CHAPTER 3

Forced induced melting of DNA in presence of an attractive surface

3.1 Introduction

As discussed in the previous chapter, there is a considerable interest in thermodynamic response of biopolymers in presence of confinement. It is well understood that biopolymers, such as dsDNA, protein when tethered to a surface behaves differently in comparison to free solution. The SMFS techniques provided the probe to explore various fields of biological research, such as adhesion of peptides near metal surfaces, nano-structured surface sensitive transistors, colloidal stabilization, chromatography etc. In bio-sensing applications, site specific sensitivity of DNA binding proteins on dsDNA, DNA repair enzymes activity on dsDNA substrate etc. restate the importance of surface adsorption studies of dsDNA [88, 89].

The adsorption of dsDNA on gold nanoparticles (Au-NP) is a promising research field due to its wide range of applications from biomedicine to biosensors [91, 92]. It is reported that the base-pairs of dsDNA get adsorbed to the Au-NP surfaces are results of the surface charge of Au-NPs, as well as the van der Waals interaction between nitrogen atoms of bases and Au-NPs [90, 93, 94] (see Fig. 3.1). Recently, few experimental approaches are developed to study the DNA denaturation or melting along with adsorption on the gold nanoparticles (Au-NPs) [95, 96]. DNA melting is the main structural transition where a double stranded DNA separates into two single stranded DNA upon increasing the temperature of the system. This happens when the free energy of the two separated ssDNA is lower than the dsDNA. Recently, theoretical develop-

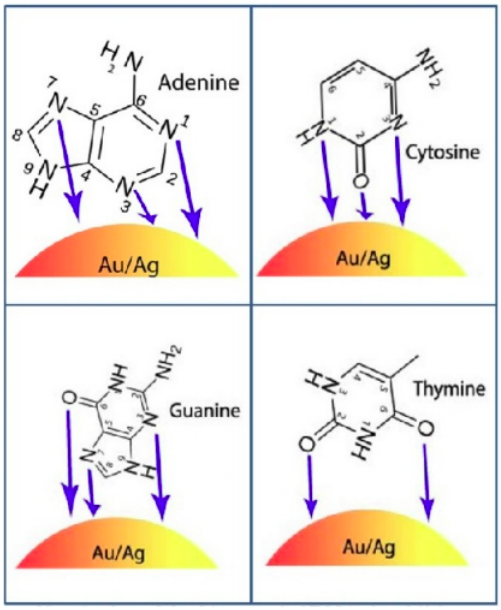

Figure 3.1. Schematic diagram showing the adsoprtion of different bases of DNA into gold-nanoparticle (Au-Np) surfaces. Image is taken from Ref.[90].

ments are also made to explore the dsDNA melting along with continuous adsorption-desorption of biopolymers with interactive surface [97]. DNA melting in presence of interactive surface has biological importance such as during replication of DNA, it gets attached to a membrane (surface), in gene therapy targeted drug delivery is made possible through DNA adsorption-desorption on oppositely charged liposomes [98, 99]. From theoretical point of view, the loss of conformational entropy of DNA near the surface is being compensated by the attractive interaction between the DNA and surface. This tug of war situation between the entropy and attractive surface energy makes free energy minimum which makes the problem complex, but to be worth exploring.

Another important structural change in DNA that does not require drastic change in the environment (pH solvent, or temperature) is force-induced unzipping. The unzipping process is the underlying mechanism during the replication process where opening of base-pair is taking place at one end of DNA due to enzymatic action [100]. Another form of force

induced unzipping studies originates from the function of single strand binding proteins (SSB) which binds to the strands of dsDNA and imparts force in opposite direction to open the base-pairing [101].

The theoretical background behind the unzipping of DNA basically rely on the co-existence of a zipped and unzipped phases, known as a Y fork.The zipped phase which is energetically favorable competes with the Y-fork phase where the single strands (in unzipped dsDNA) are entropically favorable. The critical force at which DNA unzips is a temperature dependent function and earlier force-temperature (g-T) phase diagram depicted that the critical force value decreases with increase in temperature [102, 103]. Whereas, in single strand pulling, the extension along force direction is energetically favorable and dominates over the reduced entropy (due to extension only in the force direction). These competing phenomena make the study of force induced unzipping at varied temperatures interesting.

