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ZUKUNFT SEIT 1386

How the Nucleus of Human Cells is Structured by Entropy

Dieter W. Heermann

Heidelberg University

Key Problem

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Derive a **chromosome model** that works across species, across phases, hence that is able to capture the underlying principles of chromosome folding.

Can explain data from various sources simultaneously.

Can predict biological as well as mechanical properties.

Key Problem

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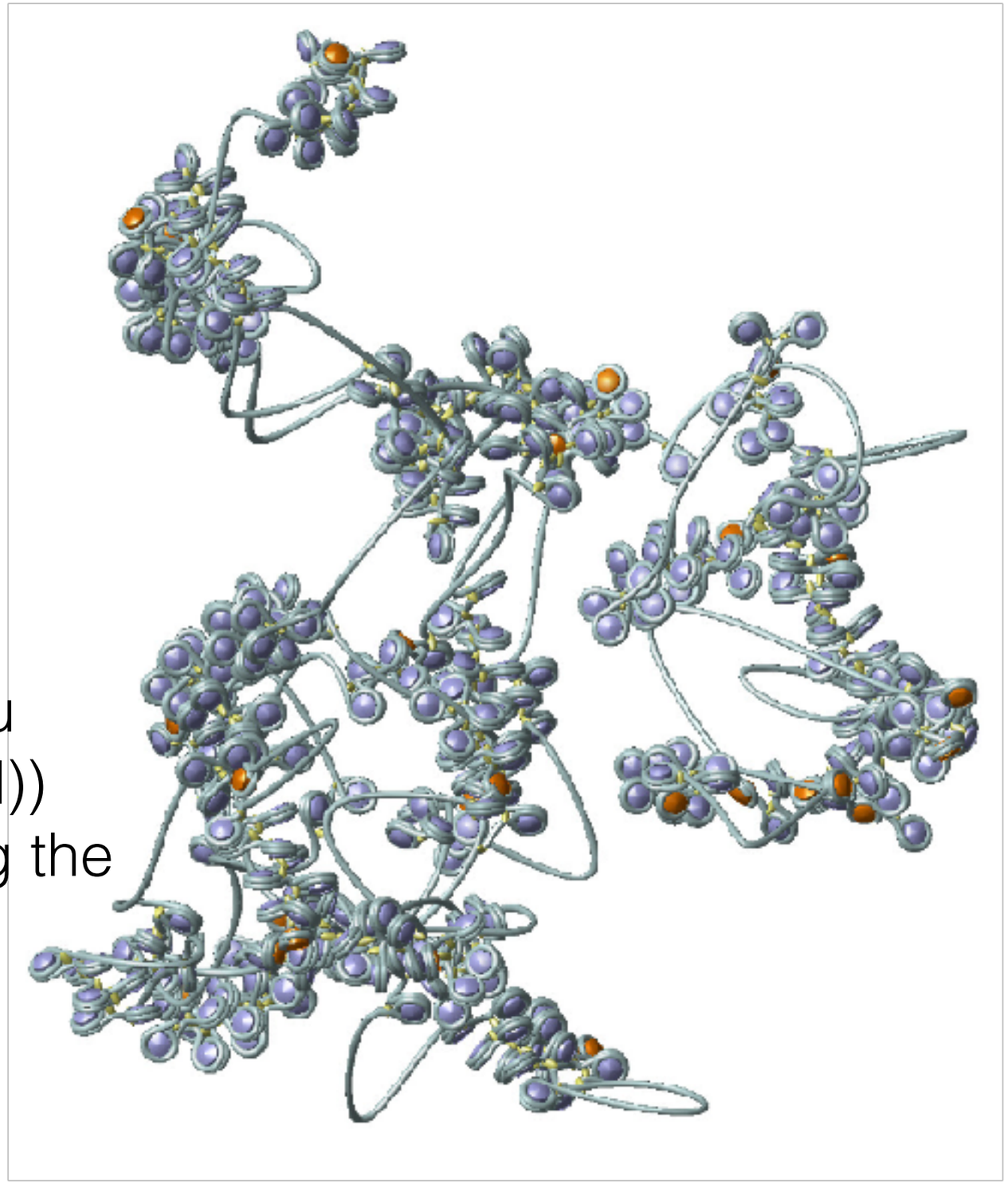
Human chromosomes (interphase and metaphase)

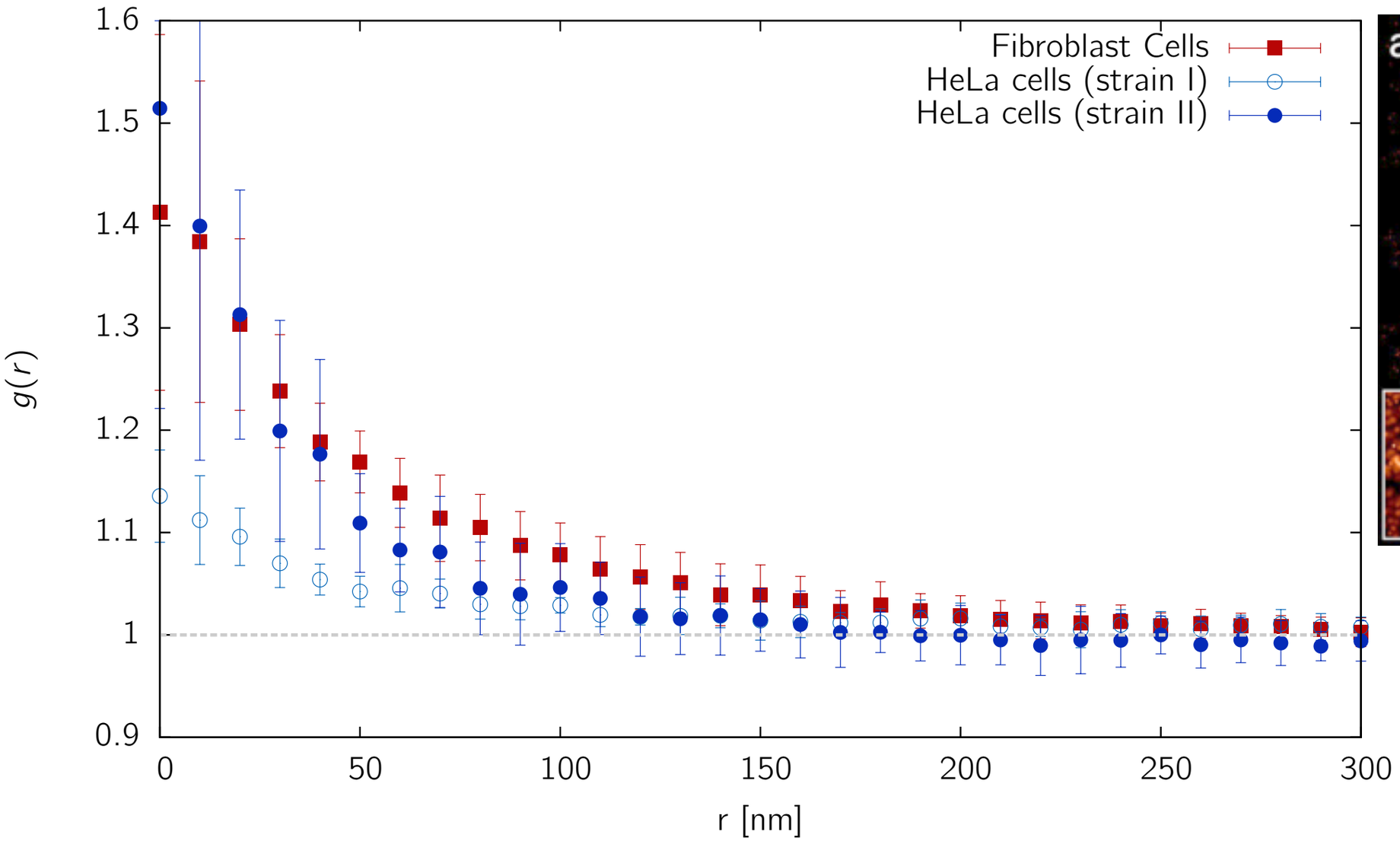
Escherichia coli

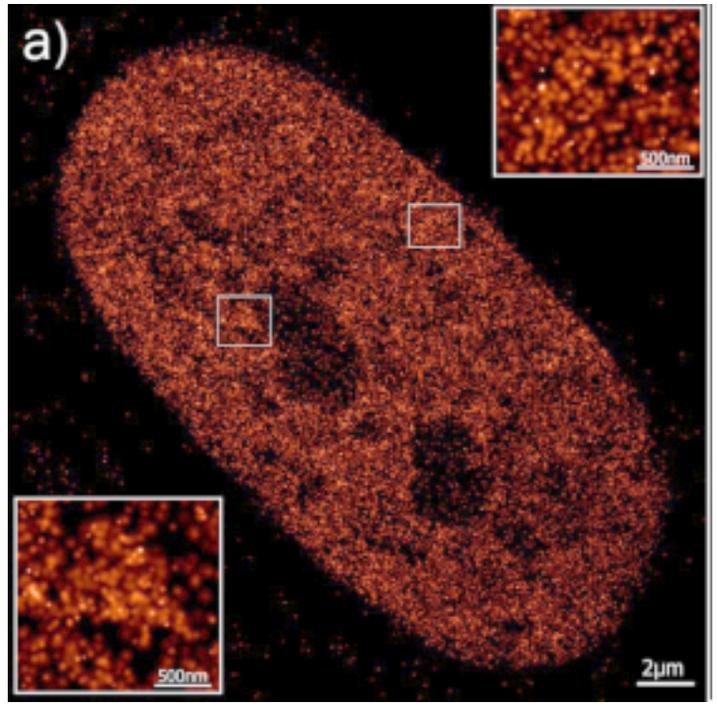
Yeast

How can we obtain information on the structure?

Label (for example fluorescence in situ hybridization (FISH)) specific sites along the chromosome.





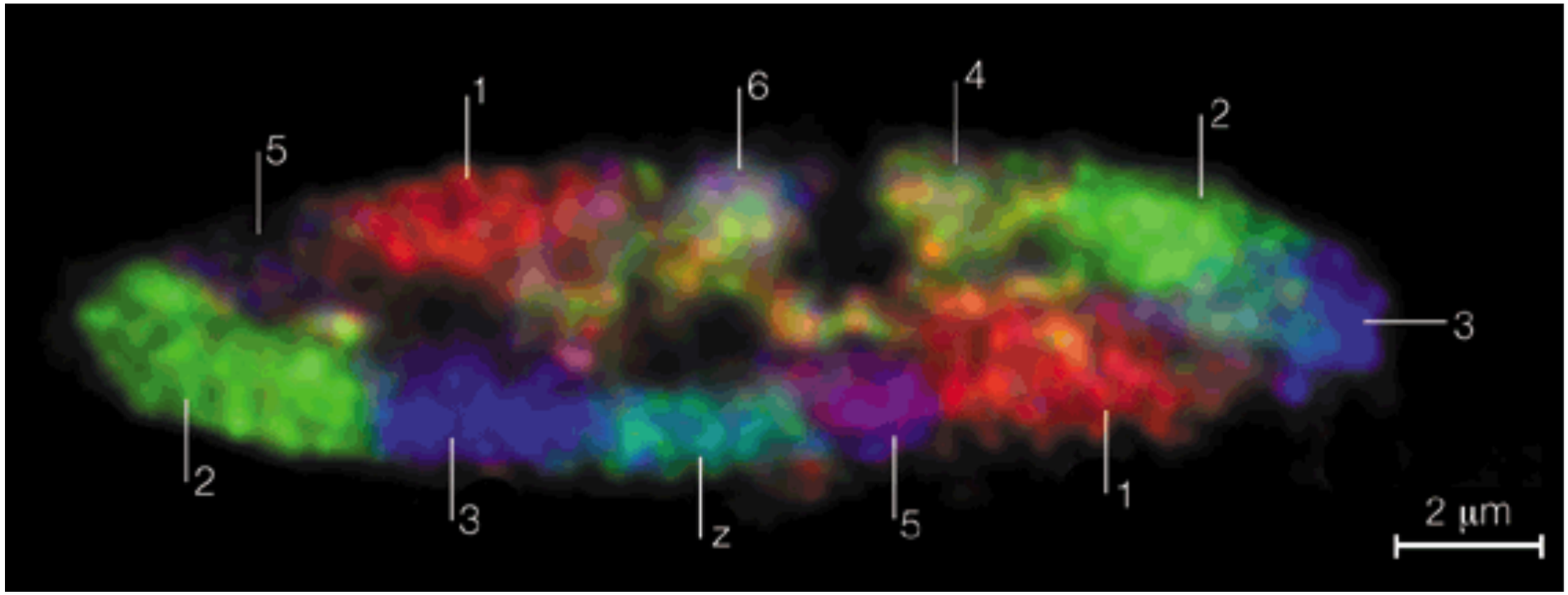


Localization microscopy reveals expression-dependent parameters of chromatin nanostructures

Manfred Bohn, Philipp Diesinger, Rainer Kaufmann, Yanina Weiland, Patrick Müller, Manuel Gunkel, Alexa von Ketteler, Paul Lemmer, Michael Hausmann, Dieter W. Heermann and Christoph Cremer

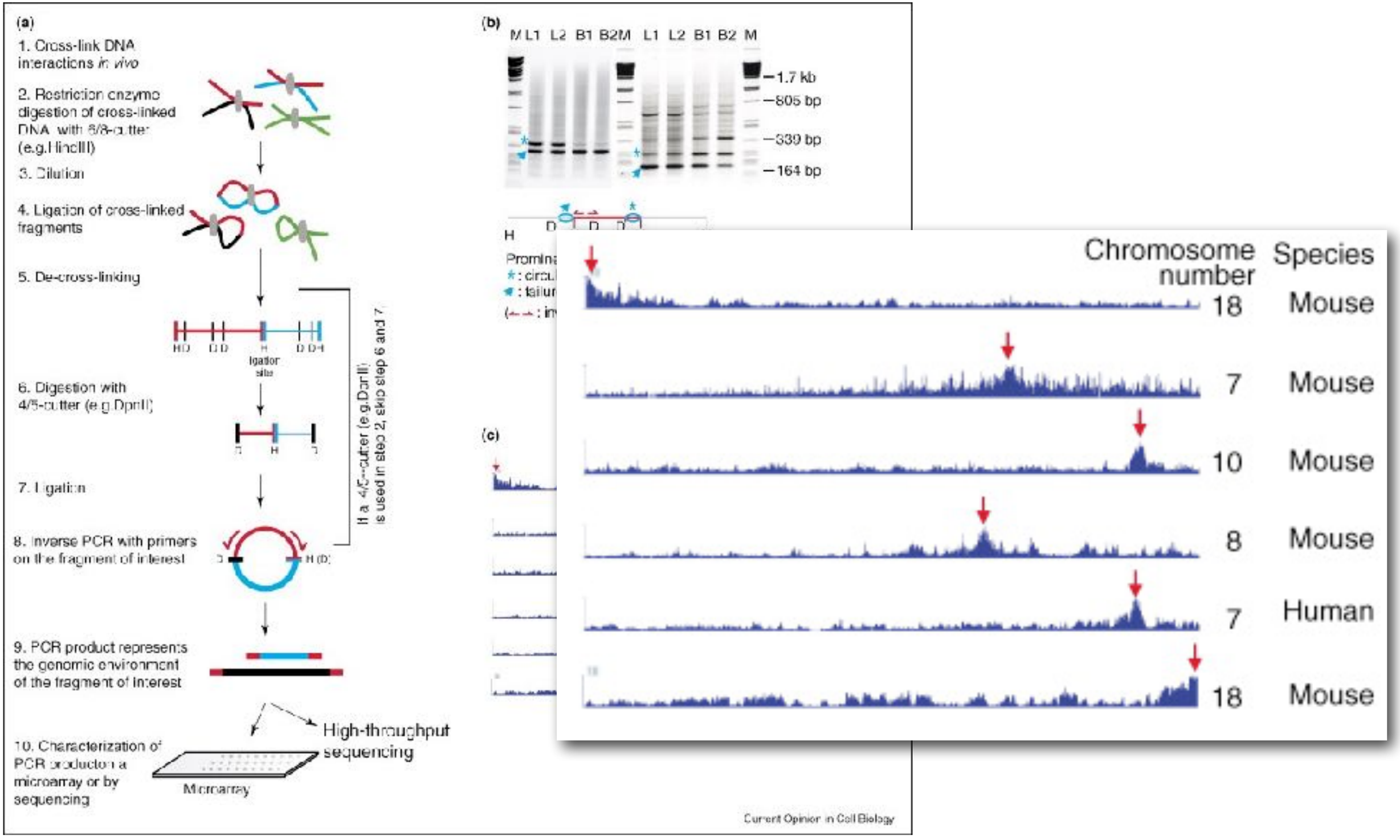
Biophysical Journal, Volume 99, Issue 5, 1358-1367, 8 September 2010

Staining of the entire chromosome

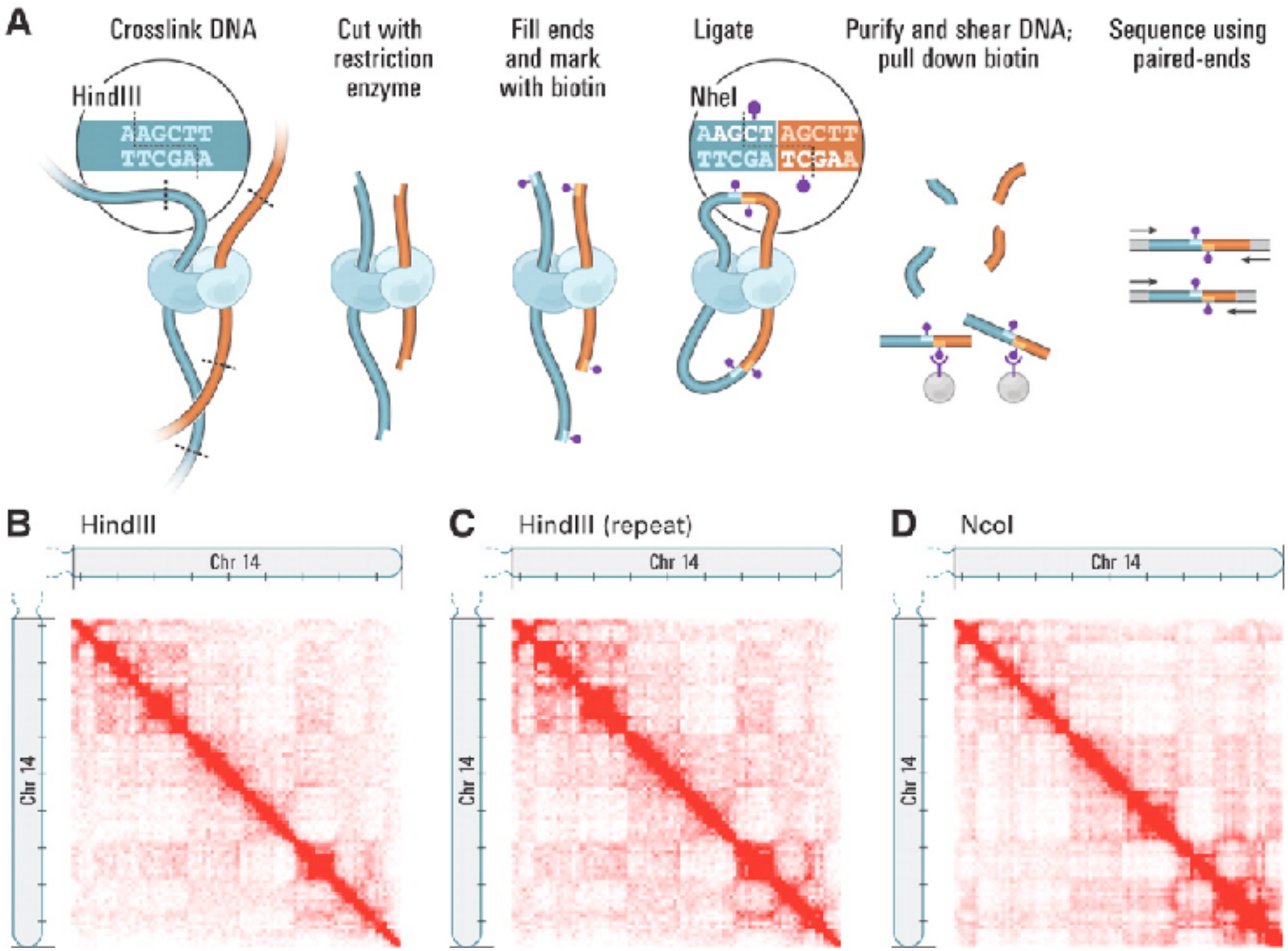


Chromosome Territories

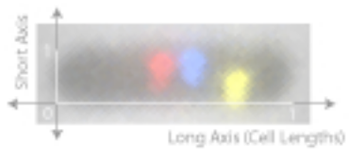
T.Cremer and C. Cremer, Nature Reviews Genetics vol. 2, no. 4, pp. 292-301 (April, 2001)



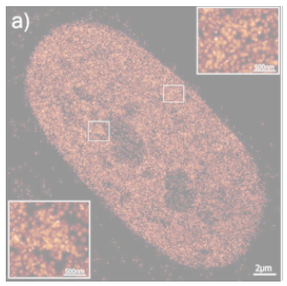
W. de Laat, Current Opinion in Cell Biology 2007, 19:317–320

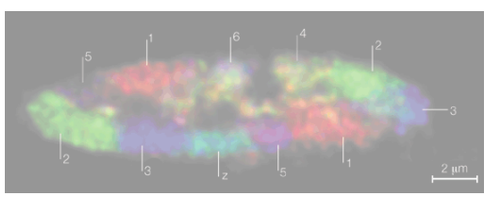


Comprehensive Mapping of Long-Range Interactions Reveals Folding Principles of the Human Genome
E. Lieberman-Aiden et. al., Science 2010

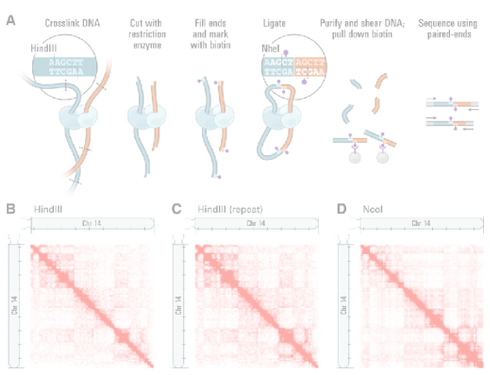


Spatial Information





Measure two, few or many physical positions

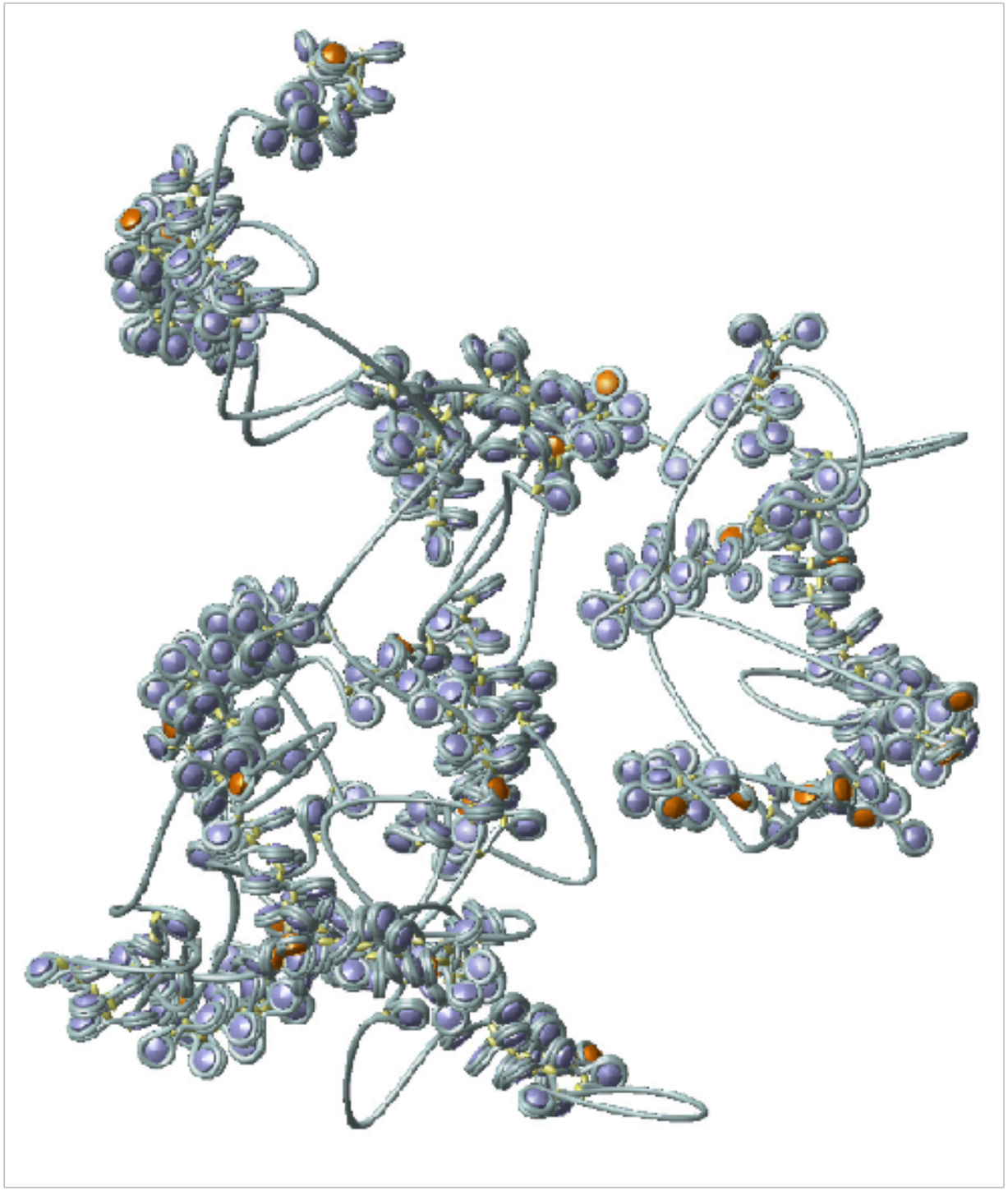


Topological Information

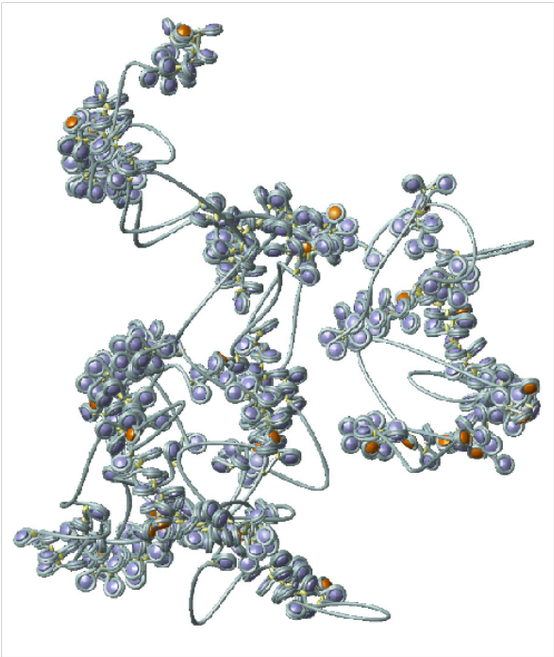
Measure contacts without spatial information

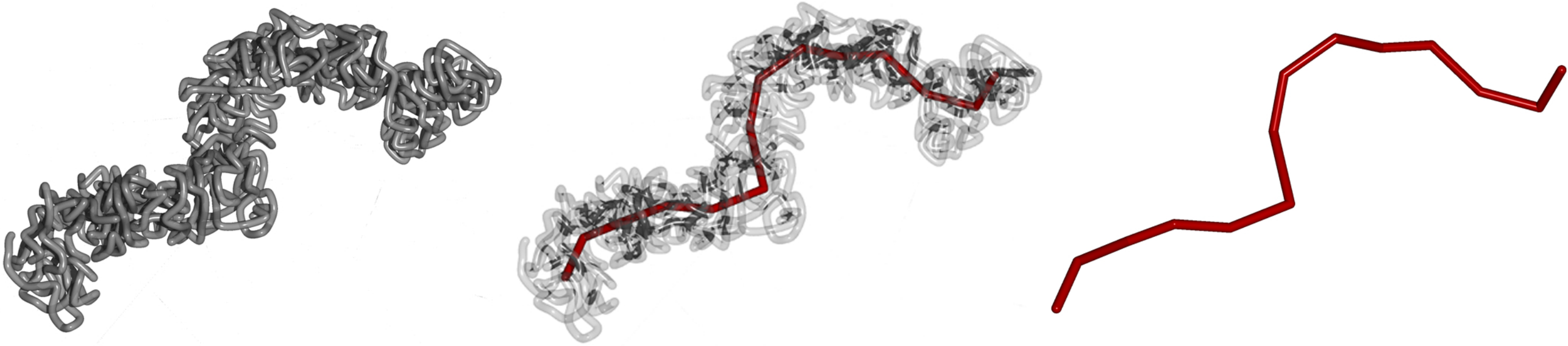
Heermann, Heidelberg University, 2017

The Model



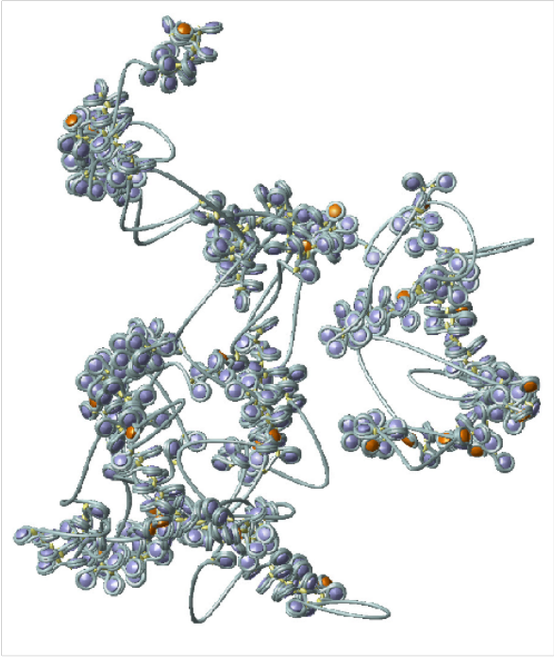
The Model





coarse grained description

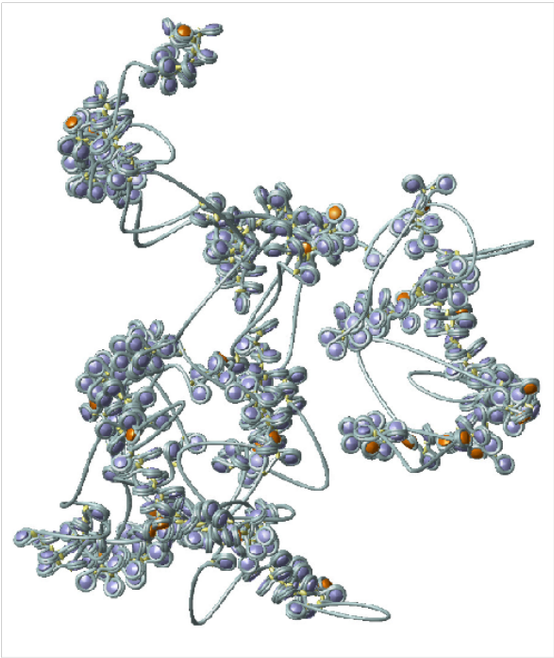
The Model

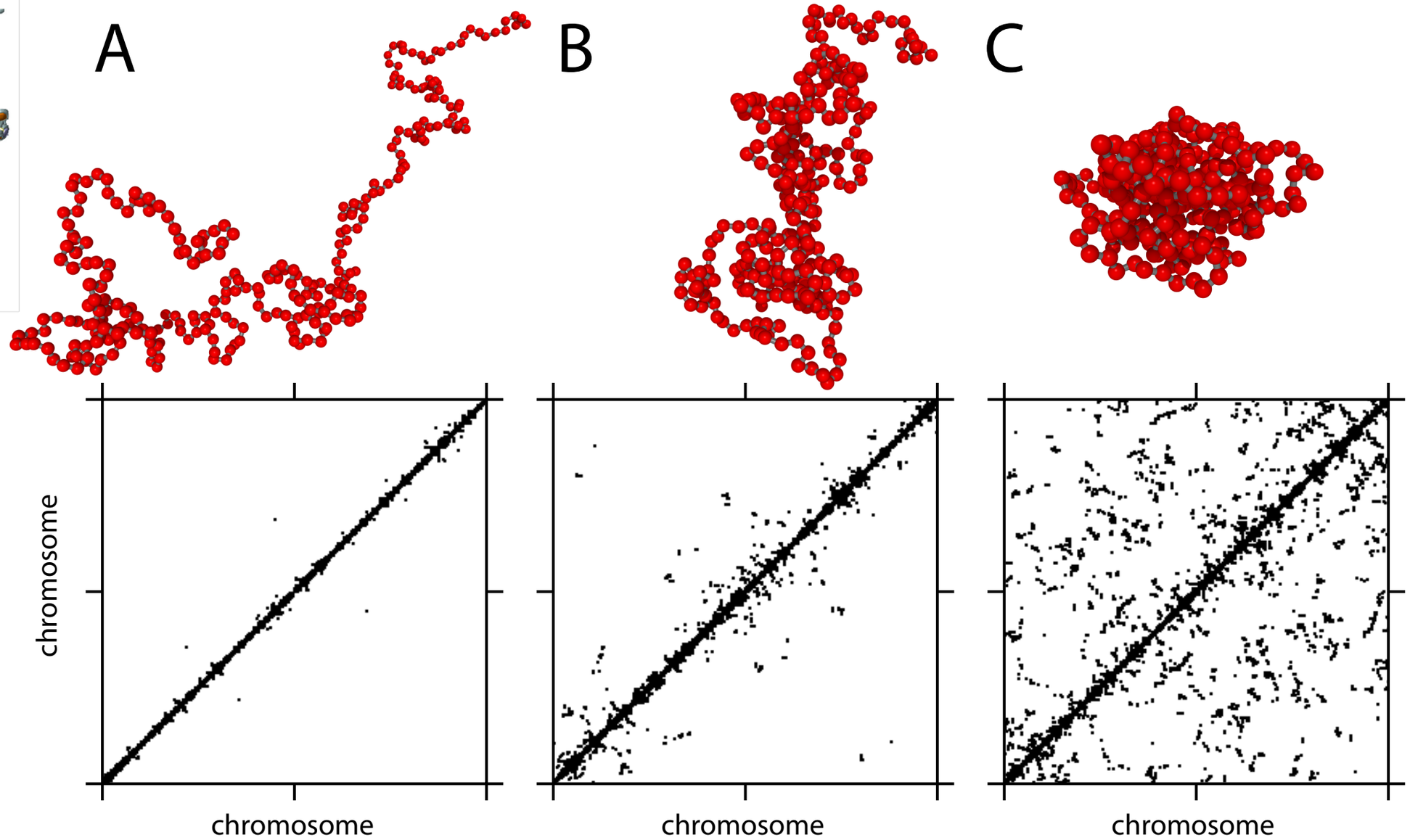


Basic assumptions:

The backbone of the chain is given by a simple self-avoiding walk.

