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

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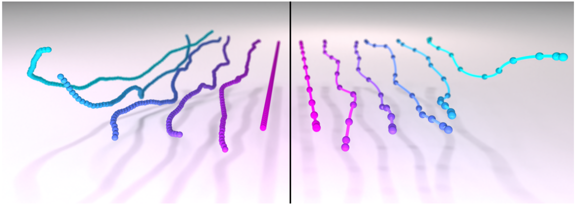

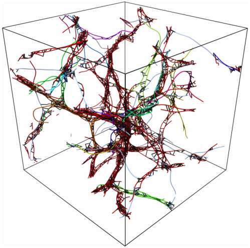

Outline

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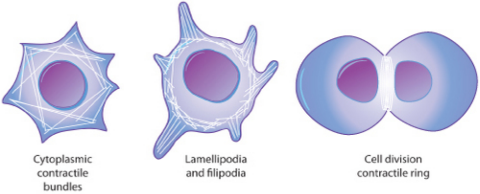
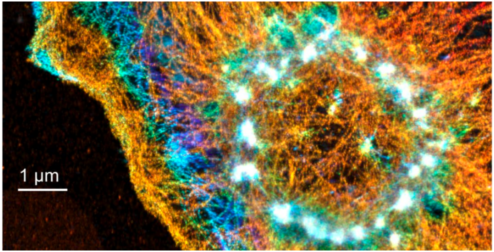
Importance of actin cytoskeleton

Dynamic cross-linked network of slender filaments

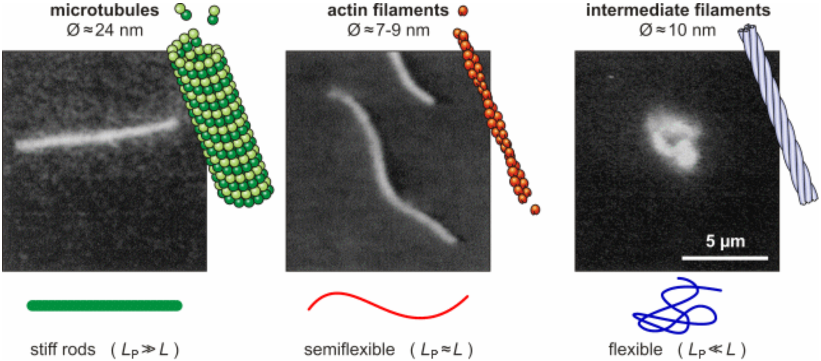
- Morphology $\leftrightarrow$ mechanical properties of cell
- Dictate cell's shape and ability to move and divide





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

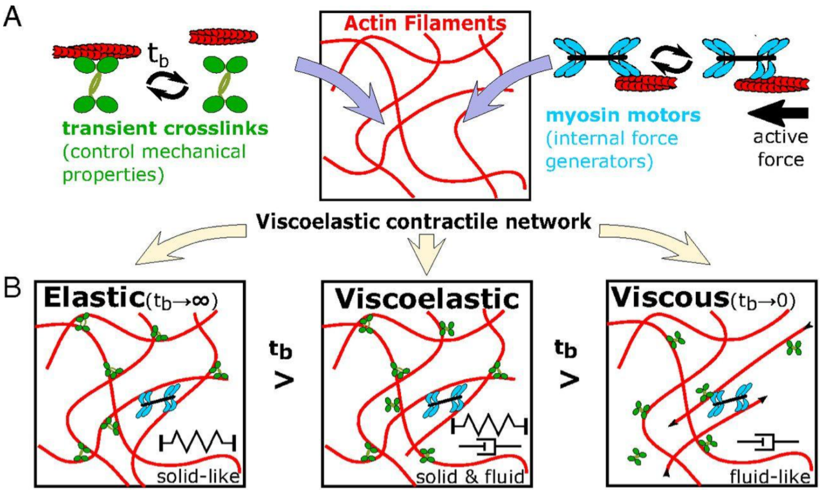
Fibers involved in cell mechanics



Pawlizak and Käs, University of Leipzig

ℓ_p =persistence length, L =fiber length, $a = \epsilon L$ =fiber radius,
ϵ =slenderness ratio
Actin filaments are *semiflexible* $\ell_p \gtrsim L$

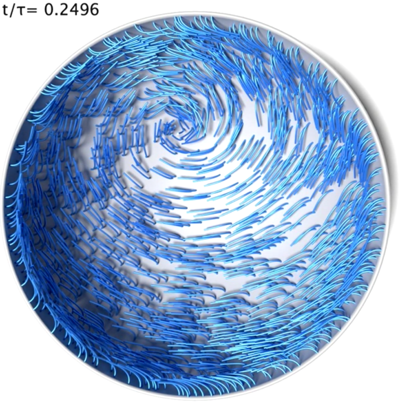
Cytoskeletal rheology



Ahmed and Betz. *PNAS*. (2015)

Importance of hydrodynamics

If we only use local drag, we cannot get large-scale flows!



