SAND2014-1491C

Self-assembly of Model Microtubules: Shape, Chirality and Twist

MARK J. STEVENS

Sandia National Laboratories

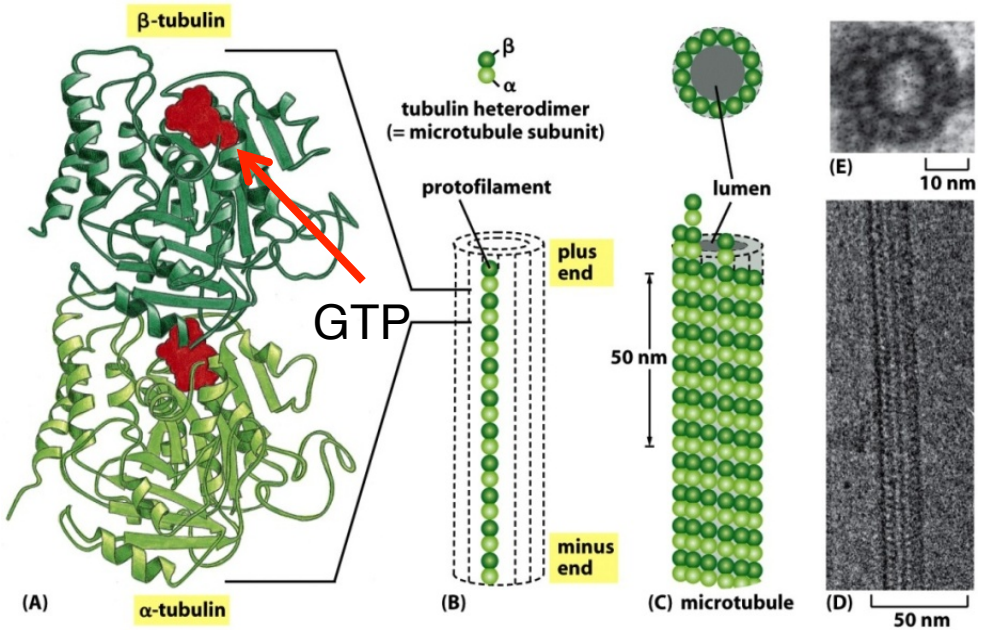
Center for Integrated Nanotechnologies(CINT)
msteve@sandia.gov

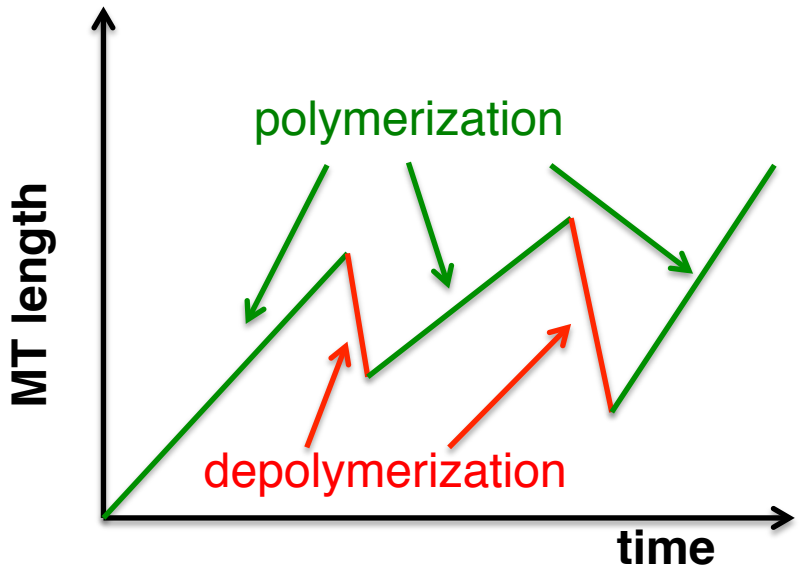
Shengfeng Cheng → Virginia Tech

Funding: Basic Energy Sciences

Microtubules

tubulin to microtubules





Alberts et al., *Molecular Biology of the Cell* (2008)

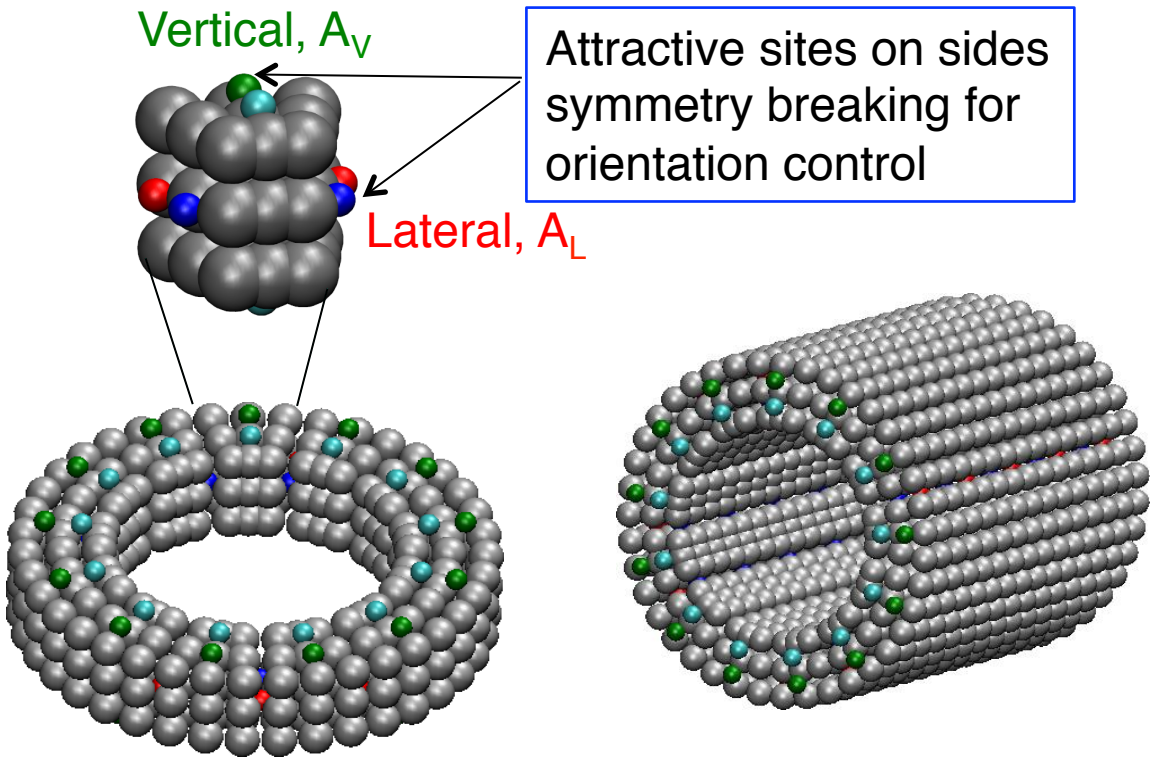
- chiral, tubular polymer
- 24 nm diameter
- most have 13 protofilaments
- very, very stiff
- dynamic growth & depolymerization
- track from motor proteins

