Nonequilibrium thermodynamics of stochastic chemical reaction systems

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BICMR: Beijing International Center for Mathematical Research
Summary of Ge group

Stochastic theory of nonequilibrium statistical mechanics
- JSP06, 08
- PRE09, 10, 13, 14
- JCP12; JSTAT15

Nonequilibrium landscape theory and rate formulas
- PRL09, 15
- JRSI11; Chaos12

Stochastic modeling of biophysical systems
- JPCB08, 13, 16; JPA12
- Science13; Cell14; MSB15

Statistical machine learning of single-cell data
- CR15

Stochastic Biophysics (Biomath)

Providing analytical tools

Providing scientific problems

Theory → Applications
What is life

• Erwin Schrödinger was the first one trying to apply mathematical/physical arguments to study living matters;
• He explains that living matter evades the decay to thermodynamical equilibrium (death) by **homeostatically** maintaining negative entropy in an open system.
Nonequilibrium thermodynamics and chemical oscillation

Belousov–Zhabotinsky reaction

Brusselator

\[ A \rightarrow X \quad 2X + Y \rightarrow 3X \quad B + X \rightarrow Y + D \quad X \rightarrow E \]

Entropy production

Nonequilibrium steady state

Nonequilibrium thermodynamics

\[ dS = d_eS + d_iS \]

\[ epr = d_iS = \sum_{k} J_k \cdot X_k \geq 0 \]
The fundamental equation in nonequilibrium thermodynamics

Clausius inequality

\[ dS \geq \frac{Q}{T} \]

Entropy production

\[ epr = dS - \frac{Q}{T} \geq 0 \]

More general

\[ dS = d_{e}S + d_{i}S \]

\[ epr = d_{i}S = \sum_{k} J_{k} \cdot X_{k} \geq 0 \]
Nonequilibrium statistical mechanics

Nonequilibrium thermodynamics is not easy to be applied.

- Needs the idea of stochastic process;
- Understand where is the energy input and output

Ion pump at cell membrane

Muscle contraction: transduction from chemical energy to mechanical energy
E. Eisenberg and T.L. Hill, Science (1985)
Mathematical theory of nonequilibrium steady state

Time-independent (stationary) Markov process

Min Qian (1927-)
Recipient of Hua Loo-Keng Mathematics Prize (华罗庚数学奖) in 2013

Second law of thermodynamics is statistical

“The truth of the second law is therefore a statistical, not mathematical, truth, for it depends on the fact the bodies we deal with consist of millions of molecules, and that we never can get hold of single molecules.”

“Hence the second law of thermodynamics is continuously violated, and that to a considerable extent, in any sufficiently small group of molecules belonging to a real body.”

*Nature* 17, 278 (1878)

J.C. Maxwell (1831-1879)
Which kind of physical/chemical processes can be described by stochastic processes?

- Mesoscopic scale (time and space)
- Single-molecule and single-cell (subcellular) dynamics
- Trajectory perspective
Stochastic trajectory observed

Single Brownian particle

Single-molecule enzyme kinetics


Second law: from inequality to equality (Fluctuation theorems)

Qian, M., et al. (1981, 1984)


Jarzynski equality

\[
\langle e^{-\beta W(\omega)} \rangle = e^{-\beta \Delta F}
\]

\[
\langle W(\omega) \rangle \geq \Delta F
\]

\[
\langle e^{-Epr(\omega)} \rangle = 1 \quad \frac{P(Epr(\omega) = z)}{P(Epr(\omega) = -z)} = e^{z} \quad I(z) = I(-z) - z
\]

Crooks, G. (1998); Van den Broeck, C. and Esposito, M. (2010); et al.

\[
\langle e^{-K(\omega)} \rangle = 1 \quad \frac{P(K(\omega) = z)}{P(K(\omega) = -z)} = e^{z} \quad \langle K(\omega) \rangle \geq 0
\]

