DNA elasticity: topology of self-avoidance

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Abstract
We present a theoretical treatment of DNA stretching and twisting experiments, in which we discuss global topological subtleties of self-avoiding ribbons and provide an underlying justification for the worm-like rod chain (WLRC) model proposed by Bouchiat and Mezard. Some theoretical points regarding the WLRC model are clarified: the ‘local writhe formula’ and the use of an adjustable cut-off parameter to ‘regularize’ the model. Our treatment brings out the precise relation between the worm-like chain (WLC), the paraxial worm-like chain (PWLC) and the WLRC models. We describe the phenomenon of ‘topological untwisting’ and the resulting collapse of link sectors in the WLC model and note that this leads to a free energy profile periodic in the applied link. This periodicity disappears when one takes into account the topology of self-avoidance or at large stretch forces (paraxial limit). We note that the difficult non-local notion of self-avoidance can be replaced (in an approximation) by the simpler local notion of ‘south avoidance’. This gives an explanation for the efficacy of the approach of Bouchiat and Mezard in explaining the ‘hat curves’ using the WLRC model, which is a south avoiding model. We propose a new class of experiments to probe the continuous transition between the periodic and aperiodic behaviour of the free energy.

1. Introduction
Motivated by experiments [1, 2] in which single DNA molecules are stretched and twisted to measure their elastic properties, Bouchiat and Mezard (BM) [3] have proposed the worm-like rod chain (WLRC) model, which gives a fair fit to the experimental data. However, several theoretical aspects of the WLRC model remain unclear, as evidenced by recent letters [4, 5]. Points of dispute are BM’s use of a local Fuller writhe formula (as opposed to the non-local Călugăreanu–White formula [6]) and the need for a phenomenologically introduced cut-off parameter, which has to be adjusted to fit the data.

The theoretical issues raised by the experiments of [2] are surprisingly subtle. A reading of the discussion by Bouchiat and Mezard of the ‘local writhe formula’ [3] may give the misleading impression that the Călugăreanu–White formula and the Fuller formula [7, 8] are
simply different ways of expressing the same quantity, the writhe. In fact, there can be no local writhe formula. The writhe which appears in Călugăreanu’s theorem $Lk = Tw + Wr$ is given by the non-local Călugăreanu–White formula and jumps by two units when the curve is passed through itself. No local integral can replicate this behaviour. Bouchiat and Mezard use the ‘local writhe formula’ under the assumption that the Euler angles are regular functions of the arc length parameter $s$. This assumption breaks down at the coordinate singularities of the Euler angles. So, Bouchiat and Mezard are effectively computing the distribution of the ‘Fuller writhe’, which is not the same as the Călugăreanu–White writhe. Nevertheless, Bouchiat and Mezard obtain good agreement with experiment. The question remains: why does it work? The purpose of this paper is to clarify these issues: we show that these questions are related to the topology of self-avoidance.

This paper is structured as follows: we first describe the experimental set-up and summarize the experimental data. We then explain the problem that we address, which concerns a global topological subtlety in the configurations of ribbons. In resolving the problem we point out the connection between the worm-like chain (WLC)\(^1\), the paraxial worm-like chain (PWLC) and the worm-like rod chain (WLRC) models. We propose an experiment which brings out the relation between the models by continuously interpolating between them. We conclude the paper by comparing with previous work.

2. Experiments

Micromanipulation techniques are now so sophisticated that experimenters can stretch and twist single DNA molecules to probe their elastic properties under a torsional constraint. In a typical experiment [2], one end of a single molecule of double stranded DNA is attached to a glass plate and the other to a magnetic bead. The glass plate is kept fixed and the bead is pulled by magnetic field gradients and rotated by magnetic fields. By such techniques the molecule is stretched and twisted by hundreds of turns and the extension of the molecule is measured as a function of the number of turns applied to the bead for a fixed force [2]. Another experiment measures the torque–twist relation at fixed force [9] using a slightly different experimental technique. The length of the DNA molecule is typically about $20 \mu m$, its thickness $2 \text{ nm}$ and the bead is about $4.5 \mu \text{m}$ in diameter. In practice, this size of bead is adequate to prevent the molecule from untwisting by looping around the bead [4]. A typical experimental plot is shown in [2]. These curves are easy to understand qualitatively: as one twists the molecule, its extension progressively decreases as one can guess by playing with a cord or ribbon. Further twisting leads to buckling and the formation of twisted braids or ‘plectonemes’, which are familiar on telephone cords. Electron micrographs [10] of DNA show branched polymeric structures, which indicate the formation of plectonemes.

To understand the experimental curves quantitatively more work is needed. Unlike telephone cords, DNA is seriously affected by thermal fluctuations and there are entropic effects to be accounted for. Several papers have already treated this problem [3, 4, 11, 12]. The high force regime, which is amenable to perturbation theory about the taut polymer configuration, is well understood [11, 12]. In the low force regime, where self-avoidance effects are appreciable [13], a consensus is still lacking, and this is the primary focus of this paper.

3. Theoretical models

To define a theoretical model we need to specify the allowed configurations $C$ of the polymer given the experimental constraints, write down a microscopic Hamiltonian or energy $E(C)$ for

\(^1\) Note that we use the term WLC model to describe a polymer with bend as well as twist degrees of freedom.
each configuration \( C \) and express the partition function as a sum over configurations with Boltzmann weight. All experimentally accessible quantities can be obtained from the partition function. The problem therefore is to calculate the partition function

\[
Z(\mathbf{r}, Lk) = \sum_{C \in \mathcal{C}} e^{-E(C)/kT}
\]

(1)

where \( \mathbf{r} \) is the vector separation between the ends of the molecule, \( Lk \) is the number of times the bead has been turned (which could be fractional) and the summation appearing in the expression for the partition function represents a sum over all allowed configurations of the polymer. \( E(C) \) is an energy functional which assigns an energy \( E(C) \) to each allowed configuration \( C \). Specification of the allowed configurations and this energy functional defines the model completely. The next step is to ‘solve’ the model, i.e. deductively work out its experimental consequences. The objective is to confront theory with experiment and learn from the discrepancy as well as the agreement. Unfortunately, ‘solving’ the model is not always a practical proposition even in idealized situations. Solvable theoretical models are therefore a valuable aid to understanding.

