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Invited Paper

Nonlocal Interactions in DNA Molecules at Nano-Scale

B. Eslami-Mossallam[1] and M.R. Ejtehadi[1,*]

Abstract. *In this paper, we try to explain the origin of the anomalous elastic behavior of nanometer-sized DNA molecules, which has been observed in all-atom molecular dynamic simulations [A.K. Mazur, Biophys. J. 2006]. It is shown that this anomalous behavior is a consequence of nonlocal interactions between DNA base pairs and the intrinsic curvature of DNA. A nonlocal harmonic elastic rod model is proposed, which can successfully describe the elastic behavior of short DNA molecules.*

Keywords: *DNA; Elasticity; Long-range interactions.*

INTRODUCTION

DNA is one of the most important biomolecules, not only for its ability in carrying and transferring genetic information of biological systems, but also because of its mechanical flexibility that helps it to do its biological function. Studying the elastic behavior of DNA is important for understanding its biological functions. One of the best theoretical models to explain the elastic behavior of DNA is the local harmonic elastic rod model (also called the wormlike chain model) [1,2]. In this model it is assumed that the base pairs only interact with their nearest neighbor, and the elastic energy is a harmonic function of the deformation. The wormlike chain model can predict the elastic properties of long DNA molecules very accurately [2]. Despite this success, there is some doubt about the applicability of the wormlike chain model for short, nanometer-sized, DNA molecules [3,4].

All-atom simulations are the best approach to study the elastic behavior of DNA at the base pair level [5,6]. Recently Mazur has performed all-atom MD simulations to study the elastic properties of a double helical DNA fragment of 25 base pairs with the AT-alternating sequence [5]. Mazur measured a quantity $D_a(L) = -\ln\langle\cos\theta(L)\rangle$, where θ is the bending angle of a DNA molecule of length L. He observed that $D_a(L)$ is a nonlinear function of L. This is contradictory to the wormlike chain model, which predicts that $D_a(L)$ is linear. In this paper we will show that the nonlinearity of $D_a(L)$ is a direct consequence of nonlocal interactions between DNA base pairs and the intrinsic curvature of DNA. We propose a nonlocal harmonic model that can explain the anomalous elastic behavior of DNA observed in [5].

1. *Department of Physics, Sharif University of Technology, P.O. Box 14588-89694, Iran.*
*. *Corresponding author. E-mail: ejtehadi@sharif.edu*

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MODEL AND METHODS

Nonlocal Harmonic Elastic Rod Model

In the elastic rod model, DNA is represented by a flexible inextensible rod [1,2], which can be deformed in response of the external forces or torques. Here we use a coarse-grained version of the elastic rod model [2] where the rod is divided into discrete segments, each representing a DNA base pair. In this model, the internal degrees of freedom of the base pairs are neglected, and each base pair is considered as a rigid body. A local coordinate frame is attached to each base pair [2,7]. Since it is assumed that the DNA is inextensible, separation of successive base pairs is fixed and each base pair only has three rotational degrees of freedom. The orientation of the $(n+1)$th base pair with respect to the nth base pair is then determined by rotation $R(n)$. The rotation matrix $R(n)$ can be parameterized by a vector $\vec{\Theta}(n)$, which its direction points to the axis of the rotation and its magnitude is equal to the rotation angle. The components of $\vec{\Theta}(n)$ in the local coordinate system attached to the

nth base pair are denoted by $\Theta_1(n)$, $\Theta_2(n)$ and $\Theta_3(n)$. These three angles can be regarded as the rotational degrees of freedom of the $(n+1)$th base pair, and are called tilt, roll and twist respectively. If the values of these three angles are known for all the base pairs, the conformation of the DNA can be uniquely determined.

For an inextensible DNA with N base pair steps, the elastic energy is a function of $3N$ rotational degrees of freedom. For small deformations, the elastic energy can be expanded in a Taylor series about the equilibrium configuration. If we expand the elastic energy to the second order, we arrive at the harmonic elastic rod model which is given by:

$$E_H[\Theta]=\frac{1}{2}k_BT\sum_{i,j=1}^{3}\sum_{m,n=1}^{N}Q^{ij}(n,m)\Delta\Theta_i(n)\Delta\Theta_j(m), \quad (1)$$

where $\Delta\Theta_i(n)$ denotes the deviation of $\Theta_i(n)$ from the equilibrium value $\Theta_i^0(n)$, $(\Delta\Theta_i(n)=\Theta_i(n)-\Theta_i^0(n))$. In Equation 1, Q^{ij}s are $N\times N$ matrices with the property $Q^{ij}(n,m)=Q^{ji}(m,n)$, and are called elastic matrices.

