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A stochastic thermostat algorithm for coarse-grained thermomechanical modeling of large-scale soft matters: Theory and application to microfilaments

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ABSTRACT

As all-atom molecular dynamics method is limited by its enormous computational cost, various coarse-grained strategies have been developed to extend the length scale of soft matters in the modeling of mechanical behaviors. However, the classical thermostat algorithm in highly coarse-grained molecular dynamics method would underestimate the thermodynamic behaviors of soft matters (e.g. microfilaments in cells), which can weaken the ability of materials to overcome local energy traps in granular modeling. Based on all-atom molecular dynamics modeling of microfilament fragments (G-actin clusters), a new stochastic thermostat algorithm is developed to retain the representation of thermodynamic properties of microfilaments at extra coarse-grained level. The accuracy of this stochastic thermostat algorithm is validated by all-atom MD simulation. This new stochastic thermostat algorithm provides an efficient way to investigate the thermomechanical properties of large-scale soft matters.

1. Introduction

Instead of relatively rigid materials that can be characterized in classic mechanics, soft matters consist of flexible material components whose mechanical performances can be significantly affected by their thermodynamic behaviors [1]. Molecular modeling approach provides a suitable way for the modeling of soft matters based on the fact that the internal entropic motion is benefiting the macroscale mechanical behaviors [2]. However, the length scale of soft matters in all-atom (AA) modeling is only hundreds of nanometers [3], which is limited to explore the overall performance of soft matters that consist of enormous randomly crosslinked chains/fibers at microscale. In order to enlarge the length scale of soft matters modeling, different coarse-grained (CG) strategies have been developed to describe the mechanical deformation of both organic and inorganic materials in terms of chemistry and physics [4–6].

Depending on the research objectives, there are two main strategies to develop corresponding CG modeling parameters: thermodynamic matching [7] and mechanical properties matching [8]. In order to guarantee the reliability of mechanical modeling of soft matters, we herein discuss the latter strategy specifically. As a typical organic soft matter, microfilament is specifically investigated in this paper as a typical application. Microfilament network plays critical roles in eukaryotic cellular processes such as cell cytokinesis, spreading and migration [9], determining the fate of living cells [10–12]. *In-vivo* biomechanics experiments on single microfilaments are difficult to be carried out at molecular level due to the limits of experimental techniques and ethical constraints. Molecular dynamics (MD) simulation has been developed to reveal the conformational changes in actin monomers, which provides insights into the molecular mechanisms of the metabolism in

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association to microfilaments dynamics [13]. A large scale coarse-grained (CG) strategy for microfilaments modeling has been proposed to study the mechanical properties of microfilament networks at microscale [8]. Each simulation bead in this CG model is made up of two neighboring G-actin monomers and the mechanical deformation of microfilament networks are evaluated based on the interaction between simulation beads. In this CG modeling strategy, there is no need to adjust the force constant with respect to the effective bond lengths, and the mechanical behaviors of microfilament are uncomplicated to be unified with AA-MD characterization by defining proper force constants between simulation beads [8]. However, each bead in this CG strategy consists of more than 700 amino acids, which is far more than the typical 'one-bead' CG strategy whose simulation bead only represents one amino acid [14]. The thermal dynamic information of each physical atom in AA modeling is described by energy equipartition theorem [15], in which the mean kinetic energy of each harmonic solid can be directly derived as,

$$E_k = \frac{3}{2} k_B T \tag{1}$$

where k_B is the Boltzmann constant and T is the absolute temperature of thermal bath, E_k is the kinetic energy of the high frequency harmonic motion of simulation beads. These random motions of single atoms due to entropic energy can lead to both the structural disorder and the random movement of G-actin monomers, which are potentially obscured on the simulation beads in CG modeling strategy. Hence, it is arguable whether CG model can fully reveal the thermal dynamic motions of microfilaments by directly implementing the classical thermostat algorithm, i.e., Eq. (1). The thermodynamic motions of microfilaments, e.g. thermal fluctuations, can lead to wormlike configurations of microfilaments, which are significant to the biological activities and mechanical deformation of microfilaments [16]. An efficient thermostat algorithm in CG modeling of microfilaments is crucial to assist the theoretical exploration of the biophysical properties of cell structures (e.g. filopodia and lamellipodia) at microscale, where AA-MD characterization is difficult to be applied due to its computational cost.

