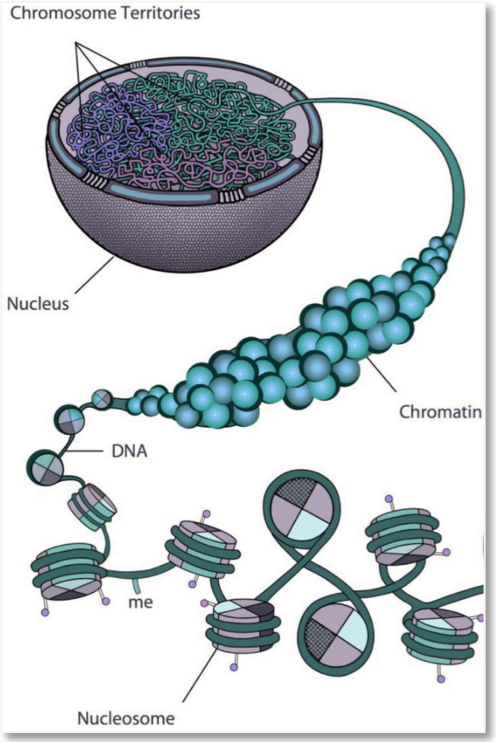
CECAM Workshop
Mesoscopic Modeling in Physics of Molecular and Cell Biology
Toulouse, october 10-13, 2016

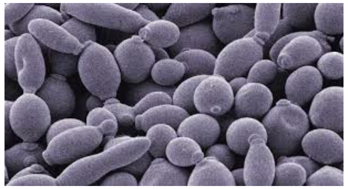
Finite-size scaling analysis of super-resolution imaging of epigenetic domains

Maria Barbi
Antony Lesage, Jean-Marc Victor

LPTMC, University Pierre & Marie Curie
and
CNRS GDR 3536 « ADN »

Chromatin organization

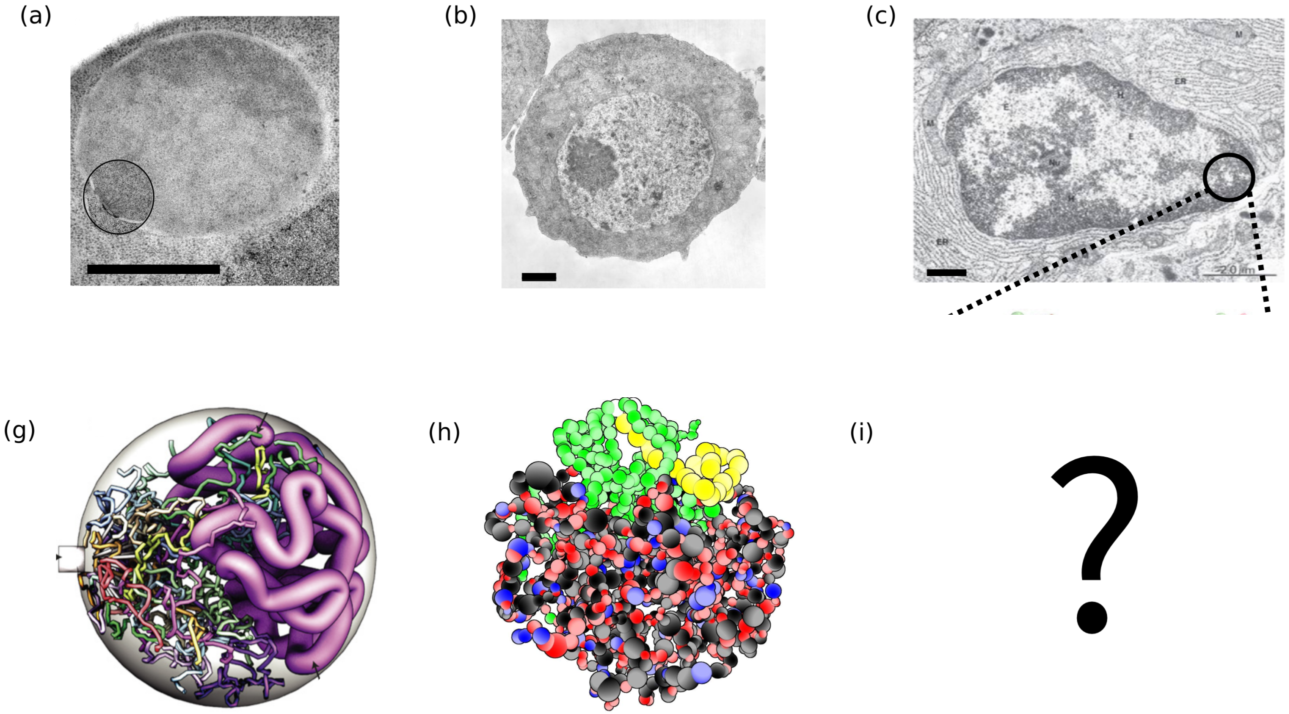




yeast

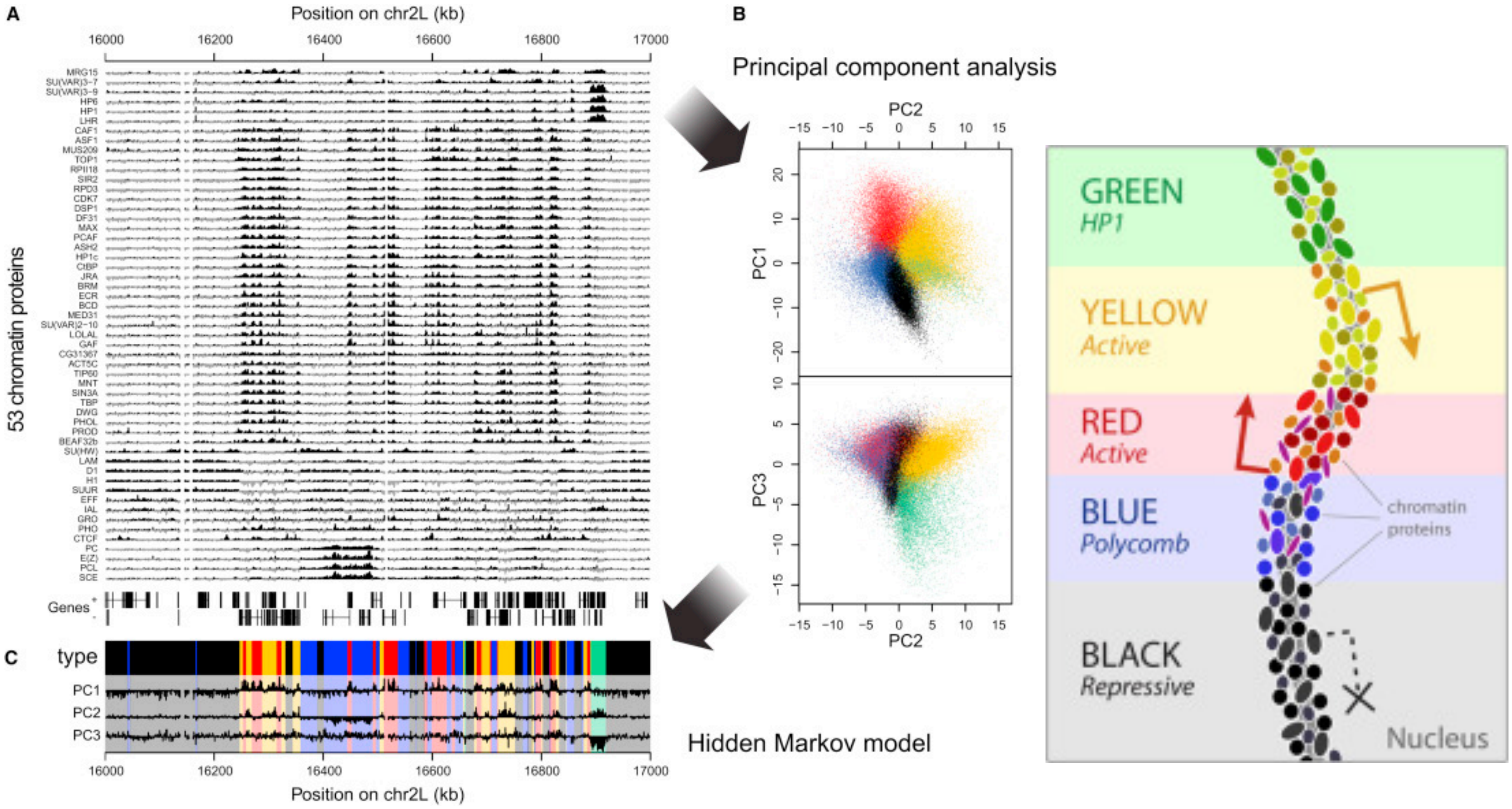
drosophila (fly)

human



Cortini et al - Rev. Mod. Phys, 2016

Epigenetic colors

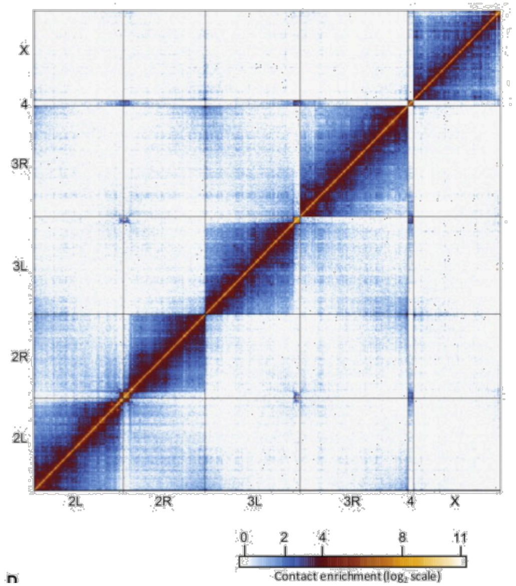


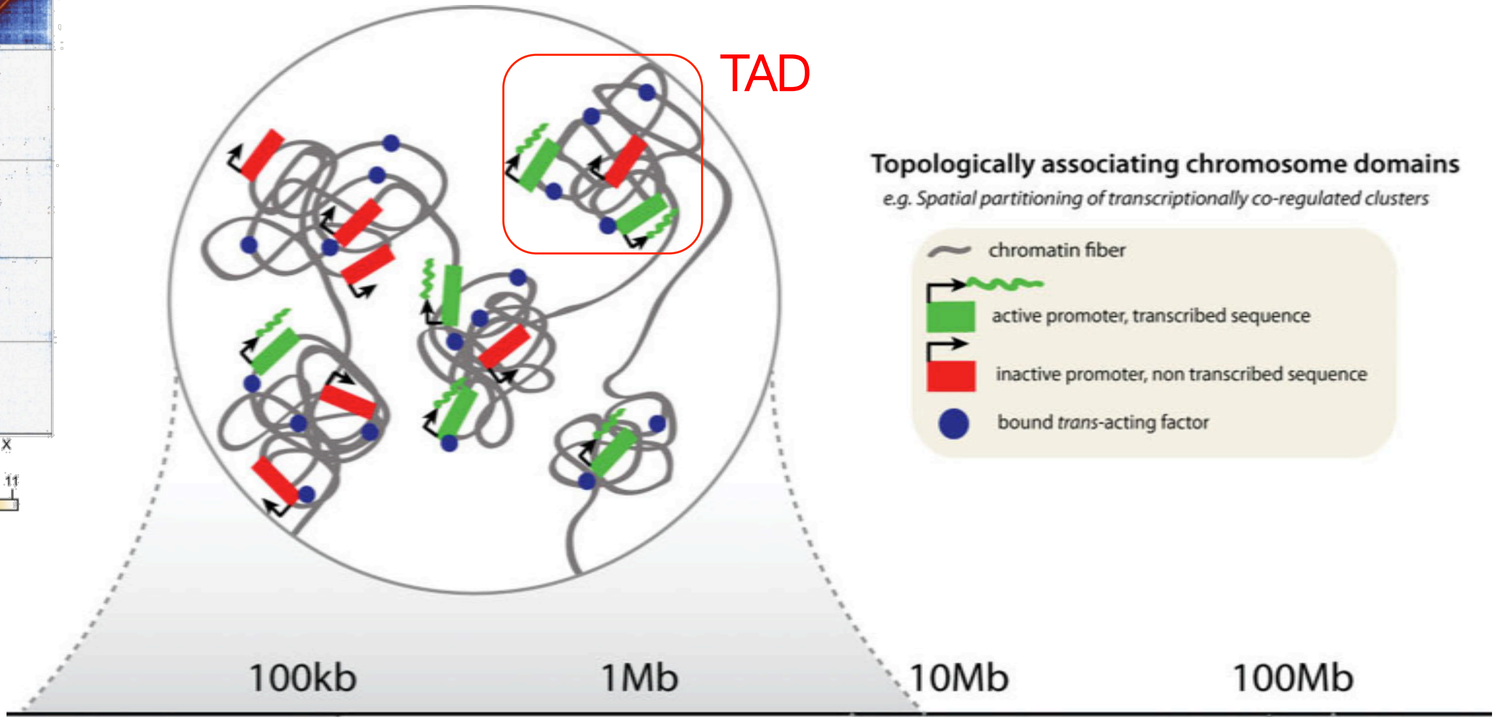
Filion et al. – Cell, 2010

« topologically associating domains » (TADs)

