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Effects of the cross-linkers on the buckling of microtubules in cells

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ABSTRACT

In cells, the protein cross-linkers lead to a distinct buckling behavior of microtubules (MTs) different from the buckling of individual MTs. This paper thus aims to examine this issue via the molecular structural mechanics (MSM) simulations. The transition of buckling responses was captured as the two-dimensional-linkers were replaced by the three-dimensional (3D) ones. Then, the effects of the radial orientation and the axial density of the 3D-linkers were examined, showing that more uniform distribution of the radial orientation leads to the higher critical load with 3D buckling modes, while the inhomogeneity of the axial density results in the localized buckling patterns. The results demonstrated the important role of the cross-linker in regulating MT stiffness, revealed the physics of the experimentally observed localized buckling and these results will pave the way to a new multi-component mechanics model for whole cells.

1. Introduction

Microtubules (MTs) are long protein polymer (Daneshmand et al., 2011), which maintain the cell stiffness/shapes, provide tracks for intracellular motility and facilitate other physiological processes (Howard and Hyman, 2003; Volokh et al., 2000). As MTs withstand compression in cells, buckling occurs for MTs (Brangwynne et al., 2006) and has attracted considerable attention from the community of cell mechanics (Bicek et al., 2009; Brangwynne et al., 2006; Heidemann et al., 1999; Sanchez et al., 2012).

The elastic beam models were employed to organize the experimental data (Felgner et al., 1996; Gittes et al., 1996; Kawaguchi et al., 2008; Takasone et al., 2002) and they provide an insight into the MT buckling (Brangwynne et al., 2006). The beam-like buckling was also reported for MTs in (Gao and Lei, 2009; Li, 2008). In 2006, an orthotropic shell model was proposed for MTs (Wang et al., 2006), and used in the analyses of MT buckling (Shen, 2010; Yi et al., 2008). Here, one of the observations is that MTs *in vivo* possess a critical buckling force (F_{cr}) higher than those *in vitro*. Attempts were then made to understand this in terms of the environmental effects, where cytoplasm of cells was simplified as an elastic media (Jiang and Zhang, 2008; Li, 2008). Years later, a one-dimension (1D) finite element (FE) model was developed (Jin and Ru, 2013) where the cytoskeleton components around MTs were treated as discrete cross-linkers. This work provides the guidance to examine the role of the discrete cross-linkers in MT buckling (Hirokawa, 1982; Rodriguez et al., 2003) and offers a pathway to more realistic delineation of MT buckling *in vivo*.

Motivated by this study the present work is devoted to further studying localized MT buckling by using a three dimensional (3D) molecular structural mechanics (MSM) model (Zhang and Meguid, 2014; Zhang and Wang, 2014). The major issue examined is the effect of the spatial, random and inhomogeneous distributions of the proteinaceous linkers. Herein, the MSM and buckling realization were introduced in Section 2 followed by the validation of the model. The obtained results and discussions were given in Section 3, and the conclusions were drawn in Section 4.

2. Model development and validation

2.1. Model development

In this study, we considered 13–3 ($N = 13$ $S = 3$) MT of the most common configuration in *in vivo* situation (Chretien and Fuller, 2000; Chretien and Wade, 1991). As shown in Fig. 1, the space structure of MT was modeled as a framed MSM model, with the intra-PF bonds and inter-PF bonds modeled as elastic beams. The details of the MSM model for MT buckling simulation were explained in the supplementary material. The structure of the cross-linkers system supporting MTs laterally was depicted in Fig. 1. All cross-linkers were modeled as springs with one end attached to the MT and the other end fixed to the surrounding media. The spring constant k was taken as 39 pN/nm (Peter and

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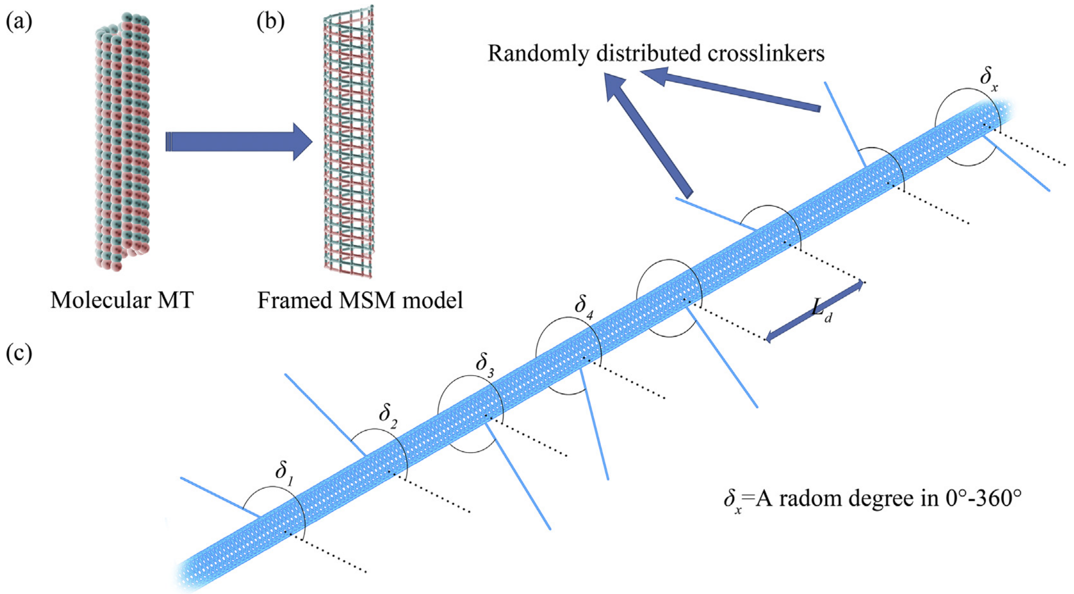

