

Bending and twisting elasticity: A revised Marko-Siggia model on DNA chirality

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A revised Marko-Siggia elastic model for the DNA double helix [Macromolecules **27**, 981 (1994)] is proposed, which includes the inextensible wormlike chain bending energy and a new chiral twisting energy term. It is predicted that the mean helical repeat length (HRL) for short DNA rings increases with decreasing chain length, while for very long chains in solution, their mean HRL has the same value longer than that for rectilinear DNAs, independent both of the chain length and of whether the ends are closed. These theoretical results are in good agreement with recent experimental investigations, and it might be possible that the chirality in twisting will account for the long-standing linking number deficit puzzle observed in organelle DNAs. [S1063-651X(98)06210-2]

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Single-molecule extension experiments on DNA molecules show that freely fluctuating open chains (FFOCs) could be well described by the inextensible wormlike chain (WLC) model [1–3]. For a WLC chain of total length L , its intrinsic elastic energy is of the form $\beta E = \int_0^L A \kappa^2 ds/2$, where $A \approx 150$ base pairs (BP) is called the bending persistence length and $\kappa = |\partial_s \mathbf{t}|$ is the curvature, the change rate of the tangent unit vector $\mathbf{t}(s)$ at arc length s , $\beta = 1/k_B T$ with k_B being the Boltzmann constant and T the environment temperature [3]. However, in addition to bending degrees of freedom, double-stranded DNA molecules have also twisting degrees of freedom, and the total intrinsic energy formula for a deformed DNA chain is still under investigation [4–10]. Knowledge of the exact form of the energy formula is necessary for the study of DNA configurational properties, especially in the case of torsionally constrained DNAs, such as covalently closed DNA rings in cells. For example, it has been widely accepted that bending elasticity and twisting elasticity determine to a large extent the particular tertiary structures (supercoils) of DNA rings [4–6]. Previous studies often regard a DNA chain as a thin elastic rod with isotropic cross section [11]; the total elastic energy is assumed to be

$$\beta E_a = \int_0^L \left[\frac{A}{2} (\Omega_1^2 + \Omega_2^2) + \frac{C}{2} (\Omega_3 - \omega_0)^2 \right] ds, \quad (1)$$

with bending and twisting deformations being independent of each other; here C is called the twisting persistence length and ω_0 is the spatial angular frequency of the unstressed DNA double helix [4–6], and $\Omega_1^2 + \Omega_2^2 = \kappa^2$ [11]. Although this simple achiral model is useful in some cases and seems to be the most natural extension of the already verified WLC model, it cannot properly describe the chiral characteristics of real DNA chains. This chirality of DNA molecules has been clearly demonstrated by the single-molecule experiment of Strick *et al.* [7]. Another very important phenomenon related to the chirality of DNA molecules is that Nature

prefers ‘‘linking number deficit’’ in circular DNAs [12], i.e., naturally occurring long closed DNAs in biological organelles are often found to have deficient linking number compared with equilibrium solution DNAs (for the definition of the linking number as well as twisting number and writhing number, please see [13,14], and references cited therein). This bias cannot be well explained by the achiral model (1) studied previously [4–6], and its real nature is still somewhat mysterious.

Theoretical investigations on the chiral properties of double-stranded DNA were initiated by Fuller more than two decades ago [13], who suggested that *B*-form DNA is a chiral structure with anisotropic cross section. Recently, a chiral elastic theory was proposed by Marko and Siggia to incorporate coupling between bending and twisting deformations in the energy formula [8]. This model was based on a careful consideration of the intrinsic symmetry of DNA chains. Later on, Kamien and co-workers and Marko extended the Marko-Siggia (MS) model to investigate twist-stretch coupling of highly extended DNA supercoils and found good agreement with experiment [9,10].

