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Twist-stretch correlation of DNA

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We present an elastic model for B-form DNA with variable radius to study the elastic twist-stretch coupling of stretched DNA. In this model, only two strain variables as well as the changes in the energy of the hydrogen and covalent bonds of DNA during the deformation are considered. It is found that, depending on the elastic constants, the correlation between twisting and stretching of a helical molecule can be positive or negative. It is shown that for the suitable elastic constants in the model, the twist-stretch coupling of DNA behaves nonmonotonically, and contrary to intuition, the DNA twisting and stretching are positively correlated for small distortions. This result is entirely consistent with recent experimental results.

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DNA contains the genetic information needed for developing and functioning of all living organisms. Many cellular processes involve different DNA-protein interactions that cause the DNA molecule to deform from its initial structure [1]. As these interactions are extremely vital for the living cells, understanding the elastic properties of DNA molecule and the elastic energies that are involved in these interactions is very important [2].

The B-DNA molecule is composed of two complementary strands of polynucleotides wrapping around each other to make a right-handed double helix with an effective diameter of about 2 nm and pitch of 3.4 nm. The bases on one strand are paired with the bases of the complementary strand by hydrogen bonding. One expects that the helical shape of the DNA molecule causes a coupling between its twisting and stretching. In fact, if DNA is considered as a helix of constant radius and arclength of the backbones, by using geometry alone, it is found that there is a negative coupling between its twisting and stretching [3]. The preliminary experimental results also predict that DNA shortens upon overtwisting [4,5]. Theoretical works [3,6–10] that analyzed these experiments and simulations [11,12] found a negative coupling between DNA's twisting and stretching.

Contrary to these results, recent two independent micromanipulation experiments by Gore *et al.* [13] and Lionnet *et al.* [14] on DNA molecules showed that there is a positive correlation between the DNA twisting and stretching for small deformations. Gore *et al.* used the rotor bead tracking technique to observe that when a DNA molecule is stretched it actually overwinds; this overwinding continues until a critical force of about 30 pN beyond which DNA begins to unwind. In addition, by the use of magnetic tweezers, they found that overtwisting the DNA causes it to extend by about 0.5 ± 0.1 nm/turn for small distortions. Lionnet *et al.* used magnetic tweezers and found that for small deformations, the length of DNA molecule increases by about 0.4 ± 0.2 nm/turn upon overtwisting. They also observed that when the imposed twisting is larger than ~2.5%, the molecule starts to shorten upon overtwisting. In both experiments DNA is stretched by a relatively high constant force ($F \sim 10$ pN), which is in the regime that thermal fluctuations are negligible, and so the molecule is essentially straight. Experimental results [14] also show that for high exerted forces ($F \gtrsim 10$ pN) the value of the increase in the length of the molecule per excess turn is independent of the applied force. Gore *et al.* [13] constructed a simple model in which the radius of DNA and the arclength of the backbones were allowed to vary to study the twist-stretch coupling of DNA. In this model, the volume of the molecule was supposed not to change as a result of applied force and torque, which corresponds to the Poisson ratio of DNA $\nu=0.5$. Although this model can give a positive correlation between the DNA twisting and stretching, it cannot explain exactly the nonmonotonic behavior of twist-stretch coupling, which has been seen in the experimental results. Upmanyu *et al.* [15] also described a nonlinear elastic model for DNA with variable radius but constant volume and showed that stretching the molecule causes it to overwind. They also found a sign reversal in the twist-stretch coupling of DNA, but the agreement of their results with the experimental ones [13] breaks down rapidly beyond the critical strain.

Motivated by the aforementioned experiments and theoretical models, we introduce a nonlinear elastic model to describe this unusual behavior of DNA more exactly. In this model the radius of the molecule and the arclength of the backbones can vary, but we do not suppose preliminarily that the volume of the molecule is constant. As a result of deformation, the changes in the energy of hydrogen bonds between the two complementary bases of DNA and the changes in the energy of covalent bonds between the monomers of each strand are also considered. We simply introduce only two strains, changes in the radius and changes in the total twist per length of the molecule, and expand the energy with respect to them. By energy minimization and geometrical considerations, we obtain results in encouraging quantitative agreement with recent experiments [13,14]. The stretched DNA elongates by about 0.5 nm/turn when overtwisted until an excess twist of about 3%, and it begins to shorten upon overtwisting for larger overwindings. The value of the DNA negative twist-stretch coupling is also in good agreement with the experiments.

