NATIONAL TAIWAN UNIVERSITY,
GRADUATE INSTITUTE OF BIOMEDICAL ENGINEERING AND BIOINFORMATICS
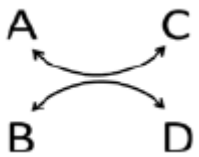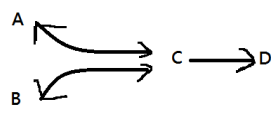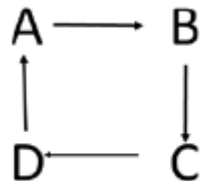
# Mathematical Modeling of System Biology Homework 1

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Complete the following table. Assume mass action kinetics for all reaction mechanisms.

	Interaction graph	Rate equation scheme	ODE
a)	$\rightarrow A \rightarrow$	$\xrightarrow{k_1} A$ $A \xrightarrow{k_2}$	$\frac{d[A]}{dt} = k_1 - k_2\,[A]$
b)	A, B, C, D crossover graph	$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C + D$	$\frac{d[A]}{dt} = -k_1\,[A]\,[B] + k_{-1}\,[C]\,[D],$ $\frac{d[B]}{dt} = -k_1\,[A]\,[B] + k_{-1}\,[C]\,[D],$ $\frac{d[C]}{dt} = k_1\,[A]\,[B] - k_{-1}\,[C]\,[D],$ $\frac{d[D]}{dt} = k_1\,[A]\,[B] - k_{-1}\,[C]\,[D]$
c)	A, B, C, D graph	$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} D$	$\frac{d[A]}{dt} = -k_1[A][B] + k_{-1}[C]$ $\frac{d[B]}{dt} = -k_1[A][B] + k_{-1}[C]$ $\frac{d[C]}{dt} = k_1[A][B] - (k_{-1}+k_2)[C]$ $\frac{d[D]}{dt} = k_2[C]$
d)	A, B, C, D square cycle graph	$A \xrightarrow{k_1} B$ $B \xrightarrow{k_2} C$ $C \xrightarrow{k_3} D$ $D \xrightarrow{k_4} A$	$\frac{d[A]}{dt} = -k_1\,[A] + k_4\,[D]$ $\frac{d[B]}{dt} = -k_2\,[B] + k_1\,[A]$ $\frac{d[C]}{dt} = -k_3\,[C] + k_2\,[B]$ $\frac{d[D]}{dt} = -k_4\,[D] + k_3\,[C]$
e)	A, A, C graph	$A + A \xrightarrow{k_1} C$	$\frac{d[A]}{dt} = -2k_1\,[A]^2,$ $\frac{d[C]}{dt} = k_1\,[A]^2$

1.1 PROBLEM SET 2.4.7 NETWORK MODELLING.

a) Consider the closed reaction network shown below:
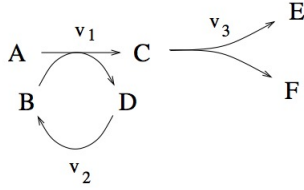
with reaction rates v_i as indicated. Suppose that the reaction rates are given by mass action as $v_1 = k_1 [A] [B]$, $v_2 = k_2 [D]$ and $v_3 = k_3 [C]$.

i) Construct a differential equation model for the network. Use moiety conservations to reduce your model to three differential equations and three algebraic equations.

Initially, we can construct a set of differential equations of every species.

$$\frac{d[A]}{dt} = -v_1, \qquad \frac{d[B]}{dt} = -v_1 + v_2, \qquad \frac{d[C]}{dt} = v_1 - v_3,$$

$$\frac{d[D]}{dt} = v_1 - v_2, \qquad \frac{d[E]}{dt} = v_3, \qquad \frac{d[F]}{dt} = v_3$$

Then, we can further combine many differential equations to make this set of equations smaller, because there are only three independent variables. Actually, we only need three linearly independent equations. That is, the three differential equations can be derived by moiety conservations:

$$\frac{d[A]}{dt} + \frac{d[C]}{dt} + \frac{d[E]}{dt} = 0, \qquad \frac{d[A]}{dt} + \frac{d[C]}{dt} + \frac{d[F]}{dt} = 0, \qquad \frac{d[B]}{dt} + \frac{d[D]}{dt} = 0$$

where the three algebraic equations are

$$v_1 = k_1 [A] [B], \qquad v_2 = k_2 [D], \qquad v_3 = k_3 [C]$$

ii) Solve for the steady-state concentrations as functions of the rate constants and the initial concentrations. (Note, because the system is closed, some of the steady-state concentrations are zero.)

