A MULTIPLE-PATCH MODEL OF MICROTUBULES

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Summary We propose a 3-dimensional coarse grain model of microtubules (MTs) and treat the tubulin monomer as a sphere of multiple patches, with parameters tuned to yield stretching/bending stiffness in the light of experimental values. The model has demonstrated the ability to reproduce the bistability of tubulin sheets, cracking and peeling of protofilaments (PFs), and tip morphology of growing MTs. We see the bistability may pay a critical role in the dynamic instability. This model is expected to take into account the structural, mechanical and kinetic aspects underlying the physical mechanism of polymerization/depolymerization of microtubules.

INTRODUCTION

Microtubules are polar linear polymers of protein tubulin heterodimers found ubiquitously in eukaryotes, usually consisting of 13 protofilaments. The length of MTs switches repeatedly and stochastically between slow growing and rapid shrinking phases both *in vivo* and *in vitro*, a dramatic nonequilibrium phenomenon called dynamic instability [1], allowing for force generation and remodeling of cytoskeleton spatial organization during mitosis or exploration of the surrounding environment. The dynamic instability roots in the molecular details of tubulin dimers, where the nucleotide state plays a central role. A single GDP-bound protofilament will naturally bend, but straightened by neighboring PFs in microtubule lattice. The pre-stressed GDP MTs is prone to disassembly at plus-end since the lateral contact is of weak electrostatic effects in contrast to the hydrophobic and polar nature of longitudinal contacts [2]. It is proposed that a layer of GTP cap or an equivalent structural cap of strong lateral contact is required to stabilize MTs, otherwise catastrophe is triggered.

Despite the substantial experimental understandings in the molecular details of tubulin, the physical mechanism underlying dynamic instability remains unclear. Various theoretical and computational models have quantified phenomenologically the stochastic growth and shrinkage in kinetic view by assuming the rate of addition and hydrolysis of tubulin [3, 4]. However, the mechanical and structural features are the crucial ingredients of dynamic instability. Several coarse-grained simulations have been devoted to understand mechanical deformation near the cap [5], force generation of shrinking MTs [6], length dependence of persistence length [7], and 3-dimensional structures of sheet-like/blunt tip and their consequence on catastrophe [8]. An important experimental observation that tubulins can first aggregate into intermediate sheets then turn over to closed tubes, igonred by most computational and theoretical models, indicate the existence of bistability in MTs [9, 10, 11].

THE MULTIPLE-PATCH MODEL

We propose a 3-dimensional multiple-patch coarse-grain model of MTs, aiming to capture the crucial role of bistability as well as the structural, mechanical and kinetic aspects. The α or β tubulin monomer is modeled as a sphere, decorated with 4 orientation-dependent patchy points on the surface (Fig. 1a). The adhesion between patches on adjacent spheres can introduce spontaneous curvatures during tubulin aggregation. The non-covalent interaction between patchy monomer *i* and *j* is described as modified Morse potential (Fig. 1)

$$V(r_{ij}) = \epsilon\{[1 - e^{-a(r_{ij}-r_0)}]^2 - 1\}e^{-b(\theta_i^2+\theta_j^2)}, \tag{1}$$

where r_{ij} and r_0 are the current and the rest center-to-center distances, θ_i and θ_j are the relative angles, a and b are the paraments related to the stiffness between monomers, and ϵ is the adhesion strength. The standard Morse potential part maintains an equilibrium distance between monomers. The exponential term enforces an orientation requirement that two patches have to align along the center-to-center line, otherwise the interaction between the two patches decays quickly (Fig. 1a). By tuning relative position of patch points, it is possible to generate a bistable microtubule with spontaneous curvatures of longitudinally outwards and laterally inwards. In addition, this simple model does not require permanent connection among monomers and therefore facilitates simulation of assembly/disassembly based on discrete tubulin dimers. From Eq. (1) one can calculate the bending and stretching stiffness of tubulin assembly, longitudinally and laterally, where parameter a determines the stretching stiffness B and parameter b for the bending stiffness B. At the limit of infinitesimal axial strain or curving, one can get

$$S = 2a^2 L\epsilon, \quad B = bL\epsilon. \tag{2}$$

where L is the rest distance between neighboring dimer-center. The relations (2) along with the interaction potential (1) allow us to determine the three parameters a, b, and ϵ using the available data of cohesive energy, stretching stiffness S and bending stiffness B from either experimental measurements or full atom molecular dynamics simulations [13].

