DNA Bubble Dynamics as a Quantum Coulomb Problem

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We study the dynamics of denaturation bubbles in double-stranded DNA. Demonstrating that the associated Fokker-Planck equation is equivalent to a Coulomb problem, we derive expressions for the bubble survival distribution $W(t)$. Below T_m, $W(t)$ is associated with the continuum of scattering states of the repulsive Coulomb potential. At T_m, the Coulomb potential vanishes and $W(t)$ assumes a power-law tail with nontrivial dynamic exponents: the critical exponent of the entropy loss factor may cause a finite mean lifetime. Above T_m (attractive potential), the long-time dynamics is controlled by the lowest bound state. Correlations and finite size effects are discussed.

Under physiological conditions the Watson-Crick double helix is the equilibrium structure of DNA, its stability being effected by hydrogen bonding of base pairs (bps) and stacking between pairs of bps [1,2]. By variation of temperature or *p*H value double-stranded DNA progressively denatures, yielding regions of single-stranded DNA (DNA bubbles) whose size ranges from a few to some hundred broken bps, depending on T and *p*H conditions [3–5]. Eventually, the double strand fully denatures, the helix-coil transition at the melting temperature T_m [3].

Fueled by thermal activation, DNA bubbles occur spontaneously and fluctuate in size until closure ($T < T_m$) or denaturation ($T > T_m$). This DNA breathing can be probed on the single molecule level in real time by fluorescence methods [6]. Assuming that bp unzipping and zipping occur on a slower time scale than the relaxation of the polymeric degrees of freedom of the bubbles, DNA breathing can be interpreted as a random walk in the 1D coordinate x, the number of denatured bps.

Based on the Poland-Scheraga model [7], DNA breathing has been studied in terms of continuous [8,9] and discrete [10–13] approaches. Here we show that the Fokker-Planck equation for bubble dynamics is equivalent to a quantum Coulomb problem with a repulsive potential ($T > T_m$) or attractive potential ($T < T_m$). This mapping allows us to derive the survival behavior of bubbles ($T < T_m$) or the double strand ($T > T_m$) and the correlations in terms of the spectrum of a "hydrogenlike" system even when explicitly taking the entropy loss factor into account, extending previous results [9,13].

Static and dynamic model.—The Poland-Scheraga free energy for the bubble statistics has the form [3,5,9]

$$\mathcal{F} = \gamma_0 + \gamma x + c \ln x, \quad (1)$$

where $x \geq 0$ is the bubble size in units of broken bps. We here assume a continuum formulation and imply a cutoff for $x \sim 1$. γ_0 is the free energy barrier for bubble initiation,

γx the free energy for the dissociation of x bps, and $c \ln x$ the entropy loss factor associated with the formation of a closed polymer ring; the critical exponent $c = 1.76$ [3,5]. We write $\gamma = \gamma_1(1 - T/T_m)$ for the free energy density γ. In units of kT_r with reference temperature $T_r = 37\,°\text{C}$, approximate values for the parameters are $\gamma_0 \approx 10 kT_r$, $\gamma_1 \approx 4 kT_r$, and $c \approx 2 kT_r$; for standard salt conditions $T_m \approx 70 \ldots 110\,°\text{C}$, depending on the relative content of adenine-thymine (AT) versus guanine-cytosine (GC) bps [3,5,6,12].

The stochastic bubble dynamics is governed by the Langevin equation with Gaussian white noise $\xi(t)$,

$$dx/dt = -D d\mathcal{F}/dx + \xi, \qquad \langle \xi\xi \rangle(t) = 2DkT\delta(t), \quad (2)$$

where the kinetic coefficient D of dimension $(kT_r)^{-1}\text{s}^{-1}$ sets the time scale, $[DkT_r]^{-1} \sim \mu\text{s}$ [6]. With dimensionless parameters $\mu = c/2kT_r$ and $\epsilon = (\gamma_1/2kT_r)(T/T_m - 1)$, and measuring time in units of μs, the Fokker-Planck equation corresponding to Eq. (2) is

$$\frac{\partial P}{\partial t} = \frac{\partial}{\partial x}\left(\frac{\mu}{x} - \epsilon\right)P + \frac{1}{2}\frac{\partial^2 P}{\partial x^2}. \quad (3)$$

Note that close to T_r, $\mu \approx 1$ and $\epsilon \approx 2(T/T_m - 1)$.

