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Twisting short dsDNA with applied tension

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HIGHLIGHTS

- The equilibrium twist of short DNA under a load is calculated by path integrals.
- The helix overtwists under a weak load and then untwists by increasing forces.
- By overtwisting the helix, its diameter shrinks and the rise distance grows.
- The helix elongation versus the super helical density is obtained.

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ABSTRACT

The twisting deformation of mechanically stretched DNA molecules is studied by a coarse grained Hamiltonian model incorporating the fundamental interactions that stabilize the double helix and accounting for the radial and angular base pair fluctuations. The latter are all the more important at short length scales in which DNA fragments maintain an intrinsic flexibility. The presented computational method simulates a broad ensemble of possible molecule conformations characterized by a specific average twist and determines the energetically most convenient helical twist by free energy minimization. As this is done for any external load, the method yields the characteristic twist-stretch profile of the molecule and also computes the changes in the macroscopic helix parameters i.e. average diameter and rise distance. It is predicted that short molecules under stretching should first over-twist and then untwist by increasing the external load. Moreover, applying a constant load and simulating a torsional strain which over-twists the helix, it is found that the average helix diameter shrinks while the molecule elongates, in agreement with the experimental trend observed in kilo-base long sequences. The quantitative relation between percent relative elongation and superhelical density at fixed load is derived. The proposed theoretical model and computational method offer a general approach to characterize specific DNA fragments and predict their macroscopic elastic response as a function of the effective potential parameters of the mesoscopic Hamiltonian.

1. Introduction

Understanding the DNA mechanics has important implications as, in cells, DNA is constantly bent, stretched, repaired and processed by proteins which, upon binding, confer to the double helix its biological functions and regulate gene expression [1–5].

The development of optical and magnetic tweezers techniques over the last twenty five years has allowed to gain remarkable insights into the elastic properties of single DNA molecules by studying their response to external forces in the pico-Newton regime [6–11]. Such forces are required to oppose the thermal bending fluctuations due to the environment

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which constantly buffet the molecular bonds thus causing the helix to assume different random walk configurations. In fact, at physiological temperatures, the thermal energy per nano-meter is ∼4 pN.

Force–extension data of kilo base pairs sequences have been well reproduced by worm-like-chain models that treat DNA as an isotropic rod whose behavior is dominated by entropic elasticity at least up to ∼10 pN [12]. Instead, at higher external forces, structural changes occur in the intra-strand base pair covalent bonds and the helix is progressively over-stretched to a length larger than its B-form contour length [13]. Later measurements by the rotor bead tracking technique [14] have shown that kilo base pairs DNA molecules over-twist upon stretching up to ∼30 pN and then untwist above such value.

Importantly, if a torque is applied in order to over-twist the double helix *under a constant load*, it has also been found that the molecule extends. While analogous results have been obtained by magnetic tweezers experiments, molecular models for DNA in a solvent [15,16] have suggested that a negative inclination of the base pairs towards the minor groove could reduce the helix diameter and elongate the rise distance. Moreover, the molecule extension appears to be a linear function of the applied over-twist in the limited range of those torsional strains which preserve the stable B-form.

Motivated by these findings pointing to a remarkable DNA flexibility together with a rich interplay between its twisting and stretching properties [17,18], we have developed in a previous work [19] a computational method based on a mesoscopic DNA Hamiltonian which treats the helix at the base pair level and retains the fundamental intra-strand and inter-strand base pair interactions, responsible for the helix stability in the presence of a solvent. Mesoscopic models have the capability to predict the thermomechanical behavior of specific sequences through optimization of the potential parameters via direct fitting of experimentally accessible data e.g., the melting profiles [20–23]. Essentially our method assumes that the single molecule may exist in a broad range of helical conformations, specified through the average number of base pairs per helix turn, and determines the energetically most convenient conformation by free energy minimization.

As the computation is carried out by varying the strength of an external load, one can predict the twisting response of the molecule as a function of the stretching perturbation. While the method has been applied to short fragments which have been the focus of recent and widespread interest in view of their unexpected flexibility [24–37], the same scheme can be used (compatibly with the available CPU time) for any sequence and length being aware that the latter generally affect the properties of the molecules [38,39].

In this paper, going beyond our previous study, we assume that the helix may be over-twisted (or untwisted) with respect to its equilibrium conformation *under a constant load* and investigate the ensuing modification on the helical shape. It is emphasized that the load has here the function to align, not that to disrupt [40], the intra-strand stacking bonds. Accordingly, the external force is tuned within a range of values which do not cause the over-stretching of the molecule backbone. In this way, the method offers a feasible approach to simulate the above described experimental setup. In particular, we derive here the quantitative relation between average helical elongation and superhelical density which, in principle, could be investigated experimentally for sequences of a few tens of base pairs. Furthermore, it is shown that the over-twisting/untwisting transition, observed in kilo-base long sequences as a function of the external force, is predicted by our model and essentially ascribed to a dependence of the helix bending fluctuation on the size of the applied load.

The geometrical representation for the helix is outlined in Section 2 while the mesoscopic Hamiltonian model is discussed in Section 3. The general features of the computational method are given in Section 4 and the formulas for the macroscopic helix parameters are defined in Section 5. The results are presented in Section 6 while some conclusions are drawn in Section 7.

2. Helical model

In previous Hamiltonian studies of DNA denaturation [41], the double helix has been described by a basic ladder model, see Fig. 1(a), in which the bases are arranged as beads along the complementary strands. The backbone of a molecule with N base pairs is thus a chain of $N-1$ segments connecting the points O_i $(i = 1, \ldots, N)$. R_0 and d, input parameters of the model, represent the bare helix diameter and rise distance along the molecule stack, respectively, in the absence of fluctuations. Each pair is formed via the hydrogen bond connecting the two mates and only two degrees of freedom per pair, $x_i^{(1)}$ and $x_i^{(2)}$, representing the displacements of the pair mates, are included in the model. The in-phase-displacement, $x_i^{(1)} + x_i^{(2)}$, yields a straightforward harmonic potential energy term in the chain Hamiltonian which can be exactly integrated. Instead the relative distance, $r_i = x_i^{(1)} - x_i^{(2)}$, measured from the central helical axis, stretches the hydrogen bond and determines the statistical mechanics of the DNA ladder model [42,43]. In fact, r_i may even become smaller than R_0 thus compressing the hydrogen bond but the pair mates cannot get too close to each other due to the strands repulsion exerted by the negatively charged phosphate groups [44].

Here we adopt a more realistic picture for the double helix which goes beyond the ladder model assuming that adjacent displacements along the molecule stack, e.g. r_i and r_{i-1}, are allowed to twist and bend as shown in Fig. 1(b). Accordingly, the distance $\overline{AB}$ between neighbor base pairs is a function of the rotational degrees of freedom with both the torsional angle θ_i and the bending angle ϕ_i being integration variables in the calculation of the partition function. Hence twisting and bending fluctuations are incorporated in our model whereas other structural deformations, such as propeller twist that enhances the intra-strand base pair stacking and the presence of grooves relevant to the sequence specific DNA-protein binding [45,46], are not taken into account. While a general description of the base pair degrees of freedom and helical parameters is given e.g., in Ref. [47], the effects of heterogeneous base pair sequence are analyzed e.g. in a comprehensive molecular dynamics simulation for a large set of oligomers [48].