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Dynamic properties of molecular motors in the divided-pathway model

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The mechanisms of molecular motors transport are important for understanding multiple biological processes. Recent single-molecule experiments indicate that motor proteins myosin V moves along protein filaments *via* a complex biochemical pathway that consists of sequentially coupled linear and parallel two-chain segments. We investigate analytically the corresponding discrete-state stochastic divided-pathway model for molecular motors transport. Explicit expressions are obtained for velocities and dispersions. The dynamic properties of motor proteins in the divided-pathway model are compared with those in single-chain linear and parallel-pathway stochastic models. It is argued that modifying biochemical pathways has a strong effect on the dynamic properties, and it allows motor proteins to be more flexible in performing their biological functions.

1. Introduction

Functioning of living systems relies to a large degree on effective biological transport processes that are supported by several classes of special enzymatic molecules, known as motor proteins or molecular motors.[1–5] These molecules transform chemical energy into mechanical motion in order to move objects in cells. Although full understanding of mechanisms that govern molecular motors is not yet available, a significant progress has been achieved in recent years with the development of single-molecule experimental techniques.[6–14] These experimental studies suggest that motor proteins move in effectively one-dimensional manner along rigid protein filaments or along DNA and RNA molecules, and their motion is fueled by hydrolysis of adenosine triphosphate (ATP) or related compounds.

Striking observations coming from single-molecule experiments stimulated significant development of multiple theoretical approaches for understanding motor proteins transport.[5,15–31] The most fundamental problem associated with the motion of motor proteins is how the chemical energy of hydrolysis is transformed into the mechanical work. Several theoretical ideas have been proposed to explain unusual dynamic properties of molecular motors. One of them utilizes the concept of thermal ratchets where motor proteins are viewed as Brownian particles diffusing in periodic asymmetric potentials and switching between them stochastically.[5,16,18,21] An alternative approach utilizes discrete-state stochastic models where the motion of motor protein molecules is associated with biochemical transitions between different states.[5,15,17,19,24,27–31] Although both theoretical approaches provided important details on mechanisms of motor proteins, it seems that discrete-state chemical kinetic models are more flexible for analysis and they can better account for available single-molecule experimental data.[5]

The dynamics of most motor proteins is typically described using the simplest linear sequential discrete-state stochastic model.[5] According to this model, the motor protein molecule moves along a linear periodic track that corresponds to a biochemical pathway of motor protein catalyzing hydrolysis of ATP. Each site on the track describes a different state of the motor protein, and the molecular motor can move between neighboring sites with corresponding chemical transition rates. This representation effectively maps the model into a discrete biased random walk on a periodic one-dimensional lattice, and it allows one to use the method of Derrida[5,32] to obtain exact and explicit formulae for the asymptotic stationary drift velocity,

$$V = \lim_{t\to\infty} \frac{\mathrm{d}\langle x(t)\rangle}{\mathrm{d}t}. \quad (1)$$

and for dispersion (or effective diffusion constant),

$$D = \frac{1}{2}\lim_{t\to\infty} \frac{\mathrm{d}}{\mathrm{d}t}[\langle x^2(t)\rangle - \langle x(t)\rangle^2]. \quad (2)$$

In addition, other important dynamic properties, such as stall forces, run lengths and dwell times, could also be explicitly calculated.[5,17] This model has been used successfully for analyzing dynamics of kinesin motor proteins.[20] However, recent single-molecule experiments on another motor protein, myosin-V, suggest that its mechanisms of functioning are more complex.[9] Baker *et al.*[9] have proposed a so-called "divided-pathway" model to describe the motion of molecular motors. The model is graphically presented in Fig. 1a, and it can be viewed as two parallel multi-state pathways that follow together part of the period between neighboring binding sites but then diverge: see Fig. 1a. It was argued that myosins V utilize this complex mechanism in order to ensure robust processivity under different physiological conditions in cells.[9] It is quite possible that the divided-pathway mechanism might also be utilized by other motor proteins, although there are no experimental confirmations yet.

