Chiral elasticity of DNA

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DNA has been described as a semiflexible polymer. But DNA is chiral, so its bending Hamiltonian contains nonlinear terms coupling the curvature \( \kappa \) to the torsion \( \tau \), leading to an average \( \langle \tau \rangle \) independent of \( \kappa \), and variance \( \langle \Delta \tau^2 \rangle \) scaling as \( 1/\kappa^2 \). We perform atomistic MD simulations of 31 base-pair DNA sequences with explicit solvent, in which “restraints” are imposed to “encourage” the DNA to bend. We extract bending moduli by fitting to bending and torsional angle distributions. We find that chiral elasticity matters whenever DNA bends on a radius less than about 5 nm.

Understanding the mechanics of DNA is relevant to many important biophysical processes such as DNA transcription [1], DNA replication and recombination [2], DNA wrapping around histones in the nucleosome [3], and indeed all situations where functionality depends on DNA conformation and dynamics [4, 5]. The unique mechanics and dynamics of DNA have been the subject of many experimental and computational studies [6, 7].

The mechanics of double-stranded DNA has been regarded as that of a semiflexible polymer, well described by the classical wormlike chain (WLC) model [8]. This approach to DNA mechanics has been extended to treat the coupling of curvature to molecular twist, [9, 10] and the coupling of twist to molecular extension [11, 12]. The WLC model has more recently been extended by Wiggins et al. [7] to address the bending mechanics of DNA at short length scales and larger deflection angles [6, 13].

In this prior work, the only consequence of DNA chirality is the presence of molecular twist as a degree of freedom. In these models, if a DNA strand is free to relax its twist in response to curvature, the twist is annealed, and the strand behaves like any wormlike chain. One may then ask, does it matter that DNA is chiral, if the twist is unconstrained?

It turns out that there are nonlinear terms in the bending Hamiltonian for a semiflexible polymer, allowed by symmetry only for chiral polymers, which couple the curvature \( \kappa \) to the torsion \( \tau \). In this Letter we identify these terms, find the elastic constants by comparison to atomistic MD simulation, and explore the physical consequences of these couplings.

The bending Hamiltonian for a semiflexible polymer with path \( R(s) \) may be expanded in derivatives of the tangent vector \( T(s) = R'(s) \) with respect to arclength \( s \):

\[
H = \int ds \left( \frac{K_1}{2} T'(s)^2 + \frac{K_2}{2} T''(s)^2 + \alpha (T(s) \cdot T'(s) \times T''(s) + \ldots) \right) \tag{1}
\]

in which the third term (\( \alpha \) may be positive or negative) is permitted only for chiral polymers such as DNA [14].

In writing Eqn. (1), we assume that we study DNA bending with no external coupling to the total molecular twist or length. DNA in our simulations is free to adopt whatever twist and stretch is optimal for a given path \( R(s) \). Hence twist and stretch degrees of freedom are annealed, and so do not appear explicitly in Eqn. (1).

Using the Frenet-Serret equations [14],

\[
T'(s) = \kappa(s) N(s) \\
N'(s) = -\kappa(s) T(s) + \tau(s) B(s) \tag{2}
\]

we can show that \( T'' = \kappa^2 \), where \( \kappa \) is the curvature of the path \( R(s) \) and \( \tau \) is the torsion, or rate at which the normal \( N(s) \) rotates around the tangent. The bending stiffness \( K_1 \) fixes the persistence length \( L_p = \beta K_1 \), the length scale at which thermal fluctuations decorrelate the tangent. Likewise, the Frenet-Serret equations simplify \( T'''' \) to \( \kappa^4 + \kappa^2 + \kappa^2 \tau^2 \). Evidently the \( K_2 \) term in Eqn. (1) penalizes torsion regardless of sign, for a curved path.

The chiral term reduces to \( \alpha \kappa^2 \tau \), which biases the torsion for a locally curved path. The physics of this term is familiar to anyone who has tried to coil hemp rope, which has a definite preference for a helical winding of a certain handedness. It is instructive to write the bending Hamiltonian in terms of \( \kappa \) and \( \tau \), using Eqn. (2), as

\[
H = \frac{K_1}{2} \kappa^2 + \frac{K_2}{2} (\kappa^4 + \kappa^2 + \kappa^2 \tau^2) + \alpha \kappa^2 \tau \tag{3}
\]

Minimizing \( H \) with respect to \( \tau \) gives \( \tau^* = -\alpha/K_2 \) independent of curvature (neglecting logarithmic effects arising from the measure).

