

The Stokes efficiency for molecular motors and its applications

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Abstract. – In many experiments it is only possible to load a molecular motor by manipulating the viscous drag from the fluid medium. In these situations, it is not clear how to measure the efficiency of energy transduction. Here we define the Stokes efficiency as the average viscous drag times the average velocity divided by the rate of free-energy consumption. We show that this efficiency is bounded by 100% and thus is well defined. We compare the Stokes efficiency with the usual thermodynamic efficiency, and discuss what information it provides about the motor mechanism.

Protein motors convert chemical energy into mechanical work while operating in an environment dominated by Brownian motion. If a molecular motor is coupled to work against a conservative force from an external agent that can be controlled by the experimenter (for example, a laser trap), then a true load-velocity curve can be measured [1]. In this situation the rate of work done by the motor on the external agent equals the rate of potential energy increase in the external agent. This can be viewed as the rate of free-energy output from the motor to the external agent. The thermodynamic energy conversion efficiency is the rate of free-energy output divided by the rate of chemical free-energy consumption by the motor. However, in many experiments the motor can be loaded only by varying the viscous drag from the fluid medium [2, 3]. If the motor is working against only the viscous drag, there is no free-energy output from the motor. In such situations, how should an efficiency be defined that will measure the effectiveness of mechanochemical energy transduction? Of course, a well-defined efficiency measure must be bounded by one. In this letter, we define an efficiency measure for viscously loaded molecular motors; we call it the “Stokes efficiency” because the viscous drag is calculated from the Stokes law. Before giving the required mathematical proof that the Stokes efficiency is always ≤ 1 , we begin with some heuristic discussion that will motivate our subsequent definitions and analysis.

Consider the case where a molecular motor, powered by chemical reaction cycles on one or more catalytic sites, drives an external object. In most experiments the external object is much larger than the motor itself [2, 3]. In the absence of an external conservative force (*e.g.*, a laser trap), the chemical reaction can only proceed spontaneously in the direction that decreases the chemical free energy of the *reaction* system. We define this reaction direction as

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the positive direction for the chemical cycle and define the associated direction of the motor *motion* as positive. Since molecular motors operate in a stochastic environment dominated by thermal fluctuations, only average quantities are measurable in repeatable experiments. To define the Stokes efficiency we introduce the following notation, where $\langle \cdot \rangle$ denotes either the time average or ensemble average:

- ν = the instantaneous (linear or angular) velocity of the motor.
- $\langle \nu \rangle$ = the *average* velocity of the motor.
- f = the conservative force acting on the motor by an external agent (*e.g.*, a laser trap).
- A = the chemical free energy consumed in one reaction cycle: $A \equiv -\Delta G_{\text{cycle}} > 0$ [4].
- $\langle r \rangle$ = the rate of the chemical reaction cycle.

For molecular motors, the magnitude of the instantaneous velocity is much larger than the average velocity: $\sqrt{\langle \nu^2 \rangle} \gg \langle \nu \rangle$. For an object in thermal *equilibrium* with surrounding fluid, the mean square of the instantaneous velocity is given by equipartition of energy: $\langle \nu^2 \rangle = k_B T / I$, where k_B is Boltzmann's constant and T the absolute temperature. I is the moment of inertia (mass) of the object if the angular (linear) velocity is considered. For a $0.5 \mu\text{m}$ bead (an object much larger than molecular motors) $\sqrt{\langle \nu_{\text{angular}}^2 \rangle} \approx 8000 \text{ Hz}$ and $\sqrt{\langle \nu_{\text{linear}}^2 \rangle} \approx 8000 \mu\text{m/s}$. In contrast, under negligible load, the average angular velocity of the F₁-ATPase rotary motor $\approx 100 \text{ Hz}$ [3]; the average linear velocity of kinesin $\approx 1 \mu\text{m/s}$ [1]. Therefore, for molecular motors, $\langle \nu^2 \rangle$ is much larger than $\langle \nu \rangle^2$.

