Anomalous reaction-diffusion as a model of nonexponential DNA escape kinetics

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We show that data from recent experiments carried out on the kinetics of DNA escape from α-hemolysin nanopores [M. Wiggin, C. Tropini, C. T. Cossa, N. N. Jetha, and A. Marziali, Biophys. J. **95**, 5317 (2008)] may be rationalized by a model of chain dynamics based on the anomalous diffusion of a particle moving in a harmonic well in the presence of a delta function sink. The experiments of Wiggin *et al.* found, among other things, that the occasional occurrence of unusually long escape times in the distribution of chain trapping events led to nonexponential decays in the survival probability, $S(t)$, of the DNA molecules within the nanopore. Wiggin *et al.* ascribed this nonexponentiality to the existence of a *distribution* of trapping potentials, which they suggested was the result of stochastic interactions between the bases of the DNA and the amino acids located on the surface of the nanopore. Based on this idea, they showed that the experimentally determined $S(t)$ could be well fit in both the short and long time regimes by a function of the form $(1+t/\tau)^{-\alpha}$ (the so called Becquerel function). In our model, $S(t)$ is found to be given by a Mittag–Leffler function at short times and by a generalized Mittag–Leffler function at long times. By suitable choice of certain parameter values, these functions are found to fit the experimental $S(t)$ even better than the Becquerel function. Anomalous diffusion of DNA within the trap prior to escape over a barrier of *fixed* height may therefore provide a second, plausible explanation of the data, and may offer fresh perspectives on similar trapping and escape problems. © *2010 American Institute of Physics*. [doi:10.1063/1.3290987]

I. INTRODUCTION

The maintenance and transmission of genetic information within and between cells is often critically dependent on the translocation of DNA and other biological macromolecules across channels of nanometer dimensions.[1] The process is intrinsically stochastic, being governed by the interplay between the effects of thermal fluctuations, conformational dynamics, and sequence-specific intermolecular interactions, many of whose characteristic timescales (milliseconds) are comparable to the time scales of translocation itself.[2] Often, these effects can therefore only be discriminated under well-controlled *in vitro* experimental conditions. Although advances in single molecule technology over the past decade or so have made it possible to meet some of these stringent requirements,[3] a great deal remains to be understood about the influence of various molecular parameters on chain crossing statistics. In this context, a recent experiment by Wiggin *et al.*[4] has been able to provide interesting new details about the escape kinetics of single-stranded DNA trapped in α-hemolysin nanopores.

The experiment monitored the fluctuations in the ionic current across α-hemolysin channels in which Avidin-coupled single-stranded polydeoxyadenine molecules of 15–65 base residues were captured at a high electrostatic potential (200 mV) and then allowed to escape thermally under a reduced potential (80 mV). The escape times of different trapped molecules (which ranged from hundreds of microseconds to tens of seconds) were recorded, and the probability of survival, $S(t)$, of the DNA molecules in the pore was determined from the escape time histogram. As a function of t, $S(t)$ was found to decay with two distinctly different profiles: exponentially at times less than about 10 ms, and as a power law at times greater than about 0.1 s. These results are quite surprising, since one would have expected (from Kramers theory,[5] for instance) that a thermally activated barrier crossing process under a relatively high barrier would lead to an exponential decay of $S(t)$ even at long times. To rationalize this anomaly, Wiggin *et al.*[4] suggested that the barrier height actually varied from one escape event to the other as a result interactions between the bases of the DNA and the surface of the nanopore. The survival probability in the pore is then given by an average over a static *distribution* of barriers of an exponential decay profile whose characteristic decay constant is a function of the barrier height. If this average is carried out with a suitably chosen barrier distribution (a gammalike distribution in this instance), one obtains for $S(t)$ a function [the Becquerel function, $(1+t/\tau)^{-\alpha}$] that fits the experimental data quite well over the entire time regime.

