

OLEIS

Towards the cellular-scale simulation of motor-driven cytoskeletal assemblies

Adam Lamson

Biophysical Modelling Group

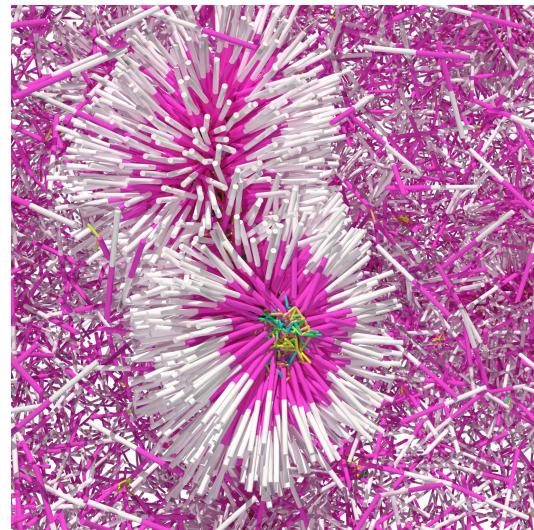
Center for Computational Biology

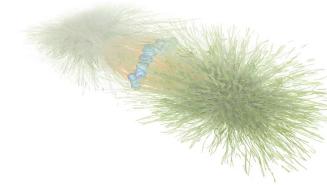
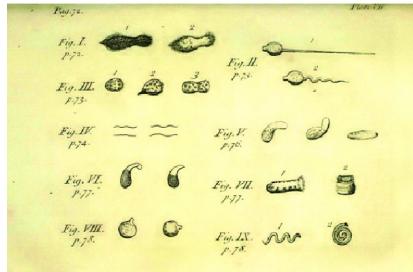
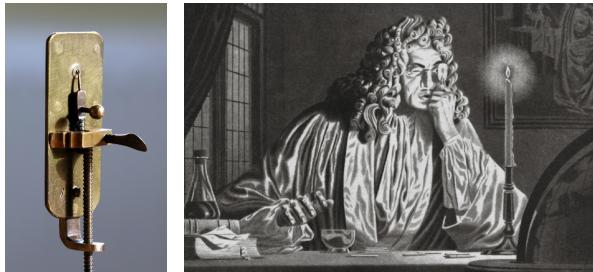
W. Yan, M. Shelley

S. Ansari, M. Glaser, M. Betterton



University of Colorado
Boulder

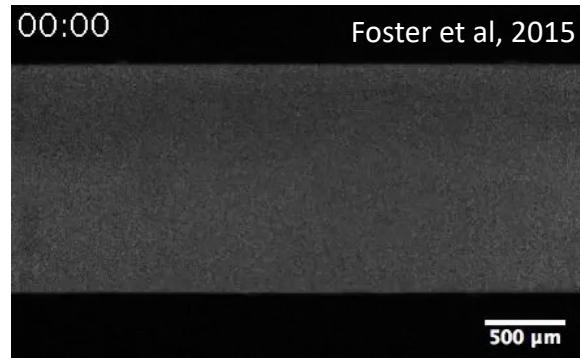
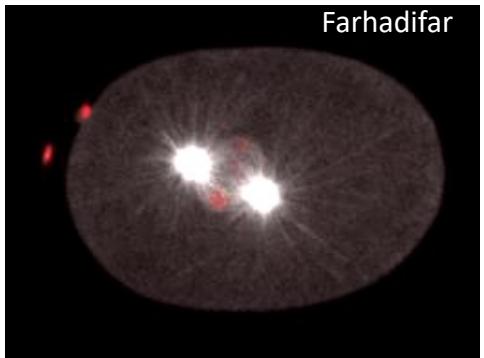




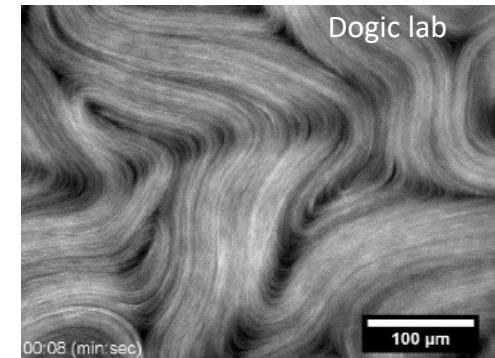
Antonie Philips van Leeuwenhoek 1632 – 1723
“Father of Microbiology”

The complexity

The dynamics

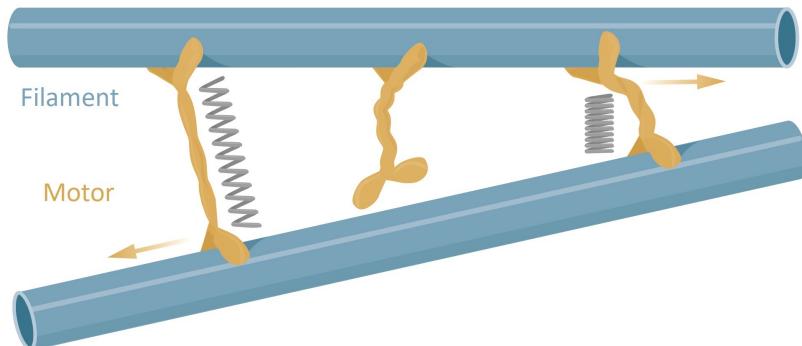


Active matter physics



Dodge lab

Model

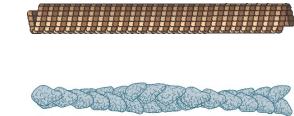


Interactions:

- Steric repulsion
- Stochastic binding/unbinding kinetics
- Motor forces

Bio-polymers are polar

- microtubule (25nm, stiff)
- actin (7nm, soft)



Motor are directed

- Dynein (-), Kinesin (+), Myosin (?),

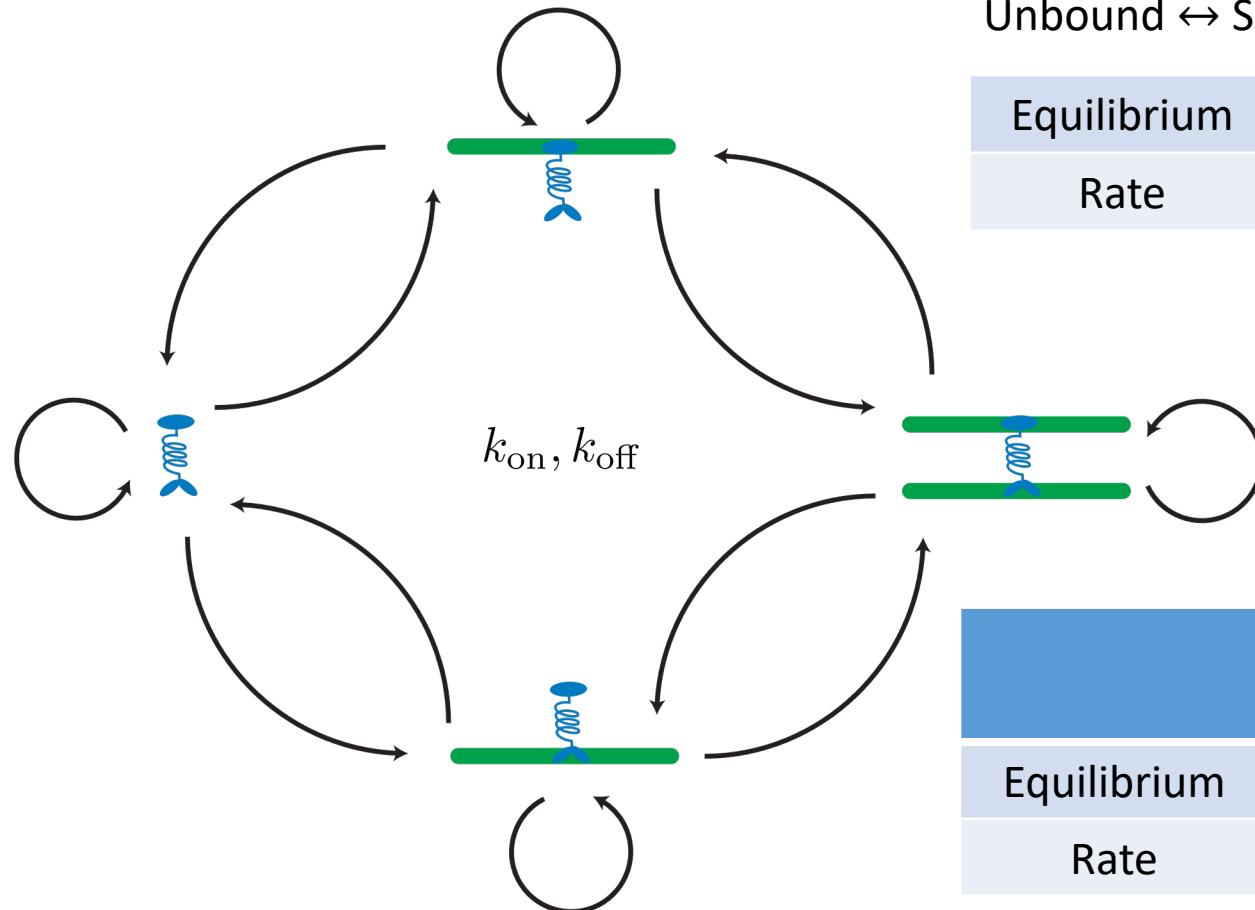
Challenges:

- Stiff interactions
- Limited spatial / temporal scales

Our approach:

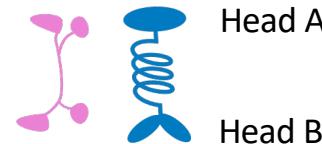
- Kinetic Monte-Carlo
- Geometric Constraint Optimization

