A Random Loop Model for Chromatin Organization

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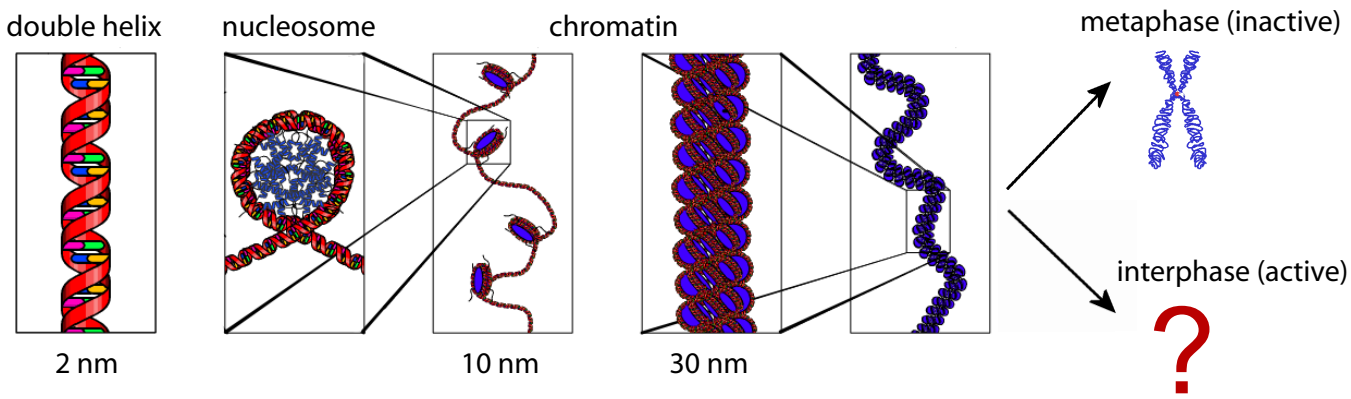
M. Bohn and D. W. Heermann, *Phys. Rev. E* **76**, 2007

Outline

Problem:

- In human cells 2 m of ds-DNA have to be packed into a nucleus of 10 μm diameter.
- The first stages of compaction are well-known



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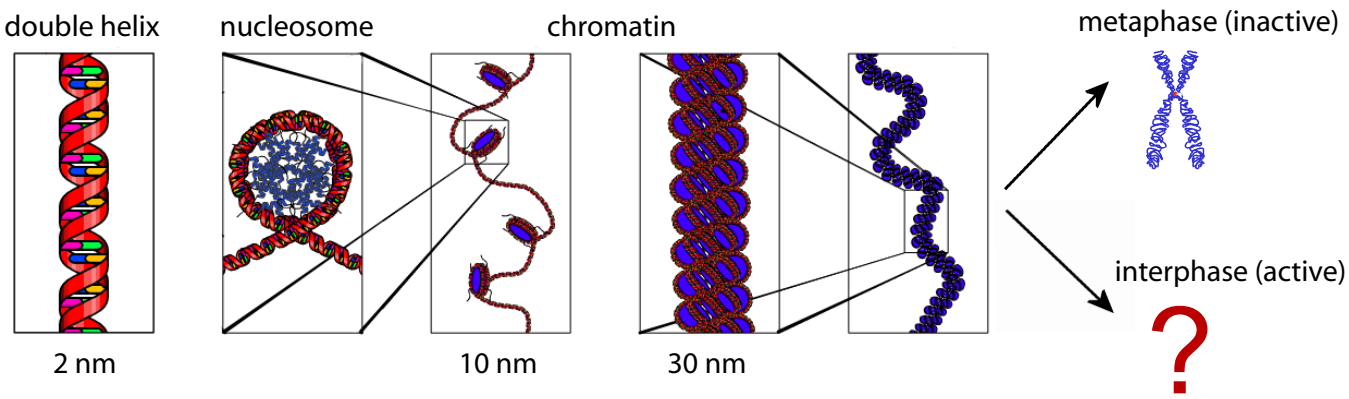
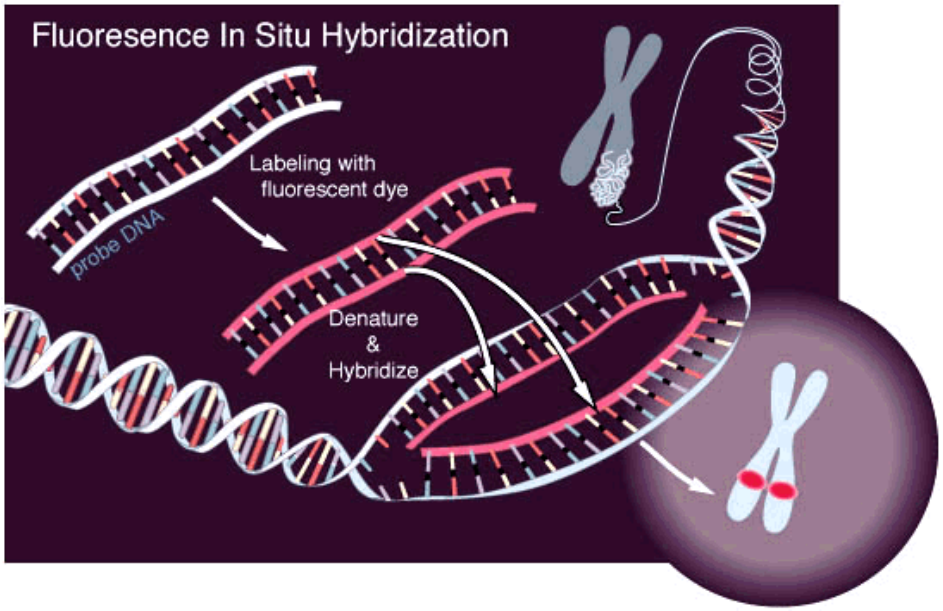
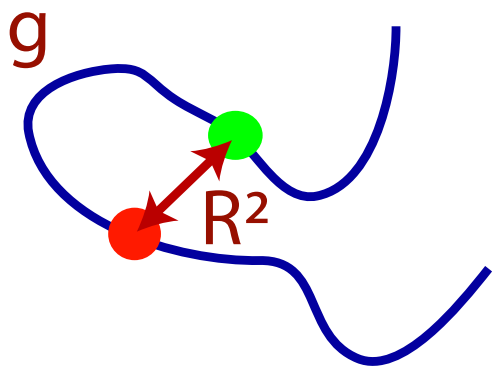


