An Algorithm for stable Microtubule Curvature Conformation

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ABSTRACT

Self-assembly is a ubiquitous, naturally occurring, robust process in many living organisms. Microtubule, a self-organization system assembles itself into functional units by attaching to cellular structures. Modeling microtubule self-organization is of interest as microtubule forms a network of protein filaments that is critical to many processes in eukaryotic cells. In this paper, we developed a modeling algorithm starting from alpha and beta tubulins as basic building block in the self-organization of microtubule. The developed algorithm and the necessary steps are described in detail. The preliminary results obtained from the model demonstrate that a stable self-organization conformation is possible for a microtubule.

General Terms

Algorithms, Measurement, Performance, Design.

Keywords

Self-organization, microtubule, stable conformations.

INTRODUCTION

Molecular self-assembly [1] is defined as the spontaneous organization of molecules, typically repeated protein subunits, under thermodynamic equilibrium into structurally well-defined and rather stable arrangements. Biological self-assembly systems include actin and tubulin filaments, which form a network of protein filaments called the cytoskeleton that is critical to many processes in eukaryotic cells.

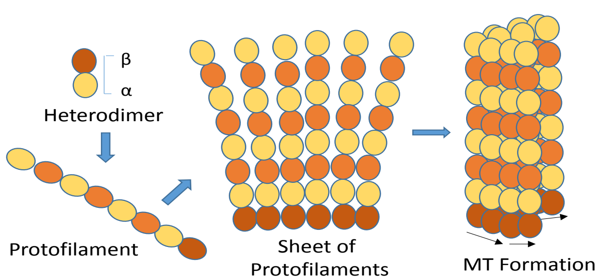

Fig. 1: Gradual formation of MT from heterodimer.

One such network formed from tubulin filaments is microtubule. Microtubules (MT) form a framework for structures such as the spindle apparatus that appears during cell division, and are responsible for various kinds of movements, cell division, intracellular structure organization and transport. The basic building blocks of MTs are "tubulin monomers" (α and β tubulins) with slightly different properties. Both α and β tubulins spontaneously bind one another through polymerization to form a functional subunit named "heterodimer". In Fig. 1 (an adapted figure developed from [1]) a gradual formation of an MT from heterodimer is shown. These heterodimers assemble themselves into linear "protofilaments" under controlled intracellular conditions that in turn assemble into MTs [1]. Certain conformations of heterodimers are allowed to contribute to MT self-assembly ([5]). Among other related works [6], [7] describe a self-assembly model guided by dynamic assembly of mitotic spindle and justify the apparent stability in the final formation of MT as "out-of-equilibrium stochastic interactions" between tubulins at the molecular level. Another related work [8] describes a mechanochemical stochastic model to describe gradual MT formation from an open sheet to a closed tube. This model is shown to be regulated by energy distribution within the MT. In one of the previous work ([9]) a variation of the current work was investigated where compactness factors were initialized randomly from a distribution without considering local geometric change between neighboring tubulins.

In order to investigate MT self-assembly, we developed a modeling algorithm starting from alpha and beta tubulins. The current model considers tubulins as basic building block in the self-organization of MT instead of dimers. In this paper, the modeling algorithm and the resulting patterns of self-organization obtained are presented and discussed in terms of the relative angular displacement tubulins may have in a finally formed MT. The algorithm considers a compactness factor resulting from geometry dependent force field within an MT to optimize initial angular distribution into an admissible final conformation.

SELF-ORGANIZATION APPROACH

An MT consists of basic building units, i.e. alpha and beta tubulins. Alpha and beta tubulins combine to form a structure referred to as dimers. Dimers have been considered as the basic building block in the formation of MT in some related works such as [1], [2] etc. In order to avoid unnecessary complications the algorithm described in this paper generates a MT structure from alpha and beta tubulins without loss of generality i.e. in this work tubulins instead of

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dimers are considered as basic building block in the final MT. This is particularly advantageous since one tubulin can be considered alone without accounting for the α-β dimer interactions and resulting dimer conformations. This consideration adds flexibility to the proposed model as we can apply finer geometric attributes in the model at molecular level. However, the alternating occurrences of alpha and beta tubulins are maintained in the final MT to make the structure biologically valid.

