Investigation of the ssDNA Backbone Molecule Mechanical Behavior Using Atomistic-Continuum Mechanics Method

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ABSTRACT

As is known, various important physiological functions and gene engineering processes, such as RNA transcription/DNA replication/DNA repair, involve specific bio-physical mechanics of DNA. Therefore, in this study, a novel single-stranded DNA (ssDNA) model based on the atomistic-continuum mechanics method (CAM) is conducted to simulate the mechanical behavior of ssDNA. It is often assumed that the elastic behavior of single-chain polymer can be modeled as the freely joint chain (FJC) of orientationally independent Kuhn segment. In this research, an atomistic-continuum mechanics model of ssDNA 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 ssDNA. To describe the material properties of the spring in ssDNA backbone structure, the Cornell's second generation force field potential energy and Universal force field is 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 function.

1 INTRODUCTION

In the molecular biology, various important physiological functions and gene engineering processes, such as RNA transcription, DNA replication and DNA repair, involve the specific bio-physical mechanics of DNA. Although the stretching mechanical behavior of ssDNA could be described by the freely joint chain (FJC) model with feasible persistent length [1] (Figure 1), the mechanical characteristics of ssDNA could not be predicted accurately by the simple FJC model because the salt buffer solutions can be selected in arbitrary experiments, as a result, the ACM ssDNA model becomes a variable and can induce the uncertainty of mechanical analysis.

To represent the mechanical response of the ssDNA under the external loading, such as axial stretching [2-3], Yuan have modeled the ssDNA and dsDNA molecules under axial and unzipping loading. 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 [4] based on the finite element method was applied to reduce the computational time. However, in order 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 we should assume some material properties in the clustered elements 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 ssDNA backbone molecule. Notably, the bond stretching energy between atoms on the backbone could be described by the Universal Force Field [5] and the bond angle energy could be described by the Cornell's second generation force field potential energy [6]. Furthermore, the numerical ssDNA 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).

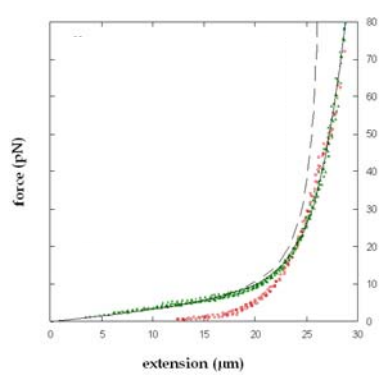


Figure 1. ssDNA stretching in different salt buffer solution. Dashed line represents the elasticity of a freely jointed chain. Green curve represents the ssDNA was stretched in 150 mM NaCl, 10 mM Tris, 1 mM EDTA, pH 8.0. Red curve represents for ssDNA molecule was stretched in 1 mM Na2.5EDTA, pH 8, 20% formaldehyde [1].

2 THEORY

2.1 Finite Element Theory

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 [7]. Moreover, the geometry of the single-stranded DNA can be described by discrete finite element with few geometrical limitations.

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 [7]

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

where the $\{d\}$ 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

$$\frac{\partial \pi_p}{\partial\{d\}}\Big|_{t=t_i} = \left(\iiint_V [\rho][N]^T[N]\{\ddot{d}\} + [B]^T[D][B]dV)\{d\}\right)\Big|_{t=t_i} - \left[\{P\} + \iint_S [N_S]^T[T_S]dS\right]_{t=t_i} = 0 \tag{3}$$

namely,

$$\text{at } t = t_i,\ \left(\iiint_V [B]^T[D][B]dV)\{d\} + \left(\iiint_V \rho[N]^T[N]dV\right)\{\ddot{d}\} = \{P\} + \iint_S [N_S]^T[T_S]dS \tag{4}$$

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

2.2 Stretching energy on the ssDNA

In this research the Morse potential function [8] is used to describe stretching force of the backbone atoms. The Morse potential function is an experiment based function, and it describes the relationship between the bone energy and the bond length of a diatomic system.

The Morse function could be expressed as:

$$E(r_{ij}) = D\left(e^{-\alpha(r_{ij}-r_0)} - 1\right)^2 \tag{3}$$

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. 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 result. 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 be presented experimentally. The Universal Force Field (UFF) theory [5] 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.

$$E_{vib} = \left(\nu + \frac{1}{2}\right)\hbar\omega \tag{5}$$

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.

$$k_{ij} = \mu\omega^2 = 664.12\frac{Z_i^* Z_j^*}{r_{ij}^3} \tag{6}$$

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}.

$$\alpha = [k_{ij}/2D]^{\frac{1}{2}} \tag{7}$$

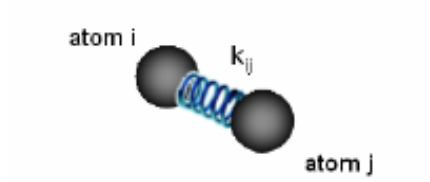


Fig. 2. Two atoms are connected with an effective spring to form a diatomic system

2.3 Angle binding energy on the ssDNA

In this research the Cornell's second generation force field potential function [6] 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:

$$E_{angle} = \sum_{angles} k_{\theta}(\theta - \theta_{eq})^2 \qquad (8)$$

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.