Mark Stevens
msteve@sandia.gov

Monomer Model

Wedge monomer

- shape designed to produce rings that stack into cylinders
  - 13 wedges/ring
  - gray particles define shape
- gray particles interact purely repulsively
- attraction only between sites of same ‘color’
- implicit good solvent

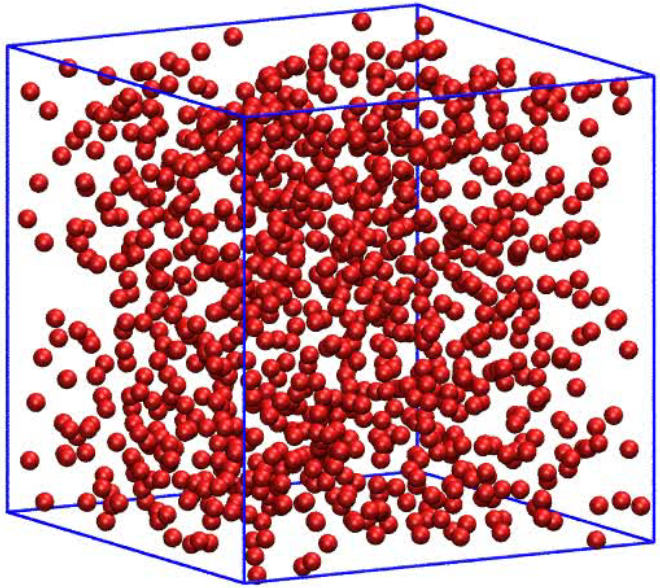


Mark Stevens
msteve@sandia.gov

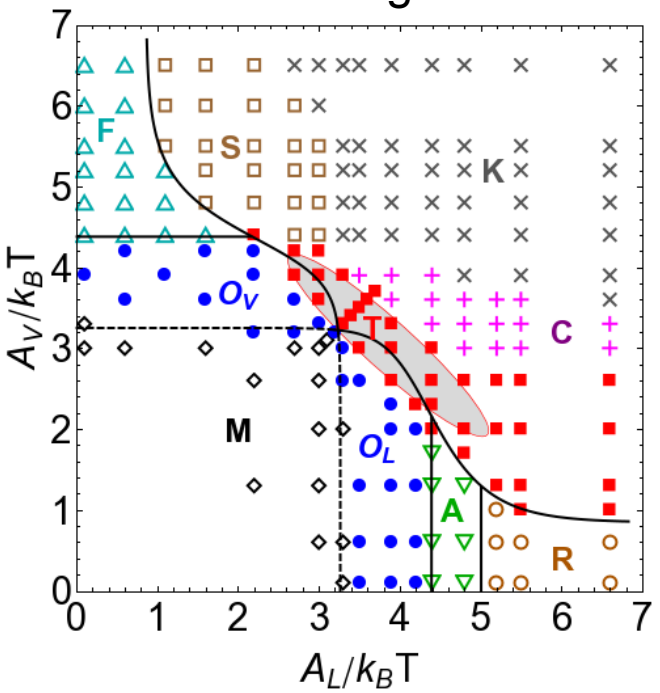
MD Simulations

- monomer is a rigid body
- standard NVT MD, ~ 1 billion time steps
- 1000 achiral wedge monomers

- Starting state: with A_L =4.2 kT and A_V =3.0 kT
- Wedge shown as single sphere
- Monomers to tubules

