Biophysics 297: Modeling Complex Biological Systems
Problem Set 2
Due: 6/2/04

Problem 1: Calcium Homeostasis Revisited

A concise model of calcium homeostasis proposed by H. El-Samad et al. predicts that perfect adaptation of blood calcium levels following the onset of lactation can be achieved by a proportional-integral (PI) control mechanism governed by parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D_3.

Recall from Hao's lecture that the rate of change of calcium is just the difference between the calcium supply rate, V_T, and the calcium clearance rate, V_C:

$$\frac{d[Ca]}{dt} = V_T - V_C$$

El-Samad's model assumes that the calcium supply rate can be modeled by a PI controller in which the set point, R, is the animal's desired calcium concentration:

$$V_T = K_p(R - Ca) + K_i \int (R - Ca)dt$$

Your task now is to investigate the transient dynamics of this model.

1. As a first step, Laplace transform the differential equation. Recall the definition:
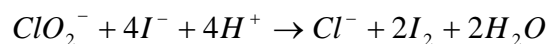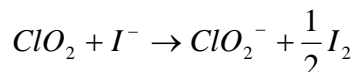
$$L\{f'(t)\} = sF(s) - f(0)$$

2. Solve the Laplace transformed equation for $\tilde{Ca}$. Having done so, write the expression for $\tilde{Ca}$ as a ratio of polynomials (you should not have any fractions in either numerator or denominator).

3. Decompose the ratio of polynomials into partial fractions. Hint: three partial fractions will be required, two of which correspond to the roots of a quadratic term.

4. Manipulate the algebra to solve for the constants A, B and C (these constants are the numerators of the three partial fractions that you have established). In solving for the constants, keep in mind that the pre-lactation calcium level is R.

5. You should now have in hand an expression for $\tilde{Ca}$ that is a sum of three fractions, where the constants A, B, and C have been replaced with parameters from the model. Use your knowledge of the inverse Laplace transform to recast the equation in the time domain.

6. Last, let's explore the behavior of the time evolution of [Ca] using your expression for Ca(t). Qualitatively describe the behavior of the transient dynamics as one incrementally turns down the strength of just the integral feedback. What happens in the limiting case of no integral feedback? You may use analytical and/or graphical methods to address these issues.

Problem 2: A Chemical Oscillator

There is a remarkable class of chemical reactions that exhibit oscillatory behavior in a test tube. An example of such chemical oscillations is the chlorine dioxide-iodine-malonic acid (ClO_2-I_2-MA) reaction. The mechanism of this reaction is very complex, but its essential behavior can be captured by the following three chemical reactions.

$$MA + I_2 \rightarrow IMA + I^- + H^+$$
$$ClO_2 + I^- \rightarrow ClO_2^- + \frac{1}{2}I_2$$
$$ClO_2^- + 4I^- + 4H^+ \rightarrow Cl^- + 2I_2 + 2H_2O$$

By applying the quasi-steady-state approximation, the rate laws describing this system can be reduced to two differential equations. After de-dimensionalization, these equations can be written as:

$$\frac{dx}{d\tau} = a - x - \frac{4xy}{1+x^2}$$

$$\frac{dy}{d\tau} = bx\left(1 - \frac{y}{1+x^2}\right)$$

Where x and y are the dimensionless concentrations of I^- and ClO_2^-, respectively and a and b are positive dimensionless parameters.

