Review article

The mathematical theory of molecular motor movement and chemomechanical energy transduction

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The mathematical formulation of the model for molecular movement of single motor proteins driven by cyclic biochemical reactions in an aqueous environment leads to a drifted Brownian motion characterized by coupled diffusion equations. In this article, we introduce the basic notion for the continuous model and review some asymptotic solutions for the problem. (For the lattice model see [17,47].) Stochastic, non-equilibrium thermodynamic interpretations of the mathematical equations and their solutions are presented. Some relevant mathematics, mainly in the field of stochastic processes, are discussed.

KEY WORDS: augmented Huxley equation, probability circulation, entropy production, macromolecular mechanics, Markov process, nano-biochemistry, nonequilibrium steady-state, protein, singular perturbation, turning point

1. Introduction

One of the fascinating aspects of protein molecules in the biological world is their ability to perform various, almost "magic-like" tasks [16]. A particular class of proteins known as molecular motors can move linearly along its designated track against an external force by utilizing the biochemical energy source, adenosine triphosphate (ATP). In this manner, the motor proteins act as miniature engines converting chemical energy to mechanical work. Movement of single protein molecules inside a cell, however, has to experience thermal agitation from the aqueous environment in the cytosol. The movement is, therefore, a Brownian motion with drift (convective diffusion) [6].

Such movement provides the molecular basis for muscle contraction and various cellular transport processes [24,25]. Motor protein kinesis is known to carry out intracellular vesicle transport along microtubules. Various polymerases are moving along their corresponding templates. All these processes are essential to a living cell. In a muscle cell, the motor protein is called myosin, and its designated track is called an actin filament. The actin filament has a periodic structure of ~ 36 nm. Therefore, without loss of generality, we assume that a myosin molecule moves in a force field with periodic potential energy function $U(x)$: $U(x + L) = U(x)$, where L is 36 nm for actin.

Treating the center of mass of the motor protein as a Brownian motion with the presence of a periodic energy potential, its movement can be modeled by the Smoluchowski equation [62]

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial}{\partial x} J(x,t) = D \frac{\partial^2 P(x,t)}{\partial x^2} - \frac{\partial}{\partial x}\left(\frac{F(x)}{\beta} P(x,t)\right), \qquad (1)$$

where D and β are respectively the diffusion and frictional coefficients. $F(x) = -\mathrm{d}U(x)/\mathrm{d}x$ is the force of the potential U, representing the molecular interaction between the motor protein and its track. $P(x,t)$ is the probability density function of the motor protein at position x for time t. The first equality in equation (1) is a continuity equation in which J is a probability flux. The first term on the right-hand side is associated with the diffusion flux according to Fick's law. The second term is due to the convection associated with an overdamped Newtonian motion: $-\beta\dot{x} + F(x) = 0$. In fact, equation (1) is mathematically equivalent to an overdamped Newtonian motion with a white random force $f(t)$ representing the incessant collisions between the motor protein and the water molecules: $\beta\dot{x} - F(x) = f(t)$ [62].

The probability density $P(x,t)$, as the solution to equation (1), gives the mean position of the motor

$$\langle x \rangle(t) = \int_{-\infty}^{\infty} x P(x,t)\,\mathrm{d}x. \qquad (2)$$

Moreover, its velocity is related to the flux $J(x,t)$:

$$\frac{\mathrm{d}}{\mathrm{d}t}\langle x \rangle(t) = \int_{-\infty}^{\infty} x \frac{\partial P(x,t)}{\partial t}\,\mathrm{d}x = -\int_{-\infty}^{\infty} x \frac{\partial J(x,t)}{\partial x}\,\mathrm{d}x = \int_{-\infty}^{\infty} J(x,t)\,\mathrm{d}x. \qquad (3)$$

When the motion of a motor protein becomes steady and if we are only interested in the mean velocity, we need only consider the steady-state solution for $x \in [0, L]$ with periodic boundary conditions. With this setting, the steady-state velocity of the motor protein movement is $v = LJ$. Therefore studies on the steady-state movement focus on the flux J. To fix our terminology, we will refer a stationary solution as a steady-state, but a stationary solution with zero flux as an equilibrium.

A little mathematical analysis immediately shows that for $U(0) = U(L)$, i.e. $\int_0^L F(x)\,\mathrm{d}x = 0$, the stationary solution of (1) allows only zero flux ($J = 0$). *Therefore, in a one-dimensional periodic structure, there is no driving force to bias an inert Brownian particle to move in either direction.* The simple model given by (1) fails to capture the essence of the motor protein movement.

