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Entropy production and excess entropy in a nonequilibrium steady-state of single macromolecules

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Based on a recently developed formalism for mesoscopic stochastic dynamics of single macromolecules, such as motor proteins, in aqueous solution, we demonstrate mathematically the principle of the nonequilibrium thermodynamics originated by the Brussels group. The key concepts of excess entropy and excess entropy production, and their mathematical properties as well as physical interpretations, are discussed. The newly developed stochastic macromolecular mechanics is consistent with the general theory of nonequilibrium thermodynamics far from equilibrium, and more importantly, it bridges the abstract theory with the current experimental and modeling work on molecular motors and other biological systems in nonequilibrium steady state.

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I. INTRODUCTION

In a previous paper [1], we have proposed an axiomatic mesoscopic statistical thermodynamic formalism for single macromolecules in ambient fluid at constant temperature. Following the standard polymer theory [2], a single macromolecule is represented by a set of N "atoms" whose configuration, $\mathbf{X}$ is described by a point in a $3N$-dimensional space. The dynamics of the atoms in the molecule is assumed to be overdamped in the fluid with hydrodynamic interactions represented by a positive matrix Ξ, the Oseen tensor. The force, both internal and external, is assumed to be $\mathbf{F}(\mathbf{X})$. With this setting, a complete thermodynamics is developed based on the stochastic dynamics of the macromolecule $\mathbf{X}_t$, in terms of its Smoluchowski equation. The theory makes connections with the classic work of Clausius, Gibbs, and Onsager, and is applicable to both systems with and without detailed balance. Hence a thermodynamics for a macromolecule such as motor proteins [3] in nonequilibrium steady-state (NESS) emerges. We suggested that the mathematical formalism provides a theoretical foundation for the future nanotechnology in which energy transduction and heat dissipation will be the essential problems, analogous to the classic thermodynamics for macroscopic engines and machines.

In this paper, we use this explicit formalism we call *stochastic macromolecular mechanics* [4] to explore the thorny issues around the entropy (heat) production rate in systems without detailed balance, particularly near a NESS, revisit the principle of minimal entropy (heat) production [5] as well as the concept of excess entropy and thermodynamic stability introduced by the Brussels school [6]. The goal is to show the consistency between the two theories. The present paper provides the macroscopic thermodynamic theory with a sound molecular basis. It shows the formalism to be sufficiently comprehensive and can be used in analyzing many current, sometime abstract, issues in nonequilibrium thermodynamics far from equilibrium with rigorous mathematics and clear physical pictures. Furthermore, our analysis clearly distinguishes two different types of stabilities in a NESS, and suggests an alternative perspective for transient kinetics approaching to NESS. In combination with the experimental development in molecular motors and nanofabrication, we believe the present theory will further deepen our understanding of nonequilibrium statistical mechanics and thermodynamics.

Stochastic macromolecular mechanics is based on the overdamped Brownian dynamics of macromolecules in aqueous solution, and defines work, entropy, and thermodynamic force

$$\Xi dX_t=\mathbf{F}(\mathbf{X}_t)dt+\Gamma d\mathbf{B}_t. \quad \text{(conformational dynamics)}, \tag{1}$$

$$dW_t=\mathbf{F}(\mathbf{X}_t)\circ d\mathbf{X}_t, \quad \text{(work)}, \tag{2}$$

$$S=-k_B\int P(x,t)\ln P(x,t)dx \quad \text{(entropy)}, \tag{3}$$

$$\mathbf{\Pi}=\mathbf{F}(x)-k_BT\boldsymbol{\nabla}P(x,t) \quad \text{(thermodynamic force)}, \tag{4}$$

in which $\Gamma d\mathbf{B}_t$ characterizes the random collision between the atoms and the fluid particles. $P(x,t)$, the probability density for $\mathbf{X}_t=x$ at time t, is the solution to the Smoluchowski equation

