

Will Solow and Skye Rhomberg

HW3 – CS346

5/7/20

1. In Exercise 1, we were tasked with implementing the HH model without the Na-K Pump. We started by initializing all the variables given to us in the tables along with several anonymous functions. The first of these anonymous functions calculated the opening and closing constants for m , n , and h , the probabilities of gates for Na, K, and Leakage being open.

Each of these functions was a function of the current voltage, as a greater voltage meant a greater opening rate constant for Na, and leakage, but less for K. Moving forward, each of these six opening and closing rate constants were used when calculating the anonymous function derivatives for n , m , and h for the RK4 approximation. Of the three anonymous functions, none of them took more than 2 variables, but for the sake of alignment and debugging, the functions were created to take V , n , m , and h as arguments so that in our RK4 approximations, each would align visually.

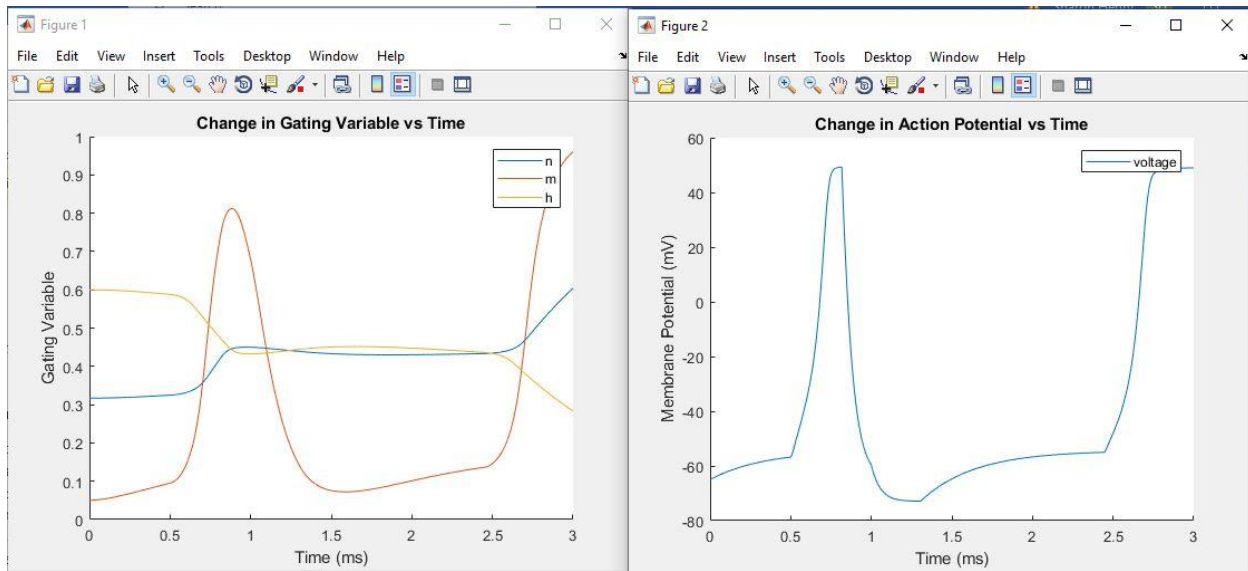
Next, we created anonymous functions to compute the currents through the K, Na, and Leakage channels. Unlike the derivative functions above, none of these were programmed to input all the same variables as they do not need to line up in the simulation loop. These equations were implemented exactly as described in the textbook.

The last anonymous function is by far the most interesting: the derivative calculation for voltage. In addition to V , n , m , and h , it also takes parameters for I , the current input current, and Na_On and K_On -- flags for if the Na and K channels are open or closed. The model gives the derivative of voltage as a function of the input current and the currents of each of the channels. However, the channels are not always open so voltage gating needed to be implemented.

To do so, the current of K was multiplied by K_On as K_On was either 1 (open) or 0 (closed), effectively controlling whether the current of K factored in the calculation of the equation for change in voltage. The same was done for the current of Na.

