Learning objectives and outcomes:

This problem set investigates two models of how neurons spike in response to current inputs. The leaky integrate and fire (LIF) model is based on the simple RC model of a cell, with an extra rule that the model neuron spikes whenever the membrane potential passes above a threshold. Despite its simplicity, the ideas behind this model constitute the cornerstone of many fundamental computational modelling approaches. In contrast to this simplified model, real neurons produce spikes due to the presence of voltage-dependent ion channels. The Hodgkin-Huxley model is the first model to capture these rich dynamics. It does so by incorporating biophysically accurate descriptions of the sodium and potassium channels. More elaborate biophysically inspired models take the work of Hodgkin-Huxley as a starting point.

These models were covered in lectures 3-5 and recitations 3&4.

The expected learning outcomes for this PSET are:

- Estimate model parameters from different plots of model behavior.
- Interpret the biophysical role of these parameters.
- Write code to simulate a model to check your parameter estimations.
- Produce f-I curves (firing rate versus current injected).
- Be able to present your results as a cohesive and well-structured report.

MATLAB functions you will need:

There is quite a lot of overlap with PSET 1 in terms of MATLAB functions needed to successfully complete this PSET.

For calculating firing rates from spike times, the function `diff` will be super helpful.

As a reminder the main plotting functions are: `figure, plot, subplot, xlim, ylim, title, xlabel, ylabel, legend, hold on, hold off.`

For more information on MATLAB functions and commands, check the provided cheat sheet or the more extensive MATLAB documentation.

Problem 1: Estimating the LIF parameters

The provided MATLAB file *LIFmodel.p* is a scrambled function that simulates a leaky integrate and fire neuron for square pulses of current injection. By scrambled we mean that you can run the function, but you cannot read the code inside the function that generates the outputs.

This function is called with the following syntax:

```
>> [V,I,t,spikeTimes] = LIFmodel(amp);
```

LIFmodel.p takes a single input argument, `amp`, which sets the amplitude of the square current pulse in units of nanoAmperes (nA). Upon being called, it returns 4 arguments `V`, `I`, `t` and `spikeTimes`. The first two outputs are column vectors of the same size containing the following quantities as a function of time: `V`, the membrane potential in millivolts (mV); `I`, the current amplitude in nanoAmperes (nA). The third output is another vector, `t`, of the same size containing the time stamps for `V` and `I` in milliseconds (msec). The last argument, `spikeTimes`, returns a list of time stamps at which spikes (action potentials) were generated. Keep in mind that the size of `spikeTimes` will vary depending on the amplitude of the current injected. In particular, if there are no spikes it will be an empty matrix.

We know that the behavior of an LIF neuron is determined by 5 parameters: the resting membrane potential (E_L), the spiking threshold (V_{thresh}), the reset membrane potential (V_{reset}), the total membrane resistance (R_m), and the total membrane capacitance (C_m).

Your job is to use plots and/or calculations to estimate each of these parameters that are obscured in the provided function. Keep in mind that you will have to run the function with different values of `amp`, to recover all 5 parameters.

Using relevant plots and or calculations complete these tasks. Make sure to justify all your answers properly and provide proper units for your estimates.

1. **Estimate E_L for this neuron. = -75 mV set amp = 0**
2. **Estimate V_{thresh} for this neuron. = -50 mV set amp = 0.275**
3. **Estimate V_{reset} for this neuron. = -70 mv set amp = 0.275**
4. **Estimate R_m for this neuron. = at Ith = Ie = 0.25 nA, fr = 0 dV = IR, V= 20mV R=100 M Ohms**
5. **Estimate the time constant for this neuron. = 20.05 ms**
6. **Estimate C_m for this neuron. = 0.2005 nF tau = RC**
7. **Estimate the rheobase[1] of this neuron. = 0.25 nA**
8. **Plot the firing rate[2] in Hertz (Hz) as a function of the injected current amplitude. This is called an f-I curve. Describe the different regions of this curve.**
9. **From the previous plot, estimate C_m. = 0.2034 nF**

Problem 2: Numerical simulation of an LIF neuron

In the previous problem you estimated the 5 parameters that control the behavior of an LIF neuron. In this problem, your job is to write MATLAB code to implement an LIF neuron model with those parameters. This will give you an opportunity to verify your parameter estimates.

[1] The current amplitude such that the steady-state is equal to V_{thresh}

[2] We are defining the rate the same way as we did in class: as the reciprocal of the time elapsed between two consecutive spikes.

