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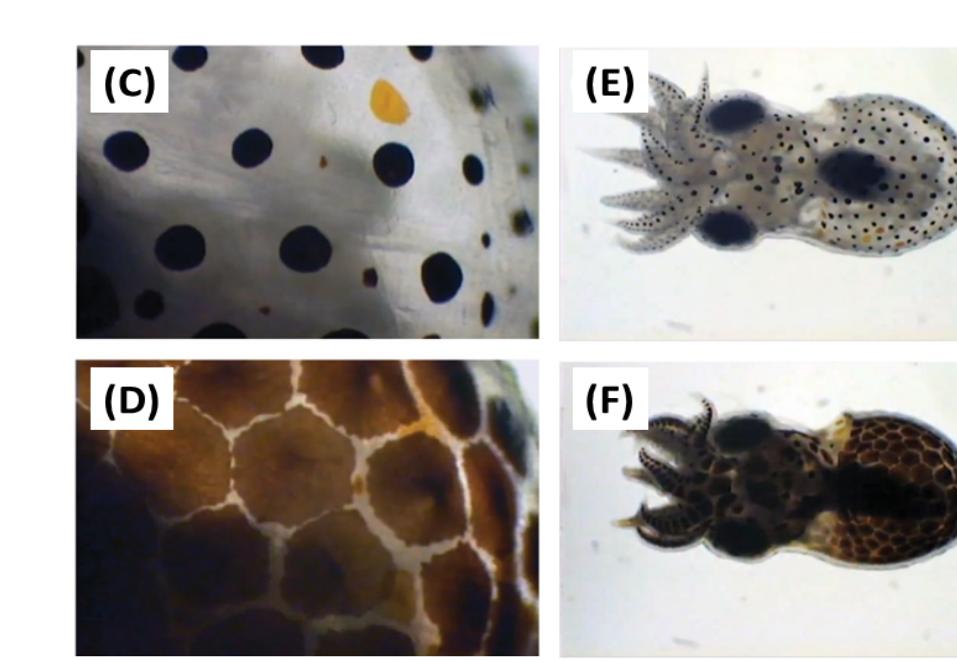
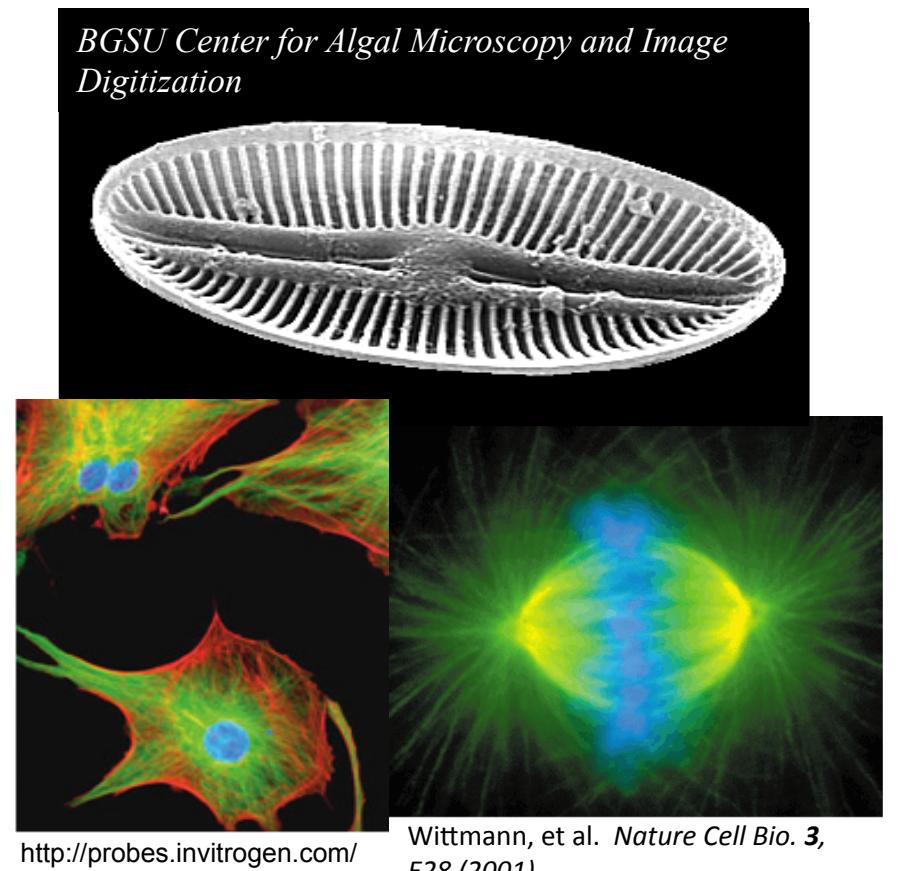
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Science Question and Significance: What are the effects of molecular shape change on dynamic assembly of biological and bio-inspired supramolecular materials? Utilizing new computational models and designer synthetic systems, we reveal new understanding of mechanisms for conformationally-mediated microtubule instability and demonstrate how directed changes in molecular shape can control dynamic nanostructures. These molecular-scale insights collectively advance new strategies to control dynamic and adaptive materials.

