Drosophila epigenetic domains at the crossover of polymer coil-globule transition

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

MULTISCALE ANALYSIS AND RECONSTRUCTION OF CHROMATIN AND NUCLEAR ORGANIZATION
PISA, 22 OCTOBER 2018 - 26 OCTOBER 2018

GDR

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Sommaire

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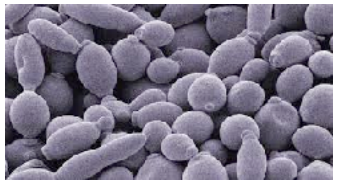
1

CONTEXT: CHROMATIN ORGANIZATION

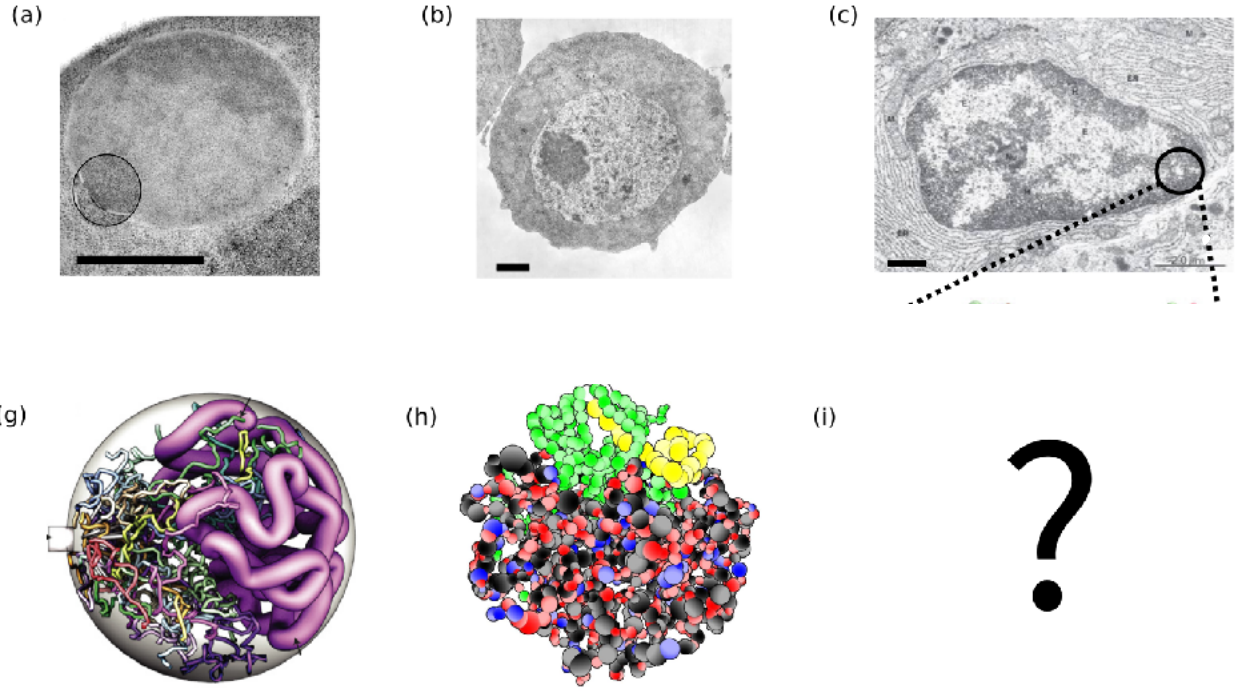
Chromatin organization



yeast

drosophila (fly)

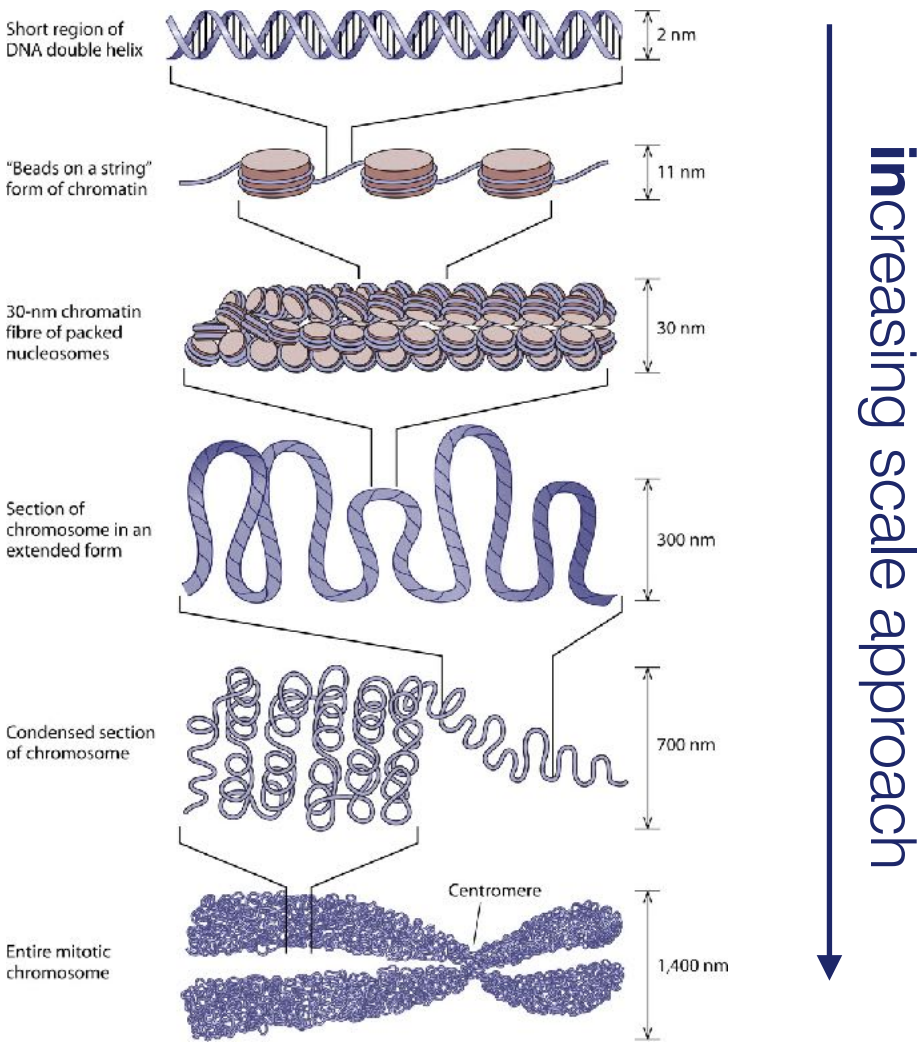
human



Cortini et al - Rev. Mod. Phys, 2016

Drosophila epigenetic marks and the polycomb complex - Maria Barbi
Drosophila epigenetic marks and the polycomb complex - Maria Barbi

Chromatin organization



Jasen A. et al., Nucleosome positioning in Saccharomyces cerevisiae, MMBR 2011

Chromatin organization

Nuclear architecture:

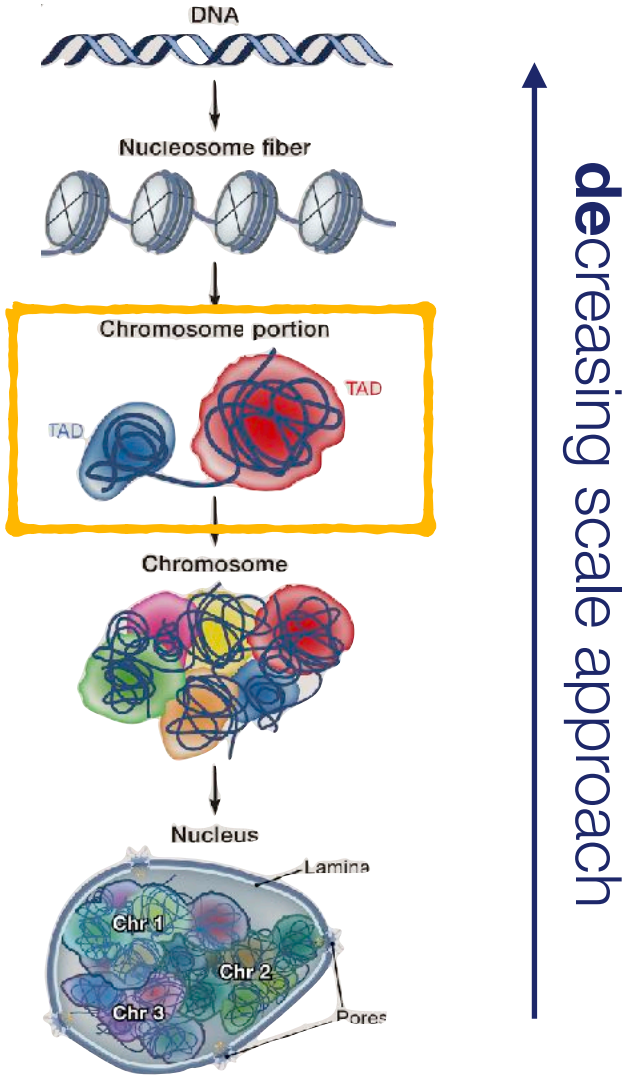
- chromosomal territories
- topologically associated domains (TADS)

⇩

- underlying chromatin (fiber) properties

⇩

- molecular scale ?



Sexton T. et al., The Role of Chromosome Domains in Shaping the Functional Genome, Cell 2015

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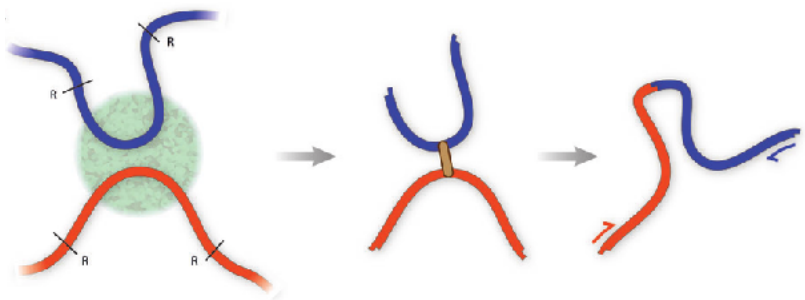
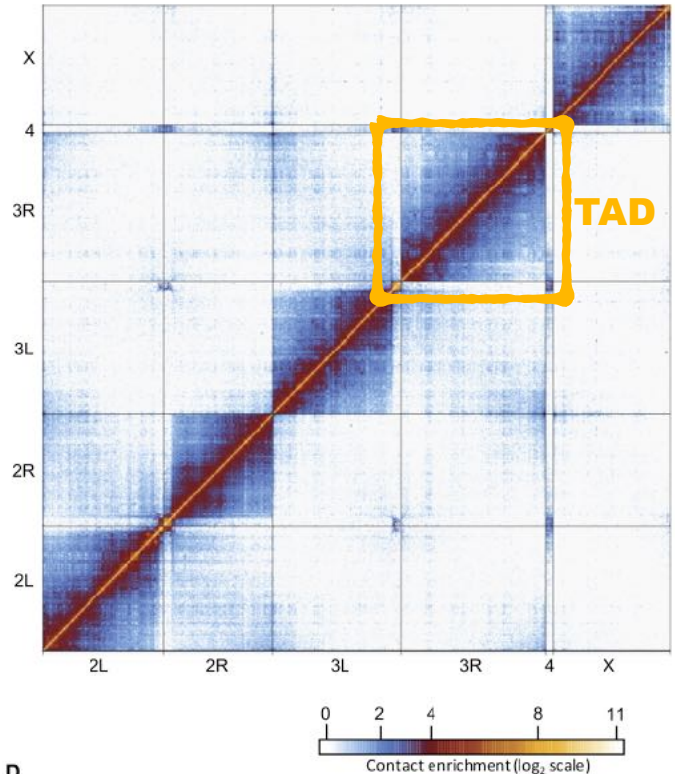
Topologically associated domains (TADs)

Chromosome conformation capture techniques (Hi-C)

