Modeling Network Motifs, II

Paul M. Magwene

January 31, 2013

Today we're going to be looking at the behavior of several 3-node transcriptional networks. Again, we're going to use the logic approximation functions to model transcription rates.

We'll start by exploring a type of network *motif* called a Feed Forward Loop (FFL). FFLs involve interactions between three components, with the basic topology illustrated in the figure below. Depending on the signs of the edges (whether activating or repressing) we can classify FFLs as 'coherent' or 'incoherent.'

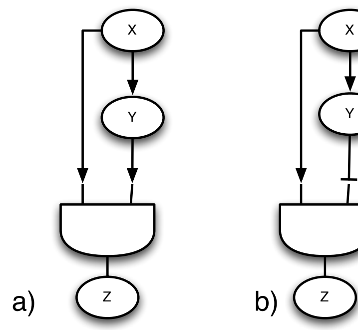

Figure 1: a) A coherent feed forward loop; b) an incoherent feed forward loop.

A coherent feed-forward loop

Let's start by exploring the coherent FFL shown in Figure 2.

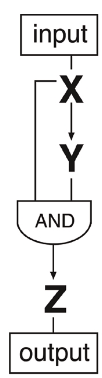

Figure 2: A coherent feed forward loop with AND logic.

- The amount of active transcription factor, X, mirrors the signal from the ligand that activates it.

- The logic function for Y is $\theta(X > K_{xy})$.
- The logic function for Z is $\theta(X > K_{xz}$ AND $Y > K_{yz})$.
  - You can think of K_{yz} as representing the time it takes for Y to be translated, and for that protein to reach a sufficiently high concentration to regulate Z.

1. Run the `ffl-coherent.py` script. There are eight parameters in this simulation.
   a) `P` controls the width of the small pulse
   b) There are three parameters for Y – β_Y, α_Y, and K_{xy}
   c) Four parameters for Z – β_Z, α_Z, K_{xz}, K_{yz}
   d) There is also a radio box that toggles whether the input signal which controls X is clean or noisy.

Problems

1. Write out the general form of the differential equations for Y and Z, describing how they change over time. Use the logic approximation function to specify the growth terms.
2. Vary the length of the initial pulse.
   a) How does Y change as you vary the length of the pulse?
   b) How does Z change as you vary the length of the pulse?
3. Using the initial set of parameters (move the sliders to the red lines), measure how long it takes for Z to turn on after Y turns on. Call this lag time T_{on}.
   - By varying the parameters of the model, figure out what parameters affect T_{on}
4. When Y starts to decrease, how long does it take before Z starts to decrease?
5. Toggle the input signal quality from “clean” to “noisy”. Explore the parameters of the model.
6. If we consider X the input signal, and Z the output signal, how would you describe the type of signal processing that goes on in this small network?
7. How do you think the behavior of Z would change if we made the logic function controlling the rate of transcription at Z based on “OR” rather than “AND” (i.e. $\theta(X > K_x$ OR $Y > K_{yz}$).

An incoherent feed-forward loop

This model has the same basic topology as in the coherent FFL, but Y is now a repressor of Z.

- The “AND” logic still applies at Z, but the growth term at Z *decreases* after Y reaches a threshold, K_{yz}.
- There is an extra parameter relative to the coherent FFL: – B'_z, gives the growth term of Z *after* repression by Y kicks in. Complete repression by Y would correspond to $B'_z = 0$.
- Run the `ffl-incoherent.py` script

Problems

1. How would you write the logic function for Z, given the description above?
2. How does varying the different parameters of Y effect the output at Z?
3. Describe the output at Z as you decrease B_z'

The repressilator

The repressilator is an artificial network first described and synthesized by Elowitz and Liebler. It consists of three transcriptional repressors arranged in a cycle, as show in Figure 3.

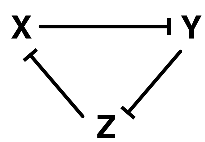

Figure 3: The topology of the repressilator synthetic network.

- Run the `repressilator.py` script
- There are 10 sliders:
  - Three for each of X, Y, and Z
  - A slider that changes the time scale over which the plot is depicted

Problems

1. What parameter settings lead to the complete loss of oscillations in the system?
2. What parameter(s) are most effective at increasing the period of time when X is at or near it's maximum? How does doing so affect Z?
3. What parameter(s) are most effective at increasing the time interval between peaks of X?
4. Spend some time exploring the parameter space of the system to see what sort of interesting behaviors you can get. If you encounter any dynamics you have a hard time reasoning about, or that look particularly interesting, you can save a picture of the plot by clicking the "floppy disk" icon at the bottom of the plot window.