Computational Methods in Biology (Spring 2019)

Fast–Slow Analysis of Bursting

Exercises due April 19

This problem examines the first 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:

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

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).

(1) 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.

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).

(2) 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). Trace out curves of saddle-node bifurcations, Hopf bifurcations, and homoclinic bifurcations. To make the homoclinic curve grab a point on the periodic branch (this should have a label) with large period, 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. However, to make this a good approximation of the homoclinic, the point that you grab must be close to the homoclinic bifurcation with large period, so make sure there is a label near the end of the branch. You can control the number of labels printed with the NPr parameter in the Numerics window of Auto.) Turn in the two-parameter bifurcation diagram (label all curves) in the *cknot* vs. λ plane with *cknot* between 0 and 0.3 and λ between 0.5 and 1.5. What happens to the Hopf and homoclinic bifurcations as λ is increased past its default value of 1.07? For some values of λ there are two Hopf bifurcations and no homoclinic bifurcations. Use your 2-parameter bifurcation diagram and trial and error to find such a λ value and, using that value, make a 1-parameter bifurcation diagram just as you did in the first problem. Print this out and turn it in. What happens to the Hopf bifurcations as λ is increased further? At approximately what value of λ do the Hopf bifurcations come together? (When two bifurcations occur at once it is called a *codimension-2 bifurcation.*)

(3) Unclamp c (set $autoc = 0$) and set $\lambda = 0.8$. What happens to the bursting? Explain, in terms of what you observed in the previous problem.

(4) Now we will examine what happens to the fast subsystem when the *gca* parameter (maximum conductance of the Ca^{2+} current) is varied. Start with the default parameter values and generate a 1-parameter bifurcation diagram with *cknot* as bifurcation parameter. Next, generate a 2-parameter bifurcation diagram with *gca* as the second parameter, tracing out the SN and HB

bifurcations. Do this for $cknot \in [-0.2, 0.4]$ and $gca \in [800, 1100]$. Turn this in, with bifurcation curves labeled.

(5) Using the 2-parameter bifurcation diagram from the previous problem, and some trial and error, find values of gca for which each of the following are true in the 1-parameter diagram (the diagram with $cknot$ as the bifurcation parameter). In each case, construct the 1-parameter diagram with Auto, print it out, and turn it in.

(a) There is one HB between the left SN and the right SN. The periodic branch that emerges from it ends at a homoclinic bifurcation.

(b) There are two HBs between the left and right SNs, and the periodic branch emerging from each terminates with a HM bifurcation.

(c) There are two HBs between the left and right SNs, and these are connected by a single periodic branch.

(d) There are no HBs and both the bottom and top stationary branches of the 1-parameter diagram are entirely stable.