Interaction between motor domains can explain the complex dynamics of heterodimeric kinesins

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Motor proteins are active enzyme molecules that play a crucial role in many biological processes. They transform chemical energy into mechanical work and move unidirectionally along rigid cytoskeleton filaments. Single-molecule experiments indicate that motor proteins, consisting of two motor domains, move in a hand-over-hand mechanism where each subunit changes between trailing and leading positions in alternating steps, and it is assumed that these subunits do not interact with each other. However, recent experiments on heterodimeric kinesins suggest that the motion of motor domains is not independent, but rather strongly coupled and coordinated, although the mechanism of these interactions is not known. We propose a simple discrete stochastic model to describe the dynamics of homodimeric and heterodimeric two-headed motor proteins. It is argued that interactions between motor domains modify original free energy landscapes for each motor subunit, while motor proteins still move via the hand-over-hand mechanism but with different transition rates specified by the new free energy profiles. Our calculations of biophysical properties agree with experimental observations. Several ways to test the theoretical model are proposed.

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I. INTRODUCTION

Several classes of enzyme molecules that convert chemical energy into mechanical motion are called motor proteins, or molecular motors. In recent years, these proteins have attracted significant attention because of their importance for multiple biological processes [1–5]. Motor proteins, such as kinesins, myosins, dyneins, polymerases, and helicases, move in a linear fashion along rigid biopolymers (actin filaments, microtubules, DNA and RNA molecules). Typically, fuel for the motion of these nanomotors comes from the hydrolysis of adenosine triphosphate (ATP) or related compounds. Although some progress in understanding the mechanisms of motor proteins has been achieved [2,4,5], there are still many unresolved issues. One of the most important fundamental questions concerning motor proteins is how different domains of these enzymes coordinate and regulate their complex dynamics and functions. The goal of this paper is to address some aspects of this issue from the theoretical point of view.

The enzymatic activity of motor proteins takes place in the so-called motor subunits that contain ATP-binding sites. Motor proteins typically have several such domains. The functioning of molecular motors strongly depends on the relative position and dynamics of these subunits [2,5]. Two possible mechanisms for two-headed motor proteins have been proposed: an inchworm motion and a hand-over-hand mechanism [2,6,7]. In the inchworm mechanism one motor domain is always in the leading position, while the other one always trails. However, in the hand-over-hand mechanism the motor domains alternate their leading and trailing positions as the motor protein molecule proceeds along the filament track. Single-molecule experiments that utilized fluorescent imaging with one-nanometer accuracy (FIONA) and optical trapping methods have shown that individual double-headed kinesins, myosins V and VI, and cytoplasmic dyneins step in the hand-over-hand fashion [8–13]. Thus, this mechanism explains the stepping dynamics of the majority of motor protein species.

In the current version of the hand-over-hand mechanism, it is assumed that the two heads move independently of each other, i.e., when the trailing motor subunit moves its dynamics is not affected by the presence of the other motor subunit. Then the mean dwell time to advance one step forward for a heterodimeric motor protein with two heads labeled as A and B is given by

$$\tau_{A\text{-}B} = \frac{1}{2}(\tau_{A\text{-}A} + \tau_{B\text{-}B}), \tag{1}$$

where $\tau_{A\text{-}A}$ and $\tau_{B\text{-}B}$ are the mean dwell times for homodimeric A-A and B-B motor proteins, respectively. The corresponding relation for the velocity can be written as

$$V_{A\text{-}B} = \frac{2V_{A\text{-}A}V_{B\text{-}B}}{V_{A\text{-}A} + V_{B\text{-}B}}. \tag{2}$$

However recent single-molecule investigations of dynamics of kinesins [14] do not support these relations, and, consequently, the independence of the two motor domains during the motion is put in doubt. In these experiments force-velocity curves and enzymatic activities have been measured for different homodimeric and heterodimeric kinesins. Surprisingly, it was shown that the velocity of the heterodimeric kinesin with a mutation in one of the motor heads is not given by Eq. (2). It was suggested that the two heads strongly influence each other's dynamic and enzymatic properties, although the mechanism was not specified. In this paper we present a simple discrete stochastic model that might explain several aspects of the complex dynamics of heterodimeric kinesins. Our main idea is that motor domains interact with each other and significantly modify the overall dynamics by changing the motor proteins' free energy landscapes.