In our discussion, we define the system as (motor + surroundings + external agent): this includes the surrounding fluid containing chemical reactants and products, and the external agent that exerts a conservative force on the motor. The rate of chemical free-energy change is $-A\langle r \rangle$ and the rate of potential energy change in the external agent is $-f\langle \nu \rangle$. The second law of thermodynamics guarantees that the rate of *total*-free-energy change is negative:

$$\text{Second law: } -A\langle r \rangle - f\langle \nu \rangle \leq 0. \quad (1)$$

In the absence of the external force ($f = 0$), (1) dictates that the chemical reaction can proceed spontaneously only in the direction that results in chemical free-energy decrease. However, it does not tell how fast the reaction will go nor how fast the motor can run. The motor velocity is restricted by the viscous drag from the fluid medium. For molecular motors, the Reynolds number is small and the average viscous drag is proportional to the average velocity: $\langle f_{\text{Drag}} \rangle = \zeta \langle \nu \rangle$, where ζ is the drag coefficient of the motor plus its load. We use $\langle f_{\text{Drag}} \rangle \langle \nu \rangle = \zeta \langle \nu^2 \rangle$, as the numerator in defining the *Stokes efficiency* as

$$\text{Stokes efficiency: } \eta_{\text{Stokes}} \equiv \frac{\zeta \langle \nu \rangle^2}{A\langle r \rangle + f\langle \nu \rangle} \leq 1. \quad (2)$$

The inequality $\eta_{\text{Stokes}} \leq 1$ is not obvious, and must be proven. The denominator of (2) is the rate of the total free-energy consumption. The numerator has the following properties:

- $\zeta \langle \nu \rangle^2$ is calculated from the observable quantities ζ and $\langle \nu \rangle$. $\zeta \langle \nu \rangle^2$ increases with the average velocity, and in some sense measures the mechanical performance of the motor.
- $\zeta \langle \nu \rangle^2$ has the dimension of energy per time, but it is *not* the rate of work done on the fluid by the motor motion. This will be illustrated below in a model system (see eq. (7)).

The rate of work done on the fluid by the motion of the motor is given by $\dot{W} \equiv \langle (\zeta v - f_{\text{Brownian}})v \rangle$, where f_{Brownian} is the rapidly fluctuating Brownian force. This quantity is neither readily observable in experiments nor calculated from observable quantities. Surprisingly, \dot{W} can exceed the rate of free-energy consumption; we give an example to show this in appendix A.

The Stokes efficiency can be viewed as a measure of how efficiently the motor can utilize the free energy to drive a load through a viscous medium. This is in contrast with the usual *thermodynamic efficiency* defined as the rate of potential energy increase in the external agent divided by the rate of chemical free-energy consumption of the motor: $\eta_{\text{TD}} \equiv -f\langle v \rangle/(A\langle r \rangle)$; η_{TD} measures how efficiently the motor can convert chemical free energy to another form of potential energy.

In order to establish inequality (2), we first must define the mathematical framework within which we shall work. The most common mathematical formulation describing molecular motors is built around the assumption that chemical transitions (*excluding the time waiting for the proper reaction conditions to occur*) take place much faster than the motion of the motor. Therefore, the mechanical motions can be modeled by Langevin equations, and the chemical reactions can be modeled by Markov processes. The probability densities of the system obey Fokker-Planck equations [5–8]. Within this framework, the phase space for a motor with one spatial degree of freedom and one chemical reaction is the product of a continuous spatial variable, x , and a discrete reaction coordinate, j , indicating the chemical state of the motor. For example, the ATP hydrolysis cycle at a catalytic site has four “occupancy” states [7, 9]:



For simplicity, we give the proof for motors with one catalytic site and point out the major steps in the proof for the case of two catalytic sites. The principle illustrated here can be applied to motors with an arbitrary number of catalytic sites and spatial degrees of freedom. For example, the F₁-ATPase and DNA helicase motors have three catalytic sites [10, 11], while the chaperonin GroEL has fourteen [12].

