MOTOR PROTEINS HAVE HIGHLY CORRELATED BROWNIAN ENGINES

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Abstract

Two headed motor proteins, such as kinesin and dynein, hydrolyze environmental ATP in order to propel unidirectionally along cytoskeletal filaments such as microtubules. In the intensely studied case of kinesin, protein heads of approximate dimension $4 \times 4 \times 7 \text{ nm}^3$ bind primarily on the $\alpha$ tubulin site of asymmetric $\alpha-\beta$ 8nm-long tubulin dimers that constitute the microtubular protofilaments. Kinesin dimers overcome local binding forces up to approximately...
5pN and are known to move on protofilaments with ATP concentration-dependent speeds in the range of $100 - 500\text{nm/sec}$ while hydrolyzing on average one ATP molecule per 8nm step. The salient features of protein trajectories are the distinct abrupt usually 8nm-long steps from one tubulin dimer to the next interlaced with long quiescent binding periods at a tubulin site. Discrete walks of this type are characterized by substantially reduced variances compared to pure biased random walks, and as a result rule out flashing-type ratchet models as possible mechanisms for motor movement. On the other hand, simple additive correlated brownian ratchets that present exactly these discrete trajectory patterns with reduced variances are compatible with the general features of the protein motion. In the simplest such model the protein is simplified to a single particle moving in a periodic non-symmetric tubulin-derived potential and the environmental and ATP interaction is included in a correlated additive noise term. For this model we show that the resulting protein walk has features resembling experimental data. Furthermore, in more realistic mechanical models of two masses connected by a spring we find qualitative agreement with recent experimental facts related to motion of protein chimaeras formed through kinesin motor domains with non-claret disjunctional (ncd) neck regions.

I. INTRODUCTION

The attempt to understand the detailed mechanism of motor protein motion in the cytoskeleton has led to the study of several stochastic ratchet (references in our bibliography not explicitly cited are important recent experimental and modeling contributions). The simplest such model involves one overdamped particle representing, for instance, the motor protein kinesin, moving in a periodic but not symmetric force field, driven by different types of correlated noises [Magnasco 1993, 1994; Astumian and Bier; Astumian; Doering et al.; Millonas and Dykman; Bartussek et al.]. The periodic forces are exerted by the 8nm-long $\alpha-\beta$ partially asymmetric tubulin dimers on kinesin while the noise terms represent the fluctuating environment. This model leads to a macroscopic particle current in a specific direction determined by the potential asymmetry and by the properties of
the noises. In the colored noise case, the finite correlation time $\tau$ corresponds to the ATP kinesin binding event time and subsequent energy release through hydrolysis. The ATP hydrolysis rate is approximately $50 s^{-1}$ and results on average in one 8nm kinesin step per ATP cycle, i.e. to a typical kinesin speed of 400nm/s [Schnitzer and Block; Hua et al.]. The single-particle colored noise model in the highly correlated noise regime leads to a natural interpretation for the kinesin steps observed in experiments. In this regime the brownian particle simply waits in the potential minimum of a tubulin unit until the appropriate fluctuation arrives that allows it to escape to the next tubulin dimer [Tsironis and Grigolini; de la Rubia et al.; Lindenberg et al.; Dykman and Lindenberg]. The noisy environment is the ambient fluid containing a variety of molecules, including ATP molecules at $\mu$M concentration levels. A large number of unsuccessful binding attempts of ATP molecules contribute to medium fluctuations, while the successful critical noise fluctuation can be interpreted as an ATP successfully binding on kinesin. The critical binding fluctuation determines the average exit time $\langle T \rangle$, or average step time, leading to a distance $x$ after $n$ steps, i.e. $x \approx n \langle T \rangle$.

![Asymmetric periodic potential](image)

**Figure 1** Asymmetric periodic potential used for analysis. The potential is piecewise linear and of height $V_0$. The distance between the peak and the minimum along the steeper portion of the potential is $d_t$. 

