A simple model for the relative stabilities of DNA hairpin structure

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(Dated: February 1, 2008)

Abstract

A model of self-avoiding walk with suitable constraints on self-attraction is developed to describe the conformational behaviour of a single stranded short DNA molecule that form hairpin structure. Using exact enumeration method we calculate the properties associated with coil-hairpin transition. Our results are in qualitative agreement with the experiment.

PACS numbers: 05.50.+q, 05.70.Fh, 87.14.Gg
The structural and dynamic behaviour of a single stranded DNA molecule that form a stem-and-loop (hairpin) structures in solutions is a subject of current interest [1, 2, 3, 4]. This is because DNA hairpin structure is known to participate in many biological functions, such as the regulation of gene expression [5], DNA recombination [6] and facilitation of mutagenic events [7]. The DNA hairpin-containing domains may provide potential binding sites for exogenous drugs and endogenous proteins [8]. It can also be used as DNA biosensor (e.g. molecular beacons) [9].

The single stranded DNA that form a stem-and-loop structures under a given set of solution conditions are formed from synthetic oligonucleotides. For example, the oligonucleotide 5′−CCCAA−(X)_m−TTGGG−3′, where X is any one of the nucleotides and m its number, is such a molecule which can easily be synthesized. Due to thermal fluctuations such a molecule may acquire different conformations. In a simplified description all of the configurations can be divided into two main states; the open and the closed one as shown in Fig. 1. The closed hairpin structure is stabilized due to pairing of complimentary bases at the two arms of the molecule when hydrogen bonds are formed between them. The open state has high entropy due to the large number of configurations achieved by a single stranded DNA chain. The closed-to-open transition requires sufficiently large energy to unzip all the base pairs, whereas the closing transition requires the two arms of hairpin to come close to each other in space so that hydrogen bonding between the complimentary nucleotides can take place. Experimentally one finds the rate of closing depends strongly on the properties of the hairpin loop, such as the length and rigidity, whereas the rate of opening is relatively unaffected by these properties [1].

In this note we describe a model and show that it explains some of the conformational behaviour associated with the formation of hairpin structure.

We represent a linear polymer chain of N monomers by a self-avoiding walk of (N − 1) steps on a two dimensional square lattice. Visited lattice sites represent the monomers of the chain. The first n sites of the walk represent nucleotides, say, A or C and the last n sites the complimentary nucleotides, T or G. The remaining (N − 2n) = m sites represent the nucleotides of one type (either A or T or C or G). The repulsion at short distance between monomers (i.e. excluded volume) interaction is taken into account by the condition of self avoidance. When the complimentary monomers in a walk occupy nearest sites in a particular direction (say, clock wise), they form a pair (known as base pair). The energy associated
FIG. 1: Schematic of the conformational fluctuations of DNA hairpin-loop. This molecular beacon can fluctuate between open and closed states in solution at ambient temperature.

with this pair is $\epsilon$ ($\epsilon < 0$). The base paring cannot take place if the nucleotides approach to each other in any other way. This condition has been imposed to take into account the fact that in a single strand DNA chain the pairing between complementary nucleotides takes place only when they approach each other directly without the sugar phosphate strand coming in between as shown in Fig. 2a. Fig. 2b shows the situation in which the sugar phosphate strand is in between and therefore pairing can not take place.

All possible conformations of walks of $N$ sites mapped by a self-avoiding walk are generated using exact enumeration technique [10, 11]. Since the time involved in enumerating these conformations increases as $\mu^N$ where $\mu$ is the connectivity constant of the lattice, we have restricted ourselves to $12 \leq N \leq 22$.

The partition function of our interest is

$$Z_N = \sum_{p=0}^{n} C_N(p)(e^{-\epsilon/k_BT})^p$$

where $p$ is the number of base pairs and $C_N(p)$ the total number of configurations corresponding to walk of $(N - 1)$ steps with $p$ number of pairs (base pairs). The Helmholtz free
energy of the system is given as

\[ F = -k_B T \ln Z_N(T) \]  

where \( k_B \) is the Boltzmann constant and \( T \) the temperature of the system. From Eq. (2) one can calculate the specific heat and entropy using the following relations:

\[ C_v = -T \left( \frac{\partial^2 F}{\partial T^2} \right) \]  
\[ S = -\left( \frac{\partial F}{\partial T} \right) \]  

In our calculation we have taken \( n = 5 \) and \( \epsilon = -0.08 \) eV. Dependence of the free energy \( F \) on temperature for \( N = 22 \) is shown in Fig. 3a.

