The energetics, chemistry, and mechanics of a processive motor protein

Martin Bier[*]

Department of Physics, East Carolina University, Greenville, NC 27858, USA

Abstract

When kinesin moves along microtubule, it can occasionally malfunction and make a backward step. Recent single molecule experiments on moving kinesin have revealed that the forward to backward step ratio depends exponentially on the load force. We introduce a model of a Brownian step that accounts for recorded data with great accuracy. We find that the forward to backward step ratio does not depend on any structural features of the kinesin. The stepping statistics appear fully determined by the 8 nanometer stepsize, the energy that drives the step, and k_BT, which is the natural "quantum" of thermal energy. With this model we next analyze the energetics of the Brownian stepper. We derive force–velocity relations for the vicinity of the "static head" case, which is when the applied force is close to the stopping force. We also derive force–velocity relations for the close-to-equilibrium case, i.e. a small load and a small ATP-ADP chemical potential.
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1. Introduction

Small cells, like bacteria, rely on diffusion for their internal transport needs. In solution a molecule the size of an aminoacid generally covers a distance of a micrometer in about a millisecond. This is fast enough for a micrometer size cell to rely on (Alberts et al., 1994).

Diffusion follows a formula $\langle L^2 \rangle \propto t$, where $\langle L^2 \rangle$ denotes the average square distance and t is the time. This means that it takes a factor λ^2 more time to cover a distance that is λ times as large. Eukaryotic cells are generally more than an order of magnitude larger than bacteria. Eukaryotic cells, furthermore, contain organelles like mitochondria, endoplasmatic reticula, etc. Such organelles are relatively large (about a micrometer) and they diffuse slowly. To speed up the internal transport eukaryotic cells have evolved a system of active transport (Boal, 2002).

The cytoskeleton is a network of "support beams" that gives the cell structural reinforcement (Boal, 2002). But it is also used as a kind of "railroad system." Motor proteins literally walk on the biopolymers that constitute the cytoskeleton and pull chemical-filled vesicles or organelles from where they are manufactured to where they are needed. Motor proteins that step along a biopolymer and stay attached are called "processive" (Howard,

2001). Kinesin is one of the most prominent and best researched among the processive motor proteins. Experimentalists as well as theoreticians and biologists as well as physicists have probed and analyzed kinesin. Theoretical interest has been driven by a desire to understand how a nanometer size engine operates. It is still very much an open problem how a single molecule can convert chemical energy into mechanical force and motion.

It was already in the 1990s that the 3D structure of kinesin was determined (Wriggers and Schulten, 1998; Vale and Milligan, 2000). One could, in principle, take such a 3D structure as a starting point for a dynamical simulation of the stepping action of kinesin. However, kinesin consists of two heads of each about 350 amino acids. Simulating the dynamics of kinesin heads surrounded by an aqueous solution for more than just picoseconds is beyond the capacity of even the most powerful computing equipment. But even if that were possible, such simulations would still not shed any light on the issue as to how the motor protein converts the free energy of ATP hydrolysis into walking action. The answer to the "how"-question would be buried in a plethora of numbers.

But the action of kinesin has also been investigated on a mechanical level and many questions on how the motor operates have been answered through sophisticated optical tweezer and microscopy experiments (Howard, 2001). Since the early 1990s experimentalists have immobilized microtubules on a slide and let kinesin pull a silica bead where it normally pulls a vesicle or organelle (Svoboda et al., 1993). A silica bead of about a

[*] Tel.: +1 252 328 6428.
E-mail address: bierm@ecu.edu.

micrometer in diameter can be tracked under a microscope and even the 8 nanometer stepping of the motor can then be resolved. When a narrow laser beam is directed at the bead, the bead will pull towards the center of the beam where the light intensity is highest. With such a so-called optical tweezer it is possible to pull forward or backward on the motor protein with piconewton magnitude forces.