Theoretical investigations of molecular motors follow several approaches that include continuum ratchets [15,16], discrete stochastic models [5], and computer simulations [17,18]. In this work we utilize a discrete stochastic approach

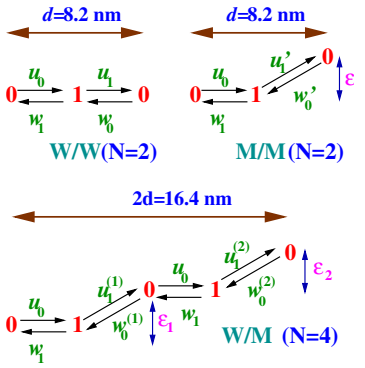

FIG. 1. (Color online) General schematic view of discrete stochastic models for kinesins. W-W labels the homodimeric motor protein with both wild-type motor heads, M-M corresponds to the homodimeric kinesins with mutations in both motor domains, while W-M describes the heterodimeric motor proteins with mutation in only one of the heads. The parameters ε, ε_1, and ε_2 describe free energy changes due to mutations relative to the wild-type motor proteins.

because it conveniently provides explicit expressions for dynamic properties, and it is able to describe successfully different aspects and trends of motor protein transport [5,7,19–26].

II. THEORETICAL MODEL

In our theoretical model it is assumed that the kinesin protein molecule steps from a given binding site to the next one at a distance $d=8.2$ nm along the microtubule through N intermediate biochemical states. Different kinetic schemes for the motion of homodimeric and heterodimeric kinesin molecules are shown in Fig. 1. A similar approach has been used successfully to describe the dynamic properties of kinesins and myosin V [5,19,23,24].

Let us label homodimeric motor proteins of wild type as W-W, homodimeric motor proteins with mutations in both heads as M-M, and heterodimeric proteins with only one mutated motor domain as W-M. Although the motion of motor proteins includes many complex biochemical and biophysical processes, in the simplest approximation it is reasonable to use only two-state ($N=2$) discrete stochastic models to describe the dynamics of both homodimeric kinesins; see Fig. 1. Note, however, that a two-state chemical kinetic model as presented here is not adequate to describe fluctuations in the dynamics [5]. The motor protein molecule can jump forward from a state 0 to a state 1 with the rate u_0, and this transition corresponds to ATP binding, yielding

$$u_0 = k_0[\mathrm{ATP}], \tag{3}$$

where k_0 is the rate constant. The reverse transition is given by the rate w_1. The forward and backward transitions between the state 1 and the state 0 on the next binding site, with the rates u_1 and w_0, respectively, describe several biochemical processes, such as ATP hydrolysis and release of hydrolysis products, but combine them in one step. We assume that mutations do not strongly affect the ATP binding process, but only the enzymatic functions are changed, which leads to a different pair of transition rates (u_1' and w_0') for the mutated molecule (see Fig. 1). Experiments show that some mutations decrease the binding affinity of motor proteins to microtubules, thus leading to decrease in enzymatic activity [14]. The transition rates for W-W and M-M motor proteins are related via the detailed balance condition,

$$\frac{u_1'}{w_0'} = \frac{u_1}{w_0}\exp(-\varepsilon/k_BT). \tag{4}$$

This expression connects the ratio of the forward and backward transition rates with a free energy difference between the corresponding states. The parameter ε describes the effect of mutation on enzymatic properties of the motor protein, i.e., how ATP hydrolysis for the mutated homodimer is thermodynamically less favorable in comparison with that of the wild-type homodimer. The microscopic origin of this parameter is the result of complex interactions between the two motor domains and between the motor heads and the microtubule track.

