Polymer Physics & Chromosomes

Angelo Rosa

Milan, July 2017

My (humble) notes on Polymer Physics:

http://sites.google.com/site/angelosissa/lecture-notes-on-polymer-physics

Outline

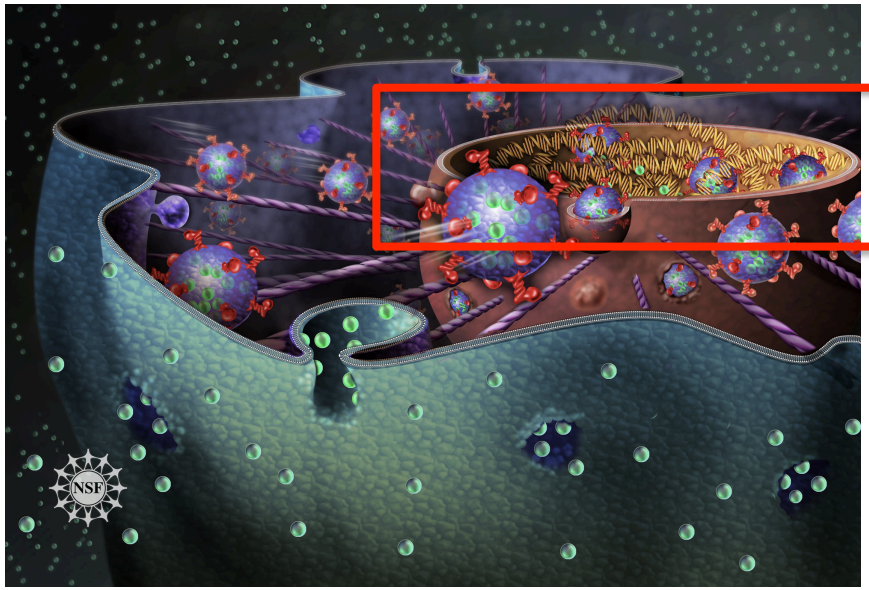
- The problem of chromosome folding
  - Generic features
  - Why is it important at all?
- Polymer Physics 1: Structure
- Polymer models for chromosome folding: a “quasi” historical perspective
- Polymer Physics 2: Dynamics
- Simulation methods: Monte Carlo & Molecular Dynamics

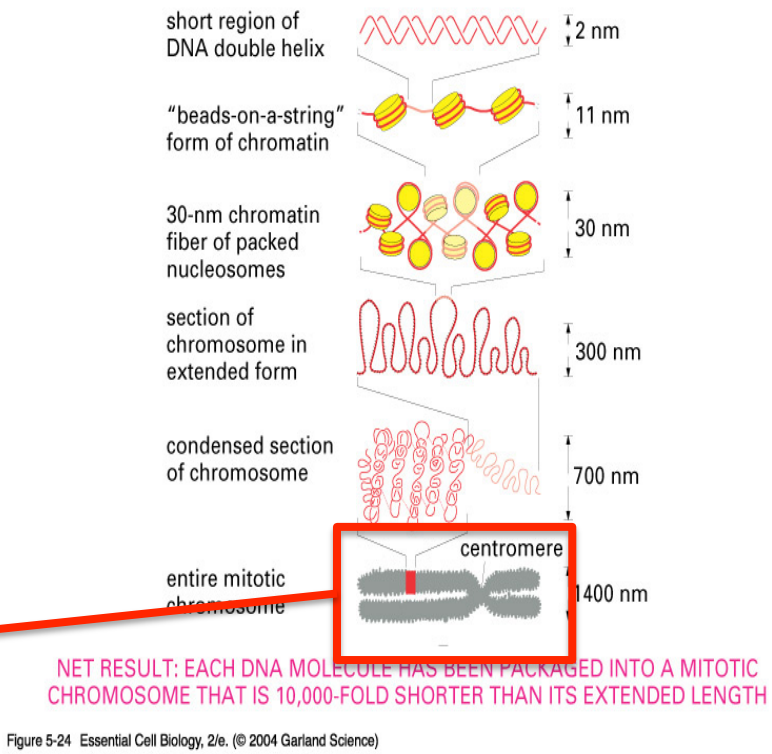
The problem of chromosome folding

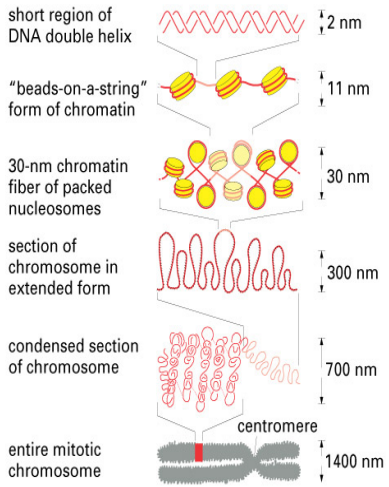
Human genome, 46 chromosomes

Each chr ~1cm of DNA ~1mm 30nm-fiber

Inside the nucleus (~10μm of diameter)
of the typical mammalian cell

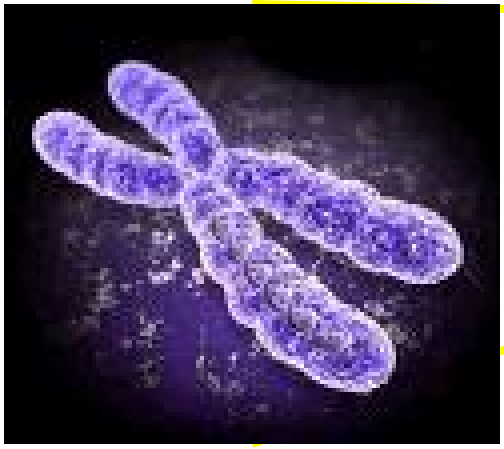


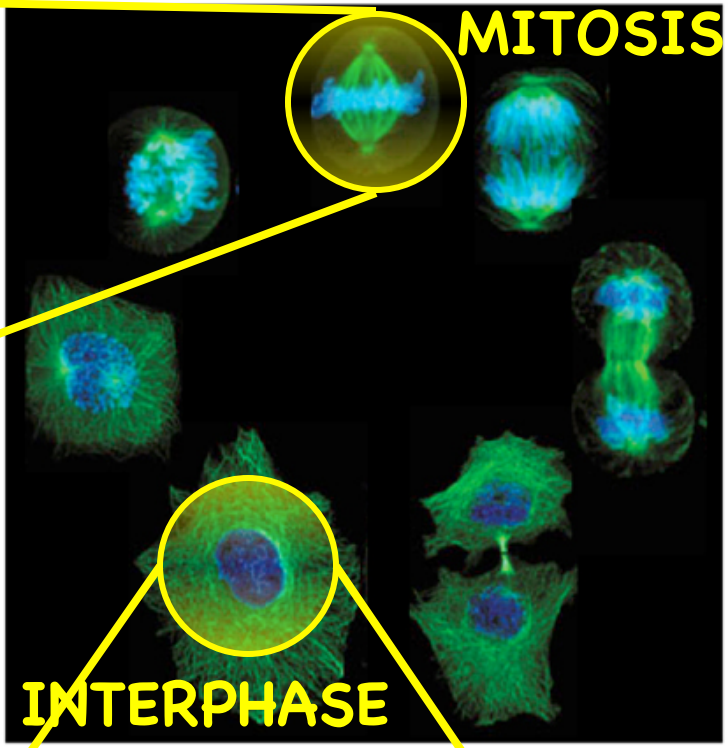




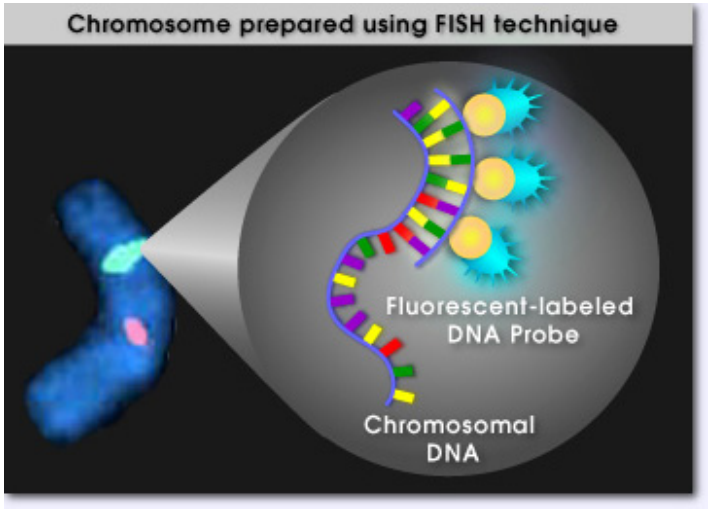
NET RESULT: EACH DNA MOLECULE HAS BEEN PACKAGED INTO A MITOTIC CHROMOSOME THAT IS 10,000-FOLD SHORTER THAN ITS EXTENDED LENGTH

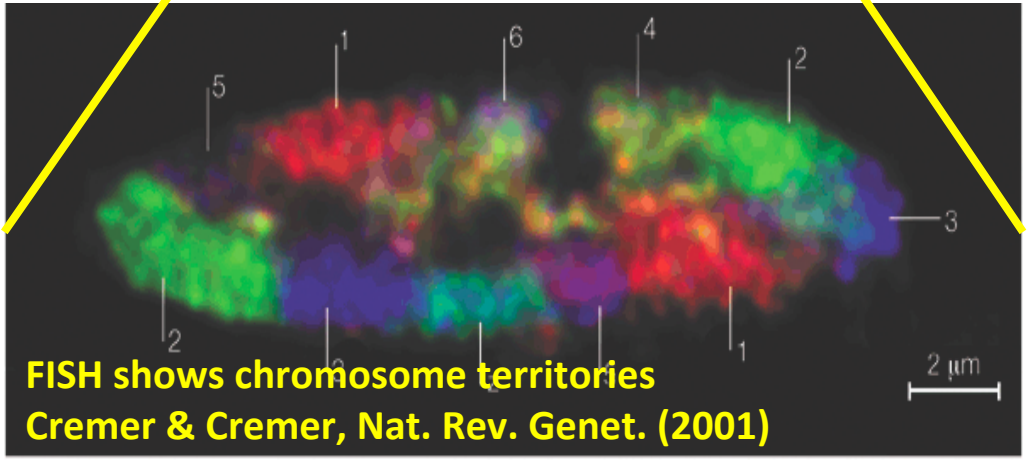
Figure 5-24 Essential Cell Biology, 2/e. (© 2004 Garland Science)





Fluorescence in-situ Hybridization (FISH)

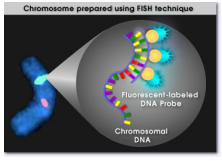


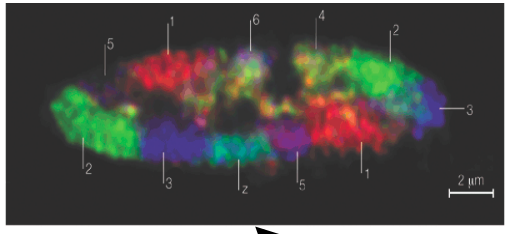


FISH shows chromosome territories
Cremer & Cremer, Nat. Rev. Genet. (2001)

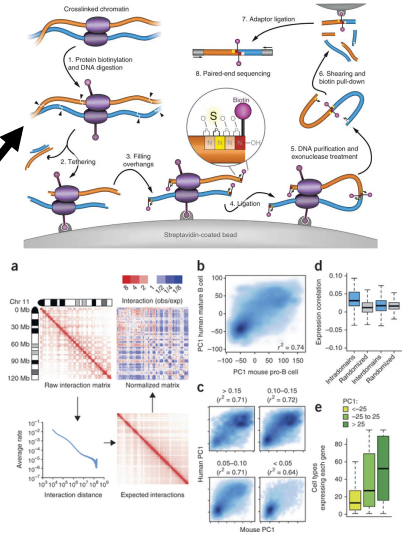
Experimental techniques reveal interesting features of eukaryotic genomes

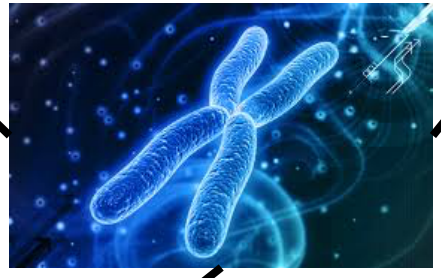
Fluorescence in-situ Hybridization (FISH)
Cremer & Cremer, Nat. Rev. Genet. (2001)



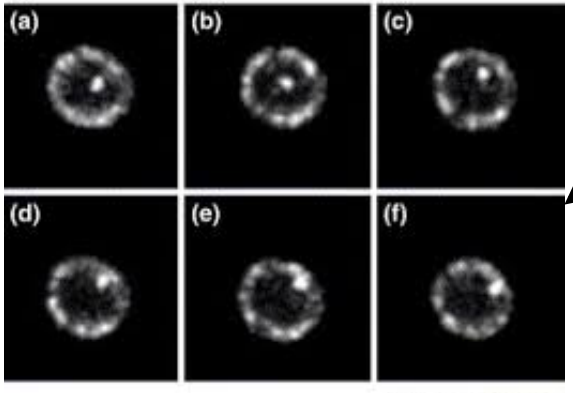


3C, HiC
Dekker and coworkers (2003, 2009)

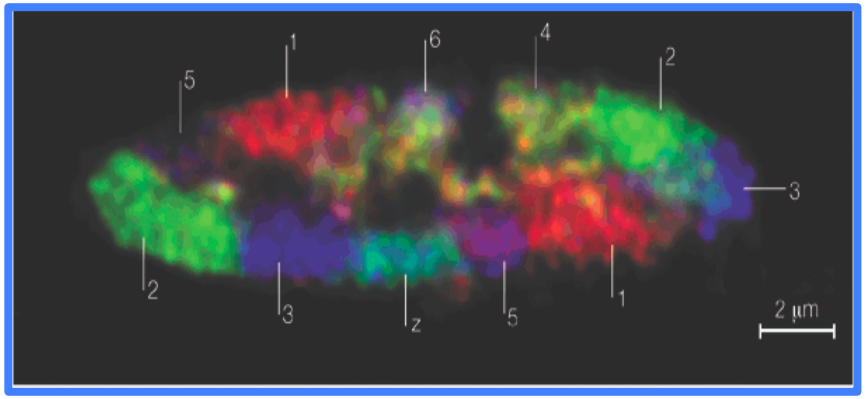




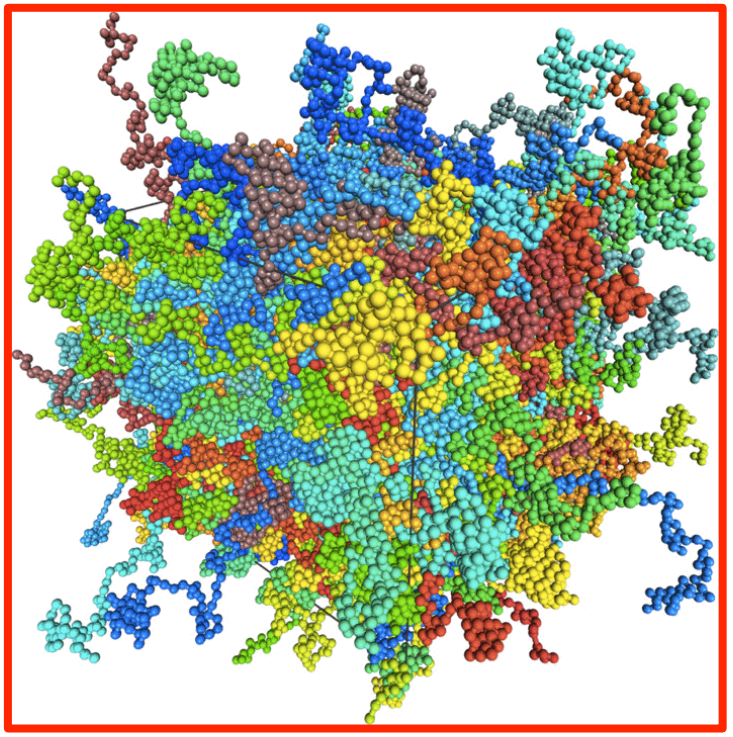
Chromatin dynamics by GFP
Belmont, Trends Cell Biol. (2001)



Differences between a **chromosome melt** and an ordinary **polymer melt**



vs.



Q: May chromosomes inspire new Physics?

Relationship between chromosome structure & function

Open access, freely available online PLoS BIOLOGY

Three-Dimensional Maps of All Chromosomes in Human Male Fibroblast Nuclei and Prometaphase Rosettes

Andreas Bolzer[1¤], Gregor Kreth[2], Irina Solovei[1], Daniela Koehler[1], Kaan Saracoglu[3], Christine Fauth[4,5], Stefan Müller[1], Roland Eils[3], Christoph Cremer[2], Michael R. Speicher[4,5], Thomas Cremer[1*]

1 Department of Biology II, Anthropology and Human Genetics, Ludwig Maximilians University, Munich, Germany, 2 Kirchhoff Institute of Physics, University of Heidelberg, Heidelberg, Germany, 3 Theoretical Bioinformatics, German Cancer Research Center (DKFZ), Heidelberg, Germany, 4 Institute of Human Genetics, Technical University Munich, Germany, 5 Institute of Human Genetics, GSF National Research Center for Environment and Health, Neuherberg, Germany

Studies of higher-order chromatin arrangements are an essential part of ongoing attempts to explore changes in epigenome structure and their functional implications during development and cell differentiation. However, the extent and cell-type-specificity of three-dimensional (3D) chromosome arrangements has remained controversial. In order to overcome technical limitations of previous studies, we have developed tools that allow the quantitative 3D positional mapping of all chromosomes simultaneously. We present unequivocal evidence for a probabilistic 3D order of prometaphase chromosomes, as well as of chromosome territories (CTs) in nuclei of quiescent (G0) and cycling (early S-phase) human diploid fibroblasts (46, XY). Radial distance measurements showed a probabilistic, highly nonrandom correlation with chromosome size: small chromosomes—independently of their gene density—were distributed significantly closer to the center of the nucleus or prometaphase rosette, while large chromosomes were located closer to the nuclear or rosette rim. This arrangement was independently confirmed in both human fibroblast and amniotic fluid cell nuclei. Notably, these cell types exhibit flat-ellipsoidal cell nuclei, in contrast to the spherical nuclei of lymphocytes and several other human cell types, for which we and others previously demonstrated gene-density-correlated radial 3D CT arrangements. Modeling of 3D CT arrangements suggests that cell-type-specific differences in radial CT arrangements are not solely due to geometrical constraints that result from nuclear shape differences. We also found gene-density-correlated arrangements of higher-order chromatin shared by all human cell types studied so far. Chromatin domains, which are gene-poor, form a layer beneath the nuclear envelope, while gene-dense chromatin is enriched in the nuclear interior. We discuss the possible functional implications of this finding.

Citation: Bolzer A, Kreth G, Solovei I, Koehler D, Saracoglu K, et al. (2005) Three-dimensional maps of all chromosomes in human male fibroblast nuclei and prometaphase rosettes. PLoS Biol 3(5): e157.

Nuclear Architecture of Rod Photoreceptor Cells Adapts to Vision in Mammalian Evolution

Irina Solovei,[1] Moritz Kreysing,[2] Christian Lanctôt,[1,5] Süleyman Kösem,[1] Leo Peichl,[3] Thomas Cremer,[1,4] Jochen Guck,[2,*] and Boris Joffe[1,*]

SUMMARY

We show that the nuclear architecture of rod photoreceptor cells differs fundamentally in nocturnal and diurnal mammals. The rods of diurnal retinas possess the conventional architecture found in nearly all eukaryotic cells, with most heterochromatin situated at the nuclear periphery and euchromatin residing toward the nuclear interior. The rods of nocturnal retinas have a unique inverted pattern, where heterochromatin localizes in the nuclear center, whereas euchromatin, as well as nascent transcripts and splicing machinery, line the nuclear border. The inverted pattern forms by remodeling of the conventional one during terminal differentiation of rods. The inverted rod nuclei act as collecting lenses, and computer simulations indicate that columns of such nuclei channel light efficiently toward the light-sensing rod outer segments. Comparison of the two patterns suggests that the conventional architecture prevails in eukaryotic nuclei because it results in more flexible chromosome arrangements, facilitating positional regulation of nuclear functions.

Cell 137 (2009)

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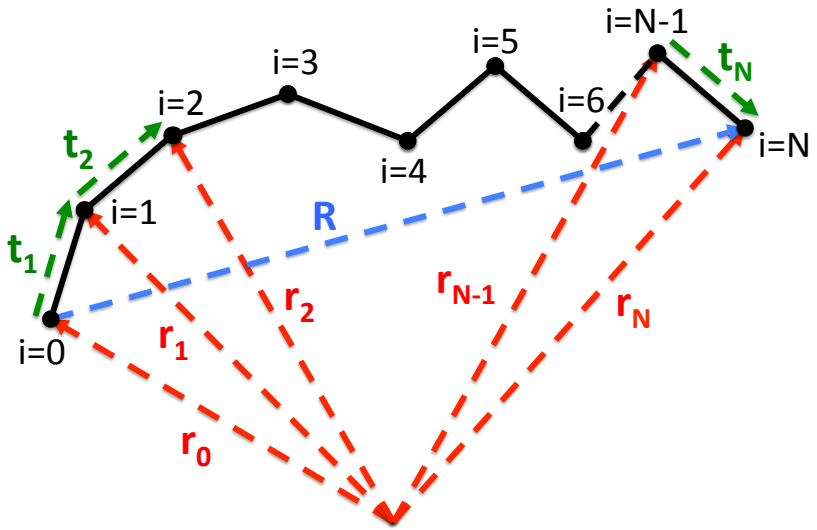
An introduction to Polymer Physics

A



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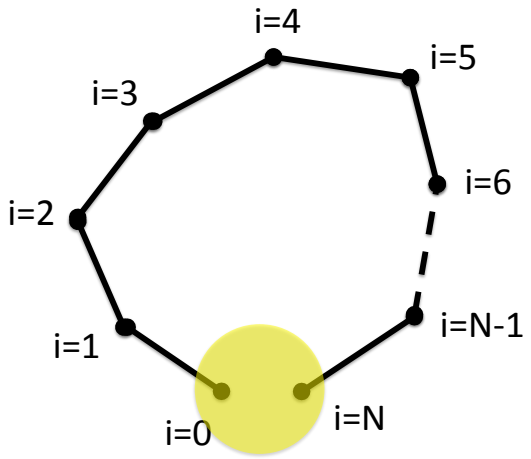

An introduction to Polymer Physics

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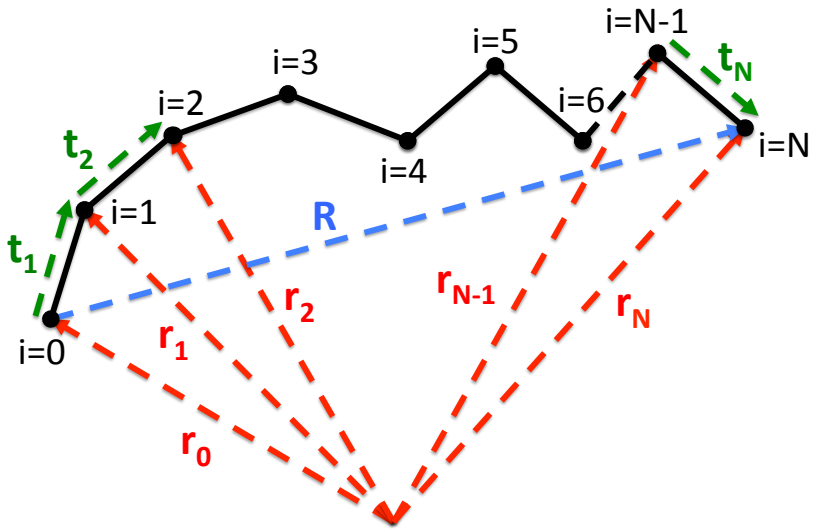

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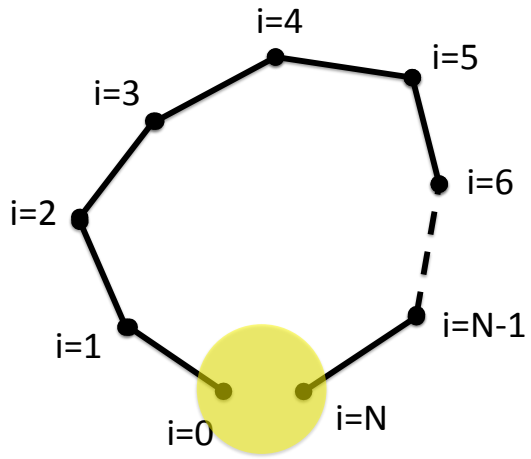

Relevant observables to characterise polymers:

1. Average-square gyration radius:
   $\langle R_g^2 \rangle \equiv \frac{1}{N+1} \left\langle \sum_{i=0}^{N} (\vec{r}_i - \vec{R}_{cm})^2 \right\rangle$, $\vec{R}_{cm} \equiv \frac{1}{N+1} \sum_{i=0}^{N} \vec{r}_i$
2. Average-square end-to-end distance:
   $\langle R_{ee}^2 \rangle \equiv (\vec{r}_N - \vec{r}_0)^2$
3. Average end-to-end contact probability:
   $\langle p_c(N) \rangle$

An introduction to Polymer Physics

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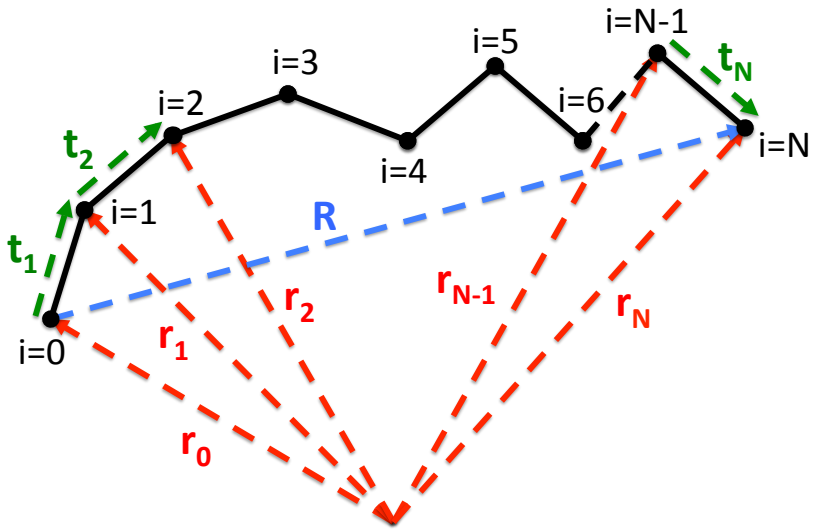

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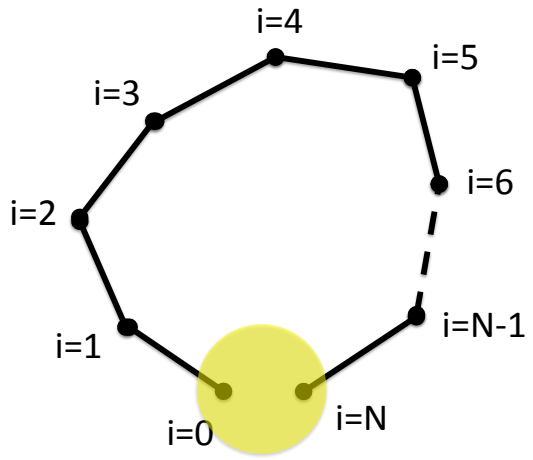


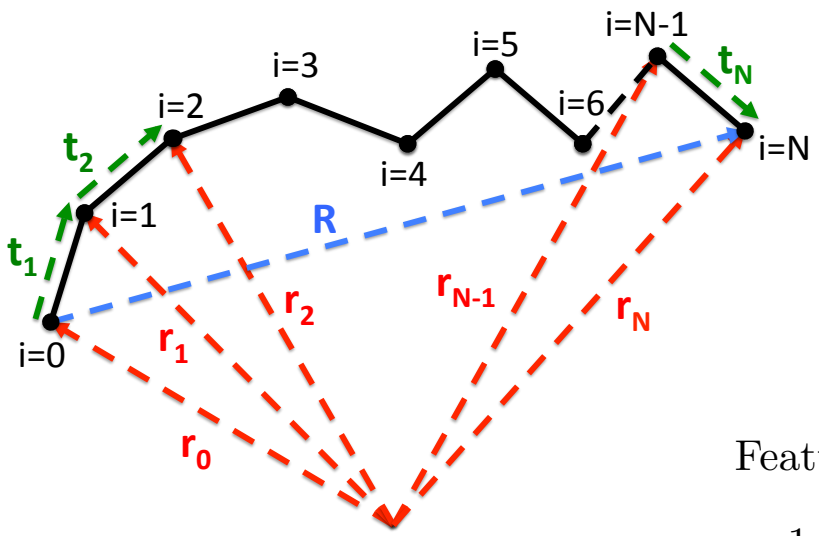
Scaling relationships:

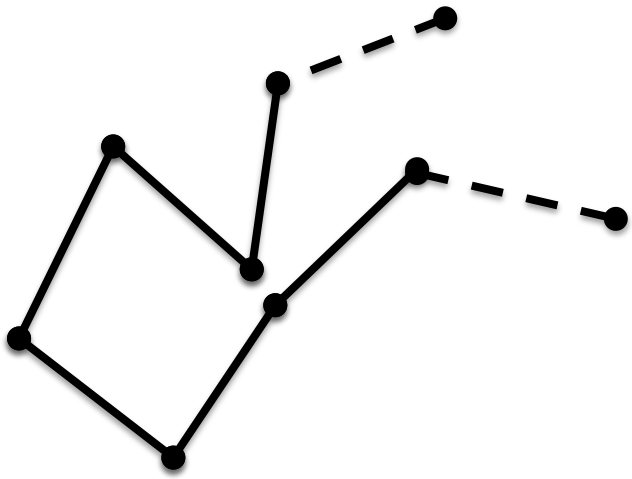
1. $\sqrt{\langle R_{ee}^2 \rangle} \sim \sqrt{\langle R_g^2 \rangle} \sim N^{\nu}$
2. $\langle p_c(N) \rangle \sim N^{-\gamma}$

ν and γ depend on the *universality class* of the chosen polymer model!!

The zero-model: The Gaussian Chain

A





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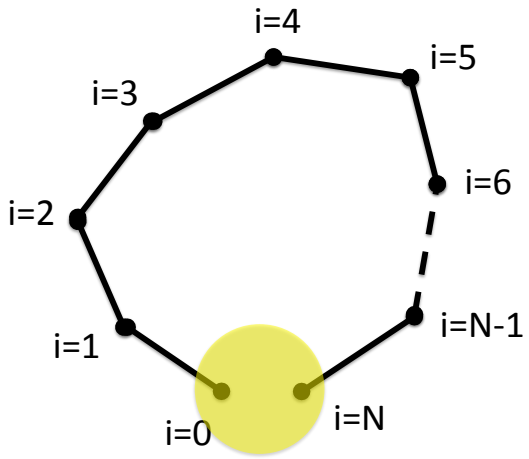

Features:

1. No excluded-volume interactions between monomers;
   Random orientations of the bonds;
   No *sequence* correlations for the bonds.
2. $\sqrt{\langle R_{ee}^2 \rangle} \sim \sqrt{\langle R_g^2 \rangle} \sim bN^{1/2} \rightarrow \nu = 1/2$
3. End-to-end distribution function is Gaussian:
   $p(\vec{R}_{ee} = \vec{R}) = \left(\frac{3}{2\pi N b^2}\right)^{3/2} e^{-\frac{3R^2}{2Nb^2}}$
4. $\langle p_c(N) \rangle \sim p(\vec{R}_{ee} = \vec{R} = 0) \sim N^{-3/2} \rightarrow \gamma = 3/2$

The zero-model: The Gaussian Chain

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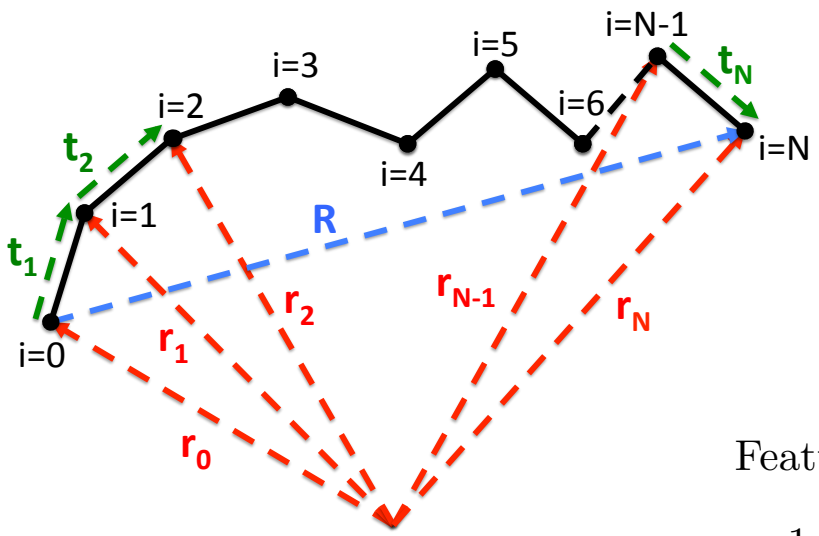

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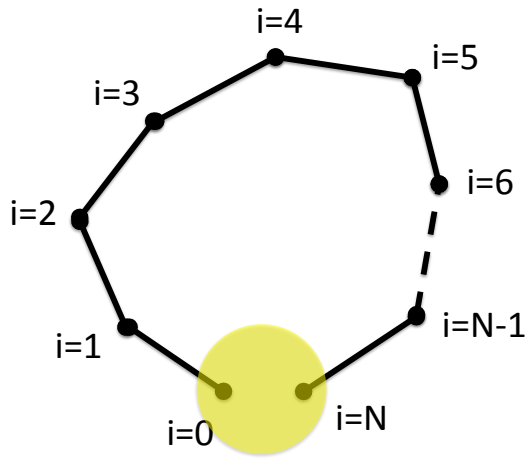

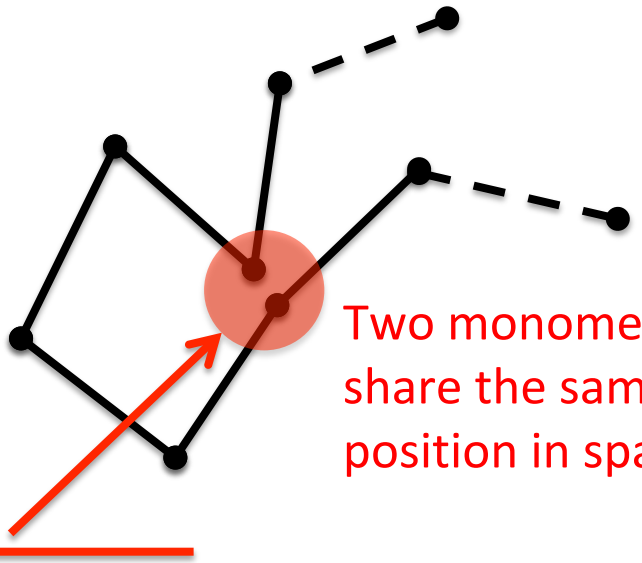

Two monomers can share the same position in space!

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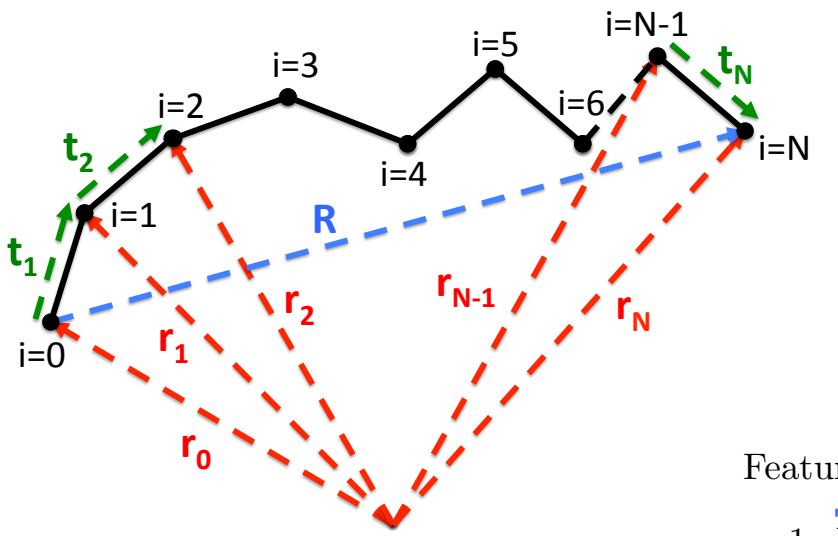
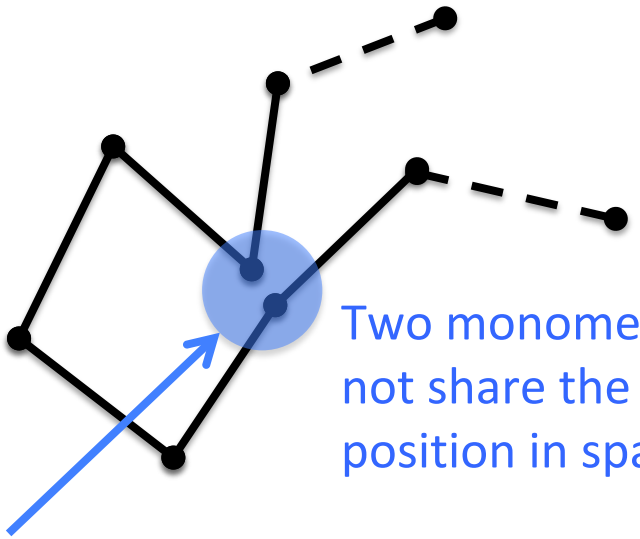
First refinement: The Self-Avoiding Chain

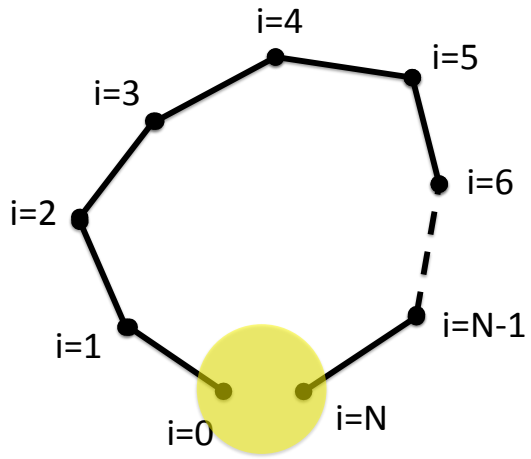
A





Two monomers can not share the same position in space!

B



Features:

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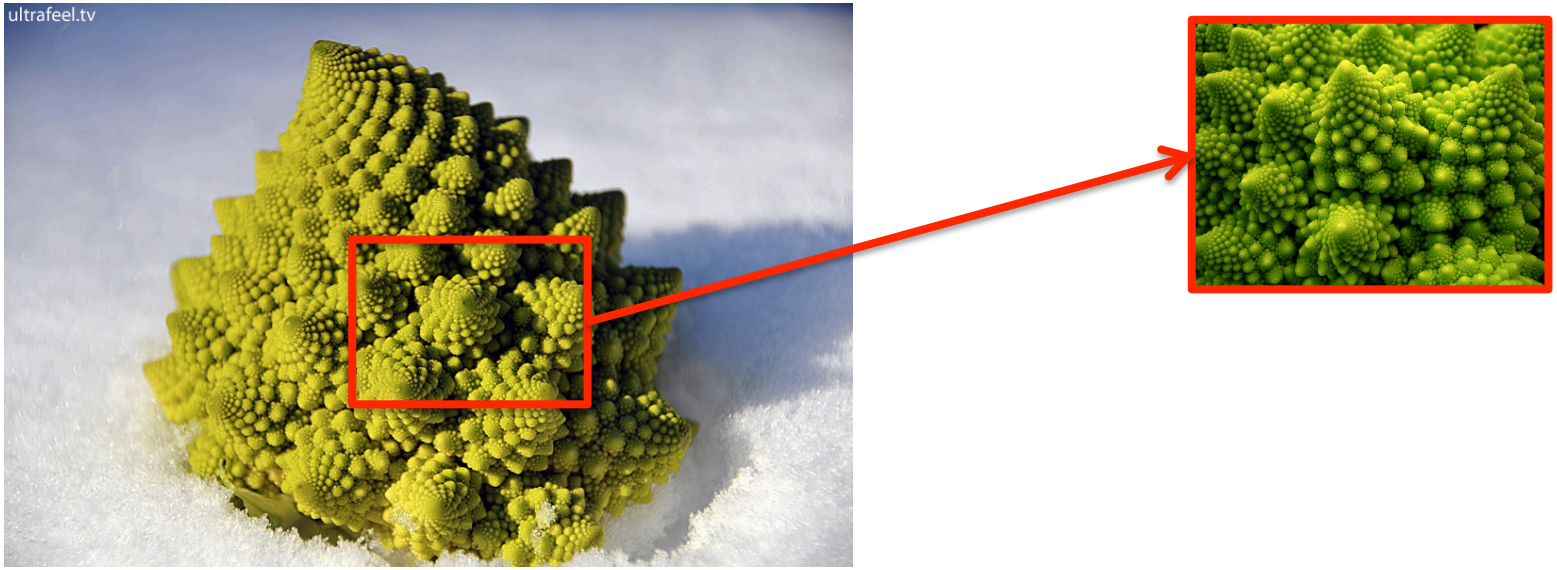
   Random orientations of the bonds;
   No *sequence* correlations for the bonds.

2. $\sqrt{\langle R_{ee}^2 \rangle} \sim \sqrt{\langle R_g^2 \rangle} \sim bN^{3/5} \rightarrow \nu = 3/5 > 1/2$

3. End-to-end distribution function is not Gaussian
   $\rightarrow$ Redner-Des Cloizeaux function:
   $$p(\vec{R}_{ee} = \vec{R}) = C \left(\frac{R}{\sqrt{\langle R_{ee}^2 \rangle}} \right)^{3+\theta} \exp\left(- \left(K \frac{R}{\sqrt{\langle R_{ee}^2 \rangle}} \right)^t \right)$$
   $\theta \approx 0.27$ and $t \approx 2.45$

4. $\langle p_c(N) \rangle \sim p(\vec{R}_{ee} = \vec{R} = 0) \sim N^{-\nu(3+\theta)} \rightarrow \gamma = 3(\nu + \theta) \approx 2.58$
   i.e. much steeper than the prediction for the Gaussian chain

The part is equal to the whole: Polymers are fractal objects



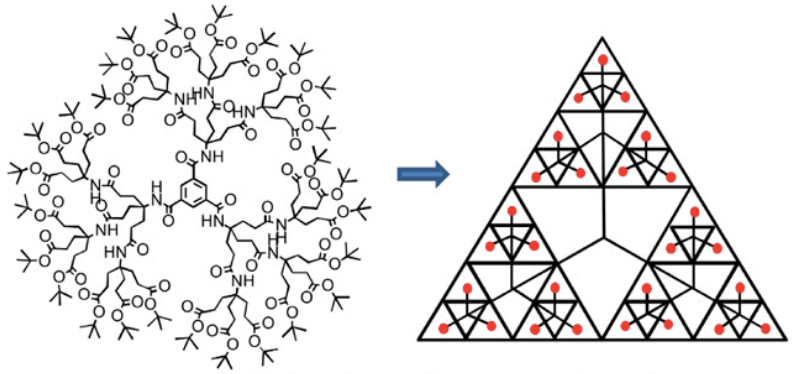
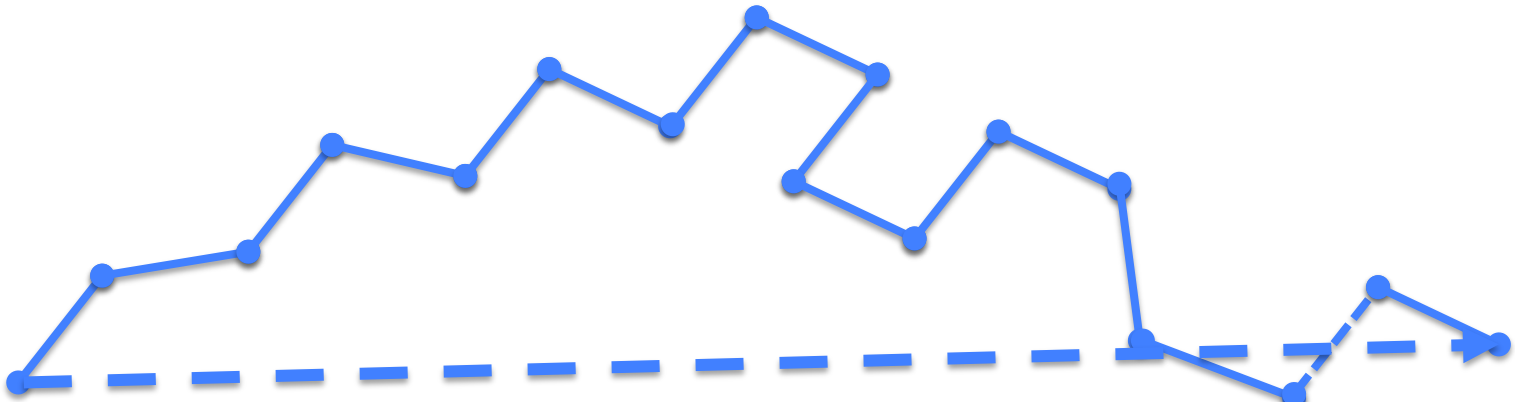


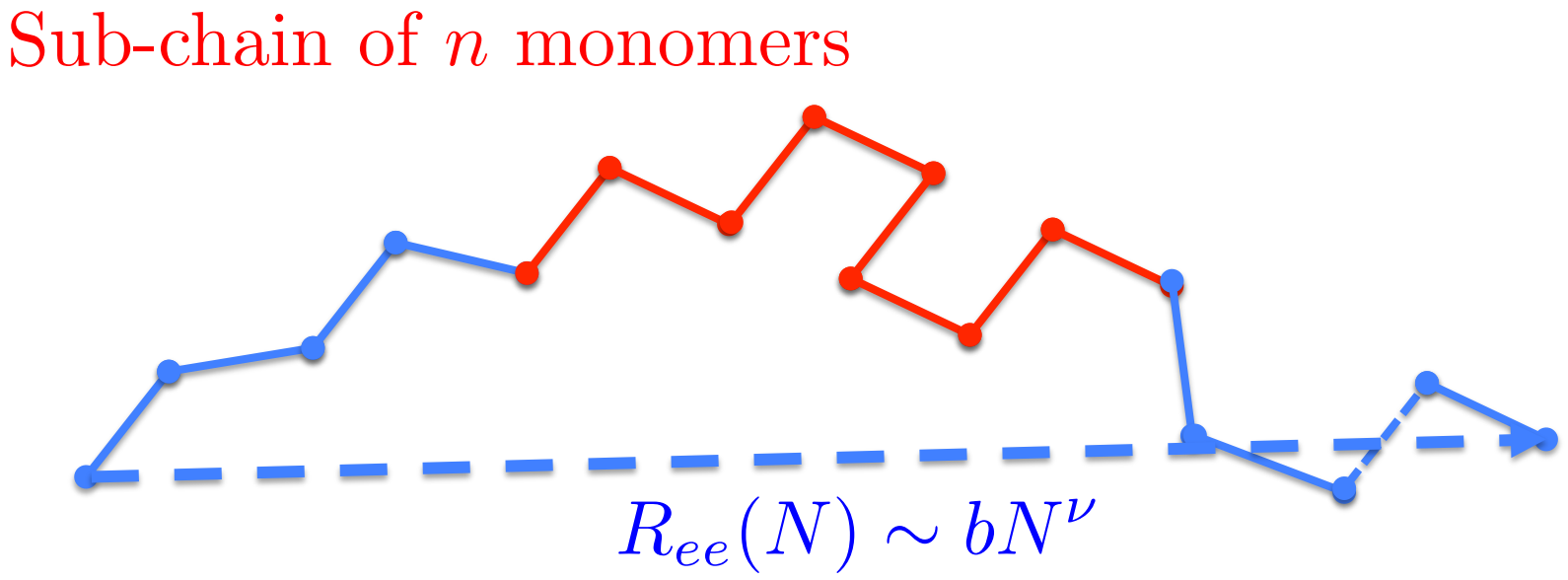
FIGURE 2 - Conceptual progression from branched dendrimer architecture to interrelated, non-tree-like fractal motifs.

The part is equal to the whole: Polymers are fractal objects



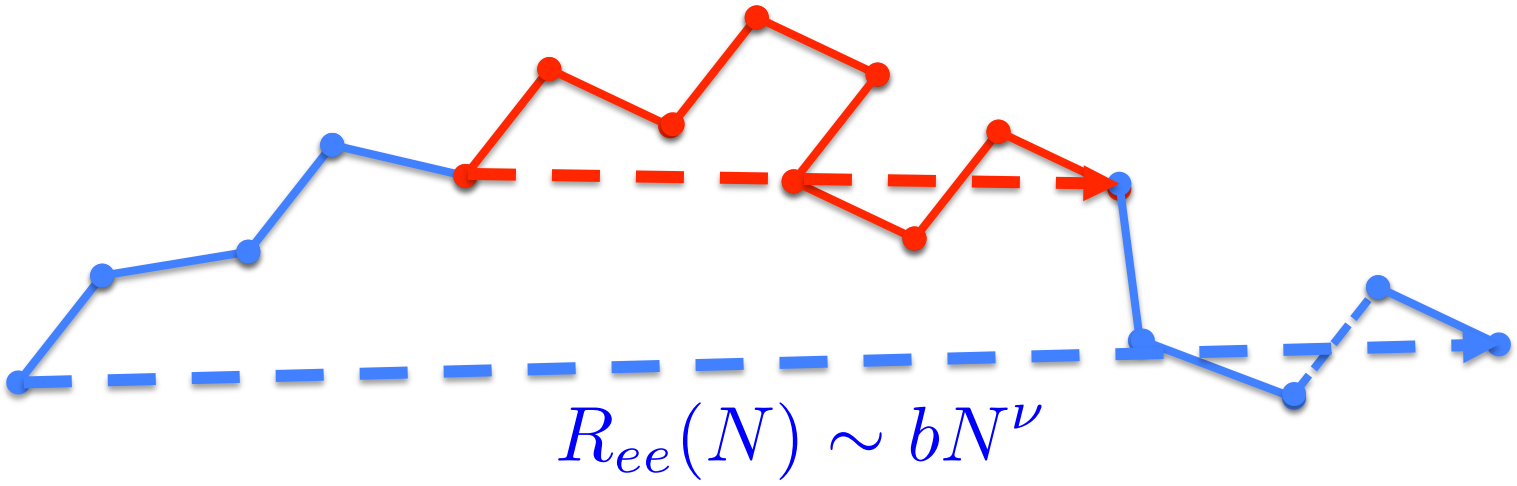
$$R_{ee}(N) \sim bN^{\nu}$$

The part is equal to the whole: Polymers are fractal objects



The part is equal to the whole: Polymers are fractal objects

Sub-chain of n monomers $\rightarrow R_{ee}(n) \sim bn^{\nu}$



- Every sub-chain behaves as the whole chain
- *Ça va sans dire*, corresponding end-to-end distribution functions have also the same functional form (Gaussian, Redner-Des Cloizeaux, …) -> The concept of universality!

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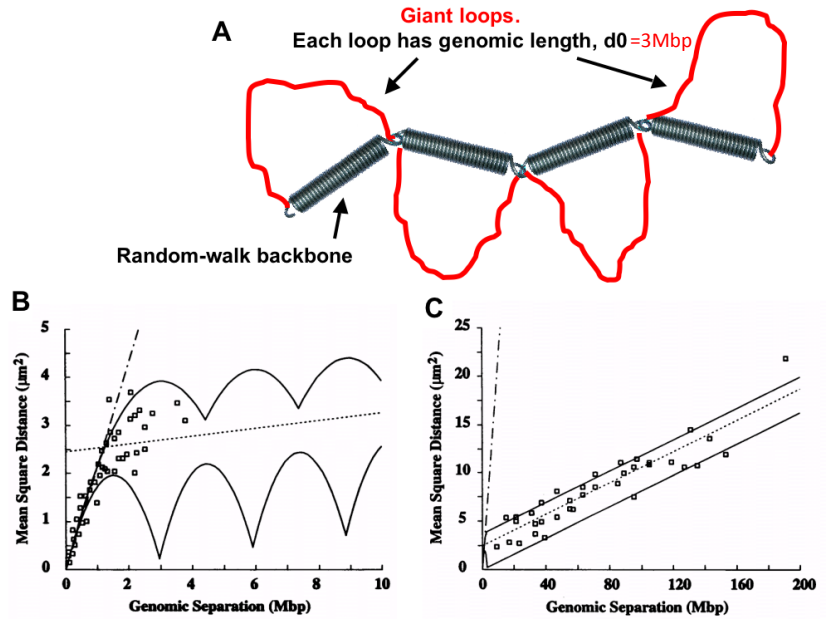
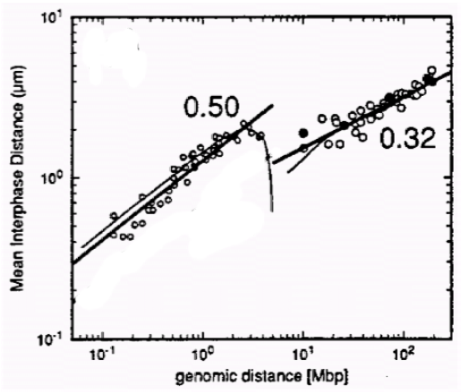
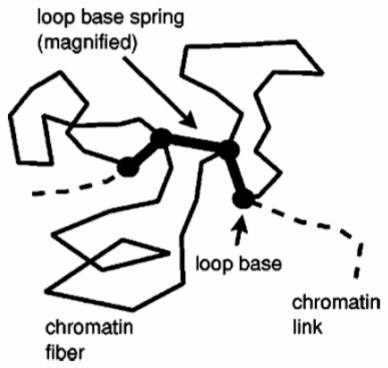
A brief history of polymer models for chromosomes: 1. ``Quenched-loop" models



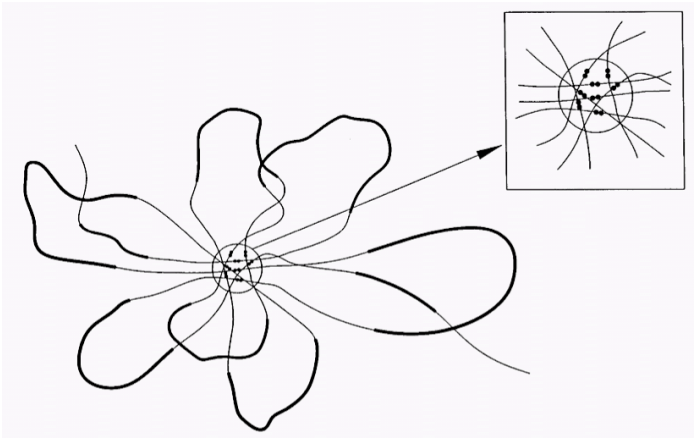
Random Walk / Giant Loop Model
(Sachs *et al.*, Proc Natl Acad Sci USA (1995))





Multi-Loop Sub-Compartment Model
(Münkel *et al.*, Phys Rev E (1998))

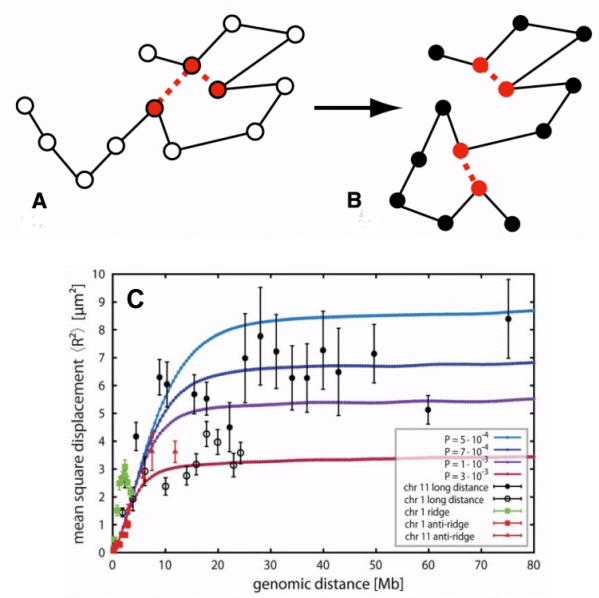
Loops positions are pre-established ("quenched" loops), and DO NOT change during time evolution



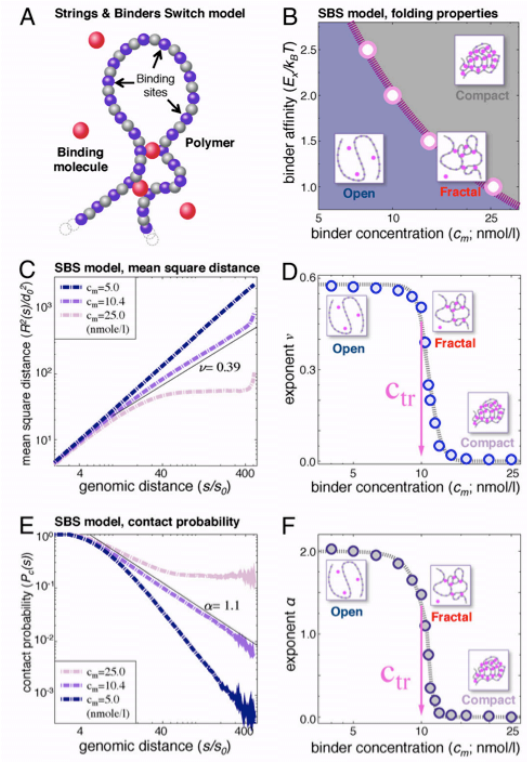
Micelles Model (Ostashevsky, Mol Biol Cell (1998))

Rosa & Zimmer, Computational Models of Genome Architecture, Intl Rev Cell Mol Biol (2014)

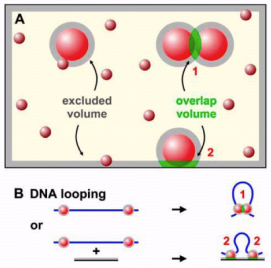
A brief history of polymer models for chromosomes: 2. ``Annealed-loop" models

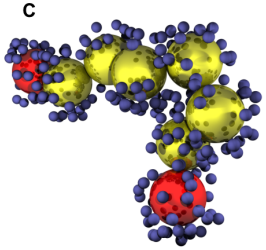


Random Loop Model
(Bohn *et al.*, Proc Natl Acad Sci USA (2007))



Strings-and-Binders Switch Model
(Barbieri *et al.*, Proc Natl Acad Sci USA (2012))





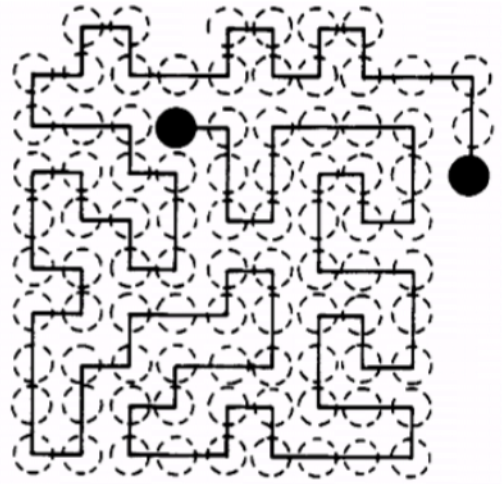
Loops may form and stabilize by depletion effects
(Marenduzzo *et al.*, Biophys J (2006))

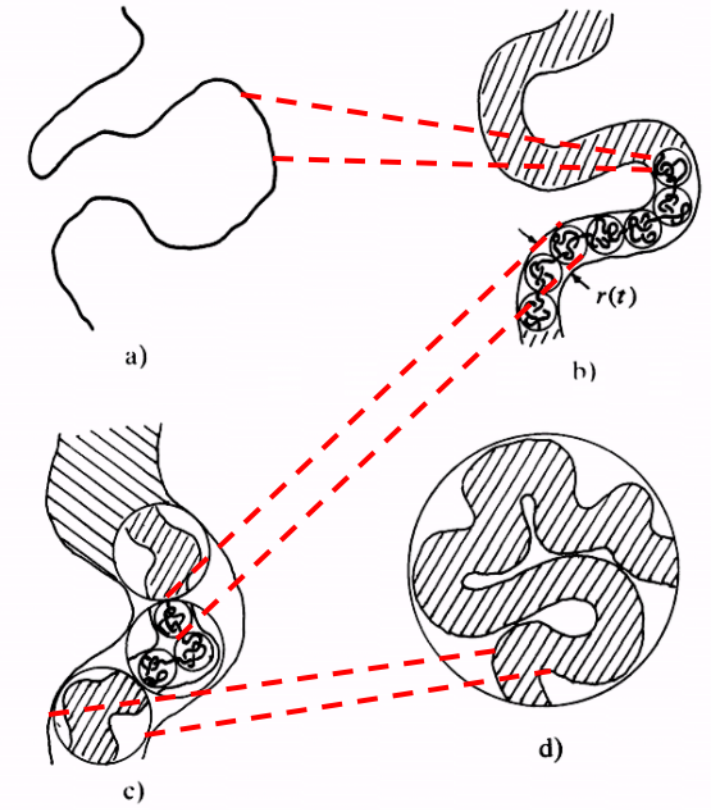
Loops positions are dynamically re-arranged ("annealed" loops)

Rosa & Zimmer, Computational Models of Genome Architecture, Intl Rev Cell Mol Biol (2014)

A brief history of polymer models for chromosomes: 3. The role of topological constraints

Fractal (originally, 'Crumpled') Globule Model
(Grosberg *et al.*, J Phys France (1988); Grosberg *et al.*, Europhys Lett (1993))





Rosa & Zimmer, Computational Models of Genome Architecture, Intl Rev Cell Mol Biol (2014)

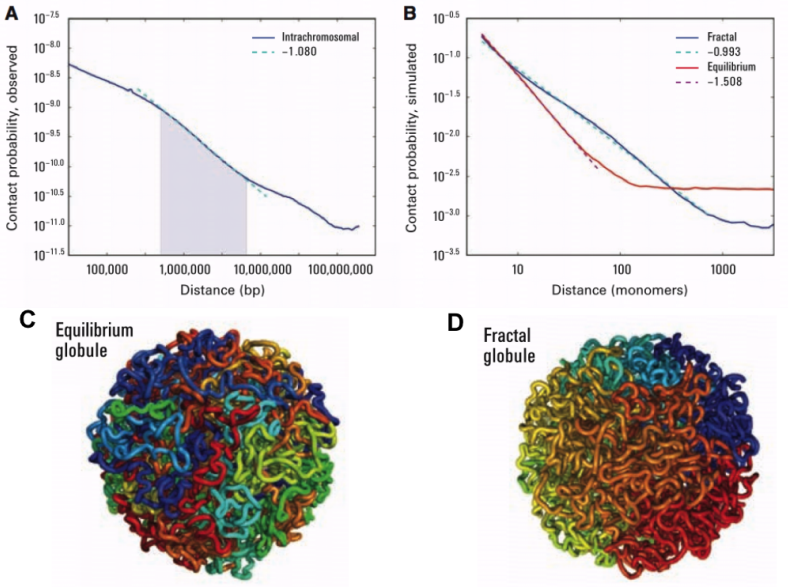
A brief history of polymer models for chromosomes: 3. The role of topological constraints

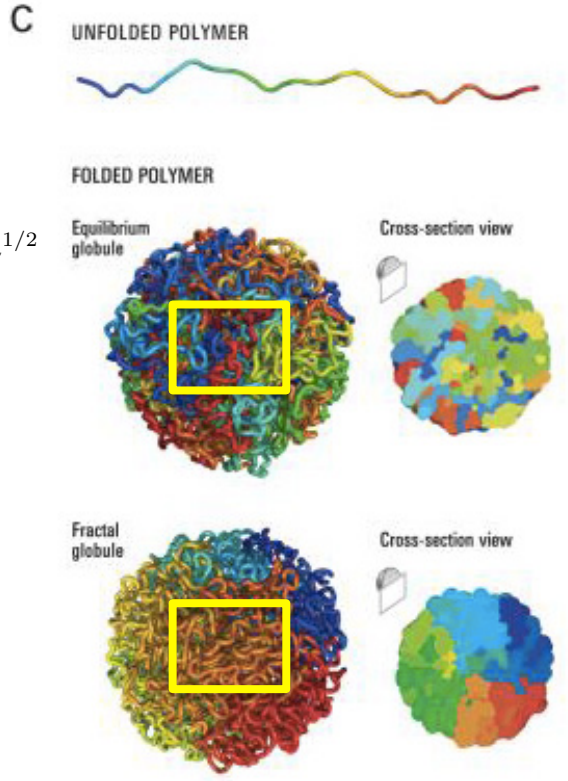
Equilibrium (EG) and fractal globules (FG) scale the same,

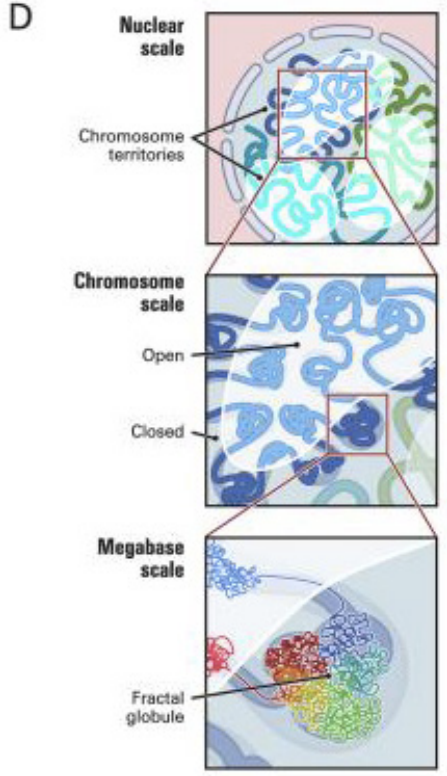
$\rightarrow R_{ee}(N) \sim bN^{1/3}$

but, LOCALLY, they have very distinct fractal properties:

- EG is not very distinct from a Gaussian chain: $R_{ee}(n) \sim bn^{1/2}$
  $\rightarrow$ fractality breaks at the globule scale
- FG is a true fractal with: $R_{ee}(n) \sim bn^{1/3}$



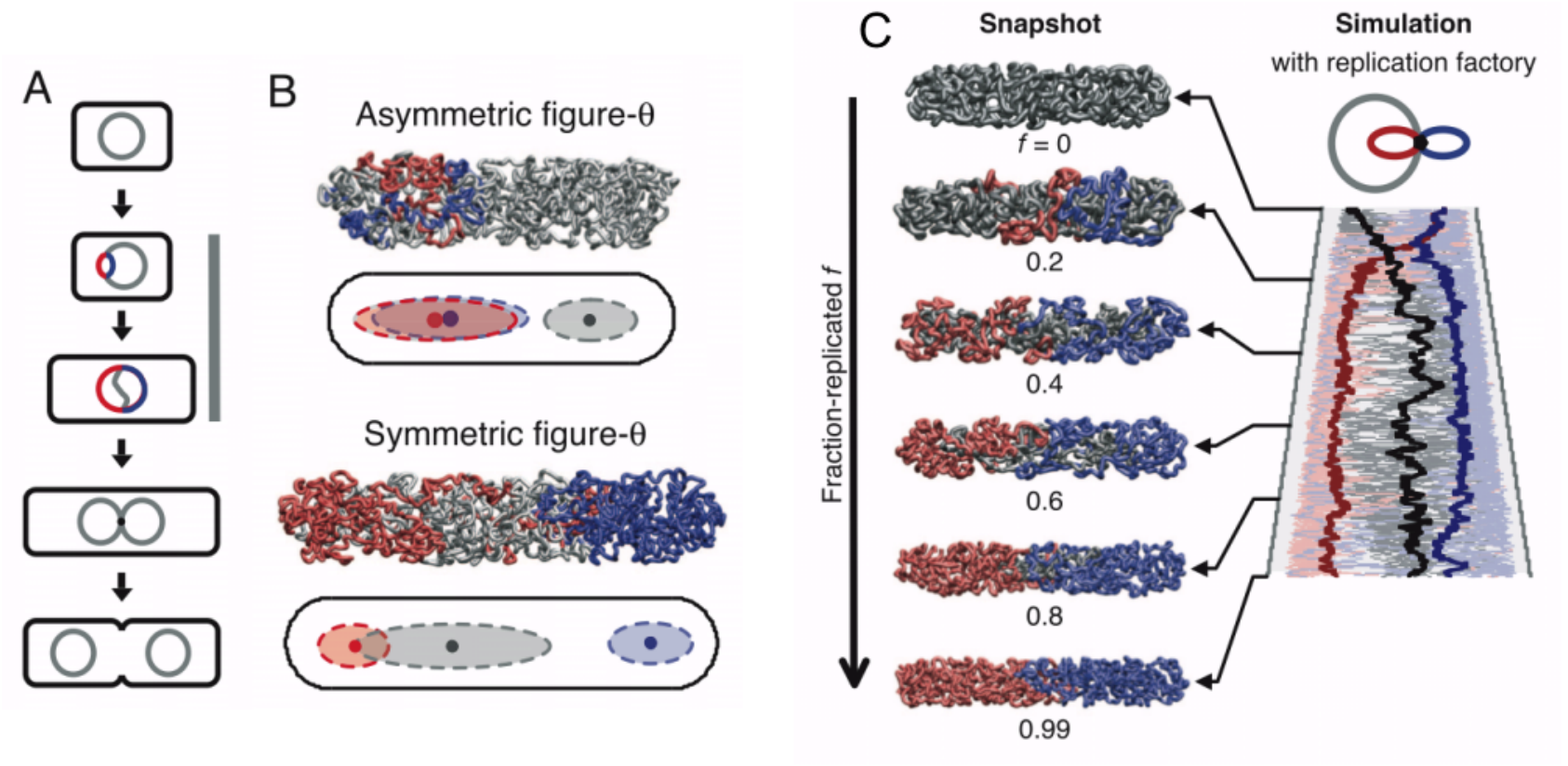




Incomplete relaxation of linear polymer chains after fast spherical compaction (Lieberman-Aiden *et al.*, Science (2009))

A brief history of polymer models for chromosomes: 3. The role of topological constraints

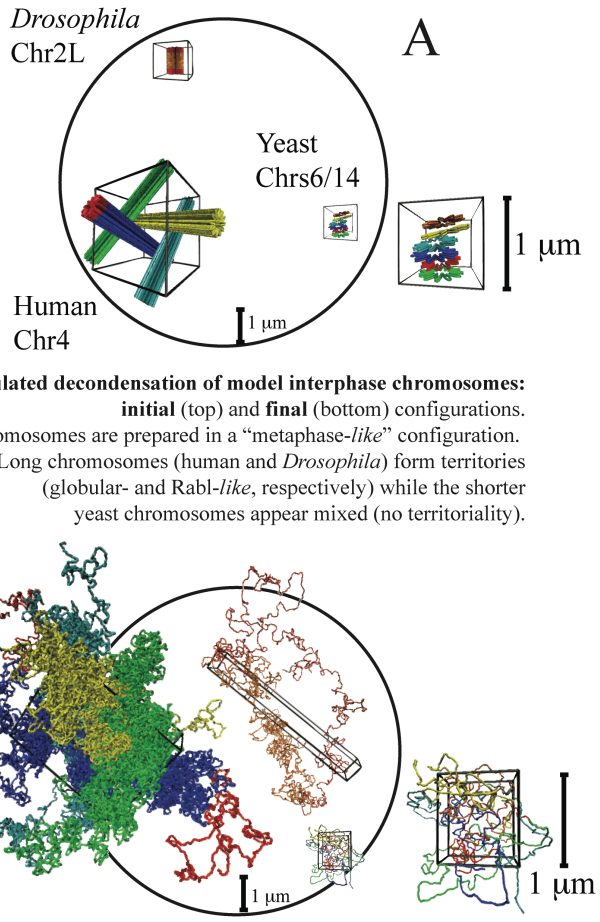
Entropic segregation of bacterial chromosomes
(Jun & Mulder, Proc Natl Acad Sci USA (2006))



Rosa & Zimmer, Computational Models of Genome Architecture, Intl Rev Cell Mol Biol (2014)

A brief history of polymer models for chromosomes: 3. The role of topological constraints

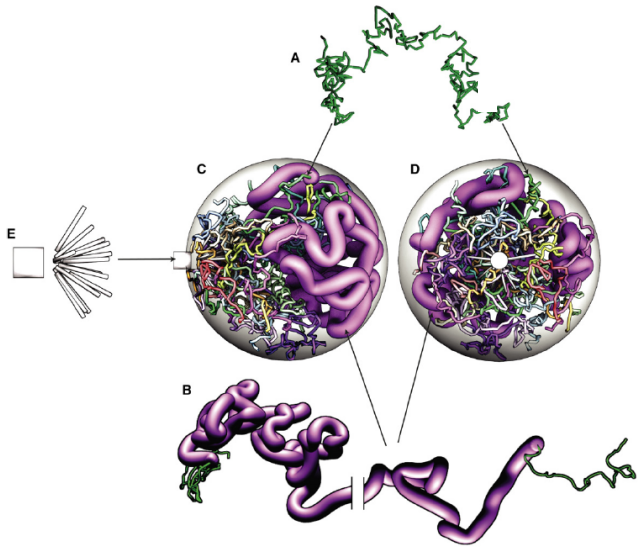
Entangled polymer model of chromosome territories
(Rosa & Everaers, Plos Comput Biol (2008))



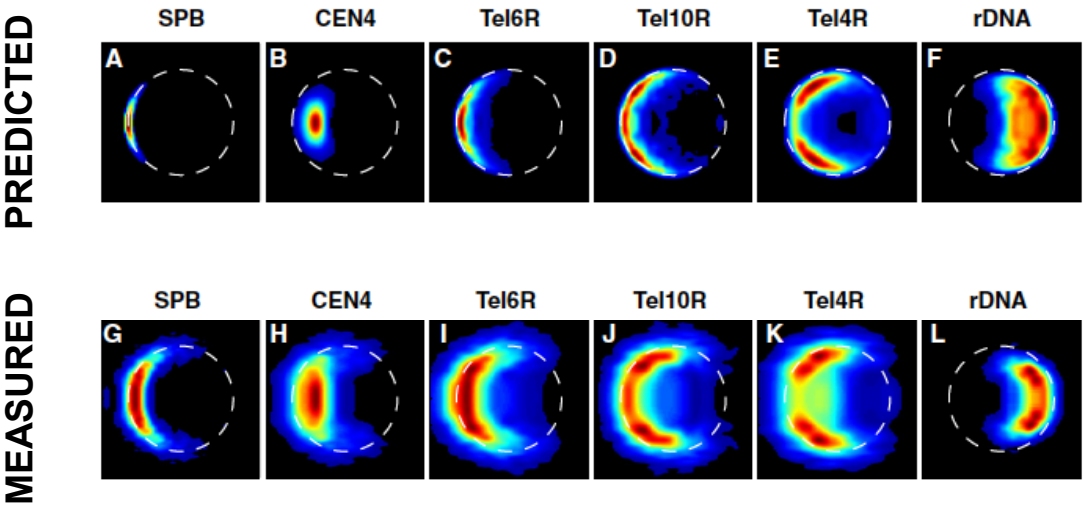
Simulated decondensation of model interphase chromosomes: initial (top) and **final** (bottom) configurations. Chromosomes are prepared in a "metaphase-*like*" configuration. Long chromosomes (human and *Drosophila*) form territories (globular- and Rabl-*like*, respectively) while the shorter yeast chromosomes appear mixed (no territoriality).

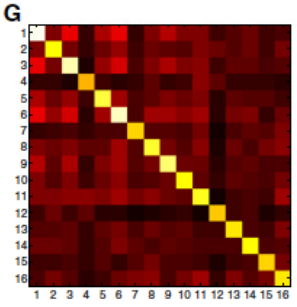
Rosa & Zimmer, Computational Models of Genome Architecture, Intl Rev Cell Mol Biol (2014)

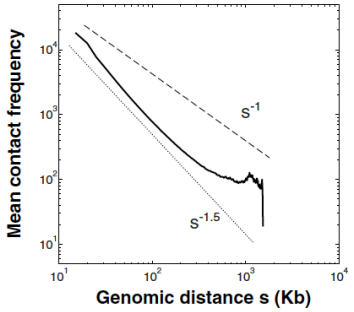
A brief history of polymer models for chromosomes: 4. Introducing sequence heterogeneity

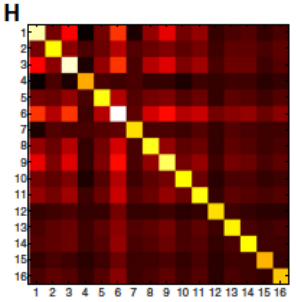


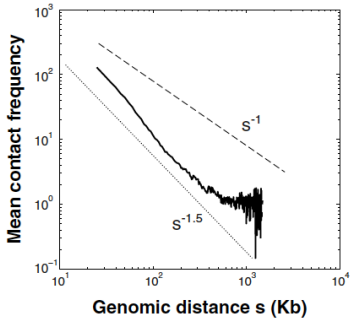
Wong *et al.*, Curr Biol (2012)





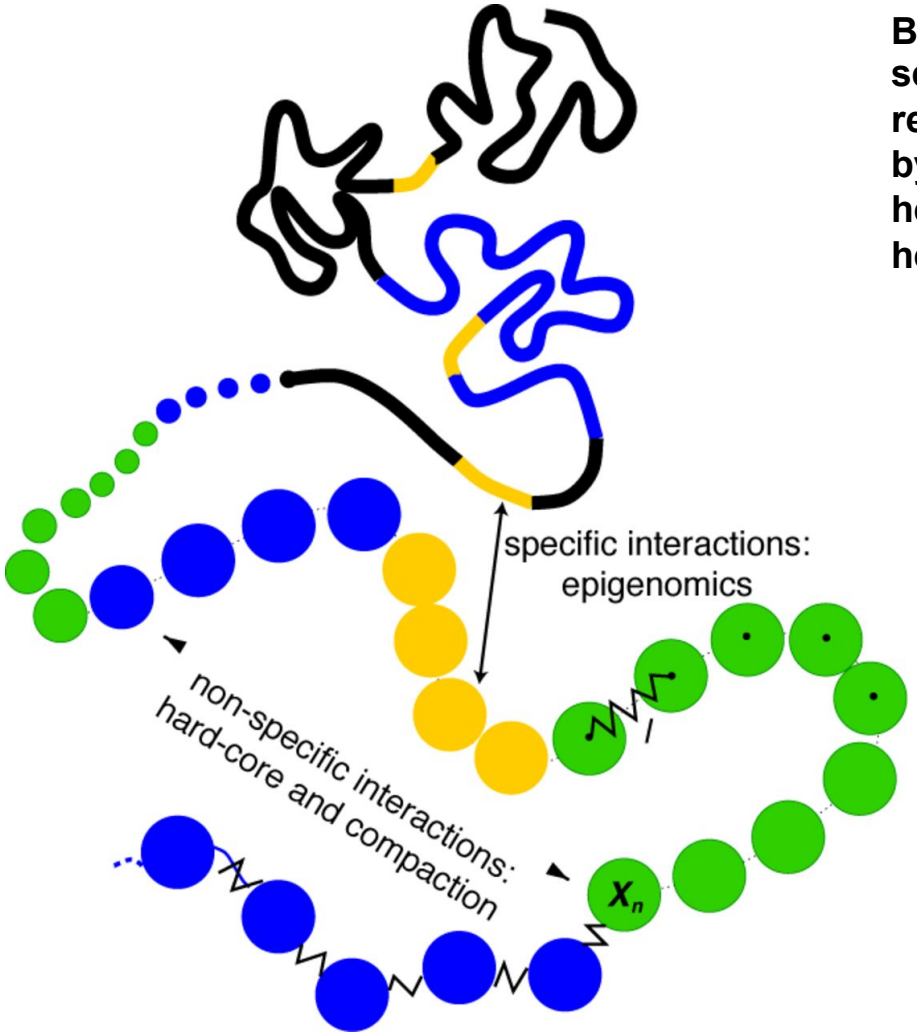






Rosa & Zimmer, Computational Models of Genome Architecture, Intl Rev Cell Mol Biol (2014)

A brief history of polymer models for chromosomes: 4. Introducing sequence heterogeneity



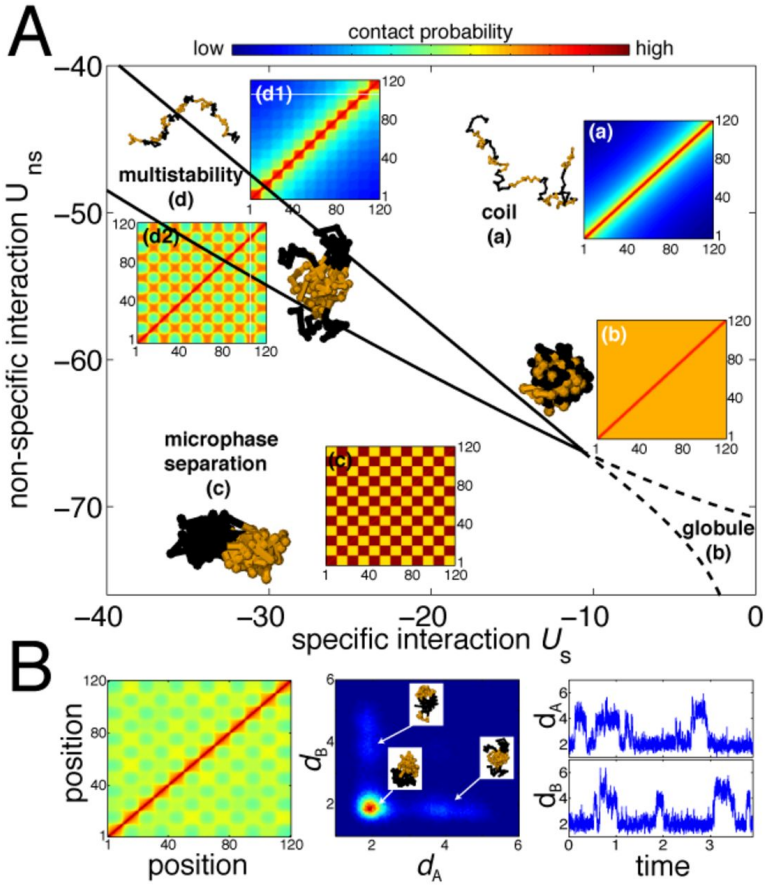
Block copolymer model: the chromatin is modeled as a self-avoiding bead-spring chain where each monomer represents a portion of DNA (10 kb) and is characterized by its epigenetic state: yellow (active), green (HP1-like heterochromatin), blue (Polycomb-like heterochromatin), black (repressive chromatin) (1).

Daniel Jost et al. Nucl. Acids Res. 2014;42:9553-9561

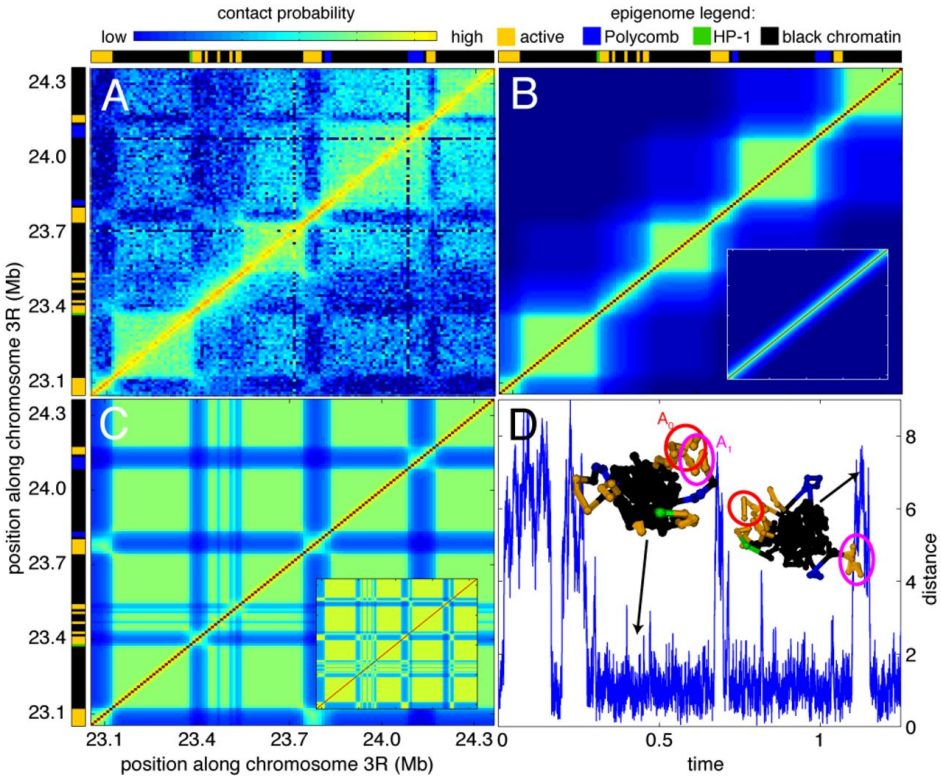
Nucleic Acids Research

A brief history of polymer models for chromosomes: 4. Introducing sequence heterogeneity

(A) Phase diagram of the copolymer as a function of the strength of specific and non-specific interactions (in kBT unit).
(B) Contact map



Experimental (A) vs. Predicted (B,C) Hi-C contact map for the chromatin region located between 23.05 and 24.36 Mb of chromosome 3R of *Drosophila*.

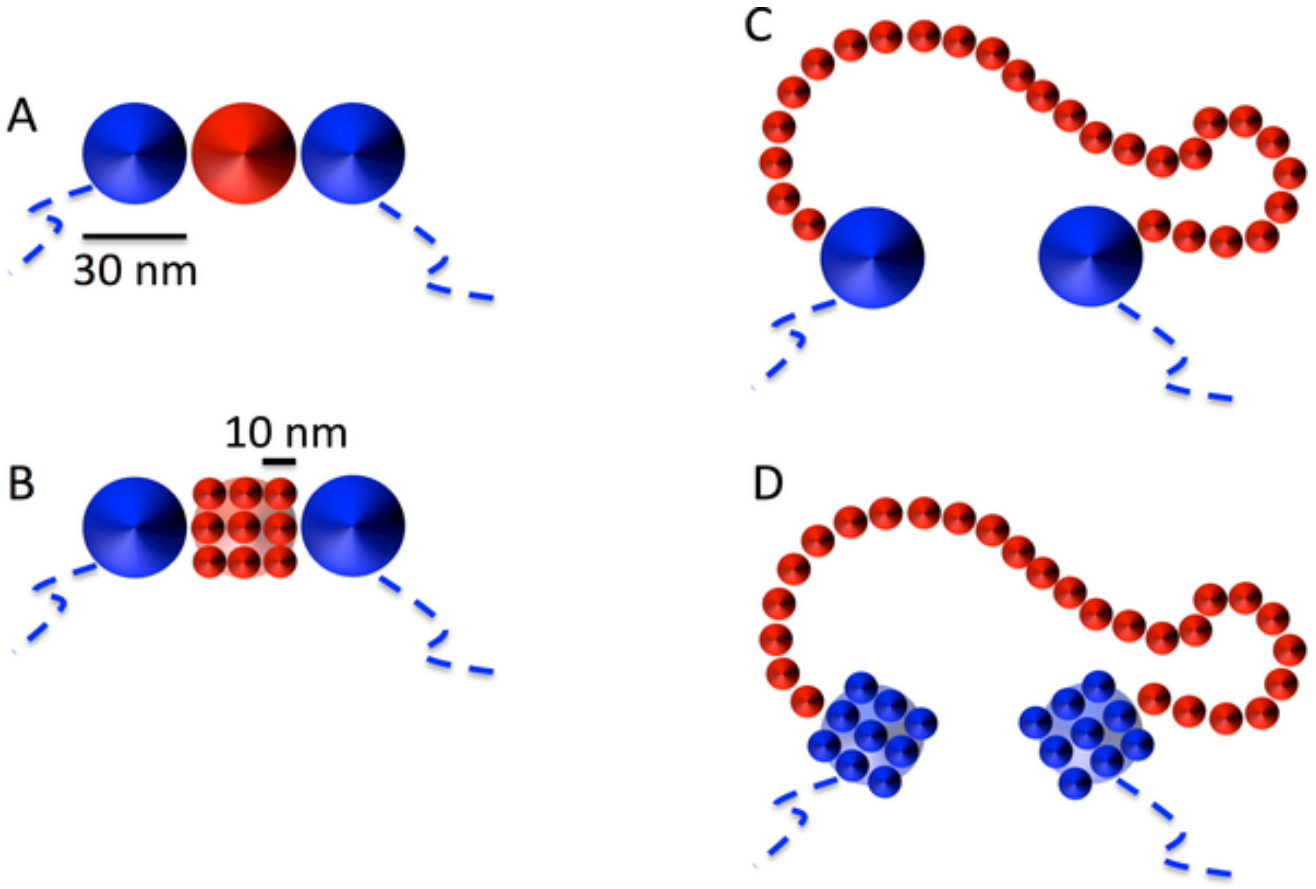


Daniel Jost et al. Nucl. Acids Res. 2014;42:9553-9561

Nucleic Acids Research

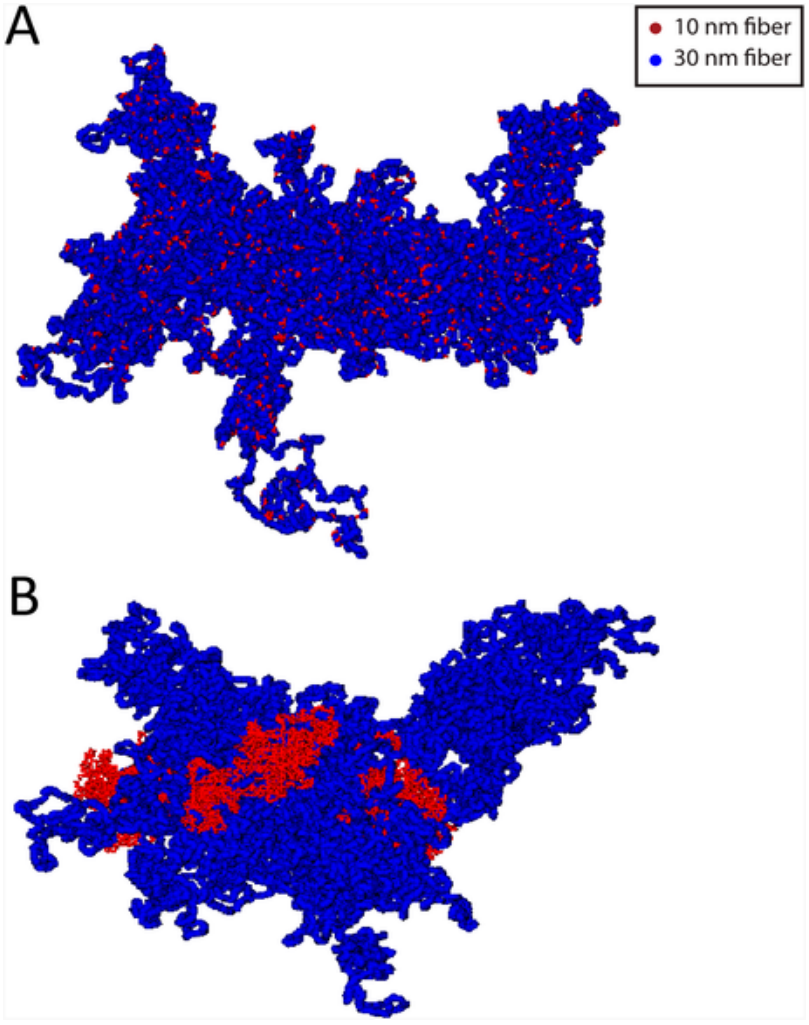
A brief history of polymer models for chromosomes: 4. Introducing sequence heterogeneity

Illustration of the adopted set-up used to model the unfolding of the 30nm model chromatin fiber into the 10nm model chromatin fiber.



