

TWIST-STRETCH ELASTICITY OF DNA

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ABSTRACT

The symmetries of the DNA double helix require a new term in its linear response to stress: the coupling between twist and stretch. Recent experiments with torsionally-constrained single molecules give the first direct measurement of this important material parameter. We extract its value from a recent experiment of Strick, *et al.* and find rough agreement with an independent experimental estimate recently given by Marko. We also present a very simple microscopic theory predicting a value comparable to the one observed.

INTRODUCTION

In this paper we will study the response of DNA to mechanical stress using the methods of classical elasticity theory[1]. While many elements of DNA function require detailed understanding of specific chemical bonds (for example the binding of small ligands), still others are quite nonspecific. Moreover, since the helix repeat distance of $l_0 \approx 3.4\text{nm}$ involves dozens of atoms, it is reasonable to hope that this length-scale regime would be long enough so that the cooperative response of many atoms would justify the use of a continuum, classical theory, yet short enough that the spatial structure of DNA matters.

Since various important biological processes involve length scales comparable to l_0 (notably the winding of DNA onto histones), the details of this elasticity theory should prove important. Yet, until recently, little was known about the relevant elastic constants. Extensive experimental work yielded fair agreement on the values of the bend and twist persistence lengths, though the former was plagued with uncertainties due to the polyelectrolyte character of DNA [2]. A simple model of DNA as a circular elastic rod gives a reasonable account of many features of its long-scale behavior, for example supercoiling [3].

Recently, techniques of micromanipulation via optical tweezers and magnetic beads have yielded improved values for the bend stiffness from the phenomenon of thermally-induced entropic elasticity [4][5][6], as well as a direct measurement of a third elastic constant, the stretch modulus[7][8]. Significantly, the relation between bending stiffness, stretch modulus, and the diameter of DNA turned out to be roughly as predicted from the classical theory of beam elasticity [7][8][9], supporting the expectations mentioned above.

Still missing, however, has been any direct measurement of the elastic constants reflecting the *chiral* (*i.e.* helical) character of DNA. One such constant, a twist-bend coupling, was investigated by Marko and Siggia [10], but no direct experimental measurement has yet been devised. We will introduce a new chiral coupling, the twist-stretch energy. Electrostatic effects do not complicate the analysis of this coupling. We will explain why our term is needed, extract its value from the experiment of Strick, *et al.* [11], and compare it to the prediction of a microscopic model to see that its magnitude is in line with the expectations of classical elasticity theory. J. Marko has independently introduced the same coupling and estimated its value from different experiments[12]; our values are in rough agreement.

EXPERIMENT

DNA differs from simpler polymers in that it can resist twisting, but it is not easy to measure this effect directly due to the difficulty of applying external torques to a single molecule. The first single-molecule stretching experiments constrained only the locations of the two ends of the DNA strand. The unique feature of the experiment of Strick *et al.* was its added ability to constrain the *orientation* of each end of the molecule.

We will study Fig. 3a of ref. [11]. In this experiment, a constant force of 8pN was applied to the molecule, and the end-to-end length z_{tot} was monitored as the terminal end was rotated through ΔLk turns from its relaxed state (which has Lk_0 turns). In this way the helix could be over- or undertwisted by as much as $\pm 10\%$. Over this range of imposed linkage z_{tot} was found to be a linear function of σ :

$$\epsilon = \epsilon_{\sigma=0} - 0.15\sigma, \quad (1)$$

where $\sigma \equiv \Delta Lk/Lk_0$ and $\epsilon \equiv (z_{\text{tot}}/z_{\text{tot},0}) - 1$. Thus σ is the fractional excess link, and ϵ is the extension relative to the relaxed state. Eq. (1) is the experimentally observed twist-stretch coupling.

