

Research Article

Stokes Efficiency of Molecular Motor-Cargo Systems

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A molecular motor utilizes chemical free energy to generate a unidirectional motion through the viscous fluid. In many experimental settings and biological settings, a molecular motor is elastically linked to a cargo. The stochastic motion of a molecular motor-cargo system is governed by a set of Langevin equations, each corresponding to an individual chemical occupancy state. The change of chemical occupancy state is modeled by a continuous time discrete space Markov process. The probability density of a motor-cargo system is governed by a two-dimensional Fokker-Planck equation. The operation of a molecular motor is dominated by high viscous friction and large thermal fluctuations from surrounding fluid. The instantaneous velocity of a molecular motor is highly stochastic: the past velocity is quickly damped by the viscous friction and the new velocity is quickly excited by bombardments of surrounding fluid molecules. Thus, the theory for macroscopic motors should not be applied directly to molecular motors without close examination. In particular, a molecular motor behaves differently working against a viscous drag than working against a conservative force. The Stokes efficiency was introduced to measure how efficiently a motor uses chemical free energy to drive against viscous drag. For a motor without cargo, it was proved that the Stokes efficiency is bounded by 100% [H. Wang and G. Oster, (2002)]. Here, we present a proof for the general motor-cargo system.

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1. Introduction and mathematical formulation

Molecular motors play a central role in many cellular functions. For example, an F_o motor utilizes the transmembrane proton gradient to power the ATP synthesis in the F_1 portion of the ATP synthase; a Kinesin dimer hydrolyzes ATP to drive intracellular vesicle transportation; and a V-ATPase hydrolyzes ATP to pump protons against a large proton gradient to regulate intracellular acidity. Understanding the operating principles of molecular motors is crucial to comprehending intracellular protein transport and cell motility.

Due to the small size of molecular motors, the inertia of the motor is negligible. As a result, the motor operation is dominated by high viscous friction and large thermal fluctuations from the fluid environment [1]. Because of these properties of molecular motors, the results for macroscopic motors, in general, do not necessarily extend to molecular motors. In both macroscopic motors and molecular motors, a chemical reaction can be used to generate a conformational change and an active force at the reaction site. The conformational change along with the active force is then mechanically delivered to drive the motor motion. This mechanism of generating directed motion is called a power stroke motor [2, 3]. However, in a molecular motor, a unidirectional motion can be generated by a completely different mechanism. For simplicity, we consider the case where a motor is restricted to moving in one spatial dimension, such as moving along a polymer track. Suppose we use the free energy released from the chemical reaction to block thermal fluctuations toward one direction. Then, the motor will move toward the opposite direction. Here the unidirectional motion is not directly driven by an active force produced at the reaction site. Rather it is directly driven by the bombardments of surrounding fluid molecules. Of course, drawing thermal energy from an isothermal environment to drive motor motion is not sustainable without a free energy input. The free energy for blocking the backward fluctuations and rectifying the forward fluctuations comes from the chemical reaction. This mechanism of generating a unidirectional motion is called a Brownian ratchet [4–7].

One of the main differences between molecular motors and macroscopic motors is manifested in the issue of efficiency. For a macroscopic motor, the efficiency is well defined no matter it is working against a conservative force or working against a friction force. For a molecular motor, we do need to distinguish these two cases. When a molecular motor is working against a conservative force, the thermodynamic efficiency is well defined and is the energy output to the external agent exerting the conservative force divided by the chemical free energy consumption in the motor. When a molecular motor is working against a viscous drag, the situation is completely different. It has no energy output at all. One way to define efficiency in this case is to proceed with the apparent energy output based on the average velocity. The efficiency defined this way, called Stokes efficiency, is different from the thermodynamic efficiency. First of all, these two efficiencies are for two different cases: the thermodynamic efficiency is for a motor working against a conservative force; and the Stokes efficiency is for a motor working against a viscous drag. But this is not the only difference. In single molecule experiments, a motor can be put to work against a conservative force. In a different experimental setup, the same motor can be put to work against a viscous drag. For a molecular motor, both the thermodynamic efficiency and the Stokes efficiency can be measured but in two different experimental setups. Before we can treat the Stokes efficiency as a valid efficiency measurement, we need to show that it is bounded by 100%. Since the apparent energy output used in the definition of the Stokes efficiency does not have a thermodynamic meaning, the Stokes efficiency being bounded by 100% cannot be argued simply from thermodynamical point of view. In this paper, we prove mathematically that the Stokes efficiency is bounded by 100%. The proof is based on the Fokker-Planck formulation of motor-cargo systems. Below we will first describe this mathematical formulation.

