CALIFORNIA INSTITUTE OF TECHNOLOGY
Bioengineering

Bi 250b

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Problem Set #4

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1. In this exercise, we will walk through doing sensitivity analysis on the system we modeled in Homework 1, Problem 1: a lacI gene driven by a constitutively active promoter and a lac promoter. To do this exercise, you will need to download and install a copy of Mathematica (from http://software.caltech.edu). After installing Mathematica, download and open "problem1.nb" from the class website.

   a) Enter expressions for $\dot{m}$ and $\dot{p}$ in the appropriate space. Expressions must be defined in terms of parameters (A, G, B, D) defined in "OpenLoopParams" and species (m and p) corresponding to the mRNA and protein numbers respectively.

   b) Run the Solve command, by pressing <Spacebar>+<Enter> at the end of the line. This should provide expressions for m_{ss} and p_{ss} for the open loop system in terms of the parameters.

   c) Copy the expression for the steady state value of protein, and paste it at the right place. The next few lines of code will calculate the partial derivative of p_{ss} with respect to each of our paramters, and normalize them. Execute the commands by pressing <Spacebar>+<Enter> at the end of the NormalizedSensitivityMatrix line. Comment on the sensitivity of protein levels to the parameters.

   d) We shall now perform sensitivity analysis on the closed-loop system assuming simple binding of lacI to the promoter ($n_H = 1$). Enter expressions for the mRNA and protein concentrations of the closed-loop system in terms of species and parameters and use Solve to find numerical and analytical expressions for the steady-state.

   e) Enter the numerical and analytical expressions for p_{ss} at their appropriate locations and calculate the sensitivity of protein levels to the parameters. Comment on the differences between the parameter sensitivity of the closed-loop and open-loop systems.

2. Consider a simple model of chemotaxis:

$$\frac{dX_m}{dt} = k_R R + k^f(L)X_m^* - k^r X_m$$
$$\frac{dX_m^*}{dt} = -k_B B^p \frac{X_m^*}{K_{X_m^*} + X*_m} - k^f(L)X_m^* + k^r X_m$$

where X_m is the concentration of methylated receptor complex, and X_m^* is the concentration of activated, methylated receptor complex. Ligand concentration enters into the equation through the rate $k^f(L)$. In this model, CheR (R) and CheB$^{\text{p}}$ (B^p) concentrations are constant. (BFS, Section 5.2)

a) Open the MATLAB script, "chemotaxis.m". This implements the chemotaxis model above and how it responds to a ligand spike, where the ligand concentration is doubled at $t = 20$. Before running the script, enter parameter values such that $k_B B^p > k_R R$. Specify initial conditions so that the system reaches an equilibrium before a ligand spike. doubling the ligand concentration at time t=20. Compare to Figure 5.11 in BFS, do you see adaptation?

b) Now assume that CheR no longer acts in saturation. The dynamics of the system are now as follows:

$$\frac{dX_m}{dt} = \frac{k_R R X}{K_X + X} + k^f(L)X_m^* - k^r X_m$$
$$\frac{dX_m^*}{dt} = -k_B B^p \frac{X_m^*}{K_{X_m^*} + X*_m} - k^f(L)X_m^* + k^r X_m$$

Modify "chemotaxis.m" to reflect this change in dynamics and plot the output. (Hint: Think about conservation of species, you will need to redefine the definition for X_m and add two new constants). Comment on how this assumption affects adaptation.