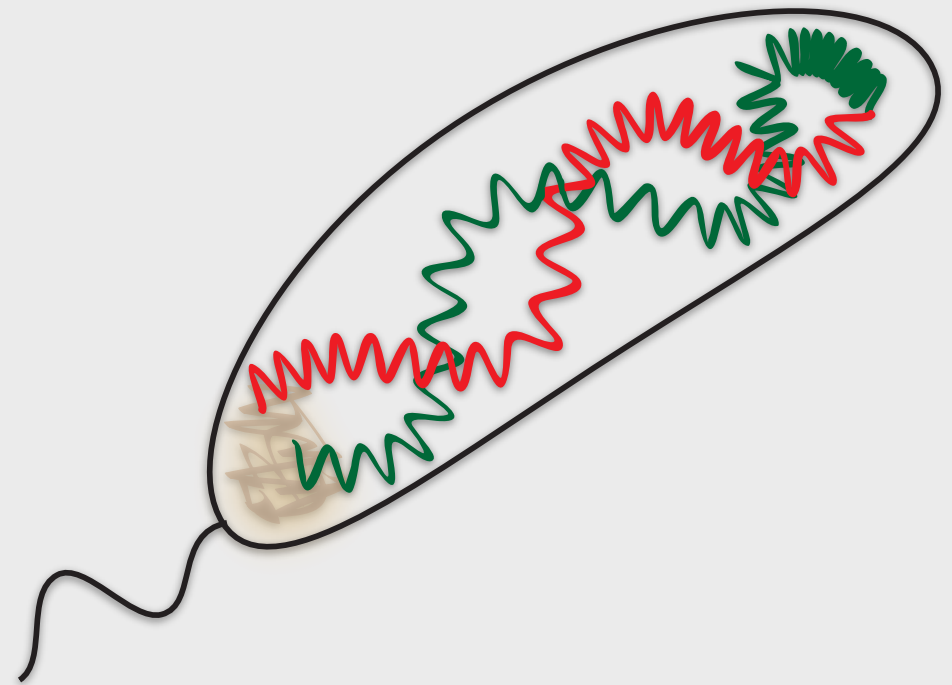
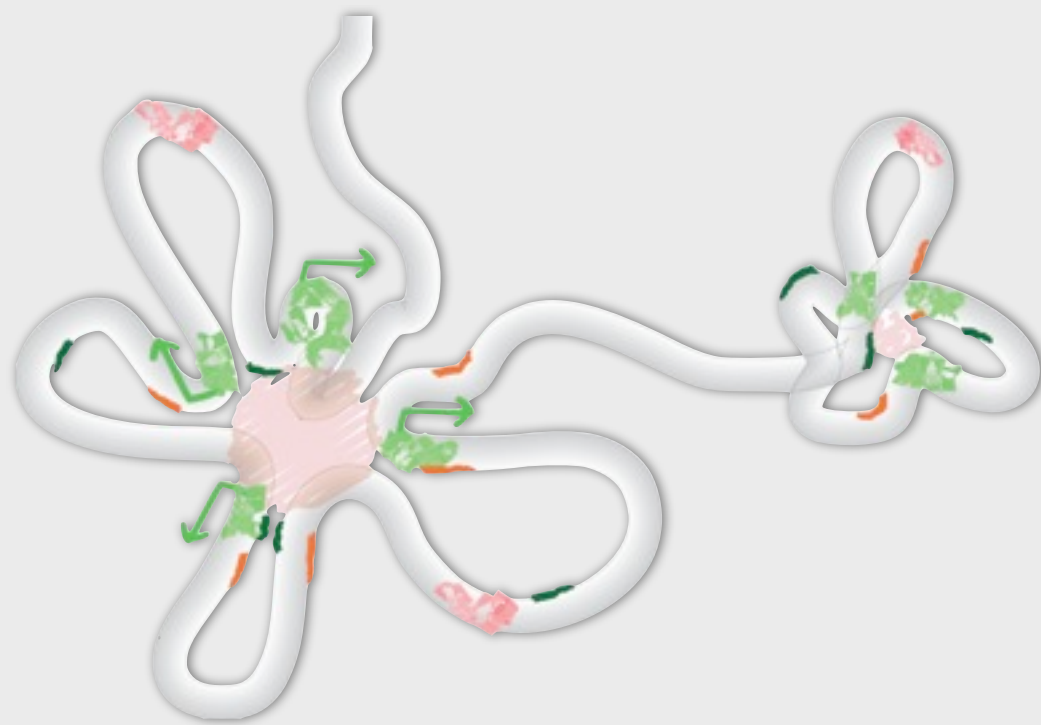


Structure determination of genomes and genomic domains by satisfaction of spatial restraints



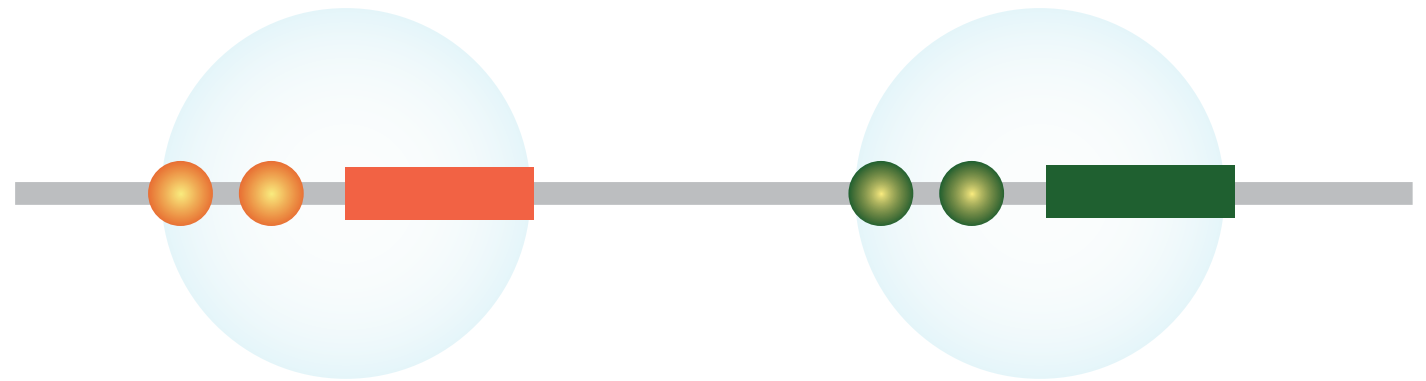
Structural Genomics Laboratory
Bioinformatics & Genomics Department
Prince Felipe Research Center (CIPF), Valencia, Spain

Marc A. Marti-Renom

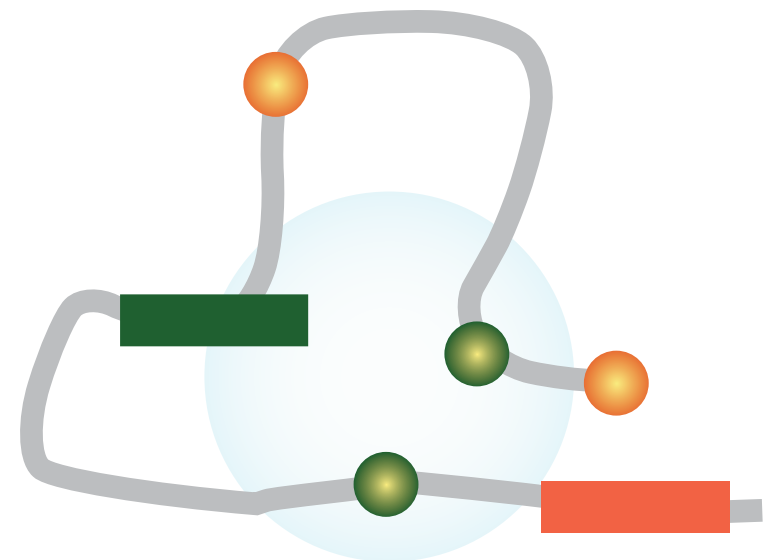
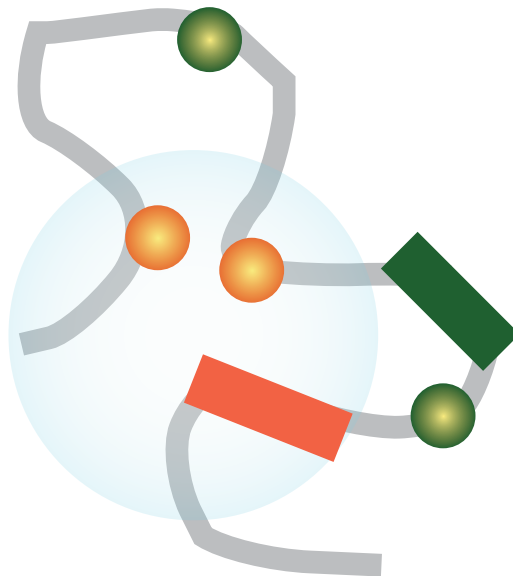


<http://sgu.bioinfo.cipf.es>

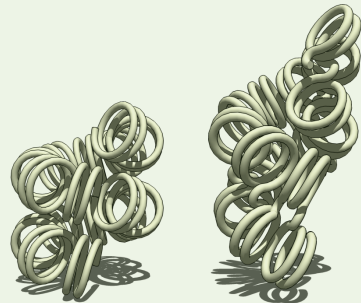
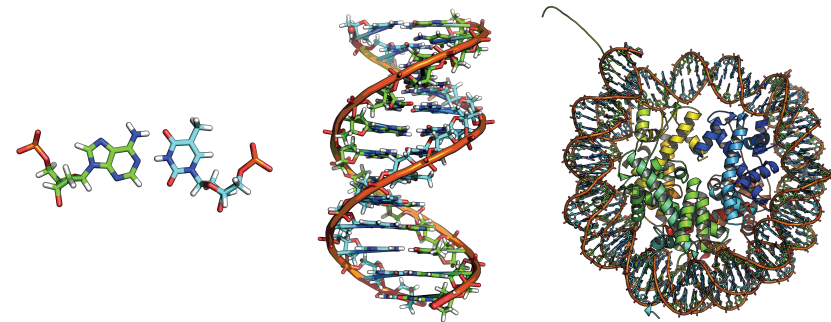
Simple genomes



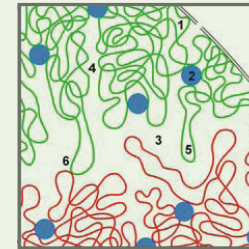
Complex genomes



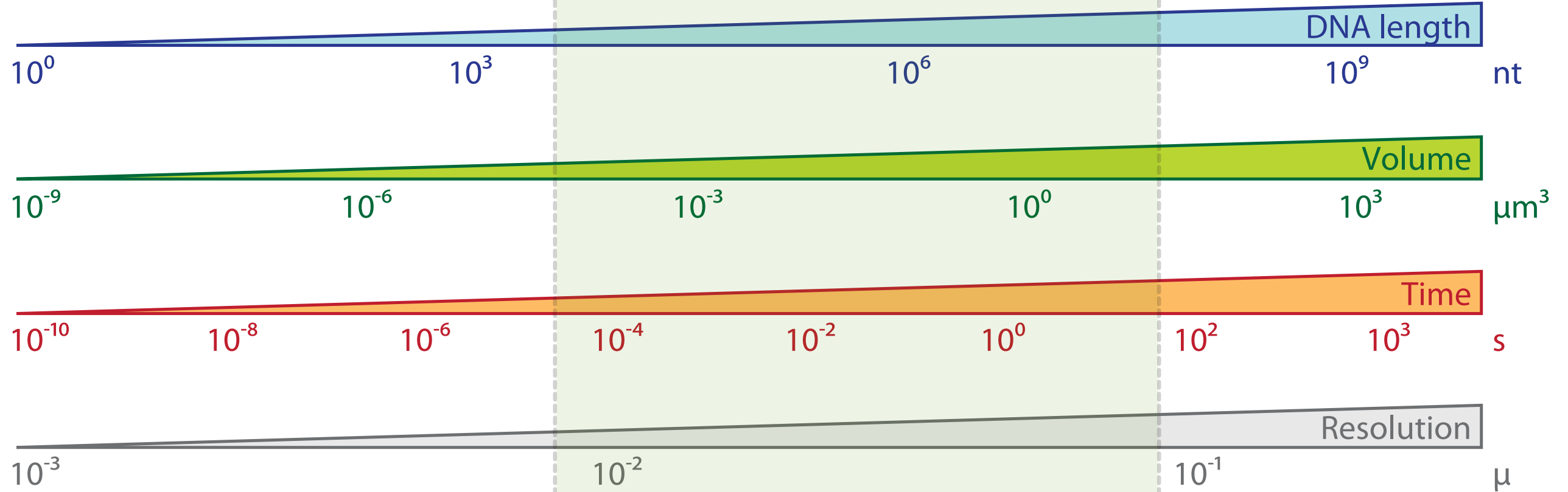
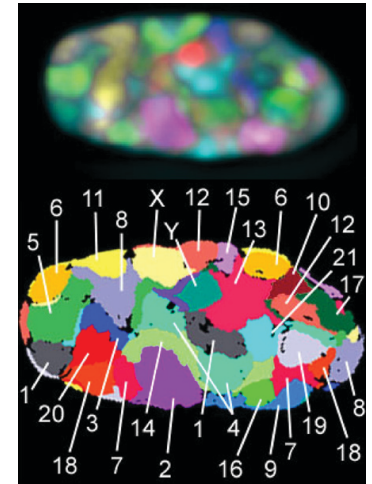
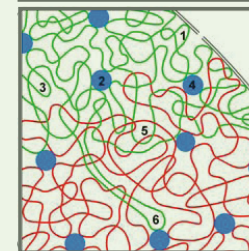
Knowledge



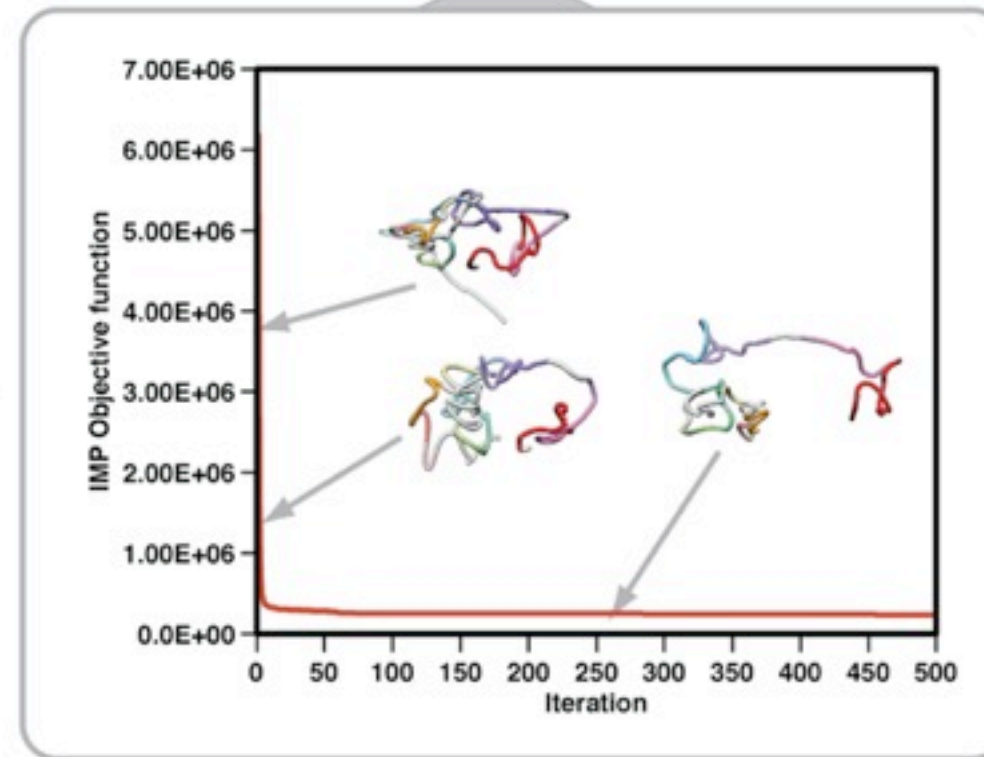
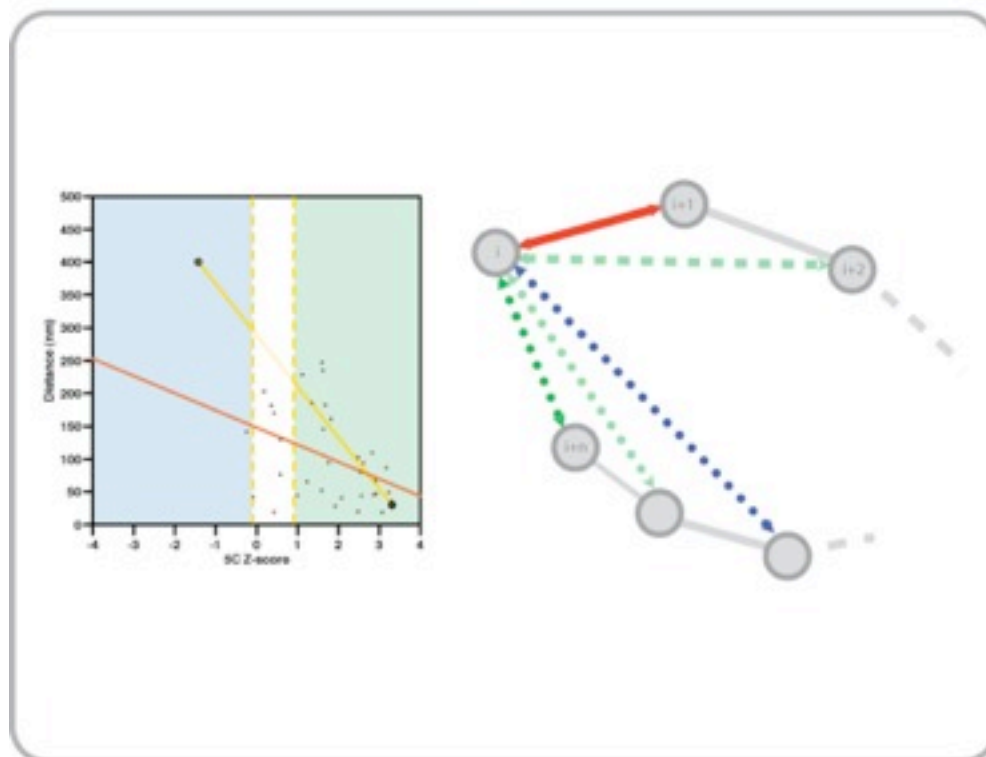
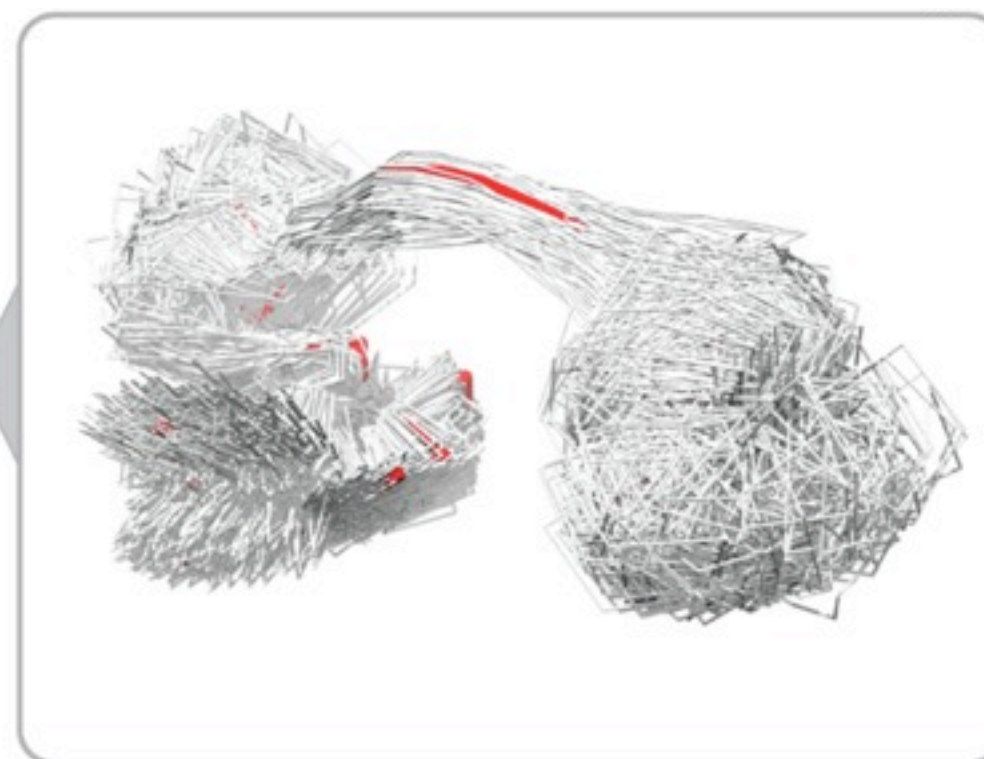
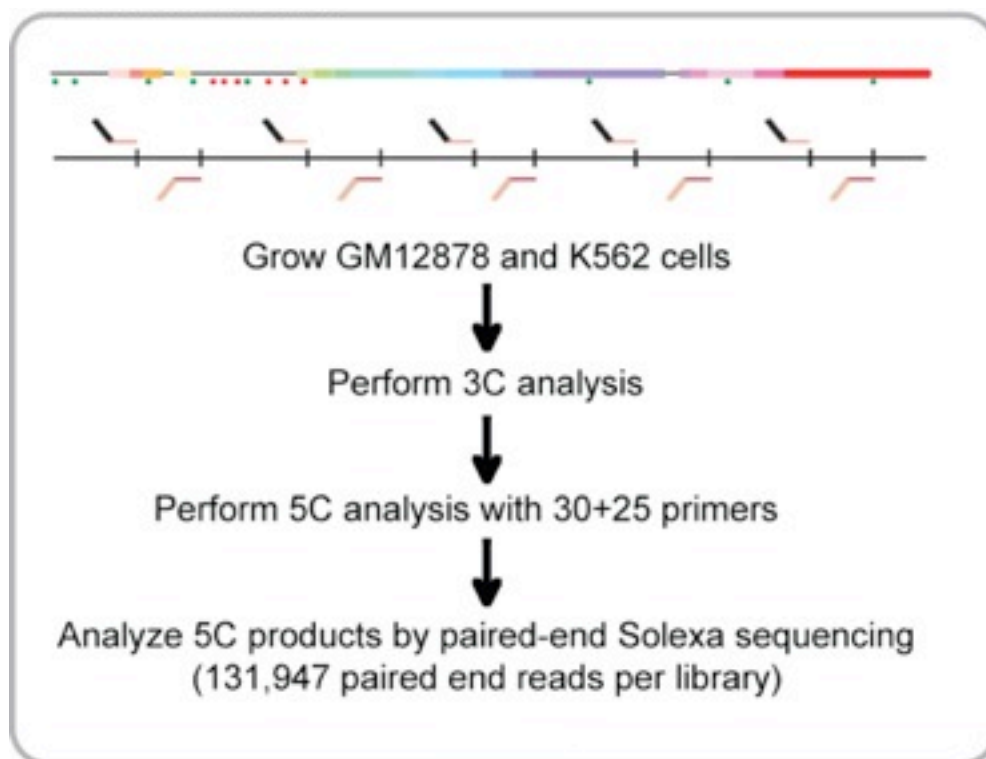
IDM

