BME 211 Hodgkin Huxley Simulation

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1 Analyzing Voltage Channels with the Hodgkin-Huxley Model

1.0.1 Abstract

Neurons, the cells in our brain that transmit nerve impulses, use the principles of Voltage, Conductance, Current, and Capacitance to connect our nervous system to our bodies, allowing for instantaneous responses to the environment. Each neuron cell is composed of dendrites, axons, and synapses where a "signal" is received, transported down the cell, and transmitted to neighboring cells, respectively. These "signals" are actually just depolarization and repolarization of the cell membrane from the movement of potassium and sodium ions, which causes a potential difference across the inner and outer spaces; the depolarization and repolarization represent a rise and fall in voltage which is called the Action Potential. The 1963 Nobel Prize in Physiology or Medicine was awarded to Alan Hodgkin and Andrew Huxley, who modeled Action Potentials by relating biological components to circuit components, allowing for a deeper understanding of how neurons work.

1.0.2 Background

The Neuron The human body is an evolutionary marvel, and its functionality is a culmination of the natural sciences. One of the most important features of the human body is its ability to communicate with itself in response to change, which is primarily governed by the Nervous System. The Nervous system is a network of fibers that transmits a signal from one part of the body to another, and is made up of the brain and spinal cord. The cells that do the transmitting are called neurons, and they transmit signals by sending electrical impulses, called Action Potentials, to a desired location. There are three functional parts of the neuron that are integral to understanding how they work: the cell body, dendrites and the axon (Figure 1). The cell body is the control center of the neuron where all inputs are gathered processed. Dendrites are an extension of the cell body that gather input from other neurons while the axon sends signals to other neighboring neurons. When a signal arrives at the dendrites on the left side of the neuron, the stimuli given to the dendrites are integrated at the cell body, which can then generate a nerve impulse (Action Potential). The impulse travels down the axon to the right side of the neuron, where it "jumps" to another set of dendrites and the process repeats.

Resource: https://www.khanacademy.org/test-prep/mcat/organ-systems/neuron-membrane-potentials/a/neuron-action-potentials-the-creation-of-a-brain-signal

Action Potential Neurons, like all cells, have a membrane that separates the inside of neuron from the outside. Potentials are able to be measured between the inside and outside because

of a concentration gradient, which is created when there is a difference in the amount of ions inside the neuron than outside. Concentration gradients in the body often involve a difference in concentration of sodium and potassium. The Action Potential is simply a shift in the neuron's membrane potential (from negative to positive) that occurs when ions start flowing in or out of the cell through "gates," known as ion channels. The gates depend on voltage, and will open and close accordingly in response to the potential of the cell. Before any signal is received, the cell sits at a constant potential called the Resting Potential (experimentally measured to be -70 mV). Under typical situations, the Action Potential propagates as follows: 1. A signal is received from a cell, and the cell becomes depolarized, meaning positive charge flows from the outside of the cell to the inside of the cell. Once a certain potential is reached (experimentally measured to be -55mV), an Action Potential will begin to fire, and a gate will activate letting a larger amount of positive charge flow in (Sodium) 2. When another positive threshold is reached, the first gate is closed and another gate will open causing positive charge (Potassium) to flow out of the cell in a process called polarization 3. After another threshold, the final gate will close and the cell will regress to its Resting Potential Again

It is important to note that the Action Potential only fires when the specific thresholds are met, known as the "All or Nothing" principle.

Resource: https://en.wikipedia.org/wiki/Hodgkin%E2%80%93Huxley_model https://neuronaldynamics.epfl.ch/online/Ch2.S2.html

Hodgkin and Huxley Alan Hodgkin and Andrew Huxley, two British born scientists, authored a series of five papers describing nonlinear ordinary differential equations that model how action potentials can be initiated and propagated through an axon. The papers detailed their research into the squid giant axon, which has an abnormally large axon (1mm in diameter) big enough to conduct experiments on. This ground-breaking work has a wide range of applications on many organisms and won Hodgkin and Huxley the Nobel Prize in Physiology in 1963.

