Developing a MATLAB script package for simulation electrical activity in cells

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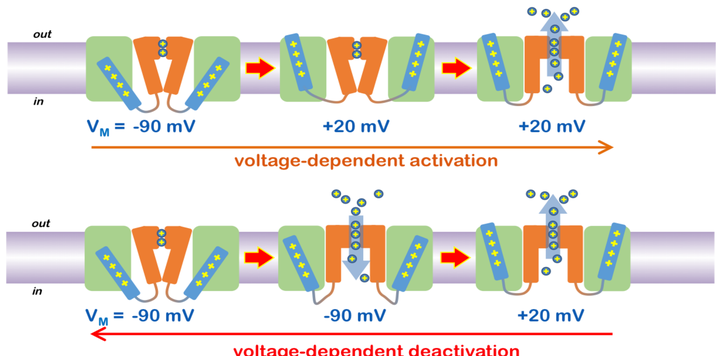
Summary

Ion channels are proteins on membranes of cells which control the flow of ions in and out of cells. These proteins transition between different formations, called states, due to changing conditions in the cellular environment, including changes in the electrical potential across the membrane and the binding of ligands. In this project, we are working on simulating the transition of ion channels between states. We have started by using a multiple-state sequential and reversible model that applies to any general chemical reaction, and will subsequently add more parameters to make the simulation specific to ion channel behavior. Using matrices to store the data for the population fraction of states and the rate constants governing change between states, we can use matrix multiplication in MatLab to simulate the behavior of the population with respect to time. The work presented here shows our progress to date on simulating the behavior of ion channel proteins.

1. $S_1 \underset{\beta_1}{\overset{\alpha_1}{\rightleftharpoons}} S_2 \underset{\beta_2}{\overset{\alpha_2}{\rightleftharpoons}} S_3 \underset{\beta_3}{\overset{\alpha_3}{\rightleftharpoons}} S_4 \underset{\beta_4}{\overset{\alpha_4}{\rightleftharpoons}} S_5$

$$\alpha = \alpha_0 e^{+z_\alpha FV/RT} \quad \beta = \beta_0 e^{-z_\beta FV/RT}$$

2.



3.

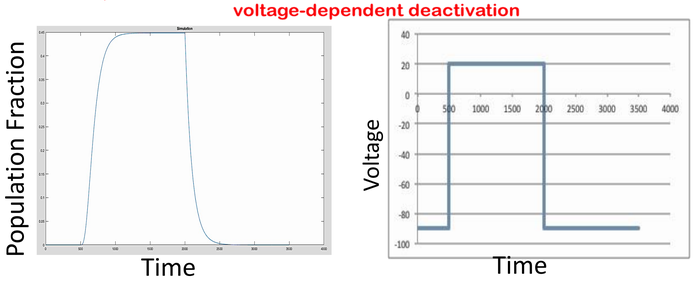


Figure 1 – Background

1. The model of a five state, sequential, reversible reaction. S_1-S_5 represent the five states, and α and β represent the rates of change between states. The ensuing equations are for calculating the rate values. 2. This illustration offers a visualization of the activation of an ion channel by changing the potential across the membrane. 3. A graph of the change in population fraction of a single state within a five state reaction, given the change in voltage on the right (the same as the illustration above in Module 2). This is a three step reaction, with the first and third step at -90 mV and the second at +20 mV.

Future Direction

The next step for this project is simulating the flow of ions, or the current, in and out of a cell through ion channels. To do this, we will be using similar graphs, graphing one state and a time and using a three step reaction with multiple different potentials tested during the middle step. However, instead of graphing the population fraction of the state with regard to time, we will be graphing the current along that state with regard to time. As a result, we will only be looking at the open states for the current, as there is no flow of ions through a closed channel. Beyond this, we will continue to develop the program to allow for more and more specific parameters, and eventually the program will be able to simulate the behavior of a system in which the voltage and current are interdependent and fluid, rather than preset and static.

Input Parameters

- # of distinct states, percentage populations of each state, rate of change between states, voltage/ligand dependencies of rates, different "steps" within experiment.
- Values are read from text files and are stored as variables in MATLAB, with the states, rates, and time stored in matrices/arrays

Calculation

- Transition rate matrix is multiplied by state matrix using nested for loops
- With every loop, a new **Δ**State (change in state) value and time value is calculated. The **Δ**State value is added to the corresponding value in the state matrix and plotted with respect to the new value in the time matrix

Editing Matrices

- Read rates are used to calculate a transition rate matrix which will be used to calculate the changes in time of each state's population

Output

- State matrix (representing population fraction of each state) is graphed with respect to time
- Output is sent to text file for graphing in other programs

