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## LETTER TO THE EDITOR

## Mechanical denaturation of DNA: existence of a low-temperature denaturation

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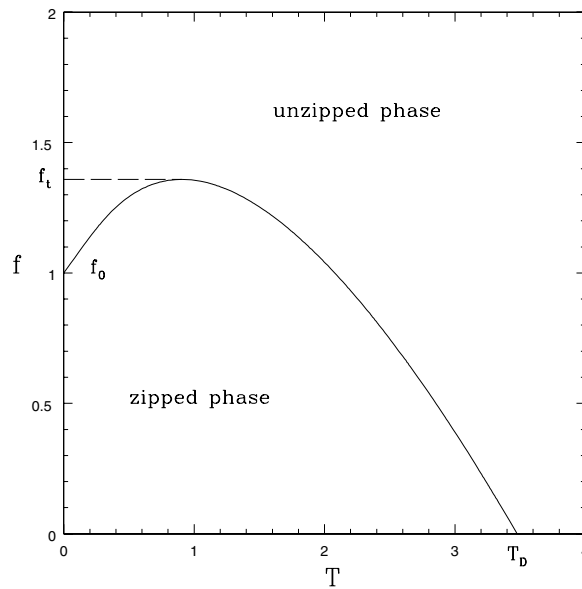
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### Abstract

Recent theoretical predictions on DNA (deoxyribonucleic acid) mechanical separation induced by pulling forces are numerically tested within a model in which self-avoidance for DNA strands is fully taken into account. DNA strands are described by interacting pairs of self-avoiding walks which are pulled apart by a force applied at the two extremities. The whole phase diagram is spanned by extensive Monte Carlo simulations and the existence of a low-temperature denaturation is confirmed. The basic features of the phase diagram and the re-entrant phase boundary are also obtained with a simple heuristic argument based on an energy–entropy estimate.

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In the last few years, the enormous technical improvements of experimental devices such as atomic force microscopes [1, 2], optical tweezers [3, 4], and glass microneedles [5, 6] have allowed micromanipulation of single biological systems, and the determination and characterization of new, in part unexpected, behaviours of biomolecules [7]. These developments have been particularly interesting and innovative for DNA molecules. DNA micromanipulation techniques involve handles attached to the two ends of the molecule which serve as anchoring points to manipulable physical supports [8]. In this way it has been possible to study the response of DNA to external torques [9, 10] and its mechanical unzipping in the absence of enzymes [11, 12]. Nevertheless, only very recently have theoretical investigations started to consider the denaturation of DNA under the presence of forces or torques [13–15]. On the other hand, theoretical studies of thermal denaturation (or melting) of DNA have a much longer history [16, 17] (for more recent studies see [18, 19]).



**Figure 1.** The exact force ( $f$ ) versus temperature ( $T$ ) phase diagram as obtained in [23] for a directed model ( $d = 2$ ) of DNA. See equation (1) for the definition of the force. The values of  $f_t$ ,  $f_0$ , and  $T_D$  are model dependent.

Recently, Bhattacharjee [20] has extended a minimal model [16] in which the two strands of DNA are ideal polymer chains, introducing a pulling force applied to two extremities<sup>5,6</sup>. By a mapping into a non-Hermitian quantum mechanics problem, he has shown that the relative polymer can be pulled out (i.e. the DNA can be unzipped) only if the applied force exceeds a critical value.

These results have been further developed [23, 24] by considering analytically solvable models in which DNA strands are represented by directed walks. Surprisingly, the force versus temperature phase diagram revealed the presence [23, 24] of a novel re-entrant unzipping transition at low temperature (see figure 1). These results have been subsequently confirmed by other authors [25, 26] within ideal chain models of DNA.

