Nonequilibrium Thermodynamic Formalism of Nonlinear Chemical Reaction Systems with Waage-Guldberg’s Law of Mass Action

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Abstract

Macroscopic entropy production $\sigma^{(tot)}$ in the general nonlinear isothermal chemical reaction system with mass action kinetics is decomposed into a free energy dissipation and a house-keeping heat: $\sigma^{(tot)} = \sigma^{(fd)} + \sigma^{(hk)}$; $\sigma^{(fd)} = -dA/dt$, where $A$ is a generalized free energy function. This yields a novel nonequilibrium free energy balance equation $dA/dt = -\sigma^{(tot)} + \sigma^{(hk)}$, which is on a par with celebrated entropy balance equation $dS/dt = \sigma^{(tot)} + \eta^{(ex)}$ where $\eta^{(ex)}$ is the rate of entropy exchange with the environment. For kinetic systems with complex balance, $\sigma^{(fd)}$ and $\sigma^{(hk)}$ are the macroscopic limits of stochastic free energy dissipation and house-keeping heat, which are both nonnegative, in the Delbrück-Gillespie description of

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the stochastic chemical kinetics. Therefore, we show that a full kinetic and thermodynamic theory of chemical reaction systems that transcends mesoscopic and macroscopic levels emerges.

1 Introduction

Inspired by the recent discovery of three non-negative entropy productions in mesoscopic, stochastic nonequilibrium thermodynamics, \( e_p = f_d + Q_{hk} \), interpreted as an equation of free energy balance:

\[
\frac{dF^{(meso)}}{dt} \equiv -f_d = Q_{hk} - e_p
\]

where \( e_p, Q_{hk}, F^{(meso)} \), and \( f_d \) are called entropy production, house-keeping heat, mesoscopic free energy and free energy dissipation [1, 2, 3, 4, 5, 6], we consider the formal kinetics of a general chemical reaction system

\[
\nu_{\ell 1}X_1 + \nu_{\ell 2}X_2 + \cdots \nu_{\ell N}X_N \xrightleftharpoons[k_{\ell - \ell}]{k_{\ell + \ell}} \kappa_{\ell 1}X_1 + \kappa_{\ell 2}X_2 + \cdots \kappa_{\ell N}X_N, \quad (1)
\]

in which \( 1 \leq \ell \leq M \): There are \( N \) species and \( M \) reactions. \( (\kappa_{ij} - \nu_{ij}) \) are stoichiometric coefficients that relate species to reactions. According to Waage-Guldberg’s Law of Mass Action for a macroscopic reaction vessel, at a constant temperature, with rapidly stirred chemical solutions, the concentrations of the species at time \( t \), \( x_i(t) \) for \( X_i \), satisfy the system of ordinary differential equations [7]

\[
\frac{dx_i(t)}{dt} = \sum_{\ell=1}^{M} \left( \kappa_{\ell i} - \nu_{\ell i} \right) \left( J_{+\ell}(x) - J_{-\ell}(x) \right), \quad (2)
\]

with \( x = (x_1, x_2, \cdots, x_N) \) and

\[
J_{+\ell}(x) = k_{+\ell} \prod_{i=1}^{N} x_i^{\nu_{\ell i}}, \quad J_{-\ell}(x) = k_{-\ell} \prod_{i=1}^{N} x_i^{\kappa_{\ell i}}. \quad (3)
\]

For a meaningful thermodynamic analysis, we shall assume in the present paper that \( k_{+\ell} = 0 \) if and only if \( k_{-\ell} = 0 \).

The kinetics of such a chemical reaction system can be very complex. The simple and well-understood cases are linear, unimolecular reaction systems, or nonlinear systems whose steady states are detail balanced [8]. For the latter, it can be shown that the steady state is unique and the net flux in each and every reversible reaction is zero [9] [10]. Therefore, it is an equilibrium steady state. Furthermore, the existence of a chemical equilibrium with detailed balance dictates that the rate constants \( \{k_{\pm \ell}\} \) in such a system satisfy the Wegscheider-Lewis cycle condition [11] [12] [13].

J. W. Gibbs was the first to formulate a free energy function and showed that Waage-Guldberg’s mass action law was closely related to a variational
principle with respect to that function, connecting thermodynamics with kinetics \[11\]. In units of $k_B T$ and per unit volume, the Gibbs function for a dilute solution \[14\]:

$$G[x] = \sum_{j=1}^{N} x_j (\mu_j - 1), \quad \mu_j = \mu_j^0 + \ln x_j,$$

in which $\mu_j^0$ is a constant associated with the structure of the $j^{th}$ chemical species in aqueous solution, and the $-1$ term is the contribution from the solvent. See Appendix A for more discussions.

If all the reaction rate constants $k_{\pm \ell}$ satisfy Wegscheider-Lewis cycle condition, the chemical potential difference \[15\]:

$$\Delta \mu_\ell [x_{eq}] \equiv \sum_{j=1}^{N} \left( \kappa_{\ell j} - \nu_{\ell j} \right) \left( \mu_j^0 + \ln x_{eq j} \right) = 0,$$

in which \{x_{eq j}\} is the equilibrium concentration. Then for the reaction system, with a constant volume, that is away from its equilibrium at time $t$,

$$\frac{d}{dt} G[x(t)] = \sum_{j=1}^{N} \frac{dx_j(t)}{dt} (\mu_j^0 + \ln x_j)$$

$$= \sum_{j=1}^{N} \sum_{\ell=1}^{M} \left( \kappa_{\ell j} - \nu_{\ell j} \right) \left( J_{+\ell}(x) - J_{-\ell}(x) \right) \left( \mu_j^0 + \ln x_j \right)$$

$$= \sum_{\ell=1}^{M} \left( J_{+\ell}(x) - J_{-\ell}(x) \right) \ln \left( \frac{J_{-\ell}(x)}{J_{+\ell}(x)} \right) \leq 0. \quad \text{(7)}$$

For open chemical systems that do not reach an equilibrium with detailed balance, Horn and Jackson introduced the notion of complex balanced reaction network in 1972 \[16\]. It is a generalization of both linear reaction networks and kinetics with detailed balance \[17, 18\]. Complex balanced kinetics can be nonlinear as well as having nonequilibrium steady states (NESS). It also has a deep relation to the topological structure of a reaction network \[19, 20\]. A complex balanced reaction system has a unique positive steady state.

For nonequilibrium chemical thermodynamics, how, or whether even possible, to generalize Gibbs’ approach, in the framework of the mass-action kinetics, to nonlinear kinetic systems without detailed balance has remained elusive. Such systems include the important class of NESS which is aptly applicable to cellular biochemistry in homeostasis \[15\]. L. Onsager’s phenomenological theory is only applicable to systems in the linear regime near an equilibrium \[21\]; T. L. Hill’s NESS thermodynamics \[22\] and the grand
canonical approach developed in [23] are applicable only to macroscopic linear chemical kinetics. But thanks to the recent development in both mesoscopic, stochastic nonequilibrium thermodynamics and the resurgent interests in the stochastic description of nonlinear mass-action kinetic systems, a cross-fertilization is possible.

