Matlab Assignment #7

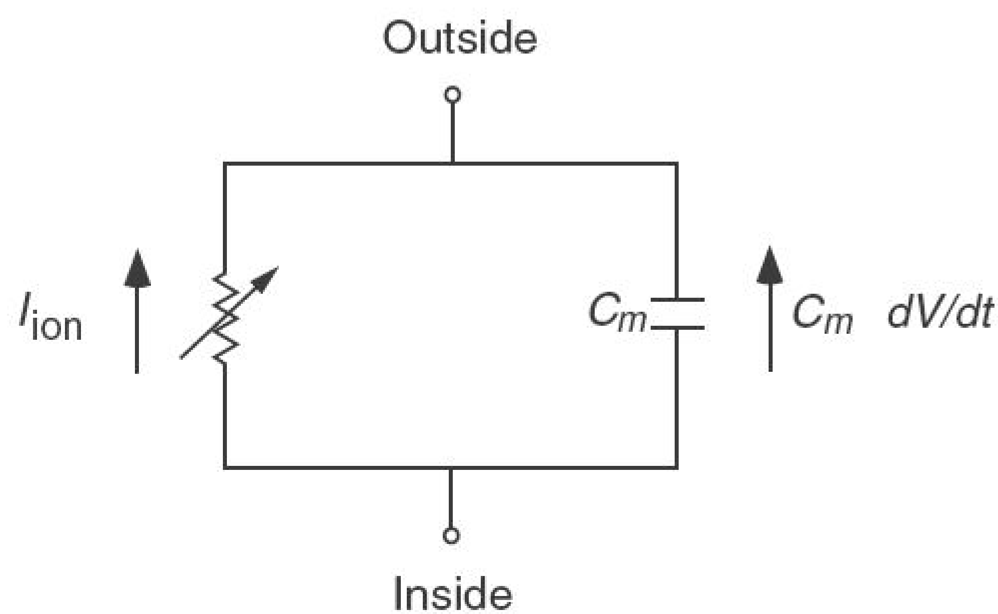
The assignment is adapted from material through volume 1 of *Mathematical Physiology*, by Keener and Sneyd. I am replacing a more standard exercise, which many students found too challenging, with a topic related to biology and oscillations and signal response, and which underpins our current understanding of neural responses.

The Hodgkin-Huxley Neuron

Here we introduce a famous work of Alan Hodgkin and Andrew Huxley, in which they develop the first quantitative model of the propagation of an electrical signal along a squid giant axon. This theory is now used in a wide variety of *excitable* cells, and is generally the way we understand *action potentials* which cause nerve cells (neurons) to fire. They later won the Nobel Prize in Biology in 1963 for their work, and the original article remains one of the most brilliant pieces of mathematical biology ever written. If you are interested, it can be found freely online: *Hodgkin, Alan L., and Andrew F. Huxley. "A quantitative description of membrane current and its application to conduction and excitation in nerve." The Journal of Physiology 117.4 (1952): 500-544.* If interested, I highly suggest reading it.

Cell membrane as an electrical circuit

The cell membrane is a semipermeable membrane separating the cell from its environment. Semipermeability means that some molecules can cross it (hence enter and/or leave the cell), while others cannot. If the molecules are ionic (i.e. have a charge), this flow then creates a charge distribution near the cell membrane, hence converting it into a *capacitor* (object that stores electrical energy via charge separation). Equilibrium is reached when the electrical force balances that of the *diffusion* through the cell membrane. We can then model this phenomena as a simple electrical circuit, shown below:



