Supercoiling and Denaturation of DNA Loops

T. B. Liverpool,[1,2,*] S. A. Harris,[3] and C. A. Laughton[4]

[1]*Department of Mathematics, University of Bristol, University Walk, Bristol BS8 1TW, United Kingdom*
[2]*Institut Curie Section Recherche (UMR 168), 11 rue P. et M. Curie, 75231 Paris Cedex 5, France*
[3]*Department of Physics and Astronomy, University of Leeds, Woodhouse Lane, Leeds LS2 9JT, United Kingdom*
[4]*School of Pharmacy, University of Nottingham, Nottingham NG7 2RD, United Kingdom*

(Received 1 August 2007; published 13 June 2008)

We study the statistical mechanics of small DNA loops emphasizing the competition between elasticity, supercoiling, and denaturation. Motivated by recent experiments and atomistic molecular dynamics simulation, we propose a new coarse-grained phenomenological model of DNA. We extend the classical elastic rod models to include the possibility of denaturation and nonlinear twist elasticity. Using this coarse-grained model, we obtain a phase diagram in terms of fractional overtwist and loop size that can be used to rationalize a number of experimental results which have also been confirmed by atomistic simulations.

DOI: 10.1103/PhysRevLett.100.238103 PACS numbers: 87.14.G−, 82.35.Pq, 87.15.A−, 87.15.La

Over the past decade and a half there has been intensive study of the mechanical properties of single molecules of DNA and their interactions [1–3]. DNA, however, is rarely in a simple linear configuration *in vivo*. Eukaryotic organisms compact their genetic material by wrapping the DNA around protein scaffolds to form nucleosomes which are then wound into a highly condensed solenoidal structure [4]. Bacteria store their genetic information as circular plasmids which are compacted by twisting the DNA into highly writhed superhelices. Variations in DNA topology and packing are known to be important in cell regulation [5]. Undertwisting and negative supercoiling (as opposed to overwinding and positive supercoiling) are thought to destabilize the duplex and promote processes which require strand separation, such as gene expression. In gene regulation, the mechanical behavior of looped DNA is also believed to play an important role by giving rise to long-range interactions between different regions of the genome [6].

Theoretical models of DNA mechanics generally fall into two classes. Molecular dynamic simulations have atomistic detail but are typically restricted to small DNA fragments [7]. Elastic rod models give (linear) coarse-grained descriptions which are valid for relatively small deformations and long sequences [8,9]. However, recent experiments have highlighted the need for descriptions which bridge these two extremes. An *in vivo* analysis of DNA looping in the lac operon repressor system found that the free energy of looping was far more sensitive to the interoperator distance than would be expected from simple continuum theories [10]. In a study of circle formation as a function of DNA length, Cloutier and Widom reported cyclization probabilities for circles containing between 89 and 105 base pairs (bp) that are greater than those expected from simple models of DNA bending [11,12], although the implications of these experiments remain controversial [13]. As well as anomalous bending rigidity, smaller circles also display a more complex asymmetric writhing behavior. Some time ago, Bates and Maxwell showed that gyrase is only able to introduce negative writhe into circles that contain more than 174 bp [14]. More recent studies of supercoiling in larger DNA circles (>300 bp) observed that underwinding by less than one helical turn induced negative writhing [15], yet it was necessary to underwind a 178 bp duplex by 2 helical turns in a high salt environment for negative writhing to occur [16].

Recent improvements in the parallel performance of molecular dynamics (MD) codes for modeling biomolecules have made it possible to simulate DNA circles as large as 178 base pairs in atomistic detail. In a recent molecular dynamics study using the AMBER force-field simulations of adenine-thymine (AT) and guanine-cytosine (GC)-rich DNA sequences for circles of between 90 and 178 base pairs in low and high salt conditions have been performed [17]. A distinct asymmetry in the behavior of overwound and underwound duplexes was observed. Although even the 90 base pair overwound circles will form writhed or supercoiled conformations in ambient salt, the formation of negative supercoils is prohibited except in high salt conditions and for circles larger than 148 base pairs. Furthermore, it was observed that underwinding induces local duplex melting at lower superhelical densities than overwinding. These calculations generated a map of the phase diagram describing the supercoiling of these small DNA circles in low and high salt conditions. The study of such *long* loops with atomistic detail is computationally difficult and expensive; however, they can suggest directions for how to construct more sophisticated coarse-grained models which encode more information about the DNA mechanics under large deformations. The subject of this Letter is the development of such a model.