Resource: https://www.swarthmore.edu/NatSci/echeeve1/Ref/HH/HHmain.htm

1.0.3 Setup

In order to describe the way Action Potentials propagate, Hodgkin and Huxley related the membrane of the neuron to a circuit (Figure 2). The membrane has a capacitance C_m, and accounts for all of the gates that were described previously. The Sodium and Potassium gates are voltage dependent, and are represented in terms of their conductances. To find the total current of ions flowing from inside to outside as a function of time, Kirchhoff's rules and the Ohm's Law were used. The capacitance of the membrane is a constant, but by virtue of ions moving, the voltage is not. Using the relationship of capacitance and charge, the membrane current can be solved as such:

$$Q = C_m * V_m$$

$$\frac{dQ}{dt} = C_m * \frac{dV}{dt}$$

Where V_m is the intracellular voltage

For the gates, Ohm's Law describes how the conductance (which is $\frac{1}{R}$) and voltage relate to current passing in and out of the membrane. Because the sodium and potassium ions themselves have voltages (represented by batteries in each branch), the voltage term in the Ohm's Law equation is the voltage of the membrane (V_m) - the Nernst potentials of the ion (E_{Na}, E_K). The third

gate is known as a leak channel, and is a gate that allows sodium and potassium to pass in order to maintain the resting potential, and is not voltage activated. The values of the conductance for sodium and potassium are dependent on the membrane voltage by formulas derived by Hodgkin and Huxley through their experiments. The equations are:

$$I_{Na} = g_{Na} * m^3 * h * (V_m - E_{Na})$$
$$I_K = g_K * n^4 * (V_m - E_K)$$
$$I_L = g_L * (V_m - E_L)$$

where:

$$\frac{dn}{dt} = \alpha_n(V_m) * (1 - n) - \beta(V_m) * n$$

$$\frac{dm}{dt} = \alpha_m(V_m) * (1 - m) - \beta(V_m) * m$$

$$\frac{dh}{dt} = \alpha_h(V_m) * (1 - h) - \beta(V_m) * h$$

The values of n, m, and h describe the probability that a gate will be open at a given time. Note that the Leak current isnt bound by any of these probabilities because it is not voltage gated. The values of n, m, and h are values between zero and one. α and β are described by the equations:

$$\alpha_n(V) = \frac{.01 * (10 - V)}{e^{\frac{10-V}{10}} - 1}$$

$$\beta_n(V) = .125 * e^{\frac{-V}{80}}$$

$$\alpha_m(V) = \frac{.01 * (25 - V)}{e^{\frac{25-V}{10}} - 1}$$

$$\beta_m(V) = 4 * e^{\frac{-V}{18}}$$

$$\alpha_h(V) = .07 * e^{\frac{-V}{20}}$$

$$\beta_h(V) = \frac{1}{e^{\frac{30-V}{10}} + 1}$$

Finally, because Kirchoff's Loop rule states that the sum of current in must equal the sum of the current out, the total current is equal to:

$$I_{ext} = I_{Na} + I_K + I_L + C_m * \frac{dV}{dt}$$

My model uses Eulers method to solve the nonlinear differential equations that describe the current flow of sodium and potassium. First, I created variables to describe the simulation time of my Action Potential. Second, I created a cell filled with tests of different currents which I control to see what impact the external current has on the Action Potential. Next, I used a for loop that goes through each time step in my simulation and calculates the value of each equation, and updates

the array at the given i value. Finally, I graph the conductances of sodium and potassium, and the Action Potential. I repeated the process for each testing current and observed how the graphs changed with different magnitudes of current, and different deliveries.

To judge the relative success/failure of the tests, it is important to note what constitutes a "correct" graph. If the plotted graph has a sharp spike that goes up, and then down past the resting potential, and exhibits repeating behavior, that means it follows a typical action potential and is a success.

