

Structural Organization and Properties of DNA in the Cell

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University of Heidelberg

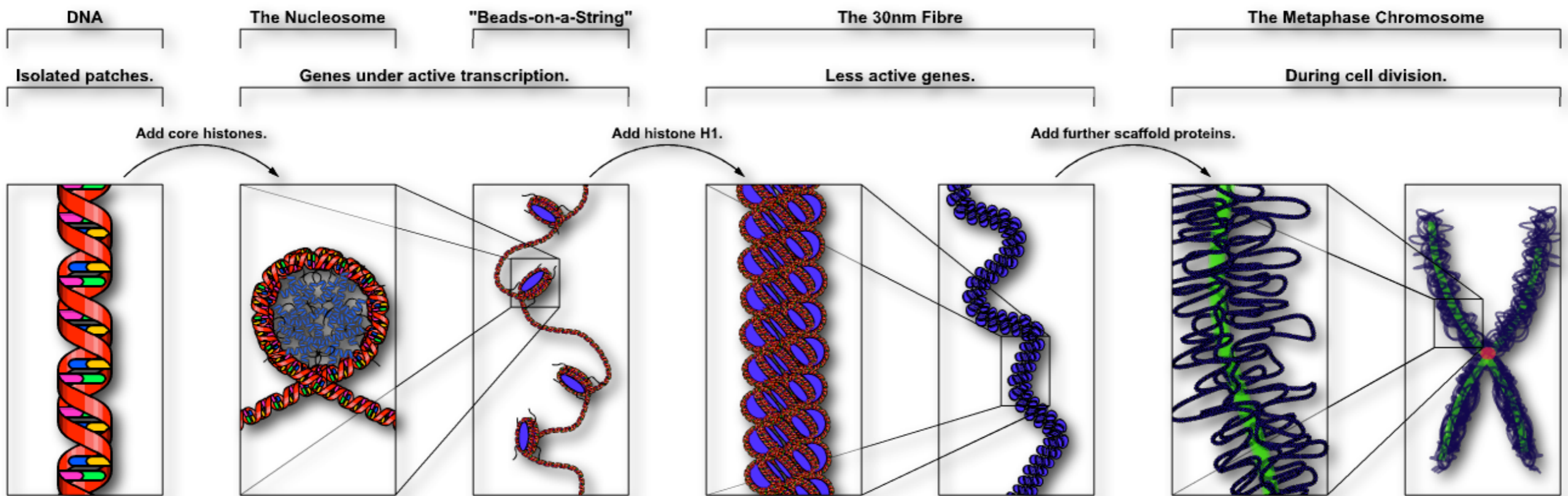
J. Odenheimer, EMBL
M. Bohn, Heidelberg Univ
S. Ritter, Heidelberg Univ
P. Diesinger, Heidelberg Univ
D. Grosse, Heidelberg Univ
Ch. Cremer, Heidelberg Univ
G. Kreth, Heidelberg Univ



S. Goetze, Amsterdam Univ
R. van Driel, Amsterdam Univ
J. Mateos-Langerak, Amsterdam Univ
W. de Leeuw, NRI for Math & Comp Sci
G. Cavalli, CNRS, Montpellier
Cornelius Murre, San Diego
L. Shopland, Jackson Lab



The Fundamental Problem





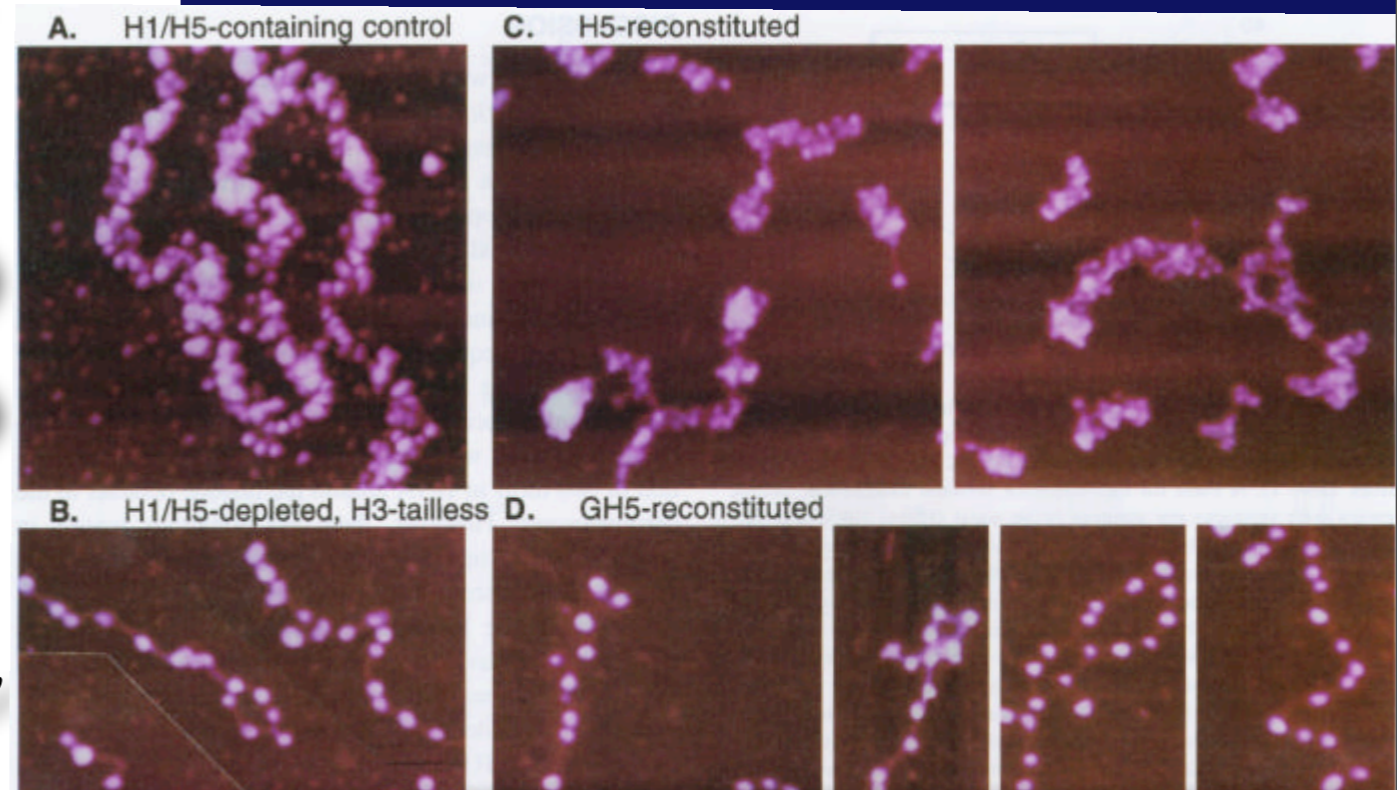
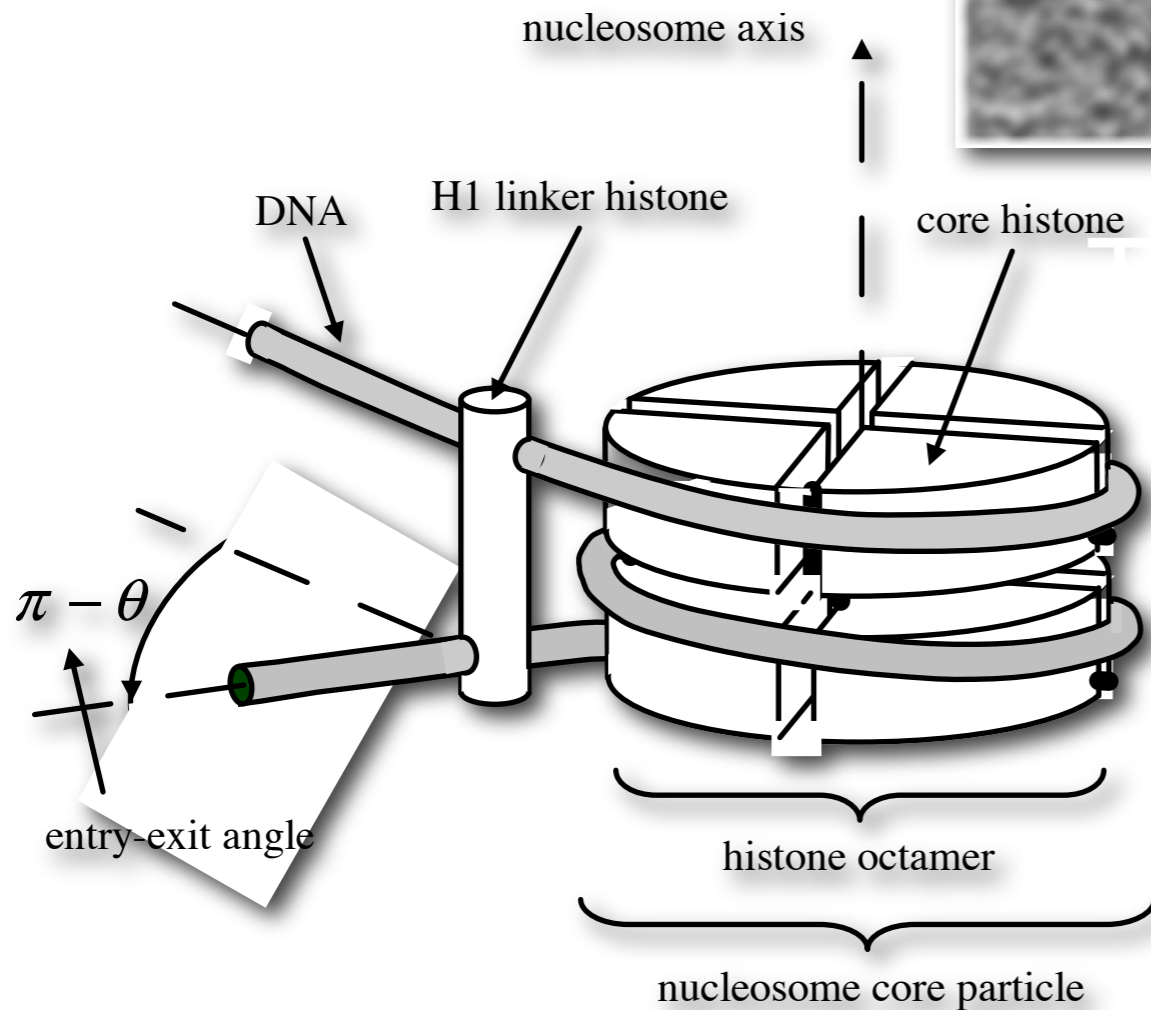
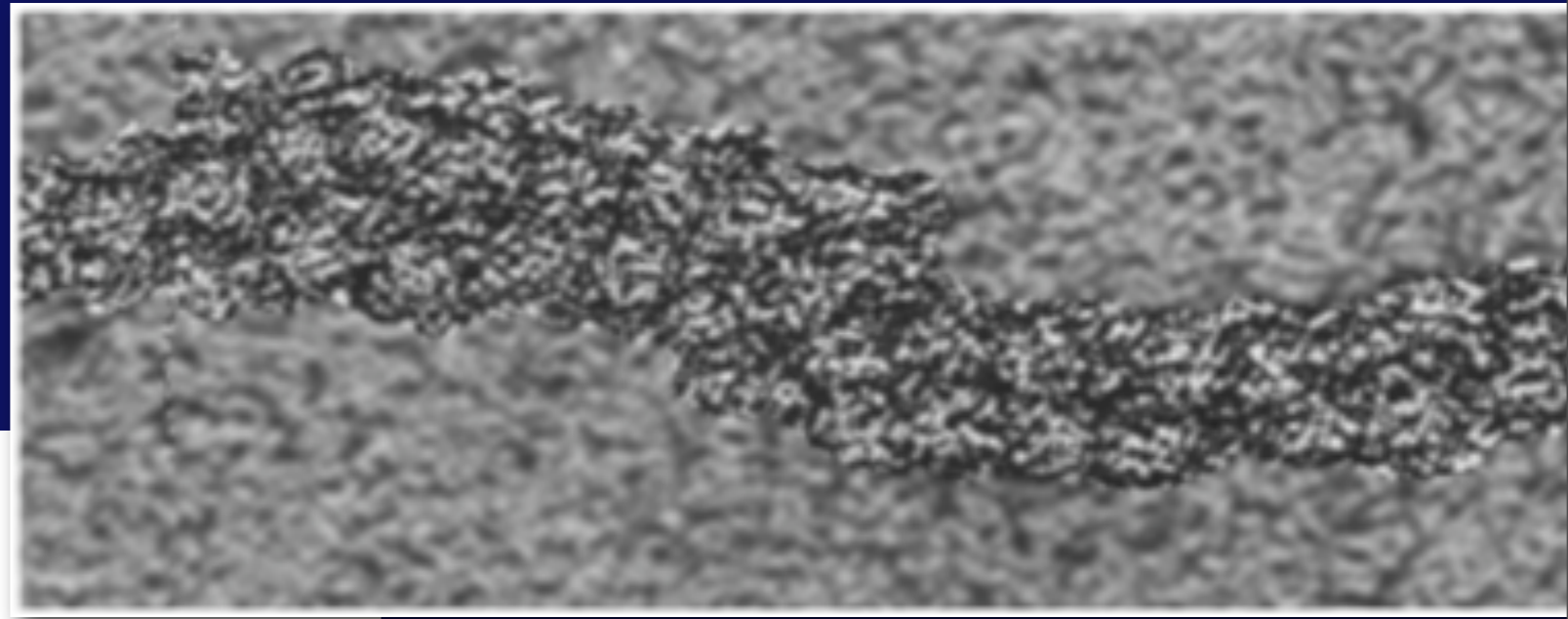
The Fundamental Problem

- **What is the structure of chromatin on the 30nm scale?**
 - What are the close packed structures?
 - What influences most the packing
- **What is the structure on scale of a chromosome in the interphase?**



30nm Fiber

Image: Waterborg, UMKC



SFM images of chromatin fibers reconstituted from intact H5 or GH5 and H1/H5-stripped, H3-tailless chicken erythrocyte chromatin fibers.