$$\frac{\partial P}{\partial t}=\boldsymbol{\nabla}\cdot\left(\tfrac{1}{2}A\boldsymbol{\nabla}P-\Xi^{-1}\mathbf{F}(x)P\right),$$

$$(A=\Xi^{-1}\Gamma\Gamma^T\Xi^{-T}=2k_BT\Xi^{-1}). \tag{5}$$

See [1] for more details. While the first law of thermodynamics is built into the theory (Eq. 2) as the definition for heat energy in NESS (similar to Carathéodory [7]), the important results in [1] are (i) the introduction of *local equilibrium*; (ii) a proof of equilibrium among local free energy, (i.e., entropy-energy compensation); and (iii) a derivation of *the equation for entropy balance* [8,6,9]

$$T\frac{dS}{dt}=Te_p-h_d, \tag{6}$$

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*Email address: qian@amath.washington.edu where e_p and h_d are entropy production and heat dissipation rates, respectively, with explicit formulas

$$e_p = \frac{1}{T}\int \left(\tfrac{1}{2}A\boldsymbol{\nabla}\ln P(x,t) - \Xi^{-1}\mathbf{F}(x)\right)^T \Xi \left(\tfrac{1}{2}A\boldsymbol{\nabla}\ln P(x,t) - \Xi^{-1}\mathbf{F}(x)\right)P(x,t)\mathrm{dx}, \tag{7}$$

and

$$h_d = \int \mathbf{F}(P(x,t)\Xi^{-1}\mathbf{F}(x) - \tfrac{1}{2}A\boldsymbol{\nabla}P(x,t))dx. \tag{8}$$

It is clear that e_p in Eq. (7) is always positive, and it equals to zero if and only if $\mathbf{F},=-\boldsymbol{\nabla}U(x)$, has a potential and the probability distribution then is Boltzmannian $P(x) = Z^{-1}e^{-U(x)/k_BT}$ (Z being the partition function). This is the second law of thermodynamics. In this paper, we are interested in **F** without potential. It then can be mathematically shown that the stationary solution to Eqs. (1) and (5) is necessarily a NESS with time irreversibility, and $e_p>0$ [10,11].

II. RELATIVE ENTROPY AND SECOND DIFFERENTIAL OF ENTROPY

Equation (6) is the starting point of all phenomenological treatment on nonequilibrium thermodynamics [12,8,6,13,14]. Equations (1)–(4) augment this equation with a mesoscopic picture of macromolecular Brownian motion. They also provide Eq. (6) with a mathematical foundation in terms of the stochastic dynamics. Note that e_p and h_d are d_iS/dt and d_eS/dt in [8,6]. We use e_p (h_d) instead of the traditional notation $\dot{S}_i$ ($\dot{S}_e$) for the entropy production (heat dissipation) rate to emphasize that it is a source (sink) term, not a time derivative.

The uniqueness of the NESS solution, $P^*(x)$, to the Fokker-Planck equation (5) without detailed balance can be demonstrated by introducing a well-known global Lyapunov function discovered by Schlögl [15]

$$\Psi[P(x,t)] = k_B\int P(x,t)\ln\left(\frac{P(x,t)}{P^*(x)}\right)dx \geqslant 0. \tag{9}$$

As the Lyapunov function, its time derivative [16]

$$\begin{aligned}\frac{d\Psi}{dt} &= k_B\int \frac{\partial P}{\partial t}\ln\left(\frac{P}{P^*}\right)dx\\ &= -k_B^2T\int P\left[\boldsymbol{\nabla}\ln\left(\frac{P}{P^*}\right)\Xi^{-1}\boldsymbol{\nabla}\ln\left(\frac{P}{P^*}\right)\right]dx \leqslant 0.\end{aligned} \tag{10}$$

It is an agonizing fact that Ψ, being such an important mathematical function, has not found a natural physical meaning. Recently [17,18], it has been established that for Eq. (5) with detailed balance, Ψ is in fact the Helmholtz free energy, also known as exergy [17].

