Simulations and Theory of Model Microtubule Self-Assembly

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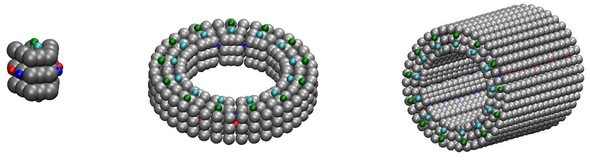
❑ Motivations

- In eukaryotic cells, α-β tubulin dimers self-assemble into microtubules (key components of cytoskeleton) with diameter ~25nm and length as larger as 25 μm. The molecular mechanism of this process is poorly understood.
- Other macromolecules, including the surface layer protein in the cell wall of prokaryotic organisms, many amphiphilic molecules, diblock/triblock copolymers, and even hybrid structures, can form tubes under the right conditions.
- What is the general scheme of making tubes out of simple building blocks?

❑ Model of Artificial Microtubule Self-Assembly

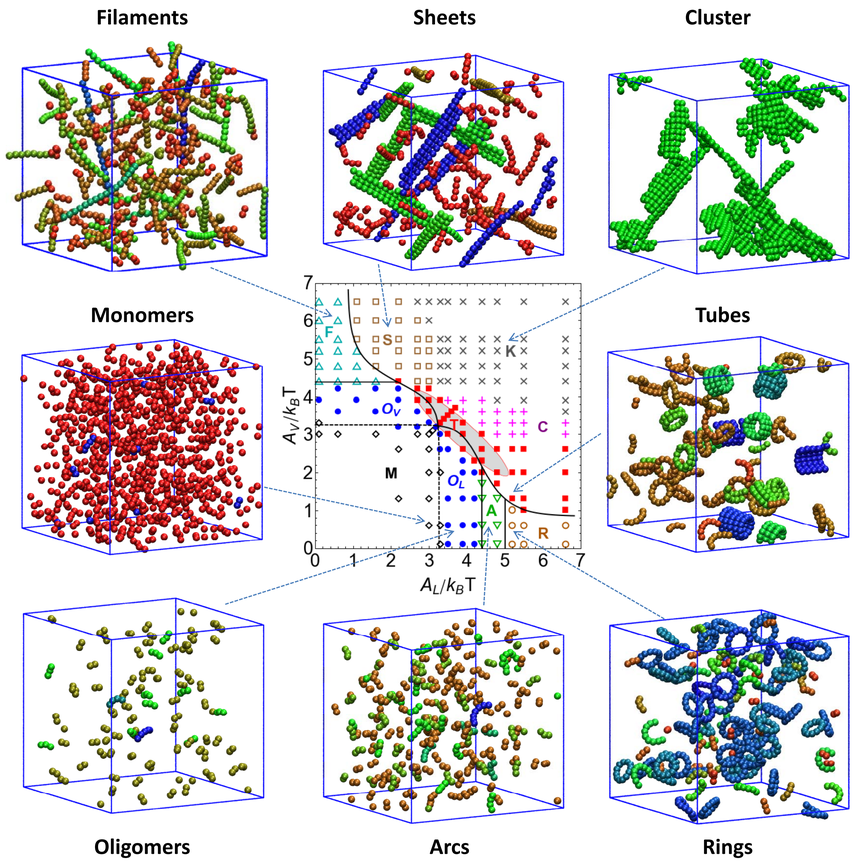


- Rigid wedge-shaped monomers (backbone + attractive sites)
- Lateral (vertical) bonding leads to rings (filaments)
- Appropriate combination of lateral and vertical bonding leads to tubes
- An ideal ring (tube) contains 13 wedges (filaments)
- Bonding interactions only between attractive sites in the same color

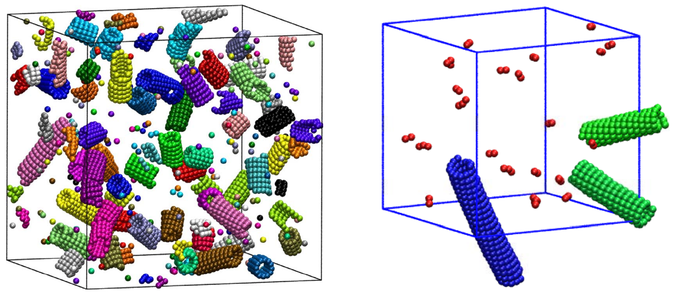
$$U(r) = -A\left[1+\cos\left(\frac{\pi r}{r_c}\right)\right] \qquad U(0) = -2A$$

- Ideal bonding strength for two wedges is 4A (two attractive sites on a face)

❑ Various structures are found from wedge self-assembly



❑ Tubes are only formed in a narrow range of interaction strengths



A_L =4.4 and A_V =2.6 (5000 wedges) A_L =3.9 and A_V =2.6 (1000 wedges)