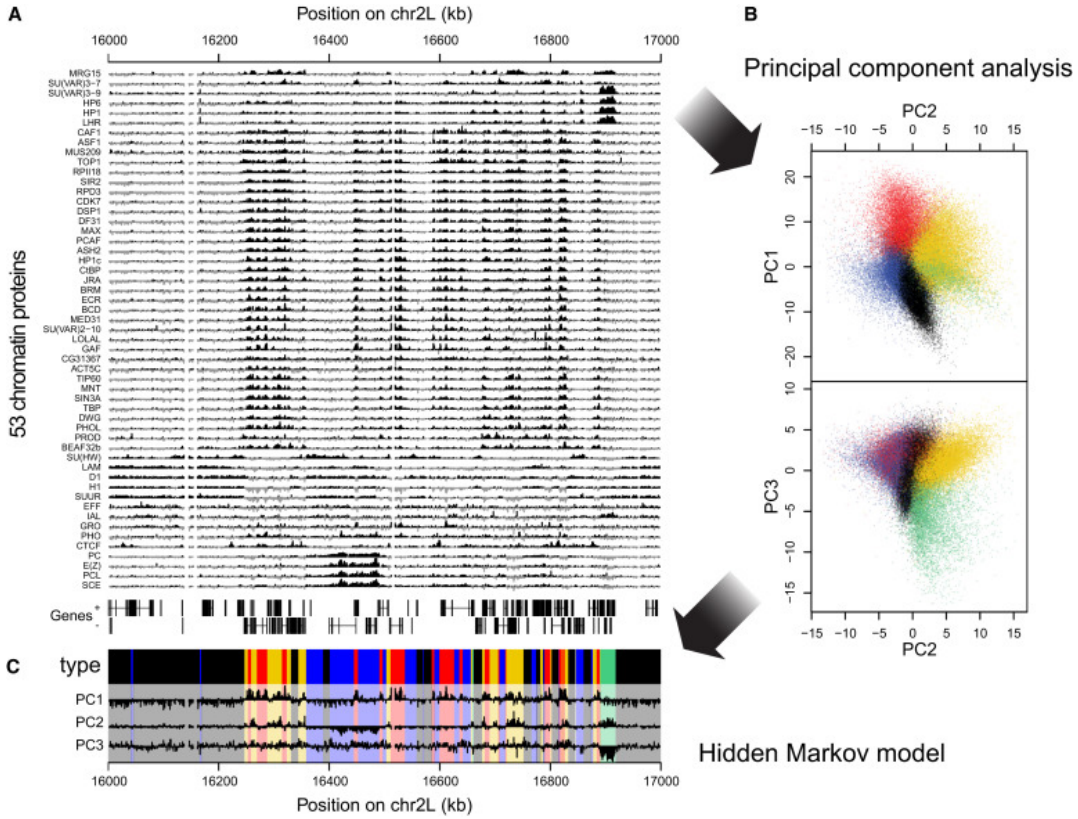


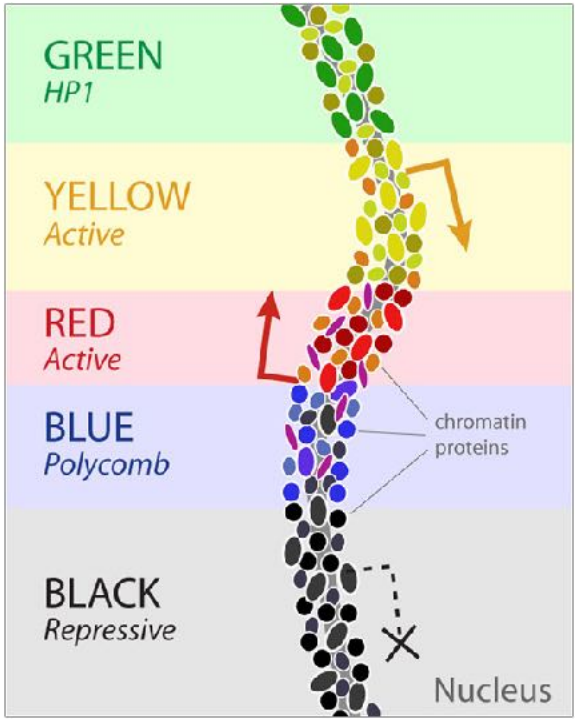
Contact map



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

Topological domains

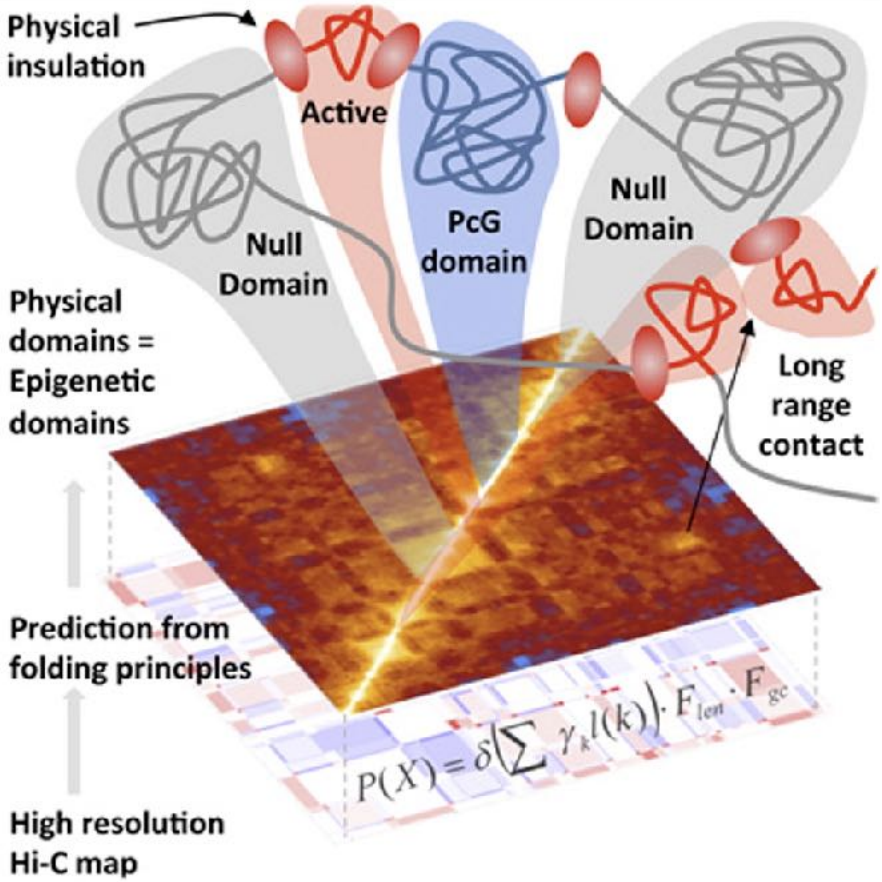




Filion et al. Systematic protein location mapping reveals five principal chromatin types in Drosophila cells, Cell, 2010

Drosophila epigenetic domains at the nanoscale - Maria Barbi
Drosophila epigenetic domains at the nanoscale - Maria Barbi

Drosophila



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

In Drosophila, epigenetic domains ≃ TADs

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2

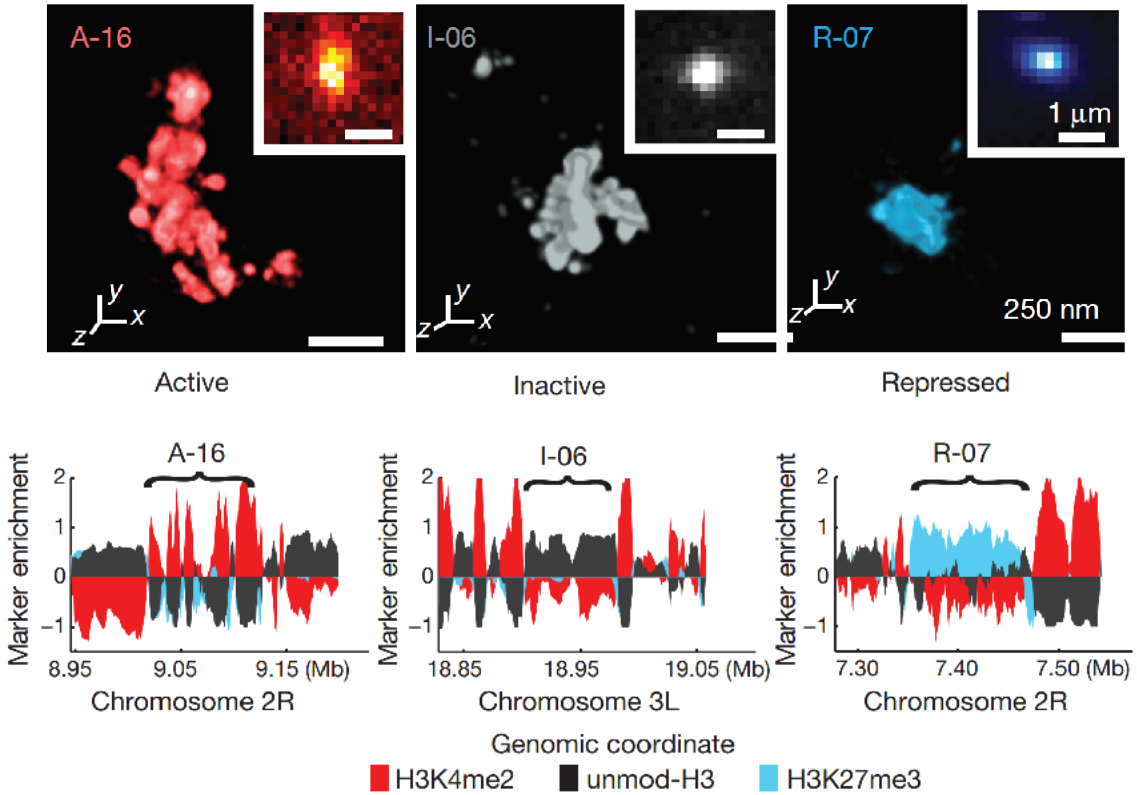
DATA: SUPER-RESOLUTION IMAGING

January 2016

418 | NATURE | VOL 529 | 21 JANUARY 2016

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]



(moving average filter with a window size of L on the marker enrichment trace)

3D imaging,
20-50-nm resolution

3 epigenetic states:

- Active
- Inactive
- Repressed

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What to measure?

mass (fluorescence) distribution :

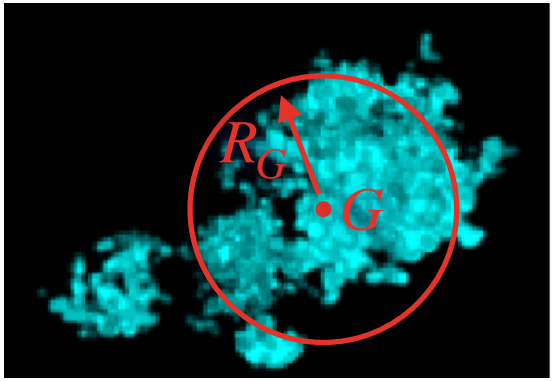
$$1 = \int \Delta(\mathbf{r}) d^3 r$$

mass (fluorescence) barycenter :

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

mass (fluorescence) variance :

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



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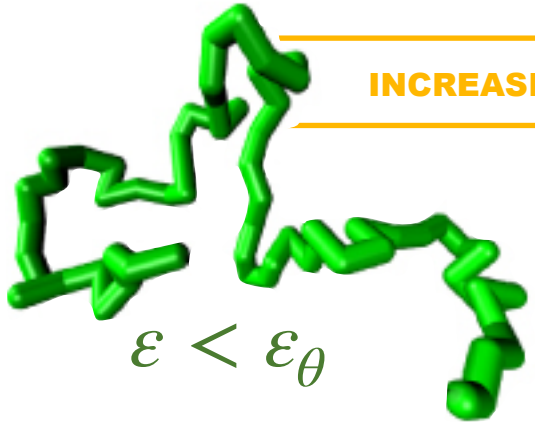
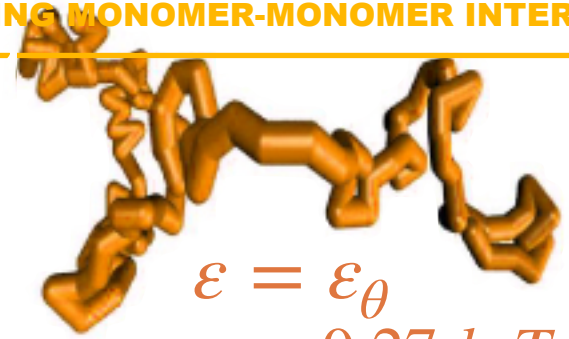
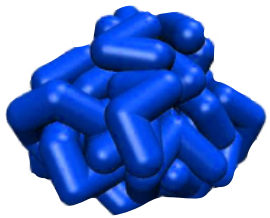
What to compare with?

Polymer model:



INCREASING MONOMER-MONOMER INTERACTION ε





$\varepsilon < \varepsilon_\theta$

Self-Avoiding Walk (SAW) coil

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

$\varepsilon = \varepsilon_\theta$

$\simeq 0.27\ k_B T$

Random Walk (RW) coil

$R_G \propto N^{1/2}$

$\varepsilon > \varepsilon_\theta$

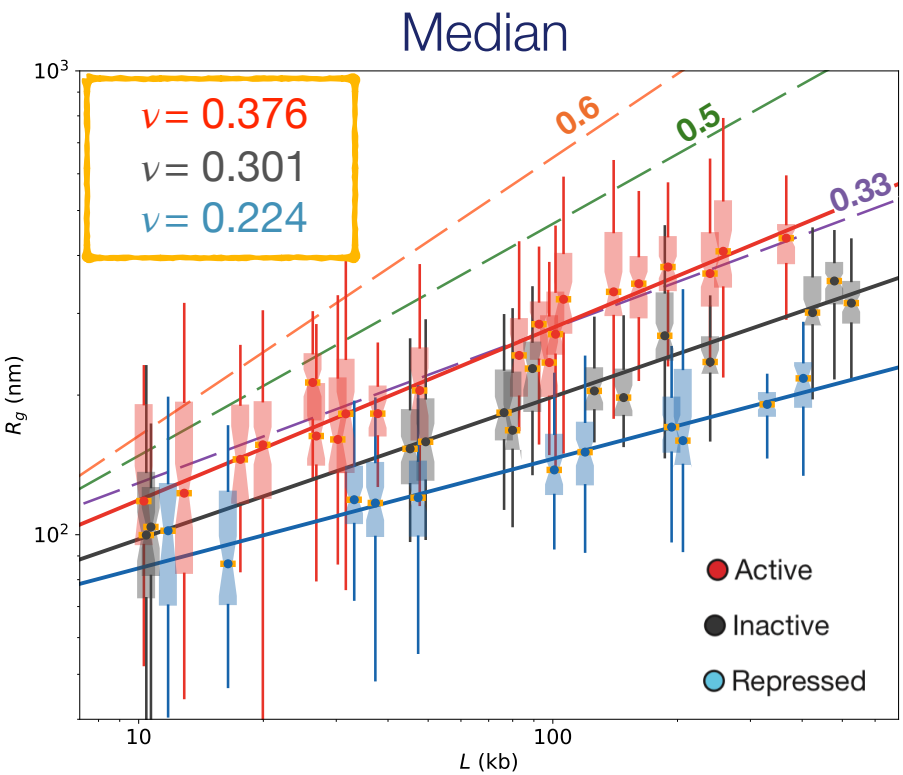
Equilibrium globule (or fractal globule)

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

$R_G \propto N^{\nu}$ scaling law

Drosophila epigenetic reprogramming of polymer coil-globule transition - Maria Barbi

First results



SAW coil $\nu = 3/5$

RW Coil $\nu = 1/2$

Globule $\nu = 1/3$

DATA FROM:

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

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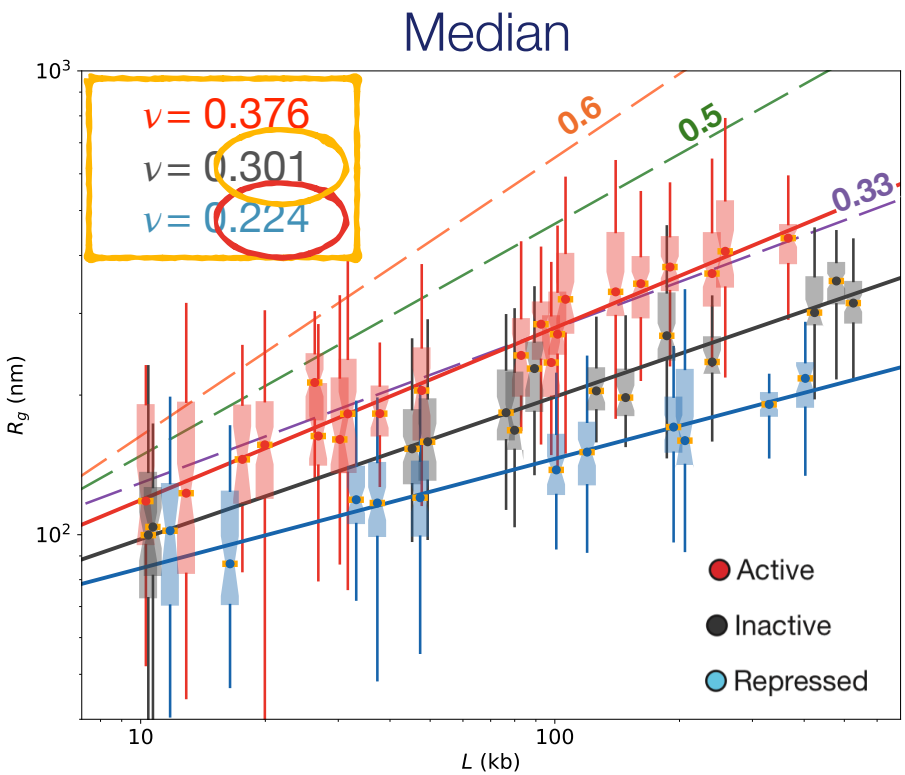
How to interpret these results?



