Force induced melting of the constrained DNA

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We develop a simple model to study the effects of an applied force on the melting of a double stranded DNA (dsDNA). Using this model, we could study the stretching, unzipping, rupture and slippage like transition in a dsDNA. We show that in absence of an applied force, the melting temperature and the melting profile of dsDNA strongly depend on the constrained imposed on the ends of dsDNA. The nature of the phase boundary which separates the zipped and the open state for the shearing like transition is remarkably different than the DNA unzipping.

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I. INTRODUCTION

Properties related to structure, functions, stability etc. of the bio-molecule are the results of inter and intra molecular forces present in the system [1, 2]. So far the measurement of these forces were possible through the indirect physical and thermodynamic measurements like crystallography, light scattering and nuclear magnetic resonance spectroscopy etc. [3]. For the direct measurement of these forces, it is essential that the state of the system be monitored while an independent force is applied [4, 5, 6, 7, 8]. In recent years single molecule force spectroscopy (SMFS) techniques such as optical tweezers, magnetic tweezers, atomic force microscope (AFM) etc have measured these forces directly and many important information about the bio-molecules have been inferred [9, 10, 11, 12, 13, 14]. Now it has also been realized that the measurement of these forces not only depend on the molecular interactions present in the system but also on the loading rate, direction of the applied force [5, 15, 16] etc. Moreover, these experiments also provide a platform where various theoretical models and their predictions can be verified.

In this context considerable efforts have been made to study the separation of a double stranded DNA (dsDNA) to two single stranded DNA (ssDNA). Understanding the mechanism involved in separation of dsDNA may shed light on the processes like transcription and replication of DNA [17]. At equilibrium, DNA will separate when the free energy of the separated ssDNA is lower than that of the dsDNA [18]. In most of the biochemical studies of DNA separation, the strands separate upon increasing the temperature (T) of the sample until the DNA melts (DNA melting or thermal denaturation). However, in vivo, DNA separation is not thermally driven, rather mediated by enzymes and other proteins [1, 19].

Mechanical separation of dsDNA using SMFS techniques is known as DNA Unzipping ( Figs. 1a and 1b) at temperatures, where the dsDNAs are stable, have recently been performed. The force (f) required to break a base pair is about 15 pN [19, 20]. A large number of theoretical and numerical efforts [21, 22, 23, 24, 25, 26] have been made to gain further insight into the mechanism of DNA opening. One of the major result from these studies was the prediction of re-entrance in the low temperature region.

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FIG. 1: Schematic representation of dsDNA: (a) dsDNA in zipped form; (b) Unzipping of dsDNA by the force (f) applied at one end (5′ − 3′); (c and d) Shearing by the force along the chain applied at the opposite ends (5′ − 5′ or 3′ − 3′) of the dsDNA; (e) represents the case where the force has been applied at 5′ − 3′ end of the same strand of the dsDNA.

In some cases, the term unzipping is not appropriate because the inter chain interactions may be carried in a different way. For example, instead of pulling a chain of opposite strands at 5′ and 3′ (Fig. 1b), it is possible to pull the chain on the opposite ends of two strands at 5′ and 5′ end (Fig. 1c) or 3′ and 3′ ends (Fig. 1d) or 5′ and 3′ ends of the same strand (Fig. 1e). It is found that in these cases [figs. 1(c) and 1(d)], transition is akin to shearing like. The unbinding force strongly depends on the pulling end and lie in between 50-150 pN [2, 13, 16] which is much larger than the unzipping force.

The aim of this paper is to understand the effect of pulling force DNA melting under the various constrain imposed on the ends of dsDNA. In section II we develop the model and discuss two methods namely the thermodynamic analysis and exact enumeration technique to study the force induced melting of dsDNA. The nature
of the phase boundary near \( T = 0 \) and the limitation of the analysis will be discussed in this Section III comprises results obtained for DNA unzipping, dissociation of dsDNA and the effect of bulge movement in dsDNA. The paper ends with brief discussion in section IV.

