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Cycle kinetics, steady state thermodynamics and motors—a paradigm for living matter physics

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Abstract

An integration of the stochastic mathematical models for motor proteins with Hill's steady state thermodynamics yields a rather comprehensive theory for molecular motors as open systems in the nonequilibrium steady state. This theory, a natural extension of Gibbs' approach to isothermal molecular systems in equilibrium, is compared with other existing theories with dissipative structures and dynamics. The theory of molecular motors might be considered as an archetype for studying more complex open biological systems such as biochemical reaction networks inside living cells.

1. Introduction

One of the origins of modern molecular biology is physical chemistry, which provides a host of quantitative techniques for studying biochemical reactions and biological macromolecules, as well as the theoretical guiding principles in terms of statistical thermodynamics for designing experiments in and analysing laboratory measurements from aqueous solutions [1–4]. The standard theory of statistical thermodynamics [5], be it on equilibrium or kinetics, however, only applies to closed systems. In cell biology, it is important to study biochemistry in open systems with constant energy inputs and dissipations [6, 7].

While there are several nonequilibrium theories for open systems, Hill's [8] was directly motivated by concrete biological problems and is most applicable to open biochemical systems. One of his motivations was studying muscle contraction. Hill's work on muscle theory is a landmark after the pioneering work of Huxley [9], with sufficient statistical thermodynamic rigour [10, 11]. The general theory, which sets up a new theoretical framework for open systems with chemical energy input but without explicit material exchange, is summarized in two books [8, 12]. Two important concepts in the new theory of open systems are the cycle kinetics and nonequilibrium steady state (NESS) thermodynamics.

Hill's work was developed before the discovery of *in vitro* motility assay of single motor proteins [13, 14]. In the 1990s, several mathematical models emerged which were applicable

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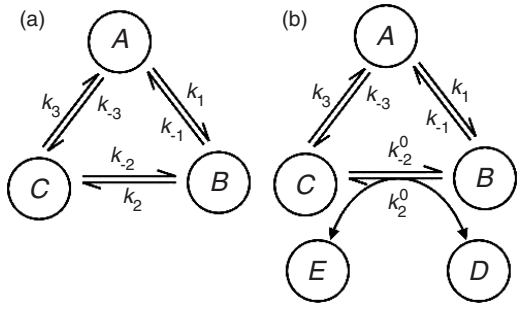

Figure 1. Fluxes are non-zero in biochemical reactions in a nonequilibrium steady state. (a) The fluxes, however, have to be balanced through kinetic cycles which contain 'driving forces', or pumping as shown (b). Continuous turning of the kinetic cycle clockwise lowers the concentration of D and accumulates the E. An ideal NESS, hence, has to be an open system to which an agent actively maintains the concentrations of D and E, i.e. the driving force. On mapping (b) to (a) in terms of pseudo-first-order rate constants $k_2 = k_2^0[D]$ and $k_{-2} = k_{-2}^0[E]$ one has the breakdown of detailed balance and the rise of cycle kinetics.

to single motor proteins. These models are kinetic in nature; they all exhibit an NESS and contain cycle kinetics. But Hill's theory has not been integrated into the various molecular motor models.

The central theme of this review is to present the theory and models for molecular motors from the NESS paradigm. The paper is developed as follows. In section 2 the essential ideas of cycle kinetics and NESS thermodynamics are presented in a nutshell. In section 3, applying the ideas to a motor protein yields the so-called chemical models. In section 4, combining the ideas with the Smoluchowski equation gives rise to the Brownian ratchet model. In section 5, a comparison between the chemical and ratchet models leads to a general theory based on the energy-landscape idea. In section 6 the analogies between the motor protein theory with energy landscape, electrical circuits, and open biochemical networks are illustrated. In section 7, closing remarks are given.

2. Nonequilibrium steady state and cycle kinetics

2.1. Breakdown of detailed balance and rise of kinetic cycle

Following classic statistical thermodynamics, the point of departure of our discussion is the breakdown of detailed balance which gives rise to the kinetic cycle. To illustrate this, let us consider the cyclic reaction in figure 1, which is a reasonable kinetic model for the phosphorylation of a protein, coupled to ATP hydrolysis.