Preliminary theoretical calculations for the specific divided-pathway model with 6 states have been already presented,[9] although only velocity has been computed. A more general

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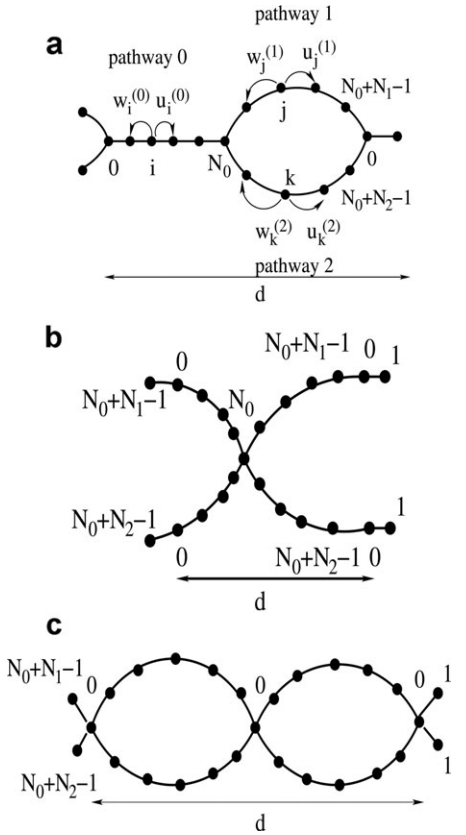

Fig. 1 (a) A general schematic view of the divided-pathway model. The linear segment (pathway 0) has N_0 states, the upper segment (pathway 1) has N_1 states, and the lower segment (pathway 2) has N_2 states; (b) an effective view of the divided-pathway as two linear chains with one common state N_0; (c) a parallel-chain discrete stochastic model.

method of analysis of the divided-pathway model for any number of states, that utilizes a graphical reduction algorithm, was recently presented by Tsygankov and Fisher.[28] This systematic approach allows one to explicitly obtain expressions for mean occupation times in individual biochemical states, for the probabilities of forward and backward steps, for the mean dwell times and for the velocities. However, this method does not allow to calculate higher moments of motion such as dispersions. A different approach for computing dynamic properties of motor proteins in the divided-pathway models has been proposed by Chemla *et al.*[31] This general method is based on solving master equations in Fourier–Laplace space, and it allows to derive mean velocities, fluctuation-related parameters and the dwell-time distributions. However, the formalism is mathematically quite involved and analytical calculations can only be performed for the divided-pathway model with a small number of states and with some irreversible transitions. For larger systems and more realistic reversible transitions between biochemical states only numerical calculations can be accomplished. However, for understanding the mechanisms of molecular motors that follow the divided-pathway model full analytical description would be the most useful. In this paper, we present a general method of obtaining explicit analytical expressions for *all* dynamic properties of motor proteins in the divided-pathway model. Our approach utilizes Derrida's method[32] of calculations, and it maps the divided-pathway model into a parallel-chain model for which exact analytical results have already been derived.[5,19]

2. Theoretical model and results

We consider a motion of a single molecular motor in the divided-pathway model that is illustrated in Fig. 1a. The model can be viewed as a sequential combination of a linear segment and a loop of two parallel pathways. The linear segment consists of N_0 states, while the upper (1) and lower (2) parallel pathways have N_1 and N_2 biochemical states, respectively. From the state i along the linear segment the molecule can move to the state $(i + 1)$ with transition rate $u_i^{(0)}$, while it can also step backward to $(i - 1)$ at rate $w_i^{(0)}$. After reaching the state N_0 the particle can diffuse along the upper or lower pathway with forward and backward transition rates given by $u_i^{(m)}$ and $w_i^{(m)}$ ($m = 1$ for the upper segment and $m = 2$ for the lower part), respectively. We assume that the spatial distance along the linear segment (0) from the state 0 to N_0 is d_0, while the spatial displacement of two parallel loops is given by d_1. The total step-size of the period in the divided-pathway model (which is the same as the distance between corresponding binding sites on the lattice) is equal to $d = d_0 + d_1$.

