SAND2013-5280C

Self-Assembly of Model Microtubules

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Research supported by the U.S. Department of Energy, Office of Basic Energy Sciences, Division of Materials Sciences and Engineering

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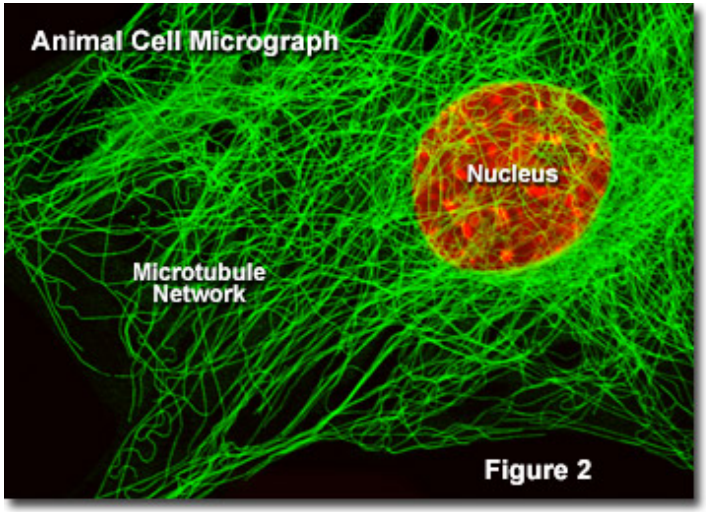
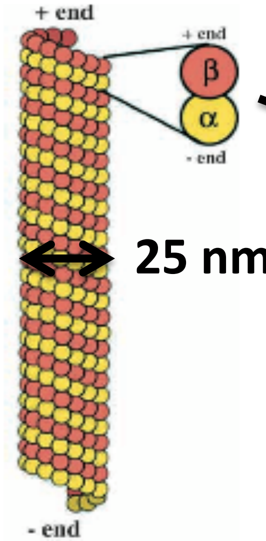
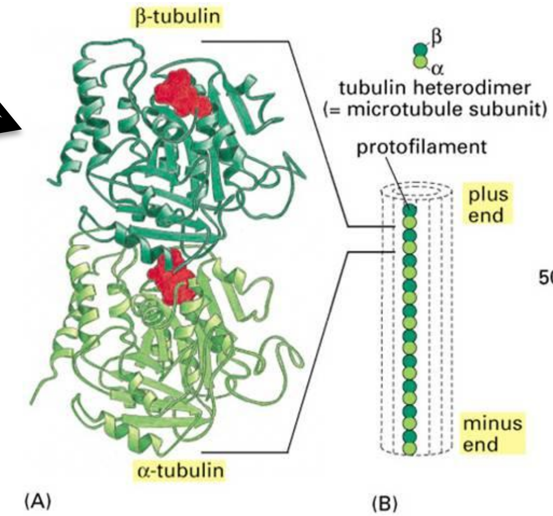
Microtubules and Tubular Structures

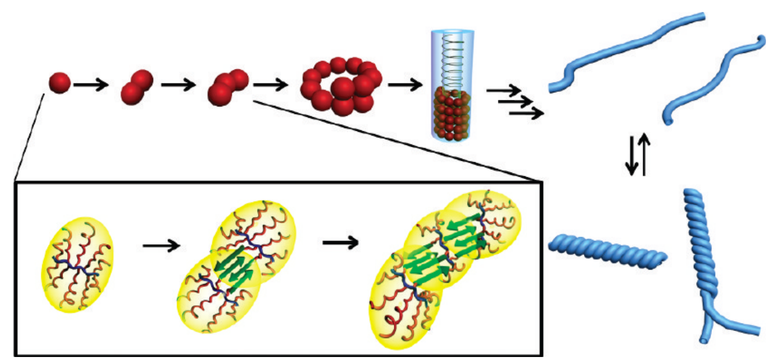


M. W. Davidson
(National High Magnetic Field Lab)

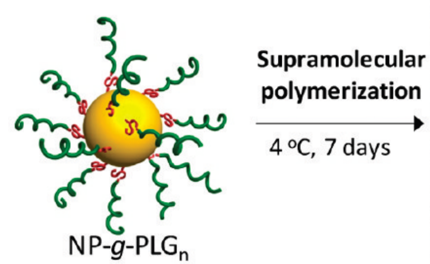


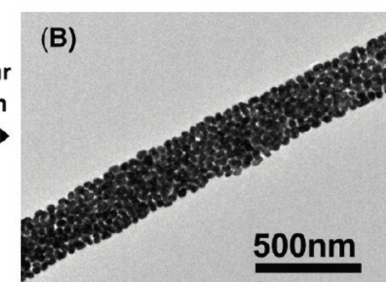


- MT dynamic/complex network
- Complex building block: $\alpha-\beta$ tubulin dimer
- Tubule contains 13 protofilaments
- Helical tubule



Wang et al. JACS (2011)

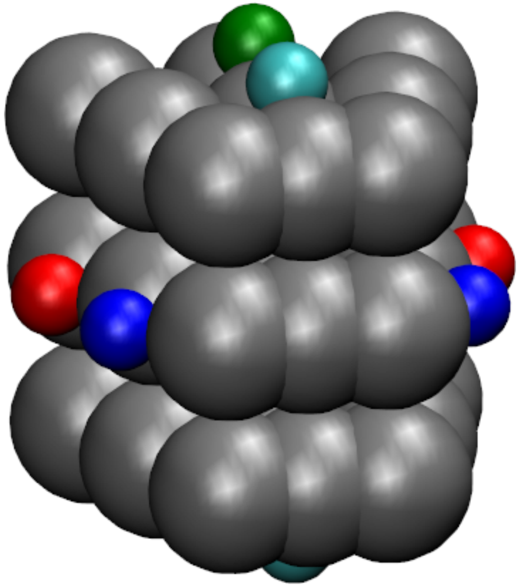




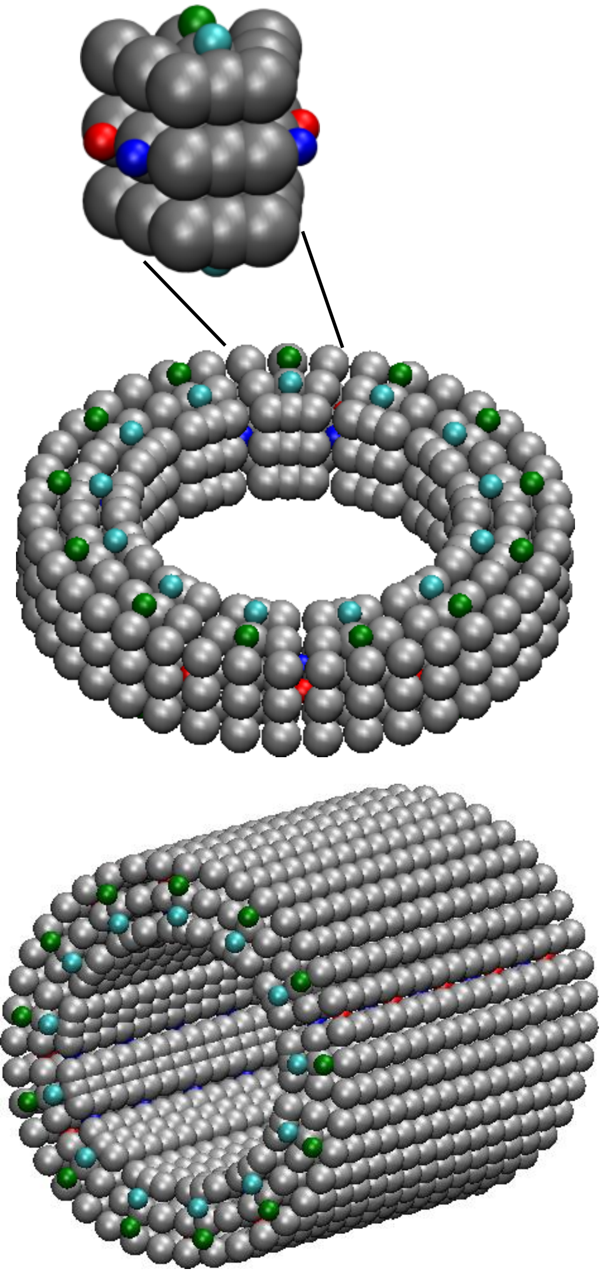
- Synthetic tubular structures

Design Building Blocks for Tubules

- What are the essential ingredients of a monomer (synthetic or tubulin) to produce microtubules?
- Specifically, what features are necessary in the building block to self-assemble into tubules?
- Molecular dynamics with a “macromolecular” building block:



Wedges as Building Blocks



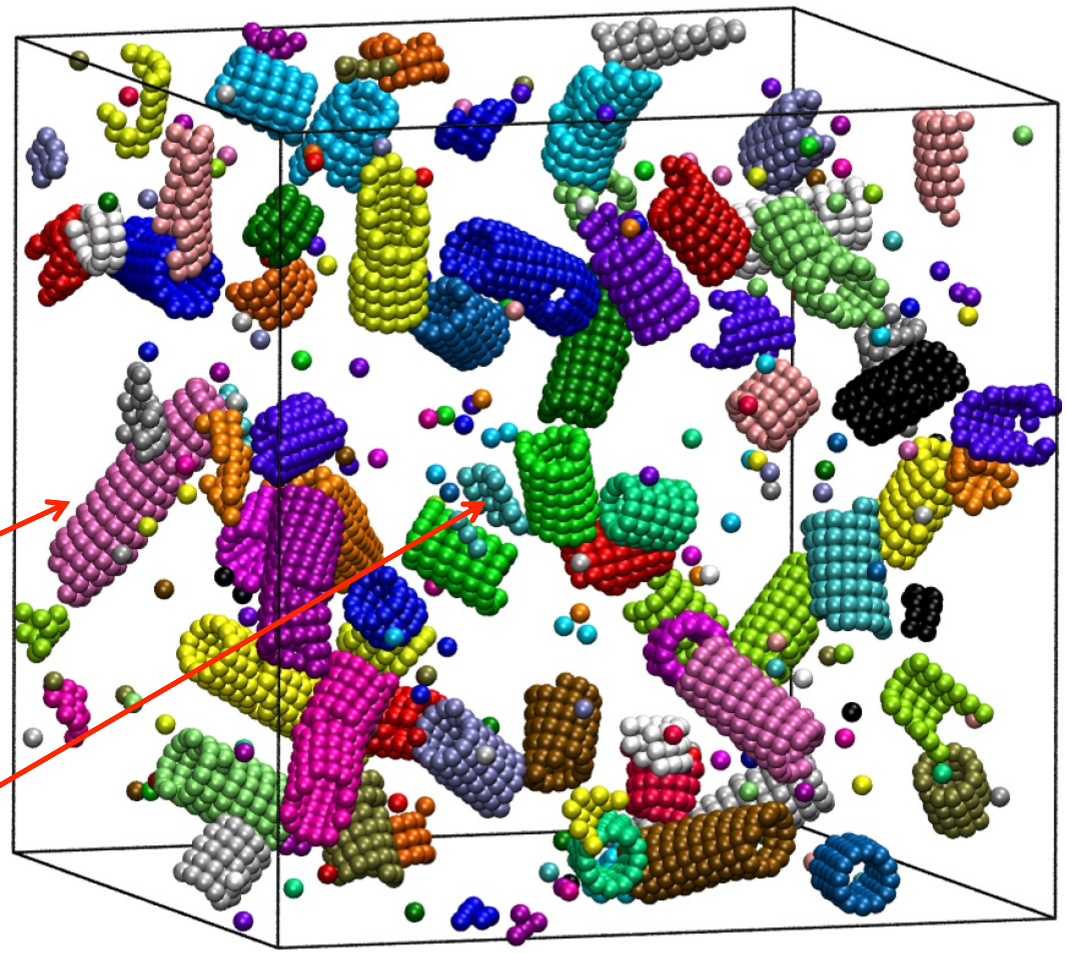
MD simulations with wedges:

- 3D composite rigid body
- pure repulsion between gray particles
- attraction only between colored sites
- lateral bonding ➔ 13-wedge rings
- vertical bonding ➔ stack rings into tubules
- independent control of A_L and A_V
- achiral ➔ nonhelical tubules
- kT as energy unit

Cheng et al., Soft Matter (2012)

Self-Assembly of Wedges

- 5000 wedge monomers
- wedges shown as spheres
- A_L =4.4 and A_V =2.6
- monomer volume fraction ~ 4%
- start with random distribution of monomers



