Spatial Fluctuations Affect the Dynamics of Motor Proteins

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Spatial Fluctuations Affect the Dynamics of Motor Proteins

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Motor proteins are active biological molecules that perform their functions by converting chemical energy into mechanical work. They move unidirectionally along rigid protein filaments or DNA and RNA molecules in discrete steps by hydrolyzing ATP (adenosine triphsophate) or related energy-rich compounds. Recent single-molecule experiments have shown that motor proteins experience significant spatial fluctuations during its motion, leading to broad step-size distributions. The effect of these spatial fluctuations is analyzed explicitly by considering discrete-state stochastic models that allow us to compute exactly all dynamic properties. It is shown that for symmetric spatial fluctuations there is no change in mean velocities for weak external forces, while dispersions and stall forces are strongly affected at all conditions. These results are illustrated by several simple examples. Our method is also applied to analyze the effect of step-size fluctuations on dynamics of myosin V motor proteins. It is argued that spatial fluctuations might be used to control and regulate the dynamics of motor proteins.

1. Introduction

Several classes of active enzymatic molecules that produce mechanical work by utilizing energy of different biochemical processes are known as motor proteins, or molecular motors.[1–4] These molecules, such as kinesins, dyneins, myosins, DNA and RNA polymerases, helicases and many others, play important roles in a variety of biological processes that include cellular transport, cell division, muscle contraction, and genetic transcription.[1–3] They typically translocate in a linear fashion along rigid protein filaments or DNA and RNA molecules, and their motion is fueled by the energy of hydrolysis of ATP (adenosine triphosphate) or related compounds. However, mechanisms of coupling between biochemical transitions and mechanical transformations in motor proteins are still not well understood.[3,4]

A large progress in understanding mechanisms of motor protein dynamics has been achieved in the past decade with the development of single-molecule experimental methods.[3–23] These investigations have revealed dynamic properties of molecular motors, such as velocities, dispersions, run lengths, dwell times, and stall forces, at different conditions for individual single protein molecules. It was shown that motor proteins can exert significant forces during their motion, and there are large fluctuations and variability in the dynamic properties. In addition, functioning of motor proteins includes multiple states and conformations that are related via complex biochemical pathways.

Significant advances in experimental investigations of motor proteins, which enabled the description of dynamics and biochemical transitions at the single-molecule level, have greatly stimulated theoretical discussions on the functioning of molecular motors.[3,4,24–31] Theoretical studies of motor proteins mostly involve two main directions: continuum ratchet models[24,29–31] and stochastic discrete-state models.[4,25–28] Current theoretical approaches can account for most available experimental observations, and they provide a reasonable framework for understanding mechanisms of molecular motor's transport.[4]

One of the most fascinating properties of motor proteins is a large variability and fluctuations in dynamic properties. The precision of existing single-molecule experimental techniques allows to quantify these fluctuations, indicating that they contain an important information about biochemical and biophysical processes in motor proteins.[8,10–23] Thus, the use of fluctuations and variability data might provide a valuable tool for understanding mechanisms of molecular motor's functioning. However, theoretical descriptions of these phenomena in motor proteins are rather very limited.[4,32] The first simplified approach to take into account spatial fluctuations has been presented in ref 27. Here, the upper bounds of the effect of fluctuations on dynamics have been obtained by assuming (obviously, unrealistically) that the myosin V molecules move via alternating long and short steps. Although the method was quite naive, it showed that fluctuations might modify the dynamics only near the stalling force conditions where the precision of experimental measurements is not high.

Recently, Shaevitz, Block, and Schnitzer[32] presented a first analytical study of spatial fluctuations in motor proteins step sizes. Using a moment-generating functions method, they calculated distribution functions for completion times that allowed them to analyze the effect of variability in the step size of motor proteins on their dynamics. Specifically, they considered a randomness parameter r defined as[4,6,32]

$$r = \frac{2D}{dV} \qquad (1)$$

where D and V are mean dispersion and velocity of the motor protein molecule and d is the average step-size. This function provides a convenient measure of overall fluctuations in molecular motors. It was shown that the randomness r can be written as a sum of two terms corresponding to fluctuations in the step-size and due to the stochastic nature of enzymatic molecules.[32] Although this theoretical work provides a valuable description of fluctuations, its application is restricted because of the assumption of irreversibility in biochemical transitions of motor proteins. Generally, all chemical reactions are reversible, and neglecting this property might lead to erroneous

Spatial Fluctuations Affect the Dynamics of Motor Proteins

J. Phys. Chem. B, Vol. 112, No. 35, 2008 **11113**

conclusions about dynamic properties and mechanisms of motor proteins.[4] In addition, the effect of fluctuations on other properties, such as velocities and stall forces, has not been described. In this paper, we present a comprehensive theoretical approach that allows to estimate explicitly the effect of spatial fluctuations on all dynamic properties of motor proteins. It is based on theoretical formalism developed by Derrida for random walks on periodic one-dimensional lattices,[33] which provides exact expressions for the asymptotic (long-time) drift velocity

$$V = \lim_{t \to \infty} \frac{d}{dt} \langle x(t) \rangle \tag{2}$$

and for dispersion (or the effective diffusion constant)

$$D = \frac{1}{2} \lim_{t \to \infty} \frac{d}{dt} [\langle x^2(t) \rangle - \langle x(t) \rangle^2] \tag{3}$$

where $x(t)$ is the position of the motor protein along the linear track at time t.

The fluctuations of motor proteins have also been successfully studied in models[34,35] that combined mechanical properties of motor proteins with ATP hydrolysis kinetics relevant for the motility. The advantage of this approach is close connection to realistic protein structures. However, these methods depend on potentials of interactions and on a choice of mechanistic parameters. To obtain dynamic properties of motor proteins, complex equations should be solved numerically[34] or stochastic Monte Carlo simulations[35] should be utilized, and it might complicate the elucidation of mechanisms of motor proteins. Our discrete-state stochastic method, although not utilizing directly structural information, can provide exact solutions for all dynamic properties of motor proteins, and thus, it might help to understand how spatial fluctuations influence the motor protein's transport.

2. Theoretical Model

Let us consider a motor protein molecule that moves along protein filaments in an effectively one-dimensional motion. There are periodically distributed binding sites with a period d. For example, $d \approx 8$ nm for the motion of kinesins and dyneins on microtubules, and for the transport of myosins V and myosins VI on Actin filaments the average step-size is $d \approx 36$ nm. Because of the structure of protein filaments there are other binding sites that can be reached by the molecular motor, although with a smaller probability as indicated by single-molecule experiments.[11,23] This suggests that the step-size of the particle varies around d. In our simplest model we assume that these fluctuations are discrete and symmetric, and that there are only three possible step-sizes,

$$d_- = d - a, \ d_0 = d, \text{ and } d_+ = d + a \tag{4}$$

where a parameter a describes the amplitude of spatial fluctuations. The motor protein could make a step d_- or d_+ with a probability p for each move, while the probability for the normal step d_0 is $1 - 2p$. Here, $p < 0.5$ reflects the fact that steps larger or smaller than d_0 are less probable.[11,23] It should be noted that our approach can be easily extended to include asymmetric fluctuations and more values of discrete step-sizes. The discreetness in step-size fluctuations is an important property that enables us to develop explicit analysis of dynamic properties of molecular motor. It also provides a realistic description of motor protein's transport.

Following the discrete-state stochastic approach for motor proteins,[4] we postulate that there are N sequential intermediate biochemical states between consecutive binding sites as shown
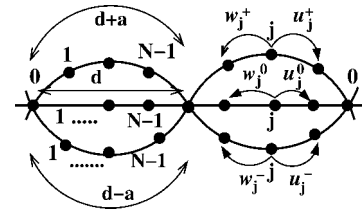

Figure 1. General schematic picture for the discrete-state stochastic model of fluctuating motor protein with three different step sizes. Each point corresponds to some motor protein's conformation, for example, the enzyme molecule bound to ATP. Arrows indicate possible biochemical transitions between different motor protein states. The upper pathway describes states when the motor protein molecule moves with long $(d + a)$ size steps between consecutive binding sites, while the lower curves are for the shorter $(d - a)$ size steps, and the middle pathway is for the normal steps of size d.

in Figure 1. The possibility of different step-sizes is reflected in three biochemical pathways: the molecular motor on the upper (lower) pathway hops with step-sizes d_+ or d^- respectively, while in the middle pathway the step-size is equal to the average d_0. The particle at the state j on the pathway λ (with $\lambda = +, -$, or 0 for the upper, lower, and middle pathways, correspondingly) can move forward or backward with rates u_j^λ or w_j^λ: see Figure 1. Note that the forward transition rates at site 0 are given by $u_0^+ = pu_0$, $u_0^- = pu_0$ and $u_0^0 = (1 - 2p)u_0$ for +, −, and 0 pathways, respectively, because of the stochasticity in the choice of the step-size. Similarly backward transition rates are $w_0^+ = pw_0$, $w_0^- = pw_0$ and $w_0^0 = (1 - 2p)w_0$ for upper, lower, and middle pathways, respectively.

