

Relative entropy: Free energy associated with equilibrium fluctuations and nonequilibrium deviations

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Using a one-dimensional macromolecule in aqueous solution as an illustration, we demonstrate that the relative entropy from information theory, $\sum_k p_k \ln(p_k/p_k^*)$, has a natural role in the energetics of equilibrium and nonequilibrium conformational fluctuations of the single molecule. It is identified as the free energy difference associated with a fluctuating density in equilibrium, and is associated with the distribution deviate from the equilibrium in nonequilibrium relaxation. This result can be generalized to any other isothermal macromolecular system using the mathematical theories of large deviations and Markov processes, and at the same time provides the well-known mathematical results with interesting physical interpretations.

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I. INTRODUCTION

Entropy is the most important concept in both statistical mechanics and information theory. In the latter [1], entropy is a quantity associated with any discrete probability distribution $\{p_k\}$ [2],

$$S[\{p_k\}] = - \sum_k p_k \ln p_k, \quad (1)$$

and its generalization to continuous probability distributions is straightforward. In statistical mechanics, the same Eq. (1) gives the entropy, in units of k_B , for a canonical ensemble of a molecular system at constant temperature. This is known as Gibbs entropy. The probability of a molecular configuration, say $\{x_k\}$, is related to its free energy $F(\{x_k\})$ according to Boltzmann's law $P(\{x_k\}) \propto e^{-F(\{x_k\})/k_B T}$, where k_B is Boltzmann's constant and T is the temperature in K [3]. It is generally accepted, however, that the entropy in information theory and that in statistical mechanics, though they share the same name, are not the same.

This paper demonstrates a second connection between the two fields: both are based on the theory of probability. There is another important concept in information theory called relative entropy $H[\{p_k\}|\{p_k^*\}]$. It is associated with probability distributions $\{p_k\}$ and $\{p_k^*\}$:

$$H[\{p_k\}|\{p_k^*\}] = \sum_k p_k \ln \left(\frac{p_k}{p_k^*} \right). \quad (2)$$

The relative entropy has many important mathematical properties; for example, it is positive, and is equal to zero if and only if $p_k = p_k^*$; furthermore, it is a convex function of p_k .

Until now, however, the relative entropy has not naturally found a physical interpretation in statistical mechanics, despite its important role as a mathematical device in the stability analysis of master equations [4] and Fokker-Planck equations [5]. In this paper, we demonstrate, using two spe-

cific examples, that the relative entropy is in fact the free energy associated with isothermal equilibrium fluctuations and a generalized free energy associated with transient nonequilibrium deviations. The two examples we use are from a recently developed stochastic theory of macromolecular mechanics [6]; however, the generalization of our result is straightforward, and in fact is known in the mathematical literature [5,7].

The statistical mechanical system we discuss is a single macromolecule in aqueous solution at a constant temperature T . The interest in such a system is motivated by recent experimental studies on single biological molecules [8,6]. We point out that such systems provide a unique type of nonequilibrium problem in which the momentum distribution is in rapid equilibrium due to collisions with the solvent molecules. Hence the nonequilibrium problem is only for the conformational, stochastic dynamics of the macromolecule. A separation of the time scales for momentum and conformation (overdamped mechanics) is assumed, which leads to the Smoluchowski equation.

The Smoluchowski approach to nonequilibrium statistical mechanics of single macromolecules in an aqueous solution is parallel and complementary to the approach based on the Boltzmann equation for gases and liquids. Both approaches are based on Newtonian mechanics, but both invoke a stochastic element *a priori* in dealing with collisions [10]. There is an extensive literature on the nonequilibrium statistical mechanics, including studies on relative entropy, based on Boltzmann's framework [9]. This work illustrates an approach based on the Smoluchowski's framework [6], which is simpler, conceptually straightforward, and applicable to biomolecular applications. We note that the rate of uncompensated heat in Ref. [9] seems to correspond to the entropy production rate in the Smoluchowski's framework. The precise and concrete relation between these two quantities remains to be established [11].

II. EQUILIBRIUM FLUCTUATIONS OF A POLYMER CHAIN

Let us consider a one-dimensional polymer chain with N identical subunits. Each subunit is an elastic element with a free energy function (potential of mean force) $\phi(x)$. Let x_1, x_2, \dots, x_{N-1} be the junctions between successive sub-

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units. We assume that the end $x_0=0$ is anchored and the end x_N is freely fluctuating. This model was motivated by mechanical studies on giant muscle protein titin [12]. According to Boltzmann's law, the joint probability for all $\{x_k\}$ is

$$P_{eq}(\{x_k\}) = Z^{-1} \exp\left[-\frac{\phi(x_1-x_0) + \phi(x_2-x_1) + \dots + \phi(x_N-x_{N-1})}{k_B T}\right], \quad (3)$$

where

$$Z = \left(\int_0^\infty \exp\left[-\frac{\phi(z)}{k_B T}\right] dz \right)^N.$$

The partition function of the equilibrium state of such a system can be obtained analytically using Laplace transform [13,14]. The theory of large deviation of level 1 serves as its rigorous mathematical foundation [7].

