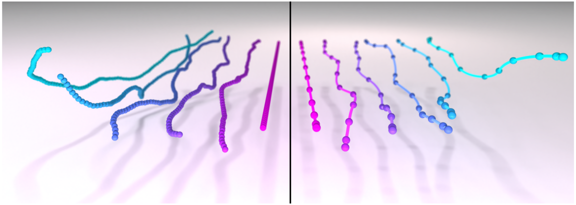
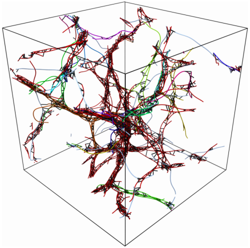
Hydrodynamics of transiently cross-linked actin networks: theory, numerics, and emergent behaviors

Ondrej Maxian, Brennan Sprinkle, and Aleks Donev
Courant Institute, NYU

Vancouver, May 2023





Outline

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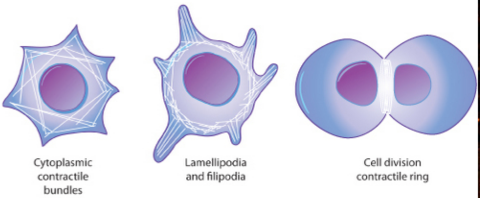
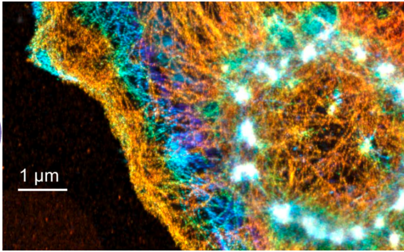
Importance of actin cytoskeleton

Dynamic cross-linked network of slender filaments

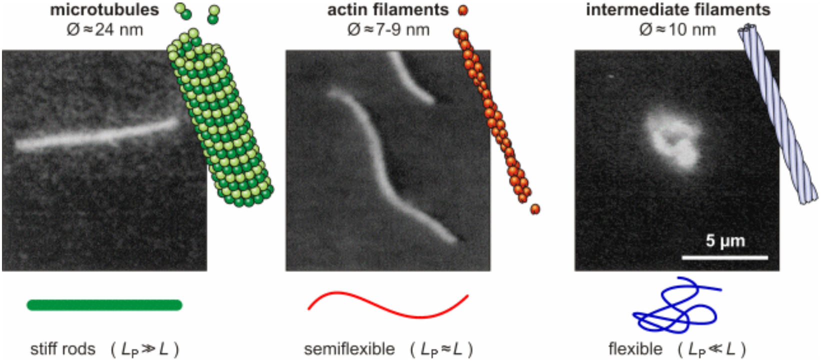
- Morphology $\leftrightarrow$ mechanical properties of cell
- Dictate cell's shape and ability to move and divide





Nature education, Herron et al. *Nat Commun.* (2022)

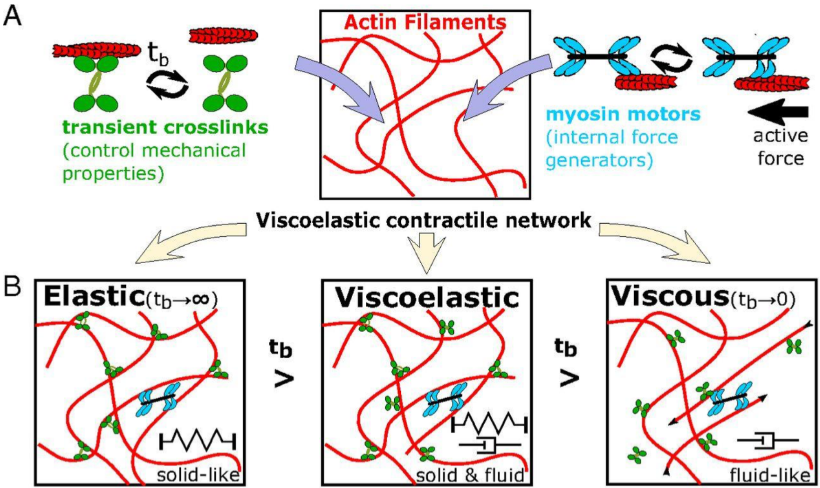
Fibers involved in cell mechanics



Pawlizak and Käs, University of Leipzig

L_p =persistence length, L =fiber length, $a = \epsilon L$ =fiber radius, ϵ =slenderness ratio

Cytoskeletal rheology



Ahmed and Betz. *PNAS*. (2015)

Fluctuating actin filaments

Actin filament *fluctuations* used for

- Sensing
- Motility
- Stress release (untying knots!)

[illegible] University of Leipzig; [illegible] *Nat. Mat.* (2015)

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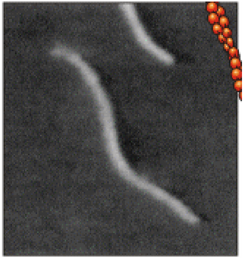
Key point: actin filaments are *semiflexible* $\ell_p \gtrsim L$

- In this sense, shapes are smooth
- Spectral methods!



$L = 5\ \mu\text{m},\ \ell_p/L \approx 3$

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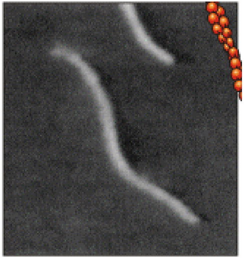

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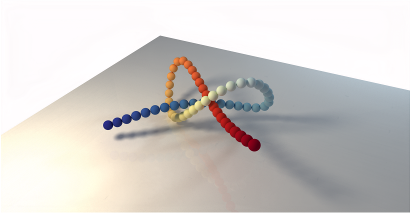

Outline

Statics: Gibbs-Boltzmann distribution

$\mathbf{X} \in \mathbb{R}^N$ = finite dimensional DOFs with energy function $\mathcal{E}(\mathbf{X})$.

- Stationary distribution (probability of observing a state)

$$d\mu_{\mathrm{GB}} = \underbrace{\frac{1}{Z}}_{\text{Normalization}} \underbrace{e^{-\mathcal{E}(\mathbf{X})/k_B T}}_{\text{Boltzmann weight}} \underbrace{d\mathbf{X}}_{\text{Lebesque measure}}$$

Gibbs-Boltzmann distribution (stat. mech.)

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- Dynamics must be time-reversible with respect to μ_{GB}

Dynamics: (Overdamped) Langevin equations

Commonly-used model for micro-structures immersed in liquid

$$\frac{\partial \mathbf{X}}{\partial t} = \underbrace{-\mathbf{M}(\mathbf{X})\frac{\partial \mathcal{E}}{\partial \mathbf{X}}(\mathbf{X})}_{\text{Deterministic}} + \sqrt{2k_B T}\,\underbrace{\mathbf{M}(\mathbf{X}) \circ \mathbf{M}^{-1/2}(\mathbf{X})}_{\text{Mixed Strato-Ito}}\;\underbrace{\mathcal{W}(t)}_{\text{White noise}}$$

- $\mathbf{M}(\mathbf{X})$ is SPD mobility operator, encoding (hydro)dynamics
- Noise form & "kinetic" interpretation chosen to sample from GB distribution & be time reversible at equilibrium

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Converting to Ito form gives