Our method allows us to incorporate easily the effect of external fields in the dynamics of fluctuating motor proteins.[4] Under the effect of the external force F the transitions rates are modified as follows,

$$u_j^\lambda(F) = u_j^\lambda(0) \exp(-\theta_j^{(\lambda)+} F d_\lambda / k_B T) \tag{5}$$

$$w_j^\lambda(F) = w_j^\lambda(0) \exp(\theta_j^{(\lambda)-} F d_\lambda / k_B T) \tag{6}$$

where $\theta_j^{(\lambda)\pm}$ are load-distribution factors[4,25] (for $j = 0, 1, \cdots, N - 1$ and $\lambda = +, 0, -$) that specify how the work done by the force F is divided between forward and backward transitions. We require that for each pathway load-distribution factors are related via[4,25,27]

$$\sum_{j=0}^{1} (\theta_j^{(\lambda)+} + \theta_j^{(\lambda)-}) = 1 \tag{7}$$

for $\lambda = +, -, 0$. To simplify calculations it is also assumed that load-distribution factors are independent of the pathway.

Theoretical analysis shows that dynamic properties of fluctuating motor proteins depend on several linear sequential products of rate ratios. To simplify our notations we define

$$\prod_{j(\lambda)}^{k} \equiv \prod_{i=j}^{k} \frac{w_i^\lambda}{u_i^\lambda}; \quad \prod_{j(\lambda)}^{\dagger k} \equiv \prod_{i=j}^{k} \frac{w_{i+1}^\lambda}{u_i^\lambda} = \frac{w_{k+1}^\lambda}{w_j^\lambda} \prod_{j(\lambda)}^{k} \tag{8}$$

with transition rates related due to periodicity of the system, $u_{j\pm N}^\lambda = u_j^\lambda$ and $w_{j\pm N}^\lambda = w_j^\lambda$.

3. Results

We present here explicit expressions for dynamic properties of fluctuating motor proteins. Our method is closely related to theoretical analysis of parallel-chain kinetic models of biological transport.[4,26] The detailed derivations are outlined in the Appendix.

3.1. Velocity. In our model, the mean velocity has three contributions corresponding to the transport across three different pathways with step-sizes d_0, d_+, and d_-, respectively,

$$V = V_0 + V_+ + V_- \tag{9}$$

where utilizing notations (eq 8) we have

$$V_0 = \frac{d_0\left[1 - \prod\limits_{1(0)}^{N}\right]}{r_0^0\left[\dfrac{R_N^0}{r_0^0} + \dfrac{R_N^+}{r_0^+} + \dfrac{R_N^-}{r_0^-} - 2\right]}$$

$$V_+ = \frac{d_+\left[1 - \prod\limits_{1(+)}^{N}\right]}{r_0^+\left[\dfrac{R_N^0}{r_0^0} + \dfrac{R_N^+}{r_0^+} + \dfrac{R_N^-}{r_0^-} - 2\right]}$$

$$V_- = \frac{d_-\left[1 - \prod\limits_{1(-)}^{N}\right]}{r_0^-\left[\dfrac{R_N^0}{r_0^0} + \dfrac{R_N^+}{r_0^+} + \dfrac{R_N^-}{r_0^-} - 2\right]} \tag{10}$$

In the above expressions the auxiliary functions R_N^λ and r_j^λ have been introduced,

$$R_N^\lambda = \sum_{j=0}^{N-1} r_j^\lambda; \quad r_j^\lambda = (u_j^\lambda)^{-1}\left[1 + \sum_{k=1}^{N-1}\prod_{j+1(\lambda)}^{j+k}\right] \tag{11}$$

for $\lambda = +, -, 0$. The motor protein that do not fluctuate has a zero probability to make steps of the size $d \pm a$ ($p = 0$), and in this case $u_0^\pm = w_0^\pm = 0$, which leads to $1/r_0^\pm = 0$. Then we have $V_- = V_+ = 0$, that is, the molecular motor advances only along the middle pathways with the fixed step-size, as expected.

If we assume that all transition rates u_j^λ and w_j^λ are same for the three pathways, the formula for the overall velocity simplifies,

$$V = \frac{d_0 u_0\left[1 - \prod\limits_{1}^{N}\right]}{\left[\dfrac{R_N^0}{r_0^0} + \dfrac{R_N^+}{r_0^+} + \dfrac{R_N^-}{r_0^-} - 2\right]\left(1 + \dfrac{w_1}{u_1}\right)} \tag{12}$$

It can be shown that the expression in the denominator can be written in the following form

$$\left[\frac{R_N^0}{r_0^0} + \frac{R_N^+}{r_0^+} + \frac{R_N^-}{r_0^-} - 2\right] = 1 + \frac{u_0\sum\limits_{j=1}^{N-1} r_j}{\left[1 + \sum\limits_{k=1}^{N-1}\prod\limits_{1}^{k}\right]} \tag{13}$$

which is independent of the probability p. Because other components of the velocity in eq 12 are also independent of p, it can be concluded that in this case symmetric fluctuations do not affect the velocity of the motor protein.

3.2. Dispersion. The expressions for dispersion in our model are much more complex, and they can be presented as a sum of five contributions,

$$D = D_0 + D_+ + D_- + D_e + D_c \tag{14}$$

The expression for dispersion cannot be written as sum of the terms from three pathways because of the strong correlations between them. The first term is given by

$$D_0 = \left(\frac{d_0}{N}\right)\left\{ VN\left(\sum_{i=1}^{N-1} b_i^+ + \sum_{i=1}^{N-1} b_i^-\right) - \frac{V(N+2)}{2} - \frac{(N-2)}{2N}\right.$$
$$\left[d^+\sum_{j=0}^{N-1}(u_j^+ - w_j^+)b_j^+ + d^-\sum_{j=0}^{N-1}(u_j^- - w_j^-)b_j^-\right] + \left.\frac{V}{1 - \prod\limits_{1(0)}^{N}}J_0\right\} \tag{15}$$

where

$$J_0 = \frac{1}{N}\left(\frac{d_+}{d_0}\right)\sum_{j=0}^{N-1} s_j^0 j\sum_{i=0}^{N-1}(u_i^+ - w_i^+)b_i^+ +$$
$$\frac{1}{N}\left(\frac{d_-}{d_0}\right)\sum_{j=0}^{N-1} s_j^0 j\sum_{i=0}^{N-1}(u_i^- - w_i^-)b_i^- + U_N^0 + \frac{V}{d_0}S_N^0 -$$
$$\frac{V}{d_0}\left[\sum_{j=0}^{N-1} s_j^0 j\sum_{i=0}^{N-1} b_i^+ + \sum_{j=0}^{N-1} s_j^0 j\sum_{i=0}^{N-1} b_i^-\right] \tag{16}$$

$$S_N^0 = \sum_{j=0}^{N-1} s_j^0\sum_{k=0}^{N-1}(k+1)b_{k+j+1}^0 \tag{17}$$

$$U_N^0 = \sum_{j=0}^{N-1} u_j^0 b_j^0 s_j^0 \tag{18}$$

The second term has a similar structure,

$$D_+ = \left(\frac{d_+}{N}\right)\left\{ VN\left(\sum_{i=1}^{N-1} b_i^0 + \sum_{i=1}^{N-1} b_i^-\right) -\right.$$
$$\frac{V(N+2)}{2} - \frac{(N-2)}{2N}\left[d^0\sum_{j=0}^{N-1}(u_j^0 - w_j^0)b_j^0 +\right.$$
$$\left. d^-\sum_{j=0}^{N-1}(u_j^- - w_j^-)b_j^-\right] + \left.\frac{V}{1 - \prod\limits_{1(+)}^{N}}J_+\right\} \tag{19}$$