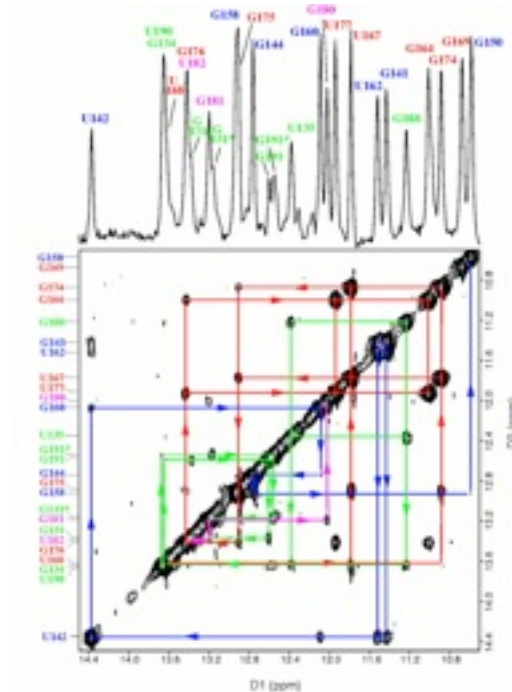
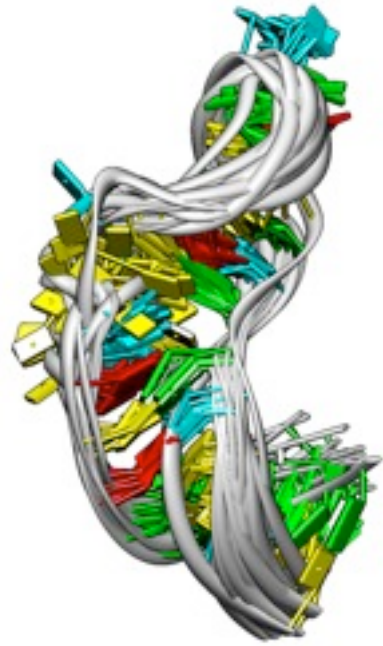


INM

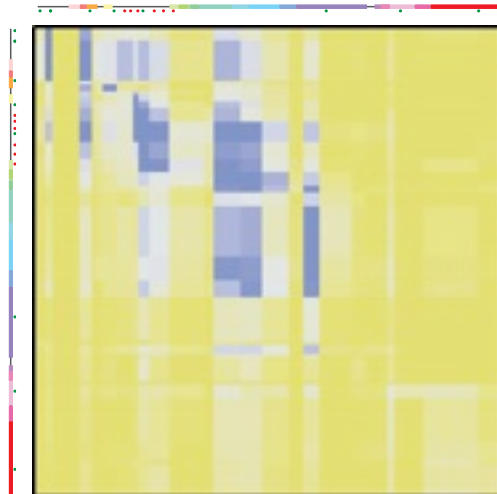
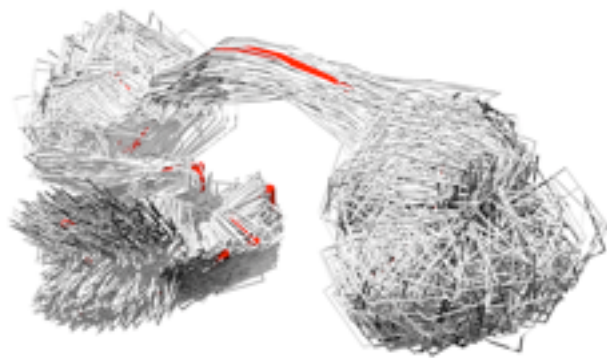


Adapted from:
Langowski and Heermann. *Semin Cell Dev Biol* (2007) vol. 18 (5) pp. 659-67





Biomolecular structure determination *2D-NOESY data*



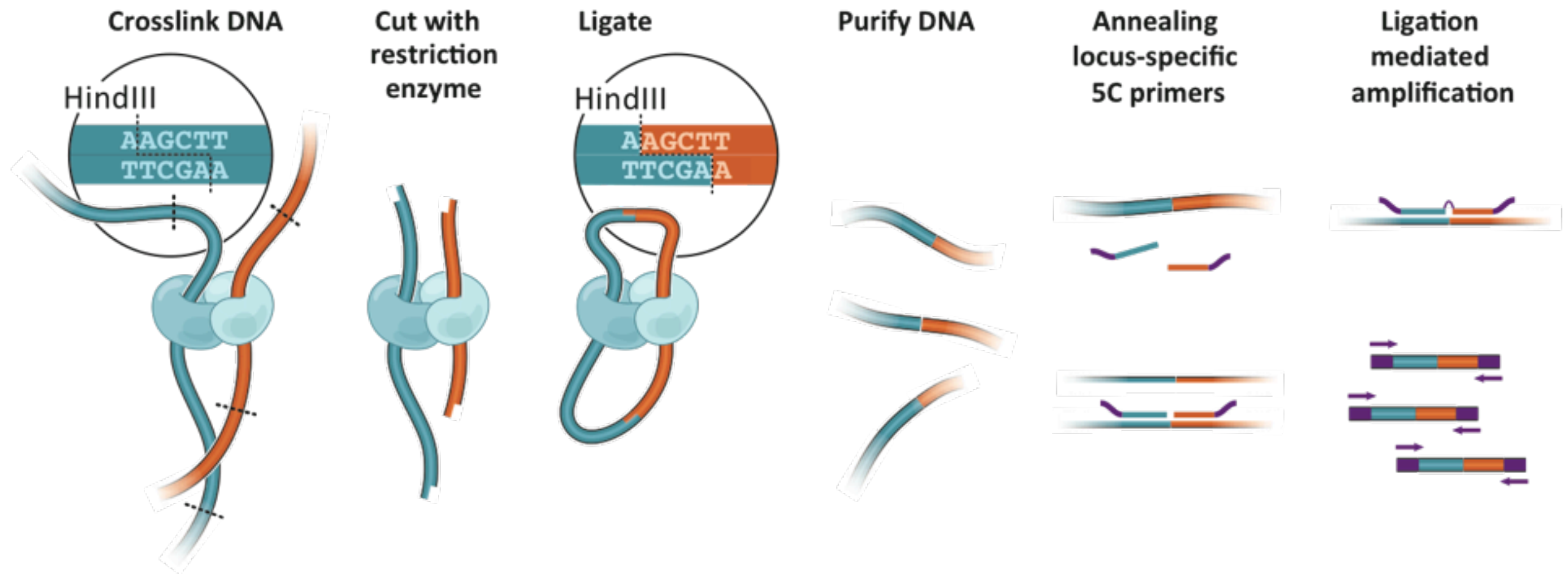
Chromosome structure determination *5C data*



5C technology

<http://my5C.umassmed.edu>

Dostie et al. Genome Res (2006) vol. 16 (10) pp. 1299-309



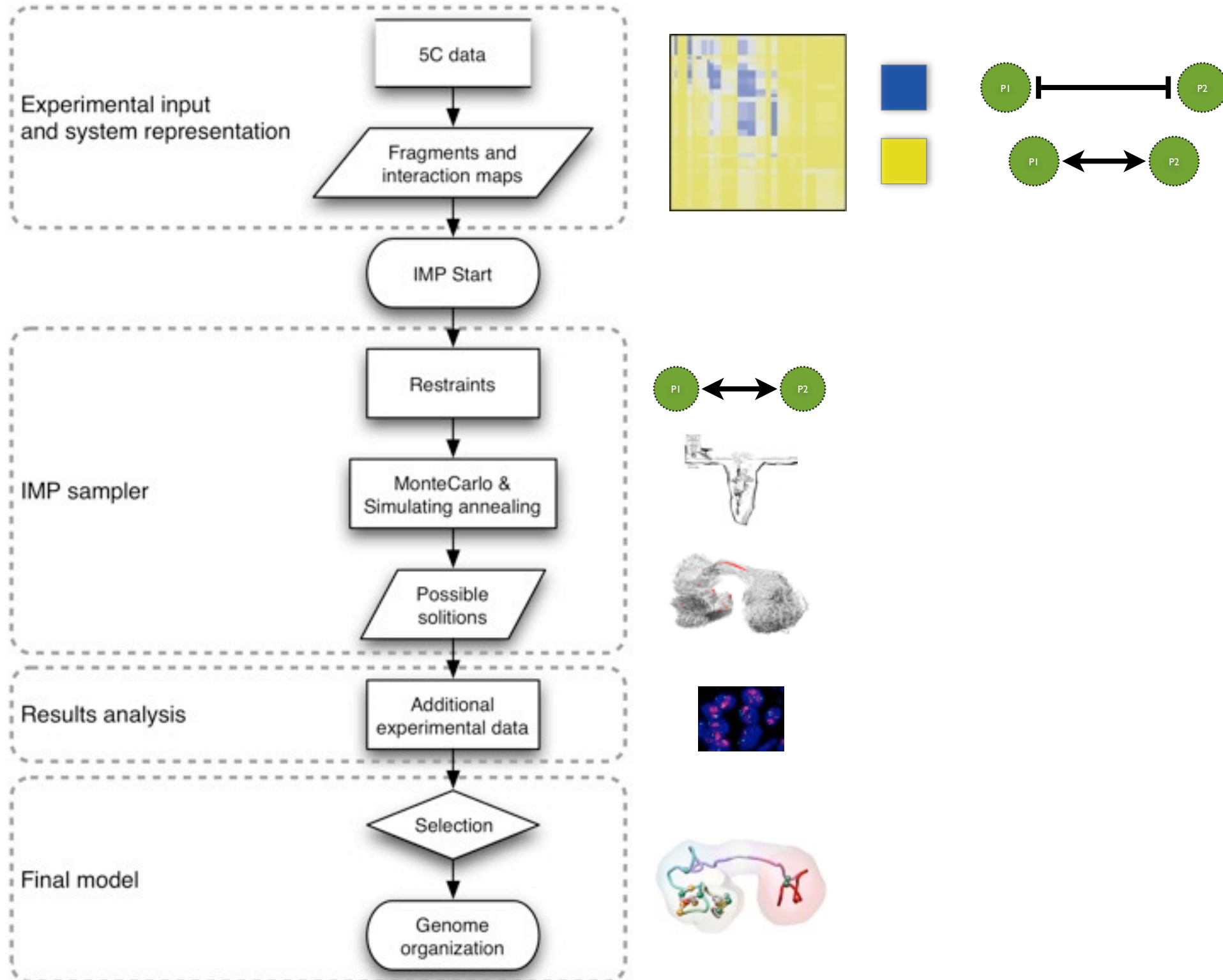
5C “copies” the 3C library into a 5C library containing only ligation junctions

Performed at high levels of multiplexing:

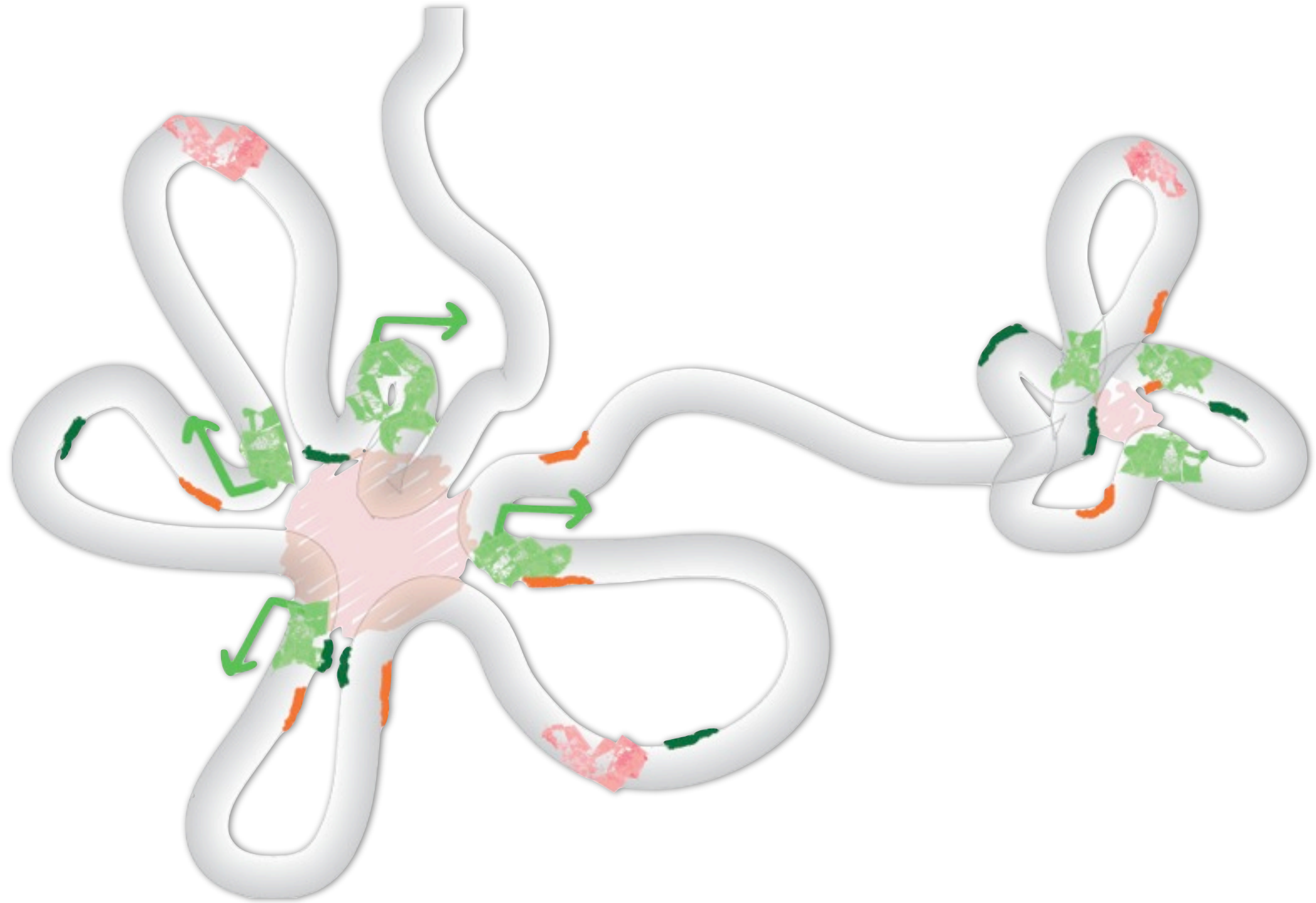
2,000 primers detect 1,000,000 unique interactions in 1 reaction

Integrative Modeling

<http://www.integrativemodeling.org>



Human α -globin domain



Human α -globin domain

ENm008 genomic structure and environment

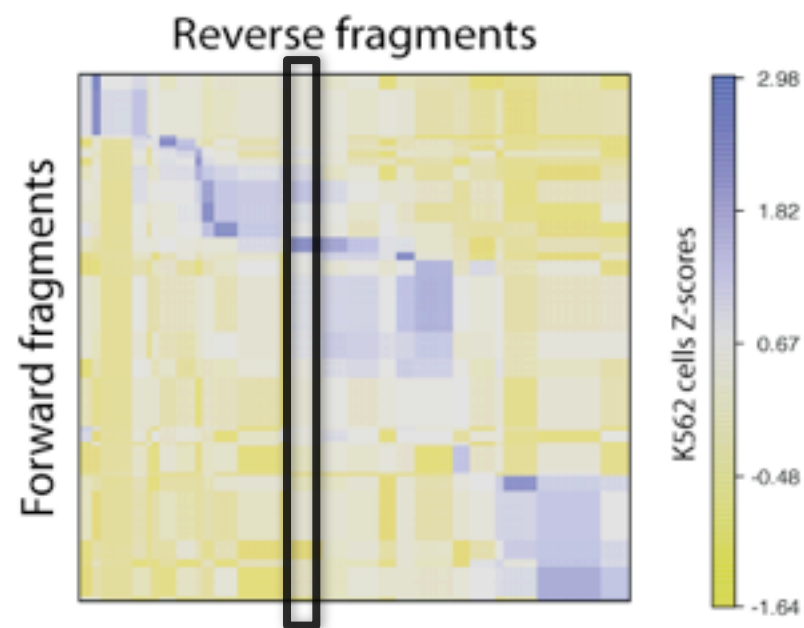
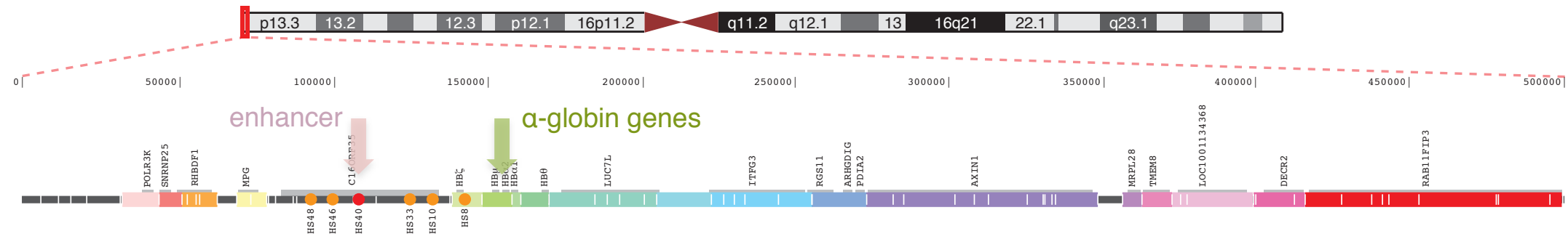
ENCODE Consortium. *Nature* (2007) vol. 447 (7146) pp. 799-816



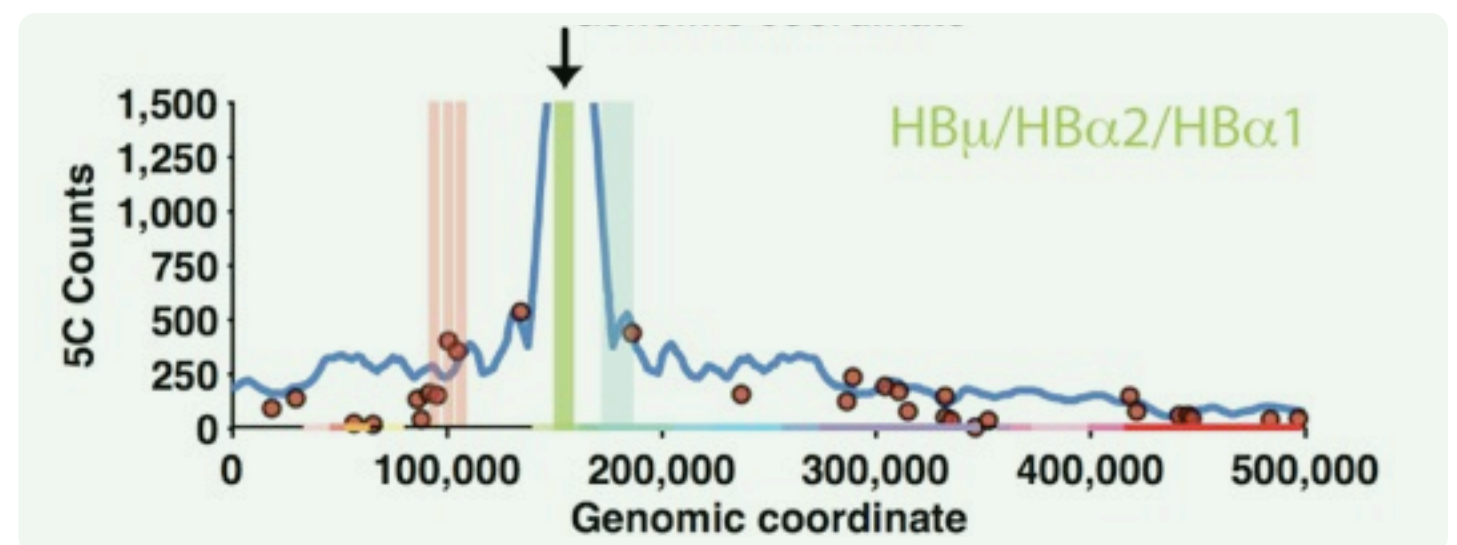
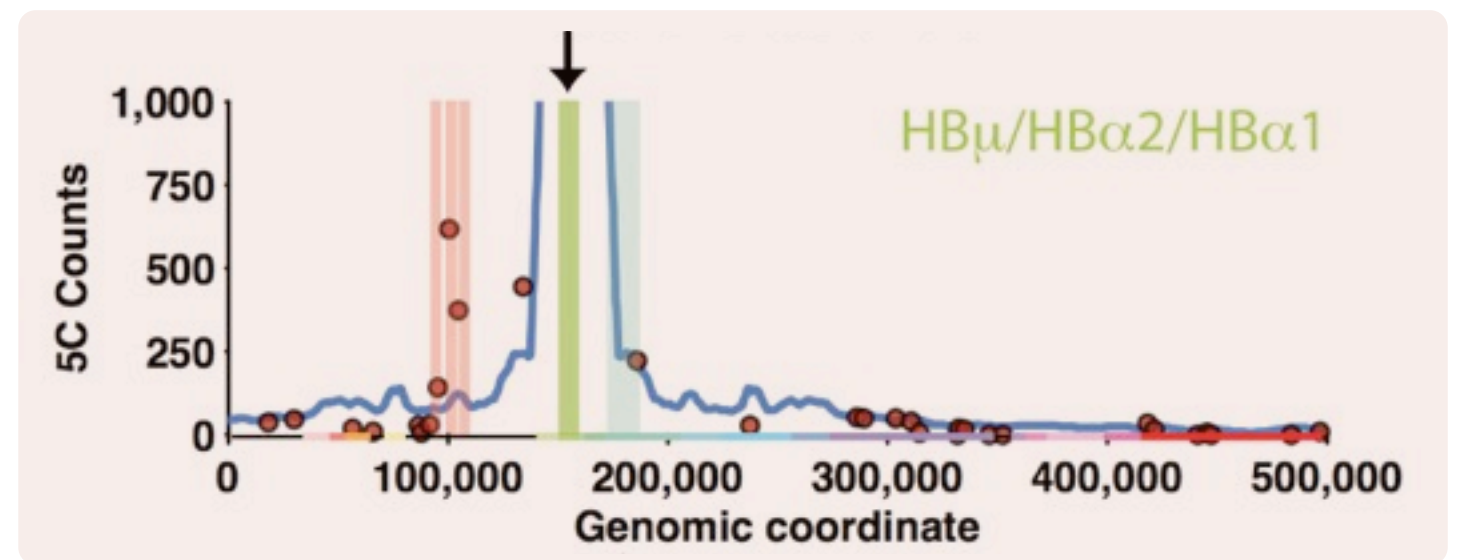
The ENCODE data for ENm008 region was obtained from the UCSC Genome Browser tracks for: RefSeq annotated genes, Affymetrix/CSHL expression data (Gingeras Group at Cold Spring Harbor), Duke/NHGRI DNaseI Hypersensitivity data (Crawford Group at Duke University), and Histone Modifications by Broad Institute ChIP-seq (Bernstein Group at Broad Institute of Harvard and MIT).

