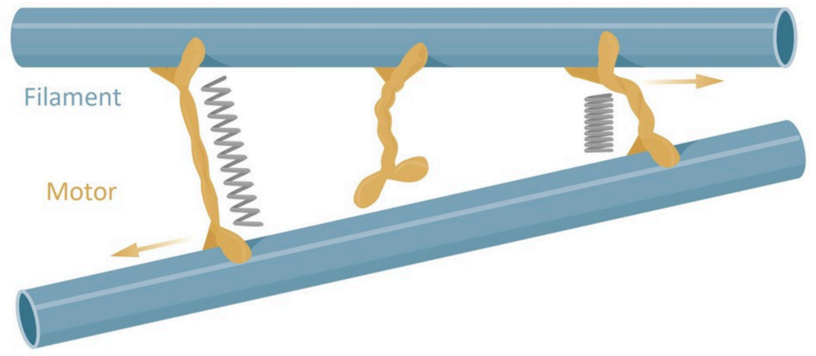

Use Fast Function Approximator in Motor-Filament Binding Kinetics

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Introduction

- Cytoskeletal filament networks provide internal structure of cells that facilitate movement, growth, and cell division.
- Motor activity is responsible for far-from-equilibrium phenomena, like active stress, self-organized flow, and spontaneous nematic defeat generation.
- **aLENS** (a Living ENsemble Simulator): high-performance software for simulating N rigid bodies interconnected by dynamic springs [1].
  - Motor diffusion and stepping.
  - Computing binding and unbinding while maintaining realistic macroscopic statistics.
  - Updating filament position while overcoming stiffness constraints and maintaining steric exclusion.
- **Kinetic Monte-Carlo** (KMC): allow fluctuations in bound protein number and binding kinetics that recovers the equilibrium distribution of static crosslinking proteins; satisfy both local and global detailed balance (4-states transitions, $U \leftrightarrows (S_A, S_B) \leftrightarrows D$) [1, 2, 3].
- **Baobzi**: N-ary tree structure; leaves represent functions in small sub-boxes of domain with Chebyshev polynomials using Clenshaw algorithm.

Background

- $(S_A, S_B) \leftrightarrows D$: filament with center mass $\mathbf{x}_i$ and orientation $\mathbf{p}_i$:

$$R_{\mathrm{on},D}(s_i,t) = \frac{\epsilon K_e k_{o,D}}{V_{\mathrm{bind}}} \sum_j \int_{L_j} e^{-\beta U_{i,j}(s_i,s_j)} ds_j,$$

$$R_{\mathrm{off},D}(s_i,s_j,t) = k_{o,D}.$$

❖ Searching volume of unbounded head:

$$V_{\mathrm{bind}} = 4\pi \int_0^{R_{\mathrm{cut},C}} e^{-\beta U_{i,j}} r^2 dr.$$

⇩ **Lookup Table Approach [4]**

- Reduce CDF dimensionality by considering the lab position of each bound motor head and an infinite carrier line defined by the position and orientation of unbound filament.

$$\mathrm{CDF}(r_\perp, s) = \mathrm{sgn}(s) \int_0^s e^{-\beta U(r_\perp, s')} ds'$$

- Discretization & 2D Linear Interpolation :

$$\mathrm{CDF}(r_\perp, s) \approx \left(1+m-\frac{r_\perp}{\Delta r}\right)\left(1+n-\frac{s}{\Delta s}\right)\mathrm{CDF}_{m,n} + \left(\frac{r_\perp}{\Delta r}-m\right)\left(1+n-\frac{s}{\Delta s}\right)\mathrm{CDF}_{m+1,n}$$
$$+\left(1+m-\frac{r_\perp}{\Delta r}\right)\left(\frac{s}{\Delta s}-n\right)\mathrm{CDF}_{m,n+1} + \left(\frac{r_\perp}{\Delta r}-m\right)\left(\frac{s}{\Delta s}-n\right)\mathrm{CDF}_{m+1,n+1}.$$

$$s, r_\perp \in \left[0, \sqrt{-\frac{2\ln(\delta)}{\beta k_{\mathrm{cl}}}} + h_{\mathrm{cl}}\right]$$

