Computational Methods in Biology (Spring 2008)

Assignment 4 (due in class on April 16)

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1. [10 points] Consider the system of linear differential equations,

$$\begin{aligned}\frac{dx}{dt} &= -3x + y \\ \frac{dy}{dt} &= 100(2x - y)\end{aligned}$$

with initial conditions $x(0) = 1$, $y(0) = 0$.

(a) Which is the fast variable and which is the slow variable?

(b) What is the quasi-equilibrium (or quasi-steady-state) approximation for this system?

(c) Use the quasi-equilibrium approximation to eliminate y and then show that the solution of the simplified system is

$$\begin{aligned}x(t) &= \mathrm{e}^{-t} \\ y(t) &= 2\mathrm{e}^{-t} \quad .\end{aligned}$$

(d) Show that the exact solution of the original system is

$$\begin{aligned}x(t) &= 0.02\mathrm{e}^{-102.02t} + 0.98\mathrm{e}^{-0.98t} \\ y(t) &= -1.98\mathrm{e}^{-102.02t} + 1.98\mathrm{e}^{-0.98t} \quad .\end{aligned}$$

(e) Compare the approximate solution with the exact solution. When do they agree and when do they disagree?

2. [20 points] This problem examines an early model for the bursting electrical activity of pancreatic β-cells. These cells are located in cell clusters called *islets of Langerhans* and secrete the hormone *insulin* when they spike. Thus, bursts of electrical activity induce pulses of insulin secretion into the capillaries that penetrate the islets. The first mathematical model for bursting in β-cells was developed by Chay and Keizer in 1983. The model we will look at is a hybrid of the Chay-Keizer model and the Morris-Lecar model. The code (**CK.ode**) can be downloaded from my web site. The differential equations are:

$$
\begin{aligned}
\frac{dV}{dt} &= -(I_K + I_{Ca} + I_{K(Ca)} + I_{K(ATP)})/C_m \\
\frac{dn}{dt} &= \lambda(n_\infty(V) - n)/\tau_n \\
\frac{dc}{dt} &= autoc * (cknot - c) + (1 - autoc) \cdot f \cdot J_{mem}
\end{aligned}
$$

where $I_{K(ATP)}$ is K^+ current that is inactivated by ATP (just think of it as a leak current), J_{mem} is the Ca^{2+} flux through the plasma membrane, and *autoc* and *cknot* are used to clamp c at the value *cknot*. To clamp c (i.e., make it a parameter), set $autoc = 1$. If $autoc = 0$ (the default value), c will change with time (i.e., it will be a variable).

(a) Start the CK.ode code with XPP. You should see a bursting pattern. The goal now is to perform a fast/slow analysis of this system by treating calcium concentration (c) as a slowly-changing parameter of the system. The first step is to construct a bifurcation diagram of the fast subsystem, with c treated as the bifurcation parameter. To clamp c so that it does not vary with time set "autoc=1". This will clamp c at the value $c = cknot$, which is currently set at 0.3. At this value of c the K(Ca) current is very active, which hyperpolarizes the cell so that it comes to rest at a low voltage. Use this as the starting point for a bifurcation diagram. Open Auto, and use *cknot* as the primary bifurcation parameter, and make λ the second parameter. Create a bifurcation diagram, showing both stationary and periodic branches for *cknot* over the range $[0, 0.3]$. Print this out and turn it in. Identify the bifurcations that occur.

(b) Save the bifurcation diagram by clicking (in Auto) File, and then Write pts. This will save a file called diagram.dat. You can read this into a window for the V-c phase plane. In XPP make a new window for V vs. c and within that window click Graphic stuff, Freeze, and then Bif. Diag. This will allow you to read in diagram.dat. Now we can treat the bifurcation diagram as a generalized V-nullcline in the V-c phase plane. Unclamp c (set $autoc = 0$) and run. Make a hand-drawn sketch of what you see and turn it in (label all curves and include an orientation on the trajectory). Include in this sketch what you think the c-nullcline looks like (note that the Nullcline command won't work right since the system is 3-dimensional, not 2-dimensional). Explain why the trajectory does what it does.

