NATIONAL TAIWAN UNIVERSITY,
GRADUATE INSTITUTE OF BIOMEDICAL ENGINEERING AND BIOINFORMATICS
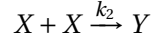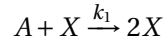
BEBI5009:
Mathematical Modeling of System Biology
Homework 3

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1 4.8.6 Global dynamics from local stability analysis.

a) Consider the chemical reaction network with mass-action kinetics:

$$A + X \xrightarrow{k_1} 2X$$

$$X + X \xrightarrow{k_2} Y$$

$$Y \xrightarrow{k_3} B$$

   i) Write a differential equation model describing the concentrations of X and Y

$$\frac{d[X]}{dt} = -k_1[A][X] + 2k_1[A][X] - k_2[X]^2 = k_1[A][X] - 2k_2[X]^2$$

$$\frac{d[Y]}{dt} = k_2[X]^2 - k_3[Y]$$

   ii) Verify that the system has two steady states.

    At steady-state,

$$\frac{d[X]_{ss}}{dt} = 0 \Rightarrow k_1[A]_{ss}[X]_{ss} - 2k_2[X]_{ss}^2 = 0 \Rightarrow [X]_{ss}(k_1[A]_{ss} - 2k_2[X]_{ss}) = 0$$

$$\Rightarrow [X]_{ss} = 0 \quad or \quad [X]_{ss} = \frac{k_1}{2k_2}[A]$$

    At the same time,

$$\frac{d[Y]_{ss}}{dt} = 0 \Rightarrow k_2[X]_{ss}^2 - k_3[Y]_{ss} = 0 \Rightarrow [Y]_{ss} = \frac{k_2}{k_3}[X]_{ss}^2$$

    Then, we can conclude that there are two steady-state:

$$([X]_{ss}, [Y]_{ss}) = (0, 0) \quad or \quad (\frac{k_1}{k_2}[A], \frac{k_1^2}{4k_2 k_3}[A]^2)$$

   iii) Determine the system Jacobian at the steady states and characterize the local behavior of the system near these points

    Let us denote the concentrations of species [X] as x and [Y] as y. Also, Let us denote the equations derived in (a) by $\frac{d[X]}{dt} = f(x, y)$ and $\frac{d[Y]}{dt} = g(x, y)$. Then,

$$J = \begin{bmatrix} \frac{\partial f(x,y)}{\partial x} & \frac{\partial f(x,y)}{\partial y} \\ \frac{\partial g(x,y)}{\partial x} & \frac{\partial g(x,y)}{\partial y} \end{bmatrix} = \begin{bmatrix} k_1[A] - 2k_2 x & 0 \\ 2k_2 x & -k_3 \end{bmatrix}$$

    When the system is at steady-state that $([X]_{ss}, [Y]_{ss}) = (0, 0)$:

$$J = \begin{bmatrix} k_1[A] & 0 \\ 0 & -k_3 \end{bmatrix}$$

Eigen values of this Jacobian matrix are $k_1[A]$ and $-k_3$. Since one of is postive and the other is negative, the steady-state here is a saddle point. When the system is at steady-state that $([X]_{ss}, [Y]_{ss}) = (\frac{k_1}{k_2}[A], \frac{k_1^2}{4k_2k_3}[A]^2)$:

$$J = \begin{bmatrix} -k1[A] & 0 \\ 2k_1[A] & -k_3 \end{bmatrix}$$

Eigen values of this Jacobian matrix are $-k_1[A]$ and $-k_3$. Since both eigen value of Jacobian matrix are negative, the steady-state here is a stable node.

iv) By referring to the network, provide an intuitive description of the system behaviour starting from any initial condition for which [X] = 0.