In this paper, we revisit the notion of macroscopic, chemical reaction entropy production $\sigma^{(\text{tot})}[x]$ \cite{15, 24, 25}, and show it can also be decomposed into two parts $\sigma^{(\text{tot})}[x] = \sigma^{(fd)}[x] + \sigma^{(hk)}[x]$, in which $\sigma^{(fd)}[x]$ is the negative time derivative of a generalized free energy function $A[x]$. More interestingly, both $\sigma^{(fd)}[x]$ and $\sigma^{(hk)}[x]$ can be mathematically proven as non-negativity for kinetic systems with complex balance. Since the $A[x]$ is defined with respect to a positive steady state of the kinetic system, it is no longer unique for systems with multi-stability. In fact, for a system with multi-stability, one can define $A[x]$ with respect to one of the stable steady states, then it necessarily has negative $\sigma^{(fd)}[x]$ for some $x$, thus $\sigma^{(hk)} > \sigma^{(\text{tot})}$ at the $x$. We further show that for complex balanced kinetic systems these naturally defined macroscopic quantities are the macroscopic limits of the mesoscopic free energy dissipation $f_d$ and house-keeping heat $Q_{hk}$, according to the stochastic kinetic description of the same chemical kinetics.

2 Nonequilibrium thermodynamics of chemical reaction network

In the present paper, we do not assume the rate constants $k_{\pm \ell}$ satisfy Wegscheider-Lewis cycle condition unless stated otherwise. We do assume, however, that the macroscopic kinetic system (2) has a positive steady state $x^{ss} = \{x_i^{ss}, 1 \leq i \leq N\}$. Motivated by the recent studies on mesoscopic, stochastic thermodynamics [1] [3] [26], we introduce a decomposition of the instantaneous rate of total entropy production of the mass-action kinetic system following Eq. (2) $\sigma^{(\text{tot})}[x]$ \cite{27, 24, 25}, into two nonequilibrium components, a house-keeping heat part \cite{28, 29, 30} and a free energy dissipation part:

$$\sigma^{(\text{tot})}[x] = \sum_{\ell=1}^{M} \left( J_{+\ell}(x) - J_{-\ell}(x) \right) \ln \left( \frac{J_{+\ell}(x)}{J_{-\ell}(x)} \right) = \sigma^{(hk)} + \sigma^{(fd)} \quad (8a)$$

$$\sigma^{(hk)}[x] = \sum_{\ell=1}^{M} \left( J_{+\ell}(x) - J_{-\ell}(x) \right) \ln \left( \frac{J_{+\ell}(x^{ss})}{J_{-\ell}(x^{ss})} \right) \quad (8b)$$

$$\sigma^{(fd)}[x] = \sum_{\ell=1}^{M} \left( J_{+\ell}(x) - J_{-\ell}(x) \right) \ln \left( \frac{J_{+\ell}(x) J_{-\ell}(x^{ss})}{J_{+\ell}(x^{ss}) J_{-\ell}(x)} \right) \quad (8c)$$
Both $\sigma^{(tot)}[x]$ and $\sigma^{(hk)}[x]$ have the generic form of “net flux in reaction $\ell$” × “thermodynamic force per $\ell^{th}$ reaction”. The latter are expressed in terms of the ratio of forward and backward one-way fluxes. This is an insight that goes back at least to T. L. Hill [22] if not earlier, as discussed in [27]. For the term in (8b), we adopt the idea of Hatano and Sasa who first introduced housekeeping heat as the product of transient thermodynamic fluxes and steady-state thermodynamic force [29]. Since then, there are several different definitions under the same name [31, 32]. We also note that the one-way fluxes in chemical kinetics are nonlinear functions of concentrations in general, while one-way-fluxes in mesoscopic stochastic dynamics are always linear functions of state probabilities, similar to a unimolecular reaction network. Thermodynamic forces of a wide range of processes have a unifying expression in terms of one-way-fluxes [27].

We also note that all three quantities in (8) can be explicitly computed if the rate laws $J^{\pm}_\ell(x)$ as well as a kinetic steady state $x^{ss}$ are known. Before introducing a further assumption of complex balanced kinetics in Sec. 2.2, we first discuss key characteristics of the three macroscopic quantities introduced in Eq. 8.

### 2.1 Key characteristics of the three macroscopic quantities

First, the foremost, $\sigma^{(tot)}[x] \geq 0$. It is zero if and only if at an $x$, $J^{+}_\ell(x) = J^{-}_\ell(x) \forall \ell$. This implies the $x$ is a steady state of (2), and it actually satisfies the detailed balance. In this case, one introduces a scalar function based on the steady state $x^{ss}$:

$$A[x] = \sum_{j=1}^{N} x_j(t) \ln \left( \frac{x_j(t)}{x_j^{ss}} \right) - x_j(t) + x_j^{ss}.$$  

Using this function, it can be shown (see below) that if a kinetic system has such an equilibrium steady state, it is unique. The equilibrium $x^{ss}$ in (9) can then be expressed in terms of intrinsic properties of the chemical species, e.g., the $\mu$'s. In the chemical kinetics literature, the $A[x]$ first appeared as Shear’s Liapunov function for kinetics with detailed balance [9, 33]. Horn and Jackson called it pseudo-Helmholtz function for complex balanced but not detail balanced systems [16].

Second, if a steady state $x^{ss}$ is detail balanced, then $\sigma^{(hk)}[x] \equiv 0 \ \forall x$. Otherwise, $\sigma^{(hk)}[x^{ss}] > 0$ for any steady state, stable or unstable. Then there must be a concentration region, near $x^{ss}$, in which $\sigma^{(hk)}[x] > 0$. Therefore, $\sigma^{(hk)}[x]$ can only be negative, if ever, when $x$ is far from any steady state.
Third, $\sigma^{(fd)}[x]$ is the time derivative of $A[x(t)]$ given in (9), when $x(t)$ follows the rate equation (2):

$$\frac{dA[x]}{dt} = \sum_{j=1}^{N} \frac{dx_j(t)}{dt} \ln \left( \frac{x_j(t)}{x_j^{ss}} \right)$$

$$= \sum_{j=1}^{N} \left[ \sum_{\ell=1}^{M} (\kappa_{\ell j} - \nu_{\ell j}) \left( k_{+ \ell} \prod_{i=1}^{N} x_i^{\nu_{\ell i}} - k_{- \ell} \prod_{i=1}^{N} x_i^{\kappa_{\ell i}} \right) \right] \ln \left( \frac{x_j}{x_j^{ss}} \right)$$

$$= \sum_{\ell=1}^{M} \left( J_{+ \ell} - J_{- \ell} \right) \ln \left( \frac{J_{+ \ell} x_j^{ss} - J_{- \ell} x_j}{x_j^{ss}} \right) = -\sigma^{(fd)}[x]. \quad (10)$$

In other words,

$$\sigma^{(fd)}[x] = -\sum_{i=1}^{N} \left( \frac{\partial A[x]}{\partial x_i} \right) F_i(x), \quad (11)$$

in which $\frac{dx_i}{dt} = F_i(x) = \sum_{\ell=1}^{M} \left( \kappa_{\ell i} - \nu_{\ell i} \right) \left( J_{+ \ell}(x) - J_{- \ell}(x) \right)$, i.e. the right hand side of (2). Noticing that $A[x]$ attains its global minimum 0 at $x^{ss}$, Eq. (11) dictates $\nabla_x \sigma^{(fd)}[x^{ss}] = 0$. To determine whether $\sigma^{(fd)}[x^{ss}]$ is a maximum, minimum, or saddle point, we compute the Hessian matrix $\mathcal{H}$:

$$\mathcal{H}_{ij}[x^{ss}] = \frac{\partial^2 \sigma^{(fd)}[x^{ss}]}{\partial x_i \partial x_j}$$

$$= -\sum_{k=1}^{N} \left[ \left( \frac{\partial^2 A[x^{ss}]}{\partial x_k \partial x_i} \right) \frac{\partial F_k(x^{ss})}{\partial x_j} + \left( \frac{\partial^2 A[x^{ss}]}{\partial x_k \partial x_j} \right) \frac{\partial F_k(x^{ss})}{\partial x_i} \right]$$

$$= -\frac{1}{x_i^{ss}} \frac{\partial F_i(x^{ss})}{\partial x_j} - \frac{1}{x_j^{ss}} \frac{\partial F_j(x^{ss})}{\partial x_i}. \quad (12)$$

Note matrix $\Gamma$, $\gamma_{ij} = \frac{\partial F_i(x^{ss})}{\partial x_j}$, defines the linear stability of $x^{ss}$. If we denote $\Theta = \text{diag}\{(x_i^{ss})^{-1}\}$, then

$$\mathcal{H} = -\left( \Theta \Gamma + \Gamma^T \Theta \right). \quad (13)$$

There is a precise relationship between the Jacobian matrix and Hessian matrix near an $x^{ss}$.