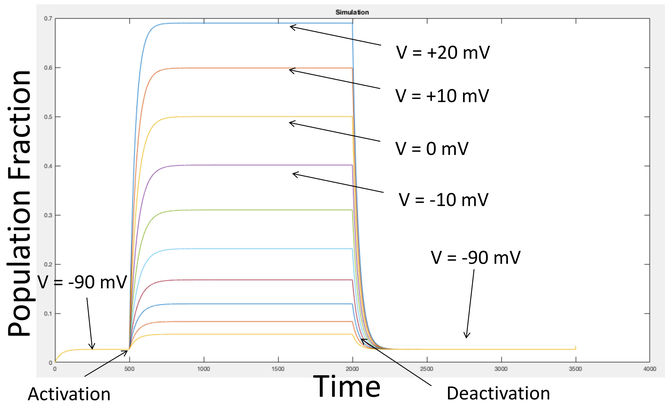


Figure 2 – 2 States

Figure 2 shows the simulation of the activation of S_1 in a 2-state model using 10 different voltages. Starting at -90 mV, we used 10 different voltages, starting at +20 mV (blue) and decreasing by 10 mV each time, and graph the population fraction of the state. This state started at a population concentration of zero and returns after deactivation.

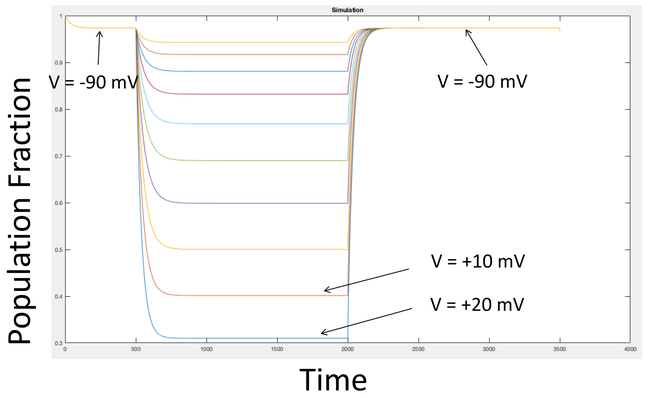


Figure 3 – 2 States

Figure 3 shows the other state (S_2) in the simulation depicted in Figure 2. S_1 in Figure 2 began at a population fraction of zero, while S_2 begins at a population concentration of one and returns to one after deactivation.

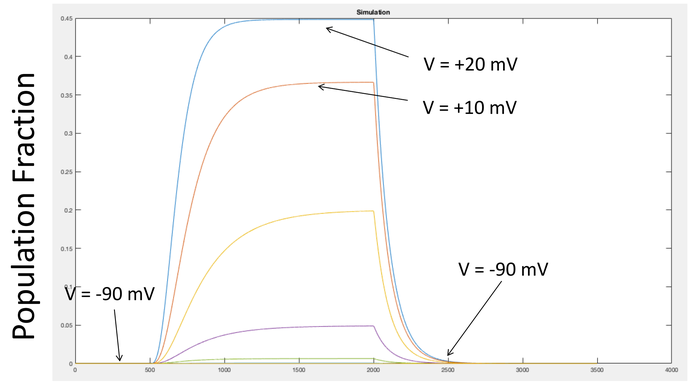


Figure 4 – 5 States

Figure 4 shows a similar simulation to Figures 2 and 3 with five states. The state depicted (S_5) has a delay in activation because of the sequential nature of the reaction (see Module 1, Figure 1). In this case, S_1 has a population fraction of 1 and the rest are zero; therefore, there is a delay in the activation of S_5. Therefore, only the five highest voltages change the population fraction of the state.

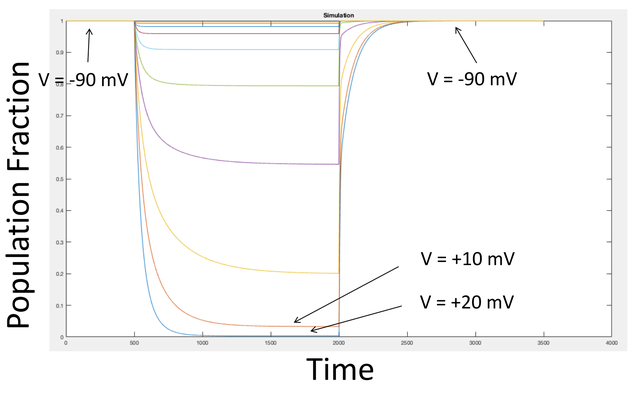


Figure 5 – 5 States

Figure 5 shows S_1 from the same simulation in Figure 4. Because all of the population started in S_1, the delay due to the sequential nature of the reaction is not as noticeable in this simulation as in Figure 4. S_1 begins at a population concentration of one and returns to one after deactivation.