THEORY

Phenomenological Model

A straight rod under tension and torque will stretch and twist. We can describe it using the following reduced elastic free energy per equilibrium length $z_{\text{tot},0}$ of the rod:

$$f_1(\sigma, \epsilon) \equiv \frac{F_1(\sigma, \epsilon)}{k_B T z_{\text{tot},0}} = \frac{\omega_0^2}{2} [\bar{C}\sigma^2 + \bar{B}\epsilon^2 + 2\bar{D}\epsilon\sigma]. \quad (2)$$

The twist persistence length is $\bar{C} \approx 75 \text{ nm}$ [2], while the helix parameter $\omega_0 = 2\pi/l_0 = 1.85/\text{nm}$. We will take $\bar{B} \approx 1100 pN/\omega_0^2 k_B T \approx 78 \text{ nm}$ [8]. In the experiment under study, there is an applied reduced force $\tau = 8 \text{ pN}/k_B T \approx 1.95/\text{nm}$. For a circular beam made of isotropic material, the cross-term \bar{D} is absent [9] because twisting is odd under spatial inversion while stretching is even. For a helical beam, however, we must expect to find this term.

Setting $\tau = \partial f_1 / \partial \epsilon|_\sigma$, we find

$$\epsilon = \epsilon_{\sigma=0} - (\bar{D}/\bar{B})\sigma. \quad (3)$$

Comparing to Eq. (1), we obtain the desired result: $\bar{D} = 12 \text{ nm}$. To compare this to Marko's analysis, we note that his dimensionless g equals our $\bar{D}\omega_0$, so that we get $g = 22$. The rough agreement with Marko's result $g = 35$ [12] indicates that the data show a real material parameter of DNA and not some artifact. We do not expect exact agreement, since Marko studied the nonlinear overstretching transition of [7][14]; our value came from the linear regime of small strains.

Microscopic Model

To gain further confidence in our result, we will now see how the expected twist-stretch coupling emerges from a simple elastic model for DNA. Fig. 1 reviews the relevant geometric

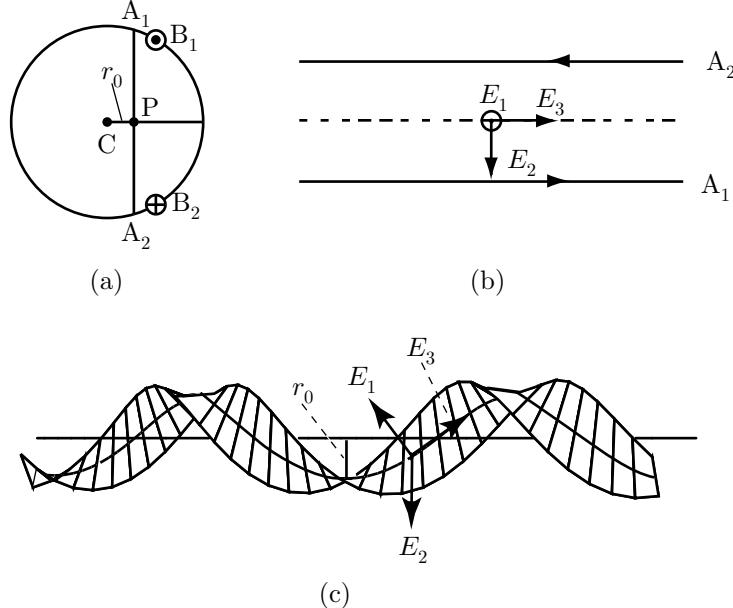


Figure 1: (a) Schematic representation of a cross section of DNA showing its intersections (B_1 and B_2) with the phosphate backbones, its intersection (line A_1PA_2) with the parameterizing helical ribbon, and its helical center C . (b) A section of ribbon showing oppositely oriented edges. At each point along the ribbon's center (dotted curve), there is a triad of orthonormal vectors, \mathbf{E}_1 , \mathbf{E}_2 , and \mathbf{E}_3 . \mathbf{E}_3 is parallel to the center line, \mathbf{E}_2 points to one of the edges, and \mathbf{E}_1 is perpendicular to the ribbon. (c) Representation of the helical ribbon.

properties of DNA. Base pairs are connected by inequivalent sugar-phosphate backbones whose twisting pattern defines the major and minor grooves. These backbones intersect a given cross section of DNA at two points. Lines parallel to the line connecting these two points sweep out ribbon-like surfaces as the DNA twists. We will parameterize the DNA structure by one of these ribbons, whose center is a distance r_0 from the central helical axis. Any choice of r_0 is acceptable. We will see, however, that a small value of r_0 can explain the measured value of D .

