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Model for bidirectional movement of cytoplasmic dynein



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HIGHLIGHTS

- Stochastic process models are developed for bidirectional motion of dynein motor.
- Probability for backward step uses Crook's like fluctuation theorem.
- Average motor velocity is negative beyond stall force.
- Backward motion beyond stall force is also powered by ATP hydrolysis.

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ABSTRACT

Cytoplasmic dynein exhibits a directional processive movement on microtubule filaments and is known to move in steps of varying length based on the number of ATP molecules bound to it and the load that it carries. It is experimentally observed that dynein takes occasional backward steps and the frequency of such backward steps increases as the load approaches the stall force. Using a stochastic process model, we investigate the bidirectional movement of single head of a dynein motor. The probability for backward step is implemented based on fluctuation theorem of non-equilibrium statistical mechanics. We find that the movement of dynein motor is characterized with negative velocity implying backward motion beyond stall force. We observe that the motor moves backward for super stall forces by hydrolyzing the ATP exactly the same way as it does while moving forward for sub-stall forces. Movement of dynein is also simulated using a kinetic Monte Carlo method and the simulated velocities are in good agreement with velocities obtained using a stochastic rate equation model.

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1. Introduction

Molecular motors are nano-machines that do work by harnessing chemical energy (Chowdhury, 2013). Cytoplasmic dynein is a minus end directed motor protein that moves on microtubule. It is implicated in intracellular transport of vesicles, mRNA, protein complexes etc., from cell cortex to center of the cell (King, 2012). Dynein is a homo-dimer with each head consisting of a ring of six domains (Vale, 2000). Four of the six domains of the ring have sites with affinity for ATP binding. Dynein motor exhibits a gear like mechanism in controlling step size in response to the load force (Mallik et al., 2004). A model of single head of a dynein motor is simulated by Monte Carlo method (Singh et al., 2005). Singh et al. computed force velocity relation, step size distribution from the simulation data and studied the ATP dependence of average velocity of the motor. Further, the load dependence of the

step size and ATP concentration dependence of the stall force are obtained by another model with a weak coupling between two reaction coordinates corresponding to chemical reactions and translocation of the motor (Gao, 2006). A complete mechano-chemical model for a hand over hand stepping model of a homodimeric dynein is developed where the ATP hydrolysis cycle is coupled to a coarse grained structural model (Tyagankov et al., 2009, 2011). Dynein motor at a different spatio-temporal resolution is studied by multi-scale modeling (Serohijos et al., 2009). Stochastic process modeling of unidirectional movement of single head of a dynein motor is carried out systematically with one-, two- and three-step process (Sutapa Mukherji, 2008). While dynein moves processively toward the minus end of the microtubule, it is observed that dynein takes backward steps once in a while and the frequency of such backward steps increases as the load increases (Gennerich et al., 2007). Further, it was observed that single head of dynein is sufficient for processive motion (De Witt et al., 2012).

In the present work, we develop a stochastic process model for bidirectional movement of cytoplasmic dynein's single head, along

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the same lines of the model of [Sutapa Mukherji \(2008\)](#). We use Crook's like fluctuation theorem to define the ratio of probability of forward step to that of backward step. Dynein can take 8, 16, 24 or 32 nm step sizes depending on the load and ATP concentration. In this study we investigate bidirectional movement of dynein's single head for all the four step sizes.

The paper is organized as follows. Description of stochastic process model, typical reaction scheme, different rate constants used in the study, a system of stochastic rate equations and the procedure to compute average velocity of the motor are presented in [Section 2](#). [Section 3](#) consists of results and discussion.

2. Model

Microtubule is modeled as a passive one dimensional lattice on which single head of dynein moves. We assume that *dynein's* head is always attached to the microtubule site. Single head of dynein consists of one primary and three secondary ATP binding sites. It is assumed that out of four ATP binding sites, ATP hydrolysis takes place only at a primary site. However, the step length depends on the occupancy of the three secondary sites. If we denote that the minimum step size dynein can take as a , where $a = 8$ nm, the step sizes are $4a$, $3a$, $2a$ and a when occupied secondary sites are 0, 1, 2 and 3 respectively.

If we consider one primary and one secondary sites, the stochastic variable S_j^{kl} denotes the probability that a *dynein's* head is on the j th lattice site of microtubule with $k, l = 0, 1$. Here $k = 0(1)$ and $l = 0(1)$ signify the corresponding primary or the secondary site being unoccupied (occupied) respectively. In this case, maximum step size of a single head of dynein is $2a$ and hence we call this a $2a$ model. If we have two and three secondary ATP binding sites considered, we refer to them as $3a$ model and $4a$ model respectively and denote the corresponding stochastic variable as S_j^{klm} and S_j^{klmp} . Since each index in the superscript of the stochastic variable can be 0 or 1 corresponding to the ATP binding site being unoccupied or occupied, we have number of stochastic variables as 4, 8 and 16 respectively for $2a$, $3a$ and $4a$ models. The rate of ATP binding on the i th binding site of *dynein's* head is denoted as k_{oni} and the rate of ATP unbinding from the same site is denoted as k_{offi} . Hydrolysis rate at the primary site must decrease with increasing load since we know that the motor stops at stall force. Further, it also depends on whether the secondary ATP sites are occupied. The load dependence of the hydrolysis rate is governed by the Boltzmann factor that is given by the following expression:

$$k_{cat,i} = A(i)k_{cat,0} \exp[-\alpha Fd(i)/k_B T] \quad (1)$$

Here, $i = 1, 2, 3$ and 4 and $d(i) = i \times a$, $k_{cat,0}$ is the hydrolysis rate for no load, α is the load distribution factor taken as positive since the hydrolysis rate should decrease with the increase in opposing external load and $A(i) = 1$ if any of the secondary sites are occupied and is 0.01 if all the secondary sites are unoccupied.

