Computational Methods in Biology (Fall 2021)

Feed-Forward Loop

Exercises due September 22

I have put an XPP program on my website for a type 1 coherent FFL with AND logic. You should download this code and complete the exercises below.

Some explanation of the program

It is called C1_FFL_AND.ode, and is basically what was described in class. A few things to notice in the program:

- Three curves are plotted together, X, Y, and Z. This is achieved in the line of code beginning with the XPP parameter *nplot=3*. You could achieve the same thing by running XPP and then in the main window clicking "Graphics Stuff" and then "Add" (or type *ga*). Then put whatever you want (like Y) on the Y-axis and set Color to some integer other than 0 (which is black). After clicking OK you will see that a second curve has appeared on the screen. You could do it again to plot the Z time course. To delete a curve, click "Graphics Stuff" and then "Delete" (or type *gd*).
- There are three switches coded into the program. The first indicates when signaling molecule S_x is initially turned on (*tonx1*) and then turned off (*toffx1*). The second indicates when this happens again, later in time (*tonx2* and *toffx2*). The third indicates when signaling molecule S_y is turned on and off (*tony* and *toffy*).
- The parameters set the production rates (β), degradation/dilution rates (α), and thresholds (K). These are all things you can vary, providing hours of entertainment.
- Notice how I defined the AND gate. This uses a Heaviside function, and says that each input must be greater than 0.9 for the function to equal 1 (ON). Otherwise it is 0 (OFF).
- I have defined the thresholds as auxiliary functions. This allows you to plot them. You can superimpose one or more of these on your plots of X, Y, or Z to see what happens when a threshold is reached. For example, if you plot X, Y, and Kxy on the same graph, then, you will see that Y starts to increase when X goes past the horizontal Kxy line.

Exercises

The work below should be turned in. Please print out relevant figures that you use to answer the questions and label them completely. Also, describe the figures fully, as one would in a journal article.

(1) Run the code with XPP and described what happens. That is, describe why X, Y, and Z change the way that they do and the timing of these changes.

(2) Change the on/off times of S_y so that only one response in Z occurs. Then, starting with the original parameter values, change the duration of one of the pulses of S_x so that only one Z response occurs. Then, starting with the original parameter values, change the threshold for Y binding to its Z-promoter so that Z never responds to the S_x pulses. Finally, adjust the Y degradation rate so that, in this last case, Z does respond to both S_x pulses.

(3) The regulator Y in C1-FFLs in transcription networks is often negatively autoregulated. Add this to the computer code (turn in a printout of the code) and use the code to determine how this autoregulation affects the dynamics of the circuit. How does it affect the delay times?

(4) Write a code for a C1-FFL-OR motif (turn in a printout of the code). The changes from C1-FFL-AND are very minor, but the behavior of the system is different. Describe how the ON and OFF responses differ from the case with a C1-FFL-AND motif.

(5) The Y regulator in an OR gate C1-FFL is often positively autoregulated. Add this to the code using a first-order Hill function for autoregulation (turn in printout). How does this affect the dynamics of the circuit? How does it affect the delay times?

(6) Code up the type-3 coherent FFL (see slides showing 8 possible FFLs) with AND logic at the Z promoter in response to steps of S_x (turn in a printout of the code). Here, AND logic means that Z is produced if neither X^* nor Y^* are above their Z-threshold. Are there delays?

(7) Write a code for a type 1 incoherent FFL (turn in a printout of the code). Consider a case where X in the I1-FFL begins to be produced at time $t = 0$, so that the level of protein X gradually increases. The input signals S_x and S_y are present throughout. Analyze a set of genes Z_1, Z_2, and Z_3, all regulated by the same X and Y in the FFL. Design thresholds such that the genes are turned ON in the rising phase in a certain temporal order and turned OFF in the declining phase of the pulse with the same order. Next, design thresholds such that the turn-OFF order is opposite to the turn-ON order. Plot the resulting dynamics and give threshold values used.