A Computational Model to Determine the Effect of Interconnecting Hydrogen Bonds in DNA Deformation

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Abstract
FEM model of the double helical structure of the DNA together with the interconnecting hydrogen bonds is developed in this work. The results of the FEM model is compared with the simplistic equivalent rod model. Simulations for deformations under axial, torsional, radial and bending loading are performed. The action of enzymes on DNA can be assumed to be in the form of combination of these loadings. Normalized results of axial, torsional, radial and bending stiffness are computed. The effect of hydrogen bond stiffness on these quantities is analysed. From the results obtained it is inferred that though the hydrogen bond stiffness value has no effect on the axial and torsional stiffness, the radial and the bending stiffness are affected by the hydrogen bonds. Beyond a critical value of the bond stiffness it is observed that the bending and radial stiffness undergo a rapid change and stabilize to a higher value. The results obtained from the present work thus identify the parameter regimes of applicability of the equivalent rod model.

1. INTRODUCTION

Deoxyribonucleic acid (DNA) is a macromolecule which stores the genetic information necessary for the development and functioning of living organisms. DNA is present in every cell of a living organism. The DNA molecule lies highly coiled (or supercoiled) within the chromosome contained mostly in the nucleus of the cell. During cell division process, the genetic code contained within the DNA is replicated. The traits of the offspring is determined by the genetic code received from its parent cells. Due to its central role in determining characteristics of living organisms, it has been an area of active research since its discovery [1].

The DNA structure comprises of double hellical strand made of sugar and phosphate groups. The individual strands are bonded together by four types of nucleobases - namely Adenine (A), Guanine (G), Cytosine (C) and Thymine (T). The sequencing of these bases determine the genetic code of an organism. Further, there is selective pairing between these bases; A bonds with T while C attaches to G. Due to this selectivity, during cell division the DNA sequence is preserved. DNA takes part in biological processes like protein synthesis and cell division through transcription and replication. A complimentary copy of Ribooxynucleic acid (RNA) is made in the transcription process, while in the replication process an identical copy of the DNA is made. In both these processes, the supercoiled DNA uncoils at the initiation of the process and then again coils back on completion of the process. Thus, due to its pivotal role in crucial biological processes, the study of DNA supercoiling has received great attention in the research community.

Numerous factors determine the mechanics of DNA supercoiling, namely :- the molecular structure, sequence of nucleobases, the strength of the hydrogen bonds, electronic interactions holding the helices, etc. But the measurement of such properties of the molecule is diffcult. Charvin *et al*. [2] have presented a review of different experimental techniques available for measuring the stretch and twist of DNA molecules. Their work detailed the process of estimating torsional modulus of DNA structures.

The measurement procedure of Young's modulus in the radial direction is described in the work of Yi *et al*. [3]. Strick *et al*. [4] discussed experimental results obtained using magnetic field gradient to measure and control the applied force on DNA. Both stretching and torsional experiments were performed in this manner. The authors were able to quantitatively monitor and control the supercoiling of the DNA on application these forces. The review by Bustamante *et al*. [5] presented different experimental methods to measure the elastic properties of DNA at the single molecule level. They present the force versus extension data obtained through experiments. Experimental techniques which can directly measure the mechanical properties of DNA are relatively new and high-resolution visualization is often difficult. Hence, modeling of the molecule is done to understand its mechanics. Further parametric study to understand the effect of the diffferent variables affecting the deformation phenomenon can be effectively carried out with the help of an accurate model. There has been a lot of effort among the researchers to arrive at a mechanical deformation model of the DNA molecule which explains the process of supercoiling and uncoiling.