The driving force for a motor protein comes from a very important biochemical reaction, occurring inside the protein, called ATP hydrolysis:

$$\mathrm{ATP} + \mathrm{H_2O} \underset{g}{\overset{f}{\rightleftharpoons}} \mathrm{ADP} + \mathrm{Pi},$$
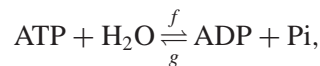
where H_2O is water, ADP is adenosine diphosphate, and Pi is phosphate. Chemical reactions like this are well characterized by a two-state Markov process (or more generally, m discrete states)

$$\frac{dP_{ATP}}{dt} = -f\,P_{ATP} + g\,P_{ADP},$$
$$\frac{dP_{ADP}}{dt} = f\,P_{ATP} - g\,P_{ADP}, \tag{4}$$

where non-negative f and g are rate constants for the reaction [35]. The deeply insightful work of Sir Andrew Huxley in 1957 was to introduce internal conformational states to the Brownian particle and to couple the (bio)chemical reaction in (4) with the motor protein movement in (1) [25]. This leads to the following equation [3,26,42,46], known as a coupled diffusion system in mathematics [53], for the movement of a Brownian particle with internal structures and dynamics:

$$\frac{\partial P(x,-)}{\partial t} = D_- \frac{\partial^2 P(x,-)}{\partial x^2} + \frac{1}{\beta_-} \frac{\partial}{\partial x}\left(\frac{dU_-}{dx}\,P(x,-)\right) - f(x)P(x,-)$$
$$+ g(x)P(x,+),$$
$$\frac{\partial P(x,+)}{\partial t} = D_+ \frac{\partial^2 P(x,+)}{\partial x^2} + \frac{1}{\beta_+} \frac{\partial}{\partial x}\left(\frac{dU_+}{dx}\,P(x,+)\right) + f(x)P(x,-)$$
$$- g(x)P(x,+), \tag{5}$$

where $f(x)$ and $g(x)$ are non-negative periodic functions. In terms of this augmented Huxley model, the motor protein can be either attached to $(+)$ or detached from $(-)$ the actin filament with respective interaction energy functions $\overline{U}_+(x)$ and $\overline{U}_-(x)$. (In the original Huxley model, $U_-(x) = 0$.) $D_\pm$ $(\beta_\pm)$ are the diffusion (friction) coefficients of the motor protein in the attached and detached states, respectively. The attach–detach transition is coupled to the ATP hydrolysis. Therefore, in (5) the biochemical reaction is coupled to the movement of the motor protein. More importantly, note that in either the attached or detached state, there is no bias for the motor protein movement! *However, the attach–detach transition driven by the ATP hydrolysis leads to a biased motion of the motor protein ($J \neq 0$). The chemical energy in ATP is converted to the mechanical motion of the motor protein.* This we shall show.

At this point, it is fascinating to read the now classic work of Huxley on the theory of muscle contraction, which was written decades before the discovery of the motor protein molecule in its individual form. The Huxley model works as follows [25, p. 281]. Initially, the myosin (M) and actin filament (A) are detached; M oscillates (fluctuates) back and forth about its equilibrium position O as a result of thermal agitation (with diffusion coefficient D_- for the Brownian motion). If A happens to be within the range of positions where f, the rate of association, is not zero, there is a chance that combination will take place (this event happens with a probability characterized by the Markov rate process); when this has happened the tension in the elastic element (F, i.e. the molecular interaction between M and A) will be exerted on the actin thread by M (and, conversely,

the actin will exert the same force with opposite sign on M). As one can see, equation (5) is the mathematical formulation of this model described in words. Readers who check Huxley's paper will find several differences between his original equation and (5). These differences arise because we have formulated a *microscopic* model for single motor proteins while a model for muscle contraction has to deal with a large number of myosin molecules. It can be shown that when stringing many motor proteins into a rigid chain, Huxley's original equation can be derived from equation (5) [26].

Since the work of Huxley, there have been many investigations following and expanding the basic notion of the Huxley equation. Most notable are the work of Hill [22,23] who provided the Huxley equation with a sound thermodynamic basis, and the work of Astumian and Bier, and Peskin et al. who arrived at (5) from the Langevin dynamics (stochastic differential equation) point of view [2,42]. There is also a body of literature on Brownian ratchet, whose basic movement is characterized by equations identical to (5) [1,7,11,43,63].[1] In a recent paper, Bentil [5] applied the Huxley model in conjunction with Langevin dynamics to simulate single myosin experiments. Qian [46,48,51] established a relationship between coupled diffusion like (5) and the circulation of a Markov process and its entropy production [27].

