Pulling short DNA molecules having defects on different locations

Amar Singh, Navin Singh
Department of Physics, Birla Institute of Technology & Science, Pilani - 333 031, Rajasthan, India

We present a study on the role of defects on the stability of short DNA molecules. We consider short DNA molecules (16 base pairs) and investigate the thermal as well as mechanical denaturation of these molecules in the presence of defects that occur anywhere in the molecule. For the investigation, we consider four different kinds of chains. Not only the ratio of AT to GC different in these molecules but also the distributions of AT and GC along the molecule are different. With suitable modifications in the statistical model to show the defect in a pair, we investigate the denaturation of short DNA molecules in thermal as well as constant force ensemble. In the force ensemble, we pulled the DNA molecule from each end (keeping other end free) and observed some interesting features of opening of the molecule in the presence of defects in the molecule. We calculate the probability of opening of the DNA molecule in the constant force ensemble to explain the opening of base pairs and hence the denaturation of molecules in the presence of defects.

PACS numbers: 87.14.gk, 87.15.Zg, 87.15.A-

I. INTRODUCTION

Defects in the DNA molecule play a crucial role in biological processes such as replication. This is a known fact that DNA is a long polymeric chain that contains different kinds of nitrogenous bases. The allowed pairing in the two complementary strands follow a simple rule, that is, Adenine (A) can form a hydrogen bond with Thymine (T) while Guanine (G) can form a hydrogen bond with Cytosine (C) [1, 2]. The hydrogen bonding strength for these two base pairs is not same as the AT base pair has two hydrogen bonds while GC base pair has three hydrogen bonds. The approximate ratio of GC and AT bond strengths varies from 1.2 to 1.5 as mentioned by various research groups [3–12]. In the absence of the complementary base on the opposite strand, the pairing between the two bases is absent. This site is called a defect site because of an absence of a stable (or non-existing) bonding between these two bases on the opposite strands [13, 14]. The presence of defects in DNA is related to interesting physics and biochemistry of the molecule. The dynamics of these defects may delay the replication process and hence lead to the breathing dynamics of opening of the chain [15]. It is predicted that in embryonic cells, these delays may cause the cell death while in mature cells like somatic cells, this damage (defect) may be an initiation step in the development of cancer [16–20]. These defects are present in the DNA based actuators. The role of the defects in the designing of molecular motor has been discussed by McCullagh et al [21]. How the defects affect the melting, elastic and other properties are problem of scientific interest. There are many paths to explore the role of the defects and the damage repair mechanism in the living cells. Theoretical approach to investigate the problem routes via molecular dynamics or model based calculations [22–31]. Our approach is a model based calculation. We use Peyrard Bishop Dauxois (PBD) model [3] to investigate the thermal and mechanical denaturation of DNA molecules in presence of defects. The main objective of the current study is to investigate the effect of density and location of defects on the denaturation of DNA molecule.

In experiments, researchers synthesis and/or characterize the samples to decipher the information stored by that sample. Accordingly, we choose four samples of DNA molecules each containing 16 base pairs. All these samples have different numbers and distribution of AT-GC pairs. We identify all these molecules according to the distribution of base pairs and named them as follows: Chain 1: 3’-AAAAA………………5’ (homogeneous), Chain 2: 3’-AGAGAGAGAGAGAGAG-5’ (alternating AT- GC pairs), Chain 3: 3’- AAAAAAAAGGGGGGGGG-5’ (50%AT+50%GC), Chain 4: 3’-TCCCTAGACTTAGGGA-5’ (random sequence). The prime motivation behind the selection of different kinds of sequences is to predict the role of defect(s) in the melting or unzipping of different kinds of DNA molecules. The next task is to introduce the defect in the model. We have continued from our previous approach [13] where the defect in the model was introduced via Morse potential that represent the hydrogen bonding. If a pair has a defect that means there is an absence of hydrogen bond and this feature is reflected from the absence of potential depth while retaining the repulsive part of the potential in order to avoid the crossing of two bases in a pair (see Fig. 1).

We present the work in different sections. In Section II we provide a brief description of the model and methodology used in this work. The effect of defect(s) on thermal denaturation of dsDNA molecule is discussed in Section III while in Section IV role of the defect(s) on the mechanical unzipping is discussed. We finally conclude our results in Section V.

