BMES-477/710: Neural Signals

Lab 3: Modeling Action Potential Generation

****Include all figures and descriptions of the results with your report submission****

Objective: This lab assignment will cover three models for action potential generation we've covered in class: the basic integrate-and-fire neuron (part I), the Hodgkin-Huxley model neuron (part II), and a Thalamic Relay model neuron (part III). In part I, you will investigate the behavior of one of the simplest models of action potential generation. In part II, you will test the Hodgkin-Huxley model by changing the input current and modifying the physical parameters of the cell. In part III, you will compare results obtained from the Hodgkin-Huxley model with those from a similar parallel conductance model that has an addition current pathway: a transient calcium conductance.

Part I: Fun with the integrate and fire neuron

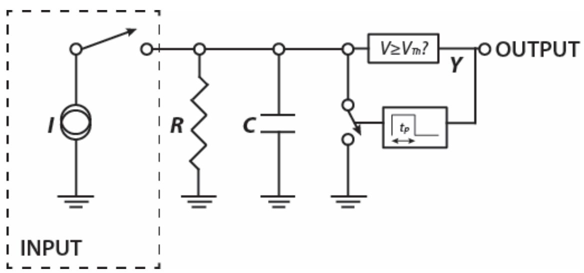

Figure 1: The equivalent circuit of the leaky integrate-and-fire neuron, with passive membrane properties modeled as R and C.

In this section, you will be evaluating the leaky integrate-and-fire neuron. The model, originally proposed in 1907 by Louis Lapique, remains widely used in large-scale network simulations. The model relies on the passive membrane properties R and C to simulate the subthreshold behavior of a neuron. When a current is input, there is a transient RC response. Once the voltage response reaches a pre-defined threshold (V_{Th}), the cell fires an action potential, at which point the voltage resets. Based on what we know, we can first analyze the circuit as a first order differential equation by substitution and rearrangement:

$$I_{in} = I_R + I_C$$

$$C\frac{dV}{dt} = -\frac{V}{R} + I_{in}$$

We will now use this model to understand its strengths and weaknesses. Open the Matlab m-file "intfire.m." In this script, you can vary the input current (I), the membrane resistance (R), and the membrane capacitance (C), and plot the output voltage (V) as a function of time.

A. Vary the input current gradually from very low to high values and find the minimum current needed to cause the neuron to spike.

B. Generate a graph showing input current (μA) versus the output firing rate (Hz = spikes/second) of the neuron. To calculate firing rate, count the number of spikes and divide this number by the simulation duration. Make sure to use multiple current values to capture the overall trend for the modeled data. What is the relationship between the current and firing rate?

C. What is the maximum firing rate of this neuron (provide example figure) and how is it related to the absolute refractory period (abs_ref) in the code?

D. Instead of injecting a constant current, make the current (I) a sinusoidal function of time (e.g. I = sin((1:tstop)*f); I(I<0)=0;) where f is the input frequency (remember the default frequency in Matlab is radians). Plot a graph showing the output firing rate (Hz) as a function of input frequency (rad/ms). Vary f from 0.01 to 0.5 rad/ms.

Note: redefine V = V - (V/(R*C)) + (I/C) to V = V - (V/(R*C)) + (I(**t**)/C);

E. Find the resonant frequencies (if any) where the neuron ‘tracks’ the input by firing exactly 1 spike for each peak in the input. Hint – replot the data from D. so that both axes are in Hz (spikes per second and cycles per second).

Part II: Delving into the Hodgkin-Huxley model

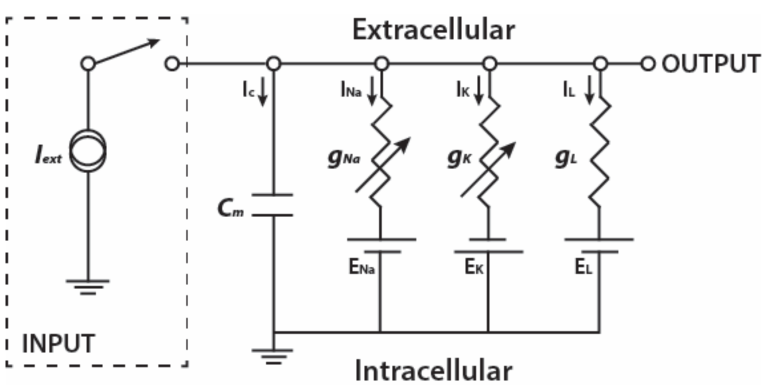

Figure 2. The equivalent circuit of the Hodgkin-Huxley model.

In this section, you will be simulating a variety of different input currents to characterize the behavior of the Hodgkin-Huxley model of action potential generation (Fig. 2). Recall that unlike the simplified RC model used above, Hodgkin and Huxley derived their model based on experimental observations of the squid giant axon. As such, the model attempts to explain action potential generation as a function of the time-varying ionic conductances g_{Na} and g_K, as well as the membrane capacitance, and a lumped g_{Leak} that remains constant (the “leak” channels that are always open that contribute to the neuron’s resting membrane potential). Solving for the equivalent circuit, and based on the theorized dynamics of the ion channels, the full Hodgkin-Huxley model is composed of a set of four coupled ordinary differential equations that describe the membrane potential, along with the ionic conductance for potassium (n), and the fast activating (m) and slow inactivating (h) sodium channel subunits:

$$I = C_m \frac{dV_m}{dt} + \bar{g}_K n^4 (V_m - V_K) + \bar{g}_{Na} m^3 h (V_m - V_{Na}) + \bar{g}_l (V_m - V_l),$$

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n$$

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m$$

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h$$

Now, open the Matlab m-files "HH_calc.m" and "HH.m." The first m-file is the control script from which you will run the simulation. The second file is the Hodgkin-Huxley model that is executed via Matlab's built-in ordinary differential equation solver ode45.

