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ORIGINAL PAPER

Thermodynamic relations for DNA phase transitions

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Abstract: The force induced unzipping transition of a double stranded DNA is considered from a purely thermodynamic point of view. This analysis provides us with a set of relations that can be used to test microscopic theories and experiments. The thermodynamic approach is based on the hypothesis of impenetrability of the force in the zipped state. The melting and the unzipping transitions are considered in the same framework and compared with the existing statistical model results. The analysis is then extended to a possible continuous unzipping transition.

Keywords: DNA unzipping; Melting and force induced transitions; Thermodynamic relations

PACS Nos.: 87.15.Zg; 05.70.Fh; 05.70.Jk; 87.14.gk

1. Introduction

To read the genetic information encoded in the base sequence, hidden in the helical structure of a DNA, it is necessary to break the hydrogen bonds of the base pairs [1]. The mechanism for doing so is the unzipping by a force [2, 3] of a double stranded DNA (dsDNA), or a thermal melting [4, 5]. In the melting transition, the hydrogen bonds of base pairing are broken by thermal energy, while in the unzipping transition, it is by a pulling force at one end of the DNA. In both cases, the strands remain intact.

While there is a long history of experimental studies of the melting transition [4, 5], the investigations of the unzipping transition or responses to external forces are of more recent origin [6]. Pioneering calorimetry studies have been done over a large range of temperature (T) from 2 to 400 K under different solution conditions [7]. So far as force is concerned, isotherms of DNA, like the response under a force have been obtained in many different types of single molecule experiments [8–10]. However, calorimetry in presence of a force is still not available.

It is known from various theoretical models that, for both melting and unzipping, the nature of the transition depends on the aspects of the DNA captured in a model [2, 8, 11–20]. Any natural DNA, because of its large length, is expected to show the characteristic features of the transitions, but the situation is not so clear on the experimental front. Since experiments are restricted to very short chains, it is not clear if the predicted transition varieties are at all seen with variations in the base sequence, as for example, across species, or there is actually only one type. We even lack a clear experimental answer about the order of the melting transition.

Cooperativity in melting comes from the entropy (S) of the DNA through the correlations introduced by the strands as long polymers [21, 22]. The unzipping transition is due to the competition between the pairing of the strands and the stretching of the unbound strands [2, 11–13]. The work done in stretching the free polymers provides the cost of unpairing the strands. This cost at zero temperature is only the pairing energy, but, because of entropy, the critical unzipping force vanishes as one approaches the melting temperature. The thermodynamic conjugate pair for the transition is g, the unzipping force, and x, the separation of the two strands at the point of application of force (see Fig. 1). It transpires that gross quantities like the entropy, the specific heat, and the response function for force, are the relevant thermodynamic quantities to study, especially as the transition point is approached. The advantage in the thermodynamic approach is that the results obtained are valid under quite general conditions without getting into the microscopic details of DNA.

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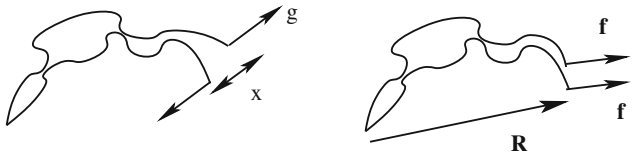
Besides the conjugate pairs (T, S), and (g, x), there could be other types of external forces, e.g., isotropic hydrostatic or osmotic pressure affecting the volume of the polymer, and a stretching force (**f**) that distorts and elongates the chain. Although there are evidences of hydrostatic or osmotic pressure affecting protein-DNA interaction, there is only a very weak effect on the melting of DNA. In contrast, a stretching force may lead to an "overstretching" transition where the length of the DNA increases by a factor of 1.7 [9, 18, 23–25]. Whether it is an equilibrium (meaning thermodynamic) transition is still debated.

The unzipping transition has been first established in a continuum model in [2, 3]. It was also proved by studying the dynamics of pulling in [26] and by several exactly solvable models [11, 12, 14]. Various aspects of the unzipping transition, and in that context the corresponding melting transition, have been studied. These include the effects of randomness in interaction, or force [27–30], semiflexibility [31], and finite length [32, 33]. Many details of the transition have also been studied, like various distributions [34], temperature dependence [35], different types of noise [36, 37], role of ensembles [38]. The dependence of melting on the nature of the space has also been studied via the choice of different fractal lattices [39–43], showing the possible variations in the melting transition. The mapping of the DNA melting problem to a quantum problem reveal the connection between the bubble entropy of DNA and the quantum transition [44]. Biological applications have also been considered, especially the motion of the interface or the Y-fork [45–47].

