

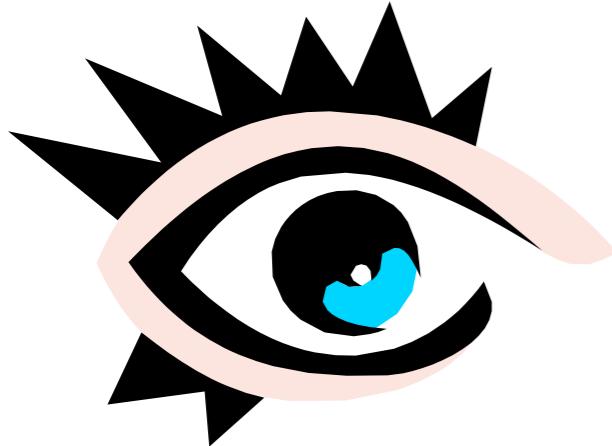
3D modeling of genomes and genomic domains: an overview.

François Serra, Marco Di Stefano & Marc A. Marti-Renom

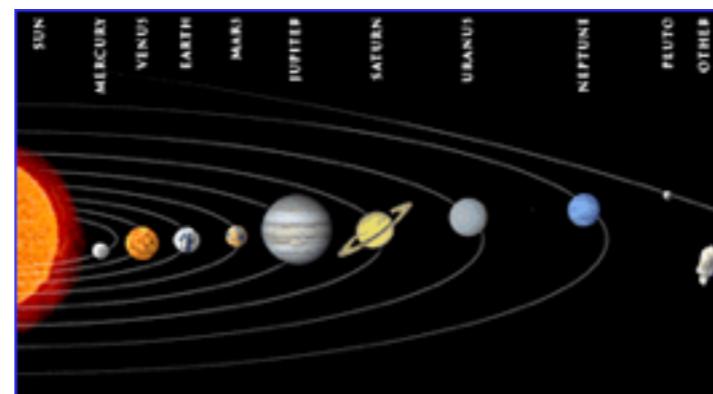
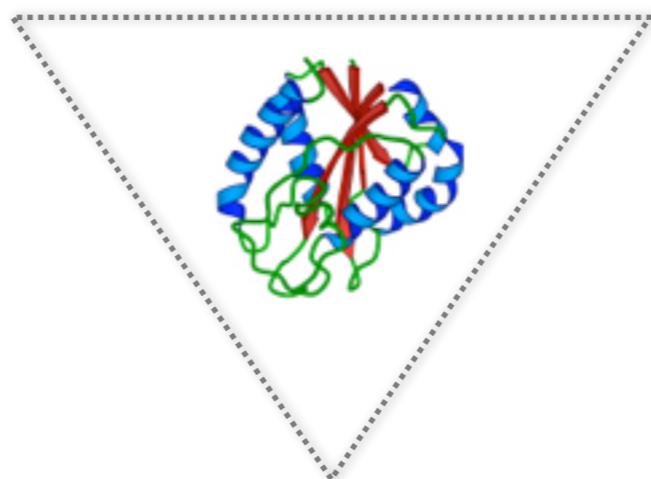
Structural Genomics Group (CNAG-CRG)



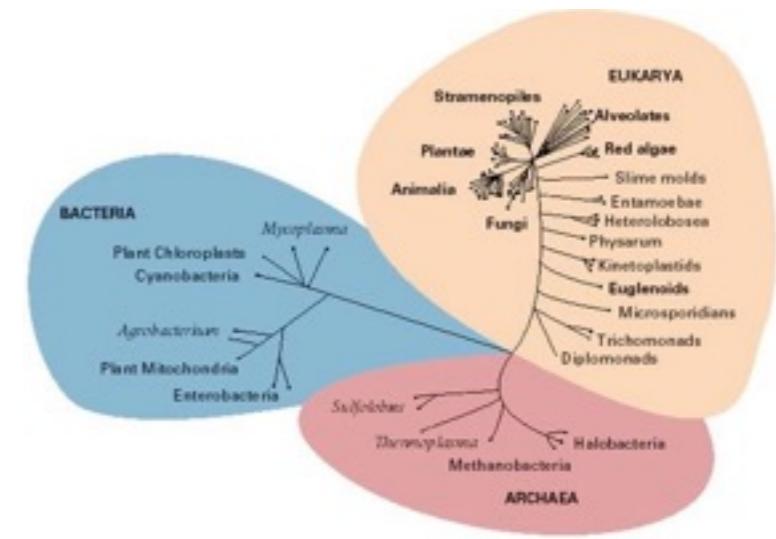
Data groups



Experimental
observations

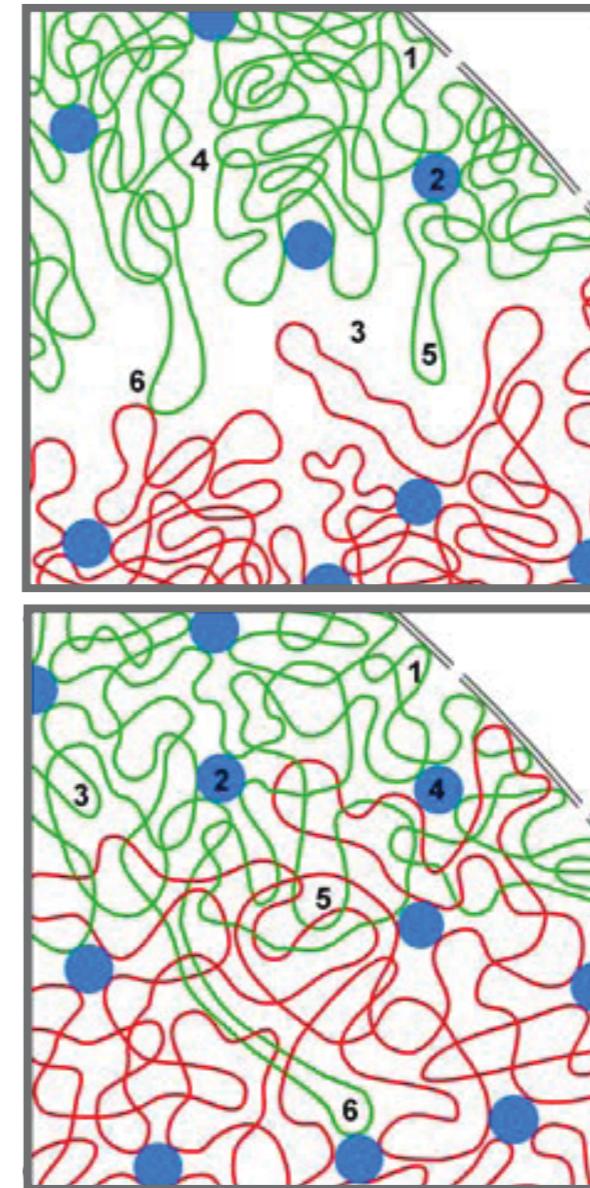
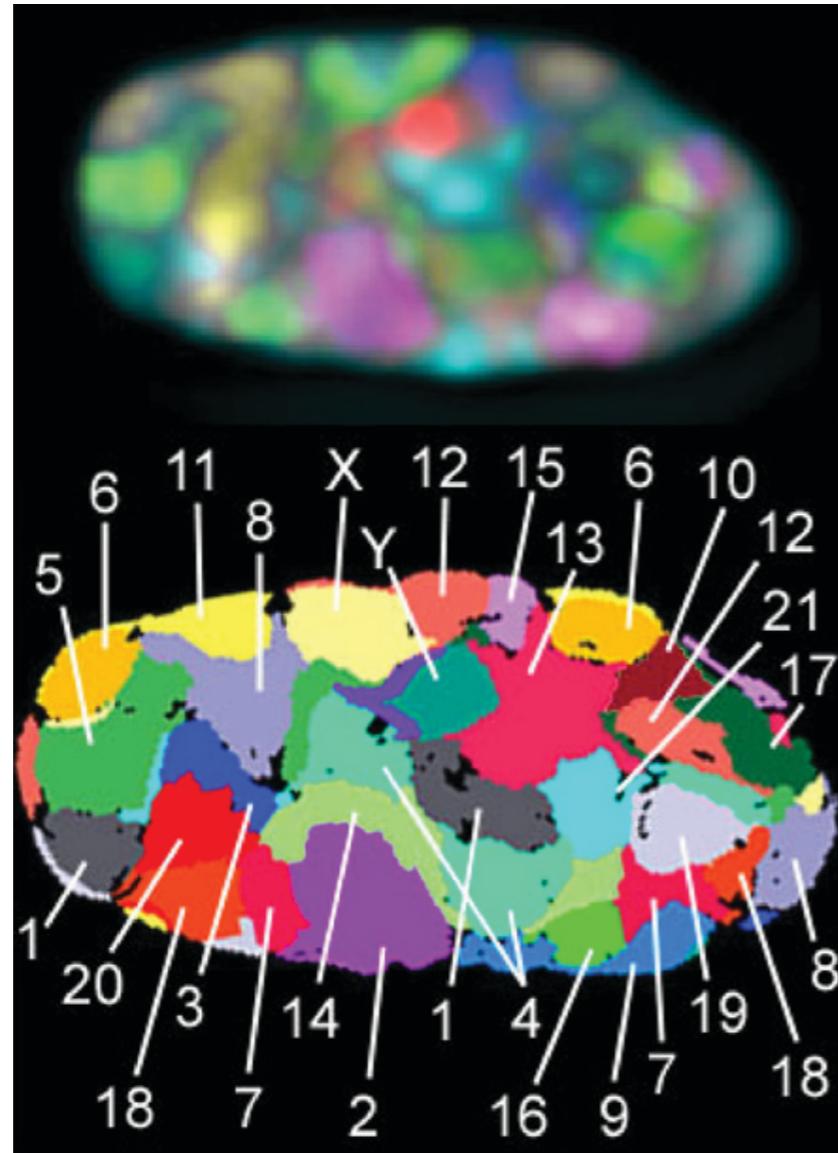


Laws of physics



Statistical rules

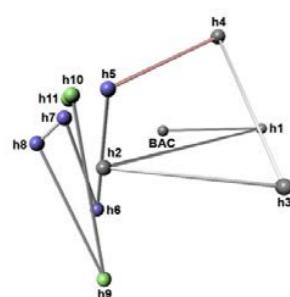
Insights from imaging



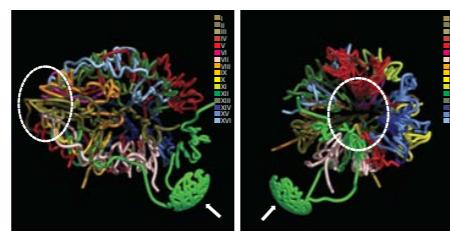
Chromosome territories

3D modeling of genomic domains: other methods

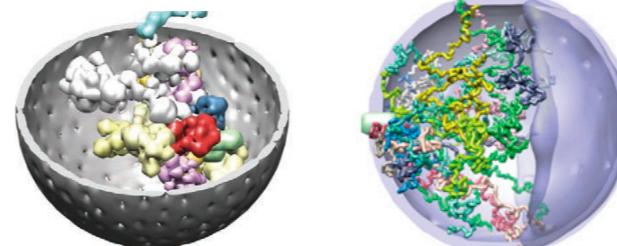
Jhunjhunwala (2008) Cell



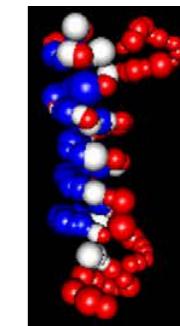
Duan (2010) Nature



Kalhor (2011) Nature Biotechnology
Tjong (2012) Genome Research

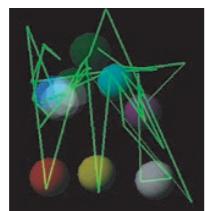


Hu (2013) PLoS Computational Biology

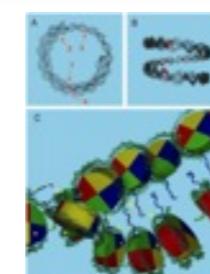
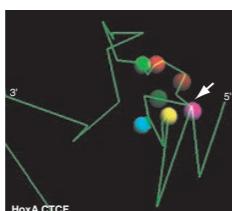


2008

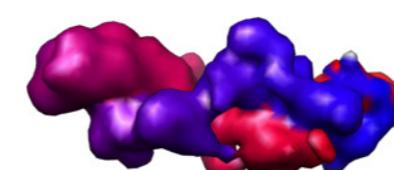
2014



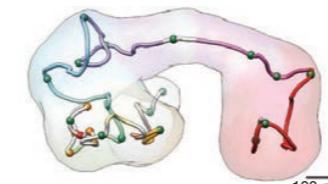
Fraser (2009) Genome Biology
Ferraiuolo (2010) Nucleic Acids Research