However, when applying the MS model to the case of FFOCs, one finds that it is in general not compatible with the already verified WLC theory for DNA bending elasticity [1–3]. To attain this compatibility, we further simplify the MS theory by assuming that the bend-twist coupling constant is related to the bending and twisting persistence lengths. The corresponding internal deformation energy also consists of two parts as in Eq. (1), the bending energy and the twisting energy. The only difference is that Ω_3 in Eq. (1) is replaced by $\Omega_3 + (B/C)\Omega_1$ in the twisting energy, where B is called the bend-twist coupling constant. After proposing this new elastic energy, we use this model to discuss the mean helical repeat length (HRL) of open and closed DNA chains in aqueous solutions. Our results show that for short ring-shaped DNAs, the shorter the chain, the longer its HRL. This tendency is consistent with experimental observations and consistent with previous theoretical work on DNA tertiary helical structure in Ref. [8]. However, for very long chains with twisting freedom, i.e., open chains or closed chains with at least one defect, we show that their mean HRL is indepen-

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dent both of the chain length and of whether the ends are closed or not, and its value is longer than that of rectilinear DNAs.

Experimentally, it was discovered that random solution DNAs have a mean HRL significantly longer than that of rectilinear DNA fibers [15,16]. However, the reason for this discrepancy has been obscure. Some researchers suggested that maybe ionic concentrations differ in fibriform and solution DNAs, causing an observable effect on the twisting manners. Our present theoretical results indicate another possibility: That the chirality of DNA might be the real reason for this discrepancy. In fact, we find that the ionic conditions in DNA fibers with high humidity and in solution DNAs differ only slightly in the experiment of Refs. [15,16], so we feel our present explanation may be more reasonable.

First we briefly review the main points of the MS model [8–10]. The configuration of an inextensible polymer are specified by three orthonormal unit vectors $\{\mathbf{u}(s), \mathbf{n}(s), \mathbf{t}(s)\}$ along the chain, where \mathbf{t} is the axial direction vector of the DNA double helix and \mathbf{u} is a unit vector perpendicular to \mathbf{t} and pointing from one backbone chain to the other, $\mathbf{n} = \mathbf{t} \times \mathbf{u}$. It proves to be convenient to use Euler angles by setting $\mathbf{e}_1 = \mathbf{u}$, $\mathbf{e}_2 = \mathbf{n}$, and $\mathbf{e}_3 = \mathbf{t}$, with $\partial_s \mathbf{e}_i = \boldsymbol{\Omega} \times \mathbf{e}_i$ ($i = 1, 2, 3$); here $\boldsymbol{\Omega} = (\Omega_1, \Omega_2, \Omega_3)$ is angular velocity of the frame $\{\mathbf{e}_i\}$ [11]. Since the two-constituent backbone chains run in opposite directions, symmetry analysis shows that the polymer elastic energy should remain unchanged under the transformation $\{\mathbf{e}_1 \rightarrow -\mathbf{e}_1, \mathbf{e}_3 \rightarrow -\mathbf{e}_3\}$, which is a rotation of 180° around the axis \mathbf{n} . Thus, after taking into account the fundamental characteristics of DNA that an undistorted open DNA form a linear double helix with spatial frequency ω_0 , the most general elastic energy up to quadratic order in the deformations should be of the form [8]

$$\beta E_c = \int ds \left[\frac{A'}{2} \Omega_1^2 + \frac{A}{2} \Omega_2^2 + \frac{C}{2} (\Omega_3 - \omega_0)^2 + B \Omega_1 (\Omega_3 - \omega_0) \right]. \quad (2)$$

The first two terms are related to bending deformations and A' , A are bending persistence lengths along the directions \mathbf{e}_2 and \mathbf{e}_1 , respectively, the third term is twisting energy, the last term is caused by bend-twist coupling, and B is the coupling constant [8]. Equation (2) can be further extended to include stretch-twist coupling [9,10], but this effect is not important for DNAs at ordinary conditions.