Entropy production along the trajectory

\[
epr = \lim_{t \to \infty} \frac{1}{t} Epr(\omega) = \lim_{t \to \infty} \frac{1}{t} \log \frac{P(\{\omega_s : 0 \leq s \leq t\})}{P(\{r \omega_s = \omega_{t-s} : 0 \leq s \leq t\})}
\]
Experimental validation and application


Reversible Michaelis-Menten enzyme kinetics

Two reversible Michaelis-Menten reactions


Kinetic scheme of a simple reversible enzyme. From the perspective of a single enzyme molecule, the reaction is unimolecular and cyclic.
From concentration to probability

Pseudo-first order reaction constants

\[ k_1 = k_1^0 [S] \quad k_{-3} = k_{-3}^0 [P] \]

The evolution of probability distribution

\[
\frac{dP_E(t)}{dt} = -(k_1 + k_{-3}) P_E(t) + k_{-1} P_{ES}(t) + k_3 P_{EP}(t)
\]

\[
\frac{dP_{ES}(t)}{dt} = k_1 P_E(t) - (k_{-1} + k_2) P_{ES}(t) + k_{-2} P_{EP}(t)
\]

\[
\frac{dP_{EP}(t)}{dt} = k_{-3} P_E(t) + k_2 P_{ES}(t) - (k_{-2} + k_3) P_{EP}(t)
\]
Cyclic kinetics of enzyme molecules

$$E + S \rightleftharpoons ES \rightleftharpoons EP \rightleftharpoons E + P.$$  

Free energy (chemical potential) 
$$\mu = \mu^0 + k_B T \ln c$$

Constant conc. $[S]$ and $[P]$ held constant 

Split it into the following three reactions:

1. $S + E \rightleftharpoons ES$ \hspace{1cm} \(\Delta \mu_1 = \Delta \mu_1^0 + k_B T \ln \frac{p_{ES}}{[S][E]}\)
2. $ES \rightleftharpoons EP$ \hspace{1cm} \(\Delta \mu_2 = \Delta \mu_2^0 + k_B T \ln \frac{p_{EP}}{p_{ES}}\)
3. $EP \rightleftharpoons E + P$ \hspace{1cm} \(\Delta \mu_3 = \Delta \mu_3^0 + k_B T \ln \frac{p_E[P]}{p_{EP}}\)

$$\Delta \mu = \Delta \mu_1 + \Delta \mu_2 + \Delta \mu_3 = \Delta \mu_1^0 + \Delta \mu_2^0 + \Delta \mu_3^0 + k_B T \ln \frac{[P]}{[S]}$$
At equilibrium

Now we need to evaluate \( \Delta \mu_1^0 + \Delta \mu_2^0 + \Delta \mu_3^0 \)

Take \( S + E \Leftrightarrow ES \) for example, at equilibrium,

\[
\Delta \mu_1 = 0 \quad k_1^0 [S]_{eq} [E]_{eq} = k_{-1} [ES]_{eq}
\]

\[
0 = \Delta \mu_1^0 + k_B T \ln \frac{[ES]_{eq}}{[S]_{eq}[E]_{eq}} = \Delta \mu_1^0 + k_B T \ln \frac{k_1^0}{k_{-1}} \quad \text{Therefore, } \Delta \mu_1^0 = -k_B T \ln \frac{k_1^0}{k_{-1}}
\]

\[
\Delta \mu_1^0 + \Delta \mu_2^0 + \Delta \mu_3^0 = -k_B T \ln \frac{k_1^0 k_2 k_3}{k_{-1} k_{-2} k_{-3}}
\]

Therefore, \( \Delta \mu = -k_B T \ln \frac{k_1^0 k_2 k_3 [S]}{k_{-1} k_{-2} k_{-3} [P]} \)

When \[
\frac{[S]}{[P]} = \frac{k_{-1} k_{-2} k_{-3}^0}{k_1^0 k_2 k_3} \quad \Delta \mu = 0
\]

\[
\frac{[S]}{[P]} > \frac{k_{-1} k_{-2} k_{-3}^0}{k_1^0 k_2 k_3} \quad \Delta \mu < 0
\]
Simulated turnover traces of a single molecule

\[ \nu(t) \]

\[ S \leftrightarrow P \]

\[ \nu_+(t) : S \rightarrow P \quad \nu_-(t) : P \rightarrow S \]

the number of occurrences of forward and backward cycles up to time \( t \)