Assume that at $t = 0$ the molecular motor starts at $l = 0$ site. The probability of finding the motor protein molecule at a site l in the biochemical state j ($j = 0, \ldots, N - 1$) on the segment (m) [$m = 0$, 1 or 2] at time t is defined by a function $P_j^{(m)}(l,t)$. Then, the dynamics of the system is governed by a system of master equations for the evolution of these probability functions,

$$\frac{\mathrm{d}P_j^{(m)}(l,t)}{\mathrm{d}t} = u_{j-1}^{(m)}P_{j-1}^{(m)}(l,t) + w_{j+1}^{(m)}P_{j+1}^{(m)}(l,t) - (u_j^{(m)} + w_j^{(m)})P_j^{(m)}(l,t), \tag{3}$$

for $j \neq N_0$. The state N_0 where the linear segment is coupled with two parallel segments is a special one since it belongs to all three segments. Here the master equation has a different form,

$$\frac{\mathrm{d}P_{N_0}(l,t)}{\mathrm{d}t} = u_{N_0-1}^{(0)}P_{N_0-1}^{(0)}(l,t) + w_{N_0+1}^{(1)}P_{N_0+1}^{(1)}(l,t) + w_{N_0+1}^{(2)}P_{N_0+1}^{(2)}(l,t) - (u_{N_0}^{(1)} + u_{N_0}^{(2)} + w_{N_0}^{(0)})P_{N_0}(l,t). \tag{4}$$

We are interested in stationary-state ($t \to \infty$) dynamics when $\frac{\mathrm{d}P_j^{(m)}(l,t)}{\mathrm{d}t} = 0$. Then eqn (4) simplifies into

$$0 = u_{N_0-1}^{(0)}P_{N_0-1}^{(0)} + w_{N_0+1}^{(1)}P_{N_0+1}^{(1)} + w_{N_0+1}^{(2)}P_{N_0+1}^{(2)} - (u_{N_0}^{(1)} + u_{N_0}^{(2)} + w_{N_0}^{(0)})P_{N_0}, \tag{5}$$

which can be rearranged into the following equation,

$$(u^{(0)}_{N_0-1}P^{(0)}_{N_0-1} - w^{(0)}_{N_0}P_{N_0}) = (u^{(1)}_{N_0}P_{N_0} - w^{(1)}_{N_0+1}P^{(1)}_{N_0+1}) + (u^{(2)}_{N_0}P_{N_0} - w^{(2)}_{N_0+1}P^{(2)}_{N_0+1}). \quad (6)$$

The stationary flux across each segment can be defined as

$$J^{(m)} = u^{(m)}_j P^{(m)}_j - w^{(m)}_{j+1}P^{(m)}_{j+1}. \quad (7)$$

Then eqn (6) can be written as

$$J^{(0)} = J^{(1)} + J^{(2)}, \quad (8)$$

which is the expected condition of stationarity of the current. This result suggests that the steady-state probability of finding the particle at any site on the linear segment can be written in the following way,

$$P^{(0)}_j = P^{(1)}_j + P^{(2)}_j, \quad (9)$$

for $i = 0,\ldots,N_0$. Note that these functions $P^{(m)}_i$ ($m = 1,2$) satisfy the following conditions for the linear segment of the pathway,

