A Model of Anomalous Chain Translocation Dynamics†

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A model of polymer translocation based on the stochastic dynamics of the number of monomers on one side of a pore-containing surface is formulated in terms of a one-dimensional generalized Langevin equation, in which the random force is assumed to be characterized by long-ranged temporal correlations. The model is introduced to rationalize anomalies in measured and simulated values of the average time of passage through the pore, which in general cannot be satisfactorily accounted for by simple Brownian diffusion mechanisms. Calculations are presented of the mean first passage time for barrier crossing and of the mean square displacement of a monomeric segment, in the limits of strong and weak diffusive bias. The calculations produce estimates of the exponents in various scaling relations that are in satisfactory agreement with available data.

1. Introduction

A number of the most important processes that occur in living cells, including gene transfer,[1] the movement of RNA through the nuclear pore complex,[2] DNA packaging in viral capsids,[3] and the uptake of oligonucleotides by membrane proteins,[4] involve the passage of polymers from one side of a barrier to another through nanometer-sized pores. The dynamics of such processes, which are governed, among other things, by steric effects, hydrodynamic and electrostatic interactions, and geometrical constraints, are generally quite complex, and for the most part remain poorly understood. Although a great deal of information about chain translocation has been generated by single-molecule experiments,[5] numerical simulations,[6] and analytical theories,[7–10] not all of the findings can be satisfactorily reconciled with existing models of confined polymer dynamics.

In particular, it is becoming increasingly clear that the motion of a polymer through a pore, whether free or driven, is anomalous,[11,12] meaning that properties such as average displacements and mean crossing times, vary as nonclassical powers of the time, the molecular weight, or other parameters. Some of these anomalies can be rationalized by scaling arguments,[13] but a fuller understanding of their microscopic origins requires less phenomenological approaches. One such approach, developed by Sung and Park,[8] replaces the many-body dynamics of a sequence of N interacting monomers by the dynamics of a single one-dimensional variable x that moves stochastically over a free energy barrier. The variable x is a measure of the progress made by the polymer in passing from one to the other side of a surface of negligible thickness through an opening that accommodates no more than a single monomer at a time; x is therefore effectively the number of monomers on a given side of the surface. This number changes randomly in time as a result of the thermal fluctuations in the medium that drive the chain to one or other side of the pore. The free energy barrier is a measure of the extent to which the surface prevents free movement of the polymer. The resemblance of this model to Kramer's model of chemical reaction dynamics[14] is obvious.

By treating the thermal fluctuations in their model as white noise, Sung and Park were able to show that, in the absence of a chemical potential difference $\Delta\mu$ between the two sides of the barrier, the mean translocation time $\bar{t}$ scaled as $N^2/D(N)$, where N is the length of the chain, and $D(N)$ is the diffusion coefficient, which was assumed to vary either as $N^{-1/2}$ (when hydrodynamic interactions are present), or as N^{-1} (when they are absent.[8]) They also showed that, in the presence of a large chemical potential difference, the scaling of $\bar{t}$ was modified to $\exp(N\Delta\mu/k_BT)/(\Delta\mu)^2D(N)$. Under conditions where the chemical potential difference and the hydrodynamic interaction both vanish, therefore, these results lead to the same N^3 dependence of $\bar{t}$ that characterizes the disentanglement time of a polymer in the melt.[15] However, in an extension of the Sung−Park model developed by Muthukumar[9] in which D is interpreted as the diffusion coefficient of a monomer, $\bar{t}$ was predicted to scale as N^2 (for unbiased translocation) and as $N/\Delta\mu$ (for biased translocation).

However, the time t_R for an *unconfined* Rouse chain to diffuse a distance on the order of its length also scales as N^2, so it would be counterintuitive for $\bar{t}$ (in the case of unbiased translocation) to scale the same way. In fact, these simple scaling predictions are widely contradicted by results from simulations. The 2-D lattice simulations of Kardar et al.,[12] for instance, indicate that $\bar{t} \sim N^{2.5}$ for unbiased translocation, and that $\bar{t} \sim N^{1.53}/\Delta\mu$ for driven translocation. In three dimensions, Wolterink et al.[16] find that $\bar{t}$ (or, more accurately, $\bar{t}_d$, the mean residence time of the chain in the pore) scales as $N^{2.4 \pm 0.05}$ for unbiased translocation, while Vocks et al.[17] find that $\bar{t}_d \sim N^{1.37}/E$ for translocation in the presence of a field E. The 3-D simulations of Dubbledam et al.[13] likewise yield the following scaling results: $\bar{t} \sim N^{2.52 \pm 0.04}$ ($\Delta\mu = 0$) and $\bar{t} \sim N^{1.5}/\Delta\mu$ ($\Delta\mu \neq 0$). All these findings seem to rule out simple Brownian motion of x over a barrier as an explanation of these chain transport processes. The observation of long-tail memory effects in experimentally determined distributions of crossing times of single molecules of DNA and RNA through nanometer-sized pores[5] is similarly inconsistent with a Brownian diffusion mechanism.

Two models of chain translocation dynamics have recently been formulated that go beyond this simple mechanism. Both

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ascribe the anomalies in the diffusion process to memory effects. In the model of Ball et al.,[18] these effects are assumed to originate in the imbalance in the monomer densities on either side of the pore, which gives rise to an effective tension along the backbone that opposes the natural tendency of the chain to move in a given direction. Scaling considerations then suggest that $\bar{t}_d \sim N^{2+\nu}$ in the absence of a field, and that $\bar{t}_d \sim N^{(1+2\nu)/(1+\nu)}/E$ in the presence of a field, with ν being the Flory exponent (equal to 0.588 in three dimensions). These predictions are, for the most part, consistent with the available numerical data, but the mechanism that underlies the occurrence of non-Markovian statistics in the pore-crossing process, though physically appealing, does not seem to be amenable to more than a semiphenomenological kind of treatment.

