Introduction:

The objective of this lab is to build a model of how action potentials in neurons are initiated and propagated. This is done by building the Hodgkin-Huxley model of action potentials. The model implemented in this lab was sourced from *Koch Ch. 6, 1997.* The equations used are as follows:

$$C_m \frac{dV}{dt} = \overline{G}_{Na} m^3 h(E_{Na} - V) + \overline{G}_k n^3 (E_k - V) + \overline{G}_m (E_{rest} - V) + I_{inj}(t) \qquad (1)$$

$$\frac{dw}{dt} = \frac{w_\infty - w}{\tau_w}, \quad \tau_w = \frac{1}{\alpha_w + \beta_w}, \quad w_\infty = \frac{\alpha_w}{\alpha_w + \beta_w} \qquad (2,3,4)$$

(Where w is n,m, or h)

$$\alpha_n(V) = \frac{10 - V}{100(e^{(10-V)/10} - 1)}, \quad \beta_n(V) = 0.125e^{-V/80} \qquad (5,6)$$

$$\alpha_m(V) = \frac{25 - V}{10(e^{(25-V)/10} - 1)}, \quad \beta_m(V) = 4e^{-V/18} \qquad (7,8)$$

$$\alpha_h(V) = 0.07e^{-V/20}, \quad \beta_n(V) = \frac{1}{e^{(30-V)/10} + 1} \qquad (9,10)$$

For this set of equations, Equation (1) represents the total circuit equation derived from the following figure:

Figure 1: Hodgkin-Huxley Model Circuit Representation

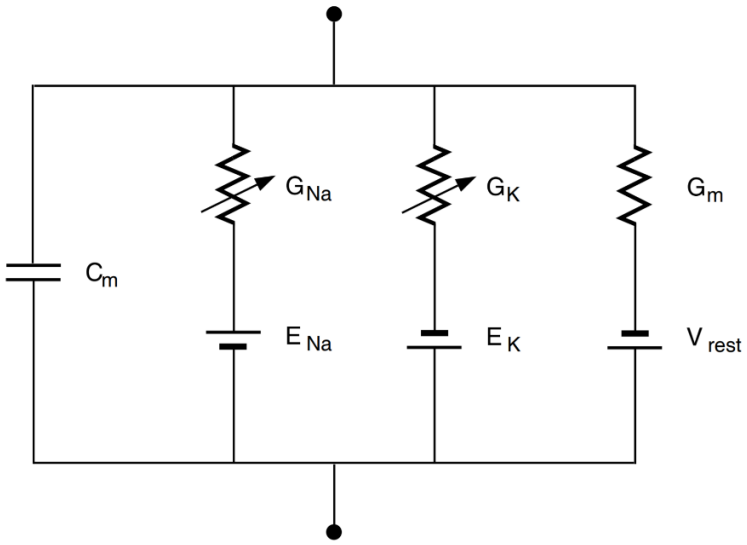

Figure 1: This figure shows a circuit representation of the Hodgkin-Huxley Model. Each ion is described by a series resistor and battery, with a capacitance in parallel. The capacitance is from the ion separation due to the cell membrane, while the battery is derived from the Nernst potential of the ions across the cell membrane. Finally, the variable resistor represents the conductance of the ion channel.

Utilizing these ten equations, the Hodgkin-Huxley model is constructed in Simulink. From this model, the students are to answer the question presented: an investigation of threshold behavior. Specifically, the lab asks the students to investigate why one current injection can lead to no AP, while a slightly larger injection can lead to an AP. The extra credit question posed askes the students to investigate the effects of changing the magnitude of τ_n and τ_m on the current required to reach the threshold for an AP.

