Comment on "Writhe formulas and antipodal points in plectonemic DNA configurations"

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We point out that the disagreement between the paper by Neukirch and Starostin [S. Neukirch and E. L. Starostin, Phys. Rev. E **78**, 041912 (2008)] and ours [J. Samuel, S. Sinha, and A. Ghosh, J. Phys.: Condens. Matter **18**, S253 (2006)] is only apparent and stems from a difference in approach. Neukirch and Starostin are concerned with classical elasticity and individual curves while we focus on statistical averages over curves.

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Recently Neukirch and Starostin [1] noted that the use of Fuller's formula for writhe may not always be justified in analyzing experiments [2] that stretch and twist single DNA molecules. They criticized some earlier works ([17–34] of Ref. [1]) for using Fuller's formula [3,4] without always being careful to checking the conditions for its validity. Readers of this paper [1] may derive the impression from some remarks made about [5] that Ref. [1] somehow invalidates the conclusions of our paper [5], which shows how Fuller's formula *can* be used in understanding entropic DNA elasticity. Here, we note that the apparent differences can be traced to a difference in approach to the problem. We will set the comment in perspective by explaining the two points of view that have influenced the literature on biopolymer elasticity. We summarize the discussion by concluding that the remarks made in [1] no way invalidate any of the claims made in [5].

Two communities with slightly different approaches have been working on biopolymer elasticity. One point of view (see, for instance, [6]) is purely mechanistic and has its roots in classical elasticity. While this point of view captures some of the qualitative features of single-molecule experiments and works well in the energy dominated regime of stiffer polymers such as actin and microtubules, it fails to capture the regime where there is a competition between the intrinsic elastic energy of the polymer and thermal fluctuations, which are present in a real cellular environment. This latter regime is better explained from a statistical-mechanical point of view (see, for instance, [7]), where the central notion is the partition function of the system. These two communities view biopolymers from slightly different perspectives: the mechanistic view emphasizes individual configurations, while the statistical view averages over configurations and focuses on the partition function, which is related to experimentally accessible quantities. The differences between our paper [5] and Neukirch and Starostin's paper [1] come from these two distinct viewpoints.

The view offered in [5] is that while it is incorrect to claim that the partition function of the self-avoiding wormlike chain (SAWLC) model *equals* that of the wormlike rod chain (WLRC) *exactly* (as what [7] seems to do), it is nevertheless a good *approximation* over a range of forces and torques. To see this, note that changes in the two notions of writhe (Fuller writhe W_F and Călugăreanu-White writhe W_{CW}) are equal $[\delta W_{CW}(\mathcal{C})=\delta W_F(\mathcal{C})]$ for small variations of the curve $\mathcal{C}$ (provided that both quantities are well defined in the variation). Integrating this equation we find that the difference $W_{CW}(\mathcal{C})-W_F(\mathcal{C})$ is constant for deformations of $\mathcal{C}$, which are neither self-crossing nor south crossing. We will follow [1] in referring to such deformations as "good" deformations. We choose for a reference curve the straight line in the z direction ($\hat{t}=\hat{z}$). Noting that the constant vanishes on the reference curve, we arrive at Fuller's formula $W_F=W_{CW}$ for all curves, which can be deformed to the reference curve by good deformations. We refer to curves related to the reference curve by good deformations as "good curves." Note that the set of good curves is much larger than just small perturbations about the straight line. For instance, curves which are nowhere back-bending ($t_z \geq 0$) are good curves and these may be far from straight.

The main point we make in Ref. [5] is that, for a range of (F,W), the set of good curves dominates both partition functions and, as a result, $Z_{SAWLC}(F,W)$ equals $Z_{WLRC}(F,W)$ *approximately*,

$$Z_{SAWLC}(F,W) \approx Z_{WLRC}(F,W). \tag{1}$$

The accuracy of the approximation is determined by the extent to which the good curves dominate the partition function. A simple example clarifies the matter. Suppose we wish to find the expectation of the function $h(x)$: $h(x)=x^2$ when $-3<x<3$; $h(x)=-1$, otherwise, defined piecewise over the real line with a Gaussian measure $\exp(-\alpha x^2)$, suitably normalized. Consider the function $g(x)=x^2$ everywhere. Certainly $h(x)$ is not equal to $g(x)$, as there are points where they differ considerably. However, in computing the expectation value $\langle h(x)\rangle$ of $h(x)$ one can approximately replace it with $\langle g(x)\rangle$, which is analytically more tractable. $\langle h(x)\rangle$ is approximately equal to $\langle g(x)\rangle$. The approximation is good if α is not too small. Likewise, for forces that are not too small, the approximate partition function is expected to be close to the exact one. This explains the efficacy of Bouchiat and Mézard's W LRC model beyond perturbation theory [8,9].

Both Refs. [1,5] attempt to understand the two writhe formulas and their use in the nonperturbative regime. However, the emphasis in [1] is on individual configurations and not on the statistical sense. It is indeed true as both Refs. [1,5] note that the writhe formulas are *not* the same on individual curves. Our claims of approximate equality of the two models are made at the level of the partition function and not individual curves. We claim that the partition functions are approximately equal [Eq. (1)] to each other for a wider range

of parameters than one would naively expect. Such an approximation works very well at very high forces. Let us now consider twisting the molecule:

(a) *At low twist:* this is the paraxial limit where the backbone of the polymer is essentially straight and the tangent vector $\hat{t}$ to the polymer explores the neighborhood of the north pole [8,9]. This is the perturbative regime, which is not controversial.

(b) *At intermediate twist:* in this regime we have a writhing polymer which may not be nearly straight. However, our argument that good curves dominate the partition function applies and we conclude that Eq. (1) holds.

(c) *At high twist:* the energy cost of accommodating writhe becomes nearly zero in self-avoiding models. This is because an infinitely thin polymer can writhe at negligible energy cost by winding around itself as a plectoneme. (The word is Greek for "twisted thread" and describes the structures often seen on telephone cords.) To render the energy finite, one has to "fatten" the thread and allow for the finite thickness of the DNA molecule (about 2 nm). This pathology of infinitely thin threads is well known to mathematicians and was quite early noticed by Fuller [3,4].

A similar pathology also afflicts south avoiding models: writhe can be stored at negligible energy cost by winding around the south pole. These configurations can be described, mixing our small Latin and less Greek, as "Australonemes" (southerly threads). If one excludes a finite region around the south pole (as Bouchiat and Mézard do [7]) by using a cutoff, one ends up with the same finite energy cost per unit writhe for appropriate cutoff. As a result, even in the high twist limit one finds that the partition functions are approximately equal and Eq. (1) holds.

To summarize, we have clarified the issues surrounding the use of Fuller's formula for the writhe of a space curve. We note that the formula, *when used with due care*, can be a valuable aid to taming an otherwise intractable calculation. It permits an approximate determination of the partition function and a prediction for the experimentally measured twist-extension relations in the presence of an applied force. We observe [5] using the closed circuit theorem that self-avoidance and south avoidance have the same topological effect of obstructing link release and topological untwisting. Our observations justify the theoretical work of Bouchiat and Mézard, which—although successful in interpreting the data—has been criticized for the incorrect use of Fuller's formula. We thus understand the "unreasonable effectiveness" of Fuller's formula in understanding DNA elasticity.

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