Biochemical Circuits: Bistability

For this lab we will be analyzing the bistability of biochemical systems via modeling of a toggle switch system. Complete the following simulations and address any included questions. For your submission, include any requested figures, answers to all included questions, and your MATLAB code.

Problem 1: Bistability of The Toggle Switch Network (Demo)

Bistability refers to the phenomenon where a system can have multiple steady states with the same set of parameters. Here, we will investigate the effects of initial conditions on steady state solutions for a bistable system. Consider the toggle switch system described by the pair of ordinary differential equations below.

$$(1) \quad \frac{du}{dt} = \frac{\alpha_1}{1 + v^{\beta}} - u$$

$$(2) \quad \frac{dv}{dt} = \frac{\alpha_2}{1 + u^{\gamma}} - v$$

Complete the following steps using parameter values of $\alpha_1 = 2, \alpha_2 = 2, \beta = 4, \gamma = 4$.

a) Write a function in MATLAB that can be passed into one of MATLAB's build in ODE solvers that calculates the rates of change $dydt = [\frac{du}{dt}, \frac{dv}{dt}]$ give time t, a vector of concentrations $y = [u, v]$, and a vector of parameter values $p = [\alpha_1, \alpha_2, \beta, \gamma]$. What are $\frac{du}{dt}$ and $\frac{dv}{dt}$ given $t = 0$, $y = [0.1\ 2]$, and the specified parameter values?

b) Write a function in MATLAB that outputs a matrix of concentrations $y = \begin{bmatrix} u_{t=0} & v_{t=0} \\ \cdots & \cdots \\ u_{t=t_f} & v_{t=t_f} \end{bmatrix}$ given a vector of initial conditions $y_0 = [u_0, v_0]$, a vector of timepoints $tspan$ from time 0 to t_f, and a vector of parameter values $p = [\alpha_1, \alpha_2, \beta, \gamma]$ using MATLAB's ODE solver ode45. Simulate the model with the specified parameter values with initial conditions $(u, v) = (0.1, 2.5), (0.9, 1.1), (1,1), (1.1, 0.9), (2.5, 0.1)$. Generate two plots of u and v v. time containing curves for each of the initial conditions simulated on the same axes over a timespan from 0 to 8. Additionally, generate a plot of u v. v with curves for each initial condition plotted on the same axes (For this plot label each curve based on the initial value of v, also for the initial condition $(u, v) = (1,1)$ change your marker in the plot function so a single point is visible). What effects do the initial conditions have on the steady state at which the system converges? What can we infer about the stability of each steady state obtained in Problem 1 from analysis of these plots?

Bifurcation plots are used to illustrate the range of parameter values in which a system exhibits bistability. Generally speaking, a bifurcation plot is a plot of the steady state value of a species in a system (e.g., v) vs. a model parameter. To generate a bifurcation plot varying a specific parameter P over the range p_i to p_f we use the following algorithm:

1. Determine the model steady state with the value of P at p_i via ODE simulation or solving numerically. If using ODE simulation estimate an initial condition value by analyzing nullclines. If solving numerically, use the same value as an initial guess. Record the determined steady state value.

2. Slightly increase the value of P and calculate the new steady state of the system using the determined steady state in step 1 as the initial condition/guess. Use your new steady state value as the initial guess for the next point in the range of P values.
3. Repeat step 2 until steady state solutions have been determined over the range $[p_i, p_f]$.
4. Repeat steps 1-3 moving in the reverse direction, from p_f to p_i using the steady state value at $P = p_f$ as your first initial guess.

We will now use the above stated algorithm to generate a bifurcation plot observing the effects of the parameter α_1 on the steady state concentration of v:

c) Generate a bifurcation plot illustrating the steady state concentrations of v over a range of α_1 values from 10^0 to 10^2 (see MATLAB's logspace command, which unlike the linspace command creates a vector of evenly spaced points on a log scale). For this, combine equations (1) and (2) into a single equation that outputs $\frac{dv}{dt}$ given v and α_1 by first calculating u with equation (1) and substituting into equation (2). Use this equation and MATLAB's fzero function to solve for the steady state of the system, v, given the value of α_1 following the steps in the general algorithm for creating a bifurcation plot. Over what range of parameters does the system appear to be bistable?

