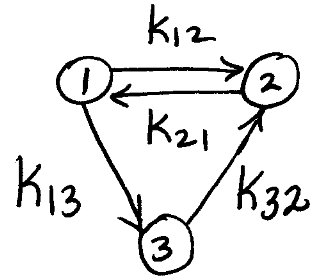
Graph $G = \{\mathcal{V}, \mathcal{E}\}$ $\begin{cases} \mathcal{V} = \{1,2,3\} & \text{set of vertices} \\ \mathcal{E} = \{(1,2),\ (2,1),\ (1,3),\ (3,2)\} & \text{set of edges} \end{cases}$

Ex. 1

Graph:



CRN:

$$X_1 \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} X_2, \qquad X_1 \xrightarrow{k_{13}} X_3, \qquad X_3 \xrightarrow{k_{32}} X_2$$

S = number of species = 3

$$\underline{x} = \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}$$

$x_i(t)$ = population fraction in state i (species i) at time t

Macroscopic model:

$$\frac{dx_i(t)}{dt} = \dot{x}_i(t) = \underbrace{\sum_{(j,i)\in\mathcal{E}} k_{ji}\, x_j(t)}_{\substack{\text{population fraction} \\ \text{per unit time entering} \\ \text{state } i \text{ from state } j}} - \underbrace{\sum_{(i,j)\in\mathcal{E}} k_{ij}\, x_i(t)}_{\substack{\text{population fraction} \\ \text{per unit time leaving} \\ \text{state } i \text{ to enter state } j}}$$

$$\dot{x}_1(t) = \sum_{(j,1)\in\mathcal{E}} k_{j1}\, x_j(t) - \sum_{(1,j)\in\mathcal{E}} k_{1j}\, x_1(t) \qquad (i=1)$$

From the edge set $\mathcal{E}$: $(2,1) \in \mathcal{E}$ $\quad (3,1) \notin \mathcal{E}$

$(1,2) \in \mathcal{E}$ $\quad (1,3) \in \mathcal{E}$

$$\Rightarrow \dot{x}_1(t) = k_{21}\, x_2(t) - (k_{12}\, x_1(t) + k_{13}\, x_1(t))$$
$$= -(k_{12} + k_{13})\, x_1(t) + k_{21}\, x_2(t)$$

Similarly:

$$\dot{x}_2(t) = k_{12}\, x_1(t) + k_{32}\, x_3(t) - k_{21}\, x_2(t)$$
$$\dot{x}_3(t) = k_{13}\, x_1(t) - k_{32}\, x_3(t)$$

Write these 3 equations in the form $\dot{\underline{x}} = -\underline{K}\,\underline{x}$:

$$\dot{\underline{x}} = \begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{bmatrix} = \begin{bmatrix} -(k_{12}+k_{13}) & k_{21} & 0 \\ k_{12} & -k_{21} & k_{32} \\ k_{13} & 0 & -k_{32} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}$$

$$\Rightarrow \underline{K} = \begin{bmatrix} k_{12}+k_{13} & -k_{21} & 0 \\ -k_{12} & k_{21} & -k_{32} \\ -k_{13} & 0 & k_{32} \end{bmatrix}$$

<u>Note that</u>: ① $\underline{1}^T \underline{K} = [1 \;\; 1 \;\; 1]\,\underline{K} = [0 \;\; 0 \;\; 0] = \underline{0}$

(Each column of $\underline{K}$ sums to 0)

② $K_{ji} < 0$ for all $(i,j) \in \mathcal{E}$

↑ entry of $\underline{K}$ at row j, column i

General structure of $\underline{K}$:

$$K_{ij} = \begin{cases} -k_{ji} & \text{if } i \neq j,\ (j,i) \in \mathcal{E}, \\ 0 & \text{if } i \neq j,\ (j,i) \notin \mathcal{E}, \\ \sum_{(i,l)\in\mathcal{E}} k_{il} & \text{if } i = j. \end{cases}$$

- Example above, row 1 of $\underline{K}$:

$$K_{1j} = \begin{cases} -k_{j1} & \text{if } j \in \{2,3\},\ (j,1) \in \mathcal{E} \\ 0 & \text{if } j \in \{2,3\},\ (j,1) \notin \mathcal{E} \\ \sum_{(1,l)\in\mathcal{E}} k_{1l} & \text{if } j = 1 \end{cases}$$

$K_{12} =$

$(2,1) \in \mathcal{E} \Rightarrow -k_{21}$

$(3,1) \notin \mathcal{E} \Rightarrow K_{13} = 0$

$\{(1,2), (1,3)\} \in \mathcal{E}$

$\Rightarrow K_{11} = k_{12} + k_{13}$

Ex. 2

CRN: $X_1 + X_2 \underset{k_{21}}{\overset{k_{12}}{\rightleftarrows}} X_3$

$X_2 + X_4 \underset{k_{43}}{\overset{k_{34}}{\rightleftarrows}} X_5$

Graph: $1 \underset{k_{21}}{\overset{k_{12}}{\rightleftarrows}} 2$

$3 \underset{k_{43}}{\overset{k_{34}}{\rightleftarrows}} 4$

complex 1: $X_1 + X_2$
complex 2: X_3
complex 3: $X_2 + X_4$
complex 4: X_5

C = number of complexes $= 4$

Graph $G = \{\mathcal{V}, \mathcal{E}\}$ $\begin{cases} \mathcal{V} = \{1, 2, 3, 4\} \\ \mathcal{E} = \{(1,2), (2,1), (3,4), (4,3)\} \end{cases}$

