ABSTRACT

A general Newtonian elastic model for both single- and double-stranded DNA is proposed, and an explicit force-extension formula is introduced to characterize their deformations. The effective elastic properties of the DNA backbone are numerically extracted from the ss-DNA experiments. The mechanical properties of long ds-DNA molecules is then studied based on this model, where the base-stacking interactions and the hydrogen bond forces are also considered. Results are obtained by the explicit force-extension formula and good agreement with the single molecule experiments is achieved.

Keywords: double-helical DNA structure; mechanical properties; single-molecule manipulation; base-stacking interactions; hydrogen bond forces.

1 INTRODUCTION

A thorough investigation of the deformation and elasticity of DNA will enable us to gain a better understanding of many important biological processes concerned with life and growth [1]. A detailed study of DNA elasticity has now become possible due to recent experimental developments, including, e.g., optical tweezer methods, atomic force microscopy, and fluorescence microscopy [2-9]. These techniques make it possible to manipulate single polymeric molecules directly, and to record their elastic responses with a high precision.

Smith et al. [5] examined the elastic properties of single- and double-stranded DNA (ss-DNA/ds-DNA) by stretching the immersed lambda DNA (48 kbps) in the aqueous buffer using the dual-beam optical tweezers system. They understood a sharp structural transition of tension under roughly 65 pN of the freely rotating ds-DNA. It was also revealed that the S-form DNA occurs at the yielding point of DNA backbone while the freely rotating ds-DNA is stretched [9]. In another study, an analytical wormlike rod chain (WLRC) model for predicting DNA mechanical response under low stretching force was proposed [10] and its accuracy was then improved in a study by Sarkar et al. [11] by considering free energies of the five DNA states experimentally. ZZO model [1], which considers the bending energy and the stacking energy of ds-DNA can successfully describe S-form DNA under high level stretching, but is not able to represent the structural transition from the B-form DNA to the P-form DNA due to its limitation of geometric assumptions [12]. Additionally, these theoretical models mentioned above do not adequately consider the sequence effects on the ds-DNA mechanics.

In the present work, we have tried to obtain a comprehensive and quantitative sequence dependant understanding of DNA elastic mechanical properties considering its double-stranded helical nature, base-stacking interactions originated from the weak van der Waals attractions between the polar groups of DNA adjacent nucleotide base pairs and the hydrogen bond force between complementary bases.

2 THEORY

A general elastic model for both single-stranded and double-stranded biopolymers is proposed (Figs. 1 and 3(a)), and a structural angle \( \alpha \) (see Fig. 1) is introduced to characterize their deformations. The geometry of DNA backbone is initially assumed based on the B-DNA helix function. For a single stranded lambda DNA at any point

Figure 1. Experimental [5] and theoretical results of single-stranded lambda-DNA in blue and red lines, respectively.
A, the force $P$ produces a bending moment $M_b = PR\sin \alpha$ and a torque $M_t = PR\cos \alpha$ about the axis $n_1$ and $n_2$ respectively. Based on the theory of elasticity, the total energy of the ss-DNA backbone can be expressed in the following form

$$\int \left( S_{p} + \int \frac{M_b^2}{EI} + \frac{M_t^2}{GI_p} \right) ds$$

where $EI$ and $GI_p$ are the elastic bending and torsional rigidity of the DNA backbone, respectively. Since the base-stacking and hydrogen bond energy of ss-DNA are negligible, the force-extension ($P - E_{ss}$) relation of a ss-DNA then is

$$P = \frac{4\pi^2 N^2 E_{ss}}{S^3 \cos^2 \alpha} \left( \frac{\sin^2 \alpha}{EI} + \frac{\cos^2 \alpha}{GI_p} \right)^{-1}$$

where $N$ is the total number of base pairs and $S$ is the contour length of DNA backbone. The experimental results of ss-DNA in phosphate buffer [5] were used as a benchmark to determine the unknown effective parameters of the elastic backbone. The experimental and theoretical results are shown as the blue and red lines in Fig. 1, respectively. To match the theoretical and experimental data, the effective elastic bending and torsional rigidities were set to 8521 pN\cdot nm$^2$ and 26 pN\cdot nm$^2$, respectively. These effective parameters are much larger than the expected ones which is mainly due to the effects of the buffer solution and the ions on the ss-DNA molecules stretching. Moreover, we assume the same effective parameters for ds-DNA molecules under the same experimental conditions which is due to their similar mechanical behaviors [5,8,9,11].

