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A Stochastic Analysis of a Brownian Ratchet Model for Actin-Based Motility

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Abstract: In recent single-particle tracking (SPT) measurements on *Listeria monocytogenes* motility in cells [Kuo and McGrath (2000)], the actin-based stochastic dynamics of the bacterium movement has been analyzed statistically in terms of the mean-square displacement (MSD) of the trajectory. We present a stochastic analysis of a simplified polymerization Brownian ratchet (BR) model in which motions are limited by the bacterium movement. Analytical results are obtained and statistical data analyses are investigated. It is shown that the MSD of the stochastic bacterium movement is a monotonic quadratic function while the MSD for detrended trajectories is linear. Both the short-time relaxation and the long-time kinetics in terms the mean velocity and effective diffusion constant of the propelled bacterium are obtained from the MSD analysis. The MSD of the gap between actin tip and the bacterium exhibits an oscillatory behavior when there is a large resistant force from the bacterium. For comparison, a continuous diffusion formalism of the BR model with great analytical simplicity is also studied.

keyword: Actin polymerization, exit problem, mean first passage time, nano-biochemistry, single-particle tracking, stochastic processes.

1 Introduction

Actin polymerization plays many important roles in nonmuscle cell mechanics, motility, and functions [Korn (1982); Frieden (1985), Pollard, Blanchoin, and Mullins (2000); Pantaloni, Boujemaa, Didry, Gounon, and Carlier (2000)]. In recent years, quantitative analyses of the molecular mechanism for actin-based motility have been made feasible by both laboratory experiments on *Listeria monocytogenes* (see van Oudenaarden and Theriot (1999); Theriot (2000); Kuo (2001) and the references cited within) and a series of insightful mathematical models [Oosawa and Asakura (1975); Hill (1981); Hill and Kirschner (1982); Hill (1987); Peskin, Odell, and Oster (1993); Mogilner and Oster (1996)]. Interactions between experimental observations and theoretical ideas have generated exciting research in both biophysics and mathematical biology [Mogilner and Oster (2003)]. The molecular theory of actin polymerization also provides a unique opportunity in which the mechanics and chemistry of a biological system are integrated. At the mesoscopic level, mechanics and chemistry are often two perspectives of a single physical process we call chemomechanics [Qian and Shapiro (1999); Qian (2000a); Qian (2002b)].

Following the seminal work of Peskin, Odell, and Oster (1993), a sizable literature now exists on mathematical models and analyses of the polymerization-based motility, known as Brownian ratchet (BR). Even though the original model on fluctuations is clearly a probabilistic one, it was cast mathematically in terms of difference and differential equations with only a minimal stochastic interpretation. In the subsequent development, this stochastic nature of the model often has been obscured. In experimental laboratories, on the other hand, researchers often use Monte Carlo simulations to model the biological problem, partly because the data are inevitably stochastic.

This situation has prevented a truly quantitative understanding of actin-based motility and a closer interaction between the experimental measurements and mathematical modeling. In a recent experiment, Kuo and McGrath (2000) used the highly sensitive single-particle tracking (SPT) methodology [Qian, Sheetz, and Elson (1991)] to measure stochastic movement of *L. monocytogenes* propelled by actin polymerization. The seemingly random data were then analyzed statistically in terms of the mean-square displacement (MSD, see Qian, Sheetz, and Elson (1991)). The exquisite data with nanometre precision reveals the discrete steps in the bacteria movement, presumably due to the actin polymerization, one G-actin

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monomer at a time.

The stochastic nature of the BR, and the statistical treatment employed in experimental data analyses, necessitate a mathematical analysis of the BR model in fully stochastic terms. This is the main objective of the present work. A unique feature of the stochastic modeling analyses is that one deals with a *single* BR rather than a polulation, and can derive theoretical MSD to compare with experiments.

In order to clearly present the stochastic approach to the BR, we only study a special, but relevant case of the generic BR model proposed by Peskin, Odell, and Oster (1993). This restriction allows for an analytical treatment of the model. Our analysis indicates that the BR model predicts a linear relationship between detrended MSD and time. The result seems to be consistent with experimental findings of Kuo and McGrath (2000). This study demonstrates the importance of carrying out stochastic modeling analysis for comparing theory with experiment.

Interestingly, the mathematical model is also identical to one for a stochastic integrate-and-fire neuron proposed many years ago by Gerstein and Mandelbrot (1964). In recent years, integrate-and-fire model has become one of the essential components in neural modeling [Hopfield and Herz (1995)]. The stochastic analysis for the present model, therefore, is expected also to have applications in other branches of biophysics and mathematical biology. The fractal nature of such models has been discussed recently [Qian, Raymond, and Bassingthwaighte (1999)].

All the mathematical background on stochastic processes used in this work can be found in the elementary text by Taylor and Karlin (1998). To help the readers who are not familiar with some of the stochastic mathematics, italic font is used for the key terms when they first appear in the text.

2 Stochastic Formulation of a Brownian Ratchet Model

(i) We consider an F-actin polymerizes in a 1-dimensional fashion with the rate of monomer addition α and the rate of depolymerization β. α is a pseudo-first order rate constant which is proportional to the G-actin monomer concentration. Each G-actin monomer has a size of δ. Hence the actin polymerization is modeled as a continuous-time biased random walk [Hill (1987)]. We shall take the growing direction as positive, and denote the position of the tip of the actin filament by $\mathbf{X}(t)$ which is a stochastic process taking discrete values $k\delta$, where k is an integer. Bold face symbols are used to represent random variables throughout this paper.

(ii) We assume that a bacterium is, in the front of the growing actin filament, located at $\mathbf{Y}(t)$: $\mathbf{X}(t) \leq \mathbf{Y}(t)$. The bacterium has an intrinsic diffusion constant D_b, and experiences (or actively exerts) a resistant force F in the direction against actin polymerization. In the absence of the actin filament, the bacterium movement is a Brownian motion with a constant drift rate $-F/\eta_b$ where η is the frictional coefficient. Since a bacterium is a living organism, the D_b and the η_b are not necessarily related by the Einstein relation $\eta_b D_b = k_B T$ as for inert equilibrium objects.

(iii) The F-actin and the bacterium interact only when they encounter: $\mathbf{X}(t) = \mathbf{Y}(t)$. The actin filament, however, can not penetrate the bacteria wall. Therefore, the motion of the bacterium and the actin polymerization are coupled via a reflecting boundary condition at $\mathbf{X}(t) = \mathbf{Y}(t)$.

(i)-(iii) are the basic assumptions of the generic BR model first proposed by Peskin, Odell, and Oster (1993). In the present work, we shall further assume that

(iv) the α is sufficiently large, and

(v) $\beta \approx 0$.

Therefore, whenever the gap $\Delta(t) \triangleq \mathbf{Y}(t) - \mathbf{X}(t) = \delta$, the gap will be immediately filled by a G-actin monomer, and the polymer does not depolymerize. These two assumptions correspond to a rapid polymerization condition under which the bacteria movement is the rate-limiting process in the overall kinetics.

