MECHANOCHEMICAL MODEL OF DYNAMIC MICROTUBULE GROWTH

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Summary The dynamics of microtubule growth have long been a fascinating issue, which is of crucial importance for many cell cycle processes. In this paper, we establish a mechanochemical coarse-grained model to study the growth of a microtubule, which involves a large conformation transition. The stabilizing mechanisms of microtubule growth are investigated by considering the intricate interplay between mechanics and chemistry. The energy evolution and its biological implications are analyzed.

INTRODUCTION

Microtubules have a well-marked lattice structure consisting of regularly arranged heterodimers and suffer stochastic transitions between growth and shrinkage. The dynamic and evolutionary attributes are intrinsic for microtubules. Such dynamic processes are highly coupled with nucleotide hydrolysis, which happens after the GTP-tubulins have assembled into the microtubule [1]. To consider the effect of hydrolysis on microtubule growth, the GTP cap model has been proposed [2]. It hypothesizes that the growth is stabilized by the several GTP-tubulin layers at the microtubule end. In addition, experiments revealed that an outward-curved open sheet exists at the growing end of a microtubule [3]. The growth is achieved by the sheet closure involving the change of curvature from longitudinal to lateral. This "sheet-to-tube" growth mode itself provides a stabilizing effect. This model is referred to as the conformational cap model [4].
Detailed probe lacks for the cap models and their relationship. Intrinsic coupling between mechanics and biochemistry has been demonstrated by experiments, and more comprehensive learning calls for well-defined theoretical models [5,6]. Here, we present a mechanochemical coarse-grained model to accomplish a detailed simulation of the microtubule growth process and to help apprehend the stabilizing mechanisms.

METHODS

A general model for microtubule structure and mechanics

We build a standard microtubule model consisting of 13 protofilaments and with a 3-monomer helical pitch. On the open sheet structure at the growing end, the protofilaments are not only bending but also twisting. The precise configuration is complicated and needs to be determined via computations. The monomers are treated as mass points and their interactions are defined according to the relative locomotion of adjacent monomers.
Seven interactions are defined in our model, i.e., the longitudinal, lateral, and diagonal tensile or compressive interactions, the longitudinal and lateral bending interactions, as well as the longitudinal and lateral dihedral angle interactions. A quadratic dependence of each interaction on the corresponding deformation is assumed. Figure 1 depicts our model and shows the interaction definitions. The free energy of tubulin association is also incorporated.

Basic algorithm

In every step, the interaction energies are computed for all the monomers according to their positions. The spatial gradient of the potential energy is then computed, giving the force exerted on each monomer. According to Newton's second law, the velocity and acceleration are then obtained, and a new position for each monomer is determined, based on which the above calculation process can be repeated. For a given event, the iterative computations of positions are continued until the total potential energy becomes stable. Then, a new event is allowed to occur, and the resultant conformation and energy changes are calculated in the same way. Thus a continuous dynamic process can be simulated.

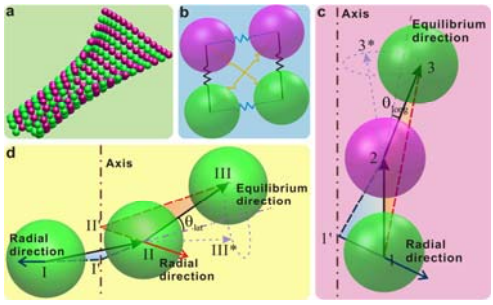

Fig. 1. Coarse-grained calculation model of a microtubule

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RESULTS

A sheet structure is stable at the microtubule ends

Based on the defined interactions, we calculate the equilibrium conformation of a sheet-ended microtubule. The sheets of different shapes and lengths are treated. The equilibrium conformations and potential energy distributions are shown in Fig. 2. The results demonstrate that a microtubule with a sheet at the end can be in equilibrium. The open sheet holds a much lower level of potential energy than the closed tubular part, and is thus more stable.

