Mechanical Response of Plectonemic DNA: An Analytical Solution

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ABSTRACT: We consider an elastic rod model for twisted DNA in the plectonemic regime. The molecule is treated as an impenetrable tube with an effective, adjustable radius. The model is solved analytically, and we derive formulas for the contact pressure, twisting moment, and geometrical parameters of the supercoiled region. We apply our model to magnetic tweezer experiments of a DNA molecule subjected to a tensile force and a torque and extract mechanical and geometrical quantities from the linear part of the experimental response curve. These reconstructed values are derived in a self-contained manner and are found to be consistent with those available in the literature.

1. Introduction

Mechanical properties of the DNA molecule play an important role in the biological processes involved in the cell, yet we only have an imprecise view of these properties. Advances in nanotechnologies make it possible to exert forces onto isolated DNA filaments: mechanical response of the molecule is now widely studied. Single molecule experiments provide a powerful way to investigate the behavior of DNA subjected to mechanical stress. In such experiments, the molecule is held by optical or magnetic tweezers and forces and torques are applied to it.[8,28] The interaction between DNA and proteins is actively investigated; for instance, the chemical and mechanical action of an enzyme on a molecule can be inferred from the global deformation of the molecule.[24]

In this paper we focus on a specific type of experiments: a double-stranded DNA molecule is fixed by one end to a glass surface while the other end is attached to a magnetic bead; using a magnet, a pulling force and a torque are applied on the DNA filament.[30] Large ranges of pulling forces, from 1/10 to 100 pN, and the number of turns can be explored in the experiments, and the molecule displays a variety of behaviors and conformations.[1,7,27] We study the response of the molecule to moderate forces, below 10 pN, and moderate to large number of turns, equivalent to a positive supercoiling ratio of the order of 0.1. In experiments, the pulling force is kept constant while the bead is rotated gradually. The vertical extension of the molecule is recorded and plotted as a function of the number of turns. Experimental rotation−extension curves have a characteristic shape and are called *hat curves*.[5,29] At zero number of turns these curves exhibit a maximum, the value of which is explained by the wormlike chain (WLC) model,[18] and its variants. For a small number of turns the vertical extension decreases and the curve takes a rounded shape. Above a threshold value of the number of turns, the extension of the molecule decreases linearly. This linear part of the curve is obtained when the molecule wraps around itself in a helical way, giving rise to a structure comprising plectonemes. The plectonemic structure is made of two interwound helical filaments whose geometry is characterized by the so-called superhelical angle and radius; note that each of these filaments is itself made of a double-stranded DNA molecule. The superhelical angle and the twisting moment in the filaments are key parameters that control the action of topoisomerases,[12] RNA polymerase,[23] or other enzymes[32] on DNA. The distance of the self-approach of DNA in supercoiled regime has been the subject of a number of studies.[3,9,25,26] In previous analytical and numerical work, the double-stranded DNA molecule has been modeled as a twist-storing elastic filament. These approaches have been successful at reproducing the response of DNA to moderate torque,[4,19] given by the central region of the experimental curves. The analysis of the linear regions of these curves, based on a detailed model of plectonemes, was lacking until recently: in ref 17 a composite model based on an empirical free energy of supercoiled DNA is proposed.

Here we present an elastic rod model for helical supercoiling of the DNA molecule, which is relevant to large number of turns. Our model is self-contained and provides a mechanically accurate description of elastic filaments in contact. The molecule is divided in two domains: one where the configuration is a wormlike chain, dominated by thermal fluctuations, and the other one, a superhelical region dominated by elasticity, where the molecule contacts itself. Several plectonemic regions may lie at various places of the molecule, but as this does not change the mechanical response of the system, we refer to these regions as if they were in one piece. We deal with self-contact by introducing an effective superhelical radius (distinct from the crystallographic radius of 1 nm, from the size of the Manning condensate and from the Debye length, although in the same range of values), which varies with external loads and salinity of the solution. The effective radius is defined as the radius of a chargeless, impenetrable, and elastic tube having the same mechanical response as the molecule. This radius is not given as a parameter of the model and is extracted from experimental data. Using an energy approach, we relate geometrical variables (superhelical radius and angle) to applied force and torque. We also characterize the response of the molecule in the plectonemic regime, extend former numerical results,[20] and show how geometrical and mechanical parameters can be extracted from experimental data.

