Biomedical Data Mining

Extended Abstract

Electrostatic interactions play key roles on the motions of molecular motors

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Abstract

Dynein is an important molecular motor which transports cargos along microtubules in the cell. Dysfunction of dynein leads to many serious diseases. Therefore, many efforts have been contributed to investigating the mechanisms of dynein's motilities on microtubules. However, the large size of the dynein and microtubule system makes it extremely challenging to study the atomic details of the dynein's motilities. Several computational approaches are developed and applied to study the dynein at different levels. Our simulations demonstrate that the long-range electrostatic interaction plays several essential roles during dynein's motion. The electrostatic forces control dynein's binding position and orientation in each step. The electrostatic binding energy funnel is found at the binding pocket, with the diameter of about 30 angstroms. Meanwhile, strong evidence indicates that the electrostatic binding affinity is also a key factor to determine dynein's velocity and run length.

Microtubule-based motors such as kinesins and dyneins are essential to a variety of processes, e.g., molecular transportation and mitotic spindle formation. The force generation is mediated by the walk of a unidirectional motor toward the plus/minus end of the microtubule (MT), following adenosine triphosphate (ATP) hydrolysis. Intuitively, highly processive and non-diffusive motor walks may be advantageous for efficient force generation. However, motors exhibiting a biased random walk toward a specific end with a large diffusion coefficient have also been reported. The questions therefore arise as to why motors with such biased random walks exist in nature and whether or not such motors play a specific role.

It was long believed that a given type of motor protein travels in a specific direction along an MT, and that this directionality remains constant in the absence of an external force. Quite recently, however, kinesin-5 Cin8, which is a tetrameric motor protein purified from budding yeast that can cross-link to two MTs, was found to exhibit directionality switching, depending on the number of motors bound to the same MT. Based on the other kinesin-5 family members, Cin8 was expected to exhibit plus-end directionality, leading to outward-force generation, which separates anti-parallel MTs with their minus-end leading during mitotic spindle formation5. However, Roostalu et al. showed that a single Cin8 molecule exhibits a biased random walk with a large diffusion constant toward the minus end. When multiple Cin8's function as a team by cross-linking antiparallel MTs simultaneously, they transport anti-parallel MTs so that each MT slides with its minus end leading, which represents the expected plus-end directionality of Cin8. These researchers also conducted an MT sliding assay, where multiple surface-immobilized motors collectively bind to MTs and transport them, and demonstrated that the motors exhibit minus-end directionality for a small number of binding motors, while they exhibit plus-end directionality for a large number of binding motors. After this finding, similar directionality switch depending on the number of motors has been also reported for kinesin-14 KlpA and kinesin-5 Cut7, which suggests that motor with such "dual-directionality" (i.e., ability to show both directionality depending on conditions) is general and plays some important roles. Note that the dual directionality exhibited by Cin8 differs from bidirectionality, where both plus- and minus-end directed motions can coexist under the same conditions.

Similarly, the emergence of a novel motility mode, other than the directionality transition, induced by team formation has also been reported in several experimental studies. In those cases, despite weakly biased or even non-biased diffusion in the walk of an individual motor, a team of motors exhibits a highly directional movement. However, the physical principle underlying both the directionality transition and the emergence of the directionality has not yet been uncovered.

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In this Paper, we introduce a mathematical model for a motor-filament system and demonstrate that directional collective motion contrary to the built-in directionality of a single motor can emerge in the absence of any external forces. This directionality transition emerges under a large diffusional component in the directional walk and asymmetry in the intra-molecular strain-dependent detachment. In addition, the collective directional motion of motors with non-biased diffusion is explained. The proposed model provides a representative example of a mechanism for embedding dual tasks into a single molecular machine, which will elucidate the role of a large diffusive component in the walk of a processive motor. The emergence of the collective motion demonstrated here is independent of, and fundamentally different from, that induced by the entropic force produced by a diffusible cross-linker or the jamming effect that facilitates opposite collective directional motion, since neither of those effects occur in the MT sliding assay considered in this study.

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