- The higher-order structure during interphase is widely unknown. Is the chromatin fibre just a random coil or is it somehow organized?
- How is the structure connected to the complex functionality of the nucleus?

Biological Background – Experimental approaches

- limitations of light microscopy $\rightarrow$ indirect approaches
- *FISH* (flourescence in situ hybridization)





- measurement of mean physical distance $\langle R^2 \rangle$ between two *FISH*-markers of known genomic distance g gives information about folding motifs and can be compared to polymer models

Polymer models

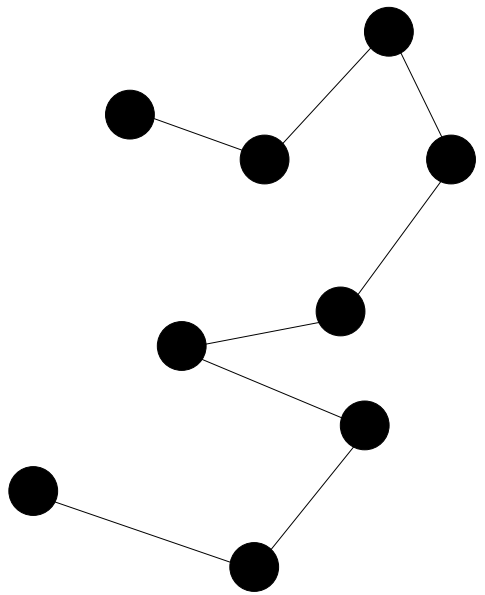
Long macromolecules often can be described by simple polymer models. On a scale much larger than a single molecule the structural details and stiffness can be neglected.

basic idea:

- divide the polymer into N equal subunits
- the subunits (beads) are connected by linkers, e.g.

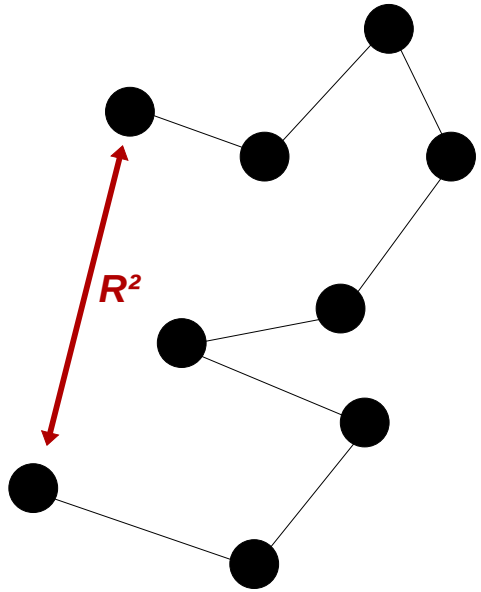
$$U = \sum_{i=1}^{N} \frac{1}{2} \kappa \parallel \mathbf{x}_i - \mathbf{x}_{i-1} \parallel^2$$

- two chain segments can rotate freely around each other



Polymer models – Gaussian chain model

- A characteristic feature of a polymer model is the mean squared end-to-end distance $\langle R^2 \rangle$



- For a Gaussian chain $U = \sum_{i=1}^{N} \frac{1}{2}\kappa \parallel \mathbf{x}_i - \mathbf{x}_{i-1} \parallel^2$, we have

$$\langle R^2 \rangle = b^2 N \qquad b^2 = \frac{3}{\kappa}$$

The proportionality to N is a universal feature and is also valid for other choices of U, e.g. stiff linkers

Polymer models – Effect of excluded volume

- In most applications, excluded volume interactions have to be taken into account, e.g. by an additional potential