$$J^{(m)} = u^{(0)}_j P^{(m)}_j - w^{(0)}_{j+1}P^{(m)}_{j+1}. \quad (10)$$

This result is important since it indicates that the divided-pathway model can be mapped exactly into a model with two parallel pathways that have a common junction site, as shown in Fig. 1b. The meaning of functions $P^{(m)}_i$ ($m = 1,2$) for $i = 0,\ldots,N_0$ is then clear: they are probabilities to find the particle in the corresponding states of the model plotted in Fig. 1b. In one pathway states are running from 0 to $N_0 + N_1 - 1$, while in the second one states start at 0 and end up at the state $N_0 + N_2 - 1$. The state N_0 is the common state for both pathways: see Fig. 1b. Our system is periodic, and motor protein dynamics should not depend on where the period starts. Let us shift the beginning of the period by N_0 sites, and we obtain the scheme shown in Fig. 1c with the common state being $i = 0$. These arguments show that the divided-pathway model is exactly equivalent to the parallel-chain discrete-state stochastic model with the shifted origin, for which *all* dynamic properties have already been explicitly calculated.[19]

Utilizing analytical results for the parallel-chain model,[19] it can be found that for the divided-pathway model the formal expression for the drift velocity consists of two terms, each corresponding to the currents across the pathways (1) and (2),

$$V = V_1 + V_2, \quad (11)$$

with

$$V_1 = d\frac{\left[1 - \prod_{j=0}^{N_0+N_1-1}\left(\frac{w^{(1)}_j}{u^{(1)}_j}\right)\right]}{\left[R_1 + \frac{r^{(1)}_0}{r^{(2)}_0}R_2 - r^{(1)}_0\right]}, \quad (12)$$

and

$$V_2 = d\frac{\left[1 - \prod_{j=0}^{N_0+N_2-1}\left(\frac{w^{(2)}_j}{u^{(2)}_j}\right)\right]}{\left[R_2 + \frac{r^{(2)}_0}{r^{(1)}_0}R_1 - r^{(2)}_0\right]}, \quad (13)$$

where the auxiliary functions are given by

$$R_1 = \sum_{j=0}^{N_0+N_1-1} r^{(1)}_j, \quad r^{(1)}_j = \frac{1}{u^{(1)}_j}\left[1 + \sum_{k=1}^{N_0+N_1-1}\prod_{i=j+1}^{j+k}\left(\frac{w^{(1)}_i}{u^{(1)}_i}\right)\right], \quad (14)$$

and

$$R_2 = \sum_{j=0}^{N_0+N_2-1} r^{(2)}_j, \quad r^{(2)}_j = \frac{1}{u^{(2)}_j}\left[1 + \sum_{k=1}^{N_0+N_2-1}\prod_{i=j+1}^{j+k}\left(\frac{w^{(2)}_i}{u^{(2)}_i}\right)\right]. \quad (15)$$

It should be noted that for $j = N_1,\ldots,N_0 + N_1 - 1$ for the pathway (1) and for $j = N_2,\ldots N_0 + N_2 - 1$ for the pathway (2) we have

$$u^{(1)}_j = u^{(2)}_j = u^{(0)}_j,\ w^{(1)}_j = w^{(2)}_j = w^{(0)}_j. \quad (16)$$

In a similar way we can write the expressions for dispersion in the divided-pathway model. However, because these expressions are quite bulky we will not present them here, but one can find them in ref. 19.

It is important to point out that our approach allows to obtain exact solutions for all dynamic properties of the system that contains a kinetic cycle, and it does not depend on the fact that the kinetic parameters within the cycle might not satisfy the detailed balance.[19] The application of Derrida's method is successful here because the system can be viewed as coupled periodic one-dimensional pathways, but inside the period all channels are independent of each other.

3. Comparison with other discrete-state models

One can argue that the ability of motor proteins to change the underlying biochemical pathways allows them to perform their biological functions in the most effective and robust way. In order to illustrate this, it is interesting to compare dynamic properties of the divided pathway model with other models of motor protein's transport. For simplicity we compare the velocities and dispersions for the simplest divided-pathway model with $N_0 = 1$, $N_1 = 1$ and $N_2 = 1$ with the parallel-pathway model with 2 states at each segment and with the single-chain model with $N = 2$ states, as shown in Fig. 2. We assume that $u^{(1)}_0 = u^{(2)}_0 = u_0$ and $u^{(1)}_1 = u^{(2)}_1 = u_1$ and all the backward rates are equal to zero. The distance between neighboring binding sites is given by d.