Our purpose in this paper is to consider the melting and the unzipping transitions from a purely thermodynamic point of view, without any consideration of any microscopic models. This way we derive the relevant thermodynamic relations applicable to these transitions. Obviously such predictions are independent of the microscopic details. We start with the definitions and standard relations in terms of the DNA variables in Sect. 2. The case of a first order unzipping transition is discussed in Sect. 3. Here we consider the case of no penetration of force in the bound state. In other words the bound state remains the same till the critical unzipping force is reached. The thermodynamic predictions are then compared, in Sect. 4, with the known exact solutions in certain class of models. Although all theoretical studies based on simple coarse-grained models predict a first-order unzipping transition, there is a proposal that local penetration of forces may lead to a continuous transition [48]. Thermodynamics does not rule out any continuous unzipping transition. A thermodynamic analysis of such a case of a continuous transition is discussed in Sect. 5. In this case we assume that for a range of force $g_{c1} \leq g \leq g_{c2}$, there is a change in the DNA bound state by the external force. A few details can be found in the Appendices. The additions of other forces like hydrostatic pressure and a stretching force are discussed in Appendix 1. The relevant Maxwell relations for DNA unzipping are listed in Appendix 2. The specific heat relation for a continuous transition can be found in Appendix 3.



(a) Unzipping force **(b)** Stretching force

Fig. 1 Various external forces on a DNA. (**a**) Unzipping force where the ends of the two strands are pulled in opposite directions. (**b**) Stretching force where the two ends are pulled in the same direction

2. Thermodynamic description

Our main concern is in the unzipping transition and therefore we restrict ourselves to the g and x pair. In absence of any other information, we may allow both the unzipping and the melting transition to be either first order or continuous. Both cases are discussed here.

What makes the problem different from others is the fact that the unzipping force does not affect the bound state for small forces. In fact only other system that shows similar thermodynamic relations is a superconductor with the Meissner phase not allowing the external magnetic field to penetrate [49]. In that analogy, a parallel scenario for DNA would be the case where the force penetrates for an intermediate range of force, leading to a continuous transition [48].

One may consider two mutually exclusive situations, either g or x is fixed. These correspond to the two possible ensembles in the statistical mechanical approach. The fixed-force case described by the Helmholtz free energy $F(T, x)$ and the fixed-distance ensemble, described by the Gibbs free energy $G(T, g)$. These are in addition to the usual canonical (fixed-T) and micro-canonical (fixed-S) ensembles. The free energies are given by

$$F(T, x) = U - T\,S, \tag{1a}$$

$$G(T, g) = U - T\,S\; -\; g\,x = F - g\,x, \tag{1b}$$

where U is the internal energy. Henceforth, we use F, G, U, S to mean the corresponding quantities per monomer or base pair. The differential form for G is

$$dG = -S\,dT - x\,dg. \tag{2}$$

It is possible to extend the thermodynamic formulation to include other external forces. Some details may be found in Appendix 1.

By integrating Eq. (2) at constant temperature, one gets the Gibbs free energy at a force g as

$$G(T,g) = G(T,0) - \int_0^g x\, dg. \tag{3}$$

This form is valid for equilibrium with $x = x(g)$ as the equilibrium isotherm of a DNA and is used extensively in this paper. The formula for work done in Eq. (3) is different from the mechanical definition of work ($\int g dx$). A justification is as follows. In a nonequilibrium situation, to change the force from zero to g, the work done on the DNA is $\int_0^g x dg$ for a trajectory. For example, an instantaneous change in force would require a work $w = xg$ if the distance remains fixed at x. Then the histogram transformation in statistical mechanics gives us the free energy difference as [50]

$$G(T,g) - G(T,0) = -k_B T \ln \langle \exp(-\beta w) \rangle, \tag{4}$$

where $\beta = (k_B T)^{-1}$, and the angular bracket indicates averaging over all possible trajectories starting with the equilibrium distribution at zero force. In this particular case of instantaneous increase, the averaging is over all values of x with the equilibrium probability distribution $P_{T,g}(x)$ at the initial force. For an infinitesimal increment dg, from g to $g + dg$, we may expand $\exp(-\beta x dg) \approx 1 - \beta(x\, dg)$. Therefore, for small dg, the equivalent of Eq. (4) is

$$\begin{aligned} \Delta G(T,g) &= -k_B T \ln\left(1 - \beta \int dx\, (x\, dg)\, P_{T,g}(x)\right) \\ &= x(g)\, dg, \end{aligned} \tag{5}$$

where the average value of x is denoted by $x(g)$. On successive integration, one recovers the thermodynamic formula of Eq. (3) (with no angular bracket). Incidentally, the mechanical work done in stretching or unzipping has been used in other contexts too, as, e.g., to obtain and use the hysteresis around the transition for thermodynamic free energies [51] and associated dynamic transitions [52–54].

The notations we are using are as follows. The zero force thermal melting temperature is denoted by T_c. The unzipping transition by a force g at temperature T takes place at a temperature dependent force $g = g_c(T)$ so that $g_c(T_c) = 0$.

