

Chromatin conformational arrangements revealed by advanced microscopy

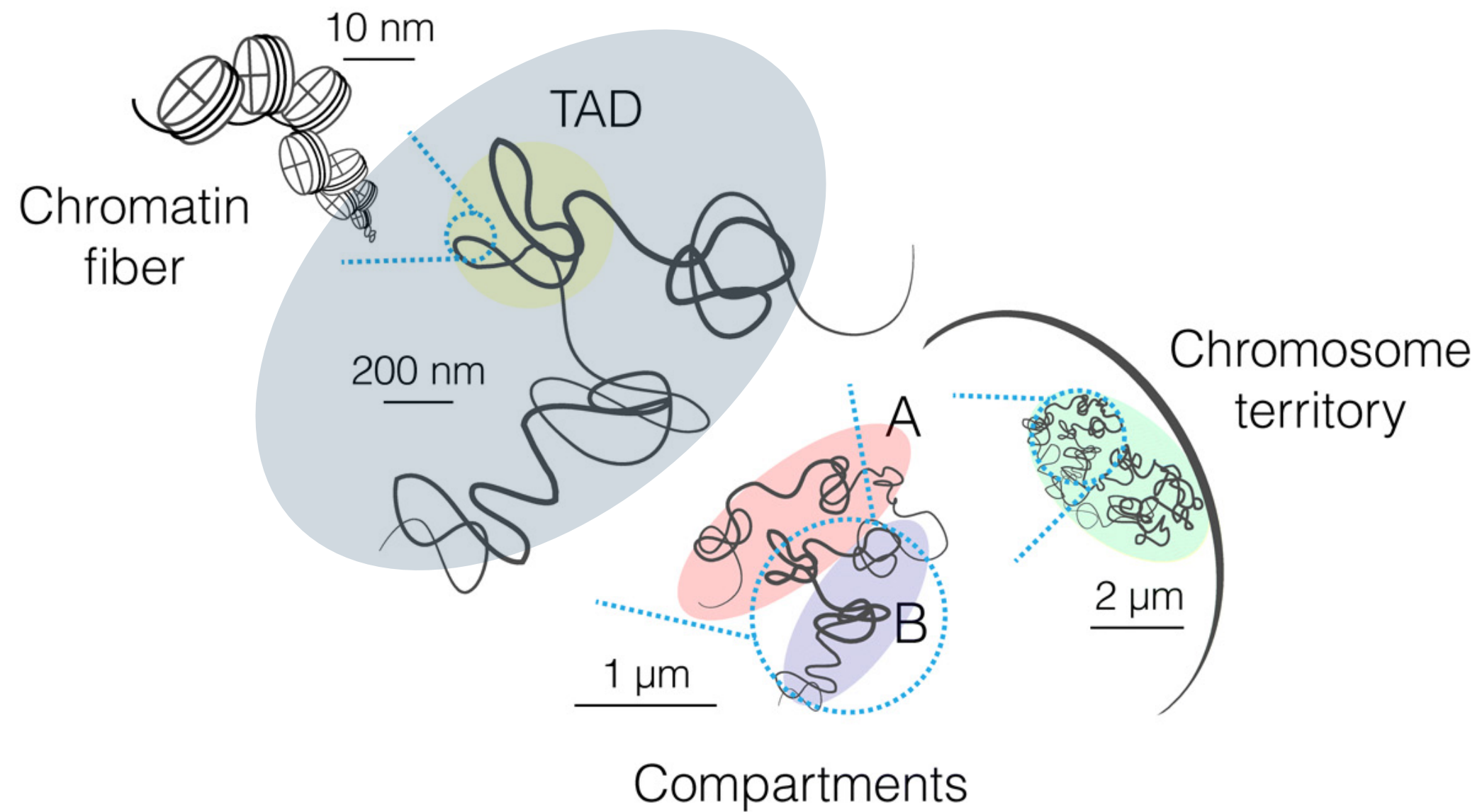
PoLS - Trieste 06/06/2024

Loucif Remini

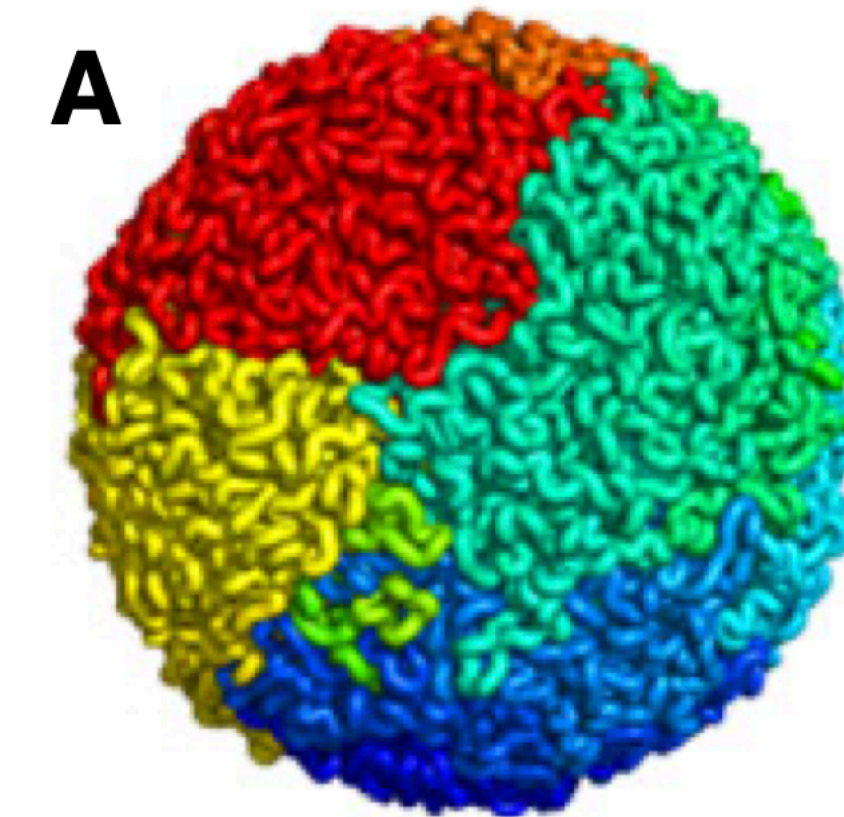
Complex Systems and Nonlinear Phenomena
Laboratoire Charles Coulomb - Montpellier



Introduction: Multi-scale organization

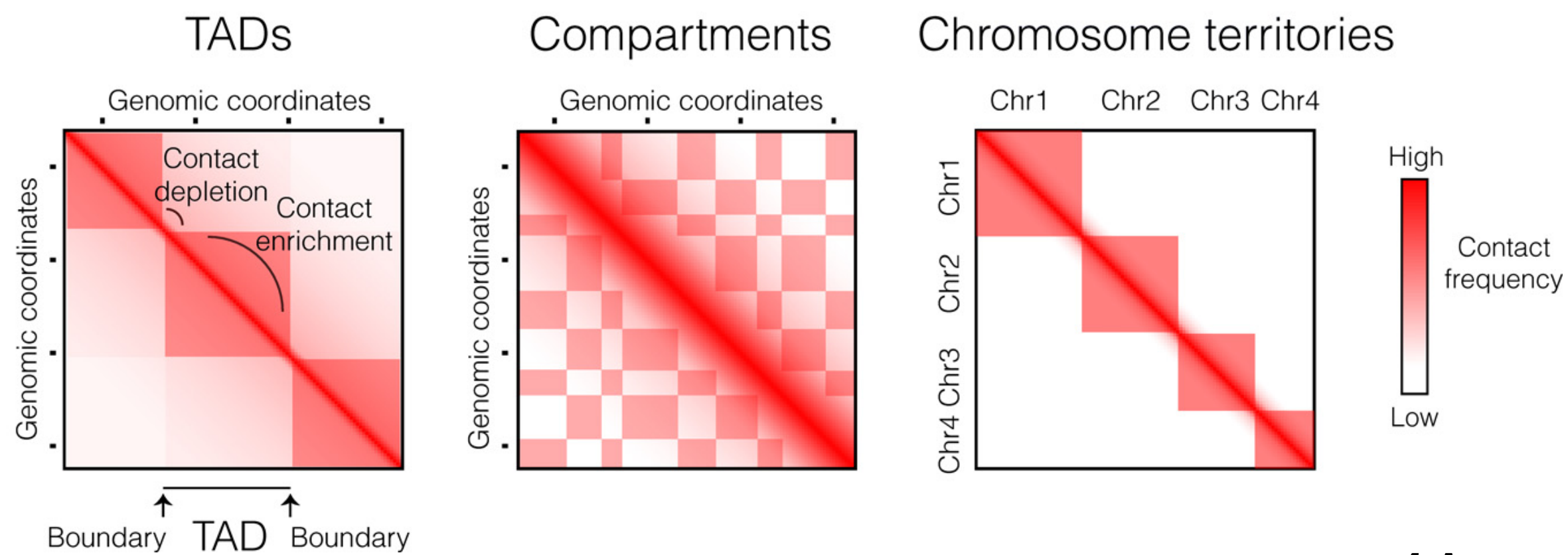


Fractal globule (*)



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

[3]

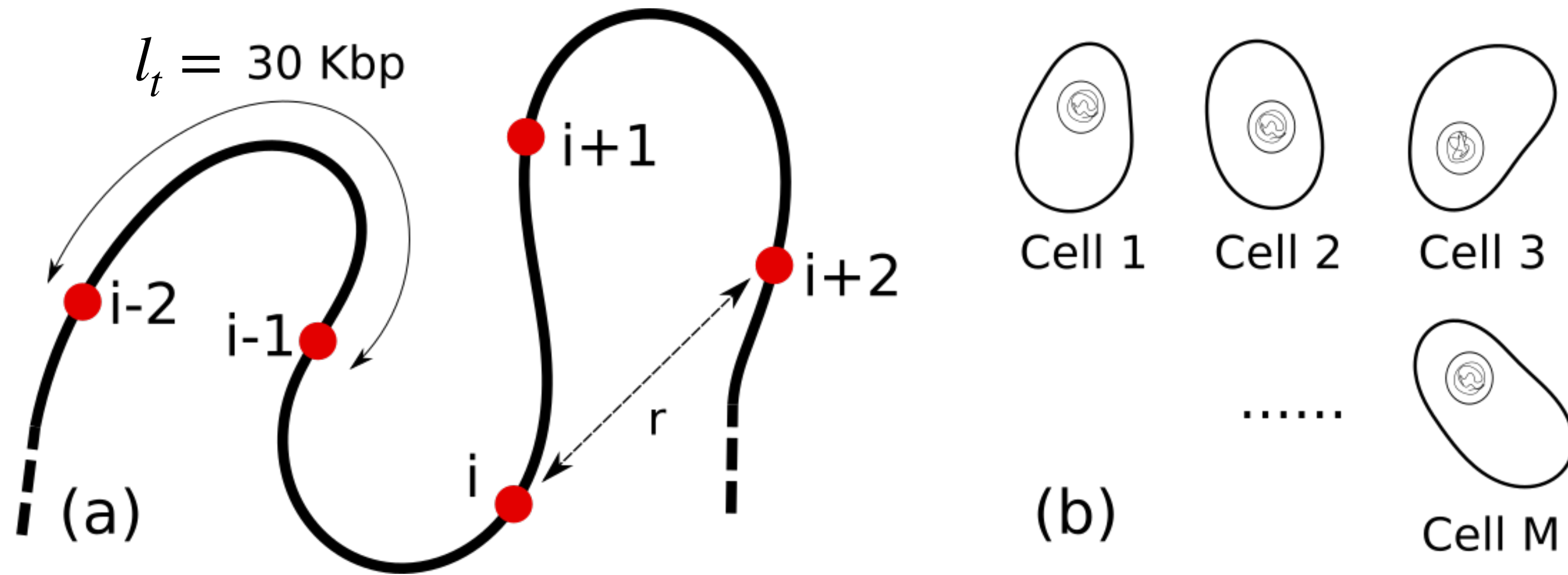


[1]

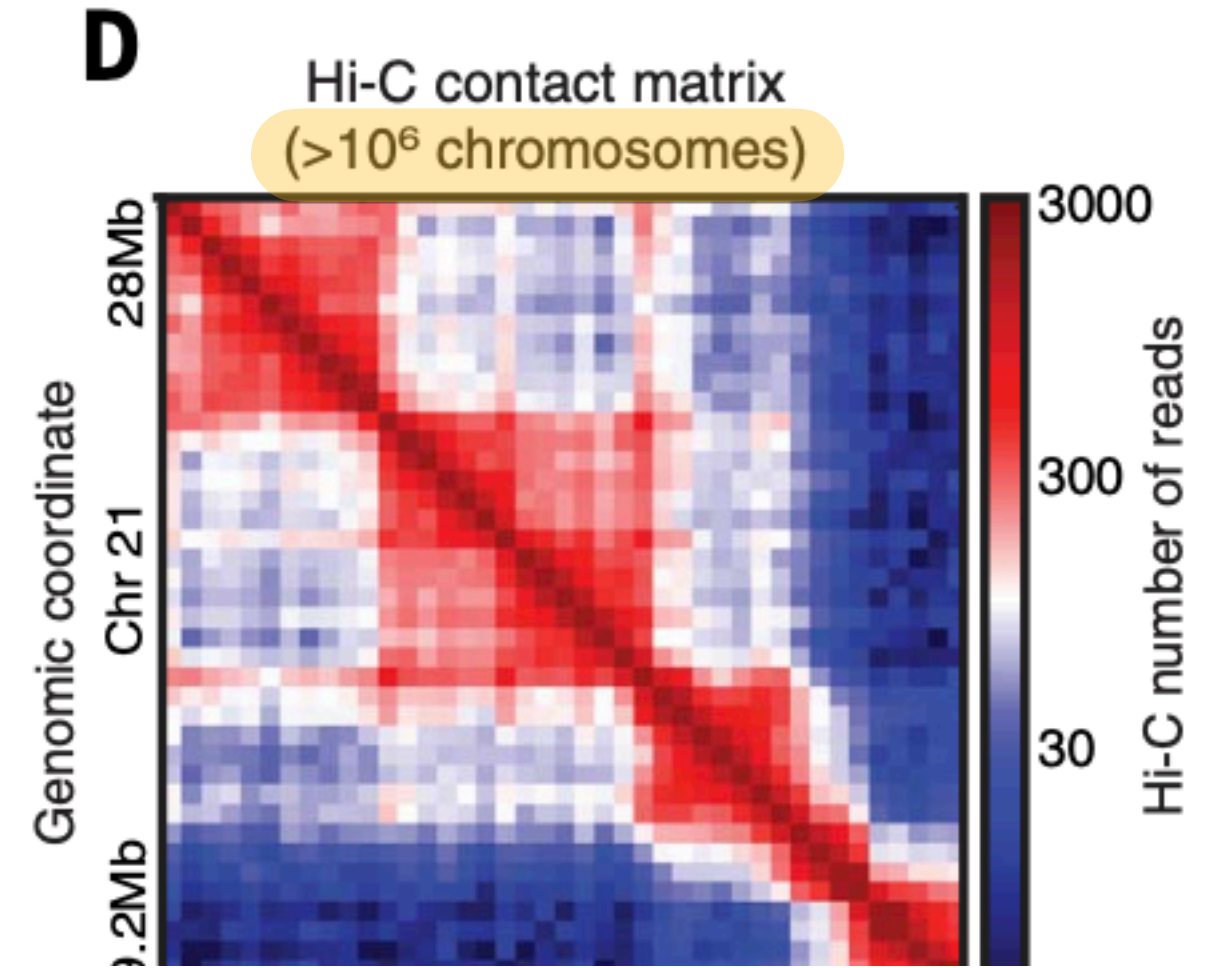
[1] Szabo et al 2019
 [2] Adapté de Bonev et al 2019
 [3] Mirny 2011