Steady-state cycle fluxes and nonequilibrium steady state

\[
J^{ss} = \lim_{t \to \infty} \frac{\nu(t)}{t} = \frac{V_S \frac{[S]}{K_{mS}} - V_P \frac{[P]}{K_{mP}}}{1 + \frac{[S]}{K_{mS}} + \frac{[P]}{K_{mP}}} = J^{ss}_+ - J^{ss}_-. 
\]

Michaelis-Menten kinetics

\[
J^{ss}_+ = \lim_{t \to \infty} \frac{\nu_+(t)}{t} = \frac{V_S \frac{[S]}{K_{mS}}}{1 + \frac{[S]}{K_{mS}} + \frac{[P]}{K_{mP}}}; \quad J^{ss}_- = \lim_{t \to \infty} \frac{\nu_-(t)}{t} = \frac{V_P \frac{[P]}{K_{mP}}}{1 + \frac{[S]}{K_{mS}} + \frac{[P]}{K_{mP}}}. 
\]

Chemical potential difference: \[
\Delta \mu = -k_B T \ln \left( \frac{k_1 k_2 k_3 [S]}{k_{-1} k_{-2} k_{-3} [P]} \right) = -k_B T \ln \left( \frac{J^{ss}_+}{J^{ss}_-} \right) \Rightarrow \Delta \mu = 0
\]

Ge, H.: *JPCB* (2008)
Waiting cycle times

The kinetic scheme for computing the waiting cycle times, which also serves for molecular motors.

\[ \langle T \rangle = \frac{1}{J_{ss}^+ + J_{ss}^-}; \langle T_+ \rangle = \frac{1}{J_+^s}; \langle T_- \rangle = \frac{1}{J_-^s}. \]
Generalized Haldane equality

\[ P_E(T = t \mid T_+ < T_-) = P_E(T = t \mid T_- < T_+). \]

Waiting cycle time \( T \) is **independent** of whether the enzyme completes a forward cycle or a backward cycle, although the probability weight of these two cycles might be rather different.

Qian, H. and Xie, X.S.: *Phys. Rev. E* (2006);
Nonequilibrium steady state

**Generalized Haldane Equality**

\[ P_E(T_+ = t \mid T_+ < T_-) = P_E(T_- = t \mid T_- < T_+) \]

**Fluctuation theorem of fluctuating chemical work**

\[ \mu_S - \mu_P = \Delta \mu = k_B T \log \frac{k_1 k_2 k_3}{k_{-1} k_{-2} k_{-3}} \]

\[ W(t) = v(t) \times \Delta \mu \]

\[ \frac{P_E(W(t) = n\Delta \mu)}{P_E(W(t) = -n\Delta \mu)} = e^{\frac{n\Delta \mu}{k_BT}} \]

\[ \langle e^{\frac{W(t)}{k_BT}} \rangle = 1 \]

**Second law in terms of equality**

\[ \Delta \mu = \mu_S - \mu_P \]

**Free energy conservation**

Equilibrium \( \iff \Delta \mu = 0 \).

**Free energy input**

**Entropy production: Free energy dissipation**

Steady state Gallavotti-Cohen-type fluctuation theorems

\[ J^+_t = \frac{\nu_+(t)}{t}, \quad J^-_t = \frac{\nu_-(t)}{t}, \quad J_t = J^+_t - J^-_t \]

\( (J^+_t, J^-_t) \) has the large deviation principle with rate function \( I_1 \).

\[ \frac{1}{t} \log P[(J^+_t, J^-_t) = (x_1, x_2)] \to -I_1(x_1, x_2), t \to +\infty \]

\[ I_1(x_1, x_2) = I_1(x_2, x_1) - \gamma(x_1 - x_2) \]

