CHROMALENS: FLEXIBLE FILAMENTS AND TRANSIENT NETWORKS

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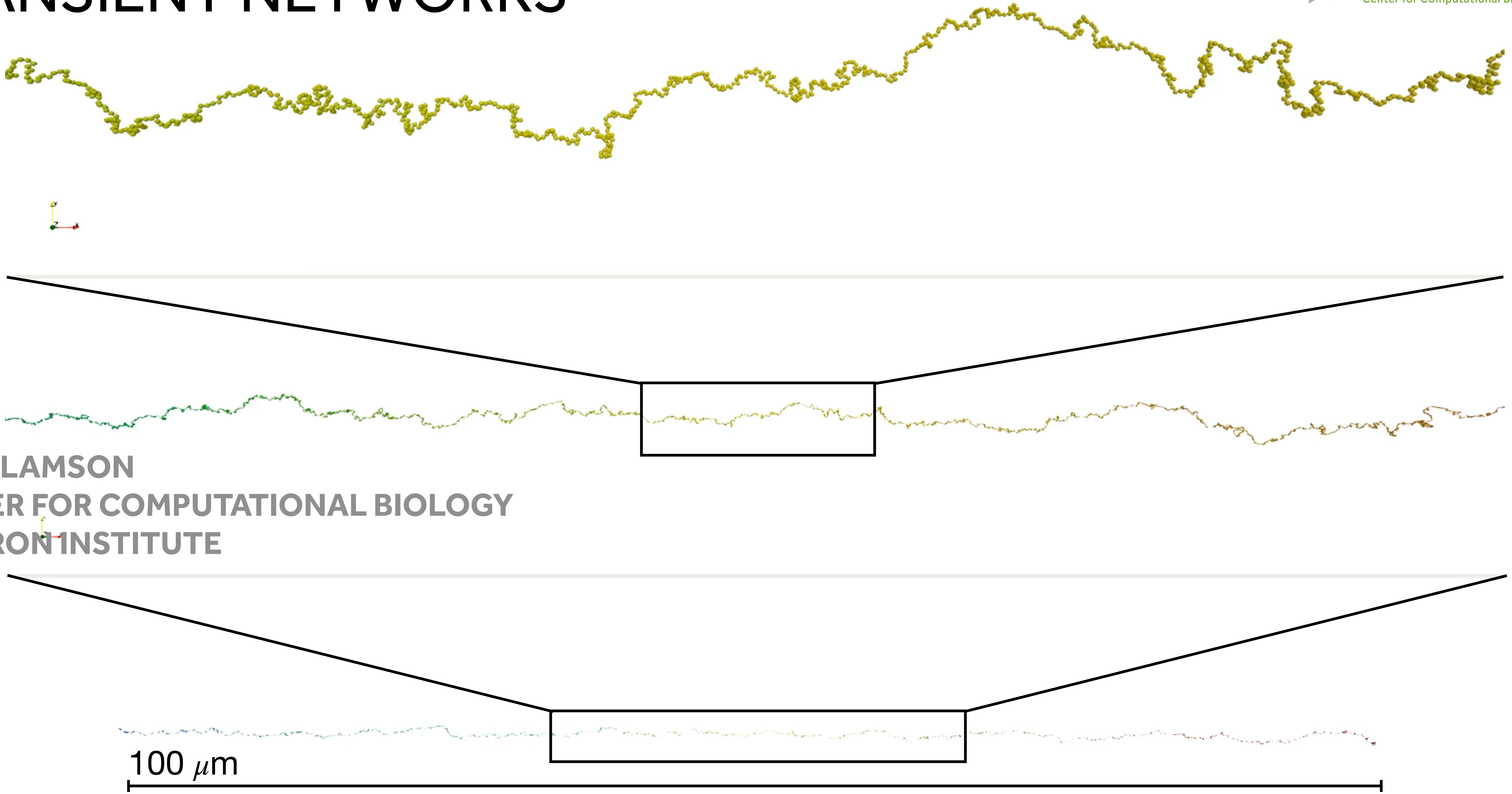

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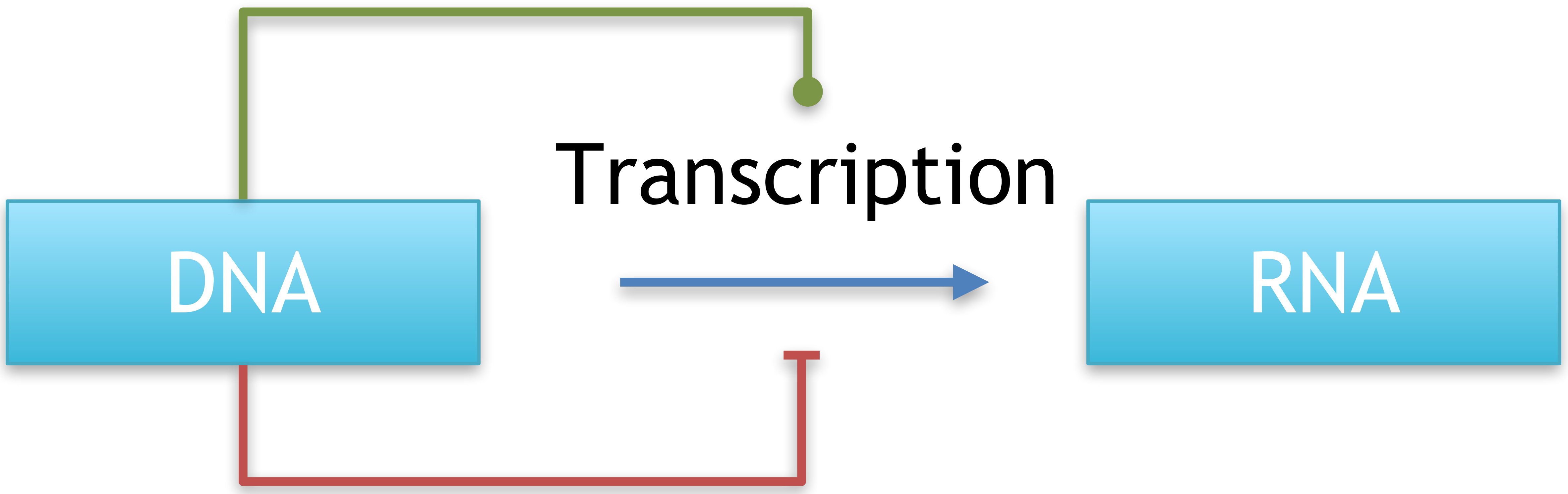
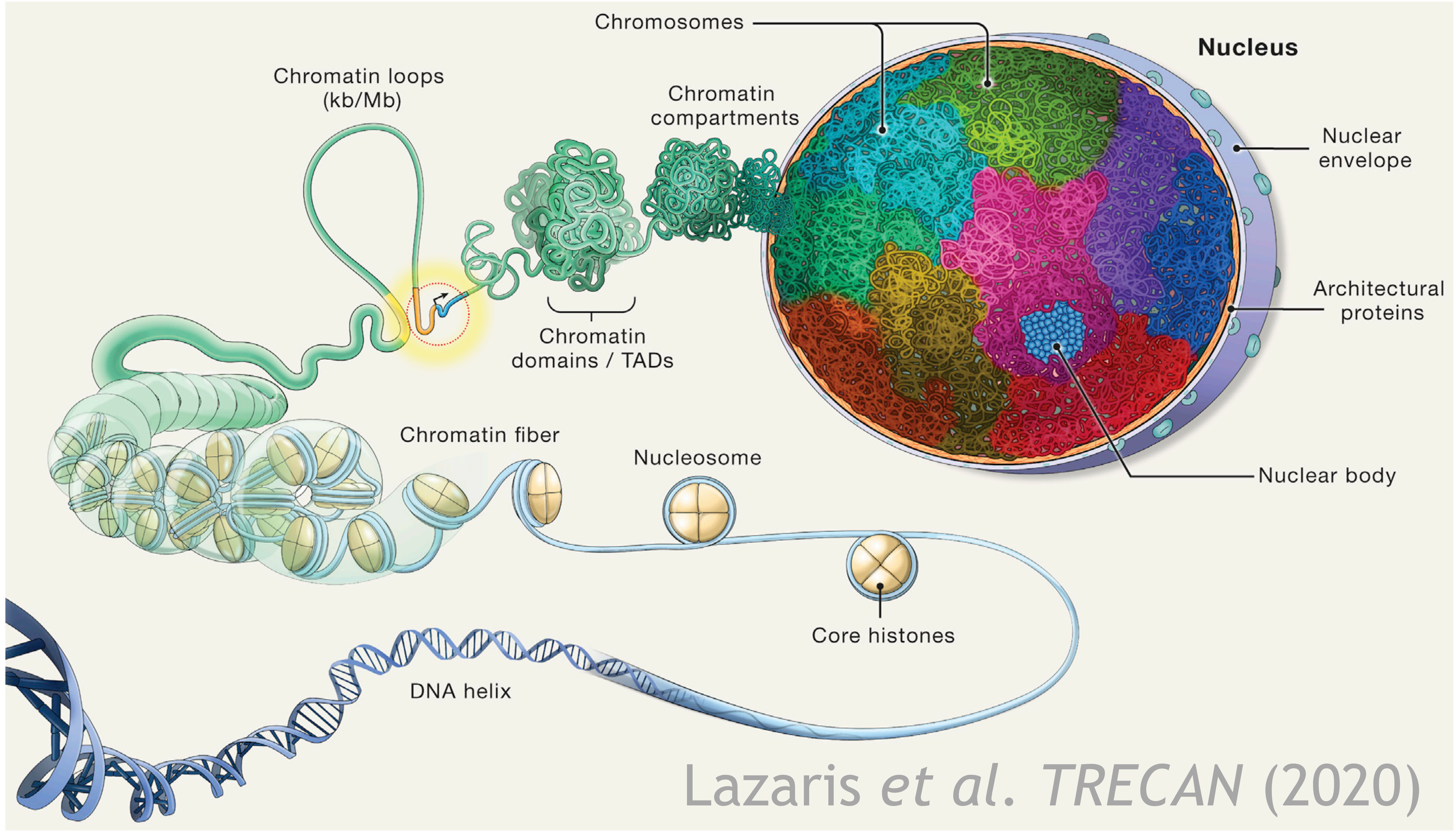
DNA organizes and interacts with itself to regulate gene expression





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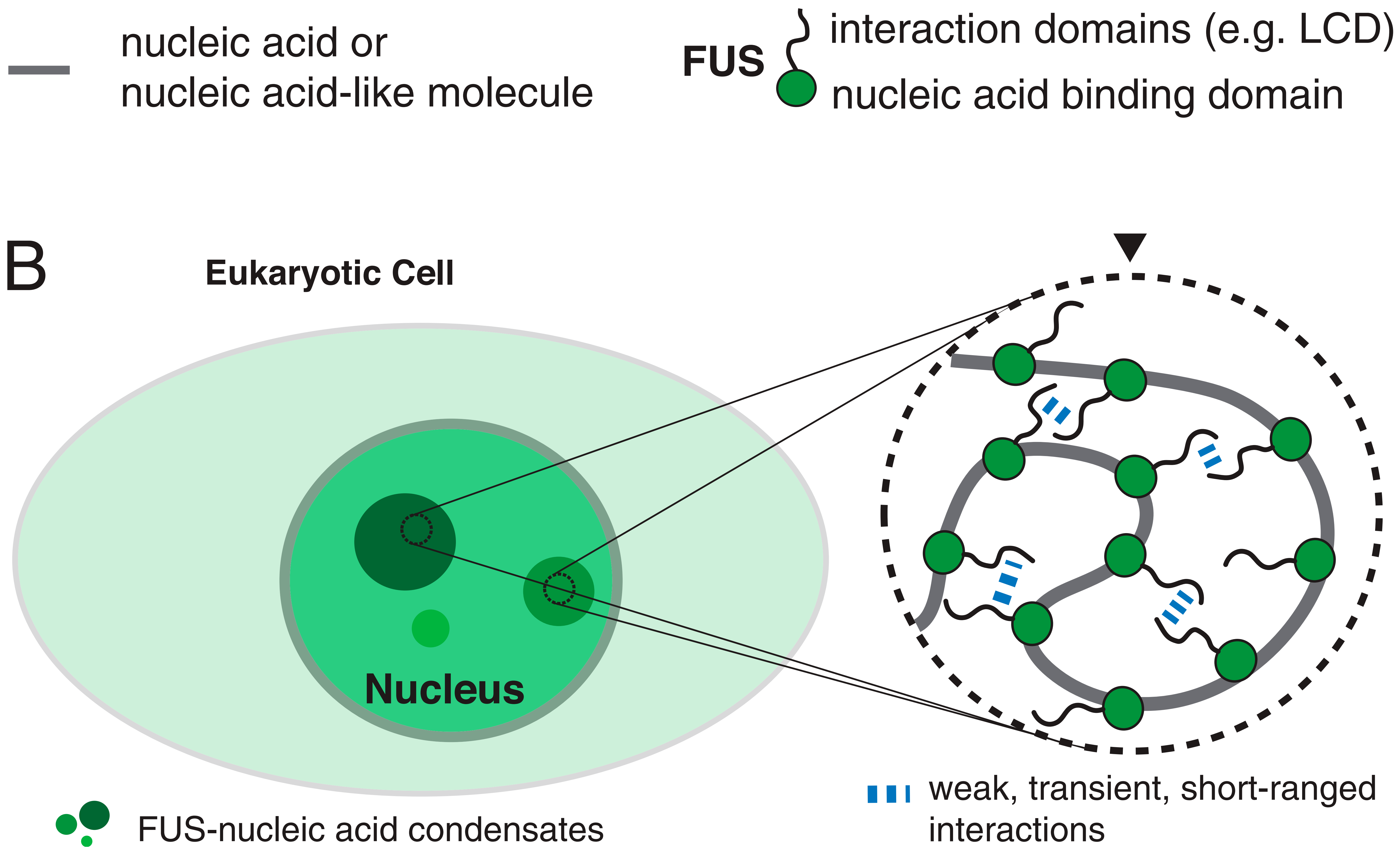
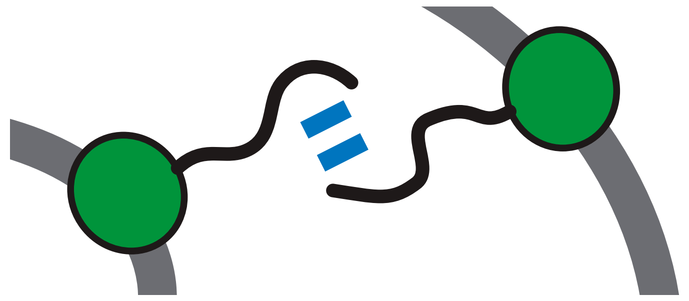
DNA binding proteins with interacting disordered domains help organize the nucleus