But this fit—though satisfactory, given the simplicity of the fitting function—is by no means quantitative, and there are deviations from the experimental curve in the regime between 1 and 10 s, where the model overestimates the likelihood of the DNA being trapped in the pore. There seems to be no simple way to account for these long-time deviations

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on the basis of the DNA-nanopore interactions that Wiggin *et al.*[4] identify as the root cause of nonexponential escape kinetics.

We would therefore like to suggest an alternative mechanism for the observed kinetics: anomalous diffusion of DNA within the pore prior to escape across a barrier of *fixed* height. By anomalous we mean that the mean squared displacement of the DNA (as measured by its center of mass motion, for instance) varies sublinearly with time. Such motion typically occurs in the presence of random thermal forces with long-ranged temporal correlations,[6] which as we have shown in several earlier applications[7] are the kinds of forces generated by systems (such as large macromolecules) with multiple time scales of relaxation. Diffusion under these conditions is very well described by a generalized Langevin equation. As we discuss in the following section, our approach to the problem posed by the Wiggin *et al.*[4] study is therefore to model the trapping and escape of DNA by the dynamics of a particle that moves in a harmonic well (the trap) under the action of fractional Gaussian noise (representing the effects of temporally correlated forces) until it attains a certain height above the potential minimum, at which time it leaves the energy surface at a rate κ (escape). We will then show (in Sec. III) that the survival probability of this particle within the well can be calculated approximately, but in closed form. Our expression for $S(t)$ involves the Mittag–Leffler function[8] and its variants, and we will also show (in the final and concluding section of the paper) that at both short and long times this expression provides a nearly quantitative fit to the corresponding experimental curve.

II. DETAILS OF THE MODEL

The calculation of the survival probability of a polymer confined within a nanopore is a complex many-body problem that probably cannot be solved in full generality. To render the problem tractable, we use a reduced description of the chain in which its many coupled conformational degrees of freedom are replaced by a single one-dimensional variable x that roughly corresponds (if a physical picture is desired) to a reaction coordinate of some kind.[9] The value of x at time t is a measure of where the chain is on a potential energy surface $U(x)$ at any given instant. To model the effects of chain confinement within a nanopore, this energy surface is chosen—for simplicity—to be a harmonic well, i.e., $U(x)=m\omega^2x^2/2$, where m is a mass, and ω is an angular frequency. The coordinate x evolves stochastically in the well as a result of thermal forces $\xi(t)$, modeled here by fractional Gaussian noise[10] (fGn), which is characterized by a vanishing mean, and a power law variance. The use of fGn rather than, say, simple white noise, is intended to mimic the long memory fluctuations that are expected to be present in a condensed phase environment with multiple timescales of relaxation. The equation for the evolution of x is therefore given by[11]

$$m\ddot{x}(t) = -\zeta\int_0^t dt' K(t-t')\dot{x}(t') - \frac{dU(x)}{dx} + \xi(t), \tag{1}$$

where the dots on x stand for time derivatives, ζ is a friction coefficient, and $K(t)$ is the memory function, which is connected to $\xi(t)$ by a fluctuation-dissipation theorem, viz. $K(|t-t'|)=(1/\zeta k_BT)\langle\xi(t)\xi(t')\rangle$, with k_B Boltzmann's constant, and T the temperature. When $\xi(t)$ corresponds to fGn, this relation becomes $K(|t-t'|)=2H(2H-1)|t-t'|^{2H-2}$, 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. If one assumes conditions of strong viscous damping, the above equation can be simplified to

$$m\omega^2x(t) = -\zeta\int_0^t dt' K(t-t')\dot{x}(t') + \xi(t) \tag{2}$$

by neglect of the inertial contribution. As shown earlier,[12] Eq. (2) is exactly equivalent to the following Smoluchowski equation for the evolution of the probability density, $P(x,t)$, that the reaction coordinate is at x at time t

$$\frac{\partial P(x,t)}{\partial t} = \eta(t)\left[\frac{\partial}{\partial x}x + \frac{k_BT}{m\omega^2}\frac{\partial^2}{\partial x^2}\right]P(x,t) \tag{3a}$$

$$\equiv \mathsf{D}P(x,t). \tag{3b}$$

Here, $\eta(t)$ is an effective time-dependent diffusion coefficient that is given explicitly by $\eta(t)=-\dot{\chi}(t)/\chi(t)$, where $\chi(t)=E_{2-2H}(-(t/\tau)^{2-2H})$, $\tau=(\zeta\Gamma(2H+1)/m\omega^2)^{1/(2-2H)}$, $\Gamma(x)$ is the gamma function and $E_a(-z)$ is the Mittag–Leffler function [defined, in general, by the relation $E_\alpha(-z)=\Sigma_{k=0}^{\infty}(-1)^kz^k/\Gamma(\alpha k+1)$].