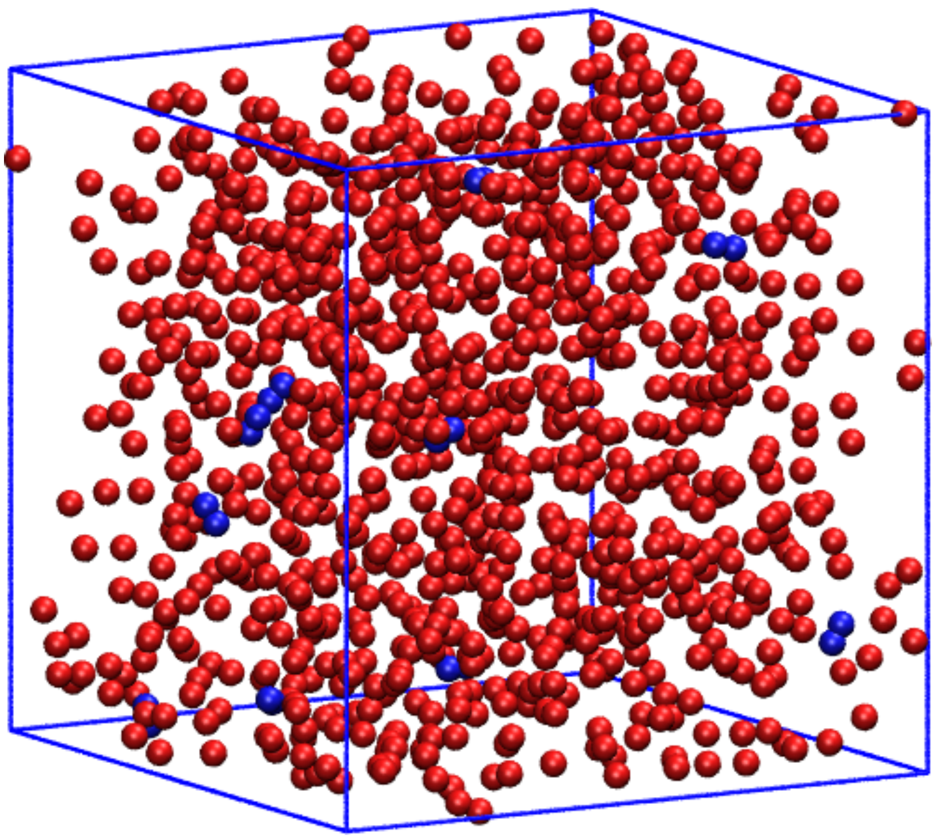
many tubules & some fragments
- helical
- defects

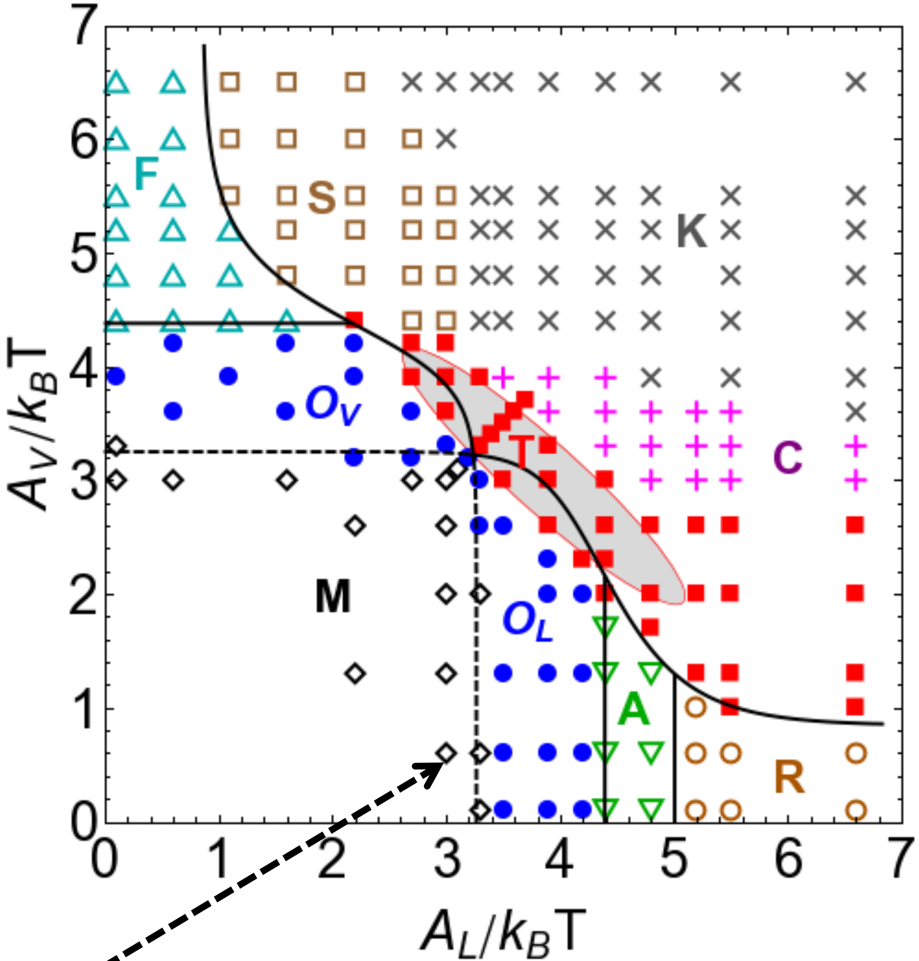
Key Question: When do tubules form? What is the best condition for tubule formation?

Structure Diagram: No Assembly

A_L=3.0, A_V=0.6

monomers



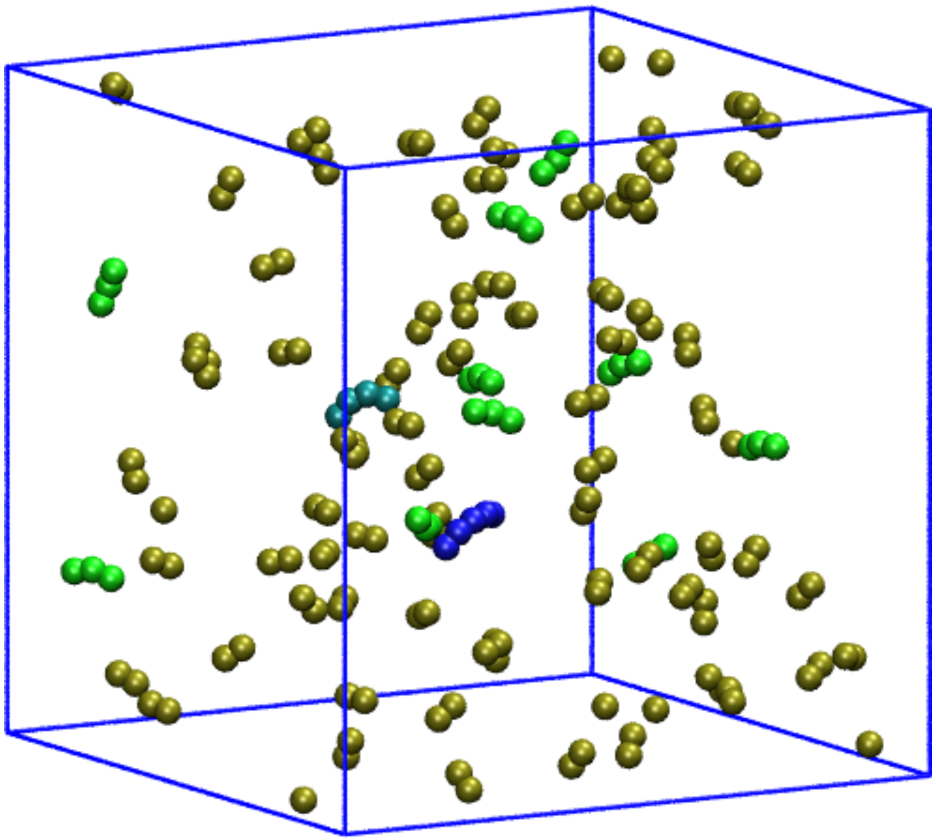


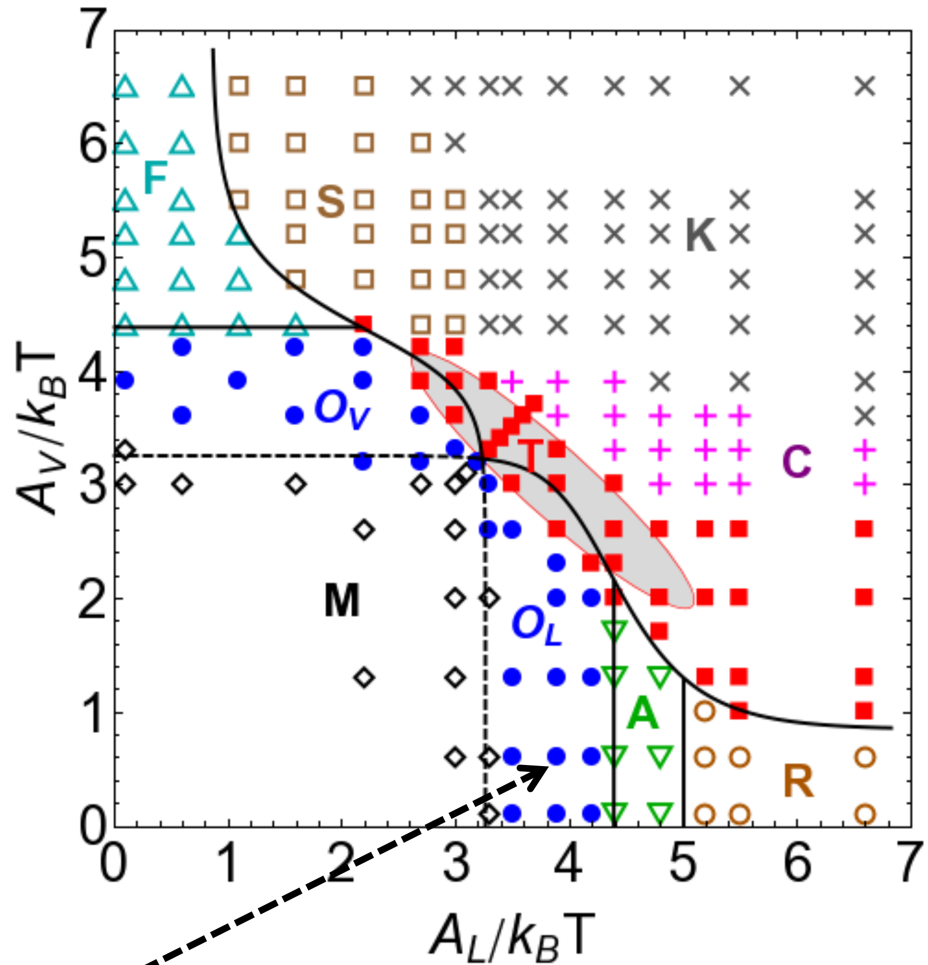
Small A_V

Structure Diagram: Oligomers

A_L=3.9, A_V=0.6

a few oligomers



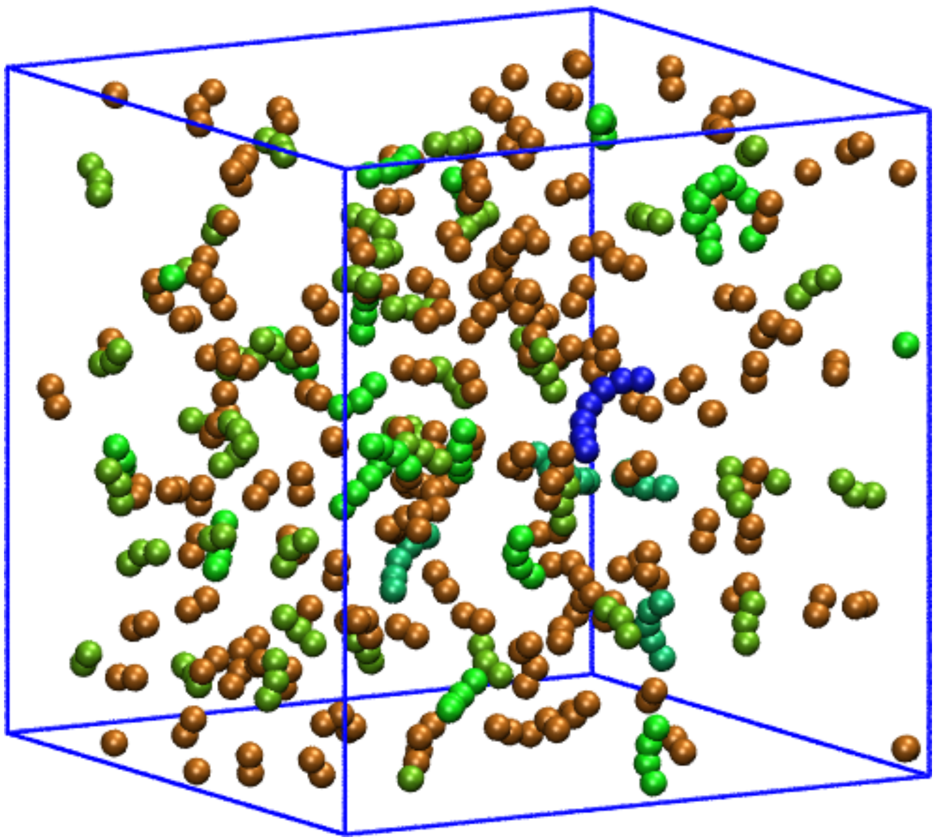


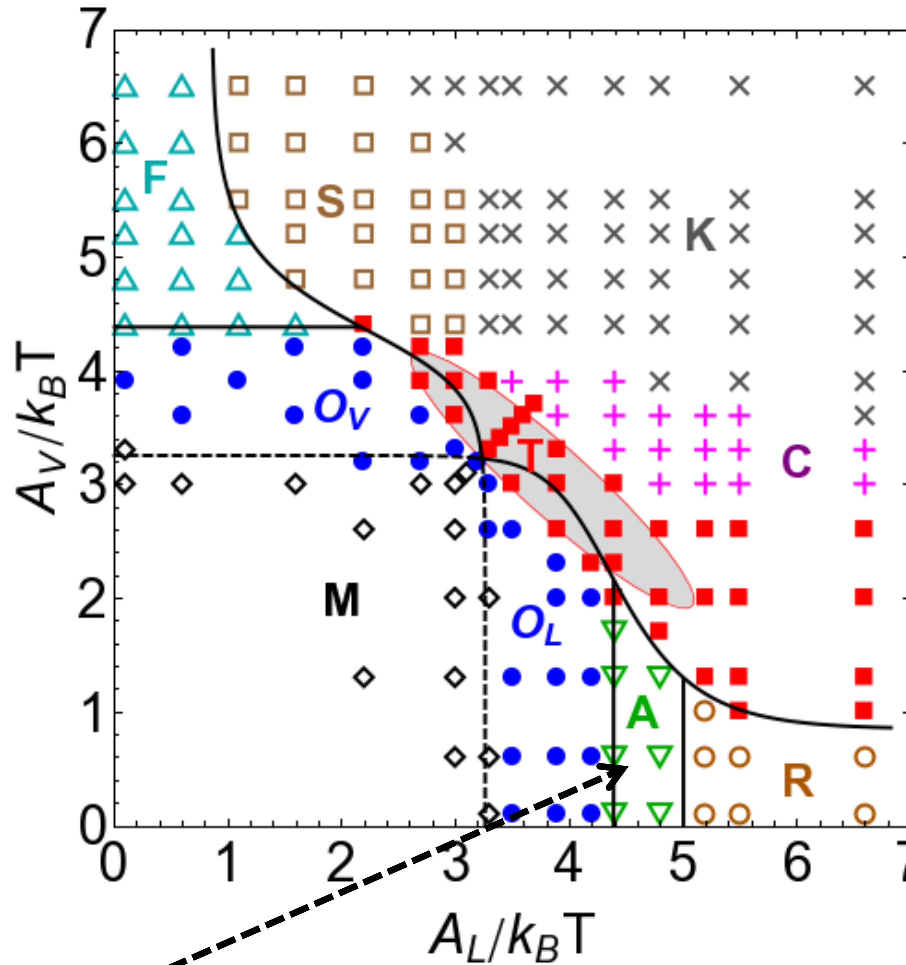
Small A_V

Monomers Not Shown

Structure Diagram: Arcs

A_L=4.4, A_V=0.6
arcs (oligomers)