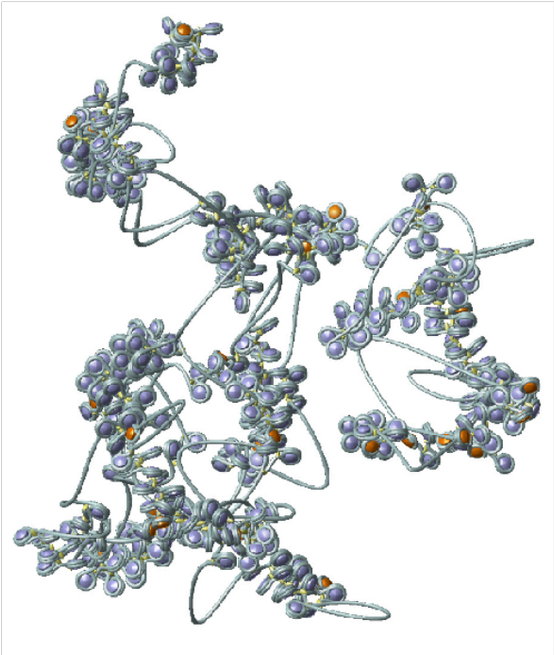
The Model

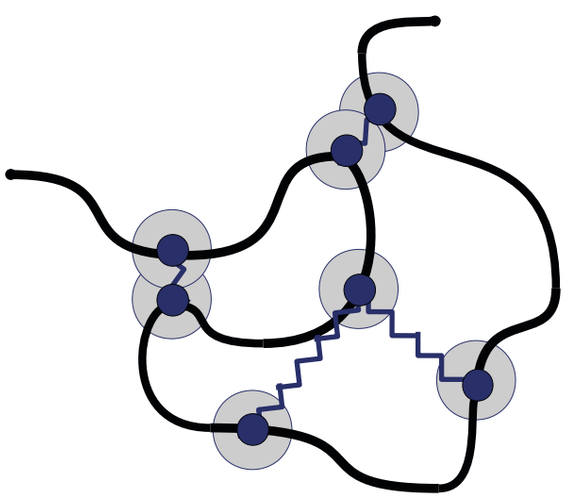




The effect of loops on the conformation

The Model





Basic assumptions:

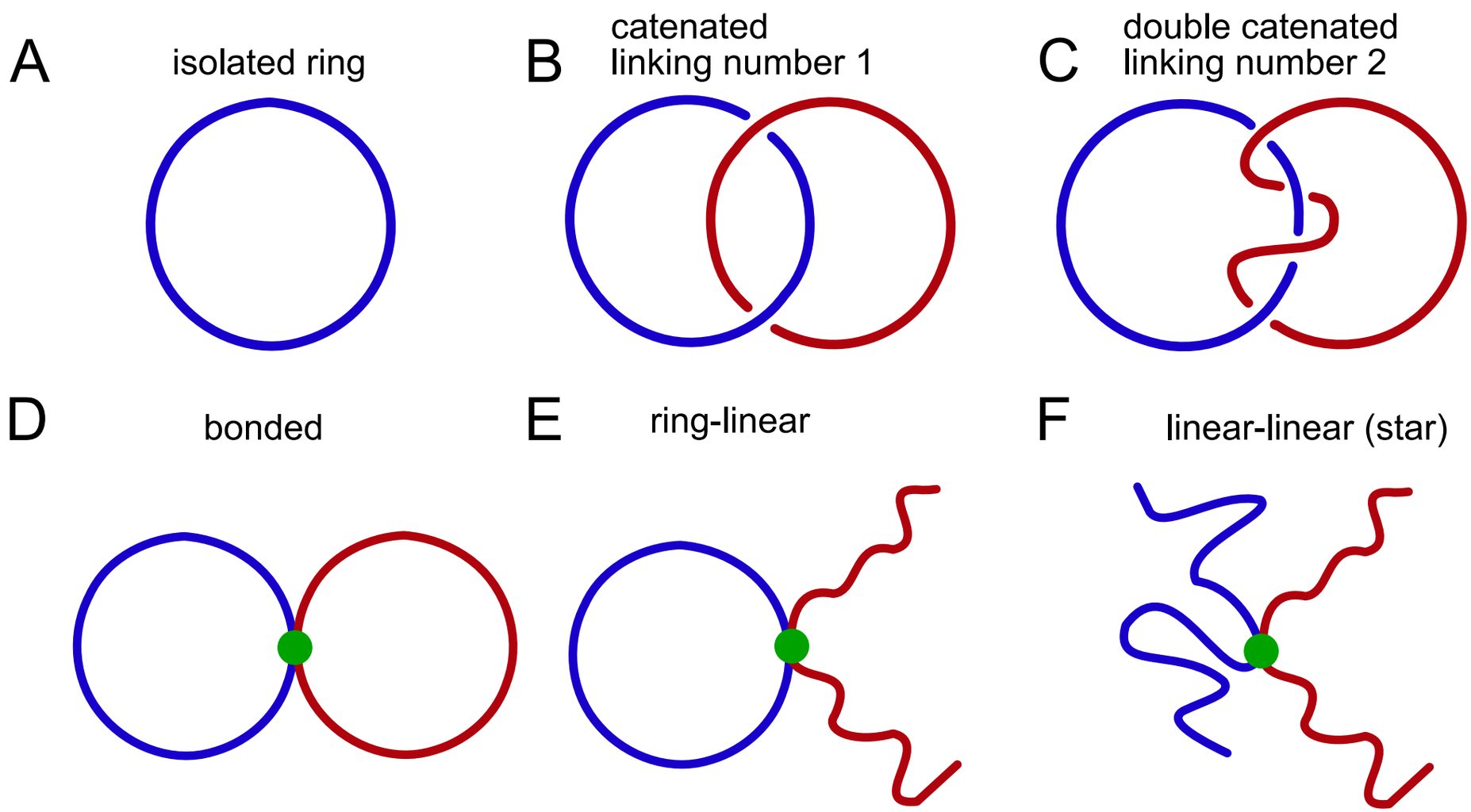
The backbone of the chain is given by a simple self-avoiding walk.

Two parts of the polymer form loops with a certain probability.

Loops are not static but can change in the course of time; their size and position are chosen from a broad range.

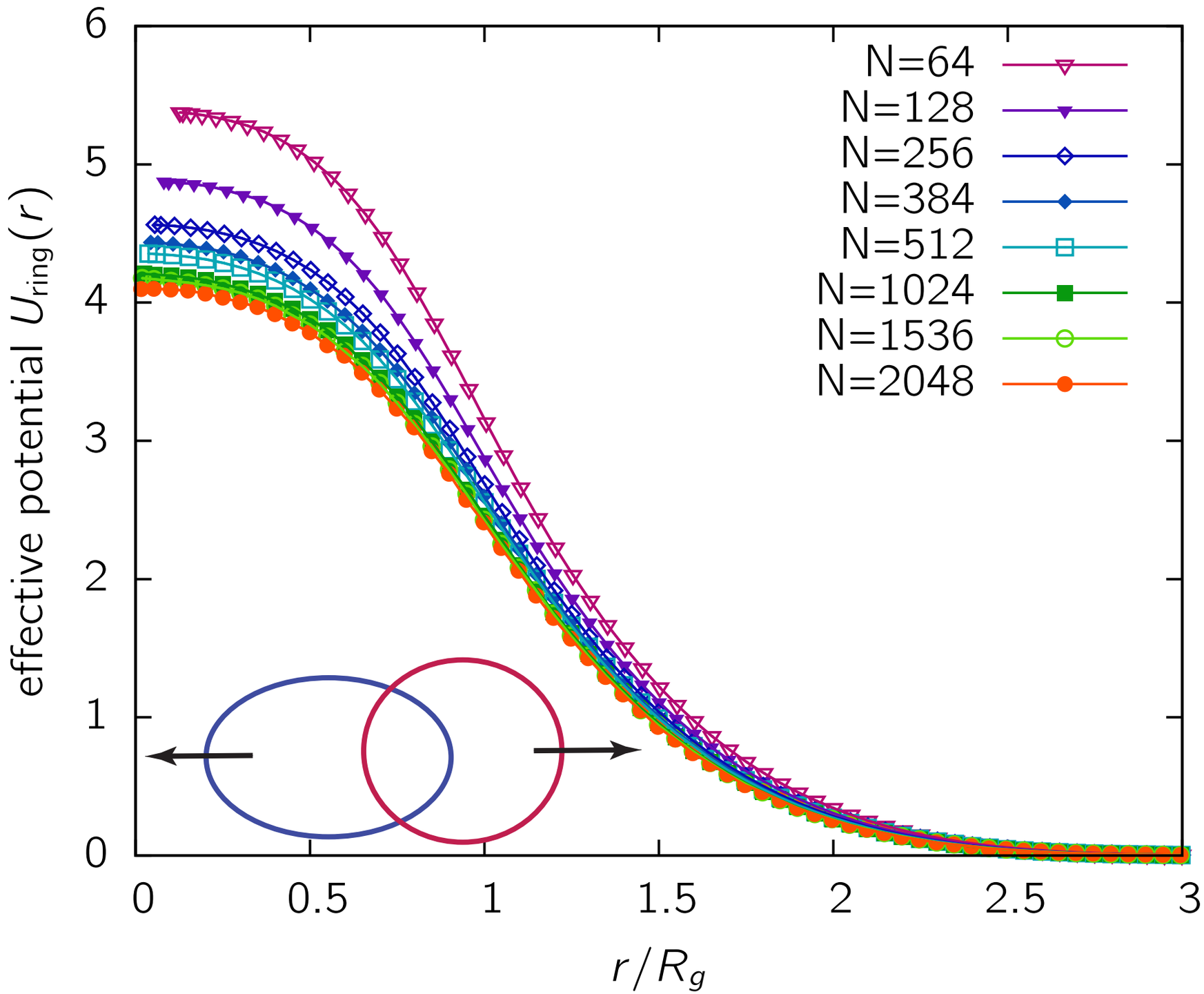
Diffusion-Driven Looping Provides a Consistent Framework for Chromatin Organization Manfred Bohn and Dieter W. Heermann
PLoS ONE 5(8): e12218. doi:10.1371/journal.pone.0012218 (2010)

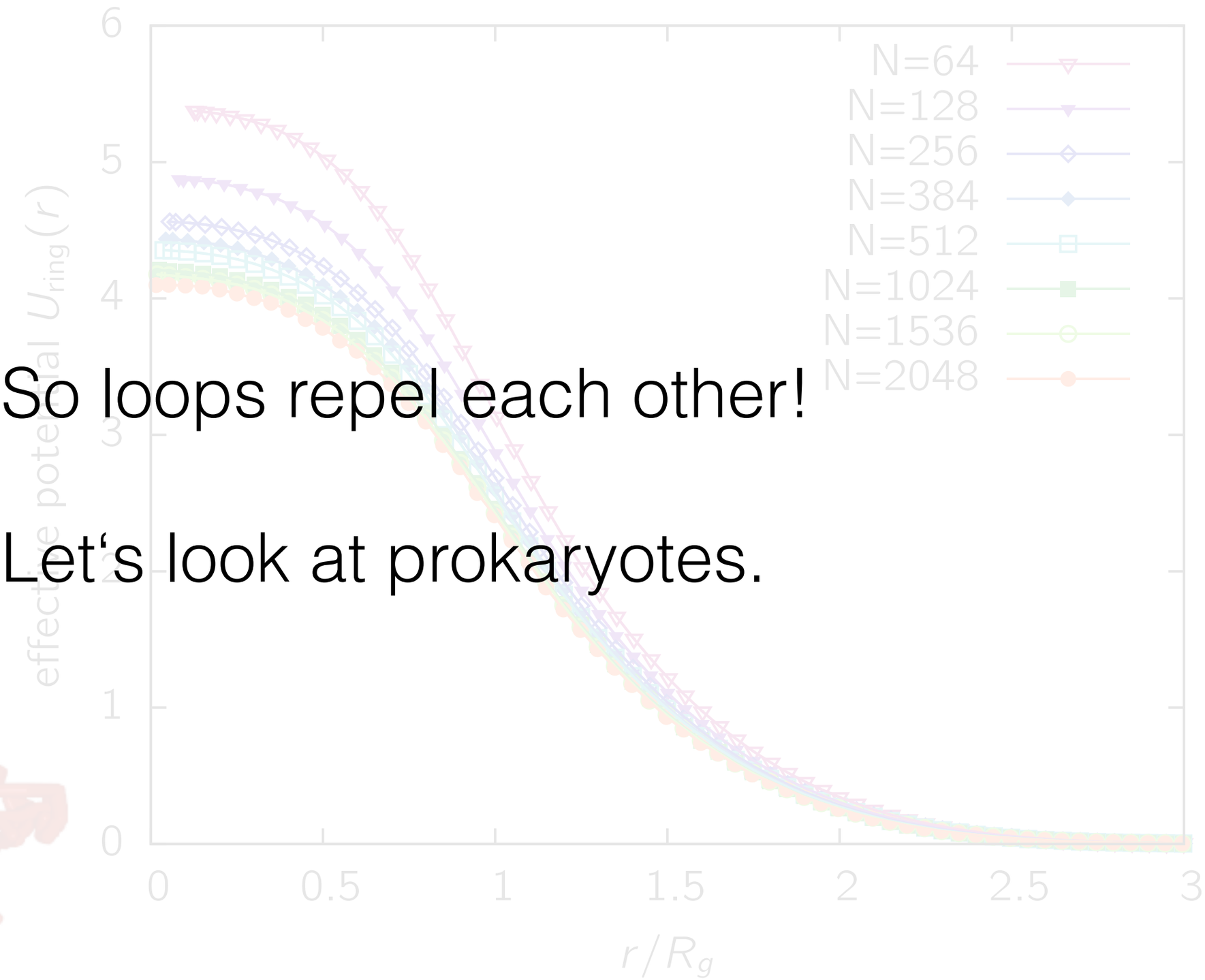
Loops



Influence of the catenation constraint on elongation and segregation of ring polymers
Manfred Bohn, Dieter W. Heermann, Odilon Lourenço, Claudette Cordeiro
Macromolecules, 43 (5), 2564–2573 (2010)

***T*opological interactions between ring polymers: Implications for chromatin loops**
Manfred Bohn and Dieter W. Heermann
J. Chem. Phys. 132, 044904 (2010)

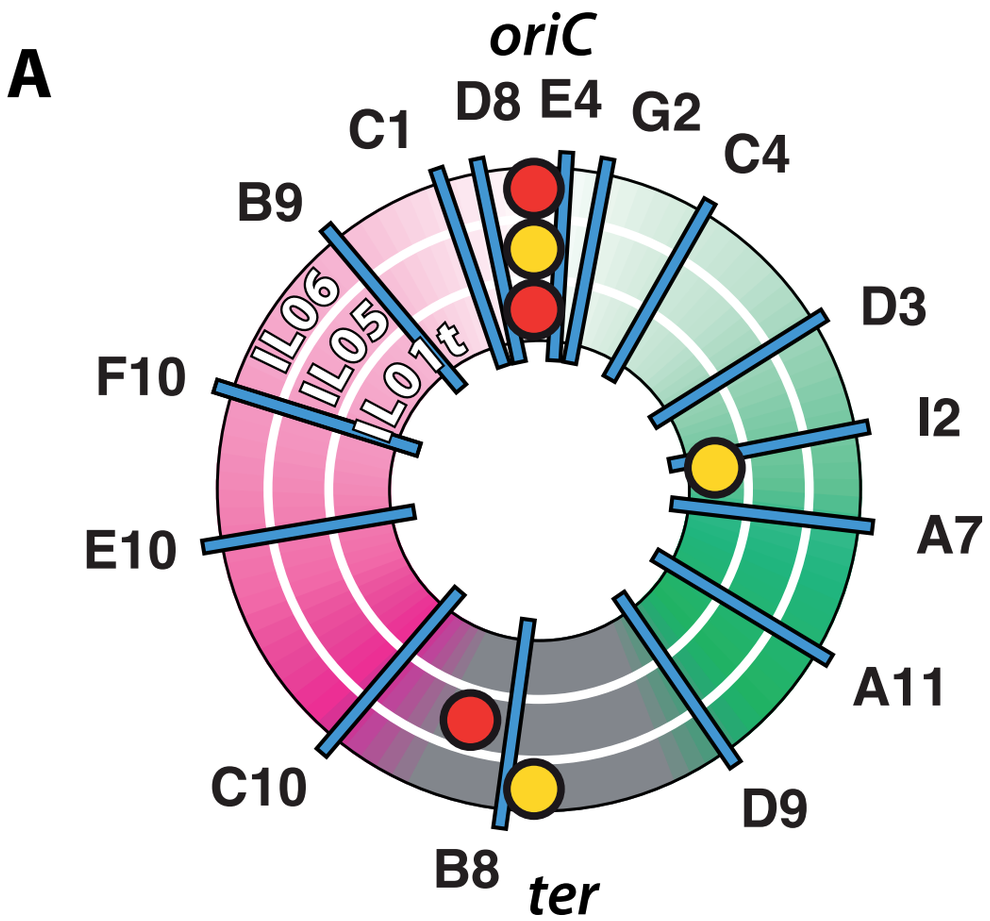

N=64
N=128
N=256
N=384
N=512
N=1024
N=1536
N=2048
effective potential $U_{\mathrm{ring}}(r)$
r/R_g
0
1
2
3
4
5
6
0
0.5
1
1.5
2
2.5
3

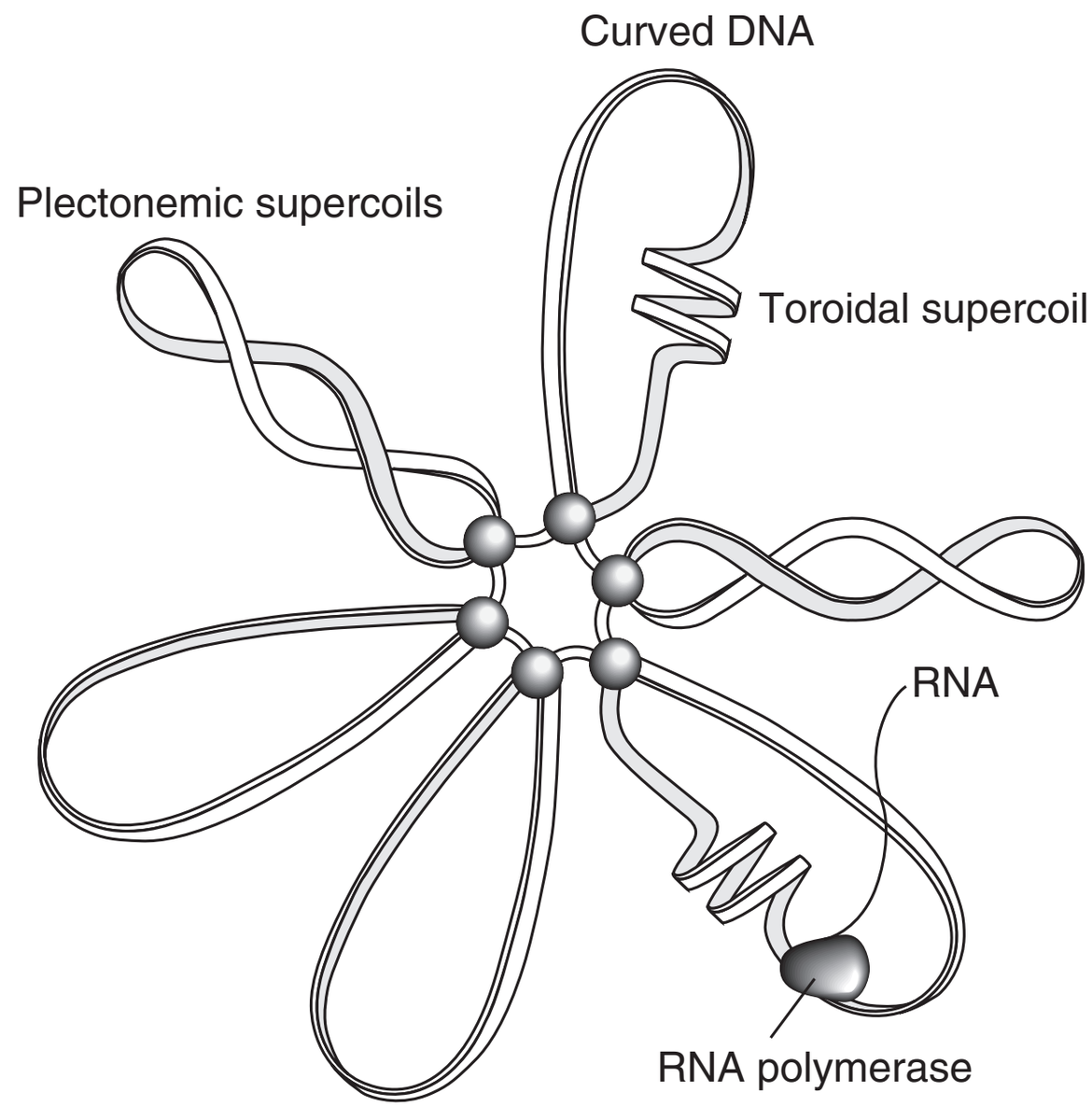


So loops repel each other!

Let‘s look at prokaryotes.

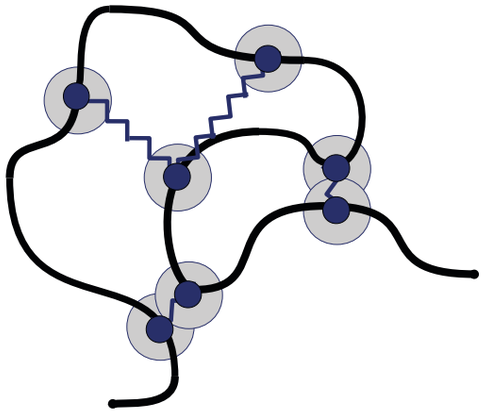
e.coli

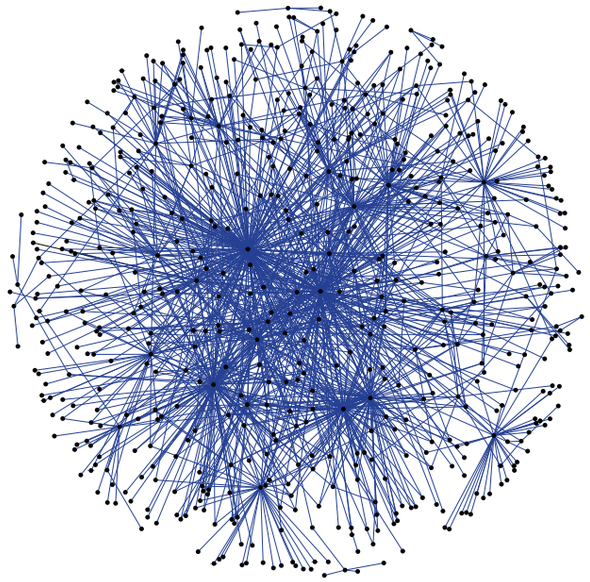




Source: Willenbrock and Ussery *Genome Biology* 2004 **5**:252 doi:10.1186/gb-2004-5-12-252

Loops: Biology and Physics





Ansatz: Dynamic Loop Model + genes that are co-regulated by a set of same or similar transcription factors, might stay in physical proximity in order to guarantee the efficiency of gene regulation and expression.

Transcription Factor Induced DNA Domain Formation Structures the E. coli Chromosome
M. Fritsche, S. Li, P. Wiggins and D.W. Heermann, Nucleic Acids Res. 2012 Feb;40(3):972-80.

Loops: One More Thing

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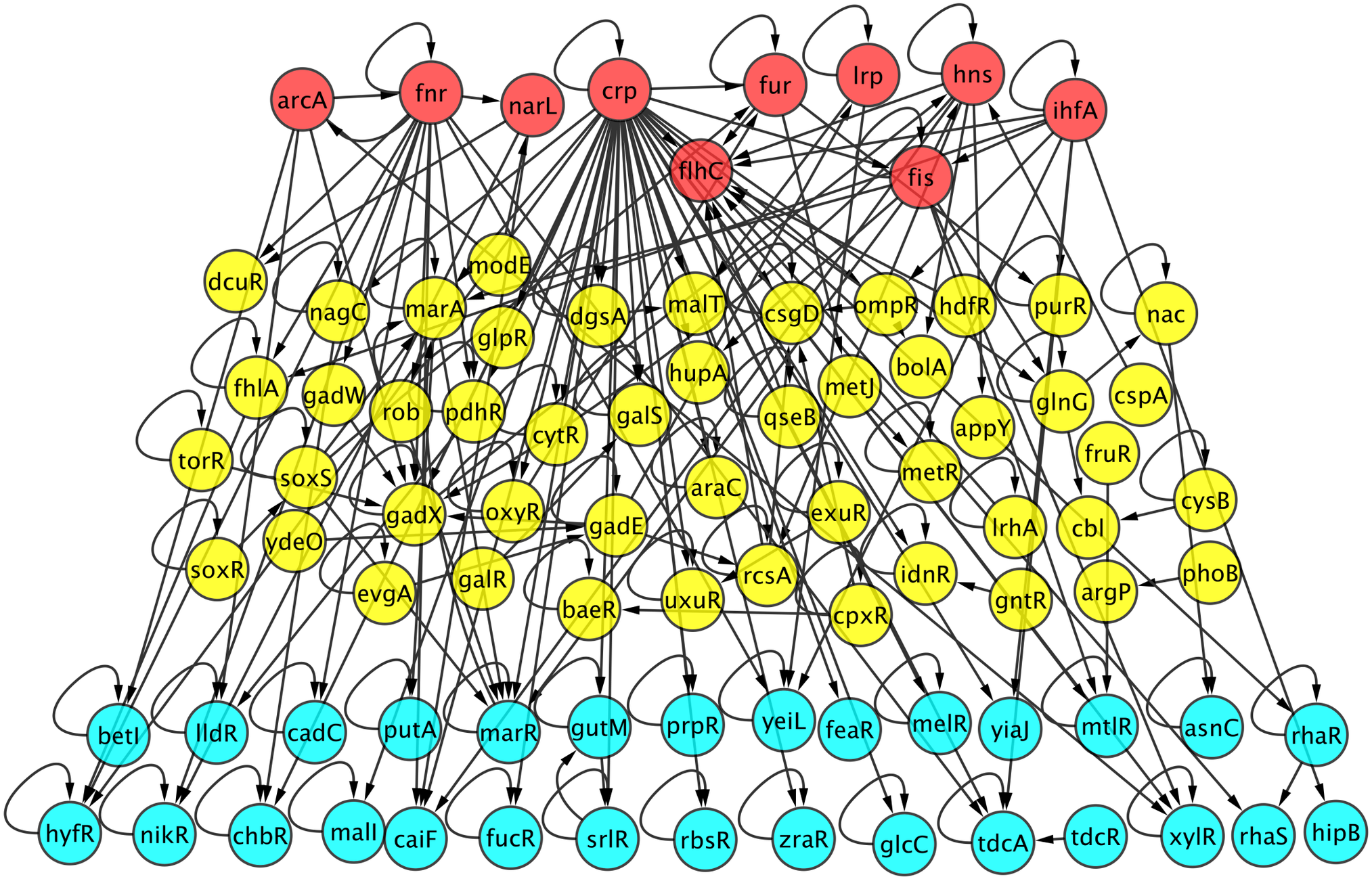

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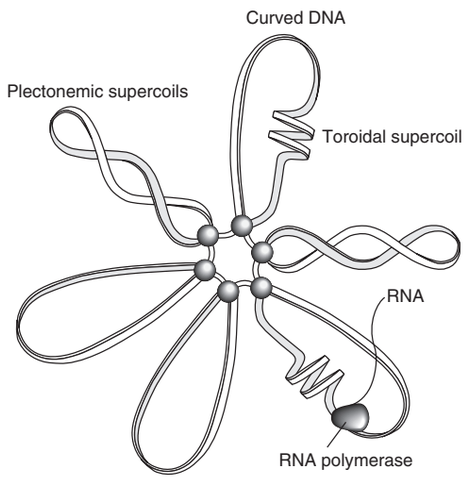
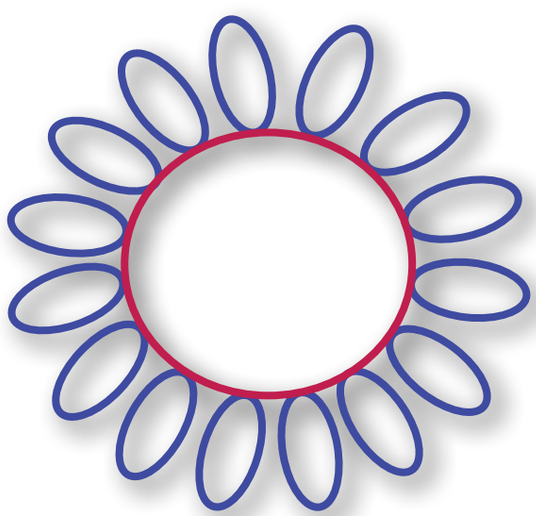
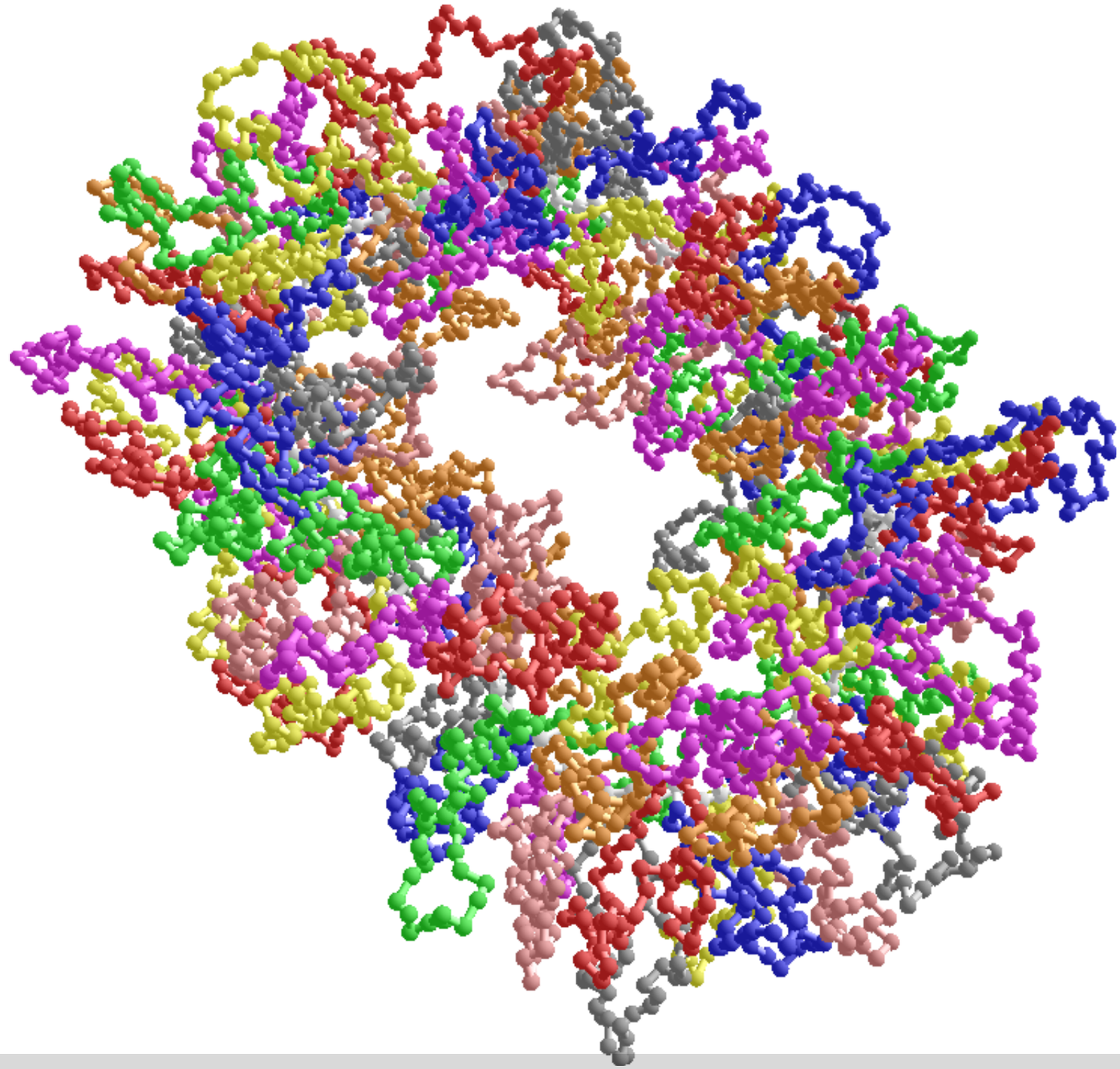
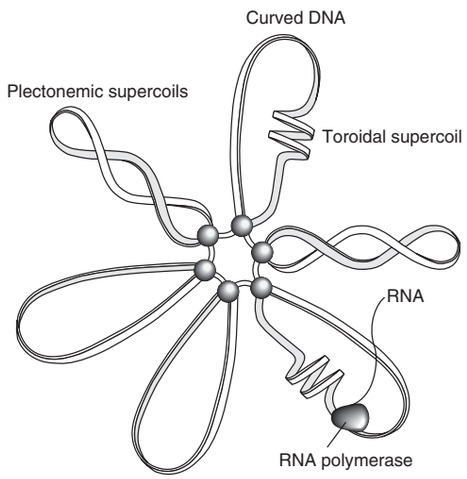