In this chapter we study force induced melting of dsDNA in presence of an attractive surface. We systematically vary the surface interaction parameter and study force induced melting transitions. Depending on the surface interaction, applied force and temperature one can expect different kinds of transitions, namely adsorption-desorption, zipping-unzipping, and melting transition. Here, focus will be to calculate various thermodynamic observables, such as, average number of intact base-pair, average number of nucleotides attached to the surface, average distance of DNA end from the surface, etc. to identify various phases of DNA when subjected to change in different thermodynamic parameters.

3.2 Model and method

We model the dsDNA as two mutually self attracting self avoiding walks (MASAW) on a square lattice in presence of an attractive surface. The starting nucleotide of one strand of dsDNA (say, strand-I) is fixed at the surface (say, x, y) while the other strand (say, strand-II) is fixed at a unit

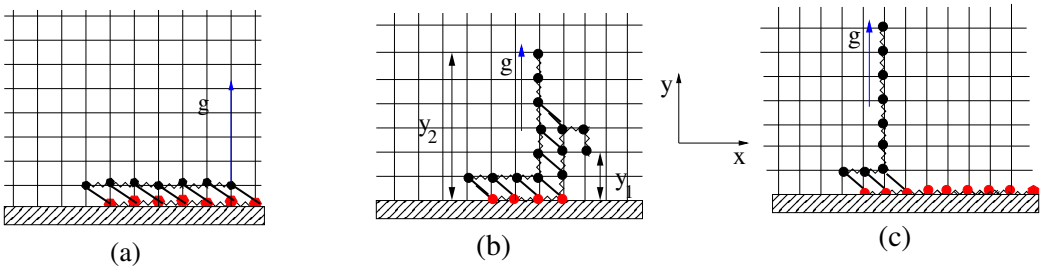

Figure 3.2. (a) Schematic diagrams of DNA adsorbed on attractive surface. The strand near the surface is called strand-I (first strand). A force (g) is applied on the one end of other strand (strand-II) along the y direction. The surface adsorbed nucleotides are shown in red circles, while black circles represent the nucleotide of strand-II. y_1 and y_2 represent the distance of end nucleotides of strand-I and strand-II from the surface respectively. Figure (b) and (c) represent some of the conformations of DNA in presence of attractive surface under the applied force g.

distance above the surface $(x-1, y+1)$ (Fig. 3.2). We apply an external force g, along the transverse direction (y-direction) on the free end of the second strand of DNA. The other end of first strand is free to be anywhere. Both strands are not allowed to cross the impenetrable surface. As discussed in Chapter 1, base pairing interactions are restricted to native contacts (diagonal) only, where i_{th} monomer of strand-I interacts with i_{th} monomer of the strand-II only [85, 104].

In the proposed model, we associate surface interaction energy ϵ_s with each nucleotide of the strand-I if they lie over the surface. Whereas the surface interaction energy associated with the nucleotide of the strand-II is zero, even if the nucleotide lies over the surface. Therefore, at any instant of time, if there are N_s monomers on the surface and N_p number of base pairs, the contribution to the total energy is given by $E = N_p\epsilon_p + N_s\epsilon_s$. In the following, we set $\epsilon_p = -1$ and vary the ϵ_s to study the force-induced melting of DNA in presence of an attractive surface.

The thermodynamic properties of the system under consideration may be obtained by the average of physical quantities calculated in the canonical ensemble for finite length of DNA. The partition function given by

equation 1.20 may be modified to incorporate the effect of surface which is given by the following expression:

$$Z = \sum_{N_p, N_s, y_2} C(N_p, N_s, y_2) e^{(-\beta \epsilon_p N_p)} e^{(-\beta \epsilon_s N_s)} e^{(\beta g y_2)} \tag{3.1}$$

Here, the sum is over all the individual chain configurations $C(N_p, N_s, y_2)$. $\exp(\beta\epsilon_p)$ and $\exp(\beta\epsilon_s)$ are the Boltzmann weights for the base-pairing interaction and surface interaction, respectively. $\exp(\beta g)$ is the Boltzmann weight for the force (g). y_2 is the transverse distance from the surface and $\beta = \frac{1}{k_B T}$, where k_B is the Boltzmann constant and T is temperature. In the following, we shall study simultaneous adsorption and force induced melting by keeping (i) temperature constant and vary the applied force, (ii) vary the temperature by keeping force constant for different values of ϵ_s.