$y_i(t)$ = product of concentrations of the species in complex i at time t

$x_j(t)$ = concentration of species j at time t

$y_1 = x_1 x_2 \quad y_2 = x_3 \quad y_3 = x_2 x_4 \quad y_4 = x_5$

$$y = \begin{bmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \end{bmatrix} = \begin{bmatrix} x_1 x_2 \\ x_3 \\ x_2 x_4 \\ x_5 \end{bmatrix} = y(\underline{x}), \quad \underline{x} = \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \end{bmatrix}$$

$S = 5$ number of species

Label the reactions: ① $X_1 + X_2 \rightleftarrows X_3$
② $X_2 + X_4 \rightleftarrows X_5$

R = number of reactions $= 2$

Forward flux of reaction 1: $k_{12} y_1 = k_{12} x_1 x_2$
Reverse flux of reaction 1: $k_{21} y_2 = k_{21} x_3$
Forward flux of reaction 2: $k_{34} y_3 = k_{34} x_2 x_4$
Reverse flux of reaction 2: $k_{43} y_4 = k_{43} x_5$

$\nu_k(t)$ = reaction rate of reaction k (involving complexes i and j)
= forward flux ($k_{ij}\, y_i(t)$) − reverse flux ($k_{ji}\, y_j(t)$)

$$\nu_1(t) = k_{12} y_1 - k_{21} y_2 = k_{12} x_1 x_2 - k_{21} x_3$$

$$\nu_2(t) = k_{34} y_3 - k_{43} y_4 = k_{34} x_2 x_4 - k_{43} x_5$$

$$\underline{\nu}(t) = \begin{bmatrix} \nu_1(t) \\ \nu_2(t) \end{bmatrix} = \underline{\nu}(\underline{x}(t))$$

Macroscopic model: $\dot{\underline{x}} = -\underline{M}\,\underline{K}\,\underline{y}(\underline{x}) = \underline{S}\,\underline{\nu}(\underline{x})$

Definitions of the matrices:

$$\underline{M} \in \mathbb{R}^{S \times C} \Rightarrow \underline{M} \in \mathbb{R}^{5 \times 4}$$

Entry M_{ji} (row j, column i) of $\underline{M}$ is the coefficient of species type j in complex i (0 if absent).

$$\underline{M} = \underbrace{\begin{bmatrix} 1 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}}_{\text{complexes}} \begin{array}{l} X_1 \\ X_2 \\ X_3 \\ X_4 \\ X_5 \end{array} \left.\vphantom{\begin{array}{l} X_1 \\ X_2 \\ X_3 \\ X_4 \\ X_5 \end{array}}\right\} \text{species}$$

$$\begin{array}{cccc} X_1+X_2 & X_3 & X_2+X_4 & X_5 \end{array}$$

$$\underline{K} \in \mathbb{R}^{C \times C} \Rightarrow \underline{K} \in \mathbb{R}^{4 \times 4}$$

$$K_{ij} = \begin{cases} -k_{ji} & \text{if } i \neq j,\ (j,i) \in \mathcal{E} \\ 0 & \text{if } i \neq j,\ (j,i) \notin \mathcal{E} \\ \sum_{(i,l)\in\mathcal{E}} k_{il} & \text{if } i = j \end{cases}$$

$\Rightarrow$ Nonzero entries of $\underline{K}$ are:

$K_{12} = -k_{21}$ $K_{21} = -k_{12}$ $K_{34} = -k_{43}$ $K_{43} = -k_{34}$

$K_{11} = k_{12}$ $K_{22} = k_{21}$ $K_{33} = k_{34}$ $K_{44} = k_{43}$

$$\Rightarrow \underline{K} = \begin{bmatrix} k_{12} & -k_{21} & 0 & 0 \\ -k_{12} & k_{21} & 0 & 0 \\ 0 & 0 & k_{34} & -k_{43} \\ 0 & 0 & -k_{34} & k_{43} \end{bmatrix}$$

$\underline{S} \in \mathbb{R}^{S \times R} \Rightarrow \underline{S} \in \mathbb{R}^{5 \times 2}$

Entry S_{ij} (row i, column j) of $\underline{S}$ is the stoichiometric coefficient of species i in reaction j.

$$\begin{array}{c c l} & \begin{array}{cc} \text{Rxn. 1} & \text{Rxn. 2} \\ X_1+X_2 \rightleftarrows X_3 & X_2+X_4 \rightleftarrows X_5 \end{array} & \\ \underline{S} = & \begin{bmatrix} -1 & 0 \\ -1 & -1 \\ 1 & 0 \\ 0 & -1 \\ 0 & 1 \end{bmatrix} & \left.\begin{array}{l} X_1 \\ X_2 \\ X_3 \\ X_4 \\ X_5 \end{array}\right\} \text{species} \end{array}$$

- If the species is in the reactants, put a negative sign in front of its stoichiometric coefficient.