Fig. 1 shows the basic, stochastic behavior of $\mathbf{X}(t)$, $\mathbf{Y}(t)$, and $\Delta(t)$. Kuo and McGrath (2000) also used a detrended $\mathbf{Y}(t)$. Let v be the mean velocity of the bacterium movement $\mathbf{Y}(t)$, then we define the detrended $\hat{\mathbf{Y}}(t)$ as $\hat{\mathbf{Y}}(t) \triangleq \mathbf{Y}(t) - vt$.[2]

Let ξ_k be the time for incorporating the kth G-actin monomer. Then at time ξ_k, $\mathbf{X}(\xi_k) = \mathbf{Y}(\xi_k) = k\delta$. When $t > \xi_k$, $\mathbf{Y}(t)$ follows a Brownian motion with diffusion constant D_b, drift rate $-F/\eta_b$, and reflecting boundary at $k\delta$. $\mathbf{Y}(t)$ moves stochastically and when it reaches

[2] Dr. S. Kuo has informed us that the method of detrend in Kuo and McGrath (2000) is slightly different from our definition. The significance of this is under current investigation.

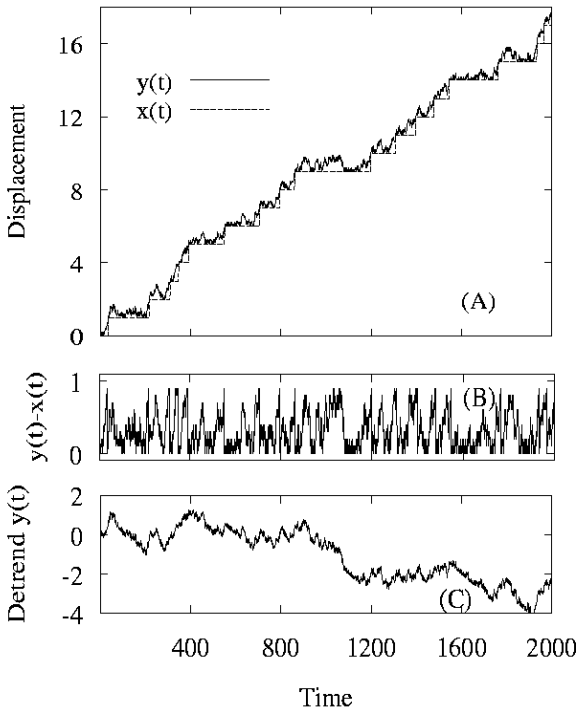

Figure 1 : A set of examples, from Monte Carlo simulations, for the stochastic trajectories of $Y(t)$, the movement of the bacterium, $X(t)$, the movement of the tip of the actin filament (A), $\Delta(t) \triangleq Y(t) - X(t)$, the gap (B), and $\hat{Y}(t)$, the detrended $Y(t)$ (C). Among the four types of data, only the $\Delta(t)$ approaches stationarity. $\hat{Y}(t)$ has zero expectation but with a linear MSD, a characteristic of Brownian motion without drift. Both $X(t)$ and $Y(t)$ show the typical diffusion with a drift [Qian, Sheetz, and Elson (1991)].

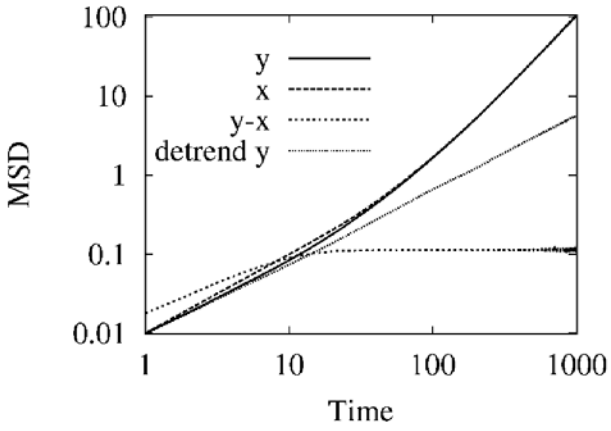

Figure 2 : The MSD, as functions of delay time, for the four types of data in Fig. 1: The movement of the bacterium $Y(t)$, the tip of the actin filament $X(t)$, the gap $\Delta(t)$, and the detrended $\hat{Y}(t)$. As expected, after a brief period of time, the $Y(t)$ and the $X(t)$ are almost indistinguishable; the gap between them quickly reaches stationarity. The detrended $\hat{Y}(t)$ shows a linear MSD, as observed in the experiments Kuo and McGrath (2000).

$(k+1)\delta$, denoted by ξ_{k+1}, the (k+1)*th* G-actin monomer is incorporated. Then the process repeats. The waiting time for the next monomer to be incorporated is a random variable, we shall denote it by $\mathbf{T}$: $\xi_{k+1} = \xi_k + \mathbf{T}$. This is our stochastic formalism for the BR model. The present analysis focuses on the stochastic properties of the random variable $\mathbf{T}$.

Fig. 2 shows the mean-square displacement (MSD) of the stochastic data in Fig. 1. The MSD for a stochastic processes $\mathbf{X}(t)$ is defined as

$$MSD(\tau) = E\left[(\mathbf{X}(\tau+t) - \mathbf{X}(t))^2\right] \tag{1}$$

which is a powerful analytical tool for analyzing stochastic processes with *independent increments* or *stationarity*. The $E[\ldots]$ in Eq. 1 denotes the expectation of random variables. For a stochastic process with independent increments, MSD(τ) is further simplified into $E\left[(\mathbf{X}(\tau) - \mathbf{X}(0))^2\right]$. In the case of a stationary process, its MSD is directly related to the autocorrelation function:

$$E[\mathbf{X}(\tau)\mathbf{X}(0)] = E[\mathbf{X}^2] - \frac{1}{2}MSD(\tau). \tag{2}$$

The significance of MSD is that it can be obtained through a statistical analysis of stochastic experimental data [Qian, Sheetz, and Elson (1991)]. Therefore it is the essential link between the experimental measurements on fluctuations and stochastic mathematical models. For an experimental time series $\{x_n | 0 \le n \le N\}$, the MSD is defined as:

$$MSD(m) = \frac{1}{N-m+1}\sum_{k=0}^{N-m}(x_{k+m} - x_k)^2. \tag{3}$$

The statistical relation between the experimentally determined MSD in Eq. 3 and the theoretical MSD in Eq. 1 can be found in Qian, Sheetz, and Elson (1991).

3 Basic Properties of the Model: Analytical Results

3.1 Mean Waiting Time and Waiting Time Distribution.

The time interval $\mathbf{T}$ between the repeated incorporation of successive actin monomer is the *exit time* of a diffusion process. By exit time $\mathbf{T}_z$, we mean the time a Brownian particle takes to reach δ the first time, starting at z ($0 \leq z \leq \delta$). Clearly $\mathbf{T}_z$ is a random variable; its expectation $T(z) = E[\mathbf{T}_z]$, known as *mean first passage time*, is the solution to the differential equation [Taylor and Karlin (1998)]

$$D_b \frac{d^2T}{dz^2} - (F/\eta_b)\frac{dT}{dz} = -1 \tag{4}$$

with boundary conditions $\frac{dT}{dz}(0) = 0$ and $T(\delta) = 0$. Hence

$$T(z) = \frac{\eta_b^2 D_b}{F^2}\left(e^{F\delta/\eta_b D_b} - e^{Fz/\eta_b D_b}\right) + \frac{\eta_b(z-\delta)}{F}. \tag{5}$$

Therefore,

$$E[\mathbf{T}] = T(0) = \left(\frac{\delta^2}{D_b}\right)\frac{e^{\omega} - 1 - \omega}{\omega^2}, \tag{6}$$

where $\omega = F\delta/(\eta_b D_b)$ is the nondimensionalized resistant force.