General results.—Eliminating the first order term by means of the substitution $P = e^{\epsilon x}x^{-\mu}\tilde{P}$, $\tilde{P}$ satisfies

$$-\frac{\partial \tilde{P}}{\partial t} = -\frac{1}{2}\frac{\partial^2 \tilde{P}}{\partial x^2} + \left(\frac{\mu(\mu + 1)}{2x^2} - \frac{\mu\epsilon}{x} + \frac{\epsilon^2}{2}\right)\tilde{P}. \quad (4)$$

This is the imaginary time Schrödinger equation for a particle with unit mass in the potential $V(x) = \mu(\mu + 1)/2x^2 - \mu\epsilon/x + \epsilon^2/2$, i.e., subject to the centrifugal barrier $\mu(\mu + 1)/x^2$ for an orbital state with angular momentum μ and Coulomb potential $-\mu\epsilon/x$. Introducing the Hamiltonian $H = -(1/2)d^2/dx^2 + V(x)$ and expanding $\tilde{P}$ on the normalized eigenstates Ψ_n, $H\Psi_n = E_n\Psi_n$, the transition probability $P(x, x_0, t)$ from initial bubble size x_0

to a final bubble size x at time t yields in closed form

$$P(x, x_0, t) = e^{\epsilon(x-x_0)}\left(\frac{x_0}{x}\right)^\mu \sum_n e^{-E_n t}\Psi_n(x)\Psi_n(x_0). \quad (5)$$

Here the completeness of Ψ_n ensures the initial condition $P(x, x_0, 0) = \delta(x - x_0)$. To account for bubble closure we imply the absorbing boundary condition $\Psi_n(0) = 0$. For a finite DNA strand of length L, i.e., maximum bubble size L, we impose the absorbing condition $\Psi_n(L) = 0$ (complete denaturation). Expression (5) is the basis for our discussion of DNA breathing, relating the dynamics to the eigenstates of the Coulomb problem [14].

The transition probability P is controlled by the Coulomb spectrum. Below T_m $[\epsilon \propto (T/T_m - 1) < 0]$, the Coulomb problem is repulsive with a continuum of states, corresponding to a (biased) random walk in bubble size terminating in bubble closure ($x = 0$). At T_m ($\epsilon = 0$), the Coulomb potential is absent and the states are solely governed by the centrifugal barrier, including the limiting case of a regular random walk. Above T_m ($\epsilon > 0$), the potential is attractive and traps an infinity of bound states; at long times the lowest bound state dominates the bubble
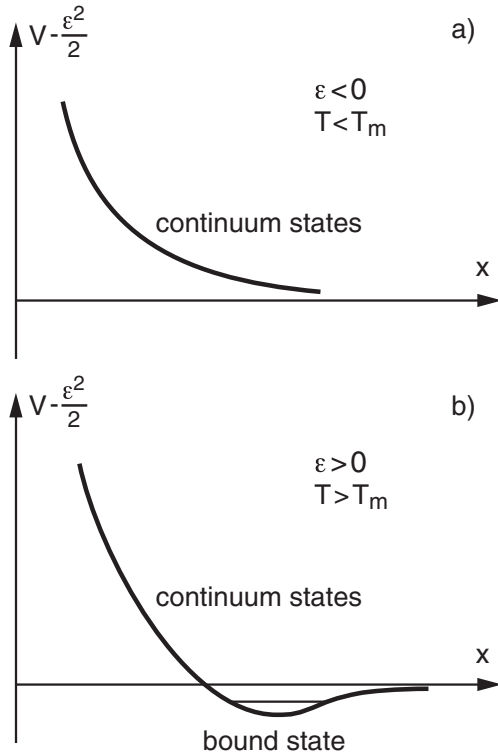

FIG. 1. Schematic of the potential $V(x) - \epsilon^2/2$ of Eq. (4). (a) $T < T_m$: repulsive potential with continuous spectrum. The bubble fluctuations correspond to a Brownian walk in bubble size x before collapse at $x = 0$. (b) $T > T_m$: attractive potential that can trap a series of bound states. At long times the lowest bound state indicated in the figure dominates. The bubbles increase in size leading to denaturation.

dynamics, associated with full DNA denaturation. In Fig. 1 we depict the two cases $\epsilon \gtrless 0$.