In this model, the helix of B-DNA molecule that is stretched by a relatively high force is considered as a straight elastic rod of length L with variable radius R. We use only two strain variables to describe the deformation of the molecule under applied force and torque: (i) the changes in the radius, $R-R_0 \equiv \eta R_0$, where R_0 and R denote the radius of undeformed and deformed DNA, respectively, and (ii) the

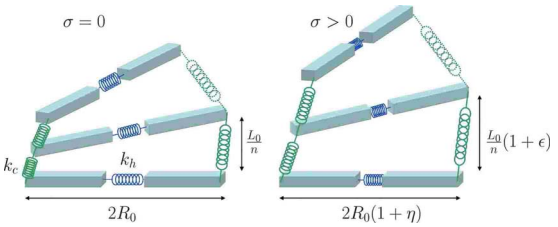

FIG. 1. (Color online) Schematic view of the adjacent base pairs and the bonds of undeformed (left) and deformed (right) DNA. The blue springs show the hydrogen bonds and the green ones show the covalent bonds along the backbones.

changes in the twist per length of the molecule, $\Delta(\frac{\theta}{L})=\frac{\theta}{L}-\frac{\theta_0}{L_0}$, where θ is the total twist of the molecule of length L, while θ_0 and L_0 are the total twist and length of the undeformed DNA, respectively. The effects of the changes in the radius and so the energy of hydrogen bonds between two complementary bases of DNA have been considered in the DNA denaturation problems [16]. Here we also take into account these effects by modeling the hydrogen bonds with springs of stiffness $k_h \simeq 1000$ pN/nm [17] (Fig. 1) for small deformations. We assume that the change in the length of each hydrogen spring is approximately equal to the change in the diameter of the molecule, which is given by $2R_0\eta$. The total hydrogen energy changes, E_h, can be written as $E_h=2nk_h(2R_0\eta)^2/2$, where n is the total number of base pairs (springs) and we assume that there are approximately two hydrogen bonds in each base pair. Moreover, as the molecule is deformed, the arclength of the backbones can be changed that results in the elastic energy of deformed covalent bonds. The changes in the arclength of the backbone, x_c, can be expressed as a function of L, θ, and R as $x_c(L,\theta,R)=\sqrt{L^2+R^2\theta^2}-\sqrt{L_0^2+R_0^2\theta_0^2}$. In order to estimate the elastic energy of a deformed covalent bond, one can consider a spring that is connecting two adjacent monomers of each strand. As the molecules is deformed, the covalent bonds (springs) are deformed. It is plausible to consider the spring constant of the covalent bonds as two orders of magnitude larger than the spring constant of hydrogen bonds [17]. The spring constant of the covalent bonds is denoted by k_c and is estimated as $k_c \simeq 50k_h \simeq 5\times 10^4$ pN/nm. As these springs are connected in series, the total energy counts the deformation energy of the covalent bonds, E_c, which is found as $E_c=2\times k_c x_c^2/(2n)$, where we have considered the energies of the two strands are the same. In Fig. 1, the schematic picture of the molecule with its hydrogen and covalent bonds that are replaced by springs is shown.

Neglecting bend fluctuations, the energy of a straight rod under tension and torque by considering the hydrogen and covalent energy changes is written as

$$E = E_{tor} + E_h + E_c - F(L - L_0), \tag{1}$$

where E_{tor} is the torsional energy of the rod and F is the force being applied to stretch the rod, which is in the range that thermal fluctuations are negligible. We can write E_{tor} for small strains as a Taylor expansion in $\Delta(\frac{\theta}{L})$:

$$\frac{E_{tor}}{k_BT} = \frac{L_0}{2}\left\{D(R)\Delta\left(\frac{\theta}{L}\right) + C(R)\left[\Delta\left(\frac{\theta}{L}\right)\right]^2 + G\left[\Delta\left(\frac{\theta}{L}\right)\right]^3\right\}, \tag{2}$$

where $D(R)$ is the coefficient of the first-order term in $\Delta(\frac{\theta}{L})$, which is a function of the DNA radius R, and $C(R)$ is the twist rigidity of the molecule [18]. The coefficient of the third-order term is shown by G, and as we only keep the expansion up to the third order of strains, G is considered as a constant and independent of the strains. This term is a consequence of the chirality of the DNA helix, making overtwisting and undertwisting distinct [18]. Therefore, for a symmetric rod, there should be no odd power of the $\Delta(\frac{\theta}{L})$ in the elastic energy.