The stability of the elastic energy imposes some constrains on the elastic matrices. We define Q as a $3N\times 3N$ matrix with nine $N\times N$ blocks whose ij block is Q^{ij}. One can see that Q is symmetric. The necessary and sufficient condition for the stability of the elastic energy is that the matrix Q is positive-definite.

The elastic energy given in Equation 1 represents the most general form of the harmonic elastic rod model. Usually it is assumed that interactions between DNA base pairs are local, that is each base pair only interacts with its nearest neighbors. In this case, there is no coupling between the rotational degrees of freedom of different base pairs. In the harmonic approximation, the locality assumption implies that the elastic matrices, Q^{ij}s, are diagonal. Thus the local harmonic elastic rod model, also known as wormlike chain model, is given by [1,2]:

$$E_{WLC}[\Theta]=\frac{1}{2}k_BT\sum_{i,j=1}^{3}\sum_{n=1}^{N}A_{ij}(n)\Delta\Theta_i(n)\Delta\Theta_j(n), \quad (2)$$

where $A_{ij}n=Q^{ij}(n,n)$.

In the general case, where nonlocal interactions exist between DNA base pairs, the elastic matrices have nonzero off-diagonal elements, and the elastic energy can be decomposed into two terms:

$$E_H[\Theta]=E_{WLC}[\Theta]+E_{NL}[\Theta]. \quad (3)$$

The first term in Equation 3 is the local part of the elastic energy given in Equation 2, and the second term comes from nonlocal interactions that can be written as:

$$E_{NL}[\Theta]=\frac{1}{2}k_BT\sum_{i,j=1}^{3}\sum_{n=1}^{N}\sum_{r=1}^{N-n}[J_{ij}(n,r)\Delta\Theta_i(n)\Delta\Theta_j(n+r)], \quad (4)$$

where $J_{ij}(n,r)$ are the nonlocal coupling constants which are related to off-diagonal elements of the elastic matrices via equation:

$$J_{ij}(n,r)=\frac{1}{2}[Q^{ij}(n,n+r)+Q^{ji}(n+r,n)]. \quad (5)$$

Calculating the Elastic Parameters of DNA from Simulation Data

In the harmonic approximation, the elastic constants of DNA can be calculated from the correlation matrices in a standard way [6]. We define a $3N\times 3N$ matrix G with nine $N\times N$ blocks whose ij block is the correlation matrix G^{ij} given by:

$$G^{ij}(n,m)=\langle\Theta_i(n)\Theta_j(m)\rangle-\langle\Theta_i(n)\rangle\langle\Theta_j(m)\rangle. \quad (6)$$

Then we have:

$$Q=G^{-1}. \quad (7)$$

Also the equilibrium conformation of DNA in the harmonic approximation is given by:

$$\Theta_i^0(n)=\langle\Theta_i(n)\rangle. \quad (8)$$

3DNA software [8] was used to calculate the rotational degrees of freedom of the base pairs for all MD trajectories obtained in [5]. In this way, we found a statistical ensemble for the rotational degrees of freedom of all DNA base pairs. We then calculated the elastic parameters of DNA using Equations 7 and 8.

It must be noted that 3DNA uses CEHS (Cambridge University, Engineering department – helix Computation Scheme) definition for the rotational degrees of freedom [9] which is different from the definition we used in this paper. However, the two definitions are related via simple equations [9], and the rotational degrees of freedom in our definition were easily calculated from 3DNA output.

Monte Carlo Simulation

We use a simple Monte Carlo simulation to calculate the statistical properties of DNA in our model. In each Monte Carlo move, we randomly choose a base pair, and for that base pair we change the vector $\vec{\Theta}$ by $\Delta\vec{\Theta}$. The direction of $\Delta\vec{\Theta}$ is random, and its magnitude is chosen randomly in the interval $[0,\Theta_{\max}]$, where $\Theta_{\max}$ is chosen so that the accept ratio is about 0.5. We do not include the self avoiding in the simulation, since the probability of self crossing is small for the short simulated DNA molecules.

RESULTS AND DISCUSSION

The nonlocal nature of elastic behavior of DNA in the MD simulations done by Mazur [5] is revealed in the autocorrelation functions of rotational degrees of freedom of DNA, which are defined as:

$$g_i(r) = \frac{1}{(N-r)\delta_i} \sum_{n=1}^{N-r} G^{ii}(n, n+r), \tag{9}$$

where G^{ij} is the correlation matrix given by Equation 6, and δ_i is a normalization constant chosen so that $g_i(0) = 1$. If the interactions between the DNA base pairs are local, the degrees of freedom of different base pairs must be uncorrelated, i.e. $g_i(r) = 0$ for $r \neq 0$. Therefore, if the auto correlation functions have a nonzero value at a nonzero distance, this implies that there exist nonlocal interactions between DNA base pairs. Figure 1 shows the autocorrelation functions of rotational degrees of freedom in MD simulations. As can be seen, there are large negative correlations, specially at $r = 1$. This indicates that there are nonlocal interactions between DNA base pairs in MD simulations. In another work, Lankas et al. have obtained a similar result for the autocorrelation functions of rotational degrees of freedoms [6].

