CALIFORNIA INSTITUTE OF TECHNOLOGY
Biology and Biological Engineering (BBE)

BE 150

M. Elowitz and R. M. Murray
Winter 2013

Problem Set #4

Issued: 30 Jan 2013
Due: 6 Feb 2013

1. Consider the following simple model for protein production:

$$\frac{dm}{dt} = F(p) - \delta m, \qquad \frac{dp}{dt} = G(m,p) - \gamma p$$

Assume that there is transcriptional self-regulation ($F(p) = \frac{\alpha}{K+p^n}$) and $G(m,p) = \beta m$. We would like to understand the sensitivity of mRNA and protein production with respect to the different parameters in the system (α, γ, etc.). Make a model of an unregulated and transcriptionally regulated circuit in Simbiology. Use the parameters $\alpha = 0.002, \beta_0 = 0.1, \gamma = 0.005, \delta = 0.001, K = 0.002$.

   (a) Run a sensitivity analysis for each of your parameters (except n) and determine the relative effects on protein production. Compare the mRNA and protein production of the unregulated (constitutive promoter) versus negatively autoregulated circuits (make sure to choose "full normalization"). You should have two charts comparing the relative sensitivities (unregulated mRNA vs autoregulated mRNA, unregulated protein vs autoregulated protein). Comment on whether or not your findings make sense in a biological context and why.

   (b) Now assume that there is no transcriptional regulation ($F(p) = \alpha$) but there is *translational* self-regulation such that $G(m,p) = \frac{\beta m}{K+p^n}$. Run sensitivity analysis for protein production in an unregulated vs translationally regulated circuit (for all parameters except n). Comment on your results.

   (c) Combine the two types of regulation (transcriptional and translational) into a new model. Run sensitivity analysis comparing the effects of all the parameters (except n) on protein production. Compare and discuss your results.

2. Consider the reduced order model of chemotaxis shown in Alon, Figure 7.9, for which the reactions can be written as:

$$\begin{aligned}
\text{R1 (Methylation of X):} \quad & \mathrm{X} + \mathrm{R} \rightleftharpoons \mathrm{X{:}R} \longrightarrow \mathrm{X_m} + \mathrm{R} \\
\text{R2 (Demethylation of X}_\mathrm{m}^*\text{):} \quad & \mathrm{X_m^*} + \mathrm{B^p} \rightleftharpoons \mathrm{X_m^*{:}B^p} \longrightarrow \mathrm{X} + \mathrm{B^p} \\
\text{R3 (activation/deactivation of X):} \quad & \mathrm{X_m^*} \underset{k^r}{\overset{k^f(L)}{\rightleftharpoons}} \mathrm{X_m}
\end{aligned}$$

In this model, ligand-binding is approximated by affecting the transition between the active ($\mathrm{X_m^*}$) and inactive states($\mathrm{X_m}$). Furthermore, we assume that the concentration of the demethylase (B) and methylase (R) are constant, and that demethylation can only occur in the active state and methylation can only occur in the inactive state.

(a) Implement this reduced order model in Simbiology. You can assume Michaelis-Menten kinetics for R1 and R2 and that $k_f(L)$ is a linear function of the ligand concentration, L. Submit a printout of the reactions used, the rate laws, and the parameter values used in the model.

(b) Assume that $X \gg K_x > 1$, where K_x is the Michaelis constant for CheR. This implies that CheR acts in saturation since there is always enough substrate for the enzyme. Consider the effect of doubling/halving the ligand concentration on the level of active receptor (X_m^*). Plot the response of X_m^* to both increases and decreases in ligand concentration and verify that the circuit adapts to the concentration. (Hint: You can use the event expression in Simbiology to double the ligand concentration at a set time. Be sure to run your simulation long enough to reach steady-state before and after the ligand spike.)

(c) Now assume that CheR no longer acts in saturation such that the total amount of X is limiting. Plot the time response for increases and decreases in ligand concentration, and comment on how this assumption affects adaptation in the system.

3. In this problem we will compare a model for chemotaxis with a single methylation site versus one with double methylation sites. Following the notation in Alon, the model with a single methylation site is given by:

$$\frac{d(X_m + X_m^*)}{dt} = V_R R - \frac{V_B B X^*}{K + X^*}$$

where the activity is given by $A = X^*$. The model with two methylation sites is given by

$$\begin{aligned}
\frac{d(X_2 + X_2^*)}{dt} &= \frac{R V_R X_1}{X_1 + X_0} - B V_B X_2^* \\
\frac{d(X_1 + X_1^*)}{dt} &= B V_B X_2^* + \frac{R V_R X_0}{X_1 + X_0} - \frac{R V_R X_1}{X_1 + X_0} - B V_B X_1^* \\
\frac{dX_0}{dt} &= -\frac{R V_R X_0}{X_0 + X_1} + B V_B X_1^*,
\end{aligned}$$

where X_i represents receptors with i sites methalated and the activity is given by $A = X_1^* + X_2^*$.

(a) Derive an analytical expression for the normalized parameter sensitivity of the activity ($\bar{S}_{y_e,\theta}$) for both the single and double methylation models. (You don't need to explicitly invert matrices, but make sure to include explicit computations for all of the relevant quantities.)

(b) Evaluate the sensitivity matrices for $K = 10$, $V_R R = 1$, $V_B B = 2$. Comment on which parameter each model is most robust and most sensitive to.

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Bi 250b

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