



The three-dimensional architecture of the human genome: understanding the physical mechanisms controlling gene expression



FAPESP School on Exact, Natural and Life Sciences
7-10 August 2022

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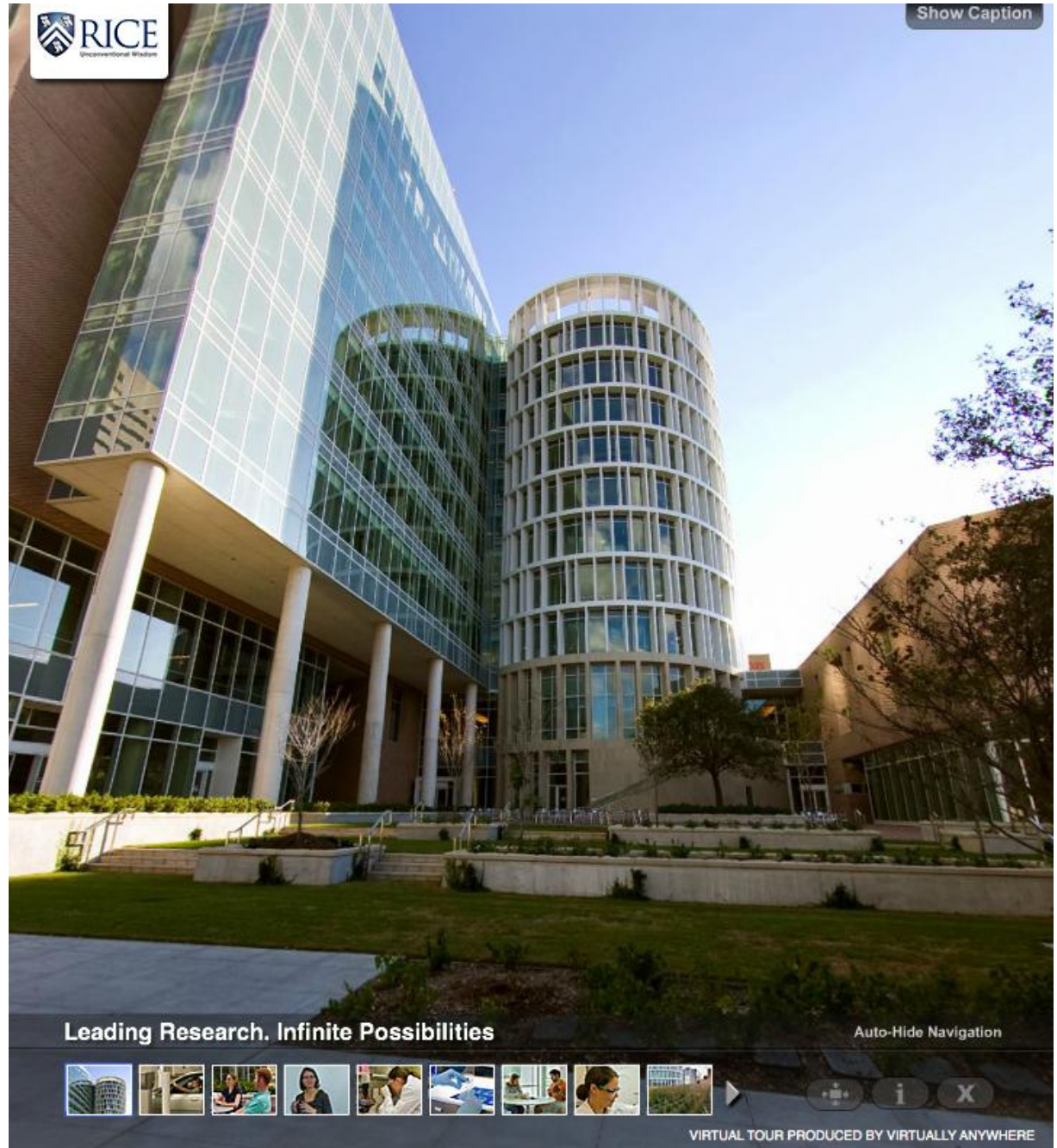
Antonio B.
De Oliveira Jr.





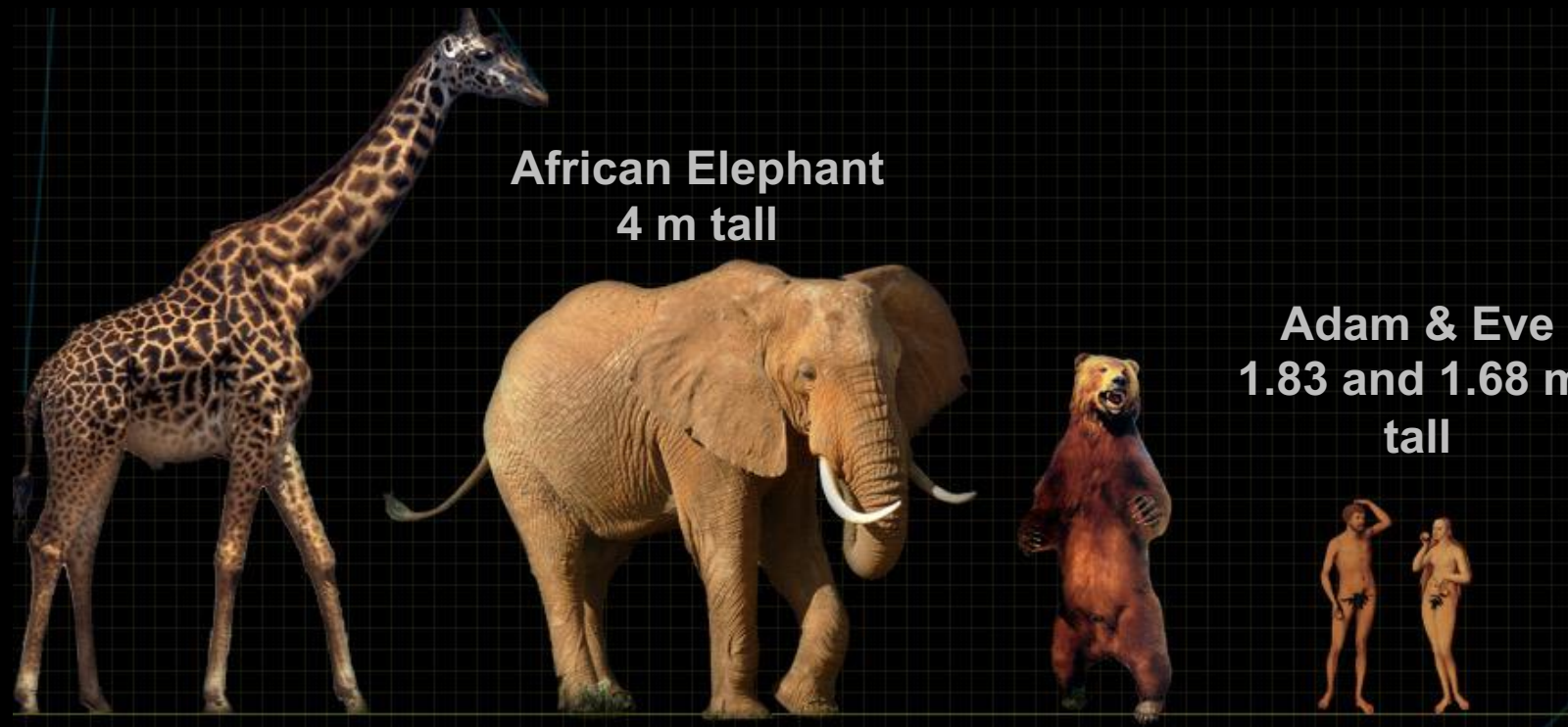
Center for Theoretical Biological Physics

10th floor of the
BioScience Research
Collaborative





Preface: A Short Survey of Length Scales

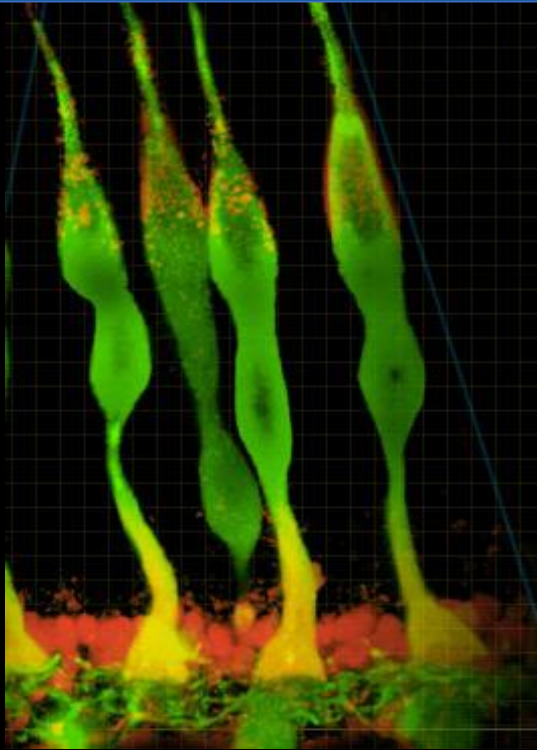


Giraffe
6.1 m tall

Kodiak
Bear 3 m
tall

**Our Genome
2 m long**

Preface: A Short Survey of Length Scales



Photoreceptors
 1×10^{-4} m



Sperm
 6×10^{-5} m

Cell Nucleus
 6×10^{-6} m



Metaphase
X Chromosome
 7×10^{-6} m



Yeast
 3×10^{-6} m

DNA must be open and knots free

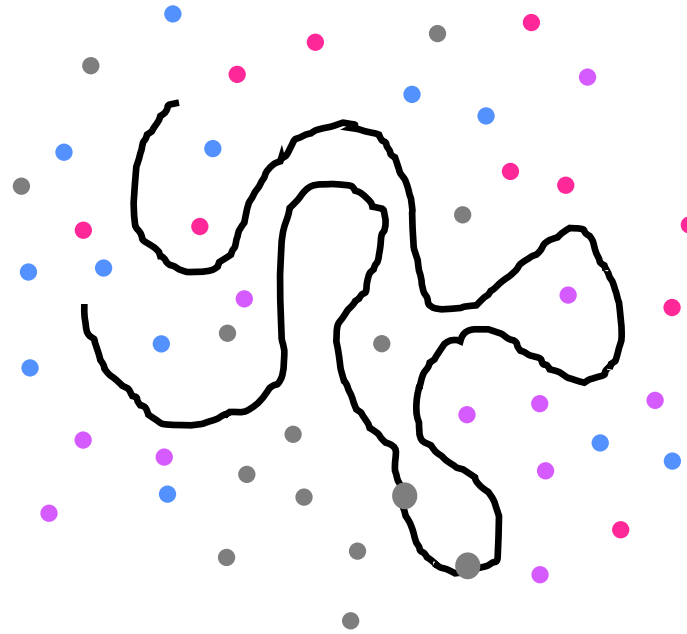


Very little accessible tape!

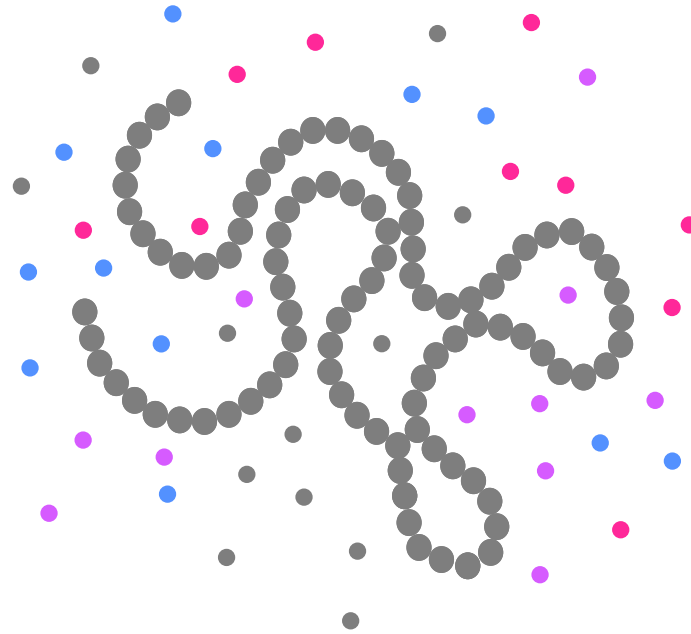


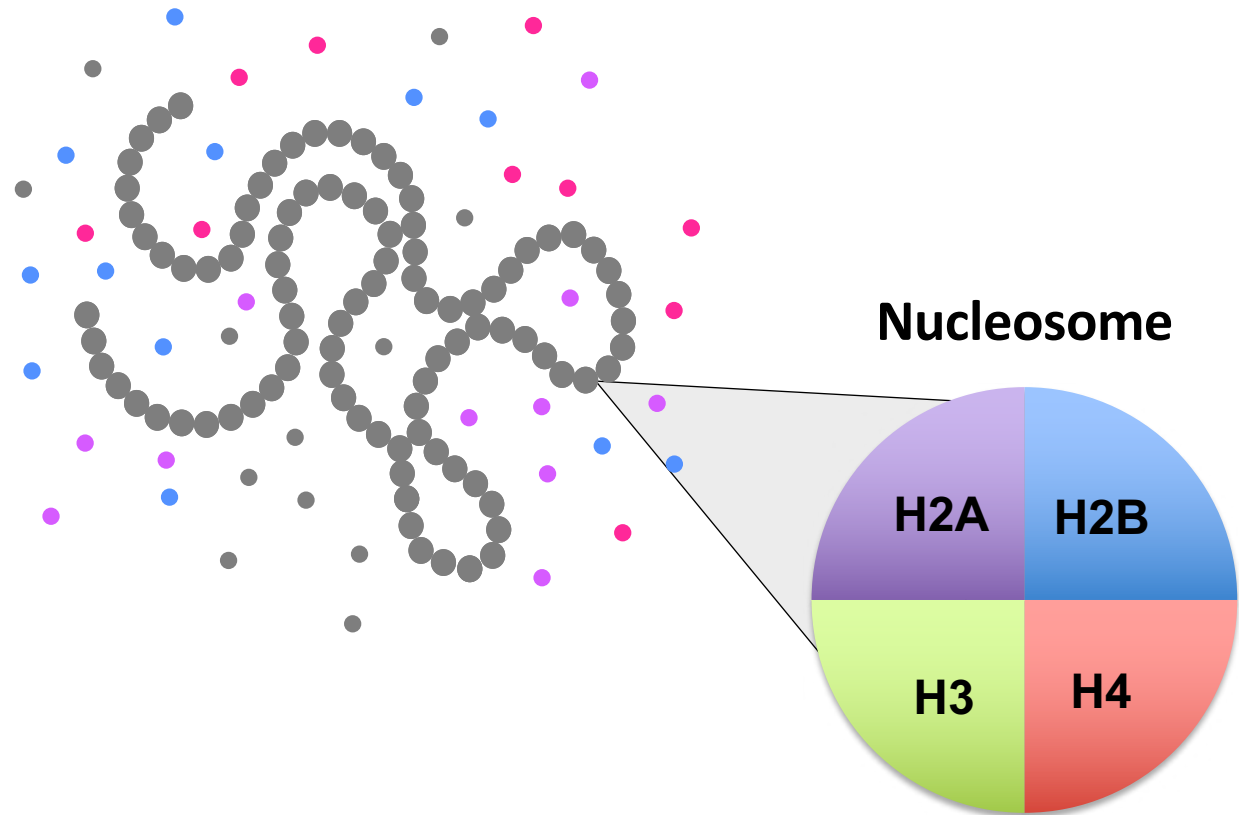
Knots don't help reading!

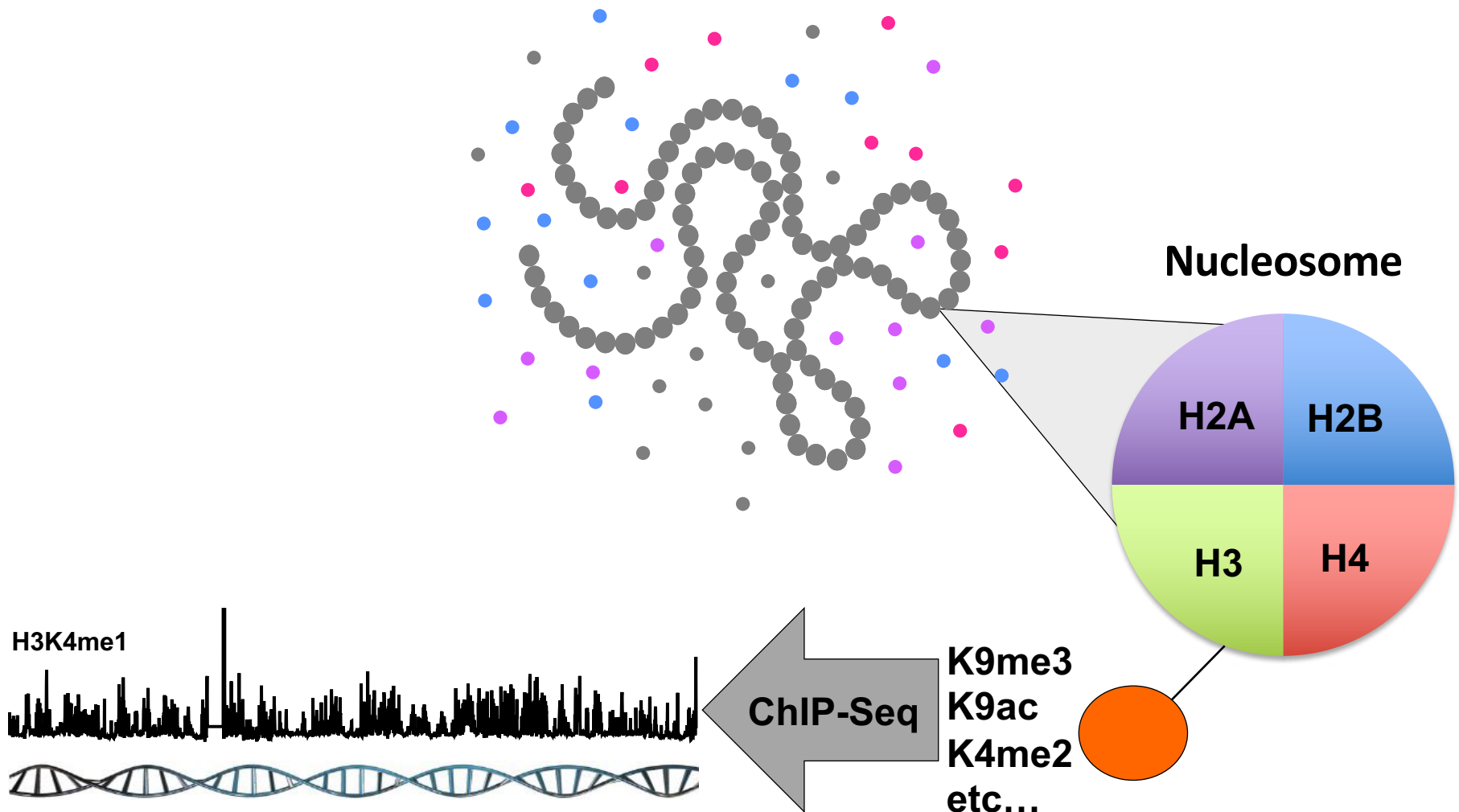




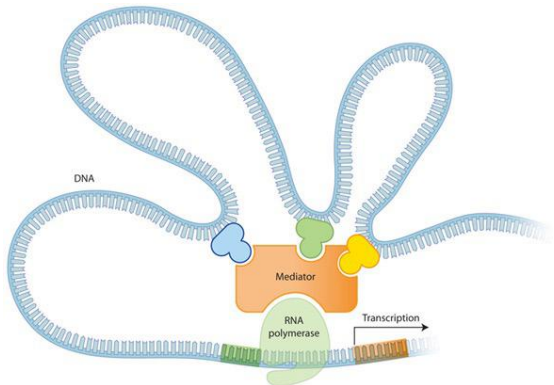
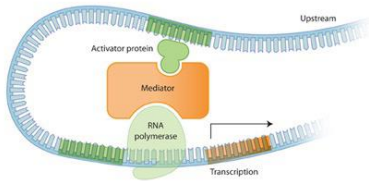
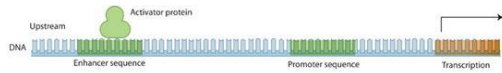
A Complex Polymer In A Complex Environment





