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# A simple theory of motor protein kinetics and energetics

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**Abstract**

A simple stochastic theory for kinetics and energetics of the movement of single motor proteins is presented. The model combines the biochemical cycle of nucleotide hydrolysis with the motor protein translocation. Based on the theory of Markov processes, the model provides the force-velocity relationship, the isometric force, and the stochastic stepping of the motor protein along its one-dimensional track. The theoretical model provides a conceptual framework for realistic studies of motor proteins. Relationship between the present theory and other existing models is discussed. © 1997 Elsevier Science B.V.

*Keywords:* Energy transduction; Markov process; Mechanical force; Mechanochemical coupling; Nano-biochemistry; Stochastic model

## 1. Introduction

Motor proteins are molecular engines that utilize biochemical energy to do mechanical work. In the past decade, a large number of experimental results from biophysical measurements of single molecules have provided much information concerning the behavior and characteristics of various motor proteins [1,2]. However, there is still no simple and comprehensive picture available on how motor proteins work, especially on the important issue of coupling between biochemical reactions of nucleotide hydrolysis and mechanical movements. We propose a simple theory which addresses various kinetic and energetic issues related to motor proteins. The model presented here is not meant to be accurate or mechanistic, but merely to serve as a conceptual and theoretical framework which will be the basis for realistic models of various different experimental systems.

## 2. The model

We consider a three-state kinetic cycle since it is the simplest model capable of capturing the essence of nonequilibrium steady-state kinetics [3]. We assume that one of the steps is the nucleotide, e.g. ATP, hydrolysis. Also one of the steps, which can be but does not have to be the same one as the hydrolysis, is coupled to motor movement — the translocation along the one-dimensional filamentary track (i.e., actin thin filament for myosins, microtubule for kinesins and dyneins, and DNA for polymerases). The kinetic model is schematically shown in Fig. 1, with first-order and pseudo-first-order rate constants $k_{\pm 1}$,

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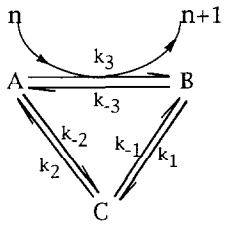


Fig. 1. A kinetic diagram for the simple three-state kinetic cycle. Many kinetic states and rate constants are lumped into only three states with six rate constants. State A: the motor before translocation; state B: the motor after translocation; state C: motor protein bound to its track. $k_{\pm 3}$ are the rate constants for the translocation, $k_{\pm 1}$ involve ADP release and ATP binding, hydrolysis etc., $k_{\pm 2}$ involve Pi release.

$k_{\pm 2}$, and $k_{\pm 3}$, where pseudo-first-order rate constants depend on the concentrations of ATP or ADP/Pi. It is important to note that since the reaction is not operating at equilibrium, in general the following equilibrium constraint among these six rate constants need not to be satisfied [4,5]:

$$\frac{k_1 k_2 k_3}{k_{-1} k_{-2} k_{-3}} = 1 \tag{1}$$

The steady state velocity, namely the number of cycles per unit time, for the enzymatic reaction can be easily obtained [3]:

$$v = \frac{k_1 k_2 k_3 - k_{-1} k_{-2} k_{-3}}{\Delta} \tag{2}$$

where

$$\Delta = k_1 k_2 + k_1 k_3 + k_2 k_3 + k_1 k_{-2} + k_2 k_{-3} + k_3 k_{-1} + k_{-1} k_{-2} + k_{-1} k_{-3} + k_{-2} k_{-3}$$

The motor-protein translocation velocity is $vd$ where $d$ is the length of a single step for each ATP cycle. This formula relates the velocity to the concentration of ATP and ADP/Pi, which are absorbed into the pseudo-first-order rate constants. We assume that the concentrations for ATP, ADP, and Pi are sustained at a fixed level. With this model, several issues immediately become clear.

### 2.1. Isotonic velocity

When a motor protein experiences a constant external force, the rate constants associated with the translocating step, designated as $k_{\pm 3}$, will be functions of the force. This is because only the translocating step can sense the external force. In fact, thermodynamics dictates the following relationship between the external force and the ratio between the $k$'s (the equilibrium constant):

$$K_3(F) = \frac{k_{+3}}{k_{-3}} = \frac{k^0_{+3}}{k^0_{-3}} e^{-Fd/kT} \tag{3}$$

where $F$ is the component of external force along the track, $k$ is the Boltzmann constant, $T$ is the temperature, and $k^0_{\pm 3}$ are the rate constants in the absence of external force (free load). Hence if the translocation step is in rapid equilibrium within the hydrolysis cycle, then the steady state velocity will be a function of the external force:

$$v(F) = \frac{k_1 k_2 K_3 - k_{-1} k_{-2}}{(k_1 + k_{-1} + k_2) K_3 + (k_2 + k_{-2} + k_{-1})} \tag{4}$$

If the translocating step is not in rapid equilibrium, then both $k_{+3}$ and $k_{-3}$, not just their ratio $K_3$, will have to appear in the expression for the steady state velocity (i.e., Eq. (2). Conceptually the situation is clear, though in this case one needs additional kinetic experiments to determine the dependence of $k_{\pm 3}$ on external force $F$. Eq. (4) naturally gives rise to the force-velocity relationship which is consistent with the existing phenomenological models [6,7].