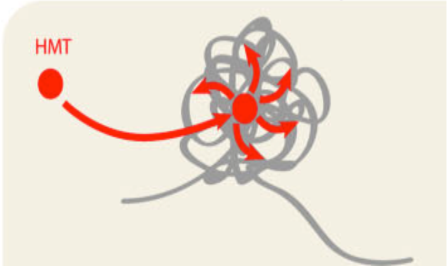
HiC contact frequency map

Sexton et al – Cell, 2012

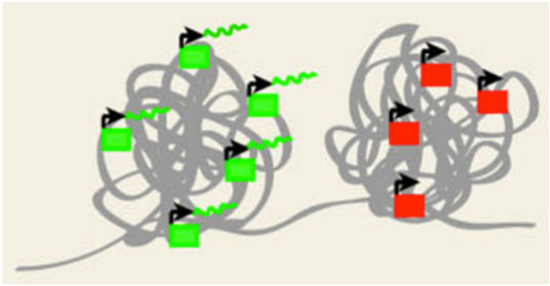




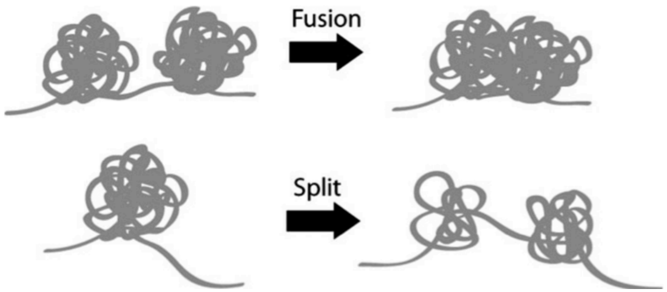
Epigenetic mark spreading



Transcription activity



Merge/split domains



Nora, Dekker, Heard - Bioessays, 2013

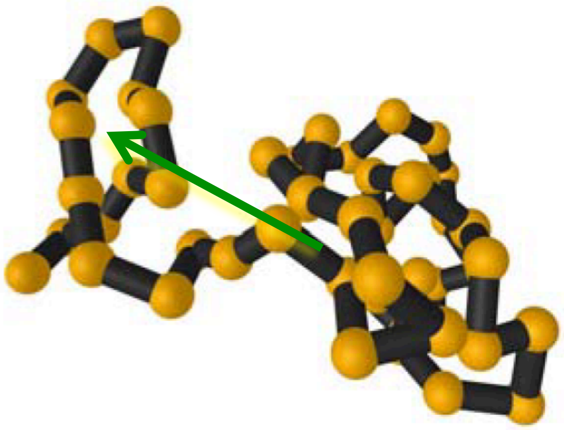
Polymer models

Radius of gyration:

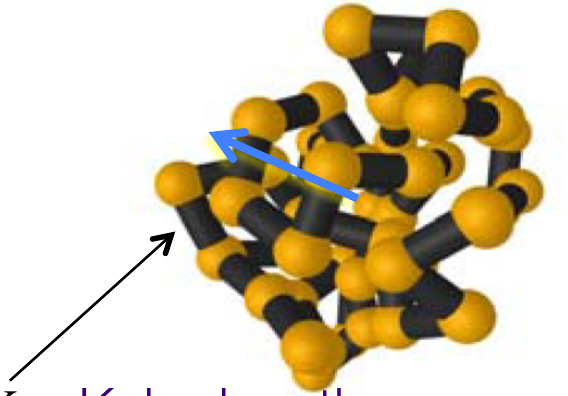
$$\boxed{R_G^2 = \left\langle \frac{1}{2N}\sum_{i=1}^{N}\sum_{j=1}^{N}(r_i - r_j)^2 \right\rangle}$$

Power law and Flory exponent:

$$\boxed{R_G \sim N^{\nu}}$$

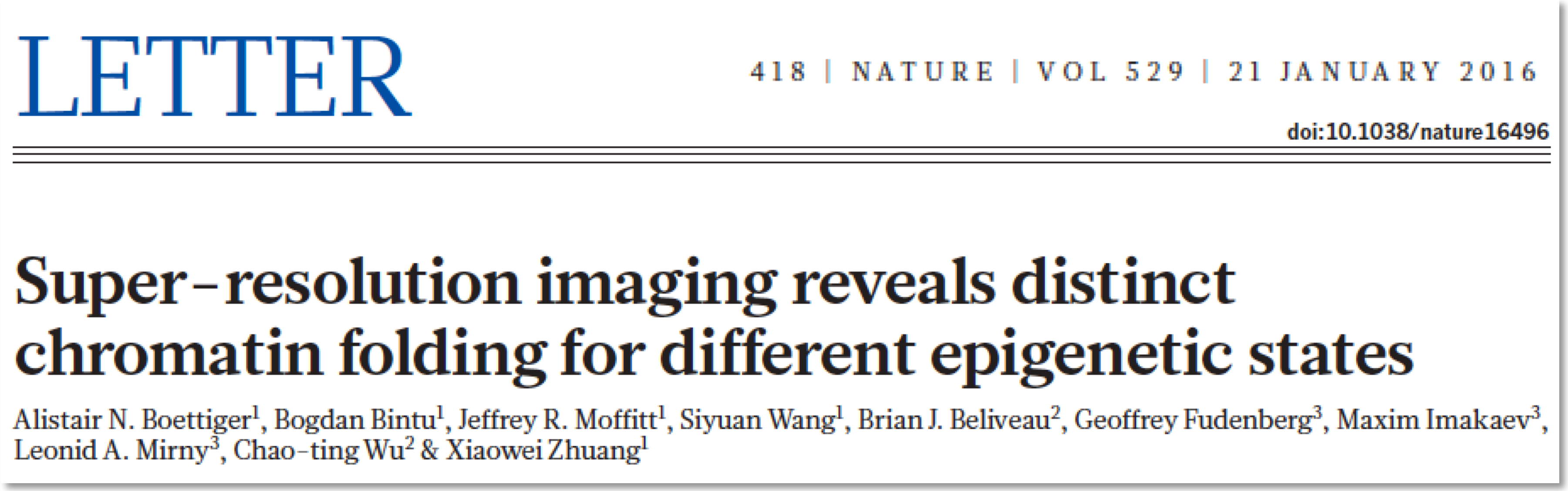


- Random Walk coil $\nu = 1/2$
- Self-Avoiding Walk (SAW) coil $\nu = 3/5$



- Equilibrium globule $\nu = 1/3$
- Fractal globule $\nu = 1/3$

(K = Kuhn length = segment length)



LETTER

418 | NATURE | VOL 529 | 21 JANUARY 2016

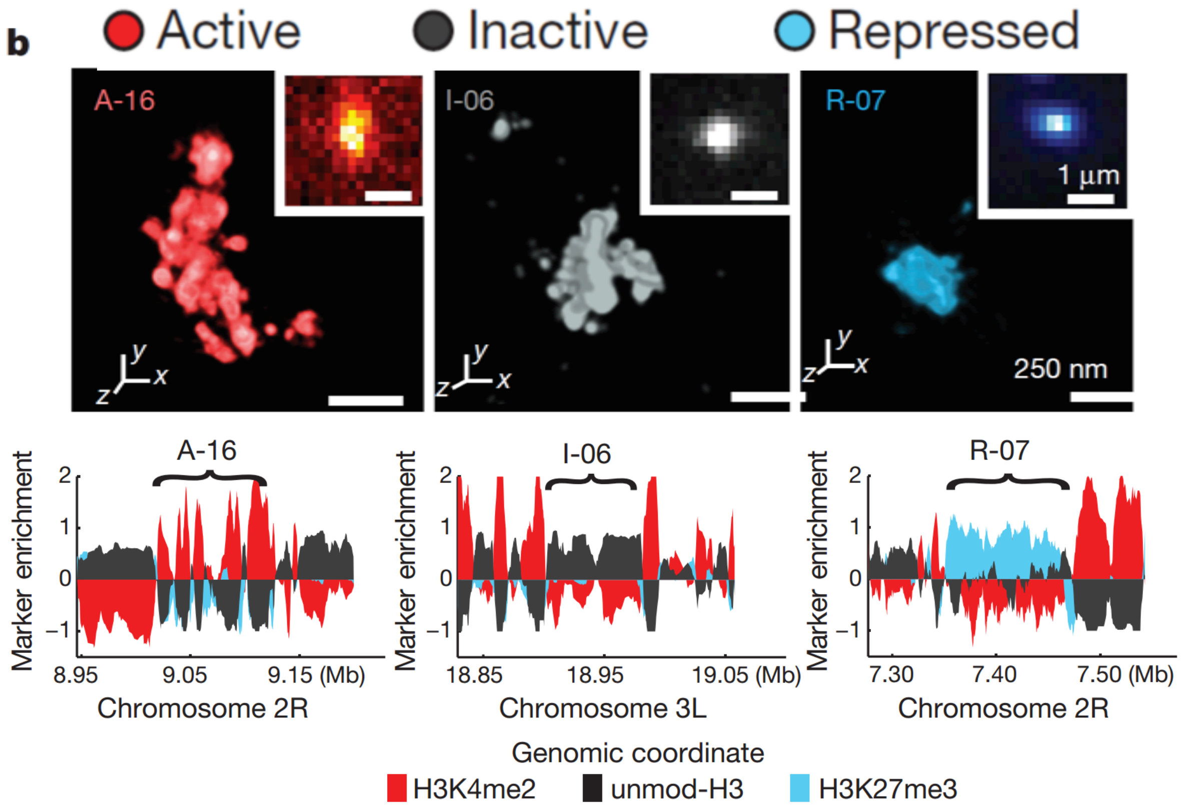
doi:10.1038/nature16496

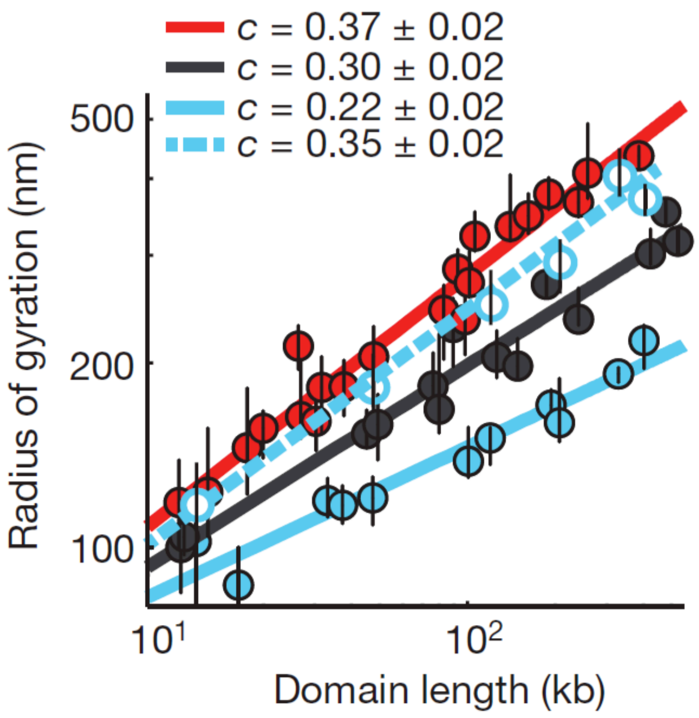
Super-resolution imaging reveals distinct chromatin folding for different epigenetic states

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]

3 epigenetic states:

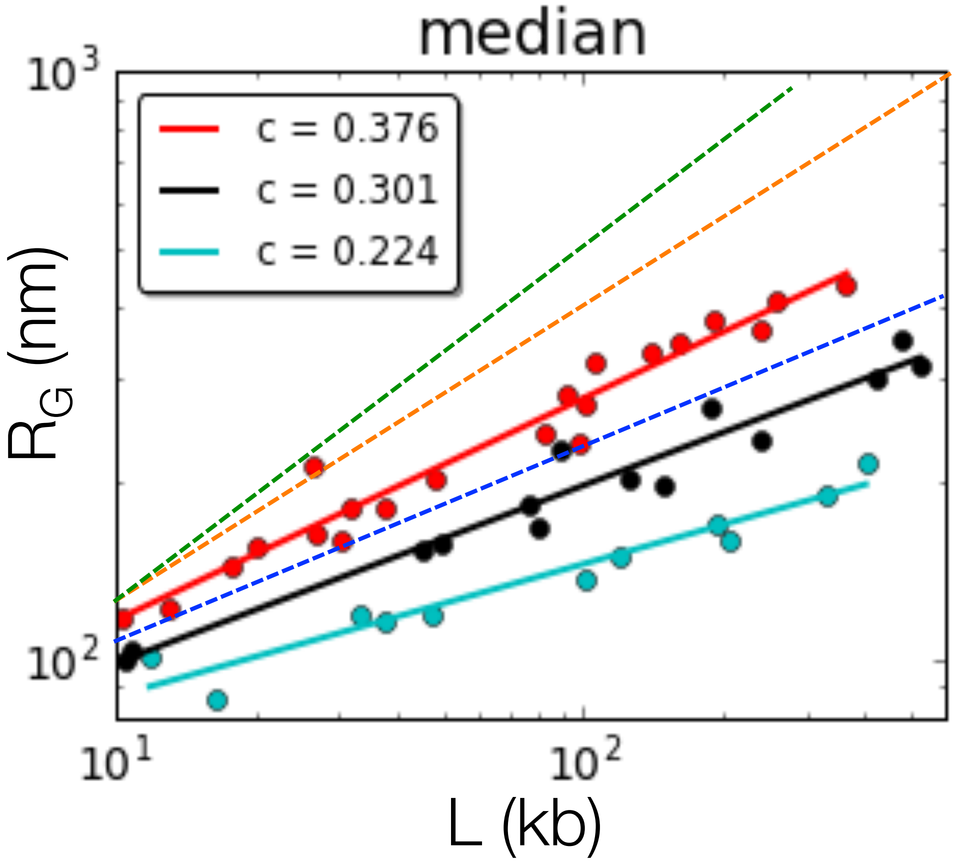
Rg scaling law :





how to interpret the experimental scaling laws?