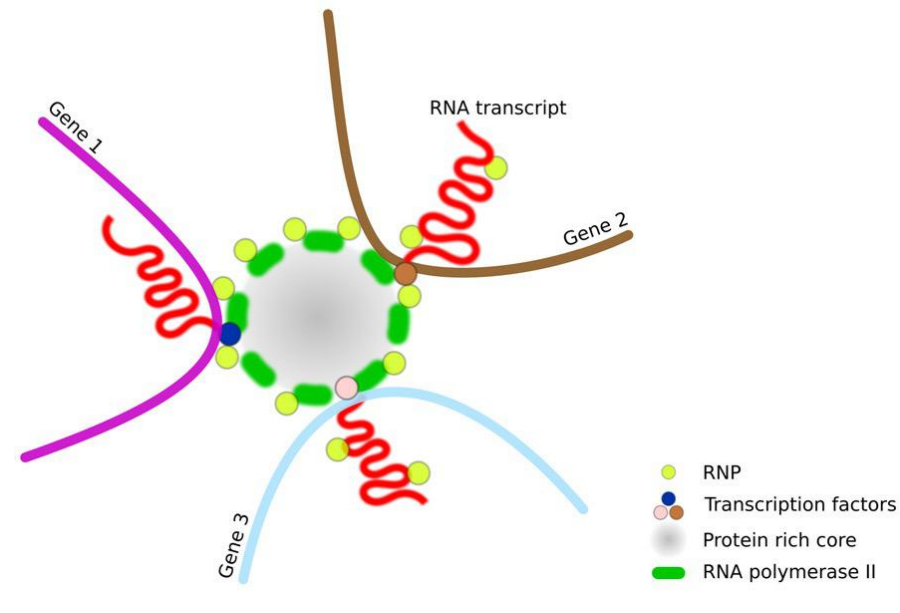


Enhancers



Transcription Factories

Structure of a transcription factory



© Nature Education

Rieder *et al.* 2012

**Fluorescence *In Situ*
Hybridization (FISH)**

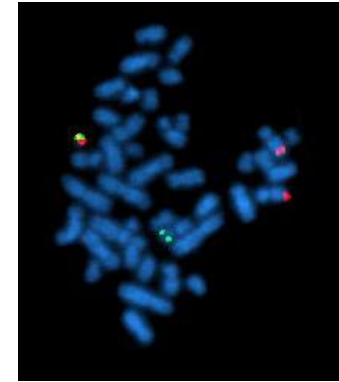
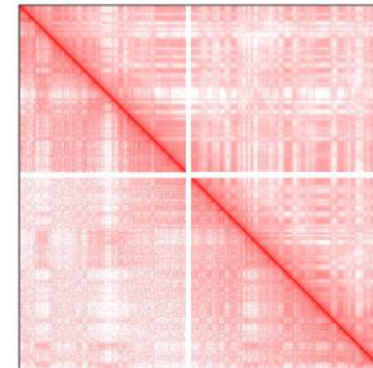
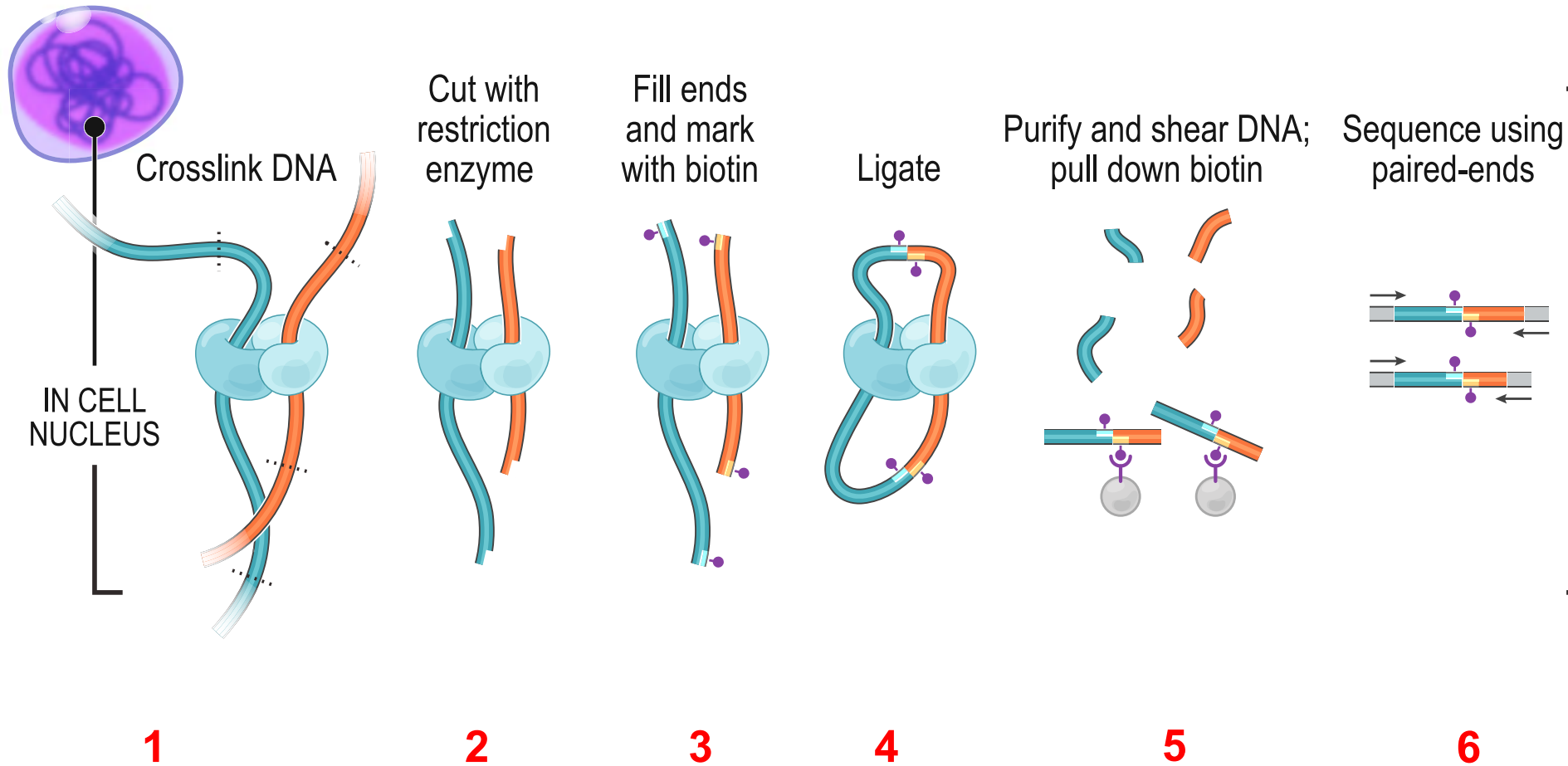


Image from Wikipedia

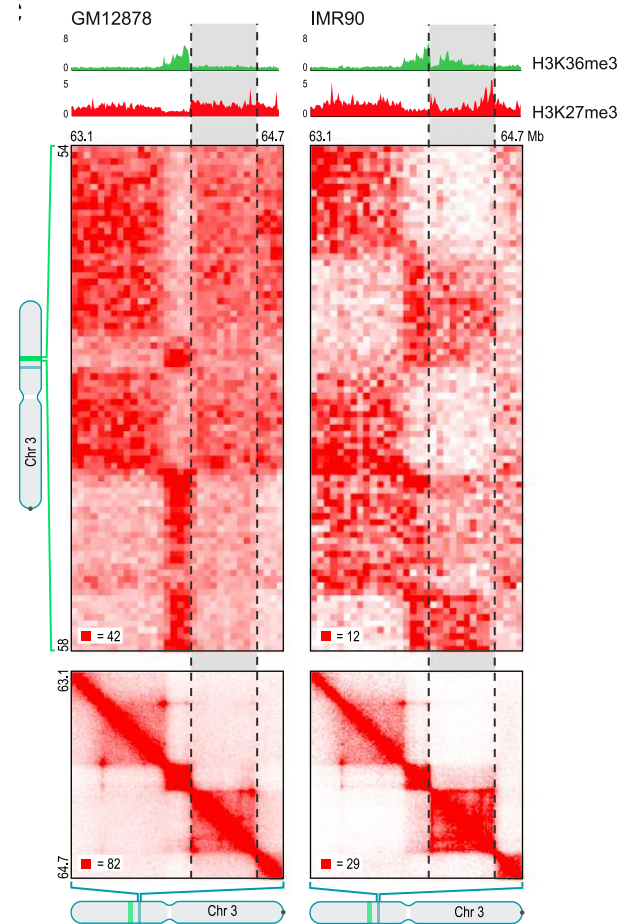
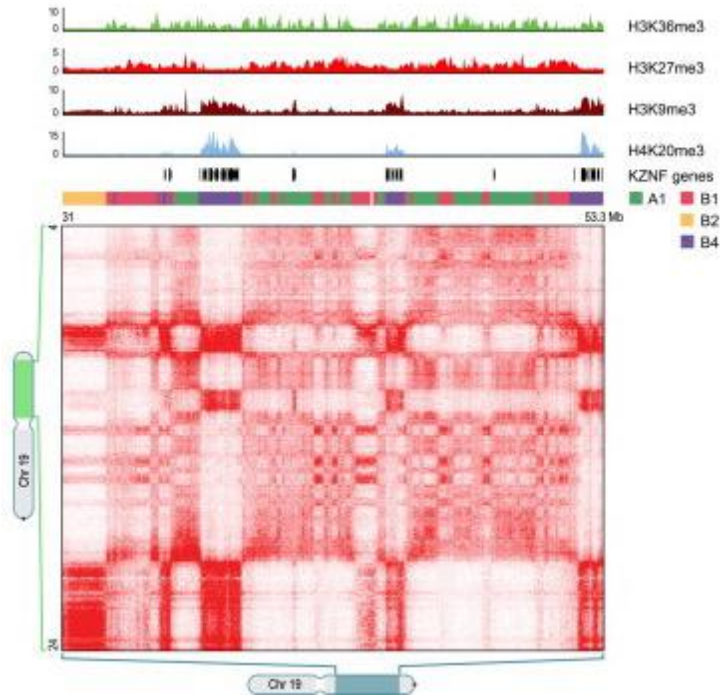
**Chromosome
Conformation Capture
(3C, 4C, 5C, Hi-C)**





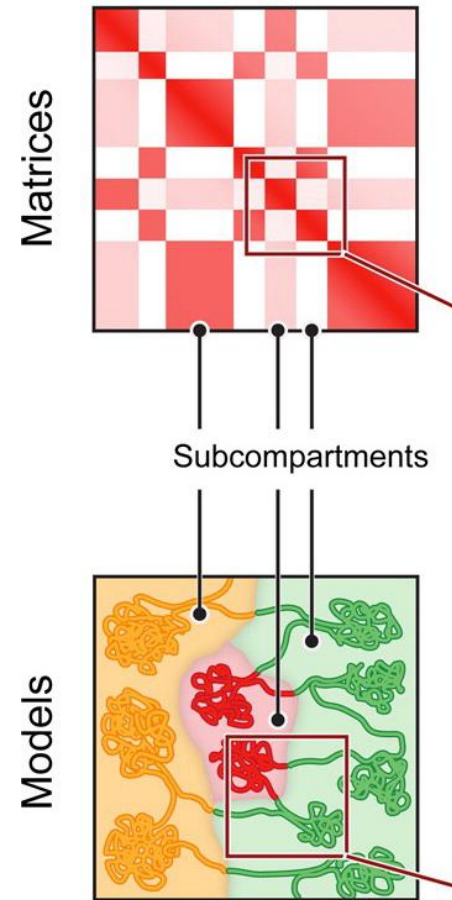
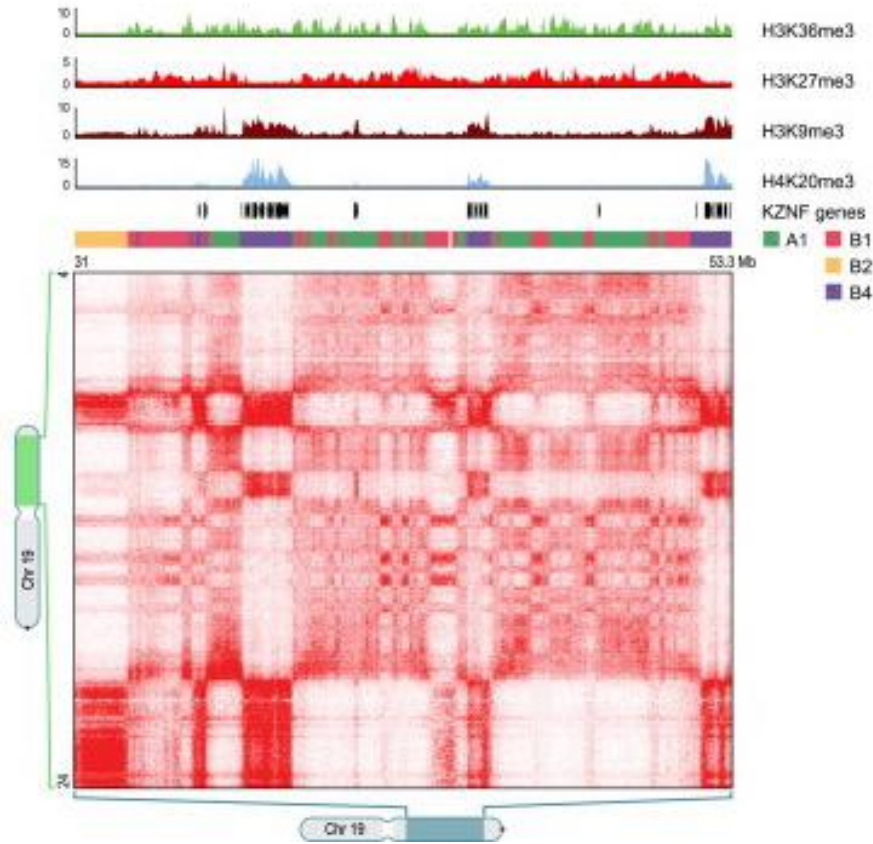
Rao *et al.* 2014

Chromatin Architecture is Specific to the Cell Type



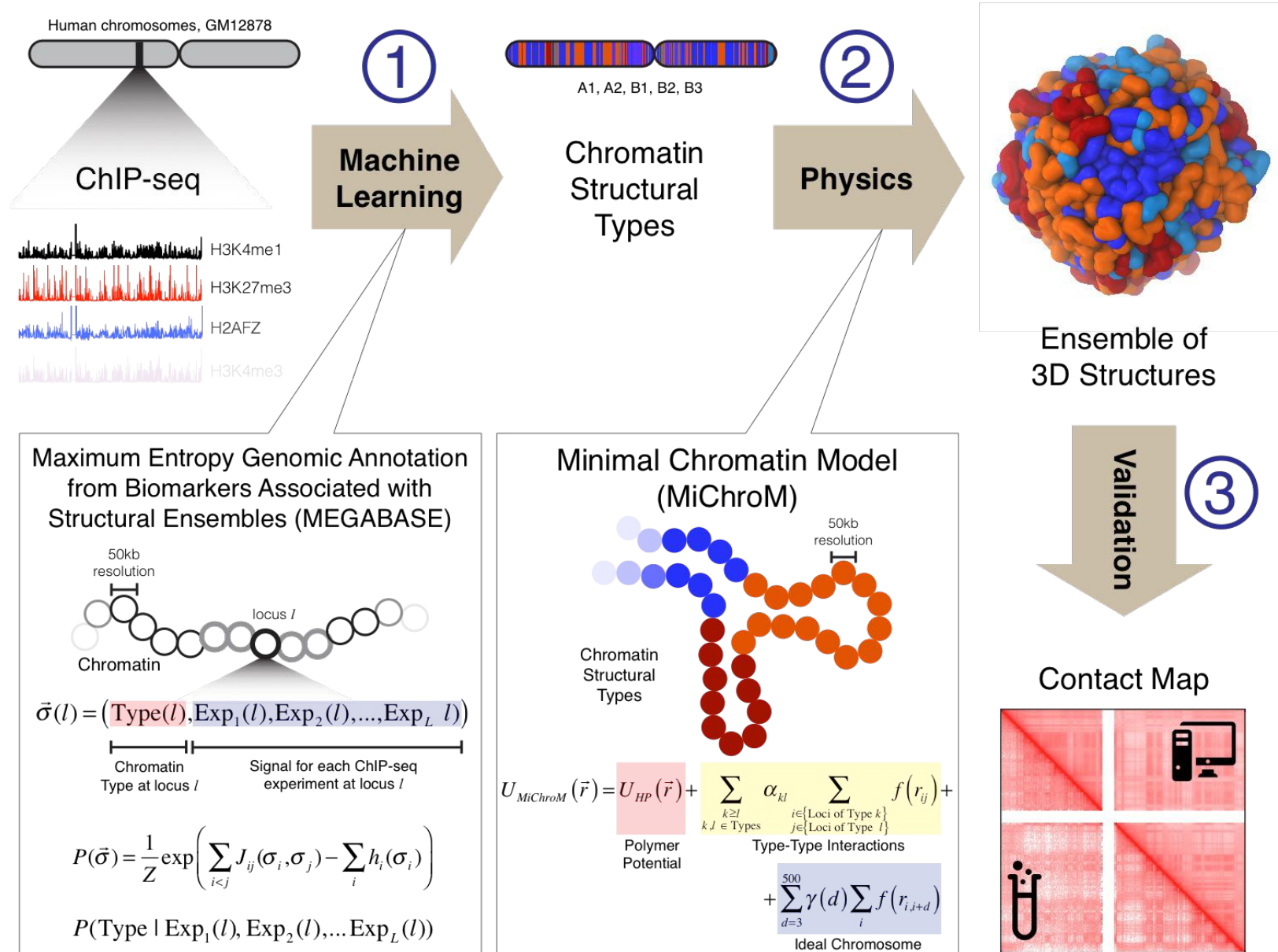
Lieberman Aiden Lab

DNA-DNA Ligation Experiments Reveals Compartments which appear to correlate with epigenetic modifications