The *probability density function* (pdf) $f_{\mathbf{T}_z}(t)$ for the waiting time, $\mathbf{T}_z$ can be obtained in terms of its Laplace transform, also known as the *characteristic function* of the random variable $\mathbf{T}_z$, $Q_{\mathbf{T}}(z,\nu) = \int_0^\infty f_{\mathbf{T}_z}(t)e^{-\nu t}dt$ which satisfies the following differential equation [Weiss (1966)]

$$D_b \frac{\partial^2 Q_{\mathbf{T}}(z,\nu)}{\partial z^2} - \frac{F}{\eta_b}\frac{\partial Q_{\mathbf{T}}(z,\nu)}{\partial z} = \nu Q_{\mathbf{T}}(z,\nu) \tag{7}$$

with boundary condition $\partial Q_{\mathbf{T}}(0,\nu)/\partial z = 0$ and $Q_{\mathbf{T}}(\delta,\nu) = 1$. Note Eq. 4 is a special case of Eq. 7 for $T(z) = -\partial Q_{\mathbf{T}}(z,0)/\partial\nu$.

Eq. 7 can be analytically solved:

$$Q_{\mathbf{T}}(0,\nu) = \frac{\lambda_- - \lambda_+}{\lambda_- e^{\lambda_+\delta} - \lambda_+ e^{\lambda_-\delta}} \tag{8}$$

where

$$\lambda_\pm = \frac{\omega}{2\delta} \pm \sqrt{\left(\frac{\omega}{2\delta}\right)^2 + \frac{\nu}{D_b}}.$$

Therefore, the variance in the waiting time

$$Var[\mathbf{T}] = \left(\frac{\delta^4}{D_b^2}\right)\frac{3e^{2\omega} - (10\omega - 6)e^{\omega} + \omega^2 - 2\omega - 9}{\omega^4}. \tag{9}$$

If there is no resistant force from the bacteria, $\omega = 0$ and we have a simple expression

$$Q_{\mathbf{T}}(0,\nu) = \left(\cosh\sqrt{\delta^2\nu/D_b}\right)^{-1}. \tag{10}$$

3.2 Renewal Processes, The Statistical Properties of $\mathbf{X}(t)$ and $\mathbf{Y}(t)$.

With $\mathbf{T}$ as the waiting time, the tip of the rapidly growing actin filament, $\mathbf{X}(t)$, is a *renewal process* [Taylor and Karlin (1998)]. There is a large literature on this subject. The most relevant result to our model is the *elementary renewal theorem* for large t

$$E[\mathbf{X}(t)] \approx \frac{\delta}{E[\mathbf{T}]}t \tag{11}$$

Therefore as a renewal process, a BR executes successive steps with size δ and average time $E[\mathbf{T}]$. The mean velocity of the BR, thus, is

$$v = \frac{\delta}{E[\mathbf{T}]} = \left(\frac{D_b}{\delta}\right)\frac{\omega^2}{e^{\omega} - 1 - \omega}. \tag{12}$$

This result is in agreement with that of Peskin, Odell, and Oster (1993).

Furthermore from the theory of renewal processes [Taylor and Karlin (1998)]

$$Var[\mathbf{X}(t)] \approx \frac{\delta^2 Var[\mathbf{T}]}{E^3[\mathbf{T}]}t \triangleq \sigma^2 t, \tag{13}$$

where, according to Eqs. 6 and 9,

$$\sigma^2 = \frac{3e^{2\omega} - (10\omega - 6)e^{\omega} + \omega^2 - 2\omega - 9}{(e^{\omega} - 1 - \omega)^3}\omega^2 D_b. \tag{14}$$

The MSD for $\mathbf{X}(t)$, therefore, is

$$E\left[(\mathbf{X}(t) - \mathbf{X}(0))^2\right] \approx \sigma^2 t + (vt)^2 \tag{15}$$

which is a quadratic function of t. The expression for σ^2 is a new result of the present work, which is comparable with experimental data. Fig. 3 shows the dependence of v and σ^2 as functions of $\omega = F\delta/\eta_b D_b$, the resistant force

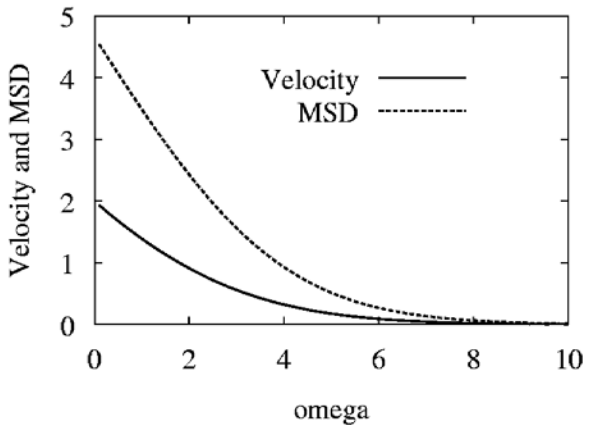

Figure 3 : The velocity $v\delta/D_b$ and MSD σ^2/D_b, nondimensionalized, as functions of the resistant force on bacterium, $\omega = F\delta/\eta_b D_b$. In the SPT experiments, the velocity can be obtained as the quadratic term in the MSD of $Y(t)$, the σ^2 can be obtained either as the linear term in the MSD of $Y(t)$, or the MSD of the detrended $\hat{Y}(t)$. The velocity v is given in Eq. 12 and the σ is given in Eq. 14.

from the bacterium. If $\omega = 0$, then $v = 2D_b/\delta$ and $\sigma^2 = 14D_b/3$.

Since $\mathbf{Y}(t) - \mathbf{X}(t) < \delta$ while both increase linearly with t, for large t $\mathbf{Y}(t) \approx \mathbf{X}(t)$ with an error less than δ, the size of a single actin monomer. Strictly speaking, the $\mathbf{Y}(t)$ is not a stochastic process with independent increments. However, the error involved, again, is only on the order of the size of a single G-actin. To understand the statistical correlation of $\mathbf{Y}(t)$ within each "step", see the section below on the gap.

3.3 *Detrended* $\mathbf{Y}(t)$ *and Its Statistical Properties.*

We define the detrended $\mathbf{Y}(t)$ as $\hat{\mathbf{Y}}(t) \triangleq \mathbf{Y}(t) - vt$, where v is the mean velocity. For $n\delta \le \mathbf{Y}(t) \le (n+1)\delta$,

$$\begin{aligned}\hat{\mathbf{Y}}(t) &\triangleq \mathbf{Y}(t) - vt \\ &= \mathbf{Y}(t) - \mathbf{Y}(\xi_n) + n\delta - v\xi_n - v(t - \xi_n) \\ &= \mathbf{Y}(\tau) - v\tau + n\delta - v\xi_n\end{aligned}$$

in which random variable ξ_n is the time for $\mathbf{Y}(t)$ to reach $n\delta$ the first time, $\tau = t - \xi_n$, and v is given in Eq. 12. Hence, $0 \le \tau \le \xi_{n+1} - \xi_n = \xi_1 = \mathbf{T}$, with its expectation, variance, and characteristic function given in Eqs. 6, 9, and 8, respectively.

The statistical properties of $\hat{\mathbf{Y}}(t)$ are readily calculated:

$$E\left[\hat{\mathbf{Y}}(t)\right] = E\left(\mathbf{Y}(\tau)\right] - v\tau \approx 0, \tag{16}$$

$$Var\left[\hat{\mathbf{Y}}(t)\right] = Var\left[\mathbf{Y}(\tau)\right] + nvVar\left[\mathbf{T}\right] \approx \sigma^2 t. \tag{17}$$

Thus, we see that the detrended $\hat{\mathbf{Y}}(t)$ does not become stationary with increasing time. While its expectation is zero, its variance increases linear with the time t, the epitome of a symmetric random movement. The parameter $\frac{\sigma^2}{2}$ is the effective diffusion constant of the BR.