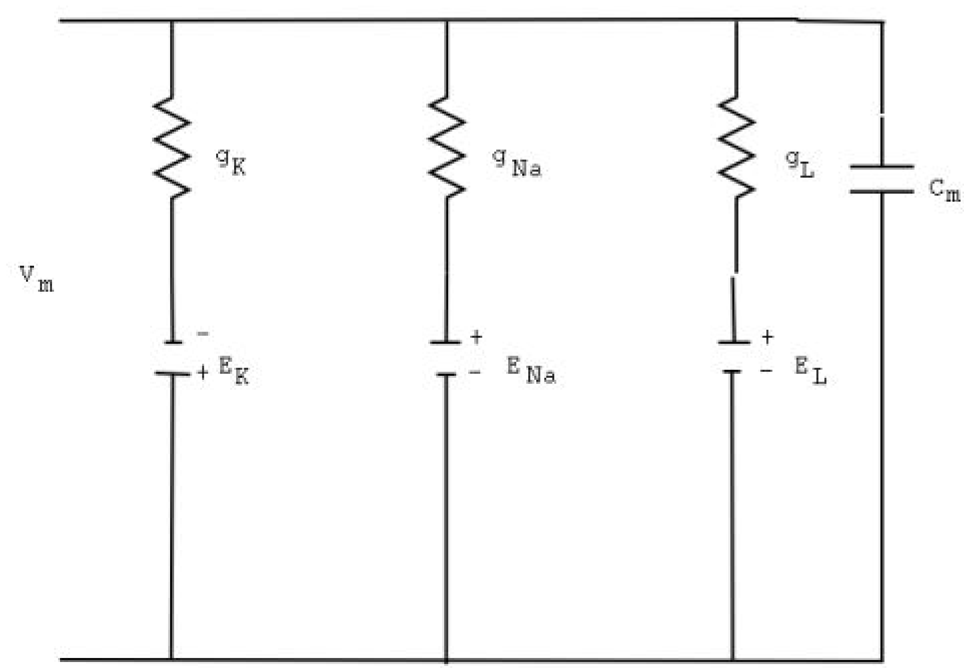
Here C_m is the *capacitance* of the cell membrane, and is just the ratio of the charge Q to the potential difference V (so $C_m = \frac{Q}{V}$), and I_{ion} is the ionic current generated in the circuit. Lastly, V is defined (by convention) to be difference between the intracellular potential and the extracellular potential, $V := V_i - V_e$. Assuming a constant C_m, and as there can be no net buildup of charge on either side of the membrane, the circuit balance implies that

$$C_m \frac{dV}{dt} + I_{\text{ion}}(V, t) = 0. \tag{1}$$

Note that we have assumed that the ionic current in general depends on the potential difference V and time t, where the latter is due to possible external inputs, i.e **forcing**, which we will study below.

Squid giant axon

In the squid giant axon (and in many neural cells, but Hodgkin and Huxley were using this as their data source), the principle ionic currents are generated by the flow of sodium Na^+ and potassium K^+, while all other small currents (primarily Cl^-) are combined into the *leakage current.* Indeed, the previous circuit can be expanded to account for these different sources of I_{ion} as below:



Note that each ion channel is viewed as a resistor, with voltage drop $V - V_i$ and conductance g_i, for $i =$ Na,K,L. Recall that resistance and conductance are inverses of one another, as $C = \frac{1}{R}$. Furthermore, writing the circuit in parallel assumes *linearity*, which is an **assumption,** chosen because there was experimental evidence. Such a choice should not be expected to hold in general. Thus, using the basic relation $I = \frac{V}{R}$, equation (1) can be written as

$$C_m \frac{dV}{dt} = -g_{Na}(V - V_{Na}) - g_K(V - V_K) - g_L(V - V_L) + I_{\text{in}}(t), \tag{2}$$

where $I_{\text{in}}(t)$ is the input current from other cells, and we view as external for this model.

1. Assume that the external current $I_{\text{in}}(t)$ is constant, i.e. $I_{\text{in}}(t) \equiv I$, AND that **all conductances are constant**. Describe the dynamics of the first-order ODE (2) for the potential V. That is, qualitatively describe the solution curves, and provide any plots which you find helpful. Note that you should provide mathematical justification, and that you should be as precise as possible.

Non-constant conductance

It is experimentally observed that your result from question **1** is observed, **at small applied currents I**. However, at larger applied currents, the result is quite different, and thus implies that the conductances appearing in equation (2) cannot be constant. To describe the complete picture would take me too far astray, but the idea of Hodgkin and Huxley was to add *gating* variables m, n, and h which themselves are described via ODEs. One should think of these as probabilities, describing the likelihood of the ionic gate of being either "open" or "closed." The full model is then a system of four ODEs:

$$\begin{aligned} C_m \frac{dV}{dt} &= -g_{Na}m^3h(V - V_{Na}) - g_K n^4(V - V_K) - g_L(V - V_L) + I_{\text{in}}(t) \\ \frac{dm}{dt} &= (1-m)\alpha_m(V - V_0) - m\beta_m(V - V_0) \\ \frac{dn}{dt} &= (1-n)\alpha_n(V - V_0) - n\beta_n(V - V_0) \\ \frac{dh}{dt} &= (1-h)\alpha_h(V - V_0) - h\beta_h(V - V_0), \end{aligned} \tag{3}$$

where the α_i, β_i, for $i = m, n, h$ are also functions of the potential difference $V - V_0$, and chosen to match experimental data:

$$\begin{aligned} \alpha_m(V) &= \frac{2.5 - 0.1V}{e^{2.5-0.1V} - 1} \\ \beta_m(V) &= 4e^{-\frac{V}{18}} \\ \alpha_n(V) &= \frac{0.1 - 0.01V}{e^{1-0.1V} - 1} \\ \beta_n(V) &= \frac{1}{8}e^{-\frac{V}{80}} \\ \alpha_h(V) &= 0.07e^{-\frac{V}{20}} \\ \beta_h(V) &= \frac{1}{e^{3-0.1V} + 1} \end{aligned} \tag{4}$$