Resource: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1392413/pdf/jphysiol01442-0106.pdf

In [228]:
```
## Import usual libraries
import numpy as np                          ## numpy is a library that inclues most of
import matplotlib.pyplot as plt             ## this is the library we use to plot
from IPython.display import Image           ## this is to import images from a file
```

In [88]:
```
# Create a time sufficient enough to deliver the impulse across the system
sim_time = 100
dt = .01
times = np.arange(0,sim_time,dt)
Ntimes = len(times)
```

In [299]:
```
## Set variable for the membrane current equal to values to simulate current inside of
IextArray = np.zeros(Ntimes)
current_1 = 20 # A current value that is within range of normal neuron Action Potentia
current_2 = 3 # A current that is much less than normal  neuron Action Potential condi
current_3 = 100 # A current that is much higher than the normal neuron Action Potentia

## Current Test 1: Constant current with each of the different testing values
#IextArray[0:Ntimes] = current_1
#IextArray[0:Ntimes] = current_2
#IextArray[0:Ntimes] = current_3

## Current Test 2: Step current with steps the size of the testing values
#IextArray[0:500] = current_1
#IextArray[501:2000] = 0
#IextArray[2001:Ntimes] = current_1

#IextArray[0:500] = current_2
#IextArray[501:2000] = 0
#IextArray[2001:Ntimes] = current_2

#IextArray[0:500] = current_3
#IextArray[501:2000] = 0
#IextArray[2001:Ntimes] = current_3


## Current Test 3: Sinusoidal current with amplitude the size of the testing values
#IextArray = current_1*np.sin(times)
```

```
#IextArray = current_2*np.sin(times)
IextArray = current_3*np.sin(times)

plt.plot(times, IextArray)
plt.xlabel('Time (ms)')
plt.ylabel('Current (mA)')
```

Out[299]: Text(0,0.5,'Current (mA)')

In [300]:
```
## These constants are used in the formulas above and were calculated from the researc
gbar_K = 36 ## conductance of the potassium channel
gbar_Na = 120 ## conductance of the sodium channel
g_L = .3 ## conductance of the leak channel
E_K = -12 ## Voltage associated with potassium
E_Na = 115 ## Voltage associated with sodium
E_L = 10.6 ## Voltage associated with the leak
C = 1 ## Membrane capacitance
```

In [301]:
```
## These are the arrays necessary to hold the values from the for loop
VArray = np.zeros(Ntimes)
I_NaArray = np.zeros(Ntimes)
I_KArray = np.zeros(Ntimes)
I_LArray = np.zeros(Ntimes)
I_totalArray = np.zeros(Ntimes)
a_nArray = np.zeros(Ntimes)
b_nArray = np.zeros(Ntimes)
a_mArray = np.zeros(Ntimes)
b_mArray = np.zeros(Ntimes)
a_hArray = np.zeros(Ntimes)
b_hArray = np.zeros(Ntimes)
nArray = np.zeros(Ntimes)
mArray = np.zeros(Ntimes)
hArray = np.zeros(Ntimes)
```