For the divided-pathway model the expression for the drift velocity yields from eqns (11), (12), (13)

$$V_{\mathrm{DPM}} = d\frac{2u_0u_1}{2u_0 + u_1}, \quad (17)$$

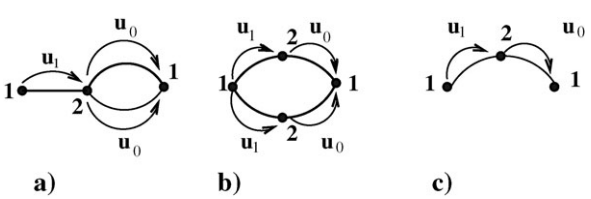

Fig. 2 Simplest discrete-state stochastic models with 2 states and irreversible forward transitions: (a) the divided-pathway model; (b) the parallel-pathway; and (c) the single-chain model.

while the velocity for the parallel-pathway model is,

$$V_{\mathrm{PPM}} = d\frac{2u_0u_1}{2u_1+u_0}, \tag{18}$$

and for the single-chain model we have

$$V_{\mathrm{SC}} = d\frac{u_0u_1}{u_1+u_0}. \tag{19}$$

In the limit when $u_0 \gg u_1$ one can easily obtain

$$V_{\mathrm{DPM}} = V_{\mathrm{SC}} = du_1 < V_{\mathrm{PPM}} = 2du_1. \tag{20}$$

In another limit, $u_1^\circ \gg u_0$, the expressions change to

$$V_{\mathrm{PPM}} = V_{\mathrm{SC}} = du_0 < V_{\mathrm{DPM}} = 2du_0. \tag{21}$$

Also, for $u_0 = u_1 = u$ we derive

$$V_{\mathrm{DPM}} = V_{\mathrm{PPM}} = \tfrac{2}{3}\,du > V_{\mathrm{SC}} = \tfrac{1}{2}\,du. \tag{22}$$

Similar calculations can be performed for dispersions of the discrete-state models presented in Fig. 2. The diffusion constant for the divided-pathway model is

$$D_{\mathrm{DPM}} = \frac{d^2}{2}\frac{2u_0u_1(u_1^2+4u_0^2)}{(2u_0+u_1)^3}, \tag{23}$$

and for the parallel-pathway the expression is

$$D_{\mathrm{PPM}} = \frac{d^2}{2}\frac{2u_0u_1(u_0^2+4u_1^2)}{(2u_1+u_0)^3}, \tag{24}$$

while for the single-chain we have

$$D_{\mathrm{SC}} = \frac{d^2}{2}\frac{u_0u_1(u_0^2+u_1^2)}{(u_0+u_1)^3}. \tag{25}$$

For the case of $u_0^\circ \gg u_1$ one can show that

$$D_{\mathrm{DPM}} = D_{\mathrm{SC}} = \frac{d^2}{2}u_1 < D_{\mathrm{PPM}} = d^2u_1. \tag{26}$$

In the other limiting case, $u_1^\circ \gg u_0$, we derive

$$D_{\mathrm{PPM}} = D_{\mathrm{SC}} = \frac{d^2}{2}u_0 < D_{\mathrm{DPM}} = d^2u_0. \tag{27}$$

Finally, for $u_0 = u_1 = u$ dispersions are the following,

$$D_{\mathrm{DPM}} = D_{\mathrm{PPM}} = \frac{5d^2}{27}u > D_{\mathrm{SC}} = \frac{d^2}{8}u. \tag{28}$$