Explicit model of motor kinetics -- Kinetic Monte Carlo



Unbound \leftrightarrow Singly bound \leftrightarrow Doubly bound

Equilibrium	1/concentration	K
Rate	1/time	k_o



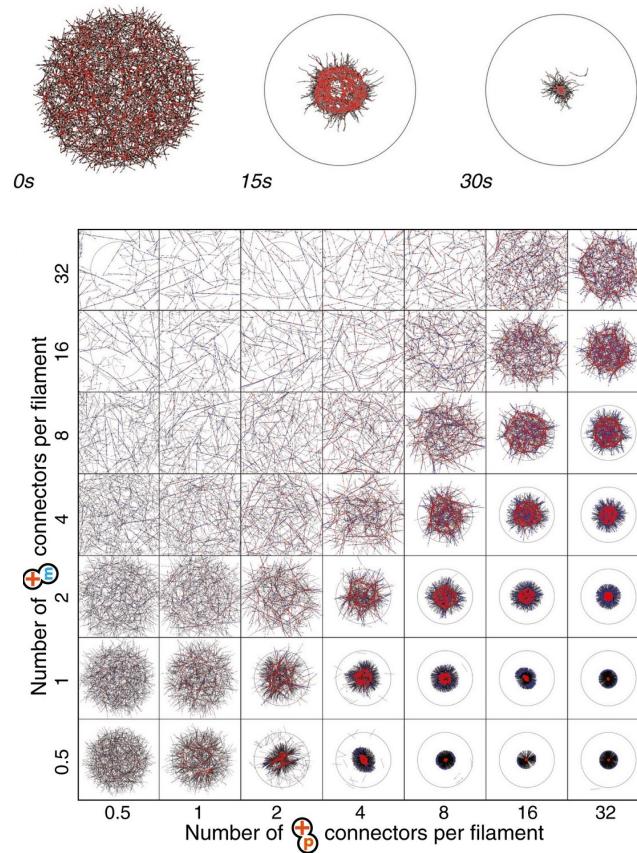
Kinetic-MC
Detailed Balance

	$U \leftrightarrow S$	$S \leftrightarrow D$
Equilibrium	K_a^i	K_E^i
Rate	$k_o^{s,i}$	$k_o^{d,i}$

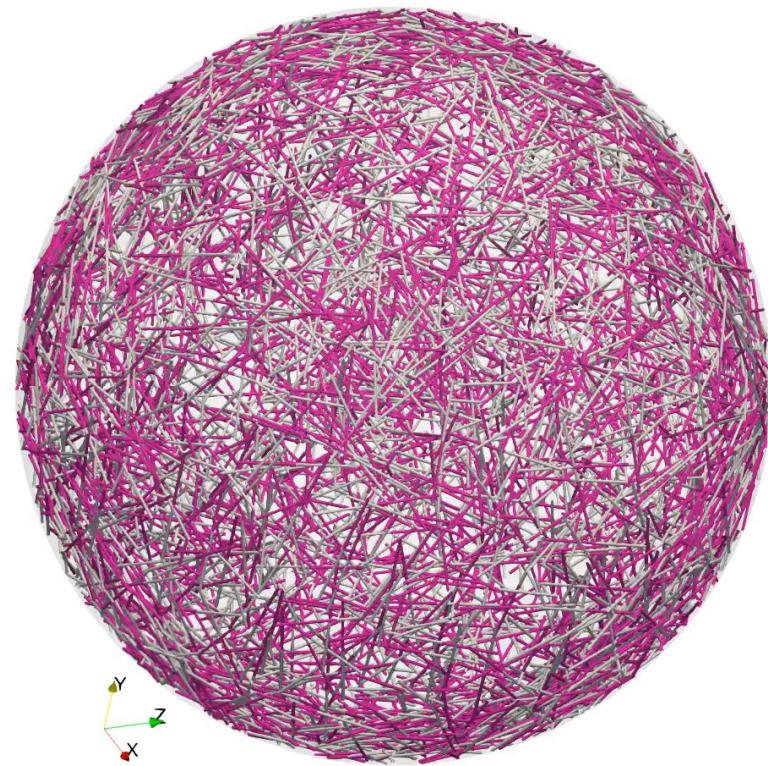
Collision forces matter

No steric interactions, 2D

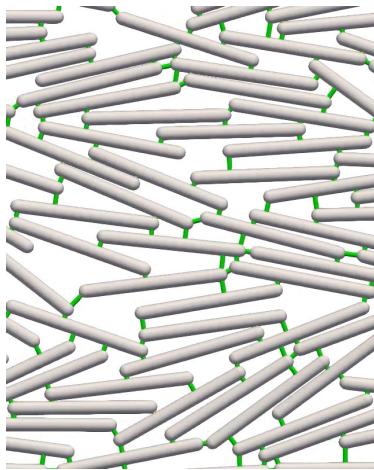
Belmonte *et al* 2017



Time: 0.00 s With steric interactions, 3D



Steric interactions as a complementarity problem



Φ : pairwise minimal distance
 γ : magnitude of contact force

For each (possible) contact:

No contact: $\Phi_\ell > 0, \gamma_\ell = 0.$

In contact: $\Phi_\ell = 0, \gamma_\ell > 0.$

For all contacts: $\Phi = (\Phi_0, \Phi_1, \dots) \in R^{n_c}, \gamma = (\gamma_0, \gamma_1, \dots) \in R^{n_c}$

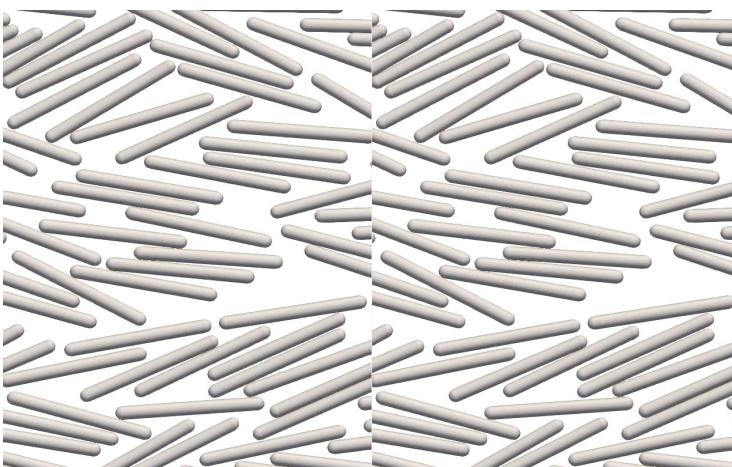
$$0 \leq \Phi(\mathcal{C}) \perp \gamma \geq 0$$