3.4 *Statistical Properties of the Gap* $\mathbf{Y}(t) - \mathbf{X}(t)$.

The gap between the bacteria, $\mathbf{Y}(t)$, and the tip of the actin filament $\mathbf{X}(t)$, $\Delta(t) \triangleq \mathbf{Y}(t) - \mathbf{X}(t)$ behaves completely differently from the detrended $\hat{\mathbf{Y}}(t)$. It reaches asymptotically to stationarity.

We can provide a reasonable estimation for the relaxation time for the gap to reach its stationarity from the largest nonzero eigenvalues (μ) of the diffusion operator

$$\left(D_b \frac{d^2}{dx^2} + \frac{F}{\eta_b}\frac{d}{dx}\right) u(x) = \mu u(x) \tag{18}$$

under the boundary condition $D_b \frac{du}{dx}(0) + (F/\eta_b)u(0) = u(\delta) = 0$. See Appendix for details. All the eigenvalues are real and ≤ 0, $\mu(z) = -\frac{D_b}{4\delta^2}(z^2 + \omega^2)$, where the z are the roots of the transcendental equation $\cos z = \frac{\omega^2 - z^2}{\omega^2 + z^2}$. Fig. 4 suggests that the largest eigenvalue corresponds to the exit time which increases with the resistant force. For resistant force $F \gg 2\eta_b D_b/\delta$, there is a separation between the time scale for the exit and the time scale for establishing a quasi-stationary distribution for $\Delta(t)$ (Appendix). Fig. 5 shows the MSD for $\Delta(t)$, which is directly related to the correlation function for the stationary process (Eq. 2). After normalization by $2Var[\Delta]$, the MSD are approximately the same for $0 \le \omega \le 6$. The correlation time decreases with ω for ω = 2, 4, 6, and 12 (i.e., the probability for a biased random walk p = 0.55, 0.6, 0.65, and 0.8), corresponding to the second largest eigenvalue in Fig. 4,

When there is a large resistant force F, the exit time $\mathbf{T}$ has a small relative variance (Eqs. 9, and 6) and the exit becomes an event with sufficient regularity. This is reflected in the oscillation of the MSD in Fig. 5.

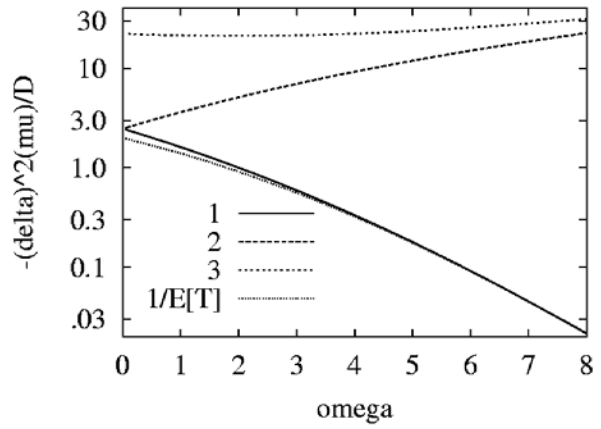

Figure 4 : Numerical computation for the three smallest eigenvalues (in magnitude, all eigenvalues are negative) of Eq. 18, $|\mu\delta^2/D_b|$, as function of the resistant force ω. These are the most relevant modes in the relaxation (and correlation function) of the gap, $\Delta(t)$, approaching to stationarity. The smallest eigenvalue corresponds to the exit time, shown in the figure (labeled $1/E[T]$).

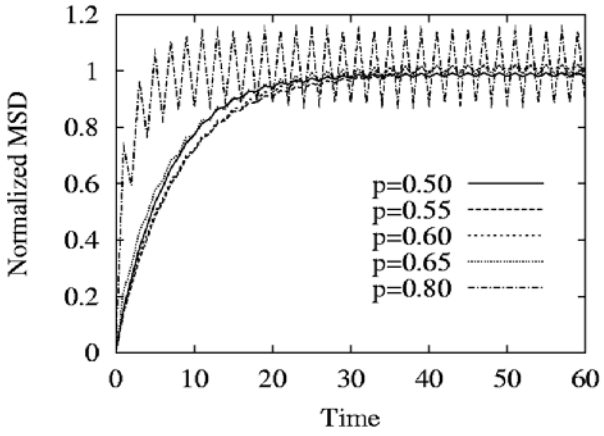

Figure 5 : The normalized MSD for the $\Delta(t)$, from Monte Carlo simulation, for different resistant force F which is related to the probability (p) shown in the figure: $F/(\eta_b\delta) = 0.1(2p-1)$. A standard MSD for a stationary process is directly related to its time correlation function $2(E[\Delta^2(t)] - E[\Delta(t)\Delta(0)])$, with its asymptote being the $2Var[\Delta]$ when $t \to \infty$. In the simulations, the diffusion constant is $D_b/\delta^2 = 0.005$. $0 \le \Delta(t) \le 1$; the stationary $E[\Delta]$ = 0.33, 0.27, 0.21, 0.16, and 0.08 for $p = 0.5 - 0.8$ respectively; the corresponding relative variances $Var[\Delta]/E^2[\Delta]$ = 0.53, 0.64, 0.79, 0.91, and 0.96. The relative variance for an exponential distribution is 1.

4 An Analytical Analysis of a Continuous Stochastic Formalism of BR

We can replace the assumptions (iv) and (v) in Section 2 with a continuous model for the discrete polymerization. In other word, we approximate the biased random walk with α, β and δ by a diffusion process with diffusion constant and drift rate [Feller (1957); Hill (1987)]:

$$D_a = (\alpha+\beta)\delta^2/2, \quad V_a = (\alpha-\beta)\delta. \tag{19}$$

where β and α are first-order and pseudo-first-order rate constants for the depolymerization and polymerization, δ is the size of a G-actin monomer. The dynamic equation governing the probability density function (pdf) $P_{\mathbf{X}}(x,t)$ for the stochastic processes $\mathbf{X}(t)$ is:

$$\frac{\partial P_{\mathbf{X}}(x,t)}{\partial t} = D_a\frac{\partial^2 P_{\mathbf{X}}(x,t)}{\partial x^2} - V_a\frac{\partial P_{\mathbf{X}}(x,t)}{\partial x} \tag{20}$$

where $P_{\mathbf{X}}(x,t)$ has the probabilistic meaning of $P_{\mathbf{X}}(x)dx = Prob\{x < \mathbf{X} \le x+dx\}$. Similarly, the dynamical equation for Brownian motion of the bacterium $\mathbf{Y}$ with resisting force F is, as before,

$$\frac{\partial P_{\mathbf{Y}}(y,t)}{\partial t} = D_b\frac{\partial^2 P_{\mathbf{Y}}(y,t)}{\partial y^2} + \frac{F}{\eta_b}\frac{\partial P_{\mathbf{Y}}(y,t)}{\partial y}. \tag{21}$$

These two equations are coupled since $\mathbf{X} \le \mathbf{Y}$. We call Eqs 19, 20, and 21 the continuous formalism for the BR. It represents two-dimensional diffusion in the triangle region of $x \le y$:

$$\begin{aligned}\frac{\partial P_{\mathbf{XY}}(x,y,t)}{\partial t} &= D_a\frac{\partial^2 P_{\mathbf{XY}}(x,y,t)}{\partial x^2} + D_b\frac{\partial^2 P_{\mathbf{XY}}(x,y,t)}{\partial y^2} \\ &- V_a\frac{\partial P_{\mathbf{XY}}(x,y,t)}{\partial x} + \frac{F}{\eta_b}\frac{\partial P_{\mathbf{XY}}(x,y,t)}{\partial y}.\end{aligned}$$