You can use the *RCpassive.m* from PSET 1 as a starting point. Don't forget to include a variable to keep track of the spike times. Also, it might be a good idea to wrap this code in a function which similar calling syntax as *LIFmodel.p*.
When you have your code working, complete the following tasks:

1. **Plot the f-I curve of this neuron.**
2. **On the previous plot overlay the f-I curve obtained in problem 1 question 8. Comment on any similarities or discrepancies between the two curves.**

Problem 3: The role of sodium channel inactivation on the refractory period in the Hodgkin-Huxley model

The gating variables, *m,h* and *n*, obey this first order linear differential equation:

$$\tau_x(V)\frac{dx}{dt} = x_\infty(V) - x,$$

where *x* is an index to reflect any of those gating variables. It is important to notice that the time constant and steady state value depend on the membrane potential:

$$\tau_x(V) = \frac{1}{\alpha_x(V) + \beta_x(V)} \qquad x_\infty = \frac{\alpha_x(V)}{\alpha_x(V) + \beta_x(V)}$$

The voltage dependency is through the rate constants α_x and β_x which have the following mathematical expressions:

$$\alpha_h = 0.07\exp\left(-0.05(V+70)\right) \qquad \beta_h = \frac{1}{1+\exp(-0.1(V+40))}$$

$$\alpha_m = \frac{0.1(V+45)}{1-\exp(-0.1(V+45))} \qquad \beta_m = 4\exp(-0.0556(V+70))$$

$$\alpha_n = \frac{0.01(V+60)}{1-\exp(-0.1(V+60))} \qquad \beta_n = 0.125\exp(-0.0125(V+70))$$

In these formulae the membrane potential is in mV and the rate constants in ms^{-1}.
In the folder *HHmodel* you will find a set of six functions that implements each of these 6 rate constants.

The file *HH.m* in the same folder implements a simulation of a Hodgkin-Huxley neuron under a current clamp experiment. Current clamp means that we control the external current applied and measure the membrane potential in response to our manipulation. Note that this is different from voltage clamp in which we control the membrane potential and measure the ionic current.

In particular, this script is set to apply a depolarizing external current of 10 $\mu A/cm^2$ for 10 milliseconds. If you run this file you will see three plots: the membrane potential as a function of time, the external current applied as a function of time, and the gating variables as a function of time.

Your job is to use those files and make modifications as instructed to study the role of sodium channel inactivation and its effect on the refractory period.

1. **Plot the steady state of the inactivation gating variables (h_∞) as a function of membrane potential. Restrict your plot to the range -100 to 100 mV.**
2. **Make a copy *HH.m* and call it *HHpaired.m*. Modify this file so that it applies two current pulses, each of amplitude 3 $\mu A/cm^2$ and a duration of 10 milliseconds. The pulses should have an inter-pulse interval of 10 milliseconds. This is they are separated by 10 milliseconds measured from end of first pulse to the start of second pulse. Look at the plots and comment on what you see.**
3. **Modify the code so that the inter-pulse interval is now 2 milliseconds but keeping the amplitude at 3 $\mu A/cm^2$. Look at the output plots, what has changed from the previous case? What is the role of the inactivation gating variable in this behavior?**
4. **Modify the file *alphah.m* so that the rate is double the value of the original function for all values of membrane potential. In a single plot overlay the h_∞ versus membrane potential curves for the original and modified version. What is the effect of this change in α_h on h_∞?**
5. **Redo question 3 but using the modified *alphah.m* function. Comment on the changes you see. Relate this to the sodium channel disorders discussed in lecture.**

Problem 4: Hyperpolarization can excite neurons

In this problem we want to study the effects of prolonged hyperpolarization on the behavior of the Hodgkin-Huxley model. In order to do so, make a copy of *HH.m* and name it *HHhyper.m*. Modify this code such as to deliver a square pulse of current that starts a 10 ms and finishes at a 100 ms. Set the amplitude to -10 microamperes/cm^2. Simulate for 150 ms total.

After running your simulation answer the following questions:

1. **Plot *V, m, h and n* as functions of time. You will see the neuron spiking at the end of the simulation**
2. **In a few sentences provide a rationale for why this is happening. Construct your argument in terms of the gating variables *m, h and n*. Hint: It will be helpful to consider the time scales involved in the activation/inactivation of the gating variables (problem 3).**
3. **In a few sentences discuss whether (and why or why not) a leaky integrate and fire neuron can exhibit this behavior.**

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