II. MODEL AND METHOD

![Diagram](image)

FIG. 2: (a & b) are the schematic representations of some of the conformations of the model introduced in Ref. [23, 26, 30, 31]. In this model, we have only one ground state conformation [Fig. 1(a)]. Because of lattice constrains, other conformations of zipped state are not possible. (c & d) are schematic representation of dsDNA conformations with diagonal interaction which leads to the large number of conformations of the zipped state.

We consider two linear polymer chains which are mutually-attracting-self-avoiding walks (MASAW’s) on a square lattice as shown in Fig. 2. This is the simplest model of dsDNA where \( i \)-th monomer of one strand can interact with the \( i \)-th monomer of other strand only [23, 26, 30, 31]. This kind of base pairing interaction is similar to the one studied in Poland Scheraga (PS) model or Peyrard Bishop (PB) model [32, 33]. However, in the present model configurational entropy of the system has been taken explicitly which is ignored in these (PS or PB) models. In order to study the response of an applied force on melting, we consider following cases as discussed above: (I) a pulling force may be applied on the chain at the 5’- 3’end (Fig. 1(b)). This will correspond to the situation of DNA unzipping. (II) For the slippage, a force may be applied along the chain at two opposite ends of the dsDNA e.g 5’- 5’end (Fig. 1(c)) or 3’-3’end (Fig.1(d)). Two interesting situations may arise for slippage: (a) if pulling is fast, at some critical force \( f_c \), the rupture occurs and dsDNA dissociates to the two single strands of DNA (Fig. 3(b)) [3]. In this case the system has a larger energy barrier for the complete unbinding. The other possibility involves the slow pulling, where small bulge loops can form in the chain and propagate to the pulling end (Fig. 3(c-e)). This process requires spontaneously binding and unbinding of few bases and through the process of diffusion, a bulge slides over the other chain with small energetic barrier [34].

Neher and Gerland theoretically studied the dynamics for force induced DNA slippage [34] for the homosequence (bulge movement) and heterosequence (dissociation of two strands) and found the expression for the critical force. However, in their studies, they have also ignored the configurational entropy of the chain and hence provide a limited picture of the mechanical separation of dsDNA.

A. Thermodynamics of force induced DNA melting

The thermodynamic of force induced DNA melting can be obtained from the following relation [35]

\[
\Delta G = \Delta H - T\Delta S - f_x
\]

where \( G, H, S \) and \( x \) are the free energy, enthalpy, entropy and reaction coordinate (end-to-end distance in this case) of the system respectively. To determine the nature of phase boundary, we put \( \Delta G = 0 \) which gives

\[
f_x = -\Delta H - T\Delta S
\]

The entropy defined in the Eq. 1 has contributions from the configurational entropy of the zipped DNA (\( S_z \)), entropy associated with the open state (\( S_o \)) and entropy associated with dissociated chains (\( S_u \)) etc. In unzipping the applied force does not influence the entropy of the chain while in shearing, it does. For the unzipping, we can write

\[
f_x = -\epsilon N' + N'TS_z - 2(N - N')TS_o
\]

where \( \epsilon \) is the effective base pairing energy. At low temperature i.e. near \( T = 0 \), all bases will be intact (\( N' = N \)) and hence there will be no contribution from the open conformations. Moreover, the second term in Eq. 2 stabilizes the zipped state. Eq. 3 may be written as

\[
2f_N = -\epsilon N + NTS_z
\]

The factor 2 comes from the fact that chain is in unzipped state and the distance between the extreme ends is equal to \( 2N \). We substitute the value of \( \epsilon = -1 \) in Eq. 4 which gives

\[
f = 0.5 + \frac{1}{2}TS_z
\]

This is in accordance with earlier studies [21, 22, 23, 26] that the applied force increases with the temperature at low temperature which is a signature of re-entrance. At higher \( T \), the chain will start opening and the third term
of Eq. 3 associated with open state will start cooperating with the applied force and hence the applied force start decreasing after certain value of temperature.

