Microtubule Biomechanical Properties under Deformation and Vibration

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ABSTRACT

Microtubules (MT) are of great engineering importance due to their potential applications as sensors, actuators, drug delivery, and others. The MT properties/mechanics are greatly affected by their biomechanical environment and it is important to understand their biological function. Although microtubule mechanics has been extensively studied statically, very limited studies are devoted to the biomechanical properties of microtubule undergoing deformation and vibration. In this study, we investigate the biomechanical properties of the microtubule under bending deformation and free vibration using 3D finite element analysis. Results of force-deformation and vibration frequencies and mode shapes obtained from the finite element analysis are presented. The results indicate that the force-deformation characteristics vary with time/phases and become non-linear at higher time intervals. The modes of MT vibration and frequencies are in the GHz range and higher modes will involve combined bending, torsion and axial deformations. These higher modes and shapes change their deformation which might have implications for physiological and biological behavior, especially for sensing and actuation and communication to cells. The bending force-deformation characteristics and vibration modes and frequencies should help further understand the biomechanical properties of self-assembled microtubules.

1. INTRODUCTION

Microtubules (MTs) are long filamentous intracellular structures (25 nm in diameter and quite long) that are formed through a self-assembly process with tubulin dimers (α and β tubulins) as the basic building blocks. MTs are responsible for various biological functions such as cell division, organization of intracellular structure and transport, and flagellar motility [1-3]. Microtubules in living cells are frequently

subjected to bending/tension/torsion as well as vibration, and these behaviors play an important role in their biomechanical behavior. Also, individual tubulins within microtubules may exist in different states, that can change on various time scales, thus exhibiting multifunctional properties of MTs.

Microtubules, either straight or curved, exhibit anisotropic properties [4] as well as length dependent mechanical properties [5]. Also, the binding of microtubule associate proteins (MAPs) greatly affects the mechanical characteristics of MTs [6]. Due to the above combination of properties, MTs can function in many activities including maintaining the cell shape, mitosis, flagella and cilia movements, and cargo transportation [7]. Several studies [8] were published to further explain these properties observed in experiments to better understand the mechanical properties of MTs.

The mechanics of individual MTs have been extensively studied, specifically the static and molecular mechanisms [9, 10]. There has been extensive study on the vibration dynamics and fluctuations of microtubules in the quest for understanding the relation between microtubule material properties and their ability to carry out several functions in cells. Several studies related to MT vibrations have been conducted due to their importance and impact on the intra-cellular processes. Li *et al.* [11] investigated the beam-like bending vibration of microtubules using 3D models. They also investigated the electromechanical vibration of microtubules and its application to sensors [12]. The transverse vibration of MTs varies from 18.4 to 240.3 MHz under an electric field and the vibrational property changes may be due to tubulin interactions that might serve as a sensor for monitoring physiological processes. Aria and Biglari [13] used a nonlocal strain gradient model to study buckling and vibration responses of microtubules in axons and found many interesting aspects of softening and hardening at higher modes of vibration. Kucera, Havelka and Cifra [14] conducted a mini-review to analyze models of microtubule vibration dynamics and pointed out the limitations of not accurately predicting the physiological or biological behavior. Havelka *et al.* [15] also investigated the deformation pattern of vibrating microtubules based on an atomistic approach and found that anisotropy determined by bonds between tubulins greatly affects the vibration frequencies. The mechanical properties (Young's modulus) of microtubules were estimated through dynamic simulation and finite element method [16] and compared to those with existing literature. Wang, Ru and Mioduchhowski [17] developed an orthotropic shell model to investigate microtubule properties under free vibration and showed the importance of vibrational models in both longitudinal and circumferential directions.