2. Backstepping

In the earliest reports it was stated that 5–10% of all kinesin steps were backward and that this percentage did not vary much with an applied force (Visscher et al., 1999). But in the last 5 years better equipment and techniques have led to more accurate observation (Nishiyama et al., 2002; Carter and Cross, 2005). In 2005 Carter and Cross reported the following empirical relationship for the forward-to-backward stepping ratio

$$\frac{P_f}{P_b} = 802 \exp[-0.95 F_{pN}], \tag{1}$$

where F_{pN} represents the applied load in piconewtons (Carter and Cross, 2005). The data appear to follow this relationship very closely. Similar numbers were found in the reference by Nishiyama et al. (2002). One may be tempted to think that the 802 and the 0.95 are consequences of the 3D structure of the kinesin and that it would be practically impossible to retrieve these numbers from the internal structure and workings of the engine. However, as will be shown below, the truth is surprisingly simple. The 0.95 is an almost trivial consequence of the nature of Brownian stepping and the 802 derives straightforwardly from the mechanical energy that drives the step.

Let's look at what happens in a Brownian step. After the detachment of the rear head, a reorientation of the attached head takes place (see Fig. 1). This reorientation brings the detached head into the vicinity of the next forward binding site. Random Brownian motion will eventually make the detached head hit this next forward binding site. Binding then occurs and a next step can commence. The Brownian trajectory of the detached head toward the next binding site does not dissipate any energy. It is pure diffusion. It is in the reorientation of the attached head that the energy of ATP hydrolysis is put to work. An energy G is utilized to cover the stepsize L and overcome internal and hydrodynamic friction (Bier, 2007). However, this power stroke is on a molecular level and takes place in a nondeterministic, Brownian environment. After the appropriate relaxation, a Boltzmann distribution is established between the lowest energy position on the right and the position on the left, which has an energy G higher. The Brownian stepping model of Fig. 1 can quantitatively account for much of kinesin's behavior (Bier, 2003, 2005, 2007, in press).

It is reasonable to assume that a backstep occurs when the detached head rebinds at the same rear binding site that it originally came from. Such binding would then trigger a backstep. Backward binding can occur when the attached head is in the grey dotted area in Fig. 1. For forward binding the attached head needs to be in the striped area. Consider the forward reorientation of the attached head as depicted in Fig. 1. As was mentioned
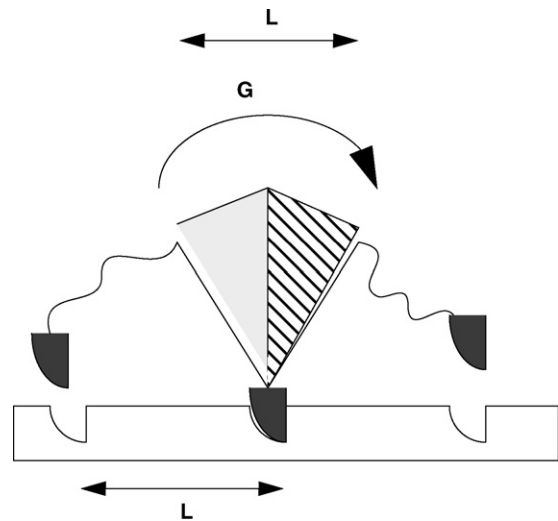

Fig. 1. A schematic depiction of the Brownian step. After detachment of the trailing head, the attached head reorients and brings the detached head to near the next binding site. Random diffusive motion will make the detached head hit the next binding site, binding then occurs and a next step can begin. Power is generated and energy is dissipated when the attached head reorients across the stepsize L driven by an energy G. With a load force F pulling back on the kinesin, the effective energy that drives the power stroke is $G - FL$ instead of just G.