Oocyte streaming from group of Mike Shelley (Flatiron)

We must include hydrodynamic interactions to capture collectively-generated flow

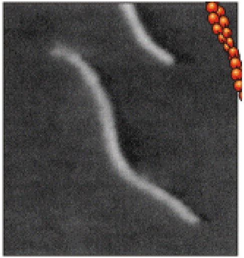
Fluctuating actin filaments

Actin filament *fluctuations* used for

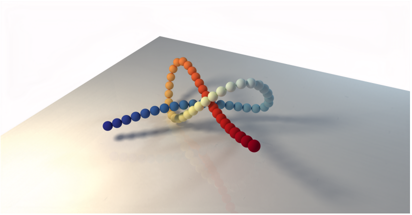
- Sensing
- Motility
- Stress release (untying knots!)

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)*

Outline

Statics: Gibbs-Boltzmann distribution

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

- Stationary distribution (probability of observing a state)

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

  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

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

- $\boldsymbol{M}(\boldsymbol{X})$ 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

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

Goal is to write and solve such an equation for fibers

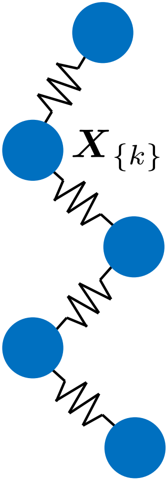
Outline

Bead/blob-spring model for fibers

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

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

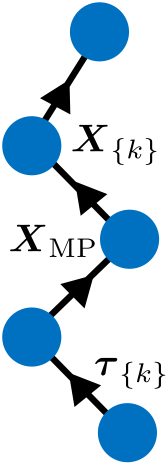
$$\boldsymbol{X}_{\{i\}} = \boldsymbol{X}_{\text{MP}} + \Delta s \sum_{\text{MP}}^{i} \boldsymbol{\tau}_{\{k\}}$$

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

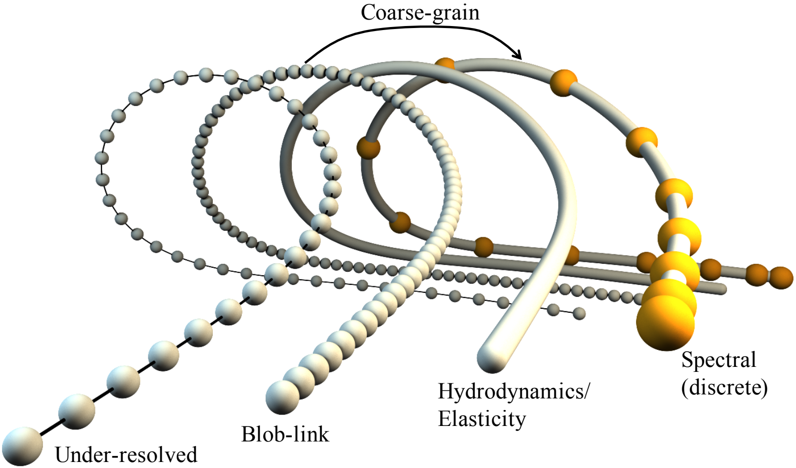
- Constraint $\boldsymbol{\tau}_{\{i\}} \cdot \boldsymbol{\tau}_{\{i\}} = 1$

Removes stiffest timescale but:

- Slender fibers $\rightarrow$ small lengthscales
- Still have small Δt!
- 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

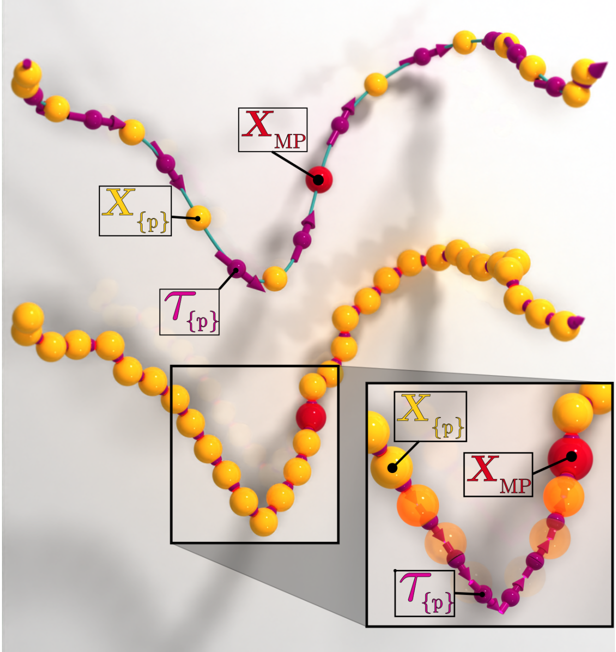
Mixed discrete-continuum description

- Hydrodynamics uses a continuum curve $\rightarrow$ special quadrature
- Discrete spatial DOFs $\rightarrow$ Langevin equation (Brennan Sprinkle)
- 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, $\boldsymbol{X}_{\text{MP}}$