It is often convenient to deal with conjugate variables \((B, f)\) instead of \((Lk, r)\) and the Fourier–Laplace transform of the partition function. \( \hat{Z}(B, f) = \int dLk \mathcal{D}r \mathcal{D}Z(Lk, r) e^{-iB Lk + f \cdot r} \).

We shall restrict ourselves to the limit of long polymers (i.e. for a polymer of contour length \( L \rightarrow \infty \)). In this limit, the \((B, f)\) and \((Lk, r)\) ensembles are equivalent. This equivalence holds only in the limit of long polymers [14].

A twist storing polymer of length \( L \) is modelled [3, 11] as a ribbon \( \{\mathbf{x}(s), \mathbf{u}(s)\} \) where \( s \)

0 \leq s \leq L, is an arc-length parameter along \( \{\mathbf{x}(s)\} \). \( \mathbf{u} \) represents the 'ribbon vector' and is required to satisfy \( \mathbf{u} \cdot \mathbf{i} = 0 \), where \( \mathbf{i} = \frac{\mathbf{L}}{\Omega_1} \).

The ribbon is described as a family of curves \( \mathbf{x}(s) + \epsilon \mathbf{u}(s) \), where \( \mathbf{x}(s) \) is a curve and \( \mathbf{u}(s) \) represents a slight \( (\epsilon) \) thickening of it along \( \mathbf{u}(s) \) with \( \epsilon \) a small parameter. Let \( \kappa(s) = \frac{1}{\mathbf{L}} \) be the curvature and \( \Omega_1(s) = \mathbf{L} \cdot \mathbf{u} / \Omega_1 \) the twist of the ribbon.

In the models we discuss, the energy \( E(C) \) of a configuration \( C \) is given by

\[
E[C] = 1/2 \int_0^L ds [\kappa^2(s) + C \Omega_1^2(s)],
\]

(2)

where \( A \) is the bending modulus and \( C \) the twist modulus. Other terms can be added as in [11] with more parameters, but these are not necessary for our purposes.

In order to compute the partition function \( Z(\mathbf{r}, Lk) \), at fixed link \( Lk \) and extension \( \mathbf{r} \), we need to specify \( C \), the allowed configurations of the polymer. This is what distinguishes the different models we now describe. In all the models we consider here, the configurations of the polymer are required to obey the following constraints: the polymer extends from \( \mathbf{x}(0) = \mathbf{0} \) to \( \mathbf{x}(L) = \mathbf{r} \) and has fixed tangent vectors at the ends, \( \mathbf{i}(0) = \mathbf{i}(L) = \hat{z} \) and the ribbon vectors at the ends are given by \( \mathbf{u}(0) = \hat{x} \) and \( \mathbf{u}(L) = R(2\pi L \hat{k}) \hat{x} \).

In addition, there may be further constraints which define the model and such constraints can alter the topology of the configuration space and qualitatively alter the predictions of the theoretical model. For quantitative agreement with experimental data one needs to take into account the geometry and the statistical mechanics of the model.

An important principle to bear in mind is that in equation (1), one should only sum over a single topological class [15]. Thermal agitation makes the polymer explore different configurations. But since these agitations only cause continuous changes, the polymer will remain in a single topological class. We should therefore sum over all configurations in a single topological class and not sum over distinct topological classes. Once this principle is understood and consistently applied, we find that the theoretical picture becomes much clearer.
(a) Worm-like chain (WLC). In this model no further constraints are imposed on $\vec{x}(s)$. Thus the polymer is allowed to intersect itself. While the set of self-intersecting configurations may be of small measure in the configuration space $C_a$, such configurations profoundly affect the topology of the configuration space, for a WLC polymer can release link two units at a time by passing through itself [16, 15, 17]. This ‘topological untwisting’ results in a collapse of link sectors. All link values differing by two are in the same topological sector and one has to sum $Z(\vec{r}, Lk)$ over $Lk$ classes differing by two. This model has been treated in [15] and leads to a partition function which is periodic in $Lk$ with period two. This periodicity is clearly at variance with the aperiodicity seen in the experimental curves [2], where, as we mentioned before, the extension progressively decreases as the bead is turned hundreds of times. The discrepancy between the WLC model and experimental data is clearly due to not taking into account the topological effects of self-avoidance.

However, there is a limit (the paraxial worm-like chain (PWLC)) of the WLC model which yields an aperiodic free energy profile. In the high tension regime (large force or $|\vec{r}|$ comparable to the contour length $L$), the polymer is essentially straight between its ends and the tangent vector $\hat{t}$ only makes small deviations from the direction $\hat{z}$ of the applied force, which we call the north pole (of the sphere of tangent directions). In this regime, one can do perturbation theory and approximate the sphere of directions by the tangent plane at the north pole. This defines the PWLC.

(b) Paraxial worm-like chain (PWLC). The tangent vector $\hat{t} = \frac{d\vec{x}}{ds}$ must be near $\hat{z}$, the direction of the applied force i.e. $\hat{t} \sim \hat{z}$. The PWLC model has been treated in [11] and a simple analytic form for the writhe distribution is given in [12]. In this model, the polymer cannot release link by passing through itself since the high force prevents the molecule from looping back on itself to release link. However, this model only works in the limit of large forces (theoretically, infinite) and does not address the low force regime, which is experimentally accessible. In order to prevent the polymer from releasing link at low forces by passing through itself, one would like to impose a condition preventing the polymer from intersecting itself. This defines the self-avoiding worm-like chain.