A molecular motor, in general, has many internal and external degrees of freedom. One of these degrees of freedom is associated with the motor's unidirectional motion, the main biological function of the motor. For example, a Kinesin dimer walks along a microtubule filament toward the positive end [8, 9]. There are many levels of models for molecular motors,

from simple kinetic models with a few states to all atom molecular dynamics. We adopt a modeling approach of intermediate level in which the unidirectional motion is followed explicitly and the effects of other degrees of freedom are modeled in the mean field potential affecting the unidirectional motion [2, 5, 7, 10]. To introduce this modeling approach of intermediate level, we start with the simple case of a small particle in a fluid environment, restricted to moving in one spatial dimension, and subject to a static potential, $\phi(x)$, where x is the coordinate along the spatial dimension. This situation is actually very close to that of a molecular motor. The main difference is that a molecular motor is driven by switching among a set of static potentials, each corresponding to one chemical occupancy state. The particle experiences are (1) the force derived from the potential, (2) the viscous drag force from the fluid environment, and (3) the Brownian force also from the fluid environment. Both the drag force and the Brownian force arise from collisions of the particle with the surrounding fluid molecules. The drag force is the mean of this stochastic bombarding force and the Brownian force is the fluctuating part of this bombarding force. The drag force on the particle is always opposing the motion and is proportional to the velocity: drag = $-\zeta\mathbf{u}$, where \mathbf{u} is the velocity and ζ is the drag coefficient of the particle. Here, we adopt the convention that stochastic processes are denoted by boldface letters. The Brownian force on the particle has zero mean and is modeled as a Gaussian white noise, which is the formal derivative of the Wiener process (the Brownian motion). The magnitude of the Brownian force is related to the drag coefficient as

$$\text{Brownian force} = \sqrt{2k_B T \zeta} \frac{d\mathbf{W}(t)}{dt}, \quad (1.1)$$

where k_B is the Boltzmann constant, T is the absolute temperature [11], and $\mathbf{W}(t)$ is the Wiener process [12]. This is a result of the fluctuation-dissipation theorem [13–15]. The stochastic motion of the particle is governed by the Langevin equation

$$m \frac{d\mathbf{u}}{dt} = -\zeta\mathbf{u} - \phi'(x) + \sqrt{2k_B T \zeta} \frac{d\mathbf{W}(t)}{dt}, \quad \frac{dx}{dt} = \mathbf{u}, \quad (1.2)$$

where m is the mass of the particle. Equation (1.2) has two very different time scales: the time scale of the motor forgetting about its current velocity (the time scale of inertia), and the time scale of moving over one period of potential $\phi(x)$ (the time scale of reaction cycle). Dividing both sides of (1.2) by m and noticing that quantity $t_0 \equiv m/\zeta$ has the dimension of time, we rewrite (1.2) as

$$\frac{d\mathbf{u}}{dt} = \frac{-1}{t_0} [\mathbf{u} - \mathbf{g}(t)]. \quad (1.3)$$

Here $\mathbf{g}(t)$ is a stochastic process given by

$$\mathbf{g}(t) = -D \frac{\phi'(x)}{k_B T} + \sqrt{2D} \frac{d\mathbf{W}(t)}{dt}, \quad (1.4)$$

where D is the diffusion coefficient of the particle and is related to the drag coefficient by the Einstein relation: $D \equiv k_B T / \zeta$ [1]. The solution of (1.3) has the form

$$\mathbf{u}(t) = \mathbf{g}(t) + \exp\left(\frac{-t}{t_0}\right) (\mathbf{u}(0) - \mathbf{g}(0)) + \frac{1}{t_0} \int_0^t \exp\left(\frac{-(t-s)}{t_0}\right) (\mathbf{g}(s) - \mathbf{g}(t)) ds. \quad (1.5)$$

Note that (1.5) does not provide an explicit expression for the solution of (1.3) since $\mathbf{g}(t)$ is unknown. Nevertheless, it is clear from (1.5) that the effect of the initial velocity $\mathbf{u}(0)$ decays exponentially with time scale $t_0 \equiv m/\zeta$. For that reason, we call t_0 the time scale of inertia. In general, the drag coefficient is proportional to the linear size of the particle [1], and the mass is proportional to the volume of the particle. For a spherical particle of radius r , the mass, the drag coefficient, and the time scale of inertia are, respectively,

$$m = \frac{4}{3}\pi\rho r^3, \quad \zeta = 6\pi\eta r, \quad t_0 = \frac{m}{\zeta} = \frac{2\rho}{9\eta}r^2, \quad (1.6)$$

