Bending and Base-Stacking Interactions in Double-Stranded Semiflexible Biopolymer

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Simple expressions for the bending and the base-stacking energy of double-stranded semiflexible biopolymers (such as DNA and actin) are derived. The distribution of the folding angle between the two strands is obtained by solving a Schrödinger equation variationally. Theoretical results based on this model on the extension versus force and extension versus degree of supercoiling relations of DNA chain are in good agreement with the experimental observations of Cluzel et al. [Science 271, 792 (1996)], Smith et al. [ibid. 271, 795 (1996)], and Strick et al. [ibid. 271, 1835 (1996)].

Recent experimental developments make it possible to investigate directly the mechanical properties of single macromolecules, and it is shown that many biopolymers should be regarded as semiflexible rather than as highly flexible ¹. The simplest and yet the most famous model for a semiflexible polymer is the wormlike chain (WLC) model, it can well describe the elasticity of DNA at the low and the moderate force ranges ². The WLC model regards a semiflexible polymer as an inextensible mathematical line characterized by a single length scale, the bending persistence length \( \ell_p ²\). However, many biologically important macromolecules, including DNA and proteins such as actin, are double-stranded. They are formed by two individual chains ("back-bones") bound together by permanent bonds ("base-pairs") such as the hydrogen bonds in the case of DNA to achieve a ladderlike architecture. Very recently, experiments on DNA and actin indicate that these interwound structures lead to non-WLC elastic behaviors ¹. To interpret these observations, Everaers et al. ¹ have made the first attempt to regard a double-stranded (DS-) polymer as a polymer with two individual wormlike chains. Later Liverpool et al. ¹ extended this work to the three-dimensional case and investigated the statistical mechanics of DS-polymers by mean-field treatments. Nevertheless, at the present time, a mathematically rigorous model for DS-polymers is still lacking and the rich phenomena observed in experiments ¹ are not convincingly explained ¹. This situation is unsatisfactory.

Based on the early efforts of Refs. ¹ and ¹, in this Letter we have developed a model for semiflexible DS-polymers. A simple bending energy expression is derived and the folding angle distribution is obtained by solving a Schrödinger equation variationally. The present model, after taking into account base-stacking interactions, is applied to DNA and the derived theoretical results are in considerable agreement with three different groups of experimental observations ¹.²

Mathematically, a DS-polymers is composed of two inextensible back-bones, \( r_1(s) = \int_t^s t_1(s')ds' \) and \( r_2(s) = \int_t^s t_2(s')ds' \), both with the same bending rigidity \( \kappa = k_BT\ell_p ¹. \) (Here the unit vector \( t_i(s) (i = 1, 2) \) is the tangent of the back-bone \( r_i \) at its arc length \( s \).) Back-bones \( r_1 \) and \( r_2 \), connected by many base-pairs of fixed length \( 2R \), are constrained to form the edges of a space ladder of fixed width, with \( r_2(s) = r_1(s) + 2Rb(s) \) [Fig. 1]. Here \( b(s) \) is a unit vector on the ladder surface pointing from \( r_1 \) to \( r_2 \) along the direction of the base-pair, it is perpendicular to both edges of the ladder, i.e., \( b(s) \cdot t_1(s) = b(s) \cdot t_2(s) = 0 ¹. \) The central axis of such a ladderlike structure is defined by \( r(s) = r_1(s) + Rb(s) \). We define the tangential (unit) vector of the central axis to be \( t(s) \) and \( n(s) = b(s) \times t(s) \) to be a unit vector perpendicular to the ladder surface. It is useful to define the rotation angle from \( t_2(s) \) to \( t_1(s) \) to be \( 2\theta \) (being the rotational axis, see Fig. 1). θ, we name it the folding angle, is in the range between \( -\pi/2 \) and \( \pi/2 \). From Fig. 1 we know that \( t_1 = \cos \theta t + \sin \theta n \) and \( t_2 = \cos \theta t - \sin \theta n \). It is not difficult to verify that ¹

\[
db/ds = [t_2 - t_1]/2R = -[\sin \theta/R]n. \tag{1}\n\]