The advantage of this version of the BR is its analytical simplicity. A coordinate transformation can be introduced:

$$\Delta = \mathbf{Y} - \mathbf{X}, \quad \mathbf{Z} = \frac{D_a\mathbf{Y} + D_b\mathbf{X}}{D_a + D_b} \tag{22}$$

where Δ represents the gap between the tip of the actin filament and the bacterium, $\mathbf{Z}$ represents an averaged position of $\mathbf{X}$ and $\mathbf{Y}$, we shall call it the *center of mass* of the

BR. With this transformation, the two differential equations are decoupled:

$$\frac{\partial P_\Delta(\Delta,t)}{\partial t} = (D_a+D_b)\frac{\partial^2 P_\Delta(\Delta,t)}{\partial \Delta^2} + \left(V_a + \frac{F}{\eta_b}\right)\frac{\partial P_\Delta(\Delta,t)}{\partial \Delta},$$

$$(\Delta \geq 0) \tag{23}$$

$$\frac{\partial P_{\mathbf{Z}}(z,t)}{\partial t} = \frac{D_a D_b}{D_a+D_b}\left(\frac{\partial^2 P_{\mathbf{Z}}(z,t)}{\partial z^2}\right) - \frac{D_b V_a - D_a F/\eta}{D_a+D_b}\left(\frac{\partial P_{\mathbf{Z}}(z,t)}{\partial z}\right)$$

$$(-\infty < z < +\infty). \tag{24}$$

It can be immediately concluded from these two equations that the gap $\Delta(t)$ approaches its stationary, exponential distribution (see Appendix)

$$P_\Delta(\Delta) = \frac{V_a + F/\eta_b}{D_a+D_b} e^{\frac{V_a+F/\eta_b}{D_a+D_b}\Delta}, \quad \Delta \geq 0. \tag{25}$$

$\mathbf{Z}$ however increases steadily with an effective diffusion constant D_z, $\frac{1}{D_z} = \frac{1}{D_a} + \frac{1}{D_b}$, and a mean velocity $V_z = \frac{D_b V_a - D_a F/\eta_b}{D_a+D_b}$. This result can be understood in terms of Newtonian mechanics: the driving force from actin polymerization is $F_a = \eta_a V_a = k_B T V_a/D_a$, and the resistant force is F, and hence the net force on the BR is $F_z = F_a - F$ with the frictional coefficient the BR (center of mass) being $k_B T/D_z$. Hence

$$\begin{aligned} V_z = \frac{D_z F_z}{k_B T} &= \frac{D_a D_b}{D_a+D_b}\left(\frac{V_a}{D_a} - \frac{F}{k_B T}\right) \\ &= \frac{D_b V_a - D_a F/\eta_b}{D_a+D_b}. \end{aligned} \tag{26}$$

The parameter D_a and V_a are defined in terms of α, β, and δ in Eq. 19. α is a pseudo-first order rate constant which is proportional to the G-actin concentration c_0, as well as the probability of the gap Δ being greater than δ. Therefore, α is a function of external force F; it can be determined in a self-consistent manner from the transcendental equation:

$$\begin{aligned} \alpha(F) &= \alpha_0 c_0 \int_\delta^\infty P_\Delta(s)ds \\ &= \alpha_0 c_0 \exp\left[-\frac{(\alpha-\beta)\delta + F/\eta_b}{(\alpha+\beta)\delta^2/2 + D_b}\delta\right] \end{aligned} \tag{27}$$

where α_0 is the intrinsic, second-order rate constant for polymerization. We see that V_z in Eq. 26 is a linear function of resistant force F explicitly; however, nonlinearity arises since D_a and V_a are implicit functions of the resistant force F, via $\alpha(F)$. In other words, the resistant force F slows down the BR by two different mechanisms: a linear Newtonian resistance and also a reduction in the rate of polymerization via a diminished gap. Eq. 27 has the general form $\alpha(F) \propto e^{-rF\delta/k_B T}$ where r is a splitting parameter. We see that in general r can be a function of F.

V_z in Eq. 26 is necessarily smaller than V_a, indicating that the bacterium retards the polymerization. When $F = \eta_b D_b V_a/D_a = \left(\frac{\eta_b D_b}{\delta}\right)\frac{2(\alpha-\beta)}{\alpha+\beta}$, the bacterium completely stalls the polymerization. This yields the critical stalling force which agrees with the well known result of Hill (1987) for an inert object: $(k_B T/\delta)\ln(\alpha/\beta)$. Furthermore, if we note that $\eta_b D_b = k_B T$, then the rate of polymerization against a resisting force F is at its maximal $V_z = V_a - F D_a/k_B T$ when $D_b \to \infty$. This is a result of Peskin, Odell, and Oster (1993) who first elucidated the crucial role played by the fluctuating "barrier" in the filamentous growth. In a more general context, the dynamic characteristics of the "force transducer" by which the resisting force is applied to the growing tip of the filament is an integral part of the molecular process.

In Hill (1981), this issue is not considered because of its quasi-thermodynamic approach. The applied force was assumed to have an instantaneous dynamic response. From equilibrium thermodynamics one knows that polymerization under resisting force F has $\alpha(F)/\beta(F) = e^{-F\delta/k_B T}$. So how does F contribute to $\alpha(F)$ and $\beta(F)$ individually? The splitting parameter r is defined as $\alpha(F) = \alpha(0)e^{-rF\delta/k_B T}$ and consequently $\beta(F) = \beta(0)e^{(1-r)F\delta/k_B T}$, where $\alpha(0)$ and $\beta(0)$ are the α and β in the above. The rate of polymerization under force F, therefore, is

$$[\alpha(F) - \beta(F)]\delta = \left(\alpha(0)e^{-rF\delta/k_B T} - \beta(0)e^{(1-r)F\delta/k_B T}\right)\delta. \tag{28}$$

With very small δ, this gives $[\alpha(0) - \beta(0)]\delta - F\delta^2[r\ \alpha(0) + (1-r)\beta(0)]/k_B T$ which should be compared with $V_z = (\alpha-\beta)\delta - F\delta^2(\alpha+\beta)/2k_B T$. See Eq. 26 and noting

$$\alpha = \frac{1}{2}\left(\frac{V_a}{\delta} + \frac{2D_a}{\delta^2}\right), \quad \beta = \frac{1}{2}\left(-\frac{V_a}{\delta} + \frac{2D_a}{\delta^2}\right), \tag{29}$$

from Eq. 19. This indicates that the BR has a splitting factor of $r = 1/2$. However, Hill's analysis does not have the contribution from the dynamic characteristics

of the barrier, i.e., D_b. Eq. 28 is the starting point of Kolomeisky and Fisher (2001).