(c) Self-avoiding worm-like chain (SAWLC). The configurations must be self-avoiding:

$$\vec{x}(s) \neq \vec{x}(s'),$$

for $s \neq s'$. However, even this condition (3) is not sufficient to prevent topological untwisting. The experiments reported in [2] study the elastic properties of linear DNA molecules, not circular ones. So we need to address the issue of modelling open ribbons. Open ribbons again need careful handling because of topological untwisting: an open ribbon can untwist itself by two turns even in model (c) by going around its end and thus can change its link $Lk$ by two. Consequently, a configuration with a link $Lk$ is in the same topological class as a configuration with link $Lk + 2$ and we once again get a collapse of $Lk$ sectors leading to a periodic partition function [15]:

$$Z(\vec{r}, Lk + 2) = Z(\vec{r}, Lk).$$

In real experiments, there is an obstruction to releasing two units of link by going around the ends: the size of the magnetic bead is large enough to prevent topological untwisting of the polymer over the duration of the experiment. To model this obstruction to topological untwisting we close the open ribbon with a reference ribbon that goes through the bead, makes a large fixed circuit and returns to meet the polymer at the glass slide. We require that the reference ribbon and the real ribbon together form a non-self-intersecting closed ribbon. (Note that we can allow for a fractional link by permitting a discontinuity in the ribbon vector $\hat{u}$ at
\[ s = L: \hat{u}(L - \epsilon) = R\hat{u}(L + \epsilon), \]  
where \( R \) represents a rotation about \( \hat{i} \) and \( \epsilon \) is a small parameter. The condition of self-avoidance keeps the real ribbon from going around its ends and effectively constrains the applied link. It is understood that when we sum over polymer configurations we only sum over configurations in which the real polymer is changed. This is the ‘active part’ of the polymer, as opposed to the ‘passive’ reference ribbon, which is not summed over. The self-avoiding worm-like chain is defined by only allowing configurations which do not intersect themselves or the reference ribbon. This configuration space is called \( C_e \).

As we mentioned before, this model is not tractable analytically. Ideally, we would like to work with \( C_e \) and sum over (the active parts of) all non-self-intersecting closed ribbons extending from 0 to \( \vec{r} \) (and returning to 0 along a reference curve) with fixed \( Lk \). However, the constraint of self-avoidance is far from easy to handle! The constraint is non-local in the arc length parameter \( s \) and is hard to implement analytically [13]. This has led Bouchiat and Mezard [3] to propose a new model which they call the worm-like rod chain (WLRC).

(d) The worm-like rod chain (WLRC) is defined by imposing the additional constraint on the WLC configuration space \( C_a \) that the tangent vector \( \hat{t} \) must nowhere point south \( \hat{t} \neq -\hat{z} \). Recall that the force is applied in the \( z \) direction, which we call north. This is also the direction in which the tangent vectors at the end are held fixed. Unlike the self-avoidance constraint, the ‘south avoidance’ constraint is local in the arc length parameter \( s \). As a result, the model is amenable to semi-analytic treatment. The authors of [3] enforce the constraint by using a repulsive potential at the south pole of the sphere of directions. The width of this potential is \( \epsilon \), which serves as a cut-off. This model gives an aperiodic free energy profile and a very good fit to the experimental data after the cut-off is suitably adjusted. While the WLRC model does agree with the data, its theoretical significance is not clear to many workers in the field (see the recent exchanges [4, 5] over the significance of the cut-off and the local writhe formula). The purpose of this paper is to explain the nature of the relationship between the WLC, the WLRC and the PWLC models, explore different regimes of the elasticity of twist storing polymers and note that one can continuously interpolate between them in experimental situations. To summarize, the self-avoiding worm-like chain (SAWLC (c)), the paraxial worm-like chain (PWLC (b)) and the worm-like rod chain (WLRC (d)) emerge by placing additional constraints on the worm-like chain (WLC) model (a) [15]. One important qualitative feature that distinguishes the WLC from the other models is the fact that the WLC predicts a periodic free energy whereas the other models predict aperiodic free energies. In the WLC model the system is delocalized over \( Lk \) sectors. This can be visualized in terms of a periodic multiple well potential where the thermal energy is high enough for a particle to visit all wells. From this point of view the SAWLC, WLRC and PWLC are topologically and qualitatively similar and markedly different from the WLC model.

The topological differences between these various models can also be expressed in terms of the variable \( B \) conjugate to the applied link \( Lk \) variable. This conjugate variable \( B \) can be interpreted as a magnetic field [3, 12, 15]. In the WLC model (a) \( B \) has the interpretation of the field of a magnetic monopole located at the centre of the sphere of tangent directions to the polymer [15]; the magnetic flux is quantized and this leads to a periodicity of the free energy. In the PWLC model (b), the excursions of the polymer are confined to the tangent plane at the north pole, and the magnetic field \( B \) is on a plane and therefore not quantized. As a result the free energy is not periodic in the link \( Lk \).

In the WLRC model, because of the constraint of south avoidance, \( B \) is defined on a sphere punctured at the south pole. Since the topology of the punctured sphere is identical (by stereographic projection) to that of the plane, there is no quantization condition just as in the PWLC model, and again this leads to an aperiodic free energy profile (see figure 1).
Figure 1. The free energy of the WLC model has a periodicity (due to a collapse of $Lk$ sectors) which can be removed by imposing self-avoidance or south avoidance or large stretch forces. All these are different ways of separating the $Lk$ sectors and preventing the ‘collapse of link sectors’.

4. Wreathe and writhe

In fact, the right model to describe a real polymer under a torsional constraint would be the self-avoiding WLC (SAWLC) model (c), which puts a constraint on the polymer passing through itself or the reference ribbon. However, as discussed earlier, such a model is hard to solve because of the non-locality of the constraint. We show below that the WLRC model captures some of the essential topological features of the SAWLC model and thus enables us to deal with a simpler and solvable model where the constraint reduces to a local one instead of a non-local one. Below, we show that (i) the WLRC model captures the right qualitative behaviour of the partition function. The WLRC partition function is aperiodic in the applied link, unlike the WLC partition function [15], which is periodic. (ii) Quantitatively, the WLRC partition function is a better approximation to the SAWLC partition function than the PWLC partition function and works even for low forces.