For small changes in the radius we can expand $D(R)$ as $D(R)\approx D_0+D_1\eta+\frac{1}{2}D_2\eta^2$, where D_0, D_1, and D_2 are constants. Since we assume that the equilibrium state is $\Delta(\frac{\theta}{L})=0$, we may have $D_0=0$. We note that the elastic coefficients D_1 and D_2 show the coupling between two strains of the molecule. From classical elasticity we know that the energy of a twisted rod is proportional to the fourth power of its radius [19]. So we can write $C(R)=kR^4\simeq kR_0^4(1+4\eta)\equiv C_0+C_1\eta$, where $C_1=4C_0$ and C_0 is the constant part of the twist rigidity that was introduced in the previous elastic models [3,6–9]. After defining $\Delta(\frac{\theta}{L})\equiv\omega_0\xi$, E_{tor} can be written as $\frac{E_{tor}}{k_BT}=\frac{L_0\omega_0}{2}[(D_1\eta+\frac{1}{2}D_2\eta^2)\xi+\omega_0(C_0+C_1\eta)\xi^2+\omega_0^2G\xi^3]$, where ω_0 is the spontaneous twist of the helix and ξ denotes the relative change in the twist per length. We may assume that the coefficients of ω_0C_0, and ω_0^2G as well as D_1, and D_2 are of the same order. Therefore, we can write $\omega_0G\approx\alpha C_0$, where α is a dimensionless constant and its absolute value is expected to be of the order of 1. The minus (positive) sign of α means that twisting a helix in its intrinsic twist direction is easier (harder) than twisting by the same amount in the opposite direction. In terms of the fractional excess in twist, $\sigma\equiv(\theta-\theta_0)/\theta_0$, and the extension relative to the relaxed state, $\epsilon\equiv(L-L_0)/L_0$, the energy of Eq. (1) is written as

$$\frac{E}{k_BT} = \frac{L_0\omega_0^2}{2}\left\{\frac{D_1}{\omega_0}\eta(1-\epsilon)(\sigma-\epsilon) + C_0(1-2\epsilon+4\eta)(\sigma-\epsilon)^2 + \alpha C_0(\sigma-\epsilon)^3\right\} - \frac{FL_0}{k_BT}\epsilon + \frac{k_cx_c^2}{nk_BT} + n\eta^2\left[4\frac{k_hR_0^2}{k_BT} + \frac{\pi}{20}D_2(\sigma-\epsilon)\right], \tag{3}$$

where we have used the relations of G and C_1 to C_0 and $\omega_0L_0=2\pi\frac{n}{10}$. Using this model introduces more coupling terms between twisting, stretching, and changes in the radius of the molecule than the terms that were introduced in the previous linear elastic models for DNA [6]. The above equation shows manifestly that there are four effective elastic parameters in the system: C_0, D_1, $\alpha\equiv\omega_0G/C_0$, and D_2. As we mentioned before, we assume that the elastic constants D_1 and D_2 are of the same order. As the parameter D_2 has appeared only in the last term and we have $D_2(\sigma-\epsilon)k_BT/(20k_hR_0^2)\sim 10^{-4}D_2(\sigma-\epsilon)$, we may neglect the term with the coefficient D_2. This is a plausible assumption, which

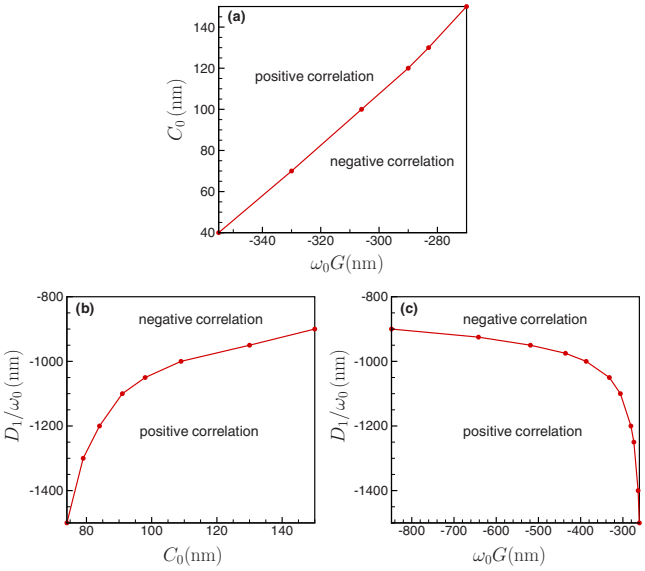

FIG. 2. (Color online) The diagram delineating the different regimes in the elastic parameter space. The plots correspond to (a) $D_1/\omega_0=-1100$ nm, (b) $\omega_0 G=-340$ nm, and (c) $C_0=100$ nm.

