Motor protein with nonequilibrium potential: Its thermodynamics and efficiency

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A nonequilibrium potential function is introduced for a motor protein modeled by a rectified Brownian motion. This result provides a concrete case for a class of nonequilibrium systems in steady state with dissipation which possess a potential function. The potential μ is a natural generalization of the chemical potential for isothermal chemical species and $\mu=$const if and only if the system is in an equilibrium. The steady-state flux $\mathbf{J}\propto-\nabla\mu$, and the total heat dissipation h_d equals a surface integral $\int\mu\mathbf{J}\cdot dS$, representing the energy input. In terms of μ and h_d the thermodynamic energy conservation in the mesoscopic stochastic system can be rigorously established and various types of motor efficiency are elucidated.

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One of the hallmarks of equilibrium statistical mechanics and thermodynamics is the existence of a potential function. Within the framework of stochastic dynamics modeled by Langevin equations [1,2] we have recently established the relations among the existence of such a potential, time-reversibility, detailed balance, and zero entropy production [3]. There is no consensus on whether such a potential exists for systems in nonequilibrium steady state (NESS) [4]. Motor proteins isolated from biological cells provide a concrete model for stochastic molecular systems that operates in NESS, converting chemical energy into mechanical work. Understanding the motor protein, on which a large body of literature already exists, is important both for the fundamental theories of NESS and for practical nanotechnology [5–10].

One class of the models of motor proteins which are most directly related to the realistic, all-atom based molecular dynamics is the rectified Brownian motion [9]. We show that one of the unique features of this class of stochastic models is its solvability in terms of a nonequilibrium potential function μ. We find that in terms of this μ, a rigorous NESS thermodynamics can be established for the stochastic system including energy conservation and efficiencies of motor proteins.

One of the next challenges in studying motor proteins is to integrate phenomenological models with realistic atomic structures, carrying out large-scale simulations by a combination of molecular dynamics, Brownian dynamics, and quantum mechanics (for enzyme catalysis) [11]. In all these approaches, protein conformational dynamics is based on a molecular energy function or potential of mean force U (which should not be confused with the μ, see below), and the conformational space for the atoms in the molecule with the presence of an appropriate linear molecular track for the motor protein is continuous. Following Refs. [8,10], we shall denote y as the internal conformational space of the motor protein, and x as its center of mass with respect to the linear track. This is the natural respresentation of motor proteins with atomic structures. y has a very high dimension and x can be either one dimensional or three dimensional if motor dissociation from the track is considered.

A key component of models for motor proteins is the ATP molecule. We foresee that the majority of the simulation effort will be focused on the ATP hydrolysis by the catalytic motor protein. For concreteness, let us denote $y=0$ as M-ATP and $y=1$ as M-ADP; with a realistic molecular structure, $y=0$ (or 1) represents a region of the conformational space of motor-ATP (ADP) complex with appropriate bond lengths and bond angles. Hence, the molecular energy function $U(x,y)$ is for the tertiary complex of motor protein, nucleotide, and linear track.

The driving force of the motor protein comes from the exchange of bounded ADP at $y=1$ for free ATP. To simplify our discussion, we neglect the orthophosphate Pi but its incorporation is straightforward. The exchange process is by Brownian collision in aqueous solution, and it can be naturally represented as a boundary condition for the hydrolysis kinetics. Note that changing the ATP and ADP concentrations in the solution does not affect the U. In Brownian dynamic term, therefore, we have a diffusion equation

$$\partial_t P(x,y,t)=D_x\partial_x\{\partial_x P+\beta(\partial_x U)P\}+D_y\nabla_y\{\nabla_y P+\beta(\nabla_y U)P\} \tag{1}$$

in which $\beta=(k_BT)^{-1}$. The boundary conditions are [12]

$$J_y(x,0)=J_y(x,1)=\nu_1(x)P(x,1)-\nu_0(x)P(x,0), \tag{2}$$

where $J_y(x,y)=-D_y\{\nabla_y P+\beta(\nabla_y U)P\}$, $\nu_1(x)$ and $\nu_2(x)$ are the x-dependent on-rate constants for ATP and ADP, respectively [7,13]:

$$\nu_1(x)=\omega_1 g(x)e^{\beta\lambda\Delta U(x)}[c_{\mathrm{T}}],$$
$$\nu_0(x)=\omega_0 g(x)e^{-\beta(1-\lambda)\Delta U(x)}[c_{\mathrm{D}}], \tag{3}$$

in which $\Delta U(x)=U(x,1)-U(x,0)$, $g(x)$ models the differential binding affinity between the nucleotide and the motor protein at different x. If one is only interested in the NESS with $\partial P/\partial t=0$, then further we have a periodic boundary condition $P(0,y)=P(L,y)$ and $\partial_x P(0,y)=\partial_x P(L,y)$, where L is the period of the linear track, i.e., 36 Å for an actin filament. The stationary flux

$$J_x=-\int_0^1 D_x\{\partial_x P(x,y)+\beta\partial_x UP(x,y)\}dy, \tag{4}$$

and $J_x L$ is the stationary velocity of the motor.

