Entropy production in mesoscopic stochastic thermodynamics: nonequilibrium kinetic cycles driven by chemical potentials, temperatures, and mechanical forces

Topical Review

Entropy production in mesoscopic stochastic thermodynamics: nonequilibrium kinetic cycles driven by chemical potentials, temperatures, and mechanical forces

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Abstract

Nonequilibrium thermodynamics (NET) investigates processes in systems out of global equilibrium. On a mesoscopic level, it provides a statistical dynamic description of various complex phenomena such as chemical reactions, ion transport, diffusion, thermochemical, thermomechanical and mechanochemical fluxes. In the present review, we introduce a mesoscopic stochastic formulation of NET by analyzing entropy production in several simple examples. The fundamental role of nonequilibrium steady-state cycle kinetics is emphasized. The statistical mechanics of Onsager's reciprocal relations in this context is elucidated. Chemomechanical, thermomechanical, and enzyme-catalyzed thermochemical energy transduction processes are discussed. It is argued that mesoscopic stochastic NET in phase space provides a rigorous mathematical basis of fundamental concepts needed for understanding complex processes in chemistry, physics and biology. This theory is also relevant for nanoscale technological advances.

(Some figures may appear in colour only in the online journal)

1. Introduction

Nonequilibrium thermodynamics (NET) concerns with dynamic processes in systems that are not in global equilibrium, either in a transient or in a stationary state. Since only few systems can be viewed as really equilibrium, the subject has a fundamental importance for understanding various phenomena in chemistry, physics and biology. It has a long history, starting with famous studies of Thomson on thermoelectricity

[1]. The work of Onsager [2, 3] has laid the foundation of the field; it puts the earlier research by Thomson, Boltzmann, Nernst, Duhem, Jauman and Einstein into a systematic framework. By following Onsager, a consistent NET of continuous systems was developed in the 1940s by Meixner [4, 5], and Prigogine [6]. Several key aspects of the Onsager's theory were clarified by Casimir [7]. The most general description of NET, so far, is the well-known book by de Groot and Mazur from 1962 [8].

The basic principles of thermodynamics asserts the existence of a special function of the macroscopic state of the system, which is called entropy S. This entropy satisfies the following balance equation[4]:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \frac{\mathrm{đ}_e S}{\mathrm{d}t} + \frac{\mathrm{đ}_i S}{\mathrm{d}t}, \tag{1}$$

in which $\mathrm{đ}_e S/\mathrm{d}t$ is the entropy supplied by the system's environment, and $\mathrm{đ}_i S/\mathrm{d}t$ is the always non-negative entropy production inside the system. The sign of $\mathrm{đ}_e S/\mathrm{d}t$, however, can be positive, zero or negative. For an isolated system that has no entropy exchange with its environment, S always increases until it attains the maximum. The system then reaches the equilibrium.

2. Theories of nonequilibrium thermodynamics

Equation (1) is a fundamental relation that describes the entropy production. It plays a key central role in NET. Macroscopic NET as presented in [8] treats various processes in the absence of fluctuations. This will be discussed shortly in section 2.1. As explained by Ortiz de Zárate and Sengers [9], it is possible to extend this macroscopic NET from top down to include hydrodynamic fluctuations using appropriate fluctuation-dissipation theorems. We will not go in this direction, but rather describe a novel, bottom-up *mesoscopic* NET with fluctuations in phase space in terms of time-dependent and stationary probability distributions. The main focus of this paper is to present a theoretical framework that will show how thermodynamic forces and fluxes in various realistic nonequilibrium processes can all be represented in terms of a unified treatment at the mesoscopic level, in phase space.

2.1. Macroscopic nonequilibrium thermodynamics

There are several theories for nonequilibrium systems that start with the entropy balance equation. de Groot and Mazur's approach [8], followed by Kjelstrup and Bedeaux [10] for heterogeneous systems, obtained a spatially resolved version of equation (1). For a homogeneous fluid in terms of continuous densities it can be rewritten as

$$S(t) = \int_V s(x, t) \mathrm{d}V, \tag{2}$$

$$\frac{\mathrm{đ}_e S}{\mathrm{d}t} = -\int_{\partial V} \mathbf{J}_s(x, t) \cdot \mathrm{d}S, \tag{3}$$

$$\frac{\mathrm{đ}_i S}{\mathrm{d}t} = \int_V \sigma(x, t) \mathrm{d}V, \tag{4}$$

where $s(x, t)$ is the entropy density per unit volume, $\mathbf{J}_s(x, t)$ is the spatial entropy flux, and $\sigma(x, t)$ is the entropy production per unit volume, which is non-negative. The second integral is over the surface of the volume V, and $\mathrm{d}S$ has the direction of

[4] In classical thermodynamics, a distinction between the total differential of a quantity Q, $\mathrm{d}Q$, and an inexact differential $\mathrm{đ}Q$, which is path dependent, has to be explicitly made.

the outward normal. Applying Gauss' theorem to equation (1) in an arbitrary sub-volume, one obtains

$$\frac{\partial s(x, t)}{\partial t} = -\mathrm{div}\mathbf{J}_s(x, t) + \sigma(x, t). \tag{5}$$

In order to calculate $\partial s(x, t)/\partial t$ one follows the Gibbs equation,

$$\mathrm{d}u = T\mathrm{d}s + \sum_{j=1}^{n} \mu_j \mathrm{d}c_j, \tag{6}$$

where u, T, μ_j, c_j are the internal energy density, temperature and the chemical potentials and molar densities of component j, respectively. The use of relation (6) implies the assumption of *local equilibrium* in space and time, meaning that all thermodynamic relations remain valid at a coarse-grained scale that is *macroscopically small but microscopically large*.

The continuity balance equations for the internal energy and the component densities are

$$\frac{\partial u}{\partial t} = -\mathrm{div}\mathbf{J}_u, \tag{7}$$

$$\frac{\partial c_j}{\partial t} = -\mathrm{div}(c_j \mathbf{v}_j) + \sum_{\ell=1}^{m} \nu_{\ell j} r_\ell, \tag{8}$$

where $\mathbf{J}_u$ is the internal energy flux, $c_j \mathbf{v}_j$ are the spatial molar fluxes, r_ℓ is the rate of the ℓth chemical reaction, and $\nu_{\ell j}$ are the corresponding stoichiometric coefficients. The internal energy flux $\mathbf{J}_u$ and the velocities $\mathbf{v}_j$ are in the laboratory frame of reference. We consider no external potentials and restrict ourselves to mechanical equilibrium. Furthermore we neglect viscous contributions to the pressure. Substituting equations (7) and (8) into equation (6) results in

$$\frac{\partial s}{\partial t} = -\mathrm{div}\left(\frac{\mathbf{J}_u - \sum_{j=1}^{n} \mu_j c_j \mathbf{v}_j}{T}\right) + \mathbf{J}_u \cdot \mathrm{grad}\left(\frac{1}{T}\right) - \sum_{j=1}^{n} c_j \mathbf{v}_j \cdot \mathrm{grad}\left(\frac{\mu_j}{T}\right) - \sum_{\ell=1}^{m} r_\ell\left(\frac{\Delta G_\ell}{T}\right), \tag{9}$$

where $\Delta G_\ell \equiv \sum_{j=1}^{n} \nu_{\ell j} \mu_j$ is the Gibbs energy difference of the ℓth chemical reaction. Comparing with equation (5) yields the entropy flux and the entropy production:

$$\mathbf{J}_s = \frac{\mathbf{J}_u}{T} - \frac{1}{T}\sum_{j=1}^{n} \mu_j c_j \mathbf{v}_j, \tag{10}$$

$$\sigma = \mathbf{J}_u \cdot \mathrm{grad}\left(\frac{1}{T}\right) - \sum_{j=1}^{n} c_j \mathbf{v}_j \cdot \mathrm{grad}\left(\frac{\mu_j}{T}\right) - \sum_{\ell=1}^{m} r_\ell\left(\frac{\Delta G_\ell}{T}\right). \tag{11}$$