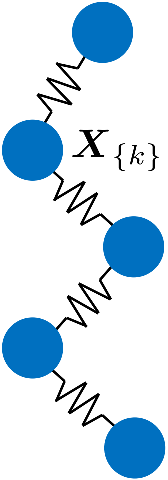
$$\frac{\partial \mathbf{X}}{\partial t} = -\mathbf{M}\frac{\partial \mathcal{E}}{\partial \mathbf{X}} + \underbrace{k_B T\,(\partial_{\mathbf{X}} \cdot \mathbf{M})}_{\text{Stochastic drift term}} + \sqrt{2k_B T}\, \underbrace{\mathbf{M}^{1/2}\mathcal{W}(t)}_{\textit{Multiplicative}\text{ noise}}$$

Goal is to write and solve such an equation for fibers

Outline

Bead/blob-spring model for fibers

Create “fiber” out of beads (blobs) and springs



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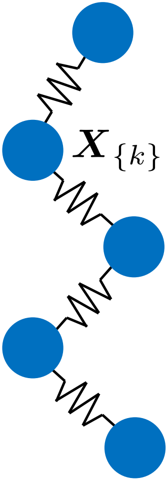

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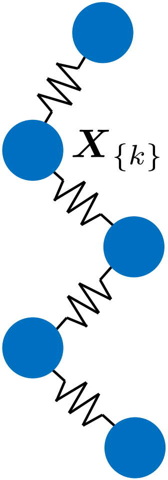

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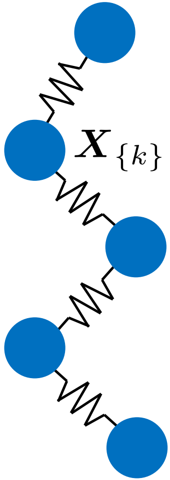

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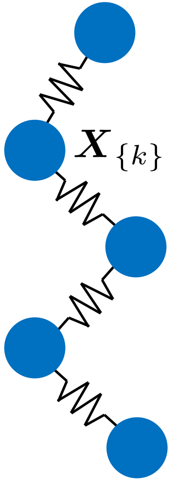

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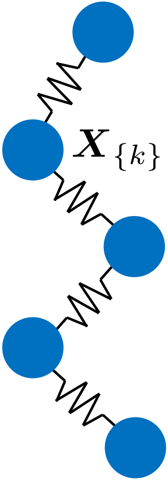
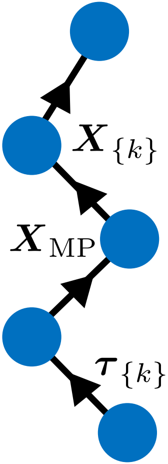
Big problem: need small Δt to resolve stiff springs



Blob-link model

Replace springs with rigid rods



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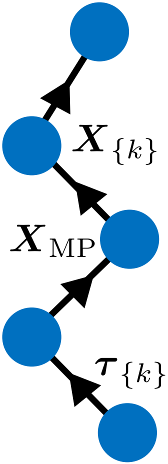

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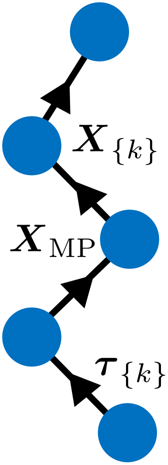

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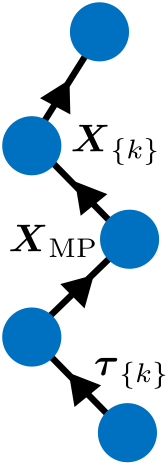

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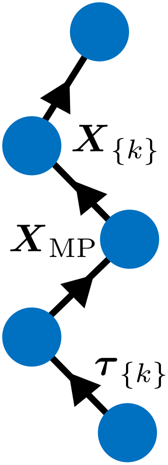

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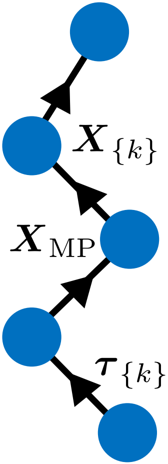

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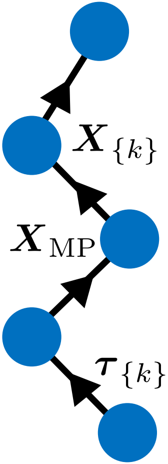

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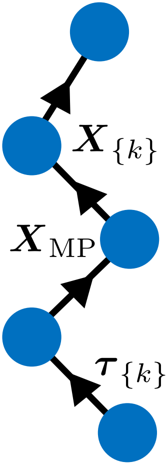
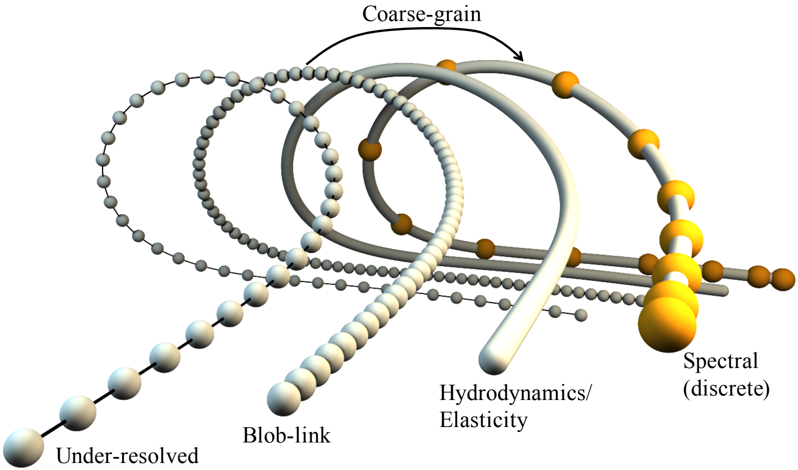
- Small lengthscales come from *hydrodynamics* of long blob-link chain



Big idea: mix continuum and discrete



“Bending fluctuations in semiflexible, inextensible, slender filaments in Stokes flow” by O. Maxian et al., 2023, **ArXiv:2301.11123**
`https://github.com/stochasticHydroTools/SlenderBody`

Spectral method

Mixed discrete-continuum description

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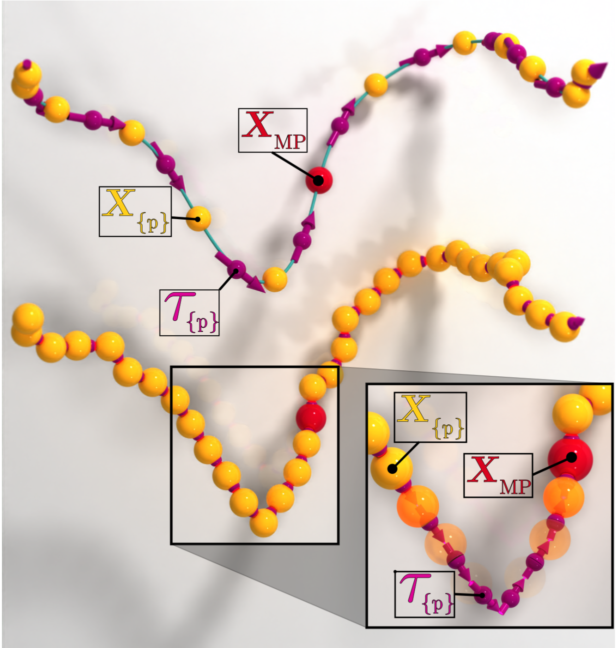
- Mix of new methods + existing rigid body methods

Blob link and spectral



Building spectral discretization

DOFs: $\boldsymbol{\tau}$ at N nodes of type 1 (no EPs) Chebyshev grid, $\mathbf{X}_{\mathrm{MP}}$

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- Can apply discrete blob-link methods (Brennan Sprinkle) for constrained *discrete* Langevin equation
- Combine with continuum methods for elasticity and hydrodynamics