We consider small loops of double-stranded DNA of length L. We model them as thin (radius $a \ll L$, the length) and possibly inhomogeneous nonlinear elastic objects. In addition we include a discrete degree of freedom associated with the maintenance of the structural coherence of the DNA which keeps track of the formation and breaking of the H bonds between the base pairs. We find that *nonlinearity* in the twist elasticity leads to supercoiling for underwound loops *only if* the loops are long or the ratio of bend to twist elasticity is small. This provides an elegant explanation of the experiments and MD results as it is well known that the bending elasticity of polyelectrolytes is strongly reduced by screening for high salt conditions [18] while the twist rigidity remains essentially unchanged [19]. Our results also show a *competition* between supercoiling and denaturation with supercoiling favored for longer loops and denaturation favored for small loops.

We can parametrize the filament by a right angle set of local axes: $(\hat{\mathbf{t}}(s) \equiv \hat{\mathbf{e}}_3(s), \hat{\mathbf{n}}(s) \equiv \hat{\mathbf{e}}_2(s), \hat{\mathbf{b}}(s) \equiv \hat{\mathbf{e}}_1(s))$. A good description of the system is a model with monomers with centers at position $\mathbf{r}(s)$ of size a which are labeled by the continuous index $0 \leq s \leq L$. We can without loss of generality choose the first of the axes as the local tangent vector of the filament $[\hat{\mathbf{t}}(s) = \partial_s \mathbf{r}(s)]$, where $\partial_s \mathbf{F}(s) = \frac{\partial \mathbf{F}}{\partial s}$ for any function $\mathbf{F}(s)$ of the variable s, choose the second as a perpendicular axis along the length of the filament $[\hat{\mathbf{n}}(s)]$, and the third defined by the cross product of the other two: $[\hat{\mathbf{b}}(s) = \hat{\mathbf{t}}(s) \times \hat{\mathbf{n}}(s)]$.

We can describe an arbitrary filament conformation by the following local (at s) infinitesimal linear transformation [9], $\partial_s \hat{\mathbf{e}}_i = \epsilon_{ijk} \Omega_j(s) \hat{\mathbf{e}}_k(s)$, where ϵ_{ijk} is the permutation symbol. Therefore the set of functions $\Omega_1(s)$, $\Omega_2(s)$ (bend) and $\Omega_3(s)$ (twist) define any conformation of the chain.

We also introduce the function $\sigma(s) = \pm 1$ which measures the structural stability of the DNA double helix. $\sigma(s) = -1$ corresponds to H bonds being present at point s and the normal double-stranded form is stable while $\sigma(s) = +1$ corresponds to denaturation or the helix falling apart. In the absence of bend and twist, there is an energy penalty (in units of $k_B T$) per unit length $k_B T h(s)$ to locally destroy the helical structure (break the H bonds) at point s—a homopolymer, e.g., poly-AT would have constant $h(s) = h_{\mathrm{AT}}$. It is clear then that the sequence information is encoded in $h(s)$. We include also the possibility of a cooperative long-range coupling $J(s)$ between structure variables (spins).

Given this we can write down a phenomenological Hamiltonian for a loop of length L as $\mathcal{H} = \mathcal{H}_d + \mathcal{H}_{el}$, where

$$\beta \mathcal{H}_d = \int_0^L ds h(s) \sigma(s) + \int_0^L ds \int_0^L ds' J(s - s') \sigma(s) \sigma(s') \qquad (1)$$

$$\beta \mathcal{H}_{el} = \frac{1}{2} \int_0^L ds (1 - \gamma \sigma(s)) [A_1 \Omega_1^2(s) + A_2 \Omega_2^2(s) + K(\Omega_3(s) - \omega_0)^2 + P(\Omega_3(s) - \omega_0)^3], \qquad (2)$$

where ω_0 is the frequency of the helix determining the ground state structure and A_1, A_2 are the two bending persistence lengths (reflecting the possibility of a soft, e.g., the position of the major or minor groove, and hard direction of bending for the filament) and K is the twist persistence length. The ground state is a *straight* rod about whose axis the pair of vectors $\hat{\mathbf{b}}(s)$, $\hat{\mathbf{n}}(s)$ rotate with frequency ω_0. We shall be concerned in this Letter with strongly overwound and underwound loops requiring that we take account of nonlinear effects in the twist elasticity described by the parameter P which has dimension of $[\text{length}]^2$. Such conformations, however, have gentle bends adequately described by linear bending elasticity. When the structural (spin) state changes from -1 to $+1$ this leads to a softening of the chain ($\gamma \leq 1$) and a lower resistance to deformation.

