

CS341 SYSTEMS BIOLOGY I

PROJECT 1

The first part of this project involves an introduction to the simplest reaction – degradation. The second two parts involve formulating a mathematical models, simulating them, and then manipulating them an effort to understand them better. Turn in a write-up with figures (a PDF or Word document would be best) and a zip-file (or tar ball) containing all of your code.

Note: In the instructions, I ask you to change parameter values several time. When you turn in the code, don't worry about trying to capture all of the different parameter sets. Just turn it in in some sort of working order.

1. UNITS AND DEGRADATION

In ODE models, it is most often the case that each state variable (e.g. $P1$) indicates a concentration. For proteins, the concentration is often given units of nano-molar (nM), which is 10^{-9} moles per liter. Any given protein in *E. coli*, has a concentration of approximately 1 nM. In mammals, proteins are often present in much smaller concentrations. Since the state variable has units of concentration, the rate of change of a state variable (i.e. $dP1/dt$) must have units of concentration divided by time. The timescale of the process generally determines which time unit we use. For circadian systems (operating on a 24-hour timescale), we use hours as the time units, but many other processes operate on faster timescales and seconds or minutes are better units.

For degradation, of protein $P1$, we have the following ODE

$$(*) \quad \frac{dP1(t)}{dt} = -d1 \cdot P1(t)$$

where $P1$ has units of nM and t has units of seconds (s).

This is a linear differential equation, which has an analytic solution

$$(\dagger) \quad P1(t) = e^{-d1 \cdot t} \cdot P1_0$$

where the initial condition is $P1(0) = P1_0$.

- (1) Demonstrate that $(\dagger)$ is the solution to $(*)$ by differentiating both sides of $(\dagger)$.
- (2) What units must $d1$ have?
- (3) The half-life of a protein is the amount of time it takes for the concentration to halve. What is the half-life of protein $P1$ (in terms of $d1$)? Show your work.

2. DIMERIZATION

Consider a system in which two proteins can bind to form a dimer, and unbind to reform the dimer. This is laid out as a network in Figure 1.

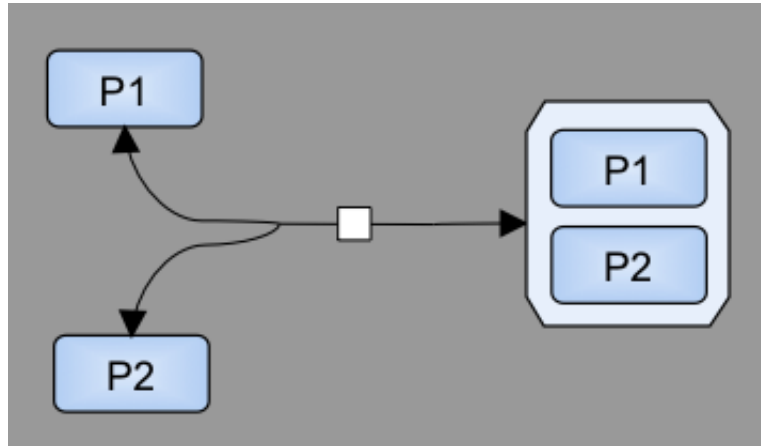
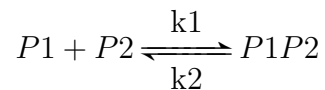


FIGURE 1. Proteins P1 and P2 can bind to form a dimer and the dimer can unbind to release P1 and P2.

For each process (indicated by the white square), we write the corresponding reaction. Since we are using mass action kinetics, we know that the mathematical expression for each reaction is dependent on the substrates and a kinetic rate constant. To be as informative as possible, we include in our reactions the kinetic rate constant associated with each reaction, i.e.



where $k1$ is the rate constant for binding and $k2$ is the rate constant for unbinding.