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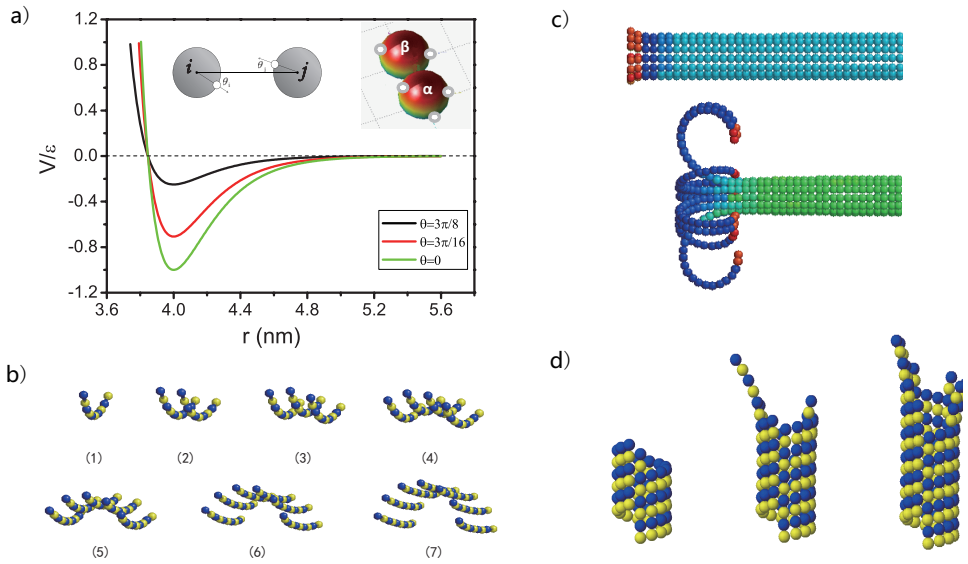

Figure 1. (a) The interaction between two patchy monomers. The white dot on the grey sphere is the patch. θ_i and θ_j are the angles between the center-to-patch line and the center-to-center line. (b) With longitudinal (upwards) and lateral (downwards) natural curvature, increasing the number of PFs causes a turn-over from longitudinal curving to lateral curving (α-tubulin is in yellow and β-tubulin is in blue). The data of spontaneous curvature are taken from the work by Nogales [12]. (c) The plus-end cracks and then PFs peel. (d) Tubulins drop randomly from above, and the tip grows (from left to right).

RESULTS

To validate our model, several simulations have been carried out via Monte-Carlo method. In all simulations, two spheres are connected permanently mimicking a stable tubulin dimer by fixing the center-to-center distance. Figure 1b shows, when the two spontaneous curvatures exist simultaneously, a tubulin sheet changes gradually from bending upwards to downwards as the number of PFs increases to a critical value, indicating a typical bistable characteristic. This bistability in tubulin sheets suggests that the irregular cylindrical PFs wall near the tip will affect the growth or shrinkage of MTs. Figure 1c depicts that cracks will nucleate at the tip of the initial straight MT due to hydrolysation, and then PFs peel outwards rapidly. Figure 1d demonstrates the tip morphology of a growing MT, when new tubulin dimers dropping from above randomly, with a given speed in hydrolyzation. We see as the addition of new dimers to the tip, originally peeled GDP PFs will straighten, or be rescued, due to the constraint from neighboring growing PFs, which root in the bistability of PF sheet.

CONCLUSIONS

In summary, we proposed a 3-dimensional patchy sphere model of MTs with multiple polarities. The parameters in the monomer-monomer interaction have been reasonably determined. We validate the patchy model via several MC simulations. We see the potentially important role of the bistability of tubulin sheets in determining the growth/shrinkage of the tip. This model is expected to be able to study structural, mechanical, as well as kinetic aspects underlying the physical mechanism during polymerization/depolymerization of MTs.

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