* : Proposed for DNA modeling by Grosberg et al. in 1988 and observed in experiments in 2009

Experimental tools: multiplexed-FISH*



Hi-C

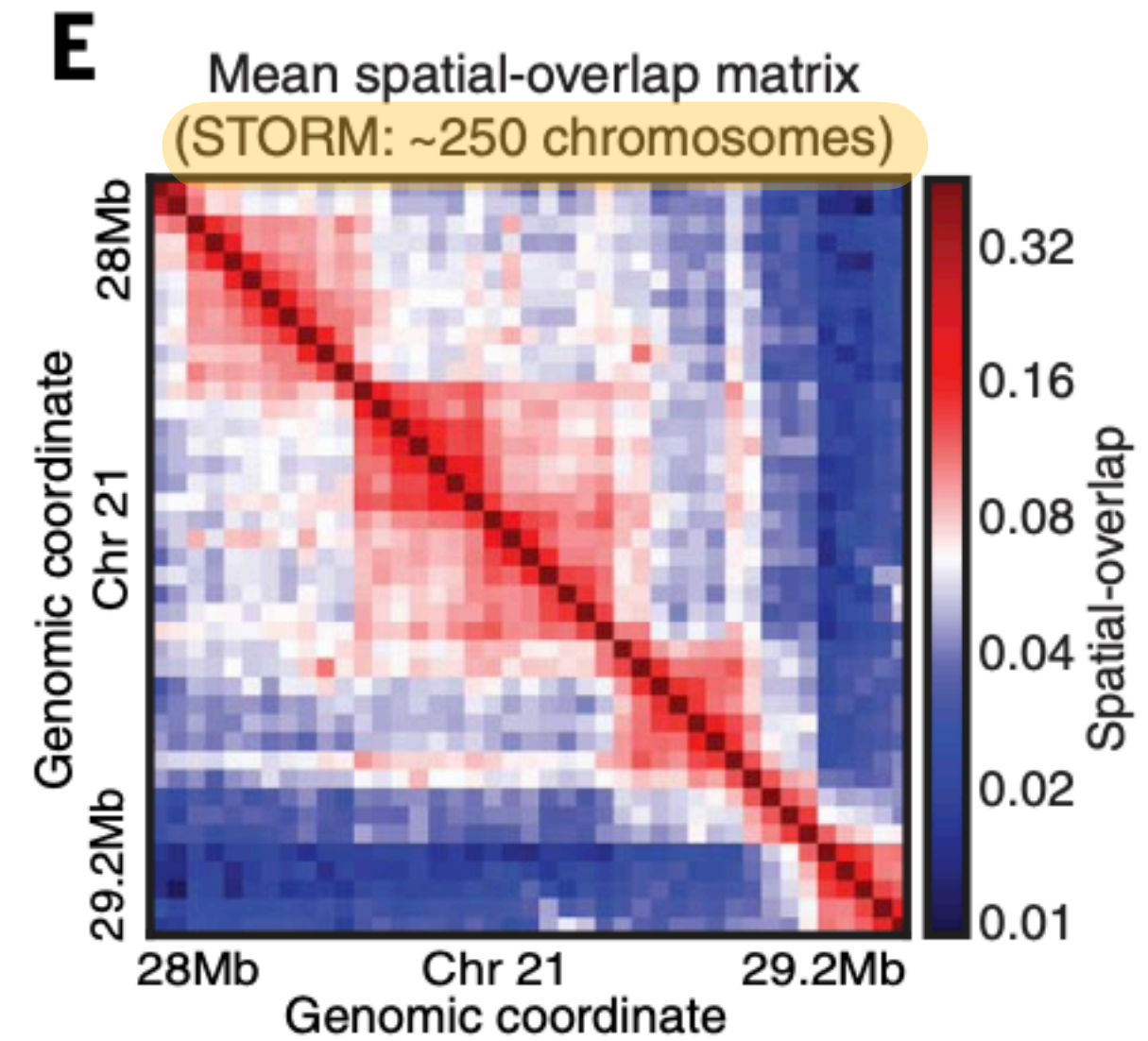


Artificial coloring

Single cell distance matrices

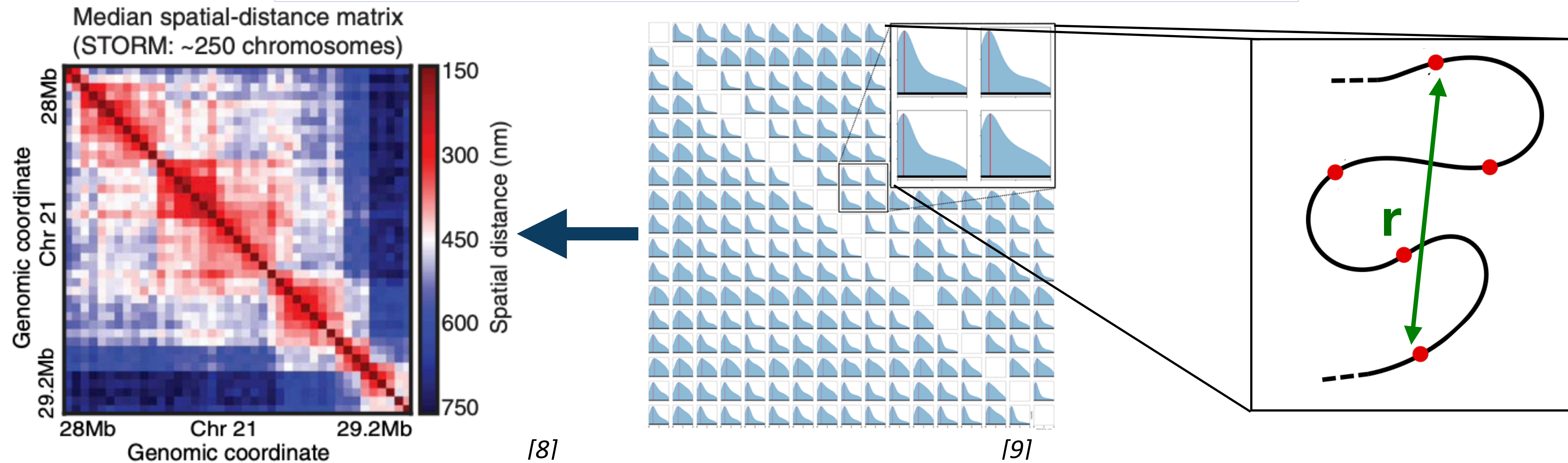
Population-averaged distance matrix (4,500 chromosomes)

mFISH



[8]

mFISH raw data encapsulate rich informations



- Each pixel from the contact/distance map hides a pairwise distance distribution.
- The value attributed to a pixel only reflects one information (mean, median or maximum value)

What can we learn from these distributions about the chromatin 3D organization?

$$P_{ij}(r) = f_{\alpha} g(r; R_{\alpha}) + (1 - f_{\alpha}) g(r; R_{\beta})$$

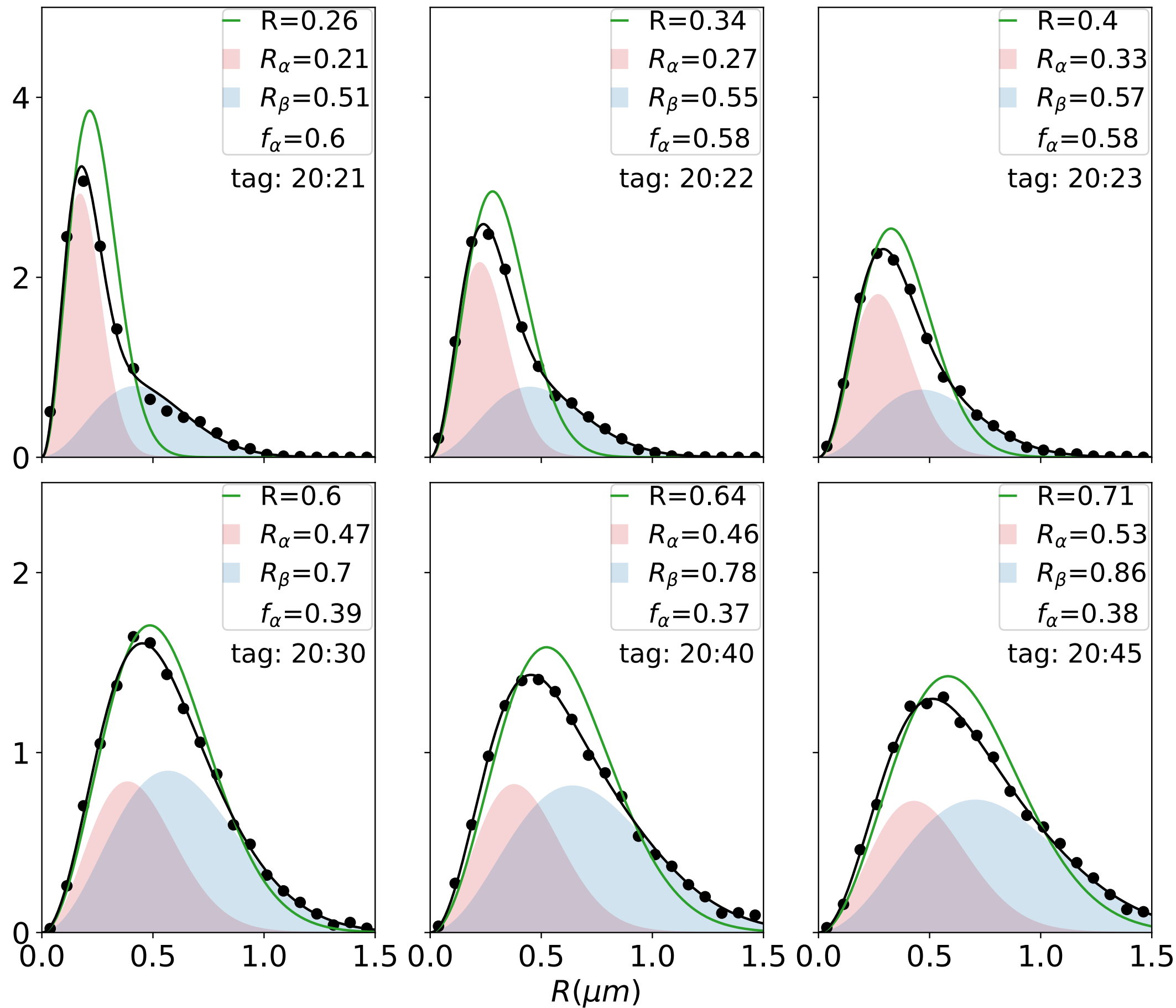
With: $R_{\alpha} < R_{\beta}$

Fraction of samples in the α phase

The gaussian distribution of the α phase

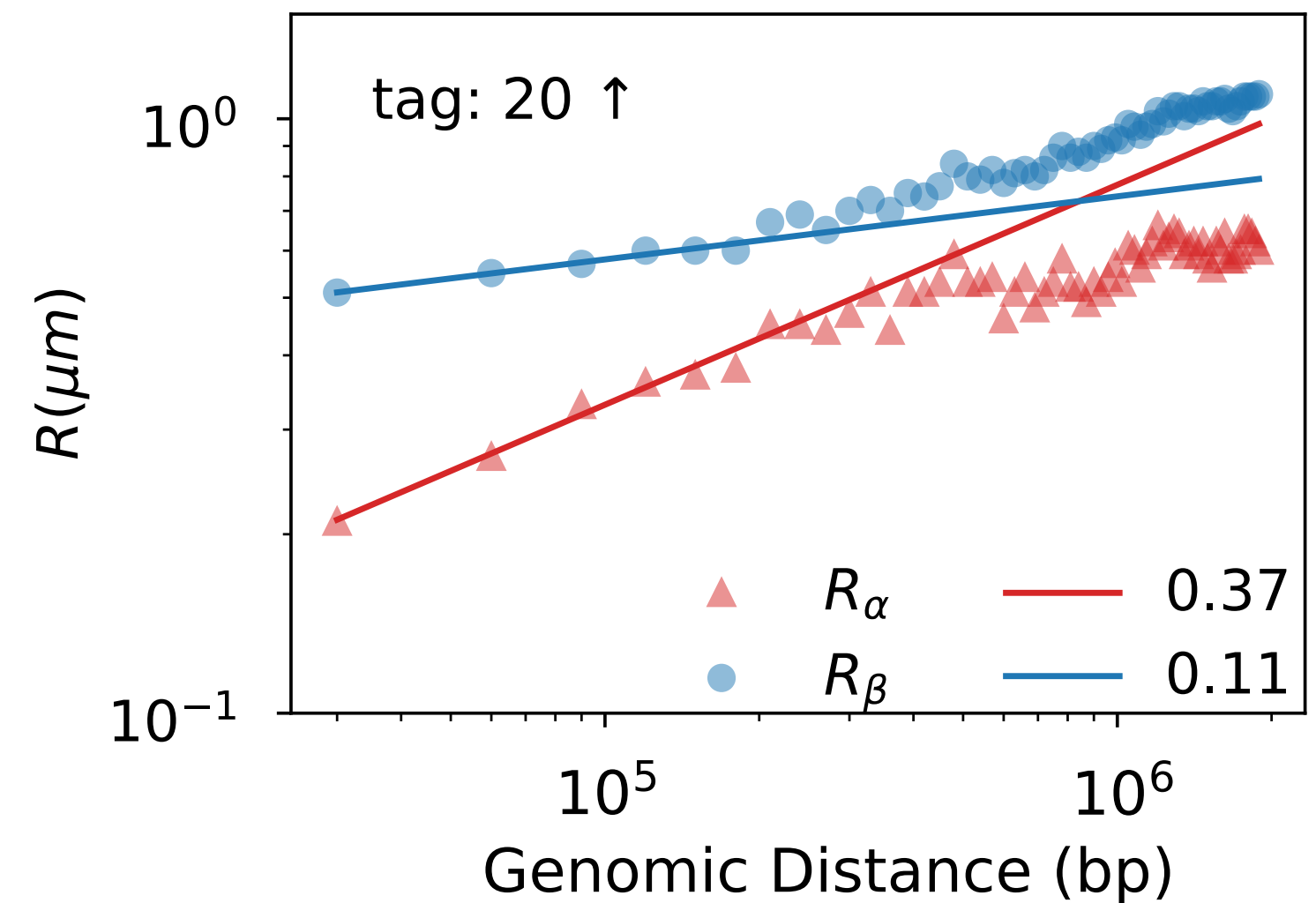
The gaussian distribution of the β phase

