Probing the Multiscale Dynamics of Linear and Branched Polypeptides: Computational and Experimental Approaches.

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Entangled Macromolecular Dynamics.

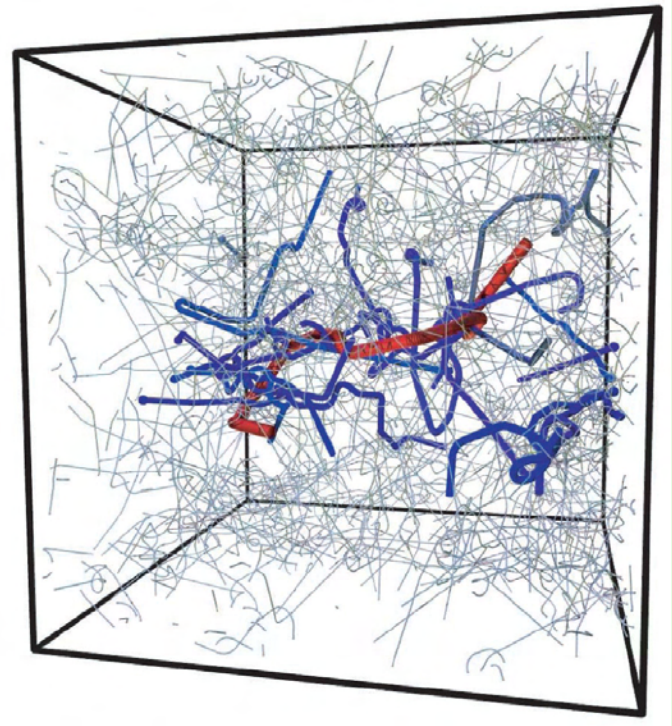
- A single mathematical and computational framework for all dynamical properties of any macromolecule in a concentrated environment.

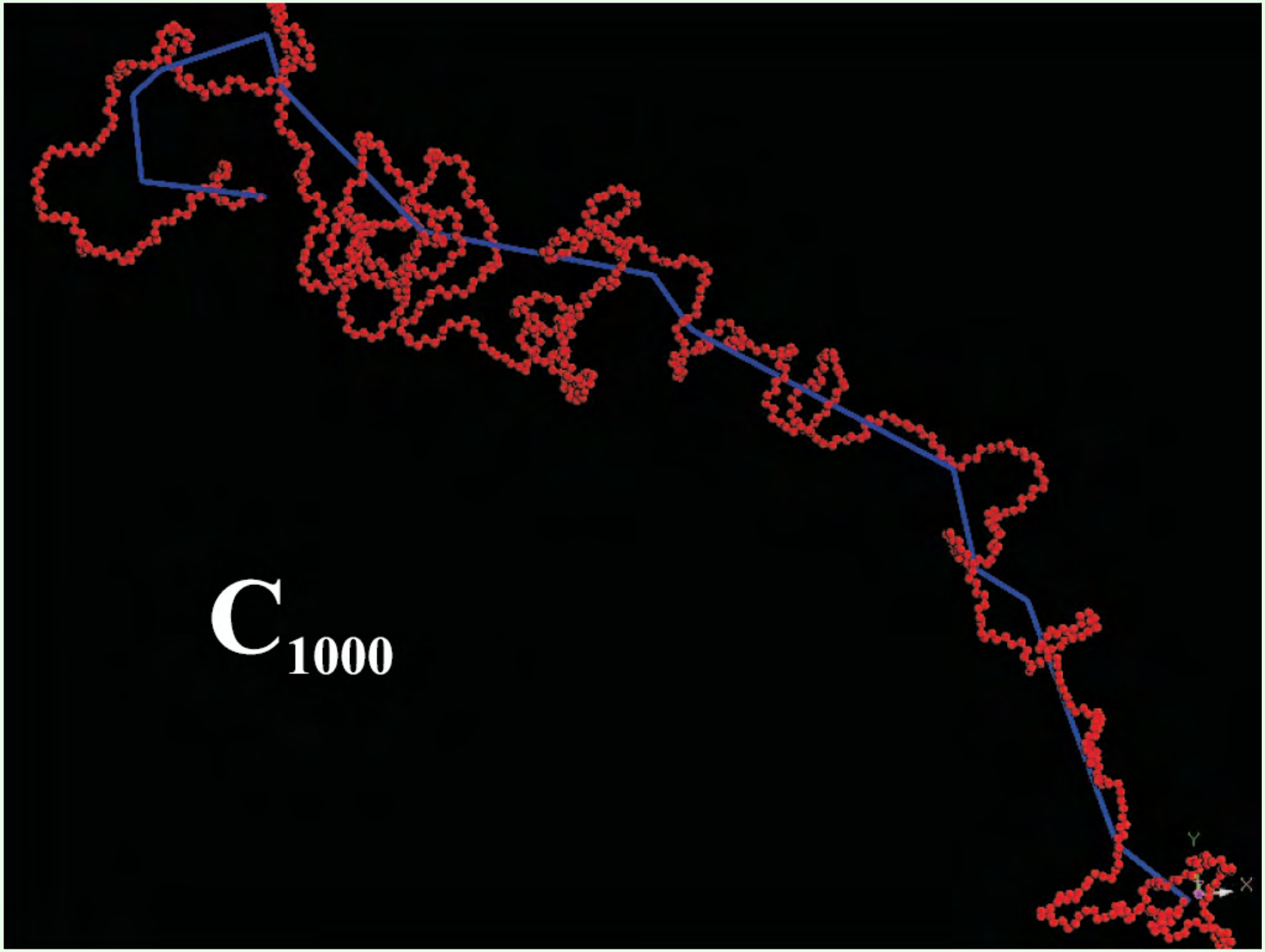
- Examples include: diffusion of DNA in a cytoskeleton, electrophoresis of denatured proteins, linear or branched architectures, rheological properties, and viscoelastic mechanical response of filament networks.