The situation is more complex for heterodimeric W-M kinesins, as illustrated in Fig. 1. The two motor domains and interactions between them are different from the cases of homodimer kinesins. As a result we have two different sets of rates to model ATP hydrolysis by the wild head ($u_1^{(1)}$ and $w_0^{(1)}$) and by the mutated head ($u_1^{(2)}$ and $w_0^{(2)}$). These rates are also related via detailed balance conditions,

$$\frac{u_1^{(1)}}{w_0^{(1)}} = \frac{u_1}{w_0}\exp(-\varepsilon_1/k_BT), \quad \frac{u_1^{(2)}}{w_0^{(2)}} = \frac{u_1}{w_0}\exp(-\varepsilon_2/k_BT). \tag{5}$$

It is important to note that generally $\varepsilon_1 \neq \varepsilon_2 \neq \varepsilon$, because of different interactions between the motor domains. Then, assuming that the hand-over-hand mechanism is still a valid description for the stepping of individual molecules, the dynamics of W-M kinesin molecules can be described by an ($N=4$)-state model with step size equal to $2d=16.4$ nm.

The explicit expressions for the rates can be obtained from Eqs. (4) and (5):

$$u_1' = u_1\gamma^{-\alpha}, \quad u_1^{(1)} = u_1\gamma_1^{-\alpha_1}, \quad u_1^{(2)} = u_1\gamma_2^{-\alpha_2} \tag{6}$$

and

$$w_0' = w_0\gamma^{1-\alpha}, \quad w_0^{(1)} = w_0\gamma_1^{1-\alpha_1}, \quad w_0^{(2)} = w_0\gamma_2^{1-\alpha_2}, \tag{7}$$

where we defined

$$\gamma = \exp\left(\frac{\epsilon}{kT}\right), \quad \gamma_1 = \exp\left(\frac{\varepsilon_1}{kT}\right), \quad \gamma_2 = \exp\left(\frac{\varepsilon_2}{kT}\right). \tag{8}$$

The parameters α, α_1, and α_2 are energy-distribution factors that describe how free energy changes due to the mutation affect corresponding forward and backward transitions. For simplicity, we assume that $\alpha=\alpha_1=\alpha_2$, although more general situations can be easily analyzed.

The advantage of using discrete stochastic models is the fact that all stationary-state dynamic properties of motor proteins, such as mean velocities, mean dispersions, and stall forces, can be obtained exactly for *any* number of intermediate states N in terms of the forward (u_j) and backward (w_j)

transition rates [5,21,23]. Specifically, exact expressions for the mean velocity can be presented in the following form:

$$V = \frac{d}{R_N}\left(1 - \prod_{j=0}^{N-1} \frac{w_j}{u_j}\right), \tag{9}$$

where d is the step size (equal to 8.2 nm for the $N=2$ model and 16.4 nm for the $N=4$ model), and the auxiliary functions R_N are given by

$$R_N = \sum_{j=0}^{N-1} r_j, \quad r_j = \frac{1}{u_j}\left(1 + \sum_{k=1}^{N-1} \prod_{i=j+1}^{j+k} \frac{w_i}{u_i}\right). \tag{10}$$

Specifically, for the velocity of homodimeric motor proteins we obtain

$$V(\text{W-W}) = d\left(\frac{u_0u_1 - w_0w_1}{u_0 + u_1 + w_0 + w_1}\right) \tag{11}$$

for W-W kinesins, and

$$V(\text{M-M}) = d\left(\frac{u_0u_1\gamma^{-\alpha} - w_0w_1\gamma^{1-\alpha}}{u_0 + u_1\gamma^{-\alpha} + w_0\gamma^{1-\alpha} + w_1}\right) \tag{12}$$

for M-M kinesins. For heterodimeric motor proteins, Eq. (9) yields

$$V(\text{W-M}) = 2d\left(\frac{u_0^2u_1^2(\gamma_1\gamma_2)^{-\alpha} - w_0^2w_1^2(\gamma_1\gamma_2)^{1-\alpha}}{A}\right), \tag{13}$$

with the parameter A given by

$$\begin{aligned} A = {} & (\gamma_1^{-\alpha} + \gamma_2^{-\alpha})u_0u_1(u_0 + w_1) + (\gamma_1^{1-\alpha} + \gamma_2^{1-\alpha})w_0w_1(u_0 + w_1) \\ & + (\gamma_1\gamma_2)^{-\alpha}(\gamma_1 + \gamma_2)u_1w_0(u_0 + w_1) \\ & + 2(\gamma_1\gamma_2)^{-\alpha}(u_0u_1^2 + w_0^2w_1\gamma_1\gamma_2). \end{aligned} \tag{14}$$

