Nonlinearity in DNA and its Relation to Specific Functions

Boian Alexandrov · Kim Ø. Rasmussen · Alan R. Bishop

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Abstract In memory of Alwyn Scott, we discuss the connection between the nonlinear dynamics of double-stranded DNA, experimental findings, and specific DNA functions. We begin by discussing how thermally induced localized openings (bubbles) of the DNA double-strand are important for interpreting dynamic force spectroscopy data. Then, we demonstrate a correlation between the sequence-dependent propensity for bubble formation and transcription initiation and other regulatory effects in viral DNA. Finally, we discuss the possibility of a connection between DNA dynamics and the ability of repair proteins to recognize ultraviolet-radiation damage.

Keywords Nonlinear dynamics of DNA · DNA modeling

1 Introduction

Throughout his career, Alwyn Scott was keenly interested in nonlinear science, in particular, as it relates to nonlinear dynamics and nonlinear wave propagation. He was among the first scientists to embrace the concept of nonlinearity and realized that it cannot simply be treated as a perturbation but must be adequately accounted for and often leading to completely new effects, such as soliton propagation [1]. Exploiting the topic of solitons and nonlinear wave propagation, he went on to make seminal contributions in diverse fields,

B. Alexandrov (✉) · K. Ø. Rasmussen · A. R. Bishop
Theoretical Division, Los Alamos National Laboratory,
Los Alamos, NM 87545, USA
e-mail: boian@lanl.gov

K. Ø. Rasmussen
e-mail: kor@lanl.gov

A. R. Bishop
e-mail: arb@lanl.gov

including the propagation of nerve impulses [2] and the dynamics of magnetic flux on long Josephson junctions [3]. Simultaneously with becoming the founding director of the Center for Nonlinear Studies at the Los Alamos National Laboratory, his research interest turned towards soliton propagation in proteins [4] and studies of nonlinear localization of vibrational energy on the model protein acetanilide [5]. This led to his formulation and study of the discrete self-trapping equation [6] as a description of energy localization on small molecules and other nonlinear dynamical systems with finite degrees of freedom. From this perspective, Alwyn Scott found the possible connection between nonlinear energy localization, in terms of bubble openings in DNA, and DNA function, fascinating. Therefore, we will here, in his honor, summarize our recent progress in this context. First, we will briefly describe the modeling framework we use. Following this, we will discuss how our modeling is able to provide insight into the role of thermally-generated bubbles in double-stranded DNA. We accomplish this by comparing our modeling results to direct experiments on bubble formation with and without the presence of an applied unzipping force. Having established that our model adequately describes bubble formation and dynamics, we move on to demonstrate how the spontaneous occurrence of bubbles may relate to DNA functions such as transcription initiation and repair of damaged sites.

2 The Peyrard–Bishop–Dauxois model

The Peyrard–Bishop–Dauxois (PBD) model for double-stranded DNA was proposed, almost two decades ago [7, 8], to describe the DNA denaturation transition. The model is highly nonlinear and simplified to only account for the two main effects dominating the physics underpinning DNA denaturation. For each base-pair, this model includes one degree of freedom y_n , which is the transverse stretching of the hydrogen bonds between complementary bases. In the PBD model, the potential energy, E , of a double strand of DNA of length N is

$$E = \sum_{n=1}^N [V(y_n) + W(y_n, y_{n-1})]. \quad (1)$$

Here, $V(y_n) = D_n (1 - \exp[-\alpha y_n])^2$ represents the hydrogen bonds between complementary bases; $W(y_n, y_{n-1}) = \frac{k}{2} (1 + \rho \exp[-b(y_n + y_{n-1})]) (y_n - y_{n-1})^2$ is the nearest-neighbor coupling that represents the (nonlinear) stacking interaction between adjacent base-pairs: it is composed of a harmonic coupling with a state-dependent coupling constant effectively modeling the change in stiffness as the double strand is opened (i.e., entropic effects). The heterogeneity of the sequence is incorporated by assigning different values to the parameters of the Morse potential, depending on the base-pair type. For simplicity, however, we use the same value for the constants k and ρ independent of the sequence. All parameters of this phenomenological model have been obtained from fitting experimental ultraviolet (UV) melting curves for a few short heterogeneous DNA sequences [9]. The specific parameter values obtained are $k = 0.025$ eV/Å², $\rho = 2$, $\beta = 0.35$ Å⁻¹ for the intersite couplings; for the Morse potential, $D_{GC} = 0.075$ eV, $a_{GC} = 6.9$ Å⁻¹ for GC base-pairs, $D_{AT} = 0.05$ eV, and $a_{AT} = 4.2$ Å⁻¹ for the AT base pairs. It is important to note that these values are maintained throughout this work without any further adjustments.

