Investigation of dsDNA Molecule Mechanical Behavior using Atomistic Continuum Mechanics Method

Cheng-Nan Han *, Chan-Yen Chou*, Chung-Jung Wu* and Kou-Ning Chiang**

*Research Assistant, Advanced Microsystem Packaging and Nano-Mechanics Research Lab, Dept. of Power Mechanical Engineering, National Tsing Hua University,
101, Sec. 2, Kuang-Fu Rd., HsinChu Taiwan 300
**Professor, Advanced Microsystem Packaging and Nano-Mechanics Research Lab, Dept. of Power Mechanical Engineering, National Tsing Hua University,
101, Sec. 2, Kuang-Fu Rd., HsinChu Taiwan 300, knchiang@pme.nthu.edu.tw

ABSTRACT

A novel atomistic-continuum method (ACM) based on the transient finite element theory is proposed herein to simulate the dynamic structural transitions of the double strand DNA (dsDNA) under external loading. Moreover, the meso-mechanics of dsDNA molecules is then studied via the ACM model, including the base-stacking interaction between DNA adjacent nucleotide base pairs, the hydrogen bond of complementary base-pairs and electrostatic interactions along DNA backbones. In this research, an atomistic-continuum mechanics model of dsDNA based on equivalent-spring method would be first conducted and the simulation result would be further validated by the experimental result. A spring element is chosen to represent the covalent bond between neighbor atoms of backbone in dsDNA. To describe the material properties of the spring in dsDNA structure, the Cornell's second generation force field potential energy and Universal force field are utilized to simulate the bond stretching and bond angle energy terms. The method proposed here would be used to study the mechanical behavior in DNA packaging and release form viral capsids in the future.

Keywords: Atomistic-Continuum mechanics method (ACM), DNA, Finite element method, Morse functions.

1 INTRODUCTION

The single molecule manipulation technique has been developed for years to measure the basic physical properties of double-stranded DNA (dsDNA) and to discover the interaction between dsDNA and proteins/enzymes [1]. Moreover, the results of the freely-untwisting dsDNA stretching experiment have indicated that a sharp structural transition occurs under roughly 60pN of tension, and that the classical B-form DNA structure dramatically transits to a S-form DNA structure [2]. However, the resolution of the single molecule measurement technique currently available restricts the researchers to completely clarify the mechanical behavior of stretching dsDNA as well as the continuous geometrical deformation of the sugar-phosphate chain during stretching. To overcome the resolution limitation of the single molecule manipulation technique, the molecular biology researcher essentially requires an accurate theoretical model to represent the dsDNA mechanical characteristics under specific external loading and boundary condition. However, a feasible numerical model to describe the dsDNA mechanics is difficult to achieve, because the meso-mechanics of single-molecule dsDNA include both quantum mechanics and continuum mechanics. Benham [3] have derived the analytical wormlike rod chain model (WLRC model), and Marko et al. [4] have improved the accuracy of Benham's WLRC model. These WLRC models could predict the DNA mechanical response under low level stretching. However, the WLRC model could not accurately describe the P-form and S-form DNA under high level stretching force and twisting torque. Zhou et al. [5] have proposed the unique Zhou, Zhang and Ou-Yang model (ZZO model), which considers the bending energy and the base pairs staking energy of dsDNA. The ZZO model could successfully describe the S-type DNA under high level stretching, but it could hardly represent the structural transition from the B-form DNA to the P-form DNA due to its limitation of geometric assumption. Additionally, these theoretical models mentioned above could not provide the dynamic dsDNA structural transition in virtuality. Therefore, a novel clustered atomistic-continuum method based on the transient finite element method with material/geometrical nonlinear properties is applied to illustrate the mechanical behavior of dsDNA under external loading.

To represent the mechanical response of the dsDNA under the external loading, such as axial stretching [2], Yuan have modeled the ssDNA and dsDNA molecules under axial and unzipping loading (as shown in Fig 1). Because the conventional molecule dynamic (MD) simulation technique would induce the small time increment step, which largely increases the total simulation time. To solve the above issue, the clustered atomistic-continuum mechanical (CACM) method [2] based on the finite element method was applied to reduce the computational time. Furthermore, to reduce the computational time efficiently, the clustered atomistic-continuum mechanical (CACM) method treats the specific clustered atom groups as the clustered elements in the modeling; hence some material properties in the clustered

elements should be assumed to coincide with the experimental data in advance.