Whenever the trajectory of x reaches the point x_b [where the energy, with respect to a reference energy of zero located at $x=0$, is $U(x_b)$], it is assumed to escape from the system at a rate κ. Under these conditions the equation for $P(x,t)$ is given by

$$\frac{\partial P(x,t)}{\partial t} = \mathsf{D}P(x,t) - \kappa\delta(x-x_b)P(x,t). \tag{4}$$

Equation (4) is the defining model for the dynamics of DNA trapping and escape.

III. CALCULATION OF THE SURVIVAL PROBABILITY

Assuming that at time $t=0$ the system is in thermal equilibrium, such that $P(x,0)=P^{\mathrm{eq}}(x)$, where $P^{\mathrm{eq}}(x)$ is the equilibrium distribution of x (to be specified later), one can formally write the solution of Eq. (4) as[13]

$$P(x,t) = P^{\mathrm{eq}}(x) - \int_{-\infty}^{\infty}dx'\int_0^t dt' G(x,t-t'|x')k(x')P(x',t'), \tag{5}$$

where $k(x)\equiv\kappa\delta(x-x_b)$, and $G(x,t-t'|x')$, the Green's function of Eq. (3), satisfies the equation

$$\left(\frac{\partial}{\partial t} - \mathsf{D}\right) G(x,t-t'|x') = \delta(x-x')\,\delta(t-t') \tag{6}$$

the solution of which, in general, is

$$G(x,t|x_0,0) = \sqrt{\frac{m\omega^2}{2\pi k_B T(1-\chi^2(t))}} \times \exp\left[-\frac{m\omega^2(x-x_0\chi(t))^2}{2k_B T(1-\chi^2(t))}\right]. \tag{7}$$

In the limit $t\to\infty$, this solution evolves to $P^{\mathrm{eq}}(x)$, where

$$P^{\mathrm{eq}}(x) = \sqrt{\frac{m\omega^2}{2\pi k_B T}} \exp\left[-\frac{m\omega^2 x^2}{2k_B T}\right]. \tag{8}$$

Because of its convolution structure, Eq. (5) can be written, formally, as an algebraic equation in $\hat{P}(x,s)$, the Laplace transform of $P(x,t)$ [the Laplace transform $\hat{f}(s)$ of a function $f(t)$ being defined as $\int_0^\infty dt f(t)\exp(-st)$]. Although this equation can be solved exactly[14] there seems to be no great advantage to doing so, as the Laplace transform of the Green's function itself [Eq. (7)] cannot be determined exactly. At this stage, it therefore proves to be much more practical to introduce into Eq. (5) a widely[15] used self-consistent closure scheme (the Wilemski–Fixman approximation[16]) that makes it possible to generate a relatively simple, closed form expression for $S(t)$.

As a first step in the application of this approximation, we introduce the following two functions:

$$w(t) \equiv \int_{-\infty}^{\infty} dx k(x) P(x,t) \tag{9a}$$

and

$$\bar{w} \equiv \int_{-\infty}^{\infty} dx k(x) P^{\mathrm{eq}}(x). \tag{9b}$$

We next use these functions to write the probability density $P(x,t)$ as

$$P(x,t) \approx P^{\mathrm{eq}}(x)\frac{w(t)}{\bar{w}} \tag{10}$$

which is the defining equation of the Wilemski–Fixman approximation. This expression for $P(x,t)$ is substituted into the right-hand side of Eq. (5) after first multiplying the equation by $k(x)$ and integrating the result over all x; this leads to the integral equation

$$w(t) = \bar{w} - \int_0^t dt' C(t-t') w(t')/\bar{w}, \tag{11}$$

where

$$C(t-t') = \int_{-\infty}^{\infty} dx \int_{-\infty}^{\infty} dx' k(x) G(x,t-t'|x') k(x') P^{\mathrm{eq}}(x'). \tag{12}$$

