

Computational Methods in Biology (Spring 2009)

Assignment 2 (due in class on Feb. 16)

The Rules

This assignment and most of the others in this course will involve computer simulations. What do I expect you to turn in? I'd like the following:

(1) Hand-written or word-processed text describing what you are doing, how you did it, and the results you got. I ask many questions, and I expect you to answer these. When I grade I will be looking to see if each question has been satisfactorily answered. Use complete sentences and make your work easy to follow.

(2) Labelled figures. Include things such as figure number, axis labels, bifurcations, types of branches (stationary or periodic), nullclines (x -nullcline or y -nullcline), and equilibrium points (what type?). In some cases I will ask for a hand-drawn figure, and this is what you should turn in. In other cases I will ask for a computer-drawn figure (the XMGR graphing package is what I use to make figures, I'll show you how to use it if you ask). In other cases I won't specify.

(3) Make it look good. Wading through disorganized and unclear work does not put me in a good mood. Ask yourself whether you would want to grade it!

(4) Turn it in on time. You can, however, turn it in up to two days late with a 20% reduction in grade. After that I won't accept it.

The free software package **XPPAUT**, written by Bard Ermentrout at the University of Pittsburgh, is a great tool for analyzing continuous dynamical systems. In this first problem I will talk you through many of the things you need to know to use this package (on the SUNs) to do phase plane and bifurcation analysis. [Versions of this software are written for unix, linux, and even Windows machines. You can download it from Bard's web page.]

The example problem will be a model of oscillatory glycolysis developed in 1972, called the **Goldbeter-Lefever model**. This describes in a very simple way how the molecule ATP is converted to ADP by the enzyme phosphofructokinase. This enzymatic function is described by “ Φ ”. The ATP input rate to the system is ν and the ADP degradation rate is η . Parameter τ is a time constant.

1. [10 points] The Goldbeter-Lefever model (*Biophysical Journal*, vol. 12, pp. 1302–1315, 1972) is

$$\begin{aligned}\frac{dATP}{dt} &= [\nu - \Phi(ATP, ADP)]/\tau \\ \frac{dADP}{dt} &= [\Phi(ATP, ADP) - \eta ADP]/\tau .\end{aligned}$$

where $\Phi(ATP, ADP) = ATP(1 + k ADP)^2$, and ν , η , k , and τ are parameters. We will use $k = 20$ and $\tau = 500$ throughout the assignment, and various values for ν and η .

(a) The computer code for the Goldbeter-Lefever model, **goldbeter.ode**, can be downloaded from my website (www.math.fsu.edu/~bertram/course_software). If you look in this file you will see how easy it is to enter ODEs and associated information into this program. On the SUNs start up xpp using the command “xppaut goldbeter.ode”. Notice the buttons on the top of the xpp screen. Clicking on these will open other windows that will allow you to do things like change the values of the system parameters.

Currently $\nu = 1$ and $\eta = 120$. From the initial values $ATP = 0.5$, $ADP = 0.5$, numerically integrate the system by clicking on Initialconds and Go (or type “ig”). You should see how ATP evolves in time. To see how ADP evolves open another window by clicking Makewindow and Create or typing “mc”. [Note that this new window becomes the active window, as indicated by the small white dot in the left corner of the new window.] To change what is plotted in this new window click on Viewaxes and 2D (or type “v2”). Put ADP on the y axis. Click on each window and type “r” (refresh) to redraw the curve on the window. You should now see that ATP approaches 0.73 and ADP approaches 0. To continue the integration from where

it left off click on Initialconds and Last (or type “il”). You can also enter initial conditions directly into the ICs window.

Open up a third window (type mc). Make this a phase plane window with ATP on the x axis and ADP on the y axis. You can trace out a trajectory from any point in this phase plane simply by clicking Initialconds and Mouse (or type “im”). Then click anywhere in the phase plane window and this will be the initial location for a trajectory. [Note: you can only do this in a phase plane window, so this must be the active window.] Trace out a number of trajectories in this way. Do there appear to be any stable equilibria or limit cycles? If so, describe their locations.

You can find all equilibria (stable and unstable) by clicking on Sing pts and Mouse (or type sm). Then click on a location in the phase plane where you suspect an equilibrium exists. [Note: equilibrium points are called singular points in XPP.] When a singular point is found you will be asked if eigenvalues should be printed. These are the eigenvalues of the Jacobian matrix formed by linearizing the system about the singular point. When you click Yes, the eigenvalues will be printed in the X-window from which XPP was started. Both real and imaginary components are printed for each of the two eigenvalues. Write down the values of the eigenvalues. Is the equilibrium point a stable node or a stable spiral?