In this Letter, we consider the homopolymer case where $J = 0$ and $h(s) = h$, constant. We will also be mainly concerned with isotropic bending $A_1 = A_2$. As we are interested in supercoiling and denaturation, we start from a reference state of $\sigma(s) = -1$, $\forall\ s$ and a circular loop. Conformations of the loop must satisfy the linking number constraint (White's theorem) $\mathrm{Lk} = \mathrm{Tw} + \mathrm{Wr} = \text{fixed}$, where the twist, $\mathrm{Tw} = \frac{1}{2\pi} \int_0^L ds \Omega_3(s)$. For conformations close to a planar circle, we can use Fuller's formula [20] to express the writhe, Wr, as an expansion about a reference curve with tangent vector $\hat{\mathbf{t}}_0(s)$, in our case a planar circle ($\mathrm{Wr}_0 = 0$) as $\mathrm{Wr} = \mathrm{Wr}_0 + \frac{1}{2\pi} \int_0^L ds \frac{\hat{\mathbf{t}}_0 \times \hat{\mathbf{t}} \cdot \partial_s (\hat{\mathbf{t}} + \hat{\mathbf{t}}_0)}{1 + \hat{\mathbf{t}}_0 \cdot \hat{\mathbf{t}}}$. The statistical mechanics and hence all the thermodynamic quantities of this model are obtained by evaluating the partition function, $Z = \sum_{\text{states}} e^{-\beta \mathcal{H}}$, with Lk fixed.

The study of the supercoiling transition requires analysis of the minimum energy conformation of the loop while denaturation requires the study of the statistical mechanics of base-pair formation and breakage. If the loop is prepared in an arbitrary initial state, the longest time scale in the system is the relaxation time of the conformations of the loop [17]. On time scales longer than this, the mean conformation of the loop has relaxed to its steady-state value and we can consider the loop conformation to be a static quenched variable in the statistical mechanics of denaturation. In addition, by the time the system has relaxed to the ground state, the denaturation fluctuations will also have attained their equilibrium values (i.e., the average values of the spin variable can be used to calculate the loop ground state).

Linear stability analysis is sufficient for obtaining a criterion for supercoiling. The nature of conformations deep in the supercoiling regime require a full nonlinear analysis which we will not address here. The center line can therefore be written without loss of generality as an expansion, $\mathbf{r}(s) = \mathbf{r}_0(s) + \delta \mathbf{r}(s)$, about a planar circle in the x-y plane centered at the origin with $\mathbf{r}_0(s) = \frac{1}{\alpha}(\cos\alpha s, \sin\alpha s, 0)$ where $\alpha = 2\pi/L$. Since the ground state is a straight linear chain, any loop even a planar circle, has nonzero bending energy. The deviations from the planar circle can be written as $\delta \mathbf{r}(s) = r_{\parallel}(s) \hat{\mathbf{t}}_0(s) + r_{\perp}(s) \hat{\mathbf{n}}_0(s) + r_z(s) \hat{\mathbf{z}}$ where $\hat{\mathbf{t}}_0 = \partial_s \mathbf{r}_0 = (-\sin\alpha s, \cos\alpha s, 0)$, $\hat{\mathbf{n}}_0 = (\cos\alpha s, \sin\alpha s, 0)$, $\hat{\mathbf{z}} = (0, 0, 1)$ such that $\hat{\mathbf{n}}_0 \cdot \hat{\mathbf{t}}_0 = \hat{\mathbf{n}}_0 \cdot \hat{\mathbf{z}} = \hat{\mathbf{z}} \cdot \hat{\mathbf{t}}_0 = 0$. For an inextensible filament, $|\partial_s \mathbf{r}|^2 = 1$, and for small deviations from a planar circle it is straightforward to show that $\partial_s r_\parallel + \alpha r_\perp \ll \partial_s r_\perp - \alpha r_\parallel$ and $\partial_s r_\parallel + \alpha r_\perp \ll \partial_s r_z$. We can therefore express the Hamiltonian and constraints completely in terms of $\theta(s) = \partial_s r_\perp - \alpha r_\parallel$ and $\phi(s) = \partial_s r_z$ and the twist angle $\Omega_3(s)$, where $\theta(\phi)$ measure the *angular* deviations of the conformations from the circle in plane (out of plane), respectively. We keep terms up to quadratic order in θ, ϕ. For a loop with no added twist, $2\pi \mathrm{Lk}_0 = \omega_0 L$, while for a twisted loop we can write $2\pi \mathrm{Lk} = \Omega_3^0 L = (\omega_0 + \bar{\omega}_3)L$ where we have defined $\Omega_3^0 = \frac{2\pi}{L}\mathrm{Lk}$ and $\bar{\omega}_3 = \frac{2\pi}{L}\mathrm{Lk} - \omega_0$. The fractional overtwist or undertwist is given as $\frac{\bar{\omega}_3}{\omega_0} = \frac{\mathrm{Lk}-\mathrm{Lk}_0}{\mathrm{Lk}_0}$. For a planar loop, all the elastic energy of overtwist is stored in twist and $\Omega_3 = \Omega_3^0$ while deviations imply a nonplanar loop of finite writhe $\Omega_3(s) = \Omega_3^0 + \delta\Omega_3(s)$; i.e., $\delta\Omega_3 \neq 0$ implies nonzero writhe. We find

