

# Mesoscopic nonequilibrium thermodynamics of single macromolecules and dynamic entropy-energy compensation

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We introduce axiomatically a complete thermodynamic formalism for a single macromolecule, either with or without detailed balance, in an isothermal ambient fluid based on its stochastic dynamics. With detailed balance, the theory yields mesoscopic, nonequilibrium for entropy ( $Y_t$ ) and free energy ( $\Psi_t$ ) of the macromolecule.  $Y_t$  and  $\Psi_t$  fluctuate. Expectation  $(d/dt)E[\Psi_t] \leq 0$ , “=” holds if and only if the macromolecule is at thermal equilibrium, in which we show that  $Y_t$  still fluctuates but  $\Psi_t$  is a constant. The entropy fluctuation of Landau,  $E[(\Delta Y_t)^2]$ , precisely matches the fluctuation in the internal energy, which in turn equals the fluctuation in heat dissipation. As a generalization of Clausius’ classic result, the dynamic fluctuations in the entropy and energy of the macromolecule are exactly compensated at thermal equilibrium. For systems with detailed balance, Helmholtz free energy is shown to be the potential of Onsager’s thermodynamic force.

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In recent years, the stochastic model for overdamped Newtonian-Brownian dynamics in a force field,

$$\Xi d\mathbf{X}_t = \mathbf{F}(\mathbf{X}_t)dt + \Gamma d\mathbf{B}_t, \quad (1)$$

has found an increasing number of applications to a host of macromolecular processes in equilibrium and more importantly nonequilibrium steady state (NESS) [1,2]. These models are generalizations of the classical theory of polymer dynamics in which  $\mathbf{F}$  usually is conservative [3]. In addition to obtaining the stochastic dynamics from the model, however, it becomes clear to us that an axiomatic isothermal thermodynamic formalism can be developed based solely on the stochastic differential equation (1) in which  $\mathbf{X}_t$  represents the coordinates of the “atoms” in the macromolecule,  $\Xi$  is a constant, positive definite hydrodynamic interaction matrix,  $\mathbf{F}$  is the force not necessarily conservative [4], and  $\Gamma d\mathbf{B}_t$  is a white noise representing the collisions between the macromolecule and the solvent.  $\Gamma\Gamma^T = 2k_B T \Xi$  according to Einstein’s relation and defines the temperature of the isothermal system. The solution to Eq. (1),  $\mathbf{X}_t$ , is stochastic, whose probability density function satisfies the Fokker-Planck equation

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

$$(A = \Xi^{-1} \Gamma \Gamma^T \Xi^{-T} = 2k_B T \Xi^{-1}), \quad (2)$$

where  $P(\mathbf{x}, t)$  is the probability of the macromolecule being in conformation  $\mathbf{x}$  at time  $t$ ,  $\mathbf{X}_t = \mathbf{x}$ . In this paper, we show how a complete, mesoscopic thermodynamic theory can be formulated based on Eq. (1), which we call *stochastic macromolecular mechanics* [2]. We then apply this formalism to further elucidate a classic observation in the equilibrium thermodynamics of proteins, the dynamic origin of entropy-enthalpy compensation [5]. Naturally, the enthalpy under

constant pressure is equivalent to the internal energy in our formalism. The significance of the nonequilibrium steady state obtained from this formalism [6] and its applications to free energy transduction in biological macromolecules, e.g., a protein molecule converting chemical potential into mechanical work, have been discussed elsewhere [1,2,4].

It is important to point out that even though there is already a vast literature on stochastic models based on Fokker-Planck equation (2) [3,7], it is not known that this approach rigorously encompasses a comprehensive statistical thermodynamics. Furthermore, it is not known whether a thermodynamics exists for individual macromolecules. In this paper, we demonstrate the logical relation between models based on Eq. (1) and (2) and the principles of equilibrium and nonequilibrium thermodynamics. A complete statistical thermodynamics for isothermal systems in equilibrium, nonequilibrium transient, and NESS, as an complementary and alternative to Boltzmann’s approach, emerges.