3. First order unzipping transition

For the unzipping transition, $G(T,g)$ is continuous across the phase boundary. This implies

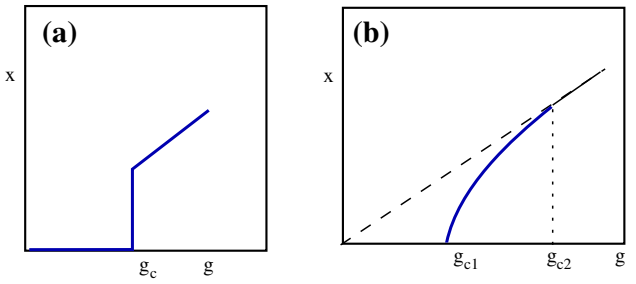


Fig. 2 Possible isotherms (constant T). (**a**) A first-order unzipping transition at $g = g_c$. There is a jump in x. (**b**) Two continuous transitions at $g = g_{c1}$ and $g = g_{c2}$. The force does not affect the DNA for $g < g_{c1}$ but penetrates and modifies the bound state continuously from $g > g_{c1}$ to $g < g_{c2}$. The unbound or stretched denatured phase occurs for $g > g_{c2}$

$$G_z(T,g_c) = G_u(T,g_c), \tag{6}$$

where subscripts z and u indicate the zipped and the unzipped phases. Equation (3) therefore allows us to write

$$G_z(T,0) - G_u(T,0) = \int_0^{g_c} (x_z - x_u)\, dg. \tag{7}$$

Here $G_u(T,0)$ is the free energy of the unzipped phase in zero force if it had existed. One way of obtaining $G_u(T,0)$ is by extrapolation of the high force free-energy, assuming that the extrapolation is thermodynamically admissible, or from the free energy of a single stranded DNA.

It is known that for the first order unzipping transition, as shown in Fig. 2(a), the force does not penetrate the bound state for $g < g_c(T)$. We take this as the starting hypothesis in the thermodynamic analysis. Therefore, effectively, $x_z = 0$, and

$$G_z(T,g) = G_z(T,0), \quad (g \le g_c). \tag{8}$$

This equation is valid at $g = g_c$ because of coexistence of phases. At this point the force-dependent unzipped phase has the same G as the zipped phase. In the linear response regime, $x_u = \chi_T\, g$ where χ_T, the extensibility, may be taken to be a constant (See Appendix 2 for definitions). Equation (7) then simplifies to

$$G_z(T,0) = G_u(T,0) - \frac{1}{2}\chi_T\, g_c^2, \tag{9}$$

where the last term is the work $W(g_c)$. A more useful form is obtained by combining Eqs. (3), (8) and (9), as

$$G_z(T,g) = G_u(T,g) + \frac{1}{2}\chi_T\, (g^2 - g_c^2), \tag{10}$$

in principle, valid for all g. This shows that for $g < g_c$, the zipped phase is more stable than the unzipped one and vice versa.

3.1. Entropy

The entropy difference, from Eq. (9), (see Appendix 2) comes out to be

$$S_z(T, g_c) - S_u(T, g_c) = \chi\, g_c(T)\, \frac{\partial g_c(T)}{\partial T} \tag{11}$$

$$= x(g_c)\, \frac{\partial g_c(T)}{\partial T}, \tag{12}$$

where the second form, a more general one, follows by noting that $\partial W(g)/\partial g = x$. For notational simplicity, we omit the subscripts of χ. The entropy difference is related to the latent heat $L = T(S_z - S_u)$ at the transition. Except for $g = 0$, energy is required to unzip a DNA. In real situations this energy is supplied by nonthermal sources like ATP etc.

The continuity of the Gibbs free energy at the unzipping transition point in a fixed force ($dG_z = dG_u$ along the phase boundary), gives the Clausius–Clapeyron equation as

$$\frac{\partial g_c}{\partial T} = \frac{S_u - S_z}{x_u - x_z}, \tag{13}$$

where all the quantities on the right hand side are on the phase boundary. The impenetrability condition, $x_z = 0$ with the linear response relation $x_u = \chi g_c$, yields the entropy relation of Eq. (11).

The sign of the right hand side in Eq. (11), i.e., the slope of the phase boundary, is not fixed a priori. This is important for identification the state which is more ordered. In a temperature driven transition, the entropy increases as one crosses a phase transition line from the low to the high temperature side. If the zipped phase is more ordered then $S_z < S_u$ requiring $\partial g_c/\partial T < 0$.

3.2. Specific heat

The specific heat relation for $g = 0$ follows from Eq. (11) as

$$C_z(T_c, 0) - C_u(T_c, 0) = T\, \chi \left(\frac{\partial g_c(T)}{\partial T}\right)^2_{g=0}, \tag{14}$$

where χ is the extensibility of the unzipped chain at the melting point $T = T_c$. Equation (14) gives the discontinuity in the specific heat expected at the melting point, provided $\partial g_c/\partial T$ is finite. If the entropy change is finite, there is a latent heat which contributes a δ-function peak at the transition point. Equation (14) is a special case of the general formula valid for all g, viz.,

$$C_z(T, g_c) - C_u(T, g_c) = T\left[\chi\left(\frac{\partial g_c}{\partial T}\right)^2 + x(g_c)\frac{\partial^2 g_c}{\partial T^2} + \frac{\partial \chi}{\partial T} g_c \frac{\partial g_c}{\partial T}\right], \tag{15}$$

with an extra latent heat contribution. The derivatives appearing in Eq. (15) may conspire to make the RHS zero. The specific heat curve has only a delta function at the transition point superposed on a continuous specific heat curve.