II. THE MODEL

For the current investigation we use a statistical model that was proposed by Peyrard and Bishop [3]. The model considers the stretching between the corresponding bases
only. Although the model ignores the helicoidal structure of the dsDNA molecule, it has enough details to analyze mechanical behavior at the few angstrom scale relevant to molecular-biological events [10]. The Hamiltonian for the considered system of $N$ base pairs unit is written as,

$$H = \sum_{i=1}^{N} \left[ \frac{p_i^2}{2m} + V_M(y_i) \right] + \sum_{i=1}^{N-1} \left[ W_S(y_i, y_{i+1}) \right]$$

(1)

where $y_i$ represents the stretching from the equilibrium position of the hydrogen bonds. The $m$ represents the reduced mass of a base pair which is taken to be same for both AT and GC base pairs. The stacking interaction between two consecutive base pairs along the chain is represented by,

$$W_S(y_i, y_{i+1}) = \frac{k}{2} (y_i - y_{i+1})^2 [1 + a e^{-b(y_i + y_{i+1})}]$$

(2)

where $k$ represents the single strand elasticity. The anharmonicity in the strand elasticity is represented by $\rho$ while $b$ represents its range. The stacking interaction $W_S(y_i, y_{i+1})$ is independent of the nature of the bases at site $i$ and $i + 1$ as these parameters are assumed to be independent of sequence heterogeneity. The sequence heterogeneity has effect on the stacking interaction along the strand. This can be taken care of through the single strand elasticity parameter $k$. One can take the variable $k$ according to the distribution of bases along the strand [31]. A defect in a pair will modify the electronic distribution around the bases hence the stacking parameters. However, for the current investigation we settled on the average of this parameter.

The hydrogen bonding between the two bases in the $i^{th}$ pair is represented by the Morse potential.

$$V_M(y_i) = D_i (e^{-a_i y_i} - 1)^2$$

(3)

where $D_i$ represents the potential depth which basically represents the bond strength of that pair. The parameter, $a_i$, represents the inverse of the width of the potential well. The heterogeneity in the sequence is taken care of by the values of $D_i$ and $a_i$. These model parameters should be tuned in order to get physical picture of DNA molecule. For the current investigations, we choose: $D_{AT} = 0.1$ eV, $a_{AT} = 4.2$ Å$^{-1}$, $D_{GC} = 0.15$ eV, $a_{GC} = 6.3$ Å$^{-1}$, $\rho = 5.0$, $b = 0.35$ Å$^{-1}$, and $\delta = 0.021$ eV Å$^{-2}$.

Thermodynamics of the transition can be investigated by evaluating the expression for the partition function. For a sequence of $N$ base pairs with periodic boundary conditions, the partition function can be written as:

$$Z = \int_{-\infty}^{\infty} \prod_{i=1}^{N} \{ dy_i dp_i \exp[-\beta H] \} = Z_p Z_c,$$

(4)

where $Z_p$ corresponds to the momentum part of the partition function while the $Z_c$ contributes as the configurational part of the partition function. Since the momentum part is decoupled in the integration, it can be integrated out as a simple Gaussian integral. This will contribute a factor of $(2\pi \hbar k_B T)^{N/2}$ in the partition function, where $N$ is the number of base pairs in the chain. The calculations of the configurational partition function, $Z_c$, is not straightforward. This is defined as,

$$Z_c = \int_{-\infty}^{\infty} \prod_{i=1}^{N-1} dy_i K(y_i, y_{i+1}) dy_N K(y_N)$$