Complementarity Problem (CP)

L-J potential: force \rightarrow no overlap

CP: no overlap \rightarrow force

Stability problem



Motion induced by protein spring force (1D case)

$$\dot{x} = \frac{P_\kappa}{\eta L} x \quad \text{Stability threshold} \quad \Delta t < \frac{\eta L}{P_\kappa}$$

In simulations:

- Effective stiffness fluctuates (more motors = more stiffness)
- Small RHS stability threshold

Solution:

Collisions as unilateral constraints:

$$0 \leq \Phi_u(\mathcal{C}) \perp \gamma_u \geq 0$$

Springs as bilateral constraints:

$$\mathcal{K} [\mathbf{L}(\mathcal{C}) - \mathbf{L}_0] = -\gamma_b \quad \mathcal{K} = \text{diag} [\kappa_1, \kappa_2, \dots]$$

$$\min_{\gamma} f(\gamma) = \frac{1}{2} \gamma^T \mathbf{M} \gamma + \gamma^T \mathbf{q}$$

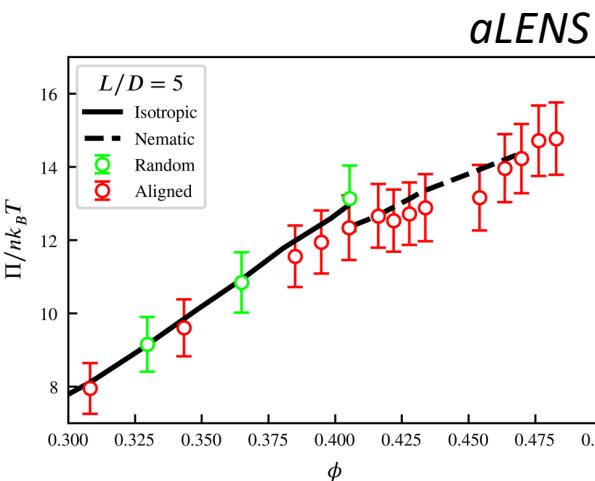
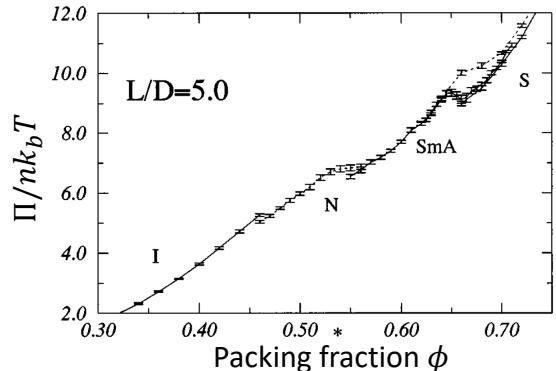
$$\gamma = \begin{bmatrix} \gamma_u \\ \gamma_b \end{bmatrix}, \quad \gamma_u \geq 0, \quad \gamma_b \in R$$

Constrained Quadratic Programming

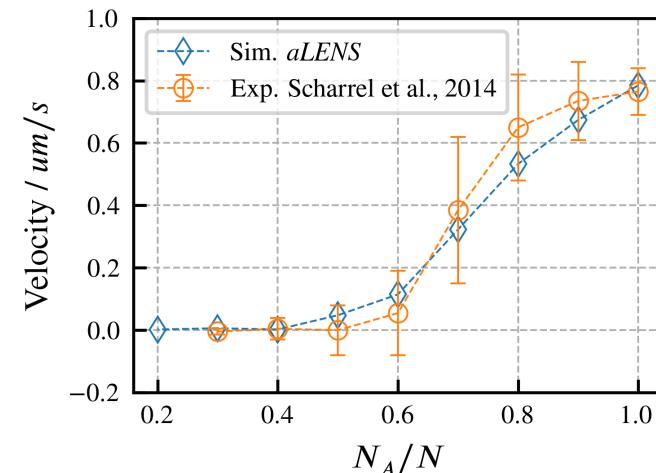
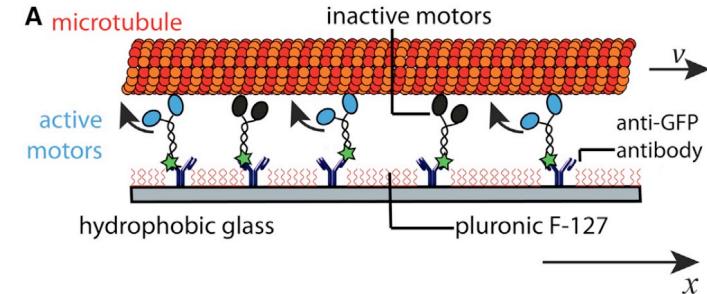
doi: 10.7554/eLife.74160