before, between the far left orientation and the far right orientation of the attached head there is a forward driving energy G. Let's call the angle of the attached head with the original far left orientation ϕ. In the simplest approximation the energy decreases linearly from zero to $-G$ as the angle goes from $\phi = 0$ to the far right orientation. It is obvious that for a smooth linear power stroke like that, there is, for every orientation in the striped area, an orientation in the grey area that is $(1/2)G$ higher in energy. We thus get with the Boltzmann distribution

$$\frac{P_f}{P_b} = \exp\left[\frac{G}{2k_B T}\right], \tag{2}$$

where k_B is the Boltzmann constant and T is the absolute temperature. Now suppose that the power stroke is also working against a load force F. This means that a force F is pulling back on the attached head right at the point where the two heads are linked. The energy difference between the far left and the far right orientation of the attached head is now diminished by FL, where L represents the 8 nm stepsize. Substituting $G - FL$ for G in Eq. (2), we then find for the forward to backward stepping ratio

$$\frac{P_f}{P_b} = \exp\left[\frac{G}{2k_B T}\right] \exp\left[-\frac{L}{2k_B T}F\right]. \tag{3}$$

With F expressed in piconewtons, the prefactor $L/2k_B T$ turns out to be exactly the 0.95 that Carter and Cross observed! It is remarkable that no structural characteristics of the kinesin heads are involved in the 0.95 prefactor. The only inputs are the stepsize L of the Brownian stepper and the natural unit of thermal energy $k_B T$. Identifying the 802 of Carter and Cross with the $\exp[G/2k_B T]$ of Eq. (3) leads to about 13 $k_B T$ units as the energy that drives the power stroke. Nishiyama et al. (2002)

measured 221 for the prefactor. This leads to 11 $k_B T$ units for the energy that drives the power stroke. Under physiological conditions the hydrolysis of ATP makes about 22 $k_B T$ units of energy available. So we have an efficiency of about 50–60% for kinesin's conversion of chemical to mechanical energy. Motor protein efficiencies of about 50% is generally what has been reported by experimentalists (Howard, 2001). The power stroke is only one step in an entire catalytic cycle and therein lies the reason that the chemical to mechanical conversion is not 100% efficient. In the course of the catalytic cycle ATP is bound, ADP and inorganic phosphate are released, and the kinesin attaches to and detaches from the microtubule. These chemical steps will be faster and more irreversible if more energy is put behind them. Forward and backward transition rates have been measured (Cross, 2004) and it appears that these chemical steps each are driven by energy drops of about 2 $k_B T$-units. It turns out that the power stroke energy and the energy behind the chemical bindings and unbindings properly add up to about 22 $k_B T$ units (Bier, in press).

3. Kinesin is not Like Membrane Pumps

Much has been made of the fact that kinesin keeps hydrolyzing ATP even when it is forced to step backward under a load that exceeds the stall force (Molloy and Schmitz, 2005). But, given the setup of Fig. 1, this is not surprising. With a load force F the energy driving the power stroke is $G - FL$ and if $FL > G$, the Boltzmann distribution over the reorientation is simply such that a backstep is more likely than a forward step. ATP, however, will continue to be hydrolyzed as backstepping dominates. This is in apparent contrast to a pump like $F_0 F_1$-ATPase. This is a membrane protein that tightly couples the transmembrane electrochemical proton potential to the chemical potential that drives ATP hydrolysis inside the cell. The behavior of this protein is well modeled by a cycle of conformational states in which both these potentials compete for the direction in which the cycle is ultimately driven (Läuger, 1991). In case these potentials cancel each other out, a condition often called "static head," the pump comes to a standstill. $F_0 F_1$-ATPase can thus hydrolyze as well as synthesize ATP. The situation is similar with Na,K-ATPase. This is a membrane pump that, under physiological conditions, utilizes the energy of ATP hydrolysis to pump sodium and potassium ions against their transmembrane potential. But if the ATP-ADP potential is low and the transmembrane sodium potential is high, the Na,K-pump can actually reverse and start producing ATP (Läuger, 1991). If, for the stepping kinesin, the mechanical load and the ATP-ADP potential had simply been pushing the same cycle in opposite directions, we would have had $G_{ATP} = F_{st}L$, where F_{st} is the stopping force and G_{ATP} represents the full 22 $k_B T$-units of energy released by ATP hydrolysis. This would have led to a stopping force of about two times the actually measured 7 pN. Fig. 2 shows an alternative to the one cycle that is pushed in opposite directions. In Fig. 2 the chemistry and the mechanics operate in perpendicular dimensions and the coupling of the dimensions goes via the probabilities P_f and P_b. This depiction allows for $G_{ATP} \neq F_{st}L$ and Fig. 2 is the more appropriate

graphical representation of the setup that is shown in Fig. 1(Bier and Cao, submitted).