We begin with the qualitative features, which are of a topological nature. The central quantity of interest (equation (1)) is the partition function $Z(Lk)$, which is the sum over ribbon configurations with fixed link ($Lk$). Călugăreanu’s theorem [6] tells us that $Lk = Tw + Wr$, where the twist $Tw = \int \Omega_2(s) ds$ is the integral of the local twist $\Omega_2(s)$ along the curve. Writhe ($Wr$) is a quantity that only depends on the curve $\{\vec{x}(s)\}$ and not on the ribbon vector $\{\vec{u}(s)\}$ [13]. The problem thus neatly splits into two parts. The link distribution is the convolution of the twist distribution and the writhe distribution [3, 12]. The twist distribution is a quadratic path integral and is easily evaluated. The problem that remains is to compute the writhe distribution. Thus the problem reduces from one defined on the space of ribbon configurations ($C$) to one defined on the space of ribbon backbones ($\tilde{C}$) or the space of curves. We can formally set the twist elastic constant to infinity ($C = \infty$, the molecule is impossible to twist) so that $Lk = Wr$ and then the $Lk$ distribution is identical to the $Wr$ distribution.

The writhe is a non-local quantity defined only on closed non-self-intersecting curves. Let $s$ range over the entire length $L_0$ of the closed ribbon (real ribbon + reference ribbon) and let
us consider \( \vec{x}(s) \) to be a periodic function of \( s \) with period \( L_0 \). Let \( \vec{R}(s, \sigma) = \vec{x}(s + \sigma) - \vec{x}(s) \). \( \vec{R}(s, \sigma) \) is non-vanishing for \( \sigma \neq 0 \), \( L_0 \) and the unit vector \( \vec{r}(s, \sigma) \) is well defined. It is easily checked that as \( \sigma \to [0, L_0], \vec{r} \to [\hat{r}, -\hat{r}] \) respectively. The Calugareanu–White writhe is given by [17, 18]2

\[
\mathcal{W}_{\text{CW}} = \frac{1}{4\pi} \oint_0^{L_0} \frac{d\sigma}{ds} \int_{0}^{L_0} \left[ \frac{d\vec{R}(s, \sigma)}{ds} \times \frac{d\vec{R}(s, \sigma)}{d\sigma} \right] \cdot \hat{R}.
\] (4)

The non-locality of \( \mathcal{W}_{\text{CW}} \) makes it difficult to handle analytically. However, the key point to note is that variations in \( \mathcal{W}_{\text{CW}} \) are local [7]. Let \( \vec{C}(\tau) \) be a family of non-self-intersecting closed curves with writhe \( \mathcal{W}_{\text{CW}}(\tau) \). Taking the \( \tau \) derivative of equation (4) we find that the resulting terms can be rearranged to give [19]

\[
\frac{d\mathcal{W}_{\text{CW}}}{d\tau} = \frac{1}{2\pi} \oint_0^{L_0} \frac{d\Omega}{d\tau} \int_{0}^{L_0} \left[ \frac{d\vec{r}}{ds} \times \frac{d\vec{r}}{d\tau} \right] \cdot \hat{r}.
\] (5)

which clearly has the interpretation of the rate at which \( \vec{r}(s, \tau) \) sweeps out a solid angle in the space of directions. Note that equation (5) is a single integral [19] and therefore a local, additive quantity. Changes of writhe are local integrals and receive contributions only from the active parts of the curve. Equation (5) can be rewritten as

\[
\frac{d\mathcal{W}_{\text{CW}}}{d\tau} = \frac{1}{2\pi} \frac{d\Omega}{d\tau}
\] (6)

where \( \Omega \) is the solid angle enclosed by the oriented curve \( \{\vec{r}(s) | 0 \leq s \leq L_0 \} \) on the unit sphere of tangent directions as \( s \) goes from \( 0 \) to \( L_0 \) [13, 15]. Note that \( \Omega \) is only defined modulo \( 4\pi \): for a solid angle \( \Omega \) to the left of the oriented curve \( \vec{r}(s) \) is equivalent to a solid angle \( (4\pi - \Omega) \) to the right. \( d\Omega/d\tau \) is, however, well defined and local. Integrating equation (6) we arrive at [7]

\[
\mathcal{W}_{\text{CW}}(\tau) = \frac{1}{2\pi} \Omega(t) - 1 + 2n
\] (7)

where \( n \) is an arbitrary integer.

There is a quantity one can construct from the writhe which is well defined on all curves (not just simple ones):

\[
w(\vec{C}) = \exp[i\pi\mathcal{W}_{\text{CW}}(\vec{C})] = -\exp[i\Omega/2]
\]

is a complex number of modulus unity which we call the wreathe. From the geometric phase point of view (see the analogy developed in [15]) the wreathe is a very natural object to consider; it is simply the geometric phase of a spin half system in a cyclically varying magnetic field. When a curve is passed through itself, \( \mathcal{W}_{\text{CW}} \) jumps by two, but the wreathe is unchanged. We can therefore smoothly extend \( w \) to all closed curves including non-simple curves. The wreathe can be used to define a local quantity, the ‘Fuller writhe’ [7], for curves which are nowhere south pointing.

Let us define the ‘wreathe angular velocity’ \( \dot{A}_r = -i\omega^{-1}\partial w/\partial \tau = \frac{1}{\tau} d\Omega/d\tau \) as a ‘vector potential’ on the space of curves. It is easily seen that \( \dot{A}_r \) is curl free. However, \( \dot{A}_r \) is not a gradient in the space of all curves: there exists no function \( W \) defined on all curves such that \( \dot{A}_r \) is given by \( dW/d\tau \). This follows because there exist closed circuits \( \vec{C}(\tau) \) in the space of curves for which the integral \( \oint \vec{r} \, dr \dot{A}_r \) is non-zero. Such circuits enclose a non-zero topological flux and are link changing changing closed circuits (LCCCs). They describe the process of topological untwisting.

