Investigation of dsDNA Stretching Meso-Mechanics Using LS-DYNA

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Abstract

This paper proposes a novel mathematical model for studying the entropic elasticity and cooperative extensibility of double strand DNA (dsDNA) using LS-DYNA and equivalent theory. Through the proposed model, the dynamic structural transitions of the dsDNA under external force/torque can be accurately simulated within an affordable CPU time. Moreover, the proposed dsDNA model comprises the meso-mechanics equivalent theory of single molecule dsDNA, including the base-stacking interaction between DNA adjacent base pairs, the Hydrogen bond of complementary base-pairs and electrostatic interactions along double-helix sugar-phosphate backbones. Good agreement is achieved between the numerical simulation and the single molecular manipulation experimental result, and the mechanical behavior of stretching nicked dsDNA could be revealed.

Introduction

During the past decade, the single molecular manipulation technique has been developed to measure the basic physical properties of double stranded double-strand deoxyribose nucleic acid (dsDNA) and to discover the interaction between dsDNA and proteins/enzymes [1]. The structure of B-DNA has been first discovered by the Watson and Crick at 1950s. The blue two double helix chains indicate the sugar-phosphate backbone of DNA. The black rods represent the base pairs. Additionally, the red and green circles represent the hydrogen bonds between bases [1]. Moreover, the results of the nicked dsDNA stretching experiment have indicated that a sharp structural transition occurs under roughly 65pN of tension, and that the classical B-DNA structure dramatically transits to a S-DNA structure [3-5].In Figure 2, (a) is the schematic illustration of the optical tweezers system, which can be used as a single-molecular manipulation. One end of dsDNA is fixed to the glass substrate; the other end is attached to the micro bead. (b) is the schematic illustration of B-DNA and S-DNA. S-DNA is proposed to be the ladder type structure. (c) is the single-molecular measurement result of stretching dsDNA, and abrupt structural transition (B-S transition) and the plateau of nicked dsDNA of 65 pN. (the experimental results are based on the [3])

However, the resolution of the single molecular 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 conquer the resolution limitation of the single molecular dsDNA manipulation technique, the molecular biology researcher essentially requires accurate theoretical model to address 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 [6] have derived the analytical wormlike rod chain model (WLRC model), and Marko et al. [7] 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 or twisting torque. Zhou et al. [8] 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, the dynamic/transient finite element method with material/geometrical nonlinear properties is applied in this study in order to comprehensively understand the mechanical behavior of dsDNA under external loading.

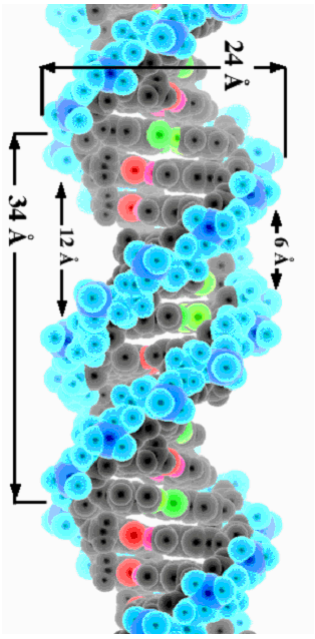
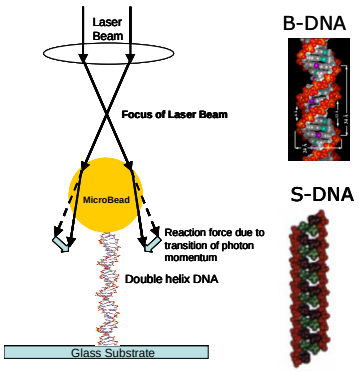
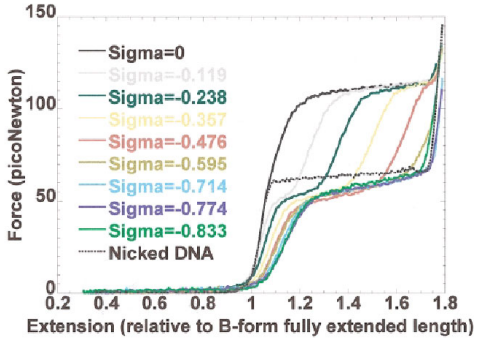


Figure 1. Schematic illustration of classic B-type dsDNA.

The finite element method considers the minimization of the total potential energy, which includes internal energy, bending energy, twisting energy, the contact energy and the external energy of dsDNA. Moreover, the complex geometry of the double helix DNA can be described by discrete finite element with few geometrical limitations. The two complementary sugar-phosphate back bones of dsDNA will be modeled as continuum double-helix curved beams. Furthermore, the interaction between complementary bases, such as hydrogen bond, can be treated as the equivalent beams. Also, due to the fact that the base-stacking interactions play a significant role in the stabilization of the DNA double helix, the van der Waals force between adjacent base pairs have evolved as the equivalent Lennard-Jones potential spring (equivalent L-J potential spring). Additionally, the simulation result of the proposed dsDNA finite element model can be accomplished by the commercial transient finite element code within affordable CPU time. Through the proposed dsDNA model, the dynamic structural transition of nicked dsDNA under external force/torque can be completely revealed. Moreover, the non-linear mechanical behavior and cooperative extensibility of dsDNA can be comprehensively understood.



