Introduction to mathematical modeling of cell signaling in MATLAB

Instructions: This document contains all the problem sets we will be working on during the workshop. We will do some of these together and the rest in groups.

DAY 1

1. Plot the building blocks functions in MATLAB for a few different parameter values.
    a. $Y = mx + b$
    b. $Y = ae^{x}$
    c. $Y = 1/(1 + x)$

2. Obtain a time course plot (in MATLAB) for all the species in the following first-order chemical reactions:

$$A \xrightarrow{k} \varnothing \qquad A \xrightarrow{k} B \qquad A \xrightarrow{k} B + C$$

3. Plot the solution for A,B and C on the same plot with k=5, A0=B0=0.5 and C0=0. Explore different values of k and the initial conditions for the second order reaction below.

$$A + B \xrightarrow{k} C$$

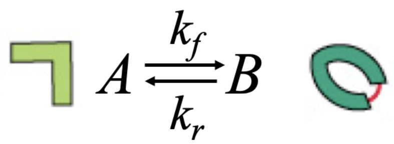
4. Find the steady state for the second order system. In MATLAB, plot the time course and the steady state values. What do you notice?

$$A + B \xrightarrow{k} C$$

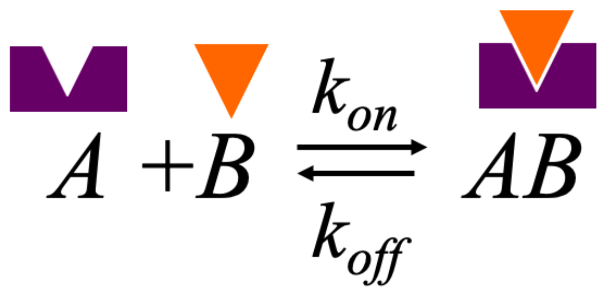
5. In the example for simple gene regulation, we have a combination of first and zero order reactions. Find the steady state of the system by hand. What parameter(s) does the steady state depend on?

$$\varnothing \xrightarrow{p} Y \xrightarrow{r} \varnothing$$

6. Let's look at the interconversion example. Plot a time course for both A & B. What do you see?

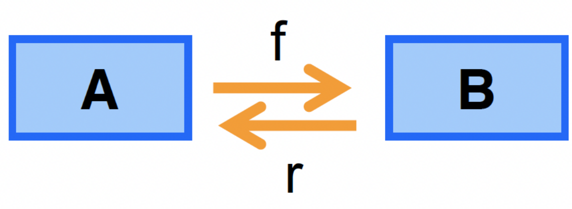


7. Take a look at the binding reaction below. What are the ODE's for each species? What does a time course look like? Can you find the steady state?

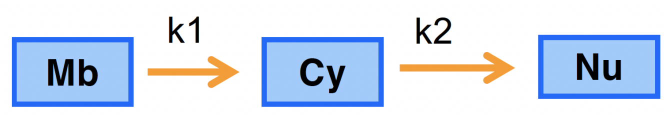


Group problems

8. Go back to problem 5. Play around with the parameters and plot various solutions. By playing with parameters and plotting the resulting solutions, see if you can answer the following question:
    a. Does this reaction reach a steady-state? Is it always the same steady state value?
    b. If it does reach a steady-state, which parameter determines how long it takes to reach ss?*
9. Combine 2 first-order reactions to model this reversible reaction using MATLAB.



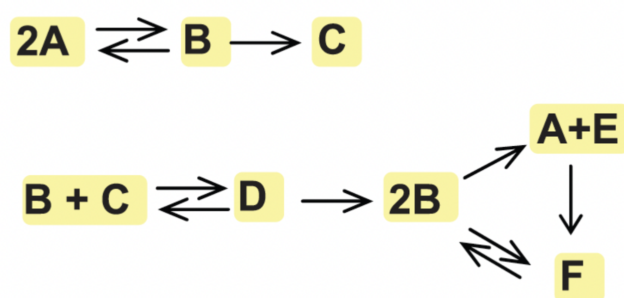
    a. Does this reaction reach a steady-state?
    b. If it does reach a steady-state, which parameter determines how long it takes to reach steady state?
10. Combine 2 first-order reactions to model the translocation of a protein from the **M**embrane to the **C**ytoplasm to the **N**ucleus.