(5)

where $K(y_i, y_{i+1}) = \exp[-\beta H(y_i, y_{i+1})]$. For the homogeneous chain, one can evaluate the partition function by transfer integral (TI) method by applying the periodic boundary condition $\bar{F}$. In case of a heterogeneous chain, with open boundary, the configurational part of the partition function can be integrated numerically with the help of matrix multiplication method $\bar{F}$ $S$ [14]. The important part of this integration is the selection of proper cut-offs for the integral appearing in Eq.5 to avoid the divergence of the partition function. The method to identify the proper cut-off has been discussed by several groups $\bar{F}$ $S$ [32]. The calculations done by T.S. van Erp et al show that the upper cut-off will be $\approx 144$ Å with the our model parameters at $T = 600$ K while the lower cut-off is $-0.4$ Å. In the earlier work by Dauxois and Peyrard it was shown that the $T_m$ converges rapidly with the upper limit of integration $\bar{F}$ [32]. In that work they considered an infinite homogeneous chain and solved the partition function using TI method. For short chains, we calculate $T_m$ for different values of upper cut-offs which are shown in Fig. $\bar{F}$. From the plot it is clear that the choice of $200$ Å is sufficient to avoid the divergence of partition function. Thus the configurational space for our calculations extends from $-5$ Å to $200$ Å. Once the limit of integration has been chosen, the task is reduced to discretizing the space to evaluate the integral numerically. The space is discretized using the Gaussian quadrature formula. In our previous studies [14], we observed that in order to...
get precise value of melting temperature \( T_m \) one has to choose the large grid points. We found that 900 is quite sufficient number for this purpose. As all matrices in Eq.\ref{eq:theta} are identical in nature the multiplication is done very efficiently. The thermodynamic quantities of interest can be calculated by evaluating the Helmholtz free energy per base pair is,

\[
f(T) = -\frac{1}{2 \beta} \ln \left( \frac{2 \pi m}{\beta} \right) - \frac{1}{N \beta} \ln Z_c; \quad \beta = \frac{1}{k_B T}.
\]

The thermodynamic quantities like specific heat \( C_v \) as a function of temperature or the applied force can be evaluated by taking the second derivative of the free energy. The peak in the specific heat corresponds to the melting temperature or the critical force of the system.

Other quantities such as the average fraction \( \theta(=1-\phi) \) of bonded (or open) base pairs can be calculated by introducing the dsDNA ensemble (dsDNAE) \cite{8} or using the phenomenological approach \cite{4,13}. In general, the \( \theta \) is defined as,

\[
\theta = \theta_{\text{ext}} \theta_{\text{int}}
\]

\( \theta_{\text{ext}} \) is the average fraction of strands forming duplexes, while \( \theta_{\text{int}} \) is the average fraction of unbroken bonds in the duplexes. The opening of long and short chains are completely different. For long chains, when the fraction of open base pairs, \( \phi(=1-\theta) \), goes practically from 0 to 1 at the melting transition, the two strands are not yet completely separated. At this point, the majority of the bonds are disrupted and the dsDNA is denatured, but the few bonds still remaining intact, preventing the two strands parting from each other. Only at high temperatures will there be a real separation. Therefore for very long chains the double strand is always a single macromolecule through the transition, thus one can calculate the fraction of intact or broken base pairs only. For short chains, the process of single bond disruption and strand dissociation tend to happen in the same temperature range. Thus, the computation of both \( \theta_{\text{int}} \) and \( \theta_{\text{ext}} \) is essential \cite{4}. The problem of computation of \( \theta_{\text{ext}} \) can be handled efficiently by working in dsDNA ensemble (dsDNAE) \cite{8}.

III. THERMAL MELTING OF THE DNA MOLECULE

We consider the defects (1-4 in number) and their effect on the melting temperature of the DNA molecule. Since the nature of each chain is different, the number and location of these defects may modify the melting profile of the chain in different manner. The melting temperature, \( T_m \), is calculated by the peak in the specific heat as well as from \( \theta \) as given in \cite{4,13}. For pure chain, we show the melting profile of the chain in Fig. 3. The melting temperatures for chain 1, 2, 3, 4 without any defect are 447.5, 508.8, 511.0 and 509.8 K, respectively. Let us now consider the chain 1 with one defect. When the first site (3' end) is a defect pair, the melting temperature is about 433 K. The melting temperature further reduces to 432 K if the 2nd pair is a defect pair. However there is something interesting to note after this. When the location of defect is 4th pair onward (towards 5' end) the melting temperature reduces to 430 K and remains constant till we reach 13th site. As we reach on the 5'
FIG. 4. (Color online) The melting temperature, $T_m$, for all the four chains with different numbers as well as the locations of these defects along the DNA molecule. Figures in a row are for a chain with different numbers of defects. Figures in a column are for different chains with same number of defect(s) displayed by $m$.

end, the $T_m$ again increases. This complete cycle displays a necklace kind of plot as shown in Fig. 4. The variation in the melting temperature when the defect is anywhere between 4 to 13 is negligible. When the number of defects in the chain is increased from 1 to 4 the width or plateau (where there is no change in the melting temperature of the molecule) decreases (∼8-12).