2. Model

The present model investigates the equilibrium behavior of an elastic rod with bending rigidity K_0 (the bending persistence length is $A = K_0/(kT)$, where k is the Boltzmann constant and T the absolute temperature) and twisting rigidity K_3 under traction and torsion, as shown in Figure 1. This is a coarse-grained model for DNA where base-pair details are neglected. For instance, the anisotropic flexibility of the molecule, originating from base pairing and major−minor groove geometry, is smoothed out at a scale of several base pairs: a highly twisted anisotropic rod can be replaced by an equivalent isotropic rod with effective bending rigidity.[11]

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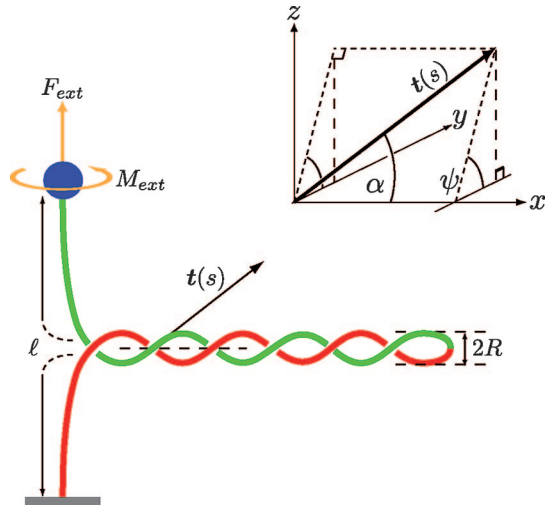

Figure 1. Sketch of the magnetic tweezers experiment. A B-DNA molecule of total contour length l is fixed in $s = 0$ to a glass surface while the other end in $s = l$ is attached to a magnetic bead. A pulling force F_{ext} and a torque M_{ext} are applied at the upper end by using a magnet. The superhelical angle and radius are denoted α and R, respectively. The zenith angle α and the azimuth angle ψ of the tangent vector with regard to the superhelical axis $\mathbf{e_x}$ are also shown.

Geometry. We start with a geometric description of the rod configurations relevant to the plectonemic regime. This defines a reduced set of configurations (Ansatz), over which we shall minimize the elastic strain energy associated with deformations. The rod, of length l, is considered inextensible and has circular cross section; let s denote the arc length along the rod. The strain energy involves, at lowest order, the geometric curvature $\kappa(s)$ of the centerline of the rod as well as the twist $\tau(s)$. We emphasize that the twist $\tau(s)$ is different from the geometrical (Frénet−Serret) torsion of the centerline as it takes into account the rotation of material cross sections around the centerline. It allows one to distinguish between twisted and untwisted configurations of the rod having the same centerline. The rod centerline is parametrized by $\mathbf{r}(s)$, and its unit tangent $\mathbf{t} \equiv \mathrm{d}\mathbf{r}/\mathrm{d}s$ can be described with spherical angles, as shown in Figure 1: $\alpha(s)$ is the zenith angle, and $\psi(s)$ the azimuth angle with respect to the direction $\mathbf{e_x}$ along the common axis of the two superhelices in the plectonemic region.

We consider the following configurations, relevant to a large applied number of turns, n. The tails are assumed to be straight but twisted. (Thermal fluctuations will be accounted for by using the rescaled tail length predicted by WLC theory.) The plectonemes are described by two identical and uniform helices where, again, each of these helices is itself a double-stranded DNA molecule. Both the end loop of the plectonemes and the matching region between the tails and the plectonemic part are neglected. Consequently, the rod comprises two phases: one made up of straight and twisted tails and the other one of plectonemic structures. The plectonemic phase is not necessarily made of a single component, but for the sake of simplicity, we discuss the case of a single plectonemic structure (our results are still valid if the plectonemes are split into several components).

