Randomly Forced DNA

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We study the effect of random forces on a double-stranded DNA in unzipping the two strands, analogous to the problem of an adsorbed polymer under a random force. The ground state develops bubbles of various lengths as the random force fluctuation is increased. The unzipping phase diagram is shown to be drastically different from the pure case.

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Biological processes such as DNA replication and RNA transcription get initiated and then proceed by unzipping of double stranded DNA (dsDNA) by various enzymes like helicase, polymerase, etc. [1]. These enzymes exert force on dsDNA often directly, but also indirectly by maintaining a fixed distance between the DNA strands (a fixed distance ensemble). It was predicted theoretically that a dsDNA unzips to two single strands (ss) when the force exceeds a critical value which depends on temperature [2–7]. The unzipping transition has also been studied experimentally by using single molecule manipulations [8]. A consequence of this force-induced unzipping transition is that in a fixed distance ensemble, a dsDNA shows a coexistence of a zipped (ds) and an unzipped phase, known as a Y fork in biology, with a ''domain wall'' separating the two phases as the junction of the Y. The motion of the domain wall under a local instability either by a direct force or by the motor action of the enzyme leads to a gradual nonequilibrium unzipping (as a propagating front) [9]. However, for RNA polymerase or even dnaA helicase, there is an additional need to open up a bubble at the right place (''origin'') for initiation. Though some force-induced mechanism is expected here, not many details are known.

The unzipping of DNA is a competition between the binding of the base pairs (to be called monomers) and the orientation of individual links connecting the monomers. A force applied at any point (say the end point) gets transmitted to individual bonds to orient each one in the direction of the force. However, for real DNA, there are various sources of inhomogeneities. Commonly studied cases of sequence heterogeneity, stacking energy, etc., generally affect the bound or the ds part of the DNA. In a cellular medium, there are single strand binding (SSB) proteins which bind to single strands. Such bound objects can lead to variation in the response of individual links (or bonds) to the external force. We study the role of such binding proteins in DNA unzipping by considering a situation where the nature of binding is modeled by a randomly oriented force. To avoid much independent randomness, we avoid other heterogeneities like sequence heterogeneity [10]. We compare our results with the DNA pulling at the end.

Polymers with various types of randomness or disorder constitute a special class of disordered problems because of the occurrence of nonsymmetry related (i.e., configurationally distinct) degenerate ground states [11]. The barriers (e.g., in space, in energy) separating these states, the widths of the local wells, etc., then determine the equilibrium and also the dynamic behavior of the polymer. The random problem we discuss here is not one of those studied earlier, but rather shows certain unique features, notably degeneracy of the ground state at special points. All these features, biological motivations apart, make this random force problem stand out on its own. A close cousin is the problem of a directed polymer in a random medium. But this problem is controlled by a ''$T = 0$'' fixed point (in a renormalization group sense) in $D = 1 + 1$ but a disorder-induced phase transition occurs in higher dimensions, $D > 3$. In the present case we shall see a disorder-induced transition, even in $D = 1 + 1$ dimension.

The strands of DNA are complementary to each other and every base in one strand knows its pair on the second strand. Considering the case where the randomness works similarly on the two strands (i.e., either trying to keep the strands closer or unzip), the Hamiltonian in the continuum can be written as [2]

$$H_2 = \int_0^N \left[\frac{1}{2}\left(\frac{@\mathbf{r}_1}{@z}\right)^2 + \frac{1}{2}\left(\frac{@\mathbf{r}_2}{@z}\right)^2 + V(\mathbf{r}(z))\right] dz - \int \mathbf{g}(z) \cdot \left(\frac{@\mathbf{r}_1}{@z} - \frac{@\mathbf{r}_2}{@z}\right) d\dot{z} \quad (1)$$

where $\mathbf{r}_i(z)$ is the d-dimensional position vector of a monomer at a length z along the contour of the ith strand from one end $z = 0$, N is the length of each strand or polymer, $V(\mathbf{r})$ is the binding potential, $\mathbf{r}(z) = \mathbf{r}_1(z) - \mathbf{r}_2(z)$, and $\mathbf{g}(z)$ is a random force. Both the polymers are tied at end $z = 0$. For the ''pure'' problem, $\mathbf{g}(z)$ is constant and the force term reduces to the standard form $-\mathbf{g} \cdot \mathbf{r}(N)$. The first two terms on the right-hand side represent the elastic energy or the connectivity of each polymer (taken to be Gaussian). The base pair interaction is for monomers at the same location on the two strands. It follows that an equivalent description can be obtained in which the two strands of the DNA are

replaced by a relative chain. The Hamiltonian in terms of $\mathbf{r}(z)$ is

$$H = \int_0^N \left[\frac{1}{2} \left(\frac{@\mathbf{r}}{@z} \right)^2 + V(\mathbf{r}(z)) - \mathbf{g}(z) \cdot \frac{@\mathbf{r}}{@z} \right] dz \qquad (2)$$

with appropriate rescaling to make the elastic constant unity. This H also describes the problem of peeling of an adsorbed polymer by a pulling force [12,13]. Naturally, both the problems have similar universal behavior and many features of DNA unzipping (at least qualitatively) can be understood by studying the unzipping of an adsorbed polymer. It is to be noted that if z is taken as an extra dimension (albeit different from the other d spatial coordinates), then these Hamiltonians also represent directed polymers in $D = d + 1$ dimensions. This is the description we use in this Letter. We choose uncorrelated randomness with $[\mathbf{g}(z)]_{\rm dis} = 0$ and $[g_i(z)g_j(z')]_{\rm dis} = g^2 \ _{ij} \ (z - z')$. Here, $[\cdots]_{\rm dis}$ denotes the quenched average over force realizations. We write $\mathbf{g}(z) = g \ ^{\wedge}(z)$, where the $^{\wedge}$ represents the random direction with unit variance.

The aim of the present Letter is to study the effect of a random force of zero mean on a bound or adsorbed polymer below its thermal unbinding or desorption temperature. If one is away from the DNA melting point or the thermal desorption transition, then the characteristics of the unzipping transition of the pure problem is not sensitive to the dimensionality of the system, as seen explicitly in the exactly solvable directed polymer problem in different dimensions, including $D = 1 + 1$ [4,5]. With that in mind, we use the discretized directed polymer model in $D = 1 + 1$ dimensions.

The lattice version of Eq. (2) is a polymer in $D = 1 + 1$ dimensions, directed along the diagonal of a square lattice [Fig. 1(a)]. At $x = 0$, there is an attractive, impenetrable wall with binding energy $-$ (> 0) which favors adsorption of the polymer on the wall. For DNA this impenetrability implies mutually avoiding chains. One end of the polymer is always kept anchored on the wall while the other is left free. On each bond between the two consecutive monomers, there is a random force $g(z) = g \ (z) [\ (z)$ same for a layer] which is always perpendicular to the wall. The magnitude g related to the standard deviation of the force is kept fixed but the direction $(z) = \pm 1$, i.e., either towards the wall or away from it, is chosen randomly with equal probability so that the average force, $[g \ (z)]_{\rm dis} = 0$. By averaging over the force configurations on the polymer (quenched averaging), we find that even in the absence of a fixed pulling force at the end, there is an unzipping transition if the variance of the force fluctuation exceeds a critical value. The force-temperature phase diagram shows an increase of the critical force with temperature [see Fig. 1(b)]. The critical force starts decreasing only near T_c and becomes zero at T_c. This is to be contrasted with the pure adsorption problem where the critical force decreases monotonically with the temperature.

For every realization of the randomness, the partition function can be calculated exactly as

$$Z^{\{ \ \}}_{n+1}(x) = \sum_{j=\pm 1} Z^{\{ \ \}}_n(x + j) e^{-j \ g \ \{ \ \}(n)} \mathcal{W}; \qquad (3)$$

where $\mathcal{W} = [1 + (e \quad - 1) \ _{x \ 0}]$. The superscript in the above expression denotes a particular realization, and $Z_n(x)$ is the partition function for a polymer with the nth (or the last) monomer at x. Physical quantities are to be averaged over the realizations. Quenched averaging is relevant here because the time scale of changes in the source of randomness is much slower compared to the thermalization of the polymer. One may note that an annealed averaging of Eq. (1) would yield an effective pure adsorption problem *without a force*, though with a reduced elastic constant. The quenched averaging is distinctly different.

To monitor whether the polymer is zipped or unzipped, one needs the average distance of the last monomer from the wall ($\langle \cdots \rangle$ denoting the thermal averaging) $[\langle x \rangle]_{\rm dis} = [\sum_x x Z^{\{ \ \}}_N(x) / \sum_x Z^{\{ \ \}}_N(x)]_{\rm dis}$, and the isothermal extensibility, being the response to the force, can be expressed in terms of position fluctuation of the end monomer

$$[\ \ ]_{\rm dis} \equiv \left[\frac{@\langle x \rangle}{@g} \Big| \ _T \right]_{\rm dis} = (k_B T)^{-1} [\langle x^2 \rangle - \langle x \rangle^2]_{\rm dis}. \qquad (4)$$

In the presence of a fixed applied pulling force at the end, the recursion relation can be solved exactly [4,5,12,13]. In this case, the critical force is $g_c(T) = (k_B T/2) \ln[e \quad - 1]$ with a temperature-driven classicalxi2.fiD40p T

obtained by flipping the adsorbed monomers. Figure 2(a) shows the four possible force configurations of a monomer which is adsorbed on the wall. Let n_1, n_2, n_3, and n_4 be the numbers of such configurations, then we have $n_1 + n_2 + n_3 + n_4 = N$=2, since the geometry of the model permits only N=2 monomers on the wall. For small g, there is no gain in energy in flipping. The only vertex for which we can gain is vertex (iii), if $-$ $+ 2g > -2g$. Therefore, if $g >$ =4, one expects to see small bubbles. Below this force, the ground state is unique. One may note that the last term of Eq. (1) on integration by parts, contributes a fixed force at the end plus a force gradient which acts locally on the chain. For a negative force gradient, the strands minimize the free energy by maximizing the distance between them. Thus, the bubble formation is not restricted to lattice models only and has wider validity. For $g >$ =4, after flipping all the type (iii) vertices, the average energy is

$$E_0 = -(n_1 + n_2 + n_4) \quad - 2g(n_2 + n_3)$$
$$= -\frac{N}{8}(3 \quad + 4g); \tag{5}$$

taking all the four possible vertices to be equally probable. Equating this with the energy of the unzipped state, $-Ng$, in which the polymer favors a configuration where each of the bond gets oriented in the local force direction, we get the critical value of the force, $g_c = 3$ =4. This analysis shows that there is a critical force fluctuation above which the polymer favors the unzipped state at $T = 0$. Similar arguments would indicate that larger bubbles are possible for $g >$ =2. These bubbles are different from the bubble (eye) phase observed when the pulling force is applied in the interior of the DNA [14].

By using the exact transfer matrix for the recursion relation of Eq. (3) (and using logs to increase numerical accuracy), the ground state energy can be determined from the free energy at very low temperatures. By averaging over 10^5 force realizations at $T = 0.001$, the estimated ground state energy per monomer for $N = 256$ is shown in Fig. 2(b) for various values of g. The same quantity is also calculated using the single flip Monte Carlo at $T = 0$ (squares) for $N = 1024$. Data from both the methods match excellently and are in agreement with the prediction by the above analysis [Eq. (5)] for =4 $\leq g \leq 3$ =4. The data also show that for $g =$, the free energy is $-Ng$, which is the energy of the unzipped state.

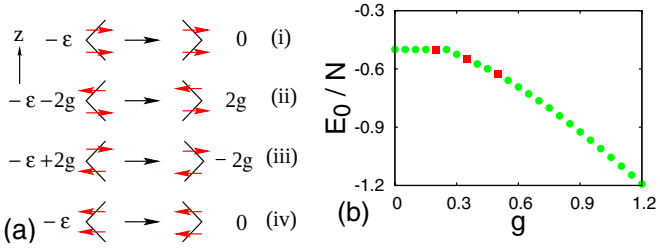

FIG. 2 (color online). (a) The energy cost in flipping a monomer on the wall. (b) Ground state energy per monomer, E_0=N, as a function of force obtained for $N = 256$ using the exact transfer matrix at $T = 0.001$ (circles). Estimates from single flip Monte Carlo at $T = 0$ for $N = 1024$ (square) (= 1).

A surprising feature of the model is that the ground state configuration of the polymer depends on g with degeneracies appearing when g is an integral multiple of =4. For example, for $g =$ =4, flipping of vertex (iii) does not cost any energy. On an average, there are N=8 such twofold degenerate vertices. Therefore, the entropy of the ground state for $g =$ =4 is $S_0(g =$ =4) = (N=8) ln2. Similarly, if in a configuration, vertices (i) and (iii) are side by side, then flipping of these two vertices does not cost any energy if $g =$ =2. Further opening of bubbles would be possible by taking advantage of the forces on sites away from the wall. One can similarly argue for other values of g. There is a gradual increase of bubble sizes as g is increased beyond $g =$ =4. From the free energy we calculated the entropy at low temperatures. After averaging over 10^6 realizations and then extrapolating to $T = 0$ one gets the zero temperature or residual entropy which for $g =$ =4 agrees nicely with the entropy calculated above.

In order to explore the effect of thermal fluctuations, we study the force-distance isotherms. The $\langle x \rangle$ vs g isotherms for four different samples of length $N = 1024$ and also the average over 10^5 samples are shown in Fig. 3(a). The isotherm of an individual sample shows steps similar (but different in origin) to the steps seen in the force-distance isotherms when an adsorbed polymer is subjected to a pulling force in a random environment [13]. The steps for the random medium case appear due to the pinning of the polymer in the attractive pockets formed by the random distribution of energy on the lattice sites with the force attempting to depin from these pockets. In the present case, there is a mutual competition between the set of bonds with the force towards the wall and the others with the force in

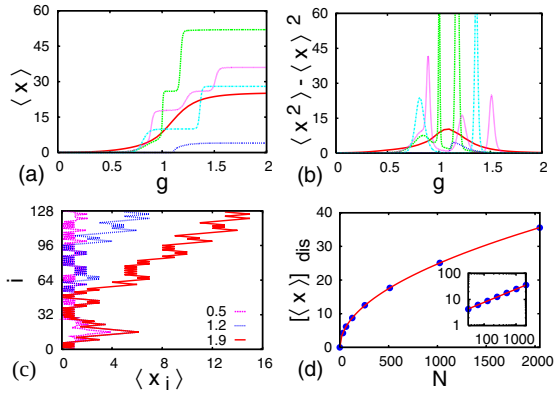

FIG. 3 (color online). (a) $\langle x \rangle$ vs g, (b) extensibility for four different samples of length $N = 1024$ and the average over 10^5 such samples (thick solid lines). (c) Typical configurations for $N = 128$ for three different g as indicated. (d) $[\langle x \rangle]_{\text{dis}}$ vs N for $g = 2$. The solid line is the best fit to the data. All at $T = 0.3$ with = 1.

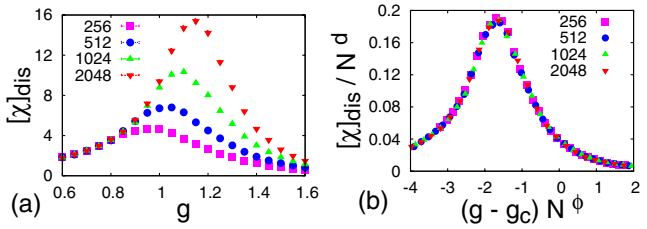

FIG. 4 (color online). (a) Extensibility $[\ ]_{\rm dis}$ vs g at $T = 0{:}3$ with $= 1$ for various chain lengths. (b) Data collapse of the extensibility.

the opposite direction. The former set would like to opt for a state with monomers on the wall while the rest are trying to unzip them. The steps in the isotherm lead every time to a comblike extensibility as shown in Fig. 3(b). This indicates that the polymer responds in a ''jerky'' manner, by opening up local pockets of pinned regions. This is corroborated in Fig. 3(c), where the locations of individual monomers for a chain of length $N = 128$ are plotted for three different g chosen from different plateaus of the isotherm. It indeed shows adsorbed regions followed by unzipped regions and unzipping of adsorbed regions as g increases.

Figure 3(d) shows $[\langle x\rangle]_{\rm dis}$ vs N for $g = 2$ at $T = 0{:}3$ (unzipped region). The solid curve which is the best fit to the data shows that $[\langle x\rangle]_{\rm dis} = aN$ with $a = 0{:}753 \pm 0{:}006$ and $= 0{:}505 \pm 0{:}001$, i.e., the polymer stays at a distance of $\sqrt{N}$ from the wall and the configuration is *not* like a directed polymer in a random medium for which $=$ 2=3. One may add that in the random medium problem the polymer gets fully stretched by the force in the unzipped state (i.e., depins from all the pockets).

The phase diagram is obtained from the disorder averaged extensibility. Figure 4(a) shows the plot of extensibility $[\ ]_{\rm dis}$ vs g, for the polymer of lengths $N = 256$, 512, 1024, and 2048 at $T = 0{:}3$ averaged over 10^5 realizations. The growth in the peak with N indicates the possibility of a divergence in the thermodynamic limit ($N \to \infty$). Its position can be located using the finite size scaling of the form $[\ ]_{\rm dis} = N^d \mathcal{Y}((g - g_c)N\ )$, where g_c is the force at which the discontinuity is located in the thermodynamic limit and d and are the characteristic exponents. The data collapse obtained using the Bhattacharjee-Seno procedure [15] is shown in Fig. 4(b) which gives $d = 0{:}58 \pm 0{:}02$, $= 0{:}22 \pm 0{:}01$, and $g_c = 1{:}46 \pm 0{:}04$, with $d= \approx 2{:}6$, so that $[\ ]_{\rm dis} \sim |g - g_c|^{-2{:}6}$. Similar collapse is also found for $[\langle x\rangle]_{\rm dis}$ (not shown). This indicates a continuous transition though the exponent is different of that of the heterogeneous DNA sequence. We adopt this procedure at various temperatures to trace out the g-T phase diagram. For temperatures near T_c, lengths up to $N = 8192$ are used.

The phase diagram is shown in Fig. 1(b). In contrast to the pure case, there is an increase in $g_c(T)$ because of the loss of the residual zero temperature entropy of the bound state [5].

In conclusion, we have introduced and studied the problem of a randomly forced DNA or its equivalent randomly forced adsorbed polymer. The fluctuating force unzips the DNA by a gradual increase of bubble sizes. For some discrete values of the force (integral multiple of =4 in our case), the ground state of the random force problem is degenerate and contains bubbles, which is in contrast to the pure problem where there is only one ground state. It suggests the possibility of opening up local bubbles in selective regions (proper pockets of force distribution) without unzipping the whole DNA. Only experiments can tell us if the initiation of DNA replication or RNA transcription is through such a mechanism with the smaller molecules playing the role of random force agents.

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