Comput. Methods Appl. Mech. Engrg. 254 (2013) 14–30

Contents lists available at SciVerse ScienceDirect

Comput. Methods Appl. Mech. Engrg.

journal homepage: www.elsevier.com/locate/cma

A computational framework for transverse compression of microtubules based on a higher-order Cauchy–Born rule

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ARTICLE INFO

Article history:
Received 29 May 2012
Received in revised form 16 October 2012
Accepted 17 October 2012
Available online 29 October 2012

Keywords:
Microtubules
Higher-order Cauchy–Born rule
Hydrostatic pressure
Transverse compression

ABSTRACT

This work presents a computational framework for the transverse compression of microtubules using the Cauchy–Born rule. Atomistic-continuum simulation and mesh-free method are employed in the computation for the theoretical scheme of the higher-order gradient continuum. Elastic properties and mechanical responses of microtubules under transverse compression are intensively studied. Without tracing each atom in large protein structures, a homogenization technique is proposed to evaluate interatomic energy stored among macromolecules. The concept of fictitious bonds is proposed for microtubules to bridge the gap between the atomistic simulation and the continuum approach, which is of great significance for application of the continuum approach to macromolecular structures. To reflect the inhomogeneous deformations of a cylindrical structure, the higher-order Cauchy–Born rule is employed to calculate the fictitious bond vectors emanating from a given evaluation point during the deformation process. By selecting a representative unit, a higher-order gradient continuum constitutive relationship is established to take atomistic interactions into consideration. Elastic modulus and transverse mechanics, including critical hydrostatic pressure and transverse compression-induced structure transitions, are numerically simulated. Example problems are carefully selected and the obtained results are discussed in detail.

1. Introduction

The biomechanical performance of the cytoskeleton is primarily governed by microtubules that are ubiquitous in eukaryotic cells. Microtubules are biologically important components, and many complex cellular activities such as growth, motility, mitosis, and meiosis are strongly dependent on the functions of microtubules. Typically, they are composed of 13 protofilaments arranged in a circumferential direction. The atomistic structure and chemical components of microtubules are quite complicated [1]. A microtubule is made up of different chemical elements, including C, H, O, N, S, and P, and takes the form of a cylindrical hollow tube made up of an orderly arrangement of tubulin (α and β) monomers. Microtubules are the major determinants of cell shape, and must perform well mechanically. However, our knowledge of the mechanical properties of microtubules is far from satisfactory. To study the overall biomechanical performance of a microtubule, hundreds of tubulin monomers must be considered, each of which contains thousands of atoms. Researchers have attempted to unfold the subtle mechanical properties and behavioral mechanism of microtubules through a range of methods, including experimental tests and theoretical analysis, but have been unable to find an efficient way to deal with them that is both sufficiently accurate and convenient.

Experimental tests were traditionally the main approach for investigating cytoskeleton networks. Various techniques, including atomic force microscopy, optical trapping and buckling, rheometry and vesicle rupturing [2–9], were used in past work. The mechanical behaviors of microtubules in response to deformation, elasticity, and vibration have also been studied [10–13]. However, the applicability of the available experimental tests is limited; the manipulation and precise operation of the instruments are difficult, as is nanoscale measurement; the mechanical responses achieved by experimentation are insufficient and unreliable for the characterization of the overall properties of the cytoskeleton. Because of these drawbacks, past measurements may not be sufficiently comprehensive, and may be unable to accurately describe the mechanical properties of individual microtubules.

Along with these experimental measurements, various theoretical attempts have been made to study the atomistic structures, mainly in the areas of atomistic simulation and continuum modeling [14–20]. Many past attempts to study the mechanical behavior of cytoskeleton networks have used molecular dynamics (MD) methods [21–23]. However, these MD simulations only focus on proteins [22,23], and neglect the mechanical behavior of filaments and whole microtubules due to the huge computational costs involved. The subunit of microtubules, a tubulin monomer, normally

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http://dx.doi.org/10.1016/j.cma.2012.10.013

contains 440 residues consisting of approximately 8000 atoms. In order to determine the mechanical response of a micrometers' long microtubule, billions of atoms would be involved in consideration, the number of atoms is computationally prohibited for MD simulations [24,25]. This size limit of computation in atomistic simulation is far short to reach polyatomic bio-materials; it is therefore not suitable for large systems, or for the rapid simulation of macro molecular microtubules. Macroscale continuum modeling has been put forward as an alternative method of simulating the mechanical responses of the cytoskeleton to alleviate computational burden. Various continuum models have been proposed [17,26–34], including the elastic solid model, isotropic shell model, and nonlinear viscoelastic solid model. Among these, viscoelastic modeling is regarded as the most reliable approach, but is still phenomenological and does not give any information on the interatomic relationship among macromolecular components. Hence, the existing continuum techniques are only efficient for studying certain properties of the cytoskeleton. Furthermore, theoretical efforts established purely in the continuum domain are limited in their ability to deal with complex atomistic structures, and no efficient continuum method is currently available for the simulation of whole microtubules.

