Polymers in the cell nucleus

A story about chromosome folding
and self-tuning polymers

with some final questions
for molecular modeling people

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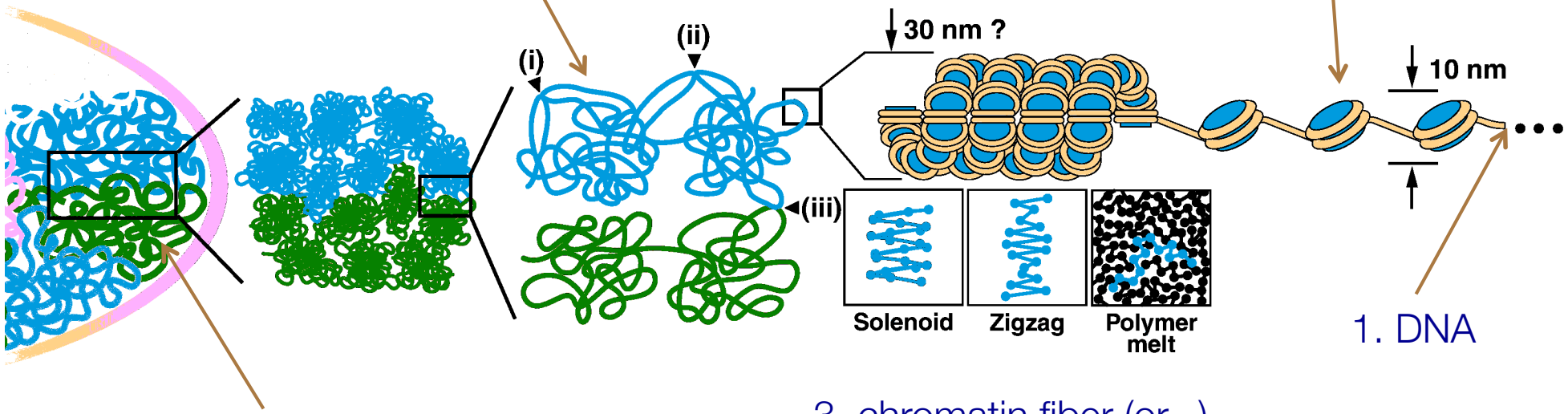
DNA IN THE NUCLEUS : CHROMATIN

The current model of nuclear architecture

4. « Topologically associating » domains (TADs, 200 kb to 1 Mb)

2. nucleosome



1. DNA

5. Chromosome territories

3. chromatin fiber (or...)

Hübner, Eckersley-Maslin, Spector, Current Opinion in Genetics & Development, 2013

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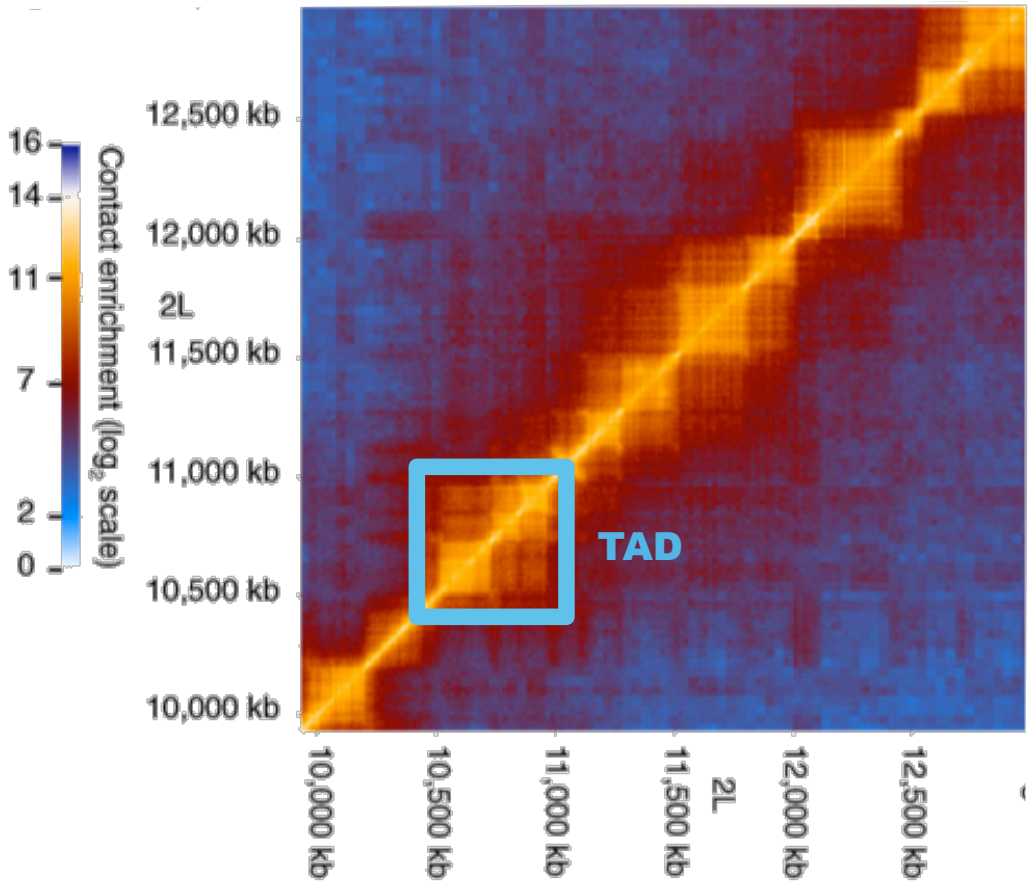
Topologically associated domains (TADs)

Chromosome conformation capture techniques (Hi-C)
Contact map



Sexton T. et al., Three-Dimensional Folding and Functional Organization Principles of the Drosophila Genome, Cell 2012

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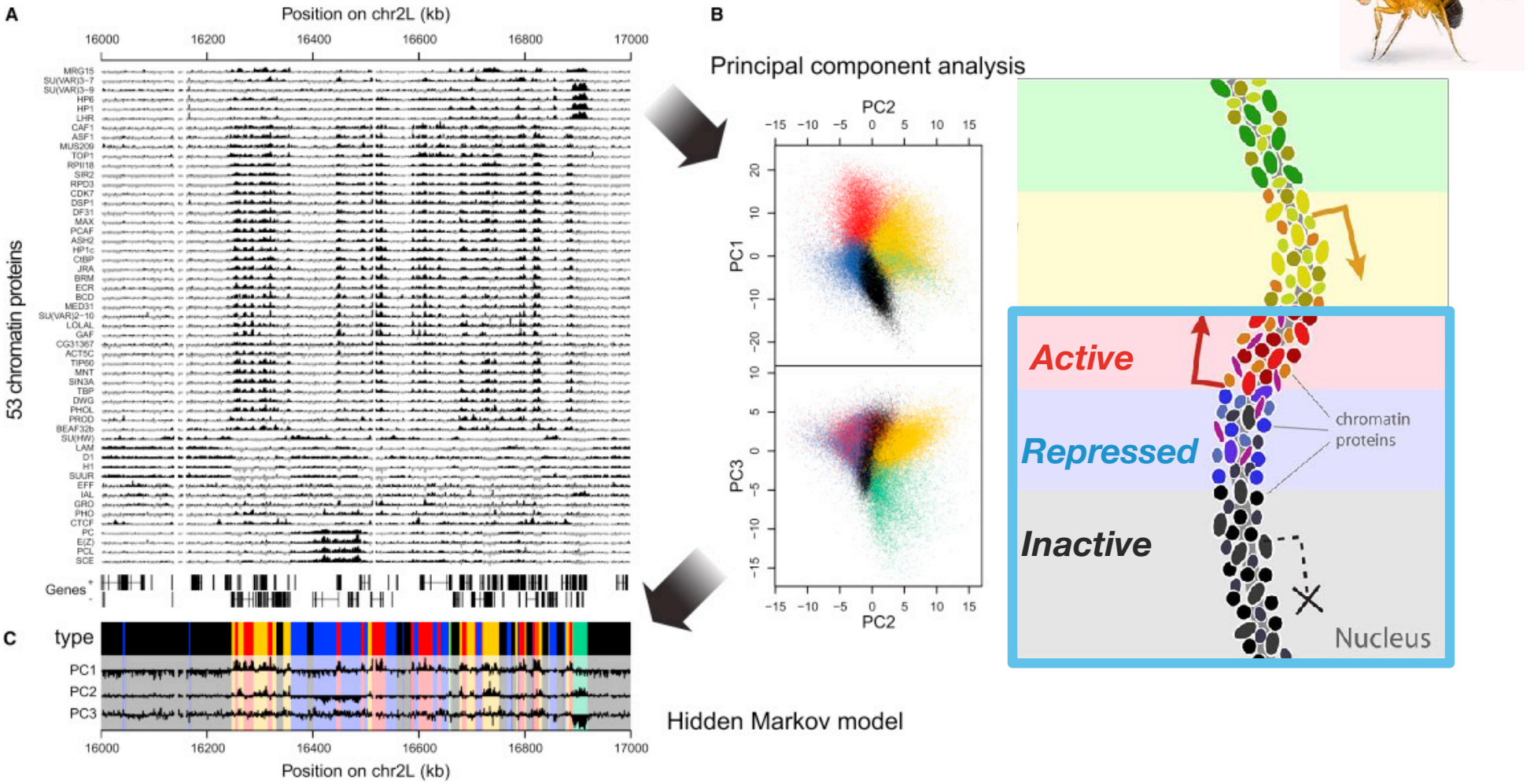
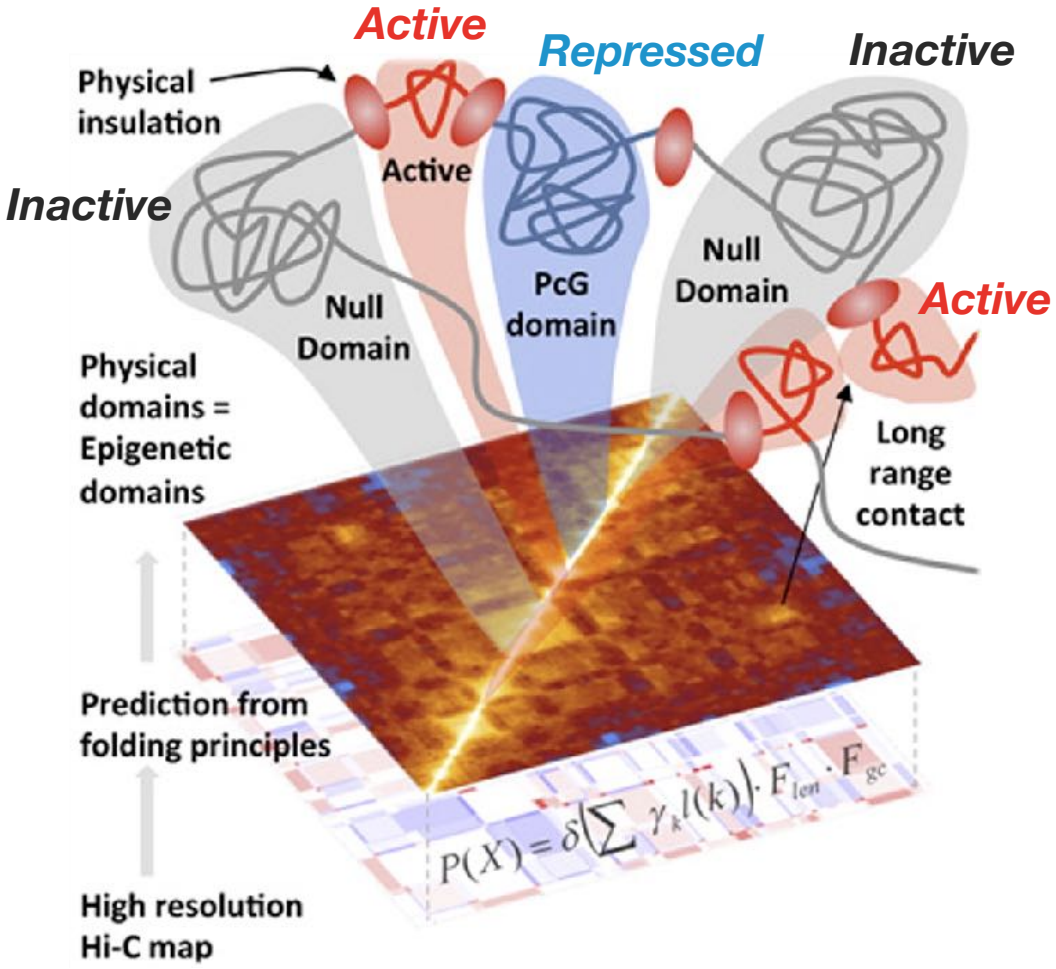
Epigenetic domains