Our ribbon is described by the triad of unit vectors \mathbf{E}_1 , \mathbf{E}_3 , and $\mathbf{E}_2 = \mathbf{E}_3 \times \mathbf{E}_1$, where \mathbf{E}_3 is the unit tangent vector to the center of the ribbon and \mathbf{E}_2 points from the center of the ribbon to one of its edges. The triad varies as we move along the arc length s of the ribbon. The motion is described by

$$\frac{d\mathbf{E}_i}{ds} = -\epsilon_{ijk}\Omega_j\mathbf{E}_k. \quad (4)$$

The parameter s labels each point along the central axis of the ribbon in its unstressed state and runs from 0 to L . The actual arc length along the distorted central axis of the ribbon will not be ds but rather $[1 + \epsilon_2(s)]ds$ where ϵ_2 is the intrinsic strain. Therefore, the total length for constant ϵ_2 is $L' = (1 + \epsilon_2)L$. The intrinsic strain allows the spacing between successive phosphate groups to change.

The edges of our ribbon, like the two sugar-phosphate backbones in DNA, are distinguishable and point in opposite directions. This symmetry can be incorporated into our microscopic model by considering a rotation of 180° about the vector \mathbf{E}_1 followed by $s \rightarrow -s$. Under this transformation \mathbf{E}_2 and \mathbf{E}_3 change sign, but s derivatives of these vectors do not. Also, \mathbf{E}_1 does not change sign, but $d\mathbf{E}_1/ds$ does. Therefore, the free energy should remain

unchanged upon changing the sign of Ω_1 but not of Ω_2 and Ω_3 [10]. The most general reduced free energy per length of ribbon relative to that of the flat unstretched ribbon up to second order in Ω_i and ϵ_2 is

$$f_{DNA} = \frac{1}{2}[A' \Omega_1^2 + A(\Omega_2 - \Omega_{20})^2 + C(\Omega_3 - \Omega_{30})^2 + B\omega_0^2 \epsilon_2^2 + 2D\omega_0 \Omega_3 \epsilon_2 + 2G\Omega_2 \Omega_3 + 2K\omega_0 \Omega_2 \epsilon_2 - A\Omega_{20}^2 - C\Omega_{30}^2]. \quad (5)$$

ϵ_2 does not change sign under $s \rightarrow -s$, and so it can appear in combination with Ω_2 and Ω_3 in Eq. (5). This model is the simplest semi-microscopic model that incorporates all of the symmetries of DNA. It is an expansion to harmonic order in first-order derivatives of the vectors \mathbf{E}_i (*e.g.* of $\Omega_3 = -\mathbf{E}_1 \cdot \frac{d\mathbf{E}_2}{ds}$). Thus, it is a model with quantitative predictive power so long as the Ω_i are slow on a scale set by the distance $a = 0.6$ nm between successive phosphate groups, (*i.e.* so long as $\Omega_i a \ll 1$). In the ground state $\Omega_3 = \Omega_{30} \approx \omega_0 = 1.85/\text{nm}$, so that $\Omega_{30} a \approx 1.1$ is not small. This implies that higher derivative terms (*e.g.* $(\frac{d\Omega_3}{ds})^2$, etc.) are needed for a quantitative theory. Nevertheless, our simple semi-microscopic model captures the essential symmetry of the DNA structure and allows us to address questions like the nature of the twist-stretch coupling.

