Pump process of the rotatory molecular motor and its energy efficiency

Hiroshi Miki, Masatoshi Sato, and Mahito Kohmoto

The Institute for Solid State Physics, The University of Tokyo,
5-1-5 Kashiwanoha, Kashiwa, Chiba 277-8581, JAPAN

(Dated: February 2, 2008)

The pump process of the ratchet model inspired by the $F_o$ rota
tory motor of ATP synthase is investigated. In this model there are two kinds of characteristic time. One is dynamical, the relaxation
time of the system. Others are chemical, the chemical reaction rates at which a proton binds to or dissociates from the motor protein.

The inequalities between these should affect the behavior of the physical quantities, such as the rotation velocity and the proton pumping rate
across the membrane. The energy transduction efficiency is calculated and the condition under which the efficiency can become higher is
discussed. The proton pumping rate and the efficiency have a peak
where a certain set of inequalities between the chemical reaction rates and the reciprocal of the relaxation time holds. The efficiency also has a peak for a certain value of the load. The best efficiency condition for the pump process is consistent with that for the motor process.

PACS numbers: 05.40.-a, 05.60.-k, 87.15.-v

I. INTRODUCTION

Biomolecular motors are kinds of protein molecules which generate
a unidirectional motion in the situation that many surrounding molecules, e.g. water molecules, collide with the protein molecule many
times due to thermal fluctuation. They play many essential roles in
life; muscle contraction, transport in cells, etc. It is interesting and
important question how motor proteins generate a unidirectional motion. It is natural to think that they utilize this random fluctuation by the collision, although there has been no unambiguous evidence reported so far that this is essential.

Ratchet systems, which take out a net finite current from random and undirected noise, have been intensively investigated for modeling molecular motors. As known by the famous Feynman’s lecture and many investigations thereafter, a net finite directed motion is the consequence of the violation of the symmetry of the system, e.g. the spatial form of the potential. In modeling molecular motors, the system also needs to violate the detailed balance between several different states, i.e. conformations. The detailed balance is violated by the undirected chemical energy supply, e.g. the ATP hydrolysis. Ratchet systems are applied to various physical systems other than modeling molecular motors.

The $F_o$ part of the ATP synthase is known as a rota
tory molecular energy transducer. It is embedded in the membrane, and transduces the energy of the transmembrane proton concentration gradient, when a proton passes through the membrane via the $F_o$ part, into that of the rotation of its internal subunits in the motor process. The ratchet model of it was presented qualitatively by Junge, Lill and Engelbrecht. Elston, Wang, and Oster improved this model by taking account of the electrostatic interaction between the residues. This ratchet model has an advantage that the coupling between the rotation and the proton flow is easy to see, therefore the energy transduction efficiency is easily estimated. In this model, there are two important kinds of characteristic time, dynamical and chemical. The former is the relaxation time of the convection-diffusion system. The latter are the chemical reaction rates at which a proton binds to or dissociate from the motor protein when it passes through the membrane. We investigated the efficiency in detail and pointed out that in the motor process, the inequalities between them affect the behavior of it.

For the motor to work most efficiently, certain inequalities between them need to hold.

The $F_o$ part also works as a pump; it gains energy from the (inverse) rotation and pumps out protons against the transmembrane proton gradient. Which process this protein adopts, motor or pump, under a given condition and what controls this determination are important questions, but satisfying answers to these have not been obtained so far.

In this paper we investigate the physical quantities in the pump process, such as the rotation velocity, the proton pumping rate, and the energy transduction efficiency. The condition under which the protein works as a pump with higher efficiency is discussed. We will compare the most efficient condition for the pump process with that for the motor process.