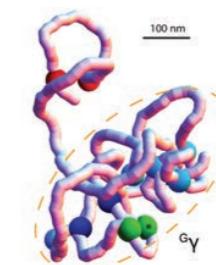
Asbury (2010) BMC Bioinformatics



Baù (2011) Nature Structural & Molecular Biology
Umbarger (2011) Molecular Cell

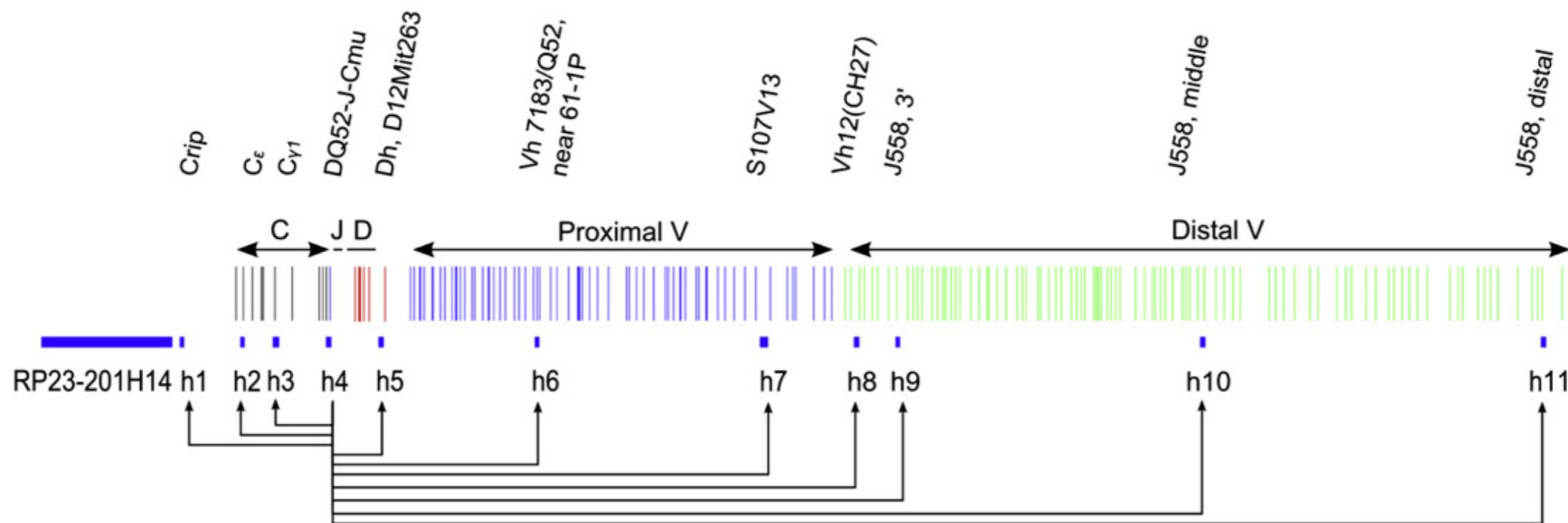


Junier (2012) Nucleic Acids Research



The 3D structure of the IgH-chain locus

Jhunjhunwala et all, (2008) Cell

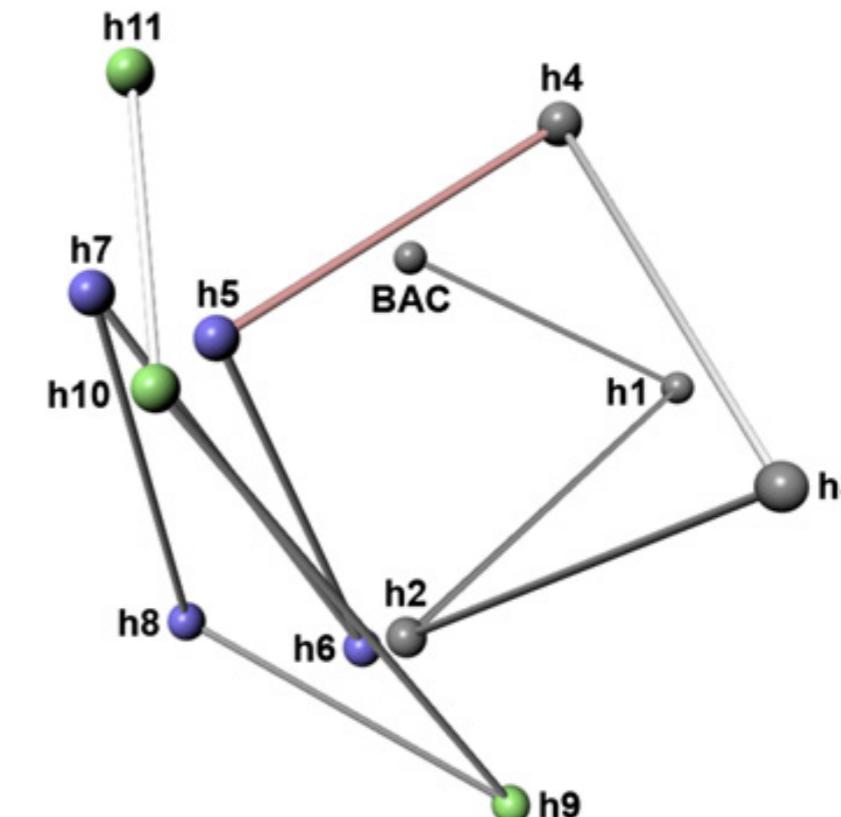
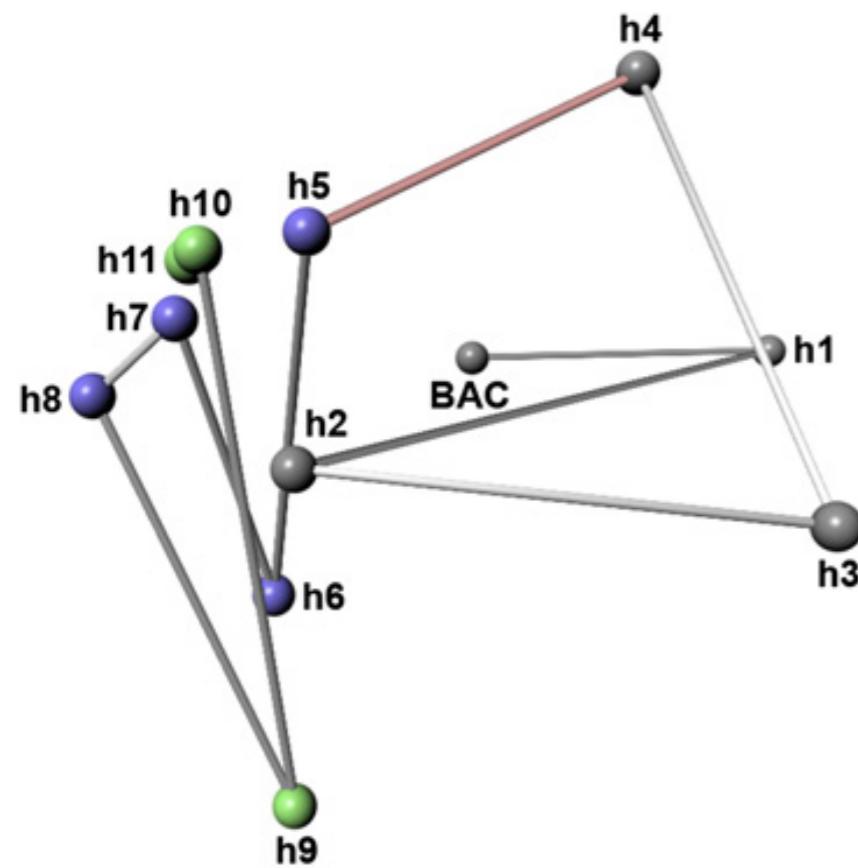


Genomic organization of the IgH locus

Adapted from Jhunjhunwala et all, (2008) Cell

The 3D Structure of the IgH-Chain Locus

Jhunjhunwala et all, (2008) Cell



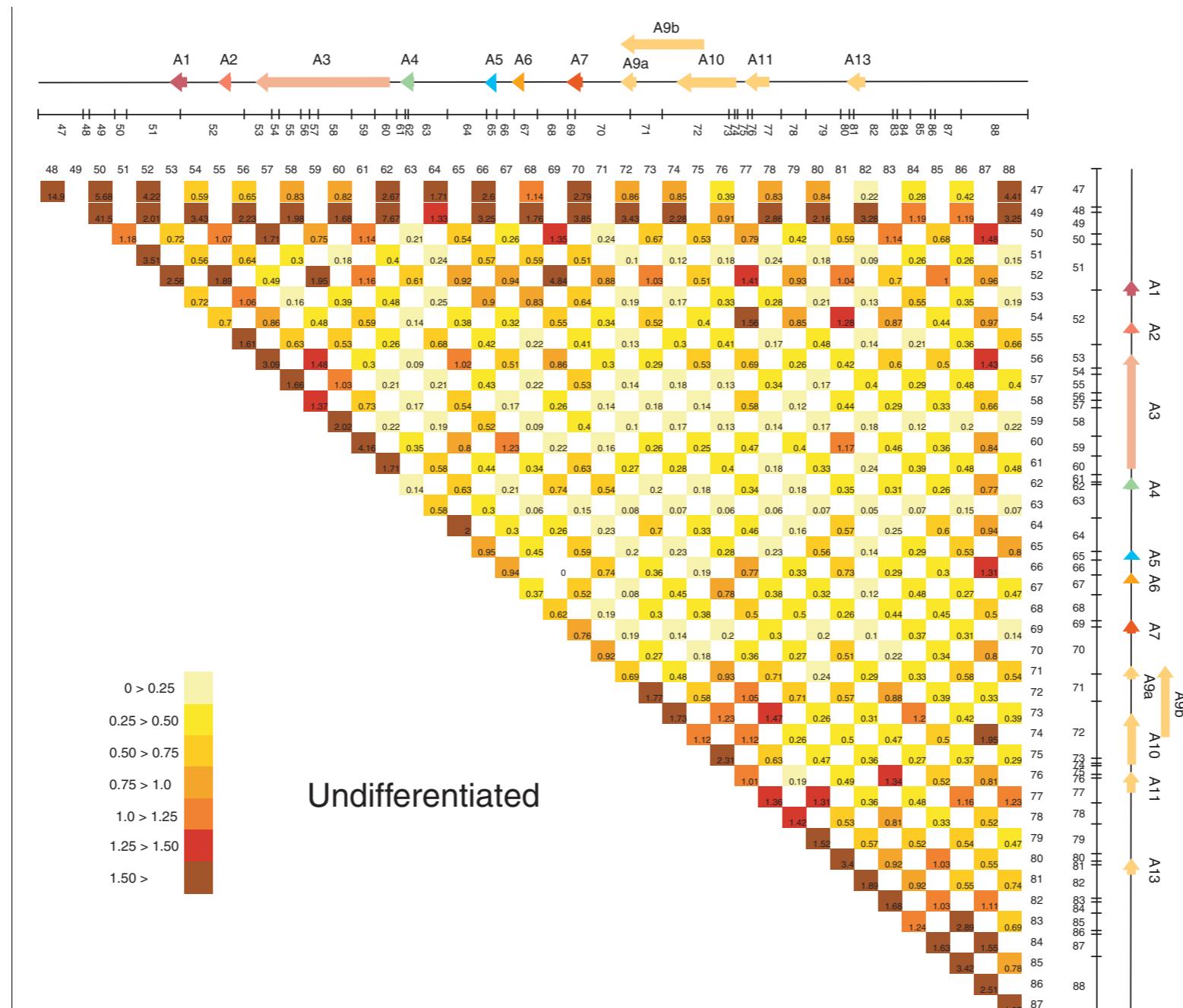
- Distal Vh
- Proximal Vh
- Dh region
- Jh, Ch

