ANOMALOUS FLEXURAL BEHAVIORS OF MICROTUBULES

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Summary Apparent controversies exist on whether the persistence length of microtubules depends on its contour length. Here we adopt a high order orthotropic shell model to study the flexural behavior of microtubules. We derive a closed-form solution for the contour-length-dependent persistence length of microtubules, with predictions in excellent agreement with experimental measurements. By studying the ratio between their contour and persistence lengths, we find that microtubules with length around 1.5 microns show lowest flexural rigidity, while those with length around 15 microns show highest flexural rigidity. This finding provides an important theoretical basis for understanding mechanical structure of mitotic spindles during cell division. Further analysis on the buckling of microtubules indicates that the critical buckling load becomes insensitive to tube length for relatively short microtubules, in drastic contrast to the classical Euler buckling. These rich flexural behaviors of microtubules are of profound implications for many biological functions and biomimetic molecular devices.

INTRODUCTION

As one of the three major classes of cytoskeletal filaments, microtubules play essential roles in many biological functions of eukaryotic cells, such as providing mechanical strength to maintain cell shape, acting as guiding tracks for intracellular transport, and supporting the movement of chromosomes during mitosis. Most of these biological functions and even some molecular devices rely on the unique mechanical properties of microtubules which are long, hollow cylinders made of typically 13 parallel protofilaments with outer diameter around 30 nm and inner diameter 20 nm. The flexural rigidity of a slender molecular chain is usually measured by its persistence length, which is defined as the length over which the contour tangent remains strongly correlated during thermal fluctuation. In the past two decades, various experimental techniques have been employed to measure the persistence length of microtubules, such as optical tweezers, atomic force microscope and analysis of thermally driven shape fluctuations. The measured values, however, vary over orders of magnitude. Recent experiments confirmed that the longitudinal bonds of microtubules are much stronger than the lateral bonds between adjacent protofilaments. Due to these structural and material characteristics, orthotropic thin shell models have been adopted in the study of mechanical properties of microtubules. While most experimental and theoretical studies on the flexural rigidity of microtubules have focused on comparing their bending behaviors with those of a stiff wormlike chain (WLC), only a few studies have approached the problem from the perspective of bending and buckling of a cylindrical shell. Recently, by using a simplified orthotropic shell model, Gao et al. [1] derived a closed form expression for the persistence length of a microtubule that depends on not only its material property but also its geometrical structure. This study provided feasible explanations for the seemingly contradictory experimental observations on the persistence length of microtubules. However, the analysis in [1] adopted a thin shell model with a number of questionable simplifications including omitting components of internal forces and moments of order (h/R) in the equilibrium equations, where R and h are the radius and thickness of the shell, respectively. In order to overcome these limitations, here we adopt a higher order shell model to conduct a systematic investigation of the flexural behaviors of microtubules from the perspectives of bending, buckling and statistical correlations of deformation in such tubular structures.

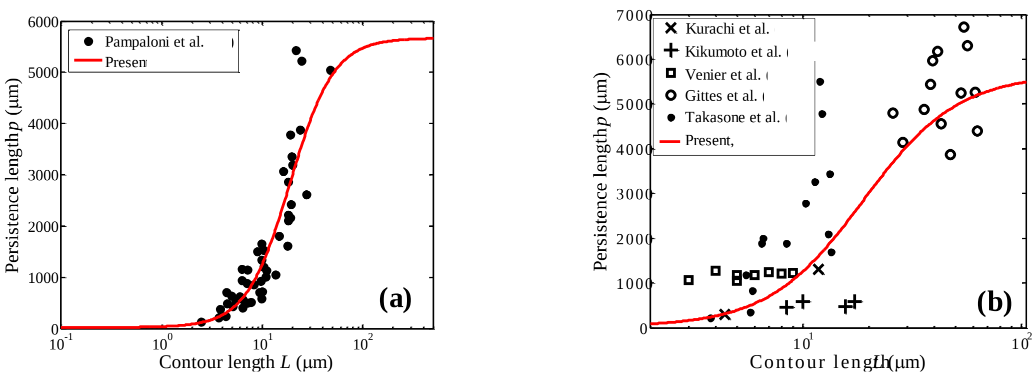

Fig.1 Comparison of the predicted persistence length with experimental measurements by (a) Pampaloni et al. and (b) others.

RESULTS AND DISCUSSIONS

We have analytically derived the persistence length of microtubules in a lengthy closed form, and investigated how the flexibility of microtubules can be influenced by their structural and material properties. Fig. 1 shows that the theoretical predictions are in reasonable agreement with experimentally measured persistence length of microtubule. It can be seen from Fig. 1a that our present predictions agree quantitatively with the most recent experimental data. However, other experimental data shown in Fig. 1b exhibit substantial scattering, which might be due to different measurement techniques or conditions. The persistence length of microtubules could be sensitive to various factors including the contour length, the shear modulus, the loading mode, the loading frequency, the boundary conditions and the orientation of the material symmetry axis.