Project Description

Programmatic Goal:

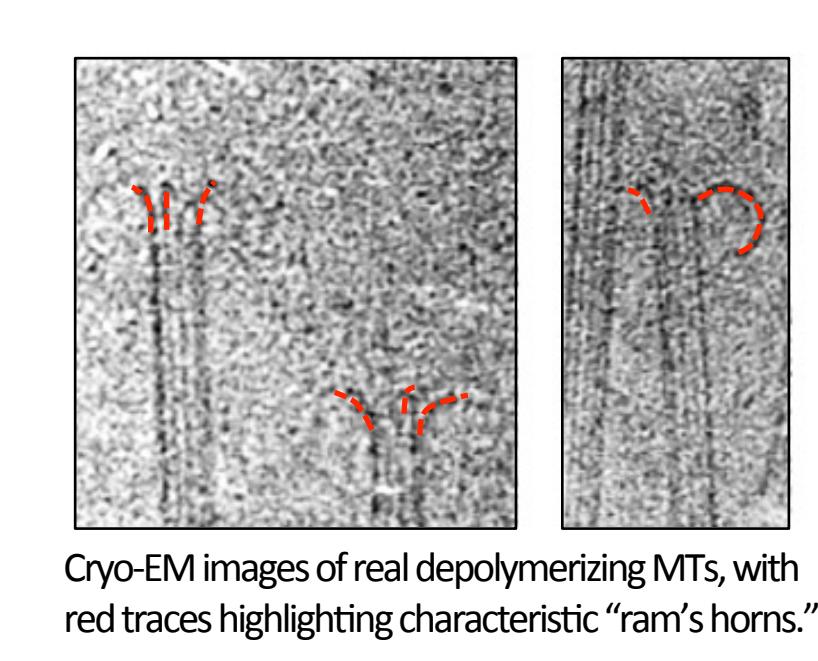
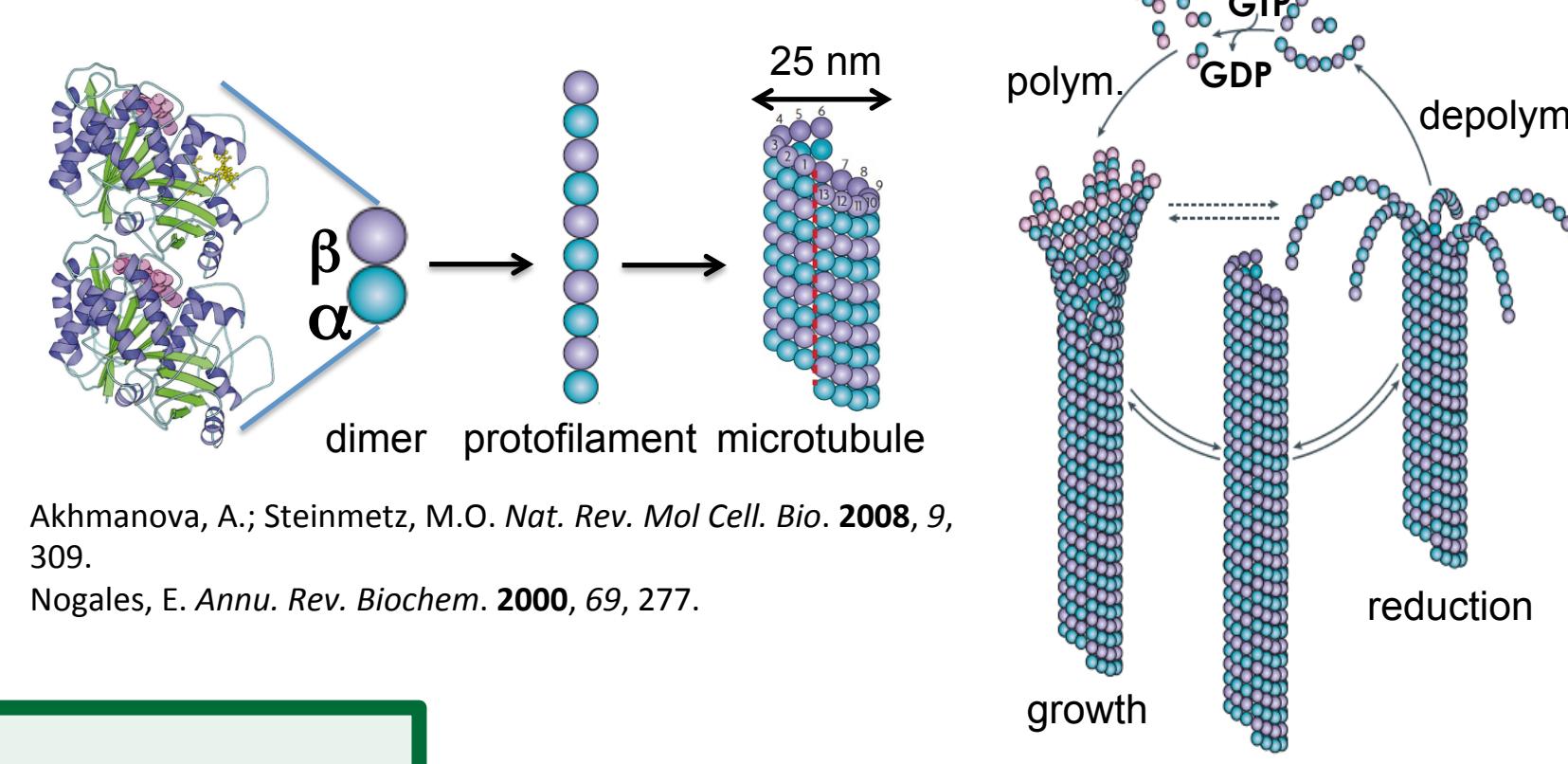
We aim to understand and apply key principles and strategies by which biomolecular and biomimetic systems exhibit programmed or self-directed dynamic, adaptable assembly, organization, and disassembly. Here, we explicitly combine theory and experiment to explore synthetic molecular systems that mimic elements of structure and dynamic function found in natural, energy consuming protein assemblies, such as microtubules (MTs).