The 3D topology of the IgH locus in pro-B cells

Adapted from Jhunjhunwala et all, (2008) Cell

Chromatin conformation signatures of cellular differentiation

Fraser et all, (2009) Genome biology

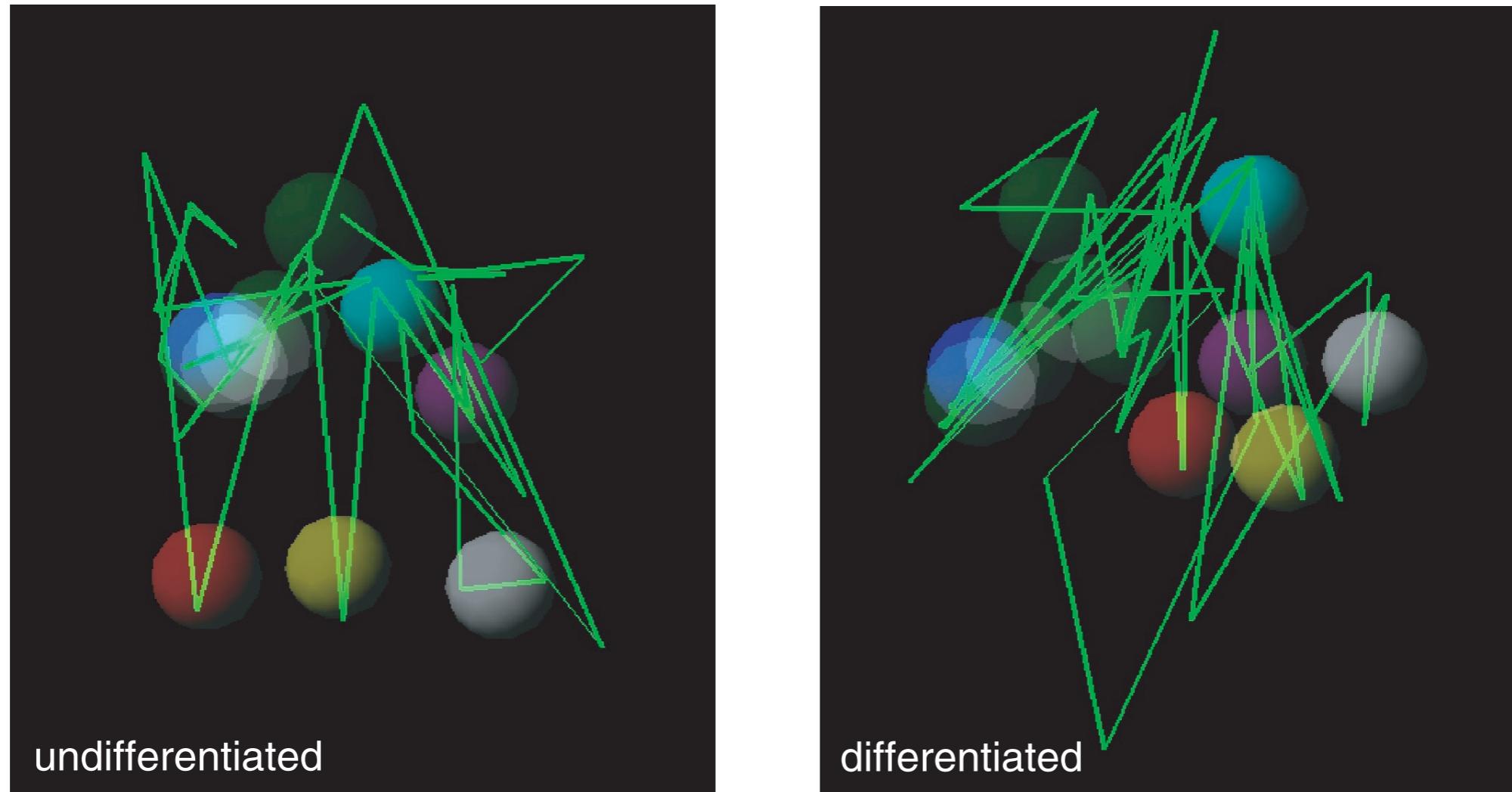


5C array datasets from undifferentiated cells

Adapted from Fraser et all, (2009) Genome Biology

Chromatin conformation signatures of cellular differentiation

Fraser et al, (2009) Genome biology



A1-5 A6 A7 A9 A10 A11 A13

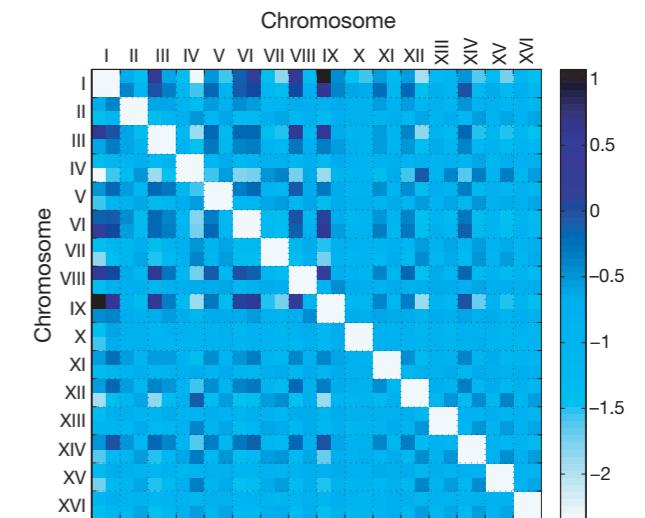
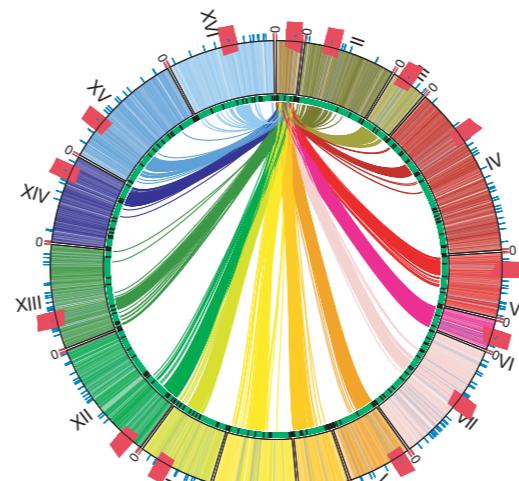
Three-dimensional models of the human *HoxA* cluster during cellular differentiation

Adapted from Fraser et al, (2009) Genome Biology

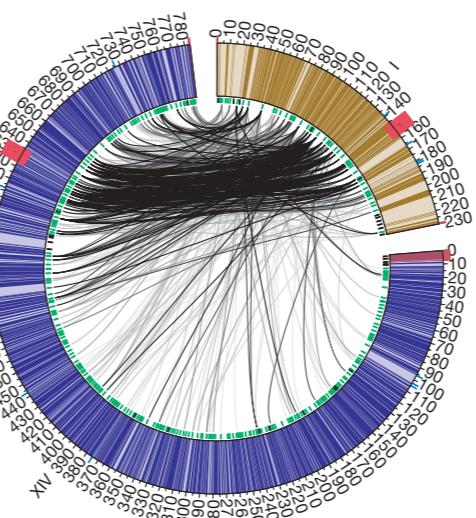
A 3D model of the yeast genome

Duan et all, (2010) Nature

Chromosome I
vs all



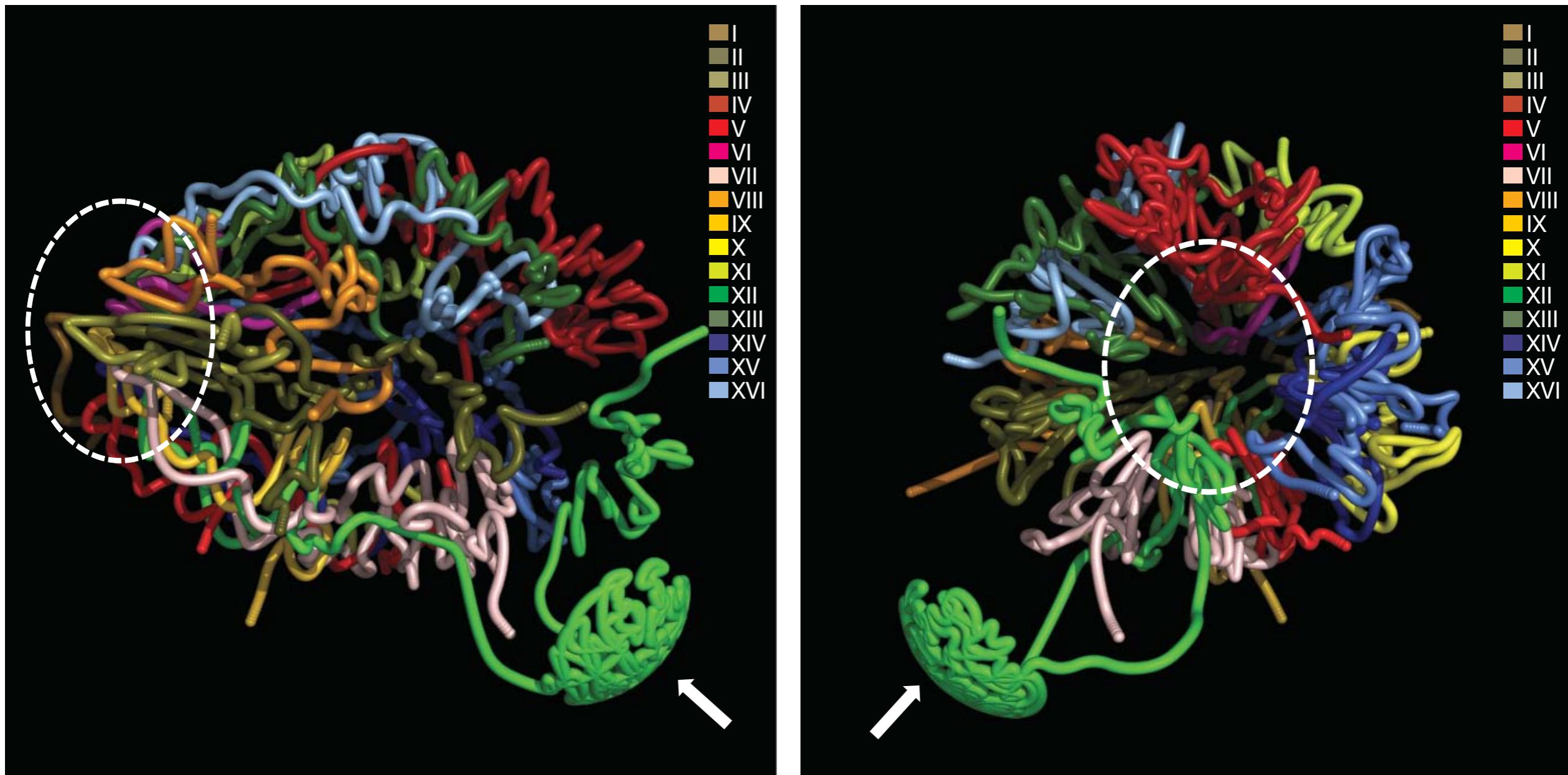
Chromosome XIV



Adapted from Duan et all, (2010) Nature

A 3D model of the yeast genome

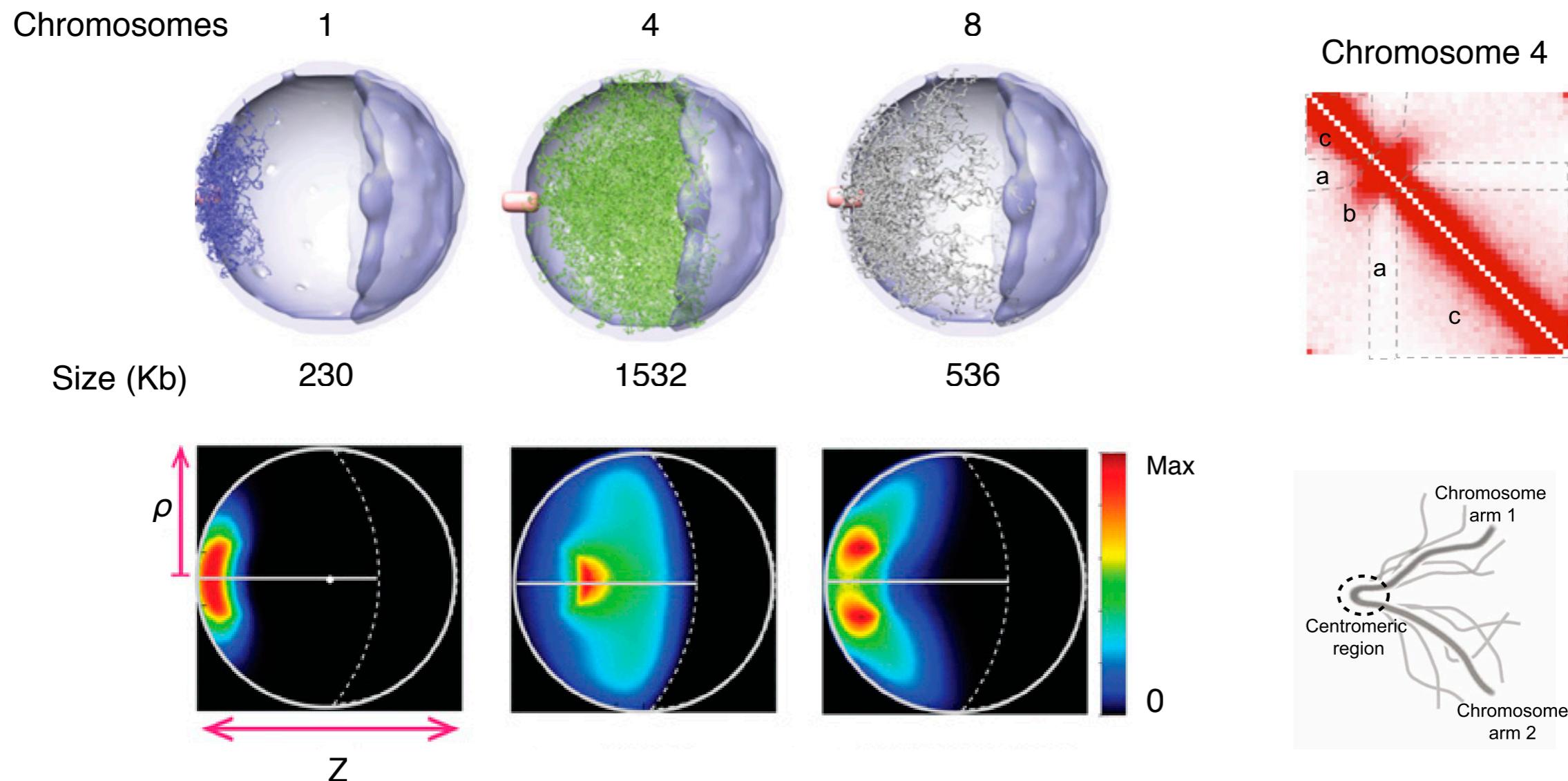
Duan et all, (2010) Nature



Adapted from Duan et all, (2010) Nature

Physical tethering and volume exclusion determine higher-order genome organization in budding yeast