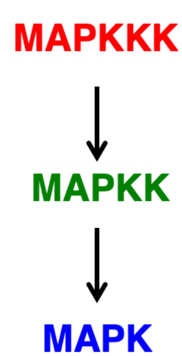
a. Plot all three time courses on the same graph, starting with 100% of the protein at the membrane.

DAY 2

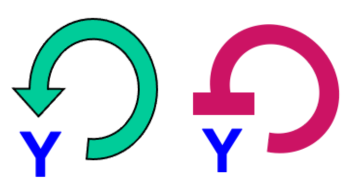
1. Write out the ODEs for the toy model below.



2. Write out the ODE's for each species in the simplified MAPK cascade.



3. Let's get MATLAB to solve these autoregulation schemes and plot a time course for each species.

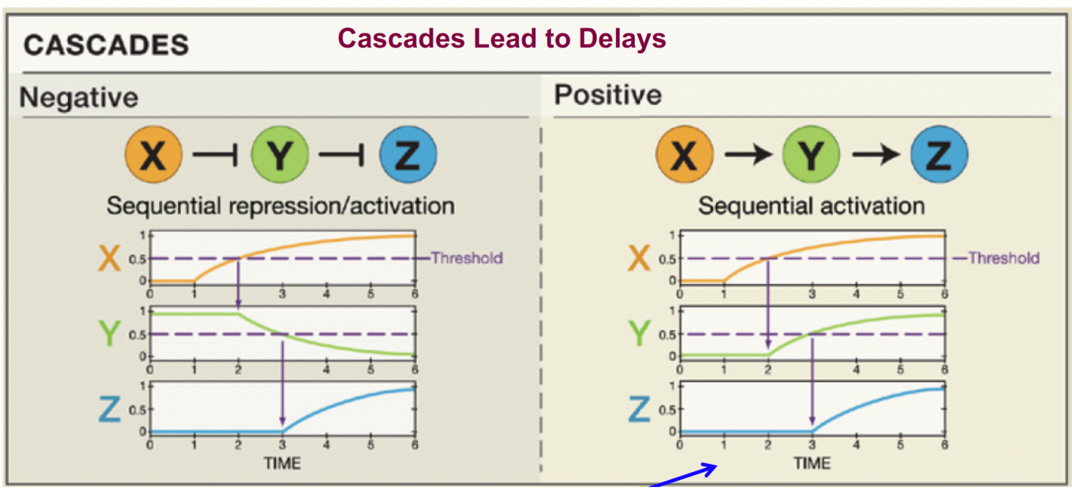


Group problems

4. Build a model of a gene Y that is regulated by transcription factor X
    a. Treat X as a constant, not a variable and solve for Y in MATLAB.
    b. get a stimulus (X) response (steady state Y) curve. You can use the template from the workshop materials.

$$[Y]' = P_{\max} \frac{[X]^n}{(K^n + [X]^n)} - r[Y]$$

5. Model the positive cascades.



   a. Obtain plots that look like this (show all 3 time courses on the same plot). Will need HIGH Hill numbers.
   b. What does your plot look like if all Hill numbers are 1? To do a valid comparison, get your graphs in 9B to reach ~ the same steady state as in 9A. In the graphs above, nothing happens for the first minute. You don't need to do this; your simulation (and graphs) can begin where X starts rising.
   c. Here are the equations if you need to get started:

