Bending fluctuations in semiflexible, inextensible, slender filaments in Stokes flow: Towards a spectral discretization

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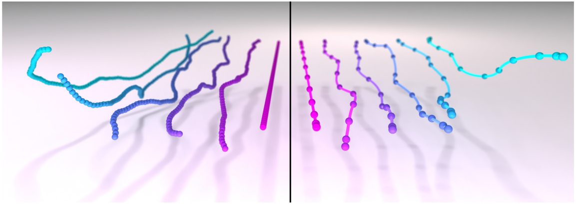
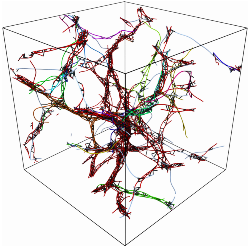
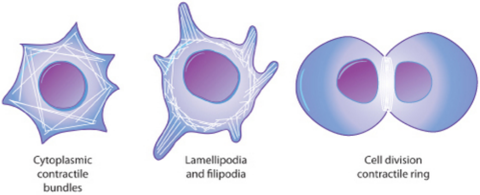


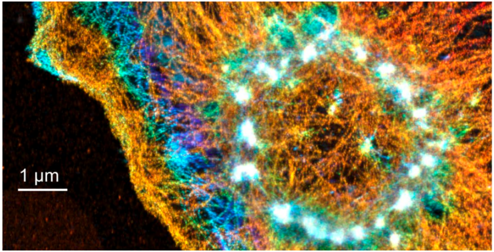


Importance of actin cytoskeleton

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)

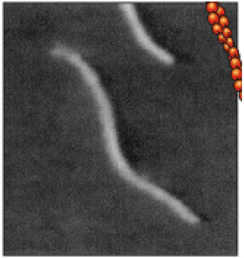
Fluctuating actin filaments

Actin filament *fluctuations* used for

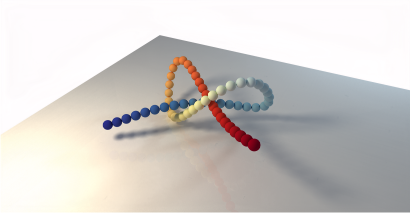
- Sensing
- Motility
- Stress release (untying knots!)

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

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



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



Pawlizak and Käs, University of Leipzig., Ward et al. (Dogic lab) *Nat. Mat. (2015)*

Stationary probability distribution

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

- Stationary distribution (probability of observing a state)

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

  Gibbs-Boltzmann distribution (stat. mech.)
- Prob. depends on ratio of energy with $k_B T$ (thermal energy)
- 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

Converting to Ito form gives

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

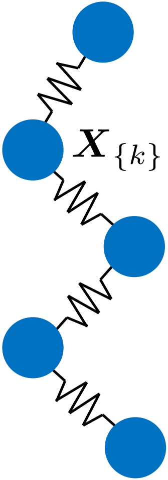
Goal is to write and solve such an equation for fibers

Bead/blob-spring model for fibers

Create "fiber" out of beads (blobs) and springs

- DOFs: $\mathbf{X}_{\{i\}}$ = bead positions
- No constraints
- Energy and Langevin equation straightforward
- Only drift terms from mobility (vanish for triply-periodic systems)

Big problem: need small Δt to resolve stiff springs



Blob-link model

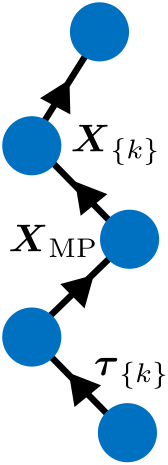
Replace springs with rigid rods

- DOFs: $\boldsymbol{\tau}_{\{i\}}$ = unit tangent vectors + $\mathbf{X}_{\text{MP}}$
- Obtain positions of nodes $\mathbf{X}$ via

$$\mathbf{X}_{\{i\}} = \mathbf{X}_{\text{MP}} + \Delta s \sum_{\text{MP}}^{i} \boldsymbol{\tau}_{\{k\}}$$

  defines invertible map $\mathbf{X} = \mathcal{X}\begin{pmatrix}\boldsymbol{\tau} \\ \mathbf{X}_{\text{MP}}\end{pmatrix}$