In the model of Dubbeldam et al.,[13] on the other hand, the translocation coordinate x is assumed to evolve by *fractional*,[19] rather than by Brownian, diffusion, and here, the memory effects originate in the power law waiting time distribution that governs the underlying equations of motion. This model predicts the scaling behavior $\bar{t} \sim N^{2/\alpha}$ for force-free translocation, and the behavior $\bar{t} \sim N^{(2/\alpha)-1}/\Delta\mu$ for translocation in the presence of a chemical potential difference, with α being a parameter that can be expressed in terms of the Flory exponent ν and a surface exponent γ_1 (equal to 0.680). In three dimensions, $\alpha = 0.801$, so $\bar{t} \sim N^{2.496}$ (when $\Delta\mu = 0$) and $\bar{t} \sim N^{1.496}$ (when $\Delta\mu \neq 0$); these results are also in agreement with data from simulations. A further prediction of the model, that the dynamics of x, as characterized by its mean square displacement, $\langle \delta x(t)^2 \rangle$, is subdiffusive, is also quantitatively supported by numerical data.

However, it is not entirely clear that these results validate the use of fractional diffusion equations in the description of anomalous translocation dynamics, since these equations are based on power law waiting time distributions,[19] which having no first moment, lead to mean first passage times that are generally not well-defined[11,20] (although that problem can be overcome by the use of other forms of the waiting time distribution). Indeed, in the calculations of ref 13, the results for $\bar{t}$ are obtained by integrating the associated crossing time distribution over a finite rather than the required infinite time interval. Also, fractional diffusion equations cannot always be relied on to provide accurate estimates of other properties, as was recently demonstrated by the discrepancies between the calculated and measured values of three and higher order time correlation functions of the distance fluctuations in single protein molecules.[21]

Some of these problems can be circumvented by the use of an approach based on the generalized Langevin equation (GLE); in combination with a noise source that is Gaussian with power law correlations, this approach leads, in general, to well-defined expressions for various quantities of physical interest, and several examples of its application have been reported,[22] including successful fits to the same experimentally measured multitime single-molecule distance correlation functions that the fractional diffusion model failed to reproduce.[21] The GLE approach has proved to be especially effective in characterizing subdiffusive motion, and is therefore naturally suited to the study of anomalous transport. The present paper describes our efforts to use this approach to develop a model of chain translocation.

These efforts center around a generalized Smoluchowski equation to which the above GLE can be transformed. Details of the transformation are described in the Appendix, while the Smoluchowski equation itself and its solutions in various limits are presented in Section 2 below. The solutions are used in Section 3 to calculate the waiting time distribution for pore crossing and the associated mean first passage time, while the GLE is used in Section 4 to calculate the mean square displacement of a chain segment. Section 5 critically reviews the results of these calculations.

2. Model of Chain Translocation Dynamics.

A. The GLE and Smoluchowski Equations. Following Sung and Park,[8] we assume that the many-body dynamics of the polymer as it traverses a pore can be reduced to the dynamics of the *number* of monomers x on one side of the pore, which changes in discrete steps whenever a single monomer crosses from one side to the other. This process occurs randomly, being driven by the thermal fluctuations of the medium. Treating x as a continuous variable, one can model its time evolution by the stochastic motion of a particle (of mass m, say) undergoing diffusion in a potential $U(x)$. As shown by Sung and Park,[8] the potential in this instance can be identified with the free energy barrier generated by the reduction (in relation to the unconfined polymer) of the number of conformations resulting from the presence of a surface. When a chemical potential difference $\Delta\mu$ (per unit length of the chain) exists between the two sides of the barrier, the dominant term in this free energy, in the long chain limit, is linear in x, and $U(x)$ can then be approximated by $-x\Delta\mu$. Furthermore, since it is known that Brownian diffusion in this potential does not lead to the observed anomalies in the translocation dynamics, we shall assume that the thermal fluctuations that change x are described by colored rather than by white noise. Under these conditions, the equation for x is a GLE:

$$m\frac{d^2x(t)}{dt^2} = -\zeta\int_0^t dt'\, K(t-t')\dot{x}(t') - \frac{dU(x)}{dx} + \theta(t) \quad (1)$$

Here, ζ is the friction coefficient of the particle, and $K(t)$ is a memory function, which is related to the statistics of the random variable $\theta(t)$ by the fluctuation–dissipation theorem, i.e., $K(|t-t'|) = (1/\zeta k_B T)\langle \theta(t)\theta(t') \rangle$, with the angular brackets denoting an average over all realizations of the noise. In these calculations, we shall choose the noise to correspond to the process referred to as fractional Gaussian noise (fGn).[23] This choice is motivated by the success of fGn in characterizing subdiffusive phenomena in single-molecule protein dynamics,[21] but it is by no means limited to fGn, and other choices can be treated as well. With $\theta(t)$ given by fGn, $K(t)$ becomes $2H(2H-1)|t-t'|^{2H-2}$, where H, the Hurst index, is a real number lying between 1/2 and 1 that is a measure of the temporal correlations in the noise.