3.3. Phase boundary

The shape of the unzipping phase boundary near the zero force melting point can be described asymptotically by Fig. 3

$$g_c(T) \sim |T - T_c|^\kappa, \text{ for } g_c(T) \to 0,\ T \to T_c. \tag{16}$$

Depending on the value of κ, a few cases can be considered as $g_c \partial g_c/\partial T \sim |T - T_c|^{2\kappa - 1}$.

1. If $\kappa > 1/2$, then $\frac{\partial g_c(T)}{\partial T}$ remains finite. At the zero force melting point, there is no change in entropy or no latent heat. In this situation, the melting transition is continuous.
2. If $\kappa = 1/2$, there is a latent heat and the melting transition is first order.
3. Since infinite latent heat is not possible, there is a strict lower bound: $\kappa \geq 1/2$.

The shape of the phase boundary, as determined by the exponent κ, is linked to the order of the melting transition.

Away from melting, in general, the right hand side of Eq. (11) is not zero, unless $\partial g_c/\partial T = 0$. The force induced unzipping transition is necessarily first order. The extremum of the phase boundary, as shown by Point C at (T_m, g_m) in Fig. 4, is a special case. In absence of any nonanalyticity in the phase boundary, both phases have same entropy but with a discontinuity in the specific heat as per Eq. (15). Since both g and T are intensive variables, every point in the T-g plane represents a unique phase of the DNA, except on the transition line. Along a path ACB,

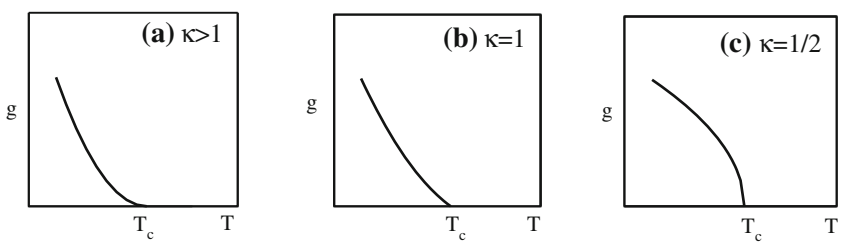


Fig. 3 The unzipping phase boundary near the melting point for different values of κ, the shape exponent

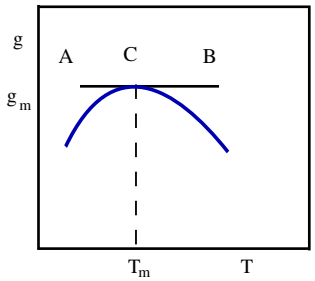


Fig. 4 A maximum at C = (T_m, g_m) in the T-g phase boundary. A path ACB sees certain special features at C. A zipped phase at $T = T_m$ can be unzipped by a force g_m without any discontinuity in entropy

there is no real change in phase and no latent heat is expected. There is however the possibility of occurrence of the zipped phase at C. One may therefore measure either C_u or C_z. If T is kept constant at T_m, specific heat will show a discontinuity as we cross C in the phase diagram vertically. This looks like a continuous transition.

When $\partial g_c/\partial T > 0$, the unzipped phase becomes more ordered than the zipped phase. This counter-intuitive behaviour is an example of a re-entrant phase transition. It occurs because the unzipping force acts as stretching forces on the two unbound chains, orienting them at low temperatures in the direction of the force reducing the entropy, while the flexibility of the zipped phase, because of the impenetrability of the force, contributes to the entropy.

4. Comparison with exact results

There are several models for which exact solutions for the unzipping transition are known. We compare the thermodynamics results with a few such cases.

4.1. Continuum Gaussian models

The unzipping transition has been first proved in [2, 3] for Gaussian polymers interacting with same monomer index as in DNA. The transition line in $(d+1)$-dimensions is given by $g_c(T) \sim |T - T_c|^{1/(d-2)}$, i.e., $\kappa = \frac{1}{d-2}$ for $2 \le d \le 4$. The zero force melting is continuous but the unzipping transition is first order. For $d > 4$, the melting transition is first order and there is a $\kappa = 1/2$ behaviour, as also found in the lattice modes of [12] discussed below.

The model shows that the bound, zipped state does not allow the force to penetrate and after the unzipping transition the strands are stretched by the pulling force. $\partial g_c/\partial T < 0$.

A necklace model analysis shows that κ is determined by the size exponent of the polymer provided there is no other length scale, i.e., $\kappa = \nu$, where ν is the size exponent [13, 16]. For a first order melting point, since all other length scales remain finite the relevant length scale is the size of the polymer. For Gaussian polymers $\nu = 1/2$, giving $\kappa = 1/2$, as we saw above for $d > 4$. For continuous melting. the thermal correlation length is going to play an important role, giving a different κ.