These results can be explained by using simple arguments. From. Fig. 2 we might conclude that for large u_0 the molecular motor will be mostly in state 1 in all three models, while for large u_1 the most probable is state 2. Note also that these calculations indicate that even a slight change in the topology of the underlying biochemical pathways leads to significant modifications in all dynamic properties. It can be better seen in calculating a randomness parameter r, defined as follows,

$$r = \frac{2D}{dV}. \tag{29}$$

It was shown before[5] that this function play a very important role in the analysis of motor proteins single-molecule experimental observations as a measure of fluctuations. Combining eqns (17), (18), (19) and eqns (23), (24), (25), we obtain for three models from Fig. 2 the following expressions for the randomness parameters,

$$r_{\mathrm{DPM}} = \frac{u_1^2+4u_0^2}{(2u_0+u_1)^2},\quad r_{\mathrm{PPM}} = \frac{u_0^2+4u_1^2}{(2u_1+u_0)^2},\quad r_{\mathrm{SC}} = \frac{u_1^2+u_0^2}{(u_0+u_1)^2}. \tag{30}$$

In Fig. 3 randomness parameters for different models are presented for some sets of parameters. It can be seen that underlying biochemical pathway has a strong effect on the dynamic behavior of molecular motors.

The importance of specific biochemical pathways for molecular motors can be illustrated by using experimental observations on dynamics and processivity of myosin V motor proteins.[9] Single-molecule analysis of the movements of individual myosin V indicated that two heads of the motor protein molecule communicate through complex cooperative mechanisms that involve divided pathways.[9] A suggested biochemical multi-pathway kinetic model is presented in Fig. 4a. According to this scheme, the transition from state 5 to state 1 describes the binding of ATP molecule to the motor protein, the transitions between states 1 and 4, and 2 and 5 correspond to the release of inorganic phosphate, while the dissociation of ADP is given in the transitions between states 4 and 5, and 1 and 2.

By applying the results (11), (12) and (13) to this model it can be shown that the velocity is given by

$$V = 2d\left\{\frac{(1+[ADP]/K_{D2})}{k_{T2}[ATP]} + \frac{1}{k_1} + \frac{1}{v_c} + \frac{1}{k_2} + \frac{1}{K_{-D2}}\right\}^{-1}, \tag{31}$$

where $d = 36$ nm is a step-size for this motor protein,

$$v_c = \frac{1}{\frac{1}{k_{-D1}} + \frac{[ADP]}{K_{D1}k_2}}, \tag{32}$$

and $K_{D1} = k_{-D1}/k_{+D1}$, $K_{D2} = k_{-D2}/k_{+D2}$. It should be noted that our equation for the velocity deviates slightly from the corresponding expression obtained in ref. 9 due to different definitions of the probability of taking a specific pathway. The experimentally observed velocity as a function of [ADP] is presented in Fig. 4b. The best fit of all experimental data to

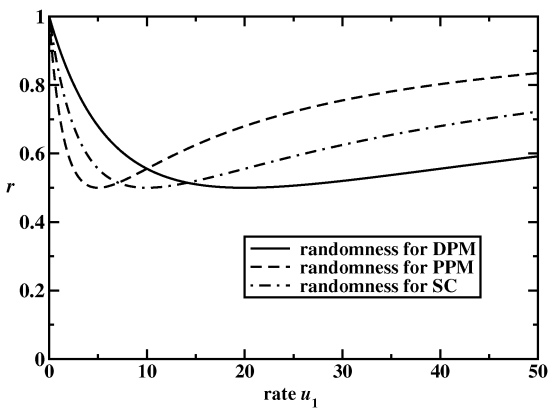

Fig. 3 Randomness parameters r as a function of the transition rate u_1 for $u_0 = 10$.