## STOCHASTIC MACROMOLECULAR MECHANICS

Following Qian [6] and Lebowitz and Spohn [8], we first introduce the instantaneous heat dissipation  $W_t$ ,

$$dW_t \equiv \mathbf{F}(\mathbf{X}_t) \circ d\mathbf{X}_t = \mathbf{F}(\mathbf{X}_t) \cdot d\mathbf{X}_t + \frac{1}{2} d\mathbf{X}_t \nabla \mathbf{F} d\mathbf{X}_t, \quad (3)$$

where  $\circ$  and  $\cdot$  denote integrations in the Stratonovich and Ito sense, respectively [9]. According to this definition, the heat dissipation,  $dW_t$ , is equal to the work done by the system, the product of force  $\mathbf{F}$  and displacement  $d\mathbf{X}$ . This is the law of energy conservation. Using the expression (1) it is easy to show that the mean rate of the heat dissipation ( $h_d$ ) [6,8]

$$h_d = \frac{d}{dt} E[W_t] = \int \mathbf{F}(\mathbf{x}) \cdot \mathbf{J}(\mathbf{x}, t) d\mathbf{x}, \quad (4)$$

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where

$$\mathbf{J}(\mathbf{x}, t) = -\frac{1}{2}A\nabla P(\mathbf{x}, t) + \Xi^{-1}\mathbf{F}(\mathbf{x})P(\mathbf{x}, t) \quad (5)$$

is the probability flux in Eq. (2),  $\partial P(\mathbf{x}, t)/\partial t = -\nabla \cdot \mathbf{J}$ . In mechanical terms, the mean heat dissipation rate is the product of the molecular force and the flux.

The dynamic of  $W_t$  is itself Brownian motionlike with  $h_d$  as its mean rate [6]. Its fluctuations can be characterized by a ‘‘heat diffusion coefficient,’’

$$E\left[\frac{(dW_t)^2}{dt}\right] = 2k_B T \int \mathbf{F}(\mathbf{x})\Xi^{-1}\mathbf{F}(\mathbf{x})P(\mathbf{x}, t)d\mathbf{x}, \quad (6)$$

which has a dimension of [energy<sup>2</sup>]/[time]. The statistical properties of  $W_t$  have been extensively explored in connection to the Gallavotti-Cohen symmetry and fluctuation theorem [6,8,10].

Onsager’s thermodynamic force is different from the mechanical force  $\mathbf{F}(\mathbf{x})$  [11]. In terms of Eq. (2), we introduce a second thermodynamic quantity,  $\mathbf{\Pi}(\mathbf{x}, t)$ , the thermodynamic force [12]

$$\mathbf{\Pi}(\mathbf{x}, t) \equiv \mathbf{F}(\mathbf{x}) - \frac{1}{2}\Xi A\nabla \ln P(\mathbf{x}, t), \quad (7)$$

and a third thermodynamic quantity, the entropy  $S$  according to the well-known formula,

$$S = -k_B \int P(\mathbf{x}, t) \ln P(\mathbf{x}, t) d\mathbf{x}, \quad (8)$$

where  $P(\mathbf{x}, t)$  is the solution to Eq. (2). In terms of Eqs. (7) and (8) we have the increase of the entropy at constant temperature  $T$ ,

$$\begin{aligned} T\dot{S} &= k_B T \int (\ln P + 1) \nabla \cdot \mathbf{J} d\mathbf{x} \\ &= - \int (k_B T \nabla \ln P - \mathbf{F}) \cdot \mathbf{J} d\mathbf{x} - \int \mathbf{F} \cdot \mathbf{J} d\mathbf{x} \\ &= \int \mathbf{\Pi} \cdot \mathbf{J} d\mathbf{x} - h_d \\ &= e_p - h_d, \end{aligned} \quad (9)$$