where ρ is the density of the particle and η is the viscosity of the surrounding fluid. In general, the time scale of inertia t_0 is proportional to the square of the linear size of particle whereas the coefficient varies with the shape of particle. Thus, for small particles, the time scale of inertia t_0 is very small. For example, for a latex bead of diameter $1\ \mu\text{m}$ in water, we have $t_0 = 56 \times 10^{-9}\text{ s} = 56\text{ ps}$. A time period of 56 ps is much smaller than the typical time scales of chemical reaction cycles in molecular motors, which are of the order of milliseconds. The short time dynamics of the particle is full of fast decaying of the instantaneous velocity in time scale of t_0 and fast increasing of the instantaneous velocity excited by the stochastic Brownian force. These short-time dynamical behaviors present significant difficulties for analysis and computations. It is desirable to capture relatively long-time behaviors of the motor in the time scales of reaction cycles, without resolving these short-time details. For that purpose, we consider the mathematical limit of (1.3) as time scale t_0 goes to zero. As time scale t_0 goes to zero, the limit of the solution of (1.3) satisfies

$$\frac{d\mathbf{x}}{dt} = -D \frac{\phi'(\mathbf{x})}{k_B T} + \sqrt{2D} \frac{d\mathbf{W}(t)}{dt}. \quad (1.7)$$

The reduction from (1.3) to (1.7) in the limit of small t_0 is called the Einstein-Smoluchowski limit [16].

In a molecular motor, the potential is not static. Instead, the potential changes with the current chemical occupancy state of the motor. In this paper, we consider the case where a motor has only one catalytic site (one reaction cycle). The extension of the analysis to the case of multiple catalytic sites is straightforward but tedious. Let N be the number of chemical occupancy states of the motor in consideration. Let $\{1, 2, \dots, N\}$ denote the set of N occupancy states, and let $\{\phi_1(x), \phi_2(x), \dots, \phi_N(x)\}$ denote the corresponding set of N periodic potentials. Here $\phi_j(x)$ is the periodic motor potential when the motor is in chemical occupancy state j . Mathematically, $\phi_j(x)$ is a periodic function of period L where the period L is either one motor step or a multiple of motor steps. For a Kinesin dimer walking on a microtubule filament, one motor step is about 8 nm. For the rotary motor of F_1 ATPase, one motor step is one third of one revolution ($2\pi/3$). The mechanical motion of the motor is governed by Langevin equation:

$$\frac{d\mathbf{x}}{dt} = -D \frac{\phi'_{\mathbf{S}(t)}(\mathbf{x})}{k_B T} + \sqrt{2D} \frac{d\mathbf{W}(t)}{dt}, \quad (1.8)$$

where $\mathbf{S}(t)$ denotes the current chemical occupancy state, and $\phi_{\mathbf{S}(t)}(x)$ is the periodic motor potential corresponding to $\mathbf{S}(t)$. Equation (1.8) can either be viewed as one Langevin equation that varies with the current occupancy state $\mathbf{S}(t)$ or be viewed as a collection of N Langevin

equations, each corresponding to an individual chemical occupancy state. Equation (1.8) describes only the spatial motion of the motor. Equation (1.8) is not closed since it depends on the current occupancy state $\mathbf{S}(t)$. To close (1.8), we need to follow the time evolution of the chemical occupancy state. In a transition from occupancy state A to occupancy state B , the commitment time is generally much smaller than the residence time. The commitment time is the time of the actual transition process. More precisely, the commitment time is the time period during which the system has left state A but has not yet arrived at state B . If we define a transition state between state A and state B , the commitment time can also be viewed as the residence time of the transition state. Because the commitment time of transition is small in comparison with the residence time, we can approximate the transition as instantaneous. Thus, we model the stochastic evolution of the motor's chemical state as a continuous time discrete space Markov process, also called a jump process:

$$\Pr[\mathbf{S}(t + \delta t) = j \mid \mathbf{S}(t) = i] = \begin{cases} (\delta t)k_{i \rightarrow j}(\mathbf{x}(t)) + o(\delta t), & j \neq i, \\ 1 - (\delta t) \sum_{l \neq i} k_{i \rightarrow l}(\mathbf{x}(t)) + o(\delta t), & j = i, \end{cases} \quad (1.9)$$

where $k_{i \rightarrow j}(\mathbf{x}(t))$ is the transition rate from state i to state j . Notice that the transition rate depends on the motor position $\mathbf{x}(t)$. In other words, in Markov process (1.9), the evolution of chemical state $\mathbf{S}(t)$ is affected by the motor position $\mathbf{x}(t)$. On the other hand, in Langevin equation (1.8), the evolution of motor position $\mathbf{x}(t)$ is affected by the chemical state $\mathbf{S}(t)$. Thus, Langevin equation (1.8) and Markov process (1.9) are coupled, and together they govern the stochastic evolution of both the mechanical motion and the chemical reaction of the motor. In most of chemical reactions, for example, in the ATP hydrolysis cycle, the system goes through the set of N occupancy states sequentially. In this case, the N occupancy states form a loop, and the only allowed transitions are either forward to the next state or backward to the previous state along the loop. Here, by convention, we represent the transition $N \rightarrow 1$ by $N \rightarrow N+1$ and represent the transition $1 \rightarrow N$ by $N+1 \rightarrow N$. With this convention, we have that $k_{i \rightarrow j}(\mathbf{x}(t)) \neq 0$ only when $j = i + 1$ or $j = i - 1$.