While de Groot and Mazur [8] always used fluxes in the barycentric (center-of-mass) frame of reference, we utilized here the fluxes in the laboratory frame of reference. The total entropy production has the important property of being invariant under the transformation of one frame of reference to another. This may easily be verified by defining the heat flux $\mathbf{J}_q = \mathbf{J}_u - u\mathbf{v}$ and the diffusion fluxes $\mathbf{J}_j = c_j(\mathbf{v}_j - \mathbf{v})$, where the velocity $\mathbf{v}$ can be chosen to be the barycentric velocity, the mean molar velocity, the mean volume velocity, the velocity of one of the components (the solvent), or the velocity of the

surface of for instance an electrode. We refer to chapter 11 of [8] for a precise definition of these velocities and a detailed discussion. Regarding the use of a surface as the frame of reference we refer to Kjelstrup and Bedeaux [10]. Substituting these definitions into equation (11), and with the Gibbs–Duhem relation and mechanical equilibrium, it follows that

$$\sigma = \mathbf{J}_q \cdot \operatorname{grad}\left(\frac{1}{T}\right) - \sum_{j=1}^{n} \mathbf{J}_j \cdot \operatorname{grad}\left(\frac{\mu_j}{T}\right) - \sum_{\ell=1}^{m} r_\ell \left(\frac{\Delta G_\ell}{T}\right). \quad (12)$$

The entropy production is a binary product of so-called conjugate thermodynamic fluxes and forces. For different choices of **v**, the heat flux and the diffusion fluxes are different, and they can be chosen depending on the experimental setting. When one introduces alternative thermodynamic fluxes one should realize that the corresponding conjugate thermodynamic forces may also change. An example is the use of the measurable heat flux [11]:

$$\mathbf{J}'_q \equiv \mathbf{J}_q - \sum_{j=1}^{n} h_j \mathbf{J}_j, \quad (13)$$

in which h_j is the enthalpic contribution to μ_j, $\mu_j = h_j - Ts_j$. When we substitute of this definition in equation (12) and use van't Hoff's equation $h_j = \partial(\mu_j/T)/\partial(1/T)$ [12, 13], the entropy production becomes

$$\sigma = \mathbf{J}'_q \cdot \operatorname{grad}\left(\frac{1}{T}\right) - \frac{1}{T}\sum_{j=1}^{n} \mathbf{J}_j \cdot (\operatorname{grad}\mu_j)_T - \sum_{\ell=1}^{m} r_\ell \left(\frac{\Delta G_\ell}{T}\right). \quad (14)$$

The subscript T in the $(\operatorname{grad}\mu_j)_T$ means that the spatial differentiation is calculated keeping the temperature constant. One can further show that the measurable heat flux is independent of the frame of reference [8, 10]. Therefore, this is the heat flux which is most convenient for the interpretation of experiments. Using the conjugate fluxes and forces in, for instance, equation (14) one can express the vectorial fluxes $\{\mathbf{J}'_q, \mathbf{J}_j\}$ linearly in the vectorial forces $\{\operatorname{grad} T^{-1}, -T^{-1}(\operatorname{grad}\mu_k)_T\}$. The proportionality matrix was shown to be symmetric by Onsager [2, 3] using microscopic reversibility. In a 3D isotropic system such as a fluid the vectorial fluxes do not couple to the scalar forces driving the chemical reactions according to Curie's principle. The net reaction fluxes are proportional to $-\Delta G_\ell/T$ in the linear description. When one considers transport into and through surfaces [10] the fluxes normal to the surface are also scalars. As a consequence, a chemical potential difference across the surface may drive a chemical reaction at the surface (membrane).

The entropy production is non-negative according to the second law. Phenomena that are of different tensorial order do not couple, which is known as the Curie's principle. Therefore, a group of phenomena with the same tensorial character must also have a positive contribution to the entropy production. Energy transduction occurs when a larger positive term overcomes a smaller negative term [14].

The vectorial contributions are zero when a chemical system is rapidly stirred. For multiple reactions the above 3D theory can then be reduced to Qian and Beard's stoichiometric network theory, which has found a successful application in

metabolic engineering [15]. See [16] for an extensive discussion on nonequilibrium steady states with regenerating system and quasi-steady state with excess chemicals using buffers and chelators. At this level, the type of ensemble, and what are controlled thermodynamic variables, matters. This is a very important result that was first discussed by Hill [17].

2.2. Stochastic Liouville dynamics

As a point of departure from the macroscopic NET theory presented above, mesoscopic NET is based on a conservation law in the phase space of any dynamics: the Chapman–Kolmogorov equation for the conservation of probability in equations of motions in the broadest sense[5]. Instead of being based on the entropy balance equation (1), the mesoscopic NET derives a mesoscopic version of it with a dynamic foundation [19], together with an explicit expression for the probability flux, and proving the non-negativity of entropy production. As will be shown in section 3, the probability flux in phase space can be interpreted, based on a *local equilibrium* assumption, to the laboratory measurements of various realistic fluxes, such as chemical reaction flux, heat, mass transport, electrical, etc.

Such a mesoscopic theory of NET, in terms of a stochastic description of dynamics in phase space, has been repeatedly alluded to by many scientists. An earlier reference is the theory of stochastic Liouville dynamics [20, 21]. We shall not present this theory in detail. Instead, we discuss the logic relation of this work to the classical work of Boltzmann and others. The present work will then focus on overdamped stochastic dynamics, which is valid for studying NET of soft condensed matter, solution chemistry and biochemistry. The stochastic description gives a natural extension of NET to mesoscopic systems, which contains fluctuations.

Statistical or kinetic theories of nonequilibrium phenomena such as the Boltzmann transport equation provide a more detailed mechanism for dynamic processes [8]. Such theories have, however, only been developed for special classes of phenomena and use particular molecular models. One should also mention here several recent developments in the more general theoretical framework for nonequilibrium dynamics, one of which is known as a general equation for nonequilibrium reversible-irreversible coupling (GENERIC) [23, 24].

There have been several theories of irreversible phenomena using stochastic processes [25]. The Klein–Kramers equation [26, 27] and the Langevin equation, together with fluctuation-dissipation relation, are a natural extension of classical conservative dynamics of a Hamiltonian system in contact with a heat bath. Cox [28, 29] developed a Markov theory for irreversible processes that generalized Gibbs statistical mechanics to irreversible processes. Cox's work was motivated by the consideration that 'In the theory of time-dependent thermal phenomena, the method of Gibbs appears to have been rather neglected in comparison with that of Boltzmann'

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[5] For deterministic, Hamiltonian systems, the dynamics of probability is formulated in term of a measure-theoretical transfer operator, also known as Ruelle–Perron–Frobenius operator [18].

[28]. Onsager and Machlup developed a comprehensive linear stochastic dynamical theory based on a Gaussian Markov description, e.g. Ornstein–Uhlenbeck processes [30, 31]. The Shannon entropy has been introduced naturally in these theories, as the dynamic counterpart of the entropy of Gibbsian statistical ensemble, an insight originated in Boltzmann's kinetic theory and his H-function. None of these works, however, connected the stochastic dynamics with the entropy balance equation in equation (1).

By using a Liouville formulation of general conservative dynamics in phase space, together with a stochastic kernel, Bergmann and Lebowitz [20, 21] assumed the entropy balance equation (equation (1))[6] and introduced $dS_{\text{total}}(t)/dt = dS(t)/dt - T^{-1}(dU/dt) \geqslant 0$ as the total entropy change, of the system and the heat bath together. They were able to show that the Helmholtz energy of a closed system, which was expressed in terms of the time-dependent probability density function $f(x, t)$ as

$$F[f] = U - TS = \int_x f(x, t)\left[H(x) + k_B T \ln f(x, t)\right] dx, \quad (15)$$

was monotonic and non-increasing. Here H is the Hamiltonian and k_B is the Boltzmann's constant. Furthermore, x is a point in the phase-space of the system. A fluctuation-dissipation relation for a stochastic kernel with temperature T was also obtained for systems that approach to $f^{\text{eq}}(x) = \exp[-H(x)/k_B T]$. Finally, they proved that Liouville dynamics with multiple heat-baths at different temperatures yield a nonequilibrium steady state (NESS) of the closed system, with a positive entropy production.

2.3. Mesoscopic stochastic thermodynamics

While the stochastic Liouville dynamics discussed in section 2.2, as a dynamic counterpart to the equilibrium statistical thermodynamics based on a microcanonical ensemble, has the virtue of being rooted in Newtonian mechanics, its applicability to condensed matter chemistry, polymer systems, and biochemistry, is limited. In chemistry it is the Gibbsian statistical thermodynamics based on a canonical ensemble that has wide and successful applications. Overdamped stochastic dynamical theory of a polymer solution is an example of such success with many applications [33, 34].