II. MODEL

The ATP synthase is schematically shown in FIG.1(a). The upper side of the figure is the basic (inner) side of the cell and the lower side is the acidic (outer) side. The proton concentration of the acidic side is kept higher than that of the basic side by respiratory chains. The $F_o$ part is composed of the subunits denoted by the Roman letters, $a$, $b$, and $c$, and the $F_1$ part by the Greek letters, $\alpha$, $\beta$, $\gamma$, and $\delta$. The rotating ring (the $c$-ring) is composed of the assembly of the $c$-subunits, each of which has a proton binding site, carboxyrate Asp61, almost in the middle of itself. The $a$-subunit is fixed in the mem-
brane. The proton channel is the interface between the a-subunit and the c-ring. There are two c-subunits and two proton paths in the channel. One of the paths connects the left binding site of the c-subunits to the basic side and the other connects the right binding site to the acidic side. The other c-subunits are in the membrane. The proton binding site can be both protonated and unprotonated only if it is in the channel. Otherwise it can be only protonated due to the hydrophobicity of the membrane. The conformational change of the c-subunits between the two states, protonated and unprotonated, is small\textsuperscript{12} and we neglect the effect on the place of the binding sites. The states of the c-ring are determined by protonations of the two proton binding sites in the channel; the empty(E) state with both binding sites unprotonated, the right(R) state with the right binding site protonated and the left binding site unprotonated, the left(L) state with the left binding site protonated and the right binding site unprotonated, and the full(F) state with both binding sites protonated. As a motor the c-ring rotates rightward and as a pump leftward in FIG\textsuperscript{1}. The γ-subunit connects the \( F_0 \) part to the \( F_1 \) part.

We investigate this system by using the ‘simply biased diffusion model’ \textsuperscript{14, 15, 16}. It works as follows: The c-ring moves randomly by collision with surrounding molecules and is forced to rotate by the external load from the \( F_1 \) part. But the hydrophobic interaction prevents the unprotonated binding site from moving into the membrane, i.e. the E and R states cannot move leftward out of the channel and the E and L states not rightward. If the chemical reaction rates, at which a proton binds to or dissociates from the binding sites in the channel, are tuned appropriately, it becomes possible to take out a net motion against the load or to pump protons against the concentration gradient.

We consider the pump process of this system. A proton passes through the channel from the basic side to the acidic side as follows: First a proton in the basic side flows into the channel and binds to the left binding site. Next the proton goes through the membrane with the leftward rotation of the c-ring. Finally the proton comes back to the channel, dissociates from the right binding site, and flows out to the acidic side. In this way, a proton is pumped out by the rotation of the c-ring driven by the external load, which is gained by the energy of the ATP hydrolysis in the external part. We assume that in the pump process, the external load exerted is larger than that in the motor process, so that the c-ring can rotate leftward. In this sense, the external ‘load’ should be exactly called ‘driving force’ of the rotation in the pump process. However, we will use the term ‘load’ in the pump process since we deal with the same model as in the motor process.

First of all, we give a qualitative consideration of the energy transduction, the coupling between the rotation and the proton flow. The good process in the channel is shown in FIG\textsuperscript{2}. A proton binds to the left binding site in the left figure. Then the c-ring moves one step leftward in the center figure. Finally the proton bound to the right binding site dissociates in the right figure and the process returns back to the start. In this process one step of the c-ring rotation corresponds to one proton pumping. This is the efficient energy transduction. A bad process is shown in FIG\textsuperscript{3}. In the upper-right figure, a proton binds to the left binding site before the proton bound to the right binding site dissociates. Then in the lower-right figure, the c-ring moves leftward without proton dissociation. Therefore more than one step of the rotation corresponds to one proton pumping. In this process the energy is transduced inefficiently. Another bad process is shown in FIG\textsuperscript{4}. In the upper-middle figure, a proton binds to the right binding site from the acidic side before the rotation of the c-ring. Next the c-ring rotates leftward in the upper-right figure. Finally the proton bound to the left binding site dissociates then the c-ring rotates rightward due to diffusion. In this process, a proton passes through the membrane along the
rotation by load

FIG. 2: The good process of the coupling between the proton pumping and the motion of the c-ring. In this process, one step of the rotation tightly couples to one proton pumping. The energy is transduced efficiently.

rotation by load or diffusion

FIG. 3: A bad process. One proton pumping corresponds to more than one step of the rotation. The energy of the motion is wasted in this process.

