BE 150 Spring 2018
Homework #3
Due at the start of lecture, April 25, 2018

Problem 3.1 (Adaptation in chemotaxis, 50 pts)**.**
Consider the robust model of chemotaxis presented in lecture 6. We can write the schematic given in that lecture (shown in Fig. 1) as a set of chemical reactions.

$$\text{Methylation of X:} \qquad \mathrm{X} + \mathrm{R} \rightleftharpoons \mathrm{X} : \mathrm{R} \rightarrow \mathrm{X_m} + \mathrm{R}$$

$$\text{Demethylation of } \mathrm{X_m^*}\text{:} \qquad \mathrm{X_m^*} + \mathrm{B^p} \rightleftharpoons \mathrm{X_m^*} : \mathrm{B^p} \rightarrow \mathrm{X} + \mathrm{B^p}$$

$$\text{Activation/deactivation of X:} \qquad \mathrm{X_m^*} \underset{k_r}{\overset{k_f(L)}{\rightleftharpoons}} \mathrm{X_m}.$$

Here, R is short for CheR and B is short for CheB. We define L as the concentration of ligand (attractant). In this model, the effect of ligand-binding is approximated by affecting the transition between the active ($\mathrm{X_m^*}$) and inactive states (X_m). We will assume the rate constant describing deactivation of methylated X, $k_f(L)$, is a linear function of L. We model the methylation and demethylation reactions with Michaelis-Menten kinetics. 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.

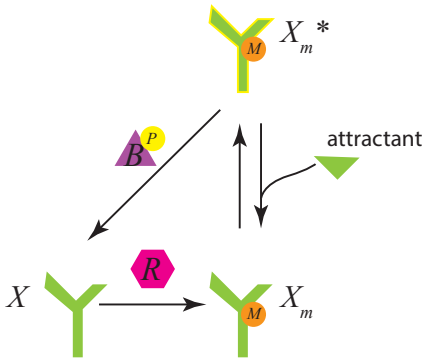

Figure 1: Schematic of Che system involved in chemotaxis.

a) Write down a system of ODEs that describe the dynamics of this system. Be sure to clearly define any constants you use in your expressions.

b) Assume that $[\mathrm{X}] \gg K_R > 1$, where K_R is the Michaelis constant for CheR. This implies that CheR acts in saturation since there is always enough substrate for the enzyme. Solve for the dynamics of $\mathrm{X_m^*}$ in response to a sudden doubling of the ligand concentration. Plot your result. Do the same for halving of the ligand concentration. You should verify that the circuit exhibits exact

adaptation. Be sure to indicate what parameter values you chose for this calculation.

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.

Problem 3.2 (Co-substrate compensation, 50 pts)**.**
This problem derived from discussions with H. Y. Kueh, and is based on his paper in Biophys J., **104**, *1338–1348, 2013.*

To put this problem in context, let us think about an intriguing question. Oxygen is delivered to the cells of your body through your blood. Naturally, cells are situated at difference distances from blood vessels. As oxygen diffuses away from the blood vessels, different cells experience different local oxygen concentrations, often very different concentrations. How, then, do cells respire at the same rate, despite the large difference in oxygen concentration?

This is a question of robustness. Is rare of respiration robust to differences in oxygen concentration over a physiologically relevant operating regime? To address this question consider a simple model of the mitochondrial electron transport chain (ETC) consisting of a single electron carrier and two reactions that catalyze its oxidation and reduction, shown in in Fig. 2.

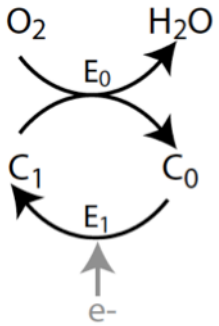

Figure 2: Simple model of the mitochondrial electron transport chain.

a) Write down a system of ODEs describing the dynamics of this network. Assume that the rate of oxygen reduction by enzyme E_0 is hyperbolic with respect to oxygen concentration with a half-maximal value K_0, i.e., $v_0 \propto [O_2]/([O_2] + K_0)$. For simplicity, also assume that the rate of carrier reduction (by enzyme E_1) is first order with respect to the carrier concentration. Finally, assume that the total carrier concentration is conserved, i.e., $C_T = [C_0] + [C_1] =$ constant.

b) Compute the response of the system to a 5-fold drop in oxygen concentration from a value greater than K_0 to one lower than K_0, for one set of parameters of your choosing. Does the system maintain a constant oxygen consumption rate after the drop in oxygen levels? If not, repeat these simulations for a different set of parameters to identify a set of parameters where rate constancy is maintained.

c) Solve for the steady-state oxygen consumption rate as a function of oxygen concentration. Using this expression, derive an analytical expression for the oxygen concentration at which oxygen consumption rate is half-maximal. We will call this concentration K_m.

d) Now, consider the regime where the maximal rate of enzyme E_0 is much greater than that of E_1. Show that, in this regime:

   i) The model recapitulates the Chance relationship (B. Chance, *J. Gen. Phys.*, 1965), which states that the K_m scales linearly with the maximal rate of electron transfer, and inversely with the reaction rate constant for oxygen reduction.

   ii) The system implements integral feedback. Specifically, show that the time integral of the difference between an enzyme's operational velocity and its steady-state velocity is conveyed to the enzyme by the levels of reduced carrier.

e) What are the main conclusions that you were able to reach from this simple toy model of the ETC?