This observation motivated a stochastic dynamics formulation of NET in phase space. The approach in section 2.1 assumes the validity of local equilibrium, meaning that all thermodynamic relations are valid locally. A mesoscopic theory can be developed based on a Markovian probabilistic description. The state space can be discrete or continuous. The Chapman–Kolmogorov equation for a Markov process can then be used to obtain a master equation. For a discrete-state space one has

$$\frac{dp_i(t)}{dt} = \sum_j [J_{ji}(t) - J_{ij}(t)] = \sum_j [p_j(t)q_{ji} - p_i(t)q_{ij}], \quad (16)$$

where $p_i(t)$ is the probability of the system being in state i at time t. Furthermore, $J_{ij}(t) = p_i(t)q_{ij}$ is the one-way flux from state i to state j at time t. For a continuous-state space the master equation becomes

$$\frac{\partial f(x, t)}{\partial t} = \int dx' \left[J(x', x; t) - J(x, x'; t)\right]$$
$$= \int dx' \left[f(x', t)q(x', x) - f(x, t)q(x, x')\right], \quad (17)$$

where $f(x, t)$ is the density of the probability of the system being in state x at time t. Similarly, $J(x, x'; t) = f(x, t)q(x, x')$ is the one-way flux density from state x to state x' at time t. If a system is not driven, then it reaches equilibrium as its stationary state. In equilibrium it follows from microscopic reversibility that the system satisfies a detailed balance [8, 25]:

$$p_j^{\text{eq}}q_{ji} = p_i^{\text{eq}}q_{ij}, \quad (18)$$

$$f^{\text{eq}}(x')q(x', x) = f^{\text{eq}}(x)q(x, x'). \quad (19)$$

The superscript eq indicates the equilibrium probability distributions for discrete systems, or probability densities of continuous systems. When the system is not in equilibrium it does not satisfy detailed balance. Yet, dynamics whose stationary state possesses detailed balance has a stringent constraint on its rate coefficients; this is known as the Wegscheider condition in chemical kinetics [35] and Kolmogorov cycle criterion in the Markov-process theory. A system may also, of course, be driven by constant external force. As a consequence, a stationary state may develop which does not satisfy detailed balance.

One should emphasize here that the linear, probabilistic description of mesoscopic NET, that we present in this work, can give rise to macroscopic nonlinear mass-action law, which is also known as a Guldberg–Waage law of chemical kinetics. It is an important part of Markov probabilistic description—see the work of Kurtz [22]. The precise relationship between our stochastic NET in phase space and recently developed nonlinear dynamic Guldberg–Waage approach [36–38] remains to be elucidated.

2.3.1. Detailed balance.
At this point, it is important to clearly explain the term 'detailed balance' because of frequent confusions and wrong applications. As we just stated above, it follows from a microscopic reversibility that the probabilistic description of a thermodynamic equilibrium system satisfies the detailed balance. For proof we refer to [8, 25]. In nature, there are many systems that never come to equilibrium. In a living being, for instance, ions are continuously pumped by ATPases through membranes. Equilibrium is obtained only when the living being dies. It follows that the detailed balance, though exact in equilibrium, is not relevant for a description of homeostatic living biological systems. In general, any nonequilibrium state in such open systems is maintained, for instance, by constantly adding ATP or other reactants. In the description of the behavior of such systems, it is common to

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[6] For a given dynamics and a definition of S, dS/dt can always be computed. The entropy production as in equation (1), however, has always been defined phenomenologically based on physical intuitions. This situation has changed since the emergence of a measure-theoretical definition(s) of entropy production in the theory of Markov dynamics [32].

introduce pseudo-first-order rate coefficients to replace the original coefficients. This is done by absorbing the concentrations of buffered components, maintained at a constant non-equilibrium value, in the rate constants. The product defines the new pseudo-first-order rate coefficient. The resulting description concerns then the behavior far from equilibrium, and the forward and backward rates are then evidently not balanced, even in a stationary state. In the *buffered pseudo-first-order rate coefficients* the system does not have an equilibrium state, and therefore never satisfies detailed balance.

Detailed balance is also a mathematical concept in the theory of Markov process and Monte Carlo statistical simulations. The mathematical concept of detailed balance is applicable to Markov models of physical and chemical origin in closed systems. A Markov model for an open (buffered) nonequilibrium system using the above mentioned pseudo-first-order rate coefficients does not satisfy detailed balance. We refer to [39, 40] for a detailed discussion. In the present work, we will also use the pseudo-first-order rate coefficients when this is convenient.

2.3.2. Entropy balance equation for continuous Markov dynamics. We consider a transition probability $q(x', x)$ from state x' to state x, which is sharply peaked in the sense that $f(x', t)$ varies slowly over the range of $q(x', x)$. One may then use a moment expansion of the transition probability to the second order:

$$q(x', x) = q_1(x') \cdot \frac{\partial}{\partial x'} \delta(x - x') + \frac{1}{2} q_2(x') \frac{\partial^2}{\partial x'^2} \delta(x - x'). \quad (20)$$

Both q_1 and $\frac{\partial}{\partial x'}$ are vectors in phase-space, the period · indicates a contraction, and $\frac{\partial^2}{\partial x'^2} \equiv \frac{\partial}{\partial x'} \cdot \frac{\partial}{\partial x'}$. A possible zeroth order contribution does not contribute to $\partial f / \partial t$. In the moment expansion we assumed that q_2 is scalar. The jump moments are given by

$$q_1(x') = \int dx \, (x - x') \, q(x', x) \quad (21)$$

$$q_2(x') = \int dx \, |x - x'|^2 q(x', x). \quad (22)$$

Substitution of equation (20) into equation (17) gives the Fokker–Planck equation[7]

$$\frac{\partial f(x, t)}{\partial t} = -\frac{\partial}{\partial x}(q_1(x) f(x, t)) + \frac{1}{2} \frac{\partial^2}{\partial x^2}(q_2(x) f(x, t)). \quad (23)$$

It is now convenient to rename

$$D(x) \equiv \frac{1}{2} q_2(x) \text{ and } V(x) \equiv q_1(x) - \frac{1}{2} \frac{\partial}{\partial x} q_2(x). \quad (24)$$

where the diffusion coefficient D is a matrix and the velocity V a vector in phase space. The Fokker–Planck equation can then be written in the form

$$\frac{\partial f(x, t)}{\partial t} = -\frac{\partial}{\partial x} \cdot J(x, t) \quad (25)$$

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[7] Alternative names are the Smoluchowski equation or the second Kolmogorov equation.

with

$$J(x, t) = V(x) f(x, t) - D(x) \frac{\partial}{\partial x} f(x, t), \quad (26)$$

in which $J(x, t)$ is a probabilistic flux. Equations (16) and (26) give expressions for the flux in terms of the probability density $f(x, t)$. The positive definite nature of the entropy production can be proven within the theory [42–45]:

$$\frac{dS}{dt} = -k_B \frac{d}{dt} \int_\Omega f(x, t) \ln f(x, t) dx$$

$$= k_B \oint_{\partial\Omega} \ln f(x, t) J(x, t) \cdot d\Omega - k_B \int_\Omega J(x, t) \cdot \frac{\partial}{\partial x} \ln f(x, t) dx$$

$$= \frac{d_e S}{dt} + \frac{d_i S}{dt}, \quad (27)$$

where $\oint_{\partial\Omega} \cdots d\Omega$ indicates an integral over the surface. The surface element $d\Omega$ has the outward direction normal to the surface. The system is now open, with

$$\frac{d_i S}{dt} = k_B \int_\Omega J(x, t) \cdot \left(D^{-1}(x) V(x) - \frac{\partial}{\partial x} \ln f(x, t) \right) dx \geqslant 0, \quad (28)$$

$$\frac{d_e S}{dt} = k_B \oint_{\partial\Omega} \ln f(x, t) J(x, t) \cdot d\Omega$$
$$- k_B \int_\Omega J(x, t) \cdot D^{-1}(x) V(x) dx. \quad (29)$$

The reason for the choices of $\frac{d_i S}{dt}$ and $\frac{d_e S}{dt}$, is that $\frac{d_i S}{dt}$ being consistent with Onsager's idea of 'force × flux', and it is non-negative. This assures validity of the Second law of Thermodynamics, and it establishes a link to NET. A complete parallel can be developed for the discrete description, equation (16) [46]. The Markov theory, which is formulated in a phase space, has fluxes which are described by the single entity $J(x, t)$, the flux of probability density.

The current stochastic thermodynamics begins with the notion of entropy production in stochastic processes, used already in Hill's stochastic cycle kinetics [14, 46, 48] and in Qians' work on irreversible Markov processes [42, 49–52]. Another origin are the fluctuation theorems and the Jarzynski–Crooks equality. See [53–56] for comprehensive reviews on the subject.