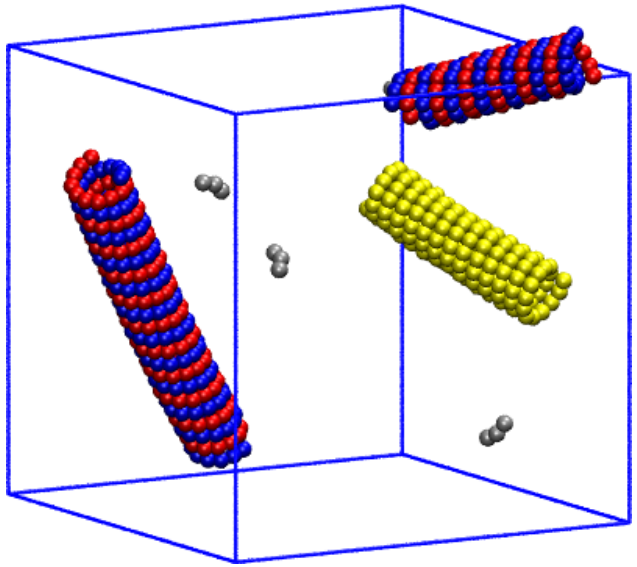


vary lateral A_L and vertical A_V interaction strengths

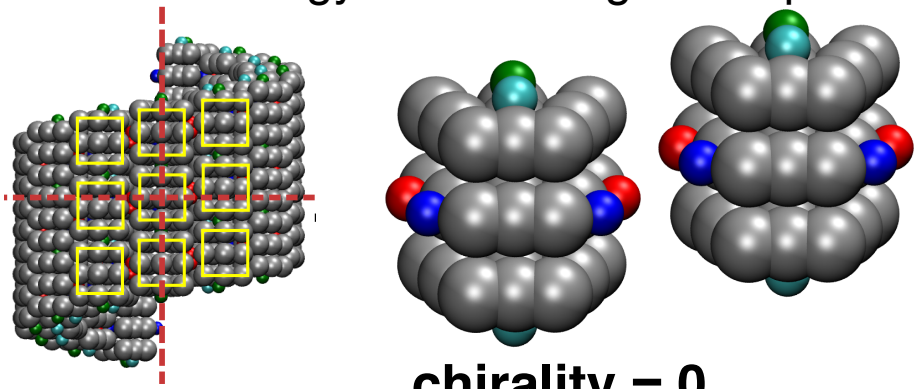


Mark Stevens
msteve@sandia.gov

Helical Tubules?



Shouldn't **mismatch** between attractive sites make the energy be much higher for pitch > 0?