Imposing a bend does not change the average value of \( \tau \), but instead sharpens the distribution of \( \tau \) about its mean. From Eqn. (3) the terms in \( H \) involving the torsion can be written \( H_\tau = (1/2) K_2 \kappa^2 (\tau + \alpha/K_2)^2 \), from which we find the variance of \( \tau \) about its mean is \( 1/(K_2 \kappa^2) \).
We seek to apply our bending Hamiltonian to describe the elasticity of DNA. Of course, even simple repeating sequences of DNA have structure on short length scales, within a single helical repeat, not captured by a continuous-path model. To focus on long-wavelength scales, within a single helical repeat, not captured by H-bonded H and N atoms on paired bases (green and orange beads), and H-bond centers of mass (red beads).

The minimum length strand of DNA we can use to investigate the chiral coupling between curvature and torsion is then about 30 base pairs, with three tangent vectors $\hat{n}_1, \hat{n}_2, \hat{n}_3$ (see Fig. 1). Such a strand has two coarse-grained bending angles and one torsional angle, analogous to the conformational degrees of freedom of butane. We define $\theta_1$ as the deflection angle from $\hat{n}_1$ to $\hat{n}_2$ (likewise for $\theta_2$). The torsional or dihedral angle $\phi$ is defined with $\phi = 0$ corresponding to successive coplanar deflections of the same sign.

Making finite-difference approximations to the various derivatives in Eqn. (1) leads after some algebra to

$$\beta H = k_1 (2 - \cos \theta_1 - \cos \theta_2) + \frac{k_2}{2} (\sin^2 \theta_1 + \sin^2 \theta_2) - k_2 \sin \theta_1 \sin \theta_2 \cos (\phi - \phi_0) \quad (4)$$

in which we have defined $k_1 = \beta K_1 / \Delta s$, $k_2 = \beta K_2 / \Delta s^3$, $\tan \phi_0 = \alpha / (K_2 \Delta s)$, and $k_2 = k_2 \sec \phi_0$. Here $\Delta s$ is the length of a helical repeat, about 3.3 nm.

To force DNA to bend in our MD simulations, we apply “restraints” to the molecule, by adding additional harmonic bending terms with nonzero preferred angle $\theta_0$, of the form

$$\beta \delta H = (\hat{k}/2)(\theta_i - \theta_0)^2 \quad (5)$$

for $i = 1, 2$. These terms “encourage” the DNA to bend, but do not constrain the bending angle. We choose the restraint spring constant $k$ to be comparable to the spring constant of DNA itself, so that $\theta$ is affected but not strictly determined by the restraint. No restraint is applied to the torsional angle $\phi$, which is free to fluctuate.

By observing how much the DNA deflects under the action of the restraint, and how the torsional angle $\phi$ responds to the imposed bend, we may infer the values of the elastic constants for the DNA strand.

We determine the coefficients $k_1$, $k_2$, and $\phi_0$ by adjusting their values so that simulation results for the probability distributions for $\theta$ and $\phi$ agree with equilibrium averages taken over $H$, given by

$$P(\theta_1) = Z^{-1} \sin \theta_1 \int \sin \theta_2 d\theta_2 d\phi e^{-\beta H}$$

$$P(\phi) = Z^{-1} \int \sin \theta_1 d\theta_1 \sin \theta_2 d\theta_2 e^{-\beta H}$$

$$Z = \int \sin \theta_1 d\theta_1 \sin \theta_2 d\theta_2 d\phi e^{-\beta H} \quad (6)$$

The parameter $\phi_0$ can be found from the relation

$$\langle \sin \phi \rangle = \tan \phi_0$$

which depends only on the fact that the Hamiltonian is an even function of $\phi - \phi_0$. By this approach, we can ultimately determine values for $K_1$, $K_2$, and $\alpha$.

For our MD simulations, we must select one or more particular base pair sequences to study. The bending stiffness of DNA has been previously shown to depend on the base pair sequence [15]. CG base pairs have stronger hydrogen bonding than do AT base pairs, so one expects a poly-(CG) sequence to be stiffer than a poly-(AT) sequence. In the present work, we have chosen to study the simplest possible sequences that allow us to investigate the dependence of mechanical response on sequence; namely, 31-mer double helix poly-(AT) [“AT31”], and analogous poly-(CG) [“CG31”].