Continuum part: energy

Fibers resist bending according to curvature energy *functional*

$$\mathcal{E}_{\text{bend}}\left[\mathbb{X}(\cdot)\right] = \frac{\kappa}{2}\int_0^L \partial_s^2\mathbb{X}(s)\cdot\partial_s^2\mathbb{X}(s)\,ds$$

- $\kappa =$ bending stiffness

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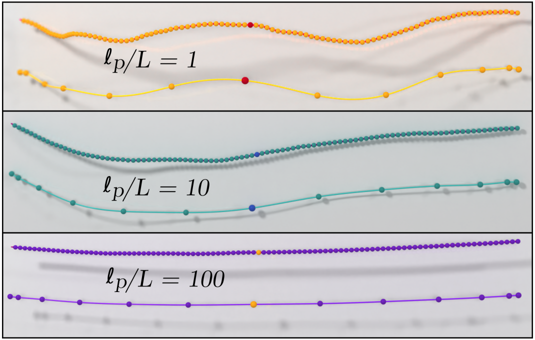
- κ = bending stiffness
- $\ell_p = \kappa/(k_B T)$ defines a "persistence length"
- Fibers bend on this length, shorter than this straight
- Hope for spectral methods when $\ell_p \simeq L$ (actin)



Discretizing energy

Discretize inner product on Chebyshev grid

$$\begin{aligned}\mathcal{E}_{\text{bend}}\left[\mathbb{X}(\cdot)\right] &= \frac{\kappa}{2}\int_0^L \partial_s^2\mathbb{X}(s)\cdot\partial_s^2\mathbb{X}(s)\,ds \\ &= \frac{\kappa}{2}\left(\mathbf{E}_{N_x\to 2N_x}\mathbf{D}^2\mathbf{X}\right)^T\mathbf{W}_{2N}\left(\mathbf{E}_{N_x\to 2N_x}\mathbf{D}^2\mathbf{X}\right) \\ &= \frac{\kappa}{2}\left(\mathbf{D}^2\mathbf{X}\right)^T\widetilde{\mathbf{W}}\left(\mathbf{D}^2\mathbf{X}\right) \\ &= \mathbf{X}^T\mathbf{L}\mathbf{X}\end{aligned}$$

- Upsampling to grid of size $2N_x$ to integrate *exactly*

Li et al. Geophys. J. Int. (2017).

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- Upsampling to grid of size $2N_x$ to integrate *exactly*
- No aliasing

Li et al. Geophys. J. Int. (2017).

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- No aliasing
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Li et al. Geophys. J. Int. (2017).

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Discretize inner product on Chebyshev grid

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Fluid dynamics of an immersed fiber

Immersed blob continuum hydrodynamic model (without Brownian fluctuations):

$$\boldsymbol{\nabla}\pi\left(\mathbf{r},t\right)=\eta\boldsymbol{\nabla}^{2}\mathbf{v}\left(\mathbf{r},t\right)+\int_{0}^{L}ds\,\mathbf{f}(s,t)\delta_{a}\left(\mathbb{X}(s,t)-\mathbf{r}\right)$$

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- For the discrete case just replace integrals by sums over blobs.

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- We can (temporarily) eliminate the fluid velocity to write an equation for **fiber only**.

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  where $\mathbb{G}$ is the Green's function for (periodic) Stokes flow.
- Choosing a surface delta function

$$\delta_a\left(\mathbf{r}\right) = \left(4\pi a^2\right)^{-1} \delta\left(r - a\right)$$

  gives the **Rotne-Prager-Yamakawa (RPY) kernel**.

Nonlocal PDE

- Define a positive semidefinite **mobility operator**

$$\mathbf{U}_k = \frac{d\mathbf{X}_k}{dt} = \left(\boldsymbol{\mathcal{M}}\left[\mathbb{X}\left(\cdot\right)\right]\mathbf{f}\left(\cdot\right)\right)\left(\mathbf{X_k}\right) = \int_0^L ds'\, \boldsymbol{\mathcal{R}}\left(\mathbf{X}_k, \mathbb{X}(s')\right)\mathbf{f}(s')$$

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- Compare to blob-link: $\mathcal{O}(L/\hat{a})$ points!
- Converting between *continuous force densities* $\mathbf{f}(s)$ to *discrete forces* $\mathbf{F}$ (Galerkin projection), we get a **mobility matrix**

$$\mathbf{U} = \widetilde{\mathbf{M}}\mathbf{F}$$

Applying mobility

$$
\begin{tikzcd}
 & & \left(\boldsymbol{\tau}_{\{k=1,\ldots N\}}, \boldsymbol{X}_{\mathrm{MP}}\right) \arrow[d, "\boldsymbol{\mathcal{X}}"] & & \\
 & & \boldsymbol{X}_{\{k=1,\ldots N+1\}} \arrow[d, "\text{Chebyshev interpolation}"] & & \\
 & & \mathbb{X}(s) \arrow[r] \arrow[dll] & \boldsymbol{M}\left[\mathbb{X}(\cdot)\right] \arrow[dd, "\text{Special quadrature}"] & \\
\mathcal{E}_{\mathrm{bend}}\left[\mathbb{X}(\cdot)\right] \arrow[dr] & & & & \\
 & \boldsymbol{F}_{\mathrm{bend}}\left(\boldsymbol{X}\right) \arrow[rr, "\widetilde{\boldsymbol{W}}^{-1}"] & & \boldsymbol{f}_{\mathrm{bend}}\left(\boldsymbol{X}\right) \arrow[r] & \widetilde{\boldsymbol{M}}\boldsymbol{F}
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Outline

Discrete part: inextensibility

Langevin equation must be modified because of inextensibility

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- Discrete time: solve for $\boldsymbol{\alpha} = (\boldsymbol{\Omega}, \mathbf{U}_{\mathsf{MP}})$, rotate by $\boldsymbol{\Omega}\Delta t$, update midpoint

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Close system by introducing Lagrange multiplier forces $\boldsymbol{\Lambda}$

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Apply $\widehat{\mathbf{N}}$ via iterative saddle pt solve with block-diagonal preconditioner.

Discrete Langevin equation

Deterministic dynamics + time reversibility → Langevin equation

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- $\widehat{\mathbf{N}}^{1/2}$ captured via saddle point solve

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$$\mathbf{K}^T\boldsymbol{\Lambda} = \mathbf{0},$$
$$\Rightarrow \boldsymbol{\alpha} = \text{Deterministic} + \sqrt{\frac{2k_B T}{\Delta t}}\widehat{\mathbf{N}}^{1/2}\mathbf{W}$$

- $\mathbf{W} \sim \mathcal{N}(0,1)$

Implied GB distribution

The overdamped Langevin equation is in detailed balance wrt the distribution

$$P_{\text{eq}}\left(\bar{\boldsymbol{\tau}}\right) = Z^{-1} \exp\left(-\mathcal{E}_{\text{bend}}(\bar{\boldsymbol{\tau}})/k_B T\right) \prod_{p=1}^{N} \delta\left(\boldsymbol{\tau}_{\{p\}}^{T} \boldsymbol{\tau}_{\{p\}} - 1\right)$$