$$\beta \mathcal{H}_{el} = \frac{1}{2}\oint ds(1-\gamma\sigma)\{A[(\partial_s\theta - \alpha)^2 + (\partial_s\phi)^2 - \alpha^2\phi^2] + K[\bar{\omega}_3 + \delta\Omega_3]^2 + P[\bar{\omega}_3 + \delta\Omega_3]^3\} \tag{3}$$

$$\mathrm{Wr} - \mathrm{Wr}_0 = \frac{1}{2\pi}\oint ds\phi(s)(\alpha - \partial_s\theta). \tag{4}$$

We now consider the loop as $\bar{\omega}_3/\omega_0$ is increased from 0 and plot a phase diagram as a function of fractional overtwist (undertwist) $\bar{\omega}_3/\omega_0$ (also known as specific linking difference or superhelical density [5]) and loop length L. We identify the following "phases," undeformed circle (C), denatured (D), supercoiled ($S+, S-$), supercoiled and denatured ($SD+, SD-$) where ± refers to positive or negative supercoiling.

Denaturation: ($C \rightarrow D$) *transition.*—We have a planar loop with an elastic energy given by $\beta E_{el} = \varepsilon(\bar{\omega}_3, L) \times \oint ds(1-\gamma\sigma)$, where $\varepsilon(\bar{\omega}, L) = \frac{1}{2}[A\alpha^2 + K\bar{\omega}^2 + P\bar{\omega}^3]$ and a partition function $Z = e^{L\varepsilon}(e^{-1+\gamma\varepsilon/h} + e^{1-\gamma\varepsilon/h})^{Lh}$ and mean value of σ as a function of overtwist or undertwist (and loop size L) given by $\langle\sigma(\bar{\omega}_3, L)\rangle = \tanh(\gamma\varepsilon(\bar{\omega}_3, L) - h)$ [21]. We define denaturation transition as the value $\bar{\omega}_3^{\mathrm{den}}$ of $\bar{\omega}_3$ for which $\langle\sigma\rangle = 0$; i.e., there are equal numbers of paired bases as nonpaired bases, which satisfies the equation

$$\varepsilon(\bar{\omega}_3^{\mathrm{den}}(L), L) = h/\gamma, \tag{5}$$

plotted in blue on the phase diagrams (Fig. 1).