Let $\rho_j(x, t)$ be the probability density for finding the motor at position x in the j -th chemical state at time t . The evolution of the probability density is governed by a set of coupled Fokker-Planck equations that ensure the conservation of probability [5–8, 13]:

$$\frac{\partial \rho_j}{\partial t} = -\frac{\partial J_j}{\partial x} + I_{j-1/2} - I_{j+1/2}. \quad (4)$$

Here J_j is the probability flux in the spatial direction for the j -th state, associated with convective transport and diffusion. $I_{j+1/2}$ is the probability flux density from state j to state $j + 1$, associated with the chemical transitions. The index j runs from 1 to N , where N is the number of chemical states in one reaction cycle. In the j -th state, the motor is driven by a periodic potential, $\phi_j(x)$,

$$J_j = -D \left[\frac{\phi'_j \rho_j}{k_B T} - \frac{f \rho_j}{k_B T} + \frac{\partial \rho_j}{\partial x} \right] = -D \rho_j \left(F'_j - \frac{f}{k_B T} \right), \quad F_j = \frac{\phi_j}{k_B T} + \ln(\rho_j), \\ I_{j+1/2} = \rho_j k_{j \rightarrow j+1} - \rho_{j+1} k_{j+1 \rightarrow j}, \quad (5)$$

where $D = k_B T / \zeta$ is the diffusion coefficient. The transition rates $k_{j \rightarrow j+1}$ and $k_{j+1 \rightarrow j}$ satisfy

$$\frac{k_{j \rightarrow j+1}(x)}{k_{j+1 \rightarrow j}(x)} = \exp \left[\frac{\phi_j(x) - \phi_{j+1}(x)}{k_B T} \right] \quad (6)$$

which ensures detailed balance at equilibrium. Since the motor operates in a chemical and mechanical cycle, the boundary conditions for eq. (4) in both the spatial direction and the reaction coordinate are periodic: $\rho_j(x + L, t) = \rho_j(x, t)$, $\rho_{N+j} = \rho_j$, $\phi_{N+j} = \phi_j - A$, where L is the motor step size. In appendix B we show that the system (4)-(6) guarantees that the

Stokes efficiency is bounded by one: $\eta_{\text{TD}} \leq 1$. Thus the Stokes efficiency defined in (2) is a legitimate measure of the efficiency of energy transduction.

Since the numerator of (2) is not an energy output, the Stokes efficiency is not a ratio of energy output to energy input. Because of this difference, a high thermodynamic efficiency and a high Stokes efficiency carry different implications for the motor mechanism. A motor is said to be *tightly coupled* if each chemical reaction cycle is one-to-one coupled to a motor step against an external force of any magnitude [14]. Mathematically, a tightly coupled motor is characterized by $\langle \nu(f) \rangle = L \cdot \langle r(f) \rangle$. For a tightly coupled motor, the second law as contained in (1) implies that the motor stalls at $f_S = -A/L$. As the motor approaches the stall ($f \rightarrow f_S^+$), $\eta_{\text{TD}} = f/f_S \rightarrow 1$. Thus, *for a tightly coupled motor, a high thermodynamic efficiency may be achieved by slowing the motor to near stall. Conversely, a high thermodynamic efficiency implies that the motor is nearly tightly coupled* because the high efficiency limits the percentage of “futile” reaction cycles.

What can we say about the motor mechanism if a motor has a high Stokes efficiency? To answer this question, we consider a motor driven by a tilted periodic potential:

$$\frac{\partial \rho}{\partial t} = -\frac{\partial}{\partial x} \left(-\frac{D}{k_B T} \psi' \rho - D \frac{\partial \rho}{\partial x} \right), \quad \psi(x) = \phi(x) - \frac{A}{L} x. \quad (7)$$