Notice that the integrals for the writhe formula are incorrectly given in [17] as two cyclic integrals (i.e. the integration ranges over a torus). The range of integration is in fact a cylinder rather than a torus. Our limits are the same as those used in [18].
Let us choose a fiducial curve $\tilde{C}_s$, which goes from $\tilde{0}$ to $\tilde{r}$ in a straight line, whose tangent vector is identically north pointing. Observe that all south avoiding curves are deformable to the fiducial curve $\tilde{C}_s$ via south avoiding curves. One simply deforms the tangent vector $\tilde{t}(s)$ along the unique shorter geodesic connecting $\tilde{t}(s)$ to the north pole. We now define the Fuller writhe as

$$\mathcal{W}_F = \frac{1}{\pi} \int_{\tilde{C}_s} \theta \, d\tau, -1.$$  

Writing the unit tangent vector as $\tilde{t} = (\sin \theta \cos \phi, \sin \theta \sin \phi, \cos \theta)$, $\int_0^1 \frac{d\theta}{\cos \theta}$ can be written as $\int ds \frac{d\theta}{\cos \theta}$ for all curves for which the tangent vector never points towards the south pole of the sphere of tangent directions. We can therefore write a ‘local writhe’ on such curves which we call ‘south avoiding curves’:

$$\mathcal{W}_F = \frac{1}{2\pi} \int ds (1 - \cos \theta) \frac{d\phi}{ds}, -1. \tag{8}$$

While (8) is expressed in local co-ordinates on the sphere, it has a clear geometric meaning: $2\pi (1 + \mathcal{W}_F)$ is equal to the solid angle swept out by the unique shorter geodesic connecting the tangent vector $\tilde{t}$ to the north pole [20, 21]. This definition is explicitly not rotationally invariant, since it uses a fixed fiducial curve $\tilde{C}_s$ and singles out a preferred direction.

This definition of ‘Fuller writhe’ is motivated by a theorem of Fuller [7], which gives the CW writhe of a curve which is deformable to the fiducial curve by a family of curves which is self-avoiding and south avoiding. For such curves, the Fuller writhe agrees with the CW writhe. However, in general, the ‘Fuller writhe’ is not equal to the CW writhe, which is what appears in the Călugăreanu–White formula. In fact, the definition of Fuller writhe extends easily to all curves which are south avoiding, since equation (8) does not require any more conditions.

We remarked earlier that $A_\tau$ is not a gradient on the space of all curves. Only in certain restricted classes of curves can it be expressed as a gradient. For example, $A_\tau$ is a gradient in the space of south avoiding curves $A_\tau = \pi \frac{d\omega}{d\tau}$. It is also a gradient in the space of south avoiding curves $A_\tau = \pi \frac{d\omega}{d\tau}$.  

To summarize, $\mathcal{W}_{CW}$ is defined on all self-avoiding curves, $\mathcal{W}_F$ on all south avoiding curves. On curves which are deformable to the fiducial curve $\tilde{C}_s$ through south and self-avoiding curves the two notions agree [7] ($\mathcal{W}_{CW} = \mathcal{W}_F$). When a curve passes through itself $\mathcal{W}_{CW}$ jumps by two, and when the tangent vector to a curve swings through the south pole $\mathcal{W}_F$ jumps by two units. The writhe is a real number which has both geometric and topological information. The topological part is the integer part of $\frac{\mathcal{W}_{CW}}{\pi}$ and the geometric part is the fractional part of $\frac{\mathcal{W}_F}{\pi}$. The geometric part is completely captured by writhe, but the topology is lost since writhe is insensitive to changes in writhe by two units. From the definitions it is clear that on curves where these quantities are well defined

$$-\frac{1}{\pi} \frac{d\omega}{d\tau} = \frac{d\mathcal{W}_{CW}}{d\tau} = \frac{d\mathcal{W}_F}{d\tau}, \tag{9}$$

so changes in writhe are the same whether measured by $\mathcal{W}_{CW}, \mathcal{W}_F$ or $\omega$. Note that $\omega$ is well defined on all curves.

Let us now apply these general topological ideas to understand the configuration space of the polymer ribbon. As stated earlier, we need to sum over a single topological sector of the configuration space. For a ribbon, this means summing over a single knot class $K$ of the ribbon backbone $\tilde{C}$ and a single link class $L_k$ of the ribbon. So, in fact the true partition function

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3 The space of south avoiding curves is contractible, unlike the space of self-avoiding curves, which splits into distinct knot class sectors.
\(Z_K(\tilde{C}, Lk)\) would depend not only on the extension and the link, but also the knot class of the ribbon backbone. Needless to say, this is a hopelessly intractable problem.

The constraint of self-avoidance is a non-local constraint in \(s\) and very hard to handle analytically. Even in the pure bend model \([22, 23]\) one cannot handle this constraint and so one just gives up self-avoidance and sums over all configurations. This is of course an approximation, but it seems to work well. Instead of evaluating (1) with \(\tilde{C}\) equal to simple curves in a single knot class \(K\) (for example, the trivial knot class),

\[
Z_K = \sum_{\tilde{C} \in K} e^{-\beta E(\tilde{C})}
\]

(10)

we are effectively summing over knot classes and computing \(Z = \sum_K Z_K\) since we are unable to impose self-avoidance. The resulting analysis still gives a reasonable account of the data \([1, 22]\). This suggests that the contribution from the non-trivial knot classes may not be significant. In fact, in the presence of a force \(f\), there is an energy cost \(f L_F\) leading to a suppression \(e^{-f L_F}\) of the probability of forming knots \([24]\).

In the case of twisting polymers, giving up self-avoidance has a more serious consequence. Giving up self-avoidance leads not only to an identification of knot sectors, but also link sectors separated by two units. This is due to LCCCs. These are closed circuits in the space of curves, which when lifted up to the space of ribbons by continuity become open and lead to an identification of link sectors. We show below that LCCCs must pass through both south pointing and self-intersecting curves.

More precisely, our main result is that in any closed circuit the number of signed self-crossings is equal to the number of signed south crossings.