with

$$J_+ = \frac{1}{N}\left(\frac{d_0}{d_+}\right)\sum_{j=0}^{N-1} s_j^+ j\sum_{i=0}^{N-1}(u_i^0 - w_i^0)b_i^0 +$$
$$\frac{1}{N}\left(\frac{d_-}{d_+}\right)\sum_{j=0}^{N-1} s_j^+ j\sum_{i=0}^{N-1}(u_i^- - w_i^-)b_i^- + U_N^+ + \frac{V}{d_+}S_N^+ -$$
$$\frac{V}{d_+}\left[\sum_{j=0}^{N-1} s_j^+ j\sum_{i=0}^{N-1} b_i^0 + \sum_{j=0}^{N-1} s_j^+ j\sum_{i=0}^{N-1} b_i^-\right] \tag{20}$$

$$S_N^+ = \sum_{j=0}^{N-1} s_j^+\sum_{k=0}^{N-1}(k+1)b_{k+j+1}^+ \tag{21}$$

$$U_N^+ = \sum_{j=0}^{N-1} u_j^+ b_j^+ s_j^+ \tag{22}$$

Similarly, the third term looks like

Spatial Fluctuations Affect the Dynamics of Motor Proteins

J. Phys. Chem. B, Vol. 112, No. 35, 2008 **11115**

$$D_- = \left(\frac{d_-}{N}\right)\left\{ VN\left(\sum_{i=1}^{N-1} b_i^0 + \sum_{i=1}^{N-1} b_i^+\right) - \frac{V(N+2)}{2} - \right.$$

$$\frac{(N-2)}{2N}\left[d^0\sum_{j=0}^{N-1}(u_j^0 - w_j^0)b_j^0 + \right.$$

$$\left. d^+\sum_{j=0}^{N-1}(u_j^+ - w_j^+)b_j^+\right] + \left.\frac{V}{1-\prod_{1(-)}^N}J_-\right\} \quad (23)$$

with

$$J_- = \frac{1}{N}\left(\frac{d_0}{d_-}\right)\sum_{j=0}^{N-1} s_j^- j\sum_{i=0}^{N-1}(u_i^0 - w_i^0)b_i^0 +$$

$$\frac{1}{N}\left(\frac{d_+}{d_-}\right)\sum_{j=0}^{N-1} s_j^- j\sum_{i=0}^{N-1}(u_i^+ - w_i^+)b_i^+ + U_N^- + \frac{V}{d_-}S_N^- -$$

$$\frac{V}{d_-}\left[\sum_{j=0}^{N-1} s_j^- j\sum_{i=0}^{N-1} b_i^+ + \sum_{j=0}^{N-1} s_j^- j\sum_{i=0}^{N-1} b_i^0\right] \quad (24)$$

$$S_N^- = \sum_{j=0}^{N-1} s_j^- \sum_{k=0}^{N-1}(k+1)b_{k+j+1}^- \quad (25)$$

$$U_N^- = \sum_{j=0}^{N-1} u_j^- b_j^- s_j^- \quad (26)$$

In the above expressions, we utilized two new auxiliary functions that are defined as

$$s_j^\lambda = u_j^{-1}\left[1 + \sum_{k=1}^{N-1}\prod_{j-1(\lambda)}^{\dagger j-k}\right] \quad (27)$$

and

$$b_j^\lambda = \left(\frac{r_j^\lambda}{r_0^\lambda}\right)\Bigg/\left[\frac{R_N^0}{r_0^0} + \frac{R_N^+}{r_0^+} + \frac{R_N^-}{r_0^-} - 2\right] \quad (28)$$

for $\lambda = +, -, 0$. The meaning of the function b_j^λ is a probability to find the molecular motor at state j on the pathway λ on any period of the lattice. It should be noted then that

$$b_0^0 = b_0^+ = b_0^- = b_0 = 1\Bigg/\left[\frac{R_N^0}{r_0^0} + \frac{R_N^+}{r_0^+} + \frac{R_N^-}{r_0^-} - 2\right] \quad (29)$$

In addition,

$$r_0^\pm = \left(\frac{1}{pu_0^\pm}\right)\left[1 + \sum_{k=1}^{N-1}\prod_{j+1(\pm)}^{j+k}\right] \quad (30)$$

which yields $b_j^\pm = 0$ for $p = 0$, as expected.

The fourth term can be written as

$$D_e = -\left(\frac{d_+}{N}\right)\frac{VJ_2}{1-\prod_{1(+)}^N} - \left(\frac{d_-}{N}\right)\frac{VJ_3}{1-\prod_{1(-)}^N}$$

$$= -2\left(\frac{d_0}{N}\right)\frac{VJ_1}{1-\prod_{1(0)}^N} \quad (31)$$

where

$$J_1 = \sum_{j=0}^{N-1}\left[\left(\frac{d_+}{d_0}\right)\frac{j\prod_{1(0)}^j}{(1-2p)Nu_0^0}\sum_{i=0}^{N-1}(u_i^+ - w_i^+)b_i^+ + \right.$$

$$\left(\frac{d_-}{d_0}\right)\frac{j\prod_{1(0)}^j}{(1-2p)Nu_0^0}\sum_{i=0}^{N-1}(u_i^- - w_i^-)b_i^- + \frac{u_j^0 b_j^0 \prod_{1(0)}^j}{(1-2p)u_0^0} +$$

$$\frac{V\prod_{1(0)}^j}{(1-2p)u_0^0 d_0}\left(\sum_{i=0}^{N-1}(i+1)b_{j+i+1}^0 - j\sum_{i=1}^{N-1} b_i^+ - j\sum_{i=1}^{N-1} b_i^-\right)\right] \quad (32)$$

$$J_2 = \sum_{j=0}^{N-1}\left[\left(\frac{d_0}{d_+}\right)\frac{j\prod_{1(+)}^j}{pNu_0^+}\sum_{i=0}^{N-1}(u_i^0 - w_i^0)b_i^0 + \left(\frac{d_-}{d_+}\right)\frac{j\prod_{1(+)}^j}{pNu_0^+}\sum_{i=0}^{N-1}(u_i^- - \right.$$

$$w_i^-)b_i^- + \frac{u_j^+ b_j^+ \prod_{1(+)}^j}{pu_0^+} + \frac{V\prod_{1(+)}^j}{pu_0^+ d_+}\left(\sum_{i=0}^{N-1}(i+1)b_{j+i+1}^+ - \right.$$

$$j\sum_{i=1}^{N-1} b_i^0 - j\sum_{i=1}^{N-1} b_i^-\right)\right] \quad (33)$$

$$J_3 = \sum_{j=0}^{N-1}\left[\left(\frac{d_0}{d_-}\right)\frac{j\prod_{1(-)}^j}{pNu_0^-}\sum_{i=0}^{N-1}(u_i^0 - w_i^0)b_i^0 + \left(\frac{d_+}{d_-}\right)\frac{j\prod_{1(-)}^j}{pNu_0^-}\sum_{i=0}^{N-1}(u_i^- - \right.$$

$$w_i^-)b_i^- + \frac{u_j^- b_j^- \prod_{1(-)}^j}{pu_0^-} + \frac{V\prod_{1(-)}^j}{pu_0^- d_-}\left(\sum_{i=0}^{N-1}(i+1)b_{j+i+1}^- - j\sum_{i=1}^{N-1} b_i^0 - \right.$$

$$j\sum_{i=1}^{N-1} b_i^+\right)\right] \quad (34)$$

The last contribution to dispersion in eq 14 can be expressed in the following way,

$$D_c = \frac{d_0^2}{N}(D_{c1} + D_{c2} + D_{c3}) \quad (35)$$

where D_{c1}, D_{c2}, D_{c3} are given by

$$D_{c1} = \left[\frac{d_+^2\left(1-\prod_{1(+)}^N\right)}{d_0 r_0^+}\sum_{j=0}^{N-1} b_j^0 - \frac{d_+\left(1-\prod_{1(0)}^N\right)}{r_0^0}\sum_{j=1}^{N-1} b_j^+\right] \times$$