Equation (5) is certainly an oversimplified model for any realistic biological system. However, it captures the essence of a theory which unifies microscopic motor protein movement and macroscopic muscle contraction; thereby it provides a concrete model for chemomechanical energy transduction in living organism. Hence, it deserves further detailed investigation as a topic in biophysics and physical chemistry. The mathematical treatment of (5) has been mainly in terms of differential equations. However, the nature of Brownian motion of the motor protein also calls for a treatment of (5) in terms of stochastic processes. We will review some of the pertinent mathematics in section 4.

2. Mathematical analysis of several limiting cases of augmented Huxley equation

While the augmented Huxley equation (5) is difficult to solve in general due to the non-local (non-equilibrium) nature of the steady-state, particular limiting cases can be analyzed to gain insights into the theoretical model. In this section, we present some known and also some new results.

2.1. Limit of rapid biochemical cycling

One particularly interesting limiting case is when the biochemical reactions are rapid with respect to the diffusion. Analysis of this limiting case clearly demonstrates how the internal biochemical reaction can give rise to a unidirectional motor protein

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[1] It is important here to qualify the term "Brownian ratchet" which does not involve any temperature gradient [43]. It is an isothermal device in which useful work is derived from nonequilibrium fluctuations. It violates the detailed balance due to active pumping [45,46].

movement. Hence, it demonstrates the validity of mathematical models for motor proteins in terms of coupled diffusion equations.

Consider equation (5), rapid biochemical reaction means we have conditional probabilities[2]

$$P(-|x) = \frac{g(x)}{f(x) + g(x)}, \qquad P(+|x) = \frac{f(x)}{f(x) + g(x)}$$

and thus $P(x) = P(x, -) + P(x, +)$ satisfies

$$\frac{\partial P(x)}{\partial t} = \frac{\partial^2}{\partial x^2}\big(\overline{D}(x)P(x, t)\big) - \frac{\partial}{\partial x}\big(\overline{F}(x)P(x)\big) \tag{6}$$

in which

$$\overline{D}(x) = \frac{f(x)D_+ + g(x)D_-}{f(x) + g(x)}, \qquad \overline{F}(x) = \frac{f(x)F_+(x) + g(x)F_-(x)}{f(x) + g(x)}.$$

Note that equation (6) is similar to equation (1) but with one crucial difference: The mean force function now satisfies $\int_0^L \overline{F}(x) \neq 0$ even though both $F_\pm(x)$ satisfy $\int_0^L F_\pm(x)\,dx = 0$. *The potential of the average of forces of periodic potentials is in general not periodic.* This indicates that *the biochemical reaction* (4) *provides a drift for the motor protein movement in a periodic system.* Finally, the transport flux can be obtained by solving (6)

$$\Phi = \frac{1 - e^{u(L)}}{\int_0^L e^{-u(x)}\,dx \int_0^L e^{u(x)}\,dx - (1 - e^{u(L)})\int_0^L e^{-u(x)}\,dx \int_0^x e^{u(x')}\,dx'}, \tag{7}$$

where $u(x) = -\int_0^x \overline{F}(x)\,dx$. Therefore, if $\int_0^L \overline{F}(x)\,dx = -u(L) > 0$, $\Phi > 0$. More recent progress can be found in [31].

2.2. Limit of rapid diffusion

Another limiting case which has been nicely analyzed by Peskin et al. [42] is when the diffusion is very rapid in comparison to the Markovian transition (Brownian ratchet): there are rapid equilibria for $P(x, -)$ and $P(x, +)$.

The mathematical problem is framed as follows. Let us consider the stationary coupled diffusion:

$$\frac{d^2 P(x, -)}{dx^2} + \frac{d}{dx}\left(\frac{dU_-(x)}{dx}P(x, -)\right) - \varepsilon\big(f(x)P(x, -) - g(x)P(x, +)\big) = 0,$$
$$\frac{d^2 P(x, +)}{dx^2} + \frac{d}{dx}\left(\frac{dU_+(x)}{dx}P(x, +)\right) + \varepsilon\big(f(x)P(x, -) - g(x)P(x, +)\big) = 0, \tag{8}$$

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[2] Readers who are familiar with the method of singular perturbation will identify this problem. Since we are seeking a nontrivial solution for a homogeneous equation, the solution is not unique. The functions $F_\pm$ has at least two zeros at which boundary layers might be expected. For more detail on this type of equations, see [39].

where $f(x)$, $g(x)$, $U_\pm(x)$ are periodic functions. When the regular perturbation parameter $\varepsilon = 0$, this system of uncoupled diffusion has zero transport flux Φ. For small ε, we therefore have $\Phi = \varepsilon\phi + \cdots$ and the asymptotics can be obtained by the method of regular perturbation [4]. At this point it is important to notice the other flux, the circular flux Π which moves the motor protein forward in the $(+)$-state but moves it backward in the $(-)$-state. Therefore Π does not contribute to the net transport but only generates heat. This type of flux is known as futile cycle in muscle biochemistry [45].