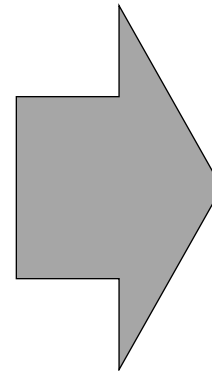
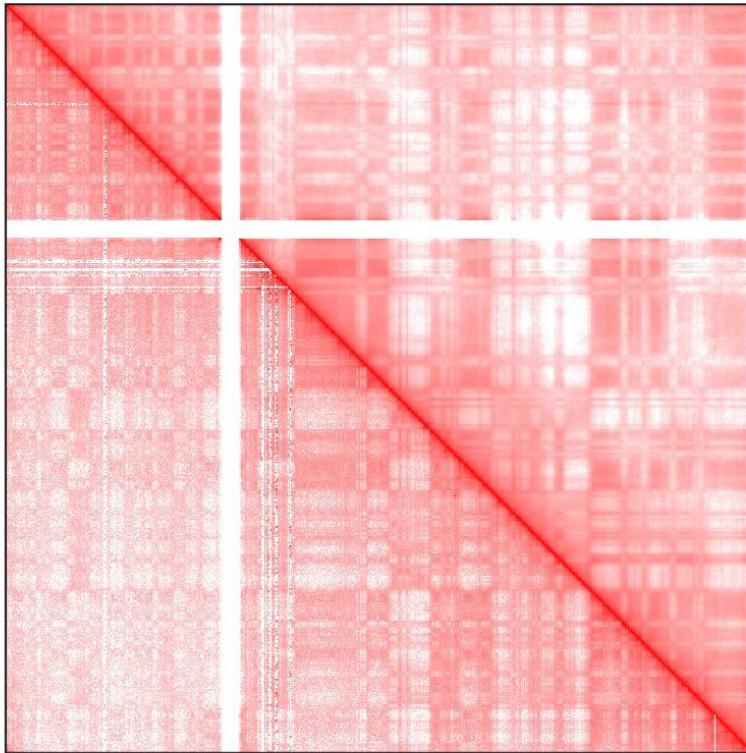


Patterns in contact probabilities identify 6 chromatin types (Sub-compartments):
A1, A2, B1, B2, B3, B4

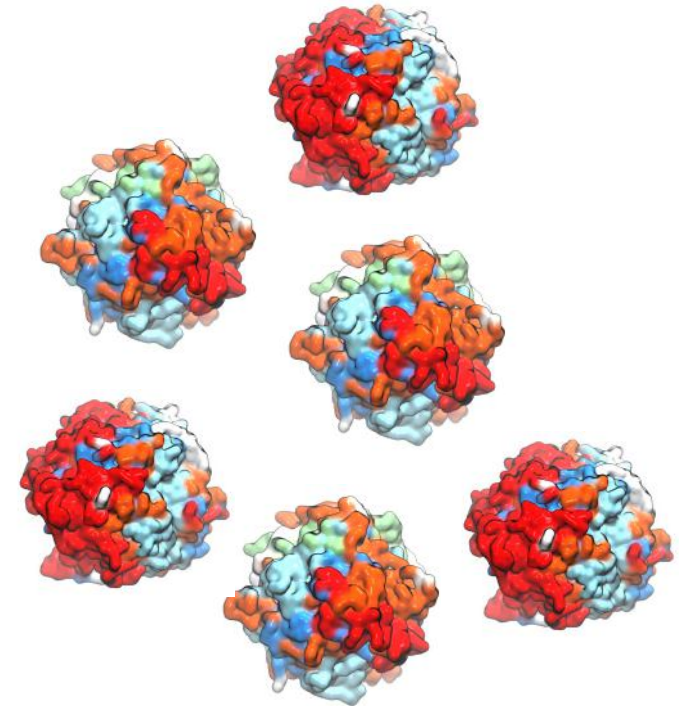
Schematic Illustration of Computational Pipeline

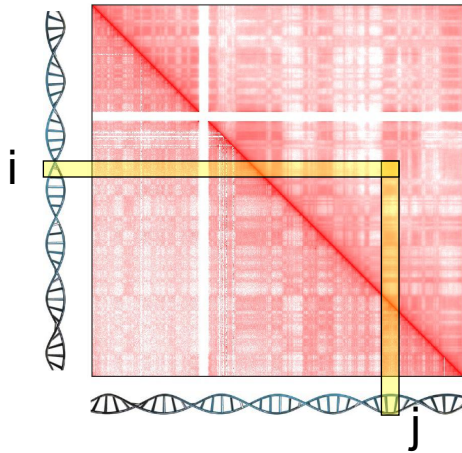


DNA-DNA ligation Assays: Hi-C

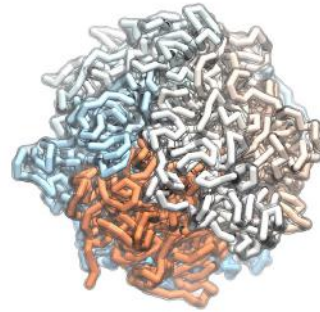


Structural Ensemble





1 Chromosome, 1 Conformation, 1 Experiment

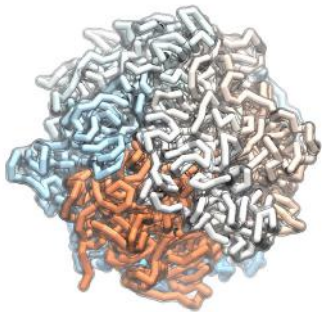


Did *i* and *j* crosslink?

- yes/no

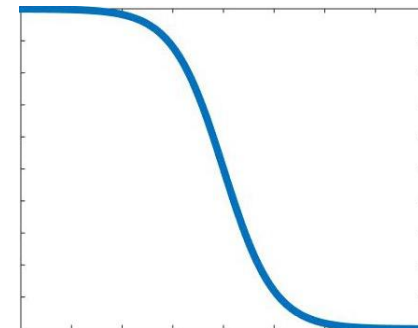
How often did *i* and *j* crosslink?

- A lot when they are close, not much when they are far.



$$f_{ij} = f(r_{ij})$$

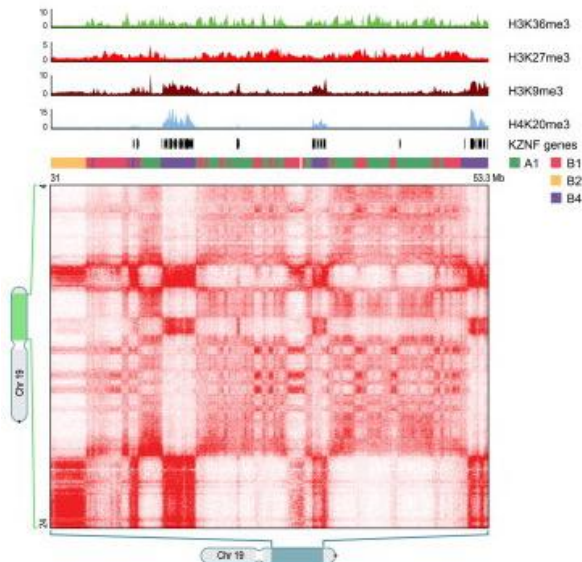
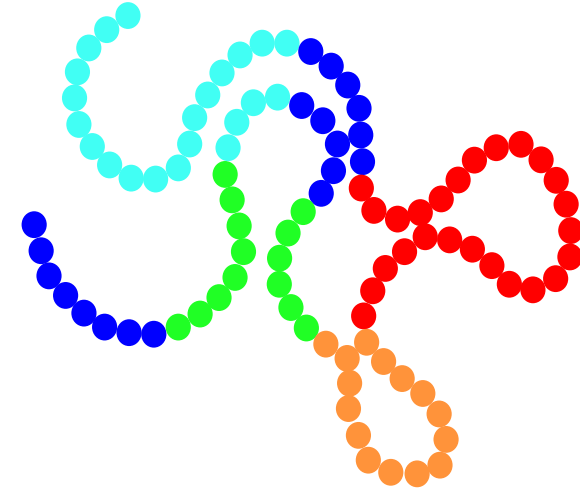
$$p_{ij} = \langle f(r_{ij}) \rangle$$



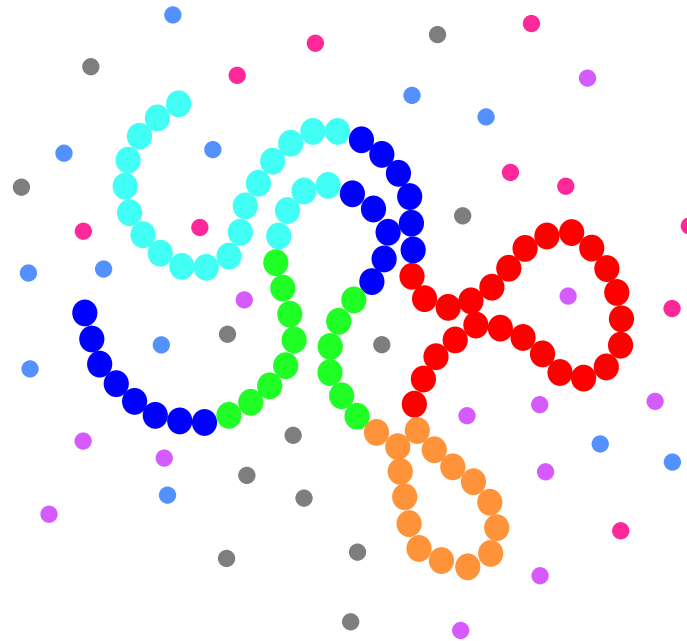
The Minimal Chromatin Model (MiChroM): Phase Separation

Fact 1. Phase Separation of Chromatin Structural Types

If and when two segments of chromatin form a contact the energy of the contact depends only on the type identity of the contact.



The Minimal Chromatin Model: Some Motivated Physical Assumptions



Implicit Protein Model

Type-to-Type Interactions are mediated by a cloud of proteins that bind with different selectivity to different sections of chromatin

The Minimal Chromatin Model: Some Motivated Physical Assumptions

Fact #2:

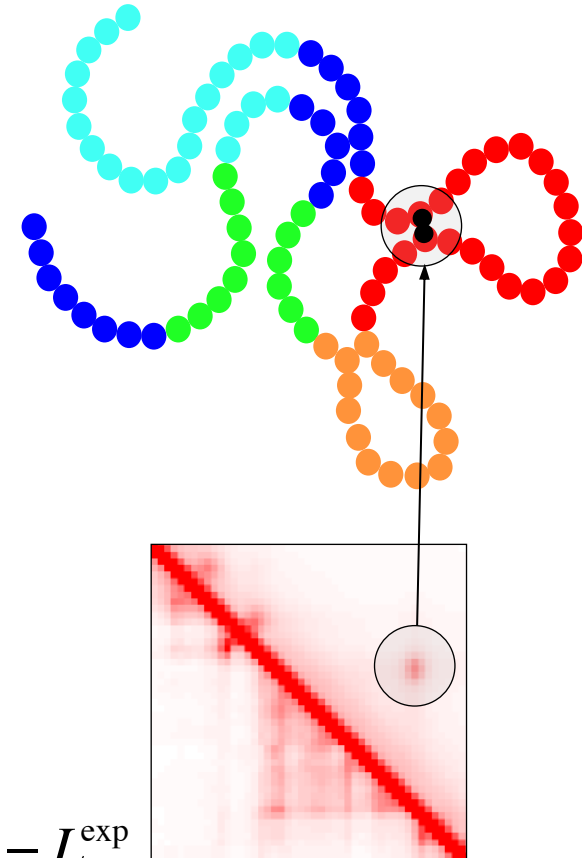
Chromatin form loops at specific locations related to the activity of the protein CTCF

Phillips and Corces 2009

Rao *et al.* 2014

Physical Assumption #2:

If and when the two ends of a loop come into contact, an there is an additional gain in effective free energy



Observable

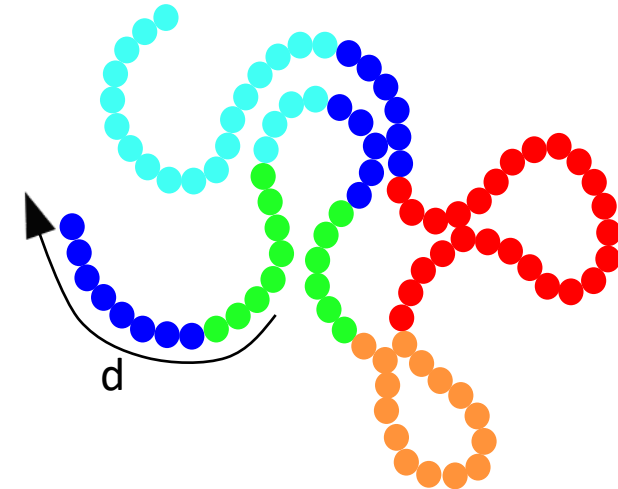
$$L(\vec{r}) = \sum_{(i,j) \in \{\text{Loops Sites}\}} f(r_{ij})$$

Constraint

$$c_L = \int L(\vec{r}) \pi^{\text{MiChroM}}(\vec{r}) d\vec{r} - L^{\text{exp}}$$

Fact #3: The effect of all protein motors acting along the DNA polymer

Ideal Chromosome/Lengthwise Compaction.
Every time two loci at genomic distance d come into contact there is a gain/loss of $\gamma(d)$ effective free energy.



A translational invariant function of the genomic distance consistent with

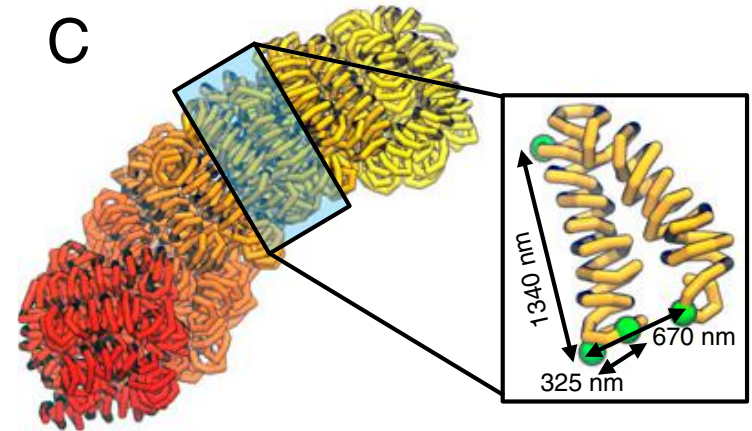
- the notion of a higher order fiber in chromatin
- liquid crystal behavior

But more general...

M.D.P. , B. Zhang, E. Lieberman Aiden, P. G. Wolynes, and J. N. Onuchic, *PNAS* 2016
B. Zhang and P. G. Wolynes, *PNAS* 2015

- **A translational invariant function of the genomic distance**
- **Consistent with**
 - the notion of a higher order fiber in chromatin
 - liquid crystal behavior

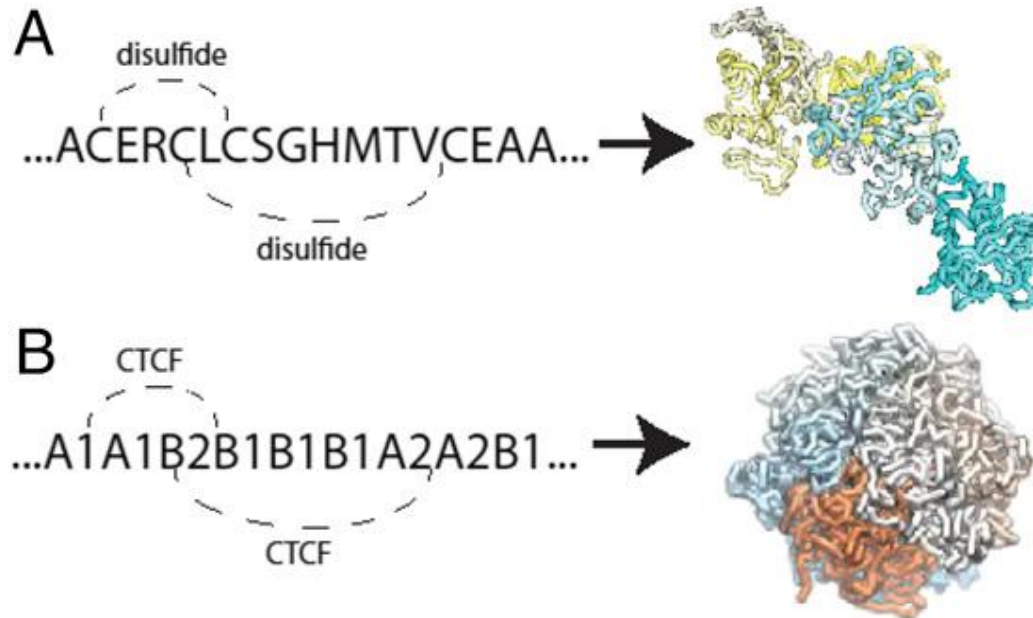
But more general...



Zhang and Wolynes 2015

The Minimal Chromatin Model (MiChroM): Phase Separation

A one-dimensional sequence encodes the three-dimensional fold of chromosomes



with



Bin Zhang

M.D.P. , B. Zhang, E. Lieberman Aiden, P. G. Wolynes, and J. N. Onuchic, *PNAS* 2016
+ Commentary by G. Gürsoy and J. Liang, *PNAS* 2016

The Minimal Chromatin Model: 3 Simple Physical Assumptions

Physical Assumption

Observable

Constraint

#1 If and when two segments of chromatin form a contact the energy of the contact depends only on the type identity of the contact.

Rao et al., 2014, Fillion et al., 2010

$$T_{kl}(\vec{r}) = \sum_{\substack{i \in \{\text{Loci of Type } k\} \\ j \in \{\text{Loci of Type } l\}}} f(r_{ij})$$

$$c_T^{kl} = \int T_{kl}(\vec{r}) \pi^{\text{MiChroM}}(\vec{r}) d\vec{r} - T_{kl}^{\text{exp}}$$

#2 If and when the two anchors of a CTCF-mediated loop come into contact, there is an additional gain in effective free energy

Phillips and Corces, 2009, Rao et al., 2014

$$L(\vec{r}) = \sum_{(i,j) \in \{\text{Loops Sites}\}} f(r_{ij})$$

$$c_L = \int L(\vec{r}) \pi^{\text{MiChroM}}(\vec{r}) d\vec{r} - L^{\text{exp}}$$

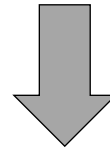
#3 Ideal Chromosome/Local Compaction. Every time two loci at genomic distance d come into contact there is a gain/loss of $\gamma(d)$ effective free energy.

$$G_d(\vec{r}) = \sum_i f(r_{i,i+d})$$

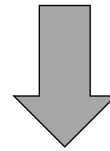
$$c_G^d = \int G_d(\vec{r}) \pi^{\text{MiChroM}}(\vec{r}) d\vec{r} - G_d^{\text{exp}}$$

The Minimal Chromatin Model (MiChroM): the Effective Energy Function

Constraints



Maximum Entropy Principle



Information Theoretic Energy Function

$$U_{\text{MiChroM}}(\vec{r}) = U_{\text{HP}}(\vec{r}) + \sum_{\substack{k \geq l \\ k, l \in \text{Types}}} \alpha_{kl} \sum_{\substack{i \in \{\text{Loci of Type } k\} \\ j \in \{\text{Loci of Type } l\}}} f(r_{ij}) + \chi \cdot \sum_{(i,j) \in \{\text{Loop Sites}\}} f(r_{ij}) + \sum_{d=3}^{500} \gamma(d) \sum_i f(r_{i,i+d})$$

Polymer
Potential

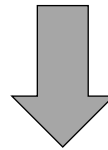
Type-to-Type
Interactions

Specific
Interactions

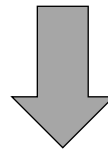
Lengthwise
Compaction

M.D.P. , B. Zhang, E. Lieberman Aiden, P. G. Wolynes, and J. N. Onuchic, *PNAS* 2016
+ Commentary by G. Gürsoy and J. Liang, *PNAS* 2016

Constraints



Maximum Entropy Principle



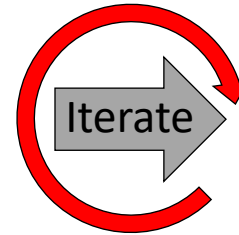
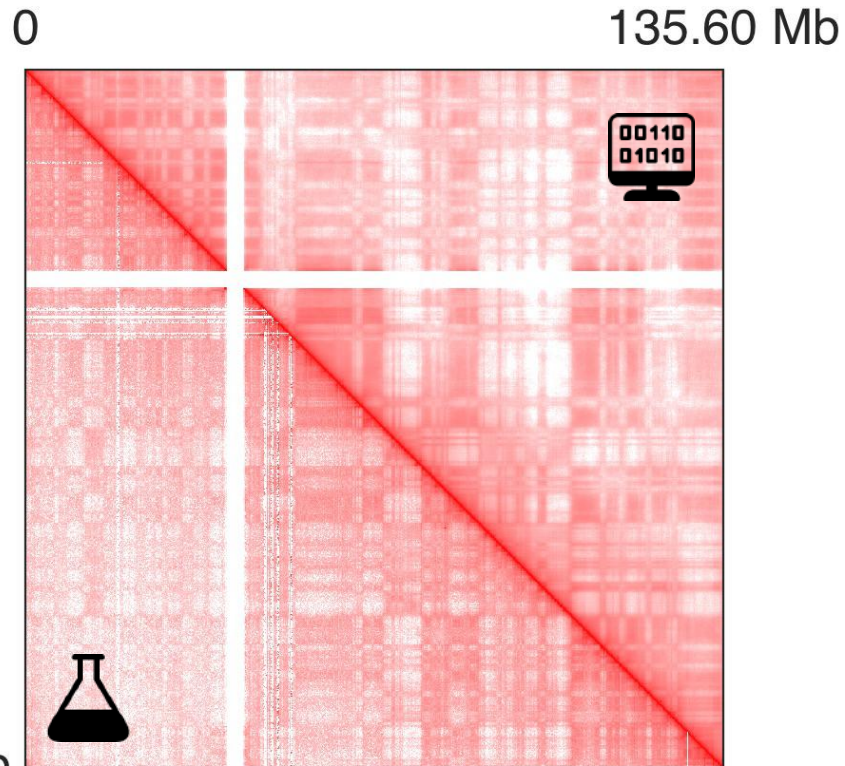
Information Theoretic Energy Function

$$U_{MiChroM}(\vec{r}) = U_{HP}(\vec{r}) + \sum_{\substack{k \geq l \\ k, l \in \text{Types}}} \alpha_{kl} \sum_{\substack{i \in \{\text{Loci of Type } k\} \\ j \in \{\text{Loci of Type } l\}}} f(r_{ij}) + \chi \cdot \sum_{(i,j) \in \{\text{Loop Sites}\}} f(r_{ij}) + \sum_{d=3}^{500} \gamma(d) \sum_i f(r_{i,i+d})$$

To Be
Determined...

