Effect of epigenetics and extrusion on chromatin organization and dynamics

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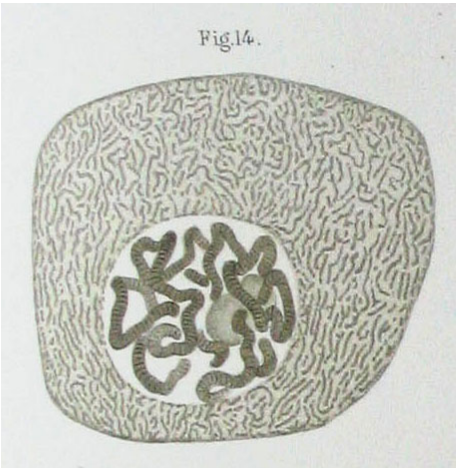
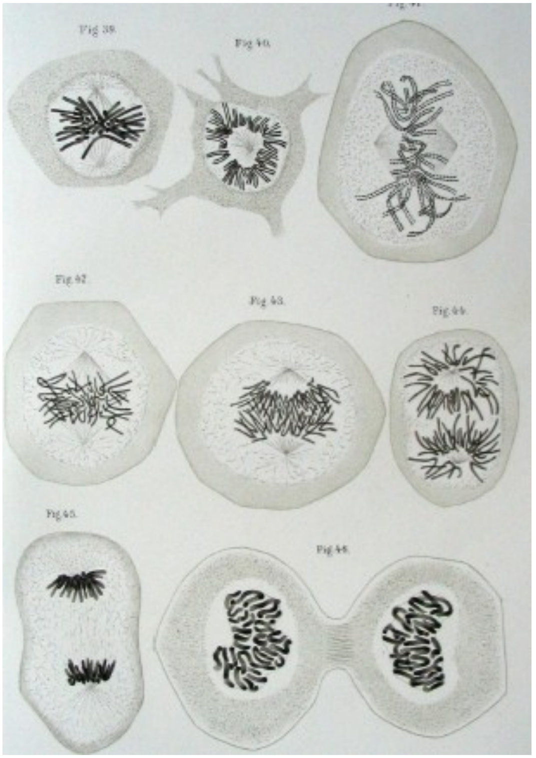
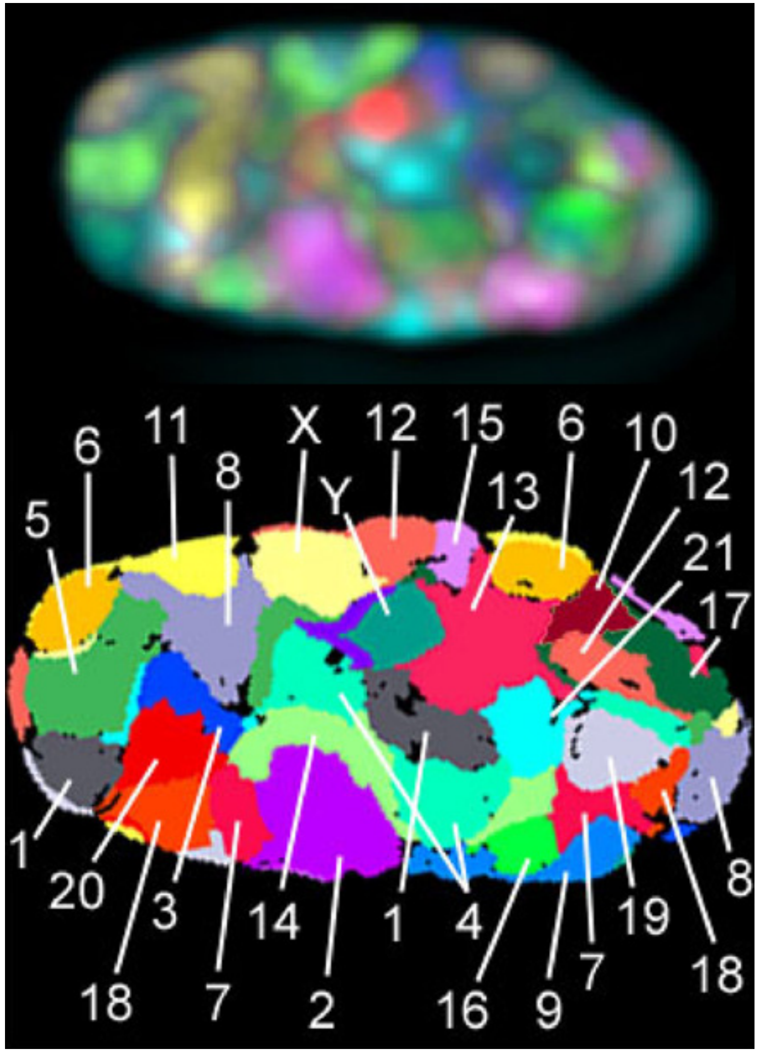
Chromosome in 3D

Walther Flemming





Chromosomes : drawing by W. Fleming, 1885

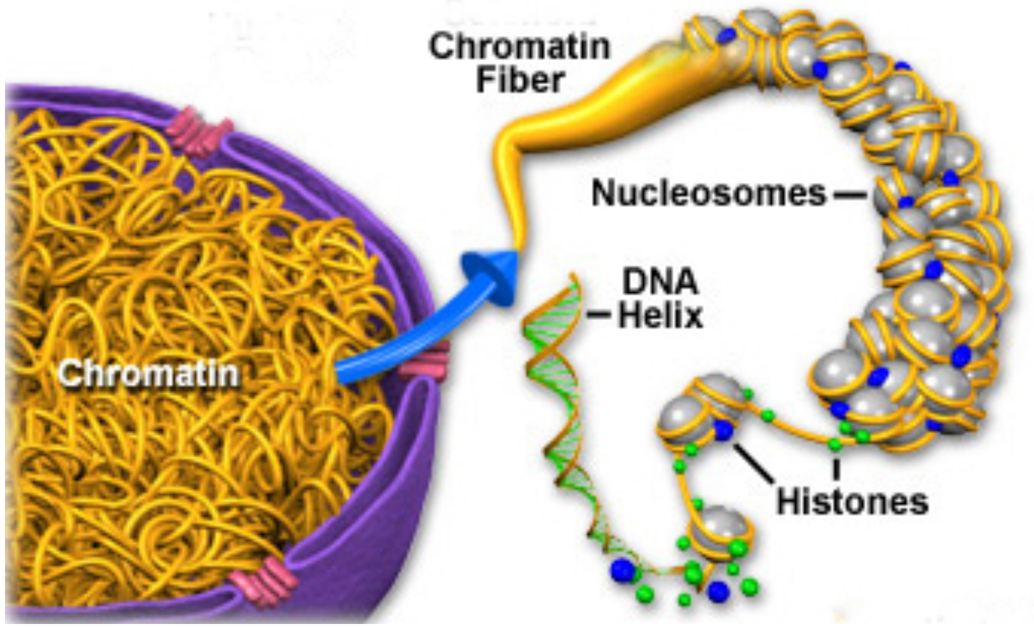


Chromosomes in 2005
by Bolzer et al. PloS Bio

The law code and executive power!

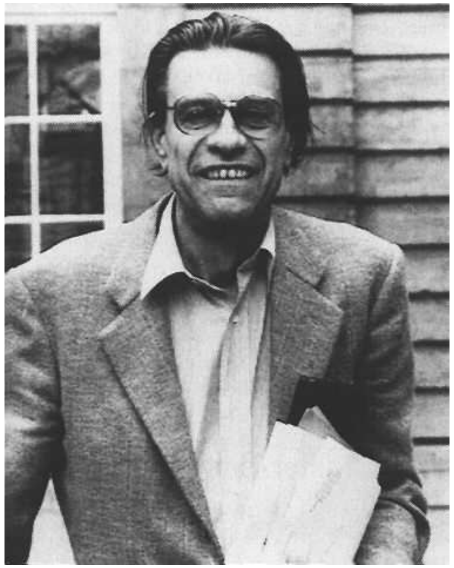
"Chromosomes are law-code and executive power - or, to use another simile, they are architect's plan and builder's craft - in one."

— Erwin Schrodinger, 1944,
What is Life?



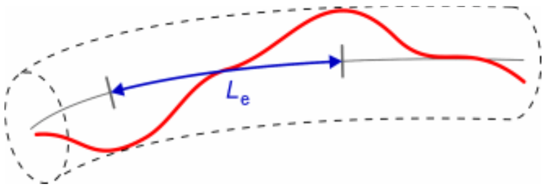
Chromosome large scale organization is a beautiful example of the interplay between Physics and Biology!

Topologically Constrained System



de Gennes, 1975

- Entanglement Length(Le)
  - Density in Kuhn segment: ρ_k
  - Kuhn Length: l_k

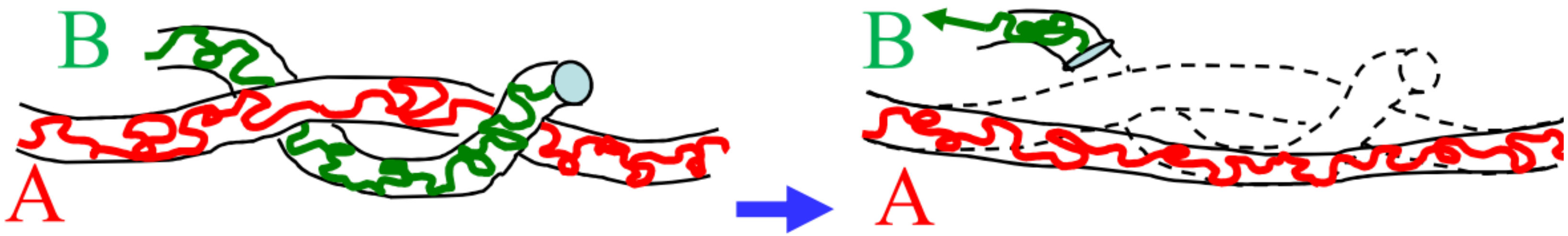


- Entanglement Length in nm:

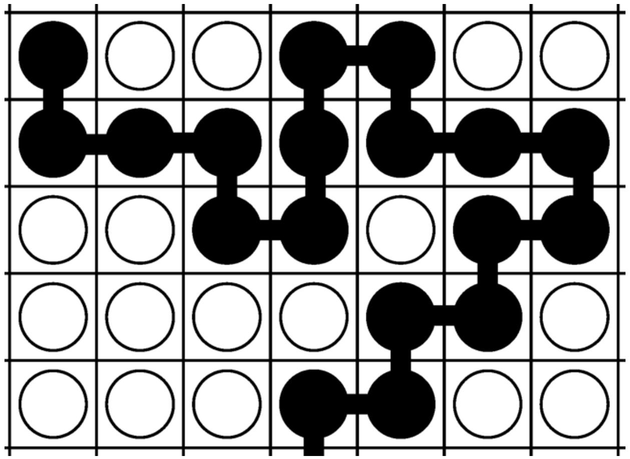
$$L_e = l_k \left(\frac{c}{\rho_k l_k^3} \right)^2$$

Ralf Everaers et. al. JCP, 2008, 128

- Reptation of Linear Chains

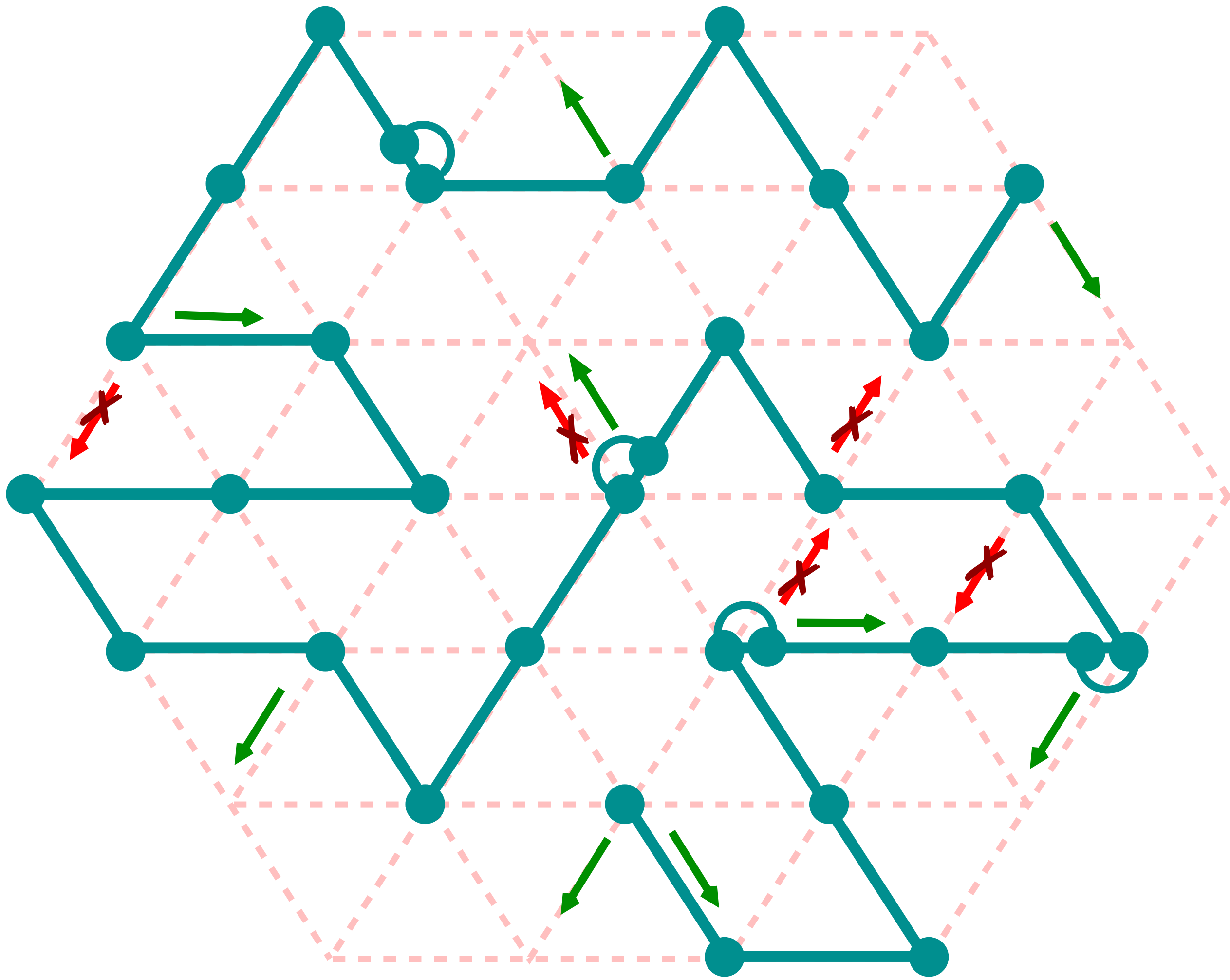


Chromosome modeled as a lattice polymer



lattice polymer model

fcc lattice polymer model



Rubinstein, PRL, 1987; Barkema et al, JCP, 2018;
Ghosh and Jost, Biorxiv 200584, 2017.

Physical quantities to measure

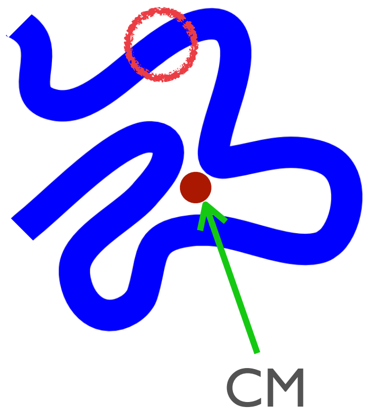
1. Mean Squared Displacement (MSD)
2. Physical Distance
3. Contact Probability

Physical quantities to measure

1. Mean Squared Displacement (MSD)

   1.1 MSD of each segment: $g_{1i}(t) = \left\langle \left(\mathbf{r}_i(t) - \mathbf{r}_i(0)\right)^2 \right\rangle$

   1.2 MSD of the center of mass: $g_3(t) = \left\langle \left(\mathbf{r}_{cm}(t) - \mathbf{r}_{cm}(0)\right)^2 \right\rangle$



2. Physical Distance

3. Contact Probability

Physical quantities to measure

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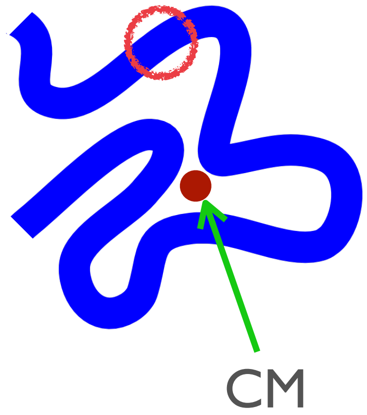

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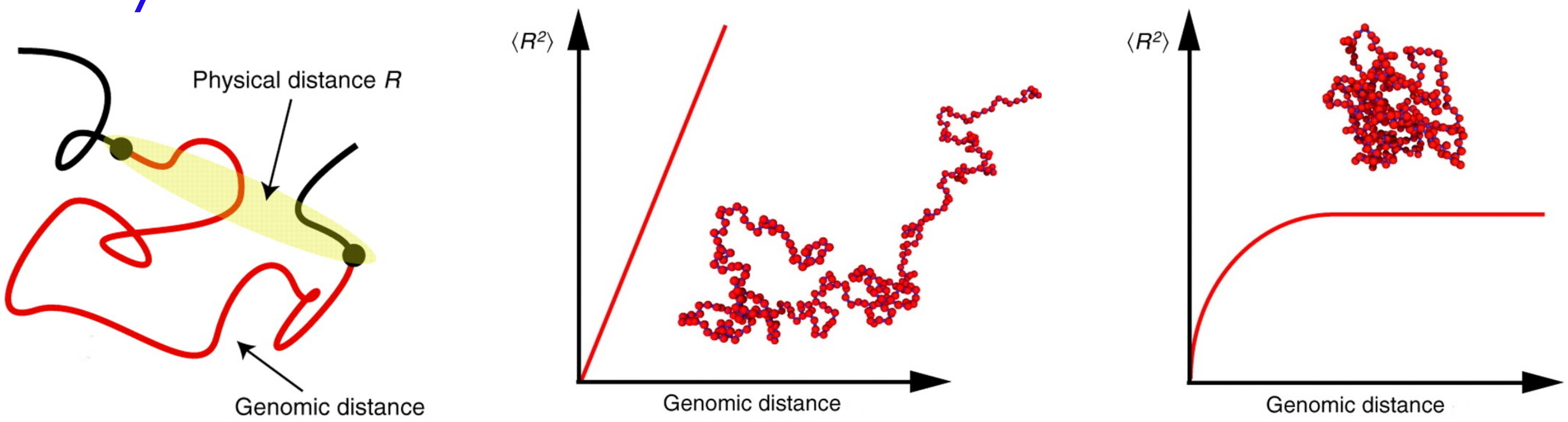
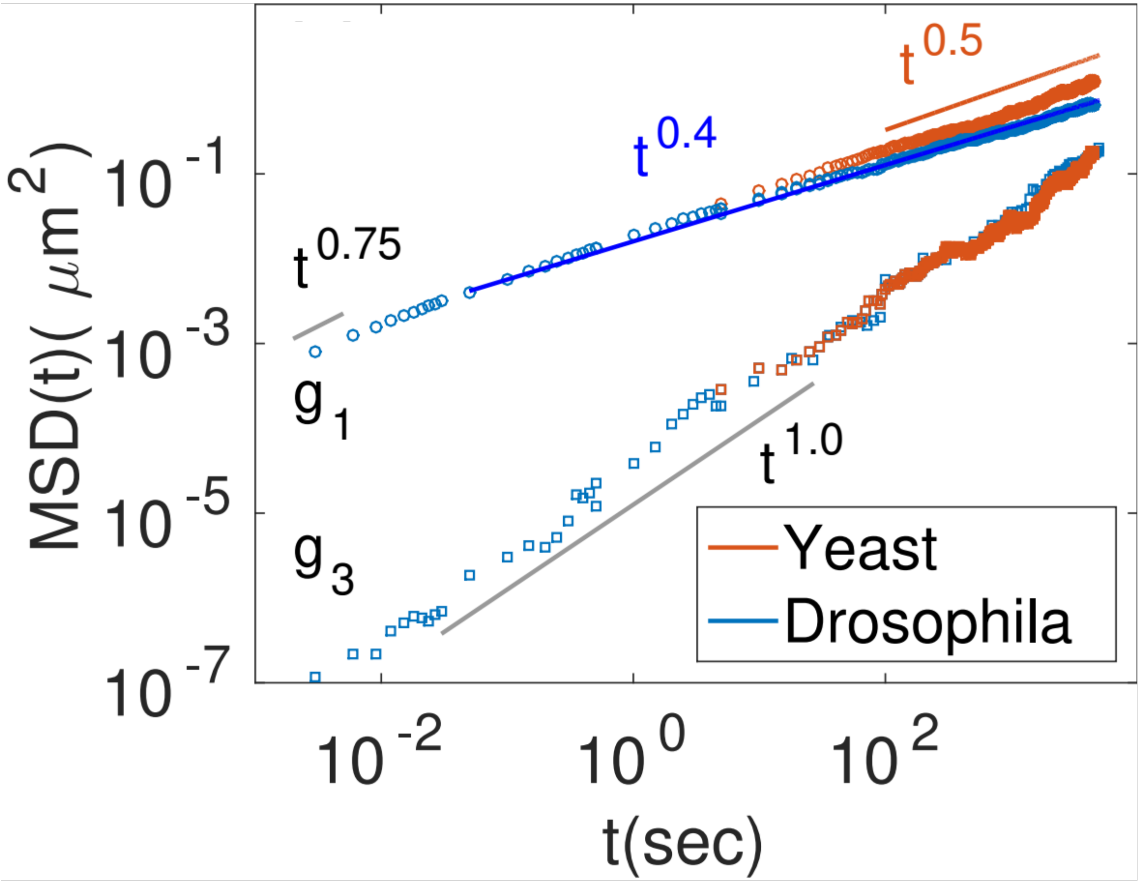
2. Physical Distance



