Biophysics I

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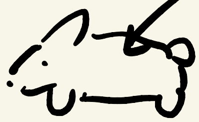
2023 Spring

Biophysics I Lecture 1

cell



living system

protein

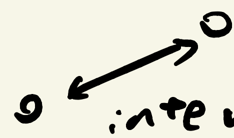
interaction

Chemical reaction

Cf.) condensed matter

atom

$\boxed{Fe}$

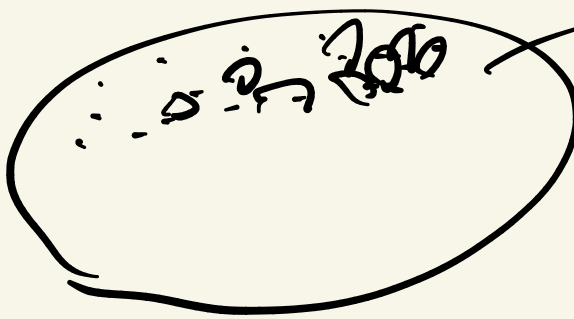


interaction

• Chemical reaction

cell

dense.



Assumption

ideal dilute solution

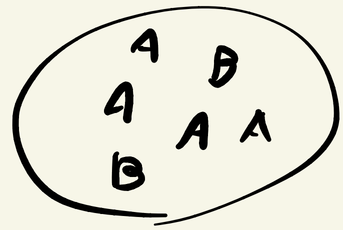
Not true,
but easy
and
practical

Example 1 : activity

A : active state

B : inactive state

cell



$$A \underset{k^-}{\overset{k^+}{\rightleftharpoons}} B$$

k^+, k^- ; rate constants

Assumption

macroscopic (• large number of molecules) Not true, but practical

C_A : concentration of A

C_B : concentration of B

$$C_A \geq 0 \ , \quad C_B \geq 0 \qquad \begin{pmatrix} C_A \in \mathbb{R}_{\geq 0} \\ C_B \in \mathbb{R}_{\geq 0} \end{pmatrix}$$

rate equation

$$\frac{dC_A}{dt} = -k^+ C_A + k^- C_B = -J(C_A, C_B)$$

$$\frac{dC_B}{dt} = k^+ C_A - k^- C_B = J(C_A, C_B)$$

1 $$\frac{dC_A}{dt} = -\frac{dC_B}{dt}$$

$$\rightarrow \quad \frac{d}{dt}(C_A + C_B) = 0$$

$$C_A + C_B = C = \text{const.}$$

more general

$\alpha \in \mathbb{R}$. $\frac{d}{dt}\alpha = 0$

$$\frac{d}{dt}(\alpha C_A + \alpha C_B) = 0.$$

conservation law

② equilibrium

$C_A^{eq} > 0$, $C_B^{eq} > 0$,

$J(C_A^{eq}, C_B^{eq}) = 0$ $\left(\begin{array}{l} C_A^{eq} \in \mathbb{R}_{>0} \\ C_B^{eq} \in \mathbb{R}_{>0} \end{array} \right)$

(Do not consider a trivial solution $C_A = C_B = 0$)

$$k^+ C_A^{eq} = k^- C_B^{eq}$$

$$\rightarrow \quad \frac{C_A^{eq}}{C_B^{eq}} = \frac{k^-}{k^+}$$

law of moss action

(detailed balance)

· $C_A^{eq} + C_B^{eq} = C$

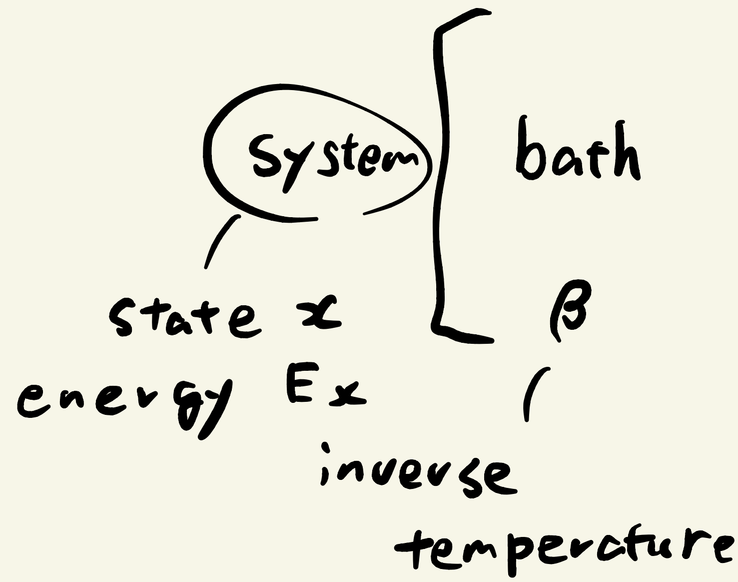
$$P_A = \frac{C_A^{eq}}{C} = \frac{1}{1 + \frac{C_B^{eq}}{C_A^{eq}}} = \frac{1}{1 + \frac{k^+}{k^-}}$$

$$P_B = \frac{C_B^{eq}}{C} = 1 - P_A = \frac{\frac{k^+}{k^-}}{1 + \frac{k^+}{k^-}}$$

$$\left(P_A + P_B = 1, \quad P_A \geq 0, \quad P_B \geq 0 \right)$$

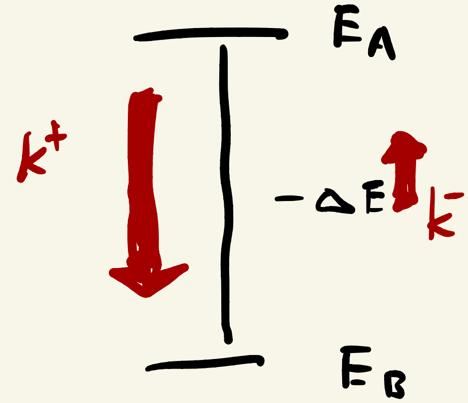
cf.) canonical distribution

$$P_x \propto \exp(-\beta E_x)$$



$$P_A = \frac{\exp(-\beta E_A)}{\exp(-\beta E_A) + \exp(-\beta E_B)}$$

$$= \frac{1}{1 + \exp(-\beta \underbrace{(E_B - E_A)}_{\Delta E})}$$



assumption $\updownarrow$

$$P_A = \frac{1}{1 + \frac{k^+}{k^-}}$$

physical interpretation

$$\frac{k^+}{k^-} = \exp(-\beta \Delta E)$$

$$\ln \frac{k^+}{k^-} = -\beta \Delta E$$

local detailed balance

③ matrix - vector notation

$$\mathbb{C} = \begin{pmatrix} c_A \\ c_B \end{pmatrix} \qquad 2 \times 1 \quad \text{matrix}$$

$$J(\mathbb{C}) = J(c_A, c_B)$$

$$\frac{d}{dt}\mathbb{C} = \frac{d}{dt}\begin{pmatrix} c_A \\ c_B \end{pmatrix} = \begin{pmatrix} -J(\mathbb{C}) \\ J(\mathbb{C}) \end{pmatrix}$$

$$= \underbrace{\begin{pmatrix} -1 \\ 1 \end{pmatrix}}_{2\times 1 \text{ matrix}} \underbrace{J(\mathbb{C})}_{1\times 1 \text{ matrix}}$$

$$\mathbb{S} = \begin{pmatrix} -1 \\ +1 \end{pmatrix}$$: Stoichiometric matrix

$$\underset{-1}{A} \xrightarrow{J(\mathbb{C})} \underset{+1}{B}$$

- rank nullity theorem

T: transpose

A : $n \times m$ (real valued) matrix

$\mathrm{rank}(A) = r \quad (\leq \min(n, m))$

$[\mathrm{rank}(A) = \mathrm{rank}(A^T) = \dim(\mathrm{Im}(A)) = \dim(\mathrm{Im}(A^T))]$

$\ker(A) = \{x \in \mathbb{R}^m \mid Ax = 0\}$

$\ker(A^T) = \{x \in \mathbb{R}^n \mid A^T x = 0\}$

$$\left[\begin{array}{l} \dim(\ker(A)) + r = m \\ \dim(\ker(A^T)) + r = n \end{array}\right.$$

$\dim(\ker(A)) = m - r$

$\dim(\ker(A^T)) = n - r$

S : 2×1 matrix

$\mathrm{rank}(S) = 1$

$\dim(\ker(S)) = 1 - 1 = 0$

$\dim(\ker(S^T)) = 2 - 1 = \underline{1}$!

$$S^T = \begin{pmatrix} -1 & 1 \end{pmatrix}$$

$$S^T \begin{pmatrix} \alpha \\ \alpha' \end{pmatrix} = 0 \rightarrow \alpha' = \alpha .$$

$$\boldsymbol{\ell} := \begin{pmatrix} \alpha \\ \alpha \end{pmatrix} = \alpha \begin{pmatrix} 1 \\ 1 \end{pmatrix} \in \ker(S^T)$$

cf.) $\frac{d}{dt}(\alpha c_A + \alpha c_B) = 0$

$$\frac{d}{dt}(\boldsymbol{\ell}^T \mathbb{c}) = 0 \quad \begin{pmatrix} \text{assumption} \\ \frac{d}{dt}\boldsymbol{\ell} = 0 \end{pmatrix}$$

Check

Rate equation

$$\frac{d}{dt}\mathbb{c} = \mathbb{S}\, J(\mathbb{c})$$

$$\frac{d}{dt}(\boldsymbol{\ell}^T \mathbb{c}) = \boldsymbol{\ell}^T \mathbb{S}\, J(\mathbb{c})$$

$$= (\mathbb{S}^T \boldsymbol{\ell})^T J(\mathbb{c})$$

$$= \mathbb{0}^T J(\mathbb{c})$$

$$= 0$$

matrix A, B

$(AB)^T = B^T A^T$

$(A^T)^T = A$

Conservation law $\longleftrightarrow$ $\boldsymbol{\ell} \in \ker(S^T)$

$\boldsymbol{\ell}^T \mathbb{c} = \mathrm{const.}$

Summary

$$A \underset{k^-}{\overset{k^+}{\rightleftharpoons}} B$$

rate equation: $\frac{d}{dt}\mathbb{c} = \mathbb{S}\, J(\mathbb{c})$

detailed balance $J(\mathbb{c}^{eq}) = 0$

$\mathbb{c}^{eq} \in \mathbb{R}^2_{>0}$

local detailed balance

$$\ln \frac{k^+}{k^-} = -\beta \Delta E$$

conservation law

$$\boldsymbol{\ell} \in \ker(S^T), \quad \boldsymbol{\ell}^T \mathbb{c} = \text{const.}$$

Biophysics I　Lecture 2

Remark.

$$\frac{d}{dt}\mathbb{c} = \mathbb{S}\,\mathbb{J}(\mathbb{c}) \in \mathrm{Im}(\mathbb{S}).$$

$$\begin{aligned}\frac{d}{dt}(\mathbb{l}^T\mathbb{c}) &= \mathbb{l}^T\mathbb{S}\,\mathbb{J}(\mathbb{c}) \\ &= (\mathbb{S}^T\mathbb{l})\,\mathbb{J}(\mathbb{c}) \\ &= 0\end{aligned} \quad \left(\begin{array}{l}\frac{d}{dt}\mathbb{l} = \mathbb{0} \\ \mathbb{l} \in \ker(\mathbb{S}^T)\end{array}\right)$$

$\Updownarrow$ 　　　$\mathbb{S}$: $n \times m$ matrix

○ $\mathrm{Im}(\mathbb{S}) \perp \ker(\mathbb{S}^T)$

$$\left[\begin{array}{l}\mathrm{Im}(\mathbb{S}) = \{\mathbb{S}\phi \in \mathbb{R}^n \mid \phi \in \mathbb{R}^m\} \\ \ker(\mathbb{S}^T) = \{x \in \mathbb{R}^n \mid \mathbb{S}^T x = \mathbb{0}\}\end{array}\right.$$

$\underline{\mathbb{R}^n}$

∵ 　　　　　　　　　　　　$(\phi \in \mathbb{R}^m)$

$\mathbb{a} \in \mathrm{Im}(\mathbb{S}) \rightarrow \mathbb{a} = \mathbb{S}\phi$

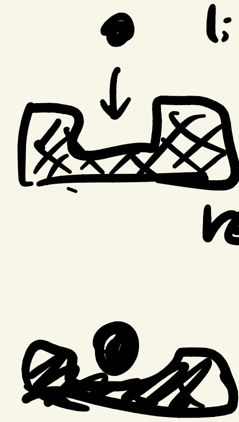
$\mathbb{b} \in \ker(\mathbb{S}^T)$

$$\mathbb{a}^T\mathbb{b} = (\mathbb{S}\phi)^T\mathbb{b} = \phi^T \underbrace{\mathbb{S}^T\mathbb{b}}_{=\mathbb{0}} = 0$$

Example 2

ligand-receptor binding.