E. Kretz, et al. *Journal of the Royal Society, Interface / the Royal Society* (2012)

Akhmanova, A.; Steinmetz, M.O. *Nat. Rev. Mol. Cell. Bio.* 2008, 9, 309.

Nogales, E. *Annu. Rev. Biochem.* 2000, 69, 277.



Cryo-EM images of real depolymerizing MTs, with red traces highlighting characteristic "ram's horns." Chretien D., Fuller S.D., and Karsenti E. *J. Cell. Biol.*, 129 (1995).

Technical Foci:

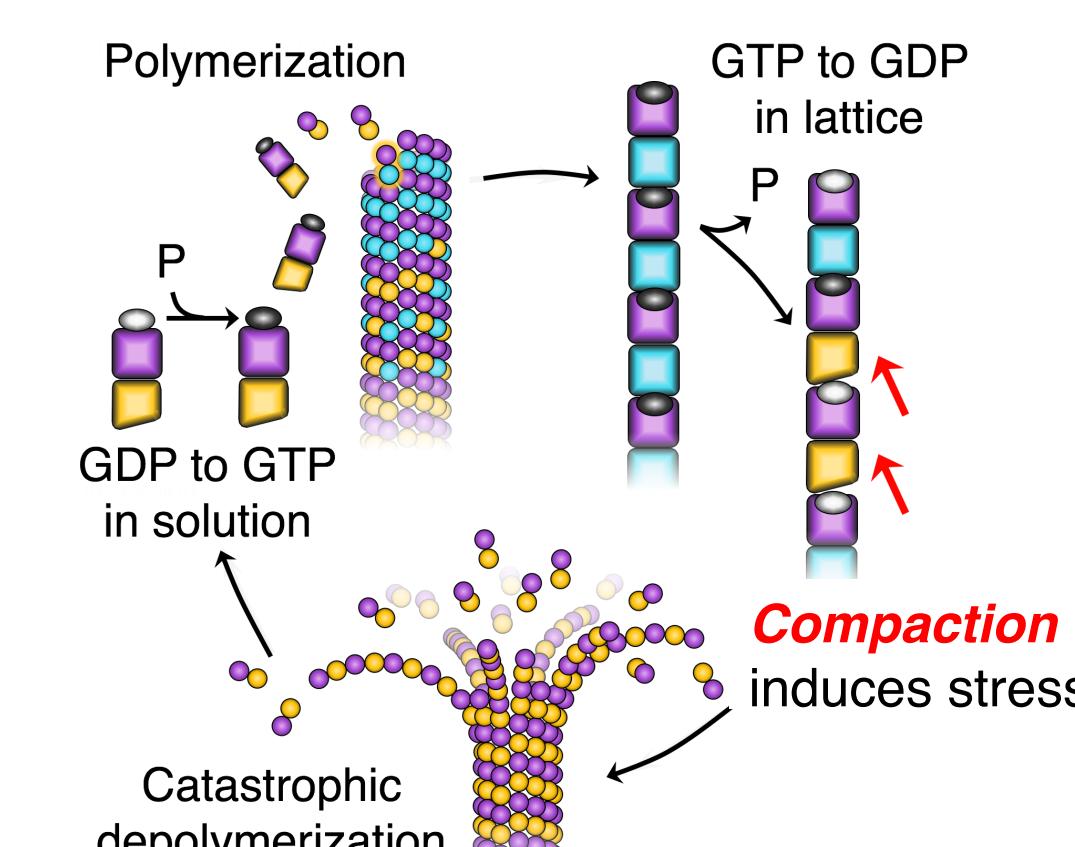
- Utilizing molecular simulations to understand driving forces for dynamic behavior in MTs
 - Intermolecular interaction strengths
 - Changes in molecular shape to control assembly
- Develop and study dynamic synthetic molecular systems that incorporate identified key driving forces to mimic dynamic supramolecular behavior seen in biology