$$\left[\frac{J_2}{d_0\left(1-\prod_{1(+)}^N\right)} - \frac{J_1}{d_+\left(1-\prod_{1(0)}^N\right)}\right] \quad (36)$$

$$D_{c2} = \left[\frac{d_-^2\left(1-\prod_{1(-)}^N\right)}{d_0 r_0^-}\sum_{j=0}^{N-1} b_j^0 - \frac{d_-\left(1-\prod_{1(0)}^N\right)}{r_0^0}\sum_{j=1}^{N-1} b_j^-\right] \times$$

$$\left[\frac{J_3}{d_0\left(1-\prod_{1(-)}^N\right)} - \frac{J_1}{d_+\left(1-\prod_{1(0)}^N\right)}\right] \quad (37)$$

$$D_{c3} = \left[\frac{d_+ d_-^2 \left(1 - \prod\limits_{1(-)}^N\right)}{d_0^2 r_0^-} \sum_{j=0}^{N-1} b_j^+ - \frac{d_- d_+^2 \left(1 - \prod\limits_{1(+)}^N\right)}{d_0^2 r_0^+} \sum_{j=1}^{N-1} b_j^- \right] \times$$

$$\left[\frac{J_3}{d_+\left(1 - \prod\limits_{1(+)}^N\right)} - \frac{J_2}{d_-\left(1 - \prod\limits_{1(-)}^N\right)} \right] \quad (38)$$

3.3. Illustrative Examples. To better understand the effects of spatial fluctuation on dynamics of motor proteins, we consider several simple examples for $N = 1$ model, assuming that transition rates u_0 and w_0 are the same in all pathways. First, we start with simplest but unphysical situation when there is no backward transition, that is, $w_0 = 0$. In this case, we get for the drift velocity,

$$V = d u_0 \quad (39)$$

which indicates that it is independent of step-size fluctuations. The expression for dispersion can be also computed, yielding

$$D = \frac{d^2}{2} u_0 + a^2 p u_0 \quad (40)$$

Here the first term corresponds to dispersion for the simple $N = 1$ model without fluctuations, while the second term is due to spatial fluctuations. Then the randomness parameter (see eq 1), important for analysis of motor proteins dynamics, is equal to

$$r = 1 + 2p\left(\frac{a}{d}\right)^2 \quad (41)$$

in agreement with theoretical calculations in ref 32. This result suggests that overall fluctuations in the system can be increased by increasing the probability p of large and small steps of the size $d \pm a$, or by increasing the amplitude a of spatial fluctuations, while the velocity of the particle is not affected by symmetric step-size fluctuations. It can be shown that the second term in the randomness is proportional to the variation in step-size fluctuations,[32]

$$\frac{\langle d^2 \rangle - \langle d \rangle^2}{\langle d \rangle^2} = 2p\left(\frac{a}{d}\right)^2 \quad (42)$$

Because all biochemical transitions are reversible, it is more realistic to consider $N = 1$ model with nonzero backward transitions. In this case, we found that

$$V = d_0(u_0 - w_0) \quad (43)$$

which again shows the independence of the velocity on symmetric spatial fluctuations. The dispersion for this model is modified in the following way,

$$D = \frac{d^2}{2}(u_0 + w_0) + a^2 p(u_0 + w_0) \quad (44)$$

These two terms again can be viewed as corresponding to the model without fluctuations and due to step-size variations. Consequently, the expression for the randomness can be written as

$$r = \frac{u_0 + w_0}{u_0 - w_0} + 2p\left(\frac{a}{d}\right)^2 + 4p\left(\frac{a}{d}\right)^2 \frac{w_0}{u_0 - w_0} \quad (45)$$

In this equation, the first term corresponds to stochastic fluctuations in transition rates, the second term is due to the step-size variations, and there is a third term that reflects the correlation between different pathways. It is expected that these
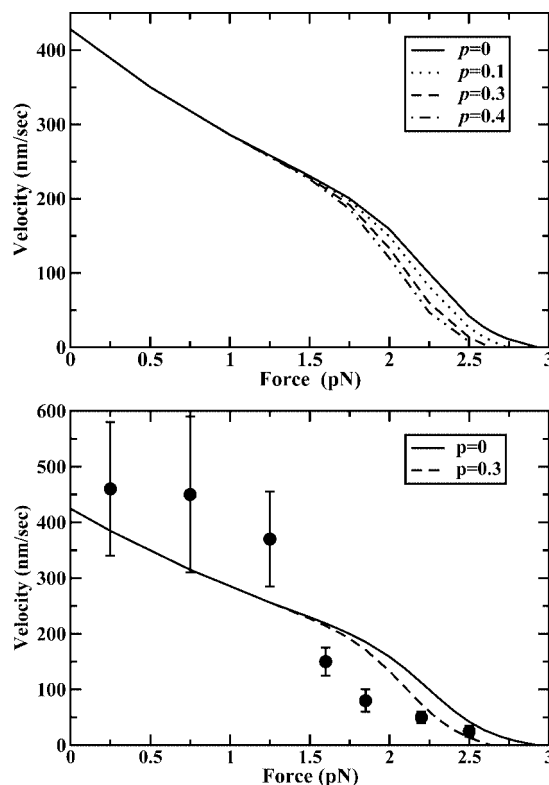

Figure 2. Effect of spatial fluctuations on force-velocity relations for myosin V molecules: (a) curves for different step-size fluctuations; (b) comparison with experimental observations from ref 14.

results hold for general N-state kinetic models with fluctuations. Thus there is a new contribution to the randomness that comes from the reversibility of biochemical transitions, and it contradicts to the earlier theoretical result[32] that the randomness can be presented only as a sum of step-time and step-size variations. This observation points out again to the importance of the reversibility in biochemical transitions for the analysis of motor proteins dynamics. Neglecting even one backward transition can lead to incorrect estimates of overall fluctuations in the system.

4. Analysis of Myosin-V Dynamics

To test our theoretical approach, we investigate the effect of spatial fluctuations on dynamics of myosin V molecules. Myosin-V is a dimeric two-headed motor protein that moves along Actin filaments.[1,2] Single-molecule experiments[11,13,22] indicate that it moves in hand-over-hand fashion making steps of approximately $d \approx 36$ nm. Distribution of experimentally observed steps have been fitted by Gaussian function with the standard deviation close to 6 nm.[11] In our analysis, we take the amplitude of fluctuations a to be equal to 5.5 nm, which corresponds to the distance to closest binding sites on Actin filaments. The value of the probability p can be estimated by comparing experimental distributions of step sizes with our model with three pathways.[11] We conclude that $p \approx 0.3-0.35$.

Dynamics of myosin V motor proteins have been studied before using discrete-state models[27,28] and more detailed mechanical approaches.[34,35] For our analysis of fluctuations, we utilize the simplest $N = 2$ model[27] that was successful in the description of dwell-time distributions and substeps for these molecular motors. It was also assumed that fluctuations are symmetric, and transitions rates are independent from the pathway. We use the same set of values for the transition rates u_0, u_1, w_0, and w_1 and for the load-distribution factors θ_0^+, θ_0^-, θ_1^+, and θ_1^- as in ref 27.

Spatial Fluctuations Affect the Dynamics of Motor Proteins

J. Phys. Chem. B, Vol. 112, No. 35, 2008 **11117**
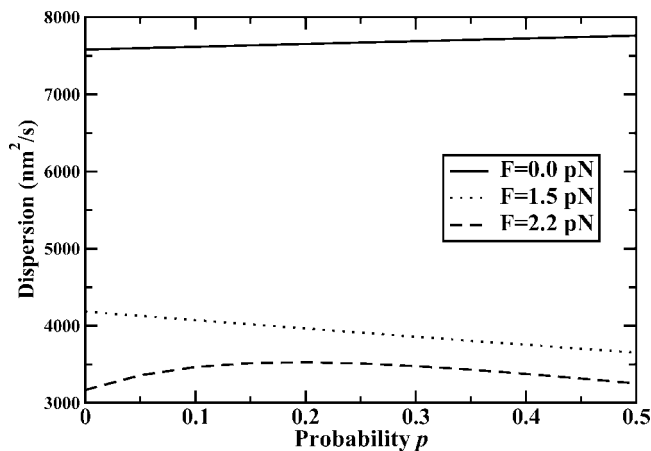
Figure 3. Dispersion as a function of probability p of spatial fluctuations for different external force.