(b) Increase the parameter ν to 5 and reintegrate starting from the last location. [You can erase old trajectories by clicking Erase or typing “e”.] What happens to the nullclines? [You can plot nullclines by clicking on Nullclines and New, or typing “nn”.] Is the equilibrium still stable? Is it a node, spiral, or saddle point? Write down the eigenvalues.

(c) Set $\nu = 7$ and rerun. What do you observe now? Are there any stable equilibria or limit cycles? What is the long-term behavior of the system? What happens to the nullclines and singular point? Write down the values of the eigenvalues. Now make a sketch of the eigenvalues for $\nu = 1, 5, 7$ in the complex plane. What type of bifurcation occurred? What is the period of the oscillation born at the bifurcation?

(d) Now we will make a bifurcation diagram with ν as the bifurcation parameter. Click on File and Auto. This brings up the Auto software. In this window, click on Parameters to enter the bifurcation parameter (this is Par1, which is already the parameter we want). Click Ok. Then click Axes and hI-lo. Currently ATP is on the y-axis and ν (the bifurcation parameter) is on the x-axis. You can adjust the dimensions of the bifurcation axes in this window. Set Xmax=70. Click Ok. Next click on Numerics. In this window you can adjust some of the numerical parameters used by Auto to make the bifurcation diagram. The important ones to know are Nmax, NPr, Ds, Dsmax, Par Min, and Par Max. The diagram is made by solving a

boundary value differential equation with variable step size. Nmax is the maximum number of steps to take, NPr tells Auto how often to print a label (NPr=50 means put a label after each 50 steps), Ds is the initial step size, and Dsmax is the maximum allowed step size. Par Min is the minimum value for the bifurcation parameter and Par Max is the maximum value. Set Nmax=500, NPr=550, Par min=0, and Par max=70. Use the default values for Ds and Dsmax. [Note: Auto will put labels at every bifurcation point it finds, so setting NPr > Nmax we ensure that any label will be an endpoint of the branch or a bifurcation point.]

We are now ready to generate the bifurcation diagram. This must start from an equilibrium point, so in the Parameter window of XPP (not Auto) set $\nu = 0$ and type “il” several times, so that the system becomes very close to the stable equilibrium. This point will automatically be fed into Auto, and can serve as the starting point for the bifurcation diagram. Back in the Auto window click on Run and Steady State. A bifurcation diagram of steady states, a *stationary branch*, should be drawn out, with endpoints and bifurcation points labelled. [If this does not work it probably means the initial point was not sufficiently close to the stable equilibrium, so go back to the XPP Parameter window, set $\nu = 0$ and try again.] The portion of the bifurcation diagram representing stable equilibria is in bold, the portion representing unstable equilibria is thin.

You can trace out the periodic branch of the bifurcation diagram by clicking Grab, then pressing Tab, then pressing Return. This Tab will move you from one labelled point to the next. The periodic branch starts at the Hopf bifurcation with label 2, so one Tab should get you there (information on the labelled point will show up at the bottom of the Auto window). Now click Run and Periodics. The periodic branch should emerge, connecting up with the Hopf bifurcation at label 3. You will have to hit the Esc key to stop AUTO on this branch, otherwise it just goes back and forth forever. Print out the full bifurcation diagram by clicking File and Postscript. This will generate a postscript file that you can then print. Print this out and turn it in.

(e) Generate a bifurcation diagram with η as the bifurcation parameter (start with $\eta = 1$). Set $\nu = 10$. [To remove the old bifurcation diagram click File and reset diagram.] Note that there should be two Hopf bifurcations. Turn in this bifurcation diagram.

2. [10 points] Use xppaut to simulate the **Morris-Lecar model** (Eqs. 2.30-2.34 in Fall et al.) for the parameter values given in Table 2.4 and the initial conditions $V(0) = -60$, $w(0) = 0.01$. You may want to use your Goldbeter program as a template.

(a) Run the program for four different values of I_{app} : 0, 60, 150, and 300 pA. In each case carry out the integration for 200 msec. Plot the four solution curves on the same graph and turn in.

(b) For each I_{app} , draw a sketch of the phase plane. Include nullclines and equilibria, indicating the type and stability of the equilibria. Also show a few representative trajectories. You should use xppaut to do this, and make your sketches from what you see on the computer screen.

