

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 Markov Chain: general solution for 2-states.** This is not a MATLAB problem. The transition probability matrix is:

$$A = \begin{pmatrix} p & 1-q \\ 1-p & q \end{pmatrix}.$$

- (a) Calculate the eigenvalues. How to do this for a general matrix  $A$ : Form the determinant  $|A - \lambda I|$ , where  $I$  is the identity (diagonal matrix of ones) and solve for  $\lambda$ . In this case this means:

$$|A - \lambda I| = \left| \begin{pmatrix} p & 1-q \\ 1-p & q \end{pmatrix} - \lambda \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \right|.$$

The determinant of a  $2 \times 2$  matrix is determined ("ta-dah!") by:

$$\left| \begin{pmatrix} a & b \\ c & d \end{pmatrix} \right| = ad - bc.$$

When you get the determinant you will find it is a 2nd order polynomial in  $\lambda$ . Solve this polynomial for the eigenvalues.

- (b) Calculate both eigenvectors  $\vec{w}^1$  and  $\vec{w}^2$ . For each eigenvalue  $\lambda$ , this means you need to solve a linear system:  $(A - \lambda I)\vec{w} = 0$  for the vector  $w = (w_1, w_2)^T$ . This is a system of 2 linear equations in the unknown variables  $w_1$  and  $w_2$ . To solve (one way), eliminate variable 1, solve for variable 2, and then plug in to get variable 1. You'll have to solve a different system for each eigenvalue.
- (c) Let the initial state probability vector  $\vec{p}(0) = (a_1, a_2)^T$ . Compute the state  $\vec{p}(k)$  for all  $k > 0$ . To do this, find  $c_1$  and  $c_2$  so that  $\vec{p}(0) = c_1\vec{w}^1 + c_2\vec{w}^2$ . Then use the properties of eigenvectors to write the solution for all time  $k$ .
- (d) **Sanity check:** Set  $\vec{p}(0) = (0, 1)^T$ ,  $p = 0.78$  and  $q = 0.95$ . Simulate the system for 100,000 steps. Numerically compute the stationary distribution by taking a time average over the last 1,000 steps of the simulation. It should be close to the theoretical stationary distribution. You may modify the code `markov_chain_simulate_twostates.m`

**II Properties of dwell time distributions.** Recall that for any Markov chain, the dwell time follows the distribution:

$$f(k) = \Pr(\text{dwell time} = k) = p^{k-1}(1-p)$$

for  $k = 1, 2, 3, \dots$  etc., where  $p$  is the probability that the state stays the same. Show all your work and compute:

- (a)  $\sum_{k=1}^{\infty} f(k)$ . Why does this have to be the case?
- (b)  $\sum_{k=1}^{\infty} kf(k) = \mathbb{E}(\text{dwell time})$ . This is called the expected value or mean. Hint: write  $kf(k)$  as a derivative, and take the sum before taking the derivative. **Important:** explain why  $p$  sets the "time scale" of the dwell time.
- (c)  $\sum_{k=m+1}^{\infty} f(k) = \Pr(\text{dwell time} > m)$  for all  $m \geq 0$ . This is called the complementary cumulative distribution.

(d) Memory-less property. By definition, the conditional “probability of  $A$  given  $B$ ” is

$$\Pr(A|B) = \Pr(A \text{ and } B)/\Pr(B).$$

Here,  $A$  and  $B$  are outcomes of a random experiment. The conditional probability of  $A$  given  $B$  is just the probability that both  $A$  and  $B$  occur divided by the probability of  $B$ .

Let  $A$  be the event “dwell time  $> m + m_0$ ” and  $B$  the event “dwell time  $> m_0$ ”. Compute “ $\Pr(A|B)$ ” and explain why this means the distribution is “memory-less.”

**III Markov chains in continuous time. This question is required for grad students, or undergrads can do it for extra credit.** There is a generalization of Markov chains to continuous time which is called a Markov process. In a Markov process, states are still discrete but time is continuous, and all the possible state transitions are characterized by a matrix  $M$ . In this case, the dwell times before a transition follow a continuous probability distribution with probability density function

$$f(x) = ce^{-\lambda x}$$

for  $0 \leq x < \infty$  and some  $c$  that you will determine. Compute and show work:

- Find  $c$  so that  $\int_0^\infty f(x)dx = 1$ . Use this value of  $c$  for the rest of the problem.
- $\int_0^\infty xf(x)dx = \mathbb{E}(\text{dwell time})$ . This is called the expected value or mean. Explain how and why  $\lambda$  sets the “time scale” of the dwell time.
- $\int_m^\infty f(x)dx = \Pr(\text{dwell time} \geq m)$  for all  $m \geq 0$ . This is called the complementary cumulative distribution.
- Compute  $\Pr(\text{dwell time} \geq m + m_0 | \text{dwell time} \geq m_0)$ . Is the distribution “memory-less?”
- Grad student extra credit:** Go back to the discrete dwell time distribution. Let  $p = 1 - \alpha h$ , where  $0 < h \ll 1$ . Derive the continuous dwell time distribution by thinking of  $h$  as the time step of the Markov chain and taking the limit as  $h \rightarrow 0$ . Hint: in the continuous version,  $f(x)dx = \Pr(\text{dwell time} \in [x, x + dx])$ . What do you get for  $\lambda$ ?
- Grad student extra credit:** The dynamical system that governs a Markov process is:

$$\frac{d\vec{p}(t)}{dt} = M\vec{p}(t),$$

where  $\vec{p}$  means the same thing as before. Euler’s method for an arbitrary ordinary differential equation

$$\frac{dx(t)}{dt} = g(x(t))$$

(vector or scalar) is to approximate the above by

$$x(t + h) = x(t) + g(x(t))h.$$

- Apply Euler’s method discretize the differential equation for the evolution of the probability distribution in a Markov process. If this describes a Markov chain, what is the state transition matrix?
- Suppose that  $h = 1$ . What condition needs to hold on  $M$  for the resulting system to be a valid Markov chain?
- Show that the condition you got in (ii) actually holds in general:  $\vec{p}(t)$  is truly a probability distribution for all  $t > 0$  for the differential equation (not the Euler approximation).

#### IV 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.

- Before you do any coding, please explain why  $C_2$  has a shorter residence/dwell time than the other two states. What is the expected time the membrane stays in each state (in steps)?
- Download `markov_chain_simulate_twostates.m` from our website. 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.
- 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.
- 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. You'll also need to zoom in at different scales!

*Note: Many steps of the above, with code, are discussed in Lab manual part 3, section 3.*

**V 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  $O$ :

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

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:

$$A_{\text{out}} = \begin{pmatrix} .9 & .1 & 0 \\ .1 & .6 & .1 \\ 0 & .3 & .9 \end{pmatrix}$$

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

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

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

Thus, the net current into the cell at timestep  $t$  is  $n_{in}(t) - n_{out}(t)$ : 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).

Your task:

- (a) 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 **binomial distribution**.
- (b) Repeat this for  $N_{in} = 10$ ,  $N_{out} = 5$  and for  $N_{in} = 1000$ ,  $N_{out} = 500$ , and for any other combinations of values you wish. Report on, and write some sentences giving a mathematical explanation of, any qualitative changes that you observe.

You do not have to simulate 1000 simultaneous Markov chains to do this problem.