Human α -globin domain

ENm008 genomic structure and environment



K562 cells:
 α -globin genes active



Representation

Harmonic

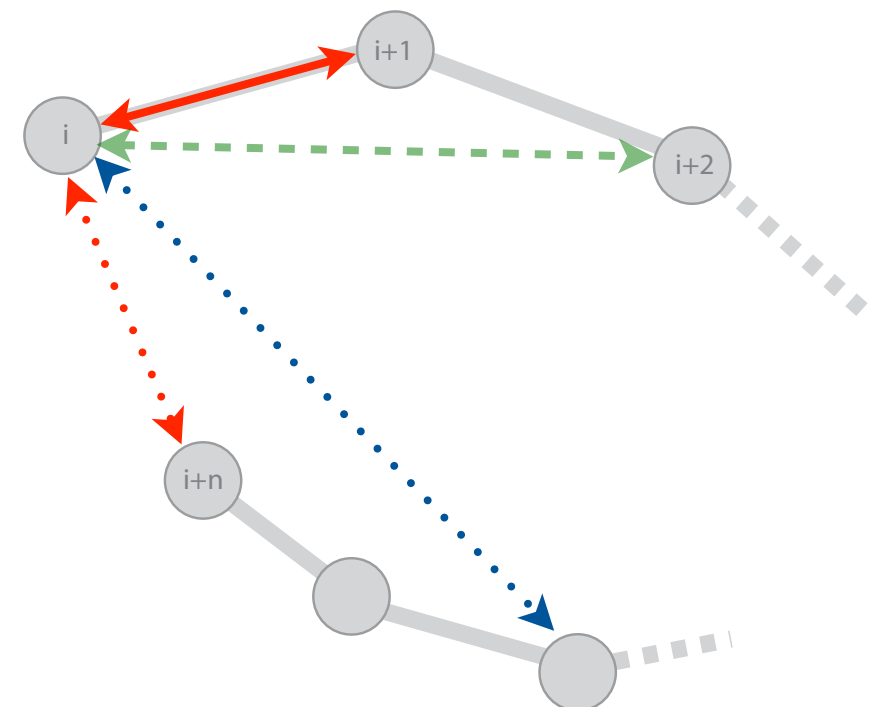
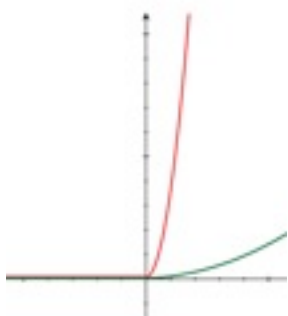
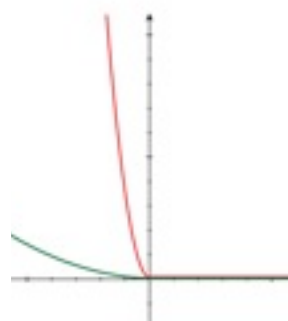
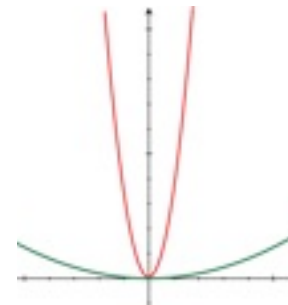
$$H_{i,j} = k(d_{i,j} - d_{i,j}^0)^2$$

Harmonic Lower Bound

$$\begin{cases} \text{if } d_{i,j} \leq d_{i,j}^0; & lbH_{i,j} = k(d_{i,j} - d_{i,j}^0)^2 \\ \text{if } d_{i,j} > d_{i,j}^0; & lbH_{i,j} = 0 \end{cases}$$

Harmonic Upper Bound

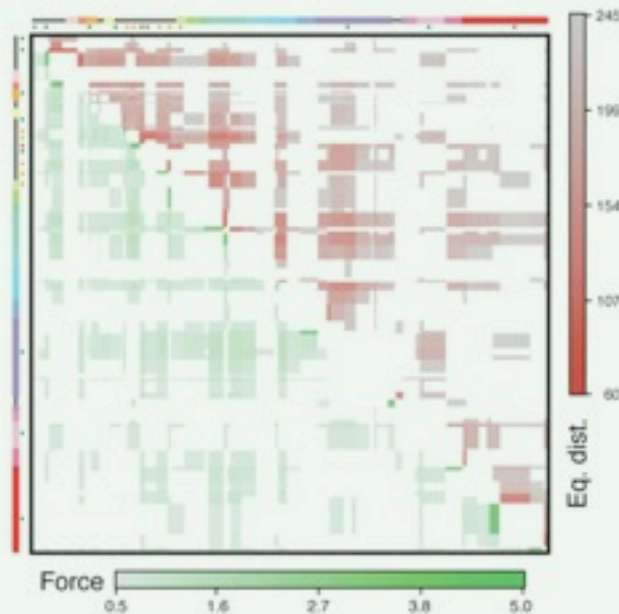
$$\begin{cases} \text{if } d_{i,j} \geq d_{i,j}^0; & ubH_{i,j} = k(d_{i,j} - d_{i,j}^0)^2 \\ \text{if } d_{i,j} < d_{i,j}^0; & ubH_{i,j} = 0 \end{cases}$$



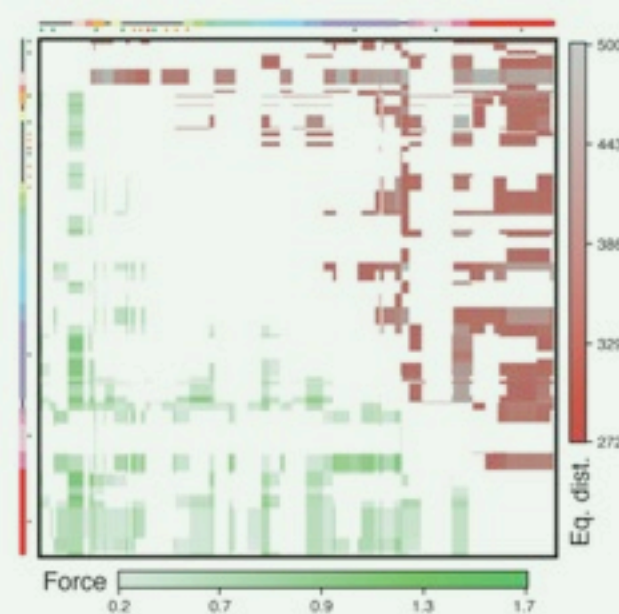
Scoring

GM12878

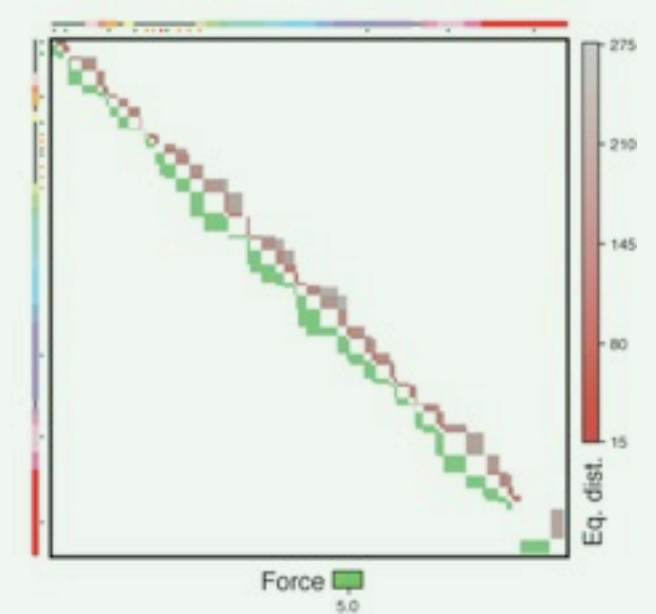
70 fragments
1,520 restraints



Harmonic



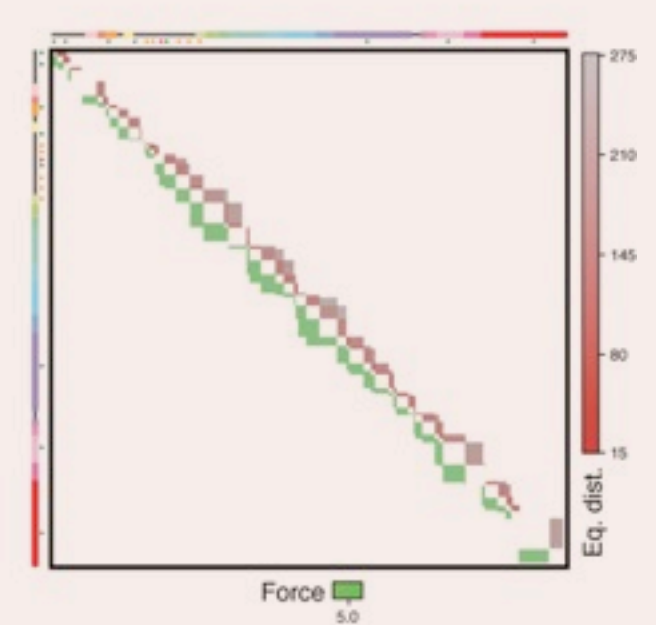
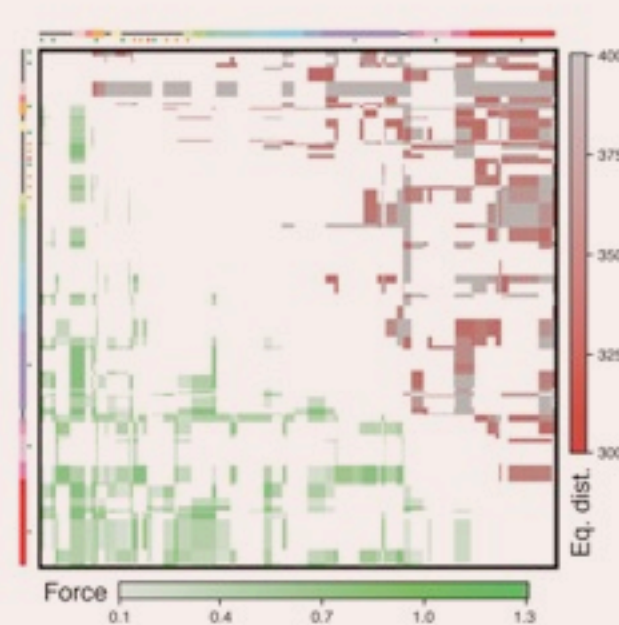
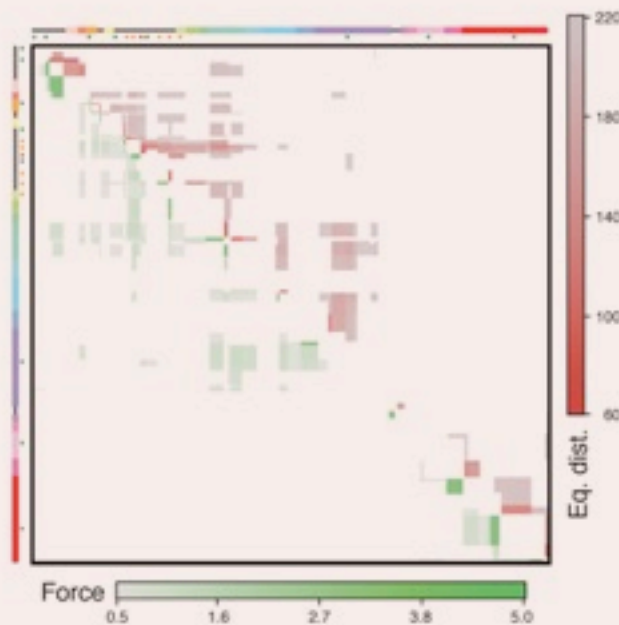
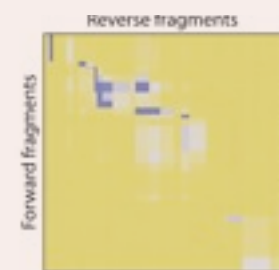
Harmonic Lower Bound



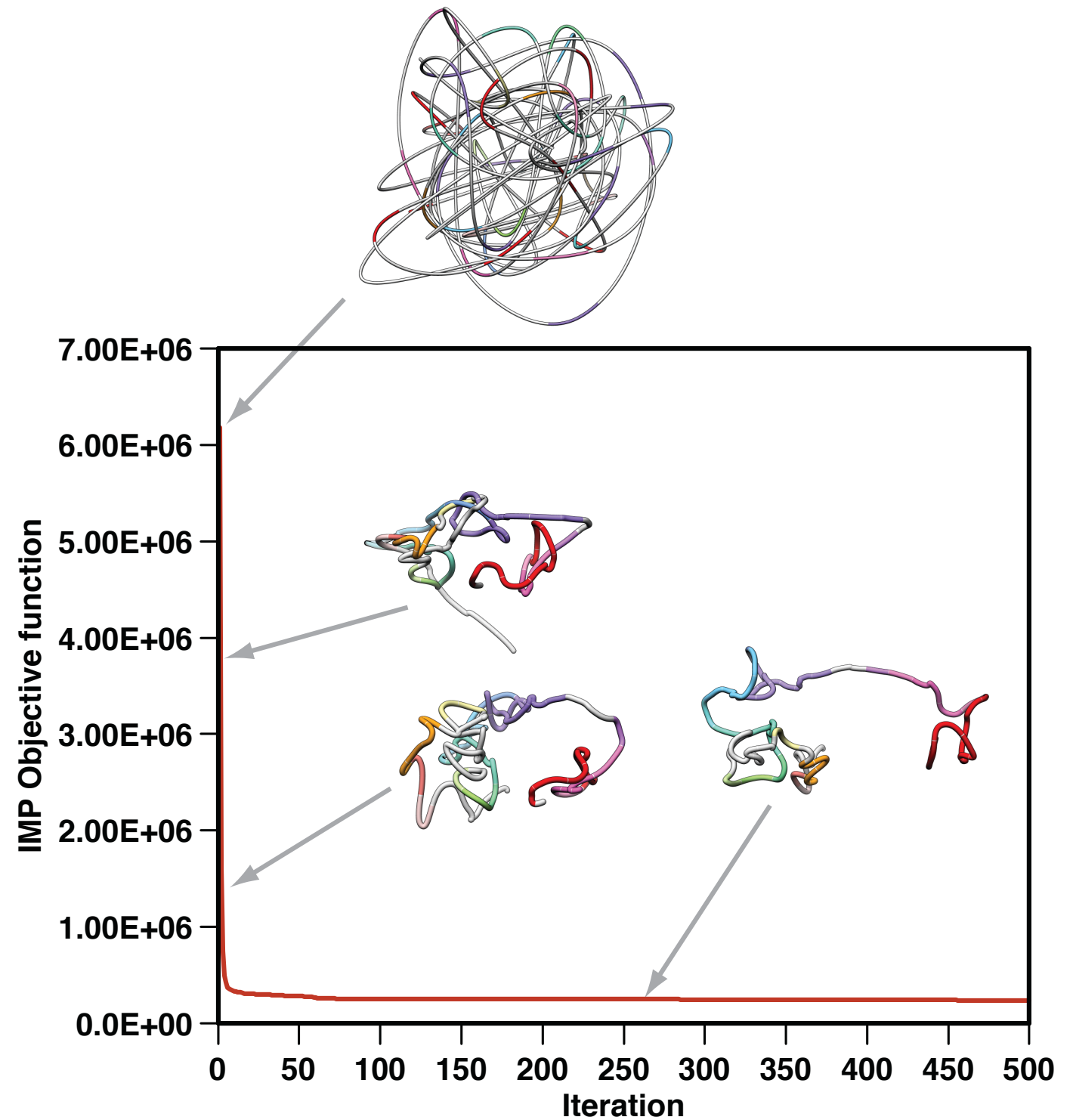
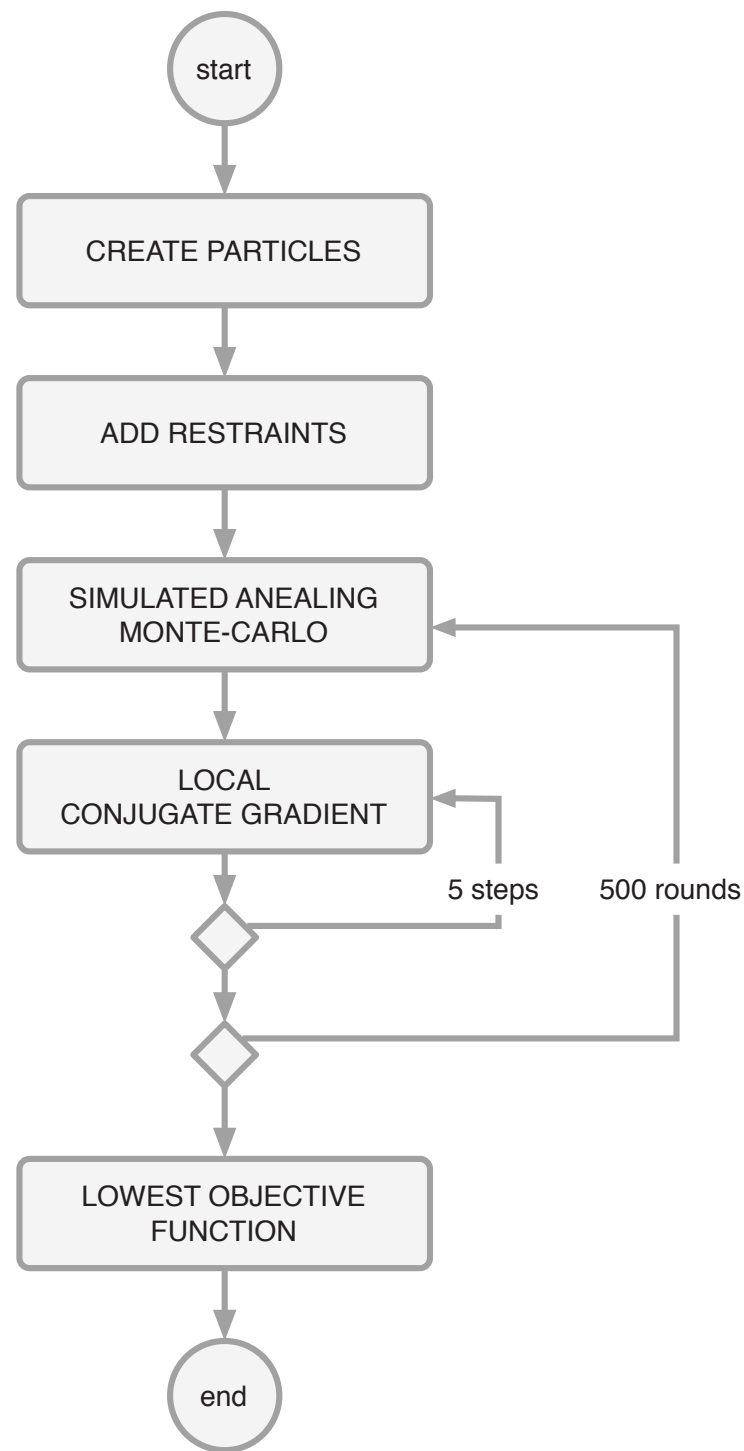
Harmonic Upper Bound