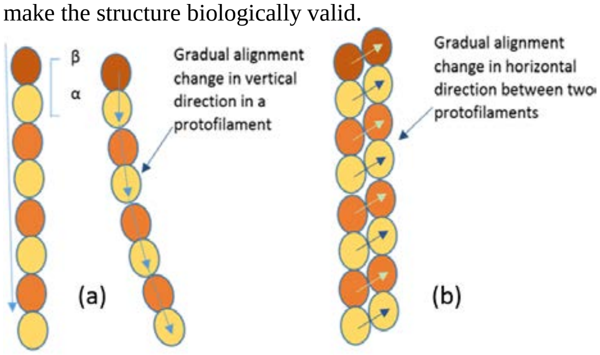

Fig. 2: (a) Formation of MT from heterodimer. (b) Longitudinal and lateral angular dispersion between neighboring tubulin.

In this approach an MT would be represented by a grid data structure that would contain all the physical and geometric parameters that would be utilized to faithfully render the corresponding 3-D structure for MT.

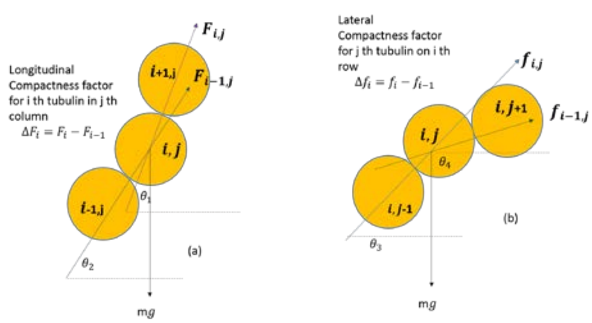

Fig. 3: Angular dependence on force driven compactness factors for (a) (i,j)th tubulin on the jth column (b) (i,j)th tubulin of ith row.

In this model we observe two types of geometric parameters that control the 3-D conformation of a dimer and hence an MT. In a MT protofilament, the dimers can have longitudinal relative angular displacement from each other, whereas the protofilaments in a microtubule themselves can have relative lateral angular displacement that gives the MT a helix like pattern. These two angular displacement (inter-protofilament and between lateral tubulin neighbors) are shown in Fig. 2.

COMPUTATIONAL MODEL

From figures of a formed MT in [1] it is evident that an alpha or beta tubulin of a MT has four sites where it can attach itself to its neighboring tubulins. These four places of one tubulin would be characterized by binding factors shared by its four neighbors. This binding force can be modeled from Newtonian force equations as shown in Fig. 3. The computational model described in this paper uses a grid structure. Within this 2-D grid (a 2-D array) the possible forces acting on a tubulin at the (i,j)th position are shown in Fig. 3. The inter-protofilament forces are shown in Fig. 3(a) whereas Fig. 3(b) models the lateral binding forces between (i,j)th tubulin and its lateral neighbors. Though individually these models represent planar force interaction model, together they provide a 3-D tubulin force model that is exploited by the proposed algorithm to help form a compact 3-D MT. The vertical inter-protofilament angles θ_1, θ_2 and lateral angular displacements θ_3, θ_4 affect the binding factors as shown by the force lines in the figure.