Let us denote by a_0, b_0 and c_0 the initial concentration. According to the three differential equations derived from i), we can further derive :

$\frac{d[A]}{dt} + \frac{d[C]}{dt} + \frac{d[E]}{dt} = 0 \Rightarrow \frac{d([A]+[C]+[E])}{dt} = 0 \Rightarrow [A] + [C] + [E] = constant = a_0 + c_0 + e_0$

$\frac{d[A]}{dt} + \frac{d[C]}{dt} + \frac{d[F]}{dt} = 0 \Rightarrow \frac{d([A]+[C]+[F])}{dt} = 0 \Rightarrow [A] + [C] + [F] = constant = a_0 + c_0 + f_0$

$\frac{d[B]}{dt} + \frac{d[D]}{dt} = 0 \Rightarrow \frac{d([B]+[D])}{dt} = 0 \Rightarrow [B] + [D] = constant = b_0 + d_0$

These equations should be hold all the time. Let us denote by $[I]_{ss}$ the steady state concentration of the species I. Then, we can further derive that:

$[A]_{ss} + [C]_{ss} + [E]_{ss} = [C]_{ss} + [E]_{ss} = a_0 + c_0 + e_0$

$$[A]_{ss} + [C]_{ss} + [F]_{ss} = [C]_{ss} + [F]_{ss} = a_0 + c_0 + f_0$$

It's because that there is no supply for A, A will be zero eventually. Additionally, $v_1 = k_1 [A]_{ss} [B]_{ss} = 0$ at steady state will induce that there is no supply for C and D either, so we can conclude that
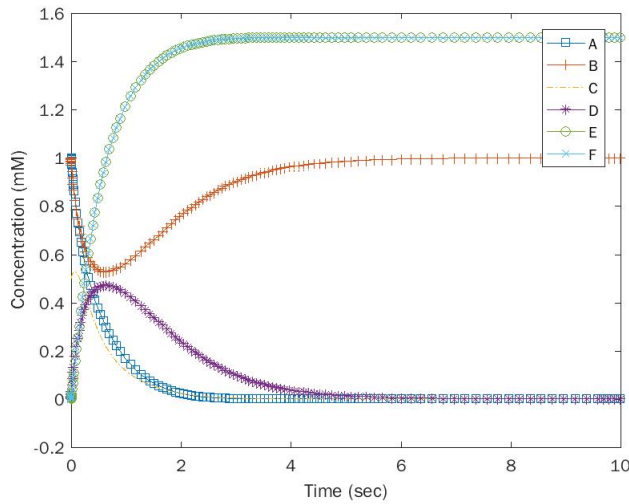
$$[C]_{ss} = 0 \Rightarrow [E]_{ss} = a_0 + c_0 + e_0, [F]_{ss} = a_0 + c_0 + e_0$$
$$[D]_{ss} = 0 \Rightarrow [B]_{ss} = b_0 + d_0$$

by further substituting the concentration at steady state back to the constant condition derived above. In summary, $[A]_{ss} = 0, [B]_{ss} = b_0 + d_0, [C]_{ss} = 0, [D]_{ss} = 0, [E]_{ss} = a_0 + c_0 + e_0, [F]_{ss} = a_0 + c_0 + f_0$

iii) Verify your result in part (ii) by running a simulation of the system from initial conditions (in mM) of $([A], [B], [C], [D], [E], [F]) = (1, 1, \frac{1}{2}, 0, 0, 0)$. Take rate constants $k_1 = 3/\text{mM/sec}$, $k_2 = 1/\text{sec}$, $k_3 = 4/\text{sec}$.

