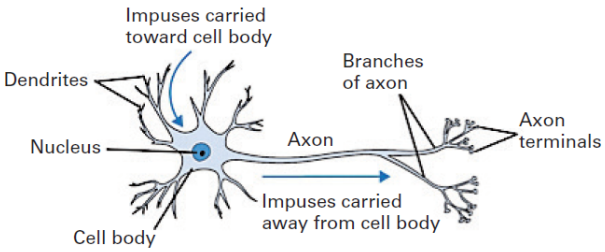
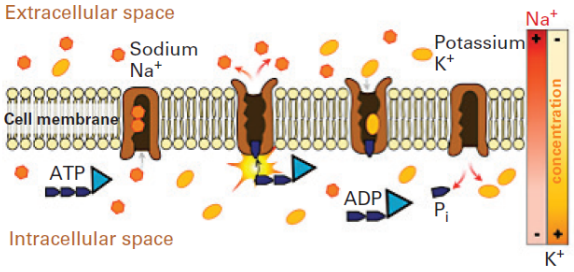
BCS410. Practical Class 3 & Homework 3 [Due: April 25]

Caution: You must submit the code you wrote and used to solve each problem to KLMS. When submitting, name the folder with your student ID and submit each problem's code file as 'ProblemX_sol' (e.g., 'Problem1_sol'). You are free to use Python libraries. However, you are not allowed to ask AI to generate the entire code for you. If detected, you will receive a score of zero. You must provide your answers in a descriptive format for each problem.

Background:





1. Overview of the Hodgkin and Huxley model: Neurons are the basic computational units within the body. They communicate by electrical signals. When a neuron receives electrical signals from other neurons, it must decide whether or not to send a signal (called an action potential) to the other neurons to which it is connected. The basic work describing the electrical behavior of neurons mathematically was conducted by Hodgkin and Huxley in the late 1940s and early 1950s (Hodgkin and Huxley 1952). They took a long time to publish their results, but the model they developed is one of the most widely studied models in all of mathematical biology. Hodgkin and Huxley won the Nobel Prize for this work in 1963, making it arguably the first Nobel Prize for mathematical biology.

2. Ordinary differential equations for a HH model: The equation for the membrane potential V is given as follows:

$$\frac{dV(t)}{dt} = \frac{1}{C}\left(g_{\mathrm{K}^+}(t)\cdot\left(E_{\mathrm{K}^+} - V(t)\right) + g_{\mathrm{Na}^+}(t)\cdot\left(E_{\mathrm{Na}^+} - V(t)\right) + g_{\mathrm{leak}}\cdot\left(E_{\mathrm{leak}} - V(t)\right) + I_{\mathrm{applied}}\right)$$

The potassium conductance is given by

$$g_{\mathrm{K}^+}(t) = \bar{g}_{\mathrm{K}^+}\left(n(t)\right)^4$$

where $\bar{g}_{\mathrm{K}^+}$ is the maximal conductance of K^+ channels and n is a gating variable. The sodium conductance is given by

$$g_{\mathrm{Na}^+}(t) = \bar{g}_{\mathrm{Na}^+}\left(m(t)\right)^3 h(t)$$

where $\bar{g}_{\mathrm{Na}^+}$ is the maximal conductance of Na^+ channels, m is an activation gating variable, and h is an inactivation gating variable.

The gating variable dynamics are given by

$$\frac{dn(t)}{dt} = \alpha_n\left(V(t)\right)\left(1 - n(t)\right) - \beta_n\left(V(t)\right)n(t) = \frac{n_\infty\left(V(t)\right) - n(t)}{\tau_n\left(V(t)\right)}$$

$$\frac{dm(t)}{dt} = \alpha_m(V(t))(1 - m(t)) - \beta_m(V(t))m(t) = \frac{m_\infty(V(t)) - m(t)}{\tau_m(V(t))}$$

$$\frac{dh(t)}{dt} = \alpha_h(V(t))(1 - h(t)) - \beta_h(V(t))h(t) = \frac{h_\infty(V(t)) - h(t)}{\tau_h(V(t))}$$

where

$$n_\infty(V) = \frac{0.01(V + 50)\,/(1 - e^{-(V+50)/10})}{0.01(V + 50)/(1 - e^{-(V+50)/10}) + 0.125e^{-(V+60)/80}}$$