Tjong et all, (2012) Genome research

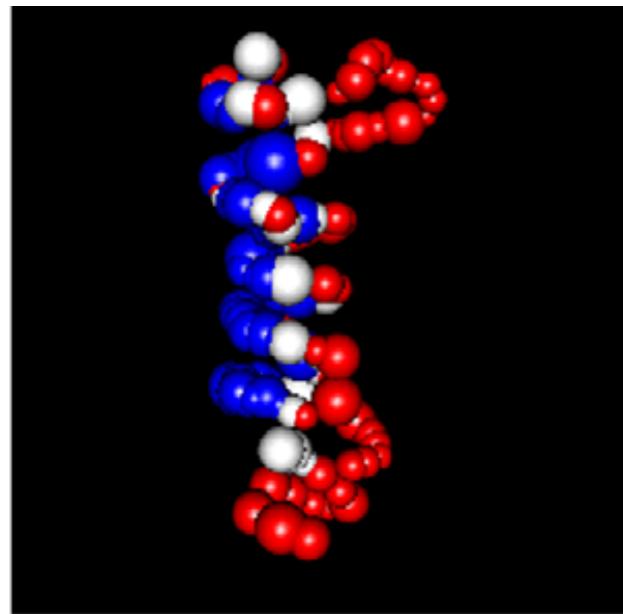


Adapted from Tjong et all, (2012) Genome research

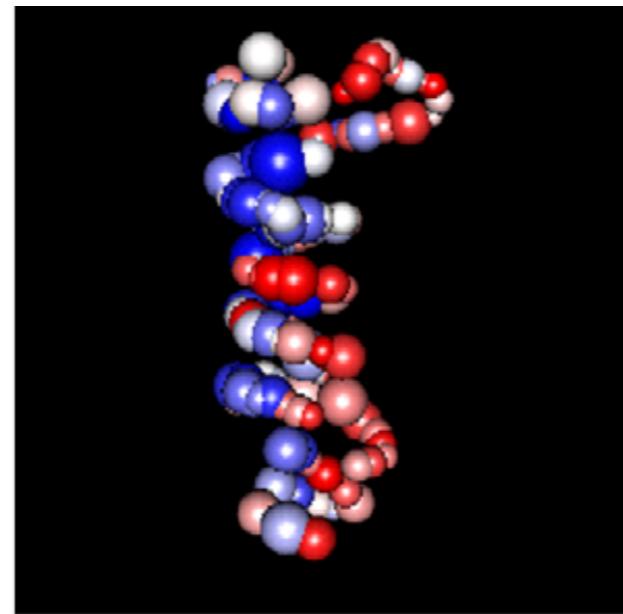
Bayesian Inference of Spatial Organizations of Chromosomes

Hu et all, (2013) PLoS computational biology

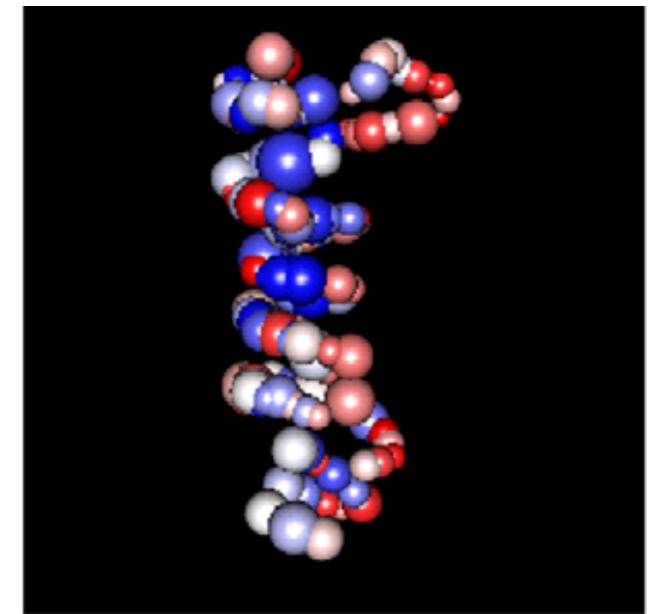
Compartment level



Gene density



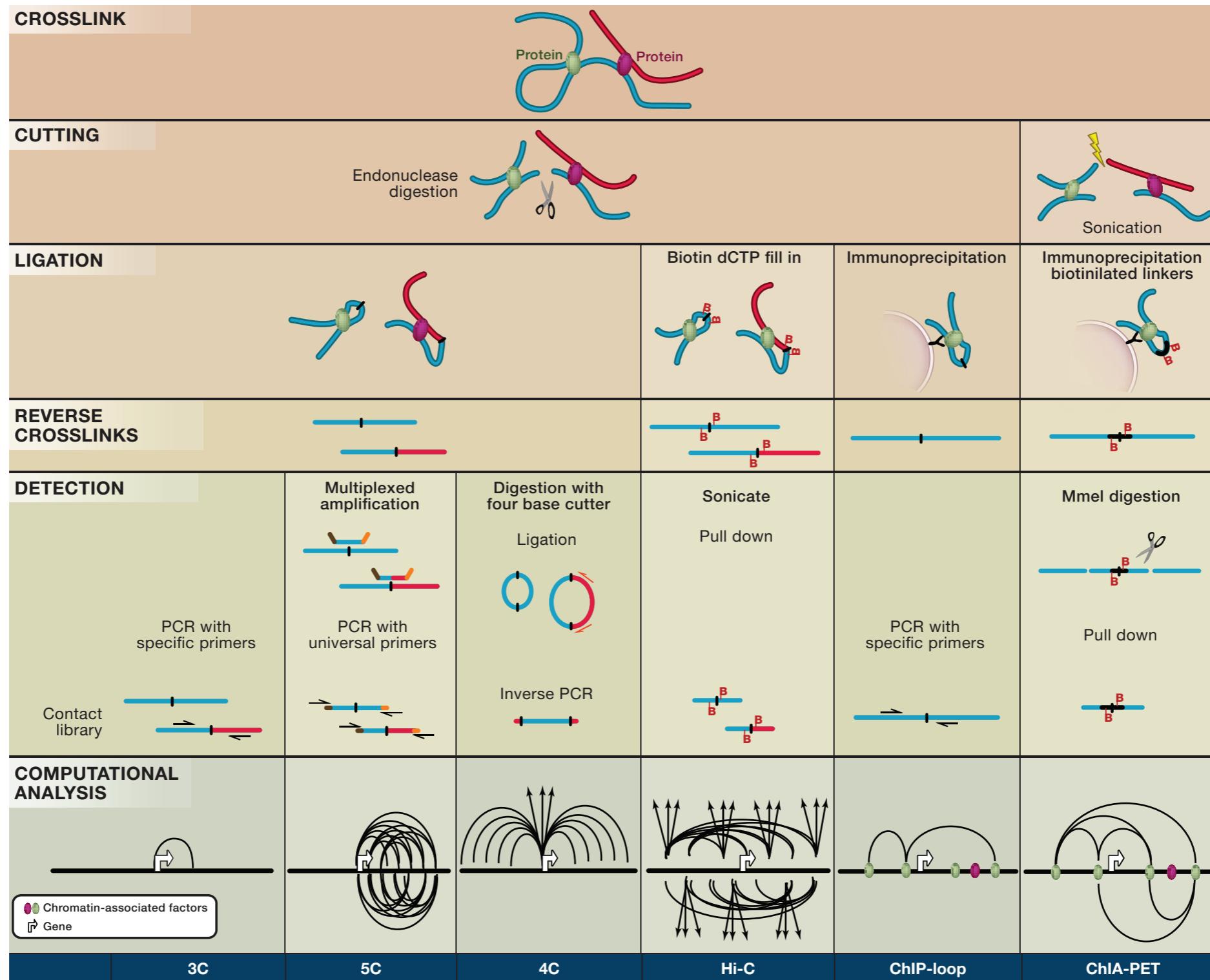
Gene expression



Spatial organization of genomic and epigenetic features

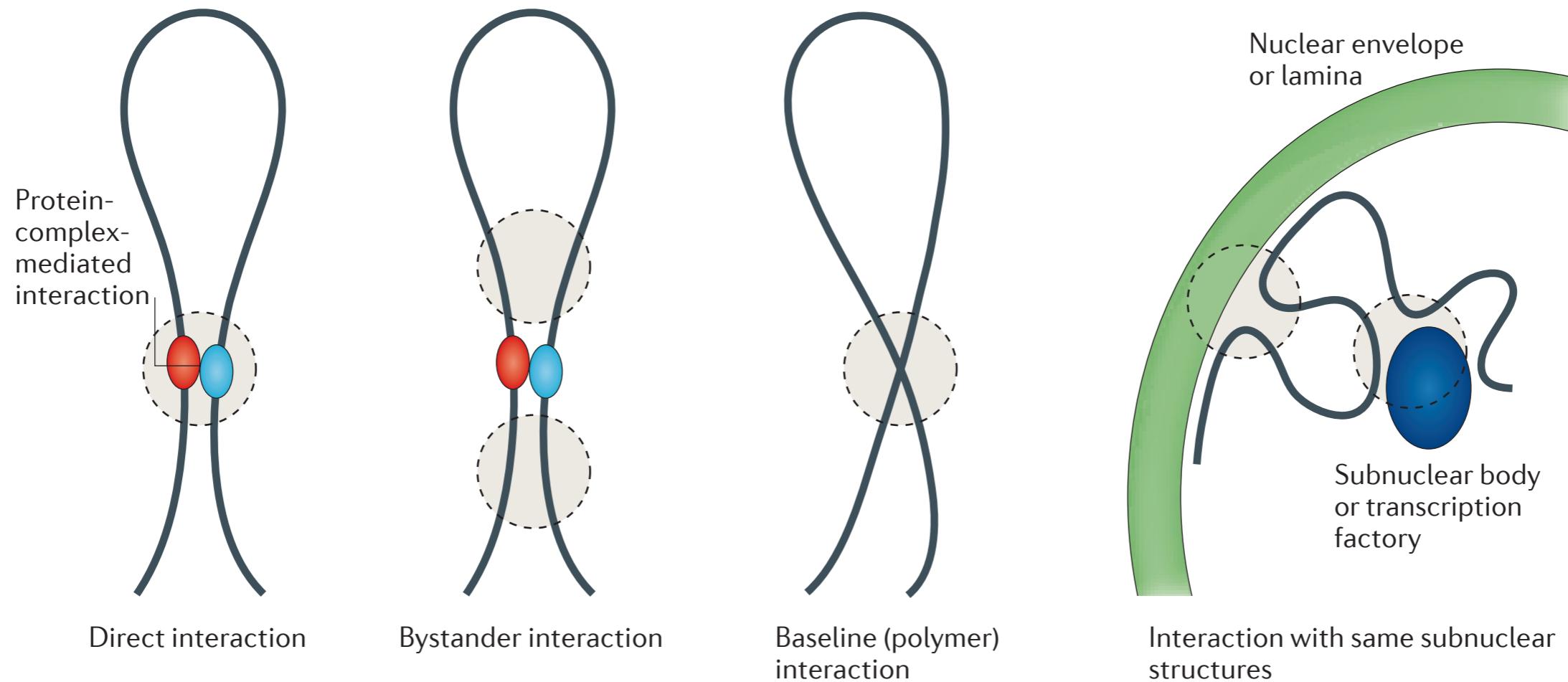
Adapted from Hu et all, (2013) PLoS Comp Bio