In the tails the rod is straight and aligned with the $\mathbf{e_z}$ axis: $\mathbf{t} = \mathbf{e_z}$. The geometric curvature $\kappa \equiv |\mathrm{d}\mathbf{t}/\mathrm{d}s|$ is zero, $\kappa(s) = 0$.

In each filament of the plectonemes, the position vector $\mathbf{r}(s)$ and the tangent vector $\mathbf{t}(s)$ describe a superhelix of axis $\mathbf{e_x}$:

$$\begin{aligned} r_x(s) &= s\cos\alpha & t_x(s) &= \cos\alpha \\ r_y(s) &= \chi R\sin\psi(s) & t_y(s) &= \sin\alpha\cos\psi(s) \\ r_z(s) &= -\chi R\cos\psi(s) & t_z(s) &= \sin\alpha\sin\psi(s) \end{aligned} \qquad (1)$$

The other filament of the plectonemes is obtained by a rotation of 180° around the axis $\mathbf{e_x}$. Here $\chi = \pm 1$ stands for the chirality of the two helices, and R and α denote the superhelical radius and angle, respectively. In eq 1, the condition $\mathrm{d}\mathbf{r}/\mathrm{d}s = \mathbf{t}$ yields $\mathrm{d}\psi/\mathrm{d}s = \chi\sin\alpha/R$. The curvature in the plectonemes is $\kappa(s) \equiv |\mathrm{d}\mathbf{t}/\mathrm{d}s| = (\sin^2\alpha)/R$.

Noting l_p the contour length spent in the plectonemes, we obtain the following expression for the integral of the squared curvature over the whole length of the rod:

$$\int_0^l \kappa^2\,\mathrm{d}s = \frac{\sin^4\alpha}{R^2} l_p \qquad (2)$$

The end torque twists the filament. For a rod with circular cross section, the twist $\tau(s)$ at equilibrium is uniform,[2] $\mathrm{d}\tau/\mathrm{d}s = 0$ for all s. As a result, the equilibrium configuration of the rod is fully specified by the centerline, through the variables α, R, and l_p, and an additional scalar τ describing twist.

The twist τ is geometrically related to the number of turns imposed on the magnetic bead, n, which is equal to the link of the DNA molecule, $n = \mathrm{Lk}$. In the present case the link reads[20]

$$\mathrm{Lk} = \mathrm{Tw} + \mathrm{Wr} = \frac{1}{2\pi}\int_0^l \tau\,\mathrm{d}s - \chi\frac{\sin 2\alpha}{4\pi R} l_p = \frac{1}{2\pi}\left(\tau l - \chi\frac{\sin 2\alpha}{2R} l_p\right) \qquad (3)$$

as we neglect the writhe of the tails.

Energy Formulation. Using the above notations, the rod is described by four variables: α the superhelical angle, R the superhelical radius, τ the twist, and l_p the contour length spent in the plectonemes. We proceed to derive the total energy of the system as a function of these four variables. It is the sum of three terms, $V = V_{el} + V_{ext} + V_{int}$, where the first term is the strain elastic energy, the second is the potential energy associated with the external loads F_{ext} and M_{ext}, and the third accounts for interaction of the filaments in the plectonemes. The strain elastic energy for the rod of total contour length l is

$$V_{el} = \frac{K_0}{2}\int_0^l \kappa^2\,\mathrm{d}s + \frac{K_3}{2}\int_0^l \tau^2\,\mathrm{d}s \qquad (4)$$

We do not take into account the reduction of the effective torsional rigidity in the tails due to fluctuations.[19] The potential energy is given by

$$V_{ext} = -F_{ext}(z(l) - z(0)) - 2\pi M_{ext} n \qquad (5)$$

where $z(l) - z(0) = l - l_p$ for straight tails and $n = \mathrm{Lk}$.

