Computational Methods in Biology (Spring 2020)

Genetic Toggle Switch

Due March 6

Write an XPP code for the genetic toggle switch, given by the equations:

$$\frac{dx}{dt} = \frac{\alpha_x}{1 + y^\beta} - x$$

$$\frac{dy}{dt} = \frac{\alpha_y}{1 + \tilde{x}^\beta} - y$$

where

$$\tilde{x} = \frac{x}{1 + \mathrm{IPTG}} .$$

The default parameter values are $\alpha_x = 10$, $\alpha_y = 10$, $\beta = 2$, and IPTG$= 0$. Various initial conditions will be used. We will explore the dynamics of this simple planar system as parameters are varied.

XPP Tips

- To print what's on the xpp screen you can click Graphic Stuff and Postscript. This will allow you to create a postscript file that you can print, or you can convert it to a pdf file by typing (on a linux window) "ps2pdf filename".
- To view a phase plane you will need to put x on the horizontal axis and y on the vertical axis. Time is implicit in the phase plane.
- To compute and see nullclines click Nullcllines New in the main XPP menu (or type NN). The nullcline of the first variable is in red, while that of the second is in green.
- To find a steady state in the phase plane in XPP, click Sing pts Go (or type SG). But this will only find one steady state. If there are more than one, then type Sing pts Mouse (or type SM) and click near where you think a singular point will be. Once an equilibrium is located you will be asked if you'd like eigenvalues printed. If you say yes, the number of positive and negative real eigenvalues will be shown, as well as the number of complex eigenvalues with positive or negative real part. If you invoke xpp from a linux window, the values of the eigenvalues will be printed on this window. If asked to print the strong set say NO. If the equilibrium is a saddle ploint then you will be asked if you want to see invariant sets. Say YES, since these are the four branches of the stable and unstable manifolds.

- In XPP, nodes and foci are represented as circles, and saddle points are represented as triangles.
- To calculate and see various trajectories in the phase plane click Initialconds and Mouse (or type IM), then click on points where you'd like a trjectory to start (this feeds in the location as initial conditions).

AUTO Tips

AUTO is a stand-alone program that was incorporated into XPP (so XPP is now called XPPAUT). It allows the user to construct bifurcation diagrams, using the XPP code to determine the equilibrium point from which the bifurcation diagram is constructed. That is, a bifurcation diagram must start from an equilibrium point, and XPP is used to find the equilbrium point. AUTO is then used to construct the diagram.

- To invoke AUTO from within XPP click on File and then Auto. This opens up an AUTO window. To construct a bifurcation diagram you first decide on a bifurcation parameter and an initial value of that parameter. Run XPP with that value several times, using Initial Conditions Go (IG) or Initial Conditions Mouse (IM) followed by Initial Last (IL) 2 or 3 times, and watching to see that your variables are very close to a stable equilibrium. IL will read the last values of the variables in as initial conditions, and these are what AUTO will use as the coordinates of the steady state.
- Next click on Parameter in the AUTO window. Put the name of the parameter that you want to use as your bifurcation parameter as Par1. When done, click OK.
- Next click on Axes and HiLo. Par1 is automatically put onto the X-axis. Put one of the variable names as the Y-axis. Then enter the parameter interval that you want to explore (Xmin and Xmax), and your best guess at the range of values needed for the Y-axis (Ymin and Ymax).
- Next click on Numerics. Ntst is the number of collocation points, and you typically don't need to change it. Nmax is the maximum number of steps to take when making bifurcation curves. I usually set it at 2000. NPr sets frequency of printing a label on a bifurcation curve. Note that bifurcation points are automatically labeled, so this just applies to points that are not bifurcations. I usually set it to 5000, which makes it so that only bifurcation points are labeled. (You can restart or continue a bifurcation diagram only from a labeled point, so using a smaller NPr would give you more potential continuation points, but I typically don't find them useful.) Ds is the initial step size. Leave it as is, unless you want to move to the left, in which case set Ds to a negative number. You won't ever need to change the next three.

Dsmax is the maximum step size, which I often make smaller than the default. I'll often use Dsmax=0.1 or 0.2, particularly for periodic branches. Par Min and Par Max are the minimum and maximum values of the bifurcation parameters. They typically match what you used in the Axes window.

- Finally, click on Run and Steady state. This will make a stationary bifurcation diagram, starting from the steady state that you achieved in the XPP window. You can start from a different steady state and make a second bifurcation curve to superimpose on this one.
- You can save the diagram (Save diagram) and read it into AUTO later (Load diagram). If you just want to print the bifurcation diagram, then click File and then Postscript. The defualt name for the saved file is diagram.dat.
- A stable branch is denoted by a thick red curve, and an unstable branch by a thin black curve. Changes in stability should only occur at bifurcation points. If the curve changes color at a point other than a bifurcation point then this is a numerical error, and can be fixed by re-doing the diagram but with a smaller Dsmax. Just try cutting it in half and re-running, don't make it too tiny. When re-running you have to go back to the XPP window, reset the bifurcation parameter to its original value, and then converge to the steady state. Only then should you return to AUTO to do a new diagram (with a smaller Dsmax).

Exercises

The work below should be turned in. Some figures are best drawn by hand, based on what you see in an xpp window. You could then color the various curves and generally make things clearer than what appears if you just print out the xpp screen. The objective here is clarity, and color helps with this. So does proper labeling, so be sure to label all of your graphs. In your responses, please use complete sentences and clearly describe figures.

(1) Using the default parameter values, construct a phase portrait of the system. Include the nullclines, equilibria and their stability, and enough trajectories so that the flow of the system is clear. What are the basins of attraction of the stable equilibria? What is the separatrix that separates the basins? How is it related to the invariant manifolds of the saddle point? Include the separatrix in your sketch.

(2) Change the IPTG parameter to 0.3. How does this effect the geometry of the phase portrait (that is, the nullclines, equilibria, and separatrix)?

(3) As you increase IPTG further what happens to the equilibria? At approximately what value of IPTG does a bifurcation occur? What type of bifurcation is it?

(4) Now construct a bifurcation diagram with IPTG as the bifurcation parameter. Start with IPTG=0. This will give one branch of the bifurcation diagram. To get another branch reset IPTG to 0, but this time start your bifurcation diagram from the other stable equilibrium (the system is bistable when IPTG=0). To do this, use IM to get into the basin of the other stable steady state, then use IL a couple of times to converge to that point. Now click Run again in AUTO, and say NO when it asks you if you'd like to delete the old diagram. This should give you a second branch.

(5) One of the two branches that you have constructed should also contain a branch of unstable equilibria. What kind of equilibria are they? Is the value of IPTG where a bifurcation occurs consistent with what you found earlier when using a phase plane approach? What type of bifurcation is it? Print out and turn in your bifurcation daigram.

(6) We will now investigate the effects of varying the cooperativity parameter β. Set IPTG=0 so that there is no inducer. What happens to the nullclines as β is increased from 1 to 1.5 in small increments? What type of bifurcation do you think occurs, and at what value of β?

(7) Construct a bifurcation diagram with β from 1 to 2, and turn it in. (Plot y vs. β, although you could also plot x vs. β.) Note that you will need to change the bifurcation parameter in the AUTO Parameter menu. Now what kind of bifurcation is there? Does it match your expectations from the nullcline analysis, or did you have to re-evaluate after doing the diagram?

(8) Redo the last problem, but with $\alpha_x = 9$. Start by looking in the phase plane and varying β, and then constructing a bifurcation diagram with β as bifurcation parameter. What has changed when compared with the last problem? Why?