FIG. 4: Another bad process. A proton flows in the undesirable direction without rotation. This process is possible since the proton concentration of the outer side is kept higher than that of the inner side. This process suppresses the efficient energy transduction.

rotation by load

FIG. 5: The $F_o$ part viewed from the basic side. The position variable $x$ is defined as a rotation angle of the c-ring.

\[
\begin{align*}
\frac{\partial}{\partial t} p(x, t) &= -\frac{\partial}{\partial x} \Pi(x, t) + \hat{K}(x) \cdot p(x, t), \\
\Pi(x, t) &= \gamma \hat{f}(x) p(x, t) - D \frac{\partial}{\partial x} p(x, t),
\end{align*}
\]  

(1)

Here $p(x, t)$ is 4-component probability where $p_i(x, t)$ describes the probability that the c-ring in state $i$ is at position $x$ at time $t$. The state index $i$ refers to the state mentioned before; E, R, L, and F. Similarly, $\Pi$ describes the flow of the probability. $\hat{K}$ is the transition matrix which describes changes between the states and will be given later. $D$ and $\gamma$ are the diffusion constant and the friction constant, respectively. They satisfy the Einstein’s relation, $D = \gamma k_B T$ where $T$ is the temperature and $k_B$ is the Boltzmann constant. The matrix $\hat{f} = \text{diag}[\tau, \tau, \tau, \tau]$ is the external load. The position variable $x$ is defined as the rotation angle with the origin placed at the center of the c-ring and takes its value from 0 to $\delta = 2\pi/N$ where $N$ denotes the number of c-subunit consisting in the c-ring. (See Fig.5) Hereafter, we fix $N = 12$, which is the case of E.Coli. The position $x = 0$ is defined as the situation where the left binding site is at the left boundary of the channel and $x = \delta$ is as that where the right binding site is at the right boundary of the channel.

As mentioned earlier, the conformational change of the c-subunit due to the protonation of the binding site is small. Therefore we have assumed that all the state take the common values of the diffusion constant $D$ and the
friction constant $\gamma$. As an effect of the conformational change, we will only take account of the hydrophobicity, which determines whether or not a c-subunit in the channel can move into the membrane.

The system has a periodicity in the sense that when one binding site in the channel goes out and moves into the membrane, another binding site comes into the channel. This periodicity and the hydrophobicity impose the boundary conditions on the flows,

$$\Pi_E(0, t) = \Pi_E(\delta, t) = 0,$$

$$\Pi_R(0, t) = \Pi_L(\delta, t) = 0,$$

$$\Pi_L(0, t) = \Pi_R(\delta, t),$$

and,

$$\Pi_F(0, t) = \Pi_F(\delta, t).$$

Similarly, the following boundary conditions of the probabilities are imposed,

$$p_R(\delta) = p_L(0),$$

$$p_F(\delta) = p_F(0).$$

The transition matrix $\hat{K}$ is given as

$$\hat{K} =
\begin{bmatrix}
-k_{in}^R + k_{out}^L & k_{in}^R & -k_{out}^R & 0 \\
k_{in}^R & -k_{in}^R + k_{out}^L & 0 & k_{out}^L \\
-k_{out}^R & 0 & -k_{in}^R + k_{out}^L & 0 \\
k_{out}^R & k_{out}^L & -k_{out}^R & -k_{in}^R + k_{out}^L
\end{bmatrix},$$

where $k_j^i (i=\text{R,L}, j=\text{in, out})$ denotes the rate at which a proton binds to (in) or dissociates from (out) the right (R) or left (L) binding site. Here we assumed that (1) the chemical reaction is sufficiently faster than the motion of the e-ring; (2) there is no proton hopping between the binding sites and no correlation between the reactions; (3) the reaction rates are independent of the position, $x$.