In one-dimensional case, $\mathcal{H}$ and $\Gamma$ always have opposite signs, since a steady state is positive. In high-dimensional case, however, even if all the eigenvalues of $\Gamma$ are negative, which implies the steady state $x^{ss}$ is stable, it
is still possible for a symmetric $\mathcal{H}$ to have negative eigenvalues, resulting in negative $\sigma_{jd}(x)$ near a stable fixed point. A simple example of such is

$$
\Gamma = \begin{pmatrix} 1 & 2 \\ -3 & -4 \end{pmatrix}, \quad \Theta = \begin{pmatrix} 5 & 0 \\ 0 & 1 \end{pmatrix}, \quad \mathcal{H} = \begin{pmatrix} -10 & -7 \\ -7 & 8 \end{pmatrix},
$$

in which matrix $\Gamma$ has eigenvalues $-1$ and $-2$, but $\mathcal{H}$ has a negative eigenvalue $-1 - \sqrt{130}$.

**Concentrations of species with linear constraints.** In chemical kinetics, the concentrations of many different chemical species are often constrained by the stoichiometric matrix. In fact, matrix $S$, with elements $s_{j\ell} = (\kappa_{\ell j} - \nu_{\ell j})$, often has a high-dimensional left null space with vector $(q_1, \cdots, q_N)$:

$$
\sum_{j=1}^{N} q_j s_{j\ell} = \sum_{j=1}^{N} (\kappa_{\ell j} - \nu_{\ell j}) q_j = 0, \quad \forall \ell.
$$

(14)

Each linearly independent null vector represents a conservation of a certain chemical group in the entire chemical reaction system:

$$
\frac{d}{dt} \sum_{j=1}^{N} q_j x_j(t) = \sum_{j=1}^{N} q_j \left( \frac{dx_j(t)}{dt} \right) = 0.
$$

(15)

If the left null space of $S$ is $d$ dimensional, then there are only $(N - d)$ independent differential equations in the system (2). The Jacobian matrix $\Gamma$ near a fixed point $x^{ss}$ has a rank equal or lower than $(N - d)$. As shown in Appendix B, there exists an $N \times (N - d)$ constant matrix $Z$ with rank $(N - d)$, the spanned space of whose column vectors are the same as the spanned space of the column vectors of $S$.

In terms of the $Z$ and an $(N - d) \times N$ constant matrix $U$, such that $UZ = I_{N-d}$, Eq. (2) becomes $\frac{d}{dt}\delta(t) = \bar{F}(\delta)$, in which $Z\delta(t) = x(t) - x^{ss}$ and $\bar{F}(\delta) = UF(x^{ss} + Z\delta)$. $\bar{F}(x) = \{F_{i}(x)\}$ is the right hand side of Eq. (2).

Therefore, $\Gamma^{\delta} = U \Gamma Z$ is the linear matrix of the equation $\frac{d}{dt}\delta(t) = \bar{F}(\bar{\delta})$ at $\bar{\delta} = 0$, which determines the stability of the original steady state $x^{ss}$ constrained by the conservation relations. And the Hessian matrix $\mathcal{H}^{\delta}$ of $\sigma_{jd}$ with respect to the variable $\delta$ without constrain becomes $\mathcal{H}^{\delta} = Z^{T} \mathcal{H} Z$.

Furthermore, since $ZUZ = Z$, $ZU$ is an identity mapping from the space spanned by the column vectors in $Z$ to itself. Hence we have $S = ZUS$ and $\bar{F} = S \bar{J} = ZUS \bar{J}$, followed by $ZU \Gamma = \Gamma$. Then

$$
\mathcal{H}^{\delta} = Z^{T} \mathcal{H} Z = -Z^{T} \left( \Theta ZU \Gamma + \Gamma^{T} U^{T} Z^{T} \Theta \right) Z
$$

$$
= - \left( Z^{T} \Theta Z \right) \Gamma^{\delta} - (\Gamma^{\delta})^{T} \left( Z^{T} \Theta Z \right),
$$

(16)

in which $(N - d) \times (N - d)$ matrix, and symmetrix matrix $(Z^{T} \Theta Z)$ is no longer diagonal (compared with Eq. (13).
2.2 Complex balanced kinetics and non-negativity of $\sigma^{(hk)}$ and $\sigma^{(fd)}$

**Macroscopic house-keeping heat.** In stochastic thermodynamics, housekeeping heat [29][3] is also known as adiabatic instantaneous entropy production rate [1][4]. If the macroscopic reaction system (1) is in a steady-state $x^{ss}$, the $\ell$th reversible reaction has a chemical free energy dissipationper occurs $\Delta \mu^{ss}_\ell = k_B T \ln \left( \frac{J_{+\ell}(x^{ss})}{J_{-\ell}(x^{ss})} \right)$ [6]. Therefore, in $k_B T$ unit and sum over all $M$ reversible reactions we have

$$
\sigma^{(hk)}[x] = \sum_{\ell=1}^{M} (J_{+\ell}(x) - J_{-\ell}(x)) \frac{\Delta \mu^{ss}_\ell}{k_B T},
$$

$$
= \sum_{\ell=1}^{M} \left[ J_{+\ell}(x) \ln \left( \frac{J_{+\ell}(x^{ss})}{J_{-\ell}(x^{ss})} \right) + J_{-\ell}(x) \ln \left( \frac{J_{+\ell}(x^{ss})}{J_{-\ell}(x^{ss})} \right) \right]
$$

$$
\geq \sum_{\ell=1}^{M} \left[ J_{+\ell}(x) \left( 1 - \frac{J_{-\ell}(x^{ss})}{J_{+\ell}(x^{ss})} \right) + J_{-\ell}(x) \left( 1 - \frac{J_{+\ell}(x^{ss})}{J_{-\ell}(x^{ss})} \right) \right]
$$

$$
= \sum_{\ell=1}^{M} \left( J_{+\ell}(x^{ss}) - J_{-\ell}(x^{ss}) \right) \left( \frac{J_{+\ell}(x)}{J_{+\ell}(x^{ss})} - \frac{J_{-\ell}(x)}{J_{-\ell}(x^{ss})} \right). \tag{17}
$$

For an equilibrium steady state, detailed balance implies $J_{+\ell}(x^{eq}) - J_{-\ell}(x^{eq}) = 0$ for all $\ell$. Therefore the rhs of (17) is zero for detailed balanced system.

