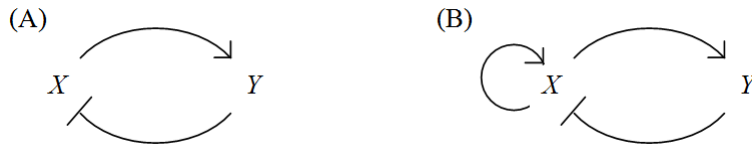# Problem Set 3

1   Circadian Clocks (30 points)

Several protein expression levels in plant and animal cells go through a daily cycle, driven by exposure to sunlight during the day and darkness at night. However, even in complete darkness, these expression levels oscillate with an intrinsic period of about 24 hours. The systems which drive these oscillations are known as circadian clocks. At the heart of most of these systems is a pair of transcriptionally regulated proteins: an activator (X) and an inhibitor (Y). In this problem set, we will see how such a simple system can be made to generate oscillations. We consider two possible system architectures (arrows represent activation, blunt ends represent inhibition):

(A)   (B)

X   Y   X   Y

Problem by Alexander van Oudenaarden. OCW 8.591J Systems Biology, Fall 2004, Problem Set 3, Problem 1.

The corresponding dynamical equations are (using $x = [X]$ and $y = [Y]$):

(A)

$$\frac{dx}{dt} = v_x + k_x \frac{A_1}{A_1 + y} - \gamma_x x$$
$$\frac{dy}{dt} = v_y + k_y \frac{x}{A_2 + x} - \gamma_y y$$

(B)

$$\frac{dx}{dt} = v_x + k_x \frac{x^2}{(A_3)^2 + x^2} \frac{A_1}{A_1 + y} - \gamma_x x$$
$$\frac{dy}{dt} = v_y + k_y \frac{x}{A_2 + x} - \gamma_y y$$

a. Identify the parameters corresponding to basal transcription rate, maximal transcription rate, and degradation rate.

b. We have assumed the following: for both (A) and (B), the X promoter is inactivated by the binding of a single molecule of Y, and the Y promoter is activated by the binding of a single molecule of X. In addition, for (B), the X promoter is activated by the cooperative binding of two molecules of X. The various fractions that appear in the equations represent the activity of promoters. Explain what each of these fractions means in the context of gene regulation.

c. Normalization of units. Assume that $A_2 \gg x$. Redefine variables and show that by choosing units properly the previous equations can be written in the form

(A)

$$\frac{d\bar{x}}{d\bar{t}} = \bar{\gamma}_x(\bar{v}_x + \bar{k}_x \frac{1}{1 + \bar{y}} - \bar{x})$$

$$\frac{d\bar{y}}{d\bar{t}} = \bar{v}_y + \bar{k}_y\bar{x} - \bar{y}$$

(B)

$$\frac{d\bar{x}}{d\bar{t}} = \bar{\gamma}_x(\bar{v}_x + \bar{k}_x \frac{\bar{x}^2}{1 + \bar{x}^2}\frac{1}{1 + \bar{y}} - \bar{x})$$

$$\frac{d\bar{y}}{d\bar{t}} = \bar{v}_y + \bar{k}_y\bar{x} - \bar{y}$$

From now on we will work with the simplified equations, dropping the bars on the variable and paramter symbols. These equations are of the general form

$$\frac{dx}{dt} = f(x, y)$$

$$\frac{dy}{dt} = g(x, y)$$

Let (x_0, y_0) be a fixed point of the system $(f(x_0, y_0) = 0, g(x_0, y_0) = 0)$ and recall that if we define

$$A = \begin{pmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial y} \\ \frac{\partial g}{\partial x} & \frac{\partial g}{\partial y} \end{pmatrix}_{|x_0, y_0}$$