**Proof.** The proof uses the fact that the wreathe is defined on all curves. Consider a closed circuit \(\tilde{C}(\tau)\) \((0 \leq \tau \leq 1)\) in \(\mathcal{C}_a\) which starts from \(\tilde{C}_a\) and returns to it: \(\tilde{C}(0) = \tilde{C}(1) = \tilde{C}_a\). If we now compute the wreathe (which is defined on all curves) we find that as \(\tau\) varies from zero to unity, \(0 \leq \tau \leq 1\), the wreathe \(w(\tau)\) describes a motion on the unit circle and returns to its starting point. The number of times \(w(\tau)\) winds around the unit circle is given by

\[
k = -i \int_0^1 \frac{d\tau}{\pi} w^{-1} dw/ \frac{d\tau}{\pi} = \frac{1}{\pi} \oint \frac{d\tau}{A_1}.
\]

Using equation (9) we find that \(k\) measures (i) the number of times (counted with sign) the polymer passes through itself (i.e. \(k = 1/2 \int_0^1 \frac{d\tau}{\pi} \frac{d\tau}{\pi}\)) and (ii) the number of times (counted with sign) the polymer tangent vector swings through the south pole (i.e. \(k = 1/2 \int_0^1 \frac{d\tau}{\pi} \frac{d\tau}{\pi}\)).

The above discussion can be ‘lifted’ in a sense (made precise in the appendix) to the space of ribbons which is the true configuration space. Starting with a closed circuit \(\tilde{C}(\tau)\) and an initial ribbon \(C_a\) whose base curve is \(\tilde{C}_a\), one can lift the circuit \(\tilde{C}(\tau)\) in the space of curves by continuity to the space of ribbons. However, closed circuits in the space of curves may be open in the space of ribbons! This is the well known anholonomy effect. Our main result can then be re-expressed on the space of ribbons: two ribbons based on the same ribbon backbone \(C_a\) are homotopic as self-avoiding ribbons if and only if they are homotopic as south avoiding ribbons.

**Proof.** The argument above also shows that \(2k\) is equal to the net change in the \(Lk\) class of a ribbon if its backbone is continuously deformed along \(\tilde{C}(\tau)\) (since \(Lk = Wr\) in our analysis).

If we specialize to self-avoiding curves \(C_a\) then \(k = \Delta W_{CW} = 0\). If we work with south avoiding curves \(C_a\) then \(k = \Delta W_F = 0\). This proves that self- and south avoidance present the same topological obstruction to release of link \(Lk\). This provides a formal justification for the work of Bouchiat and Mezard \([3]\), where they impose a south avoidance constraint in place of a self-avoidance constraint.
 Quantitatively, this is measured by a good approximation to the SAWLC partition function over a range of parameter space. Consequently, the WLRC partition function is an axially symmetric quantum mechanical problem, for which the Hamiltonian can be solved. However, in this regime, the WLRC works well since the suppression factor \( e^{\frac{-f_{eff} L}{P}} \) is small. Since the WLRC retains the geometry of the sphere (changing only the topology, by removing a point), the WLRC is an improvement on the PWLC model. (iii) At very low (or high) twist \( \langle \theta^2 \rangle \), the region \( \mathcal{R} \) dominates the partition function. More precisely, regions outside \( \mathcal{R} \) are suppressed by a factor \( e^{-f_{eff} L} \). Here \( f_{eff} = f - B^2/(4L_0) \) is an effective force [11, 12] that takes into account the competition between the stretch and the twist. Consequently, the WLRC partition function is a good approximation to the SAWLC partition function over a range of parameter space.

We successively consider the regimes of low, intermediate and high twist. Quantitatively, this is measured by \( f_{eff} \). (i) For \( f_{eff} L_0 \) large, the tangent vector makes small excursions about the north pole and \( \langle \theta^2 \rangle = 1/\sqrt{f_{eff} L_0} \) is small. In this regime, one can approximate the sphere by its tangent plane at the north pole, and as explained earlier this is the regime of the PWLC model. (ii) For \( \langle \theta^2 \rangle \) of order unity (\( f_{eff} L_0 \) of order unity), this is not a good approximation, since the geometry of the sphere is not well approximated by the planar geometry. However, in this regime, the WLRC works well since the suppression factor \( e^{-f_{eff} L_0} \) is small. Since the WLRC retains the geometry of the sphere (changing only the topology, by removing a point), the WLRC is an improvement on the PWLC model. (iii) At very low (or negative) \( f_{eff} \), in the SAWLC model, the polymer accommodates writhe by winding around itself. A similar behaviour occurs in the WLRC model, where the tangent vector is mostly near the south pole. In both models a cut-off set by the thickness of the polymer (see below) is needed to regularize the model.

Had we chosen to exclude some other direction instead of the south pole, the suppression factor would have been \( e^{f_{eff} L_0 \cos \theta} \), where \( \theta \) is the polar angle of the excluded point. Clearly, the advantageous choice is \( \theta = \pi \), i.e. the south pole of the sphere. The choice \( \theta = \pi \) leads to an axially symmetric quantum mechanical problem, for which the Hamiltonian can be solved. This is exactly what Bouchiat and Mezard choose in their WLRC model.

Need for a cut-off. In summing over all south avoiding paths one finds that the problem of computing equation (1) is ill defined. Recall that \( \tilde{S}_d \), the set of south pointing paths, has been removed from \( \tilde{C}_a \), the WLC configuration space, to get the WLRC configuration space \( \tilde{C}_d = \tilde{C}_a - \tilde{S}_d \). The problem is that near \( \tilde{S}_d \) there are paths (points in \( \tilde{C}_d \)) with arbitrarily large
writhe and vanishingly small energy. This problem is due to paths which wind around the south pole in tiny circles accumulating large writhe at zero energy cost [25].