The steady-state solution of interest therefore the time variable is omitted hereafter. Under these assumptions, this system can be solved analytically. The matrix $\hat{Q}^{-1} \hat{K} \hat{Q}$ diagonalizes the transition matrix $\hat{K}$

$$\hat{Q}^{-1} \hat{K} \hat{Q} =
\begin{bmatrix}
0 & -(k_{in}^R + k_{out}^L) & -k_{out}^R & 1 \\
-(k_{in}^R + k_{out}^L) & 0 & -k_{out}^R & 1 \\
-k_{out}^R & -(k_{in}^R + k_{out}^L) & 0 & 1 \\
-1 & 0 & -k_{out}^R & 0
\end{bmatrix}.$$ (13)

Then Eq. (1) in the steady state is reduced to

$$0 = -d \frac{d}{dx} \left[ \gamma \tau - D \frac{d}{dx} \right] (\hat{Q}^{-1} \hat{p}(x)) + \begin{bmatrix}
0 & -(k_{in}^R + k_{out}^L) & -k_{out}^R & 1 \\
-(k_{in}^R + k_{out}^L) & 0 & -k_{out}^R & 1 \\
-k_{out}^R & -(k_{in}^R + k_{out}^L) & 0 & 1 \\
-1 & 0 & -k_{out}^R & 0
\end{bmatrix} \hat{Q}^{-1} \hat{p}(x).$$ (14)

The solution is

$$(\hat{Q}^{-1} \hat{p}(x)) =
\begin{bmatrix}
C_1 + C_2 e^{\xi x} \\
C_3 e^{\eta L_x} + C_4 e^{\eta R_x} \\
C_5 e^{\eta L_x} + C_6 e^{\eta R_x} \\
C_7 e^{\eta L R x} + C_8 e^{\eta R R x}
\end{bmatrix},$$ (15)

where $C_i (i = 1, 2, \cdots, 8)$ are integral constants and

$$\xi = \frac{\gamma \tau}{D}. $$ (16)
\[ \eta_{L}^{\pm} = \frac{\gamma \tau \pm \sqrt{\gamma^{2} + 4D(k_{in}^{L} + k_{out}^{L})}}{2D}, \]  
\[ \eta_{R}^{\pm} = \frac{\gamma \tau \pm \sqrt{\gamma^{2} + 4D(k_{in}^{R} + k_{out}^{R})}}{2D}, \]  
\[ \eta_{L,R}^{\pm} = \frac{\gamma \tau \pm \sqrt{\gamma^{2} + 4D(k_{in}^{R} + k_{out}^{L} + k_{in}^{L} + k_{out}^{L})}}{2D}. \]

The integral constants \( C_i \)'s are determined by the boundary conditions of the probabilities and their flows, Eqs. (5)–(10). To close the algebraic equations for \( C_i \)'s, the normalization condition of the probability is needed.

\[ \int_{0}^{\delta} dx \sum_{i} p_{i}(x) = 1, \]

is needed.

Physical quantities which we will investigate are calculated as follows: First, the average rotation velocity \( \langle v \rangle \) is given as,

\[ \langle v \rangle = \sum_{i} \bar{\Pi}_{i}, \]

where

\[ \bar{\Pi}_{i} = \int_{0}^{\delta} dx \Pi_{i}(x) = \gamma \tau \bar{p}_{i} + D[p_{i}(0) - p_{i}(\delta)], \]

and,

\[ \bar{p}_{i} = \int_{0}^{\delta} dx p_{i}(x). \]

Next, the proton pumping rate \( N_{p}(H^{+}) \) is written as,

\[ N_{p}(H^{+}) = \frac{1}{2}(J_{R} + J_{L}) \]

where

\[ J_{R} = -k_{out}^{R} \bar{p}_{R} + k_{in}^{R} \bar{p}_{E} - k_{out}^{R} \bar{p}_{F} + k_{in}^{R} \bar{p}_{L}, \]

\[ J_{L} = k_{out}^{L} \bar{p}_{L} - k_{in}^{L} \bar{p}_{E} - k_{out}^{L} \bar{p}_{R} + k_{in}^{L} \bar{p}_{F}. \]

