Vector Field Formalism and Analysis for a Class of Thermal Ratchets

Hong Qian
Department of Applied Mathematics, University of Washington, Seattle, Washington 98195
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To understand the physics of muscle contraction and molecular motor movement, we develop a model for nonequilibrium free energy transduction based on a diffusion in a periodic force field. It is shown that a nonconservative force is sufficient and necessary for a steady state with circular flux, but is not sufficient for a global unidirectional transport synonymous to motor protein movement. A vector potential for the flux is introduced for characterizing the circular flux and global transport. The model provides a natural distinction between the two types of muscle protein movement, namely the mechanical dominant "power-stroke" and the Brownian-motion dominant ratchet. [S0031-9007(98)07336-0]

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As a device for free energy transduction, the thermal ratchet originally proposed by Feynman [1] has attracted wide attention in biophysics, especially in connection with membrane protein transport [2,3], and motor protein translocation [4–6]. While there is already a large body of literature on this subject, the field still lacks a coherent mathematical framework for analyzing such a nonequilibrium phenomenon. The objective of this paper is to provide a mathematical framework for a class of thermal ratchet models in 2-dimensional continuous space. An insightful mathematical treatment of discrete models can be found in [7].

Thermal ratchet derived from muscle contraction.—In recent years the study of thermal ratchet and noise-driven transport has become an active research area in biophysics. One of the initial motivations of this research is to reveal the molecular mechanism for muscle contraction and related motor protein movement [8]. Thus we first turn to the classic work of Huxley on muscle contraction [9]. Paraphrasing the Huxley model in stochastic terms following Hill [10], a single myosin molecule (the protein which constitutes the thick muscle filament) has probabilities $P(x,-)$ being free and $P(x,+)$ being bound to a thin actin filament at distance x from the optimal binding site. The bounding-detaching transition $(- \rightleftarrows +)$ at each x is characterized by a two-state Markov process with transition rates $f(x)$ and $g(x)$:

$$\frac{\partial P(x,+)}{\partial t} = -g(x)P(x,+) + f(x)P(x,-) - v\,\frac{\partial P(x,+)}{\partial x}, \tag{1}$$

where v is the speed by which the two filaments are sliding against each other. In the steady state, Eq. (1) is the Huxley equation. We note that this model does not consider the random fluctuation of the myosin head in x, in either the bound or the detached states. However, our current understanding on motor protein movement is that the conformational fluctuation of the myosin is an essential element in generating a contraction [4,11]. Incorporating such fluctuation into Eq. (1) can be accomplished by introducing a diffusive term [12], representing the random fluctuation (Brownian motion) of the myosin head in real space x:

$$\begin{aligned}\frac{\partial P(x,+)}{\partial t} &= -g(x)P(x,+) + f(x)P(x,-) - v\,\frac{\partial P(x,+)}{\partial x} + \frac{\partial}{\partial x}\left[D_+(x)\,\frac{\partial P(x,+)}{\partial x}\right],\\ \frac{\partial P(x,-)}{\partial t} &= g(x)P(x,+) - f(x)P(x,-) + \frac{\partial}{\partial x}\left[D_-(x)\,\frac{\partial P(x,-)}{\partial x}\right].\end{aligned} \tag{2}$$

Under thermodynamic equilibrium, there is a set of constraints on D_+, D_-, f, and g (see the details below). This does not apply, however, to the contracting muscle under nonequilibrium steady state powered by the hydrolysis of adenosine triphosphate (ATP), which is implicitly dealt with in our present model [10]. We call Eq. (2) the augmented Huxley equation. It shares many features with other ratchet models [5,6,13]. We now propose a general mathematical formalism for these types of models.

The model.—Let's assume that the myosin has a continuous conformational change, i.e., an energy landscape in the y direction to replace the simple two discrete states. x represents the real space for the position of the myosin, say, center of mass, along an actin filament. We generalize Eq. (2) to a 2D diffusion-convection equation:

$$\frac{\partial P(x,y,t)}{\partial t} = \nabla^2 P(x,y,t) - \nabla\cdot\left(\mathbf{F}(x,y)P(x,y,t)\right), \tag{3}$$

where $(x,y) \in [0,a]\times[0,b]$ called a unit cell, with reflecting boundary conditions at $y=0$ and $y=b$, periodic boundary conditions at $x=0$ and $x=a$. a

represents the repeating unit in an actin filament. For simplicity, we have assumed a constant diffusion coefficient D, and then absorbed it into the variable t. The case with variable D is conceptually similar but computationally complicated. Note that the conservation of P leads to the convection terms rather than a reaction term. This distinguishes our model from many diffusion-reaction type models. In this paper, we shall focus only on the steady state of (3).