One can easily show that the center of the ribbon describes a helix in the ground state of Eq. (5). We will assume that D , G , and K can be made small by an appropriate choice of r_0 . Then, to keep the model as simple as possible, we will simply set these parameters equal to zero for this choice of r_0 . We parameterize the helical ribbon using three angles ψ , γ , and ϕ :

$$\begin{aligned} \mathbf{E}_3 &= \sin \gamma \hat{z} + \cos \gamma \hat{\phi} \\ \mathbf{E}_2 &= \cos \psi (-\sin \gamma \hat{\phi} + \cos \gamma \hat{z}) - \sin \psi \hat{\rho} \\ \mathbf{E}_1 &= -\sin \psi (-\sin \gamma \hat{\phi} + \cos \gamma \hat{z}) - \cos \psi \hat{\rho}, \end{aligned} \quad (6)$$

where $\hat{\rho}$ and $\hat{\phi}$ are cylindrical unit vectors spinning at frequency $\dot{\phi}$. If $\dot{\phi}$ is a constant and $\psi = 0$, then the ribbon wraps around a cylinder of length z_{tot} and radius r .

$$z_{\text{tot}} = L(1 + \epsilon_2) \sin \gamma \quad \text{and} \quad r = \frac{\cos \gamma}{\omega}. \quad (7)$$

In its ground state the helix has the following properties: $\Omega_1 = \Omega_{10} = 0$, $\Omega_2 = \Omega_{20} = \omega_0 \cos \gamma_0$, $\Omega_3 = \Omega_{30} = \omega_0 \sin \gamma_0$, $\dot{\phi} = \omega_0 = \sqrt{\Omega_{20}^2 + \Omega_{30}^2}$, and $\psi = \psi_0 = 0$. Also, the ground state length and radius of the molecule are, respectively, $z_{\text{tot},0} = L \sin \gamma_0$ and $r_0 = \cos \gamma_0 / \omega_0$.

We now consider deviations in the ground state length z_{tot} and twist rate $\dot{\phi}$ of the molecule. Since the total twist is $\dot{\phi}L$, the excess twist is σL where $\sigma = (\dot{\phi} - \omega_0) / \omega_0 = \delta\dot{\phi} / \omega_0$. Using Eq. (7) we find that changes in length are produced both by intrinsic strain ϵ_2 and by changes in γ :

$$\epsilon = \frac{z_{\text{tot}}}{z_{\text{tot},0}} - 1 = \epsilon_1 + \epsilon_2 \quad \text{where} \quad \epsilon_1 = \cot \gamma_0 \delta \gamma. \quad (8)$$

The energy of harmonic deviations from equilibrium are obtained by expanding f_{DNA} to second order in $\delta\gamma(s)$, $\delta\psi(s)$, and $\delta\phi(s)$. The ground state is a periodic helix implying these variables can be expressed in terms of Fourier modes in different Brillouin zones defined by ω_0 . Rotations of the helix about space-fixed axes x , y , and z are described by the variables $\delta\theta_x$, $\delta\theta_y$, and $\delta\theta_z$. The variables $\delta\gamma$, $\delta\psi$, and $\delta\phi$ can be expressed in terms of these variables:

$$\begin{aligned}
\delta\gamma &= \cos\omega_0 s \delta\theta_x + \sin\omega_0 s \delta\theta_y \\
\delta\psi &= \frac{1}{\cos\gamma_0} (\sin\omega_0 s \delta\theta_x - \cos\omega_0 s \delta\theta_y) \\
\delta\phi &= \tan\gamma_0 (\sin\omega_0 s \delta\theta_x - \cos\omega_0 s \delta\theta_y) + \delta\theta_z.
\end{aligned} \tag{9}$$

Thus, variations of $\delta\theta_x$ and $\delta\theta_y$ in the first BZ give rise to variations in $\delta\gamma$ and $\delta\psi$ in the second BZ. A complete long-wavelength theory can, therefore, be expressed in terms of the first BZ components of $\delta\theta_x$, $\delta\theta_y$, $\delta\gamma$, $\delta\psi$, and $\delta\phi$ (whose 1st BZ component is equal to that of $\delta\theta_z$).