in which we identify, following Onsager,  $\int \mathbf{\Pi} \cdot \mathbf{J} d\mathbf{x}$  with the *entropy production rate* ( $e_p$ ) [13]. It can also be rewritten as

$$\begin{aligned} e_p &= \int \left( \frac{1}{2}A\nabla \ln P(\mathbf{x}, t) - \Xi^{-1}\mathbf{F}(\mathbf{x}) \right)^T \\ &\quad \times \Xi \left( \frac{1}{2}A\nabla \ln P(\mathbf{x}, t) - \Xi^{-1}\mathbf{F}(\mathbf{x}) \right) P(\mathbf{x}, t) d\mathbf{x}, \end{aligned} \quad (10)$$

which is always non-negative. This is the second law of thermodynamics. Equation (9) is valid for all isothermal Brownian dynamical systems, with or without detailed balance, in stationary state and in transient process. It encompasses both the first and second laws of thermodynamics. In fact, it makes the second law quantitative by providing a rate for

entropy increase. In a time independent stationary state, the  $\dot{S} = 0$  in Eq. (9), and the entropy production  $e_p$  is balanced by the heat dissipation  $h_d$ . This is the general case for an isothermal NESS.

Equation (10) also indicates that  $e_p$  equals zero if and only if  $\mathbf{F} = (\Xi A/2)\nabla \ln P = \nabla \ln P/k_B T$ . That is the force field  $\mathbf{F}$  has to be conservative with an internal potential energy,  $\mathbf{F} = -\nabla U$ . For system with the potential, also known as detailed balance [14], the stationary solution to Eq. (2) is  $P = Z^{-1}e^{-U/k_B T}$ , where the normalization factor  $Z$  is the partition function in Gibbsian equilibrium statistical mechanics (isothermal canonical ensemble). It can be mathematically shown that  $e_p = 0$  is a sufficient and necessary condition for the stationary stochastic process  $\mathbf{X}_t$  defined by Eq. (1) being time reversible [15]. Therefore, time reversibility, detailed balance, and zero entropy production are equivalent with an equilibrium [16].

For systems satisfying the potential condition  $\mathbf{F} = -\nabla U$ , the thermodynamic force  $\mathbf{\Pi}$  also has a potential,  $\mathbf{\Pi} = -\nabla \Psi$ , where  $\Psi(\mathbf{x}) = U(\mathbf{x}) + k_B T \ln P$ . We note that the expectation of  $\Psi_t \equiv \Psi(\mathbf{X}_t)$ ,

$$E[\Psi_t] = E[U(\mathbf{x}) + k_B T \ln P(\mathbf{x})] = \int P(\mathbf{x}, t) U(\mathbf{x}) d\mathbf{x} - TS, \quad (11)$$

which in fact is the Helmholtz free energy [17]. The first term in Eq. (11) is the mean internal energy. More importantly, it is easy to show that

$$E[\dot{\Psi}_t] = h_d - T\dot{S} = -e_p \leq 0. \quad (12)$$

In an isothermal system, the Helmholtz free energy decreases and reaches its minimum at the equilibrium,  $-k_B T \ln Z$ . This is precisely the statement of second law of thermodynamics for an isothermal system.

Finally, with the potential condition, we have

$$\begin{aligned} -dU(\mathbf{X}_t) &= -\nabla U(\mathbf{X}_t) \cdot d\mathbf{X}_t - \frac{1}{2}d\mathbf{X}_t \cdot \nabla \nabla U(\mathbf{X}_t) \cdot d\mathbf{X}_t \\ &= \mathbf{F}(\mathbf{X}_t) \cdot d\mathbf{X}_t + \frac{1}{2}d\mathbf{X}_t \cdot \nabla \mathbf{F}(\mathbf{X}_t) \cdot d\mathbf{X}_t. \end{aligned} \quad (13)$$

Comparing Eq. (13) with Eq. (3), we see that the heat dissipation  $dW_t = -dU(\mathbf{X}_t)$ , the internal energy fluctuation. This is the first law of thermodynamics. Hence,  $W_t = -U(\mathbf{X}_t)$  is stationary and its expectation and variance are the internal energy and heat capacity ( $C_v$ ) of a single macromolecule at thermal equilibrium.