3.3 Constant temperature

Homeostasis is the property of living systems in which temperature is actively regulated to remain almost constant [105]. Biological processes in such living systems (humans and other mammals), therefore take place at roughly constant temperature. Motivated by this, in this section, we keep the temperature constant and vary force to calculate the average number of intact base pairs ($\langle N_p \rangle$), number of base pairs on the surface ($\langle N_{ps} \rangle$), and the average number of nucleotides of strand-I on the surface ($\langle N_s \rangle$). At low temperature ($T = 0.5$) and low surface interaction parameter ($\epsilon_s = -0.1$), the variation of $\langle N_p \rangle$, $\langle N_{ps} \rangle$, and $\langle N_s \rangle$ as a function of force are shown in Fig. 3.3 (a). It is evident from the plot that DNA remains in the zipped state and away from the surface even at zero force. As force increases, $\langle N_s \rangle$ and $\langle N_{ps} \rangle$ decreases to its minimum. In Fig. 3.3 (c), we have shown the average reaction coordinate $\langle y_1 \rangle$ and $\langle y_2 \rangle$ as a function of force. Here y_1 and y_2 are the distances of the ends of strand-I and strand-II from the surface. These results clearly demonstrate that under the influence of force, DNA acquires stretched state where all the

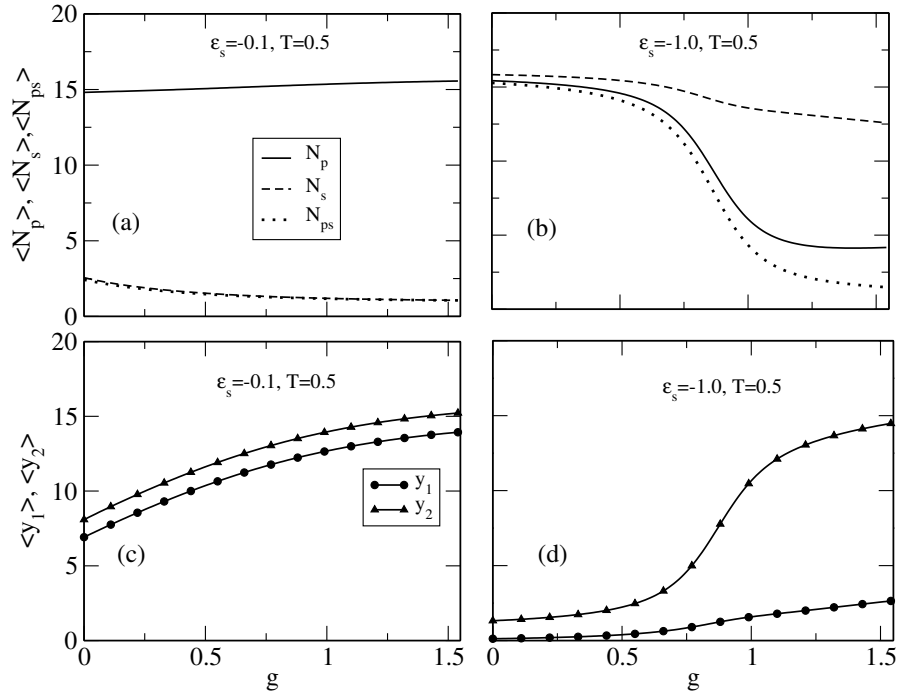

Figure 3.3. Figures (a,b) show the variation of $\langle N_p \rangle$, $\langle N_s \rangle$, and $\langle N_{ps} \rangle$ with g at $T = 0.5$ for different ϵ_s. (c, d) same as (a,b), but for $\langle y_1 \rangle$ and $\langle y_2 \rangle$.