Perturbation calculations show that [42]

$$\Pi = \varepsilon \frac{\int_0^L g(x)\mu_+(x)\,dx \int_0^L f(x)\mu_-(x)\,dx}{\int_0^L g(x)\mu_+(x)\,dx + \int_0^L f(x)\mu_-(x)\,dx} + O(\varepsilon^2), \tag{9}$$

and

$$\Phi = \varepsilon \int_0^L dx\left[v_+(x) - v_-(x)\right] \int_0^x dx'\left[f(x')\mu_-(x') - g(x')\mu_+(x')\right] + O(\varepsilon^2), \tag{10}$$

where

$$\mu_- = \frac{e^{-U_-(x)}}{\int_0^L e^{-U_-(x)}\,dx}, \qquad \mu_+ = \frac{e^{-U_+(x)}}{\int_0^L e^{-U_+(x)}\,dx},$$

$$v_- = \frac{e^{U_-(x)}}{\int_0^L e^{U_-(x)}\,dx}, \qquad v_+ = \frac{e^{U_+(x)}}{\int_0^L e^{U_+(x)}\,dx}.$$

It is interesting to note that if $f(x)\mu_-(x) - g(x)\mu_+(x) = 0\ \forall x$, then the system is reversible and the steady-state is in fact an (thermal) equilibrium. In mathematical term, the Markov process is symmetric [61]. In applied mathematics, the symmetricity leads to the Grassman–Matkowsky variational method [30]. More recent progress can be found in [31].

2.3. Limit of the original Huxley model

In the original Huxley model, the interaction between the track and the motor in the detached state is assumed to be zero. Hence $U_-(x) = 0$ in equation (5). Furthermore, it is also generally accepted that $D_+ \ll D_-$, i.e. the Brownian motion of the motor protein in the attached state is negligible. The solution of (5) when $D_+ \to 0$ is a problem of singular perturbations [30,36]. Note that because of the periodic $U(x)$, $F(x)$ has zeros on $[0, L]$. Thus the singular perturbation problem has at least two linear turning points [28,38]. The reduced equation when $D_+ = 0$ is:

$$\frac{d^2 P(x, -)}{dx^2} - f(x)P(x, -) + g(x)P(x, +) = 0,$$

$$-\frac{d}{dx}\left(F(x)P(x, +)\right) + f(x)P(x, -) - g(x)P(x, +) = 0, \tag{11}$$

in which we have set $D_- = \beta_+ = 1$ for simplicity. We are particularly interested in finding a condition for the existence of a solution corresponding to unidirectional motion. In the steady-state, the *total transport* flux of the system is a constant[3]:

$$F(x)P(x, +) - \frac{dP(x, -)}{dx} \equiv \Phi. \tag{12}$$

Using equation (12) and eliminating $P(x, +)$ from equation (11) we then have

$$F(x)\frac{d^2 P(x, -)}{dx^2} + g(x)\frac{dP(x, -)}{dx} - F(x)f(x)P(x, -) = -\Phi g(x), \tag{13}$$

where the inhomogeneous term Φ on the right-hand side is to be determined by the normalization condition $\int_0^L [P(x, +) + P(x, -)]\,dx = 1$. The boundary conditions for equation (13) again are periodic.

Equation (13) has singular points at the zeros of $F(x)$. A simple local analysis shows that for nonzero Φ and a physically meaningful $P(x, -) \geqslant 0$, the solution to equation (13) has to be non-analytic at these singularities. This non-analytic behavior, however, is expected to be obviated in an asymptotic study of the full equation (5) with small D_+.

3. Entropy production in nonequilibrium steady-state

We now give a brief discussion of the nonequilibrium thermodynamics in terms of equation (5). Hill [22,23] has given an extensive account of this subject. We only discuss some recent developments in connection with the notion of entropy production [40]. The concept of entropy production rate (e.p.r.) can be easily introduced, mathematically, in terms of equation (1). The validity of this novel thermodynamics of nonequilibrium steady state (NESS), however, remains to be experimentally tested. For more discussion see [46,48,52,55].

Associated with (1) is a functional $A[P(x)]$ called the Helmholtz free energy in thermal physics [57], which in units $k_B T$ (T is temperature and k_B is the Boltzmann constant) is defined as

$$A\big[P(x, t)\big] = \int_0^L U(x)P(x, t)\,dx + \int_0^L P(x, t)\log P(x, t)\,dx. \tag{14}$$

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[3] We use Φ to denote the transport flux $J_+ + J_-$. As will be shown below there is another type of flux, circular and non-transport $\Pi = J_+ - J_-$, in these systems [46].