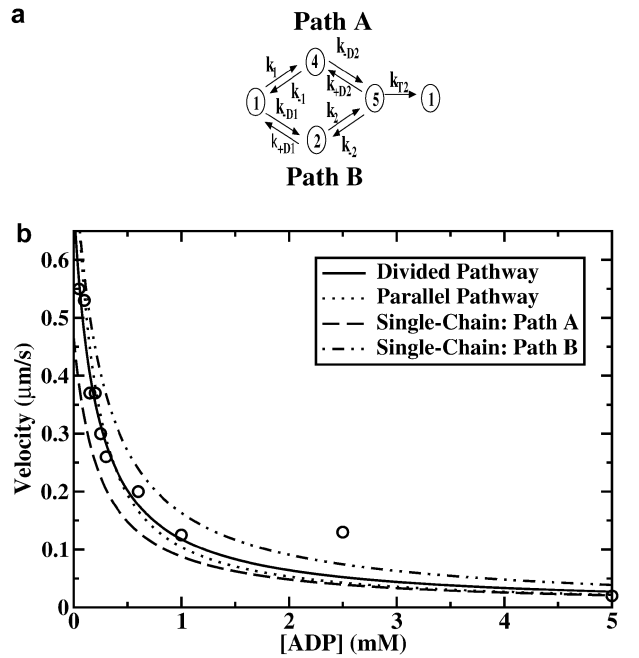

Fig. 4 (a) Biochemical multi-pathway kinetic scheme for the dynamics of individual myosin-V molecules proposed in ref. 9. (b) Velocity as a function of [ADP] for 1 mM ATP. The symbols are experimental results,[9] and the lines correspond to predictions from different theoretical models.

the divided-pathway model in Fig. 4a yields the following parameters:

$$k_{T2} = 0.05 \times 10^6\ \mathrm{M^{-1}\ s^{-1}};\ k_{-D1} = 35\ \mathrm{s^{-1}};$$
$$k_{-D2} = 60\ \mathrm{s^{-1}};\ k_1 = 20\ \mathrm{s^{-1}};\ k_2 = 5700\ \mathrm{s^{-1}};$$
$$K_{D1} = 1\ \mu\mathrm{M};\ K_{D2} = 60\ \mu\mathrm{M}. \qquad (33)$$

These values for the kinetic parameters are similar to the numbers obtained by Baker *et al.*[9] The predictions of different stochastic models with the *same* kinetic parameters as given by eqn (33) are shown in Fig. 4b. It can be seen that single-pathways models differ significantly from the divided-pathway model results. The velocities predicted by the parallel-pathway and the divided-pathway models are closer, but still deviate from each other, especially at very low and at moderate concentrations of ADP. It can also be shown that the divided-pathway model provides the best overall fit to all experimental data. Thus, the comparison of different discrete-state stochastic models for analysis of experimental single-molecule data support our conclusion that the specific biochemical pathways determine the dynamic properties of motor proteins.

4. Summary and conclusions

We presented a general theoretical method for calculating *all* dynamic properties of motor proteins that follow the divided-pathway model, *i.e.*, the model that is made of linear and parallel-chain segments coupled together sequentially. Our approach is based on the observation that the stationary current in the system consists of two terms corresponding to fluxes along each channel. Then it allows us to map exactly the divided-pathway model into the parallel-chain discrete-state model which has already been exactly solved earlier. This mapping produces explicit expressions for drift velocities and dispersions. It should be noted, however, that the divided-pathway model and the parallel-pathway models are not identical, and therefore they do not produce the same dynamic properties. We also analyze the dynamic properties of stochastic models of molecular motors with different topologies in biochemical transitions. The comparison of different discrete-state stochastic models with available experimental observations is also presented. Our analysis points out that the underlying biochemical pathways strongly define the dynamic properties of motor proteins. It could be suggested that nature might use tuning of biochemical pathways for producing very efficient and robust motor proteins. Our theoretical method provides a possible framework for analyzing the complex dynamics of molecular motors in biological systems.

It would be interesting to test our results by investigating the mechanisms of motility in myosin V and other motor proteins that might follow the divided-pathway model. It would require, however, high-resolution experiments that can measure not only velocities but also other dynamic properties such as dispersions and stall forces. Connecting the underlying biochemical pathway with observed dynamic properties will lead to better understanding of mechanisms of motor protein functioning.

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