3C-like technologies



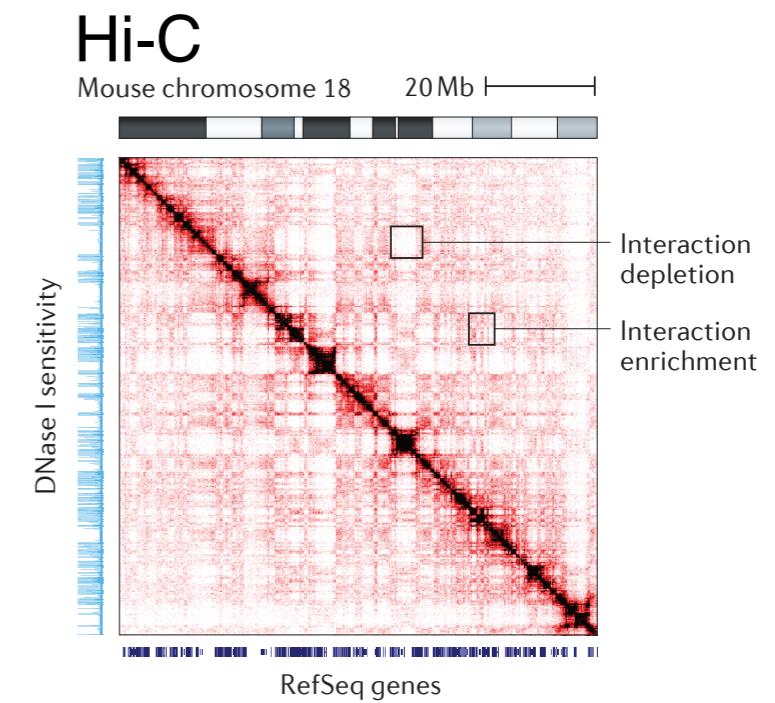
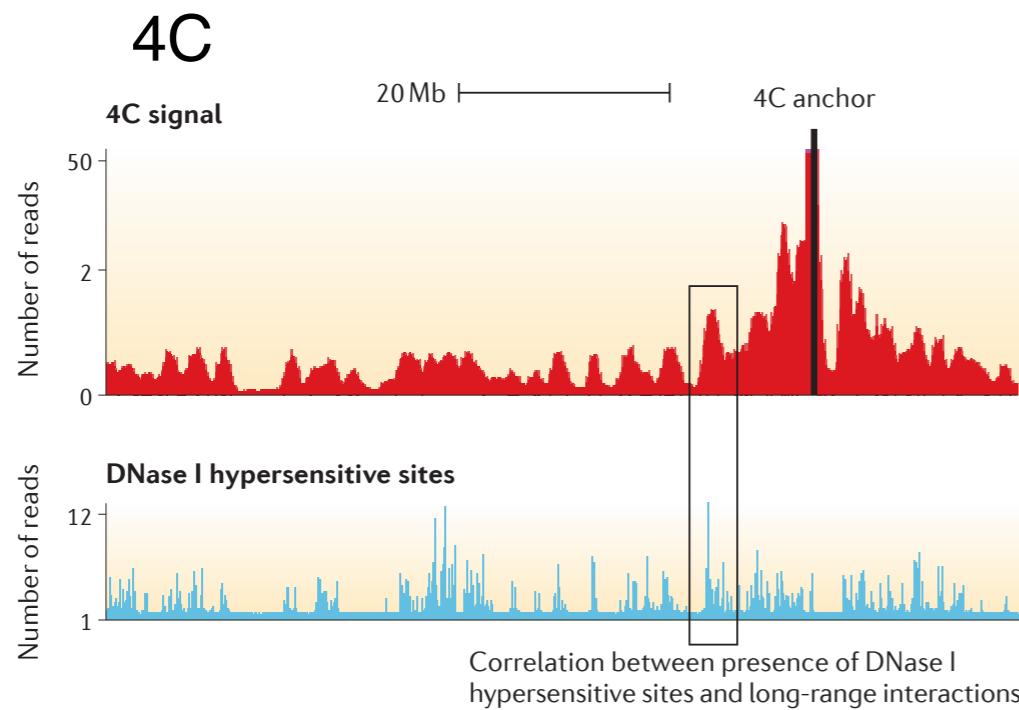
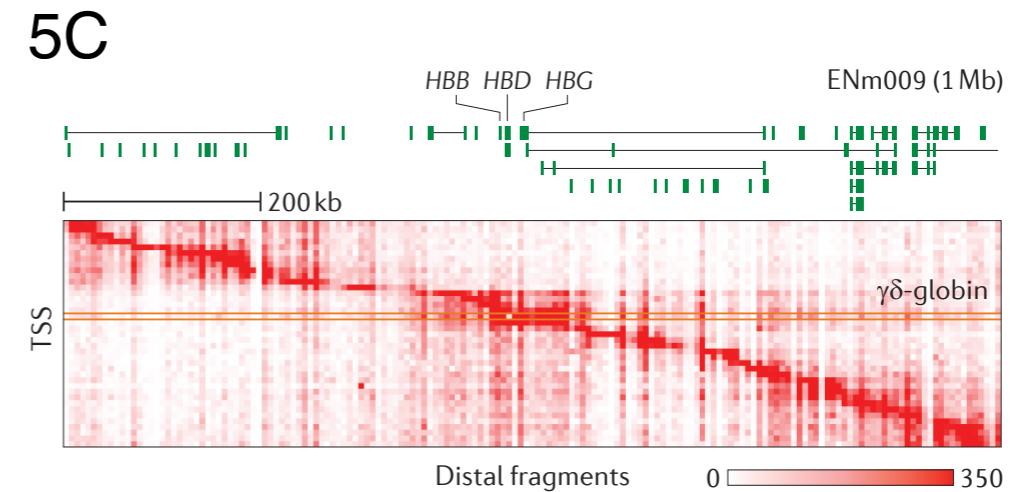
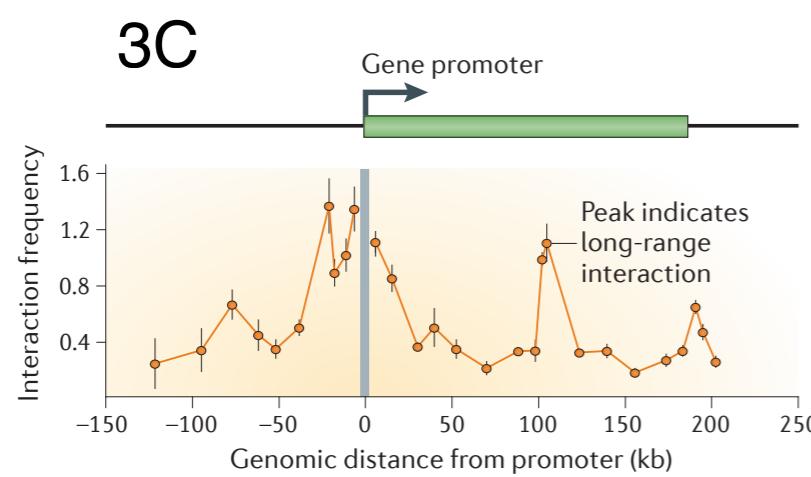
Hakim and Misteli Cell (2012) vol. 148, March 2

Interpreting chromatin interaction data



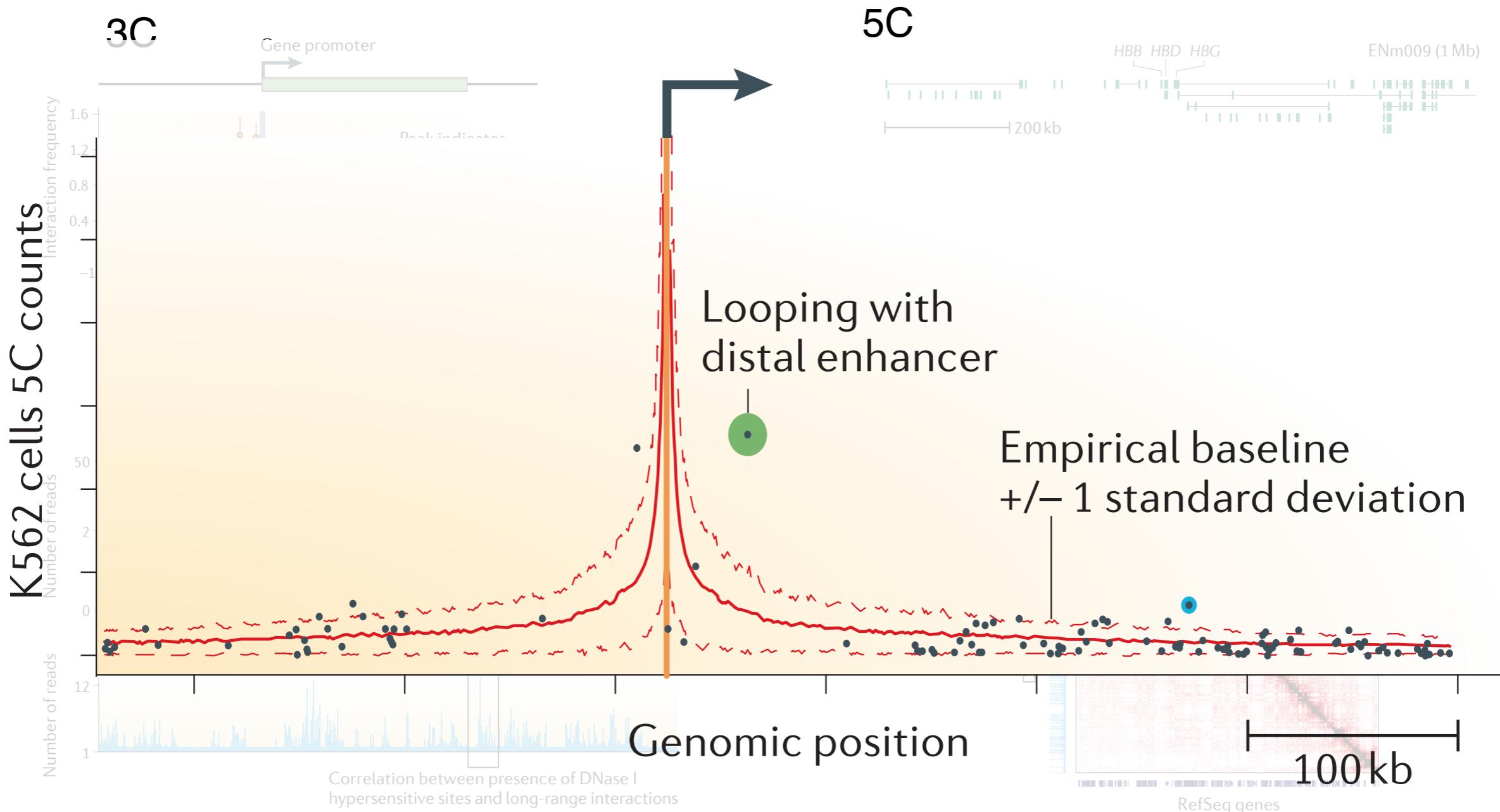
Adapted from Dekker et al., (2013) Nat Rev Genetics

Insights from 3C-based technologies



Adapted from Dekker et al., (2013) Nat Rev Genetics

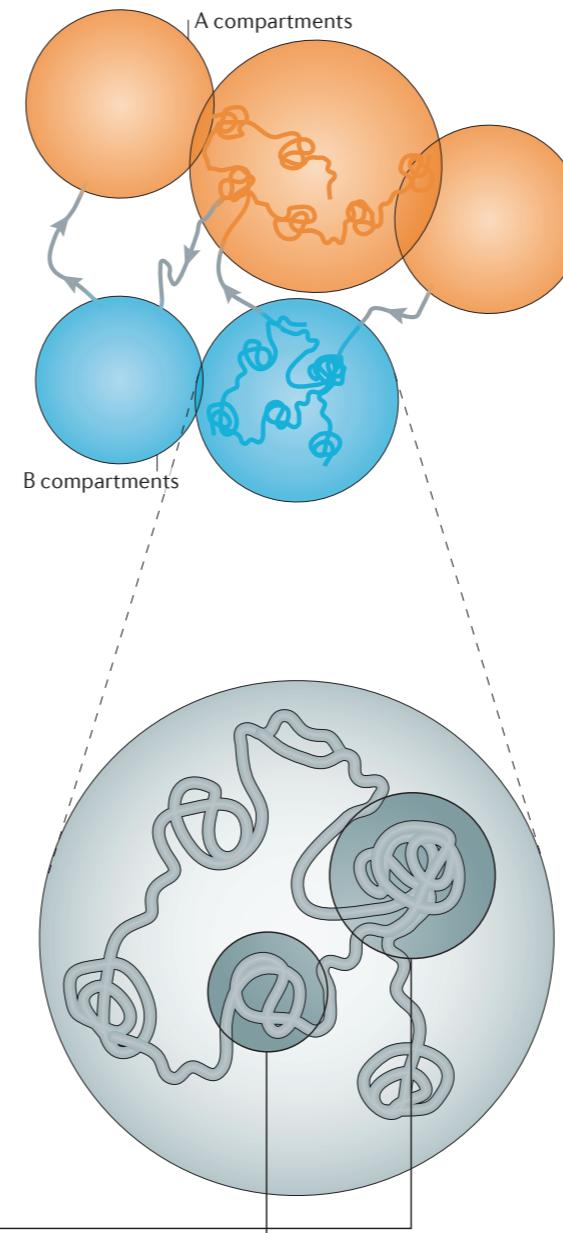
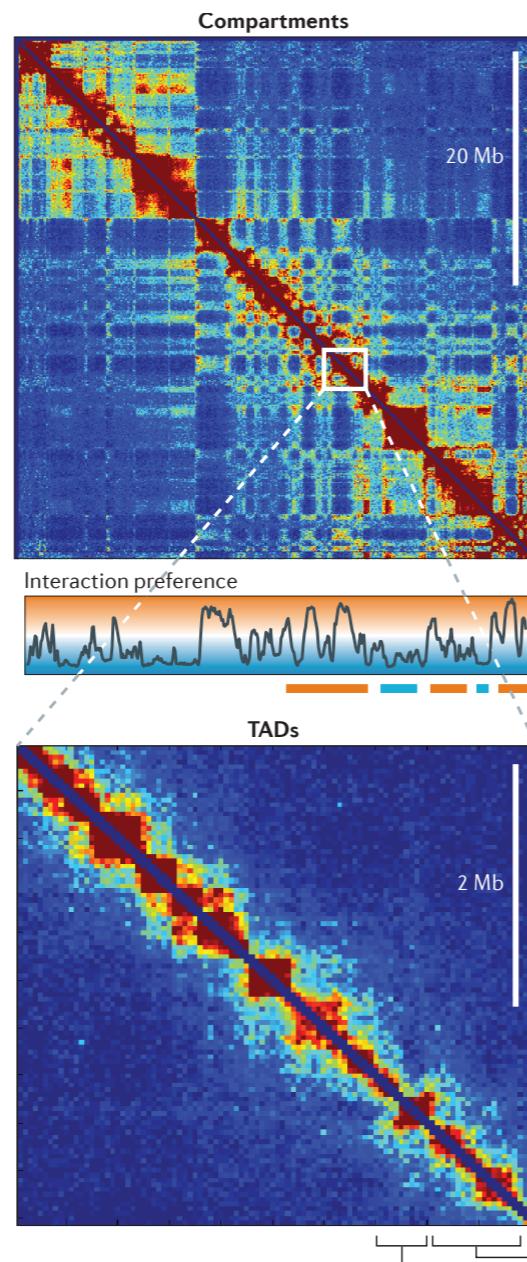
Insights from 3C-based technologies