In [302]:
```
## Create a loop to simulate the Action Potential
VArray[0] = 0 ## Initialize the Voltage to 0. This will be brought to its experimental
a_nArray[0] = .01*((10-VArray[0])/(np.exp((10-VArray[0])/10)-1)) ## Formula for alpha
b_nArray[0] = .125*np.exp(-VArray[0]/80) ## Formula for beta n with initial value for
a_mArray[0] = .1*((25-VArray[0])/(np.exp((25-VArray[0])/10)-1)) ## Formula for alpha m
```

```
        b_mArray[0] = 4*np.exp(-VArray[0]/18) ## Formula for beta m with initial value for vol
        a_hArray[0] = .07*np.exp(-VArray[0]/20) ## Formula for alpha h with initial value for
        b_hArray[0] = 1/(np.exp((30-VArray[0])/10)+1) ## Formula for beta h with initial value
        nArray[0] = a_nArray[0]/(a_nArray[0] + b_nArray[0]) ## Formula for initial n
        mArray[0] = a_mArray[0]/(a_mArray[0] + b_mArray[0]) ## Formula for initial m
        hArray[0] = a_hArray[0]/(a_hArray[0] + b_hArray[0]) ## Formula for initial h

        for i in range(Ntimes-1):
            a_nArray[i+1] = .01*((10-VArray[i])/(np.exp((10-VArray[i])/10)-1)) ## The followin
            b_nArray[i+1] = .125*np.exp(-VArray[i]/80)                          ## in the form
            a_mArray[i+1] = .1*((25-VArray[i])/(np.exp((25-VArray[i])/10)-1))
            b_mArray[i+1] = 4*np.exp(-VArray[i]/18)
            a_hArray[i+1] = .07*np.exp(-VArray[i]/20)
            b_hArray[i+1] = 1/(np.exp((30-VArray[i])/10)+1)

            I_NaArray[i+1] = (mArray[i]**3)*gbar_Na*hArray[i]*(VArray[i] - E_Na) ## Use the eq
            I_KArray[i+1] = (nArray[i]**4)*gbar_K*(VArray[i]-E_K)                ## Individual
            I_LArray[i+1] = g_L*(VArray[i]-E_L)                                  ## the total
            I_totalArray[i+1] = IextArray[i] - I_KArray[i] - I_NaArray[i] - I_LArray[i]

            VArray[i+1] = VArray[i] + dt*I_totalArray[i]/C                                  ##
            nArray[i+1] = nArray[i] + dt*(a_nArray[i]*(1-nArray[i])-b_nArray[i]*nArray[i])  ##
            mArray[i+1] = mArray[i] + dt*(a_mArray[i]*(1-mArray[i])-b_mArray[i]*mArray[i])  ##
            hArray[i+1] = hArray[i] + dt*(a_hArray[i]*(1-hArray[i])-b_hArray[i]*hArray[i])
        VArray = VArray - 70 ## Set the voltage equal to the resting potential
        print(np.max(VArray)) ## See how action potential peak changes
```

```
41.30030671753612
```

In [303]:
```
        ## Plot the conductances for Potassium and Sodium
        plt.plot(times,gbar_K*nArray**4)
        plt.plot(times, gbar_Na*mArray**3*hArray)
        plt.xlabel('Time(ms)')
        plt.ylabel('Conductance(mS)')
        plt.title('Potassium and Sodium Conductances')
        plt.legend('K')
```

Out[303]:
```
<matplotlib.legend.Legend at 0x23b953959b0>
```

```
In [304]: ## Plot the Action Potential
          plt.plot(times, VArray)
          plt.xlabel('Time(ms)')
          plt.ylabel('Voltage(mV)')

Out[304]: Text(0,0.5,'Voltage(mV)')
```

1.0.4 Results & Conclusion

Current Test 1: Constant Current Current_1: The graphs that resuted from this case exhibited Action Potential behavior. The spikes in potential occured relatively at the same time as the spikes in the conductances, meaning that the peak potential was occuring when the conductances were activated. This is consistent with the biology of the model because the Action Potential occurs when the gates open, allowing ions to flow in.

Current_2: The graphs that resulted did not exhibit the Action Potential behavior. Because the external current is so small, the voltage variable in the code was affected and thus the rest of the code since the alpha and beta values depended on voltage. The current allows for one Action Potential to fire, but as the voltage lowers, it will not reach the "all or nothing" threshold so the gates will not open and the Action Potential cannot propagate any futher.

Current_3: The graphs that resulted from this case exhibited Action Potential behavior. Like in current_1, the peaks in conductance and potential occur almost simulataneously, but now the amplitudes are different. The current_3 amplitudes are smaller than the current_1 because the alpha and beta values exhibit different behaviors as V becomes increasing large (which again, is proportional to external current getting larger). That is also why this is the only graph where the conductance of Potassium is greater than that of sodium.

