

Data integration for 3D structure determination.

Marc A. Martí-Renom

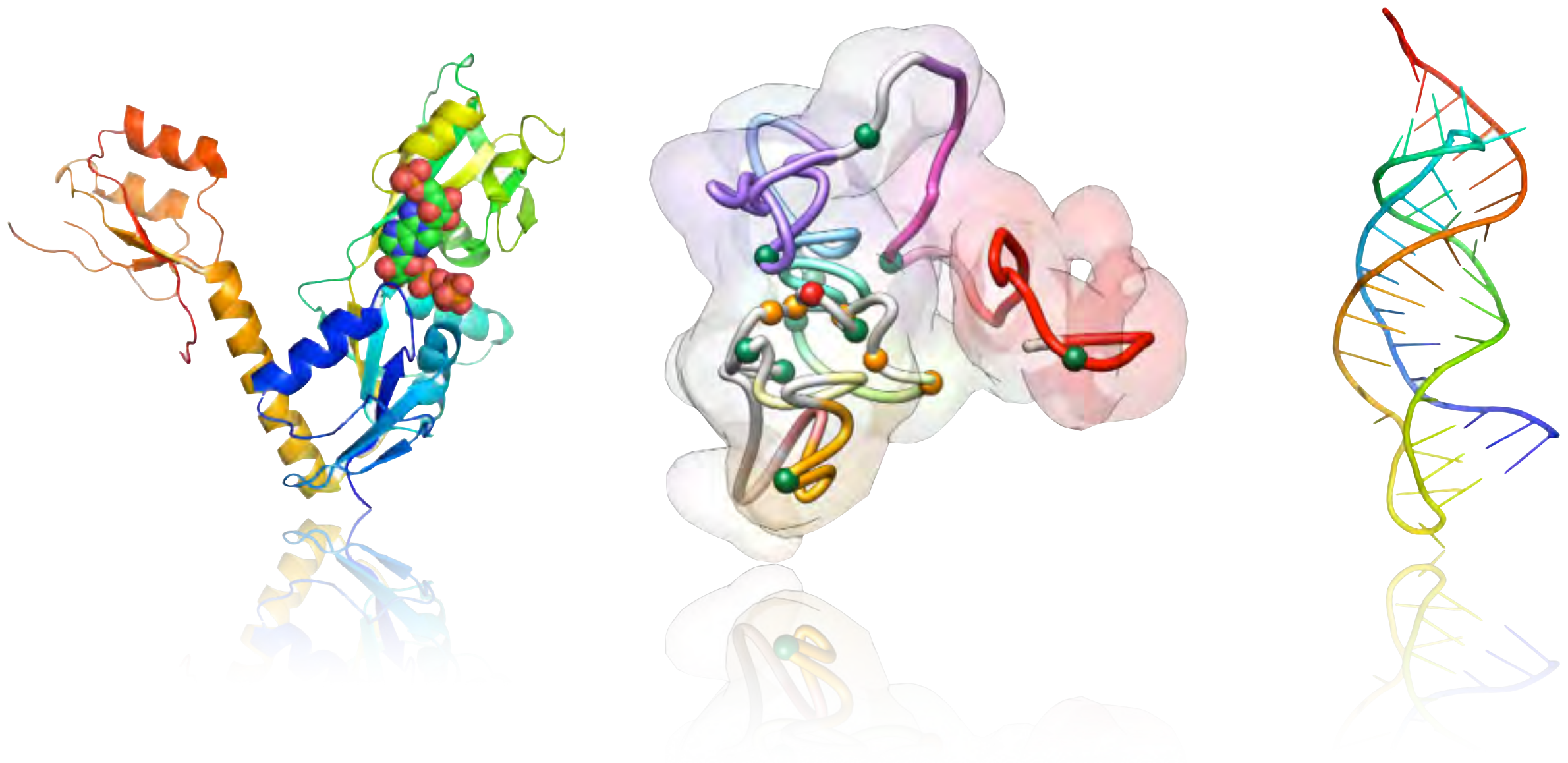
*Genome Biology Group (CNAG)
Structural Genomics Group (CRG)*

***iCrea**
INSTITUCIÓ CATALANA DE
RECERCA I ESTUDIS AVANÇATS



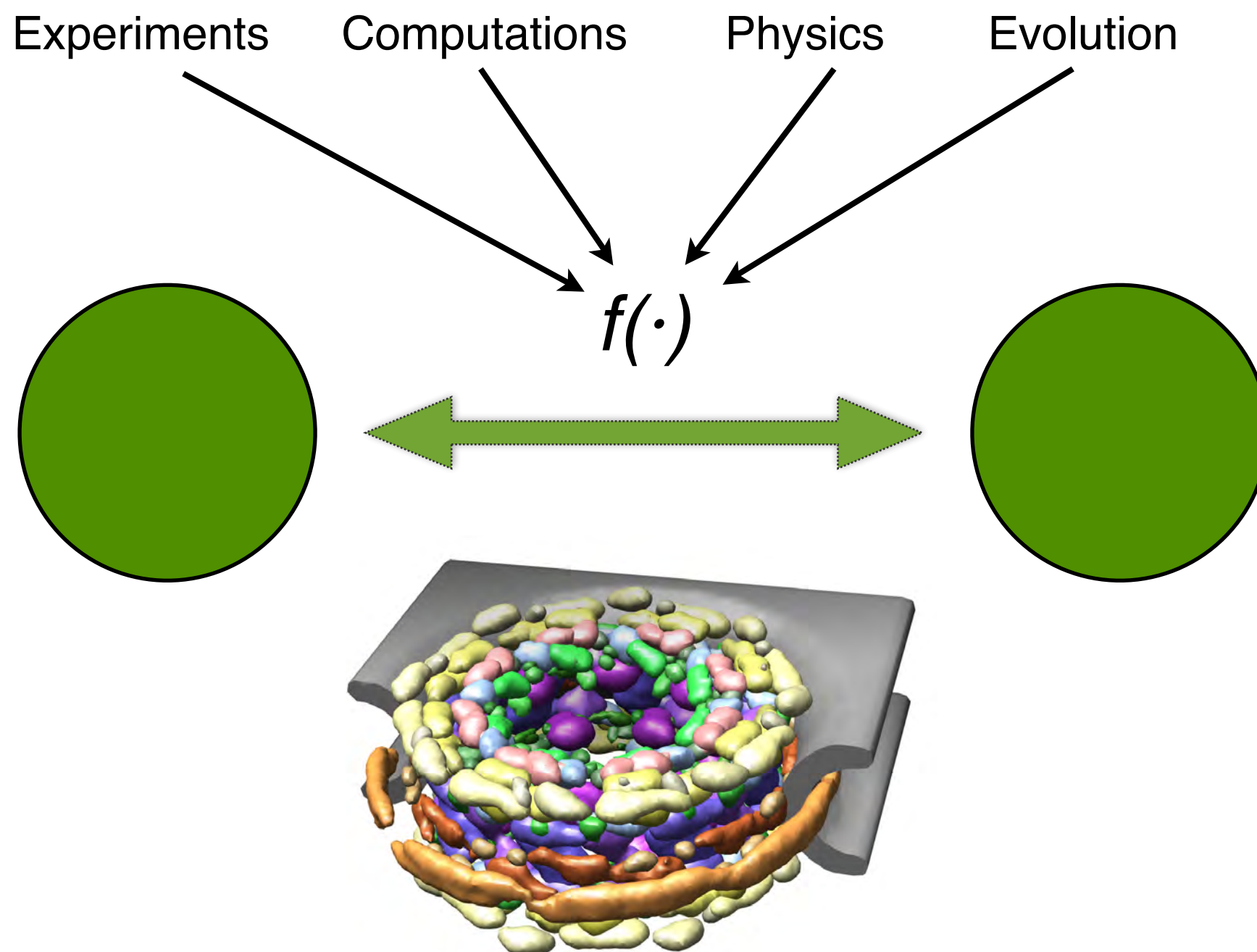
Structural Genomics Group

<http://www.marciuslab.org>



Integrative Modeling Platform

<http://www.integrativemodeling.org>



From: Russel, D. et al. PLOS Biology 10, e1001244 (2012).

Stages

Stage 1: Gathering Information. Information is collected in the form of data from wet lab experiments, as well as statistical tendencies such as atomic statistical potentials, physical laws such as molecular mechanics force fields, and any other feature that can be converted into a score for use to assess features of a structural model.