Figure 4. Randomness as a function of the external force for different probabilities of step-size fluctuations.

Figure 5. Relative stall force as a function of the probability of step-size fluctuations.

4.1. Force-velocity Relations. Utilizing the explicit expression for the drift velocity (eq 12) for $N = 2$ and substituting into it the load-dependent transition rates (see eqs 5 and 6), we obtain force-velocity relations for myosin V molecules. The corresponding curves are shown in Figure 2a for ATP saturating conditions ([ATP] = 2 mM). However, similar trends are found at all ATP concentrations (results are not shown). It can be seen that step-size fluctuations do not change the drift velocity for low external forces ($F < 1.5$ pN). However, closer to the stall force, these variations in the steps start to modify the speed of the molecular motor. Increasing the external force lowers the forward rates and increases the backward rates. However, the particle moves slower when it is found in the upper pathway with steps $d + a$ because it has to produce larger work than in other pathways to overcome the resisting force F. The larger the value p, the more probable to find the motor protein on this pathway, and this leads to overall lowering the velocity, as observed in Figure 2. Note also that the stall force is reduced when the molecular motor experiences step-size fluctuations.

It is interesting to compare our theoretical predictions for force-velocity relations with experimental observations, and the results are shown in Figure 2b. It can be seen that parameters of the model developed in ref 27 for different sets of experiments can fit reasonably well experiments of Uemura et al.,[14] suggesting that our approach is quite robust. Analysis of Figure 2b also suggests that taking into account fluctuations provides a better description of force-velocity curves, especially near the stall force.

4.2. Dispersion and Randomness. Similar calculations can be performed for dispersion of the myosin V motor protein. Changing the probability of fluctuations influences the dispersion, as shown in Figure 3 for different external loads. Generally, increasing the resisting force lowers dispersion, and this effect can be attributed to reducing the stochasticity in each pathway by decreasing the forward rates stronger than increasing the backward rates. The dependence of dispersion on the probability of step-size fluctuations p is more complex. It is linear and slowly increasing for small external forces. This observation might be explained if we recall the result for dispersion for $N = 1$ model: see eq 44. The dispersion in this case could be written as a sum of two contributions. One of them corresponds to the model without fluctuations, while the second term, which is linear in p, includes the effect of step-size fluctuations. For $F = 1.5$ pN, the dependence of D on the probability is also linear, but decreasing. It is possible that at large p the pathways with lower stochasticity dominate, and this lowers the overall
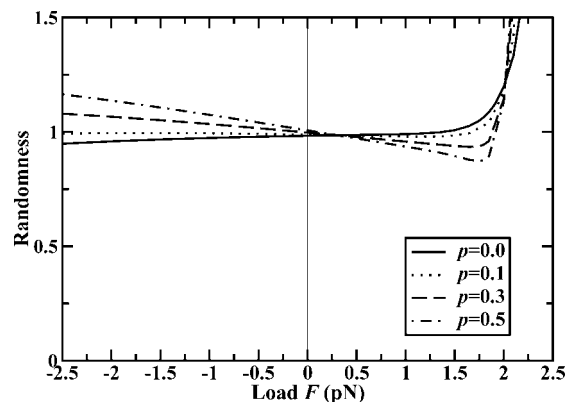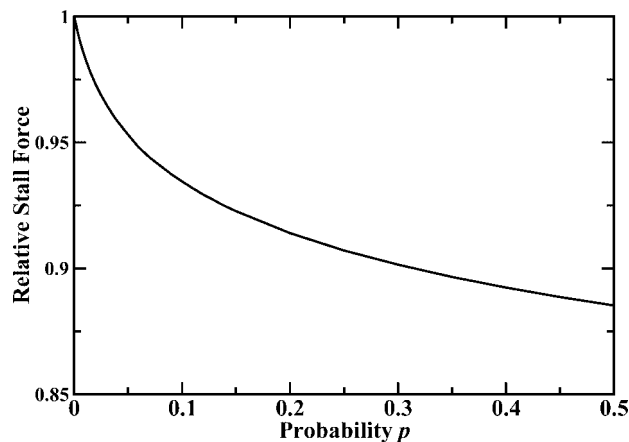
dispersion. A surprising behavior is observed for larger external force of $F = 2.2$ pN where dispersion shows a nonmonotonous dependence. This can be understood in the following way. Increasing the probability of step-size fluctuations for small values of p opens new pathways for the particle, and this obviously increases overall fluctuations. At the same time, for larger p, the motor protein mostly found in the pathways with lower stochasticity, and this leads to decrease in dispersion. Note, however, that in all cases the change in dispersion due to step-size fluctuations in myosin V is not very large, and typically it does not exceed more than 10% at all conditions.

Simultaneous knowledge of the drift velocity and dispersion allows us to analyze the effect of spatial fluctuations on the randomness of myosin V for different external loads, and the results are presented in Figure 4 for both assisting ($F < 0$) and resisting ($F > 0$) external forces. For small step-size fluctuations randomness is the increasing function of the external force approaching infinity at F_S due to decreasing of the drift velocity near the stall force. However, the increase in the probability p of step-size variations yields a surprising behavior in the randomness: there is a minimum at forces closer to $F \approx 2$ pN. This can be understood by comparing the effect of the spatial fluctuations on the velocity and on dispersion. At the conditions where the minimum is observed the change in dispersion is larger than the decrease in the velocity. Note also different behavior of the randomness for small and for large p at assisting external forces: see Figure 4.

4.3. Stall Force. We also investigated the behavior of the stall force F_S as a function step-size fluctuations. The stall force is defined as a force at which the motor protein stops its motion

completely. We obtain the stall force by numerically solving $V(F) = 0$ (see eq 12) with appropriate force-dependent transition rates, which leads us to the following equation,

$$
\frac{d_0\left[1 - \prod\limits_{1(0)}^{N} (F)\right]}{r_0^0(F)\left[\dfrac{R_N^0(F)}{r_0^0(F)} + \dfrac{R_N^+(F)}{r_0^+(F)} + \dfrac{R_N^-(F)}{r_0^-(F)} - 2\right]} +
$$

$$
\frac{d_+\left[1 - \prod\limits_{1(+)}^{N} (F)\right]}{r_0^+(F)\left[\dfrac{R_N^0(F)}{r_0^0(F)} + \dfrac{R_N^+(F)}{r_0^+(F)} + \dfrac{R_N^-(F)}{r_0^-(F)} - 2\right]} +
$$

$$
\frac{d_-\left[1 - \prod\limits_{1(-)}^{N} (F)\right]}{r_0^-(F)\left[\dfrac{R_N^0(F)}{r_0^0(F)} + \dfrac{R_N^+(F)}{r_0^+(F)} + \dfrac{R_N^-(F)}{r_0^-(F)} - 2\right]} = 0 \quad (46)
$$

Relative stall force $F_S(p)/F_S(0)$ as a function of p is presented in Figure 5. It should be noted that for the system without fluctuations ($p = 0$) the stall force is a thermodynamic quantity that corresponds to equilibrium between the force exerted by the motor protein and external load.[4,25] However, in our model with spatial fluctuations, the stall force becomes a dynamic quantity. At F_S, the negative velocity contribution from the upper pathways V_+ is compensated by positive velocities from other pathways. The increase in the step-size fluctuations lowers the effective stall force, although the effect is not very large ($\approx 10\%$), but it might explain discrepancies in experimentally measured stall forces for myosin V.[9,14,17,22] The reported values range from 1.7 to 3 pN. We suggest that this could happen due to the fact that depending on experimental conditions step-size fluctuations might have been suppressed or increased, producing different effective stall forces.

The presented theoretical model does not take into account the slipping of motor proteins along the filament, although it can be easily accomplished by adding additional pathways that do not involve ATP hydrolysis.[26] Thus, the possibility of futile hydrolysis cycles, when the motor particle consumes ATP molecule to move forward and then slips backward, is neglected in our approach. We view the effective stall condition in the following way. The motor protein molecules hydrolyzes one ATP during the motion along one of pathways, but then the ATP molecule is synthesized when the motor protein moves backward along the other pathway. The validity of this view is to be checked in future experiments.