Filion et al. Systematic protein location mapping reveals five principal chromatin types in Drosophila cells, Cell, 2010

Drosophila

In Drosophila, epigenetic domains ≃ TADs



Sexton T. et al., Three-Dimensional Folding and Functional Organization Principles of the Drosophila Genome, Cell 2012

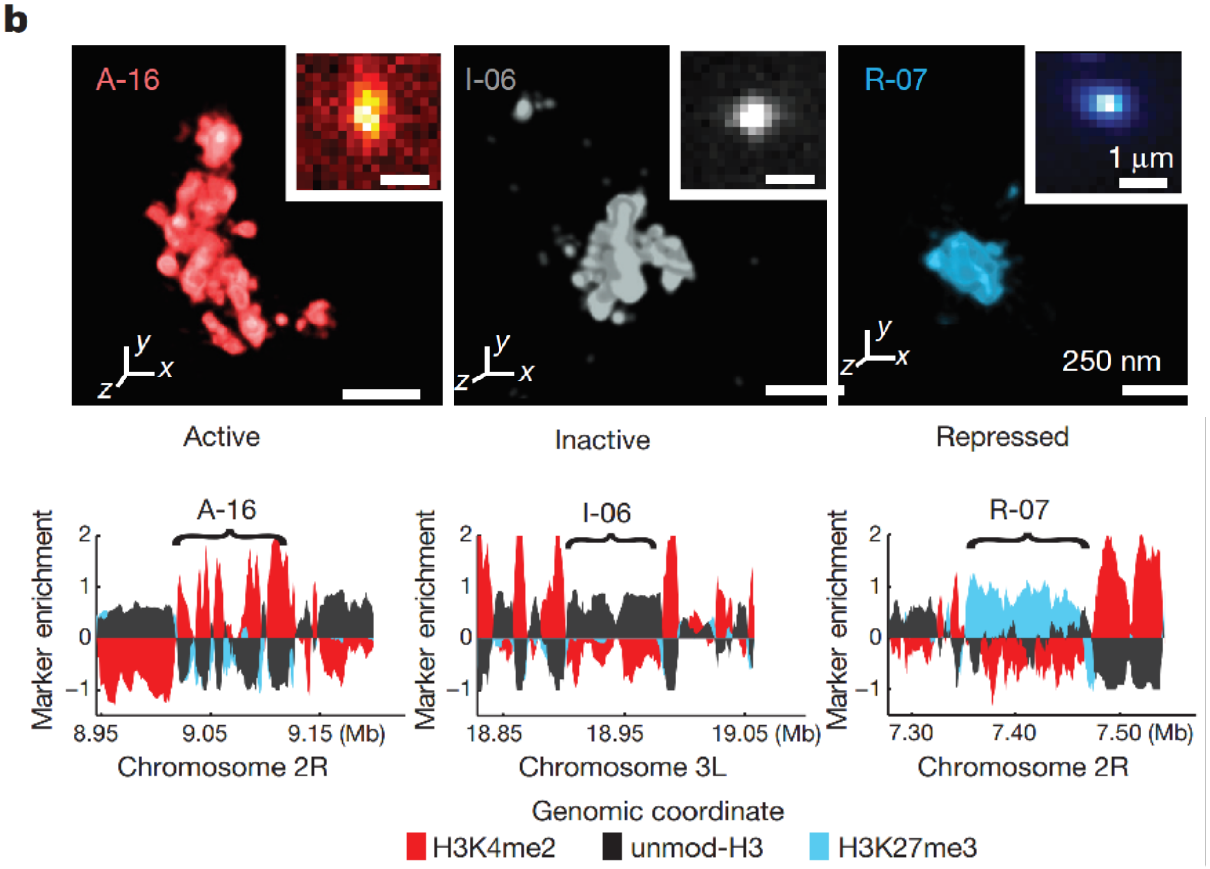
LETTER

418 | NATURE | VOL 529 | 21 JANUARY 2016

doi:10.1038/nature16496

Super-resolution imaging reveals distinct chromatin folding for different epigenetic states

Alistair N. Boettiger[1], Bogdan Bintu[1], Jeffrey R. Moffitt[1], Siyuan Wang[1], Brian J. Beliveau[2], Geoffrey Fudenberg[3], Maxim Imakaev[3], Leonid A. Mirny[3], Chao-ting Wu[2] & Xiaowei Zhuang[1]



3D imaging,
20-50-nm resolution

3 epigenetic states:

- ***Active***
- ***Inactive***
- ***Repressed***

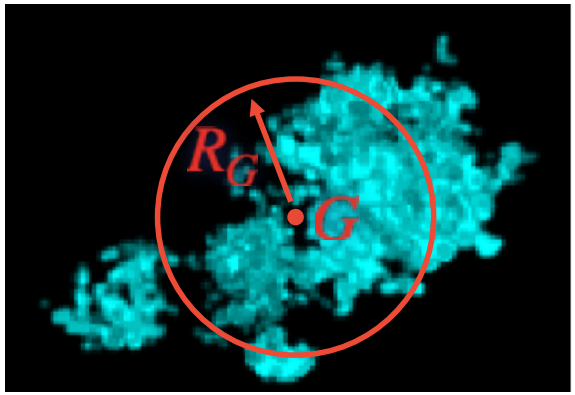
What to measure?

mass (fluorescence) distribution :

$$1 = \int \Delta(\mathbf{r}) d^3r$$

mass (fluorescence) barycenter :

$$G = \int \mathbf{r}\, \Delta(\mathbf{r}) d^3r$$



mass (fluorescence) variance :

$$R_G^2 = \int (\mathbf{r} - G)^2\, \Delta(\mathbf{r}) d^3r$$

← **radius of gyration**

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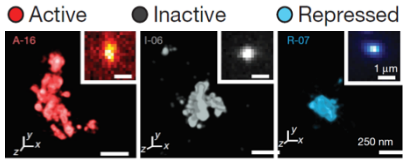

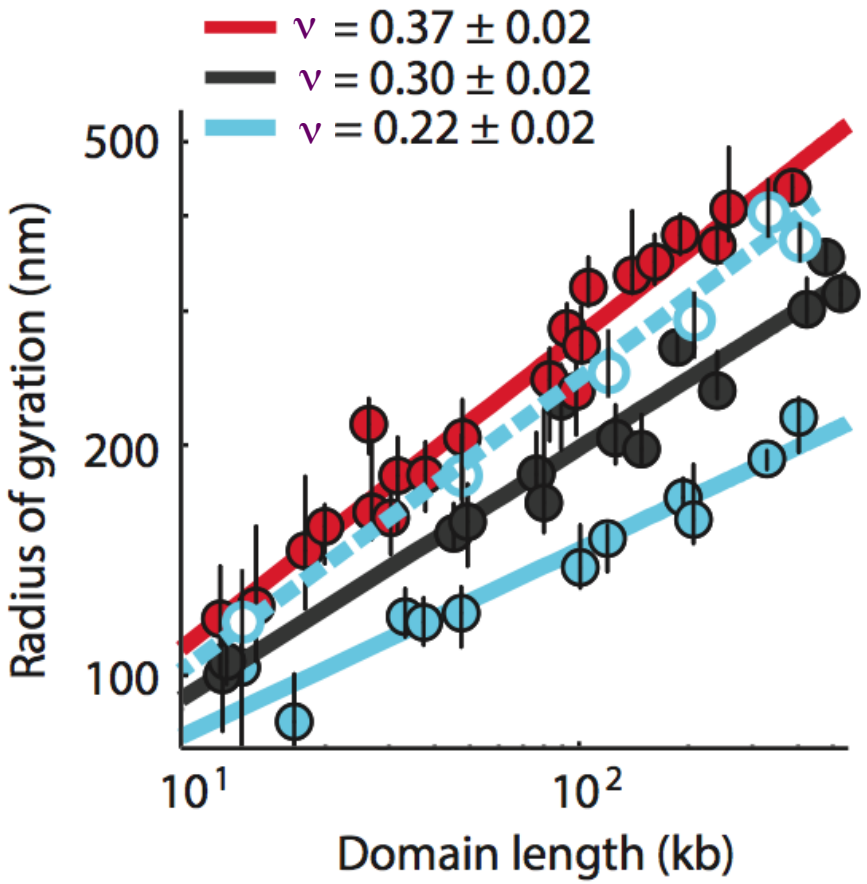

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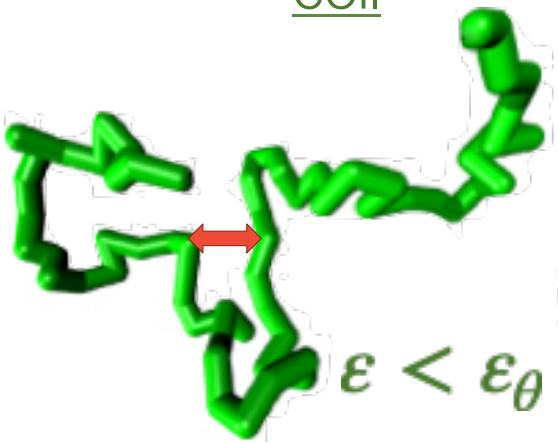
What to compare with?

