Lab #3 – Neurons

How to work as a group

This lab involves two parts – coding/simulating, thinking about the questions, and writing a report. You only need to turn in one report per group.

The goal of having only one written report per group is to save you time in writing and save me time in reading. However, my expectation is that everyone in the group runs the simulations and discusses the questions together. The goal is *not* to have only one person learn the material 😊.

Overview:

In this lab, we'll use BITSEY to simulate just one cell – a simulated neuron. Our goal will be to understand the Hodgkin-Huxley model of how a neuron creates an action potential (AP). We use the same files *sim.py*, *sim_toolbox.py*, *edebug.py* and *eplot.py* as usual, but this time augment them with *main_vlab3_neuron.py*.

The setup code for this lab is substantially more complex than for the first two virtual labs. Before you can understand it, you'll need a bit more background about neurons, which is at the end of this lab writeup. You should read that before trying to answer the questions.

The function *setup_HH*() sets up a neuron with a Hodgkins-Huxley model. It has a big comment on top describing how the code implements the model. While it will hopefully be interesting to understand it, you don't necessarily have to for this lab. Instead, you must merely run simulations with various parameters, save the graphs and answer questions about what you saw. You *do* have to understand the model at a high level.

Detailed instructions

The parameters we will change are the values of τ_m, τ_h and τ_n. The code sets them in the functions *HH_M_gen_decay*(), *HH_H_gen_decay*() and *HH_N_gen_decay*() respectively. They are originally set to τ_m=1, τ_h=10 and τ_n=10 near the top of the file; you should change them as needed.

Run the following simulations until t=230 seconds (the action-potential spike starts at t=200):

1. τ_m=1, τ_h=10 and τ_n=10 (the default)
2. τ_m=1, τ_h=20 and τ_n=20
3. τ_m=1, τ_h=50 and τ_n=50
4. τ_m=2, τ_h=10 and τ_n=10

You should turn in the V_{mem}-vs-time graphs for these four simulations (zooming around the plot so as to remove the boring part from t=0 to t=200 would be useful). You may find it useful to also make graphs of m, h, n, m^3h and/or n^4, either for your own understanding or to help answer the questions below. The code to do that is already in *post_HH*(); you need only uncomment it if you like (the resulting graphs have the V_{mem} axis on the left, and the 0-1 axis for m, n, etc. on the right).

Questions

Please answer the following questions:

1. Compare your simulations for the first three cases above (the three with τ_m=1). How does increasing τ_h and τ_n affect the peak voltage of the AP, and why? Remember that these are the slow-acting negative feedback.
2. Compare your simulations for cases #1 and #4 above (τ_m=1, τ_h=10, τ_n=10 vs. τ_m=2, τ_h=10, τ_n=10). How does increasing τ_m affect the peak voltage of the AP, and why? Remember that this is the fast-acting positive feedback.
3. Judging from your simulations, what changes in τ_m, τ_h and τ_n would widen the spike? Can your think of any biological benefits of having the spike narrower? Might there be any problems if we make the spike too narrow?
4. We briefly discussed in the lectures how neurons have a *refractory period*, where they will not refire even if their V_{mem} gets pushed above the triggering threshold. Now that you know about m^3h and n^4, can you explain how our model (and specifically m^3h and n^4) predicts the refractory period? Let's call the refractory period the time from roughly t=205 to t=220 in simulation #1.

What to turn in:

You should turn in one file: your report with the graphs and the answers to the questions.

Summary of what we learned from this lab

Hopefully a few lessons come from this lab:

- A simple model can predict how a small V_{mem} depolarization triggers an AP. The same model predicts AP shape and the refractory period
- The key to the model is voltage-controlled ion channels controlling V_{mem} in QSS. Fast-acting positive feedback kicks off the spike; slow-acting negative feedback ends the spike and creates a refractory period.

Background – the Hodgkins-Huxley model of neurons

Hodgkins and Huxley started by taking measurements of APs in a giant squid, and then made a mathematical model to fit those measurements. Their work was arguably one of the seminal discoveries of modern science; they won a Nobel Prize for it in 1963. Though numerous people have refined their model since then, it remains the basis of human bioelectricity and is still in common use.

As we discussed in class, they assumed that each neuron has Na and K ion channels that are voltage gated – i.e., the fraction of the ion channels that are turned on at any moment depends on the cell V_{mem}. At a very high level, we've built a feedback system. Changing g_{Na} and g_K quickly swings V_{mem}, which in turn changes g_{Na} and g_K, and the circle repeats. Hodgkins and Huxley came up with a particular voltage dependence that produces a correctly-shaped AP. Since all of the changes are happening in QSS, the spike can be very fast.

The first step is to write the ion-channel conductances as

$$g_{Na} = \overline{g_{Na}} m^3 h$$
$$g_K = \overline{g_K} n^4$$

So (e.g., for Na), $\overline{g_{Na}}$ is the cell's maximum sodium ion-channel conductance – i.e., its value of g_{Na} when all of its Na ion channels are turned on rather than off. It is constant for any cell

(unless the cell grows). M and h are scale factors between 0 and 1; m^3h tells what fraction of the Na ion channels are on at any time. $\overline{G_K}$ and n work similarly for K. Then m, h and n will be voltage dependent and will hopefully produce the correct AP.