Kim *et al.* [18] developed a finite element model of straight protofilaments and investigated the effects on their mechanical behavior under different loadings. They found that the protofilament behaves non-linearly under tension and torsion but linearly under bending. Pidaparti and Jakkam [19] investigated the mechanical properties of curved protofilaments of microtubules and found that curvature greatly affects the mechanical behavior, especially the stress-strain relationships. It is evident that from Refs. [18, 19] that both deformation and stiffness of microtubule/protofilaments greatly affect their stiffness under multiple loadings. Also, the protofilament/MT curvature influences the mechanical behavior through maximum stresses and stiffness in the MTs [19]. Due to the important role played by the tubulins and their interactions in microtubule self-assembly, it is important to further investigate their vibrational behavior.

In this study, we investigated the vibrational frequencies and mode shapes of microtubules through 3D finite element analysis. After creating the MT geometry and assigning the properties, bending deformation and free vibrational analyses were carried out. The results of force-deformation and free vibration characteristics obtained from the finite element analysis are presented and discussed.

2. COMPUTATIONAL APPROACH

A microtubule configuration consisting of a cylindrical hollow tube made up of protofilaments fused together in parallel to each other along the circumferential direction was considered in the computations. Typically, a microtubule is composed of 8 - 13 protofilaments, and it usually has an inner diameter of 15.4 nm and an outer diameter of 25 nm [20]. The length of MT can vary from tens of nanometers to hundreds of microns. We created 8 protofilaments along the circumferential direction, and each protofilament was composed of 10 spherical tubulins with α-tubulin and β-tubulin forming a dimer as shown in **Figure 1**. It
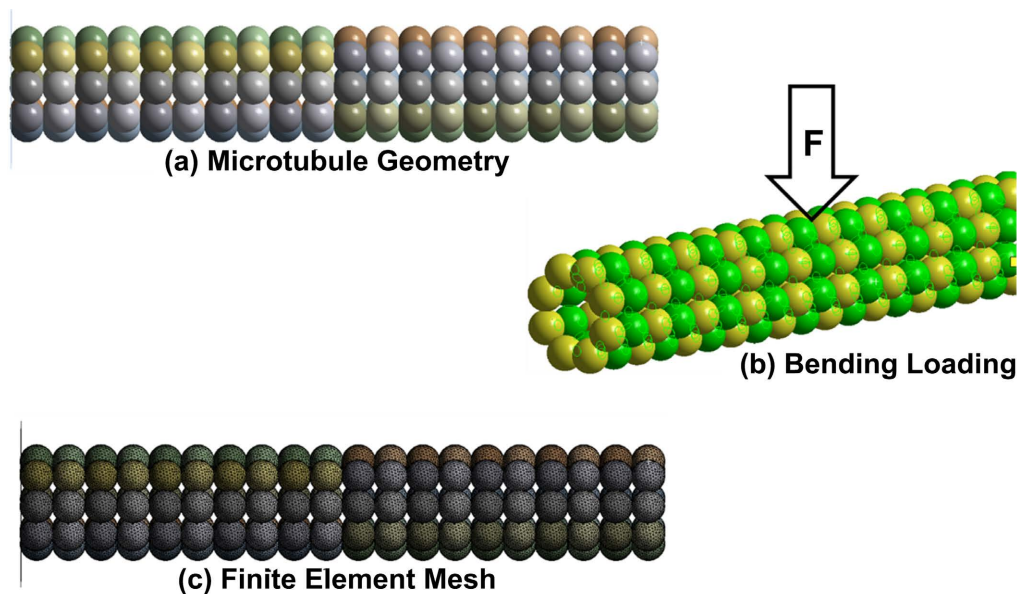
Figure 1. Microtubule considered for analysis, (a) geometry; (b) bending loading; and (c) finite element mesh.

is assumed that each tubulin is of 6 nm diameter with inner and outer microtubule diameter of 12 nm and 24 nm, respectively. The Microtubule was generated using ANSYS DesignModuler and each tubulin was connected with spring at the contact region which represents MT protein elasticity. The finite element model (FEM) of the microtubule is also shown in Figure 1.

The spring constants and material properties adopted in our study are obtained from the literature [21, 22]. The stiffness of an individual α tubulin is around 11 N/m while that of a β tubulin is around 15.6 N/m as per a molecular dynamics (MD) study [21]. The shear modulus of the spherical shell model is set to be 400 MPa [23]. α tubulins are not differentiated from β tubulins in our model due to their structural similarity and similar mechanical performance. These data are listed in Table 1.