- 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 $\boldsymbol{X}_{\{i\}} = \mathbb{X}(s_i)$.
- Defines set of nodes $\boldsymbol{X}_{\{i\}}$ and invertible mapping

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

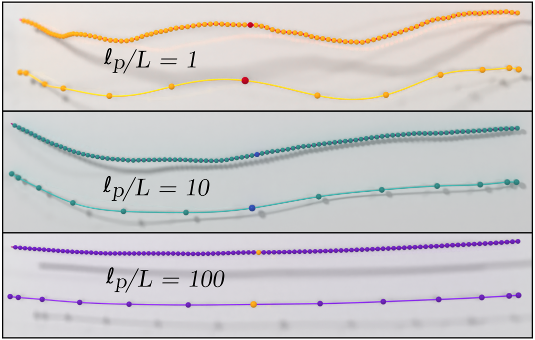
- Can apply discrete blob-link methods (Brennan Sprinkle) for constrained *discrete* Langevin equation
- Combine with continuum methods for elasticity and hydrodynamics

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

$$\begin{aligned}\mathcal{E}\left(\boldsymbol{X}\right) &= \frac{\kappa}{2}\int_0^L \partial_s^2\mathbb{X}(s)\cdot\partial_s^2\mathbb{X}(s)\,ds \\ &= \frac{\kappa}{2}\left(\boldsymbol{E}_{N_x\to 2N_x}\boldsymbol{D}^2\boldsymbol{X}\right)^T \boldsymbol{W}_{2N}\left(\boldsymbol{E}_{N_x\to 2N_x}\boldsymbol{D}^2\boldsymbol{X}\right) \\ &= \frac{\kappa}{2}\left(\boldsymbol{D}^2\boldsymbol{X}\right)^T \widetilde{\boldsymbol{W}}\left(\boldsymbol{D}^2\boldsymbol{X}\right) \\ &= \frac{1}{2}\boldsymbol{X}^T\boldsymbol{L}\boldsymbol{X}\end{aligned}$$

- Upsampling to grid of size $2N_x$ to integrate *exactly*
- No aliasing
- Corresponds to inner product weights matrix $\widetilde{\boldsymbol{W}}$
- Force $\boldsymbol{F} = -\partial\mathcal{E}/\partial\boldsymbol{X} = -\boldsymbol{L}\boldsymbol{X}$
- Force density $\boldsymbol{f} = \widetilde{\boldsymbol{W}}^{-1}\boldsymbol{F}$ (FEM: $\langle\boldsymbol{X},\boldsymbol{f}\rangle = \boldsymbol{X}^T\boldsymbol{F}$)

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

Fluid dynamics of an immersed fiber

Immersed blob continuum hydrodynamic model (without Brownian fluctuations):

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

$$\boldsymbol{U}\left(s,t\right)=\partial_{t}\mathbb{X}\left(s,t\right)=\int d\boldsymbol{r}\;\boldsymbol{v}\left(\boldsymbol{r},t\right)\delta_{a}\left(\mathbb{X}(s,t)-\boldsymbol{r}\right)$$

$$\boldsymbol{f}=-\kappa_{b}\mathbb{X}_{ssss}+\boldsymbol{\lambda}$$

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

Hydrodynamic mobility kernel

- We can (temporarily) eliminate the fluid velocity to write an equation for **fiber only**.
- Define the positive semi-definite **hydrodynamic kernel**

$$\mathcal{R}\left(\boldsymbol{r}_1, \boldsymbol{r}_2\right) = \int \delta_a\left(\boldsymbol{r}_1 - \boldsymbol{r}'\right) \mathbb{G}\left(\boldsymbol{r}', \boldsymbol{r}''\right) \delta_a\left(\boldsymbol{r}_2 - \boldsymbol{r}''\right) d\boldsymbol{r}' d\boldsymbol{r}'',$$

