Conformations of linear DNA

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We examine the conformations of a model for underwound and overwound DNA. The molecule is represented as a cylindrically symmetric elastic string subjected to a stretching force and to constraints corresponding to a specification of the link number. We derive a fundamental relation between the Euler angles that describe the curve and the topological linking number. Analytical expressions for the spatial configurations of the molecule in the infinite-length limit are obtained. A unique configuration minimizes the energy for a given set of physical conditions. An elastic model incorporating thermal fluctuations provides excellent agreement with experimental results on the plectonemic transition. [S1063-651X(97)01805-9]

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I. INTRODUCTION

Conformations of a slender elastic rod were originally viewed as an interesting problem in classical elasticity theory. Kirchhoff [1] was the first to make significant headway towards a complete solution. Almost a century later, as polymers became the subject of intense study, interest in the problem picked up once again [2]. After the discovery of biological polymers, e.g., nucleic acids and proteins, researchers recognized the importance of predicting the elastic shape of linear molecules. The shape (''tertiary structure'') of DNA and RNA plays an important role in the processes of replication and transcription. Because of this a number of authors have analyzed various aspects of elastic DNA conformation [3,4] for both closed (circular) [5–7] and open (linear) [8] configurations. The approaches taken include Lagrangian mechanics [5–8], (numerical) molecular dynamics [9], and statistical mechanics [10,11]. Despite significant progress [8], the equilibrium configurations of infinitely long open DNA have not been analytically described. Our main aims are to set up a formalism for obtaining equilibrium configurations, to find one such conformation for stretched twisted DNA, and to set up a model of plectonemic transition to compare with experimental results [12].

The elastic model of DNA represents the molecule as a slender cylindrical elastic rod. To model external forces and torques the rod is stretched (in the z direction) by a force F and is required to have a fixed linking number, Lk. The rod is parametrized by arclength s. At each point s we describe the rod by relating the local coordinate frame $\mathcal{L}$ to the frame $\mathcal{L}_0$ rigidly embedded in the curve in its relaxed configuration. The relationship between the stressed and unstressed local frames is specified by Euler angles $\theta(s),\phi(s),\psi(s)$ needed to rotate $\mathcal{L}_0$ into $\mathcal{L}$. The shape of the backbone $\mathbf{r}(s)$ is traced out by the unit tangent $\mathbf{t}(s)$. A unit normal $\mathbf{n}(s)$ keeps track of the twist $\mathcal{T}w$. In this paper we will often omit the s depen-dence for brevity. We also make use of the notation $\dot{x}\equiv(d/ds)(x)$. Then,

$$\mathbf{r}(s)=\int_0^s \mathbf{t}(s')ds', \tag{1}$$

$$\mathbf{t}(s)=(\sin\theta\sin\phi,\sin\theta\cos\phi,\cos\theta), \tag{2}$$

$$\mathbf{n}(s)=(\cos\phi\cos\psi-\cos\theta\sin\phi\sin\psi,-\cos\phi\sin\psi - \cos\theta\cos\phi\sin\psi,\sin\theta\sin\psi). \tag{3}$$

Let the elastic constants of bending and torsional stiffness be denoted, respectively, by A and C, and let L be the length of the rod. The energy of the twisted, stressed rod is the sum of bending and twisting energies and the potential energy produced by the stretching force F. Using Eqs. (2) and (3),

$$E_{\rm tot}=E_{\rm el}-\int_0^L dsF\cos\theta=E_{\rm bend}+E_{\rm twist}-\int_0^L dsF\cos\theta = \frac{A}{2}\int_0^L ds(\dot{\mathbf{t}})^2+\frac{C}{2}\int_0^L ds[(\mathbf{n}\times\dot{\mathbf{n}})\cdot\mathbf{t}]^2-\int_0^L dsF\cos\theta. \tag{4}$$

Using Es. (2) and (3) in Eq. (4), we obtain

$$E_{\rm tot}=\int_0^L ds\left[\frac{A}{2}(\dot{\phi}^2\sin^2\theta+\dot{\theta}^2)+\frac{C}{2}(\dot{\phi}\cos\theta+\dot{\psi})^2-F\cos\theta\right]. \tag{5}$$