4.2. Lattice models with bubbles: continuous melting

The unzipping transition problem can be solved exactly for a class of lattice models involving directed polymers in $d+1$ dimensions [11, 12]. For the model with bubbles, there is a continuous melting transition in dimensions $d < 4$ as for the continuum case.

1. $d = 1$

For the $1+1$ dimensional model if the two strands are not allowed to cross, the free energies are [11]

$$G_z(T, g) = k_B T \ln z_z(T), \tag{17a}$$

$$z_z(T) = \sqrt{1 - e^{-\beta}} - 1 + e^{-\beta}, \tag{17b}$$

$$G_u(T, g) = k_B T \ln z_u(T, g), \tag{17c}$$

$$z_u(T, g) = [2 + 2\cosh(\beta g)]^{-1}, \tag{17d}$$

where $\beta = (k_B T)^{-1}$. We choose $k_B = 1$, and the base pairing energy $\epsilon = 1$. Here G_z is independent of g because of the impenetration of the force. The melting transition $(g = 0)$ at $T_c = [\ln(4/3)]^{-1}$ is continuous with a finite discontinuity of the specific heat.

The unzipping phase boundary is given by

$$g_c(T) = T \cosh^{-1}(p(\beta) - 1), \quad p(\beta) = (2z_z)^{-1}, \tag{18}$$

obtained by equating the two free energies at the unzipping transition, i.e., from $G_z(T, g_c) = G_u(T, g_c)$. Close to T_c where $z_u \to 1/4$, and $g_c \to 0$. The shape is

$$g_c(T) \approx \frac{2e^{-1/T_c}}{\sqrt{1 - e^{-1/T_c}}\, T_c}\ (T_c - T), \tag{19}$$

i.e., $\kappa = 1$, shown in Fig. 3.

The extensibility comes from the derivative of G_u as

$$\chi = \frac{1}{2T}\ \mathrm{sech}^2(g/2T). \tag{20}$$

Linear response is expected in the small force limit, when $x = g/(2T)$. At the transition

$$x_c = \tanh\left(\frac{g_c}{2T}\right). \tag{21}$$

The free energy near an unzipping point (T, g_c) can be written as

$$G_z(T,g) = G_u(T,g) - T\ \ln\frac{z_u(T,g)}{z_z(T)} \tag{22}$$

$$= G_u(T,g) - T\ \ln\frac{z_u(T,g)}{z_u(T,g_c)}, \tag{23}$$

by the continuity of the free energy at the transition point. Close to the melting point $T = T_c, g_c$ is small. In this region, for a small g, an expansion gives

$$G_z(T,g) = G_u(T,g) + \frac{1}{2}\chi(T_c)(g^2 - g_c^2), \tag{24}$$

consistent with Eq. (9) based on thermodynamic work.

For specific heat, the discontinuity at $T = T_c$ for $g = 0$ is just the specific heat of the bound state because the unbound state at $g = 0$ has zero specific heat. A differentiation of Eq. (17a) shows the agreement with the RHS of Eq. (14). [32] shows the behaviour of specific heat for a force that shows reentrance. For a nonzero force, the latent heat from Eq. (11) can be verified directly. The phase diagram shows reentrance and an extrema as in Fig. 4, recovering the features discussed in the previous section. Figure 5(a)–5(d) show the specific heat as we go through the peak C in the vertical direction keeping $T = T_m$ and horizontally by keeping $g = g_m$. The entropy is continuous. The specific heat shows a discontinuity along the vertical direction. Along the horizontal direction of the phase diagram, the entropy is continuous but the specific heat has one single point for the zipped phase. There is no identifiable critical region. The results are fully consistent with our discussions in Sect. 2.

4.3. Y-model: first order melting

A model of DNA that does not allow any bubble is also exactly solvable [11, 12]. The thermal melting corresponds to an all or none type behaviour, all base pairs are either formed or broken. In the bound state, the number of configurations is 2^N for N bonds, while it is 2^N for each strand in the unzipped state. The free energies are of the form of Eqs. (17a) and (18), except

$$p(\beta) = \exp(\beta). \tag{25}$$

The all-or-none melting transition is first order with a latent heat at $k_B T_c = 1/\ln 2$.

Near the melting at $p(\beta) = 2$, the phase boundary behaves as $g_c(T) \approx 2\sqrt{T_c - T}$, matching with $\kappa = 1/2$ behaviour of Fig. 3 for a first order transition. Equation (24) is valid with appropriate T_c and g_c. Other relations like specific heat, entropy and latent heat can be directly verified.