First passage time distributions and mean first passage times for crossing the pore can be calculated once eq 1 is transformed to an equivalent equation for the probability density $P(x,t)$ that the particle is at x at time t. As shown in the Appendix, the requisite equation (a Smoluchowski-type equation) has the form

$$\frac{\partial P(x,t)}{\partial t} = A(t)\left[-\frac{\Delta\mu}{m}\frac{\partial}{\partial x} + \frac{k_B T}{m}\frac{\partial^2}{\partial x^2}\right]P(x,t) \quad (2)$$

Here $A(t)$ is an effective time-dependent diffusion coefficient defined as $A(t) = \int_0^t dt' \xi(t')$, with $\xi(t)$ being the inverse Laplace transform of the function $\hat{\xi}(s) \equiv 1/(s + \zeta\hat{K}(s)/m)$, and $\hat{K}(s)$ being the Laplace transform of the memory kernel $K(t)$. For the power law form of $K(t)$ above, $\hat{K}(s) = \Gamma(2H+1)/s^{2H-1}$, and the inverse of $\hat{\xi}(s)$ is then easily found to be $\xi(t) = E_{2H}(-(t/\tau)^{2H})$, where $E_a(z) \equiv \sum_{k=0}^{\infty} z^k/\Gamma(ak+1)$ is the Mittag−Leffler function,[24] and τ is a decay constant defined as $(m/\zeta\Gamma(2H+1))^{1/2H}$. Using results derived by Viñales and Despósito,[25] the diffusion coefficient $A(t)$ and its integral $\int_0^t dt' A(t')$ (which will be needed

later) can now be calculated; they are given by

$$A(t) = tE_{2H,2}(-(t/\tau)^{2H}) \tag{3a}$$

and

$$\int_0^t dt' A(t') = t^2 E_{2H,3}(-(t/\tau)^{2H}) \tag{3b}$$

where $E_{a,b}(z) \equiv \sum_{k=0}^{\infty} z^k/\Gamma(ak + b)$ is the generalized Mittag−Leffler function.

B. Solution of the Smoluchowski Equation. Equation 2 may be solved by the method of separation of variables using the function

$$P(x, t) = P_{\lambda_n}(x)\exp(-\lambda_n \int_0^t dt' A(t')) \tag{4}$$

where λ_n is an eigenvalue, and $P_{\lambda_n}(x)$ is an eigenfunction satisfying

$$\left[-\frac{\Delta\mu}{m}\frac{\partial}{\partial x} + \frac{k_B T}{m}\frac{\partial^2}{\partial x^2} + \lambda_n\right] P_{\lambda_n}(x) = 0 \tag{5}$$

which is solved, in general, by

$$P_{\lambda_n}(x) = \exp(fx/2)\left[C_1 \cos\sqrt{\kappa_n}x + C_2 \sin\sqrt{\kappa_n}x\right] \tag{6}$$

where C_1 and C_2 are constants, $f = \Delta\mu/k_B T$, and $\kappa_n = \lambda_n/k - f^2/4$, with $k = k_B T/m$.

The solution of eq 2 under the initial condition $P(x,0) = \delta(x - x_0)$ can be expressed as the expansion[26]

$$P(x, t|x_0, 0) = \sum_n \frac{1}{P_s(x_0)} P_{\lambda_n}(x) P_{\lambda_n}(x_0) \exp(-\lambda_n \int_0^t dt' A(t')) \tag{7}$$

where $P_s(x)$ is the solution of eq 2 satisfying $\partial P(x,t)/\partial t = 0$, and is given by $P_s(x) = C_3 \exp(fx)$, with C_3 another constant.

Distribution functions relevant to chain translocation are obtained from eq 7 by the application of suitable boundary conditions. Since the polymer is imagined to start from one side of the pore and then pass through it when the number of monomers equals N, these boundary conditions can be taken to correspond to a vanishing current at the chain origin and a vanishing probability at the chain end; in other words, $\partial P(x,t)/\partial x|_{x=0} = 0$ and $P(x = N,t) = 0$, respectively, and they lead to the following transcendental equation for the eigenvalues:[13]

$$-2\frac{\sqrt{\kappa_n}}{f} = \tan(\sqrt{\kappa_n}N) \tag{8}$$

These eigenvalues cannot be found in closed form for arbitrary f, but reasonable approximations can be obtained in two limiting cases: one, the limit $fN \to 0$ (corresponding to the absence of a chemical potential difference between the two sides of the pore), and the other, the limit $fN \gg 1$ (corresponding to a large chemical potential difference between the two sides of the pore.) The expressions for λ_n in these limits are:

$$\lambda_n = \frac{(2n+1)^2\pi^2 k}{4N^2}, \quad fN \to 0 \tag{9a}$$

and

$$\lambda_n = k\left[\frac{f^2}{4} + \frac{n^2\pi^2}{N^2}\right], \quad fN \gg 1 \tag{9b}$$

The corresponding eigenfunctions can then be written as

$$P_{\lambda_n}(x) = \sqrt{\frac{2}{N}}\cos\left[\frac{(2n+1)\pi x}{2N}\right], \quad fN \to 0 \tag{10a}$$

and

$$P_{\lambda_n}(x) = \sqrt{\frac{2}{N}}\exp\left(\frac{fx}{2}\right)\sin\left[\frac{n\pi x}{N}\right], \quad fN \gg 1 \tag{10b}$$

so the complete time-dependent solutions become

$$P(x, t|x_0, 0) = \frac{2}{N}\sum_{n=0}^{\infty} \cos\left[\frac{(2n+1)\pi x}{2N}\right]\cos\left[\frac{(2n+1)\pi x_0}{2N}\right] \times \exp\left[-\lambda_n \int_0^t dt' A(t')\right], \quad fN \to 0 \tag{11a}$$

and

$$P(x, t|x_0, 0) = \frac{2}{N}e^{f(x-x_0)/2}\sum_{n=0}^{\infty} \sin\left[\frac{n\pi x}{N}\right]\sin\left[\frac{n\pi x_0}{N}\right] \times \exp\left[-\lambda_n \int_0^t dt' A(t')\right], \quad fN \gg 1 \tag{11b}$$

Equations 11a and 11b differ from the corresponding expressions for $P(x,t|x_0,0)$ in ref 13 only in the nature of the time-dependent factor. In ref 13, this factor is just the Mittag−Leffler function itself; here it is the *exponential* of a generalized Mittag−Leffler function. The difference is central to the question of whether $\bar{t}$ is well-defined or not.

