Published in final edited form as:

Phys Life Rev. 2013 March ; 10(1): 70–84. doi:10.1016/j.plrev.2013.01.009.

Can nucleosomal DNA be described by an elastic model?:

Comment on “Sequence-dependent collective properties of DNAs and their role in biological systems” by Anita Scipioni and Pasquale De Santis

Victor B. Zhurkin* and Wilma K. Olson**

*National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA

**Rutgers, The State University of New Jersey, Wright-Rieman Laboratories, 610 Taylor Road, Piscataway, NJ 08854-8087, USA

The review of DNA sequence-dependent conformational mechanics by Anita Scipioni and Pasquale De Santis [1] is very timely in this year marking the 60th anniversary of the discovery of the DNA double helix. The authors provide an impressive compilation of the effects of DNA sequence-dependent structure and deformability on biologically important systems, ranging from the natural curvature of DNA in solution to the positioning of nucleosomes on eukaryotic genomes.

We wish to comment on two issues – one very general, and the other rather specific.

1. Our first aim is to draw the reader’s attention to the limitations of the ‘first-order elasticity’ model which is extremely popular among researchers applying principles of theoretical mechanics to questions in DNA structural biology. In our opinion, this approach is appropriate for a limited number of biological problems, where DNA deformations are relatively insignificant; the behavior of DNA packaged in chromatin is beyond the limits of the approach. That is, the small deformations of an elastic model make sense for a theoretical description of DNA curvature, where the global physical properties of the system (such as the radius of gyration, end-to-end distance, etc.) are reasonably approximated by room-temperature ($kT/2$) fluctuations in the canonical double-helical structure [2,3]. Subtle variations in the intrinsic spatial arrangements of specific nucleotides or characteristic differences in the local deformability of successive base pairs account well for the observed behavior of such systems. Another successful application of a first-order elastic treatment of DNA is the theoretical evaluation of the global configurations and looping propensities of the ~100 bp-long pieces of DNA incorporated in the GalR [4] and LacI repressomes [5]. In these cases the sequence-dependent patterns in base-pair geometry lead to the smooth bending (and concomitant untwisting) needed to close the loops between the protein headpieces. In other words, a first-order elastic approach is suitable for systems where DNA is either free or ‘relatively free’ from bound proteins.

By contrast, modeling the strong distortions of DNA in chromatin with a ‘first-order elasticity approach’ is questionable, to say at the least. Our assessment [6] of the best-resolved crystal structure of the nucleosome core particle [7] suggests that the highly deformed ‘kink-and-slide’ dimeric steps of DNA found near the points of contact with the histone proteins are of the order of 10 kT higher in energy than the canonical B DNA structure. We find these differences using both a ‘knowledge-based’ elastic model [8,9] and all-atom energy calculations [10]. Indeed, the conformational features of the high-energy state are consistent with a change of DNA helical state, a BI → BII transition, which should

not necessarily obey classical rod mechanics or the sequence-dependent rules of DNA deformability found in intact double-helical structure. Different large-scale transitions, e.g., ‘partial melting’ at TA base-pair steps [11–13], appear to accompany the formation of other nucleosome structures (the complex of the so-called 601 DNA sequence [14] with recombinant *Xenopus laevis* histones). An elastic model cannot capture the strong DNA distortions found in nucleosomes. Prediction of nucleosome positioning requires knowledge of the multi-dimensional potential energy surfaces describing the likely transition pathways between the nucleosome-bound and free DNA states, as well as understanding of the contributions of the histones to the changes in DNA helical structure.

2. Our second comment is related to the comparison made by Drs. Scipioni and De Santis between the Olson et al. [8] and Morozov et al. [15] ‘knowledge-based’ elastic models of DNA. We disagree with the authors’ claim that “the two sets of data are poorly correlated, probably, due to the more extensive database adopted by Morozov *et al.* [23].” In fact, the average Roll values in the two sets [8,15] rather strongly correlate, with a correlation coefficient $R = 0.80$. The Twist-Twist correlation is even stronger, $R = 0.93$. (We used the same approach as in Figure 2 [1], that is, asymmetric steps like AA:TT are counted twice, and symmetric steps like AT are counted once.) The number of structures used to evaluate the equilibrium values of the DNA parameters and rigidity matrix, however, is not critical in this case. In particular, Balasubramanian et al. [9] generated updated elastic functions based on 135 non-redundant protein-DNA structures (of 2.5 Å or better resolution), more than those incorporated in the two mentioned studies [8,15]. The Roll-Roll correlation between the latter dataset and that of Morozov et al. [15], $R = 0.76$, nevertheless, remains nearly the same as described above.

More likely, the differences between the two potentials stem from the ‘filtering’ used in our work and in the subsequent work of Balasubramanian et al. [8,9] to exclude dimeric steps which are too close to the ends of DNA fragments or which are distorted such that the rigid-body parameters relating successive base pairs deviate from their average values by more than three standard deviations. There is no mention of such filtering by Morozov et al. [15]. Our assumption about the impact of DNA filtering is consistent with the fact that the average Roll angles reported by Morozov et al. span a wider range of values, from -1.4° (for AT step) to 6.0° (for CA:TG), than our Roll values, which vary from 0.3° (for GC) to 5.4° (for CG).