In a closed system, unimolecular reactions among three states of a protein, say A, B, and C (figure 1(a)), necessarily satisfy the relation

$$\frac{k_1 k_2 k_3}{k_{-1} k_{-2} k_{-3}} = 1 \tag{1}$$

which is known as detailed balance in physics and thermodynamic box in chemistry [15, 16] (see below). If the reaction step between B and C is coupled to $D \rightleftharpoons E$, such as phosphorylation of a protein coupled with ATP hydrolysis (figure 1(b)), then one has

$$\frac{[D]^{\mathrm{eq}} k_2^0}{[E]^{\mathrm{eq}} k_{-2}^0} \frac{k_3 k_1}{k_{-3} k_{-1}} = 1. \tag{2}$$

In other words, when the concentrations of D and E are at their equilibrium ratio, then again, the pseudo-unimolecular reaction in figure 1(b) satisfies equation (1) if one introduces pseudo-first-order rate constants $k_2 = k_2^0[D]$ and $k_{-2} = k_{-2}^0[E]$. However, the scenario more relevant to a living cell is that the concentrations of ATP and ADP are kept at a nonequilibrium ratio. Hence, for a reaction coupled with such a nonequilibrium environment, we have

$$\frac{k_1 k_2 k_3}{k_{-1} k_{-2} k_{-3}} = \gamma \neq 1. \tag{3}$$

In fact, in physiology $k_B T \ln \gamma$ is well known as the cellular phosphorylation potential. An analogy between equations (1) and (3) and Kirchoff's loop law for an electrical circuit is appropriate. Note that in terms of Gibbs free energies for the reactions, we have $\Delta G_{AB} = k_B T \ln \frac{k_{-1}[B]}{k_1[A]}$, $\Delta G_{BC} = k_B T \ln \frac{k_{-2}[C]}{k_2[B]}$, and $\Delta G_{CA} = k_B T \ln \frac{k_{-3}[A]}{k_3[C]}$. Hence, equation (1) is equivalent to

$$\Delta G_{AB} + \Delta G_{BC} + \Delta G_{CA} = 0, \tag{4}$$

and equation (3) becomes

$$\Delta G_{AB} + \Delta G_{BC} + \Delta G_{CA} = \Delta G_{DE} = -k_B T \ln \gamma. \tag{5}$$

An open biochemical system is analogous to a circuit with a battery represented by the right-hand side (rhs) of equation (5).

With given $\gamma \neq 1$, the kinetics of figure 1 reaches a steady state with non-zero flux

$$J^{ss} = \frac{k_1 k_2 k_3 - k_{-1} k_{-2} k_{-3}}{k_2 k_3 + k_{-1} k_{-2} + k_{-1} k_3 + k_3 k_1 + k_{-2} k_{-3} + k_{-2} k_1 + k_1 k_2 + k_{-3} k_{-1} + k_{-3} k_2}. \tag{6}$$

We see that the $J^{ss} = 0$ if and only if equation (1) holds true. In fact, it can be rigorously shown that the breakdown of detailed balance is a sufficient and necessary condition of an NESS [17].

2.2. *Energy conservation and the second law*

The loop law in equation (5) is in fact the conservation of energy. To illustrate this, we note that the total Gibbs free energy of the open system, in our case just a single molecule, is

$$G = p_A G_A + p_B G_B + p_C G_C \tag{7}$$

where the state probabilities satisfy kinetic (master) equations [18]

$$\frac{\mathrm{d}p_A}{\mathrm{d}t} = -J_1 + J_3 \tag{8a}$$

$$\frac{\mathrm{d}p_B}{\mathrm{d}t} = -J_2 + J_1 \tag{8b}$$

$$\frac{\mathrm{d}p_C}{\mathrm{d}t} = -J_3 + J_2 \tag{8c}$$

in which

$$J_1 = k_1 p_A - k_{-1} p_B, \qquad J_2 = k_2 p_B - k_{-2} p_C, \qquad J_3 = k_3 p_C - k_{-3} p_A. \tag{9}$$