3. Contact Probability

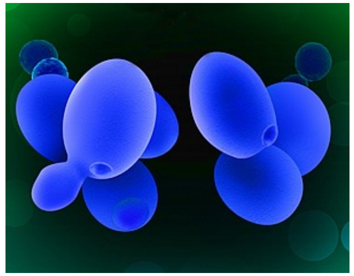
Time Mapping

- Mean Squared Displacement (MSD)
- Yeast and Drosophila Chromosome



Ghosh and Jost, Biorxiv 200584, 2017.

- **Yeast**

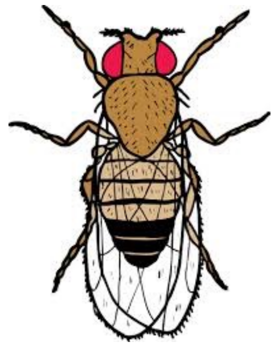


$L = 750$ kbp

$\rho \approx 0.005\, bp / nm^3$

$L_e = 920$ kbp

- **Drosophila**



$L = 20$ Mbp

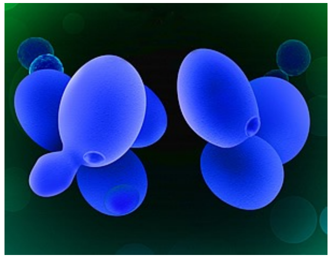
$\rho \approx 0.009\, bp / nm^3$

$L_e = 285$ kbp

Measured physical quantities

- **Yeast**

$$L = 750 \text{ kbp}$$
$$\rho \approx 0.005\, bp / nm^3$$
$$L_e = 920 \text{ kbp}$$



- **Drosophila**

$$L = 20 \text{ Mbp}$$
$$\rho \approx 0.009\, bp / nm^3$$
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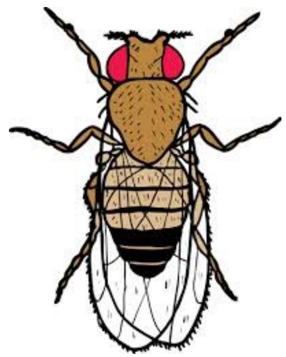
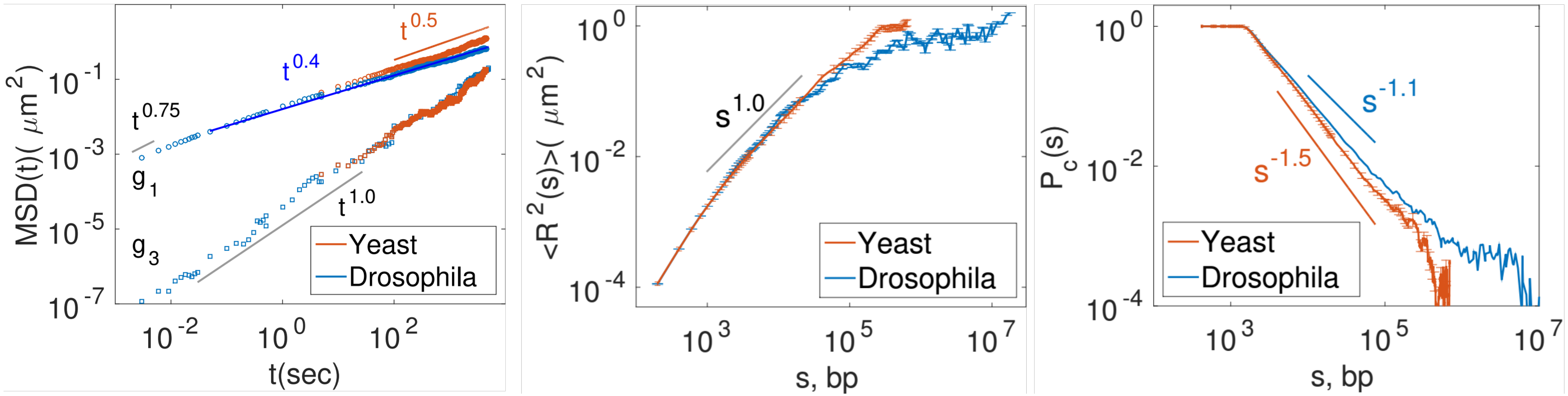
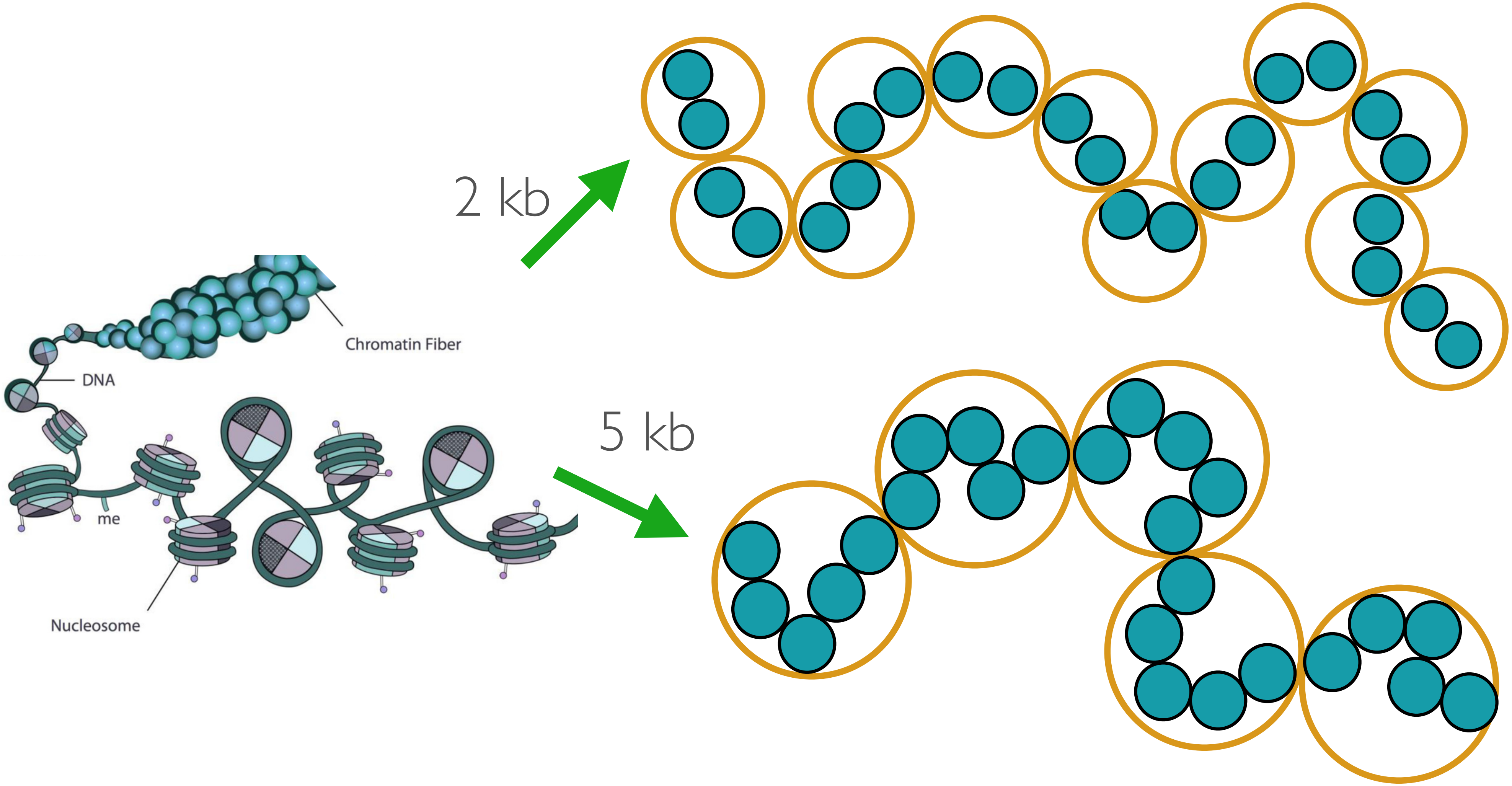


- **Yeast, Drosophila** Chromosome at nucleosome resolution



Ghosh and Jost, Biorxiv 200584, 2017.

Chromosome: Coarse Graining Long Polymers



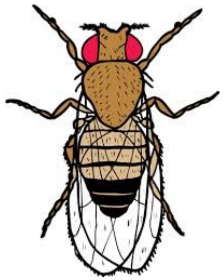
Measured physical quantities

- **Drosophila**

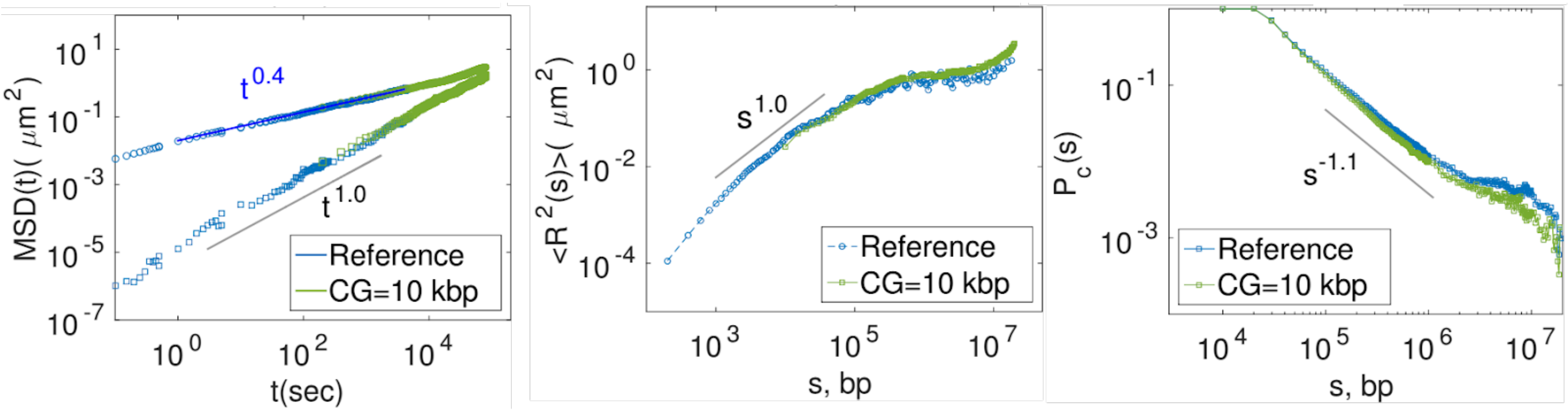
  $L = 20$ Mbp

  $\rho \approx 0.009\ bp/nm^3$

  $L_e = 285$ kbp

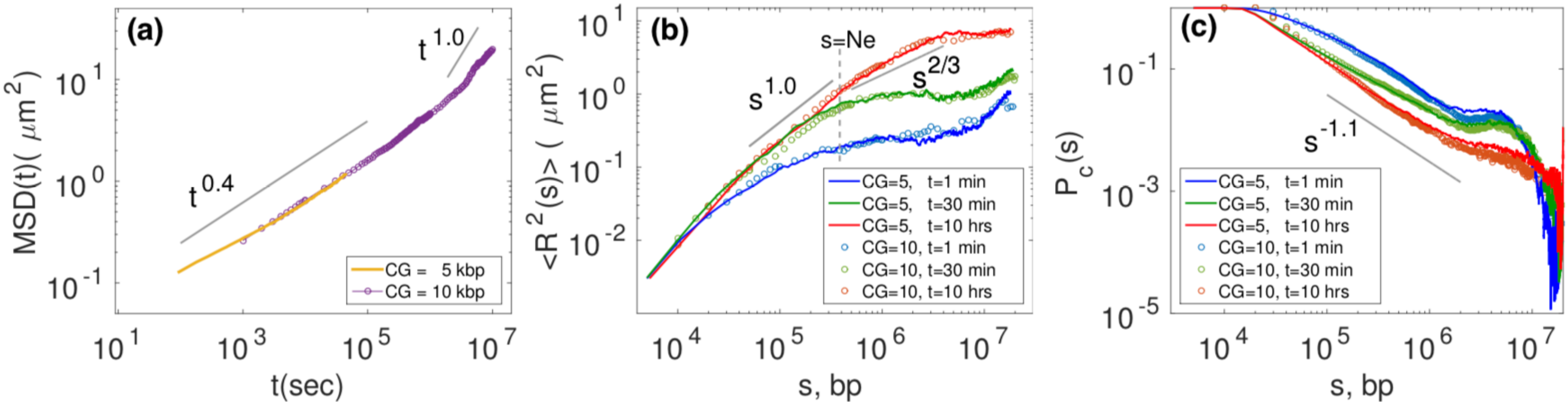


- Different Coarse Graining: CG=0.2 kbp vs. CG=10 kbp



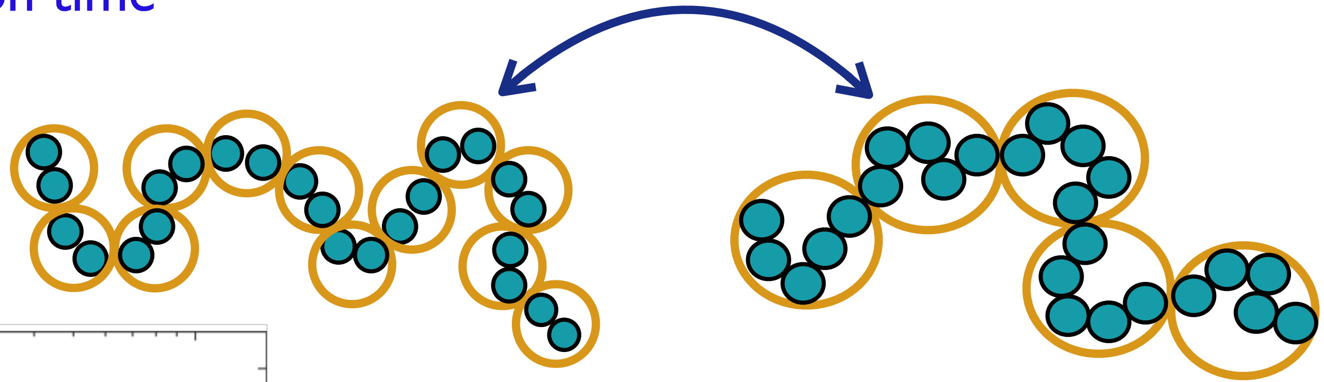
Time evolution

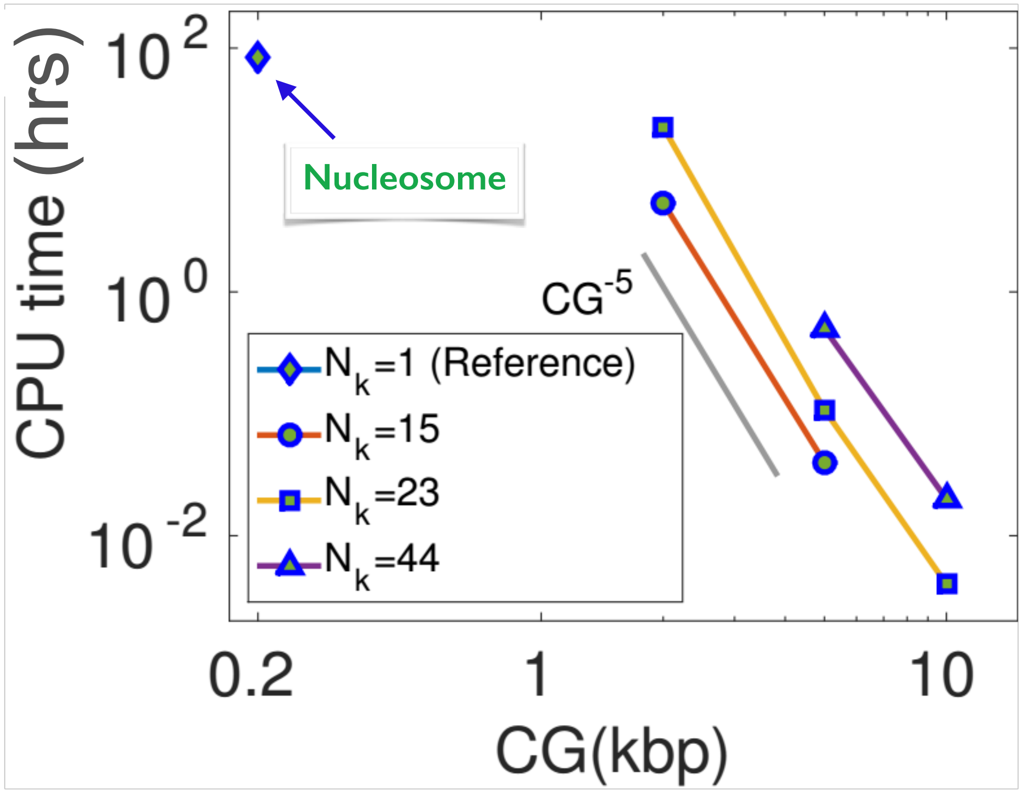
- Different Coarse Graining: CG= 5 kbp vs. CG=10 kbp