The feature that sets this work apart from previous attempts and allows us to unambiguously determine a unique configuration for a given set of initial conditions is the constraint of maintaining a fixed linking number Lk. Although linking number is usually associated with closed curves, the bound ends of our string allow us to define a fractional linking number for it. A caveat is that the local expressions we derive are only valid for the configuration (extended) we consider. White's theorem [13] allows us to express Lk in terms of its components: Lk=Tw+Wr. Using Eqs. (2) and (3),

$$\mathrm{Tw}\equiv\frac{1}{2\pi}\int_0^L(\mathbf{n}\times\dot{\mathbf{n}})\cdot\mathbf{t}ds=-\frac{1}{2\pi}\int_0^L\dot{\phi}\cos\theta+\dot{\psi}ds, \tag{6}$$

$$\mathrm{Wr}\equiv\frac{1}{4\pi}\int_0^L ds\int_0^L ds'\frac{(\mathbf{r}-\mathbf{r}')\cdot(\mathbf{t}\times\mathbf{t}')}{|\mathbf{r}-\mathbf{r}'|^3}. \tag{7}$$

A local expression for twist Tw follows straightforwardly, as evidenced by the far right-hand side of Eq. (6). The writhe Wr, however, is not yet suitable for use as a Lagrange multiplier. To express it as an integral of a local quantity we use a theorem by Fuller [4]. The theorem allows us to define Wr locally using a diffeomorphism onto a *reference* curve $\mathcal{C}_r$. (Once again, we must stress that a different configuration, e.g. a circular plasmid, would require a different reference curve, producing slightly modified local expressions.) The writhe is expressed as

$$\mathrm{Wr}=\mathrm{Wr}_r+\frac{1}{2\pi}\int_0^L\frac{\mathbf{t}_r\times\mathbf{t}\cdot\dfrac{d}{ds}(\mathbf{t}_r+\mathbf{t})}{1+\mathbf{t}_r\cdot\mathbf{t}}ds, \tag{8}$$

where Wr_r is the writhe of the reference curve. Finding a suitable reference curve proves crucial. The best choice is also the simplest: a straight line $\mathcal{C}_r=(0,0,s)$. This gives $\mathbf{t}_r=(0,0,1)$ and $\mathrm{Wr}_r=0$. Substituting (2) into Eq. (8), we obtain

$$\mathrm{Wr}=\frac{1}{2\pi}\int_0^L\dot{\phi}(\cos\theta-1)ds. \tag{9}$$

Combining Eqs. (6) and (9) we are led to the simple expression for Lk:

$$\mathrm{Lk}=-\frac{1}{2\pi}\int_0^L(\dot{\phi}+\dot{\psi})ds. \tag{10}$$

Thus we have derived a simple conservation law that expresses the invariance of Lk. Inserting $p d\mathrm{Lk}$ into the right-hand side of Eq. (5), with p a Lagrange multiplier, the expression to be minimized becomes

$$\mathcal{H}=\int_0^L ds\left[\frac{A}{2}(\dot{\phi}^2\sin^2\theta+\dot{\theta}^2)+\frac{C}{2}(\dot{\phi}\cos\theta+\dot{\psi})^2-F\cos\theta-p(\dot{\phi}+\dot{\psi})\right]. \tag{11}$$

DNA conformations of minimum energy are found among the extrema of $\mathcal{H}$.

We find the extrema of $\mathcal{H}$ by applying standard variational techniques to Eq. (11). The resulting Euler-Lagrange equations for $\theta(s)$, $\phi(s)$, and $\psi(s)$ are

$$\dot{\phi}=\frac{p(1-\cos\theta)}{A\sin^2\theta},\quad \dot{\psi}=\frac{p}{C}-\frac{p(1-\cos\theta)\cos\theta}{A\sin^2\theta}, \tag{12}$$

$$\frac{A}{2}\dot{\theta}^2=-\frac{p^2}{A(1+\cos\theta)}-F\cos\theta+E_0. \tag{13}$$

A central goal is to find a unique conformation of the rod given a set of externally imposed constraints F and Lk/L, where L is the length of the rod. We find that Eqs. (13) and (12) support two types of solutions. The first is a family of twisted vertical lines

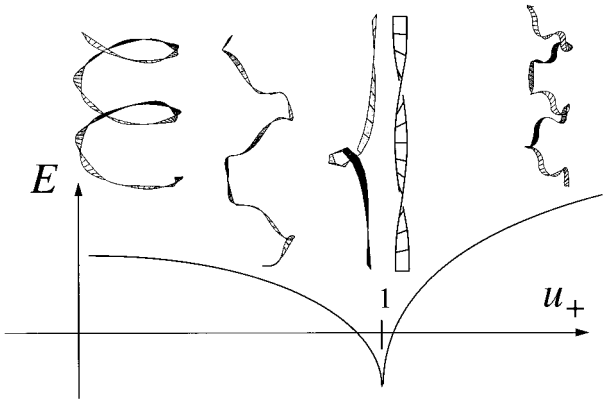

FIG. 1. Writhing family of solutions. The solution with the lowest energy is the soliton. In the infinite-length limit the soliton and the twisted line have the same energy per unit length. The total energy of the soliton exceeds the energy of the twisted line by a finite amount.