Here \( J_{R} \) and \( J_{L} \) describe the proton flow of the right and left binding site, respectively. Finally, let us define the efficiency of the energy transduction. The energy input per unit time is defined as the product of the external load torque \( \tau \) and the rotation velocity, \( \langle v \rangle \). The energy output per unit time is the product of the free energy due to the transmembrane proton gradient, \( \Delta G \), and the proton pumping rate, \( N_{p}(H^{+}) \). Therefore the efficiency \( e \) is defined as,

\[ e \equiv \frac{\Delta G \cdot N_{p}(H^{+})}{\tau \cdot \langle v \rangle}. \]

### III. RESULTS

We investigate the dependence of the quantities, \( \langle v \rangle \), \( N_{p}(H^{+}) \), and \( e \) on the transition rates, \( K \). The transition rates are given by

\[ \begin{bmatrix} \frac{K_{in}^{R}}{K_{out}^{R}} \\ \frac{K_{in}^{L}}{K_{out}^{L}} \end{bmatrix} = 10^{K} \begin{bmatrix} 10^{-pH_{A}e^{\phi/k_{B}T}} & 10^{-pH_{A}e^{\phi/k_{B}T}} \\ 10^{-pH_{B}e^{-V/2k_{B}T}} & 10^{-pK_{a}e^{-V/2k_{B}T}} \end{bmatrix}. \]

The parameters used for the calculation are, according to Ref. [17], given in TABLE I. They are plausible values in living things. In our previous work [16], we pointed out that the inequalities between the chemical reaction rates, \( k_{j}^{i} \)'s, each other and the reciprocal of the relaxation time \( \tau_{i} \), affect the behavior of the physical quantities in the motor process. It is natural to expect that these inequalities also play important roles in the pump process. The chemical reaction rates depend on many kinds of factor, e.g. the diffusion constant of the proton, the acidity of the proton binding site, the concentrations of proton of both sides, etc. The overall factor 10\( K \) means the effective proton absorption rate of the path, which is regarded as common for all the transition rates.

The free energy accompanying the proton translocation due to the transmembrane proton gradient is given as

\[ \Delta G = V + k_{B}T \ln[10^{\Delta pH}] \]

where \( \Delta pH = pH_{B} - pH_{A} \). The detailed balance is violated by this free energy and the pumping is against this energy.

We investigate in detail two sets of inequalities between the transition rates; case 1) \( k_{out}^{L} > k_{out}^{R} > k_{in}^{R} > k_{in}^{L} \) and case 2) \( k_{out}^{L} > k_{in}^{R} > k_{out}^{L} > k_{in}^{L} \). They are derived...
The rotation velocity \( \langle v \rangle \) in the case of the set of inequalities \( k_{\text{out}}^L > k_{\text{in}}^R > k_{\text{out}}^R > k_{\text{in}}^L \) (\( pK_a=4.5, \text{case } 1 \)).

from the parameters in TABLE II and the condition under which our model works well as a motor. We take the value of the acidity of proton binding site, \( pK_a=4.5 \) and 5.5 as typical value which gives the set of inequalities 1) and 2), respectively.

The external load \( \tau \) is also regarded as a controllable parameter, since the load has not been so far measured experimentally in the pump process we discuss here.

The rotation velocity \( \langle v \rangle \) is plotted in FIGs. 6 and 7 in the case 1) and 2), respectively. There is no qualitative difference between two cases. There is almost no rotation when \( K \) is small, i.e. the chemical reaction rates are low. Then it monotonically increases and finally saturates at \( K >15 \), which is out of the figures. As expected, it becomes faster for the larger load.

The proton pumping rate \( N_p(H^+) \) is plotted in FIGs. 8 and 9. Almost no pumping is observed for small \( K \) in both cases. Then it increases as \( K \) increases. It reaches a peak at a certain finite value of \( K \), such that \( k_{\text{out}}^L \sim T_{\text{relax}}^{-1} \), and then falls down abruptly. The larger the load, the more the peak value increases.