3
II. HIGHLY CORRELATED BROWNIAN MOTOR PROTEIN VELOCITY ESTIMATES

The calculation of the average step time \( \langle T \rangle \) proceeds as follows. The equations for the over-damped kinesin motion are

\[
\gamma \frac{dx}{dt} = f(x) + \xi(t),
\]

\[
\frac{d\xi}{dt} = -\frac{1}{\tau}\xi + \frac{1}{\tau}\eta(t),
\]

(1)

where \( x(t) \) is the kinesin position and \( f(x) \equiv -V'(x) \) where \( V(x) \) is the periodic non-symmetric potential of the protofilament. We use the simple piecewise linear potential shown in Figure 1. The height of the potential is \( V_0 \) and the distance from bottom to top on the steep side is denoted \( d_i \). The auxiliary variable \( \xi \) represents the coupling of the particle to the environment; if the noise variable \( \eta(t) \) is Gaussian and delta-correlated, \( \langle \eta(t)\eta(t') \rangle = D\gamma\delta(t-t') \), then \( \xi(t) \) is an Ornstein-Uhlenbeck process, that is, \( \xi(t) \) is Gaussian and exponentially correlated,

\[
\langle \xi(t)\xi(t') \rangle = \frac{D\gamma}{2\tau}e^{-\frac{|t-t'|}{\tau}}.
\]

(2)

The white noise strength \( D \) is taken to be the ambient temperature multiplied by the Boltzmann constant, i.e., \( D = k_B T \), and \( \gamma \) is the medium damping. Typical trajectories resulting from Eq. (1) are shown in Figure 2 for different, but all large, noise correlation times. There is a dramatic difference in the stochastic motor trajectory for small (white noise limit) and large (deterministic limit) correlation times \( \tau \). A short correlation time reflects a large number of successful ATP binding events that propel the stochastic motor onward. Indeed, with short correlation times the
tubulin site motor residence time and the jump time are comparable, leading to a unidirectional (due to the high asymmetry in the tubulin binding force) fluctuating non-step-like trajectory. At high correlation times, on the other hand, the nature of the walk is quite different, characterized by long waiting periods at a site until the appropriate critical ATP binding fluctuation arrives and enables the motor to perform a step that is quite abrupt relative to the waiting time. The waiting time or exit time $\langle T \rangle$ for a successful fluctuation to occur increases with the degree of the temporal correlation of the noise (reflecting slower ambient changes). This time thus determines the average clock rate for the motion.

Figure 2 Position traces (in nanometers) vs time (in seconds) for highly correlated, quasi-deterministic brownian engines showing the characteristic step-like forward motion of molecular motor proteins. The noise correlation time $\tau$ (in nanoseconds) is the unique adjustable parameter of the model. Relatively large correlation times are clearly associated with a quasi-deterministic step-like process, more markedly so with increasing correlation time. For these trajectories we used a potential barrier $V_0 = 10k_B T$ and $d_t = 2.4$nm, leading to forces of approximately $16.6$pN and $-7.1$pN. As the correlation time decreases, the steps become shorter, and the motion becomes faster but locally more erratic.

To find a rough analytical estimate for the mean exit time from one tubulin dimer to the next that serves to illustrate the parameter dependences, we assume that kinesin binds primarily to the $\alpha$-tubulin, and that the relatively large asymmetry of the hypercell tubulin potential justifies ignoring the exit times toward the high force direction because of their relatively high improbability.
The mean exit time along the forward (lower force) direction then is

\[
\langle T \rangle = \sqrt{\frac{2\pi D\gamma \tau}{|\xi_c|}} \exp \left( \frac{\xi_c^2 \tau}{2D\gamma} \right),
\]

which is just the so-called Kramers time for the fluctuating force \( \xi \) to reach the critical value \( \xi_c \) for the first time. The critical force \( \xi_c \) necessary for cancelling the tubulin force \( f(x) \) and rendering kinesin free to move to the next tubulin hypercell is equal to \( \xi_c = V_0/d_t + \gamma d_t/\tau \). The first “dominant” term is the total force needed to reach the potential maximum \( V_0 \) while the second “correction” term permits kinesin to move to the next cell before the highly correlated force \( \xi \) acquires a new value and most likely interrupts its exit flight.