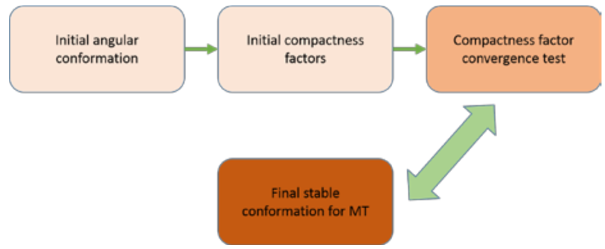

Fig. 4: Control flow within computational model

These four angles used in the current model are being initially drawn from the following normal distribution.

$$X \sim N(\mu, \sigma);\ \mu = 25;\ \sigma = 18.75; \qquad (1)$$

The random distribution is characterized by the mean μ and standard deviation σ. The algorithm considers resolution of 0.1 in stickiness factors i.e. the normal distribution sample size is ≈ 1510. From (1) above it is evident that the distribution allows negative "stickiness" factors. The negative angle values drawn from the distribution make the angular displacement between neighboring tubulin obtuse and thus produce a very divergent scenario for the algorithm to optimize.

In the model the final MT is represented as a 2-D array $M_{a\times b}$ where each element $M_{ij} \in M$ is an array of dimension 1×4. An arbitrary element M_{ij} in i^{th} row and j^{th} column is described as follows:

$$M_{ij} = [\theta_{ij}^{h1}\ \theta_{ij}^{h2}\ \theta_{ij}^{v1}\ \theta_{ij}^{v2}] \qquad (2)$$

Where θ_{ij}^{h1} and θ_{ij}^{h2} are the lateral angular displacement of tubulin M_{ij} and θ_{ij}^{v1} and θ_{ij}^{v2} are longitudinal counterpart of tubulin M_{ij}.

Fig. 4 briefly highlights control flow of the computational model. From the initial angular distribution the MT self-organization model utilize the force imbalance within longitudinal and lateral direction of the MT to formulate two compactness criteria. Iteratively the model minimizes the compactness error. Upon termination the angular distribution throughout MT represents a stable configuration for finally formed MT.

The compactness factors are important aspect of the model and can be formulated using the force imbalance shown in Fig. 3 as follows. Let's suppose the length of the entire MT is represented by grid $M_{a\times b}$ of size $a \times b$. Then we can formulate longitudinal (*CFL*) and lateral (*CFH*) compactness factors as follows.

$$CFL = \frac{\sum_{(i,j)\in M}(F_{i+1,j} - F_{i,j})^2}{|M|}$$

and (3)

$$CFH = \frac{\sum_{(i,j)\in M}(f_{i,j+1} - f_{i,j})^2}{|M|}$$

In (3) above $|M|$ represent the size of the matrix, i.e. $|M| = ab$. Conceptually, these factors represent a force imbalance average energy for the entire MT since the term is calculated as mean of squared differences of lateral and longitudinal force acting between neighboring tubulins. The model presented here finds stable configuration of final MT by minimizing both the compactness factors within an error tolerance band. We now present the algorithm SCM in the following section.

MODEL IMPLEMENTATION

We now formally represent the following algorithm **SCM** (Stable Conformation of MT) which takes into account the aforementioned parameters.

SCM:

*Input***:** Length of final MT L; Width of final MT W;

Output: The final MT stable conformation represented in array *M*.

Steps:

1. Calculate number rows a of M as $a \leftarrow \left\lceil \frac{L}{d} \right\rceil$; Here d is the diameter of one tubulin.
2. Calculate number columns b of M as $b \leftarrow \left\lceil \frac{W}{d} \right\rceil$;
   // Assign initial angular distribution that would be
   // used to compactness as shown in fig. 1.
3. For i = 1: a
   For j = 1: b
   $\theta_{ij}^{h1} \leftarrow r \in X$ from distribution (1);
   $\theta_{ij}^{h2} \leftarrow r \in X$ from distribution (1);
   $\theta_{ij}^{v1} \leftarrow r \in X$ from distribution (1);
   $\theta_{ij}^{v2} \leftarrow r \in X$ from distribution (1);
   End
   End
4. Calculate longitudinal compactness factor
   $CFL \leftarrow \sqrt{\sum_{i=1}^{a-1}\sum_{j=1}^{b}(\boldsymbol{F_{i+1,j}} - \boldsymbol{F_{i,j}})^2/(ab)}$;
5. Calculate lateral compactness factor
   $CFH \leftarrow \sqrt{\sum_{i=1}^{a}\sum_{j=1}^{b-1}(\boldsymbol{f_{i,j+1}} - \boldsymbol{f_{i,j}})^2/(ab)}$;
6. Post-processing step:
   $\delta \leftarrow 0.1$; // Factor controlling rate of convergence.