**Generalized free energy dissipation.** Free energy dissipation [1][3][4] is also known as non-adiabatic instantaneous entropy production rate [4], which is actually the negative time-derivative of a generalized free energy given in (9). This $A[x]$ figured prominently in Horn and Jackson’s theory [16]. Without the assumption of detailed balance,

$$
\sigma^{(fd)}[x] = -\sum_{\ell=1}^{M} (J_{+\ell}(x) - J_{-\ell}(x)) \ln \left( \frac{J_{-\ell}(x) J_{+\ell}(x^{ss})}{J_{+\ell}(x) J_{-\ell}(x^{ss})} \right)
$$

$$
= -\sum_{\ell=1}^{M} \left[ J_{+\ell}(x) \ln \left( \frac{J_{+\ell}(x) J_{+\ell}(x^{ss})}{J_{+\ell}(x) J_{-\ell}(x^{ss})} \right) + J_{-\ell}(x) \ln \left( \frac{J_{+\ell}(x) J_{+\ell}(x^{ss})}{J_{+\ell}(x) J_{-\ell}(x^{ss})} \right) \right]
$$

$$
\geq -\sum_{\ell=1}^{M} \left[ J_{+\ell} \left( \frac{J_{-\ell}(t) J_{+\ell}(x^{ss})}{J_{+\ell}(t) J_{-\ell}(x^{ss})} - 1 \right) + J_{-\ell} \left( \frac{J_{+\ell}(t) J_{-\ell}(x^{ss})}{J_{+\ell}(t) J_{+\ell}(x^{ss})} - 1 \right) \right]
$$

$$
= \sum_{\ell=1}^{M} \left( J_{+\ell}(x^{ss}) - J_{-\ell}(x^{ss}) \right) \left( \frac{J_{+\ell}(x)}{J_{+\ell}(x^{ss})} - \frac{J_{-\ell}(x)}{J_{-\ell}(x^{ss})} \right). \tag{18}
$$

This is exactly the same rhs of (17). Therefore, $\sigma^{(hk)}$ and $\sigma^{(fd)}$ are both
no-less than
\[
M \sum_{\ell=1}^{M} \left( J_{+\ell}(x^{ss}) - J_{-\ell}(x^{ss}) \right) \left( \frac{J_{+\ell}(x)}{J_{+\ell}(x^{ss})} - \frac{J_{-\ell}(x)}{J_{-\ell}(x^{ss})} \right) = M \sum_{\ell=1}^{M} \left( J_{+\ell}(x^{ss}) - J_{-\ell}(x^{ss}) \right) \left( \prod_{i=1}^{N} \left( \frac{x_i}{x_i^{ss}} \right)^{\nu_{\ell i}} - \prod_{i=1}^{N} \left( \frac{x_i}{x_i^{ss}} \right)^{\kappa_{\ell i}} \right)
\]

(19)

**Complex balanced chemical reaction networks.** A chemical reaction system is “complex balanced” if and only if the rhs of (19) is zero for any \(x = (x_1, x_2, \cdots, x_N)\) \[16, 17, 18\]. This is because any unique multi-type-nominal term
\[
\prod_{i=1}^{N} \left( \frac{x_i}{x_i^{ss}} \right) \xi_i
\]
represents a particular “complex” \((\xi_1 X_1 + \xi_2 X_2 + \cdots + \xi_N X_N)\). Therefore, a complex balanced steady state has all the influx to the complex precisely balanced by the outflux of that complex:
\[
\left\{ \sum_{\ell=1}^{M} \left( \delta_{\kappa_{\ell}, \xi} - \delta_{\nu_{\ell}, \xi} \right) \left( J_{+\ell}(x^{ss}) - J_{-\ell}(x^{ss}) \right) \right\} \prod_{i=1}^{N} \left( \frac{x_i}{x_i^{ss}} \right) \xi_i = 0.
\]

(20)

Detailed balance is a special case in which the \(J_{+\ell}^{ss} = J_{-\ell}^{ss}\) for every \(\ell\). Detailed balance is a kinetic concept. Complex balance, however, has a topological implication for a reaction network \[18, 19\].

**Lyapunov function of complex balanced kinetics.** Since \(\frac{d}{dt} A\{x\} = -\sigma^{(fd)}[x] \leq 0\) for a reaction network with complex balance, and \(A\{\{x\}\} \geq 0\), it is a Lyapunov function for the mass-action kinetics. The convexity of \(A\{x\}\) is easy to establish: \(\frac{\partial^2 A}{\partial x_i \partial x_j} = x_i^{-1} \delta_{ij}\). Therefore, one concludes that the steady state \(x^{ss}\) of a complex balanced reaction kinetics is unique. This is a well-known result and the proof was given in \[16\]. The existence of this Lyapunov function \(A\{x\}\) for kinetic systems with complex balance has prompted Horn and Jackson’s description of a “quasithermodynamics”.

In fact, an equally significant result is the following statement:

For reaction system with non-complex balanced kinetics, if the macroscopic free energy dissipation \(\sigma^{(fd)}[x]\) is non-negative for all \(x\), then the kinetics has a unique steady state. Equivalently, if a kinetic system is multi-stable, then \(\sigma^{(fd)}[x]\) is negative for some \(x\), where \(\sigma^{(hk)}[x] > \sigma^{(tot)}[x]\).
3 Macroscopic limit of mesoscopic stochastic thermodynamics

3.1 Kinetic description according to Delbrück and Gillespie’s model

The macroscopic chemical thermodynamics presented above does not reference to anything with probability. But the very notion of Gibbs’ chemical potential has a deep root in it. Chemical reactions at the individual molecule level are stochastic [34]. A mathematically more accurate description of the chemical kinetics in system (1) is the stochastic theory of Chemical Master Equation (CME) first appeared in the work of Leontovich [35] and Delbrück [36], whose fluctuating trajectories can be exactly computed using the stochastic simulation method widely known as Gillespie algorithm [37]. Note these two descriptions are not two different theories, rather they are the two aspects of a same Markov process, just as the diffusion equation and the Langevin-equation descriptions of a same Brownian motion. More importantly, this probabilistic description and Waage-Guldberg’s law of mass action are also two parts of a same dynamic theory: The latter is the limit of the former if fluctuations are sufficiently small, when the volume of the reaction system, \( V \), is large [38]. In fact, the key quantity in Delbrück-Gillespie’s description of mesoscopic chemical kinetics is the rate of a particular reaction, called propensity function. For the \( \ell^{th} \) forward and backward reactions, they are

\[
\begin{align*}
    u_\ell(n) &= k_+ \ell V \prod_{j=1}^n \left( \frac{n_j!}{(n_j - \nu_{\ell j})! V^{\nu_{\ell j}}} \right), \quad (21a) \\
    w_\ell(n) &= k_- \ell V \prod_{j=1}^n \left( \frac{n_j!}{(n_j - \kappa_{\ell j})! V^{\kappa_{\ell j}}} \right). \quad (21b)
\end{align*}
\]

One sees that in the macroscopic limit \( V \to \infty \), \( V^{-1} u_\ell(Vx) = J_+ \ell(x) \) and \( V^{-1} w_\ell(Vx) = J_- \ell(x) \), where \( x = n/V \).

