Self-Assembly of Model Microtubules

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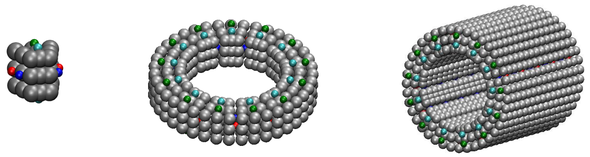
❑ Motivation

- In eukaryotic cells, α-β tubulin dimers self-assemble into microtubules (key components of cytoskeleton) with diameter ~25nm and length as large 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, some amphiphilic molecules, diblock/triblock copolymers, and even hybrid structures, can form tubules under the right conditions.
- What is the general scheme of making tubules with macromolecular building blocks?

❑ Model of Artificial Microtubule Self-Assembly

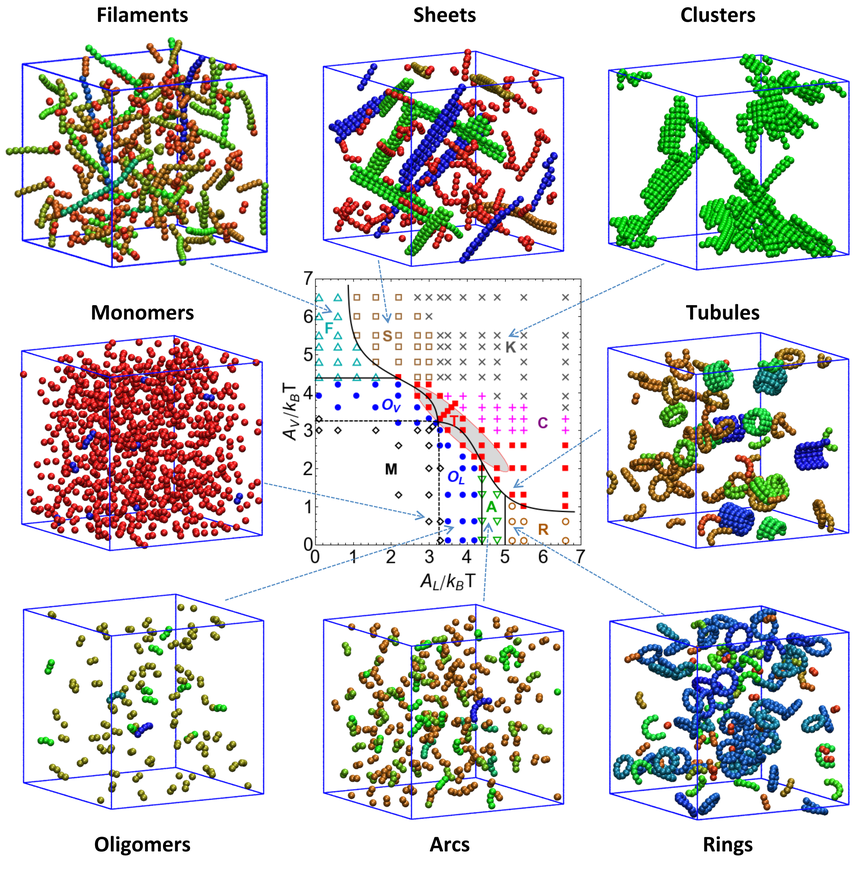


- Rigid wedge-shaped 3D monomers (core sites + attractive sites)
- Lateral (vertical) bonding leads to rings (filaments)
- Appropriate combination of lateral and vertical bonding leads to tubules
- An ideal ring (tubule) contains 13 wedges (filaments)
- Bonding interactions only between attractive sites in the same color

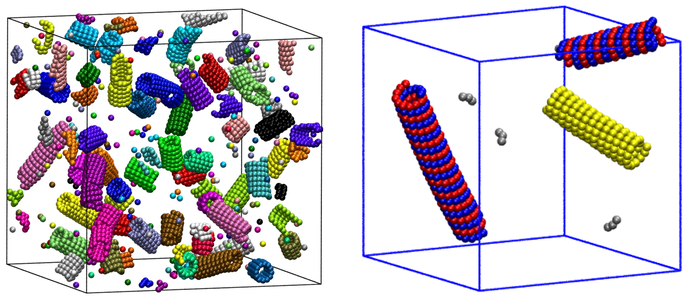
$$U(r) = -A\left[1+\cos\left(\frac{\pi r}{r_c}\right)\right] \qquad U(0) = -2A$$

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

❑ Various Structures from Wedge Self-assembly



❑ Tubules Only Form in a Narrow Range of Interaction Strengths



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

- Tubules are more readily formed when the lateral binding is slightly stronger than the vertical binding → easier to form rings first and then stack rings into tubules
- Reversibility of binding is essential to remove defects by allowing structural rearrangements
- Helical tubules are frequently formed even though wedge monomers are designed as achiral for non-helical tubules; why?