Problem 2: Generation and Analysis of Nullcline Plots

Plotting nullclines is a useful method for analyzing steady state behavior of biochemical circuits. Consider the same toggle switch system represented by the ordinary differential equations:

$$(1) \quad \frac{du}{dt} = \frac{\alpha_1}{1 + v^\beta} - u$$

$$(2) \quad \frac{dv}{dt} = \frac{\alpha_2}{1 + u^\gamma} - v$$

The nullclines of this system are a set of two curves in the (u, v) axis where u and v remain constant ($\frac{du}{dt} = 0$ and $\frac{dv}{dt} = 0$). We will use two different methods in MATLAB to plot the nullclines for this system the parameters $\alpha_1 = 2, \alpha_2 = 2, \beta = 4, \gamma = 4$.

a) Analytically solve for the points on the nullcline using equations (1) and (2) by solving the $\frac{du}{dt}$ =0 for u as a function of v and $\frac{dv}{dt} = 0$ for v as a function of u. Plot the nulllcines for equations (1) and (2) over a range of u and v values from 10^{-2} to 10^2 on a log scale. To this end generate a vector of values of one of the dependent variable that uniformly space in log space and use the equations for null-clines to generate values for another. Plot the results on the same graph.
b) Now employ an alternative, more general way to plot the nullclines. For this, use a separate figure and use MATLABs fimplicit function that can generate a plot for a function given in an implicit form f(x,y)=0 so that you don't have to solve for nullclines analytically. Use MATLAB documentation help to determine how to use fimplicit and make your nullcline plot as close as possible to that in part (a). How many times do the nullclines intersect? What to these intersections represent?
c) Use MATLAB's fsolve command to determine the intersections of the nullclines on your plot, using initial guesses close to where the intersections appear to be (Hint: You can pass your function from part a) into fsolve, and since there is no time dependence you can just set t = 0). What are the values of u and v at each intersection?

Problem 3: Analysis of IPTG Inducible Toggle Switch System

Consider the slightly modified model of a toggle switch system that includes an inducer for expression of repressor v:

$$(1) \quad \frac{du}{dt} = \frac{\alpha_1}{1 + v^{\beta}} - u$$

$$(2) \quad \frac{dv}{dt} = \frac{\alpha_2}{1 + \left(\frac{u}{\left(1 + {IPTG}/{K}\right)^{\eta}}\right)^{\gamma}} - v$$

Here we aim to analyze the bistability of this system by generating a bifurcation plot and also observing how parameter values influence the toggle switch behavior. Use the parameter values $\alpha_1 = 156.25, \alpha_2 = 15.6, \beta = 2.5, \gamma = 1, K = 2.9618\ x\ 10^{-5}, \eta = 2.0015$ for the following questions.

a) Generate a bifurcation plot for the system showing the effects of IPTG concentration on the steady state value of v following the same steps that were done in Problem 1 part c). (Hint: fzero will likely try negative numbers at certain points while solving for steady state values in this case. To avoid errors, use the absolute value of v in your function for calculating $\frac{dv}{dt}$, and on the output of fzero. In other words, the first line of your function for $\frac{dv}{dt}$ should be v = abs(v), and you should record the absolute value of the output of fzero for your steady state values.) Use a range of IPTG concentrations from 10^{-7} to 10^{-2} logarithmically spaced. Over what range of IPTG concentrations does the system appear to be unstable?

b) Generate a plot of v. vs time over a timespan of 0 to 12. From timepoints 0 to 6 set the IPTG concentration to 100 and from timepoints 6 to 12 set the IPTG concentration to zero. Use $(u, v) = (0,0)$ as the initial condition during your first simulation period and the steady state value of (u, v) at the end of your first simulation period as the initial conditions of your second simulation period. What happens to the values of v when you remove IPTG from the system?

c) Repeat part b) but with the value of β set to 1. How do your predictions compare to those from part b)?