To calculate the value of Na_On , additional constants were created for the threshold for when the Na gate opened and closed. Using a logical operator, the Na_On variable was equal to 1 if the voltage was above -55mV and below 49.3mV, and if the K_On was 0 (meaning that the K gate was closed). This meant that after the K gate opened, the Na gate had to close as required in the model and could not open again until the K gate was shut. The K gate opened if the voltage was above 49.3mV and closed during repolarization, as soon as the derivative of voltage was no longer 0. Thus, using a logical operator again, K_On was 1 if the voltage was greater than 49.3 or if the derivative was negative. This ensured that the K gate opened at the threshold, closed the Na gate, and stayed open until the voltage reached its minimum.

These variables were calculated every loop and put into the $dVdt$ anonymous function to calculate the change in voltage as a function of the current. To finish off the model, an initial current of 15mV for .5 seconds was applied beginning .5 seconds into the simulation. This .5 second offset was calculated based on the time step, and the applied current was calculated with another logical operator. If the loop was between the calculated time step in terms of iterations, the logical operator would return 1 and be multiplied by the applied current, otherwise it would return 0 meaning that the current was shut off.



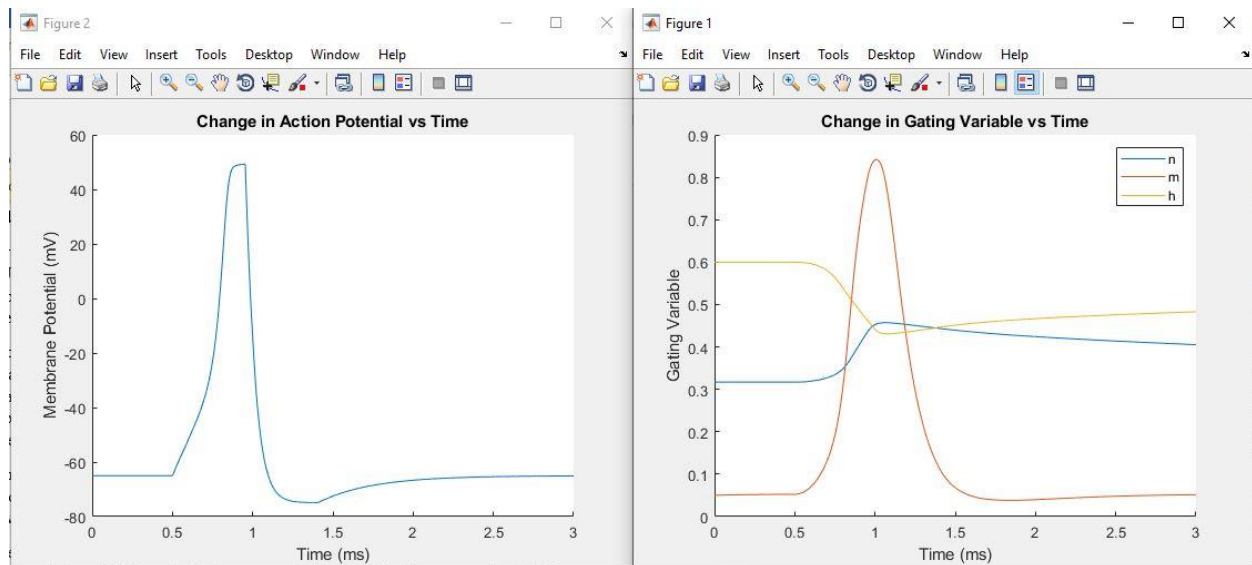
As we can see from the above simulation, the graph is a way off from the expected HH graph in the textbook. Immediately we see that the voltage climbs slowly off the start. This is because although the K and Na gates are closed, the Leakage gate is open. Without the pump to counteract the flow of K ions out of the interior through the Leakage channel, the mV difference rises slowly until the initial current is applied at .5 seconds.

The spike appears relatively normal in the voltage graph, and the graph of n , m , and h look appropriate. However, as the simulation continues, we see the importance of the pump to maintain equilibrium. Without the pump, the Leakage will continue until the membrane potential is above -55mV meaning the Na gates open again causing another action potential. Interestingly, without any more voltage being applied, the mV threshold doesn't quite reach high enough meaning the K gates never open and so the voltage never drops.