Bruant *et al*. [6] have pointed out the challenges that lie in obtaining the experimental data relating to DNA deformation. They advocate the use of appropriate modeling and simulation technique. The work has described the applicability of accurate but time consuming molecular dynamics modeling as well as simplistic mesoscopic models for DNA. Their work effectively bridges the two diverse modeling techniques . The authors argue that some useful understanding can be brought through simple continuum level models especially for long chain DNA. Lankas *et al*. [7] presented results of elastic constants of different DNA strands determined through molecular dynamics simulation. One of the simplest continuum level model is the equivalent rod model, wherein the double hellical DNA structure is approximated as a rod of uniform circular cross-section. The model has been used by different researchers in variety of applications. Balaeff *et al*. [8] have used the model to study the shape of the DNA when acted upon by a specific enzyme. Their work justifies the applicability of the inextensible rod model for DNAs. As the authors argue, the efffect of short molecular interaction forces can be adequately captured through such continuum based models. Numerical solutions are obtained based on the principle of equilibrium of applied forces and torques and principle of minimization of the elastic energy. For calculating deformation characteristics of long chain DNA, Hunt *et al*. [9] have used the elastic rod model without consideration of end effects. The bending energy per unit length of the structure was calculated and then the deformation state was found which minimized the elastic potential energy associated with bending. Stump *et al*. [10] applied the elastic rod model to predict the shape of the supercoiled DNA structure. The sugar-phosphate hellical strand is modeled as an inextensible rod. Gross properties of the supercoiled molecule (e.g. number of crossovers, ratio of end loop length to base length) were computed through this model and compared with the available experimental data. Hoffman [11] translated the DNA supercoiling problem into that of finding the stable equilibrium solution of the equivalent rod. This equivalent rod is assumed to be inextensible and unshearable. The stable equilibrium deformation state of the structure is known to minimize the elastic energy functional. Thus, the author performed a variational formulation for the problem. Additionally, there are integral constraints imposed which prohibited the direct use of known classical solution methods. A novel solution method (distinguished-diagram method) was formulated for tracking the solutions. An analytical study of the geometry and energetics of the DNA deformation process is presented by Ricca and Maggioni [12]. The derived equations prescribe the deformation state by assuming the DNA to be in the form of a circular inextensible filament. Based on the energy requirement calculations of the coiled state, the authors ascertained the favourability of coiling of the DNA structure as a means for relaxation of elastic energy. Wadati and Tsuru [13] studied the deformation pattern of DNA using the energy calculations of the equivalent rod model. The authors effectively used formulation based on topology and differential geometry in their analysis. The change in configuration from a circular DNA ring to a figure of 8 shaped pattern is desrcribed in details in their work. Tobias *et al*. [14] determined the stability of equilibrium configuration of DNA segment by minimizing the sum of the stored elastic energy and work potential of the applied forces. The stability criteria they formulated is demonstrated to be valid for both closed and open chain DNAs with strong anchoring boundary condition. Through

an example calculation performed on a DNA miniplasmid, the authors demonstrated the effect of geometrical and material parameters on the stable equilibrium configuration. The derived stability criteria was applied to DNA miniplasmids with self contact forces [15]. Herein, bifurcation studies are accomplished for all possible deformation states of the structure. Symmetry pattern of the possible solution states were also discussed in great details. A review of different analytical and numerical modeling work pertaining to DNA supercoiling is presented by Schlick [16]. Here, the author observed the diffculty in producing analogous experimental data. In particular, the review details the work done on buckling aspects of the equivalent rod model. Munteanu *et al*. [17] presented a review of different rod models (isotropic and anisotropic) of DNA. The authors compared the ability of these models in predicting local bending characteristics of DNA structures.

As highlighted by Olson and Zhurkin [18], ideal elastic rod models ignore the effect of sequence dependence of the DNA structure as also other anisotropic effects. They point out biological processes wherein such local anisotropic effects are crucial. Gromiha *et al*. [19] pointed out that sequence dependent bending cannot be captured by isotropic equivalent rod model. In their work, the authors have used a Finite Element Model through a commercially available package to calculate this anisotropic bending behaviour. The model itself is developed by considering the DNA structure to be an assemblage of short uniform rods. The properties of each of these short uniform rods is estimated based upon the sequence of nucleobases along the DNA strand. Though for each short uniform rod the governing equations are no more complicated than that obtained by the equivalent rod model, the governing equations of the assemblage turns analytically untractable and hence FEM is employed. The reported results was found to be encouraging as it compared well with other experimental data. The finite element method was used in calculations of large deformations in DNA by Bauer *et al*. [20]. The DNA structure itself is assumed to be in the form of an equivalent elastic rod. Finite element method has been employed in simulating the deformation characteristics of the equivalent rod. The results reinforce the observation that DNA structure do attain their minimum energy state. Parametric studies with differ-ential geometric parameters of the DNA hellix (e.g. linking number, writhe number, twist, etc.) are carried on. Four different relaxed DNA states are simulated - straight DNA, two straight segments of DNA having a bend of 20°, three straight segments of DNA each having a bend of 20° and circular ring shaped DNA.