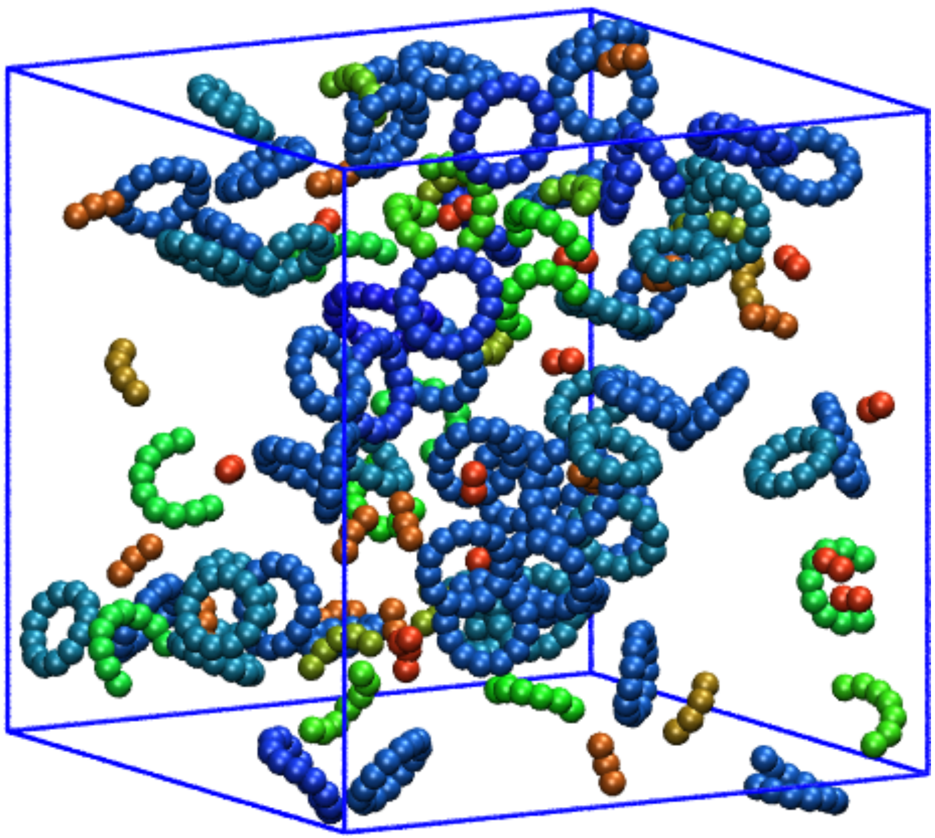


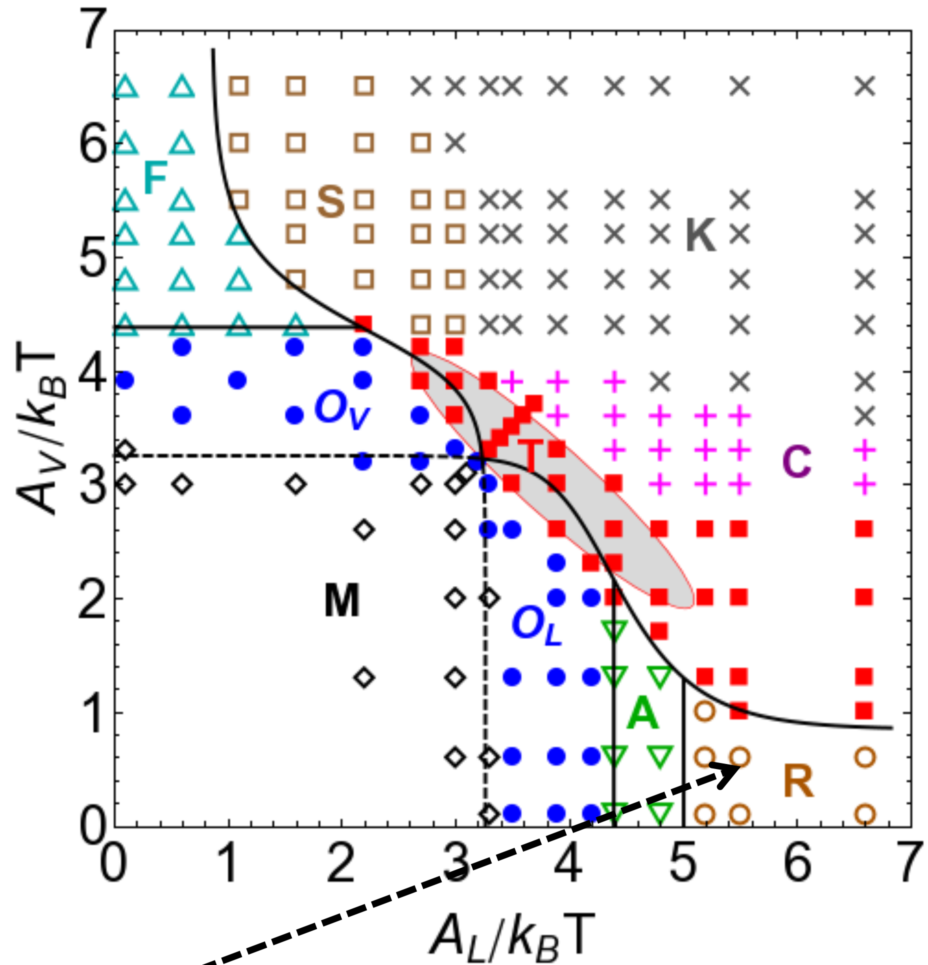
Small A_V

Structure Diagram: Rings

A_L=5.5, A_V=0.6

rings



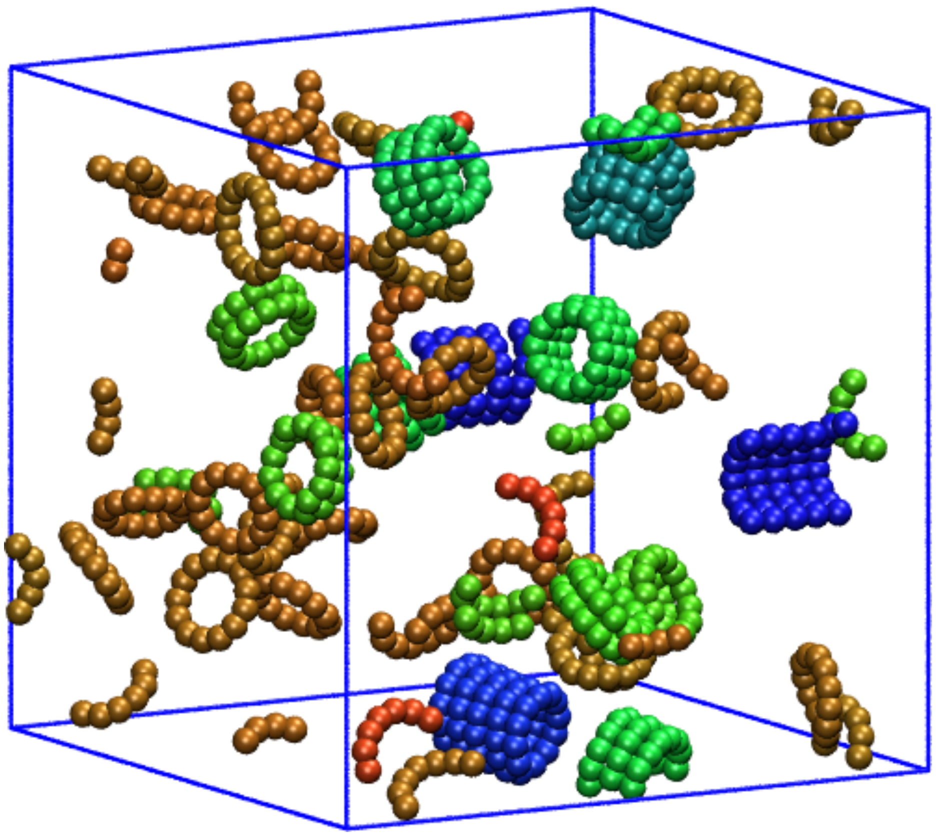


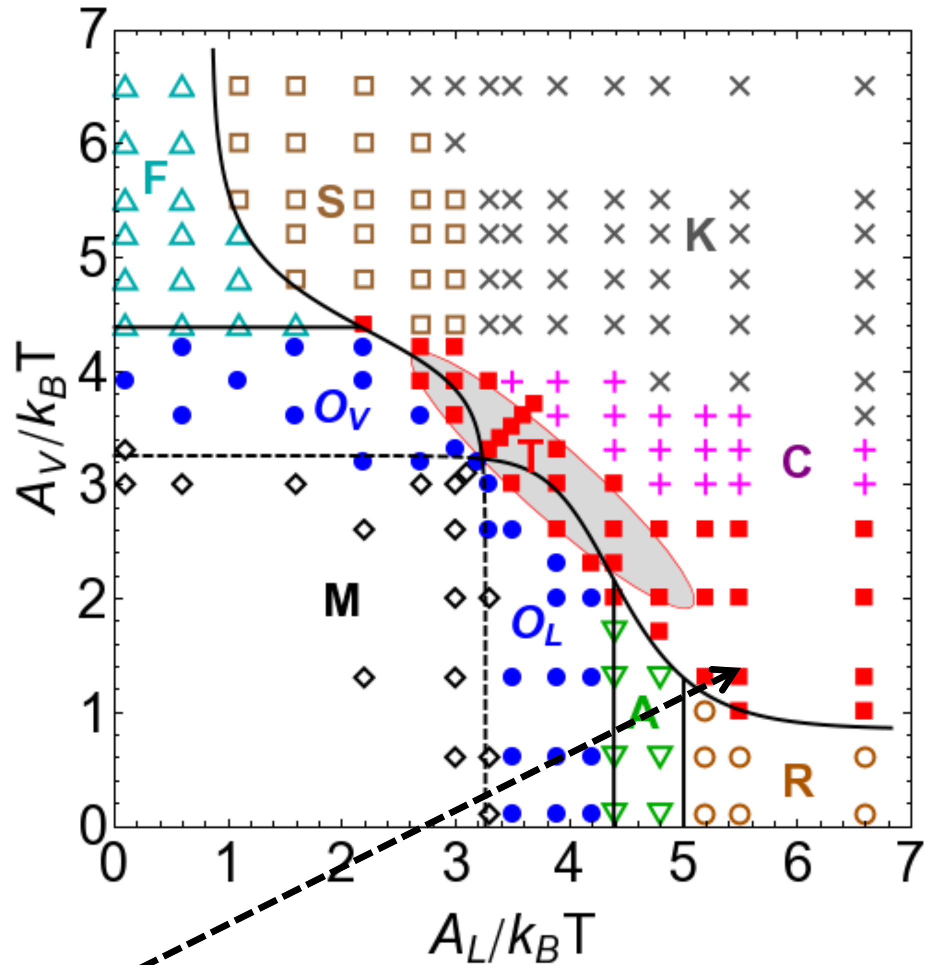
Small A_V

Structure Diagram: Tubule/Ring Mixture

A_L=5.5, A_V=1.3

tubule/ring mixture

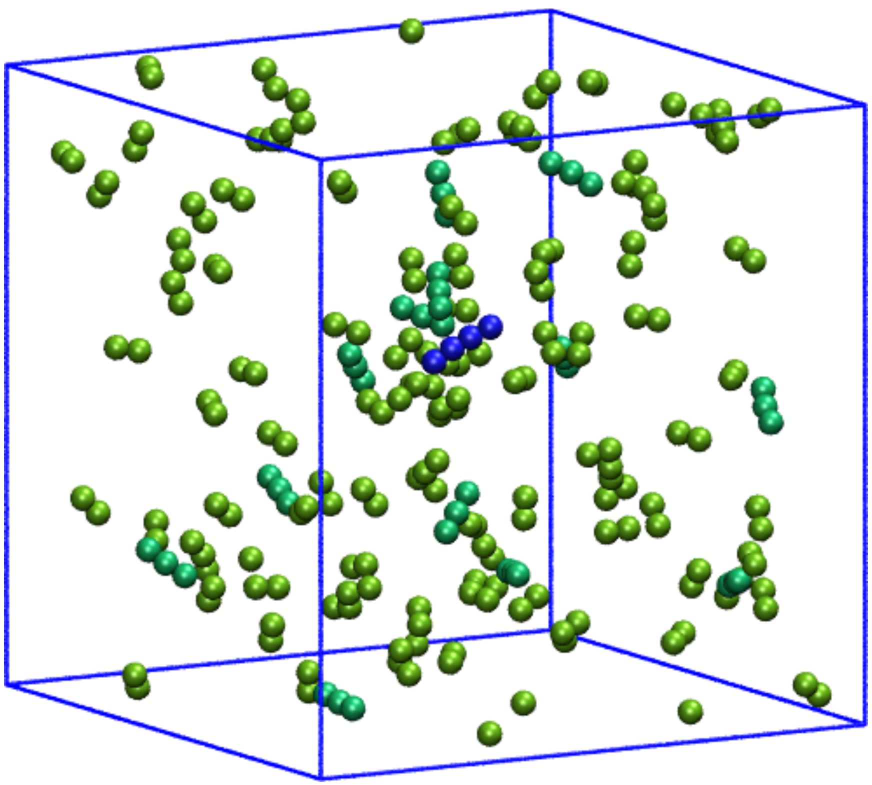


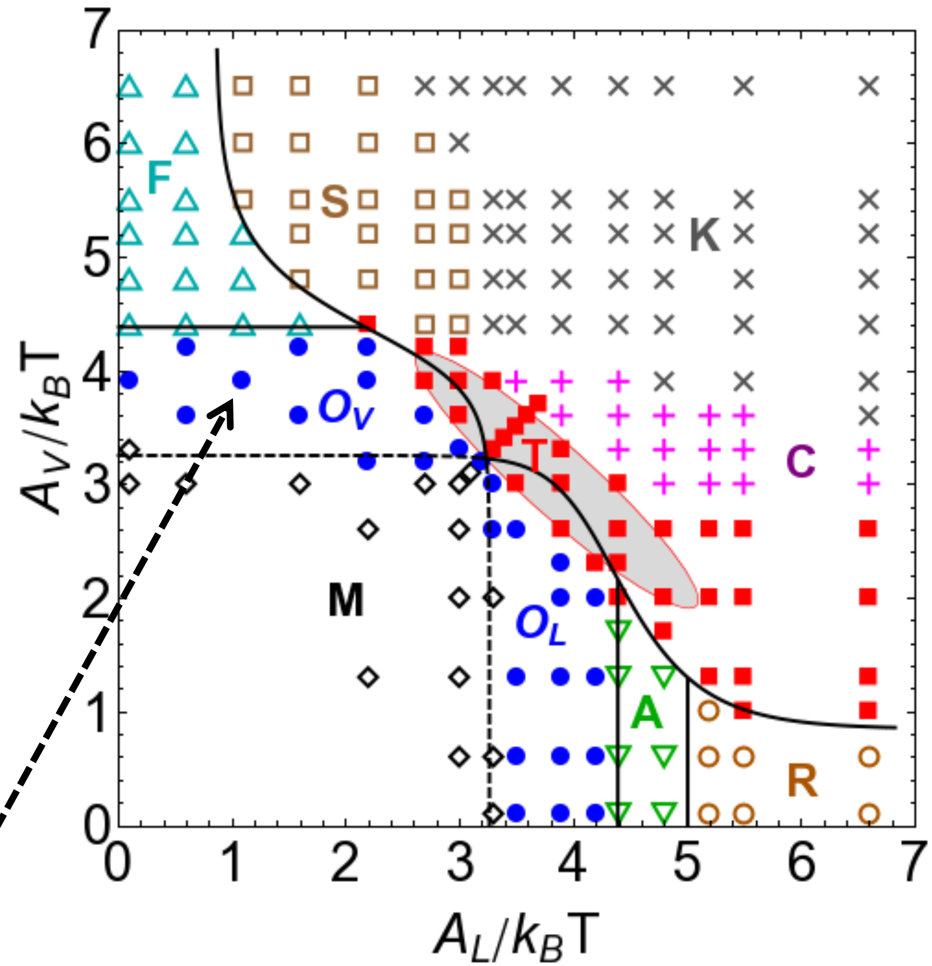


Structure Diagram: Oligomers

A_L=1.1, A_V=5.2

oligomers (vertical bonding)