Unlike unzipping, in case of shearing (rupture or slippage), the applied force competes with the entropy associated with the zipped configurations so that the chain acquires first the stretched state and then start opening. In such a situation entropic contribution of zipped chain (second term of Eq. 3) at the phase boundary will be absent. However, there will be an additional contribution of entropy associated with the unzipped chain. At low temperature for the rupture ($x = 1$), we can write

$$f = -\epsilon N' - 2NTS_u + 2(N - N')TS_o$$ \hspace{1cm} (6)

At $T = 0$, Eq. 6 gives the force required for rupture which is equal to $N$. Up to certain temperature when the intact bases remain equal to $N$ the entropy associated with open conformation will be zero and hence the expression for the applied force (rupture) can be written as

$$f = N - 2NTS_u$$ \hspace{1cm} (7)

Above this temperature, $N'$ decreases with temperature and hence bubble forms, therefore, more force is needed to keep system in the stretched state. Therefore, the phase boundary between zipped and open states should bend. For shearing like transition, $x = N$ and hence required force is equal to 1 and should have similar behavior.

The precise value of entropic contribution near the phase boundary is difficult to obtain analytically. Therefore, it is not possible to get the entire phase boundary from the Eqs. 3 & 6. Using the exact enumeration technique \[36\], contribution of $S_o$ may be obtained for the finite size chain and an estimate of the phase boundary may be obtained.

### B. Exact Enumeration Analysis

The unzipping case for the model proposed above has been studied in detail \[25, 26, 31\]. It was shown that for the temperature diagram demarcates the zipped and unzipped state and unzipping force decreases with temperature without any re-entrance. The absence of re-entrance in force-temperature plane is due to the ground state entropy of the zipped state which has been suppressed because of the imposed lattice constraint on the base pairing interaction (Fig. 2 (b)). However instead of base pairing interaction taken in Ref. \[25, 26, 31\], if one considers the diagonal interaction shown in Fig. 2(c) and 2(d), one may observe the re-entrance in the proposed model also. The choice of diagonal interaction is analogous to the walks on the oriented square lattice \[37\].

The model presented here may describe above mentioned effects provided we also incorporate effect of movement of bulge in the partition function. For the unzipping, we fix one end of the dsDNA and apply force at other ends (5'-3') as shown in Fig. 1b. In order to study the behavior of slippage, we apply force at opposite ends (5'-5' or 3'-3') of the strands. We model the fast pulling (i.e. dissociation of two strands), by not allowing the formation of base pair in the model after the chain slides over the other strand. However, for the diffusion of bulge in homo-sequence (slow pulling), we apply a force on the opposite strands (5'-5') so that chain acquires the stretched state. If force exceeds further, the chain moves one unit towards the applied force direction (Fig. 3c-e). Since spontaneous binding and unbinding is possible, now we allow the formation of base pairing of $(i + 1)$-th base of one chain to $i$th base of other chain (Fig. 3e) and calculate the partition function ($Z^{(1)}$) of the re-annealed chain. For the next unit of displacement, we allow $(i + 2)$-th base to interact with the $i$th base and calculate the partition function ($Z^{(2)}$) and so on. In this way, we can construct a series of partition functions ($Z^{(i)}$) for the slippage. It may be noted that for the unzipping case we monitor the displacement $x$ along the force direction while for the slippage case, we monitor the displacement $y$ along the force direction. The contribution to energy due to this force, $f$, is $-fx$ (or $-fy$).