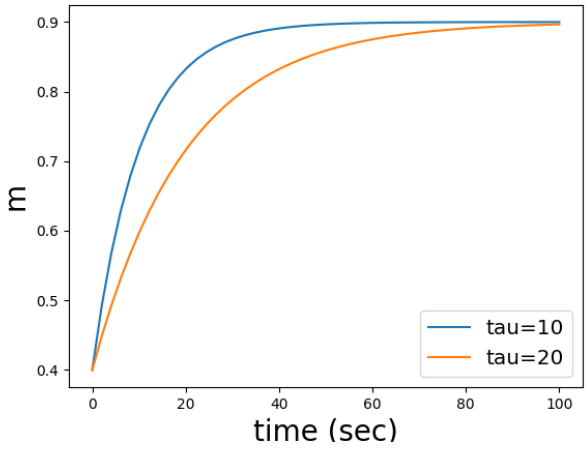
Note that there is no equation for g_{Cl}. While Cl does, of course, have ion channels, they are not gated, and so g_{Cl} is just constant.

But what are m, h and n? They are mathematical variables given by the following differential equations:

$$\frac{dm}{dt} = \frac{m_\infty(V) - m}{\tau_m(V)}$$
$$\frac{dh}{dt} = \frac{h_\infty(V) - h}{\tau_h(V)}$$
$$\frac{dn}{dt} = \frac{n_\infty(V) - n}{\tau_n(V)}$$

What are these differential equations saying? In our simple lab model, τ_m, τ_h and τ_n are just constants. The current value of V_{mem} determines values for m_∞, h_∞ and n_∞. The differential equations above represent exponential decay; m will exponentially approach m_∞ from its current value. The smaller τ_m is, the faster m moves towards m_∞.

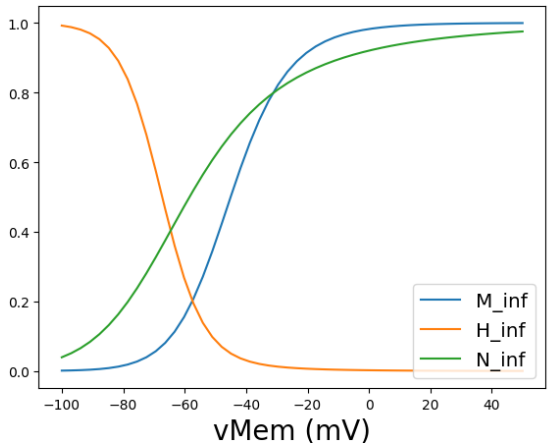
M, h and n are voltage dependent. When V_{mem} changes, it takes time for m, h and n to smoothly move to their new values. The differential equations above reflect Hodgkin and Huxley's assumption that this dynamic behavior is just an exponential ramp from the current value of (e.g.,) m to its final value m_∞ with time constant τ_m – which is why we call our symbols m_∞ and τ_m. Here is an example graph to show this:



In the graph, the current value of m is 0.4 at time 0. At that time, m_∞ goes to 0.9. The blue graph has τ_m=10 seconds, and the orange graph has τ_m=20 seconds. Both lines have m exponentially approach m_∞; τ_m controls how fast that approach happens. (The graph illustrates the differential equation for m in isolation; in a neuron the changing m would be part of the feedback system and would change V_{mem}, in turn changing m_∞).

Hodgkin-Huxley intuition

Here is a graph of how m_∞, h_∞ and n_∞ vary with V_{mem}:



First look at the blue graph of m_∞. Note that it is monotonically increasing. The more positive V_{mem} is, the bigger m_∞ gets. But since m_∞ determines what value m ramps to, this means that a more positive V_{mem} results in a higher m. And then since $g_{Na} = \overline{g_{Na}} m^3 h$, that produces a higher g_{Na}. And since $V^{N,Na}$ is positive, this gives us a more positive V_{mem} – and around and around we go, making V_{mem} higher and higher. In our system-level model of a feedback system, this is a fast-acting positive feedback that launches the AP.

This feedback is what initiates the AP spike. Some external force (e.g., neurotransmitter inputs from another neuron) pushes V_{mem} a bit higher. As soon as V_{mem} rises high enough to where m_∞ starts to ramp up (just above -70mV or so in this graph), it kicks off a virtuous cycle and the AP runs away with no external input needed.

But how do we ever leave this cycle? Why doesn't the first spike for any neuron simply leave it stuck at its maximum V_{mem}? Because of h and m.

H is in some sense the opposite of m_∞. Where m_∞ is monotonically *in*creasing, h_∞ is monotonically *de*creasing. The bigger V_{mem} gets, the closer h_∞ gets to zero. Thus, as the spike rises, h_∞ jumps in to pull m^3h back down to zero, thus preventing m from raising V_{mem} higher and higher. In fact, $\tau_h > \tau_m$; this means that m can rise quickly, but h falls more slowly. Thus, the spike is allowed to rise up high before h comes along and turns off the Na channels. I.e., h is a slow-acting negative feedback that turns off the spike.

Finally, n_∞, like m_∞, is monotonically increasing. Thus, as the AP spike rises, n also rises. But since n controls K ion channels rather than Na ion channels, and since K has a negative V^{Nernst}, then n works along with h to shut down the spike. In fact, $\tau_n \approx \tau_h$, which means that h and n in fact work quite well together to end the spike.

Going further

There are numerous textbooks that describe the Hodgkin-Huxley model for medical students; they tend to focus on which ions move which direction and ignore the electrical effects. Still other textbooks focus on the math in intricate detail. I've found it hard to locate textbooks that discuss the electrical intuition behind neurons. Here are two textbooks that I like:

- *Biological Physics: Energy, Information, Life*: mostly about the physics, but not bad intuitively.
- *An Introduction to Modeling Neuronal Dynamics*, Christoph Borgers (at Tisch online). All about the math – but the first two chapters deal with the math in a more simple and reasonable manner than most textbooks.