Before constructing the ds-DNA mechanical model, we should discuss another kind of important interactions, namely, the base-stacking interaction between adjacent nucleotide base pairs [13,14] and hydrogen bond interaction between complementary bases [15]. Base-stacking interactions originate from the weak van der Waals attraction between the polar groups in adjacent nucleotide base pairs. Such interactions are short ranged, and their total effect is usually described by a potential energy of the Lennard-Jones form (6-12 potential [13]) which contributes significantly to the stability of the double helix. In a continuum theory of elasticity, the total base-stacking potential energy can be converted into the form of the integration [1]:

$$U_{bs} = \int_0^S r_0 \left[ \frac{\sin \alpha_0}{\sin \alpha} \right]^{12} \left[ 2 - 2 \left( \frac{\sin \alpha_0}{\sin \alpha} \right)^6 \right] ds$$

where $r_0 = S/N$ is the backbone arclength between
adjacent bases; $\alpha_0$ is related to the equilibrium distance between a DNA dimer ($r_0 \sin \alpha_0 \approx 3.4$ Å); $\alpha$ can take the values between 0° and 90° and $\varepsilon$ is the base stacking intensity which in the average sense can be considered as a constant, with $\varepsilon \approx 14.0 k_BT$ averaged over quantum mechanically calculated results on all the different DNA dimers [1]. Via the Crotti-Engesser theorem [16], the base stacking stiffness ($k_{bs} = \partial^2 U_{bs}/\partial l^2$) of the Lennard-Jones potential energy could be presented as Fig. 2(a).

The hydrogen bond force is the interaction between complementary bases. Moreover, the GC base pair has three hydrogen bonds and AT has two. In the ds-DNA mechanical modeling, the three/two hydrogen bonds in GC/AT are replaced by only one virtual spring, with the axial and torsional stiffness as a function of the distance ($R_i$) and the angle ($\theta_{ij}$) between the donor and the acceptor. The single hydrogen bond energy could be expressed as [15]

$$E(R_i, \theta) = \sum_{R_i} A D_0 \left[ \left( \frac{R_0}{R_i} \right)^2 - 6 \left( \frac{R_0}{R_i} \right)^{10} \right] \cos^4 \theta_{ij},$$

(4)

where $D_0$ represents the hydrogen bond energies intensity. Through the Crotti-Engesser theorem [16], the axial and torsional stiffness of AT and CG could be presented as Fig. 2 (b-d).

Considering the effects of base-stacking interactions and hydrogen bond forces, the total energy of a ds-DNA molecule under the action of an external force (Fig. 3(a)) is expressed as

$$U_{ds} = U_{backbone} + U_{bs} + U_{Abb} + U_{Tbb},$$

(5)

where $U_{backbone} = \frac{1}{2} \int \left( M_b \frac{\partial^2 \xi}{\partial l^2} \right) ds$ is the ds-DNA backbones energy with the same ss-DNA effective elastic parameters under similar experimental conditions; $U_{bs} = \int_0^{\frac{\pi}{2}} 2k_{bs} \xi (N - 1) d\xi$ is the total base-stacking potential energy along all the adjacent nucleotide base pairs, and $U_{Abb} = \frac{1}{N^2} \times \int_0^{\chi_{max}} \left[ \left( N_{GC}/N \right) k_{A-GC} + \left( 1 - N_{GC}/N \right) k_{A-AT} \right] d\chi$ and $U_{Tbb} = \int_0^{\chi_{max}} \left[ \left( N_{GC} k_{T-GC} + (1 - N_{GC}) k_{T-AT} \right) \times \left( 4 \left( s^2 - \chi^2 \right)^{0.5} \sin \left( \chi/S \right) \right] d\chi$ are the axial and torsional parts of the total hydrogen bond energies caused by the variations in distance and angle between the donor and acceptor respectively. Because the GC and AT base pairs have three and two hydrogen bonds respectively, the ds-DNA sequence information has been embedded into the ds-DNA mechanical model based on Eq. (5). We obtain the
force-extension \((P - Ex_{ds})\) relation of a ds-DNA chain under uniaxial extension by introducing the work done by the force, \(P\), acting on the chain along its central axis explicitly into the total energy term of Eq. (5),