Validation of methods

Bolhuis & Frenkel 1997

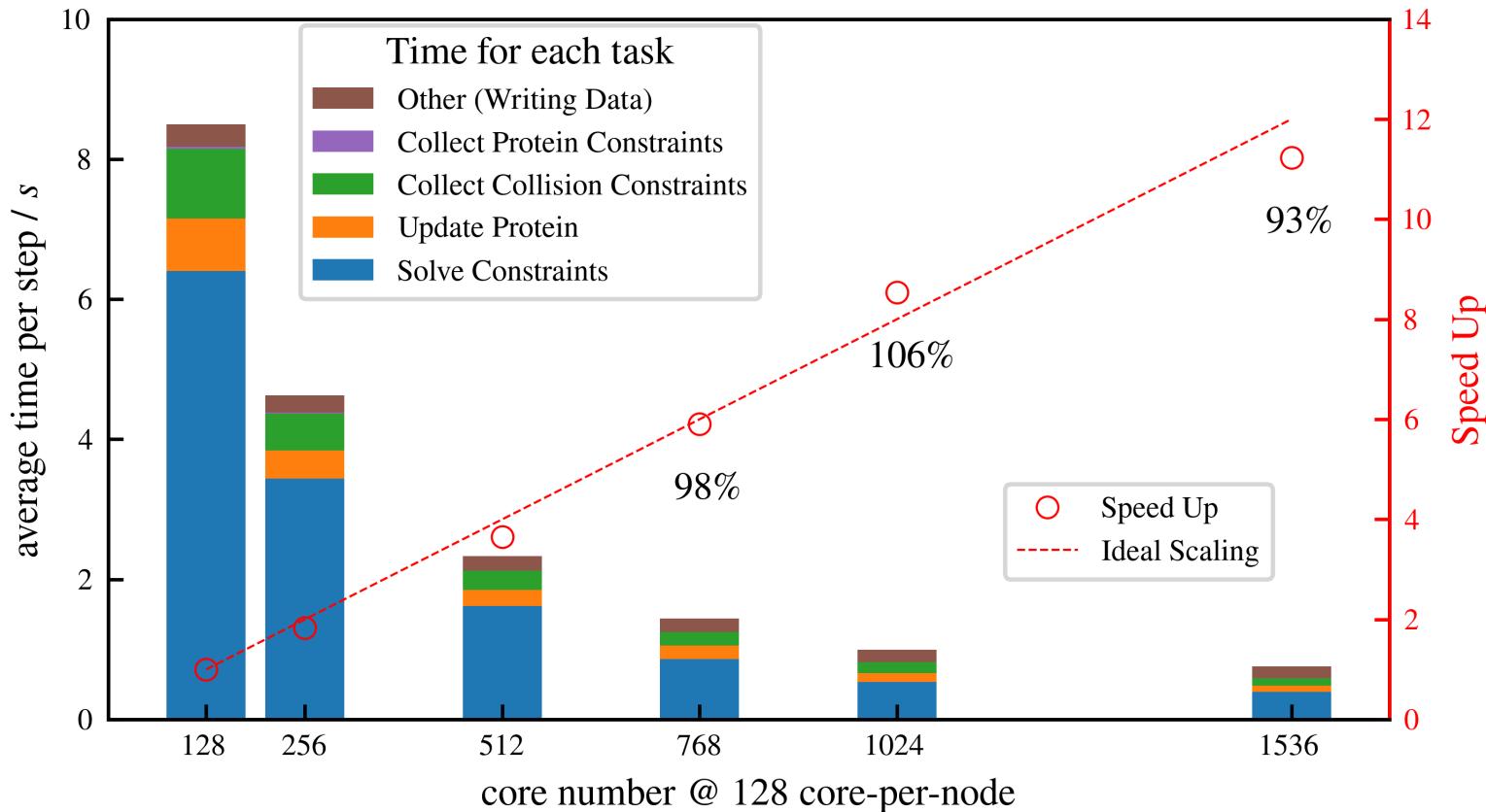


Scharrel *et al*, 2014



No fitting parameters!