It is easy to show that

$$\frac{\mathrm{d}G}{\mathrm{d}t} = \{J_1 \Delta G_{AB} + J_2 \Delta G_{BC} + J_3 \Delta G_{CA}\} - J_2 \Delta G_{DE}, \tag{10}$$

in which the term on the left-hand side (lhs) is the rate of increase in energy, and the first term on the rhs is the rate of heat dissipation, and the last term is the power of energy input. This is the conservation of energy [19]. In an NESS, $\frac{\mathrm{d}G}{\mathrm{d}t}$ in equation (10) is zero, and all the Js

become J^{ss} given in equation (6). Hence one obtains the loop law, equation (5), in a steady state. Furthermore, it is easy to see that the heat dissipation rate (hdr)

$$k_B T \left\{ J_1 \ln \frac{k_1 p_A}{k_{-1} p_B} + J_2 \ln \frac{k_2 p_B}{k_{-2} p_C} + J_3 \ln \frac{k_3 p_C}{k_{-3} p_A} \right\} \geqslant 0, \tag{11}$$

where the equality holds true if and only if the steady state fluxes and ΔGs are all zero, i.e., in an equilibrium. In an isothermal NESS, the heat dissipation has to be positive. This is the second law of thermodynamics due to Lord Kelvin: *a transformation whose only final result is to transform into work heat extracted from a source which is at the same temperature throughout is impossible* [20].

2.3. Jarzynski's equality in discrete stoichiometric chemical systems

We have illustrated how the new theory for open biochemical systems encompasses the classic thermodynamics. We now demonstrate the Jarzynski equality, one of the exciting recent developments in statistical physics [21][1].

The Jarzynski equality deals with two equilibrium states of a system connected by a time-dependent, not necessarily slow, process [21, 23]. It shows that certain appropriate exponential averaging of the fluctuating, irreversible work done to the system in the process is precisely the free energy difference between the two end states. This result has been applied to the mechanical extension of single RNA molecules in the laboratory [24]. Discussions here serve as the background for developing more general results in the NESS in the next section.

Let us consider a single molecule, P, with an isomerization reaction between P_1 and P_2 conformers: both can bind a ligand L but with different affinities. Hence, one can shift the equilibrium between P_1 and P_2 by continuously changing the concentration of L, which leads to time-dependent $a(t)$ and $b(t)$ [25]

$$\frac{\mathrm{d}p_1}{\mathrm{d}t} = -a(t)p_1 + b(t)p_2 \tag{12a}$$

$$\frac{\mathrm{d}p_2}{\mathrm{d}t} = a(t)p_1 - b(t)p_2. \tag{12b}$$

We choose the state 1 as the reference state for the energy (figure 2). Then when an L is added to the system, the amount of work done depends on the state of the P: it is zero when P is in state 1 and $k_B T \ln(b(t)/a(t))$ when P is in state 2. Hence the total work done is stochastic

$$W(t) = k_B T \int_0^t \delta_{P(s),2}\, \mathrm{d} \ln \frac{b(s)}{a(s)} \tag{13}$$

and Jarzynski's equality concerns

$$Q(t) = \langle \mathrm{e}^{-W(t)/k_B T} \rangle. \tag{14}$$

To compute the exponential average in equation (14), let us introduce a related quantity

$$Q_i(t|j) = E^j \left[\delta_{P(t),i} \mathrm{e}^{-\int_0^t \mathrm{d}W(s)/k_B T} \right] \tag{15}$$

where $i, j = 1, 2$. Then $Q(t) = Q_1(t|1) + Q_2(t|2)$.