When $P(x, t)$ changes with time according to equation (1), the rate of production of total entropy is the rate of decrease in A of the system[4], which can be computed:

$$
\begin{aligned}
\text{e.p.r.} = -\frac{\mathrm{d}A}{\mathrm{d}t} &= -\int_0^L U(x)\frac{\mathrm{d}P(x)}{\mathrm{d}t}\,\mathrm{d}x - \int_0^L \frac{\mathrm{d}P(x)}{\mathrm{d}t}\log P(x)\,\mathrm{d}x \\
&= \int_0^L \big(U(x) + \log P(x)\big)\frac{\mathrm{d}}{\mathrm{d}x}\,J(x)\,\mathrm{d}x \\
&= \int_0^L \left(F(x) - \frac{\mathrm{d}}{\mathrm{d}x}\log P(x)\right)J(x)\,\mathrm{d}x \\
&= \frac{1}{D}\int_0^L J^2(x)P^{-1}(x)\,\mathrm{d}x \geqslant 0.
\end{aligned}
\tag{15}
$$

The last step used the definition for J given in equation (1). This is the second-law of thermodynamics in terms of Smoluchowski equation, which is the nonequilibrium counterpart of a canonical ensemble in statistical mechanics. Equation (15) can be generalized to calculating the entropy production rate (e.p.r.), as well as the heat dissipation rate, in a non-equilibrium steady-state in which S_{tot} continues to increase [50]. To see this, we note that the entropy of the system is defined as

$$
S[P(x, t)] = -\int_0^L P(x, t)\log P(x, t)\,\mathrm{d}x.
\tag{16}
$$

Therefore, in NESS,

$$
\dot{S} = -\int_0^L FJ\,\mathrm{d}x + \text{e.p.r.} = 0,
\tag{17}
$$

where $F = -\mathrm{d}U/\mathrm{d}x$, and the first term on the right-hand side is the heat dissipation rate (h.d.r.). Therefore, in a NESS, the e.p.r. is equal to the h.d.r.

Recent work in mathematical physics on entropy production in nonequilibrium systems [19] also focus on appropriately setting up the non-equilibrium steady-state with an external force and a thermostat simultaneously acting on a Hamiltonian system. The force supplies energy while the thermostat removes heat in order to keep the system in a steady-state with bounded energy. This leads to a *random dynamical system* in which entropy production is cogently defined [59]. The Smoluchowski approach we adopt has a quite similar setting: a driving force due to chemical reaction (rather than mechanical force) and an implicit thermostat: The Smoluchowski equation is a consequence

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[4] From thermodynamics stand point, a macromolecule is an isothermal system in contact with a thermal environment (i.e. aqueous solution) with temperature T. There is energy (heat), but no material, exchange between the system and its environment (heat bath). The system and its environment as a whole is an isolated system with a constant total energy; and this is approximately hold also for a sufficiently large heat bath. In mathematical terms, we have $\mathrm{d}A/\mathrm{d}t = \mathrm{d}E/\mathrm{d}t - T\,\mathrm{d}S/\mathrm{d}t$ where E is the internal energy of the system and S is the entropy of a system. With respect to the system and the environment together as a whole $\mathrm{d}A = (\mathrm{d}E_{\text{tot}} - \mathrm{d}E_{\text{env}}) - T(\mathrm{d}S_{\text{tot}} - \mathrm{d}S_{\text{env}}) = -T\,\mathrm{d}S_{\text{tot}} + (T\,\mathrm{d}S_{\text{env}} - \mathrm{d}E_{\text{env}}) \approx -T\,\mathrm{d}S_{\text{tot}}$. For an isolated system (microcanonical ensemble), $\partial E_{\text{env}}/\partial S_{\text{env}} = T$ [57].

of an overdamped Newtonian system with Maxwellian distribution for the velocity of the particles [62]. In fact, the diffusion coefficient D and frictional coefficient β in (1) define the temperature of the thermostat: $T = \beta D / k_B$. The interesting mathematical questions are when these random dynamical systems become diffusion processes and whether the entropy production proposed in these studies is equivalent to equation (15) for diffusion processes [52]. The recent work by Lebowitz and Spohn [32] has provided some insights on this problem. In a different approach to weak random perturbation of Hamiltonian systems in a plane, Freidlin and Wentzell map the system to a diffusion process on a graph, which consists of vertices corresponding to the stationary states and edges corresponding to energy basins [18]. However, this approach remains to be generalized to higher-dimensional Hamiltonian systems, and its relationship to the (Kramers') transition-state rate theory in theoretical chemistry [21] also remains to be elucidated.