Computation Time

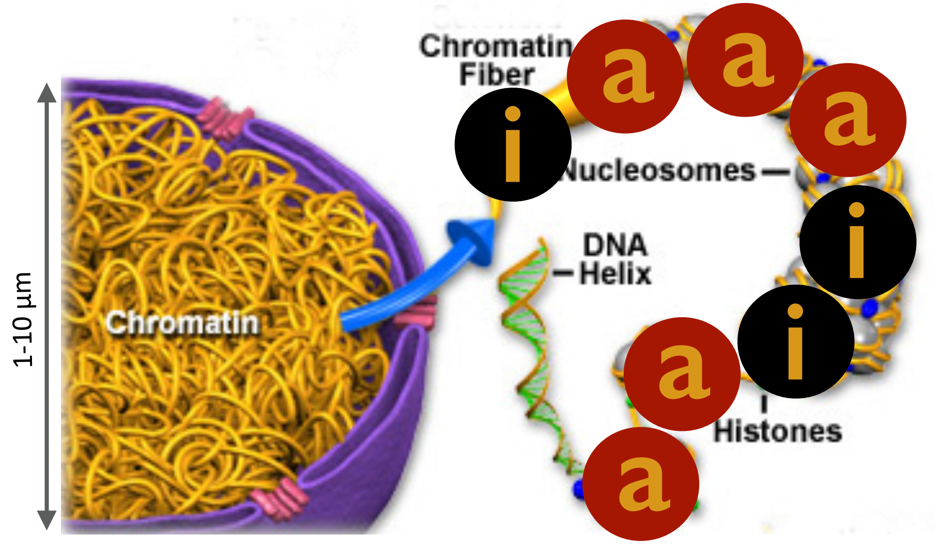
- An efficient coarse grained polymer model
- Power law gain in computation time



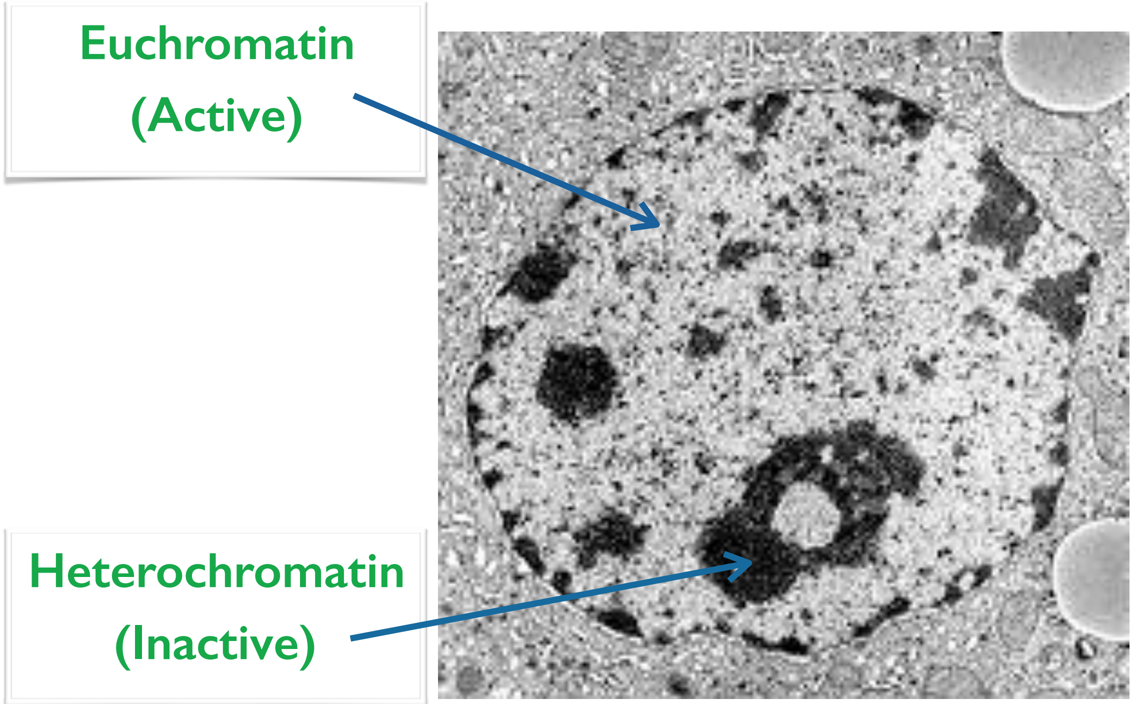


Physical Biology of Chromatin

- Active and inactive genes occupy different areas of the nucleus
- Epigenetics modifies gene expression without altering genetic information



Nucleus

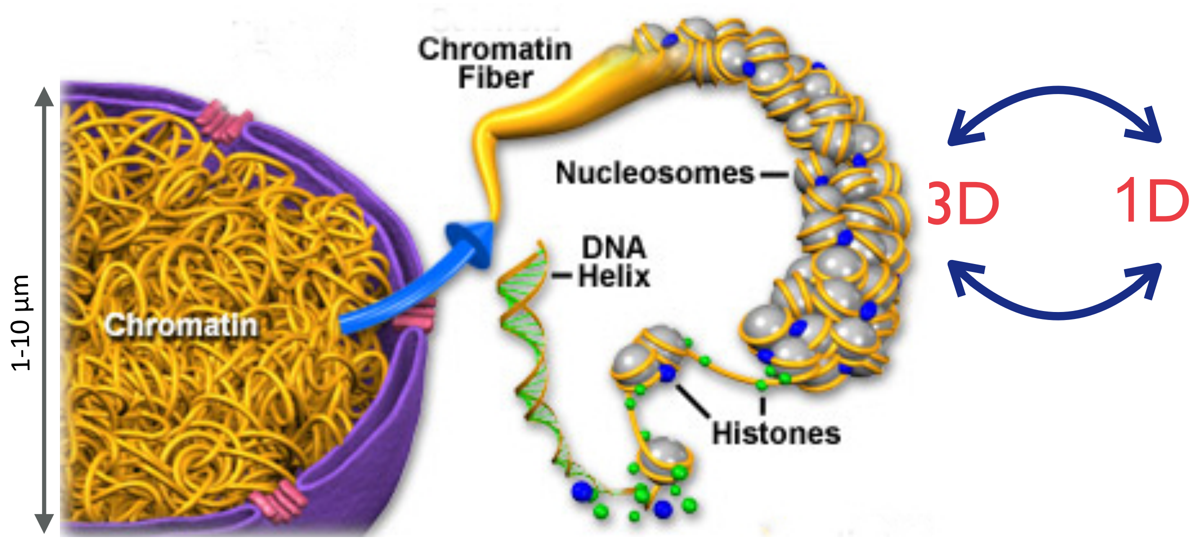


Electron Microscopy of a Nucleus

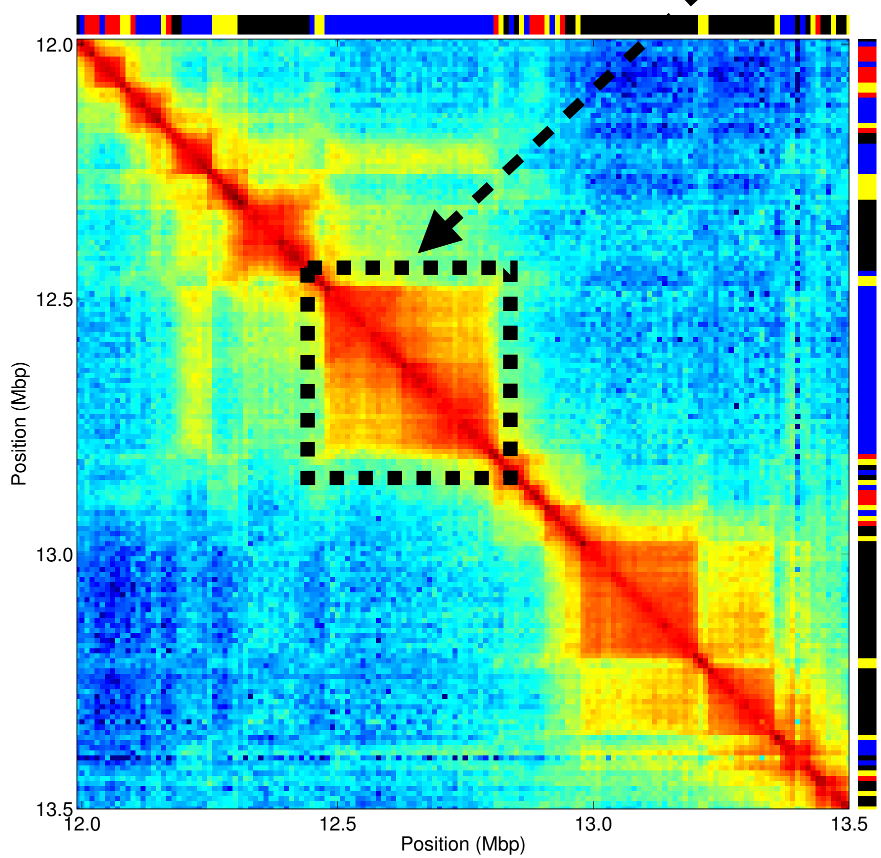
Q. What is the relation between epigenetics and chromatin organization?

Basics of Chromatin, Chromosome

- A hierarchal organized folding



- Topologically Associated Domain (TAD)

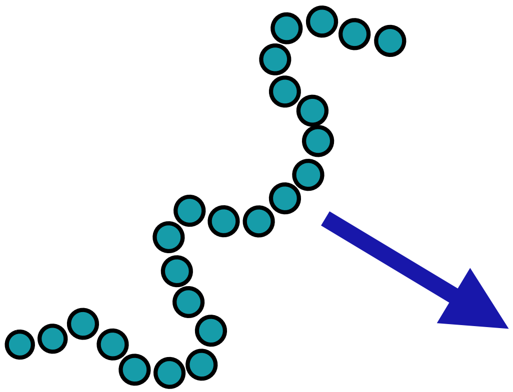


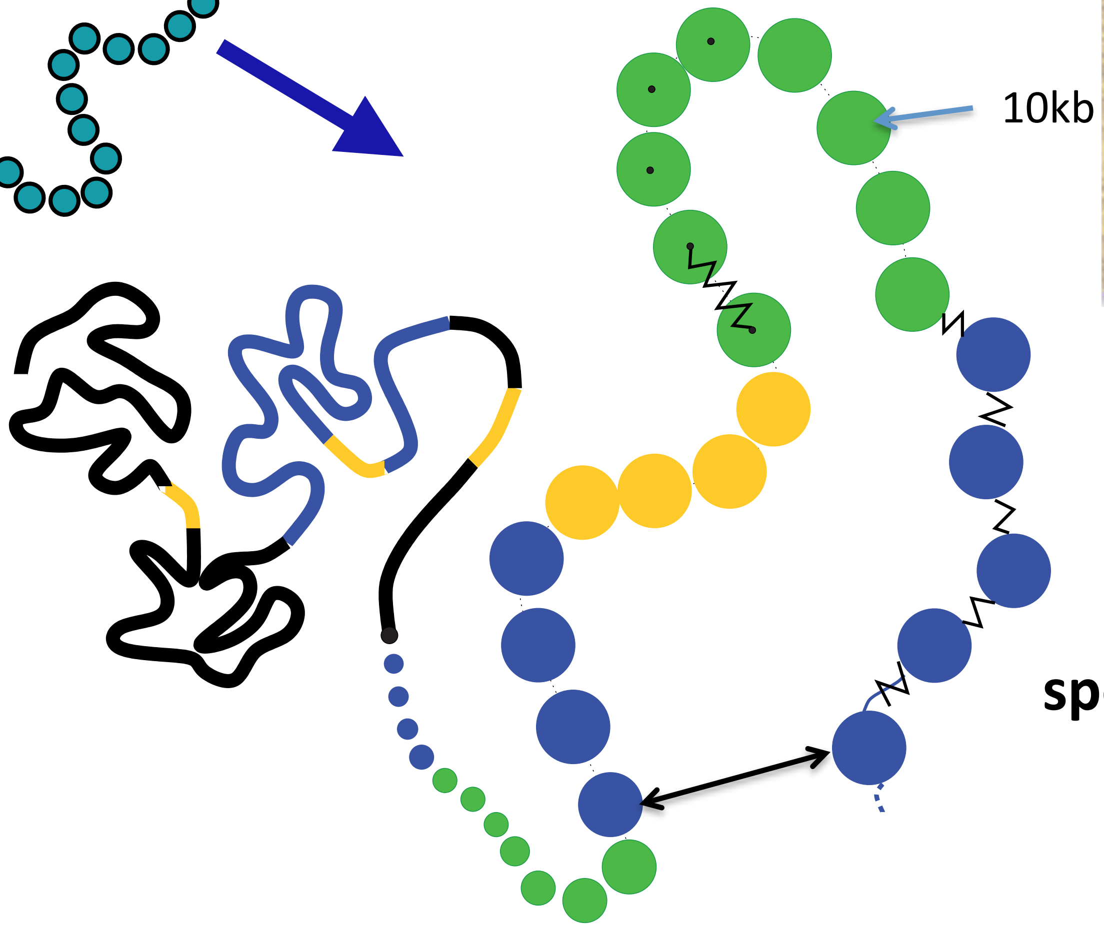
- Genome: 1Mbp - 6Gbp (few mm to m)
- Base-Pair density: 0.001-0.1 bp/nm^3

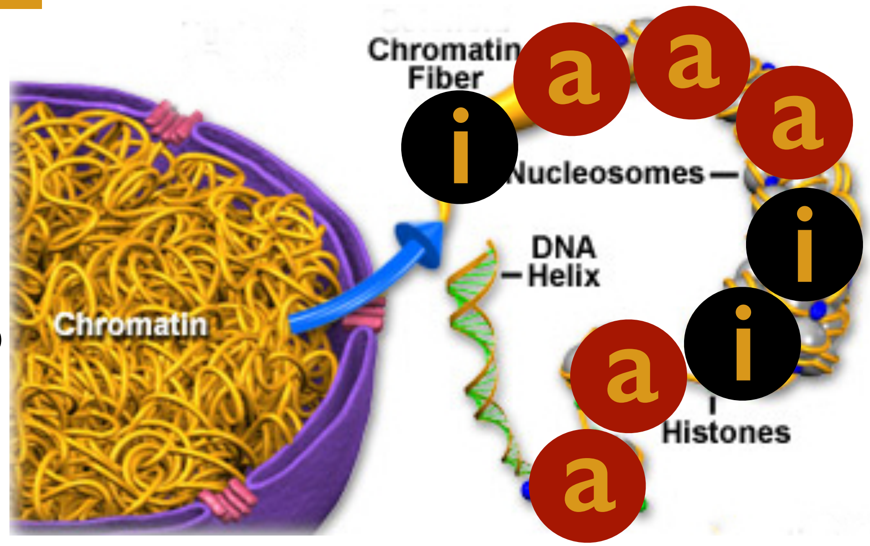
- HiC: Chromosomal Contact Map for Drosophila
- Whole genome is linearly partitioned

Sexton et. al. Cell, 2012, 148

Chromatin as a block copolymer



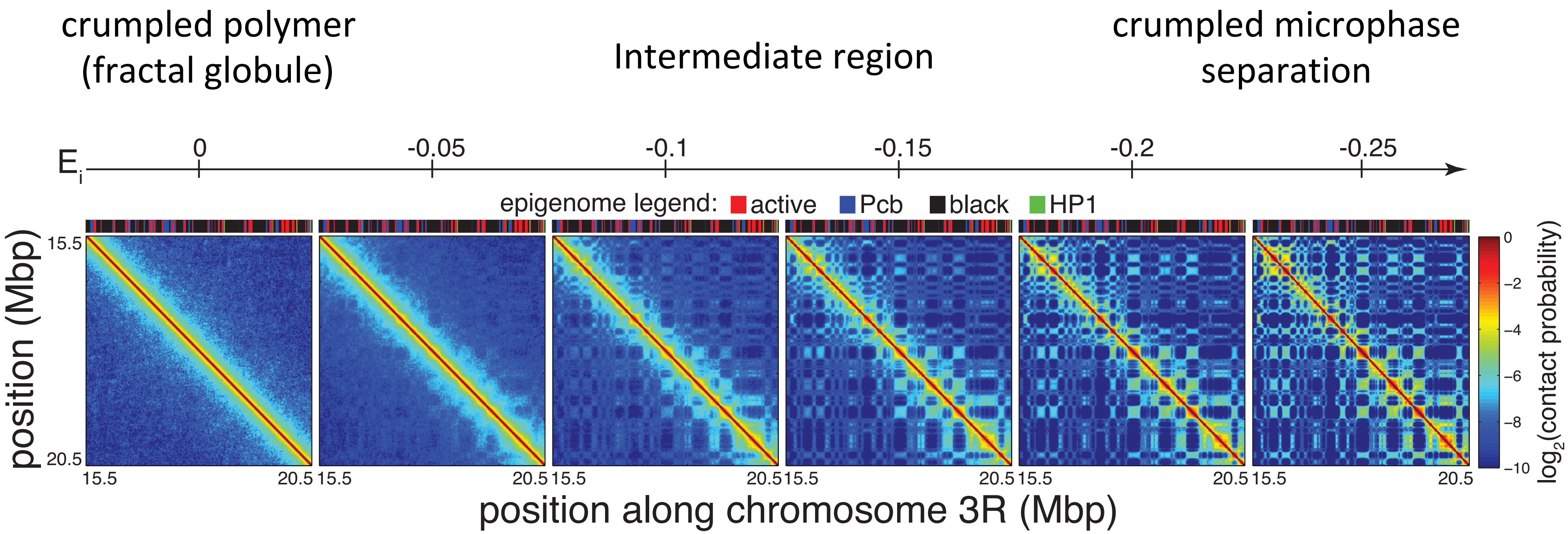




epigenome:
specific & short-range

How far can we go with this simple model?