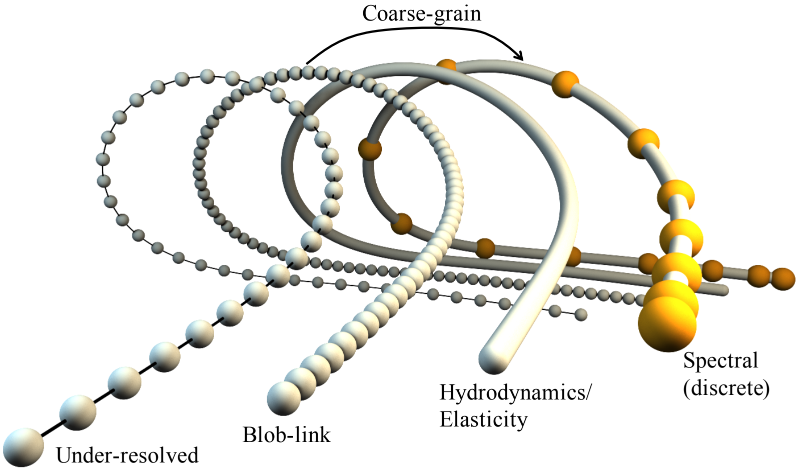
- Constraint $\boldsymbol{\tau}_{\{i\}} \cdot \boldsymbol{\tau}_{\{i\}} = 1$



Removes stiffest timescale BUT

- Slender fibers → small lengthscales
- Still have small Δt!
- Small lengthscales come from *hydrodynamics* of long blob-link chain

Big idea: mix continuum and discrete



Spectral method

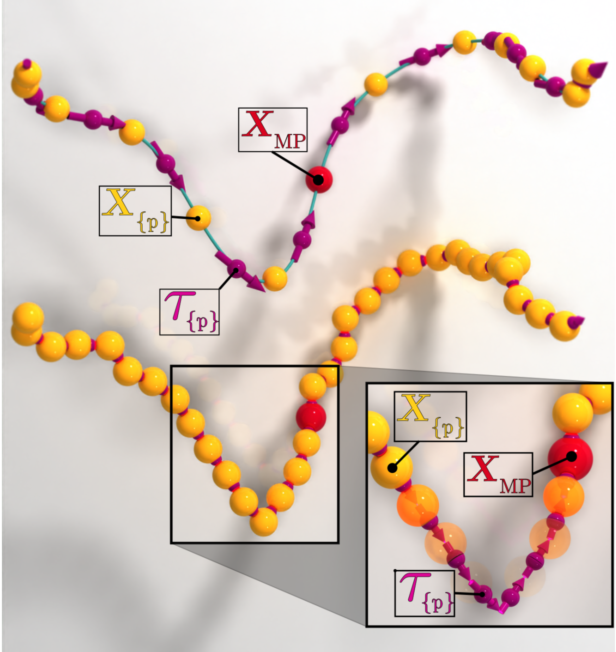
Mixed discrete-continuum description

- Hydrodynamics uses a continuum curve $\rightarrow$ special quadrature
- Discrete spatial DOFs $\rightarrow$ Langevin equation (Brennan/Aleks)
- Spectral method: the spatial DOFs define the continuum curve $\mathbb{X}(s)$ used for elasticity & hydro

Big idea: resolve hydrodynamics $\rightarrow$ reduce DOFs $\rightarrow$ increase Δt

- Small problem: constrained motion
- $\boldsymbol{\tau}$ = series of connected rigid rods
- 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, $\mathbf{X}_{\text{MP}}$