Taken from:

Sanford H. Leuba, Carlos Bustamante, Kensal van Holde, and Jordanka Zlatanova
Biophysical Journal Volume 74, June 1998, 2830-2839

Image: H. Schiessel, Leiden Univ



Modelling the 30nm Fiber

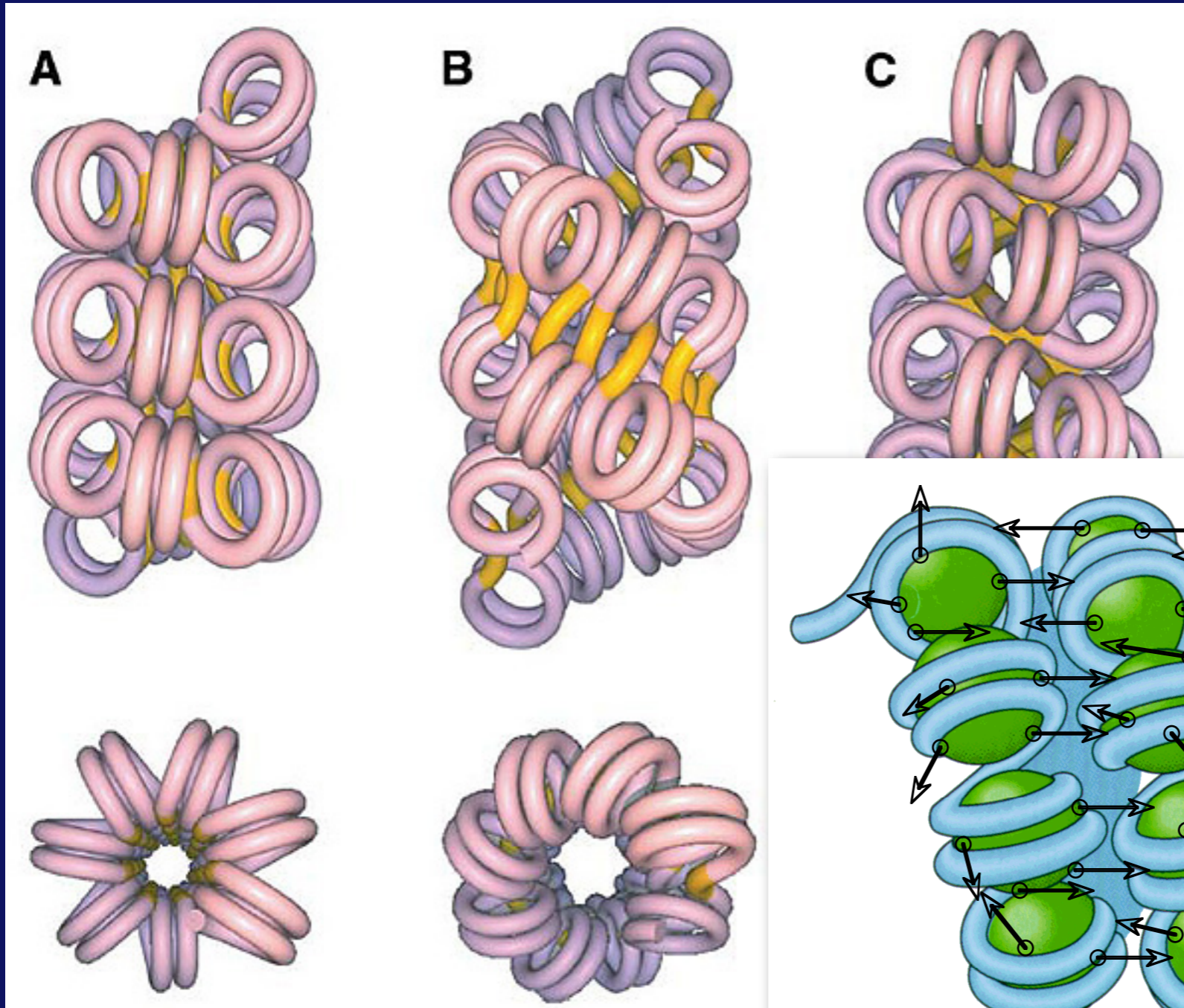
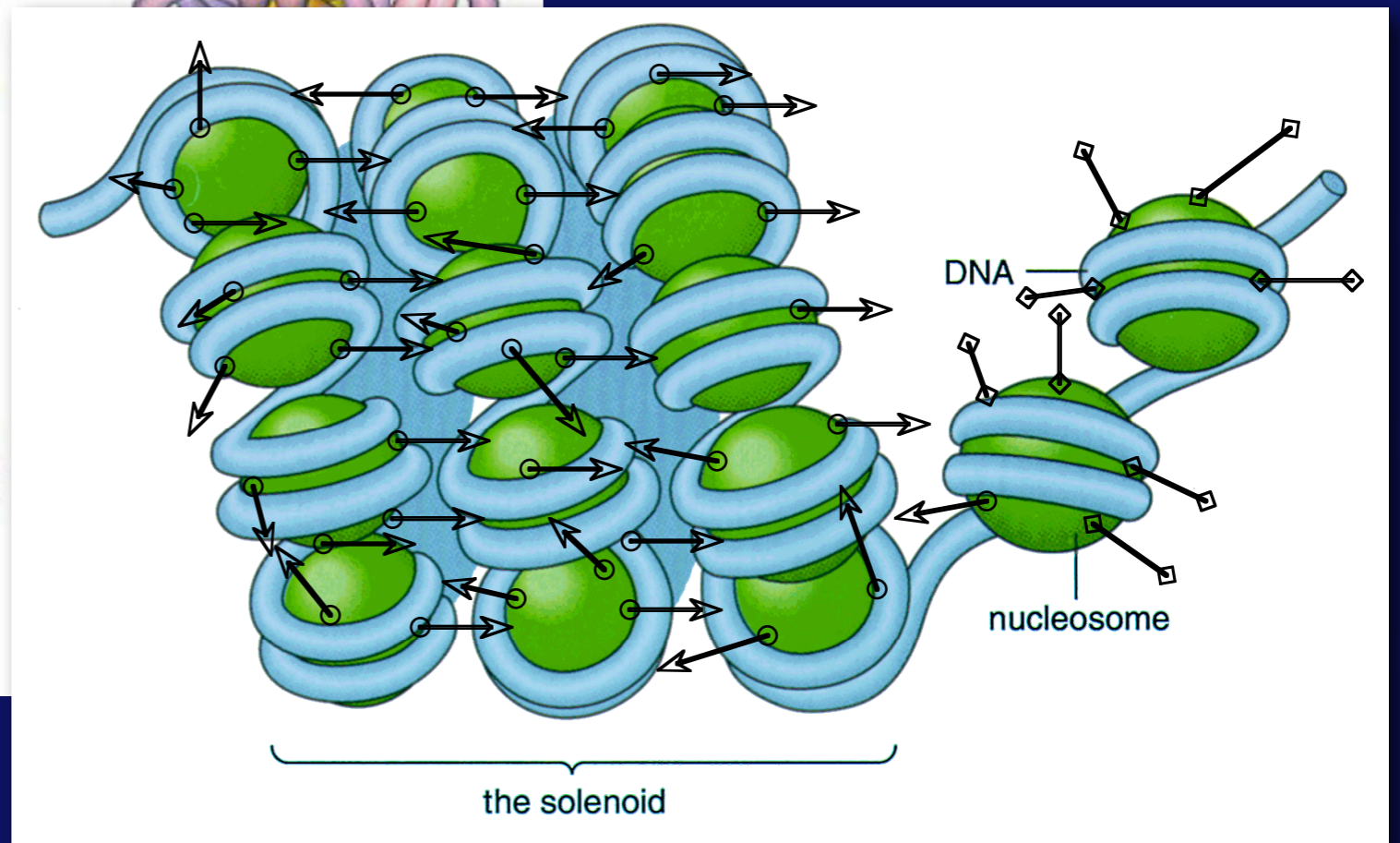


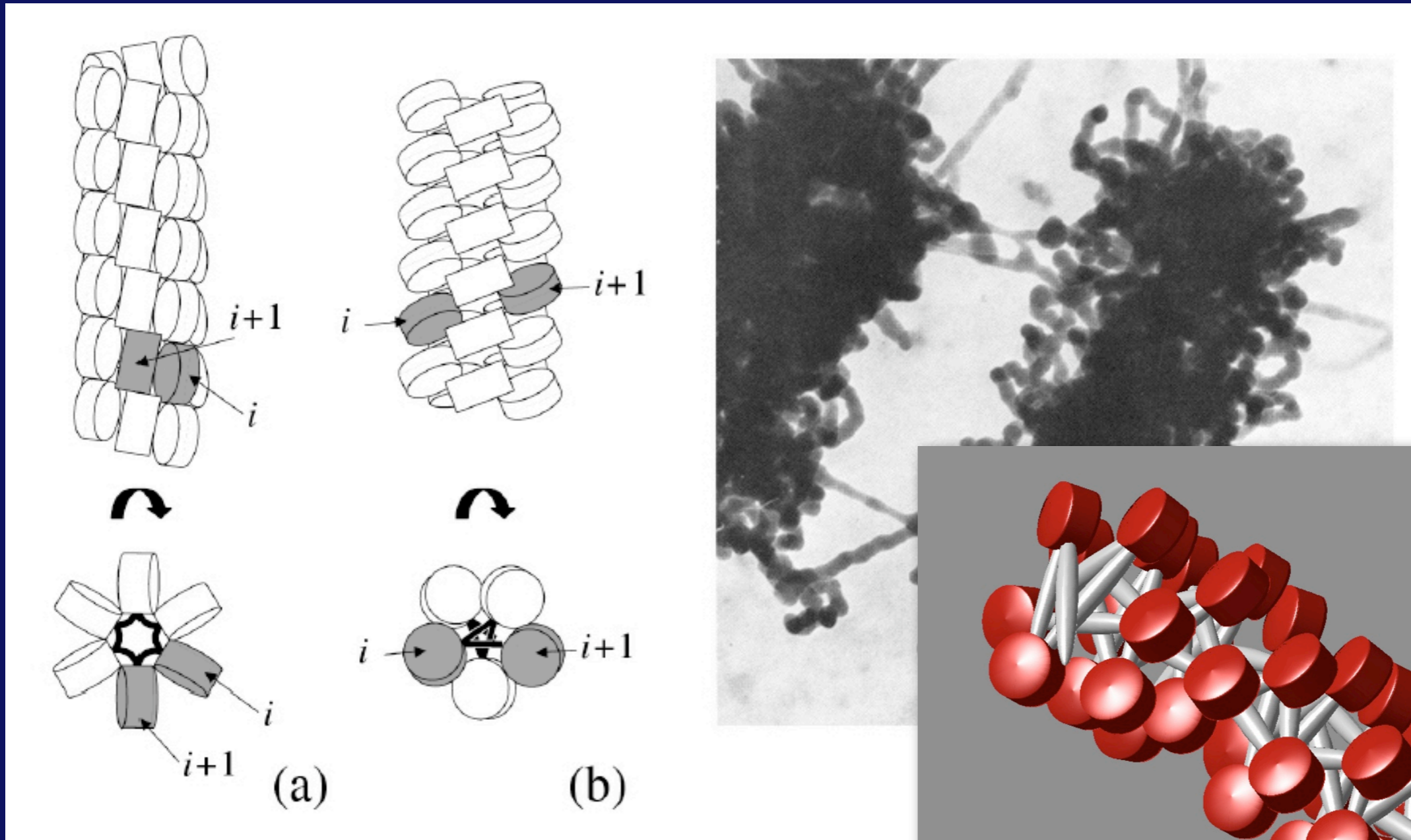
Image: Timothy Richmond

Image: Waterborg, UMKC





Modelling the 30nm Fiber

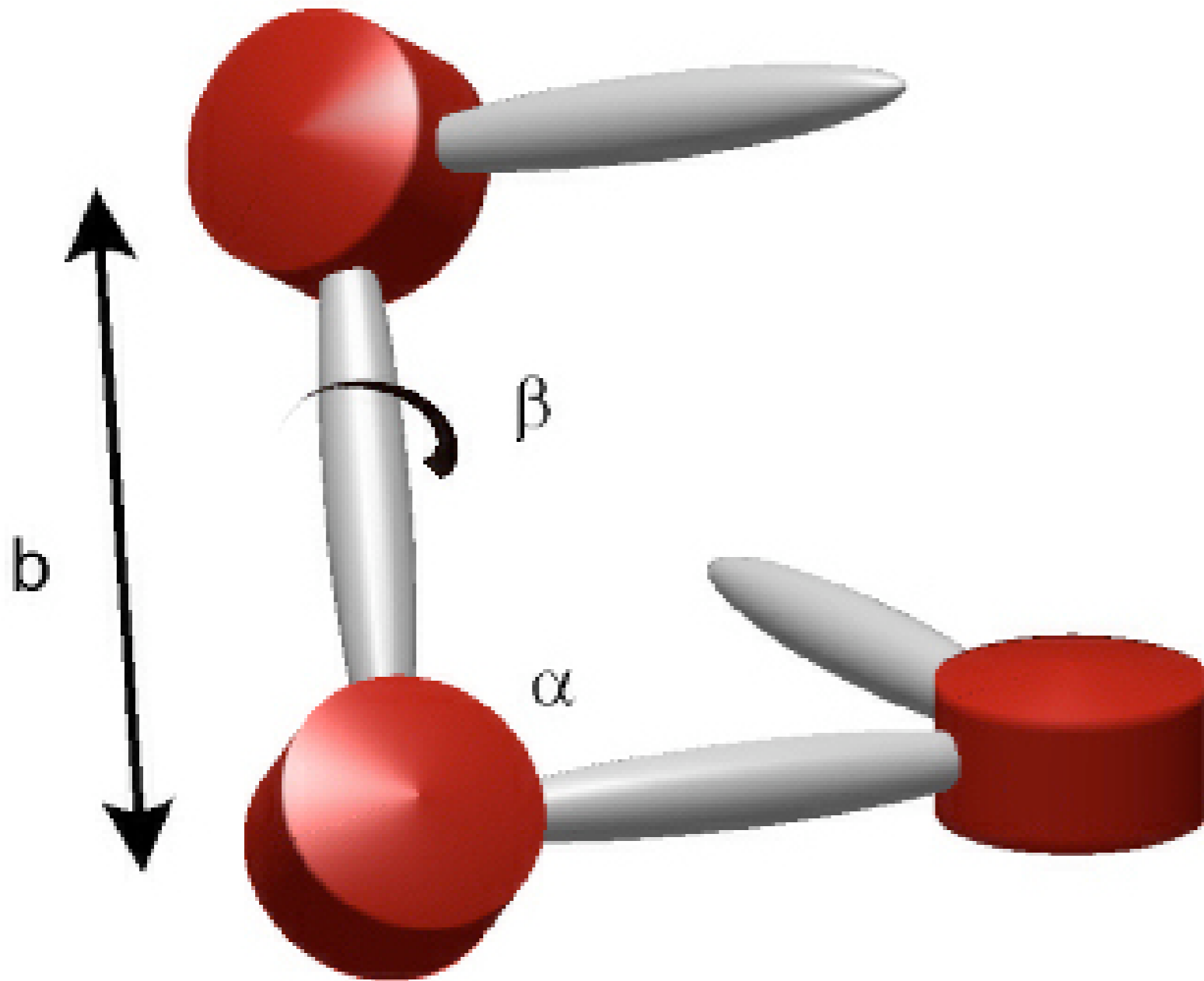


Two-Angle Model:

C. L. Woodcock, S. A. Grigoryev, R. A. Horowitz, and N. Whitaker,
Proc. Natl. Acad. Sci. USA 90:9021-9025.



30nm Fiber: *Two-Angle Model*



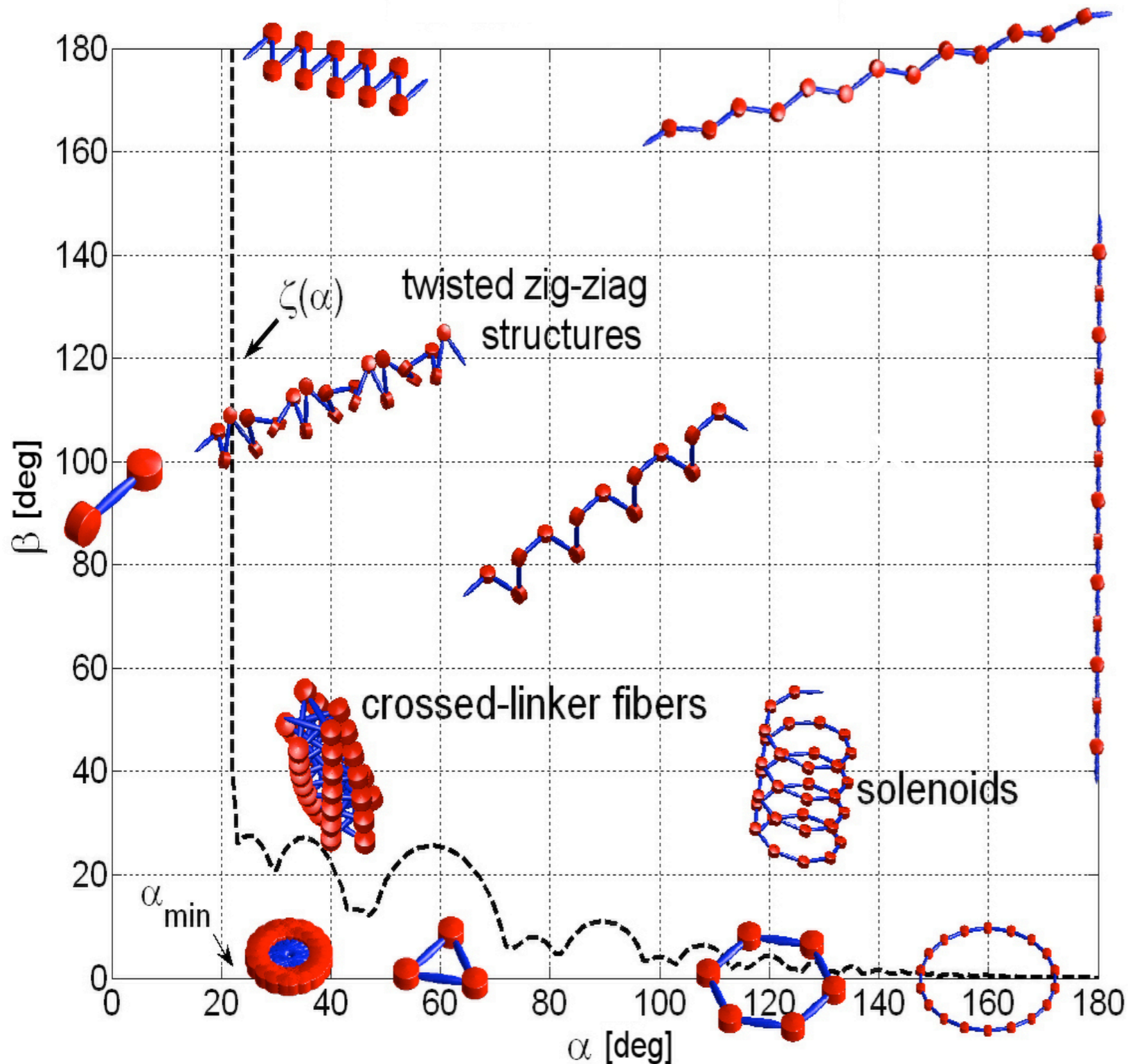
Basic definitions of the two-angle model