   1. Repeat until both
      $(CFL < error)$ and $(CFH < error)$

      a. For i = 1: a-1
      //Calculate the longitudinal compactness
      // for local tubulin
      $CF_{ij} \leftarrow F_{i+1,j} - F_{i,j}$
      // Add or subtract corrective term when
      // CF_{ij} is more than error tolerance term
      // and positive or negative, respectively.
      $F_{i+1,j} \leftarrow F_{i+1,j} \pm \delta(|CF_{ij}| - CFL)$
      $F_{i,j} \leftarrow F_{i,j} \pm \delta(|CF_{ij}| - CFL)$

      b. For i = 1: a
      For j = 1: b-1
      //Calculate the lateral compactness
      // for local tubulin
      $CH_{ij} \leftarrow f_{i,j+1} - f_{i,j}$
      // Add or subtract corrective term when
      // CF_{ij} is more than error tolerance term
      // and positive or negative, respectively.
      $f_{i,j+1} \leftarrow f_{i,j+1} \pm \delta(|CH_{ij}| - CFH)$
      $f_{i,j} \leftarrow f_{i,j} \pm \delta(|CH_{ij}| - CFH)$

      c. // Calculate new *CFL* and *CFH*.
      $CFL \leftarrow \sqrt{\sum_{i=1}^{a-1}\sum_{j=1}^{b}(\boldsymbol{F_{i+1,j}} - \boldsymbol{F_{i,j}})^2/(ab)}$;
      $CFH \leftarrow \sqrt{\sum_{i=1}^{a}\sum_{j=1}^{b-1}(\boldsymbol{f_{i,j+1}} - \boldsymbol{f_{i,j}})^2/(ab)}$;

7. Repeat step 6.1 until convergence.

Here we give a brief description of the algorithm. The algorithm, first calculate the dimension of the grid representing MT *M* in step 1 and 2. After random assignment of initial angular attributes in step 4 and 5 the model calculates horizontal and lateral compactness factors *CFL* and *CFH*. The localized forces F_{ij} and f_{ij} (shown in Fig. 2) can be obtained by mass of tubulin (*m* = 50,000 Dalton) and angular attributes as follows.

$$F_{ij} = mg\cos(\theta_{ij}^{h1})$$

and (4)

$$f_{ij} = mg\cos(\theta_{ij}^{v1})$$

where *g* is the gravitational parameter. It is to be noted that the angular parameters are shared between neighboring tubulins and therefore all four elements of M_{ij} are required in step 3 of algorithm even though in (4) only θ_{ij}^{h1} and θ_{ij}^{v1} are used. From step 4 and 5 it is evident that the compactness factors depends on the aggregate force imbalance throughout the MT in longitudinal and lateral direction. In step 6 the optimization depends on joint minimization of both *CFL* and *CFH*. In this step local force imbalance (CF_{ij}) for individual tubulin is calculated for longitudinal and lateral direction in step 6. a and 6. b respectively. Subsequently additional correction term is added (subtracted) from these local compactness factors depending on their distances from lateral and longitudinal compactness factors. New compactness factors are subsequently calculated and the step iterates until convergence is reached. This iterative process forces the global compactness factors to reach optimal range determined by step 6. 1. One additional factor, δ is used by the model to control the convergence rate of *CFL* and *CFH*.