(Data (points) from Boettinger et al. 2016)



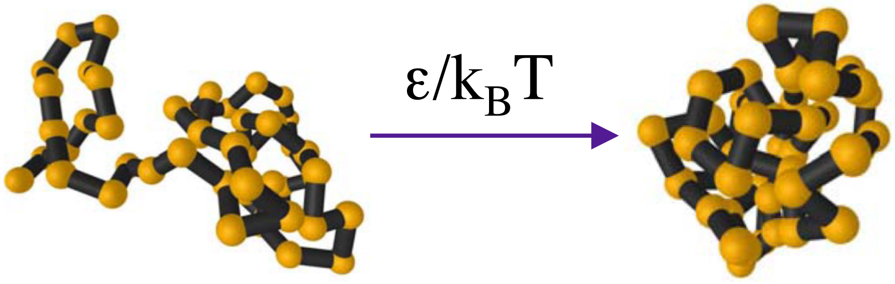
---------- Random Walk $\nu = 1/2$

---------- SAW Coil $\nu = 3/5$

---------- Eq. Globule / Fractal Globule $\nu = 1/3$

The coil-globule transition: finite-size effects

A polymer with N identical monomers:



coil-globule transition

depending on the ratio between :

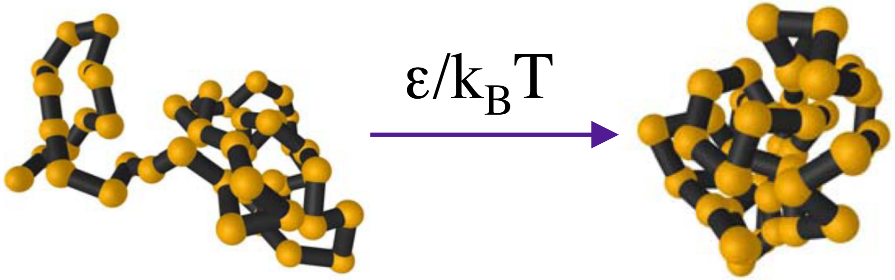
ε interaction energy per monomer

$k_B T$ thermal energy

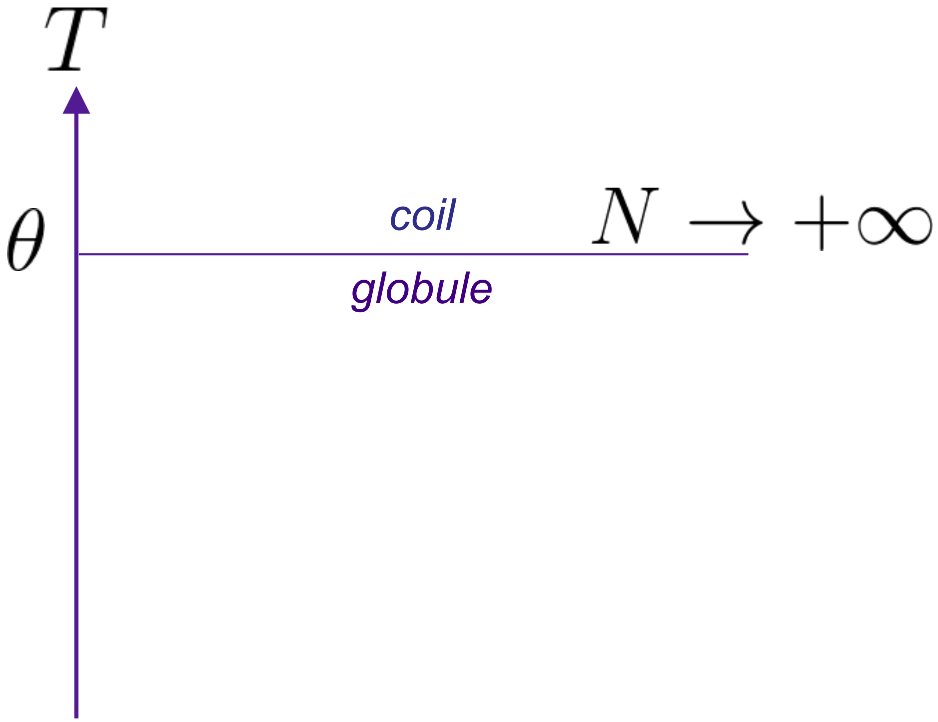
(K Kuhn length = segment length)

The coil-globule transition: finite-size effects

A polymer with N identical monomers:



coil-globule transition



depending on the ratio between :

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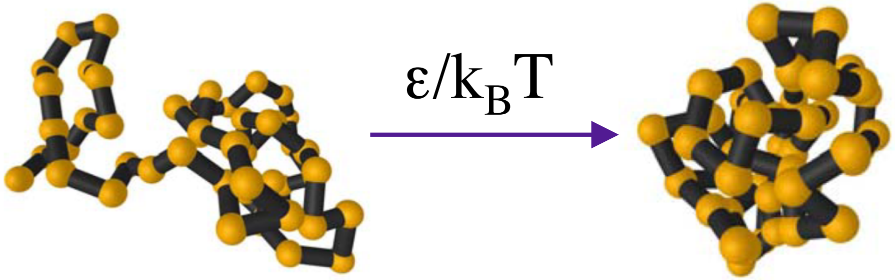
The coil-globule transition: finite-size effects

A polymer with N identical monomers:



coil-globule transition

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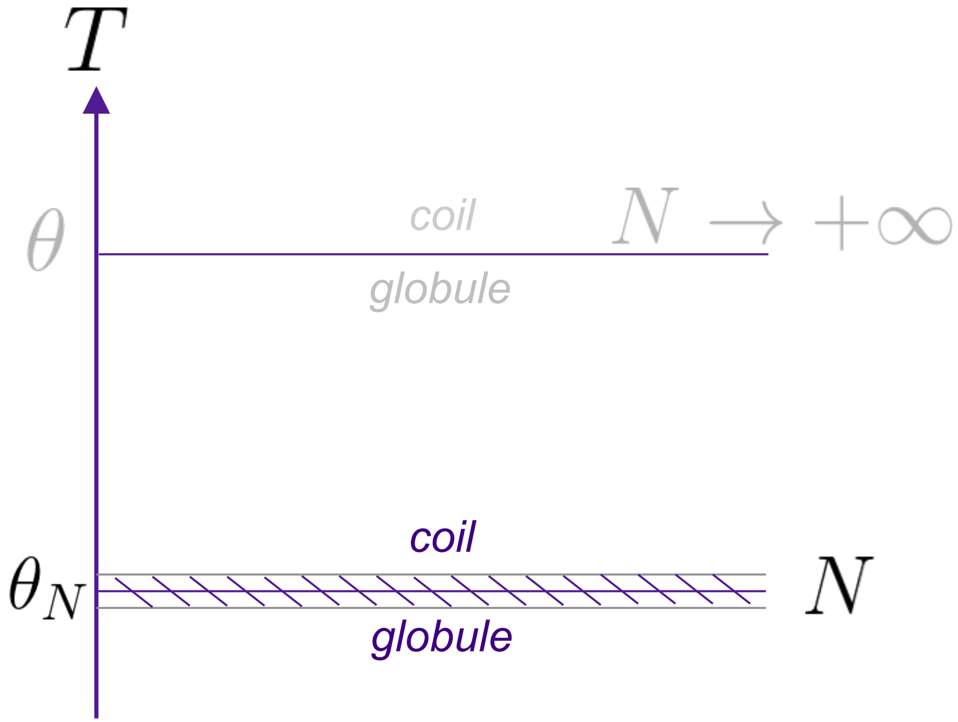
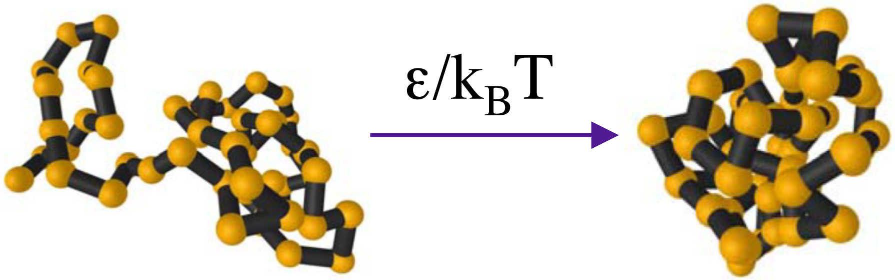


The coil-globule transition: finite-size effects

A polymer with N identical monomers:



coil-globule transition

depending on the ratio between :

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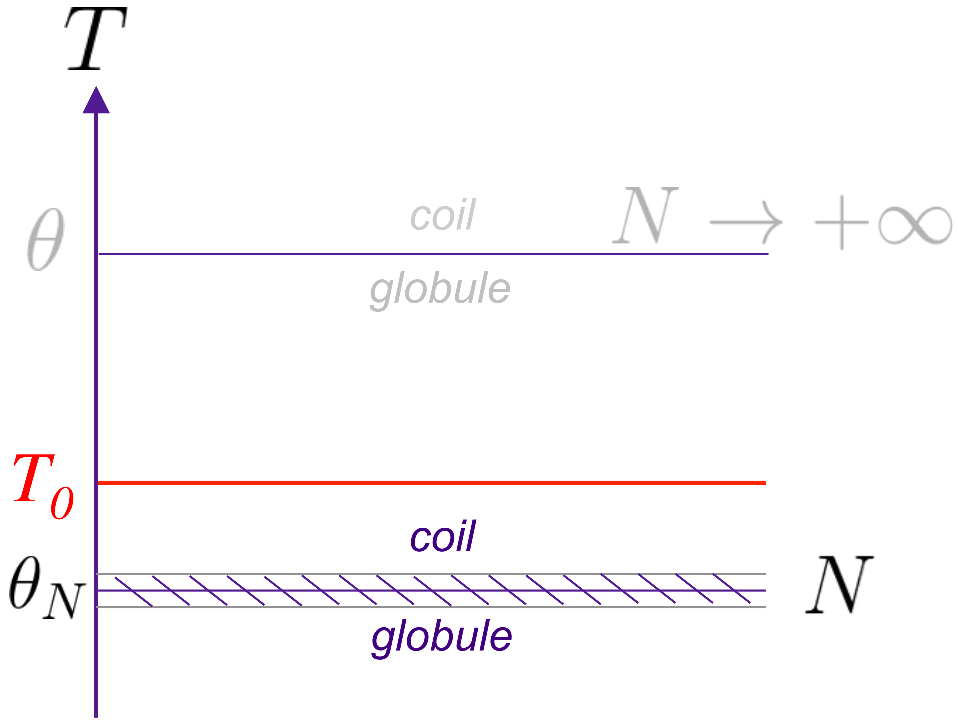
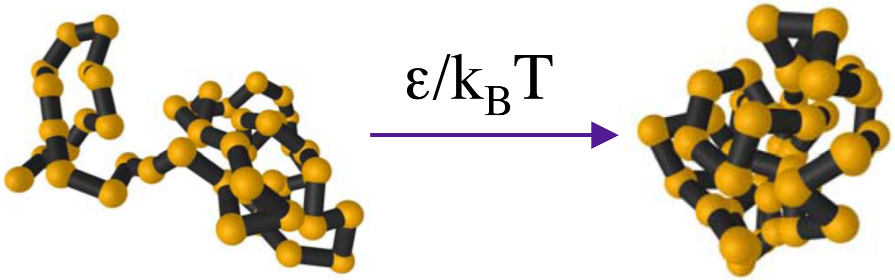
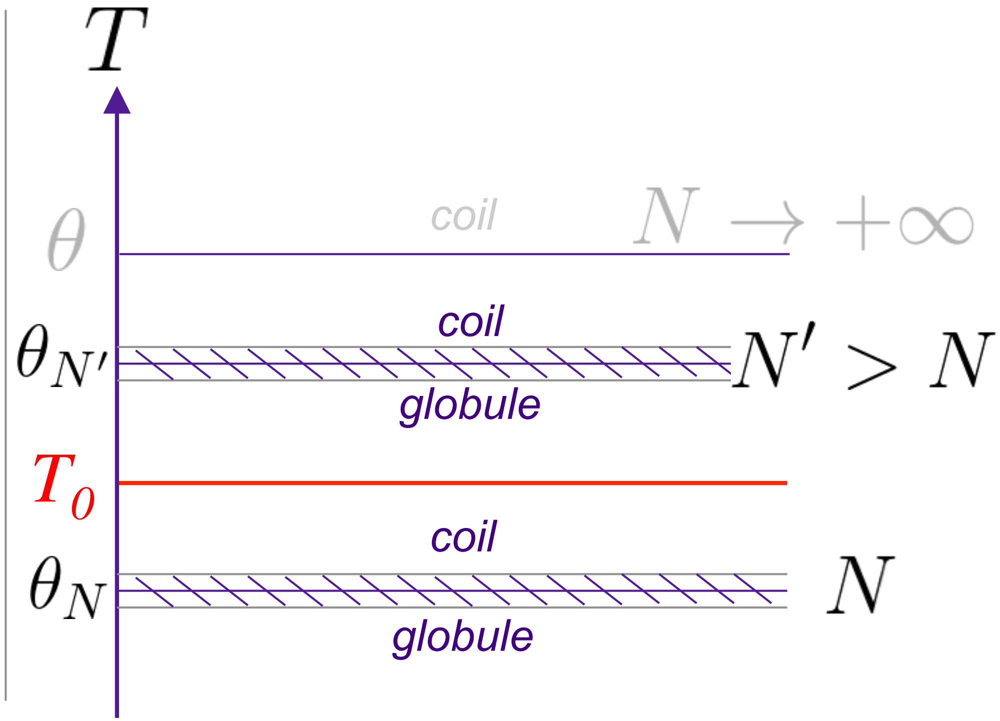