Example:





Model property wish list:

- Transient: Time-scale associated with segment-segment interactions
- Reach: Length-scale independent of filament diameter
- Valency: Limit of attractive segment interactions
- Computationally scalable

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Renger *et al. PNAS* (2022)

Overview of collapsing filament models

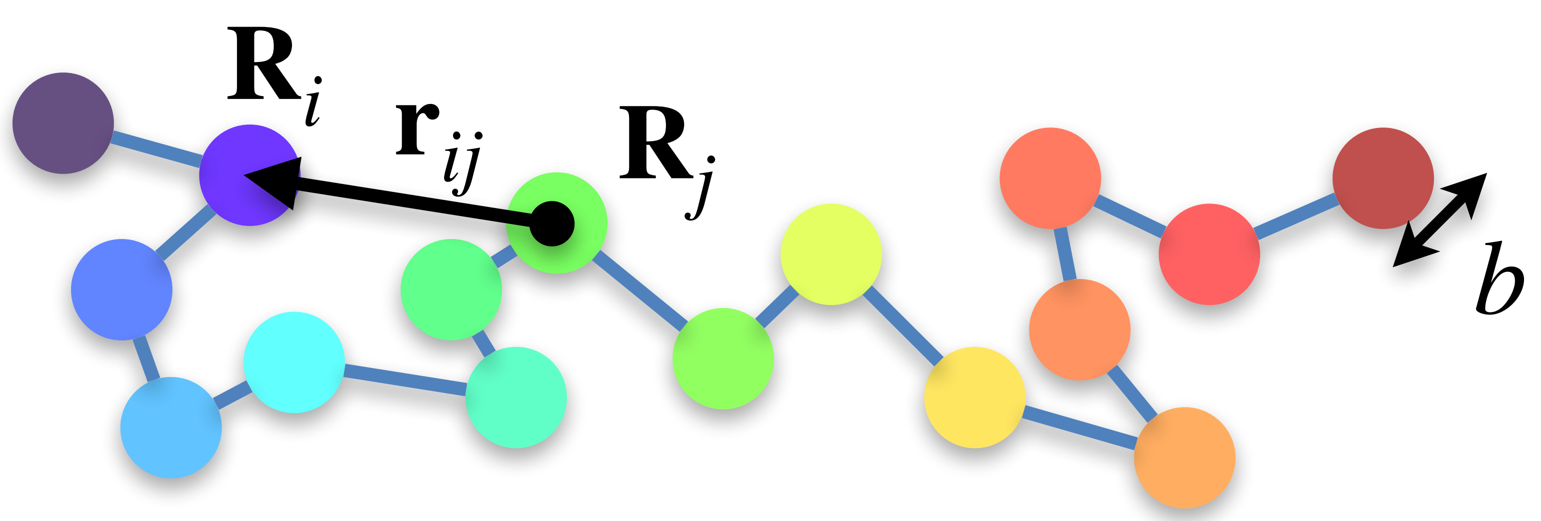
Equations of motion

ζ: drag coefficient

$\mathbf{f}_i$: Brownian noise

$\mathbf{F}_{ij}$: Other bead-bead forces

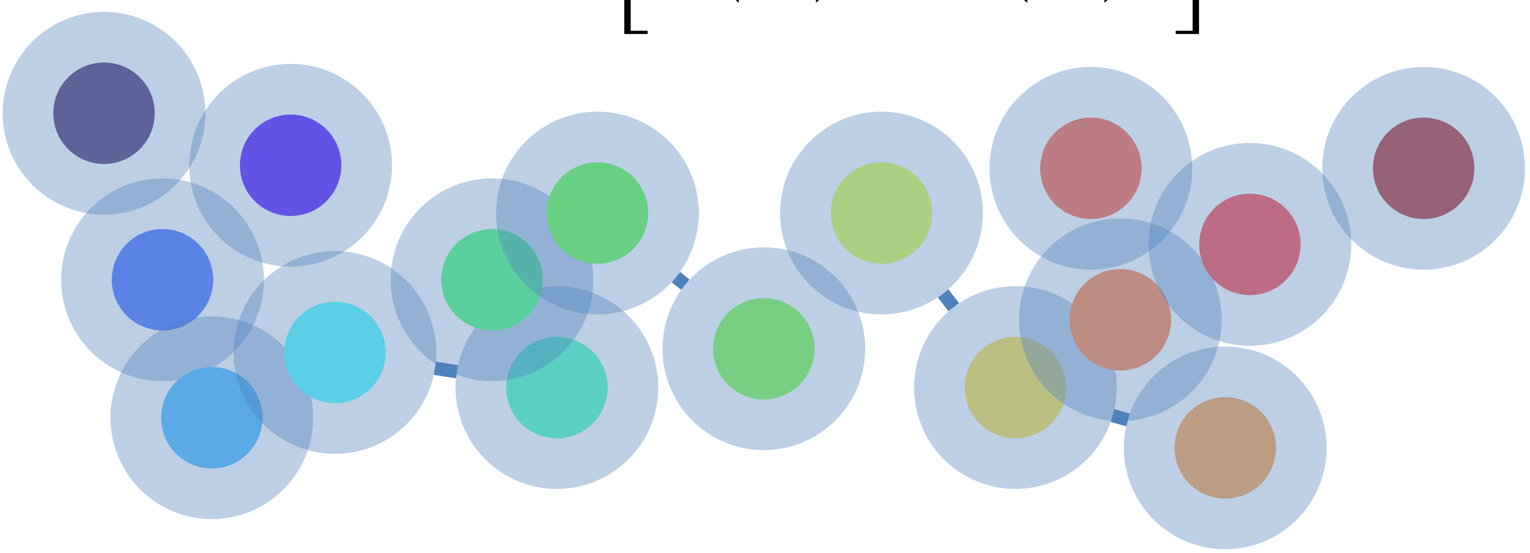
b: Bead diameter and spring rest length



$$\zeta \dot{\mathbf{R}}_i = \underbrace{\mathbf{F}_{i-1,i} + \mathbf{F}_{i,i+1}}_{\text{Spring backbone forces}} + \sum_j \mathbf{F}_{ij}(\mathbf{r}_{ij}) + \mathbf{f}_i$$

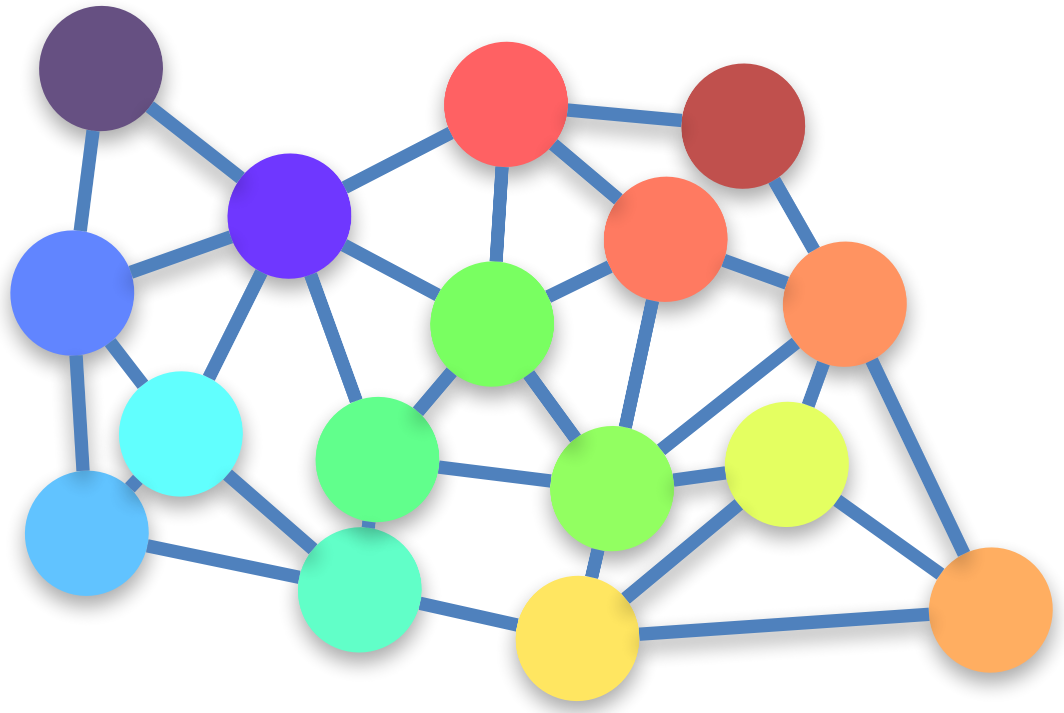
Lennard-Jones and coarse-grained potential models

$$\mathbf{F}^{LJ}(r_{ij}) = \frac{24\varepsilon}{r_{ij}}\left[2\left(\frac{b}{r_{ij}}\right)^{12} - \left(\frac{b}{r_{ij}}\right)^{6}\right]\hat{r}_{ij}$$



- Computationally efficient
- No specific valency
- Length-scale affects repulsive force
- Time-scale affects attractive force

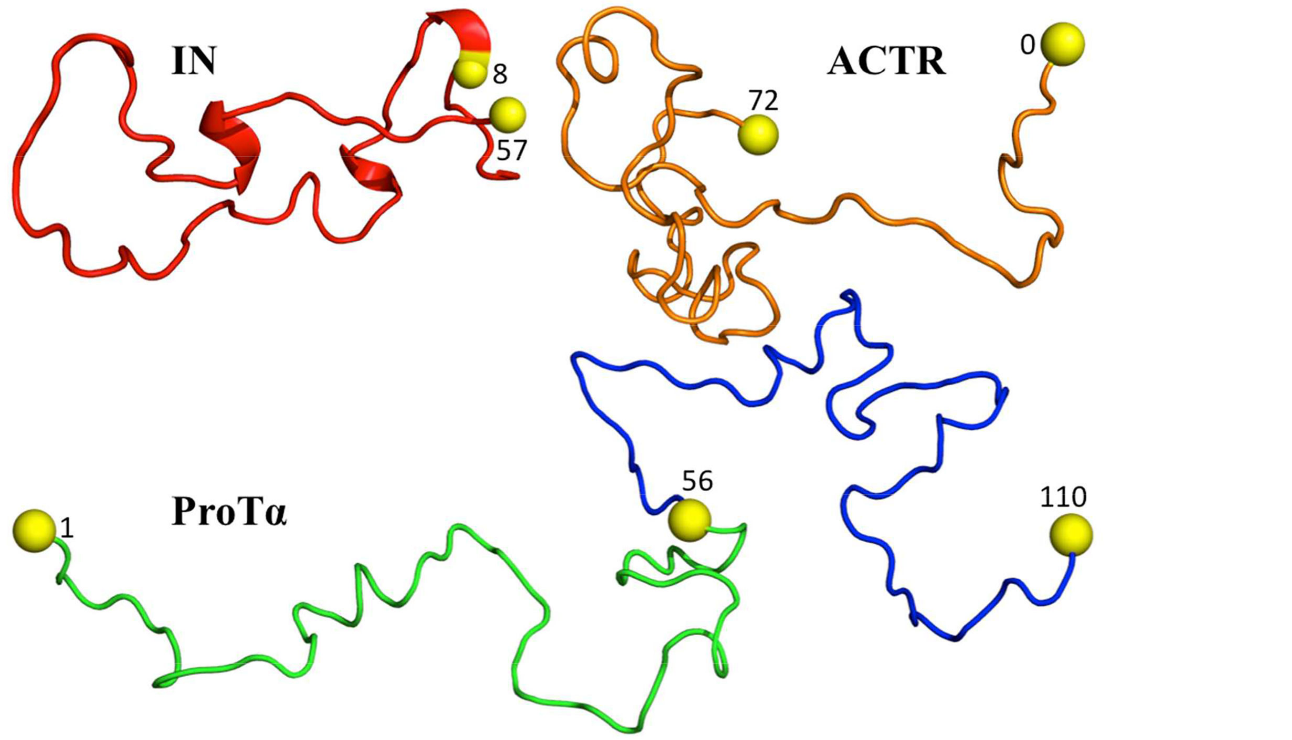
Gaussian network and Irreversible Binding models



- Computationally efficient
- Specifies interaction valency
- Defined average length between interacting polymer segments
- No transient kinetics

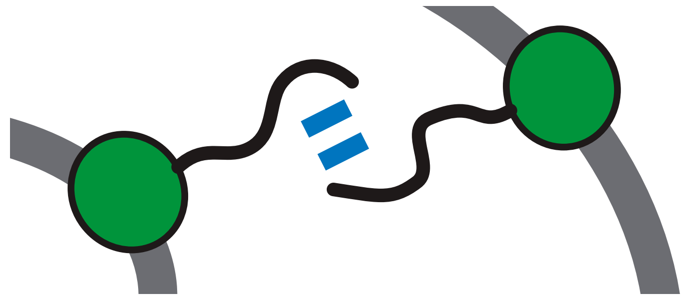
Atomistic force fields models

Valery Nguemaha et al. J Phys Chem B. (2018)



- Most accurate interactions between protein domains
- Computationally expensive!
- Unable to model large sections of DNA