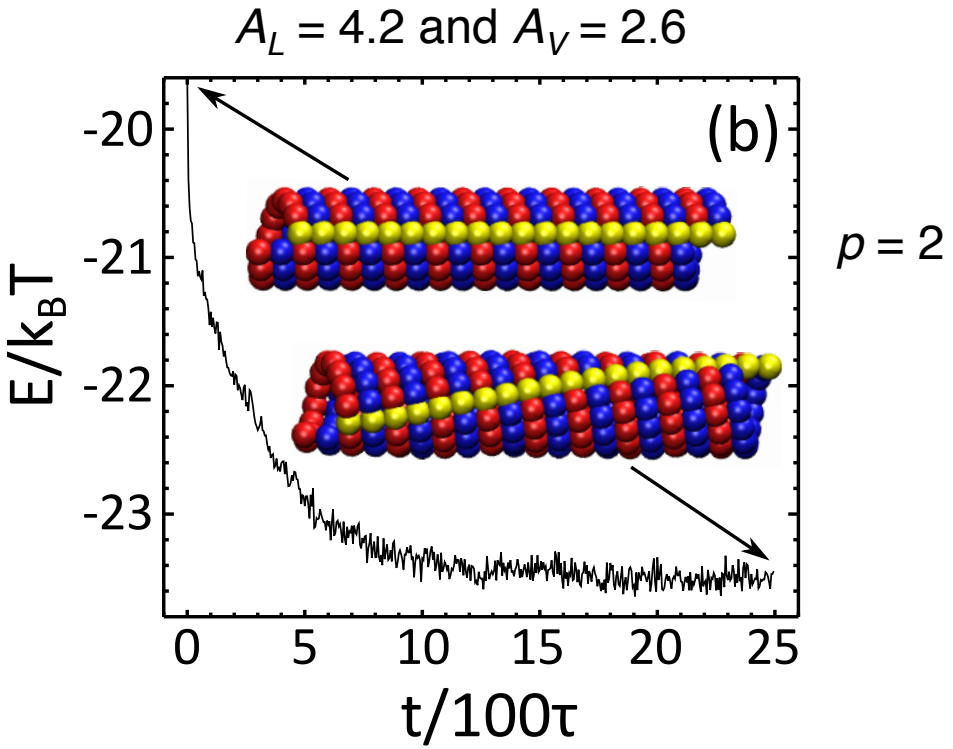
chirality = 0

Mark Stevens
msteve@sandia.gov

Twist & Energy

- Build tubule with pitch *p*
- Do MD
- Calculate energy distribution

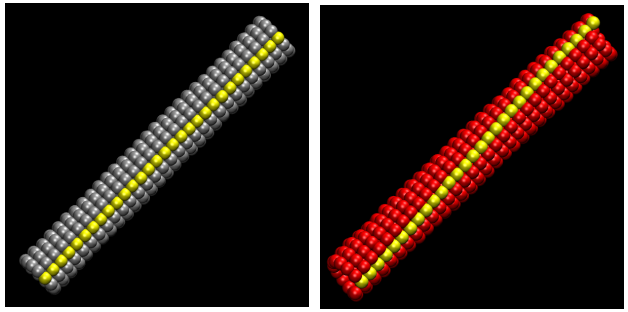
- Energy drops
- Tubule twists



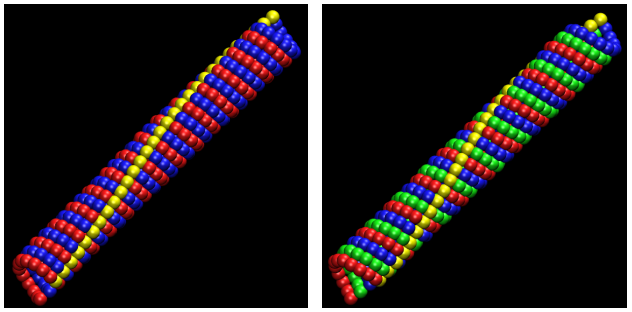
Mark Stevens
msteve@sandia.gov

Twist & Energy

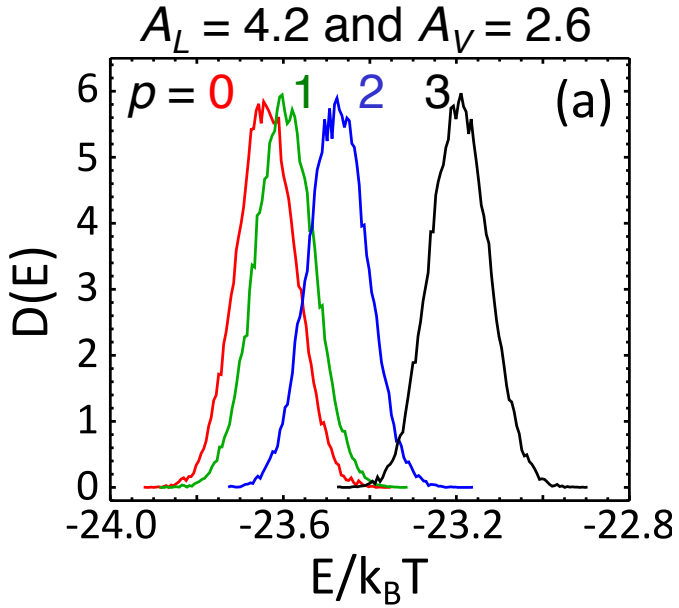
- Number of protofilaments (N)
- Pitch of helix (p)
- N_p



13_0 13_1



13_2 13_3

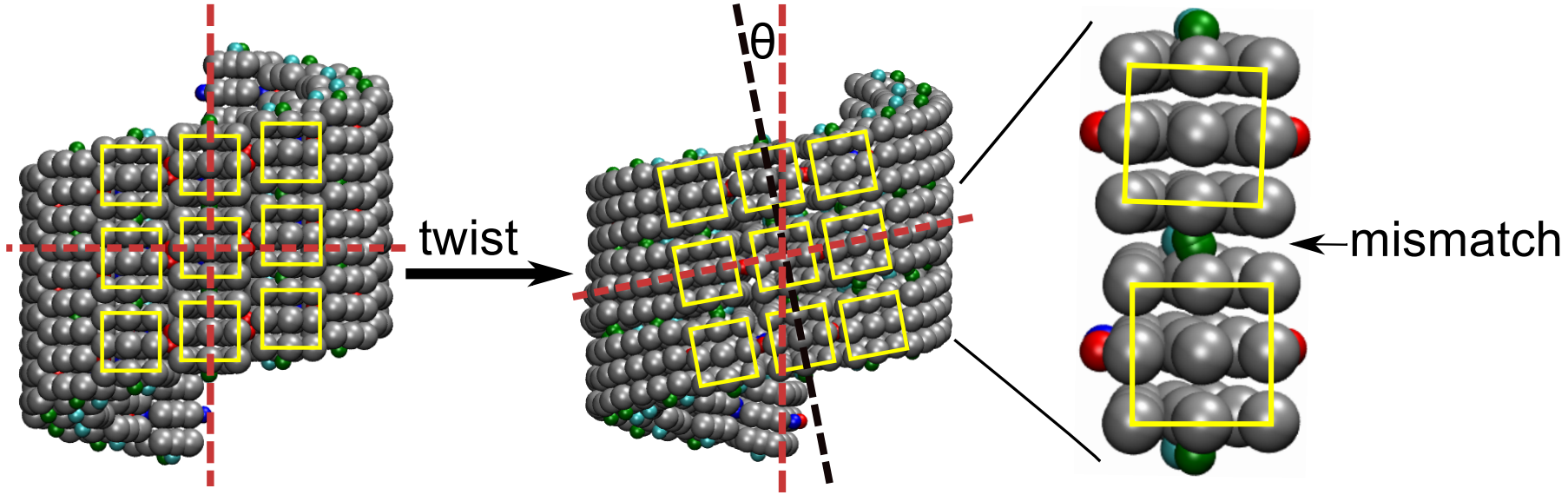


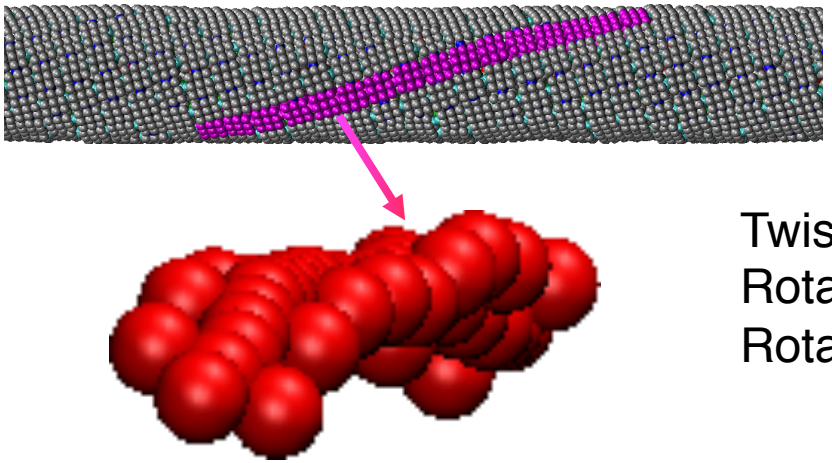
Overlap of D(E) ⟹ coexistence of different pitches

Why do p=0 & 1 overlap?
Why don't p=0 and 3 overlap?