$$\theta=0,\quad \phi=0,\quad \psi(s)=(2\pi\,\mathrm{Lk}/L)s. \tag{14}$$

The energy of the straight line follows directly from Eq. (5):

$$E_{\mathrm{line}}=\frac{2CL}{2}(\pi\,\mathrm{Lk}/L)^2 \tag{15}$$

The second family of solutions can be extracted from Eq. (13). Multiplying Eq. (13) by $\sin^2\theta$ and integrating once, we can rewrite Eq. (13) in the form ($u\equiv\cos\theta$)

$$ds=\frac{du}{\sqrt{-\dfrac{2p^2}{A^2}(1-u)+\dfrac{2}{A}(E_0-Fu)(1-u^2)}}\equiv\frac{du}{\sqrt{\dfrac{2F}{A}(u-a)(u-b)(u-c)}}\ (a\leq b\leq c). \tag{16}$$

These ''writhing'' solutions are characterized by the roots $\{a,b,c\}$ of the cubic polynomial in the denominator of Eq. (16). One of the roots, either a or b, is 1. If $u=1$ is a single root, then the configurations form ''superhelices.'' If $u=1$ is a double root ($a=b=1$) the molecule supports a solitonlike excitation (see Fig. 1). The quantity $u=\cos\theta$ takes on values between c and b, the quadrature turning points. The expressions for ϕ, ψ, and other quantities of interest follow by quadratures. The integrals are easily evaluated in terms of elliptic functions.

We have investigated the properties of solutions to Eqs. (12) and (13), with the bending and torsional stiffness A and C appropriate to DNA [14,6]. Using both numerical and analytical methods we find that, given a particular Lk/T, the member of the writhing family with the lowest energy is the soliton configuration ($a=b=1$). The shape of this solution is defined by the following relationship between the arclength s and $u\equiv\cos\theta$:

$$s(u)=\sqrt{\frac{2F}{A(1-c)}}\ln\left(\frac{1+\sqrt{\frac{u-c}{1-c}}}{1-\sqrt{\frac{u-c}{1-c}}}\right), \tag{17}$$

where the lower root c is given by

$$c=\frac{p^2}{2AF}-1, \tag{18}$$

and ϕ and ψ are similarly determined. A very interesting quantity is the energy of the soliton and its relationship to that of the twisted line solution (which are both infinite in the limit $L\to\infty$):

$$E_{\text{soliton}}=E_{\text{line}}+\Delta E$$

with

$$\Delta E=\frac{4F}{L}\sqrt{1+c}\left[\sqrt{\frac{1-c}{1+c}}-\arctan\left(\sqrt{\frac{1-c}{1+c}}\right)\right]\geqslant 0. \tag{19}$$

It is clear from Eq. (19) that the E_{soliton}, while smaller than the energies of the other members of the writhing family, is always *greater* (by a *finite* amount) than the energy of the twisting line configuration satisfying the same conditions.

II. PLECTONEMIC TRANSITION

Thus we find that an extended solution that minimizes energy and has a specified Lk/L is *always* a twisted straight line. To check stability we perturb the straight-line solution $\theta(s)=0+\delta\theta(s)$. The perturbation calculation shows that the nontrivial zero-energy mode satisfies

$$\left[A\frac{d^2}{dt^2}-\left(F-\frac{p^2}{4A}\right)\right]\delta\theta(s)=0. \tag{20}$$

Thus, for $\mathrm{Lk}/L\leqslant\sqrt{AF}/\pi C$ the straight line $\theta=0$ is stable to small fluctuations (agreeing with [15]). What happens to the molecule when the Lk/L approaches the critical value? Our results strongly indicate that the molecule attempts to loop over and pass through itself to shed a unit of Lk/L and thus starts to form a plectonemic bubble. In this sense the twisted rod is in a metastable state. The plectoneme plays the role of the ''bounce'' [23,24] via which a system tunnels out of the false vacuum. Beyond the transition to local instability the plectonemes ought to proliferate. To explore this scenario we formulate a very simple model of the plectonemic transition of stretched twisted DNA and compare its predictions with recent beautiful experiments by Strick *et al.* [12].

