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The dynamics of intermittent strand separation in double-stranded DNA

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The transient rupture and reformation of hydrogen bonds between base pairs on distinct chains of double-stranded DNA ("bubble" dynamics) is modeled in terms of the fluctuating distance between the bases. The fluctuations in the distance are assumed to be governed by a simple Langevin equation with a quadratic potential under conditions of high friction. A critical distance of separation L must be achieved before a bubble defect is considered to have been formed. The decay of the dynamic correlations between states of the DNA that have such defects and those that do not has been calculated from the above model and has been found to reproduce the trends in experimental measurements of the same quantity. © *2007 American Institute of Physics*.
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I. INTRODUCTION

The mechanism of DNA replication has proved to be a far more complex and elaborately choreographed process[1] than Watson and Crick's famously understated remarks on the subject may have suggested.[2] The copying of genetic information is now known to be more than a simple matter of adding complementary bases to each polynucleotide strand of the DNA. Nevertheless, for all its complexity, there are steps in this process that appear to be simple, random, and undirected, among them the step that may initiate replication itself: the transient localized separation of one strand of DNA from the other.[3] Strand separation and reclosing, though sometimes assisted or promoted by enzyme action, is also caused by thermal fluctuations in the medium, which lead to the intermittent disruption ("breathing") of the relatively weak [on the order of a few k_BT (Ref. 4)] H bonds that exist between opposing base pairs. As a result, the DNA forms "bubble" defects of randomly varying sizes for intervals of time that can last up to milliseconds. Understanding this most elementary of processes can be expected to enhance our understanding of the regulatory controls that govern the transmission of genetic information across repeated cycles of cell division.

Recent single-molecule experiments by Altan-Bonnet *et al.*[5] have now provided the first quantitative details of the dynamics of DNA's breathing modes of excitation. Using synthetic double-stranded DNA constructs of defined sequence and length, Altan-Bonnet *et al.* have shown from measurements of the random quenching and restoration of fluorescence emission from a donor-acceptor pair located at fixed sites on opposite strands of the DNA that the dynamic correlations in the fluctuations in the fluorescence intensity are multiexponential and can be described by a single universal decay curve. These results were found to be consistent with a model of DNA breathing dynamics based on a distribution of bubble sizes generated by the zipping and unzipping of the DNA strands at constant rates.

More recently, Fogedby and Metzler[6] have attempted to explain these results using a model derived from the Poland-Scheraga picture of DNA denaturation,[7] which they mapped on to the quantum mechanical problem of a particle moving in a Coulomb potential subject to a centrifugal barrier. The fluorescence intensity correlations calculated from this model, for temperatures below the denaturation temperature and in the asymptotic long-time limit, are in broad agreement with the experimental data for a range of values of a parameter μ that defines the strength of the centrifugal and Coulomb contributions to the effective free energy. However, the best fit to the data is achieved when μ is 0; that is, when these contributions are, in fact, neglected. However, under these conditions, the model merely describes the stochastic dynamics of a particle in a linear potential, and it is unclear how relevant such a model is to bubble dynamics. Moreover, for both the $\mu=0$ and $\mu\neq 0$ cases, the early time behavior of the theoretical intensity correlation function is predicted to fall off as a power law, which does not appear to correspond to the experimental behavior in this regime, or to agree with the corresponding limit obtained from the model of Altan-Bonnet *et al.*[5]

In this paper, we would like to consider the results of Ref. 5 from a somewhat different perspective. These results are ultimately a reflection of the fluctuations in the distance x separating the donor and acceptor chromophores attached to the two DNA strands; whenever this distance is less than some critical distance L, the fluorescence emission of the donor is turned off, and whenever it exceeds this distance, the emission is turned on. A bubble can be said to be transiently formed each time x exceeds L, and the larger the value of x, the larger the size of the bubble. In general, x cannot grow indefinitely because the fluctuating base pairs to which the chromophores are attached are held together both by H bonds between themselves and by covalent bonds to their neighbors. We show below that a model of the stochas-

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tic evolution of x that is consistent with these general considerations provides a reasonable description of the dynamics of intermittent strand separation in DNA and is in satisfactory agreement with the experimental results of Ref. 5.

II. MODEL OF BREATHING DYNAMICS

Consider a pair of complementary H-bonded bases on distinct strands of a DNA molecule, one attached to a fluorescent donor and the other to an acceptor. During the time the bases are held together at their equilibrium geometry, and the two chromophores are in close proximity, the fluorescence from the donor is quenched, whereas during the time the bases are apart, and the chromophores are separated by a distance greater than L, the fluorescence is restored. The fluorescent light intensity at time t, denoted as $I(t)$, can therefore be represented as

$$I(t) = B\theta(x(t) - L), \tag{1}$$

where $\theta(z)$ is the step function, defined as $\theta(z)=1$ for $z>0$ and $\theta(z)=0$ for $z<0$, B is a constant of proportionality (whose precise value will not be needed), and $x(t)$ is the distance separating the two chromophores at time t. The quantity determined experimentally is the normalized autocorrelation function $C(t)$ of the fluorescent intensity at times 0 and t, which can be defined as

$$C(t) = \frac{\langle I(t)I(0)\rangle - \langle I(t)\rangle\langle I(0)\rangle}{\langle I(0)^2\rangle - \langle I(0)\rangle^2}, \tag{2}$$

where the angular brackets refer to an average over the fluctuations in x.

To calculate $C(t)$ theoretically, starting from the definition of $I(t)$ in Eq. (1), we model the dynamics of $x(t)$ by the motion of a particle of mass m undergoing simple Brownian motion in a harmonic well. This is perhaps the simplest realization of the idea that the distance separating the two chromophores varies randomly in time and is mostly limited to values that do not result in large excursions of the two bases away from their equilibrium geometry. Refinements to the model—such as the introduction of colored as opposed to white noise to define the particle dynamics or the use of more realistic potentials to model the effects of confinement—are easily incorporated into this picture, but do not appear to be necessary, and are not considered further.

For the present model, the evolution of x is governed by the equation

$$\zeta\frac{dx}{dt} = -\frac{dU}{dx} + \xi(t), \tag{3}$$

where ζ is the friction coefficient of the particle, $U(x)$ is the external potential (which is given by $m\omega^2x^2/2$, with ω the well frequency), and $\xi(t)$ is white noise, defined by the correlations

$$\langle\xi(t)\rangle = 0 \tag{4a}$$

and

$$\langle\xi(t)\xi(t')\rangle = 2k_B\zeta T\delta(t-t'), \tag{4b}$$

with T the temperature and k_B Boltzmann's constant.

Equation (3) is equivalent to the following Smoluchowski equation for the probability density $P(x,t)$ that the particle is at x at time t:

$$\frac{\partial P(x,t)}{\partial t} = \left[\frac{1}{\zeta}\frac{\partial}{\partial x}U'(x) + D\frac{\partial^2}{\partial x^2}\right]P(x,t), \tag{5}$$

where $U'(x)$ stands for $\partial U(x)/\partial x$ and $D\equiv k_BT/\zeta$ is the diffusion coefficient. The solution of Eq. (5), for x starting out from x_0 at time $t=0$, is well known; it is

$$P(x,t|x_0,0) = \sqrt{\frac{m\omega^2}{2\pi k_BT(1-\chi^2(t))}} \times\exp\left[-\frac{m\omega^2(x-x_0\chi(t))^2}{2k_BT(1-\chi^2(t))}\right], \tag{6}$$

where $\chi(t)$ is the function $\exp(-t/\tau)$, τ being a characteristic decay time, defined as $\zeta/m\omega^2$. In the limit of $t\to\infty$, $P(x,t|x_0,0)$ evolves to the equilibrium distribution $P_s(x)$, where

$$P_s(x) = \sqrt{\frac{m\omega^2}{2\pi k_BT}}\exp\left[-\frac{m\omega^2x^2}{2k_BT}\right]. \tag{7}$$

Given the above expressions [Eqs. (6) and (7)] and assuming that at time $t=0$, the variable x is distributed according to Eq. (7), the correlations in Eq. (2) can be written as follows:

$$\langle I(t)I(0)\rangle = B^2\int_{-\infty}^{\infty}dx\int_{-\infty}^{\infty}dx_0\,\theta(x-L) \times\theta(x_0-L)P(x,t|x_0,0)P_s(x_0) \tag{8a}$$

and

$$\langle I(t)\rangle = \langle I(0)\rangle = B\int_{-\infty}^{\infty}dx_0\,\theta(x_0-L)P_s(x_0). \tag{8b}$$

Equations (6), (7), (8a), and (8b) are the defining equations of the present model of intermittent strand separation; they have exactly the same structure as the equations we had used earlier to describe intermittency in single-molecule enzyme kinetics,[8] differing from them only in the nature of the function $\chi(t)$ that enters into the definition of $P(x,t|x_0,0)$. [Equation (8b) corrects a typographical error in Eq. (7) of Ref. 8.] For the problem of enzyme kinetics, $\chi(t)$ is given by the Mittag-Leffler function,[9] a reflection of the choice of fractional Gaussian noise[10] rather than white noise to characterize the effects of protein conformational fluctuations.[11] The two models are otherwise entirely equivalent, so we can make use of results derived earlier[8] to write down the final expression for $C(t)$ at once,

$$C(t) = \frac{2}{\pi[1-\mathrm{erf}^2(\sqrt{E/k_BT})]}\int_0^{\chi(t)}dz\frac{1}{\sqrt{1-z^2}} \times\exp\left[-\frac{2E}{k_BT(1+z)}\right]. \tag{9}$$

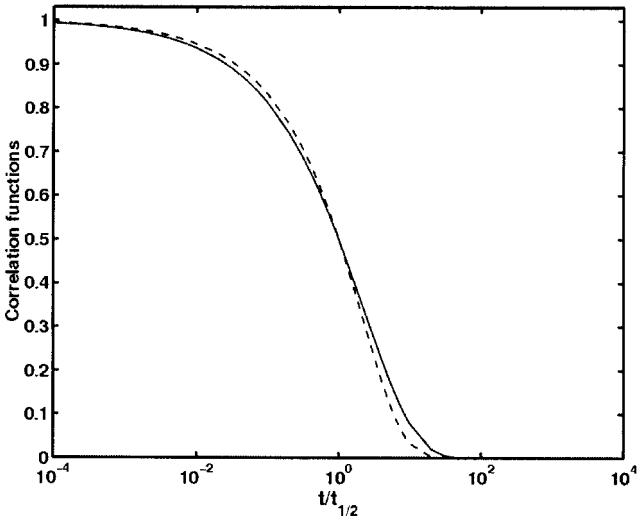

FIG. 1. Comparison of $G(x)$ [Eq. (10), full line] with $C(x)$ [Eq. (9) with t replaced by $t/t_{1/2}$ as described in the text, dashed line] after adjusting the parameters c and E/k_BT in Eq. (9) to the values of 0.015 and 29.3, respectively, so as to obtain the best fit of $C(x)$ to $G(x)$.

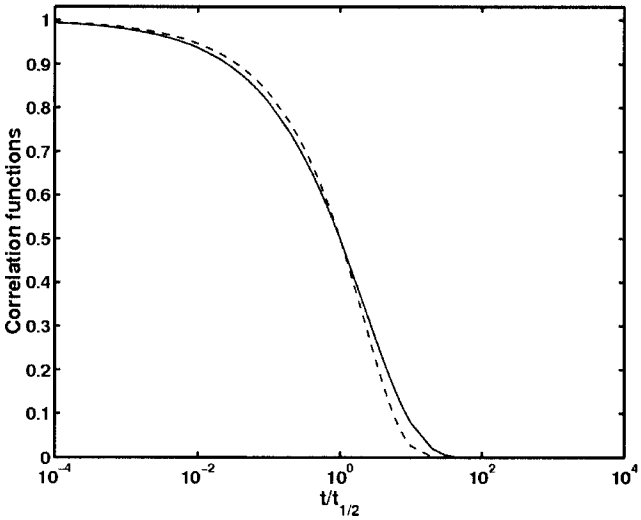

FIG. 2. The same comparison, as shown in Fig. 1, but with c and E/k_BT in Eq. (9) adjusted to the values of 0.3 and 0.29.

