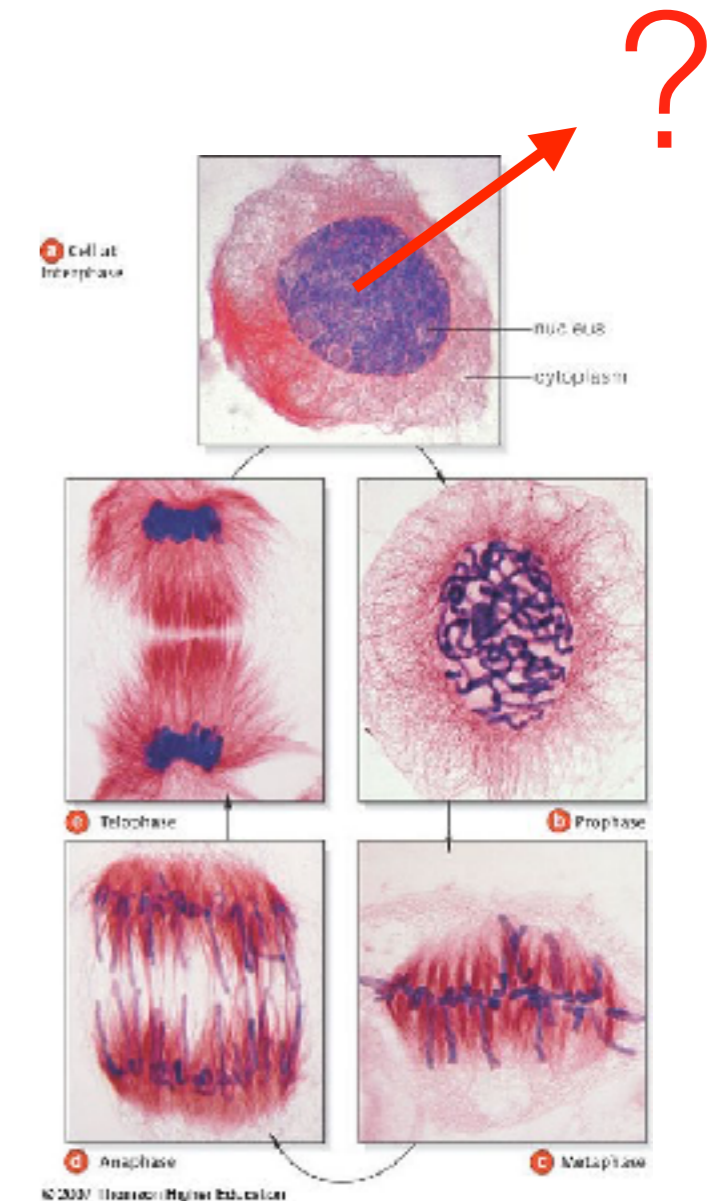
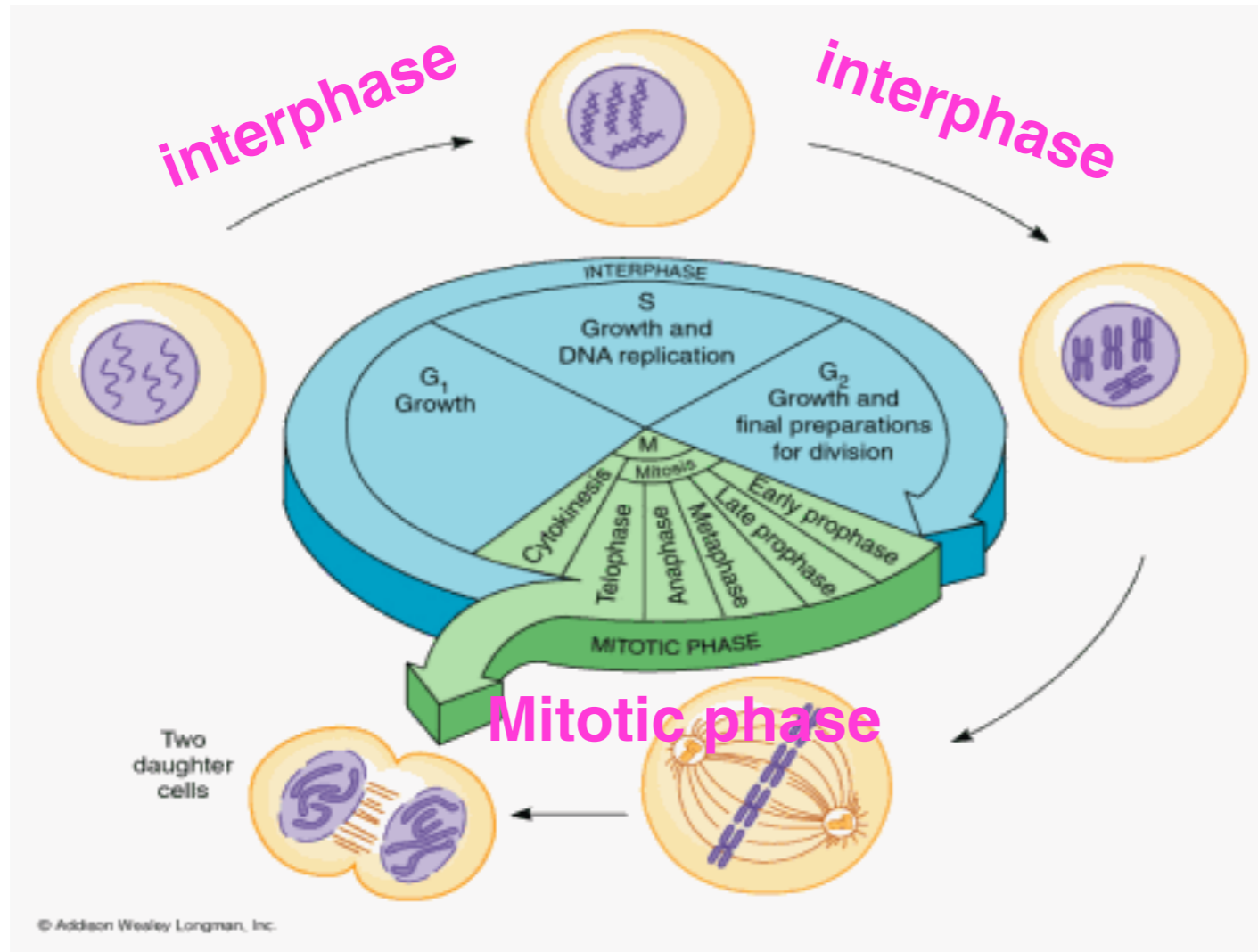


Polymer physics perspective on the chromatin inside cell nuclei



Changbong Hyeon

Korea Institute for Advanced Study

Outline

1. Chromosomes with **homopolymer models**

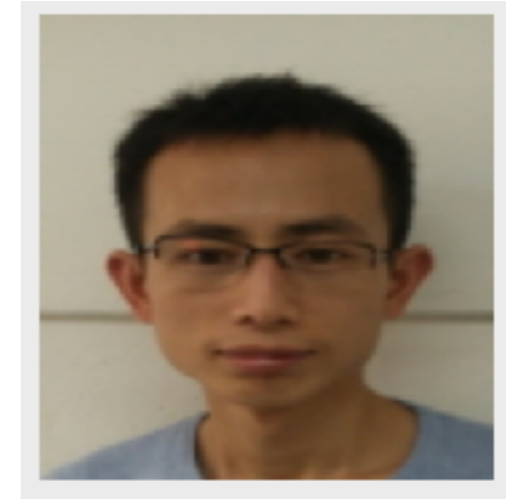
- Some basics of polymer physics.
- Equil./Crumpled globules, Chain organization (Random Walk, Space filling), Effects of confinement.

2. Chromosomes with **heteropolymer models**

- Chromosome structure from Hi-C (Heterogeneous loop model) - structure/function relationship
- Spatiotemporal dynamics of chromatin chain (with an emphasis on chromatin chain organization).

KIAS

- Lei Liu (→Zhejiang Univ. Sci. Tech.) →
- Ji Hyun Bak (→ UC Berkeley)
- Min Hyeok Kim (→ Samsung)

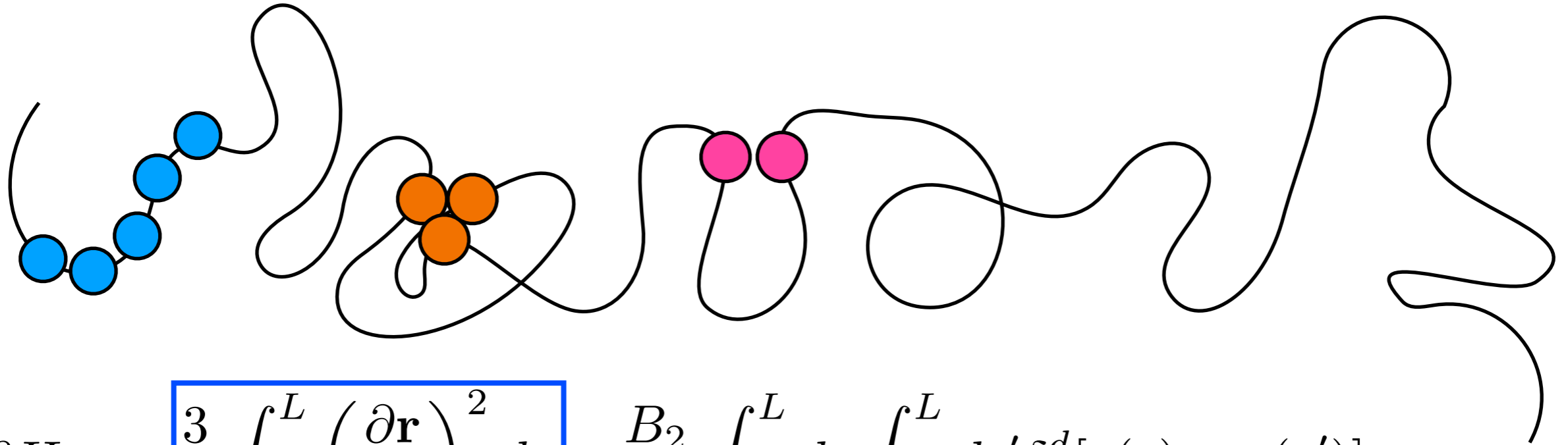


Collaborators in chromosome/polymer related projects

- Hongsuk Kang (NIST)
- Guang Shi (UT Austin)
- Dave Thirumalai (UT Austin)
- Fyl Pincus (UCSB)
- Bae-Yeun Ha (Waterloo Univ.)
- Youngkyun Jung (KISTI)

1. Chromosomes with Homopolymers

Some basics of polymer physics



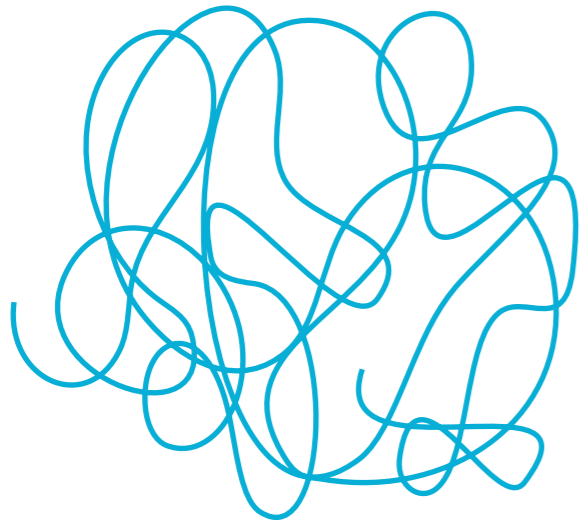
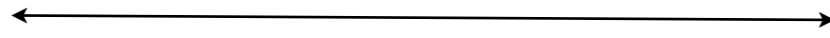
$$\begin{aligned}
 \beta H_{\text{eff}} = & \frac{3}{2} \int_0^L \left(\frac{\partial \mathbf{r}}{\partial s} \right)^2 ds + \frac{B_2}{2!} \int_0^L ds \int_0^L ds' \delta^d[\mathbf{r}(s) - \mathbf{r}(s')] \\
 & + \frac{B_3}{3!} \int_0^L ds \int_0^L ds' \int_0^L ds'' \delta^d[\mathbf{r}(s) - \mathbf{r}(s')] \delta^d[\mathbf{r}(s') - \mathbf{r}(s'')] + \dots
 \end{aligned}$$

$$\frac{3}{2a^2} \sum_{i=1}^{N-1} ((\mathbf{r}_{i+1} - \mathbf{r}_i)^2 - a^2)$$

Good ($T > \Theta$)

$T = \Theta$

poor ($T < \Theta$)



$$= \frac{1}{2} \int d^d r (1 - e^{-\beta u(r)}) \sim a^3 \left(1 - \frac{\Theta}{T} \right)$$

$$\beta H_{\text{eff}} = \frac{3}{2} \int_0^L \left(\frac{\partial \mathbf{r}}{\partial s} \right)^2 ds + \frac{B_2}{2!} \int_0^L ds \int_0^L ds' \delta^d[\mathbf{r}(s) - \mathbf{r}(s')] + \frac{B_3}{3!} \int_0^L ds \int_0^L ds' \int_0^L ds'' \delta^d[\mathbf{r}(s) - \mathbf{r}(s')] \delta^d[\mathbf{r}(s') - \mathbf{r}(s'')] + \dots$$

$$c(\mathbf{R}) = \int_0^L ds \delta^d[\mathbf{r}(s) - \mathbf{R}] = \int d^d \mathbf{R} \int_0^L ds \delta^d[\mathbf{r}(s) - \mathbf{R}] \int_0^L ds' \delta^d[\mathbf{r}(s') - \mathbf{R}] = \int d^d \mathbf{R} c^2(\mathbf{R})$$

$$\beta H_{\text{eff}} = \frac{3}{2} \int_0^L \left(\frac{\partial \mathbf{r}}{\partial s} \right)^2 ds + \frac{B_2}{2!} \int d^d R c^2(R) + \frac{B_3}{3!} \int d^d R c^3(R) + \dots$$

$$Z = e^{-\beta F} = \int \mathcal{D}[\mathbf{r}(s)] e^{-\beta H_{\text{eff}}} \sim \langle e^{-\beta H_{\text{eff}}} \rangle \geq e^{-\beta \langle H_{\text{eff}} \rangle},$$

$$\beta F \leq \beta \langle H_{\text{eff}} \rangle$$

$$\beta F \leq \beta \langle H_{\text{eff}} \rangle$$

$$= \frac{3}{2} \left\langle \int_0^L \left(\frac{\partial \mathbf{r}}{\partial s} \right)^2 ds \right\rangle + \frac{B_2}{2!} \int d^d R \langle c^2(R) \rangle + \frac{B_3}{3!} \int d^d R \langle c^3(R) \rangle + \dots$$

$$\approx \frac{3}{2} \left(\frac{R^2}{Na^2} \right) + \frac{B_2}{2!} \langle c \rangle^2 R^d + \frac{B_3}{3!} \langle c \rangle^3 R^d + \dots \quad \langle c^n \rangle \approx \langle c \rangle^n$$

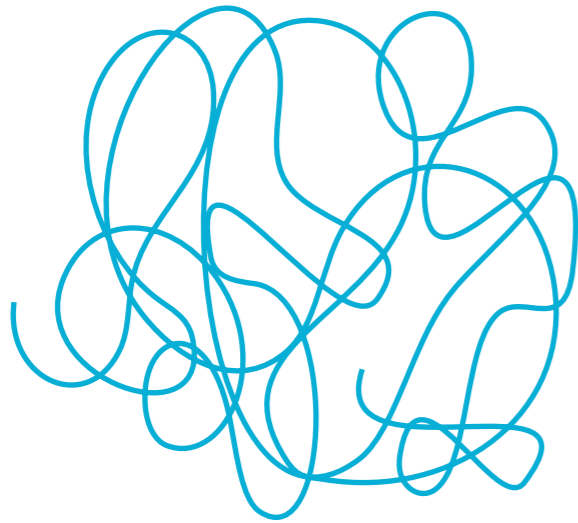
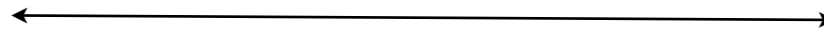
$$= \frac{3}{2} \left(\frac{R^2}{Na^2} \right) + \frac{B_2}{2!} \frac{N^2}{R^d} + \frac{B_3}{3!} \frac{N^3}{R^{2d}} + \dots \quad \langle c \rangle = \frac{N}{R^d}$$

Flory free energy

Good ($T > \Theta$)

$T = \Theta$

poor ($T < \Theta$)



$$\underline{R_F \sim N^{3/5}}$$

$$R_F \sim N^{1/2}$$

$$R_F \sim N^{1/3}$$

Flory argument

$$\beta F(R) \sim \frac{3R^2}{2Na^2} + \frac{B_2}{2} \left(\frac{N}{R^d} \right)^2 R^d$$

$$R_F^{d+2} \sim a^{d+2} N^3$$

$$R_F \sim a N^{\frac{3}{d+2}}$$

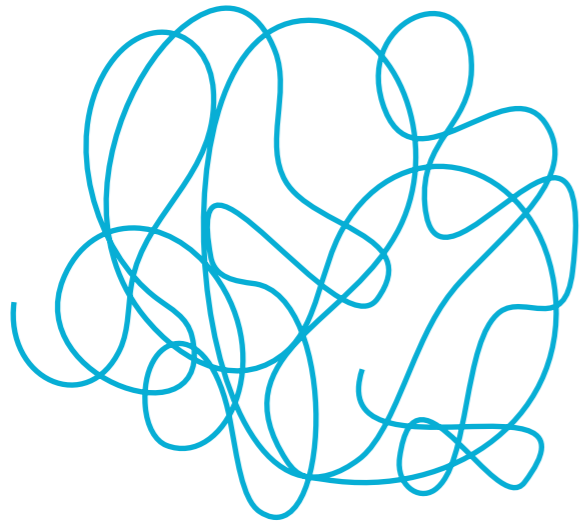
$$R_F \sim a N^{3/5} \quad (d=3)$$

$$R_F \sim a N^{3/4} \quad (d=2)$$

$$R_F \sim a N \quad (d=1)$$

Good ($T > \Theta$)

$d=3$



$$R_F \simeq aN^{3/5}$$

$$\langle c \rangle \sim \frac{N}{R_F^3} \sim N^{-4/5}$$

$$\beta F(R) \sim \underbrace{\frac{3R^2}{2Na^2}}_{\sim N^{1/5}} + \underbrace{\frac{B_2^{\nearrow 0}}{2} \langle c \rangle^2 R^3}_{\sim N^{1/5}} + \underbrace{\frac{B_3^{\nearrow 0}}{6} \langle c \rangle^3 R^3}_{\sim N^{-3/5}} + \dots$$

T=Θ



$$R_F \simeq aN^{1/2}$$

d=3

$$\langle c \rangle \sim \frac{N}{R_F^3} \sim N^{-1/2}$$

$$\beta F(R) \sim \frac{3R^2}{2Na^2} + \frac{\cancel{B_2}^0}{2} \langle c \rangle^2 R^3 + \frac{B_3}{6} \langle c \rangle^3 R^3 + \dots$$

$\sim \mathcal{O}(1)$ $\sim \mathcal{O}(1)$

Θ-chain in 3D (Duplantier 1982)

$$\frac{R_0^2}{Na^2} \sim A_0(y) \left(1 - \frac{493\pi}{33 \times 4} \frac{y}{1 + 44\pi y \log N} \right)$$

where $A_0(y) = 1 + \frac{16}{33}\pi y + \dots$ with $y = (2\pi)^{-3} B_3$.³⁴

d=3

poor ($T < \Theta$)



$$R_F \simeq aN^{1/3}$$

$$\langle c \rangle \sim \frac{N}{R_F^3} \sim \mathcal{O}(1)$$

$$\beta F(R) \sim \frac{3R^2}{2Na^2} + \frac{B_2^{\lt 0}}{2} \langle c \rangle^2 R^3 + \frac{B_3^{\gt 0}}{6} \langle c \rangle^3 R^3 + \dots$$

$\sim N^{-1/3} \quad \sim N^1 \quad \sim N^1 \quad \sim N^1$

$$\langle c \rangle \simeq -\frac{B_2}{B_3}$$

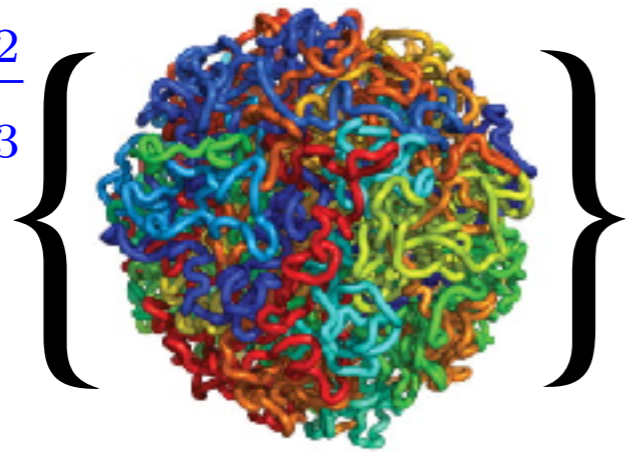


$$T < \Theta$$

(poor solvent w/ nonspecific interactions)

Well mixed,
high entropy,

$$\langle c \rangle_{eq} \simeq -\frac{B_2}{B_3}$$



equilibrium globule

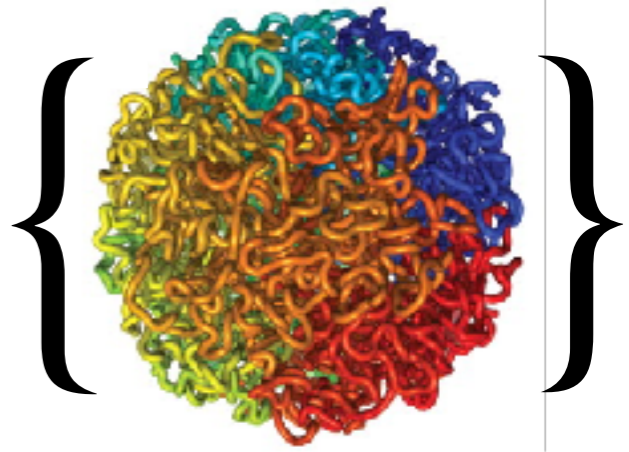
$$T \lesssim \Theta$$

?

topological relaxation

$$R_g \sim N^{1/3}$$

territorial,
low entropy,
non-equilibrium
metastable



Crumpled globule

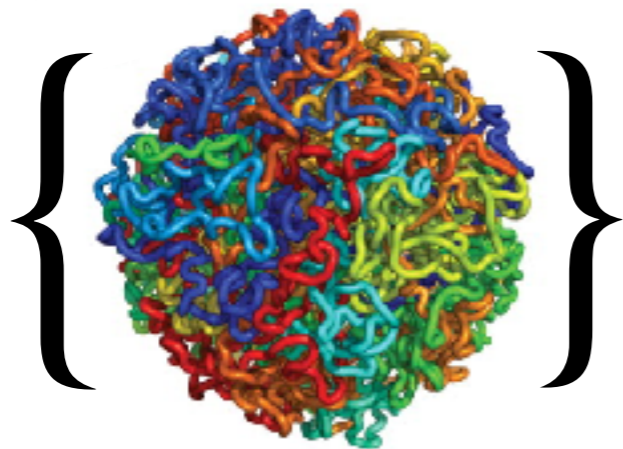
$$\langle c \rangle_{crumpled} \simeq -\frac{B_2}{B_3} \left(\frac{1}{1 + \frac{1}{N_e} \frac{a^6}{B_3}} \right)$$

Grosberg et al.. J. Phys. France (1988) 49, 2095

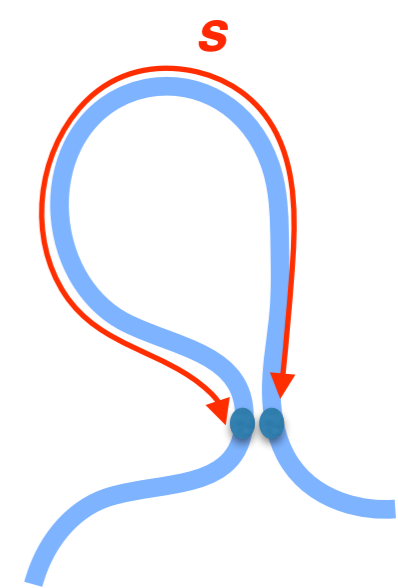
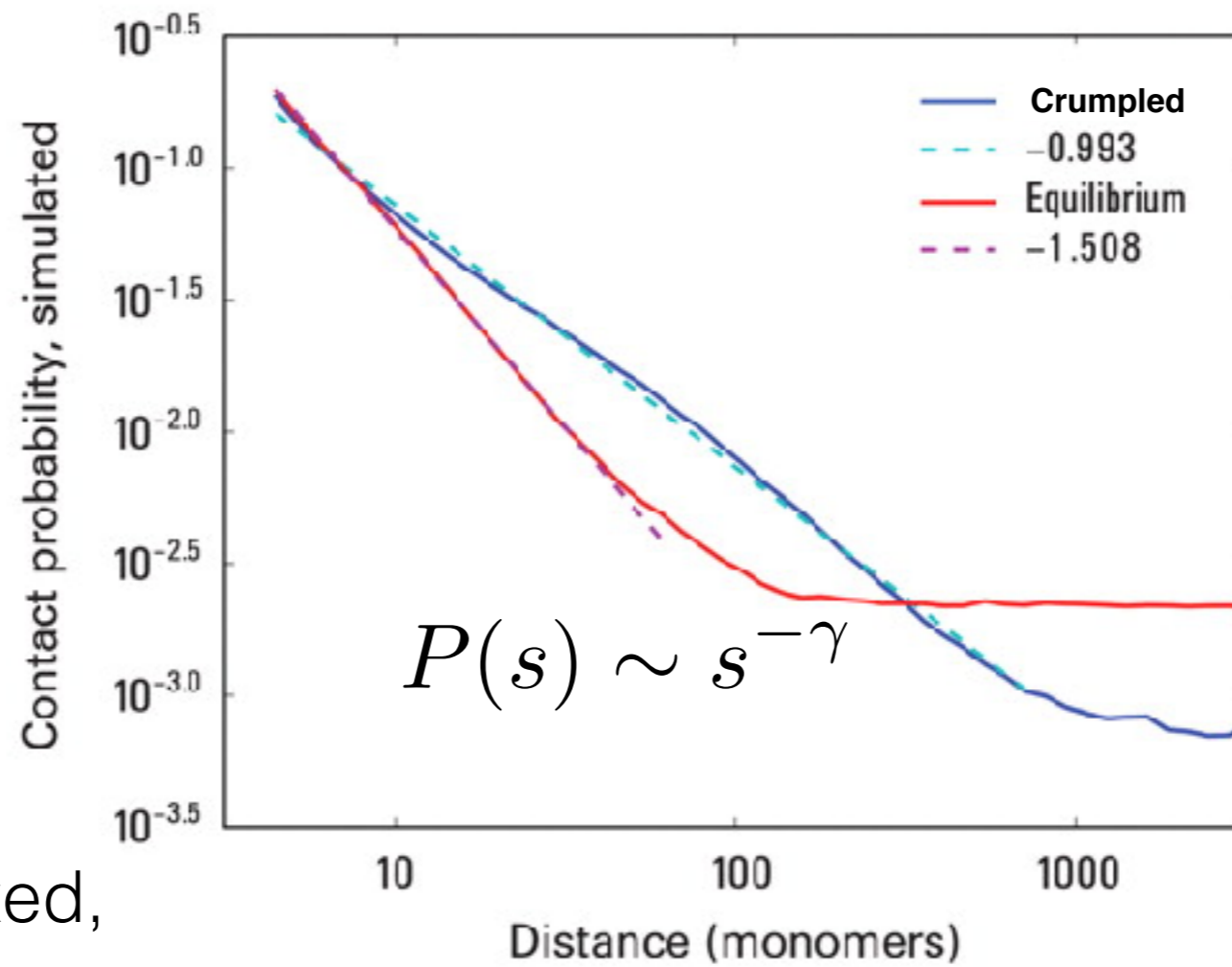
Lieberman-Aiden et al. *Science* (2009) 326, 289

$$\gamma = 1.5$$

Well mixed,
high entropy,

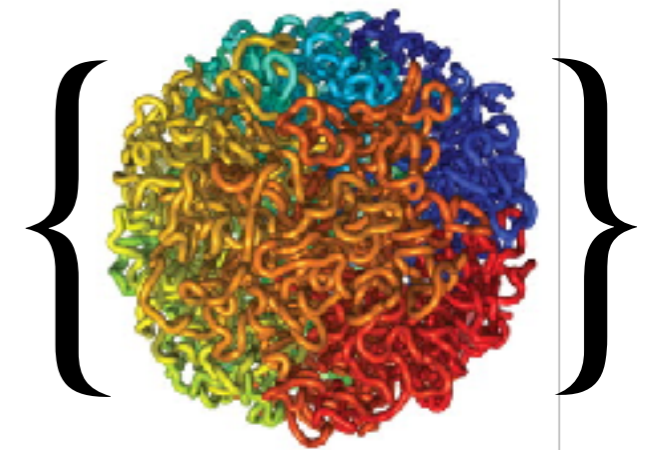


equilibrium globule



$$\gamma = 1$$

territorial,
low entropy,
non-equilibrium
metastable



Crumpled globule

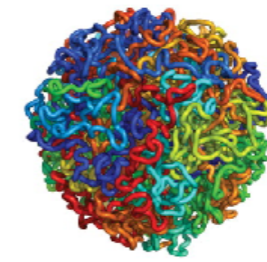
Grosberg et al.. J. Phys. France (1988) 49, 2095

Lieberman-Aiden et al. *Science* (2009) 326, 289

$$P(s) \sim s^{-3/2}$$

Yeast

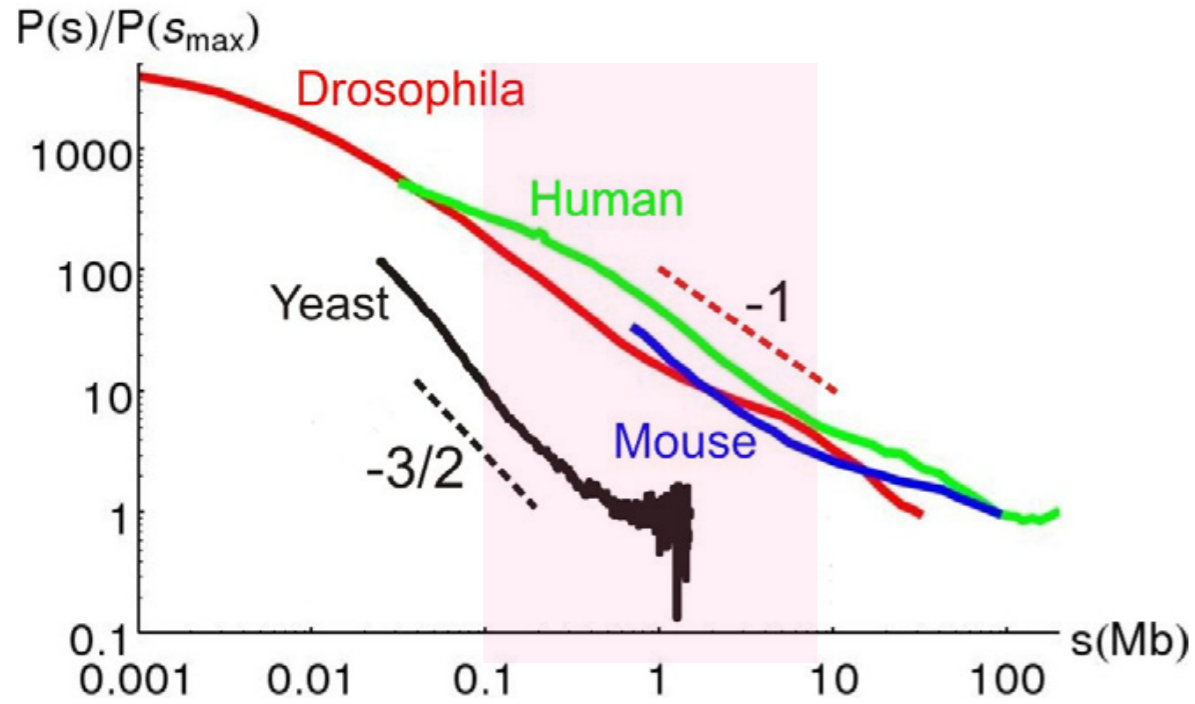
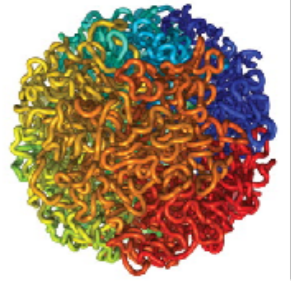
Stem cells



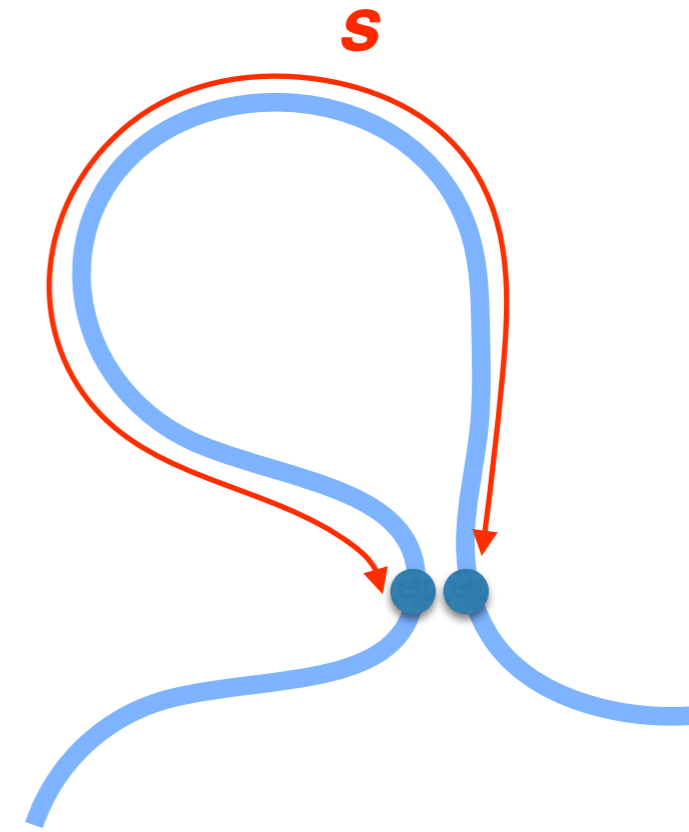
$$P(s) \sim s^{-1}$$

Drosophila, Mouse, Human

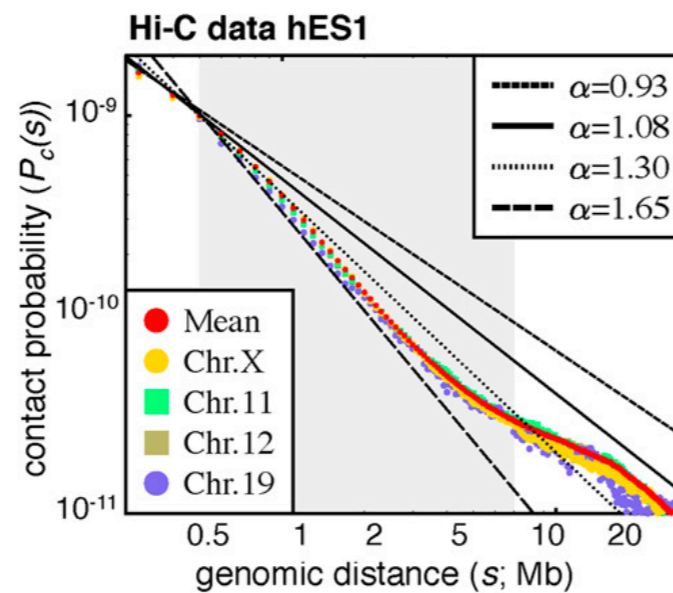
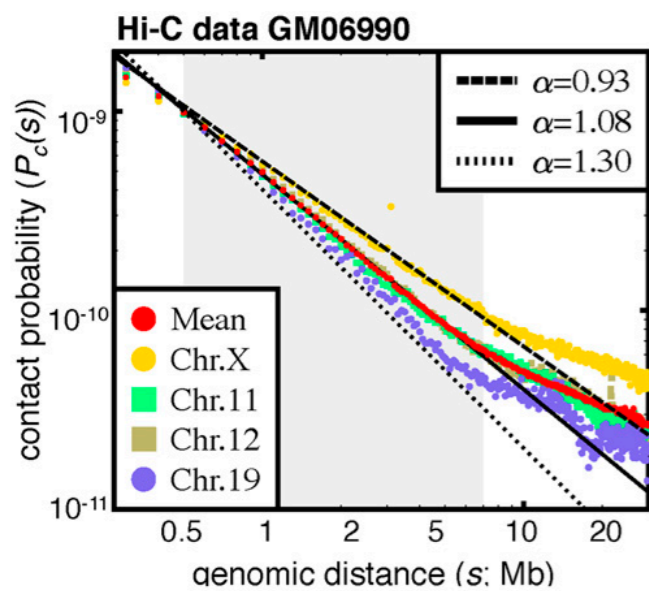
Mature cells



Halverson et al. Rep. Prog. Phys. 77, 022601 (2014).