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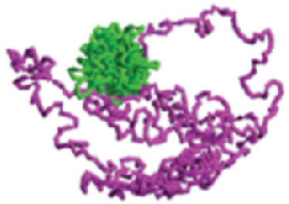
RW Coil $\nu = 1/2$

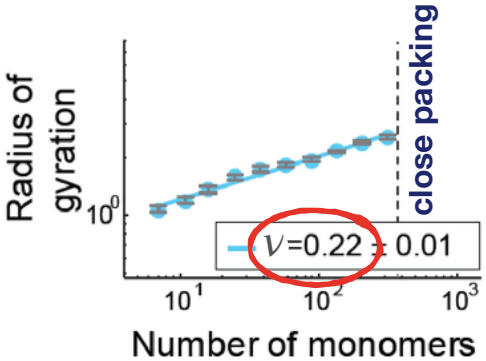
Globule $\nu = 1/3$

Computational modeling:

(Boettiger et al)

- Inactive: fractal globule → $\nu = 0.33$
- Repressed: simulation of a «sticky» polymer embedded in a «non-sticky» one + confined volume





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

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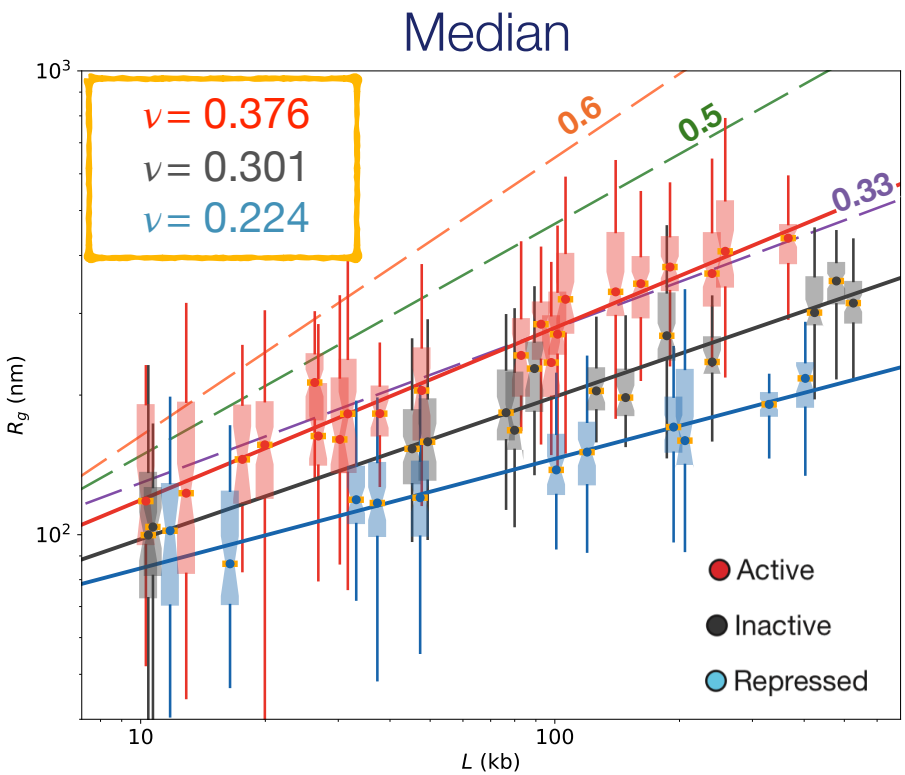
Limitations



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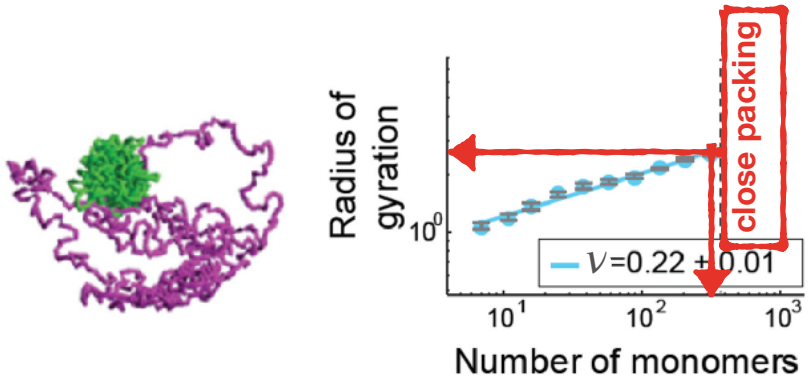

N ~ 300 monom ⟷ R_G ~ 3 (adim.)

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

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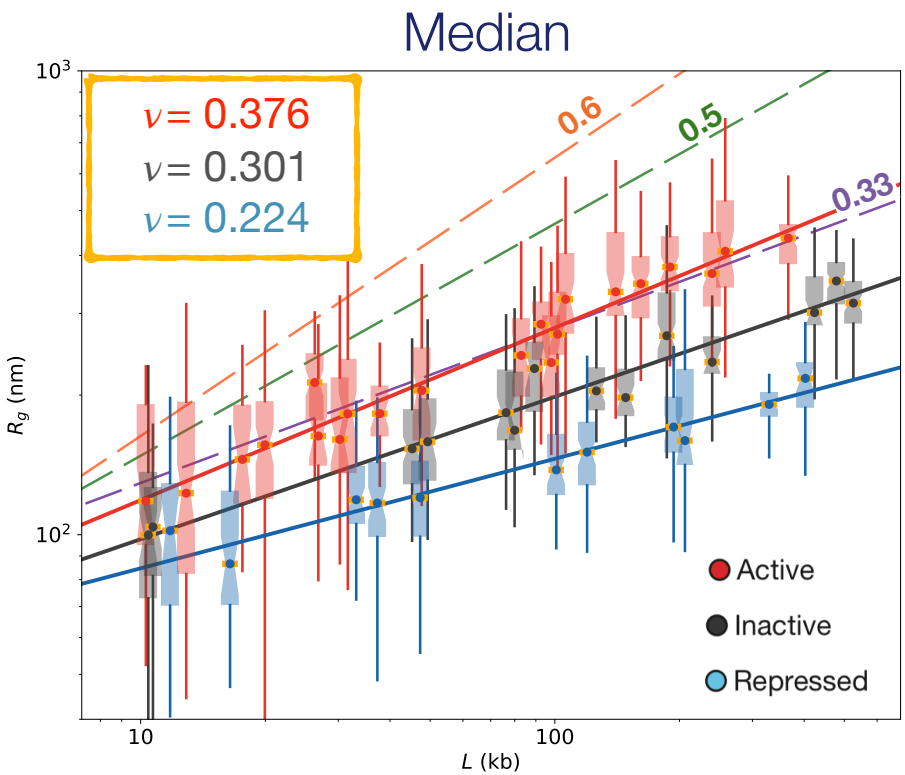
Limitations



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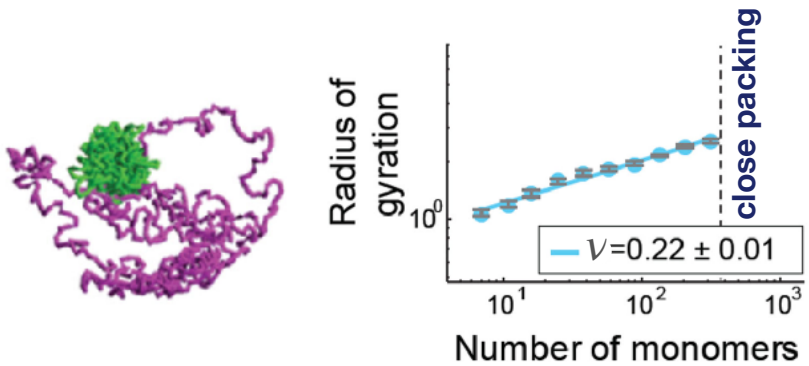

interaction energy ε = 3.5 k_BT >> ε_Θ

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

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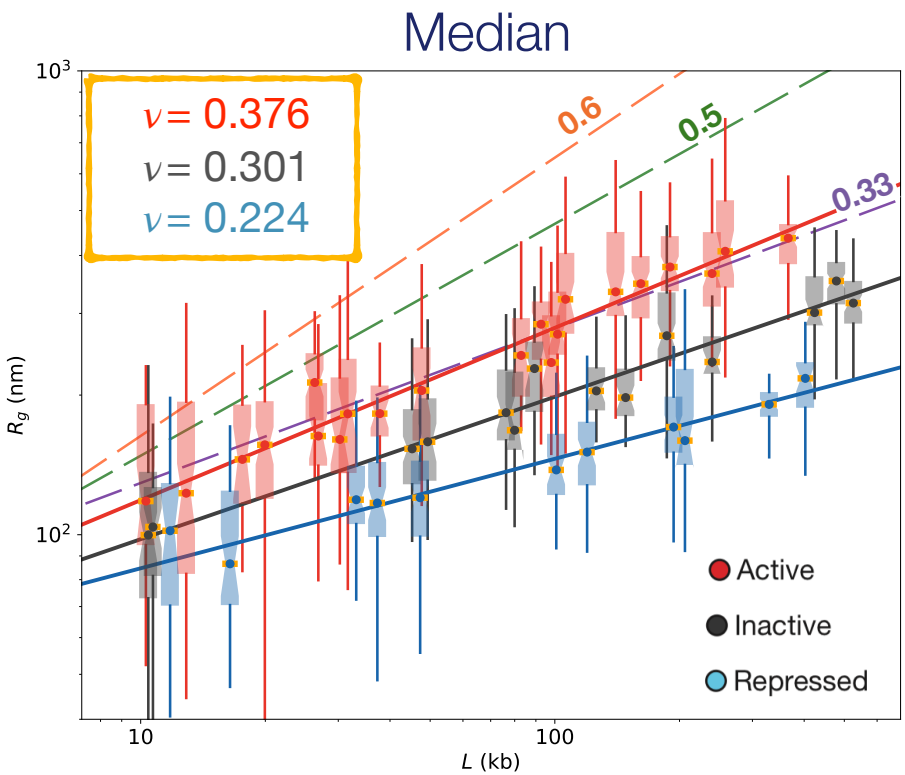
Limitations



SAW coil $\nu = 3/5$

RW Coil $\nu = 1/2$

Globule $\nu = 1/3$

Computational modeling:
(Boettiger et al)

- Inactive: fractal globule → $\nu = 0.33$
- Repressed: simulation of a «sticky» polymer embedded in a «non-sticky» one + confined volume
- Active?

  (if already $\varepsilon = 0$ for inactive?)

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

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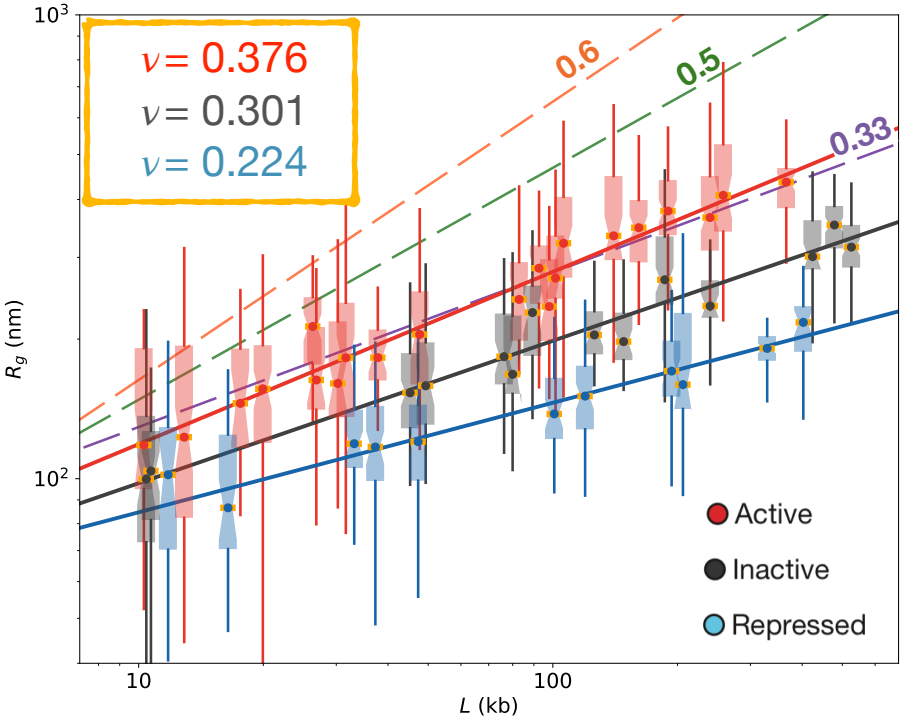
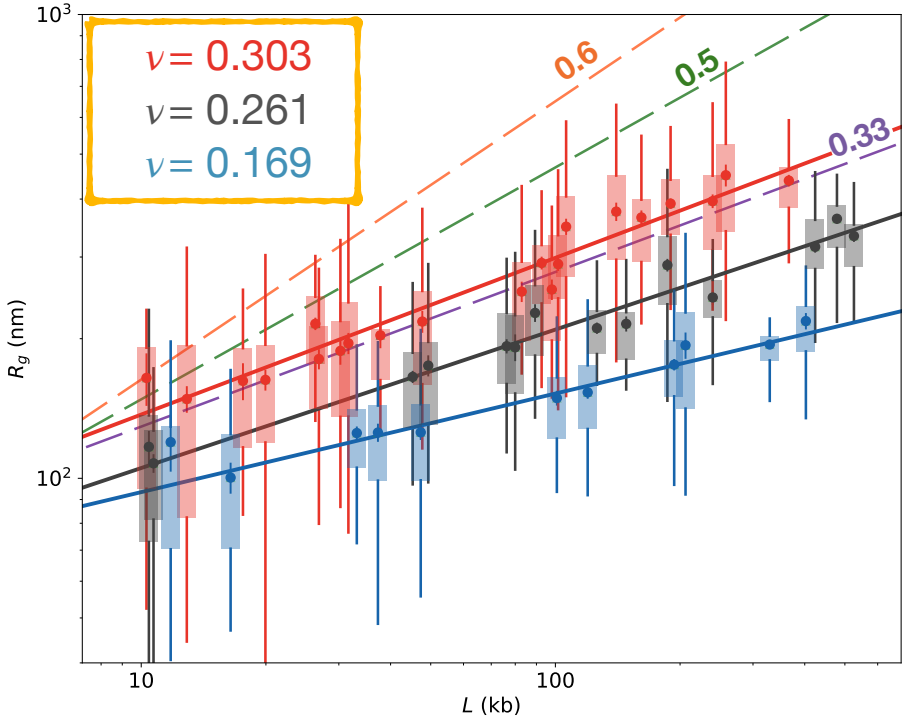
Limitations

Median → Mean





SAW coil $\nu = 3/5$

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Globule $\nu = 1/3$

Why a different scaling ?