In a laboratory, usually only x_N is observable [15]. For this case, we obtain the marginal distribution of Eq. (3):

$$P_{eq}(x_N) = \int_0^\infty \dots \int_0^\infty P_{eq}(\{x_i\}) dx_1 \dots dx_{N-1}. \quad (4)$$

Combining the probability distribution in Eq. (4) with Boltzmann's law, we obtain a free energy function for the entire polymer under the condition that the end of the chain is at x_N :

$$F(x_N) = -k_B T \ln P_{eq}(x_N).$$

In a completely parallel fashion, one can obtain the free energy function $F(x_i, x_j)$ from a marginal distribution of Eq. (3).

A different type of laboratory measurements is to obtain the density for the subunit length. Optical spectroscopy is sensitive to the length of subunits; hence it provides a measurement of the density function,

$$\nu(x) = \frac{1}{N} \sum_{k=1}^N \delta(x - x_k + x_{k-1}), \quad (5)$$

which is known as the empirical measure in the theory of large deviation of level 2 [7].

Clearly, the function $\nu(x)$ fluctuates in an equilibrium state, since $(x_k - x_{k-1})$ fluctuates. It has an expectation

$$E[\nu(x)] = p(x) = \frac{e^{-\phi(x)/k_B T}}{\int_0^\infty e^{-\phi(x)/k_B T} dx}.$$

For large N , the fluctuations of $\nu(x)$ around $p(x)$ are so small that one seldom considers their existence. Nevertheless, there is a free energy associated with each $\nu(x)$, and we now show that

$$F[\nu(x)] - F[p(x)] = N k_B T \int_0^\infty \nu(x) \ln\left(\frac{\nu(x)}{p(x)}\right) dx. \quad (6)$$

This is in fact a mathematical result for a large deviation of level 2 [7]. We give only a heuristic proof below, and leave the rigorous treatment to the mathematical literature.

Let us denote

$$\nu_n = \int_{n\delta}^{(n+1)\delta} \nu(x) dx \quad \text{and} \quad p_n = \int_{n\delta}^{(n+1)\delta} p(x) dx.$$

Because all the subunits are independent, ν_n is a multinomial distribution:

$$P(\nu_1, \nu_2, \dots, \nu_m) = \frac{N!}{(N\nu_1)!(N\nu_2)! \dots (N\nu_m)!} \times p_1^{N\nu_1} p_2^{N\nu_2} \dots p_m^{N\nu_m}. \quad (7)$$

According to Boltzmann's law, the free energy difference between configurations $\{\nu_n\}$ and $\{p_n\}$ is

$$\begin{aligned} F[\{\nu_n\}] - F[\{p_n\}] &= -k_B T \ln\left(\frac{P(\{\nu_n\})}{P(\{p_n\})}\right) \\ &\approx N k_B T \sum_{n=1}^m \nu_n \ln\left(\frac{\nu_n}{p_n}\right) \\ &\rightarrow N k_B T \int_0^\infty \nu(x) \ln\left(\frac{\nu(x)}{p(x)}\right) dx \quad (\delta \rightarrow 0). \end{aligned}$$

Therefore, the relative entropy in Eq. (6) is the free energy difference between the distribution $\{\nu(x)\}$ and its (equilibrium) expectation $\{p(x)\}$. The relative entropy is the free energy associated with a fluctuating density at equilibrium [16].

III. NONEQUILIBRIUM RELAXATION OF A POLYMER CHAIN

Our second example extends the concept of free energy beyond an equilibrium state, and reveals its central role in the transient, isothermal, relaxation processes to equilibria [17]. The dynamic model for the polymer chain in an aqueous solution at constant temperature T is a Smoluchowski equation [6],

$$\frac{\partial P(\mathbf{x}, t)}{\partial t} = \frac{k_B T}{\eta} \nabla^2 P + \frac{1}{\eta} \nabla \cdot [\nabla U(\mathbf{x}) P], \quad (8)$$

where η is a frictional coefficient, $\mathbf{x} = (x_1, x_2, \dots, x_N)$, $\nabla = (\partial/\partial x_1, \partial/\partial x_2, \dots, \partial/\partial x_N)$, and

$$U(\mathbf{x}) = \phi(x_1 - x_0) + \phi(x_2 - x_1) + \cdots + \phi(x_N - x_{N-1}). \quad (9)$$

It is easy to verify that Boltzmann's distribution $P_{eq}(\mathbf{x})$ in Eq. (3) is the stationary solution to Eq. (8). In fact, the steady-state solution of Eq. (8) defines a stationary, time-reversible, stochastic process with equilibrium fluctuations [18].