As brought out through the above discussion, there has been voluminuous work done on the mechanical modeling of DNA deformation. Among them, the equivalent isotropic continuous rod model has been well received in the research community. As pointed out in the literature, though this simplistic continuum description does explain certain observed characteristics of the DNA, it fails to capture some other effects such as anisotropic bending, sequence dependence deformation characteristics, etc. This drawback stems from the incomplete geometric modeling of the DNA structure. To mitigate this drawback, we use Finite Element Method (FEM) of modeling the DNA structure in the present work. Through FEM, the exact geometry of the double stranded linear DNA macromolecule is captured. Though there has been some earlier work on FEM modeling of DNA structures, these models have not modeled the double hellical structure of the DNA together with the connecting nucleobases. They have attempted to capture anisotropic effects by considering the DNA structure to be an assemblage of short uniform rods with varying properties along the axis. In this sense, the current work captures the exact geometry and the interatomic bonds of the double stranded DNA. The objective of the present study is to simulate the deformation of DNAs under some standard loading conditions - namely bending load, axial load, torsional load, pressure load. It is assumed that the enzyme action on DNA is a combination of these loads.

Another issue associated with modeling techniques is that the model input data is taken from different experiments scattered in the literature. The reliability of this data is not very high. In particular, the hydrogen bond stiffness values associated with the nulceobases which effectively holds the two strands have not been known to a high level of confidence. Using FEM simulation, we perform a parametric study for different values of the hydrogen bond stiffness under four different types of loading, namely - axial, bending, torsional and radial. These results are then compared with that

obtained for the simplistic model wherein the interconnecting hydrogen bonds are ignored. The aim of this parametric study is to infer the parameter regimes under which simplistic model is accurate and conversely conditions under which it is innaccurate.

2. FINITE ELEMENT MODEL DEVELOPMENT

Finite Element Method is a popular numerical technique for simulating the deformation of complicated mechanical, civil and aerospace structures. It is based on the principle that the stable equilibrium configuration is that which minimizes the elastic potential energy. The method approximates the deformation using compactly bounded local approximating polynomial field. The coeffcients associated with these interpolating functions are found by minimization of the elastic potential energy of the structure. For the purpose of implementation, the analyst needs to divide the complicated geometry into smaller, simpler blocks called elements. Equilibrium equations are formulated first at the element level and then assembled to give the equations at the global level. The solution of these equations determine the solution at discrete points known as nodes. For a more detailed introduction to this subject, the reader is referred to classical textbooks on the subject [21, 22].

In the present work, we formulate the geometry of the two hellices with its axis along the z-direction as

$$r_1(\theta) = a\cos(\theta)\hat{i} + a\sin(\theta)\hat{j} + b\theta\hat{k} \text{ and } r_2(\theta) = -a\cos(\theta)\hat{i} - a\sin(\theta)\hat{j} + b\theta\hat{k}, \quad (1)$$

where θ is the parameter for the curve, a is the radius of the helix and $2\pi b$ is the pitch of the helix. $\hat{i}, \hat{j}, \hat{k}$ represents unit vector along the x, y, z direction, respectively. Using the geometry equation described as above, discrete node points are generated. Each node points are connected with elements. The chosen element has six degrees of freedom corresponding to translations and rotations about the three axis. These are schematically illustrated in Figure 1. Accordingly, the element can capture the effects of axial force, transverse force, bending moment and twisting moment. This element can be thus considered to be a synthesis of the traditional bar, beam and rod elements. The element-wise local stiffness matrix is transformed to global coordinates using transformation matrices as described in [22]. The analysis is limited to small deformations. Large deformation of the structure entails nonlinearity in the governing equations [23] which are not accounted for in the present work. However, as pointed out in [7] this assumption is not restrictive.