Here $\phi(x)$ is a periodic potential, which causes the driving potential $\psi(x) = \phi(x) - x \cdot A/L$ to deviate from a constant slope. For the model system (7), the motor is tightly coupled: each displacement of L corresponds one-to-one to a free-energy decrease equal to A . When the motor is loaded with an external conservative force, f , the motor stalls at $f_S = -A/L$, and the thermodynamic efficiency approaches 100% as f approaches f_S no matter what the periodic potential $\phi(x)$ is. Thus, for the model system (7), a high thermodynamic efficiency does not tell us anything about the driving potential $\psi(x)$. For (7), the Stokes efficiency can be expressed as

$$\eta_{\text{Stokes}} \equiv \frac{\zeta \langle \nu \rangle^2}{A \langle r \rangle} = \frac{\int_0^1 \exp \left[\frac{-A}{k_B T} q \right] dq}{\int_0^1 \underbrace{\left\{ \int_0^1 \exp \left[\frac{\phi(qL + pL) - \phi(pL)}{k_B T} \right] dp \cdot \exp \left[\frac{-A}{k_B T} q \right] \right\} dq}_{\text{Effect of } \phi \text{ on efficiency}}} \leq 1. \quad (8)$$

The under-braced term in (8) increases with the amplitude of $\phi(x)$. Consequently, the Stokes efficiency decreases as the driving potential $\psi(x)$ deviates from a constant slope. Figure 1 shows three different driving potentials (free energy as functions of the motor position, x) and the corresponding Stokes efficiencies. It is clear that as the driving force deviates from a constant force, the Stokes efficiency decreases dramatically. Notice that, in (8), the Stokes efficiency is determined by the driving potential. In particular, the Stokes efficiency is *independent of* the drag coefficient ζ . Therefore, when the motor is loaded with a large viscous drag to slow it to near stall, the Stokes efficiency does not increase. This is a key difference between the thermodynamic efficiency and the Stokes efficiency. In (8), the effect of thermal fluctuations is represented by the thermal energy $k_B T$. The thermal fluctuations can smooth some of the unevenness in the driving force. In the absence of the thermal fluctuations, if the driving potential were not monotonically decreasing, the motor would be trapped at a local minimum.

The model system (7) also illustrates that $\zeta \langle \nu \rangle^2$ is not the rate of work done on the fluid by the motor motion. In (7), all the free energy goes to driving the motor through the viscous fluid environment; thus the rate of work done on the fluid by the motor motion is $A \langle r \rangle$. If $\zeta \langle \nu \rangle^2$ were the rate of work done on the fluid by the motor motion, the Stokes efficiency would

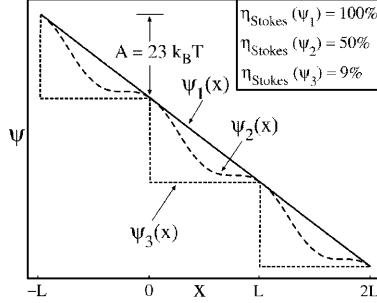


Fig. 1 – Three different driving potentials and the corresponding Stokes efficiencies. $\psi_1(x)$ has a constant slope and so produces a constant driving force. The corresponding Stokes efficiency is $\eta_{\text{Stokes}}(\psi_1) = 100\%$. $\psi_2(x)$ and $\psi_3(x)$ deviate progressively from a constant slope. The corresponding Stokes efficiencies are: $\eta_{\text{Stokes}}(\psi_2) = 50\%$ and $\eta_{\text{Stokes}}(\psi_3) = 9\%$. $\psi_3(x)$ corresponds to the driving potential of a Brownian ratchet [15].

always be 100% for the model system (7). Figure 1 shows that when the driving force is not a constant force the Stokes efficiency is strictly less than 100%. Therefore, $\zeta \langle v \rangle^2$ is not the rate of work done on the fluid by the motor motion.

In summary, the Stokes efficiency is different from the thermodynamic efficiency. Measuring the Stokes efficiency gives information about the driving potential of a motor. A high Stokes efficiency implies that the driving force is nearly constant (*i.e.*, nearly independent of the motor position). In contrast, a high thermodynamic efficiency implies that the motor is tightly coupled.

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APPENDIX A. – In this appendix we demonstrate that the rate of work done on the fluid by the motor motion (which is converted into heat) may exceed the rate of free-energy consumption.