$$\tau_n(V) = \frac{1}{0.01(V + 50)/(1 - e^{-(V+50)/10}) + 0.125e^{-(V+60)/80}}$$

$$m_\infty(V) = \frac{0.1(V + 35)/(1 - e^{-(V+35)/10})}{0.1(V + 35)/(1 - e^{-(V+35)/10}) + 4e^{-(V+60)/18}}$$

$$\tau_m(V) = \frac{1}{0.1(V + 35)/(1 - e^{-(V+35)/10}) + 4e^{-(V+60)/18}}$$

$$h_\infty(V) = \frac{0.07e^{-(V+60)/20}}{0.07e^{-(V+60)/20} + 1/(1 + e^{-(V+30)/10})}$$

$$\tau_h(V) = \frac{1}{0.07e^{-(V+60)/20} + 1/(1 + e^{-(V+30)/10})}$$

The model parameters are given as follows: $\bar{g}_{K^+} = 36\text{mS/cm}^2$, $\bar{g}_{Na^+} = 120\text{mS/cm}^2$, $g_{\text{leak}} = 0.3\text{mS/cm}^2$, $E_{K^+} = -72\text{mV}$, $E_{Na^+} = 55\text{mV}$, $E_{\text{leak}} = -49\text{mV}$, and $C = 1\mu F/\text{cm}^2$.

Problem 1: Simulate the HH model with the given parameter values above and an initial condition $[V\ n\ m\ h] = [-59.8977\ \ 0.3192\ \ 0.0536\ \ 0.5925]$ and plot the graph of membrane voltage (in mV) over time (ms) when the following stimulus is applied:

$$I_{\text{applied}}(t) = \begin{cases} 0 & t < 20 \\ 2 & 20 \le t < 21 \\ 0 & 21 \le t < 60 \\ 10 & 60 \le t < 61 \\ 0 & 61 < t \end{cases}$$

Please interpret the simulation results from the perspective of the biophysical mechanisms responsible for the initiation and development of an action potential. For instance, what is the difference between the two pulses (besides their being applied at different times, obviously)? How did the system react to each of the two pulses?

Problem 2: Simulate the model by varying g_{leak}, from 0.3mS/cm² to 1mS/cm² in increments of 0.1mS/cm². In this simulation, $I_{\text{applied}}(t) = 7\mu\text{A/cm}^2$ over time. All other conditions should remain the same as in Problem 1. Investigate how the membrane voltage changes depending on the value of g_{leak}.

Problem 3: Simulate the model by varying the applied current, I_{applied}, from 10 μA/cm² to 20 μA/cm² in increments of 1mV. In this simulation, $I_{\text{applied}}(t)$ should remain constant over time. All other conditions should remain the same as in Problem 1. Investigate how the period and amplitude of the resulting action potentials

change depending on the applied current.

Problem 4: Simulate the model by varying the maximal sodium conductance, $\bar{g}_{\mathrm{Na}^+}$, from 190mS/cm² to 200mS/cm² in increments of 1mS/cm², with $I_{\mathrm{applied}}(t) = 0$ for all time. All other conditions should remain the same as in Problem 1. Then, investigate whether and when the membrane voltage exhibits spontaneous spiking in the absence of any applied current. Similarly, simulate the model by varying the maximal potassium conductance, $\bar{g}_{\mathrm{K}^+}$, from 30mS/cm² to 20mS/cm² in decrements of 1 mS/cm², again with $I_{\mathrm{applied}}(t) = 0$ at all times, with all other conditions the same as in Problem 1. Determine whether and when spontaneous spiking occurs under these conditions. If possible, interpret the results and provide a biological explanation for why an increase in sodium conductance or a decrease in potassium conductance may lead to spontaneous spiking. A qualitative biological interpretation is sufficient; mathematical analysis is not required.

Problem 5: Verify that an activation gating variable and inactivation gating variable of Na^+ tend to cancel each other out through most of the process except during a spike by plotting $m(t)$ and $h(t)$ over time.