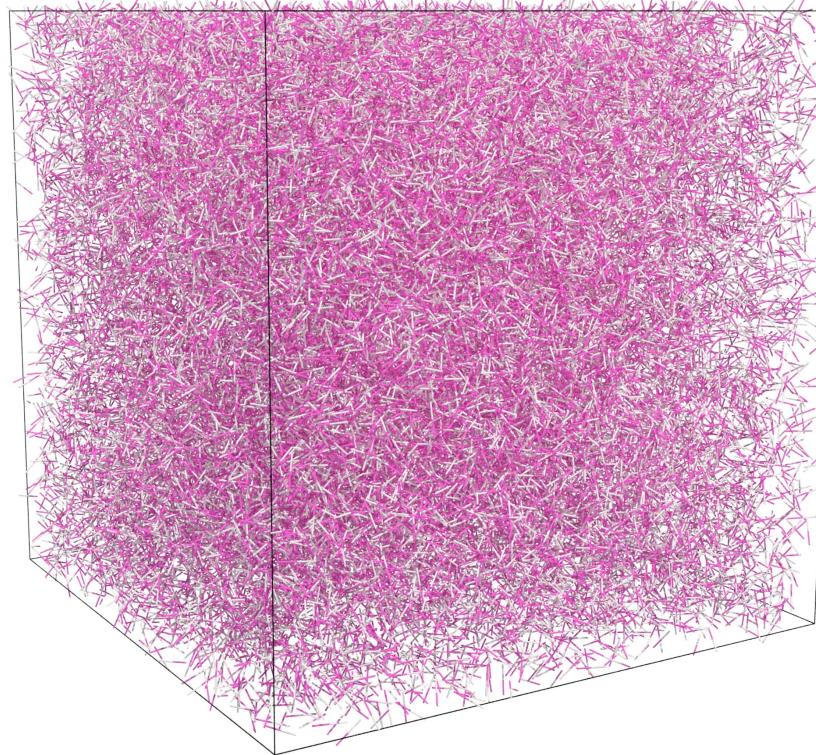
1M MT, 3M Motor, 8M Constraints



Formation of an aster gas

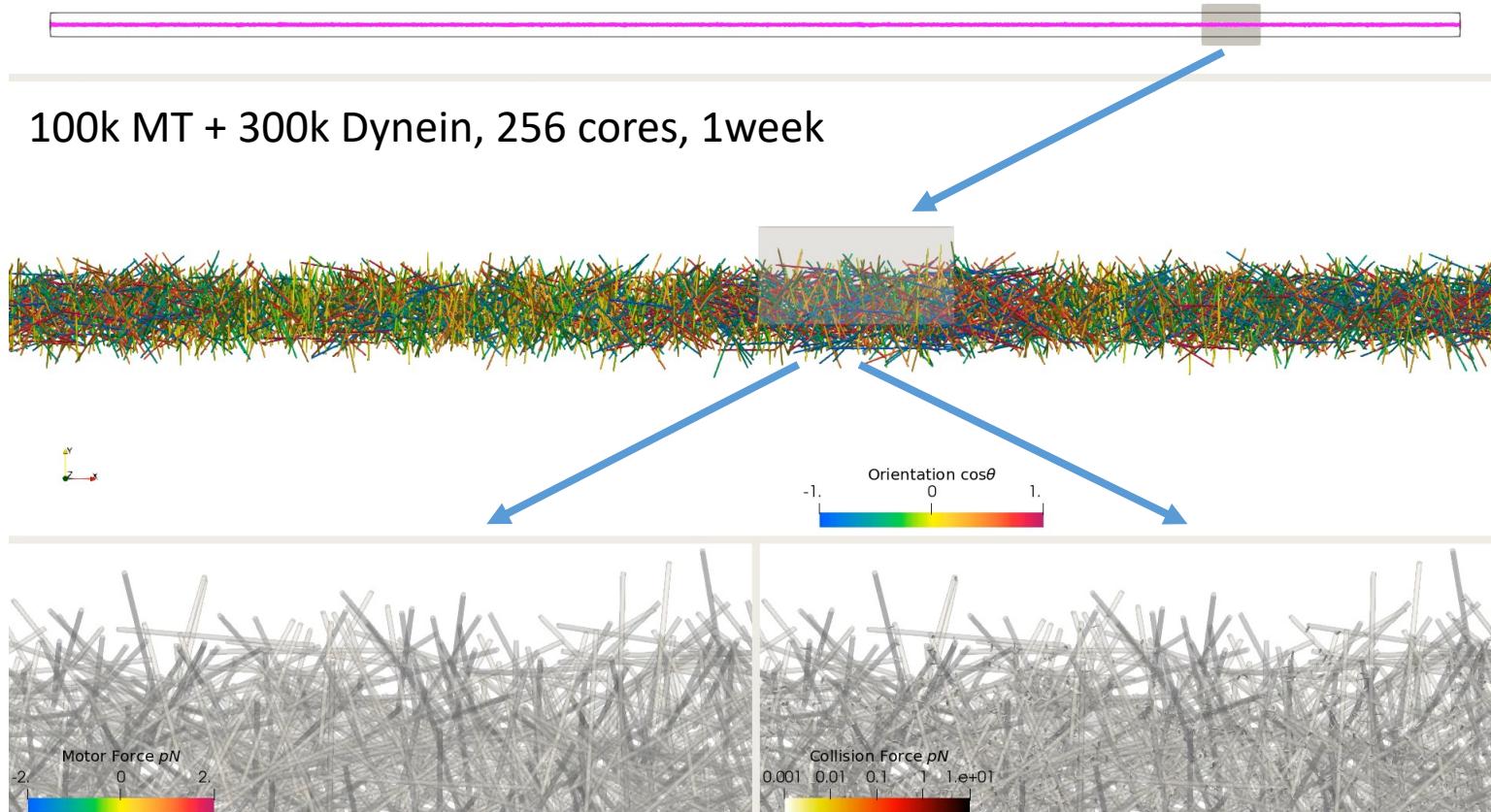
Time: 0.00 s

40k MTs + 80k two-headed, end-pausing Kinesin5-like motors

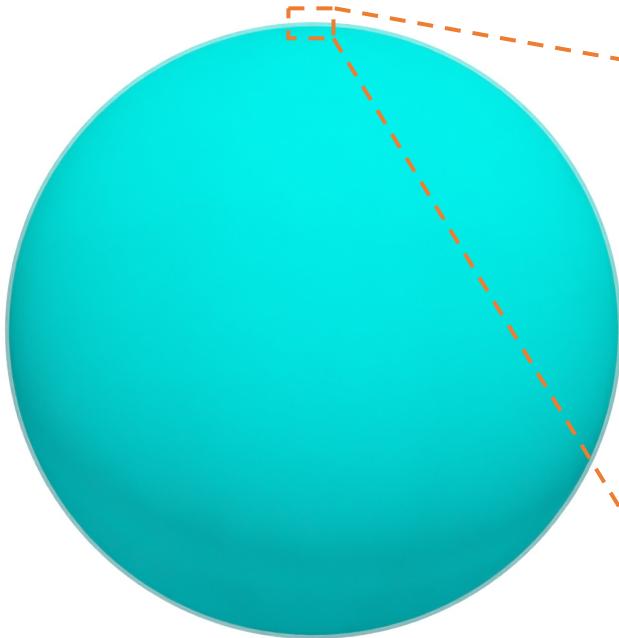


Contraction and Buckling

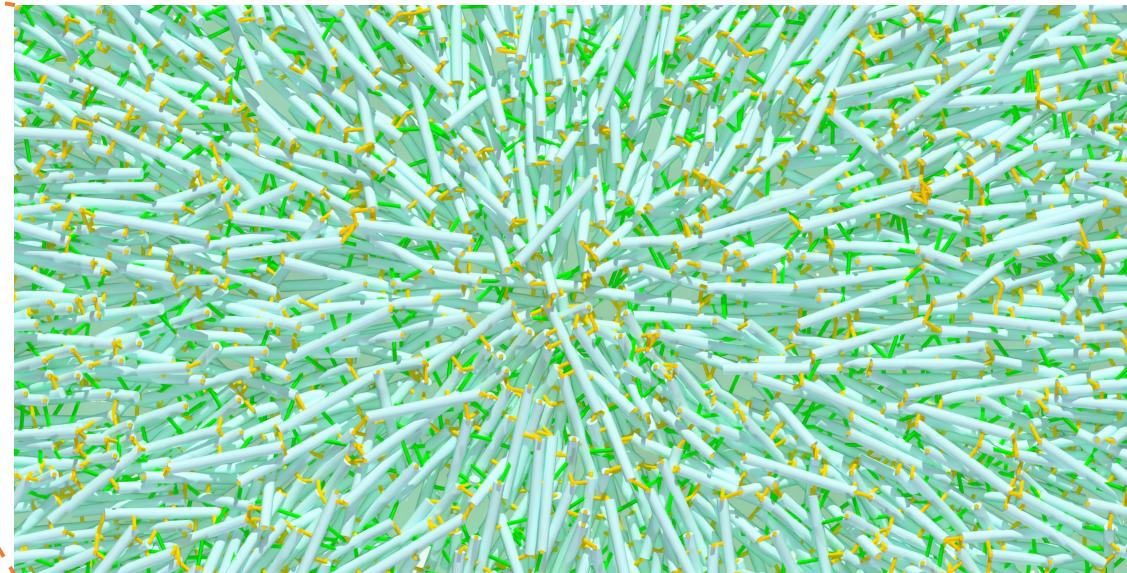
Time: 0.00 s



Example of a large simulation



1M Microtubule
3M Motor Protein
~8M Total Constraints

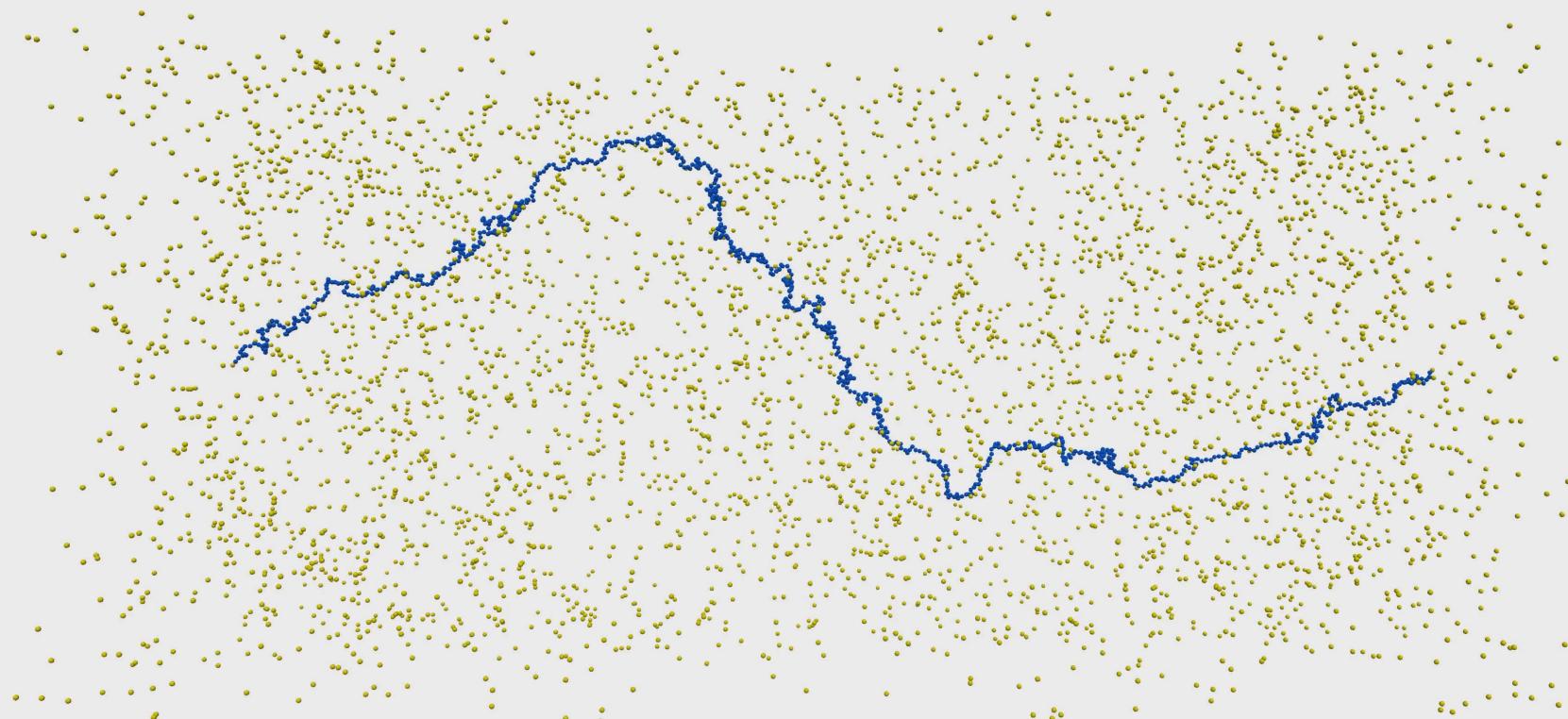


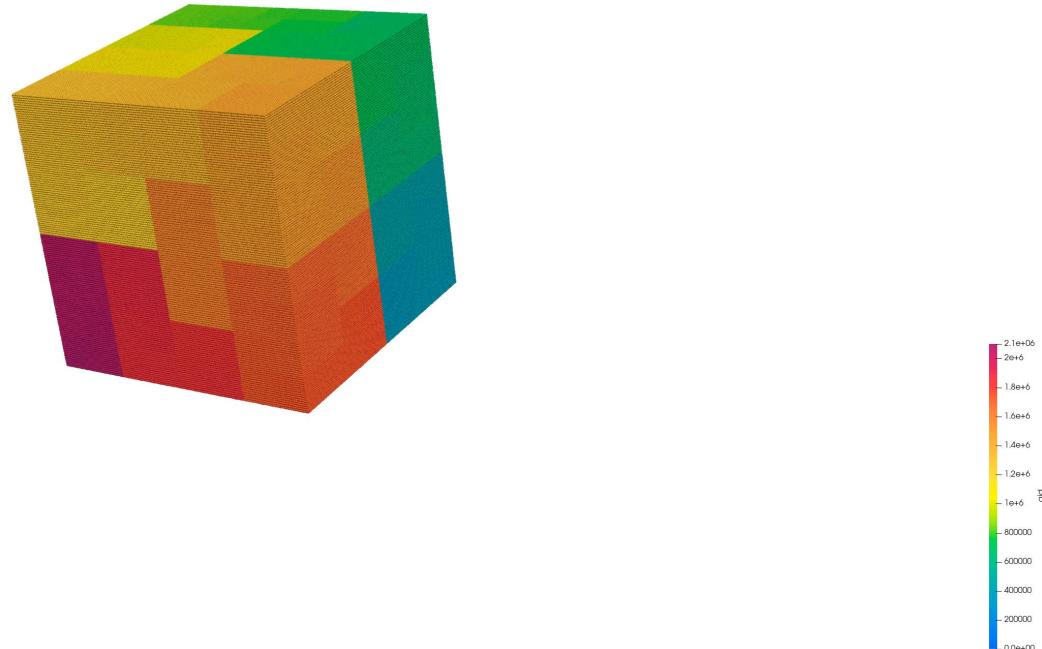
Green:
Yellow:

Motor Proteins (Bilateral Constraints)
Collisions (Unilateral Constraints)

Flexible chains with dynamically associating and sterically excluding proteins

Time: 0.00





Research Article

Computational and Systems Biology