We consider the case where a motor moves along a series of identical periodic potentials, each shifted by one half period in x and shifted down by A in free energy. Figure 2A shows the free-energy profile when the motor is working against a viscous load. The path $1 \rightarrow 2 \rightarrow 3$ corresponds to one reaction cycle. Chemical reactions can only take place in the shaded regions. The transition between the two potentials ($1 \rightarrow 2$) represents more than one chemical reaction step. The potentials for the chemical states between 1 and 2 are ϕ_{j-1} shifted in the vertical direction. These potentials have the same effect on the motor motion as ϕ_{j-1} , and are not shown in fig. 2A. The mechanical motion of the motor is governed by the Langevin equation [16]

$$\zeta \frac{dx}{dt} = -\phi'_{S(t)}(x) + f_B(t), \quad (9)$$

where $\phi_{S(t)}$ is the potential corresponding to the current chemical state. In one reaction cycle, the free energy consumed is A ; the work done on the fluid by the motor motion (which is converted into heat) is

$$\Delta Q_M \equiv \int_{t_2}^{t_3} \left(\zeta \frac{dx}{dt} - f_B(t) \right) \frac{dx}{dt} dt = \int_{x_2}^{x_3} -\phi'_j(x) dx = \phi_j(x_2) - \phi_j(x_3). \quad (10)$$

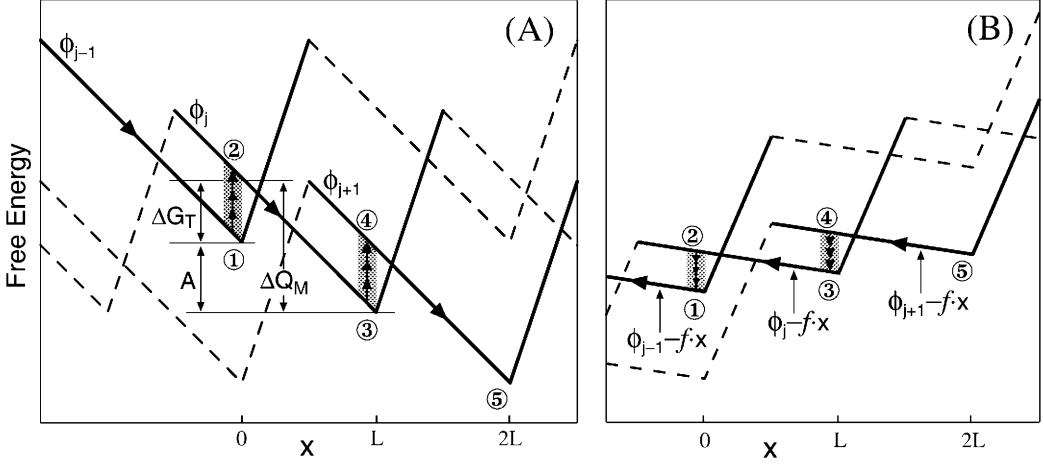


Fig. 2 – (A) Free-energy profile of a motor moving along a series of periodic potentials. The arrows show the forward progress of the motor, although all transitions are reversible. ΔG_T is the free-energy difference associated with the transition $1 \rightarrow 2$, which consists of more than one chemical reaction step. The motion $2 \rightarrow 3$ down the potential does an amount of work ΔQ_M on the fluid (which goes to heat). The free-energy consumption in the reaction cycle $1 \rightarrow 2 \rightarrow 3$ is A . In the situation shown, $\Delta Q_M > A$. (B) Free-energy profile of the motor in (A) working against a conservative force $f < -A/L$. Because of the tilting by f , the free energy at 5 is higher than that at 3, which is higher than that at 1. Consequently, the motor is forced backwards by f : 5 → 4 → 3 → 2 → 1.

The difference between ΔQ_M and A is ΔG_T , the free-energy difference associated with the transition between the two potentials. When $\Delta G_T > 0$, as in fig. 2A, the heat generated by the motor motion (ΔQ_M) is *larger* than the free-energy consumption (A).

