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 ↔ mechanical properties of cell
- Dictate cell’s shape and ability to move and divide

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!

$L = 5 \ \mu m, \ \ell_p / L \approx 3$
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)

\[
d\mu_{\text{GB}} = \frac{1}{Z} e^{-\mathcal{E}(\mathbf{X})/k_B T} d\mathbf{X}
\]

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 \( \mu_{\text{GB}} \)
Dynamics: (Overdamped) Langevin equations

Commonly-used model for micro-structures immersed in liquid

\[
\frac{\partial \mathbf{X}}{\partial t} = -\mathbf{M}(\mathbf{X}) \frac{\partial \mathcal{E}}{\partial \mathbf{X}}(\mathbf{X}) + \sqrt{2k_B T} \left( \mathbf{M}(\mathbf{X}) \circ \mathbf{M}^{-1/2}(\mathbf{X}) \right) \mathbf{W}(t)
\]

- \( \mathbf{M}(\mathbf{X}) \) 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

\[
\frac{\partial \mathbf{X}}{\partial t} = -\mathbf{M} \frac{\partial \mathcal{E}}{\partial \mathbf{X}} + k_B T \left( \partial_\mathbf{X} \cdot \mathbf{M} \right) + \sqrt{2k_B T} \mathbf{M}^{1/2} \mathbf{W}(t)
\]

- Stochastic drift term
- \( \mathbf{M}^{1/2} \mathbf{W}(t) \) Multiplicative 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: \( X_{\{i\}} = \) bead positions
- No constraints
- Energy and Langevin equation straightforward
- Only drift terms from mobility (vanish for triply-periodic systems)

Big problem: need small \( \Delta t \) to resolve stiff springs
Blob-link model

Replace springs with rigid rods

- DOFs: \( \boldsymbol{\tau}\{i\} = \text{unit tangent vectors} + \mathbf{X}_{\text{MP}} \)
- 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 \( \mathbf{X} = \mathcal{X}\left( \begin{pmatrix} \boldsymbol{\tau} \\ \mathbf{X}_{\text{MP}} \end{pmatrix} \right) \)

- Constraint \( \boldsymbol{\tau}\{i\} \cdot \boldsymbol{\tau}\{i\} = 1 \)

Removes stiffest timescale BUT

- Slender fibers \( \rightarrow \) small lengthscales
- Still have small \( \Delta t \)!
- Small lengthscales come from \textit{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 $X(s)$ used for elasticity & hydro

Big idea: resolve hydrodynamics $\rightarrow$ reduce DOFs $\rightarrow$ increase $\Delta t$

- Small problem: constrained motion
- $\tau = \text{series of connected rigid rods}$
- Mix of new methods + existing rigid body methods
Blob link and spectral
Building spectral discretization

DOFs: $\tau$ at $N$ nodes of type 1 (no EPs) Chebyshev grid, $X_{\text{MP}}$

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

$$\mathbb{X} = \mathbb{X} \left( \begin{matrix} \tau \\ \mathbb{X}_{\text{MP}} \end{matrix} \right)$$

- 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

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

- \( \kappa = \) 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 \( \ell_p \approx L \) (actin)
Discretizing energy

Discretize inner product on Chebyshev grid

\[ \mathcal{E}_{\text{bend}} \left[ \mathbf{X}(\cdot) \right] = \frac{\kappa}{2} \int_{0}^{L} \partial_{s}^{2} \mathbf{X}(s) \cdot \partial_{s}^{2} \mathbf{X}(s) \, ds \]

\[ = \frac{\kappa}{2} \left( \mathbf{E}_{N \rightarrow 2N} \mathbf{D}^{2} \mathbf{X} \right)^{T} \mathbf{W}_{2N} \left( \mathbf{E}_{N \rightarrow 2N} \mathbf{D}^{2} \mathbf{X} \right) \]

\[ = \frac{\kappa}{2} \left( \mathbf{D}^{2} \mathbf{X} \right)^{T} \sim \mathbf{W} \left( \mathbf{D}^{2} \mathbf{X} \right) \]

\[ = \mathbf{X}^{T} \mathbf{L} \mathbf{X} \]