This problem does not occur at large forces. At large forces there is a large energy cost preventing the tangent vector from visiting the south pole. Indeed, in the paraxial limit there is no pathology [4, 11, 12]. As one lowers the force, the energy cost for accommodating writhe tends to zero near \( S_d \) and these dominate the sum in equation (1). In order to get sensible results from the WLRC model one has to impose a cut-off: the tangent vector is excluded from small circles \( \theta = \theta_c = \pi - \epsilon \) around the south pole. In more detail, we see that for paths winding around the south pole the energy per unit length \( E/L \sim \epsilon^2 \) while the writhe per unit length \( W_r/L \sim 2 - \epsilon^2 \). This implies that in the limit \( \epsilon \to 0 \) any amount of writhe can be accommodated at zero energy cost. Maggs and Rossetto [4] claim that this pathology of the WLRC model is an artefact of the local Fuller writhe formulation. However, we notice that the same pathology afflicts the SAWLC model (which involves a non-local notion of writhe, the CW writhe) as well. This can be seen as follows. Consider a polymer twined on a cylindrical rod like a garden climber twines around a pole. As explained in Fuller [7], for a plectoneme of pitch angle \( \alpha \) (in the limit that \( \alpha \) goes to \( \pi/2 \) the helix is almost a straight line) the curvature goes as \( \kappa = (d/2)^{-1} \cos^2 \alpha \), while the writhe per unit length \( W_{CW}/l \) goes as \( \sin \alpha \), where \( d \) is the diameter of the rod. (See Fuller, figure 1 and its caption in the 1971 paper.) From the geometry \( \cos \alpha = \pi d/(l) \), where \( l \) is the length of the polymer. When \( \alpha \) goes to \( \pi/2 \), the writhe (per unit length) goes to a constant and the energy per unit length goes as \( d^2 \). Note that we are holding the length of the polymer constant as we take the limit \( \alpha \) going to \( \pi/2 \).

We thus come to the conclusion that both SAWLC (involving the non-local CW writhe) and WLRC (involving the local Fuller writhe) suffer from the same pathology, which can be cured by introducing a cut-off parameter which has the same origin (the finite thickness of the polymer) in both formulations. In fact the WLRC model by Bouchiat and Mezard is a simple analytically tractable model which captures the essential qualitative physics of the SAWLC model.

5. Tunnelling

So far we have used topological ideas to split up the configuration space into disconnected sectors. However, the difference between topology and energetics can be blurred by activated processes [4]. To appreciate this point, consider a Brownian particle in a double well potential. If the barrier height is not too large, the particle will randomly visit both wells during the observation time. If one increases the barrier height, the activated process is exponentially suppressed. In the limit that the barrier height goes to infinity, we may say that the two wells belong to distinct topological sectors and sum over only one of them. The transition from one regime to the other is measured by the Kramers’ time \( \tau_{\text{Kramers}} \sim \exp(V/kT) \), where \( V \) is the height of the barrier and \( kT \) the temperature. If \( \tau_{\text{Kramers}} \gg \tau_{\text{Observation}} \), then we would sum over a single well, but if the reverse is true, then we would sum over both wells. By tuning \( V \), the barrier between the wells, we can continuously interpolate between the single well and the double well descriptions. The picture can be extended to include multiple wells, for example, a potential profile \( V(x) = -V_0 \cos x \) which has multiple minima at \( x = 2n\pi \). In the polymer context, the different \( Lk \) sectors correspond to different minima of this potential. Tunnelling between different minima is an activated process and the classical solution that dominates this process is an ‘instanton’ [26]. The physics involved here is very similar to the tunnelling between different topological sectors of vacuum classical configurations in QCD.

\[ \text{In actual terms the polymer wraps around itself to form plectonemic structures as in telephone cords. Thus the thickness of the polymer plays the role of the diameter of the cylinder.} \]
The ‘θ vacua’ that emerge in QCD are delocalized over all the topological sectors, just as the WLC polymer is delocalized over link sectors. Tunnelling between different minima is ruled out in the models (b), (c) and (d) but permitted in the model (a). In order to interpolate between these models theoretically we can soften the cut-off in the WLRC model by putting a potential of height \( V_0 \) and width \( \epsilon \). As \( V_0 \to \infty \) we recover the WLRC model and as \( V_0 \to 0 \) we recover the WLC model. \( V_0 \) serves as a natural parameter in interpolating continuously between these models. In the next section we show how one can experimentally explore the continuous transition between these models using the catalytic effect of enzymes. We will see how addition of topoisomerase II enzymes effectively lowers the energy barrier \( V_0 \), permitting the molecule to pass through itself and thus enabling the polymer to be delocalized over distinct link sectors.

6. Proposed experiments

We now explore the experimental realization of the WLC model (model (a)). The process of ‘topological untwisting’ can be made possible by using the enzyme topoisomerase II to permit the DNA molecule to pass through itself [27]. (Similar experiments are referred to in [29].) As the concentration of enzyme \( c \) is increased we would expect a transition from aperiodic behaviour to periodic WLC behaviour. A low concentration would correspond to a large energy barrier to passing through itself and a high concentration lowers the energy barrier. We may expect the energy barrier \( V_0 \) to go as \( c^{-1} \). A similar effect is also expected to happen as a function of force \( f \). At large forces (or extensions), the energy barrier to looping back and passing through itself is prohibitive. As one lowers the force, one expects again a transition from the aperiodic behaviour noticed in a paraxial worm-like chain (PWLC) model [11, 12] to the periodic WLC behaviour [15]. The height of the barrier can be worked out in the WLRC model (model (d)). It is given by \( V_0 + 2f \) where \( V_0 \) is the repulsive potential at the south pole of the sphere of tangent directions and \( f \) is the applied stretching force.

Plotting the lines of constant Kramer’s time gives a qualitative phase diagram in the force–concentration (\( f–c \)) plane (see figure 2). At high forces and low concentrations the free energy is aperiodic. At low forces and high concentrations the free energy is periodic in the link.

During the process of replication the DNA molecule undergoes supercoiling and it needs to unwind to release its stress. The viscous cell environment offers resistance to this process. The unwinding of these supercoiled structures takes place via topoisomerase enzymes, which cut the polymer and help it to release its stress. This real biological context is where the WLC periodic free energy finds a natural application. These effects can be studied under controlled circumstances in single molecule experiments.

7. Conclusion

In this paper we have provided a formal justification for the WLRC model in terms of the topological effects of self-avoidance. Our main result is the following: in any closed circuit of curves, the number of signed self-crossings is equal to the number of signed south crossings. Equivalently, in the language of ribbons, two ribbons based on the same ribbon backbone \( \tilde{C} \), are homotopic as self-avoiding ribbons if and only if they are homotopic as south avoiding ribbons.