Fig. 1. (a) Structural representation of an MT, (b) the MSM model and (c) the structure of the cross-linker system supporting MTs.

Mofrad, 2012) and the spatial density of the linkers was defined by the distance $L_d = 100$ nm between the adjacent linkers for MT of length $L = 5$ µm. As the cross-linkers took axial tensile load with negligible compression (Bathe et al., 2008; Mehrbod and Mofrad, 2011), the spring modulus was set to be zero in compression. Herein, one MT end is clamped and the other is constrained by a roller. An axial compressive force was then applied to this roller end.

As shown in Fig. 1, a reference direction was picked up in the radial direction of an MT (dotted line) and the orientation of a radial linker was specified by measuring its angle δ_x relative to the reference direction. The three-dimensional (3D) cross-linkers were then achieved by generating the linkers with δ_x randomly selected between 0° and 360° (anticlockwise positive). It is thus should be pointed out that, for 'MT-cross linker' systems considered in Sections 3.1 and 3.2, L_d, L and k remain the same but the randomly generated distribution of linker orientation varied from one system to another. The non-uniform linkers (Rodriguez et al., 2003) were also considered for MTs of length 10 µm in Sectio 3.3 where a part of the MT was supported by the dense-linkers ($L_d = 25$ nm) and the rest was occupied by the low-density linkers ($L_d = 200$ nm). The cross-linker spacing 25–200 nm was observed in the experiments (Hirokawa, 1982; Svitkina et al., 1996) and later on, used in theoretical studies (Jin and Ru, 2013; Peter and Mofrad, 2012). The angle of adjacent linkers is fixed at 60°.

2.2. Validation of 3D MT model

Based on the MSM model, the length-dependent critical buckling load F_{cr} was calculated for individual MTs and shown in Fig. 2 in comparison with the experimental data obtained for *in vitro* MTs (Kikumoto et al., 2006) and an excellent agreement has been achieved.

Unfortunately, due to the uncertainty in *in vivo* condition, such a direct comparison cannot be made for the MT buckling supported by the cross-linkers. In spite of this, the MSM model predicted F_{cr} of the order of 100 pN is comparable to the experimental data (Brangwynne et al., 2006) and theoretical results (Jiang and Zhang, 2008; Li, 2008). A more detailed comparison was made in Table 1 between the MSM model and the 1D-FE model accounting for the cross-linker effect (Jin and Ru, 2013). The MT length, constant density and elastic modulus of the linkers considered for the two models are exactly the same. Here, the MSM simulations considered the cross-linkers of 10 randomly generated orientation distributions. F_{cr} achieved for the MT with the clamped-roller ends fell in the range of [86.4 pN, 294.3 pN], quite close to [93 pN, 353 pN] given by the FE model for Clamped-Free and Clamped-Clamped ends. The localized mode shapes predicted by both models (Table 1) resemble those observed experimentally in Brangwynne et al. (2006). In addition, the 3D MSM model captures the unique buckling mode observed in Brangwynne et al. (2006), i.e., the 'localized buckling' at different places of MTs. The MT buckling with radial expansion was also achieved by the 3D MSM in Table 1 and Fig. 3.

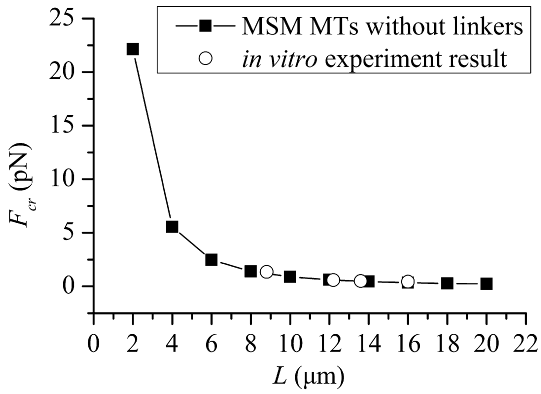

Fig. 2. The length-dependent F_{cr} calculated for individual MTs in comparison with the experimental data.

3. Results and discussions

In this section, the cross-linker model and the MSM model were employed to study the buckling of *in vivo* MTs, and examined the influence of the cross-linkers on MT buckling.

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