(a) (b)



(c)

Figure 2: Schematic illustration of dsDNA single molecular experiment.

Transient Finite Element Model for dsDNA

■ Finite Element Theory

Using the principle of minimum potential energy, one can generate the equations for a constant-strain finite element. For each specific time ($t = t_i$), the total potential energy is a function of the nodal displacements $X(x, y, z)$ such that $\pi_p = \pi_p(X)$. Here the total potential energy is given by

$$\pi_p\big|_{t=t_i} = U + \Omega_p\big|_{t=t_i} \tag{1}$$

where U and Ω_p represent strain energy and energy of external loading, respectively. The above equation can be rewritten as a finite element integrated form[9]

$$\pi_p\big|_{t=t_i} = \frac{1}{2}\iiint_V \left[\rho\{d\}^T[N]^T[N]\{\ddot{d}\}dV + \{d\}^T[B]^T[D][B]\{d\}\right]\Big|_{t=t_i} dV - \left[\{d\}^T\{P\}\big|_{t=t_i} + \iint_S \{d\}^T[N_S]^T[T_S]\Big|_{t=t_i} dS\right] \tag{2}$$

where $\{d\}$ represents the nodal vector, $\{\ddot{d}\}$ represents the nodal acceleration, ρ represents the density, $[B]$ is the strain-displacement matrix, $[D]$ is modulus of elasticity matrix, $[N]$ is the shape function matrix, $\{P\}$ is the external load vector and $[T_S]$ is the traction force matrix. The minimization of total potential energy with respect to each nodal displacement requires that

$$\left.\frac{\partial \pi_p}{\partial \{d\}}\right|_{t=t_i} = \left.\left(\iiint_V [\rho][N]^T[N]\{\ddot{d}\} + [B]^T[D][B]dV)\{d\}\right|_{t=t_i} - \left[\{P\} + \iint_S [N_S]^T[T_S]dS\right]_{t=t_i} = 0$$

namely,

$$at\ t = t_i\ ,\ (\iiint_V [B]^T[D][B]dV)\{d\} + \left(\iiint_V \rho[N]^T[N]dV\right)\{\ddot{d}\} = \{P\} + \iint_S [N_S]^T[T_S]dS \tag{3}$$

Finally, solving the linear system shown in Eq.(3) at each specific time, one can obtain the {d} and the global nodal vector can be revealed.

Equivalent Theory of Meso-mechanics

Since the meso-mechanics of dsDNA comprises both quantum mechanics and continuum mechanics, a feasible equivalent theory should be established, capable of including the chemical bond forces in the global analysis of the dsDNA finite element model. The hydrogen bond force, which is the interaction between complementary bases, could mechanically transverse both moment and force, because there are at least two hydrogen bonds in the complement bases. Accordingly, the hydrogen bond force will be treated as the equivalent beam elements in the dsDNA finite element model.

Furthermore, the base-stacking interactions originate from the weak van der Waals attraction between the polar groups in the adjacent base pairs. Such interactions are short range, and their total effect is usually described by a potential of Lennard-Jones from (6-12 potential form [10]). 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:

$$f_{LJ} = \frac{12AU_0}{l_0}\left(\frac{h_0 + \Delta l\cos\varphi_0}{h_0 + \Delta l}\right)^7\left[1 - \left(\frac{h_0 + \Delta l\cos\varphi_0}{h_0 + \Delta l}\right)^6\right] \left[\frac{h_0(1-\cos\varphi_0)}{h_0\tan\varphi_0(h_0 + \Delta l\cos\varphi_0)}\right] \tag{4}$$

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. Using Eq. (4), the non-linear mechanical properties of the equivalent L-J potential spring can be practicably established.

■ dsDNA Finite Element Model

To fully understand the dsDNA mechanical behavior, we will establish the proposed finite element model in this section. Due to that the classic B-DNA is stable in physiological aqueous solution, its geometrical structure has been chosen as the initial state of the said model, and the Writhe number of proposed dsDNA model has been assumed as zero. Moreover, both the major/minor groove and the sequence of the dsDNA were neglected for the sake of simplifying the proposed finite element model. Besides the equivalent hydrogen bond beam elements and equivalent base-stacking spring elements, the two complementary sugar-phosphate backbones of dsDNA will be modeled as continuum double-helix curved beams with geometrical nonlinear capability because the backbones would inherit the axial stress, bending moment and torque during stretching dsDNA. Additionally, the single base pair has been considered as a rigid rod, and the deformation of the base pairs are neglected.

The finite element model of dsDNA is then conducted, as shown in Figure 3. The figure 3, (a) represents the dsDNA with 147 bps (base pairs). (b) is the detail structure of (a), where the red circular double helices represent the sugar-phosphate chains and the blue rods represent the base pairs. Additionally, the yellow line and the green line in (c) represent the equivalent hydrogen bond beam type element and equivalent base-stacking spring element, respectively. Moreover, the non-linear spring constants of the equivalent L-J spring can be obtained from Eq. (4) with the folding angle equaling 55^{o}. This model comprises 147 base pairs, and the initial length of the dsDNA approximately equals 50nm. In the nicked dsDNA simulation, one end of the backbone is mechanically fixed and another end is applied the external force, which is strictly proportioned to the time in the simulation.