If the DNA−DNA interaction was clearly established, we would include the corresponding interaction energy V_{int} in the total energy V.[10] This is not the case, and we model the filaments in electrostatic interaction as effective chargeless hard-core tubes. The effective radius a of these tubes accounts for a variety of physical mechanisms, including for example the presence of counterions or thermal fluctuations in the plectonemes, which we do not attempt to model. As in refs 25 and 33, we do not try to predict the actual radius a but simply follow its variation under changing experimental conditions (applied load, salinity, etc.). Doing so, we replace the actual (unknown) interaction potential $V_{int}(R,\alpha)$ by a hard-core interaction with adjustable radius a and optimize a to best fit a given experiment. In section 3 we show how a can be extracted from experimental measurements.

The parameter a must certainly be larger than the crystallographic DNA radius 1 nm. It is different from the radius of the Manning condensate[14−16] since approximately a quarter of

the charge remains outside of the Manning condensate. The equilibrium is the solution of a constrained minimization problem for the elastic energy, subjected to the impenetrability condition

$$R \geq a \tag{6}$$

We anticipate on the fact that there is contact, $R = a$, for typical experimental conditions. Consequently, we replace the actual interaction energy with a constraint term:

$$V_{\text{int}} = -\lambda(R - a) \tag{7}$$

where λ is a Lagrange multiplier. Note that this term is not a regular energy but comes from the constraint: the multiplier λ has to be set at the end of the procedure and chosen in such a way that the constraint $R = a$ is satisfied.

Combining eqs 2–7, we write the total potential energy of the system as

$$V(\alpha, R, \tau, l_p) = \frac{K_0}{2}\frac{\sin^4\alpha}{R^2}l_p + \frac{K_3}{2}\tau^2 l - F_{\text{ext}}(l - l_p) - M_{\text{ext}}\left(\tau l - \chi\frac{\sin 2\alpha}{2R}l_p\right) - \lambda(R - a) \tag{8}$$

In ref 13 a similar energy function has been introduced, but the rest of analysis differs from ours. Indeed, their approach focuses on statistical mechanics, and the analysis of the state of lowest energy is overlooked. Moreover, the parameter a is fixed a priori to the crystallographic radius of DNA, $a = 1$ nm, which is a strong restriction and an underestimation of the actual distance of self-approach of DNA in saline solution. In contrast, we undertake a detailed analysis of the equilibrium solutions, with thermal fluctuations considered in the tails; this allows us to derive simple formulas for the force and the moment as a function of the superhelical variables, applicable to magnetic tweezers experiments.

3. Results

Mechanical equilibrium is given by the Euler−Lagrange condition for the stationarity of the potential $V(\alpha,R,\tau,l_p)$ in eq 8 with respect to its variables

$$\left(\frac{\partial V}{\partial \tau}, \frac{\partial V}{\partial \alpha}, \frac{\partial V}{\partial l_p}, \frac{\partial V}{\partial R}\right) = 0$$

The first condition $\partial V/\partial\tau$ allows one to recover the constitutive relation for twist deformations, $M_{\text{ext}} = K_3\tau$, given that the twisting moment is uniform in the filament and equal to the applied torque M_{ext}.

Variation of the total energy with respect to α gives the expression of the applied torque M_{ext} in terms of the superhelical variables α and R:

$$M_{\text{ext}} = -\frac{2\chi K_0}{R}\frac{\cos\alpha\sin^3\alpha}{\cos 2\alpha} \tag{9}$$

which is what was found for purely plectonemic solution (no tails).[31]

The condition $\partial V/\partial l_p = 0$, combined with eq 9, allows one to relate the pulling force F_{ext} to the superhelical geometry:

$$F_{\text{ext}} = \frac{K_0}{R^2}\sin^4\alpha\left(\frac{1}{2} + \frac{1}{\cos 2\alpha}\right) \tag{10}$$

This formula justifies and extends the numerical fit $F_{\text{ext}} \propto K_0\alpha^4/R^2$ found in ref 20 for small values of α.

