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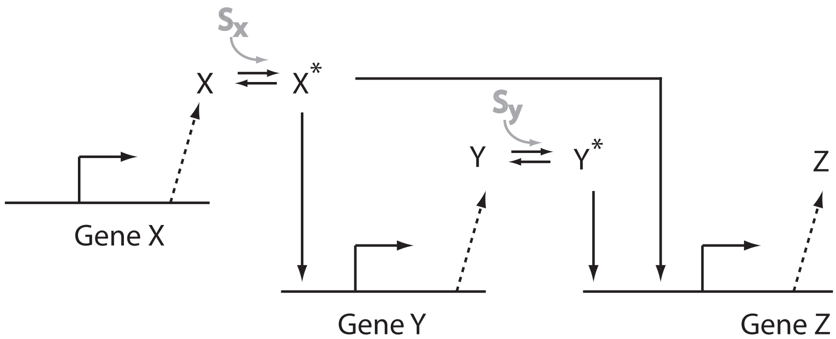
To be submitted (preferably by e-mail to pencho.yordanov@bsse.ethz.ch), by Monday, April 23^{rd}, 2012. Please include the source files of your code.

Synthetic biology (Spring 2012): Mathematical models

Exercise 3. Feed-forward loop network motif

Consider the following mechanism[1]:



where proteins X, Y and Z are expressed by their respective genes. The signals S_X and S_Y represent small molecules, protein partners, or covalent modifications activating the transcriptional activity of X and Y (Mangan and Alon, 2003). The active conformation of the protein X binds the regulatory region of the gene Y, whereas both active X and Y jointly modulate the transcription rate of Z. This mechanism corresponds to the so called coherent type 1 feed forward loop network motif (Fig. 1 a).

Signals S_X and S_Y trigger the rapid transition of X and Y to their active forms, X^* and Y^*, respectively, such that:

- $X^* = X$ if $S_X = 1$, and $X^* = 0$ if $S_X = 0$,
- $Y^* = Y$ if $S_Y = 1$, and $Y^* = 0$ if $S_Y = 0$.

In what follows, we assume that Y is in its active form ($S_Y = 1$), and that X is constitutively produced ($X = 1$). The evolution of the system with *AND*

[1] Alon (2003)

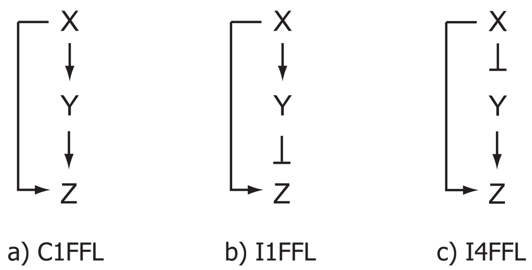


Figure 1: Feed forward motif structures.

logic at the Z promoter is given by:

$$\frac{dY}{dt} = \alpha_Y + k_Y \cdot \frac{(X/K_{XY})^n}{1+(X/K_{XY})^n} - d_Y Y \tag{1}$$

$$\frac{dZ}{dt} = \alpha_Z + k_Z \cdot \frac{(X/K_{XZ})^n}{1+(X/K_{XZ})^n} \cdot \frac{(Y/K_{YZ})^n}{1+(Y/K_{YZ})^n} - d_Z Z \tag{2}$$

where the parameters α_Y, α_Z, k_Y, k_Z, K_{XY}, K_{XZ}, K_{YZ}, d_Z, d_Y and n are defined in Table 1. Note that, as corresponds to the *AND* logic, both X and Y activities need to be high in order to turn on Z expression. By the contrary, with an *OR* gate at the Z promoter, either X or Y is sufficient to express Z. In this case, the evolution of Z, with two transcription factors competing for binding to the promoter region, will be described by:

$$\frac{dZ}{dt} = \alpha_Z + k_Z \cdot \frac{(X/K_{XZ})^n + (Y/K_{YZ})^n}{1+(X/K_{XZ})^n + (Y/K_{YZ})^n} - d_Z Z. \tag{3}$$

1. Consider the C1FFL motif with an *AND* gate for the Z promoter, and the values of the parameters given in Table 1. Matlab scripts for the simulation of C1FFL motif with *AND* gate for the Z promoter are provided (see C1FFLand, Ex3FFLmain attached).

a) Does the system show a delay in Z response after addition of the input signal S_X?. And after the removal of the input signal?

b) Perform the analysis in a) for the C1FFL motif with an *OR* logic at the Z promoter.

c) The C1FFL motif with *AND* logic is shown to respond only to persistent stimuli. Compute the maximum duration of the signal which can be filtered out by the system dynamics.

d) Repeat the analysis in c) for $K_{YZ} = 0.1$ and $K_{YZ} = 0.9$.

2. Biological systems able to respond to a change in input stimulus, and return to its prestimulated output level even when a given stimulus persists, are said to perform *adaptation* (Ma et al., 2009). For the systems under

study, adaptation can be evaluated in terms of the *sensitivity* to the input stimulus and the adaptation *precision*, defined as follows:

$$\text{Sensitivity} = \left| \frac{(Z_{peak} - Z_1)/Z_1}{(I_2 - I_1)/I_1} \right| \tag{4}$$

$$\text{Precision} = \left| \frac{(Z_2 - Z_1)/Z_1}{(I_2 - I_1)/I_1} \right|^{-1} \tag{5}$$

where the meaning of Z_{peak}, Z_1, Z_2, I_1 and I_2 is illustrated in Fig. 3.
Consider the incoherent feed forward loop motifs in Fig 1. b and c, with AND logic at the Z promoter.

a) Compare the sensitivity to the input stimulus and the adaptation precision of the I1FFL and I4FFL motifs, with the values of the parameters given in Table 1.

b) Repeat the analysis in a) for $K_{YZ} = 0.9$ and $K_{YZ} = 0.01$.

c) Repeat the analysis for the I4FFL motif with $K_{YZ} = 0.01$ and $\alpha_Z = 0.1$.

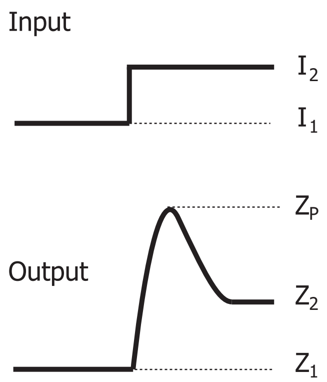


Figure 2: Input-output behaviour defining adaptation, from Ma et al. 2009.

References

Alon, U. (2003). *An introduction to systems biology: Design principles of biological circuits*. Chapman and Hall / CRC.

Ma, W., Trusina, A., El-Samad, H., Lim, W. A., and Tang, C. (2009). Defining network topologies that can achieve biochemical adaptation. *Cell*, 138:760–773.

Mangan, S. and Alon, U. (2003). Structure and function of the feed-forward loop network motif. *PNAS*, 100:11980–11985.

Table 1: Parameters

Par.	Description	Value
α_Y	basal transcription rate of Y	0
α_Z	basal transcription rate of Z	0
k_Y	maximal expression level of the promoter Y	1
k_Z	maximal expression level of the promoter Z	1
K_{XY}	activation (or repression) coef. of gene Y by X	0.1
K_{XZ}	activation (or repression) coef. of gene Z by X	0.1
K_{YZ}	activation (or repression) coef. of gene Z by Y	0.5
d_Y	degradation rate of Y	1
d_Z	degradation rate of Z	1
n	Hill coefficient	6