The point we stress here is that the average residence time depends critically on the correlation time \( \tau \) as its only adjustable parameter. In our estimate this dependence appears in the form \( \langle T \rangle = A(\tau) \exp[S(\tau)] \). With a potential barrier \( V_0 \approx 8k_BT \) and \( d_t \approx 5.3\text{nm} \) we have \( V_0/d_t \approx 6\text{pN} \). These are realistic parameter values. With the further typical values \( D = k_BT \approx 4 \times 10^{-21}\text{J} \) at room temperature and \( \gamma = 6 \times 10^{-11}\text{kg/s} \) we obtain \( \xi_c \approx 6\text{pN} + 318\text{pN}/\tau[\text{ns}] \), where \( \tau[\text{ns}] \) is the correlation time in nanoseconds. The exponent and prefactor are

\[
S(\tau) = \frac{\xi_c^2 \tau}{2D\gamma} = \frac{V_0}{D} + \left( \frac{V_0}{d_t} \right)^2 \frac{\tau}{2D\gamma} + \frac{\gamma d_t^2}{2D} \frac{1}{\tau} = 8 + 0.075\tau[\text{ns}] + \frac{210}{\tau[\text{ns}]} \tag{4}
\]

and

\[
A(\tau) = \frac{\sqrt{2\pi D\gamma \tau}}{|\xi_c|} \approx 6.5\text{ns}\sqrt{\tau[\text{ns}]} \tag{5}
\]
where in the prefactor we used only the dominant force term. Finally

$$\langle T \rangle = 6.5 \text{ ns} \sqrt{\tau_{[\text{ns}]}} e^{8+0.075\tau_{[\text{ns}]}+210\tau}.$$  (6)

We specifically note the dramatic exponential dependence of the average step time on the correlation time \(\tau\). For these numbers a correlation time of \(\tau \approx 100\text{ns}\) leads to the average exit time \(\langle T \rangle \approx 2\text{s}\) or a kinesin speed of \(4\text{nm/s}\). Although substantially smaller than observed values due to the asymptotic character of our approximation, it is nevertheless an informative estimate. Indeed, numerical simulations for similar parameter ranges give smaller mean exit times, leading to kinesin speeds one to two orders of magnitude larger, results that are compatible with experimental data. For example, in Figure 2, which corresponds to an even higher barrier, one obtains a kinesin speed of \(\sim 200\text{nm/s}\) for \(\tau = 100\text{ns}\).

Due to its quasi-deterministic character, the simple brownian ratchet model for kinesin in the high correlation regime leads to a reduced position variance as opposed to flashing ratchet models. In the latter, the source of the nonequilibrium fluctuations is the stochastic on–off switching of the entire ratchet potential (multiplicative fluctuations). In that case, the brownian particle remains in the vicinity of the binding site while the potential is on, and moves diffusively when the potential temporarily disappears. As a result, the position trace is characterized by a variance closer to that of a free diffusion process that involves not only forward steps but also multiple backward steps, a picture not compatible with experimental data. In the additive fluctuation model, on the other hand, the variance becomes substantially reduced with increasing correlation time [Lindenberg and Tsironis], while backward slips are extremely improbable even for small potential asymmetries.

From the compatibility of the simple correlated brownian ratchet model with the qualitative and quantitative features of kinesin motion, a simplified picture emerges for the movement of motor
proteins on microtubules. We find that the main features of this picture are the asymmetric periodic tubulin potential and the coupling to a stochastic environment that is necessarily highly correlated and can even be said to be quasi-deterministic. The single adjustable parameter of the model is the noise correlation time that is physically related to the event times for ATP binding at the active kinesin head as well as to the hydrolysis time. For reasonable kinesin parameters this time is of the order of 100ns to 1µs, a reasonable range for the phenomena involved. It is not the aim of this simple brownian model to account fully for the specifics of the kinesin walk by taking into account higher dimensional features. It is, however entirely possible to extend the model in this direction for more complete quantitative agreement with the data.