The coil-globule transition: finite-size effects

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)

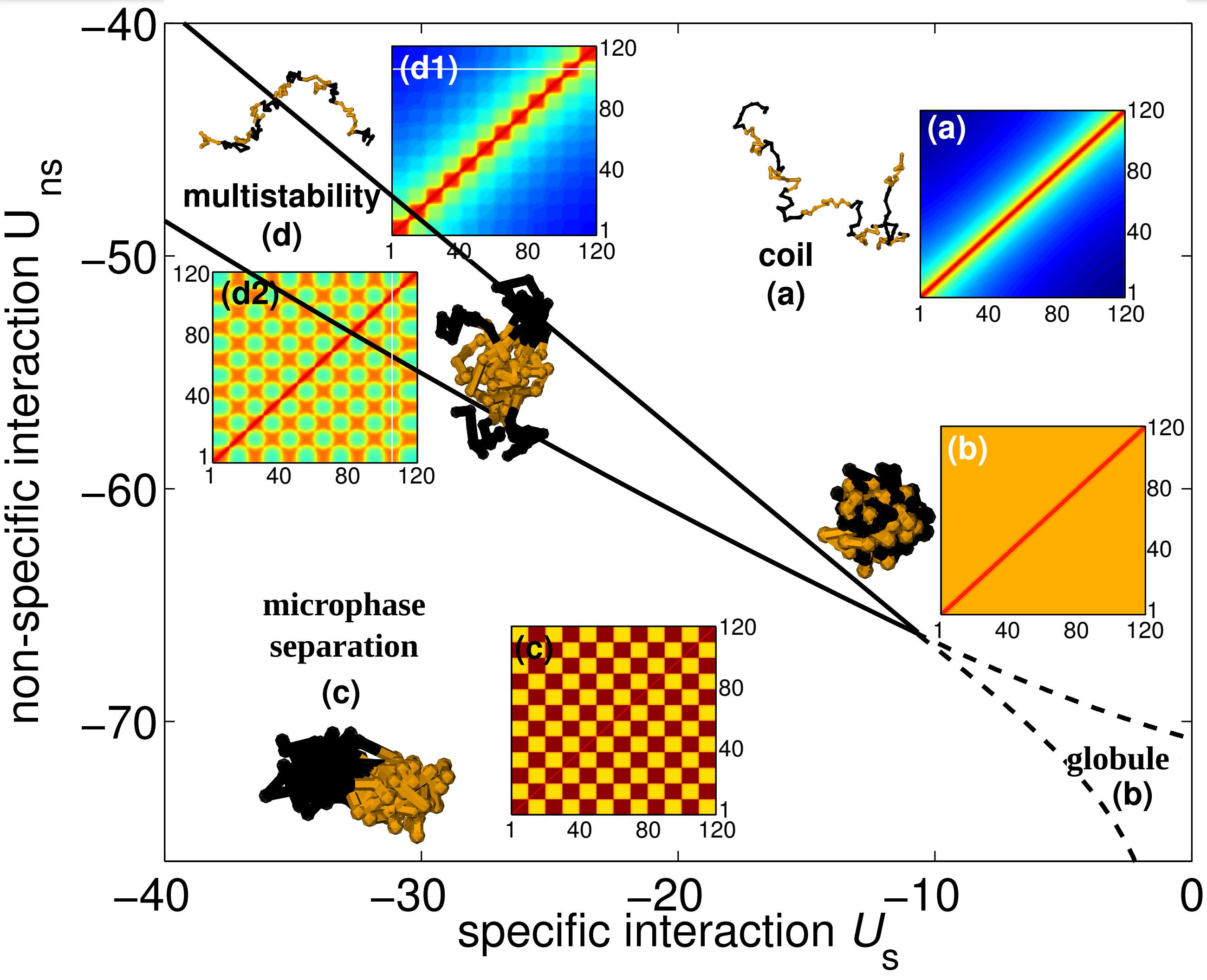
- Small polymers are coil
- Big polymers are globule

Nucleic Acids Research Advance Access published August 4, 2014

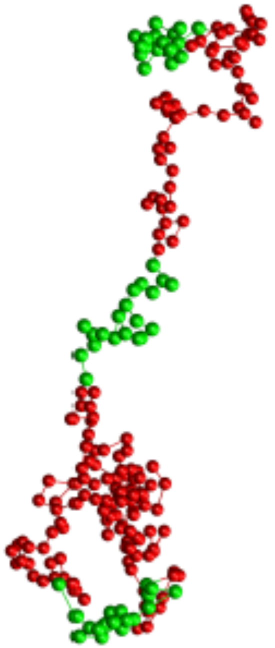
Nucleic Acids Research, 2014 **1**
doi: 10.1093/nar/gku698

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



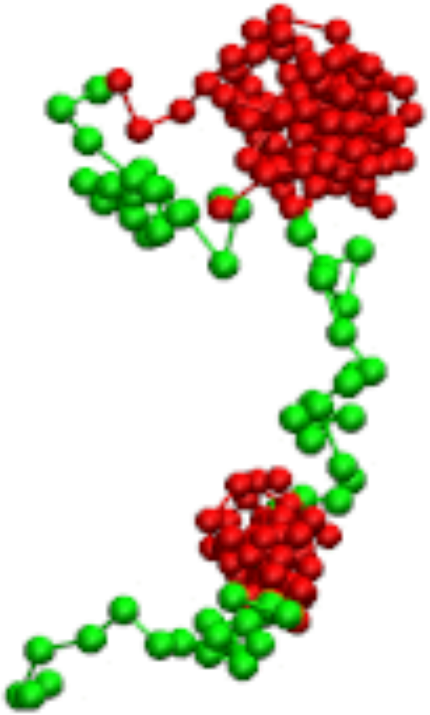
AIMS Biophysics, 2015, 2(4): 517-530. doi: 10.3934/biophy.2015.4.517

Research article **Special Issues**

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],

20 / 55 ; intra-color interaction $U = \begin{cases} -\varepsilon\left[1-e^{-a(r-r_0)2}\right] & \text{if} \quad 0 \le r \le r_{\max} \\ 0 & \text{if} \quad r > r_{\max} \end{cases}$

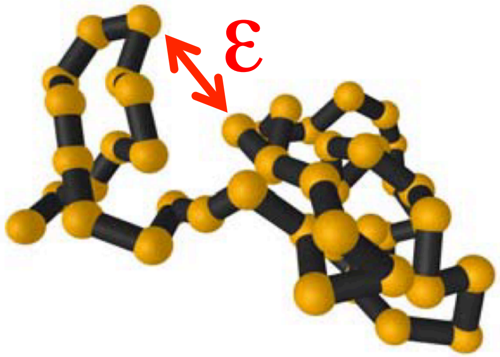


The coil-globule transition: model

«Interacting Self Avoiding Walk » (ISAW) model

Order parameter: $\hat{t} = N^{1/2}\left(\frac{N}{r_G^3}\right)^{5/4}$

Dimensionned order parameter: $s = L^{1/2}\left(\frac{L}{R_G^3}\right)^{5/4}$



Free energy : $\beta F_L(s) = A_1 N^{1/2}\; s + A_2 s^2 + A_3 N^{-1/3} s^{-2/3} + 1.13 \ln s$

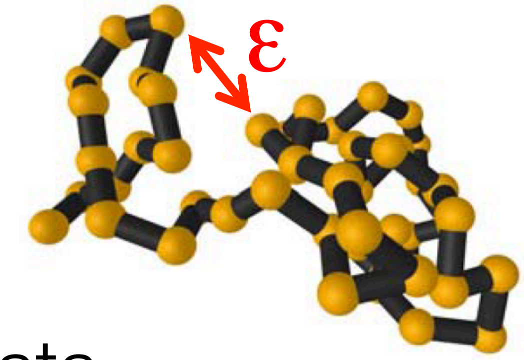
A_1 A_2 and A_3 depends on the 3 physical parameters : the energy ε, the Kuhn length K and the compaction α

JB Imbert, A Lesne, and JM Victor - PRE 56, 5630, 1997

The coil-globule transition: model

Working hypothesis:

ε, K, α are specific for a given state



Goal:

Fit A_1 A_2 and A_3 over the whole set of data,
for each state

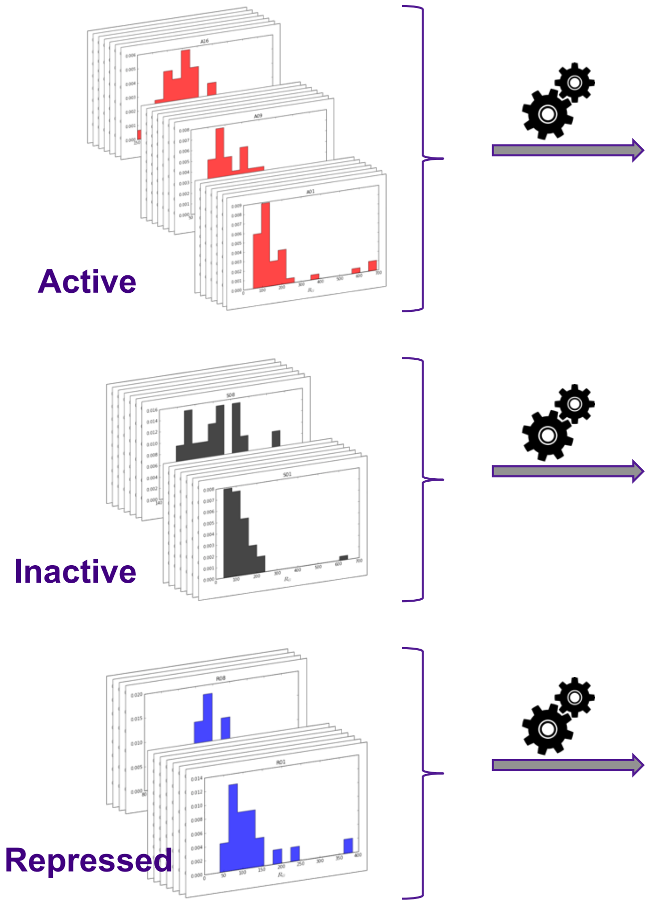
Free energy : $\beta F_L(s) = A_1 N^{1/2}\, s + A_2 s^2 + A_3 N^{-1/3} s^{-2/3} + 1.13 \ln s$