The energy transduction efficiency \( e \) is plotted in FIGs. 10 and 11. For respective fixed loads \( \tau \), it has a peak for a certain finite value of \( K \). This fact reflects the above behaviors of the rotation velocity and the proton pumping rate. The peak is placed on \( K \) such that \( T_{\text{relax}}^{-1} > k_{\text{out}}^L > T_{\text{load}}^{-1} \) holds. Here \( T_{\text{load}} \equiv \delta/\gamma \tau \) is the characteristic time that it takes for the e-ring to rotate one step leftward by the load. The variation of the peak value with respect to the load \( \tau \) is shown in FIGs. 12 and 13. For the variation of the load \( \tau \), there exists an optimal value of \( \tau \) such that the peak value of the efficiency becomes maximum. In the case 1), \( \tau \sim 75\text{pN nm} \) and \( \tau \sim 90\text{pN nm} \) in the case 2). Note that the efficiency in the case 1) is about one order larger than that in the case 2). Therefore, the pump mechanism works most efficiently when the set of inequalities \( T_{\text{relax}}^{-1} > k_{\text{out}}^L > T_{\text{load}}^{-1} > k_{\text{out}}^R > k_{\text{in}}^R > k_{\text{in}}^L \) holds and the optimal value of \( \tau \sim 75\text{pN nm} \) is fulfilled.

We can understand qualitatively the reason why the above inequalities are required for the efficient pump pro-
the increasing rates of them determines load increases. Therefore, the subtle difference between $F$ or a fixed load $\tau$ for a fixed load $\tau$.

FIG. 10: The energy transduction efficiency $e$ in the case 1). For a fixed load $\tau$, there is a peak at about $T^{-1}_{relax} \gtrsim k^L_{out} > T^{-1}_{load}$. In this case the value is about one order smaller than the former case.

FIG. 11: The energy transduction efficiency $e$ in the case 2). For a fixed load $\tau$, there is a peak at about $T^{-1}_{relax} \gtrsim k^L_{out} > T^{-1}_{load}$. In this case the value is about one order smaller than the former case.

cess. Firstly, the inequality $T^{-1}_{relax} \gtrsim k^L_{out}$ is required to suppress the bad process shown in FIG. 11. If the inequality is not satisfied, the left binding site in the channel becomes unprotonated before the relaxation by the fluctuation hence it cannot move into the membrane. As a result the bad process in FIG. 11 can occur easily. Secondly, the inequality $k^R_{out} > T_{load}$ indicates that the bad process shown in FIG. 11, rotation without proton pumping, rarely occurs. Thirdly, the inequality $k^R_{out} > k^R_{in}$, which distinguishes the case 1) from 2), is needed to prevent the c-ring from moving rightward.

For $\tau_{opt}$, we note that it is determined in highly non-trivial manners. To see this, let us go back to Eq. 27. As we see in FIGs. 11 and 12, both the numerator of Eq. 27, which is proportional to the proton pumping rate $N_p(H^+)$, and the denominator, which is proportional to the rotation velocity $\langle v \rangle$ and the load $\tau$, increases monotonically as the load increases. Therefore, the subtle difference between the increasing rates of them determines $\tau_{opt}$.

FIG. 12: The variation of the peak value of the energy transduction efficiency $e$ in the case 1) with respect to the load $\tau$. Below the critical load $\tau_c \sim 60$ (pN-nm), the system cannot work as a pump. It has a peak for a certain finite value of $\tau$, $\tau_{opt} \sim 75$ (pN-nm).

FIG. 13: The variation of the peak value of the energy transduction efficiency $e$ in the case 2) with respect to the load $\tau$. For $\tau < \tau_c \sim 70$ (pN-nm), the system cannot work as a pump. There is a peak for a certain finite value of $\tau$, $\tau_{opt} \sim 90$ (pN-nm). The value is about one order smaller than the case 1).

IV. SUMMARY AND DISCUSSION

We have investigated the pump process of the ratchet model of the rotary molecular motor. The model can be solved analytically and the physical quantities such as the rotation velocity and the proton pumping rate are calculated. The energy transduction efficiency is obtained from these physical quantities. The best efficiency condition is that the set of inequalities $T^{-1}_{relax} \gtrsim k^L_{out} > T^{-1}_{load} > k^R_{out} > k^R_{in} > k^L_{in}$ holds under an optimal value of the load $\tau_{opt}$.