Recent Progress

Simulating MT Instability

Jonathan Bollinger and Mark Stevens (msteve@sandia.gov)

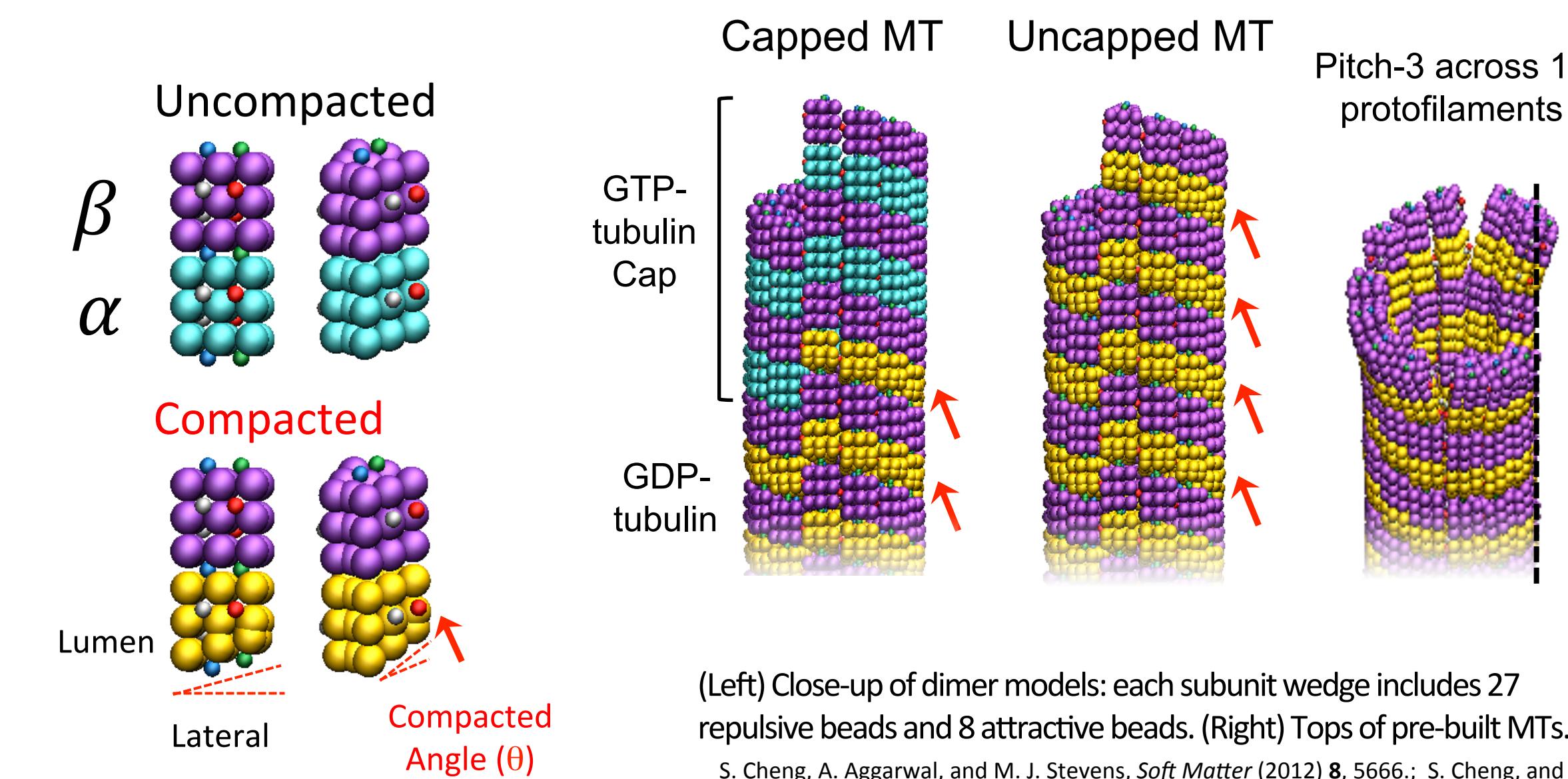
Inspiration: Dephosphorylation of tubulin-bound GTP is hypothesized to induce molecular shape changes that destabilize the MT.