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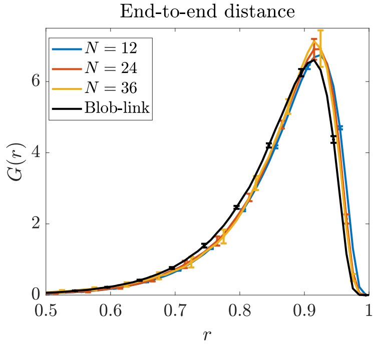
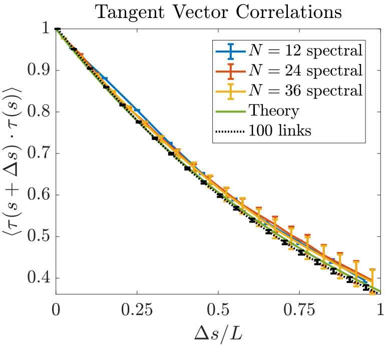
- Here: present supporting numerical results

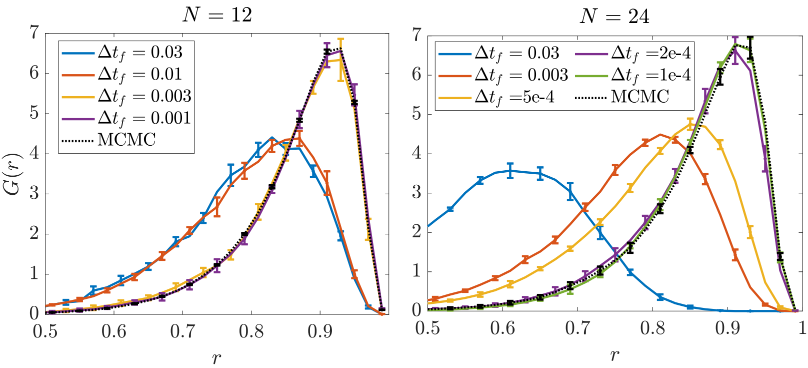
Samples from GB: free fibers





Bias for finite N which disappears as N increases

Using the Langevin integrator to sample



Conve

to MCMC for smallest Δt

- Reported in terms of longest relaxation timescale

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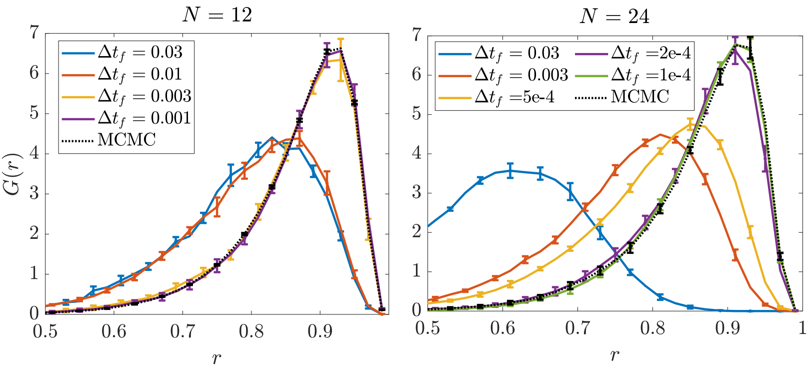

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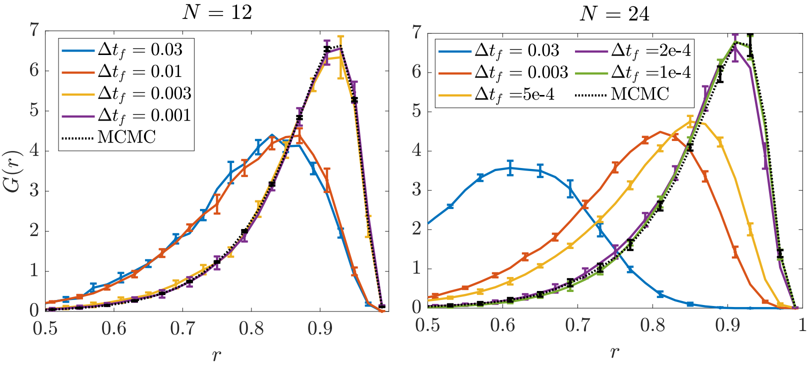

Converges to MCMC for smallest Δt

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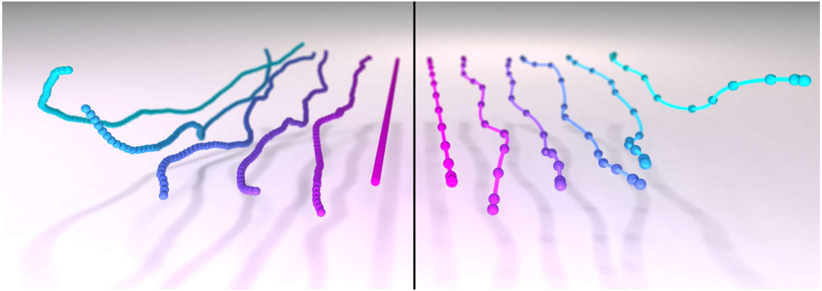
- Unchanged with ℓ_p (modes are stiffer, but fewer required)

Relaxation of fiber to equilibrium



Blob-link vs. spectral

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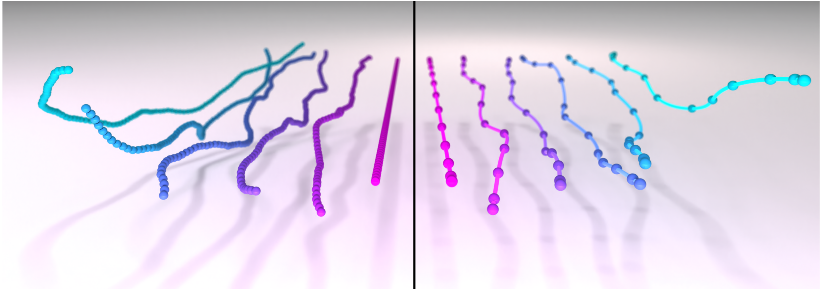

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- Getting a good approximation to mean end-to-end distance?

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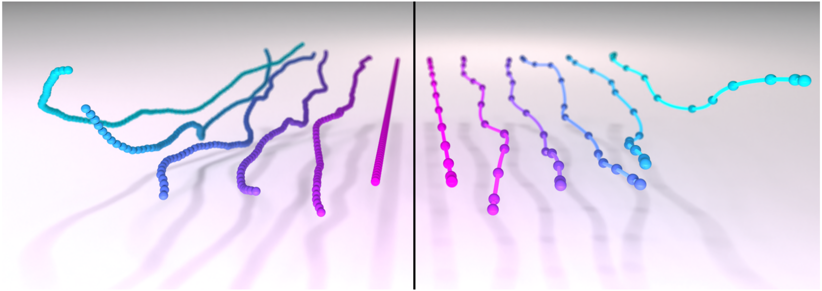
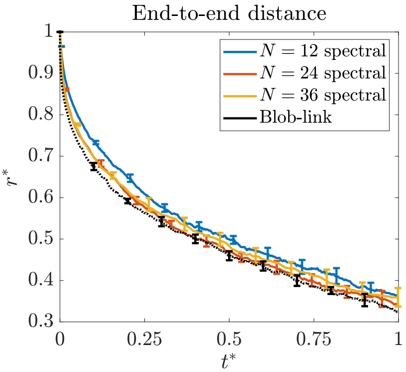
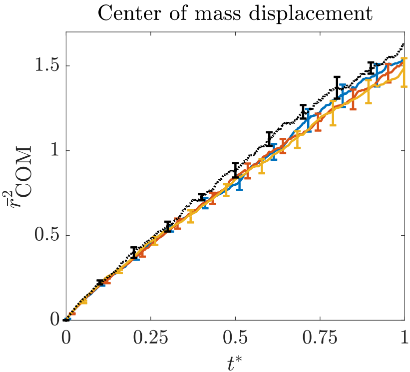


Blob-link vs. spectral

- Getting a good approximation to mean end-to-end distance?
- Is special quadrature doing what we want it to?