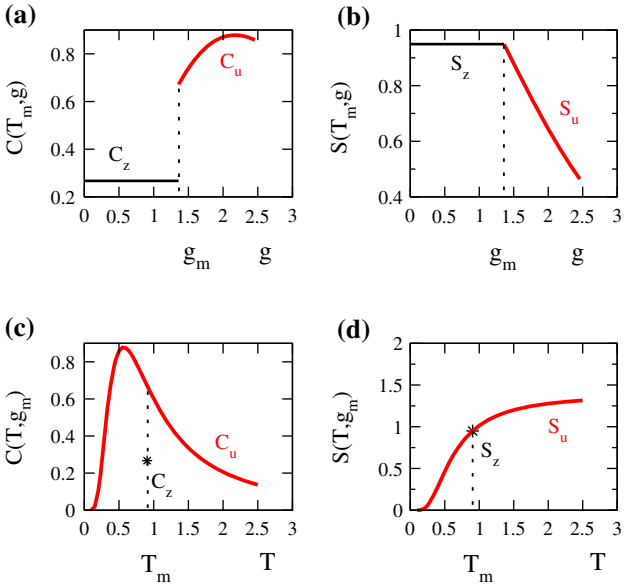


Fig. 5 Specific heat for the $d = 1$ exactly solvable model with no crossing. The phase diagram is similar to Fig. 4 with $T_m = 0.904642475...$ and $g_m = 1.358806498...$ in the units chosen. $C(T_m, g)$ (in **a**) and $S(T_m, g)$ (in **b**) vs g. In (**a**) there is a discontinuity as we go through the peak of the phase boundary vertically by changing g at $T = T_m$. In (**b**), we see that the entropy is continuous at the transition point. There is no latent heat. In (**c**) $C(T, g_m)$ versus T and in (**d**) $S(T, g_m)$ versus T are shown for a fixed $g = g_m$, i.e., along the *horizontal line* of Fig. 4. The zipped phase occurs only at one point without any signature elsewhere. This contribution is shown by a *star*. The entropy remains continuous and analytic throughout but the specific heat has one extra discontinuous point at $T = T_m$

4.4. Other special cases

[12] considers several exactly solvable models. Reentrance is observed in all situations considered except for the case of two strands with crossing in $1 + 1$ dimensions. In this case $\partial g_c/\partial T > 0$ for all T with $T_c \to \infty$. Therefore, as in Eq. (11), by increasing temperature under a force, it is possible to get a double stranded bound state at high temperatures from an unzipped state.

Another special situation is the $2 + 1$ dimensional model without crossing of chains. The phase boundary is $g_c(T) \sim \exp[-a/(T - T_c)]$ with $\partial g_c/\partial T \to 0$ as $T \to T_c$. It is possible to unzip for T close to but below T_c by an arbitrarily small force. Even though this case does not correspond to the power law form of Eq. (16), the thermodynamic relations can still be verified including the reentrance behaviour and the behaviour near the extrema of the phase boundary.

4.5. Summary of model comparison

As mentioned exact results are available for a large class of models in various dimensions. In all these cases, we find

that the general thermodynamic predictions *based on impenetrability of the force* below the unzipping transition are consistent with the extant results. This lends credence to a general thermodynamic analysis of various thermodynamic functions near the transition and phase boundary.

5. Continuous unzipping transition

Thermodynamics, by itself, does not exclude the possibility of a continuous transition under force of the type shown in Fig. 2(b). In this section we obtain the thermodynamic relations for such a continuous transition. We here assume that the force affects the bound state over a range $g_{c1} \leq g \leq g_{c2}$, but leaves the bound state as it is for smaller forces. In other words, a DNA in its bound state is resilient to small forces but allows it to penetrate and alter its nature over a range of forces.

Instead of a jump discontinuity in the isotherm, we allow a continuous transition at a force g_{c1} where the DNA goes from the bound to a phase different from the unzipped phase. The intermediate phase is further assumed to undergo a transition to the unzipped phase at g_{c2}. In case, $g_{c2} \to \infty$, there is only one phase in the high force regime. However, since single stranded DNA under a force is a stable thermodynamic system, we expect g_{c2} to remain finite. There is therefore a range of forces $g_{c1} < g < g_{c2}$ for which the DNA is affected in a nontrivial way by the force. Such a scenario was considered in [48]. The intermediate state is called a mixed state.

Near the two transition points, we take the isotherm to behave as

$$x \approx \begin{cases} a_1\,(g - g_{c1})^{\beta}, & \text{for} \quad g \to g_{c1}+, \\ \chi\, g - a\,(g_{c2} - g), & \text{for} \quad g \to g_{c2}-, \end{cases} \tag{26}$$

with $\beta, a, a_1 > 0$ (β is not to be confused with $1/k_B T$). The unzipped phase for $g > g_{c2}$ is taken, for simplicity, to be in the linear response regime, $x = \chi g$. The exponent β, by universality, is same along the transition line.