It is interesting to note that in a steady state, the flux J is a constant and all the entropy produced will become the dissipated heat. Hence, e.p.r. $= (J^2/D) \int_0^L P^{-1}(x)\, dx \geqslant J^2 L^2 / D$ which equals $\beta J^2 L^2$ due to the Einstein relation in $k_B T$ units $D\beta = 1$. The $\beta J^2 L^2$ term is the energy dissipation due to a deterministic motion with velocity $v = LJ$ and frictional coefficient β in continuous medium. The inequality indicates the additional dissipation due to random motion. It also indicates that when $P(x) = \text{const}$, the e.p.r. is at its minimum, i.e., the chemomechanical energy transduction is at its maximal efficiency.

To generalize the concept of entropy production to equation (5) is mathematically straightforward. This yields a novel thermodynamic theory for NESS, which is particularly relevant to motor proteins. The importance of the theory is that it relates e.p.r. to the heat production of a working motor, which is a quantity that can be experimentally measured. With some simple algebra, we have

$$\text{h.d.r.} = \int_0^L \left[F_+(x) J_+(x) + F_-(x) J_-(x) + j(x) \log\left(\frac{f(x)}{g(x)} \right) \right] dx, \tag{18}$$

$$\text{e.p.r.} = \int_0^L \left[J_+^2(x) P(x, +) + J_-^2(x) P(x, -) + j(x) \log\left(\frac{f(x) P(x, -)}{g(x) P(x, +)} \right) \right] dx, \tag{19}$$

in which

$$J_\pm(x) = -\frac{dP(x, \pm)}{dx} + F_\pm(x) P(x, \pm),$$

and

$$j(x) = f(x) P(x, -) - g(x) P(x, +).$$

It is obvious that e.p.r. is non-negative and equal to zero if and only if the detailed balance is hold [26,51]. In NESS without external load, h.d.r. = e.p.r.

If there is an external load F_{ext}, then equation (18) can be further broken down into

$$k_B T \ln\left(\frac{[\text{ATP}]}{[\text{ADP}][\text{Pi}]} e^{\Delta G^0_{\text{ATP}}} \right) \int_0^L j(x)\, dx - F_{\text{ext}}(J_+ + J_-)L. \tag{20}$$

Hence, the free energy from ATP hydrolysis is equal to exactly the sum of the work done against the external load, $F_{\text{ext}}v$, and positive heat dissipation, equation (19).

4.   Some relevant mathematics on coupled diffusion

While $P(x, t)$ in equation (1) characterizes a stochastic process $\mathbf{X}_t$ in terms of probability density at each time t, $P(x, t)\,\mathrm{d}x = \text{Prob}\{x \leqslant \mathbf{X}_t \leqslant x + \mathrm{d}x\}$, there is an alternative view of a stochastic process in terms of its *trajectories.* In this approach, all possible trajectories $\{\mathbf{X}_t \mid t \geqslant 0\}$ form a function space Ω and a probability density (a measure) is defined. This naturally leads to the notion of "propagator" (a semi-group) which is formally defined as

$$P(x, t) = P(x, 0)\,\mathrm{e}^{\mathcal{L}t}, \tag{21}$$

where the exponential operator $\mathrm{e}^{\mathcal{L}t}$ acts on the distribution $P(x, 0)$ as a "row vector". The operator $\mathcal{L}$ satisfies the backward Kolmogorov equation:

$$\frac{\partial P(x, t)}{\partial t} = P(x, t)\mathcal{L}, \tag{22}$$

or its conjugate $\mathcal{L}^*$ satisfies the forward Kolmogorov (or Fokker–Planck) equation:

$$\frac{\partial P(x, t)}{\partial t} = \mathcal{L}^* P(x, t). \tag{23}$$

For symmetric operator $\mathcal{L}^* = \mathcal{L}$. The symbolic relationship between the operator $\mathcal{L}$ and the propagator $\mathrm{e}^{\mathcal{L}t}$ has been made rigorous in terms of linear operators in a Banach space and is known as Hille–Yosida theorem. Hence the modern theory of Brownian motion has brought several mathematical disciplines to bear [15,29]: partial differential equations, linear operators on functional spaces, and harmonic analysis.