K562

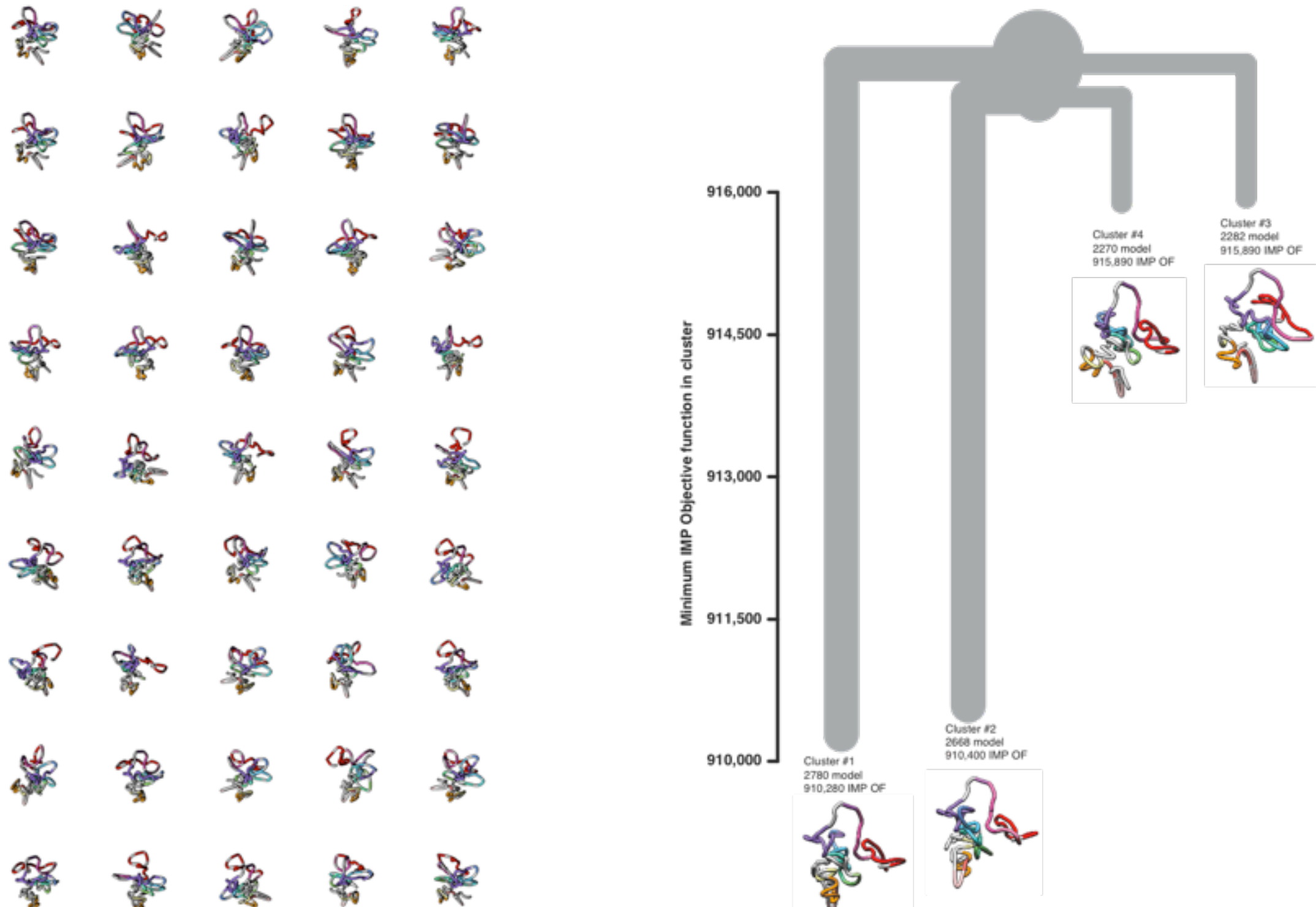
70 fragments
1,049 restraints



Optimization

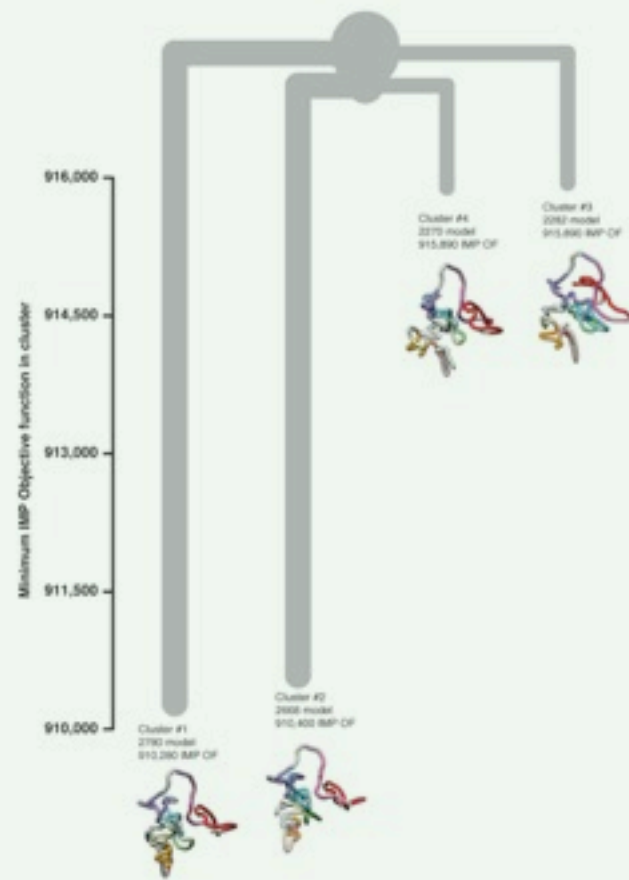
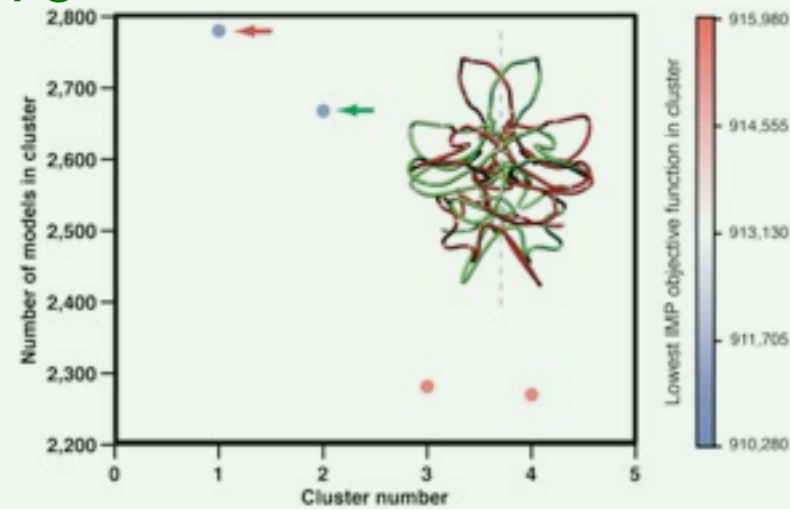


Clustering

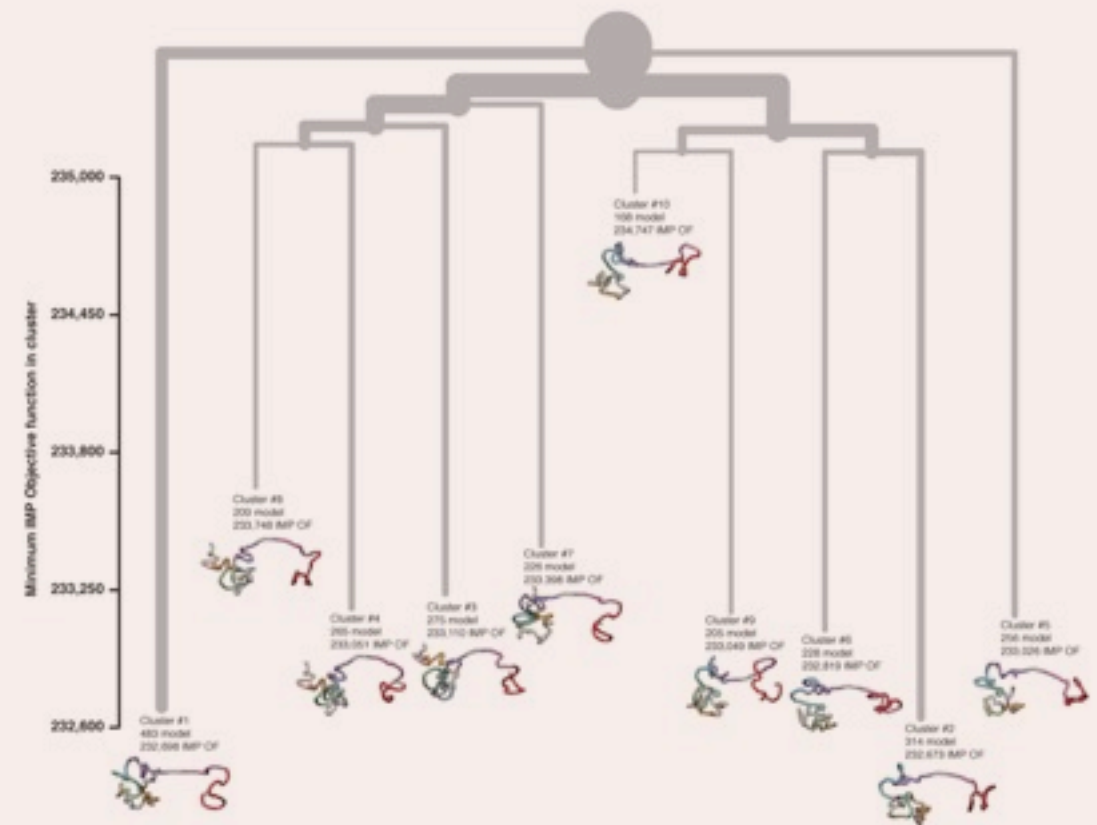
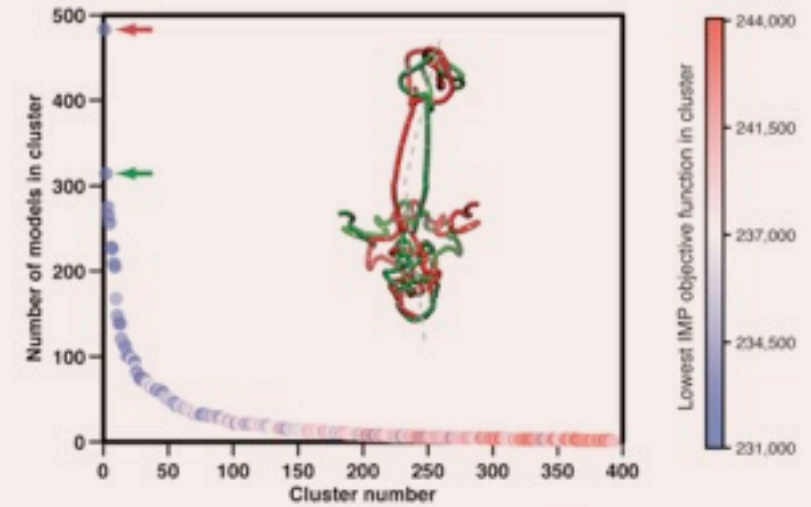


Not just *one* solution

GM12878



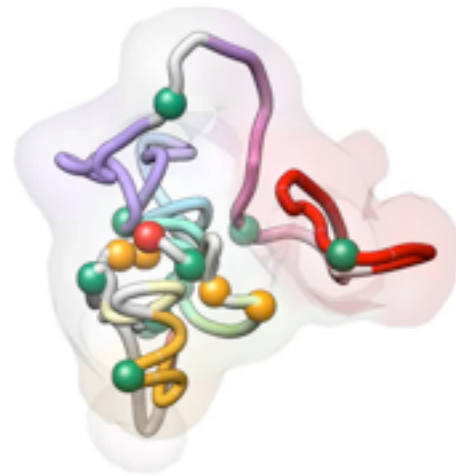
K562



Consistency

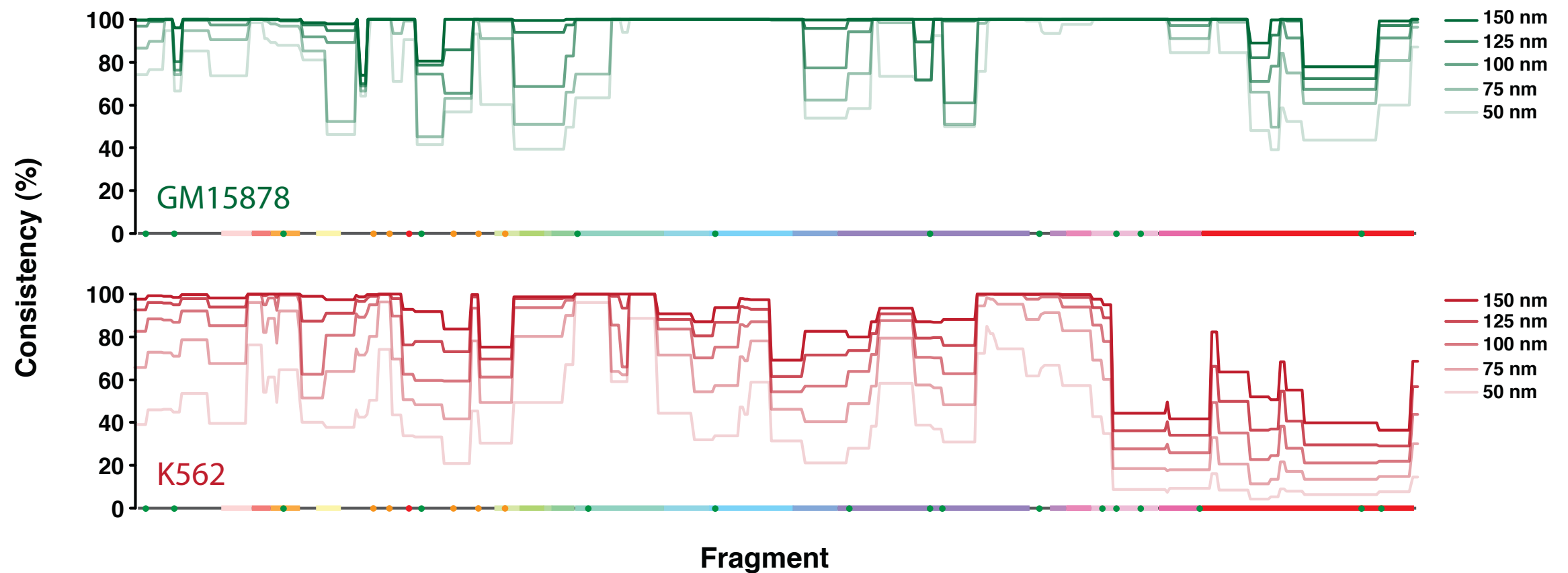
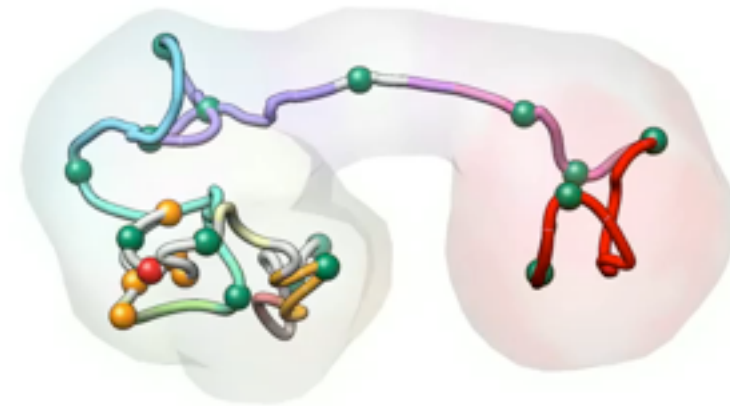
GM12878

Cluster #1
2780 model



K562

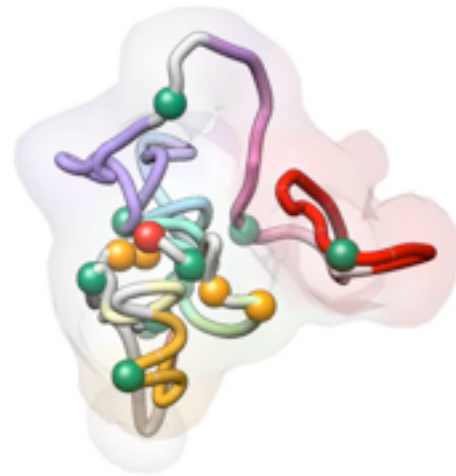
Cluster #2
314 model



Regulatory elements

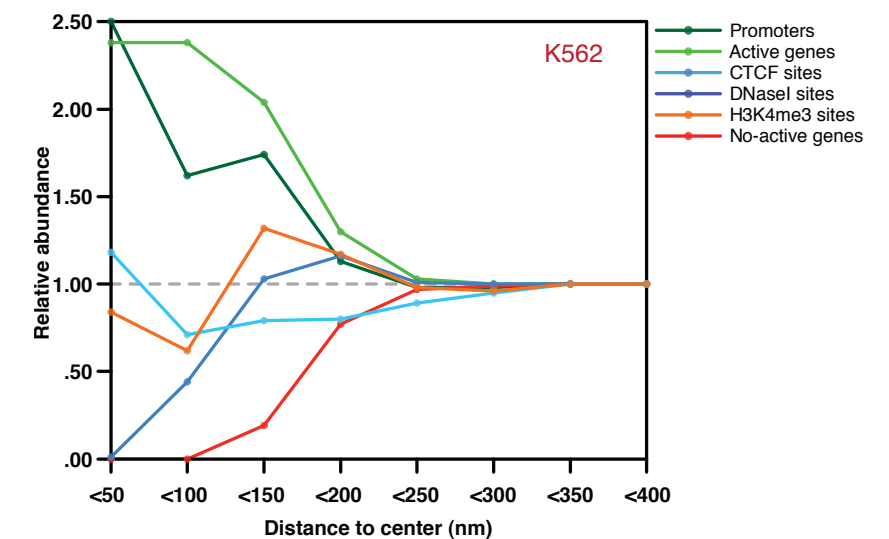
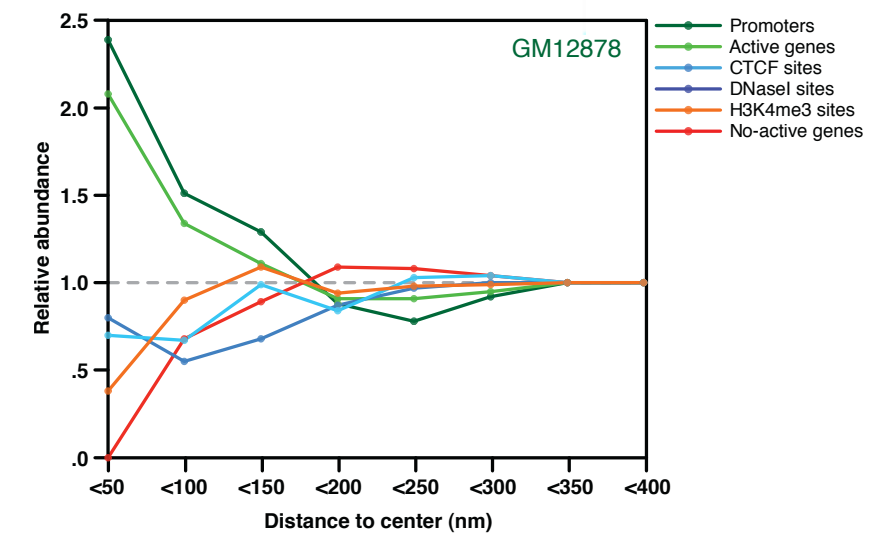
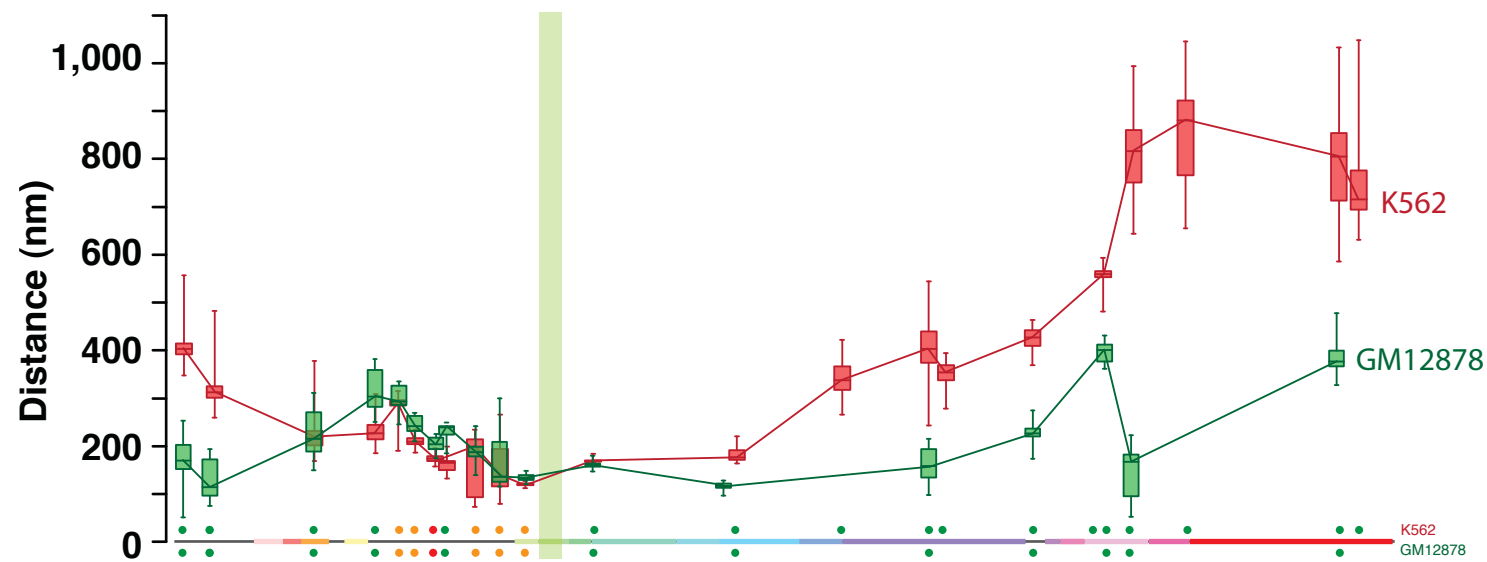
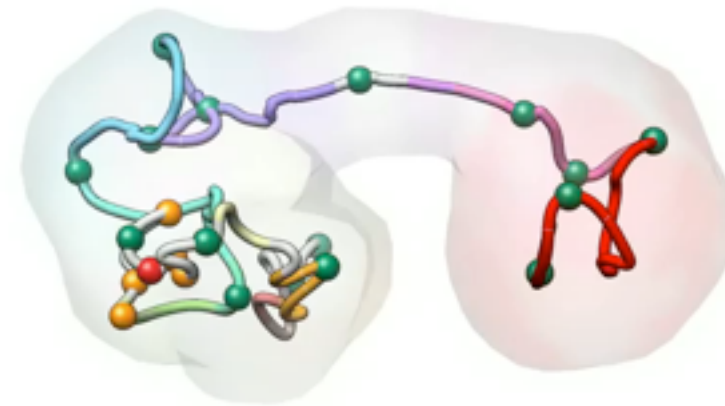
GM12878