The Euler−Lagrange condition with respect to R yields an equation involving the Lagrange multiplier λ. The quantity λ/l_p can be interpreted as the contact force per unit length, p, of one filament onto the other. Equations 8 and 9, together with the condition $\partial V/\partial R = 0$, yields

$$p = \frac{\lambda}{l_p} = \frac{K_0}{R^3}\frac{\sin^4\alpha}{\cos 2\alpha} \tag{11}$$

Note that this pressure (more accurately, force per unit length) is positive for $\alpha \leq \pi/4$; if our assumption of contact $R = a$ was incorrect, this would be indicated by a negative pressure value here.

In magnetic tweezers experiments, the pulling force F_{ext} is imposed although the applied torque M_{ext} is unknown. The two unknowns R and α are then related by eq 10; in the next section, a second equation relating those unknowns and the extension z is given, which makes it possible to solve for R and α. The twisting moment can then be found from eq 9.

Vertical Extension of the Filament. In magnetic tweezers experiments, the measurable quantities are the vertical extension z and the number of turns n imposed on the bead. Using eq 3 for $n = \text{Lk}$, the equation $z = l - l_p$ and the constitutive relation $\tau = M_{\text{ext}}/K_3$ where M_{ext} is found from eq 9, we obtain the vertical extension of the filament as a linear function of the number of turns n:

$$z = \left(1 + \frac{2K_0}{K_3}\frac{\sin^2\alpha}{\cos 2\alpha}\right)l + \chi n\frac{4\pi R}{\sin 2\alpha} \tag{12}$$

Thermal fluctuations dominantly affect the tails and make the end-to-end distance z of the molecule smaller than the contour length $l - l_p$ of the tail parts, by a factor $\rho_{\text{wlc}} \in [0, 1]$: $z = \rho_{\text{wlc}}(l - l_p)$. This factor depends on both the pulling force F_{ext} and the bending persistence length $A = K_0/(kT)$ and can either be read off an experimental hat curve from the value $z(n = 0) = \rho_{\text{wlc}}l$ or computed from theoretical formulas.[6,18] The dependence of ρ_{wlc} on the pulling force makes the tails effectively extensible (this is the classical entropic stiffness of a chain). To account for these thermal effects, we replace eq 12 with

$$z = \rho_{\text{wlc}}\left(1 + \frac{2K_0}{K_3}\frac{\sin^2\alpha}{\cos 2\alpha}\right)l + \chi\rho_{\text{wlc}}\frac{4\pi R}{\sin 2\alpha}n \tag{13}$$

One of the main features of the experimental hat curves is the linear decrease of the vertical extension with the number of turns. We define the slope q in the linear part of the hat curve as

$$q \equiv \left|\frac{dz}{dn}\right| = \rho_{\text{wlc}}\frac{4\pi R}{\sin 2\alpha} \tag{14}$$

Given experimental values of F_{ext} and q, eqs 10 and 14 can be solved for R and α. Since q (and F_{ext}) are constant along the linear part of a hat curve, the values of R and α thus determined will be constant as well. As a result, the twisting moment in the molecule, given by eq 9, is constant, for a given experiment, along the linear region of the hat curve, a property that has been previously reported in the literature[5,17] and which is a clear outcome of the present model. An interpretation of the fact that R and α are constant in the linear region of the hat curve is that each additional turn of the bead is used to convert a small piece of tail into plectonemes.

Twisting Moment. The twisting moment in the molecule, which is uniform and equal to M_{ext} at equilibrium, cannot be measured in magnetic tweezers experiments. However, it has been shown that enzyme activity such as RNA polymerase depends on the value of the twisting moment in DNA.[23] The value of M_{ext} can be determined from eq 9 once R and α are known, as explained above. Here, we give a formula for M_{ext} directly as a function of the experimental slope q and the external force F_{ext}. Indeed, using eq 14 to eliminate R in eqs 9 and 10, one obtains $M_{\text{ext}}(q,\alpha)$ and $F_{\text{ext}}(q,\alpha)$ as functions of q and α. It is then possible to eliminate α, which yields

$$M_{ext} = m + (m^2 + 2K_0F_{ext})^{1/2}, \text{ where } m = \frac{qF_{ext}}{4\pi\rho_{wlc}} - \frac{3\pi\rho_{wlc}K_0}{2q} \quad (15)$$