Near a NESS, it is known that Ψ is equivalent to the second differential of entropy S with respect to P [6,9]

$$\delta^2 S = -k_B\left[\delta^2\int P(x)\ln P(x)dx\right]_{P=P^*} = -k_B\int \frac{(\delta P)^2}{P^*}dx, \tag{11}$$

and $-2\Psi =$

$$-2k_B\int P\ln\left(\frac{P}{P^*}\right)dx = -k_B\int\frac{(\delta P)^2}{P^*}dx + o\left[\left(\frac{\delta P}{P^*}\right)^2\right], \tag{12}$$

where $\delta P = P - P^*$. Hence, one can show that $\delta^2 S$ ($\leqslant 0$) is a *local* Lyapunov function *near* a NESS

$$\begin{aligned}\frac{d}{dt}\delta^2 S &= -k_B\frac{d}{dt}\int\frac{(P-P^*)^2}{P^*}dx\\ &= -2k_B\left\{\int\left(\frac{P}{P^*}\right)\mathbf{J}^*\cdot\boldsymbol{\nabla}\left(\frac{P}{P^*}\right)dx\right.\\ &\quad\left. - k_BT\int P^*\left[\boldsymbol{\nabla}\left(\frac{P}{P^*}\right)\Xi^{-1}\boldsymbol{\nabla}\left(\frac{P}{P^*}\right)\right]dx\right\}\\ &= 2k_B^2T\int P^*\left[\boldsymbol{\nabla}\left(\frac{P}{P^*}\right)\Xi^{-1}\boldsymbol{\nabla}\left(\frac{P}{P^*}\right)\right]dx \geqslant 0,\end{aligned}$$

where $-\boldsymbol{\nabla}\cdot\mathbf{J}(x,t) = \partial P(x,x)/\partial t$ and $\mathbf{J} = P(x,t)\Xi^{-1}\boldsymbol{\Pi}(x,t)$. In terms of $\mathbf{J}$ and $\boldsymbol{\Pi}$, Eq. (7) can be rewritten as $e_p = (1/T)\int\boldsymbol{\Pi}\cdot\mathbf{J}\,dx$.

III. EXCESS ENTROPY PRODUCTION RATE

By "excess entropy," we simply mean the functional given in Eq. (11) [6]

$$\delta^2 S[P] = -k_B\int\frac{[P(x,t)-P^*(x)]^2}{P^*(x)}dx.$$

In parallel to the equation for entropy balance, one has an equation for excess entropy balance

$$T\frac{d}{dt}\delta^2 S = T\delta^2 e_p - \delta^2 h_d \tag{13}$$

in which the excess entropy production rate

$$T\delta^2 e_p = \int \delta^2\boldsymbol{\Pi}\cdot\mathbf{J}\,dx + 2\int\delta\boldsymbol{\Pi}\cdot\delta\mathbf{J}\,dx + \int\boldsymbol{\Pi}\cdot\delta^2\mathbf{J}\,dx. \tag{14}$$

The last term in Eq. (14) equals zero since $\mathbf{J}$ is a linear function of P. The first term, however, is not zero but is on the order of $o[\delta P)^2]$:

$$\begin{aligned}
\int \delta^2\mathbf{\Pi}\cdot\mathbf{J}\,dx
&=\int[\mathbf{\Pi}(P)-2\mathbf{\Pi}(P^*)+\mathbf{\Pi}(2P^*-P)]\mathbf{J}\,dx\\
&=\int 2(\mathbf{\Pi}-\mathbf{\Pi}^*)\cdot\mathbf{J}\,dx-\int[\mathbf{\Pi}(P)-\mathbf{\Pi}(2P^*-P)]\mathbf{J}\,dx\\
&=\int 2(\mathbf{\Pi}-\mathbf{\Pi}^*)(\mathbf{J}-\mathbf{J}^*)dx+k_BT\\
&\quad\times\int[\boldsymbol{\nabla}\ln P-\boldsymbol{\nabla}\ln(2P^*-P)]\mathbf{J}\,dx\\
&=-2T\frac{d\Psi}{dt}+k_BT\frac{d}{dt}\\
&\quad\times\int[P\ln P+(2P^*-P)\ln(2P^*-P)]dx,
\end{aligned}$$