Cluster #1
2780 model



K562

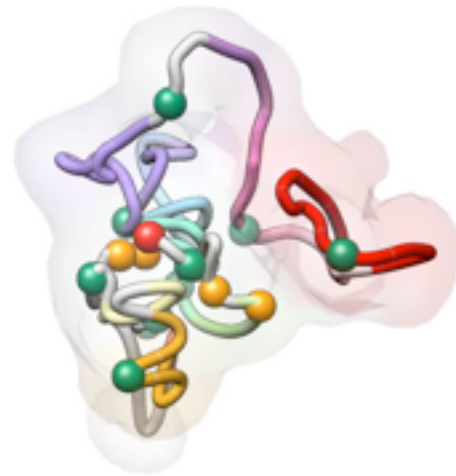
Cluster #2
314 model



Compactness

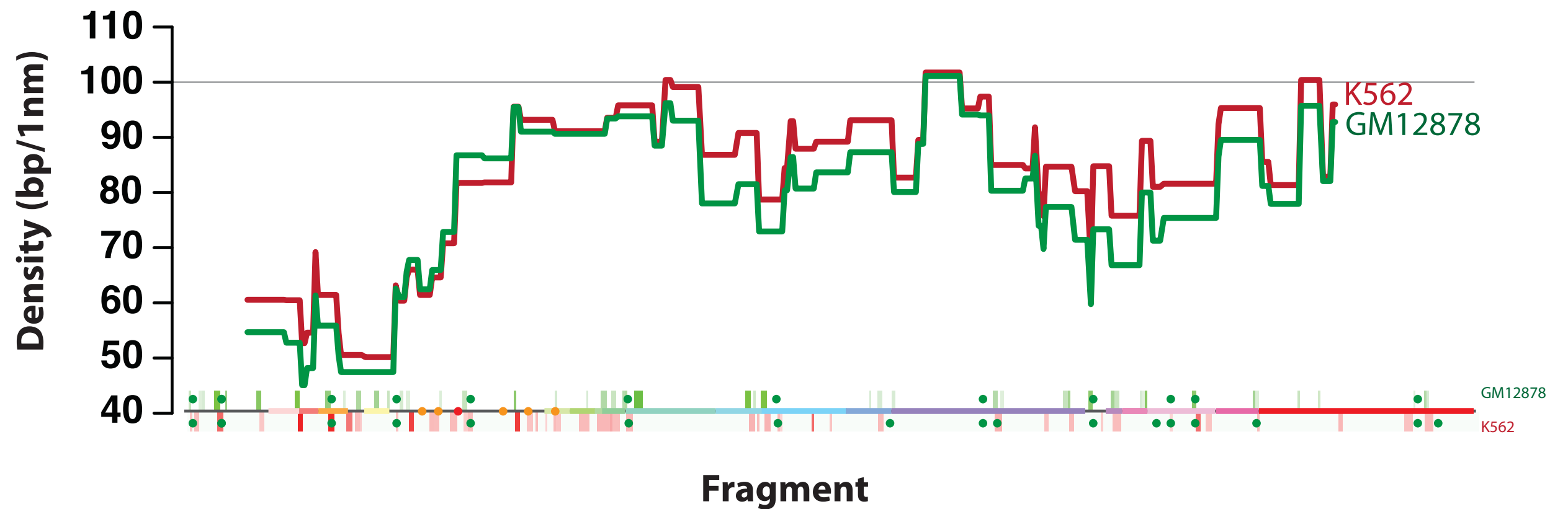
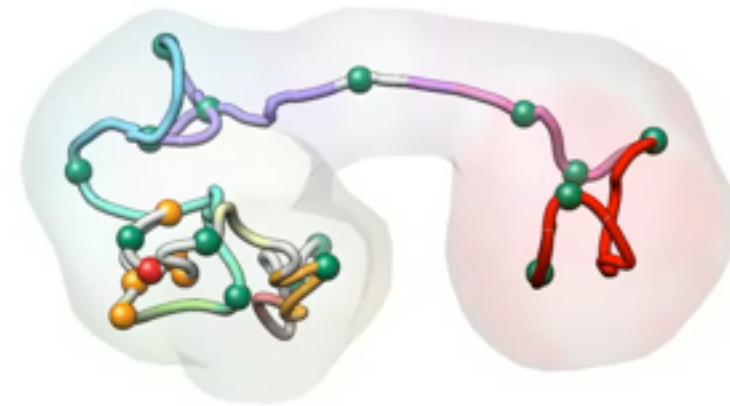
GM12878

Cluster #1
2780 model



K562

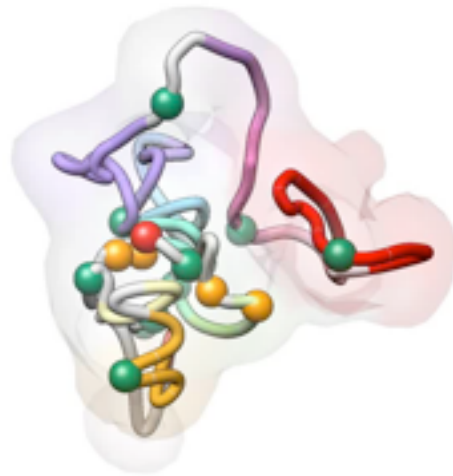
Cluster #2
314 model



Multi-loops

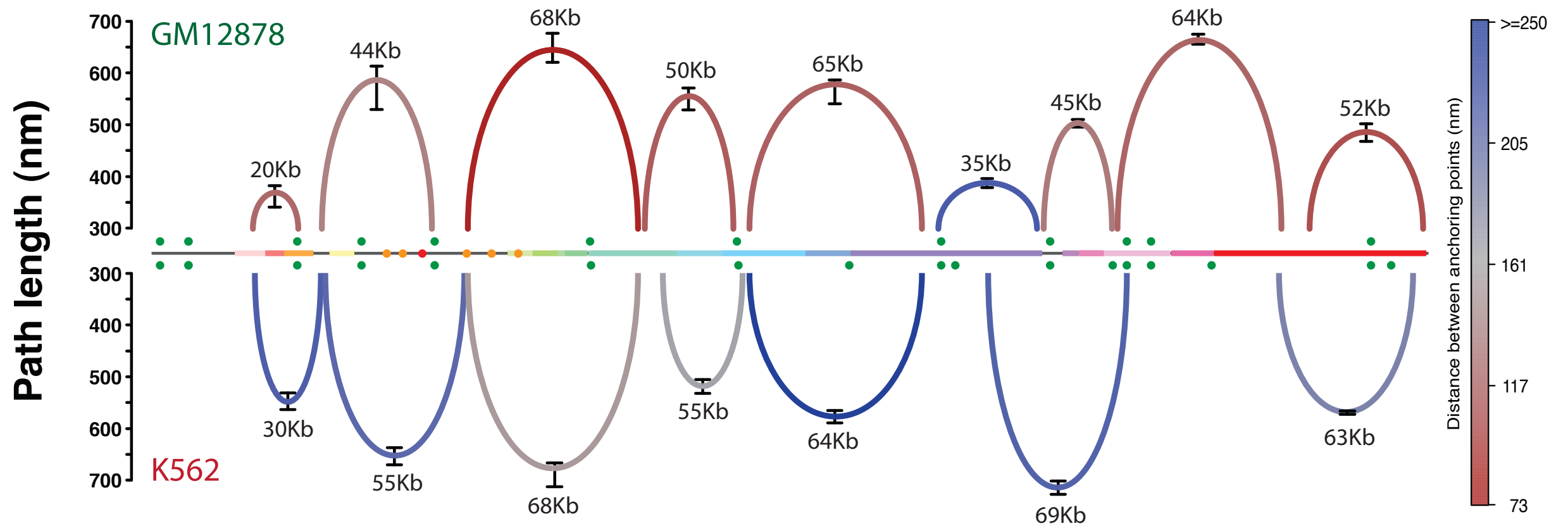
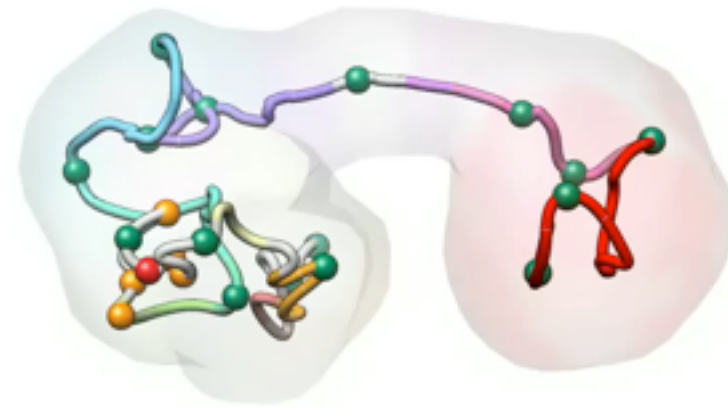
GM12878

Cluster #1
2780 model



K562

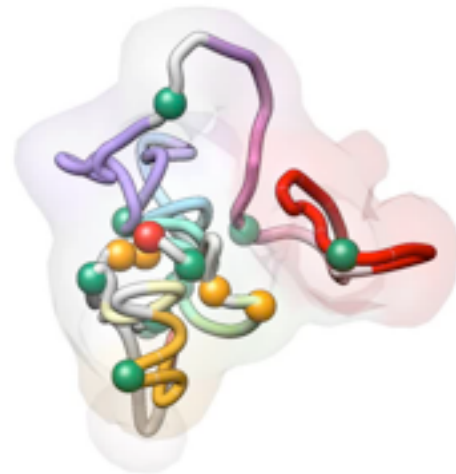
Cluster #2
314 model



Expression

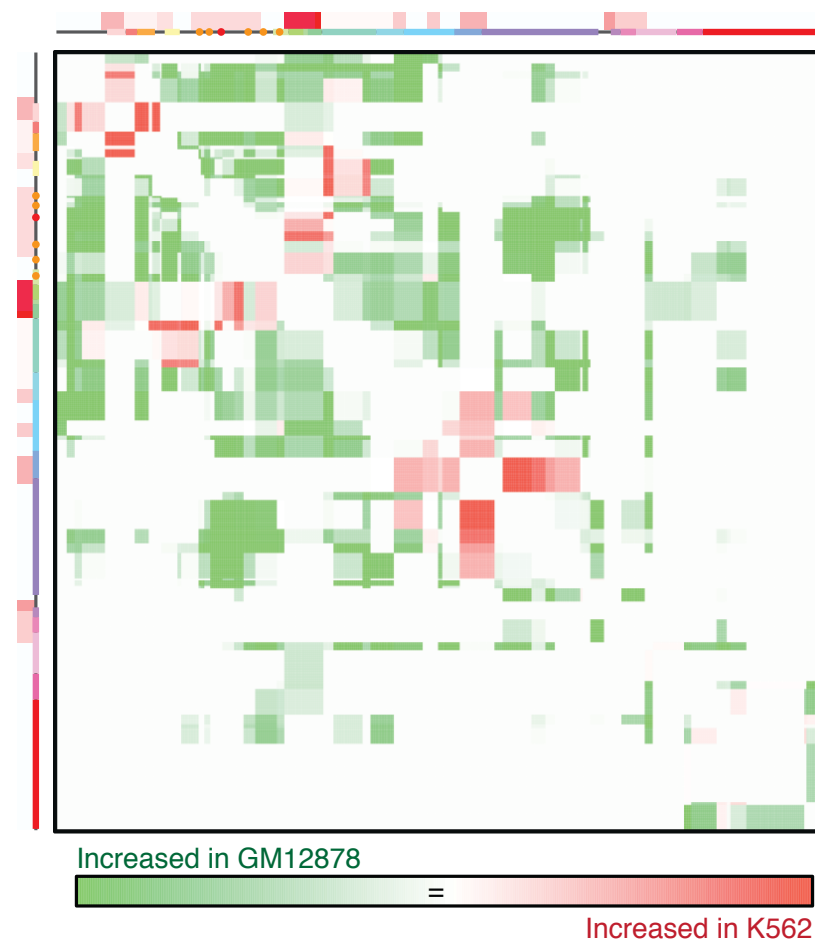
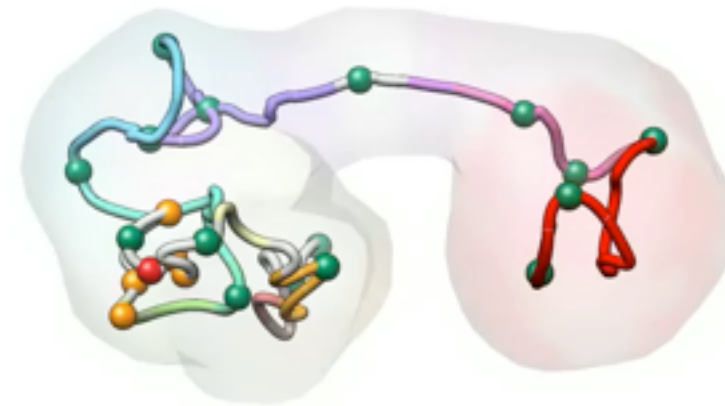
GM12878

Cluster #1
2780 model



K562

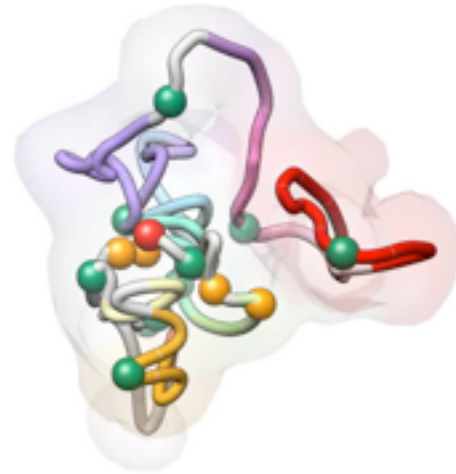
Cluster #2
314 model



FISH validation

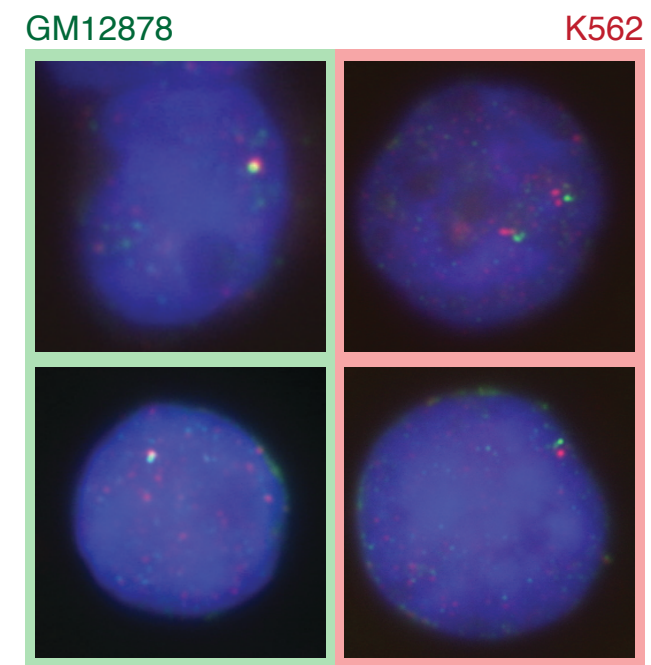
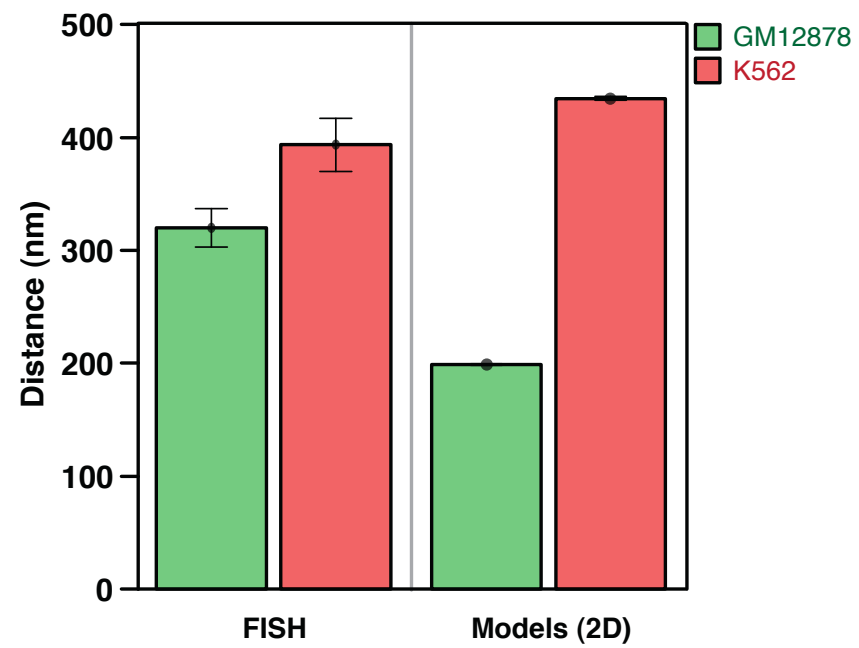
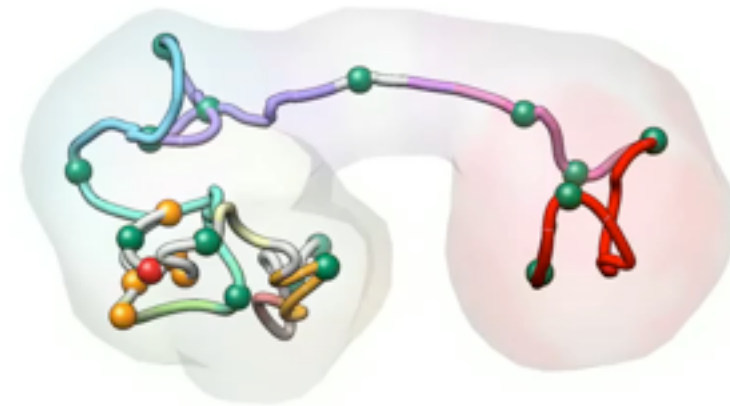
GM12878

Cluster #1
2780 model

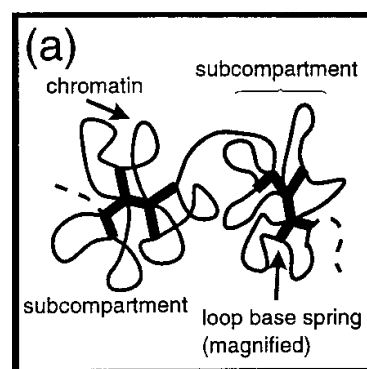
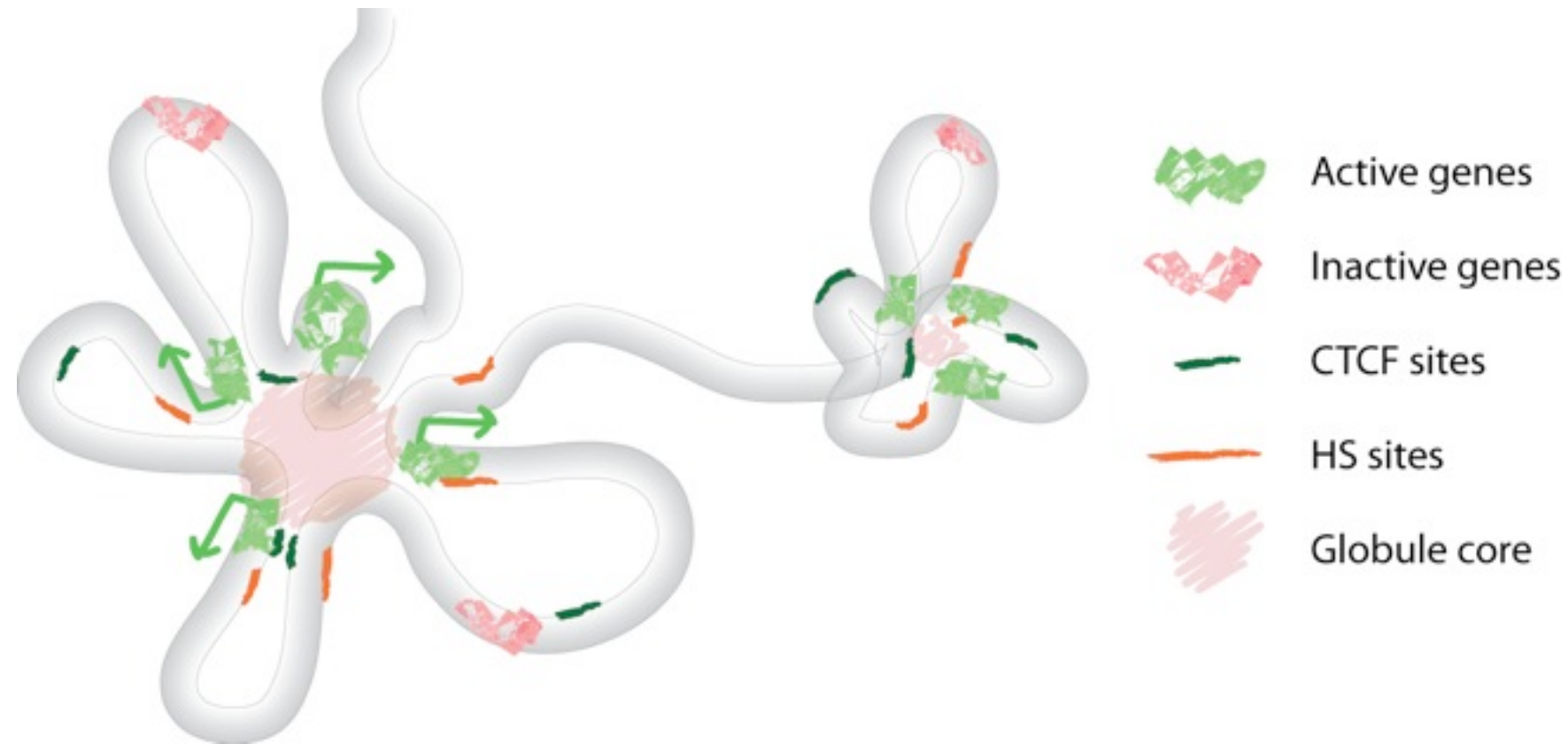


