A Stochastic Analysis of a Brownian Ratchet Model for Actin-Based Motility and Integrate-and-Firing Neurons

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Abstract. In recent single-particle tracking (SPT) measurements on *Listeria monocytogenes* motility *in vitro*, the actin-based stochastic dynamics of the bacterium movement is analyzed statistically (Kuo and McGrath, 2000). The mean-square displacement (MSD) of the detrended trajectory exhibit a linear behavior; it has been suggested that a corresponding analysis for the Brownian ratchet model (Peskin, Odell, & Oster, 1993) leads to a non-monotonic MSD. A simplified version of the Brownian ratchet, when its motion is limited by the bacterium movement, is proposed and analyzed stochastically. Analytical results for the simple model are obtained and statistical data analysis is investigated. The MSD of the stochastic bacterium movement is a quadratic function while the MSD for the detrended trajectory is shown to be linear. The mean velocity and effective diffusion constant of the propelled bacterium in the long-time limit, and the short-time relaxation are obtained from the MSD analysis. The MSD of the gap between actin and the bacterium exhibits an oscillatory behavior when there is a large resistant force from the bacterium. The stochastic model for actin-based motility is also mathematically equivalent to a model for integrate-and-firing neurons. Hence our mathematical results have applications in other biological problems. For comparison, a continuous formalism of the BR model with great analytical simplicity is also studied.

Key words: actin polymerization, exit problem, mean first passage time, nano-biochemistry, single-particle tracking, stochastic processes

1. Introduction

Actin polymerization plays an important role in nonmuscle cell mechanics, motility, and functions (Pollard et al, 2000; Pantaloni et al., 2000). In recent years, quantitative analyses of the molecular mechanism for actin-based motility are made possible by both laboratory experiments on *Listeria monocytogenes* (see van Oudenaarden and Theriot, 1999, and the references cited within) and a series of insightful mathematical models (Hill, 1981, 1987, Peskin et al., 1993, Mogilner and...
Oster 1996). The interaction between experimental observations and theoretical ideas has generated exciting research in biophysics and mathematical biology.

Following the seminal work of Peskin et al. (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 the 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 the 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 to measure the stochastic movement of L. monocytogenes propelled by actin polymerization. The seemingly random data are then analyzed statistically in terms of the mean-square displacement (MSD). The exquisite data with nanometre precision reveals the discrete steps in the bacteria movement, presumably due to the actin polymerization, one G-actin 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. Furthermore, Kuo and McGrath (2000) suggested that the BR movement, after detrending, exhibits a non-monotonic MSD. We shall investigate these practical issues as well. The significance of the stochastic interpretation is that one needs only to think about a single BR, and can derive theoretical MSD to compare with experiments.

In order to clearly present the stochastic approach to the BR, we study only a special, but relevant, case of the generic BR model proposed by Peskin et al (1993). This restriction makes the model easily analyzed analytically. Interestingly, the mathematical model is also identical to one for integrate-and-firing neuron proposed many years ago by Gerstein and Mandelbrot (1964). In recent years, integrate-and-firing model has become one of the essential components in neural modeling (Hopfield and Herz, 1995). The stochastic model is quite basic; therefore we expect that our mathematical results also have applications in other branches of mathematical biology. The fractal nature of such model has also been discussed recently (Qian et al., 1999).

All the mathematical background on stochastic processes used in this work can be found in the excellent 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 words when they first appear in the paper.

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 \( \alpha \) and the rate of depolymerization \( \beta \). \( \alpha \) is a pseudo-first order rate constant which is
proportional to the G-actin monomer concentration. Each G-actin monomer has a size of $\delta$. Hence the actin polymerization is modeled as a continuous-time random walk (Hill, 1987). We shall take the growing direction as positive, and denote the position of the tip of the actin filament by $X(t)$ which is a stochastic process taking discrete values $k\delta$, where $k$ is an integer.

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

(iii) The F-actin and the bacterium interact only when they encounter: $X(t) = Y(t)$. 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 $X(t) = Y(t)$.

(i)-(iii) are the basic assumptions of the generic BR model first proposed by Peskin et al. (1993). In the present work, we shall further assume that (iv) the $\alpha$ is sufficiently large and (v) $\beta \approx 0$. Therefore, whenever the gap $\Delta(t) \triangleq Y(t) - X(t) = \delta$, 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 $X(t)$, $Y(t)$, and $\Delta(t)$. Kuo and McGrath (2000) also introduced a detrended $Y(t)$. Let $v$ be the mean velocity of the bacterium movement $Y(t)$, then the detrend $\hat{Y}(t)$ is defined as $\hat{Y}(t) \triangleq Y(t) - vt$.