Results:

For the first part of the lab regarding the investigation of the current required to hit the action potential threshold, the model produced the following results:

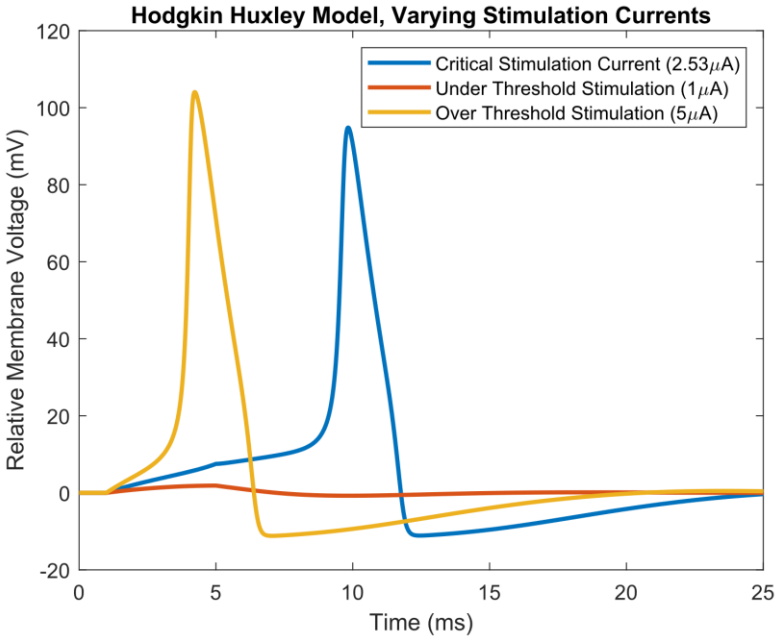

Figure 2: *This figure shows the action potentials that resulted from three different values of I_{inj} used in the model. It can be seen that regardless of the magnitude of I_{inj} the system returns to the same steady-state level (at zero mV). Similarly, it can also be seen that low values of I_{inj} to not trigger an action potential.*

From the results of this figure, along with the explanation provided in *Koch Ch. 6*, an explanation for the thresholding behavior can be drawn. As both the conductance of the sodium and potassium channels that are governed by the 'm' and 'n' gates (respectively) are voltage-dependent, changing the membrane voltage via a depolarising current (I_{inj}) changes the conductance of both channels. Specifically, from the equations 5-10, it can be seen that an increase in V leads to an increase in both m and n, which refers to both sodium and potassium activation, but a decrease in h, which represents a decreasing potassium inactivation. Furthermore, the time constant (τ) for sodium is one order of magnitude lower than τ for potassium (Eqn. 5,7). Thus the conductance change for sodium will occur much more rapidly than for potassium.

The result of this more rapid increase in sodium conductance is an increase in sodium current (I_{Na}). This sodium current drives the cell towards the positive Nernst potential of sodium (~115mV above rest). However, the depolarising current also increases the membrane voltage (V_m), allowing larger potassium currents (I_k) as the driving potential for potassium ($V_m - E_k$) is now larger. This potassium current drives the membrane voltage towards the potassium Nernst potential, which is blow resting voltage (~12mV under rest). Thus, a tug-of-war is setup between sodium and potassium immediately following a depolarizing current. Wherein, if the magnitude of the depolarising current is large enough to increase the membrane voltage to the point where the sodium current is greater than the potassium current, an action potential will follow. Similarly, if the voltage of the membrane was not increased enough due to the depolarizing current, the potassium current will be larger than the sodium current, which will prevent an action potential as the sodium current will drive the membrane voltage down. Thus, we see the hallmark thresholding phenomenon.