2. In Exercise 2, we were tasked with implementing the Na-K pump. The role of the Na-K pump is to counteract the effect of the Leakage channel during the resting phase to keep the potential at equilibrium. Thus, the only way to cause an action potential is with external stimulus.

Using the code from Exercise 1, we added a new constant I_P for the current of the pump. However, unlike the other currents, the pump current is constant and is therefore not a function of voltage. The only job of the pump is to cancel out the Leakage, so the pump constant was the negative of the initial leakage value. This constant was then added into the anonymous function

for voltage calculation. Otherwise, nothing else was changed, but the results are impressively different.



Here we finally see the importance of the pump. Unlike in Exercise 1, before the initial stimulus, the voltage stayed perfectly constant, showing the pump's role in maintaining equilibrium. Then, after the action potential, the voltage steadily climbs back to -65mV before levelling off. We see the corresponding changes in the graph of n , m , and h in that they there is one action potential before they start to return to their normal values.

Currently, the major difference between our results and the ideal HH model is that the peak of the action potential is later and less immediate, with flattening around the maximum rather than a sharp point. Additionally, the rebound of the voltage suddenly jumps up once the K channel closes as opposed to being a smooth line. On the other graph of m , n , and h , we see that n and h cross each other when they shouldn't in the graph shown in the textbook. We believe that this is because the Na-K pump is always on in this simulation whereas it is not always in real life. If, like in reality, the pump were to shut off as the Na concentration approaches 0 inside and K concentration approaches 0 outside, we might see an impact on the peak of the graph and on the rebound of potential during repolarization.

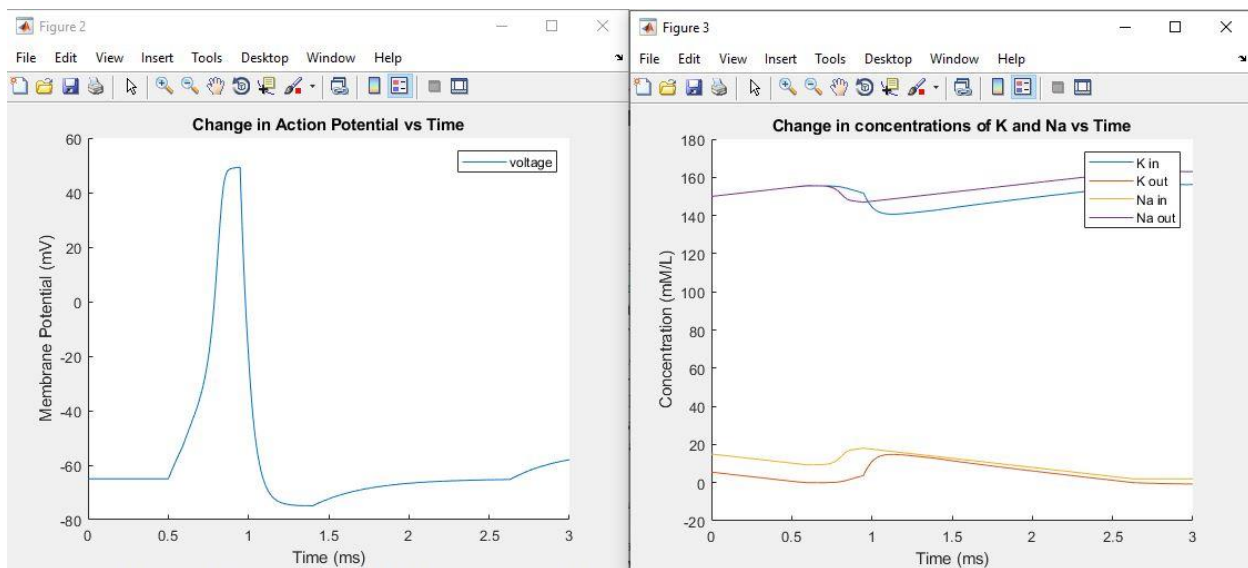
3. In Exercise 3, we were asked to simulate the concentrations of the K and Na ion concentrations inside and outside the cell membrane in addition to what we did in Exercise 2. This came with one caveat that the pump was only to run when the concentrations of K outside and Na inside were both greater than 0.