in which

$$\begin{aligned}
T\frac{d\Psi}{dt}&=-\int P(\mathbf{\Pi}-\mathbf{\Pi}^*)\Xi^{-1}(\mathbf{\Pi}-\mathbf{\Pi}^*)dx\\
&=-\int(\mathbf{\Pi}-\mathbf{\Pi}^*)\cdot\mathbf{J}\,dx+\int P(\mathbf{\Pi}-\mathbf{\Pi}^*)\Xi^{-1}\mathbf{\Pi}^*dx\\
&=-\int(\mathbf{\Pi}-\mathbf{\Pi}^*)\cdot(\mathbf{J}-\mathbf{J}^*)dx-k_BT\\
&\quad\times\int\left(\frac{P}{P^*}\right)\boldsymbol{\nabla}\ln\left(\frac{P}{P^*}\right)\cdot\mathbf{J}^*dx\\
&=-\int(\mathbf{\Pi}-\mathbf{\Pi}^*)\cdot(\mathbf{J}-\mathbf{J}^*)dx.
\end{aligned}$$

Therefore,

$$\begin{aligned}
\delta^2e_p&=-k_B\frac{d}{dt}\left[4\int P\ln\left(\frac{P}{P^*}\right)dx-\int P\ln P\,dx\right.\\
&\qquad\left.-\int(2P^*-P)\ln(2P^*-P)dx\right]\\
&=-k_B\frac{d}{dt}\left\{\int\frac{(\delta P)^2}{P^*}dx+o\left(\left(\frac{\delta P}{P^*}\right)^2\right)\right\}.
\end{aligned}$$

Neglecting higher-order terms, the δ^2S and δ^2e_p are simply related near a NESS

$$\delta^2e_p=\frac{d}{dt}\,\delta^2S, \tag{15}$$

the excess entropy production rate is the time derivative of the excess entropy, which in turn is a local Lyapunov function. Near a NESS, $\delta^2S\leqslant 0$, and $\delta^2e_p\geqslant 0$. This is an explicit demonstration of the theory on thermodynamic stability, introduced by the Brussels group [6], of a single NESS macromolecule in aqueous solution.

IV. THE MEANING OF STABILITY

Some remarks on the meaning of stability of a NESS is in order. Within the framework of Brownian dynamics at constant temperature in aqueous solution, the stability guaranteed by Eqs. (9) and (10) is the stochastic probability distribution in NESS. When applying the same mathematical theory for single macromolecules in aqueous solution to a chemical reaction, say $X+Y\rightleftharpoons 2X$, one considers the stochastic chemical reaction in terms of a birth-and-death process [14]. The birth-and-death process is a random walk in the two-dimensional *XY* plan with probability distribution $P(n_X,n_Y,t)$, and its dynamics is mathematically equivalent to a Brownian motion with nonconstant Ξ in Eq. (5) [19]. We shall call this mesoscopic stability.