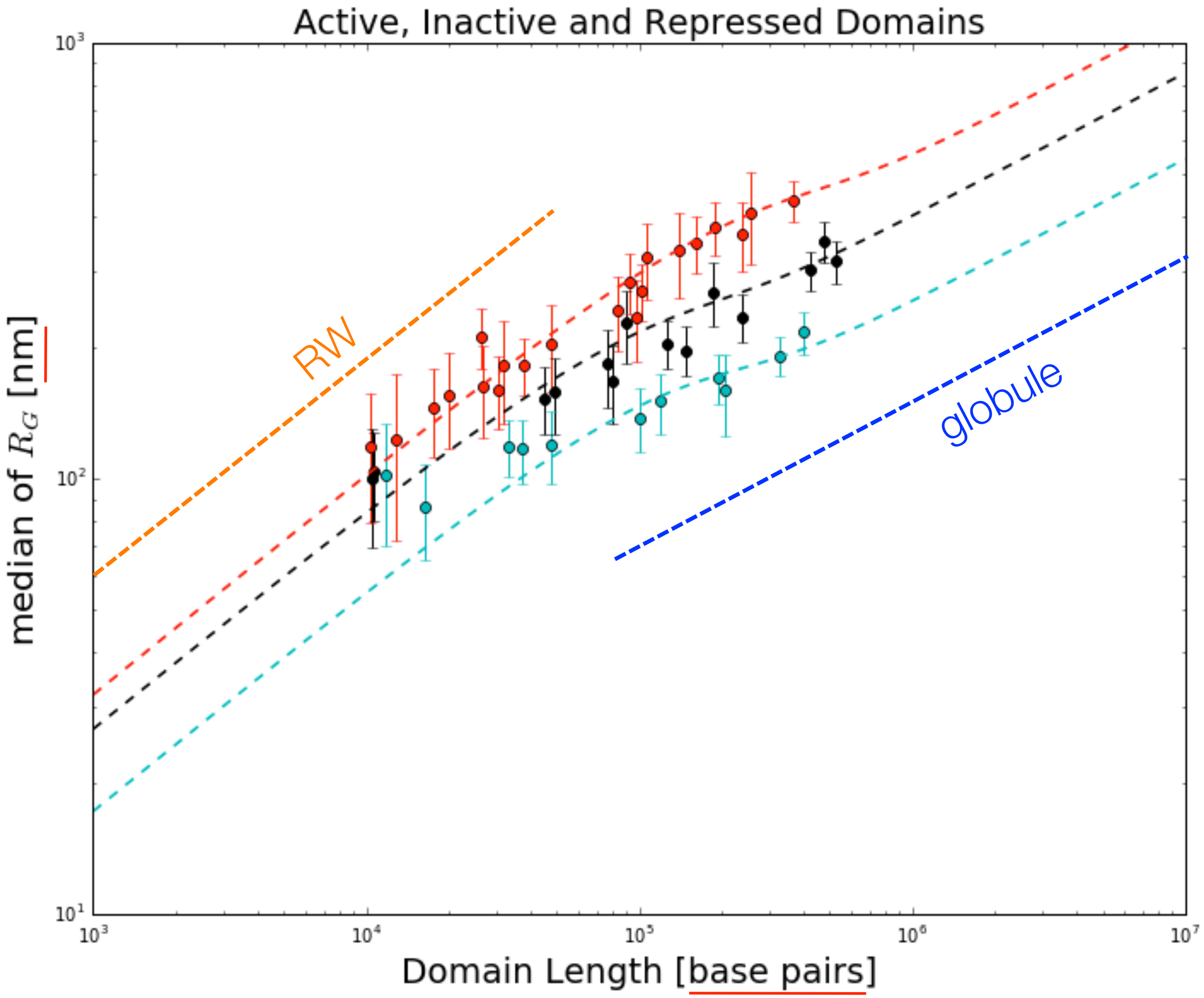
A_1 A_2 and A_3 depends on the 3 physical parameters :
the energy ε, the Kuhn length K and the compaction α

JB Imbert, A Lesne, and JM Victor - PRE 56, 5630, 1997

Fitting approach and result

⚙ = maximum likehood + Bayesian inference

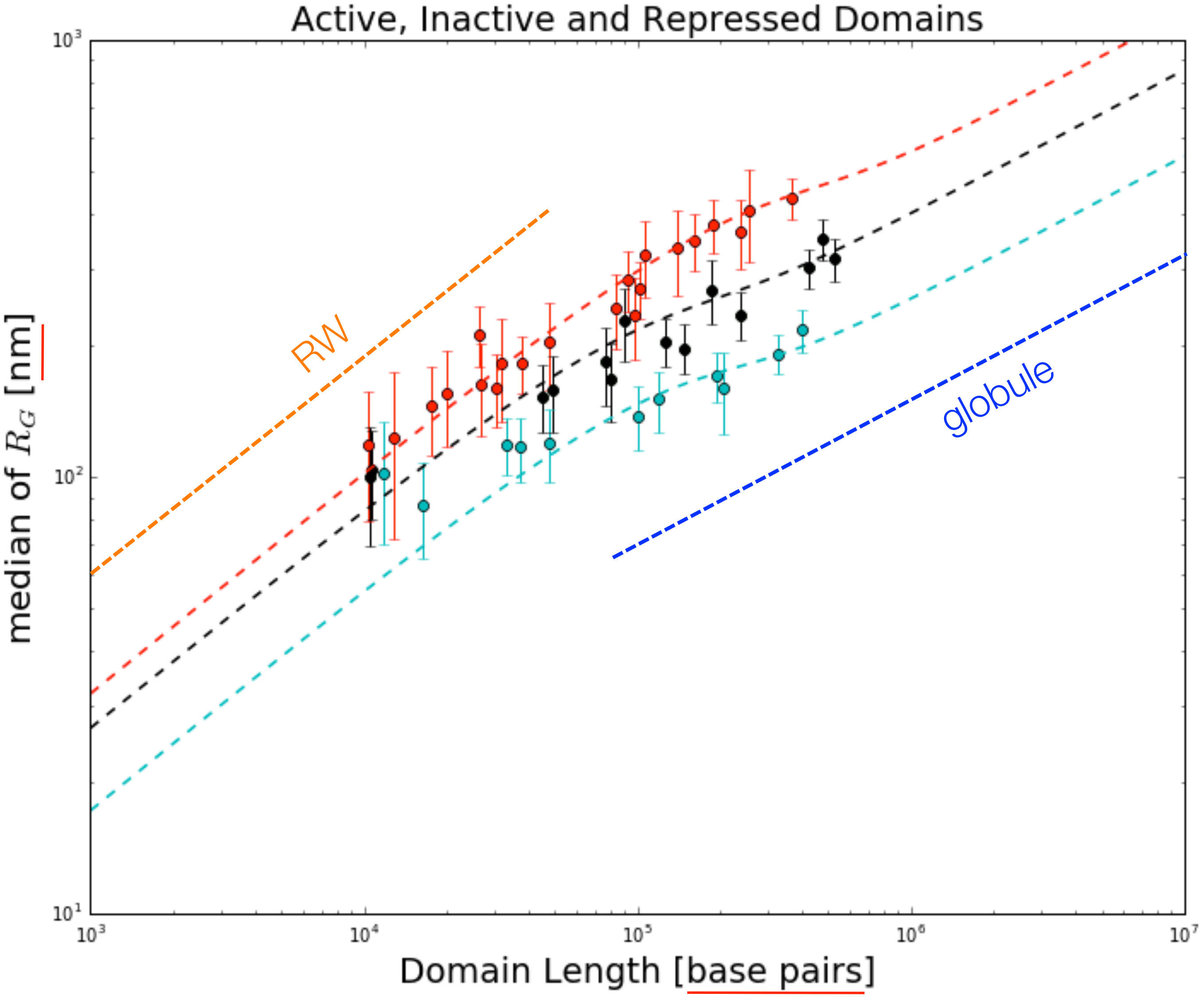




(Data (points) from Boettinger et al. 2016)

Results (0)

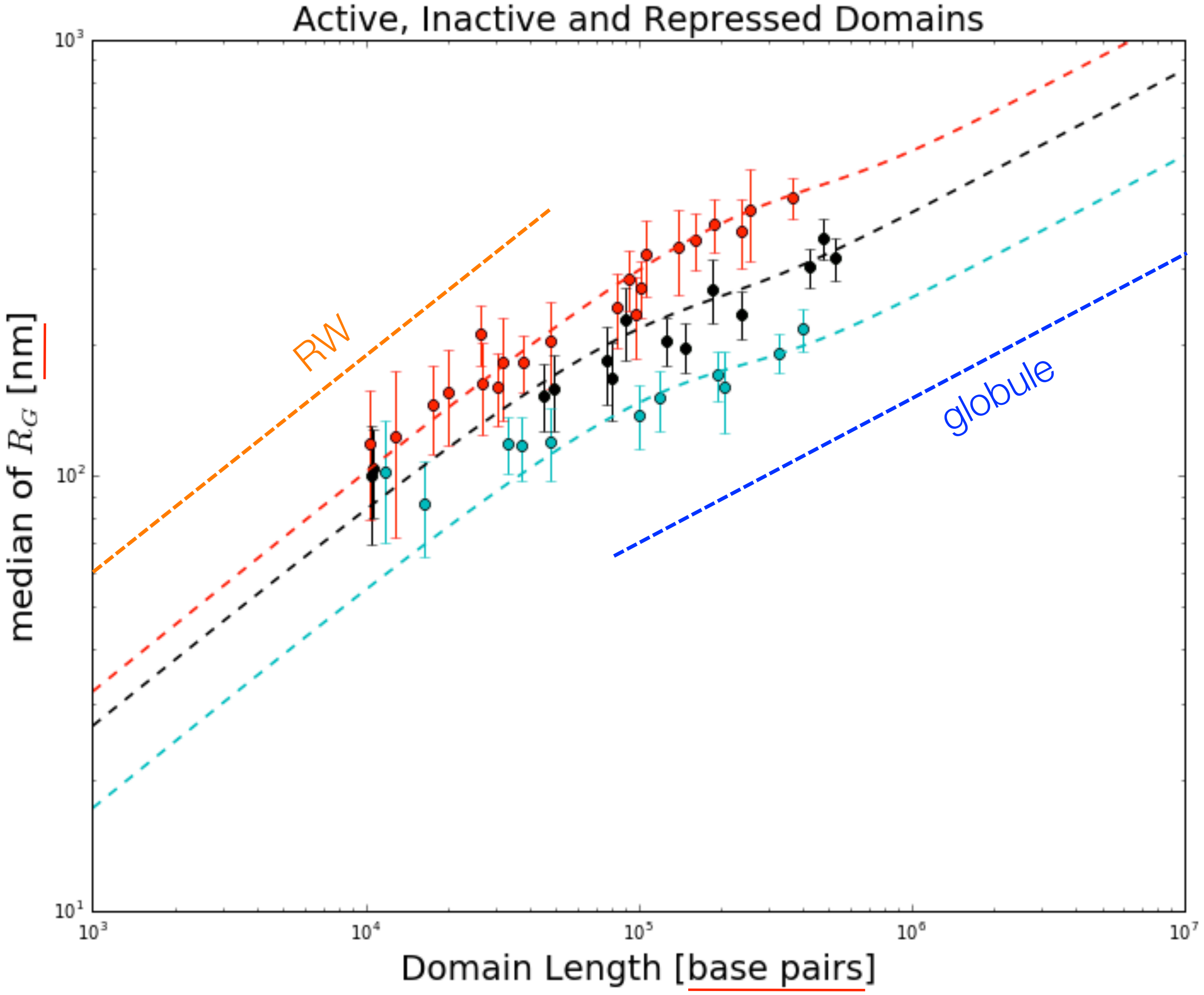
It is possible to fit the data with this model



(Data (points) from Boettinger et al. 2016)

Results (1)