3. Nonequilibrium thermodynamics of driven cycles

Stochastic thermodynamics is a mesoscopic theory in terms of probability. One of the fundamental insights from the Hill's nonequilibrium thermodynamic theory [14] is the central role of *kinetic cycles*, both in steady state and in finite time. Actually, by realizing that entropy production is a fundamental property of each and every kinetic cycle, and that cycles are completed one by one stochastically in time [48], Hill and Chen indeed have implicitly conceived the notion of entropy production at the finite time [50, 51]. It can be mathematically shown that the entropy production for a *stationary* Markov jump process with transition rates q_{ij}, e.g. systems following equation (16), has a cycle representation [32]:

$$\frac{d_i S}{dt} = k_B \sum_{i>j}(J_{ij} - J_{ji})\ln\left(\frac{J_{ij}}{J_{ji}}\right), \qquad (30)$$

$$= k_B \sum_{\text{all cycle}\Gamma}(J_\Gamma^+ - J_\Gamma^-)\ln\left(\frac{J_\Gamma^+}{J_\Gamma^-}\right), \qquad (31)$$

$$\ln\left(\frac{J_\Gamma^+}{J_\Gamma^-}\right) = \ln\left(\frac{q_{i_0 i_1}q_{i_1 i_2}\cdots q_{i_{n-1}i_n}q_{i_n i_0}}{q_{i_0 i_n}q_{i_n i_{n-1}}\cdots q_{i_2 i_1}q_{i_1 i_0}}\right), \qquad (32)$$

in which Γ-cycle $= \{i_0, i_1, \cdots, i_n, i_0\}$, where all i_k are distinct. Since a Markov process completes cycles stochastically, one can compute a finite-time entropy production along a stochastic trajectory by following the cycles. For a Markov process in equilibrium the detailed balance, $J_{ij} = J_{ji}$, is valid. The entropy production for every cycle is then zero. The entropy production is the sum of the entropy productions of the separate cycles. The entropy production per cycle is $k_B \ln(J_\Gamma^+/J_\Gamma^-)$; the rate by which a particular cycle is being completed is $(J_\Gamma^+ - J_\Gamma^-)$; thus the entropy production *rate* per cycle is $k_B(J_\Gamma^+ - J_\Gamma^-)\ln(J_\Gamma^+/J_\Gamma^-)$ [32]. While computing all the rates is challenging, it is amazing to observe that the entropy production per cycle $k_B \ln(J_\Gamma^+/J_\Gamma^-)$, is completely determined by the ratio of transition probability rates. This observation led Hill to suggest that kinetic cycles, not states, are fundamental units of NET. Indeed, the notion of 'cycle completion', which is amply emphasized in Hill's theory [48], nicely corresponds to Landauer and Bennett's principle of computational irreversibility being associated with memory erasing [57, 58].

Cyclic processes, which were extensively investigated by Carnot, Clausius, Kelvin, and many others in the 19th century, can be described as thermodynamic processes in phase space. The beauty of the stochastic description is that the physical processes are all characterized by probabilities. In applications, however, the various flux terms can and should be interpreted as temperature driven, chemical-potential driven, or mechanically driven, etc. We will now illustrate this by considering simple examples.

Let us restrict the analysis to the systems with discrete states. Following Esposito [59], we consider a mesoscopic system in state i with internal energy U_i, entropy S_i, and number of particles N_i. If the mesoscopic system is completely isolated from its environment, then it will remain in the i state indefinitely with conserved U_i, S_i, N_i. It has an equation of state $V = V_i(U_i, S_i, N_i)$ where V is the volume of the system. Now if the system is in contact with a heat bath with temperature T, and a material reservoir with chemical potential μ, then the state has a grand potential, also called Landau potential:

$$\varphi_i(T, \mu) = U_i - TS_i - \mu N_i. \qquad (33)$$

Transition to a state j can occur due to the coupling to the heat and particle bath, with transition rates q_{ij} and q_{ji} which satisfy the detailed balance [14]:

$$\frac{q_{ij}}{q_{ji}} = \frac{p_j^{eq}}{p_i^{eq}} = \exp\left(\frac{-\varphi_j + \varphi_i}{k_B T}\right). \qquad (34)$$
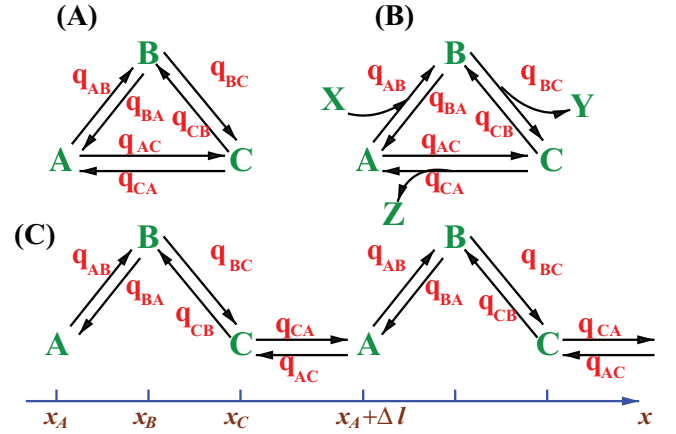

Figure 1. (A) Three-state cycle kinetics in a closed system. (B) Three-state cycle kinetics in an open chemical system with material reservoirs of X, Y, and Z, with chemical potential $\mu^{(X)}$, $\mu^{(Y)}$, and $\mu^{(Z)}$. (C) Three-state cycle kinetics in an open chemical system with 1D spatial component x (material reservoirs are not shown to avoid cluttering). A complete cycle kinetics accompanies a spatial displacement of $\Delta\ell$. Such a system has a 'tight' coupling between the cycle and the translocation. If there were nonzero transitions between $C(x_C)$ and $A(x_A)$, then the system would be loosely coupled [64].

Here we used the fact that in equilibrium the probability distribution is $p_{i,eq} \propto \exp(-\varphi_i/k_B T)$. Detailed balance implies that the forward and backward rates cannot be chosen independently if the potentials of the reservoirs are given. If one uses different heat and material reservoirs for the different states of the system, a stationary state may develop and obviously $p_i^{ss}q_{ij} \neq p_j^{ss}q_{ji}$ in that stationary state.

3.1. Chemical cycle kinetics

Consider a cycle as shown in figure 1(A), in which all three mesoscopic states A, B, and C are in contact with the same heat bath with temperature T. Then,

$$\frac{q_{AB}q_{BC}q_{CA}}{q_{BA}q_{CB}q_{AC}} = \exp\left(\frac{-\varphi_B + \varphi_A}{k_B T}\right)\exp\left(\frac{-\varphi_C + \varphi_B}{k_B T}\right)\exp\left(\frac{-\varphi_A + \varphi_C}{k_B T}\right) = 1. \qquad (35)$$

This is the detailed balance for the cycle.

If we consider a cycle in the open system with material reservoirs having chemical potentials μ_A, μ_B and μ_C (see figure 1(B)), then potentials φ_i can be replaced by the corresponding chemical potentials μ_i as the reaction only changes N_i in equation (33). Now, at constant T, if the first transition in the cycle is a part of the chemical reaction $A + X \rightleftharpoons B$, as shown in figure 1(B), and similarly the second transition is a part of $B \rightleftharpoons C + Y$, and the third transition involves $C \rightleftharpoons A + Z$, then one has the entropy production per cycle, or *cycle affinity*

$$A_C = k_B \ln\left(\frac{q_{AB}q_{BC}q_{CA}}{q_{BA}q_{CB}q_{AC}}\right)$$
$$= \left(\frac{\mu_A + \mu^{(X)} - \mu_B}{T}\right) + \left(\frac{\mu_B - \mu_C - \mu^{(Y)}}{T}\right) + \left(\frac{\mu_C - \mu_A - \mu^{(Z)}}{T}\right)$$
$$= \frac{\mu^{(X)} - \mu^{(Y)} - \mu^{(Z)}}{T}. \qquad (36)$$

Here the numerator is the chemical potential difference associated with the reaction of 'external chemical potential reservoirs' $X \rightleftharpoons Y + Z$. This is an open chemical system with a chemical-potential driven cycle. The difference between state B and state A is one X, between states B and C is one Y, and between states C and A is one Z. The corresponding steady-state cycle flux is [14]

$$J_C = \frac{q_{AB}q_{BC}q_{CA} - q_{AC}q_{CB}q_{BA}}{\left\{\begin{array}{l} q_{BC}q_{CA} + q_{CB}q_{BA} + q_{BA}q_{CA} + q_{CA}q_{AB} \\ + q_{AC}q_{CB} + q_{CB}q_{AB} + q_{AB}q_{BC} + q_{BA}q_{AC} + q_{AC}q_{BC} \end{array}\right\}}. \quad (37)$$

It is clear that $J_C \times A_C \geqslant 0$ [39]. This is the entropy production in equation (31), for one cycle. It is zero if and only if equation (35) holds true, i.e. if the chemical system is closed. It is zero for an open system if $\Delta \mu = \mu^{(X} - \mu^{(Y)} - \mu^{(Z)} = 0$, i.e. when the system is coupled to several chemical baths that are themselves at equilibrium.