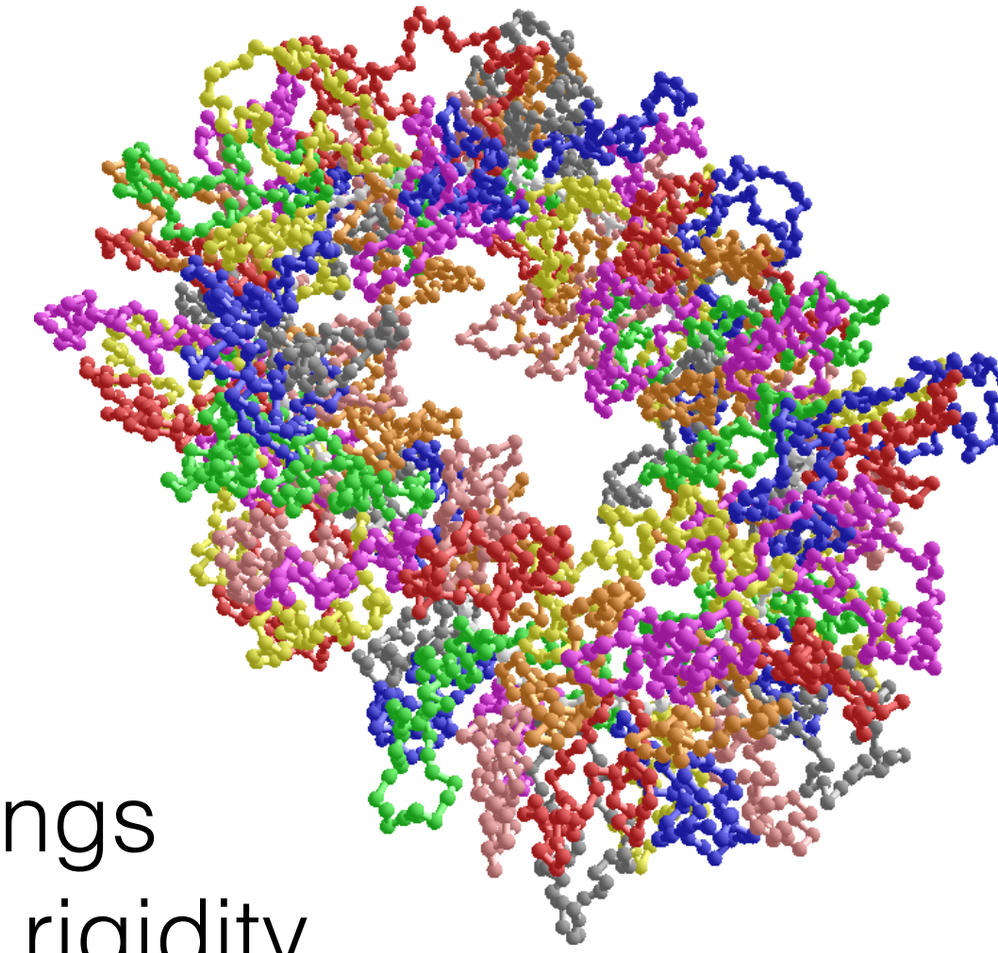




Looped Star Polymers Show Conformational Transition from Spherical to Flat Toroidal Shapes
Pascal Reiß, Miriam Fritsche, and Dieter W. Heermann, Phys. Rev. E 84, 051910 (2011)

e.coli

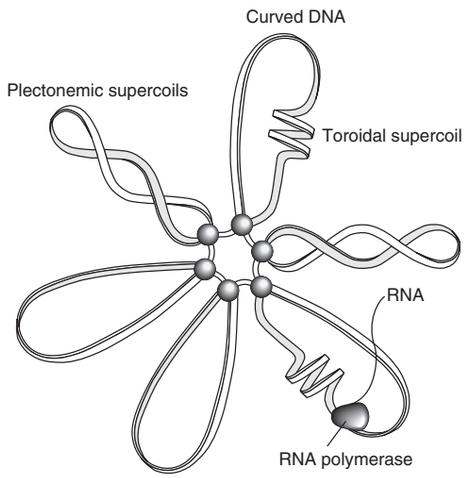


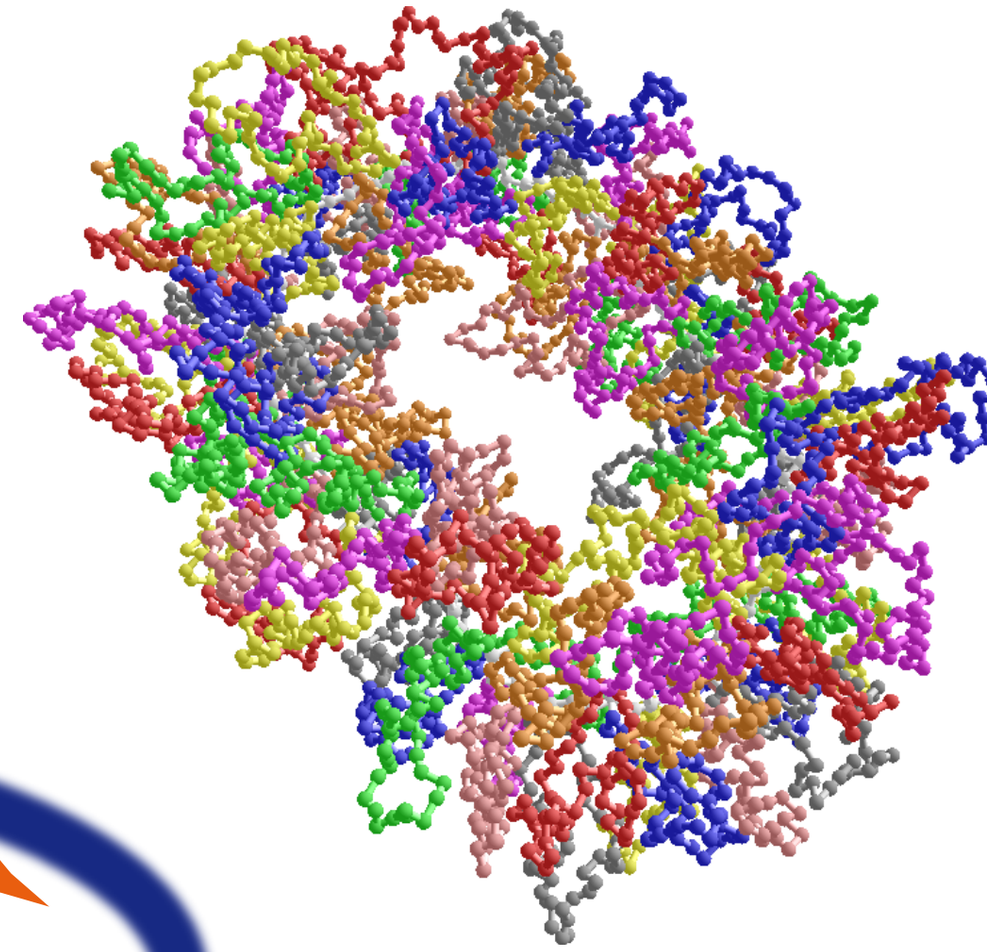


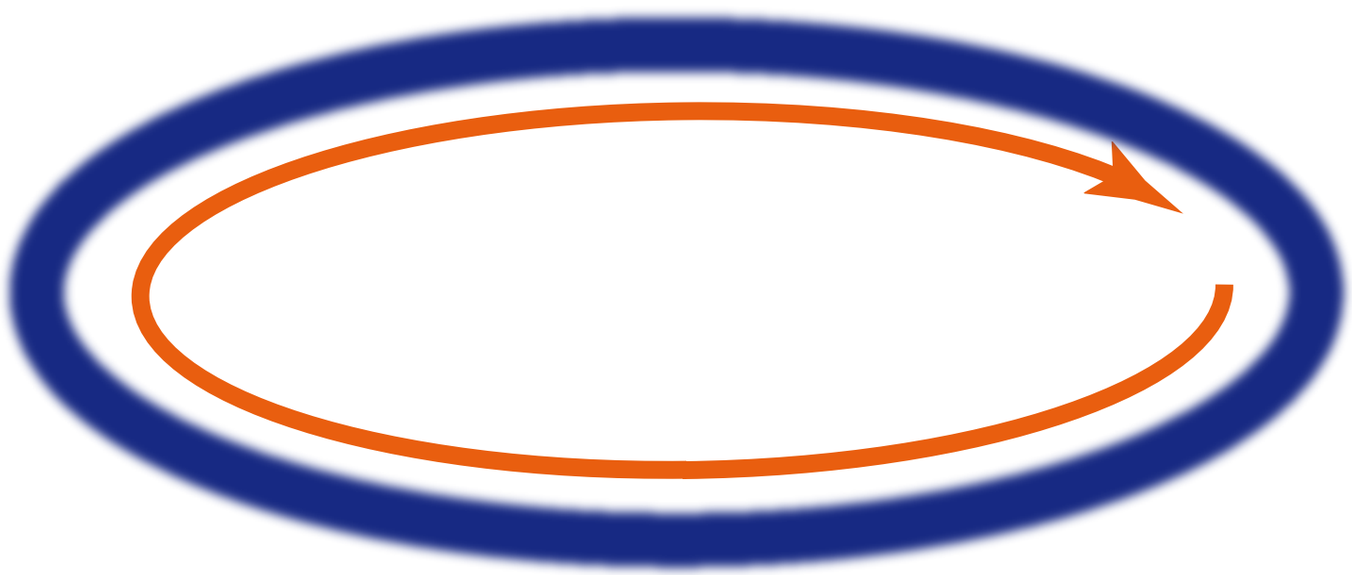
Entropic repulsion between rings
leads to an effective bending rigidity.

Looped Star Polymers Show Conformational Transition from Spherical to Flat Toroidal Shapes
Pascal Reiß, Miriam Fritsche, and Dieter W. Heermann, Phys. Rev. E 84, 051910 (2011)

e.coli


Curved DNA
Plectonemic supercoils
Toroidal supercoil
RNA
RNA polymerase





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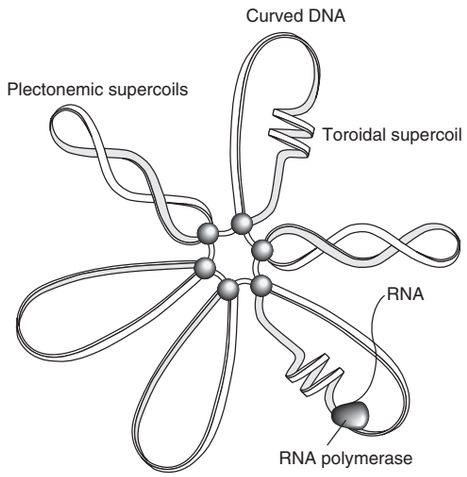
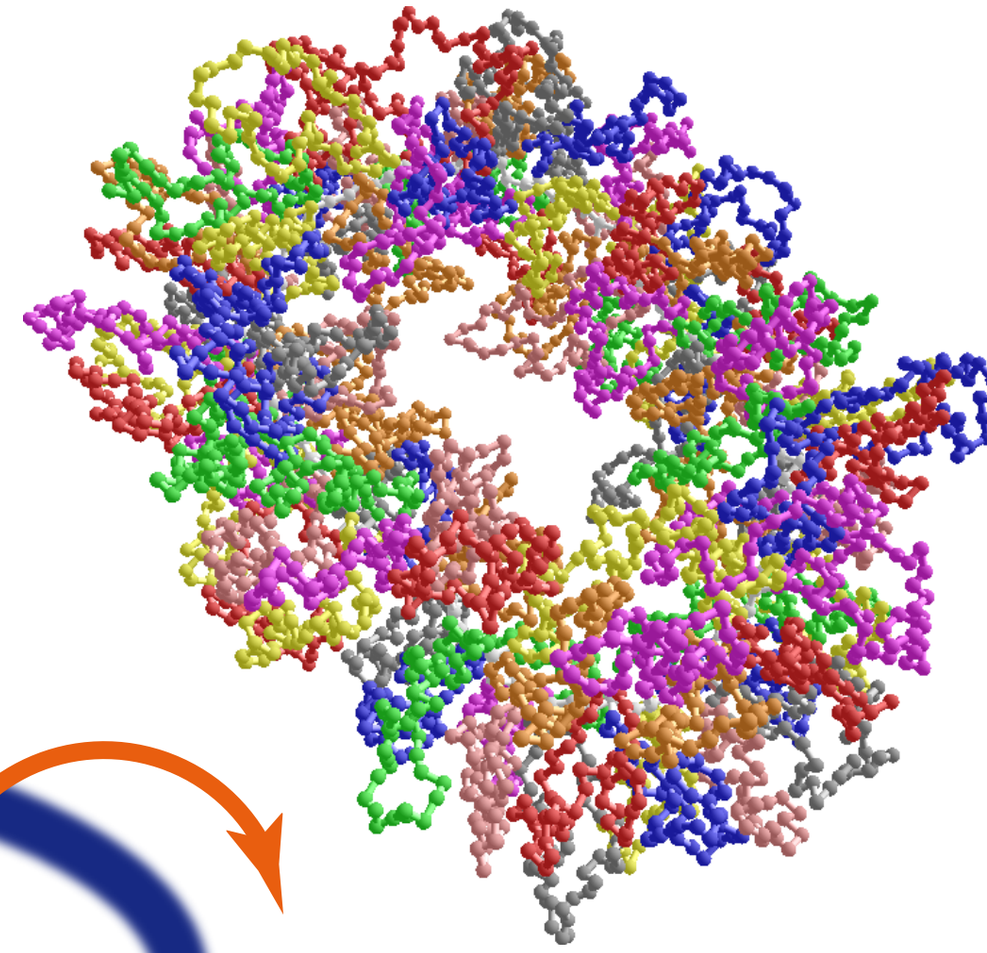

Curved DNA
Plectonemic supercoils
Toroidal supercoil
RNA
RNA polymerase



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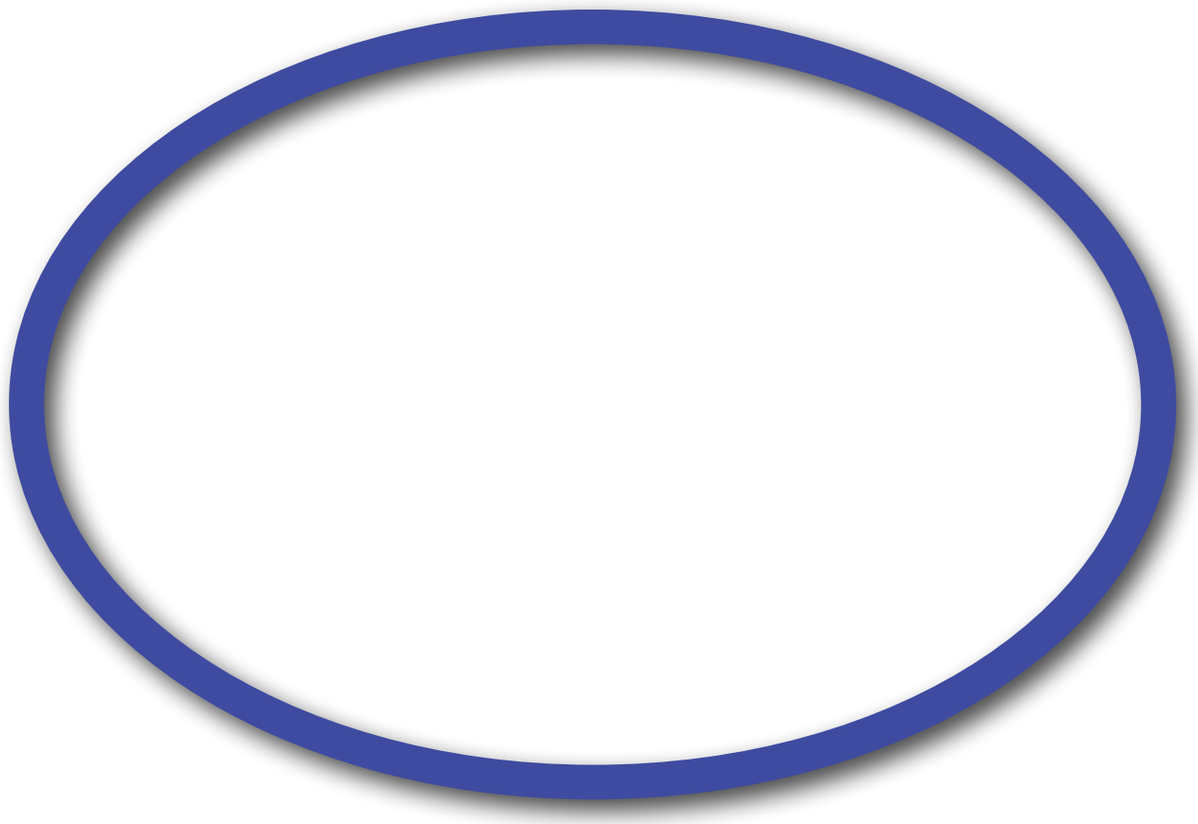

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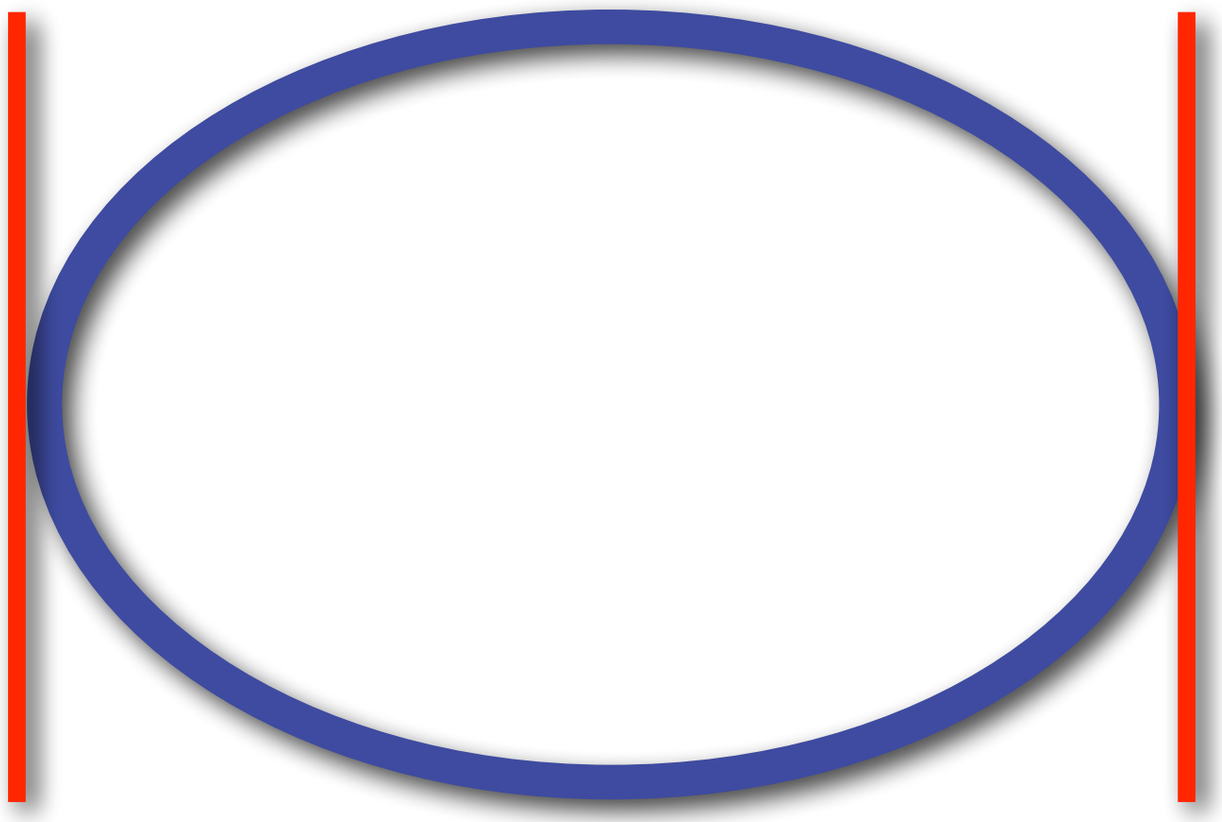

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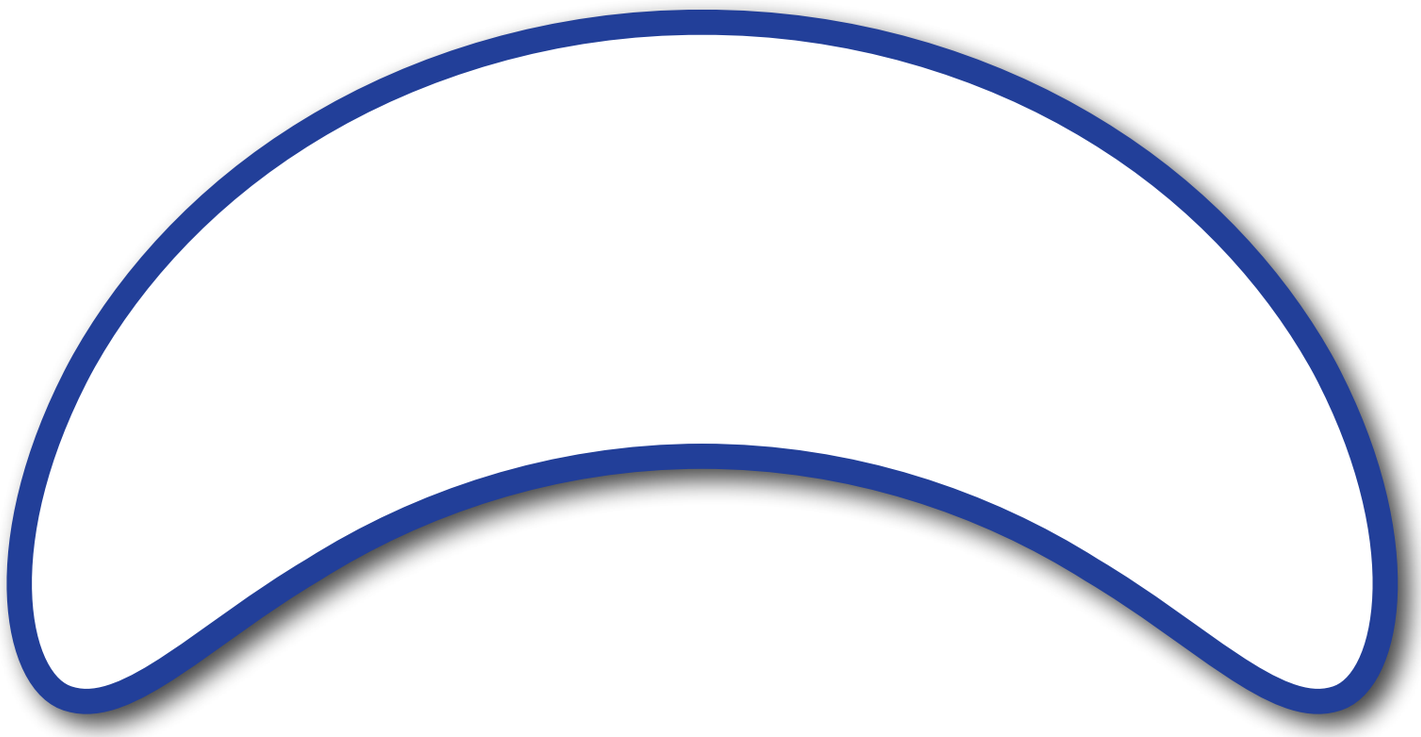

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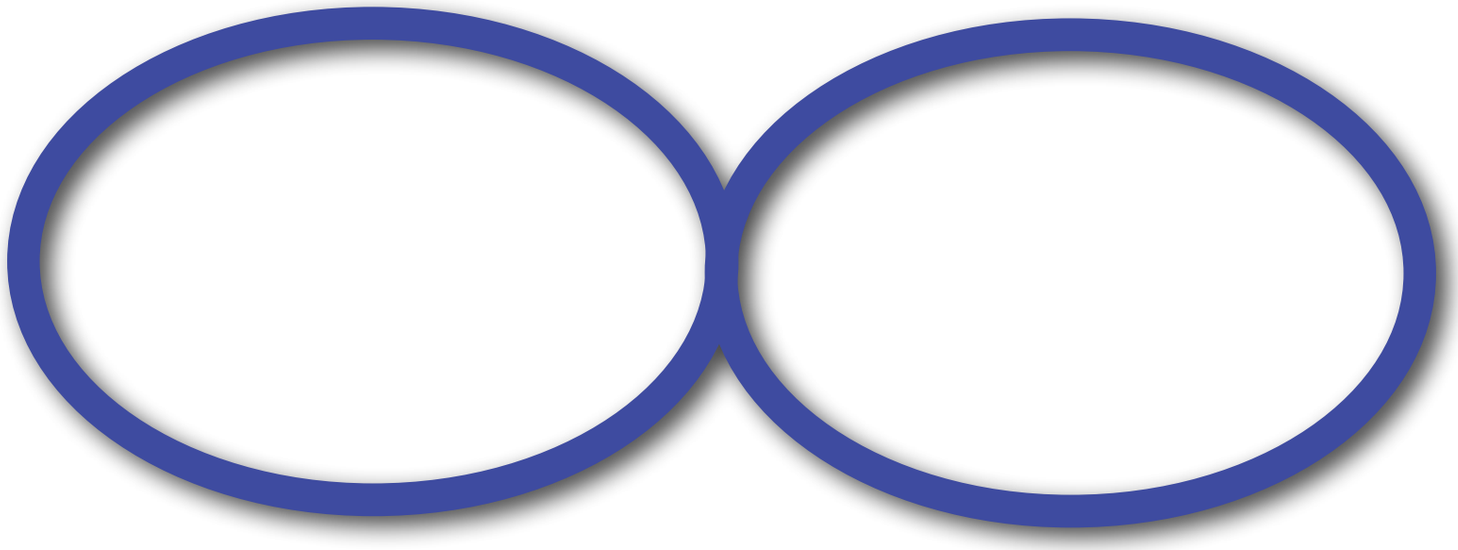

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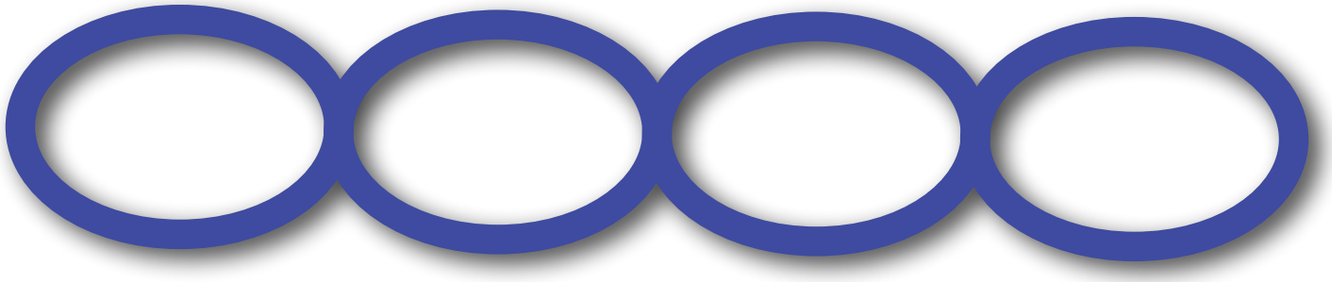

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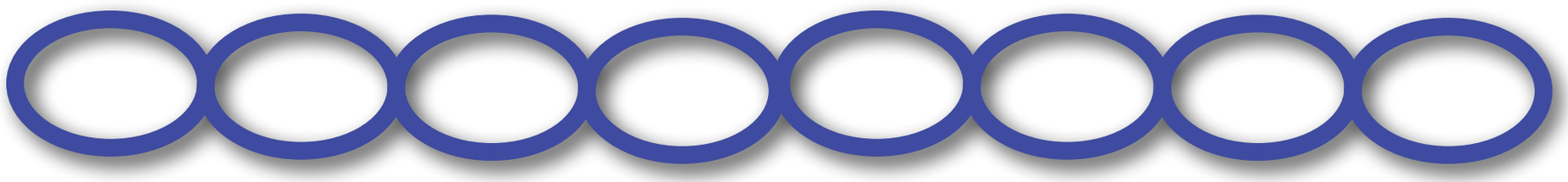

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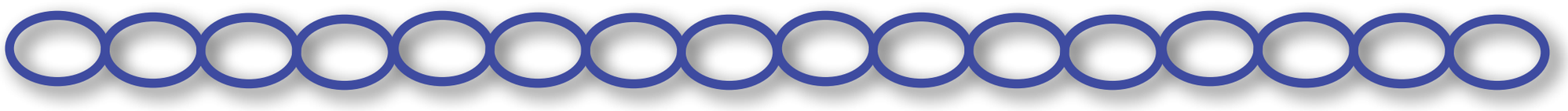

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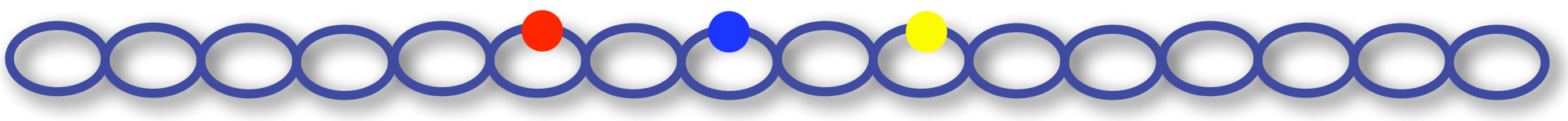