Problem 6: Check whether the action potential begins with a sodium flux, followed by the flow of potassium, by plotting the sodium and potassium currents over time, I_{K^+} and I_{Na^+}, during the occurrence of the actional potential.

$$I_{\mathrm{K}^+} = g_{\mathrm{K}^+}(t) \cdot \left(E_{\mathrm{K}^+} - V(t)\right)$$

$$I_{\mathrm{Na}^+} = g_{\mathrm{Na}^+}(t) \cdot \left(E_{\mathrm{Na}^+} - V(t)\right)$$

Problem 7: In the equations for the gating variables, $n_\infty(V)$, $m_\infty(V)$, and $h_\infty(V)$ represent the steady-state (i.e., equilibrium) values while $\tau_n(V)$, $\tau_m(V)$, and $\tau_h(V)$ represent the corresponding time constants. Why is this the case? In addition, please explain how the functions $\alpha(V)$ and $\beta(V)$ determine the steady-state values and time constants, respectively.

Bonus problem (5 bonus points):

Background (calcium oscillations): Calcium ions (Ca^{2+}) play a vital role in signal transduction cascades in many types of animal cells. They serve as key triggers for various cellular processes, including the initiation of embryonic development in fertilized egg cells, muscle cell contraction, and the release of neurotransmitters from neurons.

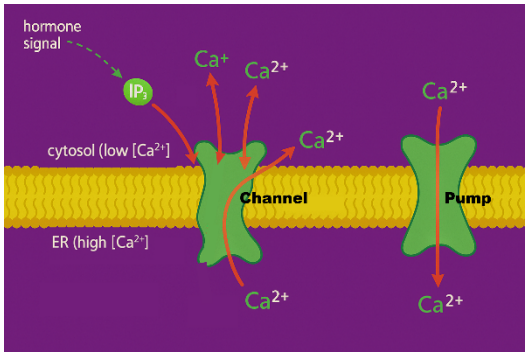
Calcium signals are generated by rapid spikes in cytosolic Ca^{2+} concentration. In cells that use these signals, cytosolic calcium levels are typically kept very low—around 10 to 100 nM. This low baseline is maintained by ATP-dependent pumps that actively transport Ca^{2+} out of the cytosol, either out of the cell or into the endoplasmic reticulum (ER). In contrast, calcium levels within the ER can reach up to 1 mM (10^6 nM). When specific signaling pathways are activated, they open calcium channels in the ER membrane, allowing Ca^{2+} to rapidly diffuse into the cytosol and produce a transient spike in concentration.

However, because calcium is involved in many cellular processes, persistent high concentrations can be detrimental. For instance, if calcium is not cleared from muscle cells, they remain in a state of continuous contraction—an effect underlying rigor mortis. To avoid the detrimental effects of prolonged calcium elevation, some cells that rely on calcium signaling generate oscillations in cytosolic Ca^{2+} levels. In this mechanism, the

frequency of the oscillations reflects the strength of the stimulus, while the amplitude remains relatively constant. The downstream cellular response is regulated by the frequency of these calcium oscillations.

Here, we will consider an instance of this frequency-encoding mechanism in mammalian liver cells. These cells respond to certain hormones with the activation of G-protein-coupled receptors. The G-protein triggers a signaling pathway that results in production of inositol 1,4,5-triphosphate (IP3). These IP3 molecules bind a receptor that is complexed with a calcium channel in the membrane of the ER.

The IP3 binding event exposes two receptor sites at which Ca2+ ions can bind. These two sites have different affinities for Ca2+. At low concentration only one site is occupied, while at higher concentrations both sites are bound. The calcium binding events have opposing effects on the receptor-channel complex. Binding of the first calcium ion causes the channel to open, allowing Ca2+ to flow into the cytosol. Binding of the second ion causes the channel to close. This interplay of positive and negative feedback generates oscillations in the cytosolic Ca2+ concentration, as follows. When cytosolic calcium levels are low, the channels are primarily in the open state, and so Ca2+ rushes into the cytosol from the ER. When high calcium levels are reached, the channels begin to shut. Once most of the channels are closed, the continual action of the Ca2+ pumps eventually causes a return to low cytosolic [Ca2+], from which the cycle repeats.



Calcium-induced calcium release. A G-protein pathway (not shown) responds to a hormone signal by inducing production of IP3, which activates calcium channels in the ER membrane. These channels bind Ca2+ ions at two sites. The first binding event causes the channel to open; the second causes it to close. Calcium pumps continually pump Ca2+ ions from the cytosol to the ER.