Stage 2: Choosing How To Represent And Evaluate Models. The resolution of the representation depends on the quantity and resolution of the available information and should be commensurate with the resolution of the final models: different parts of a model may be represented at different resolutions, and one part of the model may be represented at several different resolutions simultaneously. The scoring function evaluates whether or not a given model is consistent with the input information, taking into account the uncertainty in the information.

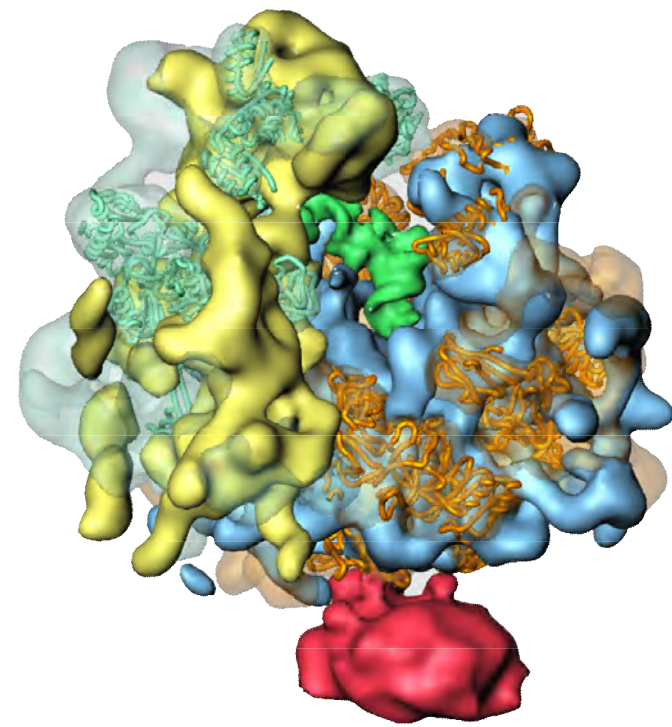
Stage 3: Finding Models That Score Well. The search for models that score well is performed using any of a variety of sampling and optimization schemes (such as the Monte Carlo method). There may be many models that score well if the data are incomplete or none if the data are inconsistent due to errors or unconsidered states of the assembly.

Stage 4: Analyzing Resulting Models and Information. The ensemble of good-scoring models needs to be clustered and analyzed to ascertain their precision and accuracy, and to check for inconsistent information. Analysis can also suggest what are likely to be the most informative experiments to perform in the next iteration.

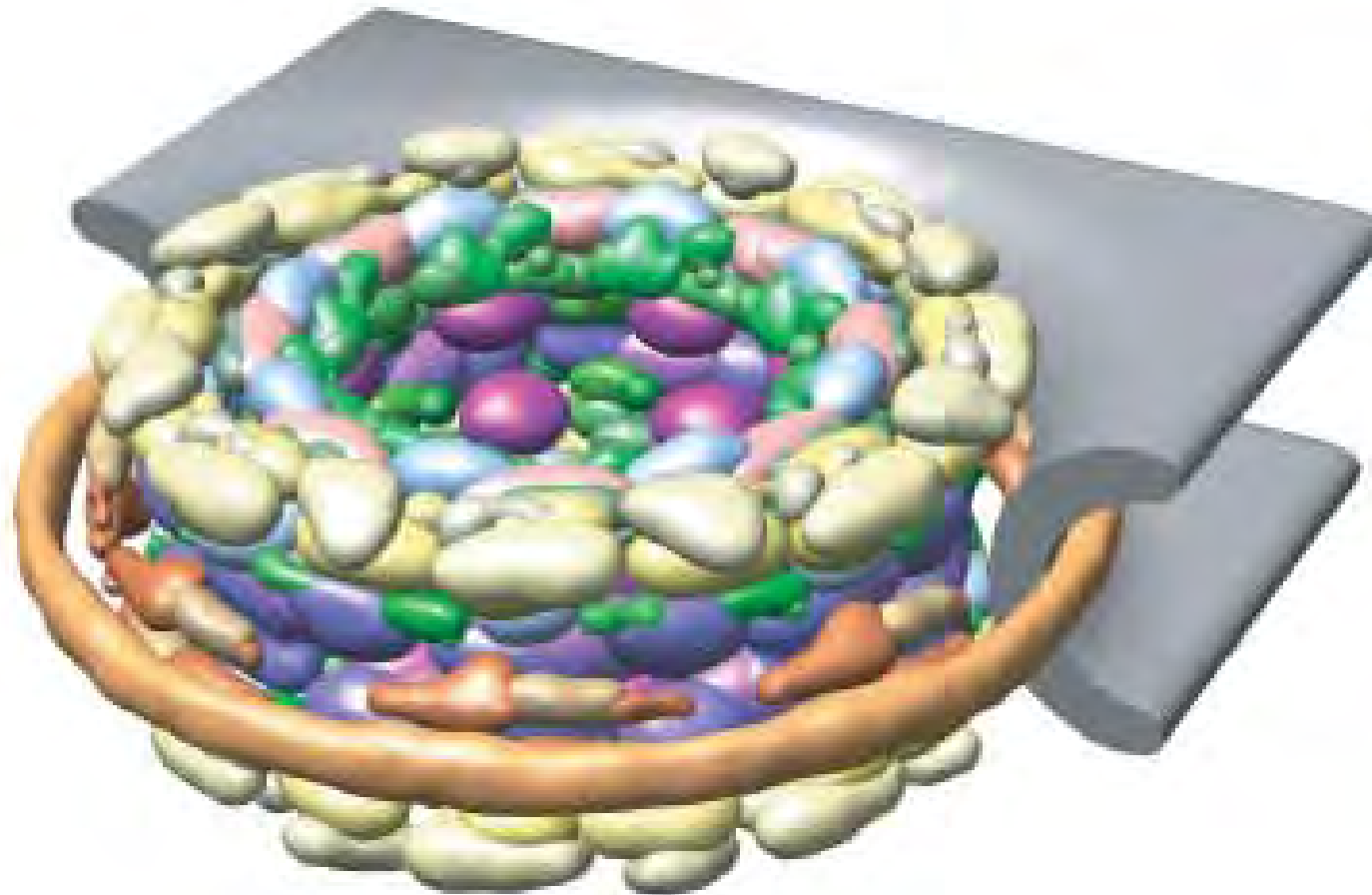
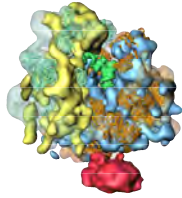
Integrative modeling iterates through these stages until a satisfactory model is built. Many iterations of the cycle may be required, given the need to gather more data as well as to resolve errors and inconsistent data.

Russel, D., Lasker, K., Webb, B., Velázquez-Muriel, J., Tjioe, E., Schneidman-Duhovny, D., Peterson, B., et al. (2012). *PLoS Biology*, 10(1), e1001244