- Requires as input the free energy of a trapped chain segment, which is found using statistical mechanics, and a single, short-time-scale, phenomenological time constant accessible by molecular dynamics.

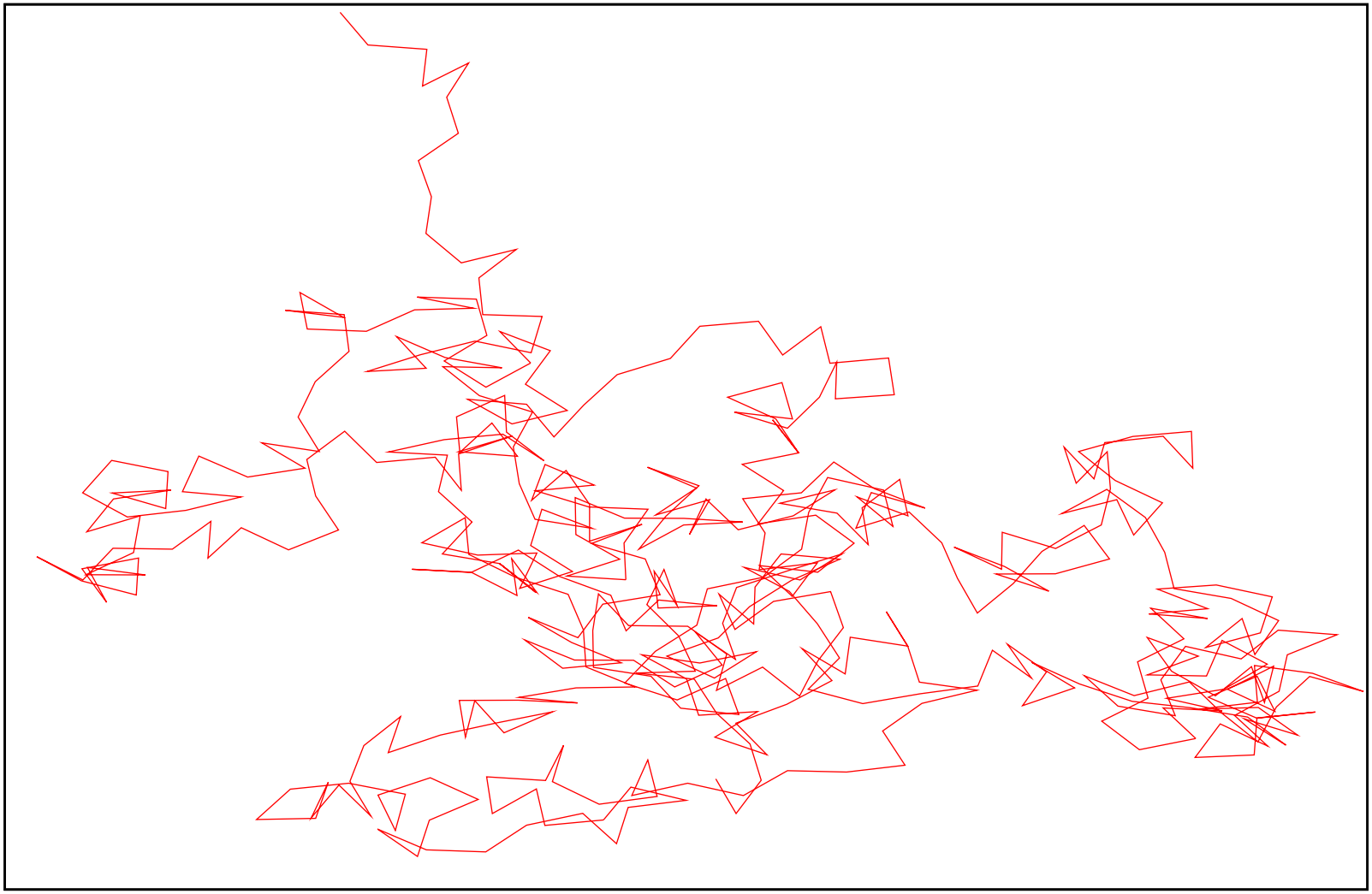
Evidence #3 Everaers, et al.; Mavrantzas, et al.

Atomistic simulations: global minimization of chain length while preserving chain-chain constraints.

