

Computational Methods in Biology (Spring 2015)

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. In some 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) I have put some MATLAB M-files on my web site (Course Software) that plot curves in a graph with a single panel or double panel (2 panels on one page). Also, there is one for plotting bifurcation diagrams that have been saved from within AUTO. See comments in the M-files for the bifurcation plotting file.

This assignment uses XPPAUT, and I assume that you remember how to use it from last semester. I will put the Goldbeter-Lefever model on my web site (Course Software) for you to use as a template. This is a code you used last semester in MAM1.

1. [20 points] Use XPPAUT to simulate the **Morris-Lecar model**. The equations are given in the Computational Cell Biology book (Eqs. 2.30-2.34 and for the parameter values given in Table 2.4). These are also given on my web site (Course Software). Use 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_{ap} : 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_{ap} , 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_{ap} as the bifurcation parameter. Do this for I_{ap} 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?

2. [40 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:

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

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 XPPAUT program for the Hindmarsh-Rose model, using the Goldbeter program as a template. Consider first the case with $c = 2$. For $I_{ap} = -2$, 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 XPPAUT 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 $I_{ap} = -0.8$. 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 $I_{ap} = -2$ and $I_{ap} = -0.8$? Explain.

(c) Now set $I_{ap} = 0$. 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 $I_{ap} = -0.8$ and $I_{ap} = 0$? Explain.

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

(e) Set $I_{ap} = 8$. 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 $I_{ap} = 2$ and $I_{ap} = 8$?

(f) Construct a bifurcation diagram with I_{ap} as the bifurcation parameter. Start from $I_{ap} = -2$ and continue out to $I_{ap} = 10$. 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? Next construct and turn in a bifurcation diagram showing period vs. I_{ap} . Is this a type 1 or type 2 oscillator?

(g) A **two-parameter bifurcation diagram** is a curve in the plane of two parameters consisting of bifurcation points. These diagrams summarize the family of one-parameter bifurcation diagrams as a second parameter is varied. For example, one could trace out the curve of Hopf bifurcations (from part (f)) as a second parameter (like C) is varied. Try this out. Reset the axes in the bifurcation diagram of part (f) so that V and I_{ap} are on the axes. Grab one of the Hopf bifurcations. Click on Axes, and then Two par. You should see that I_{ap} is the main parameter and C is the second parameter (if not, then make it so). 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. You want your diagram to contain all the important information.) Next, click on Run and Two Param. This should generate the diagram. (You may need to run twice, with Ds positive and then with Ds negative, to get both parts of the curve.) This curve shows the set of I_{ap} and C parameters where a Hopf bifurcation occurs. (You should get the same curve if you start from the other Hopf bifurcation point in the one-parameter bifurcation diagram.)

In addition to the two-parameter continuation of the Hopf bifurcation, do a two-parameter continuation of the two SN bifurcations. Put all of these curves on the same figure and turn in. Make sure to label all curves. For what region of the parameter plane (for $C > 1$) is there stable periodic motion? For what region is there a stable stationary solution? Where is there bistability between a steady state and a periodic solution?

(h) Redo part (f), but with the capacitance reduced to $C = 1$. Label all bifurcations and answer all questions.

3. [20 points] Gardner, Cantor, and Collins designed a genetic toggle switch in 2000. This is an example of **synthetic biology**, which is a field in which biological systems are constructed for specific functions, and the design is driven by mathematical models. They inserted plasmids (extra-chromosomal DNA that is capable of replicating independently of chromosomal DNA) into *E. coli*. These contained genes that when expressed as protein would inhibit the transcription of each other (they are mutually inhibitory). The goal was to engineer the correct genes with correct interactions so that the system would be *bistable*, and thus act as a switch (either one gene is expressed or the other, but not both). They modeled this reaction as

$$\begin{aligned}\dot{x} &= \frac{\alpha_x}{1 + y^\beta} - x \\ \dot{y} &= \frac{\alpha_y}{1 + x^\gamma} - y .\end{aligned}$$

They aggregated both mRNA and protein into the same variable. So there are two variables total (x and y), one for each gene. The α parameters reflect combined transcription and translation rates, and β and γ reflect the cooperativity of inhibitory feedback. All parameters are positive.

Assume for simplicity that $\beta = \gamma = b$, so that

$$\begin{aligned}\dot{x} &= -x + \frac{\alpha_x}{1 + y^b} \\ \dot{y} &= -y + \frac{\alpha_y}{1 + x^b} .\end{aligned}$$

(a) Using $\alpha_x = \alpha_y = 10$ plot nullclines and do a phase portrait for $b = 1$ (turn in a hand-drawn version). Then increase b until a bifurcation occurs. Construct a phase portrait for some value of b past the bifurcation point (again, turn in a hand-drawn version). What kind of bifurcation is it?

(b) Construct a (properly labelled) bifurcation diagram with the parameter values above, using b as the bifurcation parameter. Does this agree with your expectations from part (a)?

(c) As it stands, the system is symmetric in x and y . Break the symmetry by setting $\alpha_x = 9$ and $\alpha_y = 10$. Now repeat part (a).

(d) Construct a bifurcation diagram with the parameter values above and with bifurcation parameter b . Does this agree with your expectations from part (c)?