Exercise sheet 5
Systems Biology class 2014

May 1, 2014

Please hand in a hard copy until May 4th 2014 at the latest.

It can be handed in during the tutorial or placed in the envelope outside of room 612 at the 6th floor of the Wolfson building. Please address any questions regrading this exercise sheet and tutorial to Pablo Szekely during office hours.

1 Robust model with a single methylation site

Consider the model we looked at in class: The main equations are

$$\frac{dM}{dt} = \frac{d(X_m + X_m^*)}{dt} = V_R R - V_B B X_m^* \tag{1}$$

$$X_m^* = M \cdot g(s) \tag{2}$$

1. Explain each term in equation number 1.
2. The methylated receptor transits rapidly between the inactive form X_m and the active form X_m^*. Transitions from X_m to X_m^* occur at a rate $k(s)$, and transitions back occur at a rate $k'(s)$. Note that $k(s)$ and $k'(s)$ depend on ligand level s.

   What is the average activity, averaged over many transition events between X_m and X_m^*?
3. These transitions occur much faster than changes in the methylation level of X. How can this be useful in analyzing the model? Using this assumption, determine $g(s)$.
4. Solve for the dynamics of the model we saw in class following a step addition of attractant ligand from s_0 to s_1. What is the response time (half the time required to achieve steady state)? Plot the dynamics schematically.
5. Same as (4), for a step addition of repellent ligand.

2 Integral feedback

A heater heats a room. The room temperature T increases in proportion to the power of the heater, P, to other sources of heat, S, and decreases due to thermal diffusion to the outside at a rate proportional to T:

$$dT/dt = a\,P + S - b\,T \tag{3}$$

An integral feedback device is placed in order to keep the room temperature at a desired point T_o. In this feedback loop, the power to the heater is proportional to the integral over time of the error in temperature, $T - T_o$:

$$P = P_o - K \int (T - T_o)\,dt \tag{4}$$

This feedback loop thus reduces the power to the heater if the room temperature is too high, $T > T_o$, and increases the power when the room temperature is too low. Taking the time derivative of the power, we find

$$dP/dt = -K\,(T - T_o) \tag{5}$$

1. Show that the steady-state temperature is T_o and that this steady-state does not depend on any of the system parameters, including the room's thermal coupling to the heater, a, the additional heat sources, S, the room's thermal coupling with the outside, b, or the strength of the feedback, K. In other words, integral feedback shows robust exact adaptation of the room temperature.

2. *Optional*: Demonstrate that integral feedback is the *only* solution that shows robust exact adaptation of the room temperature, out of all possible linear control systems. That is, assume a general linear form for the controller:

$$dP/dt = c_1 T + c_2 P + c_3 \tag{6}$$

and show that integral feedback as a structural feature of the system is necessary and sufficient for robust exact adaptation.

3. Demonstrate that the simple linear form of the robust model for chemotaxis that we saw in the lecture contains integral feedback. Which of the parameters is analogous to the temperature (T)? and which to the power (P)?

3 Zero-order ultrasensitivity

(Goldbeter and Koshland, 1981)

In this exercise, we will see how two antagonistic enzymes can generate a sharp switch. *A* protein X can be in a modified X_1 or unmodified X_0 state. Modification is carried out by enzyme E_1, and de-modification by enzyme E_2. The rate V_2 of E_2 is constant, whereas the rate V_1 of E_1 is governed by an external signal.

Consider V_1 as the input and X_1 as the output of this system.

Assume that $X_0 + X_1 = X_{tot}$ doesn't change with time.

1. Assume that E_1 and E_2 work with first-order kinetics. What is the output X_1^{StSt} as a function of input V_1? (X_1^{StSt} is the steady state of X_1)

   First order kinetics can be approximated from a Michaelis-Menten kinetics production rate of a product (P) by an enzyme from a substrate (S). and taking the limit of small S, $K_S \gg S$, then

$$\frac{S}{S + K_S} \approx \frac{1}{K_S} S$$

   this approximation means that the action of the enzyme depends linearly on the substrate concentration.

2. What is the sensitivity of this circuit, defined as the relative change in X_1^{StSt} per relative change in V_1?

$$S(X_1^{StSt}, V_1) = \frac{V_1}{X_1^{StSt}} \frac{dX_1^{StSt}}{dV_1}$$

3. Assume now that E_1 and E_2 work with zero-order kinetics. What is X_1 as a function of V_1? Note that $X_0 + X_1$ cannot exceed the total concentration X_{tot} so there has to be a steady state.

   Zero order kinetics can be approximated from a Michaelis-Menten kinetics production rate and taking the limit of large S, $S \gg K_S$, then

$$\frac{S}{S + K_S} \approx \frac{S}{S} = 1$$

   this approximation means that the action of the enzyme doesn't depend on the substrate concentration.

4. What is the sensitivity of the zero-order circuit? Explain why this is called "zero-order ultra-sensitivity"?

5. *optional:* Compare the switching time (time to 50% change in X_1 upon a change in V_1) between the cases of (1) and (3) above.