The derivation in [17] was for motor systems without cargos. In many single molecule experiments, the motor is not observed/recorded directly. Instead a large latex bead is attached to the motor, the position of the bead is observed/controlled with the help of a laser trap or a force clamp [9, 18–20]. Motor-cargo systems also occur in biological settings. For example, a Kinesin dimer walks on a microtubule filament, towing a vesicle toward the membrane for exporting. To accommodate these experimental and biological settings, we need to study the behaviors of motor-cargo systems. Figure 1 shows a motor-cargo system corresponding to the experimental setups in [9, 19]. A Kinesin dimer walks on a microtubule toward the plus end and a latex bead is linked to the Kinesin dimer to visualize the motion of the Kinesin dimer and to exert a force on the Kinesin dimer. The force exerted on the Kinesin dimer is varied either by changing the drag coefficient of the latex bead [19] or by applying a conservative force on the bead using a laser trap [9]. In the recently developed 2D laser trap [20], a force perpendicular to the direction of motor motion can also be exerted on the Kinesin dimer.

Let $\mathbf{x}(t)$ be the coordinate of the motor and $\mathbf{y}(t)$ the coordinate of the cargo along the direction of motion as illustrated in Figure 1. As we discussed above, the motor is driven by switching among a set of N potentials, each corresponding to an individual occupancy state.

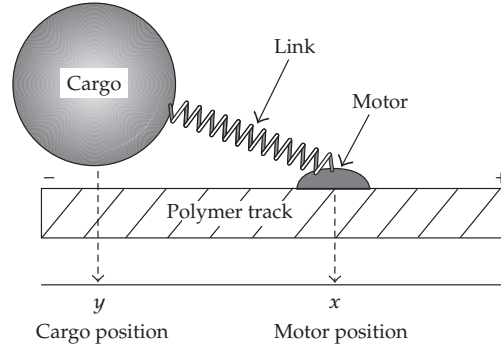


Figure 1: A motor-cargo system in single molecule experiments, corresponding to the experimental setup in [9, 19]. A Kinesin dimer walks on a microtubule filament toward the plus end, and a latex bead is linked to the Kinesin dimer to visualize the motion of the Kinesin dimer and to exert a force on the Kinesin dimer. The latex bead is either loaded by the force from a laser trap or loaded by the viscous drag from the fluid media.

The stochastic motion of the motor is governed by an overdamped Langevin equation

$$\frac{dx}{dt} = D_M \frac{[-E'(x-y-R) - \phi'_{S(t)}(x)]}{k_B T} + \sqrt{2D_M} \frac{d\mathbf{W}(t)}{dt}, \quad (1.10)$$

where D_M is the diffusion coefficient of the motor, and $-E'(x-y-R)$ is the elastic force on the motor exerted by the elastic link between the motor and the cargo. Here $E(x-y-R)$ is the elastic potential and R the rest length of the elastic link. The rest length R can be eliminated using a change of variable $\tilde{y} = y + R$. So without loss of generality, we assume $R = 0$. The stochastic evolution of the occupancy state is governed by jump process (1.9). In the motor-cargo system, the external loading force no longer acts directly on the motor. The external loading force acts directly on the cargo. The stochastic motion of the cargo is governed by

$$\frac{dy}{dt} = D_C \frac{[f + E'(x-y-R)]}{k_B T} + \sqrt{2D_C} \frac{d\mathbf{W}(t)}{dt}, \quad (1.11)$$

where D_C is the diffusion coefficient of the cargo, and f is the external loading force acting on the cargo. Note that in the motor-cargo system, the motor does not directly feel the external loading force on the cargo; the motor sees the elastic force from the cargo. On the other hand, the cargo does not directly feel the internal motor force; the cargo sees the elastic force from the motor. All communications between the motor and the cargo are done via the elastic link. In experiments, only average quantities can be measured repeatedly and reliably. All average quantities can be calculated by following the probability density of the motor-cargo system. Let $\rho_j(x, y, t)$ be the probability density that the motor has at position x , the cargo is at position y , and the chemical reaction is in occupancy state j at time t . Mathematically, $\rho_j(x, y, t)$ is defined as

$$\rho_j(x, y, t) = \lim_{\substack{\delta x \rightarrow 0 \\ \delta y \rightarrow 0}} \frac{\Pr \left[\begin{array}{l} x \leq \mathbf{x}(t) < x + \delta x \\ y \leq \mathbf{y}(t) < y + \delta y, \mathbf{S}(t) = j \end{array} \right]}{\delta x \delta y}. \quad (1.12)$$