Polymer physics:

Self-Avoiding Walk (SAW)
coil



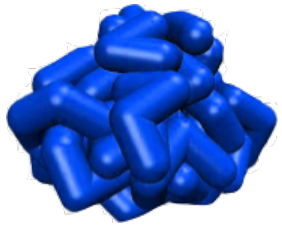
$\varepsilon < \varepsilon_\theta$

$R_G \propto N^{3/5}$

monomer-monomer
interaction $\boldsymbol{\varepsilon} = J/k_BT$

critical
$\varepsilon_\Theta = 0.27$

Equilibrium
globule



$\varepsilon > \varepsilon_\theta$

$R_G \propto N^{1/3}$

$R_G \propto N^{\nu}$

scaling law

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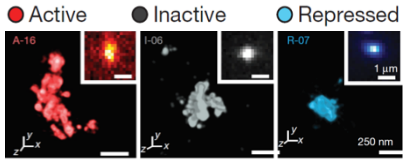
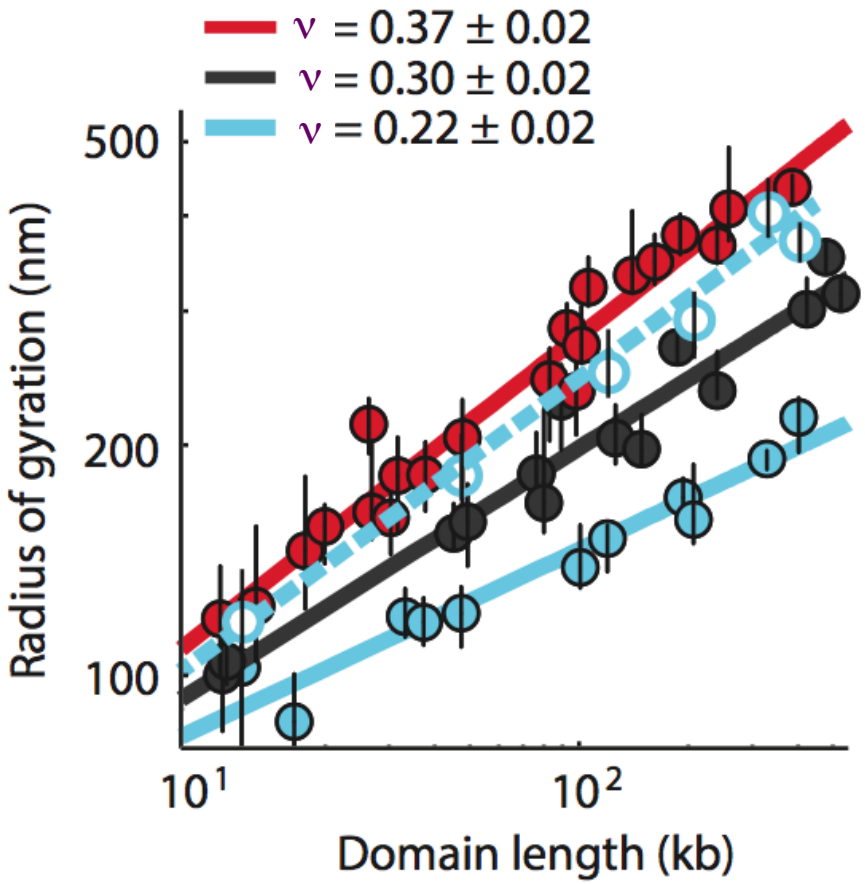


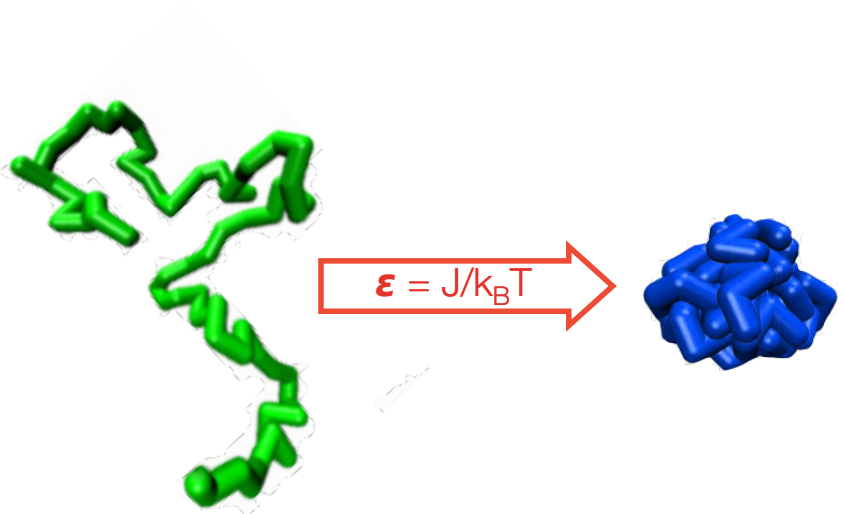


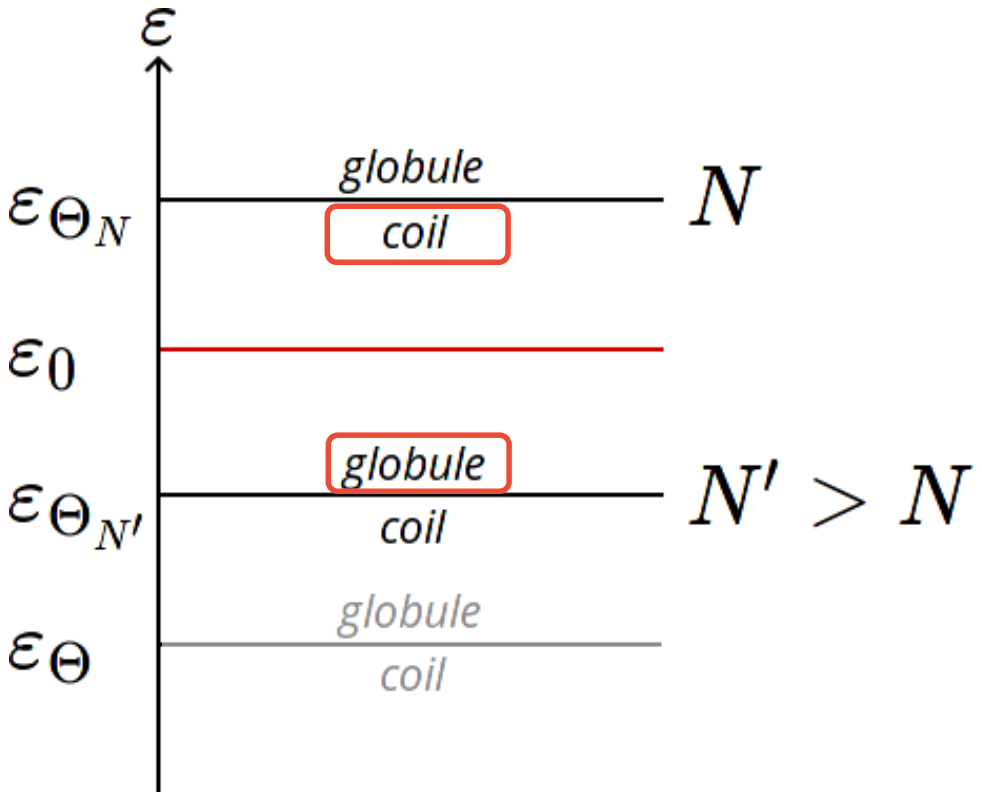
$R_G \propto N^{3/5} \rightarrow 0.6$

$R_G \propto N^{1/3} \rightarrow 0.33$

Idea: finite-size effects

A polymer with N identical monomers:





thermodynamic limit critical

coil-globule transition: ε

N

- Small polymers are coil
- Big polymers are globule

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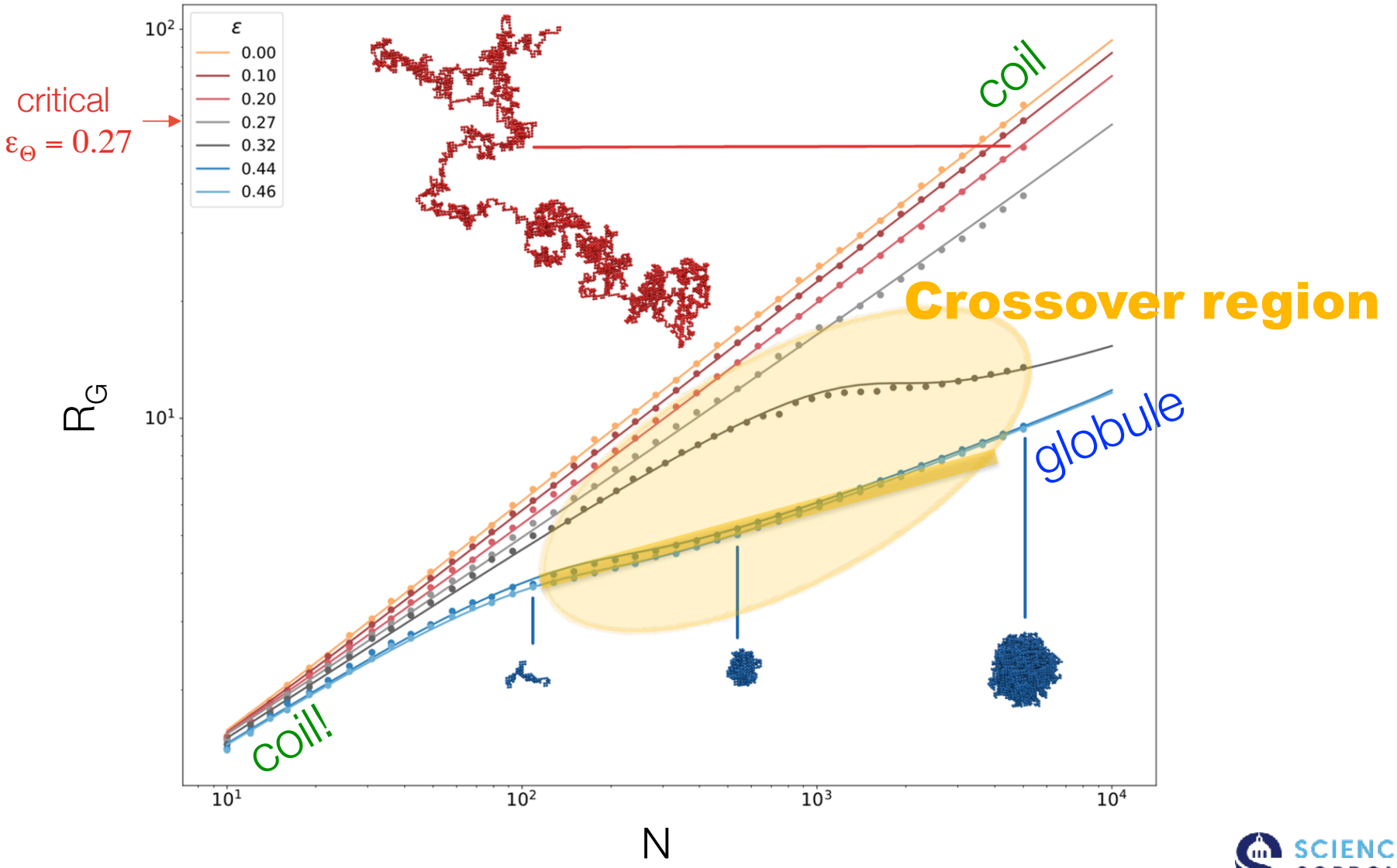
Idea: finite-size effects

