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Torsional Directed Walks, Entropic Elasticity, and DNA Twist Stiffness

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Abstract: DNA and other biopolymers differ from classical polymers due to their torsional stiffness. This property changes the statistical character of their conformations under tension from a classical random walk to a problem we call the "torsional directed walk". Motivated by a recent experiment on single lambda-DNA molecules [Strick *et al.* Science **271** (1996) 1835], we formulate the torsional directed walk problem and solve it *analytically* in the appropriate force regime. Our technique affords a direct physical determination of the microscopic twist stiffness C and twist-stretch coupling D relevant for DNA functionality. The theory quantitatively fits existing experimental data for relative extension as a function of overtwist over a wide range of applied force; fitting to the experimental data yields the numerical values $C = 120\,\mathrm{nm}$ and $D = 50\,\mathrm{nm}$. Future experiments will refine these values. We also predict that the phenomenon of *reduction of effective twist stiffness by bend fluctuations* should be testable in future single-molecule experiments, and we give its analytic form.

1. Introduction and Summary

The theory of random walks is one of the most fundamental problems in statistical mechanics, with applications throughout physics, biology, and even finance. The discovery that polymer conformations afford a concrete realization of this mathematical problem, and the understanding that rubber elasticity is inherently an *entropic* phenomenon, marked the birth of polymer physics [1]. Remarkably, it has recently become possible to apply minuscule forces to *single molecules* of DNA in solution and observe their extension [2]. Besides allowing a detailed confirmation of the directed random walk model of entropic elasticity, these experiments allow direct physical measurement of microscopic (nanometer-scale) mechanical properties of DNA relevant to its function, using mesoscopic (micron-scale) apparatus. Two linear elastic parameters of DNA have now been measured in this way: the bend persistence length A and the intrinsic-stretch modulus γ [3][4][5][6][7].

DNA and other stiff biopolymers differ from classical polymers, however, in that they exhibit *torsional* as well as bend stiffness. Thus their conformations reflect not a classical directed walk but a new fundamental problem: the "torsional directed walk" (TDW), whose random variables are the direction of each step relative to its predecessor, together with a relative axial twist. In this letter we will formulate the version of the TDW appropriate to DNA, solve it *analytically* in a regime appropriate to a recent experiment [8], and show that the model quantitatively fits the data over a wide range of applied forces (Fig. 1) [9]. Some of these results were announced in [10]. Besides being transparent, analytic formulæ permit systematic least-squares fitting to experimental data. We fit to obtain three microscopic elastic constants: the twist persistence length C, bend persistence length A, and intrinsic twist-stretch coupling D [11][12]. Since A is known independently we have a check on the model. The experiment is not sensitive to the other allowed linear-elastic constants such as twist-bend coupling [13].

We find that the existing data [8] yield $A = 49\,\mathrm{nm}$, $C = 120\,\mathrm{nm}$, and $D = 50\,\mathrm{nm}$; future experiments will refine these values when fit to our formula. Many authors have sought to extract the value of C from both cyclization experiments and fluorescence depolarization [14]. A key point of this paper is that the force regime we study is free from some vexing physical and mathematical difficulties which have helped make the determination of C from these experiments controversial. In particular, we can use a continuum model with no need for the short-length cutoff required to make Monte Carlo calculations tractable [15][16]. Our value for D is similar to within the large errors to recent estimates [11][12].