Proposal: Transiently bound (sticky) tail model



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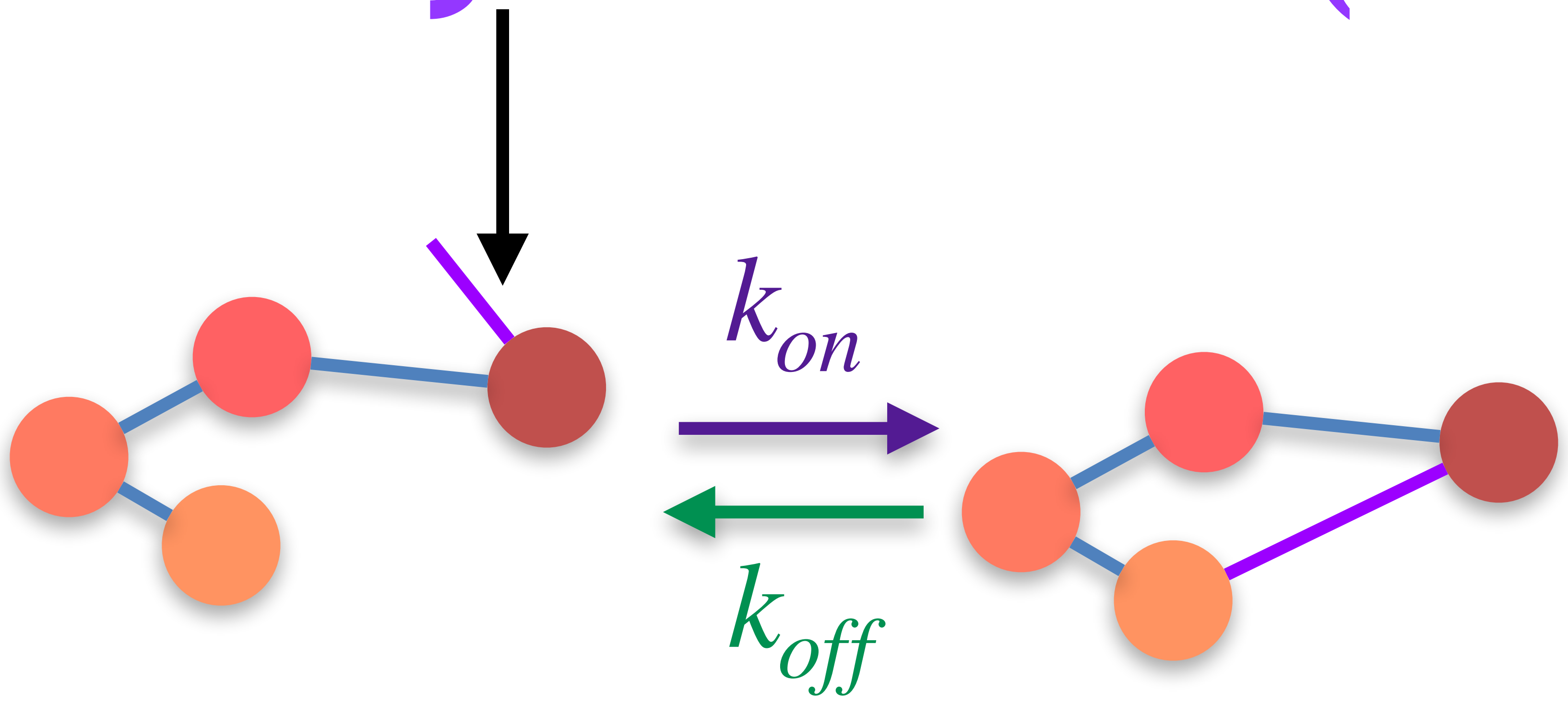
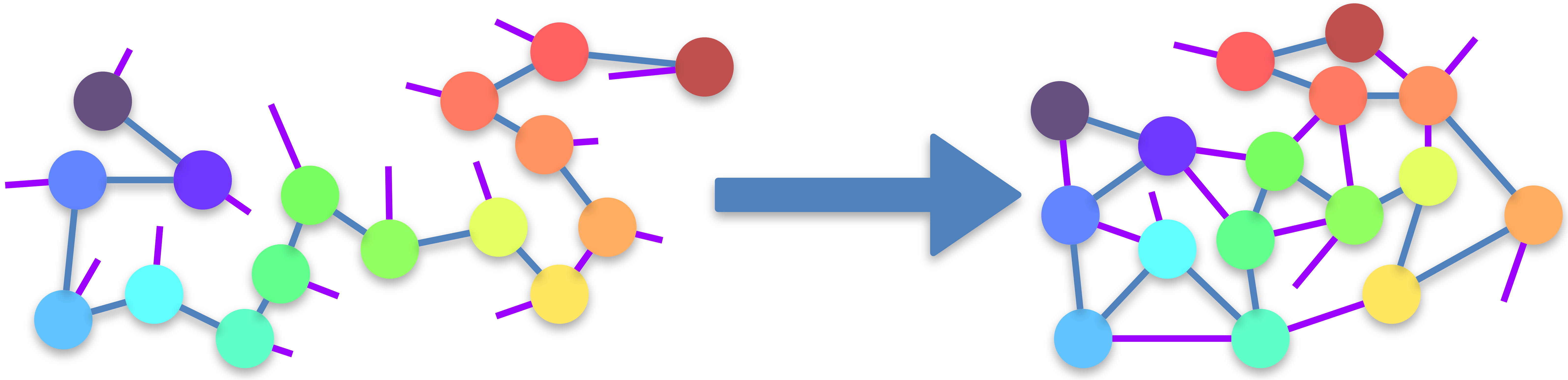


$$\frac{k_{on}(r_{ij})}{k_{off}} = K_e e^{-\beta \Delta U(r_{ij})}, \text{ where } U(r_{ij}) = \frac{\kappa_s}{2}\left(r_{ij} - \ell_s\right)^2$$

So $\mathbf{F}_{ij} = -\partial_{\mathbf{r}_{ij}} U = -\kappa_s (r_{ij} - \ell_s)\hat{r}_{ij}$



Tail parameters

k_{on}: Binding rate

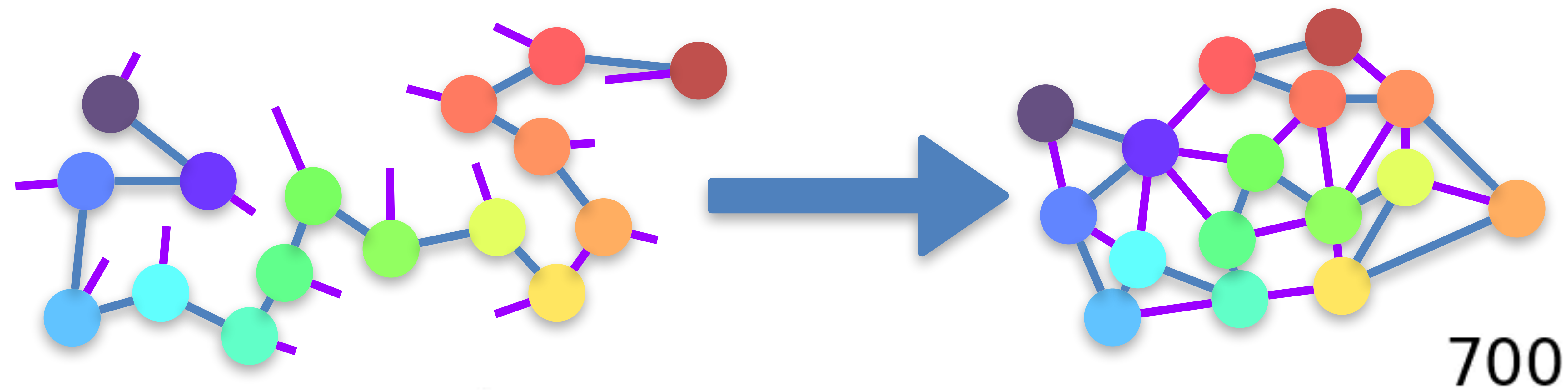
k_{off}: Unbinding rate

K_e: Binding affinity

ℓ_s: Rest length

κ_s: Spring constant

Transient binding tails compacts filaments



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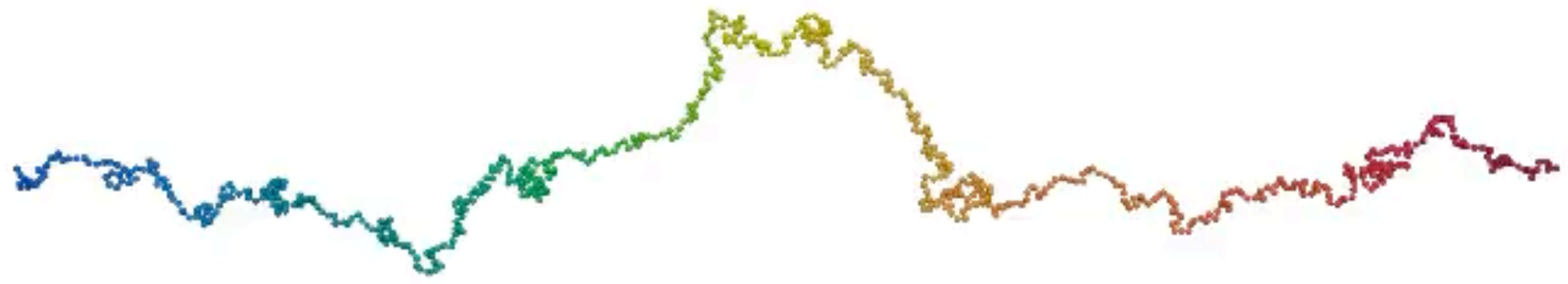
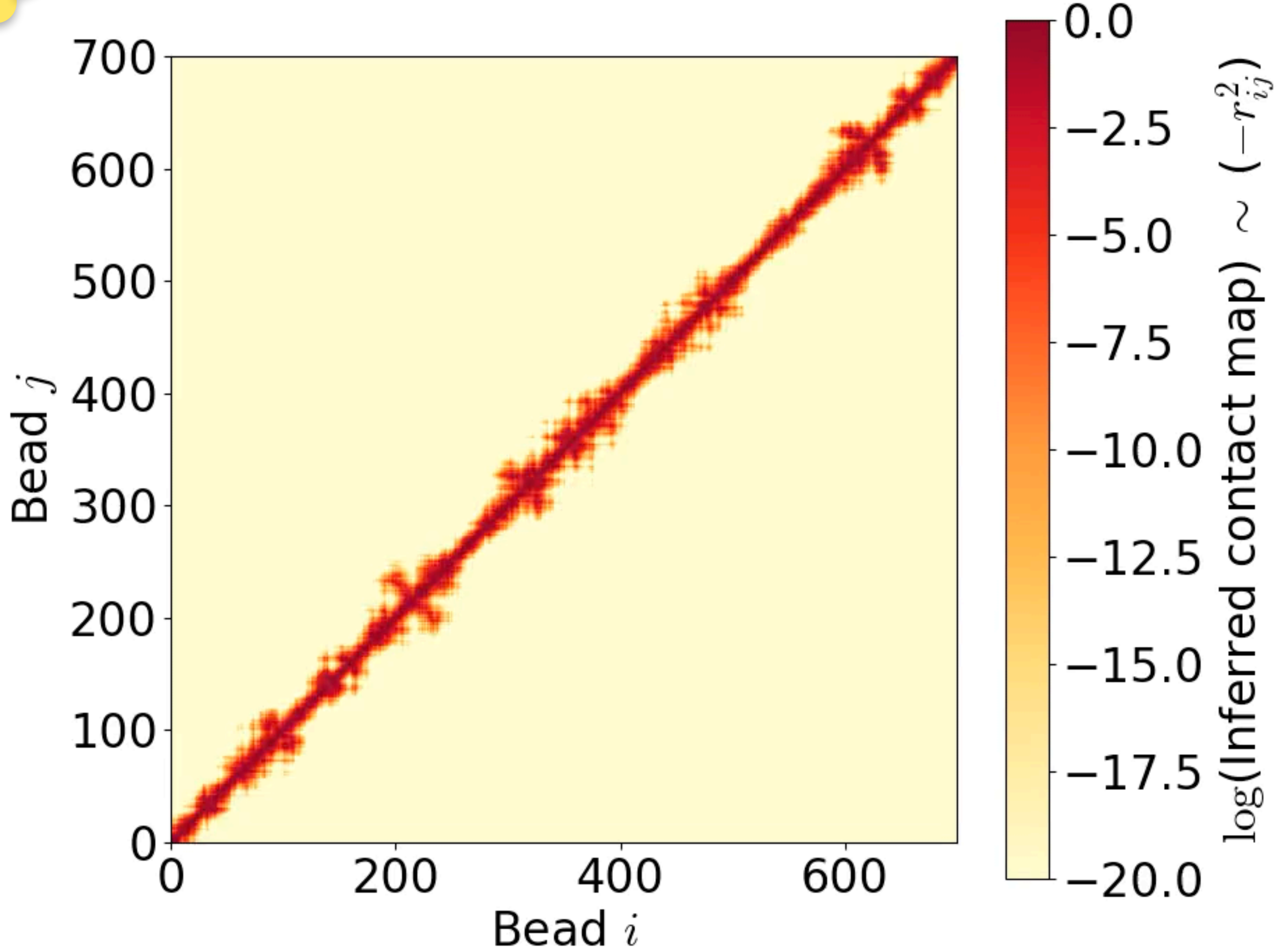




How do the kinetics affect collapse rate?

