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Geometrical correlations in the nucleosomal DNA conformation and the role of the covalent bonds rigidity

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ABSTRACT

We develop a simple elastic model to study the conformation of DNA in the nucleosome core particle. In this model, the changes in the energy of the covalent bonds that connect the base pairs of each strand of the DNA double helix, as well as the lateral displacements and the rotation of adjacent base pairs are considered. We show that because of the rigidity of the covalent bonds in the sugar-phosphate backbones, the base pair parameters are highly correlated, especially, strong twist-roll-slide correlation in the conformation of the nucleosomal DNA is vividly observed in the calculated results. This simple model succeeds to account for the detailed features of the structure of the nucleosomal DNA, particularly, its more important base pair parameters, roll and slide, in good agreement with the experimental results.

INTRODUCTION

The DNA double helix in eukaryotes is packed into nucleosomes, which are composed of repeating array of DNA–protein complexes called the nucleosome core particles, which are connected via linker DNA. DNA deforms significantly to create the nucleosome core particle; the 147 base pair DNA is wrapped in 1.84 left-handed turns around a core particle of histone proteins (1,2). The wrapped DNA–histone octamer complex is essentially ubiquitous in nature and has a major role in many vital processes in the cell (3). The tightly wrapped conformation of the nucleosomal DNA seems to hinder the accessibility of its genetic information needed for fundamental life processes such as transcription and DNA replication. In fact, nucleosome is highly dynamic (4); experiments show spontaneous conformational transitions where thermal fluctuations make part of DNA unwrap (5). 'Sliding' of the histone octamer along DNA is another strongly temperature-dependent mechanism that has been observed and modeled both experimentally, and theoretically (6). Therefore, as in many vital processes, the highly compacted conformation of the nucleosomal DNA should change to expose its genetic information to proteins involved in these processes; studying nucleosomal DNA structure and formation energies are very important.

The conformation of the 147 base pair nucleosomal DNA has been determined in a high precision experiment by Richmond and Davey (7). Mohammad-Rafiee and Golestanian (8) studied the structure of DNA in the nucleosome core particle using an elastic model that incorporates anisotropy in the bending energies and twist-bend coupling. Although their simple model can account to a good degree for the observed structure of the nucleosomal DNA, obtaining other structural properties of the nucleosomal DNA, such as shift and slide, is beyond it. Tolstorukov *et al*. (9) recently showed the importance of the lateral displacements of adjacent base pairs of the nucleosomal DNA, especially, the slide in nucleosome structure. In other more recent numerical analysis, Morozov *et al*. (10) have developed a sequence-dependent nucleosome model, and obtained all of the base pair parameters. Although their results show overall correlation with the experimental results, they find significant discrepancies. Particularly, they underestimate the magnitude of the slide peaks that are very important in the nucleosome structure.

Considering the elastic and geometrical properties of the nucleosomal DNA, we introduce a simple model to obtain its base pair parameters, roll, tilt, shift, slide and rise, so, the lateral displacements of the adjacent base pairs of DNA are considered besides the bending and twisting deformations, which are mostly studied in the previous

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theoretical works and simulations. The DNA–protein interactions in the nucleosome core particle are taken into account by directly reading off the twist angles from the experimental results of Richmond and Davey. Since adjacent base pair are coupled through the DNA sugar-phosphate backbones, the base pair parameters are not independent, and they are correlated. In this model, the covalent bonds between the adjacent base pairs of the two strands of DNA are considered deformable, and simply modeled by two stiff springs. We show that the stiffness of these covalent bonds results in strong correlations between the base pair parameters, particularly, the strong roll-slide-twist coupling. The elastic energy of the molecule consists of two terms: one shows the changes in the covalent bond energies, and the other shows the energy cost of the rotation of the base pairs. By using this simple model, we can find all of the 21 different elastic constants of DNA molecule as a function of the covalent bonds stiffness. We simply consider no sequence effect explicitly in writing the elastic energy of DNA, and without any tuning parameter, the base pair parameters of the 147 bp steps, especially, the most important ones, roll and slide, are obtained in an overall good agreement with the experimental results. In particular, the peaks of the slide values are close to the experimental ones. As we consider no sequence effect directly, these encouraging results show the important role of the rigidity of the sugar-phosphate backbones of DNA in its conformation.

MATERIALS AND METHODS

DNA geometry and the covalent bond energy

The base pairs are considered as rectangular solids of half length and width of $l = 1$ nm and $w = 1/3$ nm (11). As a result of deformation and changes in the base pair parameters values, the lengths of two strands of DNA can change. These changes result in the elastic energy of deformed covalent bonds between the monomers of each strand. DNA is an anisotropic chiral molecule, so the changes in the length of the two strands can differ. The covalent bonds between the bases of each strand are modeled by springs of stiffness of about $k_c \simeq 10^4$ pN/nm (12). These springs connect the middle of the width of one base pair to that of the adjacent base pair. At each base pair, we can affix a localized Cartesian coordinate system, so that its x and y axes lie along the width and length of the rectangular solid, respectively (Figure 1). The orientation of these localized coordinates can change from one base pair to the other and we have:

$$\frac{1}{\delta}\frac{\mathrm{d}\hat{e}_\alpha(n)}{\mathrm{d}n} = \vec{\omega}(n) \times \hat{e}_\alpha(n), \quad (1)$$

where $\alpha = 1,2,3$ labels the three axes of the localized coordinates, n is a dimensionless parameter, which labels the base pair, δ is the z component of the displacement vector between the middle of the adjacent base pairs and $\vec{\omega}$ shows the rate of the change in the orientation of the adjacent rectangular solids, and can be written in terms of the angular base pair parameters; roll, R, tilt, T and twist, θ, as:

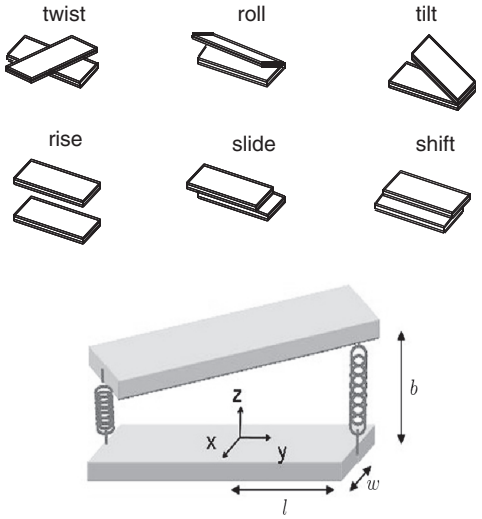

Figure 1. The six base pair parameters; twist, roll, tilt, rise, shift and slide. DNA base pairs are shown by rectangular solids (top). Schematic view of the adjacent base pairs, and the covalent bonds along the backbones, which are simply modeled by two springs (bottom). The half of the length and width of of the base pairs are shown by l and w, respectively, and b equals to the rise of undeformed DNA. At each base pair, we consider a localized Cartesian coordinate system xyz.