It is easy to know that, for FFOCs which can twist freely so we need only to consider bending deformations, the MS model (2) is in general not equivalent with the WLC internal energy $\int A(\Omega_1^2 + \Omega_2^2) ds/2$. In this case we can integrate out Ω_3 in Eq. (2) and obtain the effective bending energy to be $\beta E_b = \int [(A' - B^2/C)\Omega_1^2 + A\Omega_2^2] ds/2$. Thus, for the MS theory to correctly predict the WLC behavior for FFOCs observed in experiments [1–3], the condition $B^2 = (A' - A)C$ is required to be satisfied among these (mean-field) elastic constants. In other words, experimental observations indicate that *bend-twist coupling in DNA chains is induced by anisotropy of the chain cross section*. If $A' = A$, then B

$= 0$ and no bend-twist coupling will occur. Taking into account this compatibility, the deformation energy (2) should be revised as

$$\beta E_c = \int ds \left[\frac{A}{2} (\Omega_1^2 + \Omega_2^2) + \frac{C}{2} \left(\Omega_3 - \omega_0 + \frac{B}{C} \Omega_1 \right)^2 \right]. \quad (3)$$

The first term is just the WLC bending energy, whereas the second term of Eq. (3) is a chiral twisting energy formula suggested for DNA chains.

It is interesting to note that, compared with the previously mentioned achiral model (1), the only new thing in Eq. (3) is that a new term $(B/C)\Omega_1$ is added into the twisting energy. Therefore *model (3) can also be considered as a natural extension of the achiral model (1)*. Furthermore, experiments [17–19] show that a planar circular ring is a possible configuration of an undistorted closed DNA chain. Our detailed calculations (unpublished) show that in general the original model (2) cannot predict this kind of behavior, but the revised model will do so. Thus we feel the new elastic energy is well justified in the following senses: (i) it embodies the microscopic symmetry of DNA molecules; (ii) it predicts WLC behavior of FFOCs; (iii) it predicts the proper configurations of undistorted DNA rings; (iv) its limiting case is the achiral model (1). Model (1) has been intensely used in the literature (see, for example, Refs. [4–6], and references therein), and many interesting results have been obtained. To what extent will the new elastic energy Eq. (3) affect the configurational as well as statistical properties of DNA? This is yet to be carefully investigated. In the following, we will discuss the twisting properties of the DNA double helix based on this new chiral twisting energy. We will see that the chiral twisting energy leads to many nontrivial effects.

The HRL of the DNA double helix is defined as the arc length h traversed when one of the two constituent backbone chains winds around the central axis for one turn or 2π . In other words, it is the length over which the twisting number of the double-stranded chain increases 1. The HRL is not necessarily a constant along the chain, therefore in accordance with various previous investigations, we can define the instantaneous HRL at arc length s as the quantity h which satisfies $\text{Tw}(s+h) - \text{Tw}(s) = 1$, where

$$\text{Tw}(s) = \frac{1}{2\pi} \left[\psi(s) + \int_0^s \phi'(s) \cos \theta ds \right] \quad (4)$$

is just the twisting number [13,14], $\text{Tw}'(s) = (\psi' + \phi' \cos \theta)/2\pi$. And the mean HRL is the value of h averaged over the whole chain; here and later, $()'$ means differentiation with respect to arc length s . Based on the above mentioned knowledge, first of all we calculate the HRL of short DNA rings. In this case, thermal fluctuation can be neglected and the stable configuration of the chain will minimize the elastic energy Eq. (3). The corresponding Euler-Lagrange variational equation of model (3) is listed in the Appendix. Equations (A2)–(A4) show that, for a torsionally relaxed DNA ring the stable shape is a flat circle, with $\theta = \pi/2$, $\phi = 2\pi s/L$, and

$$\psi' = \omega_0 - \frac{2\pi B}{CL} \sin \psi. \quad (5)$$

Then we can know from the above definition that its HRL is

$$h = \left\{ \left(\frac{\omega_0}{2\pi} \right)^2 - \left(\frac{B}{CL} \right)^2 \right\}^{-1/2}. \quad (6)$$

As long as $B \neq 0$, this value for a DNA ring is longer than $h_0 = 2\pi/\omega_0$, the value for undistorted linear chains. Especially interesting of Eq. (6) is that it predicts that the shorter the chain, the longer its HRL. Such a tendency in HRL was observed in various experiments [17–19], and a very recent crystal structure of the nucleosome DNA wound on proteins is considerably higher than that of rectilinear DNAs [20]. What biological significance will this lead to? We mention here that this bend-twist couple induced HRL change may be closely related to the observed linking number deficit puzzle in organelle DNAs mentioned earlier [12–14]. Further investigations, especially computer simulations, are needed in this respect.