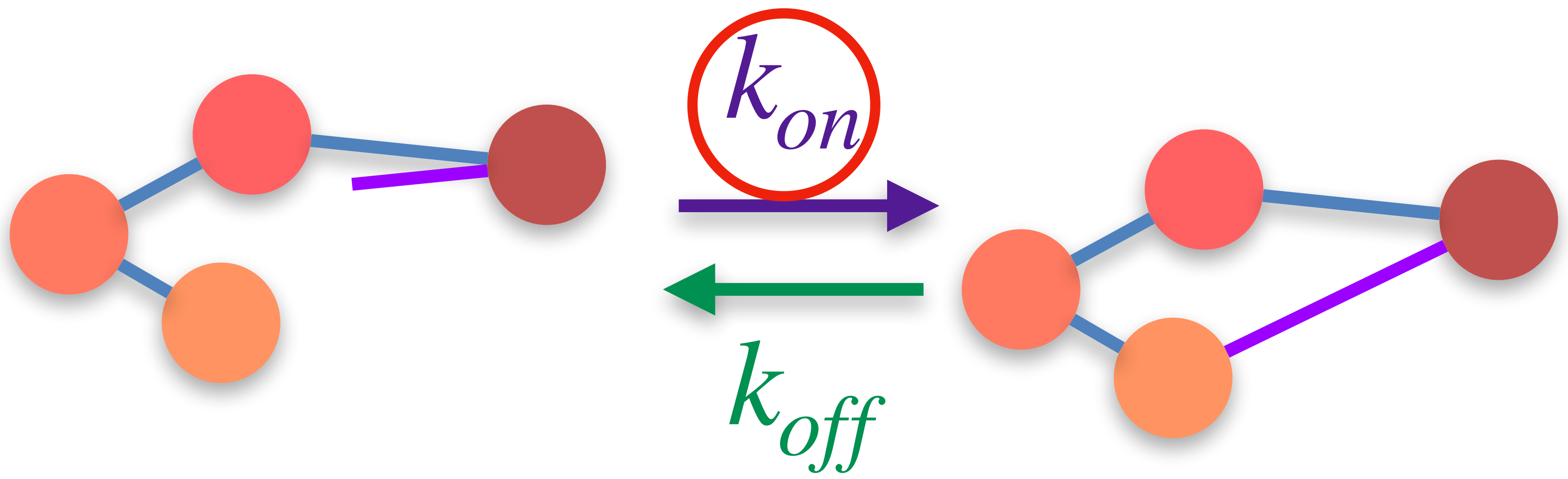
Sticky end parameters

k_o: Unbinding rate

K_e: Binding affinity

ℓ_s: Rest length

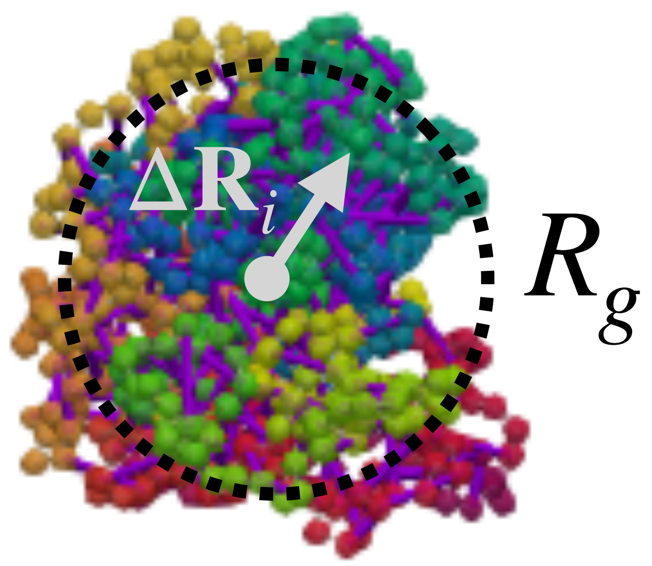
κ_s: Spring constant



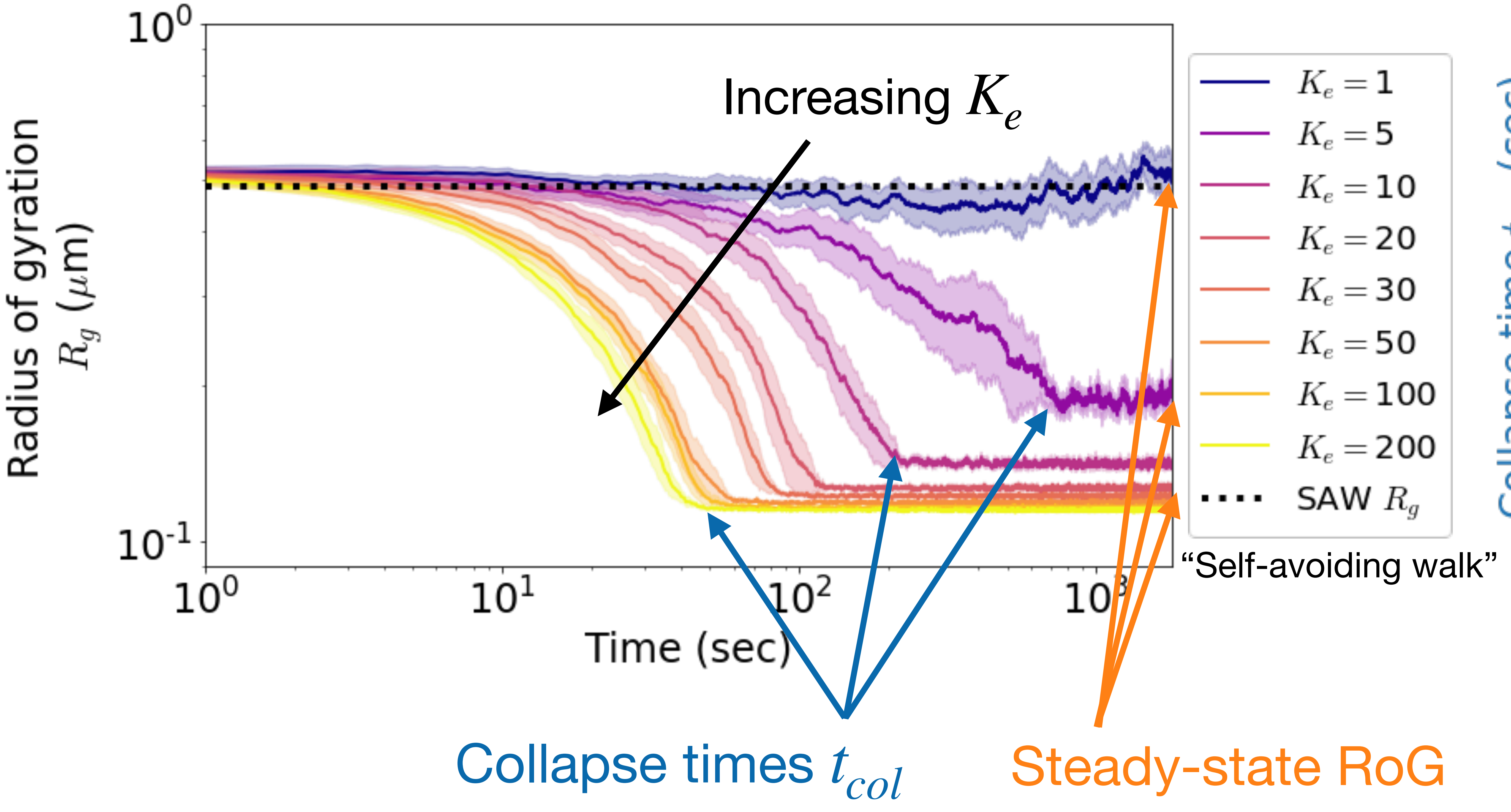
$$k_{on}(r_{ij}) = K_e k_o e^{-\beta \Delta U(r_{ij})}, \qquad k_{off} = k_o$$

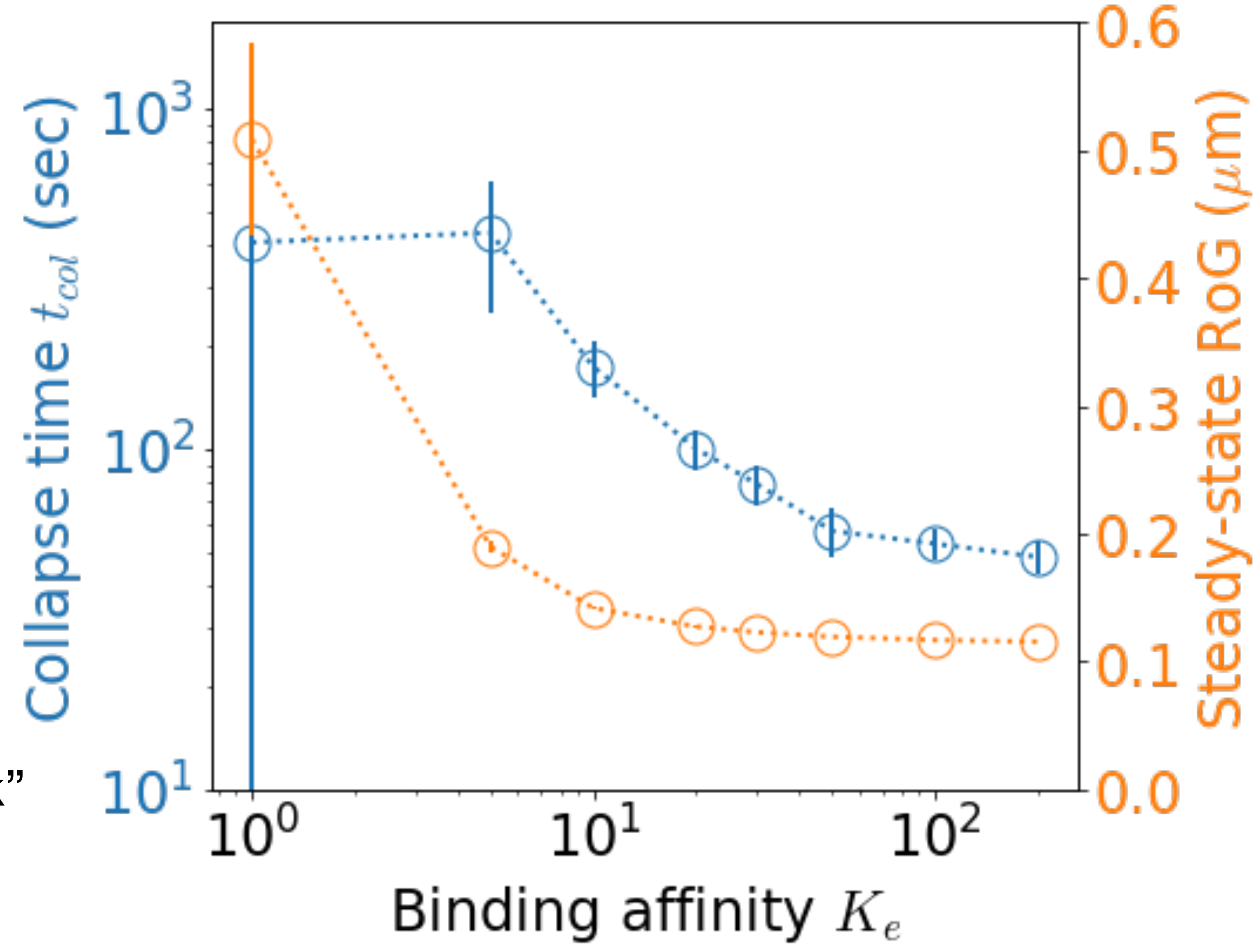
$$U(r_{ij}) = \frac{\kappa_s}{2}\left(r_{ij} - \ell_s\right)^2$$

$$\Delta \mathbf{R} = \mathbf{R_i} - \mathbf{R}_{com}$$



$$R_g = \sqrt{\frac{1}{N}\sum_i \Delta R_i^2}$$





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What about the physical characteristics of the tails?