- Chebyshev polynomial $\boldsymbol{\tau}(s)$ constrained $\|\boldsymbol{\tau}(s_j)\| = 1$
- Obtain $\mathbb{X}(s)$ by integrating $\boldsymbol{\tau}(s)$ on $N_x = N + 1$ point grid (type 2, with EPs). Set $\mathbf{X}_{\{i\}} = \mathbb{X}(s_i)$.
- Defines set of nodes $\mathbf{X}_{\{i\}}$ and invertible mapping

$$\mathbf{X} = \mathcal{X}\begin{pmatrix}\boldsymbol{\tau} \\ \mathbf{X}_{\text{MP}}\end{pmatrix}$$

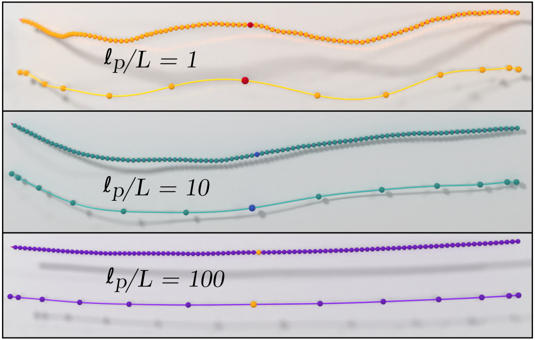
- Can apply discrete blob-link methods (Brennan Sprinkle) for constrained *discrete* Langevin equation
- Combine with continuum methods for elasticity and hydrodynamics

Continuum part: energy

Fibers resist bending according to curvature energy *functional*

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

- 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*
- No aliasing
- Corresponds to inner product weights matrix $\widetilde{\mathbf{W}}$
- Force $\mathbf{F} = -\partial\mathcal{E}/\partial\mathbf{X} = -\mathbf{L}\mathbf{X}$
- Force density $\mathbf{f} = \widetilde{\mathbf{W}}^{-1}\mathbf{F}$ (FEM: $\langle\mathbf{X},\mathbf{f}\rangle = \mathbf{X}^T\mathbf{F}$)

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

Continuum part: hydrodynamics

Goal is to approximate blob-link methods (radius $\hat{a}$), which give velocity $\mathbf{U}$ by

$$\mathbf{U}_{\{i\}} = \sum_j \mathbf{M}_{\text{RPY}} \left(\mathbf{X}_{\{i\}}, \mathbf{X}_{\{j\}}; \hat{a}\right) \mathbf{F}_{\{j\}}$$

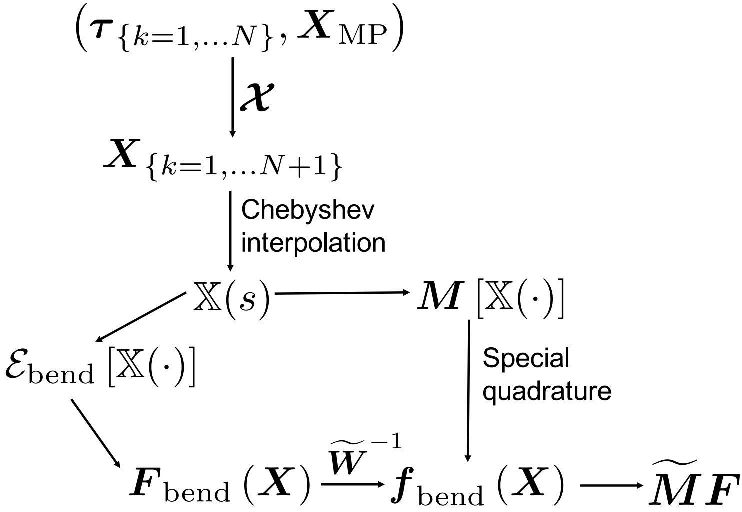
- $\mathbf{M}_{\text{RPY}}$= symmetrically regularized form of Stokeslet (RPY tensor)
- Expresses velocity on one blob from force on another

