Excitatory Dynamics in Cardiac Cells and Tissue

For this lab, we will build upon our previous lab where we modeled action potentials in neurons with the Hodgkin-Huxley model and explore how electrical signals can propagate through tissues. To do this, we will also have to learn how to simulate partial differential equations in MATLAB. For your submission, please include answers to all questions, any requested figures, and your MATLAB code.

Problem 1: Simulation of Partial Differential Equations in MATLAB

Consider the simple reaction-diffusion system where free species C diffuses along the x direction and can become immobilized via the binding reaction $C \rightarrow I$. This system is represented by the partial differential equations:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2}{\partial x^2}C - kC$$

$$\frac{\partial I}{\partial t} = kC$$

Where x is the position along the 1D space. To simulate this model, we can discretize the equation over a given Δt and Δx to obtain:

$$\frac{C_i^{t+\Delta t} - C_i^t}{\Delta t} = D\frac{C_{i-1}^t - 2C_i^t + C_{i+1}^t}{\Delta x^2} - kC_i^t$$

$$\frac{I_i^{t+\Delta t} - I_i^t}{\Delta t} = kC_i^t$$

Where X_j^k is the concentration of species X at time k and position j. These discretized equations can be used to solve for the concentrations C and I at time $t + \Delta t$ and position i explicitly. To simulate PDEs, we need to set initial conditions and boundary conditions, which set the values of C and I at time = 0 and at the edges of our one-dimensional space. Consider this reaction-diffusion system in a one-dimensional space with length 0.5, D = 0.01, and k = 1. For your initial conditions, assume that $C_{x=0.25}^{t=0}$= 1 and is zero at all other locations, and $I = 0$ at all locations. Boundary conditions set conditions that determine either concentration or flux at the boundaries of our one-dimensional space. For this problem we will be using zero flux boundary conditions, i.e., that $\frac{\partial C}{\partial x} = 0 = \frac{\partial I}{\partial x}$ at $x = 0, 0.5$. Simulate the model over a period of [0 5] with $\Delta t = 0.0025$ and Δx = 0.01. Plot C v. x and $I\ v. x$ at time points of $t = [0, 0.1, 0.5, 1, 5]$ on the same set of axes. Describe how the system behaves as time passes.

Problem 2: Simulation of Fitzhugh-Nagumo Model

The Fitzhugh-Nagumo model is a simplified version of the HH model we explored last lab that combines all of the gating variables into a grouped response variable w. This model is described by the ordinary differential equations:

$$\frac{dv}{dt} = v(a - v)(v - 1) - w + I$$

$$\frac{dw}{dt} = bv - \gamma w$$

Use the parameters $a = 0.1, b = 0.05, \gamma = 0.1$ for the following problems.

a) Simulate your model for applied currents of I = 0, 0.15, and 0.3 over a time period from 0 to 500 with initial conditions $(v, w) = (0.5, 0)$. On three separate plots, plot the model nullclines and your simulation results on a w v. v axis. Additionally, use MATLABs quiver command to plot a vector field showing $\frac{dv}{dt}$ and $\frac{dw}{dt}$ at a mesh of points from $v = [-1\ 2]$ and $w = [-0.5\ 0.5]$ with 30 points for each, and use these same ranges as the limit of your axes. Hint: see MATLABs meshgrid command to obtain coordinates for each point in the mesh. How does the value of the applied current affect how the system behaves?

b) Fix the current input at I = 0.125 and modify your values of b and γ to vary according to the variable ϵ, i.e., $b(\epsilon) = 0.01\epsilon, \gamma(\epsilon) = 0.02\epsilon$. Beginning with $\epsilon = 1$, simulate your model over a time period of 0 to 500 and confirm that the predicted voltage is oscillating. To do this, take the last ten points in your simulation and calculate the absolute % change compared to the final point, or $abs\left(\frac{v - v_{end}}{v_{end}}\right)$. Large values of this quantity indicate that your system is oscillating. Now, determine the value of ϵ that prevents voltage from oscillating. To do this, increase the value of ϵ by 0.01, simulate, and calculate the absolute % change as you did before. If this value is greater than 1%, keep increasing ϵ until the absolute % change is less than 1%. What value of ϵ lead to oscillations stopping? Why would increasing these parameters lead to oscillations stopping? Hint: Use a while loop with the break command to stop once you reach the desired behavior.

Problem 3: Simulation of the Fitzhugh-Nagumo Model in a 1D Spatial System

Now we will extend the Fitzhugh-Nagumo model to represent signal propagation through a 1D spatial system. This model is now represented by the partial differential equations:

$$\frac{\partial v}{\partial t} = v(a - v)(v - 1) - w + I + D\frac{\partial^2}{\partial x^2}v$$

$$\frac{\partial w}{\partial t} = bv - \gamma w$$

Where x is the position along a one-dimensional line. Here, the new parameter D represents the diffusivity of signal v through the tissue in the x direction. When discretized, this system of partial differential equations becomes:

$$\frac{v_i^{t+\Delta t} - v_i^t}{\Delta t} = v_i^t(a - v_i^t)(v_i^t - 1) - w_i^t + I + D\frac{v_{i-1}^t - 2v_i^t + v_{i+1}^t}{\Delta x^2}$$

$$\frac{w_i^{t+\Delta t} - w_i^t}{\Delta t} = bv_i^t - \gamma w_i^t$$

For the following problems, use $a = 0.1, b = 0.01, \gamma = 0.02, I = 0$ with the initial conditions $w_i^{t=0} = 0$, $v_{i=10}^{t=0}$ = 2.25 and 0 at all other positions. (If you've set up your vector of x points correctly, $v_{i=10}^{t=0}$ will be located on the first row and 11th column in your v matrix).

a) Simulate the model using the same methods given in problem 1 modified to represent this system of partial differential equations over a 1-dimensional tissue of length 100 with D = 1. For your simulations, use Δt = 0.025 and Δx = 1 to simulate over a period of 0 to 200. Plot v v. x at $t =$

[0 50 100 150]. If this system represents the transduction of a voltage signal through cardiac tissue, does the signal propagate through the tissue?

b) Repeat your simulations in part a using $D = 0.5, 0.75, 1.25, 1.5$ with all other parameters fixed. Do any of these values of diffusivity prevent the signal from propagating? If so, which ones and why is this the case? Hint: The signal propagating by cells reacting to the signal. Why might cells not be able to react in certain cases?