In order to explore more about the nature of denaturation, we investigate other chains that have different distribution of base pairs. Consider chain 2 with single defect. This chain is having alternate AT/GC pairs. As shown in Fig. 4, the symmetry about the middle is lost. For this chain, the location of defect site, whether it is AT or GC pair, is important. The energy landscape of this chain is not smooth over the complete length because of the difference in the dissociation energies of AT and GC pairs. For single defect that move from position 1 to 16, $T_m$ shows a zig-zag pattern and $T_m$ varies between a range of 496 K to 487 K. When we consider two consecutive defects in the chain this pattern is lost because of the loss in the sequence heterogeneity. This can be thought of as reviving the homogeneous structure of the DNA molecule with the dual pair having an average of AT and GC pair’s dissociation energies. However, the necklace pattern obtained for this case is not as symmetric as observed for the chain 1 since the end pairs are not same. Remember at 3′- end there is an AT pair while on 5′- end, there is a GC pair. For this chain, $T_m$ varies between 485 K to 476 K. The zig-zag pattern is retained when three consecutive defects are introduced. However, the $T_m$ is lower as compared to the chain with one defect. Again with four consecutive defects an asymmetric necklace is observed with short plateau.

Let us consider chain 3, that is having 50 AT + 50 GC pairs in the sequence, with one defect. In this case, we obtain a hook kind of structure in the plot. A sudden drop in the $T_m$ is observed in the middle of the chain (on 8 & 9 pair) at the interface of GC & AT pair. The smoothness at the interface increases with increase in the number of defects in the chain. As the number of defect
molecule, this is averaged to 478 K, for 5th defects in the molecule. Let us observe the single defect. The random pattern of the plot varies with number of defects in the molecule. Let us observe the single defect on 4, 5, & 6 sites. While $T_m$ is 488 K for 4th site, it is 495 K for 5th & 6th sites. For two consecutive defects in the molecule, this is averaged to 478 K, i.e. This is because of the indistinguishability of AT and GC pairs. Similarly, for three (consecutive) defects in the molecule, the high barrier on 11 & 12 sites, is lost. The pattern observed for this chain is closer to the real sequences.

IV. FORCE INDUCED TRANSITIONS

The replication process is initiated by the force exerted by DNA polymerase on a segment of DNA chain (Owczarz fragment). The replication starts at some site which is called replication origin [19, 20] and the replication fork propagates bidirectionally. The defect or mismatch pair(s) may slow or stall the replication process. As shown in the Fig. IV.3, all the base pairs of dsDNA that is kept in the entropy of the system, for mechanically stretched DNA molecules in presence of defect(s). The modified Hamiltonian for the DNA that is pulled mechanically from an end is,

$$H = \sum_{i=1}^{N} \left[ \frac{P_i^2}{2m} + V_M(y_i) \right] + \sum_{i=1}^{N-1} [W_S(y_i, y_{i+1})] - F \cdot y_1 \tag{8}$$