Now introducing the Wilemski–Fixman approximation into the definition of the survival probability, viz., $S(t) = \int_{-\infty}^{\infty} dx P(x,t)$, and using the normalization condition $\int_{-\infty}^{\infty} dx P^{\mathrm{eq}}(x) = 1$, we see that

$$S(t) = \frac{w(t)}{\bar{w}} \tag{13}$$

which is the expression we shall use to calculate the survival probability. This calculation now reduces essentially to the evaluation of the function $w(t)$ defined by Eqs. (11) and (12).

To derive an expression for $w(t)$, we first evaluate the function $C(t)$ [Eq. (12)]; from Eqs. (7) and (8), this is immediately seen to be

$$C(t) = \frac{m\omega^2\kappa^2}{2\pi k_B T}[1-\chi^2(t)]^{-1/2}\exp\left(-\frac{m\omega^2 x_b^2}{k_B T(1+\chi(t))}\right). \tag{14}$$

This expression is exact, but the presence of $\chi(t)$ (a Mittag–Leffler function) complicates matters, so we shall now seek separate approximations for the short and long time regimes that reduce $C(t)$ to an algebraic form, thereby making Eq. (11) amenable to analysis by Laplace transform methods.

A. Short time regime

In the limit $t \ll \tau$ [τ being the decay constant defined in the paragraph after Eq. (3)], we can approximate $\chi(t)$ (defined in the same place) by the expression

$$\chi(t) = 1 - a_1 t^b + O(t^{2b}), \tag{15}$$

where $a_1 = 1/\tau^b\Gamma(3-2H)$ and $b = 2-2H$. Introducing this expression into the definition of $C(t)$ [Eq. (14)], and retaining only the leading order term in the expansion of $\chi(t)$ about $t\to 0$, we find that

$$C(t) \approx A_1 t^{-b/2}, \tag{16}$$

where $A_1 = (\kappa^2 m\omega^2/2\pi k_B T\sqrt{2a_1})\exp(-m\omega^2 x_b^2/2k_B T)$. Hence, in Laplace space[17]

$$\hat{C}(s) \approx A_1\Gamma(H)s^{-H}. \tag{17}$$

This expression is to be used in the Laplace transform of Eq. (11), which is

$$\hat{w}(s) = \frac{\bar{w}}{s + s\hat{C}(s)/\bar{w}}. \tag{18}$$

Substituting Eq. (17) in Eq. (18), carrying out the simple inverse Laplace transform,[18] and combining the result with Eq. (13), we find that

$$S(t) = E_H(-(t/\tau_1)^H), \tag{19}$$

where $\tau_1 = (\bar{w}/A_1\Gamma(H))^{1/H}$, which is the first of the two main results of this paper.

B. Long time regime

At large values of its argument, the Mittag–Leffler function behaves asymptotically as[8] $E_\alpha(-z) \sim 1/z\Gamma(1-\alpha)$. In the limit $t \gg \tau$, therefore, the function $\chi(t)$ simplifies as $\chi(t) \sim a_2 t^{-b}$, where $a_2 = \tau^b/\Gamma(2H-1)$. Hence, to leading order in powers of $1/t$, the correlation function $C(t)$ becomes

$$C(t) \approx A_2 + A_3 t^{-b}, \tag{20}$$

where $A_2=(m\omega^2\kappa^2/2\pi k_B T)\exp(-m\omega^2 x_b^2/k_B T)$ and $A_3=(m\omega^2 x_b^2/k_B T)a_2 A_2$. Equation (20) is readily Laplace transformed to $\hat{C}(s)=A_2/s+A_3\Gamma(1-b)/s^{1-b}$, so from Eqs. (18) and (13), we have