Mark Stevens
msteve@sandia.gov

Twist & Alignment





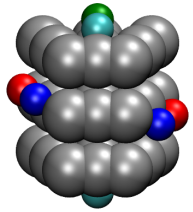
Twist:
Rotation about radial axis aligns lateral binding sites
Rotation about vertical axis misaligns vertical sites

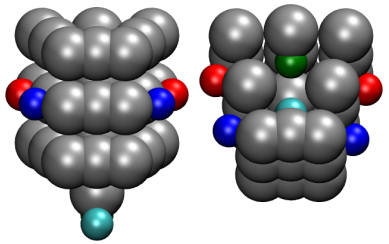
Mark Stevens
msteve@sandia.gov

Tubule Pitch

- How control pitch?
  - chiral monomer
  - reduce variation in pitch
- Twist misaligns vertical placement
  - increase A_v ?
  - lock & key

Chirality *c*
Shift positions of lateral site up/down to produce chirality





Lock & Key *LK*
Push central column down

Mark Stevens
msteve@sandia.gov

Modifying Monomer

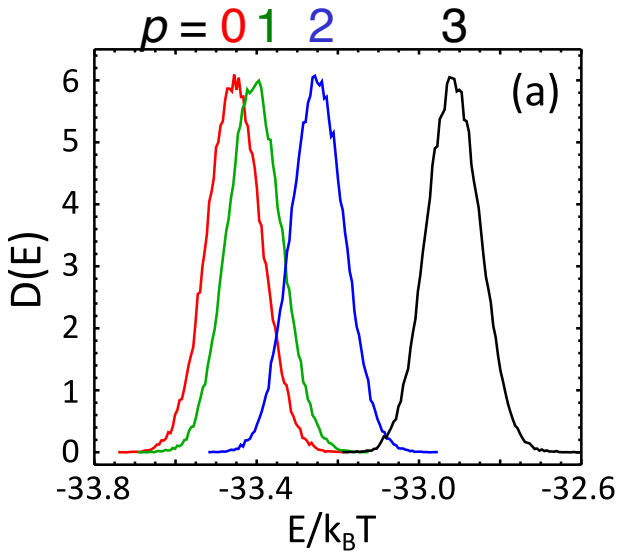
Make vertical mismatch expensive

$A_v > A_L$ better?

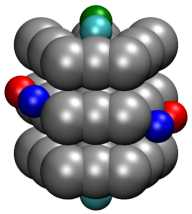
$A_V = 6.3$

$A_L = 3.0$

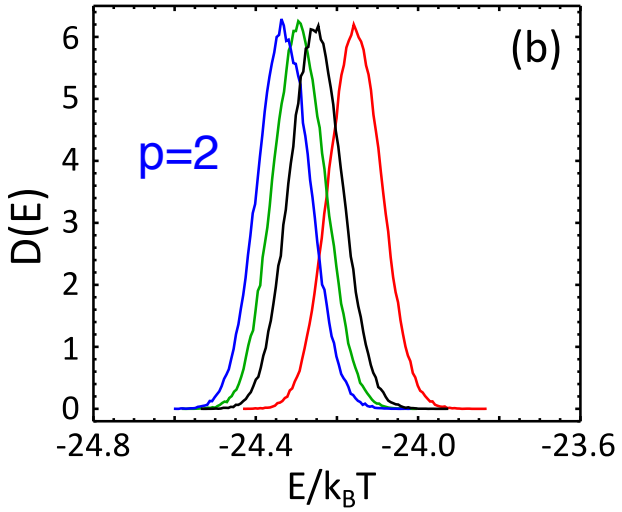
but kinetically trapped



Chirality $c \rightarrow$ tubule pitch p



Chirality does shift pitch values.



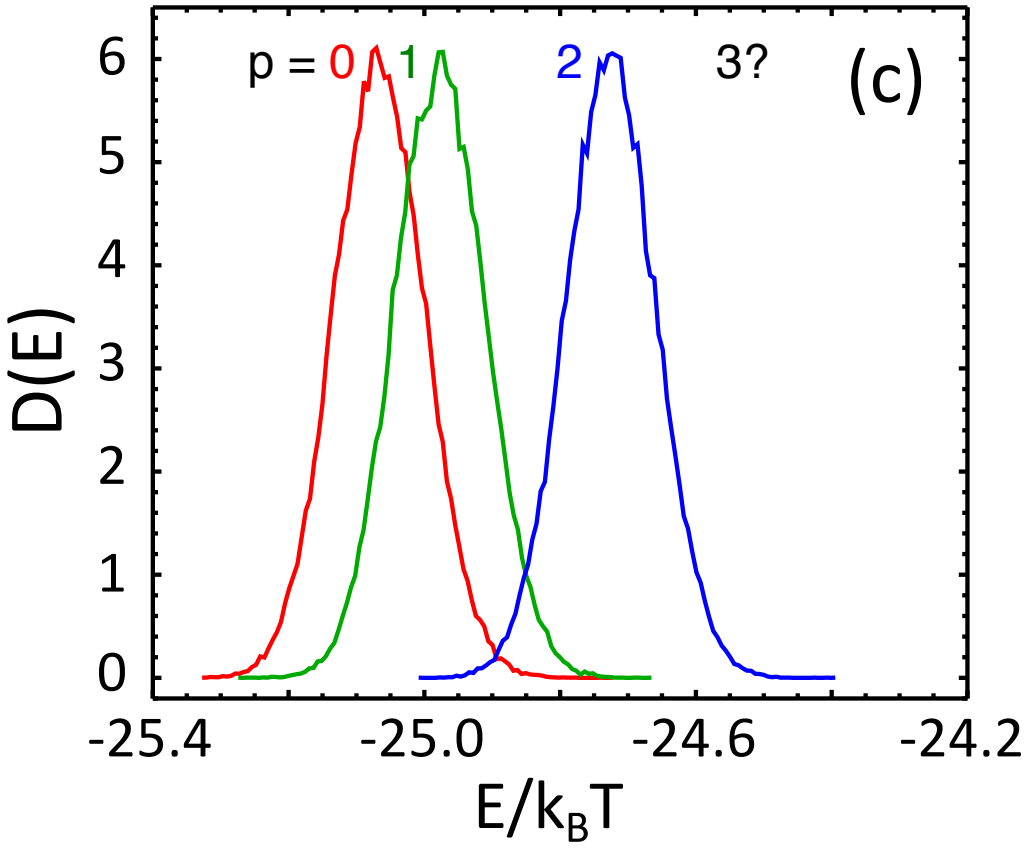
Mark Stevens
msteve@sandia.gov

Energy distribution

Lock & Key
(must increase A_V to insert key)
A_V = 6.3
A_L = 3.0

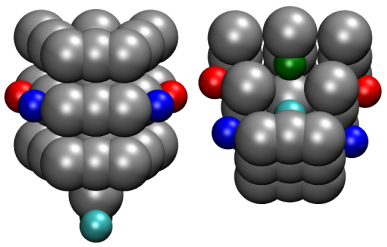
c=0

See increased separation of D(E) and disappearance of p=3.



