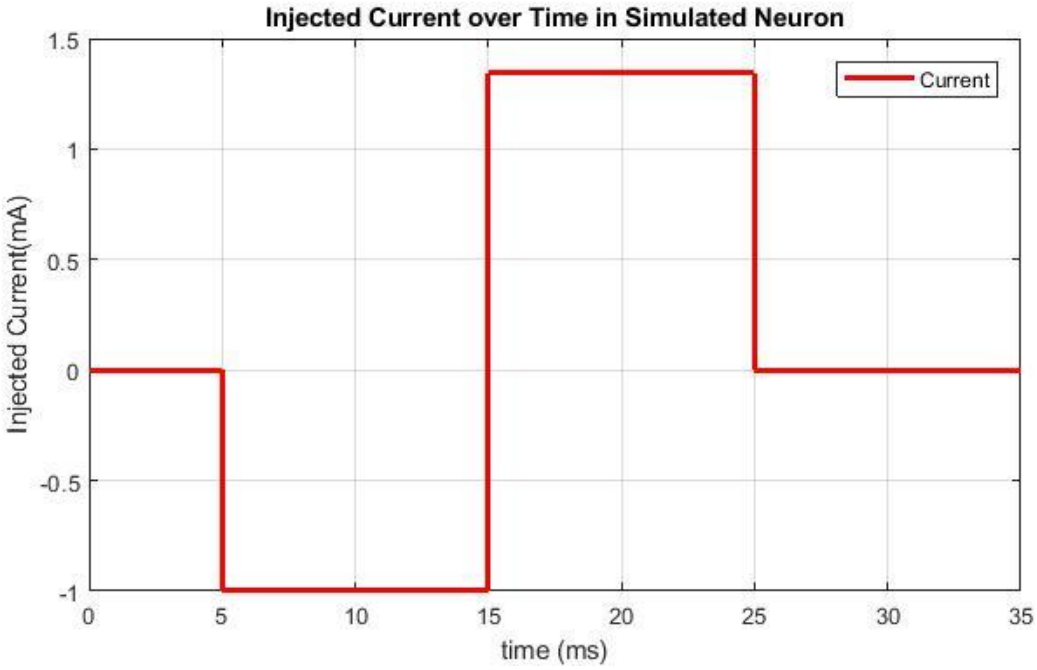
Originally the voltage was kept just under the threshold using 8.390mA of injected current at time = 55ms. In order to drive the membrane potential just over threshold 8.391mA of current was injected, which generated an action potential. Equally one can see that final current injection is enough to drive the (m) gating variable over the 20% probability limit, likewise with driving the (h) gating below the 30% probability limit. The overall results is an action potential as show below.