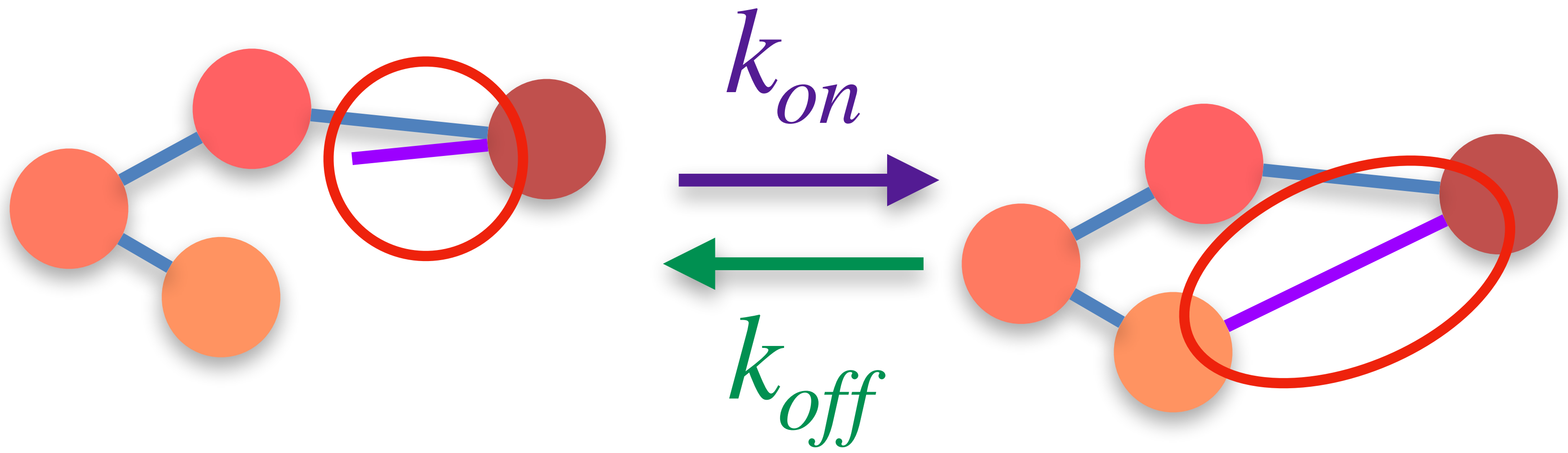
Sticky end parameters

k_o: Unbinding rate

K_e: Binding affinity

ℓ_s: Rest length

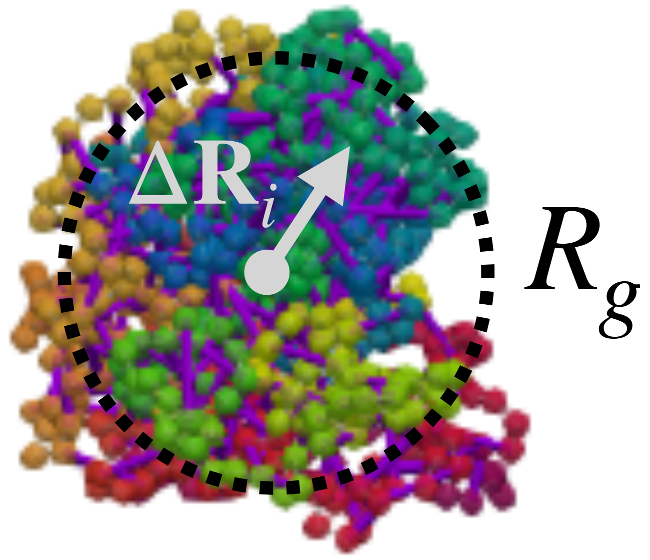
κ_s: Spring constant



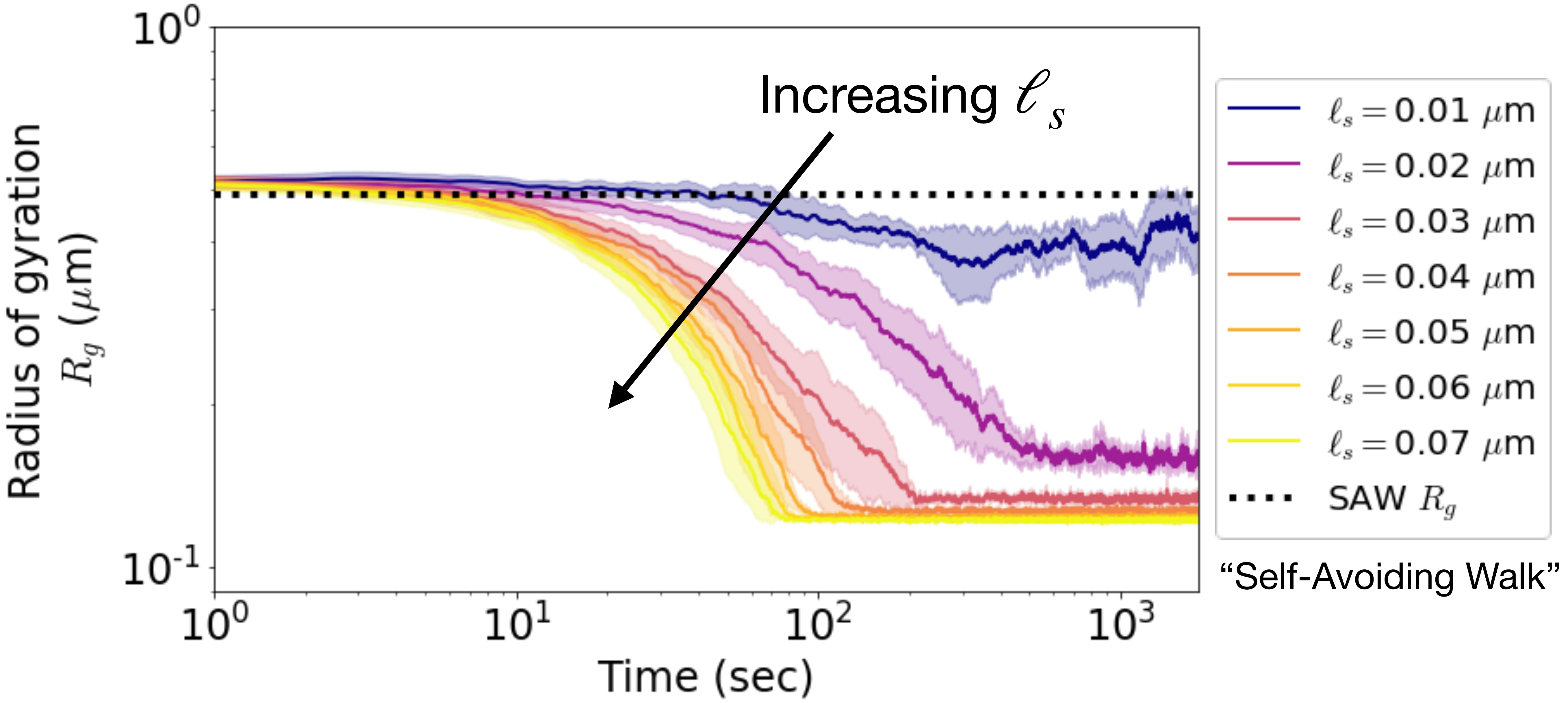
$$k_{on}(r_{ij}) = K_e k_o e^{-\beta \Delta U(r_{ij})}, \quad k_{off} = k_o$$

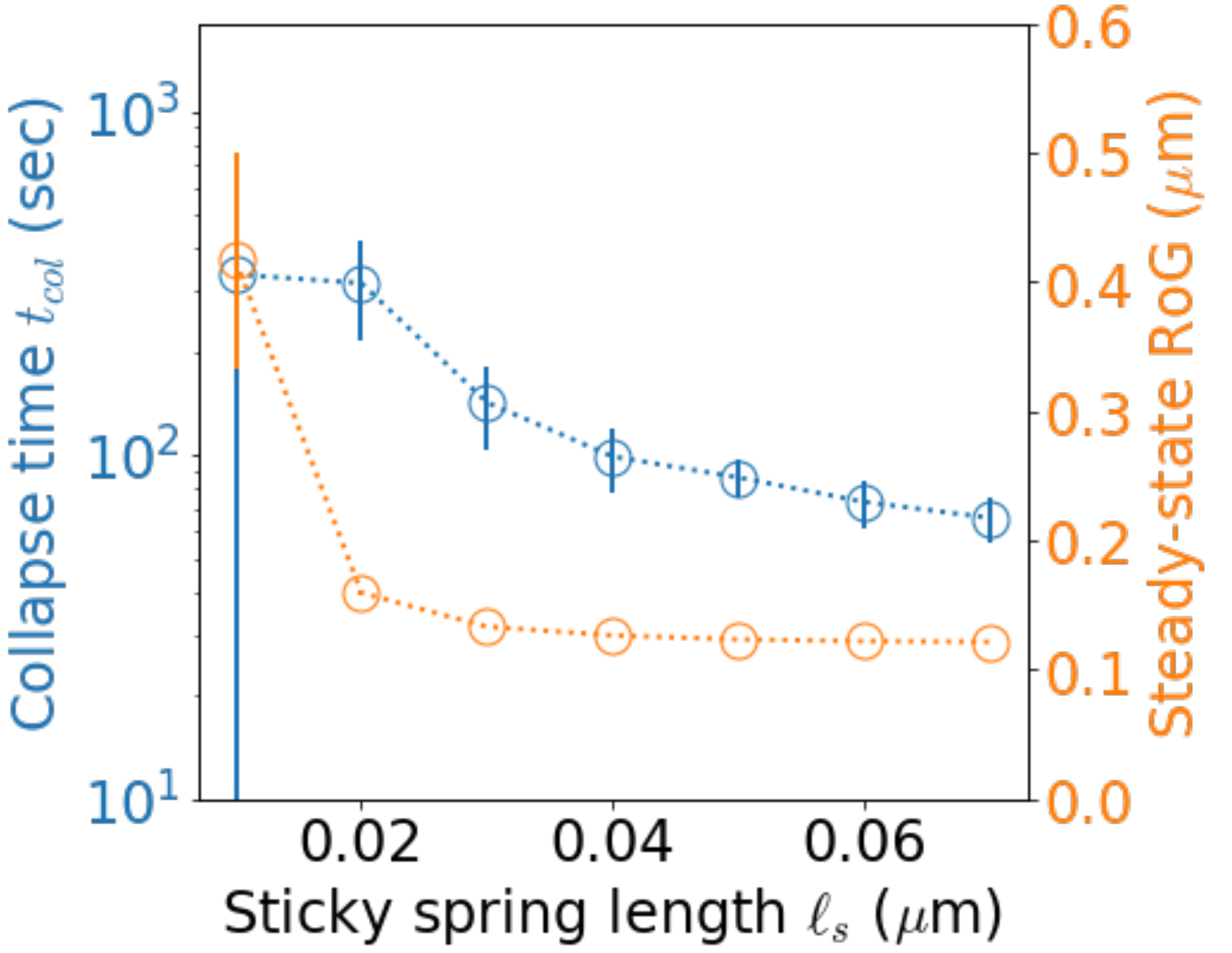
$$U(r_{ij}) = \frac{\kappa_s}{2}\left(r_{ij} - \ell_s\right)^2$$

$$\Delta \mathbf{R} = \mathbf{R_i} - \mathbf{R}_{com}$$



$$R_g = \sqrt{\frac{1}{N}\sum_i \Delta R^2}$$





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Binding affinity and tail length dictate the probability of a single tail being bound

Sticky end parameters

k_o: Unbinding rate

K_e: Binding affinity

ℓ_s: Rest length

κ_s: Spring constant

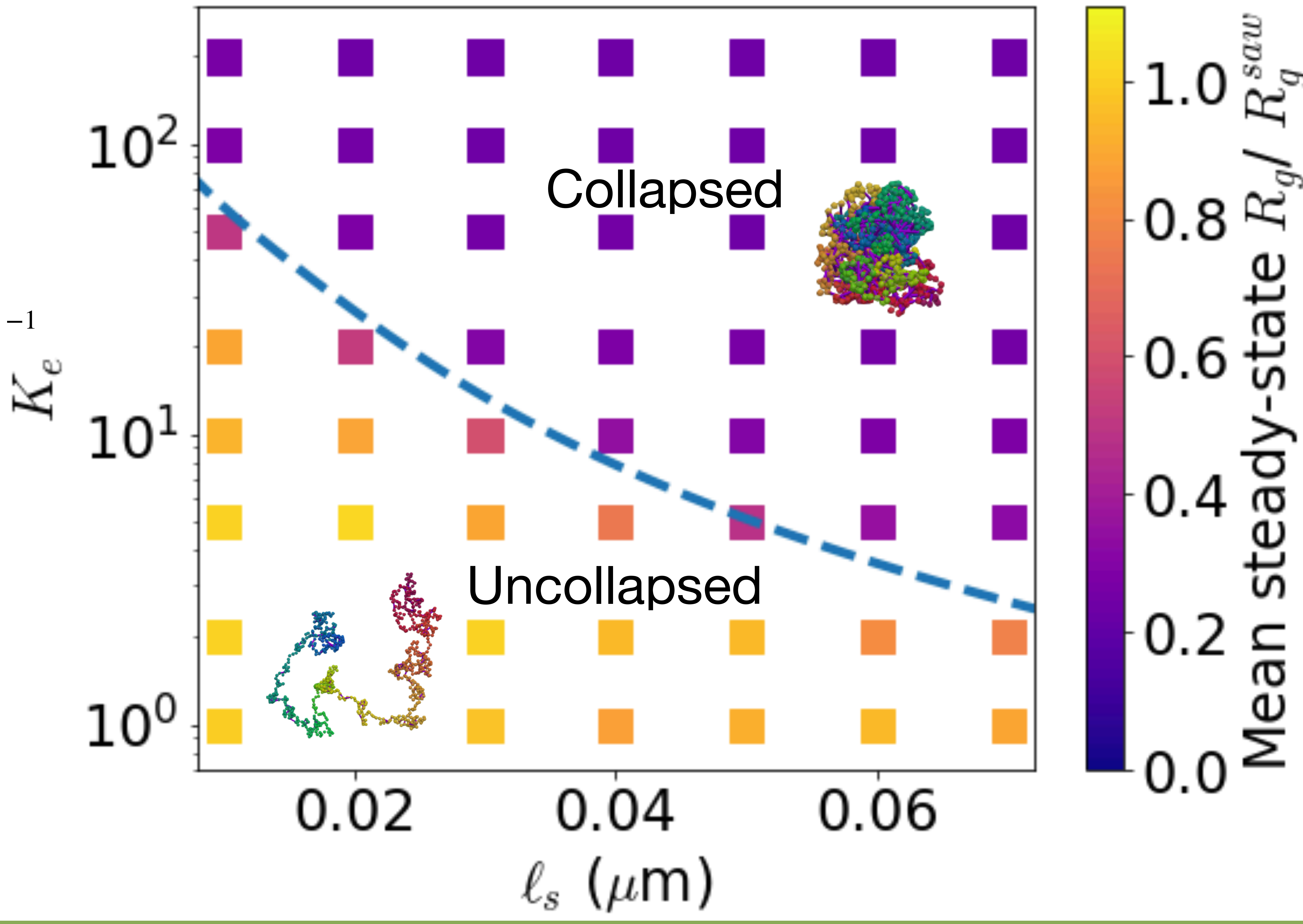
$\rho(\mathbf{r})$: Bead density

Probability of a single sticky tail being bound

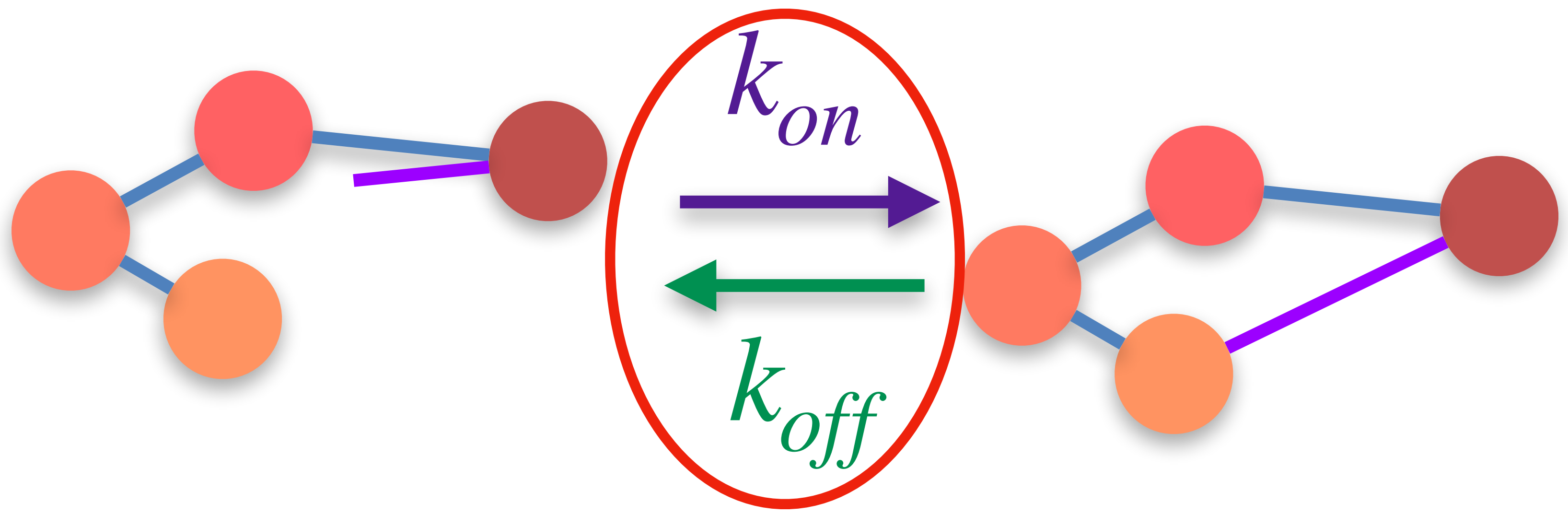
$$\Psi_B = \int d\mathbf{r} \frac{k_{on}(\mathbf{r})}{k_{off}} \rho(\mathbf{r}) = 4\pi\rho_o K_e \int d\mathbf{r} \exp\left(\frac{-\beta\kappa_s}{2}(r-\ell_s)^2\right)$$