- Reverse lookup: Interpolation & binary search: $O(\log_2(\delta s_{\max}))$.

$$s_- = \Delta s \frac{X - \mathrm{CDF}_{m,n_-}}{\mathrm{CDF}_{m,n_-+1} - \mathrm{CDF}_{m,n_-}} + \Delta s n_-,$$

$$s_- = \Delta s \frac{X - \mathrm{CDF}_{m+1,n_+}}{\mathrm{CDF}_{m+1,n_++1} - \mathrm{CDF}_{m+1,n_+}} + \Delta s n_+,$$

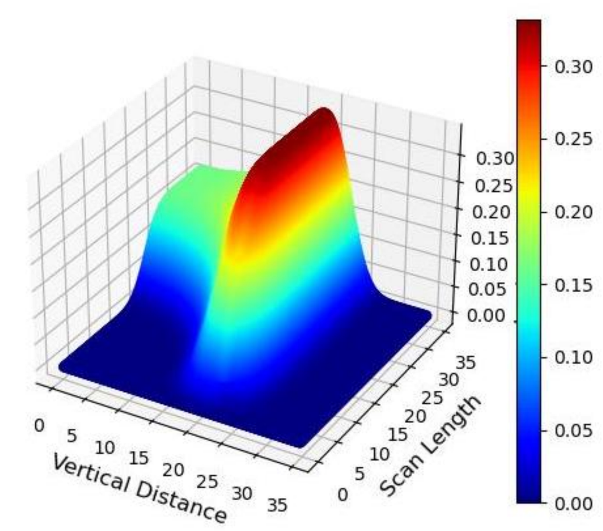
$$s \approx (s_+ - s_-)\frac{r_\perp - r_-}{\Delta r} + s_-.$$

Methods & Results

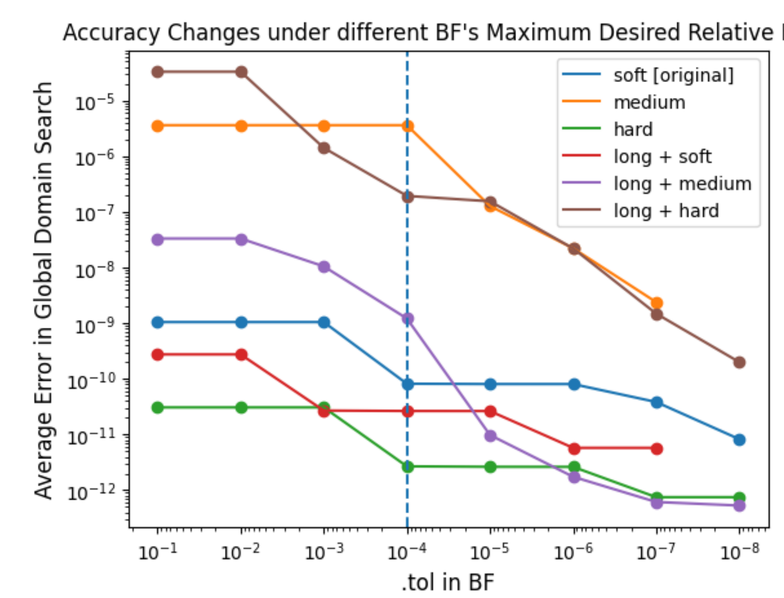
- **Normal Search of Baobzi Family (BF)**: Normalize s and discretize $r_\perp$ dimension using multiple Baobzi objects (with grid size in same [or smaller] order of magnitude); use binary search in point evaluation.