There is another type of stability, which is associated with the macroscopic behavior of the same chemical reaction. It can be shown that for a system with large number of molecules *X* and *Y*, the law of mass-action emerges and a macroscopic chemical kinetics arise [19]. According to this picture, a unimodal stationary distribution $P^*(n_X,n_Y)$ corresponds to a *fixed point* in the deterministic, macroscopic chemical kinetics. However, the distribution can bifurcate: the peak of $P^*(n_X,n_Y)$ becomes a minimum, and the high probability is associated with a ring around the minimum [19]. This stochastic picture corresponds to a macroscopic limit cycle. In the macroscopic kinetics, the fixed point is now unstable, and the chemical kinetics is oscillatory. However, the stochastic distribution $P^*(n_X,n_Y)$ still enjoys its asymptotic stability, as guaranteed by the Lyapunov functions Ψ and δ^2S [15]. This discussion on the meaning of stability sheds some light on the qualm regarding the Lyapunov function δ^2S [20–24]. It is clear that the central issue concerned by the pioneers is whether the δ^2S can also be used as a Lyapunov function for the macroscopic, deterministic kinetics. As pointed out in [25], the mathematical problem here is quite delicate. It involves the order in taking infinite-time limit (stationarity) and infinite-size (thermodynamic) limit. In the context of single macromolecules in aqueous solution, the size of the molecular system is mesoscopic; hence, the present theory does not involve the thermodynamic limit. Finally, it is interesting to point out that while the stochastic system enjoys mesoscopic stability, the underlying chemical reaction can be itself unstable. Such a generic behavior of a nonequilibrium steady state is also known as self-organized (asymptotically stable) criticality [26]. In a nonequilibrium steady state, the stationary is sustained by circular balance rather than detailed balance, and the size of the kinetic cycles ranges from small to as large as the entire system [27,10].

V. ENTROPY PRODUCTION RATE AS A LYAPUNOV FUNCTION

It is tempting to draw further physical insights from Eq. (15). We note

$$e_p[P]=e_p[P^*]+\int\left(\frac{\delta e_p}{\delta P}\right)^*\delta P\,dx+\frac{1}{2}\,\delta^2e_p+\cdots \tag{16}$$

in which

$$\left(\frac{\delta e_p}{\delta P}\right)^* = \frac{1}{T}\{-\mathbf{\Pi}^*\Xi^{-1}\mathbf{\Pi}^* + 2F\Xi^{-1}\mathbf{\Pi}^* + 2k_BT\nabla\cdot(\Xi^{-1}\mathbf{\Pi}^*)\}.$$

For a system with detailed balance, a stochastic dynamics approaching to its equilibrium has the following properties: the e_p is always positive, and it equals zero when the system reaches the equilibrium. In Eq. (16), the $e_p=0$ and $\delta e_p/\delta P^*=0$ at an equilibrium. Therefore, near the equilibrium the $e_p[P]$ is a convex function, and e_p approaches to zero monotonically without oscillation, an essential feature of any relaxation to an equilibrium. This is related to Onsager's reciprocal relation and the fact that the eigenvalue problem near an equilibrium is necessarily symmetric [11]. In mathematical term, $e_p \geqslant 0$ and in the linear neighborhood of the equilibrium

$$\begin{aligned}\frac{d}{dt}e_p &= -2k_B\int(\nabla\cdot\mathbf{J})^2P^{-1}dx - (1/T)\\ &\quad\times\int(\mathbf{J}^T\Xi\mathbf{J})(\nabla\cdot\mathbf{J})P^{-2}dx \qquad (17)\\ &\approx -2k_B\int(\nabla\cdot\mathbf{J})^2P^{-1}dx \leqslant 0.\end{aligned}$$

The second term on the right-hand side of Eq. (17) is third order in $|\mathbf{J}|$ which equals zero in an equilibrium. Therefore, combining Eqs. (16) and (17), *entropy production rate is also a local Lyapunov function for systems with detailed balance*.

How does e_p change with time in a stochastic dynamics approaching to a NESS for systems without detailed balance? This has been a nagging question in the history of nonequilibrium thermodynamics [5]. In a NESS away from an equilibrium, the stationary flux $\nabla\cdot\mathbf{J}=0$ but $\mathbf{J}\neq\mathbf{0}$ and $\mathbf{\Pi}\neq\mathbf{0}$. Hence, the second term on the right-hand side of Eq. (17), $\sim O(\nabla\cdot\mathbf{J})$, is not smaller than the first terms, $\sim O[(\nabla\cdot\mathbf{J})^2]$ near the NESS. Since there is no definiteness in the sign of $\nabla\cdot\mathbf{J}$ near NESS, $(d/dt)e_p$ can either be positive or negative. Further more, $(\delta e_p/\delta P)^*\neq 0$ in a NESS. There is no guaranteed convexity for the e_p near a NESS, and there is no principle for minimal entropy production [28,29]. Luo, van den Broeck, and Nicolis [25] have attempted to provide the two terms in Eq. (17) with further physical interpretation: they seem to be associated with the macroscopic kinetics, which can be oscillatory or even chaotic [19], and stochastic fluctuations around the macroscopic kinetics, respectively. This is an interesting idea remaining to be further investigated.