Quantifying relaxation $(\hat{\epsilon} = 10^{-2})$





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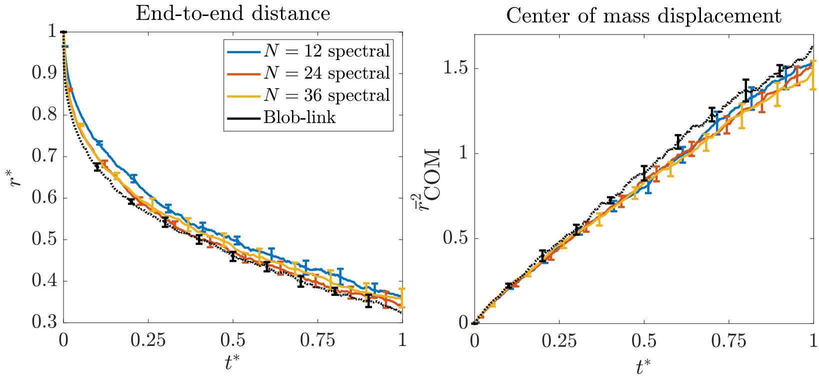

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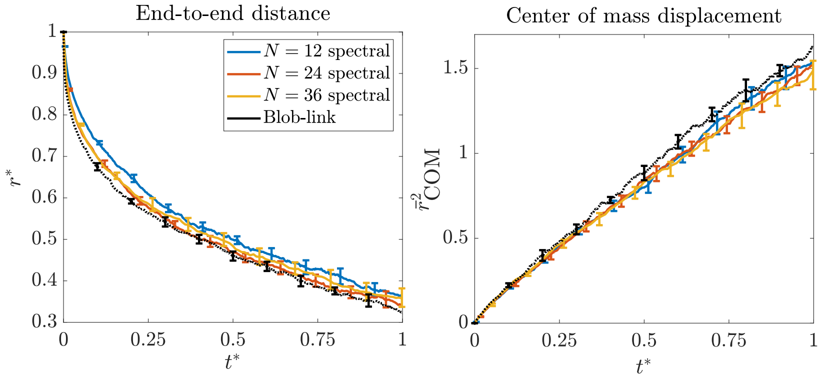
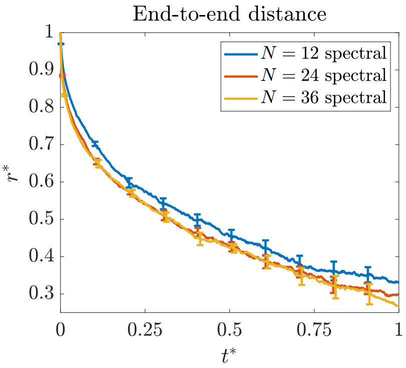
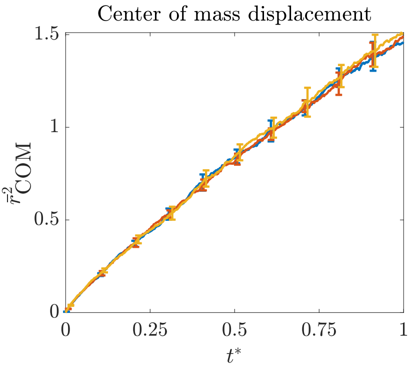


- Spectral results approach blob-link with increasing N
- Can extend spectral to smaller $\hat{\epsilon}$, but not blob-link!

Quantifying relaxation $\left(\hat{\epsilon} = 10^{-3}\right)$

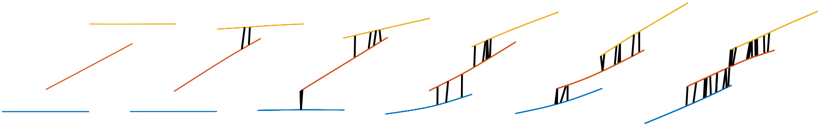


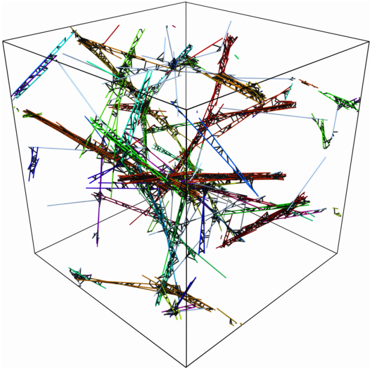


Outline

Dynamics of bundling in cross-linked actin networks

Couple the fibers to moving cross linkers (CLs, elastic springs)





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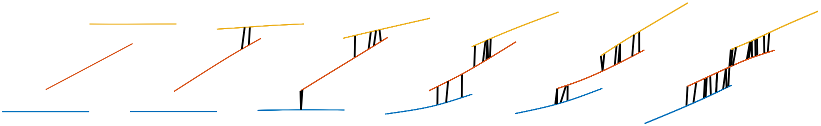
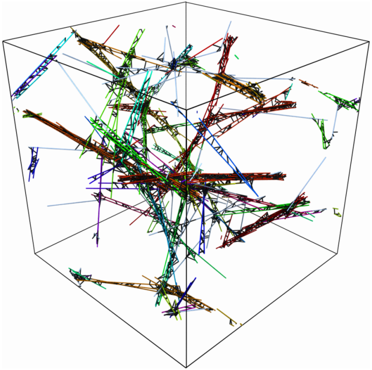
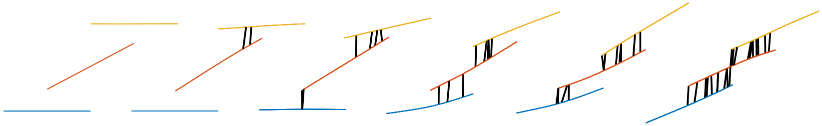




CLs bind fibers, pulling them closer together;
ratcheting action creates bundles

Goals for bundling

Filaments move in three ways:



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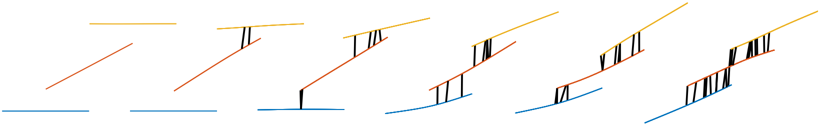

Goals for bundling

Filaments move in three ways:

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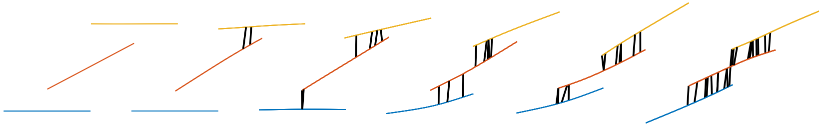
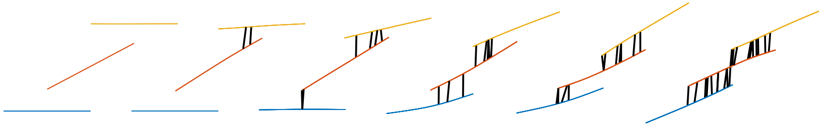
2. Rigid body translation and rotation



Goals for bundling

Filaments move in three ways:

1. Cross linking forces
2. Rigid body translation and rotation
3. *Semiflexible* bending fluctuations



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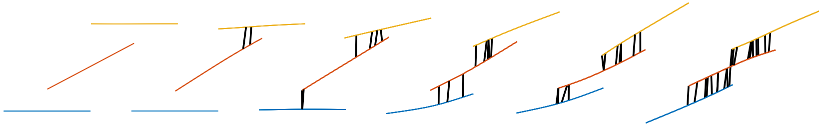