All simulations were performed using the software ANSYS 16.0 Mechanical package. We used ANSYS workbench to develop our 3D finite element model and analyzed it under a nonlinear material condition. The computational model adopted here consists of 104,000 nodes and 103,350 shell elements. Experimental observations have shown that MTs frequently bend in living cells, with a mean curvature of about 0.4 rad/nm in fibroblast cells [24]. Hence, the bending of MT was investigated similar to the study using a nanoindentation approach [25] to estimate the bending deformations. The analysis results of force-deformation and free vibration modes are presented.

3. RESULTS AND DISCUSSION

3.1. Force-Deformation Characteristics under Bending

Finite element analysis was carried out to investigate the force-deformation characteristics and results were compared to those obtained from a nanoindentation and in-silico studies [25]. Figure 2 shows the bending deformation of the MT at four different phases (times) obtained from the finite element analysis. It can be seen that bending deformation increases with increasing time. The force-deformation characteristics at various times are shown in Figure 3. It can be seen that initially the MT is stiff and starts to become softer and non-linear with increasing deformation and time.
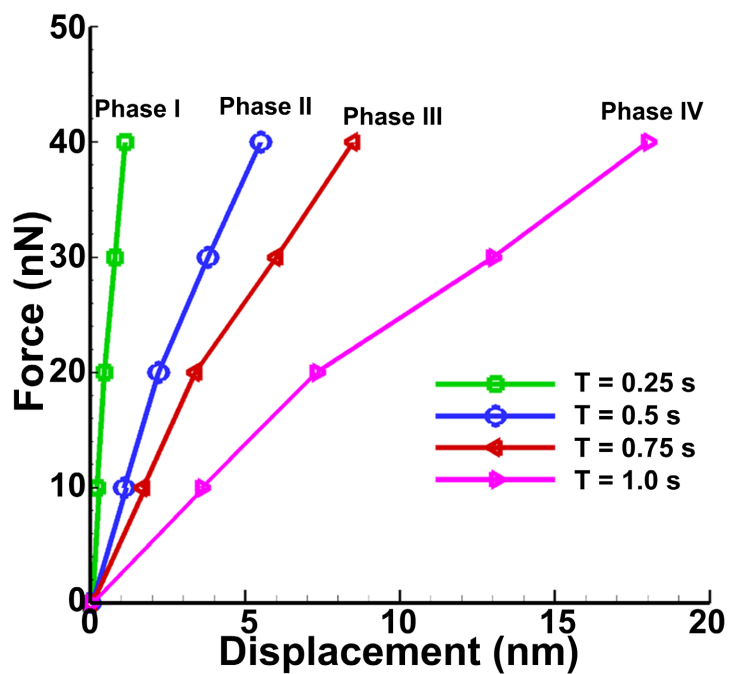
The results of maximum displacement and maximum strains at various times/phases are presented in Figure 4. It can be seen from Figure 4 that the maximum displacements and strains increase with increasing times during the bending loading on the MT. It is interesting to note that the MT bending deformation is