In chemistry, it is often conveniently to write

$$\frac{q_{AB}}{q_{BA}} = \exp\left(\frac{\mu_A + \mu^{(X)} - \mu_B}{k_B T}\right) = \frac{q_{AB}^o a_X}{q_{BA}}, \quad (38)$$

in which q_{AB}^o is a *second-order* rate constant, and $a_X = \exp(\mu^{(X)}/k_B T)$ is the activity of species X. It follows that q_{AB}^o and q_{BA} satisfy the detailed balance,

$$\frac{q_{AB}^o}{q_{BA}} = \exp\left(\frac{\mu_A - \mu_B}{k_B T}\right). \quad (39)$$

Recalling discussion in section 2.3.1, we see that q_{AB}^o and q_{BA} are the original rate coefficients, which satisfy detailed balance, while q_{AB} and q_{BA} are the pseudo first-order rate coefficients, which do not.

3.2. Chemomechanical cycle and a molecular motor

Now if the mesoscopic system has a 1D position x that experiences a constant external mechanical resistant force ξ (or a rotational angle with a constant external torque) and undergoes cyclic motion, as shown in figure 1(C) [41, 60–62] then equation (33) modifies into

$$\varphi(T, \mu; x) = U_i - TS_i - \mu N_i - \xi x, \quad (40)$$

in which the term ξx should be compared with the pV term in macroscopic thermodynamics. The entropy production per cycle, or cycle affinity, in equation (36) becomes [63]

$$A_C = \frac{\mu^{(X)} - \mu^{(Y)} - \mu^{(Z)} - \xi \Delta \ell}{T}. \quad (41)$$

The significance of this result is that it establishes, mathematically, a mesoscopic free-energy balance between input Gibbs energy $\Delta \mu \equiv \mu^{(X)} - \mu^{(Y)} - \mu^{(Z)}$, which becomes the work against the external force $\xi \Delta \ell$, and dissipation A_C, both per unit of flux. The efficiency of the chemomechanical energy transduction of the cycle immediately follows: $\eta_{\text{chemomechanic}} = \xi \Delta \ell / \Delta \mu$ [63]. One can also see that when the external force is given by $\xi = \Delta \mu / \Delta \ell$, known as a stalling force, the efficiency is 1; but

at the same time the output mechanical power, e.g. the work per unit time, is zero. This is a pathological consequence of assuming a single cycle that tightly couples the mechanical and chemical steps [64]. If this is not the case, e.g. the chemical step and the mechanical step can 'slip', then there will be at least one additional cycle in which the chemical energy dissipates.

If the force ξ is negative, it can push a negative $\Delta \mu$. Such a kinetic cycle will have mechanical force driven chemical pumping $Y + Z \longrightarrow X$, as in enzyme F_0F_1-ATP synthase [65].

3.3. Temperature-driven kinetic cycle and thermomechanical efficiency

Let us again consider the cycle kinetics presented figure 1(A). This time, the three mesoscopic states A, B, and C are in a contact with different temperature baths. Let us assume that A, B, C have the temperatures T_A, T_B and T_C. We further assume all chemical potentials are equal. Then, one has the cycle affinity given by [66, 67]

$$A_C = k_B \ln\left(\frac{q_{AB}q_{BC}q_{CA}}{q_{BA}q_{CB}q_{AC}}\right) \quad (42)$$

$$= \left(\frac{\varphi_A - \varphi_B}{T_A}\right) + \left(\frac{\varphi_B - \varphi_C}{T_B}\right) + \left(\frac{\varphi_C - \varphi_A}{T_C}\right)$$

$$= \frac{U_A - U_B}{T_A} + \frac{U_B - U_C}{T_B} + \frac{U_C - U_A - \xi \Delta \ell}{T_C}$$

$$= U_A\left(\frac{1}{T_B} - \frac{1}{T_C}\right) + U_B\left(\frac{1}{T_B} - \frac{1}{T_A}\right) + U_C\left(\frac{1}{T_C} - \frac{1}{T_B}\right) - \frac{\xi \Delta \ell}{T_C}, \quad (43)$$

in which the force ξ is a property of the external environment [41, 61]. In the special case when $T_B = T_C$, one obtains

$$A_C = \frac{U_A - U_B}{T_A} + \frac{U_B - U_A - \xi \Delta \ell}{T_B}$$

$$= (U_A - U_B)\left(\frac{1}{T_A} - \frac{1}{T_B}\right) - \frac{\xi \Delta \ell}{T_B} \geqslant 0, \quad (44)$$

Note, when $\xi \Delta \ell$ is positive, $(T_A - T_B)$ and $\mathcal{Q} \equiv (U_A - U_B)$ always have opposite signs; thus the product $(U_A - U_B)(T_A^{-1} - T_B^{-1})$ is always positive. Without loss of generality, we let $T_A > T_B$. Then, the thermomechanical (first-law) efficiency can be defined as

$$\eta_{\text{thermomechanic}} = \frac{\xi \Delta \ell}{|\mathcal{Q}|} = \frac{T_B}{\mathcal{Q}} A_C + \left(1 - \frac{T_B}{T_A}\right) \leqslant 1 - \frac{T_B}{T_A}. \quad (45)$$

The maximal first-law efficiency[8] is the Carnot limit [66]. The second-law efficiency is then equal to [68]:

---

[8] The term *first-law efficiency* is used to distinguish it from the second-law efficiency (also known as a rational efficiency and exergy efficiency) which computes the efficiency of a process taking the second law of thermodynamics into account in practical engineering. The exergy of a system is the maximum useful work possible during a process that brings the system into equilibrium with a heat bath. Note that in chemomechanical energy transduction, taking the second law into account does not reduce the upper limit of efficiency $\eta_{\text{chemomechanical}}$, when the power is zero.

$$\eta_{\text{exergy}} = \frac{\xi \Delta \ell}{\xi \Delta \ell + T_B A_C} = \frac{\xi \Delta \ell}{|\mathcal{Q}|\left(1 - \frac{T_B}{T_A}\right)}. \quad (46)$$

The entropy production is the product of J_C, given in equation (37), and A_C. With given high and low temperature baths T_A and T_B, one could ask a different question. Allowing temperature T_C to be between T_A and T_B, what is the condition for the maximum power for a given entropy production? The answer is that this situation is realized when

$$\frac{q_{AB}}{q_{BA}} = \frac{q_{BC}}{q_{CB}} = \frac{q_{CA}}{q_{AC}}, \quad (47)$$

Equation (47) is known as the 'principle of constant force' in the field of molecular motors [65, 69]. It also corresponds to equal chemical potential drops in the metabolic engineering [70]. In this case, one can write

$$k_{\text{B}} \ln\left(\frac{q_{AB}}{q_{BA}}\right) = k_{\text{B}} \ln\left(\frac{q_{BC}}{q_{CB}}\right) = k_{\text{B}} \ln\left(\frac{q_{CA}}{q_{AC}}\right), \quad (48)$$

which is a principle of constant entropy production. Equation (47) is called the principle of constant thermodynamic force in nonequilibrium thermodynamics. It is interesting to note that the same result has been found to characterize stationary-state operation of process units at minimum entropy production [71].