3 Denaturation bubbles

It is known that sequence heterogeneity in DNA interplays with entropy effects to create an extended premelting temperature window (including the biologically relevant regime), where large thermal bubbles are readily formed. The thermal effects driving the formation of denaturation bubbles can be studied in vitro and provide important insight into biological processes. Recent experimental studies [10–12] have attempted to interrogate the nature and statistical significance of such bubble states. Intriguingly, these experiments combine traditional UV absorption experiments with a novel bubble-quenching technique that traps ensembles of bubbles to capture statistical properties. In this section, we demonstrate how the PBD model can successfully describe thermally-generated bubbles by comparing our results with the recent experimental results reported in [11, 12].

Using standard Monte Carlo techniques, we have performed simulations of the PBD model applied to the specific sequences used in the above experiments. For each temperature, we performed a number of simulations. In each of these simulations, we compute the mean profile $\langle y_n \rangle$, from which we obtain the fraction of open base pairs. We consider the n th base pair to be open if $\langle y_n \rangle$ exceeds a certain threshold. Applying the same threshold, we record at the end of each simulation whether the entire molecule was open (denaturated). Performing a large number of such simulations starting from different initial conditions, we obtain the averaged fraction f of open base pairs and the averaged fraction of fully denaturated molecules p at a given temperature. In this way, we directly simulate the experiments, where the measurements are made over a large ensemble of molecules.

In the same manner as [11], we obtain the averaged fractional length of the bubbles as $\langle l \rangle = (f - p)/(1 - p)$. In Fig. 1, we illustrate the performance of the model by showing our results for the sequence CCGCCAGCGGCGTTATTACATTTAATTCTTAAGTAT TATAAGTAATATGGCCGCTGCGCC, which is labeled (L60B36 in [11, 13]) in direct comparison with the experimental results on the same sequence. A very good agreement with the experimental results is observed. Specifically, we find, as in the experimental results, that $f \simeq l$ for $50^\circ\text{C} < T < 65^\circ\text{C}$, indicating the persistent existence of bubble openings in the equilibrium configurations of the molecule at these temperatures. At higher

Fig. 1 In both panels the temperature is presented on the horizontal axis in $^\circ\text{C}$. The fraction of open base pairs (*open circles*), fraction of entirely open molecules (*filled circles*), and the average fractional length of the bubbles (*open squares*) are shown on the vertical axis

temperatures, l displays a plateau, resulting from the occurrence of completely denaturated molecules at $T \simeq 75^\circ\text{C}$. As noted in the experimental work, the plateau occurs at $l \simeq 0.6$ because this is the ratio between the AT-rich central region, of 36 base pairs, and the molecule's total of 60 base pairs. Experimental observations regarding the nucleation size of the bubbles in the middle of a molecule and the possibility of a two-state transition are recovered by the model (see details in [13]). This demonstrates that this model not only adequately describes the melting transition of very long DNA strands [7, 8], but it also provides a valuable description of bubble formation in the premelting regime of shorter strands.

4 Forced unzipping of DNA

The development of single-molecule force spectroscopy and dynamical force spectroscopy has made possible the investigation of force-induced separation of double-stranded DNA at various temperatures [14]. Studying the force-induced separation of double-stranded DNA into single-stranded DNA is an important step towards understanding replication and transcription processes. It is also known that, in living organisms, DNA separation is sometimes naturally driven by various enzymes and proteins, which can force the two strands of the double helix apart. In this sense, artificial force-induced separation of the double-stranded DNA is a tool to mimic and to understand such processes. Since a force probe can potentially accurately detect the binding strengths between complementary base pairs during the unzipping process, single-molecule mechanical unzipping of double-stranded DNA has been proposed as a possible sequencing method [15]. Several different experimental setups, such as optical tweezers [16] and atomic force microscopy [17], have been suggested for the mechanical unzipping of DNA in connection with possible fast and inexpensive sequencing. A discussion of the prospects and limitations of this approach can be found in [18].

However, for our purpose here, the most essential aspect is the ability to understand the interplay between thermal bubble formation and applied unzipping forces. A first step towards understanding the relation between thermal denaturation and force-induced separation was taken by Danilowicz et al. [14], who recently published the first experimentally determined phase diagram for DNA denaturation as a function of the applied force. The experimental data of this study confirmed intuition in the sense that the force required to unzip the DNA must decrease with increasing temperature.