Since the system is without X, the only reaction will happen in this system is $Y \to B$. The reaction will consume Y until that there is no Y any more.

v) Sketch a phase portrait for the system that is consistent with your conclusions from (iii) and (iv).
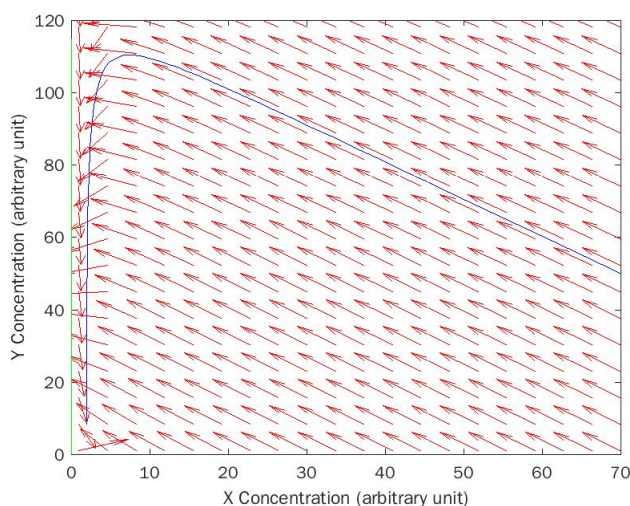
The green line is a trajectory with a [X]=0 initial condition. You can see that it has a steady state that both [X] and [Y] are zero. The blue line is a trajectory of another steady-state.

b) Repeat for the system

$$A + X \xrightarrow{k_1} 2X$$

$$X + Y \xrightarrow{k_2} 2Y$$

$$Y \xrightarrow{k_3} B$$
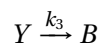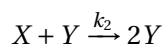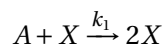
In this case, you'll find that the non-zero steady-state is a center: it is surrounded by concentric periodic trajectories.

i)

$$\frac{d[X]}{dt} = -k_1[A][X] + 2k_1[A][X] - k_2[X][Y] = k_1[A][X] - k_2[X][Y]$$

$$\frac{d[Y]}{dt} = -k_2[X][Y] + 2k_2[X][Y] - k_3[Y] = k_2[X][Y] - k_3[Y]$$

ii) At steady-state,

$$\frac{d[X]_{ss}}{dt} = 0 \Rightarrow k_1[A]_{ss}[X]_{ss} - k_2[X]_{ss}[Y]_{ss} = 0 \Rightarrow [X]_{ss}(k_1[A]_{ss} - k_2[Y]_{ss}) = 0$$

$$\Rightarrow [X]_{ss} = 0 \quad or \quad [Y]_{ss} = \frac{k_1}{k_2}[A]$$

$$\frac{d[Y]_{ss}}{dt} = 0 \Rightarrow k_2[X]_{ss}[Y]_{ss} - k_3[Y]_{ss} = 0 \Rightarrow [Y]_{ss}(k_2[X]_{ss} - k_3) = 0$$

$$\Rightarrow [Y]_{[ss]} = 0 \quad or [X]_{ss} = \frac{k_3}{k_2}$$

Then, we can conclude that there are two steady-state:

$$([X]_{ss}, [Y]_{ss}) = (0,0) \quad or \quad (\frac{k_3}{k_2}, \frac{k_1}{k_2}[A])$$

iii) Let us denote the concentrations of species [X] as x and [Y] as y. Also, Let us denote the equations derived in (a) by $\frac{d[X]}{dt} = f(x,y)$ and $\frac{d[Y]}{dt} = g(x,y)$. Then,

$$J = \begin{bmatrix} \frac{\partial f(x,y)}{\partial x} & \frac{\partial f(x,y)}{\partial y} \\ \frac{\partial g(x,y)}{\partial x} & \frac{\partial g(x,y)}{\partial y} \end{bmatrix} = \begin{bmatrix} k_1[A] - k_2 y & -k_2 x \\ k_2 y & k_2 x - k_3 \end{bmatrix}$$

When the system is at steady-state that $([X]_{ss}, [Y]_{ss}) = (0,0)$:

$$J = \begin{bmatrix} k_1[A] & 0 \\ 0 & -k_3 \end{bmatrix}$$

Eigen values of this Jacobian matrix are $k_1[A]$ and $-k_3$. Since one of is postive and the other is negative, the steady-state here is a saddle point. When the system is at steady-state that $([X]_{ss}, [Y]_{ss}) = (\frac{k_3}{k_2}, \frac{k_1}{k_2}[A])$:

$$J = \begin{bmatrix} 0 & -k_3 \\ k_1[A] & 0 \end{bmatrix}$$

Eigen values of this Jacobian matrix are roots of $\lambda^2 = -k_1 k_3[A]$. Since both eigen value of Jacobian matrix don't have zero real parts, the steady-state here is a center, which has periodic trajectories.

iv) The situation is the same as counterpart of part (a). Since the system is without X, the only reaction will happen in this system is $Y \to B$. The reaction will consume Y until that there is no Y any more.