(c) Construct a bifurcation diagram of the system with I_{app} as the bifurcation parameter. Do this for I_{app} between 0 and 300 pA. Indicate the exact locations and types of bifurcations that occur.

(d) The electrical impulses are generated because the negative feedback current I_K activates more slowly than the positive feedback current I_{Ca} . For the case $I_{app} = 150$ pA, describe what happens if you increase the speed of activation of I_K . Start with $\phi = 0.04$ (the default value) and increase it to different values up to $\phi = 0.5$. Describe what happens to the system dynamics, including the amplitude and period of the oscillation, the stability and location of the steady state, the location of the nullclines, and the existence of the limit cycle. Construct a bifurcation diagram with ϕ as bifurcation parameter to verify your answer. What is the value of ϕ where the bifurcation occurs, and what type of bifurcation is it?

3. [20 points] The **Hindmarsh-Rose model** (*Nature*, vol. 296, pp. 162–164, 1982) describes the electrical activity in a snail neuron. This planar model is not physiological in the sense that it does not include ionic currents explicitly. However, it captures the excitable dynamics exhibited by the neuron. The model is:

$$\begin{aligned}\frac{dv}{dt} &= (w - v^3 + 3v^2 + I_a)/c \\ \frac{dw}{dt} &= 1 - 5v^2 - w \ ,\end{aligned}$$

where v is voltage and w is a recovery variable. Using XPP, we will investigate the dynamics for different values of applied current I_a and capacitance c .

(a) Write an xpp program for the Hindmarsh-Rose model, using the Goldbeter program as a template. Consider first the case with $c = 2$. For $I_a = -2$, construct nullclines and classify the equilibrium (or equilibria) as stable/unstable node/spiral, etc. Record eigenvalues. Make a phase portrait sketch, including nullclines, and turn it in. [Please note that I want a hand-drawn sketch. You should use XPP to see what the nullclines and trajectories look like, but then draw by hand.] Make a sketch of v

versus t for several initial conditions.

(b) Now set $I_a = -0.8$. Sketch the nullclines. Locate and classify the equilibria and limit cycles. Record eigenvalues. For saddle points, you will be asked if you want to draw invariant sets. These are the stable and unstable manifolds. Say yes. To terminate the drawing of each branch you must hit the Esc key (otherwise it goes on forever). There are four branches (two for unstable, two for stable manifold). If you get a message about “too much work” click on Ok, the branch gets drawn anyway. Include these invariant sets in your sketch (there will be several curves sketched, so using color helps a lot). Be sure to identify which branches make up the stable and which make up the unstable manifold. Describe the basins of attraction of the stable equilibria. On a separate graph, plot v versus t for several initial conditions near each equilibrium. What kind of bifurcation occurred between $I_a = -2$ and $I_a = -0.8$? Explain.

(c) Now set $I_a = 0$. Sketch the nullclines. Locate and classify equilibria and limit cycles. Record eigenvalues. Draw and label stable and unstable manifolds of the saddle point. Identify the basins of attraction for each stable structure. What do the branches of the unstable manifold converge to? Plot v versus t for several initial conditions near each equilibrium. What kind of bifurcation occurred between $I_a = -0.8$ and $I_a = 0$? Explain.

(d) Set $I_a = 2$. Sketch the nullclines. Locate and classify equilibria and limit cycles. Record eigenvalues. What kind of bifurcation occurred between $I_a = 0$ and $I_a = 2$? Explain.

(e) Set $I_a = 8$. Sketch the nullclines. Locate and classify equilibria and limit cycles. Record eigenvalues. Plot v versus t for an initial condition near the equilibrium. Why does it take so long for transient behavior to die out? What kind of bifurcation occurred between $I_a = 2$ and $I_a = 8$?

(f) Construct a bifurcation diagram with I_a as the bifurcation parameter. Start from $I_a = -2$ and continue out to $I_a = 10$. Turn in a computer plot of the diagram. Label all bifurcation points (SN=saddle node, TR=transcritical, subPF=subcritical pitchfork, supPF=supercritical pitchfork, subHB=subcritical Hopf, supHB=supercritical Hopf, HC=homoclinic). For what values of the bifurcation parameter is the system bistable?

