

Biophysics 297: Modeling Complex Biological Systems

Problem Set 1

Due: 5/12/2004

Problem 1: Analyzing a phase space

Analyze the following equation graphically by plotting $\frac{dx}{dt}$ against x . Find the fixed points and classify the stability of each.

1.
$$\frac{dx}{dt} = 4x^2 - 16$$

2. A protein X positively regulates its own production by forming a multimer and functioning as a transcription factor. It is not known whether the multimer is a dimer, trimer, or higher order complex. X is degraded in proportion to its concentration. Use your intuition to determine whether the protein's concentration can oscillate. Why or why not?

Problem 2: Love Affairs

In the article "Love affairs and differential equations" (Strogatz, S.H. Math Magazine 61, 35. 1988), Strogatz describes a simple model of the dynamics of love affairs using a system of linear differential equations:

$$\frac{dR}{dt} = aR + bJ \qquad \frac{dJ}{dt} = cR + dJ$$

$R(t)$ = Romeo's love/hate for Juliet at time t

$J(t)$ = Juliet's love/hate for Romeo at time t

where positive values of R and J signify love and negative values signify hate and the signs of a , b , c and d specify particular romantic styles. For example, when $a, b > 0$ Romeo gets excited by Juliet's love for him and is further spurred by his own affections for her.

1. Find the fixed point in this system (does not depend on the values of a , b , c, d).
2. Suppose that $b = 0$ and $c = 0$. State in words the romantic behaviors of Romeo and Juliet in this simplified system.

3. Consider the special case where Romeo and Juliet mirror each other's feelings exactly:

$$\begin{bmatrix} a & b \\ b & a \end{bmatrix}$$

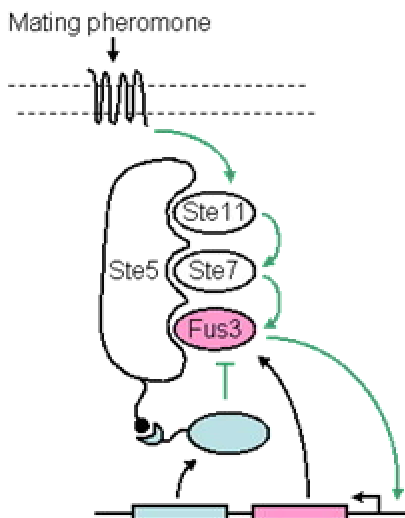
where $a < 0$ (they're both "cautious" lovers) and $b > 0$ (they're each encouraged by the other's advances). As it turns out, their eventual romantic fate (i.e. as $t \rightarrow \infty$) depends on the balance between caution and encouragement. Predict the behavior of this system when: (1) $|a| > |b|$ and (2) $|a| < |b|$.

Problem 3: MAPK Signaling Cascade

The goal of this model is to predict the functional consequences of adding negative feedback loops to the yeast mating pheromone MAPK signaling cascade. In particular, we focus on the ability to design a synthetic adaptive response. Adaptation occurs when pheromone stimulation leads to an initial increase in activity, followed by a decline. This produces a pulse-like response to an input. Perfect adaptation occurs when the response falls exactly to the pre-stimulus steady state.

The system input is mating pheromone, which directly activates the Sho1 receptor, resulting in its phosphorylation. The signal is then passed through a Ste5-scaffold mediated signal cascade, ultimately leading to the phosphorylation of Fus3. To make the problem analytically tractable, we assume that the activated state of Fus3 is directly proportional to the input signal and the remainder of the scaffold interactions is ignored.

We consider a case where a phosphatase and Fus3 is put under the transcriptional control of Fus3. The phosphatase contains a PDZ domain and Ste5 is modified to contain the cognate binding sequence. When expressed, the phosphatase is able to bind Ste5 and dephosphorylate Fus3. Thus, a negative as well as a positive feedback loop is completed. Using the model outlined below, demonstrate that a positive feedback loop mediated by Fus3 can lead to perfect adaptation.



