Sequence-dependent effects on the properties of semiflexible biopolymers

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Using a path integral technique, we show exactly that for a semiflexible biopolymer in constant extension ensemble, no matter how long the polymer and how large the external force, the effects of short-range correlations in the sequence-dependent spontaneous curvatures and torsions can be incorporated into a model with well-defined mean spontaneous curvature and torsion as well as a renormalized persistence length. Moreover, for a long biopolymer with large mean persistence length, the sequence-dependent persistence lengths can be replaced by their mean. However, for a short biopolymer or for a biopolymer with small persistence lengths, inhomogeneity in persistence lengths tends to make physical observables very sensitive to details and therefore less predictable.

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I. INTRODUCTION
The conformal and mechanical properties of double-stranded DNA (dsDNA) have attracted considerable attention due to the central role that dsDNA plays in biological processes. Recent progresses in experimental techniques such as laser or magnetic tweezers, atomic force microscopy, and other single molecule techniques make it possible to manipulate and observe single biomolecules directly [1–4], allowing better comparisons between theoretical predictions and experimental observations. In theoretical studies, a semiflexible biopolymer is often modeled as a filament. The simplest model for a filament, called the wormlike chain (WLC) model, views the filament as an inextensible continuous chain with a uniform bending rigidity but with vanishing cross section, and has been successfully applied to the entropic elasticity of dsDNA [5–8]. Furthermore, the wormlike rod chain (WLRC) model which regards the filament as a chain with spontaneous twist and a finite circular cross section, has been used to explain the supercoiling property of dsDNA [6–9]. Owing to the importance of DNA, recently there has been a lot of theoretical work on the WLC and WLRC models as well as their modifications and extensions [5–24].

Traditional models of filaments are essentially homogeneous. In other words, these models are defined by s-independent parameters, where s is the arclength. However, biopolymers are often sequence dependent and so are heterogeneous. Several recent works have revealed that the sequence disorder has remarkable effects on the properties of dsDNA [17–23]. Based on the elastic model, two effects of sequence-disorder have to be considered. First, structural inhomogeneity results in variations of the bending rigidity along the chain, and can be described by the s-dependent persistence length \( l_p(s) \) [19,23]. It has been demonstrated that for a long DNA chain without long-range correlation (LRC) in \( l_p(s) \), this effect can be well accounted for by a simple replacement of the uniform persistence length \( l_p \) in the WLC model by a proper average of the \( l_p(s) \) [19]. However, for loop formation in a short DNA chain this effect becomes complex because the looping probability of a typical filament segment is not a well-defined function of its length [19]. Second, the local structure of the dsDNA can be characterized by the sequence-dependent spontaneous curvature \( \kappa_0(s) \) [17–23]. For short dsDNA chains, special sequence order may favor a macroscopic spontaneous curvature \( \kappa_0(s) \). For long dsDNA chains, special sequence order may favor a macroscopic spontaneous curvature [20]. Moreover, computer simulations suggest that the mean of \( \kappa_0(s) \), rather than the details of its distribution, determines the looping probability of a filament [21]. However, all analytical approaches on the sequence-dependent effects are limited to specified properties and on a WLC-based model with vanishing intrinsic curvature and with weak or vanishing external force, a rigorous proof on the general elastic continuous model is yet elusive. Bearing in mind that many dsDNA possess macroscopic intrinsic curvature [20,25–27], an analytical approaches on the general model is of special importance.

II. MODEL

Using s as variable, the configuration of a filament can be described by a triad of unit vectors \( \{t_i(s)\}_{i=1,2,3} \), where \( t_3 = dr(s)/ds \) is the tangent to the center line r(s) of the filament, and \( t_1 \) and \( t_2 \) are oriented along the principal axes of the cross section. The orientation of the triad as one moves
along the filament is given by the solution of the generalized Frenet equations that describe the rotation of the triad vectors \[ 11–13 \] \[ \frac{d\mathbf{t}_i}{ds} = -\sum_{j,k} \epsilon_{ijk} a_i a_j a_k \mathbf{n}_k, \] where \( \epsilon_{ijk} \) is the antisymmetric tensor and \( \{a_i(\omega)\} \) are the curvature and torsion parameters.