Convert sum over blobs $\rightarrow$ integral over curve

$$\mathbf{U}(s) = \int_0^L \mathbf{M}_{\text{RPY}} \left(\mathbb{X}(s), \mathbb{X}\left(s'\right); \hat{a}\right) \mathbf{f}\left(s'\right) ds'$$

- Have developed special quadrature schemes on spectral grid
- Mix of singularity subtraction + precomputations
- Requires $\mathcal{O}(1)$ points to resolve integral
- Compare to blob-link: $\mathcal{O}(L/\hat{a})$ points!

Applying mobility



Discrete part: inextensibility

Langevin equation must be modified because of inextensibility

- $\boldsymbol{\tau}_{\{i\}}$ remains unit vector, rotates as rigid rod (ang. vel. $\boldsymbol{\Omega}_{\{i\}}$)

$$\partial_t \boldsymbol{\tau}_{\{i\}} = \boldsymbol{\Omega}_{\{i\}} \times \boldsymbol{\tau}_{\{i\}} \to \partial_t \boldsymbol{\tau} = -\mathbf{C}\boldsymbol{\Omega}$$

- Results in constrained motions for $\mathbf{X}$

$$\partial_t \mathbf{X} = \boldsymbol{\mathcal{X}} \begin{pmatrix} -\mathbf{C} & \mathbf{0} \\ \mathbf{0} & \mathbf{I} \end{pmatrix} \begin{pmatrix} \boldsymbol{\Omega} \\ \mathbf{U}_{\mathrm{MP}} \end{pmatrix} := \boldsymbol{\mathcal{X}} \bar{\mathbf{C}} \boldsymbol{\alpha} := \mathbf{K}\boldsymbol{\alpha}$$

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

Deterministic dynamics

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

- No work done for inextensible motions (principle of virtual work)
- Constraint $\mathbf{K}^T \boldsymbol{\Lambda} = \mathbf{0}$ (comes from L^2 adjoint of $\mathbf{K}$)

Results in saddle point system for $\boldsymbol{\alpha}$ and $\boldsymbol{\Lambda}$

$$
\begin{aligned}
\mathbf{K}\boldsymbol{\alpha} &= \widetilde{\mathbf{M}}\left(-\mathbf{L}\mathbf{X} + \boldsymbol{\Lambda}\right) \\
\mathbf{K}^T \boldsymbol{\Lambda} &= \mathbf{0},
\end{aligned}
$$

Deterministic dynamics (eliminate $\boldsymbol{\Lambda}$)

$$
\partial_t \mathbf{X} = -\widehat{\mathbf{N}}\mathbf{L}\mathbf{X}, \qquad \widehat{\mathbf{N}} = \mathbf{K}\left(\mathbf{K}^T \widetilde{\mathbf{M}}^{-1} \mathbf{K}\right)^{\dagger} \mathbf{K}^T
$$

$\widehat{\mathbf{N}}$ expensive if done densely (if nonlocal dynamics). Apply via iterative saddle pt solve with block-diagonal preconditioner (in progress)

Discrete Langevin equation

Deterministic dynamics + time reversibility → Langevin equation

$$\partial_t \mathbf{X} = - \underbrace{\widehat{\mathbf{N}}\mathbf{L}\mathbf{X}}_{\text{Backward Euler}} + \underbrace{k_B T \partial_{\mathbf{X}} \cdot \widehat{\mathbf{N}}}_{\text{Midpoint integrator}} + \underbrace{\sqrt{2 k_B T} \widehat{\mathbf{N}}^{1/2}}_{\text{Saddle point solve}} \mathcal{W}(t)$$

