Comment on "Length Scale Dependence of DNA Mechanical Properties"

Recent experimental data [1–7] indicate that the elastic wormlike rod (WLR) model of DNA that works well on long length scales may break down on shorter scales relevant to biology. According to Noy and Golestanian (NG) [8] molecular dynamics (MD) simulations predict DNA rigidity close to experimental data and confirm one scenario of such breakdown, namely, that for lengths of a few helical turns, DNA dynamics exhibit long-range bending and stretching correlations. Earlier studies using similar force fields [9–13] concluded that (i) MD simulations systematically overestimate the DNA rigidity, and (ii) no deviations from the WLR model are detectable [14,15]. Here it is argued that the data analysis in NG was incorrect and that the earlier conclusions are valid.

Measuring DNA rigidity by MD requires rigorous analysis of statistical errors. For high accuracy, trajectories must be several orders of magnitude longer than the corresponding relaxation times, and optimal conditions are met for dynamics of one helical turn [12,13,16,17]. Longer fragments are difficult to study because the relaxation times for twisting and bending grow with the DNA length as L^2 and L^4, respectively, [10].

NG reported simulations of several DNA turns and implied that by considering many internal stretches of long DNA one improves the sampling. Unfortunately, this intuitive assertion is valid only for stretching. For bending and twisting it fails and the sampling is even reduced because internal fragments are not independent and the spectrum of their relaxation times involves that of the whole DNA [16,17]. Besides, all relaxation times scale linearly with the solvent viscosity [10], which is high for the extended simple point charge model (SPC/E) water employed by NG [18,19]; therefore, the overall accuracy of their quantitative estimates is undetermined.

Complex methods of analysis of all-atom DNA trajectories may hide pitfalls. Before concluding that MD reveal a length-scale dependence these methods should be validated on *finite* WLR trajectories. Notably, the only evidence of stretching correlations is the convex plot of the variance of the end-to-end distance $V(L)$ when the bending contribution is negligible [4]. NG estimated this contribution from angle fluctuations and subtracted it. To validate this procedure one should check that it linearizes convex $V(L)$ dependences for *finite* WLR trajectories. This is impossible, however, because, in *finite* WLR ensembles, distance and angle fluctuations may correspond to different apparent persistence lengths. Further, an isolated mode extracted by the principal component analysis is correlated by construction. Such correlations, therefore, represent a supporting evidence, only if a similarly extracted WLR mode exhibits a different pattern, which was not shown.

Finally, oscillations with the helical period observed in some plots are inevitably produced by the algorithm used for constructing reference base-pair frames. This algorithm yields Cartesian frames that fit the global helical axis in an ideal B-DNA. For MD structures such frames are systematically biased. When this is taken into account WLR dynamics produces periodical patterns similar to those shown in NG (see Fig. 1). This is the main source of spurious oscillations in MD data, and it also affects the analysis of end-to-end distance fluctuations [11]. However, it is an artifact rather than an evidence of orientational memory, static curvature, and so forth.

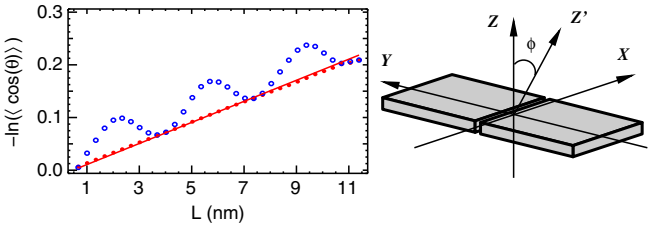

FIG. 1 (color online). Length dependence of the bend angle θ for the WLR theory (straight red line) and the Brownian dynamics of a discrete WLR model [17]. A trajectory was analyzed with bend angle θ measured between either true Z vectors (closed red circles) or Z' vectors biased by angle $\phi = 10°$ as shown on the right (open blue circles). For integral numbers of helical turns the biasing error is small.

In summary, all-atom MD simulations with currently used force fields somewhat overestimate the rigidity of the double helix [11,13], but agree with the WLR model [14], with no detectable correlations beyond a few base-pair steps [15,20]. It is possible that this agreement disappears on somewhat longer time or length scales, or that new effects will emerge with refined empirical force fields. Additional work is necessary to check this and also to clarify experimental controversies [21].

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