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The Fokker-Planck approach for the cooperative molecular motor model with *finite* number of motors

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Abstract

We provide the methodology for the analysis of the cooperative molecular motor model with *finite* number of motors, which are linearly and rigidly coupled, based on the Fokker-Planck approach. The probability density functions for the position of motors are solved numerically from the stationary Fokker-Planck equations. By using these probability density functions, we provide the analytical expressions, such as the velocity, the rate of the ATP consumption, the energetic efficiency, and the dissipation energy rates. Furthermore, we investigate three specific examples, such as single motor model, 2-motor model, and infinitely coupled motor model. Numerical algorithm to solve the Fokker-Planck equations is also provided.
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Keywords: Molecular motor; Ratchet model; Cooperativity; Fokker-Planck equation

1. Introduction

Molecular motors are proteins that convert the chemical energy into the mechanical energy. Myosin is one of the well-studied motor molecules. Myosin's sliding movement along actin filament causes the muscle contraction or intracellular movements. The three-dimensional structure of myosin and existence of the active site in myosin head for ATP binding has already been known by the X-ray diffraction analysis. However, little is known about the mechanism of the energy conversion. There are two hypotheses about the mechanism: the tight-coupling and the loose-coupling. The tight-coupling hypothesis assumes that one cycle of conformational change (∼10 nm) is tightly coupled with one ATP hydrolysis cycle (Huxley, 1969; Rayment et al., 1993). However, Yanagida et al. (1985) has experimentally shown that one cycle of conformation change (>60 nm) is much larger than the size of both myosin head and actin molecule, by using single bio-molecule detection techniques with fluorescence label imaging. Furthermore, it is experimentally shown that a single myosin head moves along an actin filament with multiple regular steps of 5.3 nm during one ATP hydrolysis (Kitamura et al., 1999). Their results indicate that ATP chemical energy and myosin's mechanical work are loosely coupled, which is called the loose-coupling hypothesis. Their experiments also show that the energy consumption for one-step movement is of the order of thermal fluctuation. Even though, the motor molecule can move to one preferable direction in such noisy environment, which is against our intuition. The thermal noise may play a positive role in the mechanism of motor molecules. The ratchet model is one of the theoretical models in order to understand the loose-coupling hypothesis (Magnasco, 1993; Tsong and Astumian, 1987; Tsong, 1990; Astumian et al., 1989; Reimann, 2002; Astumian and Bier, 1994; Shimokawa et al., 2003; Shimokawa and Mouri, 2007). In this model, motors perform like a Brownian particle on an asymmetric and periodic potential function. The association energy between an actin filament and a myosin molecule is described by the potential. The structure of actin filaments is asymmetric and periodic, and it determines the features of the model potential. A motor does not move to one direction even though the potential is asymmetric. This is because the second law of the thermodynamics. Thus the ATP consumption process is needed to move to one direction. The flashing ratchet model is one of the typical ratchet models. In this model, it is suggested that ATP energy is consumed for state transition of the potentials, and this mechanism causes

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the one directional motion. This assumption can be reasonable because the binding energy can change when an ATP molecule binds to a myosin molecule. Note that in Buonocore et al. (2005) the assumption that the existence of a tilted potential, ultimately resulting from a ratchet effect, may be consistent with the available experimental evidence even in the presence of large loads was tested and positively accepted.

However, the energetic efficiency η of the flashing ratchet model is at most 1%, which is much less than the experimental results for the muscle tissue (η is of the order of 50%). Furthermore, as mentioned above, the sliding length of the myosin filament on the actin filament can be larger than 60 nm (Yanagida et al., 1985), but such long sliding movement is quite difficult for single myosin head, and also difficult for the flashing ratchet model. Note, however, that a way to overcome such difficulties consists of referring to a ratchet model based on a traveling $2L$-periodic potential, where $L = 5.3$ nm is the myosin head's regular single step (which leads to a motility increase), that in addition is characterized by the presence of a well in each of the two half-periods (which leads to the required efficiency values) (see Buonocore et al., 2007).

Hereafter, a totally different approach will be pursued, that is based on the concept of *cooperativity*. Indeed, in the muscle tissue, the cooperative movement of multiple motor molecules may enhance the motility of the muscle, such as the velocity and the energetic efficiency. Theoretical studies for the coupled ratchet model can help in better understanding the underlying mechanism of the cooperativity. There are tons of theoretical investigations for coupled ratchet models (for review, see Reimann, 2002). Chang and Tsong (2005) has discussed 1-N motors functioning independently or in sequence, by using N-units flashing ratchet. Badoual et al. (2002) investigate the coupled ratchet for finite number of motors, based on the Langevin approach. Jülicher and Prost have provided the coupled ratchet model with finite number of motors under the mean-field assumption (Jülicher et al., 1997; Jülicher, 1999). Parmeggiani et al. (1999) have introduced how to apply the linear response theory to the ratchet model, and provided the analytical expression of the dissipative energy rate for single ratchet model. Most of the theoretical analyses for the Fokker-Planck approach are single ratchet and infinitely coupled ratchet (mean-field limit), because the number of the probability density function is one and it is theoretically tractable. For N-motor model, the number of the probability density functions is 2^N, which increases exponentially as increasing N. Of course the probability density function can be estimated as the histogram of the random variable from long time-series calculated by Langevin equation. Actually, the Langevin approach is theoretically equivalent to the Fokker-Planck approach. However, practically speaking, the Langevin approach cannot avoid numerical error, especially when we calculate the energetic efficiency, and it takes a long time to estimate smooth enough probability density functions. So that it is better to adopt the Fokker-Planck approach for the analysis of the cooperative enhancement of the efficiency. Therefore, we need to construct the theoretical framework and the methodology to investigate the coupled ratchet model with *finite* number of motors.