Crossover : scaling law rupture



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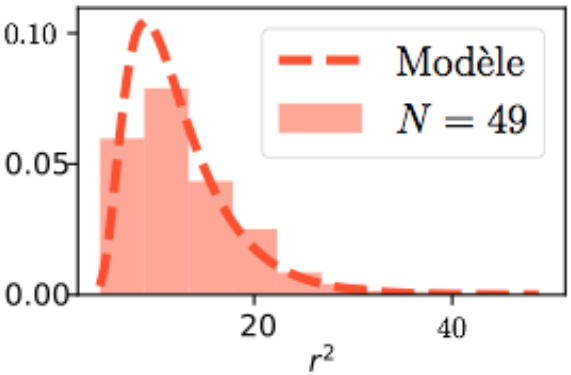
Why interesting?

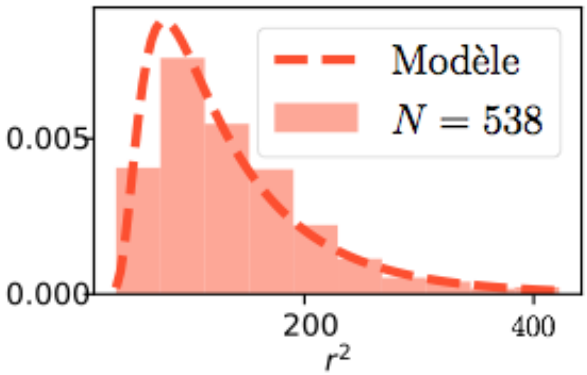
Theoretical modeling available

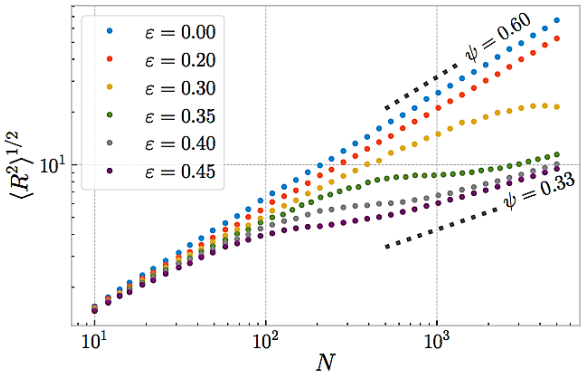
$$\frac{F_N(t)}{k_B T} = a_1(\varepsilon)\, Nt + a_2(\varepsilon)\, Nt^2 + a_3(\varepsilon)\, (Nt)^{-2/3} + a_4(\varepsilon)\, (Nt^2)^{2/3} + 1.13 \ln Nt$$

Renormalized density $t = \left(\frac{N}{R^3}\right)^{5/4}$

R_G distribution $p_N(R_G^2) \propto \exp - F_N(R_G^2)/k_B T$ (and average)







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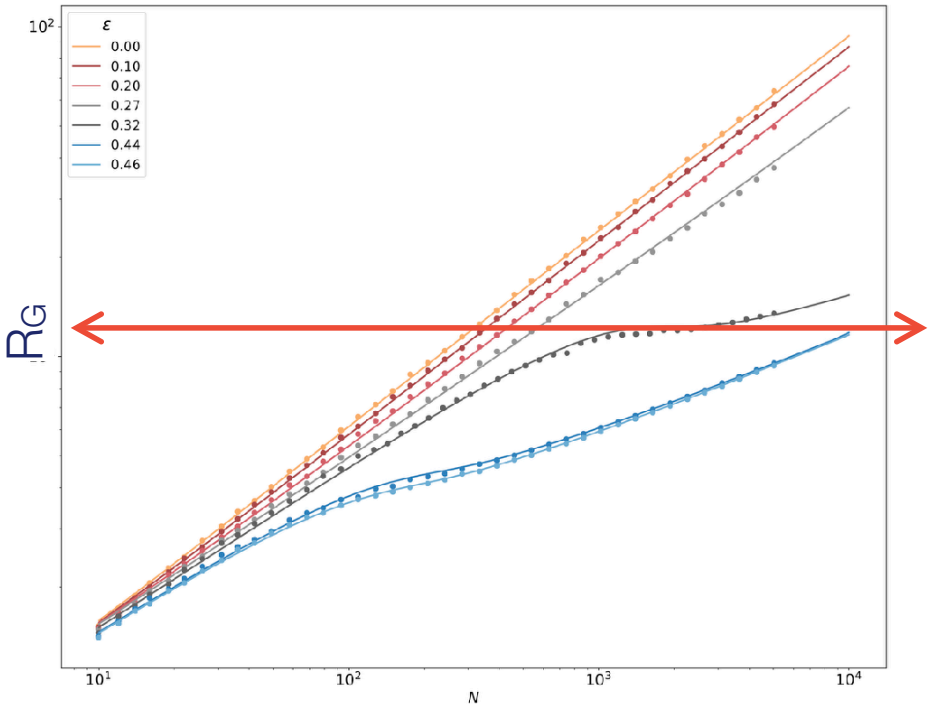
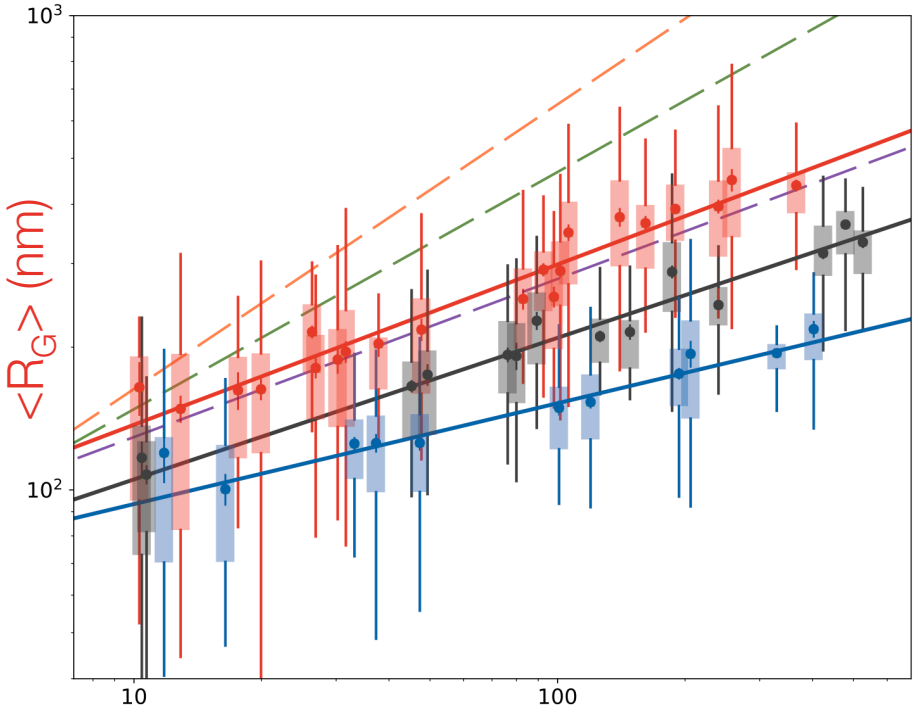
Compare with data...

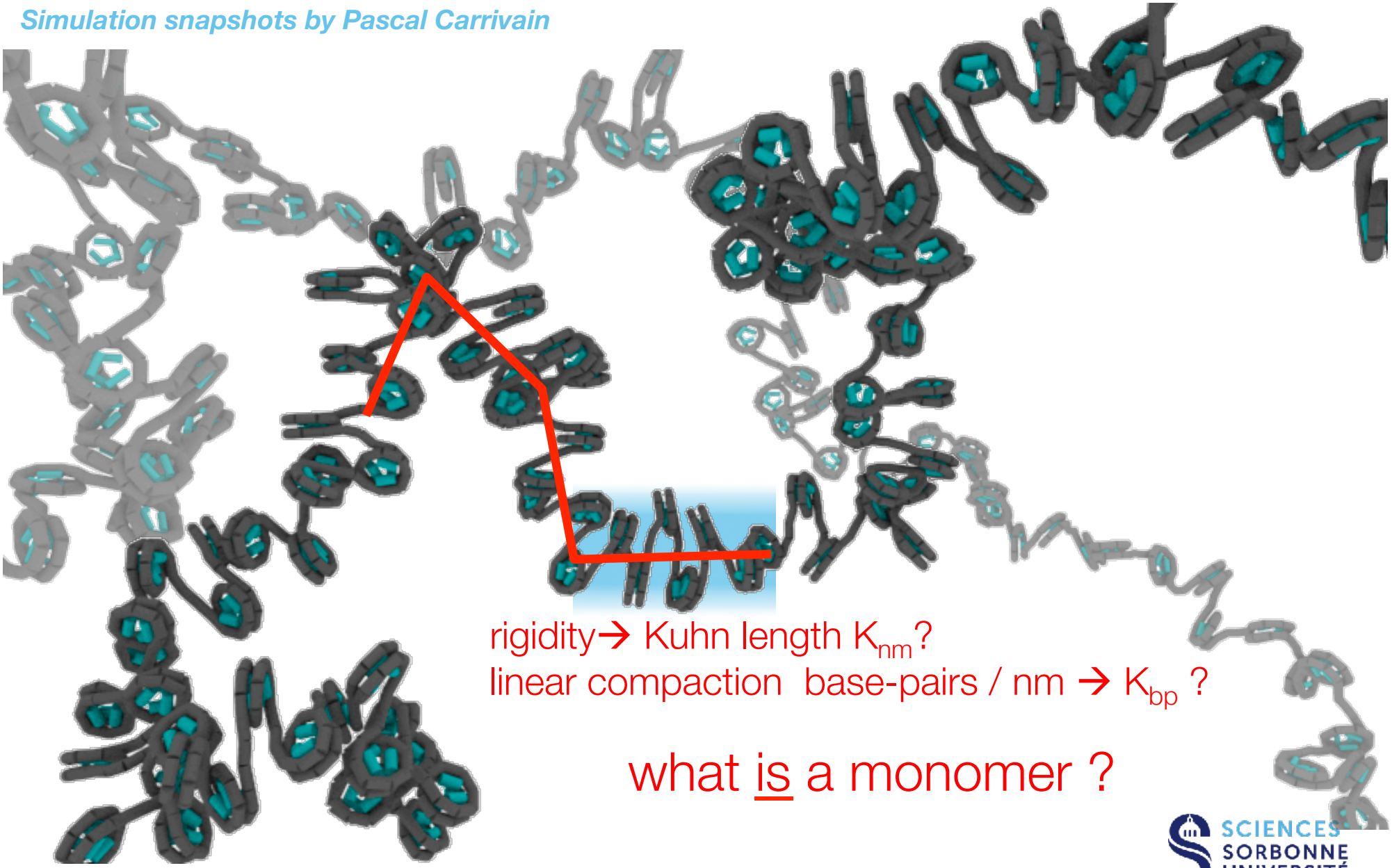




adimensional ↔ dimensional

A self-tuning polymer

Simulation snapshots by Pascal Carrivain



rigidity→ Kuhn length K_{nm}?
linear compaction base-pairs / nm → K_{bp} ?

what is a monomer ?