$$\vec{\omega} = \frac{T}{\delta}\hat{e}_1 + \frac{R}{\delta}\hat{e}_2 + \frac{\theta}{\delta}\hat{e}_3. \quad (2)$$

The length of each spring can be written as $l_c(j) = |\vec{d}(j)|$ ($j = 1, 2$), where

$$\vec{d}(j) = \Delta x(j)\hat{e}_1 + \Delta y(j)\hat{e}_2 + \Delta z(j)\hat{e}_3, \quad (3)$$

is the displacement vector between the two ends of each spring. To find $|\vec{d}(j)|$, we should solve Equation (1) and obtain the coordinates of the points of each rectangular solid in the localized coordinate system of its adjacent rectangular solid. We assume that the changes in the orientation of the adjacent base pairs are small, and estimate the coefficients of the displacement vector of the strand attached at $y = l$, $\Delta x(1)$, $\Delta y(1)$ and $\Delta z(1)$ as:

$$\begin{aligned} \Delta x(1) &\simeq -(l+D)\sin\theta\cos T + S\cos R \\ \Delta y(1) &\simeq (l+D)\cos\theta\cos T - l \\ \Delta z(1) &\simeq b(1+\varepsilon) + S\sin R + (l+D)\sin T. \end{aligned} \quad (4)$$

In the above equations, b denotes the base pair step for B-DNA, ε shows the relative changes in rise and S and D correspond to the shift and slide parameters, respectively. To obtain the above equations, we successively apply slide, tilt, twist, shift, roll and rise to the rectangular solids. Note that for small base pair parameters, considering different orders makes no difference. The coefficients of the displacement vector of the other strand, $\Delta x(2)$,

$\Delta y(2)$ and $\Delta z(2)$, are obtained by substituting $l \rightarrow -l$ in the above equation as:

$$\begin{aligned}\Delta x(2) &\simeq (l-D)\sin\theta\cos T+S\cos R\\ \Delta y(2) &\simeq -(l-D)\cos\theta\cos T+l\\ \Delta z(2) &\simeq b(1+\varepsilon)+S\sin R-(l-D)\sin T.\end{aligned} \quad (5)$$

For undeformed DNA, $R = T = 0$, $D = S = 0$, $\varepsilon = 0$ and $\theta = \theta_0 = 2\pi/10$, so the arc length of the backbone between the two adjacent base pairs of each strand of undeformed DNA is $l_{c0} = \sqrt{b^2+2l^2(1-\cos\theta_0)}$. The total energy counts the deformation energy of the covalent bonds, E_c is found to be

$$E_c = \frac{k_c}{2}\sum_{i=1}^{N}\left[x_i(1)^2+x_i(2)^2\right], \quad (6)$$

where $x(1) = l_c(1)-l_{c0}$, and $x(2) = l_c(2)-l_{c0}$ show the changes in the arc length of the backbone between the two adjacent base pairs of each strand, i and N denote the label of base pair and the total number of the base pairs of the nucleosomal DNA, respectively.

The rotational elastic energy

Besides E_c, we consider the energy cost of the rotation of the base pairs, E_{rot}, in the total elastic energy of the nucleosomal DNA, E_{el}, so we have:

$$E_{el} = E_{rot}+E_c. \quad (7)$$

In this model, the strains are considered as the amount of rotation of the localized coordinates per length of the molecule around each of the three axes of the localized coordinate of the adjacent base pairs, the components of $\vec{\omega}$ (13). Note that, as a result of deformation, δ is no longer equals to the base pair step of B-DNA, b, and for small deformations can be written as: $\delta \simeq b(1+\varepsilon)+S\sin R+D\sin T$. For small strains, we write the energy of the chain of nucleosomal DNA as a Taylor expansion of the strains as:

$$\begin{aligned}\frac{E_{rot}}{k_BT} = \frac{1}{2}\sum_{i=1}^{N}\Bigg\{&A_1\frac{T_i^2}{b}+A_2\frac{R_i^2}{b}+Cb\left[\frac{\theta_0(1+\sigma_i)}{b(1+\varepsilon_i)}-\omega_0\right]^2\\ &+2G\left[\frac{\theta_0(1+\sigma_i)}{b(1+\varepsilon_i)}-\omega_0\right]R_i\Bigg\}.\end{aligned} \quad (8)$$

Here, we consider terms up to the second order of the strains to simply have linear equations after energy minimization. Because of the anisotropy of the DNA molecule, which has two distinguishable grooves (minor and major), the asymmetric last term in the above energy equation appears (twist-bend coupling) (14). In the above equation, A_1, and A_2 are bending rigidities corresponding to tilt and roll, respectively, C is the twist rigidity, G denotes the twist-bend coupling and $\omega_0 = 1.85\,\text{nm}^{-1}$ is the spontaneous twist of the helix. Considering the anisotropic bending rigidities is important as it has been shown that the anisotropic bending elasticity can cause the curvature modulation with the period of 5 bp (8,15,16). Note that in this energy equation, we consider the elastic coefficients to be constant, and independent of the base pair steps. We estimate the values of these elastic constants by using the known values of the average rigidities of DNA defined in the previous continuous elastic rod models (14,17,18), and consider $A_1 = 75\,\text{nm}$, $A_2 = 37\,\text{nm}$ (19), $C = 100\,\text{nm}$ (20), and $G = 25\,\text{nm}$ (8) for the elastic rigidities.

Nucleosomal DNA wrapping constraint

As mentioned before, DNA is wrapped by 1.84 turns around the protein octamer, so to find the shape of DNA, we should consider a global constraint. To write this constraint, first, we recall the differential geometry of an ideal superhelix, which can be considered as an approximation of the nucleosomal DNA; at each point of an ideal superhelix, we can define orthonormal Frenet unit vectors as:

$$\begin{aligned}\hat{t}(s) &\equiv \partial_s\vec{r}(s)\\ \hat{n}(s) &\equiv \frac{\partial_s\hat{t}(s)}{|\partial_s\hat{t}(s)|}\\ \hat{b}(s) &\equiv \hat{t}(s)\times\hat{n}(s),\end{aligned} \quad (9)$$

where s is the arc length, $\vec{r}(s)$ is the position vector at each point and $\hat{t}(s)$, $\hat{n}(s)$ and $\hat{b}(s)$ are tangent, normal and binormal vectors at point s, respectively. The notation ∂_s means the derivative with respect to s. The rate of changes of these unit vectors can be written as:

$$\partial_s\hat{t}(s) = \kappa(s)\hat{n}(s) \quad (10)$$

$$\partial_s\hat{n}(s) = -\kappa(s)\hat{t}(s)+\tau(s)\hat{b}(s) \quad (11)$$

$$\partial_s\hat{b}(s) = \tau(s)\hat{n}(s), \quad (12)$$

where $\kappa(s)$ and $\tau(s)$ are curvature and torsion at each point. We keep writing s in order to emphasize that the mentioned quantities have their local values.