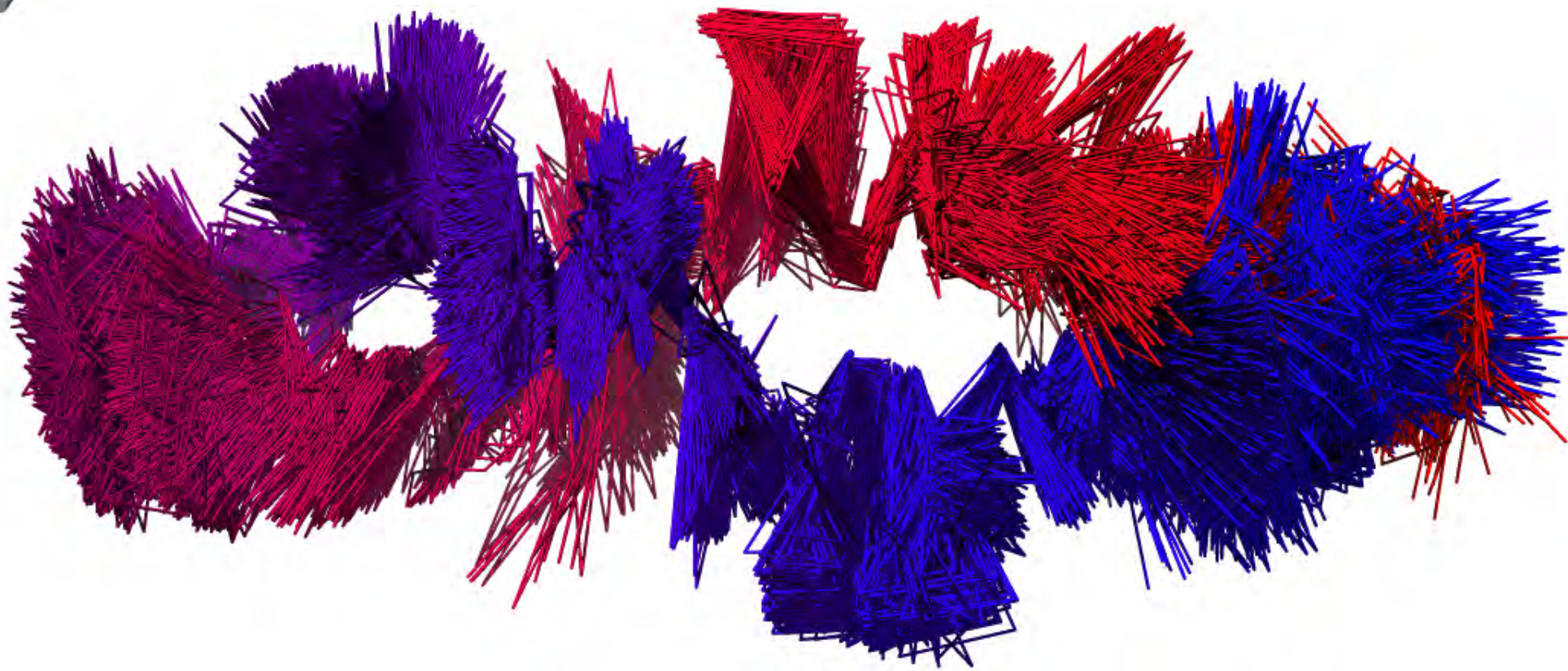
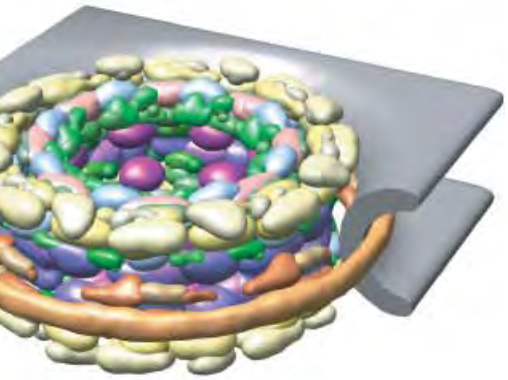
Data Integration