It is important to note that the each graph has an initial peak that is large compared to the peaks that it converges to. This happens because initially the voltage is responding to an initial Action Potential that passes the "All or Nothing" threshold but as time passes the values of potential, alpha, and beta respond to the changes. The simulation time has a dt of .01, so change isnt apparent immediately.

Current Test 2: Step Current Current_1: The graphs that resulted from this case exhibited Action Potential behavior. Like current_1 from the previous test, the peaks occur at the same times, but with one important distinction: There are two peaks that do not match the peaks after some time has passed (Reason for that is explained below).

Current_2: The graphs that resulted from this case exhibited Action Potential behavior for a few seconds, but ulitmately reverted to non-Action Potential behavior. The fact that two peaks still occur for both conductances and potentials is a consequence of the timing and type of change of the current. Because the step down from high current to 0 current occurs at the polarization

state, it does not matter that the original external current is small, another Action Potential will fire regardless. This type of external current allows Action Potentials to be fired at least once regardless of small current which has applications in studying how signals transfer down the axon.

Current_3: The graphs that resulted from this case exhibited Action Potential behavior. The relationship between current_1 and current_3 for this test is the same as in the previous test.

In this test current is supplied for a very short amount of time, decreased to 0 for a while, then allowed to return back to the original supply. The small application of current leads to an Action Potential, then at 0 it is allowed to come back to resting and spike again, and after the value is constant allowing for the smaller peaks to propogate. For the conductances, the gates are opening and closing very quickly and it makes sense that there would also be two peaks because the gates opening is a response to the potential.

Current Test 3: Sinusoidal Current Current_1: The graphs that resulted from this case exhibited Action Potential Behavior. This time around, the peaks on the graph are all the same and it maintains the relative shape that is expected. The sodium conductance is much larger than the potassium and again the peaks seem to in phase (used this terminology now that sin is involved)

Current_2: The graphs that result from this case, by my definition, displays Action Potential Behavior, but in terms of the biology of the model would not be a plausible Action Potential. The graphs have lost their Action Potential shape and resorted to essentially the same shape as the current itself. Interestingly, the potential graph shows the potential alternating between -67 and -73 which is 3 plus and 3- the resting potential, respectively. A possible explanation to this is that average of sin is 0, so the average value of the conductances are 0 since they exhibit the same sinusoidal behavior. This means the total current is just Iext-Ileak which causes the behavior that is shown (Ileak is a constant, remember).

Current_3: The graphs that result from this case, by my definition, displays Action Potential Behavior, but in terms of the biology of the model would not be a plausible Action Potential. The graph is similar to the current_1 graph as we have seen in the previous tests, with one big difference: the inability to return to resting potential. What the graph does is repeat immediately after diping below the resting potential, which could be because the negative side portion of the sin curve makes the max current negative, and the potential cannot recover to the resting potential before reaching the threshold again.

The usuage of a current that is driven like this is unrealistic because the constantly changing value of I creates a constantly changing value in alpha and beta which means the conductances and Action Potentials will not be normal. I included this current to make two points 1. Unlike the circuits in Physics 260, which seem to be more efficient operating at alternating current, this model cannot work under these conditions. The known biology of Action Potentials does not account for such a current so it makes sense the model wouldnt either 2. Systems like this may not be within the scope of normal connditions, but could possibly describe a mutation of some sort. For example, mutations in signaling could cause the ions to flow in/out at such a current which would cause problems in transmission, in which case this model would not be very helpful since assumptions are made strictly in ideal conditions

1.0.5 Figures

```
In [229]: ## Figure 1
          Image(filename = "img/neuron.png", width = 400, height = 400)
```

Out[229]:

In [230]:
```
## Figure 2
Image(filename = "img/hodgkin.png", width = 400, height = 400)
```

Out[230]: