The Physics of Chromosomes: Loops and Entropy, that's what it's all about

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Key Problem

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

Yes, we can!
Key Problem

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)
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
The Model
The Model

course grained description
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
Influence of the catenation constraint on elongation and segregation of ring polymers
Manfred Bohn, Dieter W. Heermann, Odilon Lourenço, Claudette Cordeiro

Topological interactions between ring polymers: Implications for chromatin loops
Manfred Bohn and Dieter W. Heermann
The diagram shows the effective potential $U_{\text{ring}}(r)$ as a function of $r/R_g$ for various system sizes $N$. The x-axis represents $r/R_g$, and the y-axis represents the effective potential $U_{\text{ring}}(r)$. The graph includes data points for $N=64, 128, 256, 384, 512, 1024, 1536, 2048$, each represented by a different line color. The data points are marked by symbols, and the line colors correspond to the system size.

The effective potential decreases with increasing $r/R_g$, and the curves for different system sizes converge as $r/R_g$ increases.
So loops repel each other!

Let’s look at prokaryotes.
Curved DNA

Plectonemic supercoils

Toroidal supercoil

RNA

RNA polymerase

Loops: One More Thing

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
Loops: One More Thing

Transcription Factor Induced DNA Domain Formation Structures the E. coli Chromosome
Looped Star Polymers Show Conformational Transition from Spherical to Flat Toroidal Shapes
Entropic repulsion between rings leads to an effective bending rigidity.

Looped Star Polymers Show Conformational Transition from Spherical to Flat Toroidal Shapes
Curved DNA

Plectonemic supercoils

Toroidal supercoil

RNA

RNA polymerase

e.coli
Curved DNA
Plectonemic supercoils
Toroidal supercoil
RNA
RNA polymerase
e.coli
e.coli
e.coli
e.coli
e.coli
e.coli
e.coli
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

Heermann, Heidelberg University, 2015
entropic forces alone are not sufficient to achieve and maintain full separation of chromosomes
- 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.
Transcriptional Regulatory Network Shapes the Genome Structure of Saccharomyces cerevisiae
**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.
Gene Territories

Data taken from

Transcriptional Regulatory Network Shapes the Genome Structure of Saccharomyces cerevisiae
Transcriptional Regulatory Network Shapes the Genome Structure of Saccharomyces cerevisiae
**Ansatz:** Dynamic Loop Model + gene expression.
Human Chromosomes

A

Chromosome 1

Chromosome 11

median transcription

genomic position [Mb]

mean sq. displacement $R^2$ [µm$^2$]

mean sq. displacement $R^2$ [µm$^2$]

B

Chromosome 1

Chromosome 11

mean sq. displacement $R^2$ [µm$^2$]

C

Chromosome 1

Chromosome 11

mean sq. displacement $R^2$ [µm$^2$]
Diffusion-Driven Looping Provides a Consistent Framework for Chromatin Organization

Manfred Bohn and Dieter W. Heermann

The dynamic loop model very well explains differences between ridges and anti-ridges by different local looping probabilities.
The dynamic loop model also reproduces the experimental findings on the scale of a complete chromosome arm.
Human Chromosomes

Relative abundance $h(l)$ vs. size of contact $l$.

- $h(l) \sim l^{-0.81}$
- $h(l) \sim l^{-2}$
- $h(l) \sim l^{-2.4}$

Average loop number per conformation:

- $d_1$ and $d_2$ represent specific distances.

Heermann, Heidelberg University, 2015
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 all scales mediated by proteins (transcriptional hubs, ...)
Human Chromosomes

Why do chromosomes not mix?

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

radius of gyration

overlap between chromosomes

REPLUSIVE FORCE
Human Chromosomes

A. Linear chains

B. 45 loops per chain

C. 92 loops per chain
Chromosomes in Metaphase

Ansatz: Dynamic Loop Model + gene expression.

Chromosomes in Metaphase

Chromosomes in Metaphase

Reversible and Irreversible Unfolding of Mitotic Newt Chromosomes by Applied Force
Michael Poirier, Sertac Eroglu Didier Chatenay, and John F. Marko
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.

Chromosomes in Metaphase

A

B

C

D

Heermann, Heidelberg University, 2015
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
The Physical Architecture of the Genome: Common Principles in Prokaryotes and Eukaryotes

The principles are loops, entropy and confinement

Unified Model
Thank you for your attention!