Now, we can estimate the global constraint of the nucleosomal DNA as $\sum_{i=1}^{N}\kappa_i\delta_i \simeq 2\pi\times 1.84$, where κ_i is the curvature of the superhelix of the nucleosomal DNA in segment i. Here, we neglect torsion, τ, with respect to curvature; it can be shown that the mean curvature and torsion of the nucleosomal DNA (considered to be approximately equal to those of an ideal superhelix) with radius $R\simeq 41.9$ Å and pitch of $2\pi\nu\simeq 25.9$Å are $\kappa_{av} = R/(R^2+\nu^2)$ and $\tau_{av} = -\nu/(R^2+\nu^2)$. Therefore, we have $\tau_{av}/\kappa_{av} = 0.098$, which justifies the above approximation. Moreover, localized coordinate unit vectors can be written in the Frenet frame as:

$$\begin{aligned}\hat{e}_1(s) &= -\sin\psi(s)\hat{b}(s)+\cos\psi(s)\hat{n}(s)\\ \hat{e}_2(s) &= -\cos\psi(s)\hat{b}(s)-\sin\psi(s)\hat{n}(s)\\ \hat{e}_3(s) &= \hat{t}(s),\end{aligned} \quad (13)$$

where $\psi(s)$ is the accumulated twist angle (the angle between the localized coordinate and orthonormal Frenet vectors at the plane of each base pair). Considering Equations (1, 2 and 10), we can write:

$$\frac{\Delta\hat{e}_{3i}}{\delta_i} \simeq \frac{R_i}{\delta_i}\hat{e}_{1i}-\frac{T_i}{\delta_i}\hat{e}_{2i}, \quad (14)$$

where i denotes the label of the base pair. From Equations (13 and 14) for an ideal superhelix, we have: $T_i \cos\psi_i = R_i \sin\psi_i$, and $\kappa_i\delta_i = R_i \cos\psi_i + T_i \sin\psi_i$. In other words, we have $R_i = \kappa_i\delta_i \cos\psi_i$ and $T_i = \kappa_i\delta_i \sin\psi_i$ for an ideal superhelix. Using these relations, the constraint can be written as a function of the local roll, tilt and twist angle as:

$$\sum_{i=1}^{N}(R_i \cos\psi_i + T_i \sin\psi_i) \simeq 2\pi \times 1.84. \quad (15)$$

In order to find the local conformation of the nucleosomal DNA, one should take account of the specific local DNA–histone interactions in the nucleosome core particle, which is denoted by $V_{\text{DNA-histone}}$. Due to these interactions, the total energy of the nucleosome core particle can be written as $E_{\text{total}} = E_{el} + V_{\text{DNA-histone}}$. In principle, one should consider this total energy E_{total}, and minimize it respect to the local variables subject to the constraint, and find the local conformation of the DNA.

There are fourteen binding sites, where the nucleosomal DNA contacts the histone octamer (21). In these regions, the minor grooves of the DNA face to the nucleosome core, where at each contact region, there are several hydrogen bonds between the histone proteins and the sugar-phosphate groups of the DNA backbone (2). The interactions between DNA and the histones in the binding sites are quite specific (6,22). We assume that the twist degree of freedom is mostly governed by these local interactions. Therefore, the local potential is considered as a solely function of ψ as $V_{\text{DNA-histone}}(\psi)$ (8). As far as there is no reliable quantitative model for this local potential $V_{\text{DNA-histone}}$, for the sake of simplicity, we implicitly consider the effect of these local interactions in our model: we read off the twist angle of the DNA from the experimental data from Reference (7). It also gives us some information about the sequence effects, which are not explicitly taken into account in this simple model. We now minimize the energy with respect to R, T, S, D and ε subject to the wrapping constraint. So, we can find the local conformation parameters, roll, tilt, shift, slide and rise at each base pair step. We note that considering the symmetry of the nucleosome core particle with respect to its pseudo 2-fold axis, and following Reference (7), the calculations are performed for half of the DNA length corresponding to $m = \frac{n}{2} = 73$ base pairs.

RESULTS

After minimizing the energy of the Equation (8), with considering the wrapping constraint, Equation (15) and reading off the twist values from the experimental data of Richmond and Davey, the calculated values of the roll (R), tilt (T), shift (S), Slide (D) and rise are found. We have shown the results in Figures 2 and 3. As one can see, the calculated values of the base pair parameters are significantly correlated with the experimental results of Reference (7), especially, for the roll and slide.

One way to make a quantitative comparison with the experimental results is to calculate the linear correlation coefficients between the calculated results and the experimental data. The correlation coefficient, r, of two variables X and Y is equal to

$$r = \frac{\langle XY\rangle - \langle X\rangle\langle Y\rangle}{\sqrt{\left(\langle X^2\rangle - \langle X\rangle^2\right)\left(\langle Y^2\rangle - \langle Y\rangle^2\right)}}, \quad (16)$$

where $\langle A\rangle$ shows the average of the variable A. The correlation coefficients between the calculation and the experiment for the roll, slide, tilt and shift are 0.840, 0.774, 0.127 and 0.016, respectively. We can see that there is a clear coupling between the twist, roll and slide at kinked steps (i = 36, 48 and 58) correspond to flexible CA = TG base pairs. The slide values are also large at these steps, which are one of the most overwound base pair steps. It is worth to emphasize that the slide peaks are in good agreement with the experiment. We can see the importance of this result when we note that positive slides have a significant contribution to the structure of nucleosome.

In our model, the values of the peaks of the roll are also obtained in very good agreement with the experimental results, and around twice the ones for an ideal superhelix (4.53°). For the calculated values of the tilt and shift, in spite of overall agreement with the experimental results, the magnitude of the observed oscillations is generally underestimated. In fact, the calculated results for the values of the roll and slide are in more agreement with the experimental data than the ones of shift and tilt, which is also a consequence of the more correlation between the roll and slide with the twist angles that are reading off from the experiment directly. The correlation coefficients between twist and roll, as well as, twist and slide are obtained to be −0.951 and 0.768, respectively. The correlation coefficients between shift and tilt as well as roll and slide are 0.813 and −0.917, respectively. The negative correlation coefficient between roll and slide means that as the value of the slide increases, the value of the roll decreases. In fact, the parameters are correlated so that as a result of their changes, the arc length of the backbone does not change significantly. As shown in Figure 3, the stretching of the molecule is also negatively correlated with twist and it has large peaks at the base pair steps that the molecule is highly undertwisted.