The set of probability densities $\{\rho_j(x, y, t)\}$ is governed by the two-dimensional Fokker-Planck equation corresponding to Langevin equations (1.10) and (1.11) and jump process (1.9) [16]. The Fokker-Planck equation is based on the conservation of probability

$$\frac{\partial \rho_j}{\partial t} = -\frac{\partial}{\partial x} J_j^{(x)} - \frac{\partial}{\partial y} J_j^{(y)} - (p_{j+1/2} - p_{j-1/2}). \quad (1.13)$$

In the above, $J_j^{(x)}(x, y, t)$ is the probability flux along the x -direction (the dimension of the motor position) in occupancy state j and it has the expression

$$J_j^{(x)}(x, y, t) = -D_M \left(\frac{1}{k_B T} \frac{\partial \Phi_j(x, y)}{\partial x} \rho_j + \frac{\partial \rho_j}{\partial x} \right). \quad (1.14)$$

$\Phi_j(x, y)$ is the total potential of the motor-cargo system in occupancy state j , which includes both the internal motor potential caused by the chemical reaction and the elastic energy in the link connecting the motor and cargo. $\Phi_j(x, y)$ does not contain the effect of the external loading force, which is accounted for separately. $\Phi_j(x, y)$ has the expression

$$\Phi_j(x, y) = \phi_j(x) + E(x - y). \quad (1.15)$$

$J_j^{(y)}(x, y, t)$ is the probability flux along the y -direction (the dimension of the cargo position) in occupancy state j and it has the expression

$$J_j^{(y)}(x, y, t) = -D_C \left(\frac{1}{k_B T} \left[-f + \frac{\partial \Phi_j(x, y)}{\partial y} \right] \rho_j + \frac{\partial \rho_j}{\partial y} \right). \quad (1.16)$$

$p_{j+1/2}(x, y, t)$ is the net probability flux density (net probability flux per unit area in the $x - y$ plane) along the direction of reaction from occupancy state j to occupancy state $j + 1$. It has the expression

$$p_{j+1/2}(x, y, t) = k_{j \rightarrow j+1}(x) \rho_j(x, y, t) - k_{j+1 \rightarrow j}(x) \rho_{j+1}(x, y, t). \quad (1.17)$$

Note that the transition rate $k_{j \rightarrow j+1}(x)$ does not depend explicitly on the cargo position (y). The cargo can affect the chemical reaction indirectly by changing the motor position. In the chemical reaction governed by jump process (1.9), the transition rates $k_{i \rightarrow j}(x)$ cannot be arbitrarily specified. These rates are constrained by detailed balance-like condition, which ensures that if the system is brought to an equilibrium, then the equilibrium solution is given by the Boltzmann distribution and the probability flux vanishes everywhere [11]. Specifically, suppose state A and state B have well-defined free energy G_A and G_B . Then the transition rates between these two states must satisfy

$$\frac{k_{A \rightarrow B}}{k_{B \rightarrow A}} = \exp \left(\frac{G_A - G_B}{k_B T} \right). \quad (1.18)$$

It follows that the transition rates used in (1.17) are constrained by

$$\frac{k_{j \rightarrow j+1}(x)}{k_{j+1 \rightarrow j}(x)} = \exp \left(\frac{\Phi_j(x, y) - \Phi_{j+1}(x, y)}{k_B T} \right) = \exp \left(\frac{\phi_j(x) - \phi_{j+1}(x)}{k_B T} \right). \quad (1.19)$$

The boundary conditions for (1.13) in the x -direction are pseudoperiodic:

$$\begin{aligned}\rho_j(x+L, y+L, t) &= \rho_j(x, y, t), \\ \phi_j(x+L) &= \phi_j(x), \\ k_{i \rightarrow j}(x+L) &= k_{i \rightarrow j}(x).\end{aligned}\tag{1.20}$$

In the y -direction, (1.13) extends from negative infinity to positive infinity. For fixed x and large y , the elastic energy $E(x-y)$ is large and the probability density $\rho_j(x, y, t)$ is exponentially small. Thus, at infinity, we have

$$\rho_j(x, \pm \infty, t) = 0, \quad \frac{\partial \rho_j(x, \pm \infty, t)}{\partial x} = 0, \quad \frac{\partial \rho_j(x, \pm \infty, t)}{\partial y} = 0.\tag{1.21}$$

The boundary conditions along the reaction direction are also pseudoperiodic:

$$\begin{aligned}\rho_{N+j}(x, y, t) &= \rho_j(x, y, t), \\ \phi_{N+j}(x) &= \phi_j(x) + \Delta G, \\ k_{N+i \rightarrow N+j}(x) &= k_{i \rightarrow j}(x),\end{aligned}\tag{1.22}$$

where $\Delta G < 0$ is the free energy change in one reaction cycle.