	Soft	Medium	Hard	Long&Soft	Long&Medium	Long&Hard
LT Global Test Acc	3.548e-07	7.280e-06	2.749e-06	9.596e-07	5.653e-07	6.067e-06
BF Global Test Acc	8.185e-11	3.599e-06	1.020e-12	2.651e-11	1.216e-09	1.935e-07
LT Build Time (s)	0.022	0.023	0.022	0.021	0.028	0.079
BF Build Time (s)	0.170	0.013	0.406	0.404	0.279	0.508
Build Time Ratio	7.644	0.568	17.740	18.828	10.028	6.448
LT Evaluation Time (s)	0.014	0.005	0.002	0.0219	0.012	0.009
BF Evaluation Time (s)	0.131	0.045	0.057	0.260	0.107	0.134
Evaluation Time Ratio	8.935	8.852	26.763	11.875	8.696	14.363

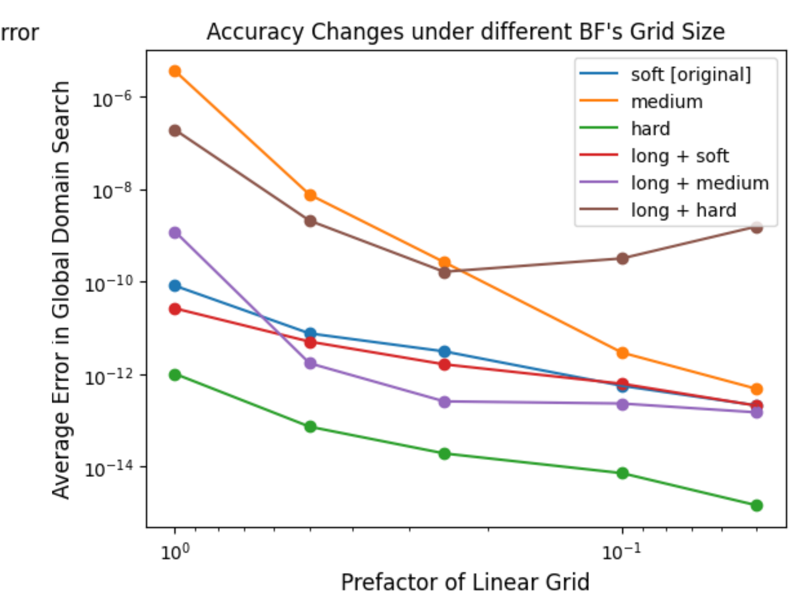
Comparison of performances between Lookup Table (LT) and Baobzi Family (BF) under different stiffness and freelength of motor spring.



Reconstructed domain within $r_{c,D}$ limit in both dimensions.



Choose maximum desired relative error (.tol in Baobzi) as 10^{-4} in implementation.

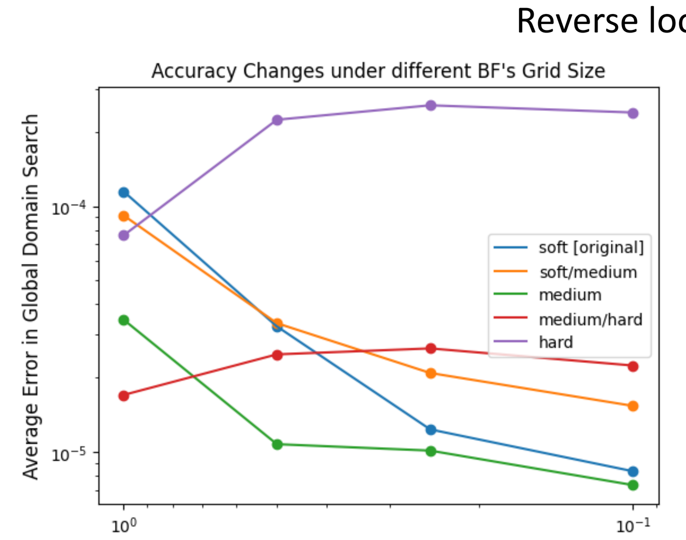


Improve all BF's accuracy to 10^{-10} level by tuning coefficient α of Baobzi's linear grid.