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

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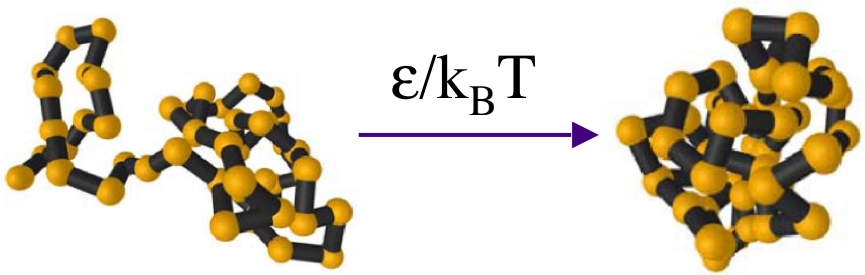
3

AN INTERPRETATION FRAMEWORK

Element #1: finite-scale effects

A polymer with N identical monomers:



coil-globule transition

depending on the ratio between :

ε interaction energy per monomer

k_BT thermal energy

(K Kuhn length = segment length)

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Element #1: finite-scale effects

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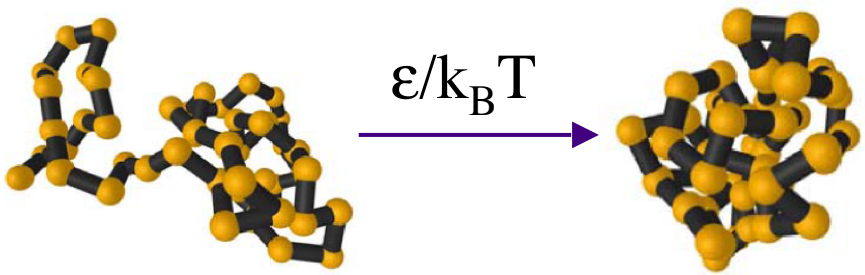

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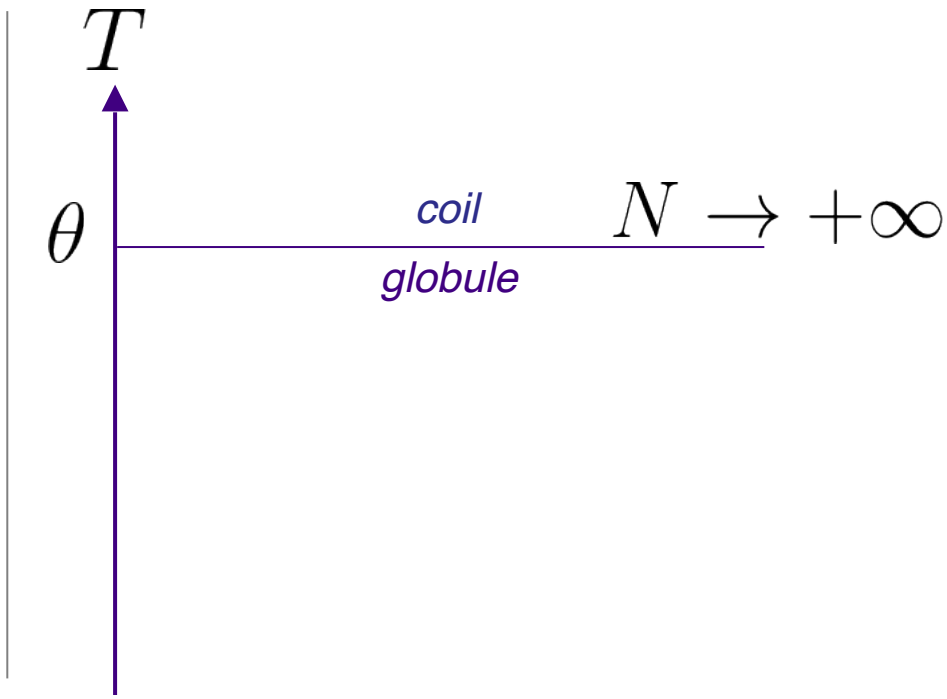

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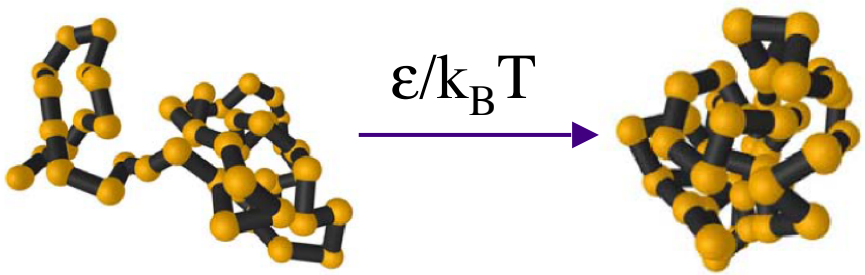

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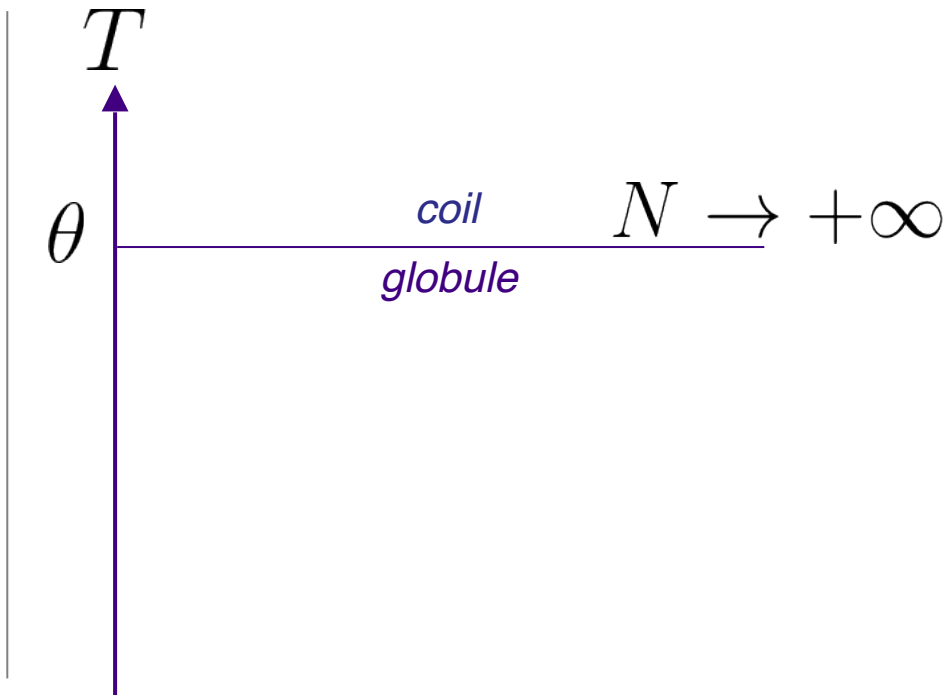

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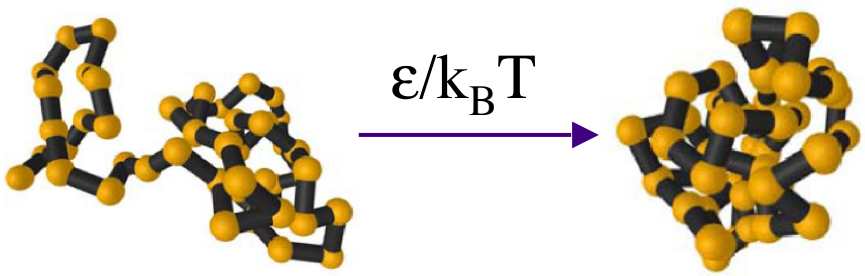

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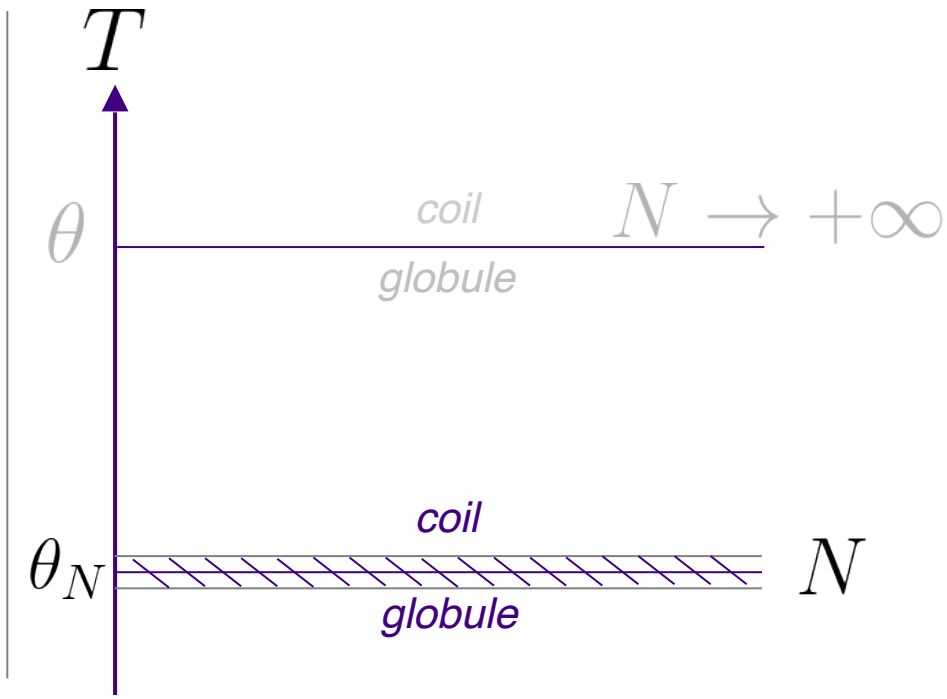

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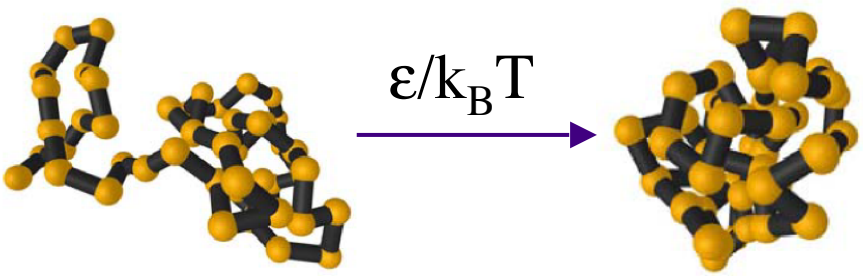
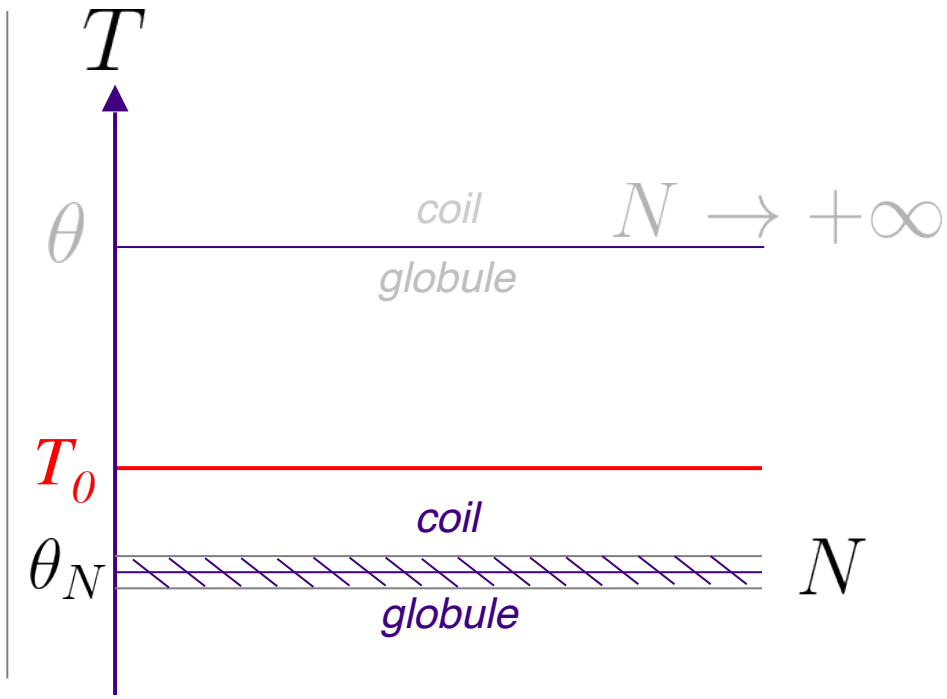


coil-globule transition



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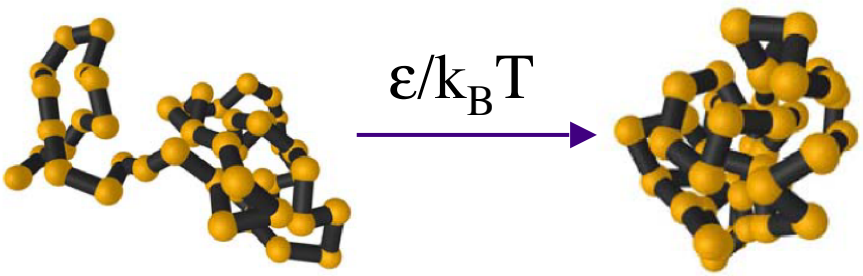