2.4 ssDNA backbone ACM numerical modeling

In this section, we will construct the ACM model to simulate the ssDNA mechanical behavior. The numerical modeling of the ssDNA would be divided into two parts. One aspect is the description of the mechanics of the stretching energy of the backbone, 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 ssDNA backbone by employing the UFF method (as shown in Figure 3).

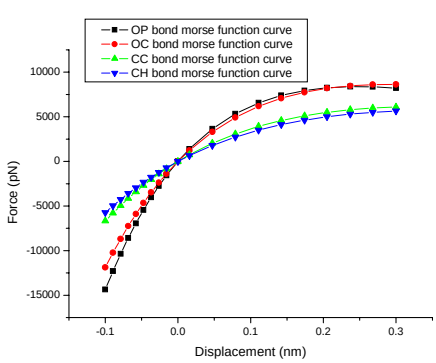


Fig. 3. Force versus displacement curve of the different bond types for ssDNA backbone by using Universal Force Field method.

The other aspect lies in the simulation is the angle binding energies which provide the stability of the ssDNA. Figure 4 shows the structure of the ACM ssDNA model. This model comprises 12 base pairs and the locations of the atoms are obtained by NMR method [9]. In the stretching ssDNA 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.

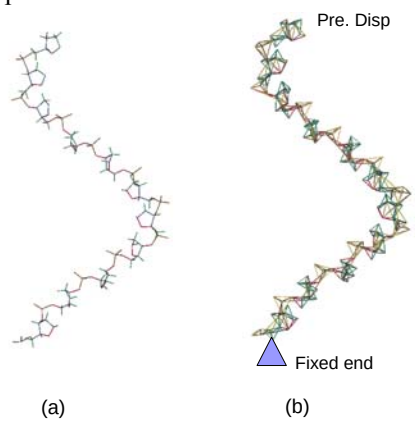


Fig. 4. Finite element model (a) The main structure of the ssDNA model. (b) The angle binding energy on ssDNA model together with its boundary condition.

3 SIMULATION RESULTS

The simulation results of the reacted forces, sensed by the bottom fixed points versus the externally applied displacement, are shown in Figure 5. Comparing with the experimental results, good agreements in tendency were achieved between each weight of ssDNA backbone model when the sensing force excesses the 30 pN. The vibration of the simulation results in Figure 5 is due to the loading rate effect of the ssDNA model.

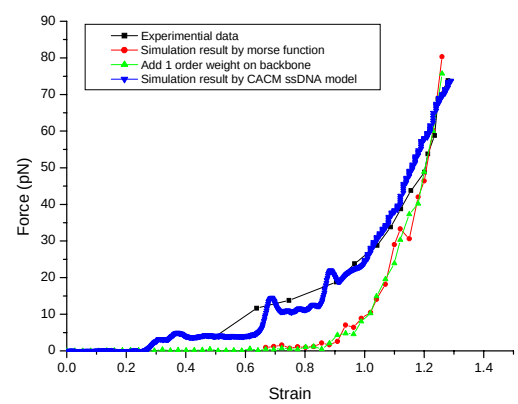
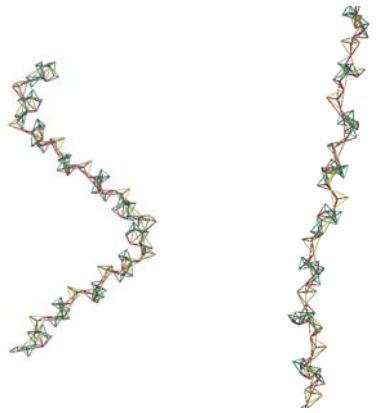


Fig. 5 The simulation result of ssDNA under external tensile loading in different atoms weight.

As the weight of atoms in ssDNA model is modified to simulate the ssDNA stretching in different salt buffer solution, no variation in the simulation obviously.

Comparing with the experimental result in Figure 1, the force-extension curves reveal distinct variation before the force excess 10 pN in the experimental data; it was the supercoiled that caused by the different salt buffer solution. However, the ssDNA model would first be untwisted under applying the external loading in the simulation as shown in Figure 6.



(a) (b)

Fig. 6 (a) The configuration of the ssDNA prior to the external loading applies on the model. (b) The external loading applies on the ssDNA model.

4 CONCLUSION

In this paper, a novel atomistic-continuum mechanics method, based on a transient finite element method was proposed to simulate the ssDNA mechanics. To completely consider the covalent bond effects between atoms in the backbone, the detail theoretical derivation would be emphasized. Good agreement was achieved between the numerical simulation and experimental results in stretching ssDNA. Furthermore, considered the supercoiled effect on this robust model, the mechanics of the stretching ssDNA and dsDNA in the different salt buffer solution could be studied.

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