(i) $T \leq T_m$. At long times and fixed x and x_0, it follows from Eq. (5) that P is controlled by the bottom of the energy spectrum. Below and at T_m the spectrum is continuous with lower bound $\epsilon^2/2$. With $E_k = \epsilon^2/2 + k^2/2$ in terms of the wave number k and noting that $\Psi_k(x) \propto (kx)^{1+\mu}$ for small kx we have $P \propto \exp[-|\epsilon|(x - x_0)] \times (x/x_0)^{-\mu} \exp(-\epsilon^2 t/2) \int_0^\infty dk \exp(-k^2 t/2)(k^2 x x_0)^{1+\mu}$; by a simple scaling argument the long-time expression for the probability distribution yields

$$P(x, x_0, t) \simeq x x_0^{1+2\mu} e^{-|\epsilon|(x-x_0)} e^{-\epsilon^2 t/2} t^{-3/2-\mu}. \quad (6)$$

The lifetime of a bubble of initial size x_0 created at $t = 0$ follows from Eq. (6) by calculating the first passage time density (FPTD) as time derivative of the survival probability, $W(t) = -\int_0^\infty dx \partial P/\partial t$ [15], or, via Eq. (3), $W(t) = (1/2)[\partial P/\partial x + (2\mu/x - 2\epsilon)P]_{x=0}$. This produces

$$W(t) \simeq x_0^{1+2\mu} e^{|\epsilon|x_0} e^{-\epsilon^2 t/2} t^{-3/2-\mu}. \quad (7)$$

Below T_m, $\epsilon < 0$ and the FPTD $W(t)$ decays exponentially. The characteristic time scale is set by $\tau = 2/\epsilon^2 \propto (T_m - T)^{-2}$, diverging at T_m. From Eq. (6) we infer that $P(x, t) \propto \exp[-c_1|\epsilon|(x + c_2|\epsilon|t)]$ with constants $c_i > 0$, indicating that the profile of the distribution has a drift $\sim|\epsilon|$ towards bubble closure at $x = 0$.

At T_m ($\epsilon = 0$) the FPTD falls off like a power law, $W(t) \propto t^{-\alpha}$, with $\alpha = 3/2 + \mu$; see the exact result in Eq. (10). The associated exponent contains the entropy loss factor, $\mu = c/2kT_r$, with $\mu \approx 1$ at $T \approx T_r$. Ignoring the logarithmic entropic effects ($\mu = 0$) we obtain $\alpha = 3/2$, characteristic of an unbiased random walk [9]. From (7) we also infer that the mean bubble lifetime scales like $\tau_{\text{mean}} \propto x_0/|\epsilon| \propto x_0(T_m - T)^{-1}$, diverging at T_m.

(ii) *Above* T_m ($\epsilon > 0$) P is controlled by the lowest bound states in the attractive Coulomb potential with discrete spectrum $E_n = (\epsilon^2/2)(1 - [\mu/(\mu + n)]^2)$, $n = 1, 2, \ldots$. The lowest state has $E_1 = \epsilon^2(\mu + 1/2)/(\mu + 1)^2$, and the corresponding nodeless normalized bound state is $\Psi_1(x) = A x^{1+\mu} \exp[-\mu\epsilon x/(\mu + 1)]$ with normalization $A^2 = [2\mu\epsilon/(\mu + 1)]^{2\mu+3}/\Gamma(2\mu + 3)$ [14]. This bound state is localized at $\sim 1/(T - T_m)$ and thus recedes to infinity as we approach T_m. From (5) we have $P(x, x_0, t) \sim e^{\epsilon(x-x_0)}(x/x_0)^{-\mu} e^{-E_1 t}\Psi_1(x)\Psi_1(x_0)$, and we note that the dominant contribution to the distribution originates from the region where the bound state peaks, i.e., at $\sim 1/(T - T_m)$. Inserting in (5) we obtain

$$P(x, x_0, t) = A^2 x x_0^{1+2\mu} e^{[\epsilon/(1+\mu)][x-x_0(1+2\mu)]}$$
$$\times e^{-\epsilon^2(1+2\mu)t/2(1+\mu)^2}, \quad (8)$$

after some reduction. The profile of the distribution (8) drifts towards larger bubble sizes with velocity $\sim\epsilon$.