The stochastic trajectory can be expressed in terms of the random-time-changed Poisson representation:

\[
n_j(t) = n_j(0) + \sum_{\ell=1}^M \left( \kappa_{\ell j} - \nu_{\ell j} \right) \left\{ Y_{+\ell} \left( \int_0^t u_\ell(n(s)) \, ds \right) - Y_{-\ell} \left( \int_0^t w_\ell(n(s)) \, ds \right) \right\}, \quad (22)
\]

where \( Y_{±\ell}(t) \) are \( 2\ell \) independent, standard Poisson processes:

\[
\Pr \{ Y(t) = n \} = \frac{t^n}{n!} e^{-t}, \ Y(0) = 0. \quad (23)
\]
The CME for the mesoscopic kinetics is

\[ \frac{dp(n, t)}{dt} = \sum_{\ell=1}^{M} \left[ p(n - \kappa + \nu + \nu + \nu) - p(n + \nu)u(n + \nu) \right] \]

\[-p(n)(u(n) + w(n)) + p(n + \kappa - \nu)w(n + \kappa - \nu) \]

The mesoscopic stochastic thermodynamics provides the following set of equations \([3]\):

\[ e_p[p(n, t)] = \sum_{\ell=1}^{M} \sum_n \left( p(n + \kappa)w(n + \kappa) - p(n + \nu)u(n + \nu) \right) \]

\)[25a]\]

\[ f_d[p(n, t)] = \sum_{\ell=1}^{M} \sum_n \left( p(n + \kappa)w(n + \kappa) - p(n + \nu)u(n + \nu) \right) \]

\)[25b]\]

\[ F^{(meso)}[p(n, t)] = \sum_n p(n, t) \ln \left( \frac{p(n, t)}{p^{ss}(n)} \right) \]

\)[25d]\]

\[ Q_{hk}[p(n, t)] = \sum_{\ell=1}^{M} \sum_n \left( p(n + \kappa)w(n + \kappa) - p(n + \nu)u(n + \nu) \right) \]

\)[25e]\]

All three \( e_p[p(n, t)] \), \( f_d[p(n, t)] \) and \( Q_{hk}[p(n, t)] \) are \( \geq 0 \) \([3, 4]\).

### 3.2 Macroscopic limits

Denote \( x(t) \) as the solution of the corresponding deterministic model (Eq. \([2]\)). In the macroscopic limit when \( n, V \to \infty \), \( x = n/V \), one has the asymptotic expressions \([40]\)

\[ p(Vx, t) \simeq \frac{1}{V} \delta(x - x(t)) \], and \( p^{ss}_V(Vx) \simeq e^{-V \varphi^{ss}(x)} \), \( 24 \)

where \( \delta(x - x(t)) \) is the \( \delta \) measure concentrating at \( x(t) \), \( p^{ss}_V(\cdot) \) is the stationary distribution of the chemical master equation \([23]\) and \( \inf_{x} \varphi^{ss}(x) = 0 \).

As a part of the theory of large deviations, the mathematical existence of
\( \varphi^{ss}(x) \) has been extensively discussed \cite{39,40}. See recent \cite{41} and references cited within. Therefore,

\[
e_p \simeq V \sum_{\ell=1}^{M} \int \! dx \delta(x - x(t)) \left( J_{-\ell}(x) - J_{+\ell}(x) \right) \times \ln \left( \frac{J_{-\ell}(x)}{J_{+\ell}(x)} \right)
\]

\[
\to V \sigma^{(\text{tot})} \left[ x(t) \right], \quad (27)
\]

where the \textit{density} of macroscopic chemical entropy production rate

\[
\sigma^{(\text{tot})}[x] = \sum_{\ell=1}^{M} \left( J_{-\ell}(x) - J_{+\ell}(x) \right) \ln \left( \frac{J_{-\ell}(x)}{J_{+\ell}(x)} \right). \quad (28)
\]

This is Eq. (8a).

On the other hand,

\[
f_d = \sum_{\ell=1}^{M} \sum_n \left( p(n + \kappa_\ell) w_\ell(n + \kappa_\ell) - p(n + \nu_\ell) u_\ell(n + \nu_\ell) \right) \times \ln \left( \frac{p^{ss}(n + \nu_\ell)}{p^{ss}(n + \kappa_\ell)} \right)
\]

\[
\simeq V \sum_{\ell=1}^{M} \int \! dx \delta(x - x(t)) \left( J_{-\ell}(x) - J_{+\ell}(x) \right) \ln \left( \frac{p^{ss}(x + \nu_\ell)}{p^{ss}(x + \kappa_\ell)} \right)
\]

\[
\simeq V \sum_{\ell=1}^{M} \int \! dx \delta(x - x(t)) \left( J_{-\ell}(x) - J_{+\ell}(x) \right) (\nu_\ell - \kappa_\ell) \cdot \nabla x \ln \left( \frac{p^{ss}(x + \nu_\ell)}{p^{ss}(x + \kappa_\ell)} \right)
\]

\[
\to V \sum_{\ell=1}^{M} \left( J_{-\ell}(x(t)) - J_{+\ell}(x(t)) \right) (\kappa_\ell - \nu_\ell) \cdot \nabla x \varphi^{ss}(x(t)). \quad (29)
\]

Comparing with Eq. (11), we thus have the following statement:

\( \sigma^{(fd)}[x(t)] \) and the macroscopic limit of \( V^{-1} f_d[p(Vx,t)] \) are equal if and only if the \( \varphi^{ss}(x) \) and the \( A[x] \) in \cite{9} differ by a conserved quantity of \cite{2}.

That is, \( \varphi^{ss}(x) = A[x] + C[x] \) where \( \vec{F}(x) \cdot \nabla x C[x] = 0 \) \cite{12}. Once the limit of \( V^{-1} f_d(t) \neq \sigma^{(fd)}[x(t)] \), it implies that the limit of \( V^{-1} Q_{hk}(t) \) will not be \( \sigma^{(hk)}[x(t)] \).
Last, but not the least,

\[
Q_{hk} = e_p - f_d
\]

\[
\approx V \sum_{\ell=1}^{M} \left( J_{-\ell}(x) - J_{+\ell}(x) \right) \ln \left( \frac{J_{-\ell}(x)}{J_{+\ell}(x)} \right)
- V \sum_{\ell=1}^{M} \left( J_{-\ell}(x) - J_{+\ell}(x) \right) \left( \kappa_{-\ell} - \nu_{-\ell} \right) \cdot \nabla_x \varphi^s(x)
\]

\[
= V \sum_{\ell=1}^{M} \left( J_{-\ell}(x) - J_{+\ell}(x) \right) \ln \left( \frac{J_{-\ell}(x)}{J_{+\ell}(x)} \right) - \left( \kappa_{-\ell} - \nu_{-\ell} \right) \cdot \nabla_x \varphi^s(x)
\]

\[
= V \sum_{\ell=1}^{M} \left( J_{-\ell}(x) - J_{+\ell}(x) \right) \ln \left( \frac{J_{-\ell}(x)}{J_{+\ell}(x)} \right) \left( \nu_{-\ell} - \kappa_{-\ell} \right) \cdot \nabla_x \varphi^s(x) \right)
\]

(30)

Therefore, the macroscopic limit of \( V^{-1}Q_{hk} \) contains the

\[
\ln \left( \frac{J_{-\ell}(x)}{J_{+\ell}(x)} \right) e^{\left( \nu_{-\ell} - \kappa_{-\ell} \right) \cdot \nabla_x \varphi^s(x)}
\]

(31)

which in turn is dependent upon the unknown function \( \varphi^s(x) \); \( \varphi^s(x) \) is an emergent, global quantity itself. In contrast, \( \sigma^{(hk)} \) depends upon only local rate laws

\[
\ln \left( \frac{J_{-\ell}(x^{ss})}{J_{+\ell}(x^{ss})} \right)
\]

(32)

which is the expression (31) evaluated at \( x = x^{ss} \), where \( \nabla_x \varphi^s[x^{ss}] = 0 \).

For kinetic systems with complex balanced, Anderson et al. have recently shown that \( A[x] = \varphi^s(x) \)[41]. Therefore, Eqs. (31) and (32) are indeed the same:

\[
\ln \left( \frac{J_{-\ell}(x)}{J_{+\ell}(x)} \right) e^{\left( \nu_{-\ell} - \kappa_{-\ell} \right) \cdot \nabla_x A[x]}
\]

\[
= \ln \left( \frac{J_{-\ell}(x)}{J_{+\ell}(x)} \right) + \sum_{j=1}^{N} \ln \left( \frac{x_j}{\nu_{s,j} - \kappa_{s,j}} \right)
\]

\[
= \ln \left( \frac{J_{-\ell}(x)}{J_{+\ell}(x)} \right).
\]

The non-local (31) is reduced to the local (32) in this case.