Data Integration

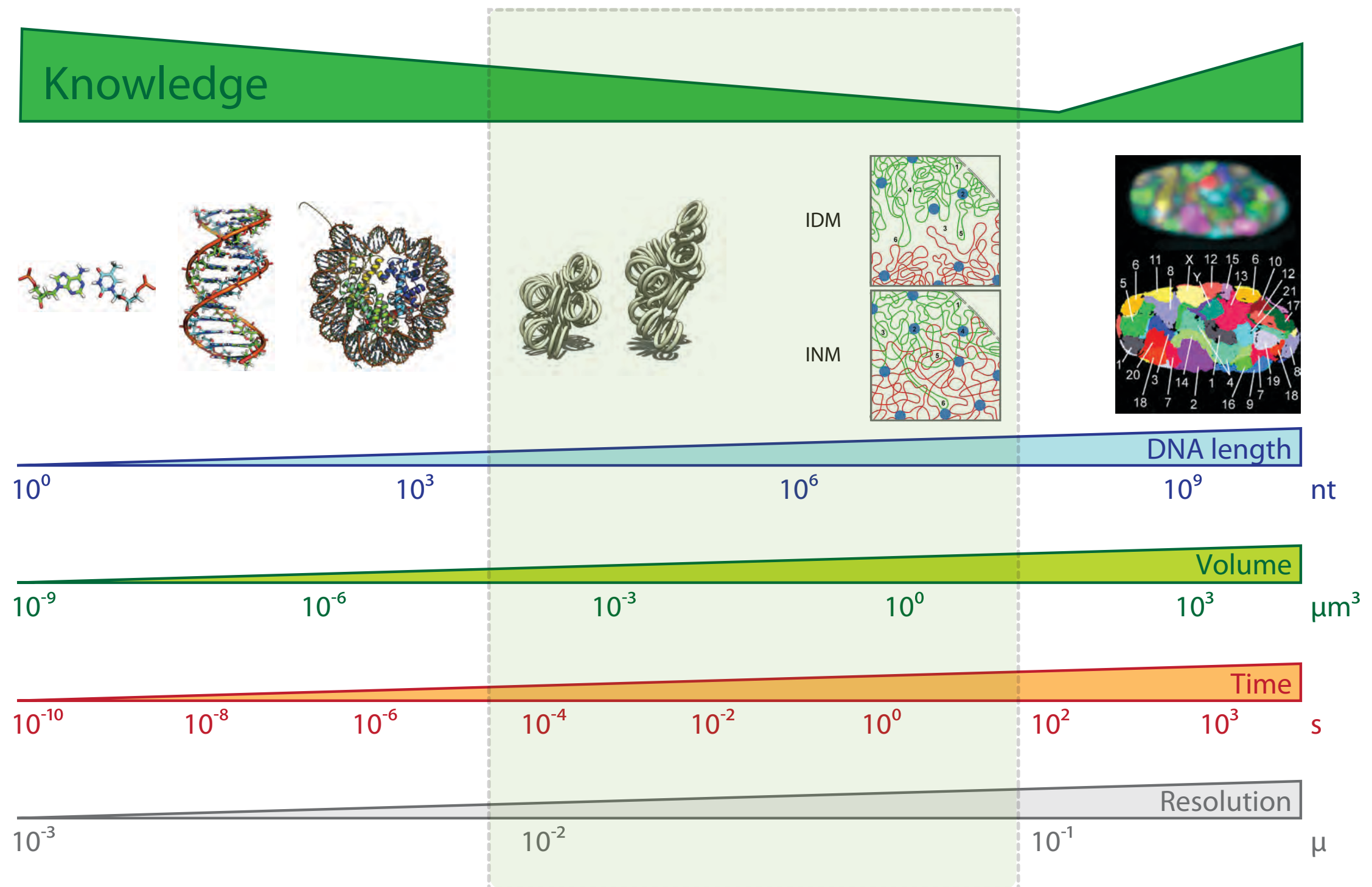


Data Integration



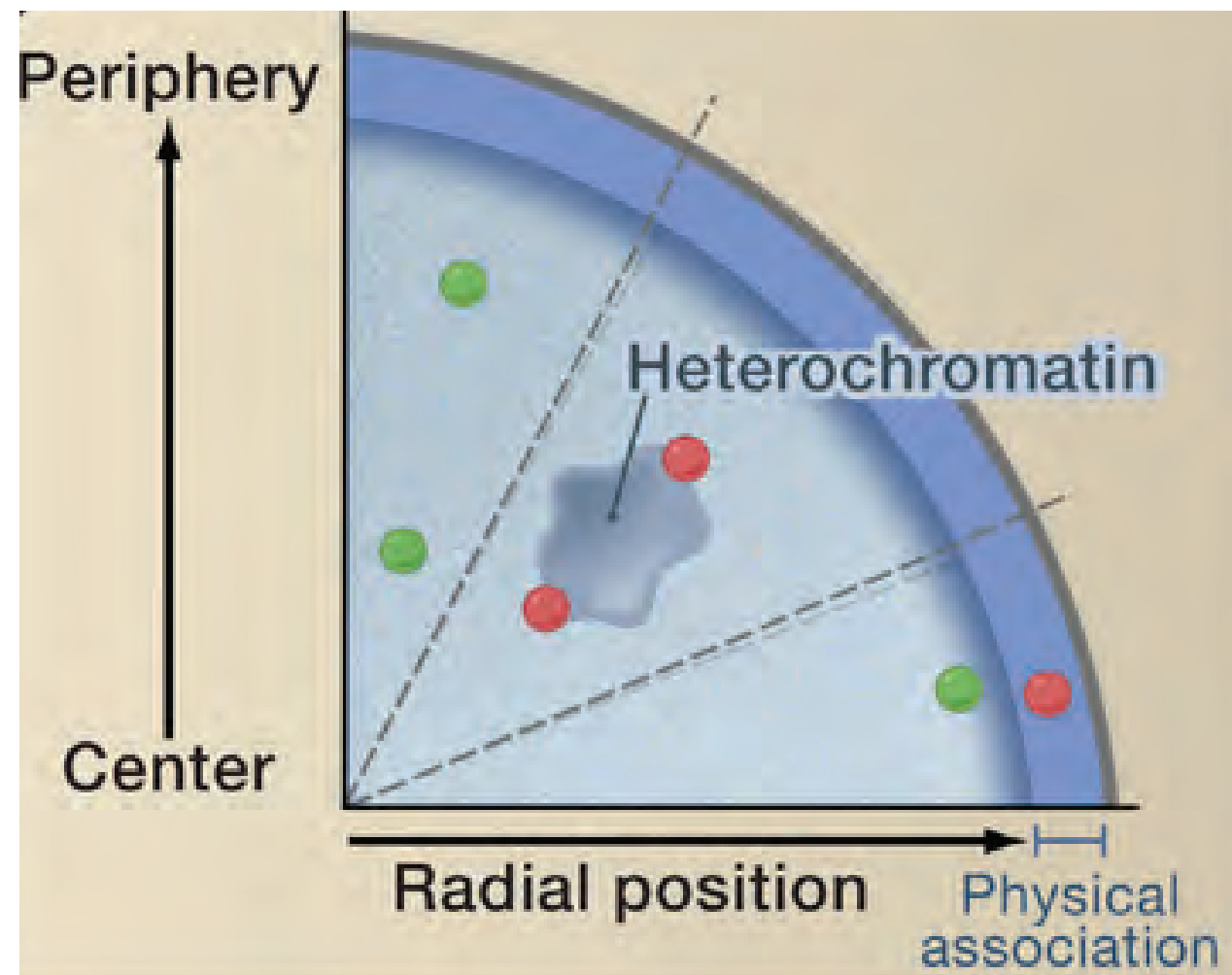
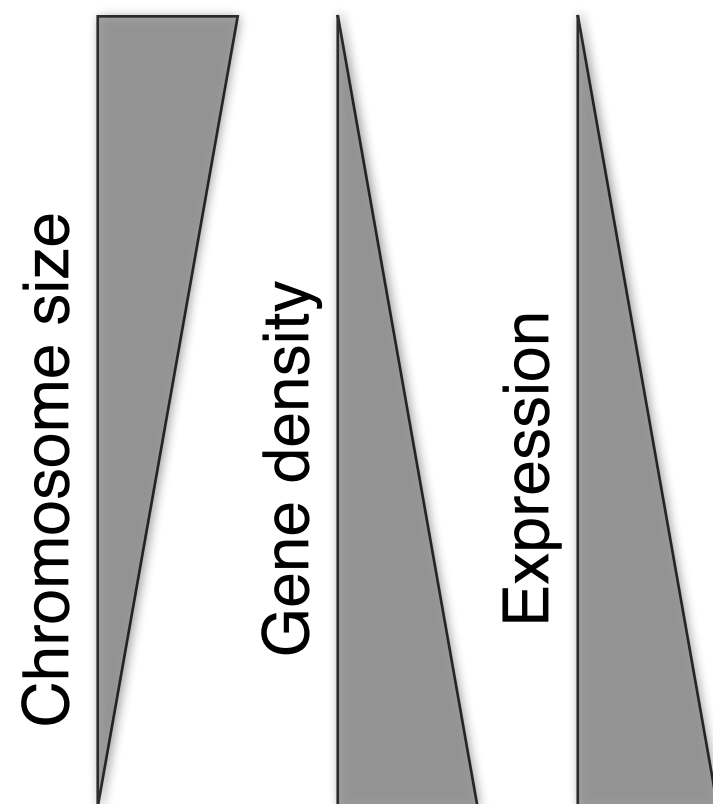
Resolution Gap

Marti-Renom, M. A. & Mirny, L. A. PLoS Comput Biol 7, e1002125 (2011)



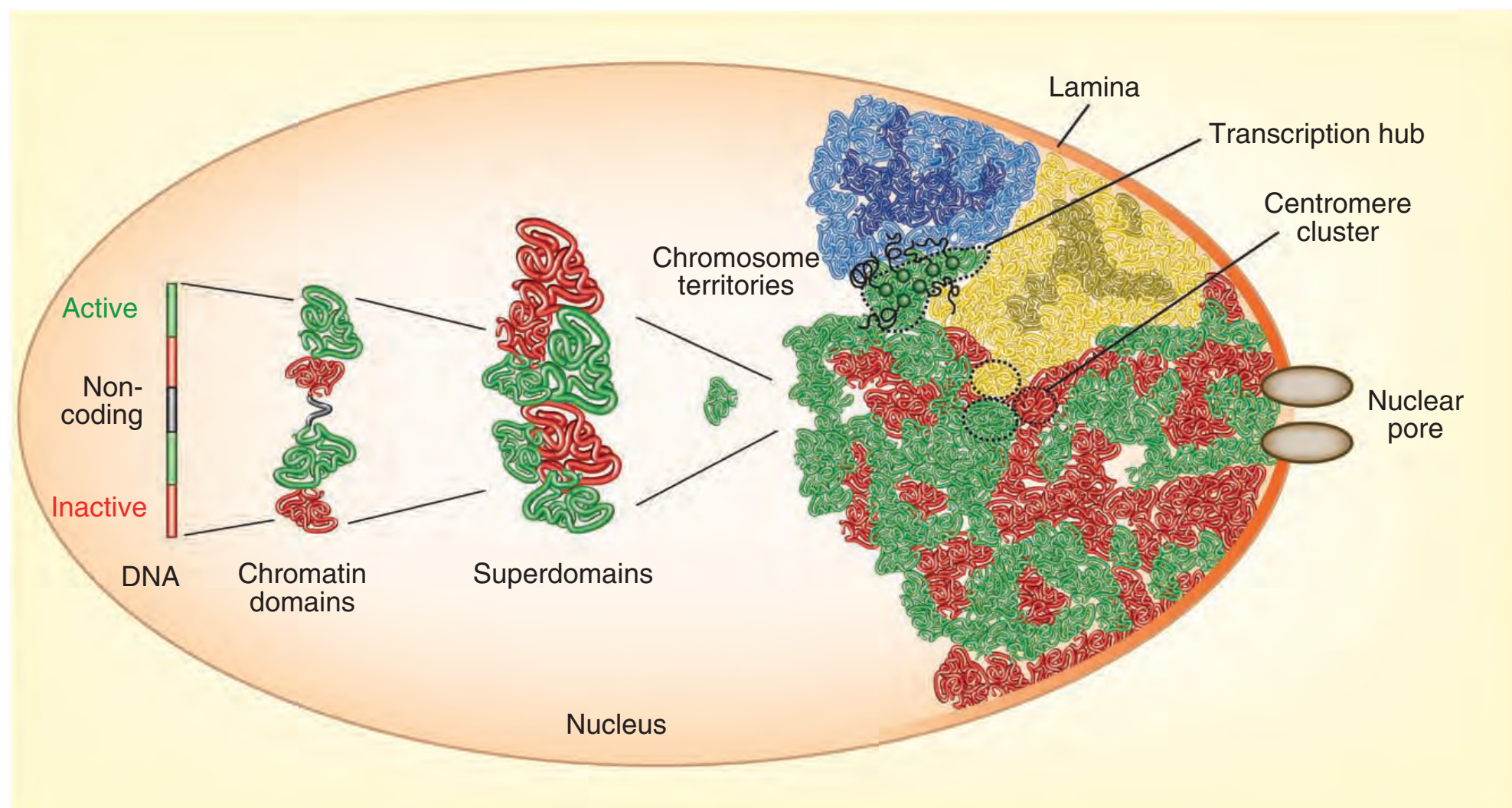
Complex genome organization

Takizawa, T., Meaburn, K. J. & Misteli, T. The meaning of gene positioning. Cell 135, 9–13 (2008).