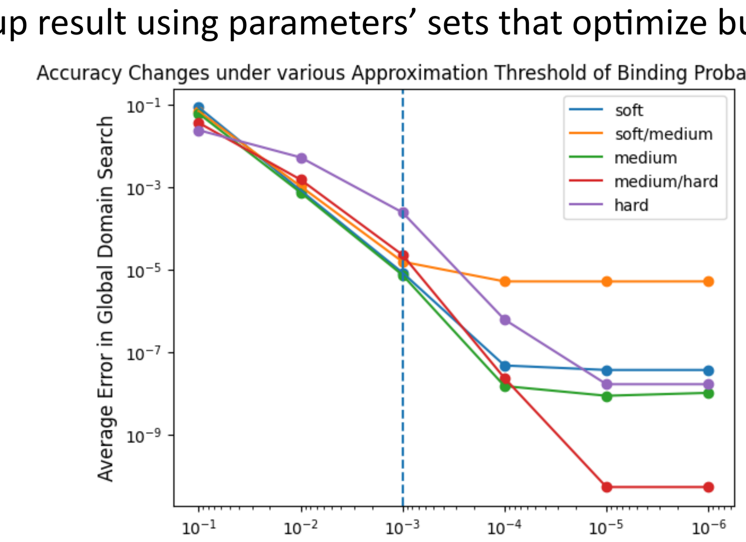
- **Reverse Search**: Precalculate integral range of each Baobzi object and match its grid along $r_\perp$; use Boost bisection method to find root without derivatives. Use OpenMP to speed up build process. Provide interface to save formulated BF object as external files and reloading for flexible time management.

	Soft	Soft/Medium	Medium	Medium/Hard	Hard
LT Global Test Accuracy	6.771e-05	2.901e-05	1.957e-05	5.701e-06	2.470e-06
BF Global Test Accuracy	1.147e-04	9.168e-05	3.451e-05	1.703e-05	7.599e-05
BF Relative Error	0.164%	0.268%	0.288%	0.569%	3.481%
BF Build Time (s)	24.336	9.196	6.109	3.204	2.271
BF Required Space (MB)	195.410	92.759	68.968	33.767	24.675

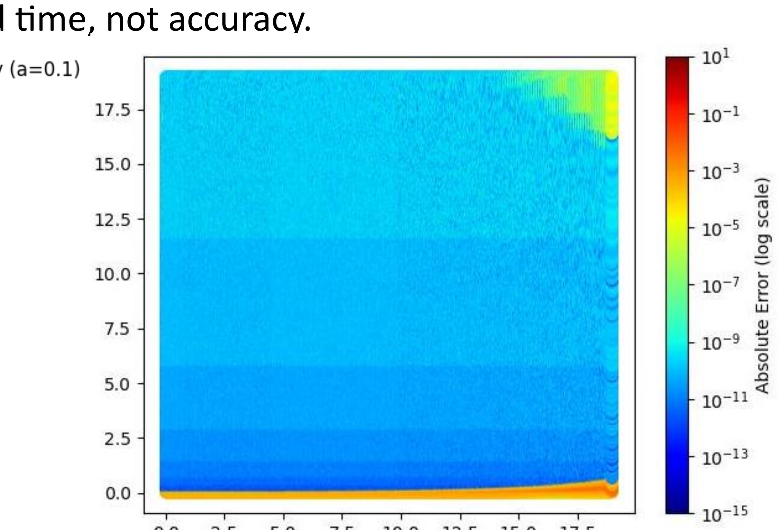
Reverse lookup result using parameters' sets that optimize build time, not accuracy.



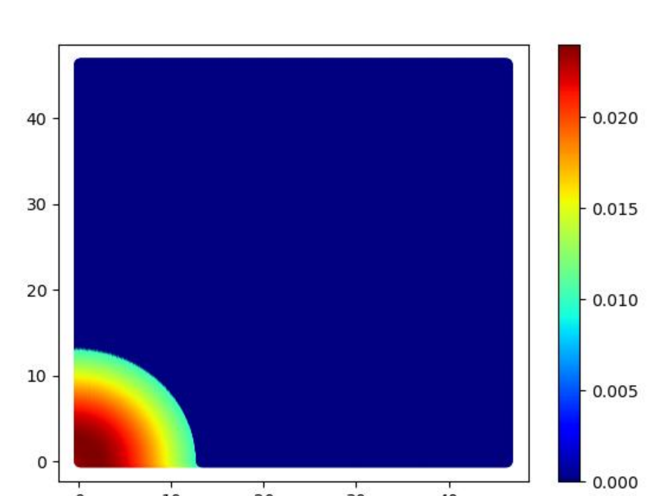
Finer grid significantly increases BF's accuracy when motor's stiffness is moderate.