Eqs. (31) and (32) are the same if and only if \( A[x] = \varphi^s(x) \). However, since the macroscopic limit of \( V^{-1}(f_d(t) + Q_{hk}) \) is the same as \( \sigma(f_d) + \sigma^{(hk)} \), the macroscopic limit of \( V^{-1}Q_{hk} \) is the same as \( \sigma^{(hk)} \) if and only if the \( \varphi^s(x) \) and the \( A[x] \) in (9) differ by a conserved quantity of (2).
3.3 Nonequilibrium free energy and its time derivative

In the theory of mesoscopic, stochastic thermodynamics, the generalized nonequilibrium free energy \[ F^{(\text{meso})} = \sum_n p(n, t) \ln \left( \frac{p(n, t)}{p^{st}(n)} \right). \] (33)

In the macroscopic limit, its density therefore is

\[
\frac{1}{V} \sum_n p(n, t) \ln \left( \frac{p(n, t)}{p^{st}(n)} \right) \simeq \frac{1}{V} \int f_V(x, t) \ln \left( \frac{f_V(x, t)}{f^{st}_V(x)} \right) dx 
\]
\[
\simeq \frac{1}{V} \int f_V(x, t) \ln \left( f_V(x, t) e^{V \varphi^{st}(x)} \int e^{-V \varphi^{st}(z)} dz \right) dx 
\]
\[
= \int f_V(x, t) \varphi^{st}(x) dx + \frac{1}{V} \int f_V(x, t) \ln f_V(x, t) dx 
\]
\[
+ \frac{1}{V} \ln \left( \int e^{-V \varphi^{st}(z)} dz \right) 
\]
\[
\rightarrow \varphi^{st}(x(t)). \]

(34) (35)

One can recognize the first two terms in the rhs of Eq. 34 as the instantaneous mean internal energy and entropy, and the last term as the logarithm of a partition function, with \( V \) playing the role of the \( \beta \). Therefore,

The macroscopic limit of the mesoscopic, stochastic thermodynamic free energy is the chemical potential of mean force for the macroscopic dynamics \[43, 44\].

For relatively simple kinetics with complex balance, the \( A[x] \) in (9) and the \( \varphi^{st}(x) \) in (35) being the same \[41\] signifies a complete consistency between the kinetics and thermodynamics. For such systems, the \( \varphi^{st}(x) \) has a generic, simple form, i.e. \( A[x] \). For complex kinetics, however, the \( \varphi^{st}(x) \) is not known \textit{a priori}. An accurate computation of the \( \varphi^{st}(x) \), as an emergent quantity, has to be computationally demanding.

\footnote{A separation of the first, instantaneous mean energy, and the last stationary free energy naturally arises in the mathematical limit: For finite \( V, -V^{-1} \ln f^{st}_V(x) \simeq \varphi^{st}(x) + \log\text{-partition function, where} \inf_x \varphi^{st}(x) = 0. \) The partition function, therefore, provides an appropriate energy reference point for a macroscopic system. This is the spirit of renormalization; its fundamental insight resides in the notion of conditional probability. H.Q. thank Dr. Panagiotis Stinis for an illuminating discussion on the theory of renormalization.}

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3.4 Keizer’s macroscopic nonequilibrium thermodynamics

For complex balanced kinetics, it can be shown (see Appendix C) that the matrix relation in Eq. 13 is in fact consistent with J. Keizer’s macroscopic, local nonequilibrium thermodynamics [45] which states: 

\[ 2D = -\left( \Gamma \Xi + \Xi \Gamma ^T \right), \]

in which \( \Xi^{-1} = \Theta \), the curvature of \( A[x] \) at \( x^{ss} \), and

\[ D(x^{ss}) = \frac{1}{2} \sum_{\ell=1}^{M} (\nu_{\ell i} - \kappa_{\ell i}) (\nu_{\ell j} - \kappa_{\ell j}) \left( J_{+\ell}(x^{ss}) + J_{-\ell}(x^{ss}) \right). \]  
(36)

Eq. 16, however, indicates that for complex balanced kinetic systems, the correlations between the concentrations fluctuations near the steady state are a simple consequence of the conservation relations in (14). For example, \( A + B \rightleftharpoons C \) has \( Z = (1, 1, -1)^T \), and \( Z^T \Theta Z = (x_A^{ss})^{-1} + (x_B^{ss})^{-1} + (x_C^{ss})^{-1} \). Such correlations are simple; they are fundamentally different from the correlations that arise in complex dynamics such as chemical oscillations [46].

4 Discussion

It is well-known that entropy is not the appropriate thermodynamic potential for isothermal systems; free energy is: Helmholtz’s for constant volume and Gibbs’ for constant pressure. Therefore, it is not surprising that while our equation \( dA/dt = -\sigma^{(tot)} + \sigma^{(hk)} \) is similar to the celebrated entropy balance equation \( dS/dt = \sigma^{(tot)} + \eta^{(ex)} \), where \( \eta^{(ex)} \) is the rate of entropy exchange of the system with its surrounding [25, 26], the new equation is a more appropriate description of the nonequilibrium, thermodynamics at a constant temperature. As a consequence, positive \( \sigma^{(hk)} \) and \( \sigma^{(tot)} \) can be interpreted as the source and the sink of the chemical free energy of a reaction system with complex balance. For non-driven chemical reaction system, \( \sigma^{(hk)} = 0 \), \( dA/dt = -\sigma^{(tot)} \), and \( \eta^{(ex)} \) is the time derivative of the total internal energy.

Macroscopic “laws” are emergent properties of complex dynamics at a level below: This is a profound insight from studies in many-body physics [47]. In the present work, we observe precisely how this idea works in terms of the \( \varphi^{ss}(x) \) as a statistical “summary” of the mesoscopic, long time dynamics; yet it serves as a “law of force” for the macroscopic behavior. For relatively simple systems, the \( \varphi^{ss}(x) \) can be known a priori, with a generic, robust form, as the Gibbs free energy for the case of detailed balance non-driven chemical systems, and the \( A[x] \) for complex balanced systems. Both systems have been known for a long time to be uni-stable.
For more complex kinetics, however, it is impossible to know $\varphi^{ss}(x)$ \textit{a priori}. It is a true emergent quantity that requires to be discovered.

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These materials are not new, we summarize them here since they are not easy to find in the literature. Since the Helmholtz free energy
\[ A(T, V, \{n_i\}) = G(T, p, \{n_i\}) - pV, \] where components are expressed in terms of mole fraction:
\[ G = \sum_{i=0}^{N} n_i \mu_i, \]
which \( \mu_i = \mu_i^c + k_B T \ln(n_i/n_0) = \partial G/\partial n_i, \) where \( n_t = n_0 + n_1 + \cdots + n_N. \) \( \mu_i \) is the per molecule chemical potential of the \( i^{th} \) component.