(c) The parameter λ changes the periodic branch without affecting the stationary branch of the fast-subsystem bifurcation diagram. Explain why. Then do a 2-parameter bifurcation diagram (*cknot* and λ are the two parameters). See the last problem of homework 2 if you need a reminder about how to make 2-parameter diagrams with Auto. Trace out the curve of Hopf bifurcations (grab the HB and trace it out in two parameters) and the curve of homoclinic bifurcations. To make the homoclinic curve grab the last point of the periodic branch (this should have a label), click Run and then Fixed period. (Auto can't follow homoclinic orbits since their period is infinite, but it can follow an almost-homoclinic orbit which has a large period.) Turn in a plot of the Hopf and homoclinic curves (label the curves) in the *cknot* vs. λ plane with *cknot* between 0 and 0.3 and λ between 0.5 and 1.5. Also indicate the *cknot* value of the lower saddle node in this diagram. Interpret the 2-parameter diagram in terms of the 1-dimensional bifurcation diagram. That is, in the z-curve diagram, what happens to the Hopf and the homoclinic when λ is decreased from its original value of 1.07?

(d) Unclamp c (set $autoc = 0$) and set $\lambda = 0.9$. What happens to the bursting? Explain, in terms of what you observed in part (c). Then set $\lambda = 0.8$. Now what happens? Again, explain.

3. [20 points] Ca^{2+}-induced Ca^{2+} release (CICR) refers to the phenomenon in which cytosolic Ca^{2+} activates ryanodine or IP_3 receptors, causing Ca^{2+} to be released from the ER. A simple model for this is:

$$\frac{dc}{dt} = J_{tot}$$

where

$$J_{tot} = L + \frac{k_1 c^2}{1 + c^2} - k_2 c.$$

Here c is cytosolic Ca^{2+} concentration, L is leakage from the ER into the cytosol, the sigmoidal term reflects the CICR, and the last term reflects pumping of Ca^{2+} out of the cell. The three parameters are L, k_1, and k_2. Assume that $k_1 > 2k_2$ throughout the problem.

(a) Show that when $L = 0$ there are two positive steady states and a trivial steady state. Determine the values of these steady states as a function of k_1 and k_2. Then determine the stability of all steady state by plotting J_{tot} vs. c for $k_1 = 4$ and $k_2 = 1$.

(b) Using these k_1, k_2 values and XPP with AUTO, determine the value of L (call this L_c) where the three steady states bifurcate to a single steady state. Turn in a printout of your bifurcation diagram.

(c) Let $L < L_c$ and suppose that the solution is initially at the lowest steady state. How does c behave when small perturbations are applied to c? How does c behave when large perturbations are applied? Interpret this in terms of the biophysics of

CICR. How does c behave when L is raised above L_c and then decreased back to its original value? Why is the bahavior of this system called a biological switch?

(d) Use a 2-parameter bifurcation diagram (with k_1 as the second parameter) to determine whether the size of the interval of bistability increases or decreases as k_1 is reduced.

4. [20 points] In the firefly model discussed in class the sinusoidal form of the firefly response function was chosen somewhat arbitrarily. Consider the alternative model,

$$\begin{aligned} \frac{d\psi}{dt} &= \Omega \\ \frac{d\theta}{dt} &= \omega + Af(\psi - \theta) \ , \end{aligned}$$

where f is given by a triangle wave, not a sine wave. That is,

$$f(\phi) = \begin{cases} \phi & \text{if } -\frac{\pi}{2} \leq \phi \leq \frac{\pi}{2} \\ \pi - \phi & \text{if } \frac{\pi}{2} \leq \phi \leq \frac{3\pi}{2} \end{cases}$$

on the interval $-\frac{\pi}{2} \leq \phi \leq \frac{3\pi}{2}$, and extend f periodically outside this interval. (Recall that the ψ ODE represents a periodically flashed flashlight and the θ ODE represents the response of a firefly.)

(a) Turn in a hand-drawn graph of $f(\phi)$.

(b) Determine the ODE for the phase difference $\phi = \psi - \theta$ and put this ODE into a dimensionless form with a single parameter $\mu = \frac{\Omega - \omega}{A}$.

(c) Draw representative phase portraits, and determine the range of values of μ for which the firefly is entrained (i.e., the entrainment window). Rewrite the entrainment window in terms of the original parameters, giving a range of values of Ω for which the firefly is entrained by the flashing of the flashlight.