The steps of computation described above was done by developing an indigenous code. For validation of the developed code, the model was used to calculate the spring stiffness of a helical spring. The answer obtained was compared with known analytical solutions [24] and was found to be in

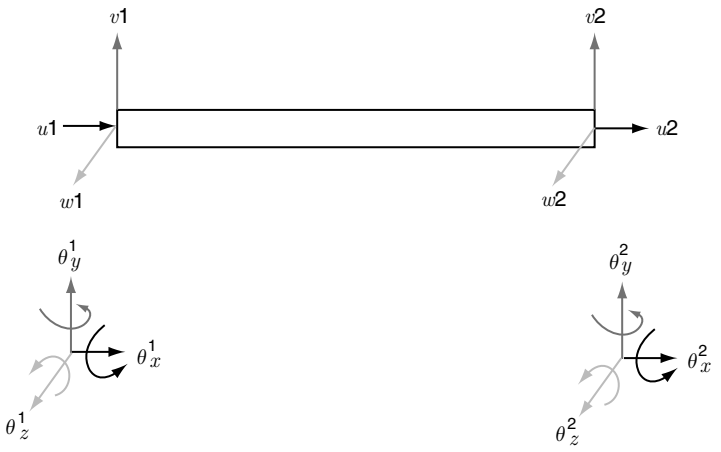

Figure 1. Schematic illustration of the degrees of freedom chosen in the element.

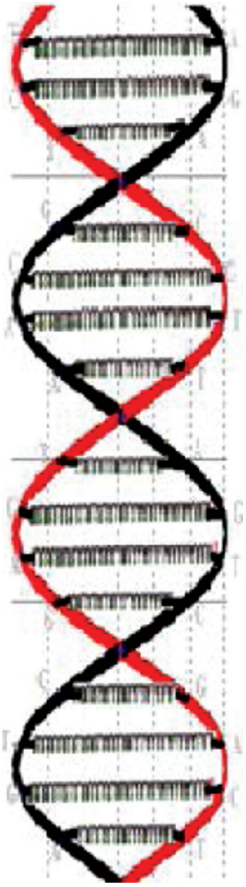

Figure 2. Finite element model of the DNA with lumped springs used to model the interconnecting hydrogen bonds.

agreement for small helix angles. The analytical solution itself had the limitation of being applicable only for small helix angles. Next, a simulation was performed to find the axial stiffness of the double helical spring. Again the computed results were found to be matching with known analytical solution of determining stiffness of springs in parallel.

Finally, the hydrogen bonds are modeled as lumped springs connecting the two strands. The changes in the stiffness matrix of the the DNA structure due to this effect can be easily incorporated. A schematic representation of the Finite Element Model for DNA thus developed is shown in Figure 2.

3. RESULTS AND DISCUSSION

As described earlier, the value of hydrogen bond stiffness is not known accurately through the literature. In the present work, we undertake a parametric study by varying this parameter through 8 orders of magnitude (10^{-2} to 10^{6} N/m). One end of the DNA is assumed fixed and on the other end four different kind of loading conditions are applied. The loading conditions are namely (i) axial loading with an axial force at the tip (ii) torsional loading with a twisting moment applied at the tip (iii) radial load along the circumference of the tip (iv) bending load in the form a transverse load acting at the tip. These loadings are schematically shown in Figure 3. More complicated loading conditions can be generated as a combination of these loads.

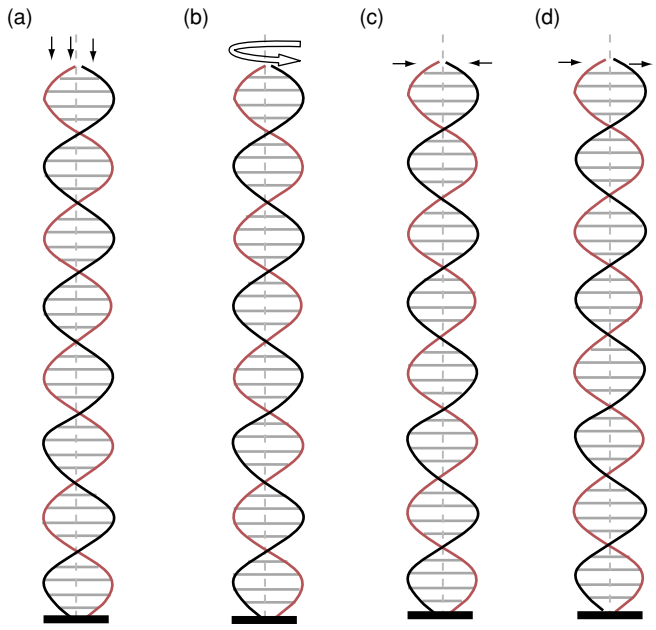

Figure 3. Schematic illustration for various loading conditions on the finite element model (a) Axial loading (b) Torsional loading (c) Radial loading (d) Bending loading.