$$L + R \underset{k^-}{\overset{k^+}{\rightleftharpoons}} LR$$



ligand L

receptor R

LR

Rate eq.

nonlinear!

$$\frac{d}{dt} c_L = -k^+ \underline{c_L c_R} + k^- c_{LR} = -J(\mathbb{C})$$

$$\frac{d}{dt} c_R = -k^+ c_L c_R + k^- c_{LR} = -J(\mathbb{C})$$

$$\frac{d}{dt} c_{LR} = k^+ c_L c_R - k^- c_{LR} = +J(\mathbb{C})$$

$$\mathbb{C} = \begin{pmatrix} c_L \\ c_R \\ c_{LR} \end{pmatrix} \qquad \mathbb{S} = \begin{pmatrix} -1 \\ -1 \\ 1 \end{pmatrix} \begin{array}{l} L \\ R \\ LR \end{array}$$

nonlinear function

$$\underbrace{\frac{d}{dt} \mathbb{C}}_{\substack{3\times 1 \\ \text{matrix}}} = \underbrace{\mathbb{S}}_{\substack{3\times 1 \\ \text{matrix}}} \underbrace{J(\mathbb{C})}_{\substack{1\times 1 \\ \text{matrix}}}$$

$$\underset{-1 \ \ -1}{L + R} \xrightarrow{J(\mathbb{C})} \underset{+1}{LR}$$

① $\mathrm{rank}(S) = 1$

$$\dim(\ker(S^T)) = 3 - 1 = 2.$$

$$S^T = \begin{pmatrix} -1 & -1 & 1 \end{pmatrix}.$$

$$\ell^{(1)} = \begin{pmatrix} 1 \\ 0 \\ 1 \end{pmatrix} \in \ker(S^T)$$

$$\ell^{(2)} = \begin{pmatrix} 0 \\ 1 \\ 1 \end{pmatrix} \in \ker(S^T)$$

$$\Rightarrow \quad \frac{d}{dt}(\ell^{(1)T} c) = 0$$

L $\quad \frac{d}{dt}(c_{\underline{L}} + c_{\underline{L}R}) = 0$

$$\frac{d}{dt}(\ell^{(2)T} c) = 0$$

R $\quad \frac{d}{dt}(c_{\underline{R}} + c_{L\underline{R}}) = 0$

- Probabilities.

① $\dfrac{c_L}{c_L + c_{LR}}$, $\dfrac{c_{LR}}{c_L + c_{LR}}$

② $\dfrac{c_R}{c_R + c_{LR}}$, $\dfrac{c_{LR}}{c_R + c_{LR}}$

② Equilibrium

$$J(c^{eq}) = 0 \qquad c^{eq} \in \mathbb{R}^3_{>0}$$

$$k^+ c_L^{eq} c_R^{eq} = k^- c_{LR}^{eq}$$

$$\frac{k^+}{k^-} = \frac{c_{LR}^{eq}}{c_L^{eq} c_R^{eq}}$$

[detailed balance
or
law of mass action

$$P_R^{eq} = \frac{C_R^{eq}}{C_R^{eq} + C_{LR}^{eq}}$$

$$P_{LR}^{eq} = \frac{C_{LR}^{eq}}{C_R^{eq} + C_{LR}^{eq}}$$

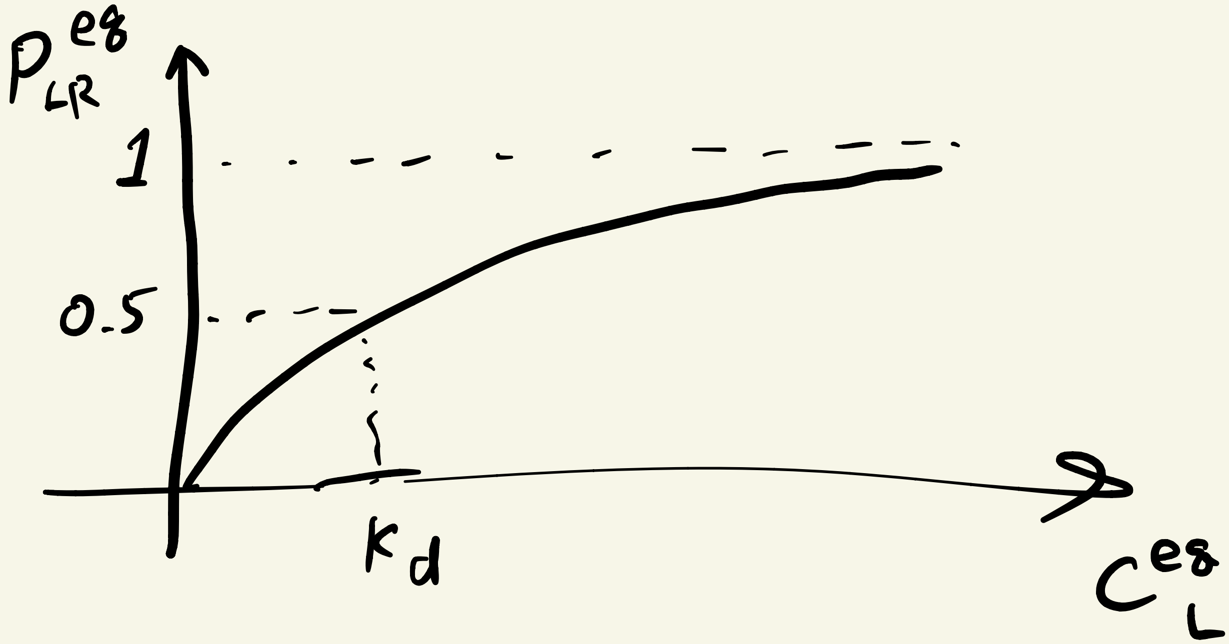
Prob.

$$P_{LR}^{eq} = 1 - P_R^{eq}$$

$$= \frac{\frac{C_{LR}^{eq}}{C_R^{eq}}}{1 + \frac{C_{LR}^{eq}}{C_R^{eq}}}$$

$$= \frac{C_L^{eq} \frac{k^+}{k^-}}{1 + C_L^{eq} \frac{k^+}{k^-}} = \frac{\frac{C_L^{eq}}{K_d}}{1 + \frac{C_L^{eq}}{K_d}}$$

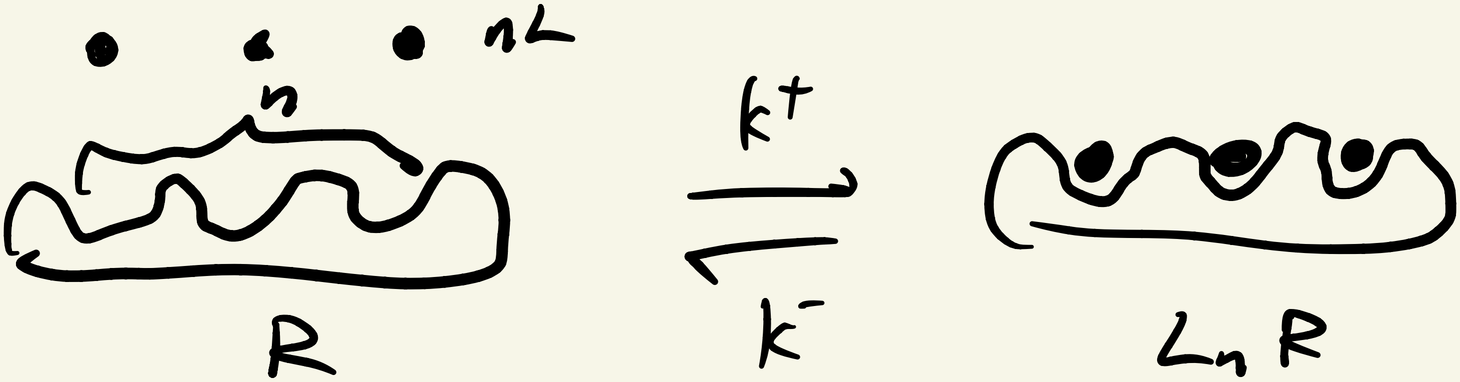
$$K_d = \frac{k^-}{k^+}$$: dissociation constant



$$\left(\begin{array}{l} c_c^{eq} = K_d \\[1em] P_{LR}^{eq} = \dfrac{\frac{K_d}{K_d}}{1 + \frac{K_d}{K_d}} = 0.5 \end{array} \right)$$

Example 3

n ligand – 1 receptor



$$nL + R \underset{k^-}{\overset{k^+}{\rightleftharpoons}} L_nR$$

$$\mathbb{C} = \begin{pmatrix} C_L \\ C_R \\ C_{L_nR} \end{pmatrix} \qquad J(\mathbb{C}) = k^+ (C_L)^n C_R - k^- C_{L_nR}$$

$$\mathbb{S} = \begin{array}{c} \begin{pmatrix} -n \\ -1 \\ 1 \end{pmatrix} \end{array} \begin{array}{l} L \\ R \\ LR \end{array} \qquad \underset{(-n)}{nL} + \underset{(-1)}{R} \longrightarrow \underset{(+1)}{LR}$$

Rate eq.

$$\frac{d}{dt} \underbrace{\mathbb{C}}_{3\times 1 \text{ matrix}} = \underbrace{\mathbb{S}}_{3\times 1 \text{ matrix}} \underbrace{J(\mathbb{C})}_{1\times 1 \text{ matrix}}$$

①

$\mathrm{rank}(\mathbb{S}) = 1$

$\dim(\ker(\mathbb{S}^T)) = 3 - 1 = 2$.

$$\ell^{(1)} = \begin{pmatrix} 1 \\ 0 \\ n \end{pmatrix} \in \ker(\mathbb{S}^T)$$

$$\ell^{(2)} = \begin{pmatrix} 0 \\ 1 \\ 1 \end{pmatrix} \in \ker(\mathbb{S}^T).$$

$$\frac{d}{dt}\left((\ell^{(1)})^T \mathbb{C}\right) = 0$$

$$\rightarrow \quad \frac{d}{dt}\left(C_L + n\, C_{LnR}\right) = 0$$

$$\frac{d}{dt}\left((\ell^{(2)})^T \mathbb{C}\right) = 0$$

$$\rightarrow \quad \frac{d}{dt}\left(C_R + C_{LnR}\right) = 0$$

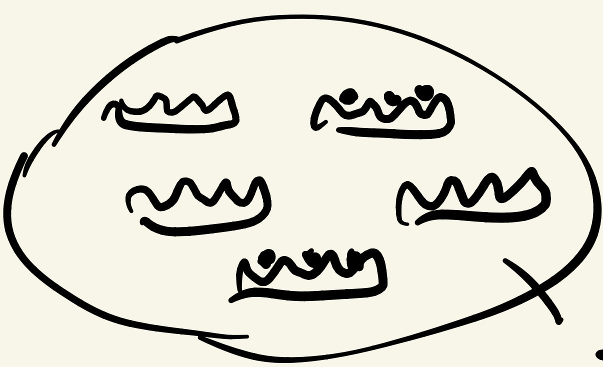
② Equilibrium

$$J(\mathbf{C}^{eq}) = 0 \qquad \mathbf{C}^{eq} \in \mathbb{R}^3_{>0}$$

$$\frac{k^-}{k^+} = \frac{C_R^{eq}\,(C_L^{eq})^n}{C_{LnR}^{eq}}$$

$$\begin{cases} P_R^{eq} = \dfrac{C_R^{eq}}{C_R^{eq} + C_{LnR}^{eq}} \\[2ex] P_{LnR}^{eq} = \dfrac{C_{LnR}^{eq}}{C_R^{eq} + C_{LnR}^{eq}} \end{cases}$$

$$P_{LnR}^{eq} = 1 - P_R^{eq} = \frac{\dfrac{C_{LnR}^{eq}}{C_R^{eq}}}{1 + \dfrac{C_{LnR}^{eq}}{C_R^{eq}}} = \frac{(C_L^{eq})^n \dfrac{k^+}{k^-}}{1 + (C_L^{eq})^n \dfrac{k^+}{k^-}}$$