Notice that in fig. 2A the free-energy profile is independent of the drag coefficient. Thus, we can slow down the motor but we cannot push the motor backwards by increasing the drag coefficient. Figure 2B shows the free-energy profile when the motor is working against a conservative force $f < -A/L$. In this case, *if the motor were still going forward*, the work done against the conservative force in one reaction cycle would exceed the free-energy consumption: $-f \cdot L > A$. However, the motor is not going forward. A key difference between a viscous load and a conservative load is that a conservative force tilts the free-energy profile. When $f < -A/L$, the free energy at 5 is higher than that at 3, which is higher than that at 1 (fig. 2B). Consequently, the motor is forced backwards by f : 5 → 4 → 3 → 2 → 1.

APPENDIX B. – In this appendix we present the mathematical proof leading to inequality (2).

The average velocity and reaction rate are determined by the steady-state solution, for which the left side of (4) is zero. The average velocity is given by $\langle v \rangle = \int_0^L \sum_1^N J_j dx$. Inserting eq. (5), applying the Cauchy-Schwarz inequality, and using the constraint $\int_0^L \sum_1^N \rho dx = 1$, we obtain

$$\langle v \rangle^2 = \left\{ \int_0^L \sum_{j=1}^N \rho_j^{1/2} \left[-\rho_j^{1/2} D \left(F'_j - \frac{f}{k_B T} \right) \right] dx \right\}^2 \leq \int_0^L \sum_{j=1}^N -J_j D \left(F'_j - \frac{f}{k_B T} \right) dx.$$

Integrating by parts, using (4), and applying boundary conditions, we have

$$\begin{aligned}\langle \nu \rangle^2 &\leq D \int_0^L \sum_{j=1}^N F_j (I_{j-1/2} - I_{j+1/2}) dx + \frac{f\langle \nu \rangle}{\zeta} = \\ &= D \int_0^L \sum_{j=1}^N I_{j-1/2} (F_j - F_{j-1}) dx + \frac{A}{\zeta} \int_0^L I_{1/2} dx + \frac{f\langle \nu \rangle}{\zeta}. \end{aligned} \quad (11)$$

Using (5) and (6), we see that the first integral on the right side of (11) is *negative*:

$$I_{j-1/2} (F_j - F_{j-1}) = \rho_{j-1} k_{j-1 \rightarrow j} (1 - G) \ln(G) \leq 0, \quad G = \frac{\rho_j}{\rho_{j-1}} \exp \left[\frac{\phi_j - \phi_{j-1}}{k_B T} \right].$$

The second integral on the right side of (11) is the total probability flux in the reaction direction, *i.e.*, the chemical reaction rate, $\langle r \rangle$. Thus, (11) leads to the desired result: $\zeta \langle \nu \rangle^2 \leq A\langle r \rangle + f\langle \nu \rangle$.

For motors with two catalytic sites (*e.g.*, the kinesin dimer), there are $N \times N$ chemical states since the reaction cycle on each site has N states. The governing equation is

$$\frac{\partial \rho_{i,j}}{\partial t} = -\frac{\partial J_{i,j}}{\partial x} + I_{i-1/2,j} - I_{i+1/2,j} + I_{i,j-1/2} - I_{i,j+1/2}.$$

The inequality corresponding to (11) is

$$\begin{aligned}\langle \nu \rangle^2 &\leq D \int_0^L \sum_{i=1}^N \sum_{j=1}^N \left(I_{i-1/2,j} (F_{i,j} - F_{i-1,j}) + I_{i,j-1/2} (F_{i,j} - F_{i,j-1}) \right) dx + \\ &+ \frac{A}{\zeta} \int_0^L \left(\sum_{j=1}^N I_{1/2,j} + \sum_{i=1}^N I_{i,1/2} \right) dx + \frac{f\langle \nu \rangle}{\zeta}. \end{aligned}$$

Again the first integral is *negative* and the second integral is the chemical reaction rate. The above argument can be carried out for any number of catalytic states.

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