Model of calcium oscillations: Taking $\mathrm{I} = [\mathrm{IP3}]$ as the system input, the receptor binding events are described by

$$\mathrm{I} + \mathrm{R} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathrm{RI} \qquad \mathrm{RI} + \mathrm{C} \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} \mathrm{RIC}^{+} \qquad \mathrm{RIC}^{+} + \mathrm{C} \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} \mathrm{RIC}^{+}\mathrm{C}^{-}$$

Where R is the receptor-channel complex, C is cytosolic calcium, RI is the IP3-bound receptor-channel complex, RIC^{+} is the open (one Ca^{2+}-bound) channel, and $\mathrm{RIC}^{+}\mathrm{C}^{-}$ is the closed (two $\mathrm{Ca2}^{+}$-bound) channel.

The rate of diffusion of calcium into the cytosol depends on the concentration of calcium in the ER (denoted $[\mathrm{C}_{\mathrm{ER}}]$, and held fixed) and the abundance of open channels. The rate of diffusion is proportional to the difference in concentration between the two compartments. This transport rate is modeled as

$$\text{rate of } \mathrm{Ca}^{2+} \text{ diffusion into the cytosol} = v_r(\gamma_0 + \gamma_1[\mathrm{RIC}^{+}])([\mathrm{C}_{\mathrm{ER}}] - [\mathrm{C}])$$

where v_r is the ratio of the ER and cytosolic volumes, and γ_0 characterizes a channel-independent "leak".

Calcium is continually pumped from the cytosol to the ER. Assuming strong cooperativity of calcium uptake, the pumping rate is modeled as

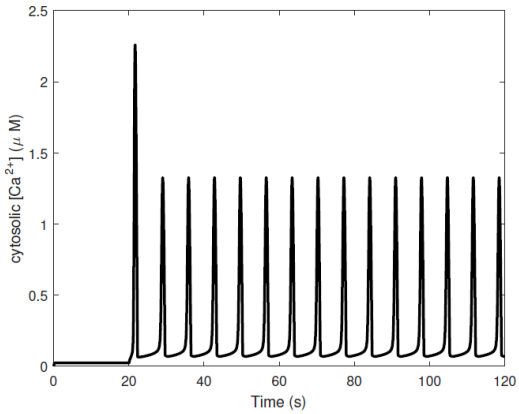
$$\text{rate of } \mathrm{Ca}^{2+} \text{ pumping out of the cytol} = \frac{p_1[\mathrm{C}]^4}{p_2^4 + [\mathrm{C}]^4}$$

for parameters p_1 and p_2.

Using the information above, complete the following ordinary differential equation (ODE) model describing calcium oscillations.

$$\frac{d[\mathrm{R}]}{dt} = ?,\ \frac{d[\mathrm{RI}]}{dt} = ?,\ \frac{d[\mathrm{RIC^+}]}{dt} = ?,\ \frac{d[\mathrm{RIC^+C^-}]}{dt} = ?,\ \frac{d[\mathrm{C}]}{dt} = v_r\left(\gamma_0 + \gamma_1[\mathrm{RIC^+}]\right)([\mathrm{C_{ER}}] - [\mathrm{C}]) - \frac{p_1[\mathrm{C}]^4}{p_2^4 + [\mathrm{C}]^4}$$

Next, please simulate the ODE model with initial condition and parameter values described below and reproduce the following result:



Initial condition: $[\mathrm{C}(0)] = 0$, $[\mathrm{R}(0)] = 1$, $[\mathrm{RI}(0)] = 0$, $[\mathrm{RIC^+}(0)] = 0$, $[\mathrm{RIC^+C^-}(0)] = 0$. The IP3 concentration, [I], is 0 before 20 seconds. and $1\mu M$ after 20 seconds.

Parameter values: $k_1 = 12$, $k_2 = 15$, $k_3 = 1.8$ (in $1/\mu M \cdot 1/\mathrm{s}$); $k_{-1} = 8$, $k_{-2} = 1.65$, $k_{-3} = 0.21$, $\gamma_0 = 0.1$, $\gamma_1 = 20.5$ (in 1/s), $[\mathrm{C_{ER}}] = 8.37\mu M$, $p_1 = 8.5\mu M \cdot 1/s$, $p_2 = 0.065\mu M$, and $v_r = 0.185$.