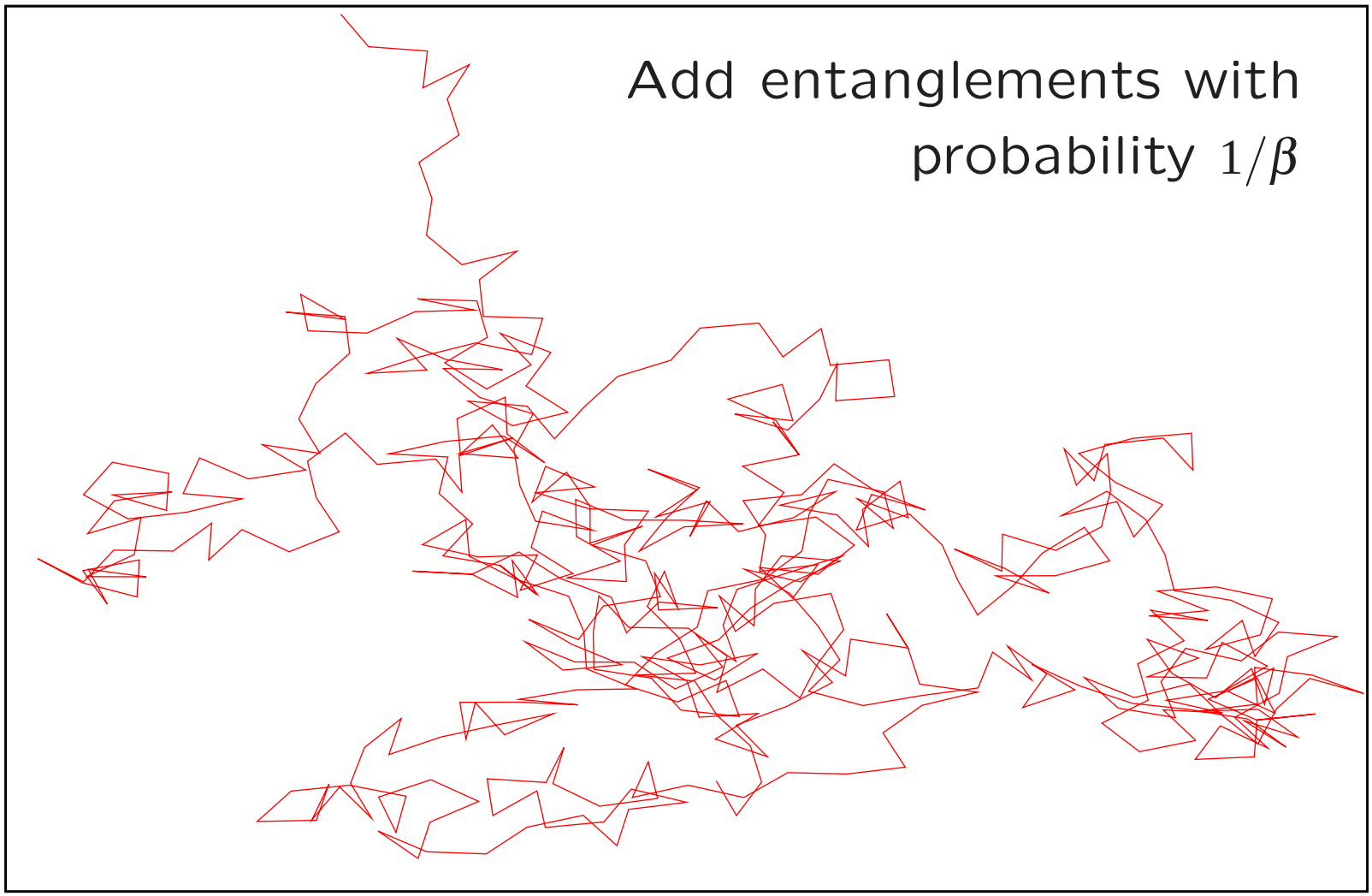



C_{1000}
Y
X

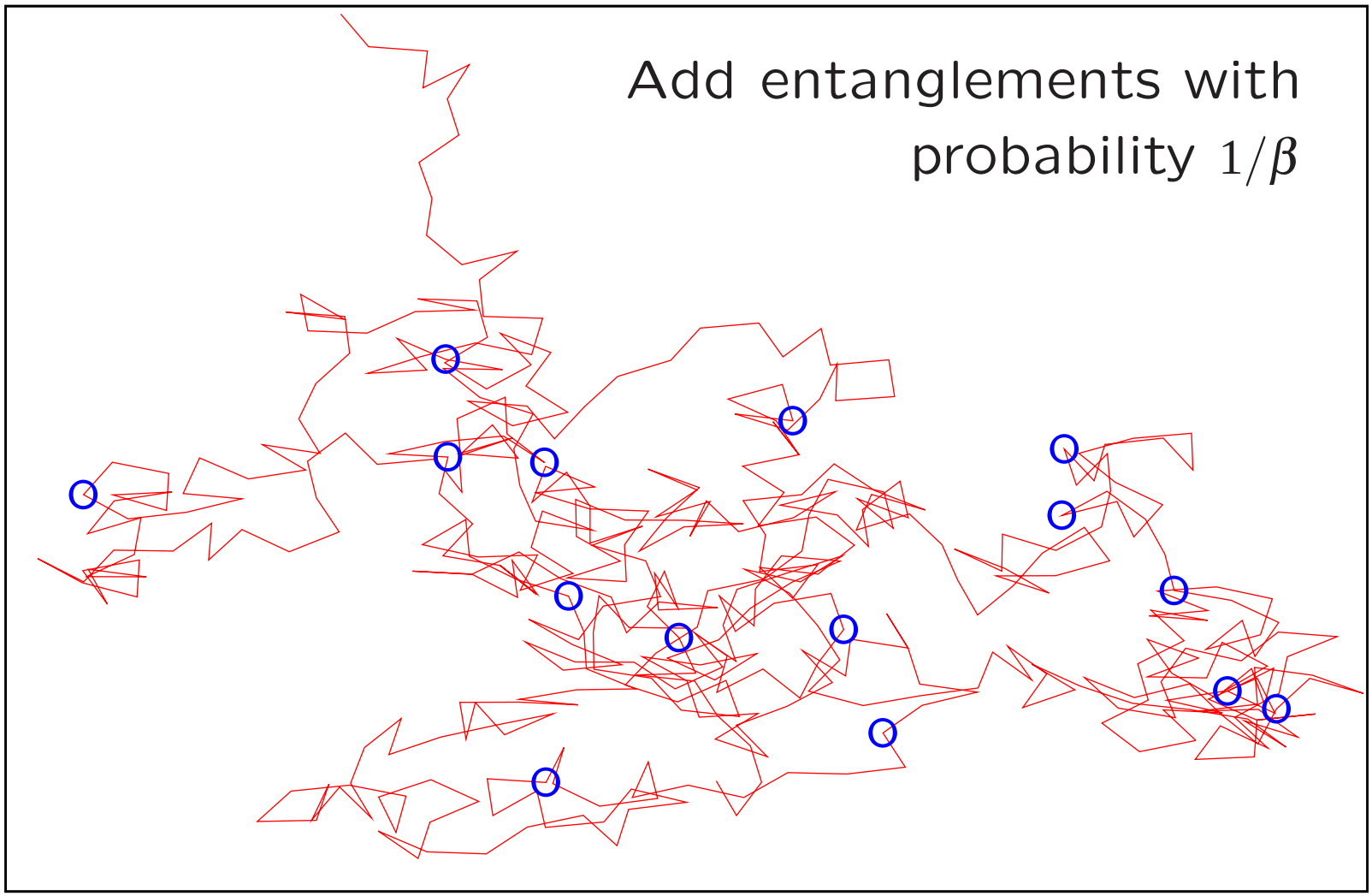
Chain as random walk



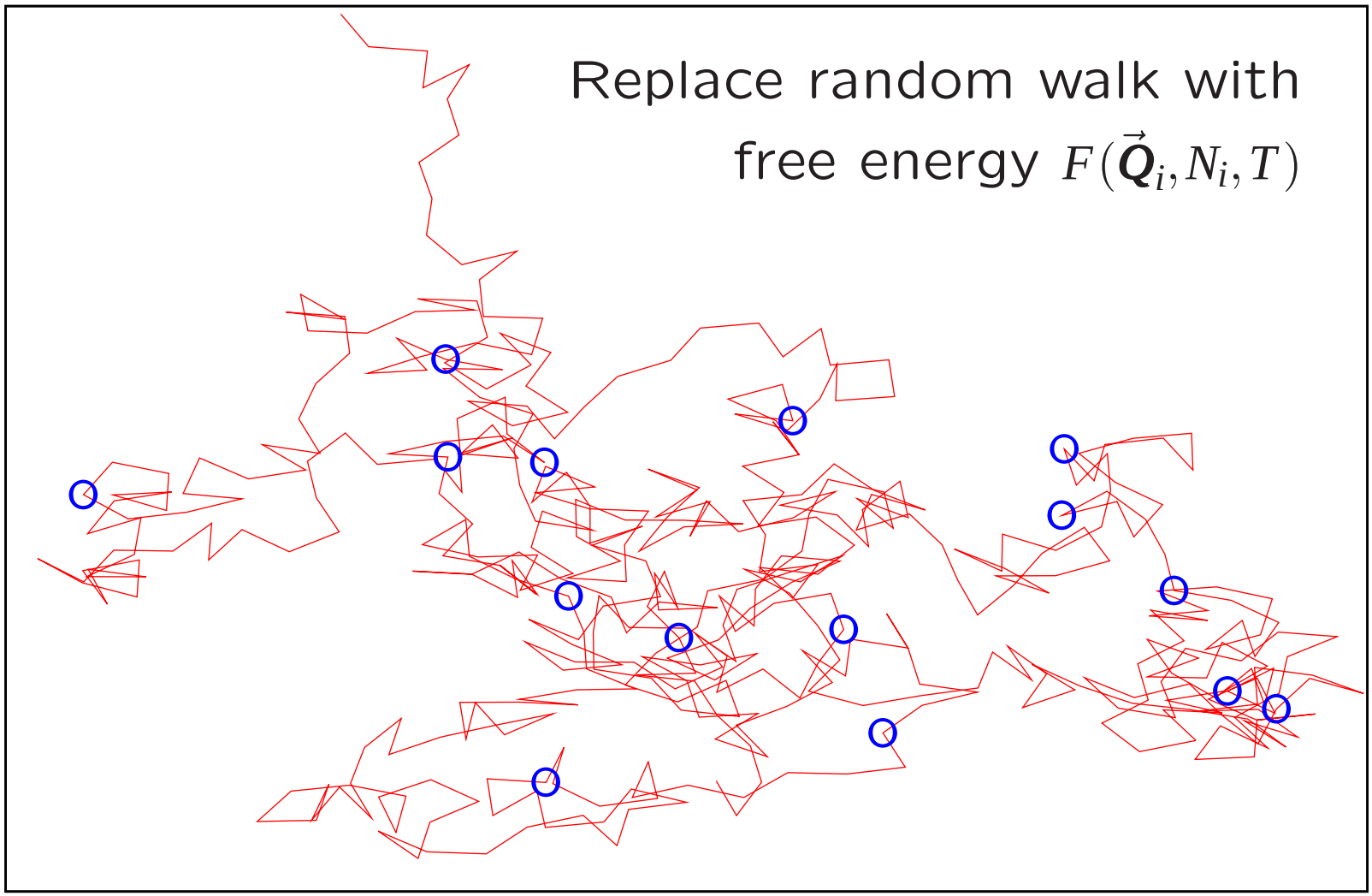
Chain as random walk



Chain as random walk

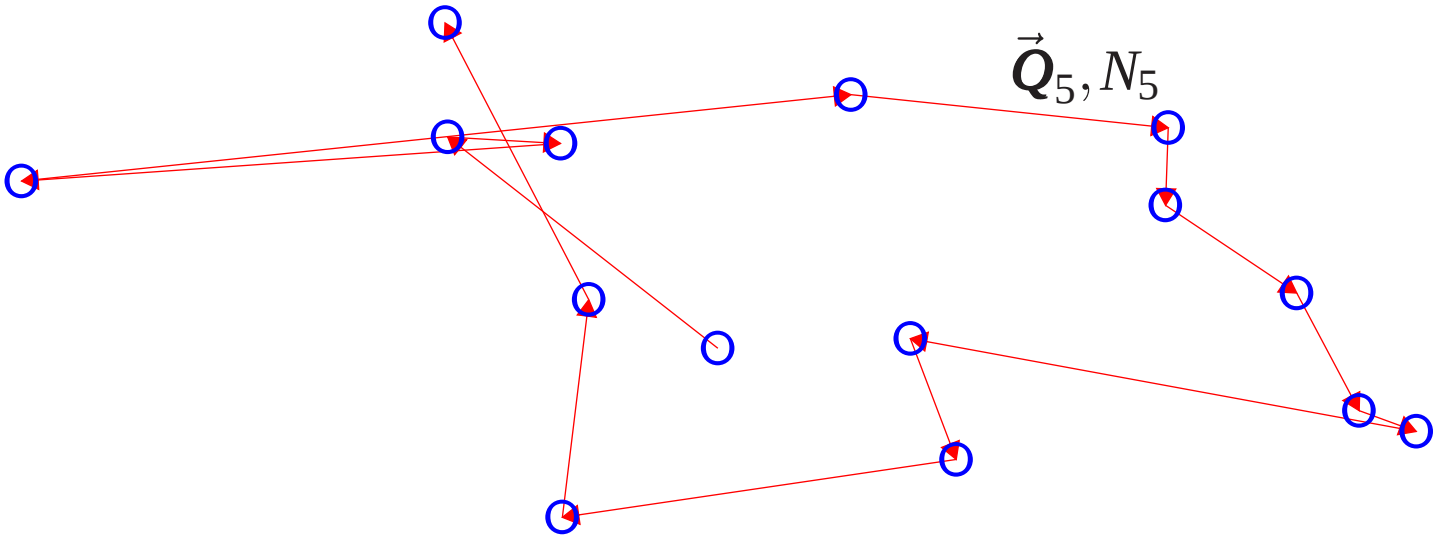


Chain as random walk



Chain as random walk

Replace random walk with
free energy $F(\vec{\boldsymbol{Q}}_i, N_i, T)$



Dynamic Variables:

- Length of strands:

$$\{\boldsymbol{Q}_i(t)\},\ i = 2,\ \ldots,\ Z(t)\text{-}1$$

- Number of Kuhn steps in strands:

$$\{N_i(t)\},\ i = 1,\ \ldots,\ Z(t)$$

Parameters:

- Ave. No. of Kuhn Steps in Strand: β ($\sim M_e$ from chemistry)
- Total number of Kuhn Steps: N_{K} (from mol. weight)
- Smallest Time Constant: $\tau_e = N_e^2 \tau_{\mathsf{K}}$ (phenomenological)

From the free energy $F(\Omega)$ we can obtain all static properties:

$$p^{\mathrm{eq}}(\Omega) \sim \underbrace{\exp\left[-\frac{F(\Omega)}{k_{\mathrm{B}}T}\right]}_{\substack{\text{Maxwell-}\\ \text{Boltzmann}}} \underbrace{\delta\left(N_{\mathrm{K}} - \sum_i N_i\right)}_{\substack{\text{monomer}\\ \text{conservation}}} \underbrace{\exp\left(\frac{\mu^Z Z}{kT}\right)}_{\substack{\text{entanglement}\\ \text{bath}}}$$

Microcanonical ensemble in N_K.

Grand Canonical in Z: $\mu^Z = \log \beta$

Can be used to check code.

