CALIFORNIA INSTITUTE OF TECHNOLOGY
Bioengineering and Biology

Bi/BE 250c

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Winter 2011 Due: Jan 13

1. Consider a cascade of three activators X→Y→ Z. Protein X is initially present in the cell in its inactive form. The input signal of X, S_x, appears at time t=0. As a result, X rapidly becomes active and binds the promoter of gene Y, so that protein Y starts to be produced at rate β. When Y levels exceed a threshold K, gene Z begins to be transcribed and translated at rate γ. All proteins have the same degradation/dilution rate α.

   a) What are the concentrations of proteins Y and Z as a function of time?

   b) What is the minimum duration of the pulse S_x such that Z will be produced?

   c) What is response time of protein Z with respect to the time of addition of S_x?

Solution. a) The rate of change of Y is

$$\frac{dY}{dt} = \beta - \alpha Y \tag{1}$$

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The solution to equation (1) is

$$Y(t) = \frac{\beta}{\alpha}(1 - e^{-\alpha t}) \tag{2}$$

given $Y(0) = 0$, and $Y_{st}(t) = \frac{\beta}{\alpha}$.

Let $t = t_z$ be the time Z begins to get transcribed. Let's consider only Y → Z for the moment so we can set $t_z = 0$.

The rate of change of Z is

$$\frac{dZ}{dt} = \gamma - \alpha Z \tag{3}$$

and has solution

$$Z(t) = c_1 + c_2 e^{-\alpha t} \tag{4}$$

We assume that at $t = t_z = 0$, we have zero concentration of Z protein, so $Z(0) = 0$. At $t = \infty$, we assume Z has reached a steady state, and so $\frac{dZ}{dt} = 0 \iff Z_{st}(t) = \frac{\gamma}{\alpha}$. Solving for c_1 and c_2,

$$Z(t) = \frac{\gamma}{\alpha}(1 - e^{-\alpha t})$$

b) When $Y(t) = K$, Z begins to get transcribed. We solve for t_z, the time it takes to start production of Z,

$$t_z = -\frac{1}{\alpha} ln\Big(\frac{\beta - \alpha K}{\beta}\Big)$$

c) The response time $T_{\frac{1}{2}}$ is the time to reach halfway between initial and final concentration levels of Z.

$$T_{1/2} = \textit{time to start Z production } (Y(t) > K)$$
$$+ \textit{ time to reach halfway between initial and final Z concentrations}$$

Since initial Z concentration is 0, and the final concentration is just the steady state concentration, Z_{st},

$$\frac{Z_{st}}{2} = \frac{\gamma}{\alpha}(1 - e^{-\alpha t})$$

$\Longleftrightarrow$

$$t = -\frac{1}{\alpha} ln\Big(1 - \frac{\alpha Z_{st}}{2\gamma}\Big)$$

So

$$T_{\frac{1}{2}} = -\frac{1}{\alpha} ln\Big[\Big(1 - \frac{\alpha Z_{st}}{2\gamma}\Big)\Big(1 - \frac{\alpha K}{\beta}\Big)\Big]$$

Note $T_{1/2} > 0$

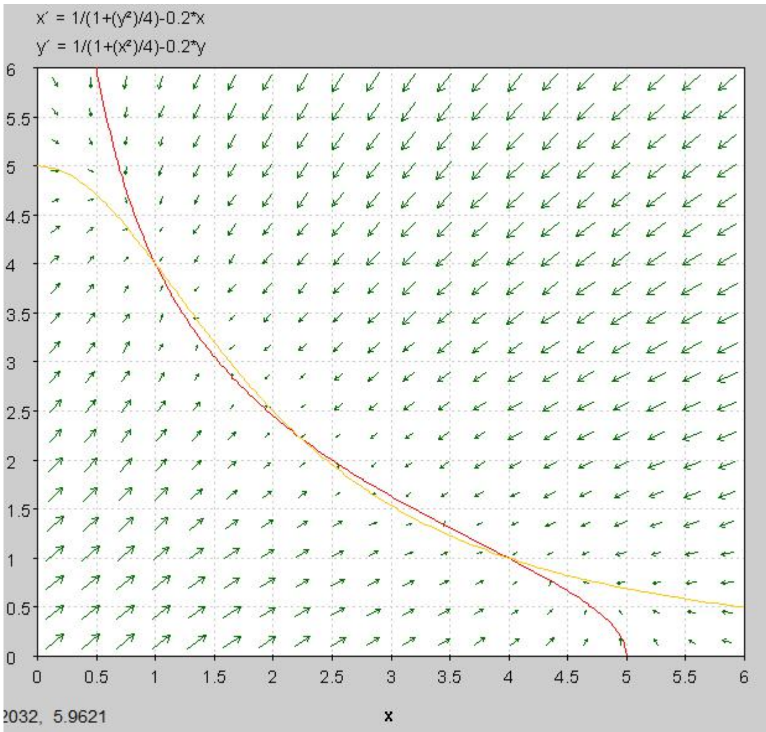
2. Consider a positive transcriptional feedback loop composed of two negative interactions $X \dashv Y$ and $Y \dashv X$.

   a) Write the ODEs for the system above. Assume that the two transcrption/repression mechanisms have the same dynamics and both genes are degraded at the same rate 0.2. Let the basal transcription rate be 1, K=2, n=2.

   b) To solve for the steady states, plot the *nullclines* by solving $\frac{dX}{dt} = 0$ and $\frac{dY}{dt} = 0$ (i.e. solve for $Y = g_1(X)$ where $\frac{dX}{dt} = 0$ and $Y = g_2(X)$ where $\frac{dY}{dt} = 0$ and plot both solutions). The steady states are given by the intersections of the two nullclines.

   c) Plot the time response of X and Y using the following two initial conditions: (X(0),Y(0))=(1, 4) and (4, 1). Next, plot the phase plane of the system using *pplane* in MATLAB. How do the responses change with initial conditions? Describe a situation where this type of interaction would be useful.