We now show that in the limit of $\delta \to 0$, our V_z from the continuous model is equivalent to the ratchet velocity in Peskin, Odell, and Oster (1993) (POO). Note that in the original work the definition for the ratchet velocity was rather convoluted. The V_z in the present model is more straightforward. Substituting the expressions in Eq. 29 into

$$V_{poo} = \delta \left(\alpha \int_{\delta}^{\infty} P_{\Delta}(\Delta) d\Delta - \beta \int_{0}^{\infty} P_{\Delta}(\Delta) d\Delta \right)$$

we have

$$\begin{aligned} \lim_{\delta \to 0} V_{poo} &= V_a - \frac{D_a}{\delta} \int_0^{\delta} P_{\Delta}(\Delta) d\Delta = V_a - D_a P_{\Delta}(0) \\ &= \frac{D_b V_a - D_a F/\eta_b}{D_a + D_b} = V_z. \end{aligned}$$

In the derivation we have used Eq. 25. Note that the basic molecular parameters for polymerization, α, β and δ are actually contained in the parameter D_a and V_a. In the mathematical limit of $\delta \to 0$, there is at the same time α and $\beta \to \infty$ such that D_a and V_a are finite [Feller (1957)].

5 Discussion

Nanometre precision measurements on *L. monocytogenes* movement [Kuo and McGrath (2000)] have shown that the bacteria move in steps. Considering there are many actin filaments in a bundle which propels a bacterium, this observation indicates a synchronized filamentous growth in the bundle. The synchronization is not inconsistent with a bundle of actin filaments propelling a bacterium with sufficiently small Brownian movement (i.e., small D_b). The significantly reduced Brownian motion is indeed observed experimentally, both in the direction parallel and perpendicular to the actin growth.

There could be several explanations for the small D_b.

(a) Kuo and McGrath (2000) suggested an association between the bacterium and the actin structure, which leads to endorsing the two-dimensional BR with bending [Mogilner and Oster (1996)].

(b) It should be noted, however, that association-dissociation can also be introduced into the one-dimensional BR in the form of an attractive force between the actin and the bacterium; thus a nonzero F as function of $(y-x)$. This, we argue, will also lead to a reduced *apparent* D_b on a longer time scale.

(c) As we have pointed out, the D_b of a living bacterium is not necessarily related to its physical size and frictional coefficient η_b. A living bacterium could have an internal mechanism, by utilizes its biochemical free energy, to localize itself near the tip of the actin filament with diminished Brownian motion. Finally, all existing models on BR have only dealt with single filaments. The continuous formalism we propose here is in fact our initial step toward extending the BR to a filamentous bundle. All these topics are currently under investigation.

In a special Science issue on *Movement: Molecular to Robotic*, two articles reviewed recent progress on force and motion generated on the molecular level by two completely different biological systems: motor protein movement and cytoskeletal filamentous polymerization [Vale and Milligan (2000); Mahadevan and Matsudaira (2000)]. Both systems can move against resistant force by utilizing chemical free energy. In the abstract of the second article, it was stated "Not all biological movements are caused by molecular motors sliding along filaments or tubules. Just as springs and ratchets can store or release energy and rectify motion in physical systems, their analogs can perform similar functions in biological systems." While there has been much work done on motor proteins and protein polymerization in connection to various cellular phenomena such as motility, less has been discussed about the fundamental physical principles of these two chemomechanical processes. It turns out, as we have shown in this work, that both molecular processes have a single, unified mathematical model which accounts for their chemomechanical energy transduction. The mechanics and chemistry are inseparable at the molecular cellular level.

Experimental measurements have been carried out on both systems [Dogterom and Yurke (1997); Kuo and McGrath (2000)]. Similar to the measurements on load-velocity curves for motor proteins, Dogterom and Yurke (1997) measured the velocity as a function of resistant force for single microtubules growing *in vitro*. Analysis of their data suggests that under the stalled (critical) condition, polymerization is in a nonequilibrium steady-state rather than a thermodynamic equilibrium [Kolomeisky and Fisher (2001); Hill (1987)].

Theoretical formalism for motor proteins are now well established (see Jülicher, Ajdari, and Prost (1997); Qian

(2000b); Bustamante, Keller, and Oster (2001); Reimann (2002); Oster and Wang (2003); Qian (2004)). Since the motion of a single motor protein is Brownian, it has to be characterized in terms of probability distribution. The simplest model is that of Huxley (1957). This model corresponds to Dogterom and Leibler (1993) for polymerization with nucleotide hydrolysis. Both models addressed the important issue of nucleotide hydrolysis, but neglected the respective stochastic nature in the movement of motor protein and actin polymerization. Without the diffusion term, such a mathematical model is known as random evolution [Pinsky (1991)].

All experimental evidences indicate that the BR model is a fundamental mathematical model for chemomechanical energy transduction. Recent work on the nonequilibrium statistical mechanics and thermodynamics of BR, in the context for single macromolecules in aqueous solution, also provided the mathematical model with a solid foundation in statistical physics of Boltzmann, Gibbs, and Onsager [Qian (1998); Qian (2001a); Qian (2001b); Qian (2002a); Qian (2002b); Qian (2004)]. The biological systems discussed in the two Science articles [Vale and Milligan (2000); Mahadevan and Matsudaira (2000)] and the mechanistic, molecular models proposed are completely different. Yet they share fundamentally the same physiochemical principle which units both models in a quantitative fashion. The mathematical model seems to capture the basic principle for molecular movements and force generation in cell biology.

To biophysicists and mathematical biologists, BR is a class of models which is based on a similar physics but can have many different mathematical representations and degree of approximations. We have shown two such analyses in the present work. The essential feature of all the models can, and should, be presented in terms of their MSD, which provides the BR, in steady-state, with an effective diffusion constant(D_z) and a mean velocity (V_z), both as functions of the resistant force. More subtle differences between models can be found in the transient behavior. The comparison between our analyses is summarized in the Table, in which the effective diffusion constant for the continuous model

$$D_z = \frac{(\alpha+\beta)\delta^2 D_b/2}{D_b+(\alpha+\beta)\delta^2/2} \longrightarrow D_b$$

when $\alpha \to \infty$, and the BR velocity

$$V_z = \frac{D_b(\alpha-\beta)\delta - D_b(\alpha+\beta)\delta\omega/2}{D_b+(\alpha+\beta)\delta^2/2} \longrightarrow (D_b/\delta)(2-\omega)$$

is a linear force-velocity relationship.

	D_z/D_b	$V_z\delta/D_b$
discrete model	$\frac{3e^{2\omega}-(10\omega-6)e^{\omega}+\omega^2-2\omega-9}{(e^{\omega}-1-\omega)^3}\omega^2$	$\frac{\omega^2}{e^{\omega}-1-\omega}$
continuous model	1	$2-\omega$

It is seen that in the continuous model, the effective diffusion constant D_z is always less than the D_b, while in the discrete model, the $D_z = \sigma^2/2$ is a function of the resistant force. When the force is small, D_z can in fact be greater than D_b. This is a type of facilitated diffusion.

It is important to point out that the results from our discrete analysis is invalid when the resistant F is sufficiently large, when the polymerization is near its stalling force. This is due to the assumption of infinite large α. This explains why there is no critical force in Fig. 3, at which the velocity $v = 0$. The more realistic model with finite α and β does lead to a finite, positive stalling force [Peskin, Odell, and Oster (1993); Kolomeisky and Fisher (2001)]. The valid regime for our discrete model is a rapid growing actin filament with the bacteria viscous drag being the limiting factor in the overall BR movement.

Finally, it is worth pointing out that mechanical studies of cellular properties and functions can be approximately classified for passive and active materials. The former can be understood in terms of the theories of viscoelasticity and polymer dynamics. See Qian (2000a) for a general approach to the problem. Materials with chemomechanical energy transduction are active. The fundamental difference is the nucleotide hydrolysis which leads to an irreversible thermodynamic nonequilibrium steady-state with heat dissipation [Qian (2002a); Qian (2002b)] rather than the usual equilibrium. Thus, the BR model is also a natural generalization of the standard polymer theory for passive, mostly synthetic, materials [Doi and Edwards (1986)] to active biological materials for which T.L. Hill has coined the term "steady-state polymer" Hill (1987).