Complex genome organization

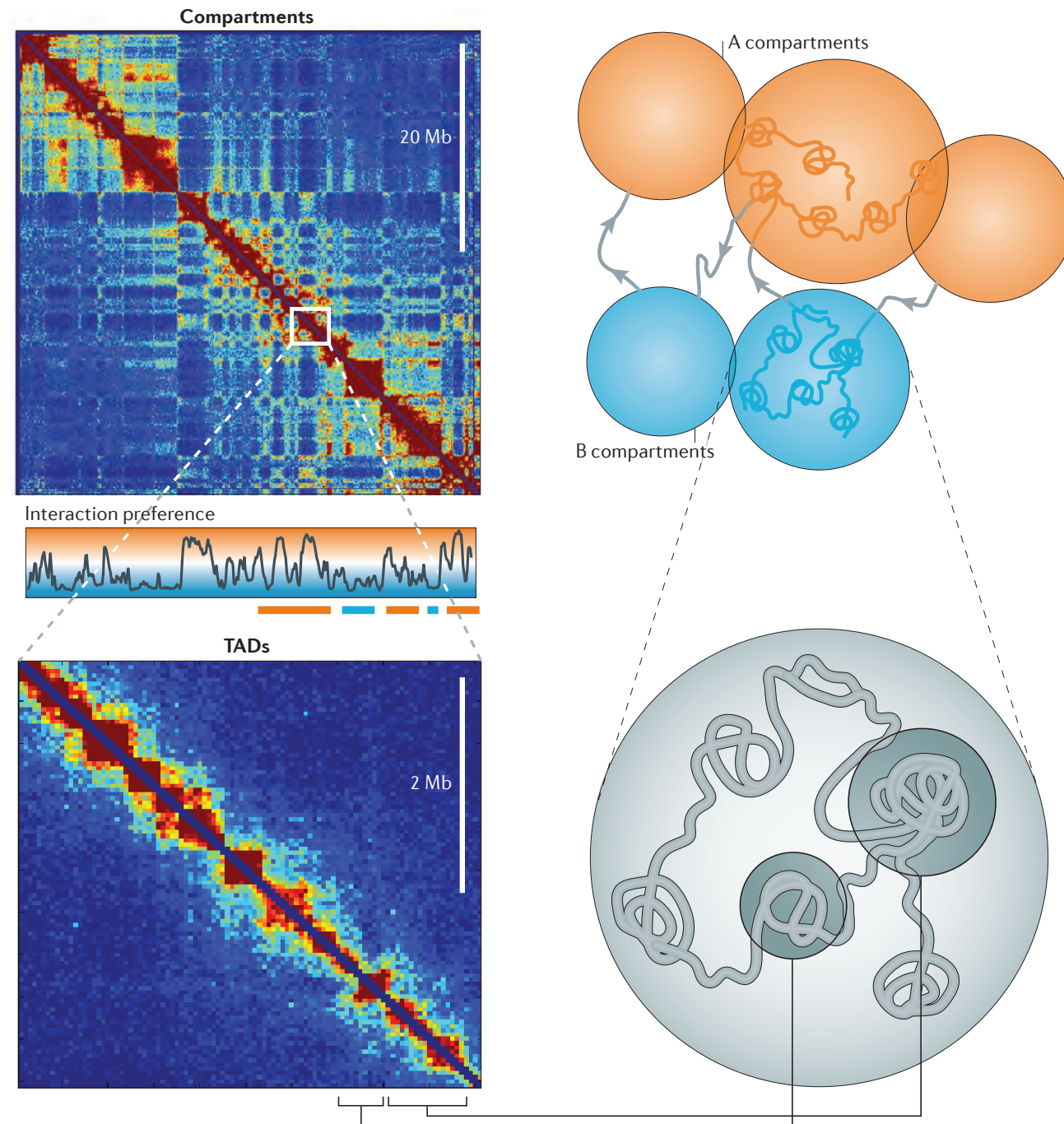
Cavalli, G. & Misteli, T. Functional implications of genome topology. Nat Struct Mol Biol 20, 290–299 (2013).



Marina Corral

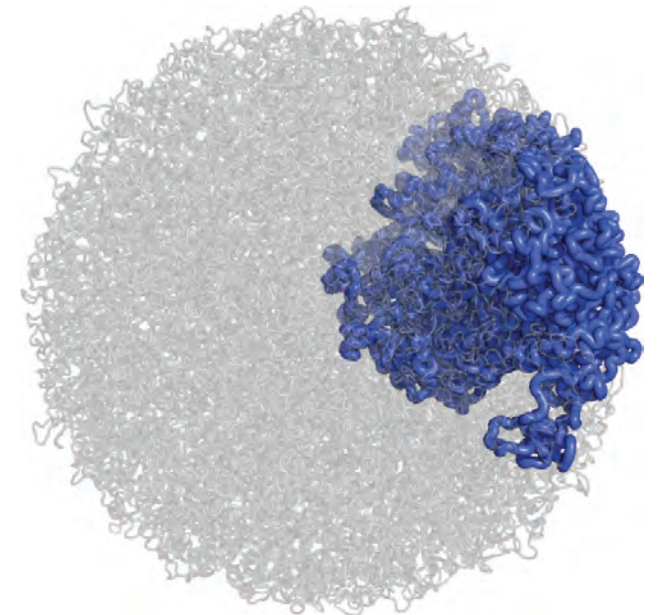
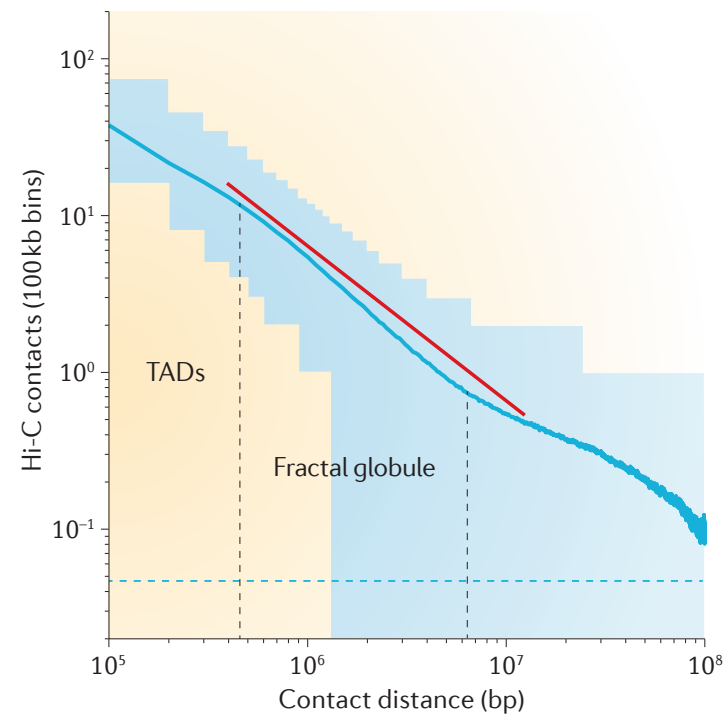
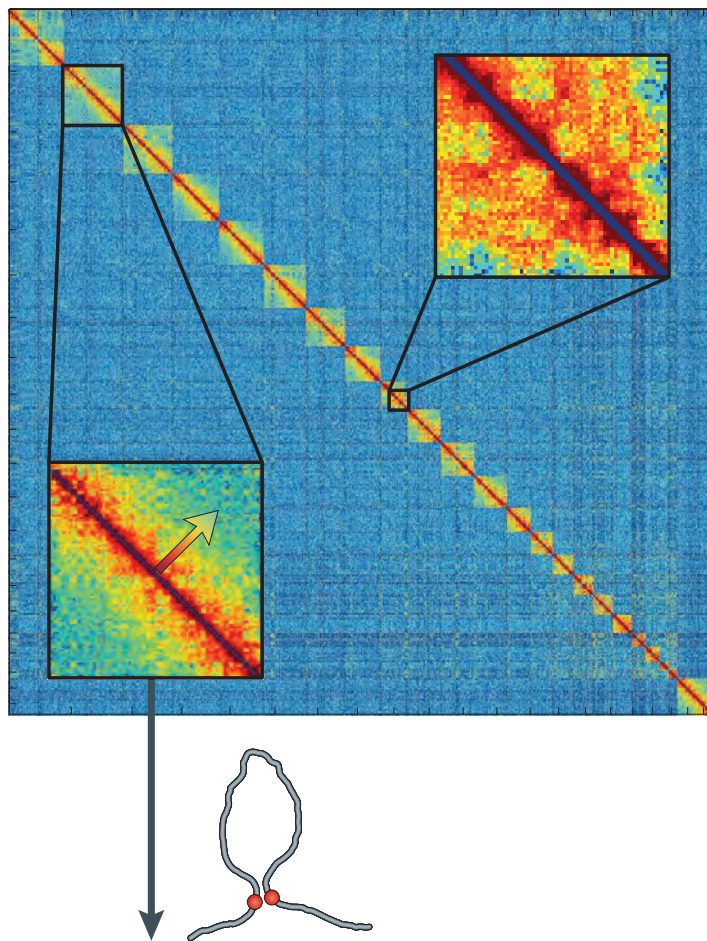
Complex genome organization

Dekker, J., Marti-Renom, M. A. & Mirny, L. A. Exploring the three-dimensional organization of genomes: interpreting chromatin interaction data. Nat Rev Genet 14, 390–403 (2013).