Strand Dynamics

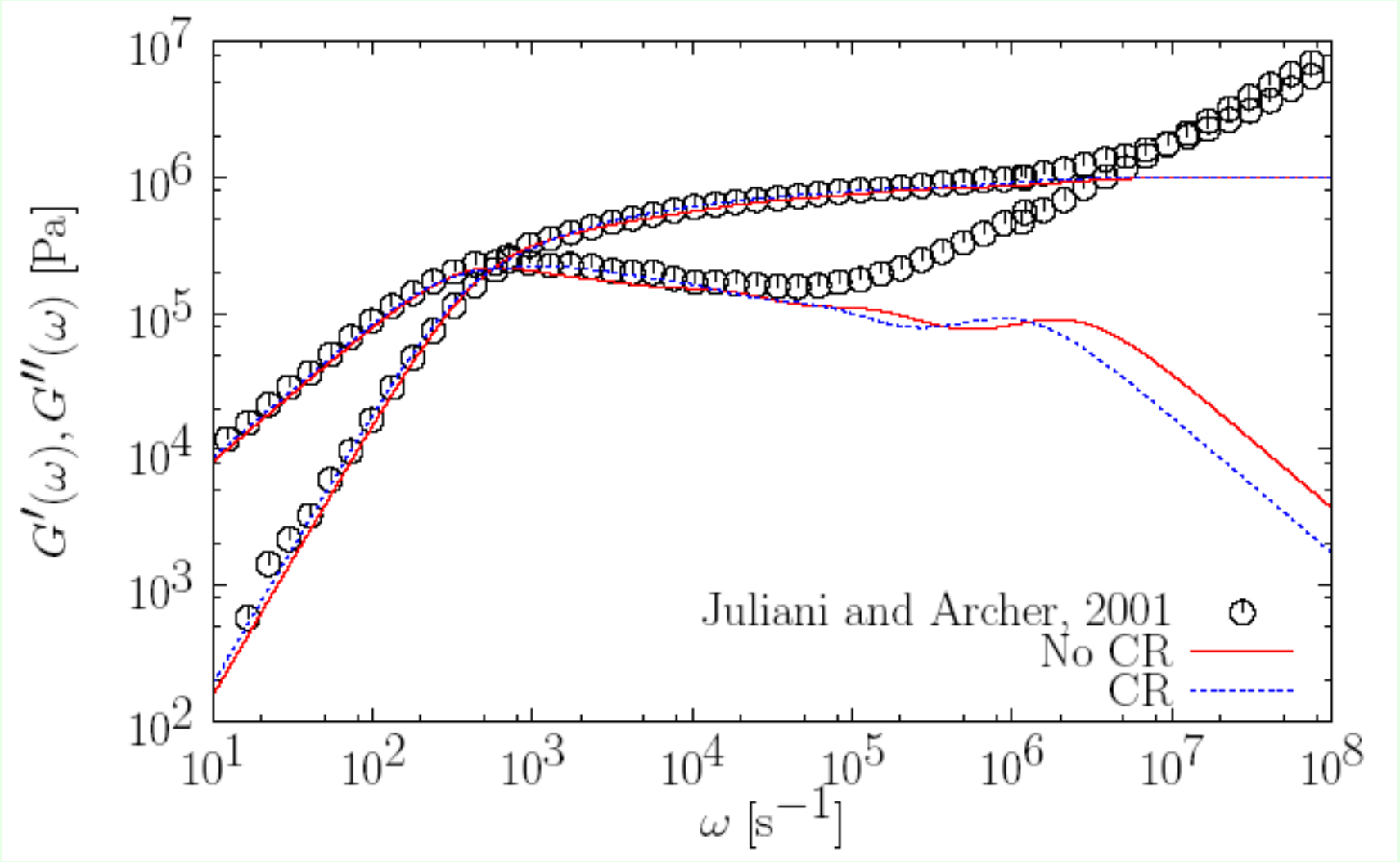
$$\frac{\partial p(\Omega;t)}{\partial t} = \underbrace{-\sum_{i=2}^{Z-1} \frac{\partial}{\partial \boldsymbol{Q}_i} \cdot [\boldsymbol{Q}_i \cdot \nabla \boldsymbol{v}]\, p(\Omega,t)}_{\text{deformation}} + \underbrace{\int \left[W(\Omega|\Omega')p(\Omega',t) - W(\Omega'|\Omega)p(\Omega,t)\right] d\Omega'}_{\text{monomer jumping through entanglements}},$$

- $p(\Omega;t) \equiv p(\boldsymbol{Q}_2,\ldots,\boldsymbol{Q}_{Z-1},N_1,\ldots,N_Z;t)$
- $W(\Omega|\Omega') \sim \frac{1}{\tau_{\mathsf{K}}} \exp\left[\frac{F(\Omega')-F(\Omega)}{2k_{\mathsf{B}}T}\right]$