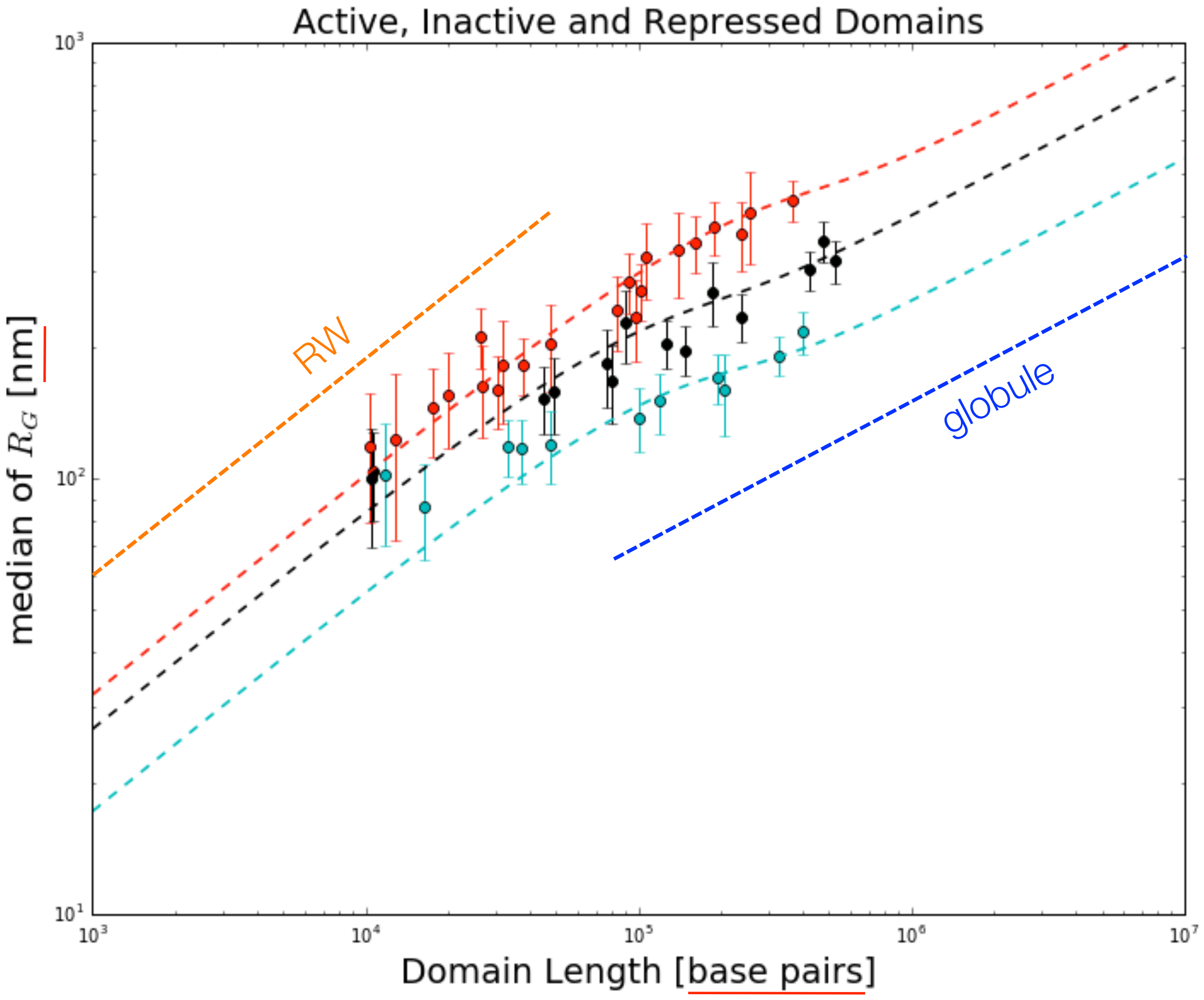
All three states are **at** the coil-globule transition



(Data (points) from Boettinger et al. 2016)

Results (2)

Fits give $\varepsilon \sim 0.3\ k_BT$ per Kuhn segment (for all...)



(Data (points) from Boettinger et al. 2016)

Results (3)

Fits give $\varepsilon \sim 0.3\ k_BT$ per Kuhn segment (for all...)

But the Kuhn length K is different for different states:

State	K [bp]	α [bp/nm]
Active	203 ± 93	6.2 ± 3.1
Inactive	154 ± 50	6.5 ± 2.3
Repres.	50 ± 8	5.8 ± 1.1

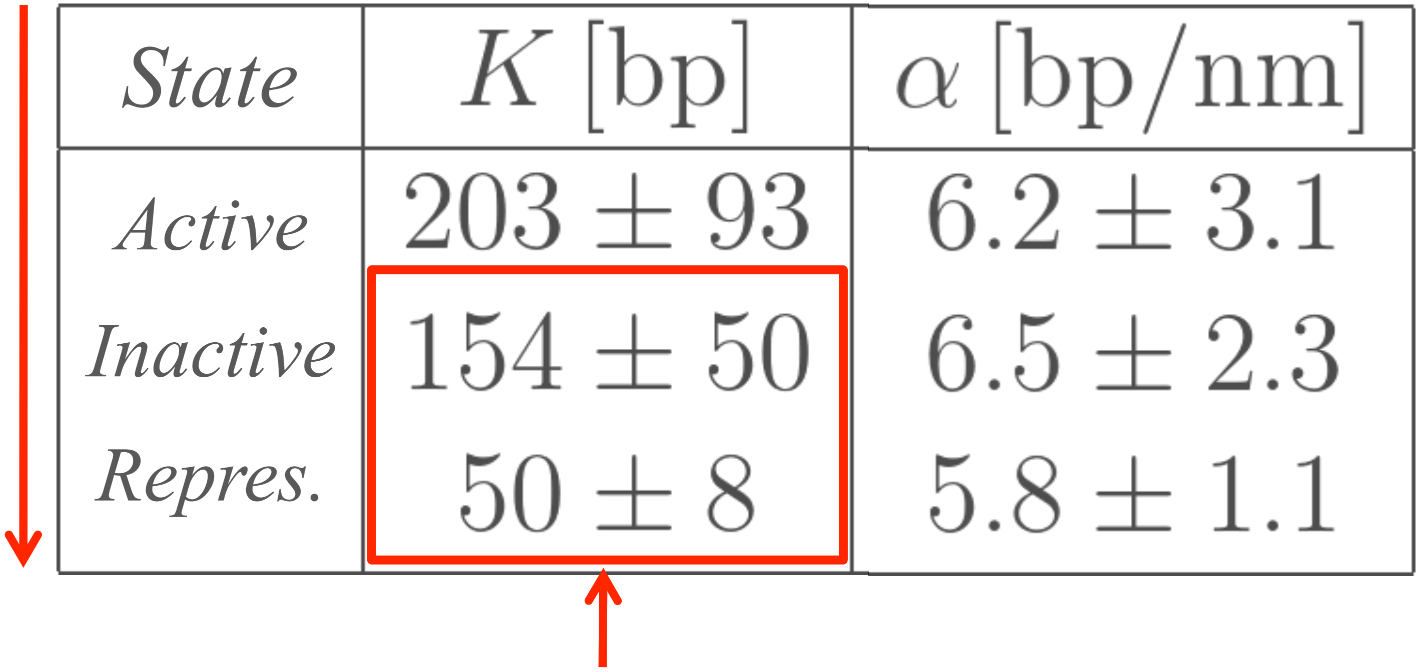
smaller Kuhn length.. (similar compaction)

...hence larger energy/bp from active to repressed

Results (4)

Up to a VERY small persistence length!

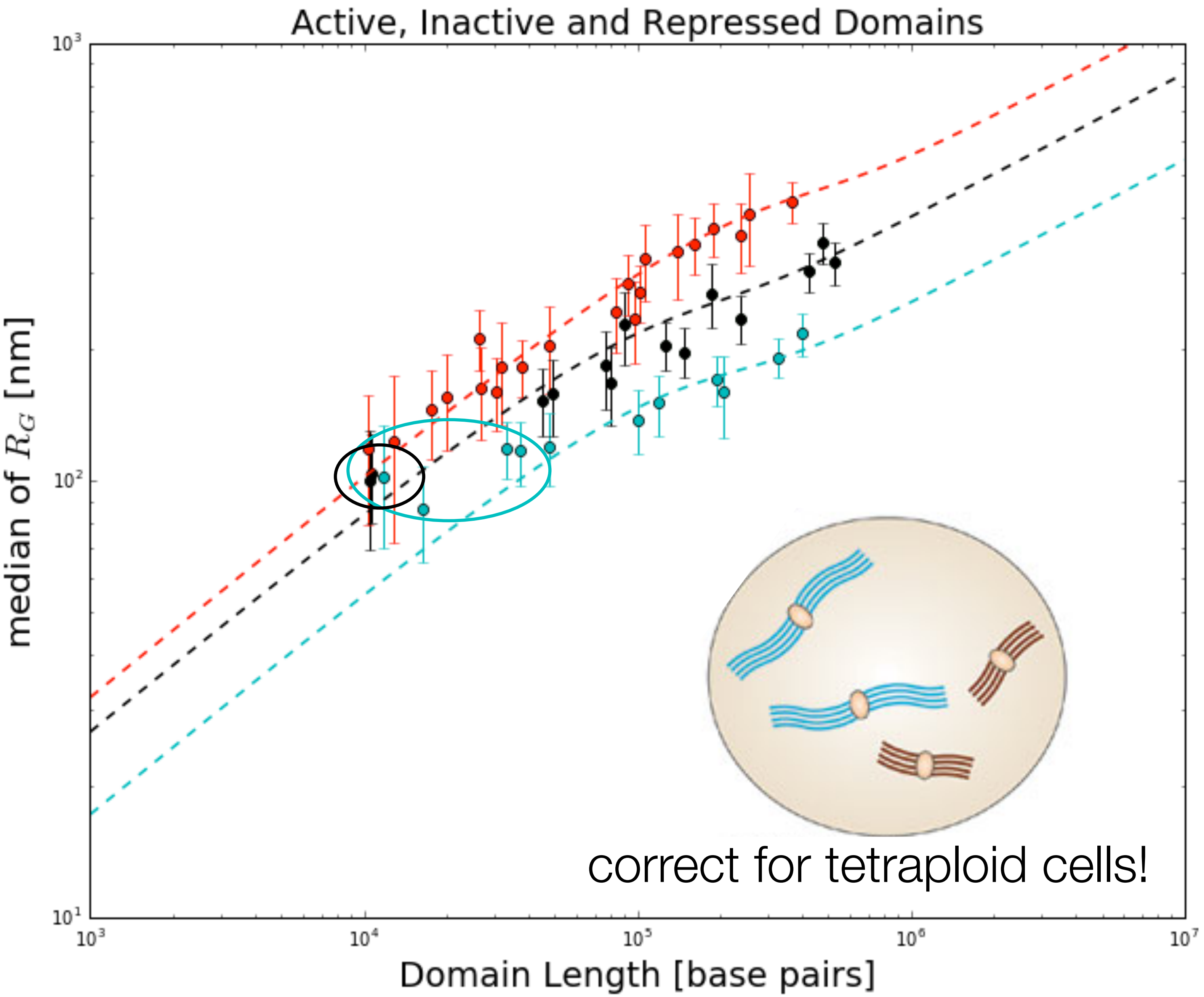
$(K = 2\ L_\mathrm{P})$



State	K [bp]	α [bp/nm]
Active	203 ± 93	6.2 ± 3.1
Inactive	154 ± 50	6.5 ± 2.3
Repres.	50 ± 8	5.8 ± 1.1

Less than une nucleosome repeat...
... to be confirmed!