The Minimal Chromatin Model: Calibration

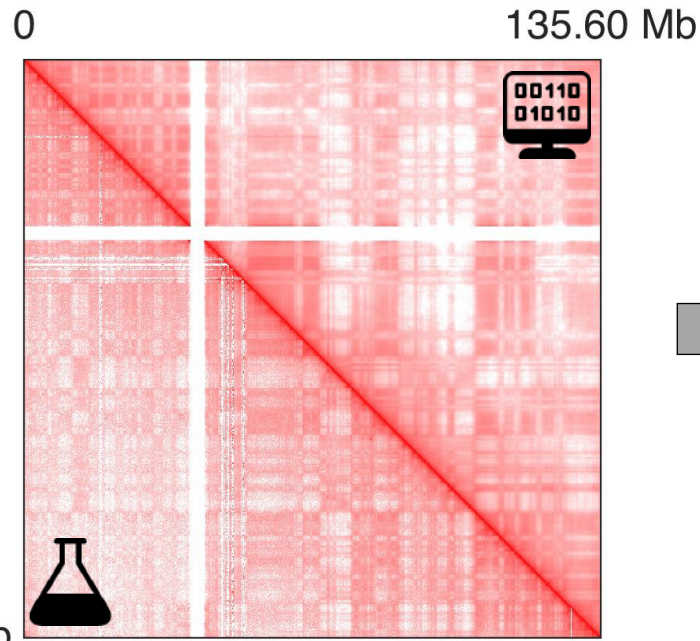
Human Chromosome 10 B-lymphoblastoid cells (GM12878)



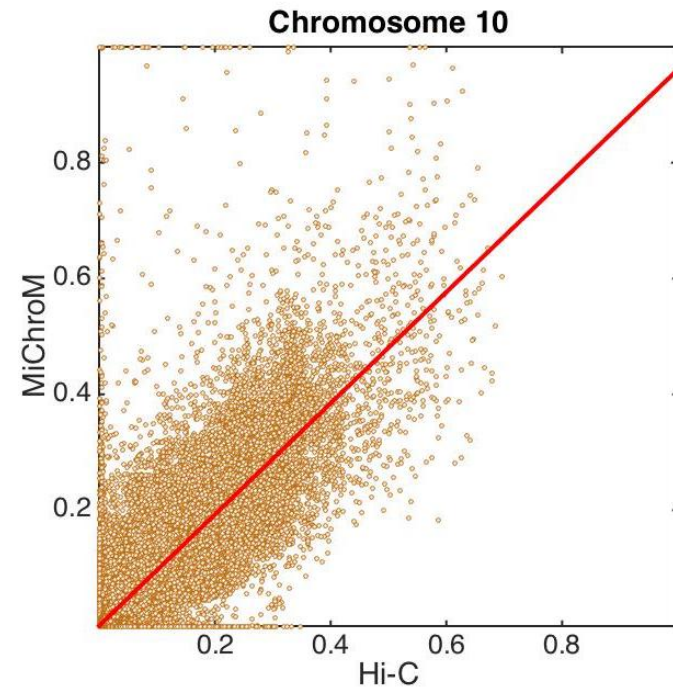
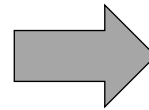
$$(\alpha_{kl}, \gamma(d), \chi)$$

The Minimal Chromatin Model: Quality Check

Human Chromosome 10 B-lymphoblastoid cells (GM12878)

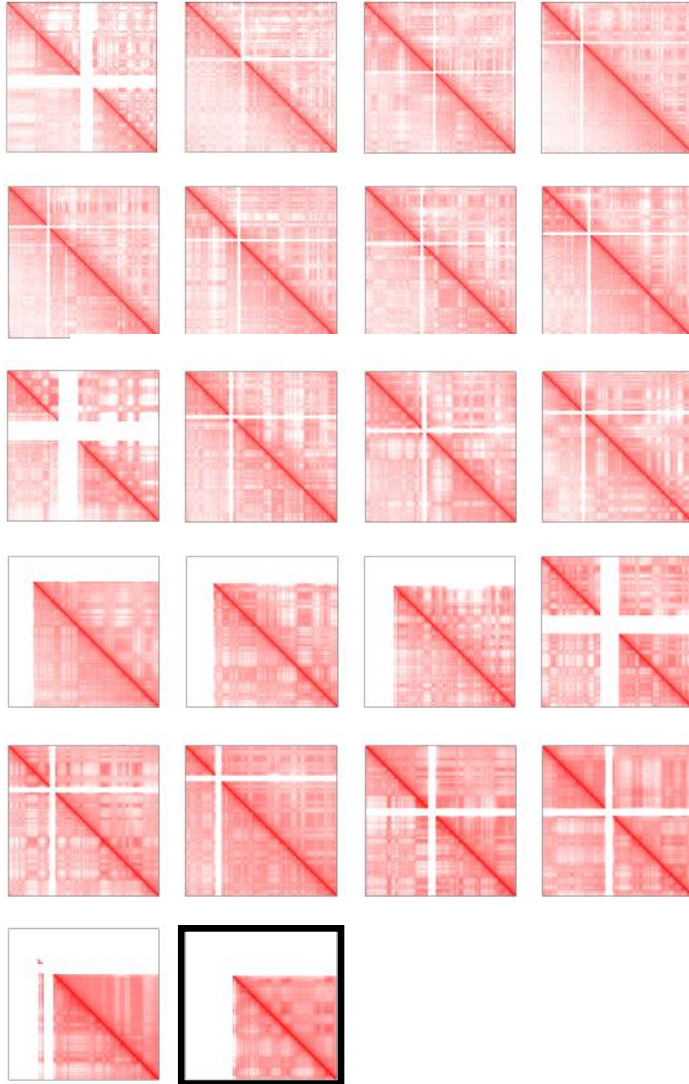


Pearson's Correlation 0.95



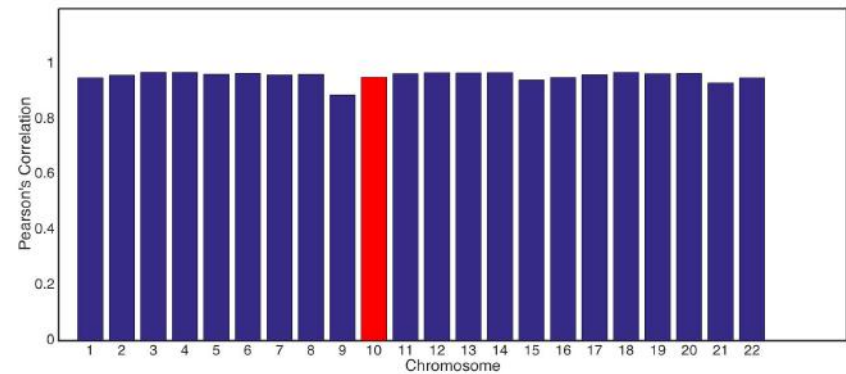
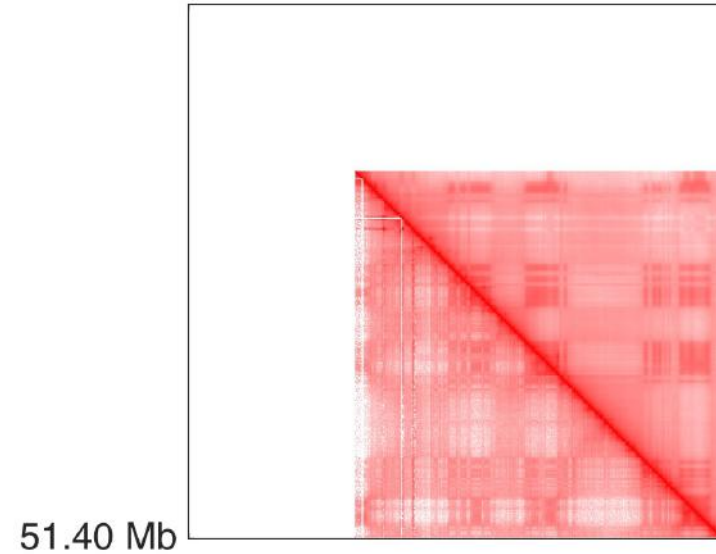
Slope 0.94
Intercept 0.0003

The Minimal Chromatin Model: Predictivity



Chromosome 22 (GM12878)

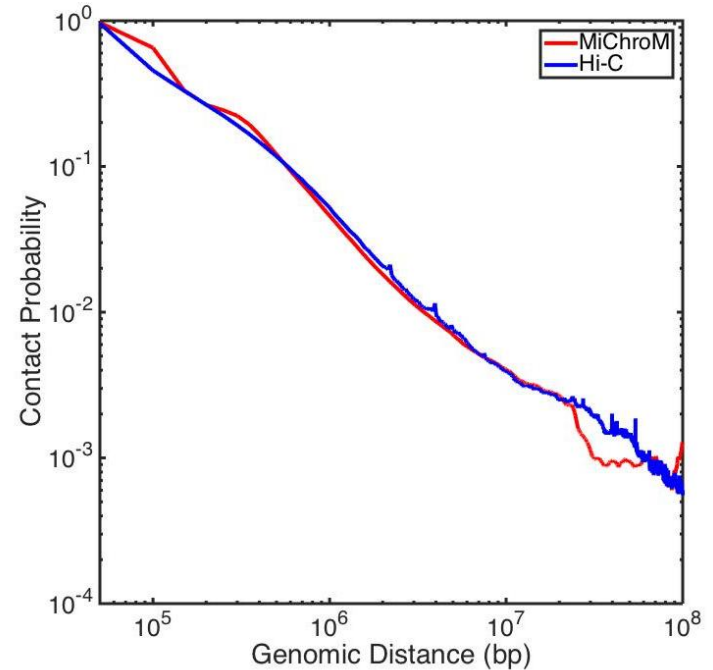
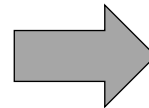
0 51.40 Mb



The Minimal Chromatin Model: Quality Check

Human Chromosome 10 B-lymphoblastoid cells (GM12878)

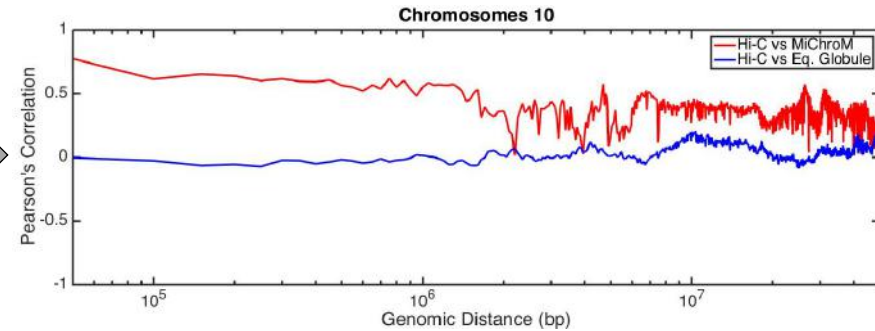
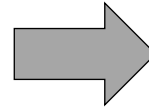
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The Minimal Chromatin Model: Quality Check

Human Chromosome 10 B-lymphoblastoid cells (GM12878)

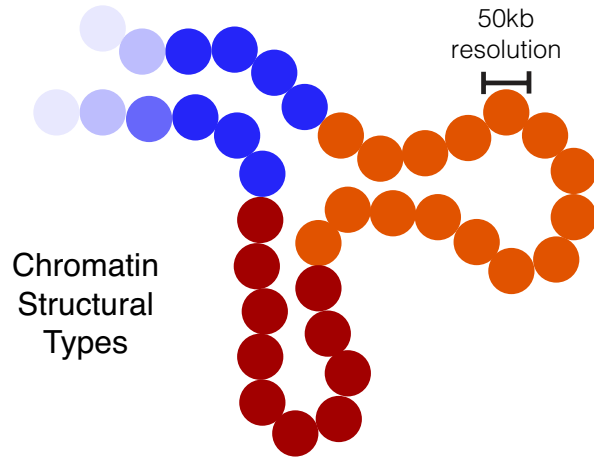
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135.60 Mb

A physical polymer model with discrete chromatin types captures compartmentalization

Minimal Chromatin Model (MiChroM)

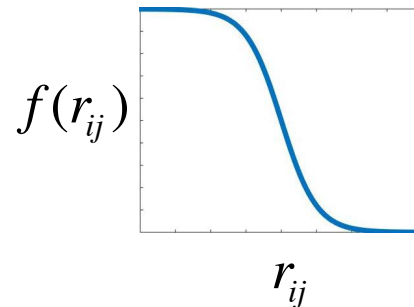
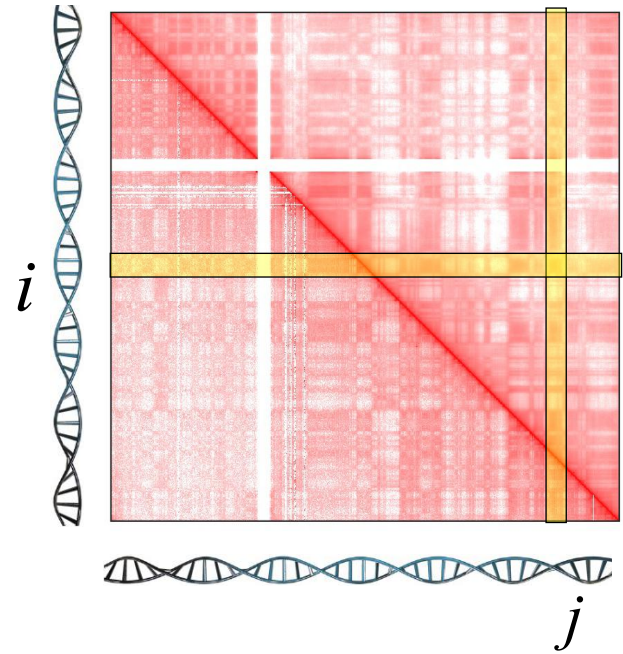


$$U_{MiChroM}(\vec{r}) = U_{HP}(\vec{r}) + \sum_{\substack{k \geq l \\ k, l \in \text{Types}}} \alpha_{kl} \sum_{\substack{i \in \{\text{Loci of Type } k\} \\ j \in \{\text{Loci of Type } l\}}} f(r_{ij}) + \sum_{d=3}^{500} \gamma(d) \sum_i f(r_{i,i+d})$$

