Denaturation Transition of Stretched DNA

Andreas Hanke
Martha G. Ochoa
Ralf Metzler

Follow this and additional works at: https://scholarworks.utrgv.edu/pa_fac

Part of the Astrophysics and Astronomy Commons, and the Physics Commons

Recommended Citation
Hanke, Andreas; Ochoa, Martha G.; and Metzler, Ralf, "Denaturation Transition of Stretched DNA" (2008). Physics and Astronomy Faculty Publications and Presentations. 320.
https://scholarworks.utrgv.edu/pa_fac/320

This Article is brought to you for free and open access by the College of Sciences at ScholarWorks @ UTRGV. It has been accepted for inclusion in Physics and Astronomy Faculty Publications and Presentations by an authorized administrator of ScholarWorks @ UTRGV. For more information, please contact justin.white@utrgv.edu, william.flores01@utrgv.edu.
Denaturation Transition of Stretched DNA

Andreas Hanke,1 Martha G. Ochoa,1 and Ralf Metzler2

1Department of Physics and Astronomy, University of Texas at Brownsville, 80 Fort Brown, Brownsville, USA
2Physics Department, Technical University of Munich, D-85747 Garching, Germany

(Received 19 September 2007; published 9 January 2008)

We generalize the Poland-Scheraga model to consider DNA denaturation in the presence of an external stretching force. We demonstrate the existence of a force-induced DNA denaturation transition and obtain the temperature-force phase diagram. The transition is determined by the loop exponent c, for which we find the new value c = 4r + 1/2 such that the transition is second order with c = 1.85 < 2 in d = 3. We show that a finite stretching force F destabilizes DNA, corresponding to a lower melting temperature Tm(F), in agreement with single-molecule DNA stretching experiments.

DOI: 10.1103/PhysRevLett.100.018106 PACS numbers: 87.14.G−, 05.70.Fh, 64.10.+h, 82.37.Rs

Under physiological conditions the thermodynamically stable configuration of DNA is the Watson-Crick double helix. The constituent monomers of each helix, the nucleotides A, T, G, and C, pair with those of the complementary helix according to the key-lock principle, such that only the base pairs (bps) AT and GC can form [1]. Upon heating or titration with acid or alkali of double-stranded DNA, regions of unbound bps proliferate along the DNA until full denaturation of the DNA molecule now depends on both temperature T and stretching force F. We find a bounded region of bound states in the (T, F) plane (Fig. 2). The shape of the transition line implies that finite stretching forces F indeed lower the melting temperature Tm(F), and the calculated force-extension relations F(L) exhibit a plateau over a certain range of DNA extension L (Fig. 3). Both observations are in agreement with force-induced DNA melting experiments.

We treat the chain in the grand canonical ensemble in which the total number N of bps and the end-to-end vector L fluctuate. The partition function in d = 3 becomes

\[ Z(z, F) = \sum_{N} \int d^{3} \Delta Z_{can}(N, L) e^{zN} \exp(\beta F L_{x}) \]  (1)

with \( \beta = 1/(k_{B}T) \). \( Z_{can}(N, L) \) is the canonical partition function of a chain of N bps with fixed end-to-end vector L, and z is the fugacity. We assume that the force F acts in the positive x direction, and Lx is the x component of L (Fig. 1). If bound segments and bubbles are independent, Z factorizes:

\[ Z(z, F) = \Omega_{e} + \Omega_{e} \left( \sum_{n=0}^{\infty} [B \Omega]^{n} \right) B \Omega_{e}, \]  (2)

FIG. 1. Stretched DNA in the PS model with bound segments B and denatured loops Ω. The DNA is attached between O and L and subject to the stretching force F in the x direction. Perfect matching in heterogeneous DNA requires both arches of a loop to have equal length ℓ.
the last term equaling $\Omega_k^2 B/(1 - B \Omega)$. The alternating sequence of bound segments and bubbles with weights $B$ and $\Omega$ in Eq. (2) is complemented by the weight $\Omega_k$ of an open end unit at both ends of the chain. Note that only one strand of the end unit is bound to the, say, magnetic bead, while the other strand is moving freely.