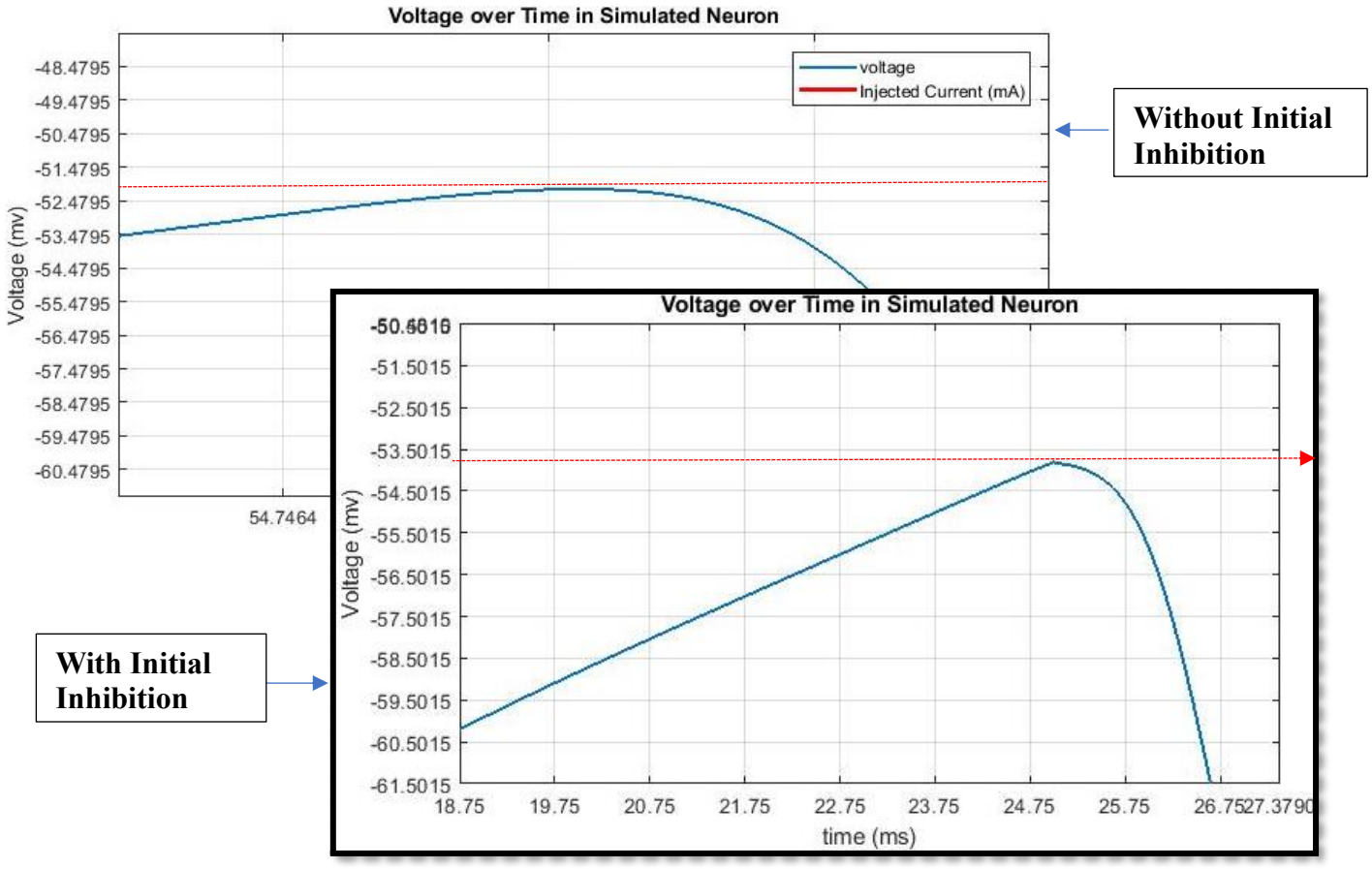
Modulating the Threshold potential:

In the above section the threshold potential was found to be -52.1313mV, nonetheless this threshold potential is relative and can change depending on the previous state of membrane itself. The state of the neuronal cell can be altered by injecting a negative current causing hyperonization, which is akin to causing the state of the membrane to become inhibited to some degree. Following this a sharp step increase of injected current will be applied, causing the membrane potential to as close as possible to threshold limit, as shown below:

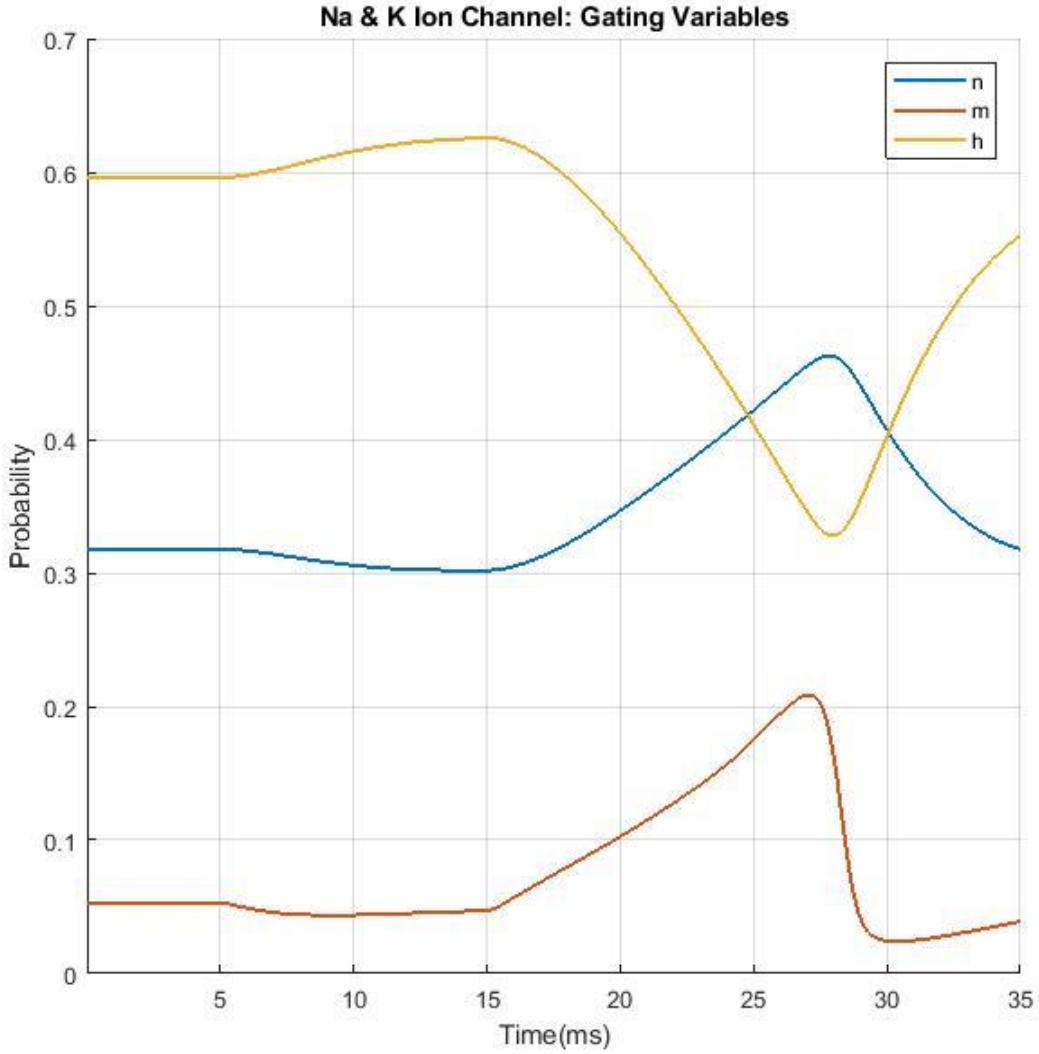




By inhibiting the neuron with a negative current injection of -1 it caused the membrane potential to be reduced by around 2.5mV with resting potential now at -67.5mV. Nonetheless when a sudden injection of excitatory stimulation is applied in increasing increments one s the new threshold potential has changed. One can see this more clearly by comparing the threshold results below:



The threshold potential without initial inhibition was -52.1313mV, whereas in contrast the threshold potential with inhibition is -53.8124. As consequence this shows that the threshold potential is not a set constant but can vary depending upon the previous state of the membrane, and specifically reducing the membrane potential by a certain degree through inhibition causes a relative reduction in the threshold potential.
In order to understand why the threshold for activation has reduced one must investigate the behavior of the Potassium and sodium gating variables during Inhibition, as shown below:

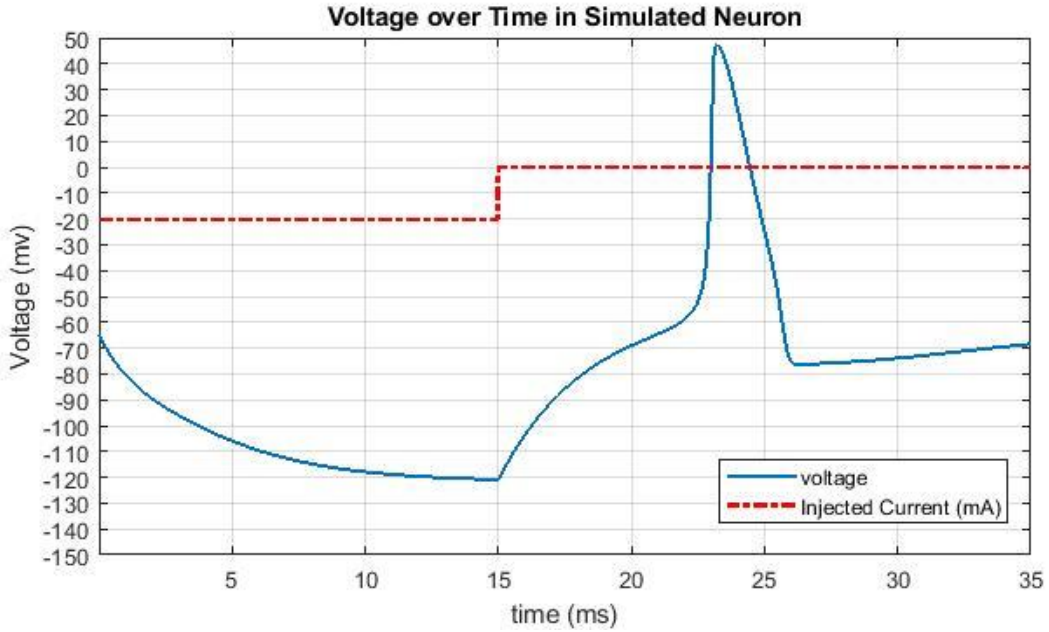


During the period of inhibition(5-15ms) one can see in the above graph that the value of (h) increases, meaning that the probability of inactivation of the sodium ion channels is reduced. However one does not observe the production of an action potential at this point due to the fact that the negatively induced inhibitory current causes a reduction in (m), meaning that the probability of the sodium ion gates being open is below 5%, and thus chance of depolarization is unlikely. Nonetheless notice that changes in (h) and (m) across time are different. More specifically, (h) increase a lot more during inhibition than (m), likewise opening rates of (m) are much larger than that of (h), meaning that (m) responsiveness to changes in voltage is a lot faster than (h's) rate of responsiveness. When inhibition is lifted at 15ms and an excitatory signal is inputted, one can see that (m) has period in which it is less suppressed by the inactivation variable (h), thus allowing (m) to reach its 20% gates open

