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Review

Nanoscale mechanical and dynamical properties of DNA single molecules

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Abstract

Experimental evidence suggests DNA mechanical properties, in particular intrinsic curvature and flexibility, have a role in many relevant biological processes. Systematic investigations about the origin of DNA curvature and flexibility have been carried out; however, most of the applied experimental techniques need simplifying models to interpret the data, which can affect the results.

Progress in the direct visualization of macromolecules allows the analysis of morphological properties and structural changes of DNAs directly from the digitised micrographs of single molecules. In addition, the statistical analysis of a large number of molecules gives information both on the local intrinsic curvature and the flexibility of DNA tracts at nanometric scale in relatively long sequences.

However, it is necessary to extend the classical worm-like chain model (WLC) for describing conformations of intrinsically straight homogeneous polymers to DNA. This review describes the various methodologies proposed by different authors.

Keywords: Persistence length; Worm-like chain; DNA curvature; DNA flexibility; DNA–mica interactions; Divalent cations effects

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1. Introduction

In the present postgenomic era, DNA sequences with billions of informational elements are currently accumulating in the data banks. Consequently, the need of translating the linear information of the base sequences into functional elements is becoming more and more crucial.

In a recent past, the DNA chain was considered to be substantially homogeneous in its canonical structure and acting as a simple repository of the genic information. This homogeneity appeared to hinder reading the information encoded in the base sequence. Therefore, DNA expression

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and control were supposed to be fully delegated to proteins.

On the contrary, DNA is now being recognised more and more extensively as a complex polymorphic macromolecule, which plays a relevant part in the management of the gene information it contains.

In fact, the present concept of gene includes the control regions preceding and following the coding region as well as the introns. Moreover, the intergenic regions could have a role in driving, e.g., in eukaryotic genomes, the complex architecture of chromatin as well as other structural and regulative functions.

Every function of DNA, including transcription, replication and recombination, is guided by deviations from the monotonous regularity of the straight canonical B-DNA structure and dynamics. Such structural deviations are an intrinsic property of the sequence and are recognized and amplified by protein binding. This requires a free-energy balance that is paid by the protein interactions, but minimized by suitable intrinsic structural properties of the DNA tract involved in the recognition. This is particularly evident in the case of sequence-dependent DNA-histone octamer association, the nucleosome, which governs the packaging and the superstructural organization of the genome as well as the gene regulation [1].

In conclusion, an important part of the DNA information content is not localized on the codogenic regions but appears to be related to the nanoscale DNA mechanical properties.

Several authors have focused their attention to the static and dynamic superstructural effects produced by the local distortions from the canonical B-DNA structure.

Historically, the first hypothesis about bent DNAs was proposed as the cause of the aberrant electrophoretic behaviour of some DNA sequences in the 1970s [2–4]. Analyzing the nucleotide sequence of eukaryotic DNAs, Trifonov and Sussman [5] found a weak periodicity of some dinucleotide steps along the sequence with a period close to the DNA helical repeat. They suggested that the angles between base-pair planes (the "wedge angle") are sequence dependent and that the observed periodicity reflects the anisotropic flexibility of the DNA molecule. As Trifonov and Sussman pointed out, even small structure variations (for example, due to wedge angles) could have a considerable influence on the global DNA bendability when they are phased with the DNA helical turn.

Two years later, Marini et al. [6] advanced the concept of the static bend as a sequence-dependent DNA property, as a result of their investigations on the electrophoretic anomalies of a Kinetoplast DNA tract of *Leishmania tarentolae*. Afterwards, Wu and Crothers [7] localized the bend in that DNA tract introducing the electrophoresis gel permutation assay. It consists in localizing the minimum of the retardation plot of cyclically permuted DNA tracts, obtained by single restrictions on the tandem dimer of the tract considered.

Systematic investigations about the origin of DNA curvature were carried out by Hagerman [8] and Koo et al. [9] using the anomalies of polyacrylamide gel electrophoresis, quantified by the retardation factors, the ratio between the apparent and actual bp numbers, associated to biosynthetic multimeric oligomers. Crothers et al. advanced the hypothesis that deviations from linearity should occur at the boundary between the normal B-DNA structure and AA·TT repeating stretches longer than three base pairs.

Later, several authors proposed models to describe the curvature in terms of the dinucleotide unit structure. The wedge angle between consecutive base pairs is assumed to be different for each dinucleotide step. Wedge angles in phase with the helix periodicity can produce an effective curvature, which could be large enough to be macroscopically detected. These models generally assume that the wedge angles are only dependent upon nearest-neighbour interactions and they are therefore called nearest-neighbour models [10–14]. They were recently reviewed by Crothers [15], who verified their effectiveness in predicting intrinsic DNA curvature in good agreement with the experiments. One of these models has been developed by our group [10,11] and will be described in more details in the next sections.

In addition, Olson et al. [14] have performed a systematic analysis of the dispersion of base-pair parameters in DNA crystal structure to have an estimate, in the framework of first-order elasticity, of the dinucleotide sequence-dependent deformability, as well as the correlation between fluctuations of different parameters. Indeed, all dinucleotide steps show concerted variations of roll, tilt, twist, shift and slide parameters, probably in order to relieve the close steric contacts between bases, whereas the rise varies almost independently of all the other parameters [14].

More recently, we proposed a set of dinucleotide rigidity parameters, expressed in terms of the normalized melting temperatures, as a measure of the DNA differential flexibility along the sequence. These parameters can predict free energies of competitive nucleosome reconstitution experiments in good agreement with the experimental results [16,17].

Moreover, since the first evidence of DNA anomalous electrophoretic mobility, large amounts of other experimental data have shown that many DNAs are curved or exhibit tracts with preferential bendability. Many different experimental methods have been used to this aim, such as light scattering [18,19], ligase-catalyzed cyclizations [20], flow dichroism [21], transient electric birefringence [22,23] and transient electric dichroism [24,25]. However, all these methods need simplifying models to interpret the data, which can affect the results.

On the contrary, progress in the direct visualization of macromolecules allows the analysis of morphological properties and structural changes of DNAs directly from the digitised micrographs of single molecules (Fig. 1).