Assume critical value for the Ψ_B and solve for K_e as a function of l_s

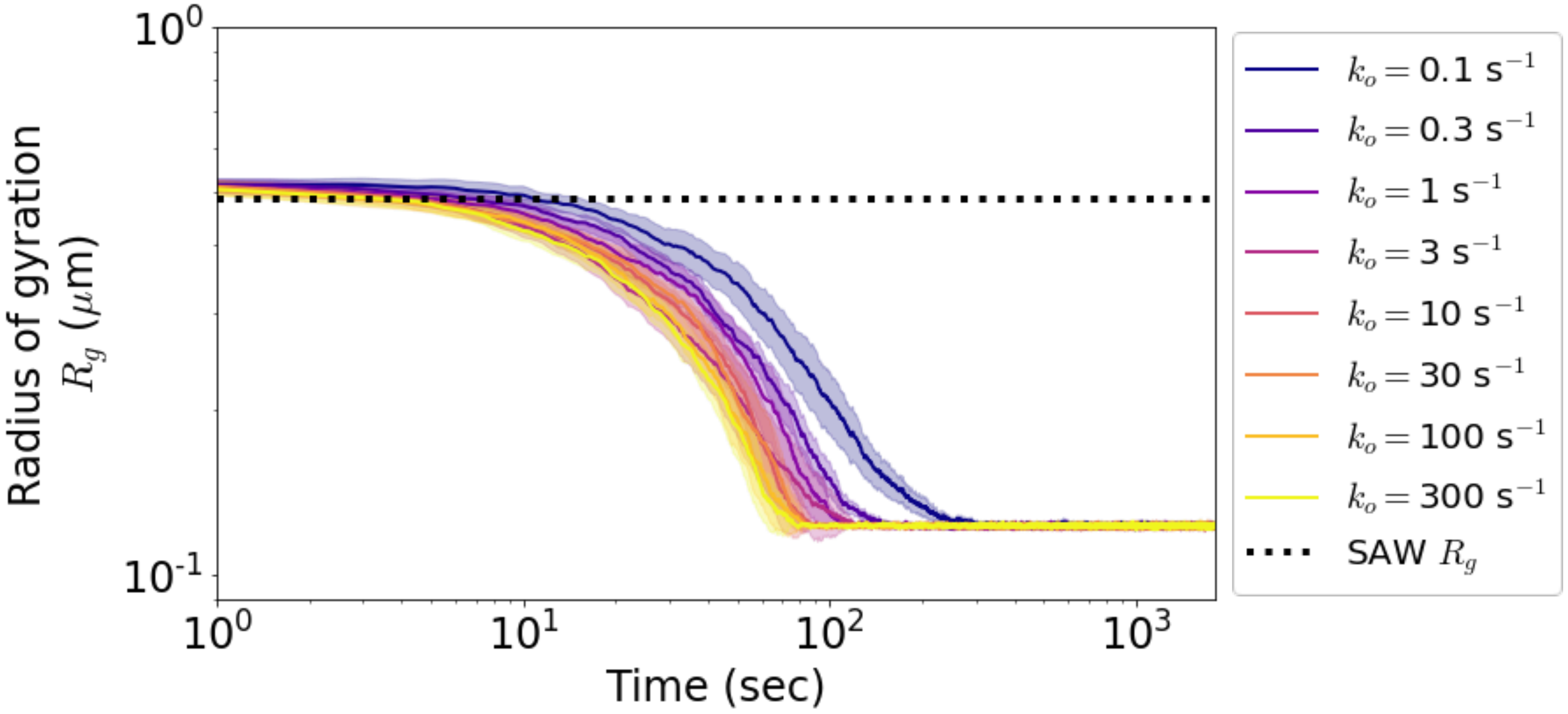
$$K_e(l_s) = \frac{\Psi_{crit}}{4\pi\rho_o\ell_s^3}\left[\frac{\sqrt{\frac{\pi}{2}}\left(\beta\kappa_s\ell_s^2+1\right)\left(\mathrm{erf}\left(\sqrt{\frac{\beta\kappa_s\ell_s^2}{2}}\right)+1\right)}{\left(\beta\kappa_s\ell_s^2\right)^{3/2}} + \frac{e^{-\frac{1}{2}\beta\kappa_s\ell_s^2}}{\beta\kappa_s\ell_s^2}\right]^{-1}$$

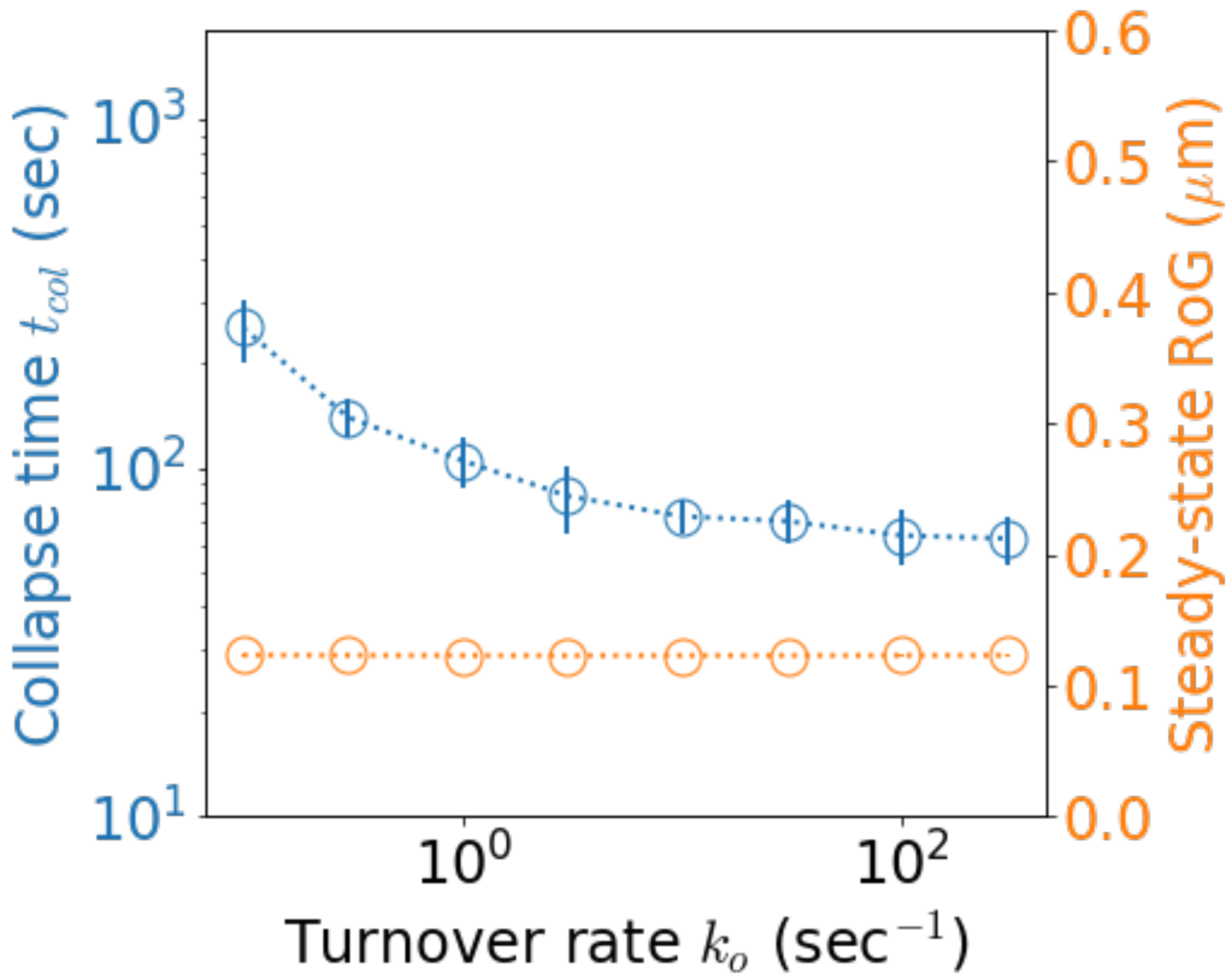


The tail turnover rate affects collapse rate but not steady-state radius of gyration



$$k_{on}(r_{ij}) = K_e k_o e^{-\beta \Delta U(r_{ij})}, \quad k_{off} = k_o$$





Binding turnover dictates the amount of anomalous diffusion inside collapsed polymer