For every given y, i.e., in a fixed myosin conformation, $F_x(x, y) = -\partial U(x, y)/\partial x$ represents the interaction between actin and myosin, where $U(x, y)$ is a periodic potential energy function of x. Therefore, the diffusion in the x direction has no bias across the unit cell:

$$\int_0^a F_x(x, y)\, dx = U(0, y) - U(a, y) = 0. \qquad (4)$$

Obviously $F_x(x, y)$ is itself periodic in x. Thus, this model is a generalization of the discrete model with fluctuating barrier [6]. In the case of fluctuating force, $U(x, y)$ for each y has a net bias across the unit cell. However, $\int_0^b U(x, y)\, dy$ has zero bias, corresponding to zero mean force. As suggested in [6], as well as becoming clear below, the fluctuation barrier scenario is more fundamental to the ratchet model.

While F_x represents the intermolecular force, the force in y direction, $F_y(x, y)$ for each given x represents an intramolecule force. Implicitly, this force is a function of ATP, ADP (adenosine diphosphate), and Pi (orthophosphate) concentrations. If this force satisfies $F_y(x, y) = -\partial U(x, y)/\partial y$, then the steady state solution is simply $P(x, y) \propto e^{-U(x,y)}$, which in fact is an equilibrium solution with detailed balance [14]. In other words, if we define the steady-state flux field as

$$\mathbf{J}(x, y) = -\nabla P(x, y) + \mathbf{F}(x, y)P(x, y), \qquad (5)$$

then equilibrium entails $\mathbf{J} = 0$. The sufficient and necessary condition for flux field $\mathbf{J} = 0$ is that the force field is conservative, $\mathbf{F} = -\nabla U$. This will be the situation when the ATP, ADP, and Pi are at their equilibria. Equation (5) indicates that if there is a flux within or across the unit cell, then the extrema of P and the locations of zero $\mathbf{F}$ no longer coincide as in a thermodynamic equilibrium.

Vector potential A as probabilistic circulation.—Since $\nabla \cdot \mathbf{J} = 0$, according to Bendixson criterion [15] $\mathbf{J}$ meets the necessary condition for being a circular field. In 2D, $\mathbf{J}$ in fact is the conjugate of a gradient system. Therefore, the $\mathbf{J}$ field is circular. We can further introduce a vector potential $\mathbf{A} = A(x, y)\hat{z}$: $\mathbf{J} = \nabla \times \mathbf{A}$. Then the circular $\mathbf{J}$ has field lines as the contour of the vector potential, $A(x, y) = C$. It is easy to show that

$$\Phi \equiv \text{global transport} = \int_0^b J_x(x, y)\, dy = A(x, b) - A(x, 0) \qquad (6)$$

for any x. The reflecting boundary conditions lead to $\partial A(x, 0)/\partial x = \partial A(x, b)/\partial x = 0$. Hence $\mathbf{A}(x, 0) \equiv$ const as well as $\mathbf{A}(x, b) \equiv$ const, and their difference characterizes the global transport across the unit cell. Similarly, the periodic boundary condition leads to $A(0, y) - A(a, y) = \int_0^a J_y(x, y)\, dx = 0$ for all y, corresponding to no net transport along the y direction across the unit cell. For our 2D problem, $\mathbf{A}$ automatically satisfies an auxiliary condition for gauge symmetry $\nabla \cdot \mathbf{A} = 0$ [16].

The vector potential $\mathbf{A}$ also has an important physical, stochastic meaning. As shown in Fig. 1 $A(x, y)$ is also the continuous counterpart of Hill's *net cycle flux*, while $\mathbf{J}$ is the counterpart of his *transition flux* [19]. Finally, Eq. (5) can be rewritten in terms of $\mathbf{A}$

$$P\mathbf{F} = \nabla P(x, y) + \nabla \times \mathbf{A}. \qquad (7)$$

This corresponds to the decomposition theorem for a Markov chain [14], which states that a stationary Markov chain can always be decomposed into a detail balanced part and a circulation part. In our continuous case, the detail balanced part has zero curl $[\nabla \times (\nabla P) = 0]$ and the circulation part has zero divergence $[\nabla \cdot (\nabla \times \mathbf{A}) = 0]$. The gauge symmetry in $\mathbf{A}$ corresponds to the nonuniqueness of the circulation decomposition.