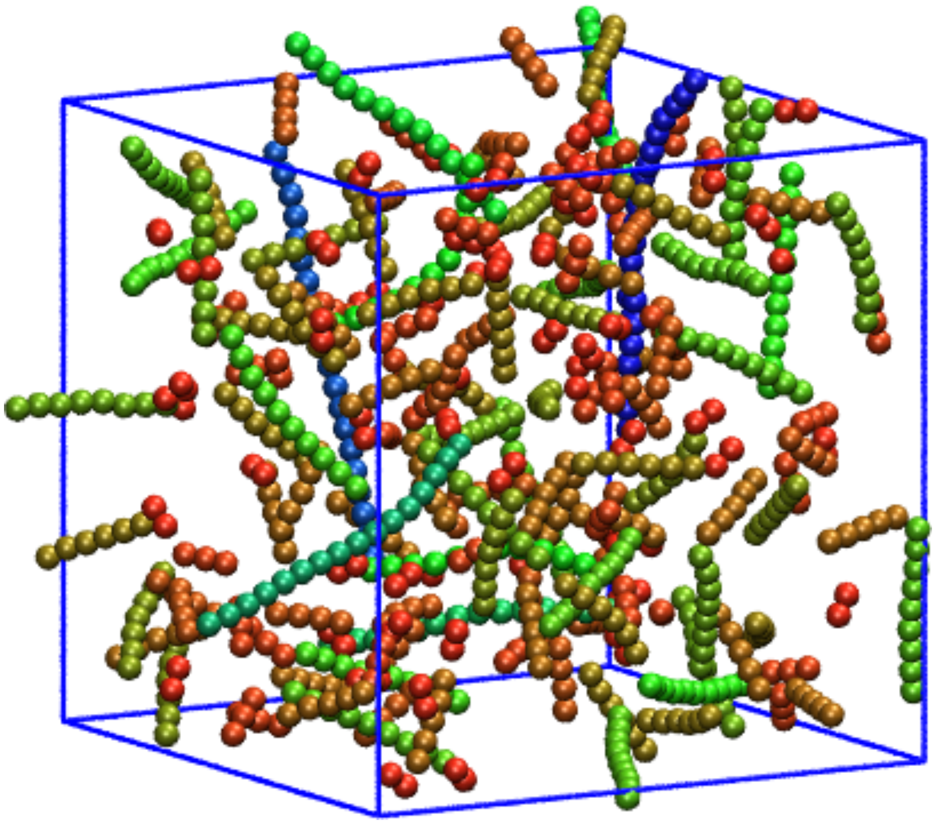


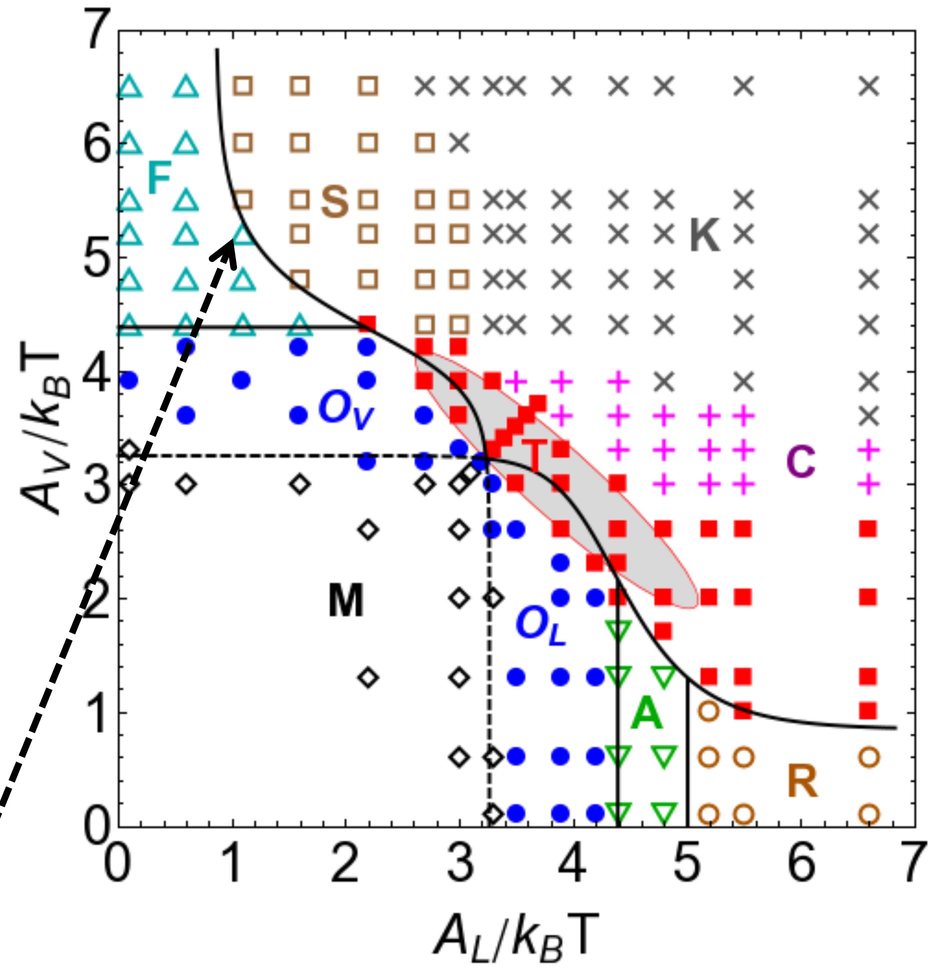


Small A_L

Structure Diagram: Filaments

A_L=1.1, A_V=5.2
filaments



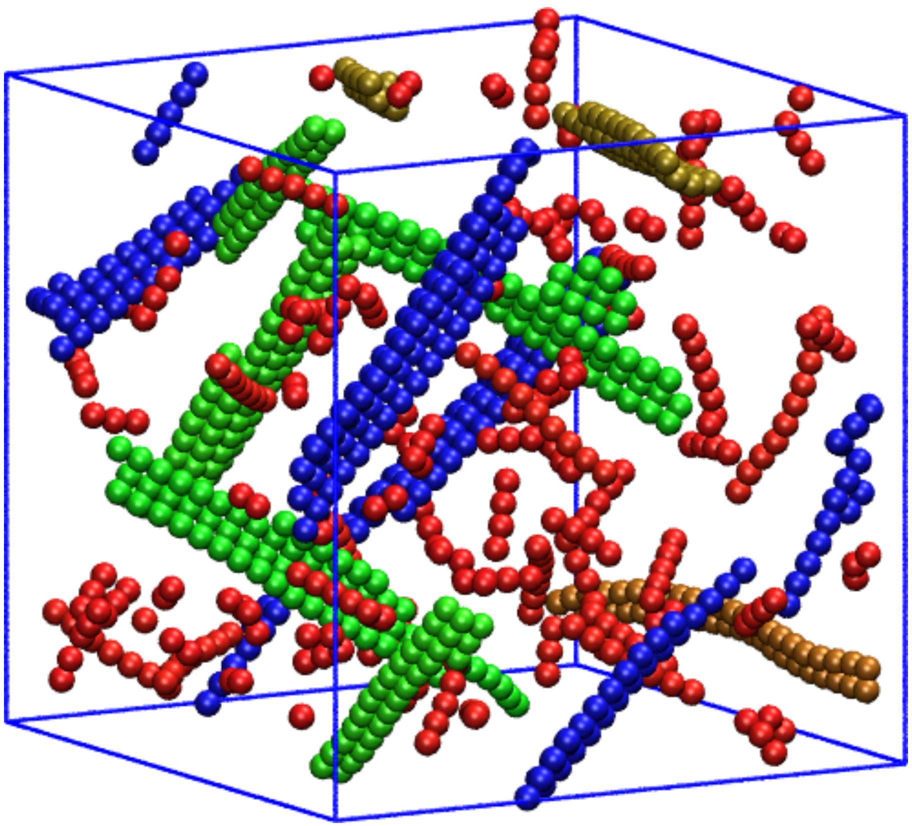


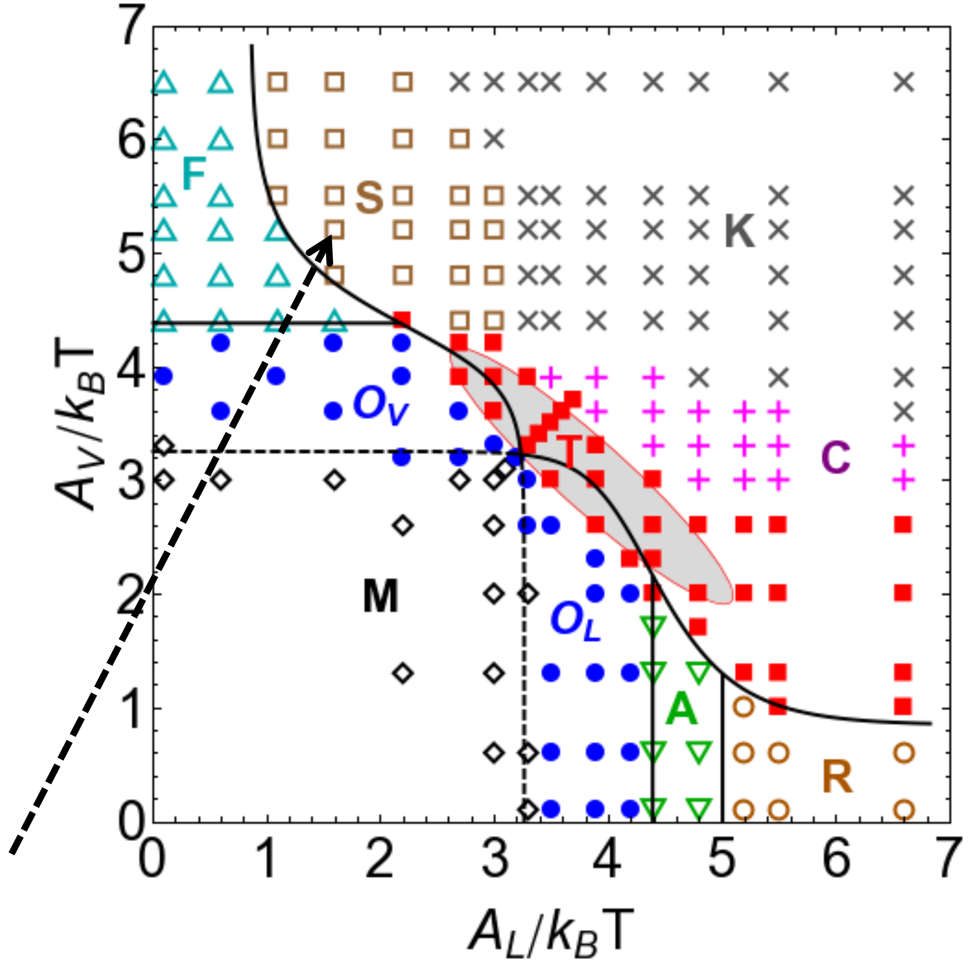
Small A_L

Structure Diagram: Sheets

A_L=1.6, A_V=5.2

sheets

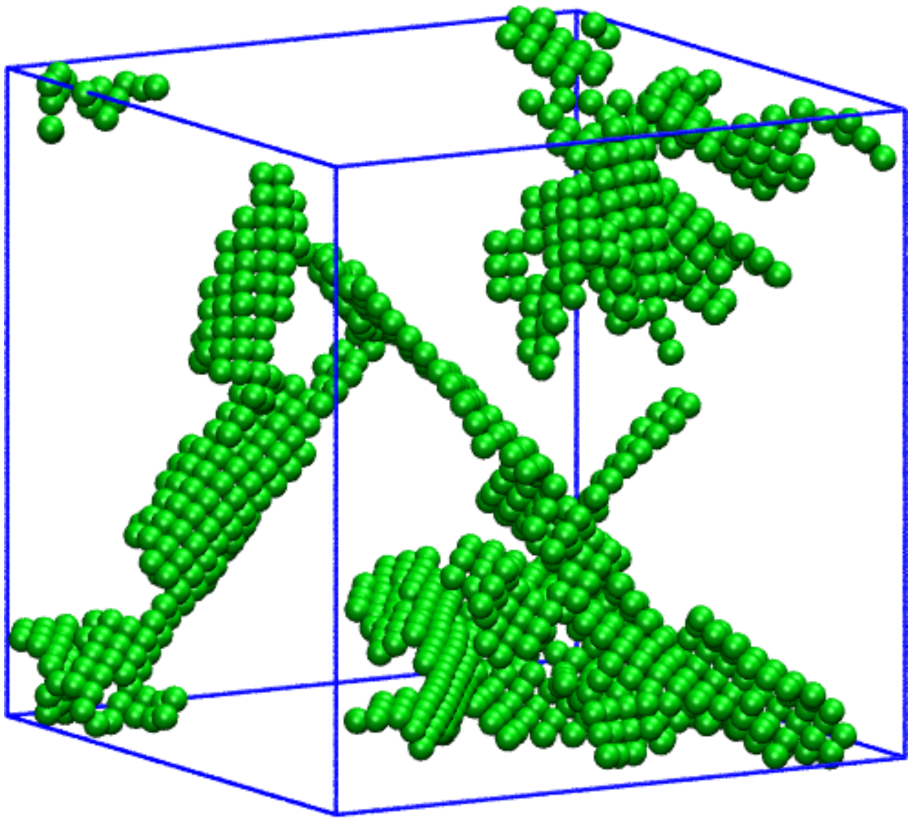