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

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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

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

- 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

\[
(\tau_{\{k=1,\ldots N\}}, X_{\text{MP}}) \xrightarrow{X} X_{\{k=1,\ldots N+1\}} \xrightarrow{\text{Chebyshev interpolation}} X(s) \xrightarrow{\mathcal{M}} [X(\cdot)] \xrightarrow{\mathcal{E}_{\text{bend}} [X(\cdot)]} F_{\text{bend}}(X) \xrightarrow{\tilde{W}^{-1}} f_{\text{bend}}(X) \xrightarrow{\tilde{M}F}
\]
Discrete part: inextensibility

Langevin equation must be modified because of inextensibility

- \( \tau_{\{i\}} \) remains unit vector, rotates as rigid rod (ang. vel. \( \Omega_{\{i\}} \))

\[
\partial_t \tau_{\{i\}} = \Omega_{\{i\}} \times \tau_{\{i\}} \rightarrow \partial_t \tau = -C \Omega
\]

- Results in constrained motions for \( X \)

\[
\partial_t X = \mathcal{X} \begin{pmatrix} -C & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} \Omega \\ U_{\text{MP}} \end{pmatrix} := \mathcal{X} \tilde{C} \alpha := \mathcal{K} \alpha
\]

- Discrete time: solve for \( \alpha = (\Omega, U_{\text{MP}}) \), rotate by \( \Omega \Delta t \), update midpoint
**Deterministic dynamics**

Close system by introducing Lagrange multiplier forces $\Lambda$

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

Results in saddle point system for $\alpha$ and $\Lambda$

\[
K \alpha = \tilde{M} (-LX + \Lambda)
\]

\[
K^T \Lambda = 0,
\]

Deterministic dynamics (eliminate $\Lambda$)

\[
\partial_t X = -\hat{N} LX,
\]

\[
\hat{N} = K \left( K^T \tilde{M}^{-1} K \right)^\dagger K^T
\]

$\hat{N}$ 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

\[
\partial_t \mathbf{X} = - \hat{\mathbf{N}} \mathbf{LX} + k_B T \mathbf{X} \cdot \hat{\mathbf{N}} + \sqrt{2k_B T \hat{\mathbf{N}}^{1/2}} \mathbf{W}(t)
\]

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

\[
K \alpha = \tilde{M} (-\mathbf{LX} + \Lambda) + \sqrt{\frac{2k_B T}{\Delta t}} \tilde{M}^{1/2} \mathbf{W}
\]

\[
K^T \Lambda = 0,
\]

\[
\Rightarrow \alpha = \text{Deterministic} + \sqrt{\frac{2k_B T}{\Delta t}} \hat{\mathbf{N}}^{1/2} \mathbf{W}
\]

- \(\mathbf{W} \sim \mathcal{N}(0, 1)\)
Implied GB distribution

The overdamped Langevin equation is in detailed balance wrt the distribution

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

- 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 $\Delta t$

- Reported in terms of longest relaxation timescale
- Goes as $N^{-4}$ (not ideal); another reason to keep $N$ low!
- Unchanged with $\ell_p$ (modes are stiffer, but fewer required)
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 ($\hat{\epsilon} = 10^{-2}$)

- Spectral results approach blob-link with increasing $N$
- Can extend spectral to smaller $\hat{\epsilon}$, but not blob-link!
Quantifying relaxation \( \hat{\epsilon} = 10^{-3} \)
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 fluncts

- Intuition: fluctuations increase binding frequency
- How small does $\ell_p$ 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 $O(1)$ points, larger $\Delta t$

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

\[
\begin{pmatrix} \tau \\ X_{MP} \end{pmatrix} = \arg\min_{X} \left\| X^{(SB)} - X^{(BL)} \right\|_2^2 = \left\| E_{S \to B} \chi \begin{pmatrix} \tau \\ X_{MP} \end{pmatrix} - X^{(BL)} \right\|_2^2 
\]

\[
\tau_{\{p\}}^T \tau_{\{p\}} = 1, \quad p = 1, \ldots, N
\]

where \( E_{S \to B} \) samples \( X(s) \) at the blob-link locations.