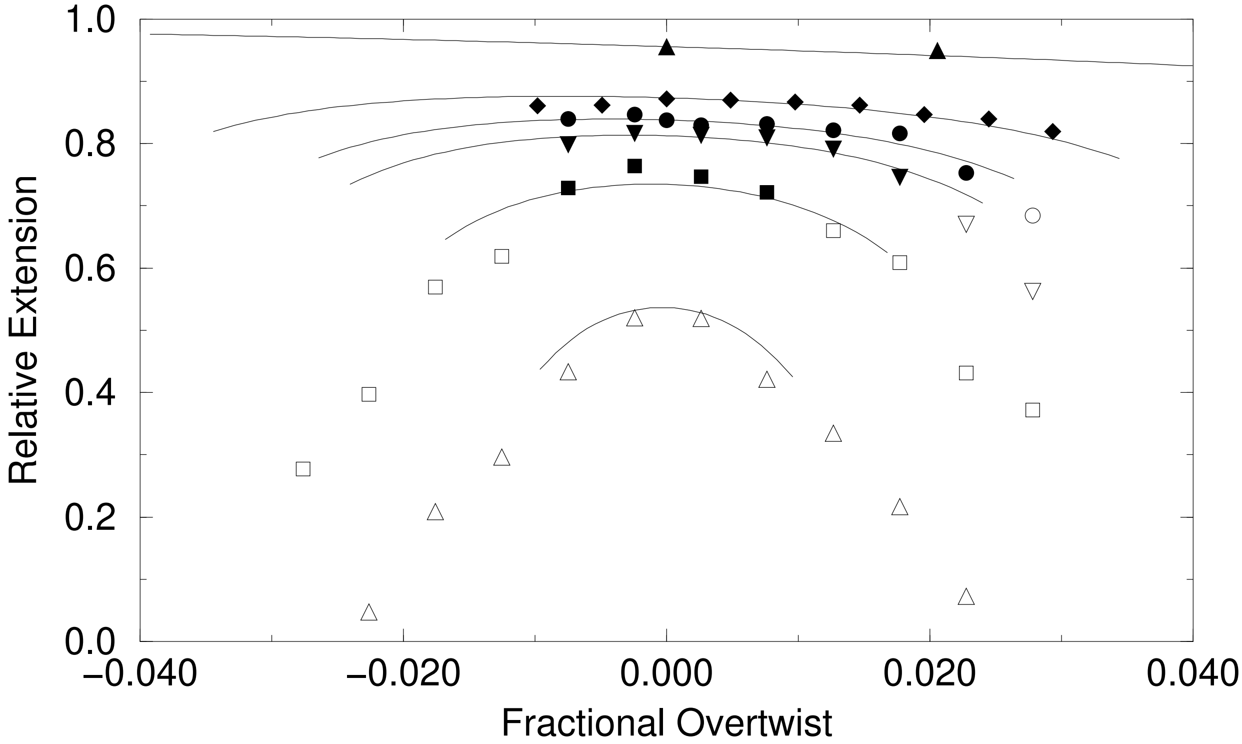

Fig. 1: Relative extension of lambda-DNA versus applied force f and overtwist σ. From top to bottom, the curves are at fixed force 8.0, 1.3, 0.8, 0.6, 0.3, and 0.1 pN. The dots are experimental data from Fig. 3 of [8], excluding values of f, σ where the DNA is known to denature by strand separation. Open dots are outside the range of validity of the phantom chain model and were not used in the fit. The corresponding points from Fig. 2 of [8] were also used in the fit (not shown), for a total of 49 points. The lines are our theoretical predictions after fitting to A, C, and D (see text).

We also give a simple analytical prediction for the *reduction of effective twist stiffness by bend fluctuations.* This renormalization may explain why some other determinations of C give lower values than ours. Its existence was appreciated long ago by Shimada and Yamakawa [17], but a clear experimental test has hitherto not been possible. While this effect is only marginally visible in the extant data, again future experiments should be able to test our prediction by checking the dependence of C_{eff} on the applied force (see below).

Bouchiat and Mézard have recently addressed several overlapping issues [16]. They independently obtained formulæ equivalent to our eqns. (4.2), (4.3) below. We comment on their approach in Sect. 5.

2. Experiment

In the experiment of Ref. [8], λ-DNA in 10 mM PB buffer was bound to a wall at one end and a magnetic bead at the other, with bonds which did not permit free pivoting.