The elastic energy of a filament with s-dependent spontaneous curvatures \( \zeta_1(s) \), \( \zeta_2(s) \), spontaneous twist rates \( \zeta_3(s) \) and persistence lengths \( a_i(\omega) \) can be written as \[ 11–13 \]

\[
\frac{E}{k_BT} = \varepsilon = \frac{1}{2} \int_0^L \sum_{i=1}^3 a_i(\omega) - \zeta_i^2 \, ds,
\]

where \( T \) is the temperature, \( k_B \) is the Boltzmann constant, and \( L \) is the total arc length of the filament and is a constant so that the filament is inextensible. If \( \zeta_i \) and \( a_i \) are well-defined (i.e., without randomness) functions of \( s \), a macroscopic quantity \( B \) is defined as the average with Boltzmann weights over all possible conformations, so is a path integral in the form \[ 11–13 \]

\[
B = \langle B(\{\omega_i(s)\}) \rangle = \frac{\int B(\{\omega_i(s)\}) e^{-\varepsilon} \, D[\omega_i]}{\int e^{-\varepsilon} \, D[\omega_i]}. \tag{2}
\]

Function \( B(\{\omega_i(s)\}) \) represents different physical situations. For instance, if \( B(\{\omega_i(s)\}) = \mathbf{t}(s_1) \cdot \mathbf{t}(s_2) \), we find the orientational correlation function between \( \mathbf{t}_1 \) and \( \mathbf{t}_2 \); if \( B(\{\omega_i(s)\}) = \mathbf{r}_L - \mathbf{r}_0 \), we obtain the end-to-end distance, where \( \mathbf{r}_L = r(L) \) and \( \mathbf{r}_0 = r(0) \); if \( B(\{\omega_i(s)\}) = \delta(\mathbf{r} - \int_0^L \mathbf{t}_i ds) \), we get the distribution function of end-to-end vector. The applied force can be evaluated using this distribution function; if \( B(\{\omega_i(s)\}) = \delta(\mathbf{r} - \int_0^L \mathbf{t}_i ds) \), we find the looping probability. Note that \( B(\{\omega_i(s)\}) \) may be a very complex function of \( \omega_i(s) \), but its detailed form is irrelevant in this work since it is independent on \( a_i \) and \( \zeta_i \). If both ends are free of external force, \( B \) represents the intrinsic property of the system. On the other hand, if we fix both ends of the filament, we obtain quantity in the constant extension ensemble.

III. THE EFFECTS OF SEQUENCE-DEPENDENT SPONTANEOUS CURVATURES AND TORSIONS

We first consider the effects of the \( \zeta_i(s) \) alone but leave \( a_i / s \) as well-defined. For a biopolymer without correlation on \( \zeta_i(s) \), or with SRA but in the coarse-grained model, the distribution of \( \zeta_i(s) \), \( W(\zeta_i) \), can be written as a Gaussian distribution with nonvanishing average \( \omega_{\zeta_0} \)

\[
W(\zeta_i) = \exp \left[ -\frac{1}{2} \sum_{i=1}^3 \int k_i^{-1} (\zeta_i(s) - \omega_{\zeta_0})^2 ds \right]. \tag{3}
\]

In other words, \( \zeta_i(s) / s \) are \( \delta \) correlated along the chain:

\[
\langle [\zeta_i(s) - \omega_{\zeta_0}] [\zeta_i(s') - \omega_{\zeta_0}] \rangle = \frac{1}{k_i} \delta_{ij} \delta(s - s'). \tag{4}
\]

In this case, we need to average over \( \zeta_i \) again for \( B \) so
The next question is would it be possible to replace the nonvanishing $\omega_0$ in the model by $\omega_0=0$ by renormalizing further $\beta$? The answer to this question depends on the situation. For the end-to-end distance of a very long filament free of external force, the answer is yes [11,12,24]. But the convergence to that limit is slow so the above replacement is poor for moderate length (from a few $l_p$ to about 20 $l_p$) two-dimensional filaments [24]. When relating applied force and extension, such a replacement is also only reasonable at low force and large $L$ [8,24].