Florescu AM, Therizols P, Rosa A (2016) Large Scale Chromosome Folding Is Stable against Local Changes in Chromatin Structure. PLoS Comput Biol 12(6): e1004987. doi:10.1371/journal.pcbi.1004987
http://journals.plos.org/ploscompbiol/article?id=info:doi/10.1371/journal.pcbi.1004987

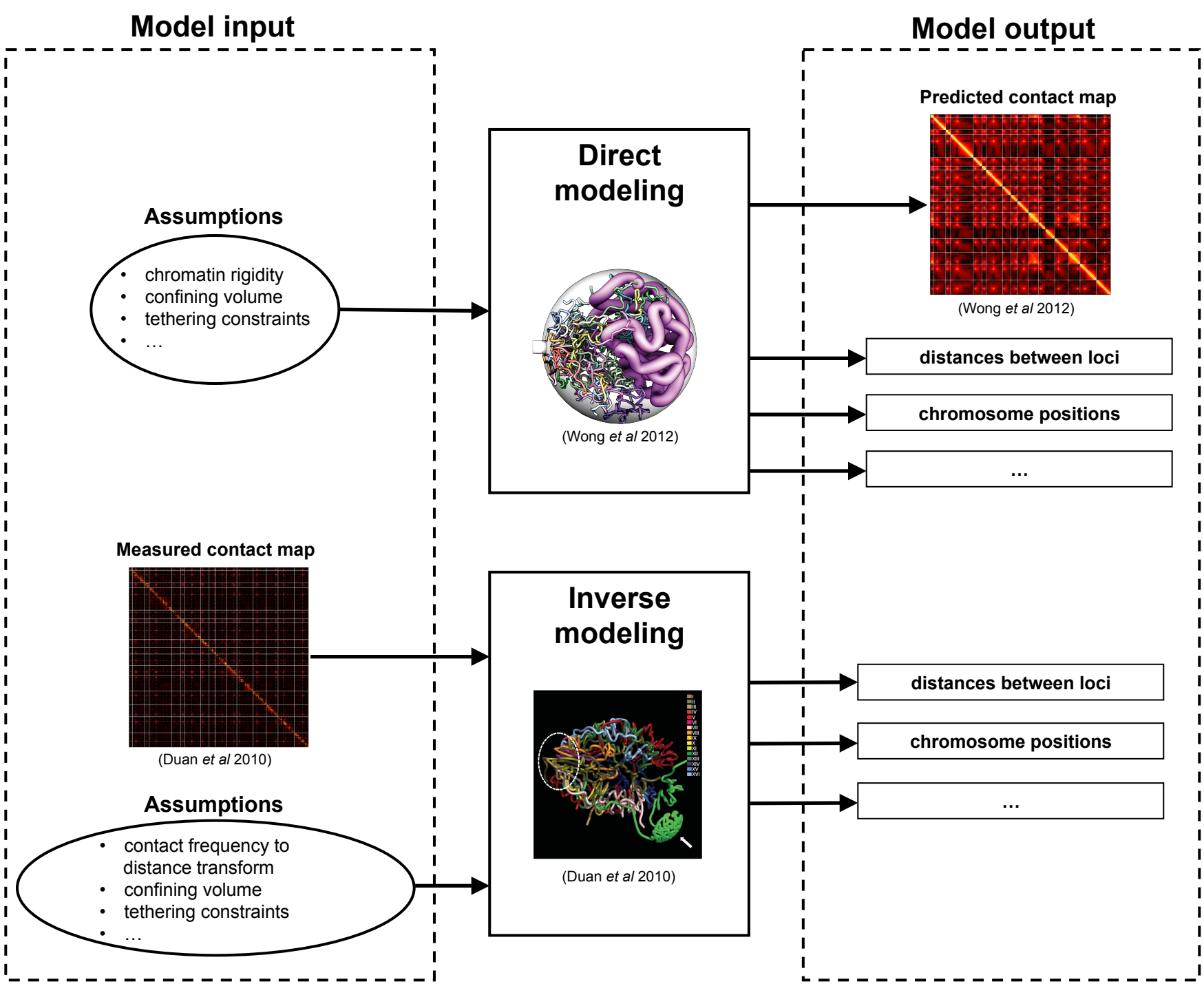
A brief history of polymer models for chromosomes: 4. Introducing sequence heterogeneity



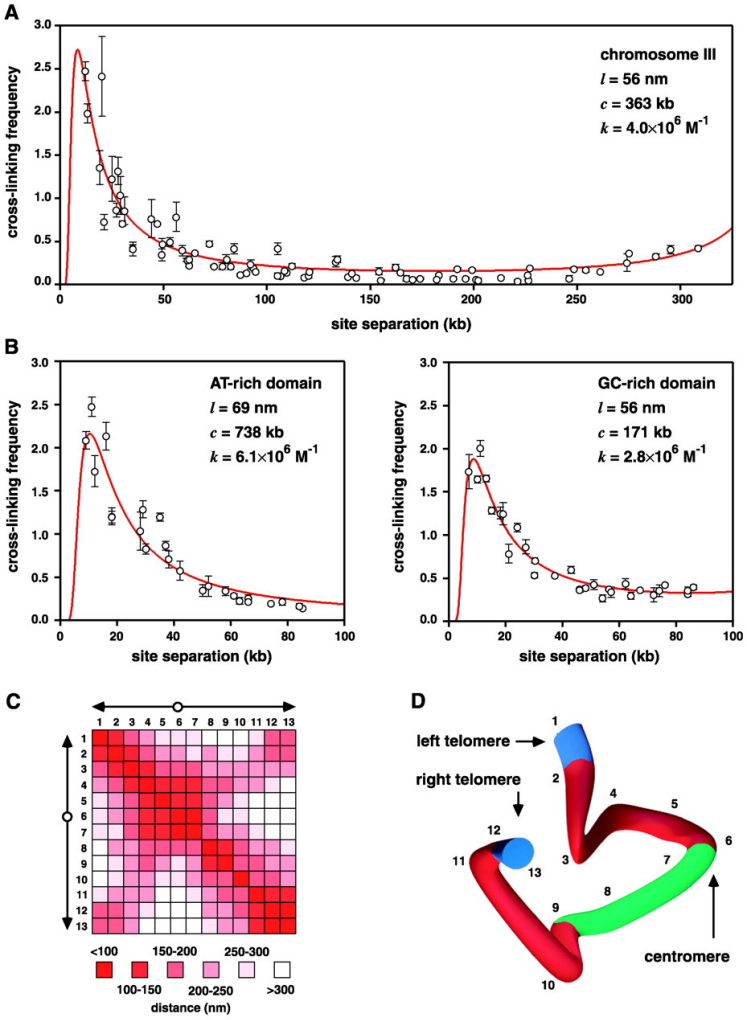
Model chromosome conformations with a 8% total amount of 10nm chromatin fiber.

Florescu AM, Therizols P, Rosa A (2016) Large Scale Chromosome Folding Is Stable against Local Changes in Chromatin Structure. PLoS Comput Biol 12(6): e1004987. doi:10.1371/journal.pcbi.1004987
http://journals.plos.org/ploscompbiol/article?id=info:doi/10.1371/journal.pcbi.1004987

PLOS | COMPUTATIONAL BIOLOGY


Model input
Model output
Assumptions
chromatin rigidity
confining volume
tethering constraints
…
Direct modeling
(Wong et al 2012)
Predicted contact map
(Wong et al 2012)
distances between loci
chromosome positions
…
Measured contact map
(Duan et al 2010)
Assumptions
contact frequency to distance transform
confining volume
tethering constraints
…
Inverse modeling
(Duan et al 2010)
distances between loci
chromosome positions
…

Reconstruction of chromosome conformations

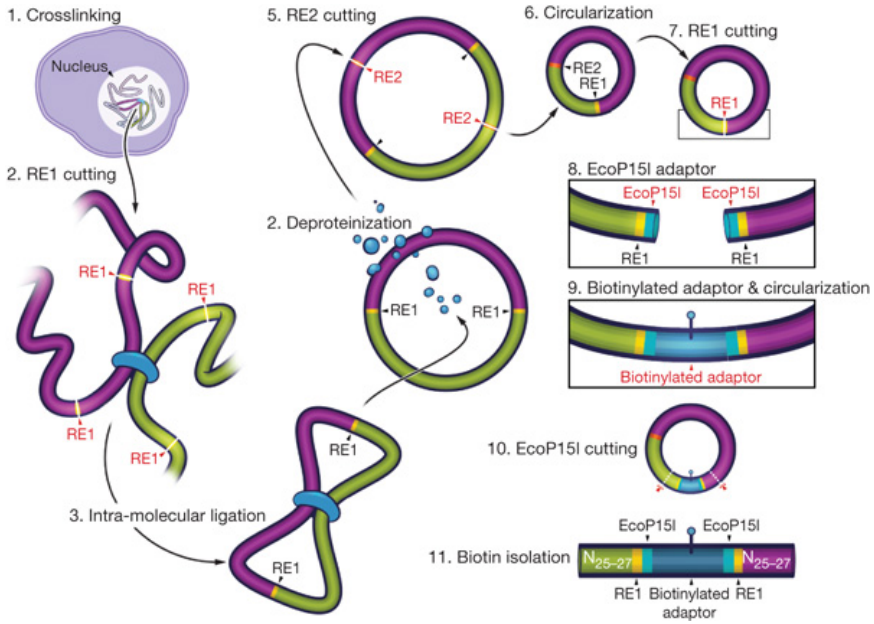


Analysis of the structure of chromosome III during interphase.

Job Dekker et al. Science 2002;295:1306-1311

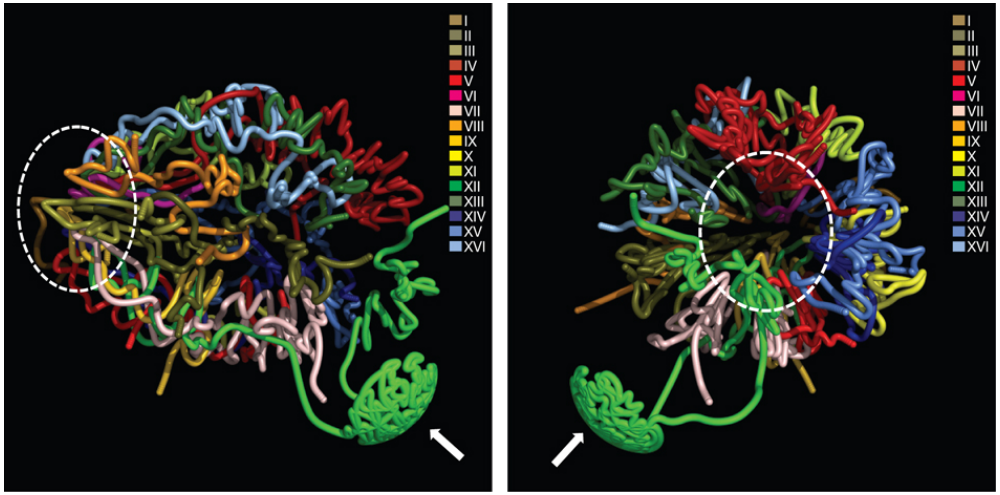
Rosa & Zimmer, Computational Models of Genome Architecture, Intl Rev Cell Mol Biol (2014)

Reconstruction of chromosome conformations



ZJ Duan *et al. Nature* **465** (2010)

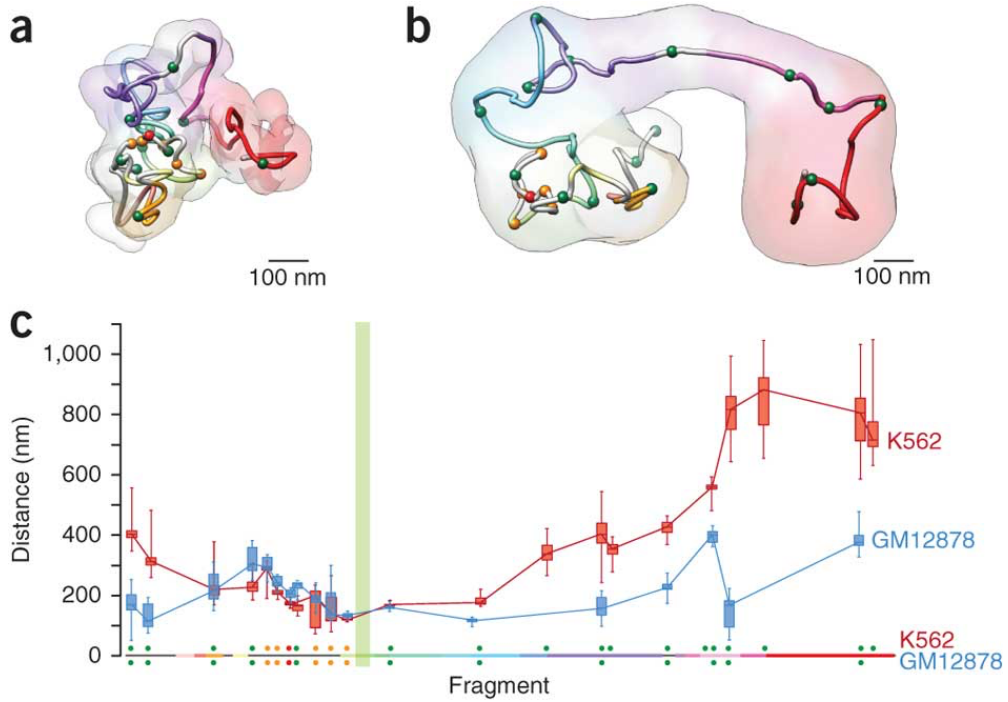
Reconstruction of fission yeast genome from HiC data



nature

Rosa & Zimmer, Computational Models of Genome Architecture, Intl Rev Cell Mol Biol (2014)

Reconstruction of chromosome conformations

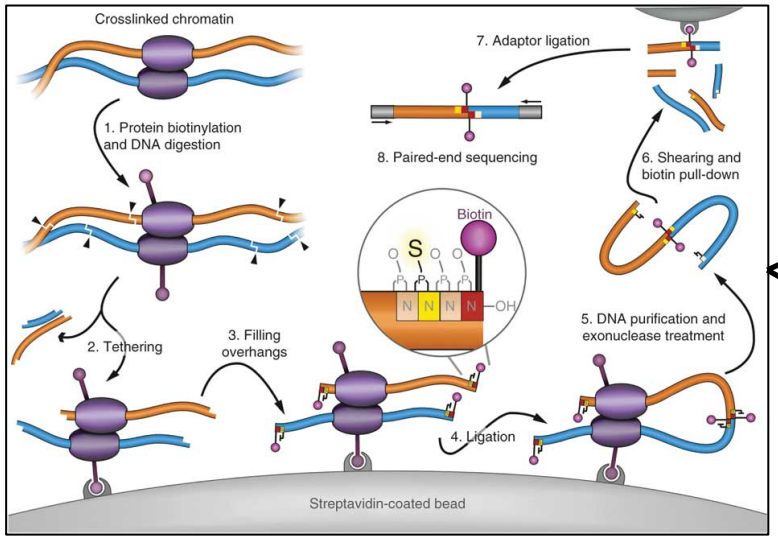


Reconstruction of a human chromatin domain from 5C data
(Baù *et al.*, Nat Struct Mol Biol (2011))

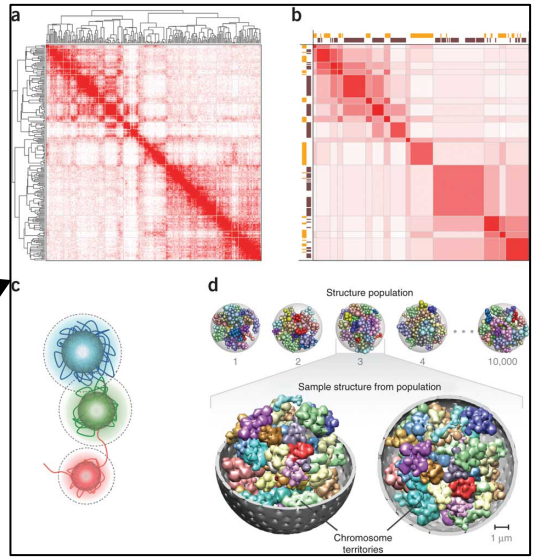
Rosa & Zimmer, Computational Models of Genome Architecture, Intl Rev Cell Mol Biol (2014)