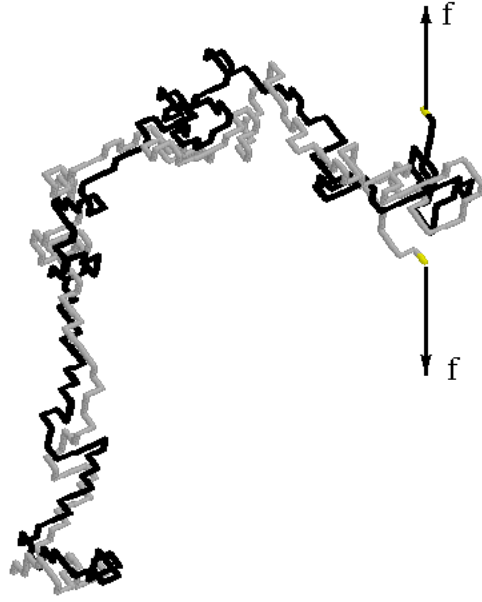
The aim of our paper is to study the phase diagram of DNA in the presence of a pulling force with a more realistic model in which self-avoidance for the DNA strands is explicitly taken into account to verify the robustness of the low-temperature re-entrance.

We model [16, 19] the two strands of a  $2N$ -base-pair DNA by two interacting  $N$ -step self-avoiding walks (SAW), on a cubic lattice,  $\Gamma^1 = \{\Gamma_0^1, \Gamma_1^1, \dots, \Gamma_N^1\}$  and  $\Gamma^2 = \{\Gamma_0^2, \Gamma_1^2, \dots, \Gamma_N^2\}$ , with  $\Gamma_p^i$  as the lattice site occupied by the  $p$ th monomer of the  $i$ th chain ( $i = 1, 2$ ). The first monomers  $\Gamma_0^1, \Gamma_0^2$  are kept fixed at one lattice unit apart. Each monomer (site) on a strand corresponds to a base and it is supposed to have its complementary monomer at the same contour position in the other strand. Two complementary monomers are favoured to be in contact (i.e., if they occupy two nearest-neighbour sites of the lattice) by an energetic gain  $\epsilon$  representing the binding energy.

In this approach [16, 19–21] the sequence of bases is not explicitly considered since the model is coarse grained in character. In this respect each monomer is not to be thought of as a

<sup>5</sup> More recently a similar model which takes into account also the presence of sequence disorder has been studied [21].

<sup>6</sup> The dynamics of unzipping has also been studied recently: see [22, 23].



**Figure 2.** A typical configuration of double-stranded DNA chains ( $2N = 200$ ) obtained with the model described in the text. The different shades indicate the two different strands.  
(This figure is in colour only in the electronic version)

single base, but as a group of bases (block). Consequently a mismatch between corresponding blocks has to be very disfavoured with respect to a correct matching. This aspect is adequately treated by our model.

To describe the mechanical unzipping of DNA, an energetic term— $\vec{f} \cdot \vec{r}$  is added where  $\vec{r} = \Gamma_N^1 - \Gamma_N^2$  is the vector joining the two ends of the strands and  $\vec{f}$  is an external force taken, without loss of generality, along the  $z$ -axis, e.g.  $\vec{f} = f\hat{e}_z$  (see figure 2). Note that at  $f = 0$ , this model is in the same universality class as that of [19].

The Hamiltonian of the problem is then given by

$$H_N = -\epsilon \left( \sum_{i=0}^N \delta(|\Gamma_i^1 - \Gamma_i^2|, 1) \right) - f\hat{e}_z \cdot \vec{r} \quad (1)$$

where  $\delta(a, b)$  is the Kronecker delta and  $|x - y|$  is the Euclidean distance between  $x$  and  $y$  in lattice units.

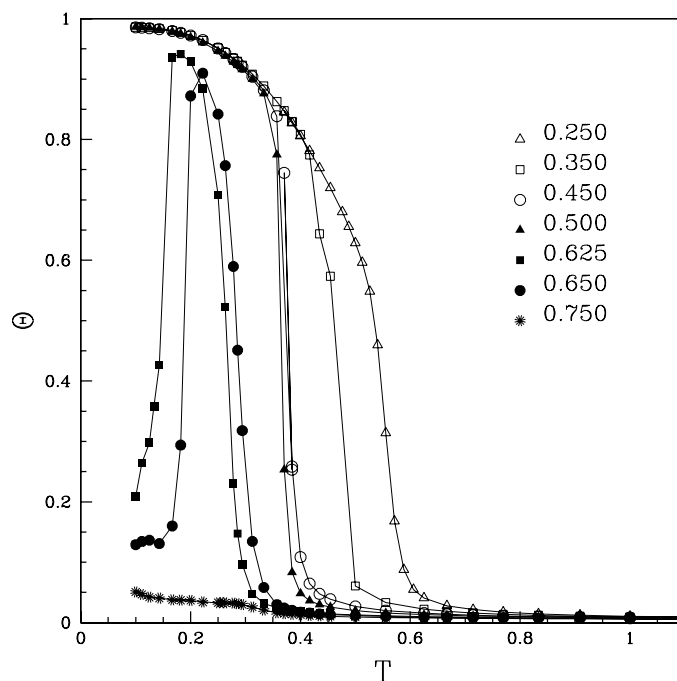
Throughout all the calculations,  $\epsilon = +1$ , and therefore all the thermodynamic properties of the systems depend on the temperature  $T = \beta^{-1}$  and on the force  $f$ . The free energy per monomer  $\mathcal{F}_N(\beta, f)$ , is