fixed points of this two dimensional system are stable if and only if $Tr(A) < 0$ and $Det(A) > 0$.
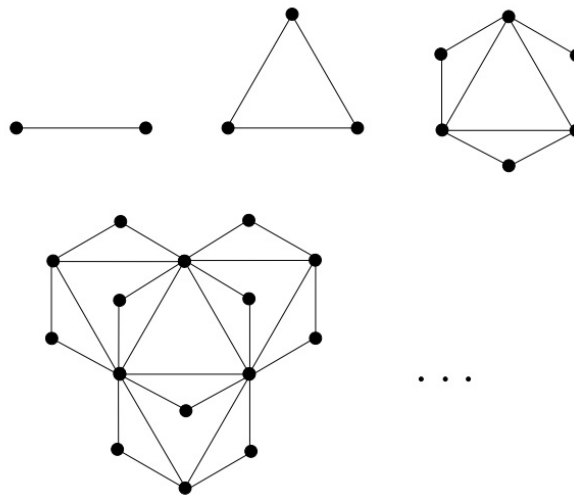
d. **COMPUTATION** For systems (A) and (B) separately, assume $v_x = 0.1$, $v_y = 0.0$, $k_x = 4.0$, $k_y = 2.0$ and $\gamma_x = 10$ and plot the nullclines $f(x, y) = 0$ and $g(x, y) = 0$ on the y vs. x phase plane. Draw the vector field indicating the direction of motion in different regions of the plane and, based on the graphs, comment on the stability of the fixed point.

e. For system (A), prove that the system will always converge to a stable fixed point.

f. For system (B),

1. Assume $v_x = 0.1$, $v_y = 0.0$, $k_x = 4.0$, $k_y = 2.0$ and let γ_x be a variable parameter. Find the fixed point of the system. If this fixed point becomes unstable oscillations will arise. By numerically analyzing $Tr(A)$ and $Det(A)$ as a function of γ_x write down the conditions on γ_x under which the system is oscillatory. What does this condition mean in terms of the timescale of X and Y?

2. **COMPUTATION** Solve the equations numerically using the parameters given in (f1). Choose two different values of γ_x, in one case the system shows sustained oscillations, while in the other case the system approaches a stable fixed point.

3. **COMPUTATION** By varying γ_x, we can tune the period of the oscillator. How much does the amplitude of oscillations change? What would you expect in the case of a repressilator? Interpret your results and comment on the tunability[1] of an oscillator.

4. System (B) is a network motif found in many biological oscillatory systems (Uri Alon's book, Chapter 6.5). Look up in the literature for an example.

2   Deterministic scale-free networks[2] (15 points)

In this problem you will study the degree distribution and clustering properties of deterministic scale-free networks. Consider the following procedure of generating a deterministic network:

- $t = -1$ Start from a single edge connecting two nodes.

- $t = 0$ Add one more node, and connect it to the two existing nodes.

  ...

- $t = n$ For every edge of the graph add a new node and connect it to the nodes of the corresponding edge.

a. Are preferential attachment and/or growth incorporated into this model?

b. How many nodes are added at $t = n$? What are the degrees k of these nodes?

c. How does the degree k of the node change over time?

d. The clustering coefficient of the node[3] C depends on the degree of the node in a scale-free manner: $C(k) \backsim k^{-\beta}$. Find β by deriving the rule of how the clustering coefficient of the node changes over time and using the result of part (c).

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[1]Tsai *et al.* Robust, Tunable Biological Oscillations from Interlinked Positive and Negative Feedback Loops. Science, 321, 126-129 (2008)

[2]SN Dorogovtsev *et al.* Pseudofractal scale-free web. Physical Review E, 65, 066122 (2002)

[3]The definition of the clustering coefficient can be found on p.259 of Alon's book.

e. One can design a scale-free network with $\beta = 0$. Which properties of the network discussed in this problem make β nonzero?

f. While k in this problem can only have discrete values, for this part of the problem we will work in the continuous limit. Thus, the probability that a given node has degree $k \in [k_0, k_0 + \delta(k_0)]$ can be written as

$$P(k_0 \leq k < k_0 + \delta(k_0)) = \rho(k_0)\delta(k_0)$$

where probability density of the degree distribution of the nodes, $\rho(k)$, is proportional to $k^{-\gamma}$. Find γ by counting the number of nodes with the degree k. (*Hint*: don't forget that δ is a function of k.) Does γ depend on time?

3 Network Motifs in Transcription Networks (5 points)

For the transcription networks of *E.coli* and *S.cerevisiae*, there is one three-node network motif and one four-node network motif, namely FFL and Bi-fan. On p.120 of Uri Alon's book, you can find data for the two real networks.

a. Please calculate the expected number of appearances of FFL and Bi-fan in E-R networks that have the same number of nodes and edges as the two real networks.

b. Compare your results with N_{rand} listed in the table, which corresponds to the appearance of each subgraph in a degree-preserving random network.

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