3.4. Non-isothermal enzyme kinetic cycle

Section 3.3 illustrated the thermomechanical energy transduction and obtained the Carnot efficiency. Nonequilibrium chemical or biochemical cycles can also be induced by temperature difference, and vice versa; thermochemical coupling can occur in an enzyme that operates under non-isothermal environment. Indeed, intracellular enzyme mediated biochemical reactions *in situ* are usually chemical-potential driven NESS cycles [72, 73]. Michaelis–Menten–Briggs–Haldane kinetics of an individual enzyme, with a single substrate and a single product, can be best understood as a steady state flux $J_C = J_C^+ - J_C^-$ [14, 74, 77] of the kinetic cycle in figure 1(B) without the Y, with a single temperature T. The one-way cycle fluxes $J_C^{\pm}$ are probability weighted inverse of the mean first-passage time ([72, 75, 77]). We will identify X and Z as the substrate S and the product P of the enzyme, with $q_{AB} = q_{AB}^o a_S$ and $q_{AC} = q_{AC}^o a_P$ where

$$\frac{q_{AB}^o}{q_{BA}} = \exp\left(\frac{\varphi_B - \varphi_A}{k_{\text{B}} T}\right), \ \mu_S \equiv \mu_S^o + k_{\text{B}} T \ln a_S, \quad (49)$$

$$\frac{q_{CA}}{q_{AC}^o} = \exp\left(\frac{\varphi_C - \varphi_A}{k_{\text{B}} T}\right), \ \mu_P \equiv \mu_P^o + k_{\text{B}} T \ln a_P, \quad (50)$$

where $\varphi_A, \varphi_B, \varphi_C$ are Landau potentials, given in equation (33), at temperature T, and a_S and a_P are the dimensionless chemical activities of the substrate and the product. For sufficiently dilute solution, they are the same as the molecular concentrations c_S and c_P, divided by the standard concentration, $c_0 = 1$ mole L^{-1}. To be consistent with the notions in the biochemical

literature, we will assume that the solution is always ideal. Then equation (37) becomes

$$J_C = \frac{\left(\frac{V_{\max}^f}{K_{\text{M}}^f}\right) c_S - \left(\frac{V_{\max}^b}{K_{\text{M}}^b}\right) c_P}{1 + \frac{c_S}{K_{\text{M}}^f} + \frac{c_P}{K_{\text{M}}^b}}, \quad (51)$$

in which Michaelis constants and maximal velocities of the forward and backward reactions, with corresponding J_C^+ and J_C^-, are equal to

$$K_{\text{M}}^f = \frac{q_{BC} q_{CA} + q_{CB} q_{BA} + q_{BA} q_{CA}}{q_{CA} q_{AB}^o + q_{CB} q_{AB}^o + q_{AB}^o q_{BC}}, \quad (52)$$

$$V_{\max}^f = \frac{q_{AB}^o q_{BC} q_{CA}}{q_{CA} q_{AB}^o + q_{CB} q_{AB}^o + q_{AB}^o q_{BC}}, \quad (53)$$

$$K_{\text{M}}^b = \frac{q_{BC} q_{CA} + q_{CB} q_{BA} + q_{BA} q_{CA}}{q_{AC}^o q_{CB} + q_{BA} q_{AC}^o + q_{AC}^o q_{BC}}, \quad (54)$$

$$V_{\max}^b = \frac{q_{AC}^o q_{CB} q_{BA}}{q_{AC}^o q_{CB} + q_{BA} q_{AC}^o + q_{AC}^o q_{BC}}. \quad (55)$$

One can find these complicated expressions in standard enzyme kinetics texts, e.g. [76]. When $B \to C$ is a rate-limiting step and q_{BC} and q_{CB} are much smaller than the others, one has $K_{\text{M}}^f = q_{BA}/q_{AB}^o$, which is the original Michaelis constant.

These equations can be viewed also a statement about the cycle affinity in equation (36) [75]

$$\frac{\left(\frac{V_{\max}^f}{K_{\text{M}}^f}\right)}{\left(\frac{V_{\max}^b}{K_{\text{M}}^b}\right)} = \exp\left(\frac{A_C}{k_{\text{B}}}\right) = e^{(\mu^{(S)} - \mu^{(P)})/k_{\text{B}} T}. \quad (56)$$

The NESS entropy production then is $J_C \times A_C$: the number of cycles completed per unit time $\times$ the entropy production per cycle.

We now consider a non-isothermal situation as in [74]: the enzyme is assumed to reside in a membrane with a temperature $T^{(1)}$. It separates two bulk solutions with a temperature $T^{(2)} \neq T^{(1)}$. We can then generalize the enzyme kinetics to non-isothermal condition with BC transitions under $T^{(1)}$ and the other two under $T^{(2)}$. Such an enzyme kinetic cycle is simply a thermochemical system, a special case of the mesoscopic thermochemomechanical machine. Then we have the cycle affinity given by

$$\begin{aligned} A_C &= \frac{U_A + \mu^{(S)} - U_B}{T^{(2)}} + \frac{U_B - U_C}{T^{(1)}} + \frac{U_C - U_A - \mu^{(P)}}{T^{(2)}} \\ &= (U_B - U_C)\left(\frac{1}{T^{(1)}} - \frac{1}{T^{(2)}}\right) + \frac{\mu^{(S)} - \mu^{(P)}}{T^{(2)}} \\ &= \mathcal{Q}^{(\text{measurable heat})}\left(\frac{1}{T^{(1)}} - \frac{1}{T^{(2)}}\right) + A_C^{(\text{substrate turnover})}. \end{aligned} \quad (57)$$

The function $\mathcal{Q}^{(\text{measurable heat})}$ is different from the total heat which should contain the part of energetic change in $\mu^{(S)} - \mu^{(P)}$ [11]. At the same time, since the transitions between B and C are under $T^{(1)}$ and the other transitions are under $T^{(2)}$, the NESS cycle flux J_C in equation (51) can be expressed as

$$J_C = \frac{q_{AB}q_{CA}\left(\frac{q_{BC}}{q_{CB}}\right) - q_{AC}q_{BA}}{(q_{CA} + q_{AB} + q_{AC})\frac{q_{BC}}{q_{CB}} + q_{BA} + q_{AC} + q_{AB} + \frac{q_{BA}q_{CA} + q_{CA}q_{AB} + q_{BA}q_{AC}}{q_{CB}}}$$

$$= \frac{\left[\left(\frac{V_{\max}^f}{K_M^f}\right)c_S - \left(\frac{V_{\max}^b}{K_M^b}\right)c_P\right]^{T=T^{(2)}}}{1 + \frac{c_S}{K_M^f} + \frac{c_P}{K_M^b}} \left\{1 + \frac{\exp\left[\frac{-U_B + U_C}{k_B}\left(\frac{1}{T^{(1)}} - \frac{1}{T^{(2)}}\right)\right] - 1}{1 - \exp\left(\frac{\mu^{(P)} - \mu^{(S)}}{k_B T^{(2)}}\right)}\right\}. \tag{58}$$

The last term in the curly brackets is a correction term for Michaelis–Menten kinetics due to non-isothermal condition. In the linear regime, the temperature difference-driven catalytic flux is equal to

$$\left[\frac{\left(\frac{V_{\max}^f}{K_M^f}\right)c_S}{1 + \frac{a_S}{K_M^f} + \frac{a_P}{K_M^b}}\right]^{eq} \left\{\frac{U_C - U_B}{k_B}\left(\frac{1}{T^{(1)}} - \frac{1}{T^{(2)}}\right)\right\}, \tag{59}$$

and the chemical potential difference-driven heat flux is

$$\left[\frac{\left(\frac{V_{\max}^f}{K_M^f}\right)c_S}{1 + \frac{c_S}{K_M^f} + \frac{c_P}{K_M^b}}\right]^{eq} \left\{\frac{\mu^{(S)} - \mu^{(P)}}{k_B T^{(2)}}\right\}. \tag{60}$$

They have the same coefficient $[\cdots]^{eq}$, the one-way flux in equilibrium, as expected from the Hill's theory.

3.5. Chemical-potential driven enzyme selectivity amplification

There is a very interesting example for the application of mesoscopic NET. It concerns with regulations of intracellular communication signals in terms of enzyme activities. Enzymes found in the living organisms has specific interaction with its cognate substrate molecules. The notion of biochemical specificity between an enzyme and its substrate has been quantified, traditionally, in terms of their equilibrium association constant. Therefore, an enzyme E interacting with two different substrates, one cognate X and another noncognate Y, via the following chemical reactions

$$E + X \rightleftharpoons EX, \quad E + Y \rightleftharpoons EY,$$
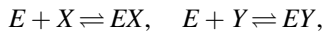
with respective equilibrium association constants K_X and K_Y, is expected to have the selectivity for X over Y given by the ratio K_X/K_Y. Recall that $K_X = [EX]^{eq}([E]^{eq}[X]^{eq})^{-1}$ and $K_Y = [EY]^{eq}([E]^{eq}[Y]^{eq})^{-1}$. The function K_X/K_Y, thus, is equal to the ratio between the equilibrium concentrations $[EX]$ and $[EY]$, when there is an equal amount of X and Y. However, it has been discovered that in living cells, the selectivity of an enzyme toward its cognate substrate can be much greater than the K_X/K_Y. This phenomenon has been termed *selectivity amplification*. These deviations in selectivity are clearly connected to the nonequilibrium nature of biological processes in living cells.

One can also recognize the ratio K_X/K_Y as the equilibrium constant for the *ligand exchange reaction* [78]

$$EY + X \rightleftharpoons EX + Y. \tag{61}$$
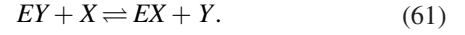
It is important to note that both K_X and K_Y are determined by the molecular structures and interactions between the enzyme and the ligands, which depend on the temperature, pH and solvents.