$F_0 F_1$-ATPase and Na,K-ATPase *convert* energy from one storable form to another and they operate reversibly. But a few billion years of evolution has optimized kinesin for a different kind of operation. A conservative load constitutes an unphysiological situation for kinesin. Friction is the force that is overcome in the routine action of kinesin and the energy of ATP hydrolysis is irreversibly dissipated into heat as kinesin is walking. In case a pulled vesicle or organelle gets entangled in the cytoskeletal network, the most efficient approach is to simply keep pulling for a little while and then give up and detach all together when the cargo does not come loose.

So with the load near the stopping force, the walking kinesin operates in a way that is fundamentally different from that of the aforementioned ion pumps. With the mechanism of Fig. 1 it is obvious that we are still far from equilibrium when the applied load equals the stopping force. ATP hydrolysis still occurs if $FL = G$. However, forward and backward step probability are now equal. With the load force in the neighborhood of the stopping force, taking $\delta u = -(G - FL)/k_B T$ as a dimensionless energy, and with an ATP turnover rate equal to γ_0, we have

$$v \approx \gamma_0 L(P_f - P_b) = \gamma_0 L \tanh\left[\frac{1}{4}\delta u\right]. \tag{4}$$

The tanh term is easily derived when P_f and P_b are evaluated explicitly. This is done by combining Eq. (3) with $P_f + P_b = 1$. At small δu we have a simple linear expression in δu for the velocity: $v \approx \gamma_0 L(\delta u)/4$. So near the stopping force the mobility, i.e. the proportionality factor μ_{st} between the velocity v and the force F, equals $\mu_{st} = \gamma_0 L^2/4k_B T$. Meanwhile, in the same neighborhood where $v \approx 0$, the ATP turnover rate equals a nonzero γ_0.

Fig. 3 depicts data that were presented in the reference by Carter and Cross (2005). Between a zero load and a load of 7 pN, we see that static head is approached at a rate of about 100 nm/s per piconewton. This implies a mobility of about
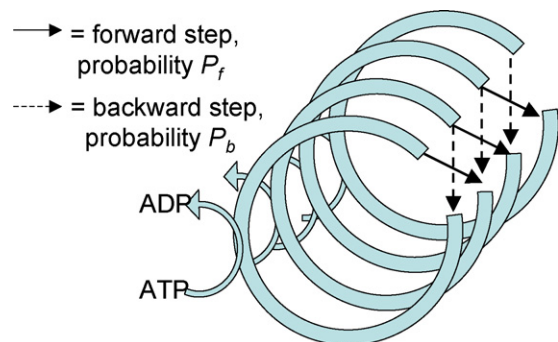

Fig. 2. Experiment has revealed that kinesin still hydrolyzes ATP when it is pulled back with a force larger than the stopping force. So for kinesin it is not appropriate to model the mechanical load and the ATP-ADP potential as pushing the same cycle in opposite directions. The setup of Fig. 1 leads to the above depiction in which the mechanics has its own dimension perpendicular to the plane of the chemical cycle. ATP hydrolysis drives the cycle in a clockwise direction. During the power-stroke-part of each cycle a mechanical forward (towards the right top "into the paper") vs. backward "decision" is made, where P_f and P_b follow Eqs. (1) and (3).
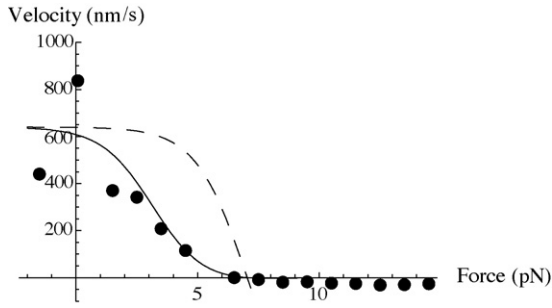
Fig. 3. The load force vs. the velocity for a stepping kinesin. The points represent data that were collected by Carter and Cross (2005). The dashed curve represents a fit according to Eq. (4). The solid curve stands for the better fit according to Eq. (6).