Mark Stevens
msteve@sandia.gov

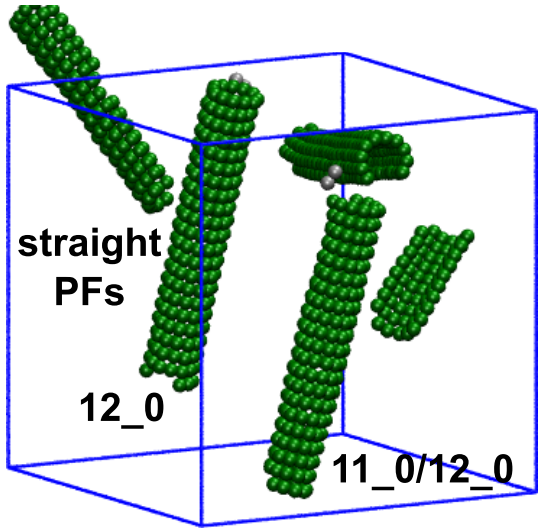
Lock & Key, Chiral Assembly



Need stronger vertical interaction, but cannot increase A_V

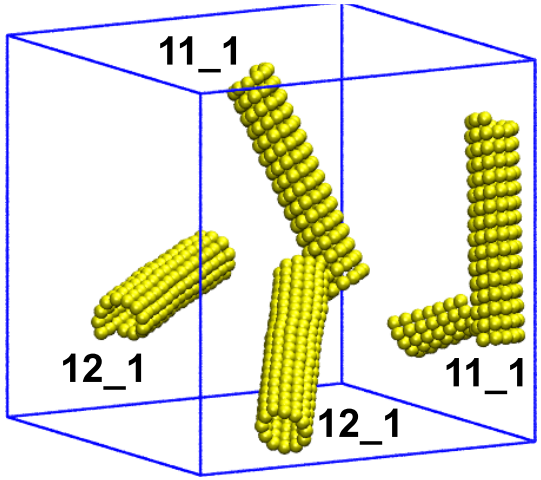
Introduce lock & key

It works!



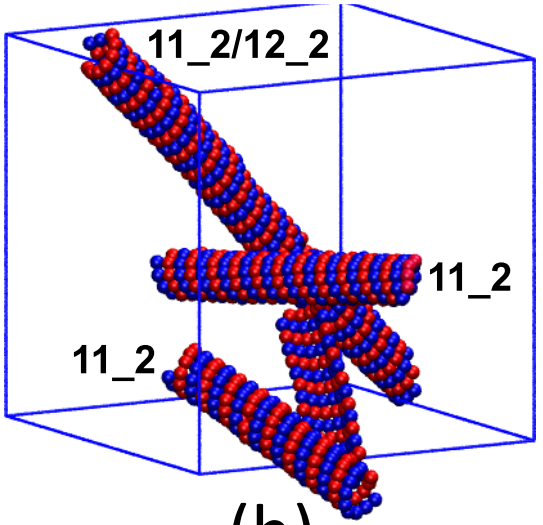
(f)

c=0
p=0



(g)

c=1
p=1



(h)

c=2
p=2

Mark Stevens
msteve@sandia.gov

Summary

- Model system forms tubules
- Have now introduced chiral and lock-and-key in monomer
- Twist allows multiple tubule pitch values
- Can control pitch better than should be able to
- Need strong vertical interaction to limit pitch values
  - true in microtubules
- Find a range of pitch and protofilament number in assembly simulations
  - true in microtubules