Polymer Potential

Type-Type Interactions

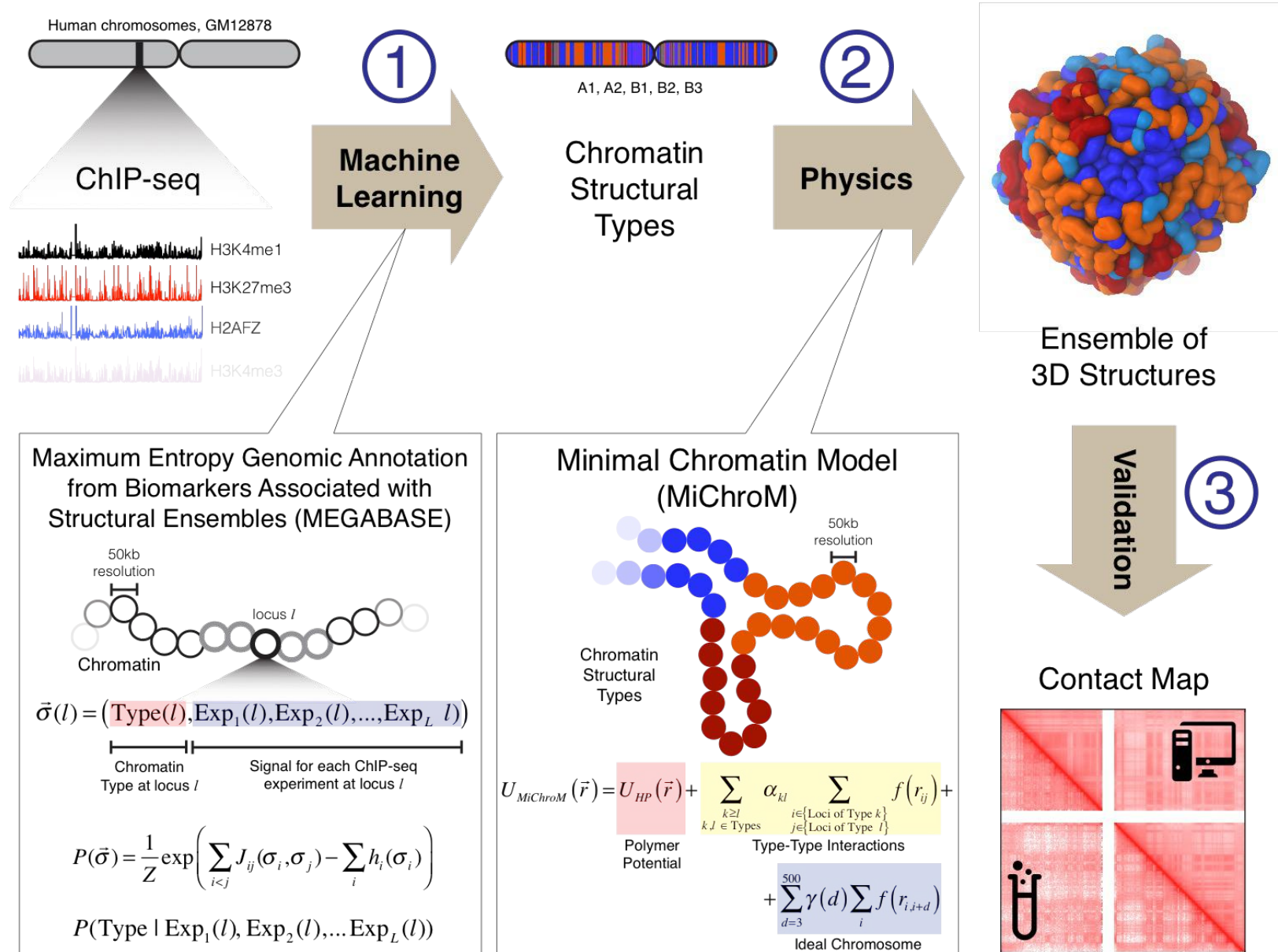
Ideal Chromosome



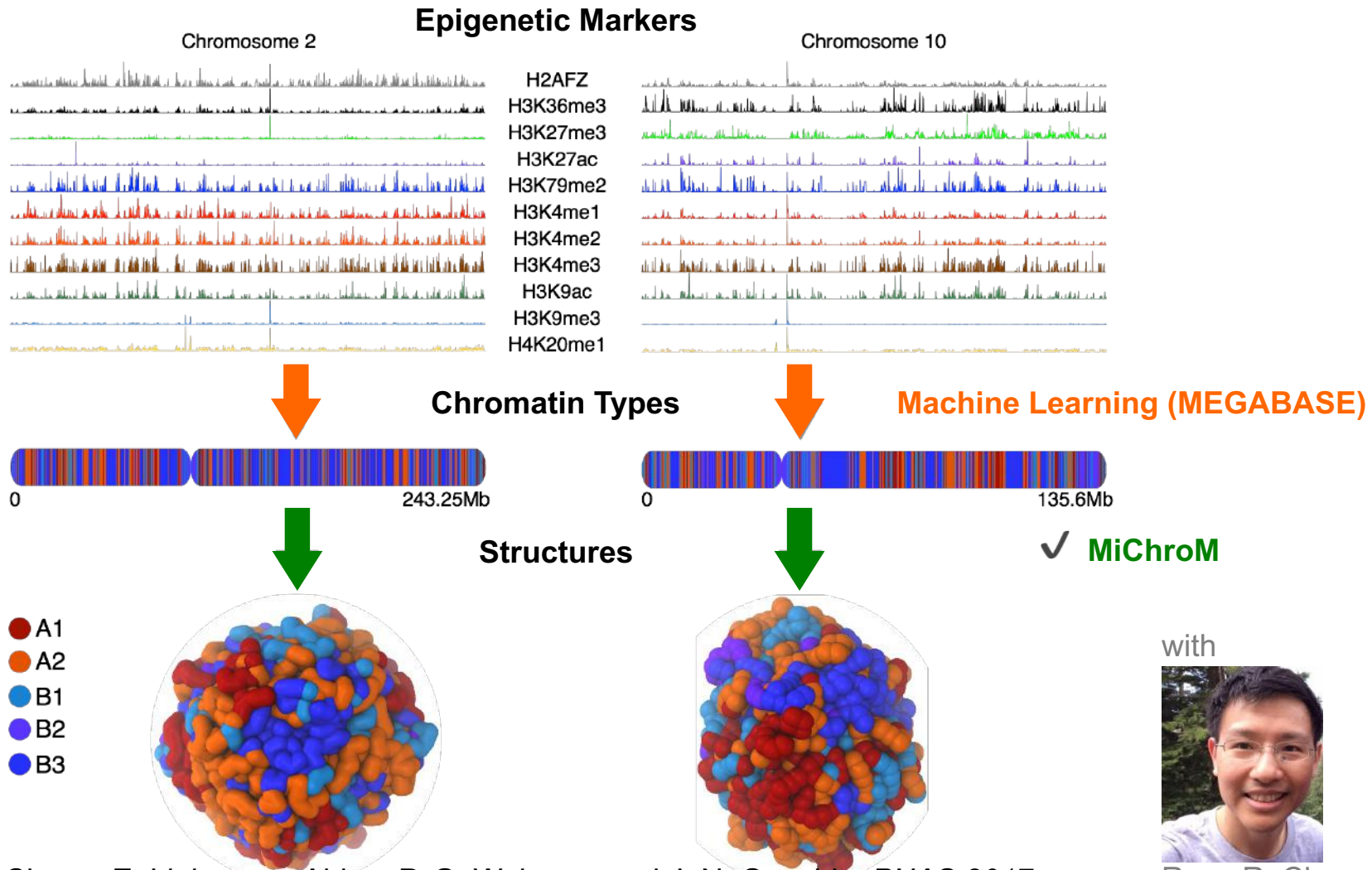
A1, A2, B1, B2, B3, B4

Di Pierro, Zhang, Lieberman Aiden, Wolynes, Onuchic, *PNAS* 2016

Schematic Illustration of Computational Pipeline



Where Is the Blueprint? From Epigenetics To Chromatin Types (MEGABASE)



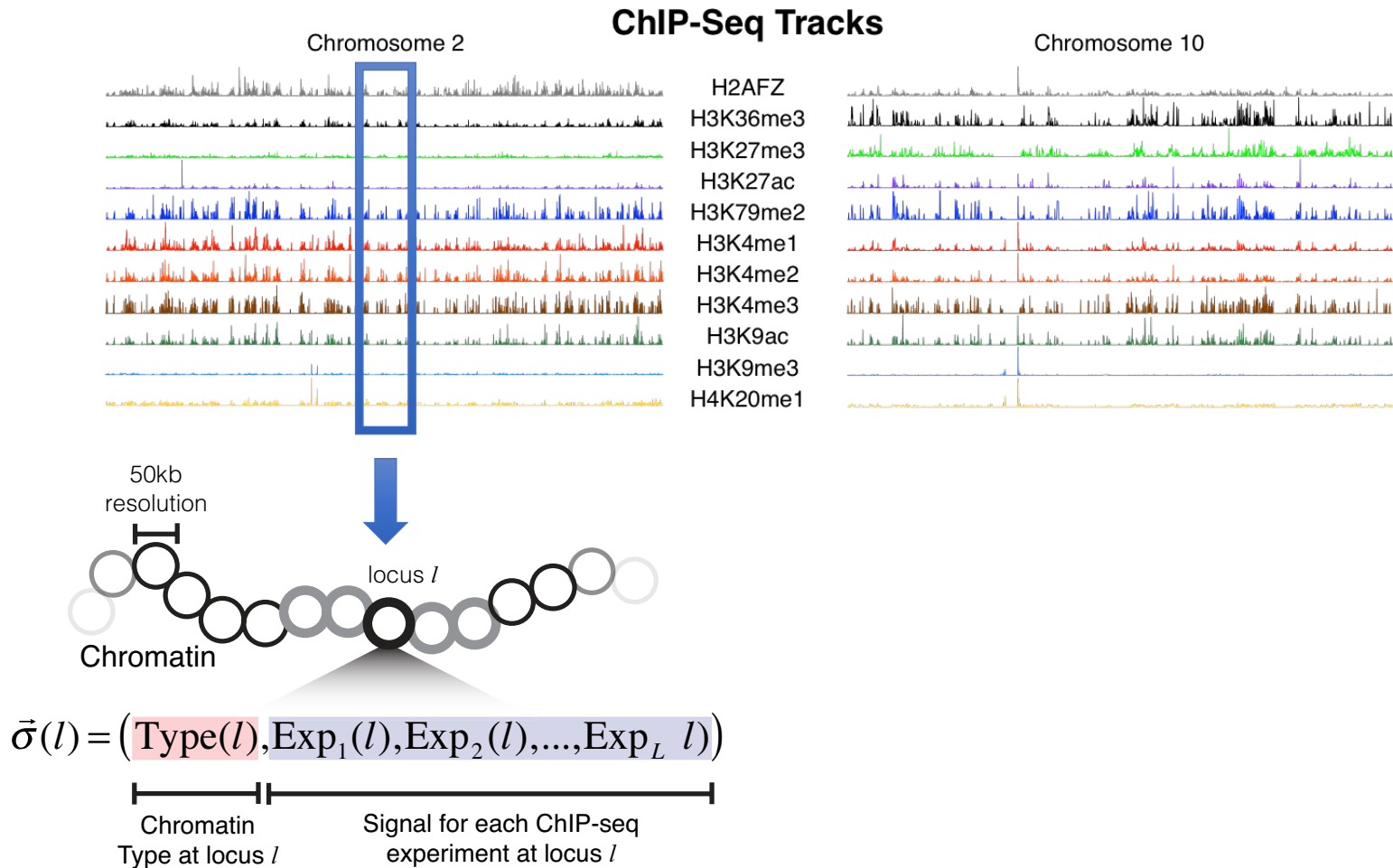
M.D.P. , R.R. Cheng, E. Lieberman Aiden, P. G. Wolynes, and J. N. Onuchic, *PNAS* 2017

with
Ryan R. Cheng

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BIOLOGICAL PHYSICS



De Novo Structure Prediction of Human Chromosomes



$$P(\vec{\sigma}) = \frac{1}{Z} \exp \left(\sum_{i < j} J_{ij}(\sigma_i, \sigma_j) - \sum_i h_i(\sigma_i) \right)$$

Amino acid coevolution in proteins

Statistical couplings
between distal residues
generally weak

Since 1998

Strong statistical
couplings between
coevolving residues
that are in contact



RPC1_BP434 VKSKRIQLGLNQAELAQKVGTTQQSIEQLENGKT-KRPRFLPELASALGVSVDWL
H3Z4N6_STAEP IKSAMKEQDMSLSELARRVGVAKSAVSRYLNLTRFPLNRTEDFAKALSISTEYL
C2X6S5_BACCE IKKLLKERALSMRQLGILLTNIDPATVSRIINGKQPPKQKHLQKFAECLQVPPQLL



Sequence probability distribution depends on pairwise and single site parameters

```

AAKAP[S]ARGHATKPRAP[K]DAQHEAA
AAKAP[S]ARGHATKPRAP[K]DAQHEAA
SAKEK[N]EKMKIIVKN-L[D]KGGKSGS
TELET[K]FTLDQVKDQLE[E]EQGKKRSS
LAPSG[N]TALATAKKKE[L]TDRTDDPV
TELET[K]FTLDQVKPRAP[K]DGGKRSS
    
```

$i = 6$

$j = 17$

$$f_{6,17}(S_6, P_{17}) = 2/6$$

Input Data :

$$P_i(A_i) \equiv f_i(A_i)$$

$$P_{ij}(A_i, A_j) \equiv f_{ij}(A_i, A_j)$$

Using maximum entropy principle to model the joint probability distribution

$$C_{ij}(A, B) = f_{ij}(A, B) - f_i(A)f_j(B)$$

$$P(A_1, \dots, A_L) = \frac{1}{Z} \exp\left\{ \sum_{i < j} e_{ij}(A_i, A_j) + \sum_i h_i(A_i) \right\}$$



Faruck Morcos Martin Weight

$$e_{ij}(A, B) \approx -(C^{-1})_{ij}(A, B)$$

Direct Information Metric

Direct Probabilities are defined as:

$$P_{ij}^{(dir)}(A, B) = \frac{1}{Z} \exp\{e_{ij}(A, B) + \hat{h}_i(A) + \hat{h}_i(B)\}$$

The probabilities for residue couplets are ranked using Direct Information

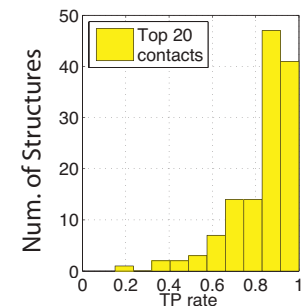
$$DI_{ij} = \sum_{A, B=1}^q P_{ij}^{(dir)}(A, B) \ln \frac{P_{ij}^{(dir)}(A, B)}{f_i(A) f_j(B)}$$

True positive contacts (<8Å) are evaluated from top couplets

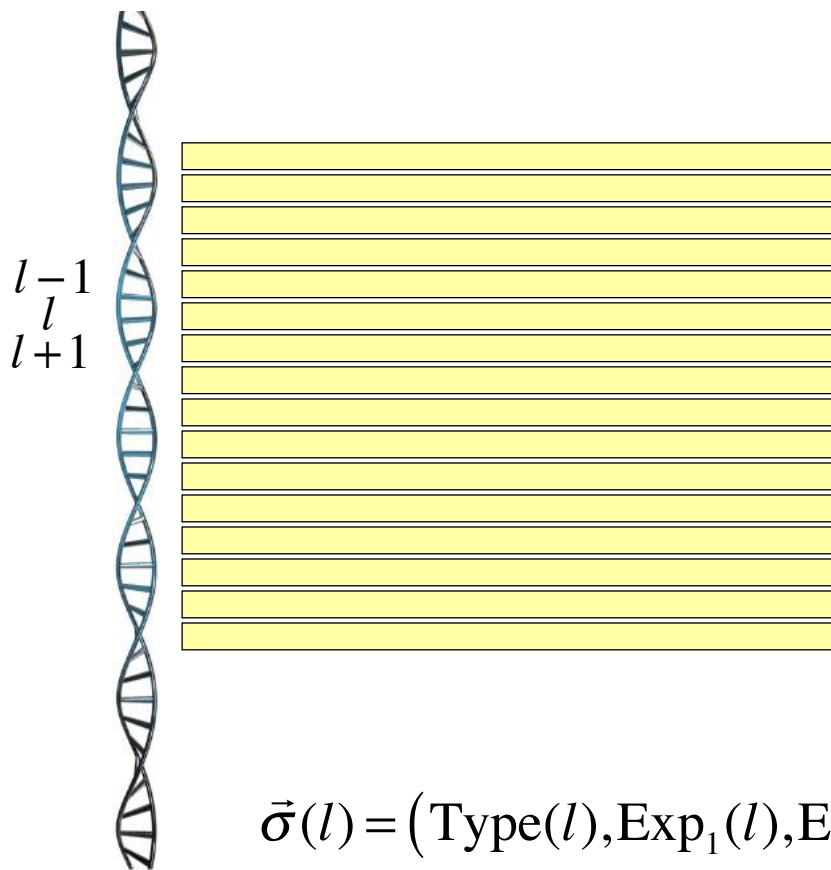
Select top couplets



$|i-j| > 4$



True Positive (TP) rates

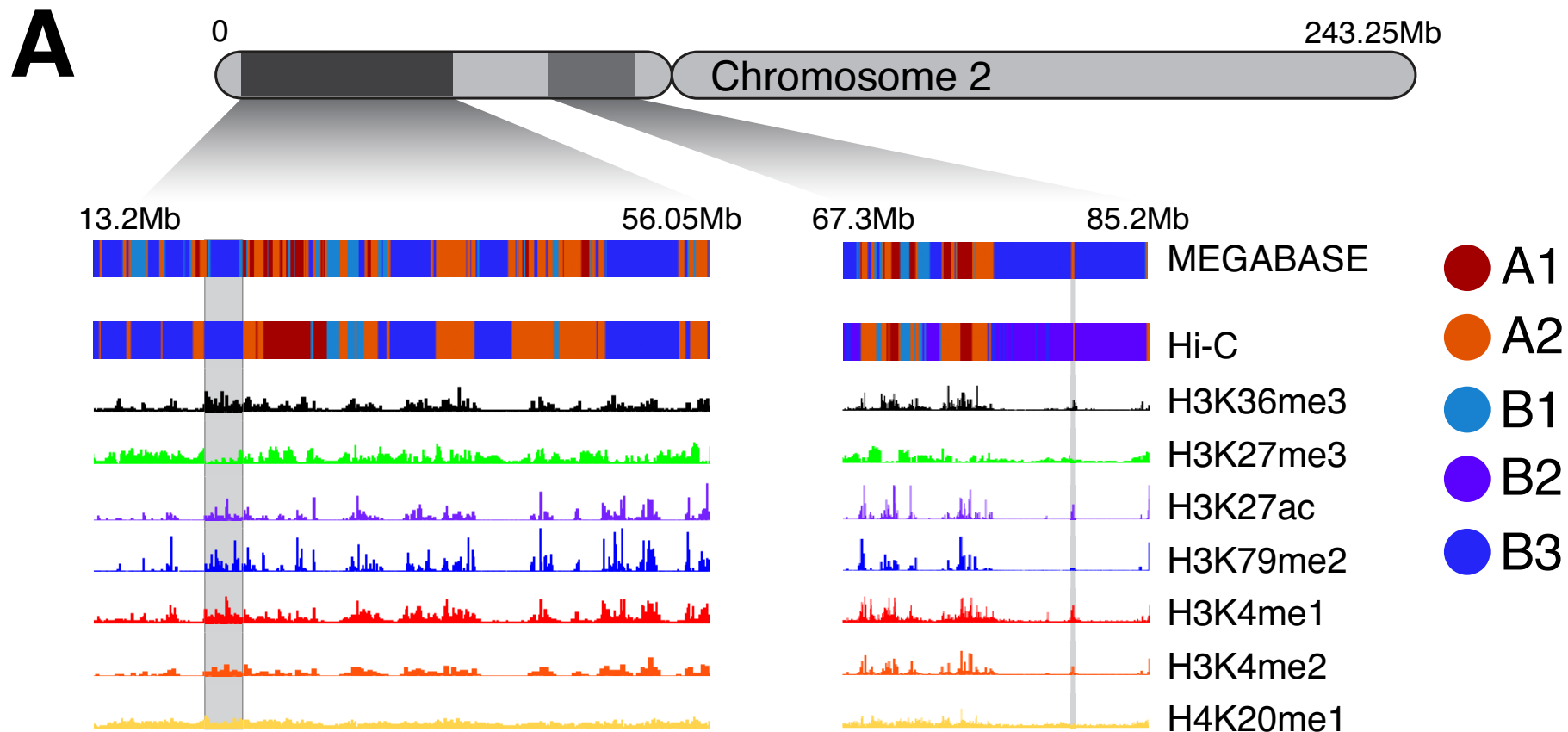


$$P(\vec{\sigma}) = \frac{1}{Z} \exp(-H(\vec{\sigma}))$$

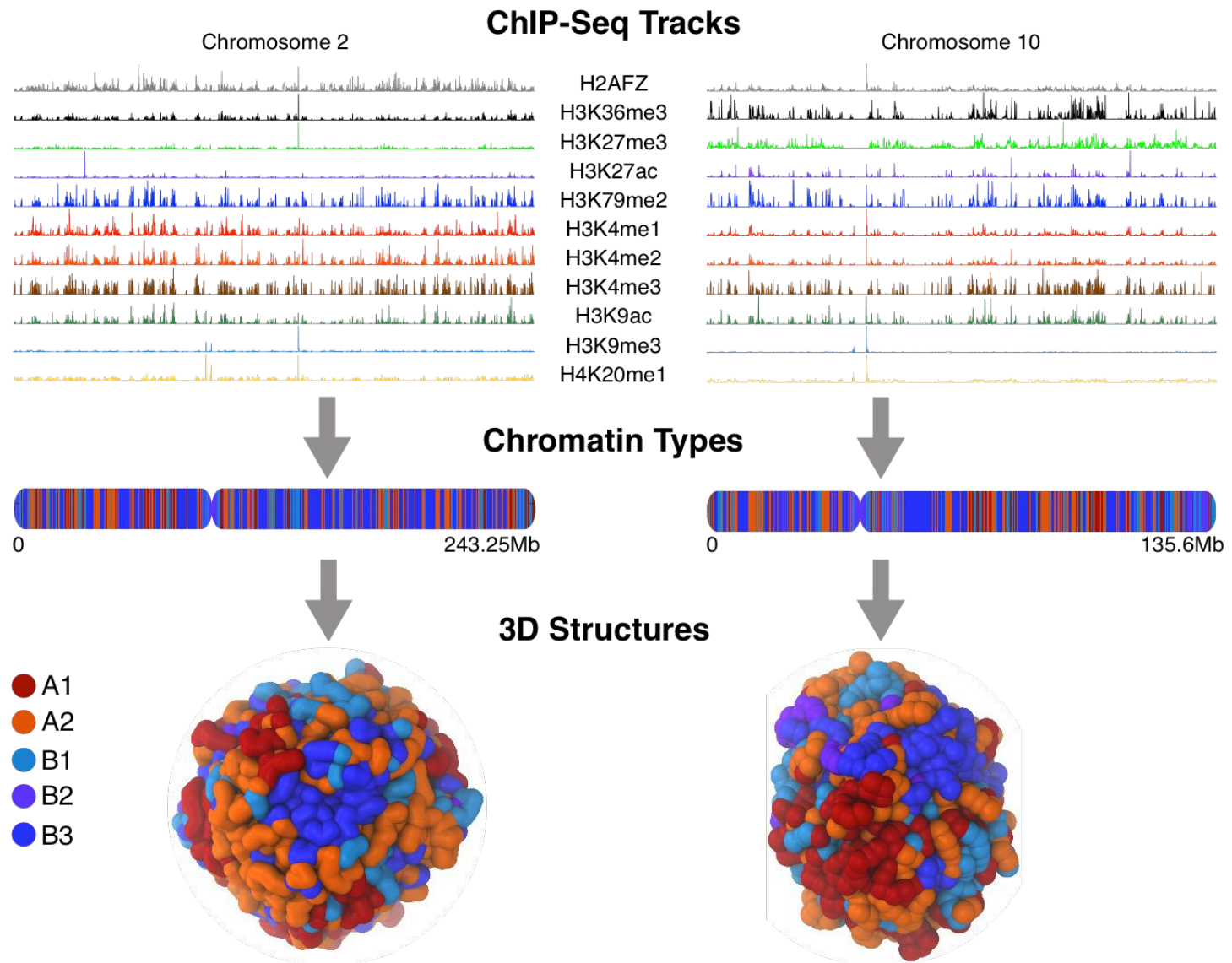
$$H(\vec{\sigma}) = -\sum_{i < j} J_{ij}(\sigma_i, \sigma_j) - \sum_i h_i(\sigma_i)$$