New fitting parameters

Fitting parameters

ε

K_{nm} [nm]

K_{bp} [bp]

$\leftrightarrow$

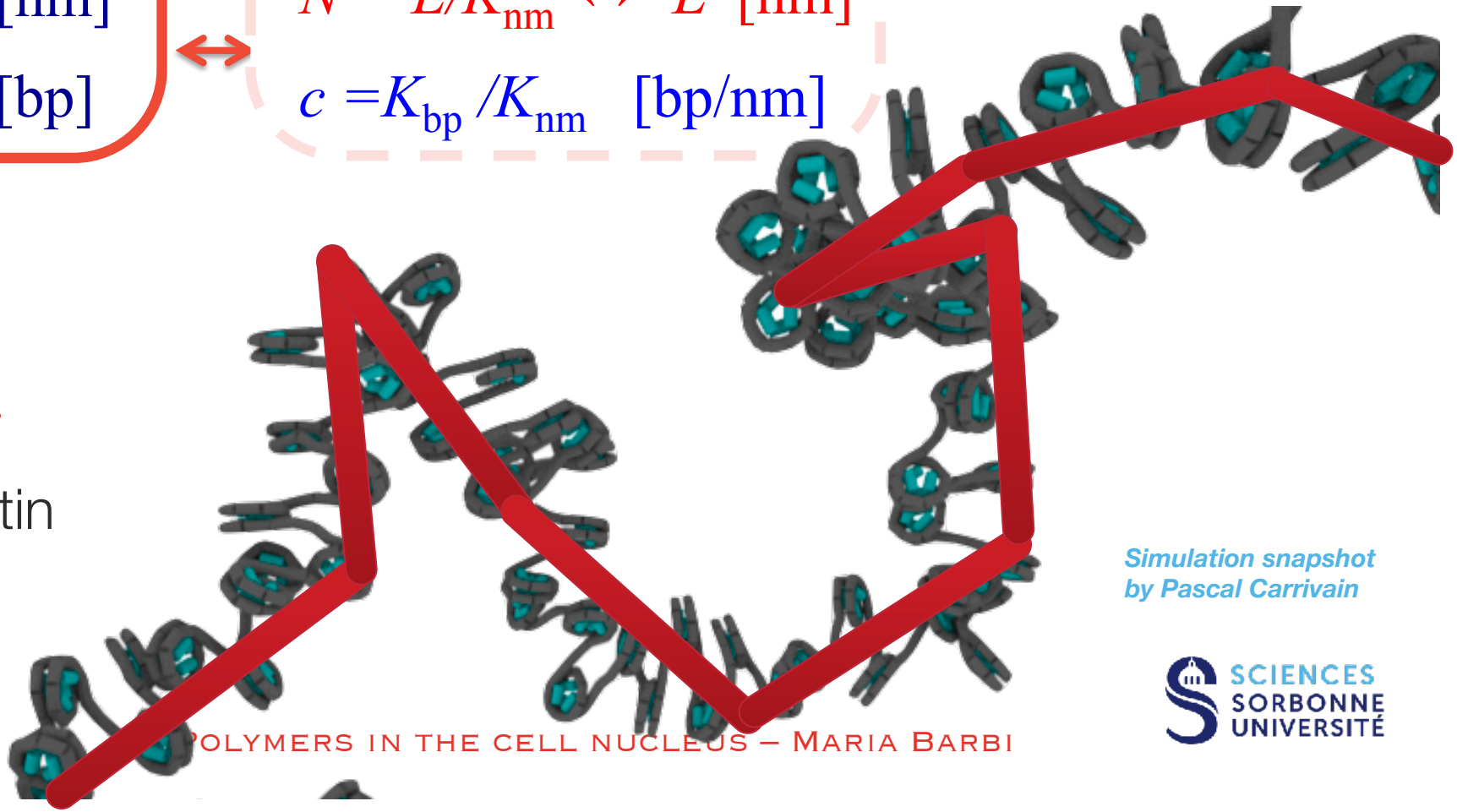
ε

$N = L/K_{nm} \leftrightarrow L$ [nm]

$c = K_{bp}/K_{nm}$ [bp/nm]

Polymer

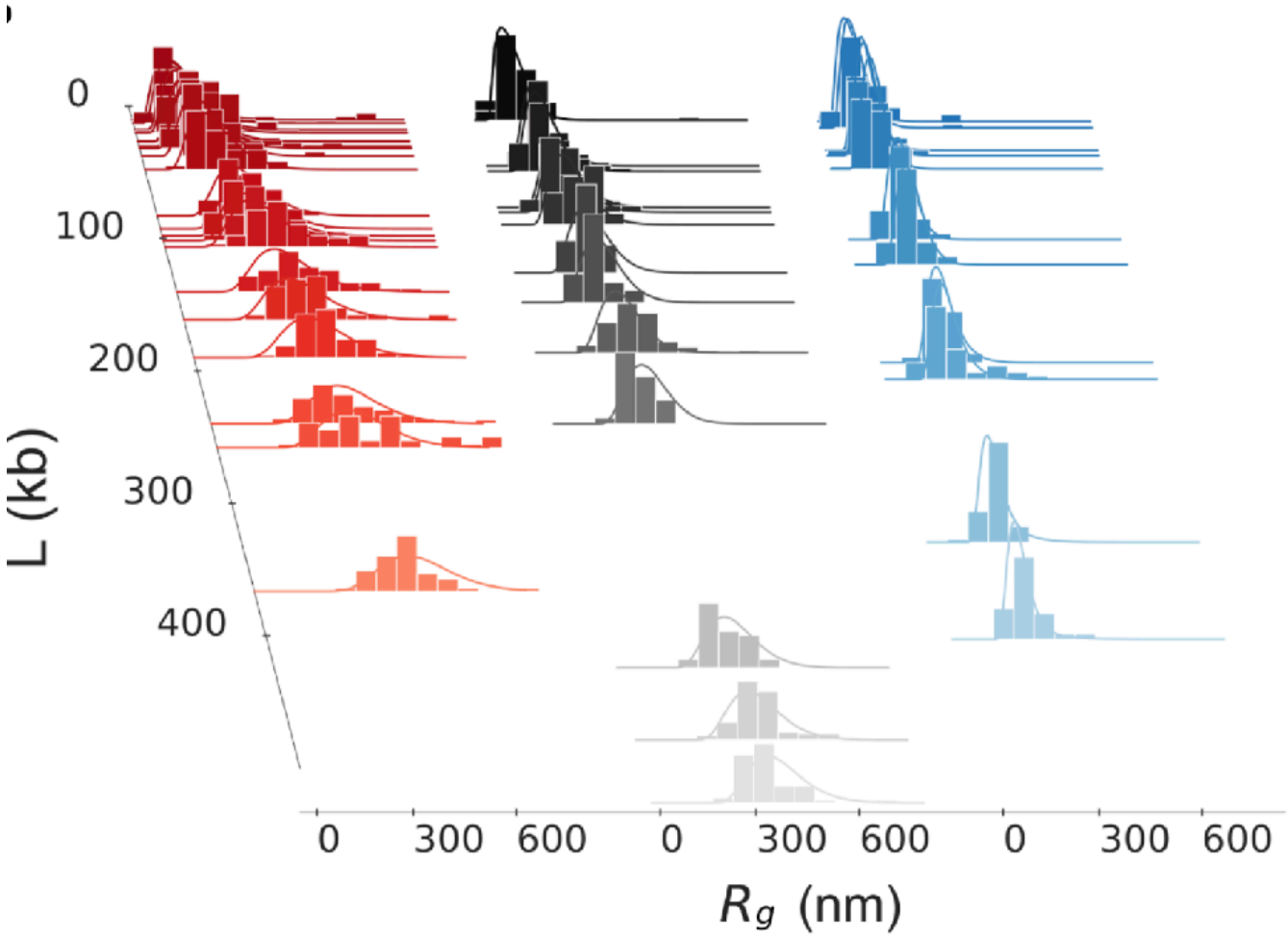
Chromatin



Simulation snapshot by Pascal Carrivain

Fit of experimental data

Fit of the whole dataset (histograms)