There are three equations for this model. First changes in unphosphorylated Fus3 (F) are captured by

$$\frac{dF}{dt} = b_F \frac{KF^*}{1 + KF^*} - g_F F + k_F F^* M - SF$$

where the first term describes the expression of Fus3 from promoter, the second term describes the degradation of Fus3, the third term describes the dephosphorylation of Fus3 by the phosphatase (M) and the last term describes the phosphorylation of Fus3 by the signal (S). The parameter b_F is the expression rate of Fus3, K is the binding constant for F^* to the promoter, g_F is the degradation rate, and k_F is the phosphatase dephosphorylation rate. The second equation captures changes in the phosphorylation state of Fus3:

$$\frac{dF^*}{dt} = SF - k_F F^* M - g_F F^*$$

and the third equation captures changes in the concentration of phosphatase

$$\frac{dM}{dt} = b_M \frac{KF^*}{1 + KF^*} - g_M M$$

where b_M is the expression rate of M and g_M is the degradation rate.

1. De-dimensionalize the equations.
2. Invoke the quasi-steady-state approximation to reduce this three-dimensional problem to two dimensions (two differential equations). HINT: The first and third equations are describing transcriptional processes which are SLOW and the second differential equation exclusively describes phosphorylation which is FAST.
3. Demonstrate that there is a steady-state at the point (0,0).
4. Find the Jacobian. Recall that

$$J = \begin{bmatrix} \frac{\partial}{\partial x} \left(\frac{dx}{dt} \right) & \frac{\partial}{\partial y} \left(\frac{dx}{dt} \right) \\ \frac{\partial}{\partial x} \left(\frac{dy}{dt} \right) & \frac{\partial}{\partial y} \left(\frac{dy}{dt} \right) \end{bmatrix}$$

5. Determine the conditions for which the (0,0) steady state is stable. Use it to predict how a circuit could be build that demonstrates perfect adaptation.

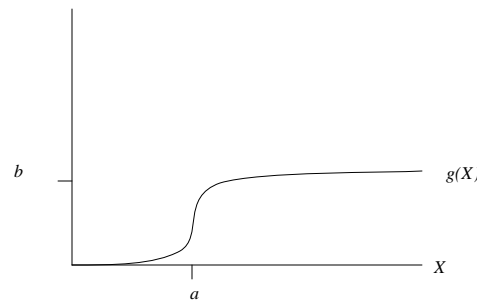
Problem 4: Grasshopper Population Explosion

One proposed model for grasshopper population dynamics is

$$\frac{dX}{dt} = rX \left(1 - \frac{X}{k} \right) - g(X)$$

where the grasshopper population $X(t)$ is assumed to grow logistically with growth rate r and carrying capacity k . The term $g(X)$ describes the effects of predation and we'll assume that it possesses the following form:

$$g(X) = \frac{bX^2}{a^2 + X^2}$$



There is little predation when the grasshoppers are scarce but once the population reaches the critical level $X = a$, predation turns on sharply.

We are interested in determining if there are solutions to the proposed model of grasshopper population dynamics that will lead to a population explosion. It turns out the values of the four parameters in our model (a , b , k , r) will influence the character of the solutions.

Let's examine the situation more closely. Our first task will be to de-dimensionalize the equation. There are several ways to do this, but we encourage you to use the following suggestion:

1. De-dimensionalize the system so that all the dimensionless parameters are attached to the logistic term and *not* the predation term. Start by dividing the whole system by b and then make a convenient substitution for X that will eliminate the parameter a from the predation term.
2. Using your final dimensionless form, let's begin to analyze the fixed points. There is one fixed point that should strike you immediately. What is it? Is it stable or not?
3. In the de-dimensionalized form you should obtain two parameters that control the logistic term. By varying the relative magnitudes of these two parameters, you can control the number of additional fixed points in the grasshopper population. How many additional fixed points could arise for this system? (To tackle this question you

will need to qualitatively explore a range of values for your two dimensionless parameters). How might you qualitatively interpret the presence of these additional fixed points in terms of a grasshopper population explosion??