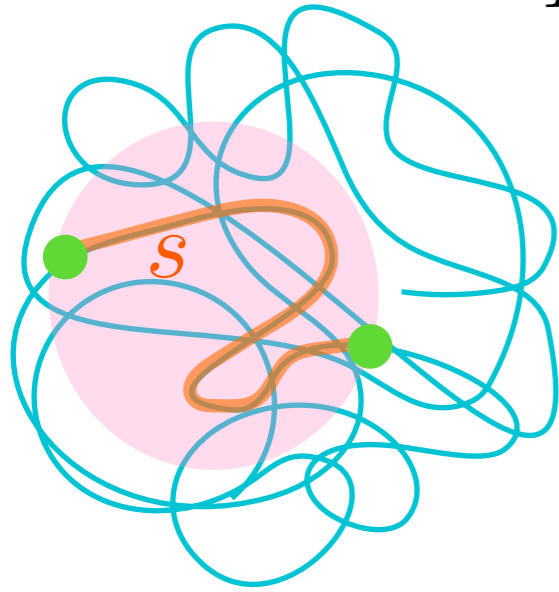


$$P(s) \sim s^{-\gamma}$$



Barbieri et al. PNAS (2012)

$$V(s) \sim R(s)^3$$



$$P(s) \sim \frac{1}{V(s)}$$

$$\sim \frac{1}{R(s)^3} \sim s^{-3\nu}$$

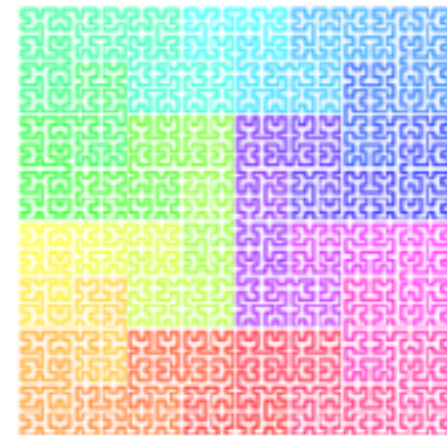
$$R(s) \sim s^{1/2} \longrightarrow P(s) \sim s^{-3/2}$$

random walk ($\nu=1/2$)



$$R(s) \sim s^{1/3} \longrightarrow P(s) \sim s^{-1}$$

Space-Filling ($\nu=1/3$)



Halverson et al. Rep. Prog. Phys. 77, 022601 (2014).

Liu & Hyeon Biophys. J. 110, 2320 (2016).

Flory theorem :

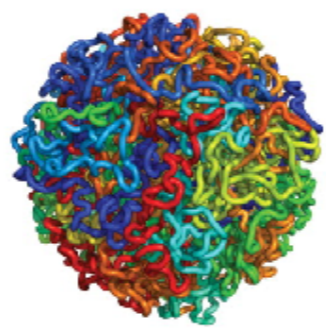


A test (linear) polymer in a “fully equilibrated” homogeneous semi-dilute or concentrated polymer melt, or even in compact globule is expected to be *ideal*, obeying the ideal chain statistics ($\langle R^2 \rangle \sim s$), because of the screening of excluded volume interaction or the compensation between attraction and repulsion.

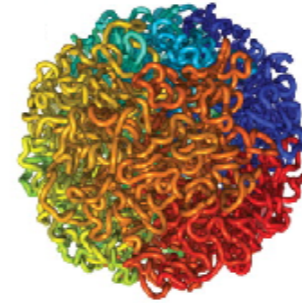
P. J. Flory, J. Chem. Phys. 17, 303 (1949)

Grosberg and Khokhlov, Statistical Physics of Macromolecules (AIP Press, 1994).

Physical Origin ?

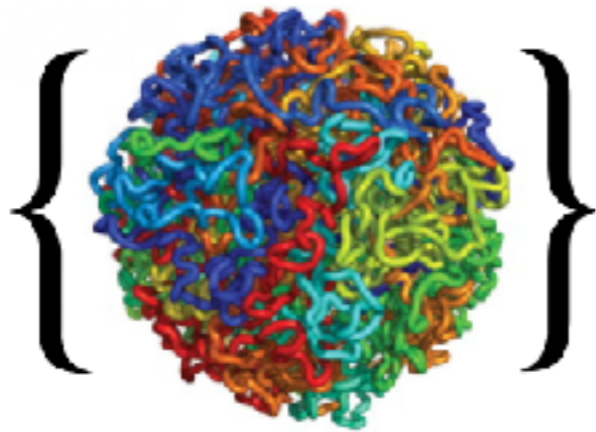


$$\nu = 1/2$$

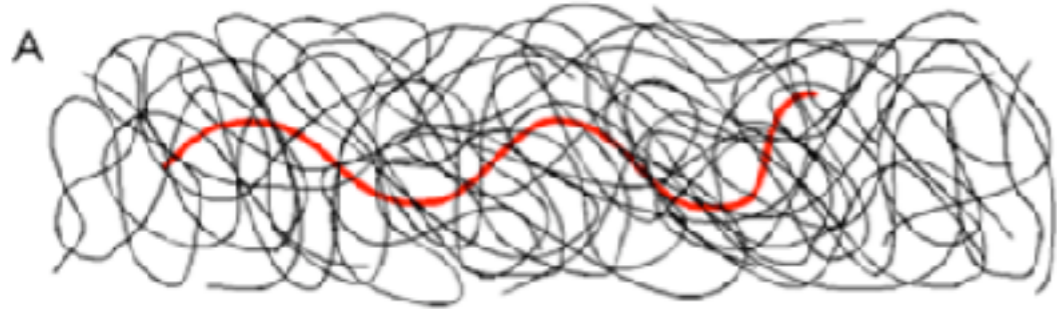
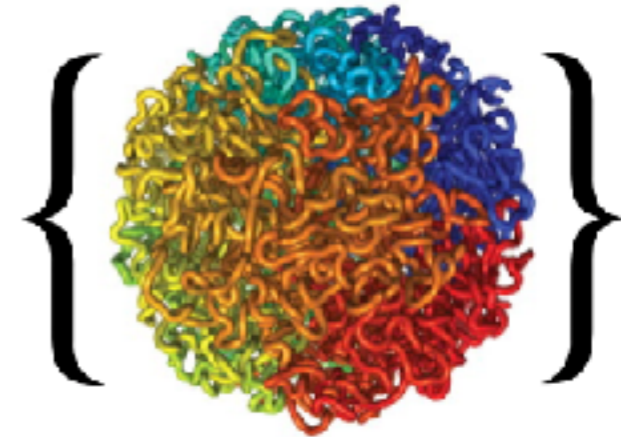


$$\nu = 1/3$$

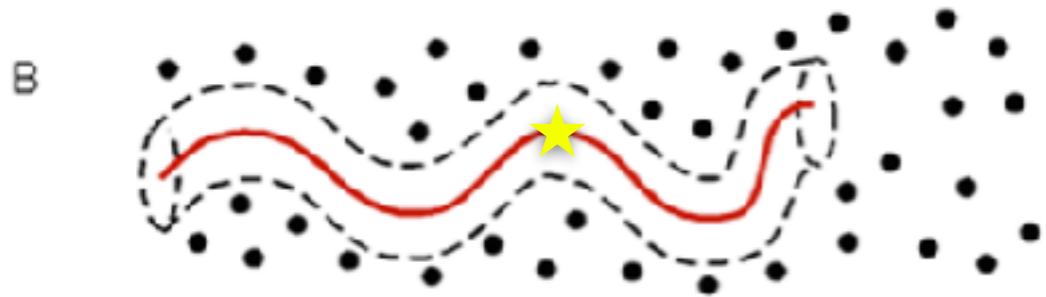
Human
Mouse
Drosophila



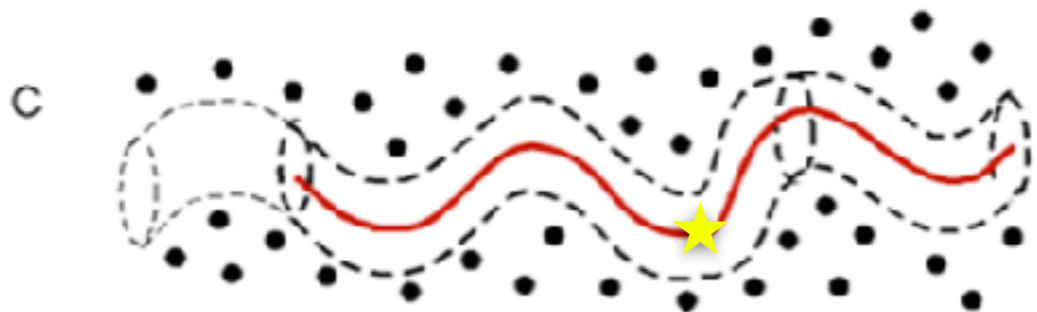
←
topological relaxation



$$\tau_{eq} \sim \tau_{rep}$$

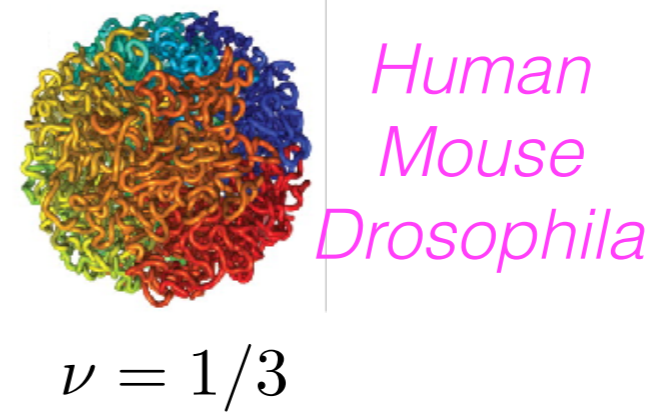
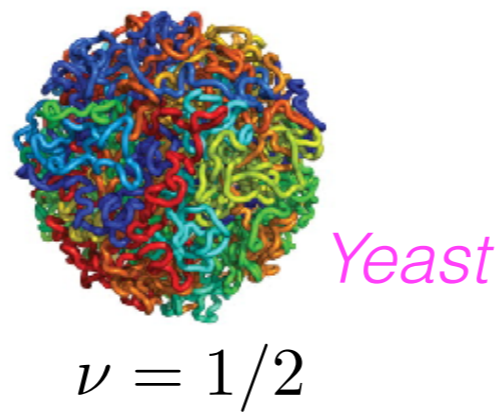


$$\tau_{rep} \sim \frac{\langle R^2 \rangle}{D_{cm}} \sim \frac{N^2}{D_o/N} \sim N^3$$



$$\tau_{rep} \sim N^{3.4}$$

Physical Origin ?



Reptation time

$$\tau_{\text{rep}} \sim N^{3.4}$$

$$N_{\text{yeast}} = 10^8 \text{ bp}$$

$$N_{\text{human}} = 6 \times 10^9 \text{ bp}$$

$$\tau_{\text{rep}}^{\text{human}} \sim 10^6 \times \tau_{\text{rep}}^{\text{yeast}}$$

$$\tau_{\text{rep}} \sim \tau_{\text{eq}}$$

$$\tau_{\text{eq}} \ll \tau_{\text{cell}} \quad : \text{equilibrium}$$

$$\tau_{\text{eq}} \gg \tau_{\text{cell}} \quad : \text{non-equilibrium}$$

Cell cycle time

$$\tau_{\text{cell}}$$

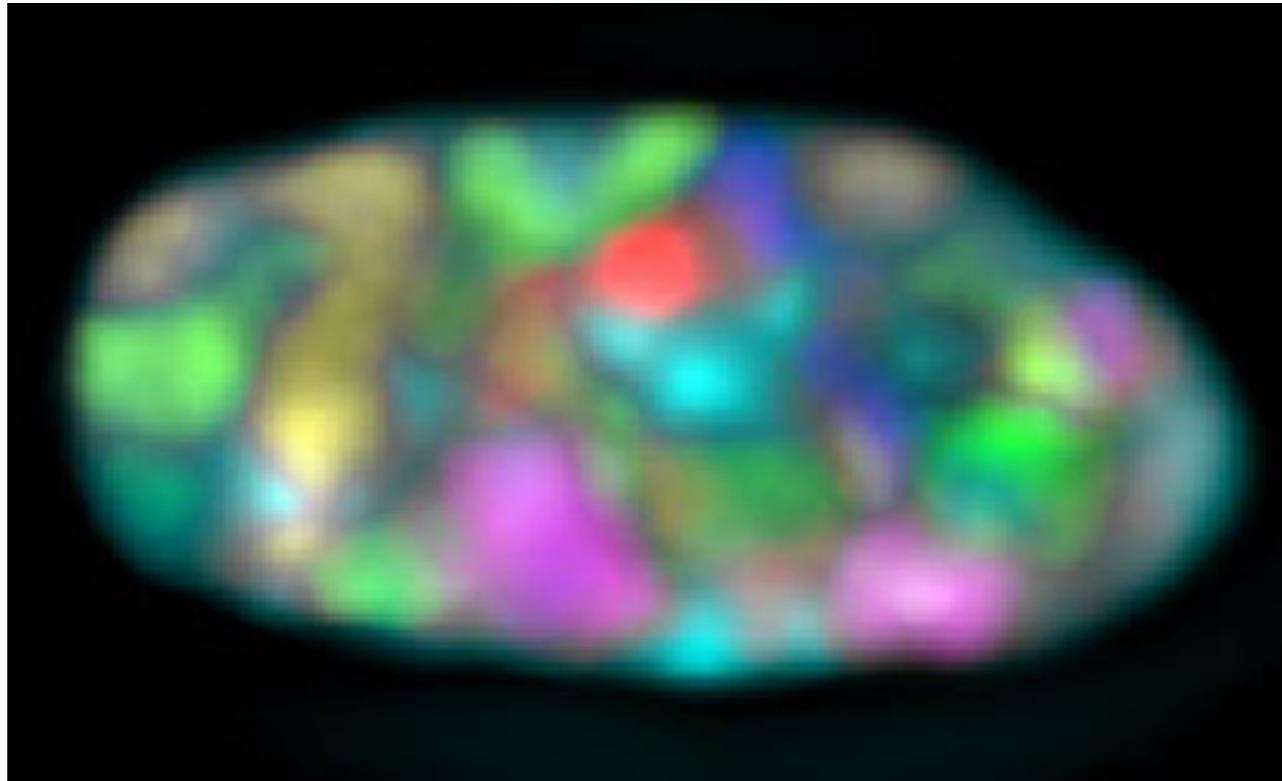
~ 140 min ~ 2 hrs (yeast)

~ 24 hrs (eukaryotes, human)

Grosberg, Nechaev, Shakhnovich.
J. Phys. France (1988)

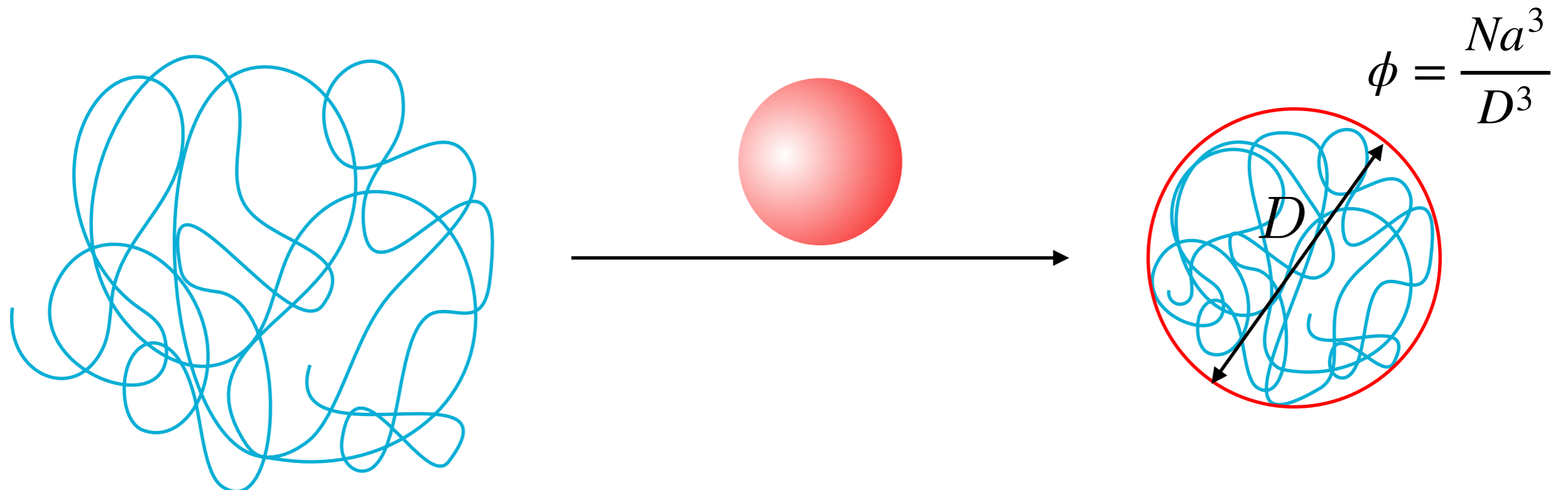
Rosa & Everaers,
PLoS Comp Biol (2008)

$$\tau_d \approx \tau_e (L_c/L_e)^3 \approx 500 \text{ yrs}$$



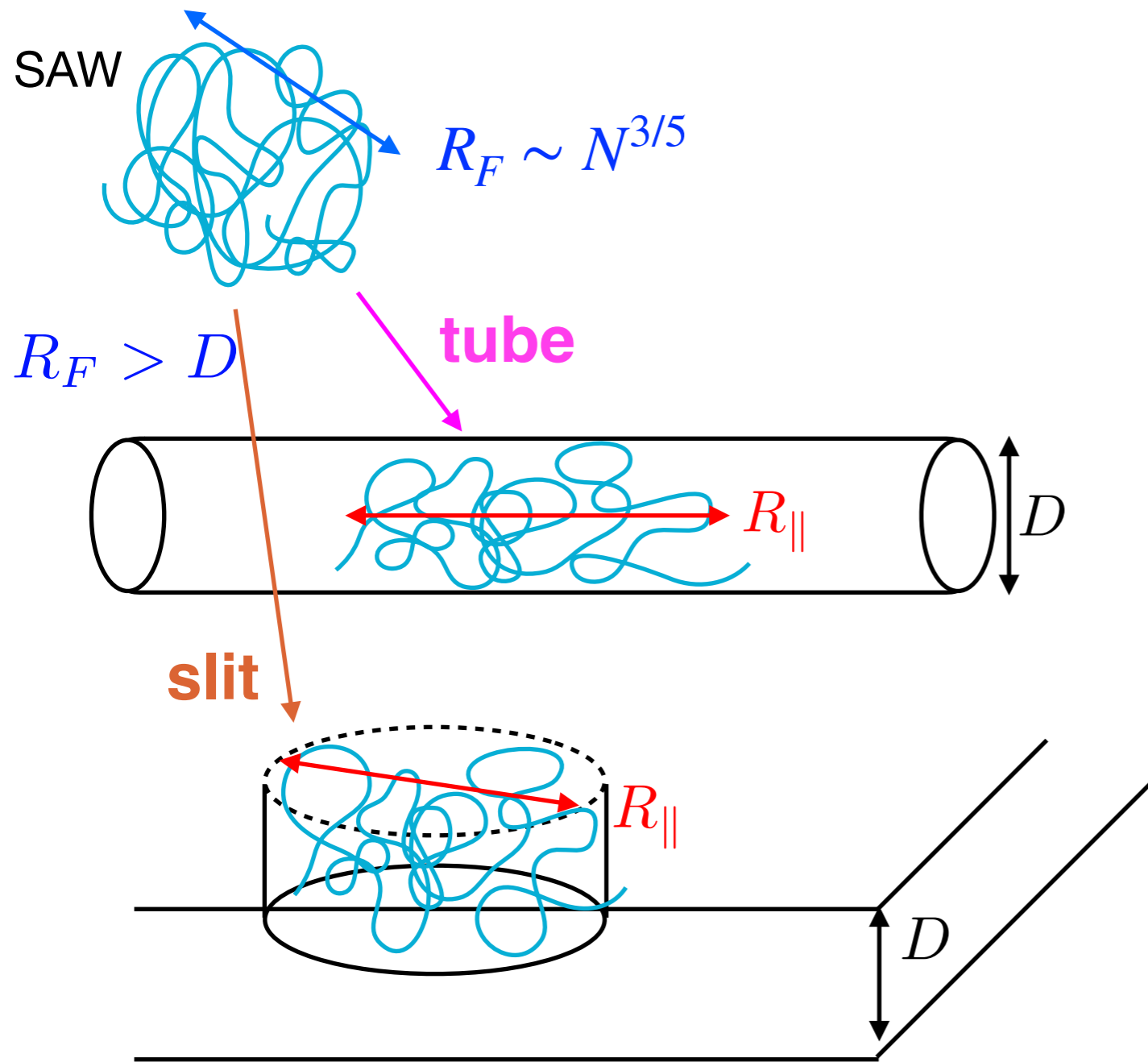
Cremer, Cremer, Nat. Rev. Genet. 2, 292 (2001).

Chromosomes are confined in space ...



Polymers in confinement

$$\beta F(R) \sim \frac{3R^2}{2Na^2} + \frac{B_2}{2} \left(\frac{N}{R^d} \right)^2 R^d + \frac{B_3}{6} \left(\frac{N}{R^d} \right)^3 R^d + \dots$$



$$R^d \rightarrow R_{||} D^2 \text{ (tube)}$$

$$R_{||} \simeq aN \left(\frac{a}{D} \right)^{2/3}$$

$$\rho_{tube} \sim \frac{N}{R_{||} D^2} \sim \text{const}$$

$$R^d \rightarrow R_{||}^2 D \text{ (slit)}$$

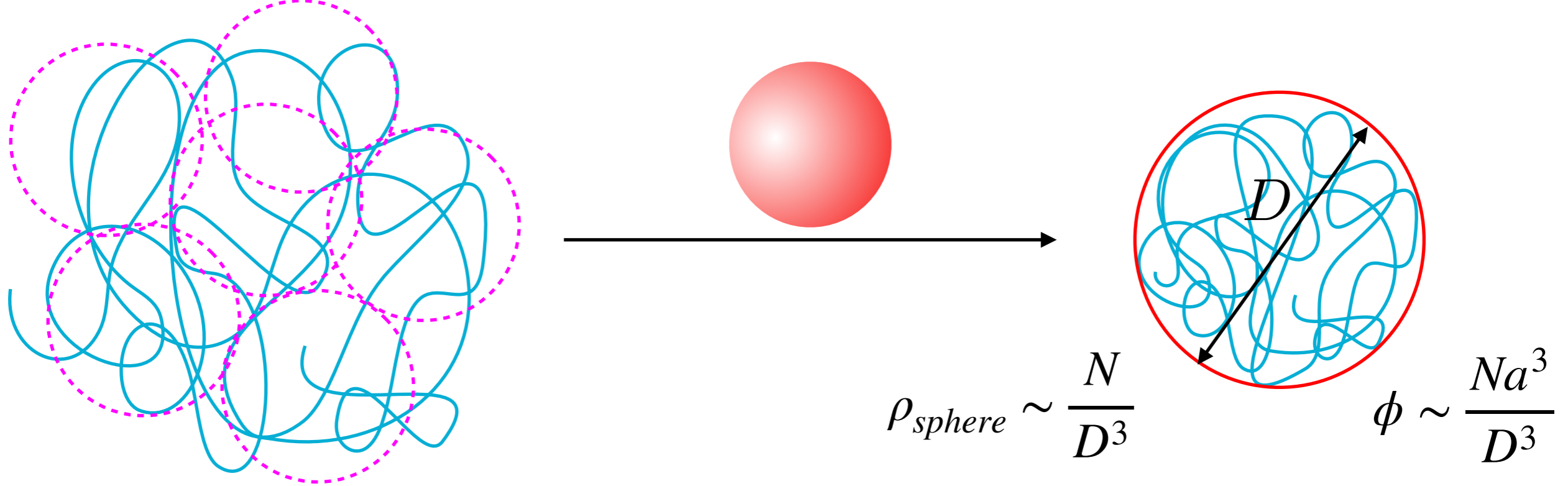
$$R_{||} \simeq aN^{3/4} \left(\frac{a}{D} \right)^{1/4}$$

$$\rho_{slit} \sim \frac{N}{R_{||}^2 D} \sim N^{-1/2}$$

$$R_{||} \sim R_F f(R_F/D) \sim N \text{ or } N^{3/4}$$

Confinement free energy

$$\Delta F/k_B T \sim \left(\frac{R_F}{D} \right)^{1/\nu} \sim N \left(\frac{a}{D} \right)^{1/\nu}$$



Osmotic pressure above semi-dilute condition

$c^* < c \ll 1$ [$c^* \sim N/R^3 \sim N^{1-3\nu}$] (overlap concentration)

$$\frac{\pi}{T} \sim \frac{c}{N} f\left(\frac{c}{c^*}\right) \sim \frac{c}{N} \left(\frac{c}{N^{1-3\nu}}\right)^m \sim N^0$$

$$\rho_{tube} \sim \frac{N}{R_{\parallel} D^2} \sim \text{const}$$

$$\rho_{slit} \sim \frac{N}{R_{\parallel}^2 D} \sim N^{-1/2}$$

$$\rho_{sphere} \sim \frac{N}{D^3}$$

$$\frac{\pi a^3}{T} \sim \phi^{\frac{3\nu}{3\nu-1}}$$

$$\pi \sim \phi^{9/4} \text{ (with } \nu = 3/5)$$

$$\pi = - \left(\frac{\partial F}{\partial V} \right)_{N,T} = \frac{\phi^2}{Na^3} \left(\frac{\partial F}{\partial \phi} \right)_{N,T}$$

$\xrightarrow{\phi = \frac{Na^3}{V}}$

$$\beta \Delta F \sim N \int \frac{\pi}{\phi^2} d\phi \sim N \phi^{\frac{1}{3\nu-1}}$$

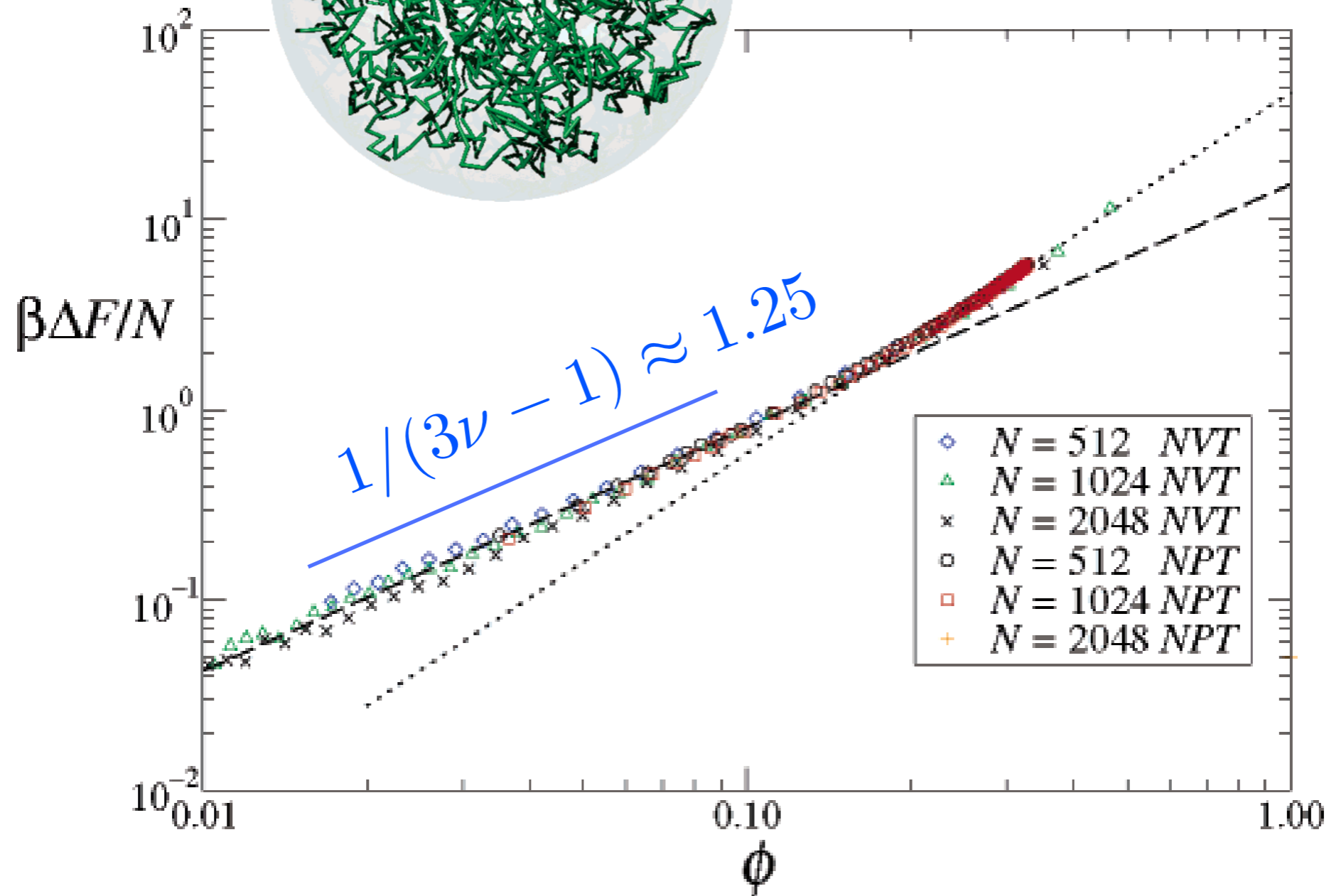
$$\sim \left(\frac{aN^\nu}{D} \right)^{\frac{3}{3\nu-1}} \approx \left(\frac{R_F}{D} \right)^{\frac{3}{3\nu-1}}$$

$$\text{cf. } \beta \Delta F \sim \left(\frac{R_F}{D} \right)^{1/\nu}$$

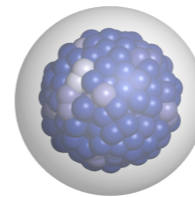
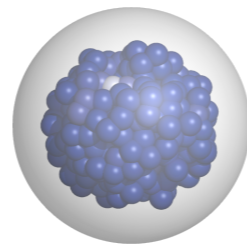
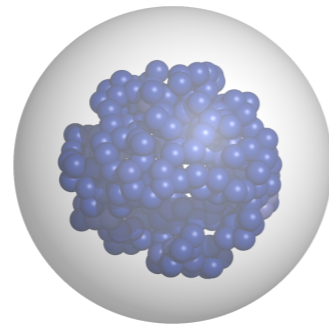
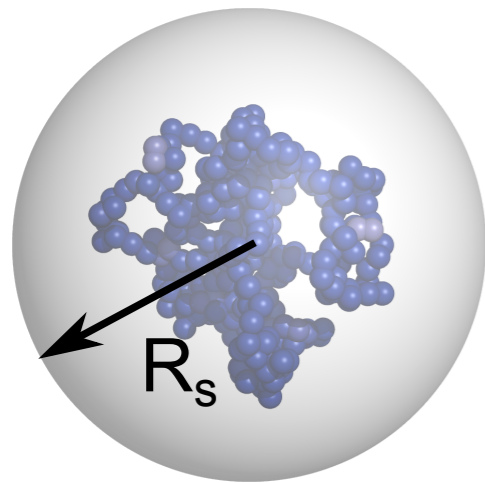
(tube, slit)

(sphere)

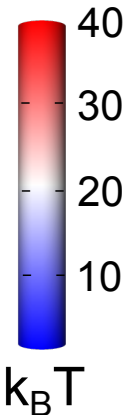
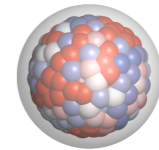
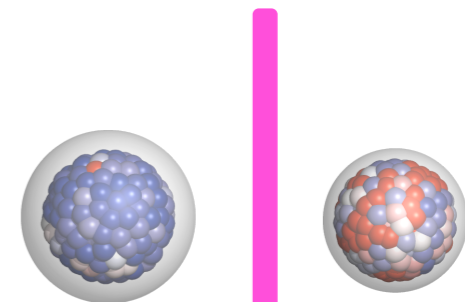
$$\beta\Delta F \sim N\phi^{\frac{1}{3\nu-1}}$$



A self-avoiding homopolymer confined inside a spherical shell with varying sizes.