\( J_t \) has the large deviation principle with rate function \( I_2 \).

\[ \frac{1}{t} \log P[J_t = x] \to -I_2(x), t \to +\infty \]

\[ I_2(x) = I_2(-x) - \gamma x \]

Quasi-time-reversal invariance of 1d B.M. and 3d Bessel process

The distribution is the same as a random flipped 3d Bessel Process

\[ P_E(T_+ = t \mid T_+ < T_-) = P_E(T_- = t \mid T_- < T_+) \]

For diffusion on a 1d circle
Master equation model for the single-molecule system

Consider a motor protein with $N$ different conformations $R_1, R_2, \ldots, R_N$. $k_{ij}$ is the first-order or pseudo-first-order rate constants for the reaction $R_i \rightarrow R_j$.

\[
\frac{dp_i(t)}{dt} = \sum_j \left( p_j k_{ji} - p_i k_{ij} \right)
\]

No matter starting from any initial distribution, it will finally approach its stationary distribution satisfying

\[
\sum_{j=1}^{N} \left( p_j^{ss} k_{ji} - p_i^{ss} k_{ij} \right) = 0
\]

Self-assembly or self-organization

\[p_j^{eq} k_{ji} = p_i^{eq} k_{ij}\]

Detailed balance (equilibrium state)
Canonical ensemble

Under detailed balance condition (equilibrium)

\[ p_{j}^{ss} k_{ji} = p_{i}^{ss} k_{ij} \]

Boltzmann’s law

\[ p_{i}^{ss} = p_{i}^{eq} = \frac{e^{-E_{i}/kT}}{\sum_{j} e^{-E_{j}/kT}} \quad E_{i} = \mu_{i}^{0} \]

Free energy

\[ F = -kT \log \sum_{j} e^{-E_{j}/kT} \]

Entropy

\[ S = -k \sum_{j} p_{j}^{eq} \log p_{j}^{eq} = \frac{\langle E \rangle - F}{T} \]
Time reversibility

Time-reversed process: still satisfy the master equation

\[
\frac{dp_i(t)}{dt} = \sum_j \left( p_j k_{ji}^+ - p_i k_{ij}^+ \right)
\]

For each cycle,

\[
k_{ji}^+ = k_{ji} \iff p_j^{ss} k_{ji} = p_i^{ss} k_{ij}
\]

Kolmogorov cyclic condition
NESS thermodynamic force

NESS thermodynamic force  \( A_{ij}^{ss} = k_B T \log \frac{p_{i}^{ss} k_{ij}}{p_{j}^{ss} k_{ji}} \)

NESS flux  \( J_{ij}^{ss} = p_{i}^{ss} k_{ij} - p_{j}^{ss} k_{ji} \)

NESS entropy production rate

\[ T \cdot epr^{ness} = \sum_{i > j} J_{ij}^{ss} \cdot A_{ij}^{ss} \geq 0 \]
Energy transduction efficiency at NESS

A mechanical system coupled fully reversibly to a chemical reactions, with a constant force resisting the mechanical movement driven by the chemical gradient.

Energy Input (Chemical) = $h_d^{ness} + $ Energy Output (Mechanical)

or

Energy Input (Mechanical) = $h_d^{ness} + $ Energy Output (Chemical)

\[ \eta = \frac{\text{Energy output}}{\text{Energy input}} = \frac{\text{Energy output}}{h_d^{ness} + \text{Energy output}} \leq 1 \]

\[ h_d^{ness} = T \cdot epr^{ness} \text{ all dissipated!} \]

Ge, H. and Qian, H.: PRE (2013)
Time-dependent case

\[
\frac{dp_i(t)}{dt} = \sum_j \left[ p_{ji}(t)k_j(t) - p_{ij}(t)k_i(t) \right]
\]

Quasi-stationary distribution
\[
\sum_{j=1}^{N} \left( p_{ji}(t)k_j(t) - p_{ij}(t)k_i(t) \right) = 0
\]