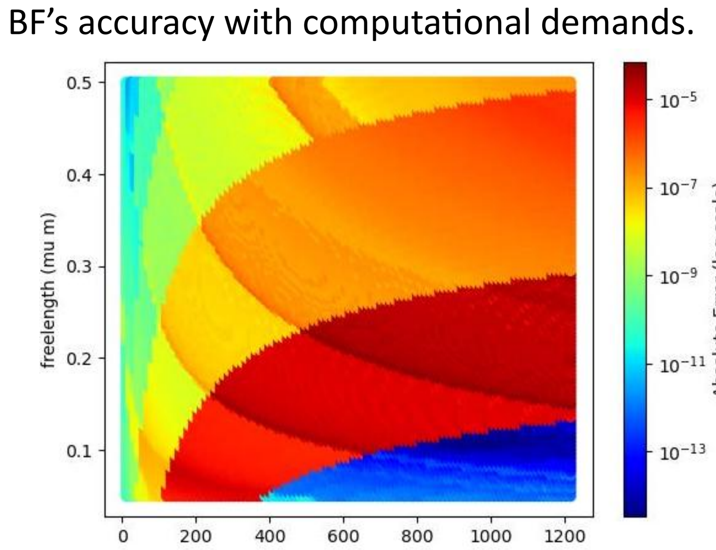
Smaller threshold filtering almost surely increases BF's accuracy with computational demands.



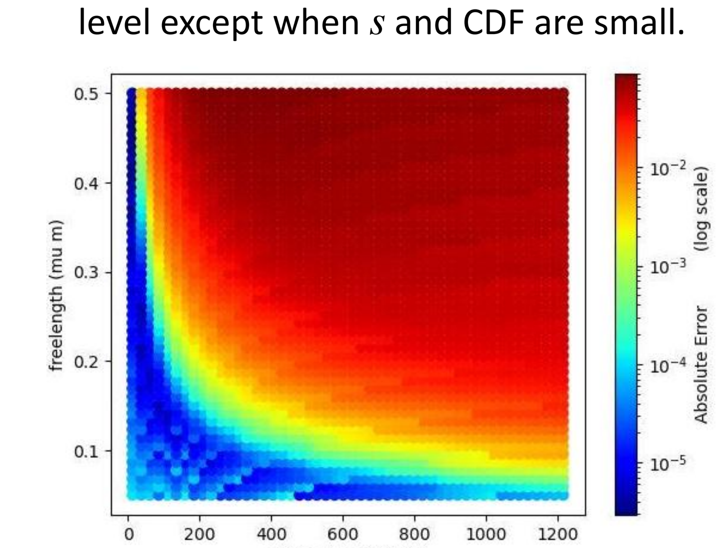
BF's accuracy maintains 10^{-7} to 10^{-9} level except when s and CDF are small.



Effective PDF with threshold filtering.
Use conformal mapping to speed domain search.