Along the lines of previous studies ([Singh et al., 2005](#); [Sutapa Mukherji, 2008](#)), we assume that the ATP binding rates of secondary sites depend on the load as follows:

$$k_{on,2-4}(F) = k_{on,2-4} \exp[Fd_0/k_B T] \quad (2)$$

d_0 is an adjustable parameter in units of length.

Cytoplasmic dynein from yeast and mammals shows difference in velocity and stall forces. Yeast dynein exhibits a higher stall force and smaller velocity compared to mammalian dynein ([Reck-Peterson et al., 2006](#); [Gennerich et al., 2007](#); [Ross et al., 2006](#); [Mallik et al., 2004](#); [Schroeder et al., 2010](#)). Experiments by [Mallik et al. \(2004\)](#) reported that cytoplasmic dynein has a stall force of 1.1 pN at saturating ATP concentration and the stall force decreases with decrease in ATP concentration. On the other hand [Toba et al.](#)

(2006) observed a stall force of 7–8 pN which is independent of ATP concentration for mammalian cytoplasmic dynein. Further, [Toba et al.](#) reported a velocity of dynein motor around 800 nm/s. It is argued that the differences observed with respect to stall force and velocity in Yeast and mammalian dynein may be of structural origin ([Hook and Vallee, 2012](#)), that is, the absence of C terminal domain in Yeast may be responsible for higher force and lower velocity. In this model we consider the stall force of 7.5 pN as an input parameter and compute the velocity of the dynein motor.

Molecular motors are known to take backward steps amidst their processive forward motion. It is observed that the directional movement of motors is governed by thermodynamics that restrict backward steps ([Dean Astumian, 2010](#)). This motivated us to examine the role of thermodynamic fluctuation theorem such as Crook's fluctuation theorem ([Crooks, 1990](#)) for motor taking backward steps. The probability ratio for forward and backward steps for kinesin motor is estimated from experiment ([Carter and Cross, 2005](#); [Nishiyama et al., 2002](#)). Subsequently, the expression for the ratio of forward and backward step probabilities was derived from Crook's like fluctuation theorem of non-equilibrium thermodynamics for kinesin motor ([Bier, 2008](#); [Calzetta, 2009](#)). In this work, we assume that the same expression is valid for dynein motor as well. The ratio of the probability for a forward step to backward step is given as

$$\frac{P_F}{P_B} = \exp\left[\frac{d_0}{2k_B T}[F_s - F]\right] \quad (3)$$

where F_s is the stall force. Also note that $P_F + P_B = 1$ since dynein motor can take only forward or backward steps in our model. Since our interest is to understand the role of backward steps in the dynamics of dynein, in order to compare the results with previous model, we considered different rate constants and parameters in this study same as in the previous studies ([Singh et al., 2005](#); [Sutapa Mukherji, 2008](#)). They are given in [Table 1](#). Here k_{BT} is the thermal energy and k_B is the Boltzmann constant.

In this study, we have computed the average velocity of single head of dynein molecule with $2a$, $3a$ and $4a$ models with and without including backward steps. We investigate the velocity of the motor as a function of force both below (substall forces) and above (super stall forces) the stall force. We present the reaction scheme and stochastic rate equation model for bidirectional $3a$ model as a representative case.

2.1. The model

In a $3a$ model, we have eight state variables for single head for dynein motor. The state variable vector on the j^{th} lattice site of microtubule is given by

$$\rho_j = [S_j^{000} S_j^{001} S_j^{010} S_j^{100} S_j^{011} S_j^{101} S_j^{110} S_j^{111}]^T \quad (4)$$

Table 1
Rate constants and parameters used in the study.

Symbol	Value
$k_B T$	4.1 pN nm
k_{off1}	10 s^{-1}
k_{off2}	250 s^{-1}
k_{off3}	250 s^{-1}
k_{off4}	250 s^{-1}
k_{on1}	$4 \times 10^5 \text{ M}^{-1} \text{ s}^{-1} [\text{ATP}]$
$k_{on2}(F=0)$	$4 \times 10^5 \text{ M}^{-1} \text{ s}^{-1} [\text{ATP}]$
$k_{on3}(F=0)$	$k_{on2}(F=0)/4$
$k_{on4}(F=0)$	$k_{on2}(F=0)/6$
d_0	6 nm
$k_{cat,0}$	55 s^{-1}
α	0.3

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