The general expression for dispersion in sequential discrete stochastic models can be written in the following form [5,21,23]:

$$D = (d/N)[(VS_N + dU_N)/(R_N)^2 - (N+2)V/2], \tag{15}$$

where

$$S_N = \sum_{j=0}^{N-1} s_j \sum_{k=0}^{N-1} r_{k+j+1}, \quad U_N = \sum_{j=0}^{N-1} u_j r_j s_j, \tag{16}$$

$$s_j = \frac{1}{u_j}\left(1 + \sum_{k=1}^{N-1} \prod_{i=j-1}^{j-k} \frac{w_{i+1}}{u_i}\right).$$

The explicit equations for dispersions of W-W, M-M, and W-M kinesins can be obtained similarly to the velocities; however, these expressions are quite bulky and they will not be presented here.

When the motor protein is subject to external loads, the resisting force that completely stops the molecule is called the stall force F_S. For general N-state sequential discrete-stochastic models the stall force can be written as [5,19]

$$F_S = \frac{k_BT}{d}\ln\left(\prod_{j=0}^{N-1} \frac{w_j}{u_j}\right). \tag{17}$$

For homodimeric kinesins our model predicts the following stall forces:

$$F_S(\text{W-W}) = \frac{k_BT}{d}\ln\frac{u_0u_1}{w_0w_1}, \quad F_S(\text{M-M}) = \frac{k_BT}{d}\ln\frac{u_0u_1}{w_0w_1\gamma}. \tag{18}$$

Comparing these equations, we obtain

$$F_S(\text{M-M}) = F_S(\text{W-W}) - \varepsilon/d. \tag{19}$$

For heterodimeric kinesins the stall force is given by

$$F_S(\text{W-M}) = \frac{k_BT}{2d}\ln\frac{u_0^2u_1^2}{w_0^2w_1^2\gamma_1\gamma_2}, \tag{20}$$

which leads to

$$F_S(\text{W-M}) = F_S(\text{W-W}) - (\varepsilon_1 + \varepsilon_2)/2d. \tag{21}$$

Equations (19) and (21) provide a simple physical interpretation and a method of estimating the parameters ε, ε_1, and ε_2.

The external force F also strongly modifies the transitions rates [5,19]:

$$u_j(F) = u_j(0)\exp\left(-\frac{\theta_j^+Fd}{k_BT}\right), \tag{22}$$

$$w_j(F) = w_j(0)\exp\left(+\frac{\theta_j^-Fd}{k_BT}\right), \tag{23}$$

where $\theta_j^{\pm}$ are load-distribution factors that describe how the external load changes the energy activation barriers for the forward and backward biochemical transitions from the state j. The load-distribution factors are related via

$$\sum_{j=0}^{N-1} (\theta_j^+ + \theta_j^-) = 1. \tag{24}$$

III. RESULTS AND DISCUSSION

In the experimental work of Kaseda *et al.* [14], the coordination of two heads for different homodimeric and heterodimeric kinesin molecules has been investigated using microtubule-gliding assays and optical trapping spectroscopy. Different homodimeric and heterodimeric motor proteins were prepared by mutations in the motor domains that affect the microtubule-binding region. It was found that dynamic properties of heterodimeric proteins with one mutated head could not be described by the independent hand-over-hand stepping mechanism.