To make a more refined quantitative comparison with the experiment, we take the Fourier transform of each base pair parameter, X, defined as $X_q = \frac{1}{\sqrt{m}}\sum_{s=1}^{m} X_s e^{2\pi i(s-1)(q-1)/m}$, for a list X_s of length m, to better resolve its feature (Figure 4). We know that the absolute value of the Fourier transform is symmetric with respect to the transformation $q \to m - q$; therefore, it is sufficient to show the first half of the plots. As one can see, there is a distinct peak in the Fourier transform of the base pair parameters at $q = \frac{73}{10}+1 = 8.3$, which is corresponding to the periodicity of 10 bp, which is equal to the helical repeat of DNA. We can also see a peak at q = 31 in the Fourier transform of the shift, which is equal to a period of about 2 bp, which is in consistence with the alternations observed experimentally in the shift values. Note that in

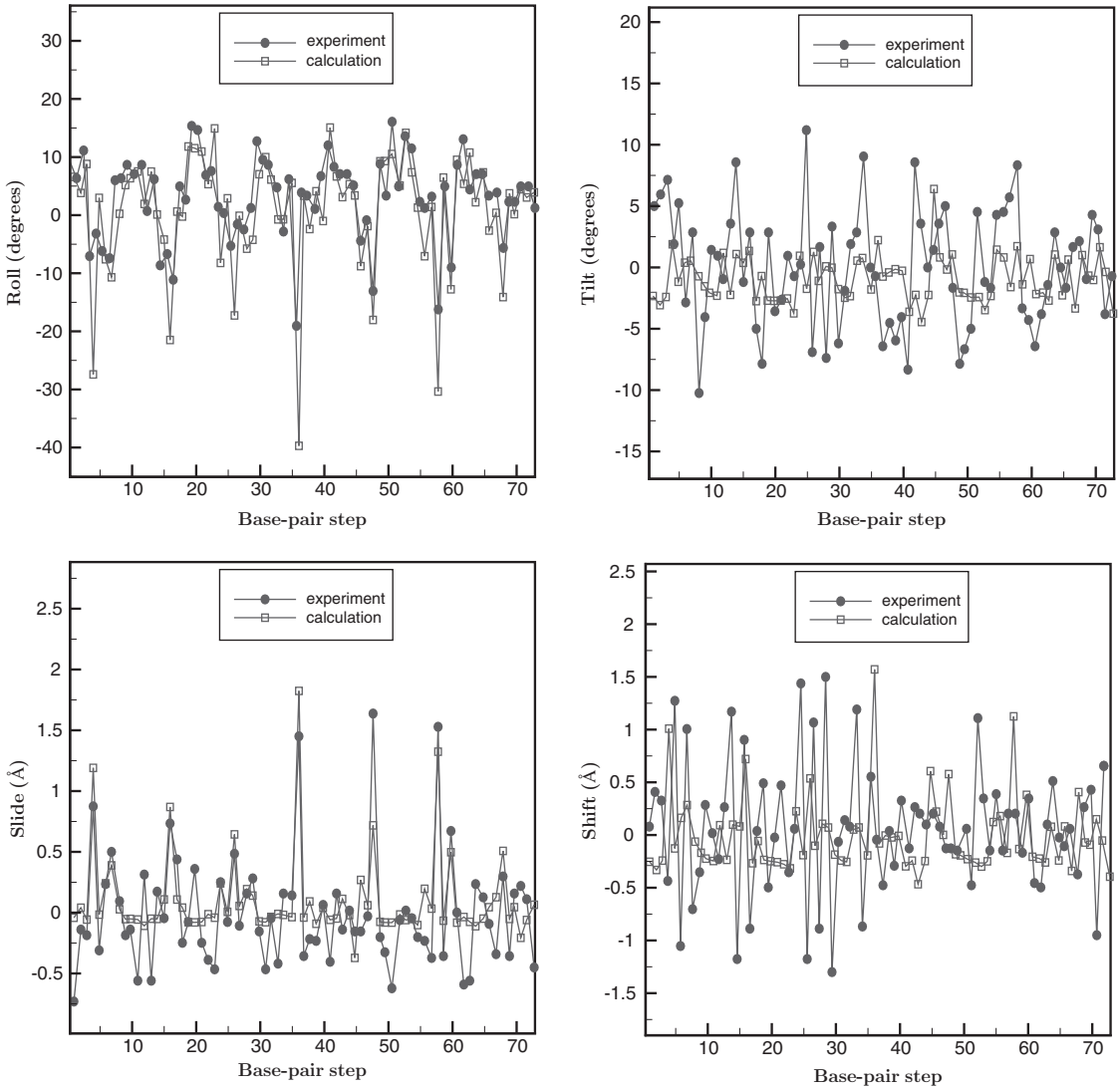

Figure 2. The calculated and the experimentally observed roll, tilt, shift and slide. The filled circles correspond to the experimental data taken from Reference (7), and the hollow squares show the calculated results using $A_1 = 75$ nm, $A_2 = 37$ nm, $C = 100$nm and $G = 25$ nm. In the calculation process, the twist angles are directly read off from the experimental data of Richmond and Davey. We can see a strong coupling between twist, roll and slide. The negative values of the roll and positive values of the slide are in good agreement with the experimental results.

spite of small obtained linear correlation coefficient between the calculated and experimental values of the shift, the Fourier transform of the calculated shift values is in encouraging agreement with that of the Experimental Data.

Using Equations (3)–(5) and the proper relations for the changes in the length of the covalent bonds between the adjacent base pairs of the two strands of DNA, one can determine the overall stretching of each strand of the nucleosomal DNA. The relative changes in the length of the covalent bonds between the adjacent base pairs of the two strands of DNA are shown in Figure 5. We see that the mentioned relative changes are less than 10 % for most of the base pair steps. As is expected, because of the rigidity of the covalent bonds, the arc length of the backbones does not vary significantly during the deformation. We note that, since DNA is an anisotropic molecule, the changes in the length of the springs of the two strands are not necessarily the same. In few base pairs, the length of the spring of one strand extends while the length of the spring of the other one decreases. In the base pair steps that the relative changes in the length of the springs are >10%, the relative changes in the twist are also large, which could be a consequence of DNA–protein interactions and sequence effects.

DISCUSSION AND CONCLUSION

Our simple model shows that the main features of the nucleosomal DNA can be determined using a proper elastic model that incorporates some correlations that come from the geometry of the molecule. We see that in this model, without considering the explicit effect of the DNA sequence, and without any tunning parameters, we

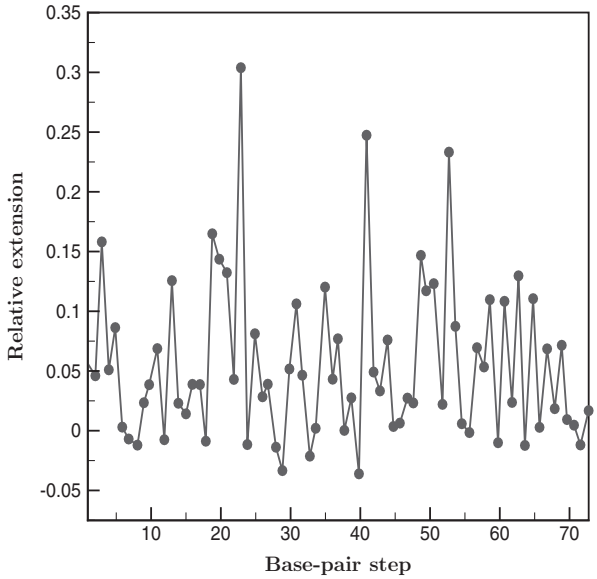

Figure 3. The relative changes in the length of the molecule, δ.