We enumerate all conformations of MASAWs whose one end is fixed and other end is attached with the pulling device (e.g. tip of the AFM). We specifically monitor the reaction coordinate i.e. end to end distance or distance between the fixed end and tip of the AFM. The partition function of the system under consideration can be written.
as a sum over all possible conformations of dsDNA:

\[
Z_N = \sum_{\text{walks}} x_1^N x_2^N \omega^m u^x
\]

where \( N \) is the chain length (i.e. \( N \) steps walks) of each strand consisting of \( N \) bases. \( x_1 \) and \( x_2 \) are the fugacities associated with each step of the two self-avoiding walks representing the two strands respectively. (For simplicity we take \( x_1 = x_2 = 1 \) for our calculation). \( \omega = \exp(-\beta \epsilon) \) is the Boltzmann weight associated with the binding energy (\( \epsilon \)) of each diagonal nearest neighbor pair and \( m \) is the total number of such pairs in the chain. \( u = \exp[\beta(\vec{f} \cdot \vec{x})] \) (unit vector along \(-\)axis) is the Boltzmann weight associated with the force. \( C(m, x) \) is the number of distinct walks of length \( 2N \) having \( m \) number of pairs whose end points are at a distance \( x \) apart. We have obtained \( C(m, x) \) for \( N \leq 15 \) bases and analyzed the partition functions.

Quantities of interest like reaction coordinate (\( x \) or \( y \)) and fraction of base pairs can be calculated from the following expressions:

\[
<x> = \frac{\sum x C(m, x) \omega^m u^x}{\sum C(m, x) \omega^m u^x}
\]

\[
<m> = \frac{\sum m C(m, x) \omega^m u^x}{\sum C(m, x) \omega^m u^x}
\]

Since dissociation of dsDNA and bulge movement are dynamic phenomena, which can be considered in a quasi-static equilibrium. Moreover, we monitor the distance of the end points of the dsDNA where the force has been applied. In view of above, we do our analysis in constant distance ensemble (CDE) where temperature has been kept constant. The partition function in CDE may be defined as \( Z_N(x, T) = \sum_m \exp(\beta \epsilon m) \). The two ensembles are related by \( Z_N(T, F) = \sum_x Z_N(x, T) \exp(\beta f x) \). The free energy is given by the relation \( F_N(x, T) = -T \ln Z_N(x, T) \) and average force \( < f_c > \) is thus \( \frac{dF}{dx} \).

It is pertinent to mention here that in CFE the average separation \( < x > \) fluctuates while in CDE one measures the average force to keep the separation constant at a fixed temperature.

Since most of the single molecule experiments are performed for finite size chain and the fact that no true phase transition can occur in single molecule, we consider only finite chain calculation and calculate the “state diagram”. The boundary of state diagram (F-T diagram) can be obtained from the maxima of fluctuation of \( m \).

It is important to note here that one can use the suitable extrapolation scheme (e.g. ratio method) to find the reduced free energy per base pair from the relation \( G(\omega, u) = \lim_{N \to \infty} \frac{1}{4N} \log Z_N(\omega, u) \) and corresponding transition points of the F-T diagram in the thermodynamic limit also. However, in our calculation we shall confine ourselves to canonical ensemble and set \( \epsilon = -1 \) in calculating all the relevant quantities.
III. RESULTS

For the finite size chain, the melting profile of dsDNA strongly depends on the constraints imposed on the strands. For example, if we keep one end of both strands fixed and other ends free (Fig. 4(a)), the melting temperature is found to be 0.86. However, if one end of both strands of the dsDNA is kept fixed and other ends are tied together (Fig. 4(b)), in that case dsDNA melts at $T = 1.11$. The other possibility is to tie one end of the dsDNA together and keep only one strand of the other side of dsDNA fixed (Fig. 4c). In this case melting takes place at $T=0.86$. Lastly we can fix one end (5'-end) of the first strand and opposite ends (5'-end) of the other strand (Fig. 4(d)), the melting occurs at $T = 0.53$. The variation in melting temperature is due to the reduction in entropy solely arising due to the imposed constrain on the ends of the chain. It may be noted here that in case of unzipping and slippage, such confinements are being generally imposed by the experimental setup, and, therefore, the resultant force-temperature diagrams may differ accordingly. In the following, we shall discuss the effect of confinement shown by Figs. 4(a) & 4(c) for DNA unzipping and slippage respectively.