In this problem, you will show that this system can exhibit oscillatory behavior under certain values of the parameters a and b using the **Poincare-Bendixson theorem**. The theorem implies that a bounded region R of the phase plane must contain a **limit cycle** (i.e a closed orbit) if:

A) R contains no fixed points and
B) All vectors along the boundary of R point "inward"

Such a region R is called a "trapping region" because, by condition B), a trajectory that starts inside R must remain in R for all future time. Intuitively, since the trapping region contains no fixed points the only possible long-term trajectory is a closed orbit. The trapping region you will be asked to investigate is given in dashed lines in the figure

below along with plots of the x- and y-nullclines. Note that the right boundary of the trapping region extends from the x-intercept of the x-nullcline to the y-nullcline.
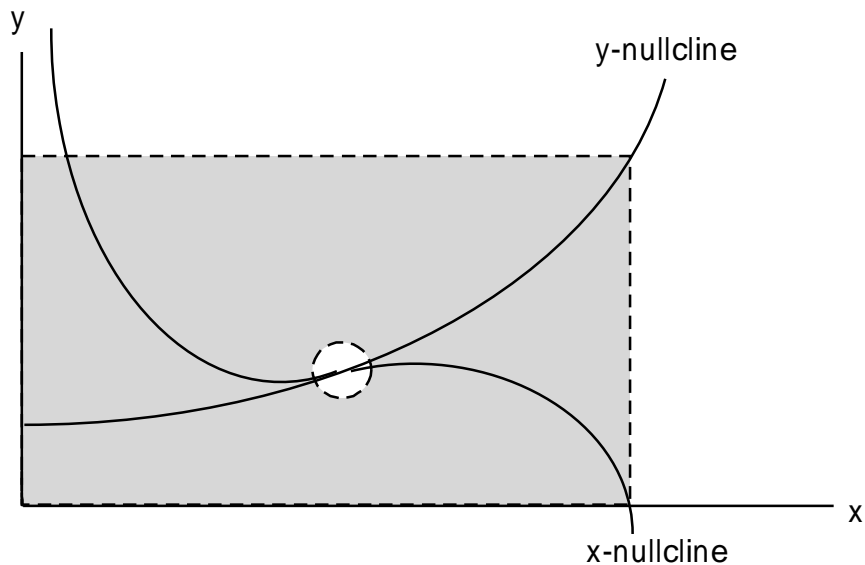

a) Verify algebraically that all vectors along the outer boundary of the trapping region point "inward" toward the shaded region.

This system has a fixed point at the intersection of the x- and y-nullclines. In order to satisfy criterion B), we exclude the fixed point from the trapping region by "cutting out" a circle of infinitesimal radius around the fixed point. We now have to show that vectors along the boundary of this circle also point into the trapping region. As it turns out, this is equivalent to showing that the fixed point is an unstable node or an unstable spiral.

b) Linearize about the fixed point by computing the Jacobian at the fixed point. You will find that the stability of the fixed point depends on the parameters a and b. Identify the region of the a-b plane where oscillations are predicted to occur.

Problem 3: Bacterial Chemotaxis

Bacteria such as E. coli are able to sense and traverse gradients of chemicals in their environment. The movement of swimming bacteria consists of an alternating series of smooth glides and random tumbles that change their direction. By adjusting its tumbling frequency, a bacterium is able to swim towards attractants or away from repellants. The protein network involved in this chemotactic response has been studied in great detail and can be summarized as:
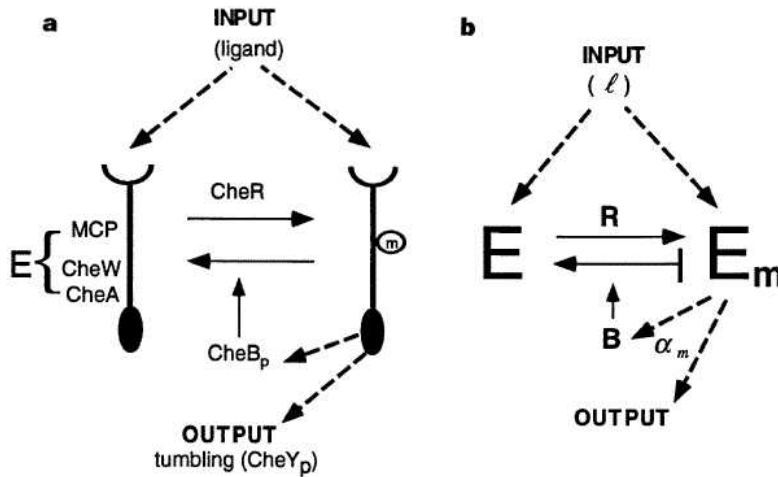
Ligands (*l*) bind to their receptors (MCP), which form stable complexes (*E*) with the proteins CheA and CheW. CheA is a kinase that phosphorylates the response regulator CheY. In its phosphorylated form, CheY binds to the flagellar motor and causes tumbling. The receptor can be methylated by CheR (*R*) and demethylated by the phosphorylated form of CheB. In its methylated form (E_m), the receptor has greater kinase activity. CheA can also phosphorylate CheB, giving rise to a negative feedback loop.