find the structure of the nucleosomal DNA in an encouraging good agreement with high precision experimental results. In the above treatment, the effect of the sequence is not considered explicitly in the elastic coefficients. Since we read off the twist of the nucleosomal DNA from the experiment, the effect of the sequence of DNA appears implicitly in the conformation of the nucleosomal DNA. Therefore, we can see the sequence effects in the behaviour of the calculated base pair parameters. For example, at steps corresponding to flexible CA = TG base pair steps, the values of roll and slide are relatively large. In fact, at these base pair steps, roll and slide are more significantly coupled with twist of the molecule. Since we read off the twist of the nucleosomal DNA from the experimental data, one may wonder what happens if the DNA twist is not determined with the experiment. In principle, the local DNA–histone potential determines the local twist of DNA. One can assume that this local potential causes the local torque and force on the DNA in such a way that the DNA is sharply bent and wrapped around the histone octamer. It has been shown

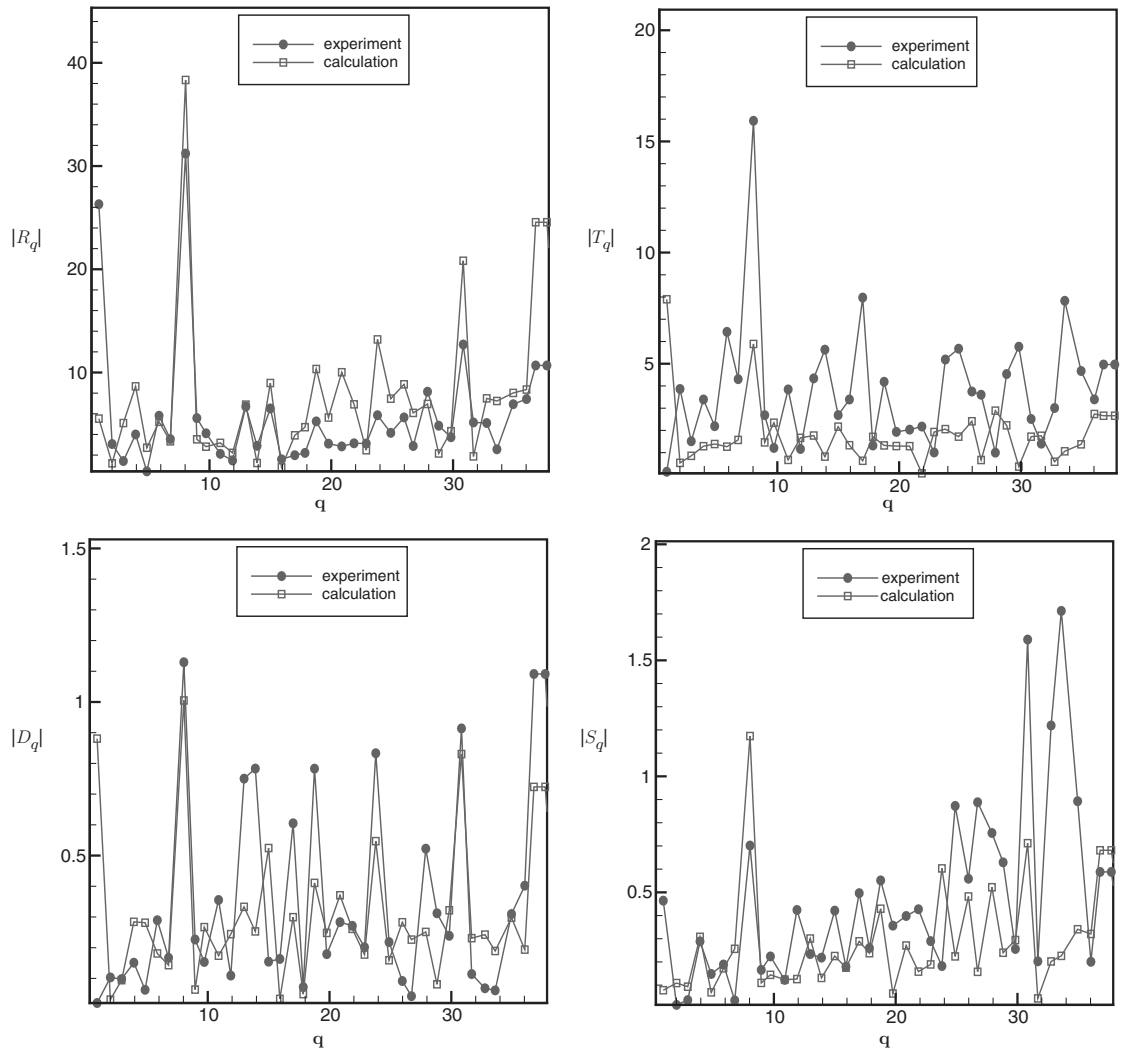

Figure 4. The Fourier transform of roll, tilt, shift and slide. The filled circles are corresponding to the calculation of Fourier transform of the experimental data taken from Reference (7), and the hollow squares are corresponding to the Fourier transforms of the calculated results using our simple elastic model. At $q = \frac{73}{10}+1 = 8.3$, corresponding to the helical repeat of DNA, the results show distinct peaks.

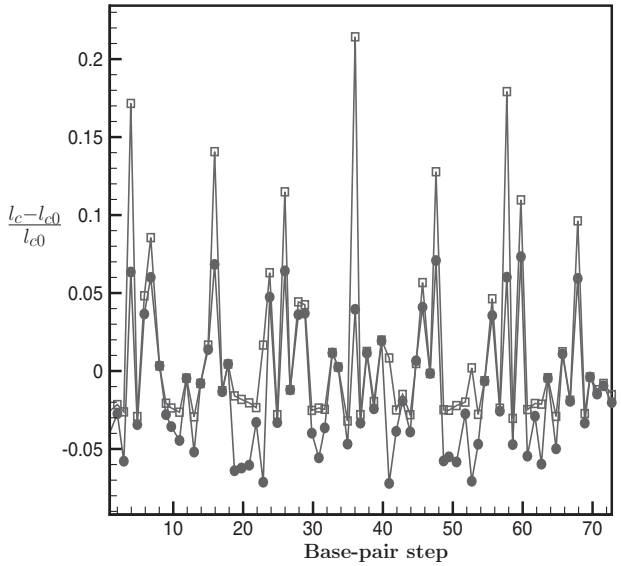

Figure 5. The relative changes in the length of the covalent bonds between the adjacent base pairs of the two strands of DNA, $\frac{x_{c1}}{l_{c0}}$ (filled circles) and $\frac{x_{c2}}{l_{c0}}$ (hollow squares).

that in the similar situations, the DNA twist changes very slightly (<2%) (15,16,19). It is worth to check the effect of the twist values on the other base pair parameters. For this purpose, we assume that the twist of the bent DNA is not changed from its natural twist. In Figure 6, we have plotted the calculated base pair parameters as functions of the base pair steps, considering a constant twist angle equal to that of the undeformed B-DNA ($\theta = \theta_0$ and $\psi_i = ib\omega_0$), together with the experimental data. As one can see, in this case, the calculated and experimental data are poorly correlated and the values of the base pair parameters at each base pair are mostly different from their experimental values. These results show that the histone-DNA local interactions have a crucial effect on the DNA twist.