Singularity of the flux field.—For nonequilibrium steady state, vector field $\mathbf{J}$ has nonzero curl. Hence according to index theory [15] the vector field has singularities. Since $\nabla \cdot \mathbf{J} = 0$, the singularities can neither be *sink* nor *source*, but *centers* or *saddles*. The presence of a center in the $\mathbf{J}$ field corresponds to the circulation in an irreversible Markov process [20]. However, since our problem has a periodic boundary condition at $x = 0$ and $x = a$, there have to be at least two centers in a unit cell. Dividing the centers are separatrices connecting saddle points (Fig. 2). At the ends of the two separatrices in each unit cell are four (half) saddle points, two along the $y = 0$ and two along the $y = b$. These singularities

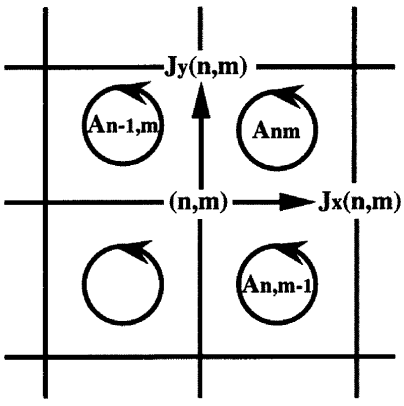

FIG. 1. A schematic showing the relation between flux $\mathbf{J}$ and its vector potential $\mathbf{A}$. This relation is analogous to T. L. Hill's operational flux and cycle flux for a discrete network (1989). This provides the vector potential $\mathbf{A}$ with a clear probabilistic meaning.

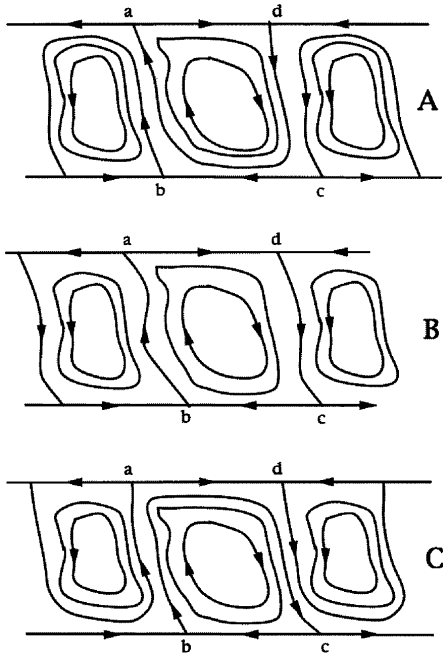

FIG. 2. Three schematic plots for vector field **J**. It is shown that the vector field **J** has circular flux lines with singularities. There are *centers* in the interior of the loops, and *saddle points* on the edges of unit cells (a, b, c, d). (A) global transport toward left; (B) no global transport; (C) global transport toward right.

divide the unit cell as shown in Fig. 2. At singular saddle points a, b, c, and d, we can expand the J_x as

$$J_x(x,y) = J_x(x^*,y^*) + \left[\frac{\partial J_x(x^*,y^*)}{\partial x}\right]dx + \frac{1}{2}\left[\frac{\partial^2 J_x(x^*,y^*)}{\partial x^2}\right]dx^2, \quad (8)$$

where the first term on the right is zero since (x^*, y^*) is a singular (stagnation) point of **J**. The second term contributes equally to the left and right, hence it does not contribute to the net transport. Thus the net transport is associated with the second derivative at stagnation points, say a. Furthermore, part of this net flux at a is balanced by the net flux at point c, where the second-order derivative has an opposite sign (if a, b is associated with the minimum of $U(x, y)$, then c, d is associated with its maximum and *vice versa*). Therefore, the overall global transport is the difference of the two second-order derivatives at a and c:

$$\Phi \propto \left(\frac{\partial^2 J_x}{\partial x^2}\right)_a + \left(\frac{\partial^2 J_x}{\partial x^2}\right)_c. \quad (9)$$

This is an insightful result, which is verified in our detailed calculation (to be published) in which the global transport is a third-order effect. If the function $U(x)$ is not smooth, then the second term in Eq. (8) will have different values for $x^{*+\delta}$ and $x^{*-\delta}$. Then the global transport is determined by the discontinuous slope at these singularities [6,13], and the global transport can be greater.