The Q_i in fact satisfies the sink equations with initial conditions $Q_1(0|1) = 1$ and $Q_2(0|2) = \frac{a(0)}{b(0)}$. (This is essentially the discrete analogue of the Feymann–Kac formula [23].)

$$\frac{\mathrm{d}Q_1}{\mathrm{d}t} = -a(t)Q_1 + b(t)Q_2 \tag{16a}$$

$$\frac{\mathrm{d}Q_2}{\mathrm{d}t} = a(t)Q_1 - \left(b(t) + \frac{b'(t)}{b(t)} - \frac{a'(t)}{a(t)} \right) Q_2 \tag{16b}$$

[1] Professor Sunney Xie first pointed out the need for realizing Jarzynski's equality explicitly in discrete stoichiometric chemical systems of single molecules [22]. I thank him for many stimulating discussions on the subject.

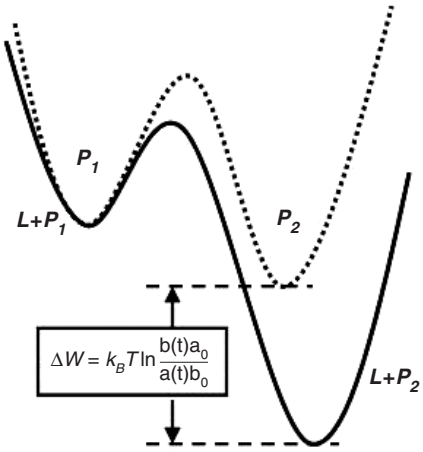

Figure 2. The isomerization reaction between P_1 and P_2 is modulated by the differential binding of P to L. In the absence of L, the energetics is illustrated by the dotted line, with the forward and backward rate constants being a_0 and b_0, respectively. With the presence of L and depending on its concentration, the forward and backward rate constants are $a(t)$ and $b(t)$ (solid line). If one chooses P_1 as the reference state for energy, then the amount of work required to introduce an additional L when P is in state 2 is the ΔW given in the box. Because the system equilibrium shifts with each additional L, the ΔW is greater than the free energy change of the system: $\Delta G = -k_B T \ln \frac{1+a(t)/b(t)}{1+a_0/b_0}$. The Jarzynski equality states, however, that $\Delta G = -k_B T \ln\langle e^{-\Delta W/k_B T}\rangle$.

whose solution is

$$Q_1 = \frac{1}{1+\frac{a(0)}{b(0)}}, \qquad Q_2 = \frac{\frac{a(t)}{b(t)}}{1+\frac{a(0)}{b(0)}}. \tag{17}$$

Hence,

$$Q(t) = \frac{1+\frac{a(t)}{b(t)}}{1+\frac{a(0)}{b(0)}}, \tag{18}$$

and $-k_B T \ln Q(t) = G(t) - G(0)$ where $G(t) = -k_B T \ln(1+\frac{a(t)}{b(t)})$ is the free energy of the isomerization system with P_1 as reference state, as expected.

2.4. Hatano–Sasa's equality and Gallavotti–Cohen symmetry in NESS

Hatano and Sasa [26] have generalized Jarzynski's work to the NESS, which is more relevant to motor proteins. Their result has also been investigated recently in the laboratory [27]. Again, the key quantity is the fluctuating, irreversible work done to the system by an external agent. In the case of figure 1(b), that is directly related to the number of turnovers of the reaction $D \rightleftharpoons E$, $n(t)$: $W(t) = n(t)\Delta G_{DE}$. To characterize the cyclic reaction in figure 1 with both the protein state (i.e., A, B, and C) as well as $n(t)$ which is represented by a random walk [28]

$$\cdots B(n-1) \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} C(n) \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} A(n) \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B(n) \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} C(n+1) \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \cdots$$

The kinetics in terms of a master equation follows

$$\frac{\mathrm{d}P_A(n)}{\mathrm{d}t} = -(k_1 + k_{-3})P_A(n) + k_{-1}P_B(n) + k_3 P_C(n) \tag{19a}$$

$$\frac{\mathrm{d}P_B(n)}{\mathrm{d}t} = k_1 P_A(n) - (k_{-1} + k_2)P_B(n) + k_{-2}P_C(n+1) \tag{19b}$$

$$\frac{\mathrm{d}P_C(n)}{\mathrm{d}t} = k_{-3}P_A(n) + k_2 P_B(n-1) - (k_{-2} + k_3)P_C(n). \tag{19c}$$