To implement this, we created four variables for the concentrations of K in and out and Na in and out. To gate the pump flow, I_P , we created a variable P_On similar to Na_On and K_On from above. P_On is initialized at 1 as the pump is initially on to create equilibrium voltage with the initial leakage of K. As the pump pumps Na out of the cell and K into the cell, we used a logical operator to evaluate the concentration of Na inside and K outside and return 1 to P_On if

they were both greater than 0. If not, P_{On} would be 0 and this was passed to our $dVdt$ function to turn off the flow of the pump.

To simulate actual flow of ions across the membrane, we created two new anonymous functions $dNadt$ and $dKdt$ that modelled the change of concentration outside of the cell. $dKdt$ was a function of I_K , I_L , and I_P , where I_P was multiplied by 2 to simulate the flow of 2 ions into the cell. Likewise, $dNadt$ was a function of I_{Na} and I_P where I_P was multiplied by 3 to model the flow of 3 Na ions out of the cell. Then, in the main simulation loop, we used an RK4 implementation to obtain the change in concentration outside. This concentration change was then added to the current concentration outside and subtracted from the current concentration inside for the respective ions.

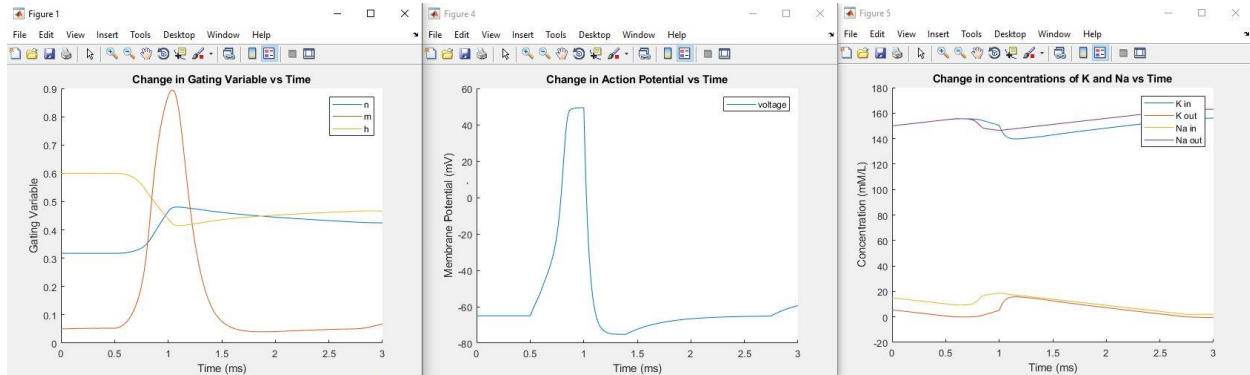
As a result of this implementation of the model, we got the following graphs below:



Notice that the concentration of Na inside and K outside is decreasing initially while the net voltage stays constant. This is what we expect as, initially, the Na and K gates are closed so the only thing impacting the concentrations are the pump and the leakage current. Thus, we expect these two concentrations to drop until an initial voltage is applied. Once the initial voltage is applied and the Na gates open, we see an increase of Na ions inside the cell as we expected. Slightly later as the Na gates close and the K gates open, we see a sharp rise in the K concentration outside. Once the gates close, the concentrations of K outside and Na inside gradually decrease until they hit 0.

At this point in this model, the pump shuts off as there are no ions to pump against the gradient. Thus, we see an increase in the voltage after 2.5ms as the pump is no longer working to counteract the leakage. As a result, the voltage increases. While this is not what we would expect in the real model, it does make sense with how we implemented the current model in our simulation. This differs from Exercise 2 as the pump is always on and we did not originally model the concentrations of the ions.