The simulation concentration profile can be seen in following figure:

As you can see, the steady state concentration of each species are equal to the result of part (ii). That is, $[A]_{ss} = 0$, $[B]_{ss} = b_0 + d_0 = 1$, $[C]_{ss} = 0$, $[D]_{ss} = 0$, $[E]_{ss} = a_0 + c_0 + e_0 = 1.5$, $[F]_{ss} = a_0 + c_0 + f_0 = 1.5$

b) Next consider the open system shown below:
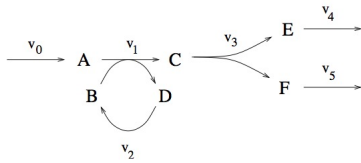
with reaction rates vi as indicated. Suppose that the reaction rates are given by mass action as $v_0 = k_0$, $v_1 = k_1 [A][B]$, $v_2 = k_2 [D]$, $v_3 = k_3 [C]$, $v_4 = k_4 [E]$, and $v_5 = k_5 [F]$.

i) Construct a differential equation model for the network. Identify any moiety conservations in the network.

The thoughts here are similar to part (a). Initially, we can construct a set of differential equations of every species.

$$\frac{d\,[A]}{dt} = v_0 - v_1, \qquad \frac{d\,[B]}{dt} = -v_1 + v_2, \qquad \frac{d\,[C]}{dt} = v_1 - v_3,$$
$$\frac{d\,[D]}{dt} = v_1 - v_2, \qquad \frac{d\,[E]}{dt} = v_3 - v_4, \qquad \frac{d\,[F]}{dt} = v_3 - v_5$$

Then, we can further combine many differential equations. Then, the three moiety conservations can be derived:

$$\frac{d\,[A]}{dt} + \frac{d\,[C]}{dt} + \frac{d\,[E]}{dt} = v_0 - v_4, \quad \frac{d\,[A]}{dt} + \frac{d\,[C]}{dt} + \frac{d\,[F]}{dt} = v_0 - v_5, \quad \frac{d\,[B]}{dt} + \frac{d\,[D]}{dt} = 0$$

where the six algebraic equations are

$$v_0 = k_0, \quad v_1 = k_1\,[A]\,[B], \quad v_2 = k_2\,[D], \quad v_3 = k_3\,[C], \quad v_4 = k_4\,[E], \quad v_5 = k_5\,[F]$$

ii) Solve for the steady state as a function of the rate constants and the initial concentrations.

We can first derive following mathematical relationships by using the fact that all change rates of species equals to zero at steady state and moiety conservations, that is:

$\frac{d[A]}{dt} + \frac{d[C]}{dt} + \frac{d[E]}{dt} = v_0 - v_4 = v_0 - k_4\,[E]_{ss} = 0 \Rightarrow [E]_{ss} = \frac{v_0}{k_4} = \frac{k_0}{k_4}$

$\frac{d[A]}{dt} + \frac{d[C]}{dt} + \frac{d[F]}{dt} = v_0 - v_5 = v_0 - k_5\,[F]_{ss} = 0 \Rightarrow [F]_{ss} = \frac{v_0}{k_5} = \frac{k_0}{k_5}$

$\frac{d[B]}{dt} + \frac{d[D]}{dt} = 0 \Rightarrow \frac{d([B]+[D])}{dt} = 0 \Rightarrow [B] + [D] = constant = b_0 + d_0 = [B]_{ss} + [D]_{ss}$

at steady-state. Also, at steady-state,

$\frac{d[A]}{dt} = v_0 - v_1 = 0 \Rightarrow v_0 = v_1$

$\frac{d[D]}{dt} = v_1 - v_2 = 0 \Rightarrow v_1 = v_2$

$\frac{d[C]}{dt} = v_1 - v_3 = 0 \Rightarrow v_1 = v_3$

Then, we can combine these two equation with the rate change of D at steady-state:

$v_0 = v_2 = k_2\,[D]_{ss} \Rightarrow [D]_{ss} = \frac{v_0}{k_2} = \frac{k_0}{k_2} \Rightarrow [B]_{ss} = b_0 + d_0 - [D]_{ss} = b_0 + d_0 - \frac{k_0}{k_2} \Rightarrow$

$v_0 = v_1 = k_1\,[A]_{ss}\,[B]_{ss} \Rightarrow [A]_{ss} = \frac{v_0}{k_1\,[B]_{ss}} = \frac{k_0}{k_1(b_0 + d_0 - \frac{k_0}{k_2})}$