K562

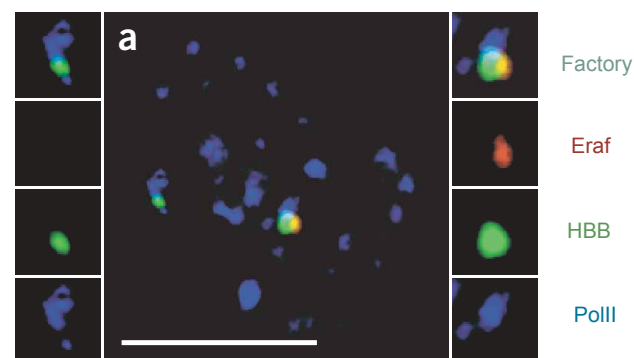
Cluster #2
314 model



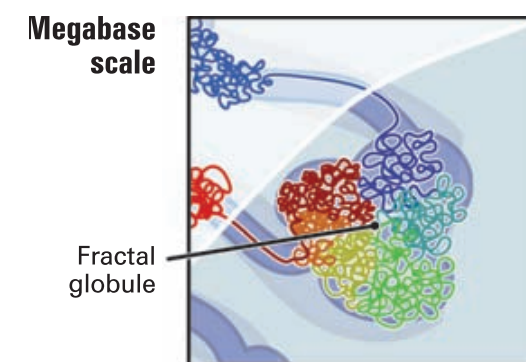
The “Chromatin Globule” model



Münkel et al. JMB (1999)



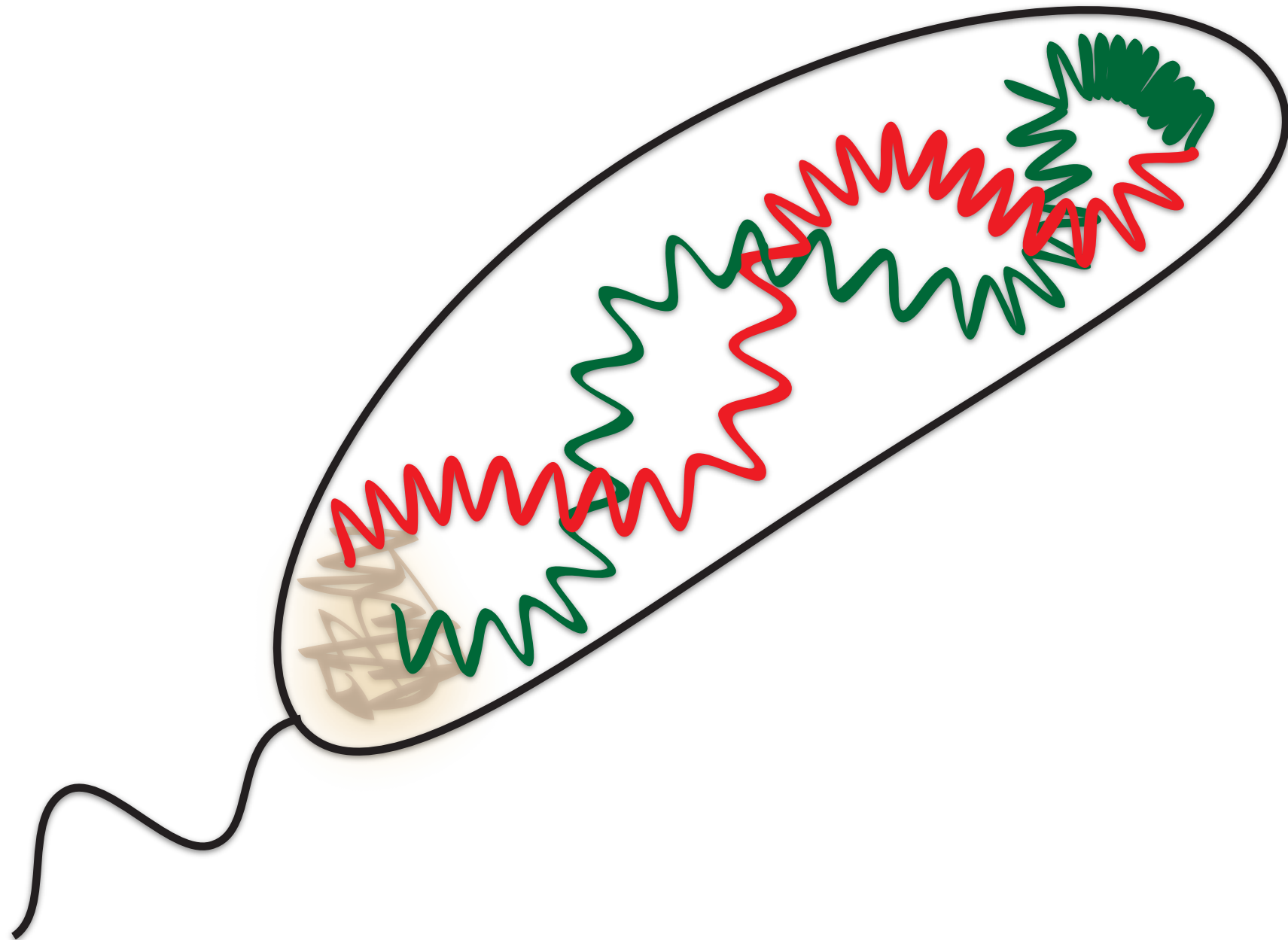
Osborne et al. Nat Genet (2004)



Lieberman-Aiden et al. Science (2009)

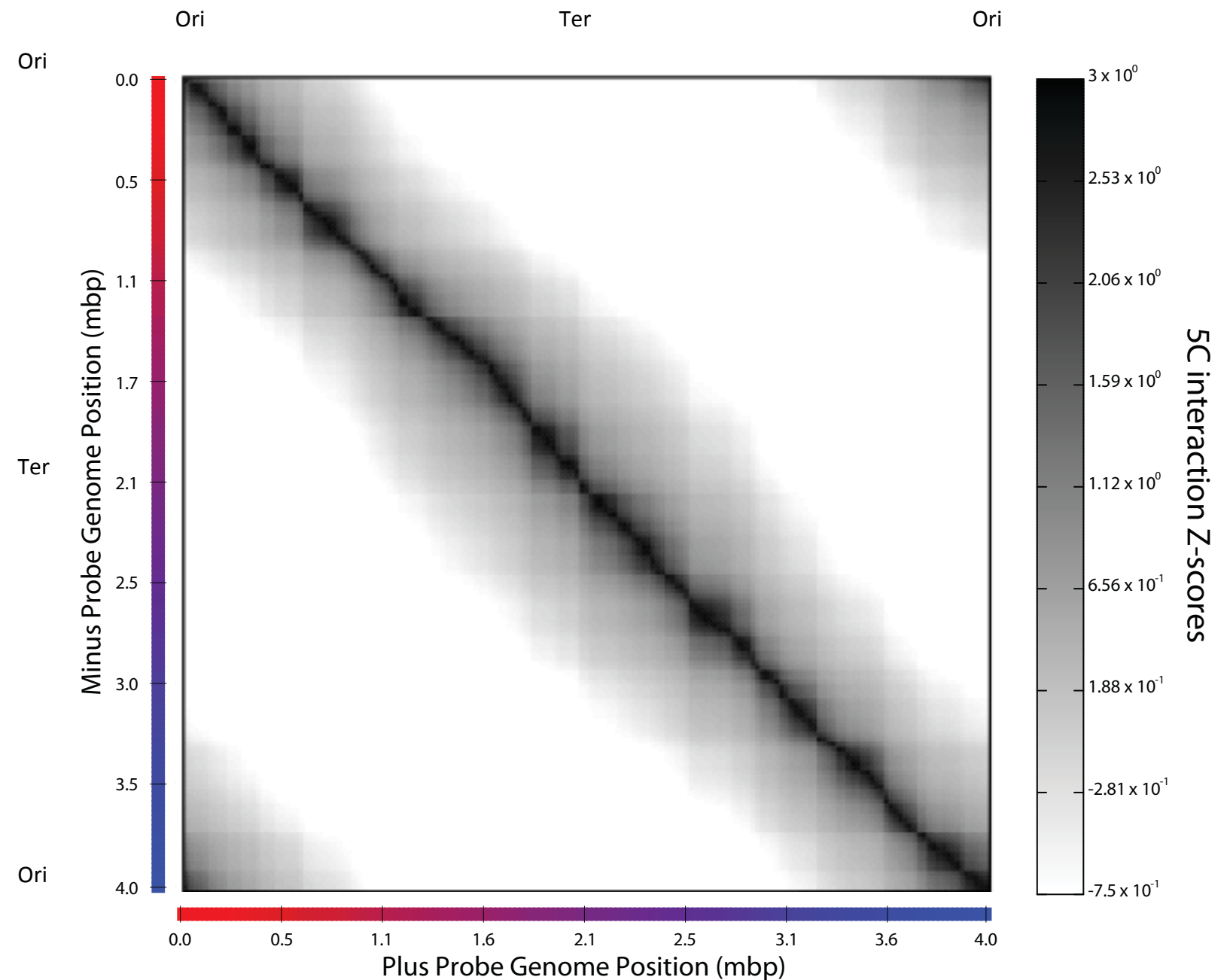
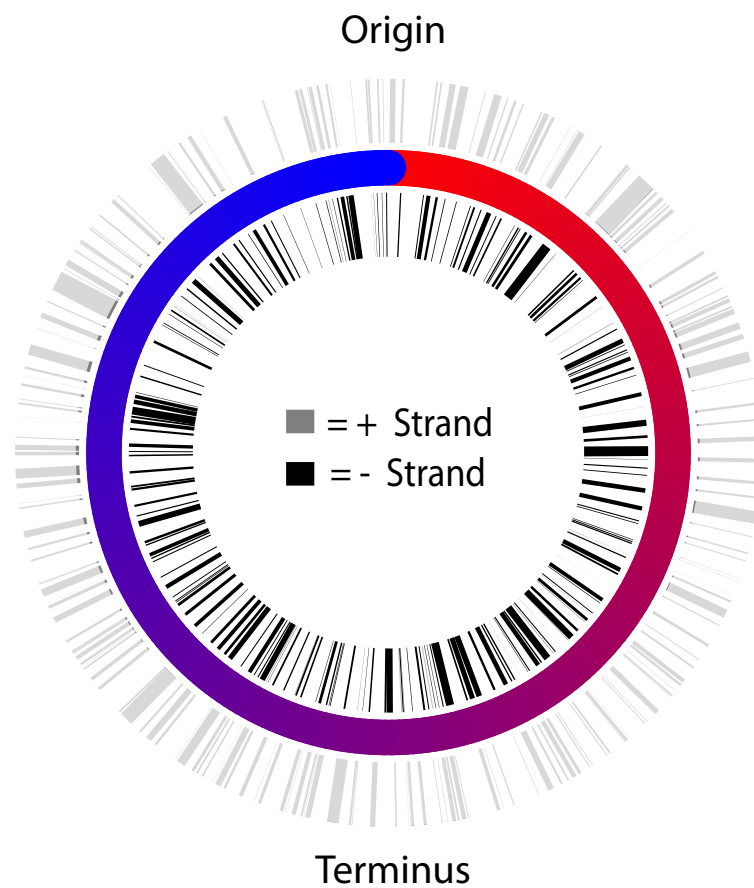
D. Baù *et al.* Nat Struct Mol Biol (2011) 18:107-14
A. Sanyal *et al.* Current Opinion in Cell Biology (2011) 23:325–33.

Caulobacter crescentus genome



The 3D architecture of *Caulobacter Crescentus*

4,016,942 bp & 3,767 genes

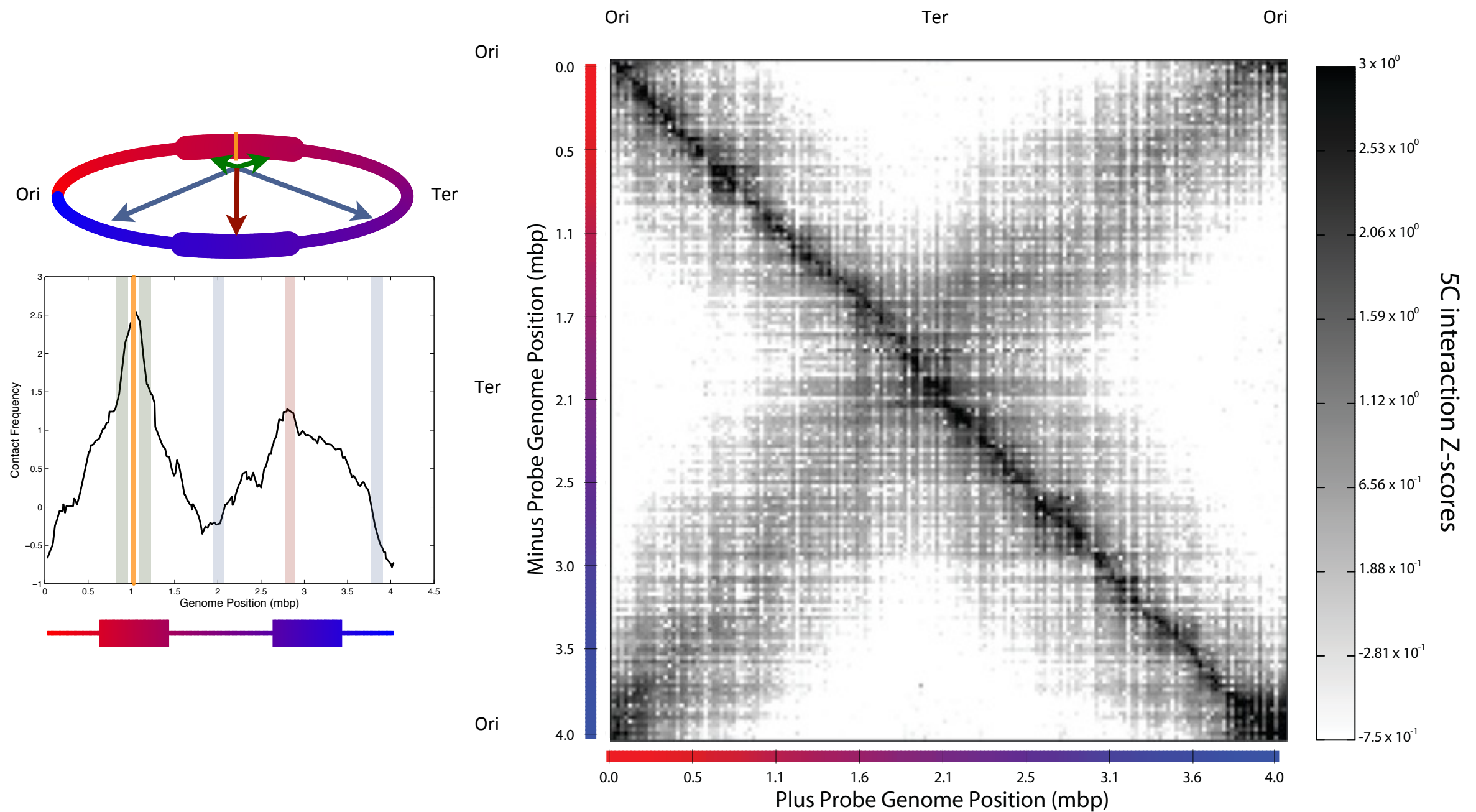


169 5C primers on + strand
170 5C primers on – strand
28,730 chromatin interactions

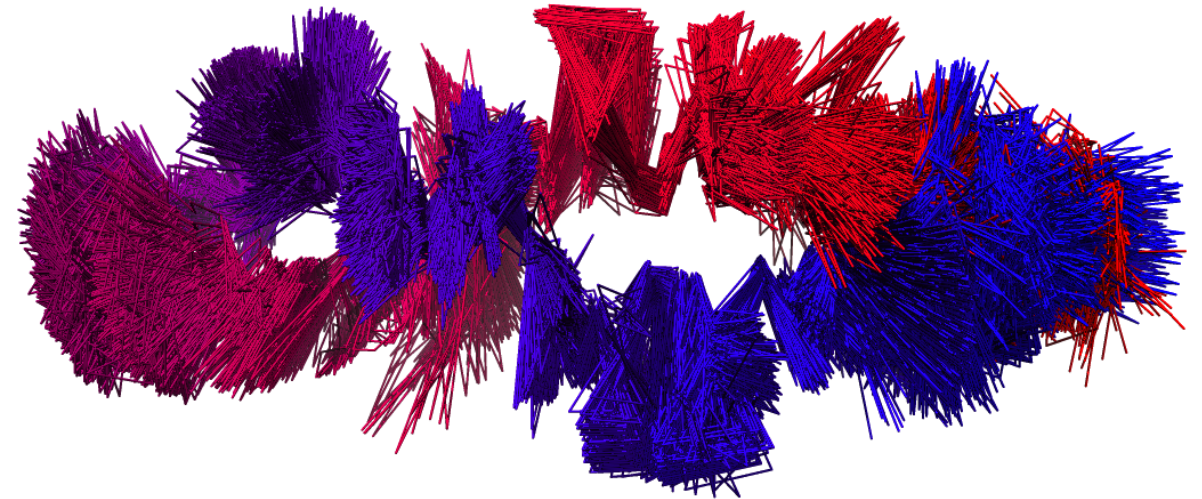
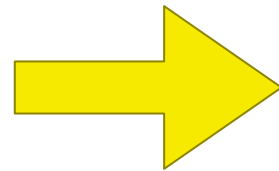
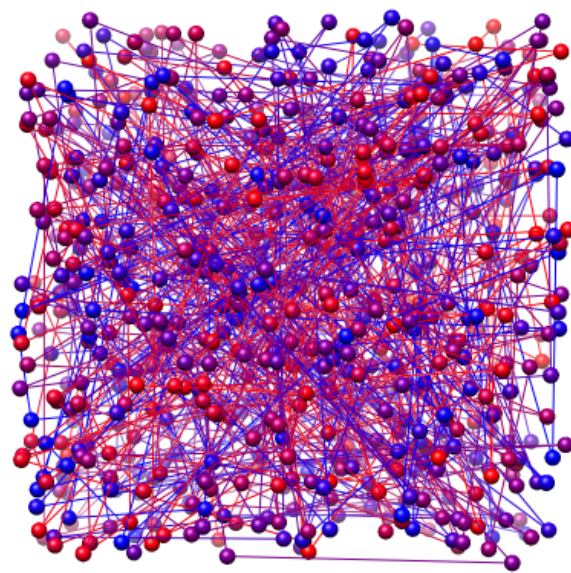
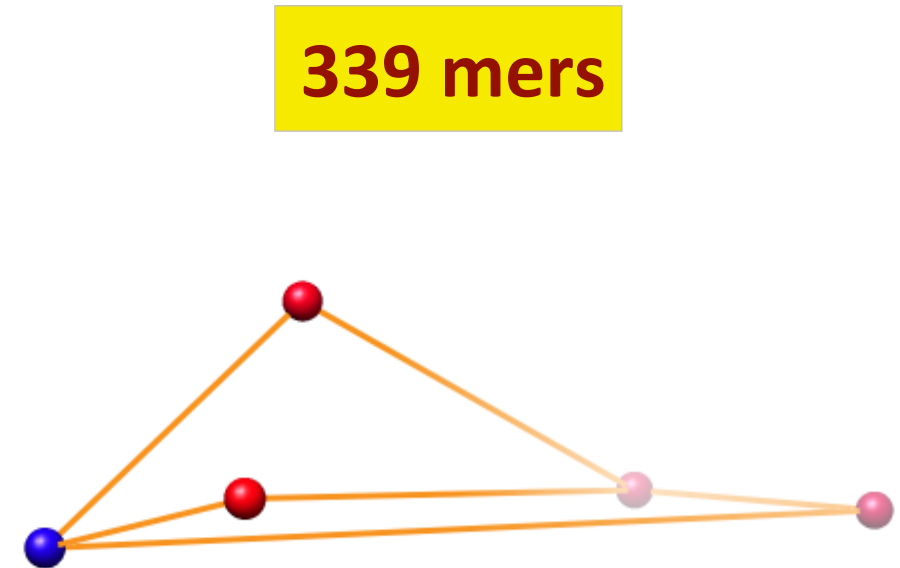
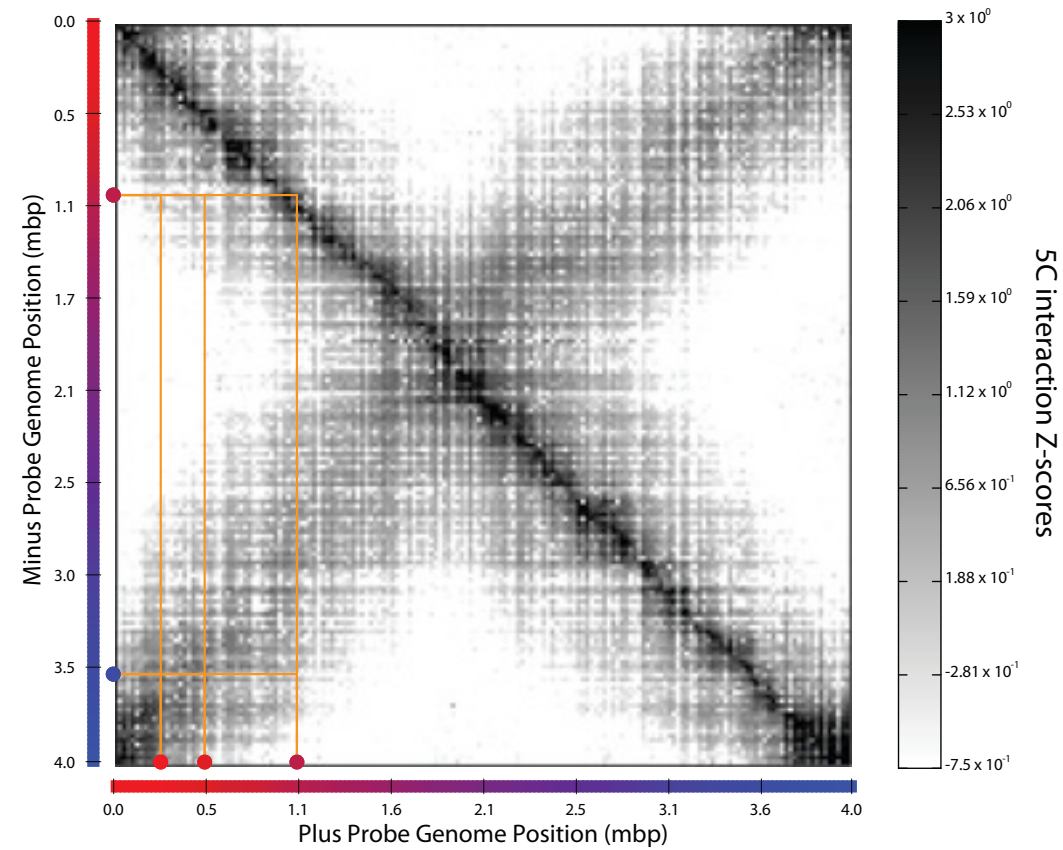
~13Kb