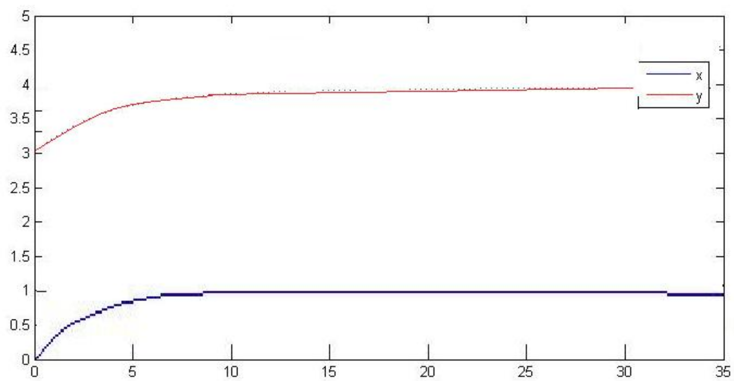
Solution.



a)

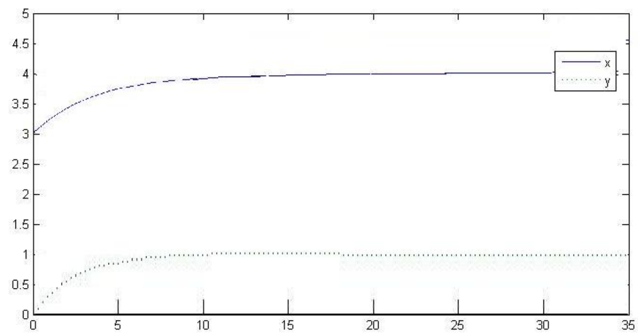
$$\frac{dX}{dt} = \frac{4}{4+Y^2} - 0.2X$$
$$\frac{dY}{dt} = \frac{4}{4+X^2} - 0.2Y$$

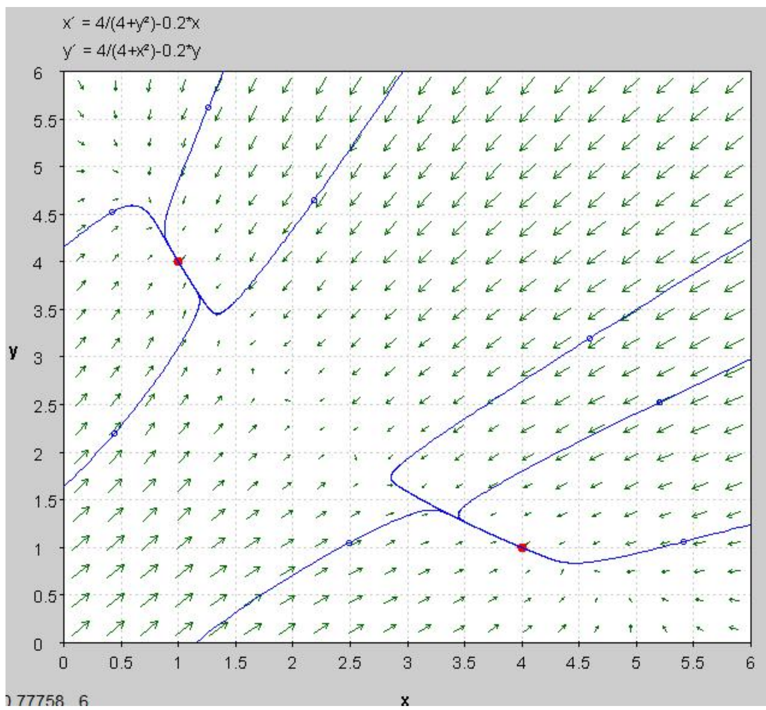
b)



c)

3. Consider the following network $X \to Y$ and $X \to X$.





a) Write the ODEs for the system above. Use basal expression $\beta_X = \beta_Y = 2$ and activation coefficients $K_X = 1$, $K_Y = 2$, $n_1 = n_2 = 2$. The degradation coefficients for X and Y are both 0.5.

b) Plot the vector field using pplane. How many steady states do you observe?

c) Solve for the steady states of the system using the derived ODEs, linearize the system and do a stability analysis.

Solution.

a)

$$\frac{dX}{dt} = \frac{2X^2}{1+X^2} - 0.5X$$

$$\frac{dY}{dt} = \frac{2X^2}{4+X^2} - 0.5Y$$

b) The steady states are (0,0), (3.7321, 0.7769), (0.2679,0.176).
The Jacobians are:

$$J(0,0) = \begin{pmatrix} -0.5 & 0 \\ 0 & -0.5 \end{pmatrix}$$

Eigenvalues are -0.5 and -0.5. (0,0) is stable.

$$J(3.7321, 0.7769) = \begin{pmatrix} -0.4330 & 0 \\ 0.0670 & -0.5 \end{pmatrix}$$

Eigenvalues are -0.5 and -0.4330. (3.7321, 0.7769) is stable.

$$J(0.2679, 0.176) = \begin{pmatrix} 0.4329 & 0 \\ 0.9329 & -0.5 \end{pmatrix}$$

Eigenvalues are -0.5 and 0.4329. (0.2679,0.176) is unstable.