Scientific Challenge: Can we simulate this process to understand the role of molecular-scale mechanical strain on MT dynamics?

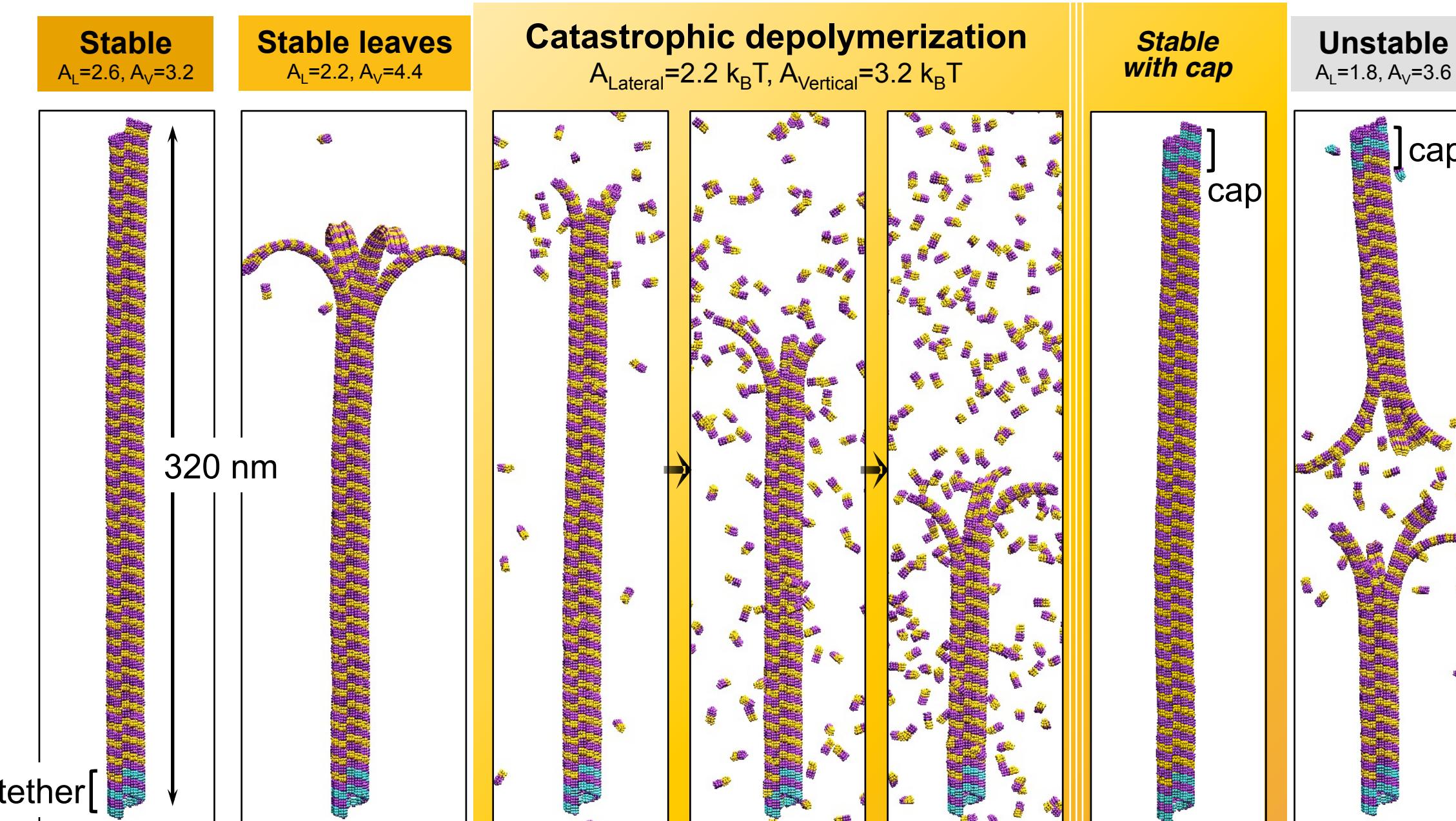
Technical Approach: Examine molecular dynamics (MD) simulations of MTs, built from a coarse-grained model of tubulin:

- Model α/β -tubulin as tubule-forming wedge-dimers with patchy attractions
- Angle $\theta=15^\circ$ mimics compaction of outer intermediate domain of α -subunit observed by cryo-EM and resembles "bent" tubulin
- Prebuild MTs with uncompacted/compacted dimers (optional cap)



(Left) Close-up of dimer models; each subunit wedge includes 27 repulsive beads and 8 attractive beads. (Right) Tops of pre-built MTs. S. Cheng, A. Aggarwal, and M. J. Stevens. *Soft Matter* (2012) 8, 5666.; S. Cheng, and M. J. Stevens. *Soft Matter*. (2014) 10, 510.