3. First Passage Time Distribution and Mean First Passage Time. Given the probability distribution of x at time t (under the condition that no monomers have passed through the pore at time $t = 0$, so that $x_0 = 0$), one can calculate the normalized waiting time distribution $f(t)$ as[26]

$$f(t) = \lim_{x_0 \to 0} \frac{w(t;x_0)}{w(x_0)} \tag{12}$$

where $w(t;x_0)$ is defined as $w(t;x_0) = -(\mathrm{d}/\mathrm{d}t)\int_0^N \mathrm{d}x\, P(x,t|x_0,0)$ and $w(x_0)$ as $w(x_0) = \int_0^\infty \mathrm{d}t\, w(t;x_0)$. Further, given $f(t)$, the mean first passage time $\bar{t}$ to cross the pore can be calculated from the integral $\int_0^\infty \mathrm{d}t\, tf(t)$. Expressions for these quantities are now derived for the two limiting cases discussed above using eqs 11a and 11b.

(i) The Force-Free Limit, $fN \to 0$. In this limit, referring to eq 12, the first passage time distribution is easily shown to be

$$f(t) = \frac{4}{\pi}tE_{2H,2}(-(t/\tau)^{2H})\sum_{n=0}^{\infty}\frac{(-1)^n}{2n+1}\lambda_n \times \exp\left[-\lambda_n t^2 E_{2H,3}(-(t/\tau)^{2H})\right] \tag{13a}$$

with λ_n given by eq 9a. Under the conditions of high friction that are expected to apply to the majority of realistic pore crossing scenarios, t/τ will generally be much greater than 1, so eq 13a can evaluated in this limit, using the asymptotic result $E_{\alpha,\beta}(-z) \overset{z\to\infty}{\sim} 1/z\Gamma(\beta - \alpha)$ to simplify the Mittag−Leffler function. This leads to

$$f(t) \approx \frac{4\tau^{2H}t^{1-2H}}{\pi\Gamma(2-2H)}\sum_{n=0}^{\infty}\frac{(-1)^n}{2n+1}\lambda_n \exp\left[-\frac{\lambda_n \tau^{2H}t^{2-2H}}{\Gamma(3-2H)}\right] \tag{13b}$$

Figure 1 shows the time dependence of $f(t)$ (as calculated numerically from eq 13b) for two values of H (3/5, main figure, and 1/2, inset) and for three different values of N (32, 64, and

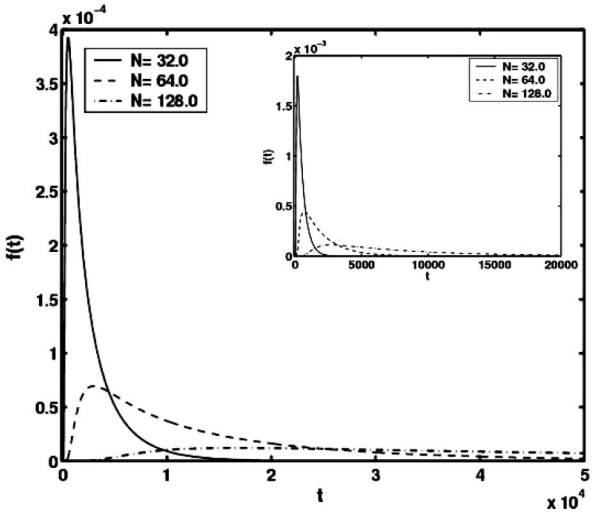

Figure 1. The time dependence of the waiting time distribution $f(t)$ for force-free translocation as calculated from eq 13b at fixed values of the Hurst index H (3/5) and the parameters $k = k_BT/m$ and τ (both 1.0), and at the following three values of the chain length N: 32 (solid line), 64 (dashed line), and 128 (dot-dashed line). The inset shows $f(t)$ vs t at the same set of parameter values but with H assigned the value 1/2.

128), at fixed values of k (1.0) and τ (1.0), in some arbitrary set of units. The inset is included for purposes of reference and comparison, since the $H = 1/2$ case describes simple Brownian diffusion. The choice of $H = 3/5$ is motivated by considerations to be discussed later, while the values assigned to N were chosen to coincide with the values used in the simulations of ref 13.

From eq 13a, the mean first passage time $\bar{t}$ is found to be

$$\bar{t} = \frac{4}{\pi}\sum_{n=0}^{\infty}\frac{(-1)^n}{2n+1}\int_0^\infty \mathrm{d}t\, \exp[-\lambda_n t^2 E_{2H,3}(-(t/\tau)^{2H})] \quad (14)$$

which in the same asymptotic long-time limit considered above can be reduced to[27]

$$\bar{t} = \frac{2^{1-2p}}{(1-H)\pi}\Gamma[1/(2-2H)]\left(\frac{4N^2\Gamma(3-2H)}{k\pi^2\tau^{2H}}\right)^{\frac{1}{2-2H}}\times [\zeta(p,1/4)-\zeta(p,3/4)] \quad (15)$$

where $p = (2 - H)/(1 - H)$ and $\zeta(a,b)$ is the zeta function.[28] As a function of N, therefore, the mean first passage time scales as

$$\bar{t} \sim N^{1/(1-H)} \quad (16)$$

(ii) The Strong Force Limit, $fN \gg 1$. In the presence of a strong driving force, the probability distribution function $P(x,t|x_0,0)$ is given by eq 11b, with λ_n given by eq 9b. In this case, the calculation of the first passage time distribution $f(t)$, is a little more involved, and first requires a consideration of the function $w(t;x_0)$ [cf. eq 12], which, in the limit $fN \gg 1$, is given by

$$w(t;x_0) = -\frac{2\pi k}{N^2}e^{f(N-x_0)/2}tE_{2H,2}(-(t/\tau)^{2H})\times \sum_{n=0}^{\infty} n(-1)^n \sin\left[\frac{n\pi x_0}{N}\right]\exp[-\lambda_n t^2 E_{2H,3}(-(t/\tau)^{2H})] \quad (17a)$$

while in the same limit, the function $w(x_0)$ [defined as $\int_0^\infty \mathrm{d}t\, w(t;x_0)$] is given by

$$w(x_0) = -\frac{2\pi k}{N^2}e^{f(N-x_0)/2}\sum_{n=0}^{\infty}\frac{n(-1)^n}{\lambda_n}\sin\left[\frac{n\pi x_0}{N}\right] \quad (17b)$$