Using the relations for the Ω_i obtained from Eq. (4) and Eq. (6), we find

$$\begin{aligned}
\Omega_2 - \Omega_{20} &= \cos\gamma_0 \dot{\delta\phi} - \omega_0 \sin\gamma_0 \delta\gamma \\
\Omega_3 - \Omega_{30} &= \sin\gamma_0 \dot{\delta\phi} + \omega_0 \cos\gamma_0 \delta\gamma.
\end{aligned} \tag{10}$$

Then, using these expressions in f_{DNA} , integrating out ψ , and remembering that length along the pitch axis is a factor of $\sin\gamma_0$ less than the ribbon length, we find that the effective reduced free energy per unit length of pitch axis is

$$f = f_B + f_{TS}, \tag{11}$$

where

$$f_B = \frac{1}{4 \sin\gamma_0} (A' + A \sin^2\gamma_0 + C \cos^2\gamma_0) (\dot{\theta}_x^2 + \dot{\theta}_y^2) = \frac{1}{2} \bar{A} (\dot{\theta}_x^2 + \dot{\theta}_y^2) \tag{12}$$

is the bending energy[16] and f_{TS} is the twist-stretch energy defined by

$$f_{TS} = \frac{\omega_0^2}{2 \sin\gamma_0} [C_{\sigma\sigma}\sigma^2 + B_{\epsilon_1\epsilon_1}\epsilon_1^2 + B\epsilon_2^2 + 2D_{\epsilon_1\sigma}\epsilon_1\sigma], \tag{13}$$

where $C_{\sigma\sigma} = (A \cos^2\gamma_0 + C \sin^2\gamma_0)$, $B_{\epsilon_1\epsilon_1} = (A \frac{\sin^4\gamma_0}{\cos^2\gamma_0} + C \sin^2\gamma_0)$, and $D_{\epsilon_1\sigma} = (C - A) \sin^2\gamma_0$. The twist-stretch energy can be expressed in terms of the total strain by setting $\epsilon_1 = \epsilon - \epsilon_2$ and integrating over ϵ_2 . The result is that f_{TS} has the same form as Eq. (2) with macroscopic elastic constants \bar{B} , \bar{C} , and \bar{D} expressed in terms of our microscopic parameters A , B , and C . The stretch moduli associated with ϵ_1 and ϵ_2 add in parallel to yield a total stretch modulus $\bar{B} = \frac{1}{\sin\gamma_0} (\frac{1}{B_{\epsilon_1\epsilon_1}} + \frac{1}{B})^{-1}$. The twist-stretch coupling is

$$\bar{D} = \frac{B}{(B_{\epsilon_1\epsilon_1} + B)} (C - A) \sin\gamma_0. \tag{14}$$

These expressions for the twist modulus $C_{\sigma\sigma}$, stretch modulus \bar{B} , and twist-stretch modulus \bar{D} are valid for arbitrary values of the helix offset r_0 .

Thus, a description of DNA in terms of a helical ribbon with an axis offset from the central helical axis generates a twist-stretch coupling even if the bare twist-stretch coupling (D in Eq. (5)) is zero. We can estimate the offset r_0 necessary to produce the measured \bar{D} assuming it arises entirely from Eq. (14). If we assume $A' \approx A$ and $\omega_0 r_0 \ll 1$, then $B \approx \bar{B} = 75\text{nm}$, $C \approx \bar{C} = 78\text{nm}$, and $A \approx \bar{A} = 40\text{nm}$, and we find $\bar{D} \approx (\omega_0 r_0)^2 (\bar{B}/\bar{A})(\bar{C} - \bar{A})$ and $(\omega_0 r_0)^2 \approx 0.176$ or $r_0 \approx 0.23\text{nm}$ [15]. Corrections to this estimate are of order $(\omega_0 r_0)^4 \sim 0.03$.

This result for the twist-stretch coupling \overline{D} in the limit of a small helix offset r_0 was found previously in [1].

CONCLUSION

We have modeled DNA as a thin helical ribbon and presented a complete long-wavelength theory which includes energy costs due to bending, stretching, and twisting the DNA molecule. Using this theory, we were able to relate semi-microscopic elastic constants to the experimentally measured macroscopic elastic constants. We have also calculated the coefficient of the twist-stretch coupling and compared it to torsionally constrained DNA stretching experiments. We have found that the experimental value of the twist-stretch coupling gives a value r_0 for the radius of the helical ribbon in rough agreement with the elastic center offset from the helix axis obtained from crystallographic data[15].

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