How is an arbitrary distribution $P(\mathbf{x}) \neq P_{eq}(\mathbf{x})$ changing with time and approaching to $P_{eq}(\mathbf{x})$? We now show that a free energy functional can be introduced, and it is in fact the relative entropy. Let us define a Ψ function

$$\begin{aligned} \Psi[P(\mathbf{x})] &= \int [U(\mathbf{x})P(\mathbf{x}) + k_B T P(\mathbf{x}) \ln P(\mathbf{x})] d\mathbf{x} \\ &= -k_B T \ln Z + k_B T \int P(\mathbf{x}) \ln \left(\frac{P(\mathbf{x})}{P_{eq}(\mathbf{x})} \right) d\mathbf{x}. \end{aligned} \quad (10)$$

The first term is the Helmholtz free energy of the entire polymer chain in its equilibrium state, and the second term should be interpreted as the free energy difference between the arbitrary distribution $P(\mathbf{x})$ and the equilibrium distribution $P_{eq}(\mathbf{x})$.

The mathematical properties of relative entropy immediately lead to the following statement: The system reaches equilibrium if and only if the free energy functional (the Ψ function) is minimized. Furthermore, if $P(\mathbf{x}, t)$ changes with t in a transient process according to Eq. (8), then

$$\dot{\Psi}[P(\mathbf{x}, t)] = - \int \mathbf{J}(\mathbf{x}, t) \Phi(\mathbf{x}, t) d\mathbf{x} \leq 0, \quad (11)$$

where

$$\mathbf{J}(\mathbf{x}, t) = - \frac{k_B T}{\eta} \nabla P(\mathbf{x}, t) - \frac{1}{\eta} \nabla U(\mathbf{x}) P(\mathbf{x}, t)$$

and

$$\Phi(\mathbf{x}, t) = -k_B T \nabla \ln P(\mathbf{x}, t) - \nabla U(\mathbf{x})$$

are fluxes and forces, which are both zero at equilibrium [19]. Furthermore, $\mathbf{J} = P \Phi_\eta$, and Eq. (11) is related to the entropy production rate [6,18,19]. Equation (11) immediately leads to a second statement: The dynamic of $P(\mathbf{x}, t)$ follows a path of decreasing free energy. The free energy functional in Eq. (10) is a Lyapunov function [5] for the stochastic dynamics of the polymer. The relative entropy is the free energy difference between an arbitrary distribution and the equilibrium distribution. It is associated with the nonequilibrium deviation from the equilibrium state. However, it is interesting to note that the dynamics does not follow the steepest descent of the free energy functional. The interpretation and significance of this observation are not clear to us at present time. We also note that Eq. (11) corresponds to the H theorem in Boltzmann's framework.

It is of course not a coincidence that the relative entropy appears as a free energy difference in both equilibrium and nonequilibrium situations. Onsager [20] pointed out that the force driving the nonequilibrium relaxations is in fact the same force causing the equilibrium fluctuations to return to its mean. Our result, therefore, firmly relates the force to a free energy difference in terms of the relative entropy.

In summary, we have shown that the relative entropy in information theory has a natural physical meaning in equilibrium and nonequilibrium statistical mechanics. It is in fact the free energy difference associated with the equilibrium fluctuations of a density function, a result known in the theory of large deviations. In nonequilibrium systems, it is the free energy difference between an arbitrary distribution and the equilibrium distribution. Again the latter result is known in the theory of Markov processes. What is interesting in the present paper is the identification of the relative entropy with Helmholtz's free energy for isothermal systems. Conversely, the mathematical theorems mentioned above become an integral part of the statistical physics of macromolecules.

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[2] We provide this information entropy formula with a Boltzmannian interpretation based on his celebrated relation

$$S_B = k_B \ln (\text{the numbers of equal possible outcomes}).$$

This formula was originally proposed for a uniform probability distribution (microcanonical ensemble, Boltzmann's framework for statistical mechanics). To generalize it to a situation with nonuniform probability distribution (canonical ensemble, Gibbs and Smoluchowski's framework) $\{p_k\}$, ($1 \leq k \leq M$), let us consider a sequence of N independent and identically distributed random variables $(\xi_1, \xi_2, \dots, \xi_N)$ all with the distri-

bution $\text{Prob}\{\xi = a_k\} = p_k$. Then the probability of a particular sequence is $p_1^{v_1} p_2^{v_2} \dots p_N^{v_N}$, where v_k is the number of occurrences of a_k in the sequence. For large N , there are essentially two types of sequences: a *typical* sequence has $v_k \approx N p_k$, and all the remaining sequences are *rare*. The probability of a typical sequence is e^{-NS} where S is given in Eq. (1). The number of the typical sequences is $\approx e^{NS}$, which among all the possible sequences M^N is essentially zero: $e^{NS}/M^N \rightarrow 0$. Therefore, for a large N , most sequences are rare; however, almost certainly none will occur. The relevant probability is defined on the *space of all typical sequences*, with the number of equal possible outcomes being e^{NS} . Therefore, by Boltzmann's relation we have $S_B = -k_B N \sum_k p_k \ln p_k$.

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