However, the detailed melting behavior, especially at higher temperatures where thermal denaturation bubbles play an increased role, is not immediately clear from these experiments. Therefore, we applied the PBD model and a dynamical Monte Carlo technique to provide further insight into the mechanisms involved. In our simulations, as in the experiments, a force is applied by immobilizing one base and attaching a linear spring to the complementary base of the first base pair. The linear spring is assigned a stiffness k_0 such that the applied force is given by Hooke's law, $F_{\text{pull}} = k_0(y_0 - y_1)$, where y_1 and y_0 are the displacements (see Fig. 2, left) of the first base pair and the spring's opposite end point, respectively. The unzipping is then performed at a constant rate by moving ($y_0 \rightarrow y_0 + \Delta$) the force probe by a distance Δ , after which N Monte Carlo steps are performed in order to compute the average displacement, $\langle y_1 \rangle$, of the first base pair. The force is subsequently calculated as $F_{\text{pull}} = k_0(y_0 - \langle y_1 \rangle)$. The more Monte Carlo steps used to determine $\langle y_1 \rangle$, the closer to equilibrium the system is before the next Δ move occurs, so that the pulling speed is $v_0 = \Delta/N$. Figure 2 (right) shows the experimental results (squares)

Fig. 2 Schematic representation of the PBD model in a dynamic force spectroscopy experimental setting (left). Force–temperature phase diagram of λ -phage DNA. Squares correspond to the experimental results of [14]. Circles represent PBD simulations [19]

[14], the theoretical result obtained with a popular thermodynamic model (green line) [14], together with our results (circles) from the described PBD simulations [19]. All results are related to the unzipping of λ -phage DNA (see [14, 19] for sequence details). It can be seen that the data obtained with the PBD model are consistent with the experimental results over a far larger temperature range than the thermodynamic model. Particularly, at higher temperatures, the thermodynamic model severely overestimates the required unzipping forces. This observation can be attributed to the fact that the thermodynamic model neglects spontaneous bubble formation [20]. The presence of thermal bubble formation leads to a considerable reduction of the measured force in the force-induced separation of the double-stranded DNA. Again, the accuracy with which the PBD model reproduces the experimental result, throughout the temperature regime, strongly suggests that the bubble formation is accurately captured.

5 Transcription and bubble formation

It is now clear that double-stranded DNA is subject to temporary, fast, localized openings of its two strands. At physiological temperatures, this thermally induced localized “breathing”, gives rise to localized DNA melting of 10 base pairs or more, which is similar in size to some transcriptional bubbles [21]. The exact location and the evolution of these collective openings of consecutive base pairs are determined by the specific sequence, which then provides motivation to investigate whether transcription initiation and other regulatory sites possess an enhanced propensity for bubble formation. By comparing experimental results for the adeno-associated viral P5 promoter and for a P5 mutant promoter that is known to be transcriptionally inactive to the predictions of the PBD model, it was, for the first time, in [22, 23], shown that the most active regions strongly correlate with the transcriptional start site and other major regulatory sites. To illustrate this, we reproduce the detailed results for the P5 promoter in Fig. 3. Figure 3 shows that, for the P5 (wild-type) promoter, we found a strong correlation between the transcription (+1) start site and the occurrence of large (> 10 base-pairs) bubble openings. This correlation is further corroborated by S1 nuclease cleavage assays, which, albeit crudely, indicates the regions most active in terms of thermally-driven strand separation. For the P5 mutant promoter, the S1 nuclease cleavage assays similarly corroborate the simulation results by the lack of any significant openings

A -46 -21
 GTGGC CATTTAGGG TATATATGGCC GAGTGAGCGA
 GCAGGATCTC CATTTTGACC GCGAAATTTG AACG
 +1 +23

B -46 -21
 GTGGC CATTTAGGG TATATATGGCC GAGTGAGCGA
 GCAGGATCTC CGCTTTGACC GCGAAATTTG AACG
 +1 +23

◀ **Fig. 3** Analysis of P5 promoter and P5 mutant promoter. **A** Upper strand, sequence of the 69-base pair (bp) P5 core promoter. **B** Upper strand, sequence of the 69-bp mutant P5 promoter. **C** Transcription assay on a 120-bp fragment containing the P5 promoter and P5 mutant fragment in nuclear extract. The arrow on the right indicates the transcription start site and the direction of transcription. The corresponding sequence position is indicated to the left of the marker. *Lane 1*, GA DNA sequencing reaction was used as a marker (*M*); *lane 2*, transcription from the P5 promoter with α -amanitin (*a*); *lane 3*, RNA transcription products with P5 promoter (*P*); *lane 4*, RNA transcription products from the P5 mutant template (*m*). **D** PBD simulation of the P5 sequence, plotting simulated instances of 2.1 Å-separated openings of 10 bp or more vs base position in the sequence. The solid line represents the results of the wild-type P5 promoter, and the dashed line represents results with the mutant P5 promoter sequence. **E** S1 nuclease cleavage of the P5 promoter and the P5 mutant promoter. The corresponding sequence position is indicated to the left of the panel. *Lane 1*, lower strand-labeled P5 promoter GA sequencing reaction (*M*); *lane 2*, P5 promoter S1 cleavage reaction (*P*); *lane 3*, P5 mutant promoter cleavage reaction (*m*). **F** Cleavage density profile of the wild-type (*wt*) P5 promoter DNA in the S1 nuclease experiment. **G** Cleavage density profile of the mutant P5 promoter DNA in the S1 nuclease experiment

around the +1 site. Similar results were obtained for a number of other viral promoters [24, 25]. In particular, it was shown that the large bubbles containing the +1 base pair are also the longest-lived (on average) bubbles [26].