The geometry of the nucleosomal DNA, and the rigidity of the covalent bonds in its structure, result in a significant coupling between its base pair parameters. Our sequence independent model, which uses experimental twist values as input, finds the values of roll and slide more significantly correlated with the experimental ones than the model of Reference (10), which uses nucleosomal DNA sequences as input. This can show the importance of the correlations between the base pair parameters, which come from the geometry and the elasticity of the DNA molecule. It also means that we can show the structure of the nucleosomal DNA with reduced number of the base pair parameters because of the strong coupling between them. Therefore, as we have shown here, instead of considering three independent base pair parameters, twist, roll and slide, we can only consider the twist of the base pairs, and obtain the other two parameters by taking into account the correlations that come from the geometry of the molecule.

As can be seen from Equation (7), in this model, we consider the elastic constants of DNA molecule as sum of two terms; the elastic constants introduced in the previous elastic rod models for DNA, and another term which is proportional to the covalent bond stiffness, k_c, and the square of the changes in the covalent bond lengths. Actually, the elastic energy of the molecule can change as a result of deformation even if the covalent bond lengths of the two springs do not vary. In fact, if we want to estimate the total changes in the elastic energy of the molecule by solely the covalent bond term, we should consider more than two springs. In our model, the elastic constants corresponding to the lateral displacements have only the covalent bond term, and so, they are obtained to be a function of the geometrical properties of DNA as well as the stiffness of the covalent bonds. These elastic constants are provided in the Appendix A. We also find that after considering the effects of the two springs up to the second-order terms of the base pair parameters, the elastic constants showing the coupling terms between R and D, R and T, T and ε, S and ε and D and ε are found to be zero, while other elastic constants have non-zero values. In fact, by using this simple model, we find all the 21 different elastic constants of DNA molecule as a function of the covalent bonds stiffness (see Appendix A for details). We can also reverse the procedure by using the previously estimated values for the elastic constants of the different 10 bp step of DNA molecule (23) to estimate the stiffness of the covalent bonds at individual base pair steps.

It is worth to discuss about the values of the elastic constants that we have used in the text. There is still no direct experimental measurements for the anisotropy bending rigidities and twist-bend coupling. Simulation results estimate the values of these elastic coefficients for each of the 10 different sequences of nucleotides, and suggest a range of values for them as $A_1 = 47$–79 nm, $A_2 = 25$–52 nm (23). In this article, for the bending rigidities, we use $A_1 = 75$ nm, $A_2 = 37$ nm (19) (note that we choose A_1 and A_2 so that the effective bending rigidity, $A = \frac{1}{2}(A_1^{-1}+A_2^{-1})^{-1}$, equals the bending persistence length of the molecule, measured to be 50 nm). For the twist-bend coupling, we use the suggested value $G = 25$ nm in Reference (8). The simulation works suggest that the twist-bend coupling is about $G = 6$–17 nm (23). We have also examined these values for the twist-bend coupling and found no significant effect. Recent direct determination of twist rigidity gives a value of $C = 100 \pm 7$ nm (20), and we use $C = 100$ nm.

Here, we simply estimate the interaction energy between DNA and histone as only a function of the accumulated angle because the experimental results show that the twist angle mostly changes, and has large positive values at all of the contact regions (2). Moreover, there are also large alternation of shift values at some contact regions, so, it is more accurate to consider the interaction energy as a function of the two less correlated base pair parameters, twist and shift rather than solely a function of twist.

Our approach can be used in the future elastic models for the nucleosome and other DNA–protein complexes, especially, to obtain the correlations between the base