A fundamental role in biology is played by the concept of *kinetic proofreading*. It is a mechanism for altered selectivity, which uses driven biochemical reactions with fluxes to regulate enzymatic specificity, breaking the conventional wisdom that enzymatic specificity is defined solely by the equilibrium affinity. More specifically, it places the reaction in equation (61) inside a driven kinetic cycle such that the ratio of concentrations is given by

$$\theta \equiv \frac{[EX][Y]}{[EY][X]} = \frac{\left(\frac{[EX]}{[E][X]}\right)}{\left(\frac{[EY]}{[E][Y]}\right)}. \tag{62}$$

In a driven NESS θ can be significantly different from its equilibrium value K_X/K_Y.

To understand the kinetic proofreading let us consider figure 2 that shows a kinetic scheme in which the association-dissociation reaction is coupled to a reaction $T \rightleftharpoons D$. Then, when T and D are not in their chemical equilibrium, there will be two kinetic cycles: one couples the $E + X \rightleftharpoons EX$ with $T \rightleftharpoons D$, and the second one couples $E + Y \rightleftharpoons EY$ with $T \rightleftharpoons D$. The ratio of NESS concentrations can be computed, leading to

$$\theta = \left(\frac{[EX][Y]}{[EY][X]}\right)^{NESS} = \frac{\left(\frac{q_{13}^o q_{21} + q_{13}^o q_{23}^o[T] + q_{23}^o q_{12}^o[T]}{q_{23}^o[T]q_{31} + q_{31}q_{21} + q_{21}q_{32}^o[D]}\right)}{\left(\frac{q_{15}^o q_{41} + q_{15}^o q_{45}^o[T] + q_{45}^o q_{14}^o[T]}{q_{45}^o[T]q_{51} + q_{51}q_{41} + q_{41}q_{54}^o[D]}\right)}$$

$$= \frac{K_X}{K_Y}\left(\frac{q_{21} + q_{23}^o[T] + q_{23}^o q_{12}^o[T]/q_{13}^o}{q_{21} + q_{23}^o[T] + q_{23}^o q_{12}^o[T]/\gamma q_{13}^o}\right)$$

$$\times \left(\frac{q_{41} + q_{45}^o[T] + q_{45}^o q_{14}^o[T]/\gamma q_{15}^o}{q_{41} + q_{45}^o[T] + q_{45}^o q_{14}^o[T]/q_{15}^o}\right), \tag{63}$$

in which $k_B T \ln \gamma = \Delta\mu_{TD} = \frac{q_{12}^o q_{23}^o q_{31}[T]}{q_{21}q_{32}^o q_{13}^o[D]}$ is the nonequilibrium thermodynamic force. The superscript ^{o} denotes second-order rate constants as indicated in figure 2.

When T and D have their equilibrium value, the detailed balance is satisfied and we have

$$q_{12}^o q_{23}^o q_{31}/(q_{21}q_{32}^o q_{13}^o) = ([D]/[T])^{eq} = q_{14}^o q_{45}^o q_{51}/(q_{41}q_{54}^o q_{15}^o). \tag{64}$$
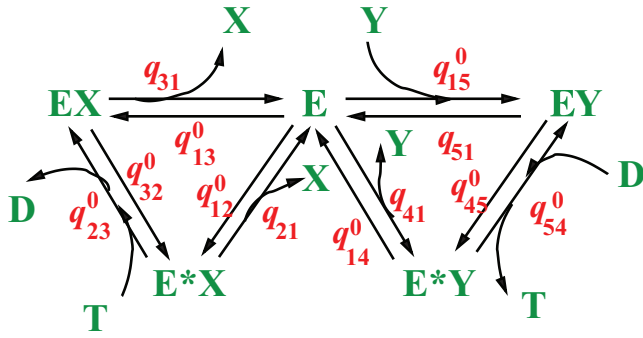
Figure 2. Cycle kinetics driven by the chemical potential difference between T and D, $\Delta\mu_{TD}$. There are two kinetic cycles going through states $E \to E^*X \to EX \to E$, on the left, and $E \to E^*Y \to EY \to E$, on the right.

Then

$$([EX][Y]/[EY][X])^{\mathrm{eq}} = ([EX]/[E][X])^{\mathrm{eq}}([E][Y]/[EY])^{\mathrm{eq}} = K_X/K_Y. \tag{65}$$

But for the deviations from equilibrium one obtains

$$\gamma \equiv q^o_{12}q^o_{23}q_{31}[T]/(q_{21}q^o_{32}q^o_{13}[D]) = q^o_{14}q^o_{45}q_{51}[T]/(q_{41}q^o_{54}q^o_{15}[D])$$
$$= \mathrm{e}^{\Delta\mu_{TD}/k_{\mathrm{B}}T} > 1. \tag{66}$$

In a well designed NESS biochemical network, $([EX][Y]/[EY][X])^{\mathrm{NESS}}$ can be as high as $\gamma(K_X/K_Y)$ and as low as $\gamma^{-1}(K_X/K_Y)$ [40].

Now if the enzyme has

$$\left(\frac{q^o_{12}}{\gamma q^o_{13}}\right) \ll \frac{q_{21}}{q^o_{23}[T]} \ll \left(\frac{q^o_{12}}{q^o_{13}}\right), \tag{67}$$

and furthermore one assumes that the corresponding rate constants in the two kinetic cycles for X and Y are essentially the same except $q_{41}/q_{21} = q_{51}/q_{31} = K_X/K_Y$, Hopfield and Ninio discovered the mechanism of the high-fidelity protein biosynthesis [79, 80]. In this case,

$$\theta = \frac{K_X}{K_Y}\left(\frac{q^o_{23}q^o_{12}[T]/q^o_{13}}{q_{21}}\right)\left(\frac{q_{41}}{q^o_{45}q^o_{14}[T]/q^o_{15}}\right) = \left(\frac{K_X}{K_Y}\right)^2. \tag{68}$$

Obviously, the enzyme selectivity can be very different from the equilibrium estimates, and this is the essence of the kinetic proofreading mechanism.

4. Coupling between nonequilibrium processes via kinetic cycles

One of the most important new features that arise in nonequilibrium thermodynamics is the coupling terms between two types of transport processes [2, 3, 8, 10]. Onsager's pioneering work elucidated a symmetry among the coupling coefficients in the force-flux relations when a system is near its equilibrium, which necessarily has a time-reversal symmetry [2, 3]. In the context of mesoscopic chemical kinetics it was shown by Hill [81, 82], that the Onsager coefficients can be expressed in terms of all equilibrium one-way cycle fluxes that couple any two processes. The beauty of stochastic thermodynamics is that the notion of 'coupling' can be formulated in phase space in terms of probabilistic fluxes irrespective of the microscopic details of underlying physical and chemical processes.

4.1. Cycles and the Onsager coefficients

Hill's theory of the Onsager's reciprocal relation is based on kinetic cycles in discrete-state space, and it employs a graph-theoretical treatment. Specifically, consider a irreducible Markov process with $q_{ij} = 0$ with all individual transition being reversible. Let the Markov network has N non-zero reversible transitions, $e_1, e_2, \cdots, e_N$, where e stands for 'edge', and κ reversible cycles $c_1, c_2, \cdots, c_\kappa$, where c stands for 'cycle'. We give every transition and cycle a defined direction, and denote a set $E = \{e_1, e_2, \cdots, e_N\}$ be the set of all transitions with nonzero net flux in NESS. Similarly, $C = \{c_1, c_2, \cdots, c_\kappa\}$ is the set of all the cycles with nonzero net cycle flux. Combinatorial calculations show that $N \leqslant \frac{m!}{2!\,(m-2)!}$ and $\kappa \leqslant \sum_{\ell=3}^{N} \frac{N!}{(N-\ell)!\,\ell}$.

Now we can introduce an $N \times \kappa$ edge-to-cycle incidence matrix:

$$\Theta_{ij} = \begin{cases} +1 & \text{if } e_i \in E \text{ is a step of } c_j \in C, e_i \text{ and } c_j \text{ in same direction;} \\ -1 & \text{if } e_i \in E \text{ is a step of } c_j \in C, e_i \text{ and } c_j \text{ in opposite direction;} \\ 0 & \text{if } e_i \in E \text{ is not any step of } c_j \in C. \end{cases} \tag{69}$$

For the same graph, there is also a $m \times N$ matrix Ξ, representing the signed incidence between node (state) to directed-edge (reversible transition). Then each column of Θ, a cycle, corresponds to a vector in the right null space of Ξ.