$v_0 = v_3 = k_3\,[C]_{ss} \Rightarrow [C]_{ss} = \frac{v_0}{k_3} = \frac{k_0}{k_3}$

In summary, $[A]_{ss} = \frac{k_0}{k_1(b_0 + d_0 - \frac{k_0}{k_2})}$, $[B]_{ss} = b_0 + d_0 - \frac{k_0}{k_2}$, $[C]_{ss} = \frac{k_0}{k_3}$, $[D]_{ss} = \frac{k_0}{k_2}$, $[E]_{ss} = \frac{k_0}{k_4}$,

$[F]_{ss} = \frac{k_0}{k_5}$

iii) Verify your result in (ii) by running a simulation of the system from initial conditions (in mM) of $([A],[B],[C],[D],[E],[F]) = (1, 1, \frac{1}{2}, 0, 0, 0)$. Take rate constants $k_0 = 0.5\,mM/sec, k_1 = 3/mM/sec, k_2 = 1/sec, k_3 = 4/sec, k_4 = 1/sec, k_5 = 5/sec$.

The simulation concentration profile can be seen on the top of the next page. As you can see, the steady state concentration of each species are equal to the result of part (ii). That is, $[A]_{ss} = \frac{k_0}{k_1(b_0 + d_0 - \frac{k_0}{k_2})} = \frac{0.5}{3 \times (1 - \frac{0.5}{1})} = \frac{1}{3}$, $[B]_{ss} = b_0 + d_0 - \frac{k_0}{k_2} = 0.5$, $[C]_{ss} = \frac{k_0}{k_3} =$

$$\frac{0.5}{4} = 0.125, \ [D]_{ss} = \frac{k_0}{k_2} = 0.5, \ [E]_{ss} = \frac{k_0}{k_4} = 0.5, \ [F]_{ss} = \frac{k_0}{k_5} = 0.1$$
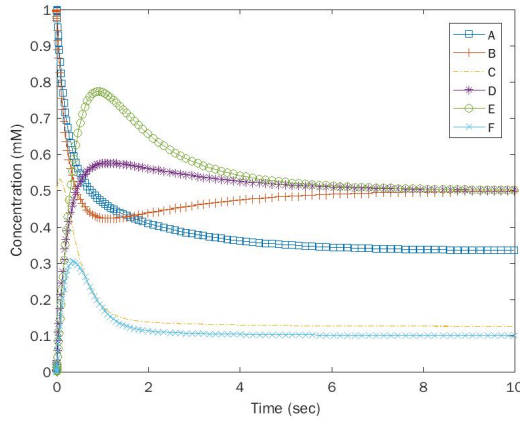

iv) Given the initial conditions and rate constants in part (iii), why would there be no steady state if we take $k_0 = 5 mM/sec$?

It's intuitive that the steady-state concentrations of a system exist if there is a steady-state of the system. Equivalently, if a system doesn't exist steady-state concentrations, the system cannot achieve steady-state. Then, according the steady-state concentration derived in part (ii), the steady-state concentration of A:

$[A]_{ss} = \frac{v_0}{k_1[B]_{ss}} = \frac{k_0}{k_1(b_0 - \frac{k_0}{k_2})}$ exists if and only if $b_0 - \frac{k_0}{k_2} > 0 \Leftrightarrow b_0 k_2 > k_0$
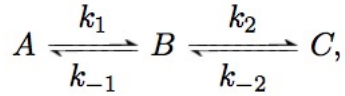
And here: $b_0 k_2 = 1 \times 1 < k_0 = 5$

