Phase diagram for unzipping DNA with long-range interactions

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We present a critique and extension of the mean-field approach to the mechanical pulling transition in bound polymer systems. Our model is motivated by the theoretically and experimentally important examples of adsorbed polymers and double-stranded DNA, and we focus on the case in which quenched disorder in the sequence of monomers is unimportant for the statistical mechanics. The critical pulling force, and we predict a re-entrancy phase at low temperatures which has not been previously discussed. We also consider the case of non-equilibrium pulling, in which the external force probes the local, rather than the global structure of the dsDNA or adsorbed polymer. The dynamics of the pulling transition in such experiments could illuminate the polymer’s loop structure, which depends on the nature of excluded volume interactions.

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Recent experiments using micromanipulation techniques to pull and stretch single molecules have led the way to a better understanding of statistical properties of polymer systems that cannot be probed in the bulk. Theoretical work on these systems has focused on the complex phenomena arising from heterogeneity in the sequence of monomers. In this Letter we study the simpler case of a homopolymer under the influence of an external force. We find that some of the same phenomena caused by disorder in a heteropolymer can arise in a homopolymer system near its thermal denaturation temperature due to inhomogeneities in the polymer’s structure. We also predict a re-entrant phase in the critical force phase diagram at low temperatures, which should be observable in both homopolymer and heteropolymer systems.

The Hamiltonian for a polymer in an external field takes the general form

\[ H_0 = \int_0^N \frac{T d}{2 b^2} \left( \frac{d \mathbf{r}(n)}{dn} \right)^2 + \phi(\mathbf{r}(n)) \right] dn + E[\mathbf{r}(n)] \]  

with \( d \) the spatial dimension and \( b \) the Kuhn length. Throughout this Letter, we set \( k_B = 1 \). \( \phi(\mathbf{r}) \) is an attractive potential arising, for example, from the interaction with an adsorbing surface, or from the attraction between two strands in double-stranded DNA (dsDNA). We assume that \( \phi \) is short-ranged, and depends only on the local coordinate, \( \mathbf{r}(n) \), describing the distance from the adsorbing surface or the separation between the two dsDNA strands. In the case of a homopolymer, \( \phi \) does not depend on the position along the sequence. Finally, the volume interactions between different segments of the chain are represented by the term \( E[\mathbf{r}(n)] \).

In the mean-field approximation, interactions between different sections of the polymer chain, together with whatever external fields are present, contribute to an overall effective potential, \( \phi_{\text{eff}} \), for each monomer. This field is derived using conditions of self-consistency, and for low temperatures it should admit bound states corresponding to adsorbed or zipped conformations. In this framework, every monomer far from the ends of the molecule experiences the same field, and thus contributes the same amount to the overall bound-state free energy. The mean-field free energy thus reduces to \( F_{\text{MF}} = N \lambda \), where \( \lambda \) is determined by the self-consistent field, \( \phi_{\text{eff}} \). Recent theoretical work has explored the effect of an external pulling force, represented by a vector potential term in the energy, on the mean-field thermodynamics. A polymer that is adsorbed to an attractive surface or “zipped” together with a complementary chain as in dsDNA, can be pulled out of the bound state by a force exerted, for example, by a glass bead attached at one end of the molecule. The desorbed section of a polymer or the unzipped part of dsDNA has a force-dependent free energy, \( F = N g(F) \), which decreases monotonically with \( F \). The functional form of \( g(F) \) can be obtained from a Gaussian or a freely-jointed chain model for the stretched polymer. At a critical force defined by \( g(F_c) = \lambda \), the adsorbed or double-stranded state becomes unstable with respect to the stretched part of the molecule, and a sharp unzipping/desorption transition occurs. The mean-field model relies on the strong assumption that every bound monomer experiences the same effective field, so that the interaction between the stretched and bound parts of the molecule is independent of the number of monomers already pulled out. This feature of the mean-field model breaks down, for example, in the presence of variations in the binding energies for different base pairs in dsDNA, or sequence disorder in an adsorbed polymer. The effect of such sequence heterogeneity on the pulling transition has been the subject of careful study, and several interesting phenomena have been predicted to emerge in these systems. Yet the simple mean-field model of the pulling transition can break
down even for totally homogeneous polymers when long length-scale correlations in the structure appear near the temperature of thermal unbinding (denaturation or desorption), $T_c$. Intuitively, thermal fluctuations near $T_c$ cause large loops and sub-chains to form. The pulling force interacts with the bound polymer only in the local region near the end of the stretched-out part of the molecule, so the local structure is important in determining the behavior of the pulled polymer. Spatial inhomogeneities caused by large loops near $T_c$ affect both the equilibrium and the non-equilibrium behavior of a bound polymer in response to a pulling force. We consider these effects in turn.