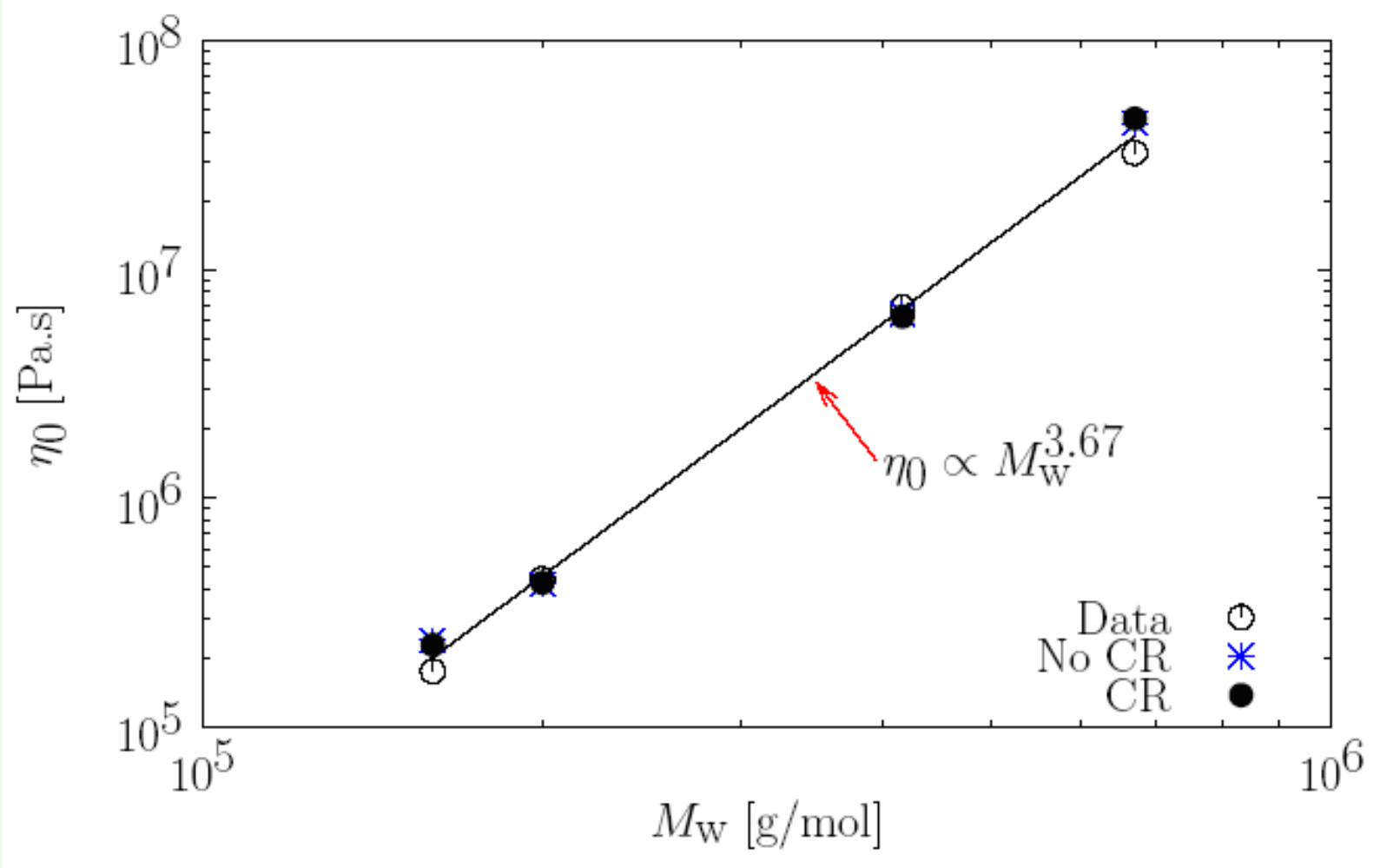
Liquid Dynamics Assumptions:

- Random walk $\rightarrow$ Gaussian chain: $\frac{F}{k_{\mathrm{B}}T} = \frac{3Q^2}{Na_{\mathrm{K}}^2} + \frac{3}{2}\log N$ (not necessary)
- Total chain friction is constant (not necessary).
- Entanglements are deformed affinely with macroscopic flow.
- Entanglements are created and destroyed at ends only (not necessary).

PB Melt, $M_n = 41\text{k}$, $\langle Z \rangle_{\text{eq}} = 22$ at 26°C



Polystyrene Melt:



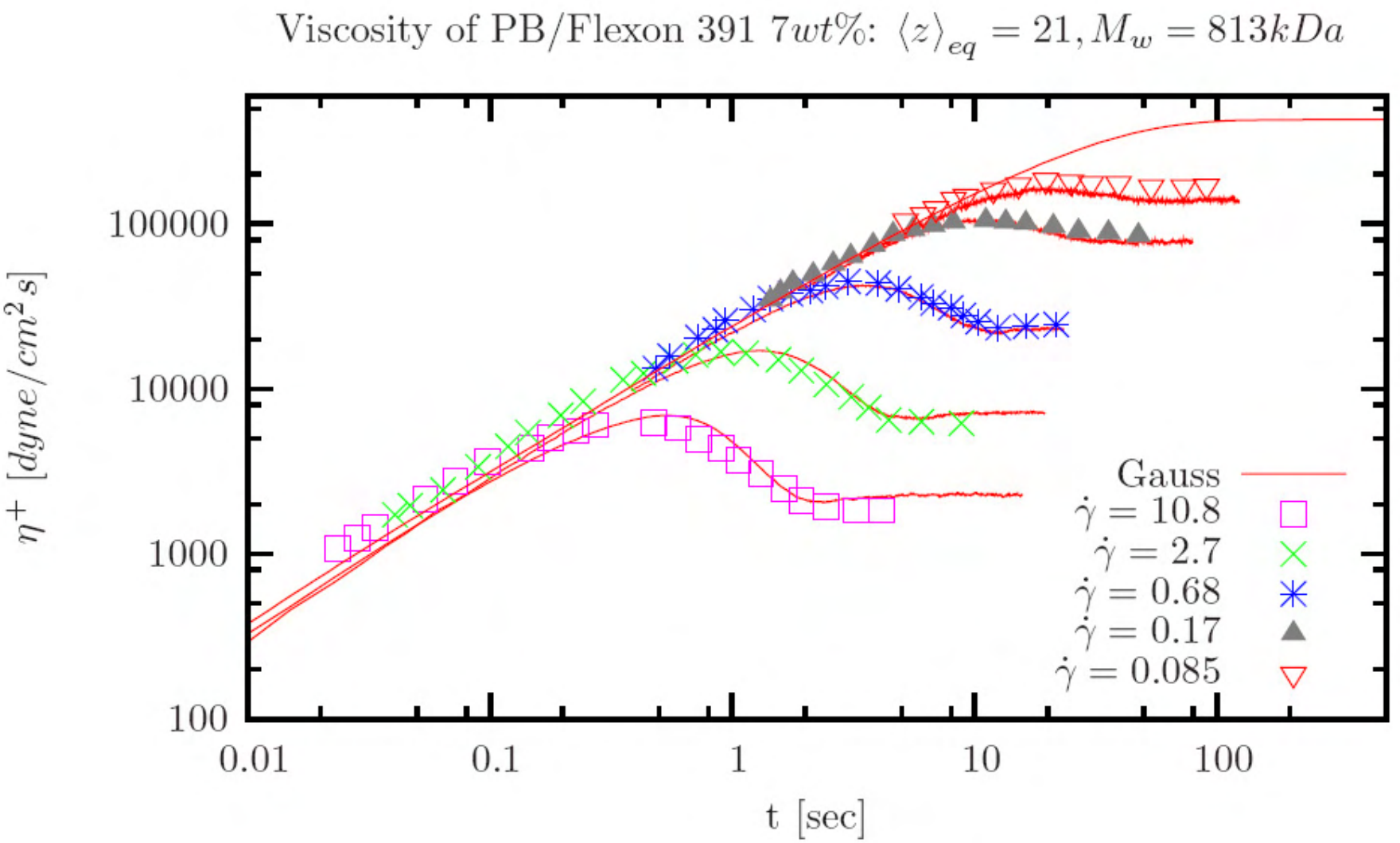


Figure 1.45: Transient viscosities as a function of time, predicted by Gaussian model with constant chain friction & constant chain friction and the experimental data, Meneze & Grassley [1982] $M_w = 813kDa$

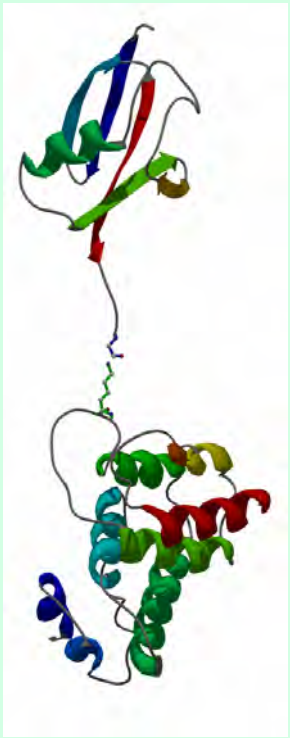
Current abilities:

- Linear chains; branched free energy derived.
- Diffusion
- Rheology
- Polydispersity
- Have derived free energy for electrophoresis; atomistic-level coarse graining

Working on:

- Electrophoresis simulations
- Branched chain simulations
- Semi-flexible fibers

SUMOylation as a tool to generate branched proteins of defined architecture



SUMOylation is a newly described cellular mechanism to generate branched proteins.

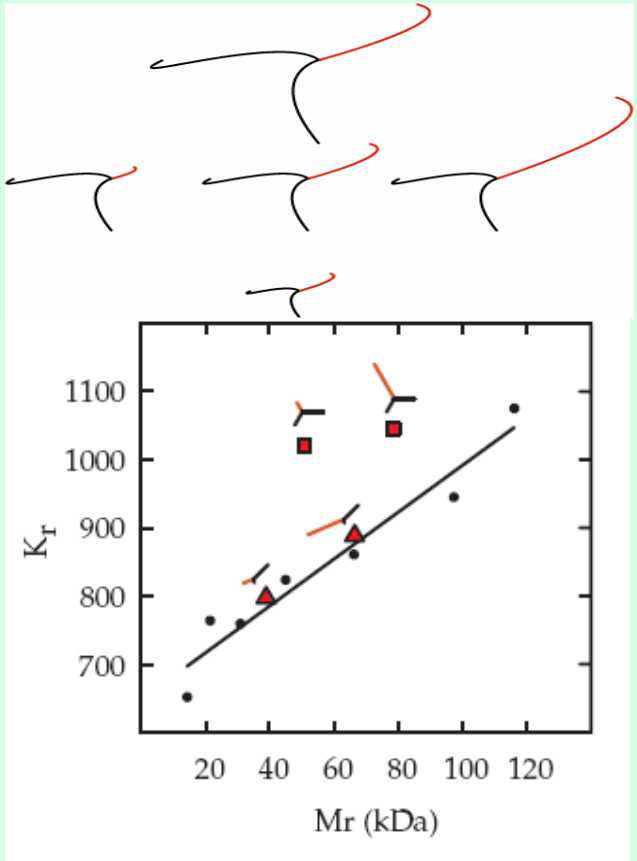
Branched proteins have unusual properties in analytical techniques such as gel electrophoresis.

Adapting our multiscale model to predict the effect of topology on the behavior of branched proteins will allow:

Direct comparison to novel experimental data

Probe the underlying physics of separation techniques.

Development of novel bioanalytical approaches.



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