Equation (¹) reveals a very important relation between \( n \) and \( b \) and it embodies the rigid constraints that the two back-bones are inextensible and that base-pairs of fixed length are formed between them. With Eq. (¹) and the definition of \( r \) it can be shown that ¹

\[
dr/ds = [t_1 + t_2]/2 = t \cos \theta, \tag{2}\n\]

i.e., \( \cos \theta \) measures the degree of folding of the back-bones on the central axis.

The deformation of the wormlike back-bones leads to the total bending energy of the system ¹, i.e.,

\[
E_{\text{bend}} = (\kappa/2) \int \left[ (dt_1/ds)^2 + (dt_2/ds)^2 \right] ds \\
= \kappa \int \left[ (d^2r/ds^2)^2 + R^2(d^2b/ds^2)^2 \right] ds.
\]

Inserting Eqs. (¹) and (²) into this expression we obtain an important result:

\[
E_{\text{bend}} = \kappa \int \left[ (dt/ds)^2 + (d\theta/ds)^2 + \sin^4 \theta/R^2 \right] ds. \tag{3}\n\]
We see that Eq. (3) is very simple as well as with clear physical meaning: The bending energy of the system can be separated into two independent parts, the energy caused by bending of the central axis and that associated with the folding of the back-bones. This observation is very useful for our following discussions. (We notice that the variables \( t \) and \( \theta \) themselves are yet not completely independent of each other, because of Eq. (4).)

\[
\frac{\partial \Psi}{\partial s} = -\frac{1}{4t_p} \left( -\frac{\partial^2}{\partial \theta^2} + 4\eta \sin^4 \theta \right) \Psi, \tag{4}
\]

where \( \eta = (\ell_p/R)^2 \) is a dimensionless constant. Since \( \theta \in (-\pi/2, \pi/2) \), the eigenvalues of Eq. (3) are all positive. Therefore, the \( \theta \) distribution is governed mainly by the ground eigenstate, \( \Psi_{gr} \), of Eq. (3). However, the eigenstates of Eq. (3) cannot be obtained exactly and we have to take a variational approach by assuming \( \Psi_{gr} \propto \cos \theta \exp(-a \sin^4 \theta) \). Here \( a \) is a variational parameter to be determined through minimization of the variational free energy density \[\int \left( \left( \frac{d\Psi_{gr}/d\theta}{\Psi_{gr}} \right)^2 + 4\eta \sin^4 \theta \frac{\partial^2 \Psi_{gr}}{\partial \theta^2} \right) d\theta \] (4). The calculated relations between \( a \) and \( \eta \) is shown in Fig. 2 (inset). With the \( \theta \) distribution \( \Psi_{gr}(\theta) \) known, the average contour length \( L_c \) of the central axis, according to Eq. (3), is related to \( \Psi_{gr}(\theta) \) via \( L_c = \int L \cos \theta \Psi_{gr}(\theta) d\theta / \int \Psi_{gr}(\theta) d\theta \), i.e.,

\[
L_c = L \pi a^{1/4} D(2a) / [\Gamma(1/4) - \Gamma(1/4, a)], \tag{5}
\]

where \( D(2a) = _2F_2(1/4, 3/4; 1, 3/2; -2a) \) is the generalized hypergeometric function and \( \Gamma(1/4, a) \) is the incomplete Gamma function, the constant \( L \) is the total contour length of the back-bones. The \( L_c \) vs. \( \eta \) relation calculated numerically and shown in Fig. 2. From Fig. 2 we find that the total contour length of the system increases nonlinearly with \( \eta \). For \( \eta \to \infty \), it approaches the upper limit of \( L \). Notice that \( \eta \) is proportional to \( T^{-2} \) [10], so the average contour length is sensitive to temperature variations. This property of DS-polymers may have some biological significance [7].