Training set: odd-numbered chromosomes

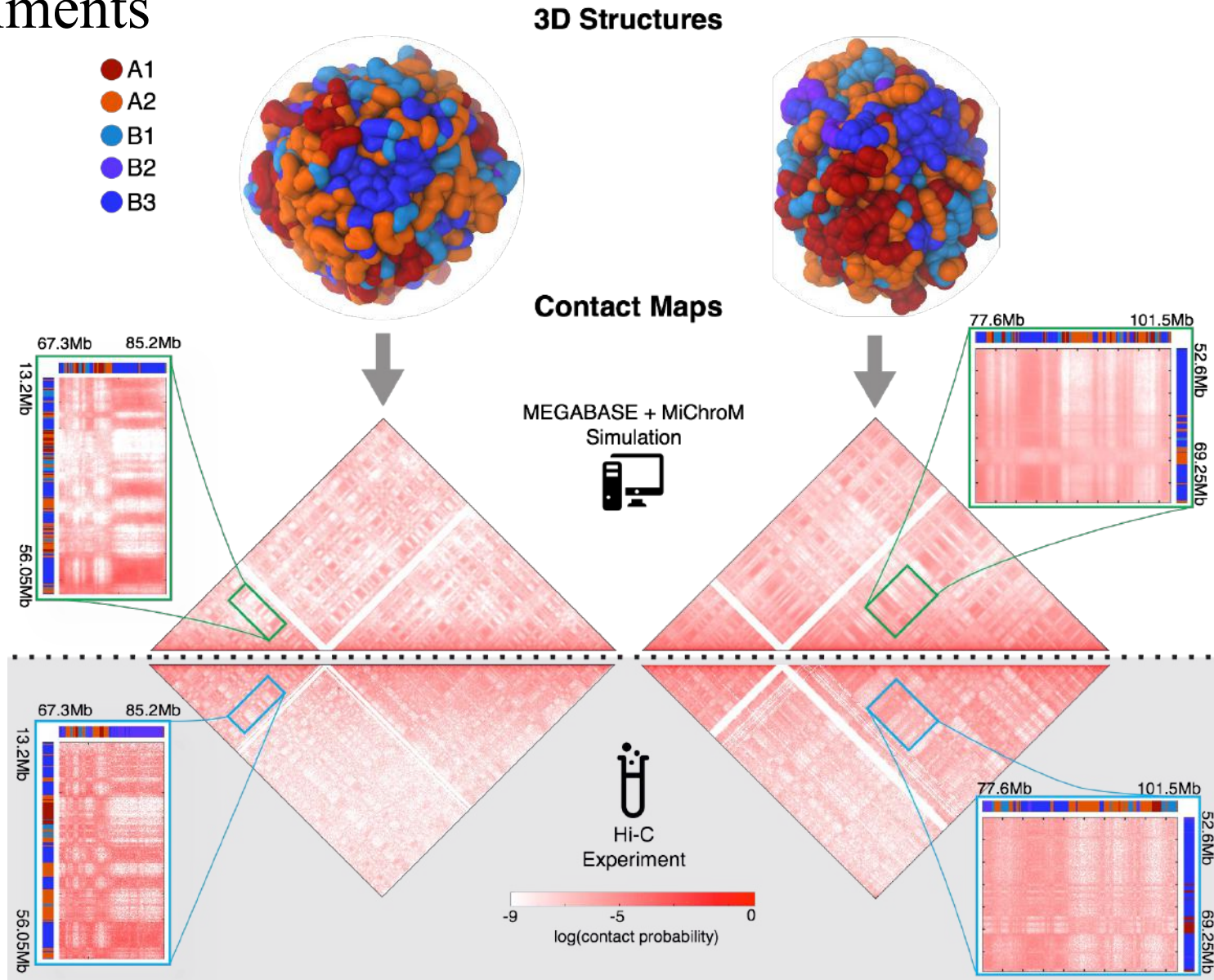
Test set: even-numbered chromosomes



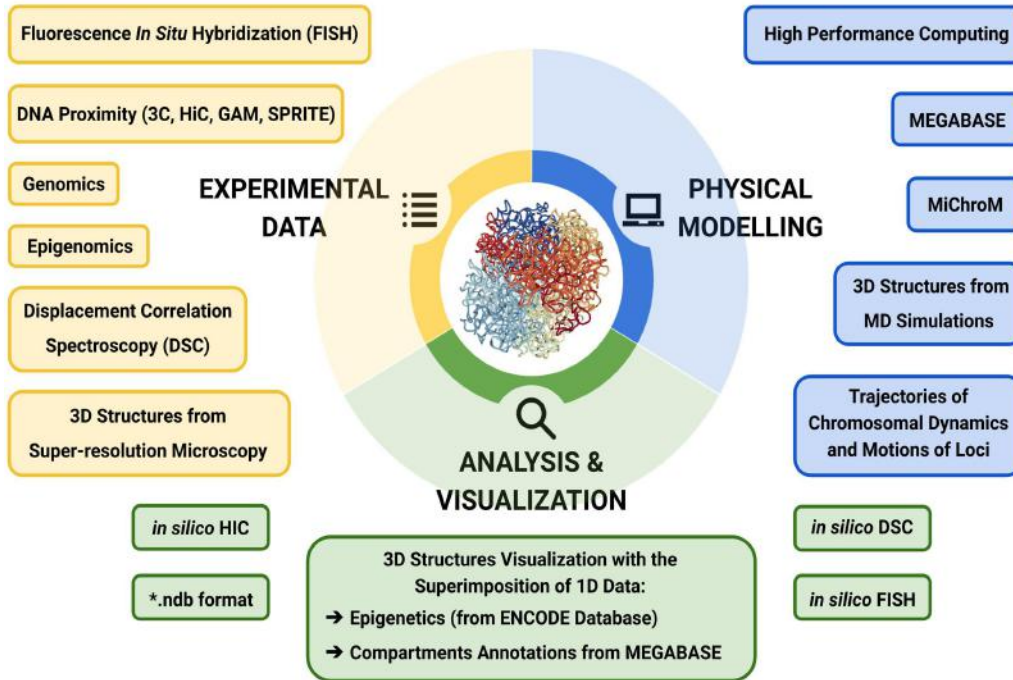
De Novo Structure Prediction of Human Chromosomes



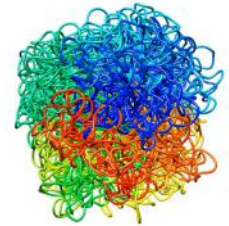
Comparison of simulated structures with DNA-DNA Ligation Experiments



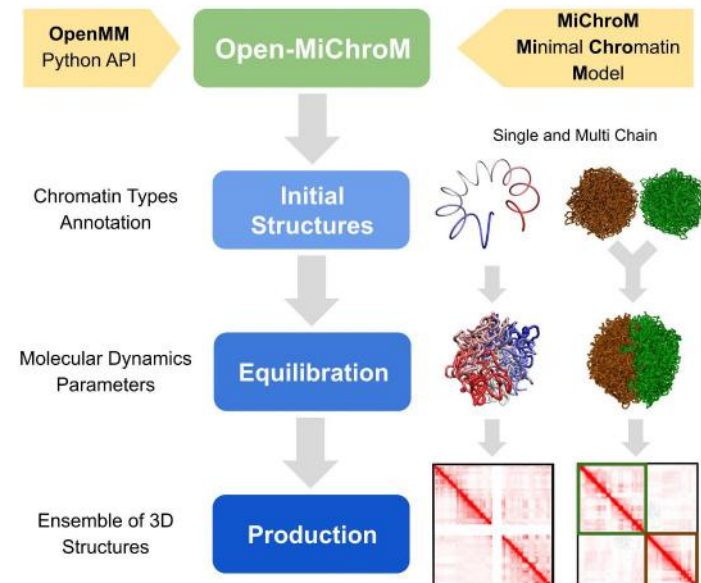
The Nucleome Data Bank



3D ensemble of Chromosomal Structures



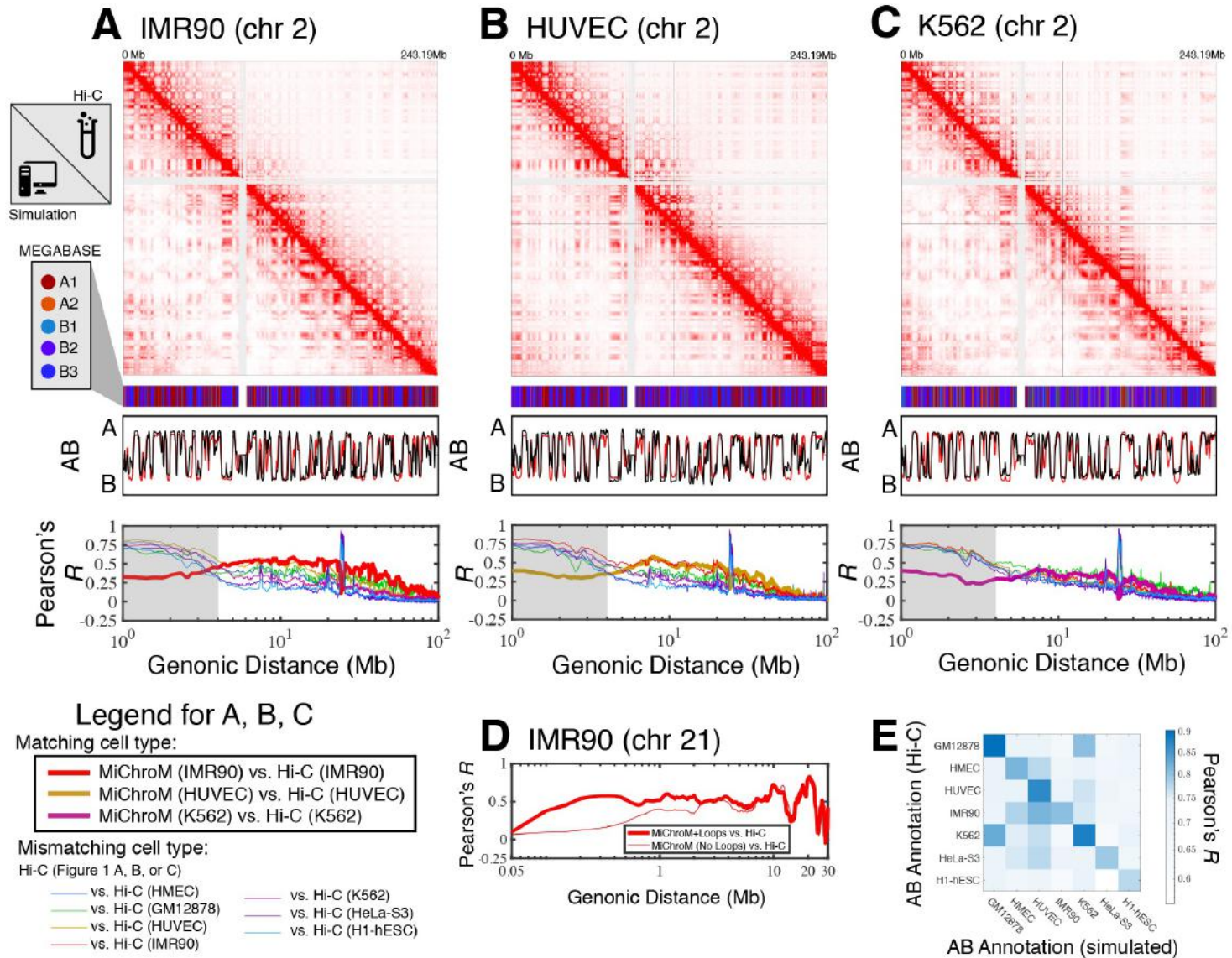
Open-MiChroM



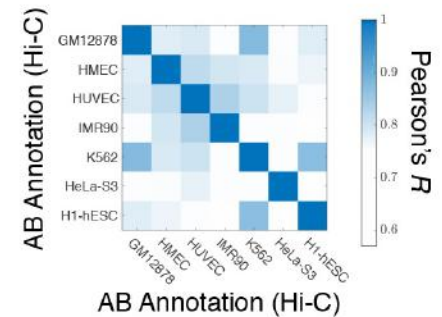
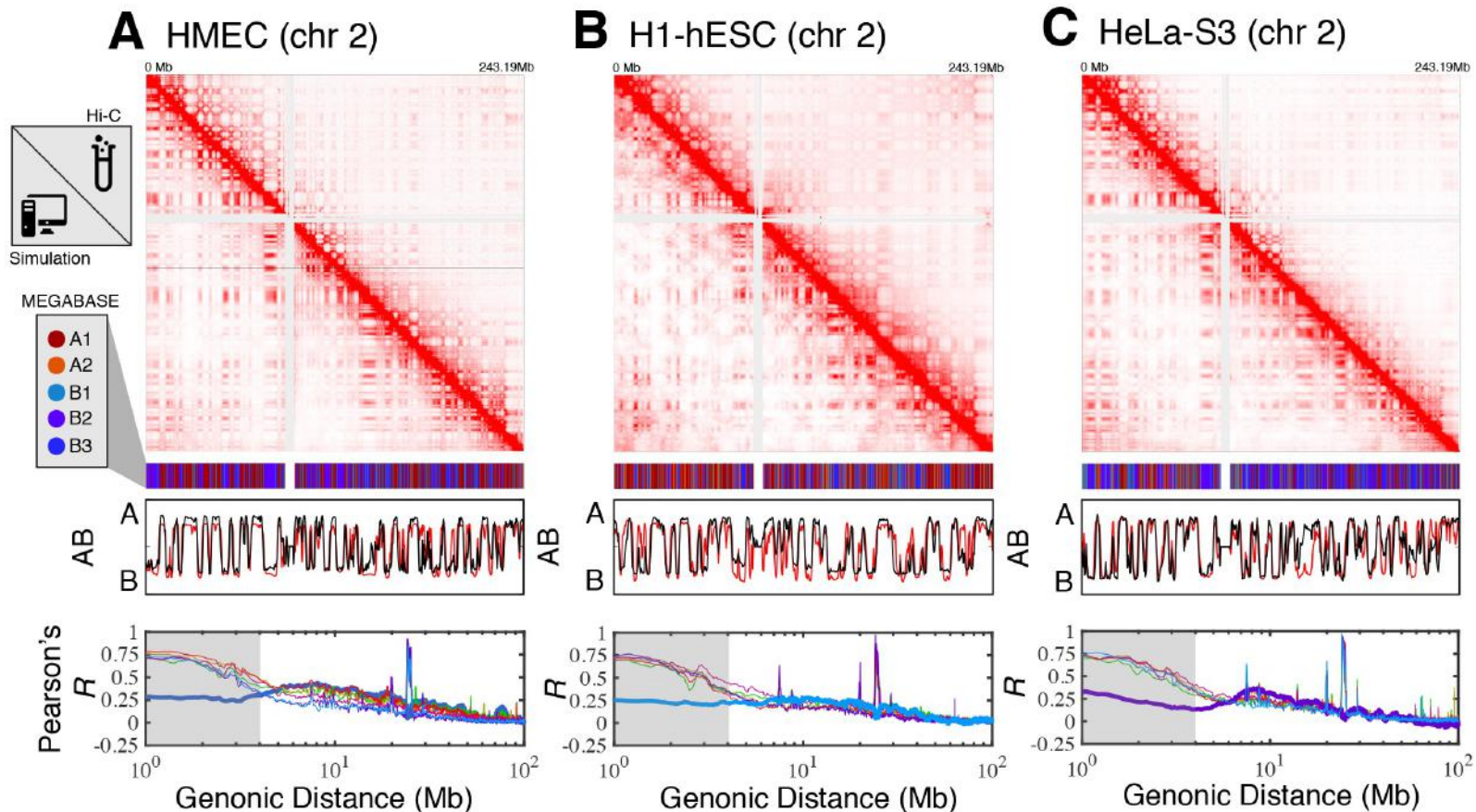
Nucleosome Data Bank

A web platform to simulate and browse the three-dimensional architecture of genomes

Prediction of chromosome structures for differentiated cell lines and for immortalized leukemia cells.