Replacing the non-local notion of self-avoidance by the local notion of south avoidance results in the analytically tractable WLRC model. The Călugăreanu–White formula for the

6 The phenomenon of ‘topological untwisting’ [27] mentioned here is to be contrasted with geometric untwisting [28], which involves a continuous release of twist through bending modes of a ribbon with a free tangent vector at the end.
writhe is explicitly non-local (the formula is expressed as a double integral) and no local formula valid on all simple curves exists. In Fuller’s treatment [7] a theorem is proved that the writhe difference for two closed non-self-intersecting space curves is given by a local formula under certain conditions [7, 8]. Taking the special case that the reference curve has constant tangent vector $\hat{z}$, we arrive at the formula (equation (8)) for non-self-intersecting (i.e. simple) curves which are nowhere south pointing. Note, however, that the restriction of non-self-intersection can be relaxed since nowhere does it appear in the Fuller writhe formula. Our treatment, which uses the writhe as the starting point, has a larger domain of validity, since writhe is well defined on all curves. Our main result provides the theoretical framework and justification for the calculational scheme employed by [3] in the WLRC model.

We have focused on long polymers to keep this discussion simple and because the experimental situation permits it. Needless to say, the general topological discussion applies to short polymers as well. In particular, consider a very rigid polymer ($L_p \to \infty, L/L_p \to 0$) with the tangent vector clamped at both ends to $\hat{z}$. This system can be modelled as a paraxial worm-like chain (even if the applied force is zero), and according to the general discussion will have an aperiodic free energy. In this case, the energy barrier to looping around is given by the elastic energy of the stiff polymer and goes as $A/L$.

We have emphasized the need for introducing a regularizing cut-off in a theoretical analysis of this problem. It has been suggested [4] that the divergence in the writhe distribution seen in [3] is an artefact of the Fuller formulation of the writhe and will not be present in a CW formulation. We have shown that the CW writhe also suffers from the same pathology. One sees [7] that it costs (almost) no energy to accommodate any amount of writhe. As a result, large values of writhe are possible. This pathology is only cured by considering the physical thickness of DNA (about 2 nm), which results in an energy cost for writhe and suppresses large writhe fluctuations. Writhe fluctuations can be suppressed either by increasing the tension on the molecule (PWLC model) or by taking into account the physical thickness of the molecule (WLRC model).

Ribbons homotopic as self-avoiding ribbons are also homotopic as south avoiding ribbons. Note that the converse is not true: knots cannot be undone if one imposes self-avoidance.
But one can remain within the set $C_d$ of south avoiding curves and undo any knot. Consider projecting the knot onto the $x-y$ plane and by small movements of the tangent vector to the polymer undo the knot by passing the ribbon through itself, since there is no self-avoidance constraint. When we sum over all south avoiding ribbons we are automatically summing over all knot classes of the central curve. This is an approximation valid only when the contribution of the non-trivial knot sectors is negligible.

In future, it would be interesting to address the theoretical issues that stem from considering distinct knot classes. The recent class of experiments [30] probing the dynamics of complex knots on single molecules of DNA would perhaps enable us to connect the theoretically challenging energetic and topological aspects of knots [24, 16] to experiments. One can also experimentally explore the low force stretching regime to explore deviation from the pure bend WLC model of [22] to probe the effect of knotting of a DNA molecule.

As an offshoot of the observation of the topological distinction between various models of twisting polymers we are led to a new class of experimentally testable predictions. We hope this work will generate interest amongst experimentalists to test these predictions.

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Appendix. Ribbons, curves and fibres

To clearly put across the topological point at issue here we use some mathematical notation. Let $C$ be the configuration space of all closed ribbons and $\tilde{C}$ the space of all curves. There is a natural map $P : C \to \tilde{C}$, which maps each ribbon $C$ to its backbone curve $\tilde{C}$. The ribbons based on $\tilde{C}$ are classified up to homotopy by their link class $Lk$. The structure $(C, \tilde{C}, P)$ constitutes a fibre bundle. Given a closed circuit in $\tilde{C}$, which starts from and returns to $\tilde{C}_s$, and a starting ribbon $C_s$, one can continuously ‘lift’ the circuit to the space of ribbons. However, a closed circuit in $\tilde{C}$ may lift to an open circuit in $C$. The initial and final ribbons have the same backbone curve, but belong to different link classes. We refer to such circuits as link changing closed circuits (LCCCs) in the text.

Let $C_s$ be a fiducial ribbon whose backbone is $\tilde{C}_s$. Our sum in equation (1) extends only over the component connected to $C_s$. We call this component $\pi_0(C_s)$. In order to perform the sum correctly we need to understand the structure of $\pi_0(C)$ and $\pi_0^*(C)$ correctly in the different models.

We start with model (c), the SAWLC model, which is the one of experimental interest. $\pi_0(C_e)$ is labelled by $K$, the knot class of the ribbon backbone $\tilde{C}$, and $Lk$, the link class of the ribbon based on $\tilde{C}$. (Strictly speaking we should write $[K]$ and $[Lk]$, the equivalence classes being denoted by the square brackets, but we do not do so here.) The link is an integer and counts the Gauss linking number of the two edges of the closed ribbon. Thus $\pi_0(C_e) = (K, Lk)$. $\pi_0^*(C_e)$, the component connected to $C_s$ consists of all ribbons in $(K_s, Lk_s)$, those in the knot class of $\tilde{C}_s$ (the unknot class) and which have the same link as $C_s$.

(a) WLC model. If one gives up self-avoidance and works with $C_a$, then the structure of $\pi_0(C_a)$ is quite different from $C_e$. There are no knot classes, since any knot can be undone.
by self-crossings. The even link classes are identified with one another and similarly the odd link classes. This is due to the presence of link changing closed circuits (LCCCs) in $\hat{C}_a$. These curves are closed circuits in $\hat{C}_a$. If one lifts them up by continuity to $C_a$, the space of ribbons, we find that the continuous lift of a closed curve in $\hat{C}_a$ may be open in $C_a$. The LCCCs can be recognized by the fact that they enclose a non-zero topological flux $k = 1/\pi \oint d\tau A_\tau$. Thus, the link classes of like parity are identified with each other and $\pi_0(C_a)$ has just two components.

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