Here, erf is the error function and E is defined as $E \equiv U(L) = m\omega^2 L^2/2$, which is effectively the barrier height that the particle must reach before it makes a transition from the off to the on state. A complete derivation of Eq. (9) may be found in Appendix A of Ref. 8.

III. DISCUSSION

In this section, we seek to compare our theoretical predictions [as contained in Eq. (9)] with results from experiment. The comparison is made, not with the actual experimental data (which are only shown graphically in Ref. 5), but with a function $G(t)$, derived by Altan-Bonnet *et al.* from the model referred to in the Introduction, which successfully reproduces the decay profile of these data. The function $G(t)$, reexpressed here in terms of the time $t_{1/2}$ at which $G(t = t_{1/2}) = 0.5$, is given by

$$G(x) = \left(1 + \frac{bx}{2}\right)\mathrm{erfc}(\sqrt{bx}/2) - \sqrt{\frac{bx}{\pi}}\exp(-bx/4), \quad (10)$$

where $x \equiv t/t_{1/2}$, erfc is the complementary error function and b is a parameter adjusted to ensure that $G(1)$ is 0.5. The value of b that yields this result is found to be 0.328. The function $C(t)$ can similarly be reexpressed in terms of x by writing the variable t/τ as cx, where c, defined as $t_{1/2}/\tau$, with τ given by $\zeta/m\omega^2$ as mentioned earlier, is taken to be an adjustable parameter. We shall regard agreement of $C(x)$ with $G(x)$ as effectively establishing the consistency of our model with the experimental results of Ref. 5.

Figure 1 is a comparison of $C(x)$ (dashed line) with $G(x)$ (full line) after the parameters c and E/k_BT in the former were adjusted so that $C(1)$ was 0.5. The best fit values of these parameters were found to be 0.015 and 29.3, respectively. The two curves are seen to be in quite close agreement with each other across essentially the entire time regime over which experimental measurements were made. Moreover, in both the short and long-time regimes (corresponding to the limits of $t \to 0$ and $t \to \infty$, respectively), it can be shown analytically that $C(t)$ and $G(t)$ vary in exactly the same way; in the limit of $t \to 0$, they decay approximately as stretched exponentials with a stretch exponent of 1/2, while in the limit of $t \to \infty$, they decay as simple exponentials. This contrasts with the behavior of the corresponding correlation function in the Fogedby-Metzler model,[6] which appears to fit the experimental data only in the long-time regime; in this regime, the decay is exponential, in agreement with the data, but in the short time regime, the decay follows a power law.

Interestingly, the best fit values obtained above for the parameters c and E/k_BT do not appear to be entirely unique; at least one other set of values, $c = 0.3$ and $E/k_BT = 0.29$, do reasonably well in comparisons of $C(x)$ with $G(x)$, as shown in Fig. 2. This seems to suggest that two possible scenarios can describe the occurrence of nonexponentiality in the dynamics of intermittent strand separation at the location of a given pair of H-bonded bases. In one, the harmonic well that confines the bases is steep (ω is large), the bases overcome a relatively large effective barrier E/k_BT to achieve a strand separation of L, and relaxation to the equilibrium geometry is fast ($t_{1/2}$ is small). In the other, the confining well is shallow (ω is small), the bases overcome a small effective barrier E/k_BT to achieve the same strand separation, and relaxation to equilibrium is slow ($t_{1/2}$ is large). The first of these possibilities seems to correspond more closely to what may actually happen in practice.

What we have attempted to do here is formulate the problem of intermittency in DNA bubble dynamics in somewhat different terms from the successful model introduced by Altan-Bonnet *et al.*[5] There (and in the Fogedby-Metzler quantum Coulomb model[6]), the principal dynamical variable was the *number* of open bases; in our treatment, it is the *distance* separating the two bases to which the chromophores are attached. Both points of view are built around roughly the same molecular considerations, chiefly the presence of a potential that holds the two strands together, and the existence of thermal fluctuations in the medium that disrupt this structure.

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