Computational Methods in Biology (Fall 2022)

Exercises due October 21

This assignment focuses on stochastic models and simulation methods, using ion channel gating as the model system. The project involves Monte Carlo simulations with Markov chain models, and the computer codes can be written in C, C++, FORTRAN, Python, Java, Matlab, or anything else with the flexibility to do Markov chain simulations. To use the Monte Carlo approach you will need to use a pseudo-random number generator, with is available on your computer with any of the computer languages you choose to code in.

1. **Single stochastic ion channel**
Consider the gating of a single two-state ion channel, with $C \to O$ transition probability k^+ and $O \to C$ probability k^- (units of both are ms^{-1}). Write a program for a Monte Carlo simulation of the gating of this channel for a duration of 1000 msec, and time step $\Delta t = 0.5$ msec. Let $S = 0$ when the channel is in a closed state, and $S = 1$ when it is in an open state. Plot S vs. time. Also, compute the running sample mean of S and plot it along with S. [Sample mean $= \frac{\sum_i^n S(i)}{n}$ where n is the current iteration number, $t = n\Delta t$, and $S(i)$ is S at iteration i.] Do this for three combinations of the transition probabilities (k^+, k^-): (0.05,0.05), (0.3,0.3), (0.05,0.3). Comment on how the channel dynamics and sample means differ for these different combinations, and compare to expected means from probability theory. Use your simulation to calculate the sample mean open and closed dwell times. Plot these vs. time. Compare the values of the sample mean dwell times at time $t = 1000$ ms to the expected equilibrium mean dwell times from probability theory.

2. **Population of stochastic ion channels**
Next consider an ensemble of five identical and independent ion channels. This could represent, for example, a patch of neural membrane containing five channels whose activity is monitored by a patch clamp electrode.

   (1) Simulate the stochastic gating of the ensemble using five Markov variables, one for the state of each channel. Suppose that the transition probabilities for each channel are $(k^+, k^-) = (0.05, 0.05)$. Turn in a plot with three panels. The first two should show the states of two of the five channels versus time. The third panel should have two superimposed curves. One curve should show the number of open channels versus time. The other curve should show the sample mean of the number of open channels. According to probability theory,

what is the expected mean number of open channels? Is this consistent with your sample mean from the Monte Carlo simulation?

(2) Simulate the stochastic gating of the ensemble using a single Markov variable for the number of open channels. What is the kinetic scheme for this simulation? Turn in a plot with three panels, corresponding to transition probabilities $(k^+, k^-) = (0.05, 0.05)$, $(0.3, 0.3)$, and $(0.05, 0.3)$. In each, plot the number of open channels versus time and the running sample mean of the number of open channels. Does the sample mean match the expected mean from probabiility theory?