where the force $F$ is applied on the 1st pair [14]. Whereas in thermal denaturation, the opening is due to increase in the entropy of the system, for mechanically stretched DNA chain, the opening is enthalpic. The thermodynamic quantities, of interest, from the modified Hamiltonian can be calculated using Eq. 5 & 6. Here we consider the same four chains that we considered for thermal denaturation studies. All the base pairs of dsDNA that is kept in a thermal bath share equal amount of energy. In the case when the chain is pulled from an end, the amount of force decreases from the pulling point to the other end of the chain. Thus the location of defect(s) should have different impact on the opening of the chain that is subjected to a mechanical pull from an end. Let us consider chain 1 with one defect. As shown in the Fig. 5, when the force is applied on the 3’-end and the defect pair is 1st pair (3’-end), the critical force reduces to 4.04 pN from 4.54 pN. This value further decreases to 3.99 pN when the defect pair is 2nd pair. When the defect is located between 3-13 pairs, there is no change in the value of critical force, it is ~3.97 pN. This means that the base pair (defected) in this section of the chain have similar response to the applied force, irrespective of their location. The defect pair means a loop in the chain which will increase the entropy of the chain. From the results, this is clear that the loop contributes to the opening of the chain in addition to the applied force and end entropy. However, as the defect location is somewhere between 14 to 16, contribution of bubble in the entropy of the chain is negligible. Hence the critical force increases. In this case too, we observe a necklace pattern. The pattern obtained here is not as symmetric as observed for thermal melting of the same chain with single defect. The reason for this difference lies in the nature of the chain opening in these two cases. We consider now the opening of the chain in another condition. The force is applied on 3’-end and defect pair is the 5’-end. In this case, the critical force is 4.02 pN which is less than for the previous case (where the force is on 3’-end and defect pair is also 3’-end) where $F_c$ is 4.04 pN. The difference is about 0.02 pN. The reason for this reduction is the difference in the end entropies for these two cases. In case when the defect end is 5’-end, the entropy of this open end contributes to the opening. While for the first case, when the defect end is the 3’-end (the force is also on this end), the contribution from the 5’-end will be less as it is an intact pair. Hence we need slightly higher force to open the chain for the first case. We obtained similar results for this chain with more defects ($m = 2, 3, 4$). For all the investigations whenever $m > 1$, all the defects are consecutive defects. As the number of defects increases in the chain, the difference in the $F_c$ for two different cases is greater. In order to verify our arguments, we calculate the probabilities of opening of the base pairs for these two cases. The probability of opening of the $j$th pair, in a sequence is defined as [37]:

$$P_j = \frac{1}{Z_c} \int_{y_0}^{\infty} dy_j \exp [-\beta H(y_j, y_{j+1})] Z_j \tag{9}$$

where

$$Z_j = \int_{-\infty}^{\infty} \prod_{j=1, j \neq i}^{N} dy_j \exp [-\beta H(y_j, y_{j+1})] \tag{10}$$

while $Z_c$ is the configurational part of the partition function defined as in eq.5. For $y_0$, we have taken a value of 2 Å. To avoid the overflow of figures, we choose to display the surface plot for chain 1 with 4 defects, see Fig. 6. We observe that the difference in the critical force for these two cases is ~ 0.04 pN.

Let us consider, the chain 2 (alternating AT and GC pairs). In this case, we have four possible combinations of force and defect locations. First, when force is applied on 3’-end and the defect is also at the 3’-end. Second one is when force is applied on 3’-end and defect is at 5’-end. The other two cases are the alternate combinations
of these two. If we fix the location of applied force at 3′ -end and change the defect locations, we find that for single defect the difference in $F_c$ is $\sim 0.3$ pN. This is because of the difference in the entropy contribution from the two ends. In one case the end is AT while in another case it is GC. If we fix the defect location and change the applied force locations from 3′ -end to 5′ -end, we find that the difference in $F_c$ is $\sim 0.02$ pN. The same argument which we gave for chain 1 with single defect is valid here too. Now consider this chain with two defects. When the force is applied on 3′ -end and the defect locations are 3′ -end and 5′ -end, the difference in $F_c$ is $\sim 0.04$ pN. This chain with two defects can be thought of as a homogeneous chain (of AT + GC block) with single defect. However, the ends in this chain can be either AT or GC and hence we get a different pattern at the ends as compare to chain 1. Similar kind of feature is observed for the same chain with four defects. For the chain 3, the difference in the energy of AT and GC pair is clearly visible. In this case, this is important on which end the force is applied. When the force is applied on 3′ -end and the defect locations are 3′ -end and 5′ -end the difference in the $F_c$ is $\sim 0.32$ pN. The chain 4 is a chain with random distribution of AT and GC pairs. Since the distribution is random the energy landscape of AT and GC pairs will play an important role in the opening of chain with different locations of defect. The unzipping behavior of this chain displays some of the features of all the three chains that we considered above. In case when the defect(s) are in the middle of the chain, the change in the value of critical force is negligible, i.e., it does not matter from which end the chain is pulled.