The atomistic-continuum method is an efficient approach that bridges the gaps between the traditional atomistic modeling and continuum theory, and has the ability to overcome the limitations of computational size without the loss of interatomic information [35–38]. Recently, much effort has been made to find an efficient continuum-based technique for lattice and crystal structures. There have also been some attempts to establish atomistic-based continuum theories or quasicontinuum theories: Liew and Sun [15,16,25,39–41] proposed multi-scale models to connect atomistic simulations with continuum mechanics; He et al. [42] and Wang et al. [43] made attempts to include the van der Waals force into the continuum theory of multiwalled carbon nanotubes and multi-layered graphene sheets; Yakobson et al. [44] studied carbon nanotubes by applying both MD simulation and the classical continuum shell theory, and illustrated that the buckling phenomena of nanotubes can be sufficiently well displayed with a continuum shell model; Rajendran and Reddy [45] presented an analytical molecular mechanics model for graphene and single-walled carbon nanotubes that related the elastic properties to the atomic structure; Ng et al. [46–48] employed a concurrent multiscale method for the investigation of copper thin films, and developed a novel multiscale numerical technique for coupling atomic and continuum domains.

Some of the more subtle aspects of mechanical responses of microtubules cannot be fully explored by experimental tests due to the difficulties with manipulation and measurement. Hence, numerical simulations are the only way of predicting the mechanical responses of microtubules under arbitrary deformation states and complex loading conditions. One of the most remarkable continuum numerical methods involves constructing a finite deformation continuum theory using the Cauchy–Born rule [15,16,39,40,47,49–51]. The first use of the Cauchy–Born rule at the nanoscale emerged from the quasicontinuum method for two-dimensional crystalline structures. However, subsequent progress of computational work revealed that the constitutive model based on the standard Cauchy–Born rule does not describe the bending effect or accurately represent the buckling deformation [15,16,39,40,49,50,52]. The reason is that the Cauchy–Born rule requires sufficiently homogeneous deformations of the underlying crystal. Then, various attempts have subsequently been made to modify the Cauchy–Born rule to overcome these obstacles [36,49,50,52–55]. Zhang et al. [50,53] applied a higher-order approach for the continuum modeling of elastic properties of carbon nanotubes. A higher-order Cauchy–Born rule has been adopted and successfully applied to the multi-scale simulation of buckling of single-walled carbon nanotubes [15,16,39,40]. More recently, the instability of microtubules has been investigated by lateral indentation with the tip of an atomic force microscope [56]. The structural transformation of microtubules under radial compression has also been studied experimentally, and their configuration measured indirectly for certain loading cases. Experimental data on pressure-induced buckling have been collected, and served as a valuable reference for the present work. In addition to the experimental approaches, a simple orthotropic elastic shell model has been used to study the critical pressure and buckling of microtubules under axial and radial compression [17], but the established conventional continuum model lacks nanoscale information, and thus neglects atomistic interaction. Microtubules are frequently subjected to transverse loadings, including hydrostatic pressure, uniform load and indentation along cross section. It is of great significance to understand and further explore mechanical behaviors of microtubules under transverse loadings [57,58]. To the best of our knowledge, there is still no efficient atomistic-continuum method that incorporates the interatomic energy into a three-dimensional continuum model of microtubules for transverse loading conditions. This work thus establishes an atomistic-continuum model for an organic macromolecule structure by applying the novel concept of fictitious bonds and a homogenization technique. This approach strategically relates the interatomic energy to the deformation gradient, and makes it possible to deal with macromolecular system problems by using a bridging-scales technique and highly efficient computation to study the mechanical responses of microtubules under transverse loading conditions. By using the higher-order Cauchy–Born rule, a mesh-free scheme is developed for microtubules based on the higher-order gradient continuum approach. The critical hydrostatic pressure and structure transitions under other complex loading states are then predicted by mesh-free computation, which is largely beyond the scope and capability of current experimental approaches. The effectiveness of mesh-free computation is evaluated, and the predicted responses provide valuable reference for biomechanics and other areas of bio-industries.

The remainder of this article is as follows. In Section 2, an atomistic-continuum model for microtubules is proposed. The fictitious bond concept is introduced, and the interatomic energy between the tubulin molecules in a representative unit is evaluated and compared with its continuum counterpart. In Section 3, a higher-order gradient continuum constitutive relationship that incorporates the higher-order Cauchy–Born rule is established, and the elastic modulus is predicted. A mesh-free computational scheme for microtubules is developed in Section 4, including a higher-order gradient continuum constitutive model that is capable of evaluating structural responses under arbitrary deformation states and loading conditions. In Section 5 the critical hydrostatic pressure is predicted, the effects of different implementations in mesh-free methods are evaluated, and some other numerical cases for modeling structural responses under transverse compressions are presented. The results are discussed and conclusions presented in Section 6.

2. Atomistic-continuum model

2.1. Model development

In macromolecular systems such as microtubules, the large numbers of atoms of various kinds present a huge obstacle to the establishment of a reliable atomistic-continuum model. The atomistic-continuum model for a single-walled carbon nanotube can be obtained intuitively by selecting a representative unit and equaling the continuum energy by summing the mono type atom C–C covalent bond energy in a representative unit [15,16,39–41]. How-