Supercoiling: ($C \rightarrow S$) *transition.*—To obtain a criterion for supercoiling we must calculate the equilibrium shape of the loop with the mean value of σ given above. This is obtained by minimizing the energy with respect to the functions $\theta(s)$, $\phi(s)$, $\delta\Omega_3(s)$ with the constraint, $\frac{1}{2\pi} \times \oint ds\delta\Omega_3(s) + \mathrm{Wr} = 0$. This leads to the coupled set of differential equations,

$$\bar{A}\partial_s^2\theta - \lambda\partial_s\phi = 0 \tag{6}$$

$$\bar{A}\partial_s^2\phi + \bar{A}\alpha^2\phi + \lambda\partial_s\theta = 0 \tag{7}$$

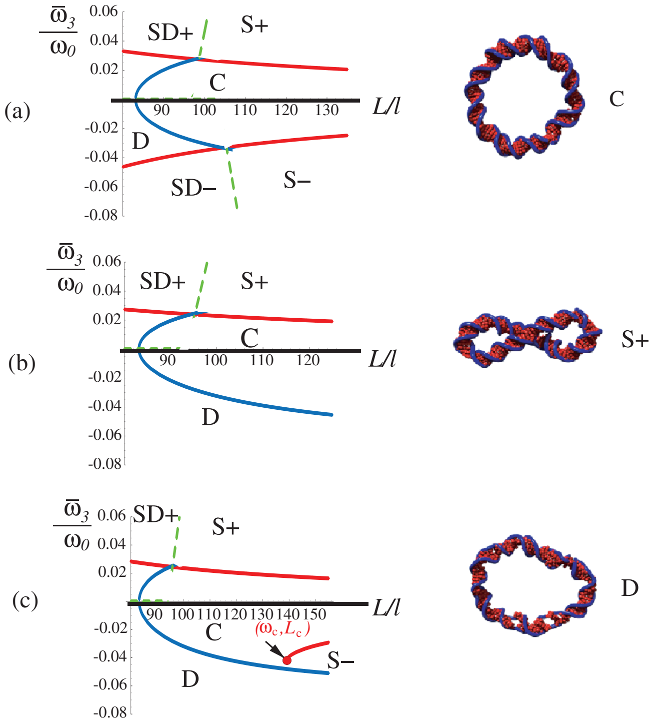

FIG. 1 (color). Phase diagrams for $A/K = 1/2$ and $\gamma = 0.7$ with lengths measured in units of $\ell = 1/h$ (we have used $A = 250\ell$) for (a) $P/(K\ell) = 1.5$, (b) $P/(K\ell) = 10$, with no negative supercoiled phase at these loop sizes, and (c) $P/(K\ell) = \frac{17}{2}$, showing the appearance of the negatively supercoiled phase. Inset: Typical configurations from MD simulations of all atom 90 bp homonucleotide DNA loop in circle, supercoiled, and denatured states.

$$\bar{K}(\bar{\omega}_3 + \delta\Omega_3) + \tfrac{3}{2}\bar{P}(\bar{\omega}_3 + \delta\Omega_3)^2 + \lambda = 0 \tag{8}$$

where λ is the Lagrange multiplier which enforces the linking number constraint and $\bar{A} = A(1 + \gamma\langle\sigma(\bar{\omega}_3, L)\rangle)$ with similar definitions for $\bar{K}, \bar{P}$. The functions θ, ϕ are periodic with $\theta(L) = \theta(0)$, $\phi(L) = \phi(0)$. Searching for solutions of the form $B_1\cos(n\alpha s) + B_2\sin(n\alpha s)$, where $n > 0$ is an integer, we obtain $\lambda(n) = \pm\bar{A}(n^2-1)^{1/2}\alpha$, $\theta(n, s) = \theta_0\sin(n\alpha s)$, and $\phi(n, s) = \theta_0\frac{n}{(n^2-1)^{1/2}}\cos(n\alpha s)$, where the sign of λ depends on the sign of $\bar{\omega}_3$. The value of the constant θ_0 is set by making sure the solutions $\theta(n, s)$, $\phi(n, s)$ satisfy the linking number constraint. The lowest value of n which gives a nonzero λ is $n = 2$. The supercoiling transition is obtained by using Eq. (8) to find the value of $\bar{\omega}_3^{\mathrm{sup}}$ for which a solution with $\delta\Omega_3 \neq 0$ exists (instability).

Let us first consider the case for purely symmetric linear twist elasticity: If $P = 0$, then $\delta\Omega_3 = -\lambda - \bar{K}\bar{\omega}_3$. In the planar unsupercoiled state $\lambda = -\bar{K}\bar{\omega}_3$ so the transition to the supercoiled state occurs when $-\bar{K}\bar{\omega}_3 = \lambda(n) = \pm\bar{A}(n^2-1)^{1/2}\alpha$. If $\delta\Omega_3 \neq 0$, then for an overtwisted loop $\delta\Omega_3 < 0$ and for an undertwisted loop $\delta\Omega_3 > 0$. Therefore, if $\bar{\omega}_3 > 0$, $\lambda(n) < 0$ and if $\bar{\omega}_3 < 0$, $\lambda(n) > 0$. The well-known supercoiling criterion is therefore set by

$|\bar{\omega}_3^{\rm sup}(L)| = \frac{\bar{A}}{\bar{K}}\alpha\sqrt{n^2-1}$ $(n = 2)$, i.e., at the same magnitude for overtwisted and undertwisted loops [22,23].