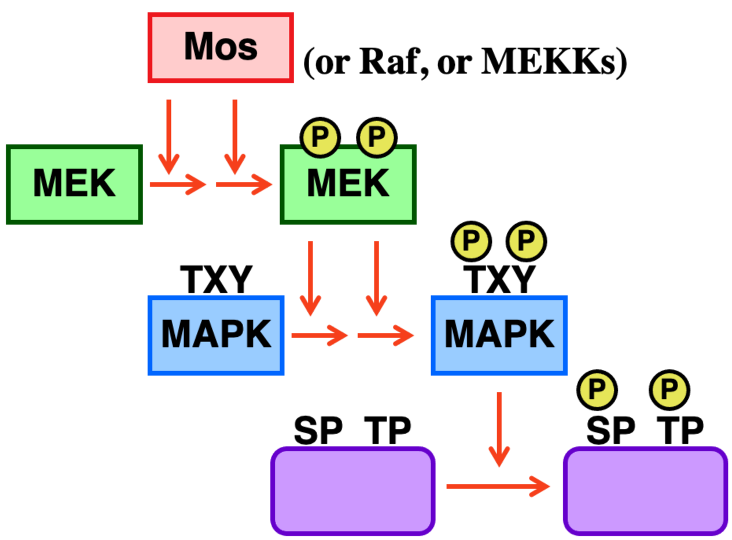
$$[X]' = X_{max} \qquad - r[X]$$

$$[Y]' = Y_{max} \frac{[X]^{ny}}{(K_y^{ny} + [X]^{ny})} - r[Y]$$

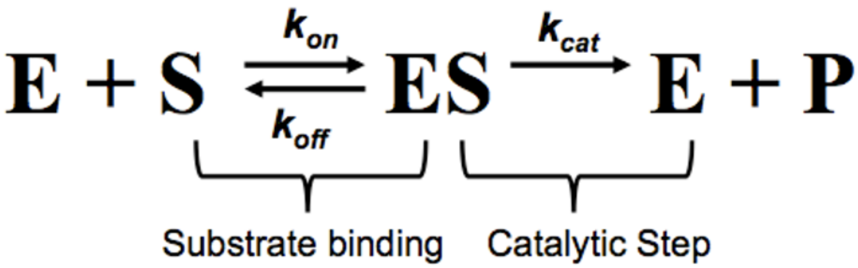
$$[Z]' = Z_{max} \frac{[Y]^{nz}}{(K_z^{nz} + [Y]^{nz})} - r[Z]$$

DAY 3

1. Model the MAPK cascade below.



2. Plot solutions for all 4 species of the Michaelis-menten kinetics reaction in MATLAB.

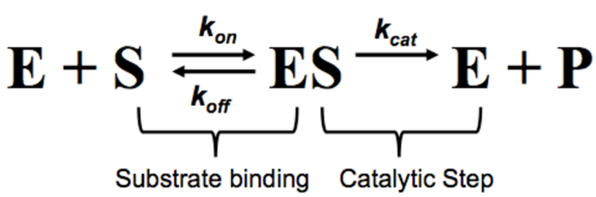


3. Plot 3 different curves with different values of n. Include n=1 (MM) for the Hill function below.

$$Y = \frac{x^n}{x^n + k}$$

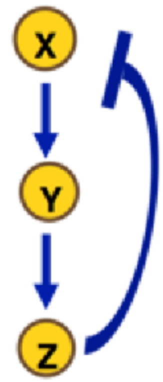
Group problems

4. Go back to problem #2. Build a model of an enzyme-catalyzed reaction.



   a. Explore the effect of kon, koff, and kcat on the amount of ES complex formed and the rate of Product accumulation.
   b. Add the simplest possible reverse reaction, P → S as a first order, uncatalyzed process, so that the system reaches a steady-state.
   c. Construct an ”Initial Velocity vs [Substrate]” dose response curve and a “Steady State [Product] vs [Enzyme] curve.

5. Consider the 3-node gene regulatory system below:



a. Plot a time course for this system with fixed parameters. If you need help developing the ODE's ask for help.
b. What do you notice about the time course?

6. If we wanted to model a system that displays displays **stable** oscillations, that is similar to the one in problem #5, we could make one regulator more Hill-like. Consider the following ODEs:

$$X' = px - dx\,(X*Z)$$
$$Y' = py * \frac{K^n}{K^n+X^n} - dy * \frac{Y^n}{K^n+Y^n}$$
$$Z' = pz * \frac{K^n}{K^n+Y^n} - dz * \frac{Z^n}{K^n+Z^n}$$

a. Solve this system and plot a time course. How does this system compare to the one from problem #5? You will need HIGH Hill numbers to see some interesting curves.