A. Pulling at 5'-3’ end of opposite strands: DNA unzipping

Pulling at one end of dsDNA (5'-3’ end) results DNA unzipping. We keep one end of the dsDNA fixed (Fig. 4a) and apply a force $f$ on the other end as shown in Fig. 1b. The force temperature diagram shown in Fig. 6 is obtained from the maxima of fluctuation of $m$ with $T$ for a given force $f$. For the sake of comparison, we also provide the result of Ref [25, 26, 31] in Fig. 6(a), where base pairing interaction is carried out along the bond as shown in Fig.2 (a) & (b). As pointed out above, the diagonal interaction gives rise the ground state entropy of the zipped state. As a result, we see two peaks in the fluctuation of $m$ (Fig. 6d) which gives rise the re-entrance in the force temperature plane (Fig. 6(c)) at low temperature. As stated earlier, it is absent in the Fig. 6(a) [25, 26, 31]. It should be noted here that the melting temperature for the diagonal interaction is much higher because of the large contribution arising due to the ground state entropy of the zipped state.

B. Pulling at 5’-5’ end or 3’-3’ end of opposite strand

1. Dissociation of two strands

If pulling is fast enough or the chain is heterogeneous, the two strands separate completely without any overlap. In short span of time rebinding of bases are not possible and rupture takes place at some critical force $f_c$ where two strands dissociate completely. In order to model such process, we consider all conformations of two MASAWs as shown in Fig. 4(c) along with the conformations where the second chain has shifted one unit (Fig. 3(b)) towards the force direction. Since pulling is fast, there is no contribution of base pairing in the displaced partition function. As a result two walks will be non-interacting and impose only the confinement arising due to mutual exclusion. The combined partition function can be written as

$$Z_N = Z^0 + Z^1$$

where $Z^0$ is the partition function of the model system in which one end of the strand is attached with the AFM tip which may vary in between 0 to N while other end of one strand (Fig. 4(c)) is kept fixed. Here formation of base pairing is possible in between any base of one strand with the any base of other strand only. The ground state is complete zipped state. The partition function $Z^1$ here corresponds to the situation, when one end of the second strand has displaced a unit distance in the force direction after acquiring complete zipped stretched state i.e $x = N$.

The force temperature diagram for the rupture is shown in the Fig. 7. It is evident from the plot that the nature of diagram is significantly different than the DNA unzipping shown in Fig. 6a & c. This is because in case of unzipping, the applied force does not affect the entropy associated with conformations and bubble while in case of rupture, because of stretching, the contribution...
FIG. 7: The force temperature diagram for the DNA dissociation. At low temperature force decreases linearly with the temperature. At $T = 0$, it intercepts y axis at 15 which is the required force for the rupture. It is clear from the Fig. 5, that above the temperature $T = 0.4$ DNA melts and because of entropic contribution, $F - T$ curve no more remain linear. Above the melting temperature ($T = 0.86$), there are still some bases are in contact and hence small force is required for the complete unbinding as shown in the inset.

of entropy goes to zero. Moreover at $f = 0$, DNA melts at some temperature where half of the bases are still in contact. It is evident from the melting profile (Fig. 5) that above the melting temperature, there are significant number of base pairs. In order to have complete unbinding (i.e. no base is in contact), one requires still some (vanishingly small) force near the melting temperature as shown in inset of Fig. 7.

The force extension curve obtained in CDE is shown in Fig. 8. At low temperature, when the dsDNA is in the zipped state, the force brings the dsDNA from coil state to the stretched state. Depending on the temperature, at a certain critical value of the force, rupture takes place and then the force becomes zero. The qualitative nature of the force extension curve is similar to the one seen in recent experiments [5, 15].