Let $\xi_k$ be the time for incorporating the $k$th G-actin monomer. Then at time $\xi_k$, $X(\xi_k) = Y(\xi_k) = k\delta$. When $t > \xi_k$, $Y(t)$ follows a Brownian motion with diffusion constant $D$, drift rate $-F/\eta_b$, and reflecting boundary at $k\delta$. $Y(t)$ moves stochastically and when it reaches $(k+1)\delta$, denoted the time by $\xi_{k+1}$, 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 $T$: $\xi_{k+1} = \xi_k + T$. This is our stochastic formalism for the BR model. Our analysis focuses on the stochastic properties of the random variable $T$.

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

$$MSD(\tau) = E \left[ (X(\tau + t) - X(t))^2 \right]$$

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, $MSD(\tau)$ is further simplified into $E \left[ (X(\tau) - X(0))^2 \right]$. In the case of a stationary process, its MSD is directly related to the correlation function:

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

(2)
The significance of MSD is that it can be obtained through a statistical analysis of stochastic experimental data (Qian et al., 1991). It is the essential link between the experimental measurements on fluctuations and stochastic mathematical models. For an experimental time series \( \{x_n | 0 \leq n \leq N \} \), the MSD is defined as:

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

The statistical relation between the experimentally determined MSD in Eq. 3 and the theoretical MSD in Eq. 1 can be found in the paper by Qian et al. (1991).

3. Basic Properties of the Model: Analytical Results

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

\[
D_b T''_{zz} - \left(\frac{F}{\eta_b} \right) T'_z = -1
\] (4)

with boundary conditions \( T'_z(0) = 0 \) and \( T(\delta) = 0 \). Hence

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

Therefore,

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

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

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

\[
D_b \frac{\partial^2 Q_T(z, \nu)}{\partial z^2} - \left(\frac{F}{\eta_b} \right) \frac{\partial Q_T(z, \nu)}{\partial z} = \nu Q_T(z, \nu)
\] (7)

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

Eq. 6 can be analytically solved:

\[
Q_T(0, \nu) = \frac{\lambda_- - \lambda_+}{\lambda_- e^{\lambda_+ \delta} - \lambda_+ e^{\lambda_- \delta}}
\] (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

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

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

\[
Q_T(0, \nu) = \left( \cosh \sqrt{\frac{\delta^2 \nu}{D_b}} \right)^{-1}. \quad (10)
\]

**Renewal Processes, The Statistical Properties of \( X(t) \) and \( Y(t) \).** With \( T \) as the waiting time, the tip of the rapid growing actin filament, \( X(t) \), is a renewal process. There is a large literature on this subject. The most relevant result to our model is the elementary renewal theorem for large \( t \)

\[
E[X(t)] \approx \frac{\delta}{E[T]} t \quad (11)
\]

Therefore as a renewal process, a BR executes successive steps with size \( \delta \) and average time \( E[T] \). The mean velocity of the BR, thus, is

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

This result is in agreement with that of Peskin et al. (1993).

Furthermore from the theory of renewal process (Taylor and Karlin, 1998)

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

where, according to Eqs. \( 6 \) and \( 9 \),

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

The MSD for \( X(t) \), therefore, is

\[
E \left[ (X(t) - X(0))^2 \right] \approx \sigma^2 t + (vt)^2 \quad (15)
\]

which is a quadratic function of \( t \). The expression for \( \sigma^2 \) is a new result of the present work, which is comparable with experimental data. Fig. 3 shows the dependence of \( v \) and \( \sigma^2 \) as functions of \( \omega = F \delta/\eta_b D_b \), the resistant force from the bacterium. If \( \omega = 0 \), then \( v = 2D_b/\delta \) and \( \sigma^2 = 14D_b/3 \).