However, once we take into account the nonlinear elasticity, i.e., $P \neq 0$, we observe quite different behavior. Similar considerations obtain the supercoiling transition (red curves on the phase diagrams in Fig. 1) as given by $(n = 2)$

$$\bar{\omega}_3^{\rm sup}(L) = \begin{cases} -\frac{\bar{K}}{3\bar{P}}[1 - \sqrt{1 + (\frac{6\bar{P}}{\bar{K}})\Lambda}], & \bar{\omega}_3 > 0 \\ -\frac{\bar{K}}{3\bar{P}}[1 - \sqrt{1 - (\frac{6\bar{P}}{\bar{K}})\Lambda}], & \bar{\omega}_3 < 0, \end{cases} \tag{9}$$

where $\Lambda(L) = \frac{\alpha\bar{A}}{\bar{K}}\sqrt{n^2-1} = \frac{\alpha\bar{A}}{\bar{K}}\sqrt{3}$. Implementing the linking number constraint leads to $\theta_0^2 = \pm\frac{2\sqrt{n^2-1}}{Ln^2\alpha}\delta\Omega_3$. We note that the asymmetry is negligible if $\bar{P} \ll LA$, i.e., that the nonlinear twist elasticity is most important for small loops.

The magnitude of the supercoiling transition is different for overtwisted and undertwisted loops. Furthermore the supercoiling transition *vanishes* for undertwisted loops if $6\bar{P}\Lambda/\bar{K} > 1$. This indicates that corrections due to higher order nonlinearities must be included. Note however that their inclusion leads to a supercoiling transition at much higher values of excess linking number. This can be translated into a condition on the length of the loops and the relative values of the elastic constants. There is a negative supercoiled state only if $L > L_c$ where $L_c = 12\pi\sqrt{3}(\frac{\bar{P}}{\bar{K}})(\frac{\bar{A}}{\bar{K}})$. The supercoiling transition at L_c is $\bar{\omega}_3/\omega_0 = -\frac{\bar{K}}{3\bar{P}\omega_0} \equiv \omega_c$.

($S \longrightarrow SD$) *transition.*—Once the loop is in a supercoiled state the value of $\langle\sigma\rangle$ will change due the additional bending contribution to the elastic energy. At values of $\bar{\omega}_3$ beyond $\bar{\omega}_3^{\rm sup}(L)$ (but still close to the transition so that linear theory works), for which $\delta\Omega_3 = \bar{\omega}_3^{\rm sup}(L) - \bar{\omega}_3$, from Eq. (3) we obtain an expression for the elastic energy $E_{el} = \varepsilon'(\bar{\omega}_3, L)\oint ds(1 - \gamma\sigma)$, where $\varepsilon'(\bar{\omega}, L) = \frac{1}{2} \times \{A\alpha^2[1 + \frac{2\sqrt{3}}{\pi}|\bar{\omega} - \bar{\omega}_3^{\rm sup}|] + K(\bar{\omega}_3^{\rm sup})^2 + P(\bar{\omega}_3^{\rm sup})^3\}$. The partition function can be evaluated as above and the transition from $S \longrightarrow SD$ occurs at $\bar{\omega}_3^{S\rightarrow SD}(L)$ defined by $\varepsilon'(\bar{\omega}_3^{S\rightarrow SD}(L), L) = h/\gamma$ which is plotted as a green dashed line in Fig. 1.

($D \longrightarrow SD$) *transition.*—In the denatured state, as we increase the amount of overtwist, we eventually encounter a supercoiling transition whose properties have been described above which is controlled by the renormalized elastic constants $\bar{A}, \bar{K}, \bar{P}$.