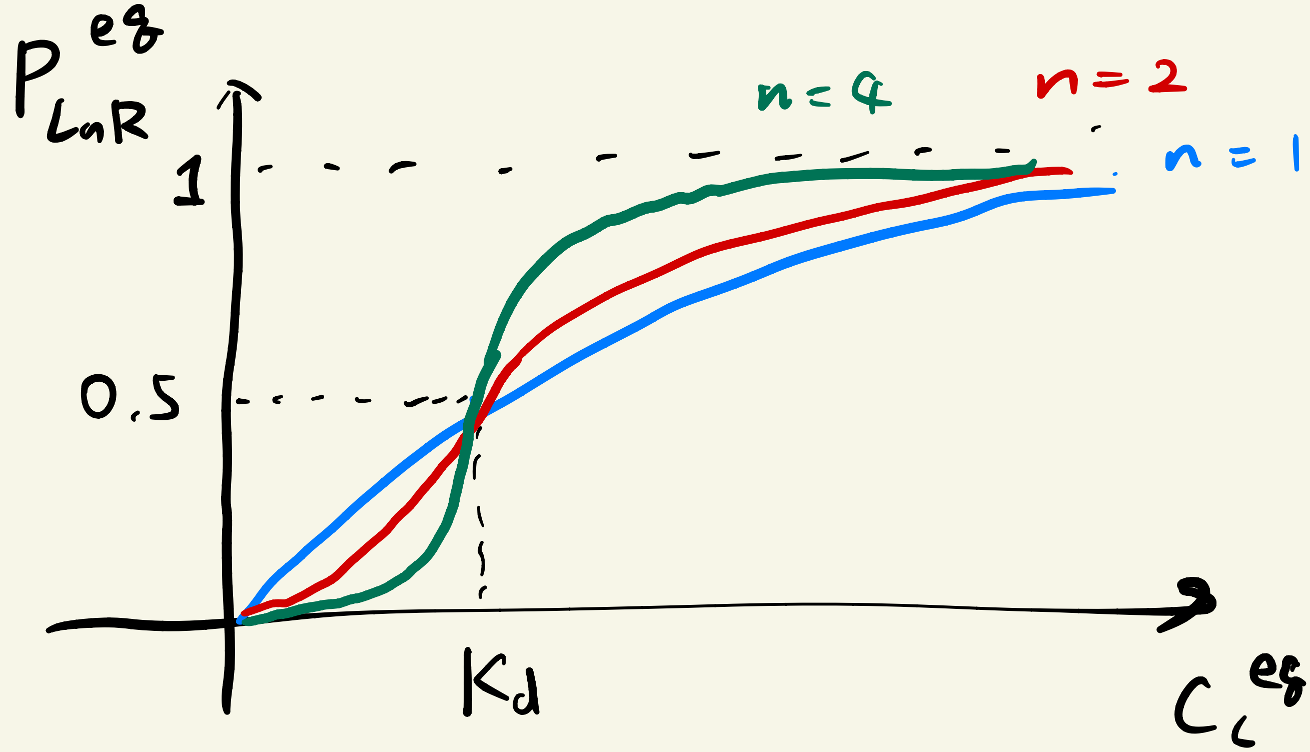


prob.

Hill equation

$$P_{LnR}^{eq} = \frac{\left(\frac{C_L^{eq}}{K_d}\right)^n}{1 + \left(\frac{C_L^{eq}}{K_d}\right)^n}$$

$$K_d := \left(\frac{k^-}{k^+}\right)^{\frac{1}{n}}$$



fitting parameter <u>n</u>

Hill coefficient

Allosteric

(Cooperative)

$n \gg 1$, $C_L^{eq} < K_d \rightarrow P_{LnR}^{eq} \sim 0$

$C_L^{eq} > K_d \rightarrow P_{LnR}^{eq} \sim 1$

Example 4 : Enzyme reaction

$$E + S \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} ES \xrightarrow{k_2^+} E + P$$

$$\left(\xleftarrow{k_2^-}\right) \text{negligible}$$

- E : Enzyme
- S : Substate
- P : product
- ES : Enzyme - substate complex.

Rate eq.

$$\frac{d}{dt}\overbrace{\mathbb{C}}^{4\times 1 \text{ matrix}} = \overbrace{\mathbb{S}}^{4\times 2\text{ matrix}}\ \overbrace{\mathbb{J}(\mathbb{C})}^{2\times 1\text{ matrix}}$$

$$\mathbb{C} = \begin{pmatrix} c_E \\ c_S \\ c_{ES} \\ c_P \end{pmatrix} \qquad \mathbb{S} = \begin{pmatrix} -1 & 1 \\ -1 & 0 \\ 1 & -1 \\ 0 & 1 \end{pmatrix} \qquad \mathbb{J}(\mathbb{C}) = \begin{pmatrix} J_1(\mathbb{C}) \\ J_2(\mathbb{C}) \end{pmatrix}$$

$$J_1(\mathbb{C}) = k_1^+ c_E c_S - k_1^- c_{ES}, \quad J_2(\mathbb{C}) = k_2^+ c_{ES}$$

① $\mathrm{rank}(\mathbb{S}) = 2$

$$\dim(\ker(\mathbb{S}^T)) = 4-2 = 2.$$

$$\mathbb{S}^T = \begin{pmatrix} -1 & -1 & 1 & 0 \\ 1 & 0 & -1 & 1 \end{pmatrix}$$

$$\mathbb{l}^{(1)} = \begin{pmatrix} 1 \\ 0 \\ 1 \\ 0 \end{pmatrix} \in \ker(\mathbb{S}^T)$$

$$\mathbb{l}^{(2)} = \begin{pmatrix} 0 \\ 1 \\ 1 \\ 1 \end{pmatrix} \in \ker(\mathbb{S}^T)$$

$$\frac{d}{dt}((\mathbb{l}^{(1)})^T \mathbb{C}) = 0$$

$$\rightarrow \quad \frac{d}{dt}(C_{\underline{E}} + C_{\underline{E}S}) = 0 \qquad E$$

$$\frac{d}{dt}((\mathbb{l}^{(2)})^T \mathbb{C}) = 0$$

$$\rightarrow \quad \frac{d}{dt}(C_{\underline{S}} + C_{E\underline{S}} + C_{\underline{P}}) = 0 \qquad S \text{ or } P$$

Summary

- ligand - receptor binding

$$nL + R \underset{k^-}{\overset{k^+}{\rightleftharpoons}} L_nR$$

$$p_{L_nR}^{eq} = \frac{\left(\frac{c_L^{eq}}{K_d}\right)^n}{1 + \left(\frac{c_L^{eq}}{K_d}\right)^n}$$

Hill equation

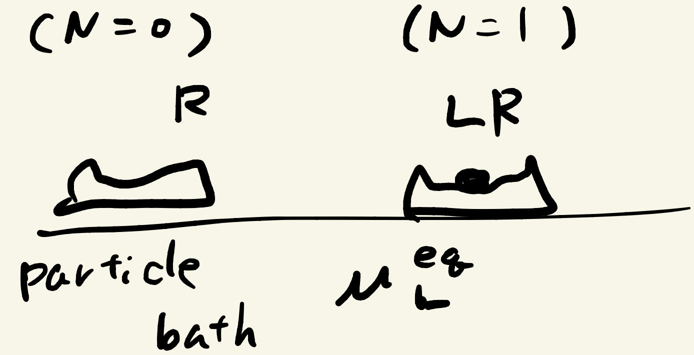
Remark

$$L + R \underset{k^-}{\overset{k^+}{\rightleftharpoons}} LR$$

$$p_{LR}^{eq} = \frac{c_{LR}^{eq}}{c_R^{eq} + c_{LR}^{eq}}$$

$$= \frac{c_L^{eq}\frac{k^+}{k^-}}{1 + c_L^{eq}\frac{k^+}{k^-}}$$

Grand canonical distribution



$$p_{LR}^{eq} = \frac{\exp(-\beta(\epsilon_{LR} - \epsilon_R - \mu_L^{eq}))}{1 + \exp(-\beta(\epsilon_{LR} - \epsilon_R - \mu_L^{eq}))}$$

$$\Rightarrow \quad \ln\left(c_L^{eq}\frac{k^+}{k^-}\right) = -\beta(\epsilon_{LR} - \epsilon_R - \mu_L^{eq})$$

local detailed balance

$$\ln \frac{k^+}{k^-} = -\beta(\epsilon_{LR} - \epsilon_R - \epsilon_L)$$

- $$\mu_L^{eq} = \epsilon_L + \beta^{-1} \ln c_L^{eq}$$

  chemical potential

Example 4: Enzyme reaction

$$E + S \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} ES$$

$$ES \underset{k_2^+}{\longrightarrow} E + P$$

② Assumption

$$\frac{d}{dt} c_{ES} = J_1(c^*) - J_2(c^*) \cong 0$$

$$k_1^+ c_E^* c_S^* - k_1^- c_{ES}^* - k_2^+ c_{ES}^* = 0$$

$$c_{Etot} = c_E^* + c_{ES}^* = \text{const.}$$

$$c_{ES}^* = \frac{k_1^+ \, c_{Etot} \, c_S^*}{k_2^+ + k_1^- + k_1^+ c_S^*}$$

$$\frac{d}{dt} c_P = k_2^+ c_{ES}^*$$

$$= k_2^+ c_{E tot} \frac{\frac{k_1^+}{k_1^- + k_2^+} c_S^*}{1 + \frac{k_1^+}{k_1^- + k_2^+} c_S^*}$$

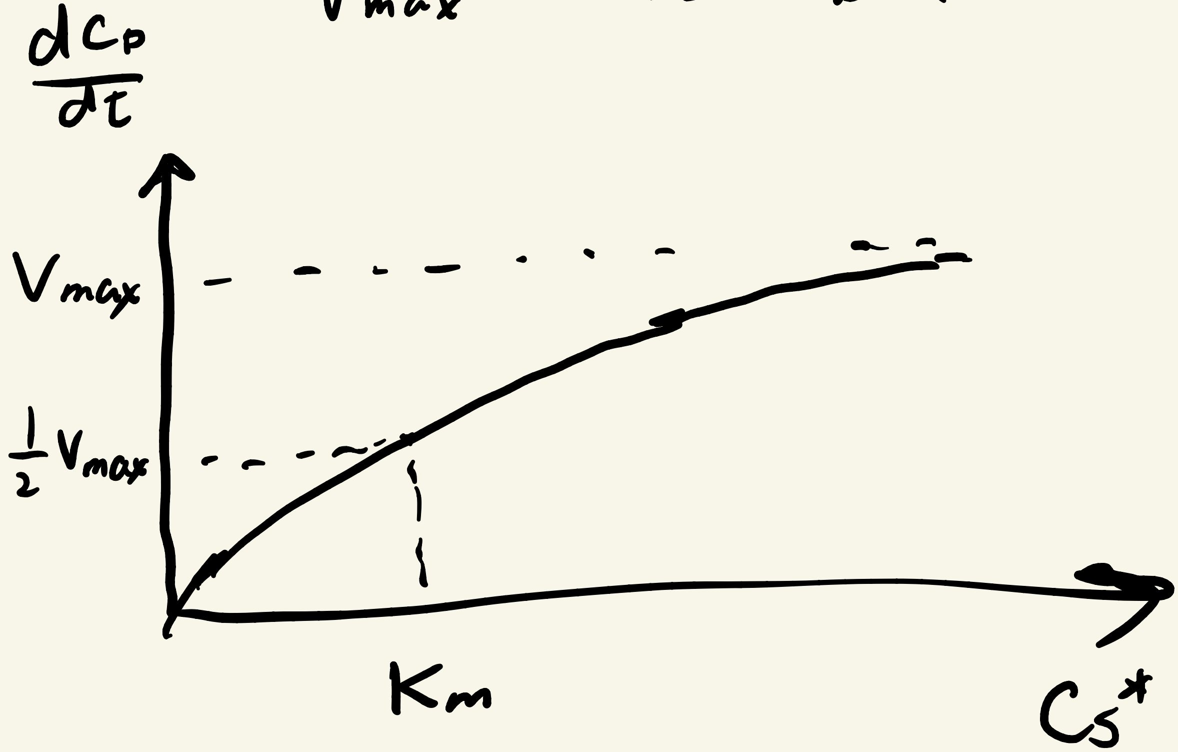
$$= V_{max} \frac{\frac{c_S^*}{K_m}}{1 + \frac{c_S^*}{K_m}}$$ Michaelis-Menten equation