To compute the exponential averaging $\langle \mathrm{e}^{-\lambda n(t)}\rangle$, where λ is a parameter, we denote [28]

$$\Psi_X(\lambda, t) = \sum_n \mathrm{e}^{-n\lambda} P_X(n), \tag{20}$$

where $X = A, B, C$; then we have linear equations for Ψs. (This result is essentially the discrete analogue of Cameron–Martin–Girsanov formula, [29].)

$$\frac{\mathrm{d}\Psi_A}{\mathrm{d}t} = -(k_1 + k_{-3})\Psi_A + k_{-1}\Psi_B + k_3\Psi_C \tag{21a}$$

$$\frac{\mathrm{d}\Psi_B}{\mathrm{d}t} = k_1\Psi_A - (k_{-1} + k_2)\Psi_B + k_{-2}\mathrm{e}^{\lambda}\Psi_C \tag{21b}$$

$$\frac{\mathrm{d}\Psi_C}{\mathrm{d}t} = k_{-3}\Psi_A + k_2\mathrm{e}^{-\lambda}\Psi_B - (k_{-2} + k_3)\Psi_C. \tag{21c}$$

We denote the matrix

$$\mathbf{A} = \begin{pmatrix} -k_1 - k_{-3} & k_{-1} & k_3 \\ k_1 & -k_{-1} - k_2 & k_{-2}\mathrm{e}^{\lambda} \\ k_{-3} & k_2\mathrm{e}^{-\lambda} & -k_{-2} - k_3 \end{pmatrix}. \tag{22}$$

It is easy to verify that as a function of λ, the characteristic polynomial for $\mathbf{A}$, $P(\lambda)$, has an interesting symmetry: $P(\lambda) = P(\ln\gamma - \lambda)$. Therefore, the Jarzynski-like quantity (it is exactly the equation (14) when $\lambda = \lambda^* \equiv \Delta G_{ED}/k_\mathrm{B}T$)

$$g(\lambda, t) = -\ln\langle \mathrm{e}^{-\lambda n(t)}\rangle = -\ln\left\{ \begin{pmatrix} 1 & 1 & 1 \end{pmatrix} \mathrm{e}^{\mathbf{A}t} \begin{pmatrix} p_A^{\mathrm{ss}} \\ p_B^{\mathrm{ss}} \\ p_C^{\mathrm{ss}} \end{pmatrix} \right\} \tag{23}$$

satisfies $g(\lambda^* - \lambda, \infty) = g(\lambda, \infty)$ in the limit of $t \to \infty$. This is known as Gallavotti–Cohen symmetry for stochastic systems [29]. Consequently, $g(\lambda^*, \infty) = 0$, which is what has been obtained in [26] and [28][2].

3. Chemical model of single motor proteins

When the kinetic cycle in figure 1 is coupled to the translocation of a single protein molecule along a periodic molecular track, we obtain a simple conceptual model for motor proteins [30, 31] by identifying $A = M\cdot\mathrm{ADP}\cdot Pi$, $B = M\cdot\mathrm{ADP}$, and $C = M\cdot\mathrm{ATP}$, where M represents the motor protein. Let us assume that the protein conformational transition $A \rightleftharpoons B$ is tightly coupled to its stepping along the linear track. Then the rate constants are given by $k_1 = k_1^0\mathrm{e}^{-Fd_1/k_\mathrm{B}T}$ and $k_{-1} = k_{-1}^0\mathrm{e}^{Fd_2/k_\mathrm{B}T}$, where $d_1 + d_2 = d$ is the size of a single motor step and F is the external force against which the motor protein moves [32, 33]. Substituting the $k_{\pm 1}$ into equation (6), we have the steady state motor protein velocity as a function of resistant force F. In particular, we have the specific force at which the motor stops, F^*, known as the isometric stall force

$$F^* = \frac{k_\mathrm{B}T}{d}\ln\gamma. \tag{24}$$

[2] Several relevant papers appeared after the completion of the present review; see [100–103]. In particular [101], showed that an entropy balance equation, similar to our equation (10), is not just valid on average, it is valid for each stochastic trajectory.