$$\mathcal{F}_N(T, f) = -\frac{1}{\beta N} \log \left( \sum \exp(-\beta H_N) \right) \quad (2)$$

where the sum is over all possible pairs of  $N$ -step SAWs  $\Gamma^1$  and  $\Gamma^2$ .

The phase diagram can be studied by looking at the average fraction number of contacts [16]  $\Theta$  and at the  $z$ -component of the average end-point separation  $\langle r^z \rangle$  defined as

$$\Theta = \frac{\langle N_c \rangle}{N} = -\frac{\partial}{\partial \epsilon} \mathcal{F}_N \quad \langle r^z \rangle \sim \frac{\partial}{\partial f} (\mathcal{F}_N N). \quad (3)$$



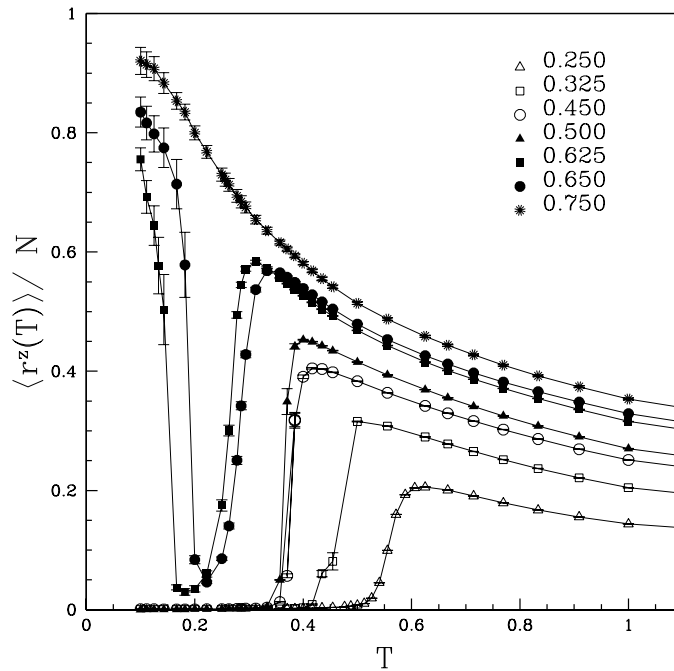
**Figure 3.** Average fraction of bound pairs  $\Theta$  versus  $T$ , for several values of the force  $f$  and for  $2N = 150$ . The error bars are of the size of the symbols. The two peaks ( $f = 0.625$  and  $0.65$ ) signal a zipped phase between two unzipped regions (re-entrance).

In the denaturated regime,  $\Theta$  should vanish, whereas it should be nonzero in the zipped phase. To compute averages, for fixed values of  $f$  and  $N$ , Monte Carlo (MC) simulations of the model have been performed by a Metropolis-based hybrid algorithm [27, 28] that consists of local and global (pivot moves) deformations attempted on each strand of the polymer. In addition, a move that tries to interchange the position of pairs of zipped (or unzipped) portions of the double chain has been considered.

The efficiency of the algorithm has been further enhanced by the multiple-Markov-chain sampling scheme [28, 29], a method that recently has been shown to be quite effective in exploring the low-temperature phase diagrams of interacting polymers. All the runs have been performed by covering, with at most 30 different Markov chains, a large portion of the temperature space ranging from  $T = 3$  down to 0.1. The values of  $N$  considered range from  $2N = 50$  up to 150 and the values of  $f$  go from  $f = 0$  up to 1.