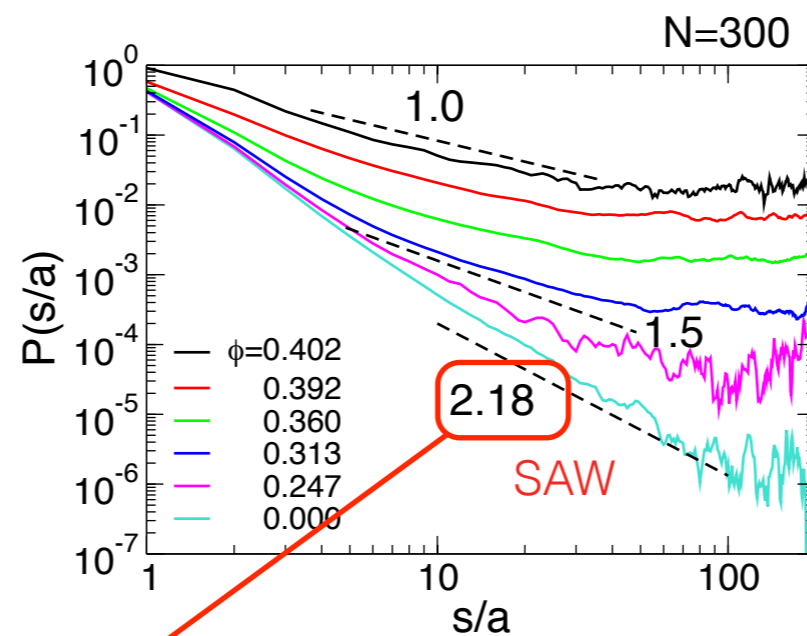
$$\phi_c \sim 0.4$$



$$\tau_\alpha(\phi; N) = \tau_0(N) [\phi_c(N) - \phi]^{-\nu_\tau}$$

$$\phi = \left(\frac{R_g}{R_s} \right)^3$$

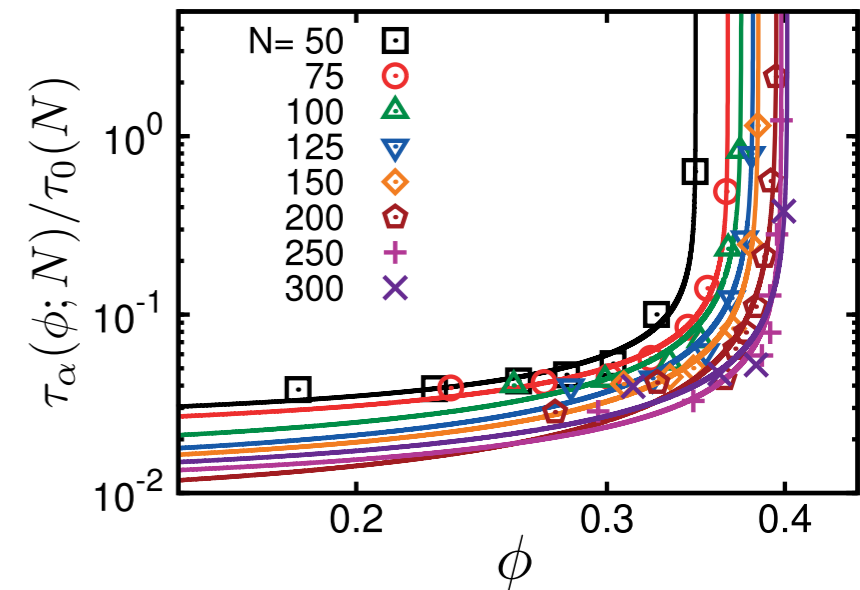
volume fraction



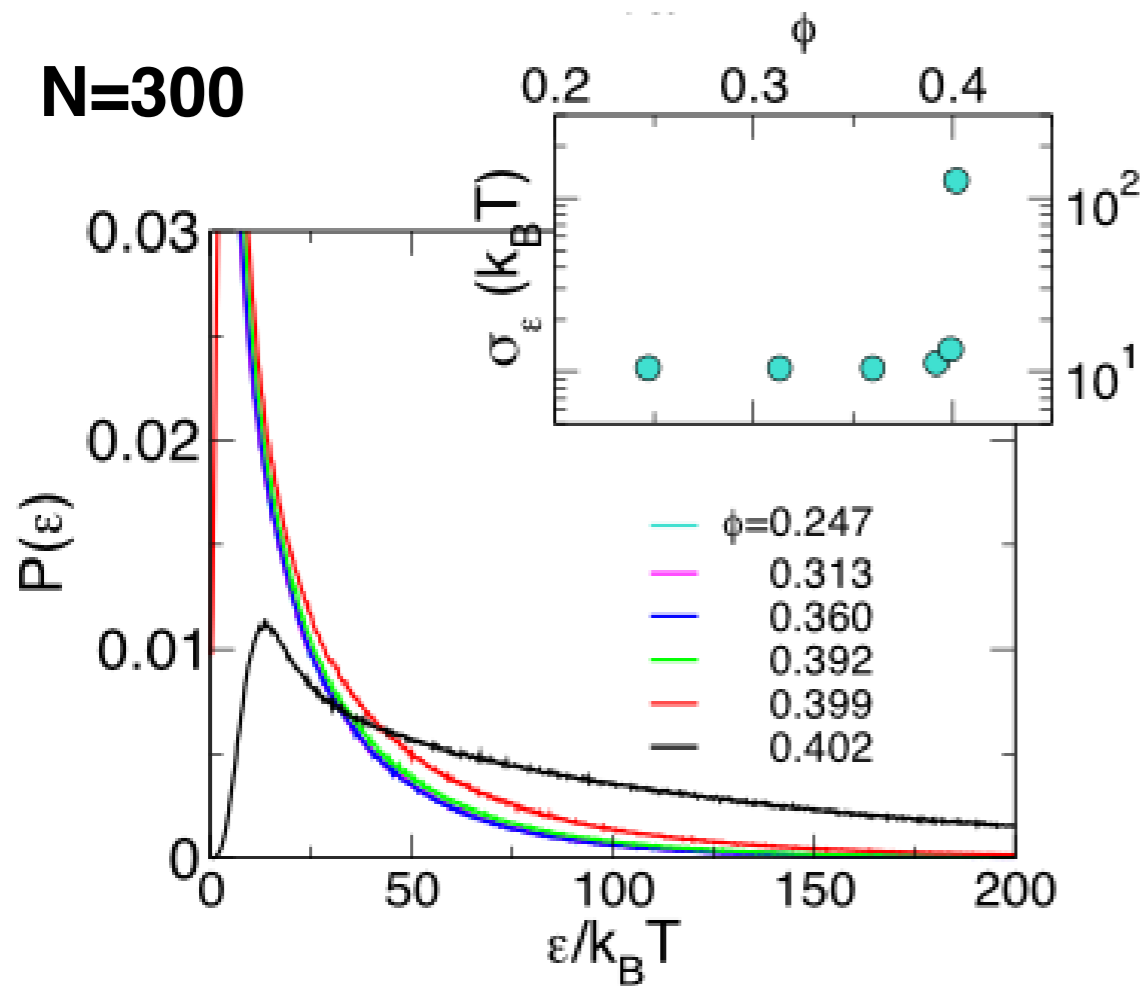
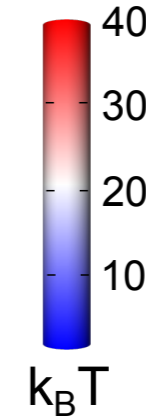
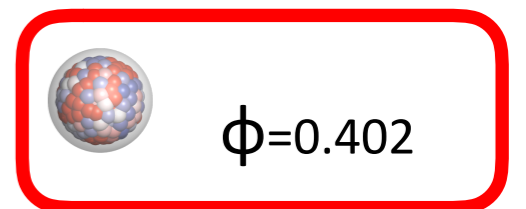
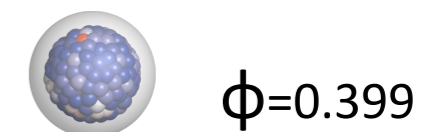
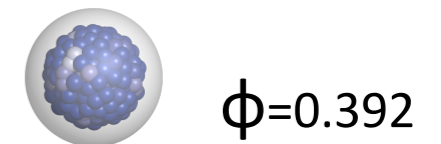
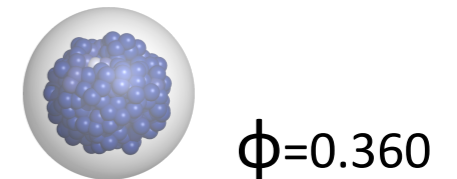
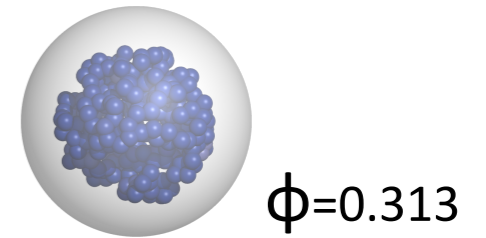
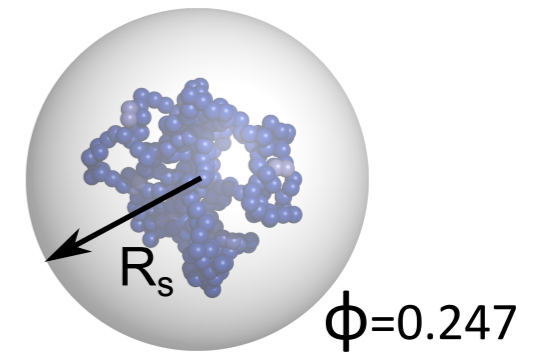
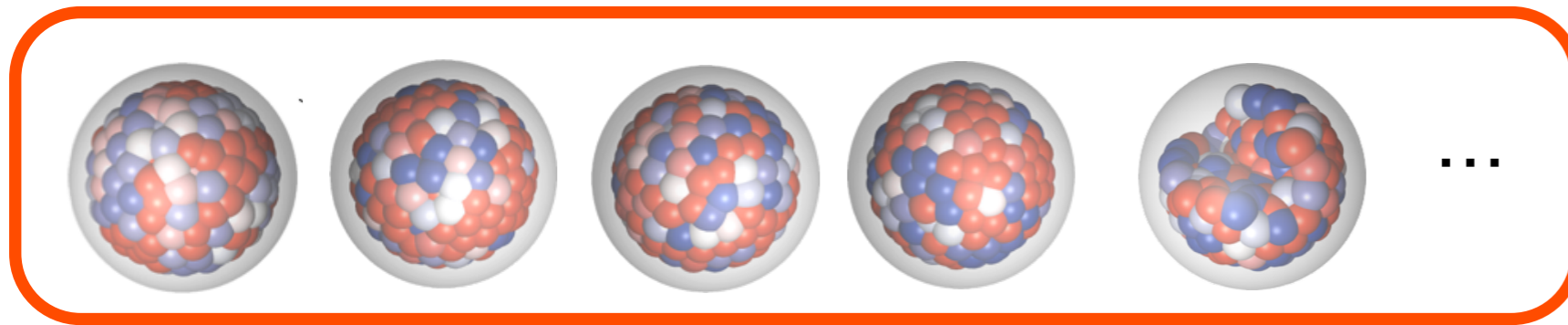
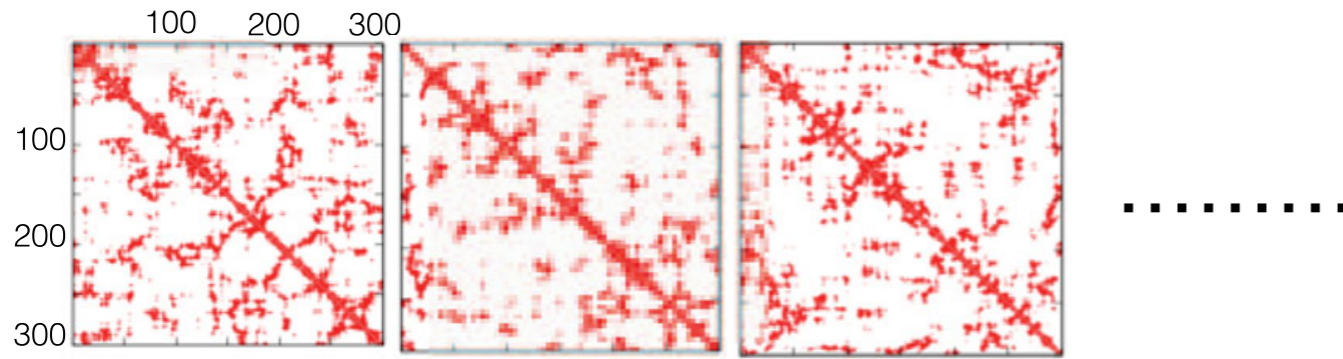
des Cloizeaux J. Phys. (1980) 41, 223

$$P(s) \sim s^{-(d+\theta_2)\nu}$$

$$d = 3, \theta_2 = 0.71, \nu = 0.588$$



Kang et al. Phys. Rev. Lett. (2015) 115, 198102

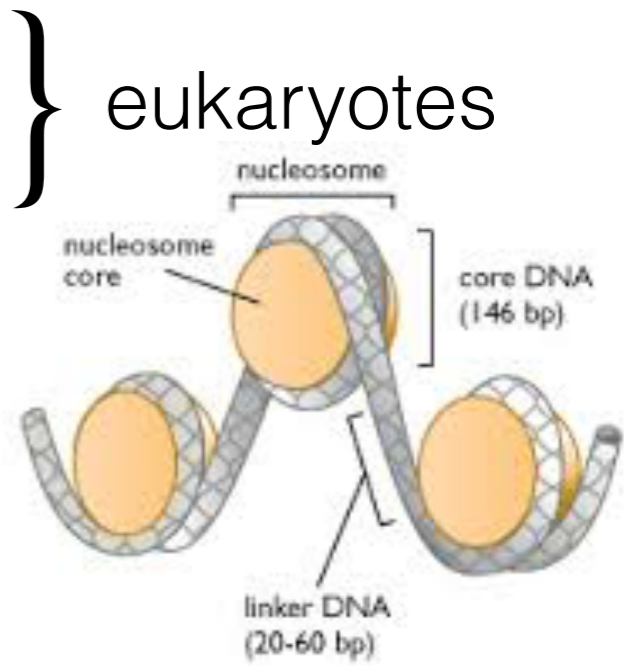
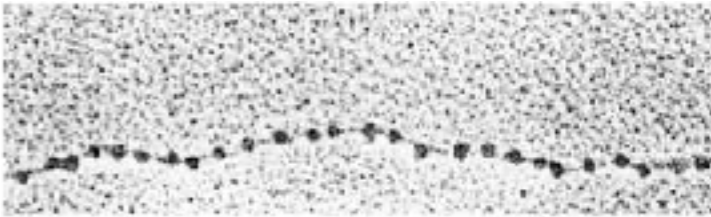


Distribution of monomer energy

Spatial heterogeneity
glassy, glassy, glassy ... !!

Implication to genome organization in different organisms

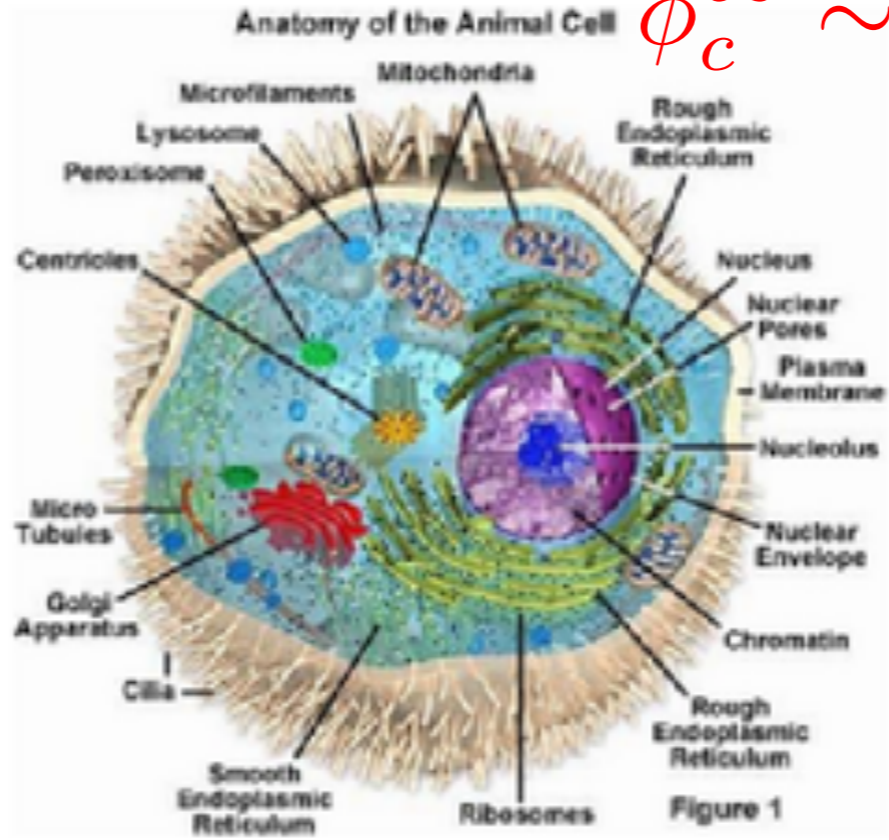
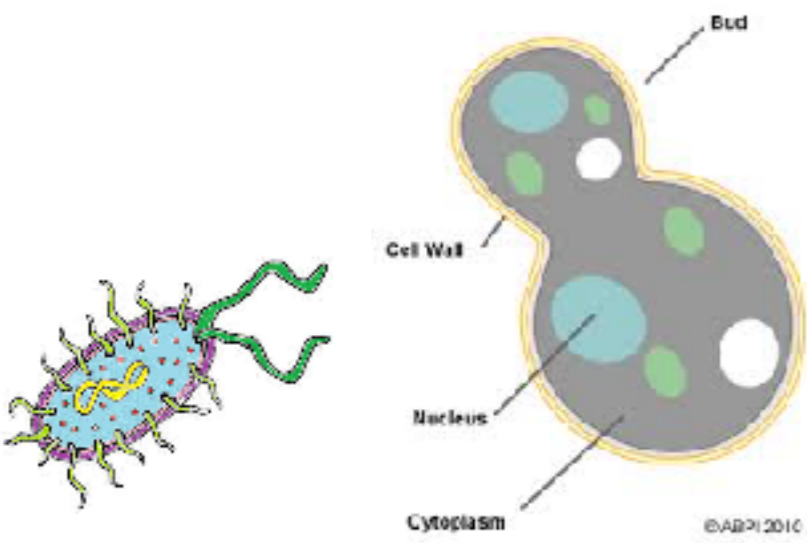
	N	V (nuclear vol.)	ϕ (vol. frac.)
bacteria	10^6 bp	$1 \mu\text{m}^3$	~ 0.001
yeast	10^8 bp	$4 \mu\text{m}^3$	~ 0.12
human	$2 \times (3 \times 10^9)$ bp	$60-100 \mu\text{m}^3$	$0.3-0.5$
virus	$< 10^5$ bp	$\sim 1.8 \times 10^{-4} \mu\text{m}^3$	~ 0.5



$1 \text{ bp} \approx 1 \text{ nm}^3$

$\phi_c^\infty \sim 0.4$

$V_{nuc} \approx 300\pi \text{ nm}^3$



■ ■ ■

- Confined self-avoiding chain ($T > \Theta$)
- Chromosomes are not in $T > \Theta$. Protein mediated interactions may be more important for the chromosome compaction.
- For functional reason, chromosomes may effectively be in $T \lesssim \Theta$
- Effects of confining **near- Θ chains** can be very subtle.
 - Virial coeff's (solvent quality) vary with confining geometry !!

“Compressing Θ -chain in slit geometry”

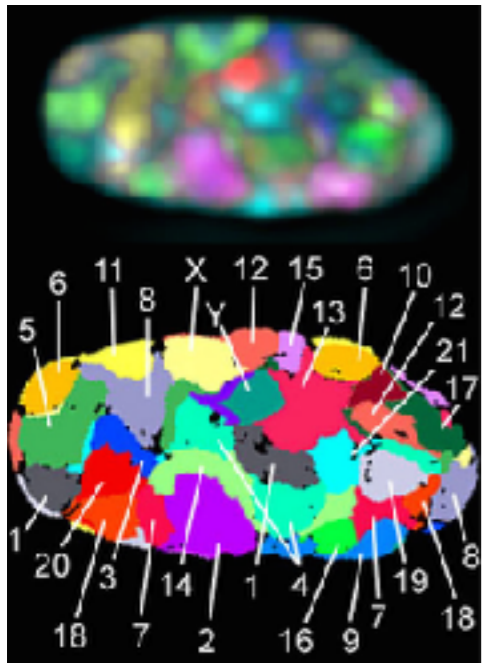
L. Liu, P.A. Pincus, C. Hyeon, *Nano Letters* (2019) 19, 5667-5673

“Near- Θ polymers in a cylindrical space”

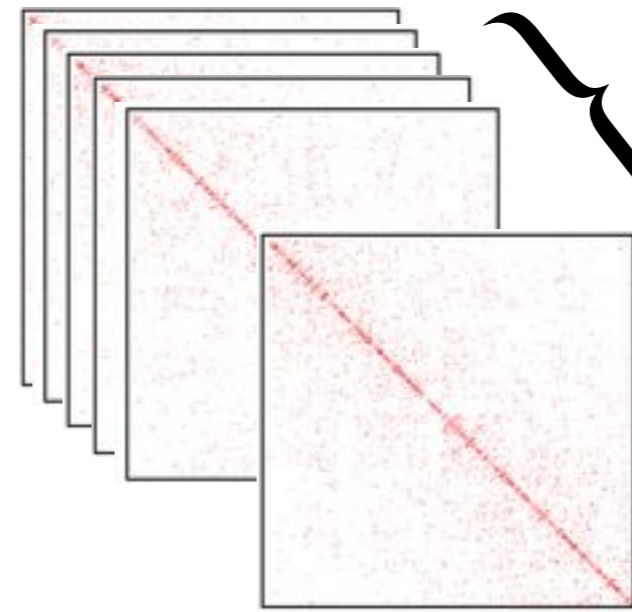
Y. Jung, C. Hyeon, B.-Y. Ha, *Macromolecules* (2020) 53, 2412-2419

2. Chromosomes with heteropolymers (Structure)

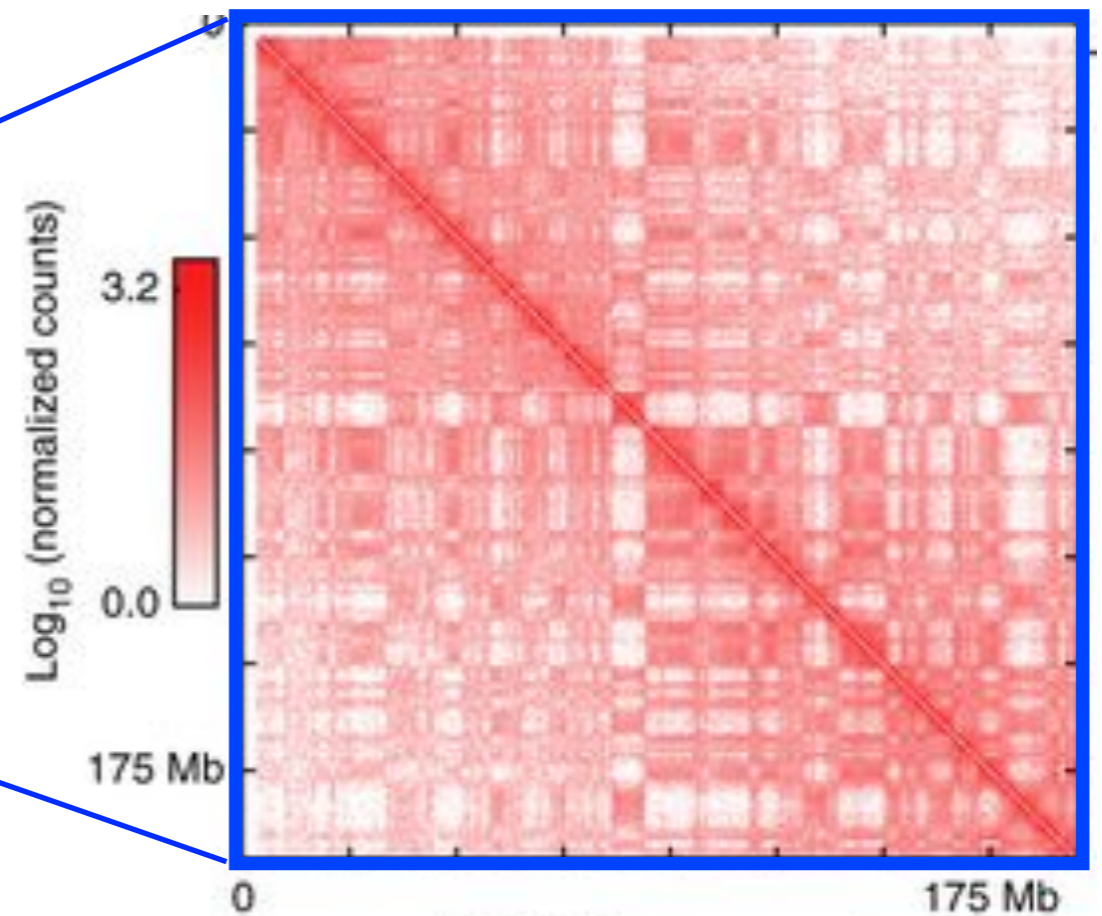
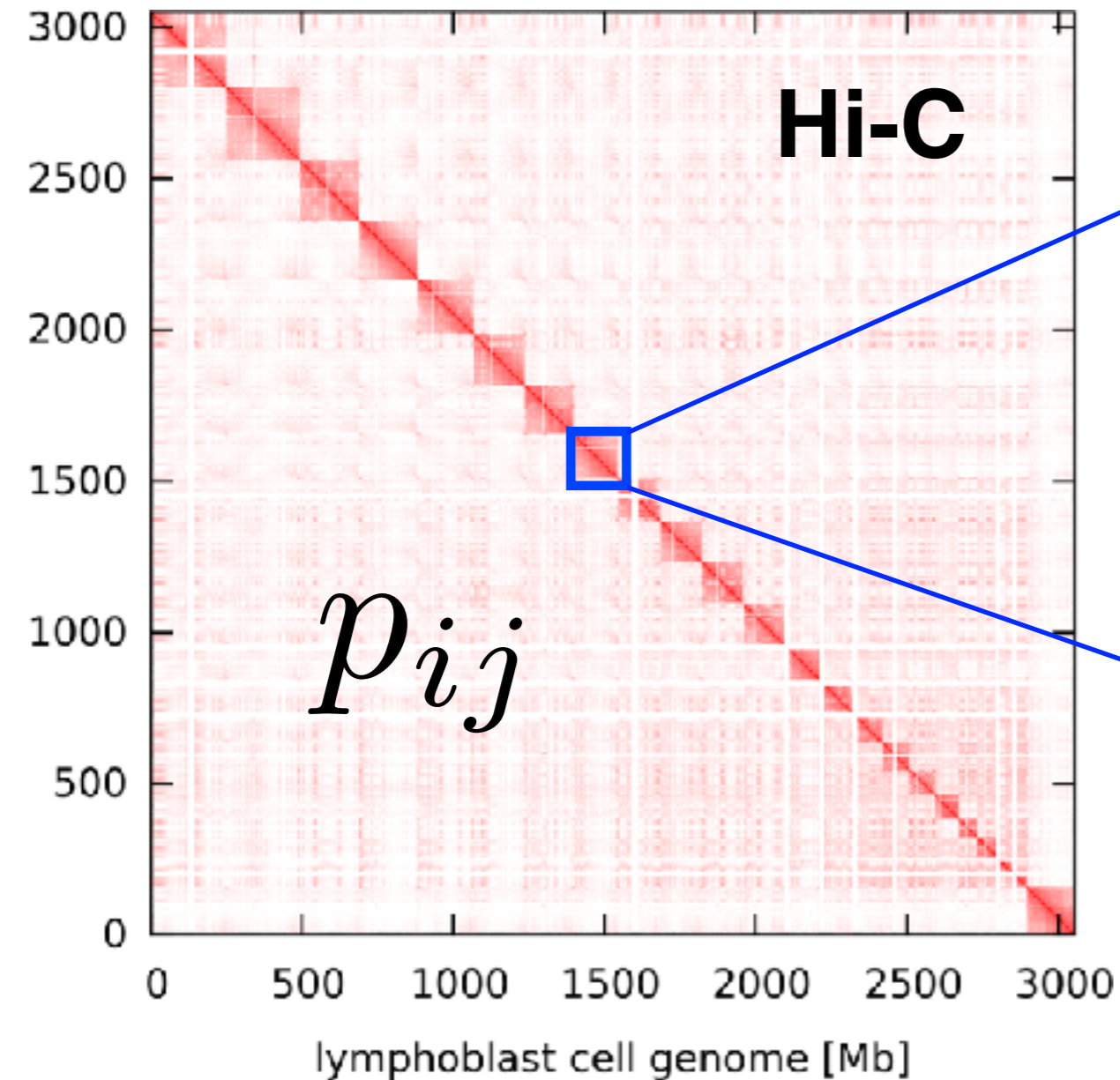
High throughput chromosome conformation capture