References

Bustamante, C.; Keller, D.; Oster, G. (2001): The physics of molecular motors. *Acc. Chem. Res.*, vol. 34, pp. 412–420.

Carslaw, H.; Jaeger, J. (1959): *Conduction of Heat in Solids, 2nd Ed.* Clarendon Press, Oxford.

Crank, J. (1975): *The Mathematics of Diffusion. 2nd Ed.* Clarendon Press, Oxford.

Dogterom, M.; Leibler, S. (1993): Physical aspects of the growth and regulation of microtubule structures. *Phys. Rev. Lett.*, vol. 70, pp. 1347–1350.

Dogterom, M.; Yurke, B. (1997): Measurement of the force-velocity relation for growing microtubules. *Science*, vol. 278, pp. 856–860.

Doi, M.; Edwards, S. (1986): *The Theory of Polymer Dynamics*. Clarendon Press, Oxford.

Feller, W. (1957): *Introduction to Probability Theory and Its Applications. Vol. 1, 2nd Ed.* John Wiley & Sons New York.

Frieden, C. (1985): Actin and tubulin polymerization: the use of kinetic methods to determine mechanism. *Ann. Rev. Biophys. Biophys. Chem.*, vol. 14, pp. 189–210.

Gerstein, G. L.; Mandelbrot, B. B. (1964): Random walk models for the spike activity of a single neuron. *Biophys. J.*, vol. 4, pp. 41–68.

Hill, T. L. (1981): Microfilament or microtubule assembly or disassembly against a force. *Proc. Natl. Acad. Sci. USA*, vol. 78, pp. 5613–5617.

Hill, T. L. (1987): *Linear Aggregation Theory in Cell Biology*. Springer-Verlag, New York.

Hill, T. L.; Kirschner, M. W. (1982): Subunit treadmilling of microtubules or actin in the presence of cellular barriers: possible conversion of chemical free energy into mechanical work. *Proc. Natl. Acad. Sci. USA*, vol. 79, pp. 490–494.

Hopfield, J. J.; Herz, A. V. M. (1995): Rapid local synchronization of action potentials: toward computation with coupled integrate-and-fire neurons. *Proc. Natl. Acad. Sci. USA*, vol. 92, pp. 6655–6662.

Huxley, A. F. (1957): Muscle structure and theories of contraction. *Prog. Biophys. Biophys. Chem.*, vol. 7, pp. 255–318.

Jülicher, F.; Ajdari, A.; Prost, J. (1997): Modeling molecular motors. *Rev. Mod. Phys.*, vol. 69, pp. 1269–1281.

Kolomeisky, A. B.; Fisher, M. E. (2001): Force-velocity relation for growing microtubules. *Biophys. J.*, vol. 80, pp. 149–154.

Korn, E. D. (1982): Actin polymerization and its regulation by proteins from nonmuscle cells. *Physiol. Rev.*, vol. 62, pp. 672–737.

Kuo, S. C. (2001): Using optics to measure biological forces and mechanics. *Traffic*, vol. 2, pp. 757–763.

Kuo, S. C.; McGrath, J. L. (2000): Steps and fluctuations of *Listeria monocytogenes* during actin-based motility. *Nature*, vol. 407, pp. 1026–1029.

Mahadevan, L.; Matsudaira, P. (2000): Motility powered by supramolecular springs and ratchets. *Science*, vol. 288, pp. 95–99.

Mogilner, A.; Oster, G. (1996): Cell motility driven by actin polymerization. *Biophys. J.*, vol. 71, pp. 3030–3045.

Mogilner, A.; Oster, G. (2003): Polymer motors: pushing out the front and pulling up the back. *Curr. Biol.*, vol. 13, pp. R721–R733.

Oosawa, F.; Asakura, S. (1975): *Thermodynamics of the Polymerization of Protein*. Adademic Press, New York.

Oster, G.; Wang, H. (2003): Rotary protein motors. *Trends in Cell Biol.*, vol. 13, pp. 114–121.

Pantaloni, D.; Boujemaa, R.; Didry, D.; Gounon, P.; Carlier, M.-F. (2000): The Arp2/3 complex branches filament barbed ends: functional antagonism with capping proteins. *Nature Cell Biol.*, vol. 2, pp. 385–391.

Peskin, C.; Odell, G. M.; Oster, G. (1993): Cellular motions and thermal fluctuations: the Brownian ratchet. *Biophys. J.*, vol. 65, pp. 316–324.

Pinsky, M. A. (1991): *Lectures on Random Evolution*. World Scientific, Singapore.

Pollard, T. D.; Blanchoin, L.; Mullins, R. D. (2000): Molecular mechanisms controlling actin filaments in nonmuscle cells. *Ann. Rev. Biophys. Biomol. Struct.*, vol. 29, pp. 545–576.

Qian, H. (1998): Vector-field formalism and analysis for a class of Brownian Ratchets. *Phys. Rev. Lett.*, vol. 81, pp. 3063–3066.

Qian, H. (2000a): Single-particle tracking: Brownian dynamics of viscoelastic materials. *Biophys. J.*, vol. 79, pp. 137–143.

Qian, H. (2000b): The mathematical theory of molecular motor movement and chemomechanical energy transduction. *J. Math. Chem.*, vol. 27, pp. 219–234.

Qian, H. (2001a): Book review for *An Introduction to Chaos in Nonequilibrium Statistical Mechanics*. *Bullet. Math. Biol.*, vol. 63, pp. 597–601.

Qian, H. (2001b): Mathematical formalism for isothermal linear irreversibility. *Proc. R. Soc. A.*, vol. 457, pp. 1645–1655.

Qian, H. (2002a): Mesoscopic nonequilibrium thermodynamics of single macromolecules and dynamic entropy-energy compensation. *Phys. Rev. E.*, vol. 65, pp. 016102.

Qian, H. (2002b): Equations for stochastic macromolecular mechanics of single proteins: equilibrium fluctuations, transient kinetics, and nonequilibrium steady-state. *J. Phys. Chem. B.*, vol. 106, pp. 2065–2073.

Qian, H. (2004): A motor protein with nonequilibrium potential: its thermodynamics and efficiency. *Phys. Rev. E.*, vol. 69, pp. 012901.

Qian, H.; Raymond, G. M.; Bassingthwaighte, J. B. (1999): Stochastic fractal behaviour in concentration fluctuation and fluorescence correlation spectroscopy. *Biophys. Chem.*, vol. 80, pp. 1–5.

Qian, H.; Shapiro, B. E. (1999): A graphical method for force analysis: macromolecular mechanics with atomic force microscopy. *Prot: Struct. Funct. Genet.*, vol. 37, pp. 576–581.

Qian, H.; Sheetz, M. P.; Elson, E. L. (1991): Single-particle tracking: analysis of diffusion and flow in two-dimensional systems. *Biophys. J.*, vol. 60, pp. 910–921.

Reimann, P. (2002): Brownian motors: noisy transport far from equilibrium. *Phys. Rep.*, vol. 361, pp. 57–265.

Taylor, H. M.; Karlin, S. (1998): *An Introduction to Stochastic Modeling, 3rd Ed.* Academic Press, New York.

Theriot, J. A. (2000): The polymerization motor. *Traffic*, vol. 1, pp. 19–28.