5C interaction matrix

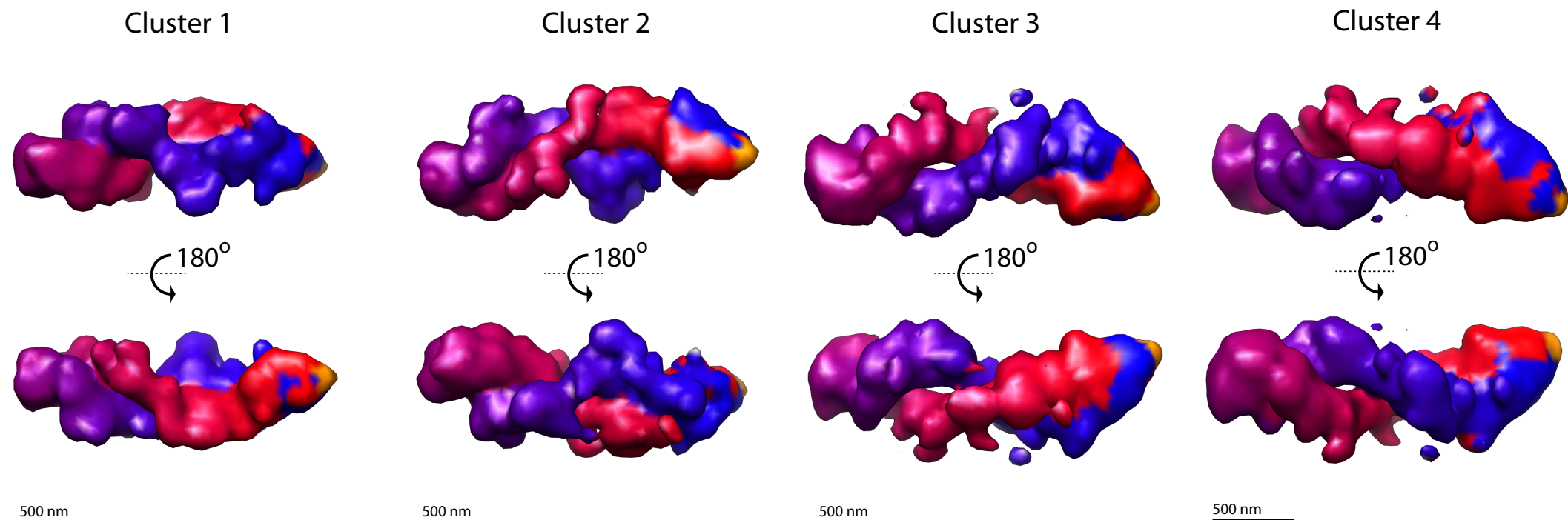
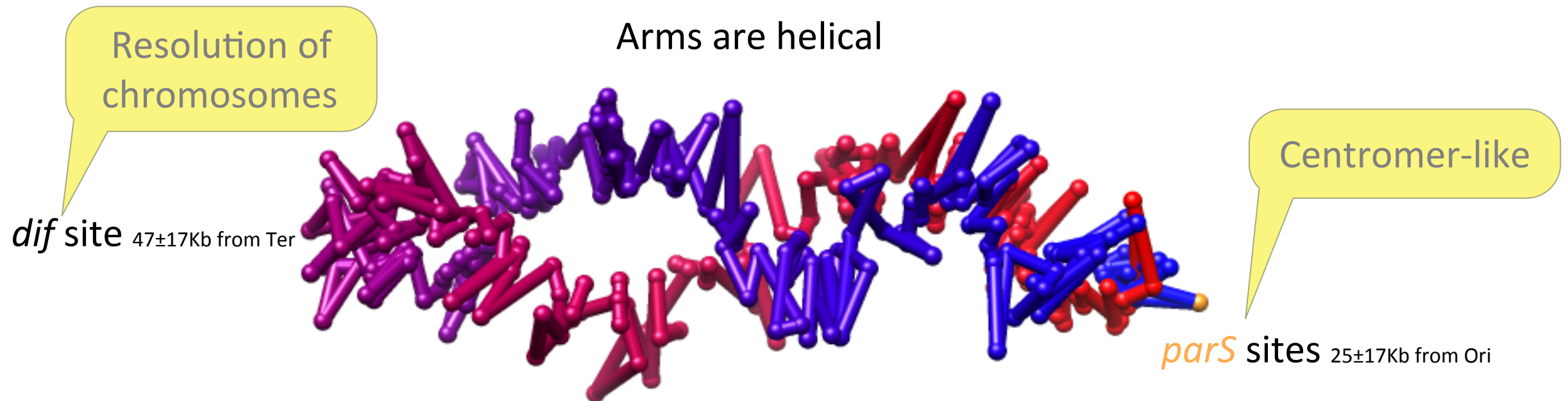
ELLIPSOID for *Caulobacter crescentus*



3D model building with the 5C + IMP approach

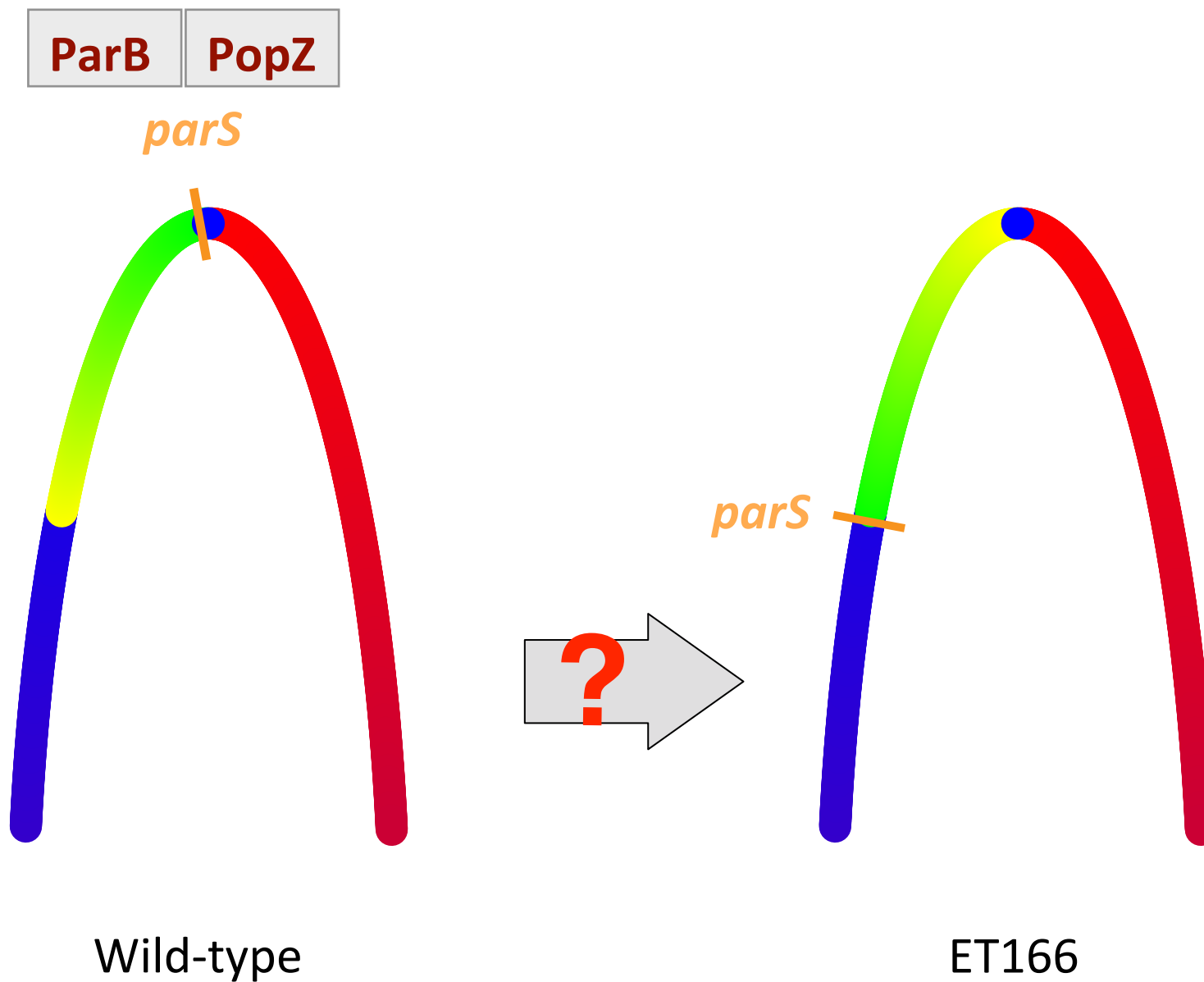


Genome organization in *Caulobacter crescentus*

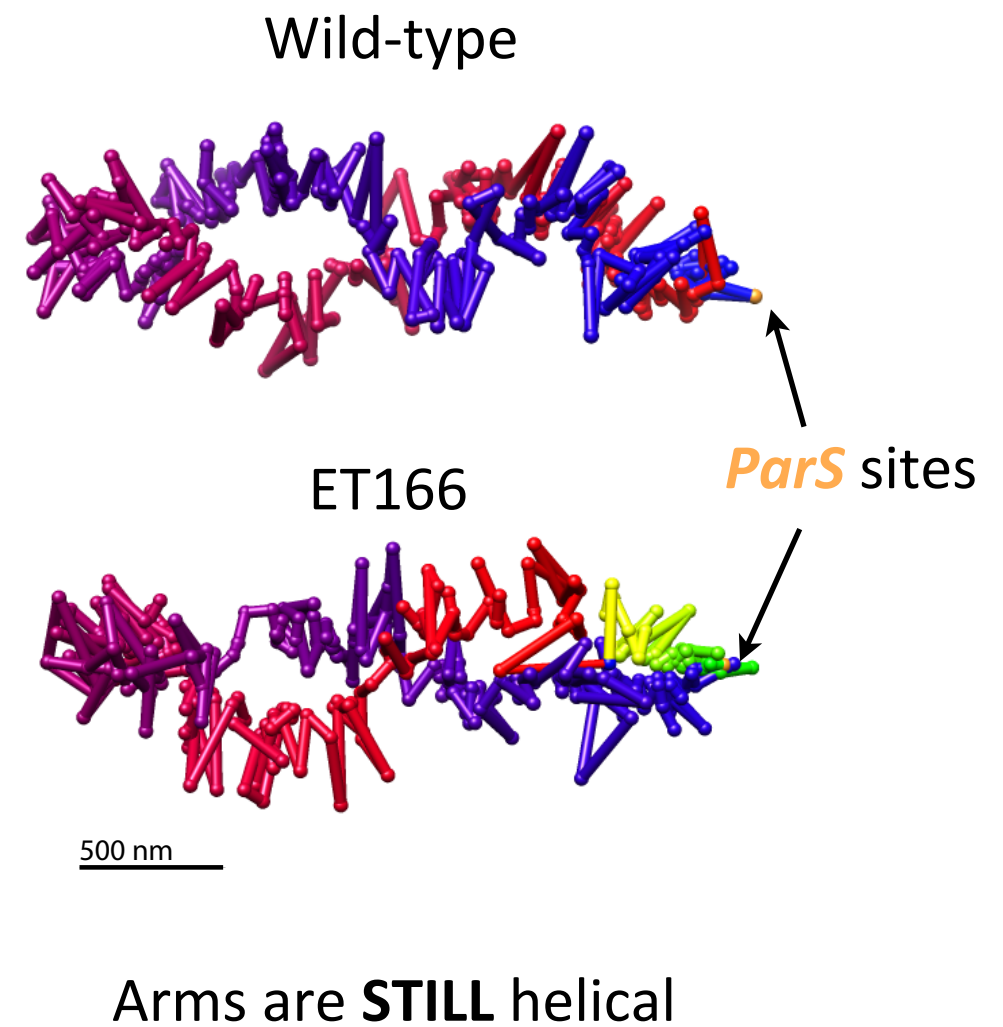
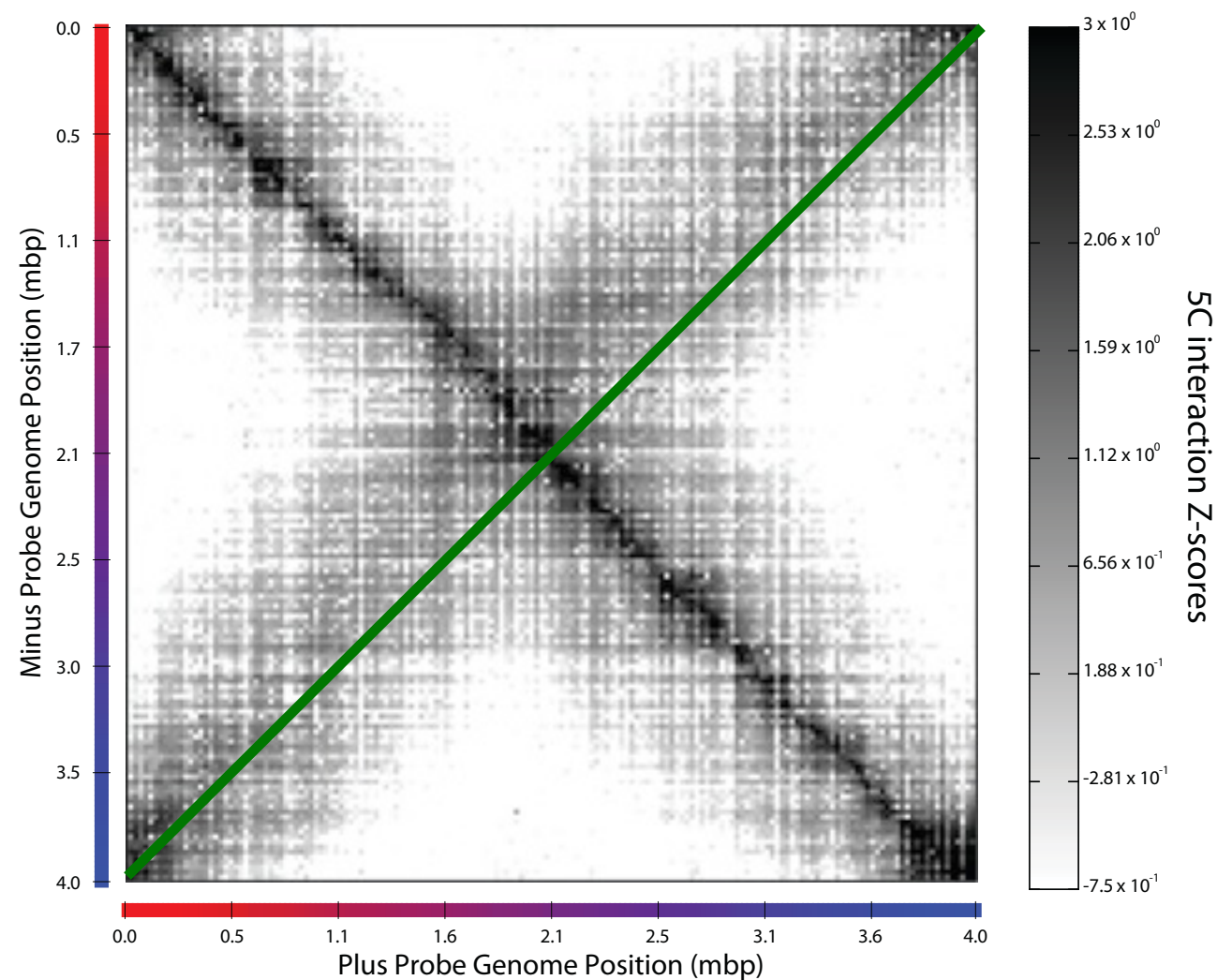


MIRRORS!

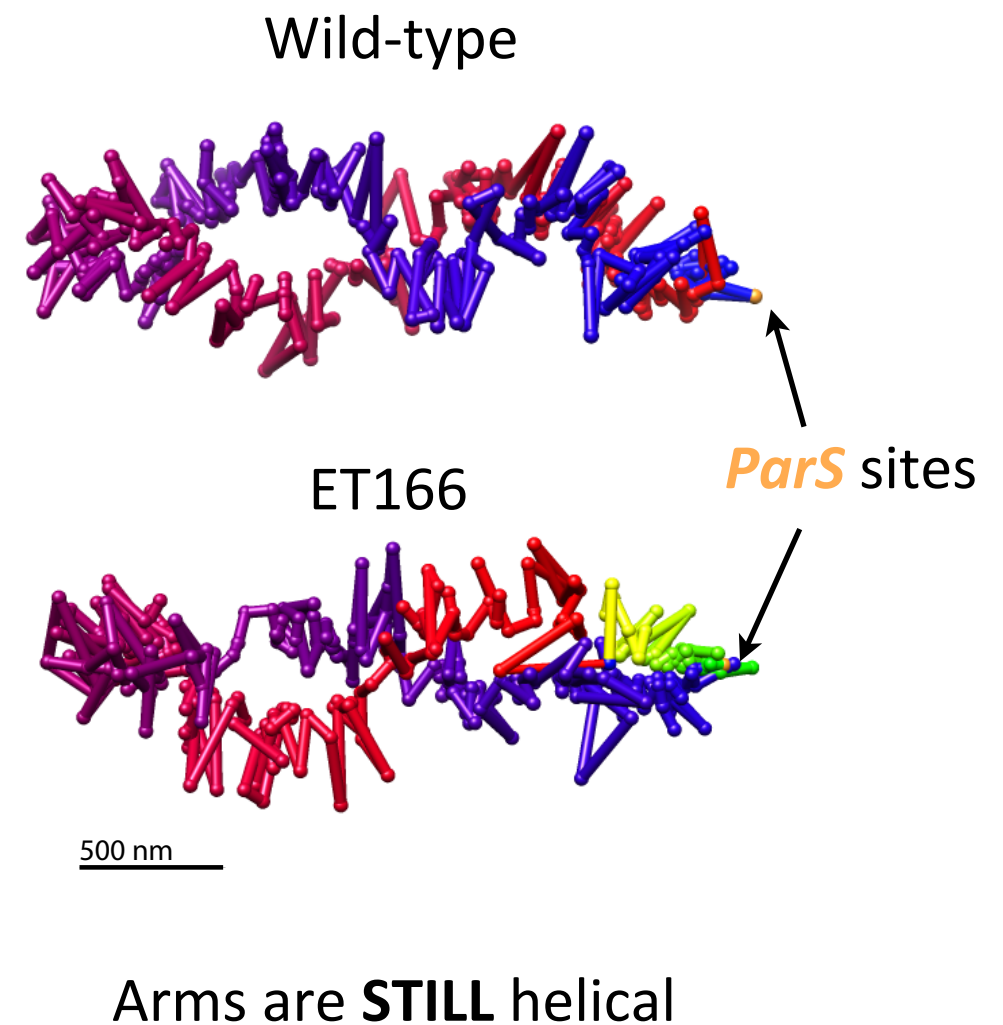
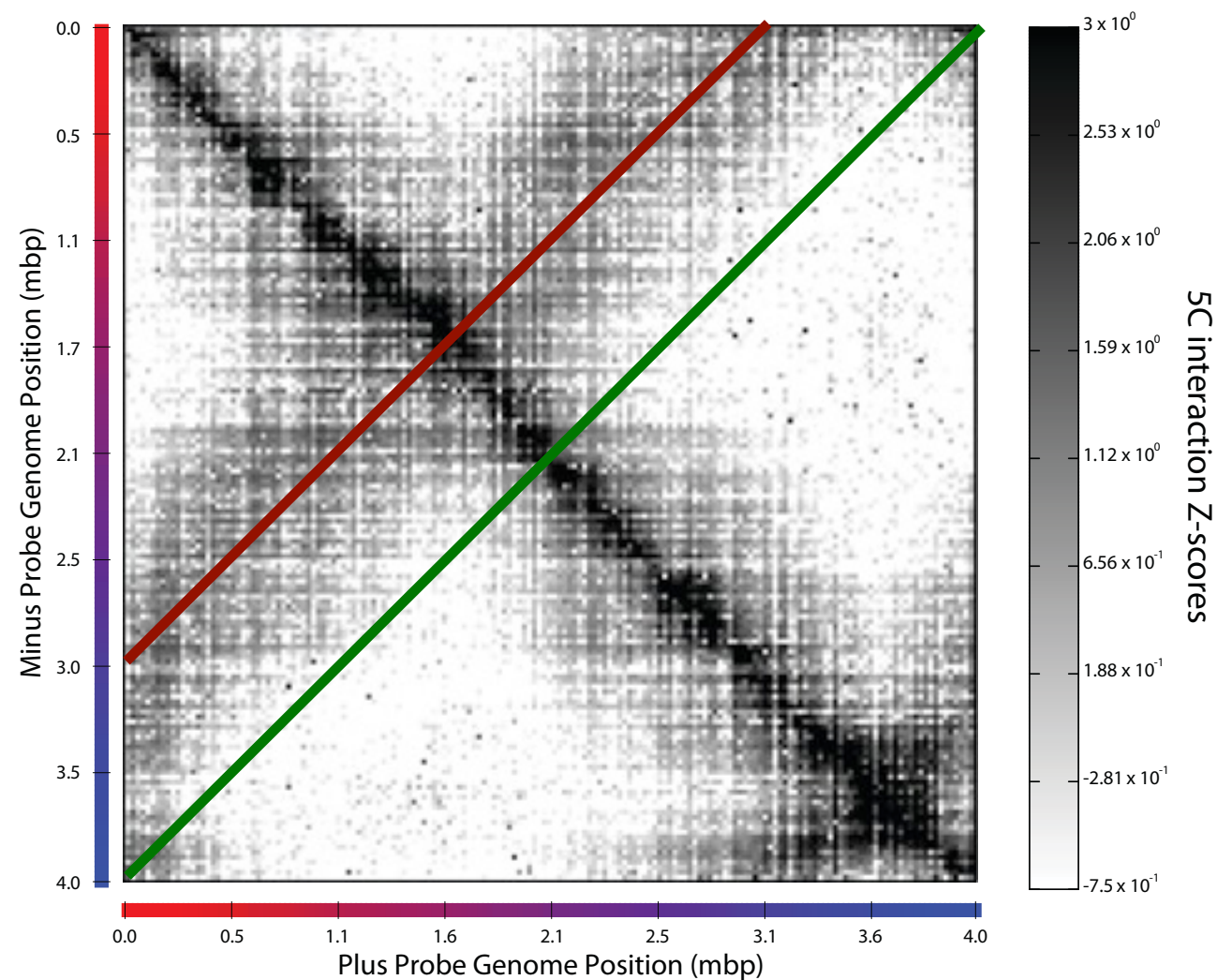
Moving the *parS* sites 400 Kb away from Ori