Force **F**, *flux* **J**, *and linear irreversibility.*—It is the nonconservative part of force **F** which drives **J**. Let's denote $\mathbf{f}_{\rm irr} = \mathbf{F} + \nabla\phi$ which is the irreversible motive force. A continuous diffusion model has the following correspondence to a random walk on a lattice, with nonuniform forward rate constants k_{+i} and reverse rate constants k_{-i}:

$$\mathbf{F}\cdot d\boldsymbol{\ell} \leftrightarrow (k_{+i} - k_{-i}), \quad D \leftrightarrow \frac{k_{+i} + k_{-i}}{2},$$

$$\frac{\mathbf{F}\cdot d\boldsymbol{\ell}}{D} \leftrightarrow \ln\left(\frac{k_{+i}}{k_{-i}}\right) \approx \frac{2(k_{+i} - k_{-i})}{k_{+i} + k_{-i}},$$

where $|k_{+i} - k_{-i}| \ll k_{+i}, k_{-i}$, D is the diffusion coefficient, and

$$\oint_\Gamma \frac{\mathbf{F}\cdot d\boldsymbol{\ell}}{D} \leftrightarrow \sum_\Gamma \ln\left(\frac{k_{+i}}{k_{-i}}\right),$$

where Γ is a closed path. Hence, according to Hill [19], the thermodynamic *cycle force* along the Γ is $\oint_\Gamma(\mathbf{F}\cdot d\boldsymbol{\ell})/D$. If $|\mathbf{f}_{\rm irr}| \ll |\nabla\phi|$, then the system is in the regime of linear irreversibility [21]. Using the linear perturbation method and assuming $P = e^{-\phi}/Z + P_1$, Eq. (5) becomes

$$\mathbf{J} = -\nabla P_1 - (\nabla\phi)P_1 + \mathbf{f}_{\rm irr}e^{-\phi}/Z,$$

where Z is a normalization constant. Solving the equation by variation of parameters $P_1(x, y) = C(x, y)e^{-\phi}$

$$\nabla C = -e^{\phi}\mathbf{J} + \mathbf{f}_{\rm irr}/Z,$$

$$\nabla \times (Ze^{\phi}\mathbf{J} - \mathbf{f}_{\rm irr}) = 0.$$

Therefore, $Ze^{\phi}\mathbf{J}$ and $\mathbf{f}_{\rm irr}$ differ by a gradient field, which has to be zero since $\mathbf{J} = 0$ when $\mathbf{f}_{\rm irr} = 0$. Hence

$$\mathbf{J} = Ze^{-\phi}\mathbf{f}_{\rm irr}. \quad (10)$$

This is the force-flux relationship in the linear irreversible regime. Finally, we have the Onsager's entropy production:

$$\mathbf{f}_{\rm irr}\cdot\mathbf{J} = Z|\nabla P - \mathbf{F}P|^2 e^{\phi} \geq 0, \quad (11)$$

which is in agreement with the general formula of entropy production for diffusion processes [14,18]. The entropy production gives the heat generated in muscle contraction.

Some further analysis.—The global transport can be written in terms of the integration of the solution of Eq. (3). From Eq. (6) we have

$$\Phi = \frac{1}{a}\int_0^a [A(x,b) - A(x,0)]\,dx = \int_0^b \frac{d}{dy}\left[\int_0^a A(x,y)dx\right]dy, \quad (12)$$

where

$$\frac{d}{dy}\int_0^a A(x,y)\,dx = \int_0^a F_x(x,y)P(x,y)\,dx. \quad (13)$$

Note that F_x satisfies Eq. (4). Therefore for every y, the right-hand side of (13) is the net flux along that horizontal strip, between y and $y + dy$, across the unit cell. On the other hand, for every y,

$$\int_0^a J_x(x,y)e^{U(x,y)}\,dx = 0. \tag{14}$$

This is because (14) equals

$$\int_0^a \left(-\frac{\partial P}{\partial x} - P\frac{\partial U}{\partial x}\right)e^{U(x,y)}\,dx = -\int_0^a d_x[P(x,y)e^{U(x,y)}] = 0$$

due to the periodic boundary condition. Equation (14) indicates that at every y, the J_x changes sign within the unit cell (cf. Fig. 2). There is no laminar flux; the global transport Φ in x direction is due to the free energy from the intramolecular force (F_y).