### THE MATCHING ENTROPY AND ENERGY FLUCTUATIONS

We now focus on systems with detailed balance. The above thermodynamic formalism suggests the fluctuating  $U_t \equiv U(\mathbf{X}_t)$  as a mesoscopic, generalization of internal energy of a macromolecule in an isothermal aqueous solution. Then its expectation  $E[U_t] = \int U(\mathbf{x})P(\mathbf{x})d\mathbf{x}$ , which equals to the standard internal energy in thermodynamics. Similarly, in

the same spirit, we can introduce fluctuating entropy  $Y_t \equiv -k_B \ln P(\mathbf{X}_t)$ , which can be viewed as the mesoscopic, non-equilibrium generalization of entropy. It is important to point out that this definition is consistent with the Boltzmann's microscopic entropy based on the volume of the phase space. In our case  $P(\mathbf{X}_t)$  is the probabilistic measure of the phase space. The expectation  $E[Y_t]$  is the Gibbs entropy in Eq. (8).

We now show that the mesoscopic generalizations immediately lead to an interesting thermodynamic result in equilibrium. We note that while  $U_t$  and  $Y_t$  are fluctuating in equilibrium, their difference,

$$U_t - TY_t = U(\mathbf{X}_t) + k_B T \ln P(\mathbf{X}_t) = -k_B T \ln Z, \quad (14)$$

the mesoscopic equilibrium free energy, however, is not fluctuating. We can further compute the fluctuations in the mesoscopic entropy and internal energy,

$$\begin{aligned} T^2 E[(\Delta Y_t)^2] &= E[(\Delta U_t)^2] \\ &= \int U^2(\mathbf{x}) e^{-U(\mathbf{x})/k_B T} d\mathbf{x} \\ &\quad - \left( \int U(\mathbf{x}) e^{-U(\mathbf{x})/k_B T} d\mathbf{x} \right)^2 \\ &= k_B T^2 \frac{\partial}{\partial T} E[U_t] \\ &= k_B T^2 C_v. \end{aligned} \quad (15)$$

Furthermore,

$$TE[\Delta Y_t \Delta U_t] = E[(\Delta U_t)^2]. \quad (16)$$

Therefore, the fluctuations of the mesoscopic internal energy  $U_t$  and entropy  $Y_t$  are perfectly correlated. They compensate in the *dynamical fluctuations* of a macromolecule.

### ENTROPY FLUCTUATION AND ITS MESOSCOPIC INTERPRETATIONS

The relation between entropy fluctuation and heat capacity in Eq. (15) was known to Landau who also advocated the concept of entropy fluctuation [18]. It has been a difficulty concept to many who consider entropy to be a functional of the distribution [19]. Here we offer a more plausible interpretation of the concept based on our mesoscopic view from the previous section.

Let us consider  $N$  identical, independent macromolecules in the aqueous solution,  $(\mathbf{X}_1, \mathbf{X}_2, \dots, \mathbf{X}_N)$ , each with its own stochastic dynamic equation (1). The concentration of the number of molecules in conformation  $\mathbf{x}$  can then be defined as

$$C_{x,t} = \sum_{j=1}^N \delta(\mathbf{x} - \mathbf{X}_j). \quad (17)$$

Note that since the  $\mathbf{X}$ 's are stochastic, the concentration  $C_{x,t}$  fluctuates. However, the classic statistical mechanics is only concerned with the *most probable*  $C_{x,t}$  since the relative fluctuation in  $C_{x,t}$  is insignificant in the thermodynamic limit when  $N \rightarrow \infty$ . Nevertheless, the  $C_{x,t}$  fluctuates.