The tangent vectors within each helical repeat are defined by connecting two centerline points, located at the two centers of mass of a selected hydrogen-bonded H and N atoms at opposite ends of the repeat, see Fig. 1. The bending angle $\theta_i (i = 1, 2)$ is defined by two adjacent vectors $\hat{n}_i$ and $\hat{n}_{i+1}$, and the dihedral angle $\phi$ is defined by three adjacent vectors $\hat{n}_1, \hat{n}_2$ and $\hat{n}_3$.

The restraint potential Eqn. (5) is imposed in terms of the angle $\theta_i$ so defined. We choose $\theta_0 = 30$ degrees, large enough so the angular deflections are large compared to thermal fluctuations, but not so large that the local bending is strongly anharmonic [7]. As discussed previously, we choose $\hat{k} = 20$ kcal/mol, the same order as the bending stiffness $k_1$ of the DNA itself.

All molecular dynamics simulations were carried out using the AMBER 10 package [16] with the parm99SB [17, 18] and parmbsc0 [19] force field parameters. The starting B-form DNA structures for AT31 and CG31 were generated using the “make-na” server [20]. Each system was neutralized with Na+ ions and solvated with TIP3P water [21]. The DNA strands were immersed in a rectangular water box $62 \times 73 \times 143$ Å³. Langevin dynamics
was used to maintain the temperature 300 K with a collision frequency of 1.0 ps\(^{-1}\). The integration time step was 0.002 ps and the nonbonded interaction cutoff distance was 10 Å. Each 31-mer was simulated for at least 28 ns, after being initially equilibrated for at least 10 ns.

We determine whether our simulation runs are long enough by evaluating the autocorrelation functions for the time series for the bending and torsional angles. (Results for \(\theta(t)\) are shown in Fig. 2.) We find the characteristic relaxation time \(\tau_\theta\) for bending angle fluctuations from the (approximately) exponential decay (see Fig. 2) is in the range of 0.25–0.3 ns. The characteristic time \(t_\phi\) for torsional angle fluctuations is likewise found to be about 1 ns. Thus our run times are about 100 times \(t_\theta\), or about 30 times \(t_\phi\), long enough to give reasonable statistics for the equilibrium distributions of \(\theta\) and \(\phi\).

The probability distribution \(P(\theta)\) for the bending angle \(\theta\) (data for both \(\theta_1\) and \(\theta_2\), taken together) and \(P(\phi)\) for the torsional angle \(\phi\) are shown in Figs. 3 and 4 respectively. Evidently, the mechanical responses of the two DNA strands AT31 and CG31 to the same restraint potential are quite different. First, from the \(\theta\) distributions (Fig. 3), we see that the CG31 strand is noticeably stiffer than the AT31 strand, because the average \(\langle \theta \rangle\) induced by the restraint is smaller for CG31 than for AT31.

More striking are the qualitative differences between the torsional angle distributions \(P(\phi)\) for CG31 and AT31. The average \(\langle \phi \rangle\) for the two strands have opposite signs. (This is allowed, since the bending coefficient \(\alpha\) may take either sign.) Also, the variance of \(\tau\) about its mean is much larger for CG31 than for AT31, which implies \(K_2\) must be smaller for CG31 than for AT31.

To analyze the distributions quantitatively and extract the elastic constants for the two strands, we begin by finding \(\phi_0\) from Eqn. (7). Then, we find best-fit values for \(k_1\) and \(k_2\) by comparing theoretical distributions of Eqns. (6) to the simulation histograms of Figs. 2 and 3.

The best-fit values for \(k_1\) and \(k_2\) appear in Table I, with corresponding theoretical distributions shown as continuous curves (solid for AT31, dashed for CG31) in the figures. The theoretical distributions correspond quite well to the simulation results, with rather narrow confidence intervals on \(k_1\) and \(k_2\). Corresponding values of \(K_1\), \(L_p\), \(K_2\), and \(\alpha\) for AT31 and CG31 are given in Table II. Our results for the bending stiffness and \(L_p\) for the CG and AT strands are consistent with previous work of

\[ P(\theta) \]

\[ P(\phi) \]

![FIG. 2. Autocorrelation function for \(\theta\), AT31 (solid) and CG31 (dashed). Inset: complete time series \(\theta(t)\) for AT31.]

![FIG. 3. Histograms of bending angle \(\theta\) for AT31 (open square) and CG31 (filled circle) from MD simulations, with best-fit theoretical distributions for AT31 (solid) and CG31 (dashed).]

![FIG. 4. Histograms of dihedral angle \(\phi\) for AT31 (open square) and CG31 (filled circle) from MD simulations, with best-fit theoretical distributions for AT31 (solid) and CG31 (dashed).]