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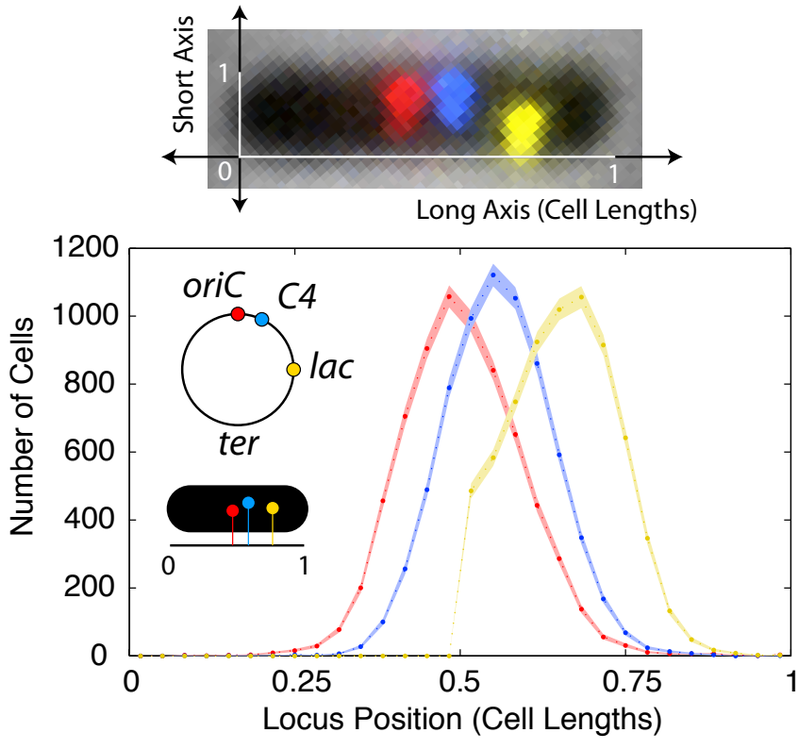
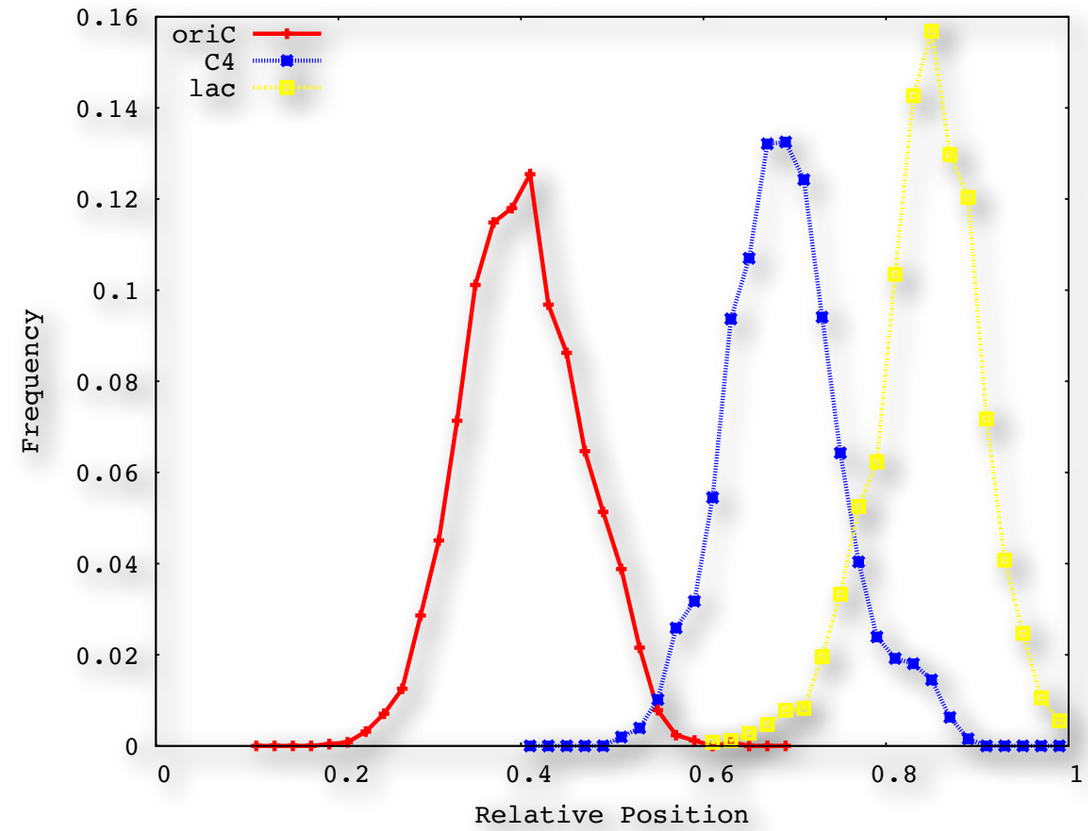
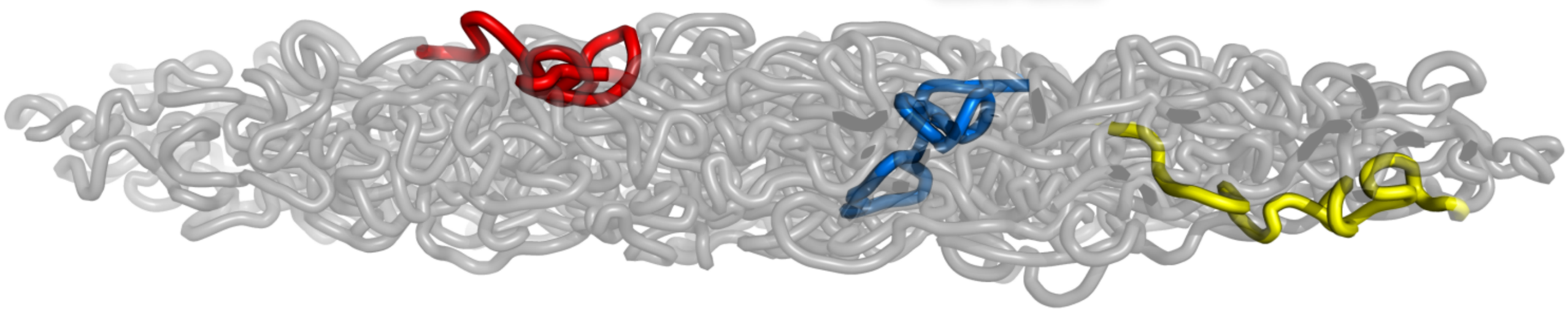
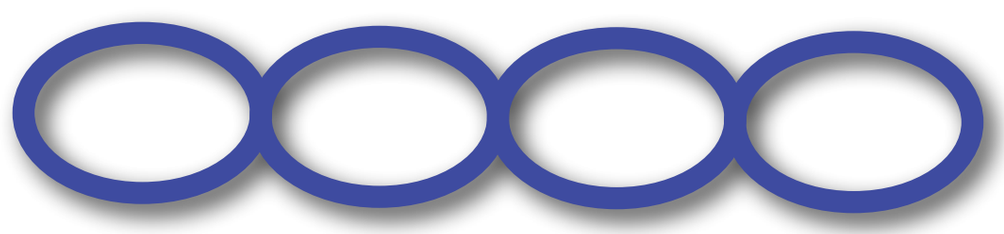

Short Axis
1
0
1
Long Axis (Cell Lengths)
oriC
C4
lac
ter
0
1
Number of Cells
1200
1000
800
600
400
200
0
0
0.25
0.5
0.75
1
Locus Position (Cell Lengths)


oriC
C4
lac
Frequency
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
0
0.2
0.4
0.6
0.8
1
Relative Position





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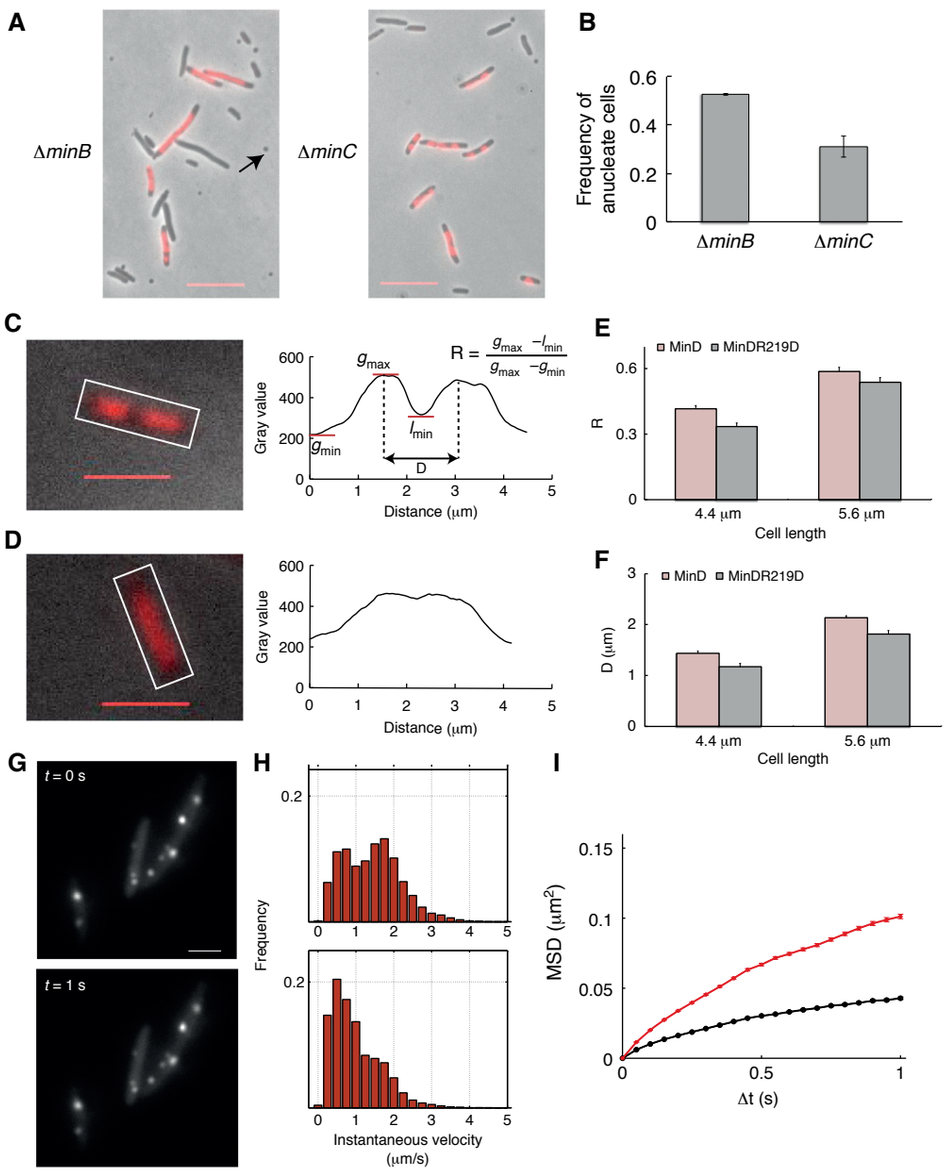
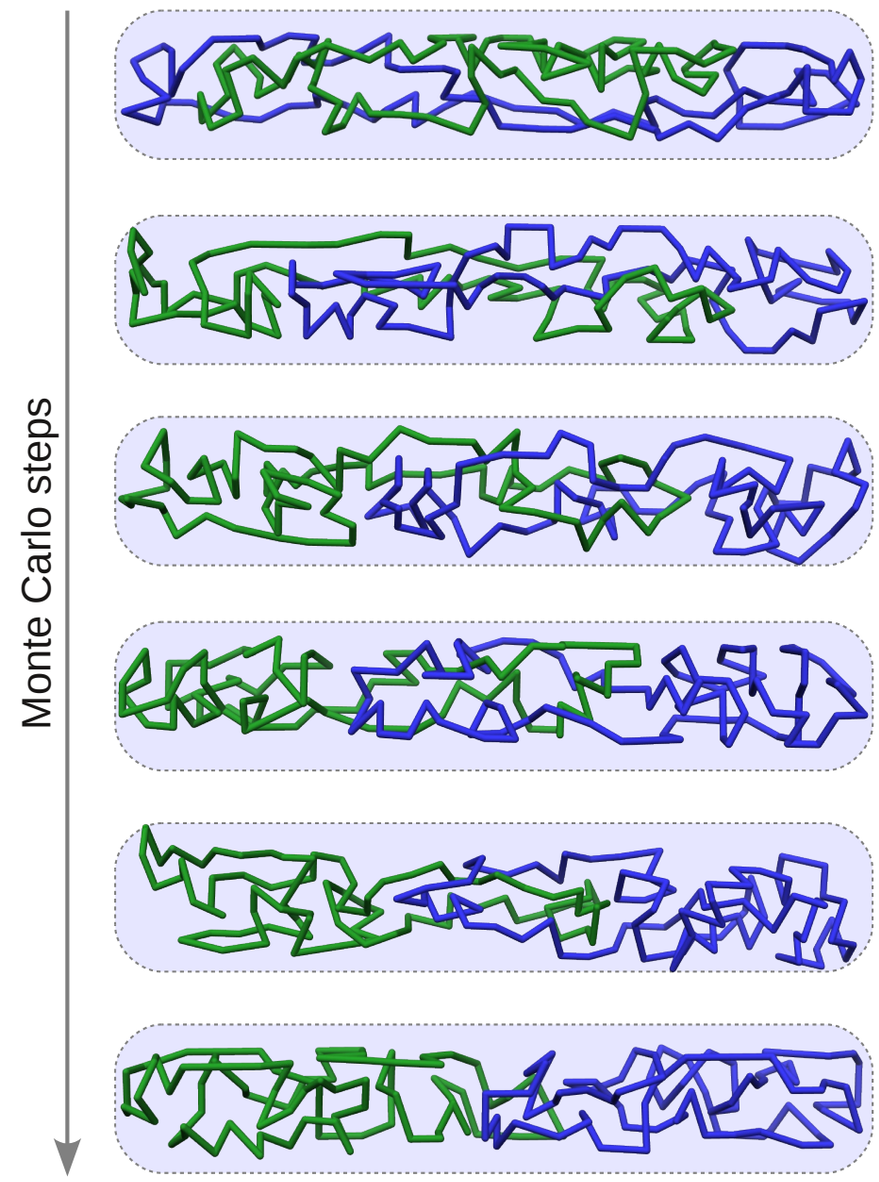


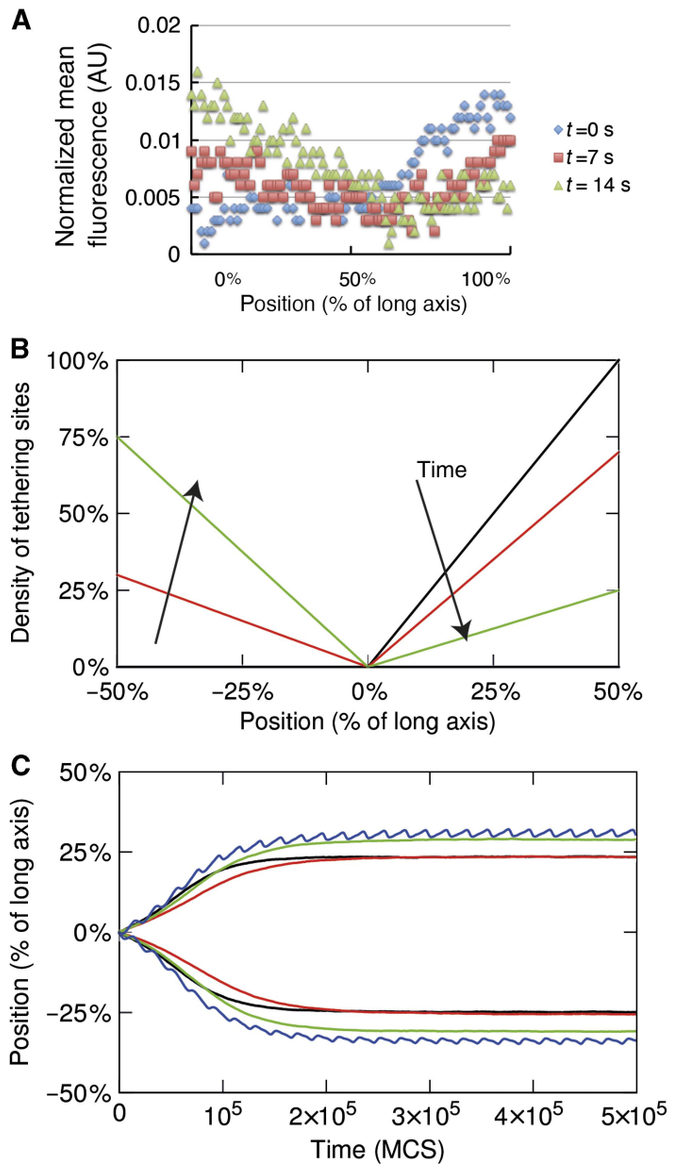


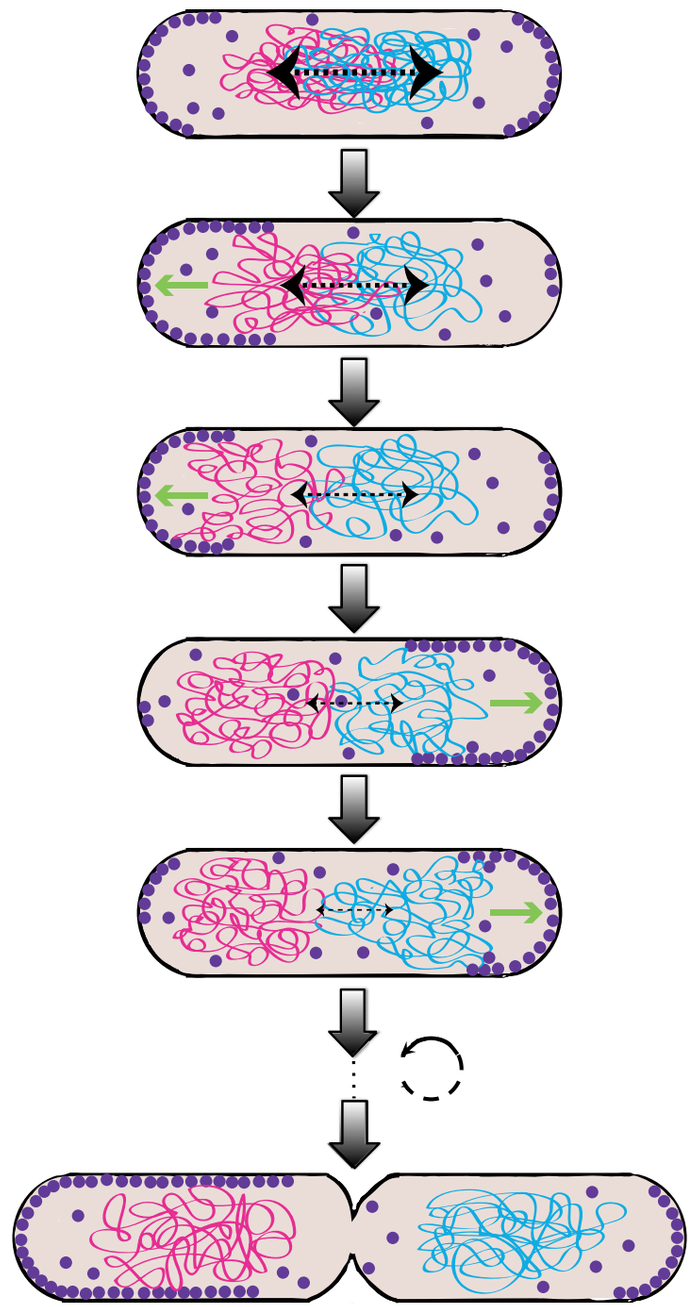
Chromosome segregation by the Escherichia coli Min system

Barbara Di Ventura, Benoit Knecht, Helena Andreas, William J. Godinez, Miriam Fritsche, Karl Rohr, Walter Nickel, Dieter W Heermann, Victor Sourjik

Molecular Systems Biology 9 Article number: 686 doi:10.1038/msb.2013.44, 2014

e.coli





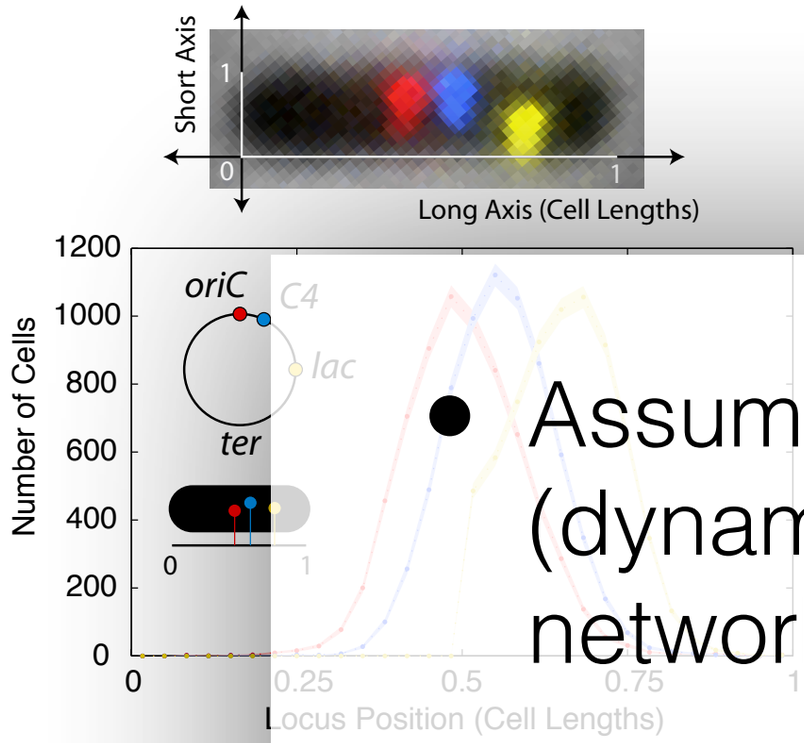
entropic forces alone are not sufficient to achieve and maintain full separation of chromosomes

Chromosome segregation by the Escherichia coli Min system

Barbara Di Ventura, Benoit Knecht, Helena Andreas, William J. Godinez, Miriam Fritsche, Karl Rohr, Walter Nickel, Dieter W Heermann, Victor Sourjik

Molecular Systems Biology 9 Article number: 686 doi:10.1038/msb.2013.44, 2014

e.coli



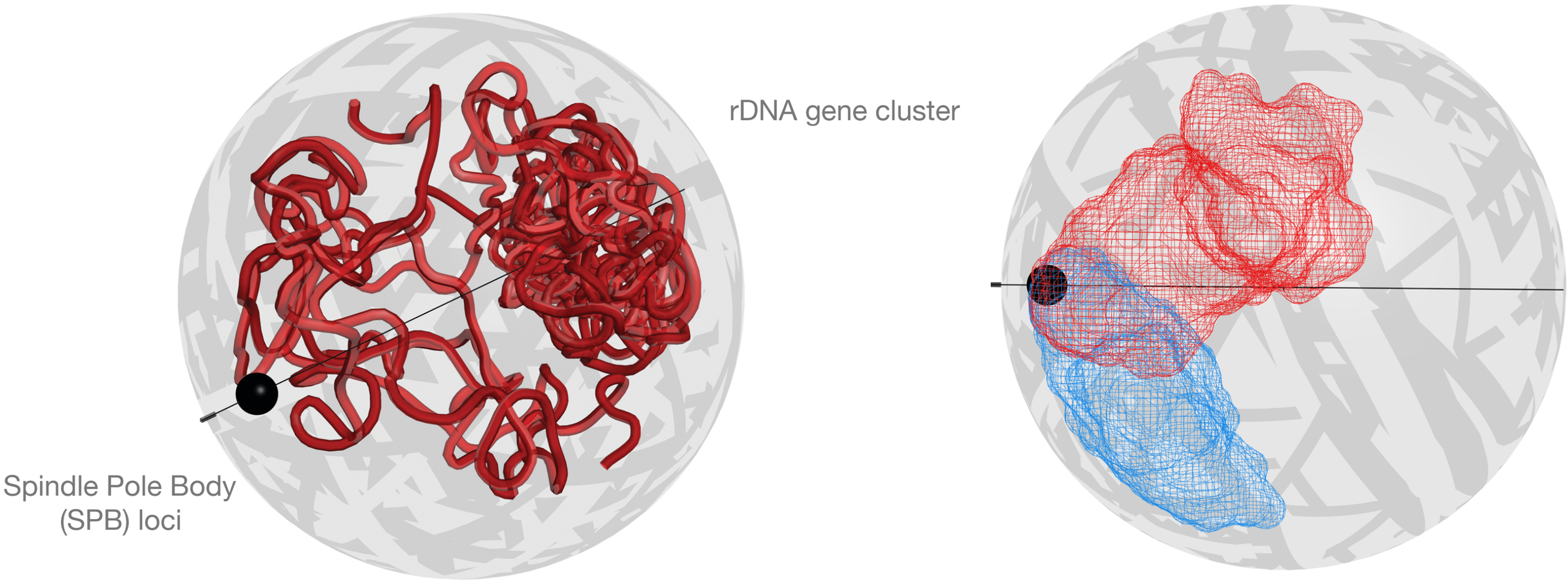
- Assumption of spatial proximity (dynamic loop model + transcriptional network) leads to a „looped-star“.

- Loop structure
  + entropic repulsion
  + confinement

  induces ordering.

- Can explain recent experiments.

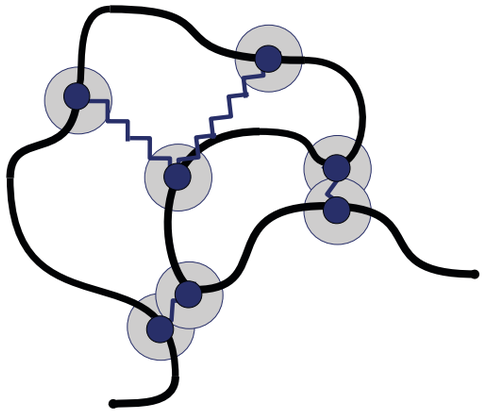
Yeast

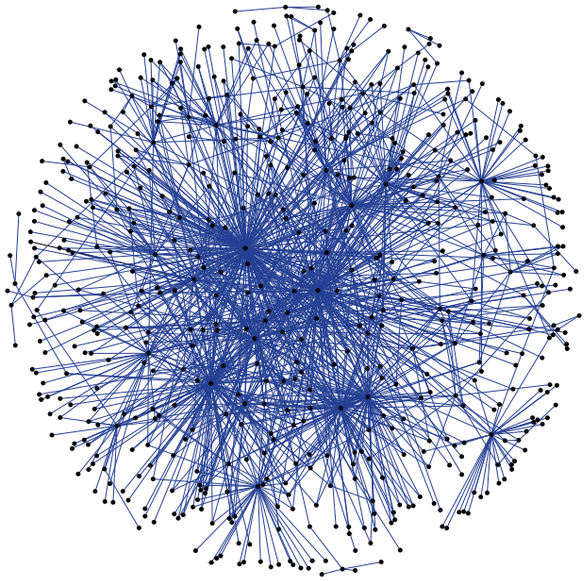


Transcriptional Regulatory Network Shapes the Genome Structure of Saccharomyces cerevisiae

Songling Li and Dieter W. Heermann, Nucleus. 2013 May-Jun;4(3):216-28

Yeast





Ansatz: Dynamic Loop Model + genes that are co-regulated by a set of same or similar transcription factors, might stay in physical proximity in order to guarantee the efficiency of gene regulation and expression.

Transcriptional Regulatory Network Shapes the Genome Structure of Saccharomyces cerevisiae
Songling Li and Dieter W. Heermann,
Nucleus. 2013 May-Jun;4(3):216-28.

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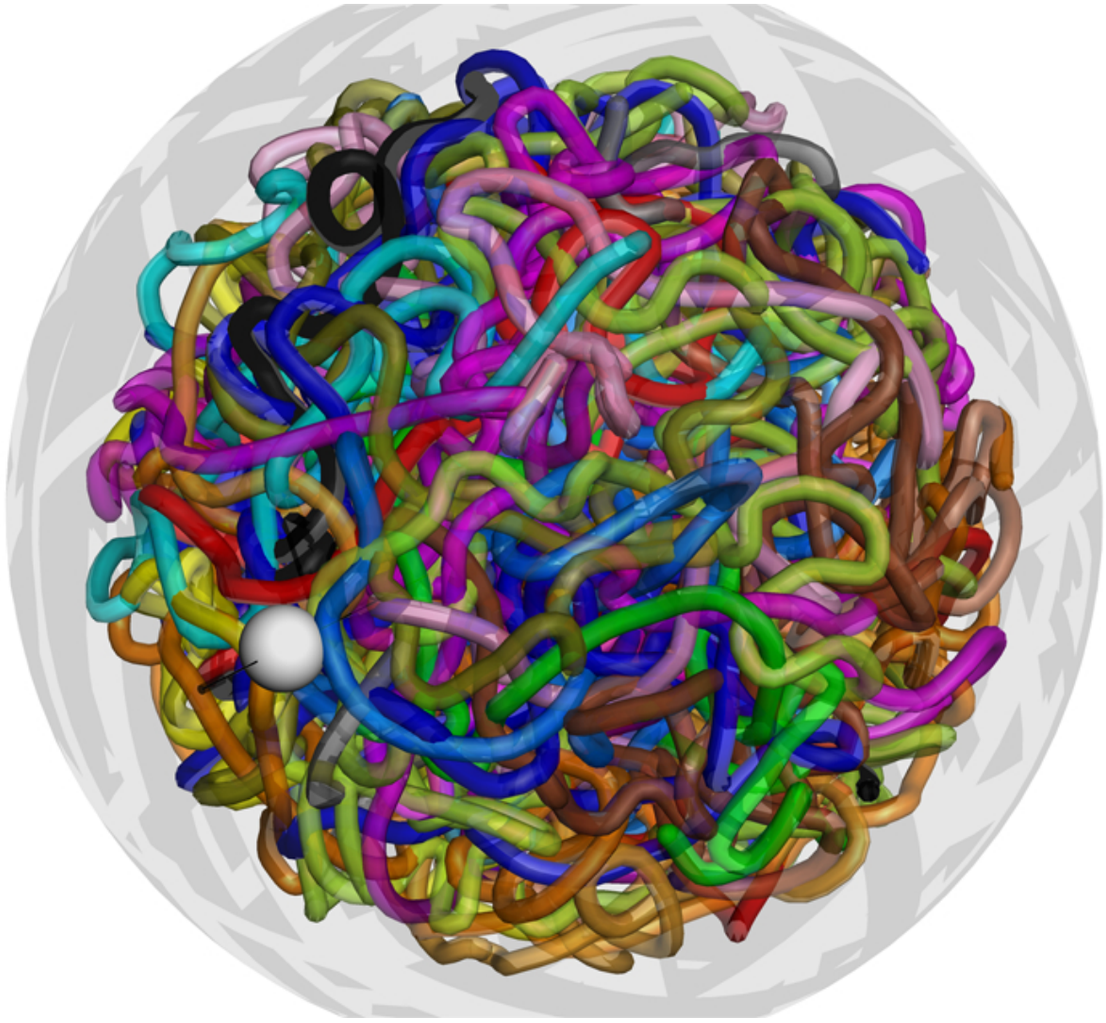

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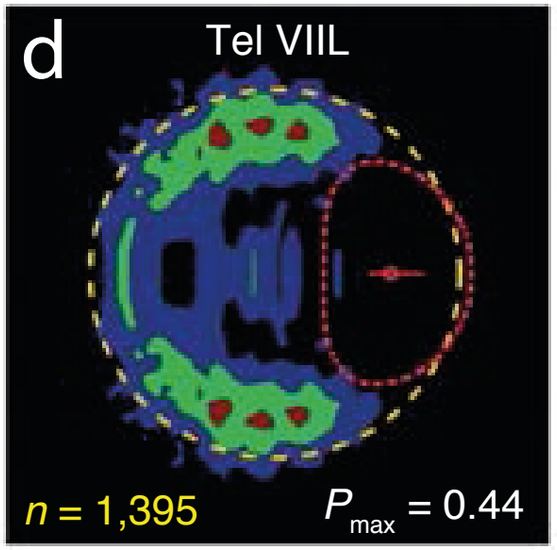
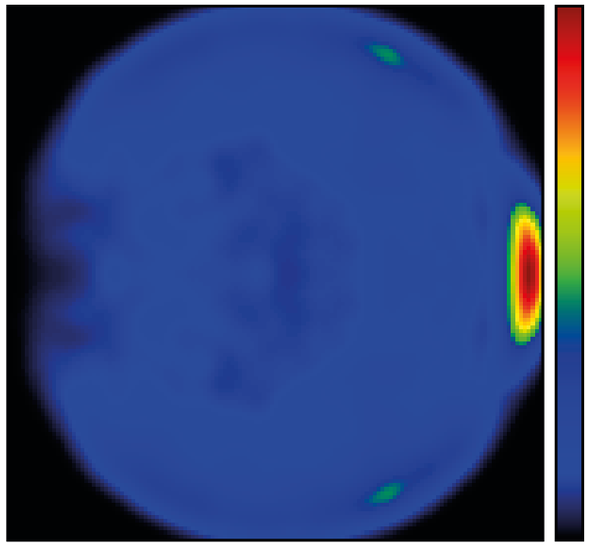
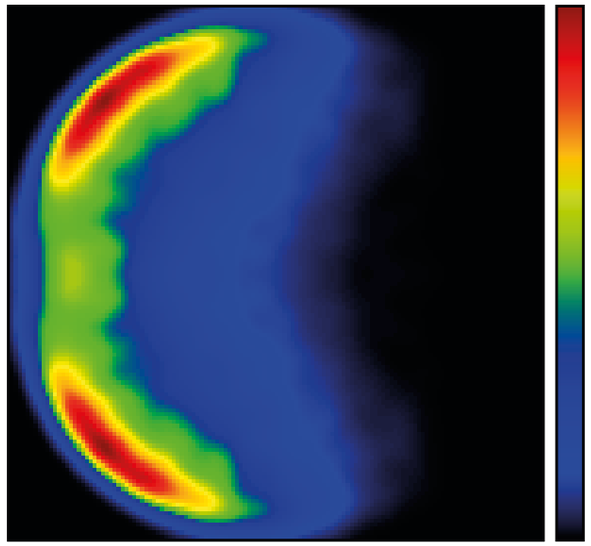


