Lab 1: Hodgkin-Huxley Single Neuron Simulation

Introduction

This lab provides an opportunity to simulate action potential generation using Hodgkin-Huxley dynamics. This will be a review of material presented in BME 417. For all remaining labs that require neuron simulation, we'll use NEURON software where people have written much more detailed and accurate channel models, but this will give you a sense of what's going on "under the hood" of those models.

Software

This lab can be completed in either Matlab or Python. Please use Matlab if you have less experience programming.

Part 1) Calculate all Initial Conditions

Start off using the Nernst and GHK equations to simulate the starting potential of the cell, as well as the driving reversal potentials associated with sodium and potassium channels. We will also calculate all of the initial conditions for the kinetic parameters in the Hodgkin Huxley model. There are many different equations/parameters for this model. You will be using the equations and parameters from the Mainen et al. 1995 paper for this lab.

1. Start by calculating the reversal potentials for sodium, potassium and chloride from the Nernst equation:

$$E_{ion} = \frac{k_B T}{ze} \ln \frac{Co}{Ci} = \frac{25}{z} \ln \frac{Co}{Ci} (mV)$$

Use the following table for the concentrations. We will treat the chloride as the "leakage" channel potential for simplicity, and only simulate the dynamics of sodium and potassium. Ignore calcium as well.

Ion species	Intracellular concentration (mM)	Extracellular concentration (mM)
K^+	155	4
Na^+	12	145
Ca^{2+}	10^{-4}	1.5
Cl^-	4	120

Table 17.1 Physical Biology of the Cell (© Garland Science 2009)

Also use a capacitance of $C_m = 1\ uF/cm^2$, and let $\bar{g}_{Na} = 100\ mS/cm^2$ and $\bar{g}_K = 50\ mS/cm^2$.

2. Next, calculate the resting potential of the cell using the GHK equation with the following relative permeabilities:

$$V_m = 25\ln\frac{P_K[K_o]+P_{Na}[Na_o]+P_{Cl}[Cl_i]}{P_K[K_i]+P_{Na}[Na_i]+P_{Cl}[Cl_o]}$$

$$P_K = 1.0 \qquad\qquad P_{Na} = 0.04 \qquad\qquad P_{Cl} = 0.45$$

Make sure all of the above numbers make sense before proceeding.

3. Next, calculate the starting (resting) point for all of the dynamic channel variables that we will simulate over time to generate the action potential, m(∞), n(∞), and h(∞). Refer to Mainen et al. 1995, Table 1 for all necessary parameters.

You can calculate these using the equation (for each of m, n, and h, which all have their own alpha and beta parameters):

$$m_0 = m_\infty = \frac{\alpha_m(V_{rest})}{\alpha_m(V_{rest})+\beta_m(V_{rest})}$$

You can obtain the alpha and beta values from the following equations, using the parameters from Mainen et al. 1995, Table 1. You will also use these in the loop below, so give all of them variable names.

$$\alpha(V) = \frac{A(V_m - V_{1/2})}{1 - e^{-(V_m-V_{1/2})/k}} \qquad\qquad \beta(V) = \frac{-A(V_m - V_{1/2})}{1 - e^{(V_m-V_{1/2})/k}}$$

At rest, m and n gates should be closed, and h gates should be partially but not dramatically inactivated.

Part 2) Write the Timestep Code Loop

We're going to simulate the time course of an action potential. It'll be a little ugly since we're using a simplified model, but it should give you a voltage spike that goes up and down within the time course of a few ms. The ordering of the code below can vary somewhat.

1. To make it easier to debug, start with a functional loop that executes and plots important parameters over time before you start populating the equations. Then you'll be able to see quickly whether the variables have the right behavior.

   Using a timestep dt = 0.01 ms, write the skeleton of a loop that steps through about 5 ms of simulation time. There are 4 variables that are changing dynamically through time, the membrane voltage V_m, and the proportion of open channels, m, n, and h. So at each timestep, you'll need to calculate ΔV_m, Δm, Δn, and Δh to update these variables as follows:

   $$V_m(t+1) = V_m(t) + \Delta V_m$$

   $$m(t+1) = m(t) + \Delta m$$

   $$n(t+1) = n(t) + \Delta n$$

   $$h(t+1) = h(t) + \Delta h$$

   Make sure your code successfully outputs and plots a run of 5 ms worth of resting potential with the delta terms set to zero before going forward. You should populate a vector with all of the running values of each of these four variables and pop up a plot or two at the end of the simulation.