2. Stokes efficiency, previous result, and a general proof

In [17], the Stokes efficiency was proposed to measure how efficiently the motor utilizes the chemical free energy to drive through the viscous fluid. Let $\langle \mathbf{u} \rangle$ denote the average velocity and let r denote the chemical reaction rate (average number of reaction cycles per unit time) of the motor system. The Stokes efficiency for a motor system without cargo is defined as

$$\eta_{\text{Stokes}} \equiv \frac{\zeta \langle \mathbf{u} \rangle^2}{r(-\Delta G) + f \langle \mathbf{u} \rangle},\tag{2.1}$$

where ζ is the drag coefficient of the motor. In a motor-cargo system, the motor part has drag coefficient $\zeta_M = k_B T / D_M$ and the cargo part has drag coefficient $\zeta_C = k_B T / D_C$. Since both the motor and the cargo move through the viscous fluid with the same average velocity, the Stokes efficiency for a motor-cargo system is defined as

$$\eta_{\text{Stokes}} \equiv \frac{(\zeta_M + \zeta_C) \langle \mathbf{u} \rangle^2}{r(-\Delta G) + f \langle \mathbf{u} \rangle}.\tag{2.2}$$

The denominator of the Stokes efficiency is the total free energy consumed per unit time: $r(-\Delta G)$ is the chemical free energy consumed in the chemical reaction per unit time and $f \langle \mathbf{u} \rangle$ is the free energy input to the motor-cargo system from the external agent exerting the conservative force. If the external conservative force is against the motor motion, then $f \langle \mathbf{u} \rangle$ is negative, which means the free energy is actually output to the external agent. The numerator of the Stokes efficiency, $(\zeta_M + \zeta_C) \langle \mathbf{u} \rangle^2$, has the dimension of energy per unit time. But it does

not have a clear thermodynamic meaning. As a result, $\eta_{\text{Stokes}} \leq 1$ cannot be derived from simple thermodynamic arguments. In [17], we proved $\eta_{\text{Stokes}} \leq 1$ for motor systems without cargos. Below we present a proof for the general motor-cargo system described by Fokker-Planck equation (1.13) with detailed balance constraint (1.19) and boundary conditions (1.20), (1.21), and (1.22). Specifically, we want to prove

$$(\zeta_M + \zeta_C) \langle \mathbf{u} \rangle^2 \leq r(-\Delta G) + f \langle \mathbf{u} \rangle. \quad (2.3)$$

Since all average quantities can be determined from the steady-state solution, we consider the steady state of (1.13) as follows:

$$\frac{\partial}{\partial x} J_j^{(x)} + \frac{\partial}{\partial y} J_j^{(y)} = -(p_{j+1/2} - p_{j-1/2}). \quad (2.4)$$

To facilitate the analysis below, we introduce a new function $H_j(x, y)$:

$$H_j(x, y) \equiv \frac{\Phi_j(x, y)}{k_B T} + \ln(\rho_j(x, y)). \quad (2.5)$$

Note that in the steady state, everything is independent of t . From the pseudoperiodic boundary condition in the reaction direction, we obtain immediately that

$$H_{N+j}(x, y) = H_j(x, y) + \frac{\Delta G}{k_B T}. \quad (2.6)$$

With the help of function $H_j(x, y)$, we rewrite the fluxes $J_j^{(x)}$ and $J_j^{(y)}$ as

$$J_j^{(x)} = -D_M \left(\frac{1}{k_B T} \frac{\partial \Phi_j}{\partial x} \rho_j + \frac{\partial \rho_j}{\partial x} \right) = -D_M \rho_j \frac{\partial H_j}{\partial x}, \quad (2.7)$$

$$J_j^{(y)} = -D_C \left(\frac{1}{k_B T} \left[-f + \frac{\partial \Phi_j}{\partial y} \right] \rho_j + \frac{\partial \rho_j}{\partial y} \right) = -D_C \rho_j \left(\frac{\partial H_j}{\partial y} - \frac{f}{k_B T} \right). \quad (2.8)$$