IV. THE EFFECTS OF SEQUENCE-DEPENDENT PERSISTENCE LENGTHS

Now we consider the effects of the $a_i(s)$ alone but keep $\xi_i$ as well defined. In this case, we assume that the distribution of the $a_i$ is half-Gaussian since $a_i<0$ is meaningless:

$$p[a_i(s)] = \exp \left[ -\frac{3}{2} \int b_i \left( a_i(s) - \tilde{a}_i \right)^2 ds \right], \ a_i > 0. \quad (9)$$

It is difficult to do an average over $a_i$ if $\tilde{a}_i$ is small. Therefore, we assume that $\tilde{a}_i$ is far from zero, which is reasonable for semiflexible biopolymers such as dsDNA, so approximately we have

$$Z_a = \int_0^\infty D[a_i] p[a_i(s)]$$

$$= \int_0^\infty D[a_i] \exp \left[ -\frac{3}{2} \int b_i \left( a_i(s) - \tilde{a}_i \right)^2 ds \right],$$

and so $Z_a$ is dependent on $b_i$ only. Thus, in this case,

$$B_a = \frac{1}{Z_a} \int D[a_i] p[a_i(s)] \left[ \int D[\omega_i] B[\omega_i(s)] e^{-E_i} \right],$$

$$= \frac{1}{Z_a'} \int D[\omega_i] B[\omega_i(s)] C[\omega_i(s)], \quad (11)$$

where

$$C[\omega_i(s)] = \int D[a_i] p[a_i(s)] e^{-E_i}, \quad (12)$$

and $Z'_a = \int D[\omega_i] e^{-E_i}$ is dependent on $a_i(s)$. Applying standard path integral methods [28] leads to

$$Z'_a \approx \lim_{N \to \infty} \prod_{i,j=1}^{N/2} \left( \frac{\pi}{2a_i(\epsilon)} \right)^{N/2}, \quad (13)$$

where $\epsilon=L/N$, and $a_{ij}=a_i[(j-1)\epsilon]$ is the discretized $a_i(s)$. The form of $Z'_a$ makes it impossible to find a closed form for $C[\omega_i(s)]$. However, if the distribution in $a_i$ is narrow, which should be the case when the molecules forming the different segments are similar such as dsDNA, we can then replace the $a_i$ in Eq. (13) by $\tilde{a}_i$, so $Z'_a$ can be taken out of the integrand in $C$ [see Eq. (12)] and written as

$$Z'_a = \int D[\omega_i] e^{-E_i}, \quad (14)$$

where

$$E_i = \frac{1}{2} \sum_{i=1}^3 \int_0^L \left[ \tilde{a}_i(\omega_i - \xi_i) \right]^2 ds. \quad (15)$$

As a consequence,

$$C[\omega_i(s)] = \frac{1}{Z'_a} \int D[\omega_i] p[\{\omega_i(s)\}] e^{-E_i}. \quad (16)$$

Now using the identity

$$b \left[ a - \tilde{a} + \frac{1}{2b}(\omega - \xi)^2 \right] + a(\omega - \xi)^2 - \frac{1}{4b}(\omega - \xi)^4,$$

we obtain

$$C[\omega_i(s)] = \frac{Z'_a}{Z_a} e^{-E_i},$$

$$B_a = \frac{1}{Z_a} \int D[\omega_i] B[\omega_i(s)] e^{-E_i}, \quad (19)$$

where

$$E_i = \frac{1}{2} \sum_{i=1}^3 \int_0^L \left[ \tilde{a}_i(\omega_i - \xi_i)^2 - \frac{1}{4b}(\omega_i - \xi_i)^4 \right] ds. \quad (20)$$

Due to the existence of the term $(\omega_i - \xi_i)^4$ in Eq. (20), $B_a$ is divergent if there is no constraint on $\omega_i$. However, biopolymers cannot have infinite $\omega_i$, so there is a cutoff for $\omega_i$. This cutoff should be large enough so that for the $(\omega_i - \xi_i)^2$ term we can remove the constraint on $\omega_i$. Moreover, it was reported that for a dsDNA chain with 64 trinucleotides, $\langle (L_1^2 - l_p^2) \rangle = 0.13 l_p^2$ [19]. This means that even for a short dsDNA chain, the distribution of $L_p$ is not very wide. It is therefore reasonable to expect that for a long semiflexible biopolymer, the distribution of $a_i$’s becomes very sharp and the $b_i$’s are large. We can then expect that the $(a_i - \xi_i)^4$ term remains small and can be neglected up to the cutoff of $\omega_i$. Consequently we have

$$B_a = \frac{1}{Z_a} \int D[\omega_i] B[\omega_i(s)] e^{-E_i}, \quad (21)$$

Equation (21) means that we can replace $a_i(s)$ by $\tilde{a}_i$. This conclusion agrees with the conclusion for the special case $a_i=1$, $\tilde{a}_i=0$, and $\omega_0=0$ [19]. However, for a short biopolymer, the contribution from $(\omega_i - \xi_i)^4$ cannot be ignored, and the results tend to be divergent making the averages poorly defined functions of $L$, as was reported for the special case [19].