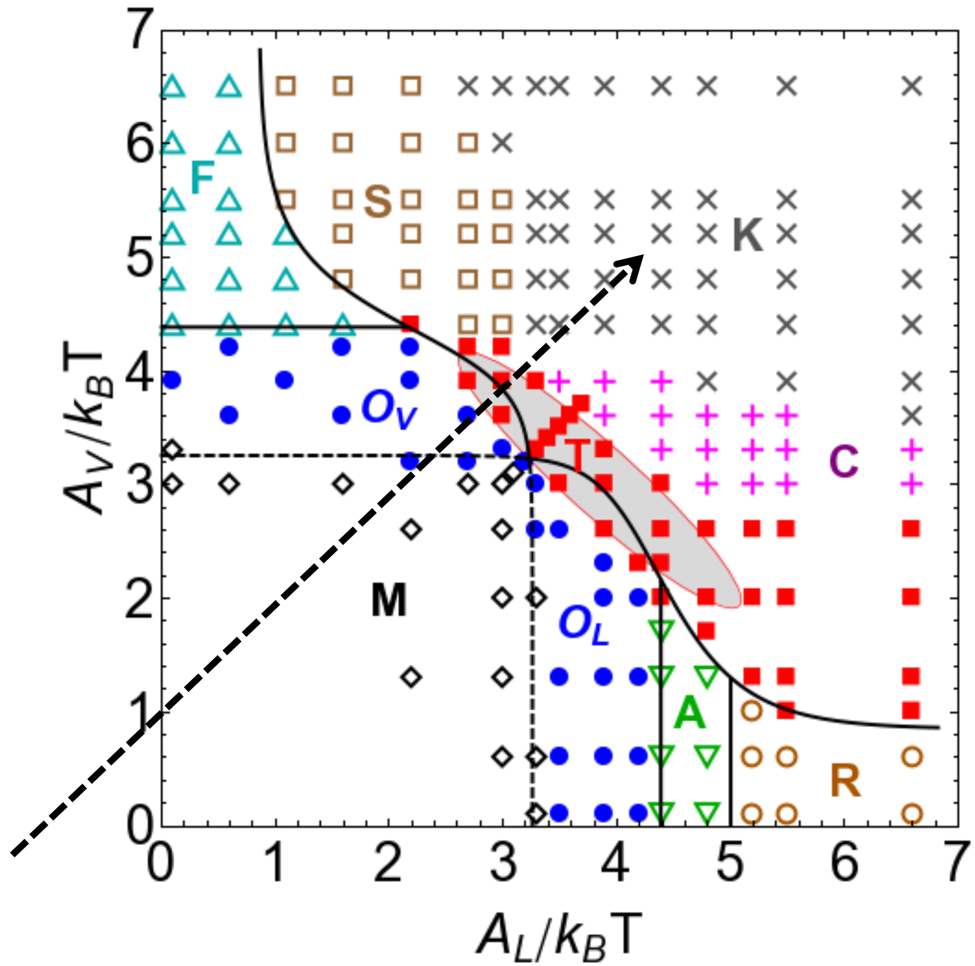


Structure Diagram: Percolated Cluster

A_L=4.4, A_V=5.2

percolated cluster



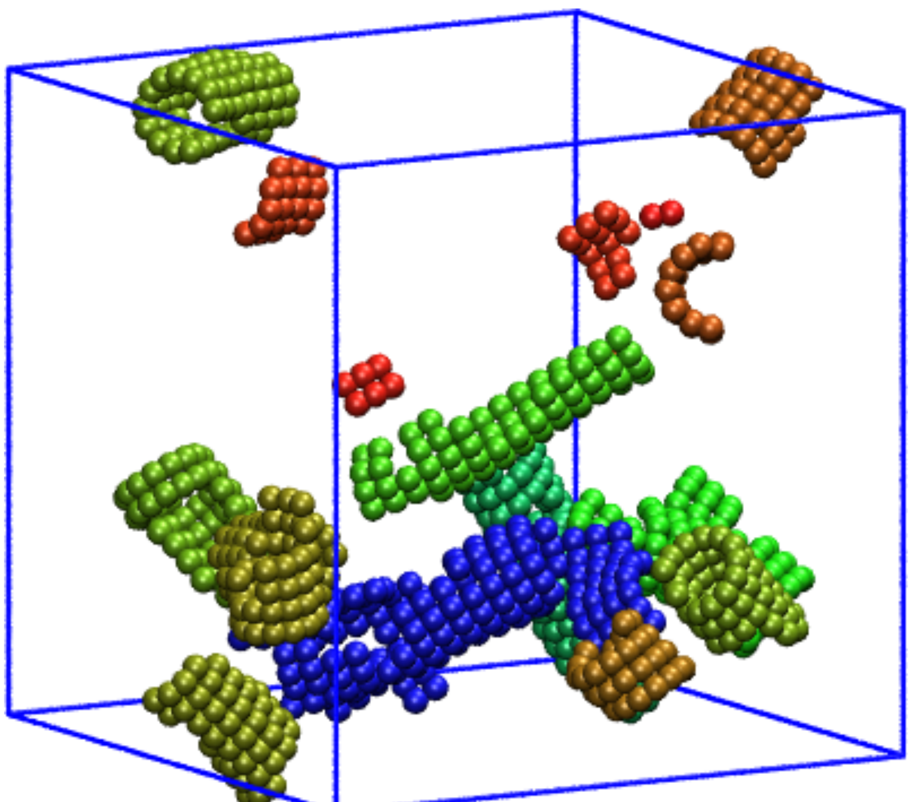


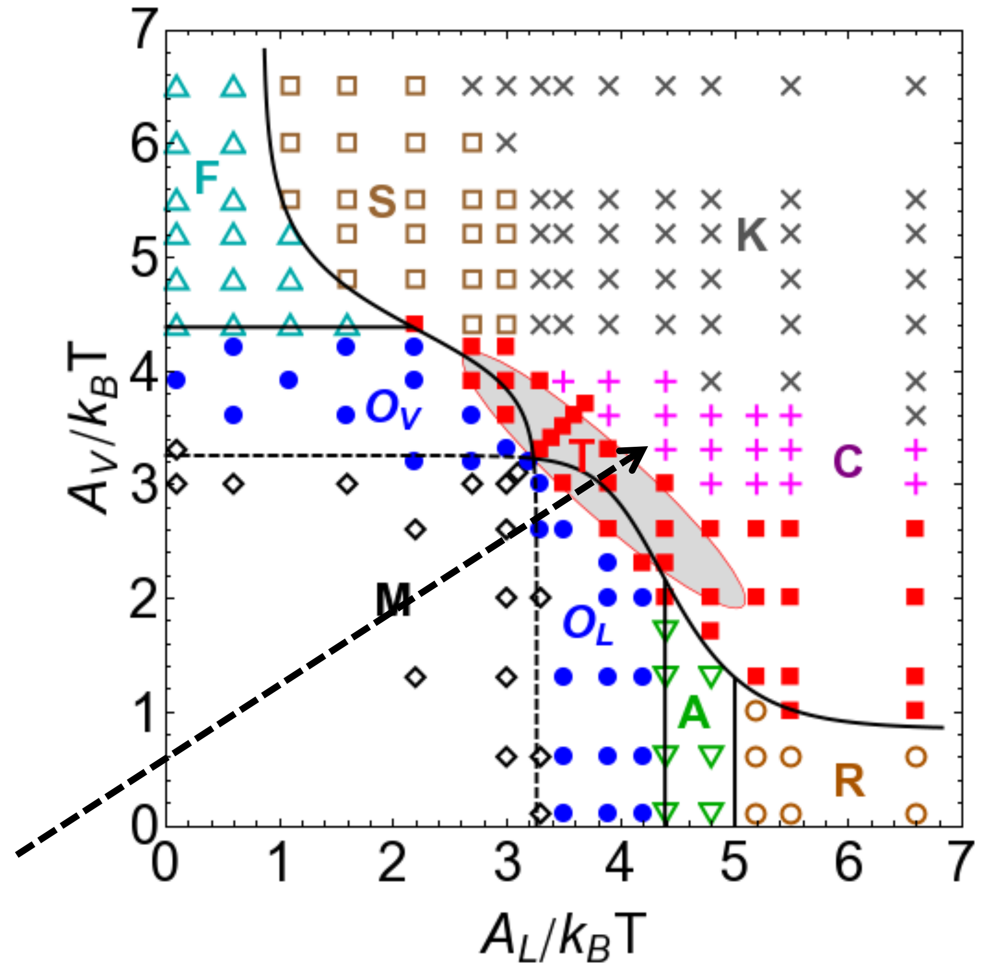
A_L and A_V both strong

Structure Diagram: Multiple Clusters

A_L=4.4, A_V=3.3

clusters (defects)