Phase diagram of chromosome 3R



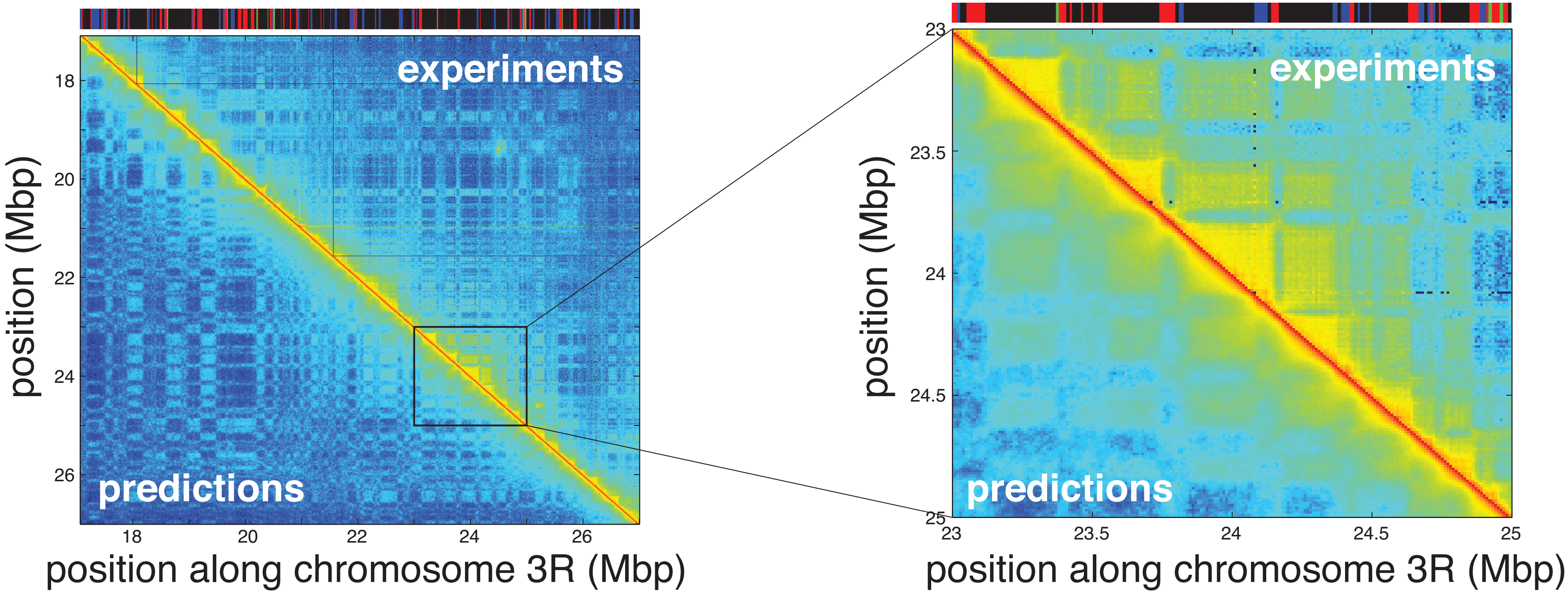
Ghosh et al. 2017

Comparison with experiments

•Experiment: **intra-state** contact frequency about **1.5** more than **inter-state** contact frequency

•Corresponds to E_i=-0.1, ie in the **intermediate region**

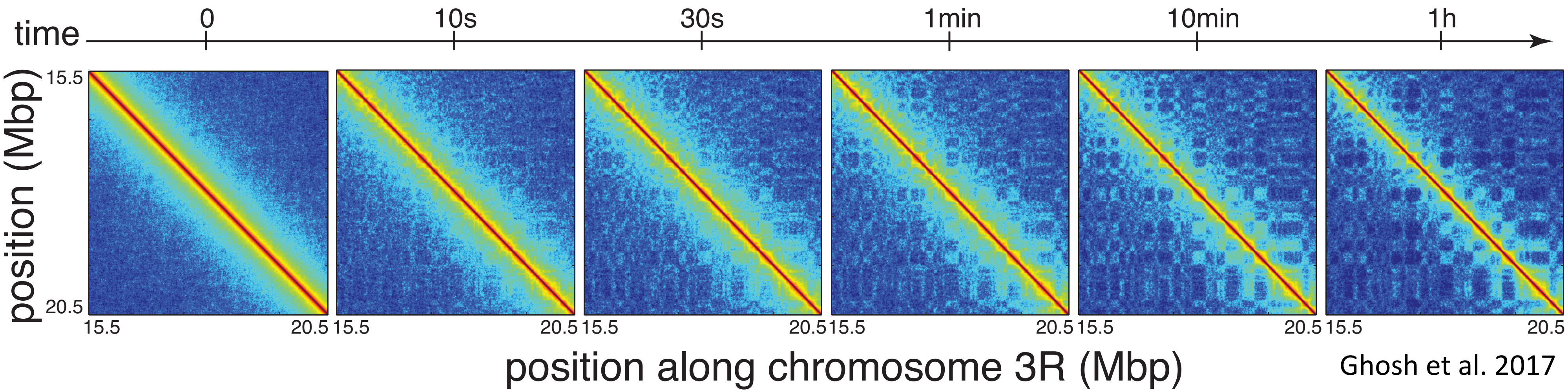
Ghosh et al. 2017



Same color legend!!

Dynamics of TAD formation

Predicted HiC-map on synchronized cells



Ghosh et al. 2017

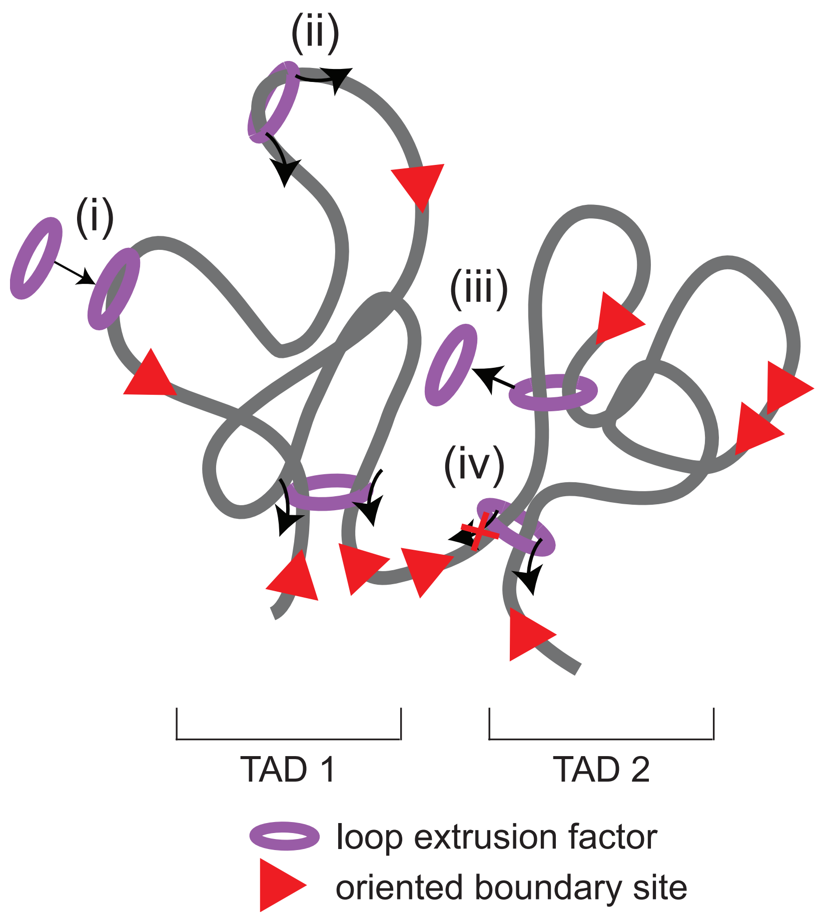
- TADs quickly form: 1-10 minutes
- Long-range inter-TAD interactions more slow >1h

- Consistent with HiC on synchronized – mammalian – cells (Naumova et al, Nature 2012)