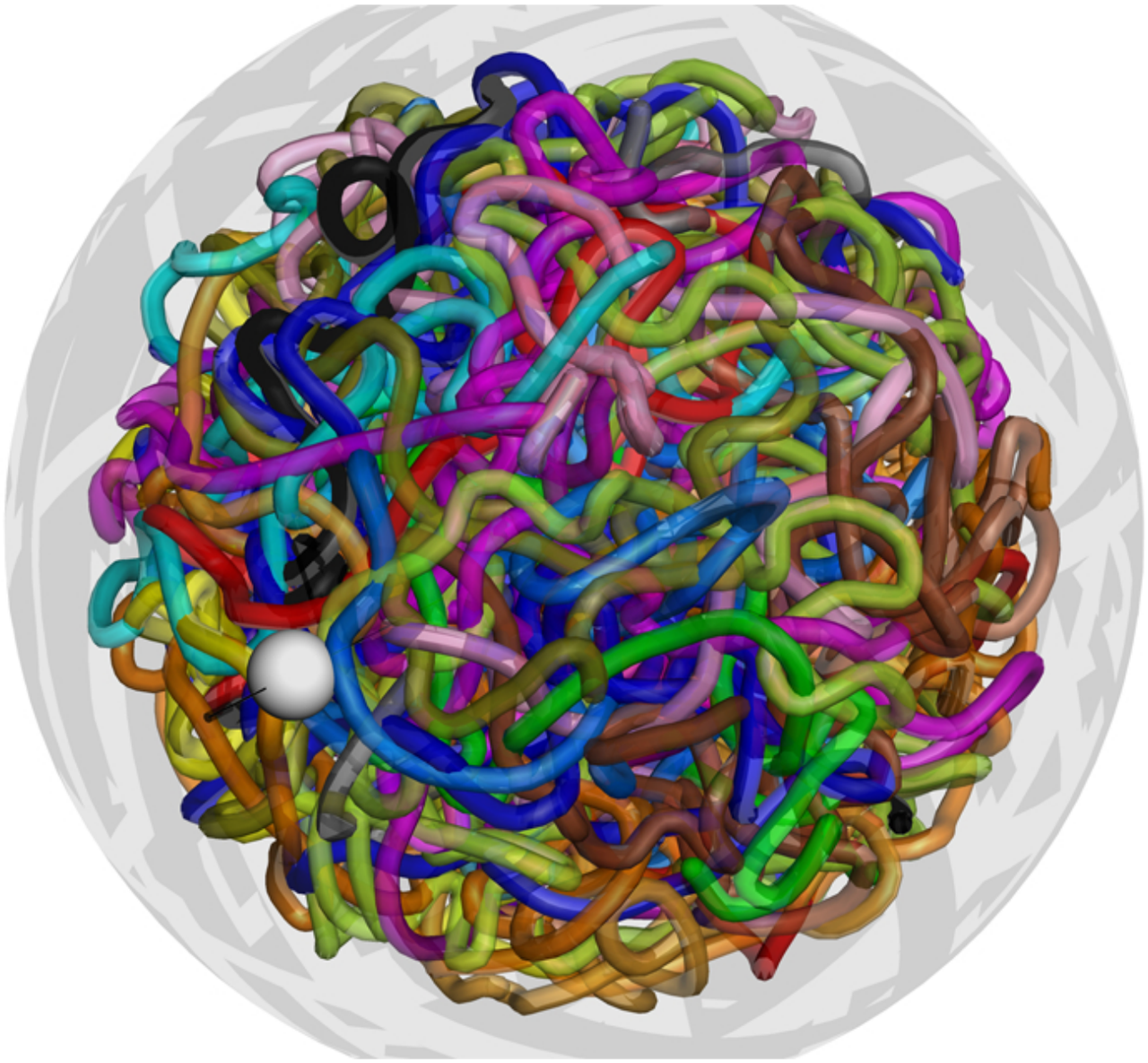




Gene Territories

Data taken from
A. B. Berger, G. G. Cabal, E. Fabre, T. Duong, H. Buc, U. Nehrbass, et al. High-resolution statistical mapping reveals gene territories in live yeast. Nat Methods, 5(12):1031–7, 2008

Transcriptional Regulatory Network Shapes the Genome Structure of Saccharomyces cerevisiae
Songling Li and Dieter W. Heermann,
Nucleus. 2013 May-Jun;4(3):216-28.



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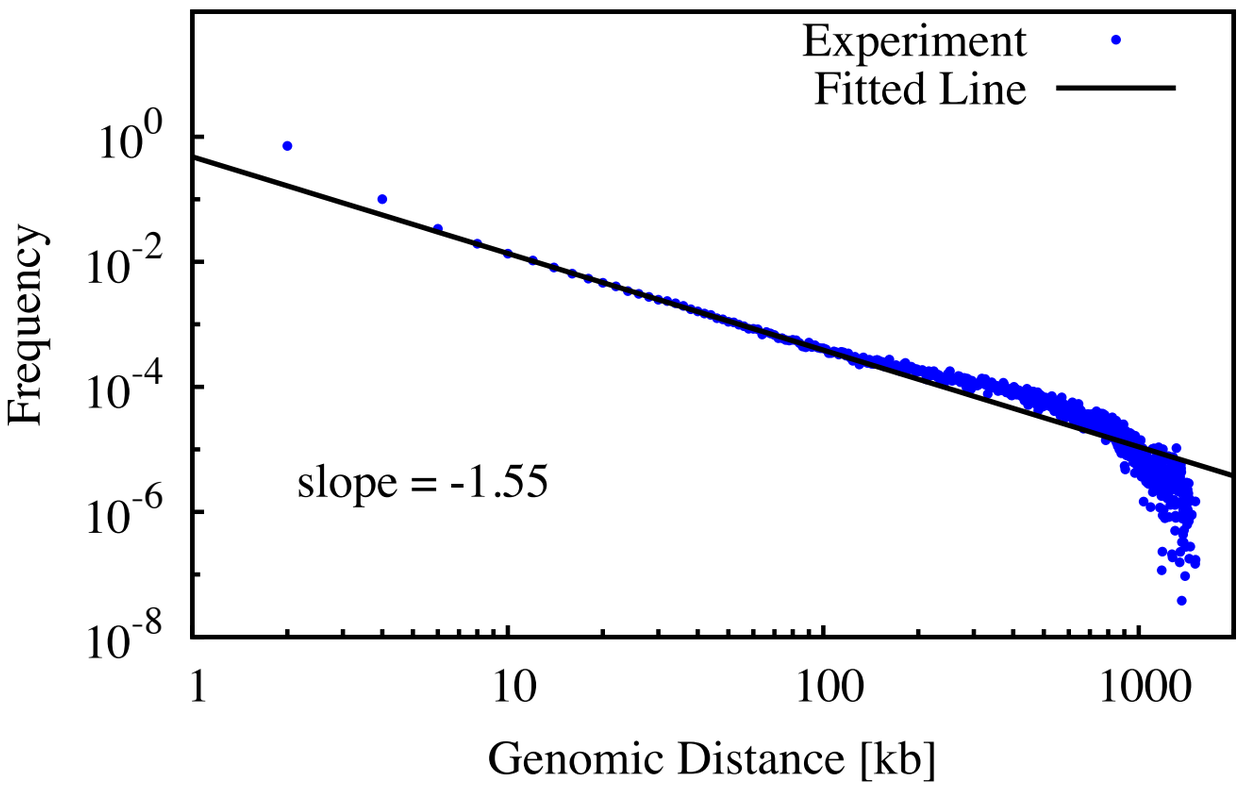
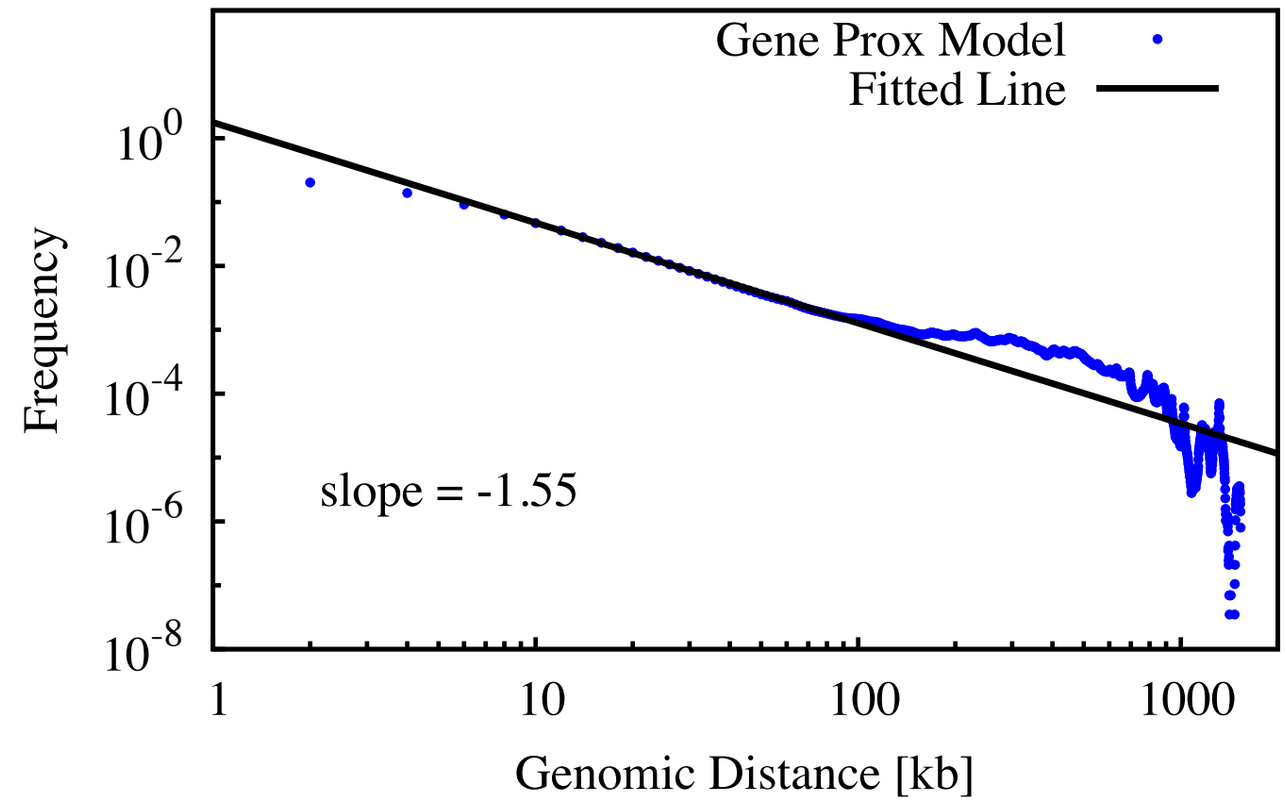
Yeast

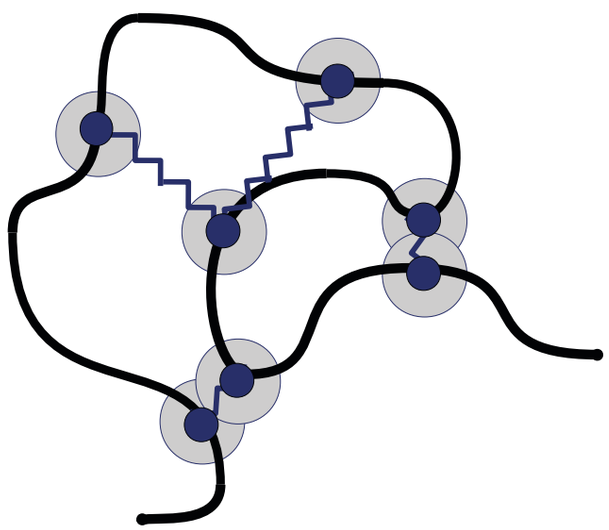


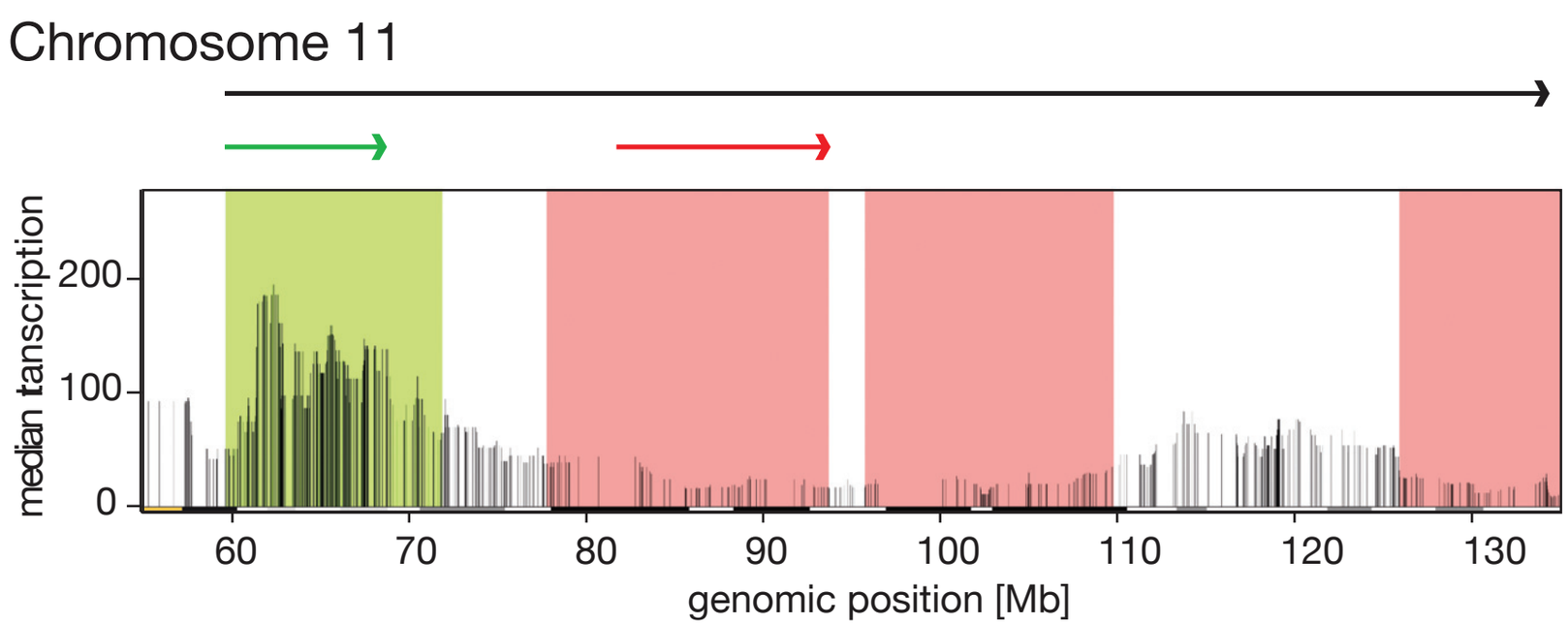


Data: Justin O'Sullivan

Transcriptional Regulatory Network Shapes the Genome Structure of Saccharomyces cerevisiae
Songling Li and Dieter W. Heermann,
Nucleus. 2013 May-Jun;4(3):216-28.

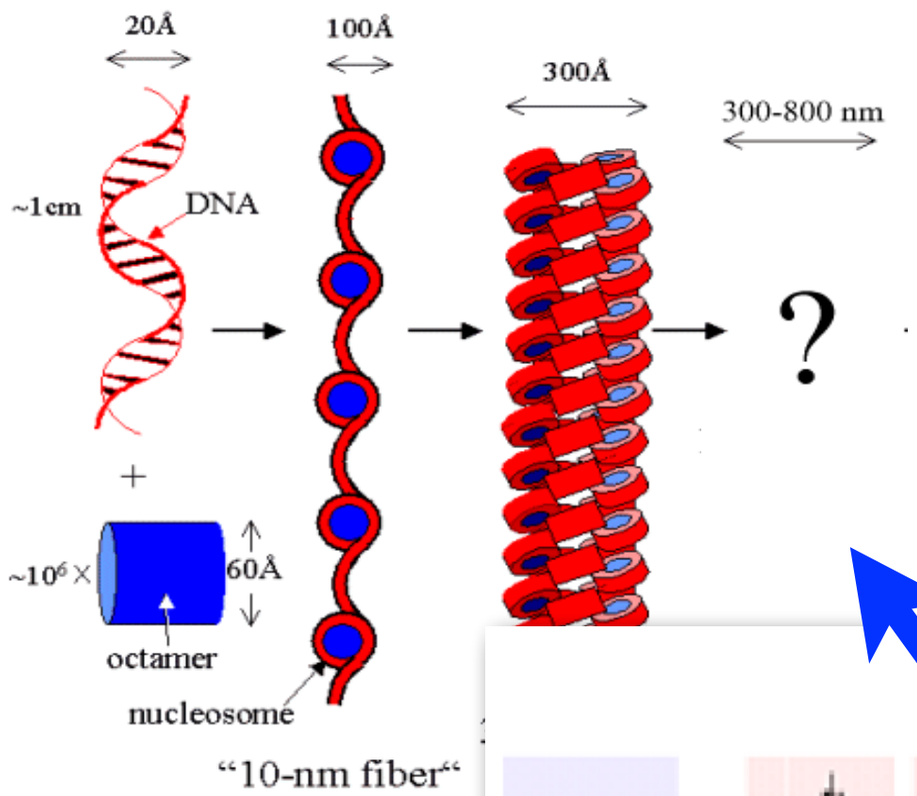
Human Chromosomes





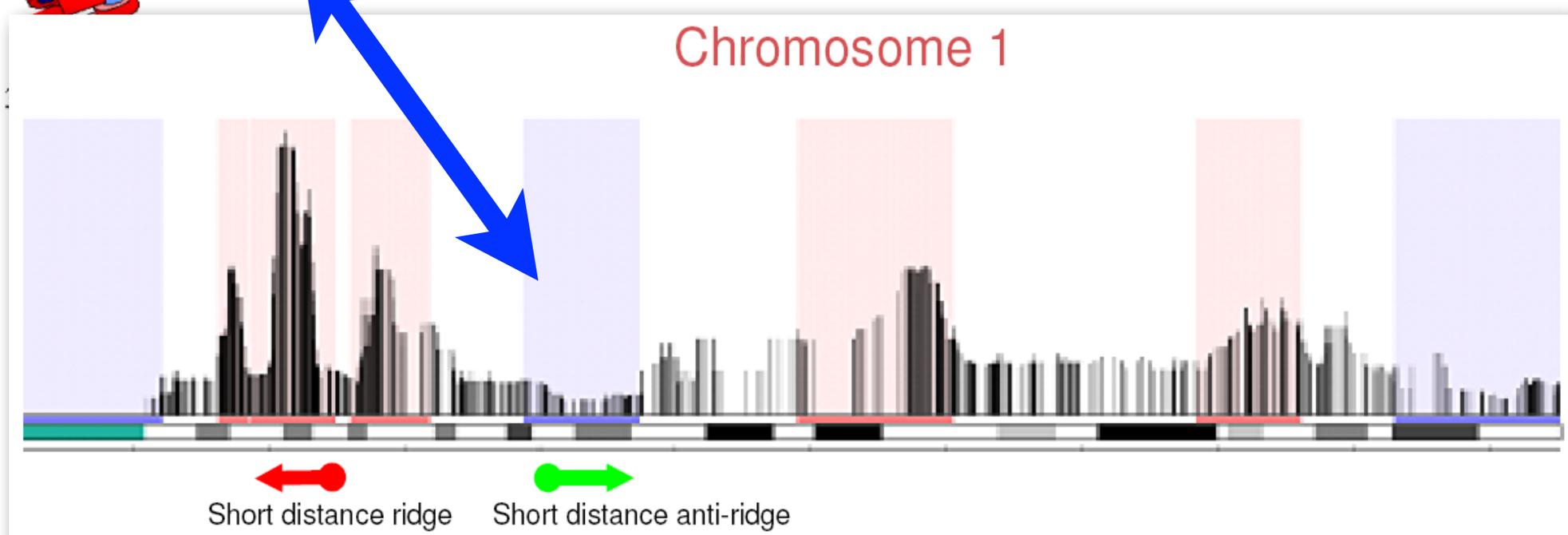
Ansatz: Dynamic Loop Model + gene expression.

Diffusion-Driven Looping Provides a Consistent Framework for Chromatin Organization
Manfred Bohn and Dieter W. Heermann
PLoS ONE 5(8): e12218. doi:10.1371/journal.pone.0012218 (2010)



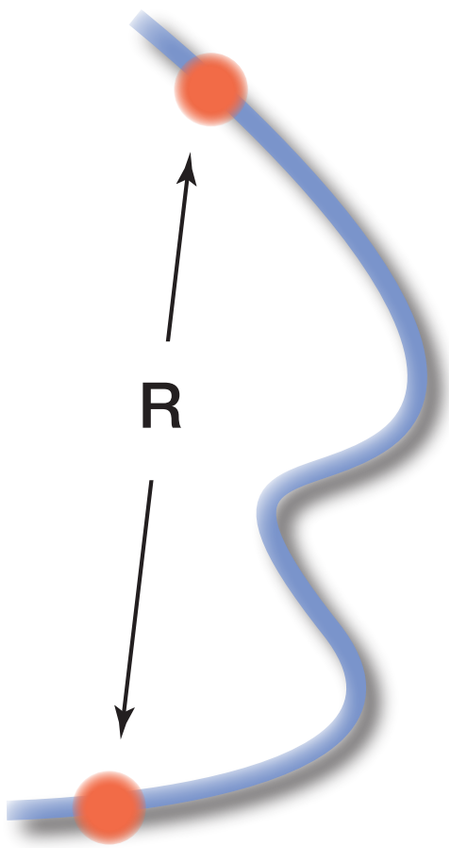
M. Bohn, D.W. Heermann and R. van Driel, **Phys. Rev. E 76**, 051805 (2007)

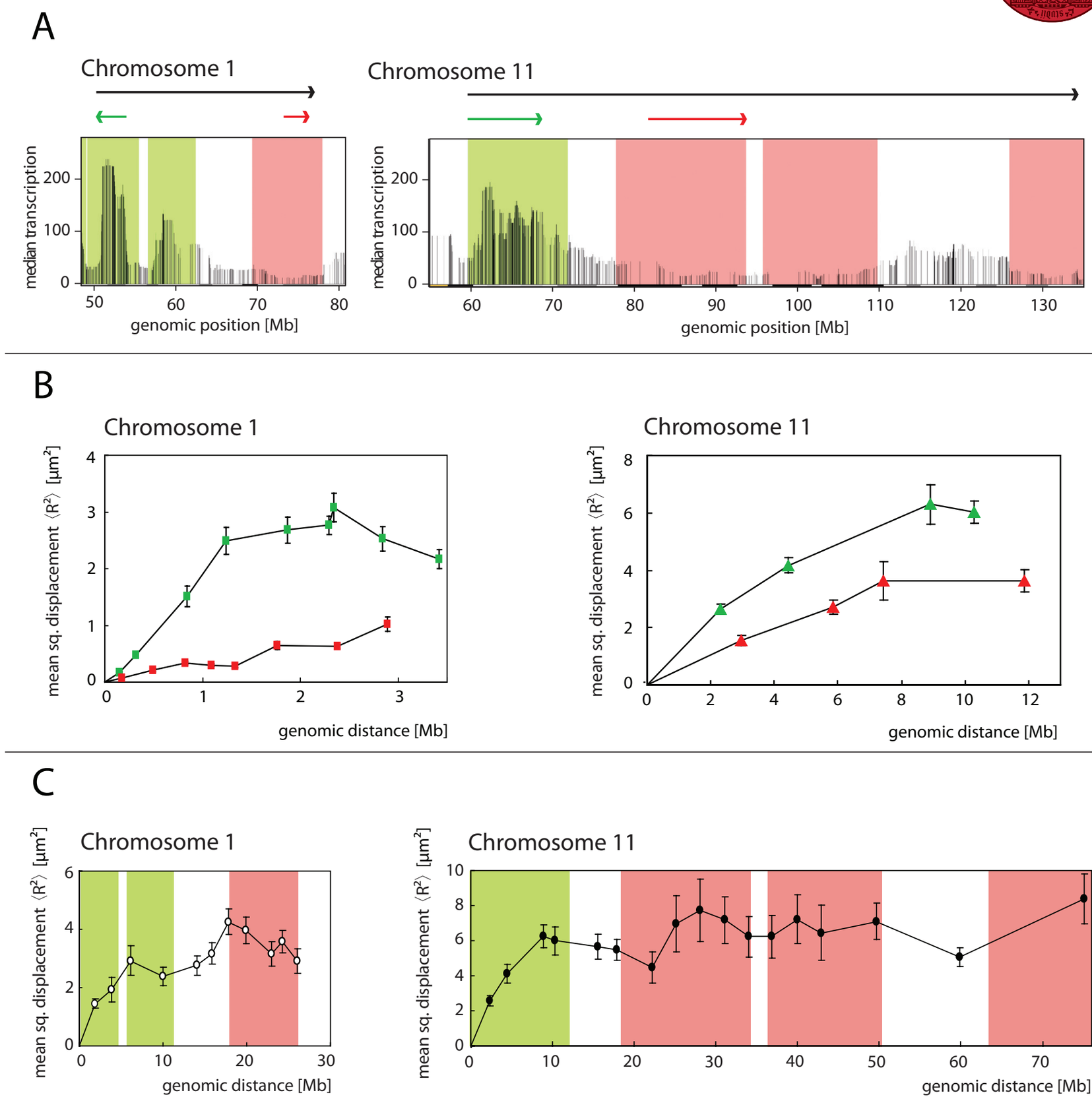
Julio Mateos-Langerak, Manfred Bohn, Dieter W. Heermann, Roel van Driel and Sandra Goetze, **PNAS** 2009



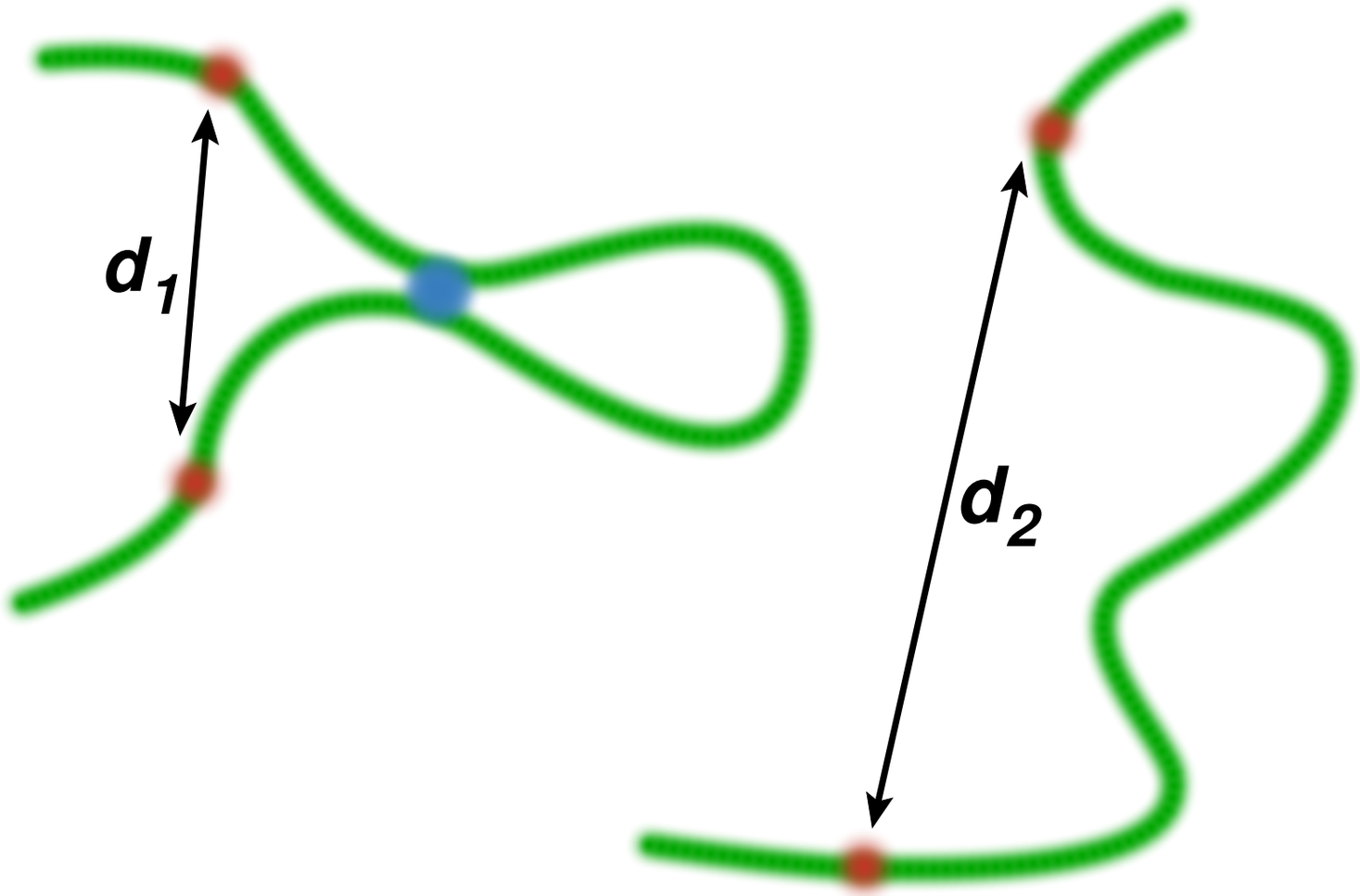
RIDGE: region of increased gene expression