**Table 1.** Parameters used to construct FE model for microtubules

| Parameter [Ref]	Value
Microtubulin radius [21, 22]	12.5 nm
Microtubulin surface area	157 nm^2
Microtubulin volume	8.2 μm^3
Each contract area	3.6 nm^2
Initial shear modulus [23]	400 MPa
Microtubule spring constant [22]	47.1 nN/nm
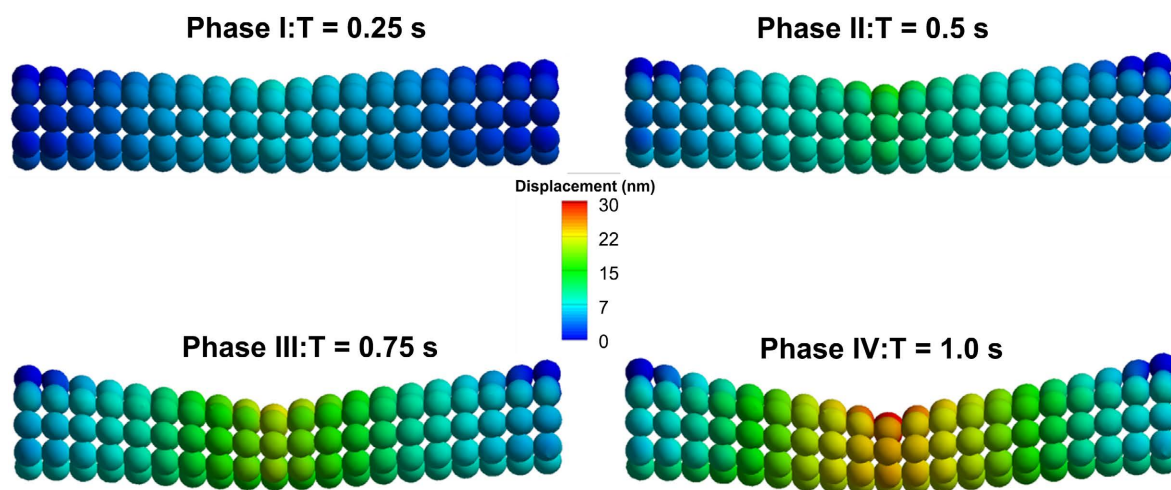
Figure 2. Microtubule bending deformation at four different times/phases.

Figure 3. Force—deformation of microtubule under bending.
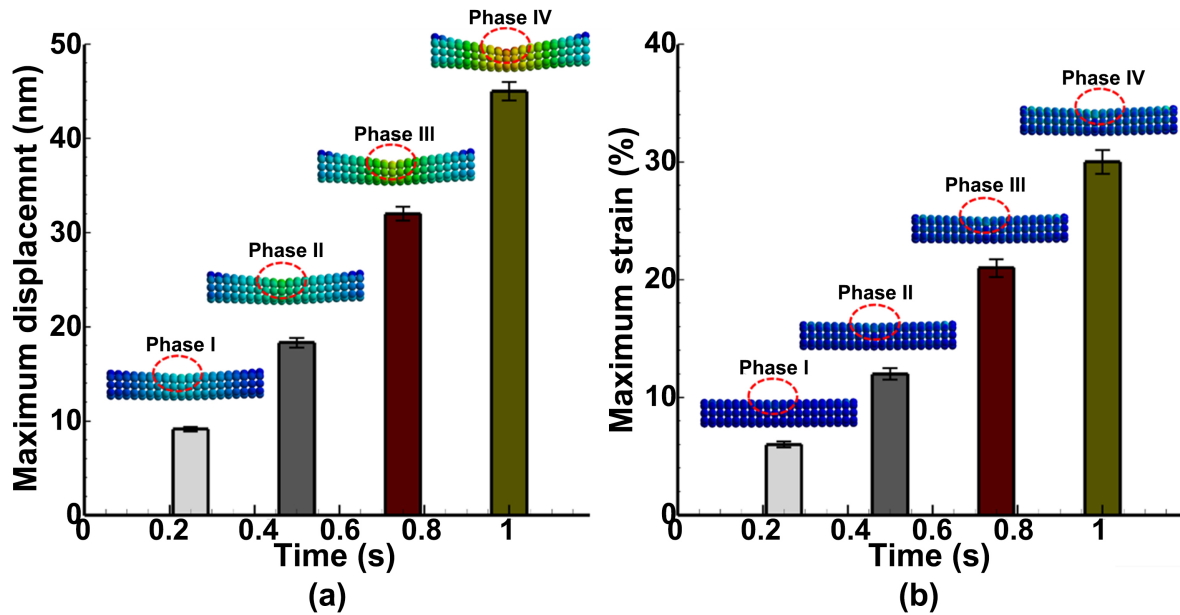
Figure 4. Maximum displacement (a) and maximum strains (b) of microtubule under bending at four different times.
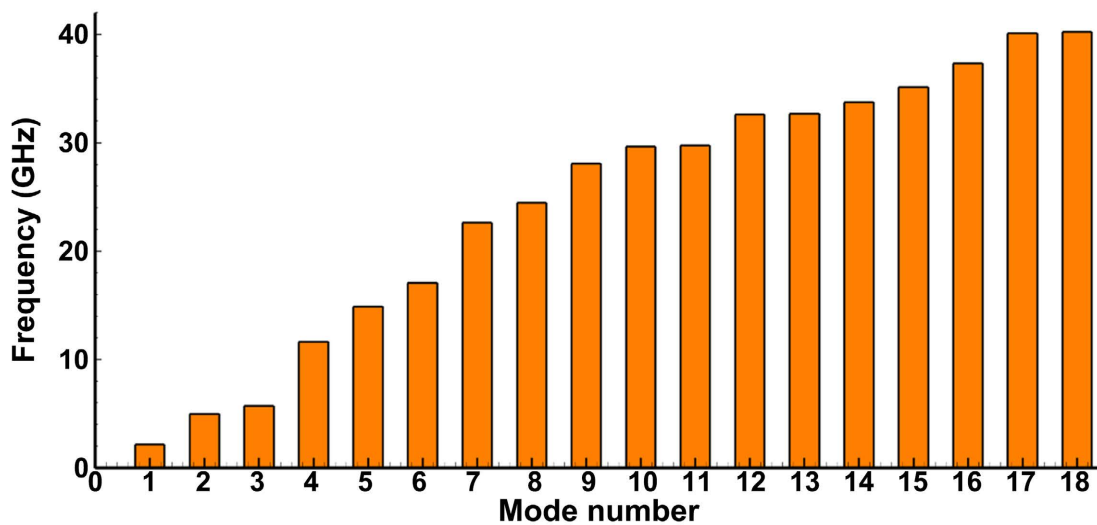
Figure 5. First 18 vibration frequencies of the microtubule obtained from the analysis.