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

van Oudenaarden, A.; Theriot, J. A. (1999): Cooperative symmetry-breaking by actin polymerization in a model for cell motility. *Nature Cell Biol.*, vol. 1, pp. 493–499.

Weiss, G. H. (1966): First passage time problems in chemical physics. *Adv. Chem. Phys.*, vol. 13, pp. 1–18.

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Appendix A: Diffusion with Drift in Semi-infinite Space with Noflux Boundary

To understand the dynamics of the gap in the continuous model, one needs to solve the time-dependent diffusion equation, Eq. 23. In nondimensionalized form:

$$u_t = u_{xx} + \omega u_x, \quad (x \geq 0), \tag{30}$$

with boundary condition $u_x + \omega u = 0$ at $x = 0$ and $x = \infty$. Surprisingly, classic texts on diffusion [Carslaw and Jaeger (1959); Crank (1975)] did not give an explicit solution to the problem. Because of its central importance in the theory of BR, we give some explicit results below. The eigenfunction of the problem associated with eigenvalue $\mu(z) = -\frac{1}{4}(\omega^2 + z^2)$ is

$$u(x,t;z) = \frac{1}{\sqrt{\pi(\omega^2+z^2)}}\left[z\cos\left(\frac{zx}{2}\right) - \omega\sin\left(\frac{zx}{2}\right)\right]$$

$$\times e^{-\frac{\omega x}{2}+\mu(z)t}, \quad (z \geq 0), \tag{31}$$

and for $\mu = 0$, $\sqrt{\omega}e^{-\omega x}$. Note there is a gap in μ between $\mu = 0$ and the continuous spectrum $\mu \leq -\omega^2/4$. The Sturm-Liouville eigenvalue problem has a complete orthonormal set

$$\int_0^\infty u(x,0;z)u(x,0,z')e^{\omega x}dx = \delta(z-z').$$

Therefore, the solution to Eq. 30 with initial data $\delta(x)$ is

$$u(x,t) = \omega e^{-\omega x} + e^{-\frac{\omega x}{2}-\frac{\omega^2 t}{4}}$$

$$\times \int_0^\infty \frac{z\,dz}{\pi(\omega^2+z^2)}\left[z\cos\left(\frac{zx}{2}\right) - \omega\sin\left(\frac{zx}{2}\right)\right]e^{-z^2t/4}, \tag{32}$$

which approaches to the exponential distribution $\omega e^{-\omega x}$ when $t \to \infty$. From Eq. 32 we have

$$\int_0^\infty u(x,t)dx = 1,$$

$$\int_0^\infty xu(x,t)dx = \frac{1}{\omega} - e^{-\frac{\omega^2 t}{4}}\int_0^\infty \frac{4z^2 e^{-z^2t/4}}{\pi(\omega^2+z^2)^2}dz$$

$$= \frac{1}{\omega}\left[(1+2\tau)erf\left(\sqrt{\tau}\right) - 2\tau + 2\sqrt{\frac{\tau}{\pi}}e^{-\tau}\right], \quad (33)$$

where $\tau = \omega^2 t/4$. The curve in the square bracket is a universal curve, we shall denote it by $1-gap(\tau)$ (Fig. 6). It is interesting to point out that there is a sharp transition between unlimited growth of x for $\omega < 0$ and a stationary state for x when $\omega > 0$ [Dogterom and Leibler (1993)]. Finally,

$$\int_0^\infty x^2 u(x,t)dx = \frac{8}{\omega^2}\int_0^\tau gap(s)ds.$$

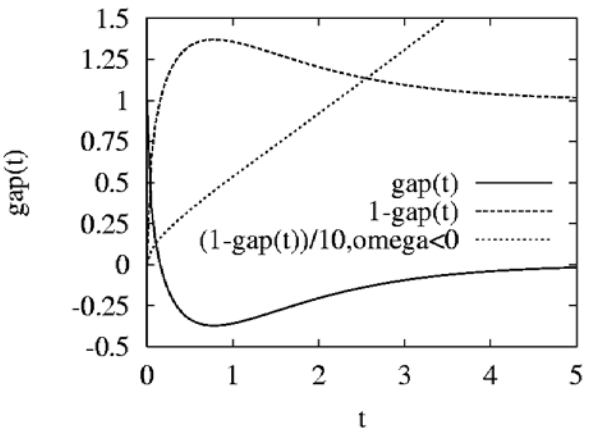

Figure 6 : The function $gap(t)$, defined in Eq. 33, is the time course for the the mean gap size to approach to its stationarity. For $\omega > 0$, the mean gap size approaches to finite size (solid line), while for $\omega < 0$, the mean gap size grows without bound (dotted line).

Appendix B: The Dynamics of Gap $\Delta(t)$ in the Discrete Model

Eq. 18 has a second boundary condition $u = 0$ at $x = \delta$, which corresponds to nondimensionalized Eq. 30 with $0 \le x \le 1$ and $u(1) = 0$. It has a set of discrete eigevalues. The eigenfunctions to the nondimensionalized Eq. 18 with eigenvalue $\mu(z) = -\frac{1}{4}(\omega^2 + z^2) \le 0$, are still given in Eq. 31, but the z's are now the discrete roots of the transcendental equation $\cos z = \frac{\omega^2 - z^2}{\omega^2 + z^2}$. When $\omega < 2$, the equation for z has only real roots; hence the largest eigenvalues is $\mu < -\omega^2/4$. If, however, $\omega > 2$, then there is a pair of imaginary $\pm iz^*$, $|z^*| < \omega$. Then the largest eigenvalue is $\mu = -\left(\omega^2 - (z^*)^2\right)/4$. Fig. 4 shows how the largest eigenvalue (smallest in magnitude) changes as functions of ω. It is seen that the largest eigenvalue can be well represented by $1/E[\mathbf{T}]$

$$\mu_1 \approx -\frac{\omega^2}{e^\omega - 1 - \omega} \quad \text{or} \quad z_1 = \omega\sqrt{\frac{4}{e^\omega - 1 - \omega} - 1}. \quad (34)$$

The solution to the time-dependent Eq. 18 with initial data $\delta(x)$ can be obtained in terms of the $u(x,t;z)$'s in Eq. 31, and approximated by the first term:

$$u(x,t) \approx \frac{z_1}{\pi(\omega^2 + z_1^2)}\left[z_1\cos\left(\frac{z_1 x}{2}\right) - \omega\sin\left(\frac{z_1 x}{2}\right)\right]$$

$$\times \exp\left(-\frac{\omega}{2}x - \frac{\omega^2 + z_1^2}{4}t\right). \quad (35)$$

Therefore,

$$\int_0^1 u(x,t)dx = \frac{2z_1}{\pi(\omega^2 + z_1^2)}e^{-\frac{\omega}{2} - \frac{\omega^2 + z_1^2}{4}t}\sin\left(\frac{z_1}{2}\right),$$

which tends to zero because the exit probability. However, the remaining probability for $\Delta(t)$ quickly approaches a quasi-stationary distribution

$$\begin{aligned} f_\Delta(x) &= \frac{z_1\cos\left(\frac{z_1 x}{2}\right) - \omega\sin\left(\frac{z_1 x}{2}\right)}{2\sin\left(\frac{z_1}{2}\right)}\exp\left(-\frac{\omega}{2}(x-1)\right) \\ &= \frac{\omega^2 + z_1^2}{2z_1}\sin\left(\frac{z_1}{2}(1-x)\right)\exp\left(\frac{\omega}{2}(1-x)\right). \end{aligned}$$

For large ω, this distribution approaches to the exponential distribution $\omega e^{-\omega x}$ as expected (data not shown).