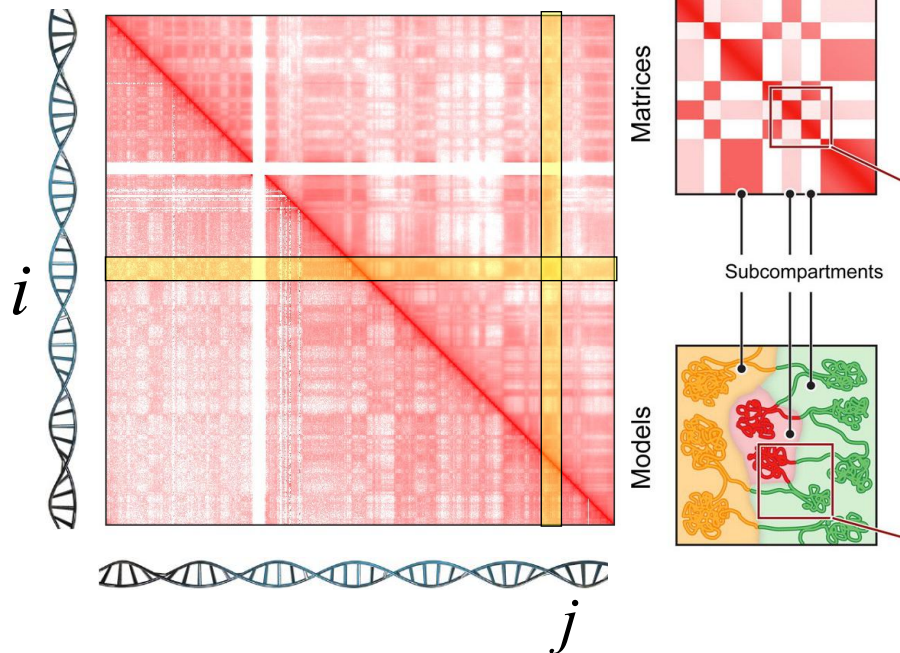


Prediction of chromosome structures for HMEC, H1-hESC, and HeLa-S3.



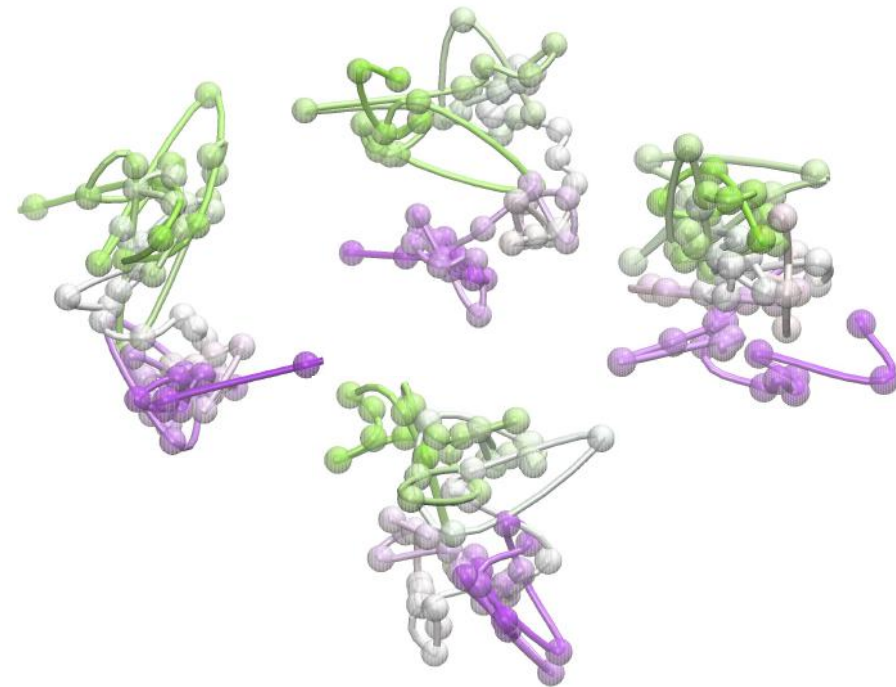
Chromosome Structural Heterogeneity: No two structures are identical

DNA-DNA ligation map
(population averaged)



Rao & Huntley et al, Cell 2014

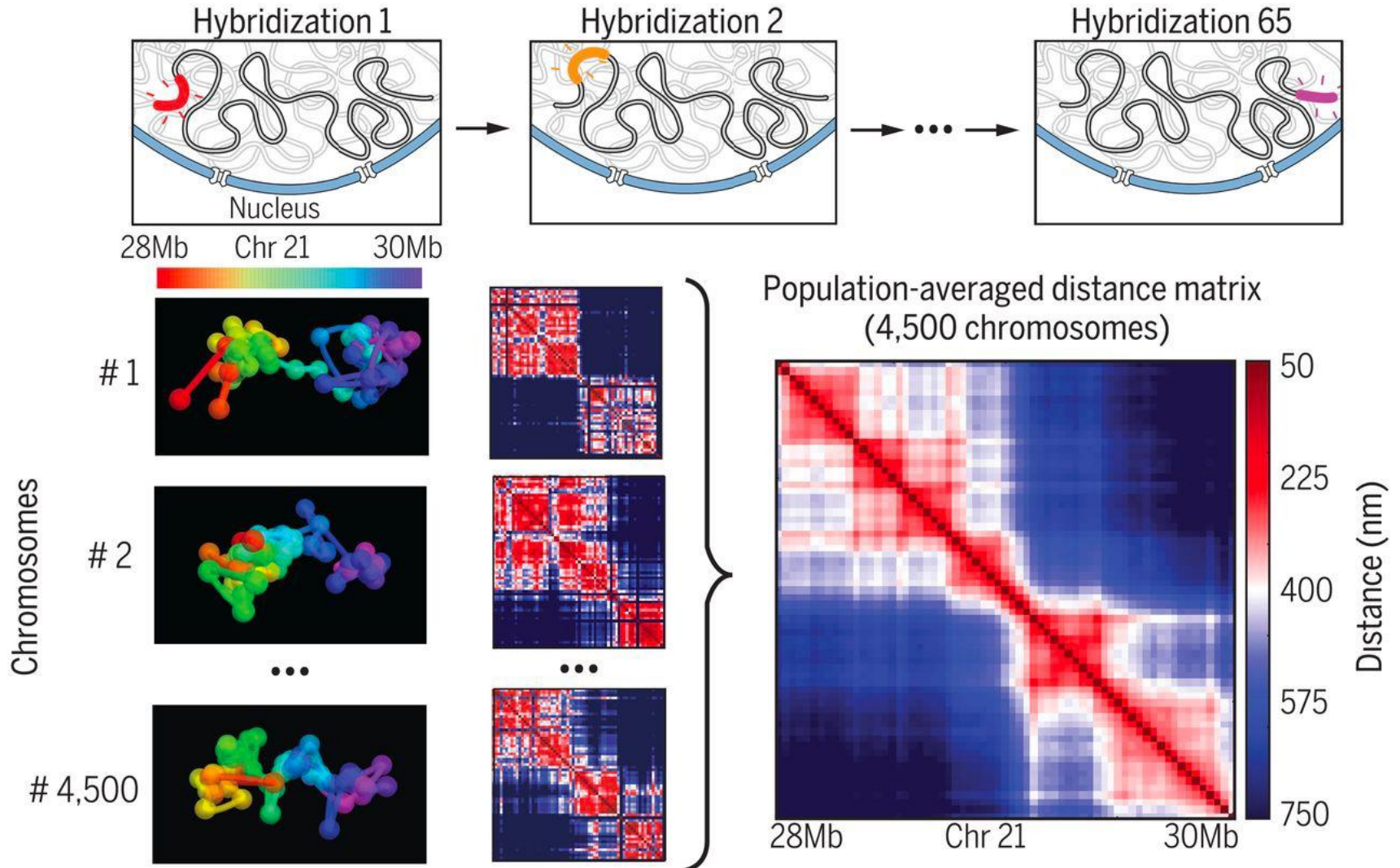
3D structures of chromatin
(DNA tracing/microscopy)



Bintu et al, Science 2018

Super-resolution imaging of chromatin

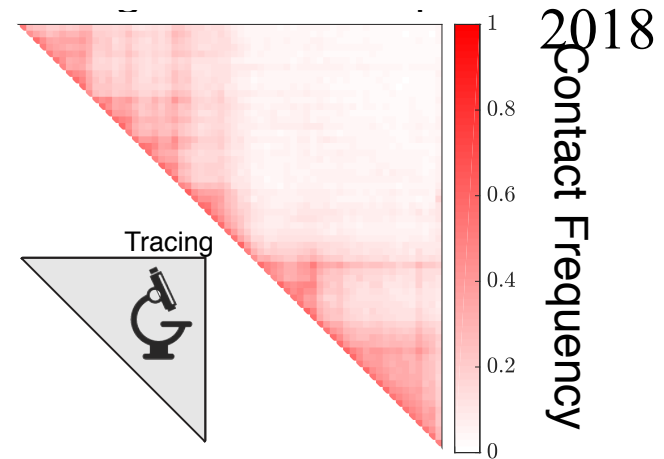
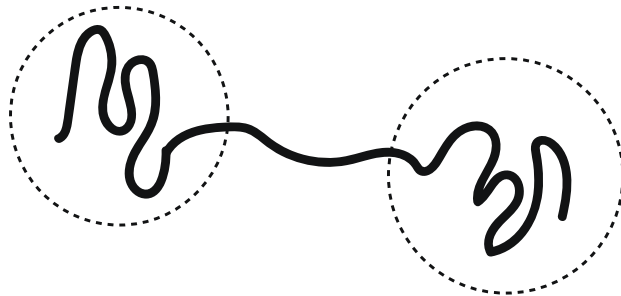
B. Bintu and L. Mateo..... A. Boettiger, Xiaowei Zhuang, *Science*



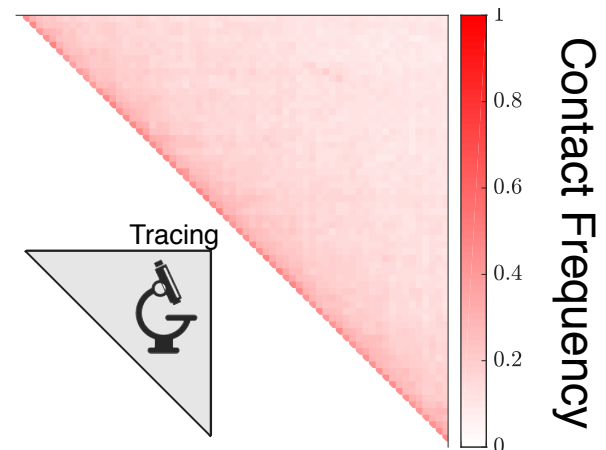
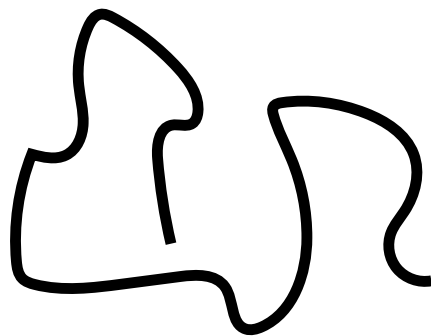
Super-resolution imaging of chromatin

B. Bintu and L. Mateo..... A. Boettiger, Xiaowei Zhuang, *Science*

Loop domains form globular lobes at the head and tail of Segment 1



Segment 1: chr21 29.37-31.32 Mb

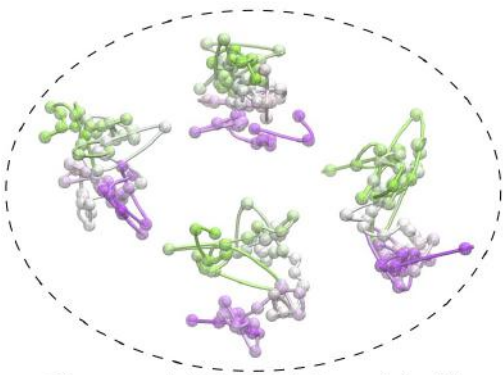


Segment 2: chr21 20.0-21.9 Mb

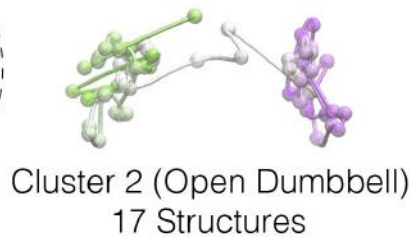
ANALYSIS OF CHROMATIN STRUCTURES REVEAL STRUCTURAL TRANSITIONS: OPEN VS. CLOSED

Experimentally Traced Structures (Bintu et al *Science* 2018)
IMR90 chromosome 21: 29.37-31.32Mb

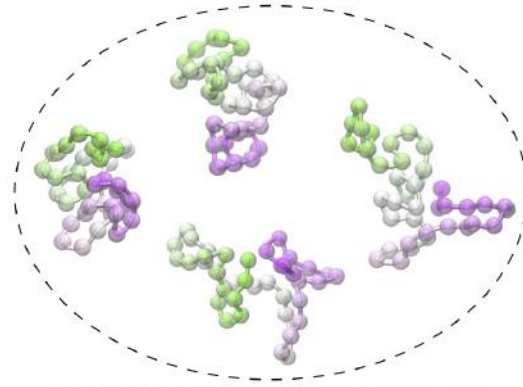
Simulated Structures (MiChroM)
IMR90 chromosome 21: 29.37-31.32Mb



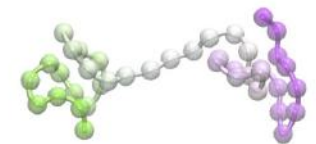
Cluster 1 (Closed Dumbbell)
912 Structures



Cluster 2 (Open Dumbbell)
17 Structures



Cluster 1 (Closed Dumbbell)
6275 Structures



Cluster 2 (Open Dumbbell)
125 Structures

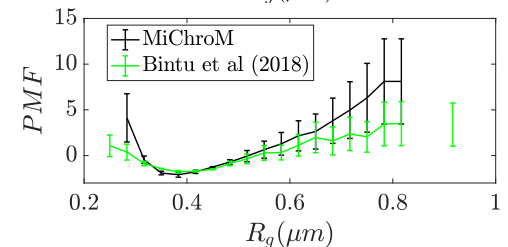
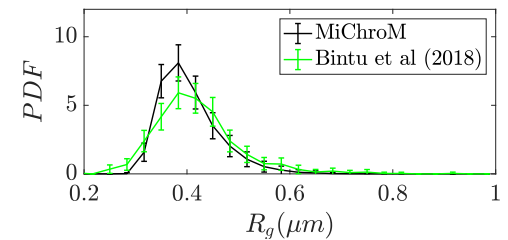
Structural similarity order parameter:

$$Q_{AB} = \frac{1}{N} \sum_{i,j} \exp\left(-\frac{(r_{ij}^A - r_{ij}^B)^2}{2\delta^2}\right)$$

$$\delta = 0.165\mu\text{m}$$

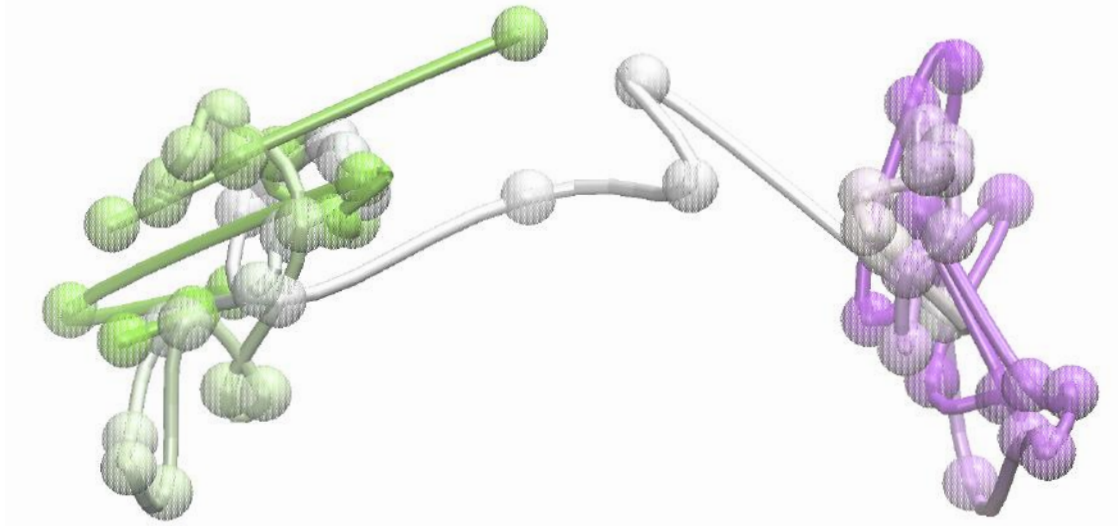
Free energy difference between open and closed structures (experiment & simulation):

$$\log(N_{\text{closed}} / N_{\text{open}}) = E_{\text{open}} - E_{\text{closed}} \sim 4k_B T$$



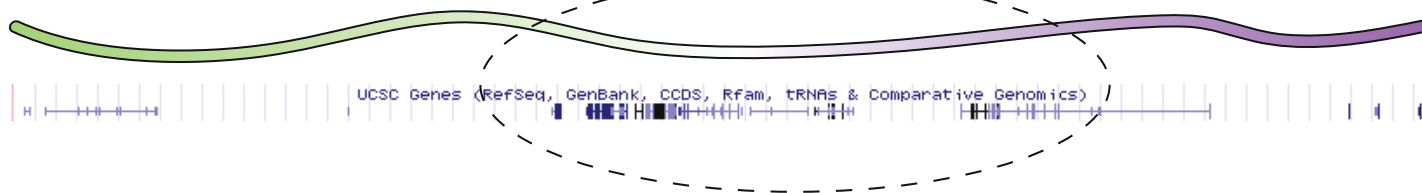
A relationship between gene expression and chromosome structure?

