AMATH 422/522
Problem set

Working together is absolutely encouraged. Please do not refer to previous years' solutions.

For each problem: together with any analysis or explanations, turn in both all code and all relevant plots, labeled and with all line styles, marker sizes etc. adjusted for readability.

Please note: E+G stands for our book, by Ellner and Guckenheimer.

I **Coding and strategies for simulating markov chains and dwell times.** Download and work through the third (and final) section of the MATLAB "lab manual," posted online.

II **Dwell time distributions: theory.** Consider an ion channel with 4 open states and 2 closed states. Give a mathematical argument, similar to that in class, that derives the typical functional form of the dwell time distribution for the channel being in any one of the open states. *Note: I am looking for a derivation here, not just a statement of the answer or a "mantra" or result from class.*

III **Simulating Markov chains and dwell times.**

Models for stochastic switching among conformational states of membrane channels are somewhat more complicated than the two-state models with which we started our discussions of Markov chains. There are usually more than 2 states, and the transition probabilities are state dependent. Moreover, in measurements some states cannot be distinguished from others. We can observe transitions from an open state to a closed state and vice versa, but transitions between open states (or between closed states) are "invisible". Here we shall simulate data from a Markov chain with 3 states, collapse that data to remove the distinction between 2 of the states and then analyze the data to see that it cannot be readily modeled by a Markov chain with just two states.

Suppose we are interested in a membrane current that has three states: one open state, O, and two closed states, C_1 and C_2. As in the kinetic scheme discussed in class, state C_1 cannot make a transition to state O and vice-versa. We assume that state C_2 has shorter residence times than states C_1 or O. Here is the transition matrix of a Markov chain that we will use to simulate these conditions. The state $S_1 = 1$ corresponds to C_1, $S_2 = 2$ corresponds to C_2, and $S_3 = 3$ corresponds to O:

$$\begin{pmatrix} .98 & .1 & 0 \\ .02 & .7 & .05 \\ 0 & .2 & .95 \end{pmatrix}$$

You can see from the matrix that the probability 0.7 of staying in state C_2 is much smaller than the probability 0.98 of staying in state C_1 or the probability 0.95 of remaining in state O.

Our goal is to compute the distribution of dwell times in the closed state for this system. Please do this in three stages. (1) Download `markov_chain_simulate_twostates.m` from our website. (2) Modify it to simulate the three-state system above. We discussed how to do this in class, splitting up the unit interval into more than three segments and using the `rand` command. (3) To compute dwell times in the closed state, it's convenient to make a "reduced" list of states `rstates` after you've simulated to produce `states`. In `rstates`, you'll lump together both closed states – say, giving them both the same numerical value of 1. (4) Compute a list of the simulated dwell times in the closed state, make a histogram of the dwell times, and see if it follows is indeed poorly fit by a single exponential, as expected from class. Note that you might need to simulate for a long time to get a sufficiently resolved histogram.

Note: Recall that many steps of the above, with code, were discussed in Lab manual part 3, section 3.

IV **Simulating Markov chains and neural spiking.** In electrically active cells, different ion channels correspond to different membrane currents. These currents can be "inward," tending to increase the intracellular potential (such as the Na current), or "outward," tending to decrease it (such as the K current). What actually happens to this potential therefore depends on the balance between inward and outward currents.

Here, we will consider an inward current carried by an ion channel with three states: one open state, O, and two closed states, C_1 and C_2. As in the above, state C_1 cannot make a transition to state O and vice-versa. We assume that state C_2 has shorter residence times than states C_1 or O. Here is the transition matrix of a Markov chain that we will use to simulate these conditions. The state $S_1 = 1$ corresponds to C_1, $S_2 = 2$ corresponds to C_2, and $S_3 = 3$ corresponds to O:

$$\begin{pmatrix} .98 & .1 & 0 \\ .02 & .7 & .05 \\ 0 & .2 & .95 \end{pmatrix}$$

When a single inward channel is open, a current of $+1$ units flows through the channel.

We will consider an outward current that is carried by an ion channel that also has one open state, O, and two closed states, C_1 and C_2. According to the same convention, the corresponding transition matrix is:

$$\begin{pmatrix} .9 & .1 & 0 \\ .1 & .6 & .1 \\ 0 & .3 & .9 \end{pmatrix}$$

When a single outward channel is open, a current of -1 units flows through the channel.

Assume there are a total of $N_{inward} = 100$ inward channels, each evolving independently under a realization of the Markov kinetics above. If n_{inward} of these channels are in the open configuration at timestep t, then the total inward current is $+n_{inward}$.

Assume there are a total of $N_{outward} = 50$ outward channels, each evolving independently under a realization of the Markov kinetics above. If $n_{outward}$ of these channels are in the open configuration at timestep t, then the total outward current is $-n_{outward}$ units.

Thus, the net current into the cell at timestep t is $n_{inward} - n_{outward}$: the number of open inward channels minus the number of open outward channels. In our model, the cell will produce an action potential (spike) in a given timestep if this net current is greater than a threshold value T.

Assume that the channels have settled into equilibrium (i.e., that a time has passed that is large enough since a simulation was initialized). Plot the probability that the cell will produce a spike in a given timestep, as a function of the spiking threshold T. (That is, T should be on horizontal axis, and a probability on the vertical axis.) There are at least two ways of doing this: (1) by computing the equilibrium state probabilities, and simulating many coin tossings, or (2) by computing the equilibrium state probabilities, and using the form of the binomial distribution.

Repeat this for $N_{inward} = 10$, $N_{outward} = 5$ and for $N_{inward} = 1000$, $N_{outward} = 500$, and for any other combinations of values you wish. Write a few sentences reporting on any qualitative changes that you observe. For AMATH 522, also either (a) give your best mathematical explanation of the trends that you see, or (b) discuss their implication for the ways that neurons might be built in order to be reliable, including one reference to the literature on "ion channel noise."