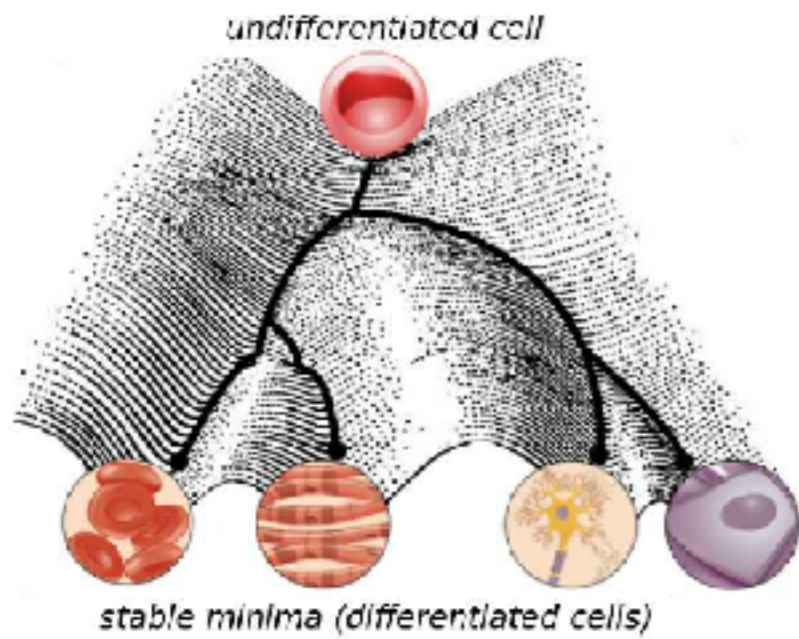
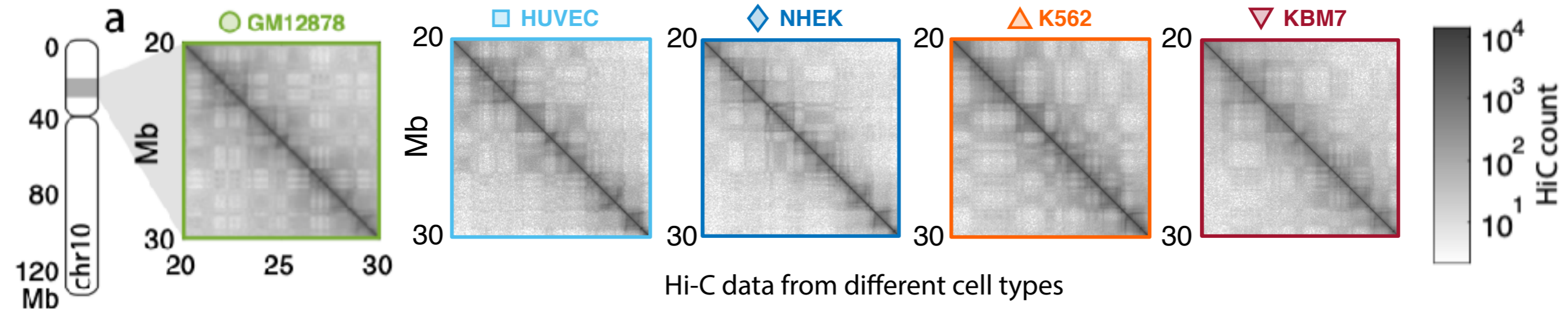
interphase



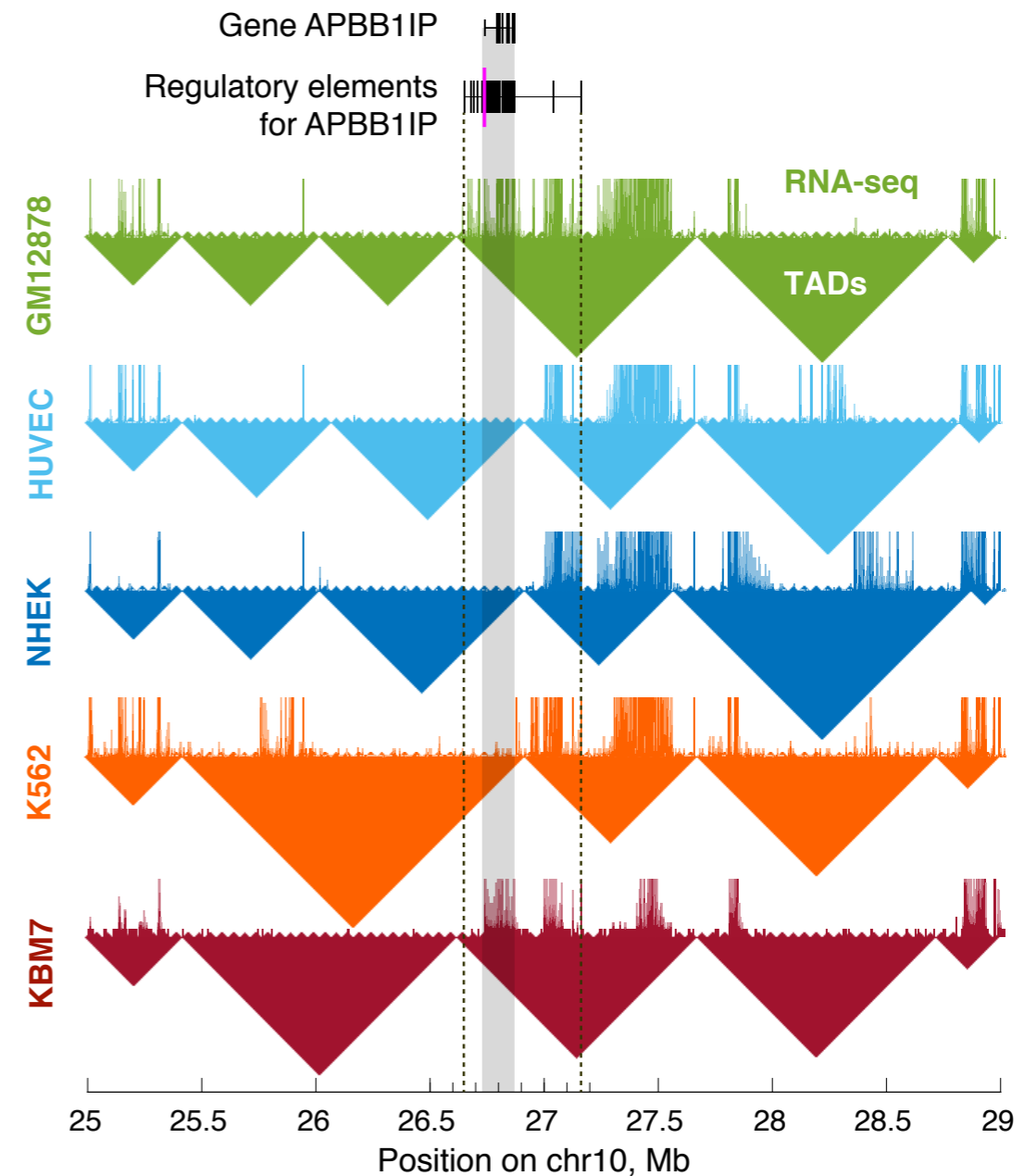
Millions of cells
(cell-to-cell variation)



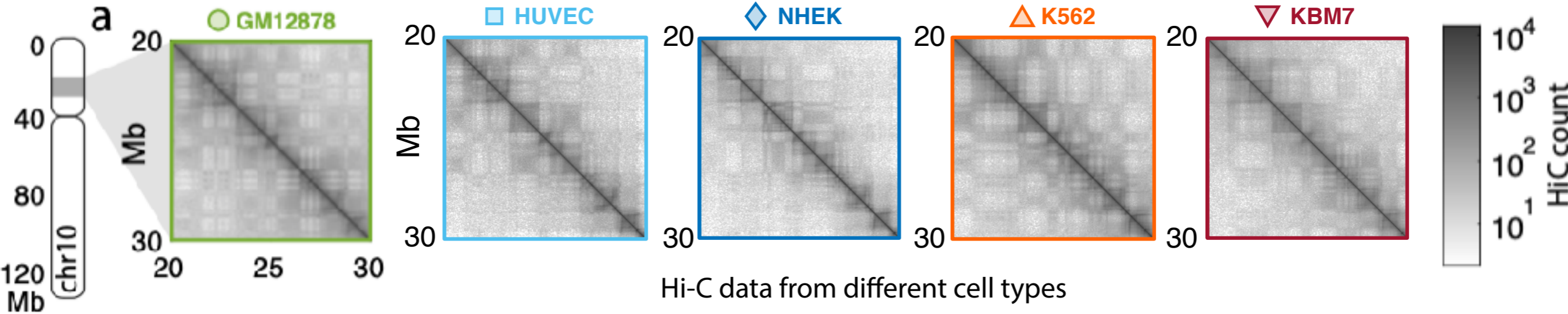
Hi-C map & chromosome structures are cell-type dependent



Waddington's (metaphorical)
epigenetic landscape



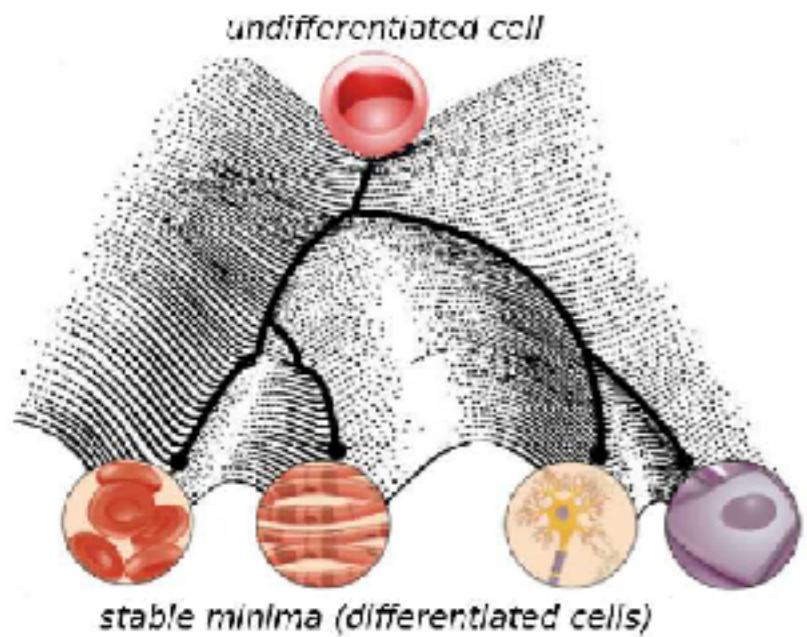
Hi-C map & chromosome structures are cell-type dependent



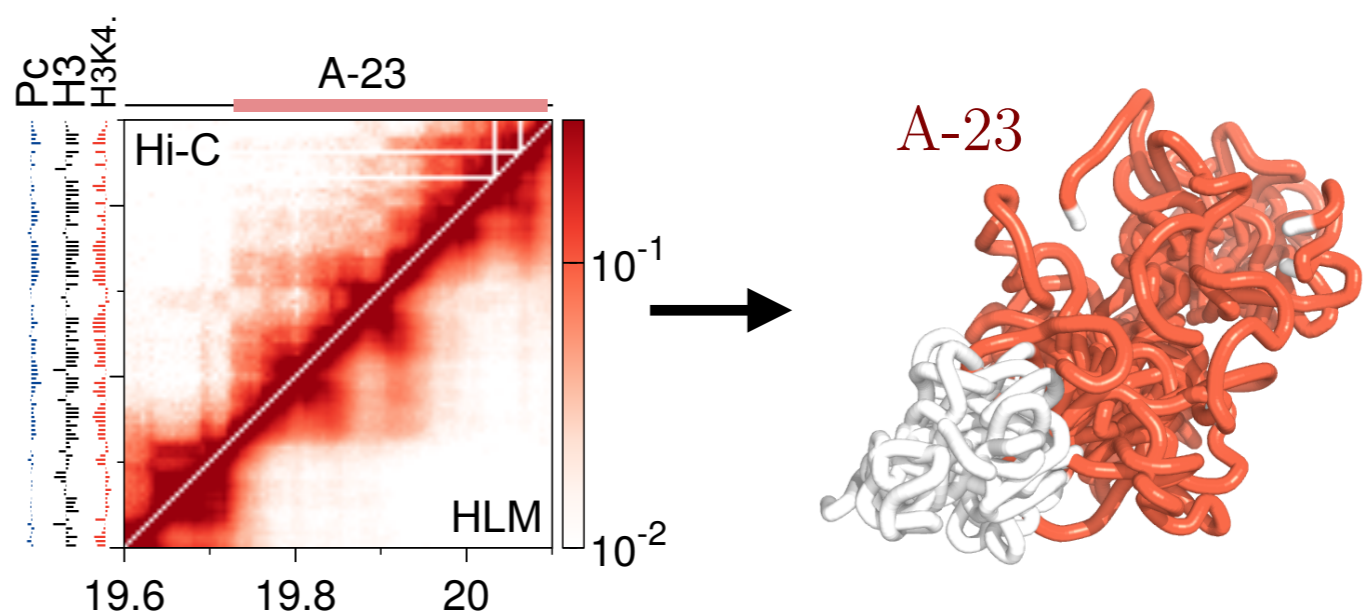
Hi-C data from different cell types

- **Strings and binders switch (SBS) model**
- **Loop extrusion model**
- **MiChroM**
- **Chromosome copolymer model (CCM)**
- ...
- ...
- **Heterogeneous loop model**

Liu et al. *Biophys. J.* (2019) 117, 613-625



Waddington's (metaphorical) **epigenetic landscape**

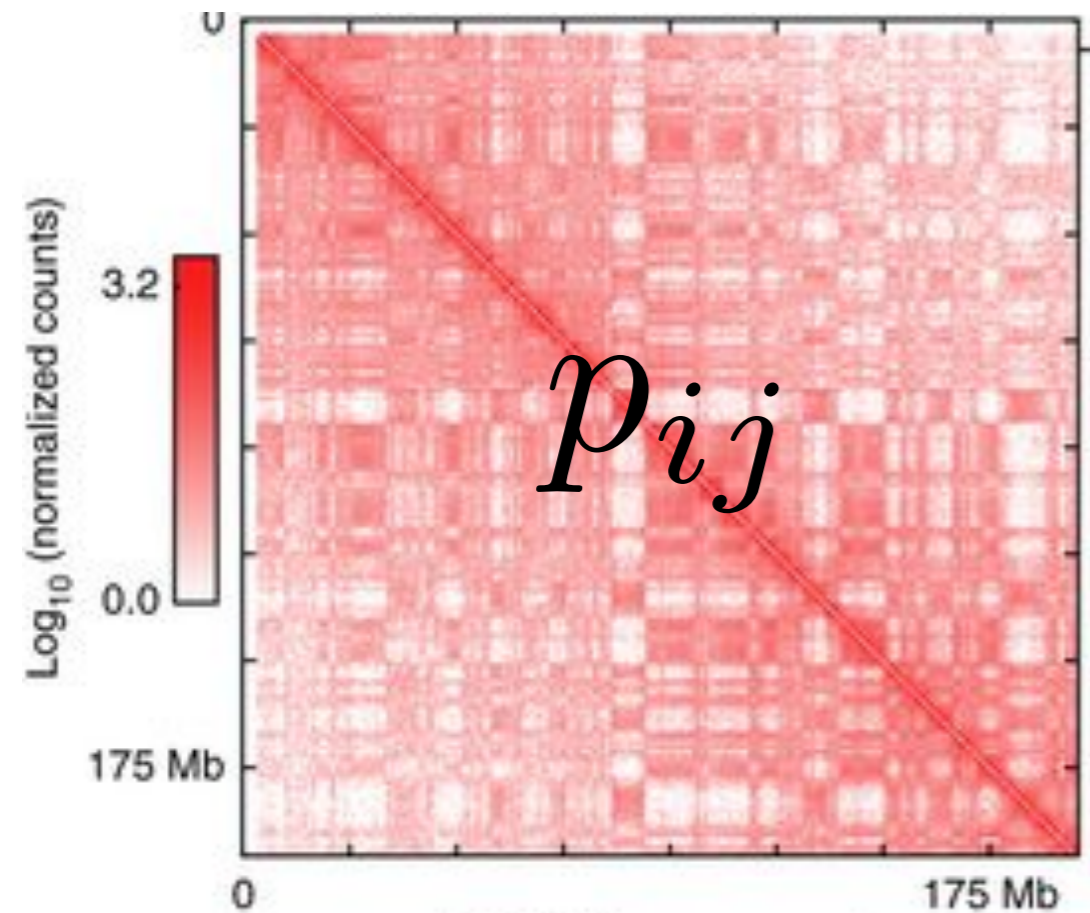


Heterogeneous Loop Model (HLM)

$$U_{\mathcal{K}}(\mathbf{r}) = \sum_{i=1}^{N-1} \frac{k}{2} (\vec{r}_i - \vec{r}_{i-1})^2 + \sum_{i=0}^{N-3} \sum_{j=i+2}^{N-1} \frac{k_{ij}}{2} (\vec{r}_i - \vec{r}_j)^2 = \frac{3}{2} \mathbf{r}^T \mathbf{K} \mathbf{r},$$

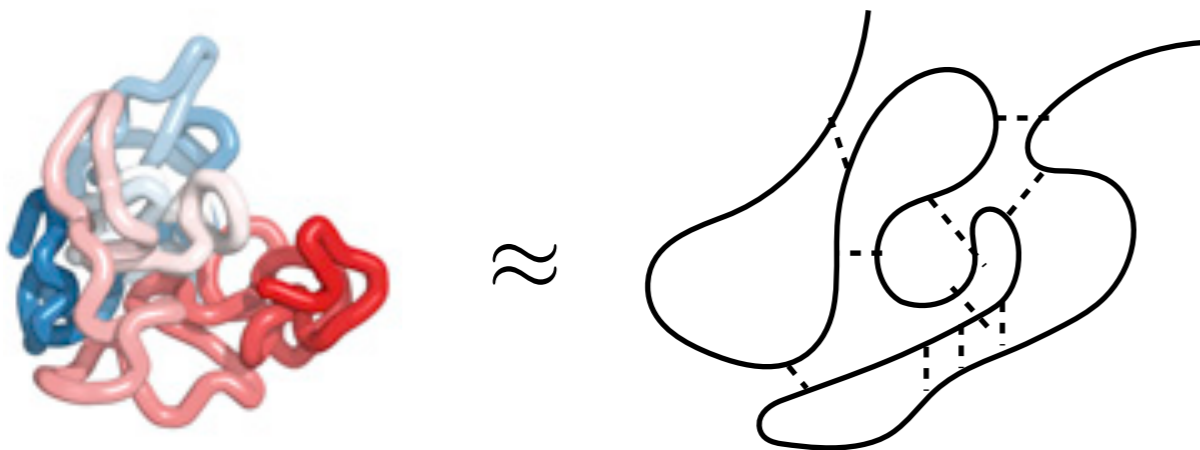
$$P(r_{ij}) = 4\pi (\gamma_{ij}/\pi)^{3/2} r_{ij}^2 e^{-\gamma_{ij} r_{ij}^2}$$

$$p_{ij} = \int_0^{r_c} P(r_{ij}) dr_{ij} = \text{erf}(\sqrt{\gamma_{ij}} r_c) - 2\sqrt{\frac{\gamma_{ij} r_c^2}{\pi}} e^{-\gamma_{ij} r_c^2}$$



$$\gamma_{ij} = \begin{cases} \frac{1}{2(\sigma_{ii} + \sigma_{jj} - 2\sigma_{ij})}, & i > 0 \\ \frac{1}{2\sigma_{jj}}, & i = 0 \end{cases}$$

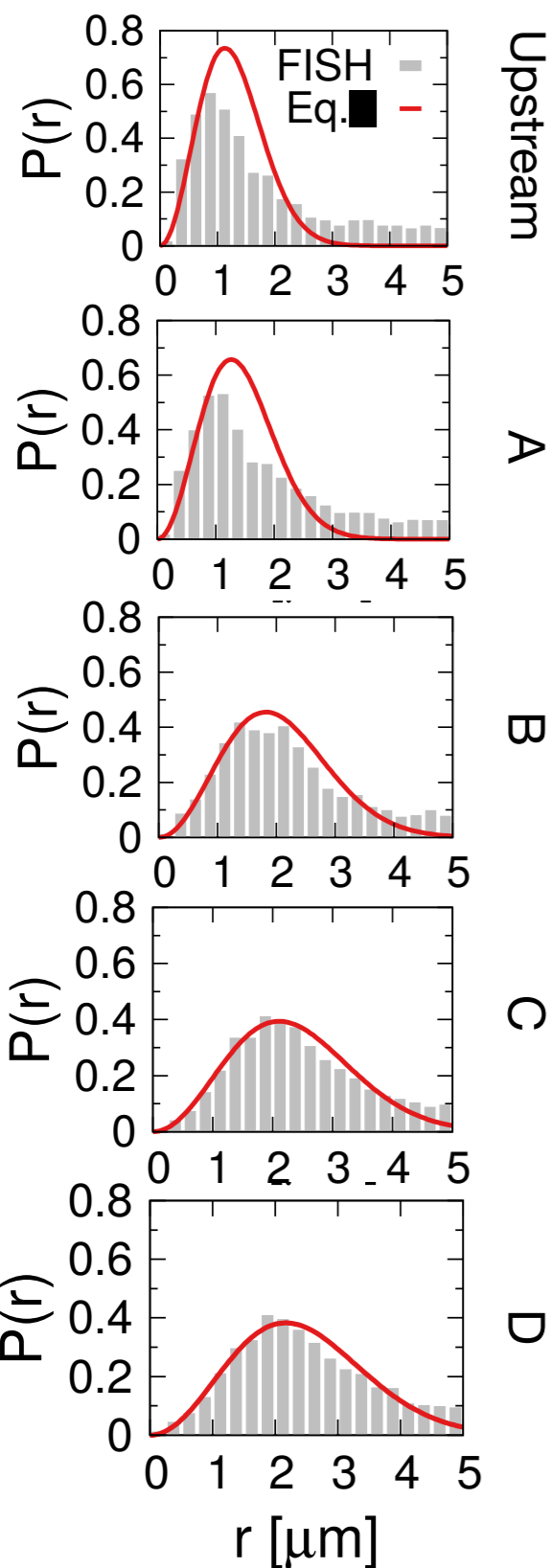
$$\sigma_{ij} [= \langle \delta r_i \delta r_j \rangle] = (\mathbf{K}^{-1})_{ij}$$



$$P_{ij} \leftrightarrow \sigma_{ij} \leftrightarrow k_{ij}$$

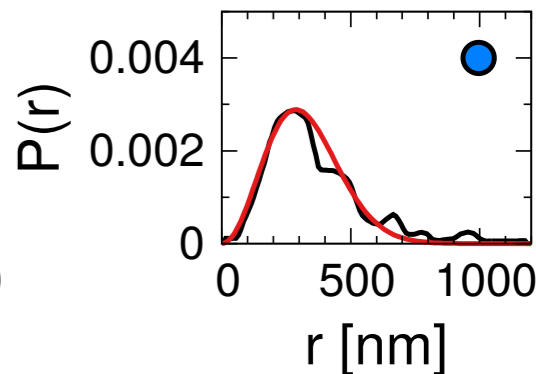
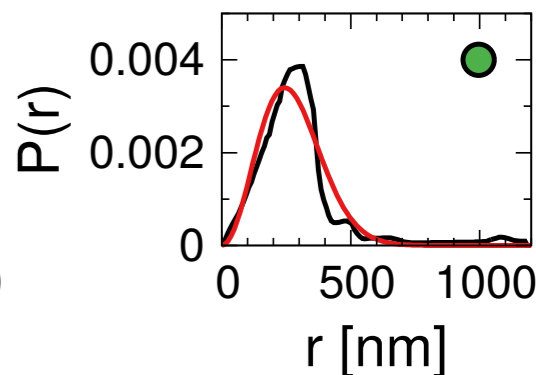
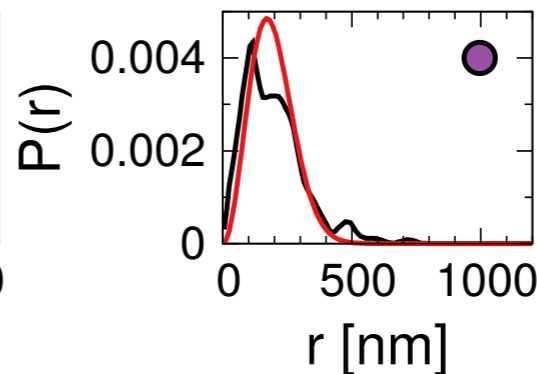
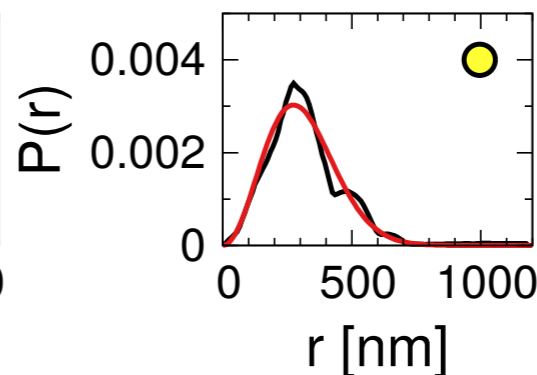
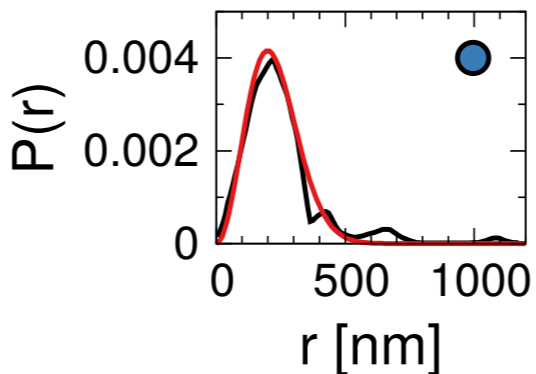
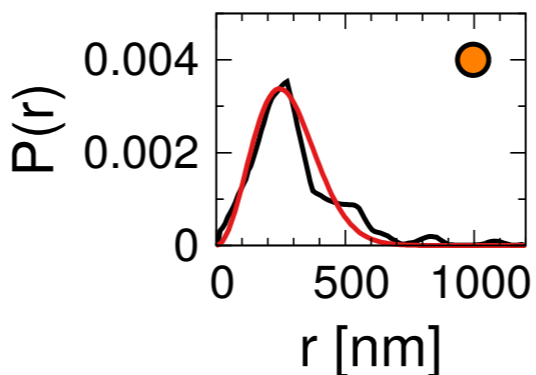
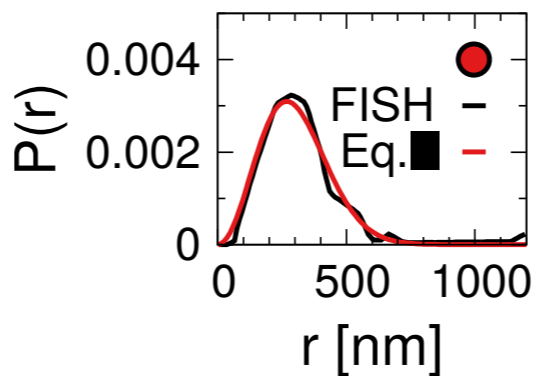


chr1 fibroblast cells

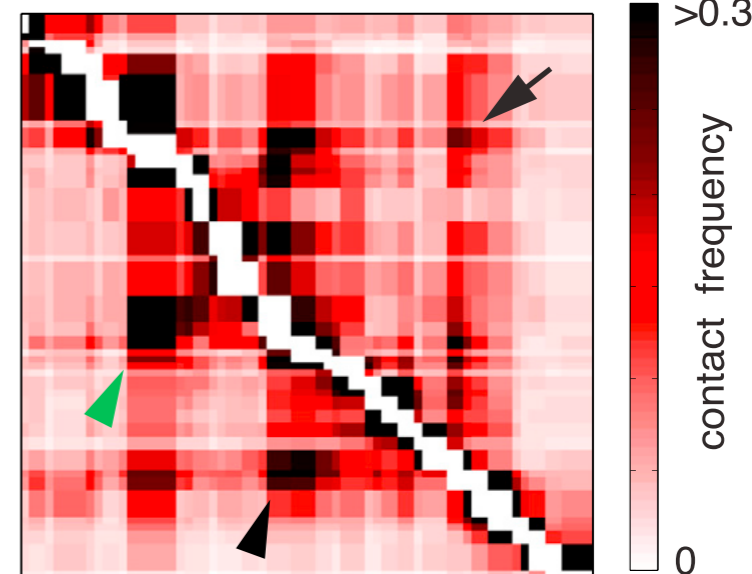


Eq. ■

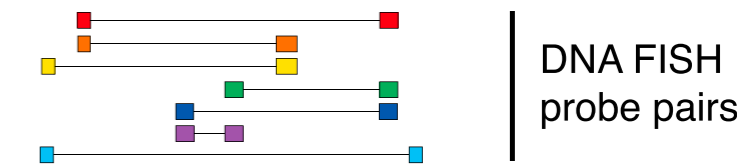
$$P(r_{ij}) = 4\pi(\gamma_{ij}/\pi)^{3/2} r_{ij}^2 e^{-\gamma_{ij} r_{ij}^2}$$



Nap1l2 Ppnx Linx Cdx4 Chic1 Tsx Xite Tsix Xist



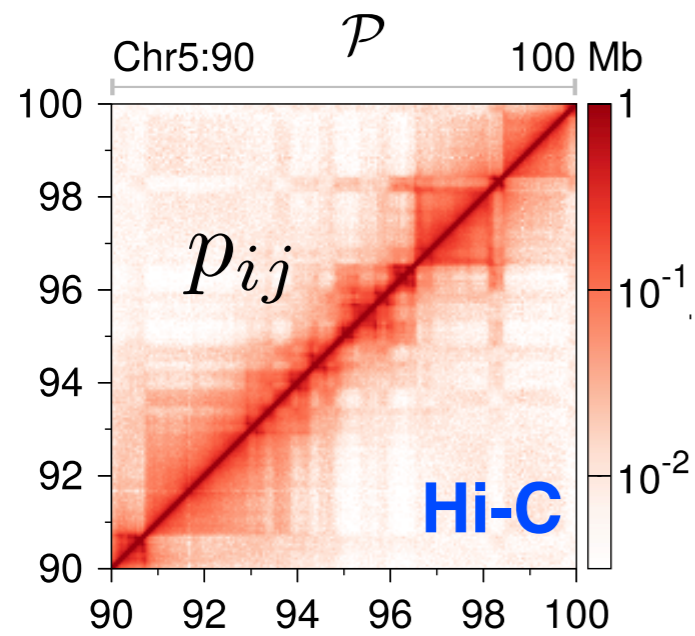
X-chr, Mouse ESC



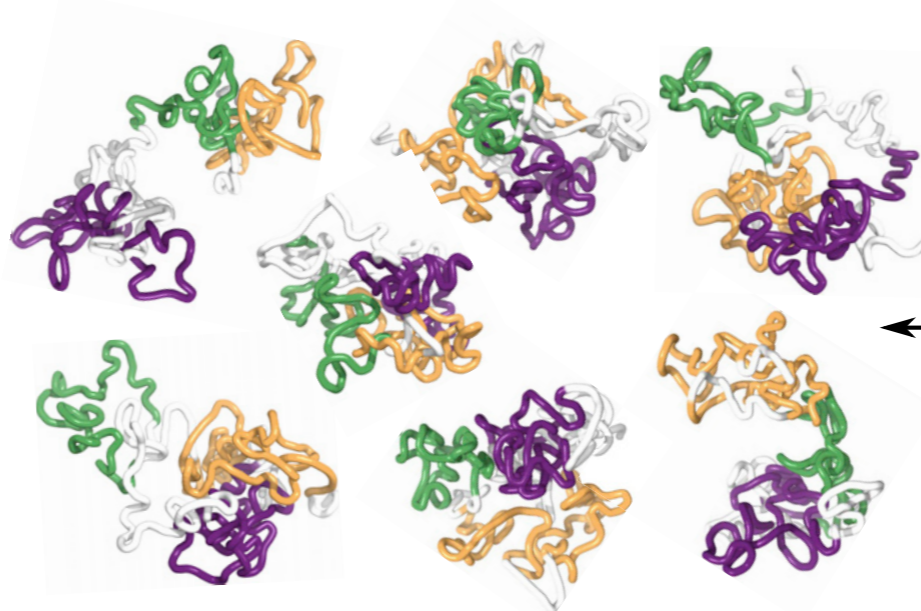
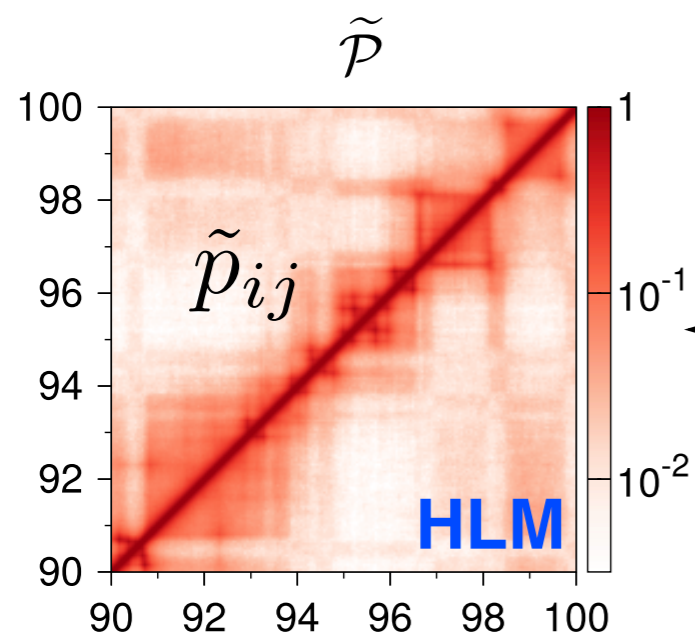
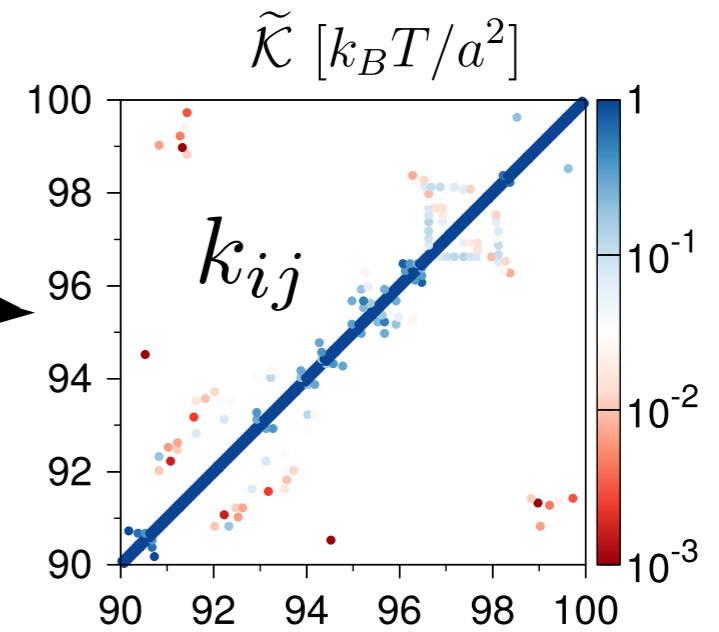
$$U_{\text{HLM}}(\mathbf{r}) = U_{\mathcal{K}}(\mathbf{r}) + U_{\text{nb}}(\mathbf{r}) \quad \dots \text{Eq.(1)}$$

$$U_{\text{nb}}(\mathbf{r}) = \sum_{ij} \chi_{t_i, t_j} u_{\text{LJ}}(r_{ij}), \quad u_{\text{LJ}}(r) = \epsilon \left[\left(\frac{a}{r} \right)^{12} - 2 \left(\frac{a}{r} \right)^6 \right] \Theta(r_c - r)$$

$$\epsilon = 0.45k_B T \quad \epsilon_{\theta} = 0.34k_B T \quad (B_2 \approx 0)$$