The dynamics of the nucleotide in this model can be schematically represented as [12] hydrolysis on the motor enzyme M-ATP $\rightleftharpoons$ M-ADP and exchange in the aqueous solution M-ADP + ATP $\rightleftharpoons$ M-ATP + ADP. In the practice of molecular simulation, an empirical boundary is drawn between these two reactions, i.e., how far apart between an M and an ATP when they are still considered as a complex M-ATP. Both reactions are x dependent since the motor protein at different x should have a different molecular structure. The chemical potentials for the species in the aqueous solution are $\mu_T = \mu_T^o + k_B T \ln[c_{\mathrm{T}}]$, $\mu_D = \mu_D^o + k_B T \ln[c_{\mathrm{D}}]$, and

$$\mu_{MT}(x) = U(x,0) + k_B T \ln P(x,0),$$

$$\mu_{MD}(x) = U(x,1) + k_B T \ln P(x,1). \tag{5}$$

We shall denote the chemical potential difference for the exchange reaction $\Delta\mu_{ex}(x) \equiv \mu_D + \mu_{MT}(x) - \mu_T - \mu_{MD}(x) = k_B T \ln \nu_0(x) P(x,0) / \nu_1(x) P(x,1)$.

Equilibrium thermodynamics. When the concentrations of ATP and ADP in solution satisfy

$$\gamma \equiv \frac{\omega_1[c_{\mathrm{T}}]}{\omega_0[c_{\mathrm{D}}]} = 1, \tag{6}$$

the stationary solution to Eq. (1) is in fact the equilibrium distribution $P(x,y) = Z^{-1} e^{-\beta U(x,y)}$, where $Z(\beta) = \int_0^1 \int_0^L \exp\{-\beta U(x,y)\} dx\, dy$. In the equilibrium, $\mu_{MT}(x) = \mu_{MD}(x)$, $\mu_T = \mu_D$, and $\omega_1 / \omega_0 = \exp\{(\mu_T^o - \mu_D^o)/k_B T\}$. Furthermore, $J_y = 0$ and $J_x = 0$. There is no ATP hydrolysis, and the motor has no velocity.

NESS thermodynamics. Under the cellular physiological condition,

$$\mu_T - \mu_D = \mu_T^o - \mu_D^o + k_B T \ln \frac{[c_{\mathrm{T}}]}{[c_{\mathrm{D}}]} = k_B T \ln \gamma > 0. \tag{7}$$

It is well known that even though Eq. (1) has a potential function, the differential operator is not self-adjoint and the diffusion process is not reversible due to the nonlocal flux boundary condition (2) [14,15]. Hence, the stationary stochastic process obtained from Eq. (1) is time-irreversible with positive heat dissipation [3].

We now show that this class of stochastic models exhibits several surprising simple thermodynamic structure in NESS. We introduce $P(x,y) = Q(x,y) e^{-\beta U(x,y)}$ which has a clear physical meaning:

$$\mu(x,y) \equiv k_B T \ln Q(x,y) = U(x,y) + k_B T \ln P(x,y) \tag{8}$$

which is the mesoscopic generalization of the NESS chemical potential (Gibbs free energy), and $-\boldsymbol{\nabla}\mu(x,y) = -\nabla U - k_B T \boldsymbol{\nabla} \ln P$ is Onsager's thermodynamic force [2]. More importantly, we have NESS Onsager thermodynamic flux

$$\mathbf{J} = -D_x\{\partial_x P + \beta(\partial_x U) P\} - D_y\{\nabla_y P + \beta(\nabla_y U) P\}$$
$$\propto -\nabla\mu(x,y). \tag{9}$$

The proportionality indicates that this class of nonequilibrium systems follows the Onsager's theory of linear irreversibility with "mobility tensor" $\beta P(x,y) D$ as the symmetric Onsager matrix. It is important to point out that while it is known that irreversibility in a closed system can be represented by a Helmholtz potential [2], it is not known that such a potential exists for an open system.

$Q(x,y)$ satisfies the equation with boundary conditions

$$D_x\{\partial_{xx} Q - \beta(\partial_x U)\partial_x Q\} + D_y\{\nabla_y^2 Q - \beta(\nabla_y U)\nabla_y Q\} = 0, \tag{10}$$

$$e^{-\beta U(x,0)} \nabla_y Q(x,0) = e^{-\beta U(x,1)} \nabla_y Q(x,1)$$
$$= -\nu(x)\{\gamma Q(x,1) - Q(x,0)\}, \tag{11}$$

in which $\nu(x) = (\omega_o[c_{\mathrm{D}}]/D_y) g(x) \exp\{-\beta[(1-\lambda)U(x,1) + \lambda U(x,0)]\}$, $Q(0,y) = Q(L,y)$, and $\partial_x Q(0,y) = \partial_x Q(L,y)$. This equation for $Q(x,y)$ provides the Kolmogorov's backward equation with an alternative physical interpretation in NESS.