### 2.2. Isometric force

The situation of isotonic movement is relatively easy to understand. There is, however, another type of experiment which measures the isometric force required to stall a motor. Our theory provides a natural interpretation for this type of measurement. Isometric force is defined as the external force under which the motor protein stops moving. Under this condition, microscopically, the motor protein can still move back and forth, but the probabilities of moving forward and backward are now equal. This is equivalent to saying that the translocating step is in detailed balance. It then can be shown, according to the theory of Markov processes [5] that in this situation the rate constants should satisfy Eq. (1). Hence, given ATP and ADP concentrations, we now

can determine the particular force $F^*$ which satisfies Eq. (1):

$$\frac{k_1 k_2 k_{+3}(F^*)}{k_{-1} k_{-2} k_{-3}(F^*)} = 1 \tag{5}$$

where $F^*$ is the isometric force which can be experimentally measured [8,9]. $F^*$ can be solved from Eqs. (3) and (5):

$$F^* = \frac{kT}{d} \ln\left( \frac{k_1 k_2 k_{+3}^0}{k_{-1} k_{-2} k_{-3}^0} \right) \tag{6}$$

From Eq. (6), isometric force is related to the concentration of ATP, ADP/Pi through the pseudo-first-order rate constants.

Under the isometric condition, a motor protein has no net directional movement but, in principle, could still undergoes an unbiased random walk along its track. One of the usefulness of the present model is that it can be applied to measurements on movement of single motor proteins by methods such as single-particle tracking [10]. The unbiased random walk can be quantitatively characterized by the mean square displacement (MSD) of random trajectories, and our model gives:

$$MSD = \frac{d^2 k_1 k_2 k_3(F^*) t}{k_1 k_2 + k_{-1} k_{-2} + k_1 k_{-2}} \tag{7}$$

where

$$\frac{k_1 k_2 k_3(F^*)}{k_1 k_2 + k_{-1} k_{-2} + k_1 k_{-2}} = \frac{k_{-1} k_{-2} k_{-3}(F^*)}{k_1 k_2 + k_{-1} k_{-2} + k_1 k_{-2}}$$

is the rate for each (reversible) step and $d$ is the step length.

## 3. Stochastic motor movement

A salient feature of the present theory is that it naturally provides a stochastic picture for the motor protein movement (stepping), which is associated with each A → B transition. A stochastic stepping process, known as the Markov renewal process [11], can be defined in terms of + and −, which represents step forward (A → B) and backward (B → A) jumping events, respectively. The conditional probabilities are readily obtained (see Fig. 2):

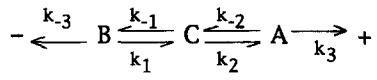


Fig. 2. A kinetic diagram for defining the stepping process from the theory. After a forward (+) step, the motor is in the state B. Hence, the probability $P(+,t|+) = P(+,t|\mathrm{B})$ and $P(-,t|+) = P(-,t|\mathrm{B})$. Similarly, after a backward (−) step, the motor is in the state A. Therefore, the probability $P(+,t|-) = P(+,t|\mathrm{A})$ and $P(-,t|-) = P(-,t|\mathrm{A})$. These conditional probabilities are readily to be calculated based on linear kinetic equations.

$$\begin{aligned} P(+,t|+) &= P(+,t|\mathrm{B}) \\ &= k_1 k_2 k_3 \left( \frac{1 - e^{-\mu_1 t}}{(\mu_3 - \mu_1)\mu_1(\mu_1 - \mu_2)} \right. \\ &\quad + \frac{1 - e^{-\mu_2 t}}{(\mu_1 - \mu_2)\mu_2(\mu_2 - \mu_3)} \\ &\quad \left. + \frac{1 - e^{-\mu_3 t}}{(\mu_2 - \mu_3)\mu_3(\mu_3 - \mu_1)} \right) \end{aligned} \tag{8}$$

$$\begin{aligned} P(-,t|+) &= P(-,t|\mathrm{B}) = k_{-3} \\ &\times \left( \frac{(k_1 + k_{-3})(\mu_2 + \mu_3) - (k_1 + k_{-3})^2 - \mu_2 \mu_3}{(\mu_3 - \mu_1)\mu_1(\mu_1 - \mu_2)} \right. \\ &\times (1 - e^{-\mu_1 t}) \\ &+ \frac{(k_1 + k_{-3})(\mu_1 + \mu_3) - (k_1 + k_{-3})^2 - \mu_1 \mu_3}{(\mu_3 - \mu_2)\mu_2(\mu_2 - \mu_1)} \\ &\times (1 - e^{-\mu_2 t}) \\ &+ \frac{(k_1 + k_{-3})(\mu_1 + \mu_2) - (k_1 + k_{-3})^2 - \mu_1 \mu_2}{(\mu_1 - \mu_3)\mu_3(\mu_3 - \mu_2)} \\ &\left. \times (1 - e^{-\mu_3 t}) \right) \end{aligned} \tag{9}$$