In figures 2 and 3 the numerical results respectively for  $\Theta$  and  $\langle r^z \rangle / (2N)$  are plotted, as a function of  $T$ , for different values of the force strength  $f$  and for systems of  $2N = 150$  monomers. The data signal clearly the presence of three distinct regimes.

- (a) For  $f < f_0 \sim 0.5$  the system undergoes a transition from the denaturated to the zipped regime. In particular at  $f = 0$  results similar to those found in [19] are re-obtained, namely a first-order-like transition at  $T_D = 0.58 \pm 0.02$ , where however the fluctuation in the size of the ‘bubbles’ diverges. Interestingly, our data support the prediction that the critical force near the melting point ( $T_D$ ) is  $f \sim |T_D - T|^a$  with  $a < 1$  [26, 30] (see also below). This is different from the three-dimensional Gaussian chain case [20] or the directed case of figure 1 [23] (for  $d = 1 + 1$ ) where one finds  $a = 1$ . In these two cases the zero-force melting transition at  $T_D$  is continuous.



**Figure 4.** End-to-end separation in the force direction versus  $T$ , for different values of the force  $f$  for  $2N = 150$ . Error bars correspond to one standard deviation. The two minima ( $f = 0.625$  and  $0.65$ ) signal a zipped phase between two unzipped regions (re-entrance).

- (b) For  $f_0 < f < f_t \sim 0.70$  the unzipped/zipped transition is still present, but if the temperature is further lowered the two strands separate again through a low-temperature denaturation or unzipping induced by the presence of the force. This is established by the peaks in figure 3 and by the minima in figure 4 for  $f = 0.625$  and  $0.65$ . Analysis of the specific heat peaks for different chain lengths supports the assertion that both of these transitions are first order. One might think of the existence of a subtle difference between the low- and the high-temperature denaturation. To explore this possibility we studied the size of the molten ‘bubbles’. For  $f = 0$  a simple argument [19] predicts that the size fluctuation of this ‘bubble’ diverges when the thermal denaturation temperature  $T_D$  is approached from below. As already mentioned we observed this effect for  $f = 0$ , but not for  $f \neq 0$ , both approaching the low-temperature transition from above and the high-temperature transition from below. We explain this fact by noticing that for  $f \neq 0$  the transition temperature is less than  $T_D$  and the part of the two strands containing the ‘bubbles’ is not influenced by the presence of the external force (the external force acts as a boundary effect). Thus, by approaching the transition line from the zipped phase, bubbles can never become critical if  $f \neq 0$ . Therefore we conclude that from a statistical point of view low- and high-temperature denaturation transitions are equivalent.
- (c) For  $f > f_t$  the pulling force always dominates over the base–base interaction and the system is always in the denaturated state. The value of  $f_0$  can be exactly calculated, and the basic features of the phase diagram and the re-entrant phase boundary can be obtained with a simple heuristic argument based on an energy–entropy estimate. Indeed at  $T = 0$ , when thermal fluctuations are absent, the only allowed configurations are those in which the first  $l$  monomers of the strands are parallel and form  $l$  contacts, whereas the remaining

$N - l$  point in opposite directions parallel to the force. Hence, the resulting energy is a simple function of  $l$ :

$$E(l) = -l(1 - 2f) - f(2N + 1). \quad (4)$$

For  $f > 1/2$  the energy minimum occurs for  $l = 0$  (complete stretching) whereas for  $f < 1/2$  it occurs for  $l = N$  (complete zipping). This argument states definitively that  $f_0 = 1/2$  in full agreement with our numerical findings. Notice that for  $f = f_0 = 1/2$ ,  $E(l)$  is independent of  $l$ , indicating coexistence.

For low enough temperatures we expect the dominant configurations to still be Y-like configurations with  $2(N - l)$  monomers zipped and two 'free' strands each of length  $l$  whose extrema are kept at a relative position  $\vec{r}$  by the force  $\vec{f}$ . In this Y-model the energy is thus given by

$$E = -(N - l)\epsilon - \vec{r} \cdot \vec{f} \quad (5)$$

whereas the entropy is

$$S = \log [P_{2l}(\vec{r})\mu_u^{2l}\mu_z^{N-l}] \quad (6)$$

where  $P_N(\vec{r})$  is the probability that an  $N$ -step strand has an end-to-end displacement  $\vec{r}$  and  $\mu_u$  and  $\mu_z$  are the effective coordination of the single strand and of the double strand respectively. For the simple model introduced before,  $\mu_z = \mu_u$ , but in general this need not be true.