From the understanding developed above, the results from Fig. 2 can be interpreted. In the case of the "critical stimulation current," it can be seen that the depolarizing stimulation current was just slightly above the threshold voltage. This means that the sodium current was just barely higher than the potassium current, which is reflected in the relatively long period it took to trigger an action potential

(~6ms). This is then contrasted with the "over threshold stimulation," where it can be seen that the action potential is fired relatively quickly (~1ms) after the current was injected. It can also be noted that the peak of the "critical stimulation current" action potential is lower than the peak of the "over threshold stimulation" action potential. Finally, there is the "under threshold stimulation," where it can be seen that the depolarizing current was not large enough, and the resulting increase in the membrane voltage was not large enough for the sodium current to overtake the potassium currents. Thus, it is seen that the stimulation leads to no action potential, and the membrane returns to resting voltage after some time (~5ms). These results can be seen in the following Figure:

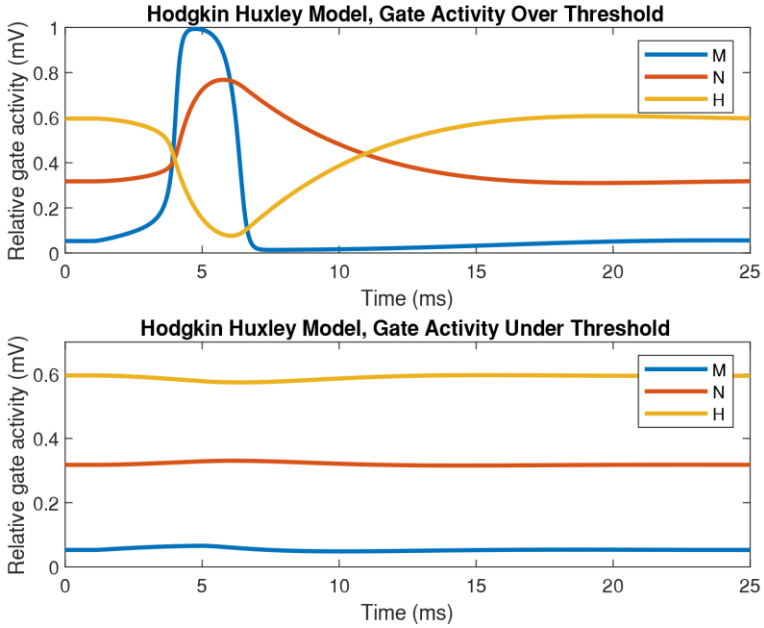

Figure 3: *This figure shows the relative activity for the three ion gates, M, N, and H, for a stimulation that is past the threshold (top) and a stimulation that does not meet the threshold (bottom). It can be seen that for the beyond threshold stimulation, all of the gate activities cross, with the M gate going from inactive to fully active, while the H gate goes inactive from being active. However, for the under threshold graph, there is a slight blip in the activities; however, they do not cross, and quickly return to the baseline.*

Extra Credit:

The second part of this lab was an exploration of the effects of changing the magnitude of the time constants of m and n, τ_m and τ_n. The results for changing τ_m are as follows:

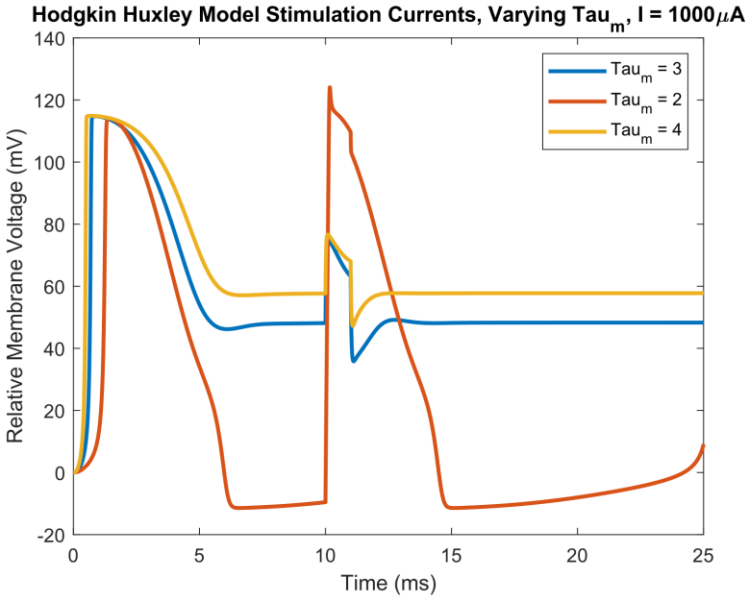

Figure 3: *This figure shows the action potentials that resulted from varying the gain for τ_m to 3 different levels (2x, 3x, 4x). It can be seen that with τ_m gain values larger than 2, the system has a new, significantly higher resting voltage. It can also be seen that even with significantly higher stimulation currents (1000μA vs. 5μA) there are no action potentials at τ_m gain values larger than 2. It is also interesting to note that the AP for a gain of 2x appears to exceed the sodium Nernst potential of 115mV.*

Further, when the analysis is expanded to vary τ_n, the following results are seen:

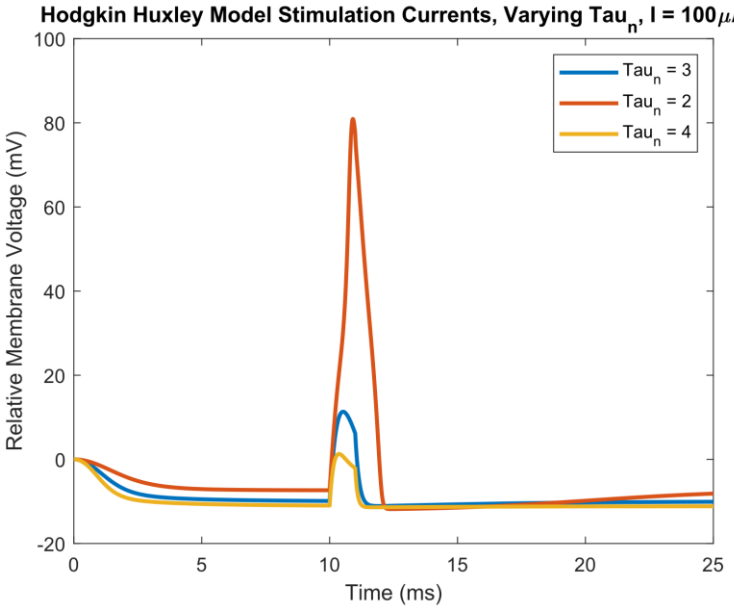

Figure 4: *This figure shows the action potentials that resulted from varying the gain for τ_n to 3 different levels (2x, 3x, 4x). It can be seen that with τ_n gain values larger than 2, action potentials do not fire, even with significantly higher stimulation currents (100μA vs. 5μA). Furthermore, it can be seen that the AP that does fire for the 2x gain does not reach as high of a voltage as the standard AP. Likewise, for all gain levels, a significantly lower resting voltage is observed.*

These results can be explained using the information provided above in the discussion for part one of the lab. From the explanation put forth above, it is known that τ represents the time constant, which governs how long the gates on the ion channel take to open. It is also known that the m and n gates refer to sodium and potassium activation, respectively. Thus, from this information, the following conclusions can be drawn for figure 4; with the gain in τ_m, the sodium channels are much more easily opened, and thus the baseline conductance is much greater. Thus the resting membrane voltage is increased. However, it also appears that a gain of 2x for τ_m is not sufficient to immediately disrupt the resting equilibrium, unlike higher gains. This disruption in resting membrane voltage is also likely what is disrupting the generation of full-fledged AP's for larger gain values.

Likewise, for the results shown in figure 5, it is known that as the gain of τ_n Increases, the activation for potassium gates increases, leading to an increase in potassium conductance. This increase in potassium conductance drives the resting membrane voltage negative towards the Nernst potential of potassium at -12mV, which is seen for all of the gain values in the figure. Similarly, it can also be seen that the higher gain values of τ_n also prevent any AP from initiating. This is because the increased potassium conductance snubs any potential membrane voltage increase from sodium currents due to its significantly higher conductance. Thus, for higher gain values of τ_n, larger and larger stimulation currents would be required.