Human Chromosomes





Human Chromosomes



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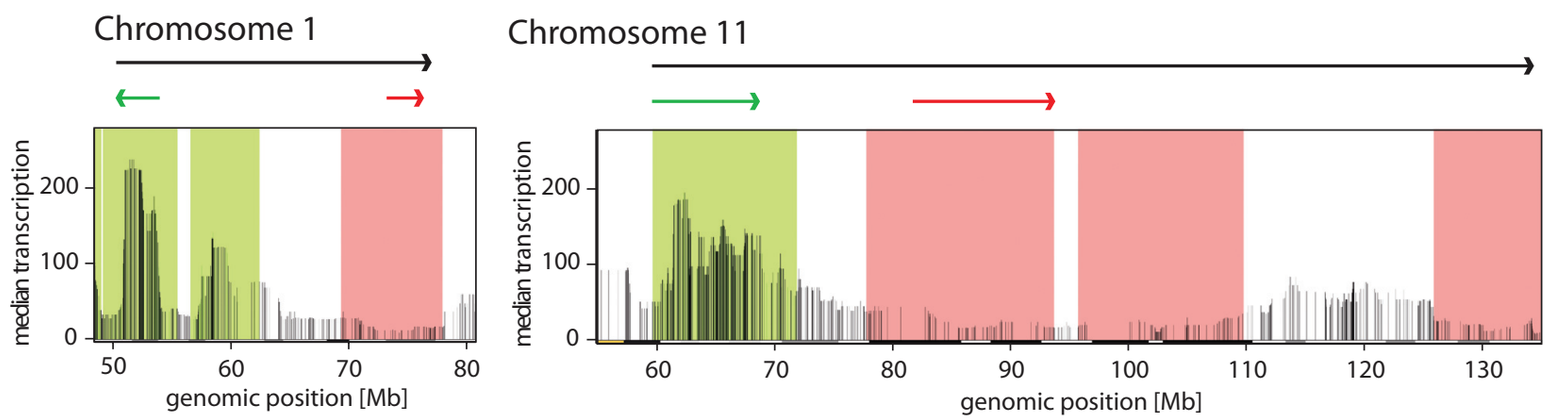
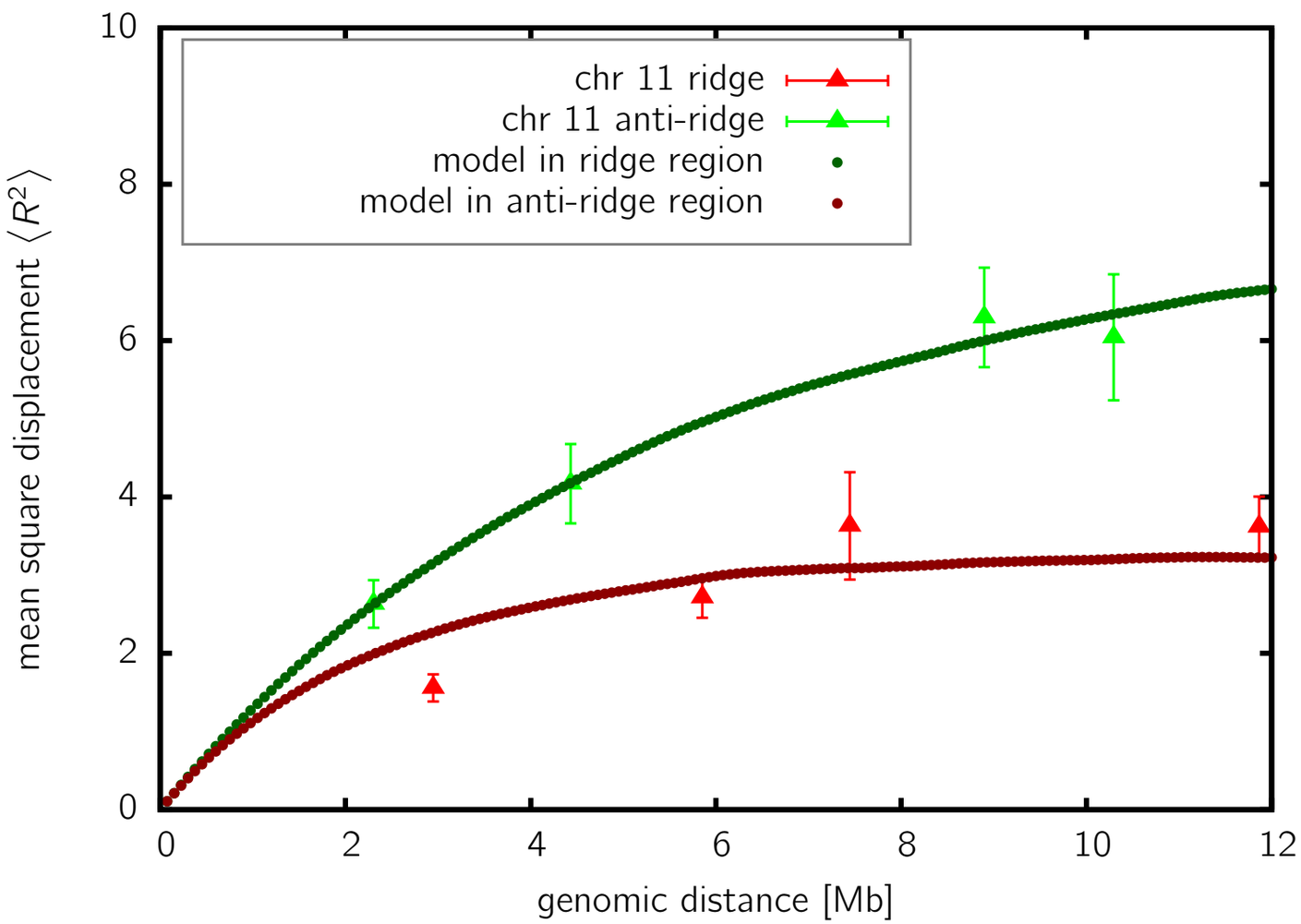
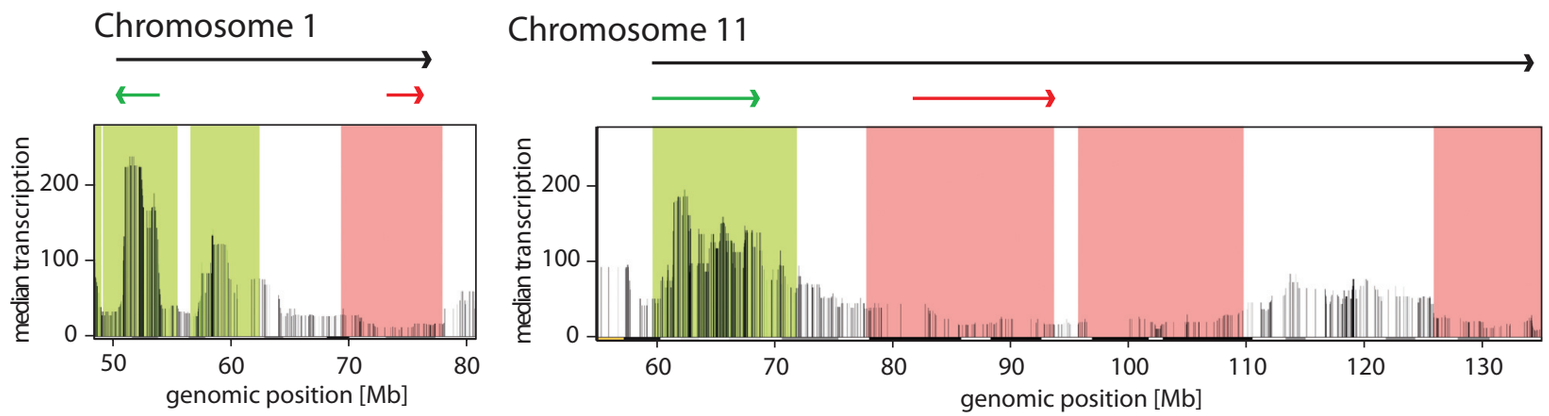
Human Chromosomes

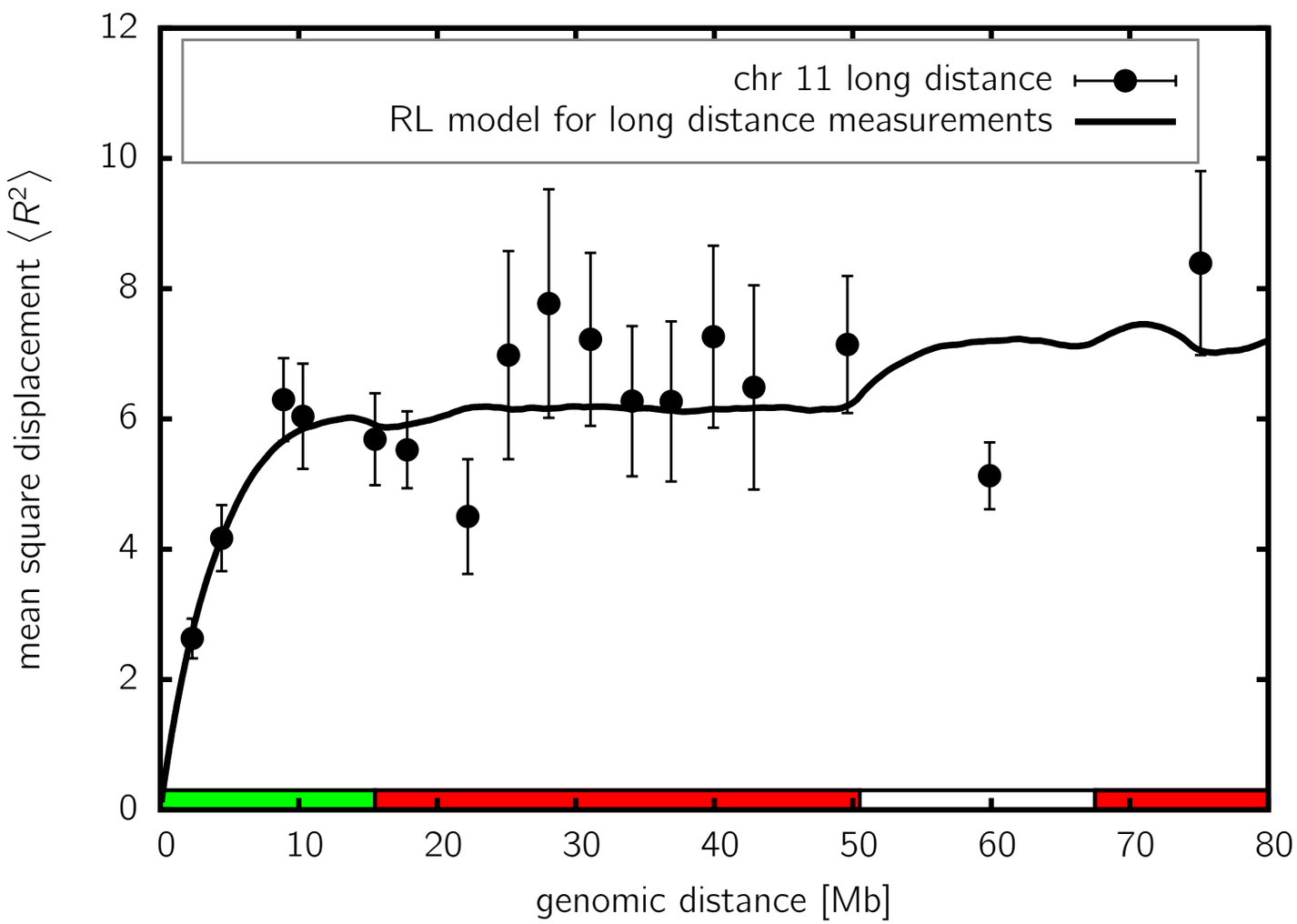




The dynamic loop model very well explains differences between ridges and anti-ridges by different local looping probabilities.

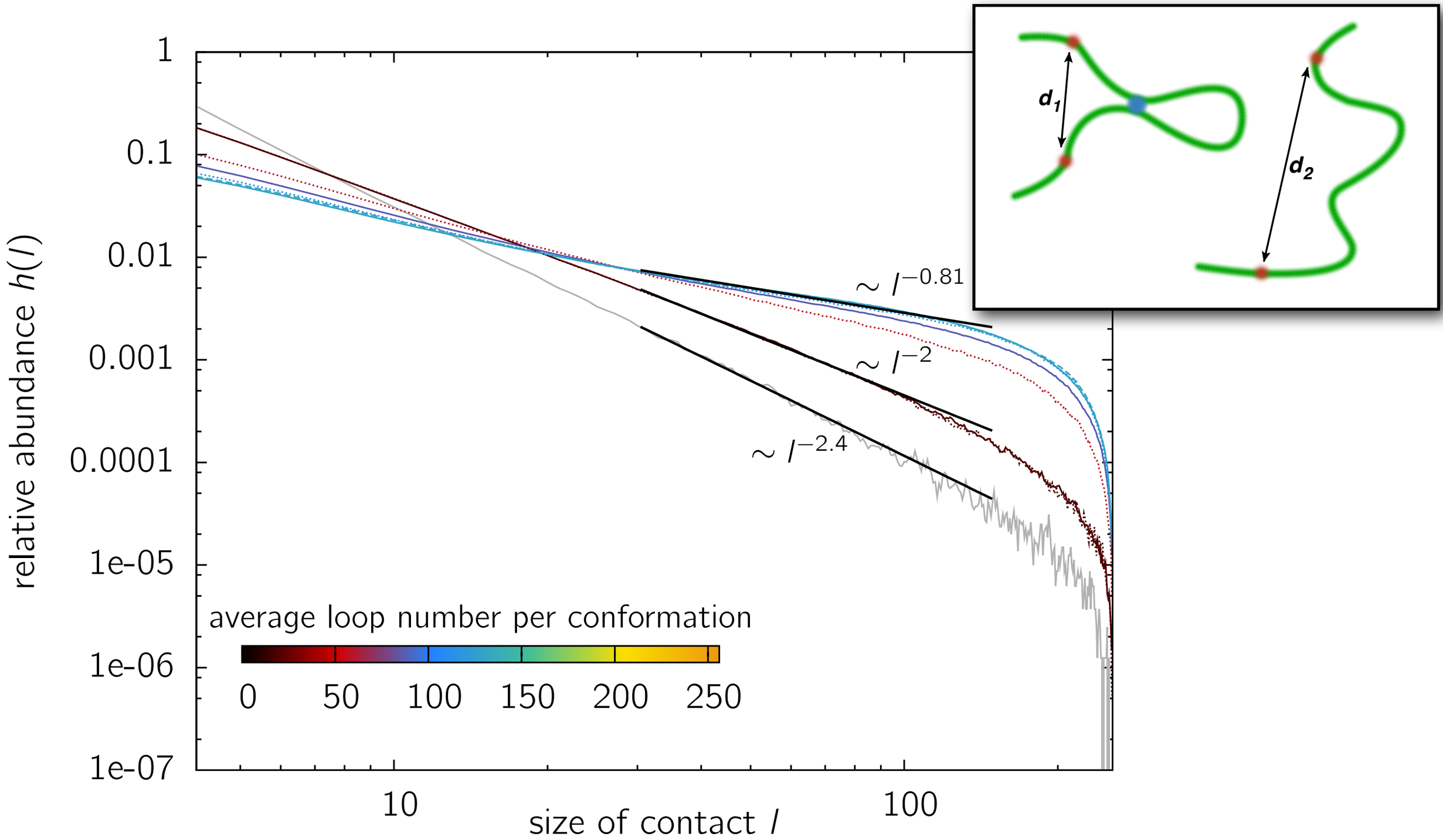
Human Chromosomes





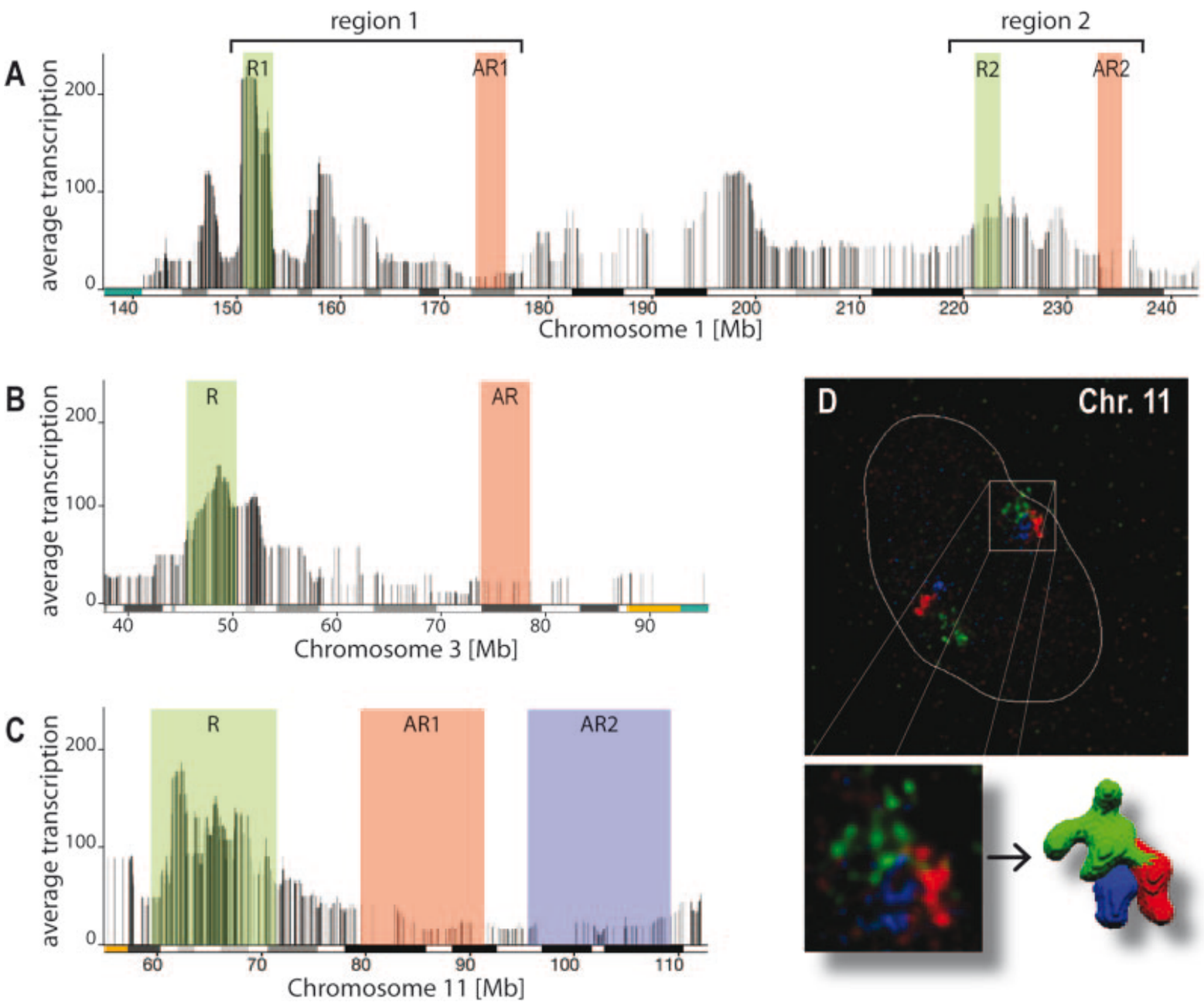
The dynamic loop model also reproduces the experimental findings on the scale of a complete chromsome arm.

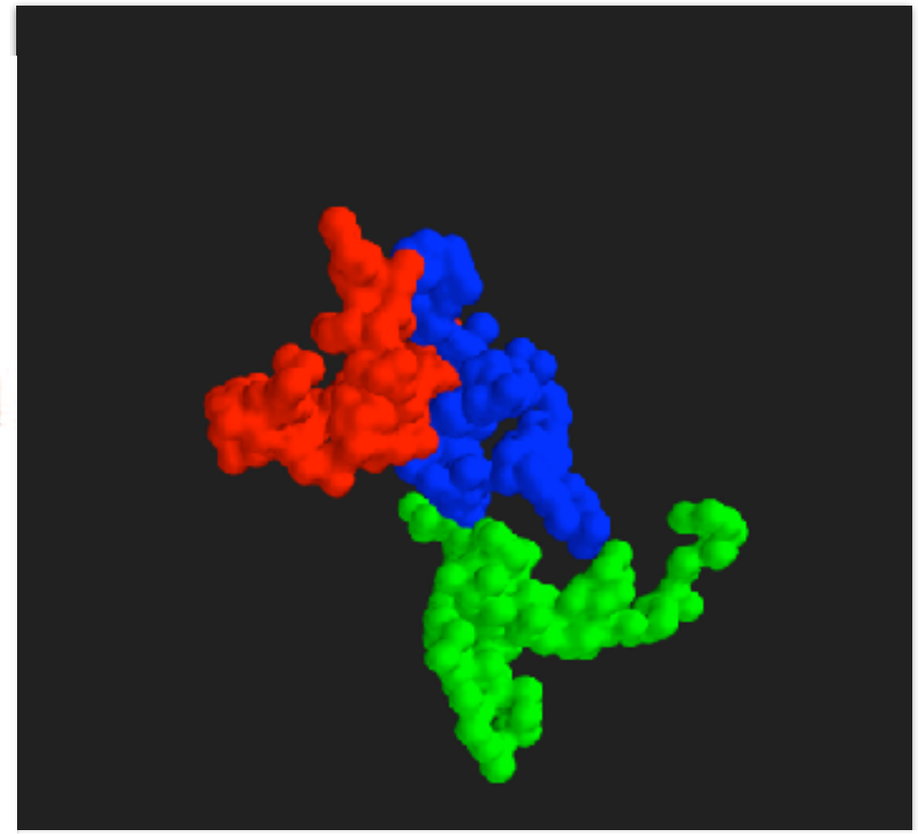
Human Chromosomes

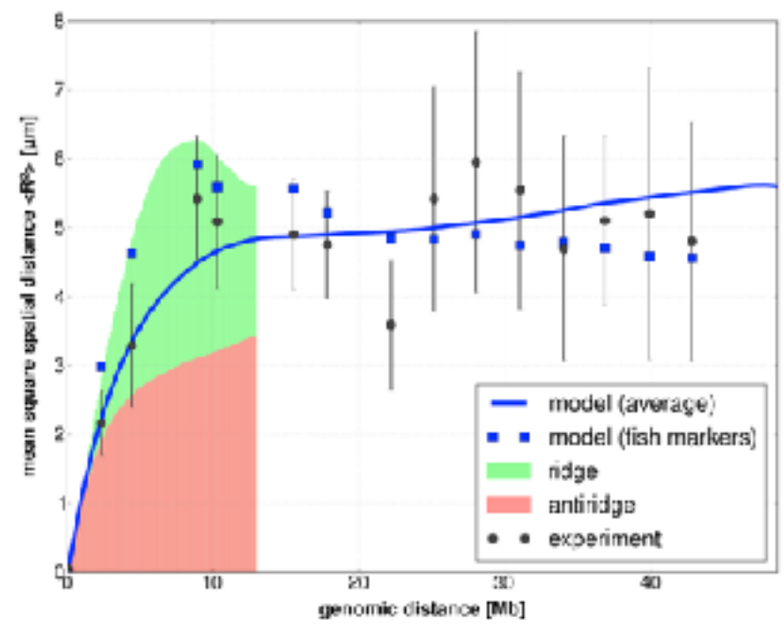


Human Chromosomes

Agrees with Sandra Goetze et. al. MOLECULAR AND CELLULAR BIOLOGY, June 2007, p. 4475–4487



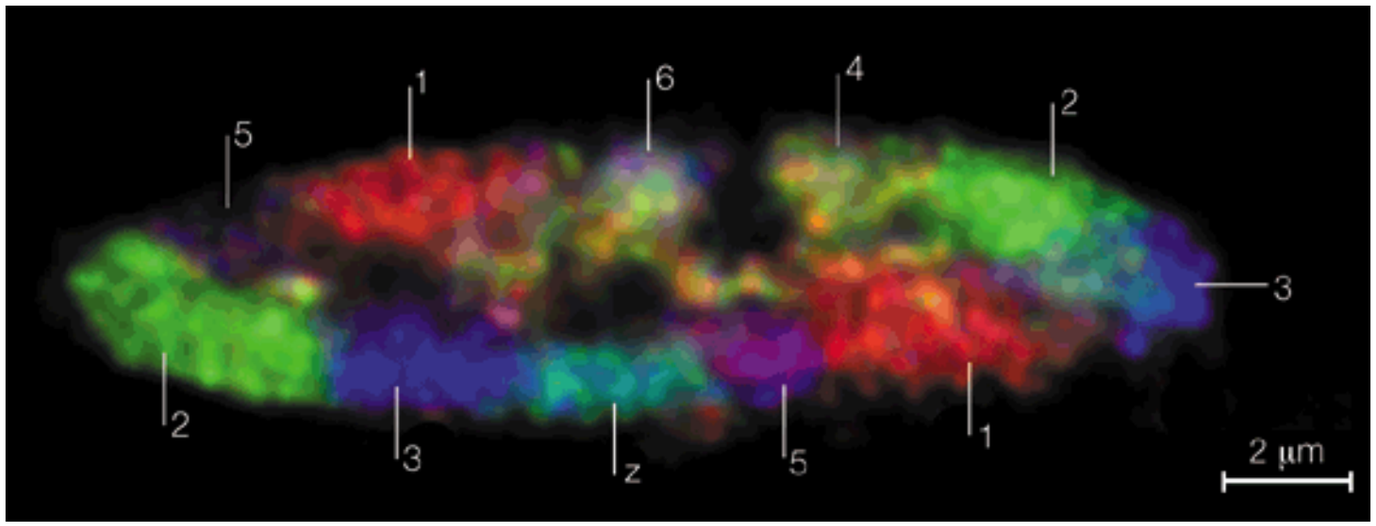




We understand the folding pattern of chromosomes in interphase:

Folding is governed by loops on <u>all scales</u> mediated by proteins (transcriptional hubs, ...)

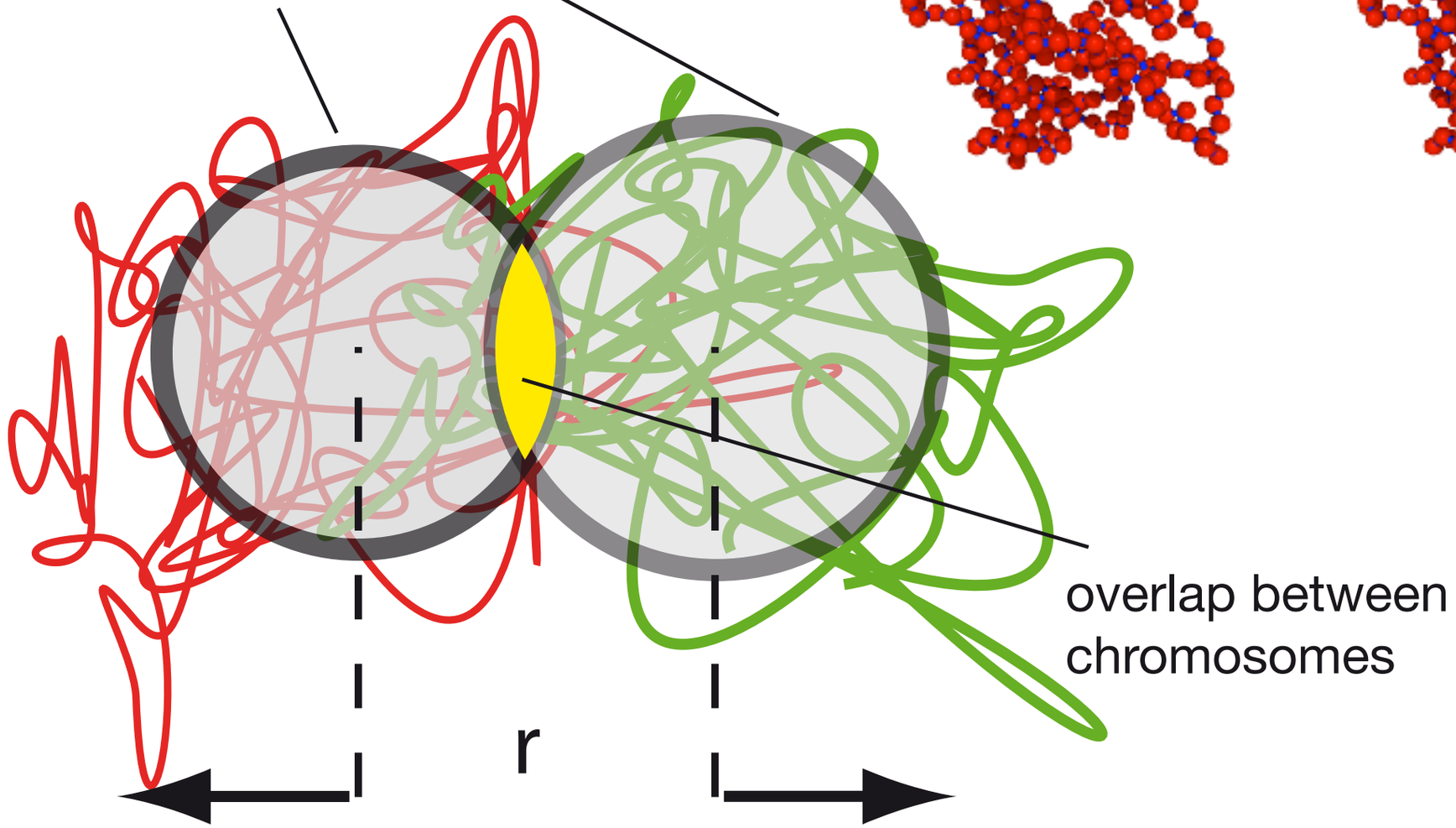
Human Chromosomes

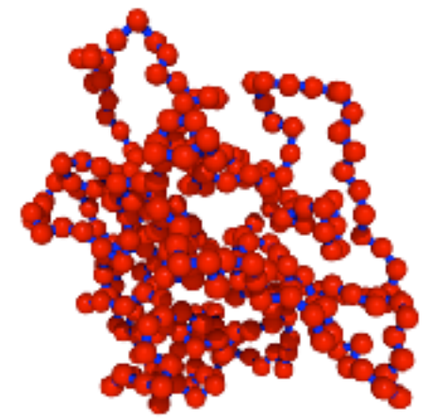


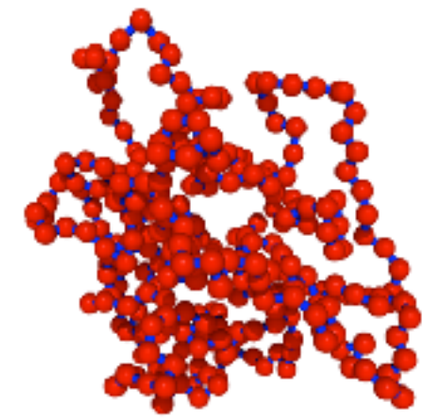
T.Cremer and C. Cremer, Nature Reviews Genetics vol. 2, no. 4, pp. 292-301 (April, 2001)

Why do chromosomes not mix?