- Drift term captured *in expectation* via solving at the midpoint (Brennan/Aleks)
- $\widehat{\mathbf{N}}^{1/2}$ captured via saddle point solve

$$\mathbf{K}\boldsymbol{\alpha} = \widetilde{\mathbf{M}} \left(-\mathbf{L}\mathbf{X} + \boldsymbol{\Lambda} \right) + \sqrt{\frac{2 k_B T}{\Delta t}} \widetilde{\mathbf{M}}^{1/2} \mathbf{W}$$
$$\mathbf{K}^T \boldsymbol{\Lambda} = \mathbf{0},$$
$$\Rightarrow \boldsymbol{\alpha} = \text{Deterministic} + \sqrt{\frac{2 k_B T}{\Delta t}} \widehat{\mathbf{N}}^{1/2} \mathbf{W}$$

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

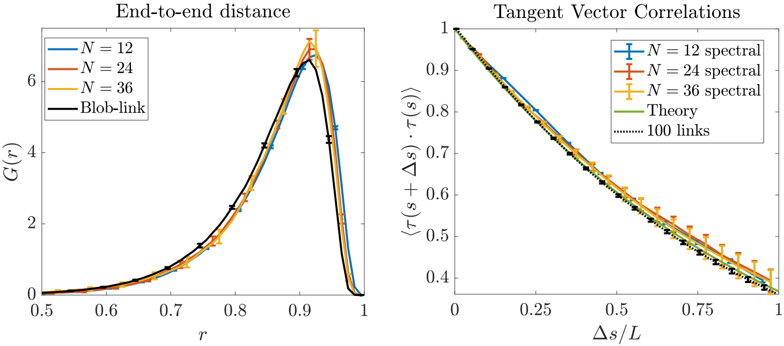
Implied GB distribution

The overdamped Langevin equation is in detailed balance wrt the distribution

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

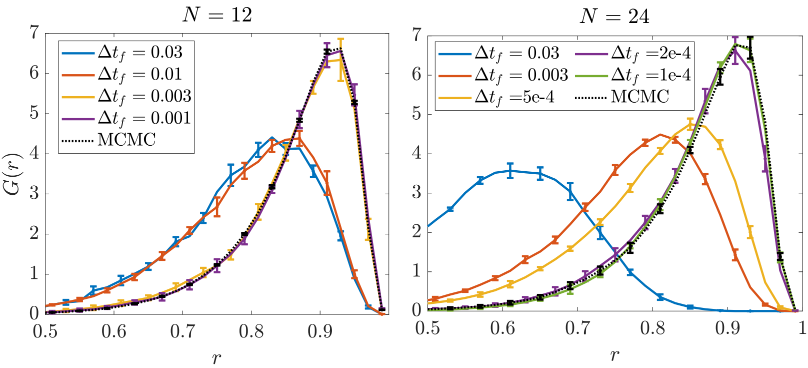
- For blob-link, physical
- Postulate that it extends to spectral (others possible)
- Justify through the theory of coarse-graining (in progress)
- Will present supporting numerical results

Samples from GB: free fibers



Bias for finite N which disappears as N increases

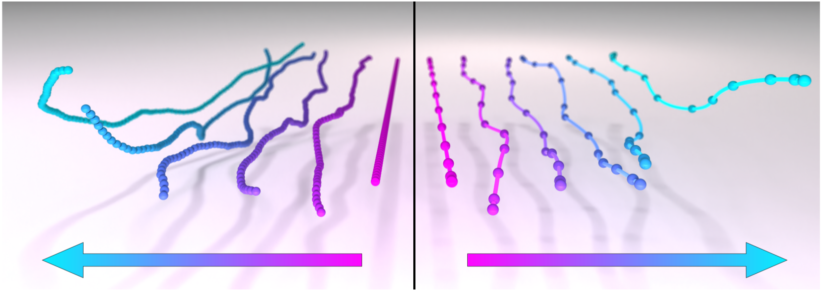
Using the Langevin integrator to sample



Convergence to MCMC for smallest Δt

- Reported in terms of longest relaxation timescale
- Goes as N^{-4} (not ideal); another reason to keep N low!
- Unchanged with ℓ_p (modes are stiffer, but fewer required)