5. Summary and Conclusions

We developed a theoretical approach that allows one to estimate the effect of the spatial fluctuations on dynamic properties of motor proteins. Our main idea is to discretize step-size fluctuations and to analyze them via multistate multipathway chemical kinetic models. Different biochemical pathways describe different step sizes. Our explicit calculations of the velocity and dispersion are performed for the model with symmetric fluctuations and three step sizes, and it is indicated how the method can be generalized for asymmetric fluctuations and more values of step sizes. It is shown that for symmetric fluctuations and zero external forces the velocity is not affected by spatial fluctuations, while dispersions depend on them.

Correlations between different pathways play important role for dispersions. It is also argued that neglect of the backward transitions in motor proteins might lead to incorrect predictions on the effect of step-size fluctuations.

Our theoretical method was applied to analyze the effect of spatial fluctuations on dynamics of myosin V motor proteins. It is shown that spatial fluctuations do not affect the velocity at lower forces, but at large external forces near the stall they lower the velocity significantly. The variations in the step sizes also decrease dispersion, although dependence on the probability of fluctuations is more complex. In addition, step-size fluctuations reduce the stall force of myosin V motor proteins. It is argued that this complex dynamics is a result of two processes that work in opposite directions. The increase in the probability of fluctuations opens new biochemical pathways for the molecular motor, and this increases the overall fluctuations. At the same time, for large probabilities the molecule starts to spend most of its time in the pathways with reduced local transition rates, thus reducing the overall stochasticity in the system.

The developed theoretical method makes several predictions that distinguish it from other theoretical models, and these results can be experimentally checked. Specifically, we predict a nonmonotonic dependence of the randomness as a function of the external forces that contrasts with predictions for the models without spatial fluctuations. An important parameter in our theoretical calculations is a degree of fluctuations expressed via the parameter p. It is suggested that it might be changed by modifying the number of IQ motifs in the lever arm region of myosins V.[34] Increasing the number of IQ motifs will probably lead to larger fluctuations because the motor head could reach more sites on Actin filaments. Measuring dynamic properties of myosins V with different lever-arm lengths will provide a valuable information on the validity of the developed theoretical picture.

Our analysis suggests that nature might utilize the spatial fluctuations as a tool of controlling and tuning dynamics of motor proteins. It will be important to test our predictions in single-molecule experiments to fully uncover the effect of spatial fluctuations for processive enzymatic molecules.

Appendix

We introduce a function $P_j^\lambda(l, t)$ as the probability to find the motor protein molecule at site l in state j on pathway λ ($\lambda = +, -, 0$) at time t. The time evolution of this probability is governed by a set of master equations,

$$
\frac{\mathrm{d}P_j^\lambda(l, t)}{\mathrm{d}t} = u_{j-1}^\lambda P_{j-1}^\lambda(l, t) + w_{j+1}^\lambda P_{j+1}^\lambda(l, t) - (u_j^\lambda + w_j^\lambda)P_j^\lambda(l, t)
$$

$$(A-1)$$

for $j \neq 0$ and $\lambda = +, -, 0$. The situation for $j = 0$ is a special one with $P_0^0 = P_0^+ = P_0$. In this case, master equations have the following form,

$$
\frac{\mathrm{d}P_0(l, t)}{\mathrm{d}t} = u_{N-1}^0 P_{N-1}^0(l-1, t) + w_1^0 P_1^0(l, t) - (1 - 2p)(u_0^0 +
$$

$$
w_0^0)P_0(l, t) + u_{N-1}^+ P_{N-1}^+(l-1, t) + w_1^+ P_1^+(l, t) - p(u_0^+ + w_0^+)P_0
$$

$$
(l, t) + u_{N-1}^- P_{N-1}^-(l-1, t) + w_1^- P_1^-(l, t) - p(u_0^- + w_0^-)P_0(l, t)
$$

$$(A-2)$$

for all three pathways. Because of conservation of probability we have

Spatial Fluctuations Affect the Dynamics of Motor Proteins

J. Phys. Chem. B, Vol. 112, No. 35, 2008 **11119**

$$\sum_{l=-\infty}^{+\infty}\left(\sum_{j=0}^{N-1}P_j^0(l,t)+\sum_{j=0}^{N-1}P_j^+(l,t)+\sum_{j=0}^{N-1}P_j^-(l,t)\right)=1 \quad (A\text{-}3)$$

at all times. It is also assumed that at $t = 0$ the molecular motor is at the origin $l = 0$ in the state $j = 0$.

Following Derrida's approach,[33] we define two auxiliary functions for each state j,

$$B_j^\lambda(t)\equiv\sum_{l=-\infty}^{+\infty}P_j^\lambda(l,t) \quad (A\text{-}4)$$

$$C_j^\lambda(t)\equiv\sum_{l=-\infty}^{+\infty}\left(j+N\frac{\sum_{k=0}^{l-1}d_\lambda(k)}{d_\lambda(l)}\right)P_j^\lambda(l,t) \quad (A\text{-}5)$$

Note that for $j = 0$ we have

$$B_0^0(t)=B_0^+(t)=B_0^-(t) \quad (A\text{-}6)$$

$$C_0^0(t)=\left(\frac{d_+}{d_0}\right)C_0^+(t)=\left(\frac{d_-}{d_0}\right)C_0^-(t) \quad (A\text{-}7)$$

The master equation eq A-1 then modifies for $j \neq 0$,

$$\frac{dB_j^\lambda(t)}{dt}=u_{j-1}^\lambda B_{j-1}^\lambda+w_{j+1}^\lambda B_{j+1}^\lambda-(u_j^\lambda+w_j^\lambda)B_j^\lambda \quad (A\text{-}8)$$

and for $j = 0$ we obtain

$$\frac{dB_0(t)}{dt}=u_{N-1}^0 B_{N-1}^0+w_1^0 B_1^0-(1-2p)(u_0^0+w_0^0)B_0+$$
$$u_{N-1}^+ B_{N-1}^+ + w_1^+ B_1^+ - p(u_0^+ + w_0^+)B_0 + u_{N-1}^- B_{N-1}^- + w_1^- B_1^- -$$
$$p(u_0^- + w_0^-)B_0 \quad (A\text{-}9)$$

Similarly, for $j \neq 0$ one can show that

$$\frac{dC_j^\lambda(t)}{dt}=u_{j-1}^\lambda C_{j-1}^\lambda+w_{j+1}^\lambda C_{j+1}^\lambda-(u_j^\lambda+w_j^\lambda)C_j^\lambda+u_{j-1}^\lambda B_{j-1}^\lambda-$$
$$w_{j+1}^\lambda B_{j+1}^\lambda (A\text{-}10)$$

while for $j = 0$ the results are

$$\frac{dC_0(t)}{dt}=u_{N-1}^0 C_{N-1}^0+w_1^0 C_1^0-(1-2p)(u_0^0+w_0^0)C_0+$$
$$u_{N-1}^0 B_{N-1}^0-w_1^0 B_1^0+\left(\frac{d_+}{d_0}\right)[u_{N-1}^+ C_{N-1}^+ + w_1^+ C_1^+ - p(u_0^+ +$$
$$w_0^+)C_0+u_{N-1}^+ B_{N-1}^+-w_1^+ B_1^+]+\left(\frac{d_-}{d_0}\right)[u_{N-1}^- C_{N-1}^- + w_1^- C_1^- -$$
$$p(u_0^- + w_0^-)C_0+u_{N-1}^- B_{N-1}^--w_1^- B_1^-] \quad (A\text{-}11)$$

Now applying Derrida's idea[33] we introduce the ansatz

$$B_j^\lambda(t)\to b_j^\lambda, \quad C_j^\lambda(t)-a_j^\lambda t\to T_j^\lambda \quad (A\text{-}12)$$

which should be valid at large times. The parameters b_j^λ, a_j^λ and T_j^λ are periodic,

$$b_j^\lambda=b_{j+N}^\lambda,\ a_j^\lambda=a_{j+N}^\lambda,\ T_j^\lambda=T_{j+N}^\lambda \quad (A\text{-}13)$$