A. Run the simulation (via HH_calc.m) with the default parameter settings and a constant current of 0.1 (currType=1;). Describe the resulting membrane potential in terms of the gating variables n, m, and h.

B. What is the minimum input current required to elicit an action potential (approximate to the nearest 0.01 μA)?

C. Run a series of simulations using constant (currType=1) stimulation currents that range from the minimum current found in (B) to ten times that value. For each current, record the number of action potentials that are elicited (N), and measure the latencies of the first and last spikes in the train (t_1 and t_N). Calculate firing frequency in Hz (spikes per second) as $(N-1)/(t_N-t_1)$. Plot the firing frequency as a function of stimulus current (μA) amplitude. What do you observe from the plot?
Note: firing frequency is 0 unless the cell fires repetitively during the stimulus current.

D. Set Imag to 0.6 μA and give a concise qualitative description of what happens to spike amplitude during a spike train. Explain why this happens in terms of the gating variables m, n, and h.

E. You have seen that depolarizing current can trigger action potentials. Can a hyperpolarizing step also trigger a spike? Set I_{mag} to 0.1μA and currType to 4 (hyperpolarizing step input). Describe the output. How does this response differ from what would occur if the membrane were passive (linear)?

F. Increase the hyperpolarizing current (Imag) to 0.3 μA. Describe what occurs.

G. Does the rebound spike seem qualitatively similar to spikes triggered by depolarizing currents?

H. You decide to go to a fancy restaurant and order fugu. Unfortunately, your chef wasn't very good and you received an unhealthy dose of tetrodotoxin (TTX). Simulate the effects of TTX on the HH model neuron. Describe what happens.

I. Luckily you recovered from your TTX poisoning, but shortly after when working in the lab, you were exposed to tetraethylammonium (TEA). Simulate the effects of TEA on the HH model neuron. Why is this such a potent neurotoxin?

Part III: The thalamic relay neuron: modeling the T-type Ca^{2+} current

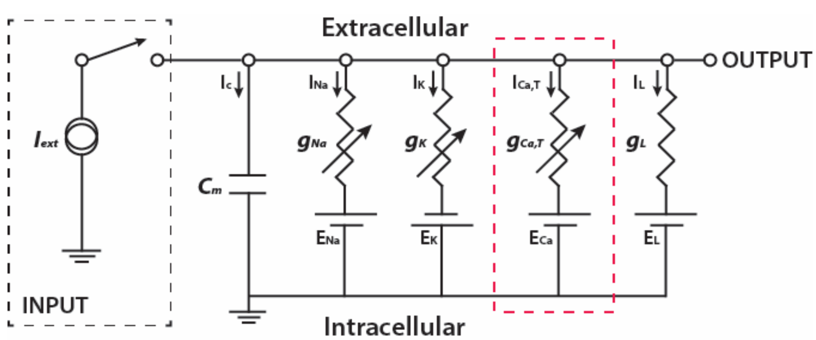

Figure 3: Equivalent circuit for part III with added T-type Ca^{2+}.

The Hodgkin-Huxley model we've investigated so far was generated from data collected during patch-clamp experiments on the squid giant axon. In the squid axon, Na^+ and K^+ currents are primarily responsible for the generation of an action potential. However, as we begin to investigate AP generation in other neuron types, it becomes necessary to modify our basic HH model to account for differences in neuron morphology. In this section, you will investigate the effects of a transient calcium current (T-type) on AP generation.

Open the Matlab m-file "pir.m"

A. Run the simulation with default settings. Describe the output.

B. What is the minimum input current (Imag) that elicits only a single spike?

C. How is the depolarizing current related to the number of spikes in the burst? Vary the input current (Imag) while keeping the stimulation times fixed. Plot number of spikes in the burst as a function of input current.

D. Now, rather than a depolarizing current, provide a short hyperpolarizing (inhibitory) input (I0 =0, Imag = -5e-9 and Iend = 0) starting at t = 0.25 and lasting 0.25 s. Describe the output.

E. Is there an effect of further increasing the magnitude of the hyperpolarization on the number of spikes generated?

F. Briefly explain why the added T-type Ca^{2+} current creates the bursting behavior.

EXTRA CREDIT:

Using the m-file "pir.m" as a template, modify it appropriately to be a Connor-Stevens model. Make sure to replace the T-type Ca^{2+} current with the transient potassium A-current of the Connor-Stevens model and change any additional constants appropriately, as described in Dayan-Abbott (pg. 197, 224-225). Describe the functionality of the model and plot your simulation results (characterize the model similarly to above, and provide general model conclusions). Remember, for this part to include your modified code (attach as m-file on Bb) in order to receive full credit.