We model a bound segment with $k = 1, 2, \ldots$ bps as a rigid rod of length $a k$ where $a = 0.34 \text{ nm}$ is the length of a bound bp in B-DNA [10]. For simplicity we assume that $E_0 < 0 \text{ per bp}$ is the same for all bps. The statistical weight of a segment with fixed number $k$ and fixed orientation is then $\omega^k$ with $\omega = \exp(\beta e)$ and $e = -E_0 > 0$. Assuming that $k$ fluctuates with fixed fugacity $z$, and rotates around one end while subject to the force $F$ (Fig. 1), the statistical weight of the segment for fixed $z$ and $F$ becomes

$$B(z, \omega, F) = \sum_{z=1}^\infty \frac{(\omega z)^k}{4\pi} \int_\Omega \exp(\beta F x) \, d\Omega \tag{3a}$$

$$= \frac{1}{2\nu} \ln \left( \frac{1 - \omega z e^{-\gamma}}{1 - \omega z e^{\gamma}} \right), \quad y = \beta Fa. \tag{3b}$$

Integration in Eq. (3a) is over the unit sphere with area $4\pi$, and $x = ak \cos \theta \text{ where } \theta$ is the polar angle between segment and $x$ axis. At $F = 0$, $B(z, \omega, 0) = \omega z/(1 - \omega z)$ as found previously for the denaturation transition of free DNA [13]. Note that $B$ is only well-defined for $\omega z e^{\gamma} < 1$; in what follows we assume $z < e^{-\gamma}/\omega$.

Denatured loops are considered as closed random walks with $2\ell$ monomers, corresponding to $\ell$ broken bps. This loop starts at $O$ and visits the point $r$ after $\ell$ monomers (Fig. 1). The number of configurations of a loop is

$$\Omega(\ell, r) = C_0(2\ell) p_{\ell}(r) \tag{4}$$

under this constraint, where $C_0(2\ell)$ counts the configurations of a loop of length $2\ell$ starting at $O$ and $p_{\ell}(r)$ is the probability that the loop visits $r$ after $\ell$ monomers. For an ideal random walk in $d = 3$, $C_0(2\ell) \sim \mu^{2\ell} \ell^{-3/2}$ ($\mu$ is the connectivity constant) and $p_{\ell}(r) \sim R^{-3} \exp[-\lambda (r/R)^2]$ where $\lambda > 0, r = |r|$, and $R = b^{1/2}$ is the scaling length of the walk. The amplitude $b$ is proportional to the persistence length of the walk. Thus, $\Omega(\ell, r) \sim s^{\ell - 3} \exp[-\lambda (r/R)^2]$ where $s = \mu^2$. We assume that $r$ moves freely and is subject to the force $F$ in the positive $x$ direction. The weight of an ideal random loop for fixed $\ell$ and $F$ is given by the Gaussian integral

$$\Omega(\ell, F) = \int d^3 r \Omega(\ell, r) e^{\beta F x} = A s^{\ell - \epsilon} c \exp(\alpha y^2 \ell) \tag{5}$$

where $A$ is an amplitude, $c = 3/2$, and $\alpha = b^2/(4\lambda a^2)$. Finally, we sum $\Omega(\ell, F)$ over $\ell$ with weight $z^\ell$ to obtain the statistical weight for an ideal random loop

$$\Omega(z, F) = A \sum_{\ell=1}^\infty u^\ell z^{\ell - \epsilon} = A Li_\ell(u), \quad u = sz \exp(\alpha y^2). \tag{6}$$

For free DNA it was found that the nature of the denaturation transition is determined by the analytic behavior of $Li_\ell(u)$ at $u = 1$: for $c \leq 1$ there is no phase transition in the thermodynamic sense; for $1 < c \leq 2$ the transition is second order, and for $c > 2$ it is first order [3,13]. One finds $c = 3/2 = 2$ if the loops are ideal random walks. Self-avoiding interactions within a loop modify this value to $c = 3\nu = 1.76$ with $\nu = 0.588$ in $d = 3$ [15]. In both cases the transition is second order. Self-avoiding interactions between denatured loops and the rest of the chain were found to produce $c = 2.12 > 2$, driving the transition to first order [13,16]. These results suggest that the inclusion of self-avoiding interactions generally shifts the loop exponent $c$ to larger values, possibly effecting a change of the transition from second to first order.