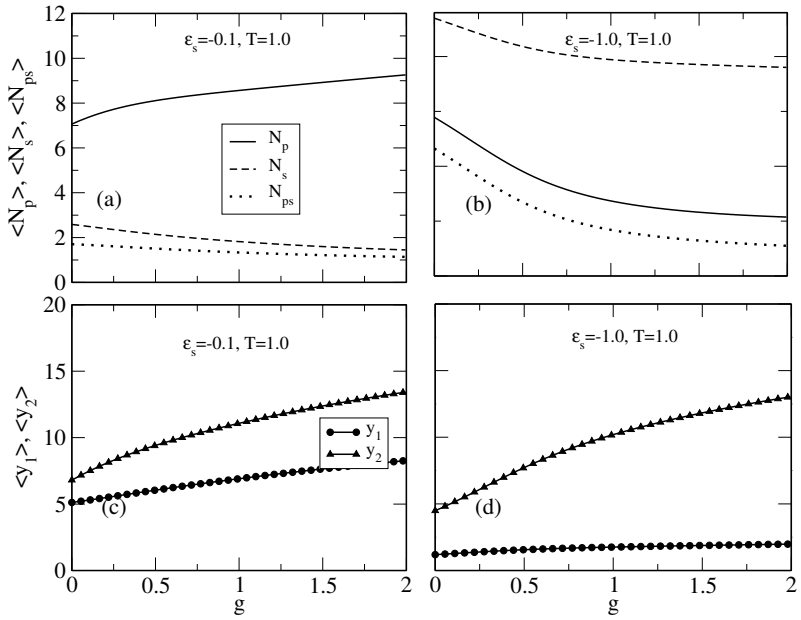

Figure 3.4. Same as Fig. 3.3, but at higher temperature $T = 1.0$

base pairs are intact. Now keeping the temperature constant, we assign a high surface interaction parameter ($\epsilon_s = -1.0$) for the nucleotide on the surface. The influence of the surface interaction parameter can be seen in Fig. 3.3 (b) and (d). One can notice that for the highly attractive surface, dsDNA remains in the adsorbed state, where all the base pairs remain intact. As force increases, the value of $\langle N_p \rangle$ and $\langle N_{ps} \rangle$ decreases, whereas $\langle N_s \rangle$ remains almost constant. This corresponds to the strand-II completely peeled off from the strand-I. This can be seen from Fig. 3.3 (d), where one observes increase in $\langle y_2 \rangle$ as a function of g, while $\langle y_1 \rangle$ remains almost zero.

At high temperature and a low surface interaction parameter ($\epsilon = -0.1$ and $T = 1.0$), dsDNA melts even at zero pulling force ($g = 0$). This is evident from Fig. 3.4 (a), where the intact base pairs is approximately equal to 7, whereas values of $\langle N_s \rangle$ and $\langle N_{ps} \rangle$ are quite low. This corresponds to DNA being desorbed from the surface and partially melted. Rise in the applied force stretched the strand-II to its maximum ($\langle y_2 \rangle \sim 15$), whereas the strand-I remains away from the second strand ($\langle y_1 \rangle \sim 7$)

[Fig. 3.4 (c)] This is because pulling the strand at higher temperature reduces the configurational entropy of the strand and thereby increases the probability of base-pairing between two strands by a small fraction.

The variation of $\langle y_1 \rangle$ and $\langle y_2 \rangle$ at high surface interaction ($\epsilon_s = -1.0$)and high temperature ($T = 1$) shows significantly different picture of DNA melting. The value of $\langle N_p \rangle$ and $\langle N_{ps} \rangle$ decreases as a function of g, whereas $\langle N_s \rangle$ remains almost constant (Fig. 3.4 (b)). This corresponds to although DNA has melted, however, one strand remains adsorbed on the surface. This can be also seen in Fig. 3.4(d), where $\langle y_1 \rangle$ remains almost zero, but $\langle y_2 \rangle$ approaches to its stretched conformation *i.e* $\langle y_2 \rangle \sim 15$. This affirms that in presence of strong attractive surface, force peeled the first strand from the surface, while a large segment of the strand-II remains adsorbed.