Since \( Y(t) - X(t) < \delta \) while both increase linearly with \( t \), for large \( t \) \( Y(t) \approx X(t) \) with an error less than \( \delta \), the size of a single actin monomer. Strictly speaking, the \( Y(t) \) 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 \( Y(t) \) within each “step”, see the section below on the gap.
**Detrend \( Y(t) \) and Its Statistical Properties.** In the recent experimental work (Kuo and McGrath, 2000), the detrended \( Y(t) \) has also been reported, which can be defined as \( \dot{Y}(t) \triangleq Y(t) - vt \), where \( v \) is the mean velocity. For \( n\delta \leq Y(t) \leq (n+1)\delta \),

\[
\dot{Y}(t) \triangleq Y(t) - vt = Y(t) - Y(\xi_n) + n\delta - v\xi_n - v(t - \xi_n) = Y(\tau) - v\tau + n\delta - v\xi_n
\]

(16)
in which random variable \( \xi_n \) is the time for \( Y(t) \) to reach \( n\delta \) the first time, \( \tau = t - \xi_n \), and \( v \) is given in Eq. 12. Hence, \( 0 \leq \tau \leq \xi_{n+1} - \xi_n = \xi_1 = T \), with its expectation, variance, and characteristic function given in Eqs. 6, 9, and 8, respectively.

The statistical properties of \( \dot{Y}(t) \) are readily to be calculated:

\[
E\left[ \dot{Y}(t) \right] = E\left[ Y(\tau) \right] - v\tau \approx 0,
\]

(17)

\[
Var\left[ \dot{Y}(t) \right] = Var\left[ Y(\tau) \right] + nvVar\left[ T \right] \approx \sigma^2 t.
\]

(18)

Thus, we see that the detrend \( \dot{Y}(t) \) 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.

**Statistical Properties of the Gap.** The gap between the bacteria, \( Y(t) \), and the tip of the actin filament \( X(t) \), \( \Delta(t) \triangleq Y(t) - X(t) \) behaves completely different from the detrend \( \dot{Y}(t) \). 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 (\( \mu \)) of the diffusion operator

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

(19)

under the boundary condition \( D_b u'(0) + (F/\eta_b)u(0) = u(\delta) = 0 \). See Appendix for details. All the eigenvalues are real and \( \leq 0 \), \( \mu(z) = -\frac{D_b}{\eta_b}(z^2 + \omega^2) \), 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. 4). After normalized by \( 2Var[\Delta] \), the MSD are approximately the same for \( 0 \leq \omega \leq 6 \). The correlation time decreases with \( \omega \) for \( \omega = 2, 4, 6, \) and 12 (i.e., \( p = 0.55, 0.6, 0.65, \) and 0.8), corresponding to the second largest eigenvalue in Fig. 4.

When there is a large resistant force \( F \), the exit time \( \tau \) 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.

4. An Analytical Analysis of a Continuous Stochastic Formalism of BR
We can replace the assumptions (iv) and (v) in the Section 2 with a continuous model for the discrete polymerization. In other word, we approximate the random walk by a diffusion with diffusion constant and drift rate (Feller, 1957; Hill, 1987):

\[ D_a = (\alpha + \beta)\delta^2 / 2, \quad V_a = (\alpha - \beta)\delta. \]  

where \( \beta \) and \( \alpha \) are first-order and pseudo-first-order rate constants for the depolymerization and polymerization, \( \delta \) is the size of a G-actin monomer. The dynamic equation governing the probability density function (pdf) \( P_X(x, t) \) for the stochastic processes \( X(t) \) is:

\[
\frac{\partial P_X(x, t)}{\partial t} = D_a \frac{\partial^2 P_X(x, t)}{\partial x^2} - V_a \frac{\partial P_X(x, t)}{\partial x} \quad (20)
\]

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

\[
\frac{\partial P_Y(y, t)}{\partial t} = D_b \frac{\partial^2 P_Y(y, t)}{\partial y^2} + \frac{F}{\eta_b} \frac{\partial P_Y(y, t)}{\partial y}. \quad (22)
\]

These two equations are coupled since \( X \leq Y \). We call Eqs 20, 21, and 22 the continuous formalism for the BR. It represents a two-dimensional diffusion in the triangle region of \( x \leq y \):

\[
\frac{\partial P_{XY}(x, y, t)}{\partial t} = D_a \frac{\partial^2 P_{XY}(x, y, t)}{\partial x^2} + D_b \frac{\partial^2 P_{XY}(x, y, t)}{\partial y^2} - V_a \frac{\partial P_{XY}(x, y, t)}{\partial x} + \frac{F}{\eta_b} \frac{\partial P_{XY}(x, y, t)}{\partial y}. \quad (23)
\]