Reconstruction of chromosome conformations

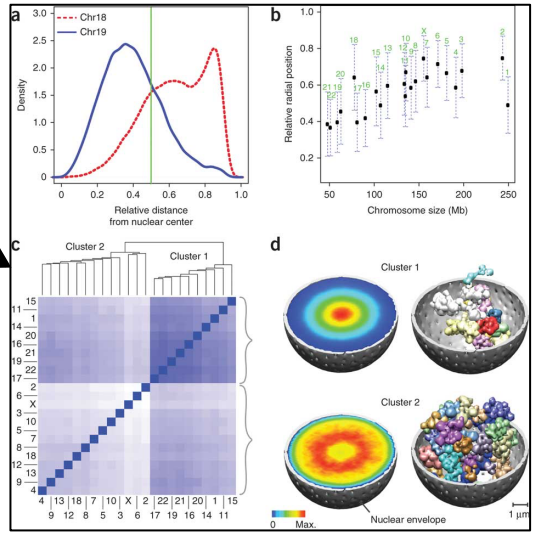
Genome reconstruction by Chromosome Conformation Capture + Population-based Modeling
(Kalhor *et al.*, Nat Biotech (2012))



1)



2)



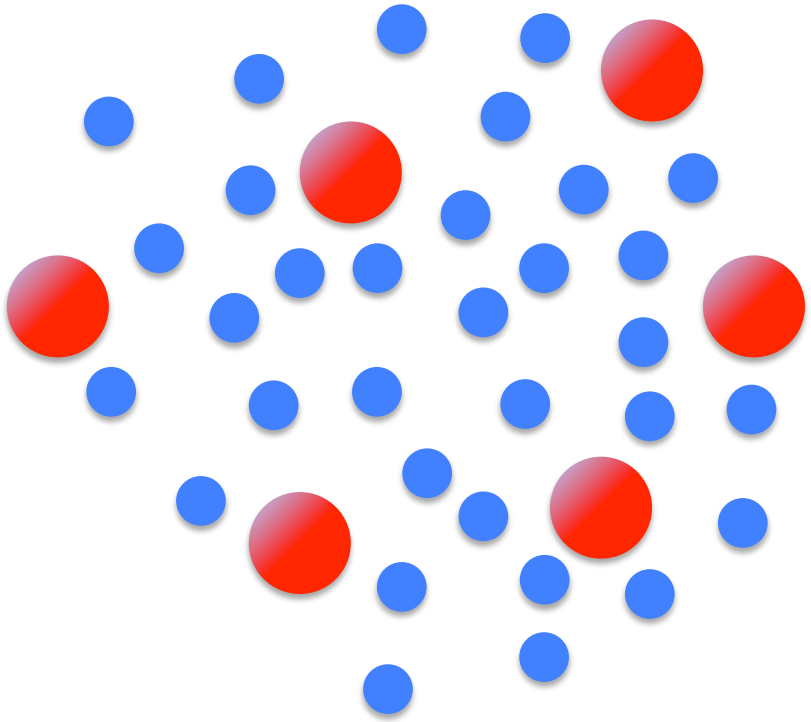
Rosa & Zimmer, Computational Models of Genome Architecture, Intl Rev Cell Mol Biol (2014)

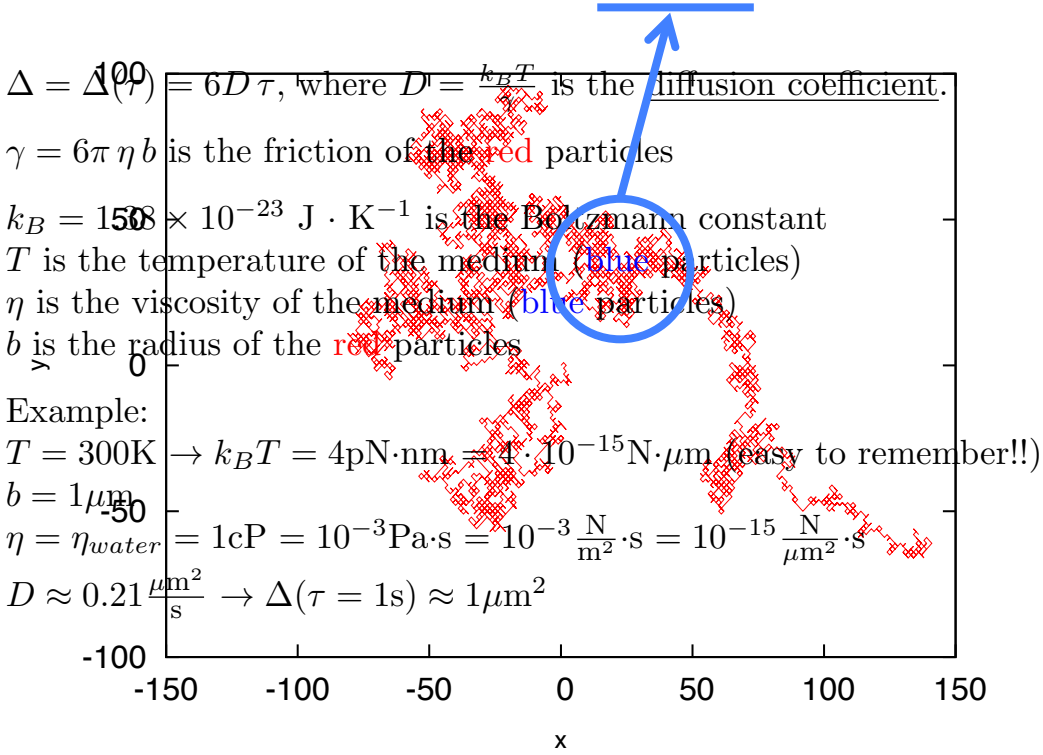
Outline

- The problem of chromosome folding
  - Generic features
  - Why is it important at all?
- Polymer Physics 1: Structure
- Polymer models for chromosome folding: a “quasi” historical perspective
- Polymer Physics 2: Dynamics
- Simulation methods: Monte Carlo & Molecular Dynamics

Polymers & Dynamics: The Rouse Model

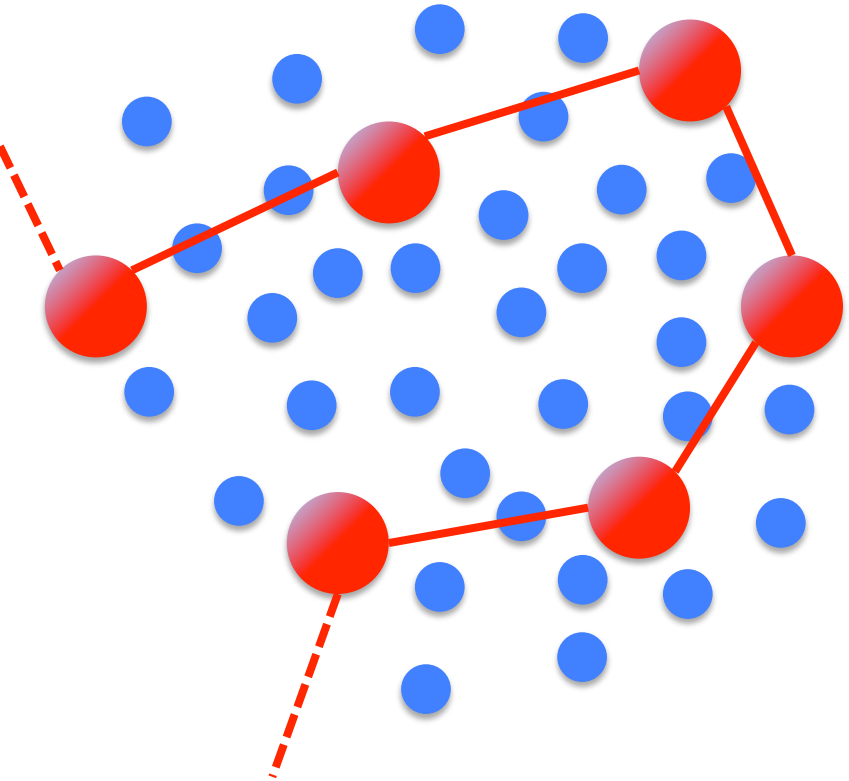
- Theoretical foundations: The Brownian motion
  1. Consider a system of `large', freely diffusing particles (red) in a homogeneous medium composed of smaller particles (blue);
  2. The red particles collide randomly with the blue particles;
  3. Due to random collisions, the motion of red particles is erratic as well
  4. After time τ, red particles have traveled – on average – a distance $\Delta=\Delta(\tau)$





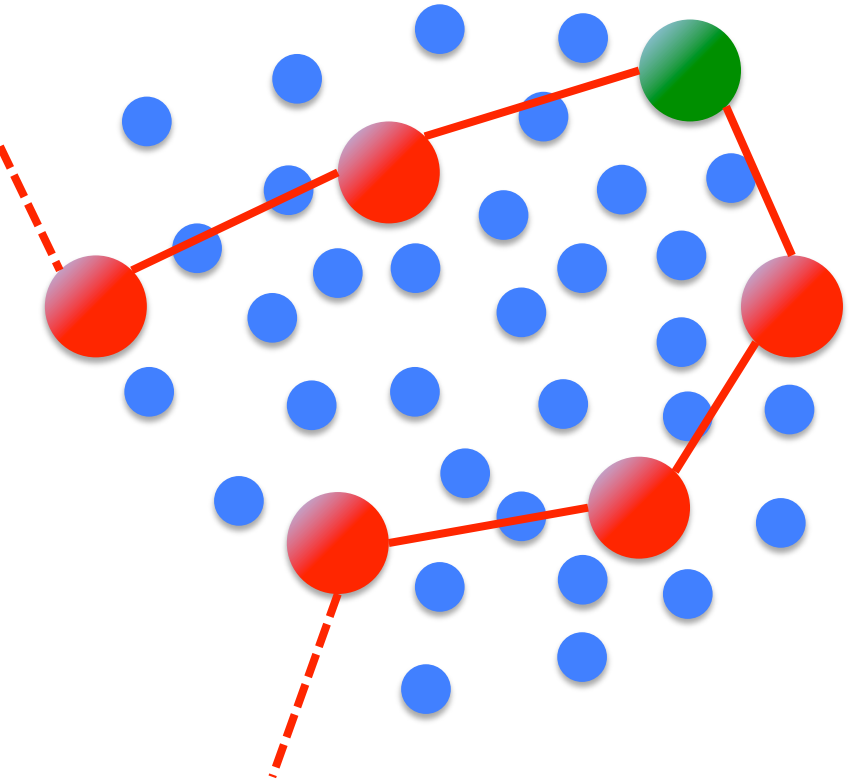
Polymers & Dynamics: The Rouse Model

- Polymer chain: the red particles are now linearly connected
  1. How does this affect the time behavior of the mean-square-displacement $\Delta=\Delta(\tau)$?



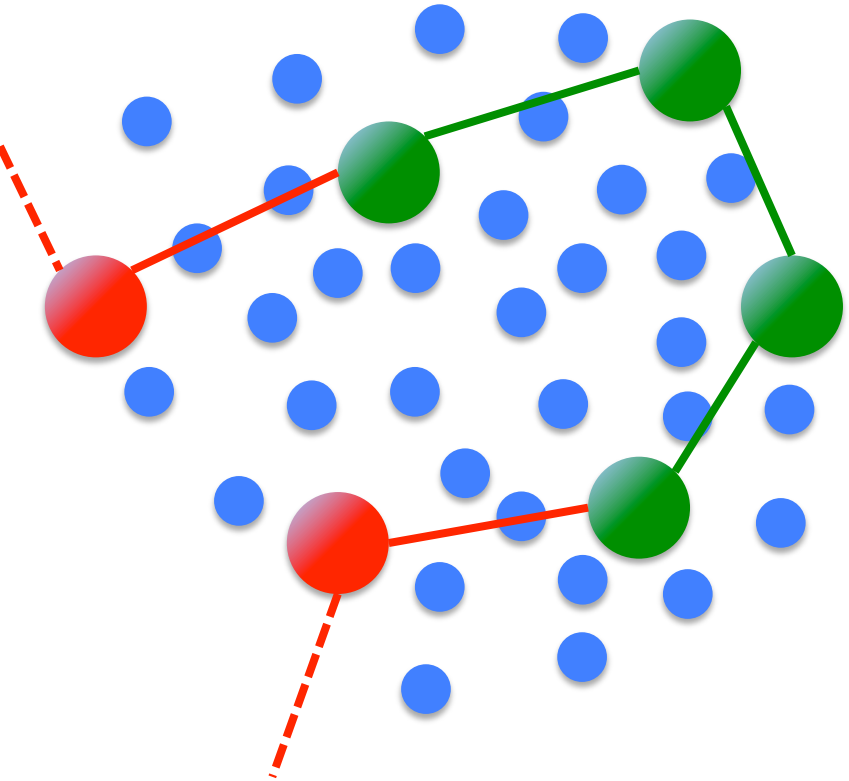
Polymers & Dynamics: The Rouse Model

- Polymer chain: the red particles are now linearly connected
  1. How does this affect the time behavior of the mean-square-displacement $\Delta=\Delta(\tau)$?
  2. Clearly, at very short times, each monomer moves does not "feel" the presence of the other monomers -> $\Delta(\tau) = 6D\tau$



Polymers & Dynamics: The Rouse Model

- Polymer chain: the red particles are now linearly connected
  1. How does this affect the time behavior of the mean-square-displacement $\Delta=\Delta(\tau)$?
  2. Clearly, at very short times, each monomer moves does not "feel" the presence of the other monomers -> $\Delta(\tau) = 6D\tau$
  3. At later times ?? More and more monomers become involved !!



Two relations:

1. $\Delta(\tau) \sim n(\tau)\, b^2$
2. $\Delta(\tau) \sim \frac{k_B T}{\gamma(\tau)}\,\tau \sim \frac{k_B T}{\eta\, n(\tau)\, b}\,\tau$
   $\gamma = \gamma(\tau)$, time-dependent friction
   HP: monomers motion is not correlated!!

By inserting Eq. (1) into Eq. (2), we get:

$$\Delta(\tau) \sim \frac{k_B T}{\eta\, n(\tau)\, b}\,\tau \sim \frac{k_B T}{\eta\, \frac{\Delta(\tau)}{b^2}\, b}\,\tau = \frac{k_B T\, b}{\eta\, \Delta(\tau)}\,\tau \rightarrow \Delta(\tau)^2 \sim \frac{k_B T\, b}{\eta}\,\tau$$

$$\rightarrow \quad \Delta(\tau) \sim \tau^{1/2}$$

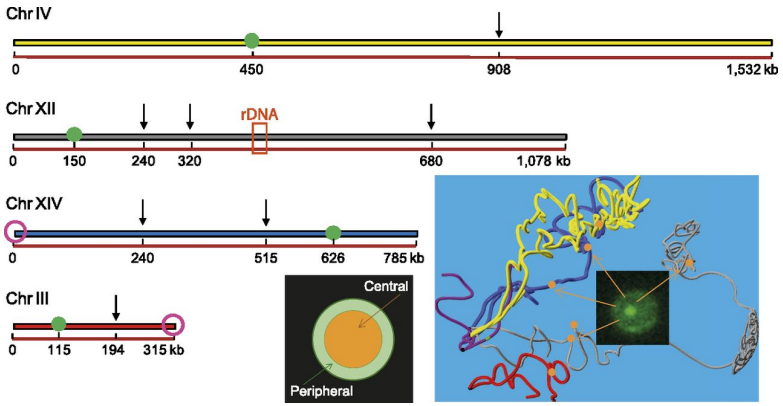
The Rouse model implies *sub-diffusive* monomer motion at intermediate times!!

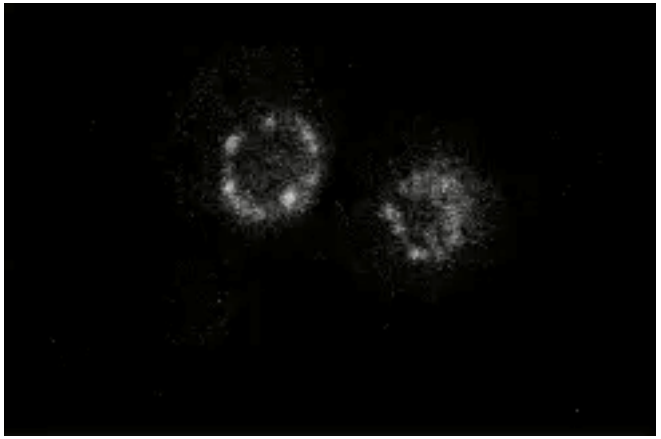
The time-scale for the relaxation of the entire chain, τ_R, is called the Rouse time. It is defined as:

$$\Delta(\tau_R) \sim \left(\frac{k_B T\, b}{\eta}\right)^{1/2} \tau_R^{1/2} \sim N b^2 \rightarrow \tau_R \sim \frac{\eta b^3}{k_B T} N^2 \sim \frac{b^2}{D} N^2$$

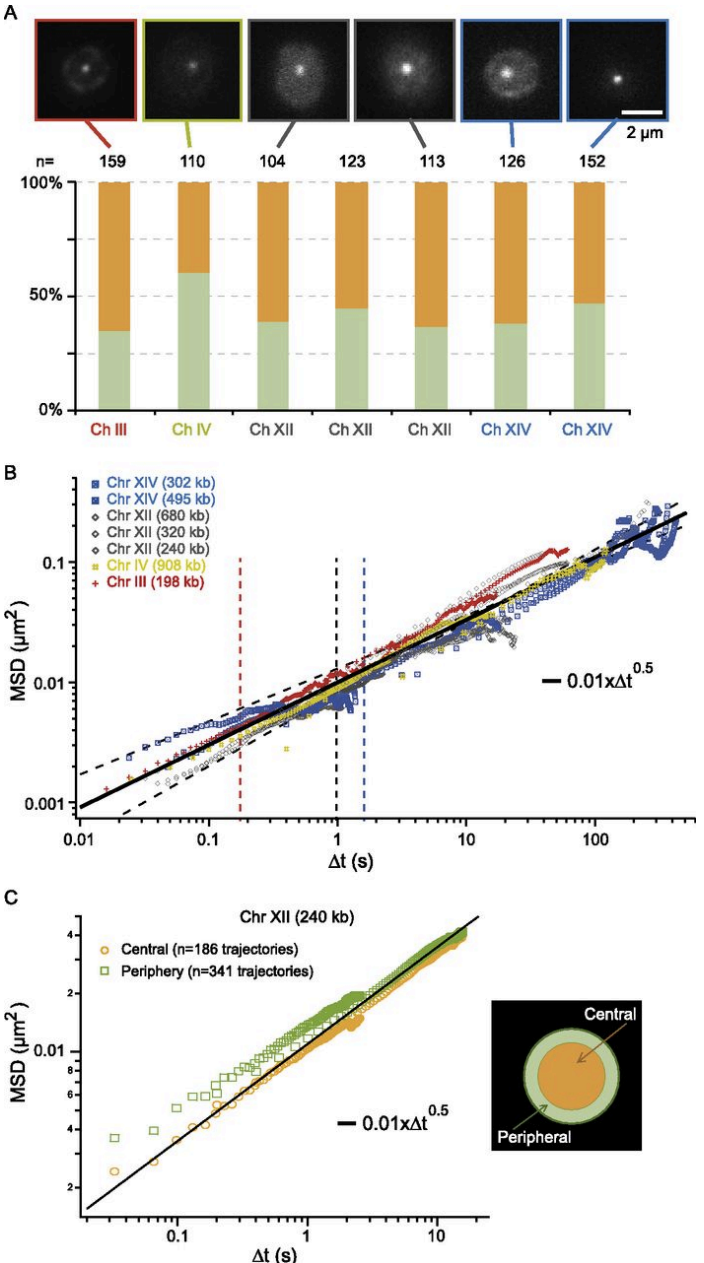
In spite of its simplicity the Rouse model describes well loci dynamics in yeasts, up to 4 order of magnitude in time-scale

Collection of loci used to monitor chromosome spatio-temporal dynamics.