Polymer phase coexistence and scaling behavior



We characterize the scaling behavior ν_α and ν_β of the radii fitting R_α and R_β

$$R_x \sim |i - j|^{\nu_x}$$



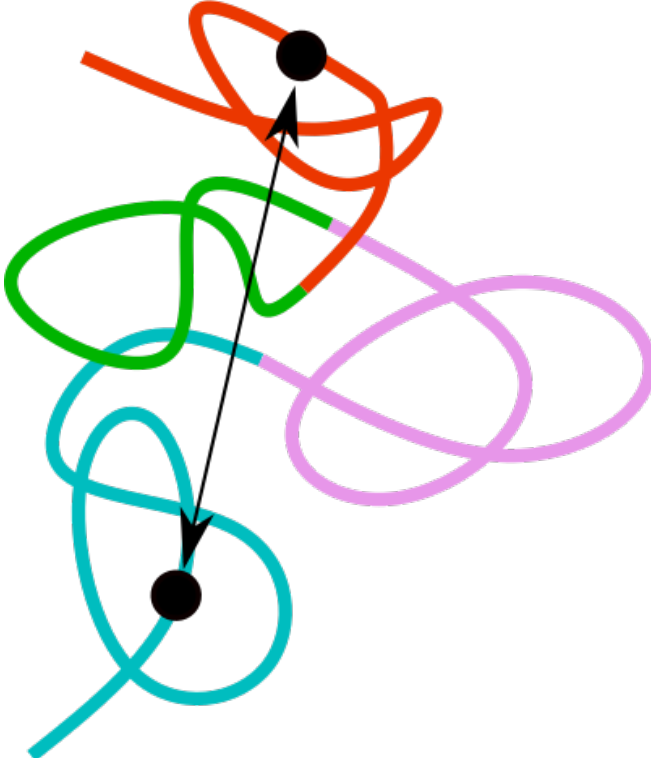
- Experimental histogram
- Gaussian distribution
- Two phases distribution
- α phase contribution
- β phase contribution

[10]

Micro-phase coexistence

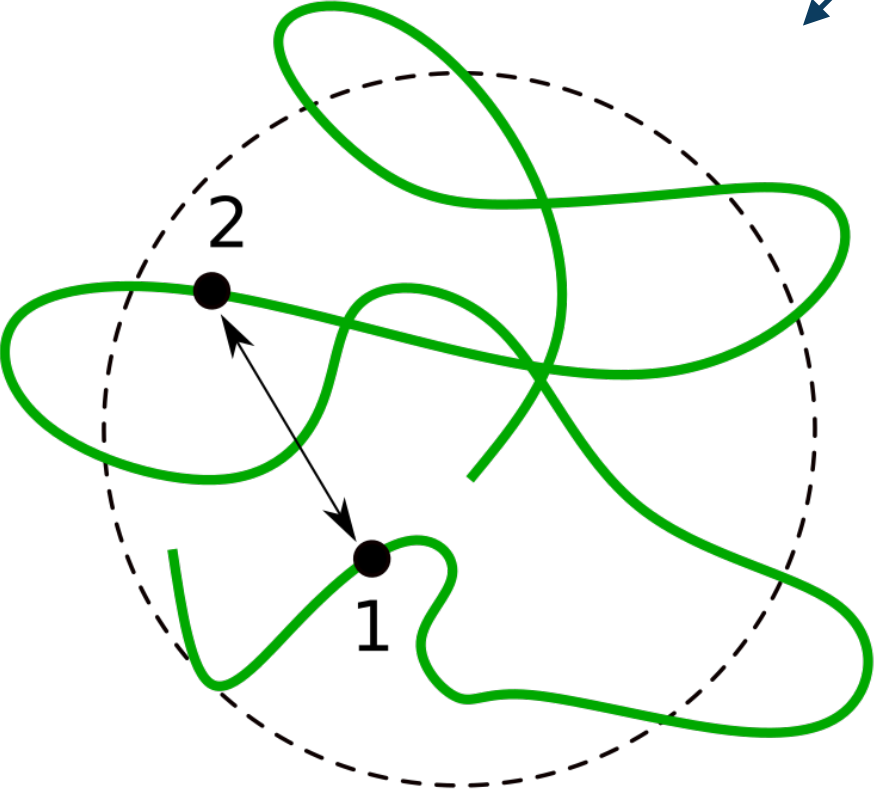
By averaging on all tags, i.e. $|i - j| \leq 6 (\equiv 180 \text{ kb})$

$$\langle \nu_\alpha \rangle \approx 1/3$$

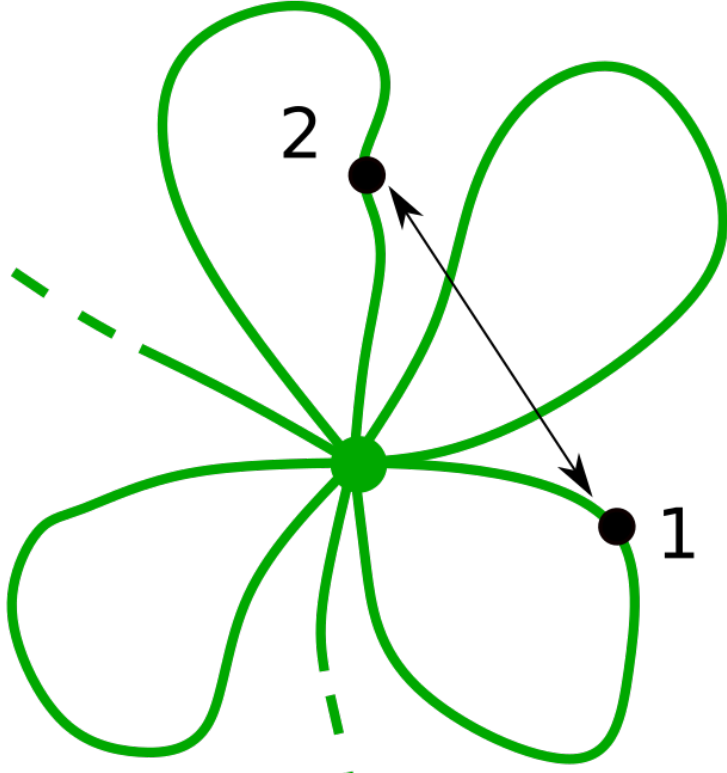


Crumpled globule model

$$\langle \nu_\beta \rangle \ll 1/3$$



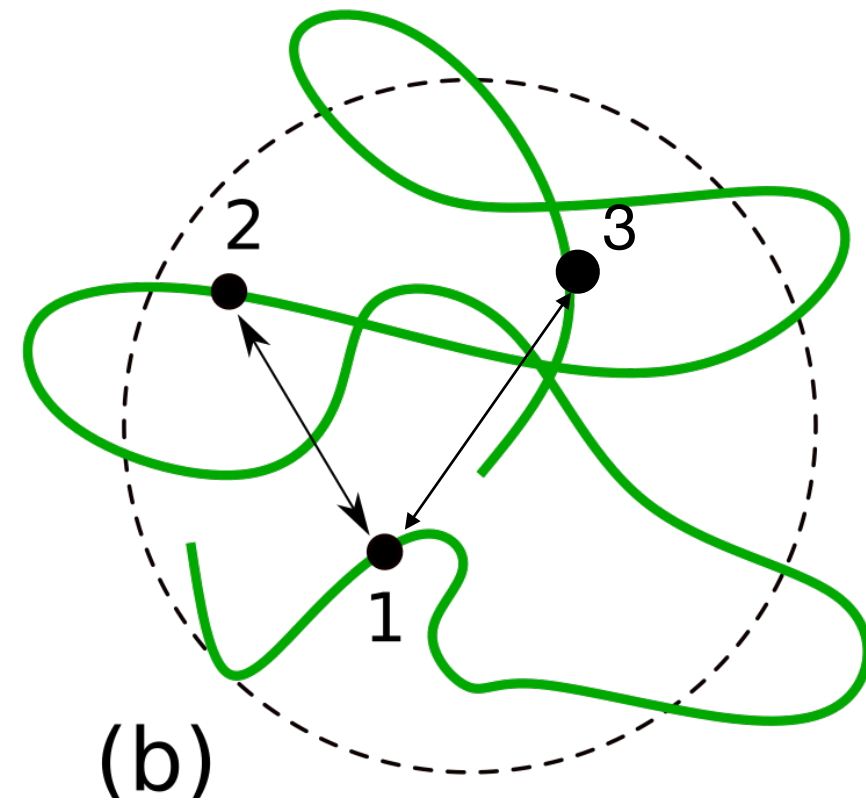
Droplet-like potential



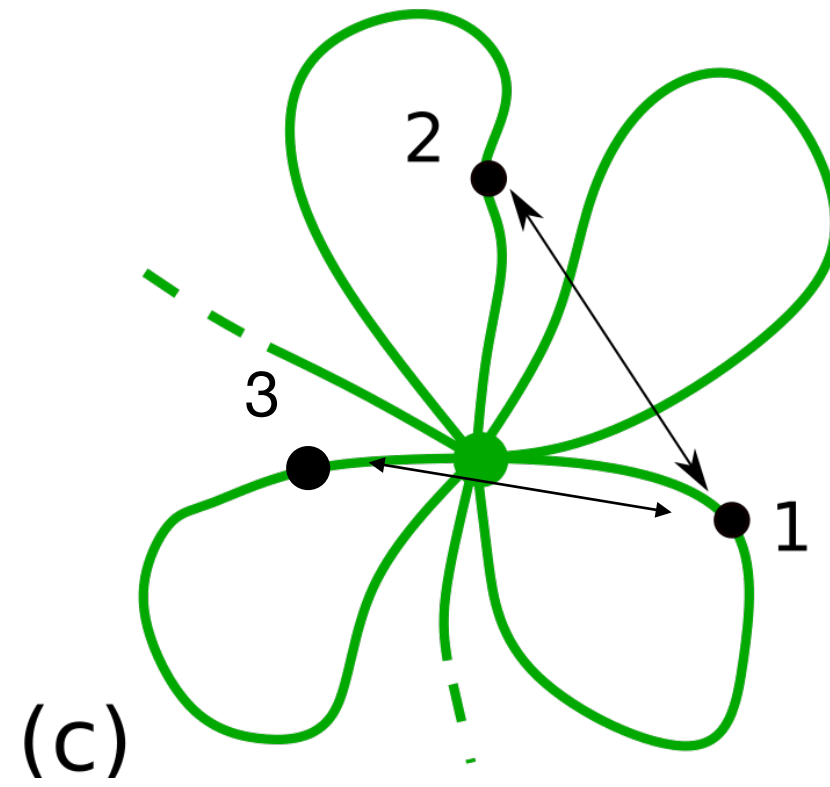
Flower shaped polymer

[10]

Micro-phase coexistence



(b) Droplet-like potential



(c) Flower shaped polymer

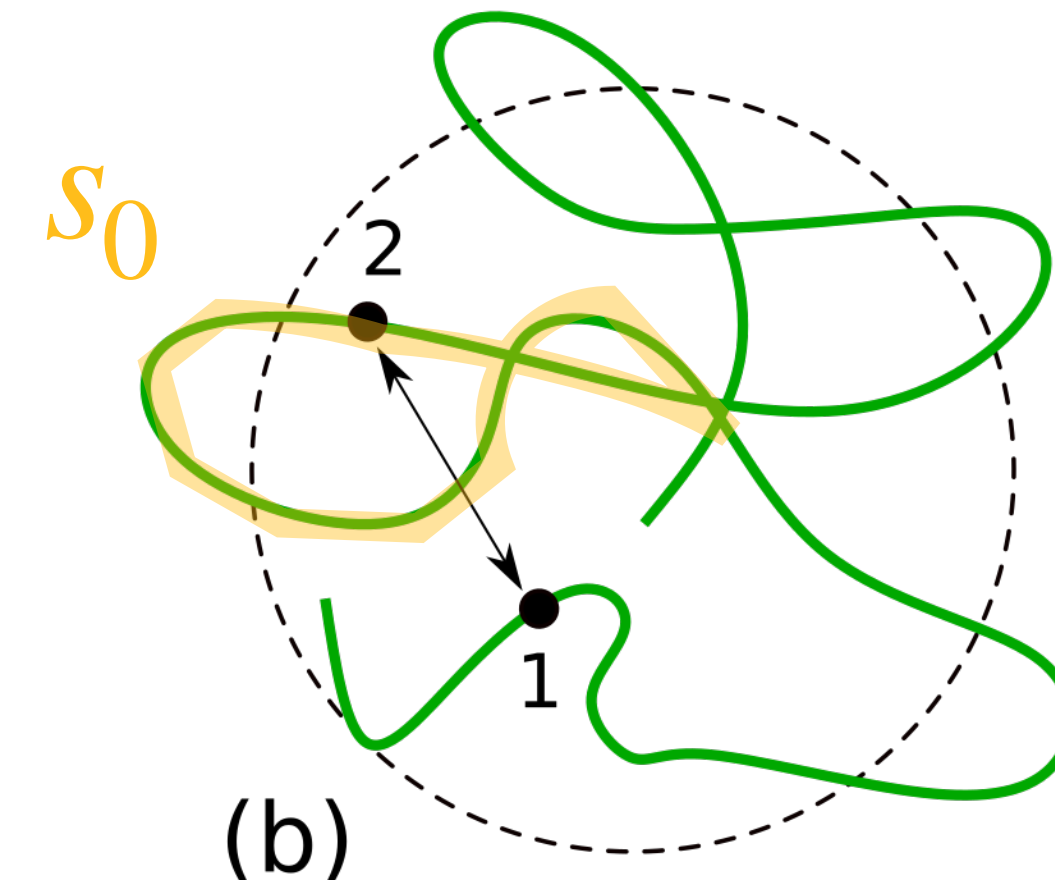
$$R_{\beta}(s) \sim s_0 \quad \text{if } s > s_0$$

where s_0 is dependent on the typical genomic length needed by the polymer to reach the **droplet surface** and bounce back to the origin in (b) or the typical **loop** genomic size in (c).