$\mu_{st} = 10^5$ m/Ns. As we are in the massless overdamped regime, there are no kilograms and the mobility simply reduces to $\mu_{st} = 10^5$ s. Substituting $\mu_{st} = 10^5$ s, the formula $\mu_{st} = \gamma_0 L^2/4k_B T$ leads to $\gamma_0 = 25\,\text{s}^{-1}$ as an estimate for the ATP turnover rate. This is a factor 4 smaller the $\gamma_0 = 100\,\text{s}^{-1}$ that we have at zero load. The dashed curve in Fig. 2 shows how Eq. (4) for $\gamma_0 = 80\,\text{s}^{-1}$ leads to a poor fit to the experimental data. Fig. 3 shows that the actual force–velocity relation flattens near the stopping force. For F larger than the stopping force the motor protein is close to standstill. An obvious explanation would lie in a distortion of the molecule and the presence of a step that becomes rate limiting at high load. We let the rate of the load dependent transition follow $k(F) = k_0 \exp[-\varepsilon F/k_B T]$, where ε represents the distance over which Brownian motion needs to "work" against the load before the activation barrier for the transition is overcome. The transfer of the load force to the microtubule involves the kinesin molecule as a lever arm. Because of torque, the actual internal forces within the molecule may be different from F and it would be wrong to interpret ε as an actual distance that is traversed within the kinesin molecule. For the net rate γ at which kinesin is turning over ATP we now have the equation

$$\frac{1}{\gamma} \approx \frac{1}{\gamma_0} + \frac{1}{k_0} \exp\left[\frac{\varepsilon F}{k_B T}\right]. \tag{5}$$

Here we have simply added the time of the load dependent transition to the time $1/\gamma_0$ of the load-free turnover rate. Obviously, we have $k_0 \gg \gamma_0$ in order to retrieve γ_0 as the turnover rate in the load-free case. From Eq. (5) we derive for γ a Michaelis–Menten-like expression

$$\gamma \approx \gamma_0 \left(\frac{1}{1 + (\gamma_0/k_0)\exp[\varepsilon F/k_B T]} \right). \tag{6}$$

To obtain the solid curve in Fig. 3, we substituted the γ according to Eq. (6) for γ_0 in Eq. (4). We took $\varepsilon = 4$ nm and $k_0/\gamma_0 = 20$ and obtain a good fit to the experimental data in the neighborhood of the stopping force. With these parameter values the ATP turnover rate is a factor 40 lower at the stopping force as compared to the γ_0 of the load-free situation.

In the reference by Schnitzer et al. (2000) an equation similar to Eq. (6) is utilized to fit various experimental data among which a force–velocity relation. These fits also result in ~ 4 nm for the

distance factor in the exponent. Eqs. (5) and (6) constitute an ad hoc "quick fix." The are more ways to cover the phenomenology. In the reference by Cuidad and Sancho (2005) the load force is elegantly modeled in analogy to a chemical inhibition and the ensuing formalism also accounts for the fact that kinesin's affinity for ATP decreases as the load increases.