The WLC model in polymer physics is frequently used to describe the behavior of semi-flexible polymers which may be regarded as a differentiable space curve of contour length L. Let $\mathbf{r}(s)$ be the radius vector at an arbitrary point along the WLC as a function of its contour distance s. The unit vector $\mathbf{u}(s)$ tangential to the curve at point s is given by $\mathbf{u}(s) \equiv \partial \mathbf{r} / \partial s$ with $\mathbf{u}^2 = 1$. It can be shown that the orientation correlation function for the WLC decays exponentially as $< \mathbf{u}(0) \cdot \mathbf{u}(L) >= e^{-L/p}$, where p is the persistence length of the chain. The orientation correlation coefficient in Eq. 30 as a function of the ratio L/p describes the degree of correlation between the two chain ends, which allows the statistical behavior of linear polymer chains to be categorized into three different regimes, flexible ($L/p >> 1$), semiflexible ($L/p \sim 1$), and rigid ($L/p << 1$). Fig. 2 plots the ratio L/p as a function of L for microtubules. It can be seen that there exists a maximum value of L/p when L is equal to about 1.5 μm. This means that a microtubule with length about 1.5 μm would appear to have the lowest stiffness. It is interesting that a microtubule with length around 15 microns, the typical size of a cell, has the maximum thermal flexural rigidity.

As a key organizer of cell interior, the length-dependent flexural behavior of microtubules may have important implications in many biological functions: for example, the lowest stiffness around 1.5 μm may allow microtubules to efficiently search the intracellular space, so as to precisely position cell organelles by having them firmly bound to and moving together with microtubules. The mitotic spindle in animal cells consists of overlapping microtubules forming a central spindle and two asters. The center of the spindle is a meeting point for the anti-parallel microtubules that grow from each spindle pole, whereas asters contain microtubules growing from a single pole outwards in all directions. During the cell cycle, the late anaphase (or Anaphase B, see Fig. 3) begins with the movement of spindle poles away from each other when chromatids are fully separated. The separation of sister centrosomes occurs through the following mechanisms: (a) the overlapping microtubules of the central spindle slide apart via molecular motors, with lengthening of the polar microtubules at the plus ends. In this process, the size of the microtubules involved is comparable to that of the cell, and their high stiffness should be helpful in pushing the two spindle poles apart; (b) the astral microtubules interact with cell cortex via molecular motors, which pull the spindle poles apart. These microtubules at the cell periphery are usually shorter than those in the center of the spindle and as they bear pulling forces, large stiffness seems not necessary.

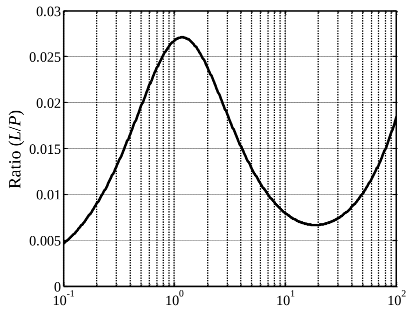

Fig. 2 The thermal flexural rigidity ratio L/p of microtubules as a function of the contour length L.

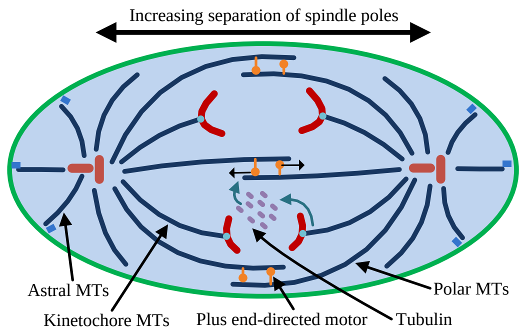

Fig. 3 Schematic representation of late anaphase stage of the cell cycle.

CONCLUSIONS

In conclusion, we have used a higher order continuum orthotropic thin shell model to study the flexural behaviors of microtubules by considering their effective bending, buckling, and the orientation correlation characteristics. Based on the proposed shell model, we have derived a more rigorous closed-form expression for the persistence length than that obtained previously by Gao et al. [1] based on a simplified shell model. In consistency with our previous analysis [1], the present more rigorous study confirms that there exists a range of tube lengths in which the persistence length of microtubules strongly depends on their contour length. It is shown that the effect of higher order load distribution modes can be strongly shielded by the lowest order load distribution mode in determining the contour-length-dependence of the persistence length of microtubules. By studying the ratio between contour and persistence lengths that characterizes the thermal flexibility of the microtubule, we have shown that microtubules with length around 1.5 micron exhibit the lowest thermal flexural rigidity, while those with length around 15 microns exhibit the maximum thermal flexural rigidity. For the buckling of microtubules, we found that there exist a range of tube lengths in which the first buckling mode is not the first wavemode of the structure, which is in drastic contrast to the classical Euler buckling of a rod. These anomalous flexural behaviors may provide a theoretical basis for understanding many biological functions that involve microtubules.

References

[1] Gao Y., Wang J., Gao H.: Persistence length of microtubules based on a continuum anisotropic shell model. *J. Comput. Theor. Nanosci.* **7**:1227-1237, 2010.