2. You'll also need a stimulation of some kind to make the cell do anything interesting. For example, you can set an istim variable equal to something > 0 for some brief amount of time early in the 5 ms.

3. First calculate the change in the membrane voltage. You'll need to calculate the current sodium and potassium conductances from the current timepoints m, n, and h variables. Solve the following equation for ΔV_m and use it to update V_m for this timestep:

   $$I_{stim}(t) = C\frac{\Delta V_m}{\Delta t} + \bar{g}_{Na}m^3(1-h)(V_m - E_{Na}) + \bar{g}_K n^4(V_m - E_K) + g_{leak}(V_m - E_{leak})$$

   Assume constant $g_{leak} = 0.5\ ms/cm^2$ and $E_{leak} = -72.5\ mV$.

4. Next, calculate how the proportions of open channels change over time (m, n, and h). You can do this from the differential equation that describes how each change over time, e. g. for n gates solve for Δn:

   $$\frac{\Delta n}{\Delta t} = \alpha_n(1-n) - \beta_n n$$

For this, you will also need to calculate the updated values for the alpha and beta terms for this timestep. Alpha and beta values are still different for each of m, n, and h, and you can using the same equations above at the end of part 1.

5. You should now be seeing an action potential when you plot the membrane voltage over time. You should also be seeing m shoot up faster than n, and h go up shortly after m to start the decline of the voltage.

   Make a well-labeled plot that shows the membrane voltage over time for your report. Make another well-labeled plot to show m, n, and h over time for your report.

Part 3) Simulate Propagation to Distant Compartment

Assume this action potential is initiating in the soma of a neuron, and that there is a 3 um diameter myelinated axon projecting away from it.

1. Fiddle with the stimulation current until you find the threshold voltage change from V_{rest} that kicks off an action potential. Make a plot to illustrate this threshold and report the number. Also, illustrate the peak voltage of your action potential at the soma compartment.

2. The resistance of the myelin is 40,000 ohm-cm^2 and the axial resistance is 200 ohm-cm. What is the length constant associated with the myelinated parts of the axon compartment? Use the length constant equation from the Cable Equation lecture to figure out how to calculate lambda.

3. Imagine that an action potential propagates according to the steady state solution to the cable equation (i.e. that it has minimal capacitance and you can treat it like a fast, passive resistor). How far can the myelin extend down this cable and still enable an action potential to be generated downstream (assuming the node has the same excitability as your simulated compartment above)?

$$V(x) = V_o e^{-x/\lambda}$$

   Hint: You will need to set the resting voltage to 0 so that the both voltages in the equation are positive.

Guidelines for Lab Report (on Labs 1 and 2 together)

Introduction: The introduction should be one paragraph long summarizing what detailed single neuron simulations can be used for (motivation), what data they draw upon from past experiments, and a brief summary of everything you will show in this lab report.

Methods: From Lab 1, there should be three methods paragraphs + equations (and diagrams if you like) on:

1. Calculating initial conditions for both the voltages and variables

2. How the dynamic variables were simulated over time

3. How you determined the critical length of myelinated segment.

Include the code as an Appendix to your report. Always say where you looked up a global value in a comment, for example from the Mainen paper.

Other Methods from Lab 2 will also go into the methods section. Make it one cohesive report.

Results: You should include the following in your Results:

1. All of the resting state values in a table, with a paragraph saying why they make sense.

2. Time course of Vm, m, n, and h over time in two well-labeled plots (Vm in one; m, n, h in the other) and a paragraph describing what is happening to all of them over time.

3. A figure illustrating how you used the model to find the critical threshold voltages and the peak voltage that would reach the axon downstream (i.e. this part uses the simulation, not the voltage equation), and text describing what the value was and whether it makes sense.

Discussion: Should summarize what was in the results and what you could use these models for in the future.

The report (not including Appendix) should be no longer than 4 pages. Use 12 pt. font and 1.15-1.5 line spacing. Figures along with their captions can go on subsequent pages. However, any text that goes beyond 4 pages will not be graded. Include your code at the end of the report as an appendix.

Please upload your report to Canvas as **a single file** (pdf or docx).