The pulling force applied to one end of the polymer adds a vector potential term in the overall Hamiltonian \[ \mathcal{H} = \mathcal{H}_0 + \mathcal{H}_{\text{pull}}, \]

\[ \mathcal{H}_{\text{pull}} = -\mathbf{F} \cdot \mathbf{r}(0) = F \int_{n=0}^{N} \left( \frac{dz}{dn} \right) dn - Fz(N). \] (2)

We have assumed that the pulling force, $\mathbf{F} = F\hat{z}$, is perpendicular to the adsorbing surface. Neglecting the effect of the finite size of the molecule, we can drop the last term. After tracing over all configurations, \( \{\mathbf{r}(n)\} \), in the partition function, we are left with the following contribution to the free energy from the pulled-away part of the molecule \[ g(F) = -\frac{F^2}{2FbT}. \] Accordingly, the freely-jointed chain model, which is more realistic at high pulling forces and low temperatures, gives:

\[ g(F) = -T \ln \left( \frac{T \sinh(Fb/T)}{Fb} \right). \]

In the mean-field framework, the pulling transition occurs at $g(F_c) = \lambda$, or

\[ F_c = \frac{\sqrt{2d} \ln T/b^2}{b} \] (Gaussian)

\[ F_c = (T/b) \sinh(F_c b/T) e^{-\lambda/T} \] (Freely-Jointed) (3)

The mean-field approximation should hold good at low temperatures, since most monomers will be in the bound state and only short loops will form. As $T \to 0$, the free energy per monomer, $\lambda$, converges to some constant value, $-\lambda_0$, corresponding to the binding energy of one monomer. The Gaussian model thus predicts $F_c \sim (\lambda_0 T)^{1/2}$; however, in this regime the Gaussian model for the free energy of a stretched chain is not valid, since there is little elasticity in the polymeric bonds. We instead rely on the freely-jointed model, which gives at low temperatures: $g(F) \approx -Fb - T \ln(T/2Fb)$, so that $F_c(T = 0) = \lambda_0 / b$. The limiting behavior for $T \ll \lambda_0 b$ is given by

\[ F_c \approx \lambda_0 / b - T \ln \frac{T}{2\lambda_0 b}. \] (4)

We thus expect to observe two desorbed phases, one at high temperature and another at sufficiently low temperature, for $F > \lambda_0 / b$. At high temperatures, the entropic advantage of the unbound monomers overrides the energetic stability of the bound phase. At low temperatures the free energy per monomer of the stretched part of the polymer or DNA increases as the chain becomes stiffer. The effect of lowering temperature near $T = 0$ is to stiffen the chain, making it easier to pull out the polymer or unzip the dsDNA. The temperature at which this re-entrant phase should exist is determined by the specific properties of the chain, in particular the Kuhn length, $b$. In fact, at low temperatures, we expect $F_c(T, b) = \frac{1}{2} F_c(T, b = 1)$. This prediction may allow for experimental determination of the relative chain stiffness, related to $b$, for different molecules, through careful low-temperature investigation of $F_c$.

Close to the thermal unbinding temperature, $T_c$, as $\lambda$ approaches zero, the mean-field approximation breaks down because of long-range correlations (corresponding to long loops) in the structure of the bound chain. Indeed, within the mean-field framework the mean size of loops grows near $T_c$, as \[ \langle k \rangle \sim \lambda^{-1} \sim |T - T_c|^{-2}. \] Forming a loop carries an entropic cost, which depends non-linearly on the loop size, not simply on the local density of monomers. Dealing directly with the interaction energy, $E[\mathbf{r}(n)]$, complicates the analytic problem, although attempts have been made to simulate this full model numerically \[ \text{[8]}. \] We will follow a different route first proposed by Poland and Scheraga \[ \text{[9, 10]}, \] in which the mean-field model is extended by introducing a general form for the entropy of a loop of length $k$,

\[ S(k) = A + k \ln(s) - c \ln(k), \] (5)

where $s$ is a non-universal constant, and $c$ is determined by the properties of the loops. In particular, for non-interacting monomers ($E[\mathbf{r}(n)] \equiv 0$) the loops are random walks in $d$ dimensions, with $c = d/2$, whereas excluded volume interactions between monomers tend to increase the value of $c$ \[ \text{[11]}. \]

The binding energy due to the potential, $\phi$, leads to a statistical weight $\omega = e^{-\phi_0/T}$ for each bounded base-pair or adsorbed link. In fact, the only relevant parameter in this model is the energy difference between the bounded and unbounded links, $\ln(\omega) - \ln(s)$, so that we can simply put $s = 1$.