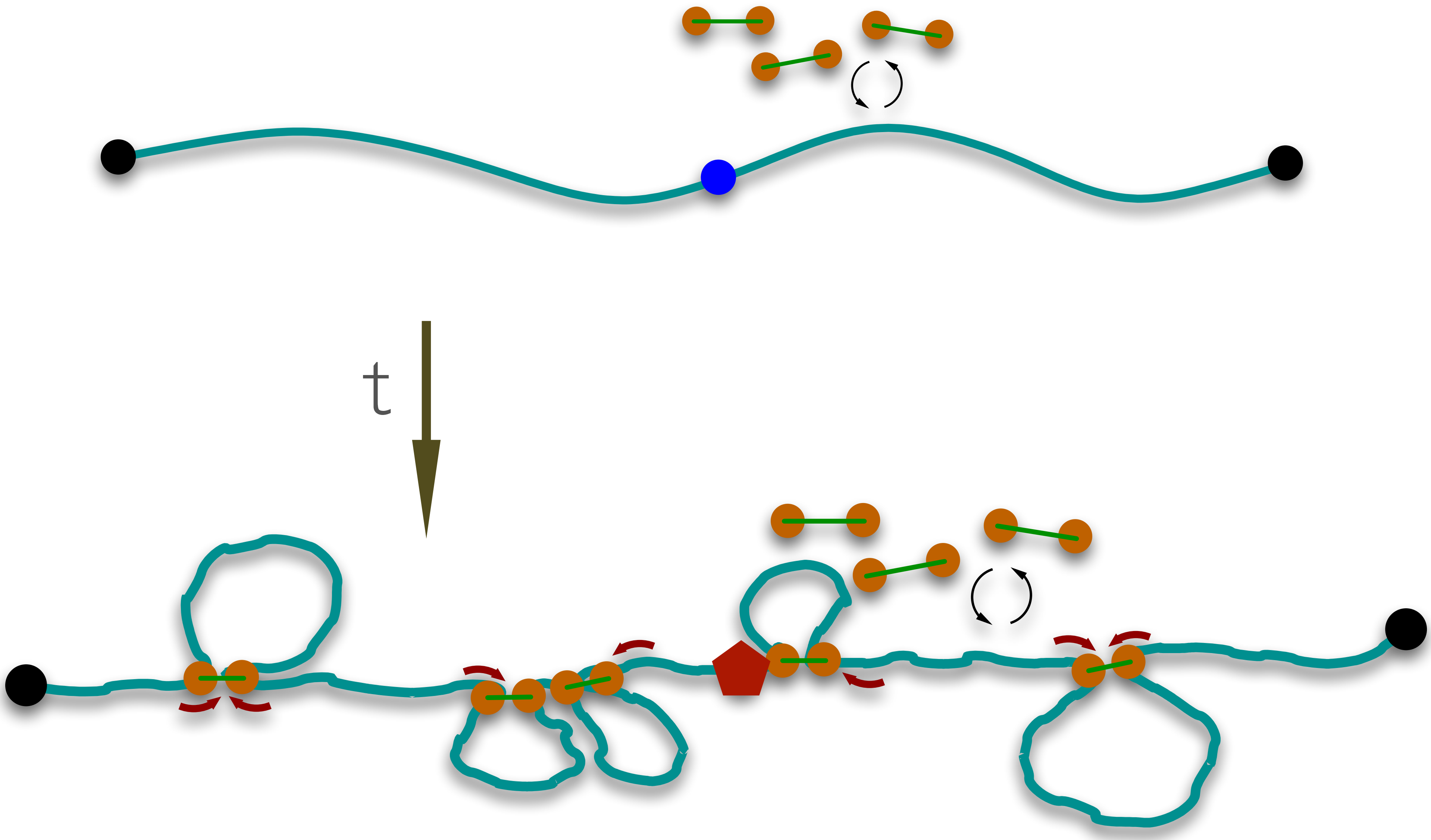
Perspective

- **Effect of extrusion on chromosome folding.**

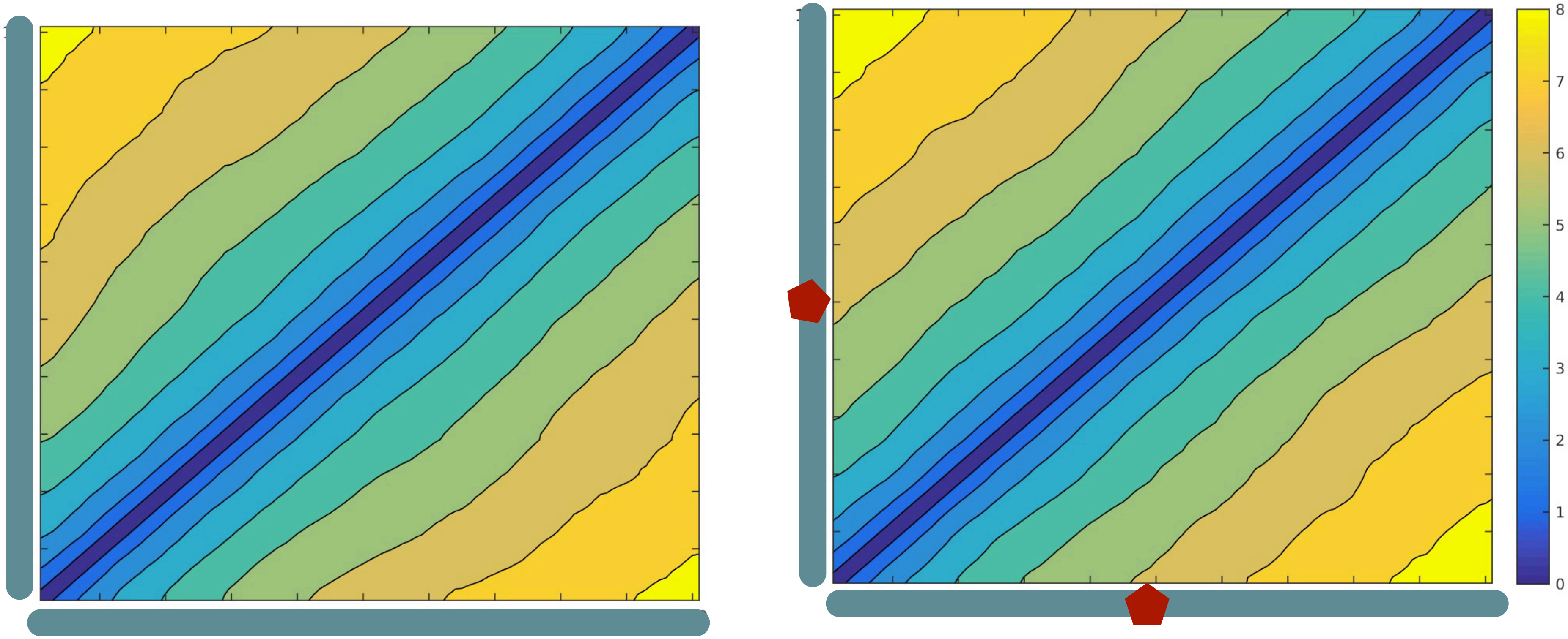
- **Interaction with membrane**

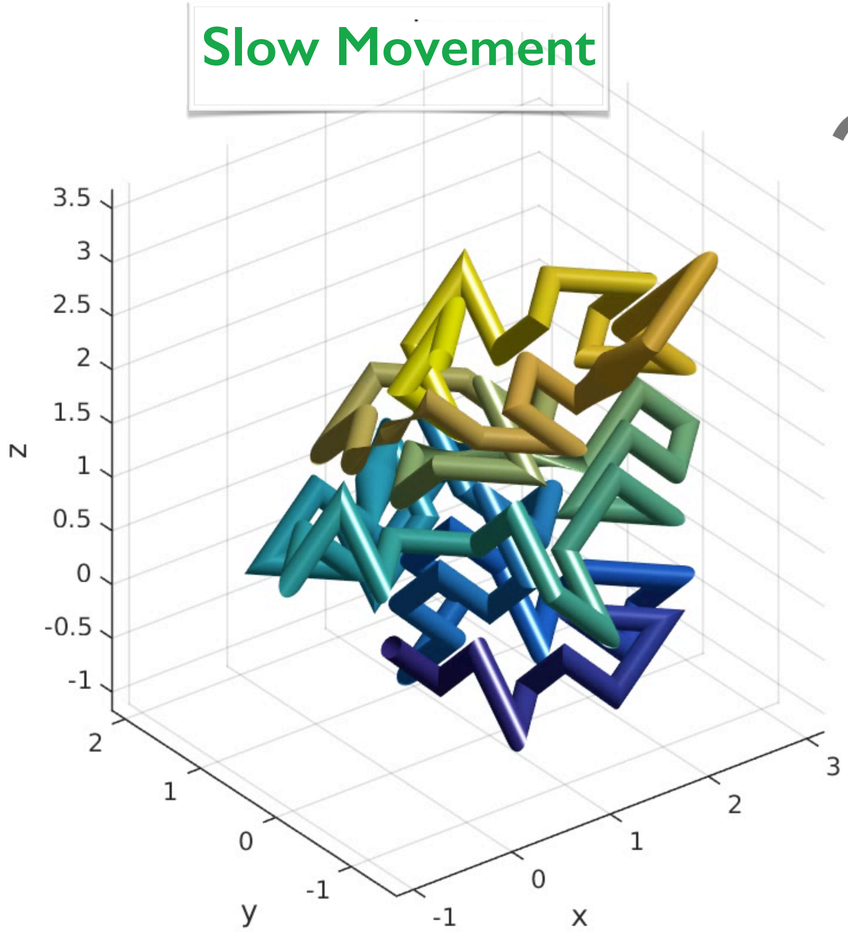


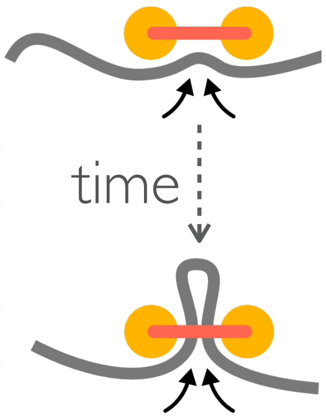
Extrusion

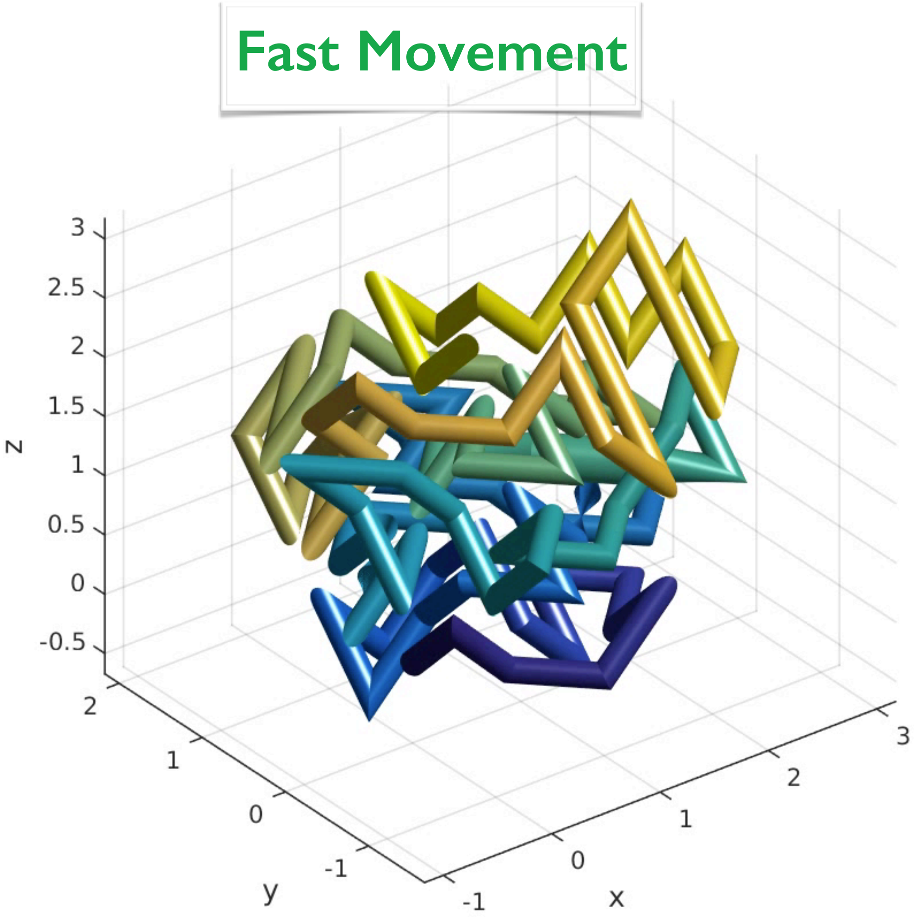


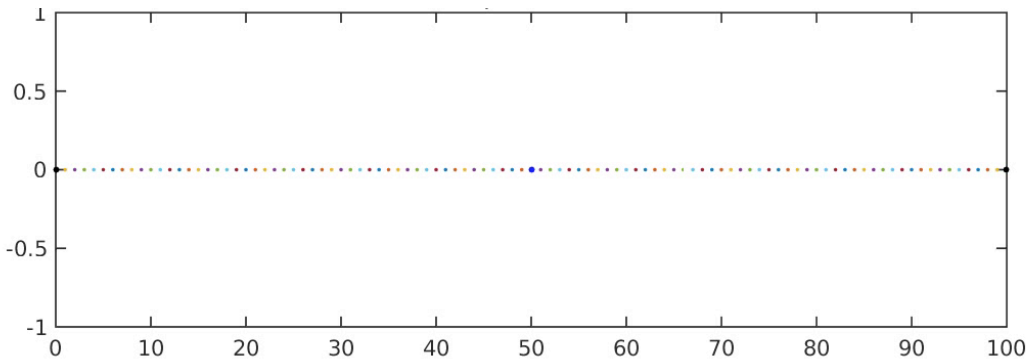
Effect of Boundary

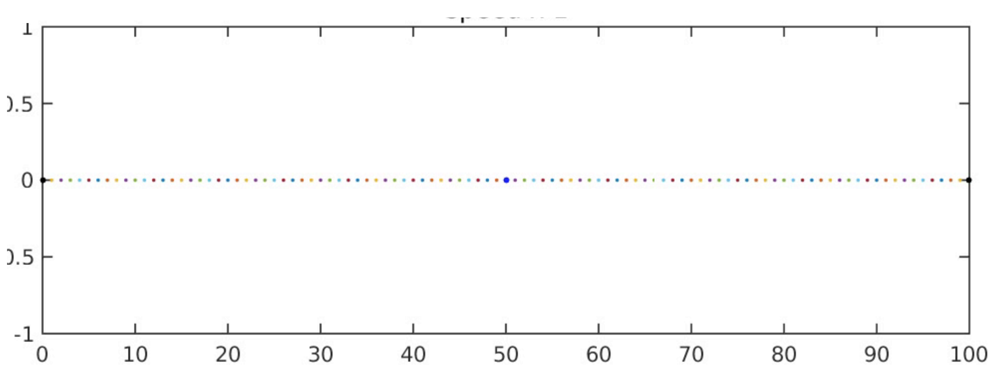



Slow Movement
z
y
x


time


Fast Movement
z
y
x



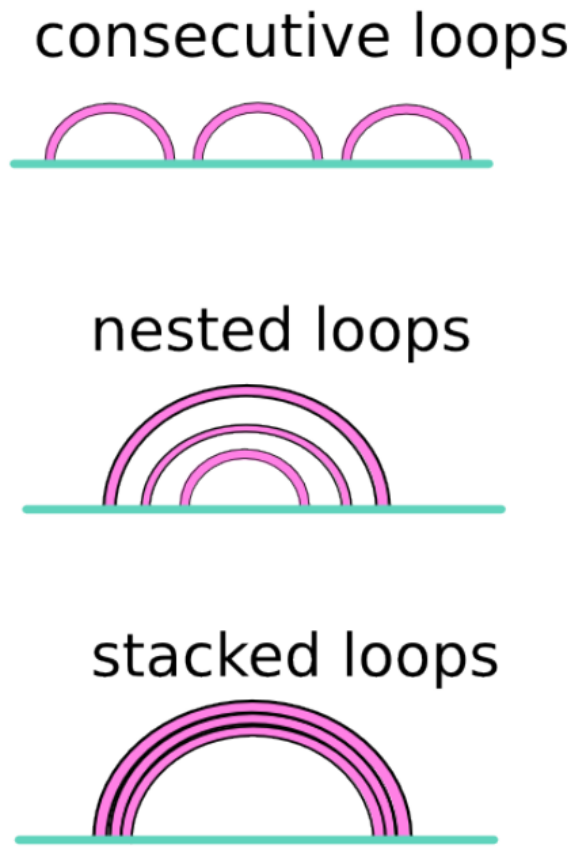


Open Questions and Challenges

Q. How can small proteins control large genome organization?

Q. How 3D contributes to 1D establishment and maintenance?

- Dramatic change in chromosome configurations when cell progress through cell cycle
- The mechanism of active loop extrusion hold a great promise for explaining chromosome folding



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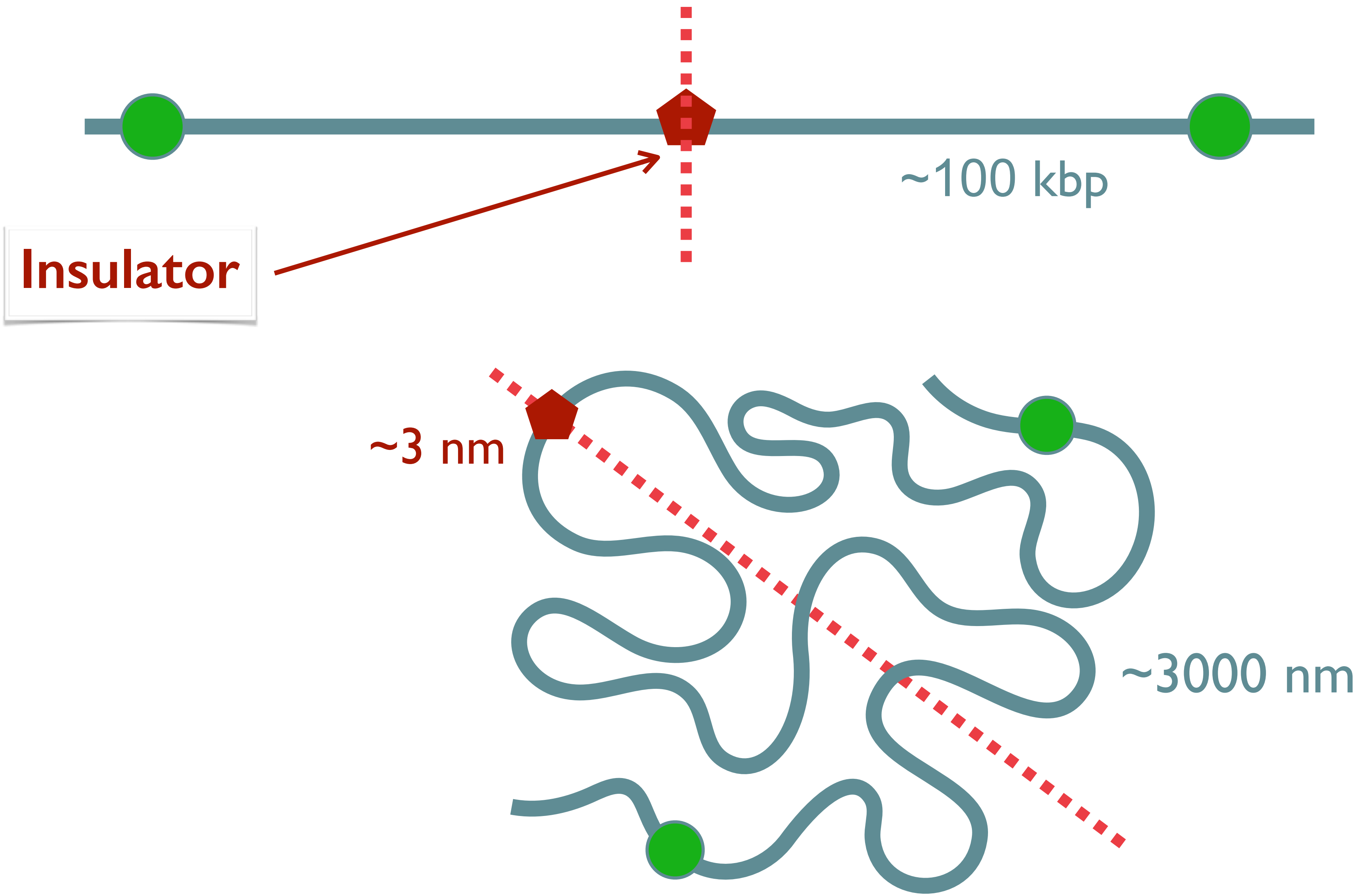
Giacomo Cavalli

University of Bern:
Peter Meister

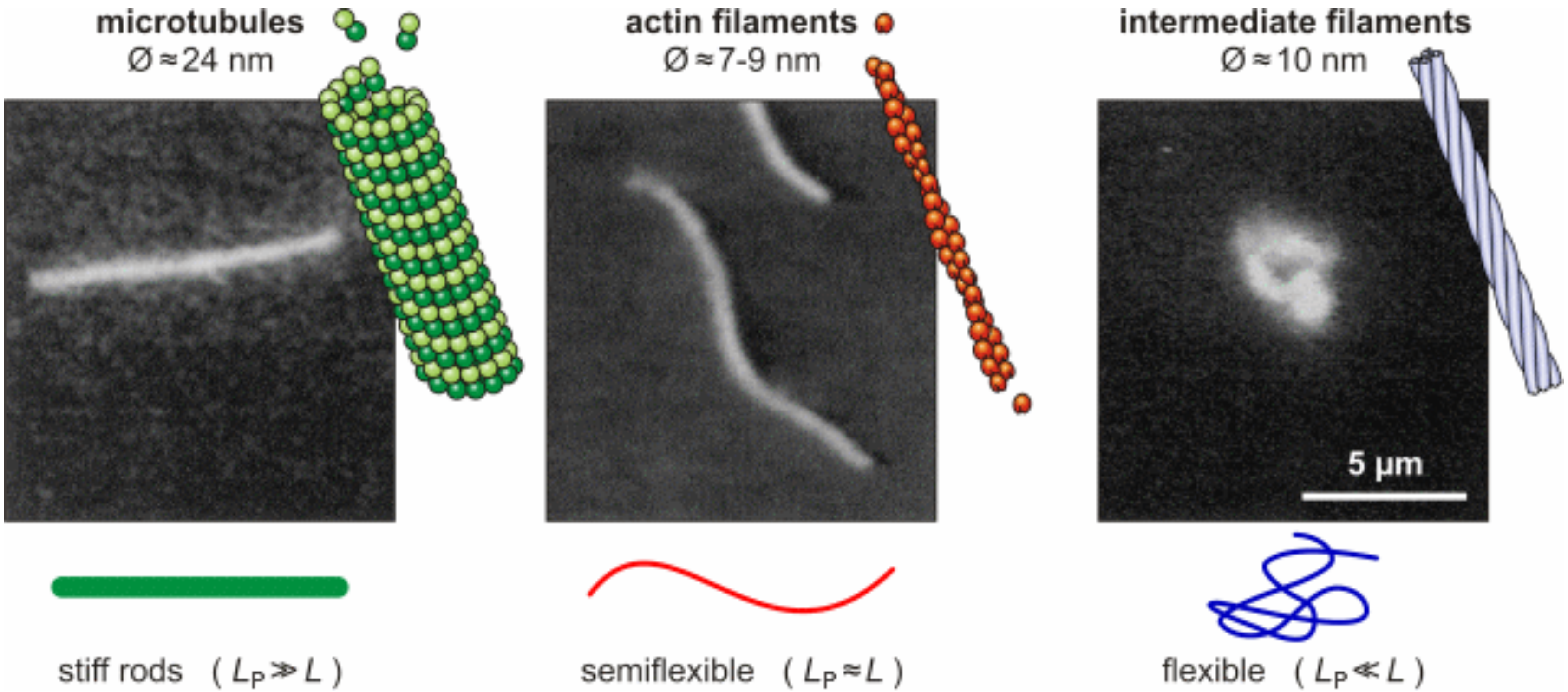
IAB, Grenoble:
Saadi Khochbin
Elisabeth Brambilla

Future Plan

Q. How can small proteins control large genome organization?



Polymers in biology



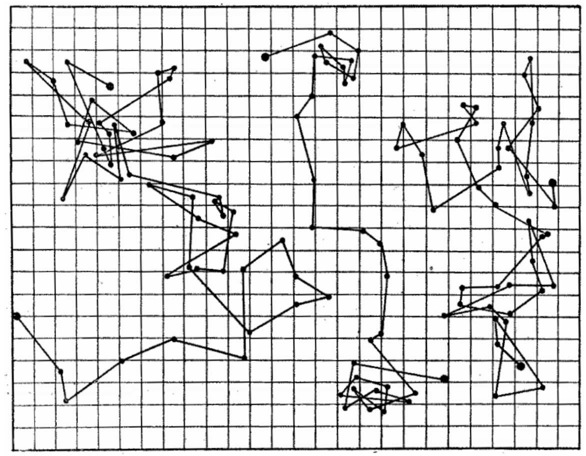
- Three different component of cytoskeleton
- They are differ in stiffness
- Characterized by the persistent length *Lp*

Polymer models

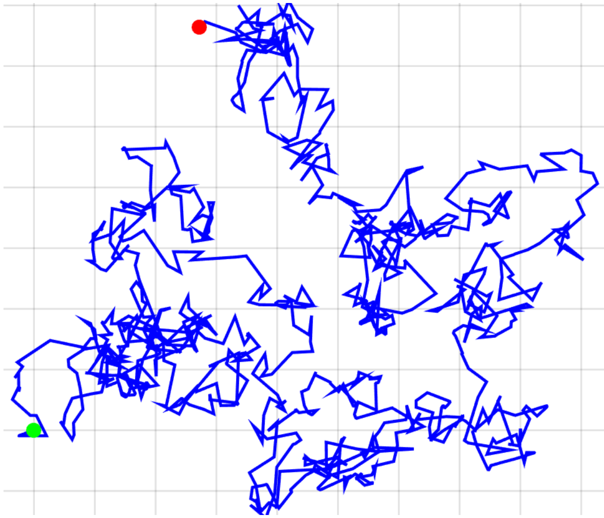
- Flexible Polymer: Random Walk
- Semi flexible polymer: Worm Like chain (WLC)

Polymer models

- Flexible Polymer: Random Walk

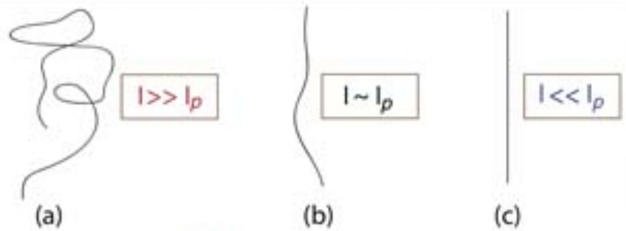


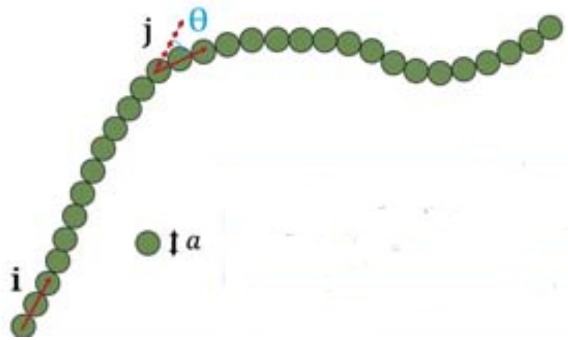
J Perrin, Comptes Rendus (Paris) 146 (1908) 967

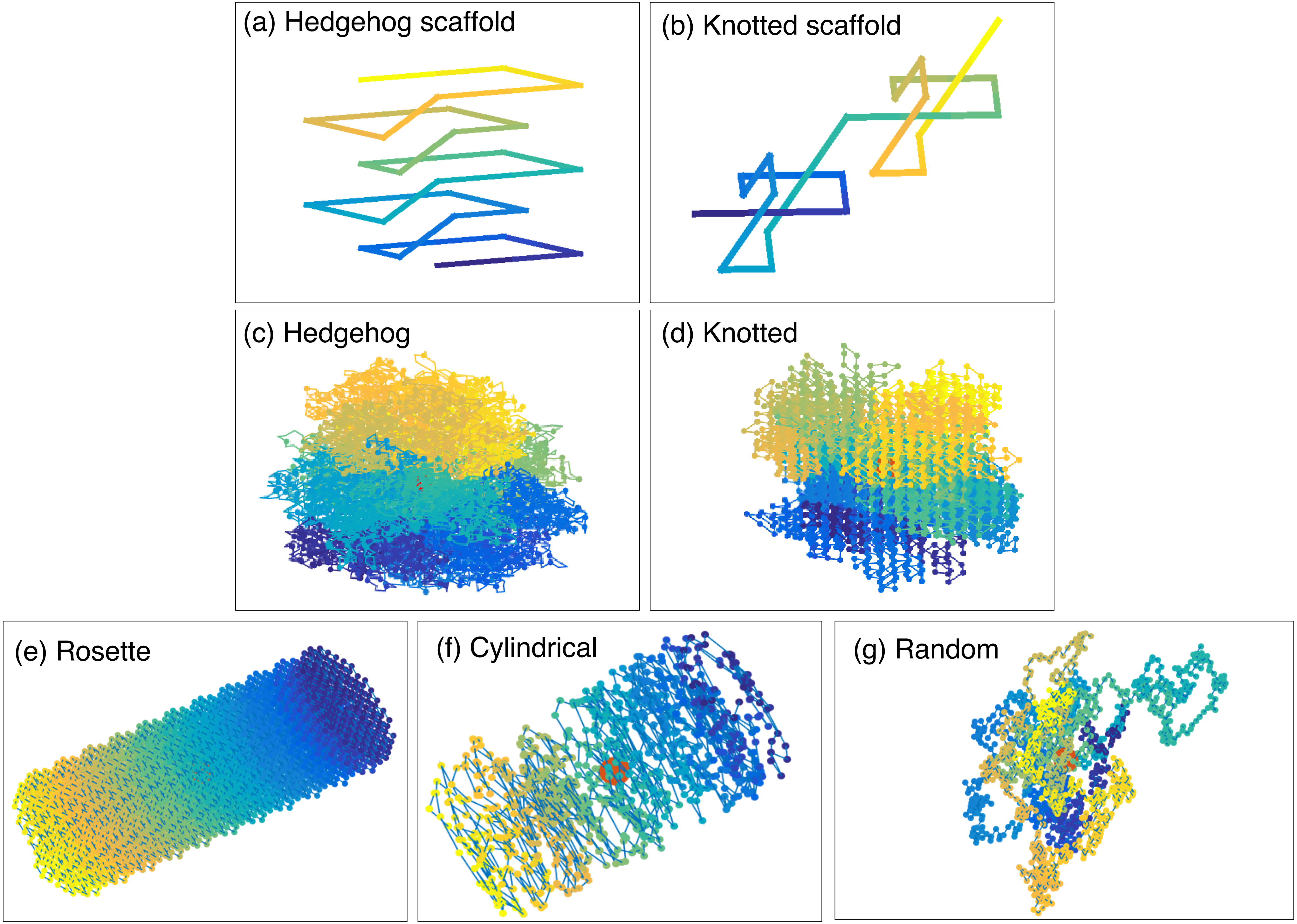


- Semi flexible polymer: Worm Like chain (WLC)