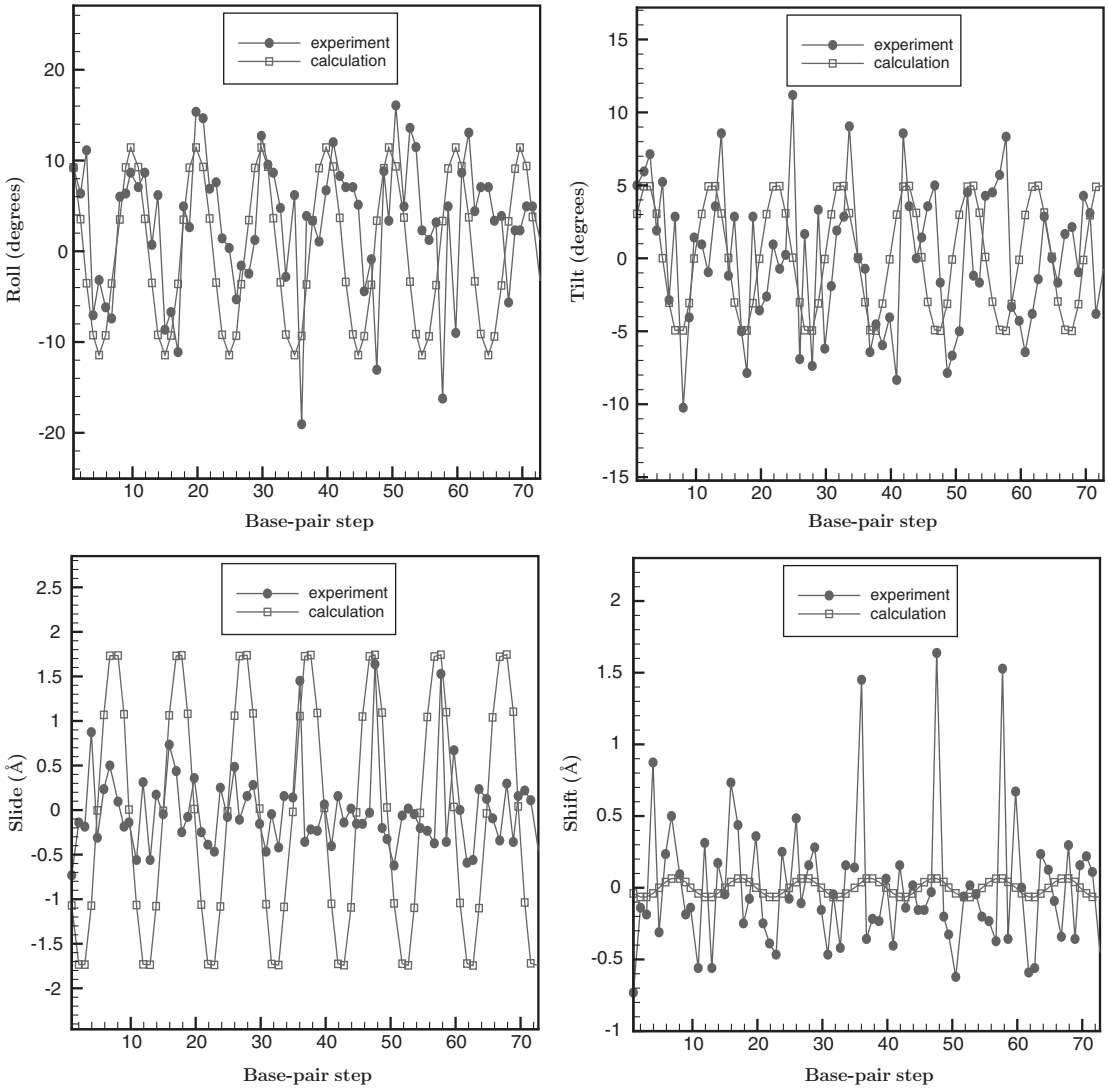

Figure 6. The calculated and the experimentally observed base pair parameters. The filled circles correspond to the experimental data taken from Reference (7), and the hollow squares show the calculated results using $A_1 = 75$ nm, $A_2 = 37$ nm $C = 100$ nm and $G = 25$ nm. In the calculation process, the twist angles are considered constant and equal to the twist of undeformed B-DNA. We can see that, in this case, the calculated and experimental data are poorly correlated and the values of the base pair parameters at each base pair are mostly different from their experimental values.

pair parameters. To show the more generality of our model, we have applied it to other sequence of DNA and studied the results: Ong *et al.* (24) have determined the crystal structure of a nucleosome core particle containing 145 bp of DNA (NCP145) and found its base pair parameters. The base pairs ± 3 of the 147 base pair nucleosomal DNA on eider side of the dyad axis are absent in the NCP145. The same as before, we directly read off the twist angles from the ones obtained by Ong *et al.* and find other base pair parameters using our simple model. The results are shown in Figure 7 together with the experimental data of Ong *et al.* (The same as before, the results are shown for half of the DNA length, in this case, corresponding to 72 bp and the average base pair parameters of the base pairs on either side of the dyad axis are shown.) We can see that there is an overall good agreement between the experimental and calculated results especially for the values of roll and slide. The peaks of the slide are also in good agreement with the experimental data and there is a large roll-slide-twist correlation. Thus, our simple model can successfully obtain the results of another DNA–protein structure and its predictive power is more general. Note that these important quantitative predictions come out naturally from the theory without having to choose a single fitting parameter. We finally note that the present model can also be applied to other protein–DNA complexes. As mentioned in the text, if the local potential of the interactions is known, one should consider this potential explicitly in the total energy E_{total} and minimize it with respect to the variables subject to the constraint and find the local conformation of the DNA.

In conclusion, by introducing a simple elastic model, we study the role of the rigidity of the sugar-phosphate backbones in the structure of the nucleosomal DNA. By this new approach, all the different correlations between the six base pair parameters are obtained as a function of the

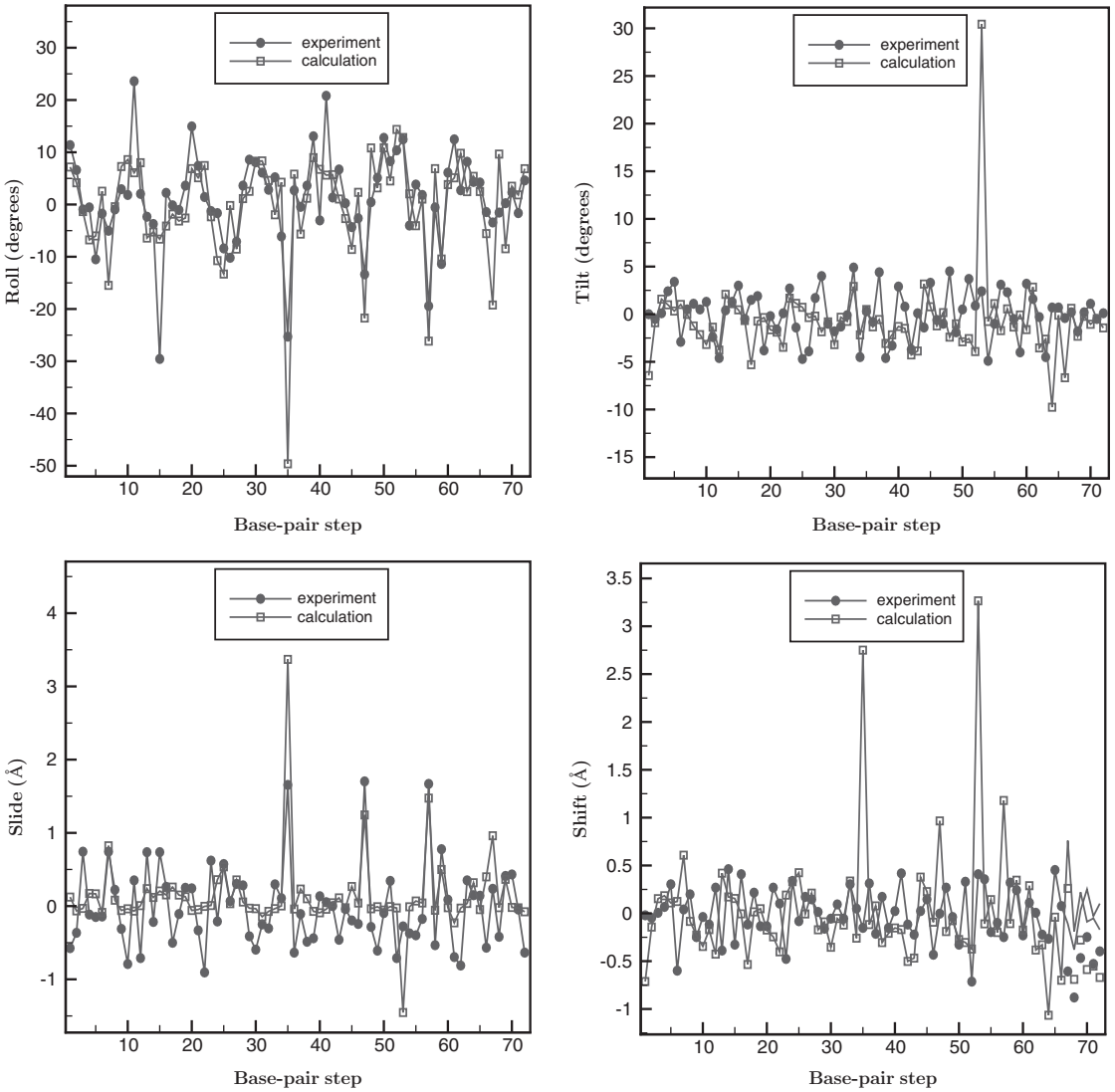

Figure 7. The calculated and the experimentally observed roll, tilt, shift and slide of the NCP145. The filled circles correspond to the experimental data taken from Reference (24), and the hollow squares show the calculated results using $A_1 = 75$ nm, $A_2 = 37$ nm, $C = 100$ nm and $G = 25$ nm. In the calculation process, the twist angles are directly read off from the experimental data of Ong *et al.* We can see a strong coupling between twist, roll and slide. The negative values of the roll and positive values of the slide are in good agreement with the experimental results. The correlation coefficients between the calculation and experiment for the roll, slide, tilt and shift are 0.702, 0.623, 0.165 and 0.104, respectively.

stiffness of the springs, which simply represent the covalent bonds between the adjacent base pairs. Our simple model succeeds to obtain some of the main detailed features of the nucleosomal DNA; in fact, we show that some of the important features of the DNA molecule can be obtained by just considering the changes in the covalent bond energies in the elastic model. The results, especially, for the roll and slide, are in encouraging quantitative agreement with the experimental results, and show obviously the two significant base pair parameter correlations, roll-slide-twist as well as tilt-shift.