3.1. Axial loading

The tip deflection of the model described above is calculated due to a unit axial load. The reciprocal of the tip deflection is the axial stiffness of the DNA molecule calculated by including the effect of hydrogen bonds. A repeat calculation of the axial stiffness is done using the same procedure but by ignoring the hydrogen bonds. This is easily implemented in the computational program by changing the stiffness of the lumped springs (making up the hydrogen bonds) to zero. The results are presented in a normalized manner in Figure 4. The axial stiffness of the actual DNA structure containing the hydrogen bonds is normalized with respect to the axial stiffness of the DNA structure ignoring the hydrogen bonds. The x-axis of the plot shows the variation in the chosen value of hydrogen bond stiffness. This is again non-dimensionalized with respect to the axial stiffness of the structure ignoring the interconnecting lumped springs. As observed from the plot, the presence or absence of the hydrogen bond does not substantially alter the results of axial stiffness. Thus, based on this result we might conclude there is no effect of hydrogen bonds on the axial stiffness of the DNA structure.

3.2. Torsional loading

The DNA structure is subjected to a unit twisting moment applied at the tip. The rotation of the end cross-section is calculated. The reciprocal of the computed rotation is the torsional stiffness. The computation is repeated by ignoring the presence of hydrogen bonds. Figure 5 shows the normalized results as a function of the hydrogen bond stiffness. The x-axis of the figure is the normalized hydrogen bond stiffness. The normalization procedure is identical to that described in the previous case of axial loading. The results in figure 5 shows that there is no effect on the torsional stiffness of the molecule due to the presence of the hydrogen bonds.

3.3. Radial loading

Radial load of unit magnitude is apportioned between all the nodes in the tip cross-section. The computed radial deflection is inverted to obtain the radial stiffness. The computation is repeated by

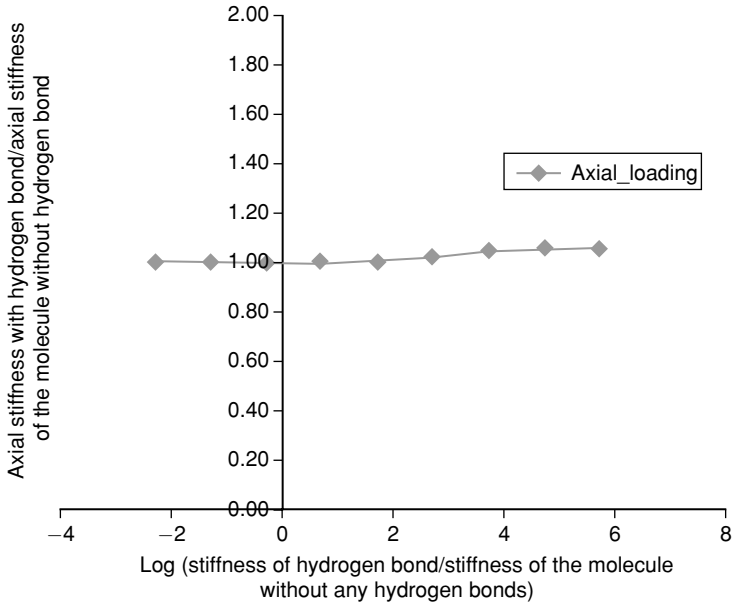

Figure 4. Variation of the axial stiffness with the stiffness of the hydrogen bond.

ignoring the presence of hydrogen bonds. Figure 6 presents of plot of the normalized results. The y-axis of the plot represents the ratio of the radial stiffness computed with and without the hydrogen bonds, whereas the x-axis is identical to that in figures 4 and 5. In this case, we observe from the results that beyond a critical value of the bond stiffness, the radial stiffness of the DNA structure does get affected with the value chosen for the compliance of the hydrogen bonds.