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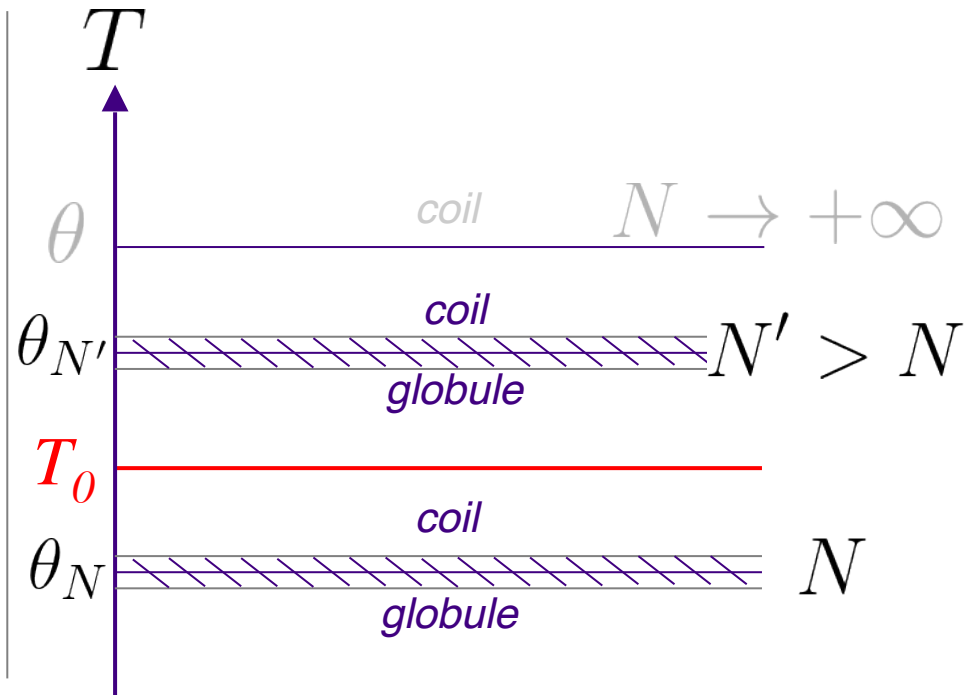


depending on the ratio between :

ε interaction energy per monomer

k_BT thermal energy

(K Kuhn length = segment length)

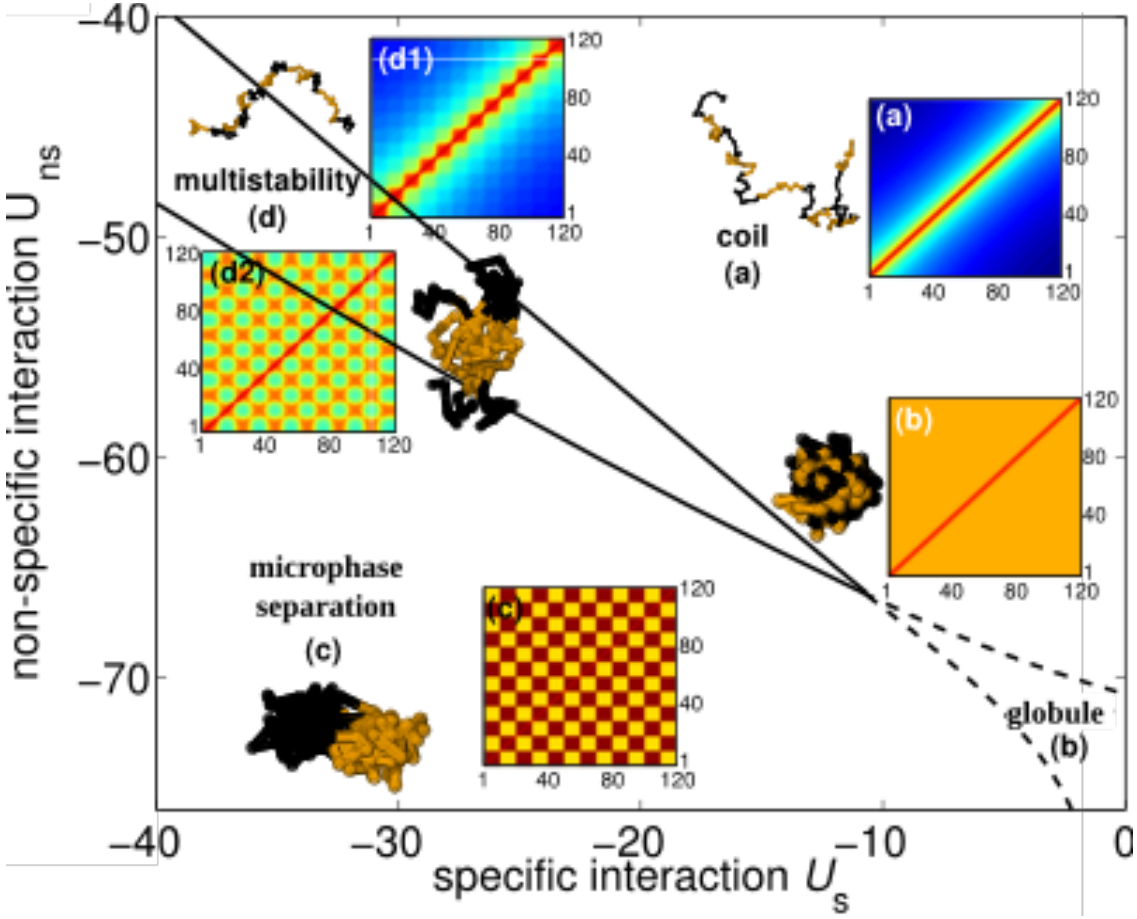
- Small polymers are coil
- Big polymers are globule

Element #1: finite-scale effects

Nucleic Acids Research Advance Access published August 4, 2014

Modeling epigenome folding: formation and dynamics of topologically associated chromatin domains

Daniel Jost[1]. Pascal Carrivain[2]. Giacomo Cavalli[2,*] and Cédric Vaillant[1,*]



block
co-polymer

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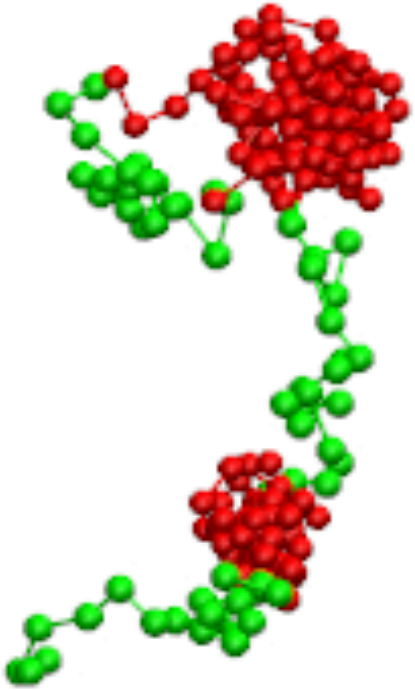
Element #1: finite-scale effects

AIMS Biophysics, 2015, 2(4): 517-530. doi: 10.3934/biophy.2015.4.517

Chromatin epigenomic domain folding: size matters

Bertrand R. Caré[1,2,3], Pierre-Emmanuel Emeriau[1,2,3], Ruggero Cortini[1,2,3], Jean-Marc Victor[1,2,3],



block
co-polymer

20 / 55 ; intra-color interaction

$$U = \begin{cases} -\varepsilon\left[1 - e^{-a(r-r_0)2}\right] & if \quad 0 \le r \le r_{\max} \\ 0 & if \quad r > r_{\max} \end{cases}$$

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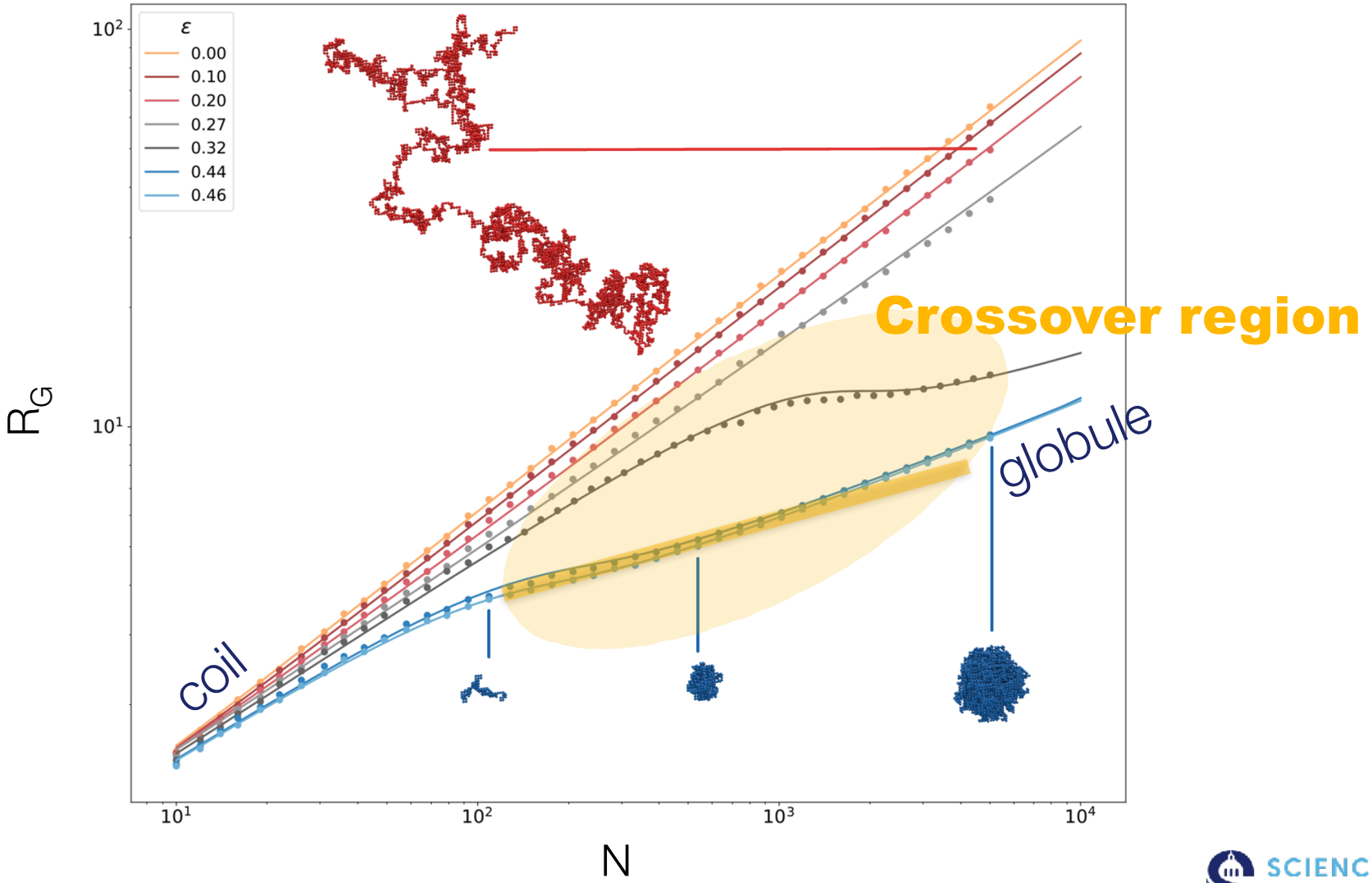
Why interesting?

Crossover : scaling law rupture



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Why interesting?

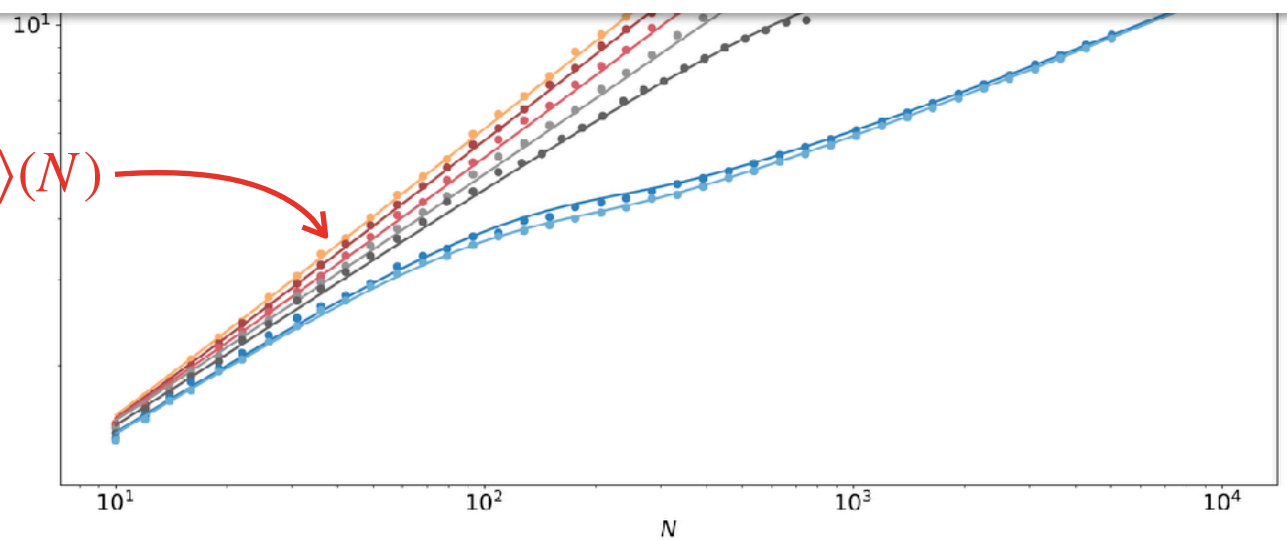
Theoretical modeling available

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

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

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

$\Rightarrow \langle R_G^2 \rangle (N)$



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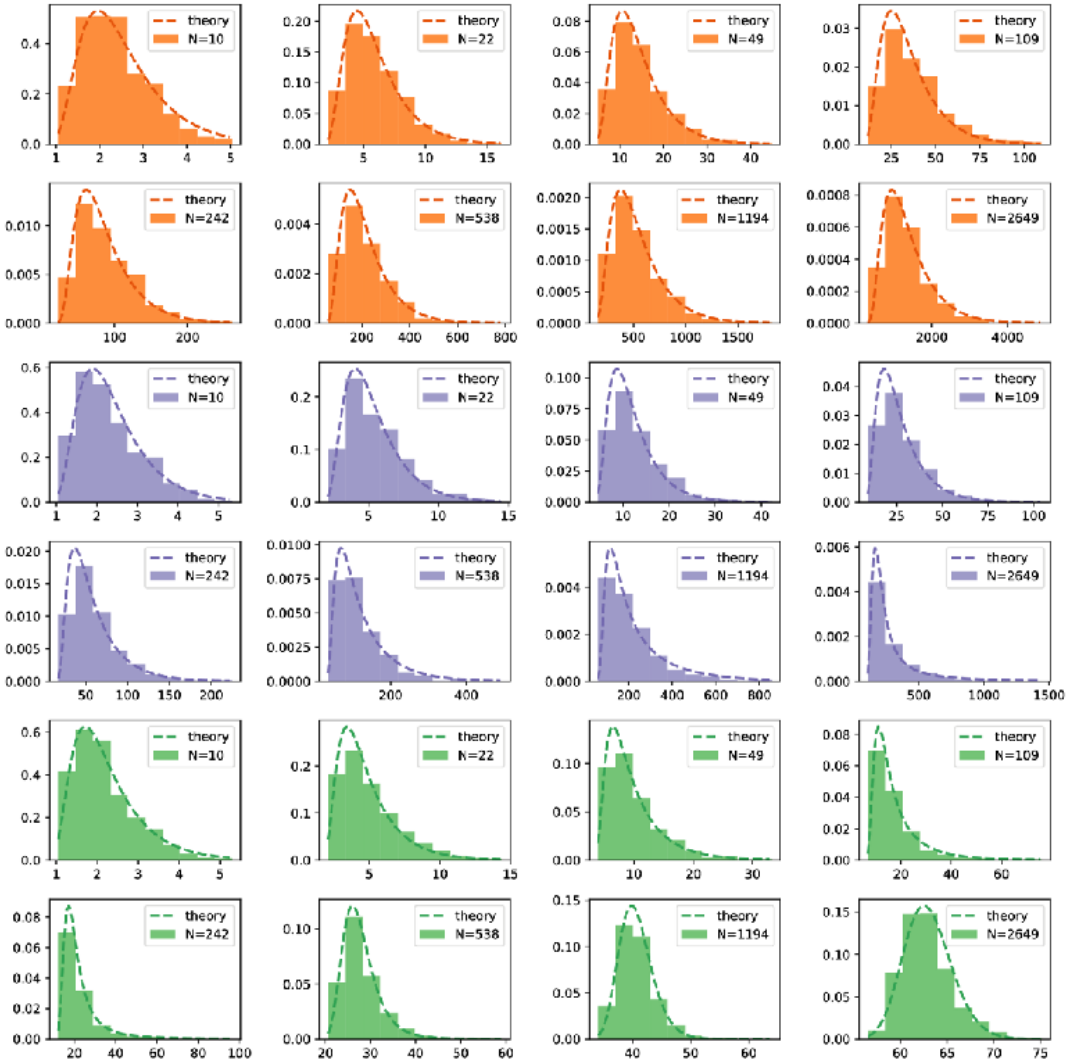
Why interesting?