Constraining the orientation of the bead with an applied magnetic field thus constrained the orientation of the DNA strand at its end (Fig. 2). Since the bead was too large for the DNA to loop around it, this procedure effectively fixed the *total Link* of the circuit consisting of the DNA plus a fixed imaginary closing path. Rotating the applied magnetic field then allowed the authors to freeze the Link to any desired value and find the extension Z for various values of the applied stretching force f. Alternatively, the force could be held fixed while the Link was varied, as in Fig. 1 above. The intensive strain variable describing Link is the *relative overtwist* $\sigma \equiv \Delta\mathrm{Lk}\cdot(3.6\,\mathrm{nm}/L)$, where $L = 16400\,\mathrm{nm}$ is the total contour length.

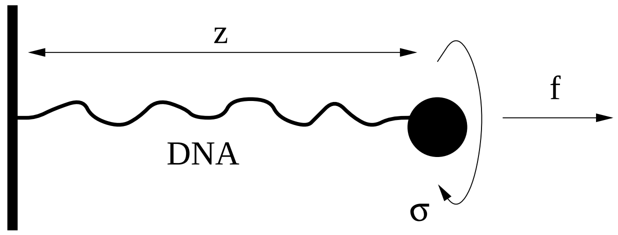

Fig. 2: Schematic of experiment. The magnetic bead imposes relative overtwist σ and stretching force f.

Subsequent work showed that the DNA undergoes structural transitio or strand separation for high applied stresses, roughly $f > 0.4\,\mathrm{pN}$ and $\sigma < -0.01$ or $\sigma > 0.03$ (D. Bensimon, private communication). The loss of twist rigidity is also clearly visible in the curves in [8]. We have omitted such points from Fig. 1. Also, DNA undergoes a dramatic overstretching transition at around 60 pN [6]; all the data discussed here concern forces $f \leq 8\,\mathrm{pN}$.

3. Physical Picture

In this section we will describe qualitatively the physics behind the analysis of the next section.

We will begin with a picture of DNA as a thin cylindrical elastic rod of fixed contour length L; below we will discuss corrections reflecting the more detailed architecture of the molecule. The conformations of such a rod under an applied tension are controlled by the elastic energy functional*

$$E/k_{\mathrm{B}}T = \frac{1}{2}\int\left[A((\Omega_1)^2 + (\Omega_2)^2) + C(\Omega_3 - \omega_0)^2\right]\mathrm{d}s - \tilde{f}\cdot Z - 2\pi\tau\cdot\mathrm{Lk} \quad . \tag{3.1}$$

* Our notation is similar to [13]. Throughout we will neglect sequence dependence. In the force regime in question we expect linear rod elasticity to be a good approximation. Higher-order

Here s is arc length, $\Omega_{1,2}(s)$ are bending strains, $\Omega_3 - \omega_0$ is twist strain, A, C are the bend and twist persistence lengths, $\tilde{f} \equiv f/k_{\mathrm{B}}T$, and $\omega_0 \equiv 2\pi/3.6\,\mathrm{nm}$ is the unstressed molecule's helix density. τ is a dimensionless torque variable whose value we will choose to obtain the required overtwist $\langle \mathrm{Lk} \rangle = (1+\sigma)L\omega_0/2\pi$.

In the absence of thermal fluctuations, a stretched elastic rod remains straight as we apply increasing torque to the ends, then buckles at a critical value of torque which increases with the applied stretching force [18]. Below $\tau_{\mathrm{crit}} = 2\sqrt{A\tilde{f}}$ the rod twists uniformly with overtwist $\sigma = \tau/\omega_0 C$. The end-to-end distance Z of the rod does not change at all for applied overtwist less than the critical value τ_{crit}, since the rod remains a straight line of constant contour length.

Thermal fluctuations change this picture completely. The rod is never straight; every Fourier mode of its shape is excited in accordance with the equipartition theorem of statistical physics, so the net length Z is always less than L. The applied tension suppresses those fluctuations of wavenumber smaller than $q_0 \equiv \sqrt{\tilde{f}/A}$, with the dominant contribution to the shortening coming from $q \approx q_0$. Now when we apply torque below the critical value, the fluctuations with the same helical sense as the torque get pushed *closer to* instability and hence grow, while those with the opposite helical sense are suppressed. Thus the distribution of rod shapes responds to external torque even below the buckling threshold τ_{crit}. Hence the rod can store imposed Link excess either in Twist, as before, or in a change of average Writhe, and so we will find $\sigma = \tau/\omega_0 C_{\mathrm{eff}}$ with a reduced (or "renormalized") effective twist stiffness C_{eff}. Since the effect depends on bend fluctuations we may expect $(C_{\mathrm{eff}})^{-1} = C^{-1} + \big(A \cdot j(Af/k_{\mathrm{B}}T)\big)^{-1}$, where $j^{-1}(x)$ is some function vanishing at large x. (We will find below that $j(x) = 4\sqrt{x}$.)