4.1. Feynman–Kac formula

A major result in this area is a relationship between the solution of a boundary value problem (BVP) and the mean exit time (first passage time) of a diffusion process. This relation also has the potential for devising numerical methods for solving BVP. Let us now consider a Brownian motion in a domain D with the diffusion equation (23) and Dirichlet boundary conditions on ∂D. Now differentiate equation (23) with respect to t, and then multiply a t and integrate over $t \in (0, \infty)$, we have

$$\int_0^\infty t\,\frac{\partial^2 P(x, t)}{\partial t^2}\,\mathrm{d}t = \mathcal{L}^* \int_0^\infty t\,\frac{\partial P(x, t)}{\partial t}\,\mathrm{d}t. \tag{24}$$

If one interprets $P(x, t \mid x_0)$ as the probability of the Brownian particle at x at time t starting at x_0 when $t = 0$, then

$$u(x_0) = -\int_D \mathrm{d}x \int_0^\infty t\,\frac{\partial P(x, t \mid x_0)}{\partial t}\,\mathrm{d}t$$

is the mean time of the particle started at x_0 to exit D. The left-hand side of (24) can be simplified into

$$\left[t\, \frac{\partial P(x,t)}{\partial t} - P(x,t) \right]_0^\infty = \delta(x - x_0).$$

If now we multiply a function $\phi(x)$, which satisfies $\mathcal{L}\phi(x) = \psi(x)$ with (24) and then integrate over $x \in D$, we have

$$\begin{aligned}
\phi(x_0) &= \int_D \mathrm{d}x \phi(x) \mathcal{L}^* \int_0^\infty t\, \frac{\partial P(x,t)}{\partial t}\, \mathrm{d}t \\
&= \int_D \mathrm{d}x \big(\mathcal{L}\phi(x)\big) \int_0^\infty t\, \frac{\partial P(x,t)}{\partial t}\, \mathrm{d}t \\
&= \int_D \psi(x)\, \mathrm{d}x \int_0^\infty t\, \frac{\partial P(x,t)}{\partial t}\, \mathrm{d}t \\
&= -E^{x_0}\left[\int_0^{\tau_D} \psi(\mathbf{X}_s)\, \mathrm{d}s \right].
\end{aligned}$$

This shows that the right-hand side, in which $\mathbf{X}_t$ is the probabilistic Brownian motion and $E^{x_0}[\cdot]$ is the average along the paths of $\mathbf{X}_t$ started at x_0, satisfies the inhomogeneous ODE

$$\mathcal{L}u(x) = -\psi(x). \tag{25}$$

This is the well-known Feynman–Kac formula [37]. When $\psi(x) \equiv 1$, $u(x)$ is the mean exit time of the Brownian motion $\mathbf{X}_t$.

4.2. Random evolution

While a deterministic dynamic equation coupled to a white noise is called a *stochastic differential equation* and leads to Brownian motion [37], a deterministic dynamic (evolution) equation coupled to a Markov process is called *random evolution* [44]. This is a class of stochastic models characterized by a system of equations like

$$\begin{aligned}
\frac{\partial P(x,-)}{\partial t} &= -\frac{\partial}{\partial x}\big(F_-(x)P(x,-)\big) - f(x)P(x,-) + g(x)P(x,+), \\
\frac{\partial P(x,+)}{\partial t} &= -\frac{\partial}{\partial x}\big(F_+(x)P(x,+)\big) - f(x)P(x,-) - g(x)P(x,+).
\end{aligned} \tag{26}$$

There is no diffusive motion in the movement. A particle follows deterministic ODEs $\dot{x} = F_\pm(x)$ and jumps between $(+)$ and $(-)$ states. Equations like (26) have wide applications in chemistry and biology. For example, the stochastic averaging problem in nuclear magnetic resonance spectroscopy is precisely such a problem [41,47]. For a recent work, see [14].

For large f and g, the motion is approximately

$$\dot{x} = \frac{g(x)F_-(x) + f(x)F_+(x)}{g(x) + f(x)}.$$

For extremely large f and g, the Markovian process approaches a rapidly varying white noise and (26) again approaches a diffusion equation [47]. In spectroscopy, this corresponds to two distinct spectral lines merging into a single broad peak.

For small f and g, if both $F_-(x)$ and $F_+(x)$ have zeros, then the motion of the particle is still qualitatively simple: the particle will stay at a $(+)$ fixed point, jumps to $(-)$, relaxes to a $(-)$ fixed point, and stays there until jumping to $(+)$ and relaxing back to the $(+)$ fixed point, or relaxing to another $(+)$ fixed point. If the two F's are arranged appropriately, the particle can be continuously unidirectionally transported, step by step, as demonstrated in [2].

One insight from this discussion is that though equation (11) has no appropriate stationary solution, the time-dependent solution should be well behaved. This points out that one should approach the time-dependent solution of (11) rather than its stationary solution (equation (13)).