Theory → fitting the R_G distribution



$\varepsilon = 0.20\, k_B T < \varepsilon_\theta$

$\varepsilon = 0.31\, k_B T \sim \varepsilon_\theta$

$\varepsilon = 0.44\, k_B T > \varepsilon_\theta$

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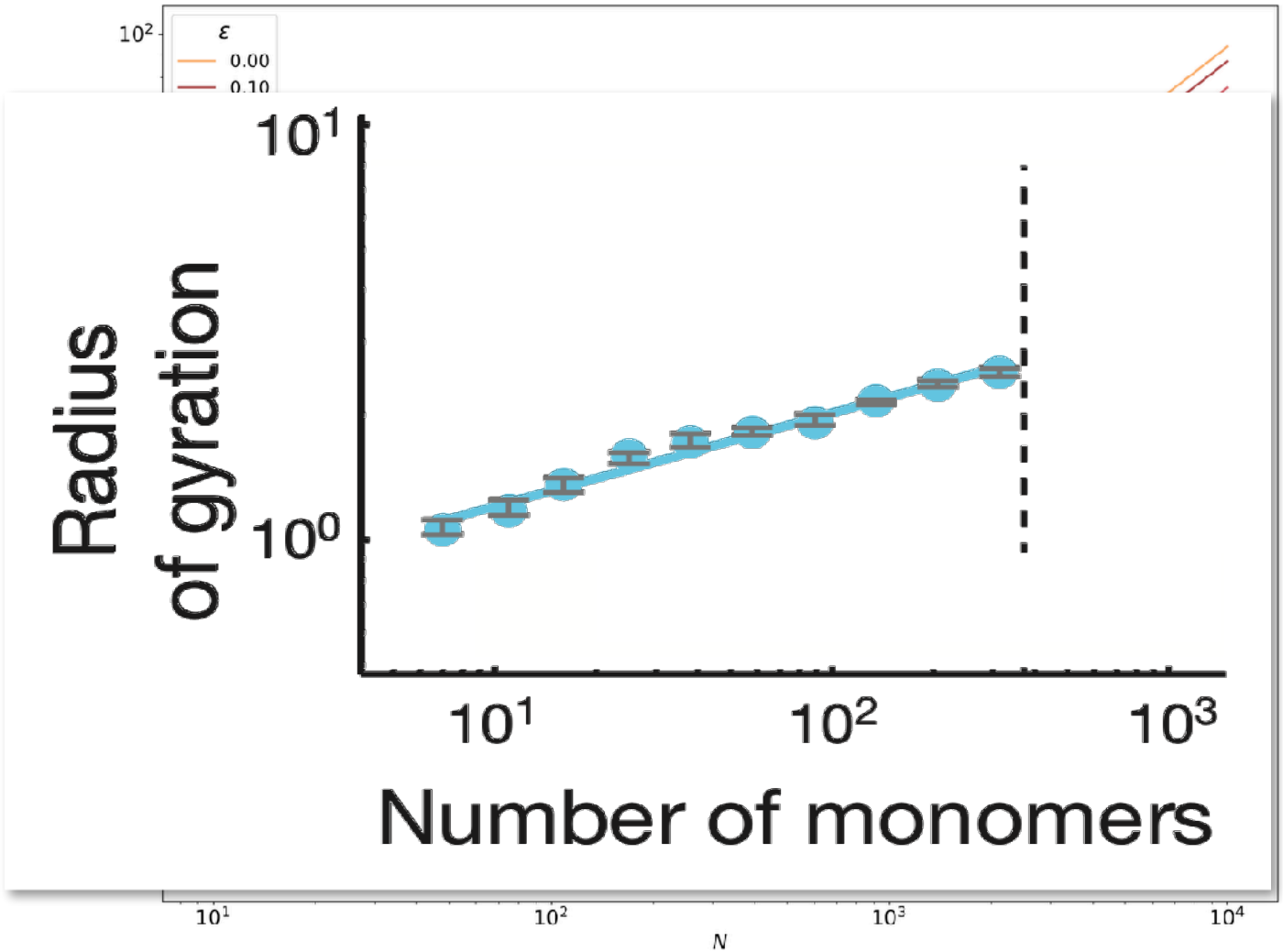
Finite-size modeling results

Compare with previous simulations



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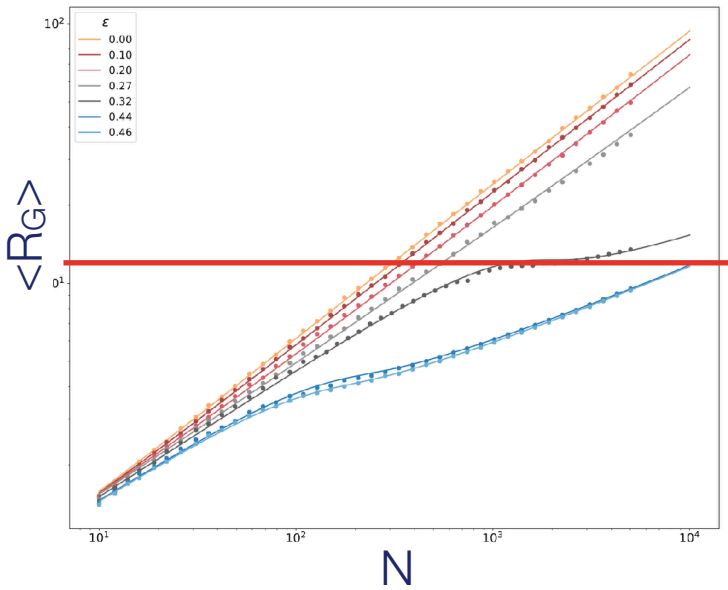
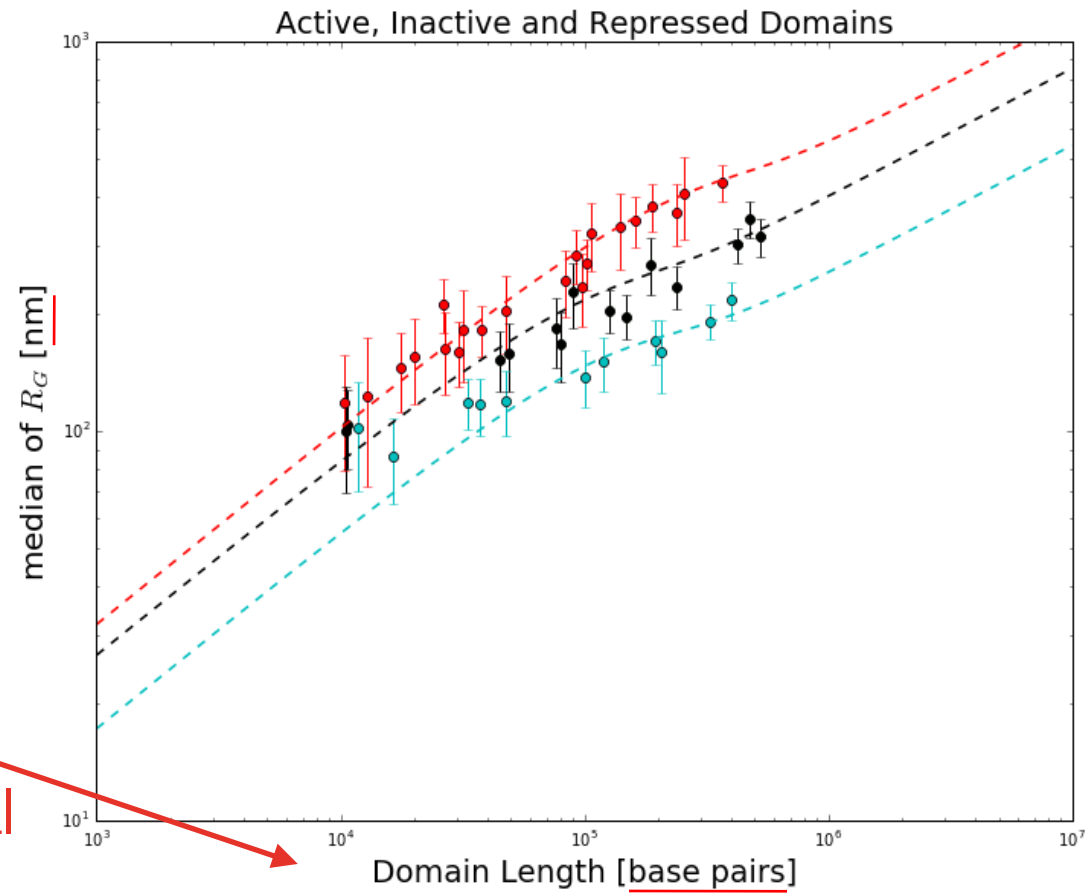
Finite-size modeling results - 1

Compare with data





Adimensional → dimensional
(to be discussed)

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

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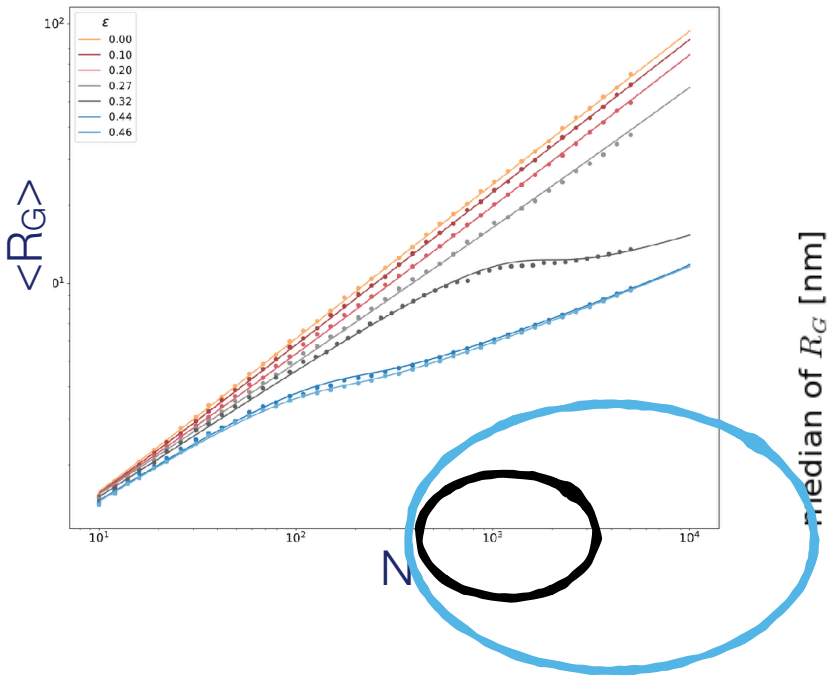
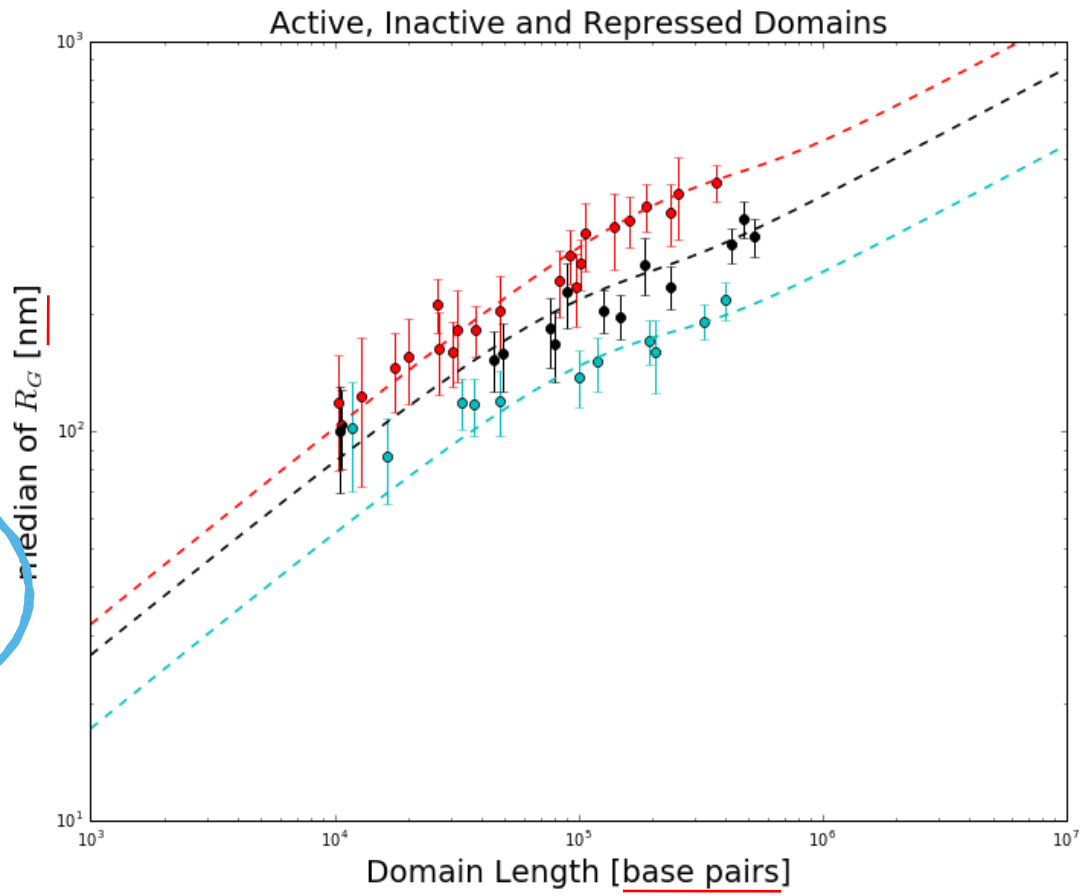
Finite-size modeling results - 1