In this paper, we provide the methodology for the analysis of the cooperative molecular motor model with *finite* number of motors, which are linearly and rigidly coupled with each other, based on the Fokker-Planck approach. The probability density functions for the position of motors are solved numerically from the stationary Fokker-Planck equations. By using these probability density functions, we provide the analytical expressions, such as the velocity, the rate of the ATP consumption, the energetic efficiency, and the dissipation energy rates. Furthermore, for the demonstration of our methodology, we investigate three specific examples, such as single motor model, 2-motor model, and infinitely coupled motor model. Numerical algorithm to solve the Fokker-Planck equations and brief discussion about the cooperative enhancement of the efficiency are also provided.

2. Methods

2.1. N-Motor Model

2.1.1. Linearly and Rigidly Coupled N Motor

Motor proteins are coupled with each other, and form a filament. Myosin filament moves directionally to either the plus or minus end of the actin filament. The analysis of this filament's movement has been given in motility assay experiments (Yanagida et al., 1985; Kitamura et al., 1999). We consider a simple one-dimensional situation similar to the motility assay. We assume N motors are attached to a rigid rod. The length of this is $L_{\rm rod} = (N-1)q_{\rm rod}$, and $q_{\rm rod}$ is a fixed length between two adjacent motors. The relative displacement between the rod (myosin filament) and the substrate (actin filament) is denoted by x. Each of the motors is represented by a two-state model (Jülicher and Prost, 1995; Jülicher et al., 1997; Parmeggiani et al., 1999). We assume that the motor can exist in two different conformations or chemical states, denoted by σ, where $\sigma = 1$ or 2. The interaction between motors and filament depends on σ and is described by potentials $W_\sigma(x)$ at position x. The potentials are periodic, giving $W_\sigma(x) = W_\sigma(x+L)$, where L is a potential period, because cytoskeletal filaments are periodic. Next, we think about the relative position of N motors on the filament. We assume that the position of the ith motor is $x_i = x + q_{\rm rod}(i-1)$, where the equal distances $q_{\rm rod}$ between adjacent motors are $q_{\rm rod} = L_{\rm rod}/(N-1)$. Under the periodic boundary condition, the distance between two adjacent motors is fixed as $q = q_{\rm rod}[\mathrm{mod}\, L]$, that is to say, $\hat{x}_i = \hat{x} + q(i-1)[\mathrm{mod}\, L]$ and $\hat{x} \equiv x[\mathrm{mod}\, L]$ (see Fig. 1). Furthermore, in order to extract the simple cooperativity in N-motor model, we assume that $q = L/N$. This assumption may be an ideal case, especially for few number of motor. However, it is natural assumption when N is large enough and the ratio between L and $q_{\rm rod}$ is irrational, because the position of motors distribute uniformly and densely in the range $[0, L)$. Under the periodic boundary condition, the coordinate $\hat{x}$ is on the unit circle, S^1. In this case, N number of motors are rigidly connected like one unit circle. It means that the translation of $\hat{x}$ with integer number of q, $\hat{x} \to \hat{x} + nq[\mathrm{mod}\, L]$ $(n = 1, 2, \ldots, N-1)$, does not affect the dynamics of the N-motor model.

2.1.2. Chemical Reaction Mechanism

We now consider about a chemical reaction mechanism for the two-state model. The scheme of chemical reactions about kinesin and myosin molecules has been previously discussed (Jülicher, 2006; Parmeggiani et al., 1999). We modeled the following chemical scheme: (a) $\mathrm{ATP} + \mathrm{M}_1 \rightleftharpoons \mathrm{M}_2 + \mathrm{ADP} + \mathrm{P}$ and (b) $\mathrm{M}_1 \rightleftharpoons \mathrm{M}_2$, where M_σ denotes myosin on the potential $W_\sigma(x)$. We describe the chemical reaction rates as $\alpha_1(\rightarrow)$ and $\alpha_2(\leftarrow)$ in (a), and $\beta_1(\rightarrow)$ and $\beta_2(\leftarrow)$ in (b), where $\alpha_\sigma = \alpha_\sigma(x)$ and $\beta_\sigma = \beta_\sigma(x)$. The reaction α_1 (change from state 1 to state 2) consumes the chemical free energy gain $\Delta\mu$ in ATP hydrolysis. The reactions β_1 and β_2 do not consume chemical energy. These parameters require $\alpha_1(x) = \alpha_2(x)\exp[(W_1(x) - W_2(x) + \Delta\mu)/T]$ and $\beta_1(x) = \beta_2(x)\exp[(W_1(x) - W_2(x))/T]$, where the temperature T is measured in units of $k_{\rm B}$. We define the transition rates $\omega_\sigma(x)$ as $\omega_1(x) = \alpha_1(x) + \beta_1(x)$, and $\omega_2(x) = \alpha_2(x) + \beta_2(x)$.

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