A. Plectonemic transition model

The model is diagramed in Fig. 2. In the following all quantities are normalized by the length L, that is, Lk now refers to link per unit length, and similarly for twist and writhe. DNA researchers prefer to use $\sigma\equiv\Delta\mathrm{Lk}_{\text{tot}}/\mathrm{Lk}_0$ to measure topological properties of DNA. Here Lk_0 is the natural link of the unstressed DNA molecule; B-DNA has one right-handed twist every $h=3.4$ nm. We will follow this notation.

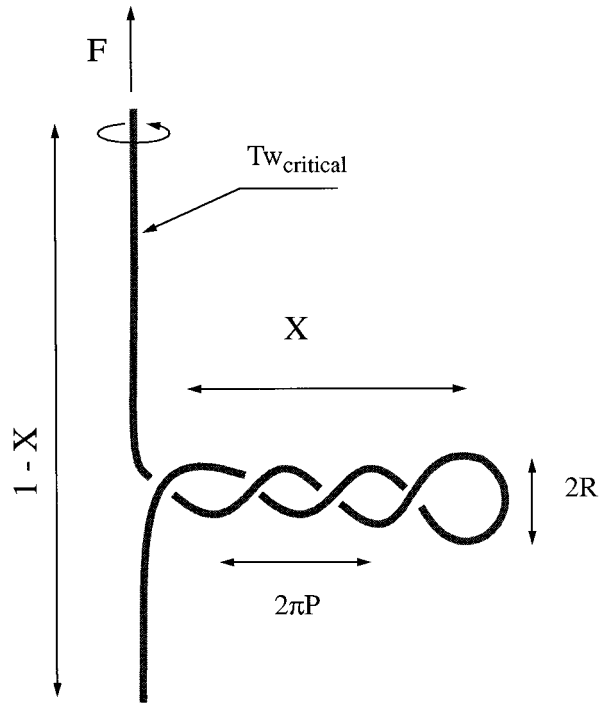

FIG. 2. Extended and plectonemic phase coexist in the molecule. The plectonemic phase takes up a portion X.

The molecule is constrained to have a total link $\mathrm{Lk}_{\text{tot}}=\sigma_{\text{tot}}/h$. The plectonemic fraction takes up X, leaving $1-X$ straight. The plectoneme has a radius R and a pitch P. The straight portion is twisted to its critical value $d\,\mathrm{Tw}=\sqrt{AF}/\pi C\equiv\sigma_l/h$. The actual twist is slightly below critical [16], but numerical results indicate that the precise value (which depends weakly on L) is adequately approximated by that of an infinite string [17]. Guided by ''twist conservation'' implied by Eqs. (12) we assign the same rate of $d\,\mathrm{Tw}$ to the plectoneme. The remaining link $\mathrm{Lk}_{\text{tot}}-(\mathrm{Tw}_{pl}+\mathrm{Lk}_{\text{l}})$ is absorbed by the plectoneme's Wr_{pl}. Let us give an account of the link distribution

$$\mathrm{Lk}_l=\mathrm{Tw}_k=\frac{\sigma_l}{h}X,$$

$$\mathrm{Lk}_{\text{pl}}=\mathrm{Lk}_{\text{tot}}-\mathrm{Lk}_l=\frac{\sigma_{\text{tot}}-\sigma_l}{h}+\frac{\sigma_l}{h}X=\mathrm{Wr}_{\text{pl}}+\mathrm{Tw}_{\text{pl}}. \tag{21}$$

Because the plectoneme has the same rate of twist as the line, we can read off its writhe from Eq. (21). At the same time the writhe of a plectoneme can be expressed as a function of P and R [18,19]. This gives us a constraint

$$\frac{\sigma_{\text{tot}}-\sigma_l}{h}=\mathrm{Wr}_{\text{pl}}=\frac{XP}{2\pi(R^2+P^2)}. \tag{22}$$

Up to now we have not considered any thermal effects or corrections. Our aim is to build a formalism of obtaining equilibrium zero-temperature solutions about which a thermodynamic theory can be obtained (e.g. by considering fluc-