$$\hat{S}(s) = \frac{1}{A_2/\bar{w} + s + A_3\Gamma(1-b)s^b/\bar{w}}. \tag{21}$$

We do not presently know of a simple, closed form expression for the inverse Laplace transform of Eq. (21), but we can determine it in the form of an infinite series. This series is obtained by first manipulating $\hat{S}(s)$ into the form

$$\hat{S}(s) = \frac{1}{s + a_3 s^b} + \sum_{k=1}^{\infty} \frac{(-1)^k (A_2/\bar{w})^k}{(s + a_3 s^b)^{k+1}}, \tag{22}$$

where a_3 is defined as $a_3=A_3\Gamma(1-b)/\bar{w}$. Results presented in Ref. 18 are then used to invert this expression, to produce

$$S(t) = E_{2H-1}(-a_3 t^{2H-1}) + \sum_{k=1}^{\infty} \frac{(-A_2/\bar{w})^k}{k!} t^k E^{(k)}_{2H-1,2k(1-H)+1}(-a_3 t^{2H-1}), \tag{23a}$$

$$= \sum_{k=0}^{\infty} \frac{(-A_2/\bar{w})^k}{k!} t^k E^{(k)}_{2H-1,2k(1-H)+1}(-a_3 t^{2H-1}), \tag{23b}$$

where $E_{\alpha,\beta}(-z) \equiv \Sigma_{n=0}^{\infty}(-z)^n/\Gamma(\alpha n+\beta)$ is the generalized Mittag–Leffler function, $E^{(k)}_{\alpha,\beta}(-z)$ stands for the k th derivative of this function with respect to its argument, and the identity $E_{\alpha,1}(-z)=E_\alpha(-z)$ has been invoked to derive the second line of the equation. Further simplification of this equation is possible by making use of the asymptotic result $E_{\alpha,\beta}(-z) \sim 1/z\Gamma(\beta-\alpha)$ to show that

$$E^{(k)}_{2H-1,2k(1-H)+1}(-a_3 t^{2H-1}) = \frac{k!}{\Gamma((k+1)(2-2H))}(a_3 t^{2H-1})^{k+1}. \tag{24}$$

After substituting Eq. (24) into Eq. (23b), the resulting series can be exactly resummed to

$$S(t) = \frac{1}{a_3 t^{2H-1}} E_{2-2H,2-2H}(-(t/\tau_3)^{2-2H}), \tag{25}$$

where $\tau_3=(\bar{w}a_3/A_2)^{1/(2-2H)}$. This is the second of the two main results of this paper.

IV. RESULTS AND DISCUSSION

As a test of our model of nonexponential DNA escape kinetics, we now compare the theoretical expressions for $S(t)$ shown in Eqs. (19) and (25) with the experimental data reported in Ref. 4. The comparison is presented in Fig. 1, where the various symbols have the following meanings: the open circles correspond to the experimental data points of Ref. 4; the full line corresponds to the function $(1+t/\tau_0)^{-\sigma}$, with the two fitting parameters τ_0 and σ set to the values that were determined by Wiggin *et al.*[4] to provide the best fit to their data, viz., 0.0515 s and 1.362, respectively, (this curve is therefore a reconstruction of the corresponding curve in Fig. 2a of Ref. 4); the dot-dashed line corresponds to Eq. (25), with the three fitting parameters a_3, τ_3, and H set, respectively, to the best-fit values of 1.6891 s^{1-2H}, 0.0825 s and 0.68; and the dashed lines corresponds to Eq. (19), with the single fitting parameter τ_1 set to the best-fit value of 0.0753 s (the parameter H being assigned the same value of 0.68 that was found to best fit Eq. (25) to the long time limit of the experimental curve).