In this research, the atomistic–continuum mechanical (ACM) method based on the finite element method is adopted to numerically simulate the mechanical response of the dsDNA molecule. Notably, the bond stretching energy between atoms on the backbone could be described by the Universal Force Field [6] and the bond angle energy could be described by the Cornell's second generation force field potential energy [7]. Furthermore, the numerical dsDNA stretching model would be applied to study the DNA conformational change which is driven by the binding of proteins/enzyme to double helix, such as Rec A, Rec BCD protein or nucleosome core particle(NCP).
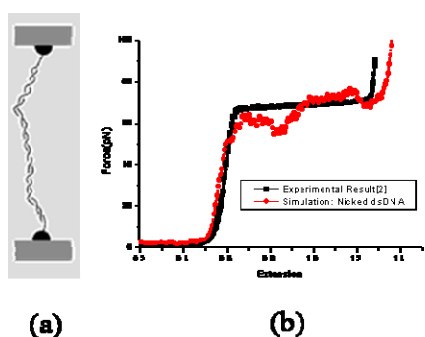

(a)   **(b)**

Figure 1. The dsDNA clustered atomistic-continuum model (CACM) and simulation result. (a) is the schematic illustration of the nicked dsDNA boundary conditions. (b) is the simulation result based on the CACM, where the plateau is occurred at about 65 pN at experimental[2] and simulation results (on average).

2 THEORY
2.1 Stretching energy on the dsDNA

In this research the Morse potential function [6] is used to describe stretching force of the backbone atoms. The Morse potential function is based on experiment, and it describes the relationship between the bone energy and the bond length of a diatomic system.

The Morse function could be expressed as:

$$E(r_{ij}) = D(e^{-\alpha(r_{ij}-r_0)} - 1)^2 \qquad (1)$$

where E represents the potential energy of the diatomic system, r_{ij} is the distance of atom I and atom j, D is the dissociation energy of the diatomic system, r_0 is the equilibrium length, and α is the characteristic constant, which should be determined by experimental result.

The Morse function describes the classical vibration of a chemical bond. The anharmonic Morse model provides a more realistic description of bond vibration than the harmonic potential functions does. First, the Morse function could describe the bond-breaching phenomenon of the chemical bond while the said bond is over-stretched. Moreover, the Morse function could also precisely prescribe the dissociation energy of the potential energy.

Furthermore, the mathematically characteristic of the Morse function could describe the physical behavior, where the ramping of the energy is more rapidly under compression than the one under extension.

However, the parameters of the potential function are not always obtained for all kinds of atoms because lack of experimental results. Therefore, the experimental theories have been established to develop specific potential functions which could, in principle, be extended to entire periodic table for obtaining the parameters have not been presented experimentally. The Universal Force Field (UFF) theory [6] has been developed to estimate the parameters in Morse function.

Based on the UFF theory, the Morse potential function parameters could be determined by force constant k_{ij}. A diatomic system could be considered as two atoms which are bonded by effective spring with force constant, as shown in Figure 2. The vibration energy of the system is expressed follows.

$$E_{vib} = \left(\nu + \frac{1}{2}\right)\hbar\omega \qquad (2)$$

Where $\nu = 1,2,3\ldots$, $\hbar = h/2\pi$, h represents the Planck's constant, and ω represents the oscillation frequency. The effective force constant could be determined from vibrational energy.

$$k_{ij} = \mu\omega^2 = 664.12\frac{Z_i^* Z_j^*}{r_{ij}^3} \qquad (3)$$

where μ represents the effective mass of the diatomic system, Z_i^* is the effective atomic charges of atom i , and r_{ij} is the distance between atom i and j . The parameter α in Morse potential function is therefore determined by force constant k_{ij}.
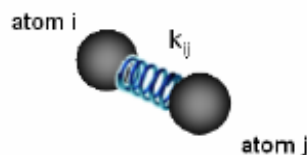
$$\alpha = [k_{ij}/2D]^{\frac{1}{2}} \qquad (4)$$

Fig. 2. Two atoms are connected with an effective spring to form a diatomic system

2.2 Angle binding energy on the dsDNA

In this research the Cornell's second generation force field potential function [7] is used to describe angle binding force of the backbone atoms. Using the Cornell's function, the angle binding energy can be represented by a simple diagonal harmonic model.

The Cornell's angle binding function could be expressed as:

$$E_{angle} = \sum_{angles} k_\theta (\theta - \theta_{eq})^2 \tag{5}$$

where E_{angle} represents the angle binding energy of the system, k_θ and θ_{eq} values were used as starting values and adjusted as necessary to reproduce experimental normal mode frequencies.

2.3   Bonding Energies of the dsDNA

In the dsDNA modeling, two kinds of the bonding energies are considered herein. First, we consider the base-stacking interactions, which originate from the weak van der Waals attraction between the polar groups in the adjacent base pairs. Moreover, the hydrogen bond forces between the adjacent base-pairs are considered.