The macroscopic entropy is defined as a functional of the density function  $C_{x,t}$ . Therefore, it fluctuates with the  $C_{x,t}$ . We now show that this fluctuation is indeed the mesoscopic fluctuation introduced in the formalism for single macromolecules. We consider a general thermodynamic quantity

$$q = \int Q(\mathbf{x}) C_{x,t} d\mathbf{x}. \quad (18)$$

If one had neglected the fluctuation in  $C_{x,t}$ , a fluctuation in  $q$  would be inconceivable.

Noting Eq. (17), the expectation of  $q$  is readily computed

$$\begin{aligned} E[q] &= \int Q(\mathbf{x}) d\mathbf{x} \sum_{j=1}^N E[\delta(\mathbf{x} - \mathbf{X}_j)] \\ &= \int Q(\mathbf{x}) d\mathbf{x} \sum_{j=1}^N \int \delta(\mathbf{x} - \mathbf{y}_j) \\ &\quad \times P(\mathbf{y}_1, \mathbf{y}_2, \dots, \mathbf{y}_N) d\mathbf{y}_1, \dots, d\mathbf{y}_N \\ &= N \int Q(\mathbf{x}) P(\mathbf{x}) d\mathbf{x} \\ &= NE[Q(\mathbf{X}_t)], \end{aligned}$$

where the joint probability for  $\mathbf{X}_1, \mathbf{X}_2, \dots, \mathbf{X}_N$ ,  $P(\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_N) = P(\mathbf{x}_1)P(\mathbf{x}_2), \dots, P(\mathbf{x}_N)$  since the macromolecules are assumed to be independent in the solution. Similarly, the variance in  $q$

$$\begin{aligned} \text{var}[q] &= \sum_{j=1}^N \text{var} \left[ \int Q(\mathbf{x}) \delta(\mathbf{x} - \mathbf{X}_j) d\mathbf{x} \right] \\ &= \sum_{j=1}^N \text{var}[Q(\mathbf{X}_j)] \\ &= N \text{var}[Q(\mathbf{X}_t)] \\ &= N \text{var}[Q_t], \end{aligned}$$

in which  $Q_t \equiv Q(\mathbf{X}_t)$  [20]. Therefore, the fluctuations in  $q$  due to fluctuating in the distribution function  $C_{x,t}$ , is exactly the mesoscopic fluctuation we have introduced in the preceding section for single macromolecules. The mesoscopic view, however, clearly indicates a stochastic dynamic origin of these fluctuations.

### ENTROPY AND HEAT

It is a classic result of Clausius that entropy change equals to heat dissipation in isothermal quasistatic processes. Our result suggests that both concepts can be generalized dynamically to isothermal equilibrium, and their fluctuations are indeed equal, as we have shown. In our formalism, the energy conservation is instantaneous, hence,  $dW_t = -dU_t$ . The free energy, on the other hand, has to be constant over the entire conformational space in an equilibrium,  $\Psi(\mathbf{x}) \equiv -k_B T \ln Z$ , while  $Y(\mathbf{x})$  and  $U(\mathbf{x})$  are not. This is a demon-

stration for the concept of *local equilibrium*, which is essential in the general theory on nonequilibrium thermodynamics [21]. Therefore,  $TdY_t = dU_t = -dW_t$  and  $dU_t/dY_t = T$ , all *instantaneously*.

### THE RATE OF $e_p$

The  $e_p$  defined in Eq. (10) is instantaneous and time dependent in a nonequilibrium transient. Thus, one can further compute its time derivative ( $de_p/dt$ ), the change in entropy production rate [7]. With some algebra we have [22]

$$\begin{aligned} \frac{de_p}{dt} = & -2k_B T \int (\nabla \cdot \mathbf{J})^2 P^{-1}(\mathbf{x}) d\mathbf{x} \\ & - \int (\mathbf{\Pi}^T \Xi^{-1} \mathbf{\Pi})(\nabla \cdot \mathbf{J}) d\mathbf{x}. \end{aligned} \quad (19)$$

Near a NESS,  $\nabla \cdot \mathbf{J}$  is small and the second term has the leading order. However, with detailed balance and near an equilibrium,  $\mathbf{\Pi}$  is also small; hence, the first term, which is negative, becomes the leading term. Therefore, near an equilibrium, the  $e_p$  *monotonically* approaches to zero. This is the Glansdorff-Prigogine's principle of minimal entropy production rate [21]. Near a NESS, however, the second term dominates, and Eq. (19) is not necessarily negative.