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

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

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

Nonlocal PDE

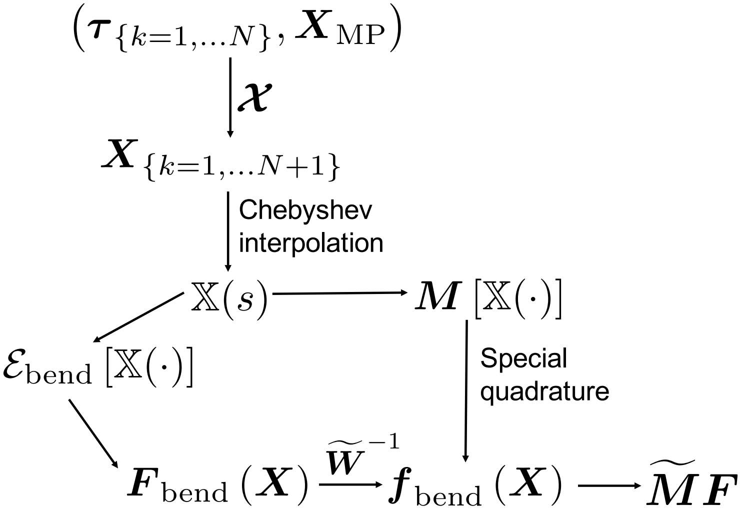
- Define a positive semidefinite **mobility operator**

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

- 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!
- Converting between *continuous force densities* $\boldsymbol{f}(s)$ to *discrete forces* $\boldsymbol{F}$ (Galerkin projection), we get a **mobility matrix**

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

Applying mobility



Outline

Discrete part: inextensibility

Langevin equation must be modified because of inextensibility

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

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

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

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

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

Deterministic dynamics

Close system by introducing Lagrange multiplier forces Λ

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

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

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

Deterministic dynamics (eliminate Λ)

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

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

Discrete Langevin equation

Deterministic dynamics + time reversibility → Langevin equation

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

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

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

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

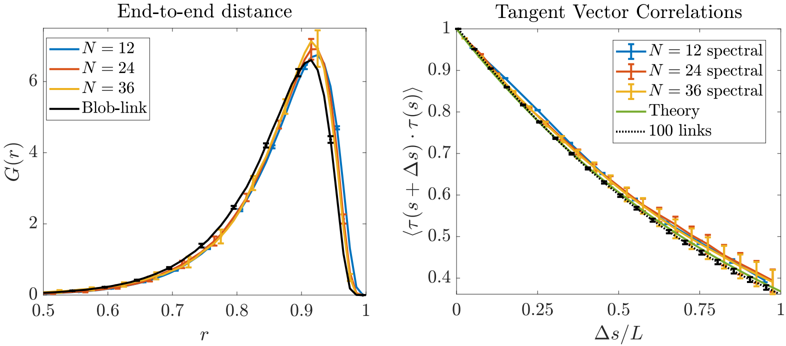
Implied GB distribution

The overdamped Langevin equation is in detailed balance wrt the distribution

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

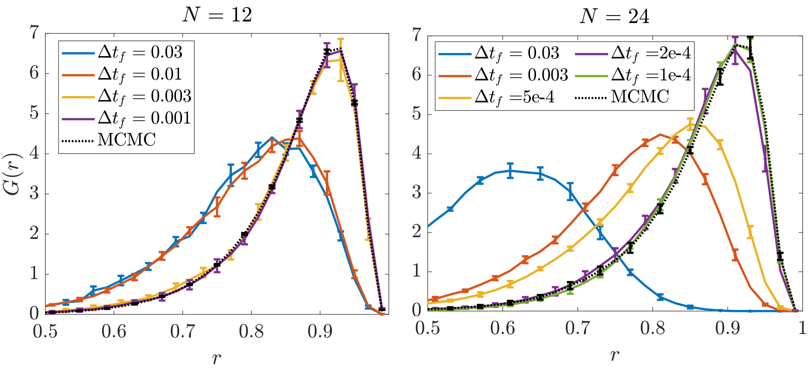
- For blob-link, seems physical
- Postulate that it extends to spectral (others possible)
- Justify through the theory of coarse-graining (in progress, Pep Espanol)
- Here: present supporting numerical results

Samples from GB: free fibers



Bias for finite *N* which disappears as *N* increases

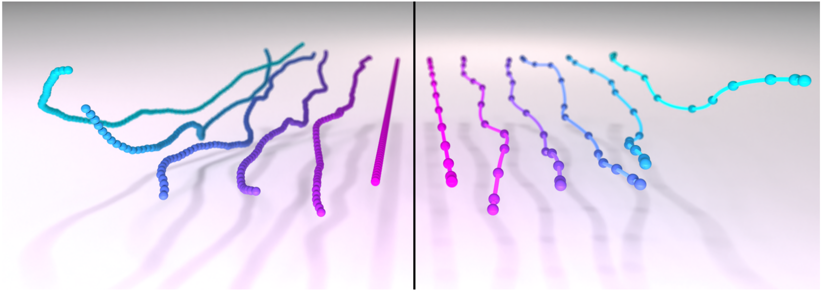
Using the Langevin integrator to sample



Convergence to MCMC for smallest Δt

- Reported in terms of longest relaxation timescale
- Δt goes as N^{-4} – must keep N low!
- Unchanged with ℓ_p (modes are stiffer, but fewer required)

