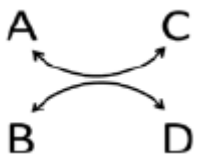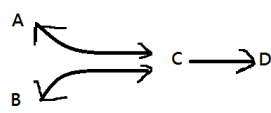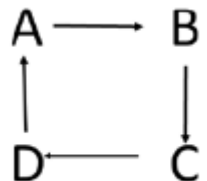# Mathematical Modeling of System Biology Homework 1

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

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

1.1 PROBLEM SET 2.4.7 NETWORK MODELLING.

a) Consider the closed reaction network in Figure 2.16 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

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

  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 and b_0 the initial concentration. According to the three differential equations derived from i), we can further derive :

$$\frac{d[A]}{dt} + \frac{d[C]}{dt} + \frac{d[E]}{dt} = 0 \Rightarrow \frac{d([A]+[C]+[E])}{dt} = 0 \Rightarrow [A] + [C] + [E] = constant = a_0$$
$$\frac{d[A]}{dt} + \frac{d[C]}{dt} + \frac{d[F]}{dt} = 0 \Rightarrow \frac{d([A]+[C]+[F])}{dt} = 0 \Rightarrow [A] + [C] + [F] = constant = a_0$$
$$\frac{d[B]}{dt} + \frac{d[D]}{dt} = 0 \Rightarrow \frac{d([B]+[D])}{dt} = 0 \Rightarrow [B] + [D] = constant = b_0$$

  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:

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

  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

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$[C]_{ss} = 0 \Rightarrow [E]_{ss} = a_0, [F]_{ss} = a_0$

$[D]_{ss} = 0 \Rightarrow [B]_{ss} = b_0$

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

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 $k_1 = 3/\text{mM/sec}$, $k_2 = 1/\text{sec}$, $k_3 = 4/\text{sec}$.

b) Next consider the open system in Figure 2.17 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:

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

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

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

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

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

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

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

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

$v_0 = v_2 = k_2 [D]_{ss} \Rightarrow [D]_{ss} = \frac{v_0}{k_2} = \frac{k_0}{k_2} \Rightarrow [B]_{ss} = b_0 - [D]_{ss} = b_0 - \frac{k_0}{k_2} \Rightarrow v_0 = v_1 = k_1 [A]_{ss} [B]_{ss}$

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

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

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 $k_0 = 0.5 mM/sec, k_1 = 3/mM/sec, k_2 = 1/sec, k_3 = 4/sec, k_4 = 1/sec, k_5 = 5/sec$.

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

1.2 PROBLEM SET 2.4.8 RAPID EQUILIBRIUM APPROXIMATION.

Consider the closed system:

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).

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 (de- scribing one of the original species and one combined species pool) and two algebraic equations (describing the contents of the combined pool).

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:

Suppose the mass action rate constants are (in min^{-1}) $k_0 = 1, k_1 = 11, k_{-1} = 8$, and $k_2 = 0.2$.

1. 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).

2. 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.

3. 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.)