- The entry-exit angle α
- The linker length b
- The rotational angle β

The red cylinders represent the nucleosomes



Two-Angle Model: *Phase Diagram*



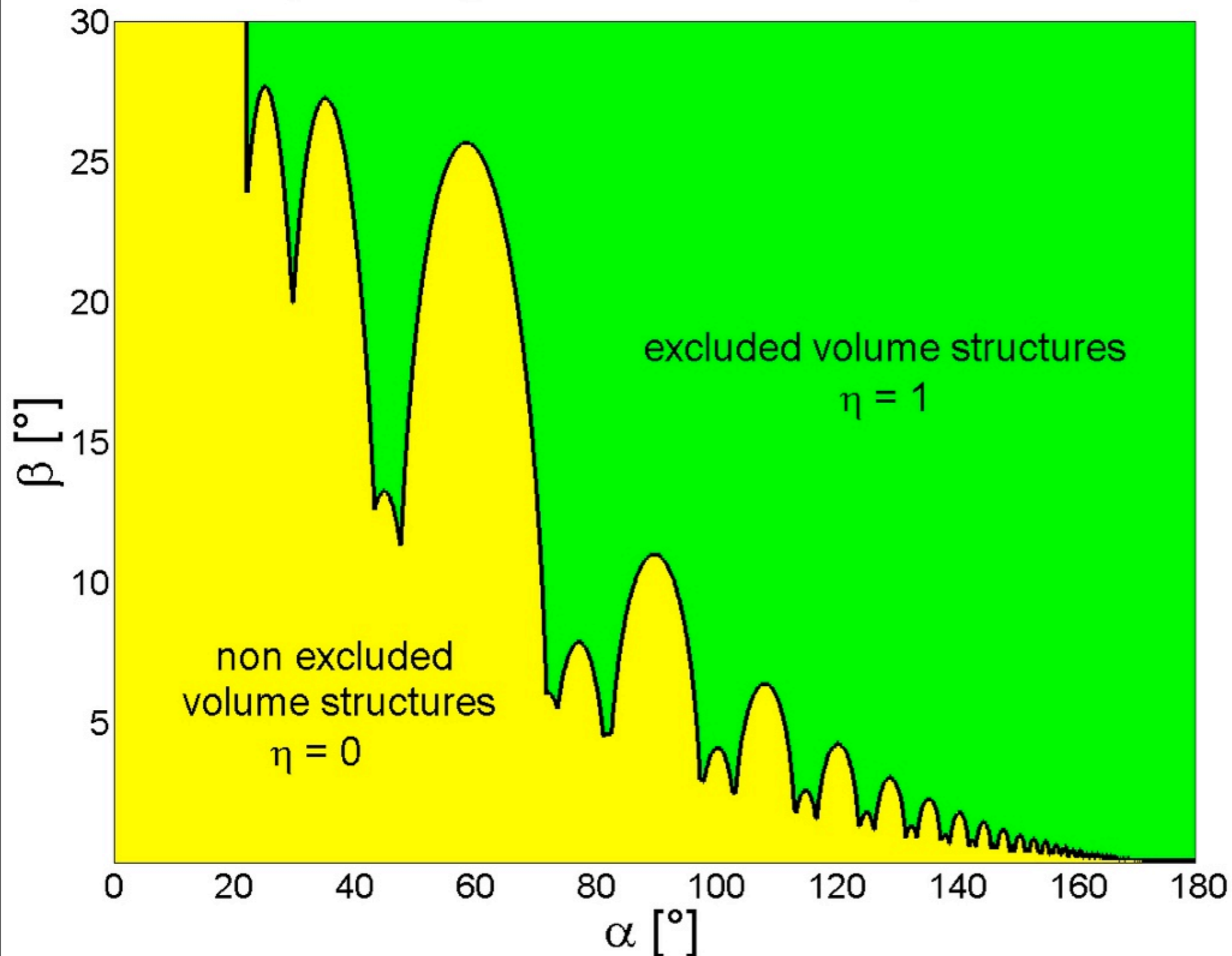
P. Diesinger, D.W.H
Phys. Rev. E 74, 031904
(2006)

The solenoid and crossed-linker structures are most important. The dotted line is the function $\zeta(\alpha)$ which represents the border of the forbidden region due to excluded volume.



Two-Angle Model: *Phase Diagram*

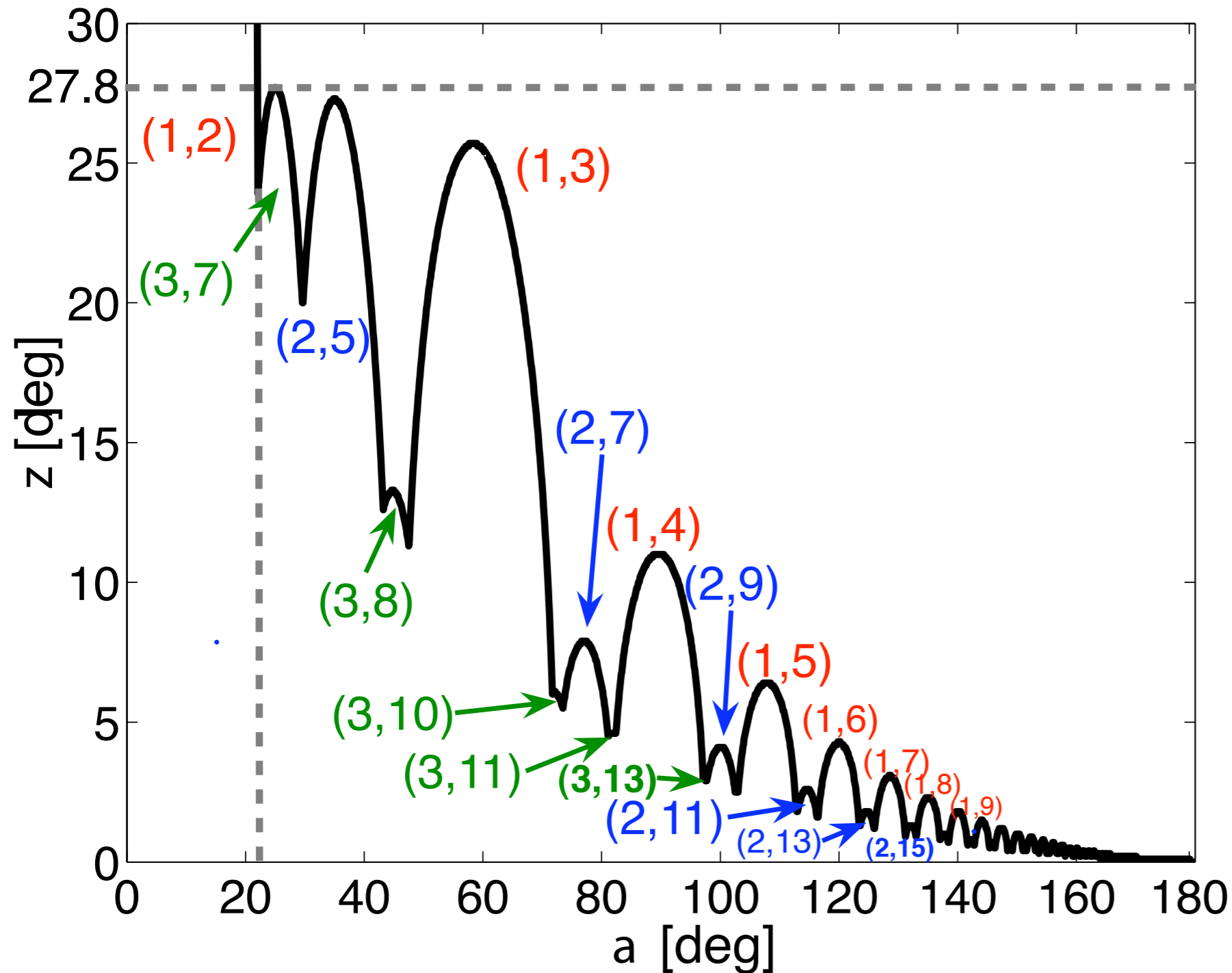
chromatin phase diagram - excluded volume "phase transition"



Fine-structure of the excluded-volume "phase transition". The chromatin fibers below the borderline fulfill the excluded volume conditions, those above do not. The borderline is the function $\zeta(\alpha)$



Two-Angle Model: *Phase Diagram*

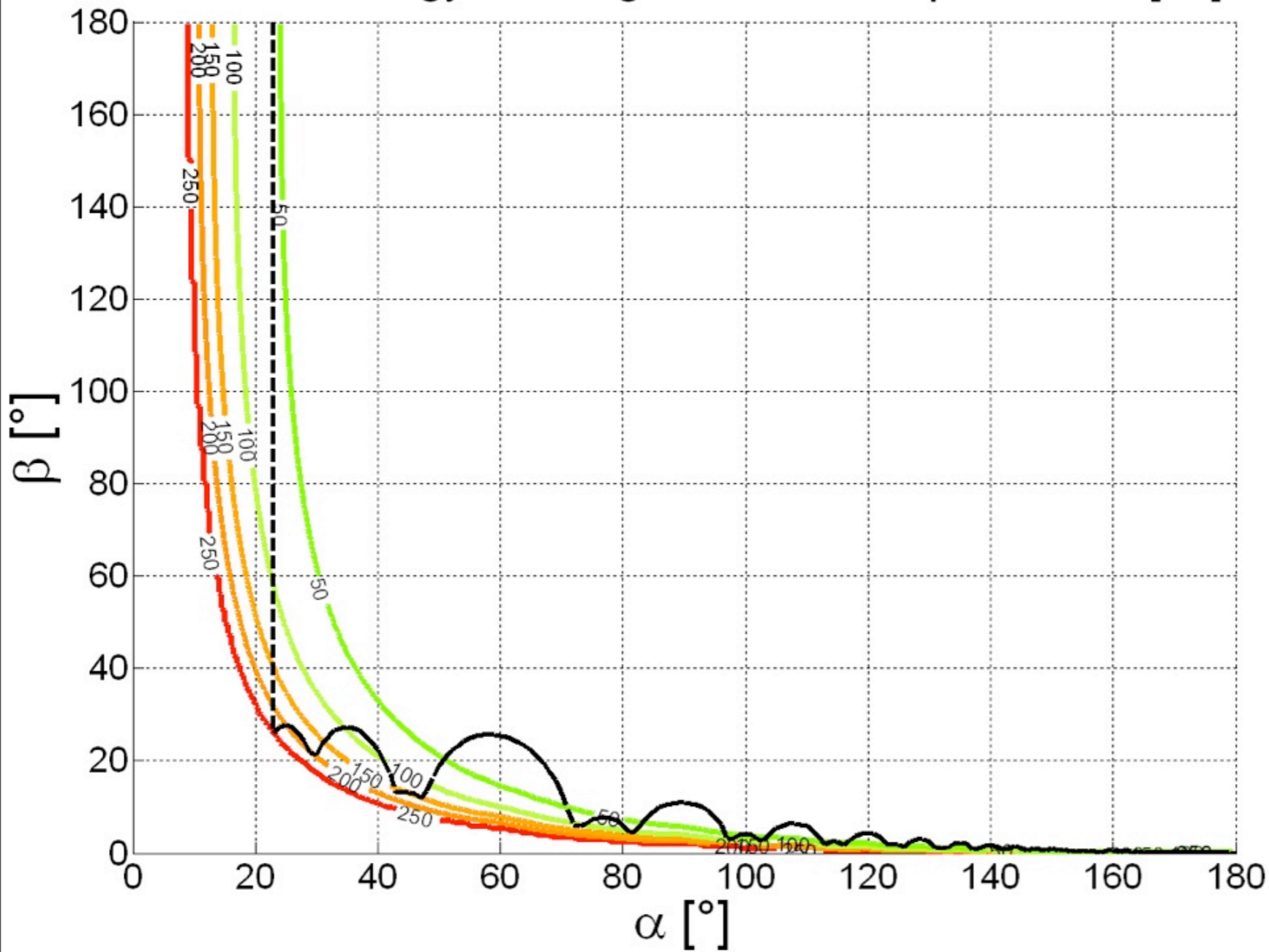


It is possible to characterize all peaks of the forbidden surface by these two parameters n and i



Two-Angle Model: Coulomb Energy

Coulomb energy of a single chromatin repeat unit V [kT]

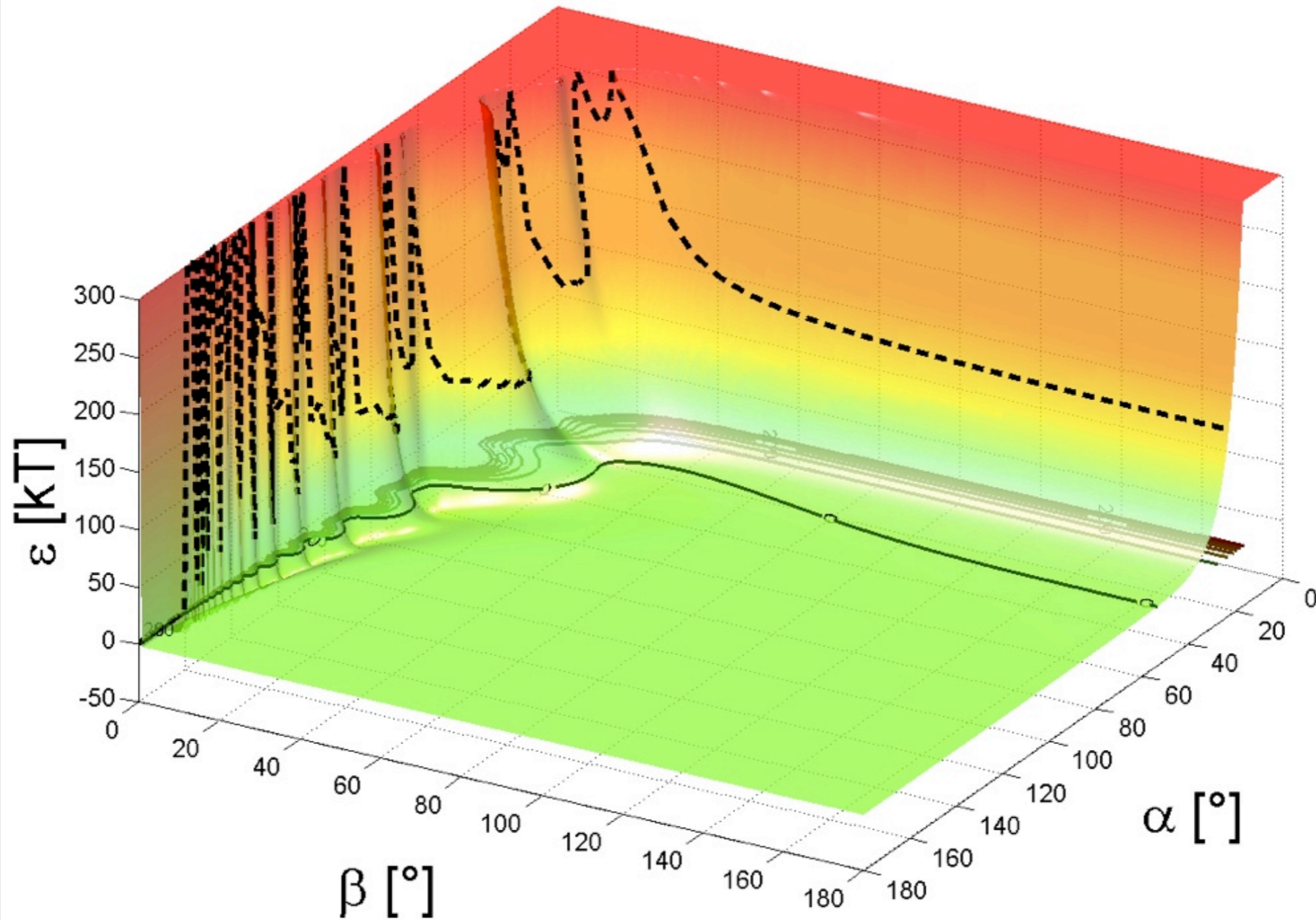


One can see that the Coulomb repulsion of the linkers is very high within the gaps of the excluded volume borderline. The repulsion also diverges for the crossed linker fibers when β becomes too small.