The suppression of some fluctuations and enhancement of others will also affect the end-to-end length Z. These effects cancel to linear order in σ since the elastic energy (3.1) does not break inversion symmetry. We do however expect an effect to $\mathcal{O}(\sigma^2)$; indeed this is the dominant feature of the data in Fig. 1. As the force decreases the effect increases, as seen in the increasing curvature of the curves in the figure.

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bend elasticity effects are expected to be suppressed by powers of the rod radius (1 nm), which is much smaller than any other length scale. Indeed a linear-elastic model, the "extensible worm-like chain", describes accurately the extension of torsionally unconstrained DNA up to forces greater than those considered here, with an intrinsic stretch modulus more than a hundred times greater than the forces of interest to us [7].

In sect. 4 we will derive explicit formulas embodying the qualitative arguments in the above two paragraphs.

In eqn. (3.1) we have neglected any self-avoidance effects; these would appear as interactions between rod elements distant in s. In the usual directed walk this is not a serious omission: the crossover to self-avoiding-walk scaling occurs only for chain lengths much longer, and forces much smaller, than those encountered in DNA. In the TDW we must be more careful, since the linking number appearing in (3.1) is undefined when the chain crosses itself. Physically the problem is that the phantom chain can form a loop, pass through itself, and in the process lose a unit of Link: the *phantom torsional chain cannot support any imposed torque.* If we seek an equilibrium at nonzero τ we thus must expect to find mathematical pathologies; they will arrive in due course. A related problem is that the statistical sum for the phantom torsional chain includes all *knotted* configurations, an error with noticeable effects [19].

One approach to this problem is to introduce realistic self-avoidance and knot rejection into eqn. (3.1) [19][15]. The resulting nonlocal model requires numerical Monte Carlo solution, and the results depend on the details of the chain interaction chosen. From the physical picture, however, it is clear that at high enough applied tension f the problematic loops and knots will be so rare as to be negligible: the chain remains nearly straight, and we may use (3.1) without modification. We will find below the precise condition to be in this regime; it corresponds to the solid dots in Fig. 1.

Eqn. (3.1) also neglects any effects of *rod anisotropy.* For example, bending into the major groove ("Roll") is easier than bending in the perpendicular direction ("Tilt"); less obvious is an allowed twist-bend coupling [13]. Such anisotropies can lead to chiral effects, for example an asymmetry between σ and $-\sigma$, but their effects on Fig. 1 are negligible (J.D. Moroz and P. Nelson, in preparation). Indeed we only expect the helical pitch to affect entropic elasticity when the dominant wavenumber q_0 approaches ω_0, *i.e.* at unattainably large forces.†

Instead the slight asymmetry visible in Fig. 1 has its origin in the *intrinsic stretch* elasticity of a chiral rod, which gives Z a contribution linear in σ and independent of f [12]. Stretching with associated unwinding occurs *in vivo* when the protein RecA binds

† Certainly the omitted anisotropic couplings will also renormalize the constants A, C in (3.1) (J.D. Moroz and P. Nelson, in preparation). The model (3.1) is to be regarded as coarse-grained to the scale of the helix pitch.

to DNA, a step in homologous recombination [20]. In the experiment of ref. [8] the effect should be masked by the entropic σ^2 term for small force, emerging when the latter is suppressed at high force, exactly as seen in Fig. 1.