V. CONCLUSIONS

In the present work, we have studied the role of defect(s) on the thermal as well as mechanical denatura-
tion of DNA molecule. It is known that the defects delay the replication process which may further cause the cell death and hence may lead to initiation of cancer. Motivated by the experimental studies, we considered four different kind of DNA molecules. These molecules have different numbers of AT and GC pairs and the distribution of these pairs along the chain is also different. We have considered all the chains with \( m \) number of defects, where \( m \) varies from 1-4. Here we assumed that for \( m > 1 \) all the defects are in a block. For the equilibrium calculations, we used PBD model and found the denaturation point in thermal as well as in constant force ensembles. For the homogeneous chain, we found that there is a segment (4-12) of the chain where \( T_m \) is unaffected by the location of the defect in the chain. In case of heterogeneous chain, there is no plateau but it matters on a location whether there is an AT pair or a GC pair. When we compared the opening in two ensembles for homogeneous chain we observed that there is a striking difference. While for the homogeneous chain we obtained a symmetric necklace kind of plot in thermal ensemble, this was missing in force ensemble. This validates the role of finite end entropy of the homogeneous chain in the denaturation of the DNA molecule. For the thermal melting the ends have less impact on the opening because of the fact that each base pair shares the same amount of thermal energy. There only the sequence of AT/GC pairs matters.

For the chain that is pulled from an end by some force, it is important for all kinds of chains (with defect) whether the force is applied on 3’- end or 5’- end. For unzipping in constant force ensemble we considered four possible cases. First two are when force is applied on 3’- end and the defect locations are either on 3’- or 5’- ends. Similarly other two combinations are when the force is applied on 5’- end and defect locations are either 3’- or 5’- ends. In all these cases, the nature of end pair is important. For the chain with alternate AT and GC sequence we observed that in addition to the ends the interface of defect and intact pair affect the opening of the chain. The interfaces for this chain with two defects are either of AGA or GAG kind. Hence there is a difference in the critical force for the four cases. To show the importance of ends in the opening we calculated the probabilities of opening for the homogeneous chain with four defects. Here we considered two cases; one when the force is applied on 3’- end and defects are either at 3’- end or at 5’- end. When the defect location is 3’- end, the end entropy is suppressed and hence we obtained a slightly higher critical force for this case. The studies on chain 4 are closer to the real chain as it has random sequence of AT and GC pairs. The force profile (Fig. 5) shows the weak and strong sections of the chain. As a future of this work, one can study the opening of DNA molecule in both the ensemble as a function of time and the exact delay in the opening can be predicted. This is an attempt to understand the defect and their effect on the replication process. However, the real picture would be clearer from non-equilibrium studies. How the cell decides which segment of DNA with a mismatch in the sequence can be repaired or which would be destroyed will be an interesting area of future studies. Is there any
role of free energies of the sequence? The time evolution of this kind of molecule may provide some useful information.

ACKNOWLEDGEMENT

We are thankful to Y. Singh and S. Kumar, Department of Physics, Banaras Hindu University, India, for useful discussions. We acknowledge the financial support provided by Department of Science and Technology, New Delhi [SB/S2/CMP-064/2013] and University Grant Commission, New Delhi, India for BSR fellowships to AS.