implies that the value of D_2 is less than about 10^3. We now minimize the energy with respect to ϵ and η at fixed F with an imposed constraint on the twist σ. This yields expressions for the ϵ and η as functions of force F, imposed twist σ, and the geometrical parameters of the helix. We observe that the problem can acquire more than one solution; the desired results correspond to the solution that minimizes the energy.

For different values of the elastic constants C_0, D_1, and G (or α), the twist-stretch coupling can be positive or negative for small deformations, $\sigma \simeq 0$. The results are summarized in Fig. 2, where diagrams are sketched in the parameter space delineating all the different regimes. A comparison with the recent experimental results [13,14] suggests that the elastic constants of B-DNA should lie in the positive part of the phase diagrams.

A recent direct determination of twist rigidity in the absence of writhe gives a value of $C=100\pm7$ nm [20]. For the twist rigidity we use $C_0=100$ nm and treat $\omega_0 G$ and D_1/ω_0 as tuning parameters and find their values by fitting to the experimental data [13,14]. The best fit to the experimental data yields $\omega_0 G=-340$ nm ($\alpha=-3.4$) and $D_1/\omega_0=-1100$ nm. In Fig. 3, the calculated relative changes in extension, $\epsilon(\sigma)-\epsilon(\sigma=0)$, in terms of σ have been plotted for two different forces $F=9$ pN and $F=18$ pN, together with the experimental data of Ref. [13]. As one can see in the left panel, there is a positive coupling between twist and stretch of the B-DNA molecule for small distortions; it elongates when overtwisted. We see that the slope of the graph at $\sigma \sim 0$ is $\frac{d\epsilon}{d\sigma}|_{\sigma=0}=0.17$ (0.5 nm/turn), which is in good agreement with the experiments [13,14]. This positive correlation continues until an excess twist of about 3%, beyond which the length of DNA begins to decrease (shown in Fig. 3, right). The value of $\frac{d\epsilon}{d\sigma}|_{\sigma=0}$ is also found to be nearly independent of the stretching force. These results are consistent with the experimental data of Ref. [14].

It is also interesting to see the relative changes in the helix radius and the overall volume of DNA for small variation in twist. In Fig. 4, we have plotted the calculated relative changes in radius, η, and the relative changes in volume, $\Delta V/V_0$, versus σ. We see that the radius of the helix decreases as the molecule is overtwisted. However, the changes in the radius within the desired range of excess twist are less than about 10%, so the harmonic approximation for the hydrogen bond energy between the complementary bases is reasonable. The relative changes in the arclength of the backbones are also found to be about one order of magnitude less than the relative changes in the radius, so as is expected because of the rigidity of covalent bonds, the arclength of the backbones does not vary significantly during the deformation. These results also show that the changes in the covalent bond length in the structure of the base pairs are negligible with respect to the changes in the hydrogen bond length. So the change in the radius is mainly a result of the change in the length of hydrogen bond between the two complementary bases. As one can see in the right panel, the volume of the molecule also changes and decreases upon overtwisting, but the changes are less than about 6%.