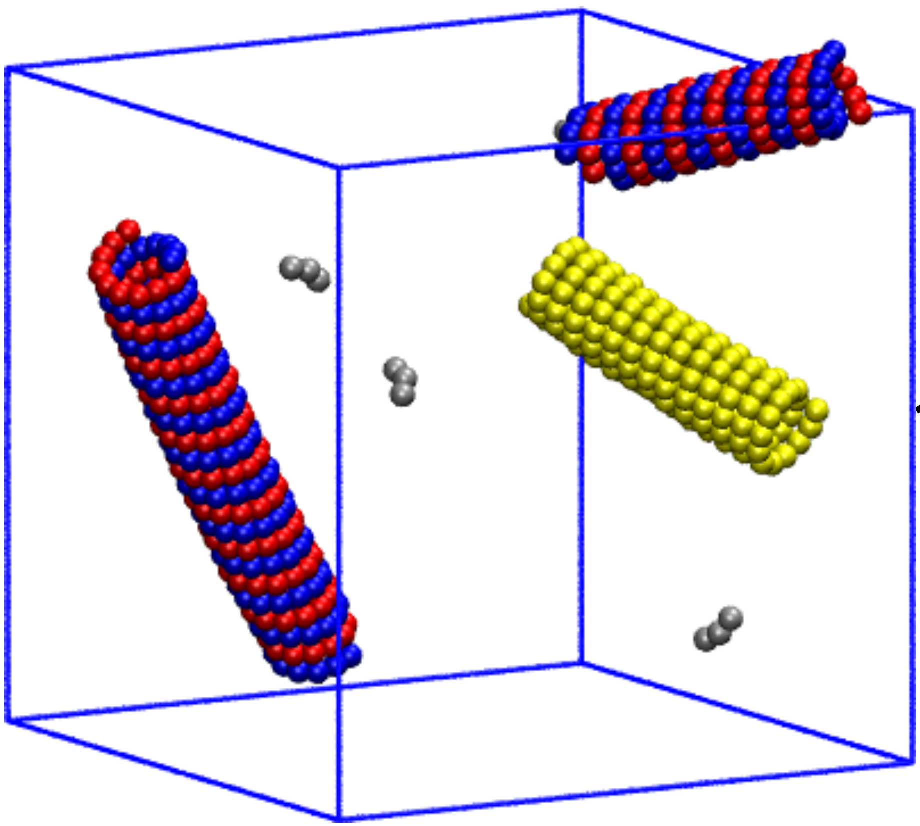


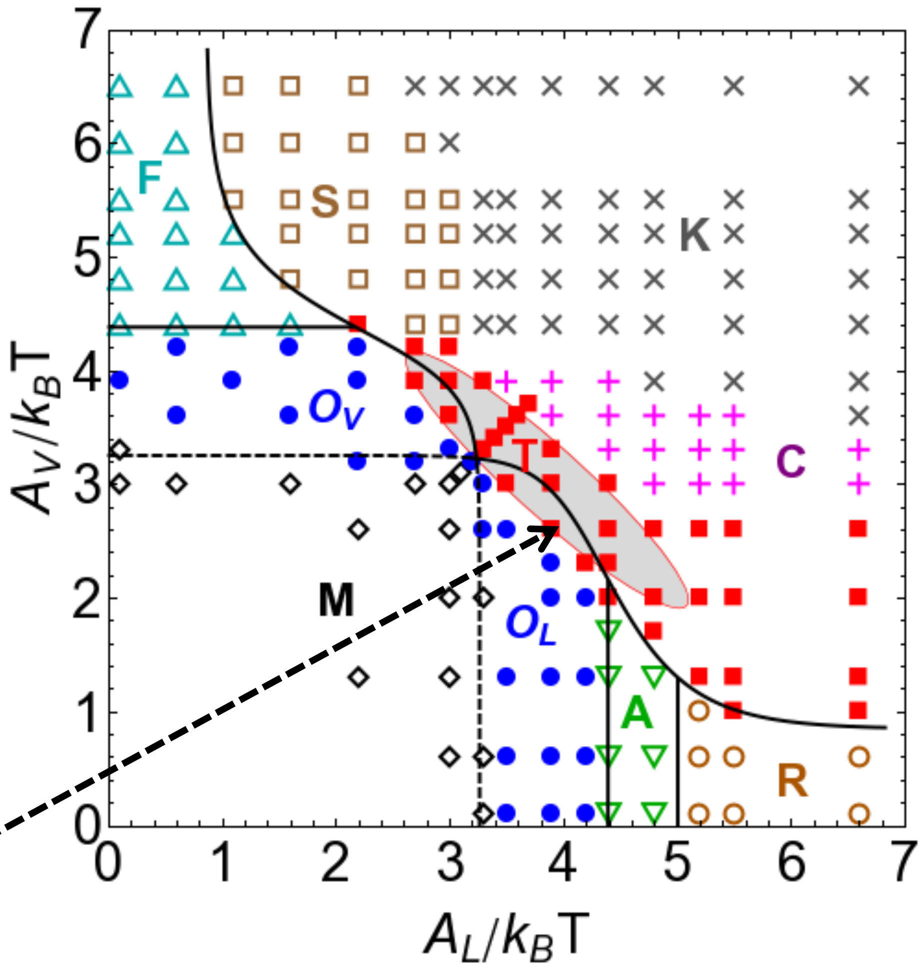


Tubule Formation at Weak Bonding

A_L=3.9, A_V=2.6

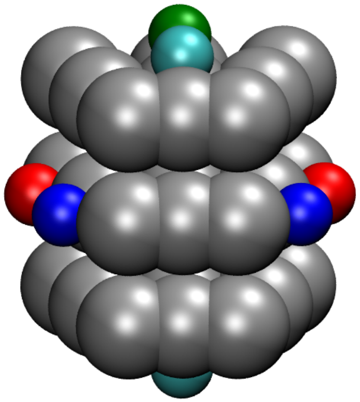
defect-free tubules (helical)





- **Tubules tend to be helical, but monomer is not chiral. Why?**

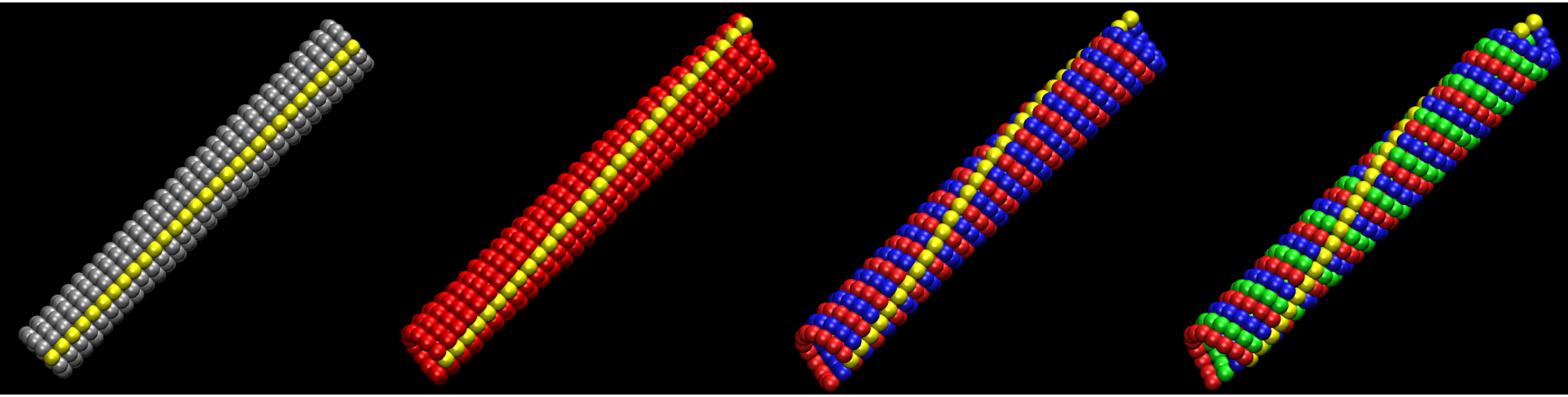
Tubular Structure Characterization



chirality = 0

Characterize tubular structure:

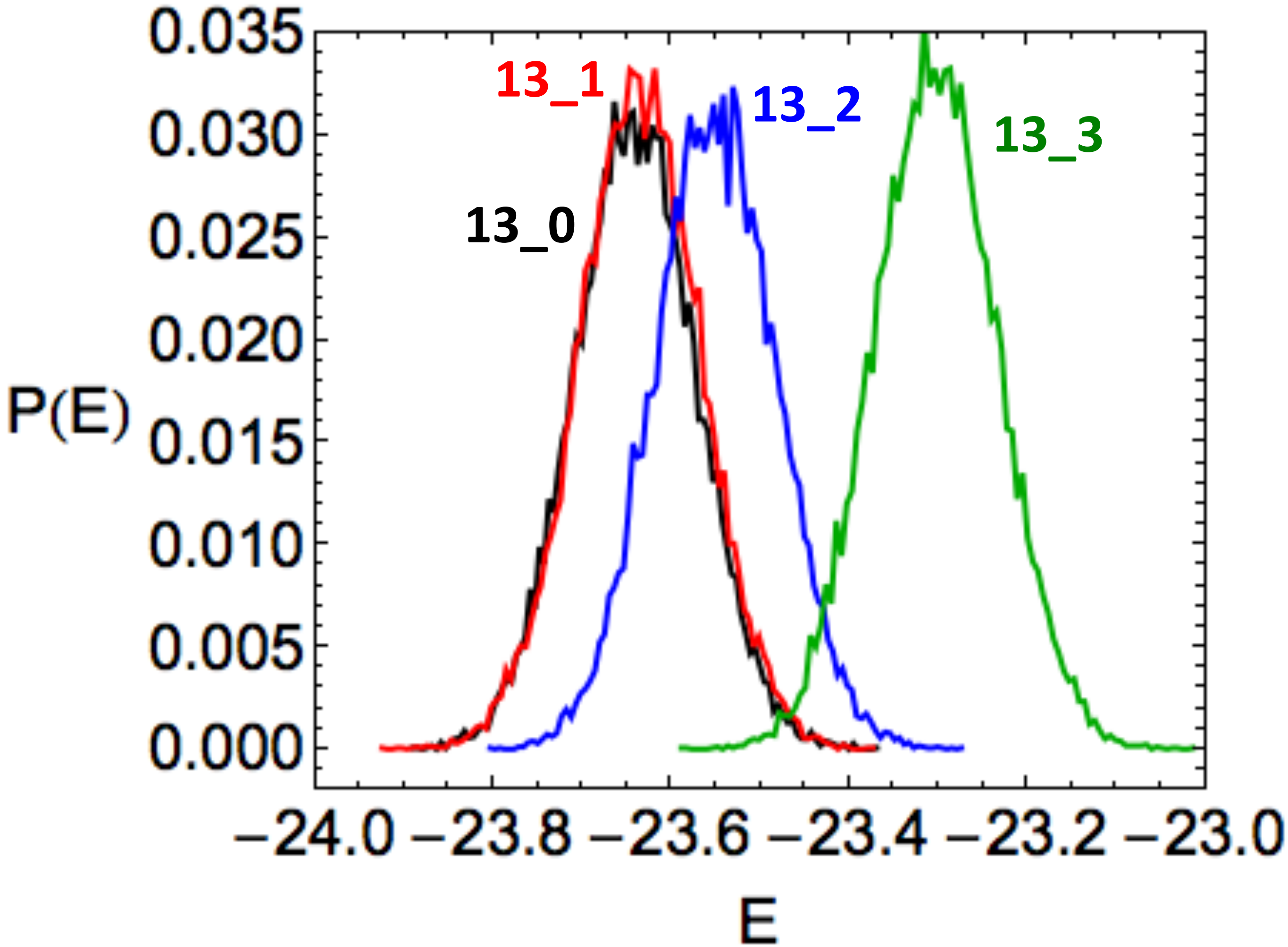
- Number of protofilaments (N)
- Pitch of helix (S)
- N_S stands for tubules with N protofilaments and pitch S
- Achiral wedges designed for 13_0 tubules



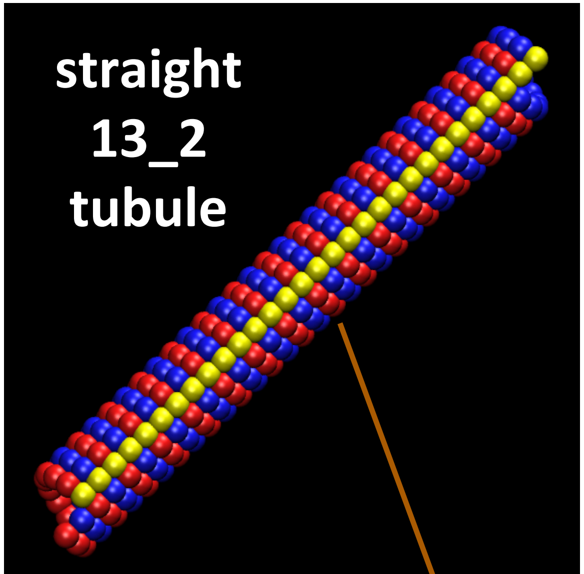
13_0 **13_1** **13_2** **13_3**

Energy Distribution

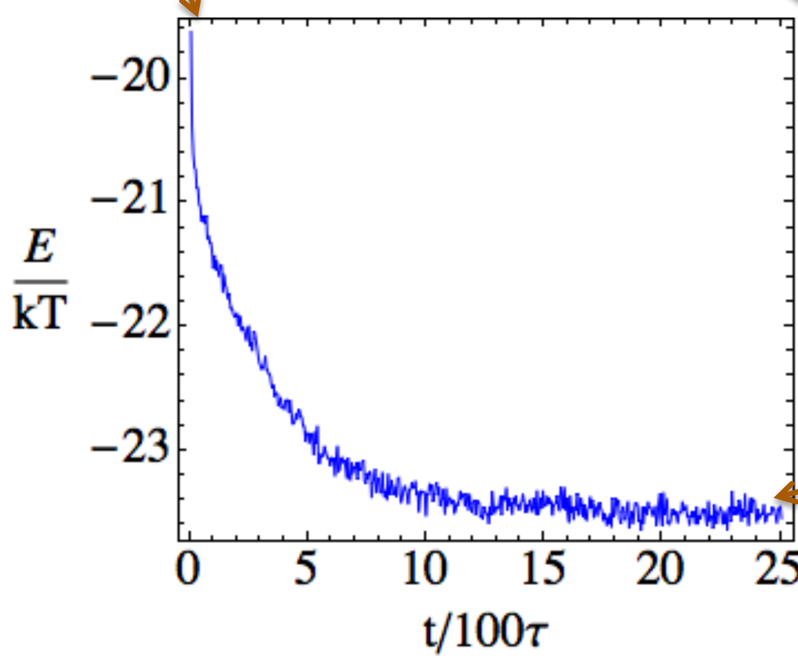
- N_S tubules with the same N but different S can have large overlap in energy distributions