**FIG. 1.** (Left) sketch of a double-stranded polymer. (Right) the definition of \( \theta \) on the local \( \mathbf{t} \cdot \mathbf{n} \) plane. (\( \mathbf{b} = \mathbf{t} \times \mathbf{n} \) is perpendicular to the \( \mathbf{t} \cdot \mathbf{n} \) plane).

**FIG. 2.** The relation between \( L_c \) and \( \eta \) according to Eq. (3). (Inset: the variational relation between \( a \) and \( \eta \).)

With the model for double-stranded polymers proposed above, it is tempting for us to study the elastic properties of DNA macromolecules [11,12]. The two back-bones of DNA are bound together by base-pairs to form a right-handed double-helix [12]. In this case, the folding energy caused by the base-stacking interactions between adjacent base-pairs should also be considered. In this article, we suppose that this base-stacking folding potential together with the back-bone folding potential [the term \( \kappa \sin^4 \theta / R^2 \) in Eq. (3)] as a whole can be modeled as a Lennard-Jones interaction \( U = \sum_i U_{i,i+1} = \epsilon (\delta / r_{i,i+1})^{12} - 2(\delta / r_{i,i+1})^6 \) [13], where \( r_{i,i+1} \) is the distance between adjacent base-pairs \( i \) and \( i+1 \). For our purpose, we convert this summation into an integral form as a continuous function of \( \theta \) [13]. Then the total energy of such a system under applied force \( f \mathbf{z}_0 \) and torque \( \gamma \) is written as [14]

\[
E_{\text{total}} = \int \left( \kappa \left( \frac{dt}{ds} \right)^2 + \kappa \left( \frac{d\theta}{ds} \right)^2 \right)
\]
where \( r_0 \) is the back-bone arc length between adjacent base-pairs and \( \theta_0 \) is the equilibrium folding angle of the back-bones when there is no force applied, \( t_x \) and \( t_y \) are the components of \( \mathbf{t} \) on the plane perpendicular to \( \mathbf{z}_0 \), the direction of the external force. \( \mathcal{L} \) is the linking number of the DS-polymer system, the total topological turns the back-bones twist on each other. \( \mathcal{L} = (1/4 \pi) \int (t_x dt_y / ds - t_y dt_x / ds) ds + (1/2 \pi R) \int \sin \theta ds \) for highly extended a DS-polymer. We define the degree of supercoiling, \( \sigma \), to be \( \sigma = (\mathcal{L} - \mathcal{L}_0) / \mathcal{L}_0 \), where \( \mathcal{L}_0 = (1/2 \pi R) \int \sin \theta_0 ds \) is the linking number of a relaxed DNA.

First, we consider the case when \( \gamma = 0 \), i.e., only external force \( f \) but no torque is applied on DNA. The theoretical results of the force-extension relation for such a model DNA chain with energy expression Eq. (6) are discussed below and demonstrated in Fig. 3.

When \( f \) is small, because of the strong folding interaction the change in \( \theta \) is negligible and the DS-polymer is in a double-helix configuration (whether right-handed or left-handed may be determined by other energy terms not included here), and the polymer can just be regarded as a wormlike chain of contour length \( L \cos \theta_0 \) and bending persistence length \( 2 \kappa_p \cos \theta_0 \) [Fig. 3 (inset)]. Therefore we focus our attention to the case when \( f \) becomes high enough so the tangent vectors \( \mathbf{t} \) fluctuates around \( \mathbf{z}_0 \) slightly. In this case the equilibrium value of \( \theta \) is related to \( f \) via

\[
\begin{align*}
\cos \theta &= \frac{\cos \theta_0}{r_0} \\
\left[ \cos \theta_0 \right]^{12} &\cos \theta \left[ \cos \theta_0 \right]^{6} - f \cos \theta_0 \cdot t \right] ds - \gamma \mathcal{L}, \quad (6)
\end{align*}
\]

i.e., the total contour length of the chain will increase slightly with \( f \). The total extension is then calculated to be

\[
\zeta = \int_0^L (\mathbf{z}_0 \cdot \mathbf{t}) \cos \theta ds \simeq \cos \theta \left( 1 - \frac{k_B T}{\sqrt{8 \kappa f \cos \theta}} \right). \quad (8)
\]