within the range (5 - 25 nm) of those obtained from molecular dynamics simulations [25], thus validating the computational model. Also, the force-deformation characteristics vary from a linear to a non-linear fashion with different phases of bending deformation. This shows that the MT can adapt to various loading conditions through bending deformations.
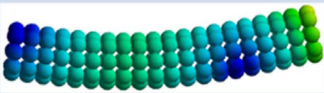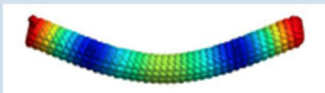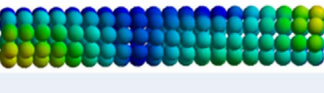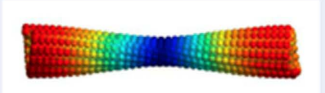
3.2. Free Vibration Characteristics
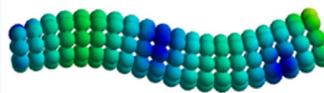
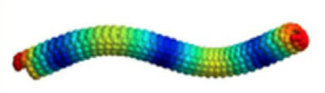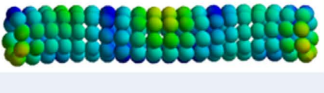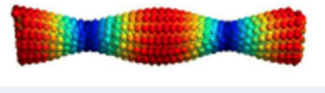The results of vibration frequencies obtained for the MT configuration from the finite element analysis are presented in **Figure 5**. The frequencies for the first 18 modes of vibration for the MT considered are in the GHz range. This finding is consistent with those obtained in previous studies [15]. The mode shapes for these 18 frequencies are presented in **Figure 6**. The primary modes include bending (mode 4), torsion

(mode 7), coupled axial and bending (mode 8) and coupled bending and torsion (mode 11). Higher modes involve combinations of higher bending, twisting and axial (modes 14, 16, 17).