Compare with data





DATA FROM:

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

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4

A FURTHER IMPROVEMENT

Kc167 cell line is tetraploid

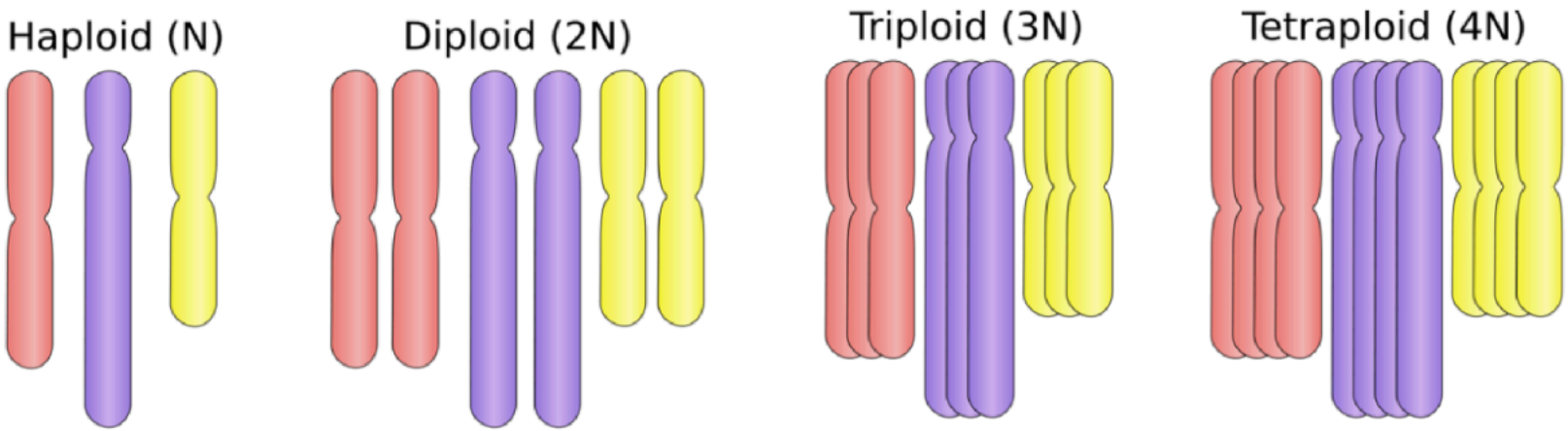
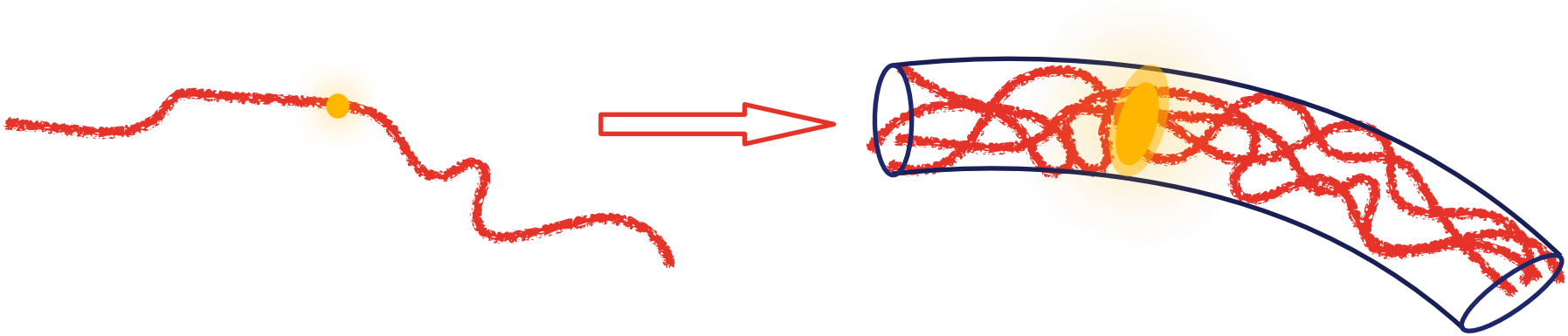


Figure 1 | Chromatin in different epigenetic states exhibits distinct packaging and power-law scaling. a, Enrichment profile of H3K4me2 (red), H3K27me3 (light blue) and unmodified H3 (black) in three genomic regions, each harbouring an example Active, Inactive or Repressed domain (indicated by brackets). Marker enrichment, as defined in Supplementary Methods, was determined from ChIP-seq data[20]. **b**, 3D-STORM images of the three distinct epigenetic domains in **a**, labelled by *in situ* hybridization with DNA probes conjugated to the photoswitchable dye Alexa-647, shown with their corresponding conventional images in the inset. Each epigenetic domain appears as a single region in nearly all cells due to homologous pairing in the tetraploid Kc_{167} cells. **c**, log–log plot of the median domain volume as a function of domain length for Active (red solid circles), Inactive

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

Chromosome Bundle model



Convolution: $\pi_N = p_N * p_{\text{bundle}}$

Bundle distribution: $p_{\text{bundle}}(R_G^2) = \frac{1}{\sigma_N^2} \exp(-R_G^2/\sigma_N^2)$

Bundle width: $\sigma_N^2 = \frac{a_\infty}{1 + (\frac{a_\infty}{a_0} - 1)\, e^{-N/N_0}}$

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Final fit

Fitting parameters

Polymer

$\varepsilon \quad (k_B T)$

$K_{\mathrm{bp}} \quad (\mathrm{bp})$

$K_{\mathrm{nm}} \quad (\mathrm{nm})$

Kuhn lengths

$\leftrightarrow$

$N = L/K_{\mathrm{nm}}$

$c = K_{\mathrm{bp}}/K_{\mathrm{nm}} \quad [\mathrm{bp/nm}]$

Bundle

n_0

$\alpha_0 \quad (\mathrm{nm})$

$\alpha_\infty \quad (\mathrm{nm})$

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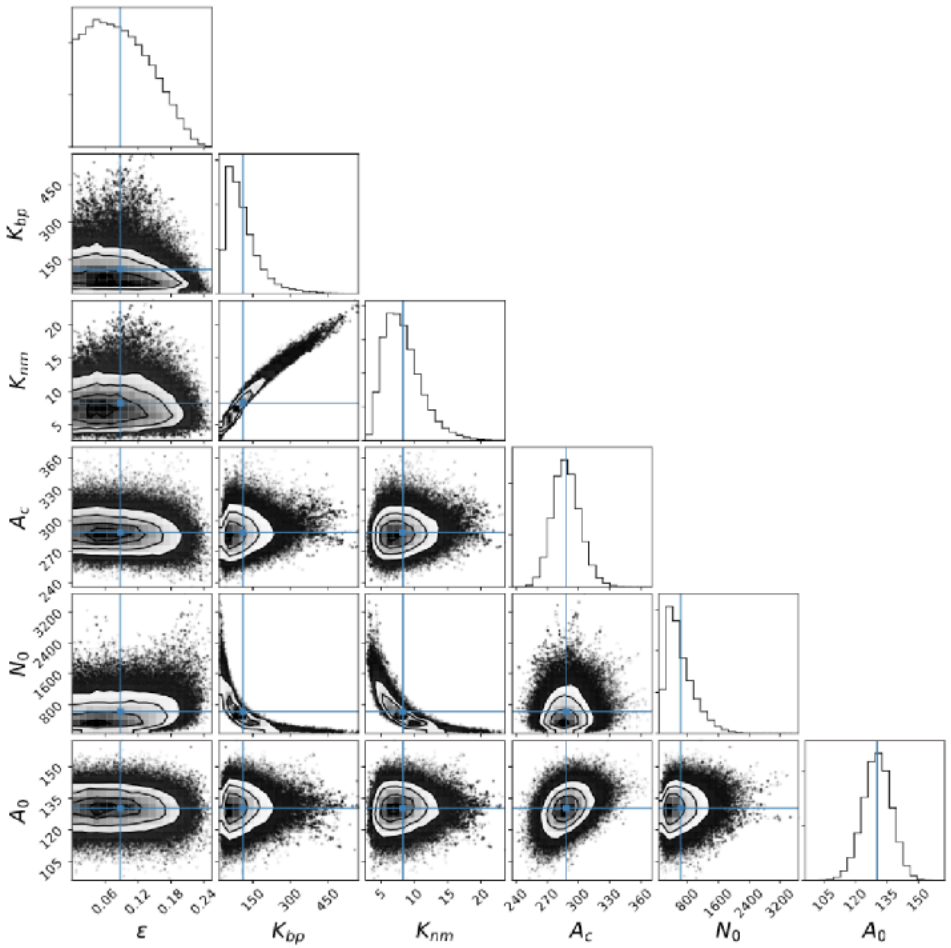
Final fit

Fitting method: Bayesian



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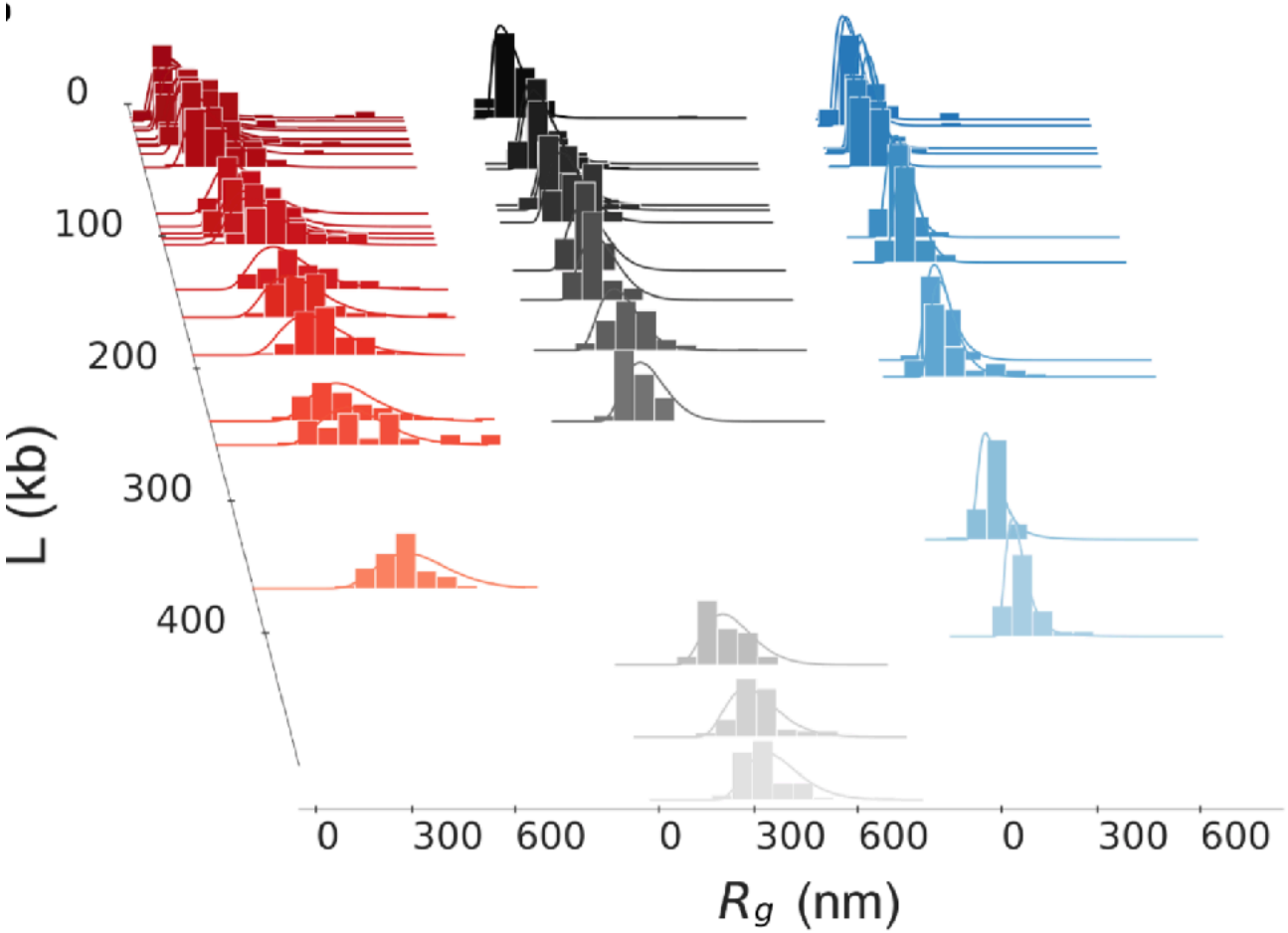
Final fit

fit of the whole dataset (histograms)