To see how $c$ changes when self-avoiding interactions within a loop are included for the case $F > 0$, we obtain the weights $\Omega$ and $\Omega_c$ for a self-avoiding walk for $\ell \rightarrow \infty$. Then, Eq. (4) holds with $C_0(2\ell) - \mu^{2\ell} \ell^{-3/2}$ being the number of self-avoiding loops with $2\ell$ monomers. The probability density $p_{\ell}(r)$ scales as $p_{\ell}(r) = R^{-d} g(r/R)$ where $R = b^{1/2}$ is the scaling length of a self-avoiding walk and $g(x)$ is a scaling function. The function $g(x)$ is not known for a self-avoiding loop. In what follows we assume $g(x) \sim x^{\phi} \exp[-\lambda x^\delta]$ for $x \rightarrow \infty$ where $\lambda > 0, \phi$ is an exponent, and $\delta = 1/(1 - \nu)$ is determined by argument by Fisher [15]. This form of $g(x)$ is consistent with $p_{\ell}(r)$ for a Gaussian loop ($\nu = 1/2, \phi = 0$) obtained above. For the related linear self-avoiding walk starting at $O$ and ending at $r$ after $\ell$ monomers, the above form of $g(x)$ also holds and $\phi$ can be expressed in terms of known exponents [15,17]. For the present case of a self-avoiding loop $\delta = 1/(1 - \nu)$ still holds but $\phi$ is unknown. However, we will see that $\phi$ drops out from the result for $\Omega(z, F)$ in the limit $\ell \rightarrow \infty$ at $F > 0$. The integral in Eq. (5) is no longer Gaussian, but can be evaluated using the steepest descent method at $\kappa = c \ell b^{1/2} \epsilon \rightarrow \infty$. It turns out that in this limit the integral is dominated by values $r/\ell \epsilon \rightarrow \infty$. With the above behavior of $g(x)$ at $x \rightarrow \infty$ we find for a self-avoiding loop [cf. Eq. (5)]

$$\Omega(\ell, F) = A s^{\ell - \epsilon} y^{1/(2\nu)} \exp(\alpha y^{1/\nu} \ell) \tag{7}$$

for $\kappa \rightarrow \infty$ with the new loop exponent in $d = 3$, $c = 4\nu - 1/2 = 1.85$. \tag{8}

Thus, in the presence of self-avoiding interactions within a
denatured loop and $F \geq 0$ the transition remains second order but moves closer to first order compared to free DNA (with $c = 3\nu = 1.76$ obtained within the same approach). The amplitude $A$ in Eq. (7) is proportional to the cooperativity parameter $\sigma_0 \ll 1$ quantifying the initiation of a loop in a previously intact double strand in the PS model [4,5], such that also $A \ll 1$. Moreover, $\alpha = 0.6 \ldots 1.7 = 1$ using $\alpha = b^2/(4\Lambda_0 a^2)$ obtained for an ideal random walk where $b^2/\Lambda = 2L_{ps}/3$; here, $x_{ps} = 0.6$ nm is the length of a base in single-stranded DNA [10] and values for the persistence length $L_p$ for single-stranded DNA were found to range between 0.7 nm [6] and 2 nm [18].

Finally, we sum $\Omega(\ell, F)$ over $\ell$ with weight $z^\ell$ to obtain the statistical weight for a self-avoiding loop [cf. Eq. (6)],

$$\Omega(z, F) = A\gamma^{-\theta} \Lambda_0 \exp(\alpha \gamma^{1/\nu})/s,$$

(9)

where $\theta = 1 - 1/(2\nu) = 0.15$ in $d = 3$. The critical fugacity $z$ is now given by $z_\infty(F) = \exp(-\alpha \gamma^{1/\nu})/s$. The weight $\Omega_c(z, F)$ for an end unit obtains similarly, the result being Eq. (9) with $c$ replaced by $\gamma = 3/2 + \nu - 2\gamma = -0.232$, using $\gamma = 1.16$.