We can show that

$$J_{e_i} = \sum_{k,c_k \in C} \Theta_{ik}(J^+_{c_k} + J^-_{c_k}) \tanh\left(\frac{1}{2k_{\mathrm{B}}} \sum_{\ell,e_\ell \in E} \frac{\Theta_{\ell k}\Delta\mu^{(\nu)}_{e_\ell}}{T^{(\nu)}}\right), \tag{70}$$

where $\Delta\mu^{(\nu)}_{e_\ell}$ is the chemical potential difference of transition $e_\ell \in E$ with the temperature $T^{(\nu)}$, $J^+_{c_k}$ and $J^-_{c_k}$ are the two opposite one-way cycle fluxes of the cycle $c_j \in C$ [14, 32, 50].

When $|\Delta\mu^{(\nu)}_{e_\ell}| \ll k_{\mathrm{B}}T^{(\nu)}$ is sufficiently small, $(J^+_{c_k} + J^-_{c_k}) \simeq 2J^{+,\mathrm{eq}}_{c_k}$, and equation (70) becomes

$$J_{e_i} \simeq \sum_{\ell,e_\ell \in E}\left[\sum_{k,c_k \in C} \Theta_{ik} J^{+,\mathrm{eq}}_{c_k} \Theta_{\ell k}\right]\left(\frac{\Delta\mu^{(\nu)}_{e_\ell}}{k_{\mathrm{B}}T^{(\nu)}}\right). \tag{71}$$

The term inside the square bracket is a symmetric matrix $M_{i\ell} = M_{\ell i}$. Onsager's reciprocal relation is immediately observed. Hill called equation (71) *the statistical mechanics of Onsager's principle* [81]. Every kinetic cycle that links transitions e_i and e_ℓ contributes to their coupling [47]. One can in fact introduce a *coupling efficiency* as $M_{i\ell}/\sqrt{M_{ii}M_{\ell\ell}}$.

For a single cycle with N transitions, Θ is $N \times 1$ with all elements 1,

$$J_{e_i} = (J_c^+ + J_c^-) \tanh\left(\frac{1}{2k_\mathrm{B}} \sum_{\ell=1}^{N} \frac{\Delta\mu_{e_\ell}^{(\nu)}}{T^{(\nu)}}\right). \qquad (72)$$

4.2. Kinematics and NET of Markov processes

In nonequilibrium thermodynamics, a passive transport typically involves a constituent following its chemical potential difference. Active transport, on the other hand, typically involves the motion of a constituent *against* its chemical potential. This cannot occur by itself. It needs the help of another process [11]. This is known as 'pumping' in classical mechanics and in biophysics. One of the most famous such examples is Mitchell's chemiosmotic mechanism of ATP synthesis in mitochondria of living cells [83].

In stochastic thermodynamics, in the passive process a system will move from a state of low probability to a state of higher probability. Being able to include the temperature differences as driving forces for transport is a particular challenge for stochastic thermodynamics, which is based on the description of Markov dynamics. The result in section 3.3 suggests that Hill's cycle kinetic approach is not merely a kinetic theory, but also a thermodynamic one [14]. In classical chemical thermodynamics, $\ln(q_{ij}/q_{ji})$ is an equilibrium thermodynamic quantity. It is now quite clear from the cycle representation of the steady-state entropy production, given in equation (31), that the term $(J_\Gamma^+ - J_\Gamma^-)$ is the kinematics of a Markov process, while the term $\ln(J_\Gamma^+/J_\Gamma^-)$ contains the essential information of nonequilibrium thermodynamics of an individual cycle.

5. Discussion and future directions

The entropy balance equation (1) is valid for a large number of nonequilibrium systems with *phenomenological laws* describing irreversible, transport processes in the form of proportionalities, e.g. Fourier's law between heat flow and temperature gradient, Fick's law between flow of a component in a mixture and its concentration gradient, Ohm's law between electrical current and potential gradient, Newton's law between shearing force and velocity gradient, the law of mass action between reaction rate and chemical potentials [8]. Each of these phenomena involves a 'flux' that characterizes transport of certain entities, like mass, charge or energy, in response to a thermodynamic force [2, 3].

Starting with Boltzmann's notion of entropy of a classical mechanical system with conserved mechanical energy U, fixed volume V, and number of particles $\{N_k\}$, the entropy $S(U, V, \{N_k\})$ can be calculated using the microcanonical

ensemble given the Hamiltonian. The Gibbs equation can be written in the form

$$dS = \frac{1}{T(U, V, \{N_k\})}dU + \frac{p(U, V, \{N_k\})}{T(U, V, \{N_k\})}dV \\ - \sum_k \frac{\mu_k(U, V, \{N_k\})}{T(U, V, \{N_k\})}dN_k. \qquad (73)$$

It is clear from the work of Boltzmann and Gibbs that a probability measure is needed to define the entropy. As was also clearly known to Boltzmann, there is simply no entropy production in a purely deterministic treatment of classical, smooth motions [84]. The Gibbs equation can be used to find both the flux and the production of entropy in a transport phenomenon [8].

5.1. The nature of stochastic dynamics

The notion of entropic force is sometimes considered to be difficult. As observed by de Groot and Mazur: '[E]ntropic forces have nothing to do with forces in the Newtonian sense', and '[P]erhaps the name *affinity* would have been preferable' [8].

In the theory of stochastic processes there is a universal equation of motion with probability fluxes in phase space. The present paper shows that starting from such a mesoscopic description, a complete NET, with fluctuations, can be developed.

There is a need for a conceptual clarification on the mathematical method of stochastic processes in the theory of mesoscopic NET. Kolmogorov's mathematical theory of stochastic processes [25] articulates a logic separation between the abstract probability of 'random events' in a probability space, and random variables defined on the space[9] as physical observables. Markov dynamics described by a probability function $f(x, t)$ follows a linear master equation. A theory of entropy and entropy production, according to current stochastic thermodynamics, can be formulated at this abstract level in terms of probabilistic flux that devoids the specific nature of the underlying dynamic phenomena.

With this new found perspective, it becomes clear that the local equilibrium assumption has to be made only when applying stochastic thermodynamics to a system with observables, as was illustrated in section 3.

5.2. The nature of nonequilibrium processes

Classical thermodynamics is a theory about the emergent behavior of a macroscopic system. It is insensitive to the details of the equations of motions of individual particles within the system. In terms of the mesoscopic description of a system, nonequilibrium thermodynamics is a theory about emergent probabilistic behavior, and it is expected to be insensitive to the details of stochastic Markov dynamics.

The term 'nonequilibrium' deserves a clarification. To some authors, the notion of 'equilibrium' is a mechanical concept. Thus, according to this usage, an oscillatory Hamiltonian

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[9] According to Kolmogorov, a probability space is a measure space, and random variables are measurable functions defined on the measure space.

dynamics is non-equilibrium. To others, however, equilibrium is a statistical thermodynamic concept. There are fluctuations in an equilibrium system. In the present work, we have used the term nonequilibrium in the statistical thermodynamic sense, as it most frequently utilized in chemistry. Nonequilibrium processes lead to 'irreversible' and 'dissipative' behavior. It can be quantified by a positive definite entropy production.

Nonequilibrium thermodynamics (NET), therefore, describes dynamic processes with dissipation. In a mesoscopic perspective in probabilistic terms, stationary transport phenomena concern with the cycle kinetics, cycle affinities, and cycle fluxes. The cycle affinity as a physical quantity is actually easy to compute. The complexities of NET are in the decomposition of a system into cycles and the computation of the cycle fluxes. A cycle flux, however, is 'driven' by thermodynamic forces. The detailed mesoscopic cycles, each with its own probability, and their coupling to outside sources, yield the reciprocal relation first formulated by Onsager [2, 3].

A mesoscopic description, consistent with experimental observations, can also be obtained by expanding the variable space by so-called internal variables [85]. One then assumes local equilibrium for any mesoscopic state, and writes linear flux-force relations following standard procedure [32]. The approach is similar to the stochastic approach given here, but note that in our master equation formalism the flux-force relation is generally not linear. The law-of-mass action [47] or the Butler–Volmer equation can easily be obtained in this manner [86]. Another general nonequilibrium dynamic approach has been proposed by Zhu and coworkers [87], but this theory is a macroscopic one, while our method is mesoscopic.

It will be important to apply and to extend the presented here stochastic mesoscopic framework of NET for different chemical, physical and biological processes. This will help to clarify mechanisms of various complex phenomena from fundamental point of views.

Acknowledgments

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