At steady state $\{[dB_j^\lambda(t)]/dt\}=0$, and for $j\neq 0$, eq A-8 gives

$$0=u_{j-1}^\lambda b_{j-1}^\lambda+w_{j+1}^\lambda b_{j+1}^\lambda-(u_j^\lambda+w_j^\lambda)b_j^\lambda \quad (A\text{-}14)$$

while for $j = 0$ from eq A-9 one can obtain

$$0=u_{N-1}^0 b_{N-1}^0+w_1^0 b_1^0-(1-2p)(u_0^0+w_0^0)b_0+u_{N-1}^+ b_{N-1}^+ +$$
$$w_1^+ b_1^+ - p(u_0^+ + w_0^+)b_0 + u_{N-1}^- b_{N-1}^- + w_1^- b_1^- - p(u_0^- + w_0^-)b_0$$
$$(A\text{-}15)$$

with $b_0^0 = b_0^+ = b_0^-$. Again, following Derrida's method,[33] the solutions of eqs A-14 and A-15 can be written as

$$b_j^\lambda=e_\lambda r_j^\lambda \quad (A\text{-}16)$$

The unknown constants e_λ can be determined using the conservation of probability requirement A-3,

$$\sum_{j=0}^{N-1}b_j^0+\sum_{j=0}^{N-1}b_j^++\sum_{j=0}^{N-1}b_j^-=1 \quad (A\text{-}17)$$

and this leads us to eqs 28 and 29.

To find the coefficients a_j^λ and T_j^λ, the ansatz (A-12) is substituted into the asymptotic ($t\to\infty$) eqs A-10 and A-11, yielding for the coefficients a_j^λ ($j\neq 0$),

$$0=u_{j-1}^\lambda a_{j-1}^\lambda+w_{j+1}^\lambda a_{j+1}^\lambda-(u_j^\lambda+w_j^\lambda)a_j^\lambda \quad (A\text{-}18)$$

The coefficients T_j^λ ($j\neq 0$) then satisfy

$$a_j^\lambda=u_{j-1}^\lambda T_{j-1}^\lambda+w_{j+1}^\lambda T_{j+1}^\lambda-(u_j^\lambda+w_j^\lambda)T_j^\lambda+u_{j-1}^\lambda b_{j-1}^\lambda-w_{j+1}^\lambda b_{j+1}^\lambda$$
$$(A\text{-}19)$$

Similarly for $j = 0$ we derive

$$0=u_{N-1}^\lambda a_{N-1}^\lambda+w_1^\lambda a_1^\lambda-(u_0^\lambda+w_0^\lambda)a_0^\lambda \quad (A\text{-}20)$$

and

$$a_0^0=\left(\frac{d_+}{d_0}\right)a_0^+=\left(\frac{d_-}{d_0}\right)a_0^-=u_{N-1}^0 T_{N-1}^0+w_1^0 T_1^0-(1-2p)(u_0^0+$$
$$w_0^0)T_0^0+u_{N-1}^0 b_{N-1}^0-w_1^0 b_1^0+\left(\frac{d_+}{d_0}\right)[u_{N-1}^+ T_{N-1}^+ + w_1^+ T_1^+ - p$$
$$(u_0^+ + w_0^+)T_0^+ + u_{N-1}^+ b_{N-1}^+ - w_1^+ b_1^+]+\left(\frac{d_-}{d_0}\right)[u_{N-1}^- T_{N-1}^- +$$
$$w_1^- T_1^- - p(u_0^- + w_0^-)T_0^- + u_{N-1}^- b_{N-1}^- - w_1^- b_1^-] \quad (A\text{-}21)$$

Comparing eqs A-18 and A-20 with eqs A-14 and A-15, we conclude that

$$a_j^\lambda=A_\lambda b_j^\lambda \quad (A\text{-}22)$$

with the constants A_λ related via the following equation,

$$A_0=\left(\frac{d_+}{d_0}\right)A_+ + \left(\frac{d_-}{d_0}\right)A_- \quad (A\text{-}23)$$

These constants can be found by from the following expressions

$$\sum_{j=0}^{N-1}a_j^0=A_0\sum_{j=0}^{N-1}b_j^0 \quad (A\text{-}24)$$

$$\left(\frac{d_+}{d_0}\right)\sum_{j=1}^{N-1}a_j^+=A_+\sum_{j=1}^{N-1}b_j^+ \quad (A\text{-}25)$$

$$\left(\frac{d_-}{d_0}\right)\sum_{j=0}^{N-1}a_j^-=A_-\sum_{j=0}^{N-1}b_j^- \quad (A\text{-}26)$$

and using the normalization condition (A-3). This procedure yields

$$A_0 = \sum_{j=0}^{N-1} a_j^0 + \left(\frac{d_+}{d_0}\right)\sum_{j=1}^{N-1} a_j^+ + \left(\frac{d_-}{d_0}\right)\sum_{j=0}^{N-1} a_j^- = \sum_{j=0}^{N-1} (u_j^0 - w_j^0)b_j^0 +$$

$$\left(\frac{d_+}{d_0}\right)\sum_{j=0}^{N-1} (u_j^+ - w_j^+)b_j^+ + \left(\frac{d_-}{d_0}\right)\sum_{j=0}^{N-1} (u_j^- - w_j^-)b_j^- \quad \text{(A-27)}$$

To determine the coefficients T_j^λ, we define

$$y_j^\lambda \equiv w_{j+1}^\lambda T_{j+1}^\lambda - u_j^\lambda T_j^\lambda \quad \text{(A-28)}$$

Then eq A-19 can be rewritten as

$$y_j^\lambda - y_{j-1}^\lambda = a_j^\lambda - u_{j-1}^\lambda b_{j-1}^\lambda + w_{j+1}^\lambda b_{j+1}^\lambda \quad \text{(A-29)}$$

while eq A-21 yields

$$y_0^0 - y_{N-1}^0 = a_0^0 - u_{N-1}^0 b_{N-1}^0 + w_1^0 b_1^0 - \left(\frac{d_+}{d_0}\right)[y_0^+ - y_{N-1}^+ +$$

$$u_{N-1}^+ b_{N-1}^+ - w_1^+ b_1^+] - \left(\frac{d_-}{d_0}\right)[y_0^- - y_{N-1}^- + u_{N-1}^- b_{N-1}^- - w_1^- b_1^-]$$

$$\text{(A-30)}$$

$$y_0^+ - y_{N-1}^+ = a_0^+ - u_{N-1}^+ b_{N-1}^+ + w_1^+ b_1^+ - \left(\frac{d_0}{d_+}\right)[y_0^0 - y_{N-1}^0 +$$

$$u_{N-1}^0 b_{N-1}^0 - w_1^0 b_1^0] - \left(\frac{d_-}{d_+}\right)[y_0^- - y_{N-1}^- + u_{N-1}^- b_{N-1}^- - w_1^- b_1^-]$$

$$\text{(A-31)}$$

$$y_0^- - y_{N-1}^- = a_0^- - u_{N-1}^- b_{N-1}^- + w_1^- b_1^- - \left(\frac{d_0}{d_-}\right)[y_0^0 - y_{N-1}^0 +$$

$$u_{N-1}^0 b_{N-1}^0 - w_1^0 b_1^0] - \left(\frac{d_+}{d_-}\right)[y_0^+ - y_{N-1}^+ + u_{N-1}^+ b_{N-1}^+ + w_1^+ b_1^+]$$

$$\text{(A-32)}$$

These equations can be solved producing

$$y_j^0 = \left(\frac{j}{N}\right)\left(\frac{d_+}{d_0}\right)\sum_{j=0}^{N-1} (u_j^+ - w_j^+)b_j^+ + \left(\frac{j}{N}\right)\left(\frac{d_-}{d_0}\right)\sum_{j=0}^{N-1} (u_j^- - w_j^-)b_j^- +$$

$$u_j^0 b_j^0 + \left(\frac{A_0}{N}\right)\left[\sum_{i=0}^{N-1} (i+1)b_{j+i+1}^0 - j\sum_{i=1}^{N-1} b_i^+ - j\sum_{i=1}^{N-1} b_i^-\right] + C_0$$