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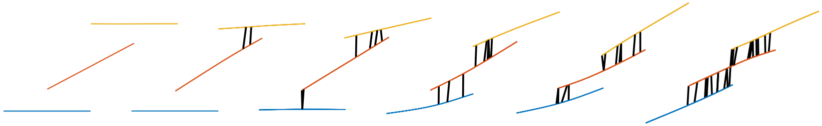

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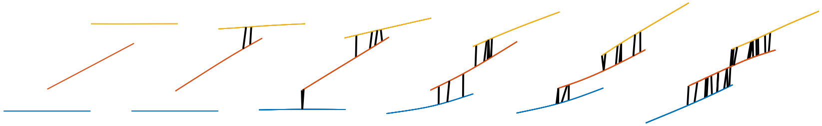

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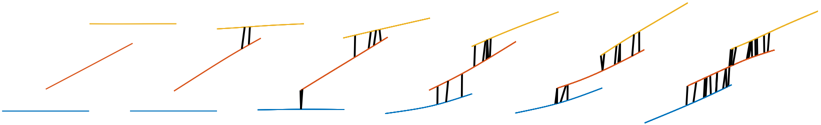
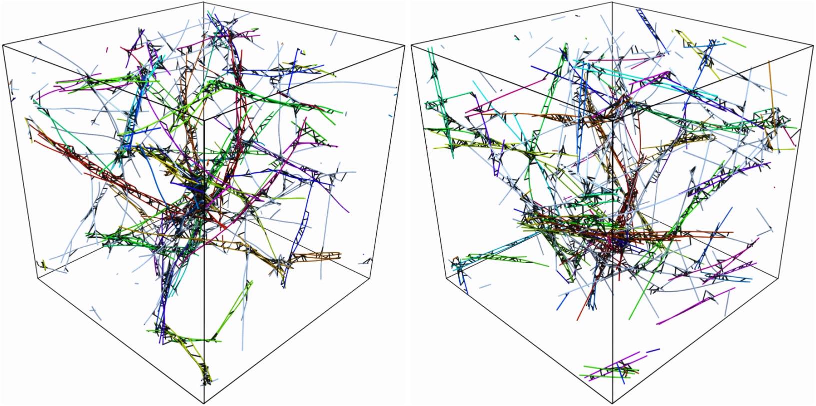
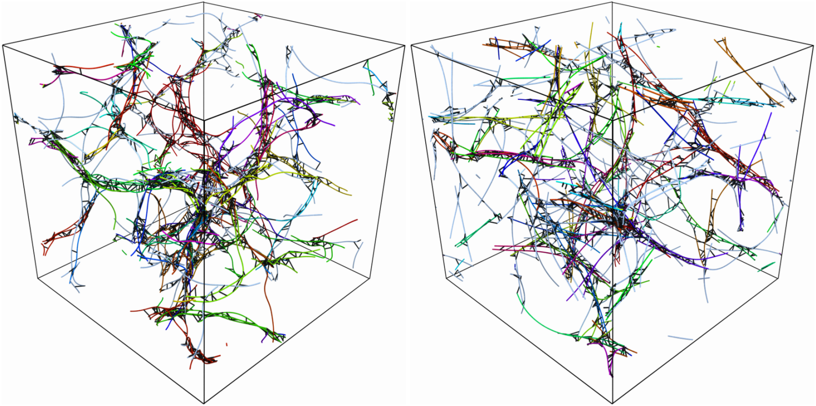
- Strategy: simulate fibers with #1 and #2 only, compare to fluctuating



Movie: $\ell_p/L = 10$

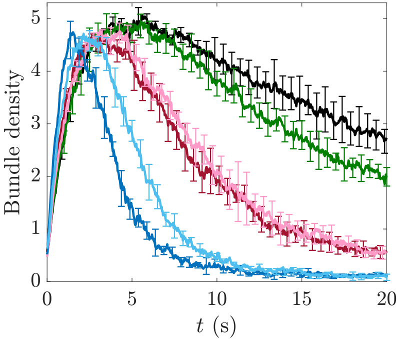


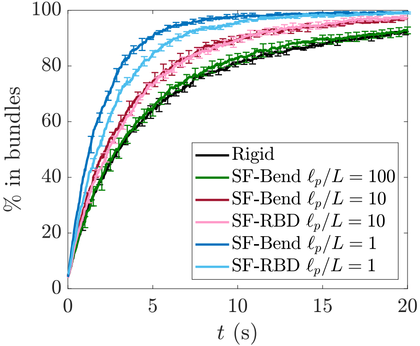
Movie: $\ell_p/L = 1$



Bundling statistics

Statistics confirm movies





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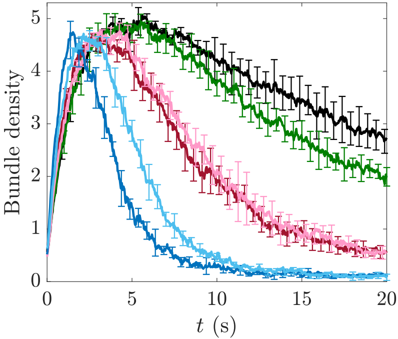

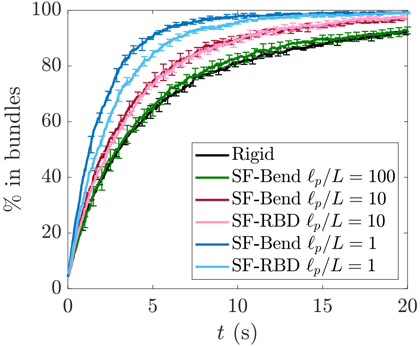

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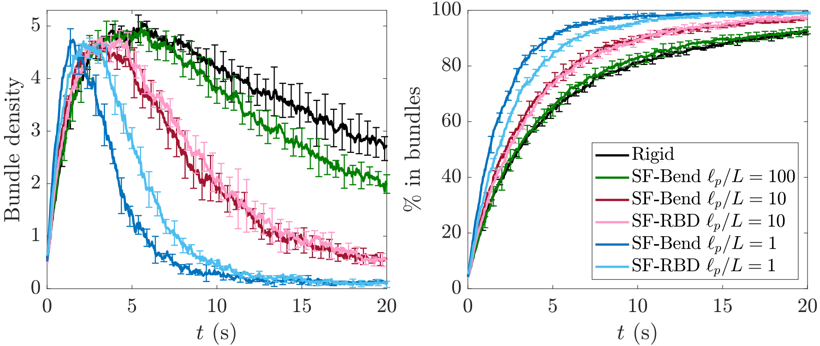

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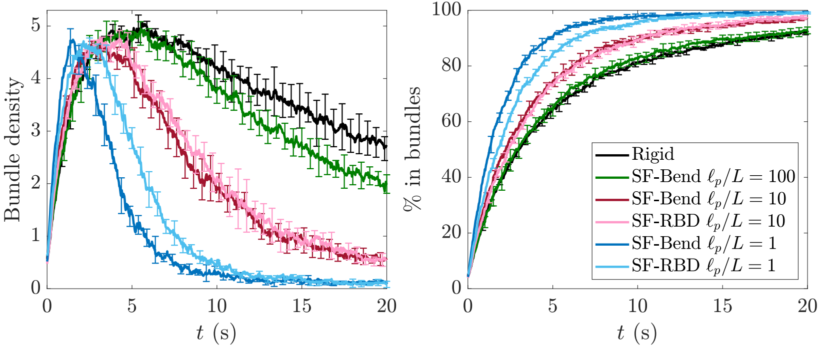