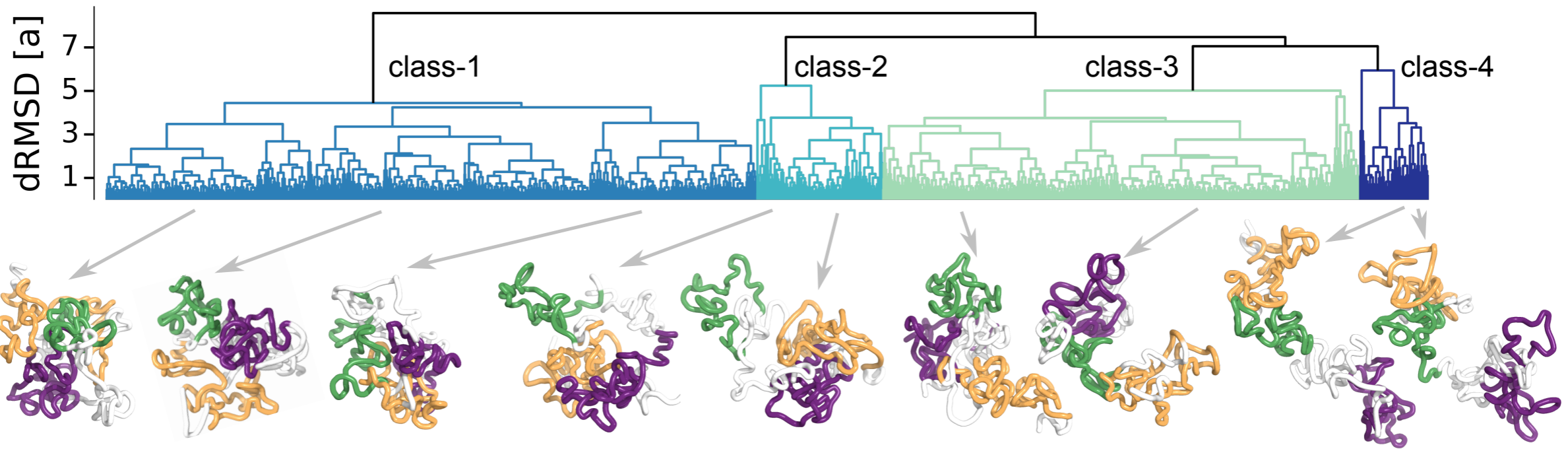


$$p_{ij} \leftrightarrow \sigma_{ij} \leftrightarrow k_{ij}$$

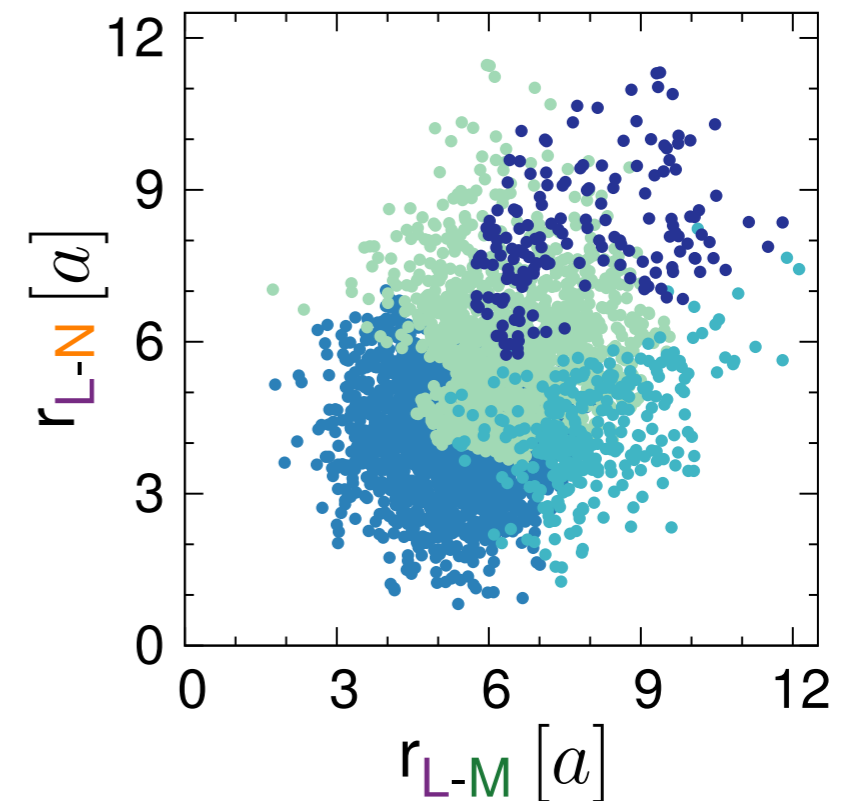


MD simulations
with U_{HLM} in Eq.(1)

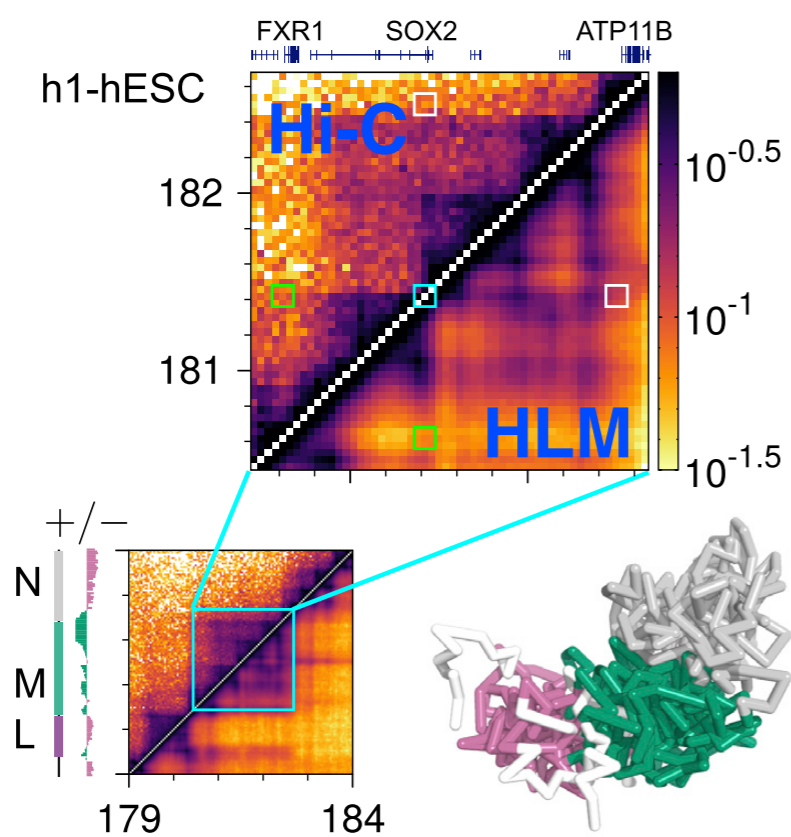
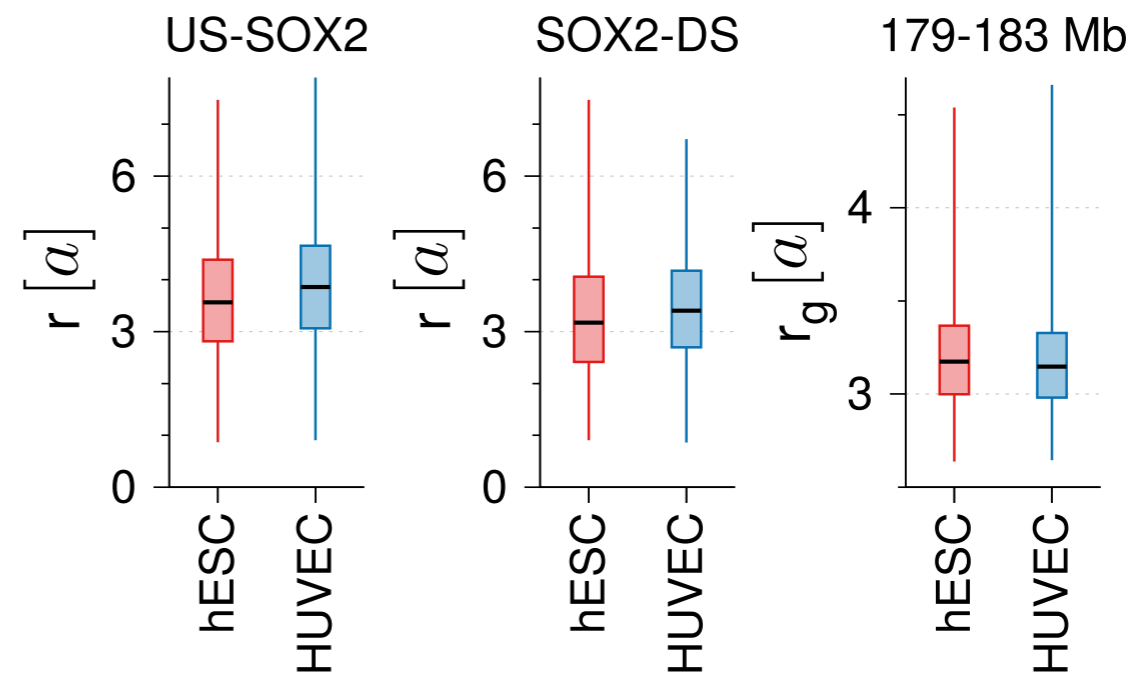
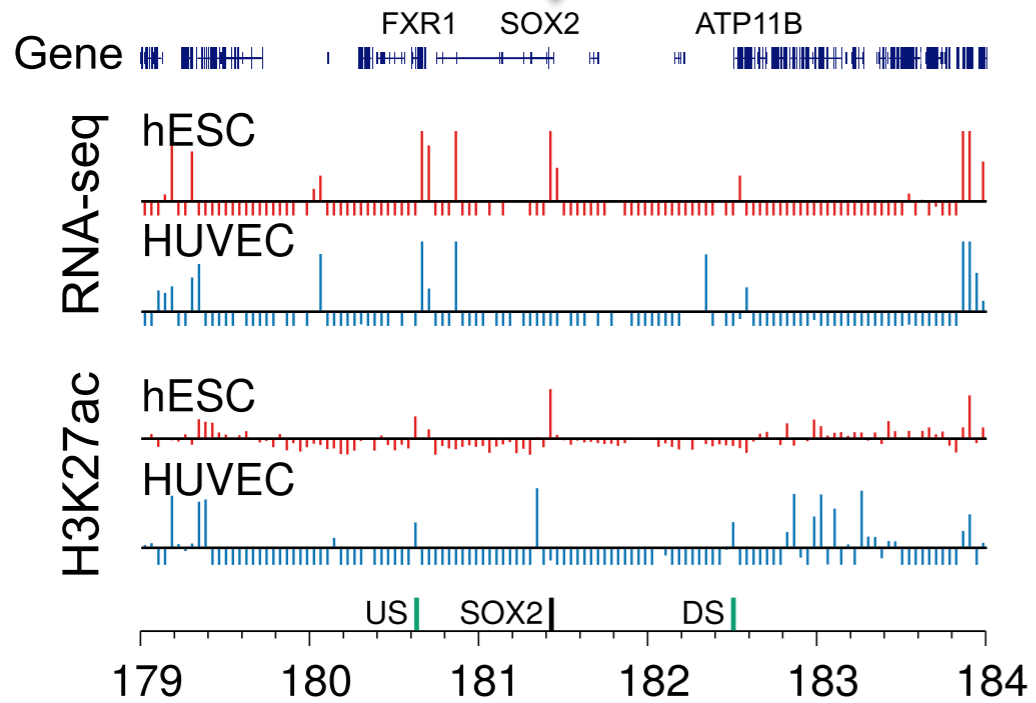
Variability in the HLM-generated ensemble for a 10 Mb-region of chr5 in GM12878.



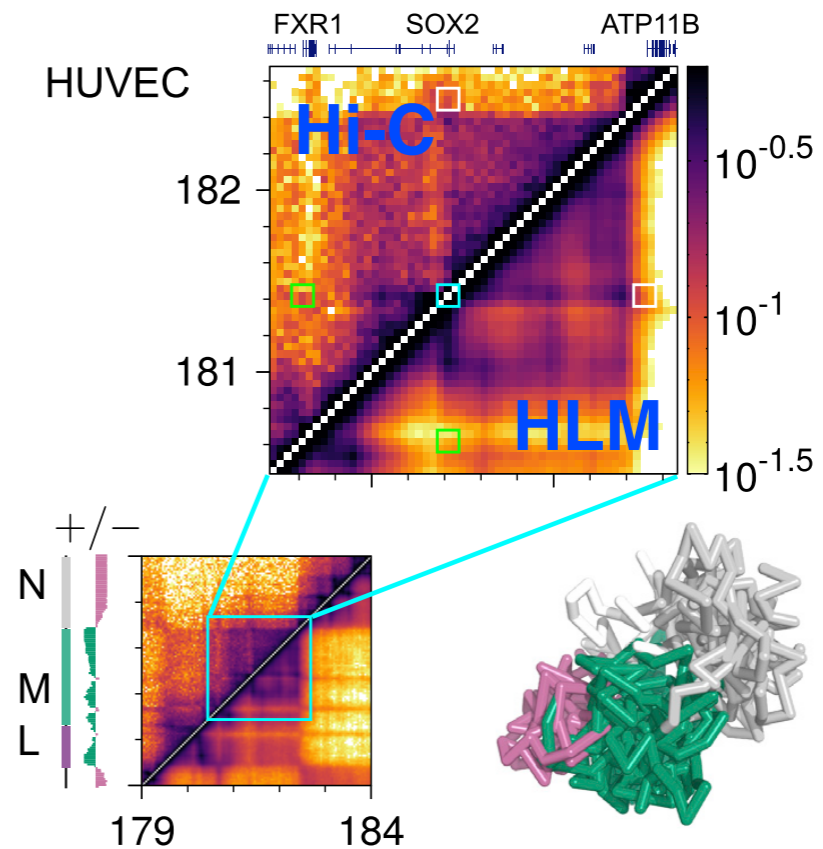
$$\text{dRMSD}_{\alpha,\beta} = \sqrt{\sum_{\{X-Y\}} \frac{1}{3} \left(r_{X-Y}^{\alpha} - r_{X-Y}^{\beta} \right)^2}$$



Structural origin of gene expression (cell type dependence)



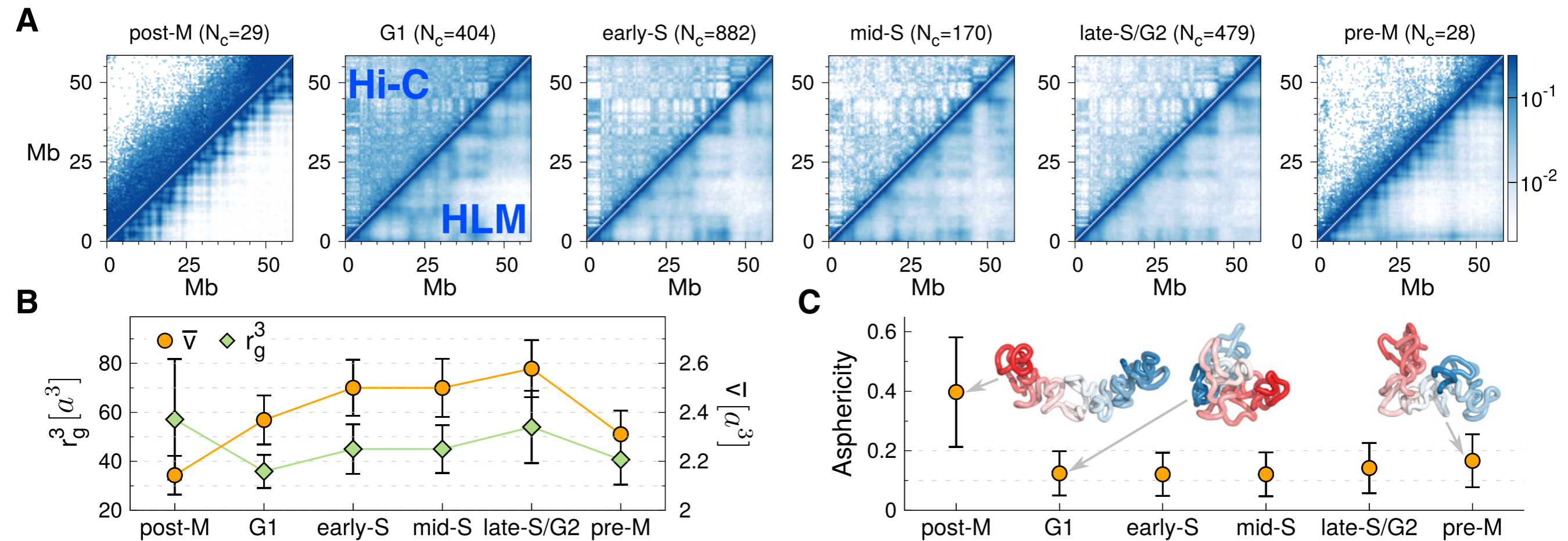
SOX2 active



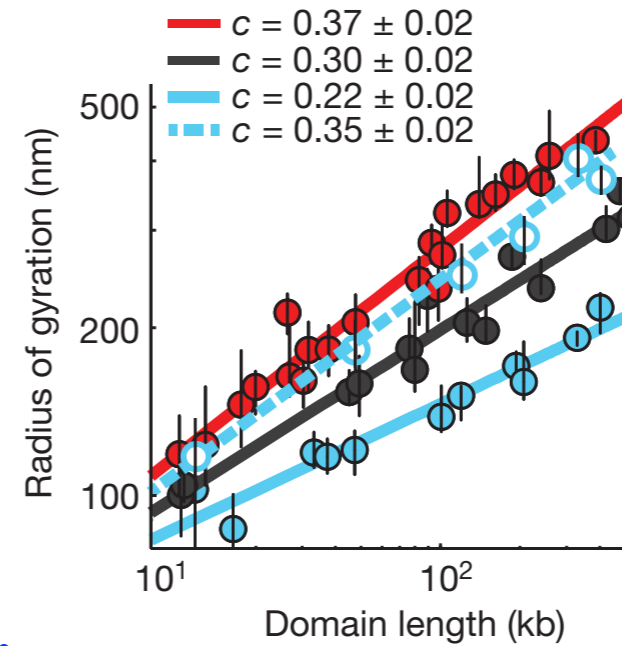
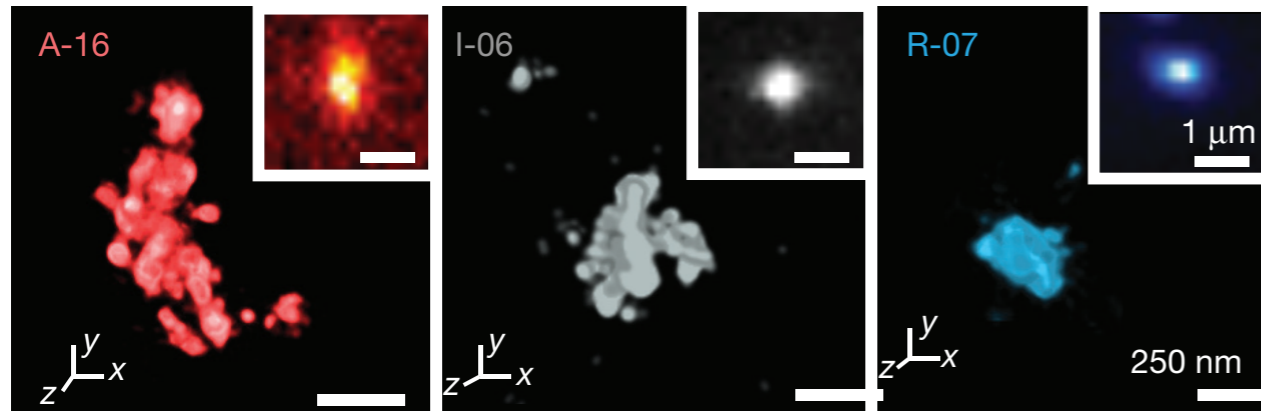
SOX2 inactive

Chromosome in different phases along the cell cycle

500 kb-res. single cell Hi-C, Chr19 of mESCs



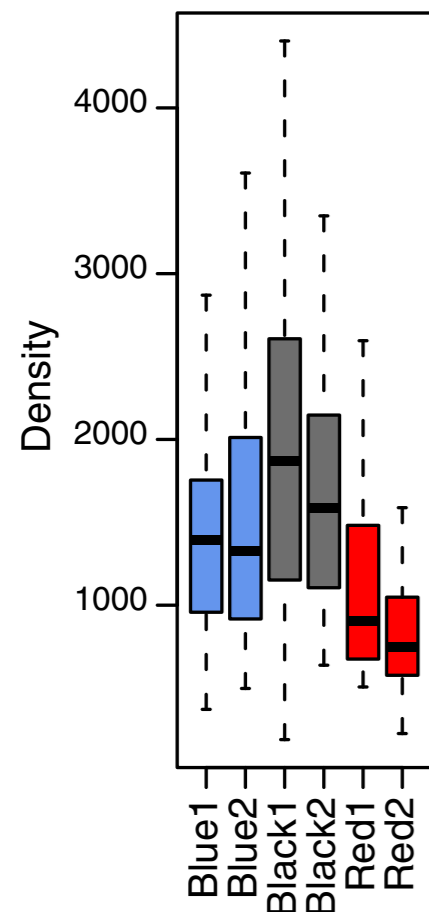
Epigenetic domains



$$R(L) \sim L^c$$

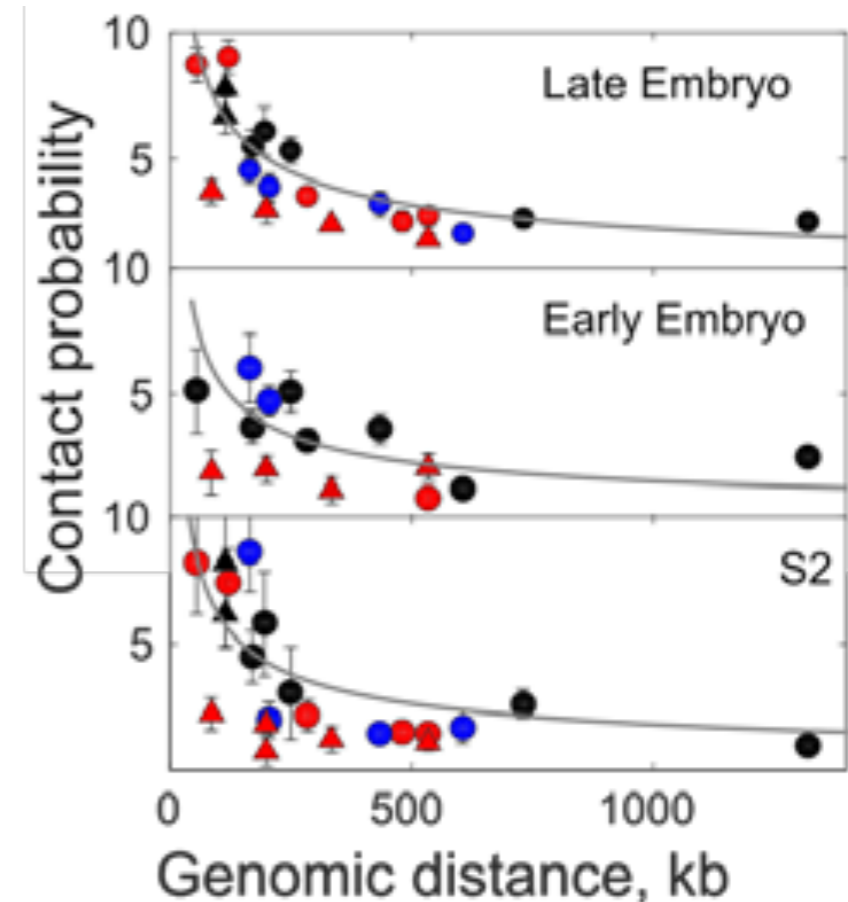
$$R < I < A$$

Boettiger et al. *Nature*, (2016) 529, 418–422.



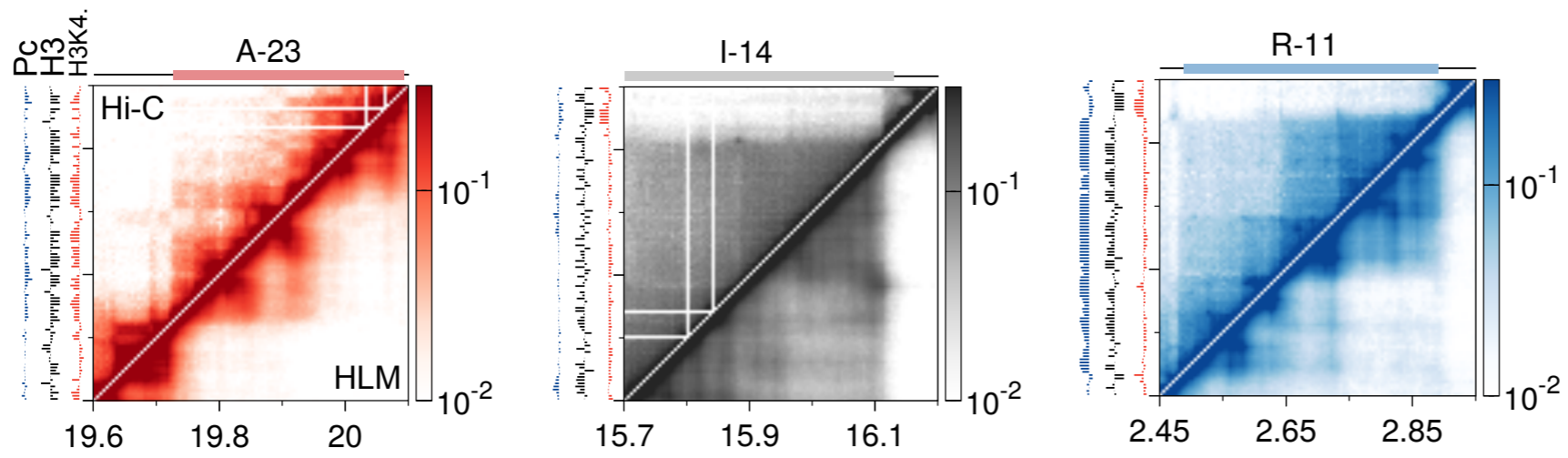
- Active
- Inactive
- Polycomb-repressed

$$I \lesssim R < A$$

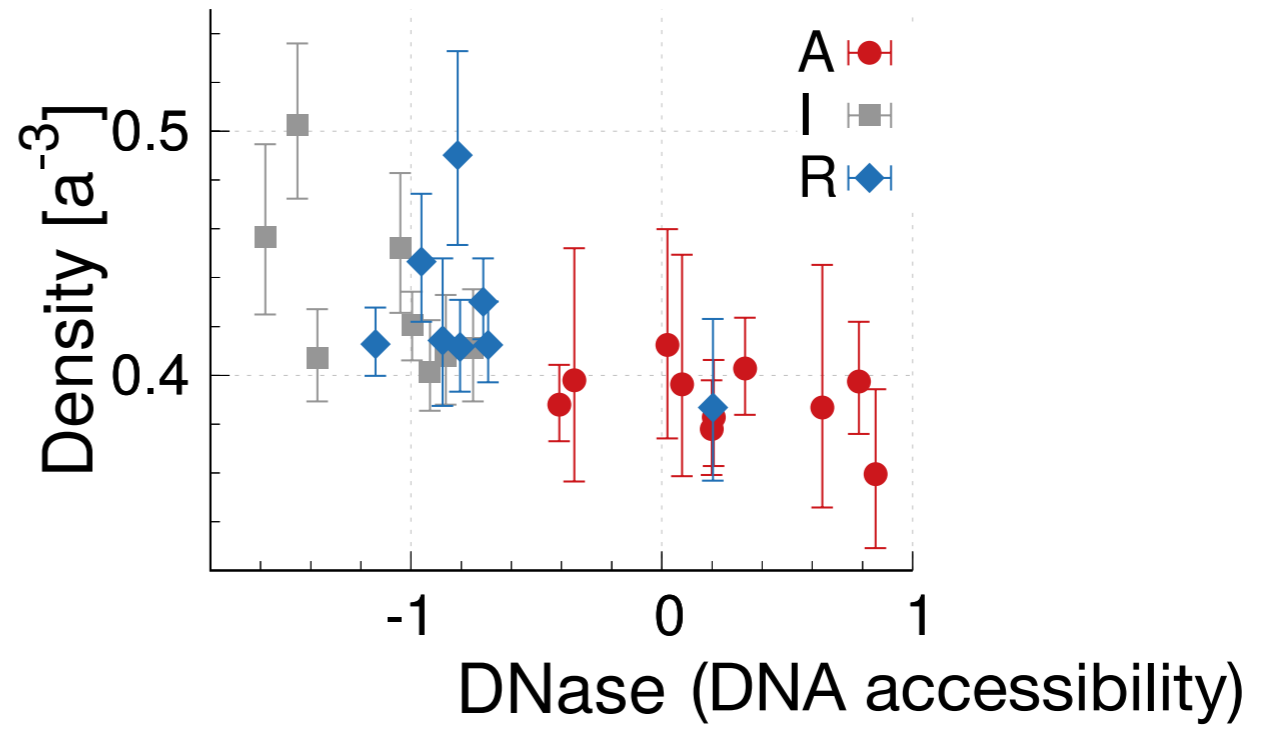
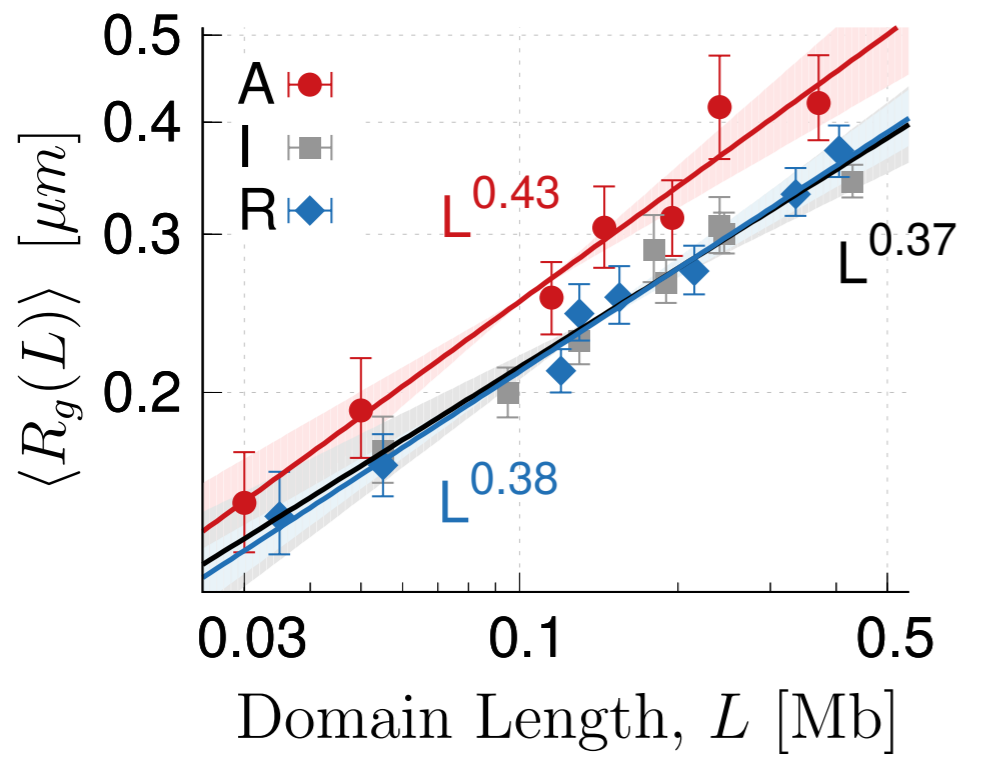