$$\text{(A-33)}$$

$$y_j^+ = \left(\frac{j}{N}\right)\left(\frac{d_-}{d_+}\right)\sum_{j=0}^{N-1} (u_j^- - w_j^-)b_j^- + \left(\frac{j}{N}\right)\left(\frac{d_0}{d_+}\right)\sum_{j=0}^{N-1} (u_j^0 - w_j^0)b_j^0 +$$

$$u_j^+ b_j^+ + \left(\frac{A_+}{N}\right)\left[\sum_{i=0}^{N-1} (i+1)b_{j+i+1}^+ - j\sum_{i=1}^{N-1} b_i^- - j\sum_{i=1}^{N-1} b_i^0\right] + C_+$$

$$\text{(A-34)}$$

$$y_j^- = \left(\frac{j}{N}\right)\left(\frac{d_+}{d_-}\right)\sum_{j=0}^{N-1} (u_j^+ - w_j^+)b_j^+ + \left(\frac{j}{N}\right)\left(\frac{d_0}{d_-}\right)\sum_{j=0}^{N-1} (u_j^0 - w_j^0)b_j^0 +$$

$$u_j^- b_j^- + \left(\frac{A_-}{N}\right)\left[\sum_{i=0}^{N-1} (i+1)b_{j+i+1}^- - j\sum_{i=1}^{N-1} b_i^+ - j\sum_{i=1}^{N-1} b_i^0\right] + C_-$$

$$\text{(A-35)}$$

where C_λ are arbitrary constants which cancel out in the final expression for dispersion D. These equations enable us to find the expressions for T_j^λ,

$$T_j^\lambda = -\left(\frac{1}{u_j^\lambda}\right)\left[y_j^\lambda + \sum_{k=1}^{N-1} y_{j+k}^\lambda \Pi_{j+1}^{j+k}(\lambda)\right]\Bigg/\left(1 - \prod_1^N (\lambda)\right)$$

$$\text{(A-36)}$$

It is now possible to obtain the explicit expressions for the drift velocity V and dispersion D using the steady-state definitions eqs 2 and 3. The mean particle position can be written as

$$\langle x(t)\rangle = \left(\frac{d_0}{N}\right)\sum_{l=-\infty}^{+\infty}\sum_{j=0}^{N-1}\left(j + N\frac{\sum_{k=0}^{l-1} d_\lambda(k)}{d_0}\right)P_j^0(l,t) +$$

$$\left(\frac{d_+}{N}\right)\sum_{l=-\infty}^{+\infty}\sum_{j=1}^{N-1}\left(j + N\frac{\sum_{k=0}^{l-1} d_\lambda(k)}{d_+}\right)P_j^+(l,t) +$$

$$\left(\frac{d_-}{N}\right)\sum_{l=-\infty}^{+\infty}\sum_{j=1}^{N-1}\left(j + N\frac{\sum_{k=0}^{l-1} d_\lambda(k)}{d_-}\right)P_j^-(l,t)$$

$$\text{(A-37)}$$

$$= \left(\frac{d_0}{N}\right)\sum_{j=0}^{N-1} C_j^0(t) + \left(\frac{d_+}{N}\right)\sum_{j=0}^{N-1} C_j^+(t) + \left(\frac{d_-}{N}\right)\sum_{j=0}^{N-1} C_j^-(t)$$

$$\text{(A-38)}$$

Using master equation A-1, the following expressions can be derived

$$V = \lim_{t\to\infty}\frac{d}{dt}\langle x(t)\rangle = \left(\frac{d_0}{N}\right)A_0\sum_{j=0}^{N-1} b_j^0(t) + \left(\frac{d_+}{N}\right)A_+\sum_{j=0}^{N-1} b_j^+(t) +$$

$$\left(\frac{d_-}{N}\right)A_-\sum_{j=0}^{N-1} b_j^-(t) = \left(\frac{d_0}{N}\right)A_0 = \left(\frac{d_+}{N}\right)A_+ = \left(\frac{d_-}{N}\right)A_- \quad \text{(A-39)}$$

$$= \left(\frac{d_0}{N}\right)\sum_{j=0}^{N-1} (u_j^0 - w_j^0)b_j^0 + \left(\frac{d_+}{N}\right)\sum_{j=0}^{N-1} (u_j^+ - w_j^+)b_j^+ \left(\frac{d_-}{N}\right)\sum_{j=0}^{N-1} (u_j^- - w_j^-)b_j^- \quad \text{(A-40)}$$

Finally, using eqs 28 and 29, the final expressions for the velocity (eq 10) are obtained.

A similar approach is used to obtain the formula for dispersion. We start from

$$\langle x^2(t)\rangle = \left(\frac{d_0}{N}\right)^2\sum_{l=-\infty}^{+\infty}\sum_{j=0}^{N-1}\left(j + N\frac{\sum_{k=0}^{l-1} d_\lambda(k)}{d_0}\right)^2 P_j^0(l,t) +$$

$$\left(\frac{d_+}{N}\right)^2\sum_{l=-\infty}^{+\infty}\sum_{j=1}^{N-1}\left(j + N\frac{\sum_{k=0}^{l-1} d_\lambda(k)}{d_+}\right)^2 P_j^+(l,t) +$$

$$\left(\frac{d_-}{N}\right)^2\sum_{l=-\infty}^{+\infty}\sum_{j=1}^{N-1}\left(j + N\frac{\sum_{k=0}^{l-1} d_\lambda(k)}{d_-}\right)^2 P_j^-(l,t) \quad \text{(A-41)}$$

and again using master Eq. (A-1) we derive

Spatial Fluctuations Affect the Dynamics of Motor Proteins

J. Phys. Chem. B, Vol. 112, No. 35, 2008 **11121**

$$\lim_{t\to\infty}\frac{\mathrm{d}}{\mathrm{d}t}\langle x^2(t)\rangle = \left(\frac{d_0}{N}\right)^2\Bigg[2\sum_{j=0}^{N-1}(u_j^0 - w_j^0)(a_j^0 t + T_j^0) +$$

$$\sum_{j=0}^{N-1}(u_j^0 + w_j^0)b_j^0\Bigg] + \left(\frac{d_+}{N}\right)^2\Bigg[2\sum_{j=0}^{N-1}(u_j^+ - w_j^+)(a_j^+ t + T_j^+) + \sum_{j=0}^{N-1}$$

$$(u_j^+ + w_j^+)b_j^+\Bigg] + \left(\frac{d_-}{N}\right)^2\Bigg[2\sum_{j=0}^{N-1}(u_j^- - w_j^-)(a_j^- t + T_j^-) + \sum_{j=0}^{N-1}$$

$$(u_j^- + w_j^-)b_j^-\Bigg] \quad \text{(A-42)}$$

By using definition 3 and A-40, it can be shown that

$$D = \left(\frac{d_0}{N}\right)^2\Bigg[\sum_{j=0}^{N-1}(u_j^0 - w_j^0)T_j^0 + \frac{1}{2}\sum_{j=0}^{N-1}(u_j^0 + w_j^0)b_j^0 -$$

$$A_0\sum_{j=0}^{N-1}T_j^0\Bigg] + \left(\frac{d_+}{N}\right)^2\Bigg[\sum_{j=0}^{N-1}(u_j^+ - w_j^+)T_j^+ + \frac{1}{2}\sum_{j=0}^{N-1}(u_j^+ + w_j^+)b_j^+ -$$

$$A_+\sum_{j=0}^{N-1}T_j^+\Bigg] + \left(\frac{d_-}{N}\right)^2\Bigg[\sum_{j=0}^{N-1}(u_j^- - w_j^-)T_j^- + \frac{1}{2}\sum_{j=0}^{N-1}(u_j^- + w_j^-)b_j^- -$$

$$A_-\sum_{j=0}^{N-1}T_j^-\Bigg] + \left(\frac{d_+}{N}\right)^2 A_+T_0^+ + \left(\frac{d_-}{N}\right)^2 A_-T_0^- \quad \text{(A-43)}$$

By substituting the expressions for T_j^λ (using also eqs A-36, A-33, A-34, and A-35) into A-43, the constants C_λ cancel out and we obtain the final expressions for dispersion.

References and Notes

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