6 UV radiation damage and PBD dynamics

UV light with a wavelength of 250 nm promotes the formation of DNA dimers, making a rather strong connection between adjacent thymine bases (see Fig. 4). If left unrepaired, these dimers may induce skin cancer. This UV dimer formation (Fig. 4) causes adjacent thymine base pairs to form a strong covalent bond, while the pairing of the complementary adjacent adenines is weakened. This weakening in turn causes a 13K decrease of the melting temperature of the double-stranded octamer d(GCGTTGCG)d(CGCAACGC) in the presence of a UV dimer [27]. Using the PBD model and a constrained Monte Carlo algorithm [28], the parameters of the PBD model were adjusted so as to reproduce this effect for the octamer d(GCGTTGCG)d(CGCAACG) [29]. A 11% reduction in the dissipation

Fig. 4 Schematic of the quasi-stable dimer configuration created by 250-nm UV light

Fig. 5 Average strand displacement of DNA with a dimer (*dashed line*) and without a dimer (*solid line*) shows the enhanced opening in the dimer neighborhood at 37°C. The *solid vertical line* indicates the position of the UV dimer

energy of the relevant Morse potential was observed to be necessary to obtain the 13K reduction in the melting temperature. Besides weakening the interaction between the adjacent adenines, the UV dimer plays the role of a structural “impurity” in the stack of the DNA sequence and, therefore, effectively changes the stacking interaction between the adjacent thymine base pairs. This impurity also decreases the spatial and temporal coherence length of the fluctuations and, additionally, enhances the decrease of the melting temperature. A random sequence of 64 base pairs was generated, and the same octamer with, and without, the presence of a UV dimer was inserted in the middle of this sequence. The same Monte Carlo technique was applied to this new sequence, and the average displacements from the equilibrium positions were obtained (see Fig. 5). As the figure illustrates, a three- to fourfold increase is evident in the relative displacements between the base pairs belonging to the two opposite strands at the dimer position, in comparison with the case where there is no UV dimer in the sequence. The DNA sequence was also investigated with Langevin molecular dynamics. In this case, the dimer’s presence was taken into account using a Lagrange multiplier. In Fig. 6, the probability for an opening

Fig. 6 The probability for bubbles with amplitude above 1.5 Å as function of bubble position and bubble length. The *upper panel* represents this probability without a UV-dimer, and the *lower panel* represents the probability with a UV dimer present, both at 37°C

larger than a given threshold is shown. It can be seen that the probability for the occurrence of large bubbles at the dimer position is approximately 25 times larger than the probability in the absence of a dimer. Finally, the data presented in [29] indicate that there are significant changes in the spatio-temporal characteristics of double-stranded DNA upon UV-dimer formation between adjacent thymine base pairs. We suggest that this changed dynamics may be part of enabling the repair proteins to very rapidly detect the occurrence of radiation damage.

7 Conclusions

DNA is a remarkable object for studies of nonlinear science. DNA's structure and dynamics are rich, yet remain simpler than those of proteins and other biological molecules. DNA embodies fundamental nonlinear science questions. Particularly, how do the sequence and nonlinearity interplay to determine the nature of the localized excitations (bubbles). DNA exhibits very large amplitude fluctuations, which are essential for biological functions, and can be studied experimentally with many tools. DNA can be meaningfully described by simple models, which are amenable to studies applying nonlinear dynamical techniques. We have demonstrated that modeling DNA, with only a single degree of freedom per base pair, gives valuable results describing essential dynamical features of the molecule. Our studies strongly suggest that this level of modeling even has biological relevance by providing a method for sequence screening that may be able to exhibit structures that are not detected by the usual methods based on a bioinformatic analysis of the sequence. We believe that this kind of meso-scale modeling with a strong coupling to experiments has the potential to enable significant insight into several of DNA's bimolecular functionalities. Very interestingly, the notion that strong local dynamic deviations from "average" or "homogeneous" structures are essential for determining function is now a major topic of research focus in hard and soft materials, organic [30] and inorganic molecules [31, 32], and increasingly in biological matter [33–35], with nonlinearity and bonding constraints the likely source [36, 37] and discrete breathers (as here) very natural realizations. Importantly, these functional heterogeneities are *equilibrium* properties, used for specific functions, very much in the spirit of "landscapes," introduced by Frauenfelder [38] and others for macromolecules such as myoglobin. Adapting the global structure of the same protein for distinct functions through specific local distortions is clearly appealingly efficient from a biological evolutionary perspective.

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