To analyze the experimental data we consider kinesins with only one type of mutation, although our method can be easily applied to different molecular motor species. Specifically, it was shown [14] that at [ATP]=1 mM a wild-type homodimer travels with the stationary velocity V(W-W)

$=679\pm59$ nm/s, and it produces the maximum stall force of $F_S(\text{W-W})=6.3\pm0.9$ pN. When the mutation labeled L12 affects both motor heads, the resulting homodimeric M-M kinesin does not attach to microtubules, indicating zero velocity and stall force. However, surprisingly, a heterodimer with the same mutation L12 in one of the motor heads can move with the velocity $V(\text{W-M})=101\pm25$ nm/s, while exerting the maximal stall force of $F_S(\text{W-M})=0.8\pm0.2$ pN. Then, from Eqs. (19) and (21) we obtain

$$\varepsilon=(12.6\pm1.8)k_BT, \quad (\varepsilon_1+\varepsilon_2)/2=(11\pm4.4)k_BT. \tag{25}$$

The important result is that $\varepsilon_1+\varepsilon_2<2\varepsilon$, which indicates that biochemical properties of mutated and wild-type motor heads in the W-M kinesin differ from the corresponding properties in the W-W and M-M motor proteins, supporting our idea of modifying the free energy landscapes for motor proteins via interaction between motor subunits.

After systematically exploring the parameter space and following the procedures outlined in Refs. [24,26], we found that all experimental data for kinesins with the L12 mutation can be well described by the following parameters:

$$k_0=1.2\ \mu M^{-1}\ \text{s}^{-1}, \quad u_1=90\ \text{s}^{-1}, \quad w_1=10\ \text{s}^{-1},$$

$$w_0=0.05\ \text{s}^{-1},$$

$$\alpha=0.14, \quad \epsilon=12.3k_BT, \quad \varepsilon_1=\varepsilon_2=10.6k_BT. \tag{26}$$

In this fitting procedure the stall forces have been calculated from the best-fitted transition rates, and then the F_S have been used to estimate energy-distribution parameters. Note that the obtained transition rates are similar to the parameters previously utilized to describe the dynamics of single kinesins, and they are consistent with chemical kinetic experimental results [23]. In addition, in our calculations we found that the following load-distribution factors fit experimental observations well:

$$\theta_0^+=0.135, \quad \theta_1^-=0.080, \quad \theta_1^+=0.035, \quad \theta_0^-=0.750. \tag{27}$$

Also, these load-distribution factors are close to the parameters used before for analyzing other single-molecule experiments on kinesins [23], suggesting that our approach is quite robust.

The results of theoretical calculations for the velocities of homodimeric and heterodimeric kinesins at different conditions are presented in Fig. 2. The effect of external loads on the motor protein dynamics is shown in Fig. 2(a), and a good agreement with experimental observations is found. Our approach allows us to estimate the effect of resisting and assisting external forces. The resisting (positive) loads slow down the motion of all motor proteins, as expected. It is also found that the stall forces F_S for W-W and W-M kinesins are equal to 6.2 and 0.8 pN, respectively, which are in excellent agreement with experimentally measured values [14]. The assisting (negative forces) accelerate both W-W and W-M motor proteins, although the effect is much weaker for the heterodimeric species. The force-velocity curve for heterodimers is essentially linear for positive forces, while for homodimeric W-W kinesins it deviates from the linear dependence. Again, this theoretical result agrees well with experimental observations [compare with Fig. 4(b) from Ref. [14]]. The dependence of the velocity on the concentration of ATP [see Fig. 2(b)] shows a typical Michaelis-Menten character, i.e., a linear behavior at small concentrations of ATP and a saturation at large [ATP]. One of the important theoretical predictions of our model is that the heterodimeric kinesin with the L12 mutation in one of the motor heads will not function ($V=0$) even without an external resisting force ($F=0$) for ATP concentrations smaller than 1.4 mM. This theoretical prediction can be easily tested in experiments.