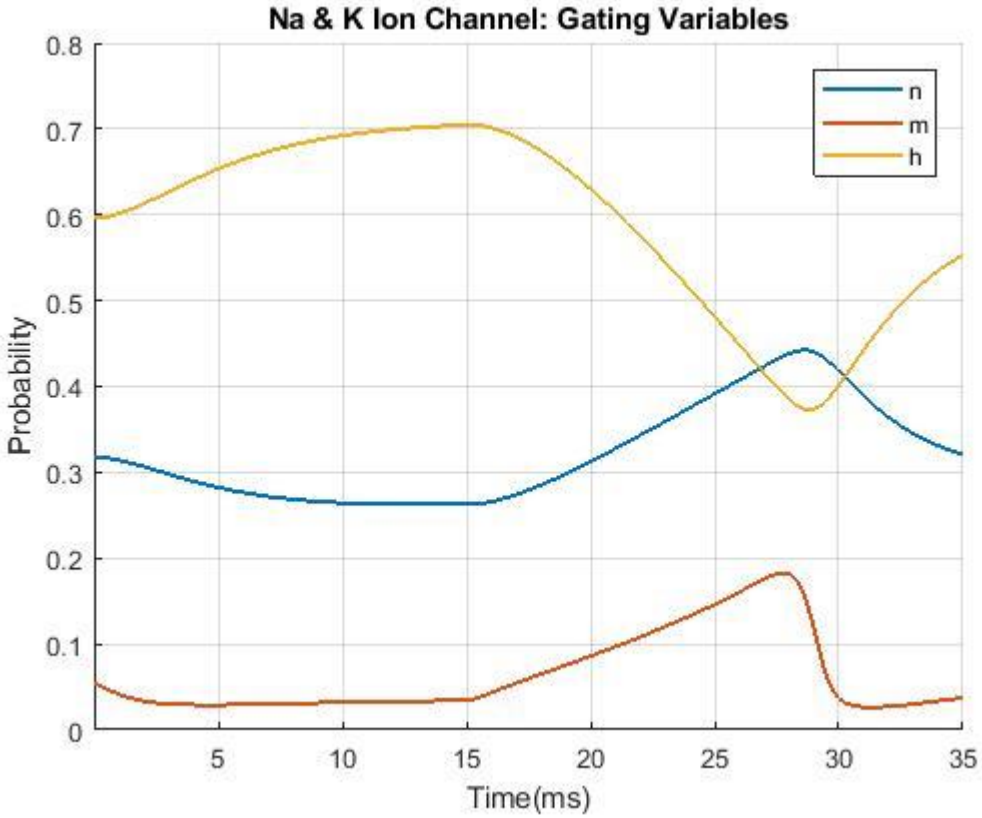
probability limit, with now a reduced value of (h) which is enough to produce an action potential. Ultimately the value of (m) will increase at a rate fast enough, whilst the value of (h) will increase at a rate slow enough to allow the membrane potential to be at a slightly smaller voltage level than before. This will create an increased positive difference between final peaks of the (h) and (m) variables as compared +10 when no inhibition was applied. It would seem that voltage threshold potential of the membrane is dependent upon the rate at which (m) can reach a high enough probability of sodium gates being in an opened (+0.20 probability) with respect to the level of suppression implemented by the rate of change of the (h)/ sodium channel inactivation state. In Summary this shows that the activation threshold of a cell is not a fixed voltage point but rather is dependent upon the interplay of the sodium inactivation variable (h) and the sodium gate opening variable (m), which themselves are ultimately modulated via the previous state of the membrane before excitation.

Rebound Firing

Rebound firing refers to an effect in which a neuron when released from inhibition will automatically fire and produce and action potential, without the need for any excitatory input. The effect can be shown below:



As you can see the neuron is able to fire an action potential when simply released from high levels inhibition, with 0 excitatory current being added. This could be explained firstly by considering the fact that functionally transitioning from a large negative value to 0 could be considered similar to transitioning from 0 to a high positive value. Therefore 0 input is more positive than the current membrane potential and is technically increasing, thus depolarizing the membrane and thus being represented as an excitatory input signal. It can be shown that 0 input is being considered as excitatory input with the below gating variable graph on the next page.



As shown above one can see that the probability of the sodium ion channel gates being in an opened state is increasing in a similar pattern when the system is injected with positive stimulation. As shown in previous graphs if the (m) variables gate state probability exceeds 20% it is very probable that an action potential will be produced. This seems to evident even with 0 current. Like wise as stated in the 'modulating the threshold' section we see the effects of inhibition on the (h) and (m) variables , but unlike before the variable (m) has been able to rapidly respond to the change in voltage with even less suppression from the inactivation variable(h) than before when less inhibition was implemented. Consequently, threshold required to trigger an action potential will also be lower than previously reduced threshold of -53.8124mV. Overall both factors may allow the membrane to depolarize enough to exceed the now reduced threshold limit to produce and automatically generated action potential.