Genes primarily located in linker region



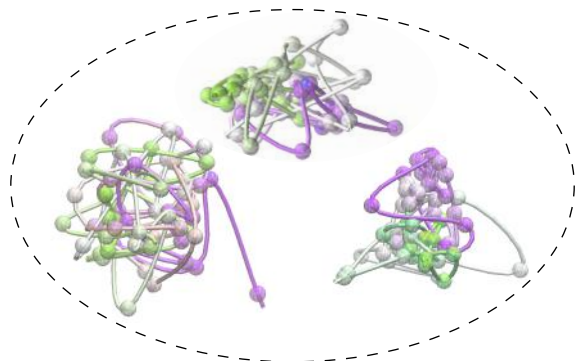
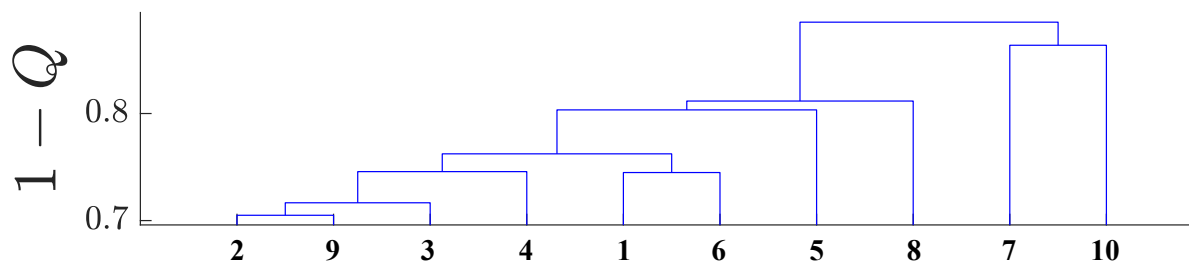
29.37Mb

31.32Mb

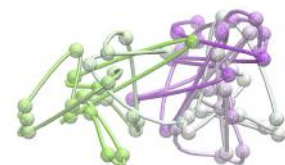


Analysis of Experimental Traced Chromatin Structures of Segment 2

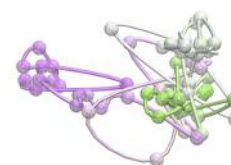
A Hierarchical Clustering of Traced Structures of IMR90 Segment 2 (chr21 20.0-21.9 Mb)



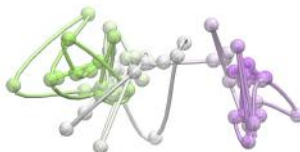
Cluster 1 (711 structures)



Cluster 6 (13 structures)



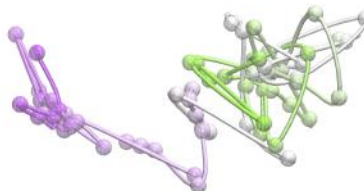
Cluster 3 (11 structures)



Cluster 5 (8 structures)

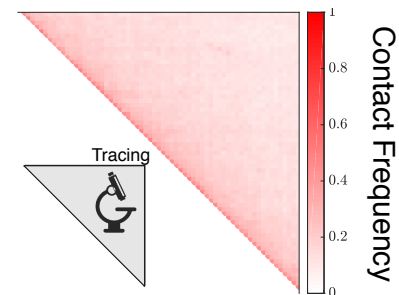
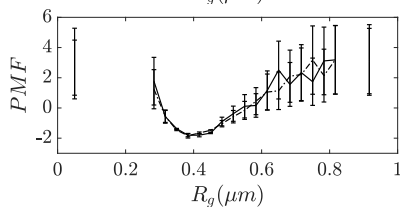
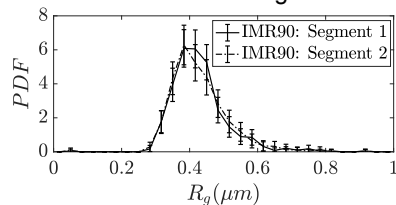


Cluster 8 (2 structures)
Artifact



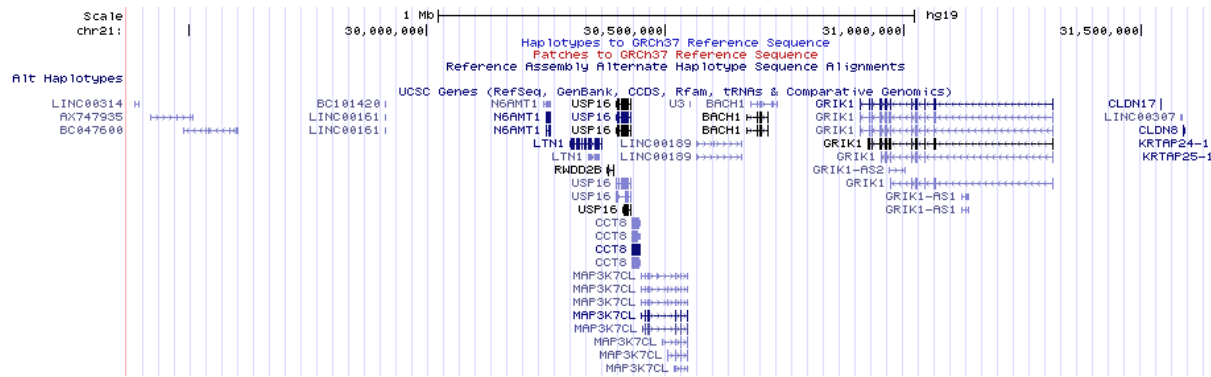
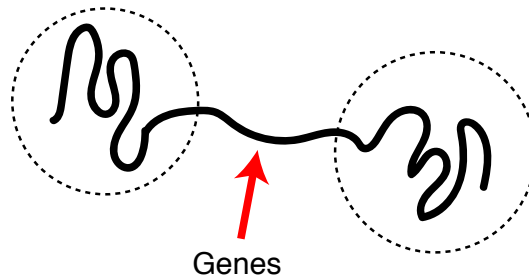
Cluster 7 (3 structures)

B Distribution of R_g and Potential of Mean Force for Segment 1

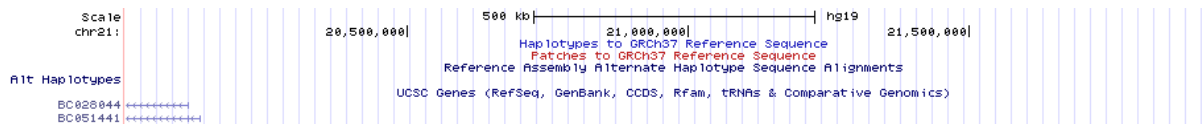
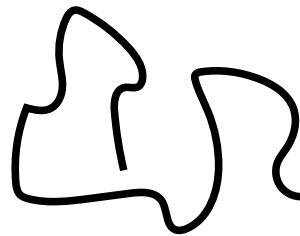


A relationship between gene expression and chromosome structure?

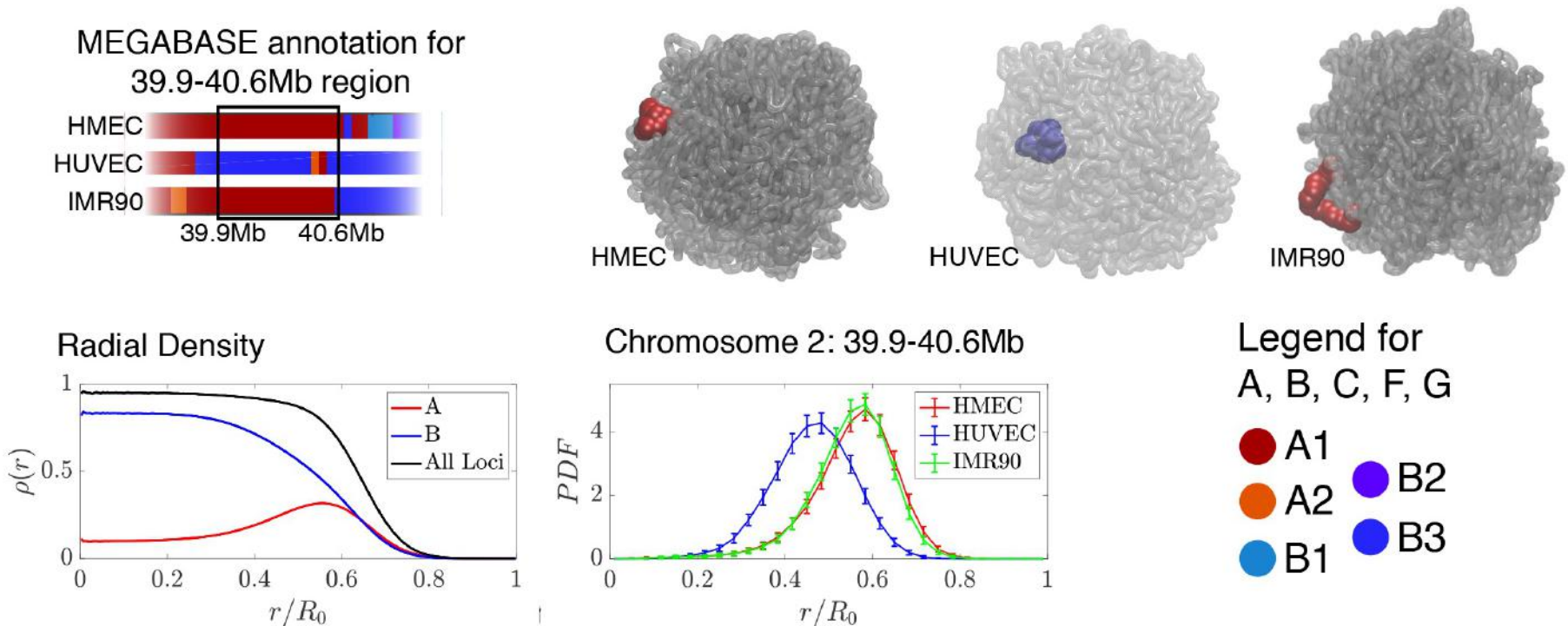
A Segment 1 (29.37-31.32Mb)
Loop domains form globular lobes at the head and tail of Segment 1



B Segment 2 (20.0-21.9Mb)
No CTCF-mediated loops
Random coil-like structures

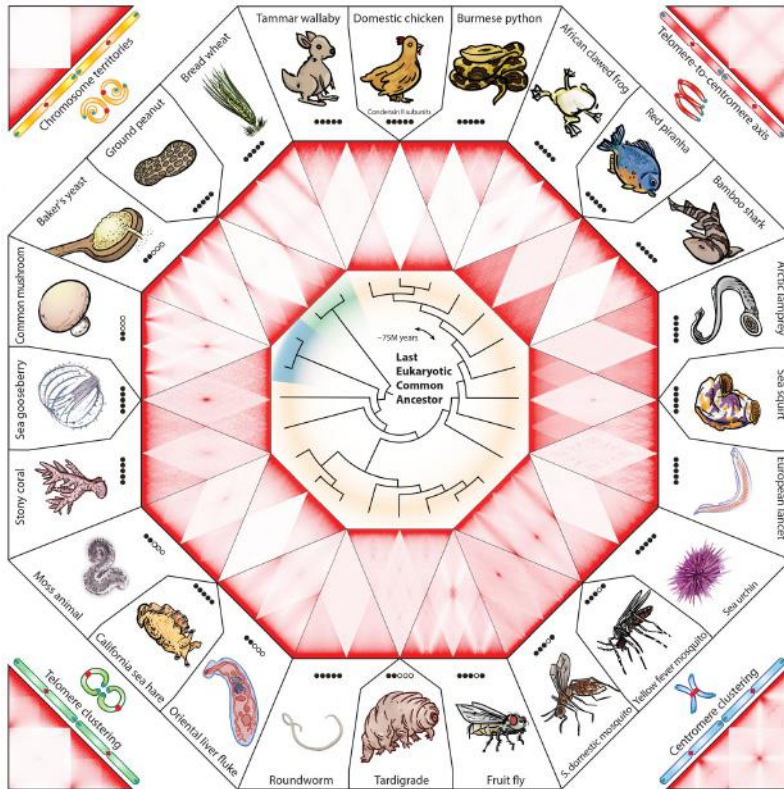


A-compartment chromatin moves to territorial surface



Consistent with experimental observations: Nagano, T., et al., Single-cell Hi-C reveals cell-to-cell variability in chromosome structure. Nature, 2013. 502(7469): p. 59-64.

CHROMOSOME ARCHITECTURE ACROSS EVOLUTION CORRELATES WITH CONDENSIN II ACTIVITY

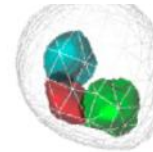
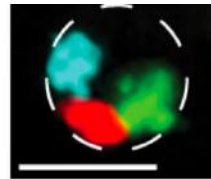


Hoencamp et al., *Science* (2021)

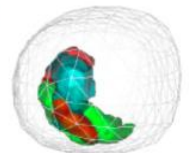
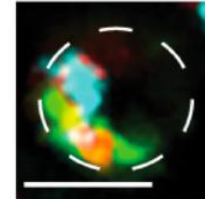
Type I architecture	Type II architecture
Centromere clustering ➤	Chromosome territories ➤
Telomere clustering ➤	
Telo-to-centromere axis ➤	All condensin II subunits present ➤
One or more condensin II subunits absent ➤	

Condensin II (loop-extruding enzyme) confers longitudinal rigidity to chromosomes and defines **chromosome territories** (Houlard et al., *Nat. Cell Biol.* 2015, Bauer et al. *PLoS Genet.* 2012; Rosin et al. *PLoS Genet.* 2018, ...)

Wild Type

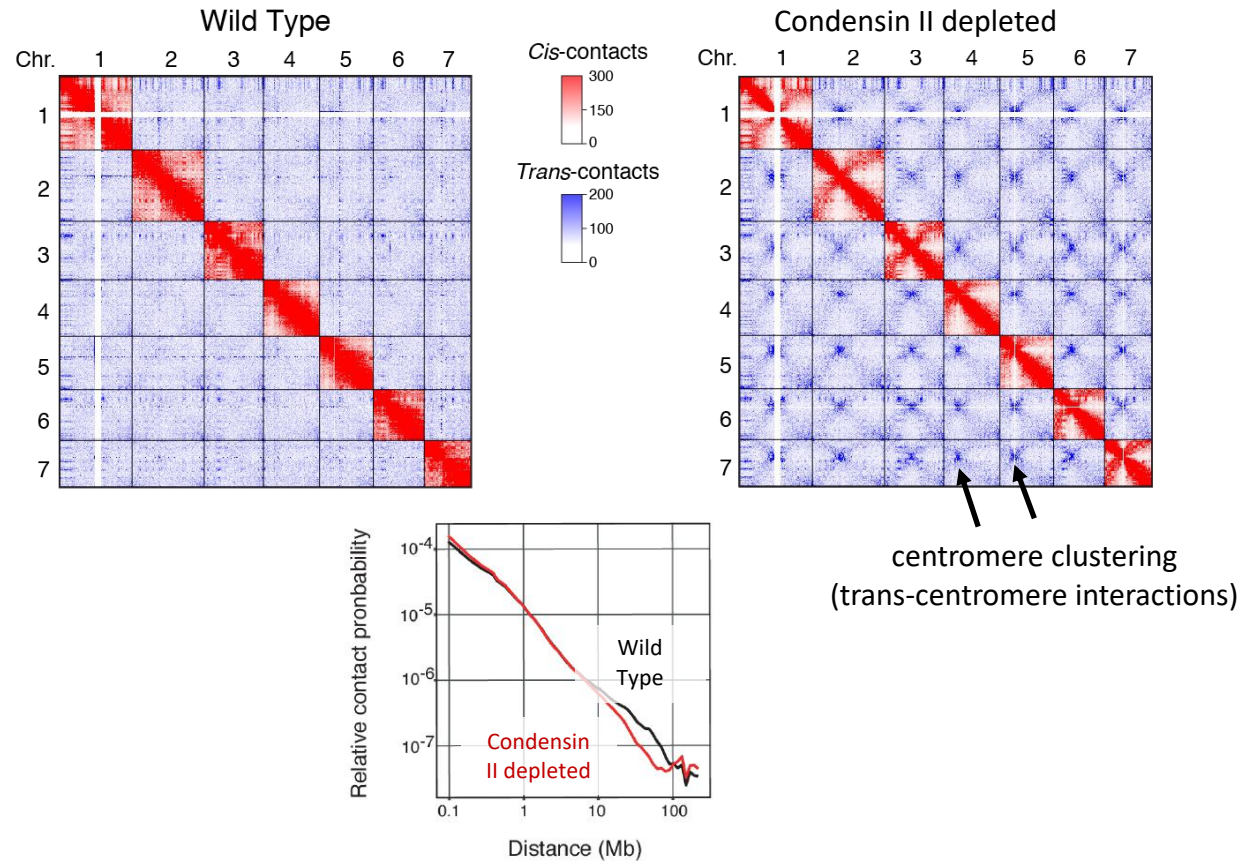
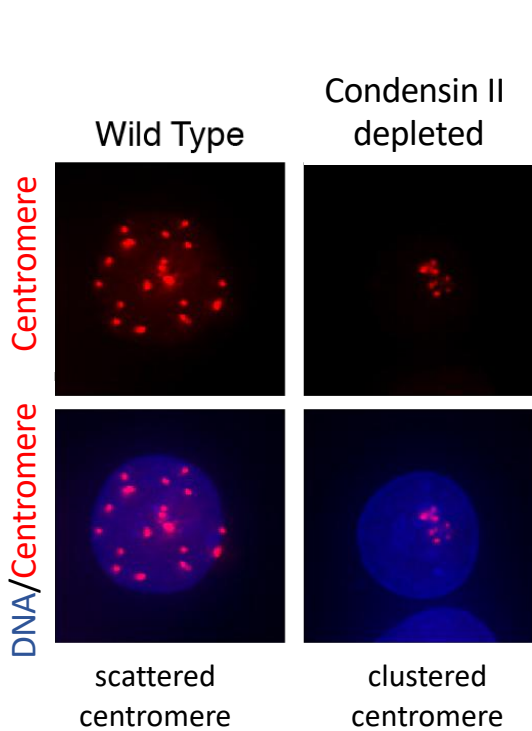


Condensin II depletion



Rosin et al. *PLoS Genet.* 2018

CONDENSIN II DEPLETION LEADS TO A PHENOTYPE WITH CLUSTERED-CENTROMERES AND LOWER CIS-COMPACTION



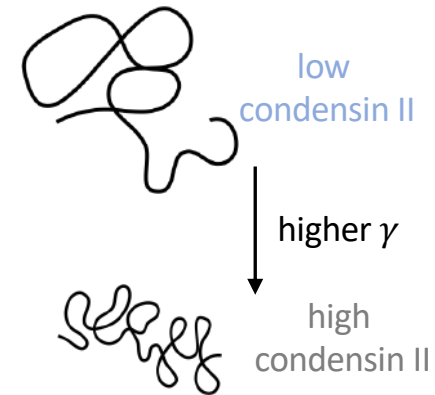
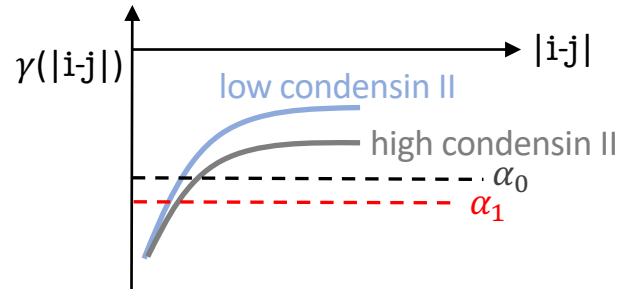
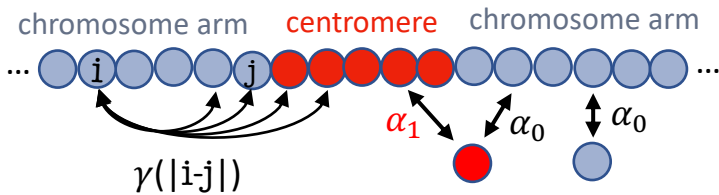
MICROM INTERACTIONS AND LENGTHWISE COMPACTION ACTIVITY OF CONDENSIN II

$$U_{MiChroM}(\vec{r}) = U_{HP}(\vec{r}) + \sum_{\substack{k \geq l \\ k, l \in \text{Types}}} \alpha_{kl} \sum_{\substack{i \in \{\text{Loci of Type } k\} \\ j \in \{\text{Loci of Type } l\}}} f(r_{ij}) + \chi \sum_{(i,j) \in \{\text{Loop Sites}\}} f(r_{ij}) + \sum_{d=3}^{d_{cutoff}} \gamma(d) \sum_i f(r_{i,i+d})$$

Homopolymer Flory-like two-body term CTCF loops Ideal Chromosome

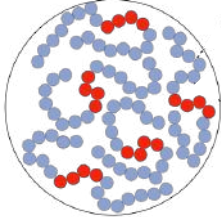
Polymer connectivity Phase separation of Heterochromatin (centromeres) Lengthwise compaction
Topology fluctuations

Simplified model (competition between phase separation and lengthwise compaction):



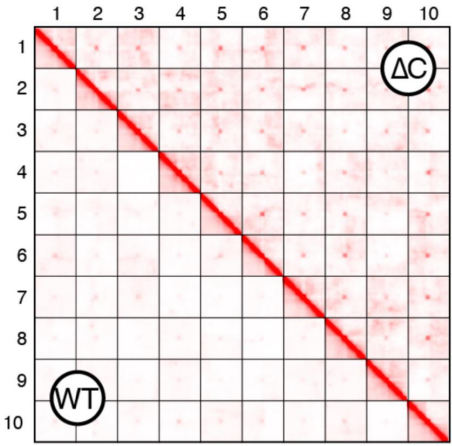
CONDENSIN II ACTIVITY (LENGTHWISE COMPACTION) COUNTERACTS CENTROMERE CLUSTERING

genome with multiple chromosomes



WT : condensin II active (high γ)

ΔC : condensin II inactive (low γ)



WT : condensin II active (high γ)

strong chromosome territories scattered centromeres (red) centromere (red) buried in a chromosome territory (cyan)

ΔC : condensin II inactive (low γ)

weak chromosome territories clustered centromeres (red) centromere (red) exposed due to weak chromosome territory (cyan)

Hoencamp et al., *Science* (2021)

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