(a) Constant pressure. We first show for the case of constant pressure, where components are expressed in terms of mole fraction:
\[ G = \sum_{i=0}^{N} n_i \mu_i, \]
in which component 0 is the solvent. For dilute solution \( n_0 \approx n_t. \) Therefore, \( \mu_0 = \hat{\mu}_0^0 + k_B T \ln(n_0/n_t) \approx \hat{\mu}_0^0 - k_B T \sum_{i=1}^{N} (n_i/n_0). \) Therefore, the Gibbs
free energy can be approximated as

\[ G = n_0 \hat{\mu}_0^o + \sum_{i=1}^{N} n_i \left[ \hat{\mu}_i^o - k_B T + k_B T \ln \left( \frac{n_i}{n_0} \right) \right], \]  
(A1)

where \( \mu_i = \hat{\mu}_i^o + k_B T \ln(n_i/n_0) \) for each \( i \geq 1 \).
Without loss of generality, we can set \( \hat{\mu}_0^o = 0 \), hence
\[ G = \sum_{i=1}^{N} n_i (\mu_i - k_B T). \]  
Define \( \mu_i^o = \hat{\mu}_i^o + k_B T \ln(n_i/V_{eq}) \) for each \( i \geq 1 \), then
\[ \mu_i = \mu_i^o + k_B T \ln(n_i/V). \]  
Hence per unit volume and in units of \( k_B T \):
\[ G = \sum_{i=1}^{N} x_i \mu_i = \sum_{j=1}^{N} x_j \mu_j, \]  
This is Eq. 6.

We now show Eq. 7:

For chemical reaction:
\[ N \sum_{i=1}^{N} \nu_i^+ X_i \underset{k_+}{\rightarrow} \sum_{j=1}^{N} \nu_j^- X_j, \]
(A2)

through minimizing \( G \) we can have [14]:
\[ \sum_{i=1}^{N} \nu_i^+ \mu_i = \sum_{j=1}^{N} \nu_j^- \mu_j, \]  
i.e.

\[ \sum_{i=1}^{N} \nu_i^+ \left[ \mu_i^o + k_B T \ln \left( \frac{n_i}{V_{eq}} \right) \right] = \sum_{j=1}^{N} \nu_j^- \left[ \mu_j^o + k_B T \ln \left( \frac{n_j}{V_{eq}} \right) \right]. \]

Hence the equilibrium constant
\[ \frac{k_-}{k_+} = \prod_{i=1}^{N} \left( \frac{\nu_i^+}{\nu_i^-}_{eq} \right) = \exp \left[ \frac{1}{k_B T} \left( \sum_{j=1}^{N} \nu_j^- \mu_j^o - \sum_{i=1}^{N} \nu_i^+ \mu_i^o \right) \right], \]
results in
\[ k_B T \ln \left( \frac{J_-}{J_+} \right) = \sum_{j=1}^{N} \left( \nu_j^- - \nu_j^+ \right) \mu_i, \]
which guarantees the decreasing of Gibbs free energy with time.

(b) Constant volume. We now rewrite \( G = \sum_{i=0}^{N} n_i \mu_i \), in which \( \mu_i = \hat{\mu}_i^o + k_B T \ln(n_i/V) \) is the per molecule chemical potential of the \( i^{th} \) component, in molarity, including the solvent as the \( 0^{th} \) component. For chemical equilibrium one minimizes the Helmholtz free energy \( A \) rather than the Gibbs free energy \( G \).
\[ A = G - pV = \sum_{i=0}^{N} n_i (\mu_i - p_i V) = \sum_{i=0}^{N} n_i \hat{\mu}_i, \]
in which \( p_i \) is the partial pressure for one molecule of the \( i^{th} \) component, and \( \hat{\mu}_i = \hat{\mu}_i^o + k_B T \ln(n_i/V), \hat{\mu}_i^o = \hat{\mu}_i^o - p_i V. \)
Again for the chemical reaction in (A2) through minimizing $A$ we can have in equilibrium

$$\sum_{i=1}^{N} \nu_i^+ (\tilde{\mu}_i + k_B T) = \sum_{j=1}^{s} \nu_j^- (\tilde{\mu}_j + k_B T).$$

Hence the equilibrium constant

$$\frac{k_-}{k_+} = \exp \left[ -\frac{1}{k_B T} \sum_{j=1}^{N} (\nu_j^- - \nu_j^+) \tilde{\mu}_j + \sum_{j=1}^{N} \left( \nu_j^- - \nu_j^+ \right) \right].$$

We can here define $\tilde{\mu}_i = \tilde{\mu}_i + k_B T$ for each $i \geq 1$, then $A = \sum_{i=1}^{N} n_i \tilde{\mu}_i - k_B T \sum_{i=1}^{N} n_i$. Hence

$$\frac{k_-}{k_+} = \exp \left( -\frac{1}{k_B T} \sum_{j=1}^{N} \left( \nu_j^- - \nu_j^+ \right) \tilde{\mu}_j \right),$$

in which $\tilde{\mu}^o_i = \tilde{\mu}_i + k_B T$. The form here is the same as that in the previous case now.

We can eliminate $n_0 \tilde{\mu}_0 = -n_0 k_B T$ from $A$, then following this condition, we can have the Helmholtz free energy decreasing with time, not the Gibbs free energy.

One can see in this case Eq. (4) is just the Helmholtz free energy. In dilute solution, $A \simeq G + \text{const.}$

## B Kinetics with conserved quantities

Denote $\mathcal{L} \subseteq \mathbb{R}^{N}_+$ as the left null space of the stoichiometric matrix $S = \{s_{i\ell} = \kappa_{\ell i} - \nu_{\ell i}\}_{N \times M}$. Any vector in $\mathcal{L}$ represents a conservation law of the chemical reaction system, i.e. for each $\vec{q} = (q_1, q_2, \cdots, q_N)$ satisfies Eq. $q^\mathcal{L} S J = 0$, in which $J = (J_1, J_2, \cdots, J_M)^T$, $J_\ell = J_{+\ell}(x) - J_{-\ell}(x)$.

Suppose the dimension of $\mathcal{L}$ is $d$, hence the dimension of the span of column vectors (also of the matrix $S$) in $S$ which is orthogonal to $\mathcal{L}$ is $N - d$. Given the $d$ conservation laws according to the basis of the space $\mathcal{L}$, the deterministic and stochastic dynamics of the chemical reaction system is constrained in this subspace.

Suppose the $(N - d)$ linearly independent column vectors of $S$ as $\vec{z}_i = (z_{i1}, z_{i2}, \cdots, z_{iN})^T$, $i = 1, \cdots, N - d$. Hence given a steady state values $\vec{x}^{ss} = (x_1^{ss}, \cdots, x_N^{ss})^T$, we rewrite the dynamics of the chemical reaction system using the new variables $\delta = (\delta_1, \cdots, \delta_{N-d})^T$ which satisfies

$$\vec{x}(t) = \vec{x}^{ss} + \sum_{j=1}^{N-d} \delta_j(t) \vec{z}_j, \quad \text{or} \quad x_i(t) = x_i^{ss} + \sum_{j=1}^{N-d} \delta_j(t) z_{ji}.$$
Let $N \times (N - d)$ matrix $Z$ taking $z_i$ as the column vectors, hence $x(t) - x^{ss} = Z \delta(t)$. Since the dimension of $Z$ is $(N - d)$, if there is a vector $\delta$ satisfying $x - x^{ss} = Z \delta$, then it is unique. Therefore, for any matrix $U = \{u_{ij}\}_{(N-d) \times N}$ satisfying $UZ = I_{N-d}$, we can have $\delta = U(x - x^{ss})$.

The deterministic dynamics of $\delta(t)$ becomes

$$\frac{d\delta(t)}{dt} = U \frac{dx(t)}{dt} = USJ(\delta(t)), \quad (B1)$$

in which $J(\delta) = J(x^{ss} + Z \delta)$. The system Eq. (B1) is a set of $(N - d)$ independent ordinary differential equations, while the system in (2) usually is not. Unfortunately, the intrinsic chemical kinetic structure is lost in the transformation of (2) to (B1).