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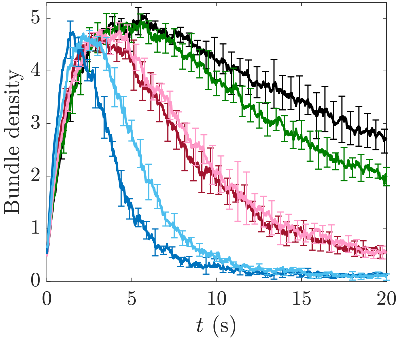

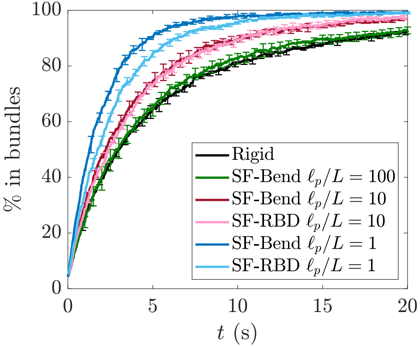

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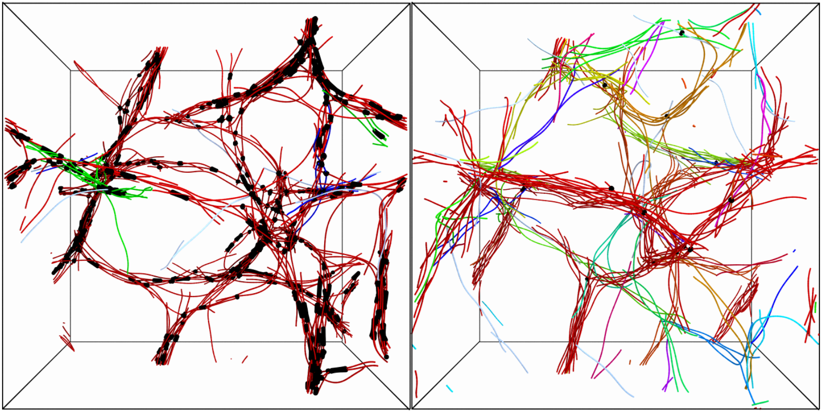
- Actin in vivo: $\ell_p/L \approx 30$

Bundling with sterics

Number of contacts reduced by 99% using "soft" erf potential (Gaussian force)

- But 5× time step reduction required



Outline

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- Incorporate nonlocal interactions between fibers (hydrodynamic+steric)
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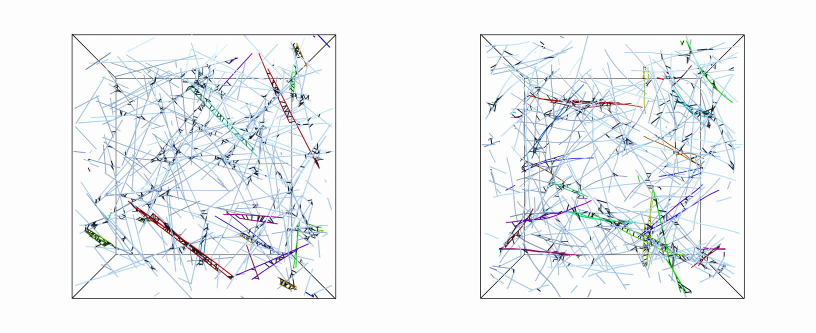
- Apply to rheology of actin networks

Rheology – effect of fluctuations

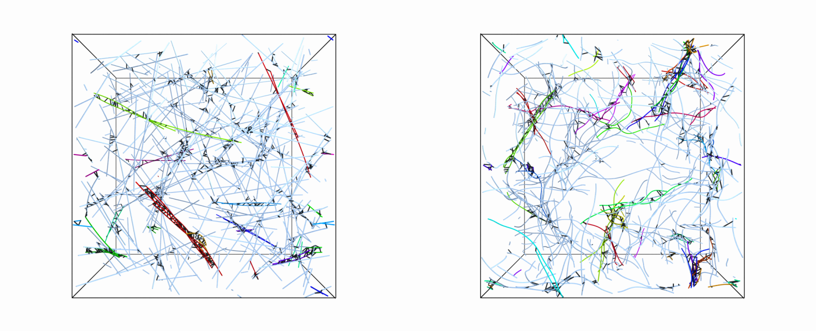
High $\ell_p = 17$ (actin): not much difference in bundle shapes in deterministic (left) vs. fluctuating (right)



Turnover time set to 60% of bundling time (match rheology)

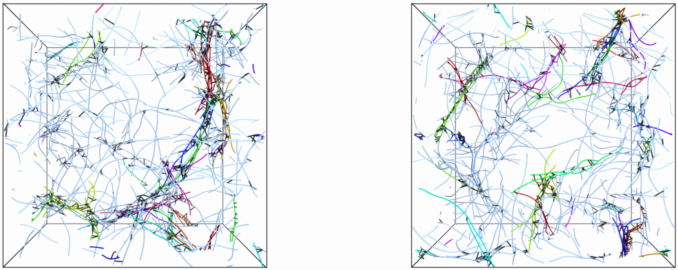
Rheology – smaller ℓ_p

High $\ell_p = 1.7$: major difference in deterministic (left) vs. fluctuating (right)



Rheology – hydrodynamic interactions

Deterministic & fluctuating – *no* difference in morphology



fluctuating fibers without (left) and with (right) hydro

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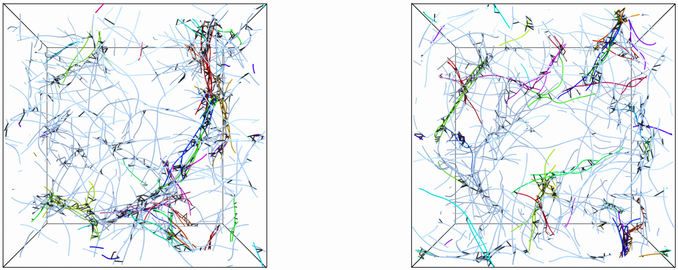


fluctuating fibers without (left) and with (right) hydro

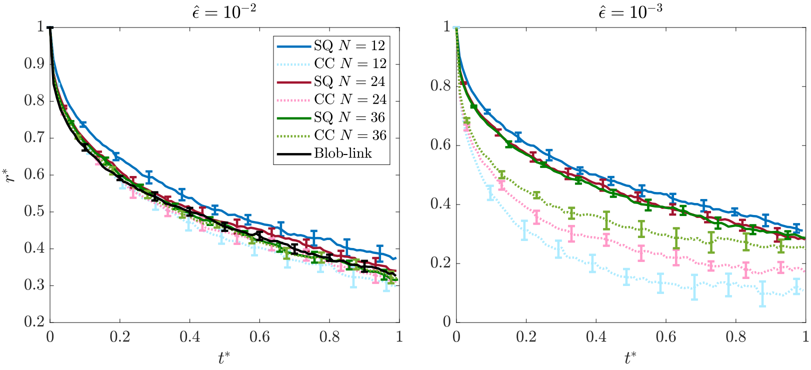
But difference in stress (need formula for Brownian stress)???