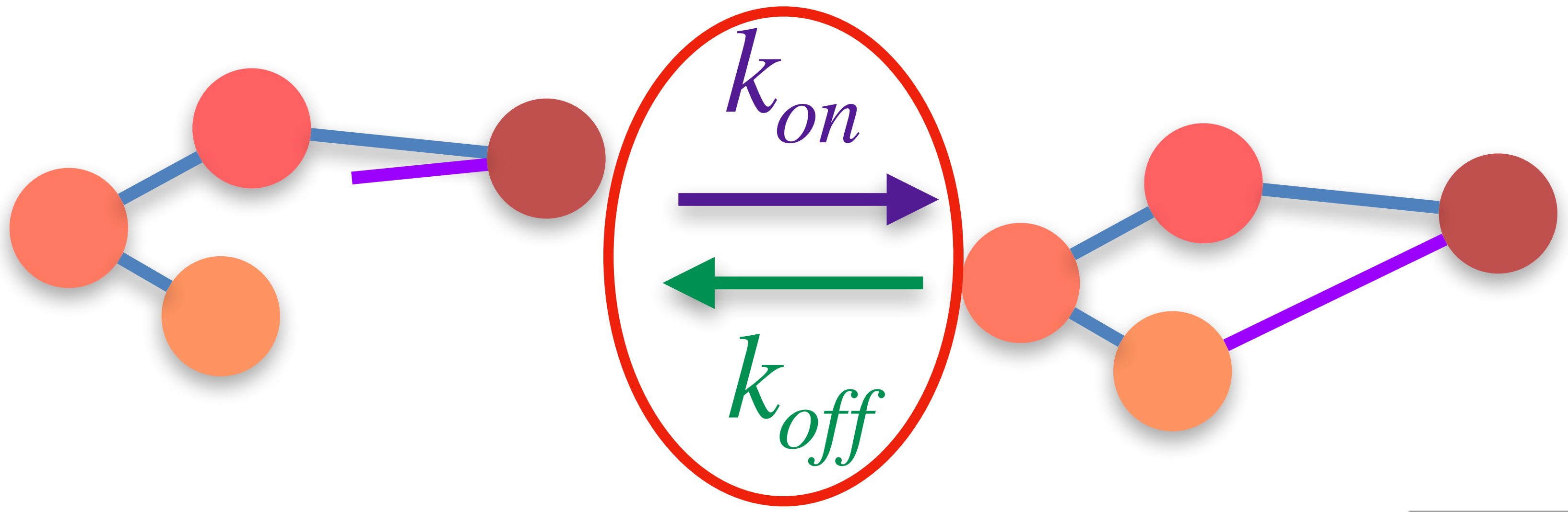
Sticky end parameters

k_o: Unbinding rate

K_e: Binding affinity

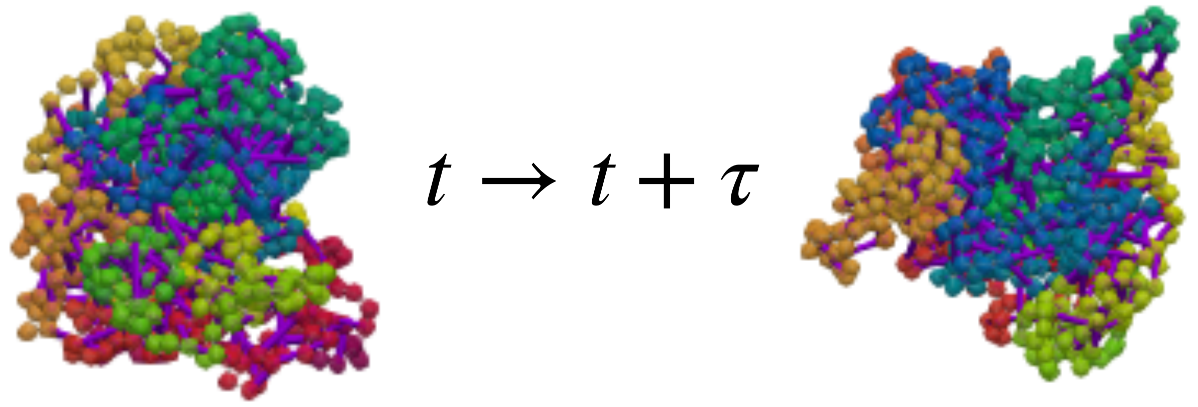
ℓ_s: Rest length

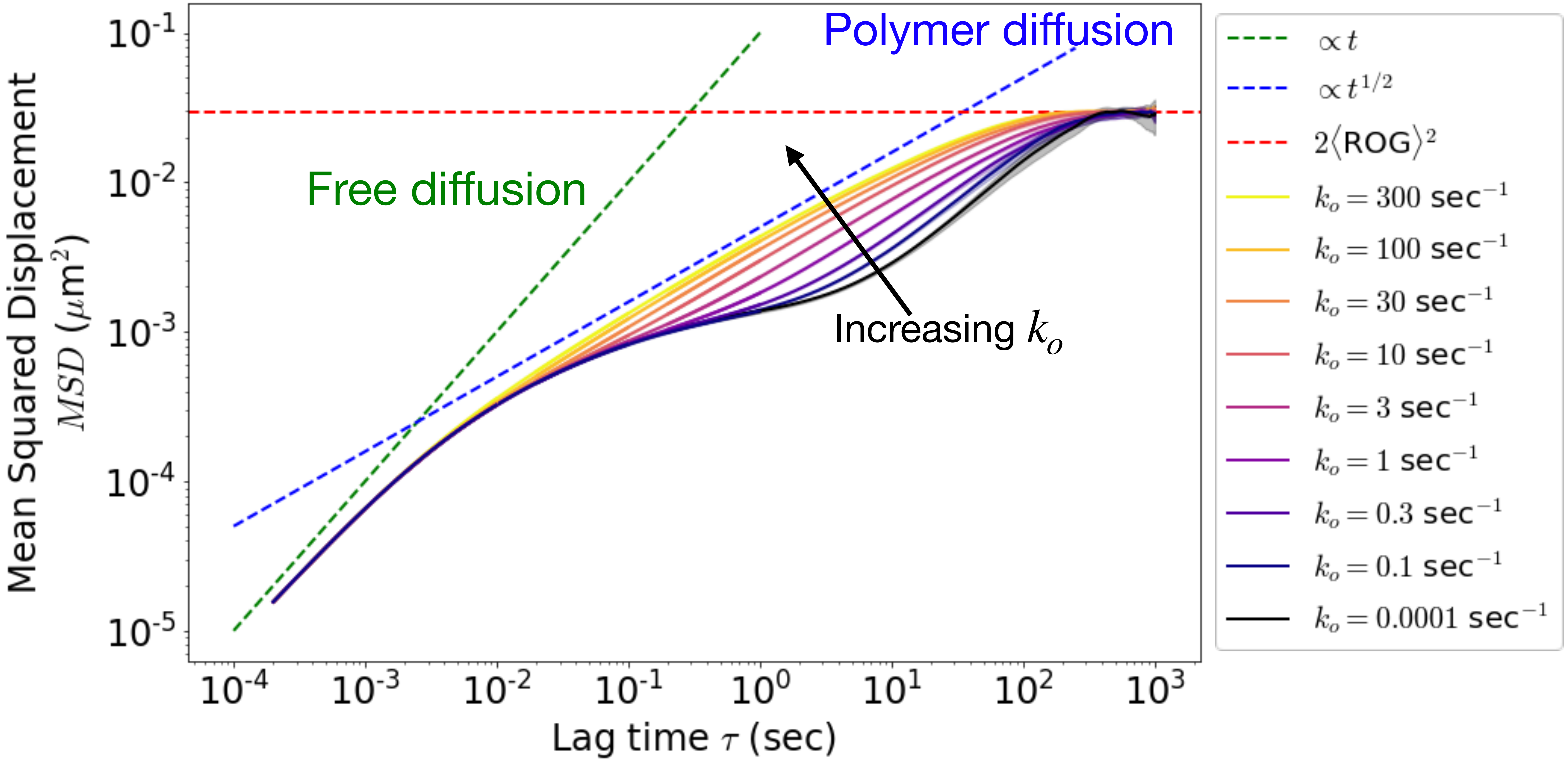
κ_s: Spring constant



$$k_{on}(r_{ij}) = K_e k_o e^{-\beta \Delta U(r_{ij})}, \qquad k_{off} = k_o$$

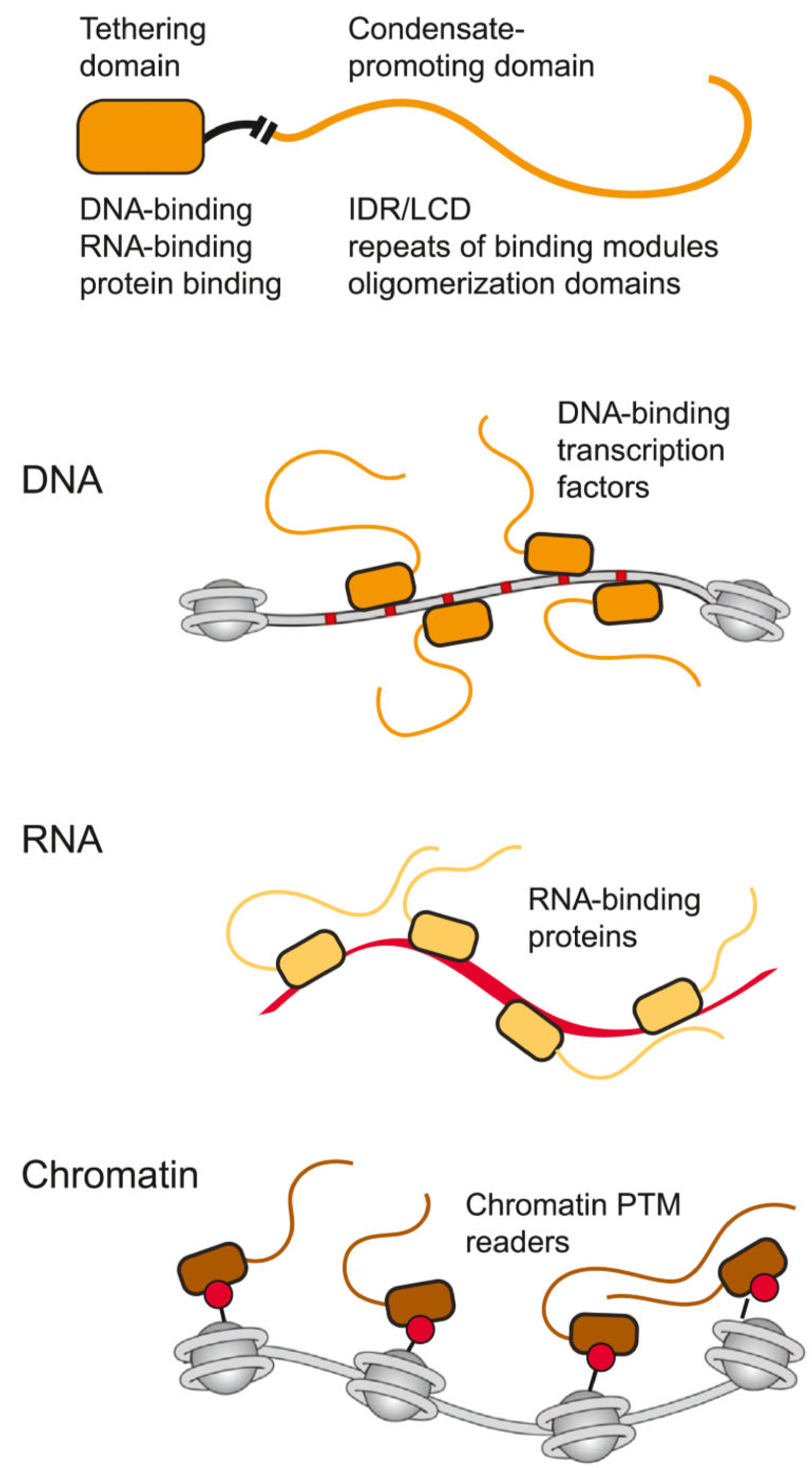
$$MSD(\tau) = \langle \, | \, \Delta \mathbf{R}_i(\tau + t) - \Delta \mathbf{R}_i(t) \, |^2 \, \rangle_{i,t}$$





Take aways

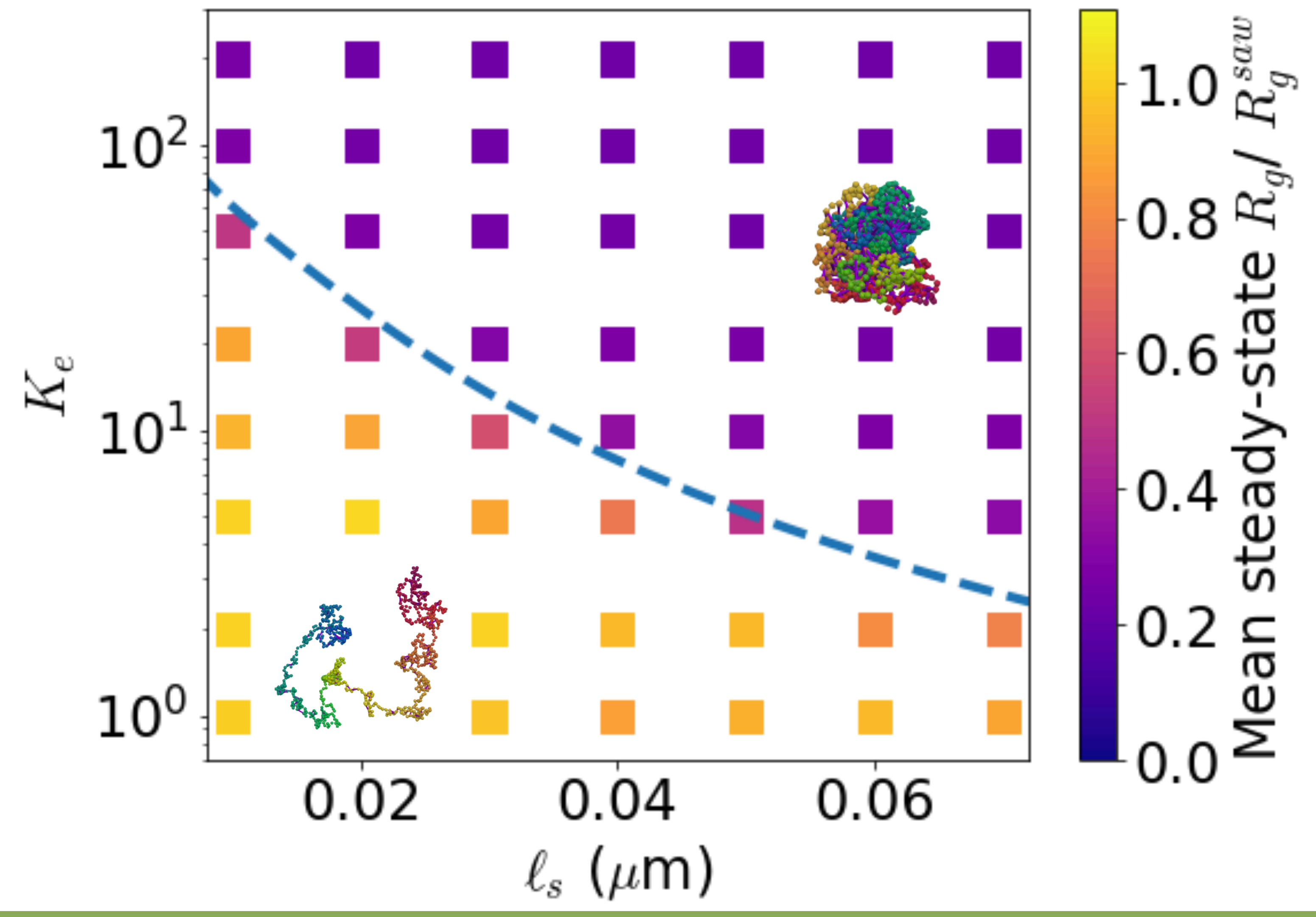
Sabari et al. *Trends in Biochem Sci* (2020)

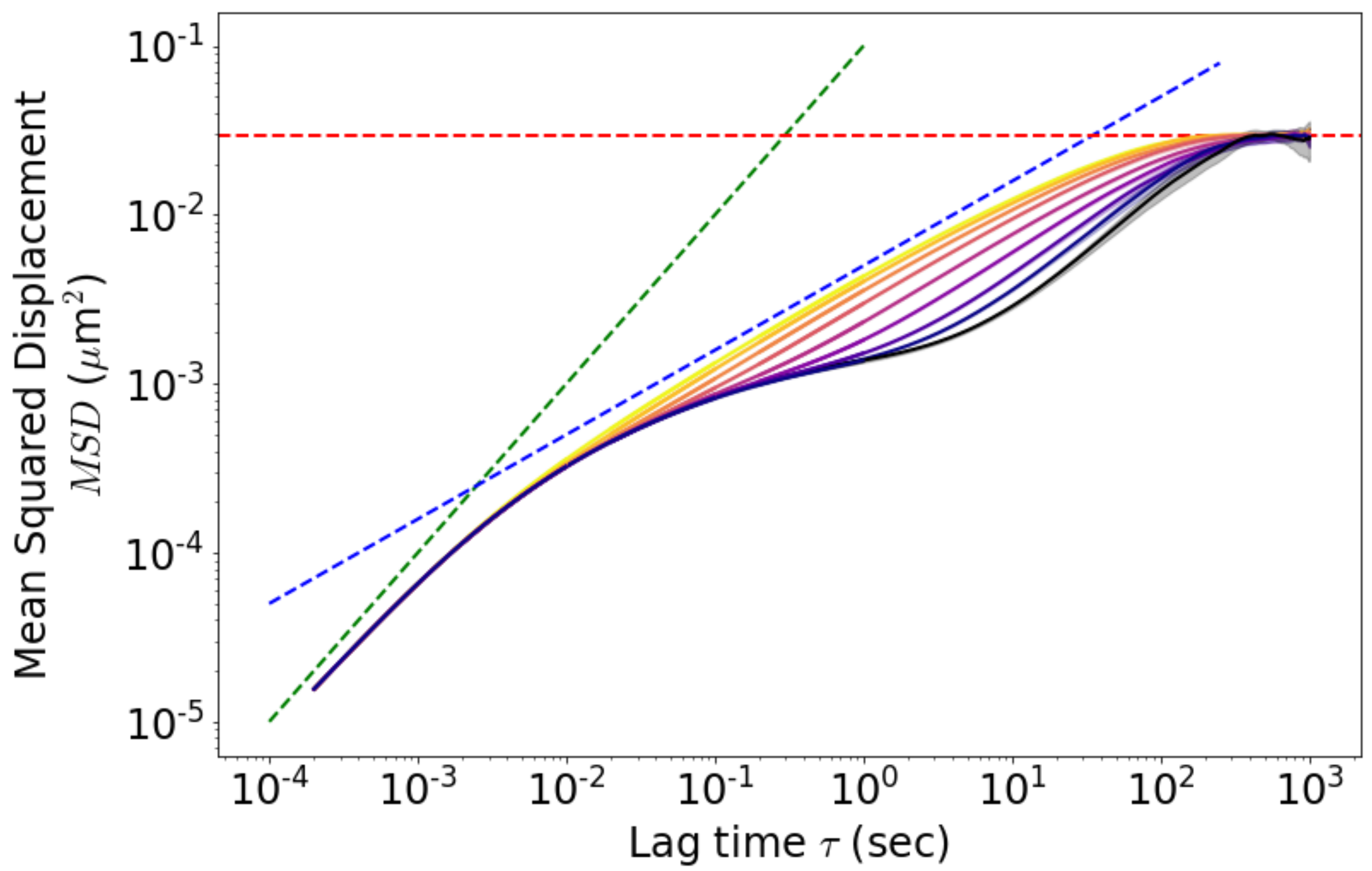


- The sticky tail model is a simplified yet computationally efficient and general model for filaments bound by proteins with attractive domains.

- We can predict polymer collapse based on the kinetic and physical parameters of tails.