The sheet-to-tube process helps accumulate energy in the microtubule lattice

We simulate the microtubule closure process and analyse the variation of the potential energy. Figure 3 shows the results. The sheet-to-tube transition can be simulated well. The closure is demonstrated to propel steadily, with identical energy barrier and energy difference between two subsequent equilibrium states. For each closure of a single monomer pair, activation energy is called for. The energy stepping after the zipping of one monomer pair and the involution into stable shows that the conformation change in the growth process contributes to the energy stored in microtubule lattice.

The microtubule growth plays Tetris

In view of the aforementioned results that the open sheet structure stabilizes the microtubule growth and the statement in literature that the total closure of the sheet into tube will trigger depolymerization[7], we propose that a stable growth should rest on the harmonization between closure and polymerization, which results in a self-similar propagation of the closure. Thereby, a Tetris-like growing style is extrapolated for the compatibility of assembly and closure during the microtubule growth. Tubulin dimers assemble stochastically at the microtubule end under the regulation of energy. When the newly added tubulins have formed a complete layer, the bottom layer at the sheet will transit to close and the seam will advance a dimer-length. Figure 4 shows some snapshots of the “fill in–close up” process.

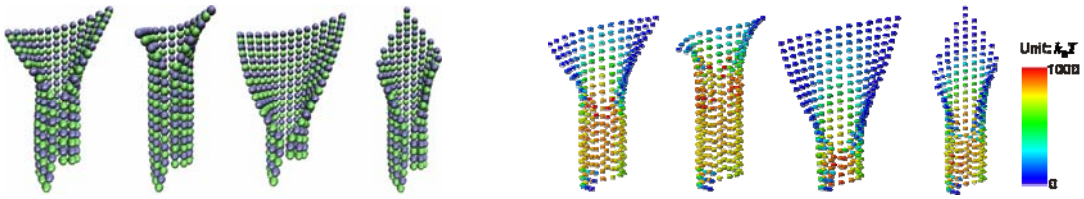

Fig. 2. Equilibrium conformations of sheet-ended microtubules (left) and the potential energy distributions (right).

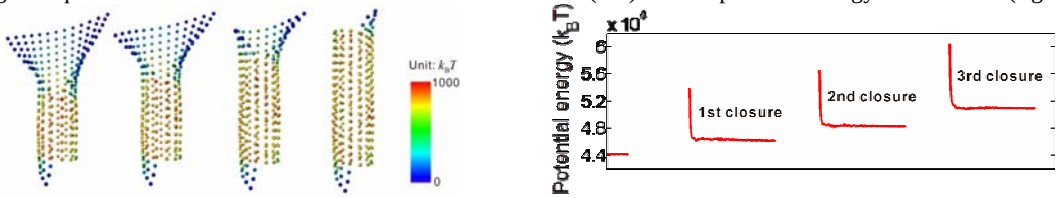

Fig. 3. Snapshots of the closure process (left) and the energy evolution during a closure of a three-monomer length (right)

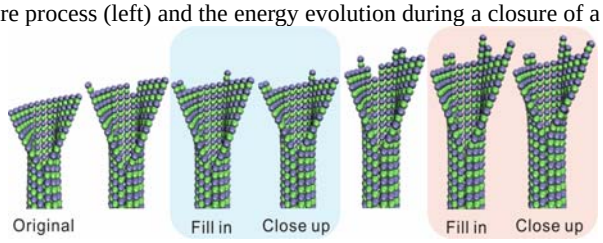

Fig. 4. Harmonized tubulin assembly and sheet closure during microtubule growth

CONCLUSIONS

In this paper, a mechanochemical model representing the microtubule growth dynamics is established. Using this model, we study the equilibrium conformation of a sheet-ended microtubule and the microtubule growth involving a sheet-to-tube transition. The sheet structure is found energetically stable and can help stabilize the microtubule growth.

References

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