The base stacking energy is a short range interation, and their total effect could be described by the Lennard-Jones potential from (6-12 potential form [8]). Base-stacking interactions play a significant role in the stabilization of the DNA double helix. By the Crotti-Engesser theorem, one can obtain the L-J potential force versus displacement relationship:

$$f_{LJ} = \frac{12AU_0}{l_0} \left(\frac{h_0 + \Delta l \cos \varphi_0}{h_0 + \Delta l} \right)^7 \left[1 - \left(\frac{h_0 + \Delta l \cos \varphi_0}{h_0 + \Delta l} \right)^6 \right] \cdot \left[\frac{h_0 (1 - \cos \varphi_0)}{h_0 \tan \varphi_0 (h_0 + \Delta l \cos \varphi_0)} \right] \tag{6}$$

where f_{LJ} represents the stacking force, U_0 represents the base stacking intensity and Δl represents the distance between the adjacent base pairs. l_0, h_0 and φ_0 represent the initial specific length, base pair height and folding angle of the dsDNA, respectively [9].

The hydrogen bond (H-bond) force is the interaction between complementary bases. Moreover, the GC base-pair has 3 H-bonds and AT has 2. These bonding energies can transverse all of the bending moments and force, because both the distance (R_i) and the angle (θ_{iHj}) between the donor and the acceptor affect the hydrogen bond energy. The single H-bond energy E of base-pairs could be expressed as [9]:

$$E(R_i, \theta) = \sum_{R_{ij}} AD_0 \left[5 \left(\frac{R_0}{R_i} \right)^{12} - 6 \left(\frac{R_0}{R_i} \right)^{10} \right] \cos^4 \theta_{iHj} \tag{7}$$

where D_0 represents the hydrogen bond energies intensity. R_0 and R_i is the initial and recent distances of the H-bond. Moreover, we assume that the distances of H-bonds are the same along the dsDNA, the B-form DNA shows the lowest H-bond potential and its D-H-A are aligned on the same line, and the H atom always at the center of H-bond at initial state. Fig. 3 illustrates the hydrogen bond model in this study, including both GC and AT cases.
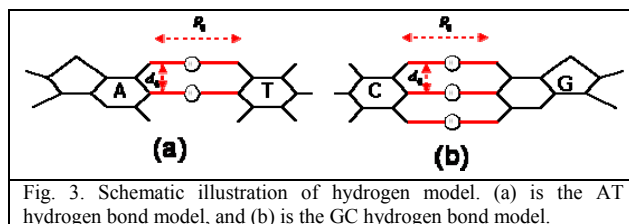

Fig. 3. Schematic illustration of hydrogen model. (a) is the AT hydrogen bond model, and (b) is the GC hydrogen bond model.

2.4   dsDNA ACM numerical modeling

In this section, the ACM model is constructed to simulate the dsDNA mechanical behavior. The numerical modeling of the dsDNA would be divided into two parts; one aspect is the description of mechanics of the backbone stretching energy, where the atoms are connected by the covalent bonds. Therefore, the spring element would be established between two atoms to represent the stretching energy. The force–displacement relationship in different bond types builds the main structure of dsDNA backbone by employing the UFF method (as shown in Figure 4).
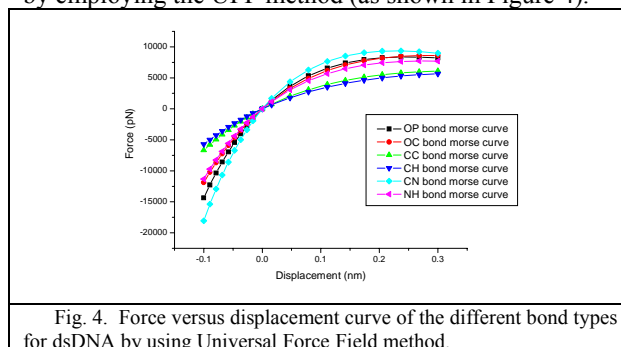

Fig. 4. Force versus displacement curve of the different bond types for dsDNA by using Universal Force Field method.

Another aspect lay in the simulation is the stacking energy and hydrogen bonds which provide the stability of the dsDNA. Figure 5 shows the structure of the ACM dsDNA model, which comprises 11 base pairs and the locations of the atoms are obtained by NMR method [10]. In the stretching dsDNA simulation, one end of the backbone was mechanically fixed. Besides, an externally prescribed displacement that is strictly proportional to the simulation time was applied on the other end.
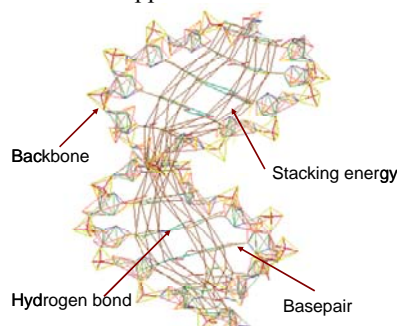

Fig. 5. Schematic illustration of dsDNA ACM model.