VI. RELATIVE THERMODYNAMICS FOR SYSTEMS WITHOUT DETAILED BALANCE

The mathematical theory for NESS we have adopted seems to suggest a mathematically attractive way to characterize systems approaching to NESS. In this section, we attempt to provide a basic idea of this approach. Whether such a perspective is beneficial, either experimentally or theoretically, remains to be seen.

We argue that a system, without detailed balance and in its transient process approaching to its unique NESS, should always be viewed in relative with respect to the NESS. More specifically, all the physical quantities expressed in *difference* with respect to the NESS counterparts enjoy a greater mathematical simplicity. We will use $\Delta\mathbf{\Pi}=\mathbf{\Pi}(x,t)-\mathbf{\Pi}^*(x)$ to denote the *relative thermodynamic force*, and $\Delta\mathbf{J}=\mathbf{J}(x,t)-\mathbf{J}^*(x)$ to denote the *relative flux*. Then,

$$\int \Delta\mathbf{\Pi}\cdot\Delta\mathbf{J}\,dx = -T\frac{d\Psi}{dt} \geqslant 0. \qquad (18)$$

The relative thermodynamic force $\Delta\mathbf{\Pi}=-k_BT\times\nabla\ln[P(x,t)/P^*(x)]$ has a potential $k_BT\ln[P(x,t)/P^*(x)]$ which is the mesoscopic (fluctuating) local entropy [1] in its relative form: $\Delta\Upsilon=-k_B\ln[P(x,t)/P^*(x)]$. The relative entropy then is the expectation of $\Delta\Upsilon:\Psi=-\int P(x,t)\Delta\Upsilon(x,t)dx$.

We shall denote the quantity in Eq. (18), which equals to $(T/2)\delta^2 e_p$ up to the second order, by $\delta^{\mathrm{II}}e_p$. This functional is locally convex near a NESS

$$\frac{\delta}{\delta P}\delta^{\mathrm{II}}e_p=0, \quad \delta^2(\delta^{\mathrm{II}}e_p)\geqslant 0.$$

VII. FROM MINIMAL HEAT DISSIPATION TO MINIMAL ENTROPY PRODUCTION

So far, we have only considered macromolecules in aqueous solution at constant temperature. Under such conditions, the heat dissipation and entropy production differ trivially by a constant temperature T in NESS [Eq. (7)]. We now generalize our formalism to some problems which involves two different temperatures. Under this condition, the entropy production and heat dissipation rates are no longer simply related. In a review article on minimal principle in NESS [5], minimal heat production (Kirchhoff's law) and minimal entropy production in NESS are extensively discussed. It states two competing minimal principles for NESS: "Two resistors R_1 and R_2 are in thermal contact with two heat reservoirs at temperature T_1 and T_2. Connecting the resistors in parallel, we send a total current $I=I_1+I_2$ through them. How does it divide? When a steady state is reached, the rates of production of heat and entropy are $h_d=R_1I_1^2+R_2I_2^2$, $e_p=R_1I_1^2/T_1+R_2I_2^2/T_2$. The entropy production is a minimum when the current distribution $R_1I_1/T_1=R_2I_2/T_2$, and the heat dissipation is a minimum when $R_1I_1=R_2I_2$." We now show that the issue here is subtle and more interesting than what is discussed in [5].