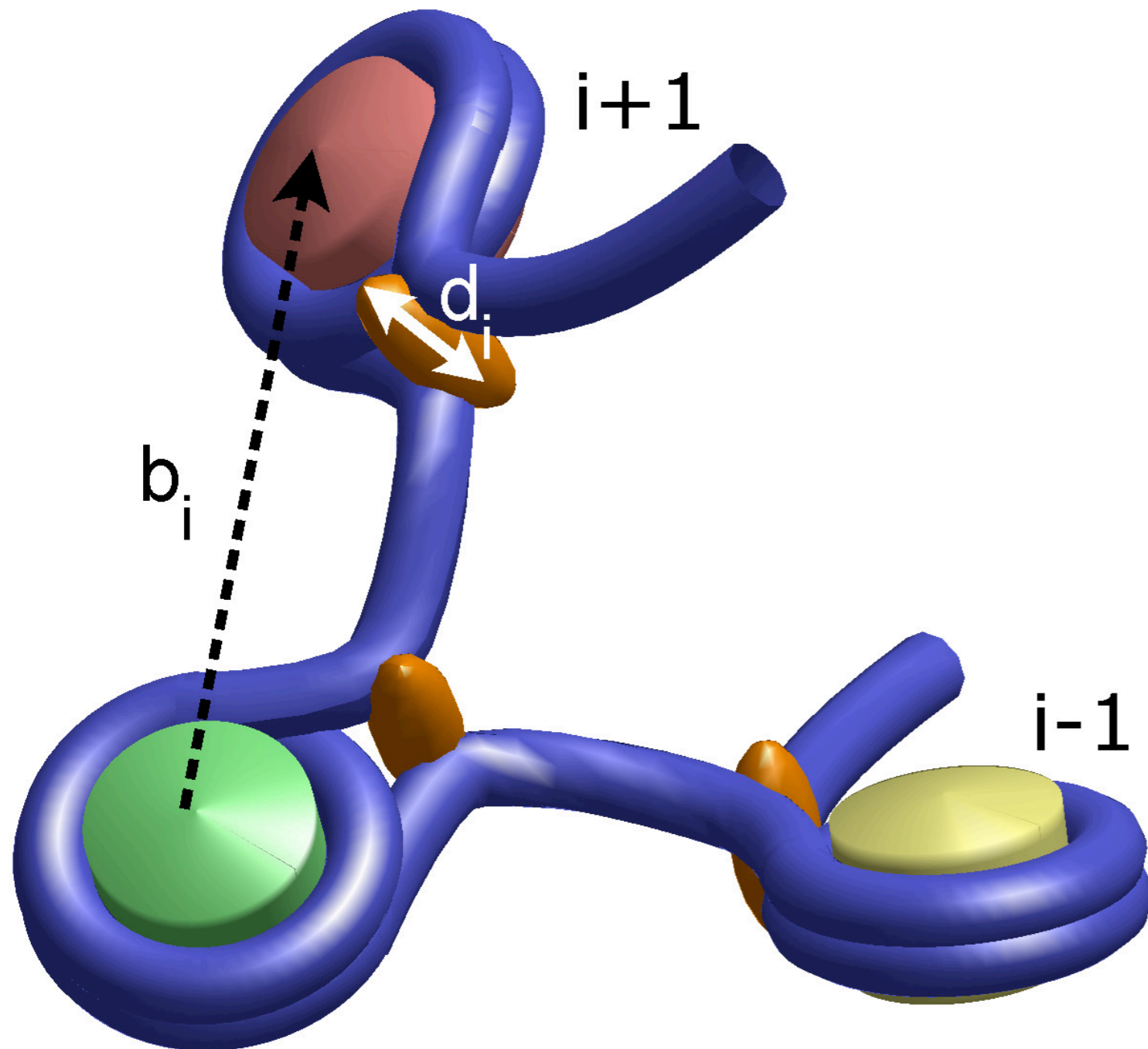
Two-Angle Model: Coulomb Energy

energy of a single chromatin repeat unit





Extended Two-Angle Model (E2A)



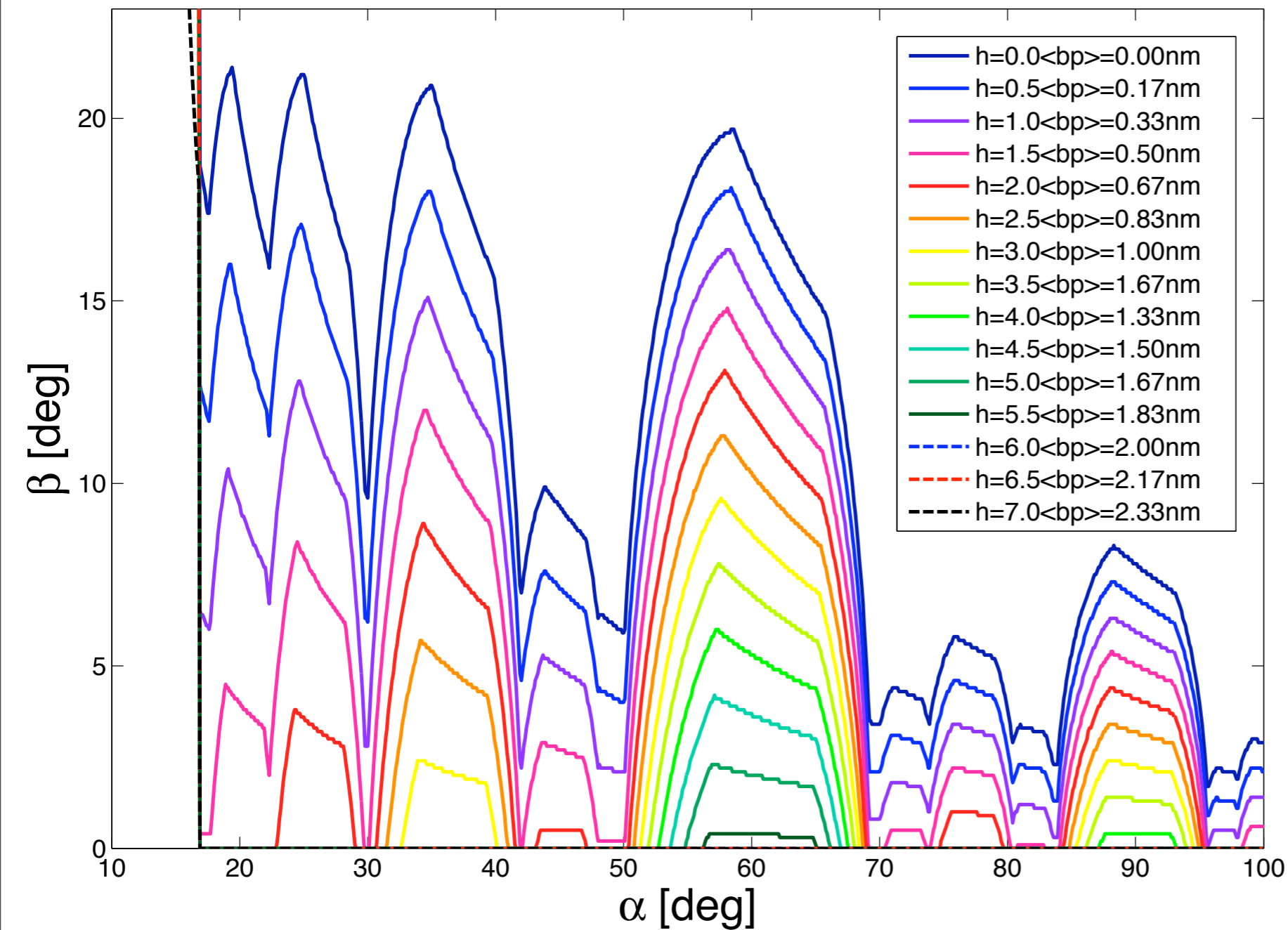
Basic definitions of the extended two-angle model

- The entry-exit angle α
- The linker length b
- The rotational angle β
- The pitch d



E2A: Classification

Phase diagram of the chromatin fiber

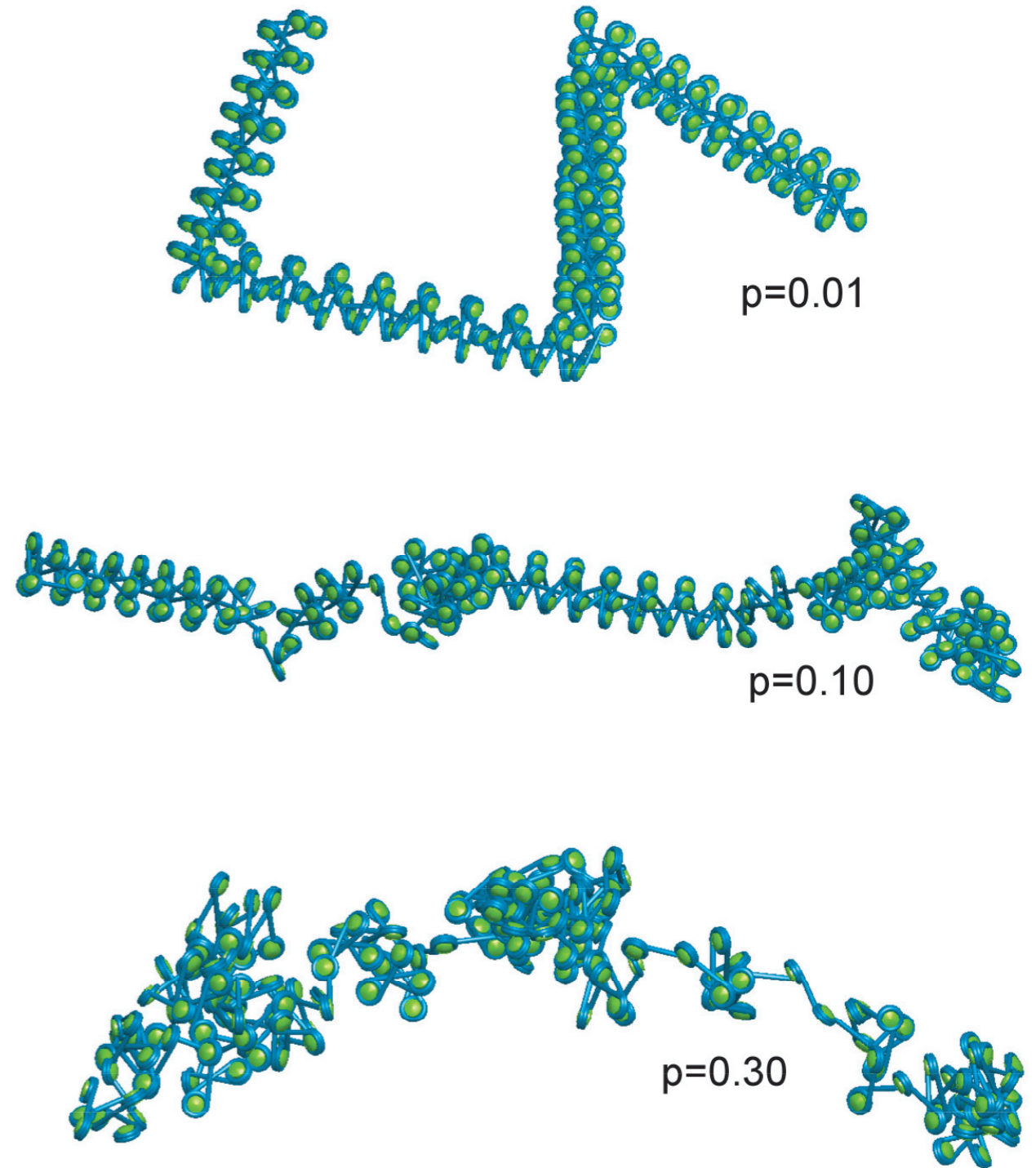
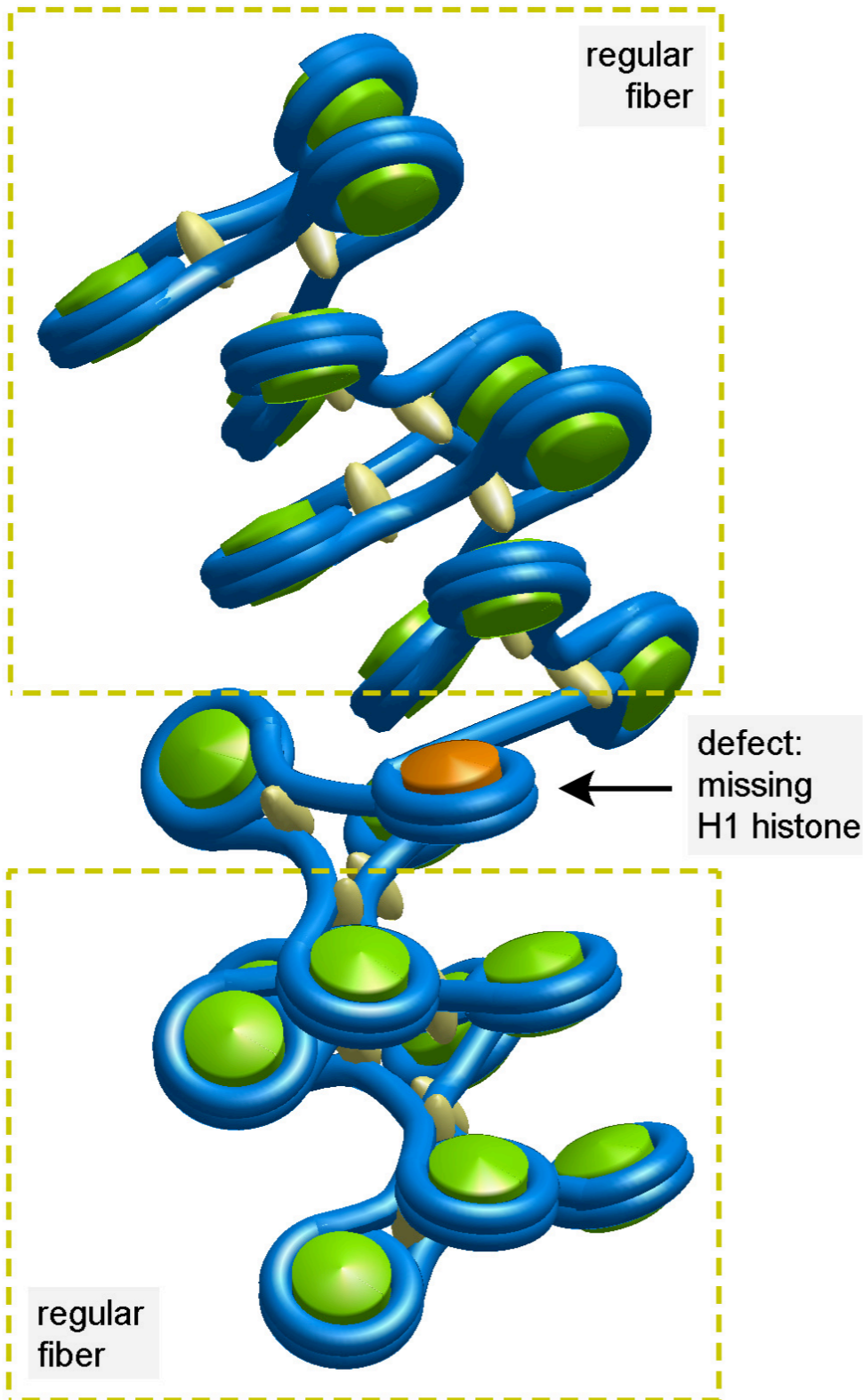