Phase diagram.—We now obtain the transition line between bound and denatured states in the $(T, F)$ plane in the thermodynamic limit $N \to \infty$. For given fugacity $z$ the average number of bps (open and closed) becomes

$$\langle N \rangle = \delta \ln Z(z, \omega, F)/\delta \ln z,$$

(10)

where we explicitly include the argument $\omega$ from Eq. (3) in the partition function (2). If $N$ is set one has to choose a fugacity $z$ such that $N = \langle N \rangle$; in this case $z$ becomes a constant of $\omega$, $F$, and $N$. We denote the value of $z$ in the limit $N \to \infty$ by $z^\infty(\omega, F) = \lim_{N \to \infty} z(\omega, F, N)$. Similar to the case $F = 0$ [13], $z^\infty(\omega, F)$ is the lowest value of $z$ for which expression (10) diverges. In the bound state the divergence turns out to occur when the denominator in $\Omega_c^2/\left(1 - B\Omega \right)$ vanishes [see text below Eq. (2)], implying $z^\infty(\omega, F)$ to satisfy

$$B[z^\infty(\omega, F)] = 1,$$

(11)

Conversely, in the denatured state the divergence occurs because $\partial_z \Omega_c(z, F)$ diverges, which implies

$$z^\infty(\omega, F) = z_m(F),$$

(12)

where $z_m(F)$ is the critical fugacity obtained above (which is independent of $\omega$). Thus, starting in a bound state in the $(T, F)$ plane and approaching the transition line by varying $T$ and $F$, the value $z^\infty(\omega, F)$ is determined by Eq. (11) and increases until it reaches the value $z_m(F)$ from Eq. (12). At this point the denaturation transition occurs. In the denatured state $z^\infty(\omega, F)$ is given by Eq. (12). Right at the transition both Eqs. (11) and (12) hold simultaneously. Using $\Omega[z_m(F), F] = A\gamma^{-\theta} \Lambda_0 (1)$ by definition of $z_m(F)$ this implies $A(\beta F a)^{\gamma} \Lambda_0 (1) = 1/[z_m(F), \omega, F]$, relating $F$ and $\omega$, or, equivalently, the reduced force $f = Fa/e$ and temperature $t = k_B T/\epsilon$, for the transition line in the $(t, f)$ plane.

The shape of the transition line $f_m(t)$ depends on $A$, $\alpha$, and $s$. Figure 2(a) shows $f_m(t)$ for $A = 1$, $\alpha = 1$, and $s = 5$ for the case that denatured loops are ideal random walks ($\theta = 0$, $\nu = 1/2$). The transition line for the more realistic value $A \ll 1$ is also shown (here $A = 0.01$). The line $f_m(t)$ separates a finite region of bound states from an infinite region of denatured states. The point $(t_0, f = 0)$ with $t_0 = t_m(f = 0)$ corresponds to the traditional melting transition for free DNA ($F = 0$). The line $f_m(t)$ for $A = 1$ contains a region in which $f_m(t)$ decreases with $t$, such that increased stretching forces $f$ lower the melting temperature $t_m(f)$, corresponding to force-induced destabilization of DNA [10]. Interestingly, for $A = 0.01$, application of a small stretching force $f$ first increases $t_m$ [19,20]. Moreover, $f_m(t)$ vanishes for both $t \to t_0$ (as $|t - t_0|^{1/2}$) and $t \to 0$ (as $\alpha^{-1/2} t^{1/2}$). This means that for given $0 < f < f_{\text{max}}$, where $f_{\text{max}}$ is the maximum of $f_m(t)$, the chain does not only denature at a large $t_m(f_0)$ but also at a small $t_m(f_0)$, as indicated in Ref. [21]. This behavior can be traced back to a balance of the terms $(\beta FA)^2$ and $\beta FA$ in $z_m(F) = \exp(-\alpha \gamma^{1/\nu})/s$ and Eq. (3b), respectively [22]. For $(\beta FA)^2 \ll \beta FA$, i.e., $k_B T \gg Fa$, the melting transition at $t_m(f_0)$ is mainly driven by the entropy gain on creation of fluctuating loops, similar as for free DNA. For $k_B T \ll Fa$ the transition at $t_m(f_0)$ is due to the fact that $B[z_m(F), \omega, F]$ decreases with $\omega = \beta FA = f/t$ in the denatured state, due to the rapid decay of $z_m(F)$ [cf. Eq. (3b)] [23]. Figure 2(b) shows the line $f_m(t)$ for self-avoiding loops with $A = 1$ and $c = 1.85$. Note that Eq. (9) reduces to the known result for a free self-avoiding loop ($\omega = 0$) only if $\theta = 0.15$ is replaced by $\theta = 0$; this is not a contradiction since Eq. (9) is based on the assumption that $\kappa = \beta FA^{\alpha} \sigma^{\nu}$ is large. To include in Fig. 2(b) the behavior of $f_m(t)$ for $f = Fa/e \to 0$ we use Eq. (9) with $\theta = 0.15$ for $y > 1$ and $\theta = 0$ for $y \leq 1$.

