BE 150

M. Elowitz and R. M. Murray   **Problem Set #6**   Issued: 21 May 2014
Spring 2014   Due: 30 May 2014

1. *Sensitivity analysis in chemotaxis model* In this problem we will compare a model for chemo-
   taxis 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:

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

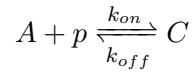   where the activity is given by $A = X^*$. The model with two methylation sites is given by

$$\frac{d(X_2 + X_2^*)}{dt} = \frac{R V_R X_1}{X_1 + X_0} - B V_B X_2^*$$

$$\frac{d(X_1 + X_1^*)}{dt} = B V_B X_2^* + \frac{R V_R X_0}{X_1 + X_0} - \frac{R V_R X_1}{X_1 + X_0} - B V_B X_1^*$$

$$\frac{dX_0}{dt} = -\frac{R V_R X_0}{X_0 + X_1} + B V_B X_1^*,$$

   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.

   (c) (Optional) Put your model into Simbiology and try the sensitivity analysis function.
       Does it give you the same conclusions you arrived at analytically?

2. *Loading effects of downstream transcriptional activation* Consider the activator-repressor
   clock from Atkinson et al. Cell 2003.

$$\frac{dA}{dt} = \mu \left(\frac{\alpha A^2 + \alpha_o}{K_1 + R^2 + A^2} - \delta A \right)$$

$$\frac{dR}{dt} = \frac{\alpha A^2}{K_2 + A^2} - \delta R$$

   (a) Pick parameter values to obtain a stable limit cycle. Simulate the system in Matlab.
       Show that you have stable oscillations.

   (b) Then, assume that the activator A connects to another transcriptional circuit through
       the reversible binding of A with operator sites p to form activator-operator complex C:

$$A + p \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} C$$

This occurs, for example, if you want to use this clock as a source generator for some downstream system. Write down equations for this new system with retroactivity. Simulate the system with this new binding phenomenon and vary the total amount of p (p_T). Explore how this affects the behavior of the clock. Provide plots to illustrate the effects of varying p_T.

(c) Discuss the implications of loading effects (retroactivity) on synthetic circuits. Would you expect loading effects to be a factor in endogenous cell circuits? What are ways in which circuits could compensate for loading effects?

3. *Coordinated Response and Frequency Modulation* (Based on Cai et al., Nature, 2008.)

(a) Read over the paper discussed in class by Cai et al., Nature, 2008 (Frequency-modulated nuclear localization bursts coordinate gene regulation). Summarize the main conclusions of the paper.

(b) One alternate explanation to the coordinated gene response observed in the paper is if the downstream genes controlled by Crz1 all have the same input function. How would you experimentally distinguish between this and a model that uses frequency modulation?

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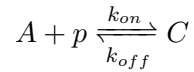1. *Sensitivity analysis* Consider the following simple model for protein production:

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

   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.

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