Analytical solution of
the two-angle model
with cylinders and
linker

Diesinger, Heermann
Bio Phys J 2008

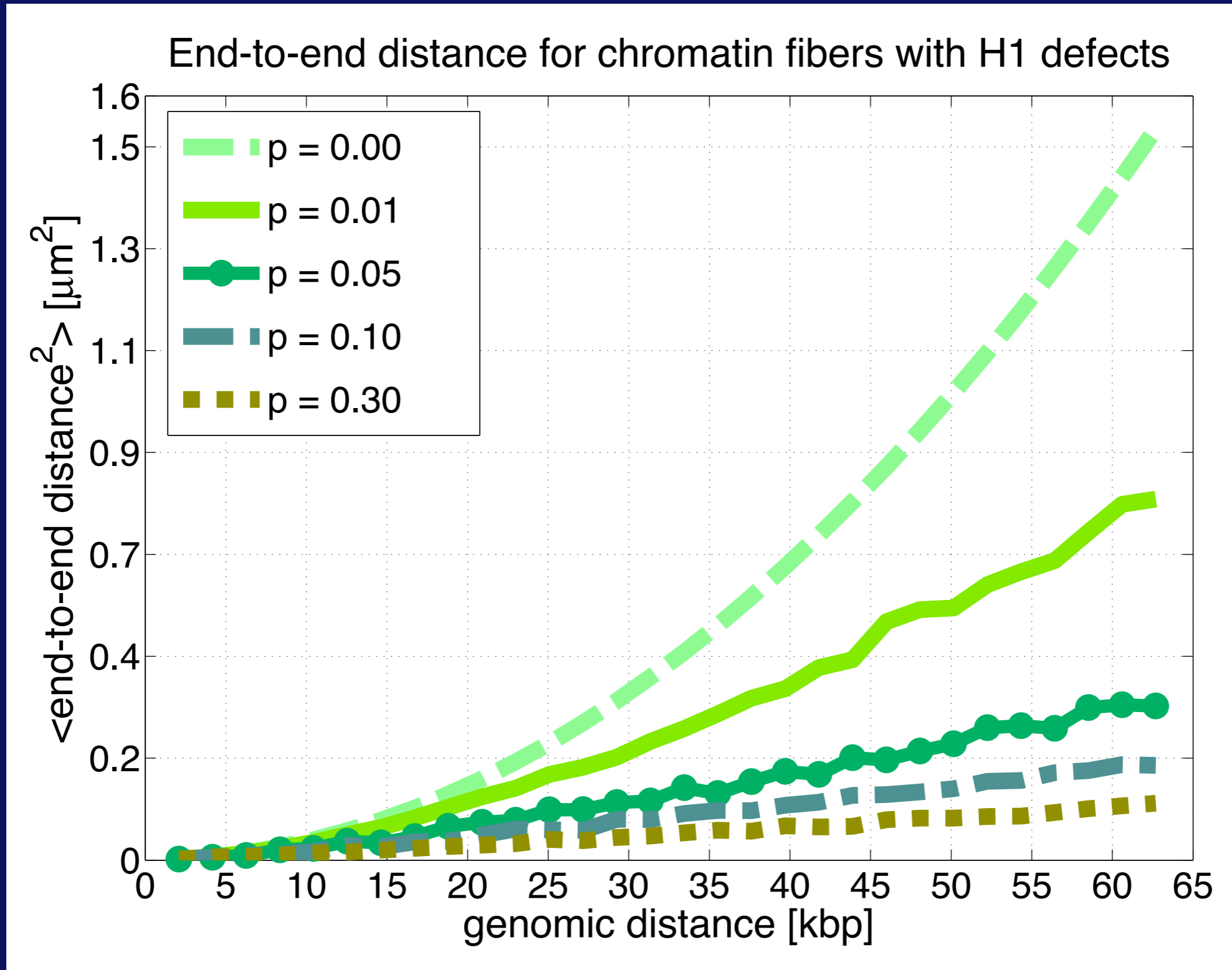


Two-Angle Model: H1-Defects





Two-Angle Model: H1-Defects



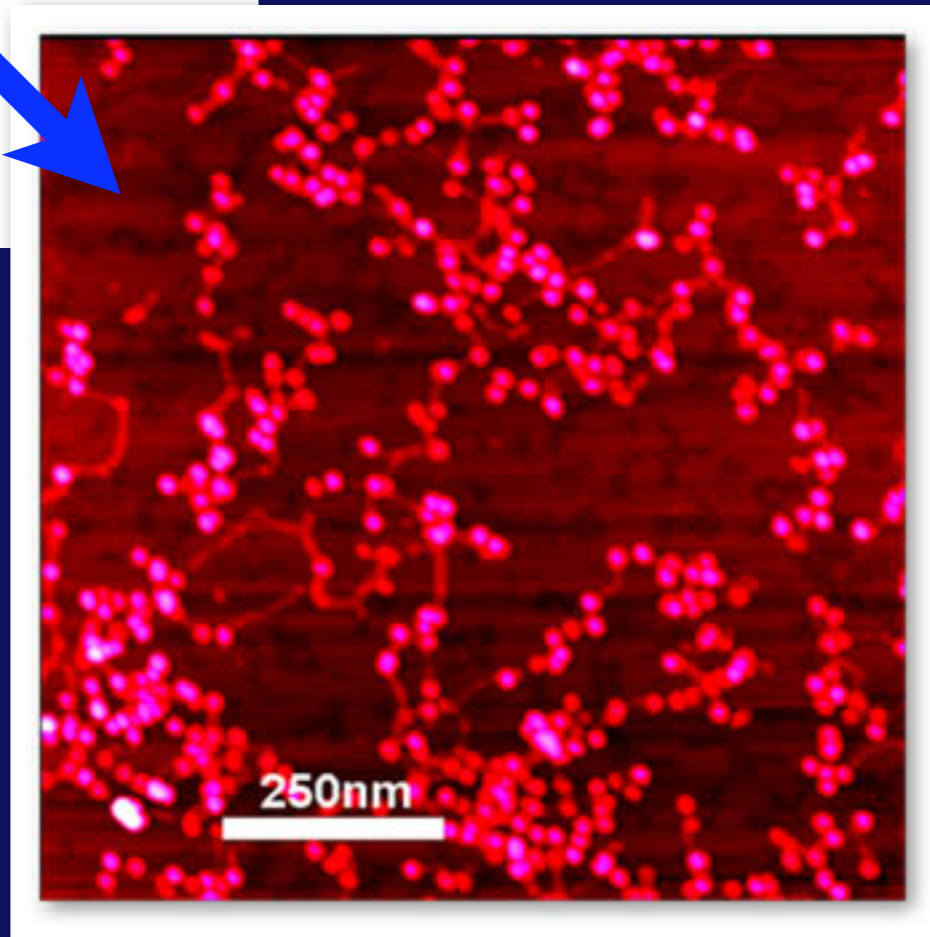
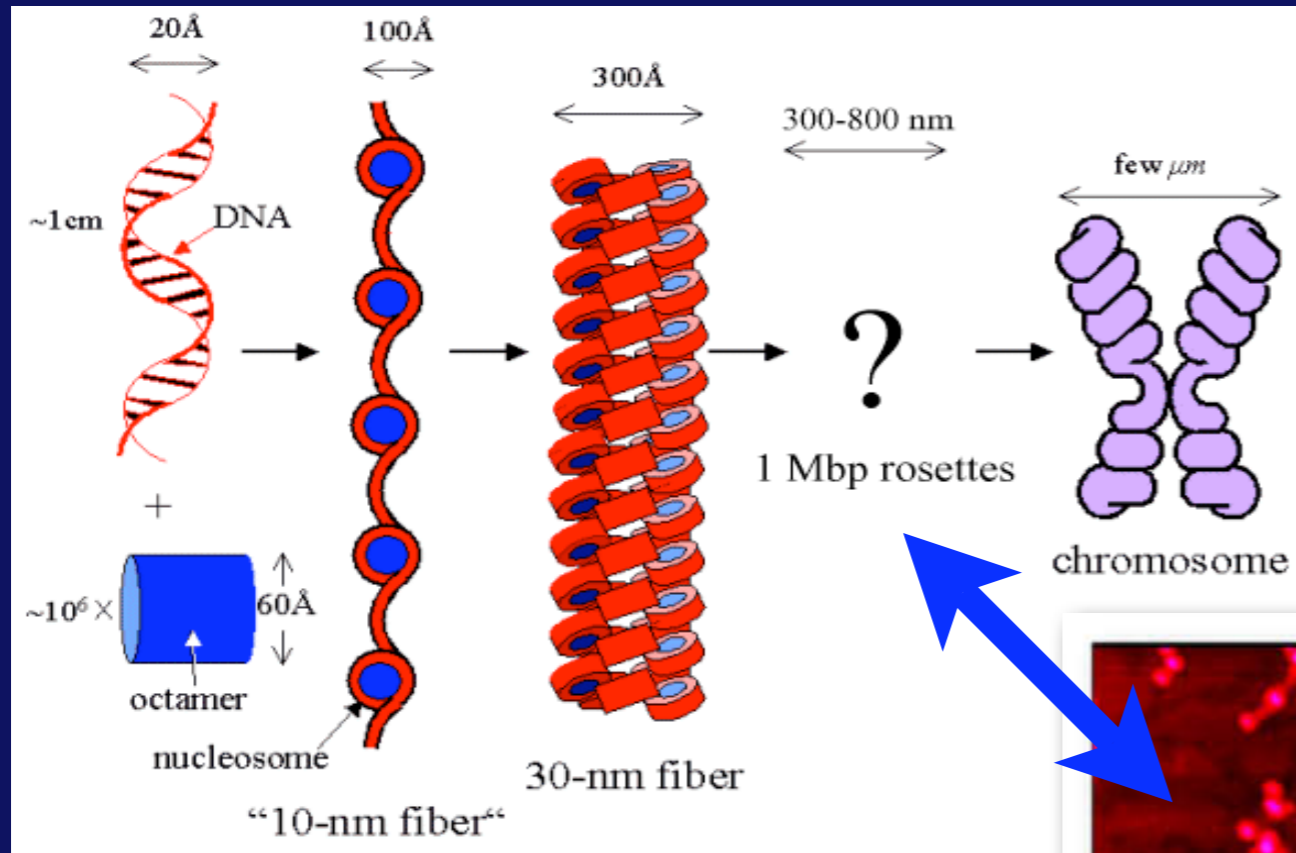


Two-Angle Model: Conclusions

- The most compact, but still allowed, states are those close to the excluded volume borderline.
- Since chromatin fibers in living cells are strongly fluctuating, it is likely that short parts of the fiber can come very close to the excluded volume borderline or even use its gaps to contribute to the compaction of the whole genome.
- Two possible strategies for chromatin compaction:
 - The use of very dense states in the phase diagram in the gaps in the excluded volume borderline or
 - missing H1 histones which can lead to very compact fibers.