In the above treatment, we have also examined the effect

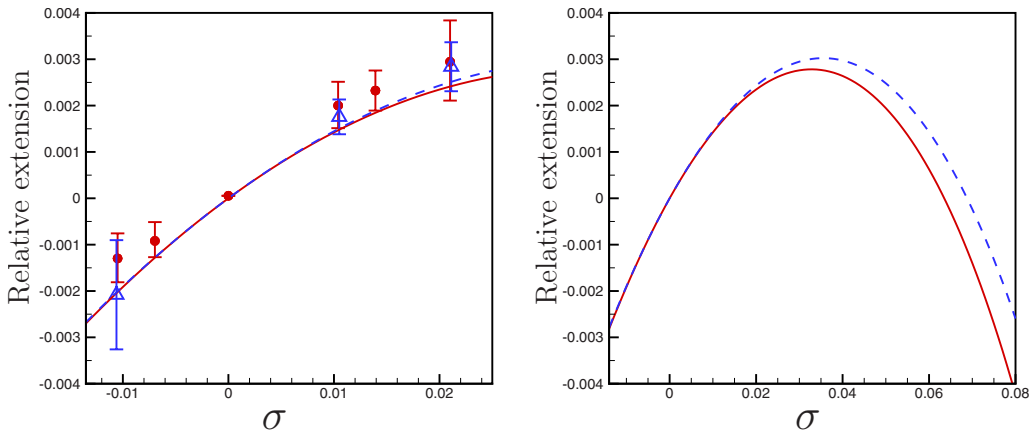

FIG. 3. (Color online) Relative changes in extension, $\epsilon(\sigma)-\epsilon(\sigma=0)$, versus relative changes in twist, σ. The points are the experimental data taken from Ref. [13], and the lines show the calculated behavior using $C_0=100$ nm, $D_1/\omega_0=-1100$ nm, and $\omega_0 G=-340$ nm. The red solid lines (solid circles) and the blue dashed lines (open triangles) correspond to $F=9$ pN and $F=18$ pN, respectively.

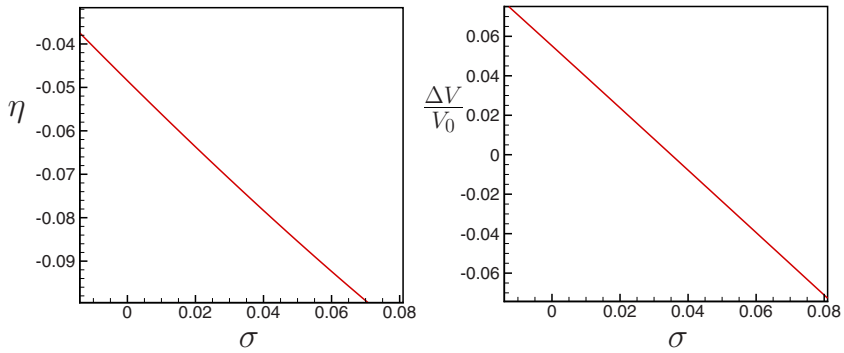

FIG. 4. (Color online) Relative changes in radius, η (left), and relative changes in volume, $\Delta V/V_0$ (right), in terms of σ.

of the elastic constant D_2 and have found that, as is expected, the trend of the twist-stretch coupling of DNA is independent of D_2 for its reasonable values, $|D_2| \lesssim |D_1|$. The sign of $\omega_0 G$ for B-DNA is found to be negative, which means that it is easier to overtwist the DNA than undertwist it. We know B-DNA is a right-handed helix. So as a result of its helical structure, the energy of B-DNA is not symmetric with respect to θ/L. Micromanipulation experiments show that both positive and negative excess twist induce a phase transition in B-DNA. In fact, B-DNA is stable in a narrow range of twist; it denatures when unwound at about $\sigma < -0.015$ and forms an scP-DNA phase if wound up at about $\sigma > 0.03$ [20,21]. So by increasing the applied excess twist to the molecule in the undertwisting direction, the molecule denatures more rapidly than in the overtwisting direction. This means that overtwisting the molecule by an absolute value of $|\sigma|$ needs less energy and so is easier than undertwisting it by the same absolute value. So the sign of α in the energy equation should be negative for B-DNA, which is in agreement with our results. In order to estimate the value of D_1, we consider the terms up to second order in Eq. (3) and minimize the energy with respect to η at $\sigma=0$. We obtain $\eta \sim \frac{\pi k_B T}{80 R_0^2 k_h} D_1 \epsilon$, which means the Poisson ratio of the molecule equals $\nu \sim -\frac{\pi k_B T}{80 R_0^2 k_h} D_1$. For a normal helix with positive Poisson ratio, there is a negative correlation between the changes in the radius and the changes in the length, which means that the sign of D_1 should be negative, which is in agreement with our results. Moreover, as the the Poisson ratio of the molecule is about 0.5, the order of D_1 should be 10^3, which is also consistent with our estimated value.

In conclusion, we have shown that by introducing a simple elastic model with only two strain variables, the nonmonotonic behavior of the twist-stretch coupling of B-DNA can be obtained in good agreement with the experimental results. For small deformations, the length of the stretched B-DNA increases as a result of overtwisting, while the radius of the molecule decreases so that the arclength of the backbones does not change significantly.

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