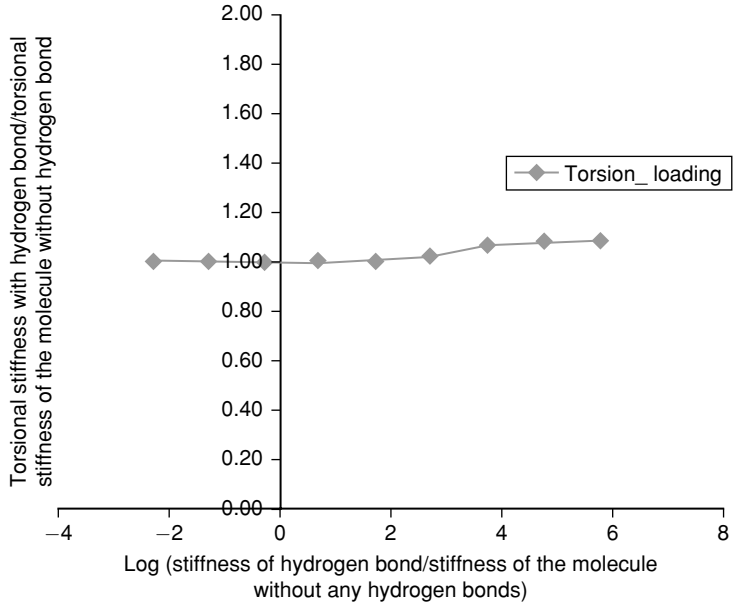

Figure 5. Variation of the torsional stiffness with the stiffness of the hydrogen bond.

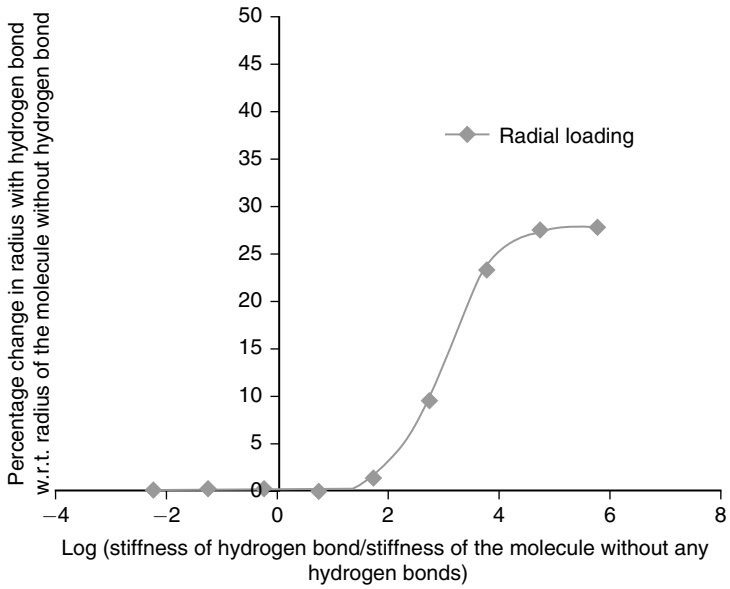

Figure 6. Variation of the radial stiffness with the stiffness of the hydrogen bond.

3.4.Bending loading

The DNA structure is subjected to a unit transverse bending load at the tip. The reciprocal of the computed tip deflection is the bending stiffness. As in the earlier cases, the calculation is repeated by ignoring the hydrogen bonds. Figure 7 shows the normalized result of the ratio of bending stiffness with and without the consideration of hydrogen bonds. The x-axis of the figure as in the earlier cases is the ratio of the hydrogen bond stiffness to the axial stiffness of the molecule obtained by neglecting the hydrogen bonds. The results obtained show that the bending stiffness does change drastically at a critical value of the hydrogen bond stiffness value.

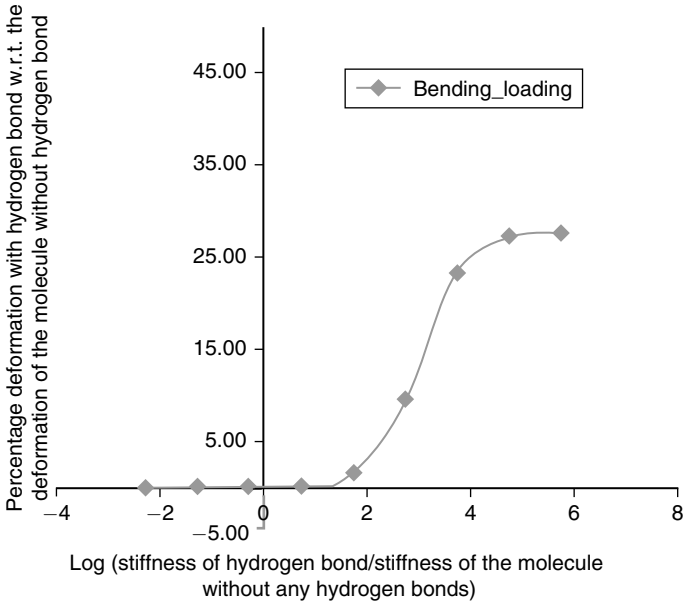

Figure 7. Variation of the bending stiffness with the stiffness of the hydrogen bond.