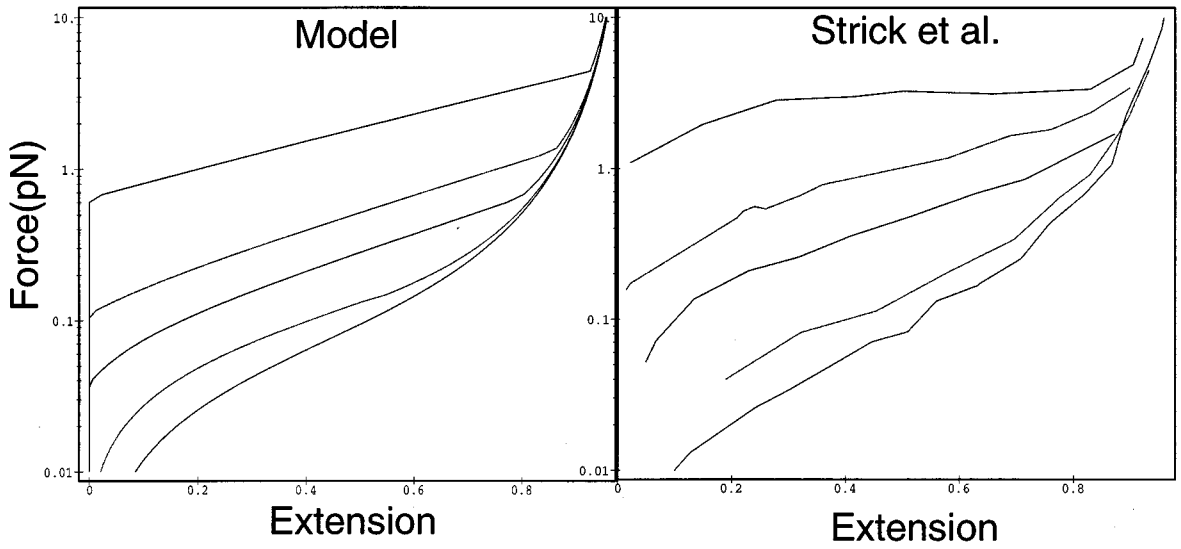

FIG. 3. Comparison of our predictions and the data of Strick *et al.* The families of curves are $\sigma=0.102,\ 0.043,\ 0.031,\ 0.001$, and 0 from top to bottom. The stretching of the untwisted ($\sigma=0$) line is purely entropic; the $\sigma=0.102$ transition is dominated by elastic energy. No attempts have been made to fit the data.

tuations) [10]. However, because the experiments we are examining contain a regime in which thermal effects play a significant role [12] we must consider them.

Marko and Siggia [18,10] have derived the free energy of a plectoneme in their examination of fluctuations about helical structures. To within order unity, constants

$$E_{\rm pl}=\frac{A}{2}\left(\frac{R}{(R^2+P^2)}\right)^2+\frac{C}{2}\left(\frac{2\pi\sigma_l}{h}\right)^2+[(R/r_0)^{-12}+(\pi P/r_0)^{-12}]/r_0+A^{-1/3}[R^{-2/3}+(\pi P)^{-2/3}]. \tag{23}$$

The first two terms in Eq. (23) are elastic contributions from the curvature and twist, respectively. The next line is the hard-core interaction ($r_0\simeq 1.75$ nm [20]). The last term is the entropic penalty incurred for winding too tightly [10]. (It is interesting to note that although we include the last term in our model, its value is *always negligible*.) Setting the plectonemic fraction X we use Eqs. (22) and (23) to minimize $E_{\rm pl}$ with respect to R and P.

Next let us determine the thermal behavior of the straight-line segment. Such behavior for the *untwisted* rod has been examined in some detail by Fixman and Kovak [21]. Equation (20) allows us to make use of their results provided we replace F with $F'\equiv F-p^2/4A$. Siggia and co-workers provided a valuable summary of their results in an approximate interpolation formula [22,10]. We employ the above substitution in the result of Siggia and co-workers to solve for the thermal shortening of the straight portion of the molecule. In the following, Z is the observed fractional extension [23,24]. That is, Z is the ratio of the *actual* linear extension of the straight-line segment to its backbone length

$$\frac{\left(F-\frac{p^2}{4A}\right)A}{k_bT}=[(1-Z/X)^{-2}-1)/4+Z/X. \tag{24}$$

In the final analysis we compute the optimum plectonemic fraction X and the extension Z for a given Lk and F. The results are plotted in Fig. 3 side by side with experimental results [12]. Because our model is a very simple one, and we have made no attempts to compute exact parameters (i.e., ''critical winding,'' etc.) we cannot claim perfect agreement. Nonetheless, the resemblance is striking. Our model shows the shift from purely thermal behavior for very small σ to a transition completely driven by elastic considerations for larger σ's and forces.

III. CONCLUSION

The primary limitation of the model investigated here is the absence of the restriction of excluded volume. Because of this, we are unable to characterize interwound configurations. However, calculations of the energetics of interwound DNA provide the basis for semiquantitative models of the plectonemic state. Work on this problem is ongoing.

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