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Boundary condition-selective length dependence of the flexural rigidity of microtubules

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ABSTRACT

Length-dependent flexural rigidity (FR) is observed experimentally for microtubules (MTs) subjected to certain boundary conditions. To shed some light on this unique feature, we have studied the FR of MTs with different boundary conditions. A molecular structural mechanics method is employed to accurately describe the real boundary conditions imposed on MTs in experiments. Some of component protofilaments of MTs are blocked at the ends while others are free. In addition, linked kinesin is treated as an elastic body rather than a rigid body. Our simulations show that for relatively long MTs having a length comparable to those measured in experiments the length-dependent rigidity is detected only for those with fixed–free and fixed–fixed ends, which is consistent with the experimental observation. To capture the physics leading to the above phenomenon, Timoshenko beam model is adopted accounting for both transverse shear effect (TSE) and imperfect boundary effect (IBE). Comparison between TSE and IBE indicates that the boundary condition-selective length-dependence achieved for the FR of relatively long MTs is primarily a result of the influence of IBE rather than TSE.

1. Introduction

Microtubules (MTs) are protein filaments that exist universally in eukaryotic cells. MTs are composed of α- and β-tubulin heterodimers [1]. These dimers attach with each other longitudinally in a head-to-tail fashion constructing a beam-like protofilament. A number of parallel protofilaments are aligned to form an elegant chiral MT structure via the lateral interaction between adjacent protofilaments. In MTs the adjacent protofilaments are shifted relatively to each other longitudinally, resulting in a helical order in the lateral direction. This unique feature is characterised by the helix-start number S. Thus, different MT types can be represented by the notation of N_S with N being the number of protofilaments included in the MT wall. According to the experimental study [2], 13_3 MTs are the most frequently observed type *in vivo*. Due to the unique molecular structures, MTs play an important role in the mechanics of the cell due to their high axial mechanical stiffness and transverse flexibility. For example, MTs are responsible for maintaining the cell structural stiffness, functioning as a track for motor proteins to transport organelles and facilitating cell division [3–5]. The mechanical properties of MTs thus become a current topic of great interest in the areas of cell mechanics and nano-biomaterials [1]. Specifically, among these properties the flexural rigidity (FR) is an important parameter for characterising bending [6–8], buckling [9–17], vibration [18–24] and wave propagation [25–28] of MTs.

In the past two decades, various experimental techniques have been employed to measure the FR of MTs, such as optical tweezers [29,30], atomic force microscope [6,31], hydrodynamic flow [32,33] and thermal fluctuations [32,34–37]. To examine the FR of an MT *in vitro*, one can fluctuate a free-standing MT through the thermal fluctuation method [36,37] or probe the MT with a direct (passive or active) force, where different constraints are enforced on the ends of the tested MTs [6,31,35,38]. Usually, the ends of MTs tested *in vitro* are covalently grafted on a microstructured substrate [6,31,35,38] (see Fig. 1a) or connected to the kinesin molecule, whose structure contains a globular head, a stalk-like central region and a globular end tail [10,39] (see Fig. 1c). Mechanics models are thus required for MTs with different end conditions to interpret the experimental data (e.g., buckling force or persistence length) and quantify the effective FR. A free-standing MT can be typically modelled as an elastic beam with free boundary conditions; an MT attached to the substrate (Fig. 1a) can normally be treated as a beam with perfectly clamped boundaries (see Fig. 1b) [6,31,35,38]; the one linked to the kinesin (Fig. 1c) is usually described as a perfect simply supported beam (see Fig. 1d) [10,39]. In

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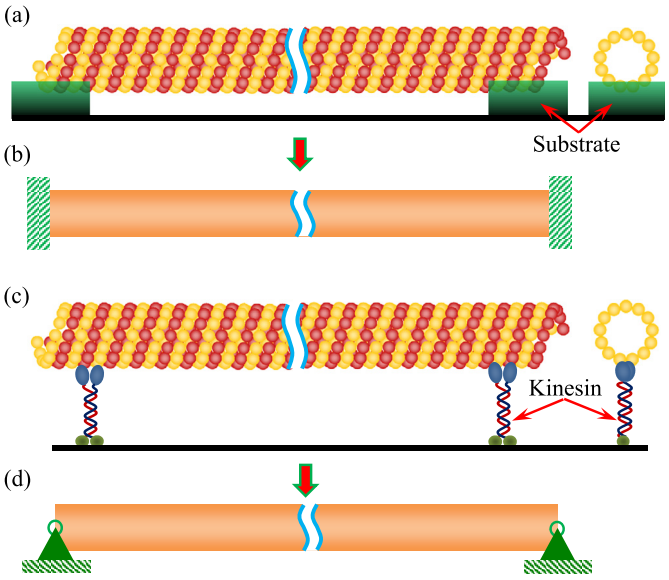

Fig. 1. (a) Atomic schematic and (b) equivalent continuum mechanics model of an MT deposited onto the surface of a substrate. (c) Atomic schematic and (d) equivalent continuum mechanics model of an MT linked to kinesin molecules.

Table 1
The boundary condition-selective length dependence of the FR of MTs measured in different experiments.