$$U_{ex} = v k_B T \sum_{i<j} \delta(\mathbf{x}_i - \mathbf{x}_j)$$

- The relation for the mean square displacement changes to

$$\langle R^2 \rangle = b^2 N^{2\nu} \qquad \nu \approx 0.588$$

- But: Exact calculations become impossible

Polymer models – globular state

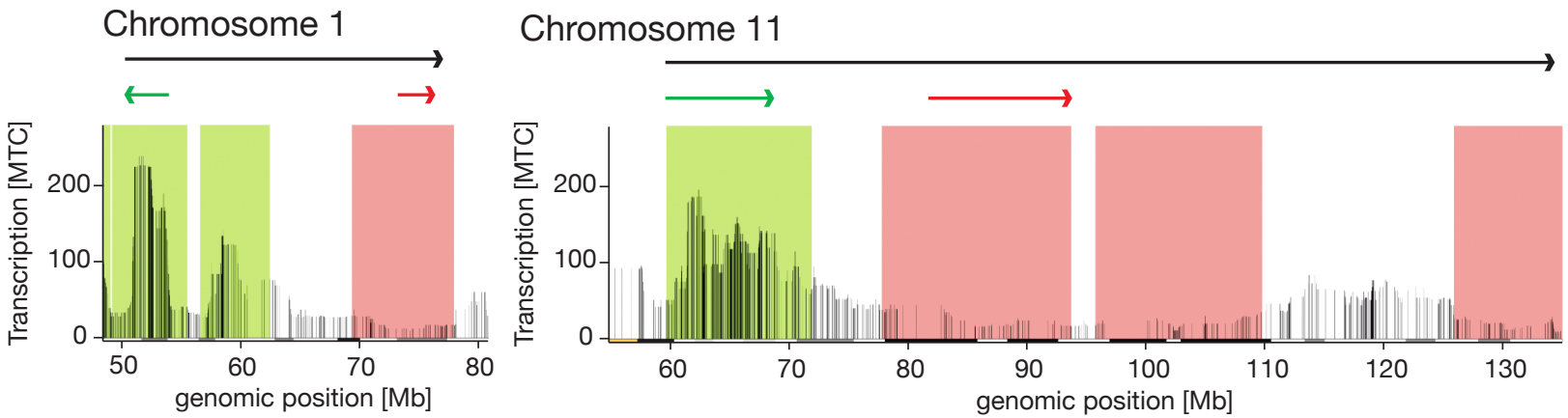
Third important polymer state: globular state

- further attractive interactions counteract excluded volume interactions
  $\longrightarrow$ collapse of the polymer
- e.g. proteins
- mean square displacement

$$\left\langle R^2 \right\rangle = b^2 N^{2\nu}, \qquad \nu = 1/3$$

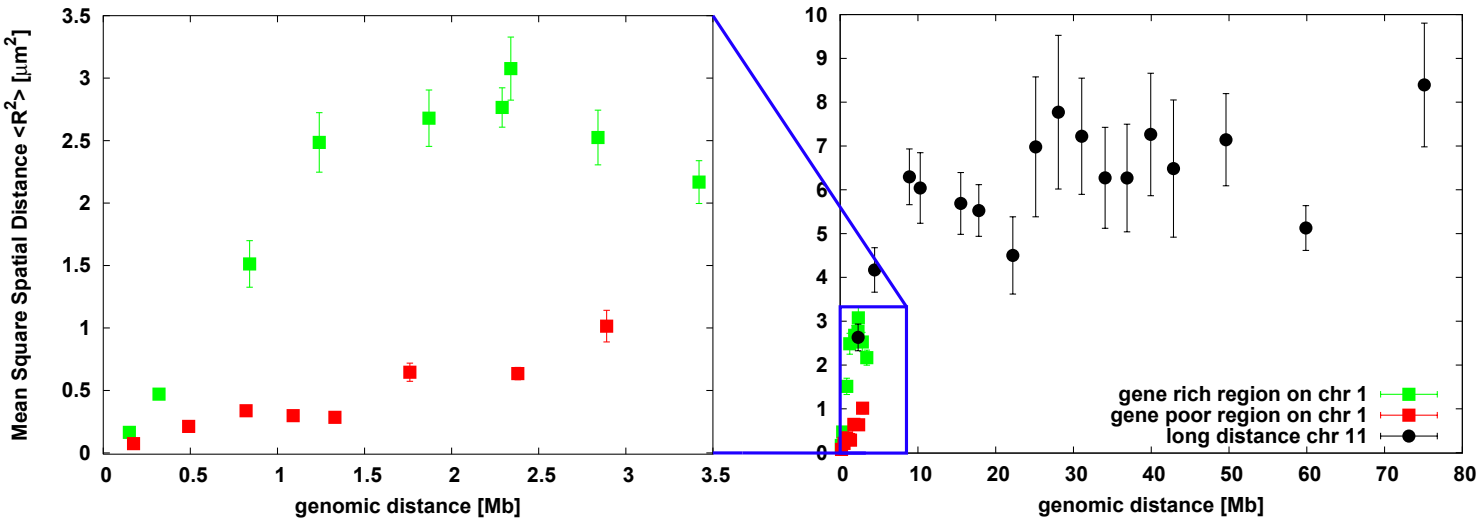
Experimental results

- Experiments (Roel van Driel, Amsterdam) measure mean square displacement in relation to genomic distance[1]
  - chromosome 1 and 11
  - gene-rich and gene-poor domains



[1] Mateos-Langerak *et al.*, 2007 (submitted to PNAS)

Experimental results



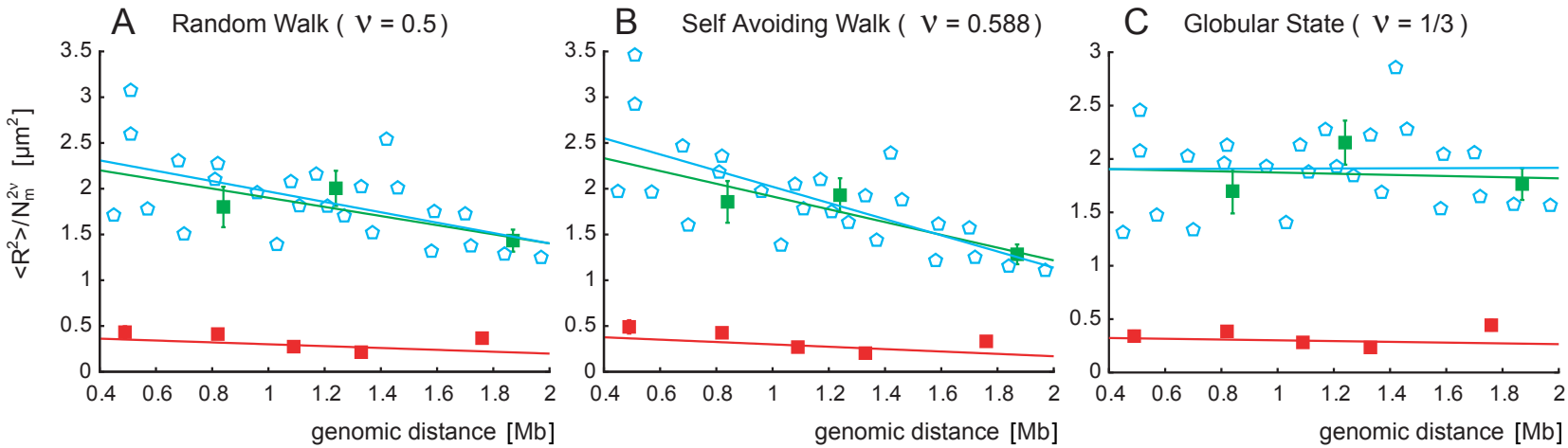
Results:

- Up to 2-3 Mb the mean square displacement (MSD) increases with genomic separation.
- Above this distance, the mean square displacement levels off and becomes independent of genomic distance

Experimental results

Which polymer model describes best the experimental results?
small genomic distances < 3 Mb

MSD increases like $\langle R^2 \rangle \sim N^{2\nu}$, but which ν (RW, SAW, GS)?

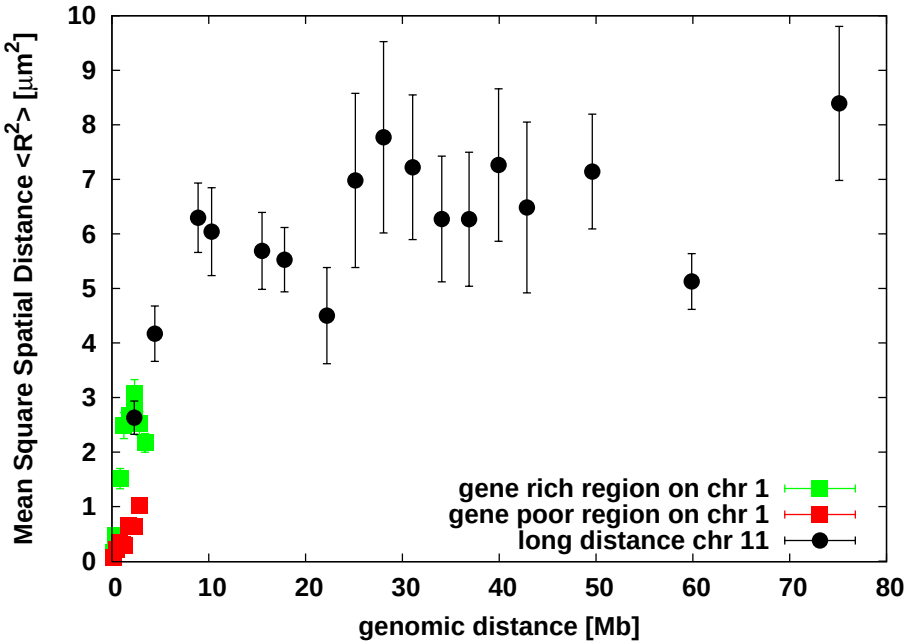


The globular state describes chromatin organization in the regime below ~ 2 Mb

additional data: Yokota *et al.*, 1995

Experimental results

Which polymer model describes best the experimental results?
large genomic distances

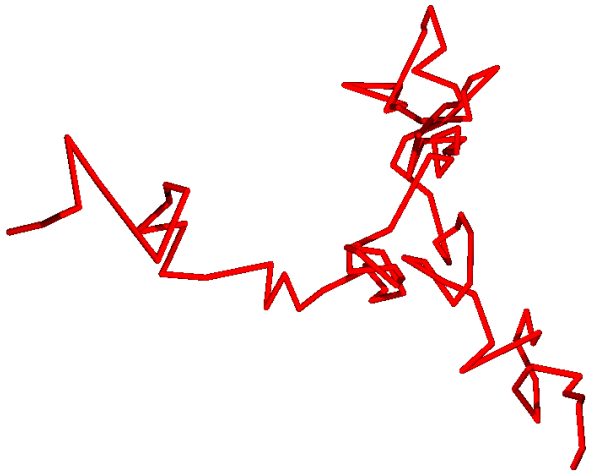


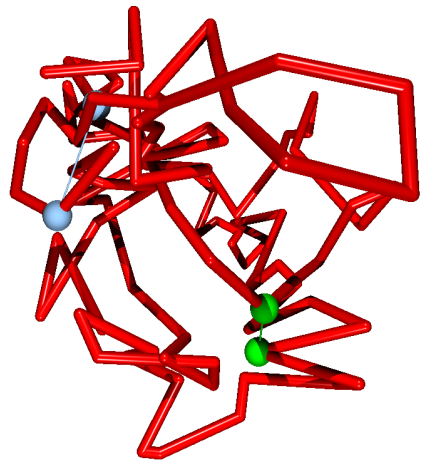
None of the polymer models with $\langle R^2 \rangle \sim N^{2\nu}$ can explain folding behaviour

A new model: the Random Loop Model

Idea

The formation of loops is necessary to obtain $\langle R^2 \rangle \sim \mathcal{O}(1)$





- The number of loops and their size are random and change in the course of time
- biological justification: there is evidence that different genes assemble to so-called “transcription factories”.

Mathematical model

- We consider $N+1$ monomers in a general potential

$$U = \frac{1}{2} \sum_{i<j} \kappa_{ij} \parallel \mathbf{x}_i - \mathbf{x}_j \parallel^2$$

- connectivity of the chain: $\kappa_{ij} = \kappa, \quad |i-j| = 1$
- random loops: The κ_{ij} with $|i-j| > 1$ are Bernoulli distributed with probability $\mathcal{P}$

Note: We neglect the effect of excluded volume

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Question: What is the mean square physical distance between two arbitrary beads *I* and *J* of the chain?