Szabo et al. *Sci. Adv.*, (2018) 4, eaar8082

Cattoni et al. *Nat. Commun.*, (2017) 8, 1753

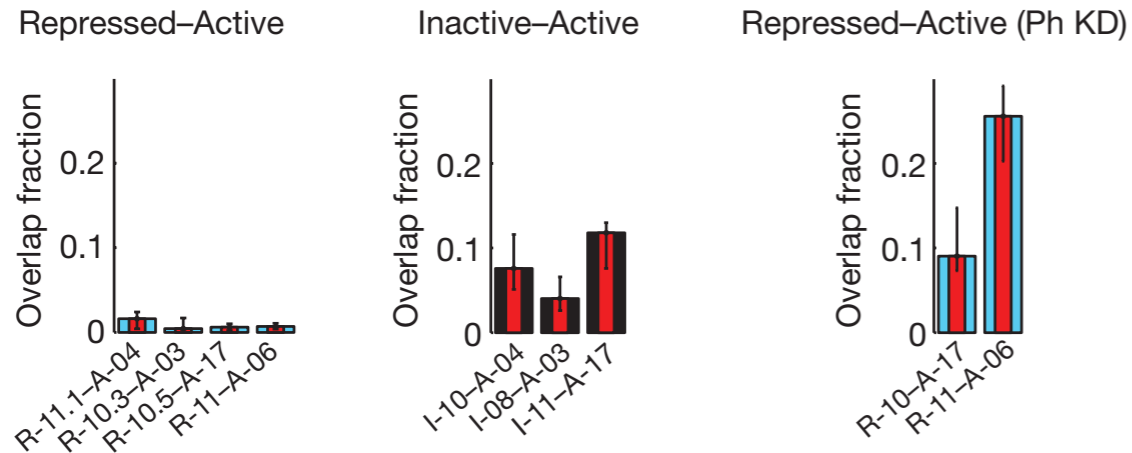
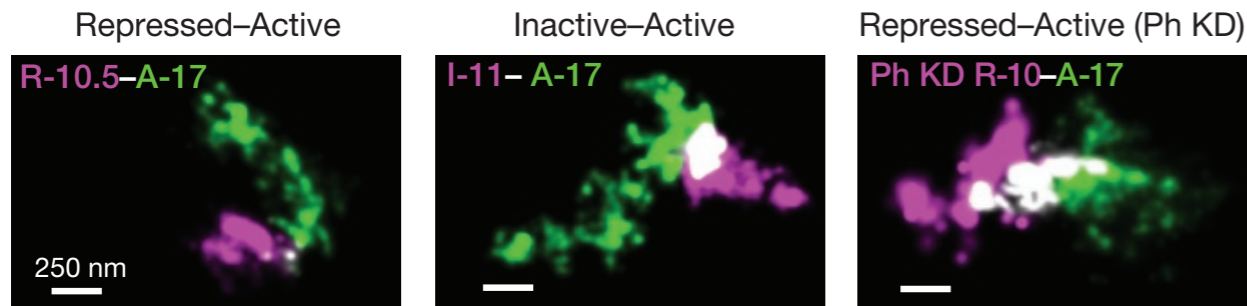


$$I \approx R < A$$



(under review)

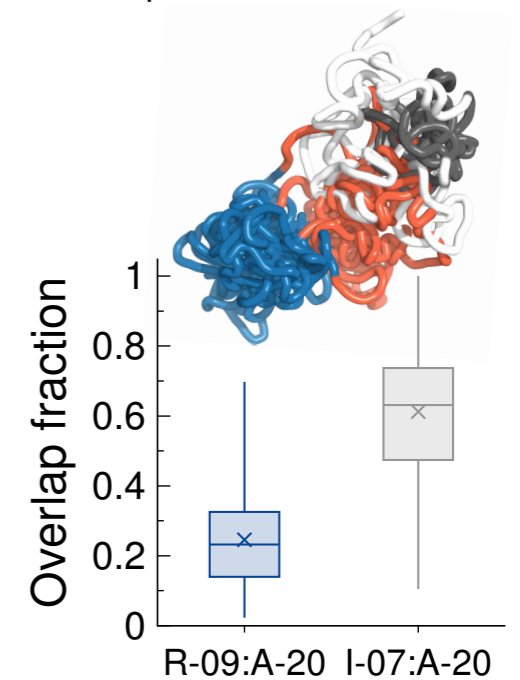
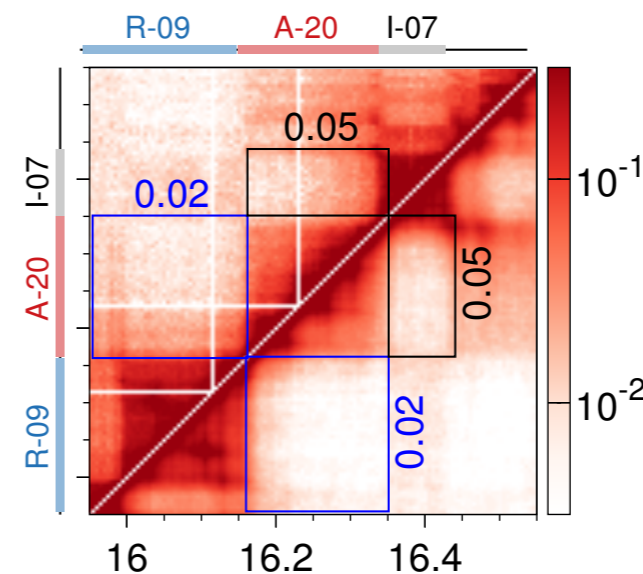
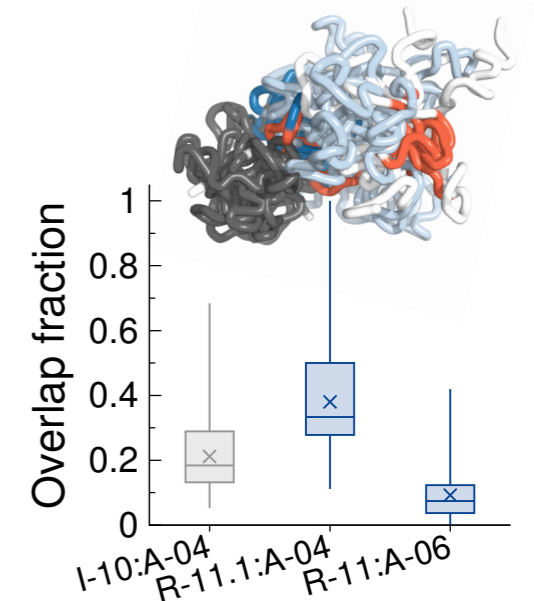
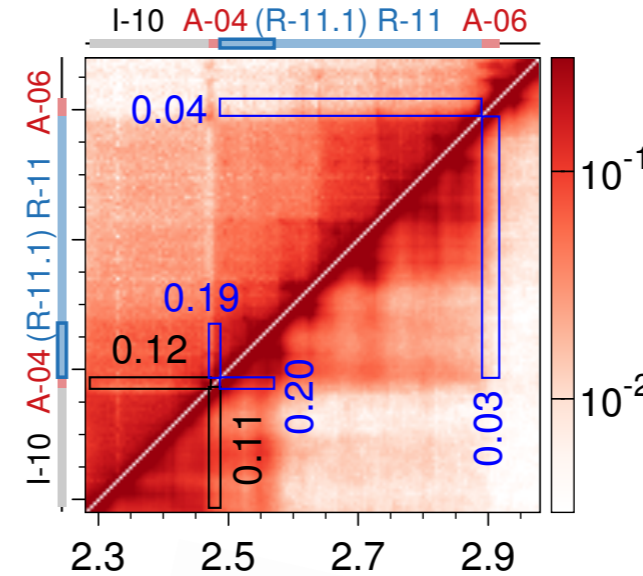
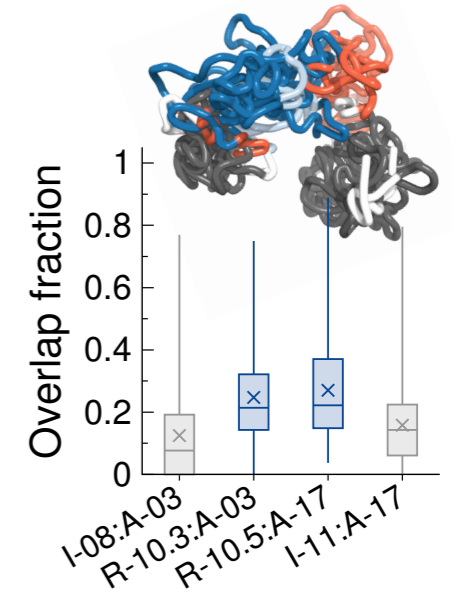
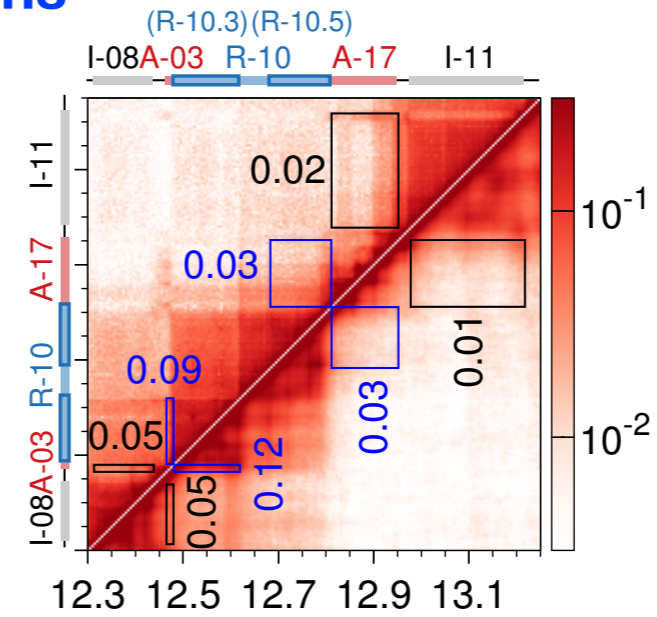
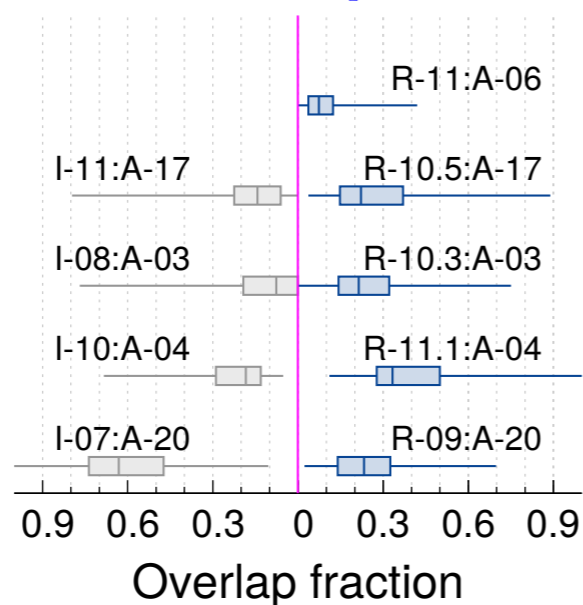
Intermixing between two different epigenetic domains



“... Compared to inactive domains, Polycomb-repressed domains spatially exclude neighbouring active chromatin to a much stronger degree....”

Boettiger et al. *Nature*, (2016) 529, 418–422.

Inactive:Active *Repressed:Active*

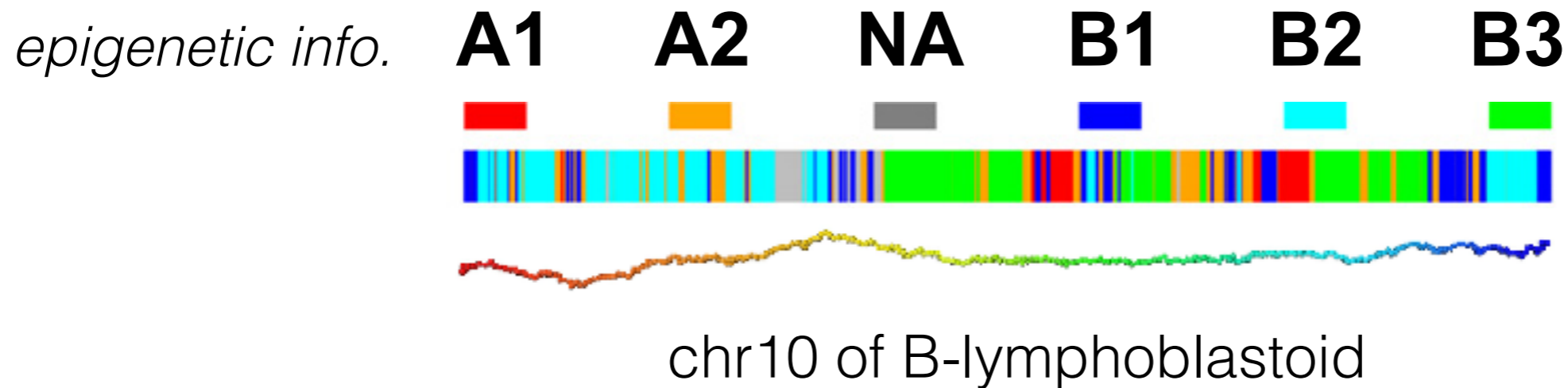


3. Chromosomes with heteropolymers

(Dynamics)

Chromosome dynamics from a heteropolymer model

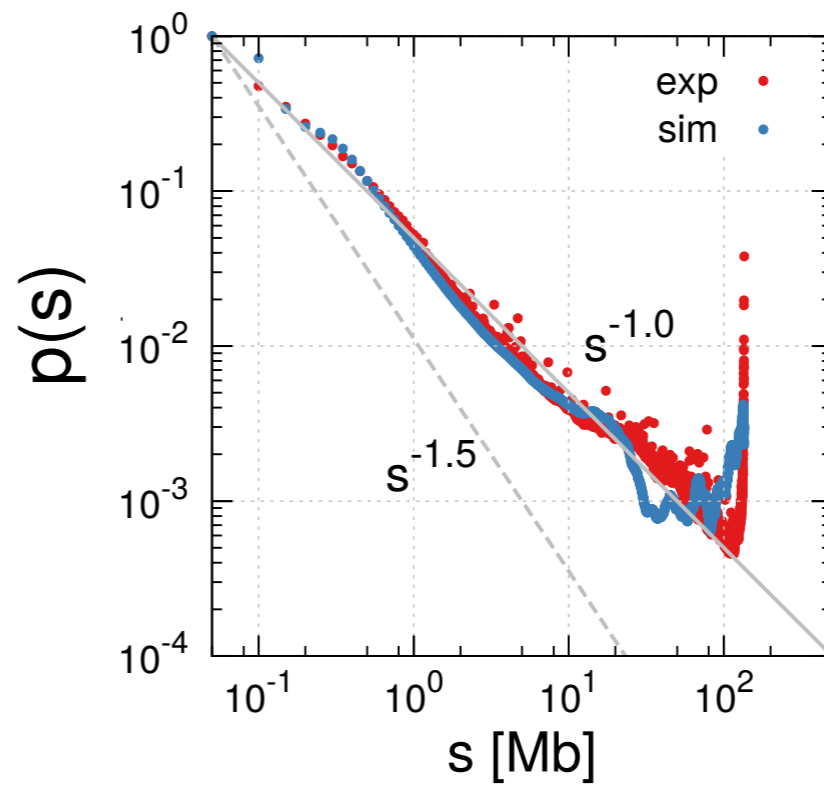
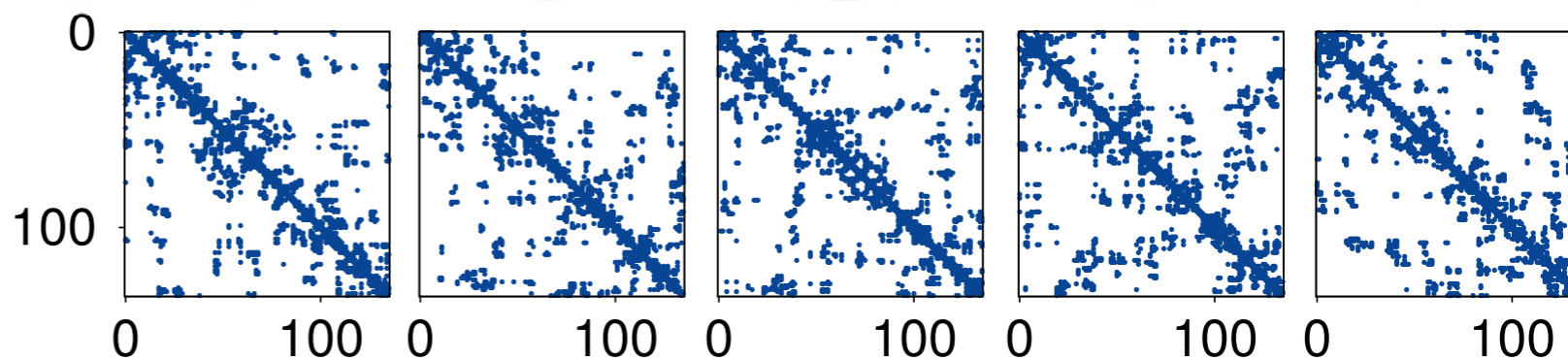
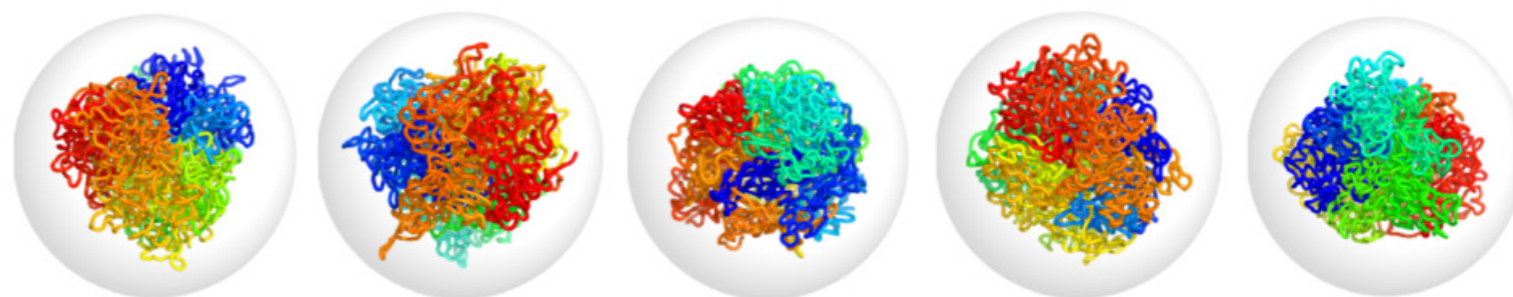
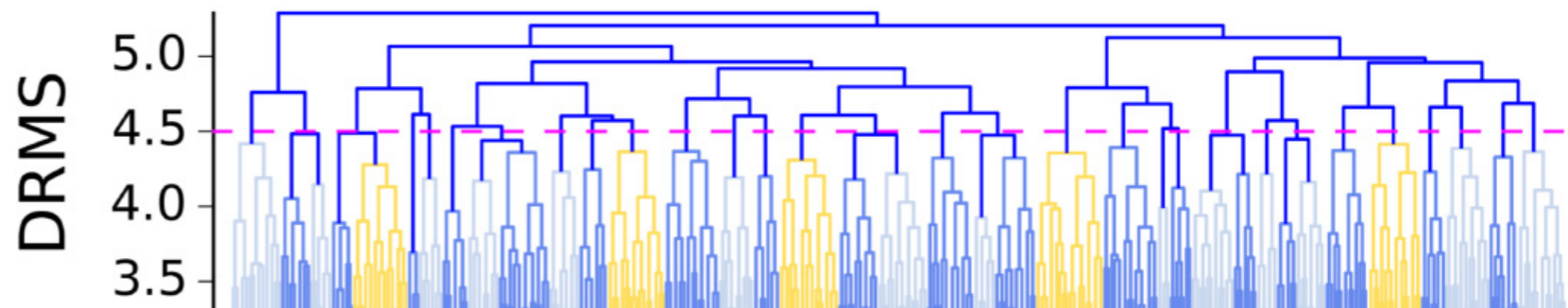
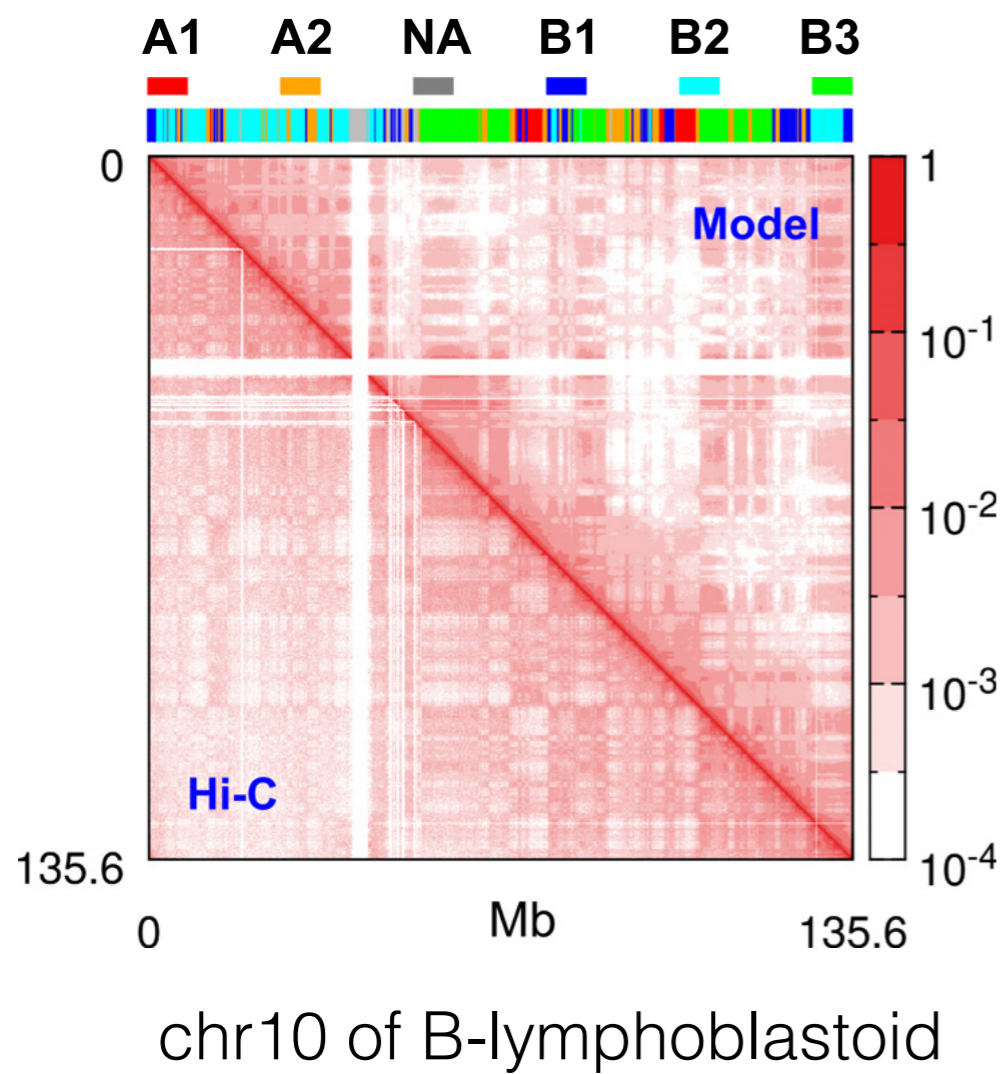
MiChroM (Di Pierro et al., PNAS (2016) 113, 12168)



$$U_{\text{MiChroM}} = U_{\text{HP}} + \sum_{i,j} \alpha_{t_i,t_j} f(r_{ij}) + \chi \sum_{(i,j) \in \text{loops}} f(r_{ij}) + \sum_{s=3}^{s_{\max}} \gamma(s) \sum_i f(r_{i,i+s}) + \sum_{i=1}^N U_w(r_{i,w}).$$

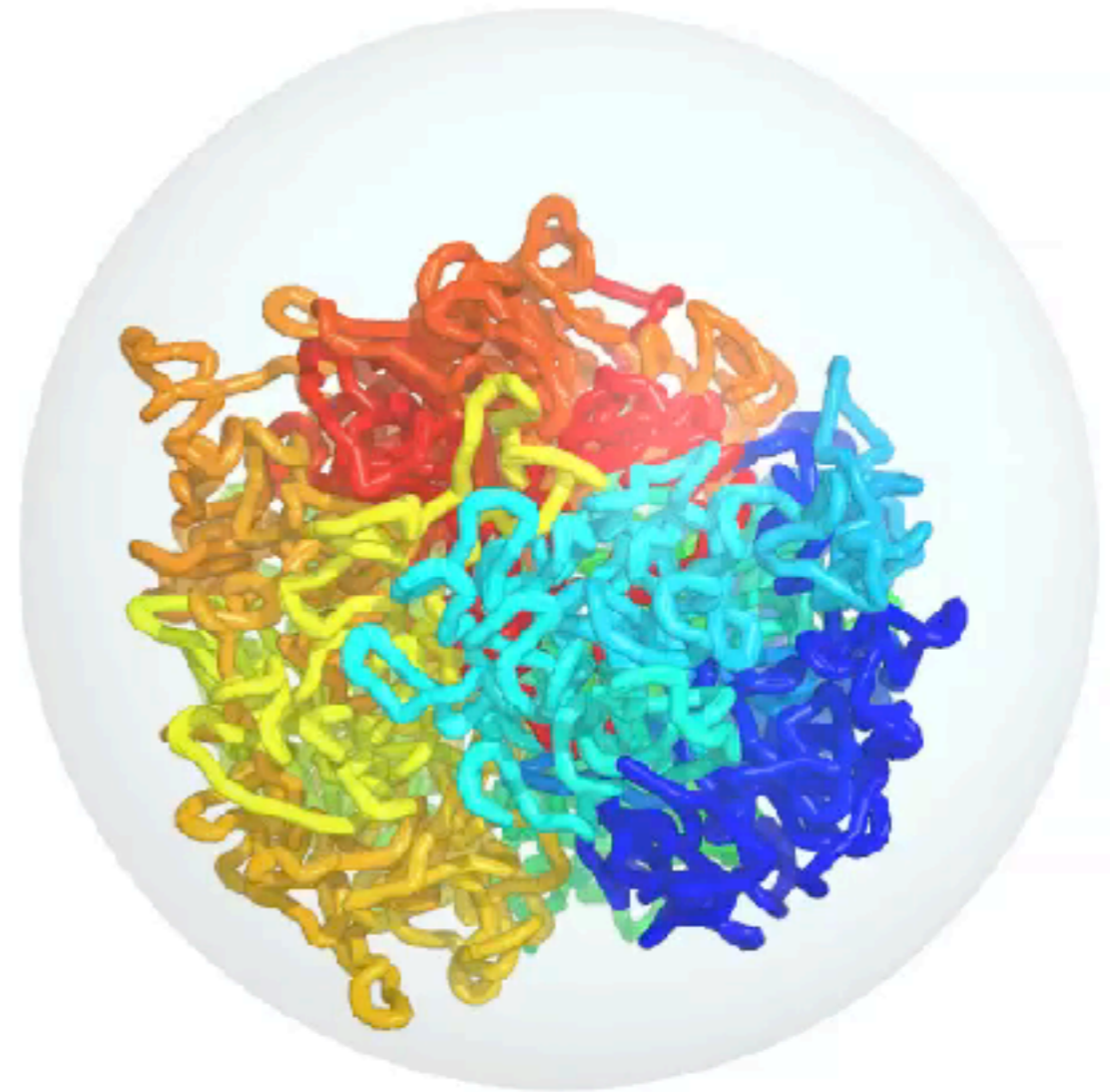
Table 2. The monomer type dependent parameter α of MiChroM (in the unit of $k_B T$).

