Homework 2 (chapters 3-6 of Alon *"An Introduction to Systems Biology"*).

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This homework tests your ability to model the dynamics of gene regulatory networks in simple examples. If gene x is regulated by gene y, let the rate of decay of the protein product X be $\alpha_X \cdot X$, and the rate of production of protein X be $f_X(Y)$. The basic equation describing the evolution of X is then

$$\frac{dX}{dt} = f_X(Y) - \alpha_X \cdot X \tag{1}$$

In the first two parts of the homework below, you are to test the three models:

◇ **Logic input function:**

    For an activator:

$$f_X(Y) = \begin{cases} 0 & \text{if} \quad Y < K_{yx} \\ \beta_X & \text{if} \quad Y > K_{yx} \end{cases} \tag{2a}$$

    For a repressor:

$$f_X(Y) = \begin{cases} \beta_X & \text{if} \quad Y < K_{yx} \\ 0 & \text{if} \quad Y > K_{yx} \end{cases} \tag{2b}$$

◇ **Michaelis-Menten function:**

    For an activator:

$$f_X(Y) = \beta_X \frac{Y}{Y + K_{yx}} \tag{3a}$$

    For a repressor:

$$f_X(Y) = \beta_X \frac{K_{yx}}{Y + K_{yx}} \tag{3b}$$

◇ **Cooperative function of Hill coefficient** 3:

    For an activator:

$$f_X(Y) = \beta_X \frac{Y^3}{Y^3 + K_{yx}{}^3} \tag{4a}$$

    For a repressor:

$$f_X(Y) = \beta_X \frac{K_{yx}{}^3}{Y^3 + K_{yx}{}^3} \tag{4b}$$

You should comment on the differences and/or similarities between the behaviour of the system with, respectively, logic input functions, Michaelis-Menten functions, and Cooperative functions.

The assignment (parts 1 and 2)

1. *(Related to second half of Exercise 3.6):* Consider two genes which repress each other, $X \dashv Y$ and $Y \dashv X$, and which both regulate a third gene as $X \dashv Z$ and $Y \to Z$. Determine the steady states. Describe the responses to a change of the state variables (X and Y, one at a time), starting from a steady state.

2. *(Related to second half of Exercise 4.10):* Consider four genes X, Y, Y_1 and Z that interact as two interconnected feed-forward loops: $X \to Y$, $X \to Z$ and $Y \dashv Z$ such that (X, Y, Z) is an incoherent FFL of type I1 in Alon's classification (Fig 4.3, page 47); $Y \dashv Z$, $Y \to Y_1$ and $Y_1 \to Z$ such that (Y, Y_1, Z) is an incoherent FFL of type I3.

   Consider as in the general set-up used by Alon that the three genes X, Y and Y_1 are driven by three input signals S_x, S_y and S_{y_1}. When the input signals are off (value 0) the corresponding protein is in its inactive form and cannot act as a transcription factor, even if present in high enough concentration. When on the other hand the signals are on (value 1) the corresponding protein is its active form and can act as a transcription factor, if in high enough concentration.

   The output node (Z) is now driven by three inputs: X, Y and Y_1. Chose one way of combining the inputs which makes Z a non-canalizing Boolean function of the inputs. We repeat from the lectures that a non-canalizing Boolean function is one which fully depends on all its arguments.

   Describe precisely which Boolean function you chose and show that it is non-canalizing. Show how the expression of Z changes in response to steps in signals S_x, S_y and S_{y_1}. Comment.

The assignment (part 3)

In this part it is sufficient to use logic input functions of the response of a down-stream element to its net input. The net input should however be taken a weighted sum of the upstream elements.

3. *(along the lines of Figure 6.9 and Exercise 6.7):*

   Consider a model of a three-level signal transduction pathway with two input signals (*e.g.* ligands) S_1 and S_2, two "MAKKK" kinases X_1 and X_2, two "MAPKK" kinases Y_1 and Y_2, two "MAPK"-level elements Z_1 and Z_2, and then an output element W, *e.g.* a transcription factor.

   The net input to X_1 is $u_1 S_1$ and the net input to X_2 is $u_2 S_2$; the net input to Y_1 is $v_{11} X_1 + v_{12} X_2$, the net input to Y_2 is $v_{21} X_1 + v_{22} X_2$, the net input to Z_1 is $w_{11} Y_1 + w_{12} Y_2$, the net input to Z_2 is $w_{21} Y_1 + w_{22} Y_2$, and the net input to W is $r_1 Z_1 + r_2 Z_2$.

   For the kinase X_1, the two weights w_{11} and w_{21} must all be non-negative, and similar for all the other kinases, while for a phosphatase all weights must be non-positive.

The thresholds for activation/repression are K_{x_1} for X_1 *etc.* and the base-line dephosphorylation rates are α_{x_1} *etc.*.

Suppose that the two "MAPK"-level elements Z_1 and Z_2 are kinases also.

Can you choose weights such that this three-layer perceptron computes the logical function XOR and EQ? If you cannot do so, can you give a reason why this is not possible?

Is the answer different if either or both of Z_1 and Z_2 acts as a phosphatase?

Define what you consider as in- and outputs for these biochemical logical functions (e.g. what corresponds to TRUE and FALSE in your system) and try to use as few free parameters as possible.