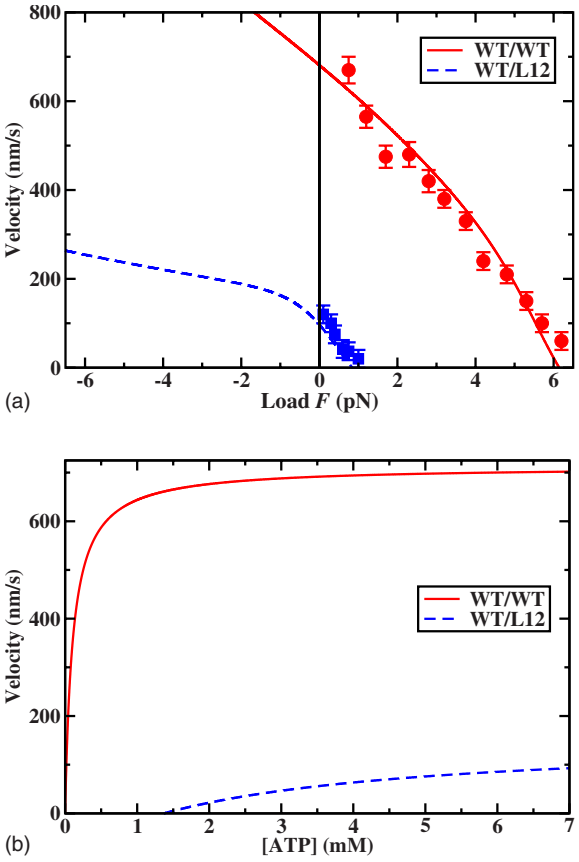

FIG. 2. (Color online) (a) Force-velocity curves for W-W homodimeric kinesins (solid line) and for W-M heterodimeric kinesins (dashed line) at [ATP]=1 mM. Symbols correspond to experimental measurements from Ref. [14]. (b) Velocities of W-W homodimeric kinesins (solid line) and W-M heterodimeric kinesins (dashed line) as a function of [ATP] at the constant external force $F=0.5$ pN. The velocity of homodimeric M-M kinesins is zero at all conditions.

In addition to the mean velocity, an important characteristic of the motor protein dynamics is the diffusion constant or dispersion [5]. In our theoretical framework it can be calculated exactly, and the results of these computations are given in Fig. 3. It should be noted that ($N=2$)-state stochastic models utilized here do not provide a correct description of dispersions [5]; however, our analysis still can be used to show relative differences in fluctuations for different motor proteins. In addition, our analysis can be easily extended to

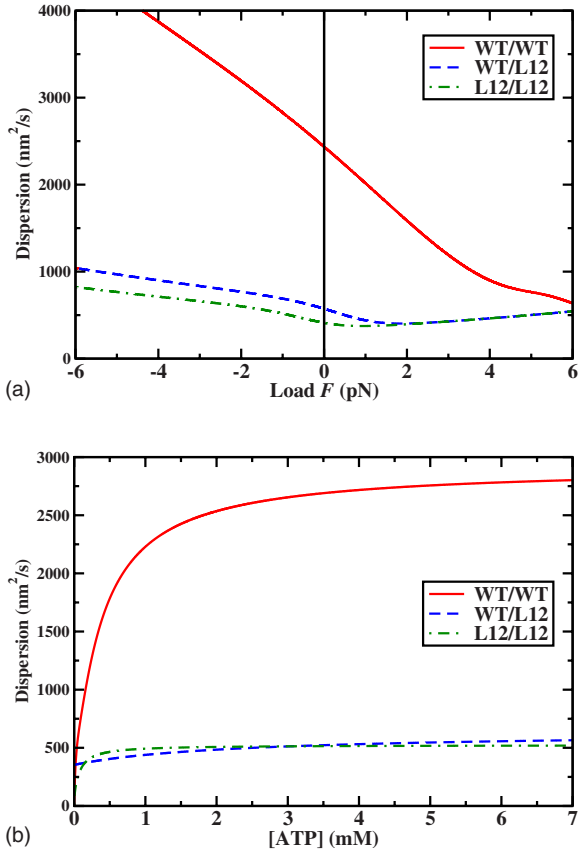

FIG. 3. (Color online) (a) Dispersion as a function of the external force for W-W homodimeric kinesins (solid line), for homodimeric M-M kinesins (dot-dashed line), and for W-M heterodimeric kinesins (dashed line) at [ATP]=1 mM. (b) Dispersions of W-W homodimeric kinesins (solid line), homodimeric M-M kinesins (dot-dashed line), and W-M heterodimeric kinesins (dashed line) as a function of [ATP] at the constant external force F =0.5 pN.