The chemical model with N states has been extensively studied by Fisher and Kolomeisky [32, 33], and this approach has been applied to fitting experimental data from kinesin [34] and myosin [35] with success. Discrete chemical models have also been developed recently [36, 37] for helicase, which unwinds the DNA double helix [38].

Applying the NESS thermodynamics to a chemical model yields a clear picture and rigorous definition for the motor efficiency [31]. Taking the above three-state model as an example, we have the heat dissipation per cycle

$$k_{\mathrm{B}}T \ln \frac{k_1^0 k_2^0 k_3 [\mathrm{ATP}] \mathrm{e}^{-Fd/k_{\mathrm{B}}T}}{k_{-1}^0 k_{-2}^0 k_{-3} [\mathrm{ADP}]} = k_{\mathrm{B}}T \ln \gamma - Fd. \tag{25}$$

The first term on the rhs is the chemical energy input due to ATP hydrolysis, and the second term is the work done by the motor against external force. For a tightly coupled motor, this is a trivial result. However, if a motor contains futile cycles, then an analysis such as illustrated above will yield an unambiguous result on efficiency [39].

4. Brownian ratchet model of single motor proteins

The idea of a 'fluctuating ratchet' has a long history with independent developments from many groups at different times. Oosawa, who has long been interested in actin and muscle contraction, used a switching Brownian motion model for directed movements of biological organisms with internal states [40, 41]. But in the early days heterogeneous temperature always played a role in ratchet models [42] due to the lasting influence of Feymann's thermal ratchet. Directed movements in membrane transporters caused by random field fluctuations were extensively studied in the late 1980s [43], and its nonequilibrium nature was analysed in terms of cycle kinetics by Chen [44]. This body of research was summarized in [45, 46]. Between 1992 and 1994, there were several groups studying isothermal, Brownian ratchet models [47–52]. Some were motivated by the fluctuating barrier problem which exhibits noise-induced transport with the breakdown of detailed balance. Others were motivated by studying forces generated during actin polymerization. Still others were interested in how nonequilibrium fluctuations can be used for molecular separation. By 1997, several comprehensive reviews were published [53, 54]. Several recent reviews are [55–58].

In the Brownian ratchet model for single motor proteins, one considers the position (say, the centre of mass) of a motor along its linear track, x, and its internal conformational state n. The protein can change its conformation with a given x, as well as move along the track with a given n. Hence for the single molecule, the probability of it being at x and in state n, $P(x, n)$, satisfies

$$\begin{aligned} \partial_t P(x,n,t) = D \left\{ \partial_{xx}^2 P(x,n,t) + \frac{1}{k_{\mathrm{B}}T} \partial_x \left(P(x,n,t) \partial_x U(x,n) \right) \right\} \\ + \sum_m \left\{ q_{nm}(x) P(x,n,t) - q_{mn}(x) P(x,m,t) \right\}, \end{aligned} \tag{26}$$

where D is the diffusion constant for the motor, and $-\partial_x U(x, n)$ is the force parallel to the track exerted on the motor by the track, when the motor is at position x and in state n. $q_{mn}(x)$ is the unimolecular rate constant for transition from state n to m, which depends on where the motor is on the track. $U(x, n)$ and $q_{mn}(x)$ are periodic functions of x due to the periodic nature of the track. An NESS thermodynamic analysis of this model based on cycle kinetics can be found in [59].

As a model for single motor proteins, one of the significant results occurs when a large number of identical motors are chained through a rigid rod [54]. The movement of the rod will

follow the original Huxley equation for sliding filaments [9]; the diffusion term diminishes and a sliding velocity emerges:

$$\partial_t u(z,n,t) = V(t)\partial_z u(z,n,t) + \sum_m \{q_{nm}(z)u(z,n,t) - q_{mn}u(z,m,t)\} \quad (27)$$

where $0 \leqslant z \leqslant L$, L being the period of the motor track. $u(z,n)$ is the density of the motors in the rigid chain at position z and in state n, and

$$V(t) = \frac{1}{\eta}\sum_m \int_0^L u(z,m,t)\frac{\partial U(z,m)}{\partial z}\,\mathrm{d}z \quad (28)$$

where the frictional coefficient $\eta = k_\mathrm{B}T/D$. In the original Huxley theory, $V(t)$ and $u(z,n,t)$ have to be solved simultaneously from the nonlinear equations (27) and (28) [60].