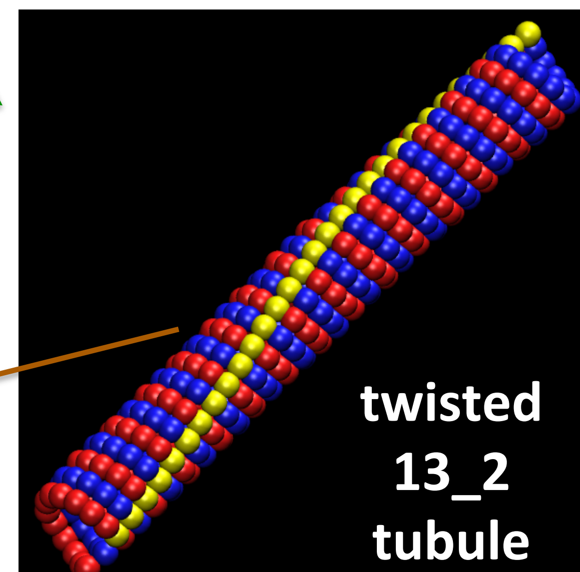


Twist Deformation of Tubules

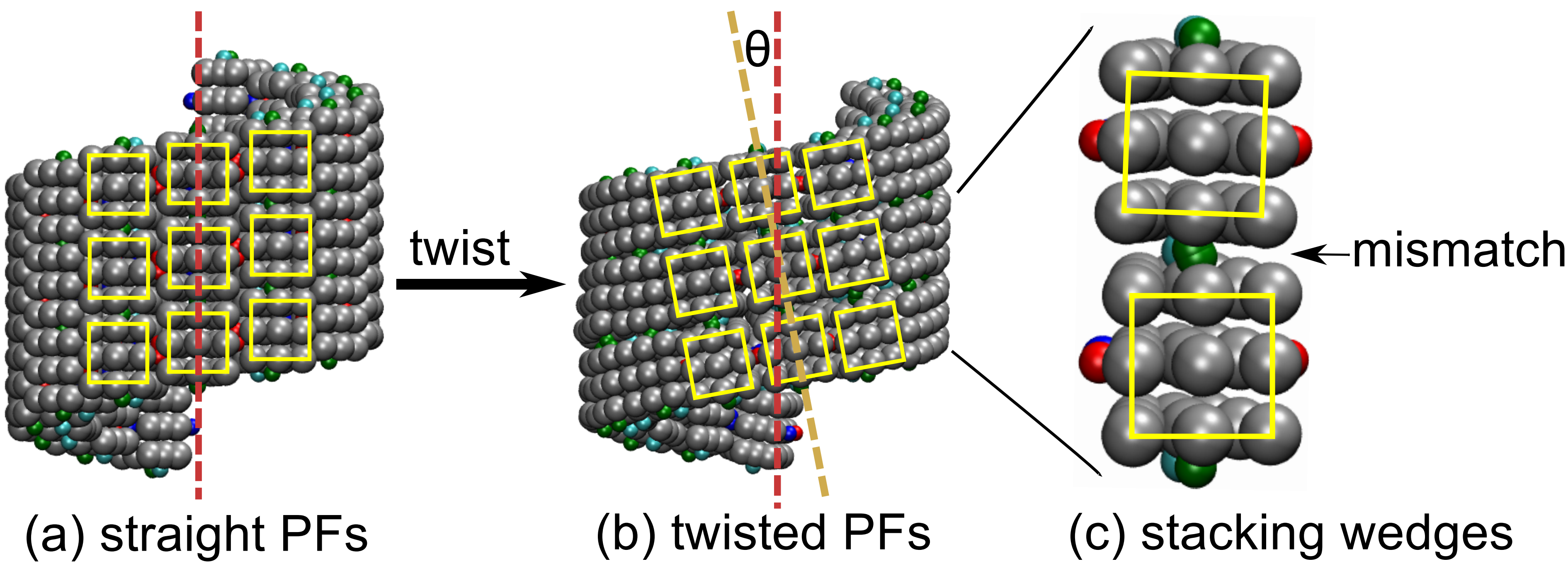


- Twist deformation stabilizes tubules with N_S ≠ 13_0





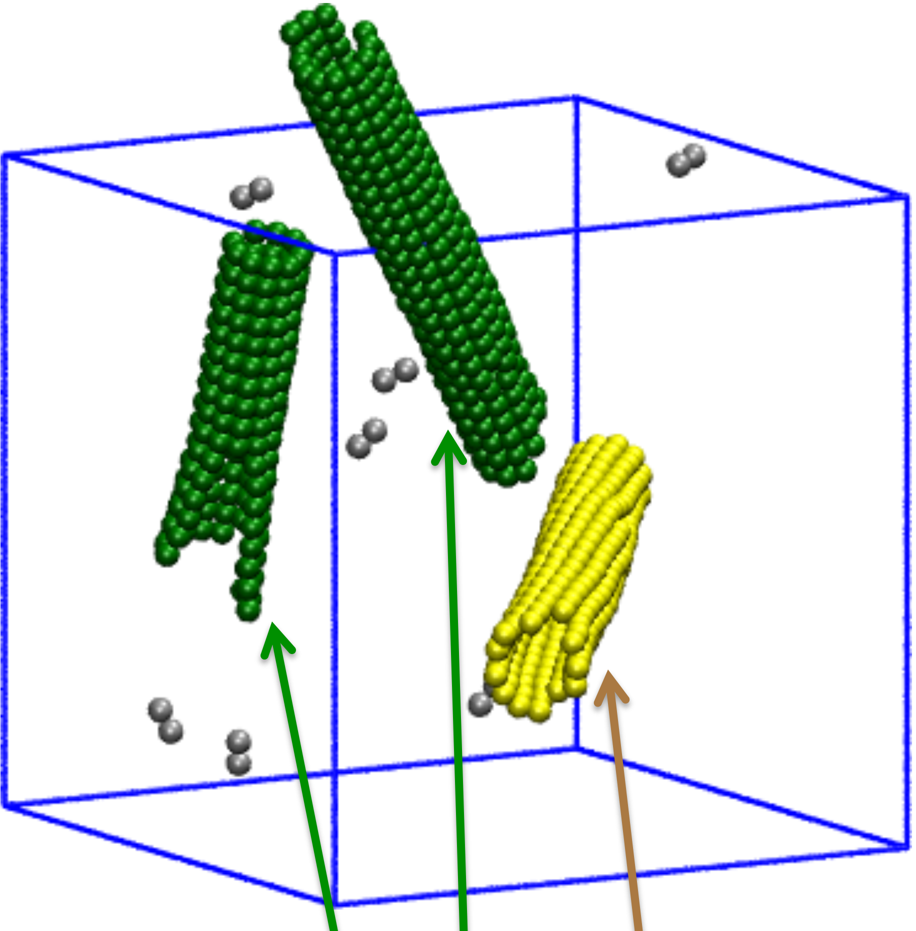
Twist Deformation of Tubules



- Twist leads to better packing of wedges ➔ lowers energy of tubules
- Twist introduces an offset between vertical binding sites ➔ constraint on twist
- Need strong vertical interaction to suppress twist

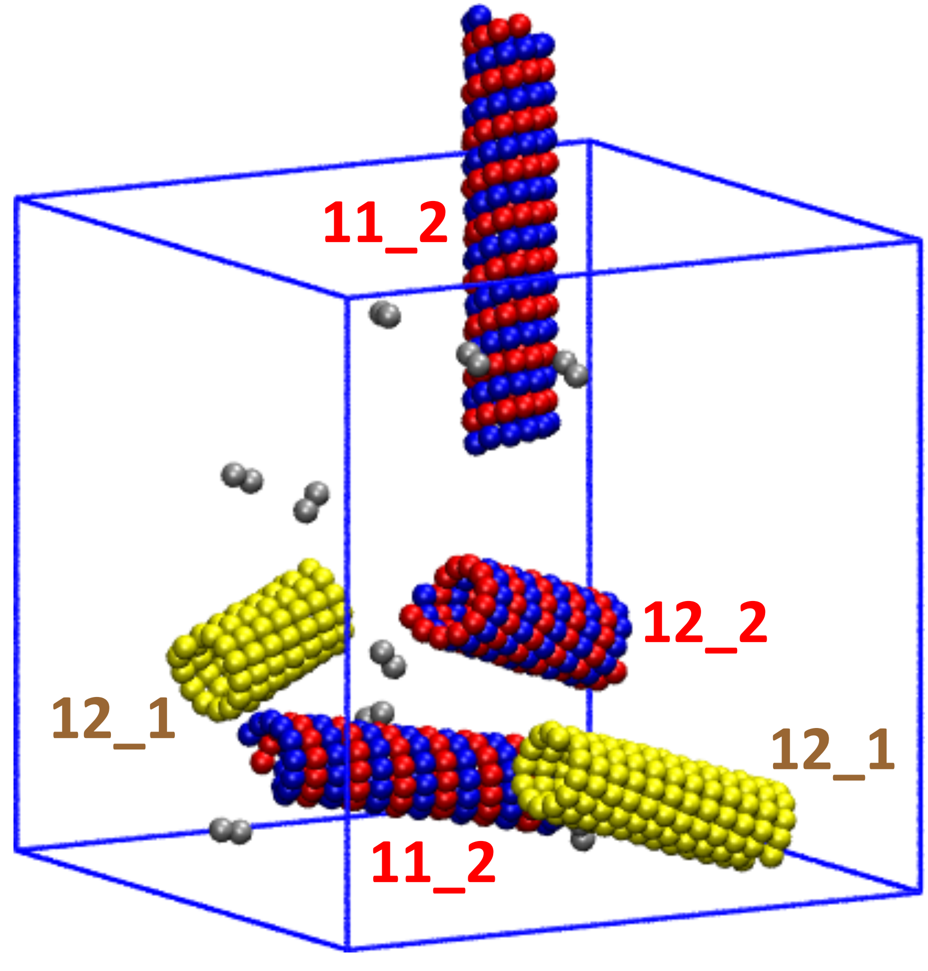
Effect of Interaction Strength on Assembly