It is interesting to see how the MT can accommodate multiple vibration modes and their combination. This is very important for MT function as it can serve as a multifunctional unit with shape organization, nanomaterial, sensing and actuation capabilities [7, 12]. Also, the vibration modes are compared qualitatively with those obtained from molecular dynamics simulations in Figure 7. A very good agreement is
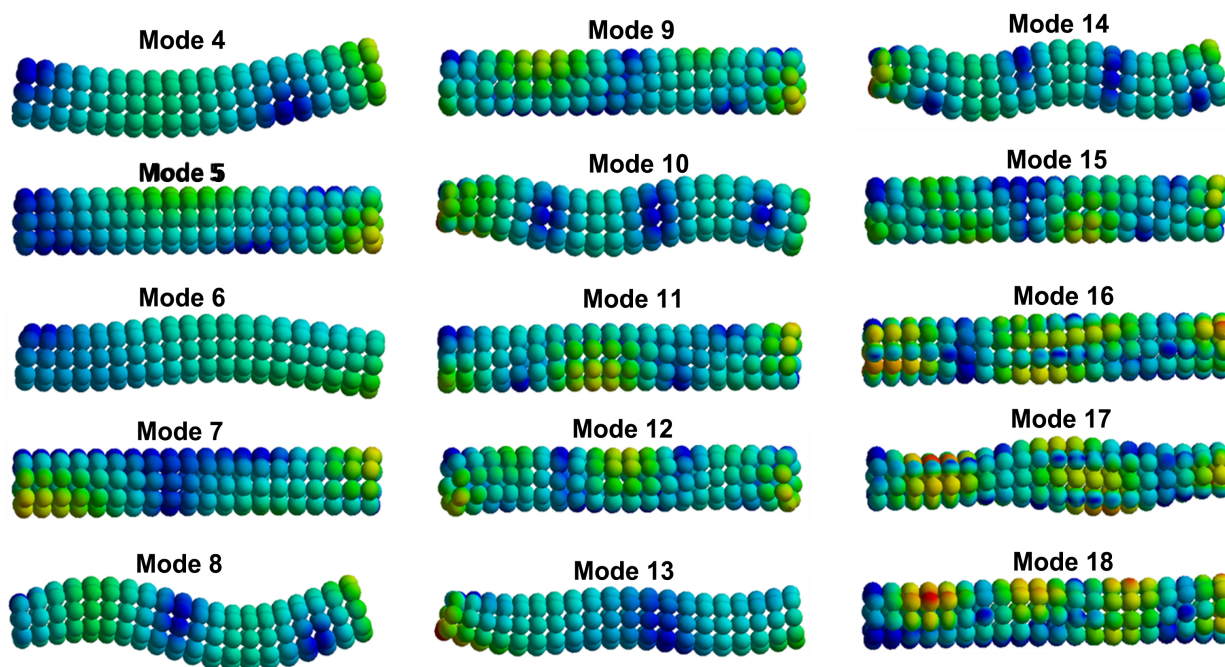
Figure 6. Mode shapes of the microtubule obtained from the analysis.

Mode of Vibration	Present Study	Reference [15]
Bending		
Torsion		
Bending & Axial Stretching		
Bending & Twisting		

Figure 7. Comparison of first few primary mode shapes of the microtubule with those obtained from molecular dynamics [15].

seen. These vibration modes reflect the deformations resulting from tubulin and their binding sites in forming the MT self-assembly [25].

4. CONCLUDING REMARKS

In this study, a 3D finite element model for microtubules based on molecular level information was adopted to perform both bending deformation and free vibration analyses. The results of bending deformation characteristics with increasing time were compared with molecular dynamics analysis results and the deformations were found to be within the range of 5 - 30 nm. The results of vibration modes and frequencies also compared well both in frequency ranges and modes of vibration. Additionally, the higher modes of vibration involved a combination of bending, axial, and torsion modes. These results further highlight the MT multifunctionality in accommodating coupled deformations, and suggest the potential for sensor and actuator applications of MT.

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CONFLICTS OF INTEREST

The authors declare that no conflict of interest regarding the publication of this paper.

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