We can derive a simple model of this system by making a number of assumptions:

Assumption 1 : The receptor contains only one methylation site. That is, the complex can only exist in one of two methylation states: E_0 (unmethylated) and E_m (methylated once).

Since the receptor can bind a single ligand (*l*), altogether we have four possible receptor states corresponding to bound/unbound and methylated/unmethylated. Each state has some probability α of being active in terms of kinase activity.

State	Meaning	Probability of being active
E_m^{u}	methylated/unbound	α_m^{u}
E_m^{b}	methylated/bound	α_m^{b}
E_0^{u}	unmethylated/unbound	α_0^{u}
E_0^{b}	unmethylated/bound	α_0^{b}

In the case where the ligand is a repellant, the bound forms are more active than the unbound forms (i.e. $\alpha_0^b > \alpha_0^u$ and $\alpha_m^b > \alpha_m^b$). The bacterium will tumble more frequently in the presence of the repellant, allowing it to move away from the repellant.

We can represent the total kinase activity (A) of all four receptor states as:

$$A = E_m^u \alpha_m^u + E_m^b \alpha_m^b + E_0^u \alpha_0^u + E_0^b \alpha_0^b$$

Assumption 2 : Ligand binding occurs much faster than the methylation and demethylation of receptor. Thus, you can apply the quasi-steady state approximation and consider the unbound forms to be in equilibrium with the bound forms with the association constant K.

Assumption 3 : The activity of the unmethylated receptor is negligible compared to the activity of the methylated receptor.

1. Using these assumptions, write an expression for A, the total kinase activity, in terms of the total concentration of methylated receptor ($E_m = E_m^u + E_m^b$), the ligand concentration (l), and the association constant for ligand binding (K).

Now let's consider the methylation/demethylation process. The activities of the methylase CheR and demethylase CheB-p can be described by Michaelis-Menten kinetics (recall this means that the rate at which the enzyme converts substrate is a function of its maximum velocity V_{max} and its Michaelis constant K_m). We can also make two additional assumptions about CheR and CheB-p:

Assumption 4 : The methylase CheR is present in such limiting amounts that it is always saturated with substrate.

Assumption 5 : The demethylase CheB-p can only demethylate active receptor.

2. With these further assumptions, write a differential equation that describes the rate of change of methylated receptor. Things this equation may depend on are the activity (A) and the maximum velocities and Michaelis constants for CheR and CheB-p (V_{max}^R, V_{max}^B, K_m^R, K_m^B).

3. Solve for the activity at steady state (A_{st}). Is the steady state stable?

Finally, we'd like to analyze the system in terms of control theory. The non-linear differential equation you derived in part 2 turns out to be too complicated to analyze, but we can simplify matters by linearizing the equation about the steady state A_{st}. Recall that the linearization of a function $f(x)$ about a point a is given by:

$$f(x) = f(a) + f'(a)(x - a)$$

4. Linearize the differential equation in part 2 about the steady state A_{st}

5. Laplace transform your solutions to parts 1) and 4). Using these two Laplace transformed equations, draw the control diagram that depicts the cyclic relationship between E_m and A in the s-domain.