Adapted from Dekker et al., (2013) Nat Rev Genetics

Complex genome organization

Human chromosome 14

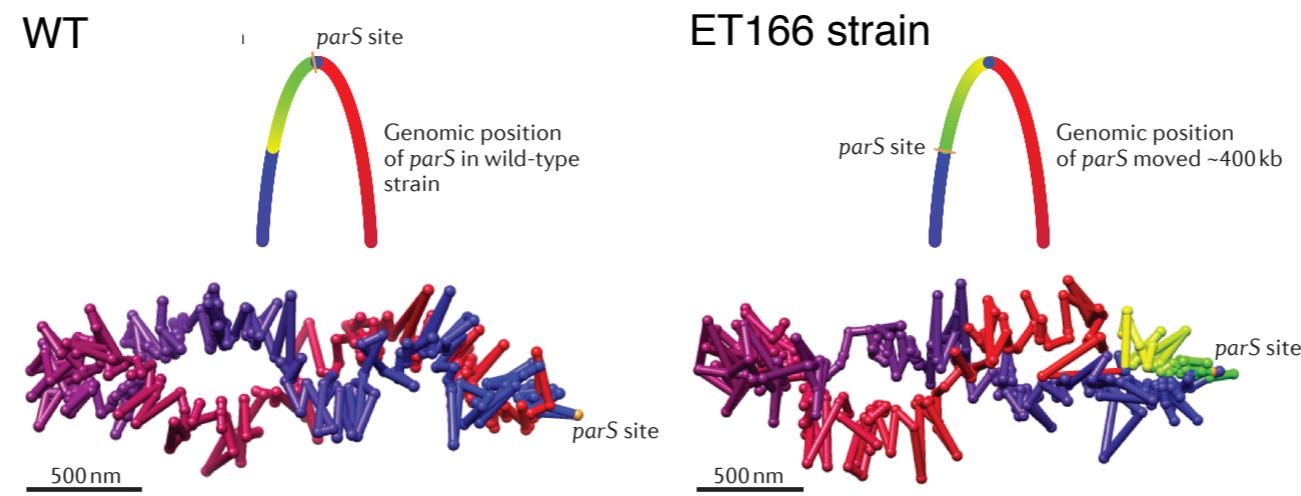
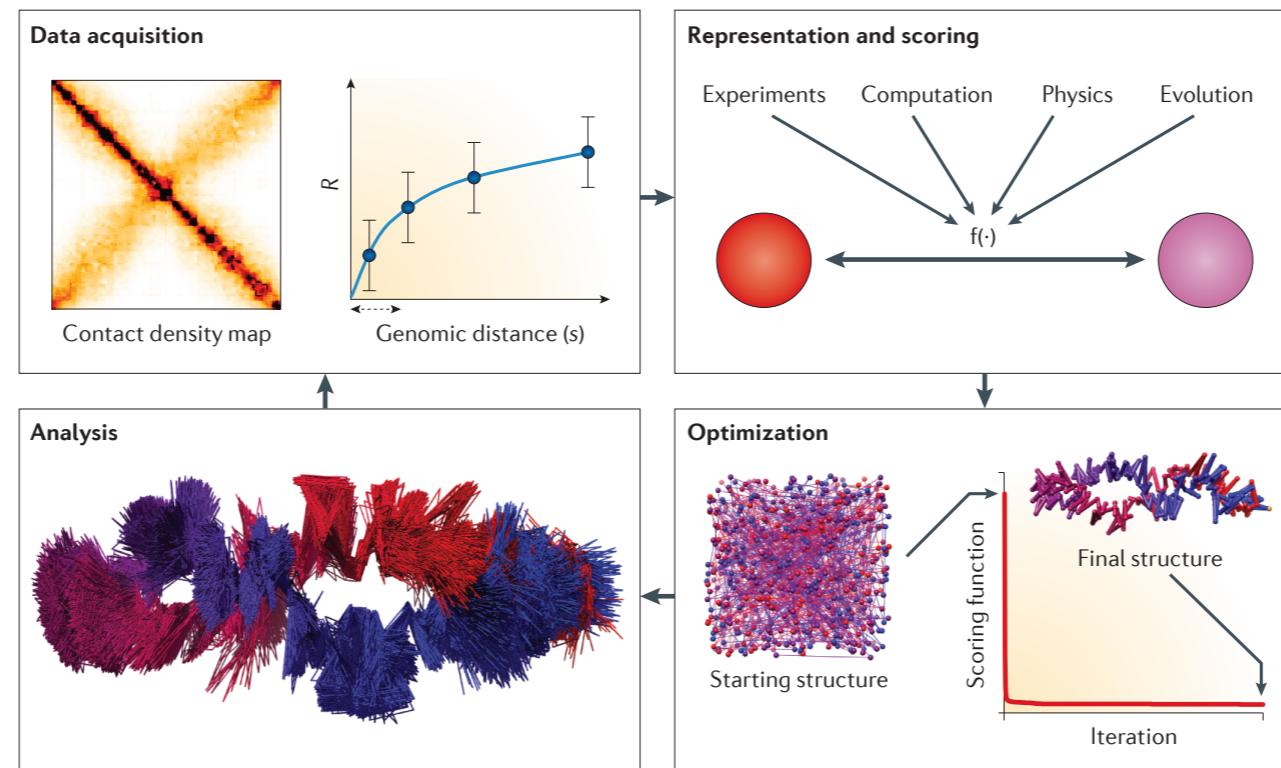


A-B compartments

TADs

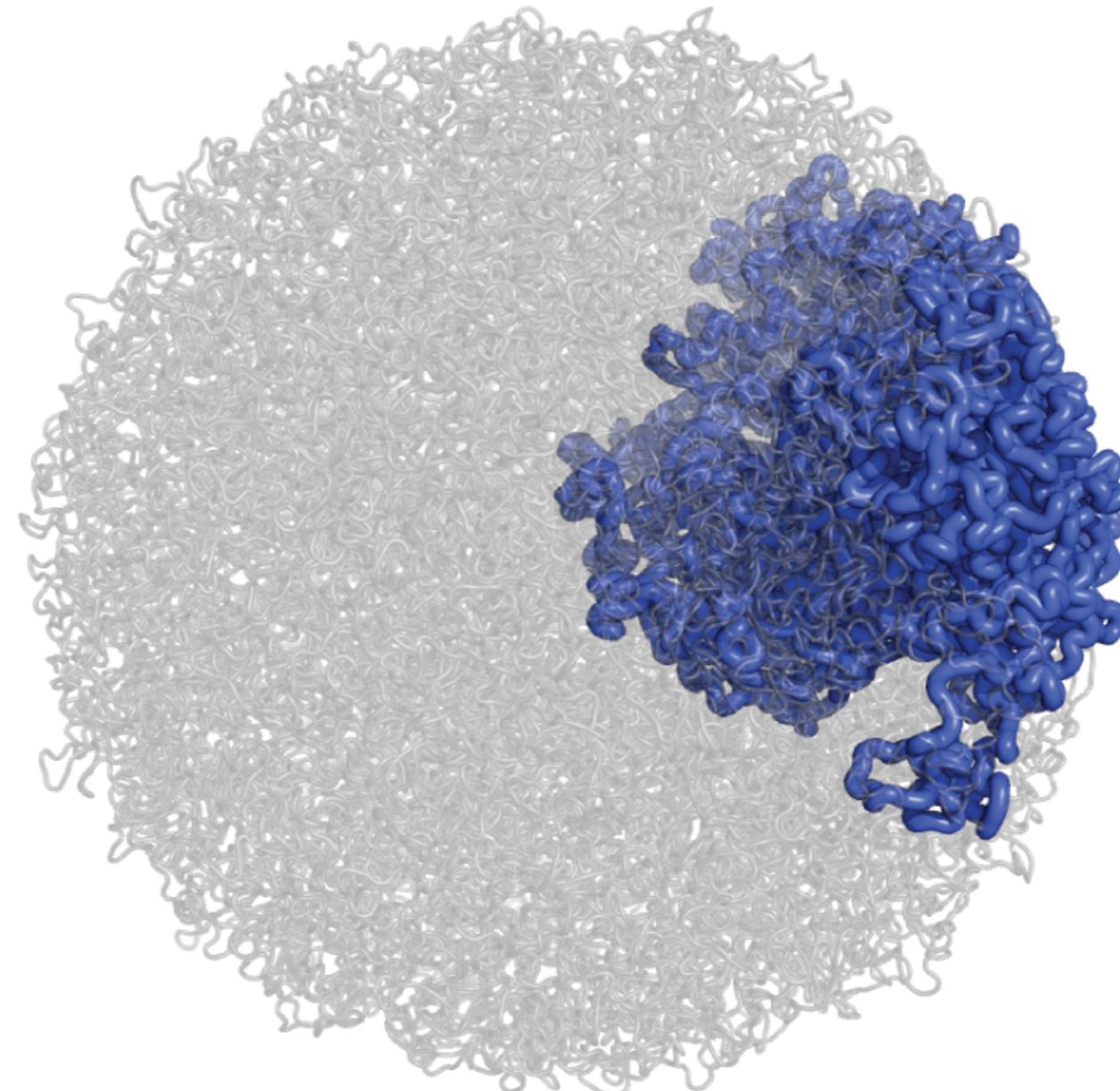
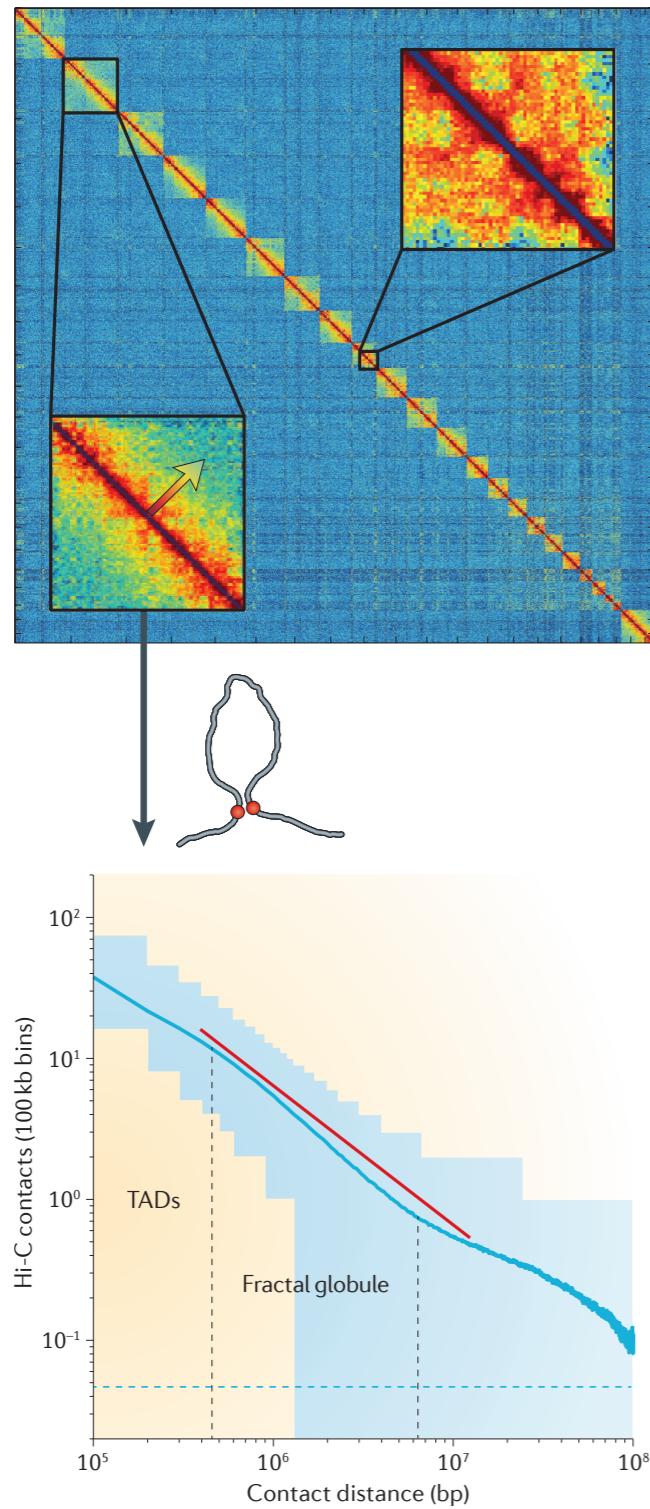
Adapted from Dekker et al., (2013) Nat Rev Genetics

