Project 2: The Bistable Genetic Switch

Due March 15, 2022

We first consider a simplified model of a bistable genetic switch. Suppose $u(t)$ and $v(t)$ represents the concentration of repressor 1 and 2, respectively. Then, we can write the model as

$$\begin{aligned} u' &= \frac{\alpha_1}{1+v^\beta} - u \\ v' &= \frac{\alpha_2}{1+u^\gamma} - v \end{aligned} \tag{1}$$

where each α_j is the effective rate of synthesis of its respective repressor and β and γ are cooperativity coefficients. We wish to understand the behavior of this model.

1. Read the paper: `https://www.nature.com/articles/35002131`

2. Let's reproduce the analysis of Figure 2. Part of the analysis of a mathematical model will typically include how *robust* the model is to parameters. If the parameters are incredibly sensitive to small changes, then the model may not be a good qualitative representation of the dynamics. On the other hand, if there are large parameter ranges where different behavior can occur that have physical meaning, then this can be one indicator of a good model.

   (a) Derive the equations for the nullclines in terms of the system parameters. What conditions on the parameters are required to have a bistable system (i.e. the behavior in Figure 2a)?

   (b) Choose parameters that will cause the system to exhibit bistable behavior (Figure 2a), monostable behavior in the low state (Figure 2b) and monostable behavior in the high state. Is it possible to have only two fixed points? Why or why not?

3. Plot a phase portrait ofr Eq. (1) using the parameters from Question 2 for the bistable and monostable cases. Identify the nullclines and fixed points in each plot.

4. Simulate Eq. (1) using an RK4 method using the parameter values from Question 2. For the bistable case, use two different initial conditions so that each one converges to a different fixed point. Will the dynamics for the monostable states depend on initial condition? Explain.

5. Add a new third repressor, w, to Eq. (1). Connect them in a ring fashion, such that the first inhibits the second, the second inhibits the third, and the third inhibits the first.

   (a) Analyze the fixed points and stability of this system. Is it possible to have a tristable system? Bistable? Monostable? Give parameter examples for each.

   (b) Using an RK4 method, simulate each possible behavior using the parameters chosen in part (a). Plot the dynamics of each in time.