- (1) Write down the set of ODEs that describe the dynamics of this system.
- (2) Using initial conditions $P1(0) = 2nM$, $P2(0) = 3nM$, and $P1P2(0) = 1nM$ and kinetic parameters $k1 = 1nM^{-1}s^{-1}$ and $k2 = 2s^{-1}$, simulate the system from time $t = 0s$ to $t = 10s$ with a time step of $0.01s$.
- (3) Plot the results, being sure to label your axes and to supply a legend.
- (4) Steady-state is achieved when the rates are at zero. What is the steady-state for this system? Explain the relationships between the steady-states of $P1$, $P2$, and $P1P2$. Why are they in such a relationship? (i.e. relate the parameters to the steady-states)

- (5) Re-run the simulation with $k_1 = 1nM^{-1}s^{-1}$ and $k_2 = 1s^{-1}$ and plot the results.
- (6) The rate constants for binding and unbinding are identical. But this does not mean that the system begins in steady-state. Why not?
- (7) Explain what has changed in the relationship between the steady-states of the molecular concentrations. Why have those changes occurred?

3. DIMERIZATION WITH DEGRADATION

We add to our system the process of degradation (see Figure 2).

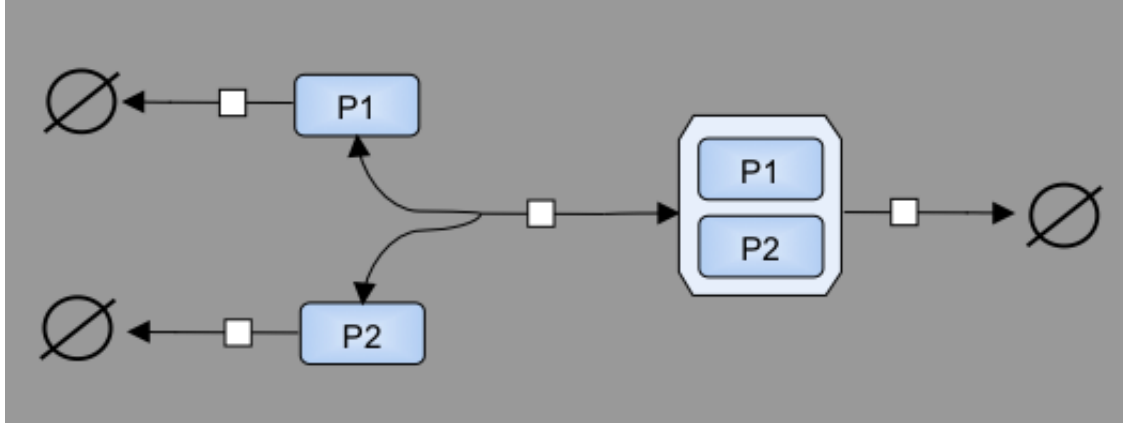
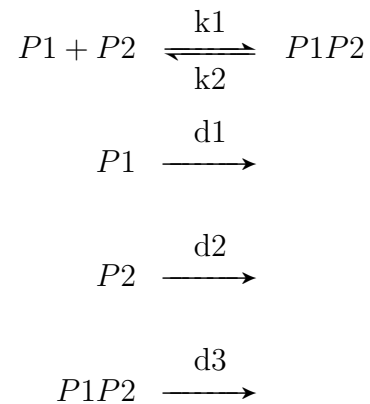


FIGURE 2. Proteins P1 and P2 can bind to form a dimer and the dimer can unbind to release P1 and P2. In addition, P1, P2, and the dimer are degraded.

For each process (indicated by the white square), we write the corresponding reaction (including rate constants), i.e.



- (1) Write down the set of ODEs that describe the dynamics of this system.
- (2) Using initial conditions $P1(0) = 2nM$, $P2(0) = 3nM$, and $P1P2(0) = 1nM$ and kinetic parameters $k1 = 1nM^{-1}s^{-1}$, $k2 = 2s^{-1}$ and $d1 = d2 = d3 = 1s^{-1}$, simulate the system from time $t = 0s$ to $t = 10s$ with a time step of $0.01s$.

- (3) Plot the results, being sure to label your axes and to supply a legend.
- (4) Describe the interesting features of the data. For example, is there a steady-state? If so, what is it and why did the system approach it? Are there any peaks? If so, why are they there?
- (5) Find a set of parameter values (all $\geq 10^{-12}$) for which the dimer's apparent steady-state¹ concentration is higher than the steady-states of $P1$ and $P2$. What intuition did you use to find these values?

¹By “apparent steady-state”, I mean the value that $P1P2$ seems to remain at during the time-period of the simulation (i.e. its value from say 5s to 10s). Given that degradation is included in the model, the steady-state as time goes to infinity will always be zero for all three proteins. But I am interested in the behavior on the timescale of seconds – not years.