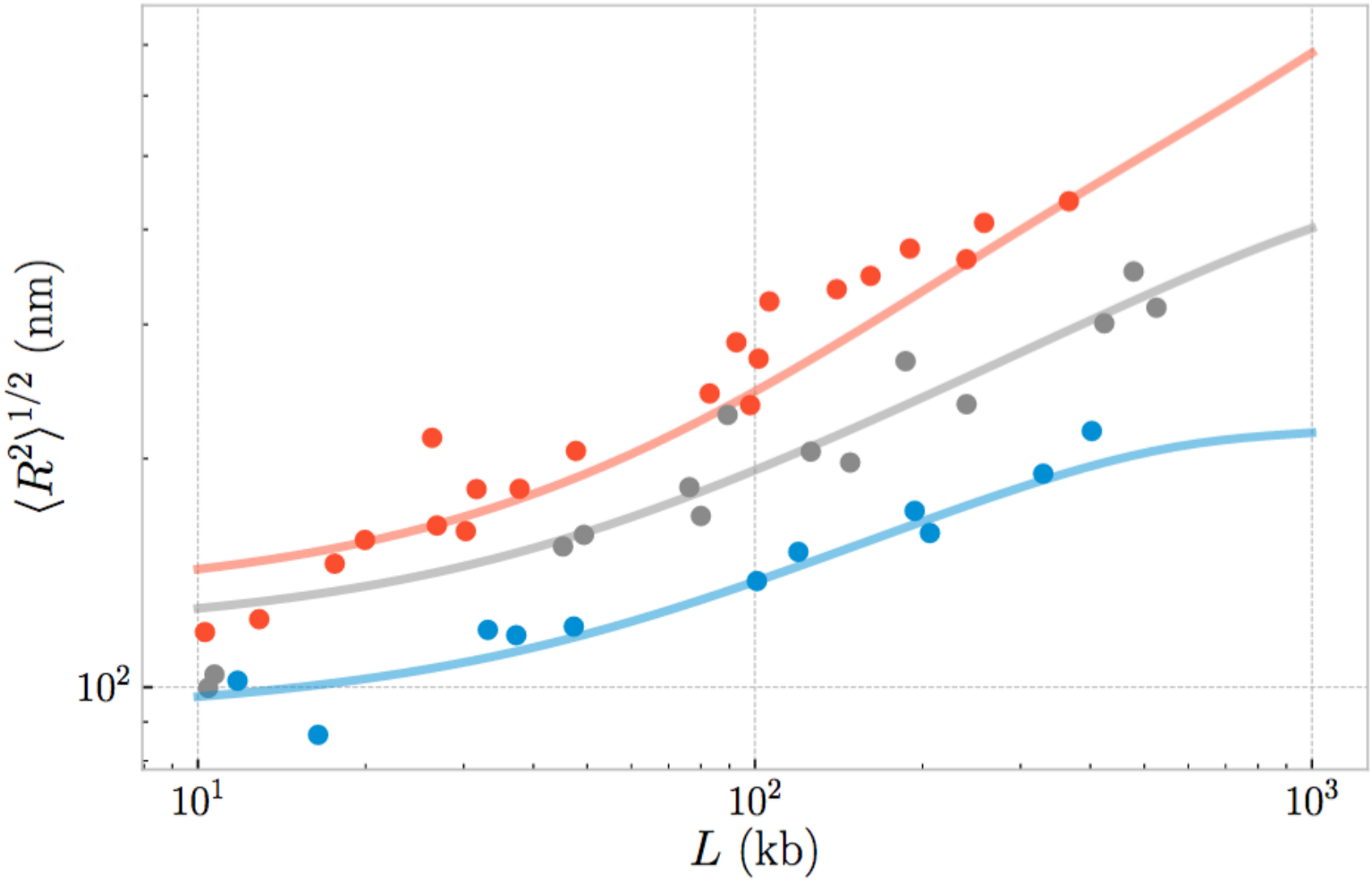


DATA FROM:

Boettiger et al. "Super-Resolution Imaging Reveals Distinct Chromatin Folding for Different Epigenetic States." Nature 2016

Fit of experimental data

Resulting average R_g



DATA FROM:
Boettiger et al. "Super-Resolution Imaging Reveals Distinct Chromatin Folding for Different Epigenetic States." Nature 2016

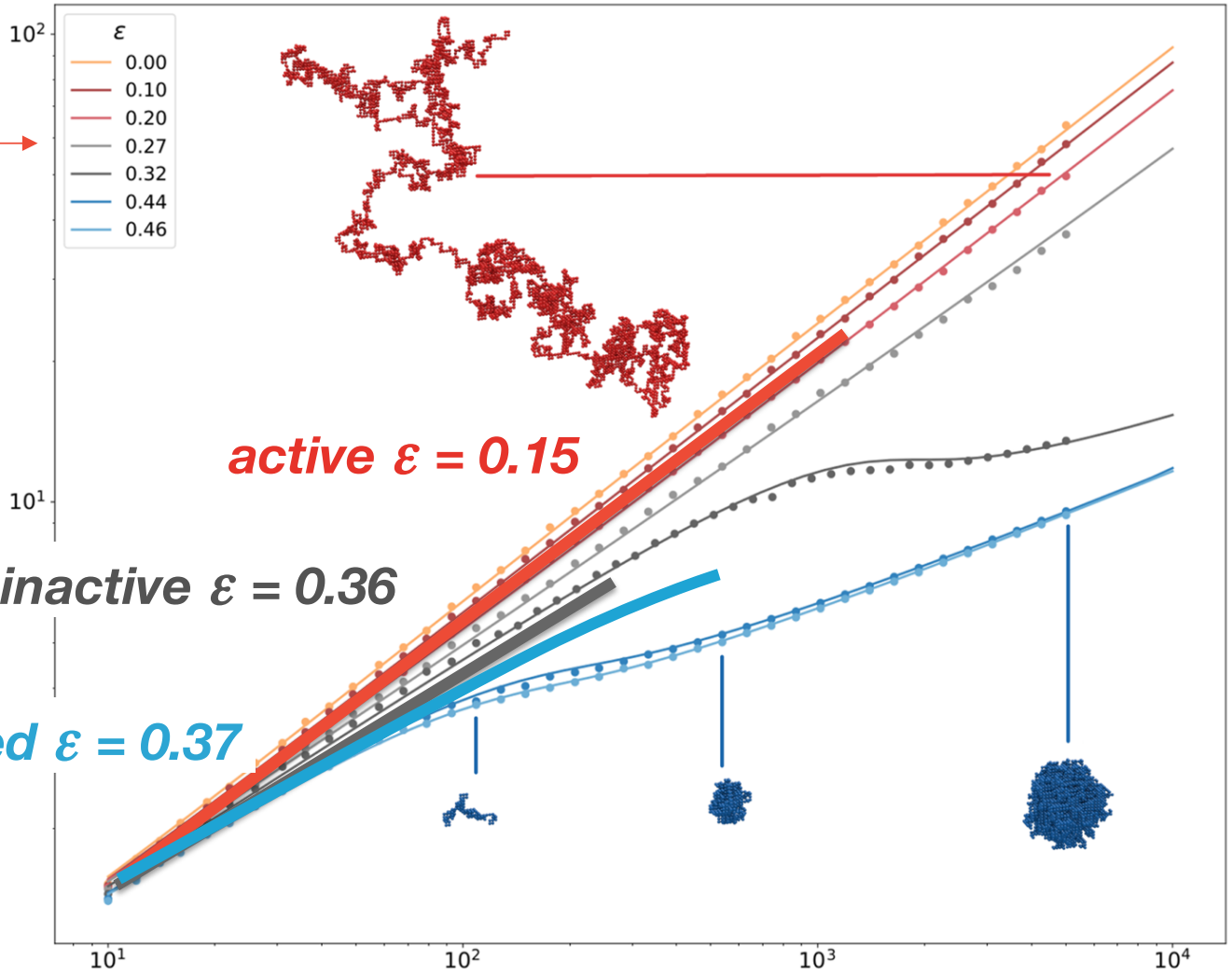
Results

Parameters

		Active	Inactive	Repressed
FIT	ε (k_BT)	$0.15^{+0.03}_{-0.11}$	0.36 ± 0.03	$0.37^{+0.04}_{-0.03}$
	K_{kb} (kb)	$0.4^{+0.5}_{-0.2}$	3^{+3}_{-1}	$1.2^{+1.5}_{-0.6}$
	K_{nm} (nm)	16^{+12}_{-6}	60 ± 20	26^{+12}_{-8}
Derived	c (bp nm^{-1})	25	50	46
	c_{10} (nuc/10 nm)	1.4	2.6	2.4
	C (nuc/K_{nm})	2.2	15.6	6.6

CLOSE TO TRANSITION → HIGHLY RESPONSIVE

Energies ε for the 3 states



N_{max} ~ 1000

N_{max} ~ 200

N_{max} ~ 300

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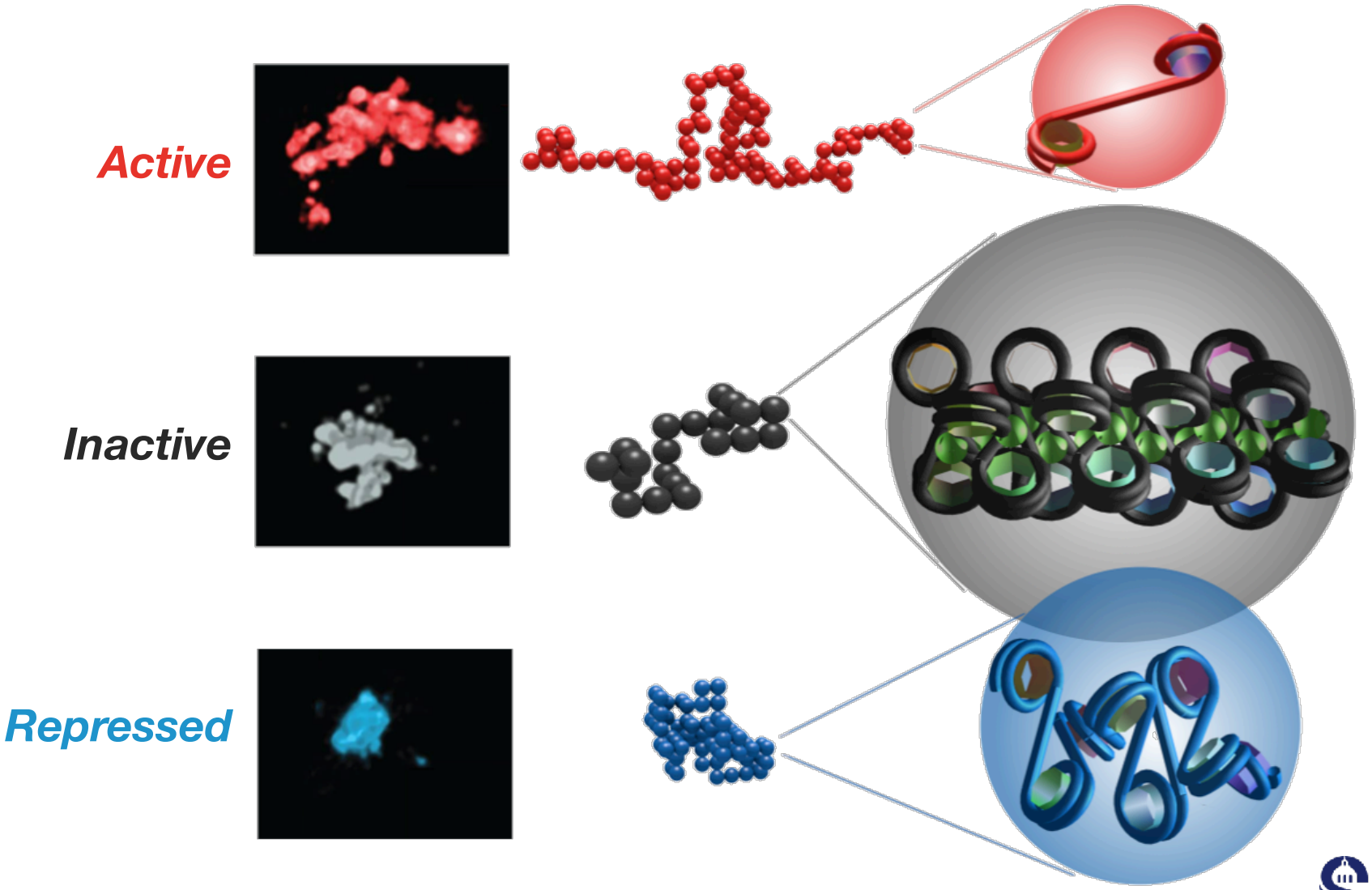
Architecture as a tuning parameter