Quenched vs. annealed average

We have two types of average in our model:

1. The thermal average over the positions $\mathbf{x}_0, \ldots, \mathbf{x}_N$, $\rightarrow$ partition sum $\mathcal{Z}$
2. The average over disorder of loops κ_{ij} (random variables)

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Two ways of averaging in disordered systems:

Quenched average	**Annealed average**
$(\tau_{dis} \gg \tau_{eq})$	$(\tau_{eq} \gg \tau_{dis})$
$\langle F \rangle = k_B T \langle \log \mathcal{Z} \rangle_{\text{dis}}$	$\langle F \rangle = k_B T \log \langle \mathcal{Z} \rangle_{\text{dis}}$

We presume that the quenched average is the relevant one!

Calculation of the quenched average

- We are interested in the mean square displacement between two arbitrary beads I and J
- The average over the thermal ensemble for quenched disorder can be calculated to be

$$\left\langle r_{IJ}^2 \right\rangle_{\text{thermal}} = 3\left(\sigma_{JJ} + \sigma_{II} - 2\sigma_{IJ}\right)$$

where

$$\sigma^{-1} = K = \begin{pmatrix} \sum_{\substack{j=0 \\ j\neq 1}}^{N} \kappa_{1j} & -\kappa_{12} & \cdots & -\kappa_{1N} \\ -\kappa_{21} & \sum_{\substack{j=0 \\ j\neq 2}}^{N} \kappa_{2j} & \cdots & -\kappa_{2N} \\ \vdots & \vdots & \ddots & \vdots \\ -\kappa_{N1} & -\kappa_{N2} & \cdots & \sum_{\substack{j=0 \\ j\neq N}}^{N} \kappa_{Nj} \end{pmatrix}$$

Calculation of the quenched average

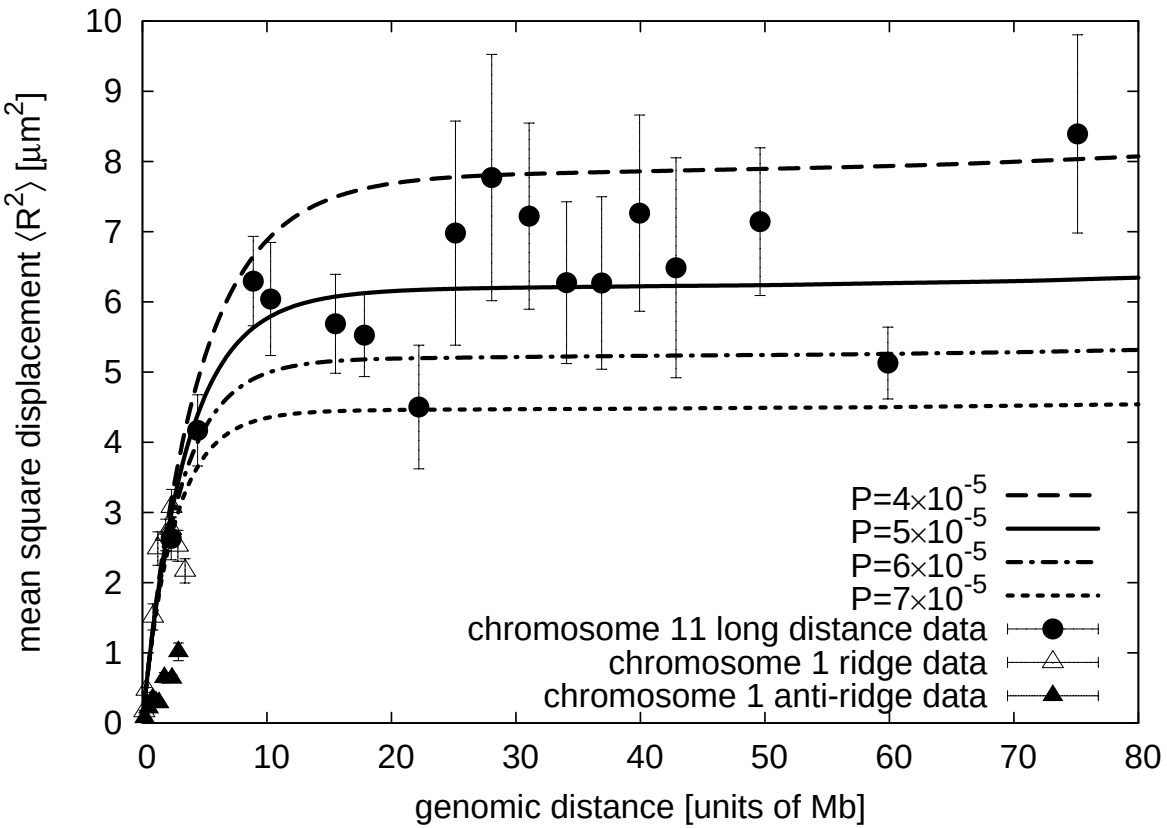
- Now we have to perform the average over the disorder of loops (the variables $\{\kappa_{ij}\}$).

$$\begin{aligned} \left\langle r_{IJ}^2 \right\rangle &= \left\langle \left\langle r_{IJ}^2 \right\rangle_{\text{thermal}} \right\rangle_{\text{loops}} \\ &= 3 \left(\left\langle \sigma_{JJ} \right\rangle_{\text{loops}} + \left\langle \sigma_{II} \right\rangle_{\text{loops}} - 2 \left\langle \sigma_{IJ} \right\rangle_{\text{loops}} \right) \end{aligned}$$

- This is equivalent to averaging over the ensemble of matrices K and can only be done numerically