We work with the grand partition function: \[ Z(z) = \sum_{m=1}^{\infty} Z(m)z^m, \] where $Z(m)$ is the canonical partition function for a chain of $m$ links, and $z$ is a fugacity which controls the size of the polymer. In this ensemble, the chain can be regarded as an infinite collection of loop-train pairs, giving:

\[ Z(z) = \frac{V_0(z)U_L(z)}{1 - V(z)U(z)} \] (6)

where $U(z) = \sum_{k=1}^{\infty} \omega^k z^k$ and $V(z) = \sum_{k=1}^{\infty} \omega^k z^k$. The boundary conditions are $V_0 = 1 + V(z)$ and $U_L = 1 + U(z)$. We will be interested in the thermodynamic limit,
The number of monomers pulled away goes like weight per monomer of the stretched part of the polymer. The thermal desorption or denaturation transition at \( z^* \) at the thermal desorption transition, with \( \omega > 0 \). We can introduce an external pulling force through an external parameter, \( F \) and \( T \), are fixed, so that the pulled polymer remains in equilibrium during the experiment. In fact, as long as these parameters are varied sufficiently slowly, the system will adjust to changes “adiabatically.” Thus, for example, the parameter \( m \) will be characterized by the force-dependent distribution described above, while the globular part of the polymer will display a corresponding, temperature-dependent distribution of loop sizes. The behavior of this distribution will depend on \( c \) close to \( c_c \).

Fast variations in the pulling force, on the other hand, may lead to non-equilibrium behavior, in which the distribution of loop sizes plays a crucial role. We can estimate the relevant timescale for this “non-adiabatic” pulling from the Rouse model for the dynamics of an ideal Gaussian chain. The relaxation time for correlations between the ends of a chain of length \( N \) is \( t_N = N^2b^2\xi/(3\pi^2T) \), where \( \xi \) is the coefficient of friction for monomers in the solvent. In general, the relaxation time for a section of the chain of length \( k \) scales as \( t_k \sim k^2 \). If the external force dislodges monomers at a rate of \( 1/t_F \), we see that for \( t_F \gg t_N \) the polymer will remain in equilibrium during the pull-out.

On the other hand, if \( t_F \) is much smaller than the relaxation time of the smallest loops, the polymer will not have time to re-arrange itself as \( F \) is ramped up, and whole loops will be pulled out at once. In this case, the force-extension curve will display jumps corresponding to the pullout of individual loops. This behavior is similar to that derived in models for polymers with sequence disorder, but the randomness in this case arises from...
rather than with the entire molecule. Near the polymer locally, at the level of an individual loop, sufficiently close to \( T \), \( \eta \) is attached to the surface or the complementary strand monomers are unbound, and we can assume the last loop containing link \( \ell \). The distribution of loop sizes has a non-Gaussian distribution, and thus \( \eta \) could be faster than the relaxation time of the loops. In this regime even relatively slow variations in the pulling force could be faster than the relaxation time of the loops. Simulations and analytical calculations on the equivalent of Eq. (1) for heteropolymers have shown how the size of jumps and plateaux in the force-extension curve vary as \( F \) approaches \( F_c \). As mentioned above, analysis of Eq. (1) is complicated by the non-Gaussian distribution of the “noise” term, \( \eta \), but simulations could elucidate the analogy between the effects of structural inhomogeneities in pulled homopolymers and sequence disorder in heteropolymer systems.

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\[ F_c = \sqrt{\frac{2dT}{b^2} \langle \eta \rangle} \]  

where the brackets indicate averaging over the distribution of loop sizes, \( \langle \eta \rangle \propto \sum \frac{\ln+\eta(S) \langle \eta \rangle^k}{k} \). Fig. 2 shows the phase diagram in the non-adiabatic regime near \( T_c \), for three values of \( c \). In all three cases, \( F_c \) vanishes at a temperature less than \( T_c \), in contrast with the adiabatic case. This temperature is determined by the binding energy, \( \lambda_0 = -T \ln \omega \), of the single bond at the loop’s end.

Note that, as the mean loop size diverges for \( c \leq 2 \), the timescale defining adiabatic pulling diverges. In this regime even relatively slow variations in the pulling force could be faster than the relaxation time of the loops. The theory of polymer dynamics in pulled homopolymers and sequence disorder in heteropolymer systems.

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\[ \mathcal{F}(m) = mg(F) + \sum_{i=1}^{N-m} \eta_k(i) \]  

where \( \eta_k(i) \) is the free energy per monomer of the loop containing link \( i \). The distribution of loop lengths is simply \( P(k) \propto e^{k\eta} = \frac{\langle \eta \rangle^k}{k} \). Eq. (1) resembles the Langevin equation recently proposed as a model for the pulling transition in a heteropolymer with sequence randomness [2], but in this case the randomness due to the loop distribution has a non-Gaussian distribution, and thus cannot be analyzed in the simple framework of Brownian motion.

Eq. (1) suggests that the critical pulling force in the non-adiabatic regime, \( F_c \), is smaller than in the adiabatic regime. This is because the configurational entropy of a single loop is smaller than that of an ensemble of loops with variable lengths. In particular,