TelVIR, G1 phase
Heun *et al.*, Science (2001)



High-throughput chromatin motion tracking in living yeast reveals the flexibility of the fiber throughout the genome

Houssam Hajjoul et al. Genome Res. 2013;23:1829-1838

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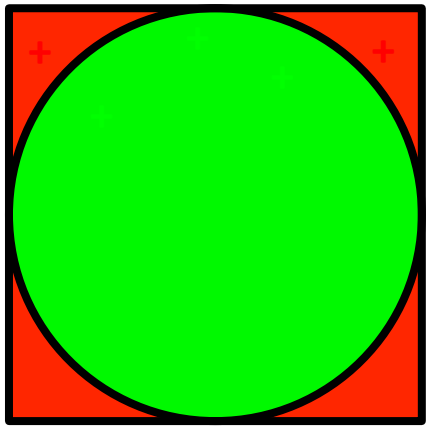
Computer simulations: 1. Monte Carlo

- Problem: Numerical evaluation of π=3.1415926535…



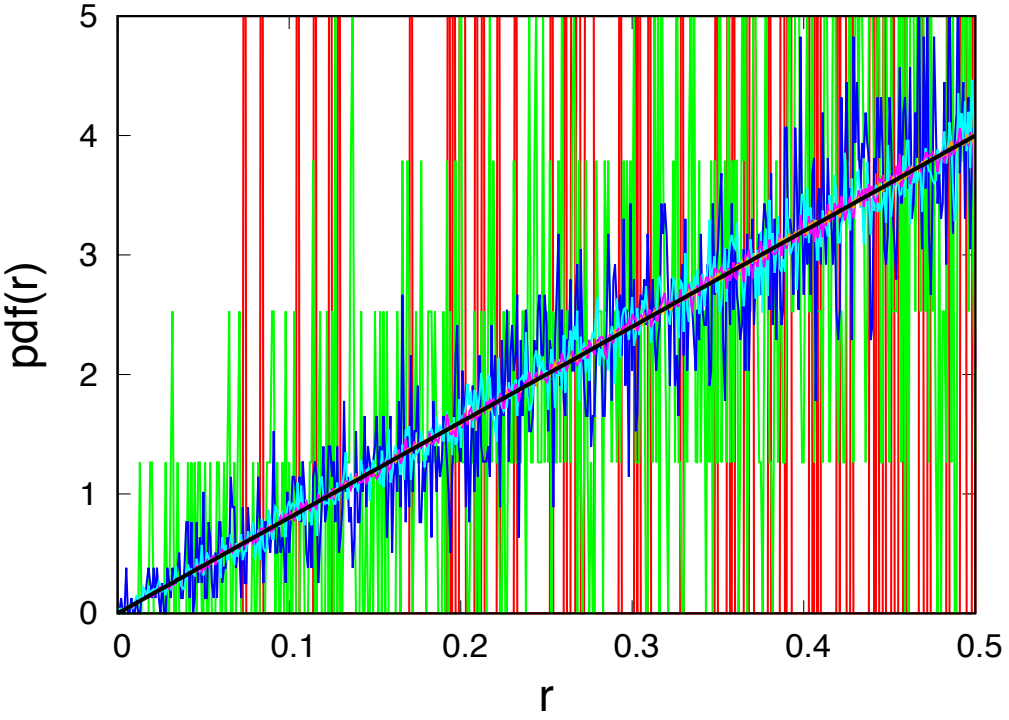
$$\pi = 4 \times \frac{\text{Area sphere}}{\text{Area square}}$$

$$\pi \approx 4 \times \frac{N_{in}}{N_{tot}} \equiv \frac{N_{in}}{N_{in} + N_{out}}$$

N_{tot}	Result
100	2.96 ± 0.18
1'000	3.17 ± 0.05
10'000	3.152 ± 0.016
100'000	3.1465 ± 0.0052
1'000'000	3.1427 ± 0.0016
10'000'000	3.14146 ± 0.00052

Computer simulations: 1. Monte Carlo

- In practice, MC means to sample the space of configurations with the "correct" probability. In this case, the uniform distribution on the 2d circle: $\mathrm{p.d.f}(r) = 8\,r$

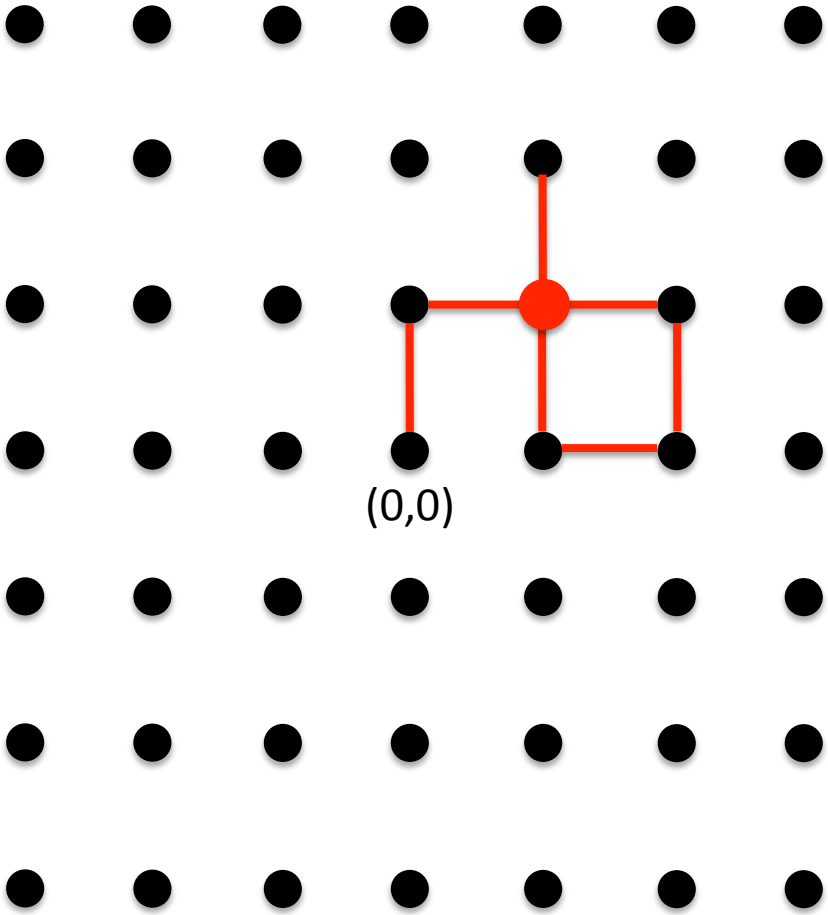


N_{tot}=100
N_{tot}=1'000
N_{tot}=10'000
N_{tot}=100'000
N_{tot}=1'000'000
N_{tot}=10'000'000

The **black line** corresponds to the exact expression

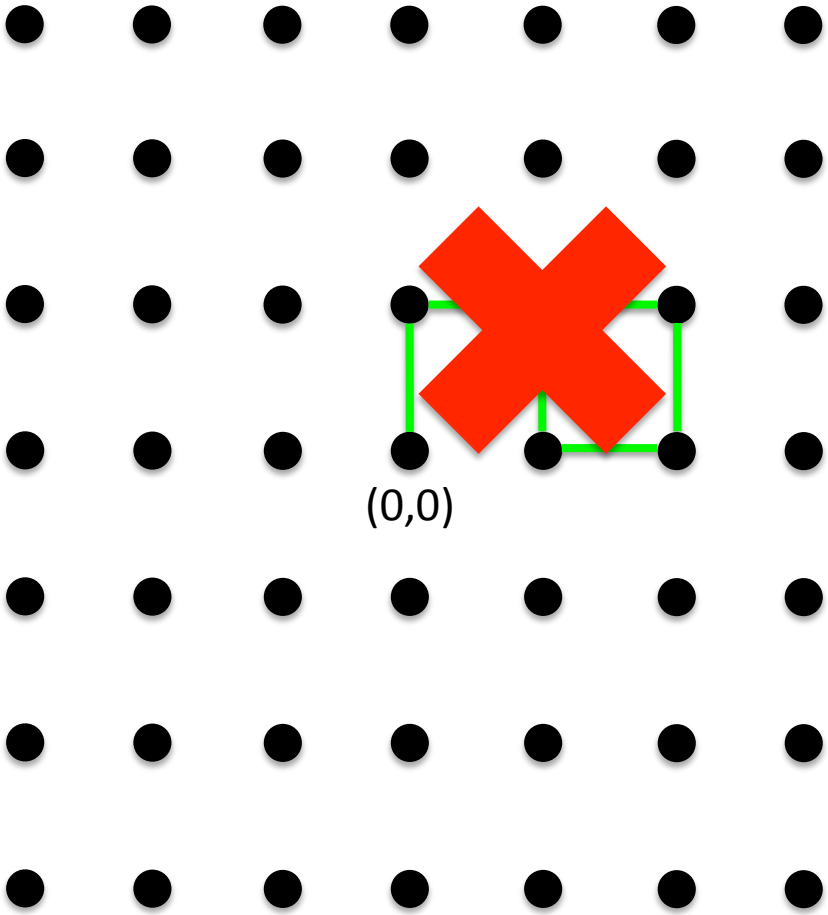
Computer simulations: 2. Monte Carlo for polymers

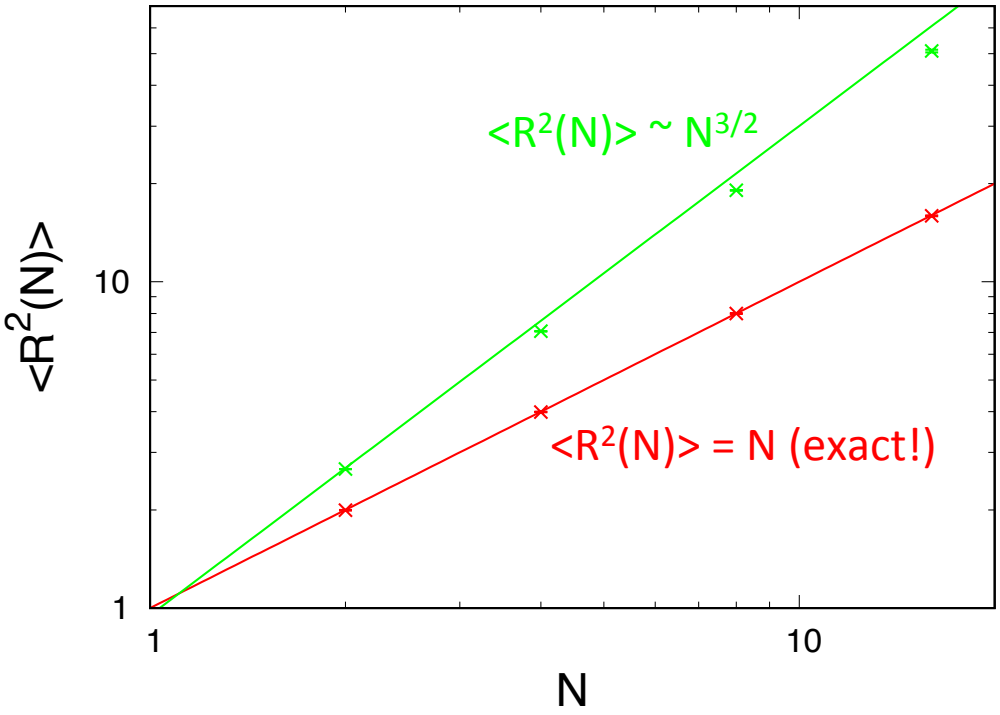
- Example: Random-walk *vs.* Self-avoiding-walk in 2 dimensions



Computer simulations: 2. Monte Carlo for polymers

- Example: Random-walk *vs.* Self-avoiding-walk in 2 dimensions





- Simple sampling not efficient, good only for very short polymers (up to ~N=30)
- More efficient methods needed, look at: Alan D. Sokal, "Monte Carlo methods for the self-avoiding walk", http://arxiv.org/abs/hep-lat/9509032

Computer simulations: 2. Molecular Dynamics

- Numerical solution of Newton's equations for a system of N particles (coupled to each other):

$$\vec{F}_n(\vec{r}_1, \vec{r}_2, ..., \vec{r}_N) = m\,\vec{a}_n = m\,\frac{d^2\vec{r}_n}{dt^2}, \quad \text{with } n = 1, ..., N$$

By Taylor expansion, the spatial positions $\vec{r}_n(t+\delta t)$ and $\vec{r}_n(t-\delta t)$ for "small" time increments δt are given by:

$$\vec{r}_n(t+\delta t) \approx \vec{r}_n(t) + \frac{d\vec{r}_n(t)}{dt}\delta t + \frac{1}{2}\frac{d^2\vec{r}_n(t)}{dt^2}\delta t^2 + \frac{1}{6}\frac{d^3\vec{r}_n(t)}{dt^3}\delta t^3 + \mathcal{O}(\delta t^4) \quad (1)$$

$$\vec{r}_n(t-\delta t) \approx \vec{r}_n(t) - \frac{d\vec{r}_n(t)}{dt}\delta t + \frac{1}{2}\frac{d^2\vec{r}_n(t)}{dt^2}\delta t^2 - \frac{1}{6}\frac{d^3\vec{r}_n(t)}{dt^3}\delta t^3 + \mathcal{O}(\delta t^4) \quad (2)$$

Adding these two expressions together and taking into account Newton's equation we obtain the following approximate expression for the "time-forward" particle position $\vec{r}_n(t+\delta t)$:

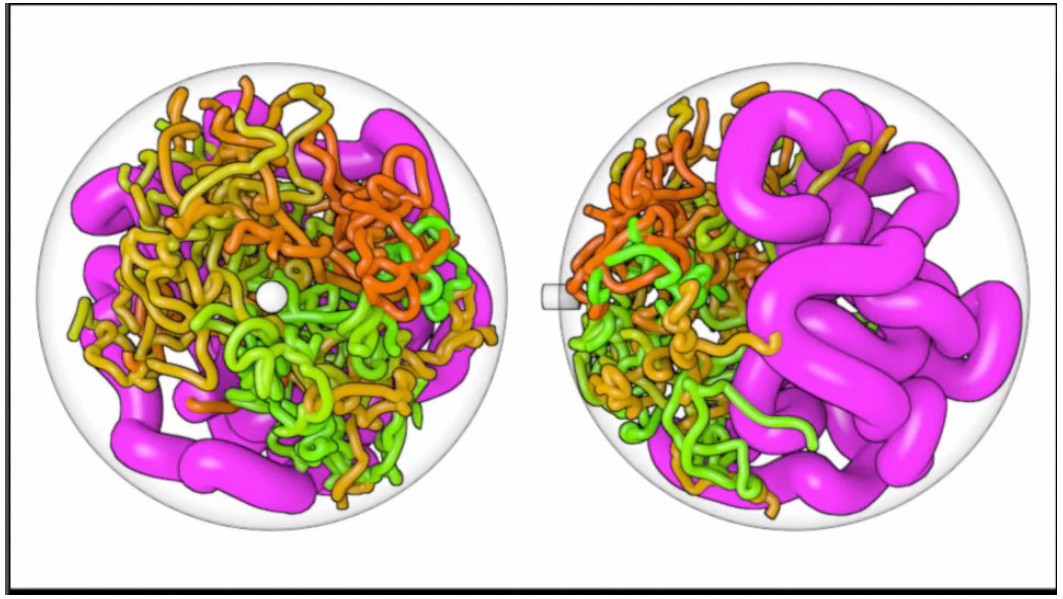
$$\vec{r}_n(t+\delta t) \approx 2\vec{r}_n(t) - \vec{r}_n(t-\delta t) + \frac{1}{m}\vec{f}_n(t)\delta t^2 + \mathcal{O}(\delta t^4) \quad (3)$$

which is accurate up to $\mathcal{O}(\delta t^4)$. Instead, by subtracting the two equations, we get an approximate expression for the velocity $\vec{v}_n(t) \equiv \frac{d\vec{r}_n(t)}{dt}$:

$$\vec{v}_n(t) \approx \frac{\vec{r}_n(t+\delta t) - \vec{r}_n(t-\delta t)}{2\,\delta t} + \mathcal{O}(\delta t^2)\,, \quad (4)$$

which is accurate up to $\mathcal{O}(\delta t^2)$.

Computer simulations: 2. Molecular Dynamics



Wong *et al.*, Curr Biol (2012)

Rosa & Everaers, PlosCB (2008)