Results

Mean square displacement



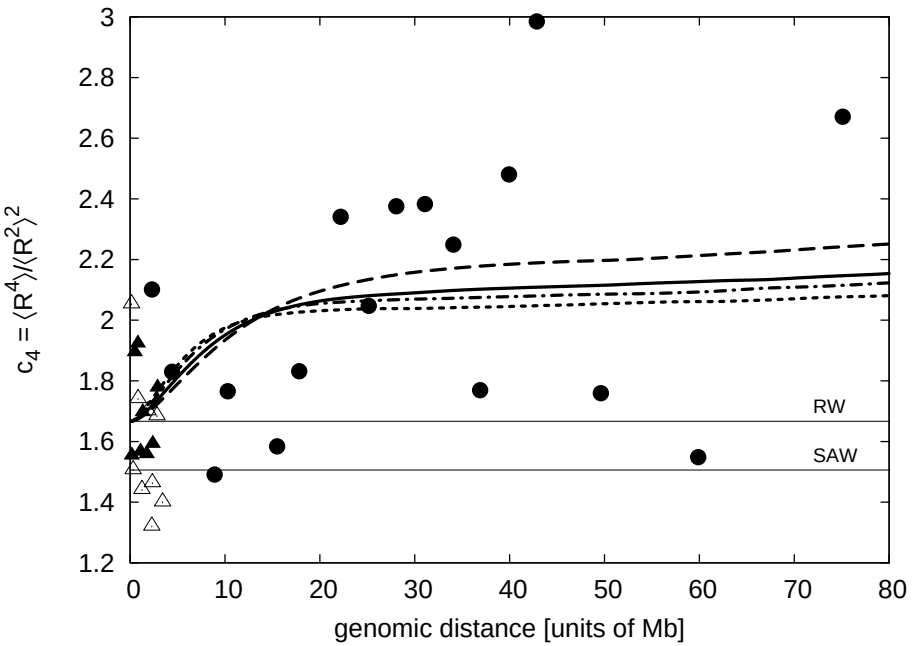
- RLM explains shows the leveling-off
- Only a few loops on all scales per 100 Mbp are necessary ($\sim$ 15)

Results

Relation between higher-order moments

$$c_4 = \left\langle R^4 \right\rangle / \left\langle R^2 \right\rangle^2$$

- Significant deviations from RW or SAW behaviour
- It is the average over the disorder in the RLM that makes c_4 larger



The effect of excluded volume

- We need to use molecular dynamics simulations (ESPResSo package)
- Excluded volume is modelled by a shifted Lennard-Jones potential with cutoff at minimum ($\rightarrow$ no attractive part).

$$U_{LJ}(r) = \begin{cases} 4\epsilon\left(\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right) + \epsilon & \text{for } r < \sqrt[6]{2}\sigma \\ 0 & \text{otherwise} \end{cases}$$

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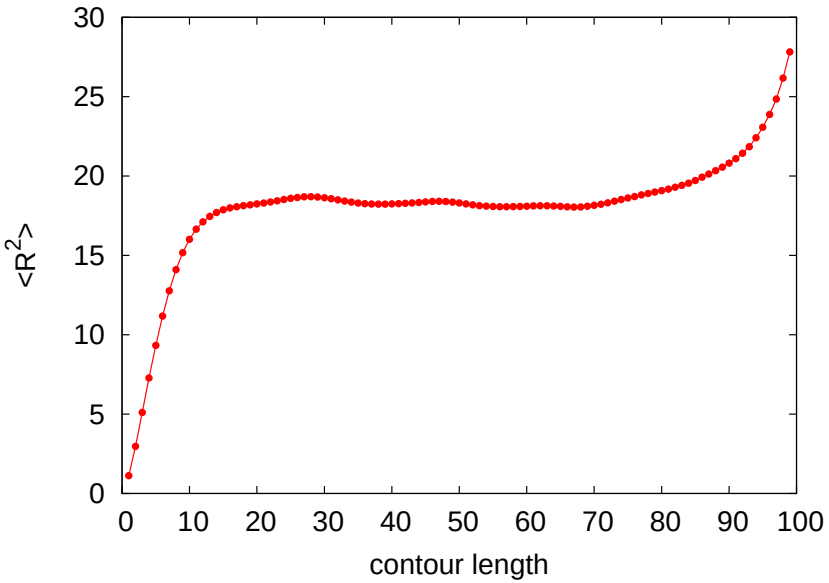

The same qualitative behaviour as without excluded volume interactions!

The annealed ensemble

- For the annealed ensemble we have to take the disorder average over the partition sum

$$\langle \mathcal{Z} \rangle_{\text{dis}} = \sum_{\{\kappa_{ij}\}} \mathcal{Z}\left(\{\mathbf{x}_k\}, \{\kappa_{ij}\}\right) \, p\left(\{\kappa_{ij}\}\right)$$