Future

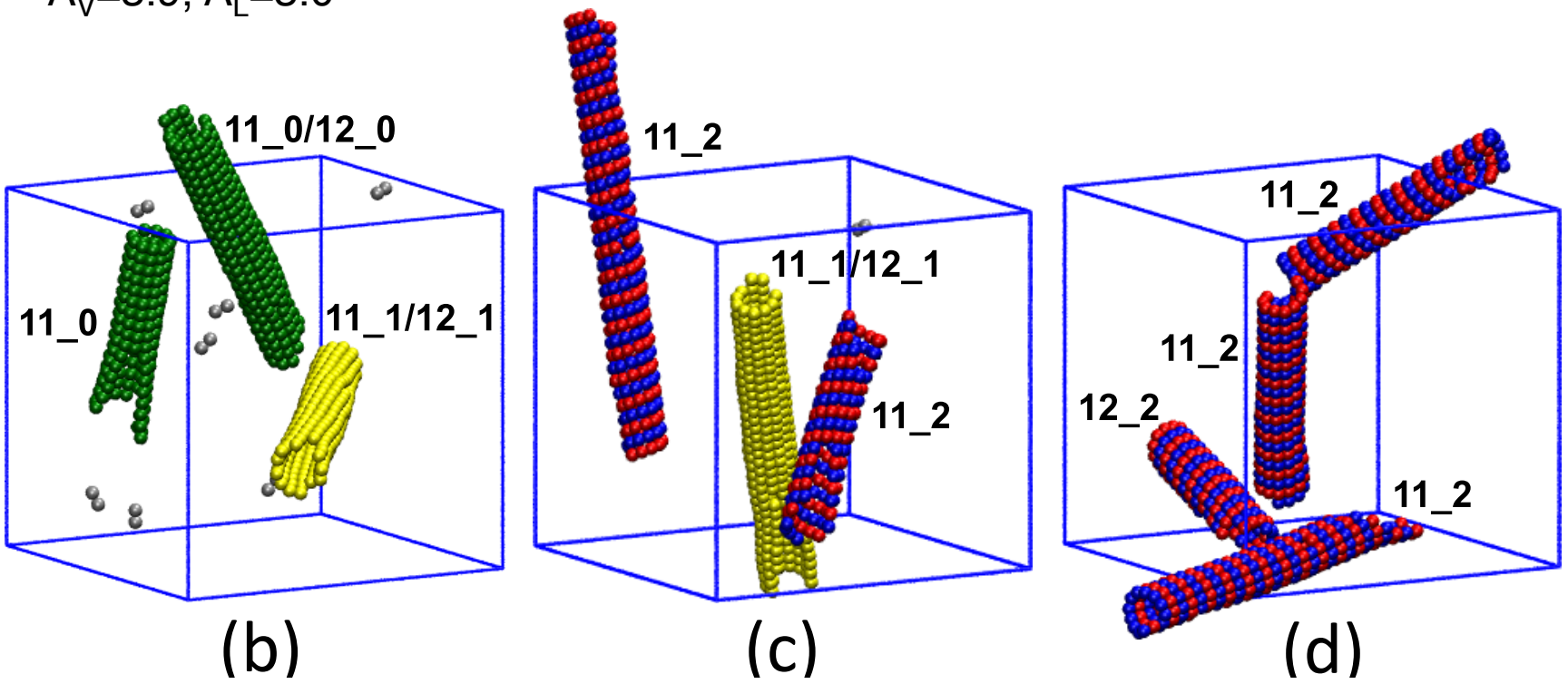
- mechanics
- model development
  - two state monomer (GTP/GDP)
  - dimer (Why is microtubule monomer a dimer?)
    - need for p=3?
  - charges (repulsion, attraction, longer range)
  - adjust wedge geometry to obtain N = 13 on average
  - explicit solvent (number of particles → ~ 1 Sagan)

Mark Stevens
msteve@sandia.gov

Mark Stevens
msteve@sandia.gov

Self-Assembly with Chiral Monomers

A_V=3.9, A_L=3.0



(b) (c) (d)

c=0
p=0,1

c=1
p=1,2

c=2
p=2!

Mark Stevens
msteve@sandia.gov

Microtubules

monomer is $\alpha-\beta$ tubulin

13 monomers per turn

24 nm diameter

polymerization/depolymerization

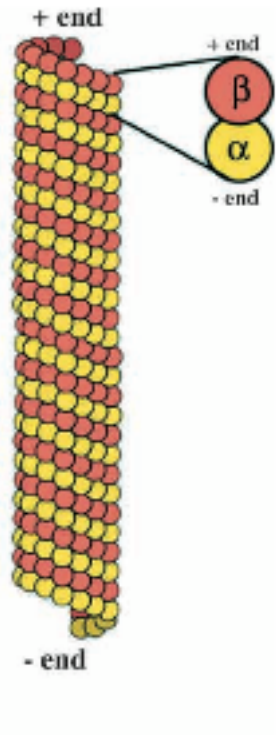
- protofilaments→sheets→tubules
- catastrophe
- polarity
- binding involves GTP/GDP

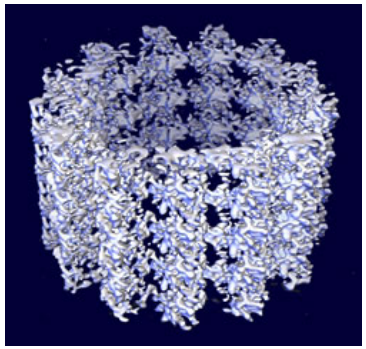
motor proteins walk on MT

tubulin polymers

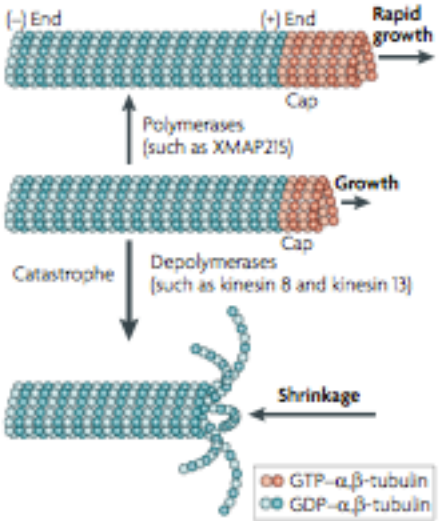
- straight: protofilaments, GTP bound
- curved: depolymerizing protofilaments/GDP bound

Microtubules are an example of heirarchically assembled structure with many interesting features.





GTP cap



GDP filaments bend

Mark Stevens
msteve@sandia.gov

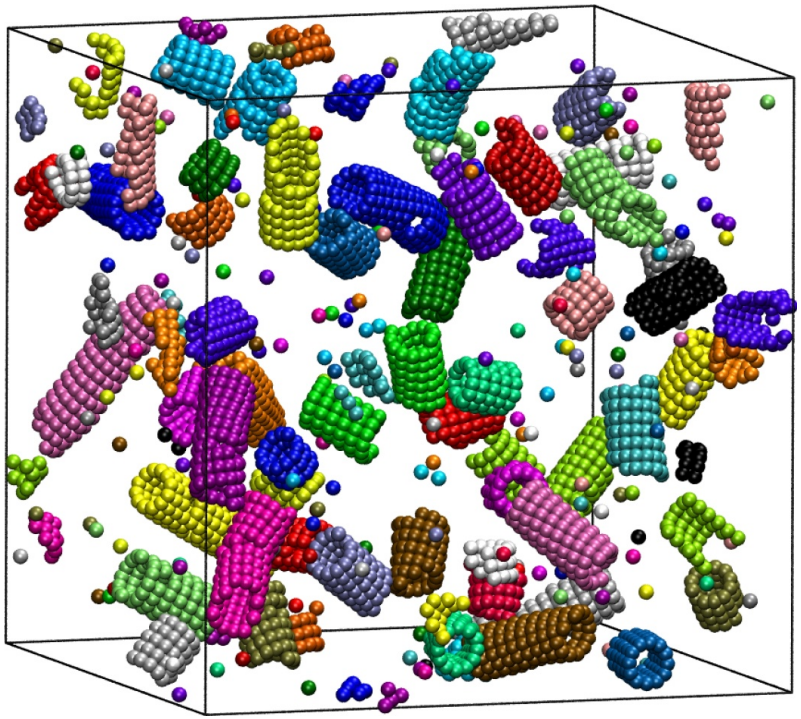
What are the factors that control assembly?