In the limit of small α, one can expand the functions $M_{ext}(q, \alpha)$ and $F_{ext}(q, \alpha)$ prior to elimination of α, and this leads to a simplified formula:

$$M_{ext} \simeq \frac{2q}{3\pi\rho_{wlc}}F_{ext} \quad (16)$$

where, as explained above, $\rho_{wlc} = z(n = 0)/l$. As shown in Figure 4, this approximation is accurate when used with typical experimental values. Equation 16 provides a simple and direct mean of evaluating the twisting moment in magnetic tweezers experiments, based on the slope of the linear part of the hat curve only. Note that it should not be inferred from eq 16 that M_{ext} depends linearly on F_{ext}, as the slope q is itself a function of F_{ext}.

Superhelical Angle Limit. It is known that the topology of contact between two impenetrable helical tubes winding along a common axis changes when α becomes larger than $\pi/4$.[21] The possibility of such a change of topology is not considered in our model (being specific to hard-core repulsion between tubes, it is not relevant to DNA molecules undergoing long-range electrostatic repulsion anyway). Nevertheless, the equilibrium solutions found here are all such that $\alpha < \pi/4$. This upper bound has a mechanical origin and not a geometrical one: the expressions for F_{ext} in eq 10 and for M_{ext} in eq 9 both diverge at $\alpha = \pi/4$ and plectonemic solutions with a superhelical angle larger than $\pi/4$ are unstable.

Application to Experiments. The model is used to extract mechanical and geometrical parameters from experimental data. To allow comparison with previous work, we use the same data as in ref 20. These data are shown in Figure 2; they were obtained on a 48 kbp lambda phage DNA molecule in a 10 mM phosphate buffer.

For each curve in Figure 2, corresponding to a given value of the external force F_{ext}, we extract the slope q by fitting the linear region. The superhelical variables R and α are found by solving eqs 10 and 14 and are plotted in Figure 3 as a function of F_{ext}. The reconstructed values of R are in the nanometric range; they decrease with the pulling force, from approximately 6 to 2 times the DNA crystallographic radius in this particular experiment. At large values of the force, R is close to (and actually smaller than) the Debye length, 3.07 nm in 10 mM salt, and the Manning condensation radius, 3.18 nm in 10 mM salt.[22] We note that the values of R found here in the presence of a pulling force are smaller than (and in the same range as) in ref 26 where no force is applied, which is consistent.

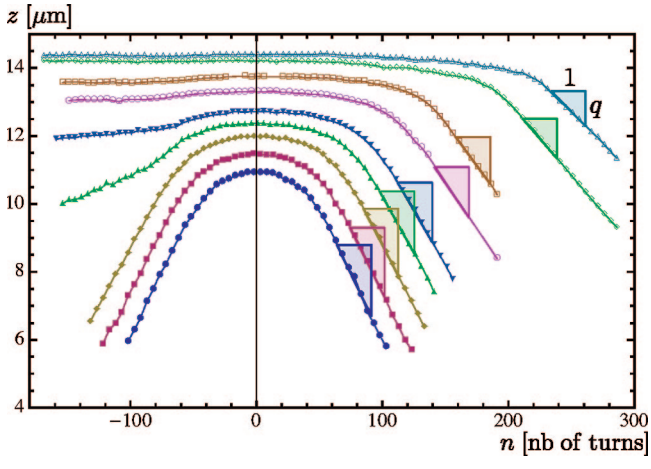

Figure 2. Experimental hat curves showing the vertical extension of a lambda phage DNA 48 kbp molecule as a function of the number of turns imposed on the magnetic bead (salt concentration 10 mM, temperature 298 K). Experimentally measured persistence length of the molecule is $A = 51.35$ nm. Each curve corresponds to a fixed pulling force F_{ext}: 0.25, 0.33, 0.44, 0.57, 0.74, 1.10, 1.31, 2.20, 2.95 pN. Triangles represent the fit for the slope q of the linear region. Data kindly provided by V. Croquette (CNRS, France).