If \{k_{ij}(t)\} satisfies the detailed balance condition for fixing \(t\)
\[
p_{ji}^{ss}(t)k_j(t) - p_{ij}^{ss}(t)k_i(t) = 0
\]

Boltzmann’s law
\[
p_{i}^{ss}(t) = p_{i}^{eq}(t) = \frac{e^{-E_i(t)/kT}}{\sum_j e^{-E_j(t)/kT}}
\]

Free energy
\[
F(t) = -k_B T \log \sum_j e^{-E_j(t)/kT}
\]
Work and heat along the trajectory

\[ X(T_k) = j \]

\[ X(T_{k-1}) = i \]

\[ \cdots \]

\[ T_{k-1} \]

\[ T_k \]

Work

\[ W = E_{X(T_{k-1})}(T_k) - E_{X(T_{k-1})}(T_{k-1}) = E_i(T_k) - E_i(T_{k-1}) \]

Heat

\[ Q = E_{X(T_k)}(T_k) - E_{X(T_{k-1})}(T_k) = E_j(T_k) - E_i(T_k) \]
Jarzynski equality with detailed balance condition

Work
\[ W = \sum_{k=1}^{\infty} E_{X(T_{k-1})}(T_k) - E_{X(T_{k-1})}(T_{k-1}) \]

Heat
\[ Q = \sum_{k=1}^{\infty} E_{X(T_k)}(T_k) - E_{X(T_{k-1})}(T_k) \]

\[ \Delta E = W + Q = E_{X(T)}(T) - E_{X(0)}(0) \]

\[ \Delta F = F(T) - F(0) \quad W_d = W - \Delta F \quad \text{Dissipative work} \]

Jarzynski equality
\[ \left\langle e^{-\frac{W}{kT}} \right\rangle_{p(0)=p_{eq}(0)} = e^{-\frac{\Delta F}{kT}} \left\langle W \right\rangle_{p(0)=p_{eq}(0)} \geq \Delta F. \]
Hatano-Sasa equality without detailed balance condition

Entropy  \[ \phi_i(t) = -\log p_i^{ss}(t) \]

\[ \Delta \phi = \left( \Delta E - \Delta F \right)/kT \]

Excess heat \[ Q_{ex} = -Q = W - \Delta E = W - kT\Delta \phi - \Delta F \]

Hatano-Sasa equality

\[ \left< e^{-\left( Q_{ex} / kT + \Delta \phi \right)} \right>_{p(0) = p^{ss}(0)} = 1 \]

\[ \Delta S = \Delta \left< \phi \right>_{p(0) = p^{ss}(0)} \geq -Q_{ex} / kT. \]
Mathematical equivalence of Jarzynski and Hatano-Sasa equalities

**Jarzynski equality: local equilibrium**

\[
\left< e^{-W/kT} \right>_{p(0)=p^{eq}(0)} = e^{-\Delta F/kT} \left< W \right>_{p(0)=p^{eq}(0)} \geq \Delta F.
\]

**Hatano-Sasa equality: without local equilibrium**

\[
\left< e^{-(Q_{ex}/kT+\Delta \phi)} \right>_{p(0)=p^{ss}(0)} = 1 \quad \Delta S = \Delta \left< \phi \right>_{p(0)=p^{ss}(0)} \geq -Q_{ex}/kT.
\]

- Are these inequalities already known in the Second Law of classic thermodynamics? Do they really need those conditions under which the fluctuations theorems is valid?
- The traditional Clausius inequality can be in a differential form.

Same theorem for time-dependent Markov process

**Using Feynman-Kac formula of the time-dependent case**

Ge, H. and Qian, M., *JMP* (2007); Ge, H. and Jiang, D.Q., *JSP* (2008);
Decomposition of mesoscopic thermodynamic forces

\[ A_{ij}(t) = k_B T \log \frac{p_i(t)k_{ij}(t)}{\langle \rangle} = A_{ij}^{ss}(t) + \delta A_{ij}(t) \]

\[ A_{ij}^{ss}(t) = k_B T \log \frac{p_i^{ss}(t)k_{ij}(t)}{\langle \rangle} \]

All the results here have also been proved for multidimensional diffusion process.