The parameter V_0 is the equilibrium potential, and is taken as $V_0 = -65$ mV. Other parameter values (in appropriate units) are fixed as $g_{Na} = 120, g_K = 36, g_L = 0.3, C_m = 1, V_{Na} = 50, V_K = -77$, and $V_L = -54.4$.

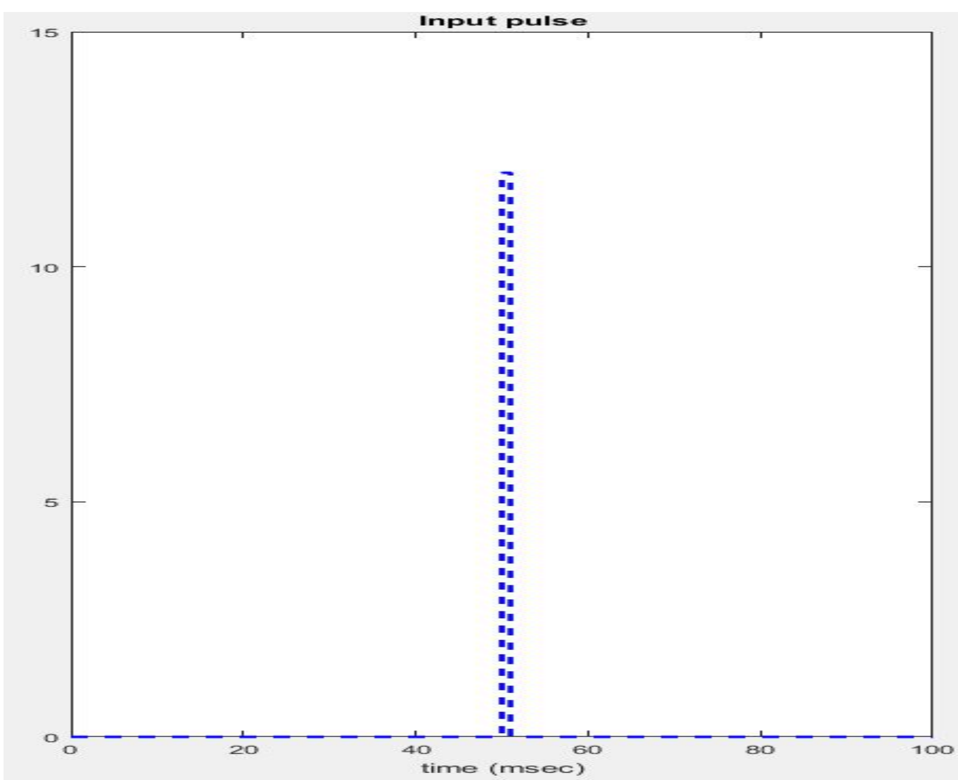
We will now investigate the dynamics of system (3), for various signaling input $I_{\text{in}}(t)$. Note that the system is **nonlinear**, so your results from Chapter 3 and 4 do not necessarily hold. Our main interest will be in connection to Chapter 4, and to how external input may influence dynamics. Also, the system is of course four dimensional, and although qualitative techniques are similar to those you have studied for 2D systems, we will focus on numerical simulations for the remainder of the assignment.

Numerical simulations

We now solve the system (3) using MATLAB, and study voltage responses to different inputs signals I_{in}.

2. Consider first a constant input signal, $I_{\text{in}}(t) \equiv I$. Run the m-file *hh_const.m* for the I values $I = 0, 5, 10$. Include temporal plots of the voltage response $V(t)$ for all I values. How does this response change as I is increased? How does this compare with your answer to question **1**? What **qualitative** difference do you observe as I is increased?

3. We now consider the response of the neuron (i.e. the model) to a discrete temporal signal. That is, what happens with an input signal of the form shown below?



Run the file *hh_pulse.m* for pulses of different magnitude, keeping the time interval when the pulse is activated fixed for $t \in [50, 51]$. Note in particular the change in response for magnitudes between 6.9μA and 7μA. How does the response change for a pulse magnitude greater than 7μA? And how do you think this might relate signaling in cells (again, specifically neurons)? Be sure to include relevant $V(t)$ plots to support your arguments.