The central idea of the thermal ratchet is the coupling of a set of stochastic processes. While each process by itself has no bias for global transport, the nonconservative coupling leads to nonequilibrium circulation. Mathematically speaking, the conflict between the vector force fields leads to singularities which drive the circulation and global transport. In the 2D case we studied, the circulation is associated with a center in the flux field, while the transport is associated with several stagnation (saddle) points.

It is appropriate here to comment on the large body of biophysical theories for enzymatic kinetics with fluctuating proteins [12]. The mathematics and physics behind those models and our thermal ratchet model share common features, but with one crucial difference: the former are for equilibrium systems which require the existence of a potential function for $\mathbf{F}(x,y) = -\nabla U$, while all the interesting nonequilibrium phenomena arise because of $\nabla \times \mathbf{F} \neq 0$. This fundamental difference leads to the reversibility for the former (which is equivalent to the Kolmogorov's condition in mathematics, fluctuation-dissipation theorem in physics, and the "thermodynamic box" in chemistry) but positive entropy production in the latter [Eq. (11)].

Another important aspect of the diffusion-convection model is that it is not just limited for the thermal ratchet. If the process is dominated by the convection (force) term, then the model is consistent with the traditional idea for motor movement which consists of well-defined steps ("power stroke"). It has been recognized that the difference between the ratchet model and power-stroke model for muscle contraction and motor protein is a quantitative one [11]; our model provides a natural mathematical definition for these models by identifying the ratchet mechanism with the diffusion term, and the power stroke with the force term.

[1] R. Feynman, R. B. Leighton, and M. Sands, *The Feynman Lectures on Physics* (Addison-Wesley, Reading, MA, 1963), Vol. 1, Chap. 46.

[2] H. V. Westerhoff and Y. D. Chen, Proc. Natl. Acad. Sci. U.S.A. **82**, 3222–3226 (1985).

[3] T. Y. Tsong and R. D. Astumian, Annu. Rev. Physiol. **50**, 273–290 (1988).

[4] T. Yanagida, Y. Harada, and A. Ishijima, Trends Biochem. Sci. **18**, 319–324 (1993).

[5] C. S. Peskin, G. B. Ermentrout, and G. F. Oster, in *Cell Mechanics and Cellular Engineering*, edited by V. C. Mow *et al.* (Springer-Verlag, New York, 1994), pp. 479–489.

[6] R. D. Astumian and M. Bier, Phys. Rev. Lett. **72**, 1766–1769 (1994).

[7] Y. D. Chen, Proc. Natl. Acad. Sci. U.S.A. **84**, 729–733 (1987).

[8] H. Qian, Biophys. Chem. **67**, 263–267 (1997).

[9] A. F. Huxley, Prog. Biophys. Biophys. Chem. **7**, 257–318 (1957).

[10] T. L. Hill, Prog. Biophys. Mol. Biol. **28**, 267–340 (1974).

[11] J. Howard, Annu. Rev. Physiol. **58**, 703–729 (1996).

[12] N. Agmon and J. J. Hopfield, J. Chem. Phys. **78**, 6947–6959 (1983).

[13] R. D. Astumian and M. Bier, Biophys. J. **70**, 637–653 (1996).

[14] M-P. Qian, M. Qian, and G. L. Gong, Contemp. Math. **118**, 255–261 (1991).

[15] S. Wiggins, *Introduction to Applied Nonlinear Dynamical Systems and Chaos* (Springer-Verlag, New York, 1990).

[16] With the condition $\nabla \cdot \mathbf{A} = 0$, the vector potential is determined up to a $\nabla\psi$ where the harmonic function ψ ($\nabla^2\psi = 0$) should be determined by the boundary conditions. Also, $\mathbf{A}$ is intimately related to the vorticity field of an "incompressible fluid" ($\mathbf{J}$): $\boldsymbol{\xi} = \nabla \times \mathbf{J} = -\nabla^2\mathbf{A}$ [17]. The vorticity is, of course, the differential form of the rotation number for a random dynamical system [18].

[17] A. J. Chorin and J. E. Marsden, *A Mathematical Introduction to Fluid Mechanics* (Springer-Verlag, New York, 1990).

[18] M. Z. Guo, M. Qian, and Z. D. Wang, Chin. Sci. Bull. **42**, 982–985 (1998).

[19] T. L. Hill, *Free Energy Transduction and Biochemical Cycle Kinetics* (Springer-Verlag, New York, 1989).

[20] S. L. Kalpazidou, *Cycle Representations of Markov Processes* (Springer-Verlag, New York, 1995).

[21] L. Onsager, Phys. Rev. **37**, 405–426 (1931).