In this paper, by analyzing the thermodynamic behaviors of microfilaments, we investigate the ability of classical thermostat algorithm for the characterization of internal dynamic motions of microfilaments in association to the mechanical deformation modeling. A new stochastic thermostat algorithm is therefore proposed and implemented in a large-scale CG modeling strategy to estimate the thermomechanical properties of microfilaments with respect to their hierarchical structures.

2. Thermodynamic characterization of microfilament fragment

In order to investigate the difference of thermodynamic predictions between AA and CG molecular dynamics (MD) simulation of microfilament, a small fragment of microfilament that consists of only four G-actin monomers is at first studied. The F-actin crystallography 2ZWH (from Worldwide Protein Data Bank) [17] is adopted in the AA-MD characterization. The AA simulations are performed in Gromacs [18] with the force field of all-atom optimized potentials for liquid simulations (OPLS-AA) [19] in isothermal–isobaric (NPT) ensemble at the temperature of 303 K (Berendsen method [15]) and the pressure of one bar (Parrinello–Rahman method [20]). Simple point-charge (SPC) water model [21] is used to explicitly consider the effects from solvent environment. The time step of AA-MD simulation is 2 femtoseconds and the simulation duration is 100 picoseconds. The longitudinal stiffness of a single microfilament is 43 pN/nm [22] and the angular stiffness is 5.3×10^4 pN nm/rad^2 [8]. The equilibrium distance between simulation beads is 5.6 nm and the equilibrium angle between adjacent bonds is 180°. The CG-MD simulations are performed in Lampps [23] by utilizing the aforementioned harmonic potential energy equation. The temperature in CG-MD simulation is controlled at 303 K by the Langevin dynamics [24]. In the Langevin dynamics algorithm, two terms are added to the force calculation on each particle: viscous damping term due to solvent and a randomly bumping term due to temperature. The combination of these two terms is $F_d = -mv/C_d + \sqrt{mk_BT/dt\,C_d}$. Where, m is the mass of particle, v is the velocity of particle, dt is the time step. C_d is the damping factor with a time unit, which determines how rapidly the temperature is relaxed in the simulation. This C_d is the only flexible parameter that needs to be set up in the simulation. This parameter has dependency on the natures of both solvent and material particle. Based on the viscosity of water at 303 K and the mass/diameter of G-actin clusters, C_d is estimated to be 1 fs. The time step and modeling time in CG-MD simulation are all the same with AA-MD simulation. All the molecular visualization work is finished by using visual molecular dynamics (VMD) [25].

Fig. 1 provides the illustration of the aforementioned simulation models of microfilament fragment (both AA and CG levels) and compares the longitudinal thermal fluctuation results from AA and CG levels MD simulations. The configuration of microfilaments is rapidly equilibrated by using the CG modeling strategy for microfilaments. The molecular simulation model is simplified from 163 thousands atoms (AA-MD simulation) to only two mass beads (CG-MD simulation, which saves enormous computational resources). However, the variation of filament length with regards to modeling time in CG-MD simulation is not significant compared to AA-MD simulation, which indicates that the thermodynamic motion of microfilament fragment is mostly missed in CG-MD simulation. This oversimplified CG-MD modeling technique with classical thermostat algorithm is sufficient to obtain stable conformation of microfilament fragment under mechanical boundary constrains [8], but inadequate in predicting the longitudinal thermal fluctuations. These results validated our concerns in the thermomechanical characterization of microfilaments by utilizing a highly CG modeling strategy.

The force applied on each atom in the molecular system includes the interatomic action force, the damping effects from solvent and the random bumping due to temperature. Compared to the AA model of a molecular system, the interatomic