Molecular Dynamics Simulations

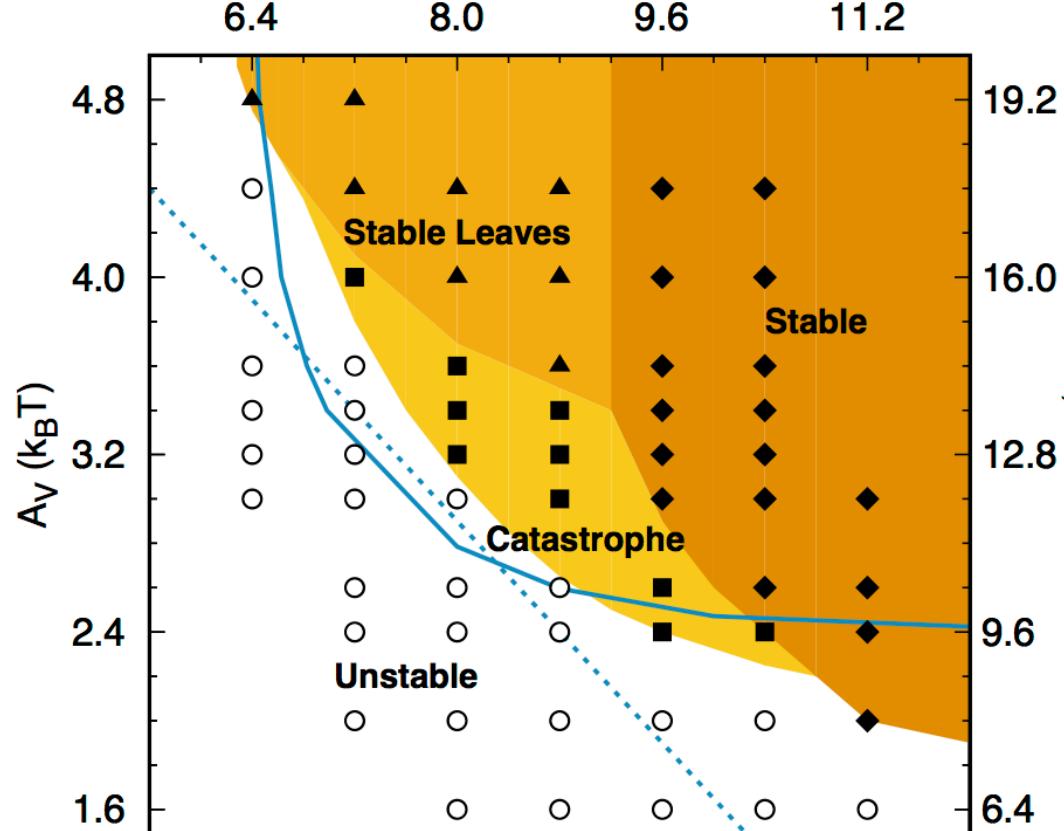


Simulation snapshots of MTs given various interaction strengths. MTs that are stable exhibit no unpeeling or breakage. MTs that exhibit stable leaves unpeel to a quasi-equilibrium length with minimal dimer ejection. MTs undergoing catastrophic depolymerization unpeel and eject dimers (shown as time-lapse) unless stabilized by an uncompacted cap. MTs are considered unstable if they exhibit spontaneous breakage even when capped. (J. Bollinger and M. Stevens 2017)

- For uncapped MTs built with **compacted** dimers, we observe catastrophic depolymerization at select attraction strengths
- Exposed dimers are released from "ram's horns," closely resembling cryo-EM images of depolymerizing MT
- Depolymerization can be **averted by cap region of GTP-tubulin**, as in experiments. (Mitchison T. and Kirschner M. *Nature*, 312 (1984).
- Sufficiently strong interactions prevent dimer dissociation and even unpeeling

Although MT instability has been **observed** experimentally, it is **extremely difficult** to explore these processes mechanistically. Our studies illustrate a **powerful new way** to systematically interrogate this type of dynamic system.