which is conflict with the sufficient and necessary condition of the steady-state concentration of A, so the system cannot achieve steady-state. Here, I also simulate the concentration profile. As you can see, the $[A]$ never reach a steady state.
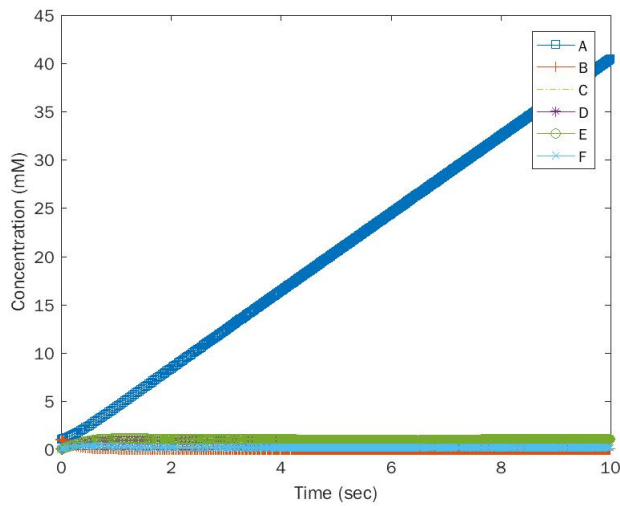
1.2 PROBLEM SET 2.4.8 RAPID EQUILIBRIUM APPROXIMATION.

Consider the closed system:

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} C,$$

with mass action rate constants as shown. Suppose the rate constants are (in min^{-1}) $k_1 = 0.05, k_2 = 0.7, k_{-1} = 0.005,$ and $k_{-2} = 0.4$.

a) Construct a differential equation model of the system. Simulate your model with initial conditions (in mM) of A(0) = 1.5, B(0) = 3, C(0) = 2. Plot the transient and steady-state behaviour of the system. You may need to make two plots to capture all of the dynamics (i.e. two different window sizes).

We can derive a model which consists of following differential equations:

$$\frac{d[A]}{dt} = -k_1[A] + k_{-1}[B], \frac{d[B]}{dt} = k_1[A] - (k_2 + k_{-1})[B] + k_{-2}[C], \frac{d[C]}{dt} = k_2[B] - k_{-2}[C]$$

The simulation result are shown below.
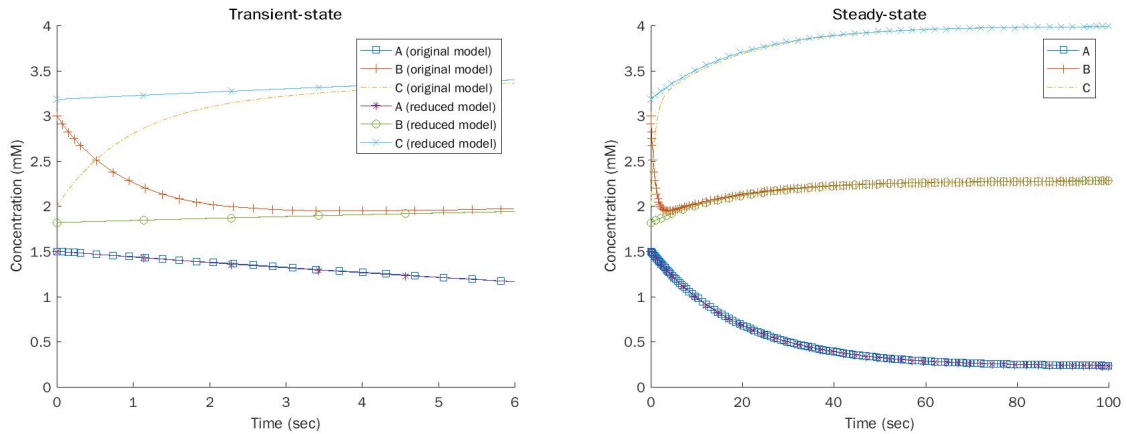
b) It should be clear from your simulation in part (a) that the system dynamics occur on two different time-scales. This is also apparent in the widely separated rate constants. Use a rapid equilibrium assumption to reduce your description of the system to two differential equations (describing one of the original species and one combined species pool) and two algebraic equations (describing the contents of the combined pool).

The rate constants of the reverse reaction between B and C are much larger than the rate constants of the reverse reaction between A and B, so we can assume rapid equilibrium between B and C. Let us denote the combined pool of B and C as D and denote the approximated concentrations of B, C, and D as $\tilde{b}(t)$, $\tilde{c}(t)$,and $\tilde{d}(t)$, respectively.