With more adjustments like Eq. (6), one could, in principle, come to a better and better fit to the actual experimental force–velocity data. The force–velocity data of the reference by Carter and Cross (2005) show, for instance, a decrease of the velocity under an assisting load. In other words, kinesin slows down (!) if it is actually pulled in its direction of motion. This feature could also be explained by a distortion under stress and could be modeled with equations like Eqs. (5) and (6). However, whereas Eqs. (2) and (3) are consequences purely of the Brownian stepping mechanism, the parameters of Eqs. (5) and (6) do relate to stresses and strains within the kinesin molecule. Stresses and strains that derive in a nontransparent way from the load and from kinesin's 3D structure.

With a load dependent decrease of the ATP turnover rate as described by Eq. (6), the motor protein protects itself against wasteful consumption of ATP when its cargo gets stuck in the cytoskeletal network. This feature can be thought of as a circuit breaker. An assisting load is, of course, a very unphysiological situation and the decrease of speed under an assisting load is probably not something that should be understood as a result of natural selection.

We end this section with a modeling of the random walk behavior near the stopping force. When F equals the stopping force, a distance s, with $\langle s \rangle = 0$ and $\langle s^2 \rangle = L^2$, is covered during $\tau = 1/\gamma$. This is a simple consequence of $P_f = P_b = 1/2$. Variances add up, so in a time t the mean square of the covered distance x is $\langle x^2 \rangle = \gamma L^2 t$. We thus see that, at the stopping force, kinesin performs 1D diffusion, following $\langle x^2 \rangle = 2D_{st}t$, with a diffusion coefficient of $D_{st} = (1/2)\gamma L^2$. It is worth pointing out that Einstein's Fluctuation–Dissipation Theorem is not obeyed near static head. This theorem applies at equilibrium and states that the mobility μ must be equal to the ratio, $D/k_B T$, of the diffusion coefficient and the natural unit of thermal energy. In our case we have, near the stopping force, a situation where the mobility is half of what the theorem would lay down. We can understand this with the realization that binding forward or backward is like a coin toss (cf. Fig. 2) and after such binding it is the continuous hydrolysis of ATP that then takes the outcome of the coin toss and provides the energy for the machinery to complete the actual forward or backward step. This is an obviously nonequilibrium state of affairs. It is the factor 2 in the denominator of the exponent of Eq. (3) that makes the backstep probability larger than what it would be in case of thermodynamic equilibrium and a Boltzmann mechanism.

4. The Situation Near Equilibrium

With $\text{ATP} \rightleftharpoons \text{ADP} + \text{P}$ close to equilibrium and the load force close to zero, we have a velocity that is linear in both

of the driving forces

$$v = \chi \Delta \psi + \mu_{eq} \Delta F. \tag{7}$$

Here

$$\Delta \psi = k_B T \ln \frac{K_h[\text{ATP}]}{[\text{ADP}][P]} \tag{8}$$

represents the chemical potential driving ATP hydrolysis. K_h is the equilibrium constant for ATP hydrolysis. For small potentials we have $K_h[\text{ATP}] - [\text{ADP}][P] = \Delta C$ and $K_h[\text{ATP}] \approx [\text{ADP}][P] = C$, where ΔC is small compared to C. This leads to $\Delta \psi \approx k_B T \Delta C / C$.

Even at equilibrium, an actual mechanical step requires the coordinated subsequent detachment and attachment of a head. We assume that such mechanical action is still an epiphenomenon of the ATP-ADP processing, i.e., that also close to equilibrium there is still a one-to-one coupling between the ATP-ADP reaction and the stepping. Working from this assumption we will next derive expressions for and find a relation between χ and the mobility μ_{eq}. The variable χ represents a kind of conductance.