	B3	B2	B1	NA	A1	A2
B3	-0.341230	-0.329350	-0.336630	-0.349490	-0.266760	-0.301320
B2		-0.330443	-0.321726	-0.282536	-0.258880	-0.281154
B1			-0.342020	-0.209919	-0.262513	-0.286952
NA				-0.255994	-0.225646	-0.245080
A1					-0.268028	-0.274604
A2						-0.299261



$$\nu = 1/3$$

- **Loci diffusion**
- **Spatial correlation**
- **Chain relaxation dynamics**
- **Effect of activities**



monomer size, $a \sim 50$ kb

$$N = 2712 \quad R_s = 30 a \quad \phi = 0.1$$

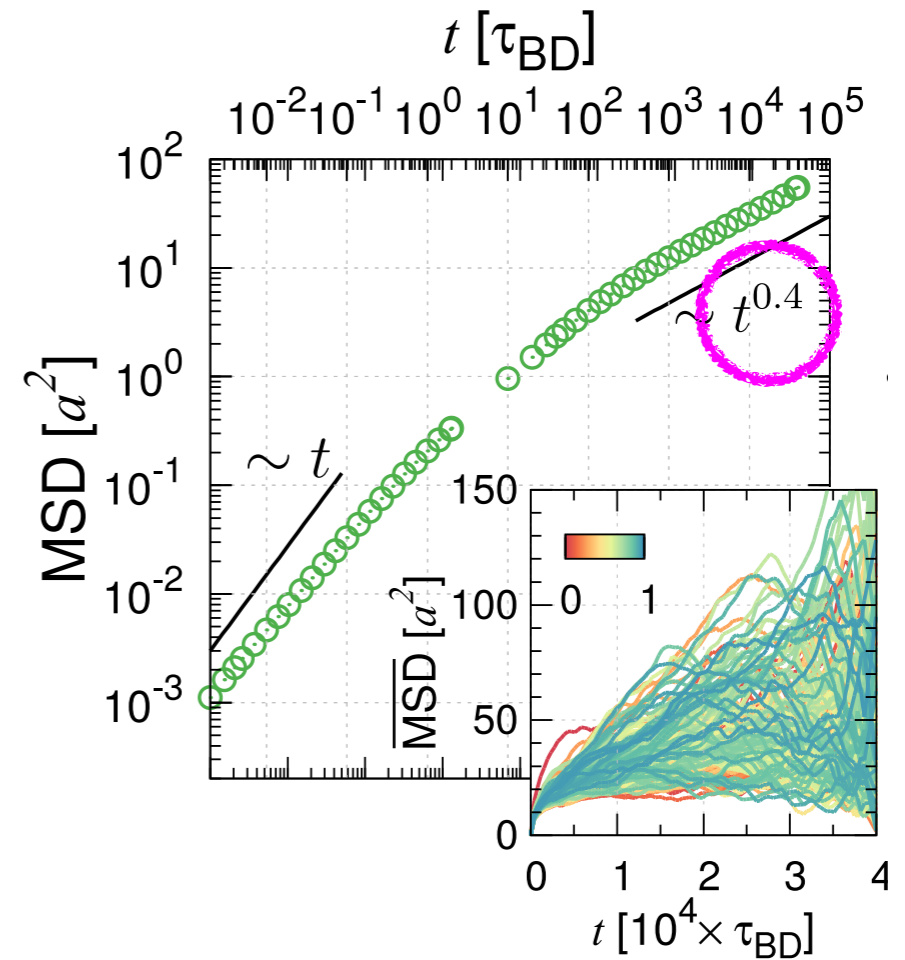
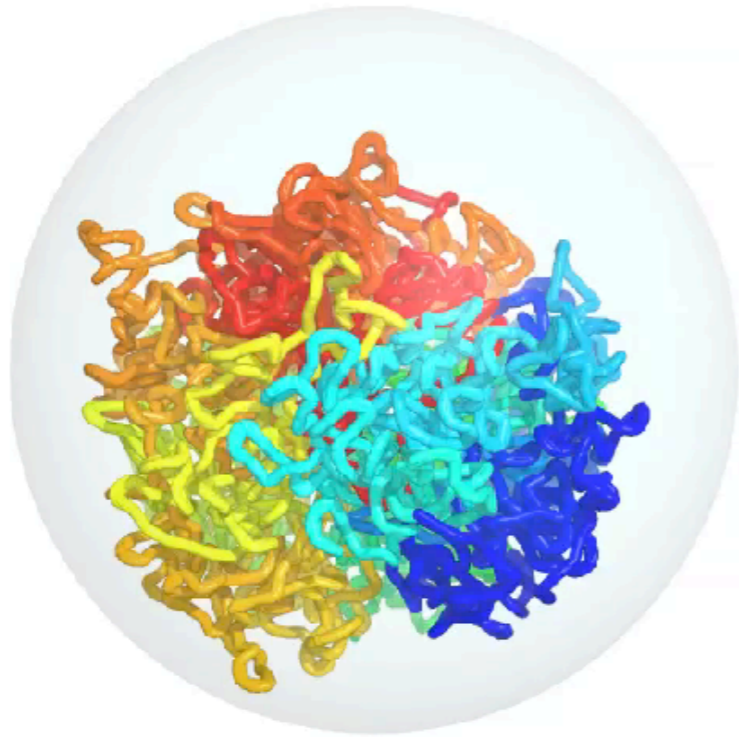
Brownian dynamics simulation

$$\tau_{\text{BD}} = 3\pi\eta a^3 / k_B T \approx 50 \text{ ms}$$

$$\eta = 7 \text{ cP}$$

(nuclear viscosity)

Sub-diffusive dynamics of chromatin loci



$$\begin{aligned}
 \text{MSD} &\sim t^\beta \\
 &\sim R(s)^2 \sim s^{2\nu} \\
 &\sim D(s) \times t \sim (D_o/s) \times t \sim t^{\beta/2\nu} \\
 &\sim t^{1-\beta/(2\nu)}
 \end{aligned}$$

Diffusion exponent is determined by the chain organization exponent

$$\beta = \frac{2\nu}{2\nu + 1} \begin{array}{l} \xrightarrow[\text{SF}]{\nu = 1/3} 0.4 \\ \xrightarrow[\text{RW}]{\nu = 1/2} 0.5 \end{array}$$

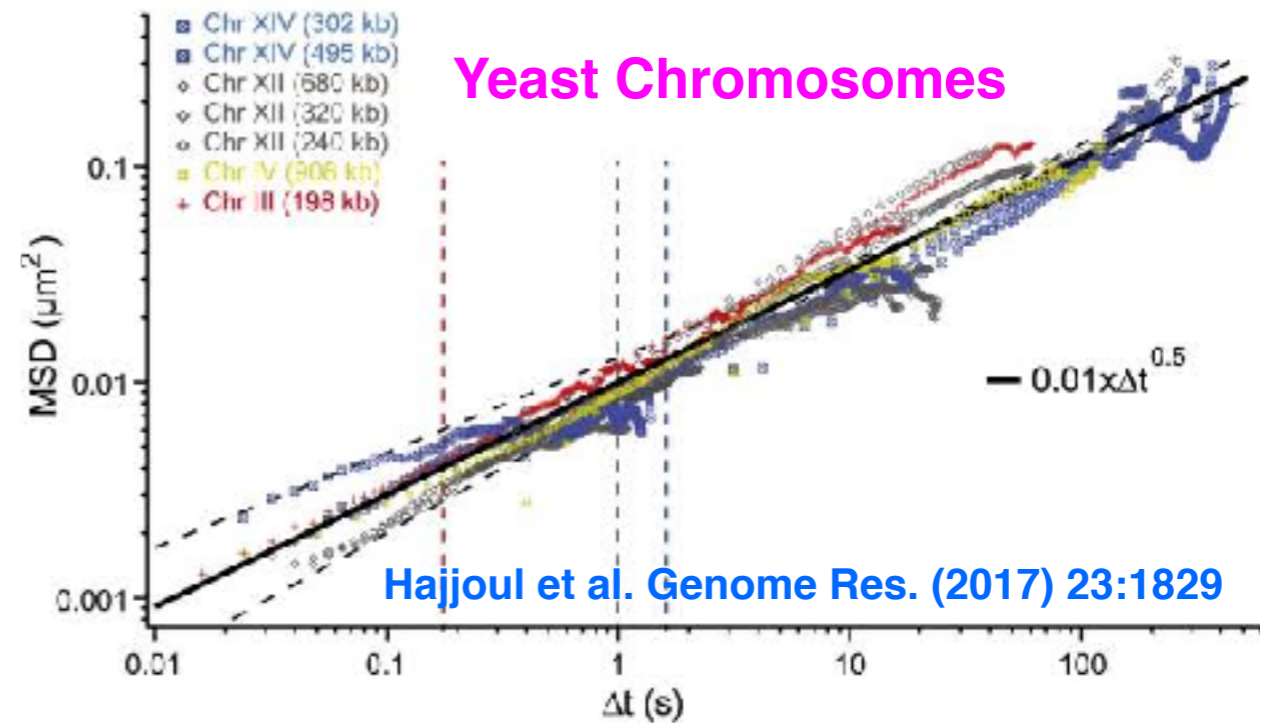
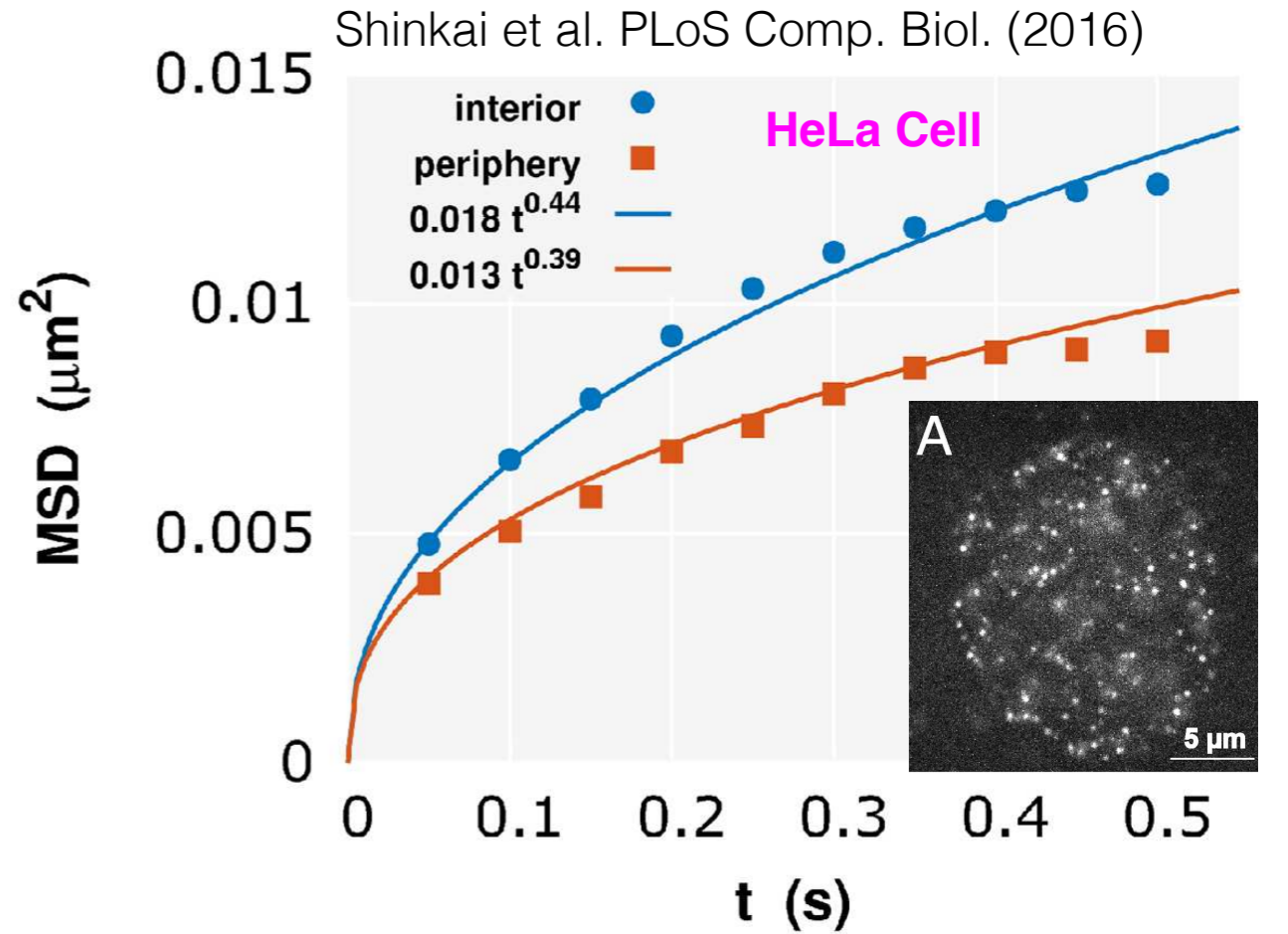
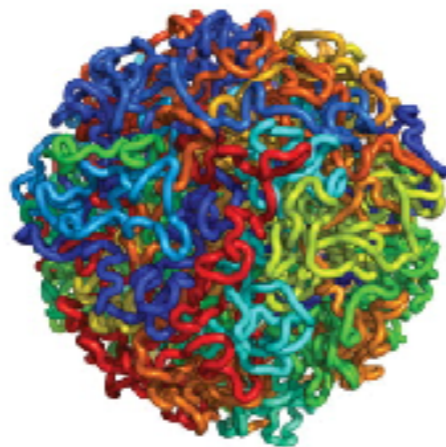
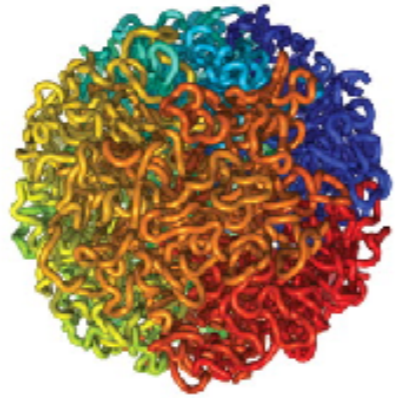
Tamm *PRL* (2015) 114:178102

Shinkai et al. *PLoS Comp. Biol.* (2016)

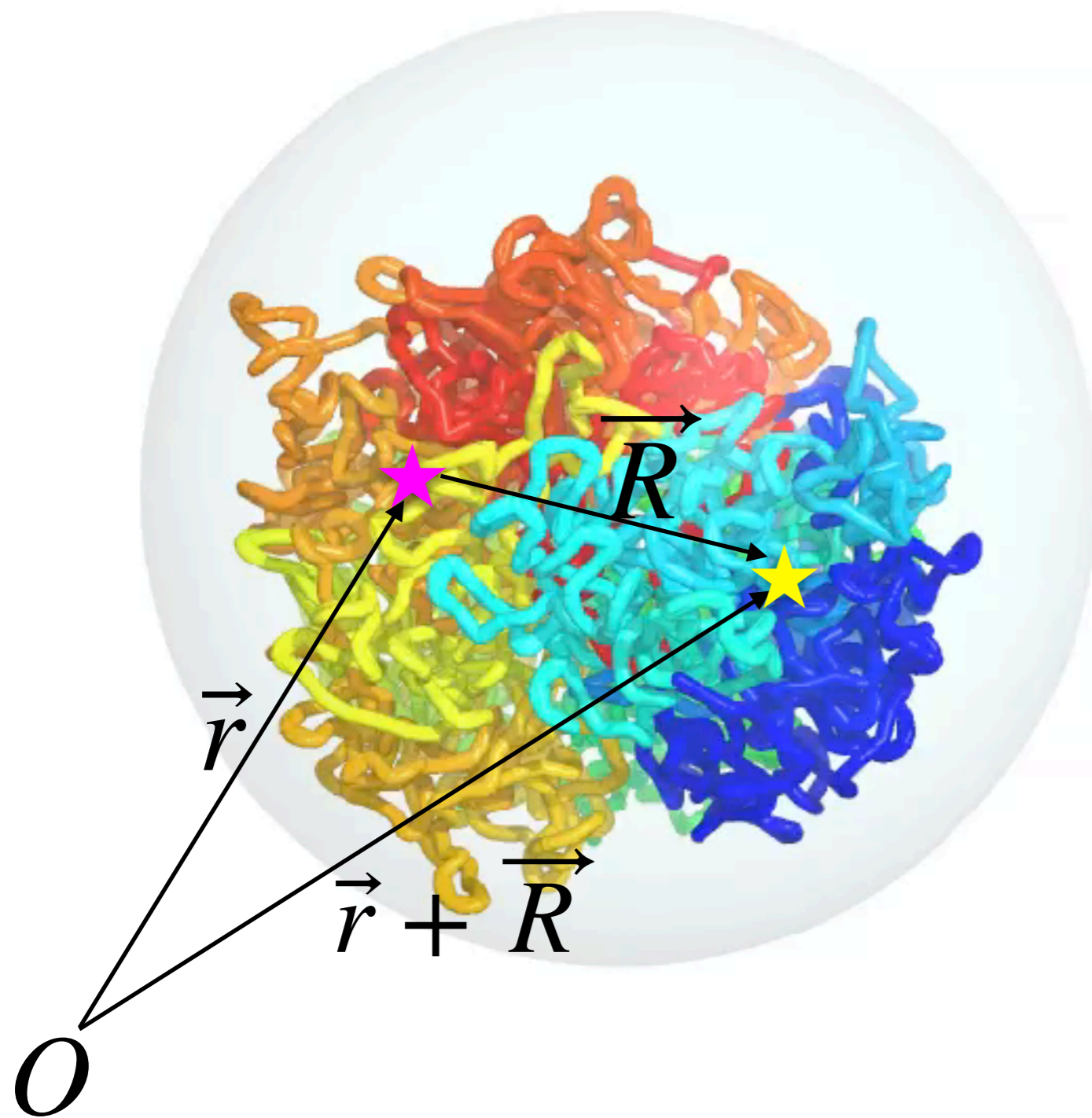
Liu et al. *PLoS Comp. Biol.* (2018) 14:e1006617

$$\beta = \frac{2\nu}{2\nu + 1}$$

$\nu = 1/3 \longrightarrow 0.4$
 $\nu = 1/2 \longrightarrow 0.5$



Relaxation dynamics



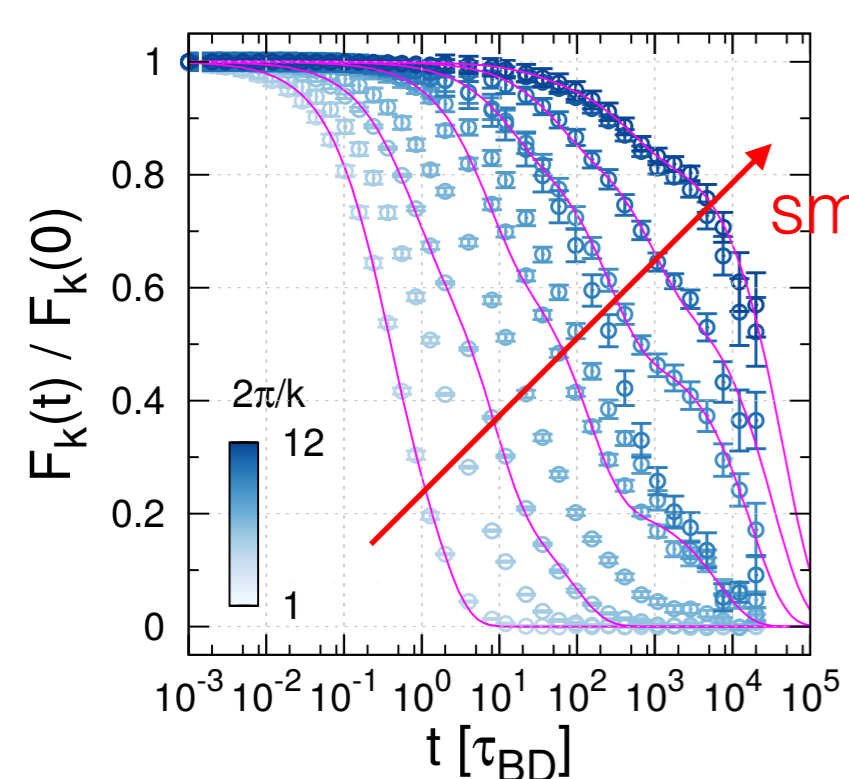
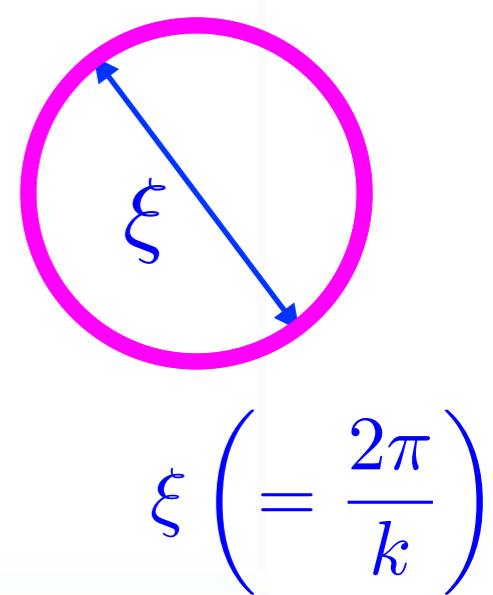
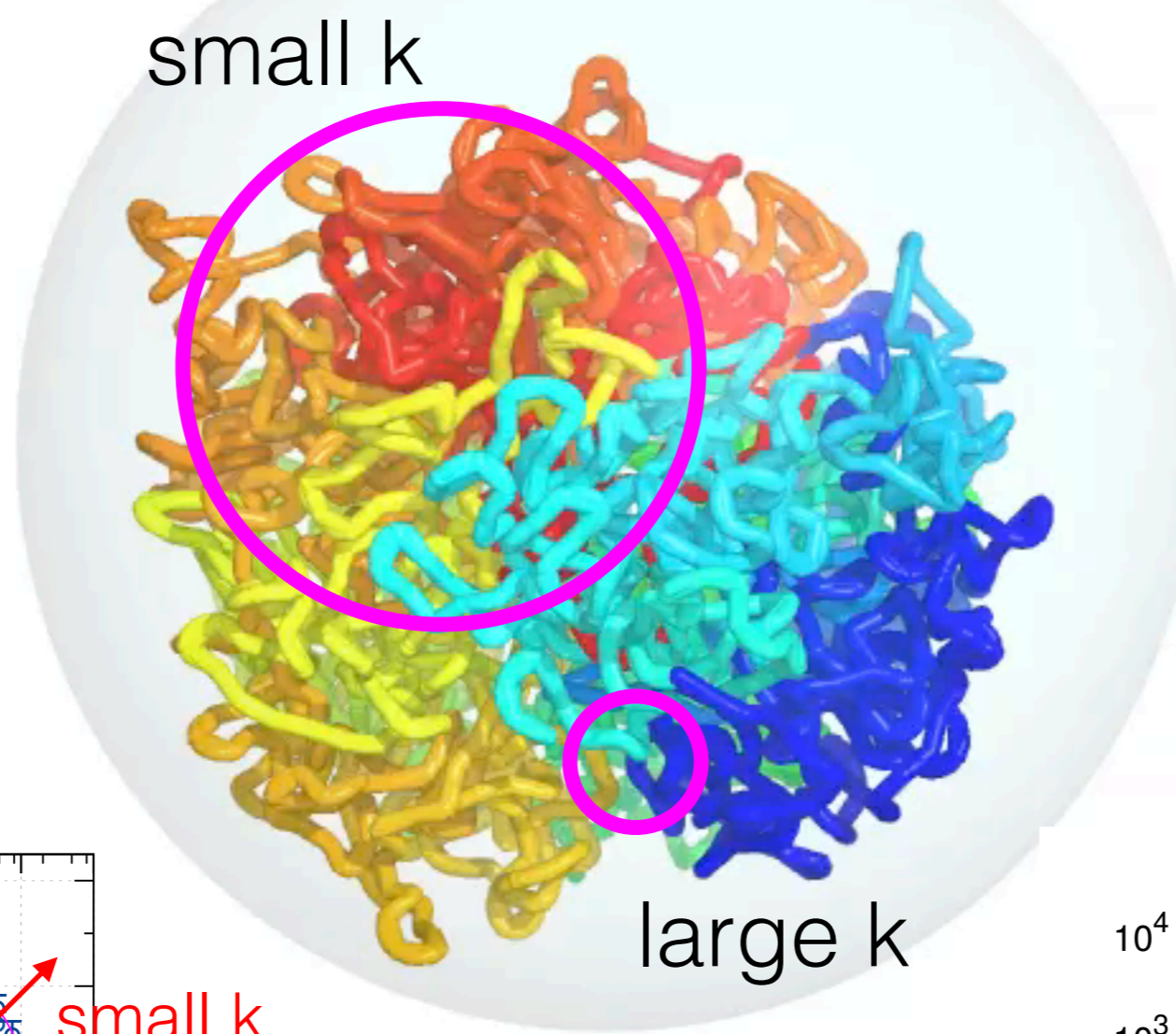
$$\rho(\vec{r}, t) = \sum_i^N \delta(\vec{r}_i - \vec{r})$$

$$\begin{aligned} C(\vec{R}) &= \frac{1}{N} \int d^3\vec{r} \langle \rho(\vec{r}, 0) \rho(\vec{r} + \vec{R}, t) \rangle \\ &= \frac{1}{N} \sum_i^N \sum_j^N \int d^3\vec{r} \langle \delta(\vec{r}_i - \vec{r}) \delta(\vec{r}_j - \vec{r} - \vec{R}) \rangle \\ &= \frac{1}{N} \sum_i^N \sum_j^N \langle \delta(\vec{r}_j - \vec{r}_i - \vec{R}) \rangle \\ &= \int \frac{d^3\vec{k}}{(2\pi)^3} \underbrace{\left[\left\langle \frac{1}{N} \sum_i^N e^{-\vec{k} \cdot \vec{r}_i(0)} \sum_j^N e^{\vec{k} \cdot \vec{r}_j(t)} \right\rangle \right]}_{=F_k(t)} e^{-\vec{k} \cdot \vec{R}} \end{aligned}$$

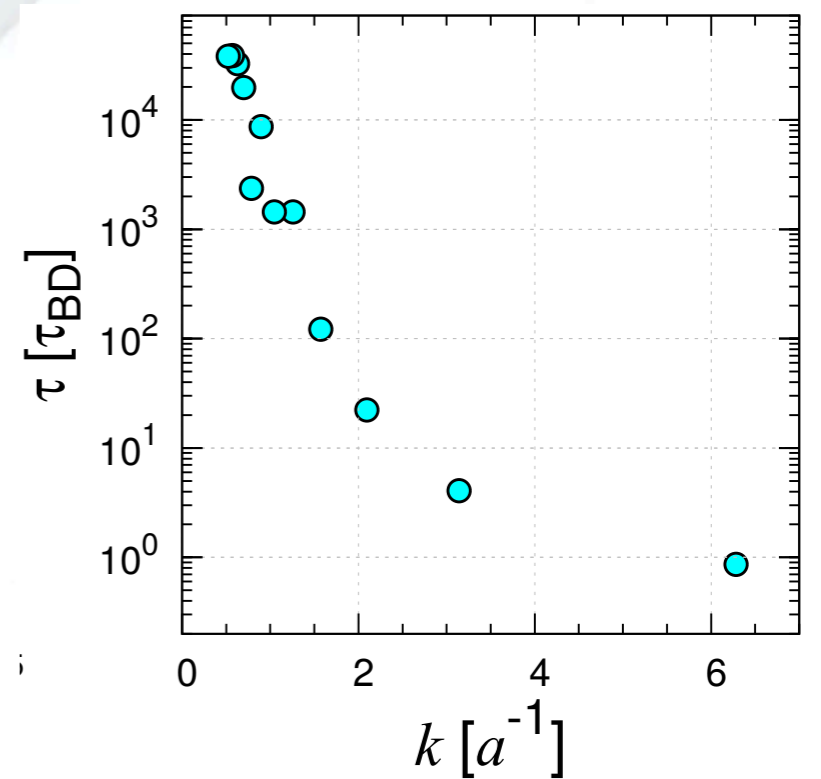
$$F_k(t) = \left\langle \left\langle \frac{1}{N} \sum_m e^{i\vec{k} \cdot \vec{r}_m(t+t_0)} \sum_n e^{-i\vec{k} \cdot \vec{r}_n(t_0)} \right\rangle_{|\vec{k}|} \right\rangle_{t_0}$$

Relaxation dynamics

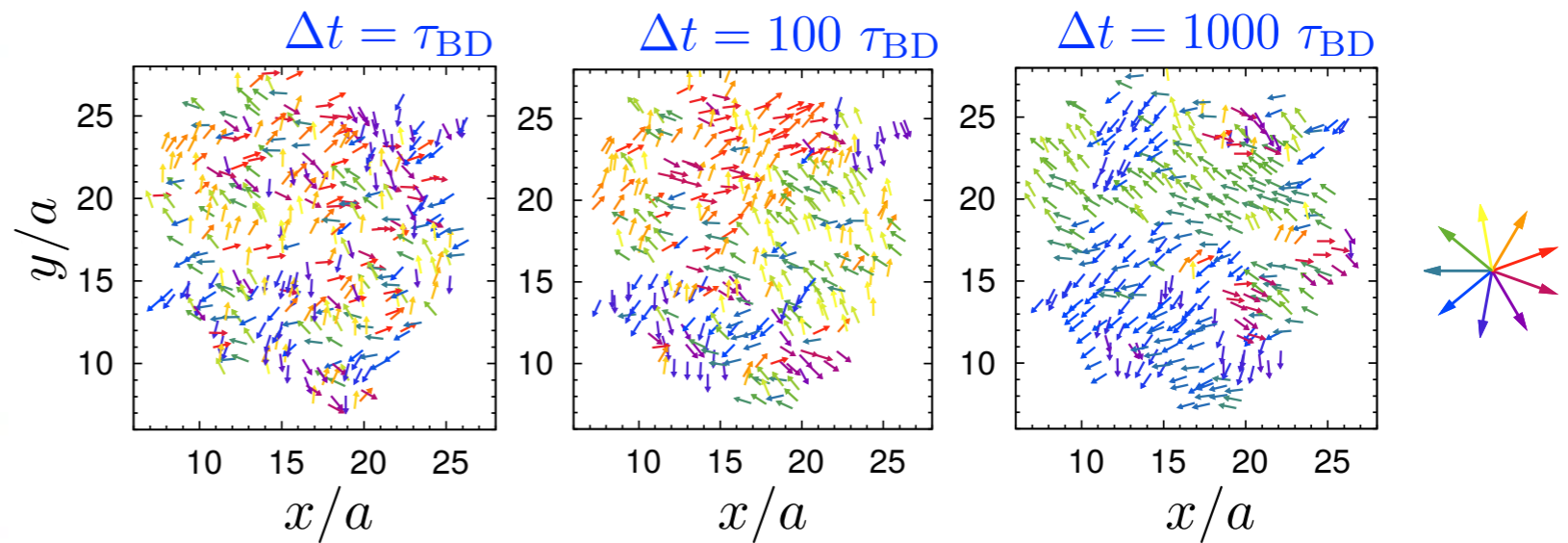
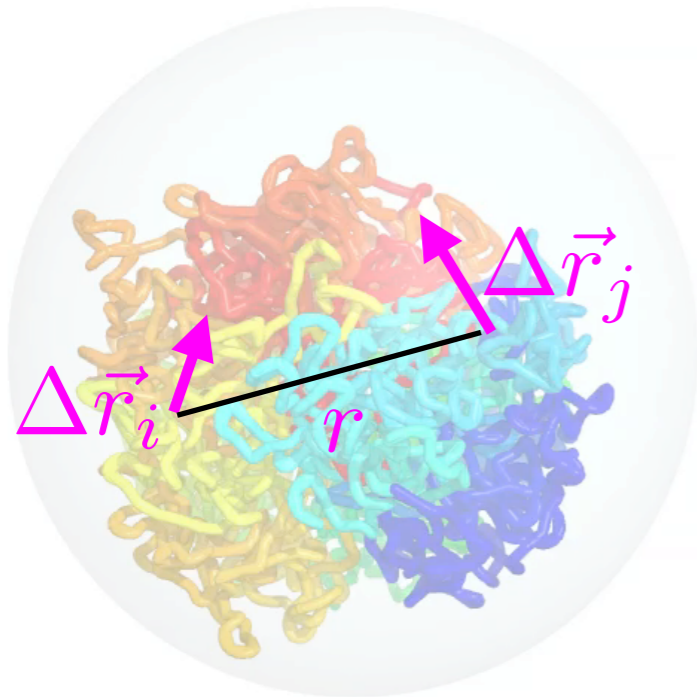
$$F_k(t) = \left\langle \left\langle \frac{1}{N} \sum_m e^{i\vec{k}\cdot\vec{r}_m(t+t_0)} \sum_n e^{-i\vec{k}\cdot\vec{r}_n(t_0)} \right\rangle_{|\vec{k}|} \right\rangle_{t_0}$$