Restraint based models



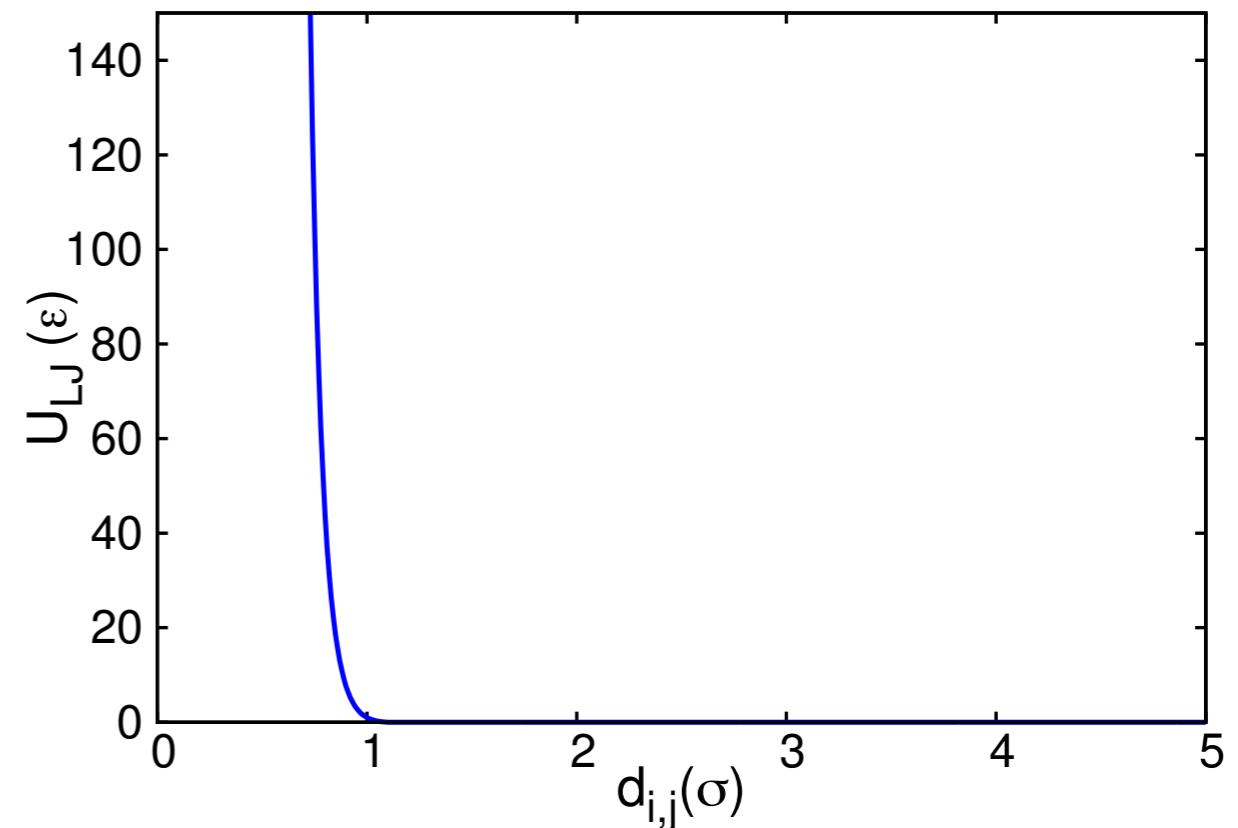
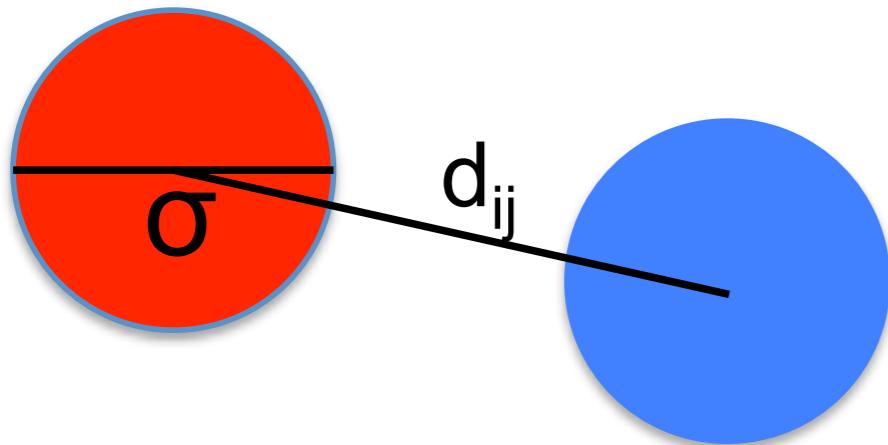
Adapted from Dekker et al., (2013) Nat Rev Genetics

Polymer approaches



Adapted from Dekker et al., (2013) Nat Rev Genetics

Physical restraints



Excluded volume

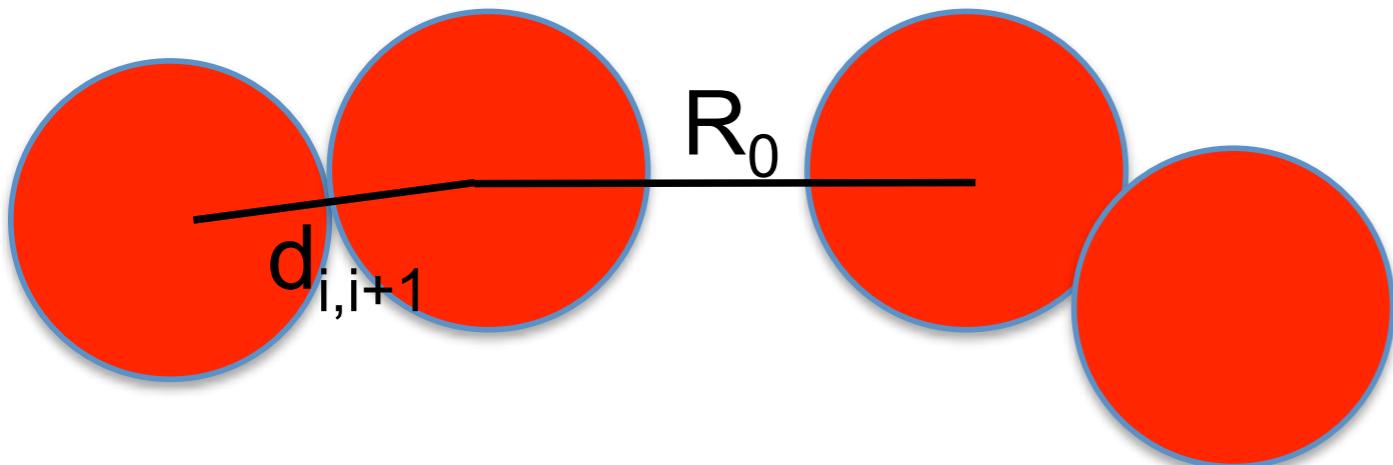
$$U_{LJ}(i, j) = \begin{cases} 4\epsilon \left[\left(\frac{\sigma}{d_{i,j}} \right)^{12} - \left(\frac{\sigma}{d_{i,j}} \right)^6 + 1/4 \right] & \text{if } d_{i,j} \leq 2^{1/6}\sigma, \\ 0 & \text{if } d_{i,j} > 2^{1/6}\sigma. \end{cases}$$

where

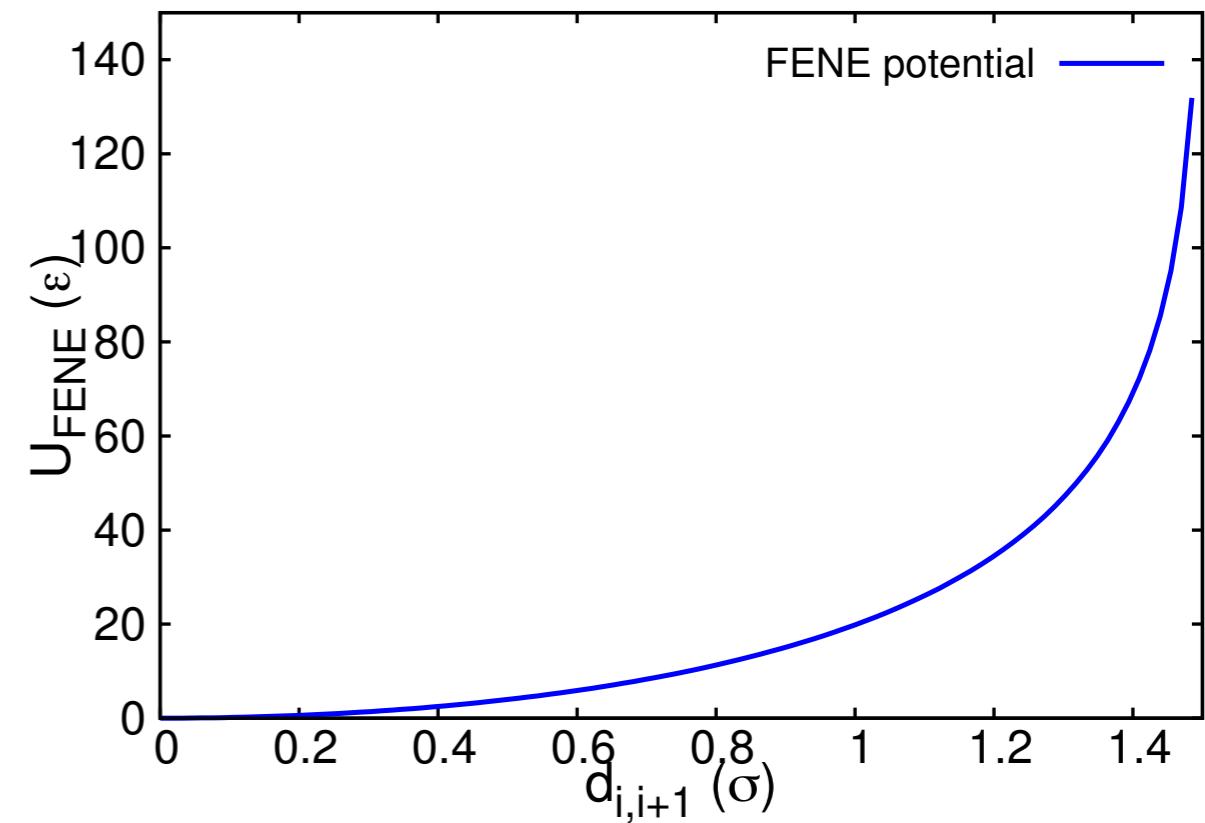
σ is the diameter of the particle

ϵ is the unit of energy

Physical restraints



Chain connectivity



$$U_{FENE}(i, i + 1) = -\frac{k}{2}R_0^2 \log \left[1 - \left(\frac{d_{i,i+1}}{R_0} \right)^2 \right]$$

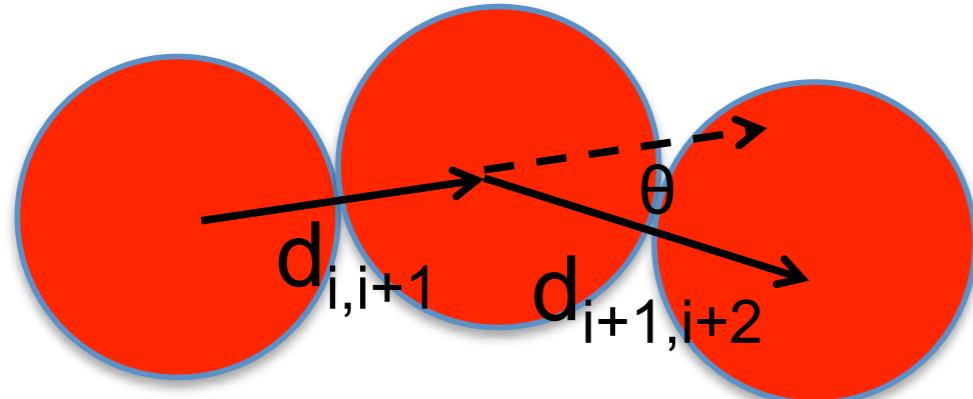
where

$k = 30.0 \epsilon/\sigma^2$ is the potential strength

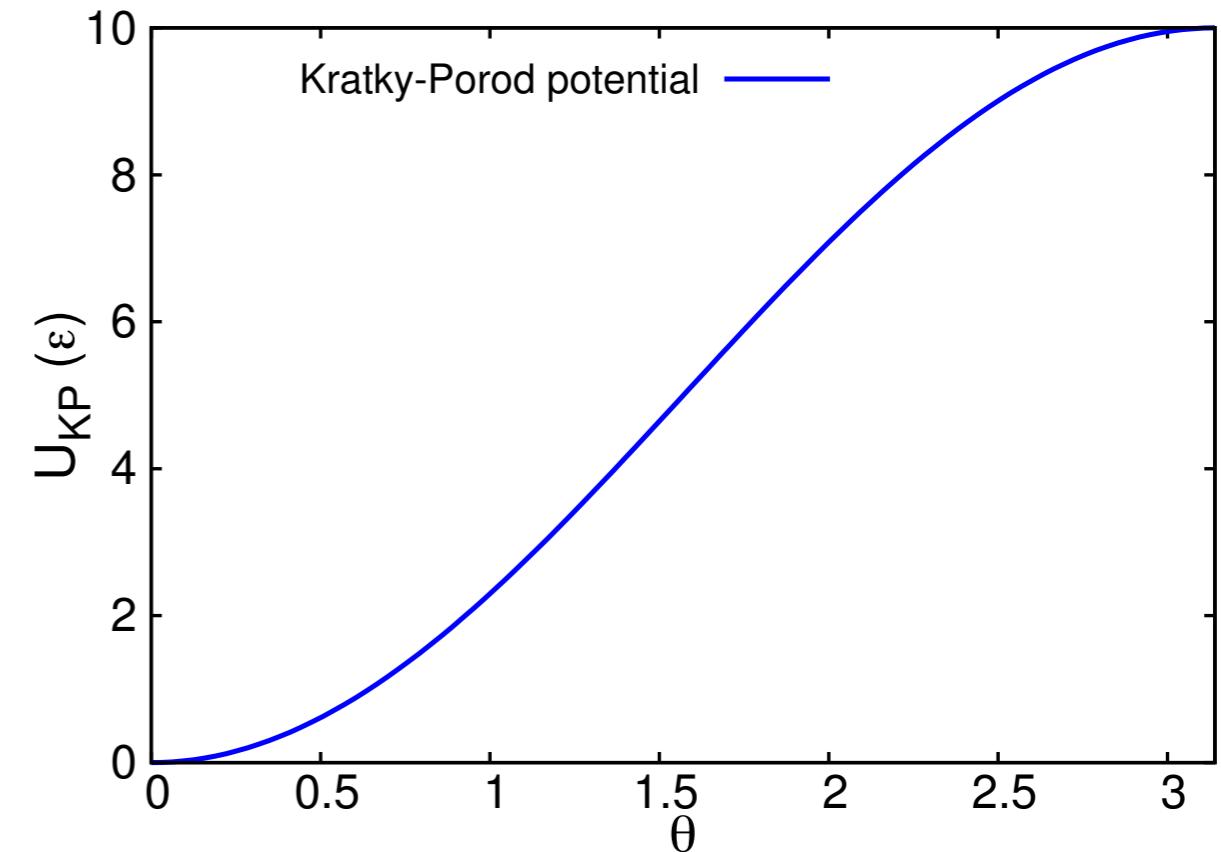
$R_0 = 1.5 \sigma$ is the maximum bond length