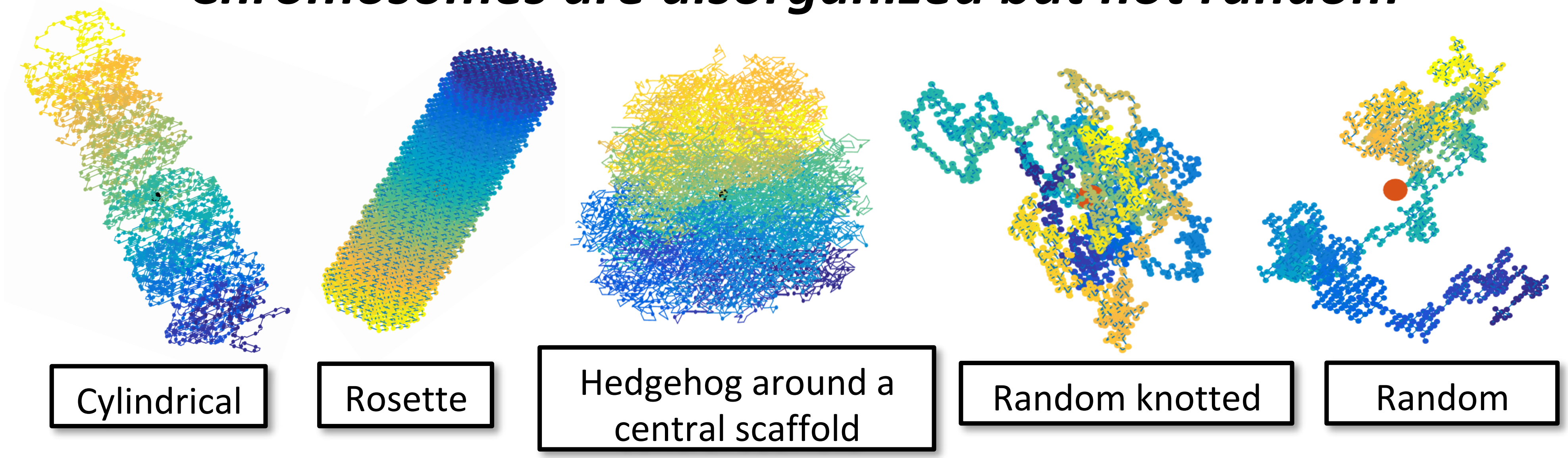
$$\frac{H}{k_B T} = \frac{L_p}{2} \int_{s=0}^{L} \kappa^2(s) ds$$






(a) Hedgehog scaffold
(b) Knotted scaffold
(c) Hedgehog
(d) Knotted
(e) Rosette
(f) Cylindrical
(g) Random

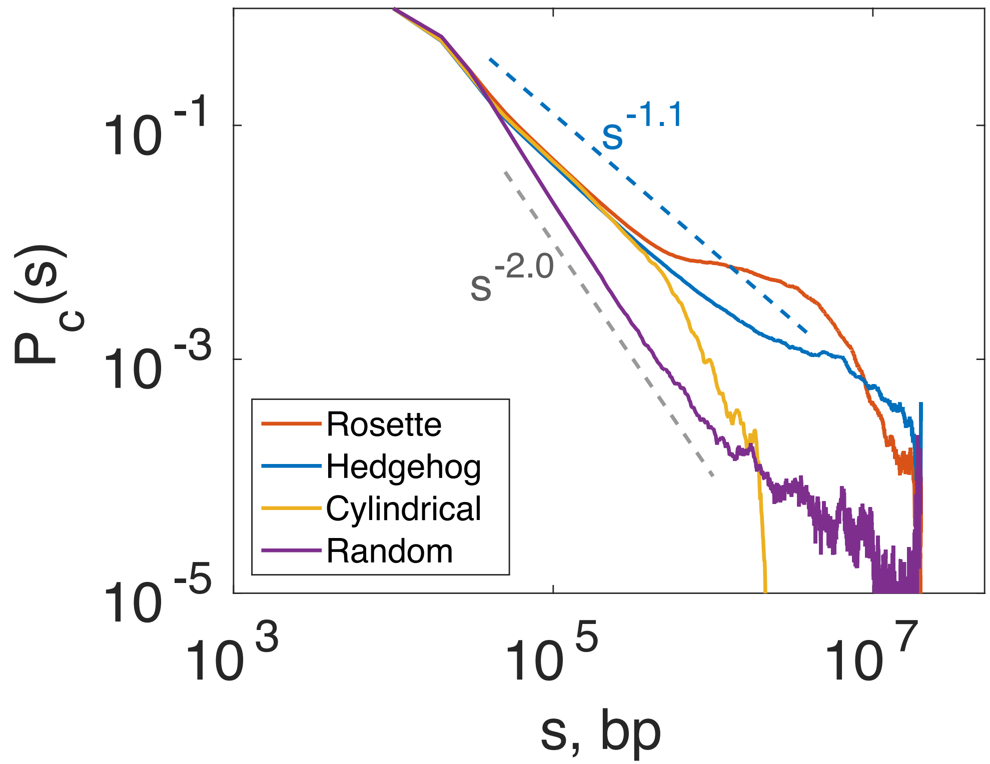
Chromosomes are disorganized but not random

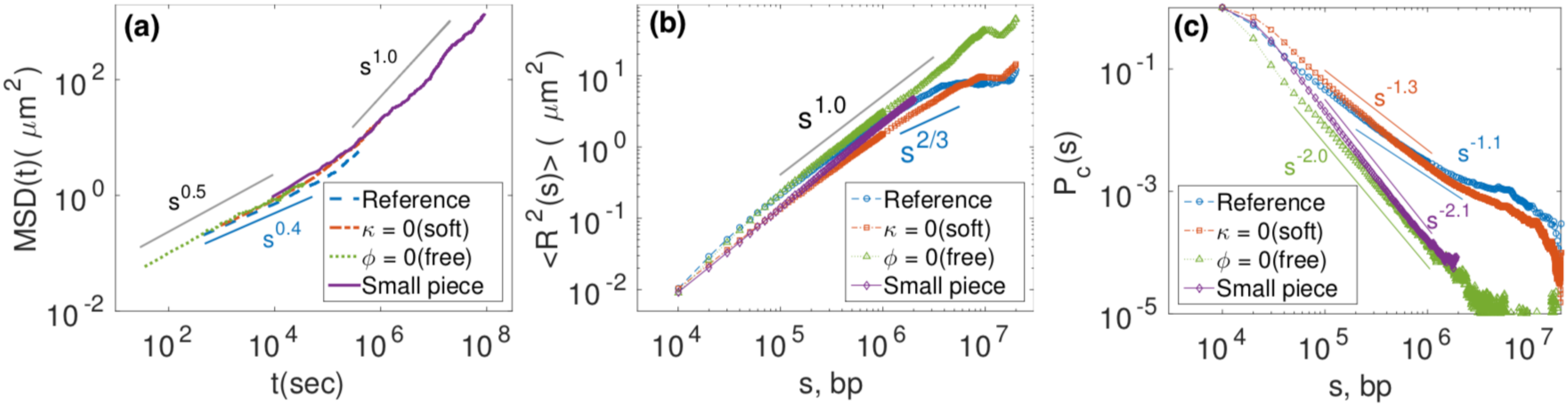


ref:
- Ghosh et al, 2017 in submission
- Naumova N. et al. 2013 Science
- Earnshaw W.C. and U.K. Laemmli. 1983. J. Cell Biol

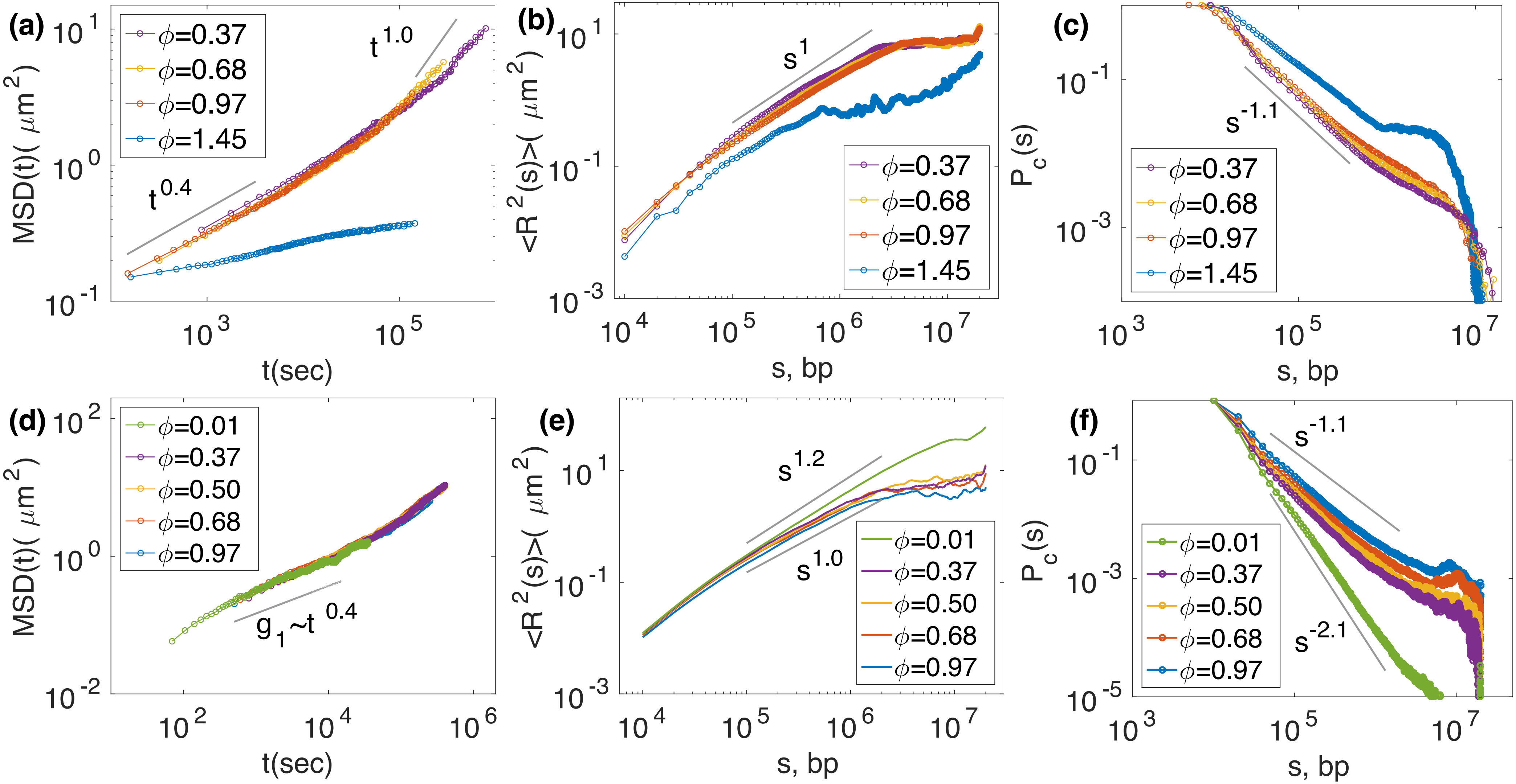
- Contact probability

$$P_c(s) \approx s^{-1}$$

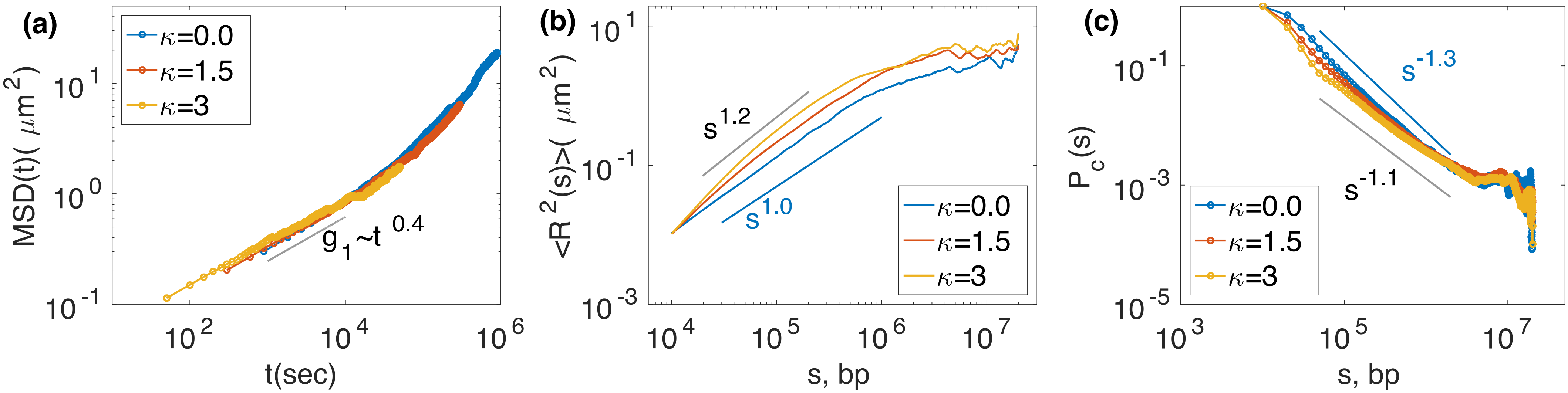



(a)
$s^{1.0}$
$s^{0.5}$
$s^{0.4}$
MSD(t)(μm^2)
t(sec)
Reference
κ = 0(soft)
ϕ = 0(free)
Small piece
(b)
$s^{1.0}$
$s^{2/3}$
<R^2(s)> (μm^2)
s, bp
Reference
κ = 0(soft)
ϕ = 0(free)
Small piece
(c)
$s^{-1.3}$
$s^{-1.1}$
$s^{-2.0}$
$s^{-2.1}$
$P_c(s)$
s, bp
Reference
κ = 0(soft)
ϕ = 0(free)
Small piece

Vary Lattice Density

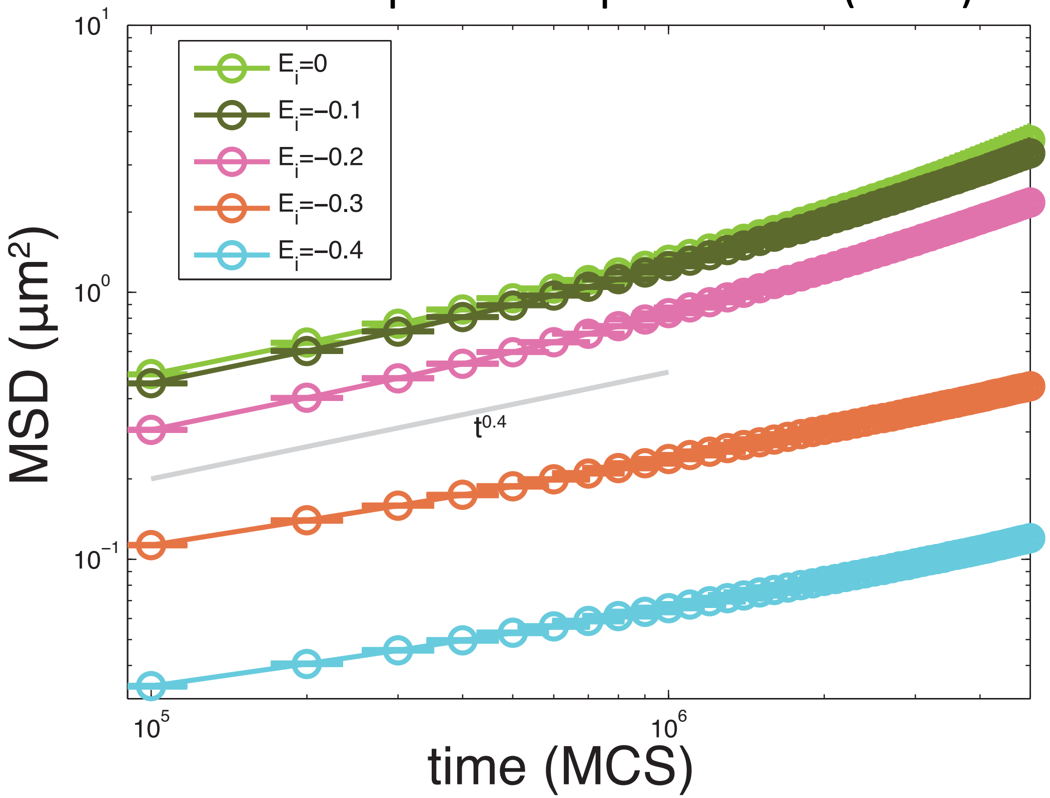


Vary Stiffness

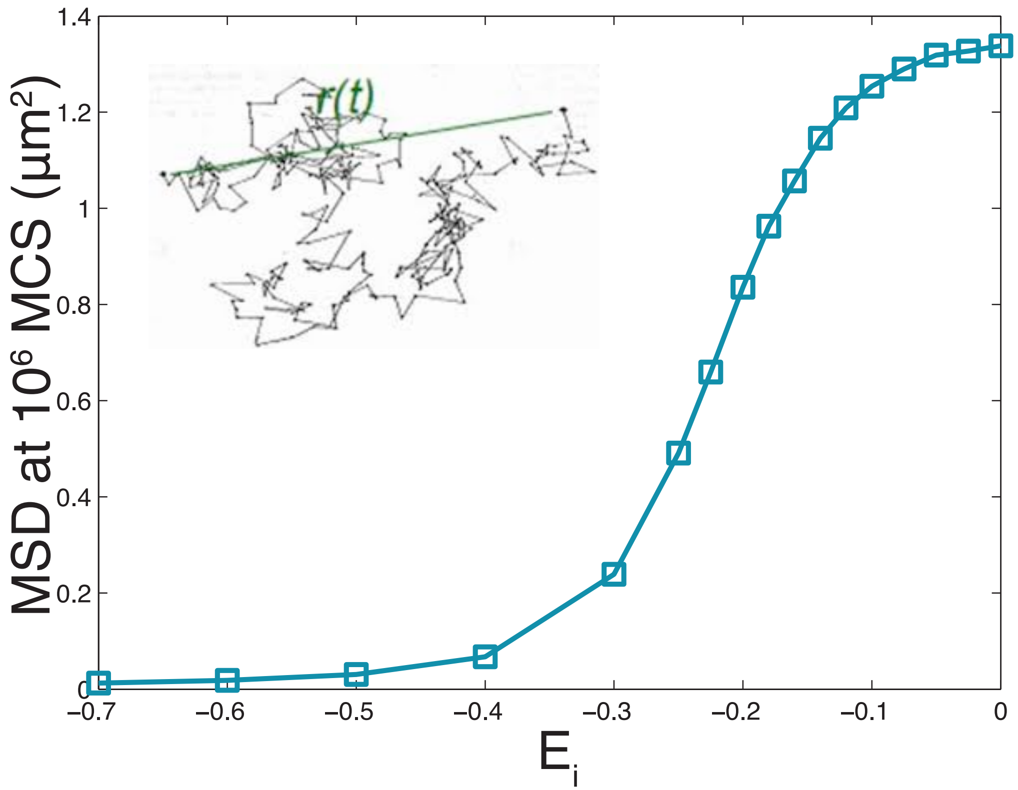


Phase diagram of chromosome 3R

Mean squared displacement (MSD)