Human Chromosomes







REPLUSIVE FORCE

Human Chromosomes

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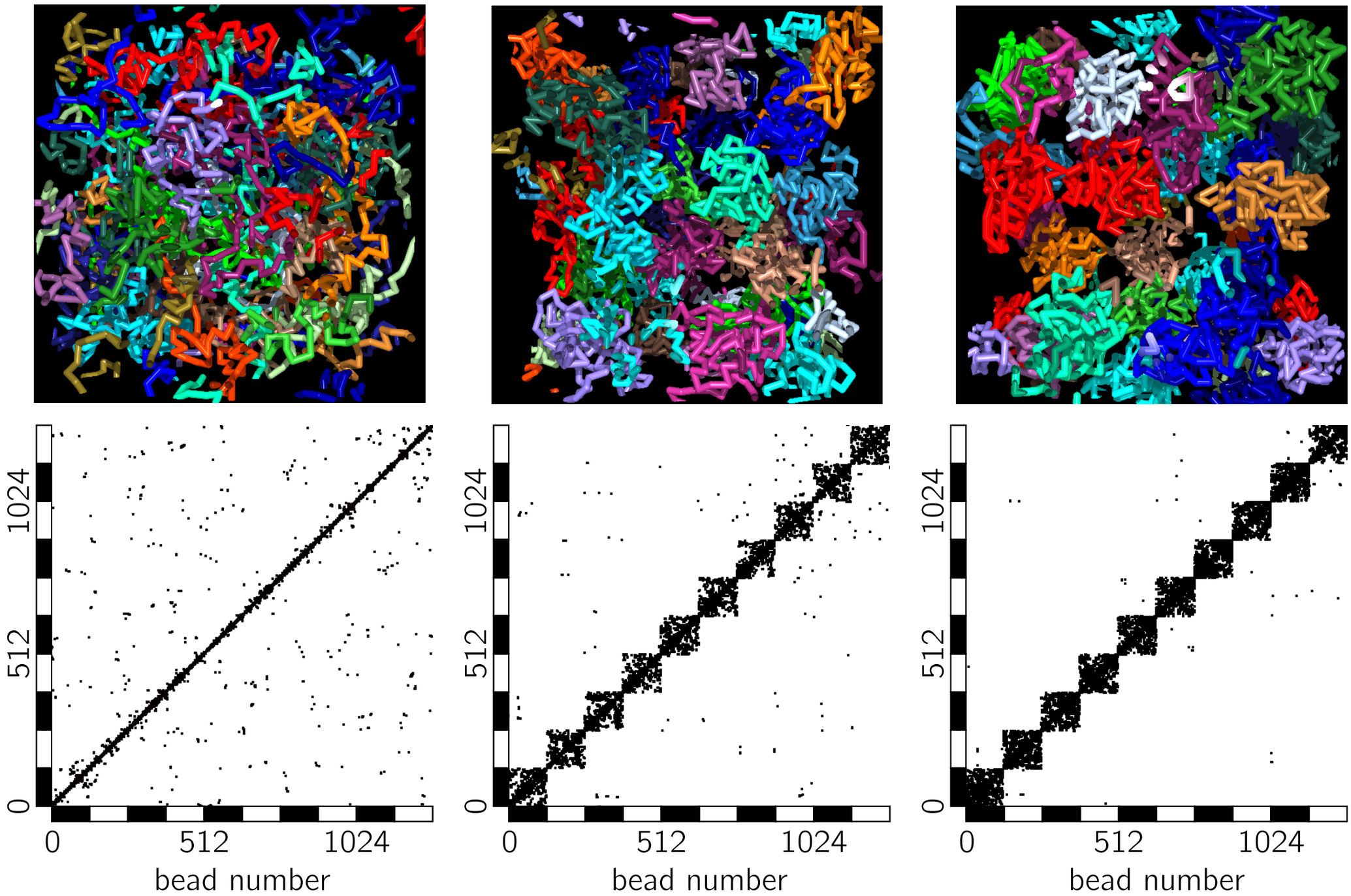
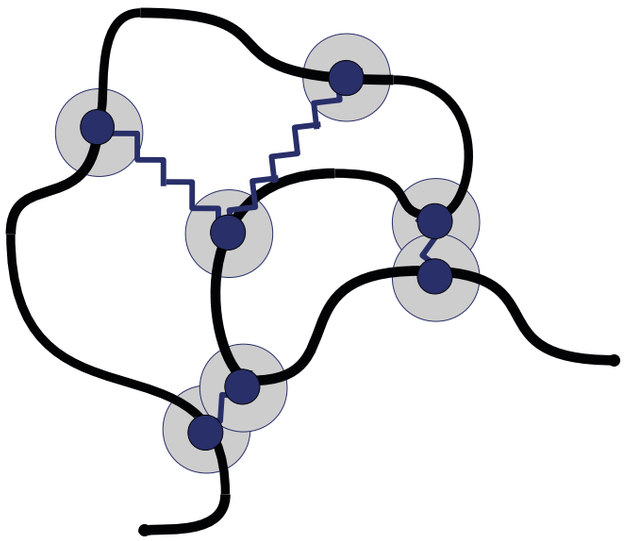
A. Linear chains

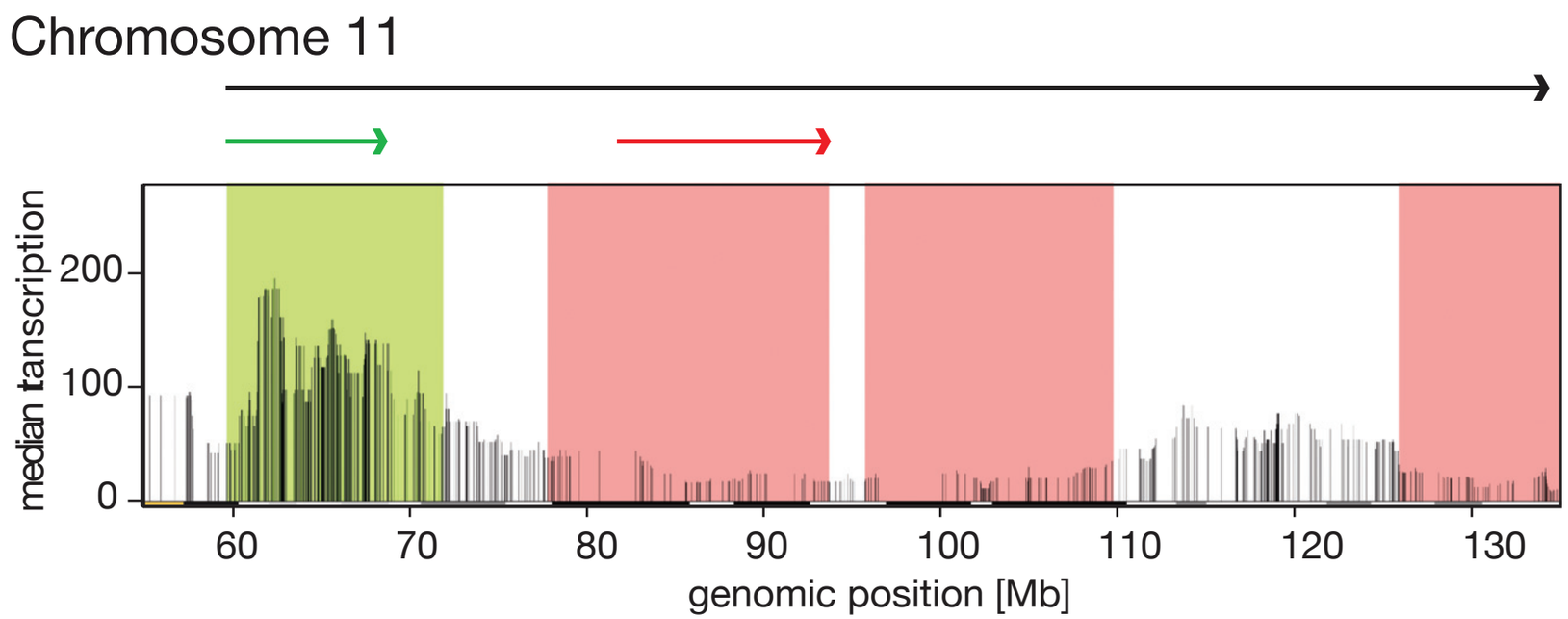
B. 45 loops per chain

C. 92 loops per chain



Chromosomes in Metaphase





Ansatz: Dynamic Loop Model + gene expression.

Loops Determine the Mechanical Properties of Mitotic Chromosomes.
Zhang Y, Heermann DW (2011)
PLoS ONE 6(12): e29225. doi:10.1371/journal.pone.0029225

Chromosomes in Metaphase

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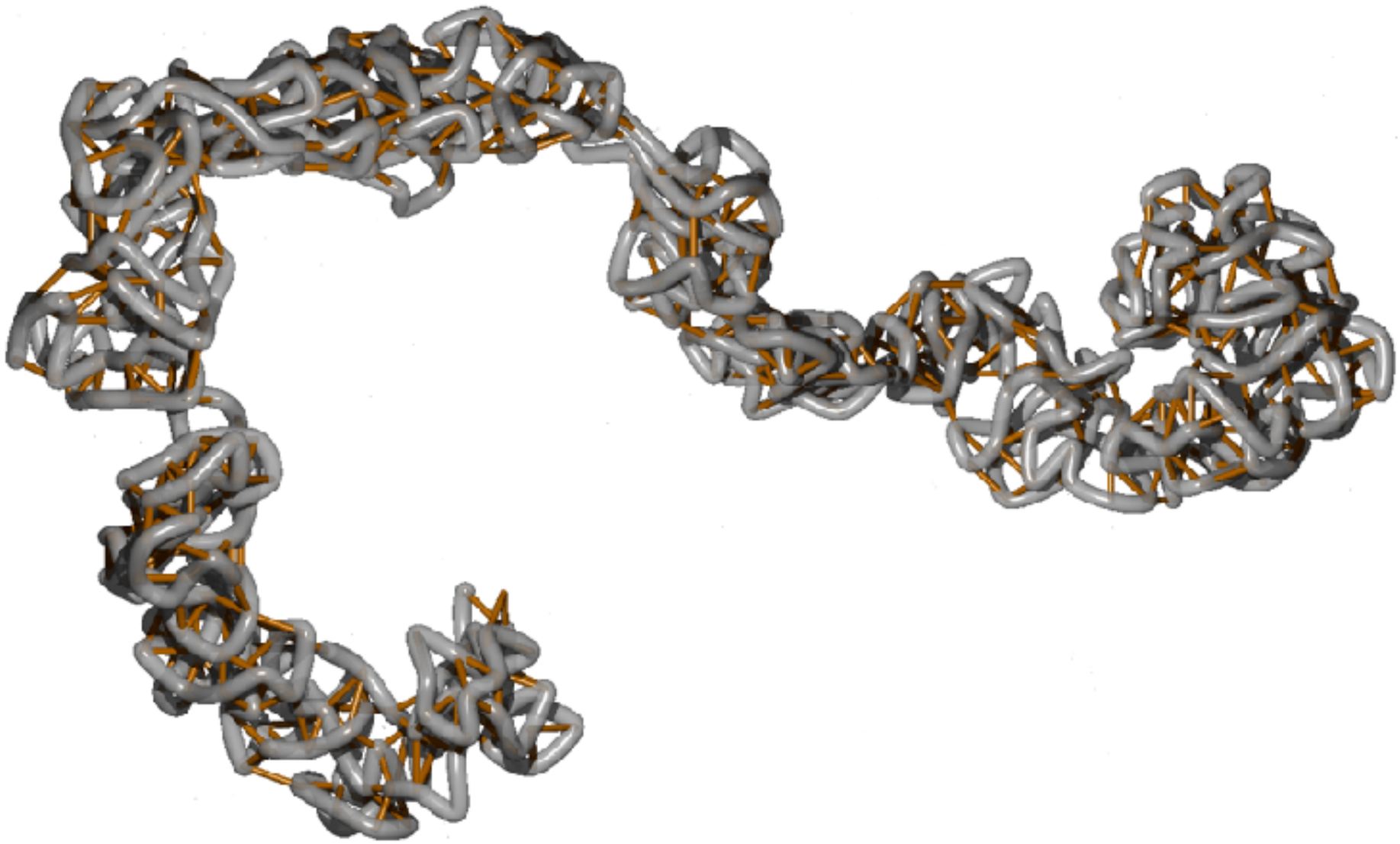

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PLoS ONE 6(12): e29225. doi:10.1371/journal.pone.0029225

Chromosomes in Metaphase

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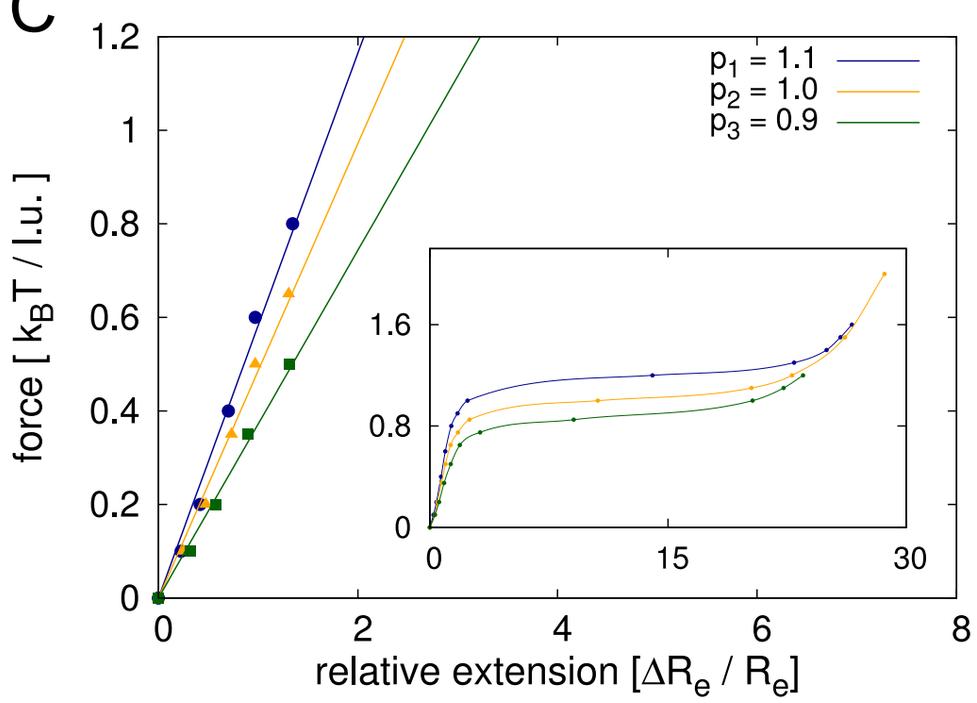
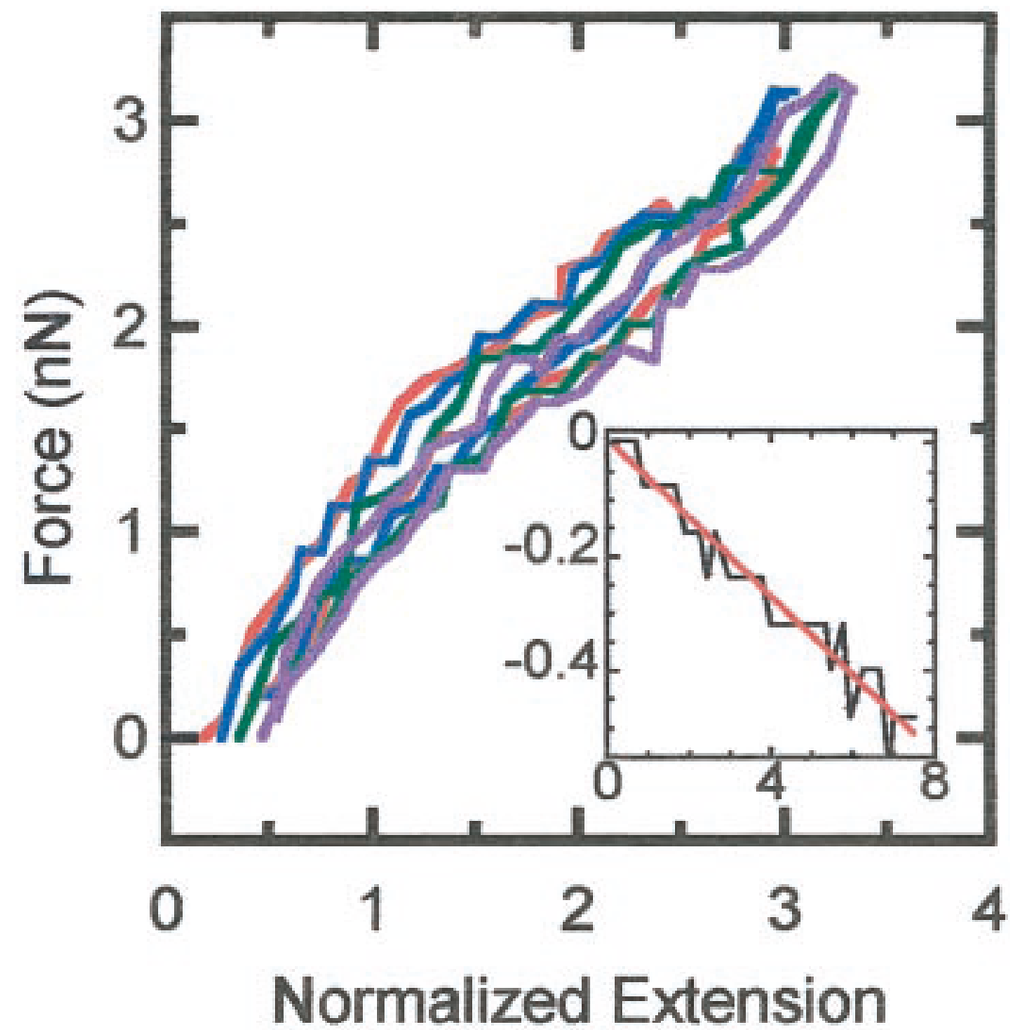
A

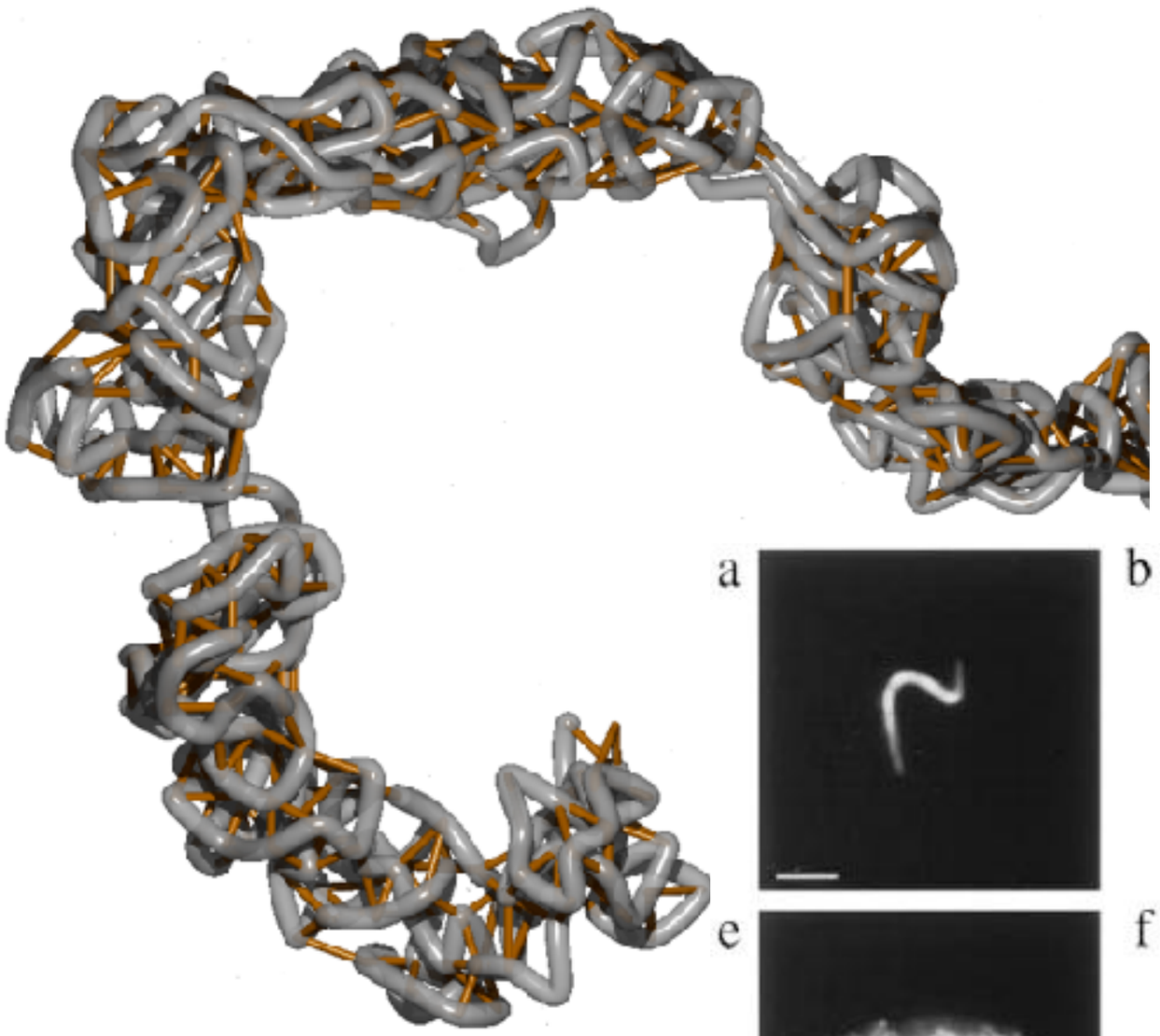
C



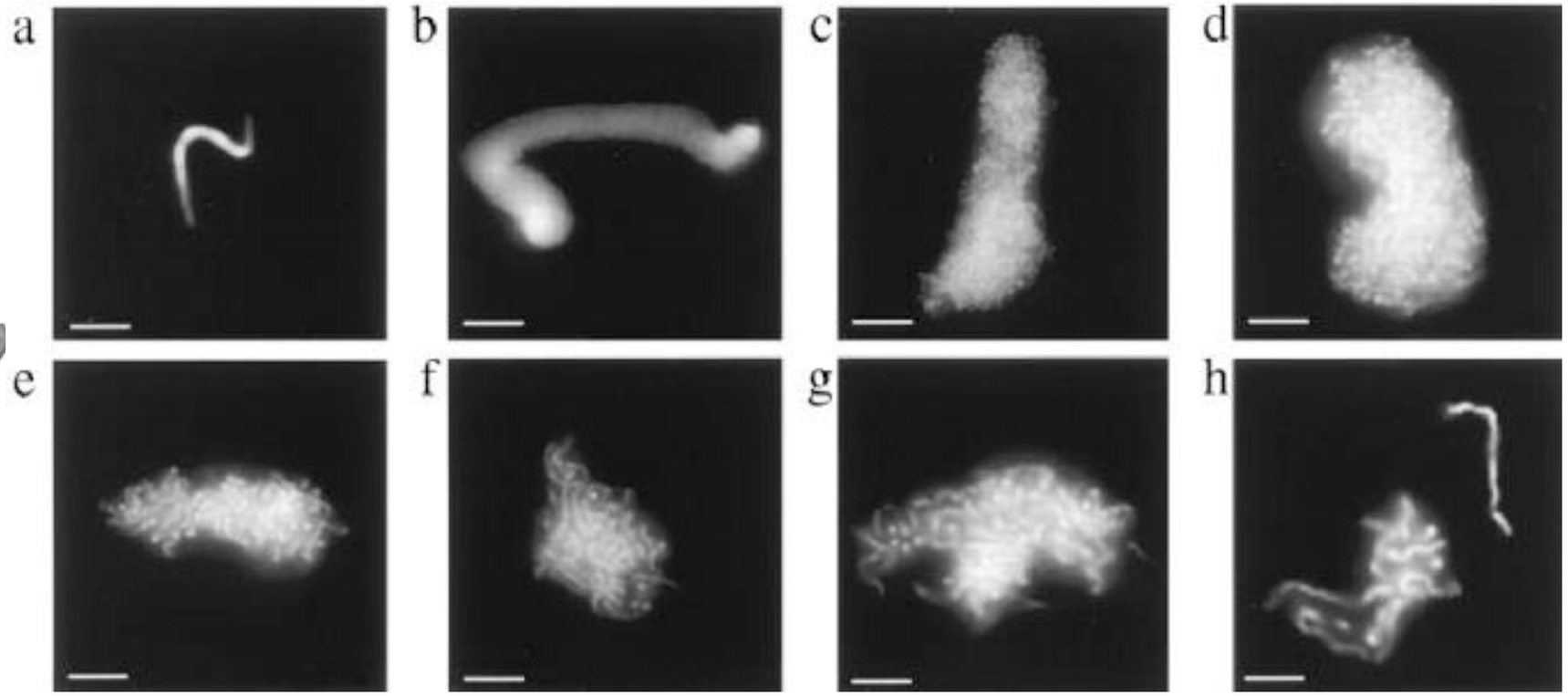


Reversible and Irreversible Unfolding of Mitotic Newt Chromosomes by Applied Force
Michael Poirier, Sertac Eroglu Didier Chatenay, and John F. Marko
Mol Biol Cell. 2000 January; 11(1): 269–276.

Chromosomes in Metaphase



Structural changes of Xenopus sperm nuclei in mitotic egg extract; control sperm nuclei (a), decondensed sperm after 10 min of incubation in the extract (b), chromosomal structures (c–g) found after 30, 60, 90, 120, and 150 min, respectively.



Houchmandzadeh B , Dimitrov S J Cell Biol 1999;145:215-223

Chromosomes in Metaphase

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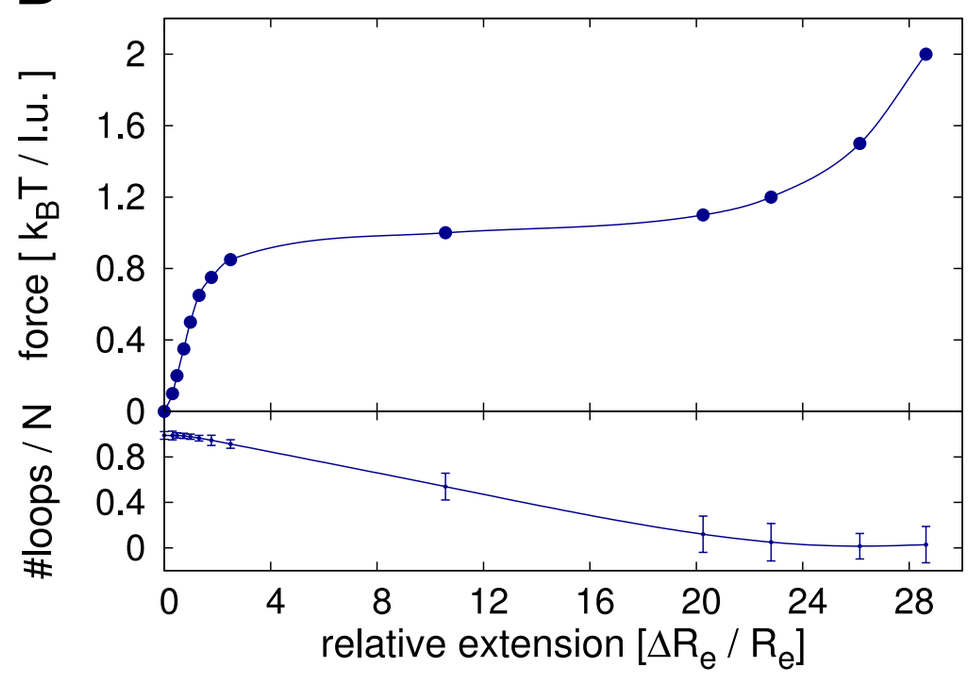
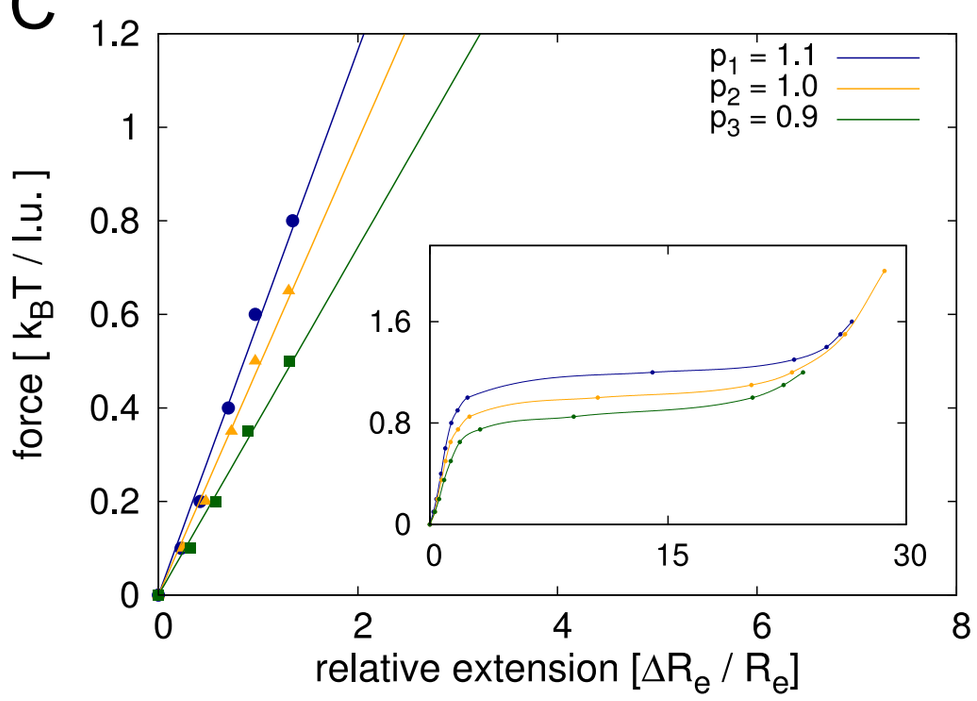
A

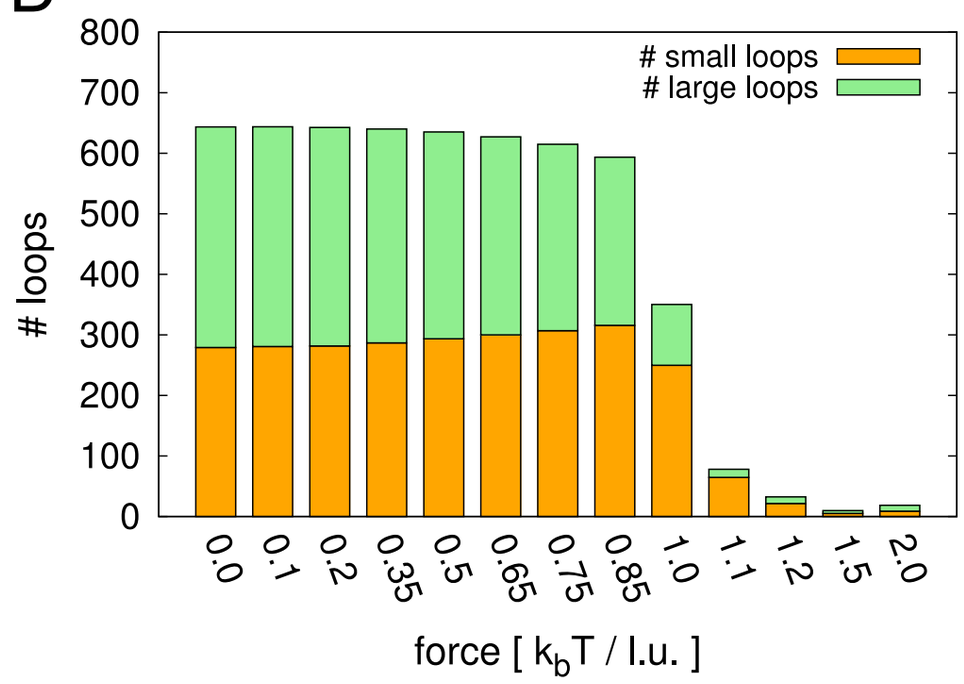
B



C



D



Key Questions

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- What is the role of the proteins in the organization of the genome
- Need to understand naturally unfolded proteins or disordered proteins, characterized by lack of stable tertiary structure

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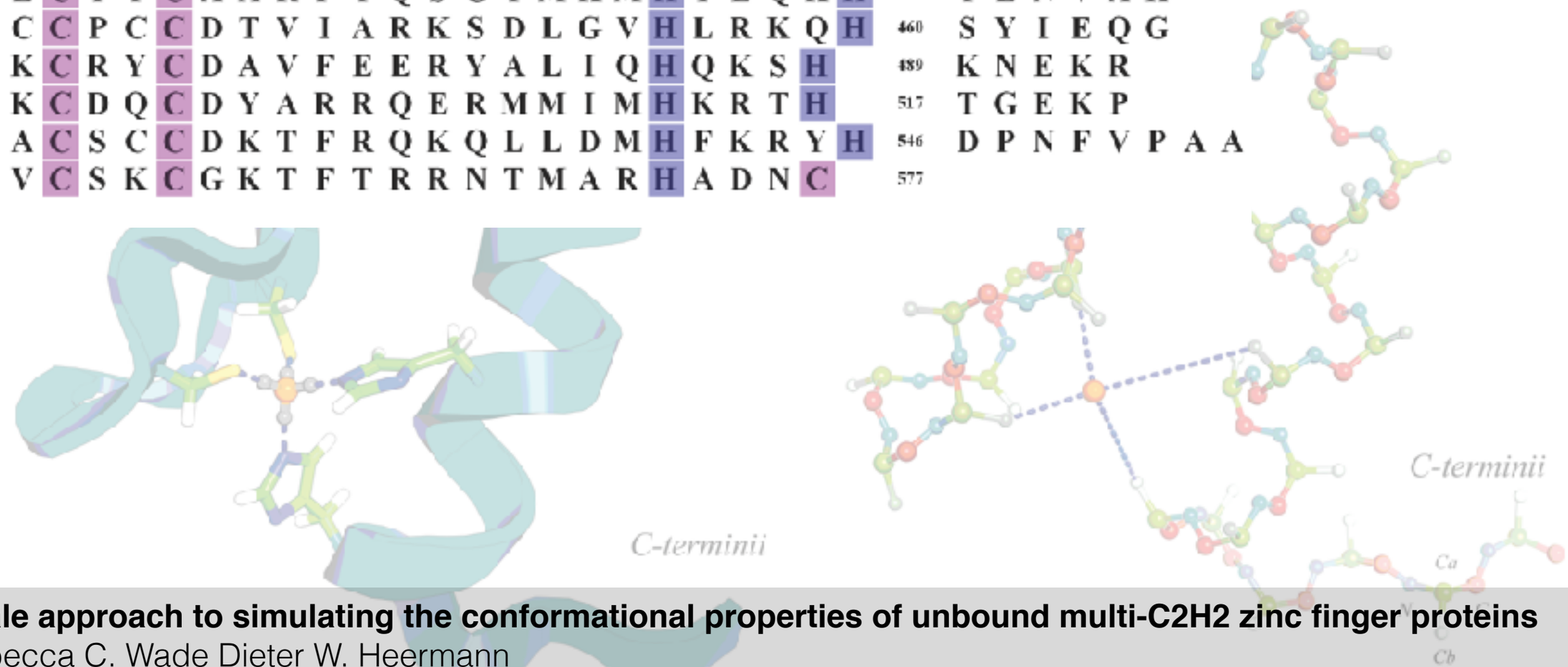
Sequence and Atomic Structure Model of CTCF

zinc finger

266	F	Q	C	E	L	C	S	Y	T	P	P	R	R	S	N	L	D	R	H	M	K	S	H		288	T	D	E	R	P				
294	K	K	C	L	L	C	G	R	A	F	R	T	V	T	L	L	R	N	H	L	N	T	H		316	T	G	T	R	P				
322	K	K	C	P	D	C	D	M	A	F	V	T	S	G	E	L	V	R	H	R	R	Y	K	H	345	T	H	E	K	P				
351	F	K	C	S	M	C	D	Y	A	S	V	E	V	S	K	L	K	R	H	I	R	S	H		373	T	G	E	R	P				
379	F	Q	C	S	L	C	S	Y	A	S	R	D	T	Y	K	L	K	R	H	M	R	T	H		401	S	G	E	K	P				
407	Y	E	C	Y	I	C	A	A	R	F	T	Q	S	G	T	M	K	M	H	I	L	Q	K	H	430	T	E	N	V	A	K			
437	F	C	C	P	C	C	D	T	V	I	A	R	K	S	D	L	G	V	H	L	R	K	Q	H	460	S	Y	I	E	Q	G			
467	K	K	C	R	Y	C	D	A	V	F	E	E	R	Y	A	L	I	Q	H	Q	K	S	H		489	K	N	E	K	R				
495	F	K	C	D	Q	C	D	Y	A	R	R	Q	E	R	M	M	I	M	H	K	R	T	H		517	T	G	E	K	P				
523	Y	A	C	S	C	C	D	K	T	F	R	Q	K	Q	L	L	D	M	H	F	K	R	Y	H	546	D	P	N	F	V	P	A	A	
555	F	V	C	S	K	C	G	K	T	F	T	R	R	N	T	M	A	R	H	A	D	N	C		577									