III. MOTION OF MOTOR CHIMAERAS

Kinesin and non-claret disjunctional (ncd) are kinesin superfamily molecular motor proteins that move towards the plus and minus ends of microtubules respectively [Svoboda and Block; Svoboda et al. 1993, 1994; Howard]. Recent experiments with synthetic protein chimaeras show that while the protein catalytic domain seems to be responsible for the processivity of the motor on the microtubule, the “neck” region adjacent to the motor heads controls the directionality of movement [Case; Henningsen and Schliwa]. The simple one-particle model presented above is clearly not adequate to describe these experimental facts either quantitatively or even qualitatively. Although some attempts in the direction of stochastic modeling of protein motion reversals have been made, the high degree of correlations in the ATP fueling process make it necessary to consider quasi-deterministic models. We argue that a simple newtonian model of two-motor-head particles connected through a neck coiled-coil spring whose rest length changes with each ATP hydrolysis event captures the essential motor dynamics features. In particular, the observed directionality reversal in chimaeras with different coiled-coil regions appears in the model from a change in the stiffness of the spring constant. Motor speed is determined by the average ATP absorption rate
while the effect of ambient temperature is very small, leading to an essentially non-brownian deterministic motor [Dialynas et al.].

![Figure 3](image)

**Figure 3** Deterministic motor dimer walk associated with one ATP per step when the coiled-coil spring is relatively soft (see text). The motor moves towards the easier macrotubule potential slope as described in this sequence of figures. Open circle denotes the “right” head. (a) The dimer is in the relaxed state associated with a shrunken spring. Both heads are in the same well. (b) An ATP hydrolysis event causes the coiled-coil spring to open. This causes the “right” head to move toward the right. The relaxed state has the heads in adjacent wells. (c) ADP release leads to the closure of the spring, which in turn causes the “left” head to rejoin the “right” one in a single well. The entire dimer has thus moved to the right and is ready for a repetition of the cycle.

The model we consider is a deterministic version of the stochastic model of Derényi and Vicsek. We show qualitatively that it can produce newtonian motion of proteins in different directions [Stratopoulos et al.]. In the model $x_1$, $x_2$ denote the positions of the two dimer heads interacting with the microtubule surface through a one dimensional periodic non-symmetric potential with a unit cell of length 8nm. The two dimer heads also interact with each other through an internal harmonic potential $V_s(x_1,x_2) = \frac{1}{2}\kappa(|x_1 - x_2| - l(t))^2$. Here $l(t)$ is the time-dependent rest length of the spring that takes on two values corresponding to two different states of the dimer. In state (a) $l(t) = l_1 = 0$, that is, the two heads are close to each other. After an ATP hydrolysis event, a protein conformational change takes place and the dimer transits to state (b), characterized by an opened $\alpha$-helical coiled-coil of length $l(t) = l_2 = 8$nm. Once ADP is released, the dimer transits back to state (a) and the conformational change cycle repeats, with an ATP hydrolysis rate taken to be approximately $50$s$^{-1}$. The assumption of a deterministic periodic $l(t)$ versus a stochastic
dichotomous time dependence is not important and leads to qualitatively similar results. We thus consider that the dimer spends equal times \( t_a = t + b \) in each state leading to a period of the conformational change cycle \( t_c = t_a + t_b = 0.02s \).

Let us first examine the case when the spring connecting the protein heads is soft. Initially \( l(t) = l_1 = 0 \) and the two heads relax to the bottom of the left well as shown in Figure 3a. When ATP binds and the coiled-coil unwinds, the rest length of the spring changes to \( l(t) = l_2 \) while the spring tension tends to move the two heads apart in order to relax the spring. For an ultra soft spring, the spring tension \( f_{spring} \) cannot surmount the microtubule potential forces \( f^r \) (caused by the steeper side of the potential, and hence the stronger of the two) and \( f^l \), and both heads remain trapped at the bottom of the well. For stiffer springs with tension force in the range between the two constant force values of the piece-wise linear microtubule potential, \( f^l < f_{spring} < f^r \), the left head tries to move to the left due to the spring force but the opposing microtubule force \( f^r \) is too strong. The left head thus remains at the bottom of the well. On the other hand, the spring pushes the right head toward the right and since its tension is stronger than the potential force, the right head moves to the right until the spring relaxes (Figure 3b). At that stage the distance between the two heads is exactly \( l_2 \), i.e., equal to the period of the potential. The spring is now relaxed (state (b)), while at the same time each single head relaxes to the bottom of two adjoining wells. Note that implicit in this analysis is the assumption that the spring remains in its extended state for a sufficiently long time for the right head to reach the neighboring well. Subsequently the motor spring again makes a transition to the shrunken state and thus the two heads again tend to move closer to each other. Again, the right head cannot move to the left, while the left head moves to the right until it reaches the right head (Figure 3c). At this point the spring is relaxed to its shrunken state (state (a)), and at the same time both heads relax at the bottom of the right well.