4.3. Small diffusion and the theory of large deviation

Is the dynamics of the degenerate equation (26) the limiting behavior of equation (5) when $D_\pm \to 0$? This is clearly an important mathematical question which also has significant relevance to the modeling of muscle contractions. As we have stated, one way to address this question is to develop a complete singular perturbation theory for (5). There is, however, also a stochastic approach called *theory of large deviations* [13] which in recent years has thrown much light on the problem. A combination of both approaches is undoubtedly desirable. This technically very demanding task has been carried out in several occasions, for example in [34]. For a review, see [60].

5. Deterministic vs. stochastic motion of molecular motors

While there is no doubt that the motor protein movement is a drifted Brownian motion, the extent of the randomness in the motion can be quantitatively characterized according to the mathematical model. Let us now again consider equation (5) in which there is no force in the detached state $(-)$. As we have discussed above, in the limit of both $D_\pm = 0$, the motion will be trapped at the zeros of $F(x)$. This indicates the importance of nonzero D_- for the motor movement in this model, as has been repeatedly pointed out by Peskin et al. [42,43].

On the other hand, when $F_-(x) \neq 0$, a motor protein can move strictly in one direction in a random evolution model. Diffusion plays no role in this mechanism. These two different modes of movement correspond nicely with "Brownian ratchet" and "power stroke" in the biochemical literature. Whether a motor protein in fact moves back-and-forth with a drift or almost unidirectional consecutively can be quantitatively analyzed. Until now, there has been no quantitative means to differentiate these two types of mo-

tion. The present theory offers a quantity method to address this issue. Taking equation (1) as an example, we can introduce a function

$$\int_0^L \left[\left(D \frac{\mathrm{d}P(x)}{\mathrm{d}x} \right)^2 + \left(F(x)P(x) \right)^2 \right] \mathrm{d}x \tag{27}$$

as the total movement of the protein. Note that the first term is associated with the Brownian motion and the second term is associated with the unidirectional movement. Hence their ratio quantitatively characterizes the mode of the motor movement. This integral is known as action in the theory of large deviations [18].

6. Future work

While the detailed mathematical analysis remain to be carried out for models of single motor movement, the mathematical analysis of a chain of motor protein is largely unknown, except for the completely rigid chain of motors (Huxley model). The general theory can be developed by connecting N motor proteins by springs. Such a "bead-and-spring" model has been the theoretical foundation of polymer physics [12,49]. The late Professor P.J. Flory was awarded the Nobel Prize in chemistry in 1974 for his contribution to this theory. The difference, however, is that a polymer is an equilibrium system, while a chain of motors is a "living creature". Let us denote the positions of N motor proteins by $x_1, x_2, \ldots, x_N$, and the corresponding internal states by $\sigma_1, \sigma_2, \ldots, \sigma_N$, where $\sigma_k = 0, 1$ for the detached and attached state of the kth motor. We, therefore, have the dynamic equation for probability $P(x_1, \sigma_1, x_2, \sigma_2, \ldots, x_N, \sigma_N, t)$:

$$
\begin{aligned}
\frac{\partial P}{\partial t} = \sum_{k=1}^N \Bigg[& \{(1 - \sigma_k)D_- + \sigma_k D_+\} \frac{\partial^2 P}{\partial x_k^2} - \frac{\partial}{\partial x_k} \Bigg(\frac{\sigma_k F_-(x_k)}{\beta_-} + \frac{(1 - \sigma_k)F_+(x_k)}{\beta_+} \\
& + \left\{ \frac{1 - \sigma_k}{\beta_+} + \frac{\sigma_k}{\beta_-} \right\} \eta(x_{k-1} - 2x_k + x_{k+1})P \Bigg) \\
& - \{(1 - \sigma_k)f(x) + \sigma_k g(x)\} P(\ldots, \sigma_k, \ldots) \\
& + \{(1 - \sigma_k)g(x) + \sigma_k f(x)\} P(\ldots, 1 - \sigma_k, \ldots) \Bigg],
\end{aligned}
\tag{28}
$$

where η is a spring constant. A computational analysis of such a model can be found in [9]. In a recent mathematical analysis, a deterministic counterpart of this system, a chain of bead-and-spring in a periodic force field, has been shown [54,56] to exhibit globally phase-locked motion. Equation (28) is an N-particle system which can be subjected to mean-field treatment as that for the N-particle Schrödinger equation. As in the genesis of nonlinear Schrödinger equation [58], such treatment will lead to a nonlinear term in the diffusion equation [20], opening a possible new mathematical approach to the problem of muscle contraction. In connection to the theory of probability, this is an interacting particle system with a nonequilibrium (Gibbsian) stationary state [33], and is a natural application for the theory of large deviations [10].

Acknowledgements

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