- Period of tail binding cycle dictates reorganization speed of condensed polymers.





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Thank you!

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aLENS

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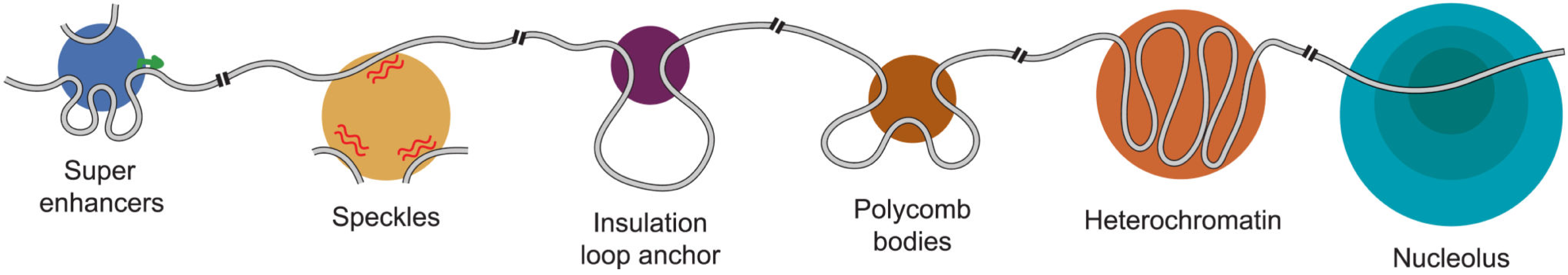
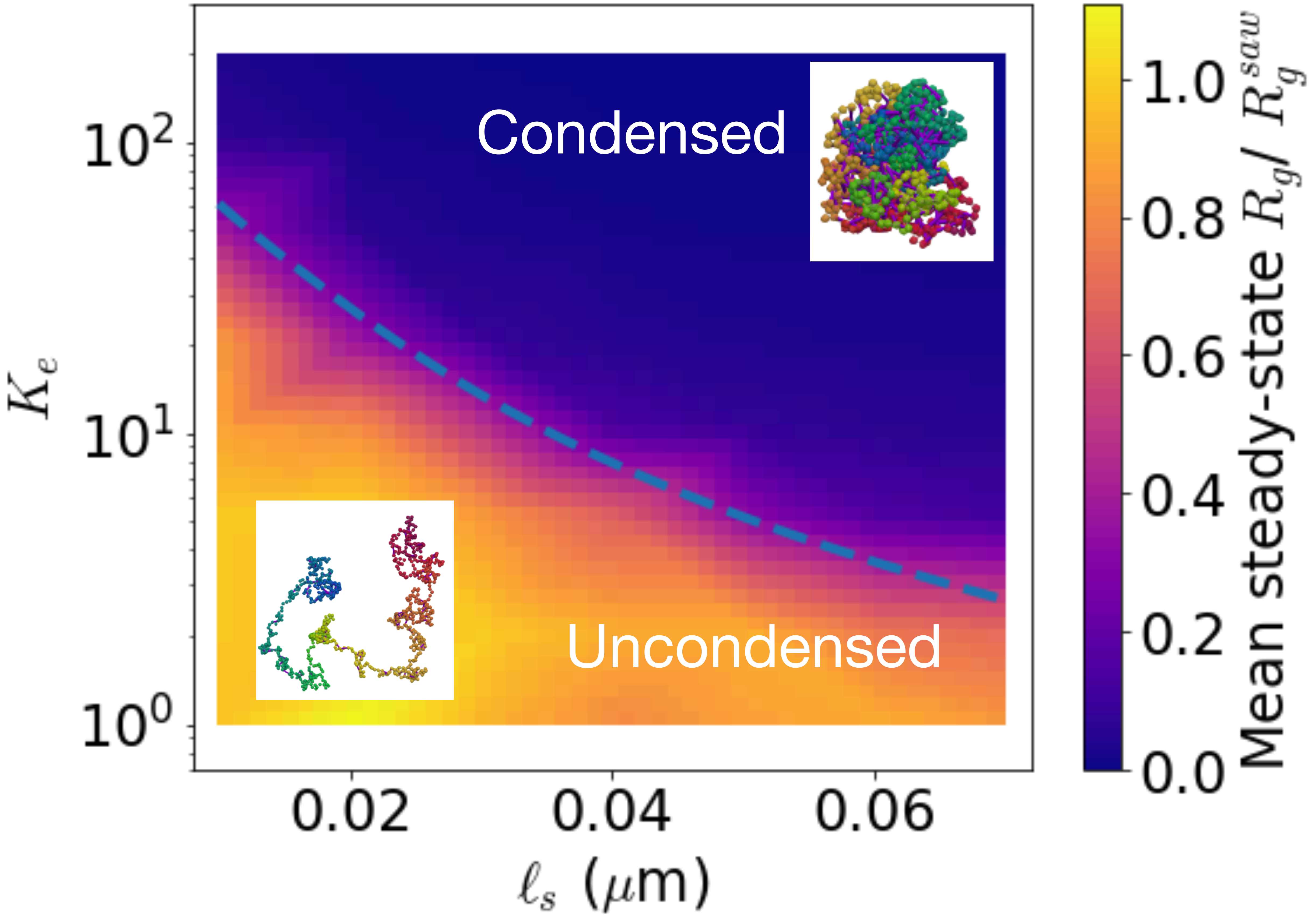
Backup slides

Different types of nuclear condensates

(B)



Interpolated map of condensed and uncondensed states with fitted boundary



$$\Psi_B = \int d\mathbf{r} \frac{k_{on}(\mathbf{r})}{k_{off}} \rho(\mathbf{r}) = 4\pi\rho_o K_e \int d\mathbf{r} \exp\left(\frac{-\beta k_s}{2}(r - l_s)^2\right)$$

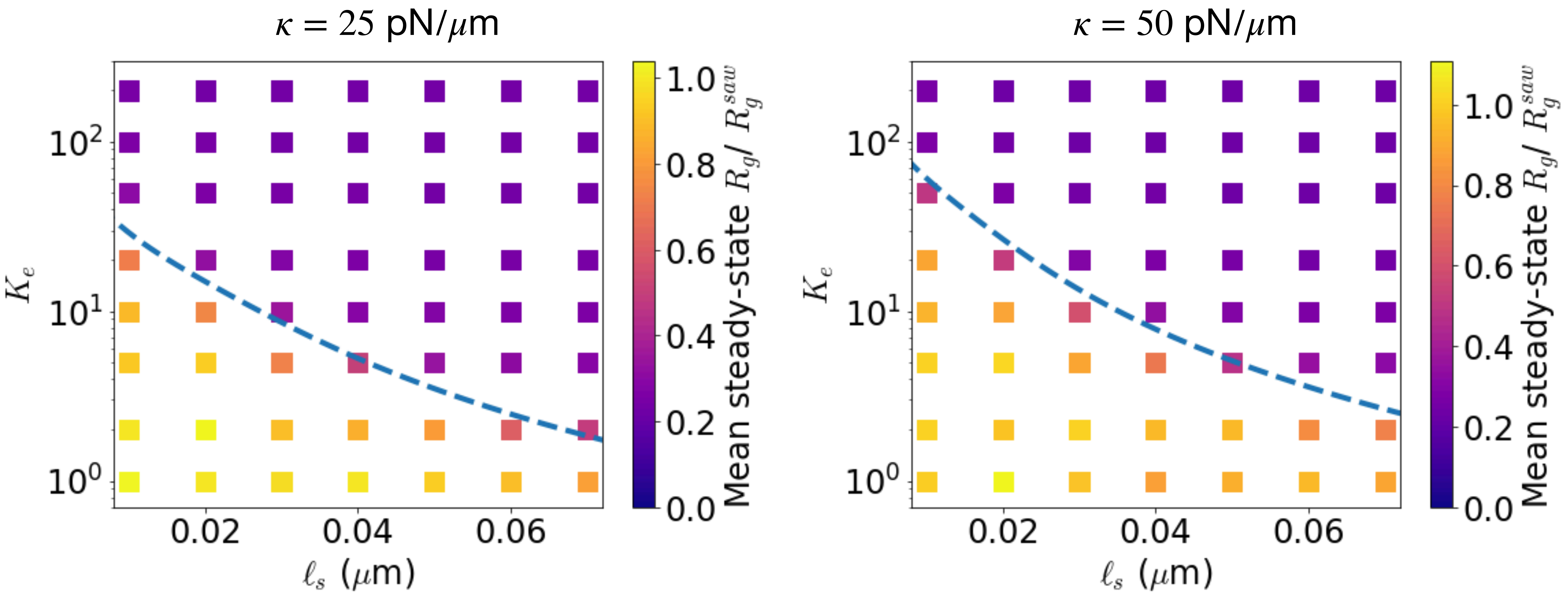
$$\Psi_B = \int d\mathbf{r} \frac{k_{on}(\mathbf{r})}{k_{off}} \rho(\mathbf{r}) = 4\pi\rho_o K_e \int dr r^2 \exp\left(\frac{-\beta k_s}{2}(r - l_s)^2\right)$$

Assume critical value for Ψ_B and solve for K_e as a function of l_s

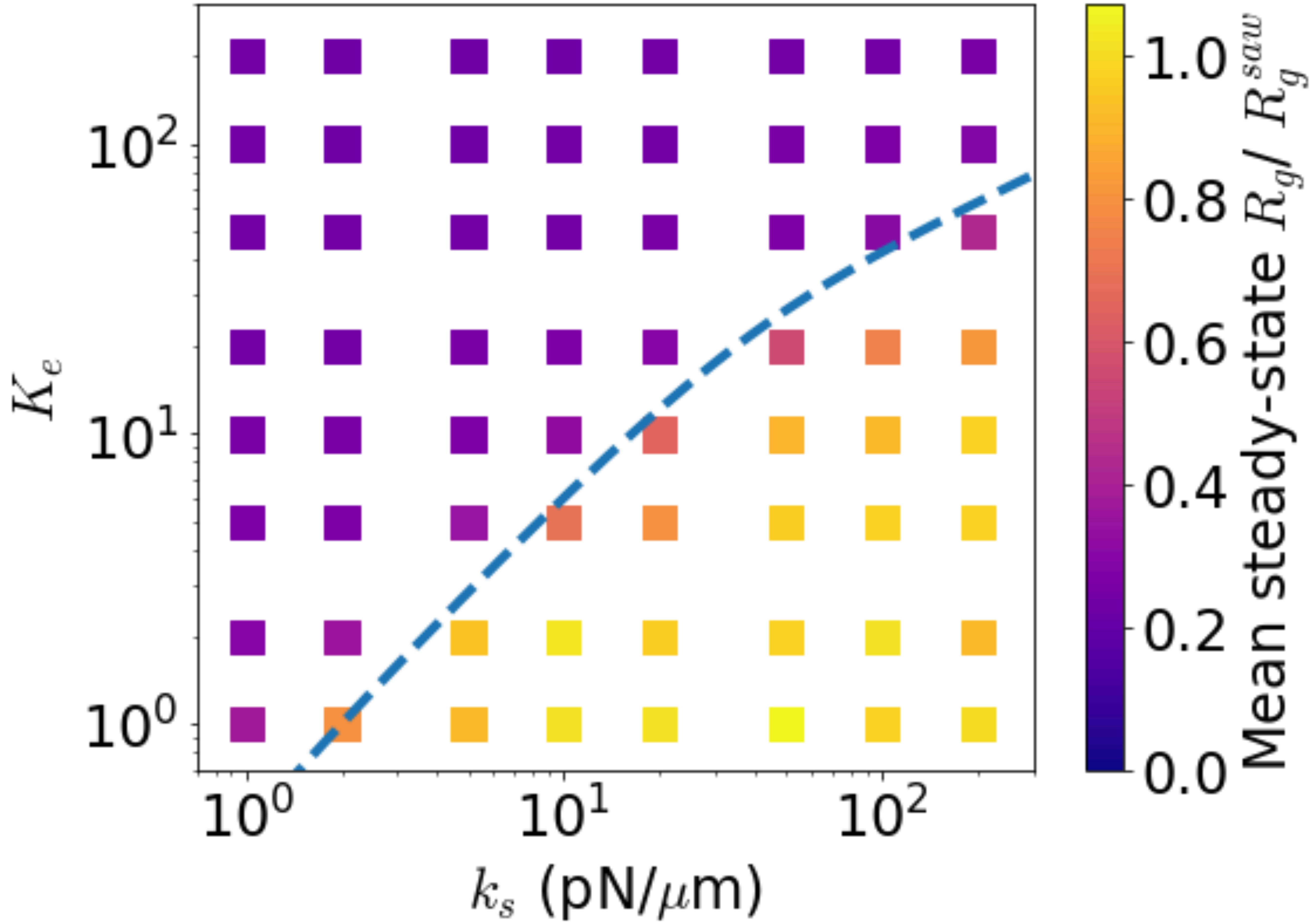
$$K_e(l_s) = \frac{\Psi_{crit}}{4\pi\rho_o}\left[\frac{\sqrt{\frac{\pi}{2}}\left(\beta k_s l_s^2 + 1\right)\left(\mathrm{erf}\left(\frac{l_s\sqrt{\beta k_s}}{\sqrt{2}}\right) + 1\right)}{\left(\beta k_s\right)^{3/2}} + \frac{l_s e^{-\frac{1}{2}\beta k_s l_s^2}}{\beta k_s}\right]^{-1}$$

Depending on what value of ρ_o you use, $\Psi_{crit} \approx \{1 - 100\}$

Radius of gyration
R_g (μm)
Time (sec)
$N = 200$
$N = 400$
$N = 800$
$N = 1600$
$N = 3200$
$N = 6400$
Collapse time t_{col} (sec)
Steady-state RoG (μm)
Number of monomers N
$\propto N^2$
$\propto N^{1/3}$



$\kappa = 25$ pN/μm
$\kappa = 50$ pN/μm
K_e
10^0
10^1
10^2
0.02
0.04
0.06
ℓ_s (μm)
Mean steady-state R_g/ R_g^{saw}
0.0
0.2
0.4
0.6
0.8
1.0



10^2
10^1
10^0
K_e
10^0
10^1
10^2
k_s (pN/μm)
1.0
0.8
0.6
0.4
0.2
0.0
Mean steady-state R_g/ R_g^{saw}

Comparison with potential-based simulations (LAMMPS)