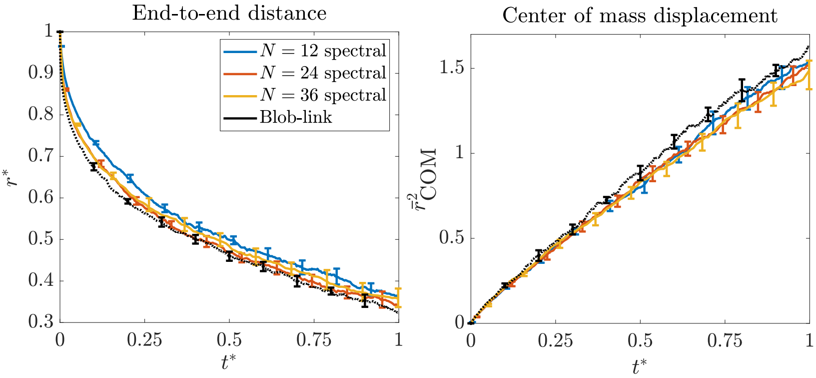
Relaxation of fiber to equilibrium



Blob-link vs. spectral

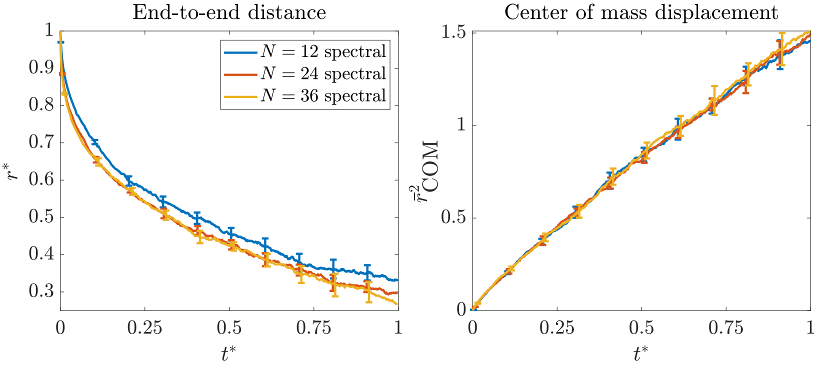
- Getting a good approximation to mean end-to-end distance?
- Is special quadrature doing what we want it to?

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



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

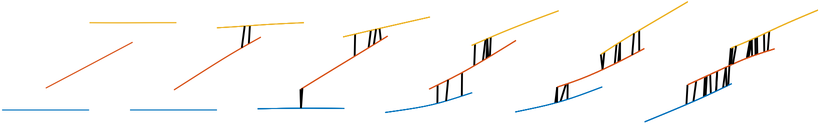
Quantifying relaxation $\left(\hat{\epsilon} = 10^{-3}\right)$

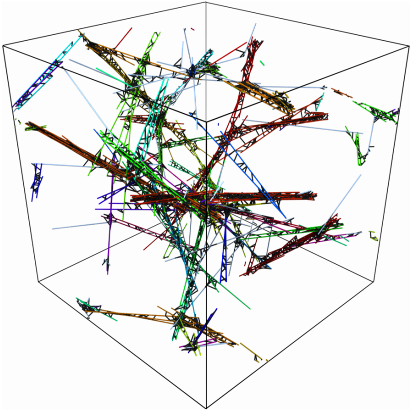


Dynamics of bundling in cross-linked actin networks

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

- CLs bind fibers, pulling them closer together
- Ratcheting action creates bundles