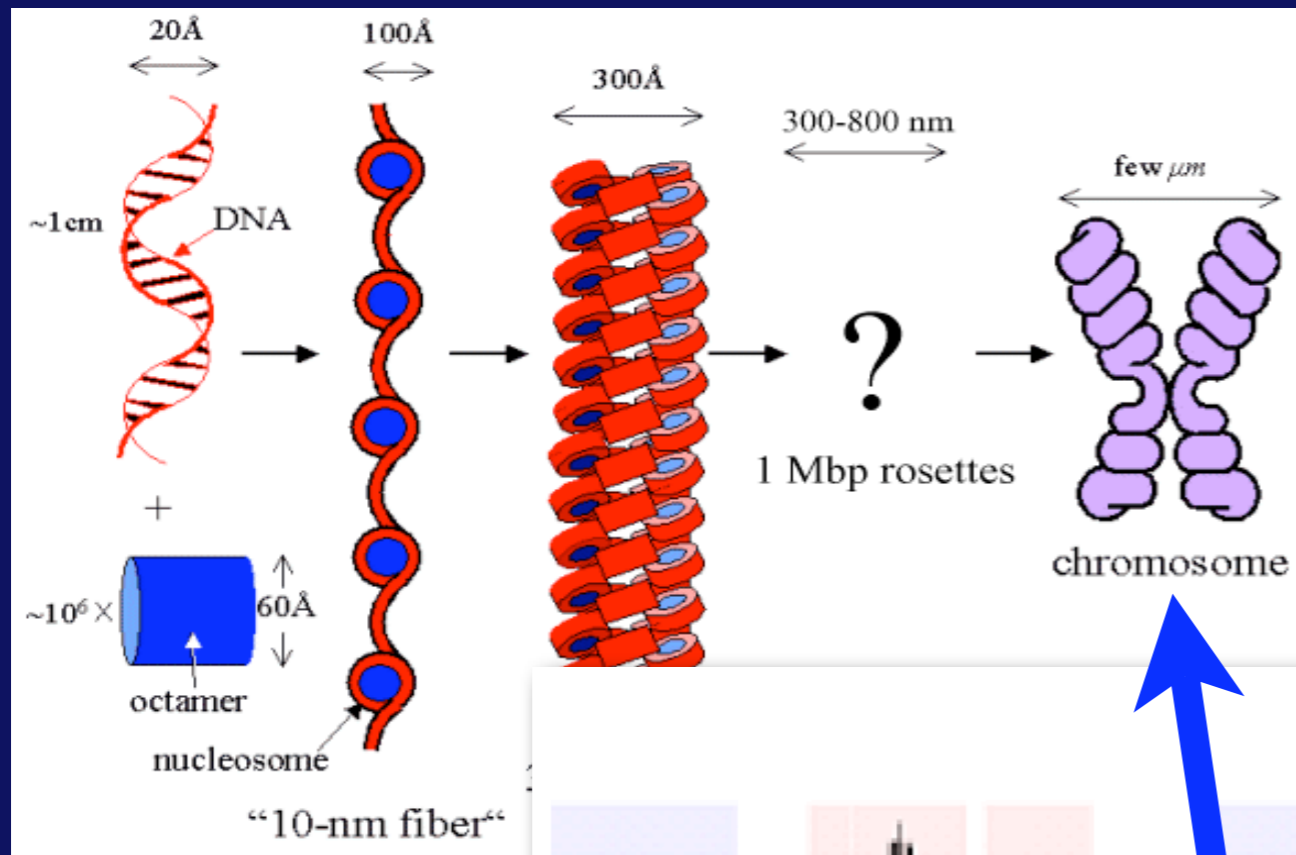


300nm - 800nm Range

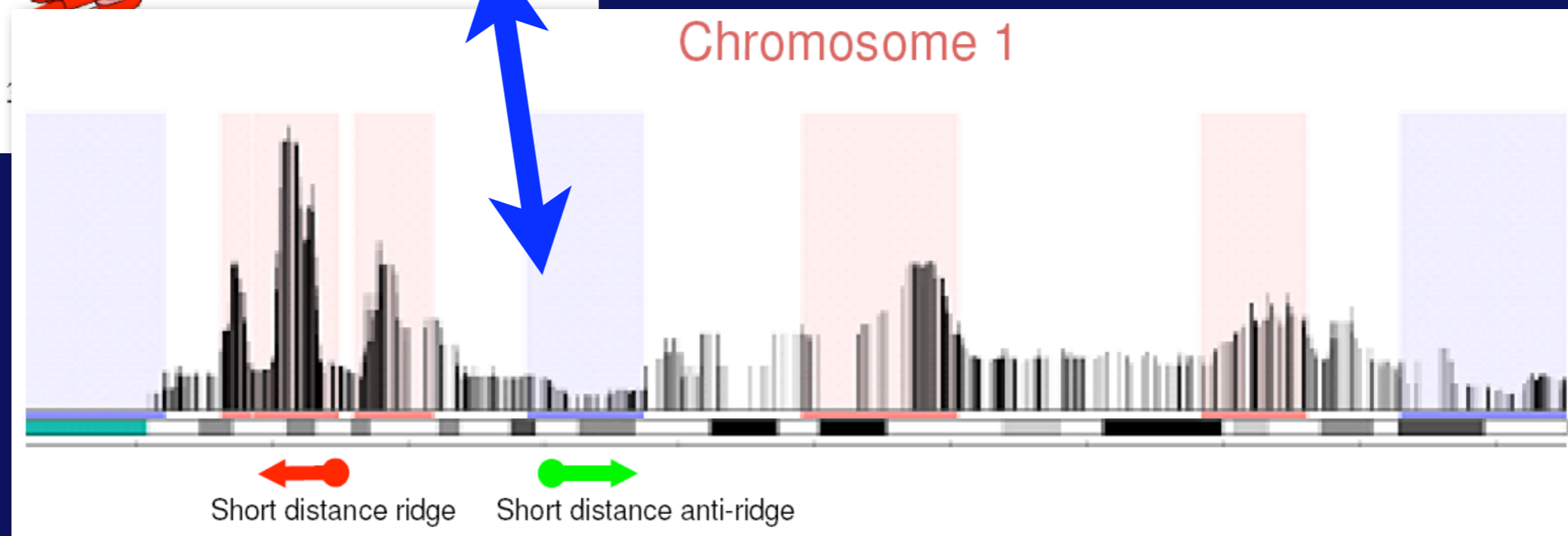




Chromosomes in Interphase



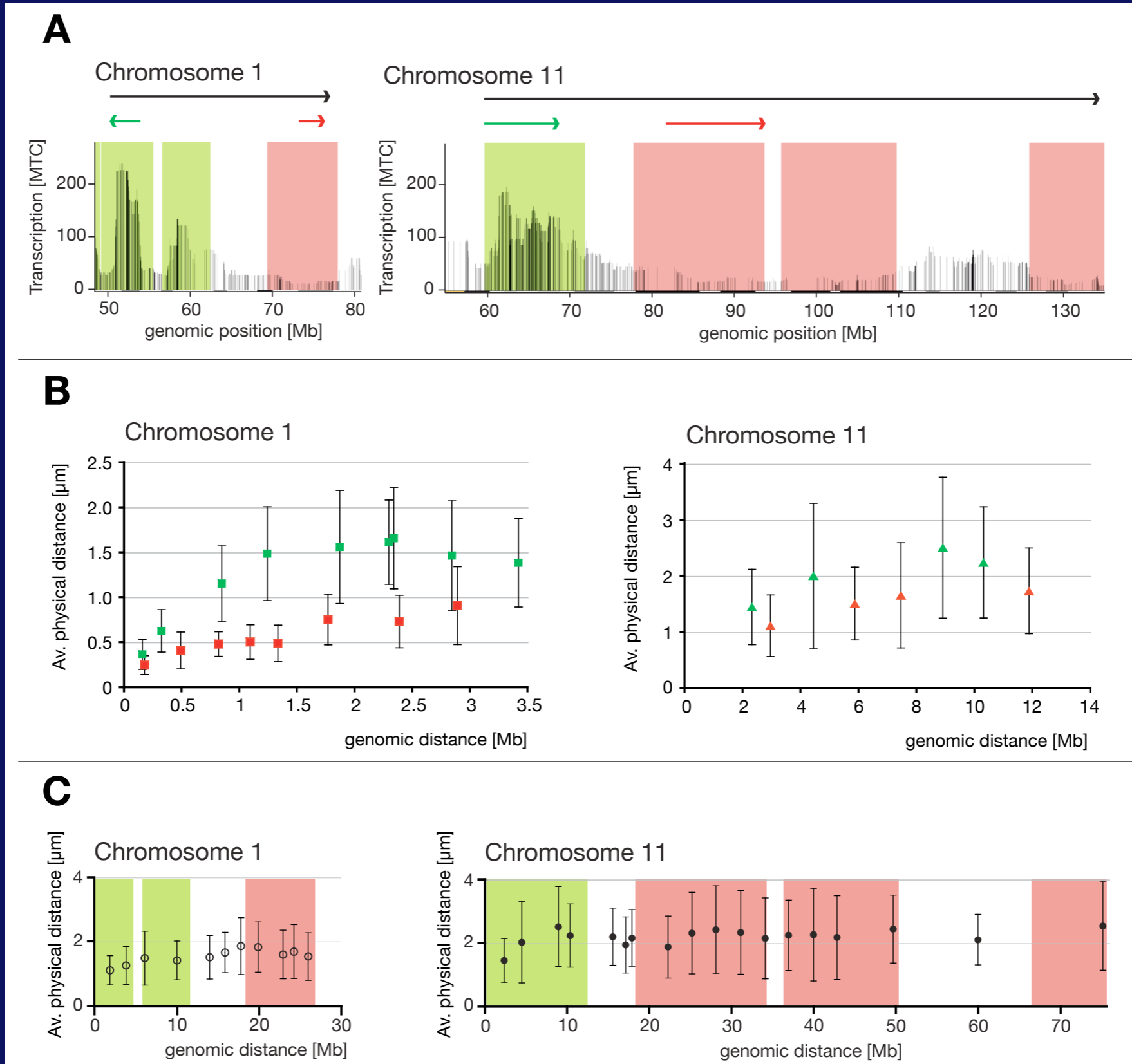
Julio Mateos-Langerak, Osdilly Giromus ,
Wim de Leeuw, Manfred Bohn, Dieter W.
Heermann, Roel van Driel and Sandra
Goetze



RIDGE: region of increased gene expression

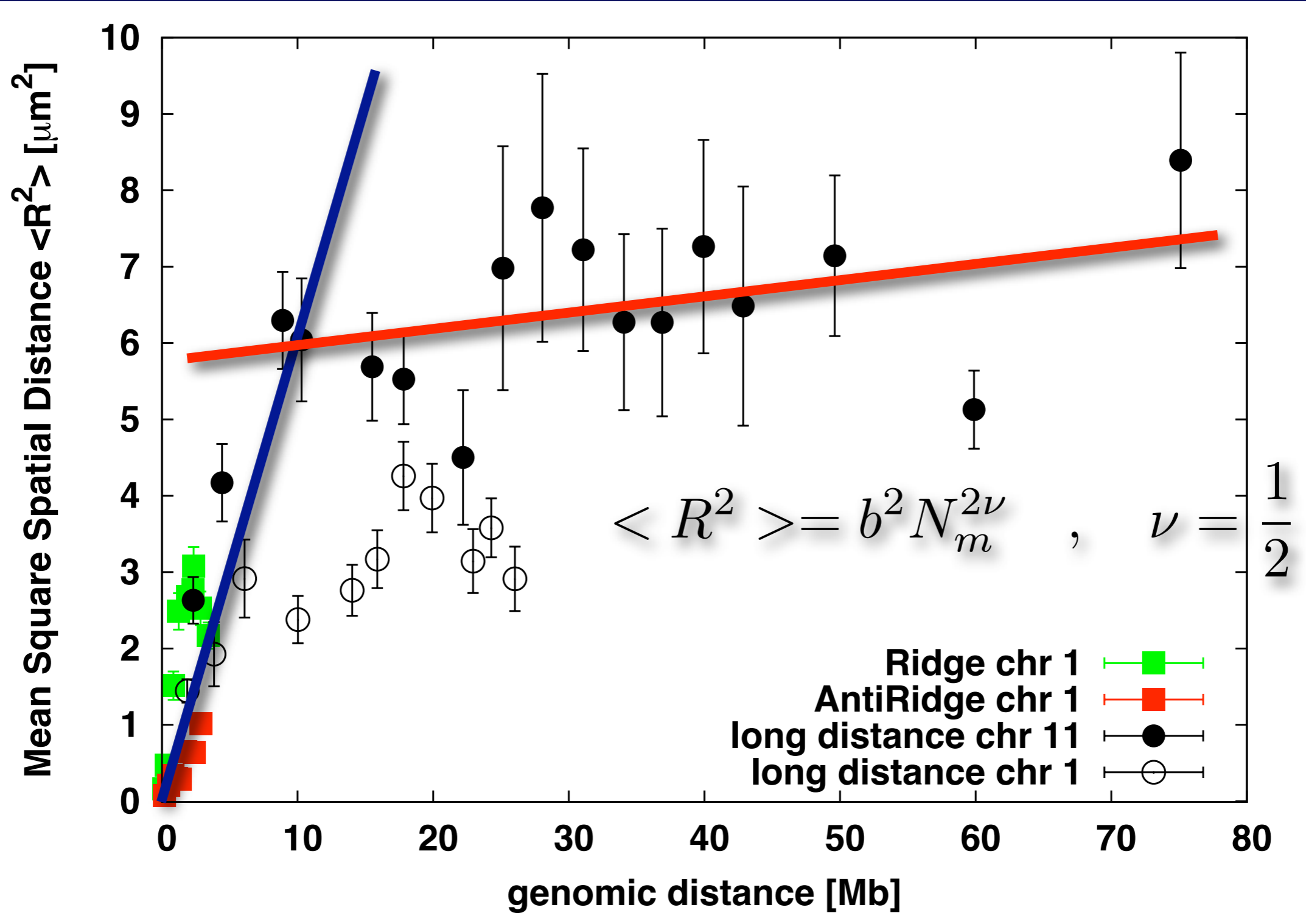


Chromosomes in Interphase





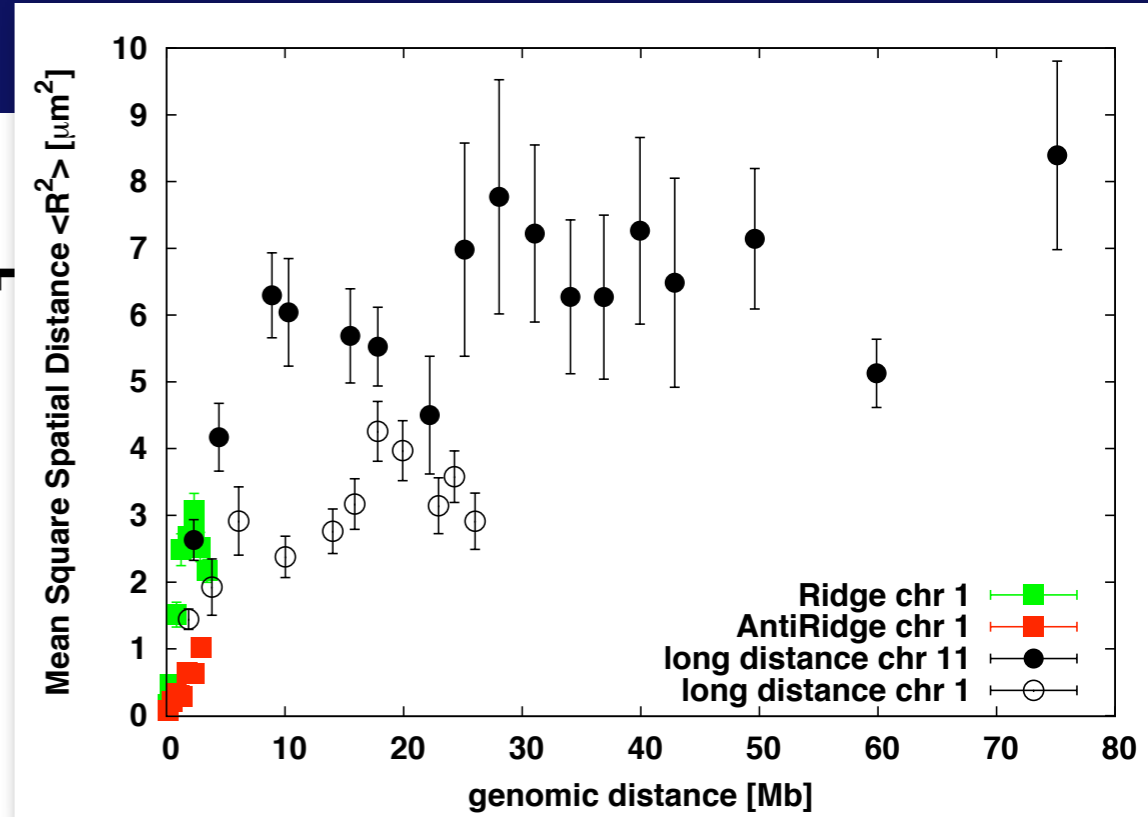
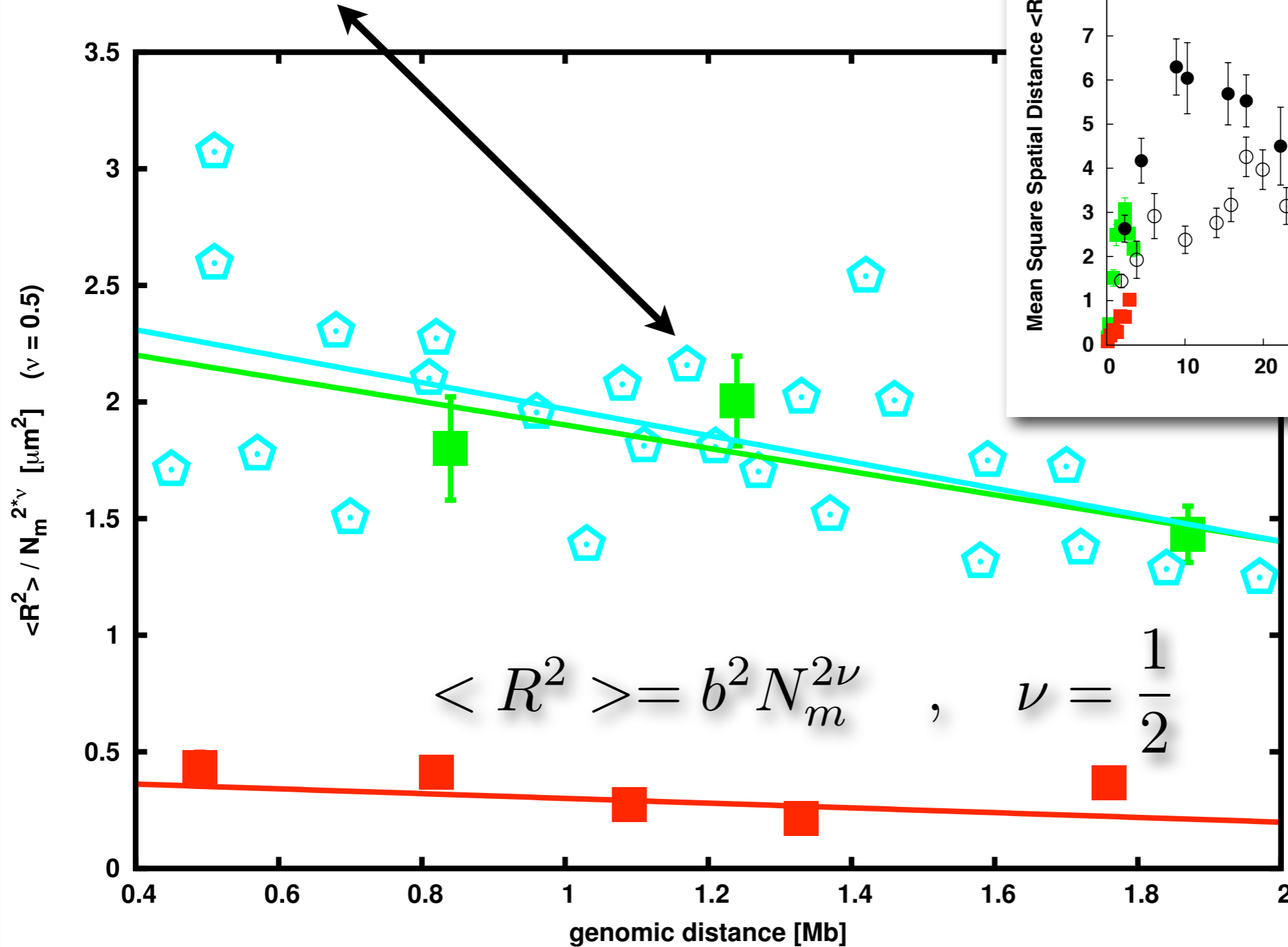
Chromosomes in Interphase