When the ATP to ADP conversion reaction is at equilibrium, we have detailed balance (Moore, 1972), i.e., ATP consumption and ATP production occur equally often. An idea of the energy profile of the reaction is depicted in Fig. 4. The steps involving ATP binding and ADP and P release are now energetically uphill. The power stroke that was analyzed in Section 2 of this paper now constitutes an activation barrier for the ATP production. The rate at which this barrier is crossed is proportional to $\exp[-G/2k_B T]$, as $(1/2)G$ is the energy necessary to bring the detached head to a position from where it can bind to backward binding site (cf. Fig. 1). This is a comparatively high barrier and overcoming it is, most likely, the rate limiting step in ATP synthesis. The $\exp[-G/2k_B T]$ factor is to be multiplied with the aforementioned γ_0, which is the rate at which rear binding takes place given that the attached leg is in the grey area (cf. Fig. 1). The ATP production rate is now simply the fraction of time the attached head spends in the grey area multiplied by the rate at which the detached head then binds to the rear binding site. At equilibrium the ATP synthesis rate equals the ATP hydrolysis rate. We thus get for the eventual total stepping rate
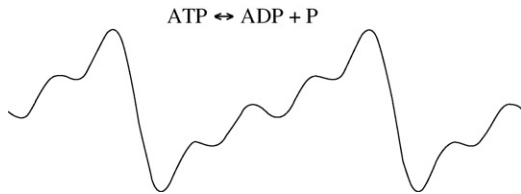
ATP ↔ ADP + P

Fig. 4. The profile along a reaction coordinate for a kinesin step when the ATP-ADP conversion is at chemical equilibrium. There is no energy difference now between an original position and a position that is a step ahead or a step back. So the profile is periodic and at any point there is as much thermally driven forward motion as there is thermally driven backward motion. At the high physiological ATP-ADP potential, the left to right staircase leads down. But at equilibrium the energy for these binding and release reactions cancels out the energy for the power stroke. The power stroke constitutes the activation barrier for the backward stepping that is linked to ATP synthesis.

at equilibrium:

$$\gamma_{eq} \approx 2\gamma_0 \exp\left[-\frac{1}{2}\frac{G}{k_B T}\right]. \tag{9}$$

There is a prefactor 2 because forward and backward steps both contribute equally to the rate. We see that, at equilibrium, kinesin performs a 1D random walk. However, near equilibrium the diffusion coefficient is a few orders of magnitude smaller than at the static head situation:

$$D_{eq} \approx \frac{1}{2}\gamma_{eq}L^2 = \gamma_0 L^2 \exp\left[-\frac{1}{2}\frac{G}{k_B T}\right]. \tag{10}$$

Because we are close to equilibrium, the aforementioned Fluctuation–Dissipation Theorem now applies. Through the Fluctuation–Dissipation Theorem, we find for the mobility, μ_{eq}, close to equilibrium

$$\mu_{eq} = \frac{D_{eq}}{k_B T} \approx \frac{\gamma_0 L^2}{k_B T} \exp\left[-\frac{1}{2}\frac{G}{k_B T}\right]. \tag{11}$$

The rate of ATP hydrolysis and the associated forward stepping is $\gamma_{eq} P_f$. Here we ignore the accidental backstepping upon ATP hydrolysis that is described in Section 2 with Eqs. (1) and (3). But, as we have seen, for small forces ΔF the failure of the chemomechanical coupling is a rare occurrence anyway. For the ATP synthesis and the accompanying backward steps the rate equals $\gamma_{eq} P_b$. We thus have for the net rate of ATP hydrolysis $j = \gamma_{eq}(P_f - P_b) = \gamma_{eq}\Delta C/C$. With $v = jL$ we find:

$$v = \frac{\gamma_{eq}L}{k_B T}\Delta\psi \approx \frac{2\gamma_0 L}{k_B T} \exp\left[-\frac{1}{2}\frac{G}{k_B T}\right]\Delta\psi \tag{12}$$

and hence

$$\chi \approx \frac{2\gamma_0 L}{k_B T} \exp\left[-\frac{1}{2}\frac{G}{k_B T}\right] \approx \frac{2}{L}\mu_{eq}. \tag{13}$$

5. Discussion

A processive motor protein is a Brownian stepper that has been subject to more than a billion years of natural selection for speed and efficiency. It is a molecular size engine that faces different demands than an ion pump or transporter. Pumps and transporters couple flows of different types of energy and simply convert energy from one storable form to another (Alberts et al., 1994). Processive motor proteins have evolved to fight friction and dissipate energy in an overdamped environment. We have seen that some of the mechanical characteristics of kinesin are simple consequences of the Brownian stepping mechanism. Such a mechanism can quantitatively account for experimental data. Other features, like the reduced ATP turnover rate when a load is applied, appear to relate to steric features and can only be fully understood in connection to the 3D molecular structure of the motor protein. However, some of these features can be comprehended, at least qualitatively, with the realization that they have evolved to facilitate optimal functioning.