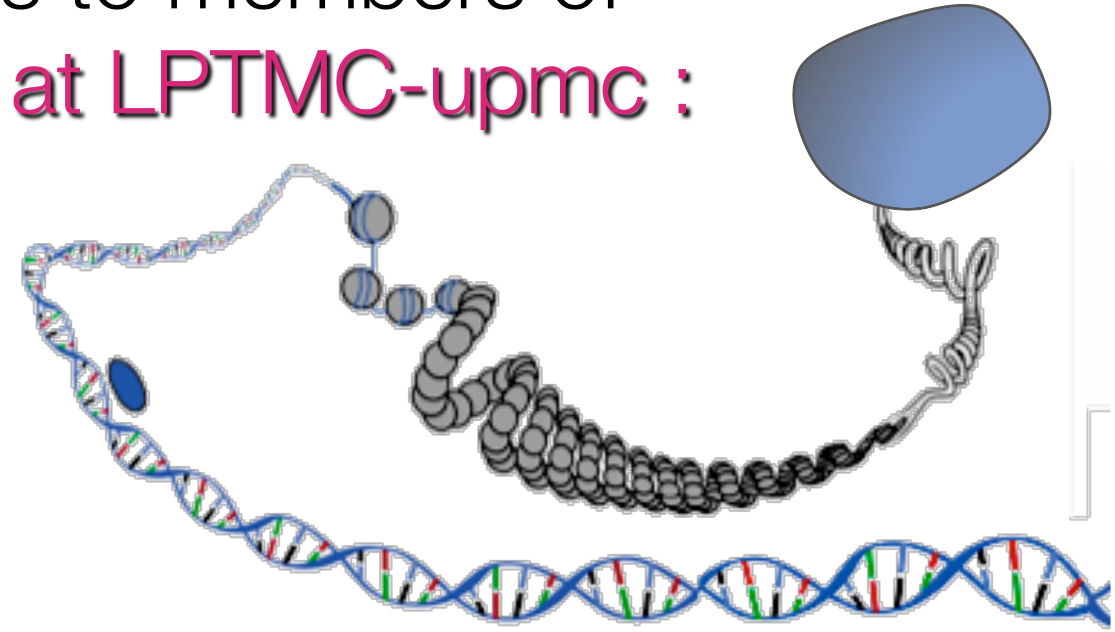
Work in progress



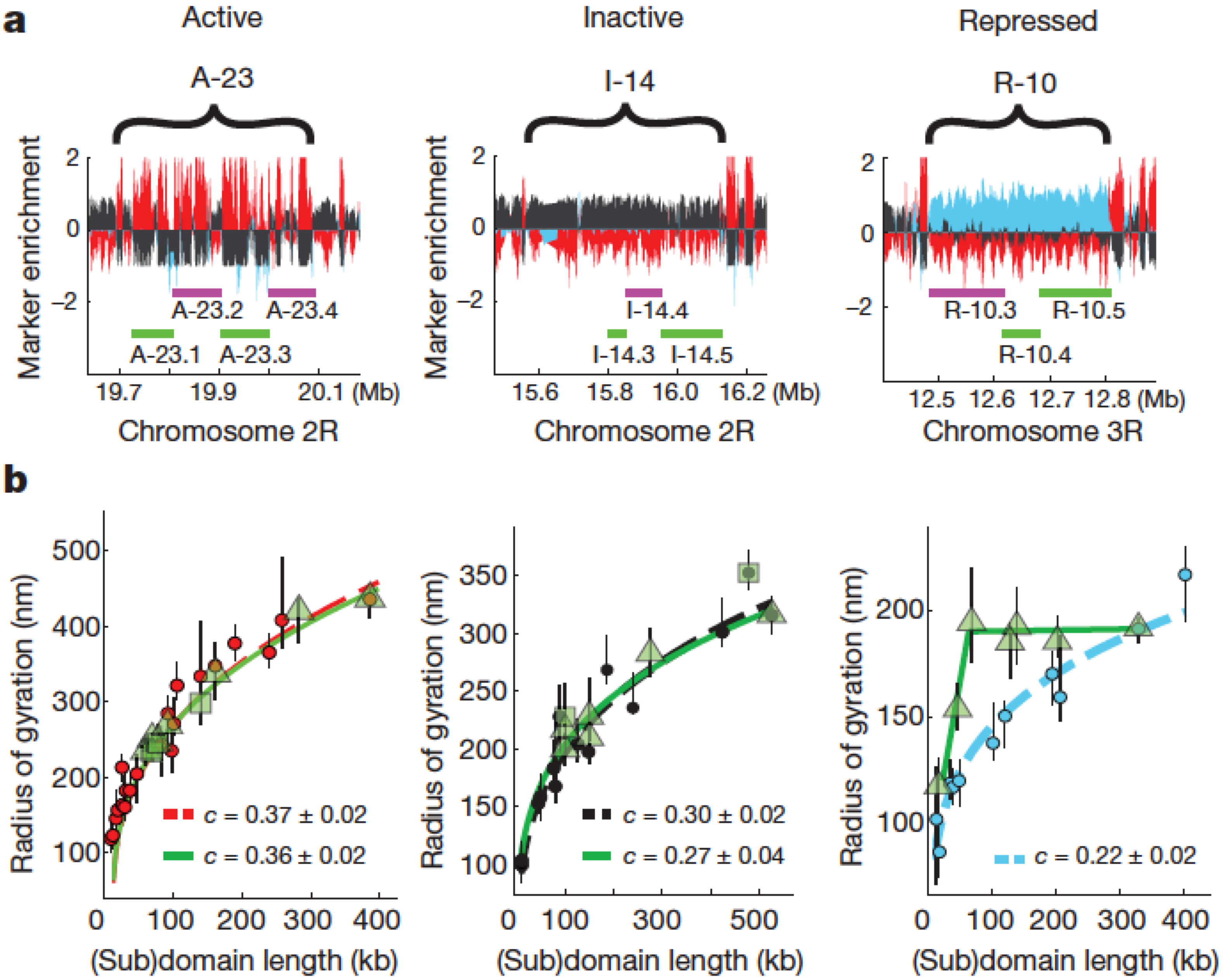
correct for tetraploid cells!

Thank you for you attention,

and thanks to members of M3V Group at LPTMC-upmc :

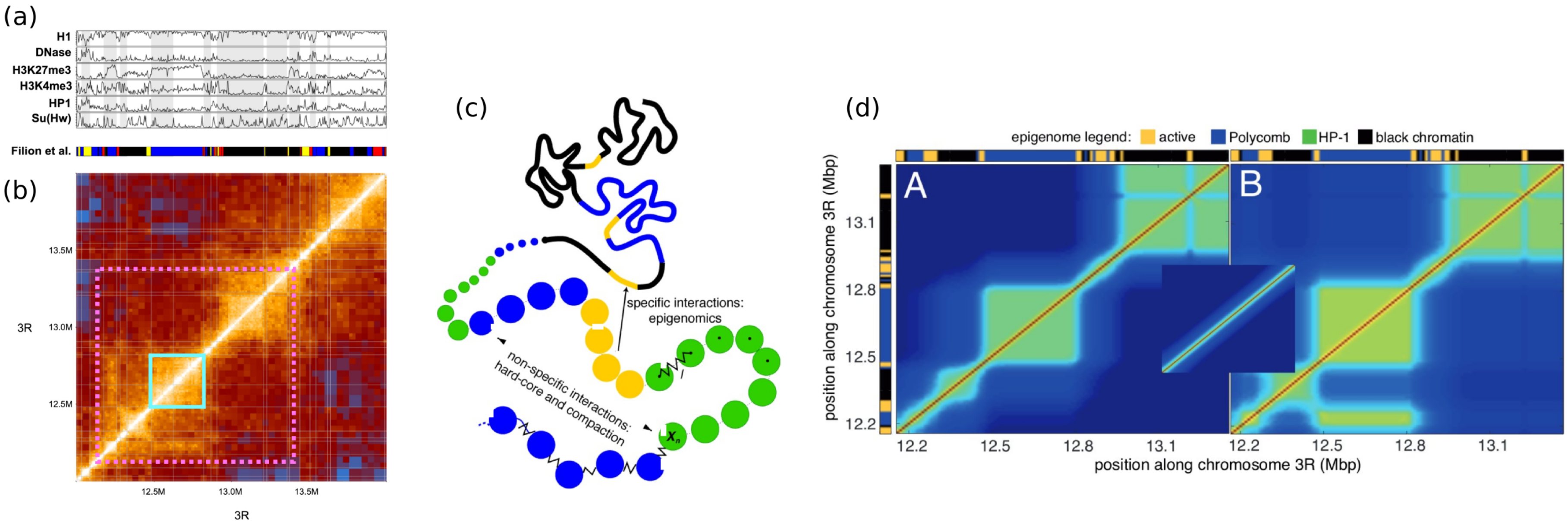


- Jean-Marc Victor
- Annick Lesne
- Julien Mozziconacci
- Bertrand Caré (postdoc ANR/INCa, 2013-2015)
- Ruggero Cortini (postdoc ANR/INCa, 2013-2015)
- **Antony Lesage** (Master student, starting PhD) << who did the work!


a
Active
A-23
Inactive
I-14
Repressed
R-10
Marker enrichment
2
0
−2
A-23.2
A-23.4
A-23.1
A-23.3
19.7
19.9
20.1 (Mb)
Chromosome 2R
I-14.4
I-14.3
I-14.5
15.6
15.8
16.0
16.2 (Mb)
Chromosome 2R
R-10.3
R-10.5
R-10.4
12.5
12.6
12.7
12.8 (Mb)
Chromosome 3R
b
Radius of gyration (nm)
500
400
300
200
100
c = 0.37 ± 0.02
c = 0.36 ± 0.02
0
100
200
300
400
(Sub)domain length (kb)
350
300
250
200
150
100
c = 0.30 ± 0.02
c = 0.27 ± 0.04
0
100
300
500
(Sub)domain length (kb)
200
150
100
c = 0.22 ± 0.02
0
100
200
300
400
(Sub)domain length (kb)

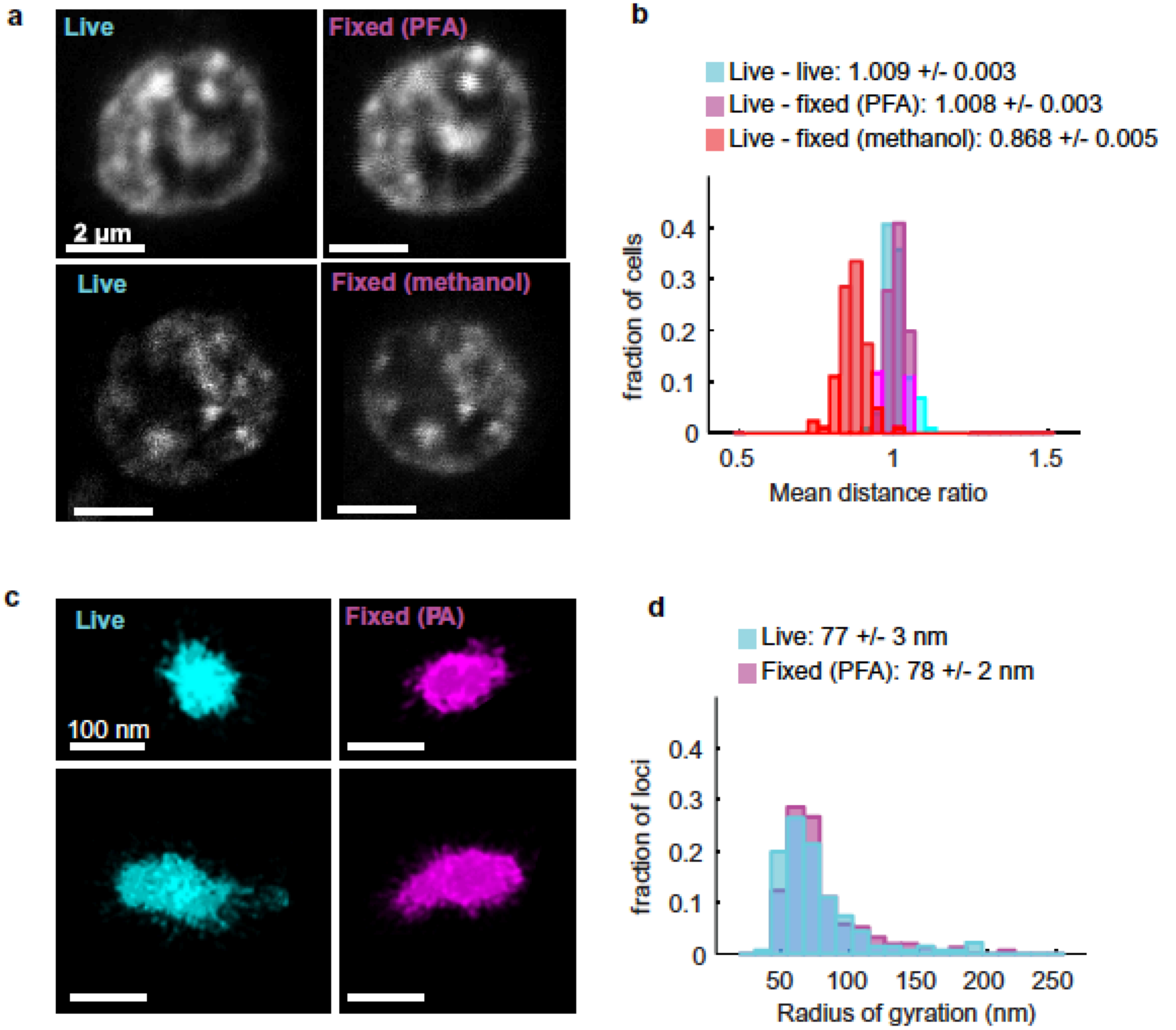
The drosophila nucleus is a copolymer brush

Jost et al, NAR 2014



$$U_{i,j} = (U_{ns} + U_s)\exp(-\frac{r_{i,j}^2}{a^2}) \quad \text{if i and j are of the same color}$$

$$U_{i,j} = U_{ns}\exp(-\frac{r_{i,j}^2}{a^2}) \quad \text{if i and j are of different colors}$$



osmotically balanced methanol-free formaldehyde in PBS

how to interprete the experimental scaling laws?