RESULTS and DISCUSSION

The developed algorithm was programmed in MATLAB and/or Eclipse platform to generate the visualization from matrix *M*. Some preliminary results are presented in Figs. 5 and 6. Fig. 5 represents the final distribution of relative angular displacements of tubulins within one protofilament within MT. It can be seen from Fig. 5 that at the final angular distribution in a stable MT are gradually converging to either 0 or π radian in longitudinal direction, suggesting perfect alignment between neighboring tubulin and thus a very stable conformation. We report that this pattern is observable across the entire MT. This also represents the model's ability to generate a stable MT configuration from a random initial configuration. Fig. 6 shows the rate of convergence for both lateral and longitudinal compactness factors. The similar convergence curves for both the compactness factors suggest that the overall formulation of the compactness factors are interdependent and thus realistic, since both lateral and longitudinal structure together gives the MT a final strength in configuration.

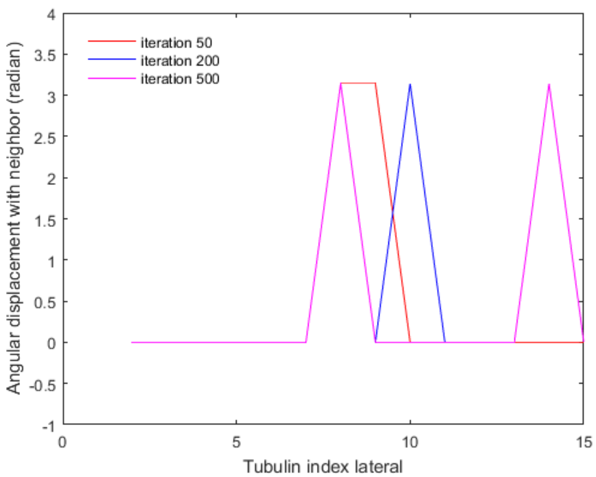

Fig. 5: Initial and final distribution of "stickiness" factor across MT shown using color codes.

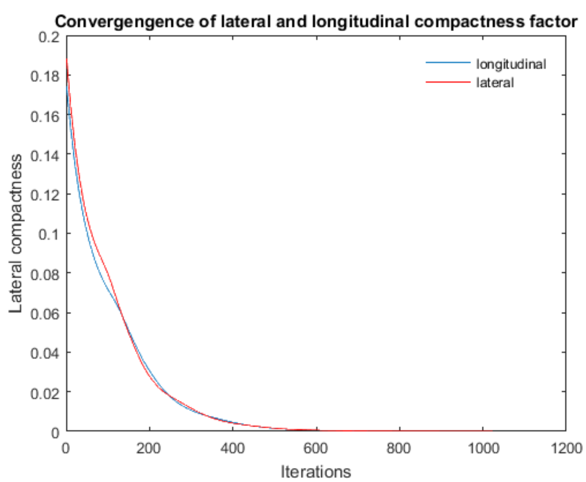

Fig. 6: Convergence trend of lateral compactness criteria over 534 iterations.

The error tolerance range for both CFL and CFH is 10×10^{-6}. Therefore, from Fig. 6 it can be seen that the algorithm converges after ~ 600 iterations for both longitudinal and lateral compactness.

CONCLUDING REMARKS

An algorithmic framework is developed to model the stable conformations of an MT from initial relatively unstable random conformation. The developed algorithm and the necessary steps are described in detail. The preliminary results obtained from the model demonstrate the effectiveness of the algorithm in generating stable conformations for MT. However, further investigation is necessary to evaluate several parameters including molecular interaction within a tubulin and their sensitivity in the model for realistically simulating the MT self-organization process.

In addition, accurate modelling of interaction between neighboring tubulins involving M-loop and H1-S2 loop at the structural level are necessary to faithfully simulate molecular level influence on MT assembly. Another aspect of MT formation is protofilament twisting where protofilaments slides with respect to each other under influence of thermal force on MT. As a result inter-protofilament bonds are stretched. This effect can be mitigated by applying a twisting force along MT axis. Therefore, effective modelling should also consider these issues.

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