In terms of the NESS $\mathbf{J}$ and μ, we now establish the law of energy conservation. Equation (9) gives $J_x(x,y) = -\beta D_x e^{\beta(\mu - U)} \partial_x \mu$ and $J_y(x,y) = -\beta D_y e^{\beta(\mu - U)} \nabla_y \mu$. The NESS heat dissipation rate, which equals the entropy production rate and is always positive [10,3], is given as

$$h_d = k_B T \int_0^1 \int_0^L e^{\beta(U-\mu)} \left(\frac{J_x^2}{D_x} + \frac{J_y^2}{D_y} \right) dx\, dy$$
$$- \int_0^L \Delta\mu_{ex}(x) J_y(x,0) dx \tag{12}$$

$$= \beta \int_0^1 \int_0^L e^{\beta(\mu - U)} \{D_x(\partial_x \mu)^2 + D_y(\nabla_y \mu)^2\} dx\, dy$$
$$- \int_0^L \Delta\mu_{ex}(x) J_y(x,0) dx$$

$$= \int_0^L [\mu(x,0) - \mu(x,1) - \Delta\mu_{ex}(x)] J_y(x,0) dx \tag{13}$$

$$= (\mu_T - \mu_D) \int_0^L J_y(x,0) dx. \tag{14}$$

The two terms in Eq. (12) are the heat dissipation rates from the hydrolysis reaction and the exchange reaction, respectively. Equations (12)–(14) establish energy conservation. The right-hand side is the ATP energy going into the system and the left-hand side is the dissipated heat.

Efficiency under an external force. We now consider that the motor is moving against a constant external force $F_{ext} > 0$. Then Eq. (1) will be modified by replacing $\partial_x U$ with $(\partial_x U - F_{ext})$. Carrying out the same analysis as above, we now have Eq. (14) becoming [16],

$$h_d = (\mu_T - \mu_D) \int_0^L J_y(x,0) dx - F_{ext} L J_x, \tag{15}$$

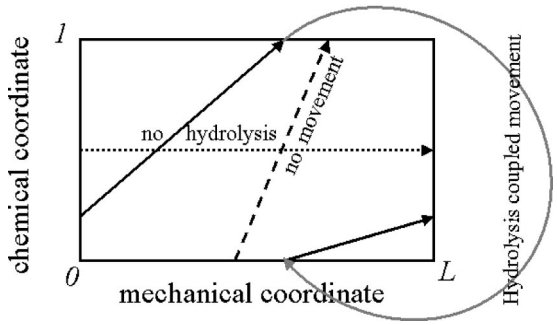

FIG. 1. Three different types of NESS flux lines of the divergent-free vector field $\mathbf{J}=(J_x,J_y)(x,y)$—solution to Eq. (1); $\partial P/\partial t = -\nabla\cdot\mathbf{J}=0$. Type I (dotted line); movement without hydrolysis; type II (dashed line), hydrolysis without movement; type III (solid line), hydrolysis coupled movement which involves nucleotide exchange, from $y=1$ back to $y=0$, as boundary condition.

where J_x is given in Eq. (4), J_xL is the motor velocity. Equation (15) establishes the energy conservation for a single motor protein moving against a constant external force, and the efficiency is thus naturally defined as

$$\eta=\frac{F_{ext}LJ_x}{f_{cm}} \tag{16}$$

in which we denote $(\mu_T-\mu_D)\int_0^L J_y(x,0)dx$ as chemical motive force (f_{cm}).

With the energy balanced, one can further discuss several different definitions of efficiency for motor proteins. This is the only logical approach to efficiency, which has been taken in Refs. [17,6]. Reference [17] called η the thermodynamic efficiency. Reference [18] suggests that the work done by a motor protein to overcome the translational friction is a useful work. Hence their efficiency has an additional term $(k_BT/D_x)(J_xL)^2$ on the numerator of Eq. (16). This efficiency emphasizes the internal dissipation due to intramolecular friction [J_y^2/D_y term in Eq. (13)]. According to this definition, a motor protein with rapid biochemical reaction [10], thus a tight-coupling between hydrolysis and movement, has $J_y=0$, $J_x(x)=\text{const}$, and 100% efficiency.

