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The coordination of protein motors and the kinetic behavior of microtubule — A computational study

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Abstract

Utilizing the mechanical energy converted from chemical energy through hydrolysis of ATP, motor proteins drive cytoskeleton filaments to move in various biological systems. Recent technological advance has shown the potential of the motor proteins for powering future nano-bio-mechanical systems. In order to effectively use motor proteins as a biological motor, the interaction between the protein motors and bio-filaments needs to be well clarified, since such interaction is largely influenced by many factors, such as the coordination among the motors, their dynamic behavior, physical properties of microtubules, and the viscosity of solution involved, etc. In this study, a two-dimensional model was proposed to simulate the motion of a microtubule driven by protein motors based on a dissipative particle dynamics (DPD) method with attempt to correlate the microtubule's kinetic behavior to the coordination among protein motors.

Keywords: Motor protein; Dissipative particle dynamics; Coordination; Nano-machines

1. Introduction

In recent decades, the rapid development of advanced experimental techniques, such as atomic force microscopy, optical trap nanometry, and fluorescence microscopy, has made it possible to investigate the dynamics of proteins at single-molecule level with different time scales from millisecond to second. The high resolution of the experimental techniques permits probing conformational changes and functions of motor proteins, such as myosins, kinesins and dyneins. These protein-based supramolecular complexes have been extensively studied due to their great potential to act as a biological motor at the molecular scale for nano-bio-mechanical systems or devices. These biological motors can convert chemical energy to mechanical energy through ATP hydrolysis, thus providing power to drive cytoskeletal filaments such as actin filaments and microtubules [1–5]. Efforts have also been made to control the path for these cytoskeletal filaments to move, which makes the development of nano-bio-machines provided by the motor proteins possible. Using a highly oriented polymer film functionalized with myosin subfragments [6] or kinesin [7], the success in driving actin filaments or microtubules in straight lines has been demonstrated. Suzuki and co-workers [8] reported the directional motion of actin filaments driven by aligned and immobilized myosin molecules using microlithographically-patterned resist polymers. In the presence of detergent, kinesin can be selectively attached onto a glass surface, from which the photo-resist polymer has been removed, rather than on the photo-resist polymer itself [9]. The tracks are channels bordered by walls of the resist material, within which microtubules rarely climb up the walls, so that the microtubules can move only along the designed tracks. Controlled movement of microtubules along tracks can also be achieved using micrometer-scaled grooves abricated lithographically on glass surfaces [10,11]. These recent studies have brought the motor proteins closer to bio-engineering applications as a molecular motor. Among different motor proteins, dynein has attracted increasing interest due to the fact that it moves 10 times faster than kinesin [12].

