Lab 7: Matrix Methods for Linear Systems

Simple model for ion channels  (adapted from Prof. Walcott’s 27A Homework WQ2019)
Ion channels are special proteins that are situated in the membranes of cells and (sometimes) allow ions to pass through the membrane. They are critical to processes like the signaling of brain cells and the contraction of heart muscle. For this reason, many drugs target ion channels to, say, make a heart attack less likely.

Figure 1 shows a diagram that represents a model for an ion channel. The ion channel can be closed (state 1) or open (state 2), and $k_o$ and $k_c$ are the rate constants of opening and closing, respectively. Supposing that there are $n_1$ closed channels and $n_2$ open channels, the equations that govern this model are

$$\frac{dn_1}{dt} = -k_on_1 + k_cn_2$$  
$$\frac{dn_2}{dt} = k_on_1 - k_cn_2.$$  

1. Write the above linear system in matrix form $d\vec{n}/dt = K\vec{n}$.

2. Because the total number of ion channels $N_{tot}$ is constant with time, $n_1(t)$ and $n_2(t)$ are not linearly independent. Show that this is the case by showing that the coefficient matrix $K$ is singular.

3. Rewrite the linear system into a single linear differential equation using the change of variables

$$n_2 = N_{tot} - n_1.$$  

4. Let $N_{tot} = 3000$, and use the following rate constants: $k_o = 2, k_c = 1$. Solve the system (by hand) with all ion channels closed initially.
5. What are the steady-state values of \( n_1 \) and \( n_2 \)? Are more channels open or closed?

6. Check your work by solving the original matrix system numerically.

Now let’s examine the ion channel model with drug-binding dynamics.

![Figure 2: Ion channel with drug-binding state model.](image)

Figure 2 shows a diagram that represents a model for an ion channel. In the top row, the ion channel can be closed (state 1) or open (state 2). The remaining two states (states 3 and 4) represent the ion channel with drug bound – you can see the drug molecule at the upper right of the ion channel. Supposing that there are \( n_1 \) closed channels, \( n_2 \) open channels, \( n_3 \) drug-bound closed channels, and \( n_4 \) drug-bound open channels, the equations that govern this model are

\[
\begin{align*}
\frac{dn_1}{dt} &= -(k_o + k_c^+) n_1 + k_c n_2 + k_c^- n_3 \quad (3) \\
\frac{dn_2}{dt} &= k_o n_1 - (k_c + k_c^+) n_2 + k_c^- n_4 \quad (4) \\
\frac{dn_3}{dt} &= k_c^+ n_1 - (k_c^- + k_{do}) n_3 + k_{dc} n_4 \quad (5) \\
\frac{dn_4}{dt} &= k_c^+ n_2 + k_{do} n_3 - (k_o^- + k_{dc}) n_4 \quad (6)
\end{align*}
\]

7. Write the above linear system in matrix form \( \frac{d\vec{n}}{dt} = K\vec{n} \). The entries of your coefficient matrix \( K \) should contain combinations of the constants \( k_o, k_c, k_c^+ \ldots \).
8. Because the total number of ion channels $N_{tot}$ is constant with time, $n_1(t)$, $n_2(t)$, $n_3(t)$, and $n_4(t)$ are not linearly independent. Show that this is the case by showing that the coefficient matrix $K$ is singular.

9. Rewrite the system as a matrix equation with a 3x3 coefficient matrix using the change of variables

$$n_4 = N_{tot} - n_1 - n_2 - n_3.$$

10. Let $N_{tot} = 3000$, and use the following rate constants: $k_o = 2, k_c = 1, k_c^+ = 8, k_c^- = 1, k_{do} = 1, k_{dc} = 4, k_o^+ = 2$, and $k_o^- = 2$. Solve the matrix system with all ion channels closed and drug-free initially.

11. What are the steady-state values of $n_1, n_2, n_3$, and $n_4$ in this case?

12. Check your work by solving the original matrix system numerically.

13. Suppose that the constants for questions 10-12 come from a particular drug. The purpose of this drug is to decrease the flow of ions through this ion channel by increasing the probability that the ion channels are closed. Does the drug work? (Hint: The number of closed channels is the number of channels in states 1 and 3 ($n_1 + n_3$) and the number of open channels is $n_2 + n_4$. In the absence of drug, we get the system from questions 1-5.)
14. Suppose another drug has a similar binding affinity, but once bound to an ion channel the
drug never unbinds and once the channel opens the drug locks the ion channel in the open
state. What do you think will happen to the ion channels in this case?

15. Suppose this drug has rate constants $k_o = 2, k_c = 1, k_c^+ = 8, k_c^- = 1, k_{do} = 1, k_{dc} = 0, k_o^+ = 2,$ and $k_o^- = 0$. Solve this matrix system, either numerically or by hand, with all ion channels
closed and drug-free initially. Does the behavior match your prediction in question 14?

16. After finishing your write-up for this lab, answer the following questions. What was your
favorite part of this lab? What was the easiest part of this lab? The hardest?
What was confusing? What was interesting?