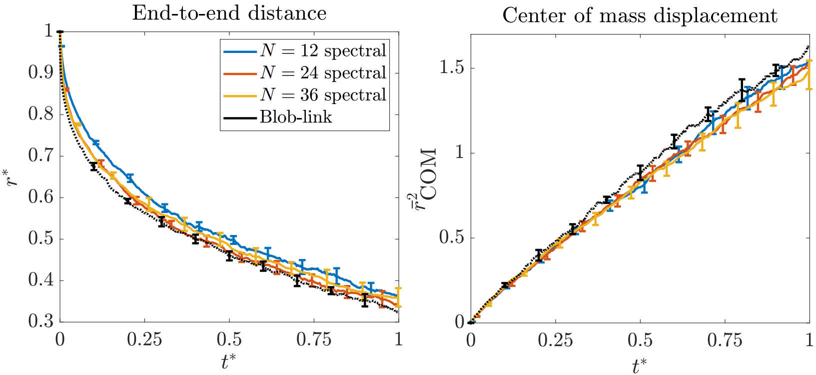
Relaxation of fiber to equilibrium



Blob-link vs. spectral

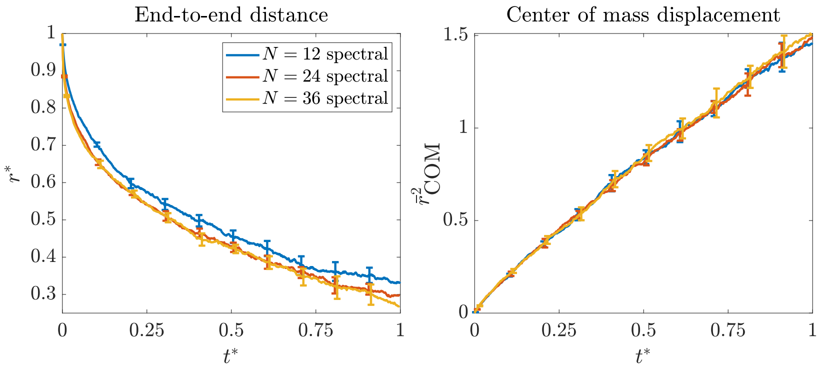
- Getting a good approximation to mean end-to-end distance?
- Is special quadrature doing what we want it to?

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!

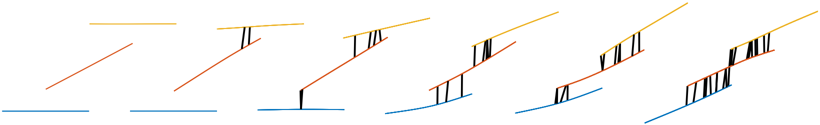
Quantifying relaxation $\left(\hat{\epsilon} = 10^{-3}\right)$

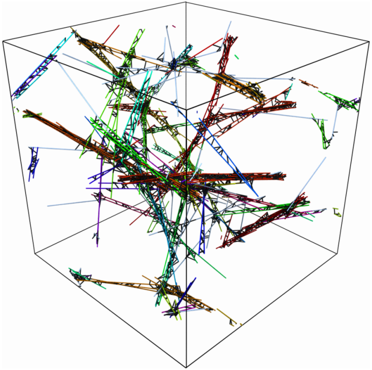


Outline

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

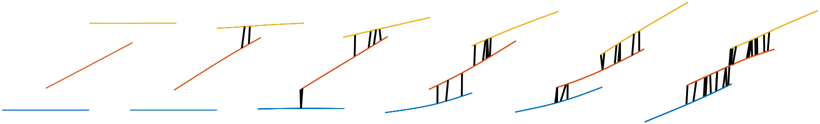
Goals for bundling

Filaments move in three ways:

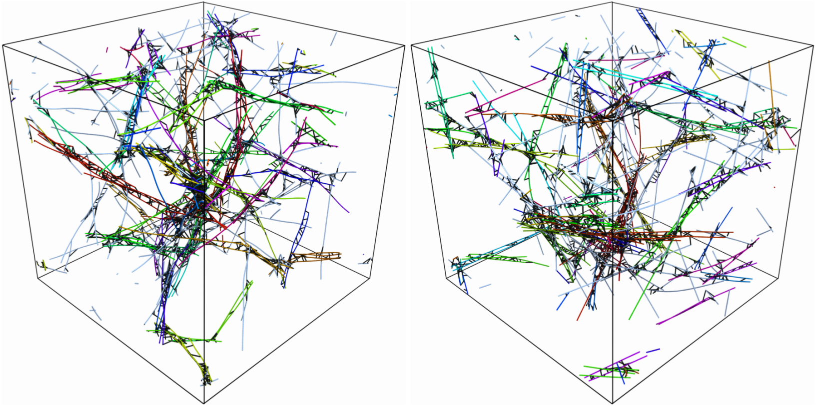
1. Cross linking forces
2. Rigid body translation and rotation
3. *Semiflexible* bending fluctuations