Let $F(\delta) = USF(x) = USJ(x^{ss} + Z \delta)$, in which $N$ dimensional vector $F(x) = S \tilde{J}(x)$ is the right hand side of the original Eq. (2). Hence a new Jacobian matrix, $\Gamma^\delta = US \Gamma Z$, has elements

$$\gamma_{ij} = \frac{\partial F_i^\delta(0)}{\partial x_j} = \sum_{k=1}^{N-d} u_{ik} \sum_{q=1}^{N} \frac{\partial F_q(x^{ss})}{\partial x_k} z_{qj}, \quad (B2)$$

$1 \leq i, j \leq N - d$.

Therefore, suppose $\eta$ is an eigenvector of $\Gamma$ with eigenvalue $\lambda$. If $\lambda \neq 0$, $\tilde{\eta}$ is in the space $L^+$; hence there exists a corresponding vector $\eta^\delta$ satisfying $Z \eta^\delta = \tilde{\eta}$, followed by $\Gamma^\delta \eta^\delta = \lambda \eta^\delta$. So the dimensions of eigenspaces of non-zero eigenvalues for $N \times N$ Jacobian matrix $\Gamma$ and $(N - d) \times (N - d)$ matrix $\Gamma^\delta$ are the same. This implies that the sufficient and necessary conditions for the steady state $x^{ss}$ to be stable are the real parts of all eigenvalues of $\Gamma^\delta$ are negative, i.e. the eigenspace of zero eigenvalue for $\Gamma$ has dimension $d$, and all the non-zero eigenvalues have negative real parts. Note that the remaining $\Gamma^\delta$ is still possible to have zero eigenvalue(s) at $\delta = 0$ due to dynamics. This yields a center manifold.

Next we will consider $\sigma^{(fd)}[x]$. Denote $\sigma^{(fd)}(\delta) = \sigma^{(fd)}[x^{ss} + Z \delta]$. Then

$$\frac{\partial \sigma^{(fd)}[x^{ss} + Z \delta]}{\partial x_j}(\delta) = \sum_{j=1}^{N} \frac{\partial \sigma^{(fd)}[x^{ss} + Z \delta]}{\partial x_j} z_{ji}, \quad (B3)$$

Therefore, we know that at $x = x^{ss}$, i.e. $\delta = 0$,

$$\frac{\partial \sigma^{(fd)}[x^{ss} + Z \delta]}{\partial x_i}(0) = \frac{\partial \sigma^{(fd)}[x^{ss}]}{\partial x_i} = 0,$$

for each $i$. Furthermore, let us compute $\frac{\partial^2 \sigma^{(fd)}}{\partial x_i \partial x_j}(0)$. Since

$$\frac{\partial \sigma^{(fd)}[x^{ss} + Z \delta]}{\partial x_k}(\delta) = \sum_{k=1}^{N} \frac{\partial \sigma^{(fd)}[x^{ss} + Z \delta]}{\partial x_k} z_{ki}, \quad (B4)$$
\[
\frac{\partial^2 \sigma(f_d)}{\partial \delta_i \partial \delta_j} = \sum_{k=1}^{N} \sum_{m=1}^{N} z_{ki} \sum_{m=1}^{N} \frac{\partial^2 \sigma(f_d)}{\partial x_k \partial x_m} \left[ x^{ss} + Z \delta \right]_{zmj} \times \frac{\partial}{\partial x_k} \left[ x^{ss} + Z \delta \right] \delta_{jm}.
\]

Hence define matrix \( H^\delta = \{ H^\delta_{ij} \} \), in which
\[
H^\delta_{ij} = \frac{\partial^2 \sigma(f_d)}{\partial x_i \partial x_j} \left[ x^{ss} + Z \delta \right] \times \frac{\partial}{\partial x_i} \left[ x^{ss} + Z \delta \right] \delta_{jm}.
\]

C Keizer’s theory with complex balanced kinetics

According to Keizer’s theory \[45\], at a steady state \( x^{ss} \) with complex balance, \( 2D = -(\Gamma \Xi + \Xi \Gamma^T) \), in which \( \Theta = \left\{ \frac{\partial A[x^{ss}]}{\partial x_i \partial x_j} \right\} \),
\[
\Xi_{ij} = (\Theta^{-1})_{ij} = x^{ss}_i \delta_{ij},
\]
\[
\Gamma_{ij} = \frac{\partial F_i(x^{ss})}{\partial x_j} = \frac{1}{x_j} \sum_{\ell=1}^{M} (\kappa_{\ell i} - \nu_{\ell i}) \left( \nu_{\ell j} J_{+\ell}(x^{ss}) - \kappa_{\ell j} J_{-\ell}(x^{ss}) \right) + \frac{1}{2} \sum_{\ell=1}^{M} (\nu_{\ell i} - \kappa_{\ell i})(\nu_{\ell j} - \kappa_{\ell j}) \left( J_{+\ell}(x^{ss}) + J_{-\ell}(x^{ss}) \right).
\]

We note that \( \Xi = \Theta^{-1} \) in Eq. \[13\] and
\[
- \sum_{k=1}^{N} \left( \Gamma_{ik} x^{ss}_k \delta_{kj} + x^{ss}_i \delta_{ik} \Gamma_{jk} \right) = -(\Gamma_{ij} x^{ss}_j + \Gamma_{ji} x^{ss}_i)
\]
\[
= \sum_{\ell=1}^{M} \left( (\nu_{\ell i} - \kappa_{\ell i}) \nu_{\ell j} + (\nu_{\ell j} - \kappa_{\ell j}) \nu_{\ell i} \right) J_{+\ell}(x^{ss}) - \left( (\kappa_{\ell i} - \nu_{\ell i}) \kappa_{\ell j} + (\kappa_{\ell j} - \nu_{\ell j}) \kappa_{\ell i} \right) J_{-\ell}(x^{ss}).
\]
Now for each complex \((\xi_1 X_1 + \cdots + \xi_N X_N)\), represented by \(\xi\), a steady state \(x^{ss}\) being complex balanced means

\[
\sum_{\ell=1}^{M} \left( \psi(\kappa_{\ell}) \delta_{\kappa_{\ell}, \xi} - \psi(\nu_{\ell}) \delta_{\nu_{\ell}, \xi} \right) \left( J_{+\ell}(x^{ss}) - J_{-\ell}(x^{ss}) \right) = 0, \quad (C5)
\]

for any functions \(\psi\). If we choose \(\psi(\xi) = \xi_i \xi_j\), then

\[
\sum_{\ell=1}^{M} \left( \kappa_{\ell i} \kappa_{\ell j} - \nu_{\ell j} \nu_{\ell i} \right) \left( J_{+\ell}(x^{ss}) - J_{-\ell}(x^{ss}) \right) = 0. \quad (C6)
\]

Combining (C4) and (C6), we have

\[
\sum_{\ell=1}^{M} \left( \nu_{\ell i} - \kappa_{\ell i} \right) \left( \nu_{\ell j} - \kappa_{\ell j} \right) J_{+\ell}(x^{ss}) - \left( \left( \nu_{\ell i} - \kappa_{\ell i} \right) \kappa_{\ell j} \right) \left( J_{+\ell}(x^{ss}) - J_{-\ell}(x^{ss}) \right) + \left( \kappa_{\ell j} \nu_{\ell i} - \nu_{\ell j} \nu_{\ell i} \right) \left( J_{+\ell}(x^{ss}) - J_{-\ell}(x^{ss}) \right) = \sum_{\ell=1}^{M} \left( \nu_{\ell i} - \kappa_{\ell i} \right) \left( \nu_{\ell j} - \kappa_{\ell j} \right) \left( J_{+\ell}(x^{ss}) + J_{-\ell}(x^{ss}) \right) = 2D_{ij}. \quad (C7)
\]