Exact result at T_m.—At criticality ($\epsilon = 0$) the problem of bubble dynamics is equivalent to the noisy finite-time

singularity studied in Ref. [16]. The eigenstates of H are Bessel functions, $\Psi_k(x) = (kx)^{1/2}J_{1/2+\mu}(kx)$; we obtain via a well-known identity [17,18]

$$P = \left(\frac{x_0}{x}\right)^{\mu}(xx_0)^{1/2}t^{-1}e^{-(x^2+x_0^2)/2t}I_{1/2+\mu}(xx_0/t), \quad (9)$$

where I_ν is the Bessel function of imaginary argument [17]. From Eq. (9) we infer the FPTD

$$W(t) = \frac{2x_0^{1+2\mu}}{\Gamma(1/2+\mu)}e^{-x_0^2/2t}(2t)^{-3/2-\mu}, \quad (10)$$

whose maximum at $t = x_0^2/(3+2\mu)$ assumes the value

$$W_{\max} = \frac{2}{\Gamma(1/2+\mu)}\left(\frac{2e}{3+2\mu}\right)^{-3/2-\mu}x_0^{-1/2}. \quad (11)$$

Note that the correction by the exponent μ causes a *finite* mean lifetime for $\mu > 1/2$, in contrast to previous results based on an unbiased random walk ($\mu = 0$). Figure 2 shows the bubble lifetime distribution for two different values of T_m corresponding to different power-law tails of $W(t)$.

Correlations.—In the experiments of Ref. [6] the correlation function $C(t)$ of a labeled bp is recorded. $C(t)$ is proportional to the integrated survival probability, $C(t) \propto \int_0^L P(x, x_0, t)dx$, where L is the chain length [12]. By definition of $W(t)$ we have $C(t) = 1 - \int_0^t W(t')dt' = \int_t^\infty W(t')dt'$ [19]. We distinguish three cases:

(i) Below T_m ($\epsilon < 0$) we obtain from Eq. (6) $C(t) = 1 - x_0^{1+2\mu}e^{|\epsilon|x_0}\int_0^t e^{-\epsilon^2 t'/2}(t')^{-3/2-\mu}dt'$, or, in terms of the incomplete Gamma function Γ [17],

$$C(t) \approx x_0^{1+2\mu}e^{|\epsilon|x_0}(\epsilon^2/2)^{1/2+\mu}\Gamma(-1/2-\mu, \epsilon^2 t/2). \quad (12)$$

With $\Gamma(\alpha, x) \approx x^{\alpha-1}e^{-x}$ for $x \to \infty$ we find

$$C(t) \approx x_0^{1+2\mu}\epsilon^{-2}e^{|\epsilon|x_0}t^{-3/2-\mu}e^{-\epsilon^2 t/2} \quad (13)$$

for long t, that for $\mu = 0$ matches the asymptotic behavior of the model derived in Ref. [6]. Note that the basic time scale of the correlations is set by $\epsilon^{-2} \propto (T_m - T)^{-2}$. For $t \ll \epsilon^{-2}$ we find the power law $C(t) \propto t^{-3/2-\mu}$; at $t \gg \epsilon^{-2}$ the correlations fall off exponentially. The size of the time window showing power-law behavior increases as T_m is approached. In frequency space the structure function $\tilde{C}(\omega) = \int \exp(i\omega t)C(t)dt$ has a Lorentzian shape for $|\omega| \ll \epsilon^2$, with power-law tails for $|\omega| \gg \epsilon^2$:

$$\frac{\tilde{C}(\omega)}{x_0^{1+2\mu}} \sim \begin{cases} e^{|\epsilon|x_0}[\omega^2 + (\epsilon^2/2)^2]^{-1}, & \text{for } |\omega| \ll \epsilon^2, \\ e^{|\epsilon|x_0}|\epsilon|^{-2}|\omega|^{1/2+\mu}, & \text{for } |\omega| \gg \epsilon^2. \end{cases} \quad (14)$$

In Fig. 3, we demonstrate the correct long-time asymptotics of our Γ model (12) with the drift-diffusion approximation and the autocorrelation data from Ref. [6]. We also show that with a rescaling of the characteristic time the Γ model with $\mu = 0$ (magenta line) and $\mu = 1$ (cyan) describes the long-time behavior of the data well.

(ii) At T_m ($\epsilon = 0$) the exact expression for the FPTD (10) combined with relation $C(t) = \int_t^\infty W(t')dt'$ yield

$$C(t) = 1 - \frac{\Gamma(1/2+\mu, x_0^2/2t)}{\Gamma(1/2+\mu)}. \quad (15)$$

For short times ($t \to 0$) the behavior

$$C(t) \approx 1 - \frac{(x_0^2/2)^{\mu-1/2}}{\Gamma(1/2+\mu)}t^{1/2-\mu}e^{-x_0^2/2t} \quad (16)$$

obtains, while in the long-time limit ($t \to \infty$) we find

$$C(t) \approx \frac{2(x_0^2)^{1/2+\mu}}{(1+2\mu)\Gamma(1/2+\mu)}t^{-1/2-\mu}. \quad (17)$$