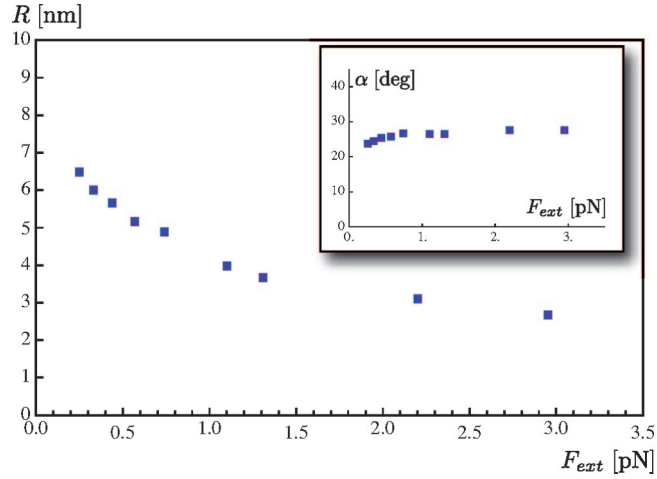

Figure 3. Reconstructed values of the plectonemic radius R as a function of the pulling force, from the data in Figure 2 by solving eqs 10 and 14. The angle α is shown in the inset.

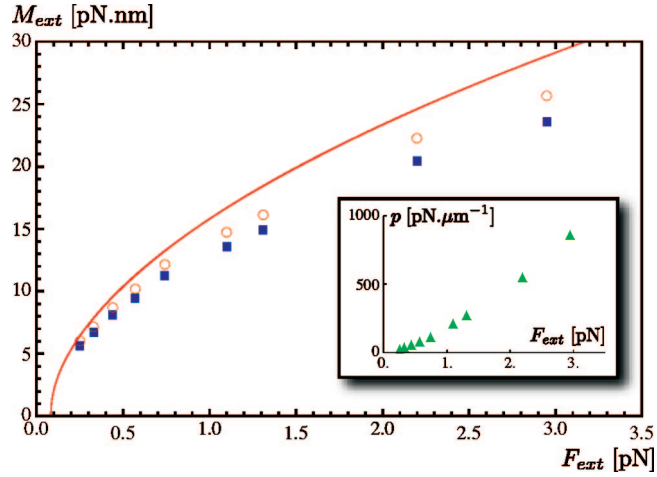

Figure 4. Reconstructed values for the twisting moment in the molecule based on the data shown in Figure 2, using the exact formula in eq 9 (solid squares), and the small angles approximation in eq 16 (open circles). Comparison with the prediction of the composite model in ref 17 (curve). Contact pressure is shown in the inset.

The reconstructed values of the twisting moment M_{ext} and of the contact pressure p are given in Figure 4, based on the same experimental data. The values of M_{ext} are determined both by eq 9 using the previously computed values of R and α and by the approximate formula 16 directly. A good agreement is obtained, which validates the proposed approximation. The values of M_{ext} are also compared to those predicted by a composite analytical model; see eq 17 in ref 17 (this model uses effective parameters determined from Monte Carlo simulations[34]).

4. Conclusion

We have shown that, under the approximation that thermal fluctuations are neglected in the plectonemes, one can calculate analytically the response of twisted DNA: supercoils are

described by a mechanically exact and self-contained model. Self-contact in the plectonemic region is treated with a hard-core potential; an expression for the contact pressure between the two dsDNA is derived. The hard-core radius is an effective parameter determined, for a given value of the applied force, from the slope of the linear region of the experimental curve. A formula for the twisting moment is proposed, as a function of the slope of the linear region of the experimental hat curve only. We apply this analysis to experimental data from which we extract the mechanical quantities: superhelical radius and angle, contact pressure, and twisting moment. We compared these values with predictions from previous analyses, when available, and found that they are consistent. In future work, we shall extend the present model to deal with long-range interaction potentials, predict the superhelical radius, and utilize magnetic tweezers experiments to probe DNA−DNA electrostatic interaction. The present paper is a first step toward a mechanically accurate description of bare dsDNA subjected to tensile and torsional loads, a problem relevant to the architecture of DNA in the cell nucleus where proteins come into play.

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