An image of the 3 states



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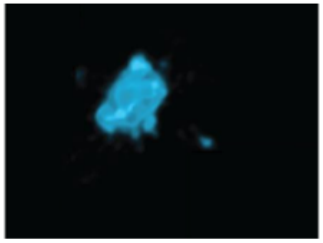
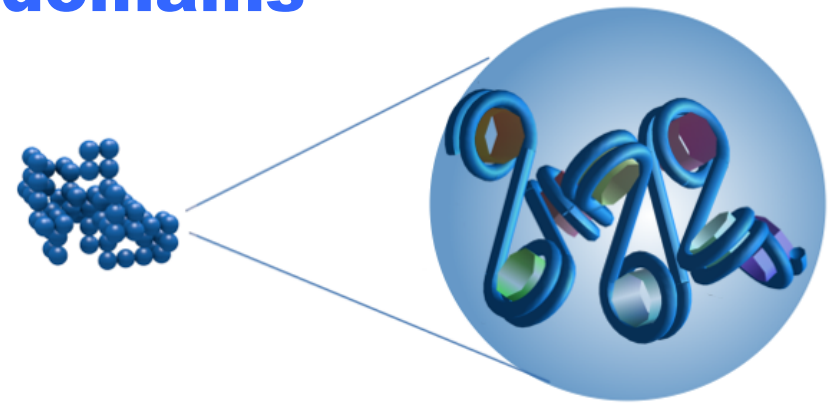
Interpretation, and questions

Repressed domains

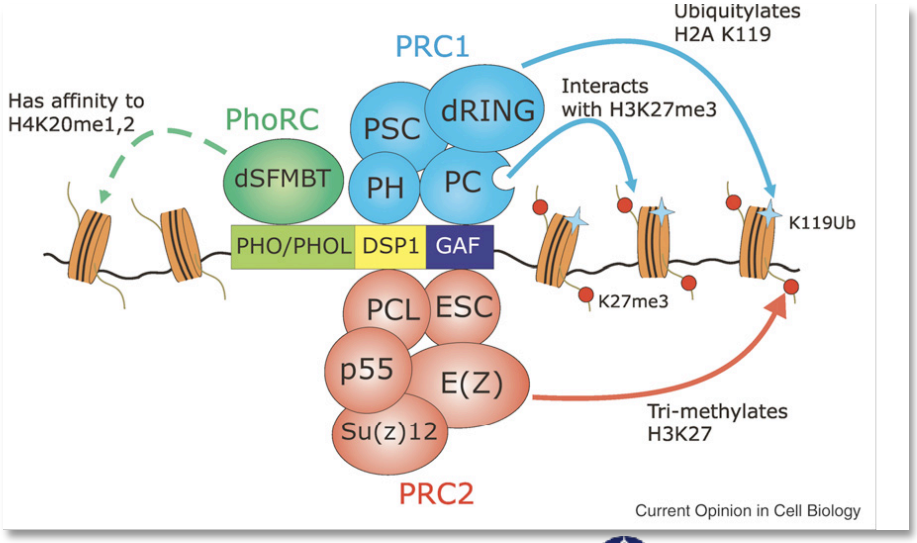




actively repressed by
proteins of the polycomb group

→ ε justified

→ mechanistic scenario?



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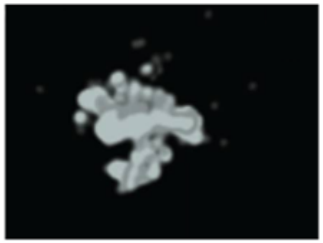
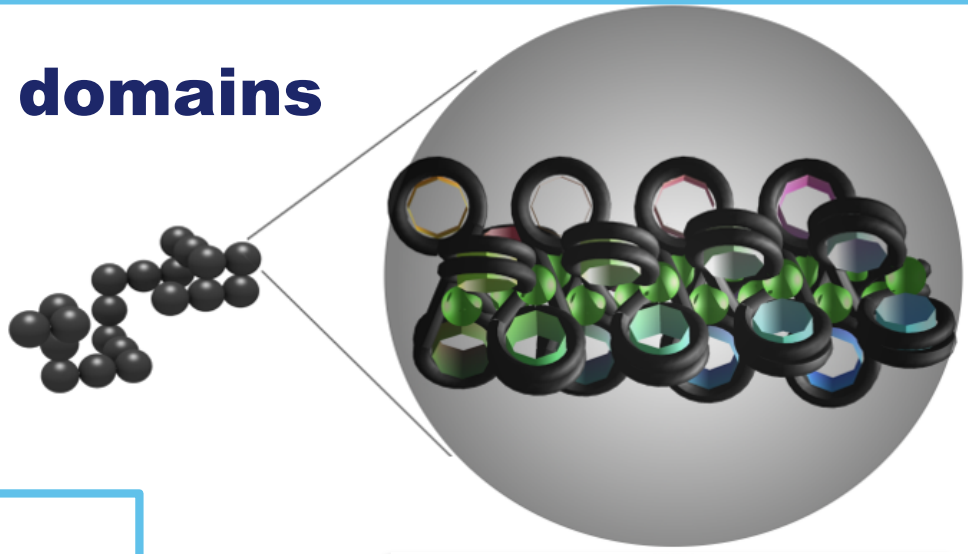
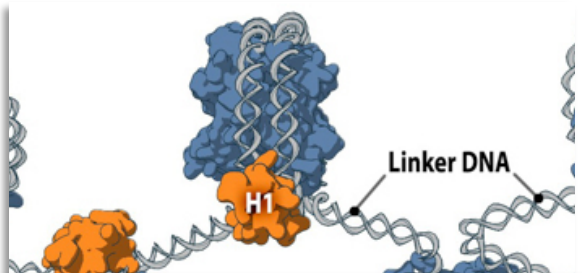
Interpretation, and questions

Inactive domains

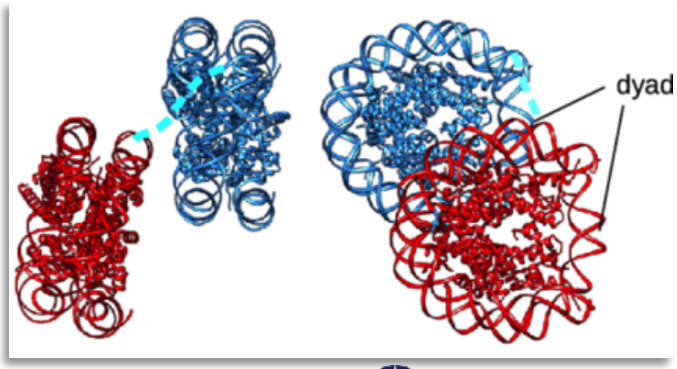




much larger persistence length:
~ 60 nm ~ 17 nucl.
→ role of histone H1?



no known binding proteins:
how ε can be justified?
→ nucleosome-nucleosome interactions?



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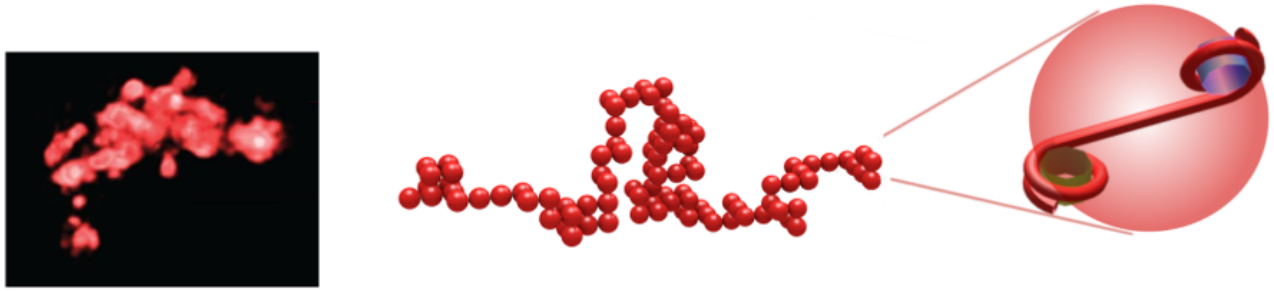
Interpretation, and questions

Active domains

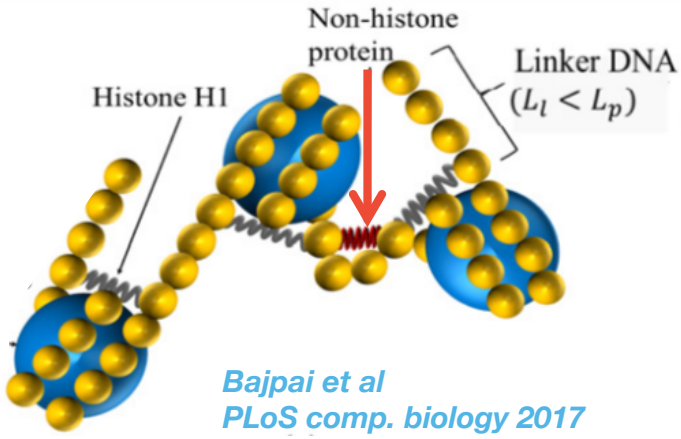


low ε: different nucleosome-nucleosome interaction?

very low persistence ~ 16 nm ~ 2 nucl.

less than for DNA (50 nm)!

→ softening effect of non-histone binding (and bending) proteins as HMG ?



Bajpai et al
PLoS comp. biology 2017

Conclusion

Experimental data

↓

coarse-grained model

↓

fit

↓

underling structural features

Ref:

Polymer coil–globule phase transition is a universal folding principle of Drosophila epigenetic domains

Epigenetics & Chromatin volume 12, Article number: 28 (2019)

***Antony Lesage**, Vincent Dahirel, Jean-Marc Victor & Maria Barbi*

LPTMC | cnrs | SCIENCES SORBONNE UNIVERSITÉ

Thank you for your attention !