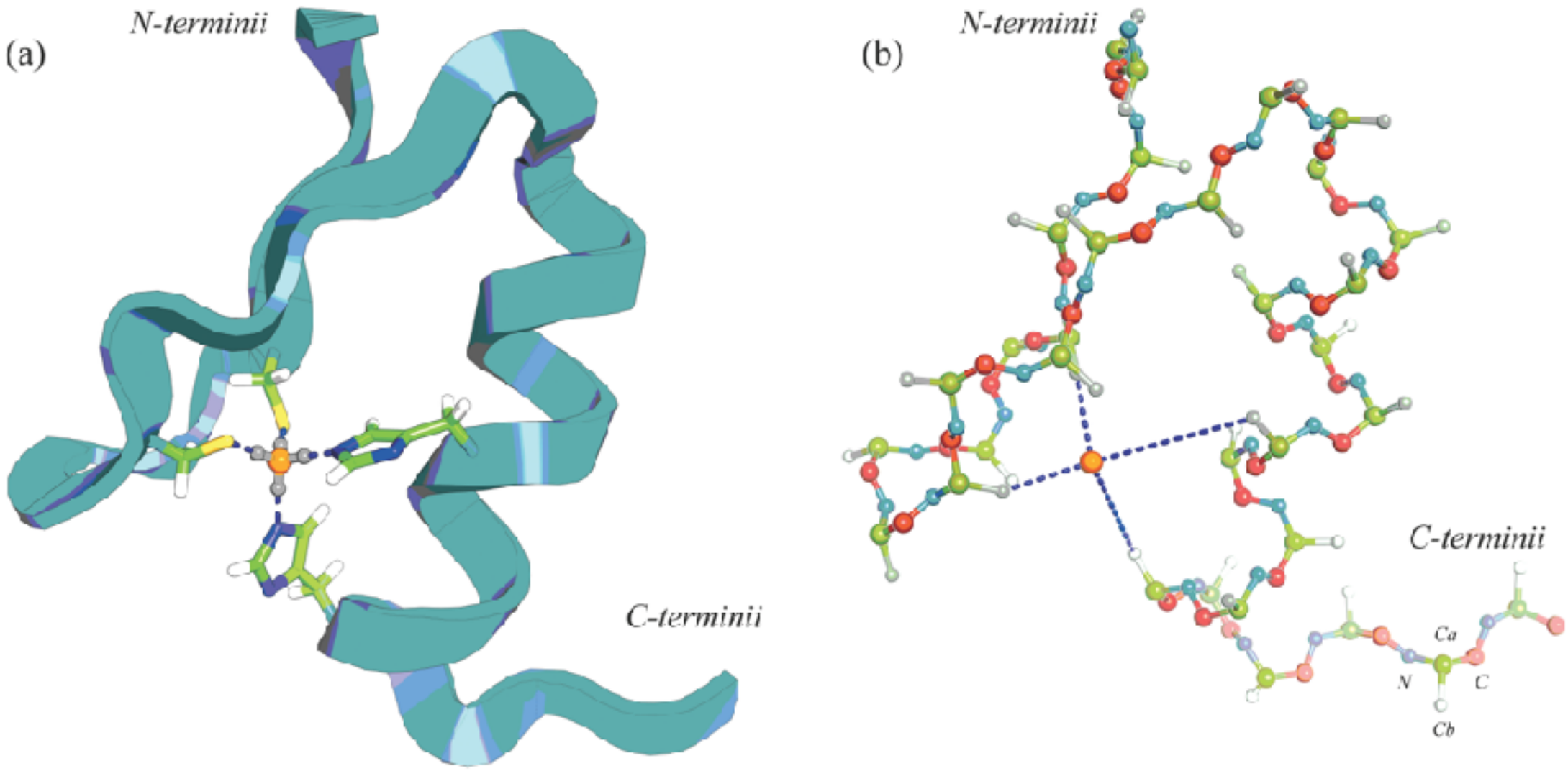
linker



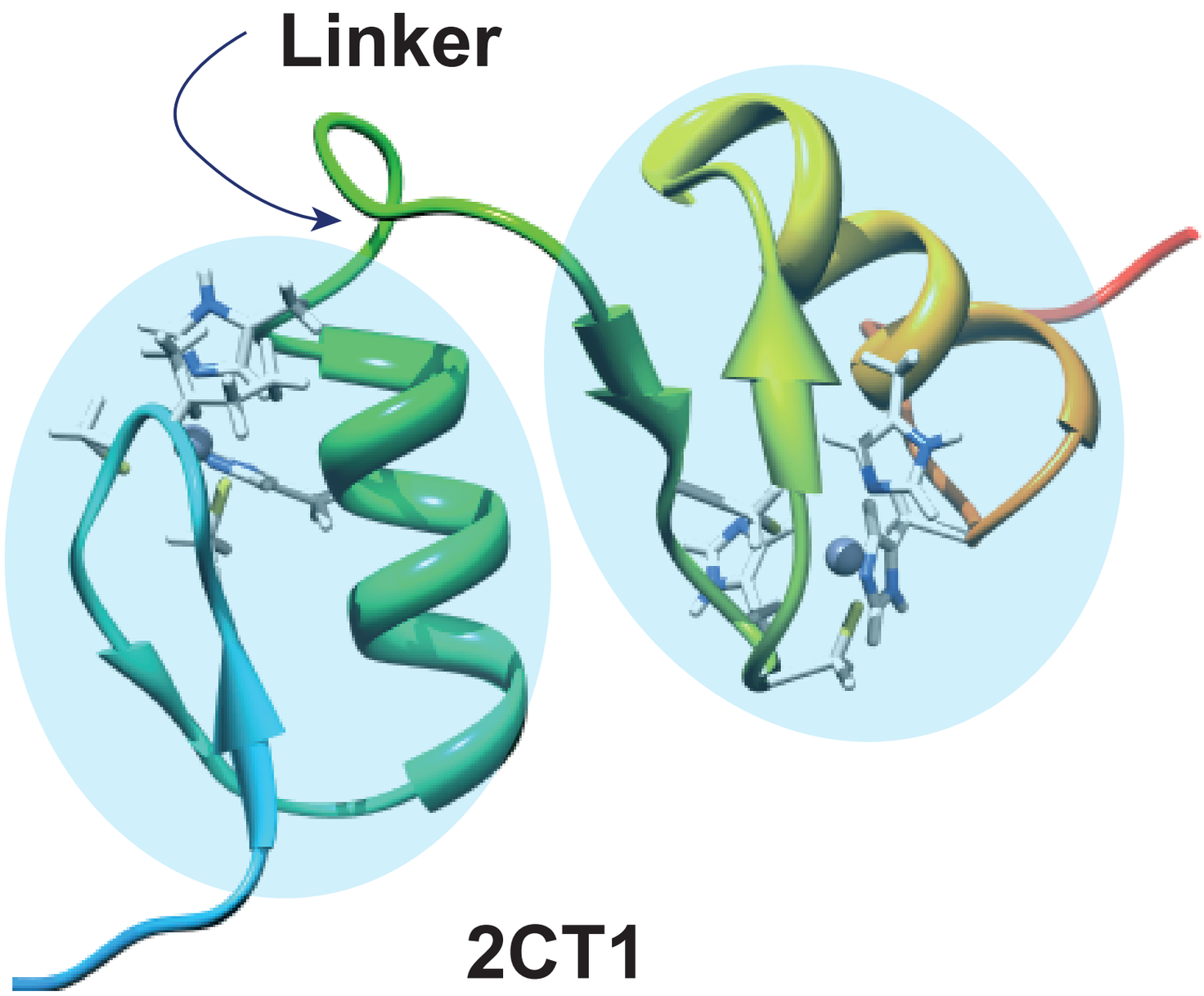
A multiscale approach to simulating the conformational properties of unbound multi-C2H2 zinc finger proteins
Lei Liu Rebecca C. Wade Dieter W. Heermann
Proteins. 2015 Sep;83(9):1604-15. doi: 10.1002/prot.24845. Epub 2015 Jul 1.

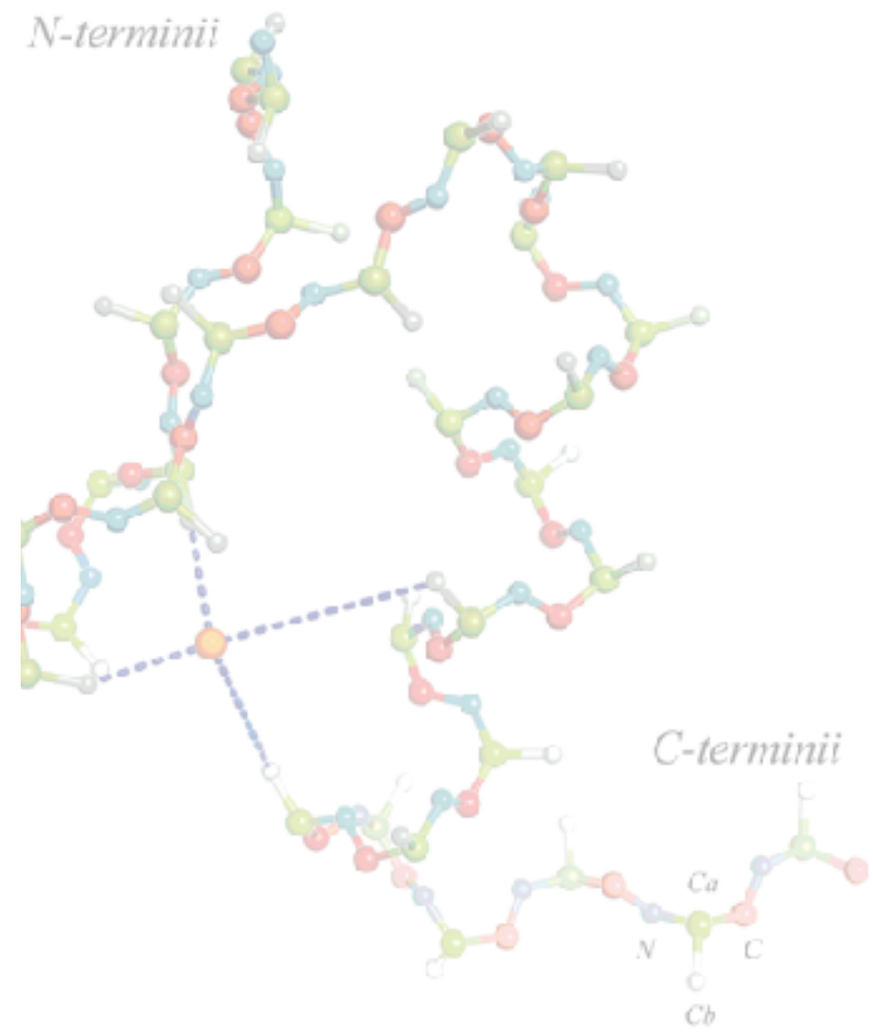
Sequence and Atomic Structure Model of CTCF

Atomic and mesoscale models of 1aay_1. (a) The CaDA representation, where the orange Zn^{2+} ion is surrounded by four gray dummy atoms. (b) Mesoscale model, where each AA is presented by three backbone beads (*N*, *Cα*, *C'*) and one side chain bead (*Cβ*). The Zn^{2+} ion is explicitly modeled as one additional bead, which interacts with *Cβ* of its coordinating residues.



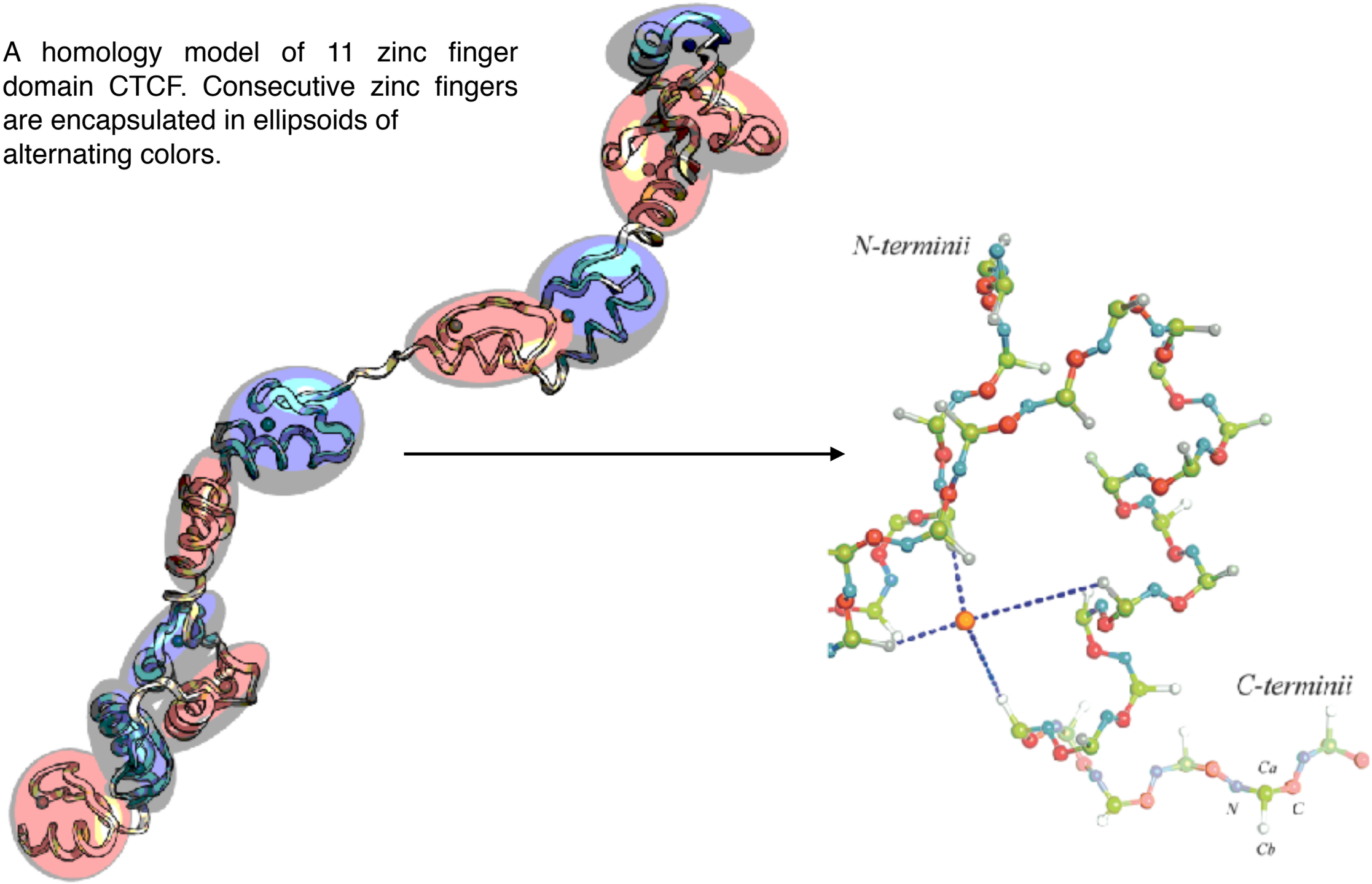
Unbound Zinger Proteins



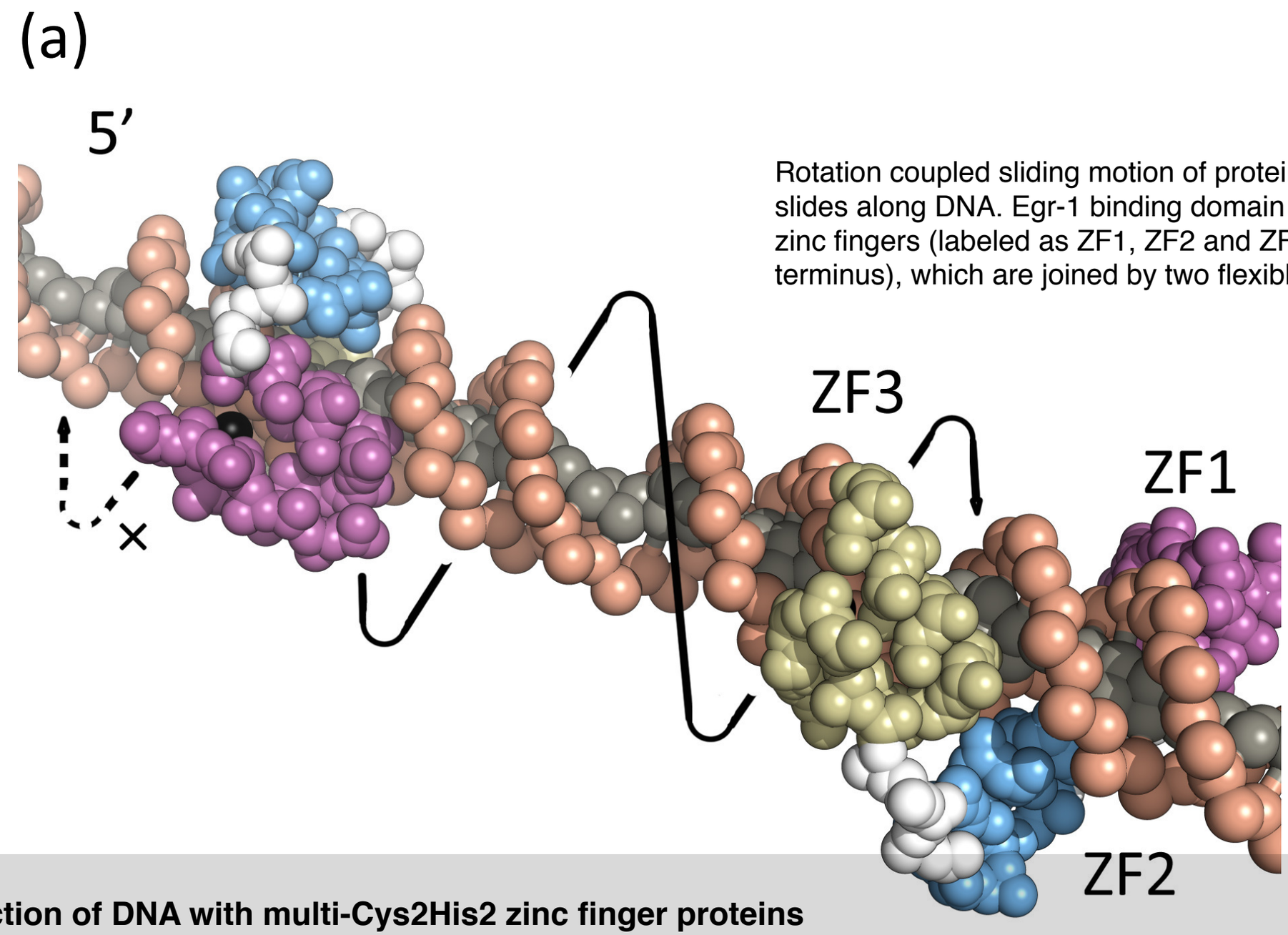


Unbound Zinger Proteins

A homology model of 11 zinc finger domain CTCF. Consecutive zinc fingers are encapsulated in ellipsoids of alternating colors.



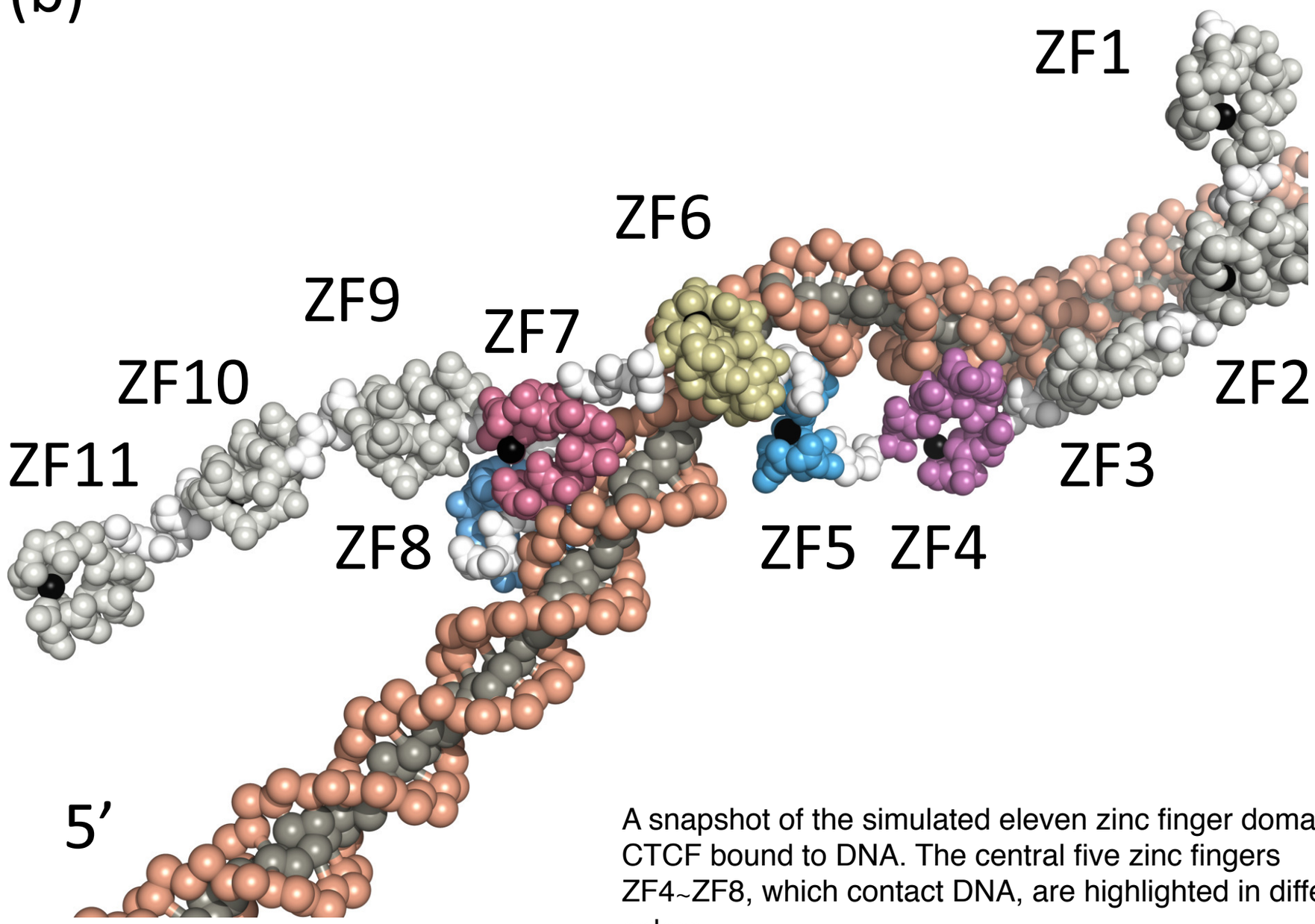
Zinc Finger Proteins in Complexes with DNA



Rotation coupled sliding motion of protein Egr-1 when it slides along DNA. Egr-1 binding domain contains three zinc fingers (labeled as ZF1, ZF2 and ZF3 from N to C terminus), which are joined by two flexible white linkers.

The interaction of DNA with multi-Cys2His2 zinc finger proteins
Lei Liu and Dieter W Heermann
J Phys Condens Matter. 2015 Feb 18;27(6):064107. doi: 10.1088/0953-8984/27/6/064107. Epub 2015 Jan 7.

Zinc Finger Proteins in Complexes with DNA



A snapshot of the simulated eleven zinc finger domains of CTCF bound to DNA. The central five zinc fingers ZF4~ZF8, which contact DNA, are highlighted in different colors.

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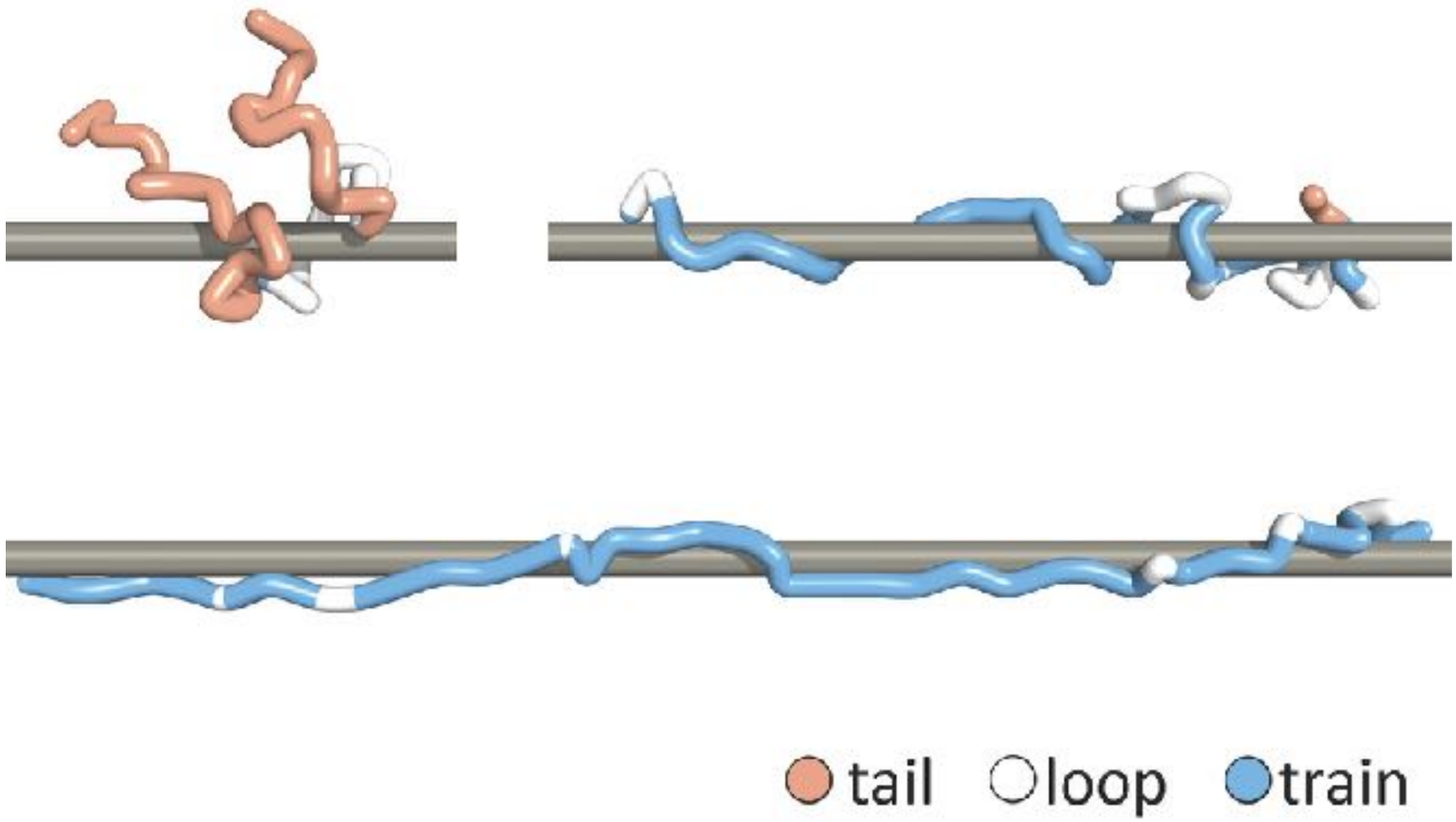
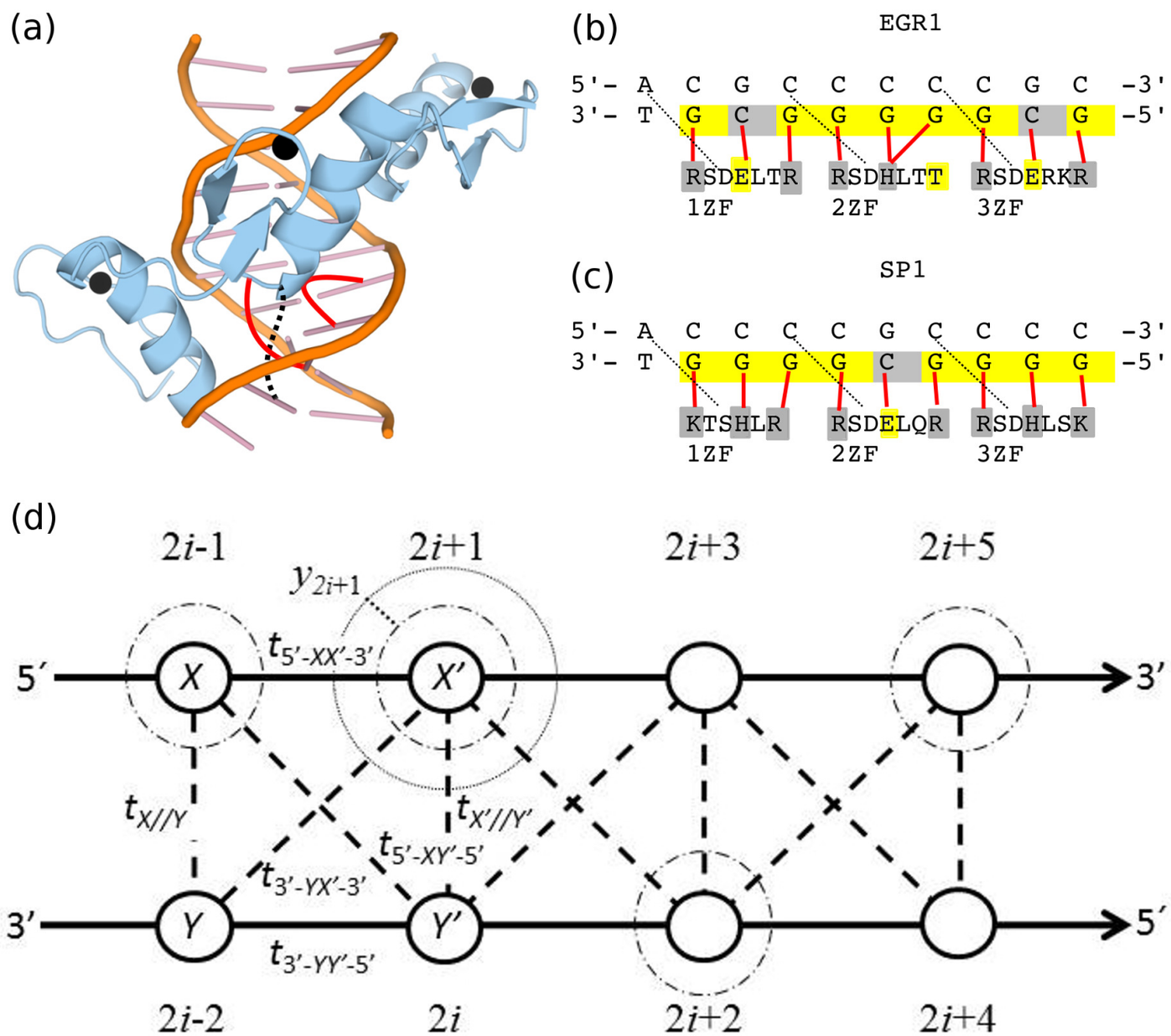
The Model



Typical conformations of a flexible polymer of chain length L = 40 adsorbed to a rigid polymer, with the adsorption interaction strength ε = 0.4, 2.7, 4.7 (top-left, top-right and bottom panel, respectively). The flexible polymers are divided into three kinds of segments, tail(brown), train(blue) and loop(white).

Phase Transition and Winding properties of a Flexible Polymer adsorbed to a Rigid Periodic Copolymer
Lei Liu, David Schubert, Min Chu, and Dieter W. Heermann
Phys. Rev. E 91, 032601 - Published 11 March 2015

Protein Binding



- **ab initio quantum mechanical model** for binding
- correctly identifies the binding cites of zinger fingers
- **de novo prediction** of binding locations

The Electronic Behavior of Zinc-Finger Protein Binding Sites in the Context of the DNA Extended Ladder Model
Nestor Norio Oiwa, Claudette Elisea Cordeiro and Dieter W Heermann
Front. Phys., 11 May 2016 | https://doi.org/10.3389/fphy.2016.00013.

Dynamic Loop Model + Biological Input:

Human Chromosomes

- FISH experiments on single chromosomes
- Bio-chemical experiments (4c, Hi-C)
- Partial genome staining experiments
- Whole genome staining experiments
- Mechanical data (metaphase)

Escherichia coli

Yeast

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The Physical Architecture of the Genome: Common Principles in Prokaryotes and Eukaryotes

The principles are loops, entropy and confinment

Unified Model

Heermann, Heidelberg University, 2017

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DFG Deutsche Forschungsgemeinschaft

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Thank you for your attention!