The case of long chains is more important and interesting, but much more difficult to tackle. In this case thermal fluctuation becomes the most important and we must make use of statistical methods. Model (3) shows that for a chain with twisting freedom its axial (\mathbf{t}) distribution is just that of a wormlike chain, which is

$$\rho(\mathbf{t}_1, \mathbf{t}_0, s) = \int_{\mathbf{t}_0}^{\mathbf{t}_1} D[\mathbf{t}(s)] \exp \left\{ -\frac{A}{2} \int_0^L \mathbf{t}'^2 ds \right\}, \quad (7)$$

and for each specific axial configuration $\mathbf{t}(s)$,

$$\begin{aligned} \psi'(s) = \omega_0 - \phi'(s) \cos \theta - \frac{B}{C} \phi'(s) \sin \theta \sin \psi \\ - \frac{B}{C} \theta'(s) \cos \psi. \end{aligned} \quad (8)$$

To calculate the thermal average of the HRL, as the first step we will focus on a simpler case, in which the DNA chain lies on a plane. Then $\phi(s) = 0$ in this two-dimensional (2D) situation and Eq. (8) reduces to $\psi'(s) = \omega_0 - (B/C)\theta'(s)\cos\psi$, and the HRL h is just the length needed for ψ to increase 2π . Because the value of ψ increases 2π about every 10 BPs while it must take about 150 BPs for θ to increase the same value, we can reasonably take $\theta'(s)$ as constant while calculating the instantaneous HRL h . Thus the instantaneous HRL at arc length s is $h(s) = (2\pi/\omega_0) [1 - B^2\kappa^2(s)/C^2\omega_0^2]^{-1/2}$, where $\kappa^2(s) = \theta'(s)^2$ for the 2D case.

Similarly, for the general 3D case we can get the same result, merely that now $\kappa^2(s) = \phi'^2 \sin^2 \theta + \theta'^2$. Consequently the mean HRL is calculated to be

$$\bar{h} = \langle h(s) \rangle_{\text{bend}} = h_0 \left[1 + \frac{B^2}{2C^2\omega_0^2} \langle \kappa^2(s) \rangle_{\text{bend}} \right], \quad (9)$$

where $\langle \cdots \rangle_{\text{bend}}$ means average with respect to the WLC distribution Eq. (7). We see from Eq. (9) that $\bar{h} > h_0$ whenever

$B \neq 0$, in qualitative agreement with the experiment of Wang [15]. However, $\langle \kappa^2(s) \rangle_{\text{bend}}$ is difficult to calculate for a WLC chain, partly due to the fact that $|\mathbf{t}|^2 = 1$. Here, we have to adopt a self-consistent field method to convert this local constraint to a global one such that $\int_0^L \mathbf{t}^2 ds = L$ and determine the corresponding Lagrangian multiplier self-consistently by requiring $\langle \mathbf{t}^2 \rangle = 1$ (the validity of such a treatment has been argued in Ref. [21]). The self-consistent field internal energy is

$$\beta E_{\text{SC}} = \int_0^L \left(\frac{A}{2} \mathbf{t}'^2 + \gamma \mathbf{t}^2 + \boldsymbol{\lambda} \cdot \mathbf{t} \right) ds, \quad (10)$$

where $\boldsymbol{\lambda}$ is for possible end constraints. Detailed calculation shows that

$$\langle \kappa^2(s) \rangle_{\text{bend}} = \frac{9}{4A^2}, \quad (11)$$

which is independent of the value of $\boldsymbol{\lambda}$, i.e., independent of whether the chain is open ($\boldsymbol{\lambda} = 0$) or closed ($\boldsymbol{\lambda} \neq 0$); and it is also independent of chain length L , provided that the chain is long enough. The self-consistent result Eq. (11) demonstrates that the mean curvature of a WLC chain is $3/2A$. Thus Eq. (9) predicts that long solution DNA, whether linear or circular, has the same mean HRL longer than that of the rectilinear DNA.