From rapid equilibrium approximation,
$$\frac{\tilde{b}(t)}{\tilde{c}(t)} = \frac{k_{-2}}{k_2}$$

and from total concentration in the pool of B and C,
$$d\tilde{(t)} = b\tilde{(t)} + c\tilde{(t)} = (1 + \frac{k_2}{k_{-2}}) b\tilde{(t)}$$

so we can rewrite the reaction of the system as $A \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} D$

$\frac{d(d\tilde{(t)})}{dt} = v_3 - v_{-3}$
$\frac{da\tilde{(t)}}{dt} = -v_3 + v_{-3}$ (two differential equations)
where
$v_3 = k_1 a\tilde{(t)} = k_3 a\tilde{(t)}$
$v_{-3} = k_{-1} b\tilde{(t)} = k_{-1} \frac{k_{-2}}{k_2 + k_{-2}} d\tilde{(t)} = k_{-3} d\tilde{(t)} =$ (two algebraic equations)

That is, we can represent the reverse reaction as $A \underset{\frac{k_{-1}k_{-2}}{k_2+k_{-2}}}{\overset{k_1}{\rightleftharpoons}} D$

c) Run a simulation of your reduced model in part (b) to compare with the simulation in part (a). Verify that the simulation of the reduced system is in good agreement with the original, except for a short initial transient. (Note, you will have to select initial conditions for the reduced system so that the initial total concentration is in agreement with part (a), and the rapid equilibrium condition is satisfied at time t = 0.)

1.3 PROBLEM SET 2.4.9 QUASI-STEADY-STATE APPROXIMATION.

Consider the reaction network:

$$\xrightarrow{k_0} A \xrightarrow{k_2} \qquad\qquad A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B.$$
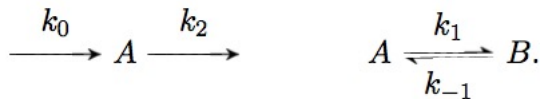
Suppose the mass action rate constants are (in min^{-1}) $k_0 = 1, k_1 = 11, k_{-1} = 8$, and $k_2 = 0.2$.

a) Construct a differential equation model of the system. Simulate your model with initial conditions A(0) = 6 mM, B(0) = 0 mM. Plot the transient and steady-state behaviour of the system. You may need to make two plots to capture all of the dynamics (i.e. two different window sizes).

We can derive a model which consists of following differential equations:

$$\frac{d[A]}{dt} = k_0 - (k_1 + k_2)[A] + k_{-1}[B], \qquad\qquad \frac{d[B]}{dt} = k_1[A] - k_{-1}[B]$$

The simulation result are shown in next page.

b) It should be clear from your simulation in part (a) that the system dynamics occur on two different time-scales. This is also apparent in the widely separated rate constants. Use a quasi-steady-state assumption to reduce your description of the system by replacing a differential equation with an algebraic equation.

The rate constants of the reverse reaction between A and B are much larger than the rate constants of input and output of the reaction network, so we can assume quasi-steady-state on species B. Let us denote the approximated species concentration of A as $a\tilde{(t)}$, and denote the quasi-steady state for [B] as $b^{qss}(t)$.

That is,

$0 = k_1 a\tilde{}(t) - k_{-1} b^{qss}(t) \Rightarrow b^{qss}(t) = \frac{k_1}{k_{-1}} a\tilde{}(t)$

Also,

$\frac{da\tilde{}(t)}{dt} = k_0 - (k_1 + k_2) a\tilde{}(t) + k_{-1} b^{qss}(t) = k_0 - k_2 a\tilde{}(t)$

c) Run a simulation of your reduced model in part (b) to compare with the simulation in part (a). Verify that the simulation of the reduced system is a good approximation to the original at steady state, but not over the initial transient. (Note, you will have to select initial conditions for the reduced system so that the total concentration is in agreement with part (a), and the quasi-steady state condition is satisfied at time t = 0, as in Exercise 2.2.4.)

The initial condition of this simulation can be calculated by the relationship:

$a(0) + b(0) = 6 = a\tilde{}(0) + b^{qss}(0) = (1 + \frac{k_1}{k_{-1}}) a\tilde{}(0) \Rightarrow a\tilde{}(0) = \frac{6k_{-1}}{k_1 + k_{-1}} = \frac{48}{19}$ mM