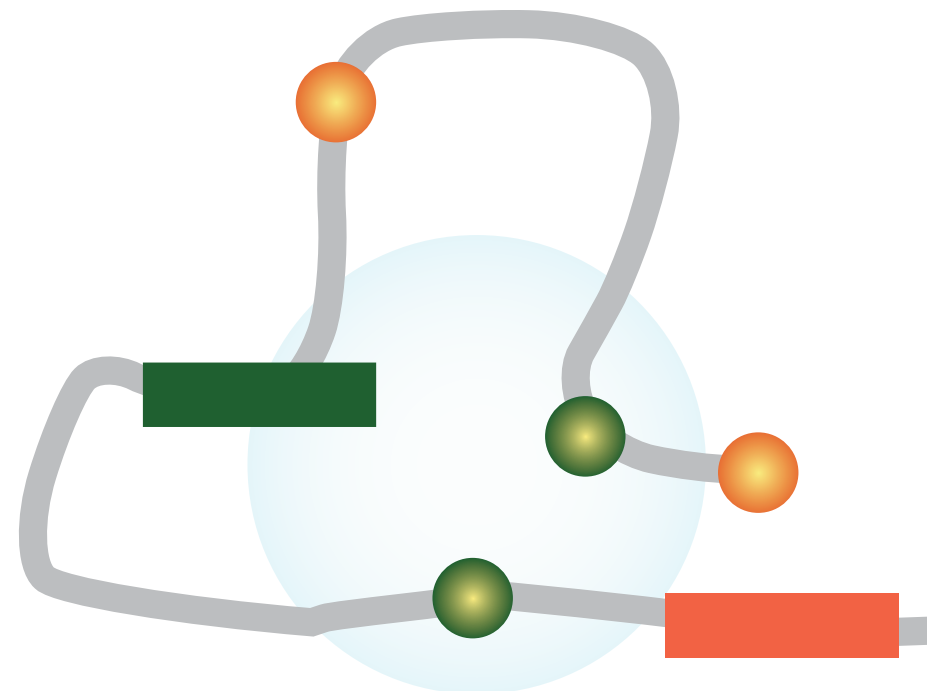
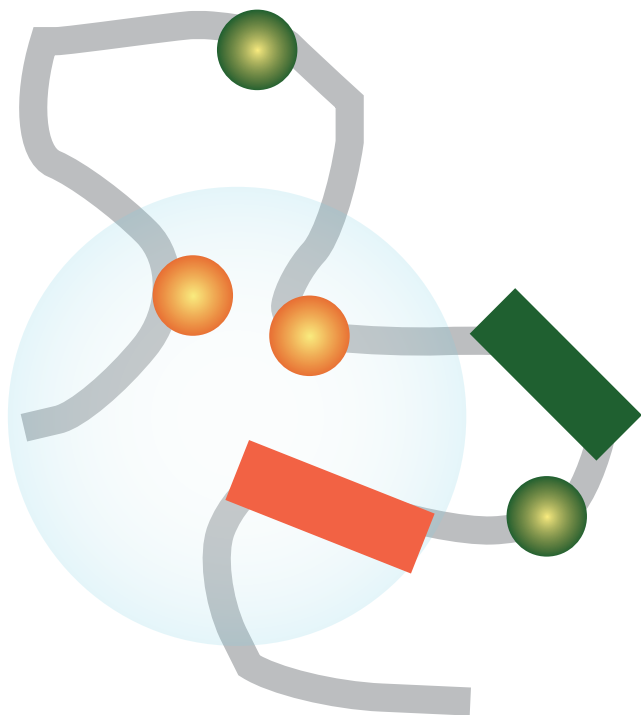