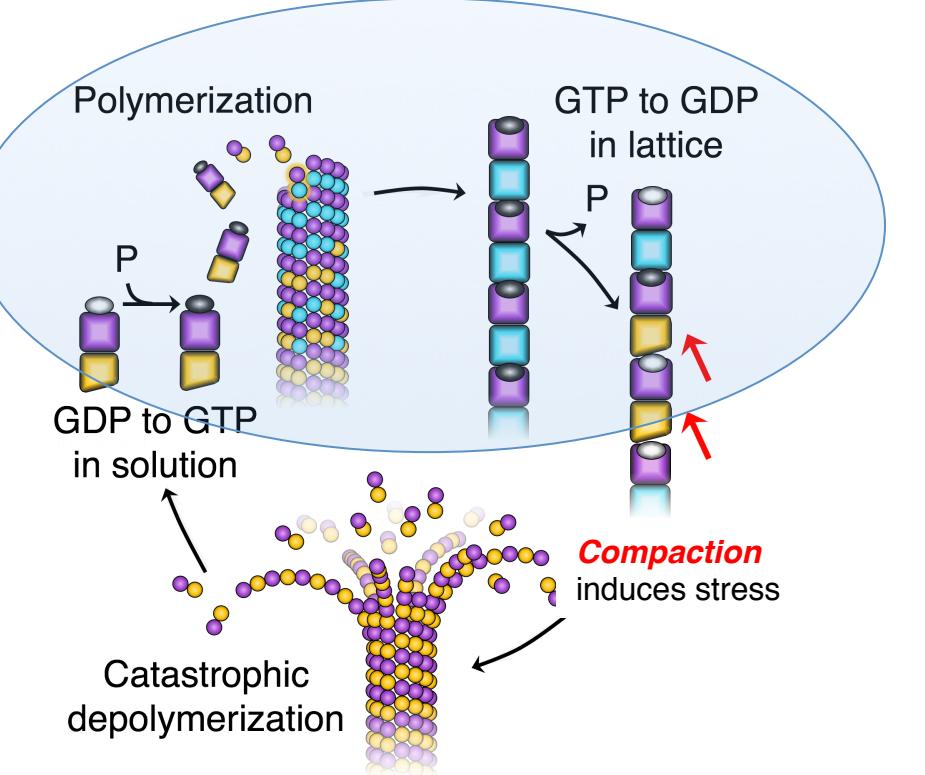
- Biologically, this work helps confirm hypotheses around the role of molecular contraction and GTP hydrolysis on dynamic instability.
- In materials science, this work reveals key parameters and new mechanisms to control dynamic, synthetic materials.



Behaviors of **compacted** MTs as function of vertical A_v and lateral A_l attraction strengths. Secondary axes show the total absolute attraction energies possible between bonded lateral or vertical surfaces of subunits on two adjacent dimers. Solid symbols denote where uncapped MTs exhibit catastrophe, stable leaves, or stability, but capped MTs are perpetually stable. Open circles denote where compacted MTs are unstable with or without caps. Blue lines show boundaries of rapidly increasing stability for **uncompacted** MTs.

A. Martinez, E.D. Spoerke, et al. (2017)

Simulation and Modeling



Depolymerization

- Vary distribution of compacted entities and introduce assembly defects
- Explore alternative stabilizers (e.g., MAPS, Taxol, etc.)