However, the right-hand part in Eq. (6) attains its maximal value of

\[
f_c \simeq 2.69e / (r_0 \cos \theta_0) \quad (9)
\]

at \( \theta_c \simeq \arccos(1.1087 \cos \theta_0) \). Therefore, for \( f > f_c \) the force equilibrium condition Eq. (6) can no longer be satisfied and the back-bones will be fully extended, with \( \theta \sim 0 \). In other words, with the increase of external force, a double-stranded polymer will undergo an abrupt phase transition from a double-helix (B-DNA) to a fully extended ladder (S-DNA or denatured DNA) at force \( f_c \) [Fig. 3]. This phase transition for over-stretched DNA is indeed observed in lambda-phage DNA (see Fig. 2 in [1] and Figs. 2, 4 and 5 in [2]). Ref. [1] reports \( f_c \) to be about 65 pN at room temperature, then we estimate that \( e \sim 600k_B = 2k_B T \) from our theoretical formula Eq. (6). This value of \( e \) is in close agreement with the estimation of Strick et al. [3].

Now we study the case when a nonzero torque \( \gamma \) as well as a force \( f \) are applied on the molecule. In this case the DNA will be supercoiled [11,2]. An analysis similar with what we have done in the above shows that, at certain fixed \( f (< f_c) \) there exists a negative-valued critical torque \( \gamma_c^d \),

\[
\gamma_c^d = R(f - 2.6899e / r_0 \cos \theta_0) \tan \theta_c, \quad (10)
\]

if \( \gamma \leq \gamma_c^d \), the DNA will no longer be in its native structure and it will denature [11,2]. However, there also exists another critical torque \( \gamma_c^d \simeq \sqrt{8 \cos \theta_0 f \kappa} \) at the point where \(|\gamma| = \gamma_c^d \) the DNA chain will begin to take on plectonemic configurations, with the total extension nearly zero [13,23]. Thus, for positive torques only the transition to plectonemes is possible; while for negative torques, there are two possibilities: (i) if \( \gamma_c^d < -\gamma_c \), transition to plectonemes will occur, and (ii) if \( -\gamma_c < \gamma_c^d = \gamma \), the DNA will denature. The numerically calculated relations between extension and degree of supercoiling \( \sigma \) demonstrated in Fig. 4 has confirmed this theoretical picture.

From Fig. 3 we know that, (a) at low forces (curves E and F), the DNA chain will change to plectonemes at high degrees of supercoiling and the curve is symmetric (achiral) with \( \sigma \rightarrow -\sigma \); (b) at moderate forces (curves C and
D) the chirality of DNA begins to emerge, a positively supercoiled DNA will shrink continuously, while a negatively supercoiled one will shrink at first till some turning point is reached, then it will swell again, followed by denaturation of the double-helix; (c) at large forces (curves A and B) the turning points disappear, and the more negatively supercoiled is the chain the more extended it is. All these predictions are in excellent qualitative agreement with the experiment of Strick et al. [6]. This can be seen clearly by a direct comparison of Fig. 4 with Fig. 3 of [6].

FIG. 4. The extension-degree of supercoiling curves at various fixed forces for a model DNA.

However, we should point out that, for supercoiled DNA, the quantitative agreement is not so encouraging. Fig. 4 indicates negatively supercoiled DNAs will denature rather than form plectonemes for applied forces ≥ 8 pN, while the experimental value is just about 1 pN.

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