4. Calculation

We now sketch a calculation embodying the above physical picture (J.D. Moroz and P. Nelson, in preparation). We introduce three local configuration variables: a unit vector $\mathbf{t}(s)$ describing the tangent to the chain, and an angle $\zeta(s)$ for the remaining torsional degree of freedom. We take the applied force along the $\mathbf{z}$ direction and orient the chain so that $\mathbf{t}$=$\mathbf{z}$ in equilibrium. To define $\zeta(s)$ we use Fuller's local formula for the writhe of a curve whose tangent never points along the -$\mathbf{z}$ axis [21][22]: Wr= $\frac{1}{2\pi}\int \mathrm{d}s(\mathbf{t}\times\frac{\mathrm{d}\mathbf{t}}{\mathrm{d}s})\cdot\mathbf{z}/(1+\mathbf{t}\cdot\mathbf{z})$. Combined with White's theorem that $2\pi\mathrm{Wr}+\int\Omega_3\mathrm{d}s$ is a topological invariant, we see that $\Omega_3+(\mathbf{t}\times\frac{\mathrm{d}\mathbf{t}}{\mathrm{d}s})\cdot\mathbf{z}/(1+\mathbf{t}\cdot\mathbf{z})$ must be a total derivative; we will call this quantity $\omega_0+\frac{\mathrm{d}\zeta}{\mathrm{d}s}$ and eliminate $\Omega_3(s)$ in favor of $\zeta(s)$.‡ The advantage of this choice is that (3.1) is now quadratic in ζ, which may be summarily eliminated.

It proves convenient to define dimensionless quantities $K\equiv\sqrt{A\tilde{f}-\tau^2/4}$ and $\bar{s}\equiv Ks/A$; we then find

$$E/k_{\mathrm{B}}T=\mathcal{E}_0+\frac{K}{2}\int\mathrm{d}\bar{s}\left[\|\dot{\mathbf{t}}\|^2+\frac{2\tilde{f}A}{K^2}(1-\mathbf{z}\cdot\mathbf{t})-\frac{2\tau}{K}(\mathbf{t}\times\dot{\mathbf{t}})\cdot\mathbf{z}/(1+\mathbf{t}\cdot\mathbf{z})\right]\ , \tag{4.1}$$

where $\mathcal{E}_0\equiv-L(\tilde{f}+\tau^2/2C)$ and dot denotes $\frac{\mathrm{d}}{\mathrm{d}\bar{s}}$. The second term defines a nonlinear fluctuation problem, which we will expand in powers of $1/K$. From its partition function $\mathcal{Z}(f,\tau)$ we may then extract the extension and excess link as

$$Z=\left.\frac{\partial}{\partial\tilde{f}}\right|_{\tau}\log\mathcal{Z}\ ,\quad \omega_0(1+\sigma)=\frac{1}{L}\left.\frac{\partial}{\partial\tau}\right|_{\tilde{f}}\log\mathcal{Z}\ . \tag{4.2}$$

We will use the second of these to solve for $\tau(f,\sigma)$, then substitute into the first to get the desired extension $Z(f,\sigma)$.

To find $\mathcal{Z}$ we adapt the standard trick used in the wormlike chain [23][5]: for long chains $\mathcal{Z}$ approaches the unnormalized correlation function of $\mathbf{t}$. Holding $\mathbf{t}(0)$ fixed, this

‡ The leading-order perturbative formulas can be obtained directly, without appeal to White's formula [10]. A more elegant approach takes the configuration variables to be a 3×3 rotation matrix; the torque term then takes the form $-\tau\int\mathrm{d}s[\Omega_3+\check{\Omega}_3]/(1+\mathbf{t}\cdot\mathbf{z})$, where $\check{\Omega}_i$ are the *space-fixed* angular velocities of a rigid body (J.D. Moroz and P. Nelson, in preparation).

correlator $\psi(\mathbf{t}, s)$ obeys the Schrödinger-like equation $\dot{\psi} = -H\psi$, where [16](J.D. Moroz and P. Nelson, in preparation)

$$H = K(1 - \cos\theta) - \tfrac{1}{2K}\mathbf{L}^2 + \tfrac{\tau}{K}(1 + \cos\theta)^{-1} L_z + \tfrac{\tau^2}{2K}\left(\tfrac{1}{2} - (1 + \cos\theta)^{-1}\right)(1 - \cos\theta)\ . \quad (4.3)$$