• Note that $\text{rank}(\underline{S}) = 2$.

• The macroscopic model is subject to $S - \text{rank}(\underline{S})$ linearly independent conservation constraints on the $x_i(t)$, each of the form $\underline{c}^T \underline{x} = \alpha$, where $\underline{S}^T \underline{c} = \underline{0}$.

$\Rightarrow$ the example system has $5 - \text{rank}(\underline{S}) = 3$ conservation constraints. The corresponding $\underline{c}$ vectors can be found by typing null(S') in MATLAB.

Analysis of the macroscopic model in Ex. 2

- Linkage class of a CRN : a set of complexes connected by reactions

  ℓ = number of linkage classes = 2

- Network rank of a CRN = rank of the matrix (call it $\underline{R}$) with rows $\underline{m}_i - \underline{m}_j$, $(i,j) \in \mathcal{E}$, where $\underline{m}_i$ is the i^{th} column of the matrix $\underline{M}$.

$\underline{m}_1 = [1 \ 1 \ 0 \ 0 \ 0]^T \qquad \underline{m}_3 = [0 \ 1 \ 0 \ 1 \ 0]^T$

$\underline{m}_2 = [0 \ 0 \ 1 \ 0 \ 0]^T \qquad \underline{m}_4 = [0 \ 0 \ 0 \ 0 \ 1]^T$

$$\underline{R} = \begin{bmatrix} \underline{m}_1^T - \underline{m}_2^T \\ \underline{m}_2^T - \underline{m}_1^T \\ \underline{m}_3^T - \underline{m}_4^T \\ \underline{m}_4^T - \underline{m}_3^T \end{bmatrix} = \begin{bmatrix} 1 & 1 & -1 & 0 & 0 \\ -1 & -1 & 1 & 0 & 0 \\ 0 & 1 & 0 & 1 & -1 \\ 0 & -1 & 0 & -1 & 1 \end{bmatrix}$$

s = network rank = 2

- C = number of complexes = 4
- Deficiency of the network = $\delta = C - \ell - s$

$$= 4 - 2 - 2 = 0$$

- A network is <u>weakly reversible</u> if whenever there is a directed arrow pathway from complex i to complex j, there is also one from j to i.
  - The example CRN is weakly reversible.

- Each equilibrium of the macroscopic model can be classified as a <u>positive equil.</u> $\underline{x}^e > \underline{0}$ or a <u>boundary equilibrium</u> in which $x_i^e = 0$ for some species i, which can be found by solving $\underline{y}(\underline{x}^e) = \underline{0}$.

$$\underline{y}(\underline{x}^e) = \begin{bmatrix} x_1^e x_2^e \\ x_3^e \\ x_2^e x_4^e \\ x_5^e \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

$$\Rightarrow \; x_3^e = 0, \quad x_5^e = 0, \quad \underset{\substack{\Downarrow \\ x_1^e = 0 \text{ or } x_2^e = 0}}{x_1^e x_2^e = 0}, \quad \underset{\substack{\Downarrow \\ x_2^e = 0 \text{ or } x_4^e = 0}}{x_2^e x_4^e = 0}$$

Possible

$\Rightarrow$ $$\underline{x}^e = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 0 \\ 0 \\ 0 \\ c_4 \\ 0 \end{bmatrix}, \begin{bmatrix} c_1 \\ 0 \\ 0 \\ c_4 \\ 0 \end{bmatrix}, \begin{bmatrix} c_1 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 0 \\ c_2 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad (c_1, c_2, c_4 > 0)$$

(boundary equilibria)

<u>Deficiency Zero theorem:</u>

$\delta = 0$, CRN is weakly reversible and has mass-action kinetics (the reaction fluxes are proportional to the products of concentrations of the reactants / products)

$\Rightarrow$ The macroscopic model has <u>one positive equilibrium</u> $\underline{x}^e > \underline{0}$, which is <u>asymptotically stable</u>, and <u>no</u> nontrivial periodic solution $\underline{x} : [0, T] \to \mathbb{R}^s$, $\underline{x}(0) = \underline{x}(T)$ in the positive orthant of $\mathbb{R}^s$ (a <u>positive cyclic trajectory</u>).

The equilibrium $\underline{x}^e$ is globally asymptotically stable if the CRN does not admit any boundary equilibria.

- In the example CRN, if you start with a vector initial concentrations $\underline{x}(0)$ that has nonzero amounts of species in a reactant or product complex (ex) ($x_1(0), x_2(0) > 0$; $x_3(0) > 0$), then reactions will occur and there will be nonzero concentrations of both reactants and products at equilibrium. Thus, the system will converge to the unique positive $\underline{x}^e$ and not to any of the boundary equilibria.