4. [20 points] In this exercise we will investigate the dynamics of two coupled Goldbeter glycolytic oscillators. Coupling will in general be through both ADP and ATP,

but we will first look at coupling through each nucleotide separately. The coupled system is

$$\begin{aligned}\frac{dATP_1}{dt} &= [\nu - \Phi(ATP_1, ADP_1) + p_{ATP}(ATP_2 - ATP_1)]/\tau \\ \frac{dADP_1}{dt} &= [\Phi(ATP_1, ADP_1) - \eta ADP_1 + p_{ADP}(ADP_2 - ADP_1)]/\tau \\ \frac{dATP_2}{dt} &= [\nu - \Phi(ATP_2, ADP_2) + p_{ATP}(ATP_1 - ATP_2)]/\tau \\ \frac{dADP_2}{dt} &= [\Phi(ATP_2, ADP_2) - \eta ADP_2 + p_{ADP}(ADP_1 - ADP_2)]/\tau .\end{aligned}$$

Write an XPP program for this system, with $\nu = 10$, $k = 20$, $\tau = 500$, and we will be using various values for η and the coupling parameters p_{ADP} and p_{ATP} .

(a) Use the initial conditions $ATP_1(0) = 10$, $ADP_1(0) = 10$, $ATP_2(0) = 0.01$, $ADP_2(0) = 0.01$ and parameters $\eta = 120$, $p_{ADP} = 0$, $p_{ATP} = 0$. Integrate for 500 seconds and turn in a plot of ATP_1 and ATP_2 superimposed on the same graph. What is the phase difference (in seconds) between the two oscillators? Run again, but with $p_{ADP} = 17.5$. What happens?

(b) Determine the range of η values that give synchronous oscillations with $p_{ADP} = 17.5$ (and with $p_{ADP} = 0$). Do this by constructing a bifurcation diagram, with η the bifurcation parameter and ATP_1 on the ordinate. Enter p_{ATP} as the second parameter (you will need this later). Turn in the bifurcation diagram. (Note: you may get a lot of BP labels on the periodic branch. These are spurious, don't worry about them if they occur here.)

(c) Using the default initial conditions and $\eta = 60$, what happens to the long-term behavior when $p_{ADP} = 0$, $p_{ATP} = 17.5$? What happens to the long-term behavior if the initial conditions $ATP_1(0) = 0.7$, $ADP_1(0) = 0.08$, $ATP_2(0) = 0.4$, $ADP_2(0) = 0.25$ are used?

(d) Explain the results from part C. To do this, construct a bifurcation diagram with η as the bifurcation parameter (and $p_{ATP} = 17.5$). (You will need to click on the "abort" button several times to stop AUTO from retracing the diagram multiple times.) Describe the important bifurcations that occur on the stationary branch, and turn in a hand-drawn sketch of the bifurcation diagram. (Use different colors to improve clarity.) Be sure to highlight the most important regions of the diagram. Use this to explain the bistable behavior observed in part C. For what range of values of η do synchronous oscillations occur? For what range of values does oscillator death

occur?

(e) A **two-parameter bifurcation diagram** is a curve in the plane of two parameters consisting of bifurcation points. These diagrams are nice ways of summarizing the behavior of a system. For example, one could ask for what values of the coupling parameter p_{ATP} oscillator death occurs. The most efficient way to answer this is to construct a two-parameter bifurcation diagram of the Hopf bifurcations that delimit the oscillator death region (this curve will consist of Hopf bifurcation points). For p_{ATP} sufficiently small the Hopf bifurcations will coalesce, so that the region of oscillator death disappears. Try this out. Grab one of the Hopf bifurcations that delimits the oscillator death region. Click on Axes, and then Two par. You should see that η is the main parameter and p_{ATP} is the second parameter. You can also enter the max and min values for the two-parameter diagram. (Enter values that you think are appropriate, you can change them after the diagram has been created.) Next, click on Run and Two Param. This should generate the diagram. (You may need to run twice, with D_s positive and then with D_s negative, to get both parts of the curve.) Do this, and turn in a hand-drawn sketch of the diagram. Interpret this diagram. That is, tell me what it means. From the diagram, determine the smallest value of p_{ATP} for which oscillator death occurs.

(f) Finally we will investigate the case of coupling through both ATP and ADP. The ADP coupling tends to produce synchronous oscillations, while the ATP coupling allows for oscillator death. So with enough ADP coupling, the possibility of oscillator death should be eliminated. To see this, construct a new 1-parameter bifurcation diagram, with η as bifurcation parameter and $p_{ATP} = 17.5$. This time, enter p_{ADP} as the second parameter. Once you have constructed the diagram, grab a Hopf bifurcation delimiting the region of oscillator death and construct a two-parameter bifurcation diagram, with main parameter η and second parameter p_{ADP} . Turn in a hand-drawn diagram. For what value of p_{ADP} does the oscillator death region disappear?