Ghosh et al. 2017

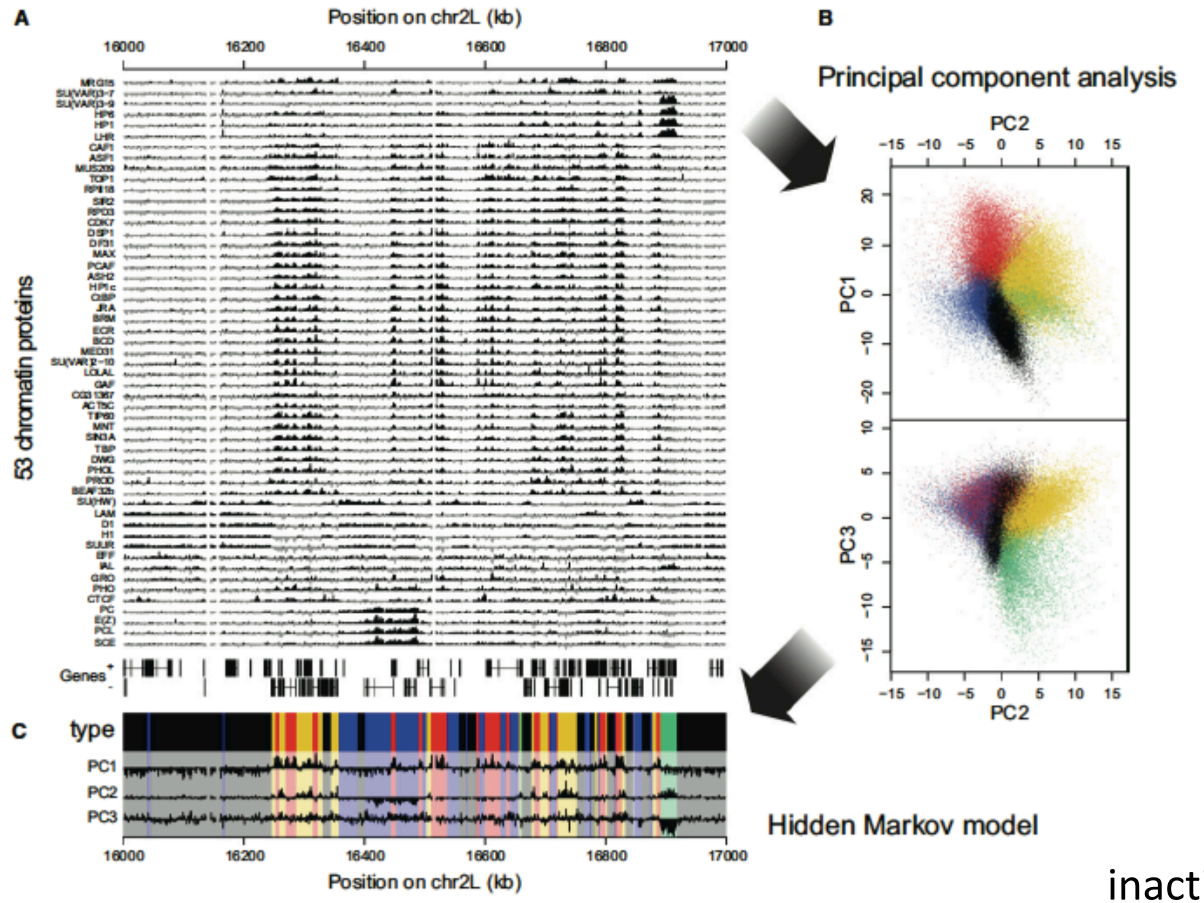


- MSD ~ $t^{0.4}$, typical of crumpled polymers (Tamm et al , PRL 2015)
- Critical slowing-down at high interaction strength values: glass-like dynamic transition

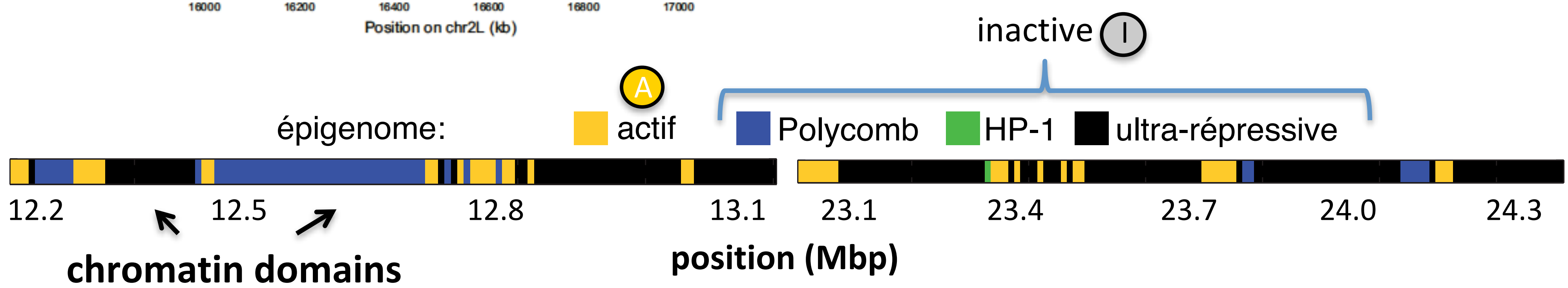
- **Time mapping: MSD_{exp}(μm^2)≈0.01 $t^{0.5+/-0.1}$ (t in sec.) 1 MCS=0.04 sec**

From many chromatin tags to few chromatin states

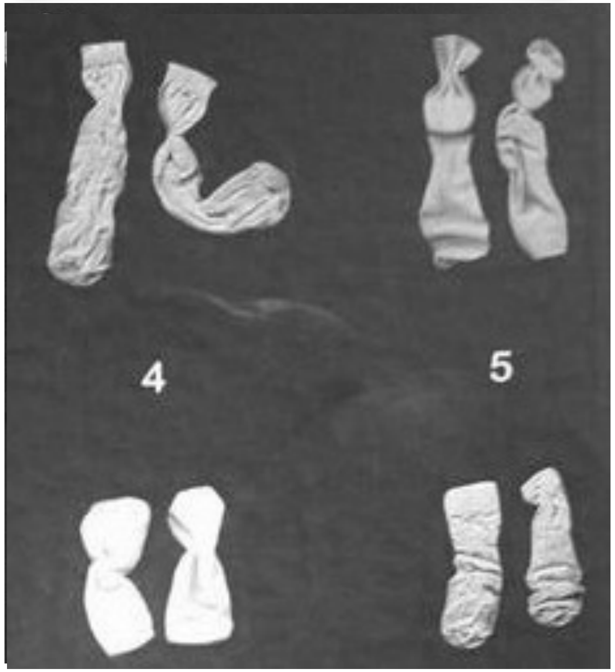
•Genome-wide characterization of epigenome (drosophila, human, mouse, plants, yeast, etc.)



Drosophila
(Filion et al., 2010)



Drosophila :



For 2 kbp : 10001 , Ne = 285.25 kbp

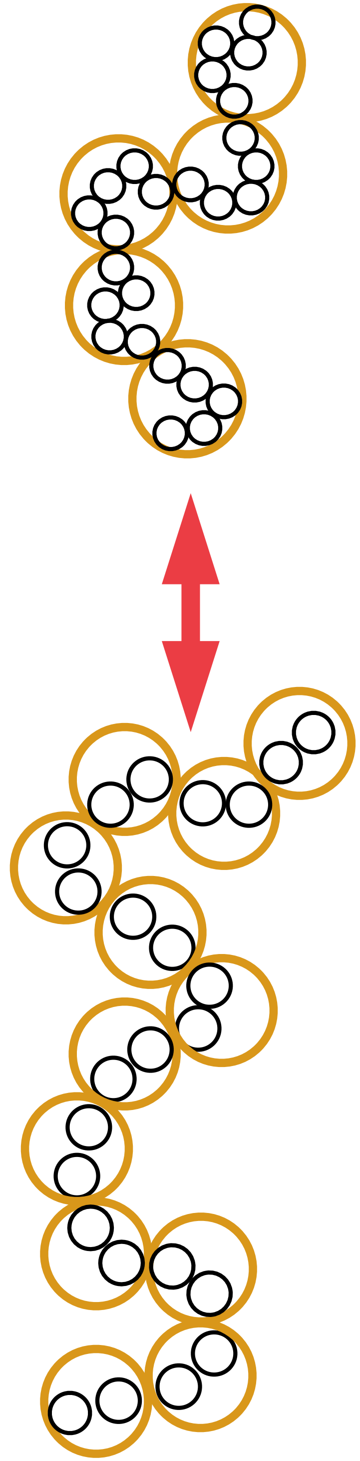
L	Phi	k	Nk (kbp)	1 MCS (10^-3)
45	0.0274	7.1	29.96	0.004
40	0.0391	6.05	23.67	
37	0.0494	5.45	20.25	0.03
32	0.0763	4.45	15.15	0.18
28	0.1139	3.62	11.60	0.41

For 5 kbp : 4001

L	Phi	k	Nk (kbp)	1 MCS (10^-1)
22	0.0939	5.00	44.76	0.004
18	0.1715	3.70	29.96	0.019, 0.020
16	0.2441	3.05	23.67	0.054
15	0.2963	2.70	20.80	0.066
11	0.7513	1.40	11.19	0.160

For 10 kbp : 2001

L	Phi	k	Nk (kbp)	1 MCS
14	0.1822	4.3	72.50	
11	0.3757	2.9	44.76	0.0188
9	0.6859	1.95	29.96	0.0423
8	0.9766	1.5	23.67	0.0381



Entanglement Length

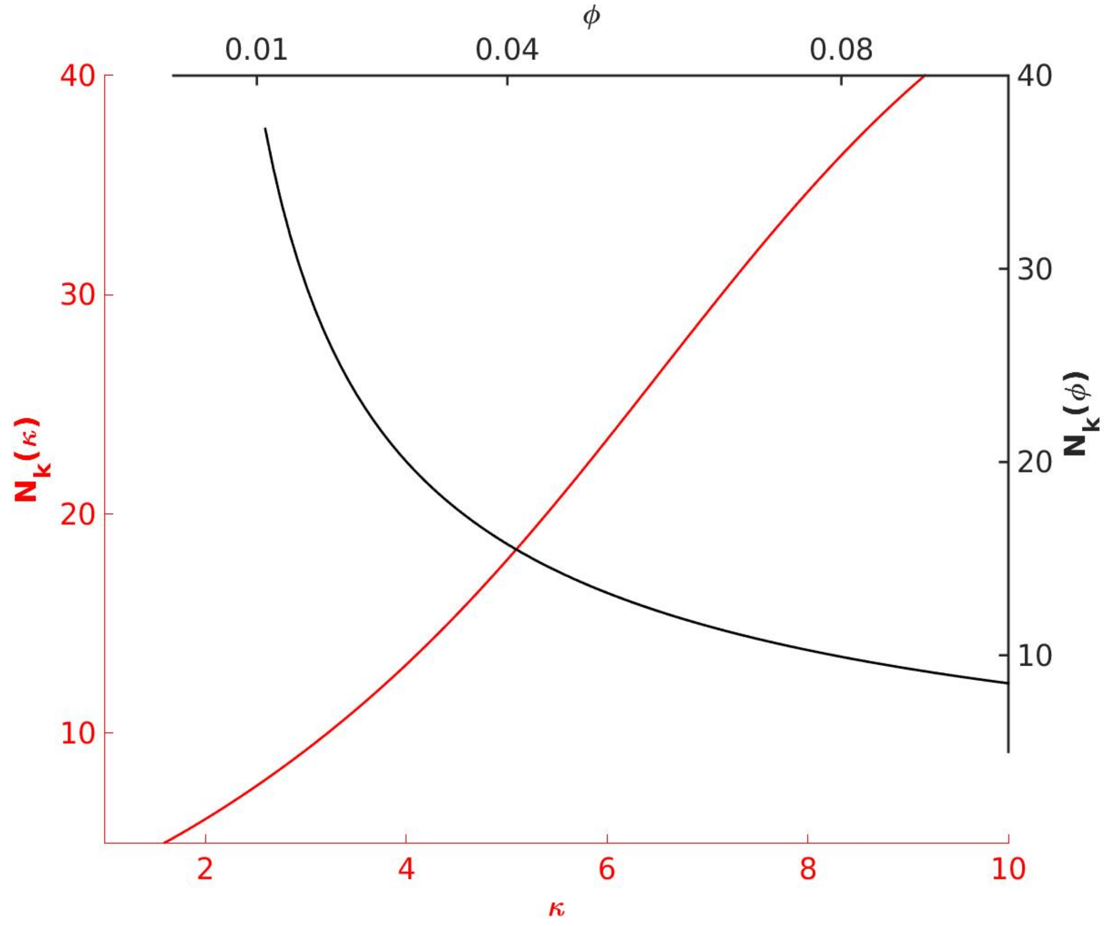
- Key parameters in our Model

- Bending stiffness : κ

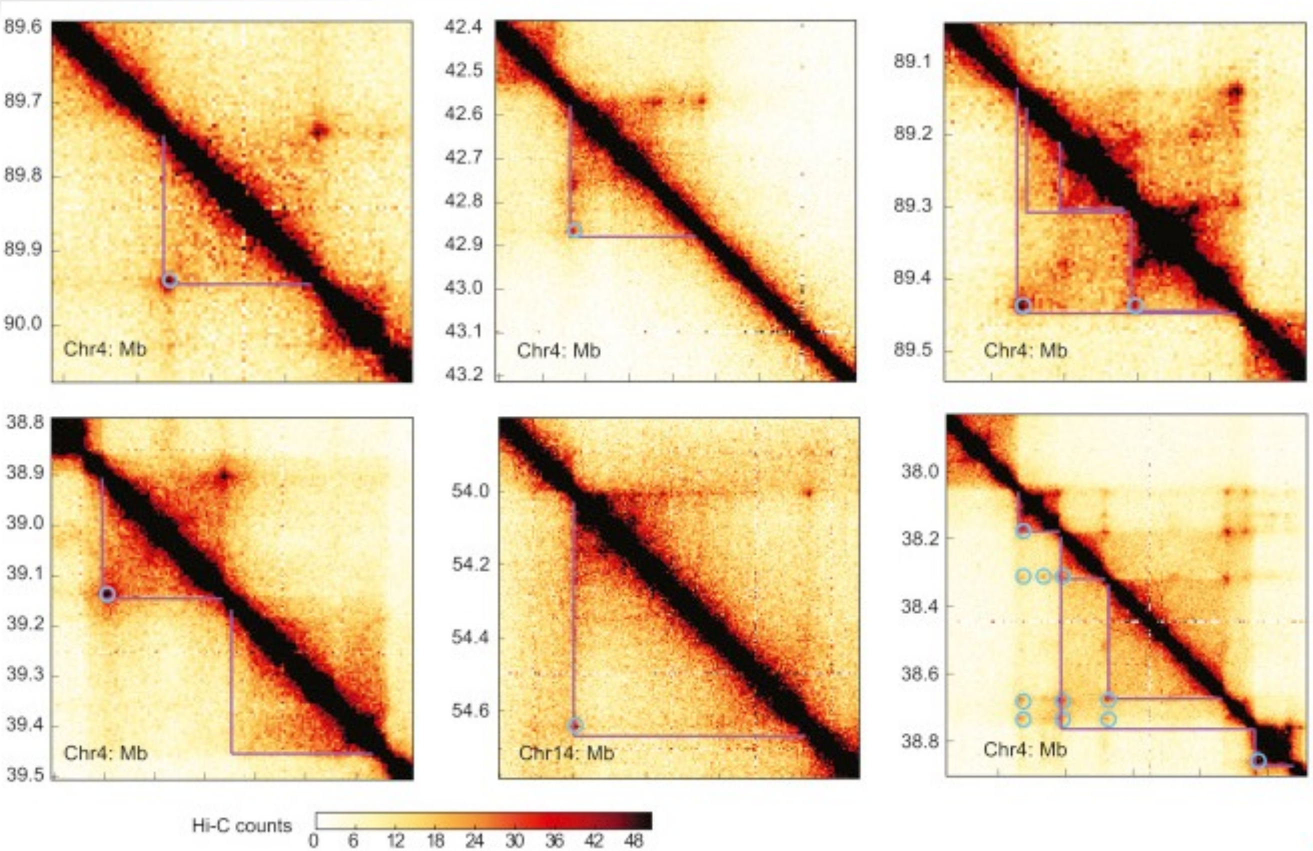
$$N_k(\kappa) = n\frac{1 + x(\kappa)}{1 - x(\kappa)}$$