Toward the cellular-scale simulation of motor-driven cytoskeletal assemblies

Wen Yan , Saad Ansari, Adam Lamson, Matthew A Glaser, Robert Blackwell, Meredith D Betterton, Michael Shelley 

Center for Computational Biology, Flatiron Institute, United States; Department of Physics, University of Colorado Boulder, United States; Department of Molecular, Cellular, and Developmental Biology, University of Colorado Boulder, United States; Courant Institute, New York University, United States

May 26, 2022 · <https://doi.org/10.7554/eLife.74160>  



lamsoa729/alens 

By [lamsoa729](#) · Updated 13 days ago

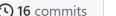
Precompiled binary for <https://github.com/flatironinstitute/aLENS>

Container

 flatironinstitute / aLENS 

 Code  Issues  Pull requests  Actions  Projects  Wiki  Security  Insights 

 main  3 branches  1 tag  Go to file  Add file  Code

 wenyan4work fix rpath in installed target	bdc6129 20 days ago	 16 commits
 Dep	use absolute path for destination	21 days ago
 Examples	rename to 'examples'	20 days ago
 KMC @ 58f5cbb	initial commit	5 months ago
 Protein	initial commit	5 months ago
 Run	update document and scripts	21 days ago
 SRC	bugfix: timer setup	3 months ago
 SimToolbox @ 80efd7a	initial commit	5 months ago
 cmake	update build script	2 months ago
 .clang-format	initial commit	5 months ago
 .gitignore	add file download script	21 days ago
 .gitmodules	initial commit	5 months ago

Thank you

Flexible chains with dynamically associating and sterically excluding proteins