Free energy dissipation
\[ f_d(t) = \sum_{i>j} J_{ij}(t) \cdot \delta A_{ij}(t) \geq 0 \]

\[ T \cdot epr(t) = Q_{hk}(t) + f_d(t) \]

Ge, H., \textit{PRE} (2009);
Two origins of nonequilibrium

\[ e_{pr}(t) = 0 \text{ for any time } t \iff \text{In the absence of external energy input and at steady state.} \]

\[ Q_{hk}(t) = 0 \text{ for any time } t \iff \text{In the absence of external energy input} \]

\[ f_d(t) = 0 \text{ for any time } t \iff \text{At steady state} \]

The evolution of entropy and relative entropy

Generalized free energy: \( H = k_B T \sum_i p_i \log \frac{p_i}{p_i^{ss}} \)

Relaxation to steady state (Time-independent system)

\[
\frac{dS}{dt} = epr - \frac{Q_{tot}}{T} \quad \frac{dH}{dt} = -f_d;
\]

Time-dependent system

\[
\frac{dS}{dt} = epr - \frac{Q_{tot}}{T} \quad \frac{dH}{dt} = W_d - f_d
\]

Entropy: \( S = -k_B \sum_i p_i \log p_i \)

Dissipative work in Jarzynski equality
Extended Clausius inequality

\[ f_d \geq 0, \quad Q_{hk} \geq 0, \]

\[ T \cdot epr = f_d + Q_{hk} \geq 0. \]

\[ \frac{dS}{dt} = epr - \frac{Q_{tot}}{T} \]

\[ \frac{dS}{dt} \geq - \frac{Q_{tot}}{T} (epr \geq 0) \]

\[ \frac{dS}{dt} \geq - \frac{Q_{ex}}{T} = - \frac{(Q_{tot} - Q_{hk})}{T} (f_d \geq 0) \]

The new Clausius inequality is stronger than the traditional one.

Ge, H., *PRE* (2009);
A generalization of free energy and its balance equation

\[
\frac{dH}{dt} = E_{in} - E_{dis} \leq 0.
\]

\[E_{in} = Q_{hk} \geq 0\] \hspace{1cm} \text{Generalized free energy input}

\[E_{dis} = T \cdot epr \geq 0\] \hspace{1cm} \text{Generalized free energy dissipation}

Ge, H., *PRE* (2009);
Quasi-steady-state perspective versus steady-state perspective

Very slowly changing [ATP], [ADP] and [Pi]

- Quasi-steady-state (QSS) approaching equilibrium state

The chemical kinetics of the internal system (B+C) are the same.

- Approaching nonequilibrium steady state (NESS)

Ge, H. and Qian, H., *PRE* (2013); in preparation (2016)
Thermodynamics of a closed isothermal “universe”

In this case, everything is well defined from traditional chemical thermodynamics.

\[ \frac{dF_{\text{close}}}{dt} = -f_d^{\text{close}} = -T \cdot e_p^{\text{close}} \leq 0. \]

Gibbs states free energy never increase in a closed, isothermal system; while Prigogine states that the entropy production is non-negative in an open system. They are equivalent.

Ge, H. and Qian, H., *PRE* (2013); in preparation (2016)
Thermodynamics of the open system with regenerating system

\[
\frac{dS_{\text{open}}}{dt} = e_{p}^{\text{open}} - \frac{h_{d}^{\text{open}}}{T}
\]

\[e_{p}^{\text{open}} = e_{p}^{\text{close}} = f_{d}^{\text{close}} = -\frac{dF^{\text{close}}}{dt}\]
A quasi-steady-state interpretation of epr decomposition

\[ f_d^{\text{open}} \geq 0, \quad Q_{hk}^{\text{open}} \geq 0, \]
\[ T \cdot e_p^{\text{open}} = f_d^{\text{open}} + Q_{hk}^{\text{open}} \geq 0. \]