Rosa and Everaers PLoSCB 2008; Rosa and Everaers BJ 2010

Physical restraints



Bending rigidity



$$U_{KP}(i, i + 1, i + 2) = \frac{k_B T \xi_p}{\sigma} (1 - \cos(\theta))$$

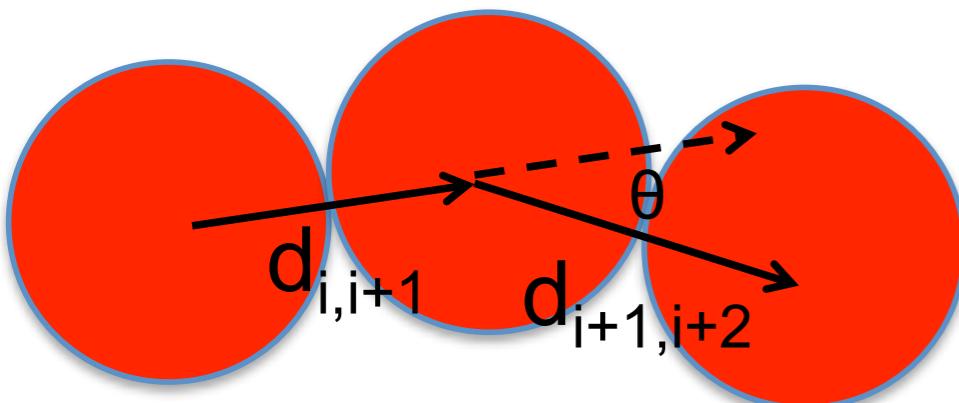
where

$\xi_p = 5 \sigma$ is the persistence length of the fiber

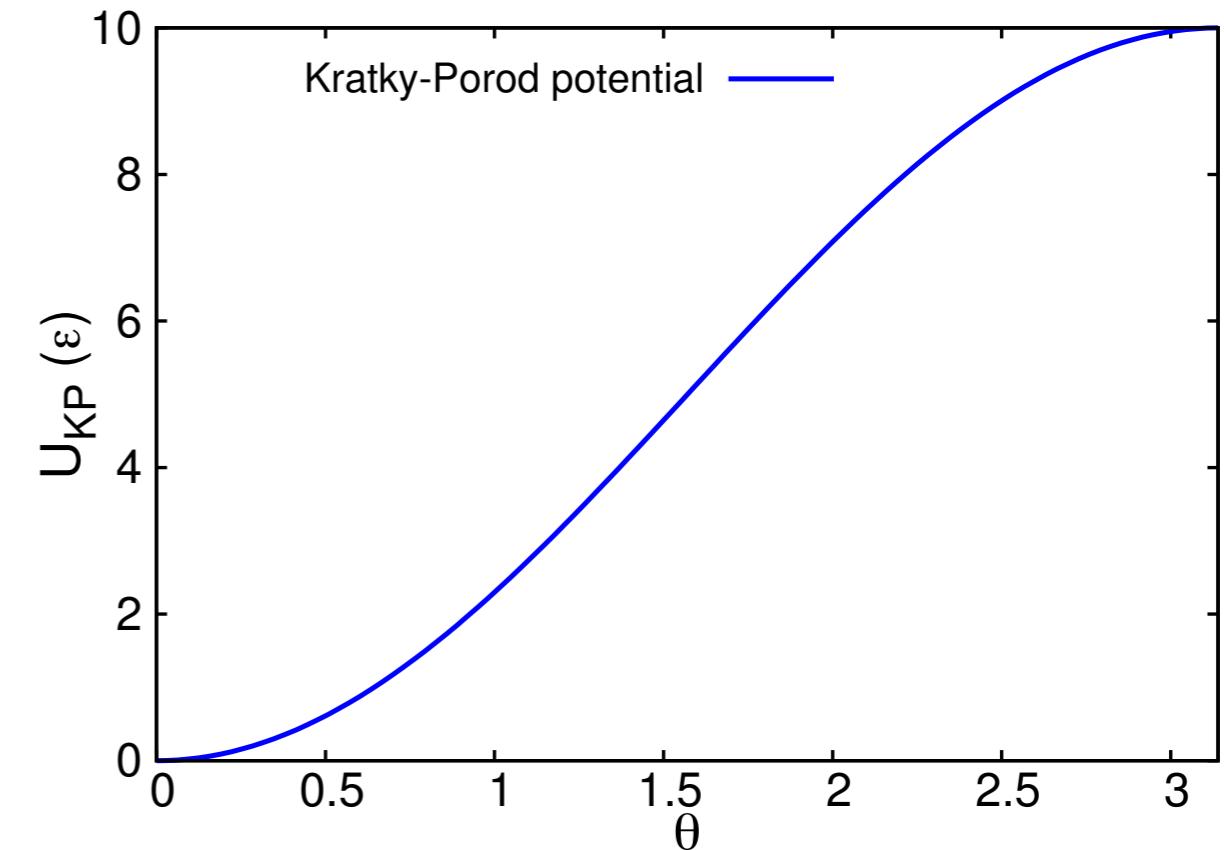
$k_B T = \epsilon$ is the thermal energy

Rosa and Everaers PLoSCB 2008; Rosa and Everaers BJ 2010

Physical restraints



Bending rigidity



$$U_{KP}(i, i + 1, i + 2) = \frac{k_B T \xi_p}{\sigma} (1 - \cos(\theta))$$

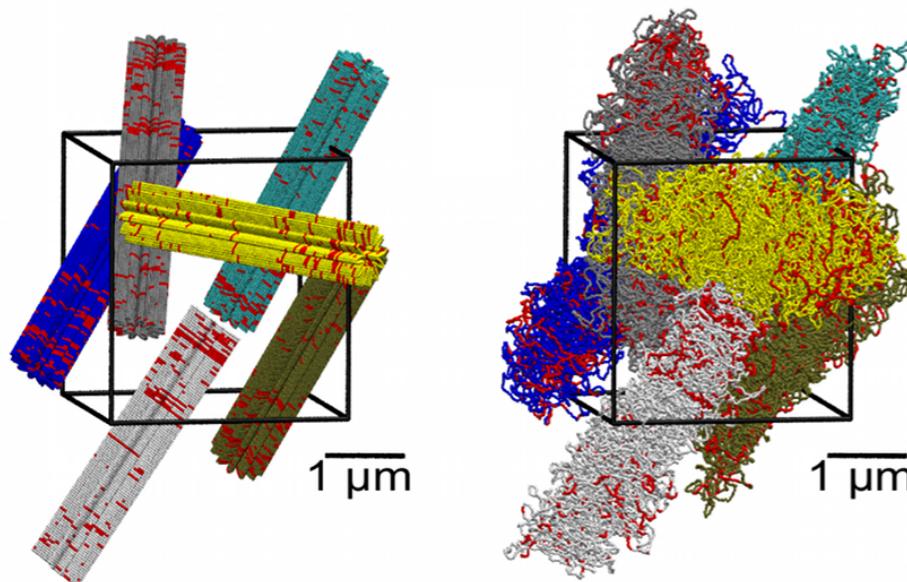
where

This length-scale should be compared to the resolution!

$\xi_p = 5 \sigma$ is the persistence length of the fiber

$k_B T = \epsilon$ is the thermal energy

Application: Physical models of chromosome 19



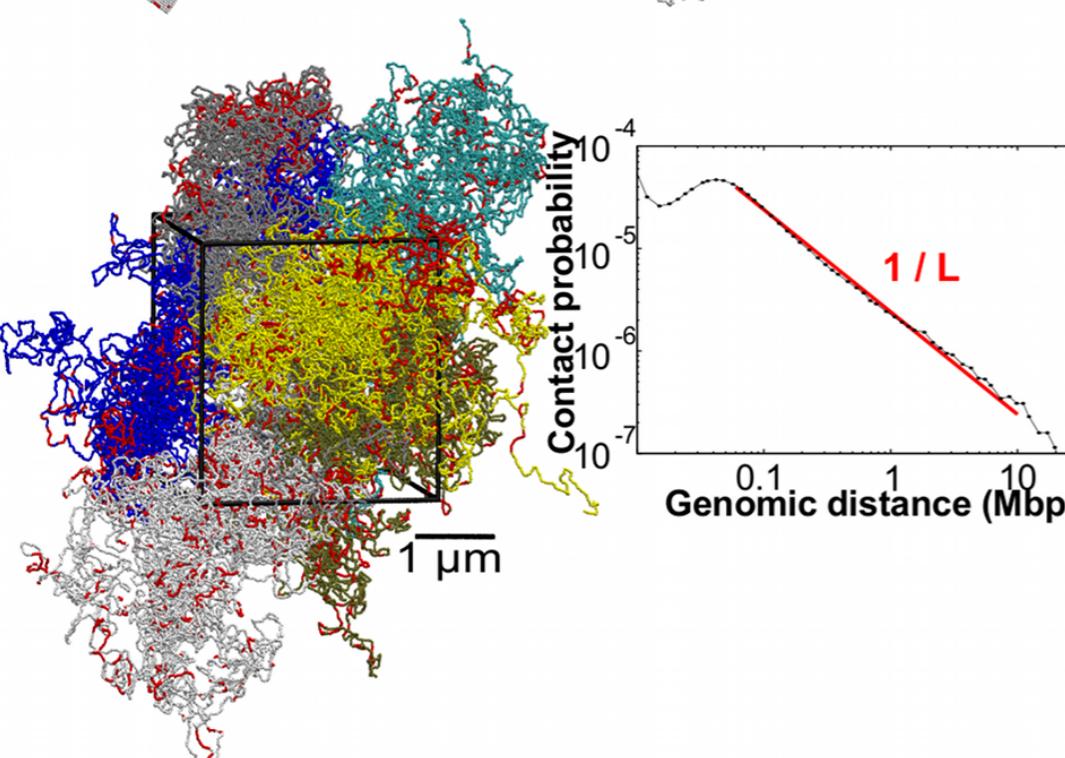
591μm long at 30nm (3kb)

6 copies at typical nuclear density

Excluded volume

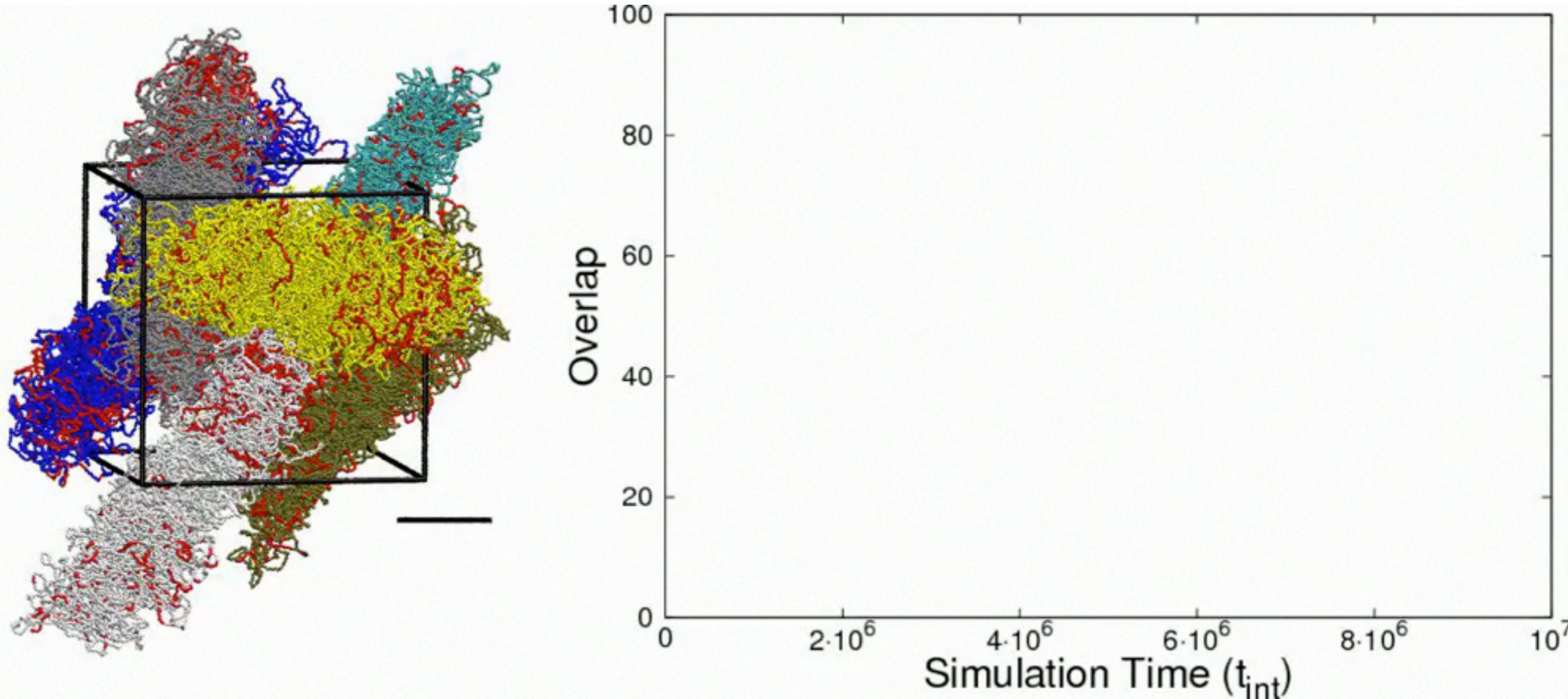
Chain connectivity

Bending rigidity



After simulating 7 hours (real time) of chromosome decondensation, the average structure of the model chromosomes is a **crumpled globule**.

Steered brownian dynamics



Harmonic restraints are used to colocalize pairs of chromosomal regions. The final conformations are analysed to get biological insight.

3D modeling of genomic domains: other methods