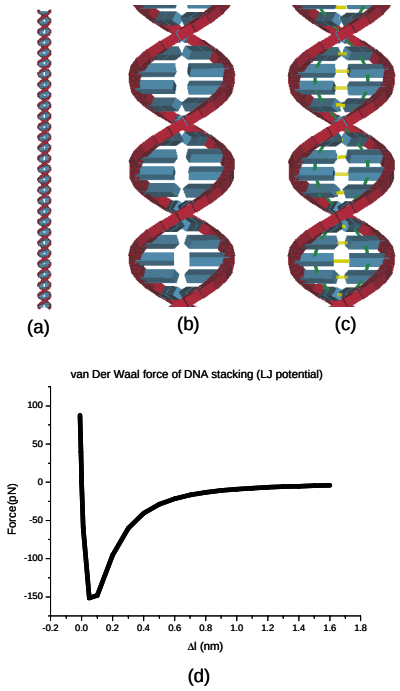


Figure 3: Finite element model of dsDNA.

Simulation Result of Nicked dsDNA Structural Transition

The dsDNA finite element model consists of 2,213 beam elements and 292 discrete spring elements, and is comprised of 4,281 nodes. The transient finite element model has been solved by commercial finite element analysis code LS-DYNA® (version 970) with the a CPU time of 20,652 seconds on IBM® SP2 SMP hardware.

The finite element simulation results of stretching nicked dsDNA revealed a continuous structural transition, which can be characterized by the three main stage of stretching the nicked dsDNA (Fig. 4). We will discuss the mechanical characteristics of these three stages in the following section.

- **Stage 1: B-DNA**

When the external force is first applied on the B-DNA, the base pairs and the hydrogen bond balance the mechanical equilibrium between the two complementary sugar-phosphate backbones of the dsDNA. In this stage, both the backbone and the equivalent base-stacking spring inherit uniform axial reactant forces. However, the torsional rigidity of the dsDNA backbones resists the twisting of the complementary base pairs. As a result the geometry of the dsDNA remains B-DNA in stage 1 without structural transitions.

- **Stage 2: B-DNA to S-DNA (B-S Transition)**

As the external force increases, so does the van der Waals reactant force between the adjacent base pairs increase. Until the distance between adjacent base pairs exceeds the limitation, the base-stacking fails and the B-S transition occurs at approximately 65 pN of tension. Meanwhile, the torque of the dsDNA local structure overcomes the backbone torsional rigidity and begins to untwist the double helix of the complementary backbone. Due to the transient mechanical effect, the untwisting starts from the nearest base pair where the external force applied, and propagates along the rest of the dsDNA. As the rotation of backbone, the double helical B-DNA transits to laddered S-DNA.

- **Stage 3: S-DNA**

After the dsDNA has fully transited to the ladder-type S-DNA, the rotation of the local sugar-phosphate backbone terminates. In Stage 3, the base pairs and the hydrogen bond balance the mechanical equilibrium between two complementary sugar-phosphate backbones of dsDNA. Due to the fact that the ultimate loading of backbone molecules is approximately 476pN [11], the dsDNA structure will be broken if the hydrogen bond between the complimentary base pairs fails and the dsDNA will then be unzipped and opened.

Conclusion

In this paper, a novel transient finite element method with equivalent mesh-mechanics has been applied in a dsDNA stretching simulation. The dsDNA complementary sugar-phosphate chains were modeled as continuum double-helix curved beams. In addition, the Hydrogen bond and base-stacking between bases were modeled as the equivalent beam elements and spring elements in the proposed model, respectively. The continuous dynamic structural transition of stretching nicked dsDNA was revealed in the finite element simulation results. Moreover, the structural transition was characterized as three main stages, and the mechanical behavior of

stretching dsDNA was thoroughly elucidated. Furthermore, the proposed finite element model was applied in the analysis and prediction of the biological interactions between DNA and other proteins/enzymes, such as DNA binding protein or RNA polymerase.

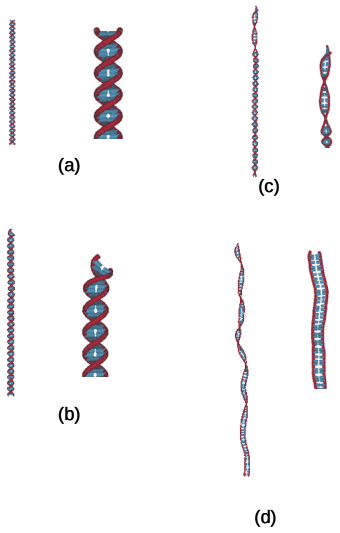


Figure 4: Structural transition of dsDNA. The left side figure represents the total dsDNA with 147 bps, and the right side figure represents the detail structure of left side dsDNA. (a) represents the initial condition of B-DNA. (b). (c) and (d) represent stage 1, stage 2 and stage 3, respectively.

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