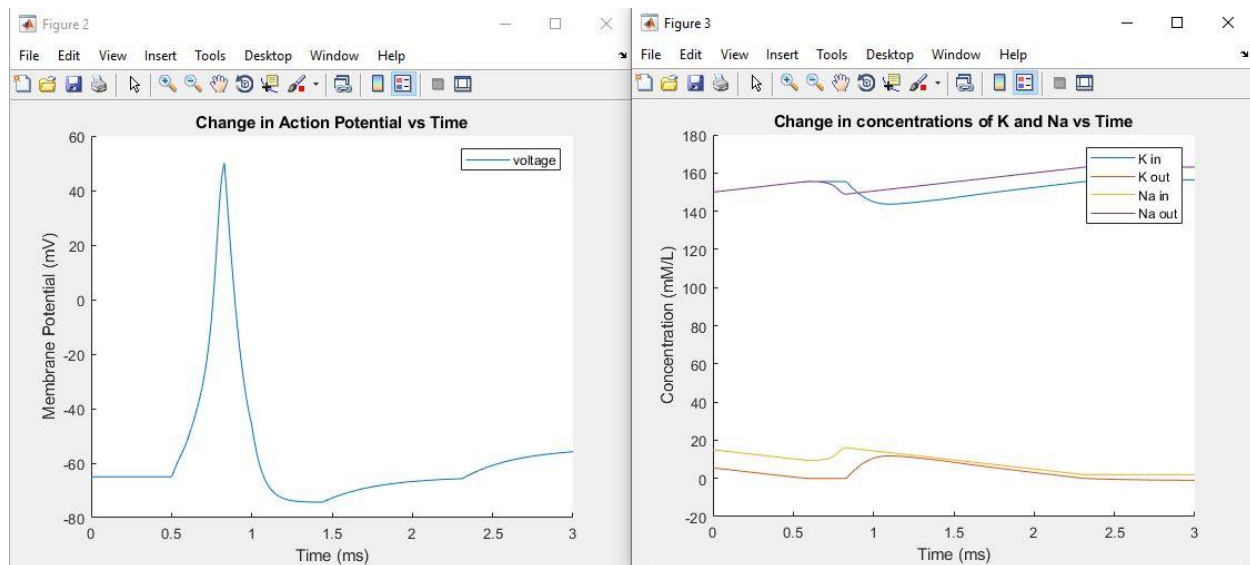
4. In Exercise 4, we were asked to use our model from Exercise 3 except to change when the Na gates closed and the K gates opened from 49.3mV to 50.0mV. Otherwise, the model was kept the same using the code from Exercise 3. Results are pictured below:



Immediately, we see some differences from the graph shown in Exercise 3. At the peak of the voltage, it takes a longer period of time before it drops. This is likely because there is a higher threshold of 50mV before the K gates open and Na gates close. However, the initial current applied is not quite enough to push it over that threshold immediately, and so we see a slight lull and a bit of a more elongated curve at the peak of the voltage before it drops down like normal. After dropping, the voltage behaves as expected in correspondence to Exercise 3 given that the pump shuts off when the concentrations of Na inside and K outside hit 0.

A similar change is seen in the concentrations that correspond to the change in the gating value. The Na gate opens at the same time as in Exercise 3 but does not close until later (eyeballing it looks like in Exercise 3 it closes at around .75ms compared to .9ms in Exercise 4). Likewise, the K gate opens later and so we see a delay in the sharp spike of K outside like in Exercise 3. Again, this is in line with what we observed in the graph for the voltage in that there was a longer delay until the K gates opened.