To reduce eqs 17a and 17b to closed form, the term $(-1)^n \sin(n\pi x_0/N)$ in these expressions is rewritten as $\{\sin[n\pi(1 + x_0)/N] - \sin[n\pi(1 - x_0)/N]\}/2$, the sums $\sum_{n=0}^{\infty}$ are replaced by the integrals $\int_0^\infty \mathrm{d}n$, and the limit $x_0 \to 0$ is taken at the end of the calculations. This leads after some algebra to

$$f(t) = \frac{tE_{2H,2}(-(t/\tau)^{2H})}{2f\sqrt{k\pi}[t^2E_{2H,3}(-(t/\tau)^{2H})]^{3/2}}\left[\frac{N^2}{kt^2E_{2H,3}(-(t/\tau)^{2H})}-2\right]\times \exp\left\{-\frac{[N-fkt^2E_{2H,3}(-(t/\tau)^{2H})]^2}{4kt^2E_{2H,3}(-(t/\tau)^{2H})}\right\} \quad (18a)$$

which in the limit $t/\tau \gg 1$ can be simplified to

$$f(t) = \frac{\alpha}{2ft}\sqrt{\frac{\Gamma(1+\alpha)}{\pi kt^\alpha\tau^{2H}}}\left[\frac{N^2\Gamma(1+\alpha)}{kt^\alpha\tau^{2H}}-2\right]\times \exp\left\{-\frac{[N-fkt^\alpha\tau^{2H}/\Gamma(1+\alpha)]^2}{4kt^\alpha\tau^{2H}/\Gamma(1+\alpha)}\right\} \quad (18b)$$

where $\alpha = 2 - 2H$. Barring a factor of 2 in the prefactor, and a slightly different interpretation of the parameters k and τ, eq 18 is identical, surprisingly, to the expression for $f(t)$ derived by Dubbeldam et al.[13] from a fractional Fokker–Planck approach using a *short* time rather than a long time approximation. In that work, the short time limit was justified by arguing that large values of f led to short crossing times, but we believe that the limit used here, viz., $t/\tau \gg 1$, is more meaningful, as it only assumes overdamped conditions. Figures 2 and 3 show the time dependence of $f(t)$ at, respectively, fixed N and different f and at fixed f and different N, for values of H equal to 2/3 (main figures) and 1/2 (insets), and with k and τ set to 1.0. The choice of parameter values in these figures is again motivated by scaling results that will emerge later and by data from the simulations of refs 13 and 16–18.

The mean first passage time $\bar{t}$ can be readily calculated from eq 12 if one carries out the time integral first (after approximating the Mittag−Leffler function by its asymptotic expansion); this leads to

$$\bar{t} = \lim_{x_0\to 0}\Delta_H\frac{\sum_{n=0}^{\infty} n(-1)^n\frac{\sin(n\pi x_0/N)}{(f^2/4+n^2\pi^2/N^2)^{(3-2H)/(2-2H)}}}{\sum_{n=0}^{\infty} n(-1)^n\frac{\sin(n\pi x_0/N)}{(f^2/4+n^2\pi^2/N^2)}} \quad (19)$$

where $\Delta_H = \Gamma(1/(2 - 2H))\Gamma(3 - 2H)^{1/(2-2H)}/(2 - 2H)(k\tau^{2H})^{1/(2-2H)}$. Equation 19 is now evaluated using the same set of steps that led to eq 18. The result is

$$\bar{t} = -\frac{2\Delta_H}{\Gamma(q)\sqrt{\pi}}e^{fN/2}N^{q-3/2}f^{1/2-q}K_{\nu+1}(fN/2)\left[\frac{fN}{2}\frac{K'_{\nu+1}(fN/2)}{K_{\nu+1}(fN/2)}-\nu\right] \quad (20a)$$

where $q = (3 - 2H)/(2 - 2H)$, $\nu = 1/2 - q$, $K_b(z)$ is the modified Bessel function of order b,[28] and $K'_b(z) \equiv \mathrm{d}K_b(z)/\mathrm{d}z$. Since fN is large, the asymptotic result $K_b(z) \sim e^{-z}(\pi/2z)^{1/2}$, along with the identity $K_{b+1}(z) + K_{b-1}(z) = -2K'_b(z)$, can be introduced to further simplify eq 20a to

$$\bar{t} = \frac{\pi^{1/2-q}\Delta_H}{\Gamma(q)}\left(\frac{N}{f}\right)^{q-1} \tag{20b}$$

4. Mean Square Displacement

The foregoing results for $f(t)$ and $\bar{t}$ are expressed in terms of the Hurst index H, which, in the absence of additional information, is not known à priori. To predict the numerical values of the exponents in the scaling relations for $\bar{t}$, therefore, we derive, as a function of H, and in the low and high force limits, expressions for one other measurable quantity, viz., the mean square displacement, $\langle \delta x(t)^2 \rangle = \langle [x(t) - x(0)]^2 \rangle$. We then determine the values of H that lead to agreement between our calculated $\bar{t}$ and known results. These values of H are used in the expressions for $\langle \delta x(t)^2 \rangle$ to generate testable predictions about its scaling behavior.