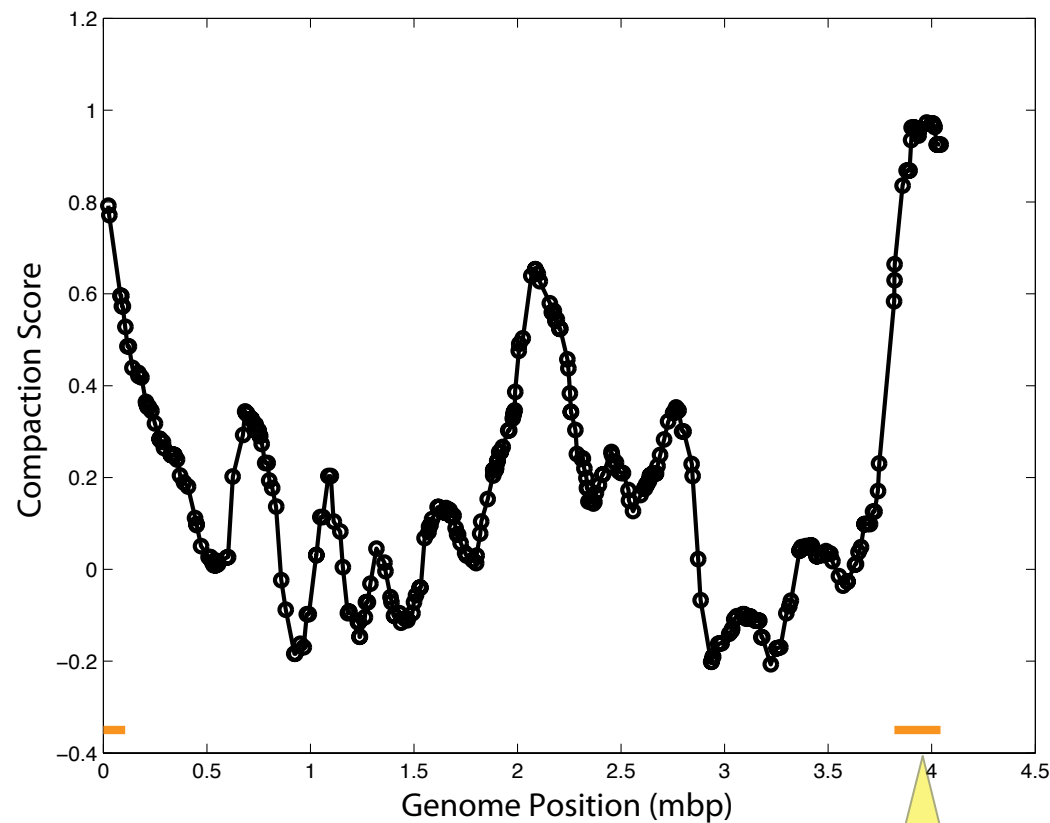
Moving the *parS* sites results in whole genome rotation!



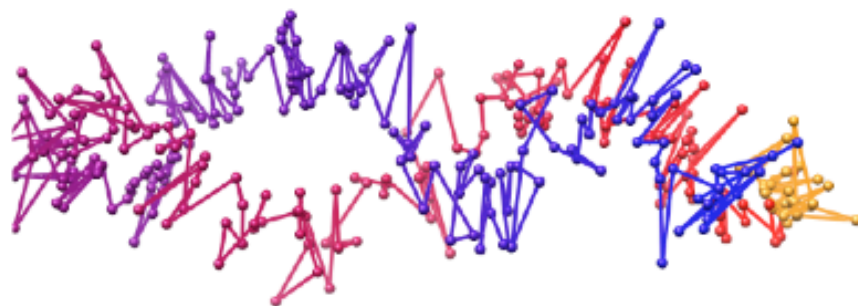
Moving the *parS* sites results in whole genome rotation!



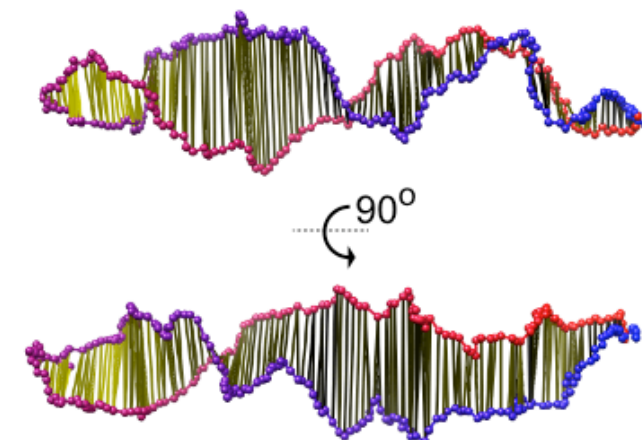
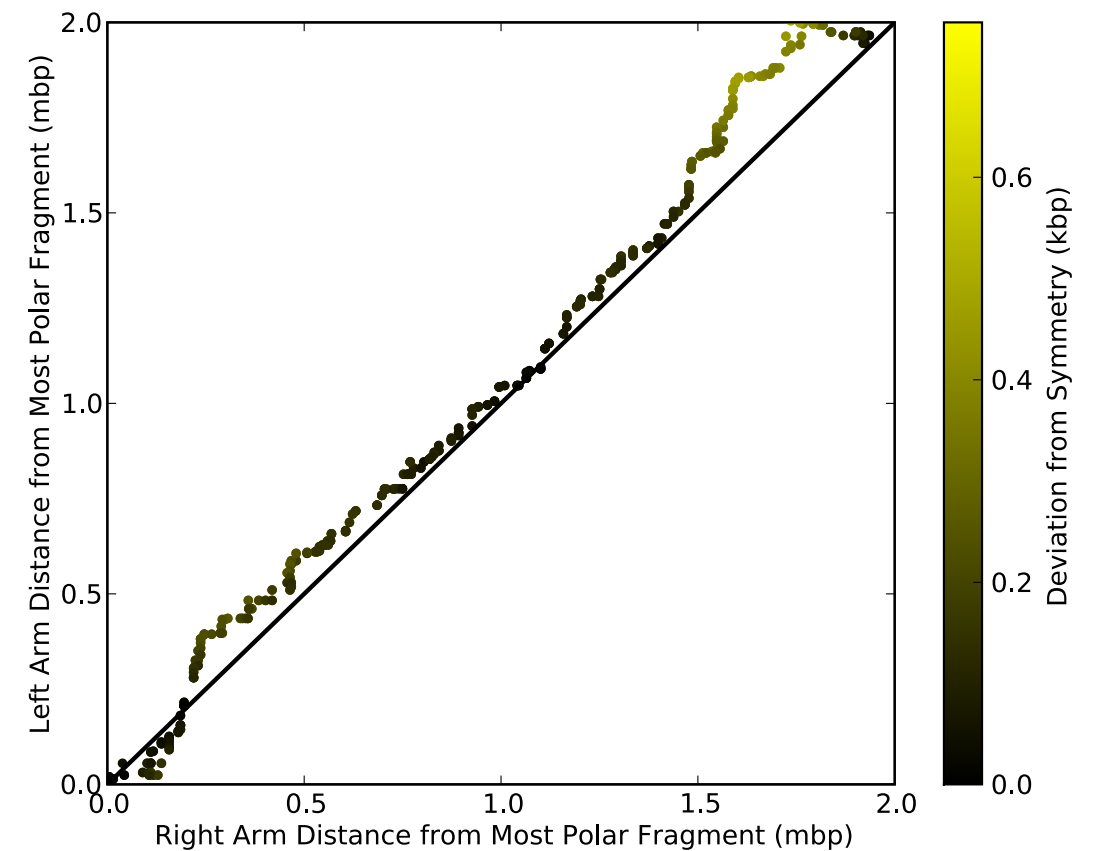
parS sites initiate compact chromatin domain



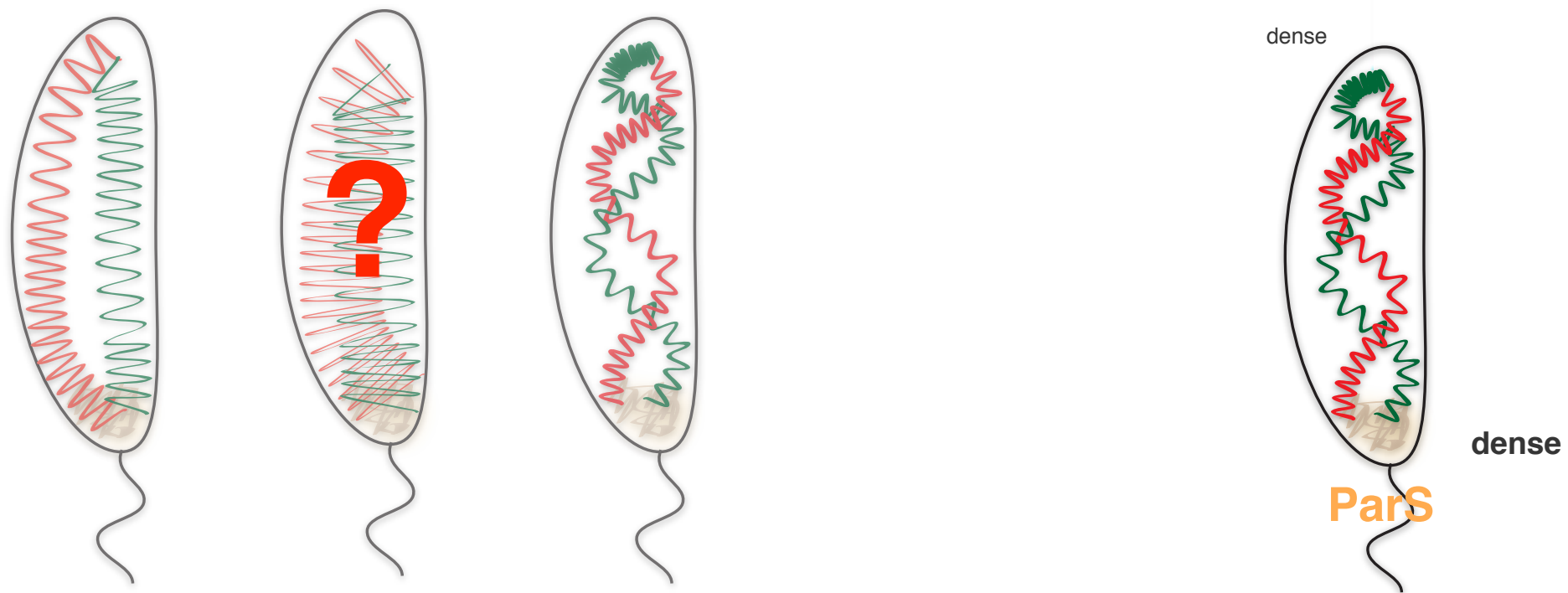
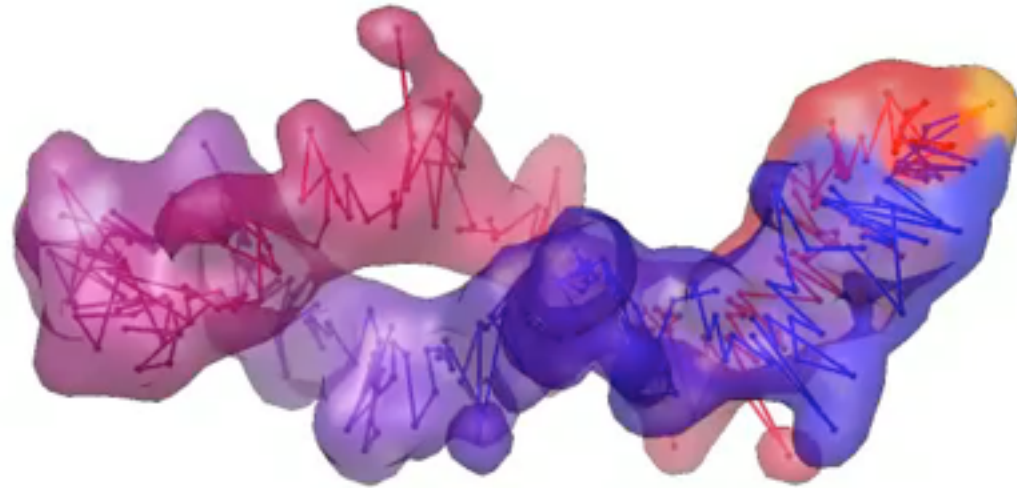
100-200Kb



Chromosome arms are equidistant to the cell center



Genome architecture in *Caulobacter*

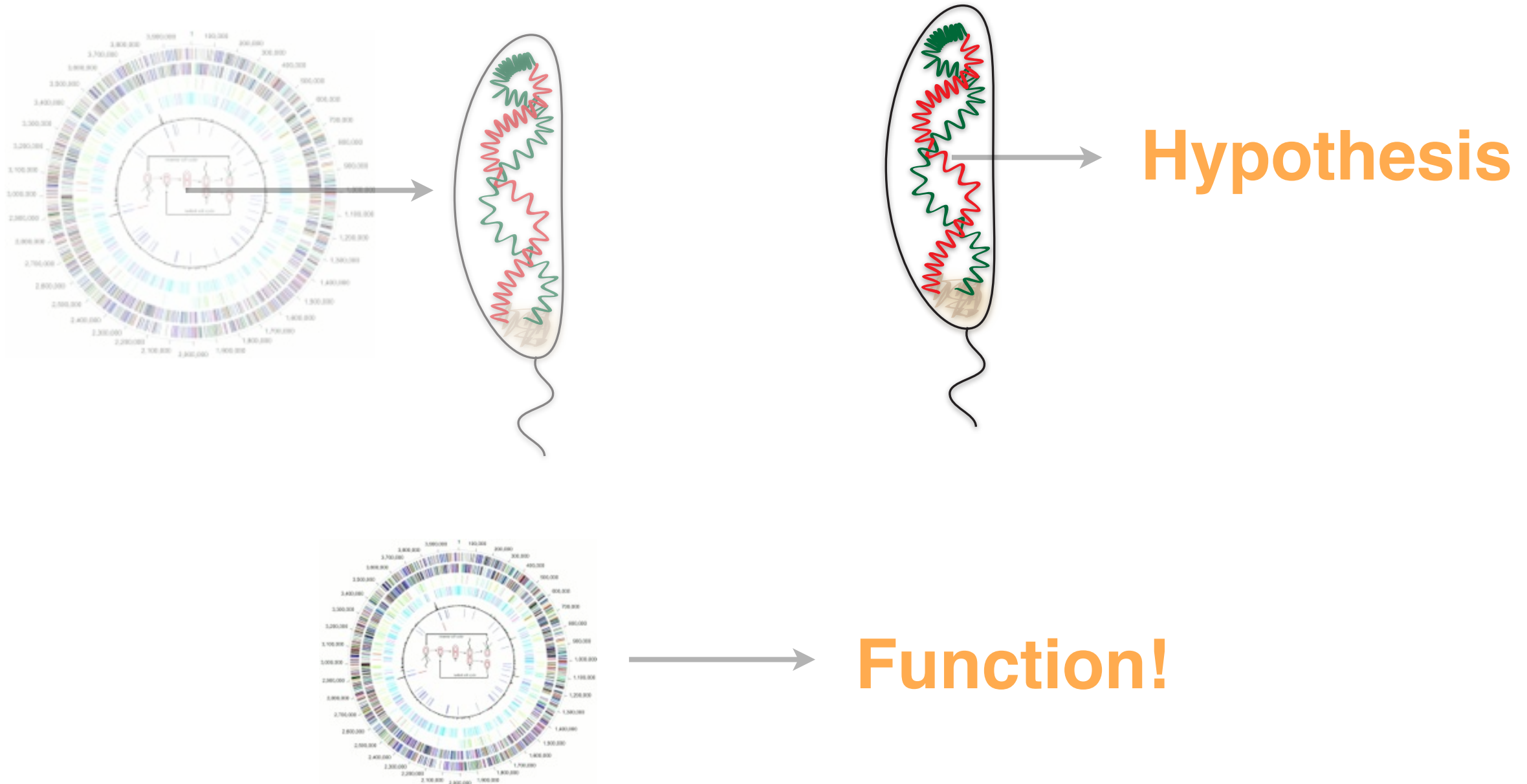


M.A. Umbarger, *et al.* **Molecular Cell** (2011) 44:252–264

From Sequence to Function

5C + IMP

Technology



D. Baù and M.A. Marti-Renom **Chromosome Res** (2011) 19:25-35.

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Review

Bridging the Resolution Gap in Structural Modeling of 3D Genome Organization

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Abstract: Over the last decade, and especially after the advent of fluorescent *in situ* hybridization imaging and chromosome conformation capture methods, the availability of experimental data on genome three-dimensional organization has dramatically increased. We now have access to unprecedented details of how genomes organize within the interphase nucleus. Development of new computational approaches to leverage this data has already resulted in the first three-dimensional structures of genomic domains and genomes. Such approaches expand our knowledge of the chromatin folding principles, which has been classically studied using polymer physics and molecular simulations. Our outlook describes computational approaches for integrating experimental data with polymer physics, thereby bridging the resolution gap for structural determination of genomes and genomic domains.

This is an “Editors’ Outlook” article for PLoS Computational Biology

Recent experimental and computational advances are resulting in an increasingly accurate and detailed characterization of how genomes are organized in the three-dimensional (3D) space of the nucleus (Figure 1) [1]. At the lowest level of chromatin organization, naked DNA is packed into nucleosomes, which forms the so-called chromatin fiber composed of DNA and proteins. However, this initial packing, which reduces the length of the DNA by about seven times, is not sufficient to explain the higher-order folding of chromosomes during interphase and metaphase. It is now accepted that chromosomes and genes are non-randomly and dynamically positioned in the cell nucleus during the interphase, which challenges the classical representation of genomes as linear static sequences. Moreover, compartmentalization, chromatin organization, and spatial location of genes are associated with gene expression and the functional status of the cell. Despite the importance of 3D genomic architecture, we have a limited understanding of the molecular mechanisms that determine the higher-order organization of genomes and its relation to function. Computational biology plays an important role in the plethora of new technologies aimed at addressing this knowledge gap [2]. Indeed, Thomas Cremer, a pioneer in studying nuclear organization using light microscopy, recently highlighted the importance of computational science in complementing and leveraging experimental observations of genome organization [2]. Therefore, computational approaches to integrate experimental observations with chromatin physics are needed to determine the architecture (3D) and dynamics (4D) of genomes.

We present two complementary approaches to address this challenge: (i) the first approach aims at developing simple polymer models of chromatin and determining relevant interactions (both

physical and biological) that explain experimental observations; (ii) the second approach aims at integrating diverse experimental observations into a system of spatial restraints to be satisfied, thereby constraining possible structural models of the chromatin. The goal of both approaches is dual: to obtain most accurate 3D and 4D representation of chromatin architecture and to understand physical constraints and biological phenomena that determine its organization. These approaches are reminiscent of the protein-folding field where the first strategy was used for characterizing protein “foldability” and the second was implemented for modeling the structure of proteins using nuclear magnetic resonance and other experimental constraints. In fact, our outlook consistently returns to the many connections between the two fields.

What Does Technology Show Us?

Today, it is possible to quantitatively study structural features of genomes at diverse scales that range from a few specific loci, through chromosomes, to entire genomes (Table 1) [3]. Broadly, there are two main approaches for studying genomic organization: light microscopy and cell/molecular biology (Figure 2). Light microscopy [4], both with fixed and living cells, can provide images of a few loci within individual cells [5,6], as well as their dynamics as a function of time [7] and cell state [8]. On a larger scale, light microscopy combined with whole-chromosome staining reveals chromosomal territories during interphase and their reorganization upon cell division. Immunofluorescence with fluorescent antibodies in combination with RNA, and DNA fluorescence *in situ* hybridization (FISH) has been used to determine the colocalization of loci and nuclear substructures.

Using cellular and molecular biology, novel chromosome conformation capture (3C)-based methods such as 3C [9], 3C-on-chip or circular 3C (the so-called 4C) [10,11], 3C carbon copy (5C) [12], and Hi-C [13] quantitatively measure frequencies of spatial contacts between genomic loci averaged over a large

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MURRE
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The 3D Structure of the Immunoglobulin Heavy-Chain Locus: Implications for Long-Range Genomic Interactions

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DOSTIE/BLANCHETTE
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Chromatin conformation signatures of cellular differentiation

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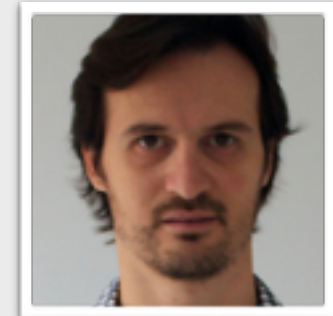
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