5. In Exercise 5, we tested the hypothesis that a voltage gated leakage channel could increase the maximum height of the action potential reached in terms of voltage. To do this, we created a new constant called L_{close} which was initialized to -54.4mV. It represents when the leakage channel closes. We also created a new variable L_{On} which was initialized to 1. In the simulation loop, we used a logical operator to evaluate L_{On} each loop. L_{On} was 1 when the voltage was less than L_{close} (-54.4mV) and 0 otherwise. L_{On} was passed into our anonymous functions for $dVdt$ and $dKdt$, being multiplied by I_L any time it appeared. Our results are below:



At first glance it does not appear that the voltage reached much higher. However, what is immediately more noticeable is the fact the spike in the voltage and the sequential drop is much more immediate. This change is in line with what we expected from the actual Hodgkin Huxley model for action potential. Additionally, we see the change in the graph of ion concentrations as well. The changes of all ions are much more abrupt than they were in Exercise 4 which accounts for the closure of the leakage channel during the action potential. This makes sense as the leakage closing means the change is more drastic and we don't get the slow uptick to 50mV before the K gates open and the voltage drops. This implies that the voltage does in fact obtain a higher action potential as it reached 50mV much quicker than in Exercise 4.

The only noticeable difference between our final graph of our model and the actual Hodgkin Huxley model is that at around 2.3ms the voltage starts to creep up again. This is because the concentrations of K outside falls to 0 (with Na inside being close behind) and so the pump shuts off. Clearly, it does not make sense to have the pump running when we do not have any ions to pump, however in this model with the simplifying assumptions that we made, it is logical that the ion concentrations would drop to 0.

We never experienced negative concentrations in our model, however the concentration of K outside does drop to 0. At this point, as described in Exercise 3, the pump does shut off, effectively stopping the concentrations from going negative. At this point, we decided to leave the model as it is. Given that we are missing some complications from the model like the Ca ions and sodium leakage channels, it seems okay that we do not have a perfect model. We have the correct action potential graph and a good curve for repolarization which is what is important in this model.

6. Our first hypothesis was that an increased initial voltage (tested from $I=15$, the base, to $I=20$) will result in a higher action potential. This made sense as a greater initial voltage should push the total voltage higher as it accounts for a more rapid change initially. However, as it was

impossible to eyeball the change, we printed out the maximum voltage at the end of the simulate. For an initial current of 15, the max voltage was 50.0117mV. However, for an initial current of 20, the max voltage was only 50.1247. We expected a much larger change than that, but it might be that this is the most that we can get. In hindsight, it makes some sense than the cap is near 50 as the K gates open at 50, meaning that many positive ions are leaving the cell and so the voltage cannot continue to increase.

Following the logic in the above hypothesis, we then hypothesized that increasing the gating constants of Na_close and K_open from 50 to 55mV would increase the size of the action potential. By doing this, we found that the maximum voltage reached 51.0395. While this is more than in the previous hypothesis, we still felt that it is a fairly small change in the maximum value. It appears that there is some other limiting factor at play that accounts for why the sodium no longer continues to flood into the cell. We recall that the K gates open if the voltage is over a threshold or if the change in voltage is negative. Thus, given that the voltage never reaches its threshold of 55mV, there must be some limiting factor in the way the Na ions enter the cell that stops the voltage from climbing to the threshold at which the K gates would open.

In an attempt to increase the spike caused by a sodium influx into the cell, we then hypothesized that changing the activation and inactivation variables for m (the sodium gating variable) would cause an increase in maximum voltage. Keeping the voltage gating constants at 55mV, we then changed h_init -- the sodium inactivation variable -- from .6 to .3. This led to a maximum voltage of 51.4431mV. While this is an increase from before, we still fail to see the voltage reach 55mV, meaning that the voltage is no longer increasing to the point where the potassium gates open as the change in voltage is negative. We tried again with a value for h_init of .1 and got a maximum voltage of 52.4088mV which is more of a noticeable increase. Interestingly, when decreasing it by an order of 10 to .01, the maximum voltage actually decreased to 50mV and never dropped. This is likely due to some effect on the gating probabilities meaning that no ions were flowing through meaning that the potassium gates never opened to decrease the concentration inside the cell.

In summary, we were able to get a small change in maximum voltage by tweaking the constants. Clearly, if we changed the anonymous functions we could have gotten a much larger change in voltage, but this would not have been true to the model. Instead, we attempted to change the constants to differ each simulation. This worked with the varying results as described above.