From this figure it is clear that there is a “discontinuous” change in the free energy at \( T = 338^\circ K \). In Fig. 3b we plot the specific heat as a function of temperature for several values of \( N \). This curve has a peak suggesting a transition from the hairpin structure to the coil (or open) state. For \( N = 22 \), the peak is at \( 337 \pm 2^\circ K \). Since we are describing a finite system, the transition is not sharp; it takes place over an interval of temperature. This interval is obvious from the width of the peak in \( C_v \) and also from Fig. 3c in which

FIG. 2: Schematic of configurations showing the (a) formation and (b) non-formation of base pairs.
FIG. 3: (a) Plot of free energy ($F$) as a function of temperature ($T$) for $N = 22$; (b) Specific heat ($C_v$) as a function of temperature ($T$) for different $N$; (c) Entropy ($S$) vs temperature ($T$) for $N = 22$. 
we plot entropy \( (S) \) as a function of \( T \) for \( N = 22 \). The entropy is low at low temperature as the molecule is in a hairpin structural form whereas at high temperature the entropy is higher as the molecule in coil form assesses a large number of conformations.

The partition function defined by Eq. (1) has six terms corresponding to six values of \( p \) from 0 to 5 (\( p = 0 \) corresponds to open state of the chain whereas \( 1 \leq p \leq 4 \) corresponds to partially closed state and \( p = 5 \) the final state of hairpin structure. We can find the probability of each of these states in the following way.

\[
P_p(T) = \frac{Z_p}{Z}
\]

where \( Z = \sum_{p=0}^{5} Z_p \)

We compare \( P_p(T) \) for different values of \( p \) in Fig. 4a. It shows that the dominating structure are either all closed or all open.

The other quantity of interest is the fraction of open to closed structures at a given temperature. The fraction of all open structure can be derived from the relation

\[
\chi^- = \frac{Z_0}{Z_0 + Z_c}
\]

where \( Z_0 \) is for \( p = 0 \) and \( Z_c = \sum_{p=1}^{5} Z_p \) and the fraction of closed structures

\[
\chi^+ = \frac{Z_c}{Z_0 + Z_c}
\]

From Eq. (5) and (6) we get

\[
\frac{\chi^-}{\chi^+} = \exp \left[ -\frac{1}{k_B T} (F_0 - F_c) \right]
\]

where \( F_0 = -k_B T \ln Z_0 \) and \( F_c = -k_B T \ln Z_c \)

The fraction of all closed structure at a given temperature is found from the relation

\[
\chi'_+ = \frac{Z_5}{Z_0 + Z_c}
\]

From this figure [Fig. 4b] one may note that while \( \chi^- \) and \( \chi'_+ \) intersects at \( T = 337 \pm 2^\circ K \) in agreement with the coil-hairpin transition temperature, \( \chi^- \) and \( \chi^+ \) intersects at \( T = 366 \pm 2^\circ K \). As shown in Fig. 4a the probability of partially connected conformations are small and confined to narrow temperature region. One may therefore conclude that the conformational properties of this kind of single DNA strand is primarily controlled by either all open or all closed states.
FIG. 4: (a) Probability of opening ($p = 0$), closed ($p = 5$) and partially closed ($p = 1, 2, 3, 4$) states as a function of temperature ($T$); (b) (i) Fraction of all open structure ($\chi_-$), (ii) fraction of closed structure ($\chi_+$) and (iii) fraction of all closed structure ($\chi'_+$) as a function of temperature ($T$).

By varying the value of $\epsilon$, one can study the effect of base pair interaction on coil-hairpin transition. The change in $\epsilon$ value from -0.08 eV to -0.05 eV leads to the decrease in transition temperature by 100$^\circ$K.

In conclusion, we have studied a simple model for DNA hairpin loop structure and their relative stabilities. We use lattice models of polymers along with exact enumeration technique to study the stability of different conformations of DNA hairpin loop and the corresponding hairpin-coil transition. Our results are in qualitatively agreement with the reported experimental work by Bonnet et al [1].
Acknowledgments

We thank Navin Singh for many helpful discussions. Financial assistance from INSA, New Delhi and DST, New Delhi are acknowledged.

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