Fitting parameters

$\varepsilon \ (k_B T)$

K_{nm} [nm]

K_{bp} [bp]

Kuhn lengths

$\leftrightarrow$

$N = L/K_{nm} \leftrightarrow L$ [nm]

$c = K_{bp}/K_{nm}$ [bp/nm]

Bundle

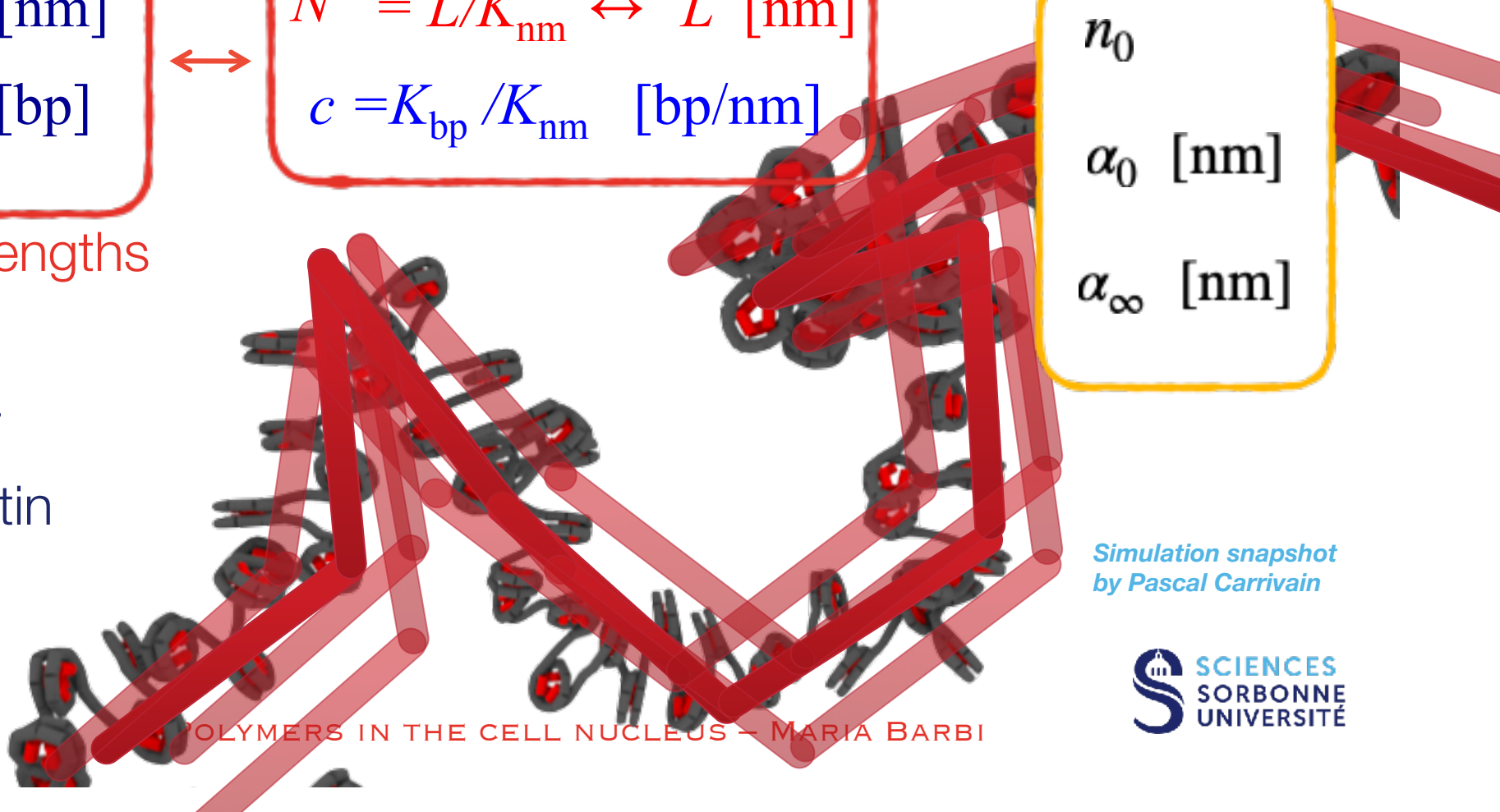
n_0

α_0 [nm]

α_∞ [nm]

Polymer

Chromatin



Simulation snapshot by Pascal Carrivain

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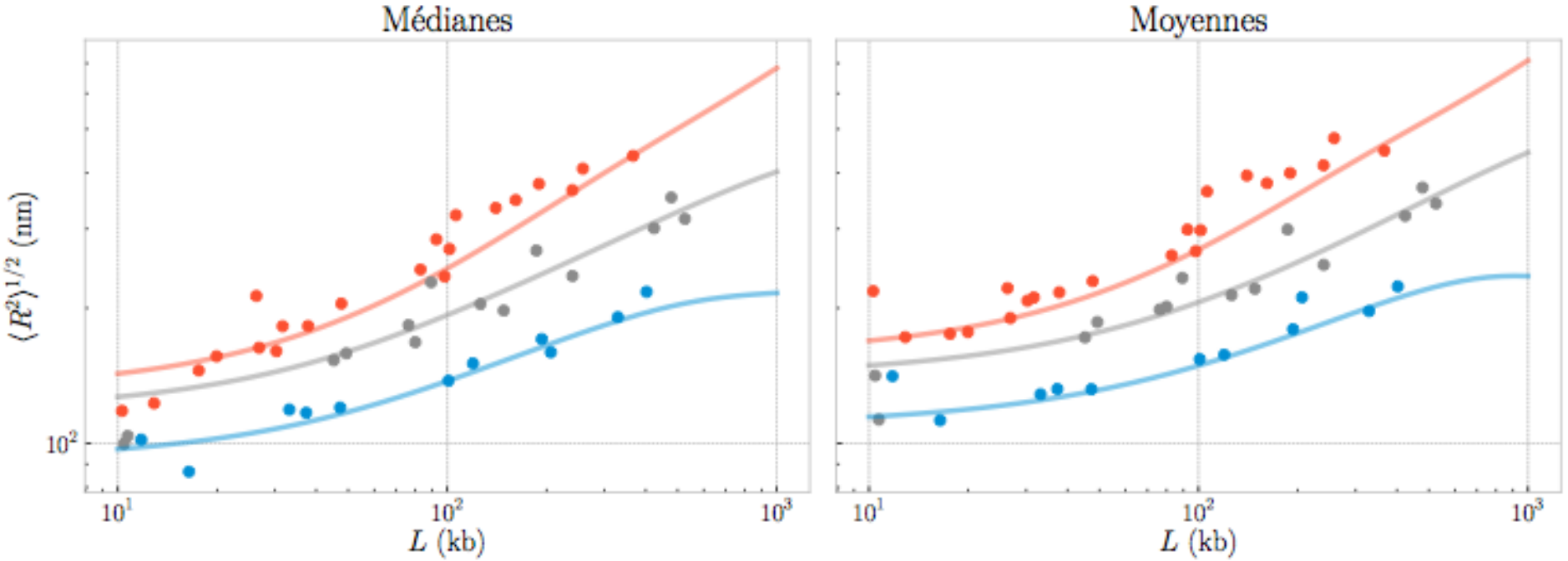
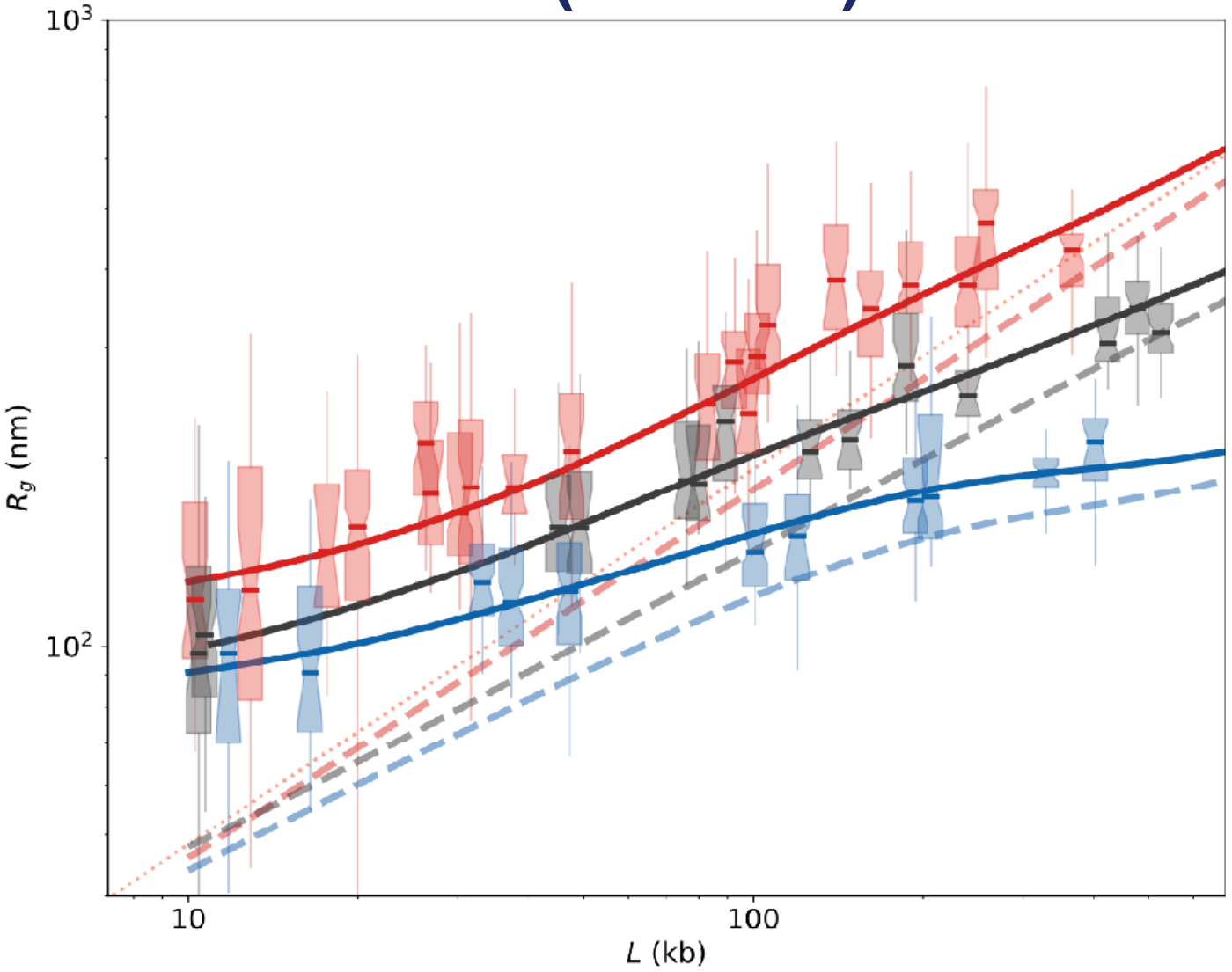

Médianes
Moyennes
$\langle R^2 \rangle^{1/2}$ (nm)
10^2
10^1
10^2
10^3
L (kb)

Final fit

(Medians)



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