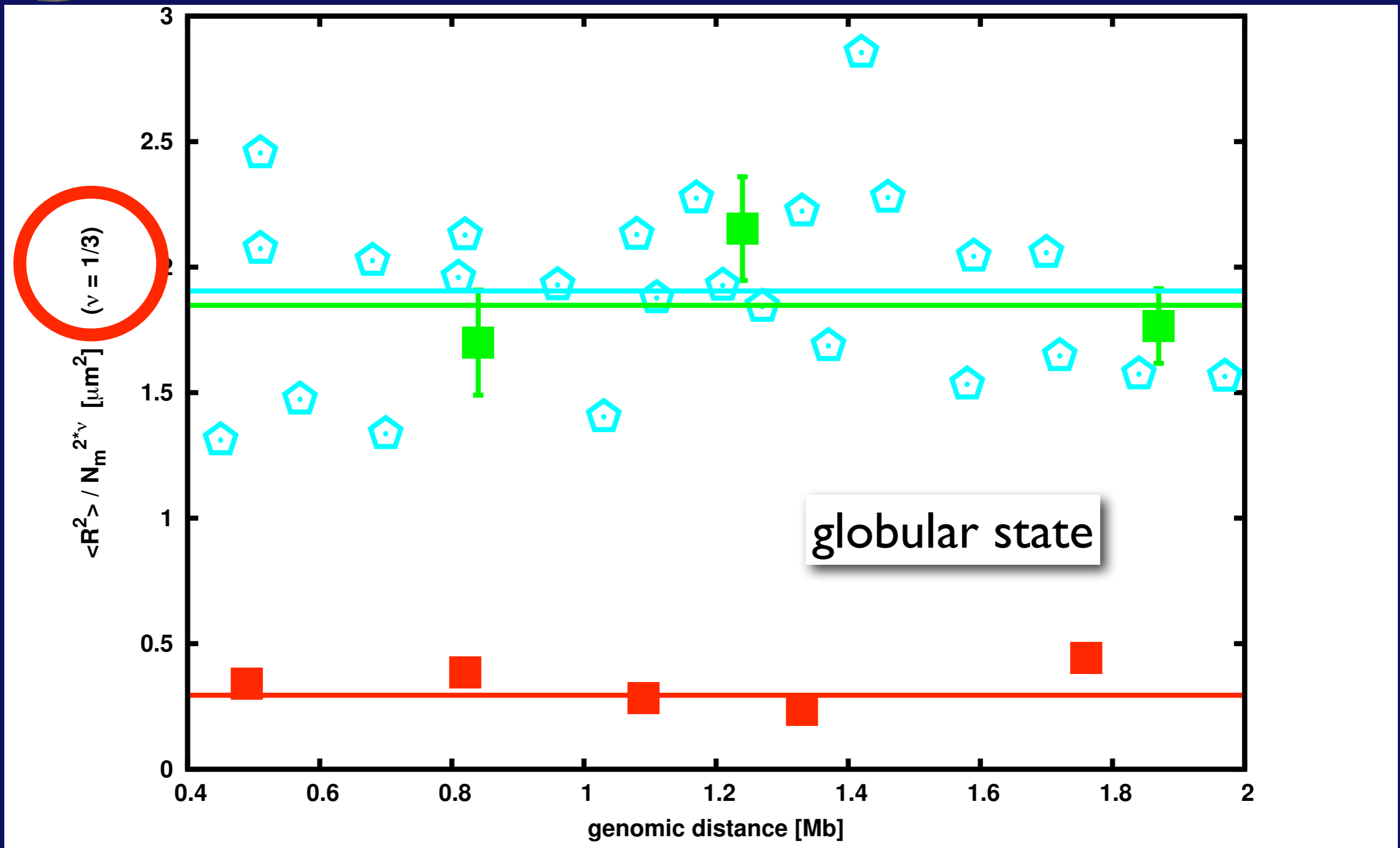
Chromosomes

Data by Yokota et. al.





Chromosomes



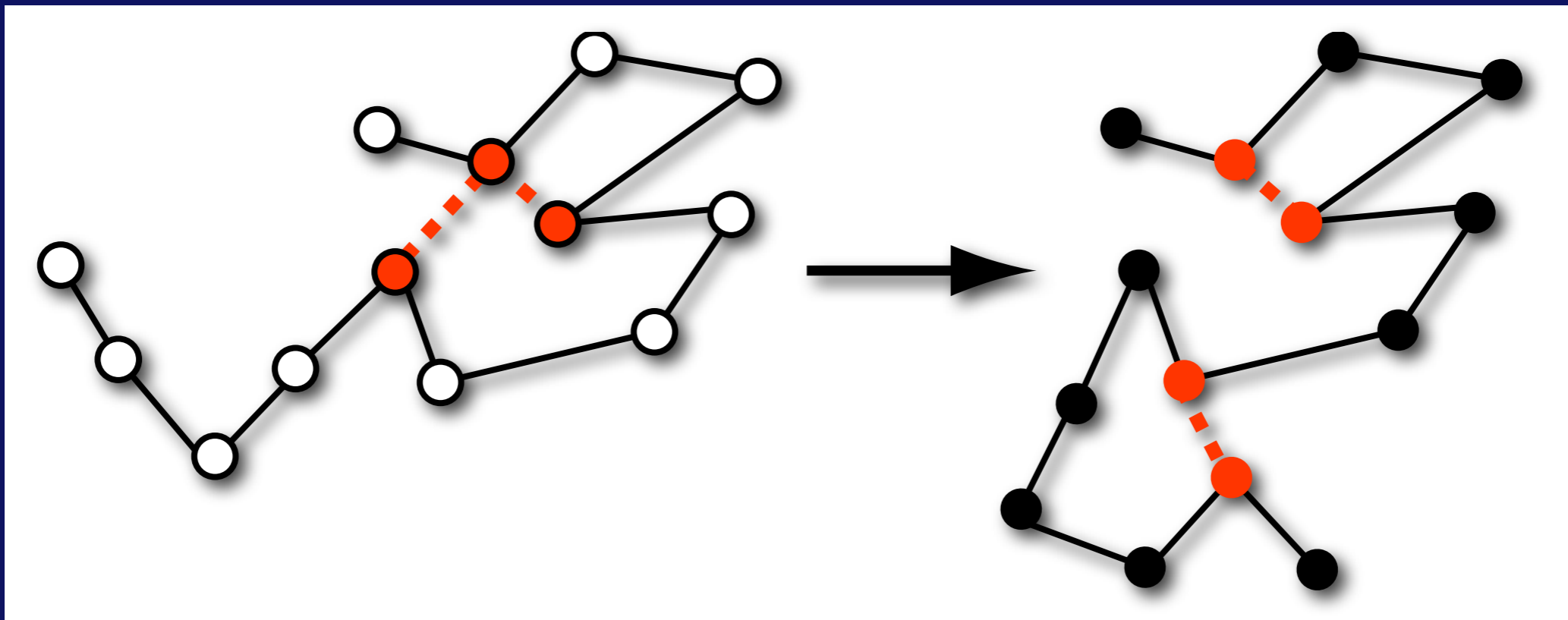


Random Loop Model

Construct a polymer model that explains the flattening of a physical distance for large genomic distances.

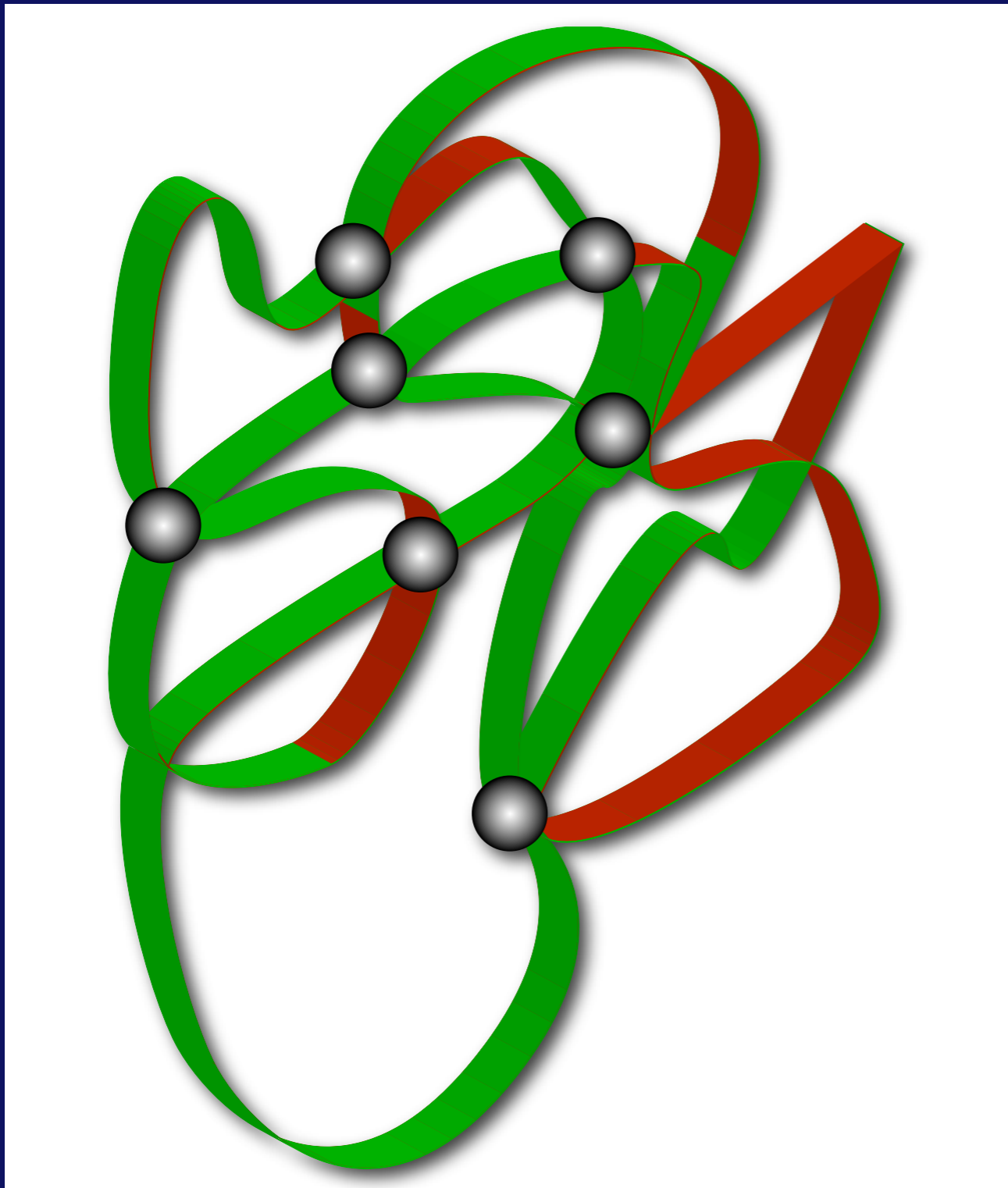
Use the fact that there is gene kissing and gene factories

Take into account the cell to cell variations which reflect the underlying ensemble





Random Loop Model

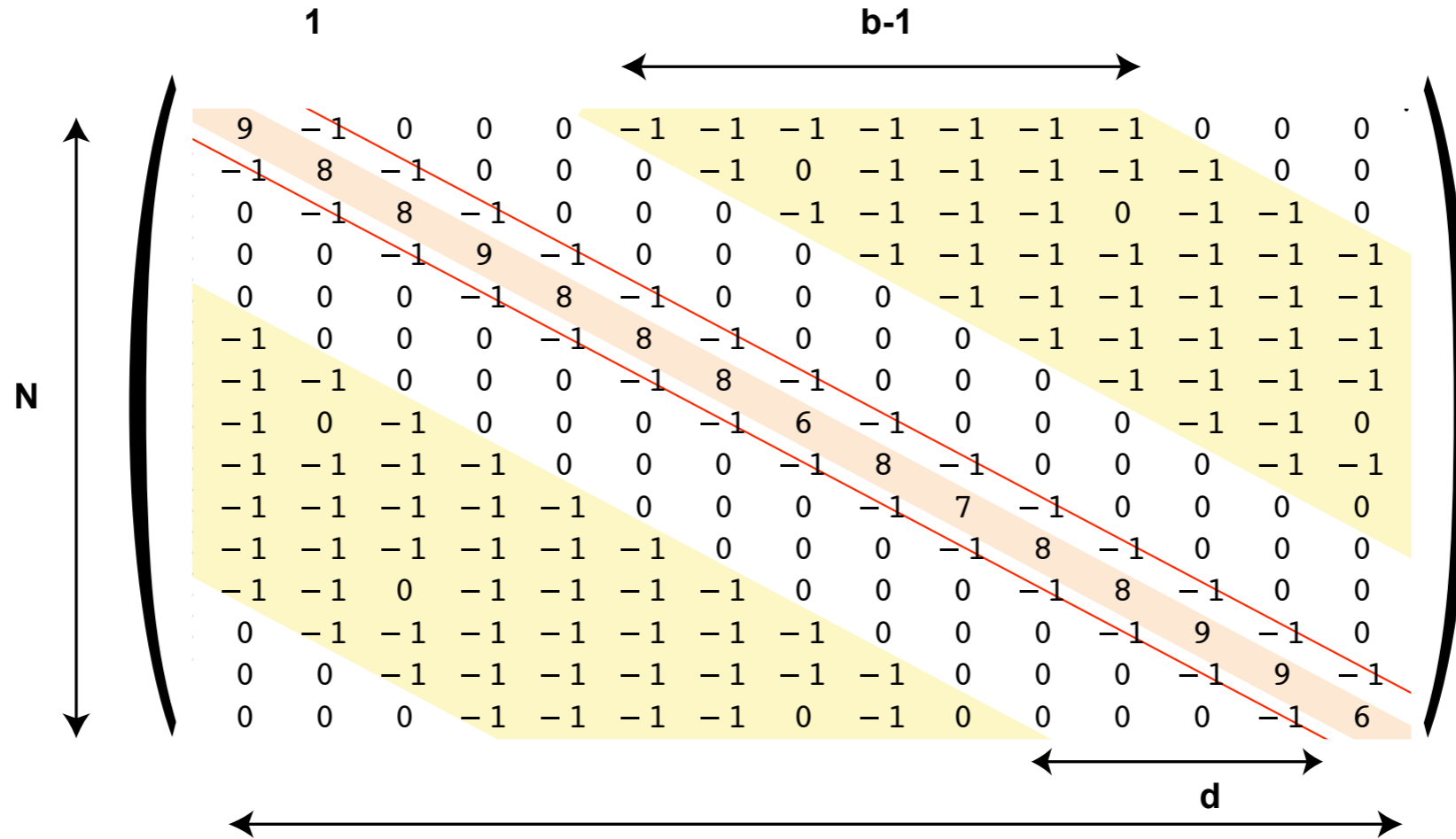


State of chromatin at a particular instance in time and cell. with a frozen conformation. The state changes in time and from cell to cell.