To study the effect of nonlocal interactions on the elastic properties of DNA, we calculated $D_a(L) = -\log\langle\cos\theta(L)\rangle$ as a function of DNA length L, where $\theta(L)$ is the bending angle of a DNA of length L. We define the bending angle as:

$$\cos\theta = \hat{d}_3(1).\hat{d}_3(N+1), \tag{10}$$

where $\hat{d}_3(n)$ is a unit vector perpendicular to the surface of the nth base pair. Defining the bending angle as in Equation 10 has some advantages. This definition does not involve any fitting, and the bending angle depends only on the definition of the local coordinate frames. For an inextensible DNA, the normal vectors to the base pairs are locally tangent to the DNA helical axis. Since the translational degrees of freedom of DNA usually take small values, Equation 10 is a good approximation for the bending angle of DNA. Nevertheless, the bending angle of DNA defined in this way does not depend on the translational degrees of freedom. Thus the results presented here will not change if we include the translational degrees of freedom in the model. Most important of all it is known that with the bending angle defined as in Equation 10, $D_a(L)$ is a linear function of L, provided that DNA has no intrinsic curvature and the interactions are local. Therefore, $D_a(L)$ is a good candidate to identify the effect of nonlocal interactions.

Figure 2 shows $D_a(L)$, calculated directly from MD simulations data [5] (diamonds). It can be seen that $D_a(L)$ is highly nonlinear. Similar results are obtained if one uses 3DNA or curve softwares to find the bending angle [5,10]. Using Monte Carlo simulation, we calculate $D_a(L)$ for the nonlocal harmonic elastic rod model, parameterized by Equations 6 and 7. The result is shown in Figure 2 (solid line). It can be seen that

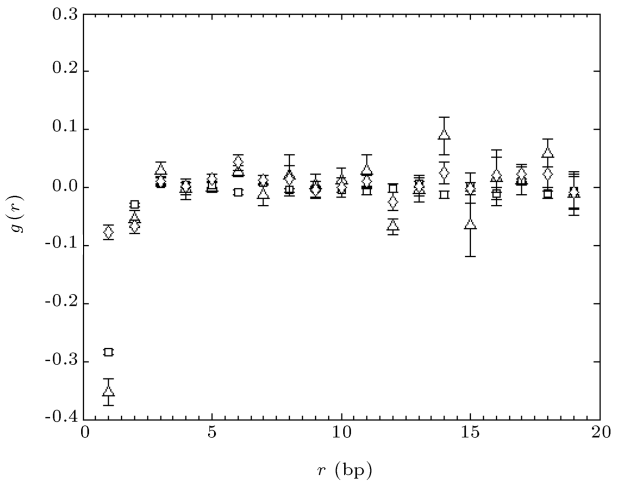

Figure 1. Autocorrelation functions as a function of separation. Squares: $g_1(r)$, diamonds: $g_2(r)$, triangles: $g_3(r)$. There are large negative correlations, specially at $r = 1$.

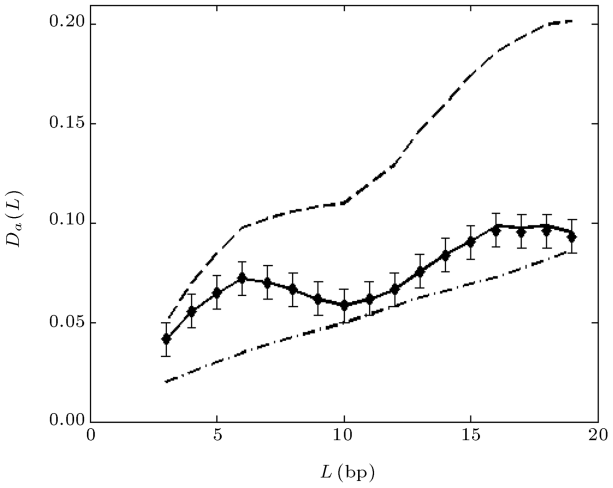

Figure 2. $D_a(L)$ as a function of L. Diamonds show the functional form of $D_a(L)$ as directly calculated from the MD simulation data [5]. The curves show the predictions of harmonic elastic rod models with various parametrizations. Solid curve: the nonlocal model. Dashed curve: local model. Dot-dashed curve: nonlocal model with zero intrinsic curvature. As can be seen, in the local model, as well as the nonlocal model with zero intrinsic curvature, there is a significant discrepancy between the prediction of the model and the MD simulation data. However, if both the intrinsic curvature and the nonlocal interactions are included, the MD simulation data can be successfully explained by the model.

there is a perfect agreement between the prediction of the model and MD data. This indicates that the harmonic elastic rod model is capable to describe the nonlinear behavior of $D_a(L)$.