As a result of this purely mechanical cycle the motor protein has consumed one ATP molecule and
has advanced one step to the right.

**Figure 4** Deterministic motor dimer walk associated with one ATP per step when the coiled-coil spring is hard (see text). The motor moves towards the steeper macrotubule potential slope as described in this sequence of figures. Open circle denotes the “right” head. (a) The dimer is in the relaxed state associated with a shrunken spring. Both heads are in the same well. (b) An ATP hydrolysis event causes the coiled-coil spring to open. This causes the “left” head to move toward the left. The relaxed state has the heads in adjacent wells. (c) ADP release leads to the closure of the spring, which in turn causes the “right” head to rejoin the “left” one in a single well. The entire dimer has thus moved to the left and is ready for a repetition of the cycle.

For the strong spring case, $f_{spring} \gg f^r > f^l$, we consider again the two heads initially relaxed but in the right well as in Figure 4a, i.e., $l(t) = l_1$. When the spring transits from state (a) to state (b), the spring tension pushes the two heads apart. Since the potential forces are small compared to the spring tension, the right and the left heads move to the right and left respectively with almost equal speed until the spring is relaxed. Because of the asymmetry of the potential, at the time the spring is relaxed in its extended state the left head has already jumped to the left neighboring well while the right head is still in the original well. The spring is now relaxed and the two heads roll to the bottom of the wells until they relax at the bottom of the respective wells (Figure 4b). When now the spring transits back to the shrunken state, the two heads move towards each other with almost equal speed. again due to the asymmetry, at the time that the two heads meet (i.e., when the spring has relaxed), the right head has already jumped to the adjacent left neighboring well while the the left head remains in that same (left) well. Finally the two heads relax to the bottom of the left well (Figure 4c). In this case after one ATP cycle the motor protein
This qualitative analysis, supported by a quantitative analysis of this quasi-deterministic model [Stratopoulos et al.], indicates that the specific value of the spring constant connecting the two protein dimers plays a decisive role in the selection of directionality of motion. This is compatible with the protein chimaera experiments if we interpret the latter in the following way: Both kinesin and ncd are characterized by an α-helix coiled-coil that can be modeled by linear springs each of different spring constants. This feature enables them to move in opposite directions along the same microtubule potential. When a chimaera is constructed, the protein neck region of kinesin, and therefore its spring, is replaced by that of ncd while leaving the motor region intact. The model thus predicts motion reversal, a fact that is readily supported by experiments.

IV. CONCLUSIONS

A simple single-particle stochastic ratchet model for motor proteins shows reasonably good qualitative and even quantitative agreement with biological experiments when the correlation time of the noise is high. In this regime, the particle motion is controlled by a Kramers rate that depends strongly (exponentially) on the correlations of the fluctuating environment. As a result, the protein motion is essentially step-like and unidirectional, characterised by long “waiting times” interrupted by fast steps. These motion features are rather deterministic, even though they stem from a fundamentally fluctuating process. The results are compatible with the experimental observations of reduced motion variances and step-like protein motion. The basic model of a motor protein moving in a very organized, quasi-deterministic way in the stochastic environment of the cell is carried one step further with a more realistic newtonian two-particle-and-spring model. The two motor heads are each in contact with the microtubule through a periodic non-symmetric potential, while the α-helical coiled-coil interaction is modeled through a spring of variable (binary) rest length. The ATP hydrolysis process powers the engine through a cycle that first unwinds the coil.
and subsequently renews its. As a result, the protein moves one step per ATP cycle in a direction that depends on the value of the α-helical spring constant. A kinesin-ncd chimera is simply effected in the model when the α-helix spring of one is replaced by that of the other, resulting, as in the experiments, in direction reversal. Stochastic fluctuations do not affect the movement process substantially, thus reconfirming the basically deterministic nature of the process.

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