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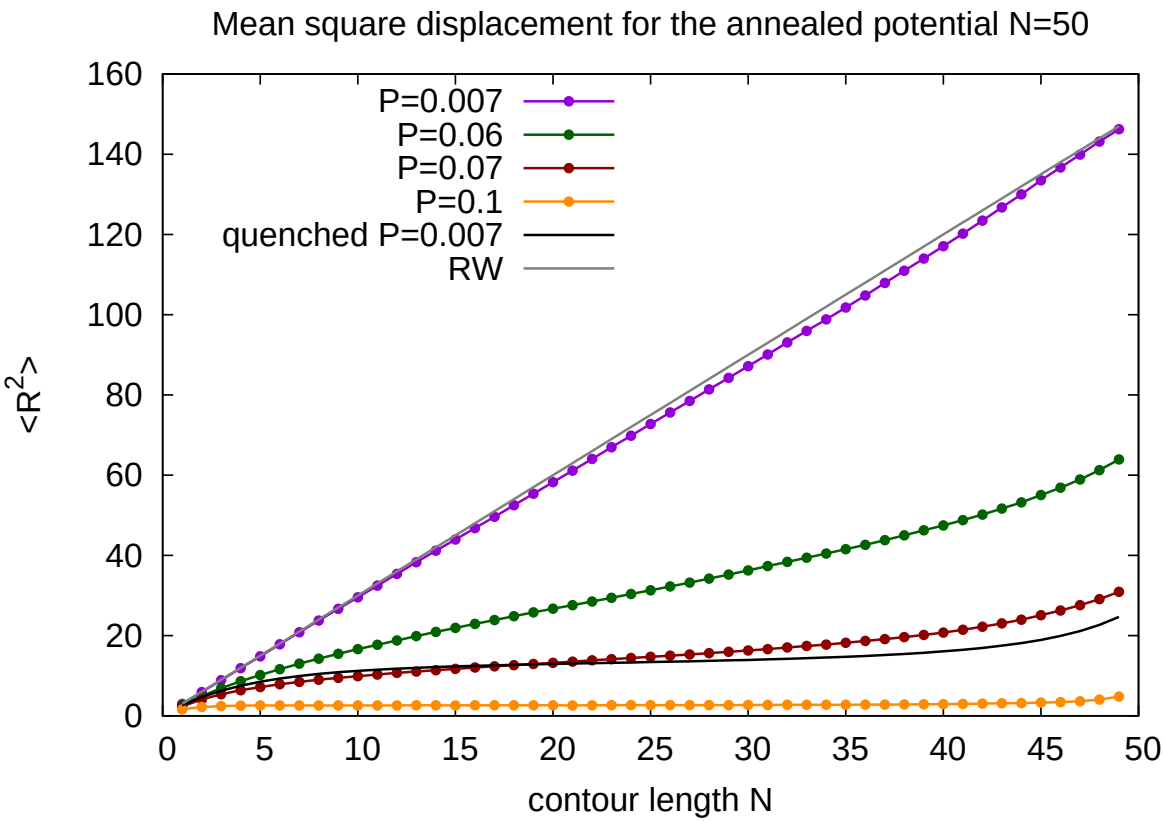
- The disorder average can be carried out, and the partition sum can be rewritten in terms of an effective potential

$$\langle \mathcal{Z} \rangle_{\text{dis}} = \int \int d\mathbf{x}_1 \ldots d\mathbf{x}_N \exp(-U_{\text{eff}})$$

$$U_{\text{eff}} = \frac{1}{2}\kappa \sum_{i=0}^{N-1} r_{i,i+1}^2 - k_B T \sum_{|i-j|>1} \log\left[1 + \mathcal{P}\left(e^{-\frac{1}{2}\kappa r_{ij}^2} - 1\right)\right]$$

The annealed ensemble

- MD simulations with annealed potential
- Leveling-off does occur only at much larger probabilities $\mathcal{P}$