The Brownian ratchet approach has been extensively developed by Oster and his co-workers into a successful model for an F_1 ATPase rotor [61].

One observation from the mathematical study of ratchet models of motor proteins is that it is rather easy to make a non-motor protein move. We shall make a concrete theoretical prediction here. Make a two-dimensional asymmetric, periodic molecular surface. Choose a protein with certain nonspecific affinity with the surface. Let the protein have a natural enzymatic activity, say for biochemical reaction $S \rightleftharpoons P$. Then the protein is likely to have a biased movement on the surface in an aqueous solution with very high S concentration and low P concentration ($[P]/[S] \ll$ the equilibrium constant). The velocity and efficiency of 'the motor' are more difficult to predict.

5. The x–y formalism of single motor proteins

The basic assumption in the chemical models is that the physical movement of a molecular motor, i.e. its centre of mass, is always coupled to chemical state transitions of Arrhenius type. In the work of Fisher and Kolomeisky, and Qian [30–35, 59], it is further assumed that a complete hydrolysis cycle is tightly coupled to the motor stepping along its track. This leads to the impossibility of a futile cycle. The maximal efficiency is when the motor is stalled. While there is no heat dissipation, there is also no movement [31]. This is a very singular situation.

The Brownian ratchet model, on the other hand, assumes that chemical transitions are decoupled from motor movements. There is no simultaneous, concerted motion between the chemical transition and centre-of-mass translocation [62]. This is in stark contrast to the popular idea of a 'power stroke'. Both the chemical model and the ratchet model are special situations of a more complete theoretical framework which we shall call the **x–y model**, following [51]. In the x–y model, the x-coordinate represents the centre of the mass of a motor and the high-dimensional y-coordinate represents the conformational space of the motor [51, 63, 64]. Both x and y are conceptually continuous, but they can be discrete [65, 66].

There is an energy landscape, $E(x, y)$ on the xy space [39]. It is periodic in the x-direction $E(x + L, y) = E(x, y)$ where L is the period of the motor track. There is a non-zero flux in the y-direction brought about by the appropriate boundary conditions in y: at one end, say $y = 1$, there is ATP and at another end ($y = 0$) there is ADP. At both locations exchange free nucleotides with solution occur. The non-zero phosphorylation potential in the solution dictates that $G_1 = -\ln \int \mathrm{e}^{-E(x,1)/k_\mathrm{B}T}\,\mathrm{d}x > G_0 = -\ln \int \mathrm{e}^{-E(x,0)/k_\mathrm{B}T}\,\mathrm{d}x$ [39]. In an NESS, the total amount of energy input to a motor is simply $(G_0 - G_1)$ times the boundary flux. A non-trivial mathematical result is that the flux in y induces a flux in x. Ultimately, to show the power stroke mechanism is to characterize this energy landscape and to demonstrate a dominant pathway in the 'diagonal direction'.

If one simplifies the hydrolysis kinetics into a simple kinetic cycle as in figure 1(a) without detailed balance, then the y-direction is also a cycle, while the x-direction is periodic. Hence, an abstract, but appropriate and elegant, mathematical representation for the xy space is a torus on which the breakdown of detailed balance in y induces cycle kinetics in x. This viewpoint was explored in [63].

Applying the NESS thermodynamics to the general x–y model, we were able to identify an important difference in motor efficiencies based on a motor working against an elastic force or a viscous drag force [39]. It turns out that these two different types of experiments are represented by significantly different mathematical terms in the theory. The former enters the drift term while the latter enters the diffusion coefficient of the Fokker–Planck equation. This insight might also have relevance to the chemical model; the elastic force enters the activation energy of a rate constant while viscous drag enters its prefactor.