Complex genome organization

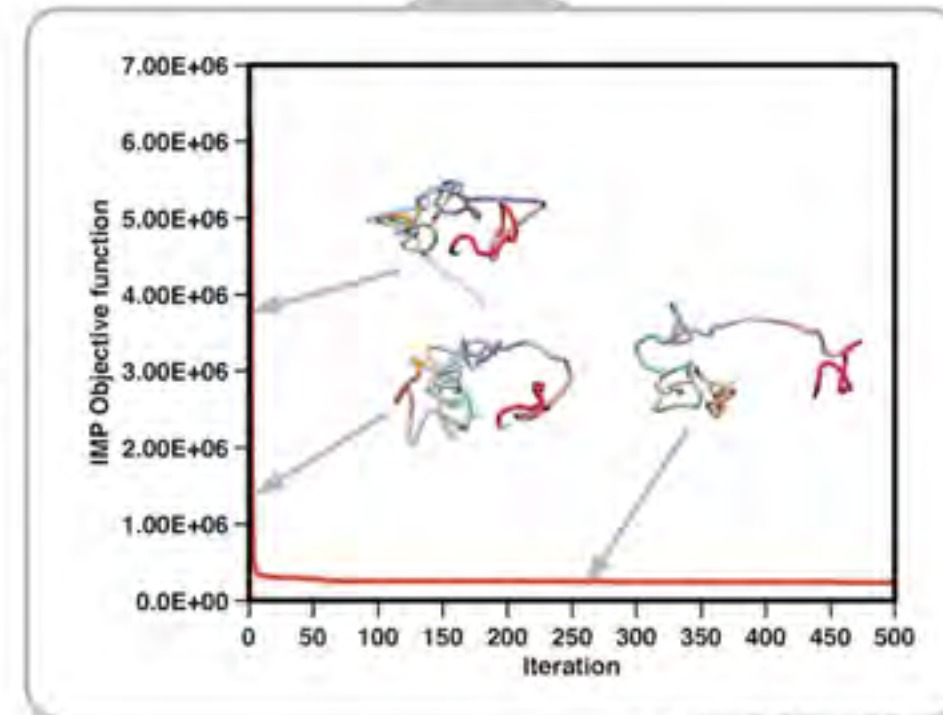
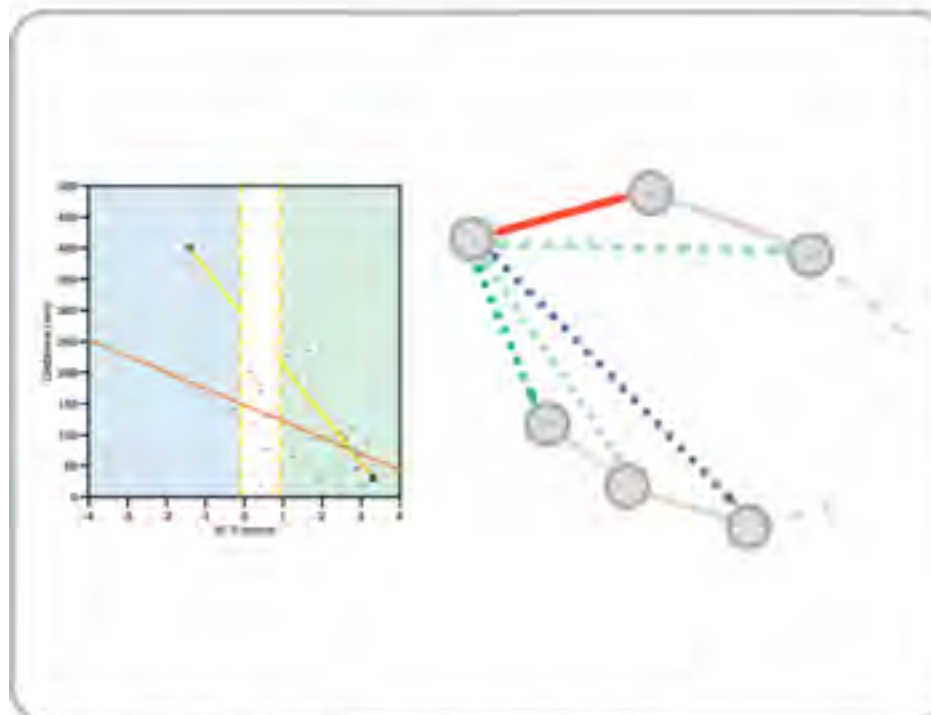
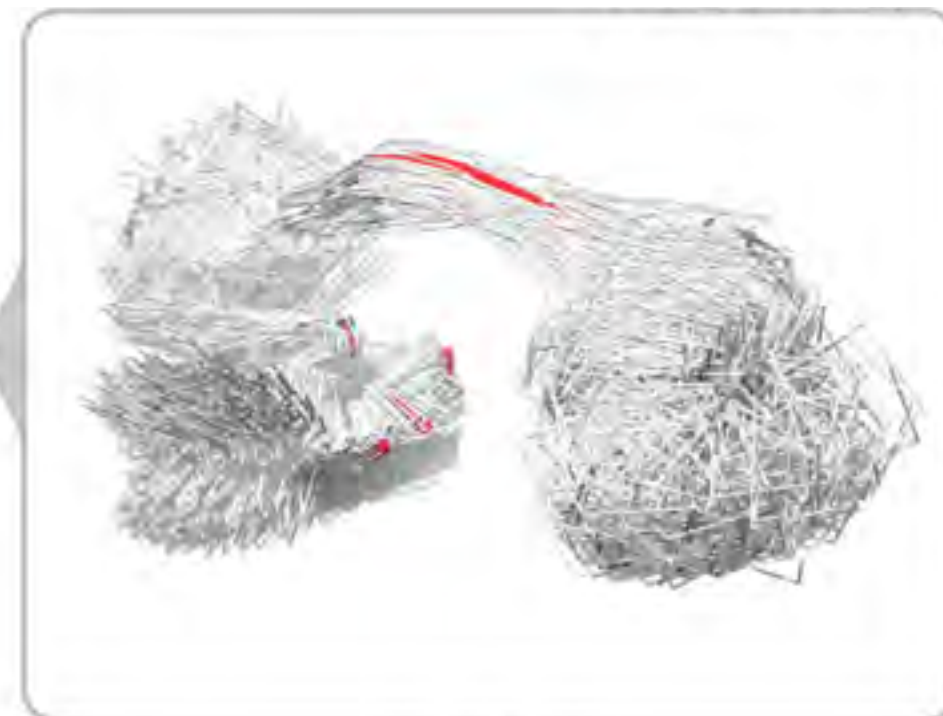
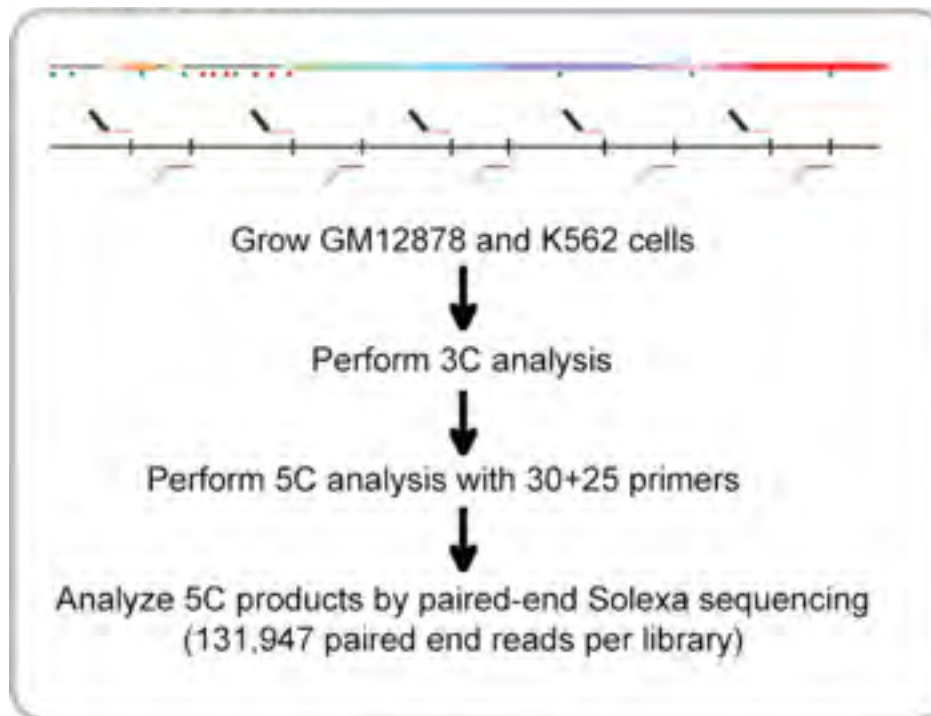
Lieberman-Aiden, E. et al. Comprehensive mapping of long-range interactions reveals folding principles of the human genome.
Science (New York, NY) 326, 289–293 (2009).



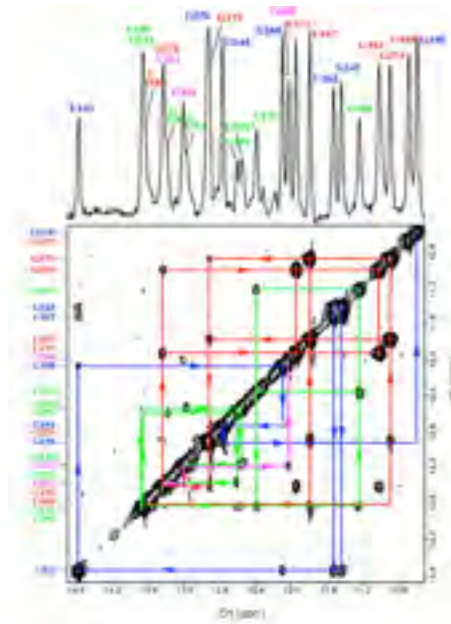
Complex genome organization



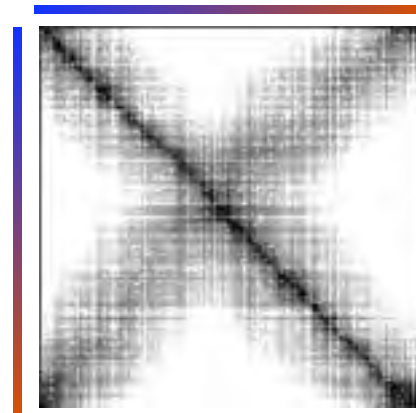
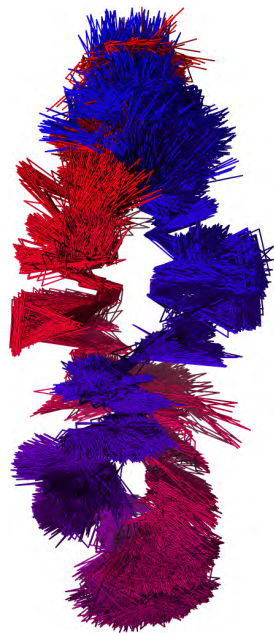
Experiments