Here $\cos\theta = \mathbf{t}\cdot\mathbf{z}$, $\mathbf{L}^2$ is the angular part of the Laplace operator, and L_z is the azimuthal derivative. The main novelty of this derivation is the presence of first-order derivatives in (4.1) when $\tau \neq 0$, leading to the τ^2 terms in K and in (4.3). The asymptotic value of $\mathcal{Z}$ is then controlled by the lowest ("ground-state") eigenvalue λ_0 of (4.3) via $\mathcal{Z} \propto \mathrm{e}^{-\mathcal{E}_0 - \lambda_0 L}$.

Unfortunately (4.3) has *no* ground state for any nonzero τ, due to its singularity at $\theta = \pi$! This unphysical pathology was predicted in the previous section; its mathematical origin is the breakdown of Fuller's formula when $\mathbf{t} = -\mathbf{z}$. To see the connection to the physical discussion, note that the unphysical link-dropping process in the phantom torsional chain necessarily involves the tangent $\mathbf{t}(s)$ passing through -$\mathbf{z}$ at some intermediate point. As discussed above, a physically meaningful and analytically tractable resolution to the problem is to restrict attention to large f. We can then solve (4.3) in perturbtion theory about $\theta = 0$, where the problem is invisible, provided the perturbative ground state value is smaller than the "tunneling barrier" of (4.3).§ Imposing this condition and $K^2 > 2$ selects the solid dots in Fig. 1.

The perturbative solution of (4.3) gives the ground state eigenvalue $\lambda_0 = 1 - 1/4K - 1/64K^2 \cdots$, so (4.2) gives $\sigma = \frac{\tau}{\omega_0}\left(C^{-1} + (4KA)^{-1} + \mathcal{O}(K^{-3})\right)$, $Z/L = 1 - (2K)^{-1}\left(1 + 1/64K^2 + \mathcal{O}(K^{-3})\right)$. The leading-order approximations to these formulæ were announced in [10]. Solving by iteration gives the torque

$$\tau(f,\sigma) = \omega_0\sigma/\left[C^{-1} + \left(4A\sqrt{Af/k_{\mathrm{B}}T}\right)^{-1}\right]\ , \quad (4.4)$$

plus corrections of $\mathcal{O}(K^{-3})$. Formula (4.4) displays the promised renormalization of twist stiffness by bend fluctuations. While direct torque measurements are not currently possible, this effect nevertheless enters the force curves since τ enters Z/L.

§ To justify perturbation theory itself we note that it gives an excellent approximation to the exact solution of the wormlike chain [5] when $K > 1$, as may be expected from the form of the leading anharmonic correction below. Nonperturbative effects in the variational approach to the WLC [5] are also small when $K > 1$. Note that our data cuts also eliminate the region $\sigma > 2\pi/C\omega_0$ where plectoneme formation (and hence large self-avoidance effects) is expected [24]. Raising our threshold on K selected fewer points with little effect on our result.

Assembling the pieces gives our theoretical prediction for the force curve: the relative extension Z/L is

$$Z(f,\sigma)/L = 1 - \tfrac{1}{2}(Af/k_{\rm B}T - (\tau/2)^2 - 1/32)^{-1/2} + (f - k_{\rm B}TD{\omega_0}^2\sigma)/\gamma + A/LK^2 \ , \quad (4.5)$$

with τ from (4.4). We have improved the formula for Z/L given above by summing perturbation theory and including a small finite-length correction (J.D. Moroz and P. Nelson, in preparation). We also introduced the intrinsic-stretch terms mentioned in the previous section [5].