(iii) Above T_m ($\epsilon > 0$) the DNA chain eventually fully denatures, and the correlations diverge in the thermody-
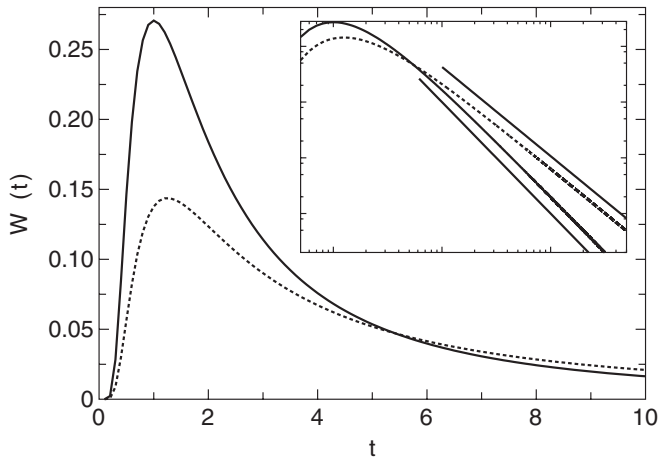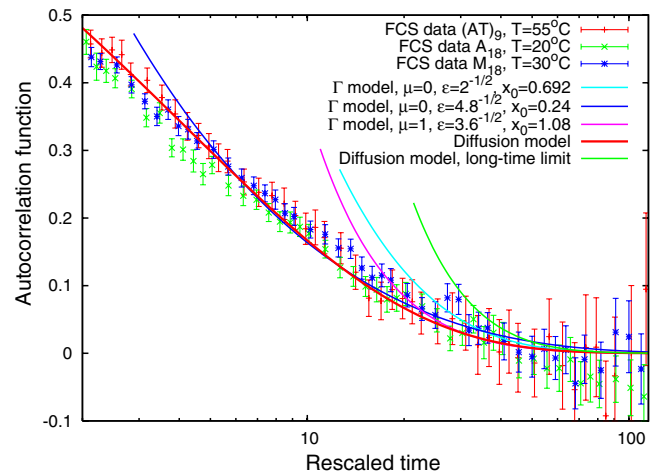

FIG. 2. Bubble lifetime distribution $W(t)$, Eq. (10), for $T_m = 2T_r$ (full line) and $T_m = 10T_r$ (dashed line). Inset: log-log plot at long t, with slopes -2, -1.6 indicated by the straight lines.

FIG. 3 (color online). Drift-diffusion model and experimental data from Ref. [6] compared to the Γ model, Eq. (12), for various parameters. The curve for $\mu = 0$ and $\epsilon = 1/\sqrt{2}$ exactly matches the long-time behavior from Ref. [6].

namic limit. We can, however, at long times estimate the size dependence for a chain of length L. From the general expression (5) we derive

$$C(t) \simeq e^{-\epsilon x_0} x_0^{\mu} \sum_n e^{-E_n t} \Psi_n(x_0) \int_0^L e^{\epsilon x} \Psi_n(x) \frac{dx}{x^{\mu}}. \quad (18)$$

We obtain with the lowest bound state $\Psi_1(x) = Ax^{1+\mu} \exp[-\mu\epsilon x/(\mu+1)]$ of energy $E_1 = \epsilon^2(\mu + 1/2)/(\mu+1)^2$ and after integration over x

$$C(t) \propto A^2 e^{-\epsilon x_0 (2\mu+1)/(\mu+1)} e^{-\epsilon^2 [(\mu+1/2)/(\mu+1)^2]t}$$
$$\times x_0^{1+2\mu}(1+\mu)\epsilon^{-2}\{1 + [L\epsilon/(1+\mu) - 1]$$
$$\times e^{\epsilon L/(1+\mu)}\}. \quad (19)$$

The correlations decay exponentially with time constant $\sim \epsilon^{-2}(\mu+1)^2/(2\mu+1)$. In frequency space the structure function has a Lorentzian line shape of width $\sim \epsilon^2(2\mu + 1)/(\mu+1)^2$, and for the size dependence one obtains

$$C(t) \sim \begin{cases} Le^{\epsilon L/(1+\mu)}, & \text{for } \epsilon L/(1+\mu) \gg 1, \\ L\epsilon/(1+\mu), & \text{for } \epsilon L/(1+\mu) \ll 1 \end{cases}. \quad (20)$$

Note that close to T_m the correlation $C(t) \propto L$.