more realistic stochastic models. The effect of external forces on dispersions for homodimeric and heterodimeric kinesins is shown Fig. 3(a). External loads have qualitatively different effects on the fluctuations of wild-type and mutated motor proteins. Dispersion for homodimeric W-W kinesins is a decreasing function of the external load, while for homodimeric M-M and heterodimeric proteins it has a nonmonotonic behavior. At negative loads up to low positive forces ($F \leq 1$ pN) the dispersions of W-M and M-M kinesins decrease, although weakly. However, for larger opposing external forces dispersions start to increase. Dispersion as a function of [ATP] is plotted in Fig. 3(b). Again, the behavior of heterodimeric W-M proteins and fully mutated homodimeric kinesins are similar, and it deviates significantly from W-W motor proteins.

In the presented theoretical calculations we assume that the step size for wild-type and mutated motor proteins is the same. This is based on the fact that the L12 mutation affects only microtubule binding affinity [14]. However, exact measurements of step sizes have not been performed. Even in the case of variability of step sizes for different motor proteins, our approach is flexible enough to take this effect into account [5].

The presented theoretical method is closely related to an earlier approach of Peskin and Oster [6], where a model of force generation in kinesins coupled to ATP hydrolysis has been developed. Similarly to this approach, we suggest that the transition rates for the leading and trailing motor heads depend on complex interactions between the motor heads and protein filaments. In contrast to Ref. [6], we analyze heterodimeric motor proteins with a more detailed description of chemical processes and ATP hydrolysis. Our method allows us to estimate the effect of mutations in the transport of motor proteins on qualitative and quantitative scales.

Our theoretical calculations of dynamic properties and analysis of the experimental observations for homodimeric and heterodimeric kinesins suggest the following mechanistic (however strongly simplified) picture of the motor protein dynamics. Mutations change the free energy landscapes for the enzymatic activity and the mechanical progression of molecular motors. However, motor domains in W-W, M-M, and W-M proteins interact with each other differently, leading to different free energy surfaces. As a result, the two heads in the heterodimeric molecule become very similar in biochemical properties, but different from the corresponding motor domains in the homodimers. The heterodimeric motor protein still moves along the microtubules in the hand-over-hand mechanism, although with the transition rates modified by interaction between the motor heads. We suggest that this theoretical picture can be tested in experiments by, for example, labeling the two motor domains differently to obtain necessary dynamic information.

Although our theoretical approach does not explain the origin of the interactions between motor heads, we can discuss several possible sources of these interactions. In the hand-over-hand mechanism of the motion of motor proteins [2,6], when the back motor head moves forward, it is always connected to the linear track via the forward head, leading to an effective interaction between motor domains. In addition, the coiled-coil region that connects motor domains might also coordinate their motion. The heads can also interact via electrostatic interactions, dipole interactions, and van der Waals forces. However, these suggestions are speculative, and the nature of interactions should be determined in more detailed experiments.

IV. CONCLUSIONS

We developed a simple theoretical description of the dynamics of motor proteins based on discrete sequential stochastic models. This approach allows us to resolve the contradiction between experimental observations on homodimeric and heterodimeric kinesins and the widely accepted hand-over-hand stepping mechanism for two-headed molecular motors. It is argued that the interaction between motor domains can modify free energy landscapes for the motor protein motion, and the transitions rates change depending on the nature of these domains. Explicit calculations of dynamics properties, such as velocities, dispersions, and stall forces, T are presented for homodimeric and heterodimeric kinesins with L12 mutations. The theoretical predictions agree well with available experimental data. Several

suggestions for testing theoretical predictions are discussed.

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