From the results arising out of the different cases of loading reported above, we infer that the axial and torsional mechanics of DNA structure is not affected by the hydrogen bonds. However, bending and radial mechanics is grossly changed beyond a critical value of the hydrogen bond stiffness. Further the results in Figure 6 and 7, suggest a two-layered asymptotic behaviour of the axial and radial stiffness. Below the critical value of hydrogen bond stiffness, results of the axial and radial stiffness are virtually unaffected. For values of hydrogen bond stiffness much greater than this critical value, the stiffnesses again is observed to be constant. In the intermediate values of bond stiffness, there is a transition region connecting the low stiffness values with the higher stiffness values. These results clearly suggest the inadequacy of the equivalent isotropic rod model to capture the overall mechanics of the DNA structure. Though certain aspects of the deformation mechanics can be captured using the equivalent rod model, a wholistic understanding of the mechanics may not be possible.

The inference arising out of the above numerical simulation is further reinforced by consideration of principle of minimum potential energy. This well-known principle in mechanics states that the equilibrium state of a deformable body is that which minimizes the stored elastic potential energy and the work potential of the applied forces [22]. Accordingly, for the interconnecting lumped springs to have a role in the deformation process of the DNA, there should be a stretch or compression of the springs. Due to axial loading applied to the DNA structure, the particles move mainly in the axial direction. There is a minor change in the coil radius brought about due to the Poisson effect. As the coil radius remains unchanged, the interconnecting springs are in a relaxed state throughout the deformation process for any value of the applied loading (within the linear regime). Thus, it is expected that the deformation due to axial loading is unaffected by the presence of the hydrogen bonds. Similar analogy also holds for the torsional loading in which case the cross-sections of the structure undergo relative rotation. These rotations do no affect the length of the interconnecting springs. As such, the springs have no contribution to the total elastic potential energy of the structure. The situation is changed for radial loading which tends to create a radial deformation in the coil. The radial deformation causes a change in length in the interconnecting springs and as a result a difference in the potential energy of the DNA structure. In case the springs are compliant, the additional energy stored in the springs is a small fraction of the total elastic potential energy of the structure. However, for stiffer springs the elastic potential energy in the springs have a major contribution to the total stored energy of the structure. Therefore, the torsional mechanics is affected by the interconnecting springs. Similarly, the lumped springs act as stiffeners to the DNA structures in case of bending deformation. The effective moment of inertia of the bending cross-section increases as the stiffness of the interconnecting springs increases. It is know that the moment of inertia of the cross-section is directly proportional to the bending stiffness [24]. Hence, it is expected that the interconnecting spring stiffness will be an important factor for the bending type deformation. Thus, the results obtained from the FEM simulation are in corroboration with the fundamental principles of mechanics.

4. CONCLUSION

Equivalent rod model of DNA structures has received wide patronage in the research community in describing different facets of DNA mechanics. The principal source of limitation of the equivalent rod model arises due to the approximation of the double hellical structure into a uniform circular rod. Also, the effect of interconnecting hydrogen bonds is neglected. In this work, a finite element model is developed for the DNA structure. The present model captures the exact double hellical geometry as well as the interconnecting hydrogen bonds of the DNA. However, the stiffness value of the interconnecting hydrogen bonds is not known accurately from the available literature. A parametric study is thus undertaken for a range of values (8 orders of magnitude) of the hydrogen bond stiffness. Computations are done to find the stiffness due to axial, torsional, radial and bending load conditions. The results indicate that for axial and torsional loading the presence of the hydrogen bonds have no effect. Thus, under these loading conditions the equivalent rod model is inferred to be accurate. However, for radial and bending loads the hydrogen bonds is observed to have a pronounced effect. Beyond a critical value of the hydrogen bond stiffness parameter, the radial and bending stiffness rapidly increases and saturates to a high value. These findings are also justified qualitatively based on

the principle of minimum potential energy. Therefore, we conclude from this study that for accurate modeling of the general deformation characteristics of the DNA structure, the FEM based model is more accurate than the equivalent rod model.

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