With the help of the formula for work at a constant temperature from g to g_{c2}, the Gibbs free energy, Eq. (7), can be written as

$$G_{\rm m}(T,g) = G_{\rm m}(T,g_{c2}) + \frac{1}{2}\chi(g_{c2}^2 - g^2) - \frac{1}{2}a\,(g_{c2} - g)^2, \tag{27}$$

where the subscript m indicates the mixed or the intermediate state. By continuity, $G_{\rm m}(T,g_{c2}) = G_{\rm u}(T,g_{c2})$, and therefore,

$$G_{\rm m}(g,T) = G_{\rm u}(g,T) - \frac{1}{2}a\,(g_{c2} - g)^2, \tag{28}$$

for g close to but smaller than g_{c2}. This form not only shows that the mixed state has a lower free energy than the unzipped state, but also gives the specific heat behaviour at g_{c2}, as (see Eq. 42)

$$C_{\rm m}(T,g_{c2}) - C_{\rm u}(T,g_{c2}) = -Ta\left(\frac{\partial g_{c2}}{\partial T}\right)^2. \tag{29}$$

The specific heat relation derived in the appendix is also applicable for the z to m transition. In this case the zipped phase has zero extensibility and therefore

$$C_{\rm m}(T,g_{c1}) - C_{\rm z}(T,g_{c1}) = -T\left(\frac{\partial g_{c1}}{\partial T}\right)^2 a_1\beta(g - g_{c1})^{\beta-1}, \tag{30}$$

indicating the possibility of a diverging specific heat if $\beta < 1$.

6. Conclusions

In this paper, the thermodynamic description of the DNA unzipping phase transition is discussed. Without considering any microscopic details, we show that the thermodynamic relations in the fixed force ensemble have all the important features of the phase transition. Here we concentrate only on the force induced unzipping by pulling the two strands apart. A linear response has been used for evaluating the work by force, but the analysis can be carried out keeping the full form. Although a first order phase transition is observed in various models, the possibility of a continuous transition havn′t got much attention. Thermodynamics does not discard this possibility and hence we extend our study to the case of continuous transition. The only information we use as an input to our analysis is that the zipped phase does not allow the force to penetrate below a certain critical force in the first order phase transition. The behaviour of the change in entropy and the specific heat go in accordance with the observed features in some known models. Various cases of the phase boundary line near the melting point are also analyzed. For the continuous transition there is an additional region in the phase diagram, showing a possible mixed phase, which allows the force to penetrate. We proceed with the general forms of the isotherms. This phenomenon of partial penetration of force looks very much like type II superconductors. Even though the variables and the microscopic origins are different in the two cases, there is a striking similarity between the relations obtained here for DNA and thermodynamic relations for superconductors. Lastly, we restrict ourselves to the unzipping force here but similar analysis can be done for the other forces like stretching force and pressure. It would be interesting to observe the effect of these forces on such transitions.

Appendix 1: Other external forces

As discussed in the Introduction, there could be other forces like pressure and the stretching force. To include these external forces, the Gibbs free energy of Eq. (1a) needs two additional terms

$$G(T, g, P, f) = U - T\,S - g\,x + P\,V - \mathbf{f}\cdot\mathbf{R}, \tag{31}$$

where V refers to the volume and $\mathbf{R} = \mathbf{R}_1 + \mathbf{R}_2$ to the end to end distances of the chains. In this notation $x = |\mathbf{R}_1 - \mathbf{R}_2|$ with the subscript denoting the two chains. The conjugate variable is volume (V), but it is the volume of the polymer with the surrounding distorted solvent layers. For simplicity we have ignored the terms involving $\mathbf{f}$ and P, and considered only the unzipping force g. The extended form of the free energy shows that it is possible to have cross-effects like the f and P dependence of x.

Different studies looked at the effect of hydrostatic pressure, e.g., the stability of hairpins, B-DNA, the stalling of transcription elongation complexes [55–60]. The melting temperature T_c seems to depend on the hydrostatic pressure, P, only at a very high P [55]. It is possible to measure the adiabatic compressibility (constant entropy) of a DNA molecule by measuring the velocity of ultrasonic waves [56]. A different way of exerting a pressure is to use osmolytes like polyethylene glycol (PEG) and other molecules that cannot penetrate the DNA. There are reports of hydrostatic pressure reversing the effect of osmotic pressure in protein-DNA interaction [59, 60].

There can be a stretching force (f) that distorts the shape and tries to elongate the chain. What one finds is a transformation of a dsDNA to an "overstretched" state with its length increasing by a factor of 1.7 [9, 18, 24, 25]. Whether it is an thermodynamic (meaning equilibrium) transition is still debated. The conjugate variable is the end-to-end distance ($\mathbf{R}$), if the end points are tied together. The conjugate variable becomes the length of the polymer for the overstretching transition. This is the usual force considered for a polymer [21, 22], but coupling to unzipping seems to lead to the new feature of overstretching. As a perturbation to an entropy-dominated polymer configuration, the response to the stretching force need not be linear, if the chain does not behave as Gaussian, but the overstretching transition is beyond this regime where the finite extensions of the bonds need to be taken into account. There are evidences of overstretching being coupled with unzipping making cross terms important. The response functions needed for such cross effects would be $\chi_i = \partial x/\partial f_i, \chi_P = \partial x/\partial P$ with other appropriate variables kept constant.