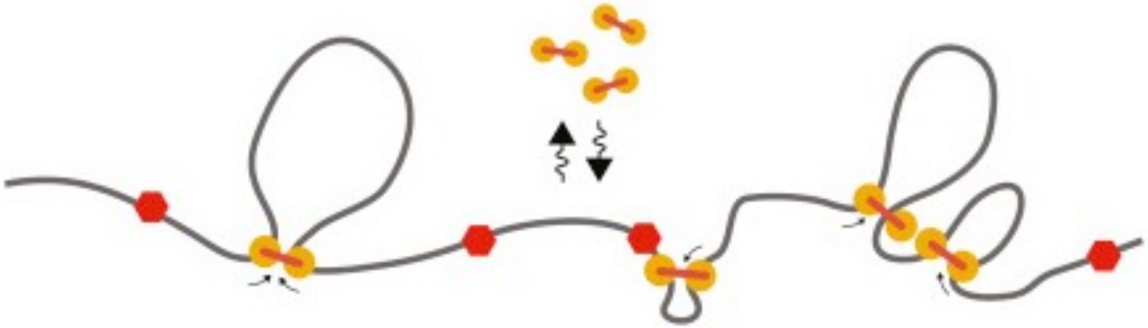
- Lattice density : ϕ

$$N_k(\phi) = \left(\frac{c^2 n^4}{N_e \phi^2}\right)^{\frac{1}{3}}$$

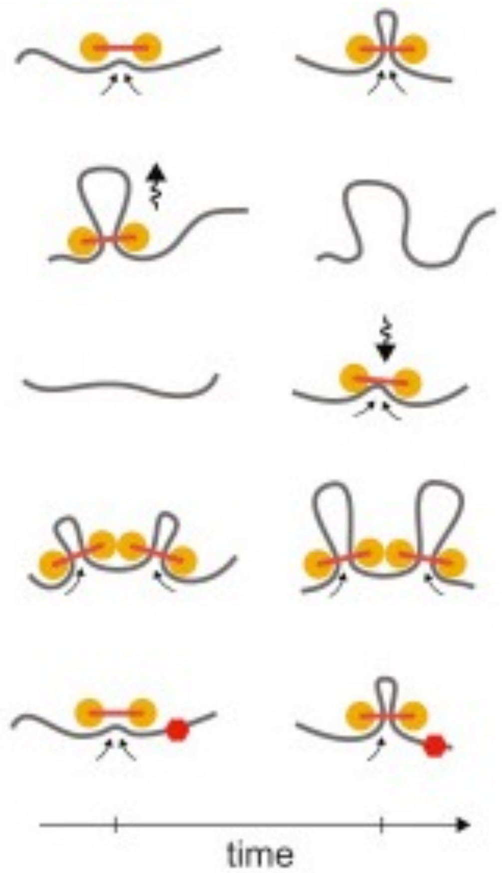


TAD : Topologically associated domain





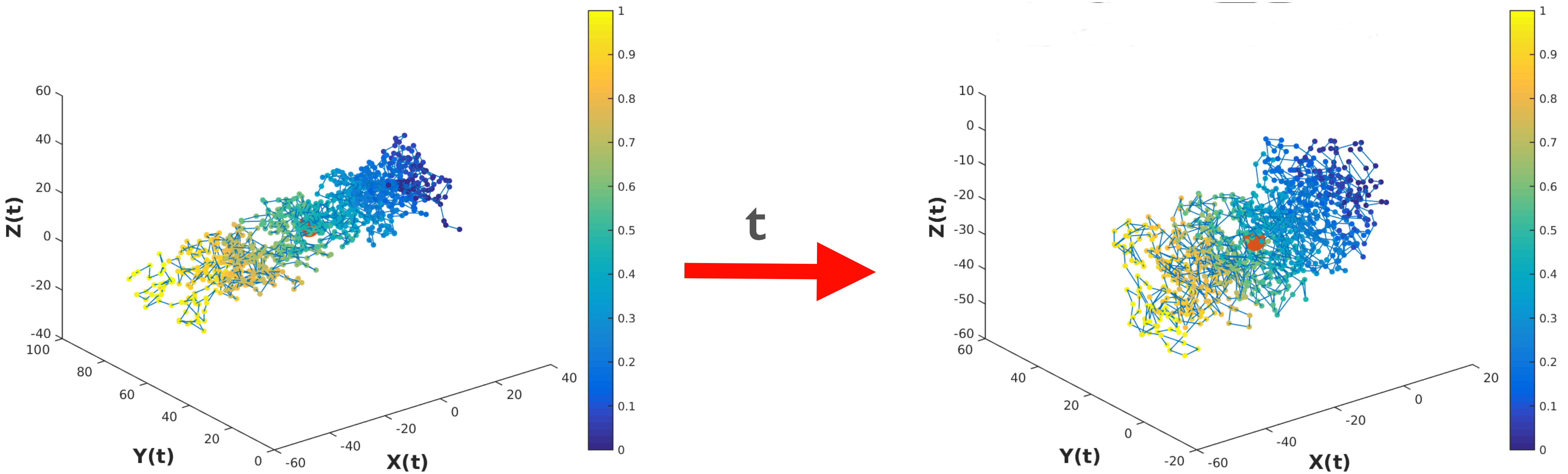
TAD : Topologically associated domain



Key physical quantity to measure

1. Mean squared displacement : MSD

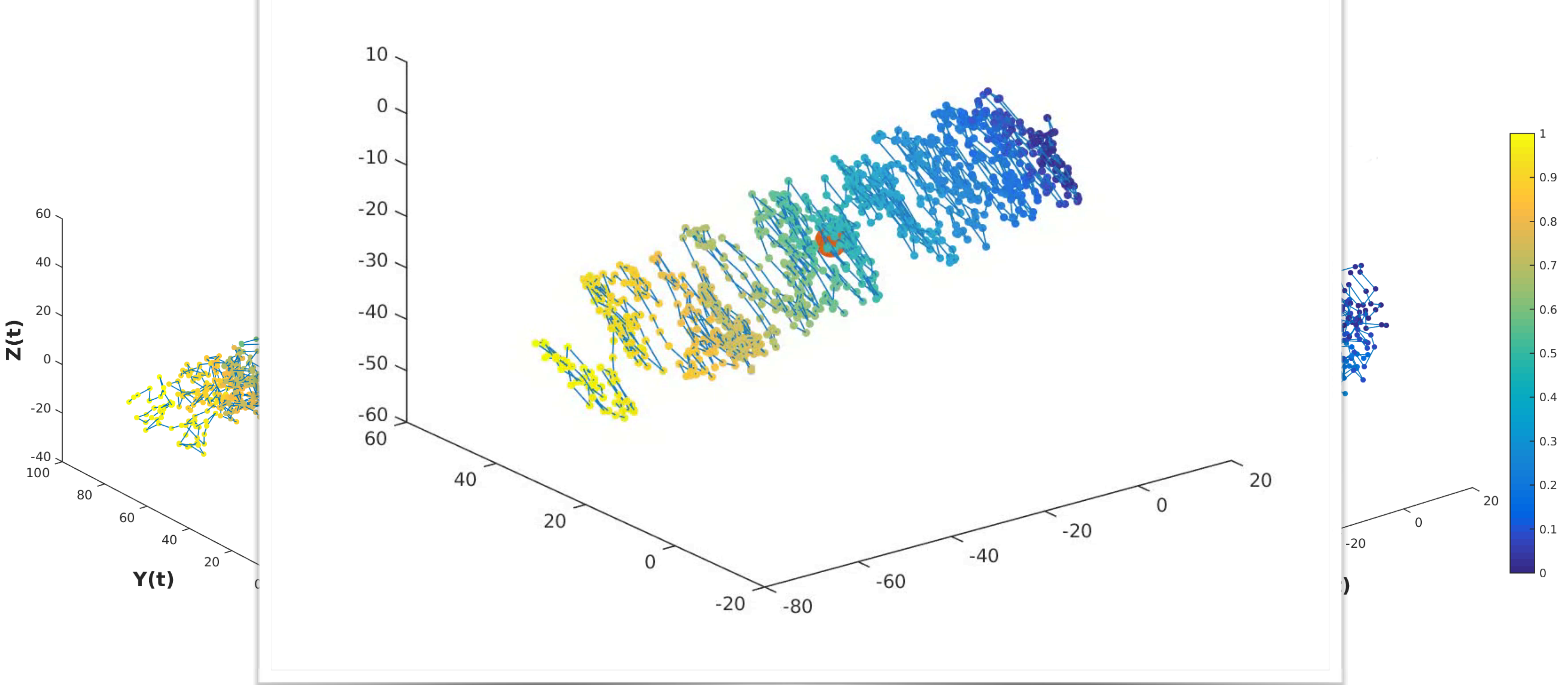
$$MSD(t) =< (x - x_0)^2 >= \frac{1}{N}\sum_{1}^{N}(x_n(t) - x_n(0))^2$$



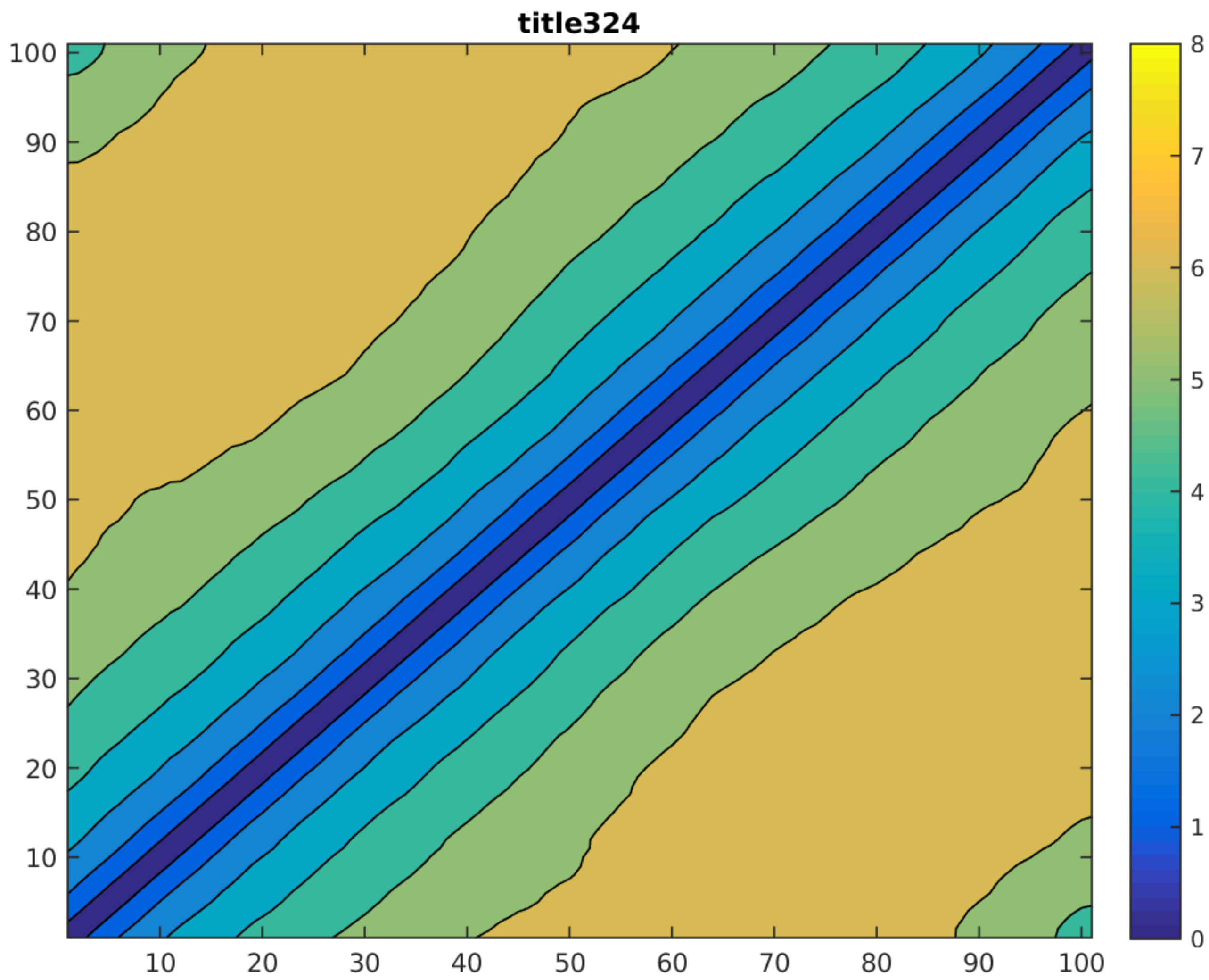
Key physical quantity to measure

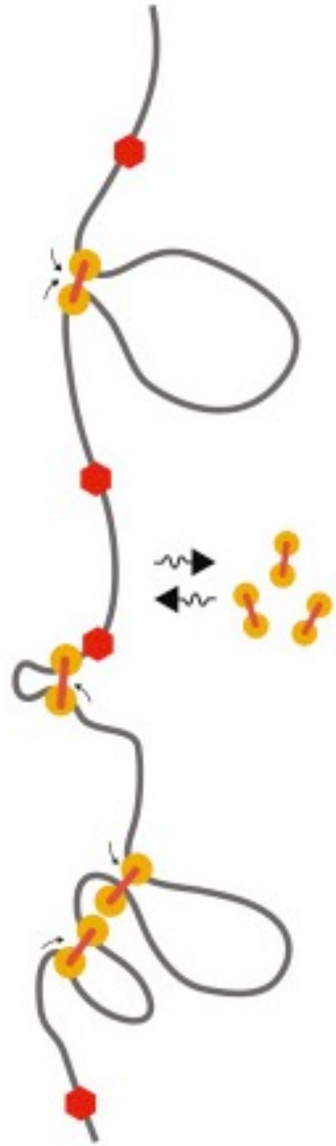
1. Mean squared displacement : MSD

$$MSD(t)$$

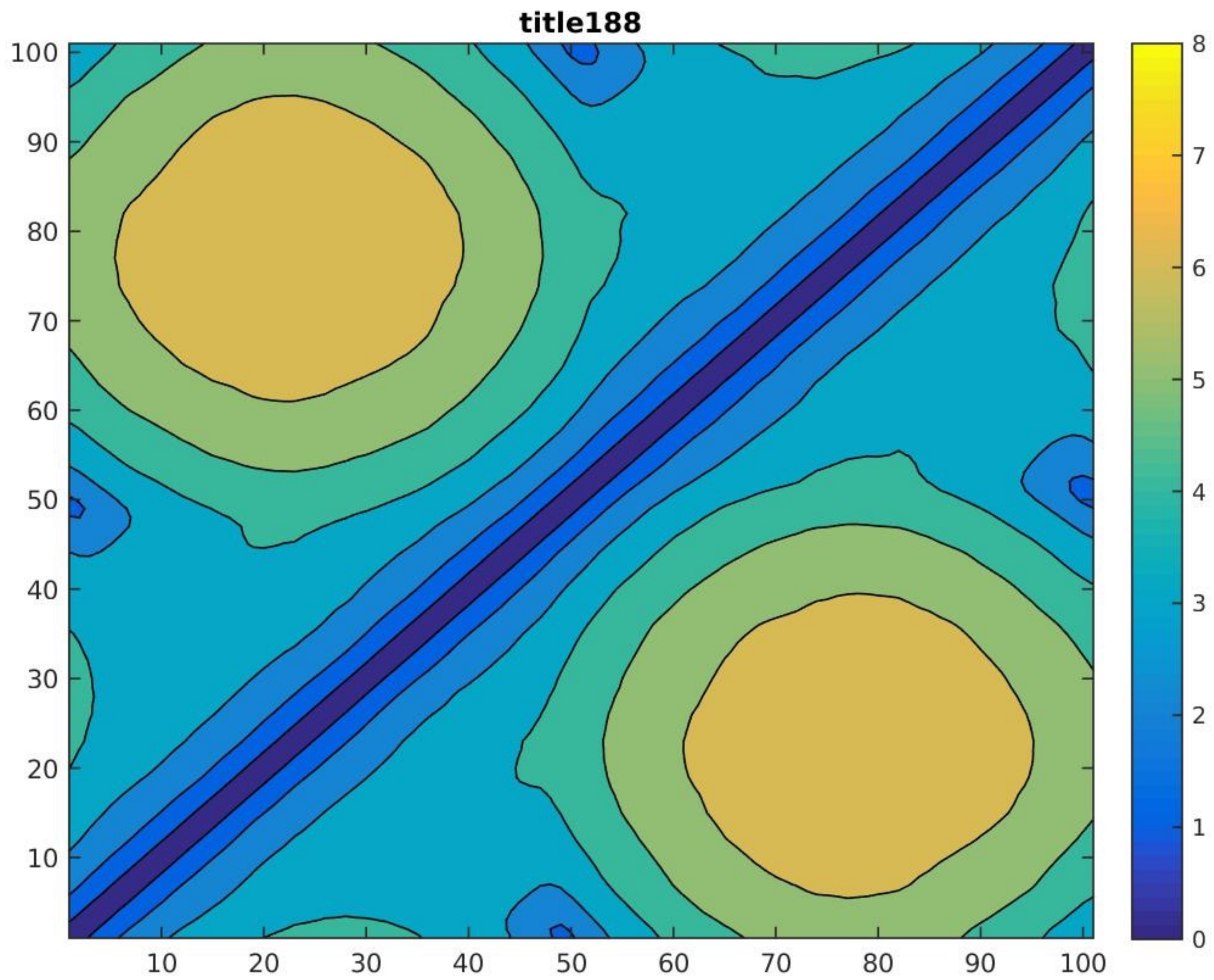


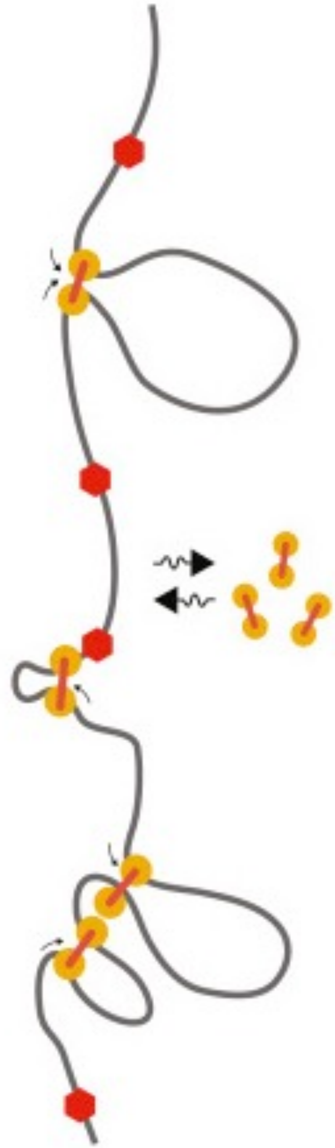
Normal Polymer : No extruder



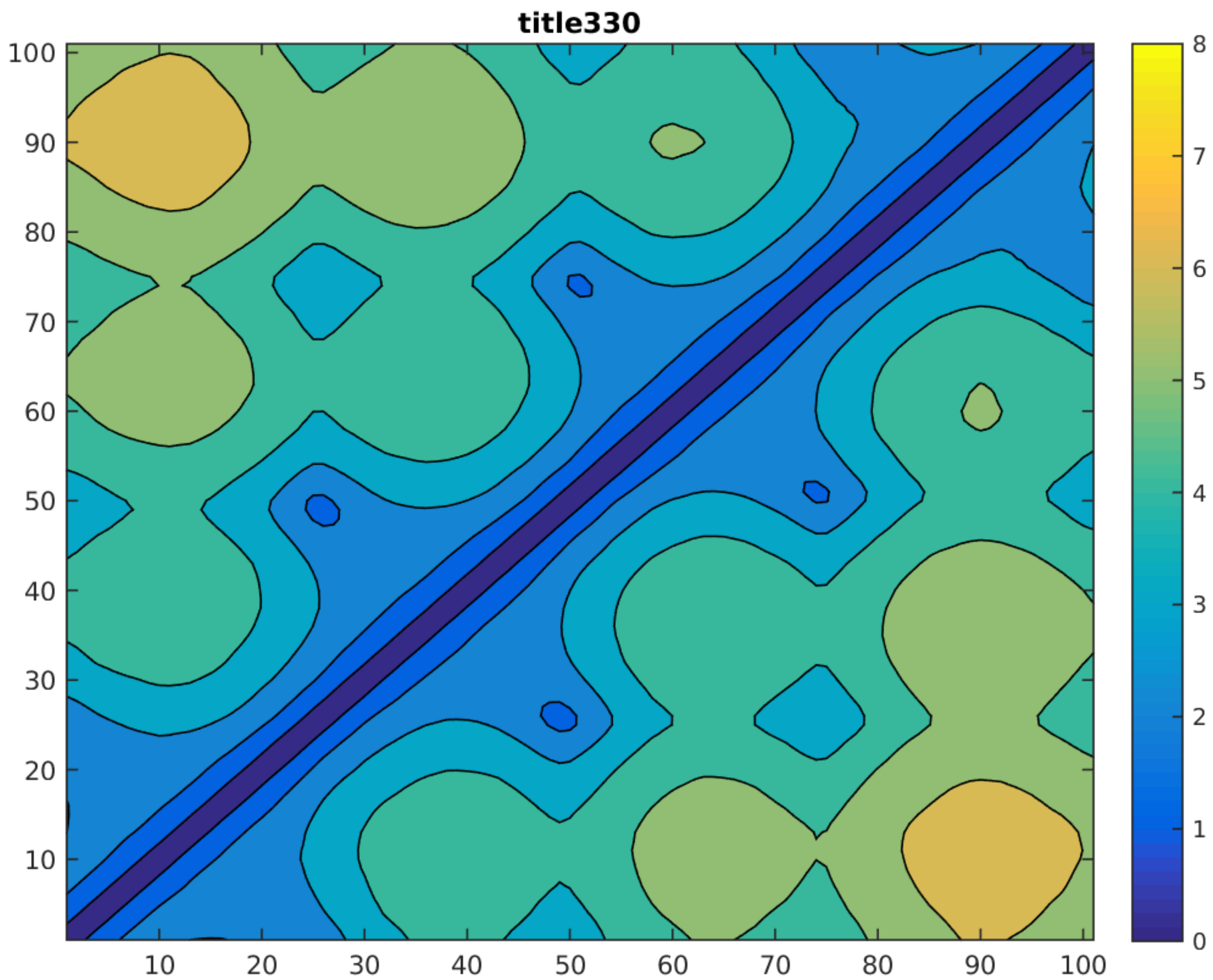


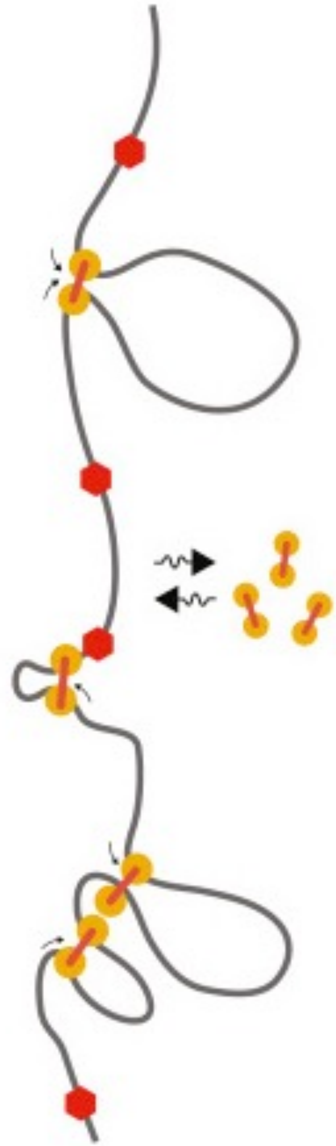
Normal Polymer : With extruder





Normal Polymer : With extruder , more boundary





Polymer : with extruder, more boundary