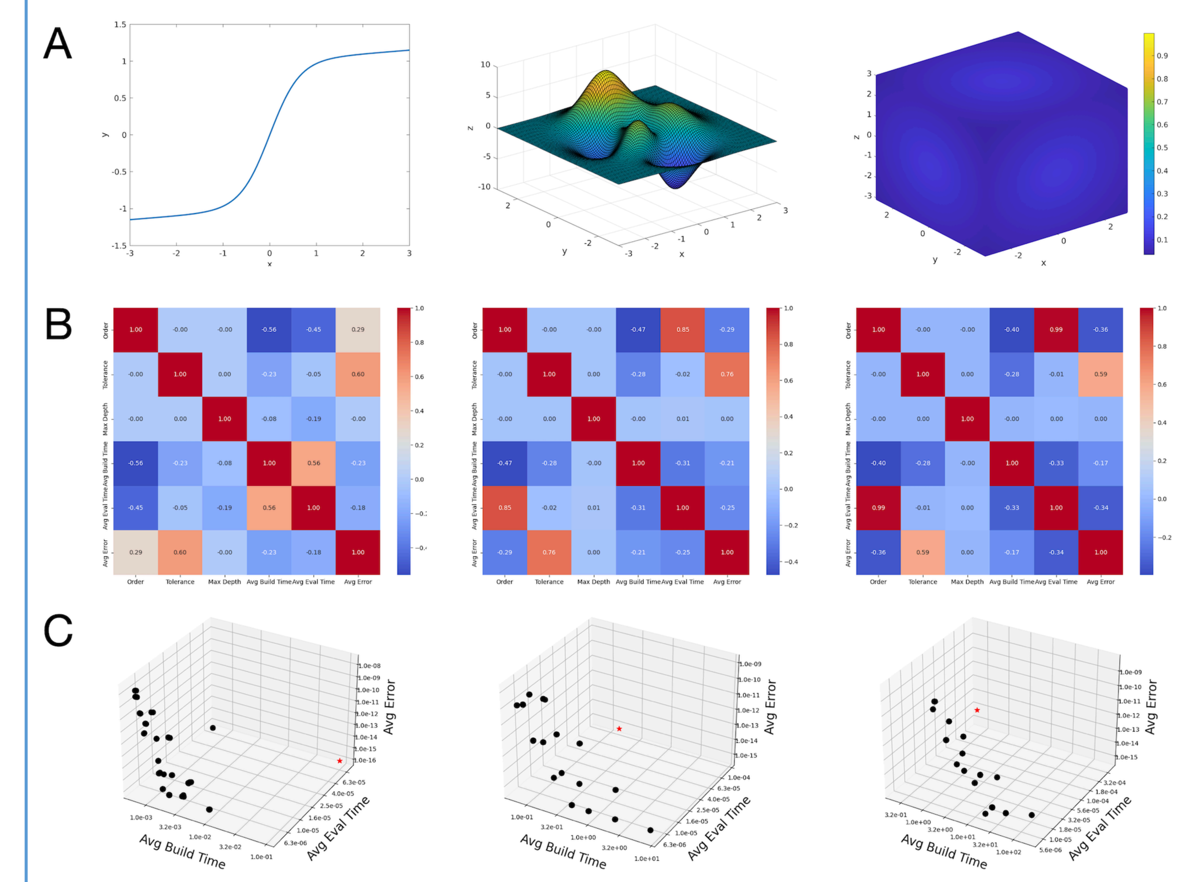


BF's average error in normal lookup



BF's average error in reverse lookup

Comparison with Chebfun



Comparison analysis across multiple dimensions. With fine-tuning, Baobzi advances in accuracy and building & evaluation time.

Conclusion

- Apply adaptive Chebyshev approximation with parallel computing to simulate motors' binding rate on filaments with better accuracy and affordable costs in both directions searching.
- Together with lookup table, set up benchmarks after fine-tuning of parameters for further KMC tests.
- Provide extensible functionalities including pre-building and loading other formulations of integrand.
- Not scalable to more than 3-factors dependence.
- Exponential costs growth for better BF's accuracy.
- Small scale simulation only. Further test in cellular-scale modeling in aLENS.
- Potential application of rejection sampling or MCMC.

References

1. Wen Yan, Saad Ansari, Adam Lamson, Matthew A Glaser, Robert Blackwell, Meredith D Betterton, Michael Shelley (2022) **Toward the cellular-scale simulation of motor-driven cytoskeletal assemblies** *eLife* **11**:e74160.
2. Tong Gao, Robert Blackwell, Matthew Glaser, Meredith Betterton, and Michael Shelley (2015) **Multiscale Polar Theory of Microtubule and Motor-Protein Assemblies** *Phys. Rev. Lett. 114, 048101.*
3. Robert Blackwell et al. (2017) **Physical determinants of bipolar mitotic spindle assembly and stability in fission yeast** *Sci. Adv.***3**,e1601603.
4. Adam Lamson, Jeffrey Moore, Fang Fang, Matthew Glaser, Michael Shelley, Meredith Betterton (2021) **Comparison of explicit and mean-field models of cytoskeletal filaments with crosslinking motors** *Eur. Phys. J. E* ***44***, *45*.

➡ Source code: https://github.com/StevenZhang0116/KMC/

➡ Baobzi: https://github.com/flatironinstitute/baobzi/

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