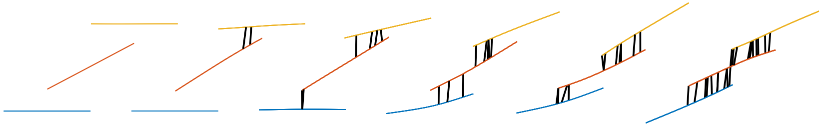
Goals for bundling

Filaments move in three ways

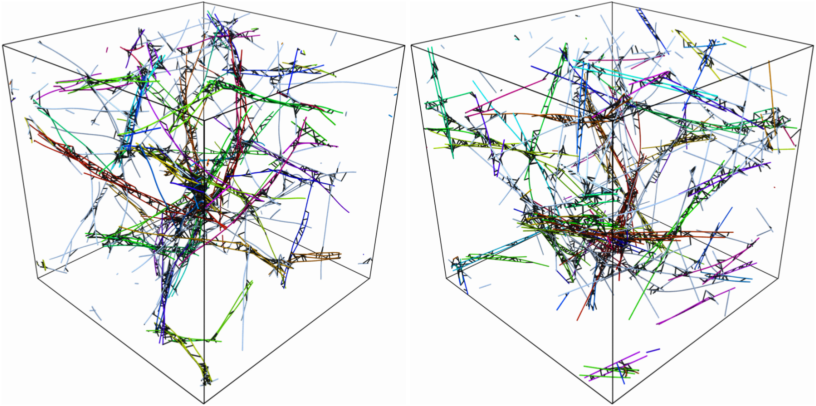
1. Cross linking forces
2. Rigid body translation and rotation
3. *Semiflexible* bending fluctuations

Goal is to explore the role of the bending flucts

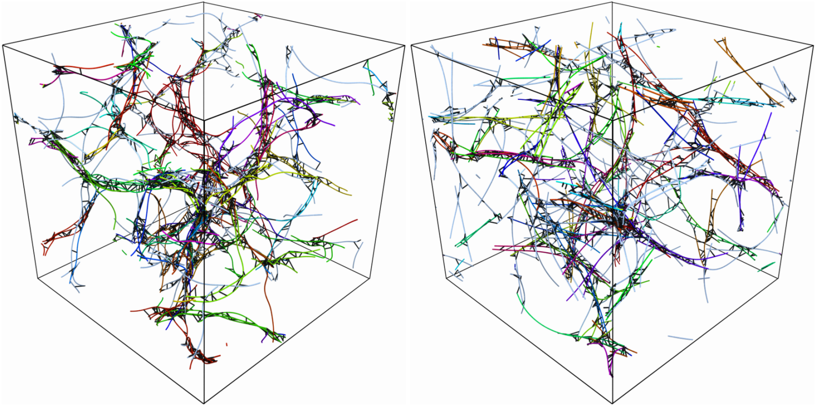
- Intuition: fluctuations increase binding frequency
- How small does ℓ_p have to be?
- Strategy: simulate fibers with #1 and #2 only, compare to fluctuating



Movie: $\ell_p/L = 10$

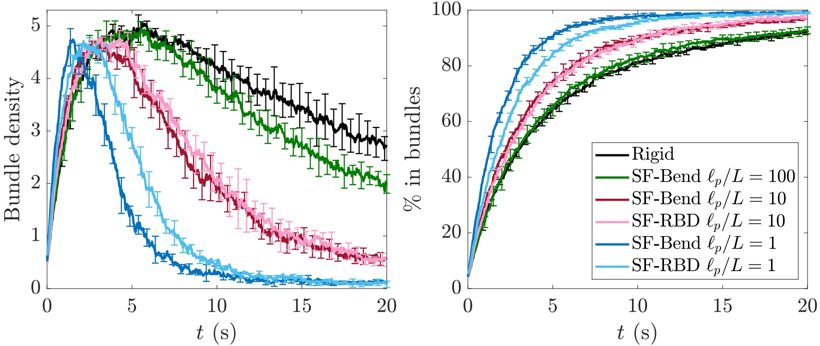


Movie: $\ell_p/L = 1$



Bundling statistics

Statistics confirm movies



- $\ell_p/L = 100$: similar to rigid
- $\ell_p/L = 10$: small difference from "RBD" filaments *without* bending fluctuations
- $\ell_p/L = 1$: speed-up due to semiflexible bending fluctuations
- Actin in vivo: $\ell_p/L \approx 30$