In formulas (4.4)(4.5) the parameters ω_0, L are known and we use the value $\gamma = 1100\,\mathrm{pN}$ for the linear stretch constant obtained from higher-force experiments [7]. This leaves A, C, and D which we fit to the experimental data after the cuts described above. Fig. 1 shows that a single choice of $A = 49\,\mathrm{nm}$, $C = 120\,\mathrm{nm}$, $D = 50\,\mathrm{nm}$ fits all the curves.¶ We note that the fit value of A is consistent with the experiment of Wang *et al.* [7]. Another nontrivial check is that several points just outside our accepted set, not used in the fit (open symbols in Fig. 1), nevertheless lie on our theoretical curves.

5. Discussion

Our value for C is larger than previous determinations. Cyclization experiments give values like $C = 85\,\mathrm{nm}$, while fluorescence polarization anisotropy (FPA) gives still smaller values [14][17]. Significantly, experiments on *short* ($< 100\,\mathrm{nm}$) DNA yields torsion constants about 50% larger than those for longer strands [25]. It is tempting to speculate that the difference is due to the reduction of effective twist stiffness derived in the previous section. Indeed, neglecting this renormalization by replacing (4.4) with the naïve $\tau = \omega_0\sigma/C_{\rm eff}$ and fitting the data gives the value $C_{\rm eff} = 98\,\mathrm{nm}$, closer to earlier determinations than our true microscopic value of C. More generally, equilibrium measurements, like the

¶ The variance of the data from our curves is $\sigma_{Z/L} = 0.013$, comparable to the visible scatter in the data. The formal covariances for A, C, D correspond to very small errors; in practice the fit is visibly worse for C outside the range $70 < C < 150$. Omitting either the f/γ or the $-D\sigma/\gamma$ terms makes a poorer fit, as does replacing (4.4) by the naïve $\tau = \omega_0\sigma/C_{\rm eff}$ with constant $C_{\rm eff}$.

one reported here, are far more straightforward to interpret than dynamical measurements like FPA.‖

Actually, our seemingly large value of C/A could have been anticipated. Random natural bends in DNA reduce the net persistence length at zero applied tension to a value significantly below the value implied by the elastic stiffness alone [26]. A similar effect reduces the effective A measured in stretching experiments, but not C (P. Nelson, in preparation, 1997.). Estimates for the true elastic contribution to the bend persistence length (the "dynamic persistence length" A_d) range from 80 nm to as much as 210 nm [27], and so the elastic C/A_d could be much smaller than the C/A found here.

Bouchiat and Mézard have recently analyzed the $f = 0.1\,\mathrm{pN}$ curve [16]. Since the 0.1 pN curve is entirely outside the range of validity of the phantom chain model, however, they were obliged to address the unphysical pathology of (4.3), both by Monte Carlo simulation and by introducing a new short-scale cutoff. The new cutoff introduces a new unknown parameter into the theory, and moreover does not correspond in a simple way to the actual physics of self-avoidance. They found an impressive match to the $f = 0.1\,\mathrm{pN}$ curve using $C = 75\,\mathrm{nm}$, and relative insensitivity to their choice of cutoff for $|\sigma| < 0.015$. Nevertheless we believe our value of C better describes the experiment, since we simultaneously fit to several different values of f.

In this paper we have introduced an abstract statistical-mechanics problem, the torsional directed walk. We solved it in a simple regime and found a clean confirmation in the experiment of ref. [8] with three adjustable parameters, the nanometer-scale elastic constants of DNA. We also predicted quantitatively the reduction of twist stiffness due to bend fluctuations; a definitive test of (4.4) must await further experiments.

Note added: Further details of the experiment can be found in (T.R. Strick, J.-F. Allemand, D. Bensimon, and V. Croquette, preprint 1997).

‖ An independent check of our measured value of the twist-stretch coupling D is not available, but it is interesting to compare to the situation with RecA. Binding to RecA unwinds it to $\sigma = -0.52$ and stretches it by 0.54 times its natural length. Unwinding DNA slightly at constant tension lengthens it by $D\sigma k_{\mathrm{B}}T{\omega_0}^2/\gamma$ [12]. While $\sigma = -0.52$ is outside the domain of linear elasticity, applying the formula gives an extension of 0.33; much of the extension is explained by the unwinding without requiring additional tension. This argument at best confirms that our value of D is not unreasonable.

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