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v) The simulation result is shown below:
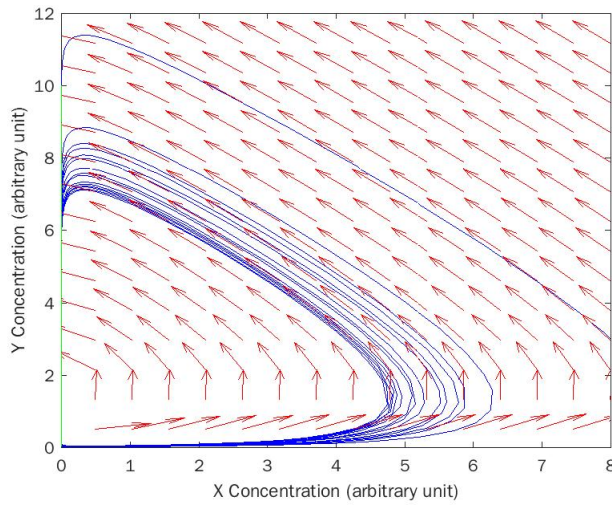
The green line is a trajectory with a [X]=0 initial condition. You can see that it has a steady state that both [X] and [Y] are zero. The blue line is a trajectory of another steady-state, which is a center.

2 4.8.8 Linearization.

Consider the simple reaction system $\rightarrow S \rightarrow$, where the reaction rates are

$$production : V_0 \qquad consumption : \frac{V_{max}[S]}{K_M + [S]}$$

a) Write the differential equation that describes the dynamics in s = [S]. Find the steady state. Next, approximate the original system by linearizing the dynamics around the steady state. This approximation takes the form of a linear differential equation in the new variable $x(t) = s(t) - s^{ss}$.

It's intutive to construct the system:

$$f(s) = \frac{ds}{dt} = V_0 - \frac{V_{max}s}{K_M + s}$$

and we can find steady state.

$$\frac{ds^{ss}}{dt} = V_0 - \frac{V_{max}s^{ss}}{K_M + s^{ss}} = 0 \Rightarrow s^{ss} = \frac{K_M V_0}{V_{max} - V_0}$$

Then, we can approximate original system by linearizing the dynamics around the steady

state.

$$f(s) \approx f(s^{ss}) + \frac{df}{ds}\big|_{s=s^{ss}}(s - s^{ss})$$

$$= 0 + \left(-\frac{V_{max}(K_M + s^{ss}) - V_{max}s^{ss}}{(K_M + s^{ss})^2}\right)(s - s^{ss})$$

$$= -\frac{V_{max}K_M}{(K_M + s^{ss})^2}\big)(s - s^{ss})$$

$$\Rightarrow f(x) = -\frac{V_{max}K_M}{(K_M + s^{ss})^2})x(t) = -\frac{V_{max}K_M}{(K_M + \frac{K_M V_0}{V_{max}-V_0})^2})x(t) = -\frac{V_{max}}{K_M(1 + \frac{V_0}{V_{max}-V_0})^2})x(t)$$

b) Take parameter values $V_0 = 2$, $V_{max} = 3$, and $K_M = 1$ and run simulations of the nonlinear and linearized systems starting at initial conditions [S] = 2.1, [S] = 3, and [S] = 12. Comment on the discrepancy between the linear approximation and the original nonlinear model.