Michaelis constant

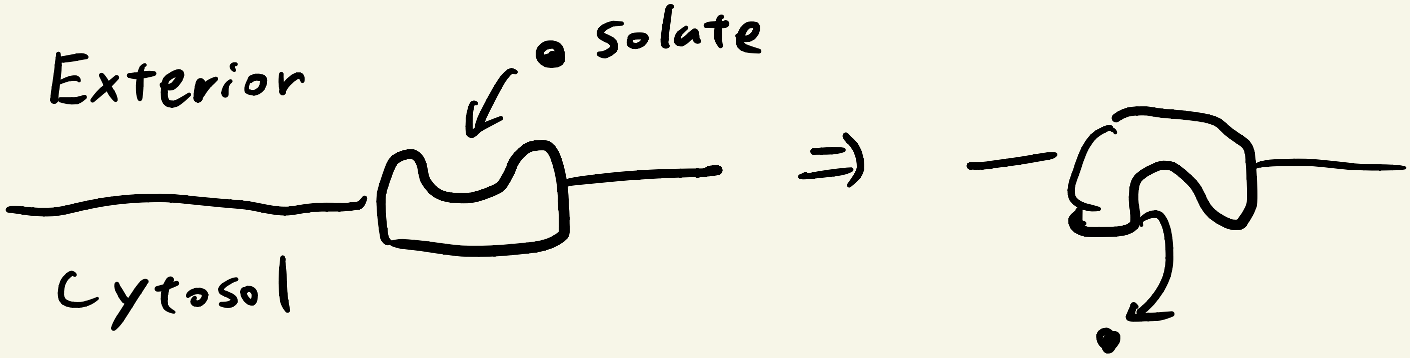
$$K_m = \frac{k_1^- + k_2^+}{k_1^+}$$

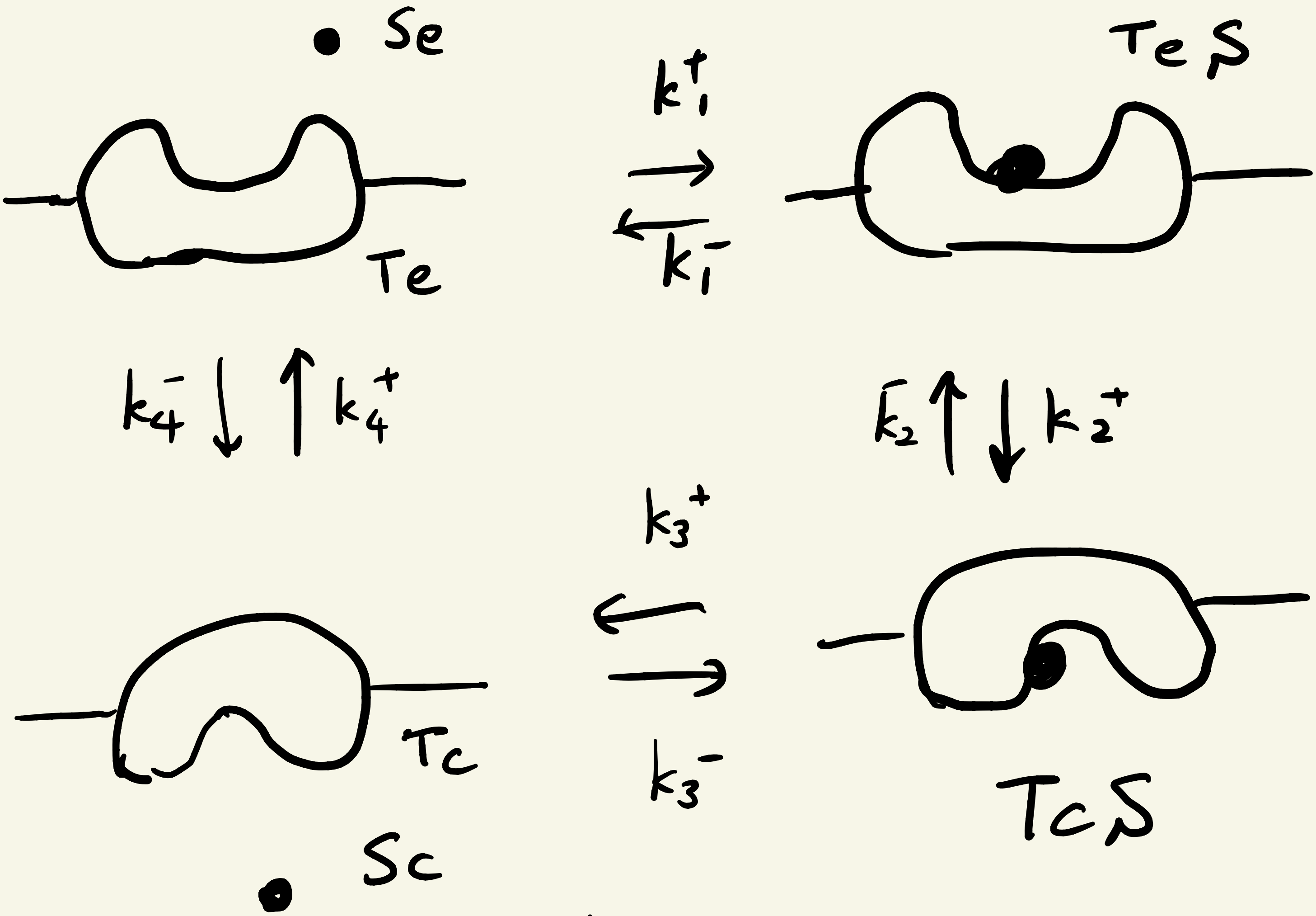
limiting rate

$$V_{max} = k_2^+ c_{E tot}$$



Example 5 : Membrane transport





$$T_e + S_e \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} T_eS$$

$$T_eS \underset{k_2^-}{\overset{k_2^+}{\rightleftharpoons}} T_cS$$

$$T_cS \underset{k_3^-}{\overset{k_3^+}{\rightleftharpoons}} S_c + T_c$$

$$T_c \underset{k_4^-}{\overset{k_4^+}{\rightleftharpoons}} T_e$$

$$\mathbb{C} = \begin{pmatrix} c_{Te} \\ c_{Tc} \\ c_{TeS} \\ c_{TcS} \\ c_{Se} \\ c_{Sc} \end{pmatrix} \qquad \mathbb{J}(\mathbb{C}) = \begin{pmatrix} J_1(\mathbb{C}) \\ J_2(\mathbb{C}) \\ J_3(\mathbb{C}) \\ J_4(\mathbb{C}) \end{pmatrix}$$

$$J_1(\mathbb{C}) = k_1^+ c_{Te} c_{Se} - k_1^- c_{TeS}$$

$$J_2(\mathbb{C}) = k_2^+ c_{TeS} - k_2^- c_{TcS}$$

$$J_3(\mathbb{C}) = k_3^+ c_{TcS} - k_3^- c_{Sc} c_{Tc}$$

$$J_4(\mathbb{C}) = k_4^+ c_{Tc} - k_4^- c_{Te}$$

$$\frac{d}{dt}\mathbb{C} = \underbrace{\begin{pmatrix} -1 & 0 & 0 & 1 \\ 0 & 0 & 1 & -1 \\ 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & 0 \\ -1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 \end{pmatrix}}_{\mathbb{S}} \mathbb{J}(\mathbb{C})$$

1 $\operatorname{rank}(\mathbb{S}) = 4$

$\dim(\ker(\mathbb{S}^T)) = 6 - 4 = 2$

$$\mathbb{S}^T = \begin{pmatrix} -1 & 0 & 1 & 0 & -1 & 0 \\ 0 & 0 & -1 & 1 & 0 & 0 \\ 0 & 1 & 0 & -1 & 0 & 1 \\ 1 & -1 & 0 & 0 & 0 & 0 \end{pmatrix}$$

$$\mathbb{S}^T \begin{pmatrix} 1 \\ 1 \\ 1 \\ 1 \\ 0 \\ 0 \end{pmatrix} = \mathbb{0} \qquad \begin{pmatrix} 1 \\ 1 \\ 1 \\ 1 \\ 0 \\ 0 \end{pmatrix} \in \ker(\mathbb{S}^T)$$

$$\mathbb{S}^T \begin{pmatrix} 0 \\ 0 \\ 1 \\ 1 \\ 1 \\ 1 \end{pmatrix} = \mathbb{0} \qquad \begin{pmatrix} 0 \\ 0 \\ 1 \\ 1 \\ 1 \\ 1 \end{pmatrix} \in \ker(\mathbb{S}^T)$$

$$\frac{d}{dt}\left(C_{Te} + C_{Tc} + C_{TeS} + C_{TcS} \right) = 0$$

T

$$\frac{d}{dt}\left(C_{TeS} + C_{TcS} + C_{Sc} + C_{Se} \right) = 0$$

S

② Equilibrium

$$\mathbb{J}(\mathbb{C}^{eq}) = \mathbb{0} \qquad \mathbb{C}^{eq} \in \mathbb{R}^6_{>0}$$

$$\frac{k_1^+}{k_1^-} = \frac{C_{TeS}^{eq}}{C_{Te}^{eq}\, C_{Se}^{eq}}, \qquad \frac{k_2^+}{k_2^-} = \frac{C_{TcS}^{eq}}{C_{TeS}^{eq}}$$

$$\frac{k_3^+}{k_3^-} = \frac{C_{Sc}^{eq}\, C_{Tc}^{eq}}{C_{TcS}^{eq}}, \qquad \frac{k_4^+}{k_4^-} = \frac{C_{Tc}^{eq}}{C_{Te}^{eq}}$$

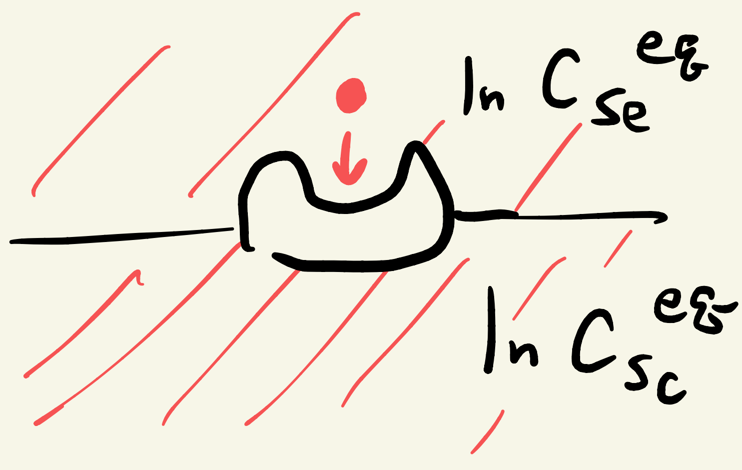
law of mass action

Check

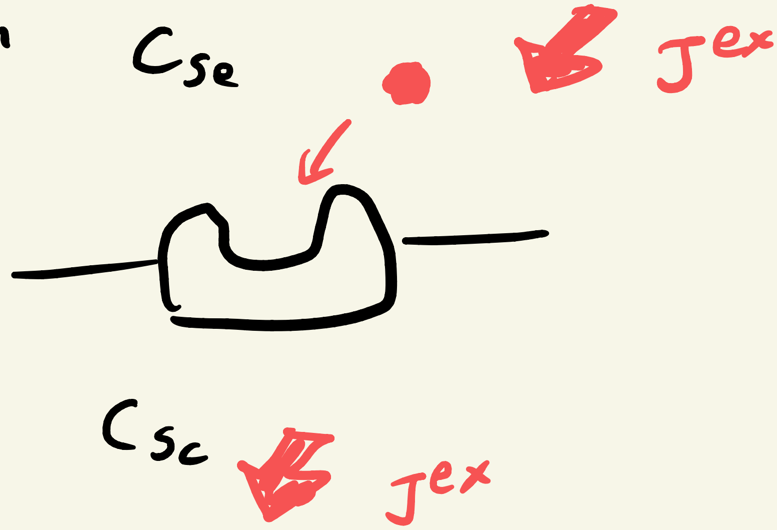
$$\frac{C_{Sc}^{eq}}{C_{Se}^{eq}} = \frac{k_1^+ k_2^+ k_3^+ k_4^+}{k_1^- k_2^- k_3^- k_4^-}$$

or $$\ln \frac{k_1^+ k_2^+ k_3^+ k_4^+}{k_1^- k_2^- k_3^- k_4^-} = \ln C_{Sc}^{eq} - \ln C_{Se}^{eq}$$

- Energy difference (local detailed balance)
- chemical potential difference



③ Open system



$$\begin{cases} \dfrac{d}{dt} C_{se} = 0 \\ \dfrac{d}{dt} C_{se} = 0 \end{cases}$$

Chemostat.

$$\frac{d}{dt}\mathbb{C} = \underbrace{\begin{pmatrix} -1 & 0 & 0 & 1 \\ 0 & 0 & 1 & -1 \\ 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}}_{\tilde{\mathbb{S}}} \mathbb{J}(\mathbb{C})$$

$$\mathbb{J}^{ex}(\mathbb{C}) = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 \\ 0 & 0 & -1 & 0 \end{pmatrix} \mathbb{J}(\mathbb{C})$$

$$\frac{d}{dt}\mathbb{C} = \tilde{\mathbb{S}}\,\mathbb{J}(\mathbb{C}) = \mathbb{S}\,\mathbb{J}(\mathbb{C}) + \mathbb{J}^{ex}(\mathbb{C})$$

$$\text{rank}(\tilde{S}) = 3 \;!$$

$$\dim(\ker(\tilde{S}^T)) = 6 - 3 = 3$$

$$\dim(\ker(\tilde{S})) = 4 - 3 = 1 \;!$$

$$\tilde{S}^T = \begin{pmatrix} -1 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & -1 & 1 & 0 & 0 \\ 0 & 1 & 0 & -1 & 0 & 0 \\ 1 & -1 & 0 & 0 & 0 & 0 \end{pmatrix}$$

$$\tilde{S}^T \begin{pmatrix} 1 \\ 1 \\ 1 \\ 1 \\ 0 \\ 0 \end{pmatrix} = \mathbb{0} \qquad \frac{d}{dt}\left(C_{T_eS} + C_{T_cS} + C_{T_e} + C_{T_c}\right) = 0$$

$$\tilde{S}^T \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix} = \mathbb{0} \qquad \frac{d}{dt} C_{S_e} = 0$$

$$\tilde{S}^T \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \end{pmatrix} = \mathbb{0} \qquad \frac{d}{dt} C_{S_c} = 0$$