Random Matrices

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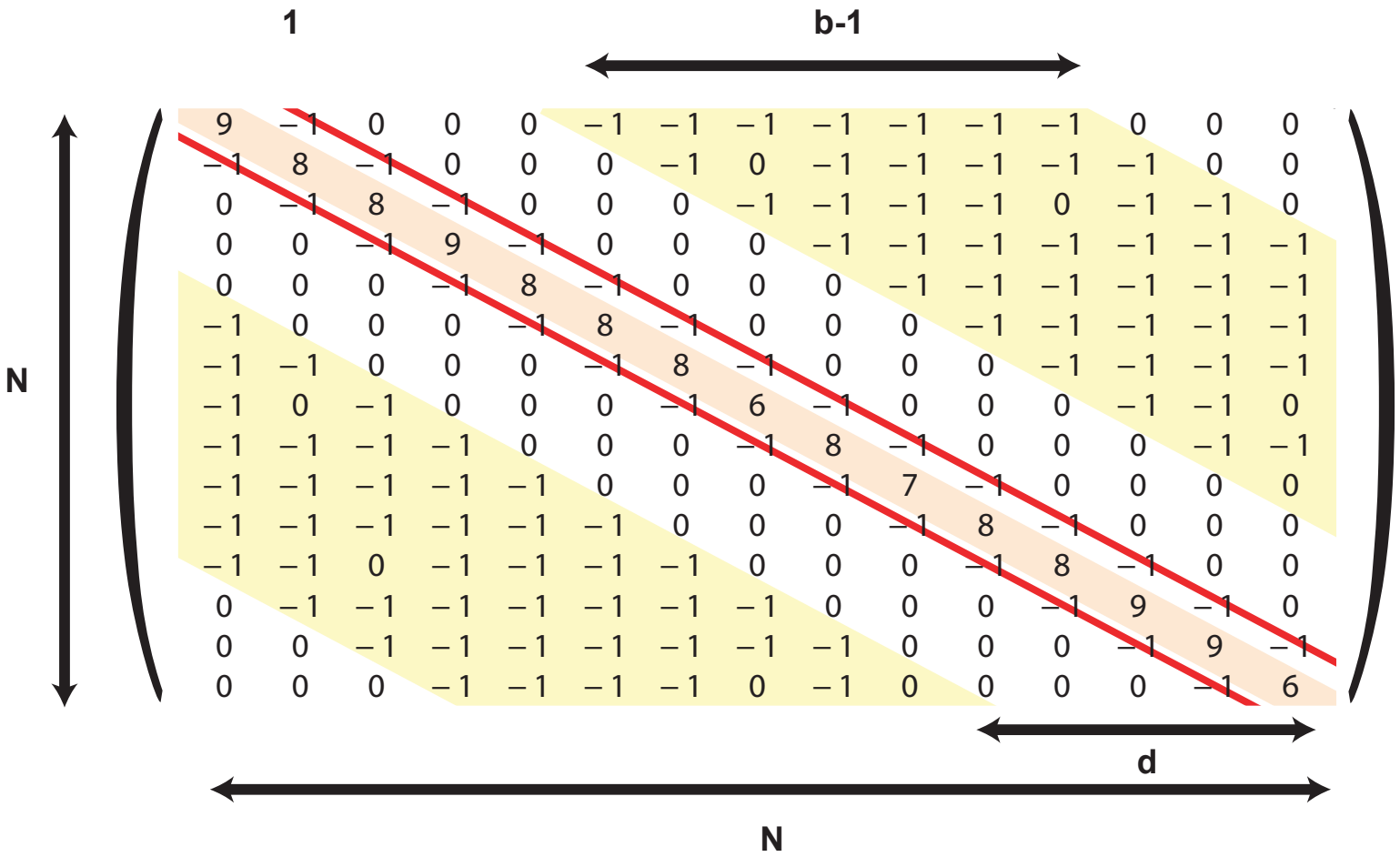
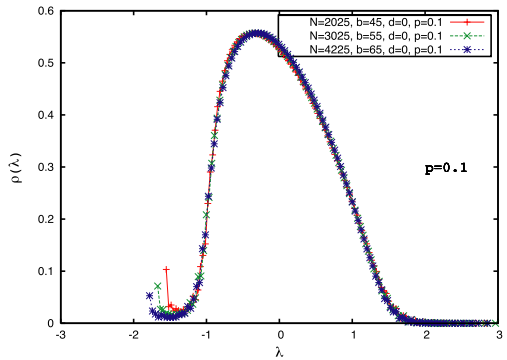
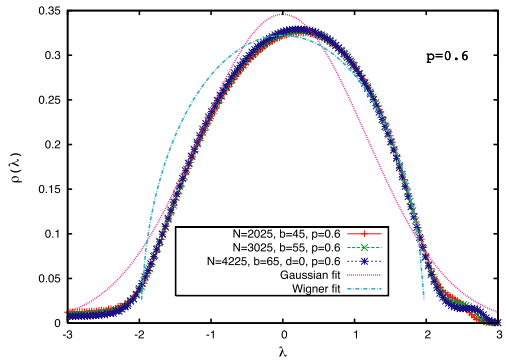
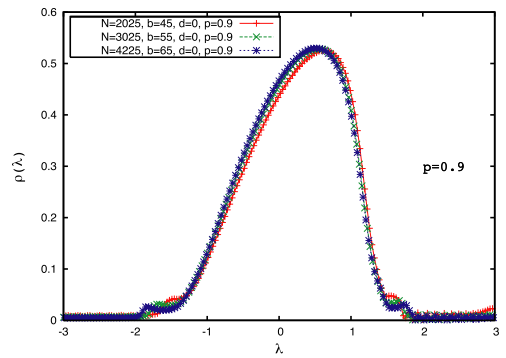


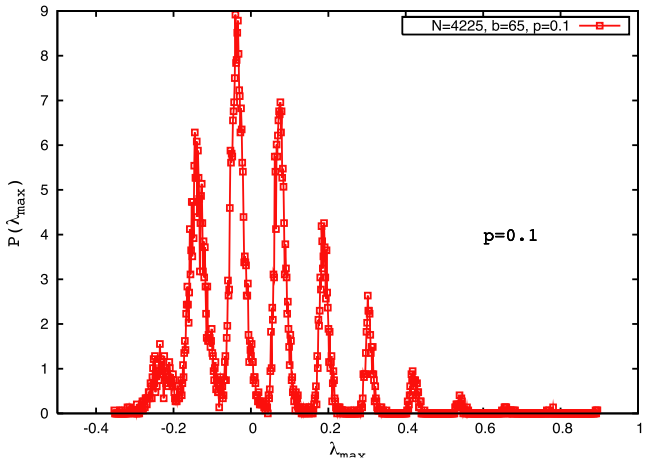
Random Matrices

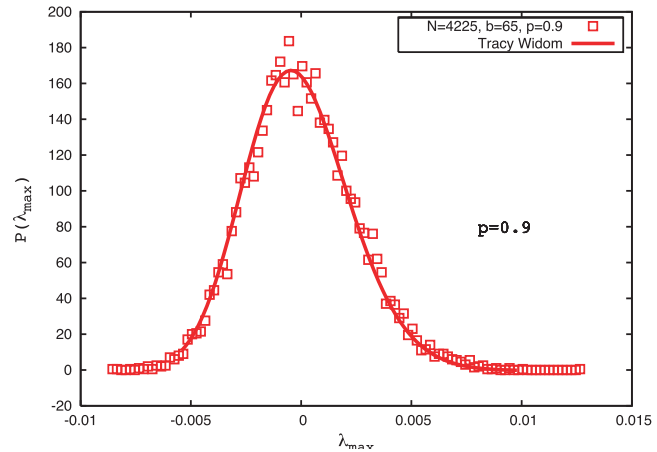
The eigenvalue distribution changes its skew at the percolation threshold. Above it shows a universal behaviour.











Conclusions

Results:

- There are two folding regimes:
  - On small genomic distances (< 2 Mb) the folding of chromatin can be described by a globular state
  - On large genomic distance ($> 5 - 10$ Mb) the folding motifs can be characterized by the formation of random loops

Open Questions:

- How can the crossover region ($2 - 10$ Mb) be described?
- Can one generalize this model to describe the common structure and intermingling of all chromosomes in the nucleus?

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Thanks for your attention!