3.4 Constant force

The partition function defined in 3.1 is sufficient enough to study the effect of temperature on simultaneous adsorption and force induced melting of DNA keeping the force constant. Like the previous section, here we consider two cases of interactive surface: (i) $\epsilon_s = -0.5$, and (ii) $\epsilon_s = -1.0$. We keep applied force constant at one end of the strand-II, whereas the other strand (strand-I) interacts through ϵ_p with strand-II and with surface through ϵ_s. For low surface interaction ($\epsilon_s = -0.5$), and $g = 0.4$ (Fig. 3.5 (a)), dsDNA remains in the adsorbed state in the zipped form at low temperature. As temperature increases, $\langle N_s \rangle$ and $\langle N_{ps} \rangle$ decreases much sharply compare to $\langle N_p \rangle$. Keeping the value of ϵ_s same, at slightly higher force ($g = 0.5$), the chain is partially detached from the surface, but remains in the zipped state. As temperature increases, $\langle N_p \rangle$, $\langle N_s \rangle$ and $\langle N_{ps} \rangle$ decreases and DNA acquires unzipped conformations in the bulk. At higher force, even at low temperature, the chain remains in the desorbed state in zipped form. As temperature increases, the value of $\langle N_p \rangle$ decreases, and DNA acquires conformation of melted state as shown in Fig. 3.5 (c). The variation of $\langle y_1 \rangle$ and $\langle y_2 \rangle$ are shown in Fig. 3.5 (d-f) for

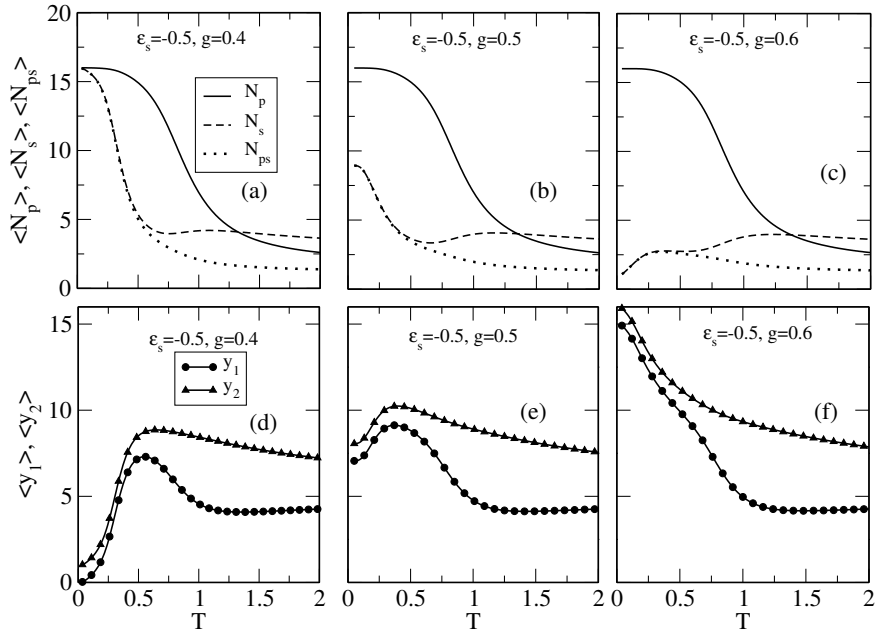

Figure 3.5. Figures (a-c) show the variation of $\langle N_p \rangle$, $\langle N_s \rangle$ and $\langle N_{ps} \rangle$ with T at different value of g at $\epsilon_s = -0.5$. Figure (d-f) are same as (a-c), but for $\langle y_1 \rangle$ and $\langle y_2 \rangle$.

different forces. It is interesting to note that at $g = 0.4$, DNA remains in the adsorbed state. As temperature increases, both $\langle y_1 \rangle$ and $\langle y_2 \rangle$ increases indicating the chain detached from the surface in the zipped conformation. At certain temperature, the DNA melts and $\langle y_1 \rangle$ decreases as there is no applied force on it. This is because at low temperature base-pairing energy dominates while at higher temperature entropy of the single strand (strand-I) dominates. It can be seen that at force $g = 0.5$, chain is partially detached from the surface in the zipped state at low temperature which is consistent with Fig. 3.5 (b). Increase in temperature leads to decrease in $\langle y_1 \rangle$ and $\langle y_2 \rangle$ which is similar to Fig. 3.5 (d). The most interesting finding may be noted from Fig. 3.5 (f) where at low temperature DNA remains in the stretched state away from the surface in the zipped form. As temperature increases, DNA acquires the coil form in the zipped state. This is easy to notice that the difference between $\langle y_1 \rangle$ and $\langle y_2 \rangle$ is almost constant upto certain temperature ($T = 0.4$). As temperature increases further, DNA melts and the value of y_1 decreases much faster than $\langle y_2 \rangle$. We expect a single molecule experiment will be able to detect such behaviour.