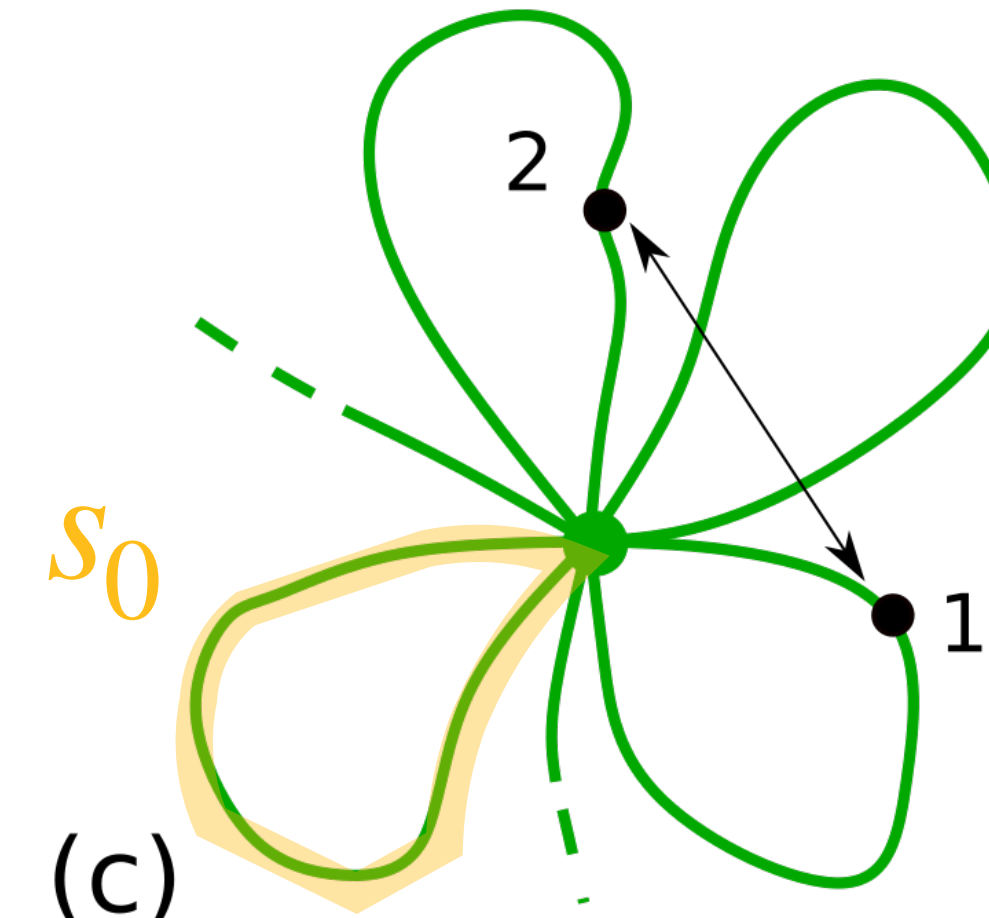
Experimental data show no “ideal” confinement ($\nu = 0$) although very small $\nu_{\beta} \approx 0.1$.

The genomic distance between neighboring tags is constant:

$$s_{1,3} = 2 \times s_{1,2}$$



(b)



(c)

[10]

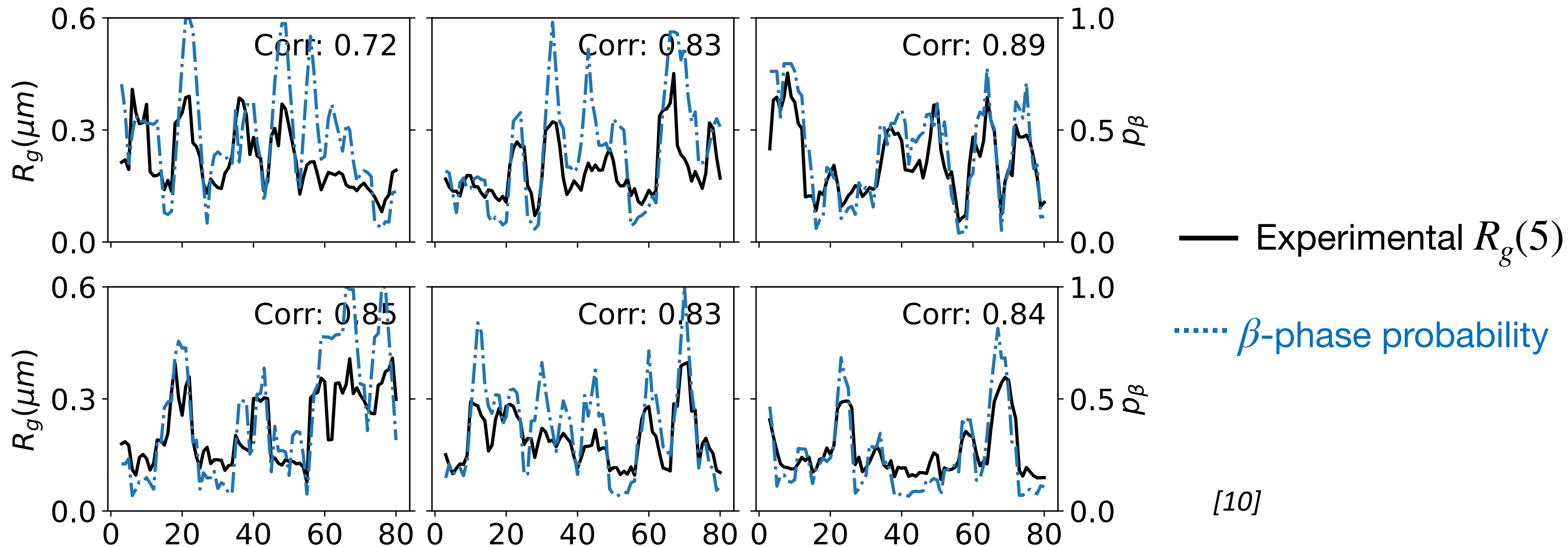
Prediction of single cells 3D organization

The β phase probability at tag i for a given cell

The β phase contribution to a given single cell organization

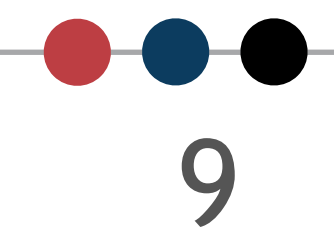
$$p_{\beta}(i) = \frac{(1 - f_{\alpha})g(r; R_{\beta})}{\langle P_{i,i+1}(r) \rangle_i}$$

Average distribution of first neighbors pairwise distances



[10]

High probability β regions inferred from the micro-phases coexistence model co-localize with direct measurements of the sliding radius of gyration in single cells with a high correlation score