Outline

Special quadrature vs. direct quadrature

Compare to direct quadrature on Chebyshev grid, giving an **symmetric positive definite** (SPD) mobility matrix

$$\left(\widetilde{\mathbf{M}}^{(\text{direct})}\mathbf{F}\right)_{\{i\}} := \sum_j \widetilde{\mathbf{M}}^{(\text{RPY})}_{\{i\},\{j\}}\mathbf{F}_{\{j\}}$$



Direct quadrature abysmal failure for $\hat{\epsilon} = 10^{-3}$

Special quadrature vs. oversampled quadrature

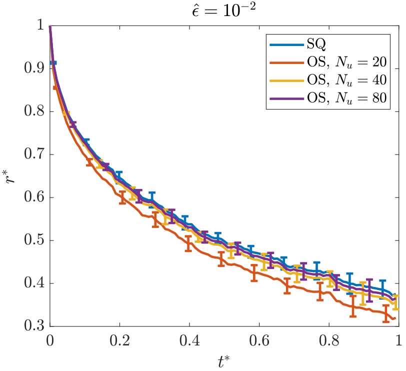
Given force on N point grid

- Construct Galerkin SPD mobility matrix on oversampled grid:

$$\widetilde{\mathbf{M}}_{\text{ref}} = \widetilde{\mathbf{W}}^{-1}\mathbf{E}_u^T \mathbf{W}_u \widetilde{\mathbf{M}}_{\text{RPY},u} \mathbf{W}_u \mathbf{E}_u \widetilde{\mathbf{W}}^{-1}$$

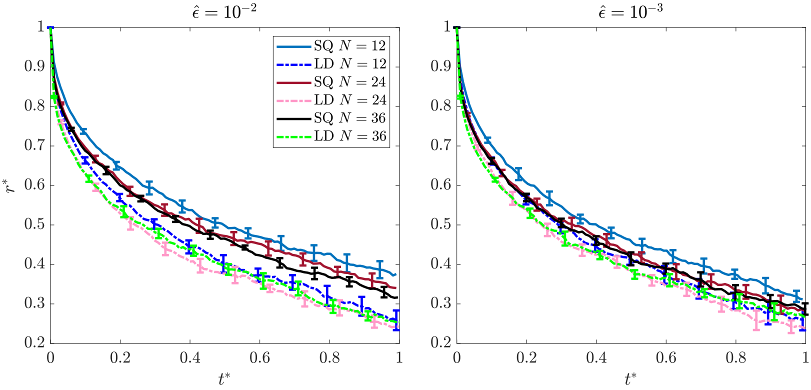
  - Apply $\widetilde{\mathbf{W}}^{-1}$ to get force density
  - Upsample to N_u pt grid with matrix $\mathbf{E}_u$
  - Oversampled RPY quad on upsampled grid with weights $\mathbf{W}_u$
  - Downsample velocity in L^2 with matrix $\widetilde{\mathbf{W}}^{-1}\mathbf{E}_u^T\mathbf{W}_u$.
- $N_u \approx 0.4/\epsilon$ required for engineering (2 digits) accuracy

Special vs. oversampled quadrature: convergence



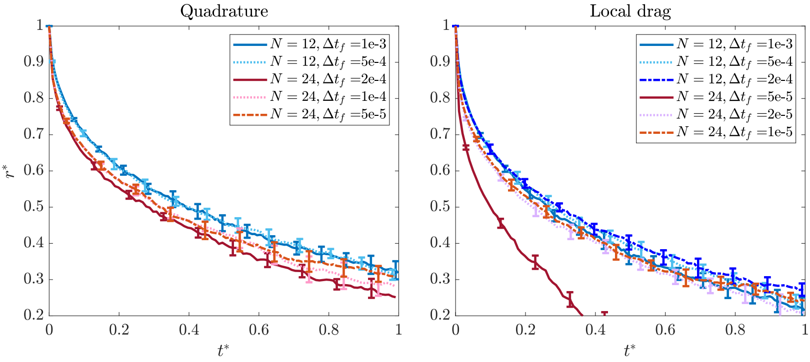
Special quadrature vs. local drag

Local drag is other theory which scales with $\hat{\epsilon}$



Special quad better for $\hat{\epsilon} = 10^{-2}$

Temporal convergence: local drag vs. special quad



Local drag requires time step 4–10 times smaller ($\hat{\epsilon} = 10^{-3}$)

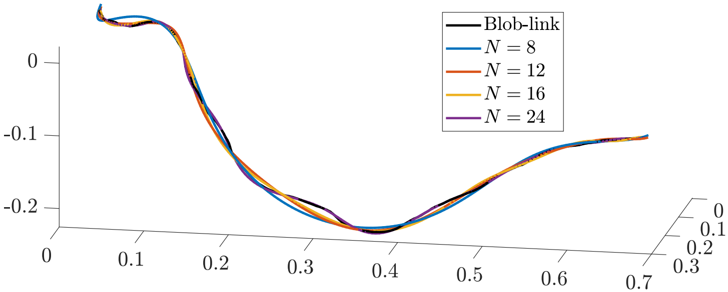
Coarse-graining: geometric perspective

Solve the quadratic programming problem

$$\begin{pmatrix} \boldsymbol{\tau} \\ \mathbf{X}_{\mathrm{MP}} \end{pmatrix} = \operatorname{argmin} \left\| \mathbf{X}^{(\mathrm{SB})} - \mathbf{X}^{(\mathrm{BL})} \right\|_2^2 = \left\| \mathbf{E}_{S \to B} \boldsymbol{\mathcal{X}} \begin{pmatrix} \boldsymbol{\tau} \\ \mathbf{X}_{\mathrm{MP}} \end{pmatrix} - \mathbf{X}^{(\mathrm{BL})} \right\|_2^2$$

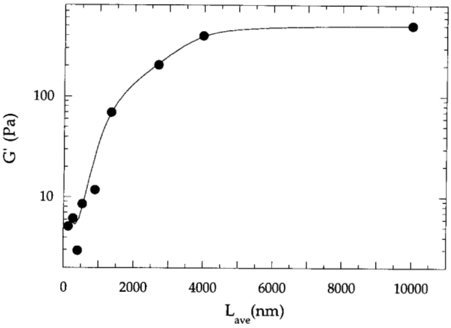
$$\boldsymbol{\tau}_{\{p\}}^T \boldsymbol{\tau}_{\{p\}} = 1, \qquad p = 1, \dots, N$$

where $\mathbf{E}_{S \to B}$ samples $\mathbb{X}(s)$ at the blob-link locations.

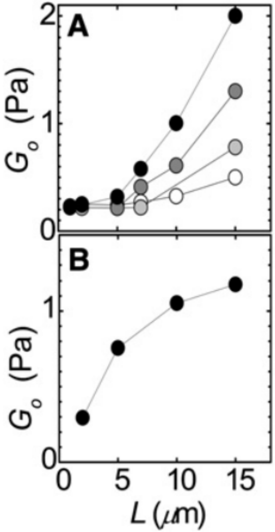


Experimental measurements vary widely

Parallel plate rheometer in both cases!



Jamney et al. *J. Biol. Chem.* (1994)

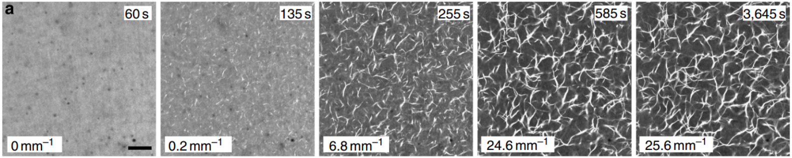


Kasza et al. *BJ* (2010)

Variety of measurements due to morphological changes

Morphology can vary over time and with CL/actin concentration

- Changing network morphology → changing shear modulus
- Viscoelastic moduli should be steady state properties



Falzone et al. *Nat. Commun.* (2012)