<table>
<thead>
<tr>
<th></th>
<th>(k_1)</th>
<th>(k_2)</th>
<th>(\tan \phi_0)</th>
<th>(\phi_0)</th>
</tr>
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<tr>
<td>AT31</td>
<td>19.6±0.1</td>
<td>10.8±0.3</td>
<td>-1.11</td>
<td>48°</td>
</tr>
<tr>
<td>CG31</td>
<td>27.1±0.1</td>
<td>5.3±0.4</td>
<td>0.84</td>
<td>40°</td>
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With a quantitative account of DNA chiral elasticity in hand, we can answer the question we posed earlier, as to when chirality matters for the mechanical behavior of DNA. We now develop two physical criteria for when chiral elasticity noticeably affects DNA conformations.

First, we noted that the average torsion is independent of curvature, while the variance of the torsion about its mean scales as $1/\kappa^2$. This means that if a chiral polymer is only weakly curved, thermal fluctuations will cause the torsional angle to be nearly uniformly distributed, just as is only weakly curved, thermal fluctuations will cause the angles about a nonzero value of $\phi_0$, at which point the influence of chiral elasticity is evident.

It is easily shown that $\kappa$ and $\tau$ are given in terms of the angles $\theta$ and $\phi$ in the discrete model with a uniform helical bend, by the relations $\kappa^2 = 2(1 - \cos \theta)/\Delta s^2$ and $\tau^2 = \sin^2 \theta/(1 - \cos \theta)/(1 - \cos \theta)\Delta s^2$, which in the limit of small angles become simply $\kappa \approx \theta/\Delta s$ and $\tau \approx \phi/\Delta s$. Thus the variance of $\phi$ is of order $\Delta s/(\beta K_2 \kappa^2)$.

Noting that for both AT31 and CG31 the mean torsional angle $\phi_0$ is of order unity, chiral effects become important when the variance in $\phi$ is also of order unity. Using values from Table II, this corresponds to bending radii for the AT31 and CG31 strands of 6.5 nm and 4.5 nm respectively, or a deflection angle $\theta$ per helical repeat of 29 and 42 degrees respectively. Hence DNA bends at these or smaller radii are noticeably chiral, as were our MD simulations (in which $\theta \approx 20$ degrees; see Fig. 3).

A second criterion for judging when chiral effects matter is to imagine imposing a constant curvature on a long, regular DNA strand. In response, the strand will adopt a uniform superhelix, with radius $r$ and pitch $2\pi h$ (pitch $= \text{rise per helical turn}$). The helical path takes the form $r(\theta) = r(\cos \theta x + \sin \theta y) + h\theta x$ [23], from which the curvature and torsion can be found as $\kappa = r/(r^2 + h^2)$ and $\tau = h/(r^2 + h^2)$. Note that the ratio $r/h$ equals $\kappa/\tau$.

We recall that the average torsion is independent of the imposed curvature; for very small curvature, the lowest-energy shape is a superhelix of very small radius $r$ and finite pitch $2\pi h = 1/\tau$ — essentially a straight line (this configuration would of course be strongly affected by thermal fluctuations). As we increase the imposed curvature, eventually $r/h$ is of order unity, at which point we would certainly identify chiral elasticity as having produced a superhelix in response to curvature.

Making use of the relations between $\kappa$, $\tau$ and $\theta$, $\phi$, and the observed mean values for $\phi$ for the AT and CG strands, we can solve for the $\theta$ values at which this condition holds. Expressed as curvature radii, we find for the AT31 and CG31 DNA strands values of 4.3 nm and 5.0 nm respectively, which correspond to deflection angles per helical repeat of 44 and 38 degrees respectively. By either this or the previous criterion, it is evident that chiral elasticity effects are relevant in DNA when bent at a radius below about 5 nm, certainly a relevant conformational length scale for many biologically important processes involving DNA.

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### Table II. DNA elastic constants (energies in kcal/mol, lengths in nm)

<table>
<thead>
<tr>
<th></th>
<th>$K_1$</th>
<th>$L_\nu$</th>
<th>$K_2$</th>
<th>$\alpha$</th>
</tr>
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<tbody>
<tr>
<td>AT31</td>
<td>38.5±0.2</td>
<td>64.7</td>
<td>233±6</td>
<td>-78.5</td>
</tr>
<tr>
<td>CG31</td>
<td>53.3±0.2</td>
<td>89.4</td>
<td>113±9</td>
<td>28.9</td>
</tr>
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