[1] J.D. Watson, F.H.C. Crick, Nature 171, 737 (1953).
[2] L. Stryer, Biochemistry, Freeman, New York 1995.
[3] M. Peyrard and A.R. Bishop, Phys. Rev. Lett. 62, 2755 (1989); T. Dauxois, M. Peyrard and A.R. Bishop, Phys. Rev. E 47, R44 (1993).
[4] A. Campa and A. Giansanti, Phys. Rev. E 58, 3585 (1998).
[5] Yong-li Zhang, Wei-Mou Zheng, Ji-Xing Liu, and Y. Z. Chen, Phys. Rev. E 56, 7100 (1997).
[6] S. Ares, N.K. Voulgarakis, K.O. Rasmussen, A.R. Bishop, Phys. Rev. Lett. 94, 035504 (2005); G. Kalosakas and S. Ares, J Chem. Phys., 130, 235104 (2009).
[7] N.K. Voulgarakis, A. Redondo, A. R. Bishop, and K. O. Rasmussen, Phys Rev Lett, 96, 248101 (2006).
[8] T.S. van Erp, S. Cuesta-L´opez, J.G. Hagmann, M. Peyrad, Phys. Rev. Lett. 95, 218104 (2005); T.S. van Erp, S. Cuesta-L´opez, M. Peyrad, Eur. Phys. J. E 20, 421 (2006).
[9] G. Weber, N. Haslam, J.W. Essex and J. Neylon, J. Phys. Condens. Matter 21, 034106 (2009).
[10] M. Peyrard, S. Cuesta-L´opez and G. James, J. Biol. Phys. 35 , 73 (2009).
[11] B. Alexandrov, N.K. Voulgarakis, K.O. Rasmussen, A. Usheva and A.R. Bishop, J. Phys: Conden. Matter, 21, 034103 (2009).
[12] M. Zoli, J. Theor. Biol. 354, 95 (2014).
[13] N. Singh and Y. Singh, Phys. Rev. E 64, 042901 (2001).
[14] N. Singh and Y. Singh, Eur. Phys. J. E 17, 7 (2005).
[15] M.G. Gauthier, J. Herrick, and J. Bechhoefer, Phys. Rev. Lett. 104, 218104 (2010).
[16] Piiivi Peltonäki, J. of Clinical Oncology, 21, 1174 (2003).
[17] C. Hensey, and J. Gauthier, Mechanisms of Development 69, 183 (1997).
[18] M.M. Vilenchik and A.G. Knudson, Proc. Natl. Acad. Sci. USA 100, 12871 (2003).
[19] D. Branzei and M. Foiani, Curr. Opin. Cell Biol. 17, 568 (2005).
[20] W. K. Kaufmann, Carcinogenesis 31, 751 (2010).
[21] M. McCullagh, I. Franco, M.A. Ratner, G.C. Schatz, J. Phys. Chem. Lett. 3, 689 (2013).
[22] Y. Kafri, D. Mukamel and L. Peliti, Phys. Rev. Lett., 85, 4988 (2000); ibid Eur Phys J. B, 27, 135 (2002).
[23] T. Ambjörnsson and R. Metzler, Phys. Rev. E 72, 030901(R) (2005).
[24] S. Buyukdagli, M. Joyceux, Phys. Rev. E 77, 031903 (2008).
[25] C.I. Duduiala, J.A.D. Wattis, I.L. Dryden, C.A. Laughton, Phys. Rev. E 80, 061906 (2009).
[26] S. Kumar and M. S. Li, Phys. Rep 486, 1 (2010).
[27] M. D. Frank-Kamenetskii, Shikha Prakash, Physics of Life Reviews 11, 153 (2014).
[28] A.E. Bergues-Pupo, J.M. Bergues, F. Falo, Physica A, 396, 90 (2014); A.E. Bergues-Pupo et al, EPL 105, 68005 (2014).
[29] D.X. Macedo, I. Guedes, E.L. Albuquerque, Physica A 404, 234 (2014).
[30] Nikos Theodorakopoulos, Phys. Rev. E 82, 021905(2010).
[31] A. Singh and N. Singh, Physica A: Statistical Mechanics and its Applications, 419, 328 (2015) and references therein
[32] T. Dauxois, M. Peyrard, Phys. Rev. E 51, 4027 (1995).
[33] Garima Mishra, Pouliou Sadhukhan, Somendra M. Bhattacharjee, and Sanjay Kumar, Phys. Rev. E 87, 022718 (2013); Pouliou Sadhukhan, Somendra M. Bhattacharjee, arXiv:1401.5451.
[34] K. Hatch, C. Daniłowicz, V. Coljee and M. Prentis, Nucleic Acids Res. 36, 294 (2008).
[35] Josep M. Huguet et al, Proc. Natl. Acad. Sci., USA 107, 15431 (2010).
[36] F. Ritort, J. Phys. Condens. Mat. 18, R531 (2006).
[37] S. Srivastava and N. Singh, J. Chem. Phys., 134, 115102 (2011).