6. Open system NESS on an energy landscape

We do not see the theory for motor proteins as the completion of motor protein research, rather as the beginning, the 'hydrogen atom', of the coming nonequilibrium physics of living matters in open systems.

There is a close analogy between the x–y, energy-landscape formalism of the motor protein and an electrical network. The energy landscape itself is equivalent to a linear resistance network. We emphasize that any open system has a closed system counterpart and it is important to identify the latter as a reference for the former. The open system NESS is sustained by the energy input at the boundary of the landscape, just as batteries for an electrical network. Each internal chemical reaction dissipates heat similar to a resistor. The well-known 'current $\times$ voltage = power' becomes the heat dissipation rate in equation (11)

$$(J_+ - J_-)\, k_{\mathrm{B}} T \ln\left(\frac{J_+}{J_-}\right) \tag{29}$$

where J_+ and J_- are the fluxes of the forward and backward reactions, and $k_{\mathrm{B}} T \ln(J_+/J_-) = \Delta\mu$ is the chemical potential difference of the reaction [67]. In an NESS, the total amount of energy input is simply the μJ integrated over the entire boundary [39].

As we have stated, the point of departure for our present analysis of motor proteins is the breakdown of detailed balance. Detailed balance provides certain mathematical symmetry in the theory of equilibrium statistical mechanics, as well as the Hermiticity in the quantum many-body problem [68]. Mathematically, this symmetry is equivalent to a potential condition [69, 70], which makes the steady state locally determined via Boltzmann's formula. The non-zero flux boundary conditions make the problem non-Hermitian [68] and non-local. Complex eigenvalues then are possible and oscillatory kinetics appear; these are distinct characteristics of open systems [71–73]. Another intimately related phenomenon is the stochastic resonance [74–76].

This analogy can be carried further to nonlinear biochemical reaction networks in which boundary fluxes are responsible for their NESS, and it can have no internal kinetic cycles [19, 77]. The chemical kinetics can be described in terms of an irreversible Markov processes [70]. In small systems, chemical oscillations with stochasticity exhibit rotational Brownian motions in concentrations [78]. Increasing the system size reduces the stochasticity while accentuating temporal oscillations.

7. Beyond motor proteins: living matter physics

The thermodynamic theory of the open system NESS presented here provides a unique opportunity for us to revisit the validity of many previous theories, developed by the

Brussels school [6, 79], by Graham and Haken [80], and more recently the theory of self-organized criticality (SOC) [81], to name only a few. Much work needs to be developed in the theoretical front and applications to biological systems are wide open [82, 83]. Lately, Rubí and his colleagues, carrying on the tradition of de Groot and Mazur [84, 85], have developed a mesoscopic nonequilibrium thermodynamic approach [86] which yields a stochastic description for open systems precisely in terms of Fokker–Planck equation (i.e., equation (26)) [87]. This theory has been applied to biological membrane transporters [88]. Using a recently developed stochastic theory of dissipative dynamics [89], Ao and his colleagues have studied the stability of lambda phage with success [90].

The theory of the open system NESS can be formulated either in terms of Hamiltonian systems [91] or boundary-driven stochastic systems [92]. The former, which follows the tradition of Boltzmann's microcanonical ensemble, has been an active area of mathematical physics [93] with applications to complex fluids [94]. As in equilibrium statistical mechanics, where the Gibbsian canonical and grand canonical approaches are more appropriate for studying biochemical systems in isothermal aqueous solutions, the latter stochastic approach to the NESS offers a powerful modelling tool with greater appeal. The stochastic approach is not inferior, but complementary, to the Hamiltonian system approach to the NESS. A rigorous mathematical relation between these two approaches, in the spirit of Khinchin [95], remains to be established [70]. It is worth pointing out that the self-organization in SOC implies a globally attractive, initial-state independent, NESS [96, 97]. Stochastic models has been suggested for SOC [98]. The relation between the avalanches in SOC and the non-local kinetic cycles in stochastic models [99], if any, remains to be explored.

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