For very long closed DNA chains (about several tens of thousands of base pairs), gel electrophoresis experiments did reveal a significant increase in mean HRL, with $h = 10.4$ BPs [15], however, the HRL for rectilinear DNAs is only 10 BPs long [16]. As mentioned before, for a long time the real reason for this phenomenon has not been clear. Our present theory gives a natural and reasonable explanation, proposing that this discrepancy is induced by the chiral twisting energy in model (3). To be more quantitative, we insert the experimental values into Eq. (9) and estimate that $B/C \approx 17.8$. This relatively large value indicates that the persistence length A' is much longer than A in Eq. (2). However, *this anisotropy cannot be observed by force versus extension experiment on torsionally relaxed chains*. We hope that future experiment on torsionally constrained DNAs will provide reliable values for the bending persistence lengths, and thus further check the results obtained by our theoretical work.

In summary, we have proposed a revised Marko-Siggia chiral elastic model for DNA molecules and discussed its predictions on DNA double helix mean helical repeat length. The theoretical results show that for short DNA rings, their mean HRL increases with the decreasing of chain length; while for very long chains, whether open or closed, their mean HRL is independent of chain length and is longer the value for rectilinear DNAs. These results are in good agreement with experiments.

APPENDIX: THE EULER-LAGRANGE VARIATION OF EQ. (3)

The possible stationary configurations of an elastic filament with energy functional Eq. (3) and subjected to the constraint of fixed end-to-end distance are governed by the

following Euler-Lagrange equation:

$$\delta^{(1)}\left(\beta E_c - \lambda \cdot \int \mathbf{t} ds\right) = 0, \quad (\text{A1})$$

where $\lambda = (\lambda_1, \lambda_2, \lambda_3)$ is the Lagrange multiplier. This variation (with respect to the three Euler angles) leads to the following shape equations:

$$\begin{aligned} & A\phi'^2 \sin \theta \cos \theta - A\theta'' - (C\phi' \sin \theta - B\phi' \cos \theta \sin \psi) \\ & \times \left(\phi' \cos \theta + \psi' - \omega_0 + \frac{B}{C}(\phi' \sin \theta \sin \psi \right. \\ & \left. + \theta' \cos \psi) \right) - C \left[\cos \psi \left(\phi' \cos \theta + \psi' - \omega_0 \right. \right. \\ & \left. \left. + \frac{B}{C}(\phi' \sin \theta \sin \psi + \theta' \cos \psi) \right) \right]' - \lambda_1 \sin \phi \cos \theta \\ & + \lambda_2 \cos \phi \cos \theta + \lambda_3 \sin \theta = 0, \end{aligned} \quad (\text{A2})$$

$$\begin{aligned} & -A(\phi' \sin^2 \theta)' - \left[(C \cos \theta + B \sin \theta \sin \psi) \left(\phi' \cos \theta + \psi' \right. \right. \\ & \left. \left. - \omega_0 + \frac{B}{C}(\phi' \sin \theta \sin \psi + \theta' \cos \psi) \right) \right]' \\ & - \lambda_1 \cos \phi \sin \theta - \lambda_2 \sin \phi \sin \theta = 0, \end{aligned} \quad (\text{A3})$$

$$\begin{aligned} & -C \left(\phi' \cos \theta + \psi' - \omega_0 + \frac{B}{C}(\phi' \sin \theta \sin \psi + \theta' \cos \psi) \right)' \\ & + (B\phi' \sin \theta \cos \psi - B\theta' \sin \psi) \\ & \times \left(\phi' \cos \theta + \psi' - \omega_0 + \frac{B}{C}(\phi' \sin \theta \sin \psi \right. \\ & \left. + \theta' \cos \psi) \right) = 0. \end{aligned} \quad (\text{A4})$$

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