The simulation result is shown below.
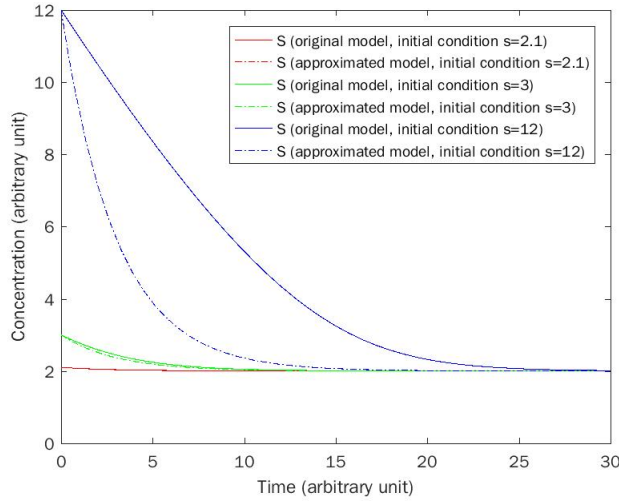
The steady-state concentration of [S] is

$$s^{ss} = \frac{K_M V_0}{V_{max} - V_0} = \frac{1 \times 2}{3 - 2} = 2$$

which is no matter what initial condition of the system. Although all linearized model can predict the same steady-state under different initial conditions, the transient of the systems have discrepancy between the linear approximation and the original nonlinear model. Larger the difference between inital condition and steady-state concentration, more discrepancy exist. The linear approximations here always achieve equlibriums faster and have higher initial consumption rates than original non-linear models.

3 4.8.13 Sensitivity analysis: reversible reaction.

Consider the reversible reaction with mass-action rate constants as shown.

$$A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} A*$$
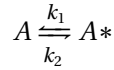
Let T be the total concentration of A and A*.

a) Solve for the steady-state concentration of A* and verify that an increase in k_1 leads to an increase in $[A*]^{ss}$.

First, we can write down these relationships:

$$\frac{d[A]}{dt} = -k_1[A] + k_2[A*]$$

$$\frac{d[A*]}{dt} = k_1[A] - k_2[A*]$$

$$T = [A] + [A*]$$

Then, we can utilize differential equation of one of species and total concentration of A and A*.

$$\frac{d[A]^{ss}}{dt} = -k_1[A]^{ss} + k_2[A*]^{ss} = -k_1[A]_{ss} + k_2(T - [A]^{ss}) = -(k_1 + k_2)[A]^{ss} + k_2 T = 0$$

$$\Rightarrow [A]^{ss} = \frac{k_2 T}{k_1 + k_2}$$

$$\Rightarrow [A*]^{ss} = T - [A]^{ss} = \frac{k_1 T}{k_1 + k_2}$$

To verify the statement of the question, we can simply take derivative of $[A*]^{ss}$.

$$\frac{d[A*]^{ss}}{dk_1} = \frac{d(\frac{k_1 T}{k_1 + k_2})}{dk_1} = \frac{T(k_1 + k_2) - k_1 T}{(k_1 + k_2)^2} = \frac{k_2 T}{(k_1 + k_2)^2} > 0$$

where the positive slope verifies that the increasement in k_1 will lead to an increase in $[A*]^{ss}$

b) Use parametric sensitivity analysis to determine whether the steady state concentration of A* is more sensitive to a 1 % increase in T or a 1 % increase in k_1. Does the answer depend on the values of the parameters?

First, we can extend the result of (a).

$$\frac{\frac{d[A*]^{ss}}{[A]^{ss}}}{\frac{dk_1}{k_1}} = \frac{d[A*]^{ss}}{dk_1} \frac{k_1}{[A*]^{ss}} = \frac{k_2 T}{(k_1 + k_2)^2} \frac{k_1}{\frac{k_1 T}{(k_1 + k_2)}} = \frac{k_2}{k_1 + k_2}$$

Then, we can also derive the relative sensitivity of T.

$$\frac{\frac{d[A*]^{ss}}{[A]^{ss}}}{\frac{dT}{T}} = \frac{d[A*]^{ss}}{dT}\frac{T}{[A*]^{ss}} = \frac{k_1}{k_1 + k_2}\frac{T}{\frac{k_1 T}{k_1 + k_2}} = 1$$

Finally, we can conclude that the steady state concentration of A* is more sensitive to a 1 % increase in T than a 1 % increase in k_1, because $\frac{k_2}{k_1 + k_2} < 1$ and it's independent to the values of the parameters.