We compare the result obtained here with that for the motor process. In Ref. 16 we find that the most efficient condition for the motor process is that the set of inequalities $k^L_{out} > T^{-1}_{relax} > k^R_{out} > k^R_{in} > k^L_{in}$ holds under the experimentally reported load, $\tau \sim 40$ pN-nm [13]. The set of inequalities required between the chemical reaction
rates coincide with that for the pump process obtained here. Therefore the $F_0$ part can work both as a motor and a pump efficiently by tuning the load $\tau$. In this sense these conditions are consistent.

As far as we know, experiments which directly measures the physical quantities, such as the rotation velocity and the pumping rate, have not been reported so far. However an experiment has been reported that in a whole $F_0F_1$ ATP synthase the conformational change of one subunit of $F_1$ part suppresses electronically and/or sterically the rotation hydrolysing ATP[17]. This effect may be interpreted to vary the load effectively and control which process occurs.

In the model we considered here, only the diffusion process is taken into account. The highest efficiency obtained is $e \sim 0.3$, and it seems to be not high enough, since molecular motors are thought to transduce energy almost without loss [18]. There are several possibilities to solve this problem. The first is to reconsider the definition of the efficiency (27), since our definition, following the argument in Ref.[19], is different from that in Ref.[18]. The second is to reconsider the relations between physical quantities appropriate near the equilibrium, such as the Einstein’s relation, since the system is far from equilibrium. The third is to introduce another mechanism, such as the electrostatic interaction between residues in Ref.[15]. These may lead to our better understanding of the energetics of non-equilibrium systems.

[1] J.Howard, *Mechanics of Motor Proteins and the Cytoskeleton* (sinauer,2001)
[2] R.D.Vale and R.A.Milligan, Science 288, 88 (2000).
[3] R.D.Vale and F.Oosawa, Adv. Biophys. 26, 97 (1990), A.Adjari and J.Prost, C. R. Acad. Sci. Paris II 315, 1635 (1992), N.J.Cordova, B.Ehmentrout, and G.F.Oster, Proc.Natl.Acad.Sci.U.S.A. 89, 339 (1992), M.O.Magnasco, Phys.Rev.Lett. 71, 1477 (1993), R.D.Atsumian and M.Bier, Phys.Rev.Lett 72, 1766 (1994).
[4] R.P.Feynman, R.Rayton, M.Sands, *Feynman Lectures on Physics* (Addison-Wesley,1963).
[5] F.Jülicher, A.Ajdari, and J.Prost, Rev. Mod. Phys. 69, 1269 (1997).
[6] P.Reimann, Phys. Rep. 361, 57 (2002).
[7] H.Linke, Appl. Phys. A. 75, 167 (2002) special issues on Brownian motors.
[8] R.D.Atsumian and P.Hänggi, Physics Today 55(11), 33 (2002).
[9] S.B.Vik and B.J.Antonio, J.Biol.Chem. 269,30364 (1994).
[10] Y.Sambongi et al.,Science 286, 1722 (1999).
[11] S.P.Tsunoda et al., Proc.Natl.Acad.Sci.U.S.A. 98, 898 (2001).
[12] V.K.Rastogi and M.E.Garvin, Nature(London) 402, 263 (1999).
[13] M.L.Hutchon et al., Proc.Natl.Acad.Sci.U.S.A. 98, 8519 (2001).
[14] W.Junge, H.Lill, and S.Engelbrecht, Trends. Biochem. Sci. 22, 420 (1997).
[15] T.Elston, H.Wang, and G.Oster, Nature(London) 391, 510 (1998) and Supplementary Material.
[16] H.Miki, M.Sato and M.Kohmoto, Phys.Rev.E 68,061906 (2003).
[17] S.P.Tsunoda et al., Proc.Natl.Acad.Sci.U.S.A. 98, 6560 (2001).
[18] H.Noji, R.Yasuda, M.Yoshida, and K.Kinoshita, Nature(London) 386, 299 (1997).
[19] K.Sekimoto, J. Phys. Soc. Jpn. 66, 1234 (1997).