To clarify the origin of nonlinearity, we study two other harmonic elastic rod models with different parametrizations. The dashed line in Figure 2 shows the prediction of the local harmonic elastic rod model. We parametrized the local model by Equations 6 and 7, assuming the correlation matrices are all diagonal and calculating the diagonal elements of the correlation matrices from MD simulations data. As can be seen, $D_a(L)$ is not linear, but there is a significant discrepancy between the prediction of the local model and the MD simulation data. The nonlinearity observed for the local model is due to the intrinsic curvature of DNA. All base pairs in AT_{25} molecule have positive intrinsic roll and tilt. The intrinsic curvature changes the equilibrium bending angle and the effective bending rigidity of DNA. These variations are oscillatory functions of DNA length, and lead to the nonlinear functional form of $D_a(L)$. If we assume that the DNA has zero intrinsic curvature, the resultant curve is a straight line as it is expected (data not shown). The dot-dashed curve in Figure 2 shows the prediction of the nonlocal harmonic elastic rod model with zero intrinsic curvature where the elastic matrices are parametrized by Equation 6, but we set $\Theta_1^0 = \Theta_2^0 = 0$ for all base pair steps. As can be seen, the resultant curve has no resemblance to the simulation data. The above analysis indicates that the nonlinearity of $D_a(L)$ is a result of the combined effect of DNA intrinsic curvature and the nonlocal interactions between the base pairs.

CONCLUSION

In summary we proved that there are nonlocal interactions between DNA base pairs at nanometer length scales. We showed that these interactions affect the elastic behavior of DNA, and contribute to the nonlinear length dependence of $D_a(L)$. We proved that the nonlinearity originates from the combined effect of DNA intrinsic curvature and the nonlocal interactions.

It is important to find the origin of the nonlocal interactions. The electrostatic interactions and the backbone elastic properties probably play an important role [11]. More detailed analysis is required to determine the contributing factors to the nonlocal interactions in DNA molecule.

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REFERENCES

1. Marko, J.F. and Sigga, E.D. "Bending and twisting elasticity of DNA", *Macromolecules*, **27**, pp. 981-988 (1994).
2. Towles, K., Beausang, J., Garcia, H., Phillips, R. and Nelson, P. "First-principles calculation of DNA looping in tethered particle experiments", *Biophys. J.*, **96**, p. 556a (2009).
3. Cloutier, T.E. and Widom, J. "DNA twisting flexibility and the formation of sharply looped protein-DNA complexes", *Proc. Natl. Acad. Sci.*, **102**, pp. 3645-3650 (2005).
4. Wiggins, P.A. et al. "High flexibility of DNA on short length", *Nature Nanotechnol.*, **1**, pp. 137-141(2006).
5. Mazur, A.K. "Evaluation of elastic properties of atomistic DNA models", *Biophys. J.*, **91**, pp. 4507-4518 (2006).
6. Lankas, F., Sponer, J., Hobza, P. and Langowski, J. "Sequence-dependent elastic properties of DNA", *J. Mol. Biol.*, **299**, pp. 695-709 (2000).
7. Eslami-Mossallam, B. and Ejtehadi, M.R. "Asymmetric elastic rod model for DNA", *Phys. Rev. E*, **80**, p. 011919 (2009).
8. Lu, X.-J. and Olson, W.K. "3DNA: a software package for the analysis, rebuilding and visualization of three-dimensional nucleic acid structures", *Nucleic Acid Res.*, **31**, pp. 5108-5121 (2003).
9. El Hassan, M.A. and Calladine, C.R. "The assessment of the geometry of dinucleotide steps in double-helical DNA; a new local calculation scheme", *J. Mol. Biol.*, **251**, pp. 648-664 (1995).
10. Mazur, A.K. "Kinetic and thermodynamic DNA elasticity at micro and mesoscopic scales", *J. Phys. Chem. B*, **113**, pp. 2077-2089 (2009).
11. Mazur, A.K., personal communications.

BIOGRAPHIES

Behrouz Eslami-Mossallam is a Physics Ph.D. student in Sharif University of Technology and is working on modeling DNA Molecule Elasticity in different scales.

Mohammad Reza Ejtehadi obtained his Ph.D. in 1998 from Sharif University of Technology. He has worked in Max-Planck institute in Mainz, University of British Columbia in Vancouver. In year 2004 he joined Sharif University of Technology where he holds an associate professor position since 2008. He applies statistical physics and simulation to various problems in soft matter and biological systems. He has also been appointed as treasurer and board member of Physics Society of Iran since 2009.