- Tubes are better formed when the lateral bonding is slightly stronger than the vertical bonding → easier to form rings first and then stack rings into tubes
- Reversibility of bonding is essential to remove defects by allowing structural rearrangements
- Helical tubes are frequently formed even though wedge monomers are designed for non-helical tubes

❑ Flory-Huggins Lattice Theory of Straight Polymerization of Wedges

Following previous theoretical work on self-assembly of viral capsids [2, 3, 4], we start from straight polymerization of wedges (e.g., A_L=0 and A_V≠0). We calculate the entropy of the system by counting the number of ways to put all chains onto a lattice (with M cells and coordination number z) that discretizes the simulation box. The free energy of the system is

$$F = \sum_{p=1}^{p_{\max}} n_p\left((p-1)g - kT\ln z + kT\ln\frac{n_p}{M} - kT\right) \qquad (1)$$

where p is the filament length, n_p is the number of chains of length p, and g is the mean binding energy of a bond. The conservation of total number of wedges leads to a constraint

$$N = \sum_{p=1}^{p_{\max}} p n_p \qquad (2)$$

Minimizing the free energy under this constraint yields

$$n_p = zM\exp(g/kT)\exp[-p(g-\mu)/kT] \qquad (3)$$

where μ is chemical potential. Combining Eqs. (2) and (3) leads to

$$z\exp(g/kT)\frac{x}{(1-x)^2} = \frac{N}{M} \qquad (4)$$

where

$$x = \exp[-(g-\mu)/kT]$$

For a given g, Eq. (4) is used to solve for x, which in turn gives μ. Then n_p is calculated with Eq. (3). The transition to a state dominated by p-segment chains is determined by the condition

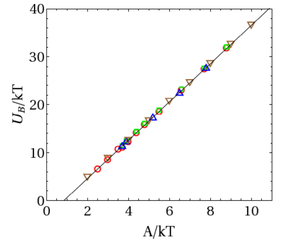
$$\frac{\partial n_p}{\partial g} = 0$$

Combining this condition with Eqs. (3) and (4) yields the critical binding energy for the transition to p-segment chains

$$g_p = kT\left(\ln\frac{N}{M} - \ln z - \ln\frac{p^2-1}{4}\right)$$

With n_p and g_p, we are able to determine the critical binding energy for the transition to filaments/arcs/rings.

❑ Bonding Energy U_B from MD Simulations

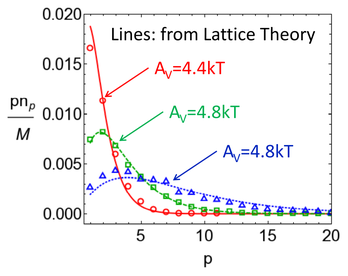


- U_B is the mean potential energy of two bonded wedges before the bond breaks
- Calculate U_B with various starting configurations (lateral/vertical dimers, rings) and at different temperatures
- U_B scales with temperature
- No many-body effect
- Same trend for lateral/vertical bonding

- U_B less than ideal strength 4A because of thermal fluctuations

$$U_B = 4A - 3.4kT$$

❑ Mapping A in Simulations to g in Theory



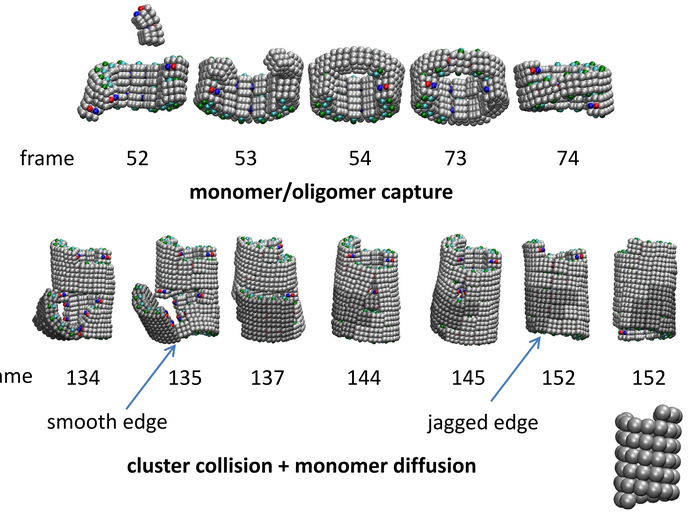
Comparing n_p calculated directly from simulations with theoretical predictions provides a mapping between U_B/A and g:

$$g = U_B - 9.6kT$$
$$= 4A - 3.4kT - 9.6kT$$

where 4A is the ideal bonding strength, the second term -3.4kT represents the contribution of thermal fluctuations, and the third term -9.6kT reveals an energy barrier of the formation of a stable bond between two rigid building blocks.

Combining the lattice theory of straight polymerization with the energy barrier of stable bonding allows us to determine the boundaries (lines in the structure diagram) between various structures formed by wedges, which agree with MD calculations quite well.

❑ How helical tubes are formed?



❑ References

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