③

$$\tilde{S}\begin{pmatrix}1\\1\\1\\1\end{pmatrix} = \begin{pmatrix}-1&0&0&1\\0&0&1&-1\\1&-1&0&0\\0&1&-1&0\\0&0&0&0\\0&0&0&0\end{pmatrix}\begin{pmatrix}1\\1\\1\\1\end{pmatrix} = \mathbb{0}$$

$$\begin{pmatrix}1\\1\\1\\1\end{pmatrix} \in \ker(\tilde{S})$$

$$\frac{d}{dt}\mathbb{c} = \tilde{S}\,\mathbb{J}(\mathbb{c})$$

$$J(\mathbb{c}^{st}) = \alpha\begin{pmatrix}1\\1\\1\\1\end{pmatrix} \in \ker(\tilde{S})$$

$$(\alpha \neq 0,\quad \alpha \in \mathbb{R})$$

$$\frac{d}{dt}\mathbb{c}^{st} = \tilde{S}\,\mathbb{J}(\mathbb{c}^{st})$$

$$= \alpha\,\tilde{S}\begin{pmatrix}1\\1\\1\end{pmatrix} = \mathbb{0}$$

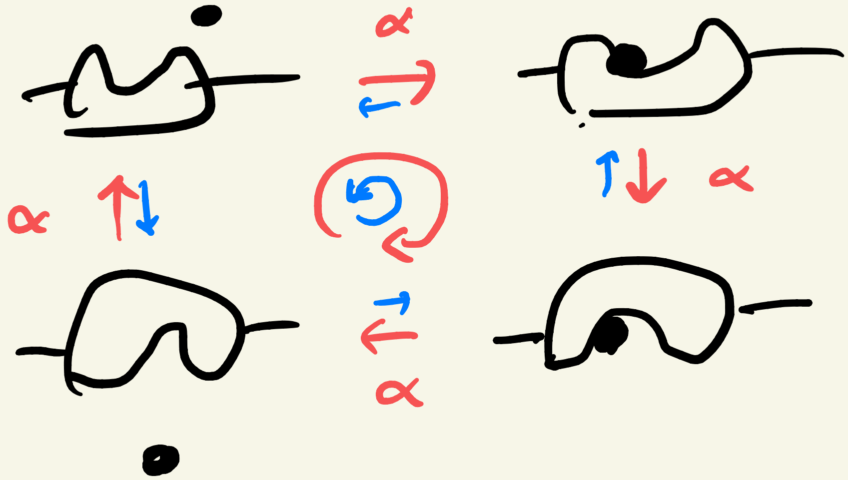
$\mathbb{c}^{st}$: non-equilibrium steady state

$J_1(\mathbb{C}) = \alpha$

$J_2(\mathbb{C}) = \alpha$

$J_3(\mathbb{C}) = \alpha$

$J_4(\mathbb{C}) = \alpha$



$\ker(\tilde{\mathbb{S}})$

cycle !

cf.) Electromagnetics

$\nabla \cdot \mathbb{B} = 0$

$\rightarrow \quad \nabla \times A = B$ rotation

$\mathbb{S}\,\mathbb{J} = \mathbb{O}$

$\mathbb{J}$: cycle .

$\mathbb{S} \leftarrow \cdots \rightarrow -\nabla \cdot$

$-$ div

$(\mathbb{S}^T \leftarrow \cdots\cdots \rightarrow \nabla)$

grad

$\alpha = 0$ .... equilibrium.

$\alpha > 0$ or $\alpha < 0$

2nd law of thermodynamics

⑤ 2nd law of thermodynamics

$$J_i(\mathbb{C}) = \underbrace{J_i^+(\mathbb{C})}_{\geq 0} - \underbrace{J_i^-(\mathbb{C})}_{\geq 0}$$

e.g.) $J_1(\mathbb{C}) = \underbrace{k_1^+ C_{T_e} C_{T_{se}}}_{J_1^+(\mathbb{C})} - \underbrace{k_1^- C_{T_e S}}_{J_1^-(\mathbb{C})}$

$$F_i(\mathbb{C}) = \ln \frac{J_i^+(\mathbb{C})}{J_i^-(\mathbb{C})}$$

$J_i(\mathbb{C}), F_i(\mathbb{C})$: same sign.

$$\left(\begin{array}{lll} J_i(\mathbb{C}) > 0, & F_i(\mathbb{C}) > 0 & (J_i^+(\mathbb{C}) > J_i^-(\mathbb{C})) \\ J_i(\mathbb{C}) = 0, & F_i(\mathbb{C}) = 0 & (J_i^+(\mathbb{C}) = J_i^-(\mathbb{C})) \\ J_i(\mathbb{C}) < 0, & F_i(\mathbb{C}) < 0 & (J_i^+(\mathbb{C}) < J_i^-(\mathbb{C})) \end{array} \right.$$

$$\Rightarrow \quad J_i(\mathbb{C}) F_i(\mathbb{C}) \geq 0$$

- Entropy production rate

$$\sigma(\mathbb{C}) = \sum_i J_i(\mathbb{C}) F_i(\mathbb{C}) \underline{\geq 0}$$

2nd law of thermodynamics

- $\mathbb{C} = \mathbb{C}^{eq}$ $\quad J(\mathbb{C}^{eq}) = \mathbb{0}$

$(\mathbb{F}(\mathbb{C}^{eq}) = \mathbb{0})$

$\sigma(\mathbb{C}^{eq}) = 0$ equilibrium

- $\mathbb{C} \neq \mathbb{C}^{eq}$, $\quad J(\mathbb{C}) \neq \mathbb{0}$

$\sigma(\mathbb{C}) > 0$ non-equilibrium

Entropy change

$$F_1 = \ln \frac{k_1^+ \, C_{Te} C_{Se}}{\underbrace{k_1^-}_{\text{energy change}} \, \underbrace{C_{TeS}}_{\text{chemical potential change}}}$$

(local detailed balance)

Entropy production rate

$$\sigma(\mathbb{C}) = \sum_i \underbrace{F_i(\mathbb{C})}_{\text{entropy change}} \underbrace{J_i(\mathbb{C})}_{\text{flow}}$$

$$\mathbb{J}(\mathbb{C}^{st}) = \begin{pmatrix} \alpha \\ \alpha \\ \alpha \\ \alpha \end{pmatrix} \qquad \alpha \neq 0$$

$$\begin{aligned}
\sigma(\mathbb{C}^{st}) &= \sum_i J_i(\mathbb{C}^{st})\, F_i(\mathbb{C}^{st}) \\
&= \alpha \sum_i F_i(\mathbb{C}^{st}) \\
&= \alpha \ln \frac{k_1^+ k_2^+ k_3^+ k_4^+ \; C_{se}^{st}}{k_1^- k_2^- k_3^- k_4^- \; C_{sc}^{st}} \\
&= \alpha \left(\ln \frac{C_{se}^{st}}{C_{sc}^{st}} - \ln \frac{C_{se}^{eq}}{C_{sc}^{eq}} \right) \underline{\geq 0}
\end{aligned}$$

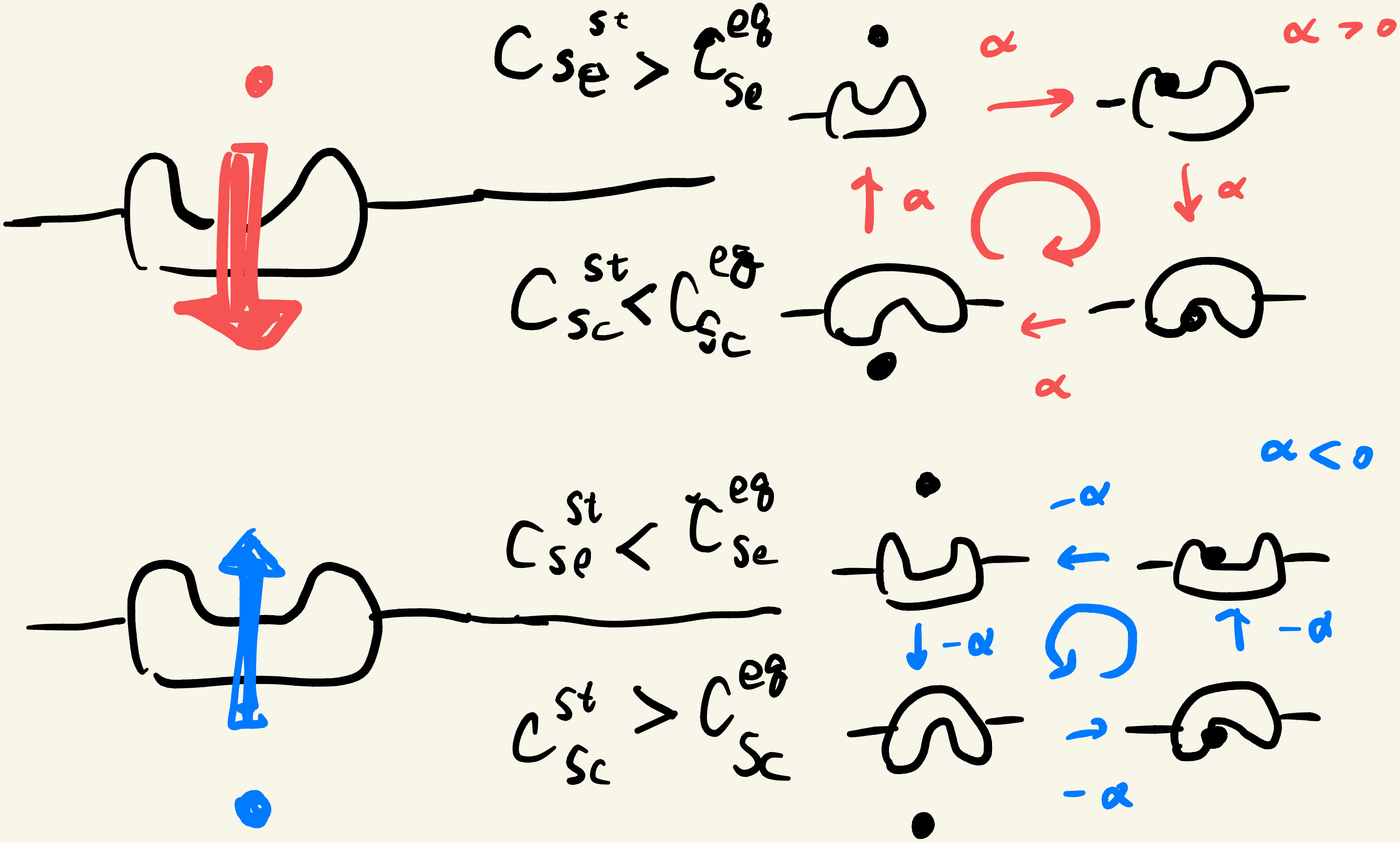
2nd law

$(\alpha \neq 0,\ \sigma(\mathbb{C}^{st}) > 0)$

$$\frac{C_{se}^{st}}{C_{sc}^{st}} > \frac{C_{se}^{eq}}{C_{sc}^{eq}} \Rightarrow \alpha > 0$$

$$\frac{C_{se}^{st}}{C_{sc}^{st}} < \frac{C_{se}^{eq}}{C_{sc}^{eq}} \Rightarrow \alpha < 0$$

$$\left(\frac{C_{se}^{st}}{C_{se}^{st}} = \frac{C_{se}^{eq}}{C_{sc}^{eq}} \Rightarrow \alpha = 0 \quad (\text{equilibrium}) \right)$$



$C_{se}^{st} > C_{se}^{eq}$
α
$\alpha > 0$
α
α
$C_{sc}^{st} < C_{sc}^{eq}$
α
$\alpha < 0$
$C_{se}^{st} < C_{se}^{eq}$
$-\alpha$
$-\alpha$
$-\alpha$
$C_{sc}^{st} > C_{sc}^{eq}$
$-\alpha$

Summary

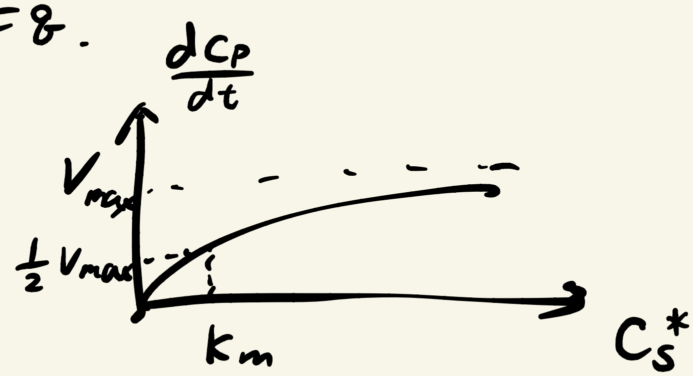
- Enzyme reaction

$$E + S \rightleftarrows ES : 1$$
$$ES \rightarrow P : 2$$

$$\cdot\ J_1(\mathbb{C}^*) - J_2(\mathbb{C}^*) \simeq 0$$

$$\frac{d}{dt} c_P = V_{max} \frac{\frac{c_S^*}{K_m}}{1 + \frac{c_S^*}{K_m}}$$

Michaelis-Menten Eq.