In Fig. 3.6, we have studied the effect of higher attractive strength ($\epsilon = -1.0$) on simultaneous adsorption and force induced melting. In this case, DNA remains in the zipped state and adsorbed at force $g = 0.9$ (Fig. 3.6(a)) at low temperature. Whereas at high force ($g = 1.1$), it remains in the unzipped state, however, due to the high value of ϵ_s, one of the strands remains in the adsorbed state. As temperature increases for lower force ($g = 0.9$), DNA melts and as a result $\langle N_p \rangle$ and $\langle N_{ps} \rangle$ decreases in compare to $\langle N_s \rangle$ of first strand. At high temperature, DNA acquires melted conformation in the bulk irrespective of the strength of the applied force. This has also been substantiated by monitoring $\langle y_1 \rangle$ and $\langle y_2 \rangle$ in Fig. 3.6(d-f), where one of the strands (strand-I) remains in the adsorbed state. The value of $\langle y_2 \rangle$ increases due to the applied force and acquires the stretched state, however, due to increase in temperature, entropy dominates and the value of $\langle y_2 \rangle$ acquires the coil state.

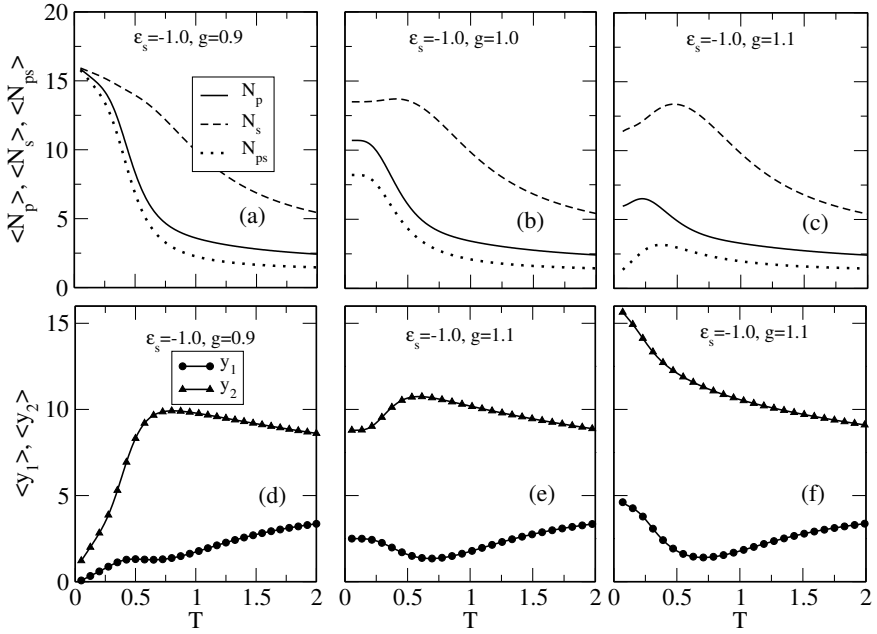

Figure 3.6. Same as Fig. 3.5 but for $\epsilon_s = -1.0$

3.5 Summary

By employing Exact Enumeration technique, we have studied the force induced melting of a short dsDNA in presence of an attractive surface. Various states of DNA are explored by studying the different observables, such as N_p, N_s, N_{ps}, y_1,and y_2. We used constant temperature and constant force to analyse the partition function to get these observables. We used low and high attractive surfaces to study simultaneous adsorption and force induced melting of DNA. At a low attractive surface, depending on the force DNA can be in the zipped state either on the surface or in the bulk. However, at a highly interactive surface, one of the strand (strand-I) always remains in the adsorbed state. As a result, one finds the zipped state of DNA in the adsorbed state only. As temperature increases, $\langle N_p \rangle$, $\langle N_s \rangle$ and $\langle N_{ps} \rangle$ decreases and acquires the value of bulk state. One may observe a non monotonic behavior which arises due to the competition between the applied force which try to bring the system in the stretched state (low entropy state) and the temperature which drives the system to

the coil state (high entropy state). In summary the simple lattice model of a small DNA captures the essential physics of simultaneous adsorption and force induced melting of DNA.