The average velocity and the chemical reaction rate have the expressions:

$$\langle \mathbf{u} \rangle = \int_0^L \int_{-\infty}^{\infty} \sum_{j=1}^N J_j^{(x)} dy dx, \quad (2.9)$$

$$\langle \mathbf{u} \rangle = \int_0^L \int_{-\infty}^{\infty} \sum_{j=1}^N J_j^{(y)} dy dx, \quad (2.10)$$

$$r = \int_0^L \int_{-\infty}^{\infty} p_{j+1/2} dy dx. \quad (2.11)$$

In the above, we have two expressions for the average velocity $\langle \mathbf{u} \rangle$. The first expression (2.9) is the average velocity of the motor, and the second expression (2.10) is the average velocity of the cargo. Since the motor and the cargo are elastically linked, they must have the same

average velocity. Substituting flux (2.7) into the average velocity for the motor given in (2.9) and applying the Cauchy-Schwarz inequality yield

$$\begin{aligned} \langle \mathbf{u} \rangle^2 &= \left[\int_0^L \int_{-\infty}^{\infty} \sum_{j=1}^N -D_M \rho_j \frac{\partial H_j}{\partial x} dy dx \right]^2 \\ &= \left[\int_0^L \int_{-\infty}^{\infty} \sum_{j=1}^N \rho_j^{1/2} \left(-D_M \rho_j^{1/2} \frac{\partial H_j}{\partial x} \right) dy dx \right]^2 \\ &\leq \left[\int_0^L \int_{-\infty}^{\infty} \sum_{j=1}^N \rho_j dy dx \right] \cdot \left[\int_0^L \int_{-\infty}^{\infty} \sum_{j=1}^N D_M^2 \rho_j \left(\frac{\partial H_j}{\partial x} \right)^2 dy dx \right]. \end{aligned} \quad (2.12)$$

Using the fact that the total probability is one and converting back to flux $J_j^{(x)}$, we get

$$\langle \mathbf{u} \rangle^2 \leq -D_M \int_0^L \int_{-\infty}^{\infty} \sum_{j=1}^N J_j^{(x)} \frac{\partial H_j}{\partial x} dy dx. \quad (2.13)$$

Pseudoperiodic boundary condition (1.20) implies

$$\int_{-\infty}^{\infty} \sum_{j=1}^N J_j^{(x)} H_j dy \Big|_{x=0} = \int_{-\infty}^{\infty} \sum_{j=1}^N J_j^{(x)} H_j dy \Big|_{x=L}. \quad (2.14)$$

Integrating by parts the right-hand side of (2.13) and using (2.14), we have

$$\langle \mathbf{u} \rangle^2 \leq D_M \int_0^L \int_{-\infty}^{\infty} \sum_{j=1}^N H_j \frac{\partial J_j^{(x)}}{\partial x} dy dx. \quad (2.15)$$

Equation (2.15) is an inequality for $\langle \mathbf{u} \rangle$ based on the average velocity of the motor. Now using the average velocity for the cargo given in (2.10) with flux (2.8), applying the Cauchy-Schwarz inequality, converting back to flux $J_j^{(y)}$, and then converting back to $\langle \mathbf{u} \rangle$, we obtain

$$\begin{aligned} \langle \mathbf{u} \rangle^2 &= \left[\int_0^L \int_{-\infty}^{\infty} \sum_{j=1}^N \rho_j^{1/2} \left(-D_C \rho_j^{1/2} \left(\frac{\partial H_j}{\partial y} - \frac{f}{k_B T} \right) \right) dy dx \right]^2 \\ &\leq \int_0^L \int_{-\infty}^{\infty} \sum_{j=1}^N D_C^2 \rho_j \left(\frac{\partial H_j}{\partial y} - \frac{f}{k_B T} \right)^2 dy dx \\ &= -D_C \int_0^L \int_{-\infty}^{\infty} \sum_{j=1}^N J_j^{(y)} \left(\frac{\partial H_j}{\partial y} - \frac{f}{k_B T} \right) dy dx \\ &= -D_C \int_0^L \int_{-\infty}^{\infty} \sum_{j=1}^N J_j^{(y)} \frac{\partial H_j}{\partial y} dy dx + D_C \frac{f}{k_B T} \langle \mathbf{u} \rangle. \end{aligned} \quad (2.16)$$

Integrating by parts and using boundary condition (1.21) lead to another inequality for $\langle \mathbf{u} \rangle$:

$$\langle \mathbf{u} \rangle^2 \leq D_C \int_0^L \int_{-\infty}^{\infty} \sum_{j=1}^N H_j \frac{\partial J_j^{(y)}}{\partial y} dy dx + D_C \frac{f}{k_B T} \langle \mathbf{u} \rangle. \quad (2.17)$$