It is well known [31] that

$$P_{2l}(\vec{r}) \sim \exp \left[ - \left( \frac{r}{l^\nu} \right)^\delta c \right] \quad l^\nu \ll r \ll l \quad (7)$$

where  $r = |\vec{r}|$ ,  $\delta = (1 - \nu)^{-1}$ ,  $\nu$  is the usual polymer critical exponent [31], and  $c$  is a constant. For an ideal polymer,  $\nu = 1/2$ , and one recovers the usual Gaussian distribution.

In the last equation power-law corrections lead to subleading terms in the entropy estimate. From the last three equations the following free energy is obtained:

$$F(l, \vec{r}) = l \left( \epsilon - T \log \frac{\mu_u^2}{\mu_z} \right) - \vec{r} \cdot \vec{f} + cT \left( \frac{r}{l^\nu} \right)^\delta + \text{constant}. \quad (8)$$

Minimization of  $F$  with respect to  $\vec{r}$  yields

$$r(l, f) = l \left( \frac{f}{c\delta T} \right)^{\frac{1}{\delta-1}} \quad (9)$$

where  $r$  is the magnitude of  $\vec{r}$  in the direction of  $\vec{f}$ . This  $r$  gives a free energy

$$F(l) \equiv F(l, r(l, f)) = l \left[ \epsilon - T \log \frac{\mu_u^2}{\mu_z} - \frac{\delta - 1}{\delta^{\frac{1}{\delta-1}}} (cT)^{-\frac{1}{\delta-1}} f^{\frac{1}{\nu}} \right] \quad (10)$$

implying that  $F(l)$  takes its minimum at  $l = 0$  (zipped phase) and  $l = N$  (unzipped phase) when  $f < f_c(T)$  and  $f > f_c(T)$  respectively with

$$f_c(T) \sim T^{1-\nu} \left( 1 - \frac{T}{T_D} \right)^\nu \quad (11)$$

where  $T_D = \epsilon / \log \left( \frac{\mu_u^2}{\mu_z} \right)$  is the thermal denaturation temperature for this Y-model. Thus at  $f_c(T)$  a first-order phase transition occurs where the fraction of the bounded bases has a jump. The last equation predicts a re-entrance with  $f_c \rightarrow 0$  when  $T \rightarrow 0$ . This limit is given by a spurious effect due to the assumption that equation (7) applies also at very low  $T$  where

equation (9) predicts  $r \rightarrow \infty$ . Indeed if equation (7) is assumed to hold until  $P_{2l}(r)\mu_u^{2l} \sim 1$ , e.g.  $r \leq r_M \sim 2l$  and after that  $r$  remains constant, then we easily find that at low  $T$

$$f_c(T) = \frac{1}{2}(\epsilon + T \log \mu_z). \quad (12)$$

Equation (11) near the denaturation temperature and equation (12) at the lowest  $T$  predict a behaviour qualitatively in agreement with the one described in figure 1<sup>7</sup> and confirmed by our simulation analysis<sup>8</sup>.

In conclusion, we have shown how a pulling force applied to the extrema of a model of a double-stranded DNA molecule could introduce nontrivial effects in the phase diagram. The results obtained on MC simulations in which, unlike in previous studies, excluded volume effects are fully taken into account, confirm the existence of a low-temperature denaturation. Although in our approach the intrinsic helicity of the DNA and the randomness of the base sequences have not been incorporated, we believe, on the basis of preliminary numerical results, that they should not affect the main features of the phase diagram and in particular the existence of a re-entrance region. Therefore we expect that such an effect could be pinpointed by high-precision measurements of DNA denaturation under a pulling force.

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<sup>7</sup> In the critical case of figure 1,  $\nu$  is the critical correlation length exponent for melting as in [20].

<sup>8</sup> Note that the model that we simulated on the lattice, at  $T = 0$ , behaves essentially as a locally flat ribbon. This means that our numerical model presents a value for  $\mu_z$  slightly lower than one would expect for a pure three-dimensional model. This implies a smaller slope of the boundary curve at  $T = 0$ . However, the existence of the re-entrance itself is not influenced by this artifact which is model dependent. We thank a referee for raising the issue of clarification of this point.



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