2. Bulge movement

Due to the formation of a bulge and application of shearing force at opposite ends of the dsDNA, one strand slowly moves over the other strand along the force direction. Since pulling is quite slow, there is enough time for unbinding and rebinding of the bases. In order to study the effect of bulge on the force temperature diagram, we consider the following partition function:

$$Z_N = \sum_{i=0}^{N} Z^i$$  \hspace{1cm} (12)

Unlike the model for rupture, we calculate the partition function $Z^1$, where allowed the formation of the base pairs in between ith base of one strand with the (i+1)th base of the other strand when the chain slides one unit distance along the force direction. Similarly $Z^2$ corresponds to the situation where the chain slides two units along the force direction and base pairing now takes place in between ith base of one strand with (i+2) base of the other chain and so on. In quasi static equilibrium this represents the bulge movement along the chain.

The force temperature diagram is shown in Fig. 9. The nature of phase boundary between zipped state and open state is different than the one obtained for DNA unzipping (Fig. 6(c)) but similar to the dissociation of two strands (Fig. 7). Moreover, the magnitude of the required force is much less than the one found for the dissociation of two strands. At low temperature, the entropy contribution is negligible and hence force required to break a base pairing is nearly equal to 1. However, at higher temperature, contribution arises due to entropy,
the applied force decreases with the temperature. The force extension curve in CDE ensemble has been shown in Fig. 10. With the rise of force, the dsDNA acquires the stretched state. Because of the formation of bulges and applied force, chain slides over the other chain along the force direction. This is evident from Fig. 10, where without increase in the applied force, extension increases. It may be noted here that the force required to bring chain from coiled state to the stretched state for both cases rupture and slippage are the same. However, in order to have dissociation, a large force is required while for the slippage comparatively less force is needed.

IV. CONCLUSIONS

Because of the constrained imposed on the pulling end of dsDNA, there are significant differences in the melting temperature and melting profile. Inclusion of diagonal interaction in the model shows the re-entrance in force-temperature diagram of DNA unzipping which were remain elusive in earlier studies. Furthermore, with proper modification in the model we could describe the phenomena like stretching, unzipping, dissociation and slippage of dsDNA. The force-temperature diagram of slippage and dissociation of dsDNA are significantly different than the DNA unzipping. This is mainly because in dsDNA unzipping, entropy of the chain and force competes with the enthalpy while in dissociation and slippage, it is the result of an applied force and enthalpy only. Being in stretched state, the entropic contribution of the chain is almost zero.

At low temperature, the qualitative nature of the force extension curve for dissociation of dsDNA (Fig. 8) is similar to the one observed in experiments. At high temperature, few bases are opened and hence applied force decreases as shown in Fig. 7. The slippage like transition has already been seen in experiments where the existence of plateau has been understood in the form of re-annealing of two strands. The qualitative nature of the plateau obtained here is similar to one seen in experiment.

At $T = 0$, Eq. 6 gives the force required for rupture which is equal to $N$. This is evident from the Fig. 7. Up to $T = 0.45$, the number of intact base remain ($N'$) equal to $N$ and hence entropy associated with open state is zero. The value found from the above equation matches exactly with the one shown in Fig. 7 up to $T = 0.45$. Above this temperature, $N'$ decreases with temperature and hence bubble forms. Therefore, more force is needed to keep system in the stretched state. This is reflected in Fig. 7 where the phase boundary between zipped and open states bends. For slippage like transition, $x = N$ and hence required force is equal to 1 consistent with the plot shown in Fig. 9.

In this paper, we consider effective base pairing energy and hence interaction associated with inter strand and intra-strand stacking interaction have been ignored. If one also includes these interactions in the model introduced in Ref, one may get different response for pulling at 5'-5' end and 3'-3' end. At this stage of time a long chain simulation along with hetero sequence is needed to understand the mechanism of slippage and dissociation at vanishingly small force.

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