(i) The Force-Free Limit $fN \rightarrow 0$. The calculation of $\langle \delta x(t)^2 \rangle$ proceeds from the equation for the time evolution of x (eq A.5 with $\Delta\mu = 0$):

$$\dot{x}(t) = v(0)\xi(t) + \frac{1}{m}\int_0^t dt'\, \xi(t-t')\theta(t') \tag{21}$$

whose solution is

$$x(t) = x(0) + v(0)\int_0^t \xi(t')dt' + \frac{1}{m}\int_0^t dt'\, \bar{\theta}(t') \tag{22}$$

where $\bar{\theta}(t) = \int_0^t \mathrm{d}t' \xi(t-t')\theta(t')$. Hence,

$$\langle \delta x(t)^2 \rangle = \langle v^2(0) \rangle \int_0^t \xi(t_1)\mathrm{d}t_1 \int_0^t \xi(t_2)\mathrm{d}t_2 + \frac{2}{m^2}\int_0^t dt' \int_0^{t'} \mathrm{d}t_1 \langle \bar{\theta}(t')\bar{\theta}(t_1) \rangle \tag{23}$$

As shown in the Appendix, the term $\int_0^{t'} \mathrm{d}t_1 \langle \bar{\theta}(t')\bar{\theta}(t_1) \rangle$ (defined there as $D(t')$) can be simplified to $mk_BT[A(t') - \xi(t')A(t')]$, where $A(t)$ has been defined in eq 3a. Substituting this relation into eq 23, and, using the relation $\langle v^2(0) \rangle = (k_BT)/m$, the mean square displacement is found to be

$$\langle \delta x(t)^2 \rangle = \frac{2k_BT}{m}\int_0^t dt'\, A(t') \tag{24}$$

Thus, from the relation $\int_0^t \mathrm{d}t' A(t') = t^2 E_{2H,3}[-(t/\tau)^{2H}]$ (cf. eq 3b), and from the asymptotic limit of the Mittag−Leffler function, we see that

$$\langle \delta x(t)^2 \rangle \sim t^{2-2H} \tag{25}$$

which correctly recovers the Brownian diffusion limit when $H = 1/2$.

(ii) The Strong Force Limit $fN \gg 1$. Proceeding as before from the equation for the time evolution of x (eq A.5), but now retaining the term in $\Delta\mu$, we find in the limit $fN \rightarrow \infty$ that

$$\dot{x}(t) = \frac{k_BT}{m} f \int_0^t dt'\, \xi(t') \tag{26}$$

which, after solving for $x(t)$, leads to

$$\langle \delta x(t)^2 \rangle = \left(\frac{k_BT}{m}\right)^2 f^2 \int_0^t \mathrm{d}t_1 A(t_1) \int_0^t \mathrm{d}t_2 A(t_2) \tag{27}$$

In the long time limit, this yields the scaling result

$$\langle \delta x(t)^2 \rangle \sim f^2 t^{4-4H} \tag{28}$$

5. Discussion

The key findings of this paper are contained in eqs 16, 20b, 25, and 28, which describe the N dependence of $\bar{t}$ in the weak and strong force regimes (eqs 16 and 20b), and the t dependence of $\langle \delta x(t)^2 \rangle$ in the same regimes (eqs 25 and 28). Both sets of relations are in the form of power laws, the power law exponents being functions of the Hurst index H. Since H is undetermined, the actual numerical values of these exponents remain unknown. However, the internal consistency of the present model can be assessed by setting H to a value that leads to agreement between the scaling behavior of one of the calculated quantities, $\bar{t}$ or $\langle \delta x(t)^2 \rangle$, and independent data from simulations, and then using that value in the expression for the other calculated quantity, and establishing whether theory and simulation (or experiment) remain in agreement.

The simulations of Kardar et al.,[12] Dubbeldam et al.,[13] and Wolterink et al.[16] provide one set of observational results for force-free diffusion, viz., $\bar{t}(\Delta\mu = 0) \sim N^{2.5}$ (ref 12), $\bar{t}(\Delta\mu = 0) \sim N^{2.52\pm0.04}$ (ref 13) and $\bar{t}_d(E = 0) \sim N^{2.4\pm0.05}$ (ref 16). In the case of biased diffusion, the following results are available: $\bar{t}(\Delta\mu$

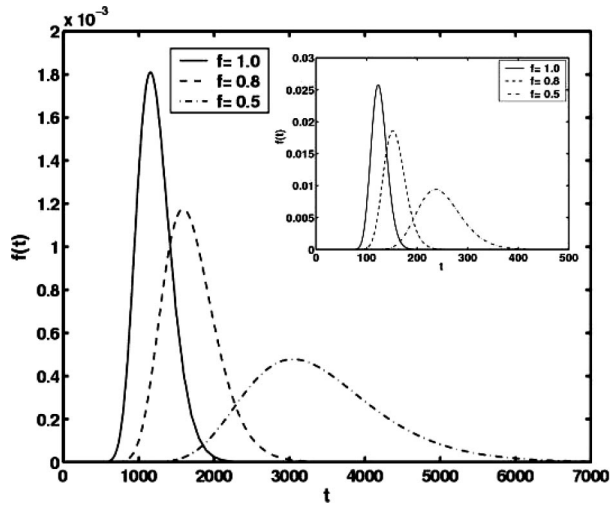

Figure 2. The time dependence of the waiting time distribution $f(t)$ for biased translocation as calculated from eq 18 at fixed values of N (128), H (2/3), k (1.0), and τ (1.0), and at the following three values of the force f: 1.0 (solid line), 0.8 (dashed line), and 0.5 (dot-dashed line). The inset shows $f(t)$ vs t at the same set of parameter values but with H assigned the value 1/2.