(1) \[ e_p^{\text{open}} = e_p^{\text{close}} = f_d^{\text{close}} = -\frac{dF^{\text{close}}}{dt} \]

(2) \[ f_d^{\text{open}}(t) = \sum_{i>j} J_{ij}(t) \cdot k_B T \log \frac{p_i(t)\pi_{qss}^{\text{qss}}(t)}{p_j(t)\pi_{i}^{\text{qss}}(t)} \]

Quasi-steady-state distribution depending on certain parameters which is slowly changing with time

\[ \approx -\frac{dH_{qss}^{\text{close}}}{dt} \]

Holds under quasi-steady-state assumption

\[ H_{qss}^{\text{close}} = k_B T \sum_i p_i(t) \log \frac{p_i(t)}{\pi_{i}^{\text{qss}}(t)} \]
Chemical reaction system at macroscopic level

Forward flux $R_+(x)$

\[ v_{l_1}^+ X_1 + v_{l_2}^+ X_2 + \cdots + v_{l_N}^+ X_N \leftrightarrow v_{l_1}^- X_1 + v_{l_2}^- X_2 + \cdots + v_{l_N}^- X_N \]

Backward flux $R_-(x)$

Stoichiometric matrix $S_{N \times M} = \{s_{ij}\}$, $s_{ij} = v_{ji}$

Flux vector $J_{M \times 1} = \{j_l(x)\}$, $j_l(x) = R_+(x) - R_-(x)$

$x_{N \times 1}$: concentration vector

Rate equation

\[ \frac{dx}{dt} = S \cdot J(x) \]

$SJ(x^*) = 0$

Steady state
Entropy production rate

\[ epr(x) = \sum_{l=1}^{M} \left(R_{+l}(x) - R_{-l}(x)\right) \log \frac{R_{+l}(x)}{R_{-l}(x)} \geq 0 \]

\[ epr(x) = 0 \iff R_{+l}(x) = R_{-l}(x), \forall l \]

Equilibrium state: detailed balance
Equilibrium state is always steady state

Wegscheider-Lewis cycle condition:
For any M-dimensional vector \( \xi = (\xi_1, \xi_2, ..., \xi_M) \) satisfying \( S\xi = 0 \)

have \[ \sum_{l=1}^{M} \xi_l \log \frac{R_{+l}(x)}{R_{-l}(x)} = 0, \forall x. \] Right-null-space
Chemical reaction system at the mesoscopic level

Copy number of all the chemical species \( n = (n_1, n_2, \ldots, n_N) \quad n = x \cdot V \)

Denote \( \mathbf{v}_l = (v_{l1}, v_{l2}, \ldots, v_{lN}), v_{li} = v_{li}^- - v_{li}^+ \)

\( n \rightarrow n + \mathbf{v}_l \) with rate \( r_+(n) \) \quad \( n \rightarrow n - \mathbf{v}_l \) with rate \( r_-(n) \)

Assuming Markovian dynamics

Chemical master equation

\[
\frac{dp_V(n,t)}{dt} = \sum_{l=1}^M \left[ p_V(n - \mathbf{v}_l, t) r_+(n - \mathbf{v}_l) + p_V(n + \mathbf{v}_l, t) r_-(n + \mathbf{v}_l) - p_V(n, t) r_+I(n) - p_V(n, t) r_-I(n) \right]
\]
Mesoscopic nonequilibrium thermodynamics

\[
\frac{dF^{(meso)}}{dt} = E_{in} - epr.
\]

\[
F^{(meso)} = \sum_n p_V(n, t) \log \frac{p_V(n, t)}{p_V^{ss}(n)}
\]

\[
E_{in} = \sum_{l=1}^{M} \sum_n (p_V(n, t)r_{+l}(n) - p_V(n + v_l, t)r_{-l}(n + v_l)) \log \left( \frac{p_V^{ss}(n)r_{+l}(n)}{p_V^{ss}(n + v_l)r_{-l}(n + v_l)} \right)
\]

\[
epr = \sum_{l=1}^{M} \sum_n (p_V(n, t)r_{+l}(n) - p_V(n + v_l, t)r_{-l}(n + v_l)) \log \left( \frac{p_V(n, t)r_{+l}(n)}{p_V(n + v_l, t)r_{-l}(n + v_l)} \right)
\]