Force-extension relations.—In thermal denaturation of DNA one measures the fraction $\Theta$ of bound bps as function of $T$. From the partition function (1) the average number $\langle M \rangle$ of bound bps is $\langle M \rangle = \delta \ln Z/\delta \ln \omega$ and $\Theta = \langle M \rangle/\langle N \rangle$ with $\langle N \rangle$ from Eq. (10). Conversely, stretching experiments on DNA reveal its response to an applied mechanical stress. The mean of the component of the DNA extension along $F$ is $\langle L_\parallel \rangle = \beta^{-1} \partial \ln Z/\partial F$. The

![FIG. 2 (color online). Transition lines $f_m = F_m(t)/\epsilon$ as function of $t = k_B T/\epsilon$ for $\alpha = 1$, $s = 5$ for denatured loops modeled as (a) ideal random walks and (b) self-avoiding walks (cf. Fig. 3).](image-url)
average extension per bp in units of the bp-bp distance $a$ is $l = \langle L_z \rangle / (a N)$. For comparison with experiments and simulations we calculate $l$ in the thermodynamic limit $\langle N \rangle \to \infty$. Consider the Gibbs-Duhem relation for the thermodynamic potential $\ln Z(\omega, F)$:

$$Nd\ln z + M d\ln \omega + \beta l dF = 0.$$  

If $N$ is fixed one obtains $d\ln z + \Theta d\ln \omega + ldF = 0$ where $z$ is a function of $\omega$, $F$, and $N$. For $N \to \infty$, $d\ln z^* + \Theta d\ln \omega + ldF = 0$, $z^*(\omega, F)$ being the fugacity for $\langle N \rangle \to \infty$ as discussed above; $\Theta (\omega, F)$ and $l(\omega, F)$ are the bound bp fraction and reduced DNA extension in the same limit. For constant $y = \beta Fa$ (or $y = 0$) one finds $\Theta = -\beta \ln z^*(\omega, F) / \beta \ln \omega$ [so that $\Theta = 0$ in the denatured state due to Eq. (12) as expected]. For constant $\omega$, corresponding to constant $t = k_B T / \epsilon$, we find $l(\omega, F) = -\omega \beta z^* / \partial \ln \omega$, $z^* = (\omega, F)$ being the partition function is dominated by parameter values for which $z^*$ is a combination of both branches of the solution.

We have shown that a longitudinal stretching force $F$ results in a reduced denaturation temperature $T_m(F)$, corresponding to force-induced destabilization of DNA. For the loop exponent in the presence of a finite $F > 0$ we found $c = 4\nu - 1/2 = 1.85$, so that the denaturation transition remains second order, but with an increased exponent. It would be interesting to study how the value of $c$ is modified when self-avoiding interactions between a loop and the rest of the chain are included [13,16].

This work was supported by the NIH through SCORE Grant No. GM068855-03S1 and by the AFOSR through Grant No. FA9550-05-1-0472 (A. H. and M. G. O.).

[22] One may study the interplay between $\beta F a^2$ and $\beta F a$ explicitly in a simplified model in which bound segments are always aligned along the $x$ direction. This produces a quadratic equation for $f_m$ with $a$ as a parameter, and $f_m(t_F)$ is a combination of both branches of the solution.
[23] This relies on the assumption that $p_t(r)$ is Gaussian for ideal random loops and as described above Eq. (7) for self-avoiding loops. For very large $\beta F$ denatured loops are stretched out and aligned along $F$ so that the partition function is dominated by parameter values for which $p_t(r)$ deviates from this form. A suitable $p_t(r)$ should be used to obtain the phase diagram in this regime.
[24] As such the potential $\ln Z(\omega, F)$ depends only on intensive parameters and would vanish due to the Euler equation. This is avoided by formally including the system volume $\mathcal{V}$ in the potential. Here $\mathcal{V} = \infty$ is understood.