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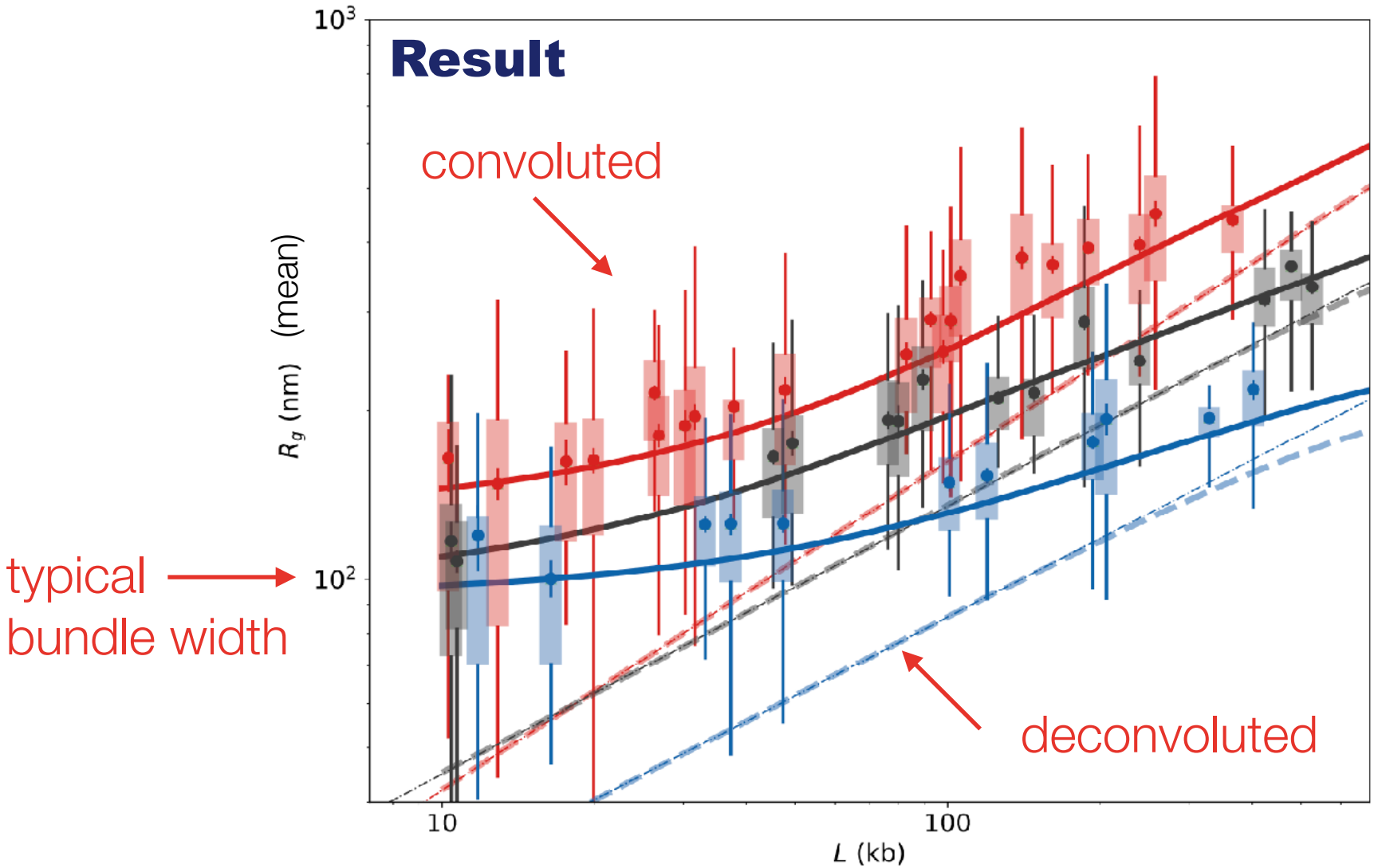
Final fit

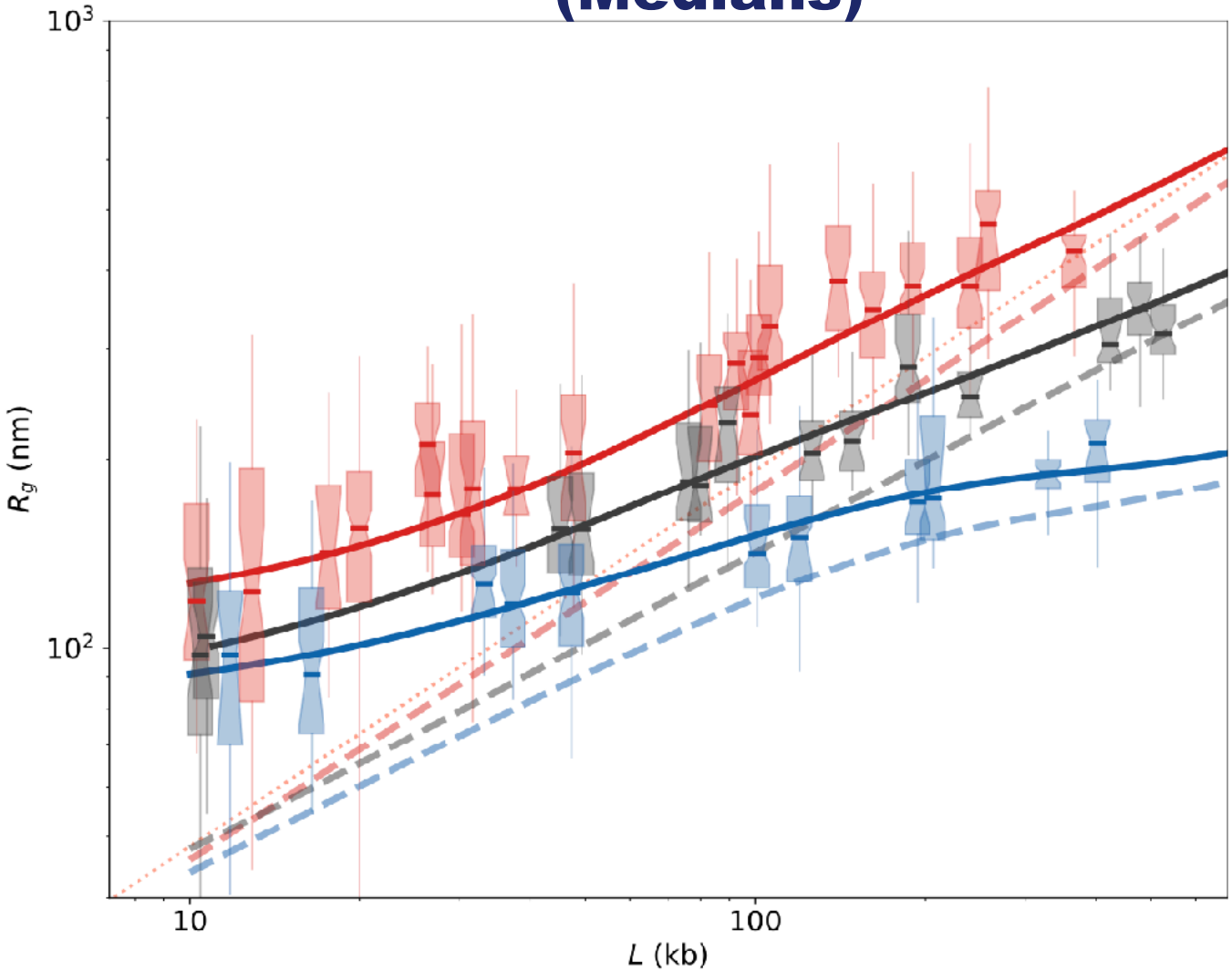


DATA FROM:

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

Final fit

(Medians)



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Final fit

Parameters

	Active	Inactive	Repressed
ε (kT)	0.09	0.32	0.44
K_{bp}	110	3900	1500
K_{nm}	8	59	36
α (bp/nm)	14	66	42
a_0 (nm)	130	93	94
a_∞ (nm)	630	170	N/A

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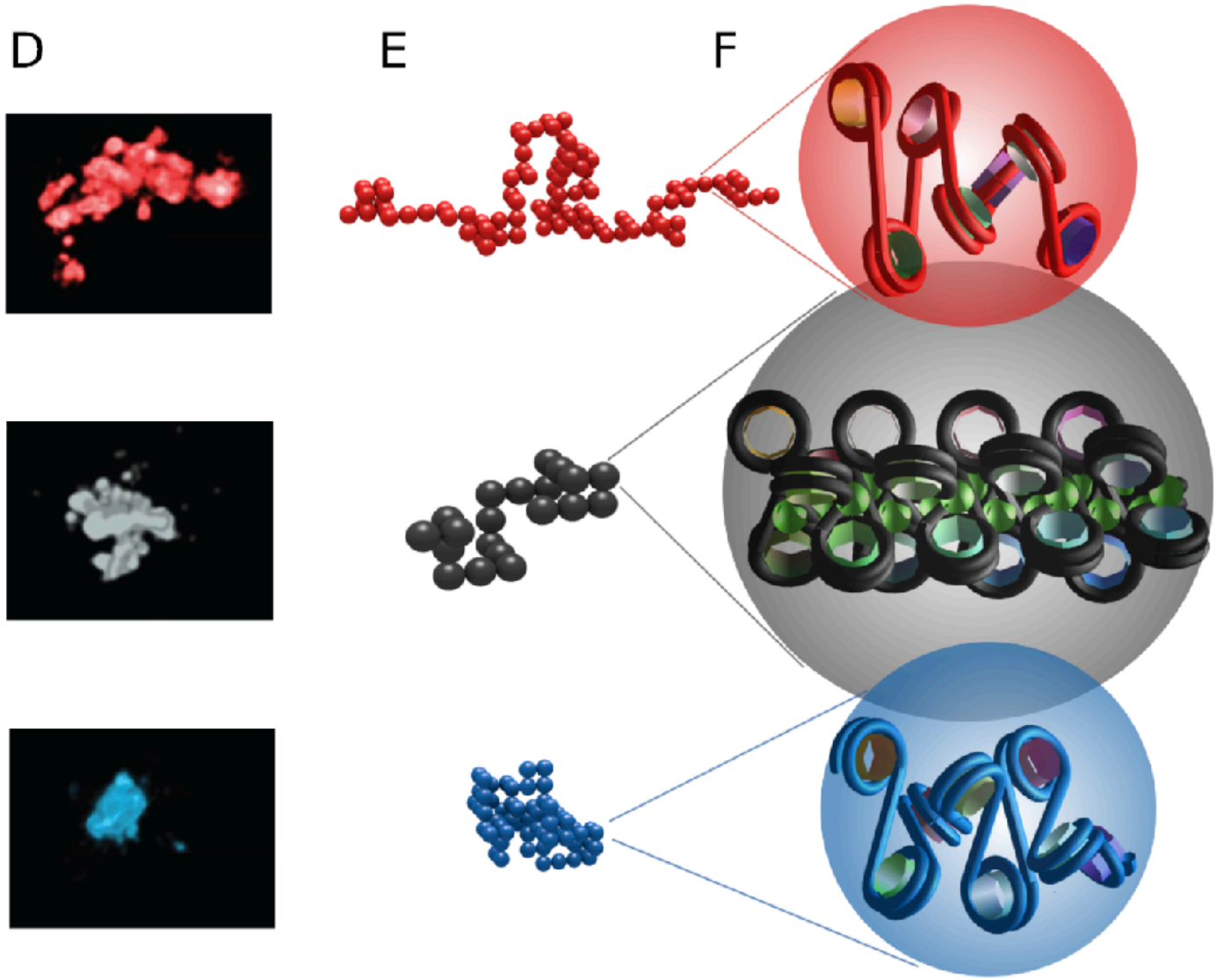
Final fit



Texte de niveau 1

Texte de niveau 2

Texte de niveau 3

- Texte de niveau 4

Pour changer le niveau d'un paragraphe et donc son style :

Avec la souris et les outils de retrait de l'onglet [Accueil] :

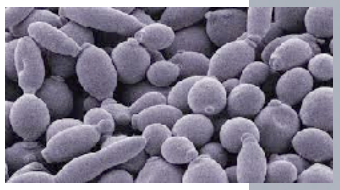
- cliquez sur l'icône **"Augmenter le retrait"** ou **"Augmenter le niveau de liste"** pour passer au niveau/style suivant ;
- cliquez sur l'icône **"Diminuer le retrait"** ou **"Diminuer le niveau de liste"** pour revenir au niveau/style précédent.

Avec le clavier

- **[Alt] [Maj] [→] (flèche droite)** pour passer au niveau/style suivant ;
- **[Alt] [Maj] [←] (flèche gauche)** pour revenir au niveau/style précédent.

Nota : les 3 premiers niveaux de texte ne possédant pas de puce, les habituelles touches [Tabulation] et [Maj] [Tabulation] ne peuvent pas être utilisées pour hiérarchiser les paragraphes.

Titre de la diapo



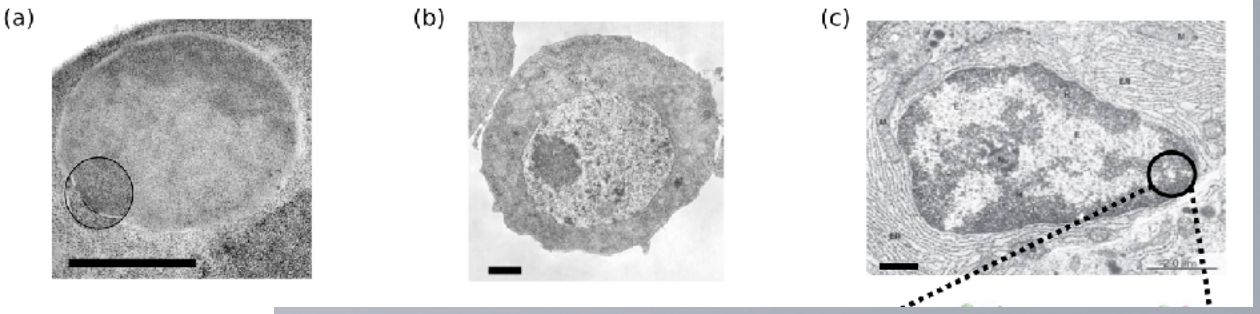
yeast

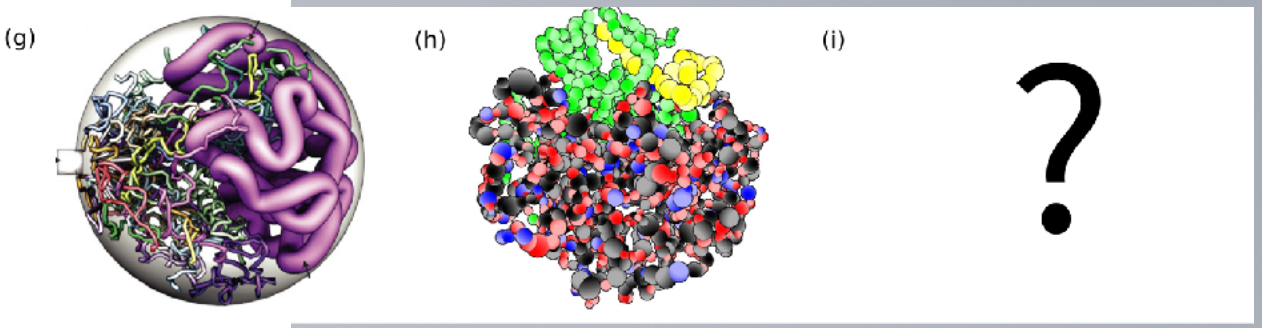
drosophila (fly)

human

Texte de nive

- Texte de niveau 2





DESCRIPTION, LÉGENDE OU SOURCE DE L'IMAGE

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