$$P(+,t|-) = P(+,t|\mathrm{A}) = k_3 \times \left( \frac{(k_{-2}+k_3)(\mu_2+\mu_3) - (k_{-2}+k_3)^2 - \mu_2\mu_3}{(\mu_3-\mu_1)\mu_1(\mu_1-\mu_2)} \times (1-e^{-\mu_1 t}) + \frac{(k_{-2}+k_3)(\mu_1+\mu_3) - (k_{-2}+k_3)^2 - \mu_1\mu_3}{(\mu_3-\mu_2)\mu_2(\mu_2-\mu_1)} \times (1-e^{-\mu_2 t}) + \frac{(k_{-2}+k_3)(\mu_1+\mu_2) - (k_{-2}+k_3)^2 - \mu_1\mu_2}{(\mu_1-\mu_3)\mu_3(\mu_3-\mu_2)} \times (1-e^{-\mu_3 t}) \right) \quad (10)$$

$$P(-,t|-) = P(-,t|\mathrm{A}) = k_{-1}k_{-2}k_{-3} \left( \frac{1-e^{-\mu_1 t}}{(\mu_3-\mu_1)\mu_1(\mu_1-\mu_2)} + \frac{1-e^{-\mu_2 t}}{(\mu_1-\mu_2)\mu_2(\mu_2-\mu_3)} + \frac{1-e^{-\mu_3 t}}{(\mu_2-\mu_3)\mu_3(\mu_3-\mu_1)} \right) \quad (11)$$

where $\mu$'s are the three roots of the polynomials:

$$\mu^3 + (k_1+k_{-1}+k_2+k_{-2}+k_3+k_{-3})\mu^2 + [(k_1+k_{-3})(k_{-1}+k_2) + (k_1+k_{-3}) \times (k_3+k_{-2}) + (k_{-1}+k_2)(k_3+k_{-2})]\mu + k_1k_2k_3 + k_2k_3k_{-3} + k_{-1}k_{-2}k_{-3} + k_{-1}k_3k_{-3} = 0 \quad (12)$$

Clearly, when $k_{-3} = 0$, $P(-,t|+) = P(-,t|-) = 0$, as expected. In other words, the motor can not move backward. The stepping therefore is reduced to a stochastic process with independent increments $P(+,t|+)$. When only one step is rate limiting, this result reduces to a Poisson stepping process with exponentially distributed waiting time between successive steps [8].

### 3.1. Futile cycle

Since there is only one cycle in our kinetic scheme, the isometric situation also dictates the reversibility of the ATP hydrolysis step. Whether this picture is realistic depends on whether there is futile cycle on the single enzyme level [8,9]. If there is an additional cycle which contains the hydrolysis step but not the translocating step, then it is a futile cycle. The mathematical theory of circulation decomposition provides an natural tool for studying this problem [5,12].

## 4. Discussion

To put various classes of motor proteins within a single unified picture, Leibler and Huse [7] have explored the connection between the cooperativity of multiple motor proteins and their kinetic behavior on the level of individual molecules. Their study leads to the limiting behavior of the 'porters' and the 'rowers'. The present model has much less structural and kinetic details than theirs. However, we seek the basic physics within the coupling between the biochemical reaction (i.e., ATP hydrolysis) and the movement. Collaborations with experimentalists are urgently needed to further develop comprehensive and realistic models for motor proteins. Our present theory only deals with single motor proteins (the 'porters'), but its generalization to multiple motors (the 'rowers') is straightforward.

Many theoretical work which address the free energy transduction in nonequilibrium kinetics have appeared in recent years. Nonequilibrium fluctuation induced (noise-driven) unidirectional reactions in the membrane [13] and in enzymes [14] have been studied. When coupled to a nonequilibrium biochemical cycle, a Brownian particle can perform unidirectional movements in a periodic potential which can be either static [15] or dynamic [16]. In all these work, the concept of biochemical coupling is an essential element. In the extreme of completely stochastic coupling, the thermal ratchet model arises [16–18]. The key element in these noise-driven movement models is the nonequilibrium fluctuation which defines an irreversible Markov process with cycles [5,12]; while an equilibrium noise defines a reversible Markov process with detailed balance through the well-known fluctuation-dissipation theorem [19]. Our model shares many of the same physical principles with the others, but is conceptually the

simplest. The concept of biochemical coupling has wide applications in many other biochemical processes, for example in membrane transport [20] and protein folding [21].

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I would like to dedicate this work to Professor Terrell Leslie Hill, a teacher and a friend, on the occasion of his 80th birthday [22]. His work on biological energy transduction and cycle kinetics has had major influence on my science, and will have long-lasting consequences in physical and mathematical biochemistry.

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