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

\[
\Delta = Y - X, \quad Z = \frac{D_a Y + D_b X}{D_a + D_b} \quad (24)
\]

where \( \Delta \) represents the gap between the tip of the actin filament and the bacterium, \( Z \) represents an averaged position of \( X \) and \( Y \), we shall call it the center of mass of the BR. With this transformation, the two differential equations are decoupled:

\[
\frac{\partial P_{\Delta}(\Delta, t)}{\partial t} = (D_a + D_b) \frac{\partial^2 P_{\Delta}(\Delta, t)}{\partial \Delta^2} + \left( V_a + \frac{F}{\eta_b} \right) \frac{\partial P_{\Delta}(\Delta, t)}{\partial \Delta}, \quad (\Delta \geq 0) \quad (25)
\]

\[
\frac{\partial P_Z(z, t)}{\partial t} = \frac{D_a D_b}{D_a + D_b} \left( \frac{\partial^2 P_Z(z, t)}{\partial z^2} \right) - \frac{D_b V_a - D_a F / \eta}{D_a + D_b} \left( \frac{\partial P_Z(z, t)}{\partial z} \right) \quad (-\infty < z < +\infty). \quad (26)
\]

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

\[
P_{\Delta}(\Delta) = \frac{V_a + F / \eta_b}{D_a + D_b} e^{-\left( \frac{V_a + F / \eta_b}{D_a + D_b} \right) \Delta}, \quad \Delta \geq 0. \quad (27)
\]

\( Z \) however increases steadily with an effective diffusion constant \( D_z = \frac{1}{D_a} + \frac{1}{D_b} \), and a mean velocity \( V_z = \frac{D_a V_a - D_b F / \eta_b}{D_a + D_b} \). 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

\[
V_z = \frac{D_z F_z}{k_B T} = \frac{D_a D_b}{D_a + D_b} \left( \frac{V_a}{D_a} - \frac{F}{k_B T} \right) = \frac{D_b V_a - D_a F / \eta_b}{D_a + D_b}.
\] (28)

The parameter \( D_a \) and \( V_a \) are defined in terms of the \( \alpha, \beta, \) and \( \delta \) in Eq. 21. \( \alpha \) 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 \( \Delta \) being greater than \( \delta \). Therefore, \( \alpha \) is a function of external force \( F \); it can be determined in a self-consistent manner by the transcendental equation:

\[
\alpha(F) = \alpha_0 c_0 \int_{\delta}^{\infty} P_{\Delta}(s) ds = \alpha_0 c_0 \exp \left[ -\frac{(\alpha - \beta)\delta + F / \eta_b}{(\alpha + \beta)\delta^2 / 2 + D_b \delta} \right]
\] (29)

where \( \alpha_0 \) is the intrinsic, second-order rate constant for polymerization. We see that \( V_z \) in Eq. 28 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. 23 has the general form \( \alpha(F) \propto e^{-r F \delta / k_B T} \) with an entropic barrier.

\( V_z \) in Eq. 28 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 et al. (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.

We now show that in the limit of \( \delta \to 0 \), our \( V_z \) from the continuous model is equivalent to the ratchet velocity derived by Peskin, Odell, and Oster (POO, 1993). Note that in the previous work the definition for the ratchet velocity was rather convoluted; The \( V_z \) in the present model is more

\[ [\alpha(F) - \beta(F)] \delta = \left( \alpha(0) e^{-r F \delta / k_B T} - \beta(0) e^{(1-r) F \delta / k_B T} \right) \delta. \] (30)

With very small \( \delta \), this gives \( [\alpha(0) - \beta(0)] \delta - F \delta^2 \left[ r \alpha(0) + (1-r) \beta(0) \right] / k_B T \) which should be compared with \( V_z = (\alpha - \beta) \delta - F \delta^2 (\alpha + \beta) / 2 k_B T \) from the main text. 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. 21 is the starting point of the recent work of Kolomeisky and Fisher (2001).
straightforward. From Eq. 20 we have \( \alpha = \frac{1}{2} \left( \frac{V_a}{\delta} + \frac{2D_a}{\delta^2} \right) \) and \( \beta = \frac{1}{2} \left( -\frac{V_a}{\delta} + \frac{2D_a}{\delta^2} \right) \). Substituting these two expressions 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

\[
\lim_{\delta \to 0} V_{poo} = V_a - \frac{D_a}{\delta} \int_{0}^{\delta} P_\Delta(\Delta) d\Delta = V_a - D_a P_\Delta(0) = \frac{D_b V_a - D_a F/\eta_b}{D_a + D_b} = V_z.
\]

In the derivation we have used Eq. [27]. Note that the basic molecular parameters for polymerization, \( \alpha, \beta \) and \( \delta \) 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 \( \alpha \) 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 McGarth, 2000) have shown that the bacteria move with steps. Considering there are many actin filaments in a bundle which propels a bacterium, this observation indicates a synchronized filamental 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 suspect, 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 \( \eta_b \). A bacterium could have an internal mechanism, by utilizing 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 proposed here is in fact our initial step to extend 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 filamental 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 processes. It turns out that both molecular processes have a single, unified mathematical model which accounts for their chemomechanical energy transduction.