Goal is to explore the role of the bending flucts

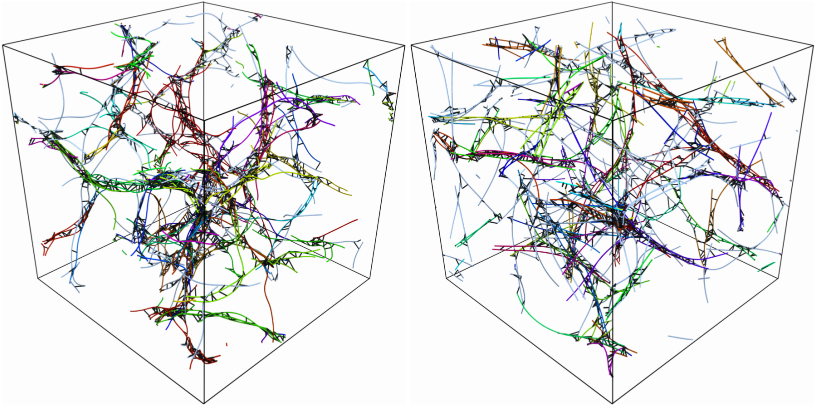
- Intuition: fluctuations increase binding frequency
- How small does ℓ_p have to be?
- Strategy: simulate fibers with #1 and #2 only, compare to fluctuating



Movie: $\ell_p / L = 10$

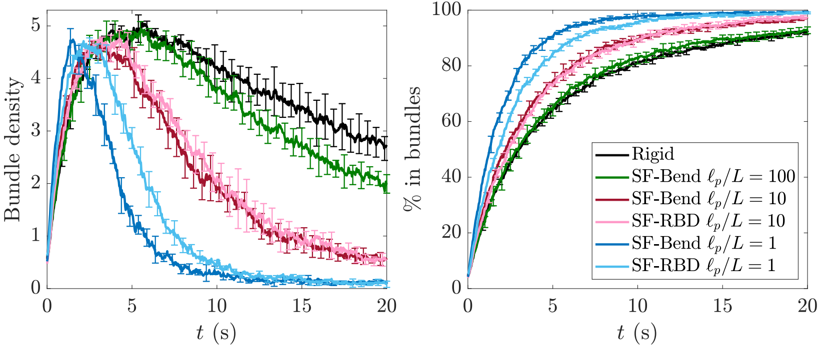


Movie: $\ell_p/L = 1$



Bundling statistics

Statistics confirm movies

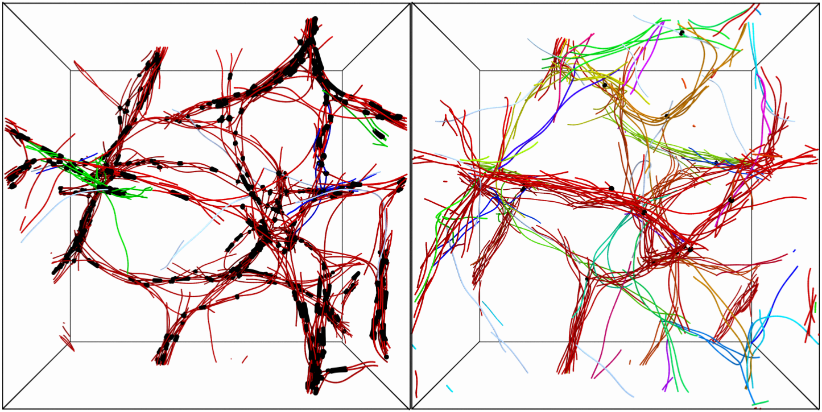


- $\ell_p/L = 100$: similar to rigid
- $\ell_p/L = 10$: small difference from "RBD" filaments *without* bending fluctuations
- $\ell_p/L = 1$: speed-up due to semiflexible bending fluctuations
- Actin in vivo: $\ell_p/L \approx 30$

Bundling with sterics

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

- But 5× time step reduction required



Outline

Conclusions

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

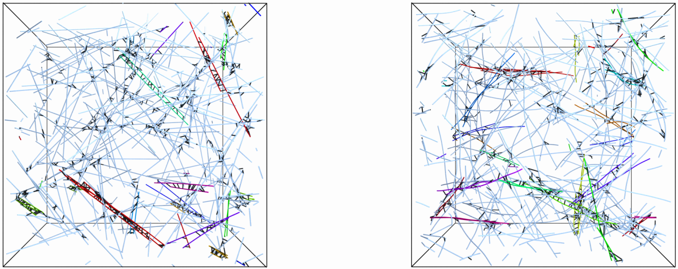
- Resolve hydrodynamics and elasticity with continuum interpolant
- Langevin equation over discrete collection of points
- Good accuracy with $\mathcal{O}(1)$ points, larger Δt