- Open system

$$\frac{d}{dt} \mathbb{C} = \tilde{\mathbb{S}}\, \mathbb{J}(\mathbb{C}) = \mathbb{S}\, \mathbb{J}(\mathbb{C}) + \mathbb{J}^{ex}(\mathbb{C})$$

$$\mathrm{Ker}(\tilde{\mathbb{S}}) : \text{cycle}$$

- Entropy production rate

$$\sigma(\mathbb{C}) = \sum_i J_i(\mathbb{C}) F_i(\mathbb{C}) \quad (\geq 0 \quad \text{2nd law})$$

$$J_i(\mathbb{C}) = J_i^+(\mathbb{C}) - J_i^-(\mathbb{C})$$

$$F_i(\mathbb{C}) = \ln \frac{J_i^+(\mathbb{C})}{J_i^-(\mathbb{C})}$$

Biophysics I Lecture 4

Remark

$$\sigma(\mathbb{C}) = \sum_i F_i(\mathbb{C})\, J_i(\mathbb{C}) \geq 0$$

$$\forall i, \quad F_i(\mathbb{C}^{eq}) = 0$$

$$\Leftrightarrow \forall i, \quad J_i(\mathbb{C}^{eq}) = 0$$

$$J_i(\mathbb{C}^{st}) = \begin{pmatrix} \alpha \\ \alpha \\ \alpha \\ \alpha \end{pmatrix}$$

$$\sigma(\mathbb{C}^{st}) = \alpha \sum_i F_i(\mathbb{C}^{st})$$

$$\alpha = 0 \Rightarrow \forall i, \ J_i(\mathbb{C}^{st}) = 0$$

$$\Rightarrow \forall i, \quad F_i(\mathbb{C}^{st}) = 0$$

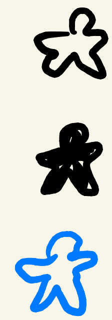
$$\Rightarrow \sum_i F_i(\mathbb{C}^{st}) = 0$$

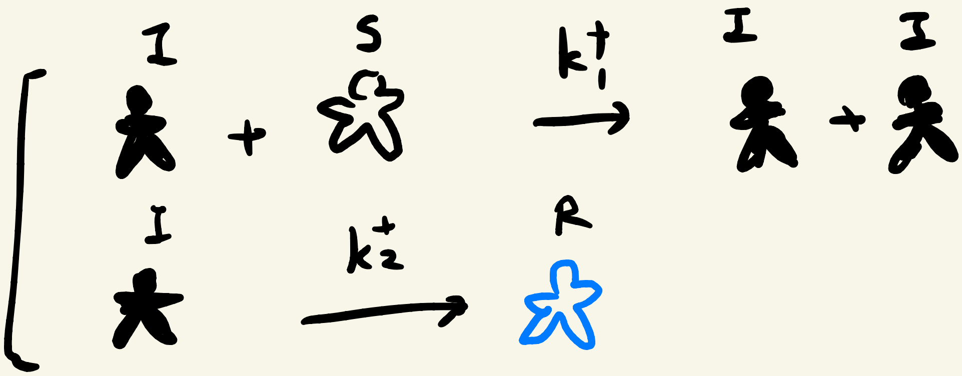
Thus,

$$\alpha = 0 \Rightarrow \sum_i F_i(\mathbb{C}^{st}) = 0$$

Example 6 : SIR model

- Susceptible S
- Infected I
- Recovered R.





$2I$

(autocatalytic reaction)

$$\begin{cases} I + R \xrightarrow{k_1^+} 2I \\ I \xrightarrow{k_2^+} R \end{cases}$$

$$\mathbb{C} = \begin{pmatrix} c_S \\ c_I \\ c_R \end{pmatrix}$$

$$J_1(\mathbb{C}) = k_1^+ C_I C_S$$

$$J_2(\mathbb{C}) = k_2^+ C_I$$

$$\frac{d}{dt}\mathbb{C} = \underbrace{\begin{pmatrix} -1 & 0 \\ 1 & -1 \\ 0 & 1 \end{pmatrix}}_{\mathbb{S}} \mathbb{J}(\mathbb{C}), \quad \mathbb{J}(\mathbb{C}) = \begin{pmatrix} J_1(\mathbb{C}) \\ J_2(\mathbb{C}) \end{pmatrix}$$

① $\mathrm{Rank}(S) = 2$

$\dim(\ker(S^T)) = 3 - 2 = 1$

$$S^T = \begin{pmatrix} -1 & 1 & 0 \\ 0 & -1 & 1 \end{pmatrix}$$

$$S^T \begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix} = \mathbb{0} \qquad \begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix} \in \ker(S^T)$$

$$\Rightarrow \frac{d}{dt}(C_S + C_I + C_R) = 0$$

$$N = C_S + C_I + C_R.$$

② $$\frac{d}{dt} C_I = J_1(\mathbb{C}) - J_2(\mathbb{C})$$
$$= (k_1^+ C_S - k_2^+) C_I$$

$$k_1^+ C_S - k_2^+ < 0, \qquad \frac{d}{dt} C_I < 0$$

$$R_0 C_S = \frac{k_1^+}{k_2^+} C_S < 1$$

$$R_0 = \frac{k_1^+}{k_2^+} : \text{basic number of reproduction}$$

③ Steady state.

$$J(C^{st}) = 0 \quad \rightarrow \quad C_I^{st} = 0$$

$$C_S^{st} = N - C_R^{st}$$

additional conservation law

$$\frac{d}{dt} C_S = -k_1^+ C_I C_S$$

$$\frac{d}{dt} C_R = k_2^+ C_I$$

$$\rightarrow \quad \frac{d}{dt} C_S = -\frac{k_1^+}{k_2^+} C_S \frac{d}{dt} C_R$$

$$\rightarrow \quad \frac{d}{dt}(\ln C_S + R_0 C_R) = 0$$

$$\ln C_S + R_0 C_R = \text{const.}$$

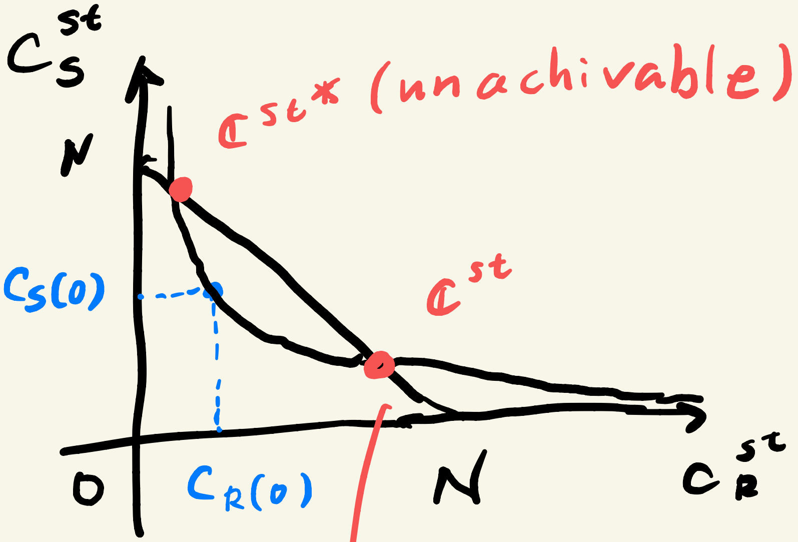
$C_S(0)$, $C_R(0)$: C_S and C_R at time $t=0$

$$\ln C_S^{st} + R_0 C_R^{st} = \ln C_S(0) + R_0 C_R(0)$$

$$\Rightarrow \quad C_S^{st} = C_S(0) \exp\left[R_0 [C_R(0) - C_R^{st}] \right]$$

$$C_S^{st} = N - C_R^{st}$$

$$C_S^{st} = C_S(0)\exp[k_0(C_R(0) - C_R^{st})]$$

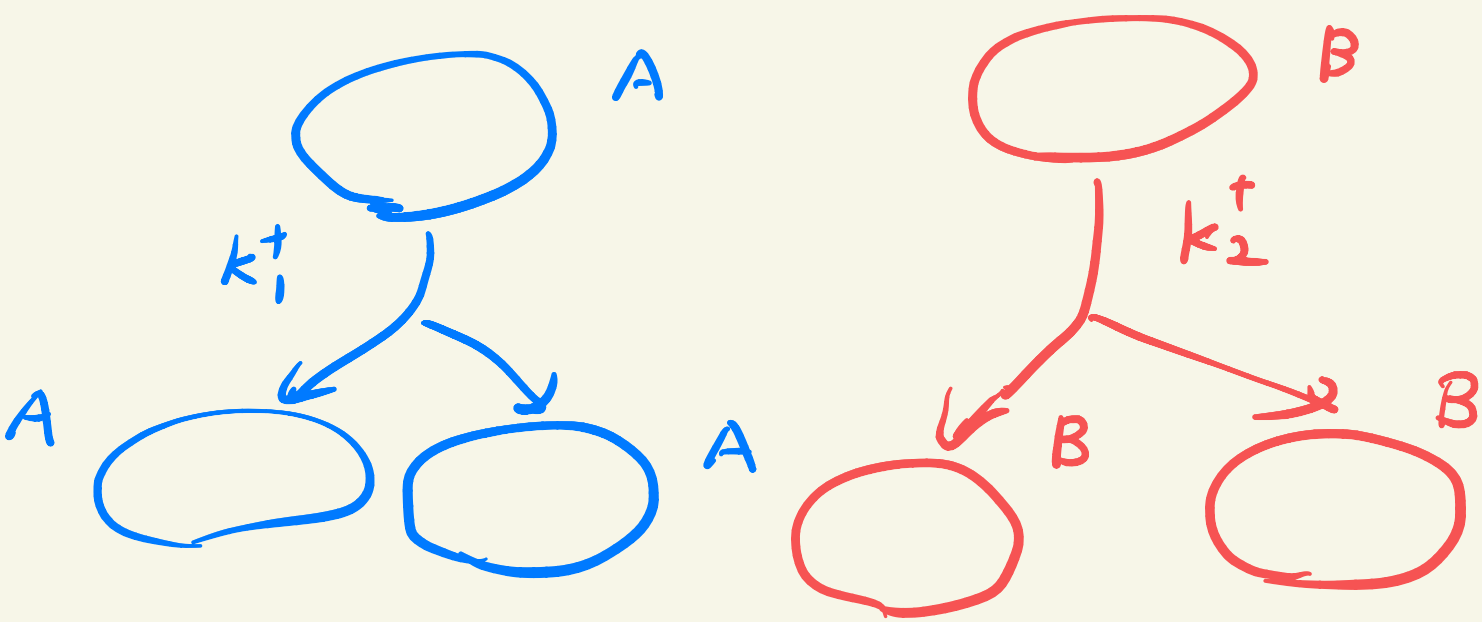


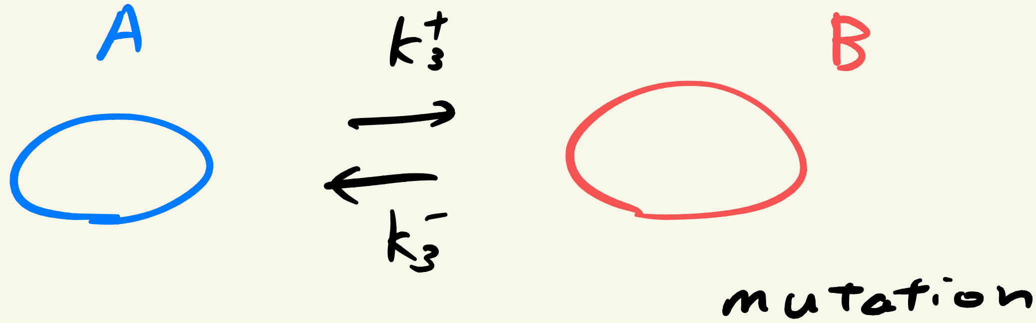
$$\left(\begin{array}{l} C_I(0) \geq 0 \\ \rightarrow \quad C_S(0) + C_R(0) \leq N \end{array} \right)$$

$\frac{d}{dt} C_R \geq 0 \rightarrow$ achivable steady state

Example 7: Cell differentiation

type A   type B





$$\left[\begin{array}{l} A \xrightarrow{k_1^+} 2A \\ B \xrightarrow{k_2^+} 2B \\ A \underset{k_3^-}{\overset{k_3^+}{\rightleftharpoons}} B \end{array}\right.$$

