

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 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.*

II 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.ipynb` 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 two segments. (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 0. (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.