Law of large number: from mesoscopic to macroscopic

In the limit of $V$ tending to infinity, with the same initial state

$$r_+(xV)/V \to R_+(x) \quad r_-(xV)/V \to R_-(x)$$

$$\frac{n_V(t)}{V} \to x(t), \text{ for any } t.$$  

Large deviation principle and rate function

$$\frac{1}{V} \log p^_{SS}(xV) \to -\varphi^{SS}(x)$$

$$\sum_{l=1}^{M} R_+(x)[1 - e^{v_l \cdot \nabla x \varphi^{SS}(x)}] + R_-(x)[1 - e^{-v_l \cdot \nabla x \varphi^{SS}(x)}] = 0$$


Kurtz, T. JCP (1972)

Emergent macroscopic nonequilibrium thermodynamics

\[
\frac{dF^{(meso)}}{dt} = E_{in} - epr. \\
V \rightarrow +\infty.
\]

\[
\frac{d\varphi^{ss}(x)}{dt} = cmf(x) - \sigma(x) \leq 0.
\]

\[\frac{F^{(meso)}}{V} \rightarrow \varphi^{ss}(x) \quad \text{A generalization of macroscopic free energy}\]

\[
\frac{E_{in}}{V} \rightarrow cmf(x) = \sum_{l=1}^{M} (R_{+l}(x) - R_{-l}(x)) \log \left( \frac{R_{+l}(x)}{R_{-l}(x)} e^{v_{l} \cdot v_{x} \varphi^{ss}(x)} \right) \geq 0
\]

\[\text{Free energy input}\]

\[\frac{epr}{V} \rightarrow \sigma(x) = \sum_{l=1}^{M} (R_{+l}(x) - R_{-l}(x)) \log \left( \frac{R_{+l}(x)}{R_{-l}(x)} \right) \geq 0 \quad \text{Entropy production rate}\]

Strong and weak detail balance conditions

Strong detailed balance condition (equilibrium)

\[ \sigma(x) = 0 \text{ if and only if } R_{+l}(x) = R_{-l}(x) \]

Weak detailed balance condition

\[ \text{cmf}(x) = 0 \text{ if and only if } \log\left(\frac{R_{+l}(x)}{R_{-l}(x)}\right) = -v_l \cdot \nabla_x \varphi^{ss}(x), \forall l \]

Weak detailed balance condition for each \( x \) is equivalent to Wegscheider-Lewis cycle condition.

\[ \frac{d\varphi^{ss}(x)}{dt} = 0 \text{ if and only if the systems is at steady state.} \]

Ge, H. and Qian, H., arxiv:1601.03159; arxiv: 1604.07115 (2016)
General fluctuation-dissipation theorem for chemical reactions

\[ \nu_{l_1}^+ X_1 + \nu_{l_2}^+ X_2 + \cdots + \nu_{l_N}^+ X_N \leftrightarrow \nu_{l_1}^- X_1 + \nu_{l_2}^- X_2 + \cdots + \nu_{l_N}^- X_N \]

\[ l = 1, 2, \ldots, M \]

**Rate equation**

\[ \frac{dx}{dt} = S J(x) \overset{\text{def}}{=} F(x) \]

Stable fixed point

\[ F(x^*) = 0 \]

**Variance matrix**

\[ \Xi_{ij} = \frac{\partial^2 \varphi^{ss}(x^*)}{\partial x_i \partial x_j} \]

**Fluctuation matrix**

\[ A_{ij} = \sum_{l=1}^{M} (R_{+l}(x^*) + R_{-l}(x^*)) \nu_{li} \nu_{lj} \]

**Dissipation matrix**

\[ B_{ij} = \frac{\partial F_i(x^*)}{\partial x_j} \]

**Equation**

\[ \Xi A \Xi = -\Xi B - B \Xi \]

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