Relevance to experiment.—Explicit expressions for bubble lifetimes and correlations are important for the design and interpretation of DNA-breathing experiments. Thus, the presence of the exponent μ changes the slope of the correlation function at the midpoint, and the slope of the power-law region at higher T. For the DNA constructs studied in Ref. [6], we have $\mu \approx 1$ and $T \approx T_r \approx T_m/2$, so that by Eq. (7) a typical bubble lifetime of 1 ms or slightly above corresponds to an initial (mean) bubble size of 5 to 6 open bps, somewhat larger than the typical size found in Ref. [5]. Both points would allow one, together with additional experiments as those outlined in Ref. [20], to obtain more accurate information on the time scales of bp zipping, and the stacking interactions of DNA.

Summary and conclusion.—We demonstrated that the fluctuation dynamics of DNA denaturation bubbles can be mapped onto the imaginary time Schrödinger equation of the quantum Coulomb problem, allowing us to calculate the bubble lifetime distributions and associated correlation functions, below, at, and above the melting temperature T_m. At T_m, the DNA breathing corresponds to a one-dimensional finite-time singularity [18]. The detailed study of DNA breathing is of particular interest as the bubble dynamics provides a test case for new approaches in small scale statistical mechanical systems where the fluctuations of DNA bubbles can be probed on the single molecule level in real time.

Our analysis reveals nontrivial scaling of the survival time of a bubble after its original nucleation. The associated critical exponents depend on the parameter μ stemming from the entropy loss factor of the flexible bubble, i.e., on the ratio T_r/T of reference and actual temperature. This correction through μ decreases with increasing T; at

physiological temperature, $\mu \approx 1$ significantly changes the power-law exponents. Thus, at T_m the typical bubble lifetime becomes finite due to the logarithmically increasing entropy loss factor. FPTD and correlations also depend on the difference $T/T_m - 1$, and therefore explicitly on the melting temperature T_m (and thus the relative content of AT or GC bps). We also obtained the critical dependence of the characteristic time scales on $T - T_m$ as well as the finite size dependence of the correlation function.

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[1] A. Kornberg, *DNA Synthesis* (Freeman, San Francisco, 1974).
[2] J. D. Watson and F. H. C. Crick, Cold Spring Harbor Symposia on Quantitative Biology **18**, 123 (1953).
[3] D. Poland and H. A. Scheraga, *Theory of Helix-Coil Transitions in Biopolymers* (Academic, New York, 1970).
[4] M. Guéron, M. Kochoyan, and J. L. Leroy, Nature (London) **328**, 89 (1987).
[5] A. Krueger, E. Protozanova, and M. D. Frank-Kamenetskii, Biophys. J. **90**, 3091 (2006).
[6] G. Altan-Bonnet, A. Libchaber, and O. Krichevsky, Phys. Rev. Lett. **90**, 138101 (2003).
[7] D. Poland and H. A. Scheraga, J. Chem. Phys. **45**, 1456 (1966).
[8] T. Hwa *et al.*, Proc. Natl. Acad. Sci. U.S.A. **100**, 4411 (2003).
[9] A. Hanke and R. Metzler, J. Phys. A **36**, L473 (2003).
[10] S. K. Banik, T. Ambjörnsson, and R. Metzler, Europhys. Lett. **71**, 852 (2005).
[11] T. Ambjörnsson and R. Metzler, Phys. Rev. E **72**, 030901(R) (2005); J. Phys. Condens. Matter **17**, S1841 (2005).
[12] T. Ambjörnsson, S. K. Banik, O. Krichevsky, and R. Metzler, Phys. Rev. Lett. **97**, 128105 (2006); Biophys. J. (to be published).
[13] D. J. Bicout and E. Kats, Phys. Rev. E **70**, 010902(R) (2004).
[14] L. Landau and E. Lifshitz, *Quantum Mechanics* (Pergamon, New York, 1959).
[15] N. G. van Kampen, *Stochastic Processes in Physics and Chemistry* (North-Holland, Amsterdam, 1992).
[16] H. C. Fogedby and V. Poutkaradze, Phys. Rev. E **66**, 021103 (2002).
[17] N. N. Lebedev, *Special Functions and Their Applications* (Dover, New York, 1972).
[18] H. C. Fogedby and R. Metzler (to be published).
[19] As we are only interested in the temporal behavior of $C(t)$, we neglect the additional average over the equilibrium distribution of x_0.
[20] T. Novotný *et al.*, Europhys. Lett. (to be published); cond-mat/0610752.