- Fewer twisted tubules at $A_L < A_V$ for achiral wedges



11_0/12_0/12_1

A_L=3.0 < A_V=3.9

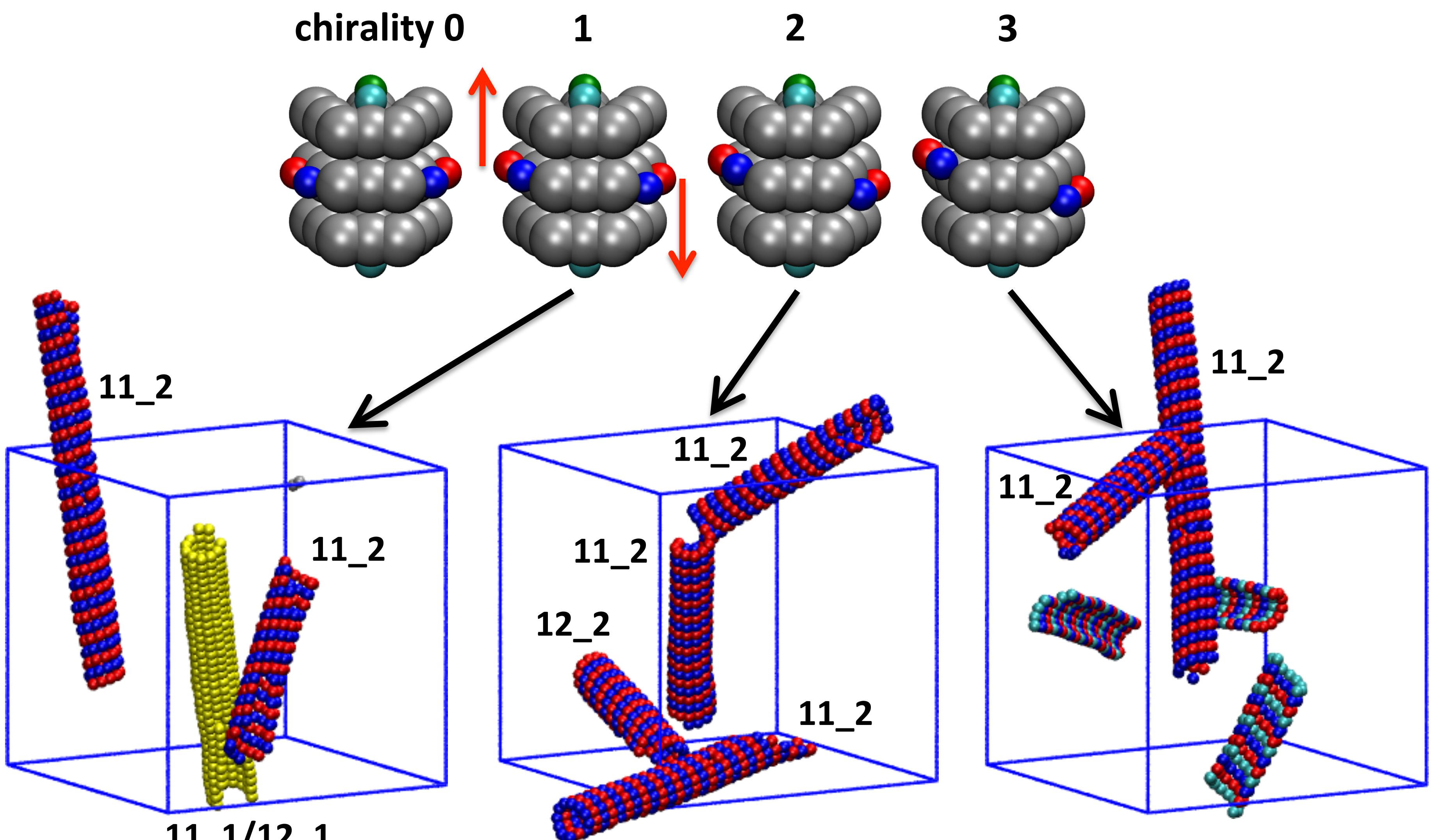


11_2/12_1/12_2

A_L=4.2 > A_V=2.6

Chiral Wedges

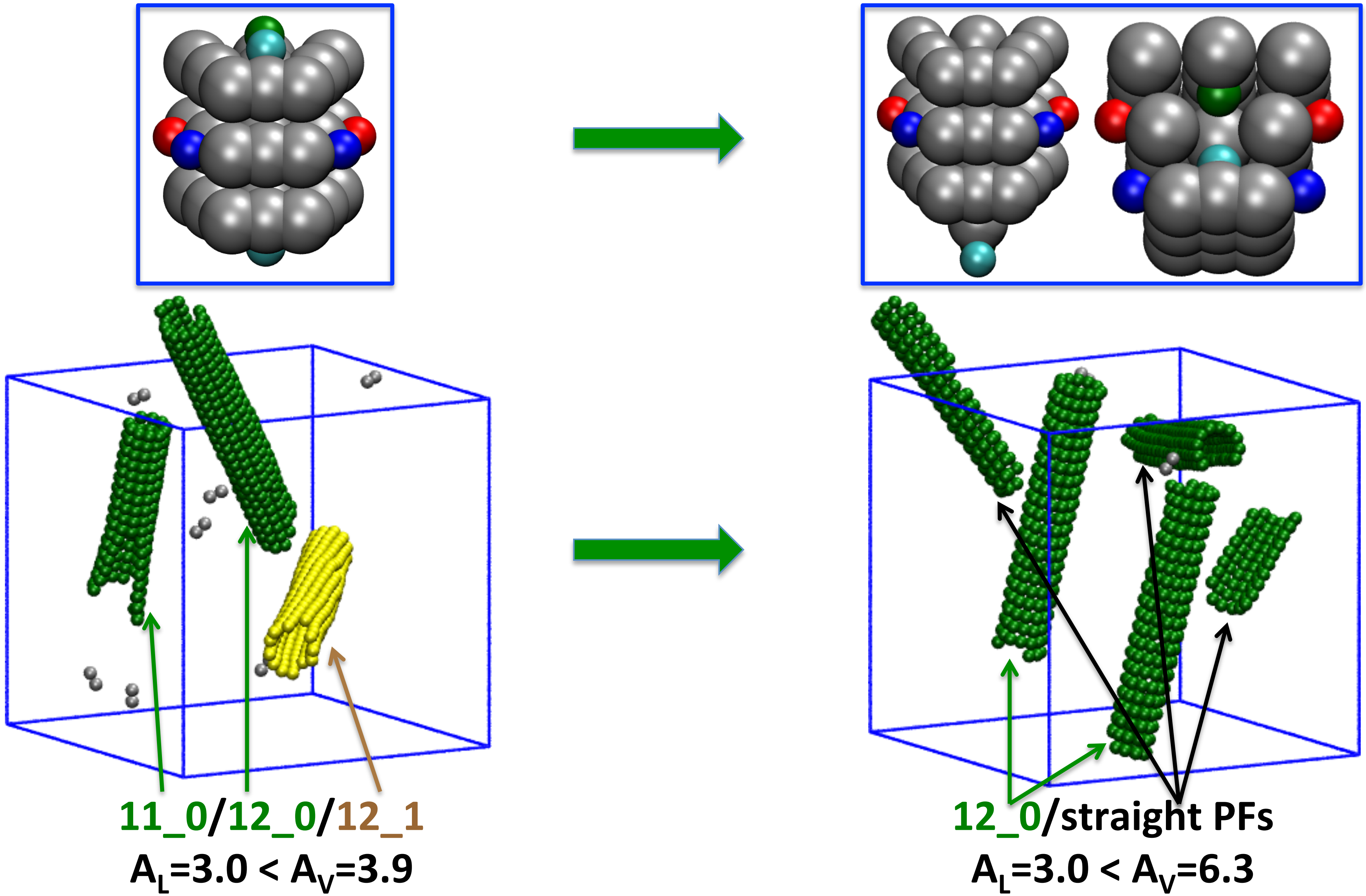
- **Shift lateral binding sites to make chiral wedges**



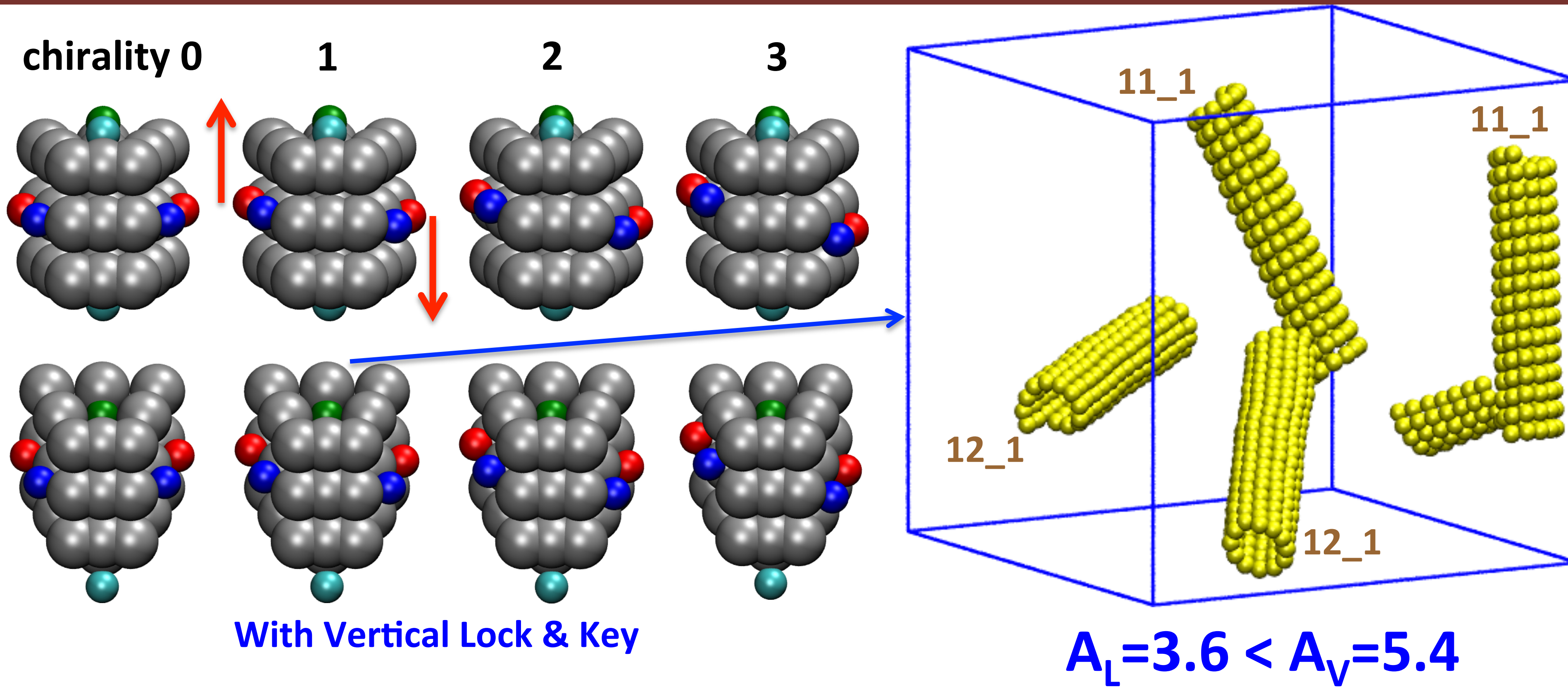
$A_L=3.0 < A_V=3.9$

Wedges with Lock & Key Vertical Binding

- **Shift vertical binding sites to make lock & key configuration**



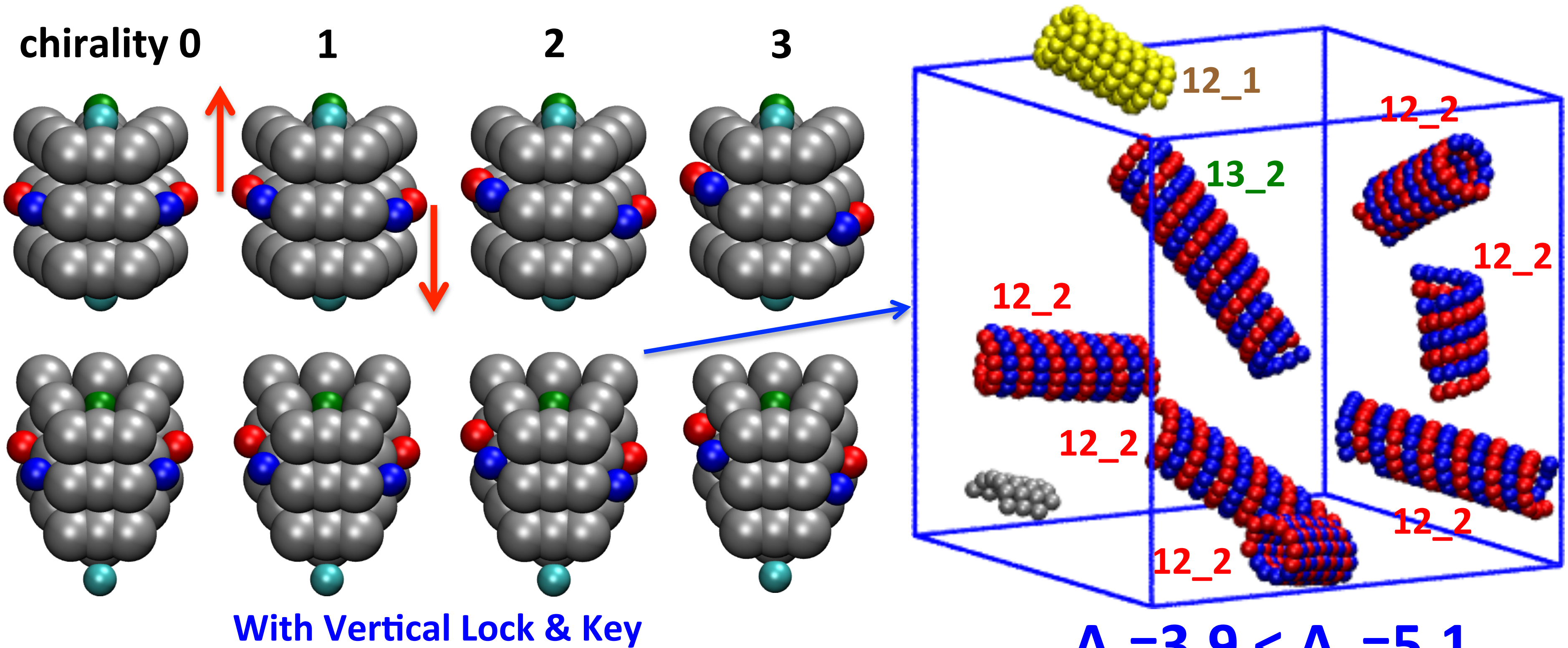
Combining Chirality and Lock & Key



- Shift lateral binding sites ➔ chiral wedges
- Combining chirality and vertical lock & key for structural control: **pitch of tubules = chirality of wedges**
- Better control occurs when $A_L < A_V$

Cheng and Stevens, in preparation

Combining Chirality and Lock & Key



$A_L=3.9 < A_V=5.1$

- Shift lateral binding sites ➔ chiral wedges
- Combining chirality and vertical lock & key for structural control: **pitch of tubules = chirality of wedges**
- Better control occurs when $A_L < A_V$

Cheng and Stevens, in preparation

Summary

- Tubules are only formed in a narrow range of interaction strengths
  - Delicate balance between energy and entropy
- Structural control in tubule self-assembly
  - Twist deformation
  - Interactions: need $A_L<A_V$
  - **Lock & key mechanism**
  - **Chiral building blocks**
  - Helicity of tubules
- Implications for microtubules and other macromolecule-assembled tubular structures