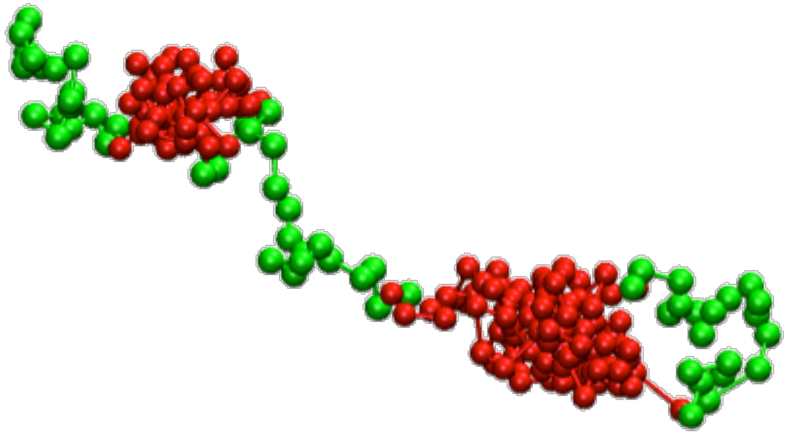
AIMS Biophysics, 2015, 2(4): 517-530. doi: 10.3934/biophy.2015.4.517

Research article **Special Issues**

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],

co-polymer model



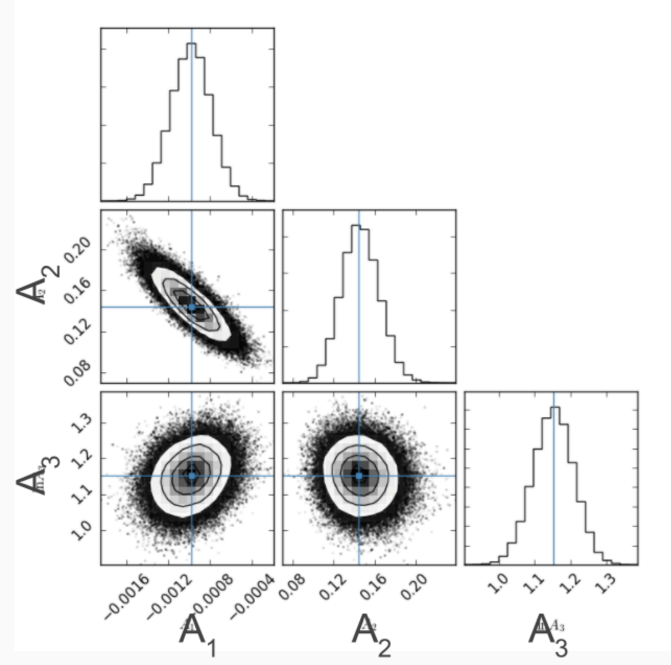
$$\theta(N) = \theta_\infty\left(1 - \frac{c}{N^{1/2}}\right)$$

$$\Delta T(N) \sim \frac{1}{N^{1/2}}$$

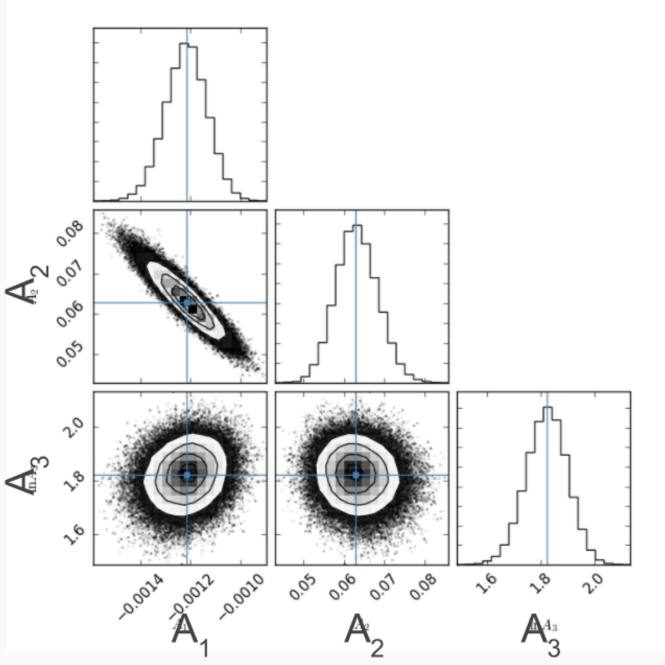
$$U = \begin{cases} -\varepsilon\left[1 - e^{-a(r-r_0)^2}\right] & if \quad 0 \le r \le r_{\max} \\ 0 & if \quad r > r_{\max} \end{cases}$$

« A key prediction of the model is that <u>chromatin compaction should increase with block size</u> for a given epigenomic state (i.e. for a given interaction between beads of chromatin in a block). »

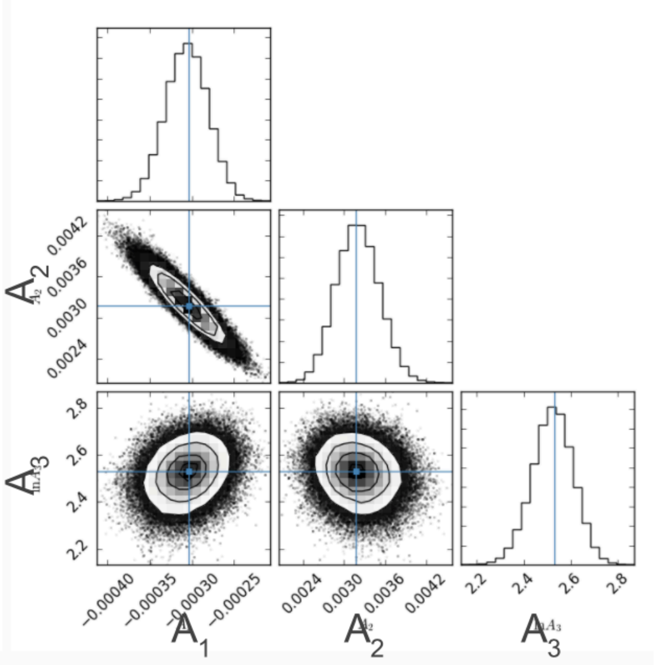
Bayesian inference



Active



Inactive



Repressed

coming back to the adimensional model

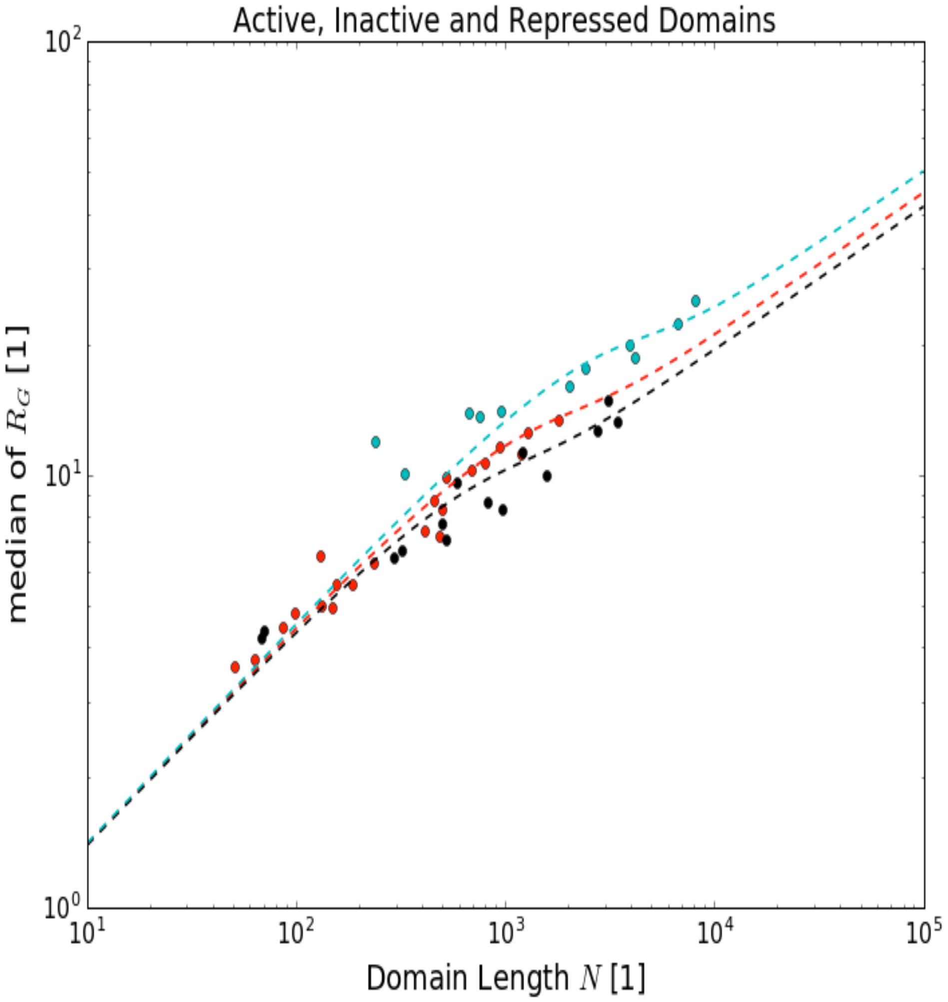
a_2, a_3 constants, determined by simulations

$a_1(U/k_BT)$

$$a_1 = A_1\left(\frac{A_3}{a_3}\right)^{\frac{3}{2}} \rightarrow \beta\varepsilon$$

$$K_{bp} = \frac{A_2}{a_2}\left(\frac{A_3}{a_3}\right)^{3}$$

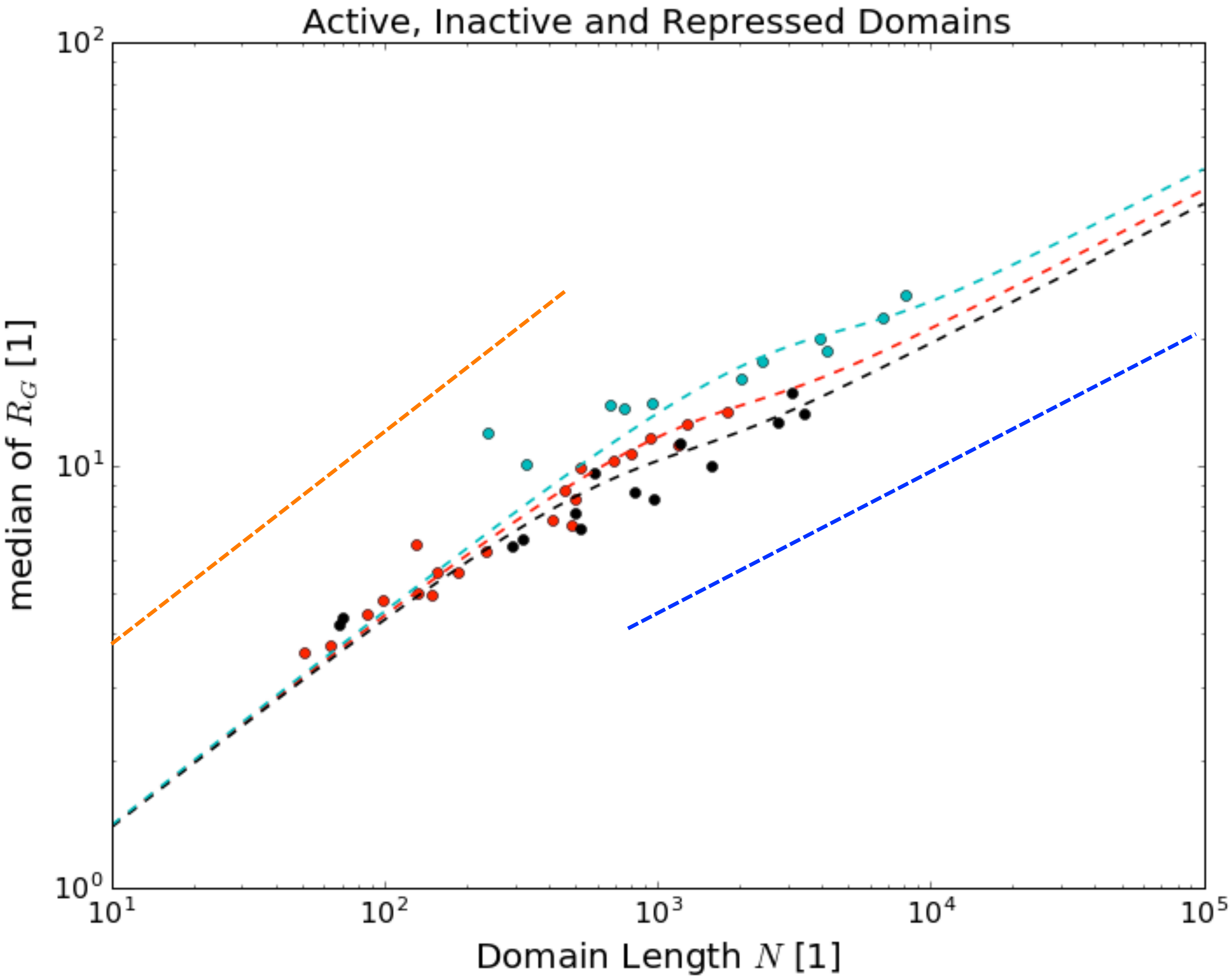
$$K_{nm} = \left(\frac{A_2}{a_2}\right)^{\frac{3}{5}}\left(\frac{A_3}{a_3}\right)^{\frac{7}{5}}$$



coming back to the adimensional model

physical data → dimensionless quantities

→ can be compared with simulations of model polymers



$$N = \frac{L}{K_{bp}}$$

$$r = \frac{R_G}{K_{nm}}$$