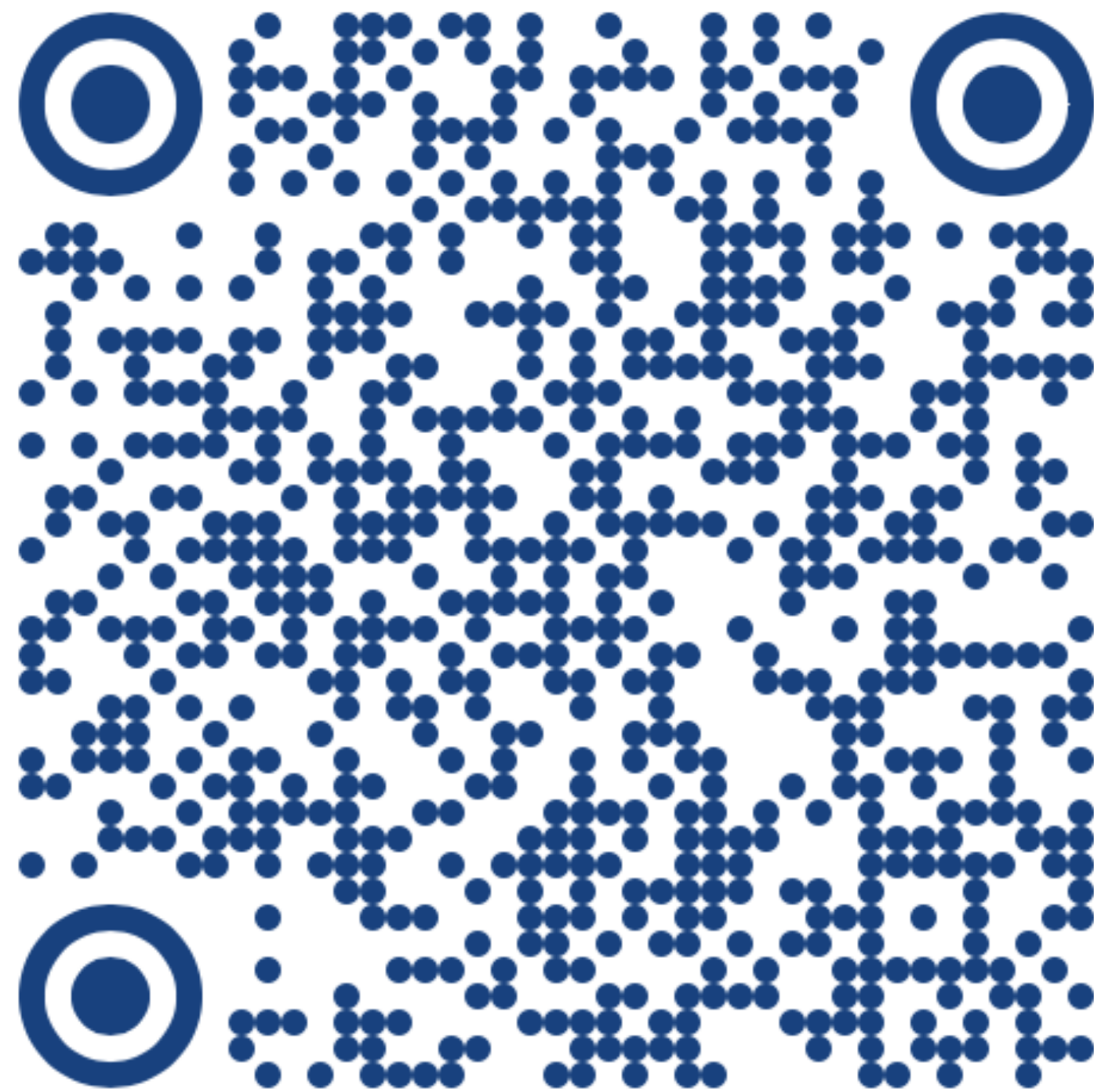
Conclusion

- Multiplexed-FISH distance maps encapsulate under-exploited informations
- Pairwise distances distribution analysis reveals at least two coexisting micro-phases
 - A **compact α phase** characterized by a **fractal globule** scaling behavior
 - A **less-compact β phase** characterized by a strong confinement at long range ($\nu_\beta \approx 0.1$)
- We propose two models; a **polymer under a droplet-like confinement** and a **Rosette polymer** to explain the β phase scaling
- We studied cell-to-cell variability and confronted the micro-phase coexistence model's predictions to a measured local quantity (R_g)

Thanks for your attention!

Learn more about how this method can be used to study:

- Phase coexistence in various cell types
- Chromatin structure in single cells



Now in Physical Review E

L2C - SCPN

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Soft matter physics

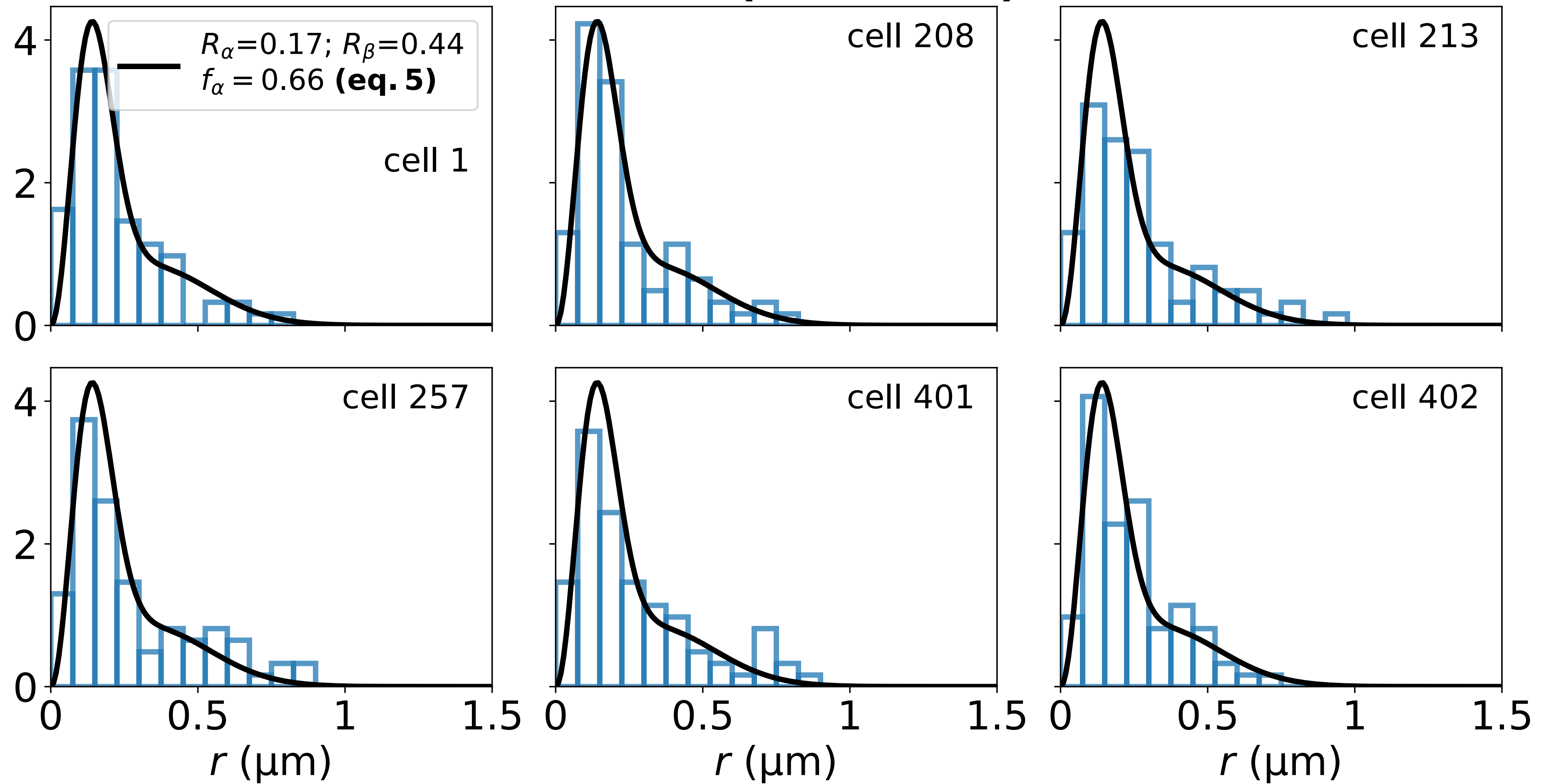
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Midas Segers

KU LEUVEN

Cell-to-cell variability

HCT116 (untreated)



— $\langle P_{i,i+1}(r) \rangle_i$

□ Experimental single cell distribution



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