Reference [19] points out an important difference between thermodynamic and Stokes efficiencies. The external force F_{ext} is assumed to be a potential force, i.e., $U_{ext}(x)=-F_{ext}x$. If the external force is introduced via a hydrodynamic drag on a spherical object with frictional coefficient ζ, then one can no longer compute the stored energy in the external force, instead one needs to compute the mean work done against the external drag force. The work in terms of Stratonovich integral is rigorously defined for the Brownian dynamics [2]. In this case, the h_d in Eq. (15) has two parts: an intrinsic heat dissipation and a heat dissipation associated with the work against the applied darg which should be now also on the numerator of Eq. (16).

For applied viscous drag, D_x in Eq. (1) should be modified to $\tilde{D}_x=D_x/(1+\beta\zeta D_x)$. The heat dissipation associated with $\tilde{D}_x$ in Eq. (13) is decomposed into [20]

$$\underbrace{\beta\tilde{D}_x\int_0^1\int_0^L e^{\beta(U-\mu)}(\partial_x\mu)^2dx\,dy+\cdots}_{hdr}=\underbrace{\frac{\beta^2\zeta D_x^2}{(1+\beta\zeta D_x)^2}\int\int\cdots}_{hdr_{ext}}+\underbrace{\frac{\beta D_x}{(1+\beta\zeta D_x)^2}\int\int\cdots+\cdots}_{hdr_{int}} \tag{17}$$

The thermodynamic efficiency, in this case, can be defined as

$$\eta=\frac{hdr_{ext}+F_{ext}LJ_x}{f_{cm}}\geqslant\frac{hdr_{ext}}{f_{cm}-F_{ext}LJ_x}=\frac{hdr_{ext}}{hdr}=\eta_{Stokes}. \tag{18}$$

The efficiency also has an interesting topological representation. In a NESS, the solution to Eq. (1) gives a stochastic flux distribution (J_x,J_y) in the (x,y) phase space with $\nabla\cdot\mathbf{J}=0$. In Fig. 1, three types of flux lines are illustrated. It can be shown that the type I is impossible [10]; and the type II is a futile cycle. Hence, the efficiency is the fraction of type III flux lines in the (x,y) space. If there is no type II flux line, the motor efficiency is 1 [21].

Microscopic reversibility and rectified Brownian motion. The present model for motor proteins differs fundamentally from the existing models in several key aspects [5,7,6]. First, in the bulk of the conformational space, there is a potential function $U(x,y)$, hence it satisfies the microscopic reversibility [22]. In this respect, our model belongs to the class of NESS models such as boundary-driven lattice gases and the asymmetric exclusion process, also called rectified Brownian motion [9]. One of the unique features of this class of stochastic models is its solvability in terms of a free energy function (8): $\mu=k_BT\ln Q$. For each open driven system, there exists a well-defined corresponding closed nondriven system with no-flux boundary conditions. The latter system has Boltzmann distribution $Z^{-1}e^{U(x,y)/k_BT}$ as its stationary, equilibrium distribution. When the driven boundary is imposed, the NESS solution $P^{ness}(x,y)$ is directly related to the chemical potential through the well-known formula $\mu(x,y)=U(x,y)+k_BT\ln P^{ness}(x,y)$.

From Brownian dynamics to phenomenological models. With further analysis, the present model naturally leads to a class of widely studied motor-protein models which treat the chemical transformation as discrete events [5,7,17]. In this case, we realize that the ATP hydrolysis involves a large activation energy barrier (Eyring's transition state). Let us assume that, for each x, the position of the transition state is $y^{\ddagger}(x)$, a hypersurface in the (x,y) conformational space.

Then one can define a discrete, x-dependent M-ATP state as $\{y(x)|0\leqslant y(x)<y^{\ddagger}(x)\}$ and a discrete M-ADP state as $\{y(x)|1\geqslant y(x)>y^{\ddagger}(x)\}$. Furthermore, computational methods can be used to compute the chemical potentials for the discrete M-ATP and M-ADP [23], as well as the first-order rate constants between the two states. Thus, the present model puts the phenomenological models on a rigorous molecular basis.

In summary, molecular dynamic study of motor proteins necessitates a continuous formalism for the protein conformational space. This model introduces a feature that differs from the general stochastic theory of NESS [3] which assumes a nonpotential force field. In the more realistic model the irreversibility (non-self-adjointness) is derived from a nonlocal boundary condition [14,15]. Such models have a complete and solvable thermodynamic structure in terms of NESS flux and most importantly it possesses a NESS chemical potential. Since the conservation of energy can be mathematically established, the model offers a rigorous introduction of and provides a comprehensive theory for motor efficiency.

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$$\mu^{o}_{M\text{-}ATP}(x)=-k_BT\ln\int_0^{y^{\ddagger}(x)}e^{-\beta U(x,y)}dy$$

and similarly for $\mu^{o}_{M\text{-}ADP}(x)$.