Theoretical formalism for motor proteins are now well established (see Jülicher et al., 1997; Qian, 2000b, and references cited within). 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 one on polymerization with nucleotide hydrolysis proposed by Dogterom and Leibler (1993). Both models addressed the important issue of nucleotide hydrolysis, but neglected the stochastic nature in the movement of motor protein and actin polymerization, respectively. Without the diffusion term, such mathematical model is known as random evolution (Pinsky, 1991).

With the ATP cap and hydrolysis, the model for the stochastic dynamics of actin polymerization will be precisely in the same class of the models for single motor proteins (S.-D. Liang, G. Martinez, G.M. Odell, and H. Qian, work in progress). The experimental measurements on both systems also proceed with parallel paths, as demonstrated by Dogterom and Yurke (1997), and more recently Kuo and McGrath (2000). Similar to the measurements on load-velocity curves for motor proteins, Dogterom and Yurke 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).

All these experimental evidences indicate that the class of BR model (or augmented Huxley 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, 2000b, 2001a,b,c). 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 forces in cell biology.

To mathematical biologists, BR is a class of models which is based on a similar physical model but can have many different mathematical representations and different 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

\[ D_z = \frac{(\alpha + \beta)\delta^2 D_b/2}{D_b + (\alpha + \beta)\delta^2/2} \rightarrow D_b \]

when \( \alpha \rightarrow \infty \), and the BR velocity

\[ V_z = \frac{D_b(\alpha - \beta)\delta - D_b(\alpha + \beta)\delta \omega/2}{D_b + (\alpha + \beta)\delta^2/2} \rightarrow (D_b/\delta)(2 - \omega) \]

is a linear force-velocity relationship.

|            | \( D_z/D_b \) | \( V_z\delta/D_b \) |
|------------|----------------|----------------------|
| discrete model | \( \frac{3\omega^2-(10\omega-6)e^\omega+\omega^2-2\omega-9}{(e^\omega-1-\omega)^3} \omega^2 \) | \( \frac{\omega^2}{e^\omega-1-\omega} \) |
| 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 \( \alpha \). This explains why there is no critical force in Fig. 3, at which the velocity \( v = 0 \). The more realistic model with finite \( \alpha \) and \( \beta \) does lead to a finite, positive stalling force (Peskin et al., 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 as 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, 2001c), in the latter rather than the usual equilibrium. Thus, the BR model is also a natural generalization of the standard polymer theory for passive materials (Doi and Edward, 1986) to active materials for which T.L. Hill (1987) has coined the term “steady-state polymer”. There is a continuous intellectual thread in all these mathematical theories.

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8. Appendix

**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. 25. In nondimensionalized form:

\[ u_t = u_{xx} + \omega u_x, \quad (x \geq 0), \quad \text{(31)} \]

with boundary condition \( u_x + \omega u = 0 \) at \( x = 0 \) and \( x = \infty \). Amazingly, 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 the eigenvalue \( \mu(z) = -\frac{1}{4}(\omega^2 + z^2) \) is

\[ u(x, t; z) = \frac{1}{\sqrt{\pi(\omega^2 + z^2)}} \left[ z \cos \left( \frac{zx}{2} \right) - \omega \sin \left( \frac{zx}{2} \right) \right] e^{-\frac{\omega^2 t}{4} + \mu(z)t}, \quad (z \geq 0), \quad \text{(32)} \]

and for \( \mu = 0 \), \( \sqrt{\omega} e^{-\omega x} \). Note there is a gap in \( \mu \) 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. (31) with initial data \( \delta(x) \) is

\[ u(x, t) = \omega e^{-\omega x} + e^{-\frac{\omega^2 t}{4}} \int_0^\infty \frac{zdz}{\pi(\omega^2 + z^2)} \left[ z \cos \left( \frac{zx}{2} \right) - \omega \sin \left( \frac{zx}{2} \right) \right] e^{-z^2t/4}, \quad \text{(33)} \]

which approaches to the exponential distribution \( \omega e^{-\omega t} \) when \( t \to \infty \). From Eq. (33) we have