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APPENDIX A: ELASTIC CONSTANTS OF DNA AS A FUNCTION OF THE COVALENT BONDS STIFFNESS

Here, we obtain the elastic constants of DNA molecule corresponding to different couplings of R, T, ε, S and D, as explicit functions of the geometrical properties as well as the stiffness of the covalent bonds. First, we find the total energy counts the deformation energy of the covalent bonds, E_c, given by Equation (6), as an explicit function of the base pair parameters considering terms up to the second order of R, T, ε, S and D. The length of each spring is equal to:

$$\begin{aligned} l_c(j) &= \left[\Delta x(j)^2+\Delta y(j)^2+\Delta z(j)^2\right]^{\frac{1}{2}} \\ &\simeq l_0+\frac{1}{2l_0}[l_1(j)+l_2(j)]-\frac{l_1(j)^2}{8l_0^3}, \end{aligned} \tag{A.1}$$

where $j = 1,2$ shows the label of the springs, $l_1(j)$ and $l_2(j)$ are the first and second order terms of R, T, ε, S and D, respectively and l_0 is the term that is independent of these base pair parameters and from Equations (4 and 5), we have:

$$\begin{aligned} l_0 &= \sqrt{2l^2(1-\cos\theta)+b^2} \\ l_1(1) &= 2lD(1-\cos\theta)+2blT-2lS\sin\theta+2b^2\varepsilon \\ l_1(2) &= -2lD(1-\cos\theta)-2blT+2lS\sin\theta+2b^2\varepsilon \\ l_2(1) &= S^2+D^2-2SD\sin\theta+l^2T^2\cos\theta+b^2\varepsilon^2 \\ &\quad +2bSR+2bDT+2bl\varepsilon T \\ l_2(2) &= S^2+D^2-2SD\sin\theta+l^2T^2\cos\theta+b^2\varepsilon^2 \\ &\quad +2bSR+2bDT-2bl\varepsilon T. \end{aligned} \tag{A.2}$$

Note that for simplicity, we do not write the label of each base-pair in the equations. The square of the changes in the arc length of the backbone between the two adjacent base pair of each strand, $x(j)$, up to the second-order terms of the strains is equal to:

$$\begin{aligned} x(j)^2 &= [l_c(j)-l_{c0}]^2 \simeq (l_0-l_{c0})^2 \\ &\quad +\frac{l_{c0}}{4l_0^3}l_1(j)^2+(1-\frac{l_{c0}}{l_0})[l1(j)+l2(j)]. \end{aligned} \tag{A.3}$$

Considering the above equation and Equations (6 and A.2), we have E_c as an explicit functions of the base pair parameters up to the second-order terms of R, T, ε, S and D, as:

$$\begin{aligned} E_c \simeq k_c \sum_{i=1}^{N} \Bigg\{ & (l_0-l_{c0})^2+\frac{l_{c0}}{l_0^3}l^2\Bigg[b^2T^2+\frac{b^4}{l^2}\varepsilon^2+\sin^2\theta S^2 \\ & +(1-\cos\theta)^2D^2+2b(1-\cos\theta)DT-2\sin\theta(1-\cos\theta)SD \\ & -2b\sin\theta TS]+(1-\frac{l_{c0}}{l_0})\big(l^2\cos\theta T^2+b^2\varepsilon^2+S^2+D^2 \\ & -2\sin\theta SD+2bSR+2bDT+2b^2\varepsilon\big)\Bigg\}. \end{aligned} \tag{A.4}$$

Now, if $A_{\alpha\beta}$ shows the elastic constant corresponding to the coefficient of $\alpha \times \beta$ in the elastic energy, where

$\alpha,\beta\in\{R,T,\varepsilon,\sigma,S,D\}$, from Equations (7), we can consider these elastic constants as summation of rotational and covalent bond terms as:

$$A_{\alpha\beta} = A^{rot}_{\alpha\beta}+A^{c}_{\alpha\beta}. \quad \textbf{(A.5)}$$

From Equations (8), it is obvious that the values of $A^{rot}_{\alpha\beta}$ are given by A_1,A_2,C and G that are the elastic constants introduced in the previous elastic rod models for DNA. Note that the elastic constants corresponding to the lateral displacements have only the covalent bond term. The non-zero values of $A^{c}_{\alpha\beta}$ for different couplings of R,T,ε,S and D can be obtained easily from Equations (A.4) and are given by these functions:

$$\begin{aligned}
A^{c}_{TT} &= k_c\left[\frac{l_{c0}}{l_0^3}l^2b^2+\left(1-\frac{l_{c0}}{l_0}\right)l^2\cos\theta\right]\\
A^{c}_{\varepsilon\varepsilon} &= k_c\left[\frac{l_{c0}}{l_0^3}b^4+\left(1-\frac{l_{c0}}{l_0}\right)b^2\right]\\
A^{c}_{SS} &= k_c\left[\frac{l_{c0}}{l_0^3}l^2\sin^2\theta+\left(1-\frac{l_{c0}}{l_0}\right)\right]\\
A^{c}_{DD} &= k_c\left[\frac{l_{c0}}{l_0^3}l^2(1-\cos\theta)^2+\left(1-\frac{l_{c0}}{l_0}\right)\right]\\
A^{c}_{SR} &= 2k_c\left(1-\frac{l_{c0}}{l_0}\right)b\\
A^{c}_{TS} &= -2k_c\frac{l_{c0}}{l_0^3}l^2b\sin\theta\\
A^{c}_{DT} &= 2k_c\left[\frac{l_{c0}}{l_0^3}l^2b(1-\cos\theta)+\left(1-\frac{l_{c0}}{l_0}\right)b\right]\\
A^{c}_{SD} &= -2k_c\left[\frac{l_{c0}}{l_0^3}l^2\sin\theta(1-\cos\theta)+\left(1-\frac{l_{c0}}{l_0}\right)\sin\theta\right].
\end{aligned} \quad \textbf{(A.6)}$$

Note that as we read off the twist angles directly from the experiment, up to now, we do not treat the twist as a variable and so do not expand the covalent energy with respect to σ. Thus, our elastic constants are functions of σ and the elastic constants showing the coupling of the twist to other base pair parameters are not obtained, but in general, we can easily expand Equation (A.4) with respect to σ and find all of the elastic constants independent of the changes in the twist.