❑ Flory-Huggins Lattice Theory of Straight Polymerization of Wedges

Following previous theoretical work on self-assembly of viral capsids, 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

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

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

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

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

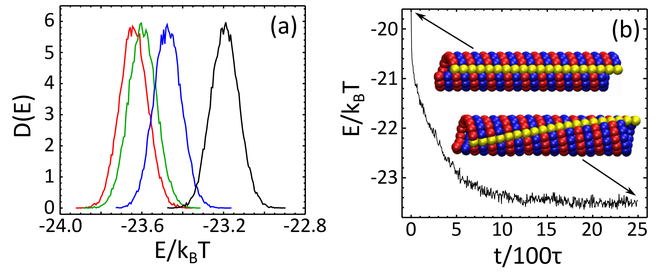
$$\frac{\partial n_p}{\partial g} = 0$$

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

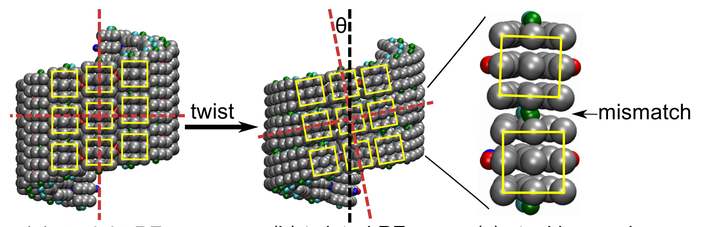
$$g_p = kT\left(\ln\frac{N}{M} - \ln z - \ln\frac{p^2-1}{4}\right)$$

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

❑ Energy Distributions Overlap for Tubules with Various Pitches

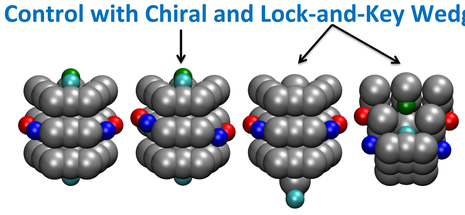


- Calculate energy distribution density, D(E), using tubules with 13 protofilaments, each of which has 60 monomers
- Protofilaments are twisted in tubules with pitches different from monomer chirality
- Energy of tubules decreases when protofilaments become twisted
- Large overlap in energy distributions for tubules with different pitches
- Protofilament twisting leads to a better monomer packing
- Twist deformation leads to a mismatch between vertical binding sites

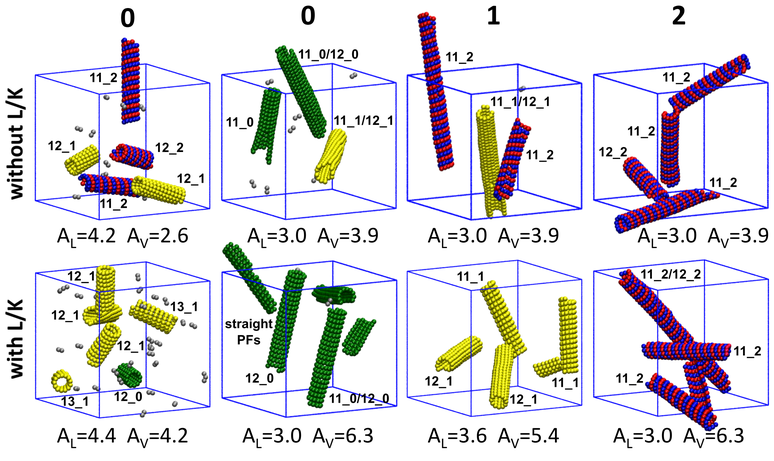


(a) straight PFs (b) twisted PFs (c) stacking wedges

❑ Structural Control with Chiral and Lock-and-Key Wedges



Monomer Chirality



- Tubule pitch matches with monomer chirality for chiral wedges with lock-and-key vertical binding at A_L<A_V
  - Lock-and-key monomers need stronger A_V to self-assemble
  - Twist deformation of protofilaments is suppressed at stronger A_V

All simulations were done with LAMMPS developed at Sandia (http://lammps.sandia.gov). Research supported by the U.S. Department of Energy, Office of Basic Energy Sciences, Division of Materials Sciences and Engineering.
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