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

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

\[ = \frac{1}{\omega} \left[ (1 + 2\tau) \text{erf} \left( \sqrt{\tau} \right) - 2\tau + 2\sqrt{\frac{\tau}{\pi}} e^{-\tau} \right], \quad \text{(34)} \]

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

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

**The Dynamics of Gap \( \Delta(t) \) in the Discrete Model.** Eq. 19 has a second boundary condition \( u = 0 \) at \( x = \delta \), which corresponds to nondimensionalized Eq. 31 with \( 0 \leq x \leq 1 \) and
\( u(1) = 0 \). It has a set of discrete eigenvalues. The eigenfunctions to the nondimensionalized Eq. 19 with eigenvalue \( \mu(z) = -\frac{1}{4}(\omega^2 + z^2) \leq 0 \), are still given in Eq. 32, 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 \( \mu = -\frac{(\omega^2 - (z^*)^2)}{4} \). Fig. 4 shows how the largest eigenvalue (smallest in magnitude) changes as functions of \( \omega \). It is seen that the largest eigenvalue can be well represented by \( 1/E[T] \)

\[
\mu_1 \approx -\frac{\omega^2}{e^{\omega - 1} - \omega} \quad \text{or} \quad z_1 = \omega \sqrt{\frac{4}{e^{\omega - 1} - \omega} - 1}.
\]

(35)

The solution to the time-dependent Eq. 19 with initial data \( \delta(x) \) can be obtained in terms of the \( u(x, t; z) \)'s in Eq. 32 and approximated by the first term:

\[
u(x, t) \approx \frac{z_1}{\pi(\omega^2 + z_1^2)} \left[ z_1 \cos \left( \frac{z_1 x}{2} \right) - \omega \sin \left( \frac{z_1 x}{2} \right) \right] \exp \left( -\frac{\omega^2 x}{2} - \frac{z_1^2 t}{4} \right).
\]

(36)

Therefore,

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

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

\[
f_\Delta(x) = \frac{z_1 \cos \left( \frac{z_1 x}{2} \right) - \omega \sin \left( \frac{z_1 x}{2} \right)}{2 \sin \left( \frac{z_1}{2} \right)} \exp \left( -\frac{\omega}{2}(x - 1) \right)
\]

\[
= \frac{\omega^2 + z_1^2}{2z_1} \sin \left( \frac{z_1}{2}(1 - x) \right) \exp \left( \frac{\omega}{2}(1 - x) \right).
\]

For large \( \omega \), this distribution approaches to the exponential distribution \( \omega e^{-\omega x} \) as expected (data not shown).
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, $\Delta(t) \triangleq Y(t) - X(t)$, the gap, and $\hat{Y}(t)$, the detrended $Y(t)$. 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 et al., 1990).
Figure 2: The MSD calculated for the four types of data in Fig. 1. $Y(t)$, the movement of the bacterium, $X(t)$, the movement of the tip of the actin filament, $\Delta(t)$, the gap, and the detrend $\hat{Y}(t)$. As expected, after a brief period of time, the $Y(t)$ and $X(t)$ are almost indistinguishable; the gap between them quickly reaches stationarity. The detrend $\hat{Y}(t)$ shows a linear MSD, as observed in the experiments (Kuo and McGarth, 2000).
Figure 3: The velocity $v\delta/D_b$ and MSD $\sigma^2/D_b$, 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 $\sigma^2$ can be obtained either as the linear term in the MSD of $Y(t)$, or the MSD of the detrend $\hat{Y}(t)$. The velocity $v$ is given in Eq. [12] and the $\sigma$ is given in Eq. [14].
Figure 4: Numerical computation for the three smallest eigenvalues (in magnitude, all eigenvalues are negative) of Eq. $\frac{\mu \delta^2}{D_b}$, as function of the resistant force $\omega$. 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 $D_b/\delta^2 = 0.005$. $0 \leq \Delta(t) \leq 1$; the stationary $E[\Delta] = 0.33, 0.27, 0.21, 0.16, \text{and } 0.08$ for $p = 0.5 - 0.8$ respectively; the corresponding relative variances $Var[\Delta]/E^2[\Delta] = 0.53, 0.64, 0.79, 0.91, \text{and } 0.96$. The relative variance for an exponential distribution is 1.
Figure 6: The function $\text{gap}(t)$, defined in Eq. \ref{eq:gap}, is the time course for the mean gap size to approach to its stationarity. For $\omega > 0$, the mean gap size approaches to a finite size, while for $\omega < 0$, the mean gap size grows without bound.