From the above derivations, we see that it is not a simple task to study the combined effects of the sequence dependence of $a_i$ and $\xi_i$ because of the term $(\omega_i - \xi_i)^4$ and the fact that $\beta_i$ is not a linear function of $a_i$. However, when Eq. (21)
is valid, Eqs. (7) and (8) can be recovered with the replacement of $a_i$ by $\tilde{a}_i$.

V. CONCLUSION AND DISCUSSION

In summary, we present a rigorous and general proof that for a biopolymer without correlation or with SRC on spontaneous curvatures and torsions $\zeta$, the effects of sequence disorder on $\zeta$ can be incorporated into a model with well-defined mean $\zeta_i$ [i.e., $\omega_i$] as well as renormalized persistence length, no matter how long the biopolymer and how large the external force may be. Moreover, if the biopolymer is sufficiently long and has a large enough mean persistence length, the sequence-dependent persistence length $a_i(s)$ can be replaced by its mean $\tilde{a}_i$. Note that “semiflexible” in general means that the biopolymer has a sufficiently large $\tilde{a}_i$, our above conclusions can be safely applied to long semiflexible biopolymers such as dsDNA. However, for a short biopolymer or for a biopolymer with small $\tilde{a}_i$, the effects of homogeneity in $a_i(s)$ become very complex and tend to make physical observables very sensitive to the details of $a_i(s)$. Our derivations are quite general, so the conclusions can be applied to various conformal and mechanical properties.

We should remind the reader that our proof only works in the constant extension ensemble. But it is reasonable to expect that these conclusions also can be applied to sufficient long biopolymers since in this case the structural details must be immaterial. It has been known that the constant extension ensemble and the constant force ensemble may be inequivalent at finite $L$. For constant force ensemble, the same conclusion has been achieved at a special case with $a_i=\omega_i$, $\omega_{i0}=\omega_{00}=0$, and under weak applied force [17], but a proof for the general case is not yet available. In constant force ensemble, we need to add a term, which is the contribution of the external force, into the energy, and the energy becomes [12–15]

$$\mathcal{E} = \int_0^L \left[ \frac{1}{2} \sum_{i=1}^3 a_i(\omega_i - \zeta)^2 - F \cos \theta \right] ds,$$  

where $F = f/(k_BT)$ and $f$ is the applied force. $\theta$ is the angle between force and the tangent of the central line of the filament and is a very complicate function of $\omega_i$. This force term makes $Z_{aw}$ dependent on $\zeta$ and so renders the exchange of the order in integral [from Eqs. (5)–(7)] illegal. Therefore, whether the same conclusion is valid in the constant force ensemble for a short biopolymer is still an open question.

Moreover, we should recall that SRC in this work means that with proper length scale, the distribution function is Gaussian. What is the proper length scale is not yet very clear. It has been reported that the most bendable DNA sequences are those that wrap around nucleosomes, and there exists a correlation in the way they are arranged. Along the DNA contour, AA/TT/TA dinucleotides have a periodicity of about 10 base pairs and this is the signature of the region with high affinity to nucleosomes [25]. Therefore, a reasonable estimate of the proper length scale for dsDNA is about 10 base pairs. We do not consider systems with LRC in $\zeta_i$ and/or $a_i$ in this work so it deserves further investigation. But we should point out that LRC in sequences is not the same as LRC in $\zeta_i$. For instance, for a homopolymer, the correlation in sequences is 100%, but it can be described by constant (or vanishing) $\zeta_i$ so can be regarded as no correlations in $\zeta_i$ since it corresponds to the limit case of Gaussian distribution with vanishing variances. In the more general case, LRC in sequences tends to make neighbor sequences have similar bending so to develop a macroscopic intrinsic curvature, and the local intrinsic curvatures may have only a small random deviation from its mean, it in turn leads to the SRC in $\zeta_i$ at least in the first approximation. As a consequence, many properties, such as the behavior of the end-to-end distance [24], of such a biopolymer can be well accounted for by a model with constant (or well-defined) spontaneous curvature. Finally, the method used in this work may be applied to some other similar systems, such as Hookian springs with random natural lengths, or a quantum harmonic oscillator with randomly moving centers, or a quantum planar rotor in a randomly rotating coordinate system.

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