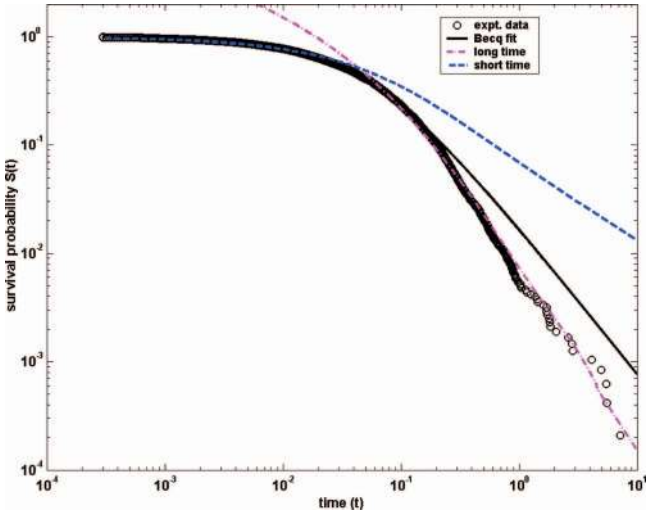

FIG. 1. Comparison of the time dependence of the experimentally determined survival probability $S(t)$ (open circles; data of Ref. 4) with three different theoretical curves of the same quantity: Eq. (19) (dashed line), corresponding to the short time limit of the model introduced in the present paper; Eq. (25) (dot-dashed line), corresponding to this model's long-time limit; and the Becquerel function (full line), corresponding to the model of multiple barrier heights developed in Ref. 4. Additional information about the parameter values used in the theoretical curves may be found in the text.

It is clear from an examination of Fig. 1 that in the short time regime (extending from about 0.1 ms to 0.015 s) both the Becquerel function and the Mittag–Leffler function [Eq. (19)] coincide almost exactly with the experimental curve (and with a suitably chosen exponential, although this is not shown in the figure in the interests of clarity; a comparison of an exponential with the data may be found in Ref. 4. At early times, therefore, it may reasonably be concluded that the escape of DNA from the pore can be described by simple Brownian diffusion over a barrier, as in Kramer's theory of chemical reaction dynamics. But Wiggin *et al.*[4] showed that an analysis of the escape process according to this theory would predict an exponentially decaying survival probability *even* at long times, in marked disagreement with the experimentally observed behavior, which clearly follows a power law. It was to rationalize this anomaly that Wiggin *et al.*[4] proposed a mechanism of chain translocation based on the idea of diffusion over of a *distribution* of barriers, a mechanism that does produce—through the appearance of the Becquerel function—a long-time power law profile. The possibility that multiple barrier heights may be responsible for this behavior is also partly supported by theoretical models of barrier crossing that are based on fractional diffusion equations,[6] which are generally formulated in terms of multiple waiting times between dynamical transitions. Such

models can produce long-time tails in the survival probability for escape from a well,[19] and for translocation through a pore.[20] However, the best fit of the experimental data to a power-law decay (in the form of the Becquerel function) is only semiquantitative, suggesting that other factors may also be at work. As is evident from Fig. 1, a far better fit between experiment and theory can be achieved by the mechanism underlying the present model: *anomalous* diffusion over a barrier. The anomalies in this mechanism originate in the temporal correlations of the fluctuating forces in the dissipative medium, rather than in the nature of the distribution of barrier heights or of waiting times.

There is considerable evidence from single molecule studies of proteins,[21] as well as from experimental,[22] simulation,[23] and analytical[24] studies of DNA translocation to suggest that the motion of large macromolecules in viscous media is indeed often anomalous (specifically subdiffusive), and stems from the dynamics of interconnected parts with different rates of relaxation. Such subdiffusive motion has been successfully described by a generalized Langevin equation in which the random forces are modeled as fractional Gaussian noise,[10] and in particular, a calculation of the mean square displacement of the reaction coordinate using this equation yields (for the case of no external potential) the scaling relation $\langle x^2(t)\rangle \sim t^{2-2H}$, $1/2 < H < 1$. We have now shown that the same model can be adapted to a consideration of the interesting problem posed by Wiggin *et al.*[4] of DNA escape from nanopores. Indeed, it can probably serve as a paradigm for a much wider class of problems involving anomalous diffusion and reaction.

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