Rate eq.

$$\mathbb{C} = \begin{pmatrix} c_A \\ c_B \end{pmatrix} \qquad \mathbb{J}(\mathbb{C}) = \begin{pmatrix} k_1^+ c_A \\ k_2^+ c_B \\ k_3^+ c_A - k_3^- c_B \end{pmatrix}$$

$$\frac{d}{dt}\mathbb{C} = \underbrace{\begin{pmatrix} 1 & 0 & -1 \\ 0 & 1 & 1 \end{pmatrix}}_{\mathbb{S}} \mathbb{J}(\mathbb{C})$$

① $\operatorname{rank}(\$) = 2$

$$\dim(\ker(\$^T)) = 2 - 2 = 0$$

$$\dim(\ker(\$)) = 3 - 2 = 1$$

$$\begin{pmatrix} 1 & 0 & -1 \\ 0 & 1 & 1 \end{pmatrix} \begin{pmatrix} 1 \\ -1 \\ 1 \end{pmatrix} = \mathbb{0}$$

$$\begin{pmatrix} \alpha \\ -\alpha \\ \alpha \end{pmatrix} \in \ker(\$)$$

$$\mathbb{J}(\mathbb{C}^{st}) = \begin{pmatrix} \alpha \\ -\alpha \\ \alpha \end{pmatrix} \quad (\alpha \neq 0)$$

is <u>not</u> achivable !

$$\left.\begin{array}{l} J_1(\mathbb{C}) \geq 0 \\ J_2(\mathbb{C}) \geq 0 \end{array}\right. \rightarrow \quad \alpha = 0$$

(2) $$p_A = \frac{c_A}{c_A + c_B}$$

$$p_B = \frac{c_B}{c_A + c_B}$$

Remark $\frac{d}{dt}(c_A + c_B) \neq 0$

$[\dim(\ker(S^T)) = 0]$

Notation

$k_1^+ = \lambda_A$

$k_2^+ = \lambda_B$

$k_3^+ = W_{BA}$ $\qquad k_3^- = W_{AB}$

$\hookrightarrow$

$$\frac{d}{dt} p_A = \frac{1}{c_A + c_B} \frac{d}{dt} c_A + c_A \frac{d}{dt}\left(\frac{1}{c_A + c_B}\right)$$

$$= \lambda_A p_A + W_{AB} p_B - W_{BA} p_A$$

$$- p_A (\lambda_A p_A + \lambda_B p_B]$$

(nonlinear master Eq.)

Expected value $\langle \lambda \rangle = \lambda_A P_A + \lambda_B P_B$

$$\frac{d}{dt} P_A = (\lambda_A - \langle \lambda \rangle) P_A + W_{AB} P_B - W_{BA} P_A$$

For P_B

$$\frac{d}{dt} P_B = (\lambda_B - \langle \lambda \rangle) P_B + W_{BA} P_A - W_{AB} P_B$$

$$\mathbb{P} = \begin{pmatrix} P_A \\ P_B \end{pmatrix} \qquad \tilde{\mathbb{J}}(\mathbb{P}) = \begin{pmatrix} (\lambda_A - \langle \lambda \rangle) P_A \\ (\lambda_B - \langle \lambda \rangle) P_B \\ W_{BA} P_A - W_{AB} P_B \end{pmatrix}$$

$$\frac{d}{dt} \mathbb{P} = \underbrace{\begin{pmatrix} 1 & 0 & -1 \\ 0 & 1 & 1 \end{pmatrix}}_{\text{same } \mathbb{S}\,!} \tilde{\mathbb{J}}(\mathbb{P})$$

$$\tilde{\mathbb{J}}(\mathbb{P}^{st}) = \begin{pmatrix} \alpha \\ -\alpha \\ \alpha \end{pmatrix} \in \ker(\mathbb{S})$$

<u>achivable</u> !

$$\frac{d}{dt}\mathbb{p}^{st} = \mathbb{S}\,\tilde{\mathbb{J}}(\mathbb{p}^{st}) = \mathbb{S}\begin{pmatrix}\alpha\\ -\alpha\\ \alpha\end{pmatrix} = 0 .$$

"steady"- state.

Check.

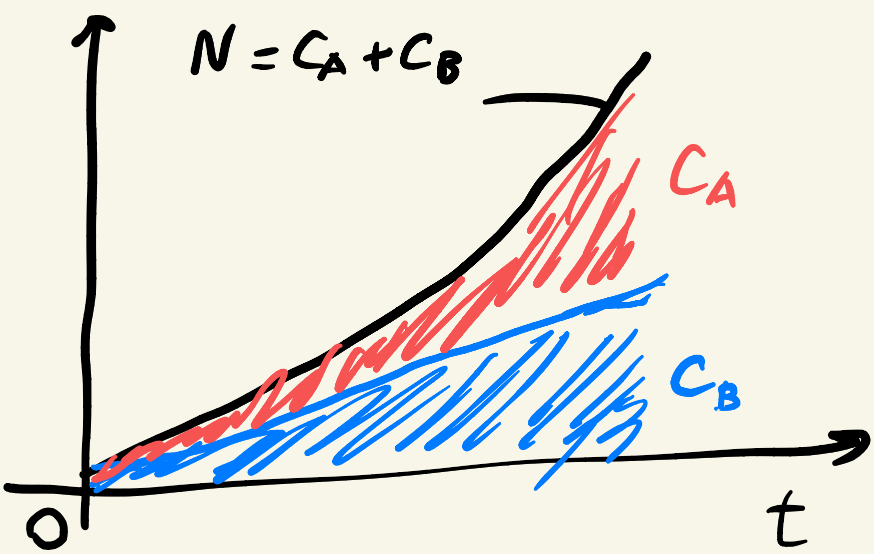
$$\begin{cases} \lambda_A P_A - \langle\lambda\rangle P_A = \alpha \\ \lambda_B P_B - \langle\lambda\rangle P_B = -\alpha . \end{cases}$$

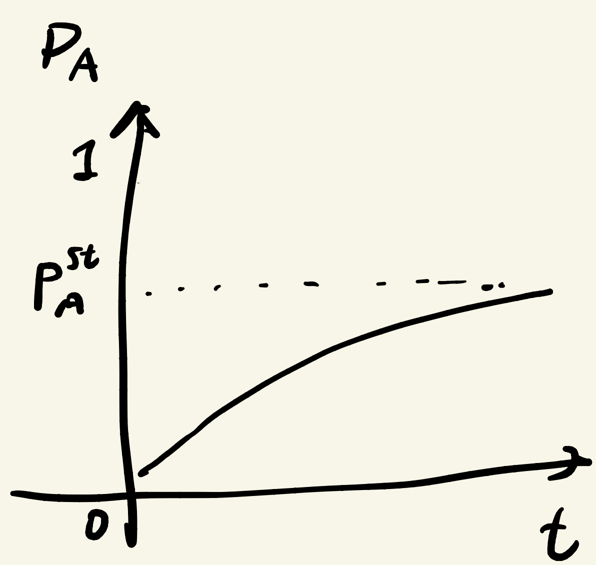
$$\rightarrow \lambda_A P_A + \lambda_B P_B - \langle\lambda\rangle (P_A + P_B) = 0$$

ok.

$$\underbrace{(\lambda_A p_A - \langle\lambda\rangle) P_A}_{\text{selection}} = \underbrace{W_{AB} P_B - W_{BA} P_A}_{\text{mutation}}$$

balanced!





Summary

- SIR model

It is difficult to obtain a steady-state in general.

some steady states are not achivable.

- Cell differentialiton

$$\frac{d}{dt}\mathbb{C} = \mathbb{S}\mathbb{J}(\mathbb{C})$$

$\mathbb{S}\mathbb{J}(\mathbb{C}^{st}) = \mathbb{0}$ is not achivable.

$$\frac{d}{dt}\mathbb{P} = \mathbb{S}\tilde{\mathbb{J}}(\mathbb{P})$$

$\mathbb{S}\tilde{\mathbb{J}}(\mathbb{P}^{st}) = \mathbb{0}$ is achivable?

③

fitness

$$f_A = \frac{d}{dt} \ln c_A$$

$$f_B = \frac{d}{dt} \ln c_B$$

Effective growth

$$\frac{d}{dt} \ln(c_A + c_B)$$

$$= \frac{1}{c_A + c_B} \frac{d}{dt} c_A + \frac{1}{c_A + c_B} \frac{d}{dt} c_B$$

$$= p_A f_A + p_B f_B$$

$$= \langle f \rangle$$

$$\frac{d}{dt} \ln p_A = -\frac{d}{dt} \ln(c_A + c_B) + \frac{d}{dt} \ln c_A$$

$$= f_A - \langle f \rangle$$

$$\frac{d}{dt} \ln p_B = f_B - \langle f \rangle$$

- Price equation

observable $R_A \in \mathbb{R}$

$R_B \in \mathbb{R}$

$$\langle R \rangle = R_A P_A + R_B P_B$$

$$\frac{d\langle R \rangle}{dt} = \left\langle \frac{dR}{dt} \right\rangle + \mathrm{cov}(f, R)$$

- $\mathrm{cov}(f, R) = \langle (f - \langle f \rangle)(R - \langle R \rangle) \rangle$

∴
$$\frac{d\langle R \rangle}{dt} - \left\langle \frac{dR}{dt} \right\rangle = \frac{d}{dt}(P_A R_A + P_B R_B) - P_A \frac{dR_A}{dt} - P_B \frac{dR_B}{dt}$$

$$= R_A \frac{dP_A}{dt} + R_B \frac{dP_B}{dt}$$

$P_A + P_B = 1$

$\rightarrow \frac{d}{dt}(P_A + P_B) = 0$

$$= R_A \frac{dP_A}{dt} + R_B \frac{dP_B}{dt} - \langle R \rangle \frac{d}{dt}(P_A + P_B)$$

$$= (R_A - \langle R \rangle) \frac{dP_A}{dt} + (R_B - \langle R \rangle) \frac{dP_B}{dt}$$

$$= (R_A - \langle R \rangle) P_A \frac{d \ln P_A}{dt} + (R_B - \langle R \rangle) P_B \frac{d \ln P_B}{dt}$$

$$= (R_A - \langle R \rangle)(f_A - \langle f \rangle) P_A + (R_B - \langle R \rangle)(f_B - \langle f \rangle) P_B = \mathrm{cov}(f, R)$$

- Cauchy - Schwarz inequality

$$\underset{\underset{Var(f)}{\shortparallel}}{Cov(f,f)}\ \underset{\underset{Var(R)}{\shortparallel}}{Cov(R,R)} \geq (Cov(R,f))^2$$

$$\left[\begin{array}{l} \langle\langle a,a\rangle\rangle \langle\langle b,b\rangle\rangle \geq \langle\langle a,b\rangle\rangle^2 \\ \qquad \langle\langle \ldots,\ldots\rangle\rangle \text{ inner product} \\ a = f - \langle f\rangle \\ b = R - \langle R\rangle \\ \langle\langle \ldots,\ldots\rangle\rangle = \langle\ ,\ \rangle \end{array}\right.$$

- Cramér-Rao inequality

$$Var(f) \geq \frac{Cov(R,f)^2}{Var(R)}$$

Price eq.

$$= \frac{\left(\frac{d\langle R\rangle}{dt} - \langle\frac{dR}{dt}\rangle\right)^2}{Var(R)}$$

$$Var(f) = \left\langle \left(\frac{d\ln P}{dt}\right)^2 \right\rangle$$

: Fisher information (of t)

$$= P_A\left(\frac{d\ln P_A}{dt}\right)^2 + P_B\left(\frac{d\ln P_B}{dt}\right)^2$$

$$= \frac{1}{P_A}\left(\frac{dP_A}{dt}\right)^2 + \frac{1}{P_B}\left(\frac{dP_B}{dt}\right)^2$$

$\langle R \rangle = t, \quad \left\langle \frac{dR}{dt} \right\rangle = 0$

$$\rightarrow \quad \left\langle \left(\frac{d \ln P}{dt} \right)^2 \right\rangle \geq \frac{1}{\mathrm{var}(R)}$$

Cramér-Rao inequality.

