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HW3 – CS346

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1. In Exercise 1, we were tasked with implementing the HH model without the Na-K Pump. To do so, we started by initializing all the variables given to us in the tables along with a large number of anonymous functions. The first of the anonymous functions were 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 function was created to take V, n, m, and h so that in our RK4 approximations, each would be in line.

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 as it is the derivative calculation for voltage. In addition to V, n, m, and h, it also takes parameters for I, the current inputted current, and Na\_O and K\_O, flags for if the Na and K channels are open or closed. The model gives the derivative of voltage as a function of the inputted current and the currents of each 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\_O as K\_O was either 1 (open) or 0 (closed), effectively controlling the role of the current of K in the calculating for the equation for voltage. The same was done for the current of Na.

To calculate the value of Na\_O, additional constants were created for the threshold for when the Na gate open and closed. Using a logical operator, the Na\_O variable was equal to 1 if the voltage was above -55mV and below 49.3mV, and if the K\_O was 0, meaning that the K gate was closed. This mean 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 opens if the voltage is above 49.3mV and closes during repolarization, as soon as the derivative of voltage is no longer 0. Thus, using a logical operator again, K\_O was 1 if the voltage was greater than 49.3 or if the derivative was negative. This ensured that the gate opened at the threshold, closing the sodium 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 was applied .5 seconds into the simulation. This .5 second offset was calculated based on the time step, and so the applied current 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.

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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 mV 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.

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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 only difference is the drop at the top of is later and less immediate, and 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 due to the fact that the Na-K pump is always on in this simulation whereas it is not always in real life. Thus, assuming it shuts off as the Na concentration approaches 0 inside and K concentration approaches 0 outside, its shutting off during the simulation may impact the peak of the graph and how it rebounds.

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\_O similar to Na\_O and K\_O from above. P\_O 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\_O if they were both greater than 0. If not, P\_O 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:

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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 exactly the same using the code from Exercise 3. Results are pictured below:

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Immediately, we see some differenced 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.