Finally, it is not entirely correct to compare ‘knowledge-based’ elastic models of DNA derived from protein-DNA complexes [8,9,15] with the *in silico* Roll values reported by Scipioni and DeSantis [1]. The latter model does not capture the effects of protein forces that are averaged out in statistical analysis of crystal data [8,9,15]. Instead, it may be more appropriate to compare the simple *in silico* model of DNA elasticity [1] with recent sequence-dependent elastic models deduced from all-atom molecular dynamics simulations [16]. The latter computations hint of correlations between bases sequentially distant along DNA that may prove important in the treatment of long polymers [17].

References

1. Scipioni A, De Santis P. Sequence-dependent collective properties of DNAs and their role in biological systems. *Phys Life Rev.* 2013; (in this issue)
2. Olson WK, Marky NL, Jernigan RL, Zhurkin VB. Influence of fluctuations on DNA curvature. A comparison of flexible and static wedge models of intrinsically bent DNA. *J Mol Biol.* 1993; 232:530–554. [PubMed: 8345522]
3. Olson WK, Zhurkin VB. Modeling DNA deformations. *Curr Opin Struct Biol.* 2000; 10:286–297. [PubMed: 10851199]

4. Geanakopoulou M, Vasmatzis G, Zhurkin VB, Adhya S. Gal repressosome contains an antiparallel DNA loop. *Nat Struct Biol*. 2001; 8:423–436. [PubMed: 11323717]
5. Swigon D, Coleman BD, Olson WK. Modeling the lac repressor-operator assembly. I. The influence of DNA looping on Lac repressor conformation. *Proc Natl Acad Sci USA*. 2006; 103:9879–9884. [PubMed: 16785444]
6. Tolstorukov MY, Colasanti AV, McCandlish DM, Olson WK, Zhurkin VB. A novel roll-and-slide mechanism of DNA folding in chromatin: implications for nucleosome positioning. *J Mol Biol*. 2007; 371:725–738. [PubMed: 17585938]
7. Davey CA, Sargent DF, Luger K, Mäder AW, Richmond TJ. Solvent mediated interactions in the structure of the nucleosome core particle at 1.9 Å resolution. *J Mol Biol*. 2002; 319:1097–1113. [PubMed: 12079350]
8. Olson WK, Gorin AA, Lu XJ, Hock M, Zhurkin VB. DNA sequence-dependent deformability deduced from protein–DNA crystal complexes. *Proc Natl Acad Sci USA*. 1998; 95:11163–11168. [PubMed: 9736707]
9. Balasubramanian S, Xu F, Olson WK. DNA sequence-directed organization of chromatin: structure-based analysis of nucleosome-binding sequences. *Biophys J*. 2009; 96:2245–2260. [PubMed: 19289051]
10. Wang D, Ulyanov NB, Zhurkin VB. Sequence-dependent Kink-and-Slide deformations of nucleosomal DNA facilitated by histone arginines bound in the minor groove. *J Biomol Struct Dyn*. 2010; 27:843–859. [PubMed: 20232937]
11. Tan S, Davey CA. Nucleosome structural studies. *Curr Opin Struct Biol*. 2011; 21:128–136. [PubMed: 21176878]
12. Olson WK, Zhurkin VB. Working the kinks out of nucleosomal DNA. *Curr Opin Struct Biol*. 2011; 21:348–357. [PubMed: 21482100]
13. Chua EYD, Vasudevan D, Davey GE, Wu B, Davey CA. The mechanics behind DNA sequence-dependent properties of the nucleosome. *Nucleic Acids Res*. 2012; 40:6338–6352. [PubMed: 22453276]
14. Thastrom A, Bingham LM, Widom J. Nucleosomal locations of dominant DNA sequence motifs for histone-DNA interactions and nucleosome positioning. *J Mol Biol*. 2004; 338:695–709. [PubMed: 15099738]
15. Morozov AV, Fortney K, Gaykalova DA, Studitsky VM, Widom J, Siggia ED. Using DNA mechanics to predict in vitro nucleosome positions and formation energies. *Nucleic Acids Res*. 2009; 37:4707–4722. [PubMed: 19509309]
16. Lankas F, Sponer J, Langowski J, Cheatham TE 3rd. DNA basepair step deformability inferred from molecular dynamics simulations. *Biophys J*. 2003; 85:2872–2883. [PubMed: 14581192]
17. Lankas F, Gonzalez O, Heffler LM, Stoll G, Moakher M, Maddocks JH. On the parameterization of rigid base and basepair models of DNA from molecular dynamics simulations. *Phys Chem Chem Phys*. 2009; 11:10565–10588. [PubMed: 20145802]