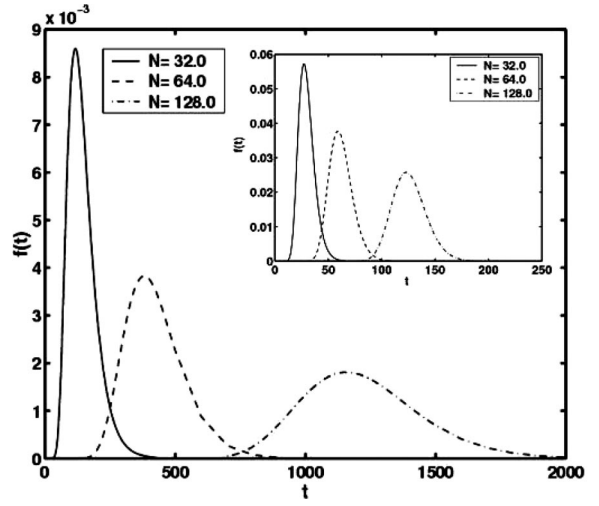

Figure 3. The time dependence of the waiting time distribution $f(t)$ for biased translocation as calculated from eq 18 at fixed values of f (1.0), H (2/3), k (1.0), and τ (1.0), and at the following three values of the chain length N: 32 (solid line), 64 (dashed line), and 128 (dot-dashed line). The inset shows $f(t)$ vs t at the same set of parameter values but with H assigned the value 1/2.

$\neq 0) \sim N^{1.5}$ (ref 12), $\bar{t}(\Delta\mu \neq 0) \sim N^{1.496}/f$ (ref 13) and $\bar{t}(E \neq 0) \sim N^{1.37}/E$ (ref 17). Our results can be made to agree *approximately* with these by choosing $H = 3/5$ (when $\Delta\mu$ or $E = 0$) and $H = 2/3$ (when $\Delta\mu$ or $E \neq 0$). (The latter choice does not quite reproduce the scaling result of ref 17, but given the general level of uncertainty in the numerical data, small differences between theory and simulation do not necessarily undermine the overall conclusions. Also, there is no reason why the *same* value of H should characterize biased and unbiased motion, since the conformations of the chain in the two situations, and hence the nature of their temporal correlations as characterized by H, are generally different.) For the internal consistency of our model, these values of H, when used in our expressions for $\langle \delta x(t)^2 \rangle$ (eqs 25 and 28), should be in broad agreement with known results. Such results have been reported in refs 13 and 18, where it is found that $\langle \delta x(t)^2 \rangle (\Delta\mu = 0) \sim t^{0.8}$ (ref 13) and $\langle \delta x(t)^2 \rangle (E = 0) \sim t^{0.73}$ (ref 18). Furthermore, $\langle \delta x(t)^2 \rangle (\Delta\mu \neq 0) \sim f^2 t^{1.334}$ (ref 13). Our predictions, using $H = 3/5$ and $2/3$ for unbiased and biased translocation, respectively, are consistent with these results, although the agreement with the results of ref 18 is only semiquantitative.

Despite the similarities between the present GLE approach and the earlier fractional Fokker–Planck approach,[13] there are nevertheless differences between them, and these may have a bearing on the treatment and solution of other chain translocation problems. For one thing, the GLE is an exact equation, and can be derived from the Liouville equation by application of projection operators.[29] It provides a natural generalization of the Langevin equation in those situations (by far the vast majority) where the thermal fluctuations of the bath have a finite decay time. The fractional Fokker–Planck equation (FFPE), on the other hand, cannot be similarly obtained from first principles, although its derivation from the continuous time random walk formalism using a power law waiting time distribution is quite rigorous, and can be justified on physical grounds.[19]

The use of this power law waiting time distribution in the fractional diffusion formalism has the effect of producing a divergent mean first passage time $\bar{t}$. As a result, the scaling relations for $\bar{t}$ derived in ref 13 are, strictly speaking, not well-defined. Nevertheless, there is almost certainly some time regime where they are found to hold. At the same time, although the GLE approach does yield sensible expressions for $\bar{t}$ and higher moments, it is also somewhat phenomenological, and does not really identify the microscopic source of anomalous diffusion.

Additionally, even when their calculations yield similar results, the GLE and FFPE approaches rely on quite different limiting approximations: one invokes a short time approximation (the FFPE), and the other a long time approximation (the GLE). We have already argued that the latter may be more relevant to physical situations.

Finally, it should be noted that the scaling structure of $\bar{t}$ determined in our calculations in the large f limit [viz., $(N/f)^b$, cf. eq 20b] is different from the structure determined earlier[13,17] (viz., N^c/f). The difference may provide an important test of the relative merits of these various approaches.

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Appendix

Derivation of Eq 2

The starting point for the derivation of the Smoluchowski equation shown in eq 2 is the following definition of the probability density function $P(x,t)$:

$$P(x,t) = \langle \delta(x - x(t)) \rangle \tag{A.1}$$

where the angular brackets denote an average over realizations of the noise $\theta(t)$, with $x(t)$ regarded as a functional of $\theta(t)$ and of the initial velocity $v(0)$. Using the chain rule and the properties of the delta function, this equation is first differentiated with respect to t, producing

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial}{\partial x}\langle \delta(x - x(t))\dot{x}(t) \rangle \tag{A.2}$$