In summary, we have introduced a new model for DNA mechanics which extends linear elastic models of bend and twist to include denaturation and emphasized the role of nonlinear twist elasticity. We applied it to the description of loops of DNA and find, in particular, that nonlinear twist elasticity leads to supercoiling for underwound loops only if the loops are long or the ratio of bend to twist elasticity is small. We also find a competition between supercoiling and denaturation with supercoiling favored for longer loops and denaturation favored for small loops. Variants of the model can be used as the basis of computational studies of longer DNA segments, beyond the scope of current atomistic simulations which become prohibitively computationally expensive for DNA segments longer than 200 base pairs.

T. B. L. acknowledges the support of the Royal Society and the EPSRC under Grant No. EP/E065678/1. T. B. L. acknowledges the hospitality of the Aspen Center for Physics and the ICTP, Trieste where some of this work was done.

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[*] t.liverpool@bristol.ac.uk

[1] S. B. Smith, L. Finzi, and C. Bustamante, Science **258**, 1122 (1992).

[2] T. R. Strick, J. F. Allemand, D. Bensimon, A. Bensimon, and V. Croquette, Science **271**, 1835 (1996).

[3] P. Cluzel, A. Lebrun, C. Heller, R. Lavery, J.-L. Viovy, D. Chatenay, and F. Caron, Science **271**, 792 (1996).

[4] B. Alberts *et al.*, *Molecular Biology of the Cell* (Garland, New York, 2002).

[5] A. D. Bates and A. Maxwell, *DNA Topology* (Oxford University Press, Oxford, 2006).

[6] A. Balaeff, L. Mahadevan, and K. Schulten, Phys. Rev. Lett. **83**, 4900 (1999).

[7] A. Lebrun and R. Lavery, Nucleic Acids Res. **24**, 2260 (1996).

[8] J. F. Marko and E. D. Siggia, Macromolecules **28**, 8759 (1995).

[9] C. Bouchiat and M. Mézard, Eur. Phys. J. E **2**, 377 (2000); T. B. Liverpool and S. F. Edwards, J. Chem. Phys. **103**, 6716 (1995).

[10] L. Saiz, J. M. Rubi, and J. M. G. Vilar, Proc. Natl. Acad. Sci. U.S.A. **102**, 17642 (2005).

[11] T. E. Cloutier and J. Widom, Proc. Natl. Acad. Sci. U.S.A. **102**, 3645 (2005).

[12] Y. Seol, J. Li, P. Nelson, T. T. Perkins, and M. D. Betterton Biophys. J. **93**, 4360 (2007).

[13] Q. Du, C. Smith, N. Shiffeldrim, M. Vologodskaia, and A. Vologodskii, Proc. Natl. Acad. Sci. U.S.A. **102**, 5397 (2005).

[14] A. D. Bates and A. Maxwell, EMBO J. **8**, 1861 (1989).

[15] J. M. Fogg, N. Kolmakova, I. Rees, S. Magonov, H. Hansma, J. J. Perona, and E. L. Zechiedrich, J. Phys. Condens. Matter **18**, S145 (2006).

[16] J. Bednar, P. Furrer, A. Stasiak, J. Dubochet, E. H. Egelman, and A. D. Bates, J. Mol. Biol. **235**, 825 (1994).

[17] S. A. Harris, C. A. Laughton, and T. B. Liverpool, Nucleic Acids Res. **36**, 21 (2008).

[18] T. Odijk, J. Polym. Sci. B **15**, 477 (1977); J. Skolnick and M. Fixman, Macromolecules **10**, 944 (1977).

[19] F. Mohammad-Rafiee and R. Golestanian, Phys. Rev. E **69**, 061919 (2004).

[20] F. B. Fuller, Proc. Natl. Acad. Sci. U.S.A. **68**, 815 (1971).

[21] Anisotropic rigidity, $A_1 \neq A_2$, leads to an oscillatory variation in denaturation reflecting the periodicity of the DNA helix, $\langle\sigma(s)\rangle = \tanh(\gamma\epsilon(s) - h)$ where $\epsilon(s) = \frac{\alpha^2}{4} \times (A_1 + A_2)\alpha^2 + \frac{K}{2}\bar{\omega}^2 + \frac{P}{2}\bar{\omega}^3 + \frac{\alpha^2}{4}(A_2 - A_1)\cos(2\omega_0 s)$.

[22] E. Guitter and S. Leibler, Europhys. Lett. **17**, 643 (1992).

[23] C. J. Benham, Phys. Rev. A **39**, 2582 (1989).