CALIFORNIA INSTITUTE OF TECHNOLOGY
BioEngineering

BE 250C

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1. *Repressilator.* Using MATLAB, simulate the following simplified version of the Repressilator:

$$\frac{dm_1}{dt} = \frac{k_p}{1 + (\frac{p_3}{K_M})^n} - k_{mdeg} m_1$$

$$\frac{dm_2}{dt} = \frac{k_p}{1 + (\frac{p_1}{K_M})^n} - k_{mdeg} m_2$$

$$\frac{dm_3}{dt} = \frac{k_p}{1 + (\frac{p_2}{K_M})^n} - k_{mdeg} m_3$$

$$\frac{dp_1}{dt} = k_{trans} m_1 - k_{pdeg} p_1$$

$$\frac{dp_2}{dt} = k_{trans} m_2 - k_{pdeg} p_2$$

$$\frac{dp_3}{dt} = k_{trans} m_3 - k_{pdeg} p_3$$

   a) Simulate the system using the following parameters: $k_p = 0.5, n = 2, K_M = 40, k_{mdeg} = 0.0058, k_{pdeg} = 0.0012, k_{trans} = 0.1155$. Assume that $p_3(0) = 100$ and all other species start at 0.

   b) Suppose the protein half-life suddenly decreases by half. Which parameter(s) will change and how? Simulate what happens. What if the protein half-life is doubled? How do these two changes affect the oscillatory behavior?

   c) Now assume that there is leakiness in the transcription process. How does the system's ODE change? Simulate the system with a small leakiness (say, 5e-3) and comment on how it affects the oscillatory behavior.

2. *Glycolytic Oscillations.* In almost all living cells, glucose is broken down into the cell's energy currency, ATP, via the glycolysis pathway. Glycolysis is autocatalytic in the sense that ATP must first be consumed in the early steps before being produced later and oscillations in glycolytic metabolites have been observed experimentally. We will look at a minimal model of glycolysis:

$$\frac{dX}{dt} = \frac{2Vy^a}{1 + y^h} - kx$$

$$\frac{dY}{dt} = (q+1)kx - q\frac{2Vy^a}{1 + y^h} - 1$$

   Note that this system has been normalized such that $Y_{ss} = 1$.

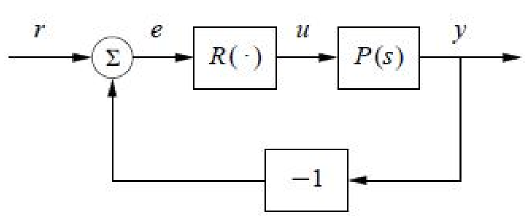
a) While a system may have the potential to oscillate, the behavior still depends on the parameter values. The glycolysis system undergoes multiple *bifurcations* as the parameters are varied. Using linear stability analysis, find the parameter conditions where the system is stable vs. unstable. Next, find the conditions where the system has eigenvalues with nonzero imaginary parts.

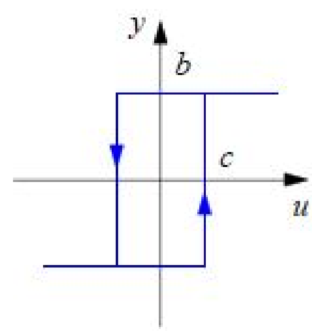
b) Let *q=k=V=1*. Find the relationship between h and a where the system is stable or not. Draw the stability diagram and mark the regions where the system is stable vs. unstable. In the same plot, mark the regions where the system has eigenvalues with nonzero imaginary parts.

c) Let *q=k=V=1*. Choose h and a such that the eigenvalues are unstable and have nonzero imaginary parts. Use these parameter values and simulate the nonlinear system in MATLAB. Sketch the time response of the system starting with initial condition X(0) =1.2, Y(0) = 0.5 (you may use MATLAB or sketch by hand). Comment on what you see compared to what linear stability analysis told you about the system.

3. (Optional) Finding limit cycles for nonlinear systems and understanding how changes in parameters affect the amplitude and period of the oscillation is difficult to do in analytical form. A graphical technique that gives some insight into this problem is the use of *describing functions*, which is described in *Feedback Systems*, Section 9.5. In this problem we will use describing functions for a simple feedback system to approximate the amplitude and frequency of a limit cycle in analytical form.

   Consider the system with the block diagram shown below.





   The block R is a relay with hysteresis whose input/output response is shown on the right and the process transfer function is $P(s) = e^{-s\tau}/s$. Use describing function analysis to determine frequency and amplitude of possible limit cycles. Simulate the system and compare with the results of the describing function analysis.

   (This problem is optional. If you give it a try, we will grade your solutions and use any points to make up for points taken off on other problems.)