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In order to drive a cytoskeleton filament, motor proteins must grab the filament, hydrolyze ATP and then convert released chemical energy to mechanical energy, thus driving the filament to move. Understanding the mechanism responsible for this energy conversion and driving process is of importance to utilization of motor proteins in future molecular machines. Considerable experimental efforts have been made to investigate relevant issues, including the structure of motor proteins [13–15], elastic behavior of motors and cytoskeletal filaments [16–19], and the motility of motor proteins [20,21], etc. In addition, the rapid progress in the development of advanced experimental techniques, such as atomic force microscopy [22], optical trap nanometry [23] and fluorescence microscopy [24], has provided researchers effective tools to investigate the dynamics of single-molecule in situ with spatial and temporal resolutions down to Å and μs ranges, respectively. This allows direct observation of dynamic processes involving motor proteins, for which macroscopic ensemble-averaged measurements do not work. Two fundamental protein-motor parameters, coupling efficiency and step-size, which can only be indirectly inferred from in vitro motility assays are now accessible using single-molecule techniques that allow direct and simultaneous observation of ATP-turnover and force generation. However, the filament's motion driven by a number of motor proteins is a very complex process, involving ATP hydrolysis, energy conversion, driving and drag actions, which are greatly influenced by the coordination among protein motors. It is not easy to experimentally determine the roles that the individual factors play in the entire process. In order to elucidate experimental observations and understand mechanisms involved, computer modeling has been used to achieve the goal. In 1957, Huxley suggested that a motor protein could be treated as an elastic spring storing mechanical energy and this idea became the basis of a powerstroke model [25]. A swinging lever-arm model, in which the neck region of a myosin consisting of one or more so-called IQ motifs serving as binding sites for calmodulin or calmodulin-like light chains, was proposed [26]. The resultant complex of extended α-helical heavy chain and tightly bound light chains serves as a lever arm to amplify and redirect smaller conformational changes within the myosin motor domain, which occurs when interacts with nucleotide and actin filaments. A so-called biased Brownian ratchet model was proposed to study the action of myosin on actin filament, including directionally biased Brownian motion [27]. A hand-over-hand model was proposed to simulate the walking motion of two-headed kinesin [28]. In the model, two identical motor domains alternatively swing forward at each step while one motor domain remains attached on the track. Further studies suggest that some kinesin molecules exhibit a marked alternation in the dwell times between sequential steps, causing the motors to "limp" along the microtubule. Such type of movement of microtubule suggests an asymmetric hand-over-hand mechanism, called an inchworm mechanism [29], in which one head always leads in the movement. In addition, Qian studied force–velocity relationship and the stochastic stepping of single kinesin based on the theory of Markov processes [30]. Gao et al. proposed a molecular dynamics model based on free energy simulations and experimental binding constant measurements, which makes it possible to develop a kinetic scheme to understand the ATP hydrolysis by F1-ATPase [31].

The previously proposed models are primarily used to explore the driving mechanism for a single motor on a cytoskeleton filament. However, a filament is usually driven by a number of protein motors, which is influenced by many factors, including the density of motors, the coordination among motors that largely affects the driving and drag forces, and the resistance of surrounding liquid to the filament's motion, etc. The existing models are not very suitable for investigating the effects of these factors on the filament's movement.

In recent years, the dissipative particle dynamics (DPD) technique [32] attracted interest due to its large time steps that markedly decrease the computing time so that the powering process of motor proteins involving many factors could be investigated. In 1992, Hoogerbrugge and Koelman proposed a simulation model based on the dissipative particle dynamics (DPD) to study the hydrodynamic behavior of motor proteins [32,33]. In this model, a liquid phase is modeled using dissipative particles and their motion is simulated based on some collision rules. Thermal and hydrodynamic effects could be included in the model, which are of importance to studies on the fluctuation of a microtubule. The DPD method has demonstrated its advantages in simulation of complex fluids and soft materials [34–38]. This method may provide more details of the motor protein's behavior than the stochastic model [30] or the ratchet model [27]. It should be indicated that, compared to the molecular dynamics model such as that used by Gao et al. [31], the DPD model may be limited for qualitative prediction and explanation due to its non-conservation of energy. Since the objective of this study is to improve the understanding of the driving mechanism of dyneins on a microtubule, especially to study the coordination functions of motor protein, rather than quantitative prediction, the DPD appears to be a suitable approach for the present study.

In this study, the authors combined the dissipative particle dynamics (DPD) technique with a bead-and-spring model, and applied the developed method to investigate the motility of a filament driven by motor proteins. Effects of motor density, the coordination among motors, and the microtubule length on the movement of a bio-filament and related issues such as the driving and drag forces were investigated to gain an insight into the interaction between motor proteins and the bio-filament.

2. Model design

2.1. Part A: principles

2.1.1. The DPD simulation method

DPD is a particle-based method [32], in which a fluid is treated as a group of interacting particles. Each particle represents a fluid element containing a number of molecules. The interaction between two particles is a sum of conservative force, dissipative force and random force:

$$F_{\mathrm{is}} = \sum_{j \neq i} (F_{ij}^{\mathrm{C}} + F_{ij}^{\mathrm{D}} + F_{ij}^{\mathrm{R}}). \tag{1}$$