$\left\langle \frac{dR}{dt} \right\rangle = 0$

$$\rightarrow \quad \left\langle \left(\frac{d \ln P}{dt} \right)^2 \right\rangle \geq \left(\frac{\frac{d\langle R \rangle}{dt}}{\sqrt{\mathrm{var}(R)}} \right)^2$$

$$\| \qquad\qquad\qquad\qquad)$$

$$\mathrm{var}(f) \qquad\qquad \text{speed}$$

$$\| \qquad\qquad\qquad \text{of } R$$

$$\left(\frac{\frac{d\langle f \rangle}{dt} - \left\langle \frac{df}{dt} \right\rangle}{\sqrt{\mathrm{var}(f)}} \right)^2$$

$$\|$$

$$\frac{ds^2}{dt^2} \leftarrow (\text{speed})^2$$

information geometry

$$\frac{ds^2}{dt^2} = \left\langle \left(\frac{d}{dt}\ln P\right)^2 \right\rangle$$

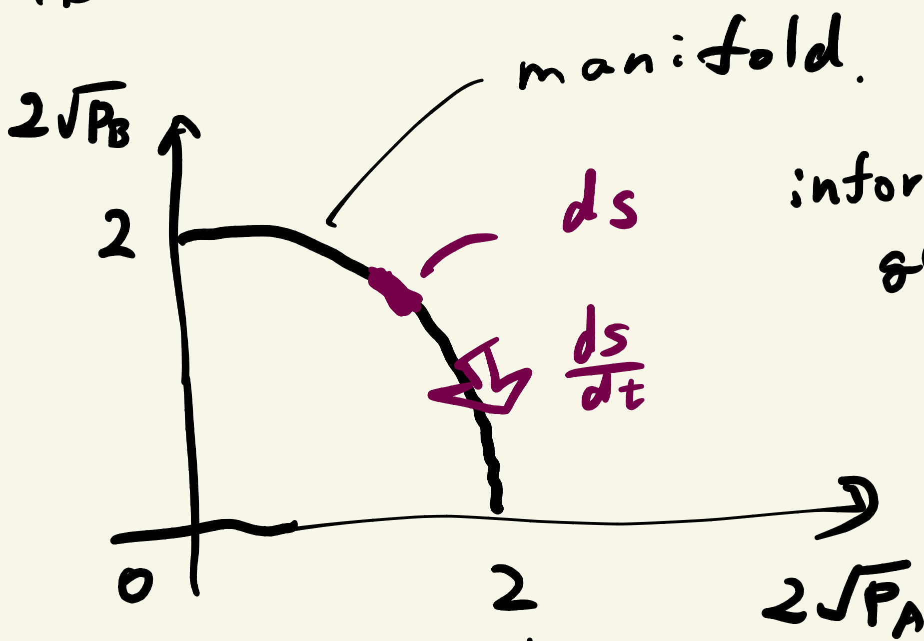
$$= P_A\left(\frac{d}{dt}\ln P_A\right)^2 + P_B\left(\frac{d}{dt}\ln P_B\right)^2$$

$$= \frac{1}{P_A}\left(\frac{dP_A}{dt}\right)^2 + \frac{1}{P_B}\left(\frac{dP_B}{dt}\right)^2$$

$$= \left(\frac{2\,d\sqrt{P_A}}{dt}\right)^2 + \left(\frac{2\,d\sqrt{P_B}}{dt}\right)^2$$

$$ds^2 = \left(2\,d\sqrt{P_A}\right)^2 + \left(2\,d\sqrt{P_B}\right)^2$$

$$P_A + P_B = 1 \;\rightarrow\; \left(2\sqrt{P_A}\right)^2 + \left(2\sqrt{P_B}\right)^2 = 4$$



information geometry.

Cramér-Rao inequality.

$$\frac{ds^2}{dt^2} \geq \left(\frac{\frac{d\langle R\rangle}{dt}}{\sqrt{\mathrm{Var}(R)}}\right)^2$$

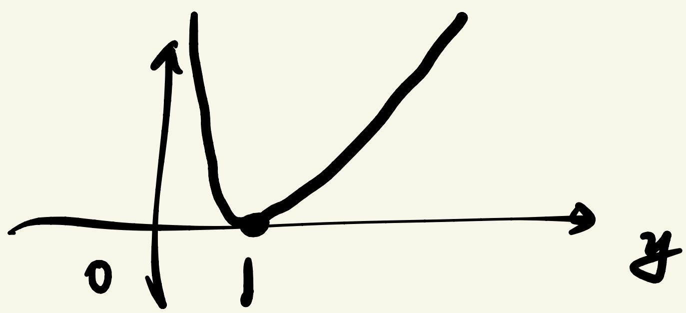
- Kullback-Leibler divergence

$x_i > 0 \quad x_i' > 0$

$$D_{KL}(x \| x') = \sum_i \left(x_i \ln \frac{x_i}{x_i'} - x_i + x_i' \right)$$

$$= \sum_i x_i' \, f\left(\frac{x_i}{x_i'} \right)$$

$$f(y) = \ln y - 1 + \frac{1}{y}$$



① $D_{KL}(x \| x') \geq 0$

$\because \; f\left(\frac{x_i}{x_i'}\right) \geq 0$

$x_i > 0$

② $D_{KL}(x \| x') = 0 \iff \forall i, \; x_i = x_i'$

$\because \; f(y) = 0 \iff y = 1$

③ $2 D_{KL}(x \| x + dx)$

$$= \underbrace{\sum_i \frac{(dx_i)^2}{x_i}}_{ds^2} + O(dx^3)$$

$D_{KL}(x \| x')$: <u>global</u>

$$\frac{1}{2} ds^2 = D_{KL}(x \| x + dx)$$

<u>local</u>

- Chemical thermodynamics

$$\sum_{i=1}^{N} \nu_{i\rho} X_i \underset{k_\rho^-}{\overset{k_\rho^+}{\rightleftarrows}} \sum_{i=1}^{N} \kappa_{i\rho} X_i$$

X_i : chemical spicies (closed)

$\kappa_{i\rho} \in \mathbb{N}$, $\nu_{i\rho} \in \mathbb{N}$

$\rho \in \{1, \ldots, M\}$

$$\mathbb{C} = \begin{pmatrix} C_{X_1} \\ \vdots \\ \vdots \\ C_{X_N} \end{pmatrix} \qquad \mathbb{S}_{i\rho} = \kappa_{i\rho} - \nu_{i\rho}$$

$\mathbb{S}$: $N \times M$ matrix

$$J_e^+(\mathbb{C}) = k_e^+ \prod_{i=1}^{N} C_{x_i}^{\nu_{ie}}$$

$$J_e^-(\mathbb{C}) = k_e^- \prod_{i=1}^{N} C_{x_i}^{\kappa_{ie}}$$

$$J_e^+(\mathbb{C}) - J_e^-(\mathbb{C}) = J_e(\mathbb{C})$$

$$\mathbb{J}(\mathbb{C}) = \begin{pmatrix} J_1(\mathbb{C}) \\ \vdots \\ J_M(\mathbb{C}) \end{pmatrix}$$

Rate eq.

$$\frac{d}{dt}\mathbb{C} = \mathbb{S}\,\mathbb{J}(\mathbb{C})$$

Entropy production rate

$$\sigma = \sum_{e=1}^{M} J_e(\mathbb{C}) F_e(\mathbb{C}) \ (\geq 0)$$

$$F_e(\mathbb{C}) = \ln \frac{J_e^+(\mathbb{C})}{J_e^-(\mathbb{C})}.$$

$$\sigma = \sum_{\rho=1}^{m} \left[J^{+}_{\rho}(\mathbb{C}) - J^{-}_{\rho}(\mathbb{C}) \right] \ln \frac{J^{+}_{\rho}(\mathbb{C})}{J^{-}_{\rho}(\mathbb{C})}$$

$$= \sum_{\rho=1}^{m} \left[J^{+}_{\rho}(\mathbb{C}) \ln \frac{J^{+}_{\rho}(\mathbb{C})}{J^{-}_{\rho}(\mathbb{C})} - J^{+}_{\rho}(\mathbb{C}) + J^{-}_{\rho}(\mathbb{C}) \right]$$

$$+ \sum_{\rho=1}^{M} \left[J^{-}_{\rho}(\mathbb{C}) \ln \frac{J^{-}_{\rho}(\mathbb{C})}{J^{+}_{\rho}(\mathbb{C})} - J^{-}_{\rho}(\mathbb{C}) + J^{+}_{\rho}(\mathbb{C}) \right]$$

$$= \underline{D_{KL}\left(\mathbb{J}^{+}(\mathbb{C}) \| \mathbb{J}^{-}(\mathbb{C})\right) + D_{KL}\left(\mathbb{J}^{-}(\mathbb{C}) \| \mathbb{J}^{+}(\mathbb{C})\right)}$$

$$\mathbb{J}^{+}(\mathbb{C}) = \begin{pmatrix} J^{+}_{1}(\mathbb{C}) \\ \vdots \\ J^{+}_{M}(\mathbb{C}) \end{pmatrix} \qquad \mathbb{J}^{-}(\mathbb{C}) = \begin{pmatrix} J^{-}(\mathbb{C}) \\ \vdots \\ J^{+}(\mathbb{C}) \end{pmatrix}$$

<u>geometric!</u>

$$\sigma \geq 0$$

$$\sigma = 0 \Rightarrow \mathbb{J}^{+}(\mathbb{C}) = \mathbb{J}^{-}(\mathbb{C})$$

$$(\mathbb{J}(\mathbb{C}) = 0)$$

Assumption : detailed balanced condition

$$\cdot \ \frac{k_\rho^+}{k_\rho^-} = \prod_{i=1}^{N} \left(C_{x_i}^{eq}\right)^{\kappa_{i\rho} - \nu_{i\rho}}$$

$$F_\rho(\mathbb{C}) = \ln\left[\frac{k_\rho^+}{k_\rho^-} \prod_{i=1}^{N} \left(C_{x_i}\right)^{\nu_{i\rho} - \kappa_{i\rho}}\right]$$

$$= \ln\left[\prod_{i=1}^{N} \left(\frac{C_{x_i}^{eq}}{C_{x_i}}\right)^{\kappa_{i\rho} - \nu_{i\rho}}\right]$$

$$= \sum_{i=1}^{N} (\kappa_{i\rho} - \nu_{i\rho}) \ln\left(\frac{C_{x_i}^{eq}}{C_{x_i}}\right)$$

$$= \sum_{i=1}^{N} \mathbb{S}_{i\rho} \ln\left(\frac{C_{x_i}^{eq}}{C_{x_i}}\right)$$

Entropy production rate

$$\sigma = \sum_{\rho=1}^{M} F_\rho(\mathbb{C})\, J_\rho(\mathbb{C})$$

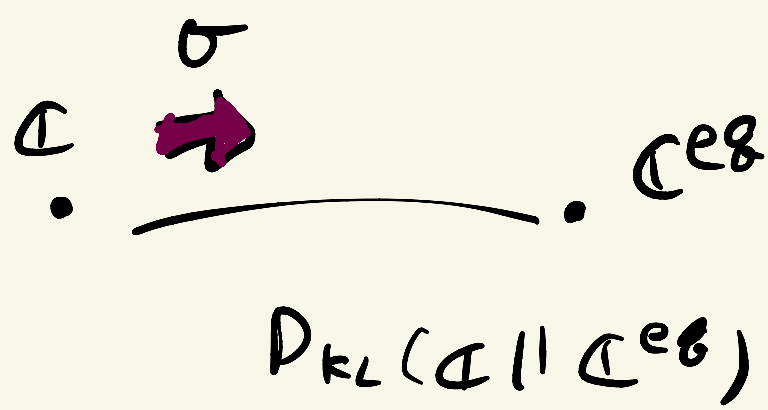
$$= \sum_{i=1}^{N} \underbrace{\left[\sum_{\rho=1}^{M} \mathbb{S}_{i\rho} J_\rho(\mathbb{C})\right]}_{\text{Rate eq.}} \ln\left(\frac{C_{x_i}^{eq}}{C_{x_i}}\right)$$

$$\sigma = \sum_{i=1}^{N} \left(\frac{dc_{x_i}}{dt}\right) \ln \frac{c^{eq}_{x_i}}{c_{x_i}}$$

$$= -\frac{d}{dt}\left[\sum_{i=1}^{N} c_{x_i} \ln \frac{c_{x_i}}{c^{eq}_{x_i}} - c_{x_i} + c^{eq}_{x_i}\right]$$

$$\left(\frac{d}{dt} c^{eq}_{x_i} = 0\right)$$

$$= -\frac{d}{dt} D_{KL}(\mathbb{C} \,\|\, \mathbb{C}^{eq}) \quad (\geq 0)$$



<u>speed</u>

Summary

★ population dynamics

- Price eq.

$$\frac{d\langle R\rangle}{dt} = \left\langle \frac{dR}{dt} \right\rangle + \mathrm{cov}(f, R)$$

- Cramér-Rao inequality

$$\mathrm{var}(f) = \frac{ds^2}{dt^2} \geq \frac{\left(\frac{d\langle R\rangle}{dt}\right)^2}{\mathrm{var}(R)}.$$

★ chemical thermodynamics

$$\sigma = D_{KL}(J^+(\mathbb{C}) \| J^-(\mathbb{C})) + D_{KL}(J^-(\mathbb{C}) \| J^+(\mathbb{C}))$$

detailed balance condition

$$\Rightarrow \quad \sigma = -\frac{d}{dt} D_{KL}(\mathbb{C} \| \mathbb{C}^{eq})$$