### DISCUSSIONS AND SUMMARY

While our thermodynamic formalism is strictly for isothermal processes, it can be used to compare a system under different temperature. In a thermal equilibrium, as we have shown, the fluctuation in internal energy  $U_t \equiv U(\mathbf{X}_t)$  is directly related to the heat capacity  $C_v = dE[U_t]/dT$ . Such relations, if any, in nonequilibrium steady state have not been explored. Furthermore, one can easily introduce an external force into the Eq. (1) to represent the pressure, and thus we expect a thermodynamic formalism for isobaric systems can be developed in parallel.

It is also noted that there is a difference between the me-

soscopic energy  $U_t \equiv U(\mathbf{X}_t)$  and entropy  $Y_t \equiv -k_B \ln P(\mathbf{X}_t)$ . While the former can be computed along a stochastic trajectory, the latter cannot until the probability distribution function  $P(\mathbf{x}, t)$  is known. This difference reflects the fundamental difference between the two physical quantities, energy and entropy. The former is *local* while the latter is *nonlocal* due to circular balance. One cannot know the value of entropy of a state until knowing how likely it occurs in comparison with other states. It is possible to formally express the  $P(\mathbf{x}, t)$  in terms of a path integral [23]. Maes also suggested a space-time approach to the problem [24]. In a thermodynamic equilibrium, however,  $P(\mathbf{x})$  can be determined locally up to a normalization factor due to detailed balance. Hence,  $dY_t = TdU_t$ .

In summary,

$$\begin{aligned} \Xi d\mathbf{X}_t &= \mathbf{F}(\mathbf{X}_t) dt + \Gamma d\mathbf{B}_t & (\text{conformational dynamics}), \\ dW_t &= \mathbf{F}(\mathbf{X}_t) \circ d\mathbf{X}_t & (\text{heat dissipation}), \\ Y_t &= -k_B \ln P(\mathbf{X}_t, t) & (\text{entropy}) \\ \mathbf{\Pi}_t &= \mathbf{F}(\mathbf{X}_t) + T \nabla Y(\mathbf{X}_t, t) & (\text{thermodynamic force}), \end{aligned}$$

is a complete set of equations that provides the stochastic dynamics of a macromolecule, its heat dissipation, its entropy (Boltzmann), and its thermodynamic driving force (Onsager). With this set of equations, one can compute  $h_d = (d/dt)E[W_t]$  and  $e_p (\geq 0)$  from entropy balance  $T(d/dt)E[Y_t] = e_p - h_d$ . If a system is detail balanced, i.e.,  $\mathbf{F} = -\nabla U$ . Then  $W_t = U_t \equiv U(\mathbf{X}_t)$ , and  $\mathbf{\Pi} = -\nabla \Psi(\mathbf{X}_t)$  where  $\Psi(\mathbf{X}_t) \equiv \Psi_t = U_t - TY_t$  is free energy,  $(d/dt)E[\Psi_t] = -e_p \leq 0$  and reaches its minimum  $-k_B T \ln Z$  at equilibrium. In the equilibrium, the probability distribution for  $\mathbf{X}_t$  is  $Z^{-1} e^{-U(\mathbf{x})/k_B T}$ ,  $U_t - TY_t = -k_B T \ln Z$ , and  $E[(\Delta Y_t)^2] = (1/T^2)E[(\Delta U_t)^2] = k_B C_v$ , the heat capacity.

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