Future challenges

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

Rheology – effect of fluctuations

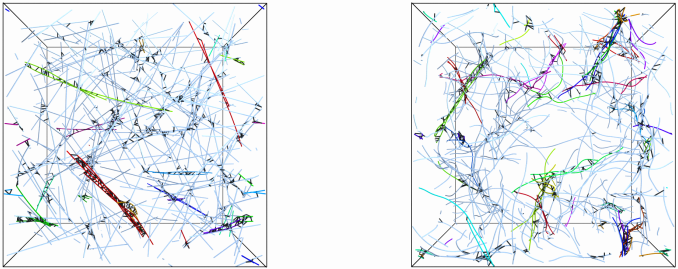
High $\ell_p = 17$ (actin): not much difference in bundle shapes in deterministic (left) vs. fluctuating (right)



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

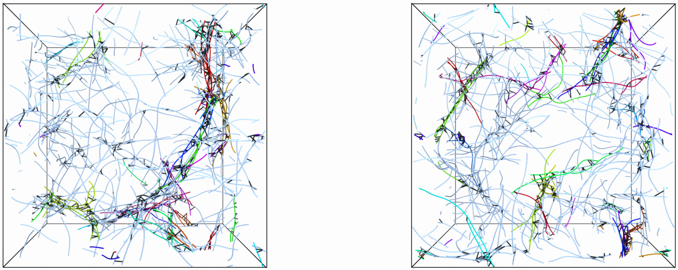
Rheology – smaller ℓ_p

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

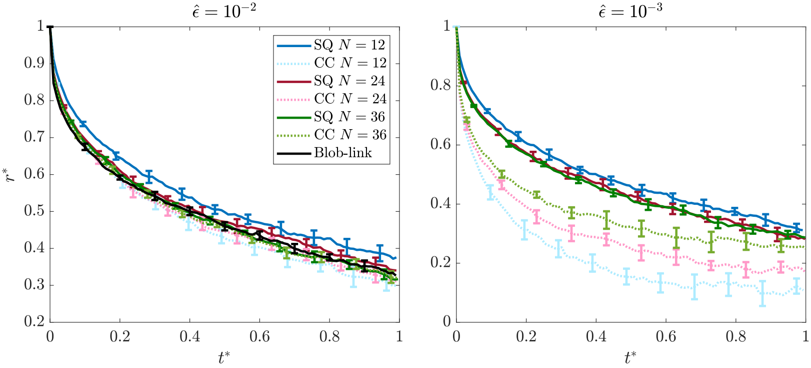
But difference in stress (need formula for Brownian stress)???

Outline

Special quadrature vs. direct quadrature

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

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



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

Special quadrature vs. oversampled quadrature

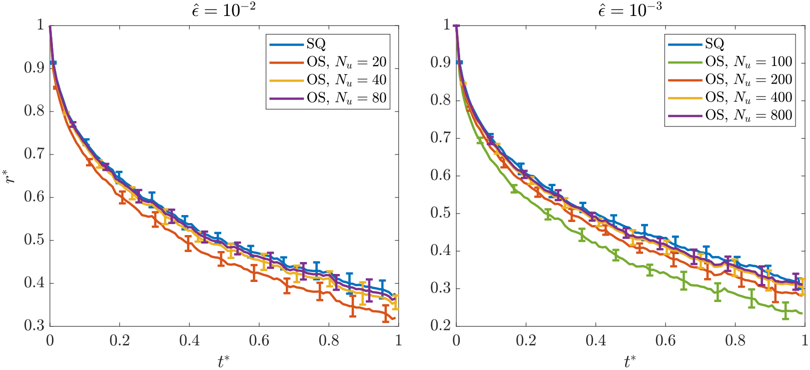
Given force on N point grid

- Construct Galerkin SPD mobility matrix on oversampled grid:

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

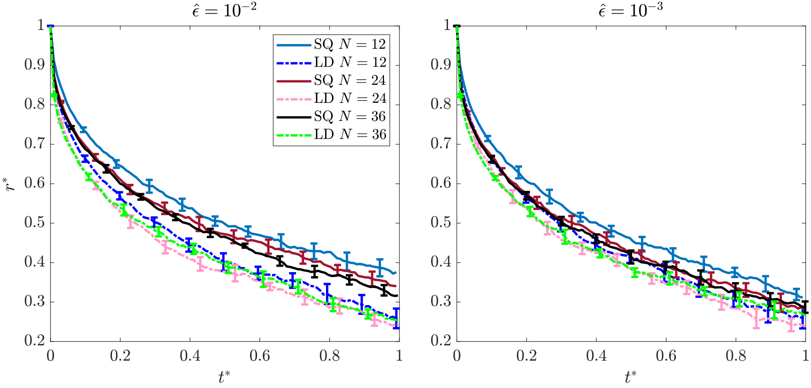
  - Apply $\widetilde{\boldsymbol{W}}^{-1}$ to get force density
  - Upsample to N_u pt grid with matrix $\boldsymbol{E}_u$
  - Oversampled RPY quad on upsampled grid with weights $\boldsymbol{W}_u$
  - Downsample velocity in L^2 with matrix $\widetilde{\boldsymbol{W}}^{-1} \boldsymbol{E}_u^T \boldsymbol{W}_u$.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

Special vs. oversampled quadrature: convergence



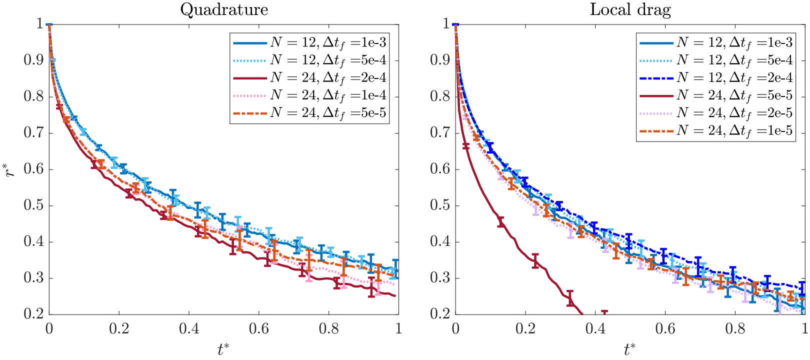
Special quadrature vs. local drag

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 ($\hat{\epsilon} = 10^{-3}$)

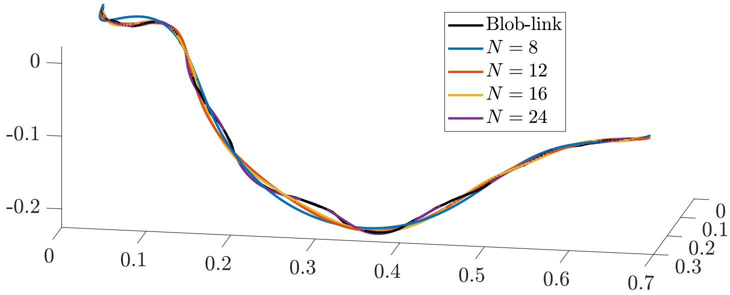
Coarse-graining: geometric perspective

Solve the quadratic programming problem

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

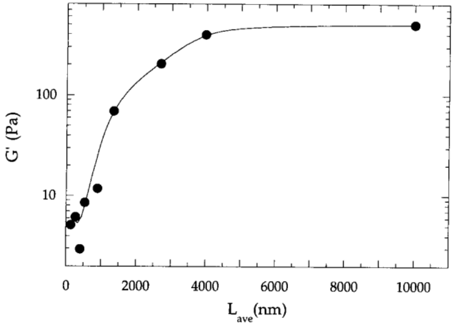
$$\boldsymbol{\tau}_{\{p\}}^T \boldsymbol{\tau}_{\{p\}} = 1, \qquad p = 1, \dots, N$$

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

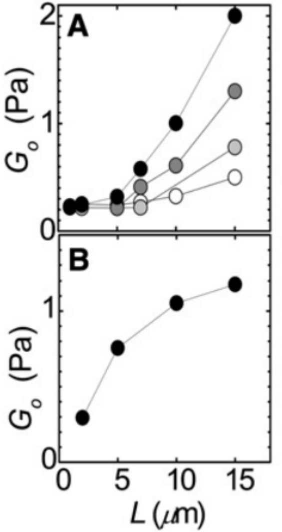


Experimental measurements vary widely

Parallel plate rheometer in both cases!



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

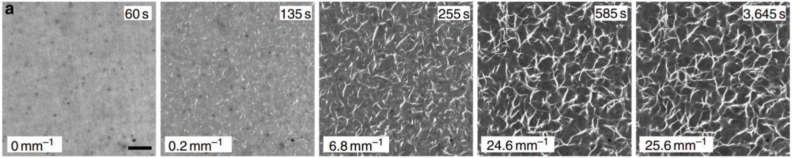


Kasza et al. *BJ* (2010)

Variety of measurements due to morphological changes

Morphology can vary over time and with CL/actin concentration

- Changing network morphology $\rightarrow$ changing shear modulus
- Viscoelastic moduli should be steady state properties



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