Combining inequalities (2.15) and (2.17) gives us

$$\begin{aligned} \langle \mathbf{u} \rangle^2 &= \frac{D_C}{D_M + D_C} \langle \mathbf{u} \rangle^2 + \frac{D_M}{D_M + D_C} \langle \mathbf{u} \rangle^2 \\ &\leq \frac{D_C D_M}{D_M + D_C} \int_0^L \int_{-\infty}^{\infty} \sum_{j=1}^N H_j \left(\frac{\partial J_j^{(x)}}{\partial x} + \frac{\partial J_j^{(y)}}{\partial y} \right) dy dx + \frac{D_C D_M}{D_M + D_C} \cdot \frac{f}{k_B T} \langle \mathbf{u} \rangle. \end{aligned} \quad (2.18)$$

Up to now, we have not yet used the steady-state Fokker-Planck equation (2.4). Using (2.4), applying summation by parts, and using relation (2.6), we have

$$\begin{aligned} \langle \mathbf{u} \rangle^2 &\leq \frac{-D_C D_M}{D_M + D_C} \int_0^L \int_{-\infty}^{\infty} \sum_{j=1}^N H_j (p_{j+1/2} - p_{j-1/2}) dy dx + \frac{D_C D_M}{D_M + D_C} \cdot \frac{f \langle \mathbf{u} \rangle}{k_B T} \\ &= \frac{D_C D_M}{D_M + D_C} \int_0^L \int_{-\infty}^{\infty} \sum_{j=1}^N p_{j+1/2} (H_{j+1} - H_j) dy dx \\ &\quad + \frac{D_C D_M}{D_M + D_C} \cdot \frac{(-\Delta G)}{k_B T} \int_0^L \int_{-\infty}^{\infty} p_{1/2} dy dx + \frac{D_C D_M}{D_M + D_C} \cdot \frac{f \langle \mathbf{u} \rangle}{k_B T} \\ &\equiv Q_1 + Q_2 + Q_3. \end{aligned} \quad (2.19)$$

Let us examine the three terms Q_1 , Q_2 , and Q_3 defined above one by one. For Q_3 , we use the relation $(D_C D_M / (D_M + D_C)) \cdot (1/k_B T) = 1/(\zeta_M + \zeta_C)$ to write it as

$$Q_3 = \frac{1}{\zeta_M + \zeta_C} \cdot f \langle \mathbf{u} \rangle. \quad (2.20)$$

In Q_2 , converting the integral back to the chemical reaction rate gives us

$$Q_2 = \frac{1}{\zeta_M + \zeta_C} \cdot r(-\Delta G). \quad (2.21)$$

For Q_1 , we first use detailed balance (1.19) to write flux density $p_{j+1/2}$ as

$$\begin{aligned} p_{j+1/2} &= k_{j \rightarrow j+1} \rho_j \left(1 - \frac{k_{j+1 \rightarrow j}}{k_{j \rightarrow j+1}} \cdot \frac{\rho_{j+1}}{\rho_j} \right) \\ &= k_{j \rightarrow j+1} \rho_j \left(1 - \exp \left(\frac{\phi_{j+1}(x) - \phi_j(x)}{k_B T} + \ln \frac{\rho_{j+1}}{\rho_j} \right) \right). \end{aligned} \quad (2.22)$$

Then we use definition (2.5) to write $H_{j+1} - H_j$ as

$$H_{j+1} - H_j = \frac{\phi_{j+1}(x) - \phi_j(x)}{k_B T} + \ln \frac{\rho_{j+1}}{\rho_j}. \quad (2.23)$$

Using these two results, we write Q_1 as

$$Q_1 = \frac{D_C D_M}{D_M + D_C} \int_0^L \int_{-\infty}^{\infty} \sum_{j=1}^N k_{j \rightarrow j+1} \rho_j (1 - \exp(-\Delta H_{j+1/2})) \Delta H_{j+1/2} dy dx, \quad (2.24)$$

where $\Delta H_{j+1/2} \equiv H_{j+1} - H_j$. Since the expression $(1 - \exp(\alpha))\alpha$ is always nonpositive for any value of α , it follows that Q_1 is always nonpositive: $Q_1 \leq 0$. Finally, substituting Q_1 , Q_2 , and Q_3 into (2.19), we arrive at

$$\langle \mathbf{u} \rangle^2 \leq \frac{1}{\zeta_M + \zeta_C} (r(-\Delta G) + f \langle \mathbf{u} \rangle) \quad (2.25)$$

which leads directly to the desired result (2.3). Thus, the Stokes efficiency is indeed bounded by 100% for a motor-cargo system.

In summary, for the general case where a motor is elastically linked to a cargo, we have proved mathematically that the Stokes efficiency is bounded 100%. Therefore, the Stokes efficiency is a justified efficiency measure for motor-cargo systems.

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