Since there is nothing special about electric current, let us consider an overdamped particle in a force field with two possible channels in contact with different temperatures T_1 and T_2. We have a mathematical model according to stochastic macromolecular mechanics

$$\frac{\partial P_1(x,t)}{\partial t}=\frac{k_BT_1}{\eta_1}\frac{\partial^2 P_1(x,t)}{\partial x^2}-\frac{F}{\eta_1}\frac{\partial P_1(x,t)}{\partial x},$$

$$\frac{\partial P_2(x,t)}{\partial t}=\frac{k_BT_2}{\eta_2}\frac{\partial^2 P_2(x,t)}{\partial x^2}-\frac{F}{\eta_2}\frac{\partial P_2(x,t)}{\partial x},$$

where $P_k(x,t)$ is the probability for the particle in kth channel at position x at time t. In steady state, we have

$$\frac{k_BT_1}{\eta_1}\frac{\partial P_1(x,t)}{\partial x}-\frac{F}{\eta_1}P_1(x,t)=-J_1, \tag{19}$$

$$\frac{k_BT_2}{\eta_2}\frac{\partial P_2(x,t)}{\partial x}-\frac{F}{\eta_2}P_2(x,t)=-J_2, \tag{20}$$

with boundary conditions

$$J_1+J_2=J;\;\; P_1(0)=P_2(0);\;\; P_1(L)=P_2(L);$$

$$\int_0^L[P_1(x)+P_2(x)]dx=1.$$

This mathematical problem can be completely solved. The solution is

$$\frac{J_2}{J_1}=\frac{\gamma\frac{\eta_1LJ}{F}+\left(\frac{\eta_1LJ}{F}-1\right)}{\gamma\frac{\eta_2LJ}{F}-\left(\frac{\eta_2LJ}{F}-1\right)}, \tag{21}$$

in which

$$\gamma=\frac{(1-e^{-\sigma_1})(1-e^{-\sigma_2})}{e^{-\sigma_2}-e^{-\sigma_1}}\left(\frac{1}{\sigma_1}+\frac{1}{\sigma_2}\right),\;\; \sigma_1=\frac{FL}{k_BT_1};$$

$$\sigma_2=\frac{FL}{k_BT_2}. \tag{22}$$

Two limiting cases are particularly interesting. If σ_1 and $\sigma_2\rightarrow\infty$, then we have $\gamma\rightarrow\infty$, and

$$\frac{J_2}{J_1}=\frac{\eta_1}{\eta_2}. \tag{23}$$

If, however, σ_1 and $\sigma_2\rightarrow 0$, then we have $\gamma\approx(\sigma_1+\sigma_2)/(\sigma_1-\sigma_2)(1+\sigma_1\sigma_2/12)$, and

$$\frac{J_2}{J_1}=\frac{\eta_1T_2}{\eta_2T_1}=\frac{D_2}{D_1}, \tag{24}$$

where $\eta D=k_BT$ according to Einstein's relation. We note that Eqs. (23) and (24) are expected from minimal heat dissipation rate and entropy production rate, respectively. For large σ, the convection dominates the diffusion, and hence, it approaches to Kirchhoff's macroscopic law. For small σ, on the other hand, the process is diffusion dominant and close to thermal equilibrium. Hence, it approaches to the Onsager's linear regime in which the principle of minimal entropy production rate hold (Glansdorff-Prigogine excess entropy criterion). In general, however, neither of these are strictly valid, as we have already shown in the previous sections. Therefore, the minimal entropy production of Onsager and minimal heat production of Helmholtz are limiting behaviors for near reversible systems and highly irreversible systems, respectively.

In summary, we have shown the consistency between the mesoscopic theory of stochastic macromolecular mechanics [1–4] and the macroscopic nonequilibrium thermodynamics [6,8,12,13]. Our results indicate that the nonequilibrium thermodynamics is applicable to molecular systems as small as a single macromolecule in aqueous solution. In return, our theory also provides the nonequilibrium thermodynamics a sound molecular basis. We expect this physical theory to have a wide range of applications to cellular and molecular biology and nanotechnology.

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