Conclusions

Spectral method as a way to coarse-grain blob-link simulations

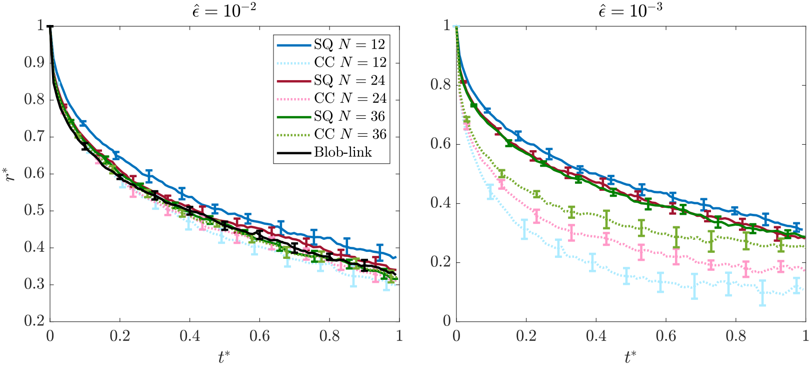
- Resolve hydrodynamics and elasticity with continuum interpolant
- Langevin equation over discrete collection of points
- Good accuracy with $\mathcal{O}(1)$ points, larger Δt

Future challenges

- Incorporate nonlocal interactions between fibers (hydrodynamic+steric)
- More rigorous justification of GB (continuum limit?)
- Apply to rheology of actin networks

Special quadrature vs. direct quadrature

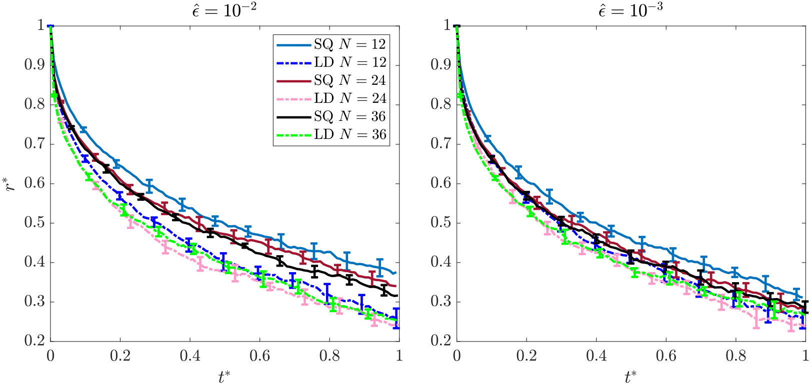
Compare to direct quadrature on Chebyshev grid



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

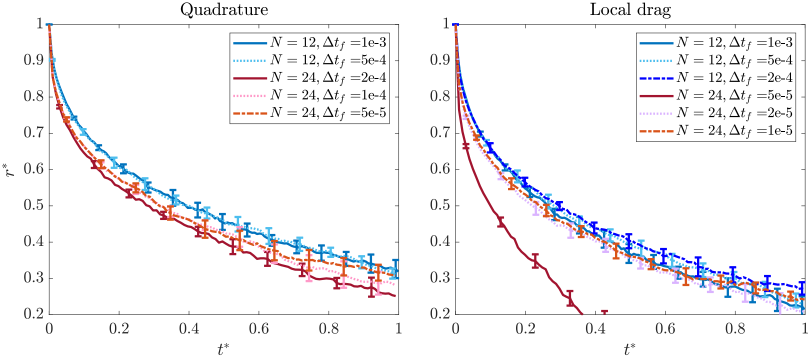
Special quadrature vs. local drag

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

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

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

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