3. SIMULATION RESULT

The simulation result of the reacted forces, sensed by the bottom fixed points versus the externally applied displacement, is shown in Figure 5. A good agreement is achieved between the numerical simulation and single molecular manipulation experimental result, and the mechanical behavior of stretching nicked dsDNA could be revealed. First, when the external force is first applied on the B-DNA, the base pairs and hydrogen bond balance the mechanical equilibrium between two complementary sugar-phosphate backbones of dsDNA. Second, it is found that, as the increasing of external force, the van der Waals reactant force between the adjacent base pairs increases. Until the distance between adjacent base pairs exceeds the limitation, the base-stacking fails and the B-S transition occurs at approximately 60 pN of tension. Eventually, after the dsDNA has fully transited to the ladder-type S-DNA, the rotation of the local sugar-phosphate backbone terminates. In this Stage, the base pairs and hydrogen bond achieve the mechanical equilibrium between two complementary sugar-phosphate backbones of dsDNA.
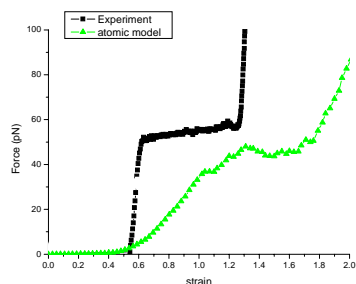

Fig. 6 The simulation result of dsDNA under external tensile loading in different atoms weight.

The figure 7(a) represents the total dsDNA with 11 bps, and the figure 7(b) represents the dsDNA structure stretched after applied force.
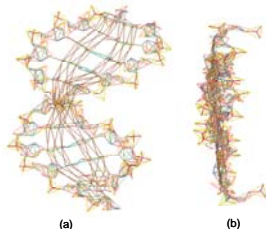

(a)   (b)

Fig. 7 (a) The configuration of the dsDNA prior to the external loading applies on the model. (b) The external loading applies on the dsDNA model.

4. CONCLUSION

In this paper, a novel atomistic-continuum mechanics method, based on a transient finite element method was proposed to simulate the dsDNA mechanics. To completely consider the covalent bond effects between atoms in the backbone, the stacking energy and the hydrogen bond between base pairs, the detail theoretical derivation would be emphasized. A good agreement was achieved between the numerical simulation and experimental results in stretching dsDNA. Furthermore, the proposed finite element model could be applied in the analysis and the prediction of biological interactions between DNA and other proteins/enzymes, such as DNA binding protein or RNA polymerase.

REFERENCES

[1] S. B. Smith, Y. Cui, C. Bustamante "Overstretching B-DNA: The Elastic Response of Individual Double-Stranded and Single-Stranded DNA Molecules, "Science, vol. 271,795-799, 1996.

[2] K. N. Chiang, C. A. Yuan, C. N. Han, C. Y. Chou, and Yujia Cui "Mechanical characteristic of ssDNA/dsDNA molecule under external loading , " PhD dissertation, Appl. Phys. Lett. 88, 2006.

[3] C. Benham, "Onset of writhing in circular elastic polymers," Phys. Rev. A, 39, 2582-2586, 1989.

[4] J. F. Marko and E. D. Siggia, "Statistical mechanics of supercoiled DNA," Phys. Rev. E, 52, 2912-2938, 1995.

[5] H. Zhou, Y. Zhang and Z. Ou-Yang, "Elastic property of single double stranded DNA molecules: theoretical study and comparison with experiments," Phys. Rev. E, 62, 1045-1058, 2000.

[6] A. K. Rappe et al, "UFF, a full periodic table force field for molecular mechanics and molecular dynamics simulations," J. Am. Chem. Soc., vol. 114, pp 10024-10035, 1992.

[7] W. D. Cornell et al, "A second generation force field for the simulation of proteins, nucleic acids, and organic molecules," J. Am. Chem. Soc., vol. 117, pp5179-5197, 1995.

[8] P. M. Morse, "Diatomic molecules according to the wave mechanics. Ⅱ. Vibrational levels", Phys. Rev., vol. 34, 57, 1929.

[9] G. A. Jeffery, W. Saneger, "Hydrogen Bonding in Biological Structures", 1st ed., Springer-Verlag, Germay, 1994

[10] A. Mujeeb, S. M. Kerwin, G. L. Kenyon, T. L. James, "Solution Structure of a Conserved DNA Sequence from the HIV-1 Genome: Restrained Molecular Dynamics Simulation with Distance and Torsion Angle Restraints Derived from Two-Dimensional NMR Spectra" Biochemistry, 32, pp. 13419, 1993.