Random Loop Model

$$U = \frac{1}{2} \sum_{i < j}^N \kappa_{ij} \|\vec{x}_i - \vec{x}_j\|^2 = \frac{1}{4} \sum_{\substack{i,j=0 \\ j \neq i}}^N \kappa_{ij} \|\vec{x}_i - \vec{x}_j\|^2$$



$$\Sigma = K^{-1} = (\sigma_{ij})_{i,j}$$



Random Loop Model

$$U = \frac{1}{2} \sum_{i < j}^N \kappa_{ij} \|\vec{x}_i - \vec{x}_j\|^2 = \frac{1}{4} \sum_{\substack{i, j=0 \\ j \neq i}}^N \kappa_{ij} \|\vec{x}_i - \vec{x}_j\|^2$$

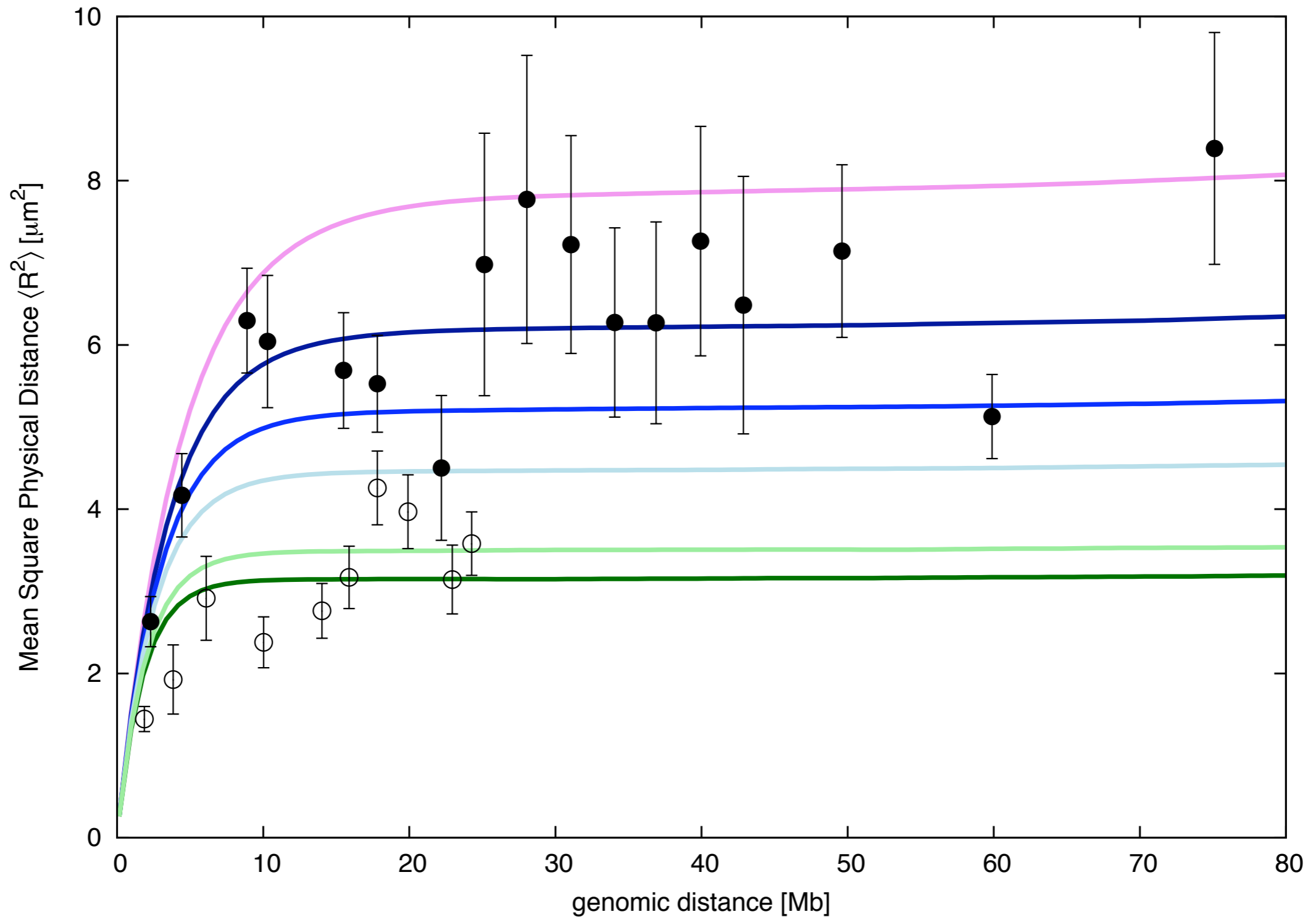
$$P(\vec{x}_I, \vec{x}_J) = \int \cdots \int \prod_{\substack{i=0 \\ i \neq I, J}}^N d\vec{x}_i C \exp(-U(\vec{x}_0, \dots, \vec{x}_N)/k_B T)$$

$$P(\|\vec{x}_I - \vec{x}_J\|) \equiv P(r_{IJ}) = \tilde{C} r_{IJ}^2 \exp\left[-\frac{1}{2} \frac{1}{\sigma_{JJ} + \sigma_{II} - 2\sigma_{IJ}} r_{IJ}^2\right]$$

$$\langle R^2 \rangle = \langle \langle R^2 \rangle_{\text{thermal}} \rangle_{\text{loops}}$$

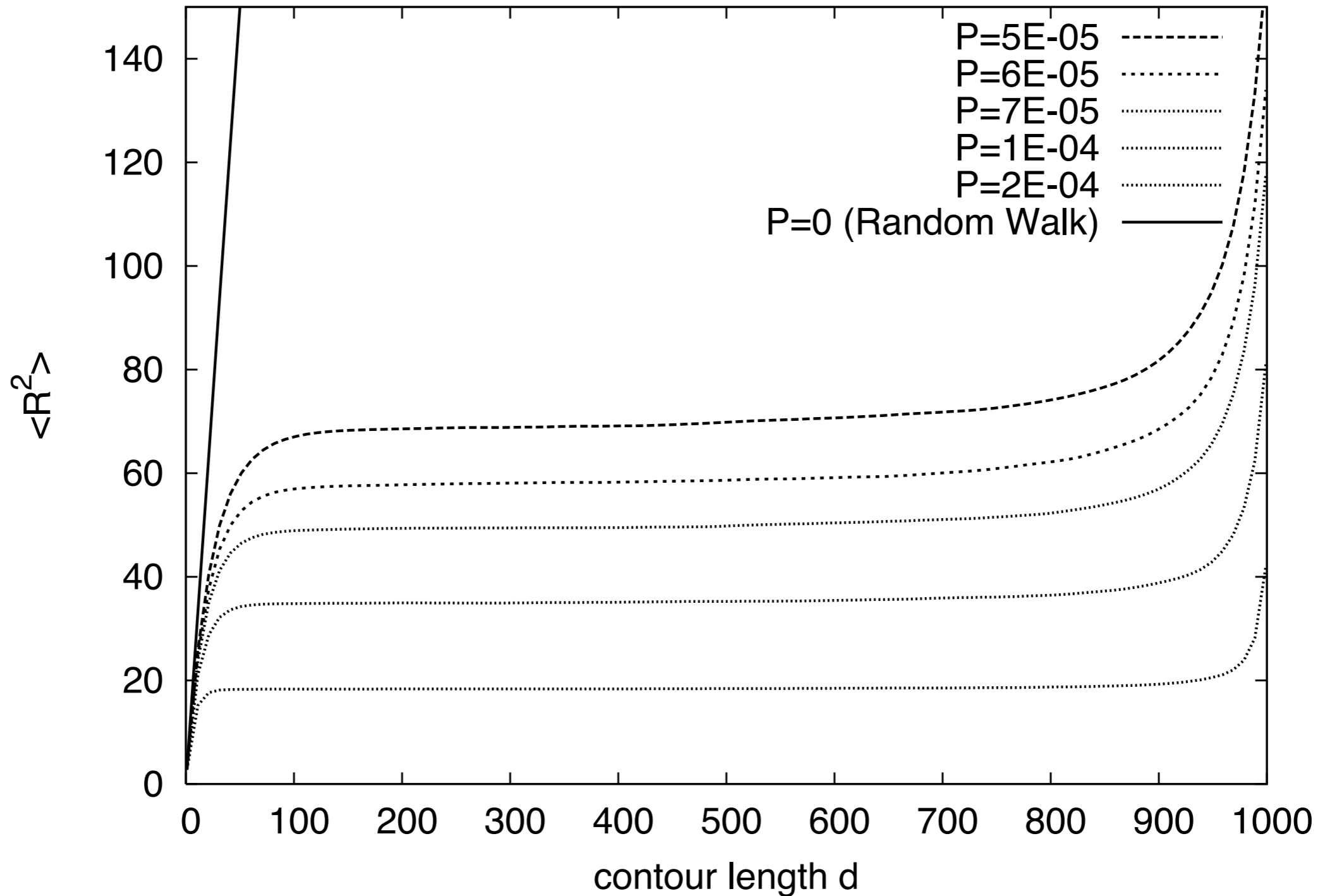


Random Loop Model



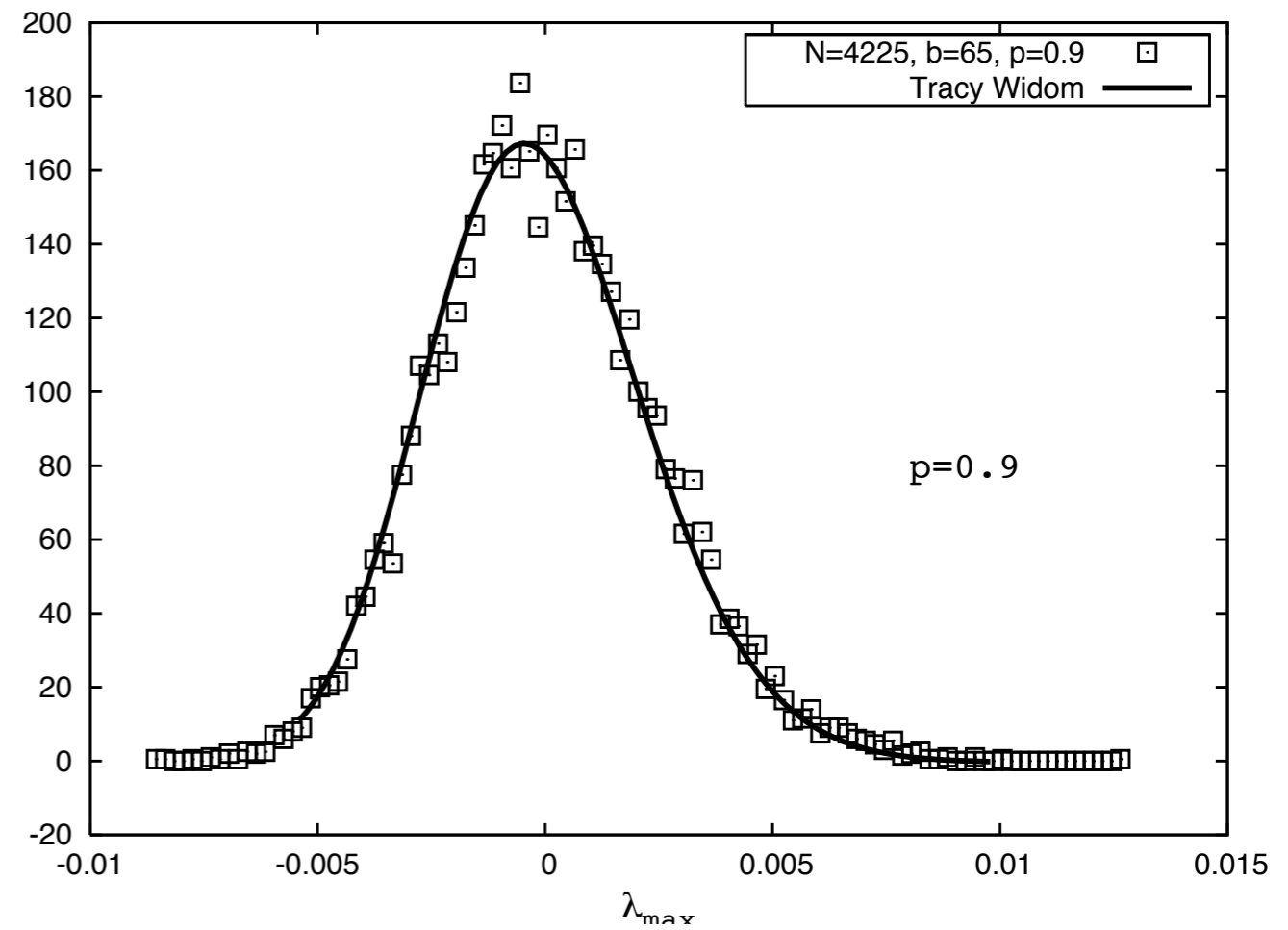
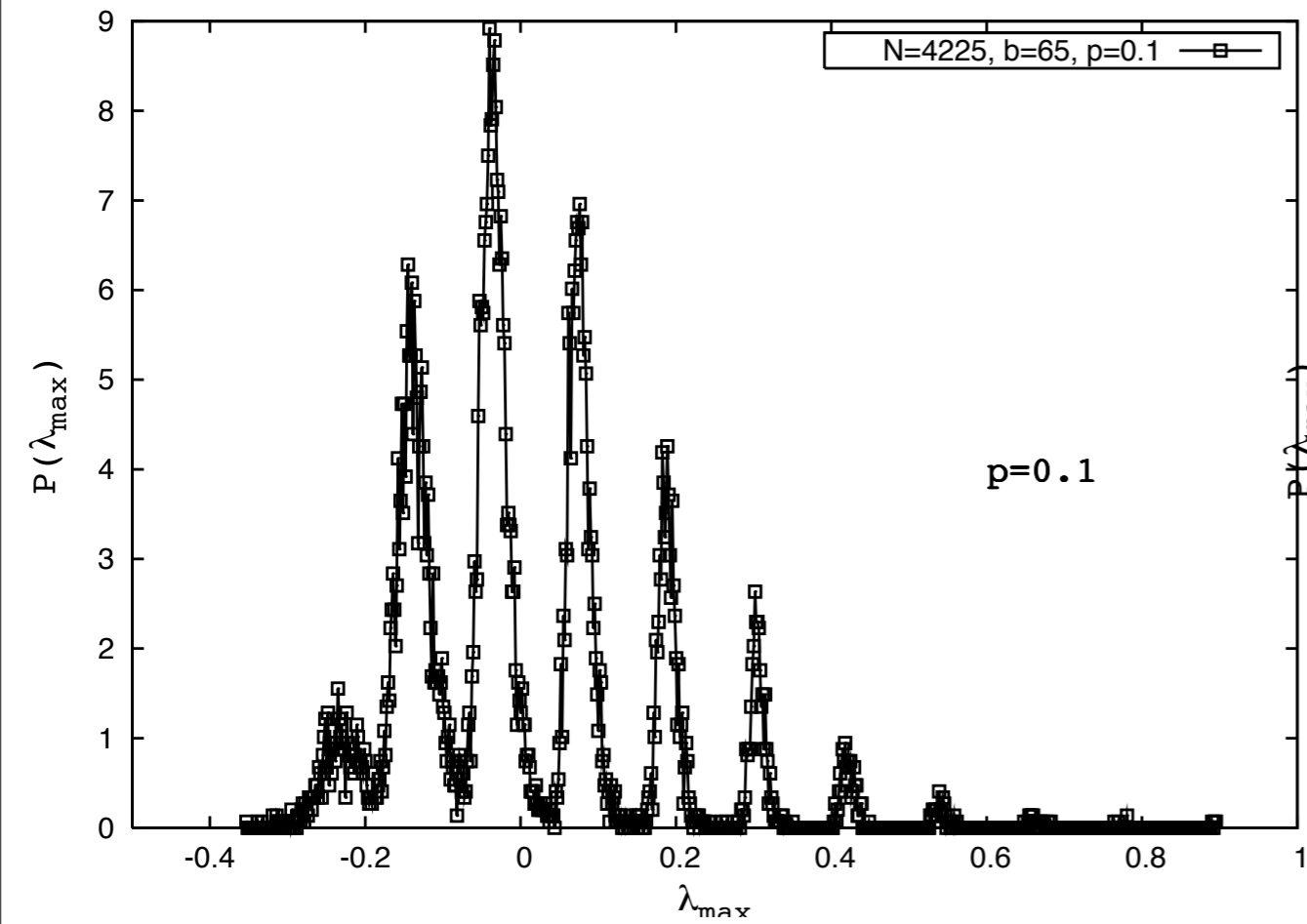


Random Loop Model





Random Loop Model





Random Loop Model

- We propose a polymer model that can explain this levelling-off by means of „random looping“.
- The model so far is able to explain some basic features of chromatin folding revealed in recent experiments.
- The model takes into account the cell to cell variability and the conformational fluctuations.