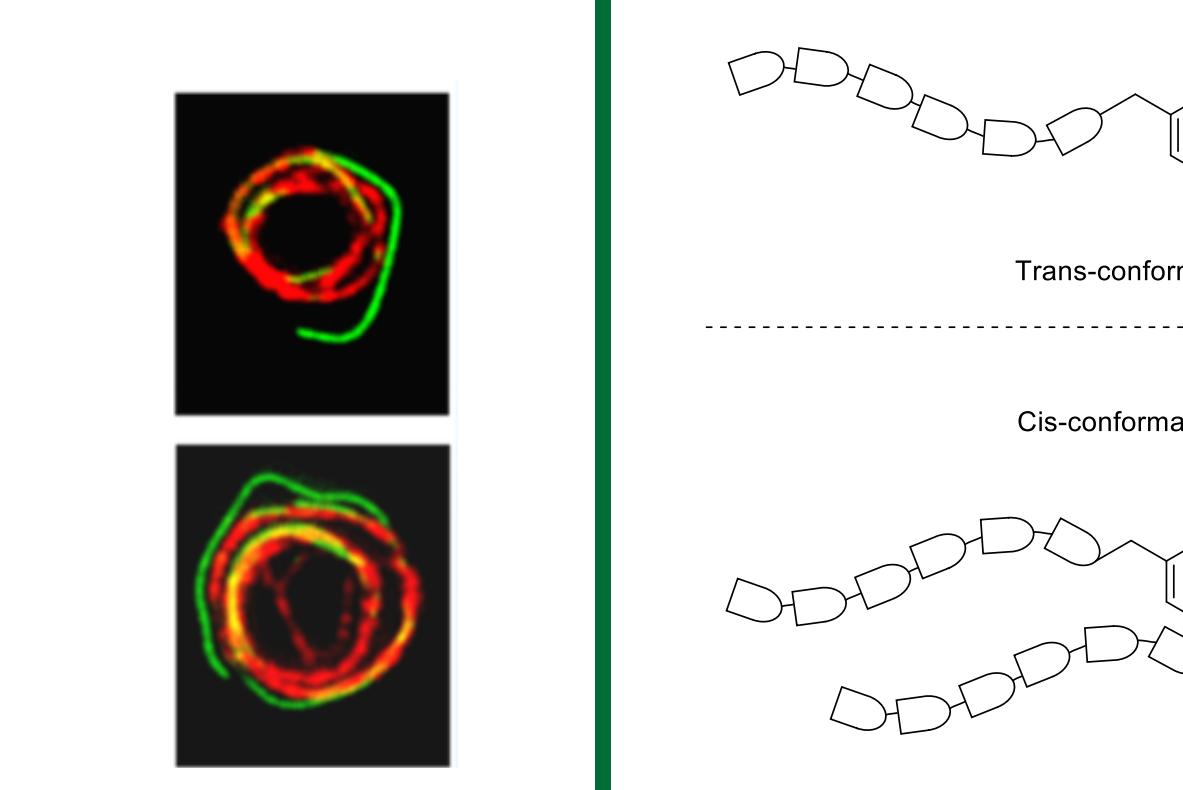
Full cycle dynamic assembly

- Demonstrate MT polymerization
- Introduce "change of state" function for autonomous dynamic assembly/disassembly

Expanded "switch-based" simulations

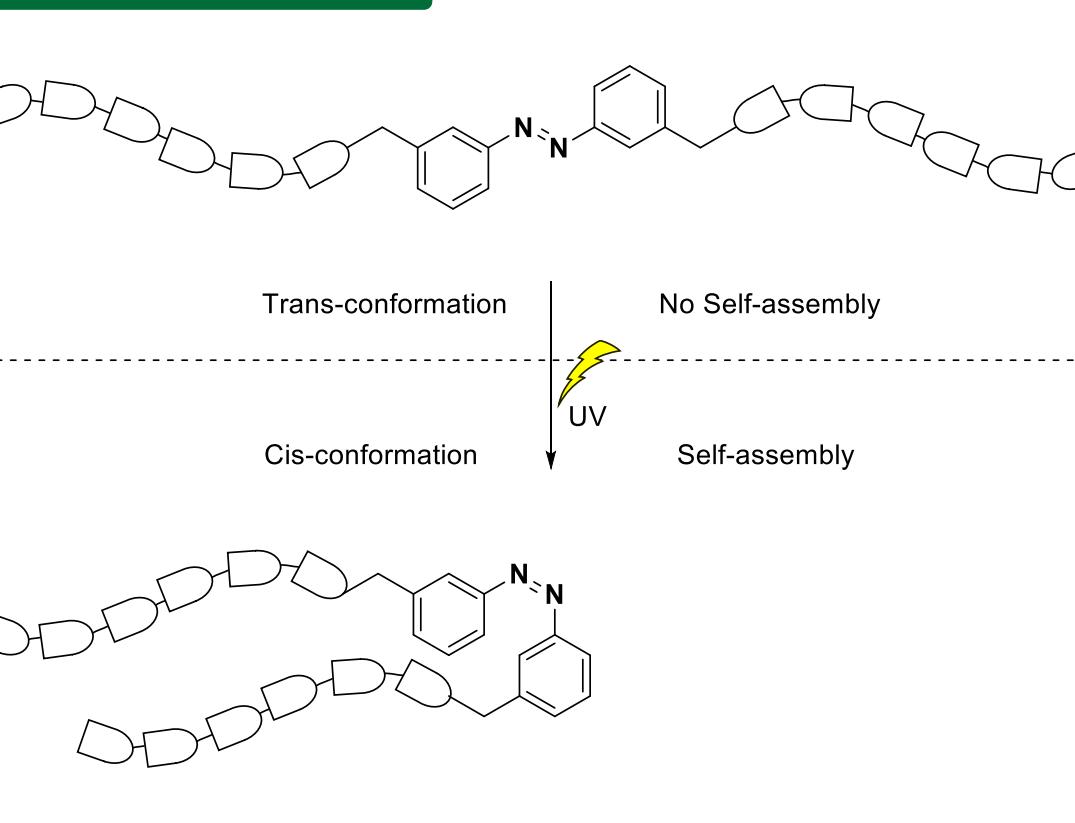
- Create coarse grain model of motor proteins
- Explore motor binding and motility
- Investigate mechanical properties and defect impact in dynamic MT "rings"

Future Work



Expanded shape change behavior

- Reverse energy/assembly relationship to better mimic stabilized "instability" in biological systems
- Explore alternative stimuli (light, heat, chemical)
- Introduce more diverse building block compositions



Bio-Inspired Dynamic Synthetic Materials

Varied sites of dynamic molecular behavior

- Vertical versus lateral interactions in an assembly
- Incorporate "weak links" into new molecular building blocks
- Utilize orthogonal chemical and physical triggers for dynamic assembly/disassembly