Appendix 2: Maxwell relations

The differential relations of the free energy are of the expected type

$$dU = T\,dS + g\,dx, \tag{32}$$

$$dF = -S\,dT + g\,dx, \tag{33}$$

In the canonical fixed-g case, the conjugate parameters and the response functions are the first and second derivatives respectively of the appropriate thermodynamic potential as

$$S = -\left.\frac{\partial G}{\partial T}\right|_g, \quad \frac{1}{T}C_g = \left.\frac{\partial S}{\partial T}\right|_g = -\left.\frac{\partial^2 G}{\partial T^2}\right|_g, \tag{34a}$$

$$x = -\left.\frac{\partial G}{\partial g}\right|_T \quad \chi_T = \left.\frac{\partial x}{\partial g}\right|_T = -\left.\frac{\partial^2 G}{\partial g^2}\right|_T, \tag{34b}$$

where C_g is the constant force heat capacity and χ_T is the extensibility at constant temperature, the local slope of a g-x isotherm. As usual, the positivity of C_g and χ_T, needed for stability, are related to the convexity conditions satisfied by G.

The differential forms yield the Maxwell relations for DNA as

$$\left.\frac{\partial x}{\partial T}\right|_g = \left.\frac{\partial S}{\partial g}\right|_T, \quad \text{and} \quad \left.\frac{\partial x}{\partial T}\right|_S = \left.\frac{\partial S}{\partial g}\right|_x, \tag{34c}$$

$$\left.\frac{\partial S}{\partial x}\right|_T = -\left.\frac{\partial g}{\partial T}\right|_x, \quad \text{and} \quad -\left.\frac{\partial T}{\partial g}\right|_S = \left.\frac{\partial x}{\partial S}\right|_g, \tag{34d}$$

of which the first two relate the thermal expansion of the open fork to the heat flow for change in force.

Appendix 3: Specific heat near a line of continuous transition

Let us consider a phase boundary $g = g^*(T)$, where at any point $(T, g^*(T))$, the Gibbs free energies and the entropies of the two phases A and B are the same, i.e.,

$$G_{\mathrm{A}}(g^*, T) = G_{\mathrm{B}}(g^*, T), \tag{35}$$

and

$$S_{\mathrm{A}}(g^*, T) \tag{36}$$

Along the phase boundary, at a neighbouring point, $G_{\mathrm{A}}(g^* + dg^*, T + dT) = G_{\mathrm{B}}(g^* + dg^*, T + dT)$. An expansion gives

$$\frac{\partial G_{\mathrm{A}}}{\partial T}\,dT + \frac{\partial G_{\mathrm{A}}}{\partial g^*}\,dg^* = \frac{\partial G_{\mathrm{B}}}{\partial T}\,dT + \frac{\partial G_{\mathrm{A}}}{\partial g^*}\,dg^*, \tag{37}$$

which tells us that at the transition point, the conjugate variable x is continuous, because of the continuity of the entropy ($S = -\partial G/\partial T$).

The constant force specific heat is given by

$$C_{\mathrm{A}} = T\frac{\partial S_{\mathrm{A}}}{\partial T}\bigg|_{g}. \tag{38}$$

The derivative of the entropy can be expressed in terms of the derivative along the transition line as

$$\frac{dS_{\mathrm{A}}}{dT} = \frac{\partial S_{\mathrm{A}}}{\partial T}\bigg|_{g} + \frac{\partial S_{\mathrm{A}}}{\partial g}\bigg|_{T}\frac{\partial g^{*}}{\partial T}, \tag{39}$$

and a similar relation for phase B. Since at each point on the transition line entropy is continuous, $\frac{dS_{\mathrm{A}}}{dT} = \frac{dS_{\mathrm{B}}}{dT}$. Equation (38) can now be used to express the constant force specific heat difference as

$$C_{\mathrm{A}} - C_{\mathrm{B}} = T\frac{\partial g^{*}}{\partial T}\left[\frac{\partial S_{\mathrm{A}}}{\partial g}\bigg|_{T} - \frac{\partial S_{\mathrm{B}}}{\partial g}\bigg|_{T}\right]. \tag{40}$$

A further simplification can be achieved by using one of the Maxwell relations, Eq. (34d),

$$\frac{\partial S_{\mathrm{A}}}{\partial g}\bigg|_{T} = \frac{\partial S_{\mathrm{A}}}{\partial x}\bigg|_{T}\frac{\partial x}{\partial g}\bigg|_{T} = \frac{\partial g^{*}}{\partial T}\,\chi_{A}, \tag{41}$$

where χ_{A} is the extensibility of phase A. With a similar relation for phase B, we obtain

$$C_{\mathrm{A}} - C_{\mathrm{B}} = -T\left(\frac{\partial g^{*}}{\partial T}\right)^{2}(\chi_{\mathrm{A}} - \chi_{\mathrm{B}}). \tag{42}$$

If the extensibility of phase A is less than that of B, then the specific heat of phase A is higher than that of B.

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