The situation around the stopping force has been experimentally examined. This far-from-equilibrium static head case

was discussed in Section 3. So far, no experimental results are available for the close-to-equilibrium case that is the subject of Section 4. Theoretically, a close-to-equilibrium regime is easier to analyze. The linear Eq. (7) should be generally valid near equilibrium and not depend on any model. Eqs. (9)–(13), however, constitute verifiable consequences of the Brownian stepper model presented in this paper. Our model predicts, for instance, that the mobility near equilibrium (cf. Eq. (11)) should be more than two orders of magnitude smaller than the mobility near static head.

Acknowledgments

References

Alberts, B., Bray, D., Lewis, J., Raff, M., Roberts, K., Watson, J.D., 1994. Molecular Biology of the Cell. Garland Publishing Inc., New York and London.

Bier, M., 2003. Processive motor protein as an overdamped Brownian stepper. Phys. Rev. Lett. 91, 1481041–1481044.

Bier, M., 2005. Modeling processive motor proteins—moving on two legs in the microscopic realm. Contemp. Phys. 46, 41–51.

Bier, M., 2007. The stepping motor protein as a feedback control ratchet. Biosystems 88, 301–307.

Bier, M., in press. Accounting for the energies and entropies of kinesinōs catalytic cycle. Eur. Phys. J. B.

Bier, M., Cao, F.J., submitted for publication. How occasional backstepping can speed up a processive motor protein. Phys. Rev. Lett.

Boal, D., 2002. Mechanics of the Cell. Cambridge University Press, Cambridge, UK.

Carter, N.J., Cross, R.A., 2005. Mechanics of the kinesin step. Nature 435, 308–312.

Cuidad, A., Sancho, J.M., 2005. External mechanical force as an inhibition process in kinesin's motion. Biochem. J. 390, 345–349.

Cross, R.A., 2004. The kinetic mechanism of kinesin. Trends Biochem. Sci. 29, 301–309.

Howard, J., 2001. Mechanics of Motor Proteins and The Cytoskeleton. Sinauer Associates, Sunderland, MA.

Läuger, P., 1991. Electrogenic Ion Pumps. Sinauer Associates Inc., Sunderland, MA.

Molloy, J.E., Schmitz, S., 2005. Kinesin steps back. Nature 435, 285–286.

Moore, W.J., 1972. Physical Chemistry, 5th ed. Prentice Hall Inc., Englewood Cliffs, NJ.

Nishiyama, M., Higuchi, H., Yanagida, T., 2002. Chemomechanical coupling of the forward and backward steps of single kinesin molecules. Nat. Cell Biol. 4, 790–797.

Schnitzer, M.J., Visscher, K., Block, S.M., 2000. Force production by single kinesin motors. Nat. Cell Biol. 2, 718–723.

Svoboda, K., Schmidt, C.F., Schnapp, B.J., Block, S.M., 1993. Direct observation of kinesin stepping by optical interferometry. Nature 365, 721–727.

Vale, R.D., Milligan, R.A., 2000. The way things move: looking under the hood of molecular motor proteins. Science 288, 88–95.

Visscher, K., Schnitzer, M.J., Block, S.M., 1999. Single kinesin molecules studied with a molecular force clamp. Nature 400, 184–189.

Wriggers, W., Schulten, K., 1998. Nucleotide-dependent movements of the kinesin motor domain predicted by simulated annealing. Biophys. J. 75, 646–661.