$$\tau = \int_0^\infty \frac{F_k(t)}{F_k(0)} dt$$

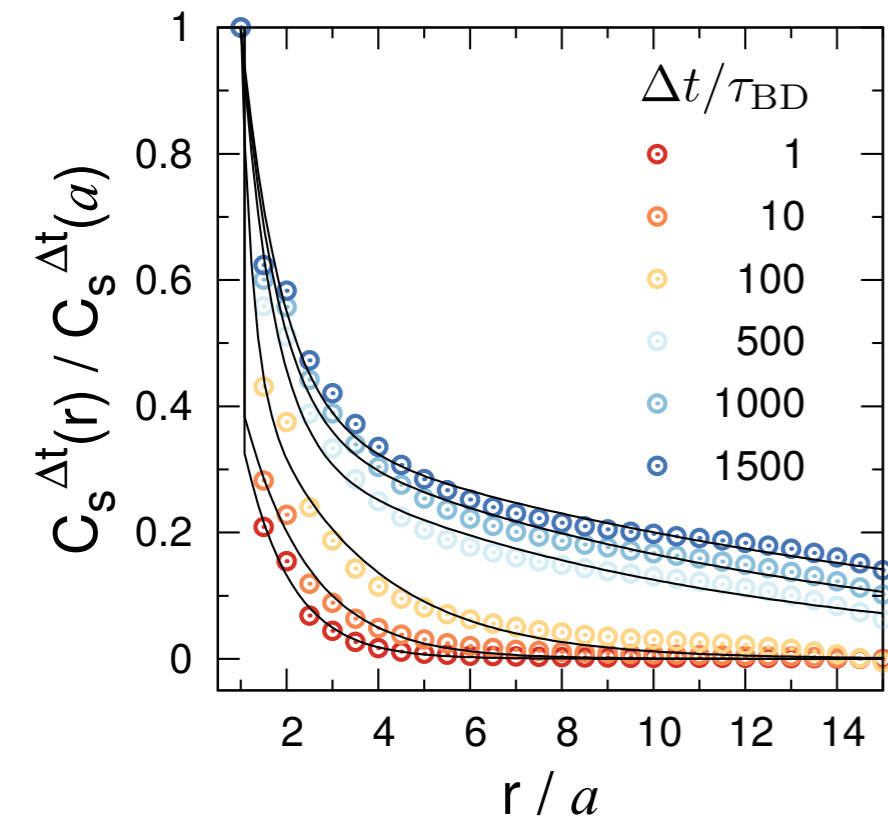


Spatial correlation between loci

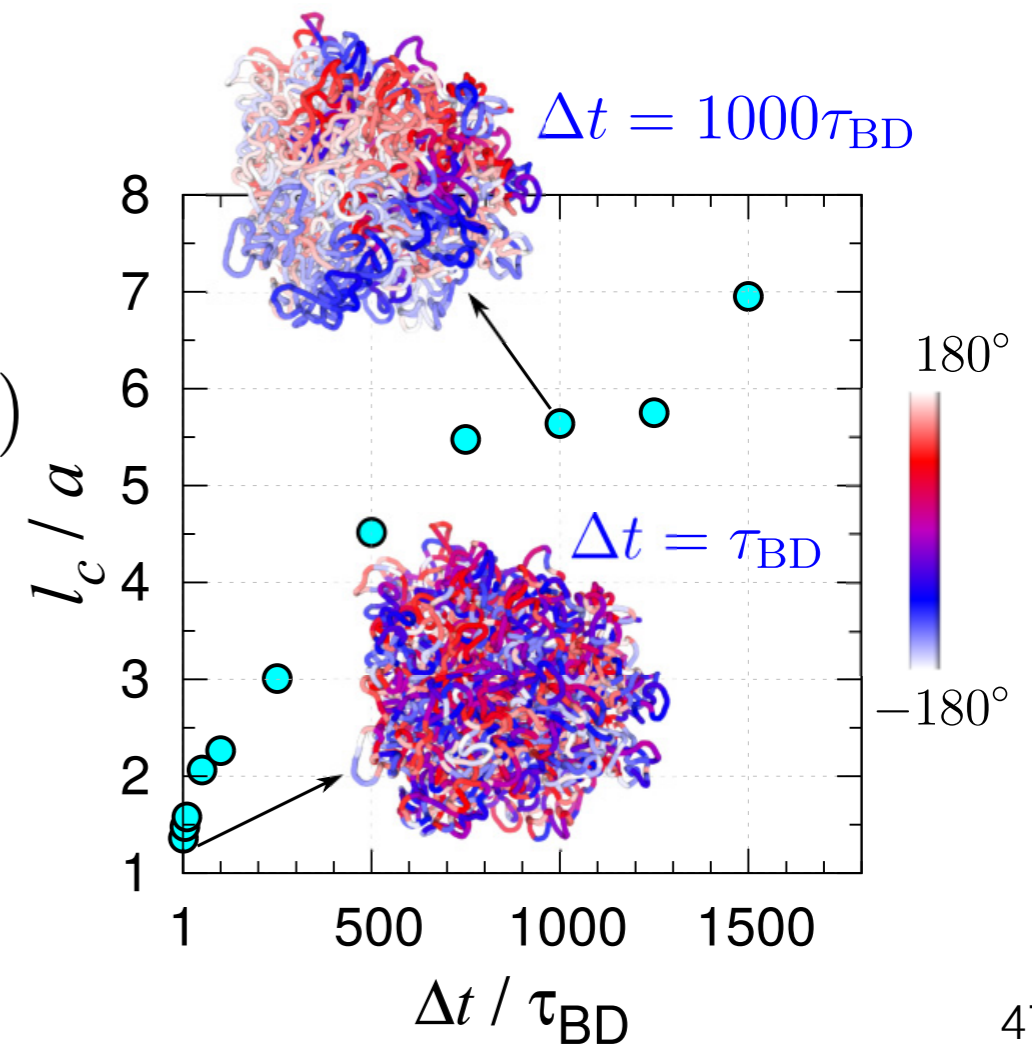


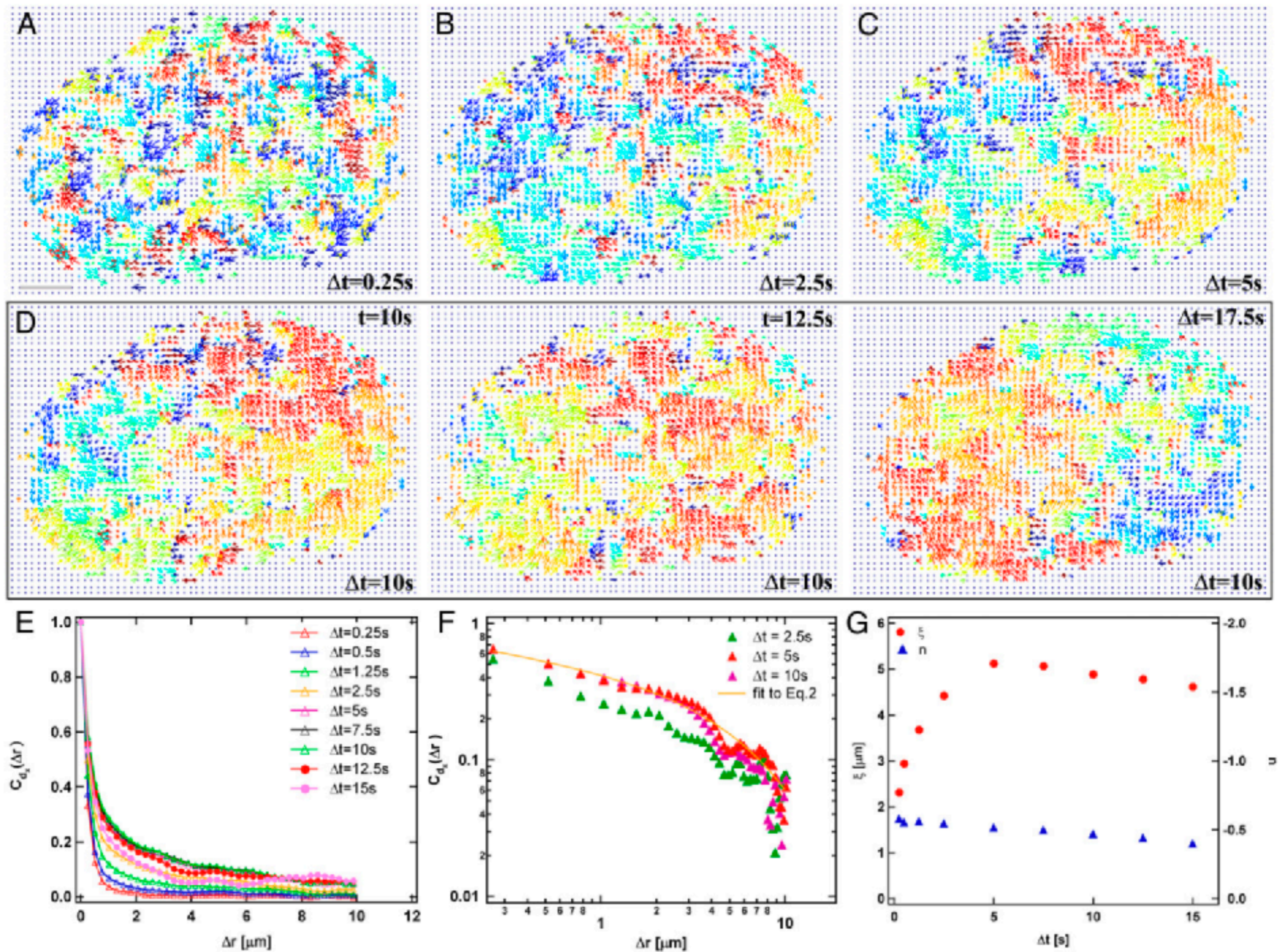
cf. Dynamic Correlation Spectroscopy (DCS), Zidovska et al. PNAS (2013)

$$C_s^{\Delta t}(r) = \left\langle \frac{\sum_{i>j} [\Delta \vec{r}_i(t; \Delta t) \cdot \Delta \vec{r}_j(t; \Delta t)] \delta(r_{i,j} - r)}{\sum_{i>j} \delta(r_{i,j} - r)} \right\rangle_t$$



$$l_c \left(= \int_0^\infty [C_s^{\Delta t}(r) / C_s^{\Delta t}(a)] dr \right)$$





Effects of activity on loci diffusion

Activities inside cell nuclei.

DNA polymerase

RNA polymerase

Cohesin (Loop extrusion)

vectorial, force dipole, ... at small scales Bruinsma et al. Biophys. J. (2014), 106, 1871

But, beyond a certain spatiotemporal scale, activities may be randomized and deemed isotropic w/o correlation in the ‘interphase’

$$\gamma \dot{x} = -\partial_x U(\{\mathbf{r}\}) + \xi(t)$$

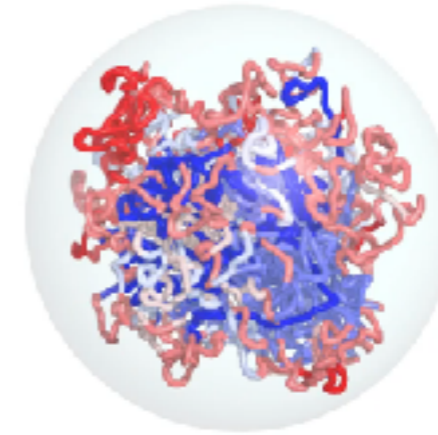
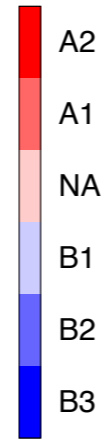
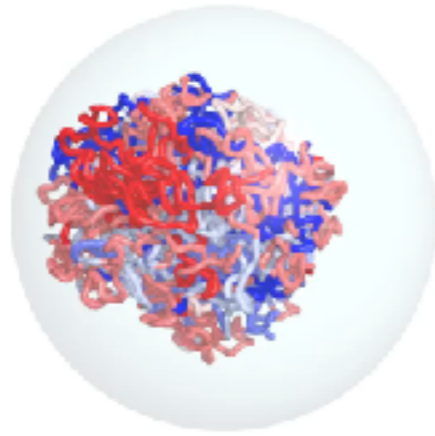
$$\langle \xi(t) \xi(t') \rangle = 2\gamma k_B T_a \delta(t - t')$$

$$T_a = 2 \times T$$

Smrek & Kremer, PRL 118, 098002 (2017).

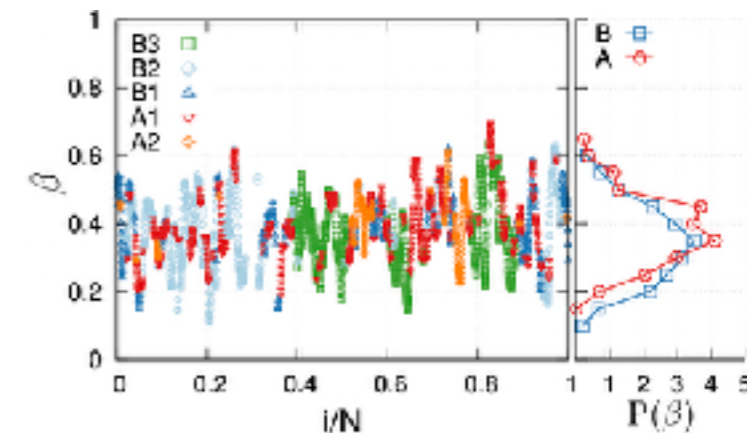
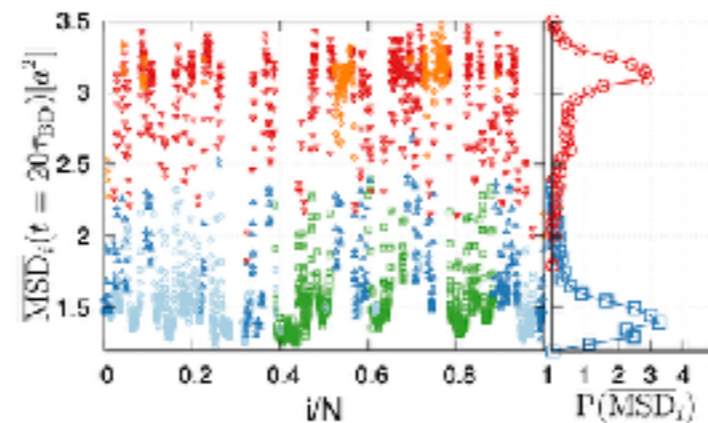
Effects of activity on loci diffusion

Passive

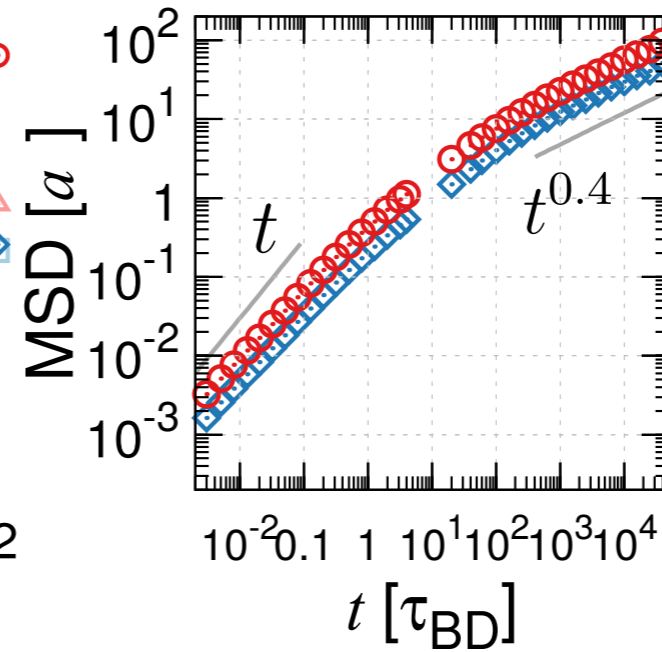
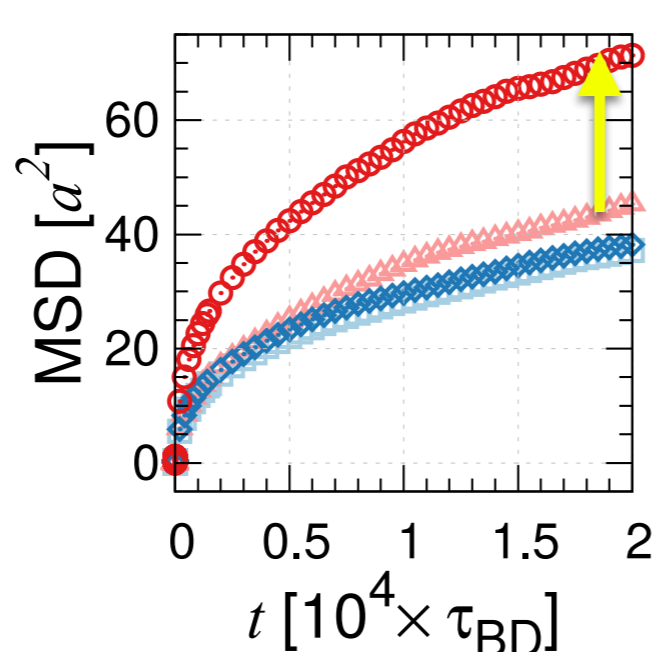


Active

stronger isotropic white noise on active loci

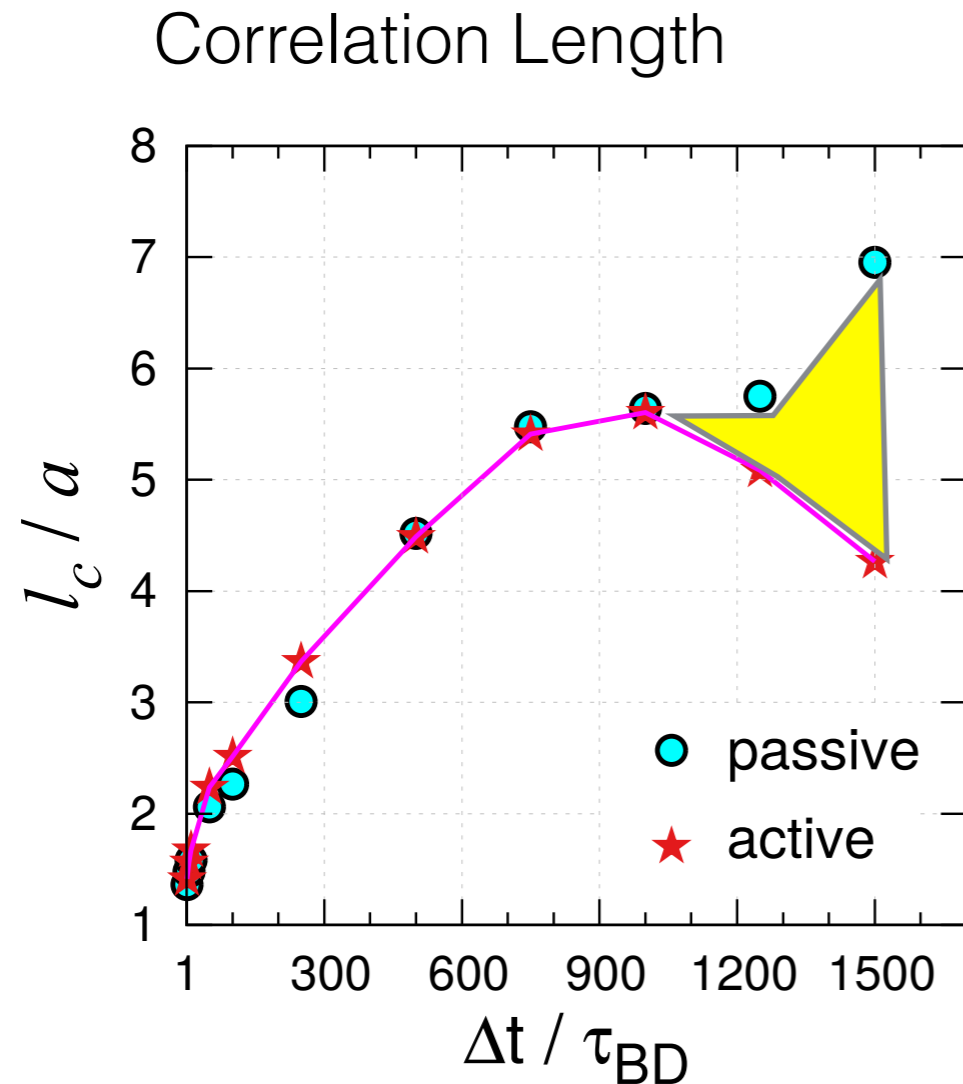


- B3 (passive) ■
- A1 (passive) ▲
- B3 (active) ◆
- A1 (active) ⊕

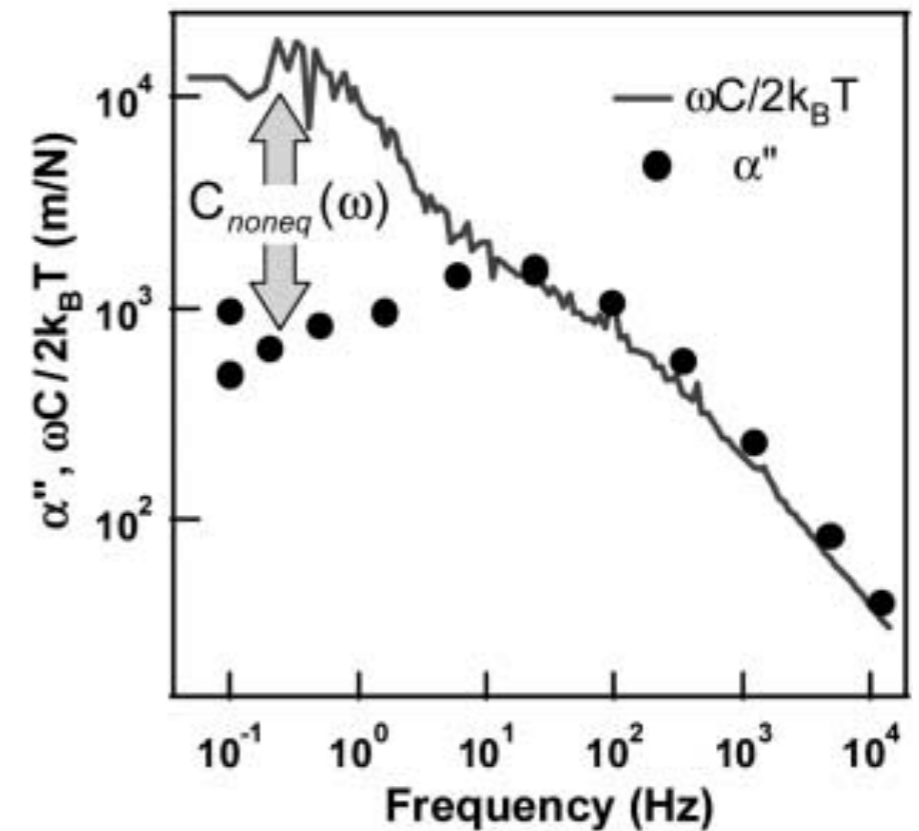


Effects of activity on spatial correlation

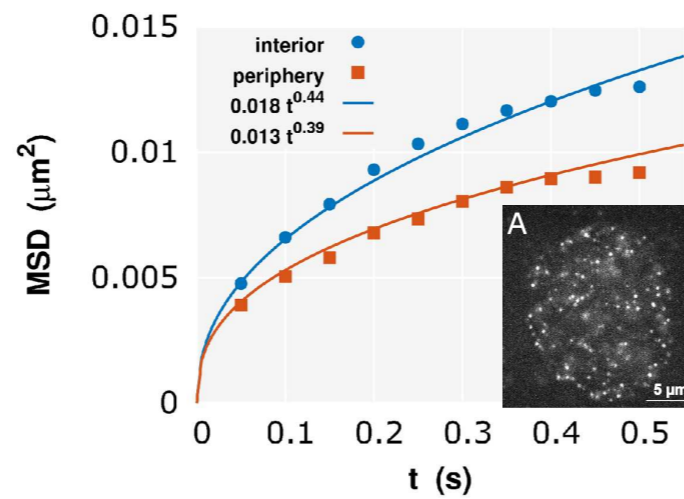
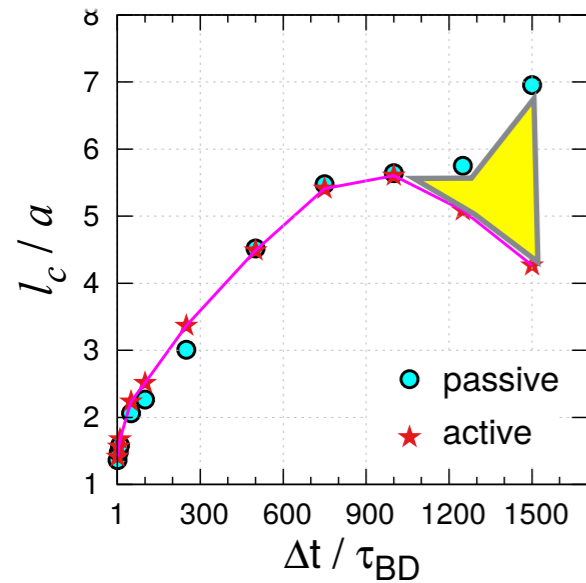
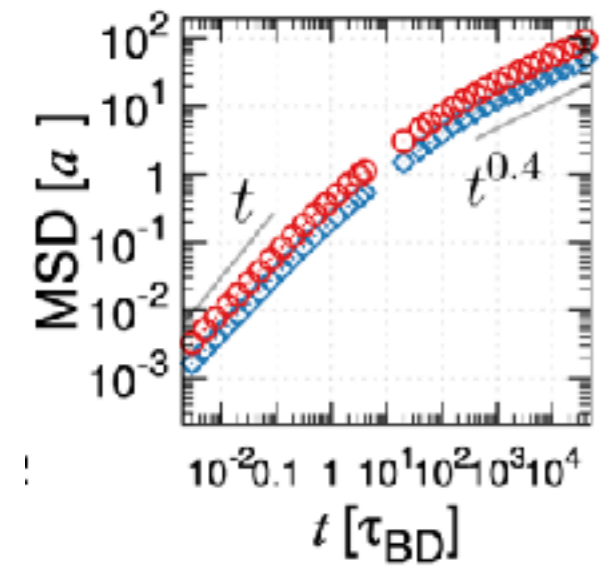
Displacement Correlation



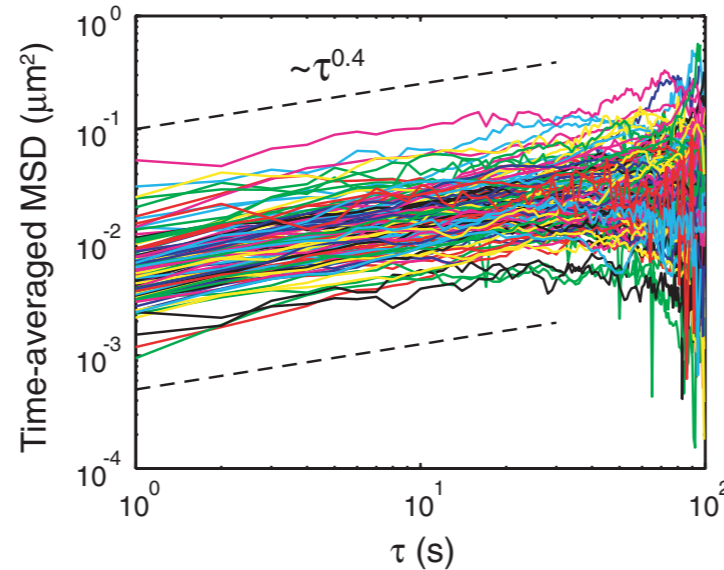
cf. active actin network



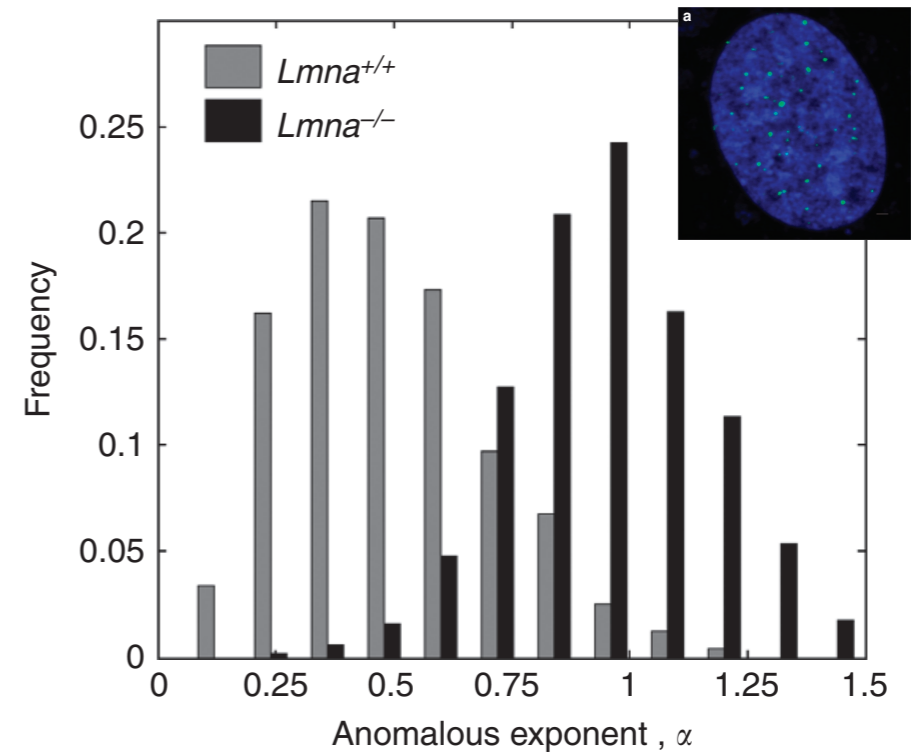
Mizuno et al. Science (2007)



Shinkai et al. PLoS Comp. Biol. (2016)



Weber et al. PRL (2010) 104, 238102



Bronshtein Nat. Comm. (2015) 6:8044

Biological activities in the INTERPHASE

1. do NOT affect the diffusion exponent ($\beta=0.4$) — SF organization ($\nu=1/3$) unaltered.
2. only affect the low frequency modes

Thermal power

$$\sim k_B T / \text{ps}$$

$$= 10^{12} k_B T / \text{s}$$

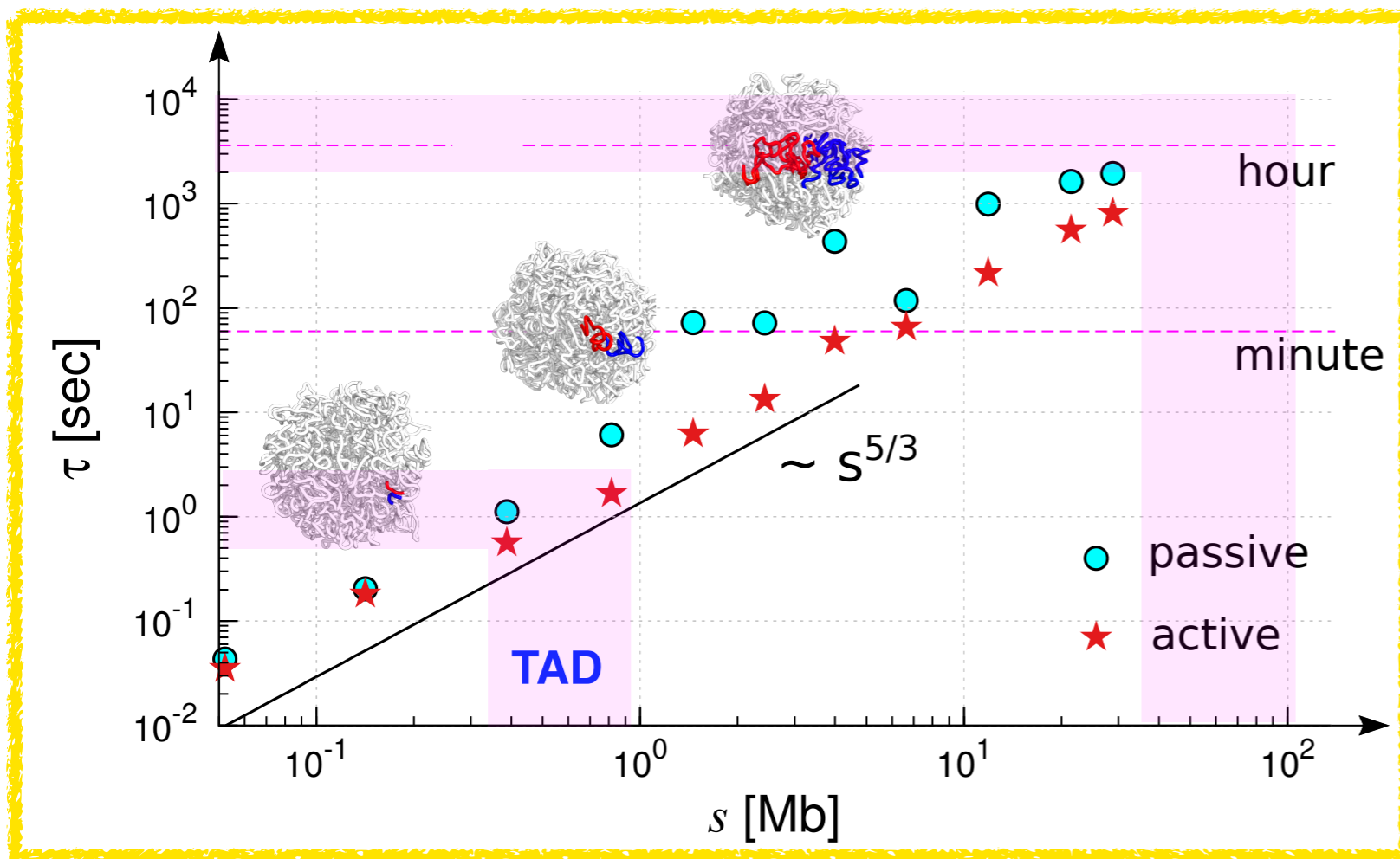
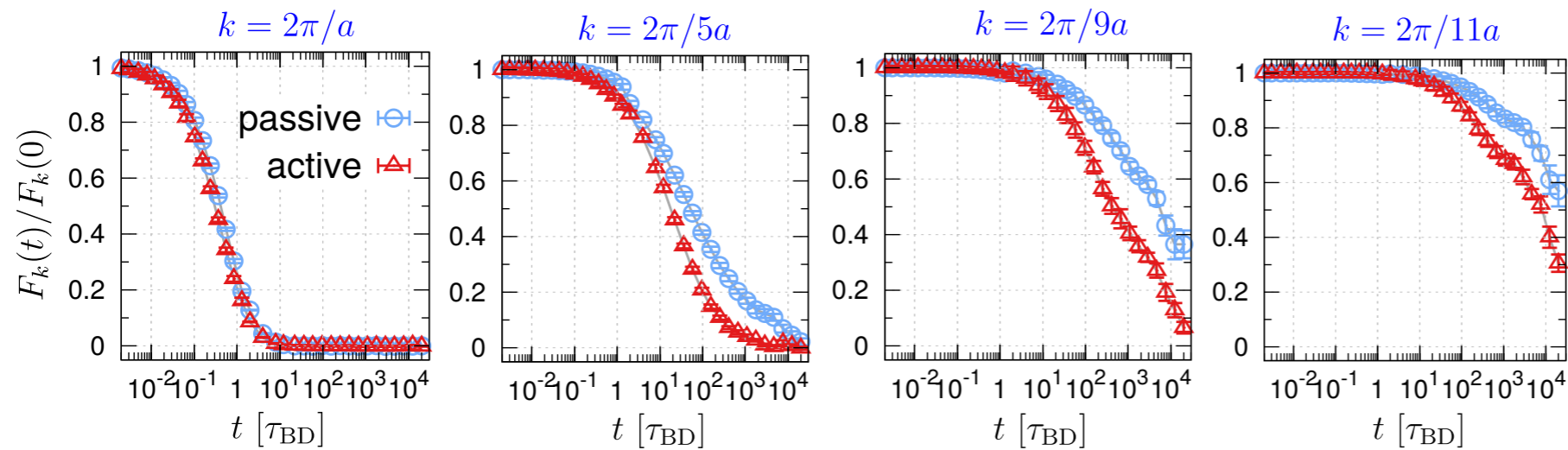


Power by ATP hydrolysis

$$\sim 20 k_B T / \text{ms}$$

$$= 2 \times 10^4 k_B T / \text{s}$$

Effects of activity on chain relaxation



$$\tau(k) \xrightarrow{\frac{2\pi}{k} = \xi \sim s^\nu} \tau(s)$$

$$\tau \sim \frac{\xi^2}{D_{\text{eff}}} \sim \frac{(s^\nu)^2}{D_0/s} \sim s^{2\nu+1}$$

Summary

- **Chromosome structure and dynamics using homopolymers**
 $P(s) \sim s^{-\gamma}$: equilibrium/crumpled globule, reptation, slow dynamics due to confinement
- **HiC data-based heteropolymer model** to study chromosome structure and dynamics
- Chain organization of chromosome at intermediate length scale and its **dynamical behaviors are determined by the SF organization** ($\nu=1/3$) of chromatin chain.
- Effects of “**biological activity**” on the interphase chromatin organization and dynamics. (Only the **low frequency modes** are affected).

$$W_p \sim k_B T / \text{ps} \gg W_a \sim 20k_B T / 10\text{ms} \quad N_p W_p \gg N_a W_a \text{ (for interphase)}$$