\[
P = \frac{Ex_{ds}}{2R^{2}S} \left[1 + \left(1 - \frac{8R^{2}S}{Ex_{ds}} \left(\frac{\sin^{2} \alpha}{EI} + \cos^{2} \alpha \frac{G}{I_{p}}\right)\right)\right] \left(U_{bs} + U_{Abh}\right)^{0.5} + U_{Thb}^{-1} \left(\frac{\sin^{2} \alpha}{EI} + \cos^{2} \alpha \frac{G}{I_{p}}\right)^{-1}
\]

3 DISCUSSIONS AND CONCLUSIONS

In the simulation, a prescribed displacement is applied to the free end of the freely rotating ds-DNA. The mechanical ds-DNA model is then solved on Eq. (6) (see Fig. 3(c)). A good agreement was achieved between the numerical and the experimental results [5] considering that the information of ds-DNA at low applied forces (under \(-10\) pN) is ignored because the mechanical characteristics at large applied forces \((10-80\) pN) are focused. When the applied forces are lower than \(-10\) pN (entropic regime), the molecule behaves as an ideal (WLC) polymer of persistence length \(\xi \approx 50\) nm [2]. Its elastic behavior is due purely to a reduction of its entropy upon stretching. From 10 pN and up to about 80 pN, DNA stretches elastically as does any material (see Eq. 3), i.e., following Hooke’s law: \(F \approx \Delta l\) (where \(\Delta l = l - l_{0}\) is the increase in the extension \(l\) of the molecule of contour length \(l_{0}\)). However, at about 65 pN a surprising transition occurs, where DNA stretches to about 1.8 times of its crystallographic length. This transition is highly cooperative, i.e., a small change in force results in a large change in extension. To address the possible structural modification in the results of DNA molecule stretching, three stages are considered here.

When the external applying force is in a range of \(10-65\) pN (first stage), the energy required for twisting the complementary base pairs is higher than the backbones bending and torsional energies and part of the work done by the external force acting on the chain is accumulated in the base-stacking and hydrogen bonds virtual springs. As the applied force is more increased (second stage), the virtual base-stacking springs release most of their absorbed energy because the distance between adjacent base pairs exceeds the limitation. This will enforce the base pairs and the backbones to store more energy which causes the torque of the ds-DNA local structure to overcome the backbone torsional rigidity and B-S conformational transition occurs. The exact structure of the new ds-DNA which is indeed \(-80\%\) longer than B-DNA depends on which extremities of the DNA are being pulled \((3\' - 3\'\) or \(5\' - 5\'\)). If both \(3\’\) extremities are being pulled, the double helix unwinds upon stretching, but in the case of pulling both \(5\’\) ends, the helical structure is preserved and characterized by a strong base pair inclination, a narrower minor groove and a diameter roughly 30\% less than that of B-DNA [17]. In both cases, if the loading further increases (third stage), the backbones are forced to absorb more energy by stretching as a S-form DNA double helix in a linear manner (Hooke’s law). Rupture of the molecule (by unpairing of the bases) has been predicted to occur as the extension is more than twice that of B-DNA [3,18,19].

In conclusion, we have constructed an elastic model for both single- and double-stranded biopolymers such as DNA molecules through experimental single-molecule manipulation. The key progress was that the bending and torsional deformations of the DNA backbones, the base-stacking interactions and the hydrogen bond force between complementary base pairs were quantitatively considered in this model. A general sequence-dependant Newtonian elastic model for both single- and double-stranded biopolymers was proposed, and an explicit force-extension formula was introduced to characterize their force-extension relationships in torsionally relaxed DNA chains. Good agreement was achieved between the theoretical results and experimental data. Based on this robust model, further study may be warranted on the mechanical response of ss- and ds-DNA molecules.

REFERENCES