Equation A.2 is converted to an equation in $P(x,t)$ by substituting a suitable expression for $\dot{x}(t)$, and simplifying the result. The required equation for $\dot{x}(t)$ is obtained from the GLE of eq 1 by first rewriting it in terms of the velocity $v(t)$, and using the relation $U(x) = -x\Delta\mu$. This yields

$$m\dot{v}(t) = -\zeta \int_0^t dt'\, K(t - t')v(t') + \Delta\mu + \theta(t) \tag{A.3}$$

which can be Laplace transformed to

$$\hat{v}(s) = v(0)\hat{\tilde{\xi}}(s) + \frac{\Delta\mu}{m}\frac{\hat{\tilde{\xi}}(s)}{s} + \frac{1}{m}\hat{\theta}(s)\hat{\tilde{\xi}}(s) \tag{A.4}$$

where the Laplace transform $\hat{g}(s)$ of a function $g(t)$ is defined as $\hat{g}(s) = \int_0^\infty dt e^{-st} g(t)$, and where the function $\hat{\tilde{\xi}}(s)$ is given by $\hat{\tilde{\xi}}(s) = 1/(s + \zeta\hat{K}(s)/m)$. In terms of the variable x, eq A.4 leads to the following evolution equation:

$$\dot{x}(t) = v(0)\xi(t) + \frac{\Delta\mu}{m}\int_0^t dt'\, \xi(t') + \frac{1}{m}\int_0^t dt'\, \xi(t - t')\theta(t') \tag{A.5}$$

This equation is now substituted for $\dot{x}(t)$ in eq A.2, whereupon the right-hand side of eq A.2 becomes a sum of three terms, T_1, T_2, and T_3, which are given by

$$T_1 = -\frac{\partial}{\partial x}\langle \delta(x - x(t))v(0)\xi(t) \rangle \tag{A.6a}$$

$$T_2 = -\frac{\partial}{\partial x}\langle \delta(x - x(t))\frac{\Delta\mu}{m}\int_0^t dt'\, \xi(t') \rangle \tag{A.6b}$$

and

$$T_3 = -\frac{\partial}{\partial x}\langle \delta(x - x(t))\frac{1}{m}\int_0^t dt'\, \xi(t - t')\theta(t') \rangle \tag{A.6c}$$

We now consider each of these in turn, starting with T_1. Since $x(t)$ is a functional of $v(0)$, which is a Gaussian random variable, one may use Novikov's theorem[30] in the evaluation of the average to produce

$$T_1 = -\xi(t)\langle v^2(0) \rangle \frac{\partial}{\partial x}\left\langle \frac{\partial}{\partial x(t)}\delta(x - x(t))\frac{\delta x(t)}{\delta v(0)} \right\rangle \tag{A.7}$$

An expression for $\delta x(t)/\delta v(0)$ can be obtained from eq A.5 by differentiating it with respect to $v(0)$ and solving the resulting differential equation. The result is

$$\frac{\delta x(t)}{\delta v(0)} = \int_0^t dt'\, \xi(t') \equiv A(t) \tag{A.8}$$

which, when substituted into eq A.7 (after using the relation $\langle v(0)^2 \rangle = k_B T/m$), yields

$$T_1 = \frac{k_B T}{m}\xi(t)A(t)\frac{\partial^2}{\partial x^2}P(x,t) \tag{A.9}$$

The term T_2 can be immediately reduced to

$$T_2 = -\frac{\Delta\mu}{m}A(t)\frac{\partial}{\partial x}P(x,t) \tag{A.10}$$

but the term T_3, on the other hand, must be analyzed along the lines of T_1. This is done by noting that the integral $\int_0^t dt'\xi(t-t')\theta(t')$, being a linear combination of the Gaussian random variable $\theta(t)$, is itself a Gaussian variable $\bar{\theta}(t)$ that can also be treated using Novikov's theorem.[30] The application of the theorem to the average in T_3 leads to

$$T_3 = -\frac{1}{m}\frac{\partial}{\partial x}\int_0^t dt'\langle\bar{\theta}(t)\bar{\theta}(t')\rangle\left\langle\frac{\delta}{\delta\bar{\theta}(t')}\delta(x-x(t))\right\rangle \tag{A.11a}$$

which can be rewritten as

$$T_3 = -\frac{1}{m}\frac{\partial}{\partial x}\int_0^t dt'\langle\bar{\theta}(t)\bar{\theta}(t')\rangle\left\langle\frac{\partial}{\partial x(t)}\delta(x-x(t))\frac{\delta x(t)}{\delta\bar{\theta}(t')}\right\rangle \tag{A.11b}$$

The quantity $\delta x(t)/\delta\bar{\theta}(t')$ in this expression can be obtained by functionally differentiating eq A.5 with respect to $\bar{\theta}(t')$, and solving the resulting differential equation; in this way it can be shown that $\delta x(t)/\delta\bar{\theta}(t') = 1/m$. T_3 now becomes

$$T_3 = \frac{1}{m^2}\frac{\partial^2}{\partial x^2}P(x,t)D(t) \tag{A.12}$$

where $D(t) = \int_0^t dt'\langle\bar{\theta}(t)\bar{\theta}(t')\rangle$.

The evaluation of $D(t)$ is carried out using methods exactly analogous to those used in refs 22 and 31 to evaluate related noise-averaged integrals. Briefly, the calculation proceeds by substituting the definition of $\bar{\theta}(t)$, along with the definitions of the functions $\xi(t)$ and $K(t)$, into the expression for $D(t)$, and then using double Laplace transforms to simplify the resulting expression. In this way, omitting details that may be found in the above references, one can show that

$$D(t) = mk_BT\int_0^t dt'\,[\xi(|t-t'|) - \xi(t)\xi(t')] \tag{A.13}$$

T_3 is now given by

$$T_3 = \frac{k_BT}{m}\left[\int_0^t dt'\,\xi(|t-t'|) - A(t)\xi(t)\right]\frac{\partial^2}{\partial x^2}P(x,t) \tag{A.14}$$

After substituting the expressions for T_1, T_2, and T_3 (eqs A.9, A.10, and A.14, respectively) into the equation for $\partial P(x,t)/\partial t$, we are finally led to eq 2, viz.,

$$\frac{\partial P(x,t)}{\partial t} = A(t)\left[-\frac{\Delta\mu}{m}\frac{\partial}{\partial x} + \frac{k_BT}{m}\frac{\partial^2}{\partial x^2}\right]P(x,t) \tag{A.15}$$

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