What features are necessary in the monomer?

The monomer is going to be a nanoparticle or a macromolecule (e.g. dendrimer) with large surface area.

- How do monomer shape and structure influence polymer structure (i.e. tubule).
- Where are interaction sites placed?
- How strong should they be?

Proteins as monomers possess a complex set of interactions.



Mark Stevens
msteve@sandia.gov

Artificial Microtubules (?)

Can we generalize microtubules? Can we make synthetic variations?
What do we need to know about the monomer building block?

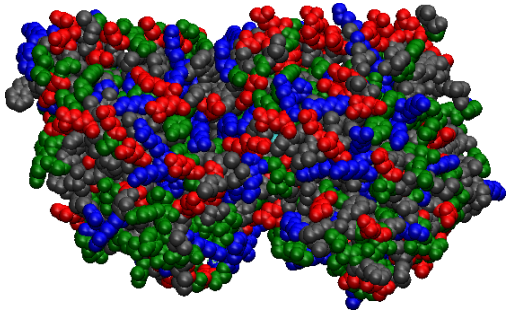
complex surfaces → set of interactions → complex systems

shape change (GDP/GTP binding) [energy driven system]

Very complex. Let's start 'simple.'

How assemble tubular polymer?
(focus on geometry first)

tubulin dimer



acidic, basic, polar, nonpolar

What features are necessary in the monomer?

- How do monomer shape and structure influence polymer structure (i.e. tubule).
- Where are interaction sites placed?
- How strong should they be?

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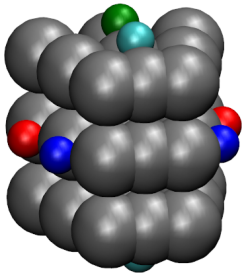
msteve@sandia.gov

Theoretical Structure Diagram

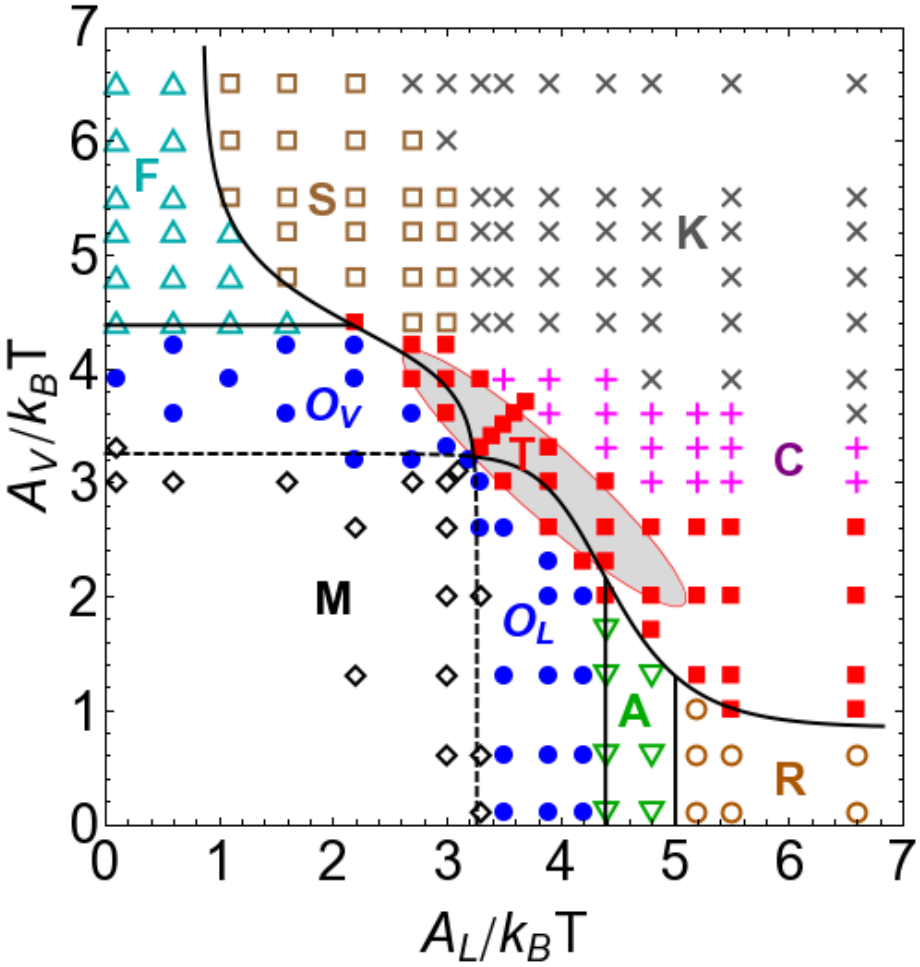
Each wedge is represented by a sphere.
Color represents cluster size.

M) no assembly
O) oligomers
F) filaments
A) arcs
R) rings
S) sheets
K) kinetically trapped (gunk)
C) clusters
T) Tubes

vertical, A_v



Lateral, A_L



Soft Matter, 2012

Mark Stevens
msteve@sandia.gov