Exercise sheet 4
Systems Biology class 2014

April 13, 2014

Print and return to during classes, tutorials or office hours to Jean Hausser until April 27th 2014.

1 Type one incoherent feed-forward loop

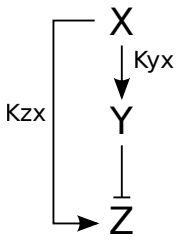

Figure 1:

In the third lecture, we saw that incoherent feed-forward loops can speed-up the response time and generate pulses in gene expression. In this exercise, we will highlight an additional possible function of incoherent type-1 FFLs.

Consider the I1-FFL illustrated by Figure 1, such that the activation threshold of Z by X, K_{zx} is smaller than the activation threshold of Y by X, K_{yx}. That is, Z production is activated when $X^* > K_{zx}$, but it is partially repressed by Y when $X^* > K_{yx}$. Assume that Z production is a step function of X^*.

1. Schematically plot the steady-state concentration of Z as a function of X^*. Make sure that the range of X^* includes K_{yx} and K_{zx}.
2. What concentration range of X^* leads to the highest Z expression?
3. What new regulatory function does this suggest for incoherent feed-forward loops? When might such a function be biologically useful?

2 Equal timing in single input modules

Consider a Single Input Module (SIM) controlled by a regulator X that activates downstream genes $Z_i, i = 1, \ldots, n$ with thresholds K_i. At time $t = 0$, $X = 0$ and begins to be produced at a constant rate β. The signal is present, and therefore $X^* = X$.

1. Assuming that X is not removed (no degradation, no cell division, $\alpha = 0$), determine the concentration of X at each point in time $X(t)$. Assuming Z_i is only produced if $X > K_i$, design thresholds K_i such that the genes are turned on one after the other at equal time intervals.
2. Now assume that $X = 0$ at time $t = 0$ and begins to produced at rate β and removed at rate α. What formula describes the concentration of X at each point in time $X(t)$? Assuming that Z_i is produced if and only if $X_i > K_i$, design thresholds K_i such that the genes are turned on one after the other at equal time intervals.

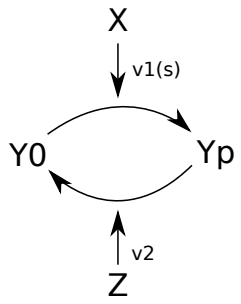

Figure 2:

3 A non robust circuit

Consider the circuit sketched on Figure 2. The input to the circuit is $v_1(s)$, the output is Y_p.

The total concentration of Y is constant throughout the experiment, and therefore $Y_T = Y_0 + Y_p$.

1. What differential equation for Y_p describes the circuit? Show that, at steady-state, $Y_p = Y_T \frac{v_1(s)}{v_1(s)+Zv_2/X}$.
2. Assume that $v_1(s) = v_{10}\frac{s}{s+K}$. What is the concentration s_{50} of signal s that provides 50% of the maximal ouput Y_p?
3. Plot qualitatively s_{50} as a function of the concentrations of the proteins in the circuit, X, Y_T and Z. You will need three plots for this, with either X, Y_T or Z on the x-axis, and s_{50} on the y-axis.
4. Interpret this using the terms *robust* and *fine-tuned*.

4 A robust circuit

The signaling network sketched on Figure 3 can implement absolute concentration robustness.

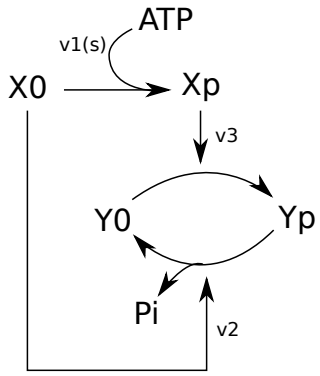

Figure 3:

We assume that the total concentration of proteins X and Y is constant over the course of the experiment. Therefore we can write $X_0 + X_p = X_T$ and $Y_0 + Y_p = Y_T$. Under this assumption, we can describe the network dynamics by two differential equations for X_0 and Y_p:

$$\frac{dX_0}{dt} = -v_1(s)X_0 + v_3(X_T - X_0)(Y_T - Y_p) \quad (1)$$

$$\frac{dY_p}{dt} = v_3(X_T - X_0)(Y_T - Y_p) - v_2 X_0 Y_p \quad (2)$$

1. Define the following terms: kinase, phosphatase, auto-kinase, phospho-transferase.
2. In a few words, explain the meaning of each term of the right hand in the equations above.
3. Determine the two steady states of Y_p. Are these steady-state robust to the concentration of the proteins in the circuit?

4. *Optional (requires background in dynamical systems):* Analyze the stability of the two steady states.

5. *Optional (requires background in dynamical systems):* Repeat the two previous questions assuming that Y_p undergoes background dephosphorylation at rate v_4, that is:

$$\frac{dY_p}{dt} = v_3(X_T - X_0)(Y_T - Y_p) - v_2 X_0 Y_p - v_4 Y_p$$