Technique	Boundary conditions	Length dependence
Thermal fluctuation [35]; Laser trapping technique [38]	Fixed–free	Yes
Atomic force microscope [6,31]	Fixed–fixed	Yes
Temperature pulse microscopy [10]	Pinned–pinned	No
Thermal fluctuation [36,37]	Free–free	No

Table 1 we have summarized the FR of MTs measured by different experimental methods. From Table 1 some experiments reported the length-dependent FR, while others claimed the constant FR independent with the contour length. Moreover, the achieved length dependence of the FR seems to be sensitive to the boundary conditions of MTs. For instance, the length-dependent FR is found for fixed–free and fixed–fixed ends, while the constant FR is achieved for pinned–pinned and free–free boundary conditions. This observation infers a possible correlation between the boundary conditions and the length-dependent FR. Motivated by this idea, we are interested in further examining the issue in detail and capturing the physical origin of the experimentally observed length dependence of the FR. In the literature, there are three theories proposed to explain the length dependence of the FR of MTs: (1) the effect of transverse shear deformation proposed for short beams in Timoshenko beam theory [6,20,31,35], (2) the effect of the imperfect constrains at MTs' ends (imperfect boundary conditions) [18,40], and (3) the nonlocal effect [8,13–15,25,27]. According to our recent analyses [41,42] the nonlocal effect actually has no effect on the mechanics of relatively long MTs. Thus the former two effects would be responsible for the length-dependent FR. It thus becomes essential in the present study to identify the key factor that controls the length dependence of the FR.

In this paper, the FR of MTs whose ends are free or attached to the substrate or linked to kinesin molecules has been studied based on the molecular structural mechanics (MSM)-based vibration analysis. The concept of the MSM method originates from the observation of geometric similarities between the coarse-grained molecular dynamics (MD) model of MTs and macroscopic space frame structures [18,41,42]. As the MSM model ignores the thermal vibration of the atoms, it can economise the computational cost. In the meantime, this technique still retains the ability to account for the effect of the molecular structures on the mechanical responses of biomaterials. In the present MSM study the length dependence of the FR of MTs is found to be significantly boundary condition-selective, which is similar to the experimental observation. This phenomenon however cannot be explained by the conventional Timoshenko beam model considering the transverse shear effect (TSE) only. The general boundary conditions is then adopted for Timoshenko beam model, which enables one to quantify both TSE and the imperfect boundary effect (IBE) on the FR.

2. MSM model for the vibrations of MTs

MSM method [18,41,42] will be employed in the present study for the vibration analysis of MTs. The robustness and efficiency of this technique have been demonstrated in modelling the static deformation (tension, torsion and bending) [41], the elastic buckling [42] and the free vibration of MTs [18]. The calculated results of Young's modulus, shear modulus, bending stiffness and critical buckling force of MTs are in good agreement with available simulation and experiment results [41,42]. In this work, the MSM method will be extended to the vibration of MTs whose ends attached to the substrate or linked to kinesin molecules.

2.1. A brief review of MSM method for MTs

In the MSM method, the interactions between two neighbouring constitutive monomers (i.e., $\alpha\beta$ bond along the protofilament direction and $\alpha\alpha$ or $\beta\beta$ bond along the helical direction) are simulated as equivalent structural beams with circular cross-sections [41]. According to the theory of structural mechanics, only three stiffness parameters, i.e., the extensional stiffness E_bA_b, the bending stiffness E_bI_b, and the torsional stiffness G_bJ_b, need to be determined for the analysis of the deformation of the MSM model. Here, E_b and G_b are, respectively, Young's modulus and shear modulus of the beam; A_b, I_b and J_b are, respectively, the area, the moment of inertia and the polar inertia of the beam cross-section. Based on the energy equivalence between local potential energies in computational chemistry and elemental strain energies in structural mechanics, the extensional stiffness, the bending stiffness and the torsional stiffness for an equivalent beam can be determined from force field constants in molecular mechanics via the following equations $E_bA_b = k_rl$, $E_bI_b = k_\phi l$ and $G_bJ_b = k_\tau l$. Here, k_r, k_ϕ and k_τ are the force constants for bond stretching, bond angle bending and bond torsion, respectively; l is the length of the equivalent beam. The values of these constants are different for $\alpha\beta$ along the protofilament direction and $\alpha\alpha$ or $\beta\beta$ bond along the helical direction and can be taken from Ref. [43]. These parameter values have been proven to be accurate through a series of MD simulations and MSM simulations on the mechanical behaviours of MTs [18, 41–43]. In addition, the mass of each (α or β) tubulin monomer m_t is taken as 55 kDa [44] and acts at the mass centre of the monomer.

After applying the above equivalent beam model to all the tubulin–tubulin bonds we will finally turn an MT into a space-frame structure, where the overall mass matrices $\mathbf{M}$ and stiffness matrices $\mathbf{K}$ of the MSM model are generated based on the mass and stiffness of the individual equivalent beams. The equation of motion of the MT can then be written as $\mathbf{M}\ddot{\mathbf{x}} + \mathbf{K}\mathbf{x} = \mathbf{0}$, where $\ddot{\mathbf{x}}$ is the second time derivative of the displacement $\mathbf{x}$, i.e., the acceleration. This equation of motion further gives the eigenequation as $(\mathbf{K} - \omega^2\mathbf{M})\mathbf{x} = \mathbf{0}$, where ω is the angular natural frequency. The frequency of an MT can be obtained by solving this eigenvalue problem. The calculation was implemented via the block Lanczos algorithm [18,45].