Computation

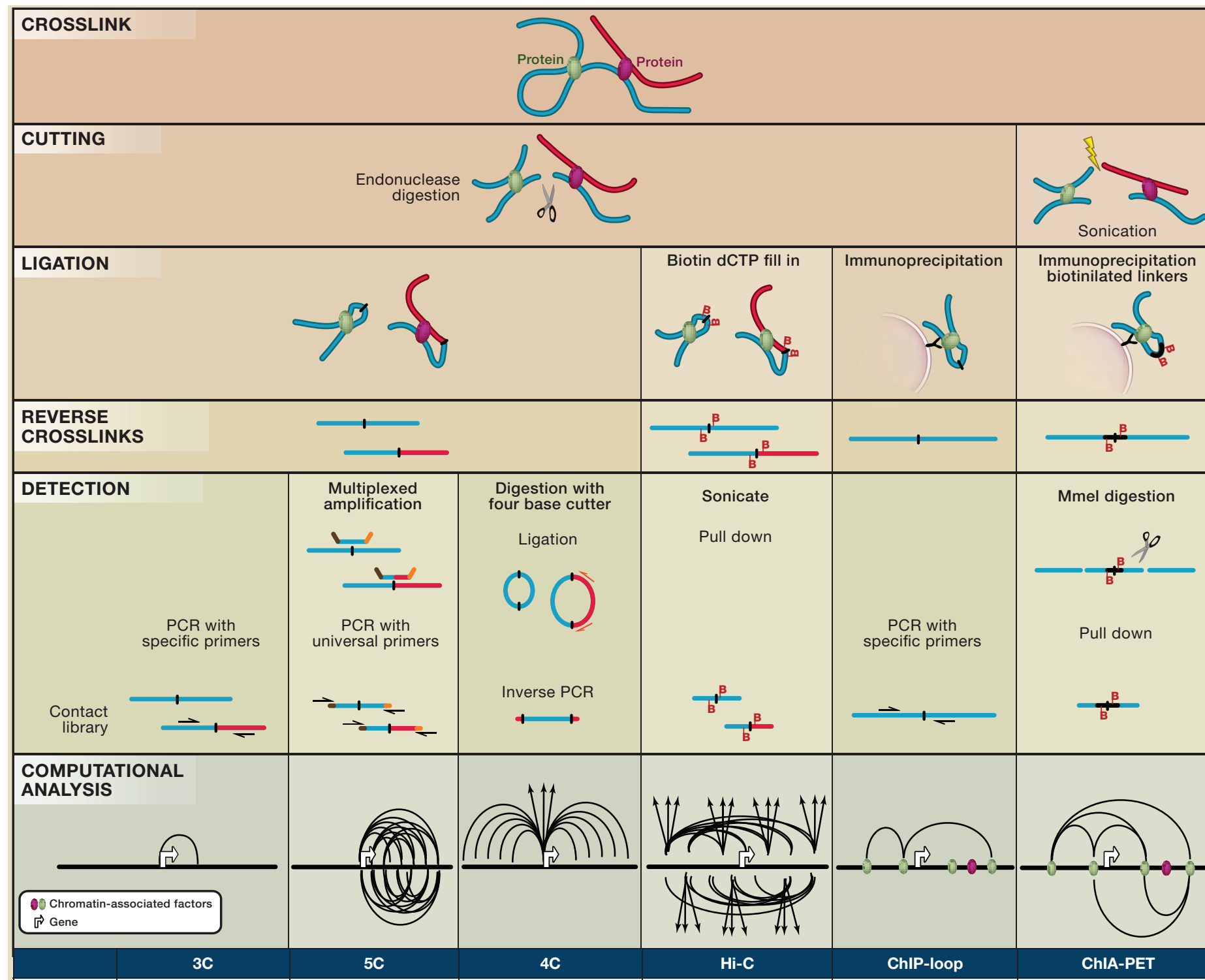


Biomolecular structure determination 2D-NOESY data



Chromosome structure determination 5C data

Chromosome Conformation Capture



Hakim, O., & Misteli, T. (2012). SnapShot: Chromosome Confirmation Capture. Cell, 148(5), 1068–1068.e2.

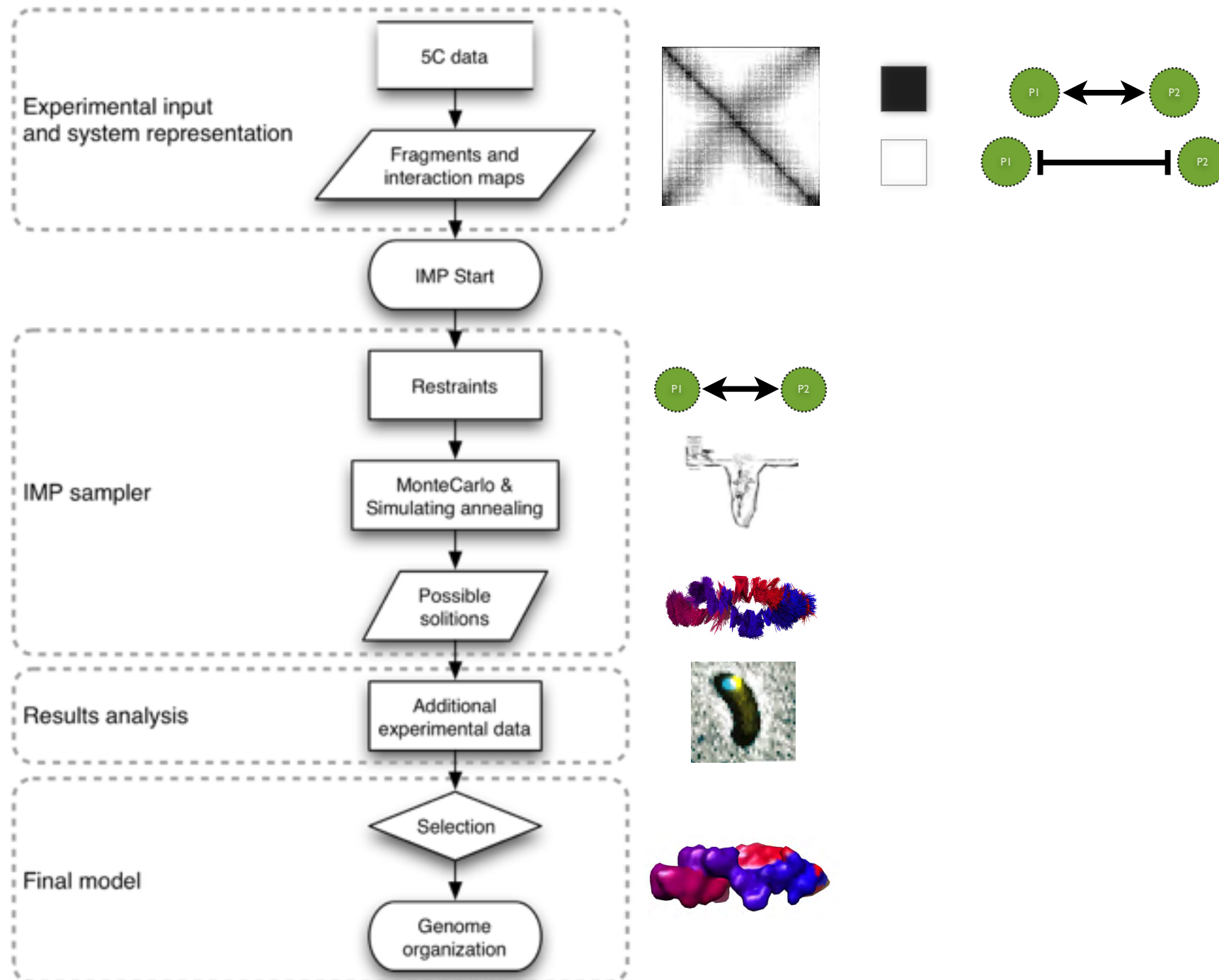
Chromosome Conformation Capture

	3C	5C	4C	Hi-C	ChIP-loop	ChIA-PET
Principle	Contacts between two defined regions ^{3,17}	All against all ^{4,18}	All contacts with a point of interest ¹⁴	All against all ¹⁰	Contacts between two defined regions associated with a given protein ⁸	All contacts associated with a given protein ⁶
Coverage	Commonly < 1Mb	Commonly < 1Mb	Genome-wide	Genome-wide	Commonly < 1Mb	Genome-wide
Detection	Locus-specific PCR	HT-sequencing	HT-sequencing	HT-sequencing	Locus-specific qPCR	HT-sequencing
Limitations	Low throughput and coverage	Limited coverage	Limited to one viewpoint		Rely on one chromatin-associated factor, disregarding other contacts	
Examples	Determine interaction between a known promoter and enhancer	Determine comprehensively higher-order chromosome structure in a defined region	All genes and genomic elements associated with a known LCR	All intra- and interchromosomal associations	Determine the role of specific transcription factors in the interaction between a known promoter and enhancer	Map chromatin interaction network of a known transcription factor
Derivatives	PCR with TaqMan probes ⁷ or melting curve analysis ¹		Circular chromosome conformation capture ²⁰ , open-ended chromosome conformation capture ¹⁹ , inverse 3C ¹² , associated chromosome trap (ACT) ¹¹ , affinity enrichment of bait-ligated junctions ²	Yeast ^{5,15} , tethered conformation capture ⁹		ChIA-PET combined 3C-ChIP-cloning (6C) ¹⁶ , enhanced 4C (e4C) ¹³

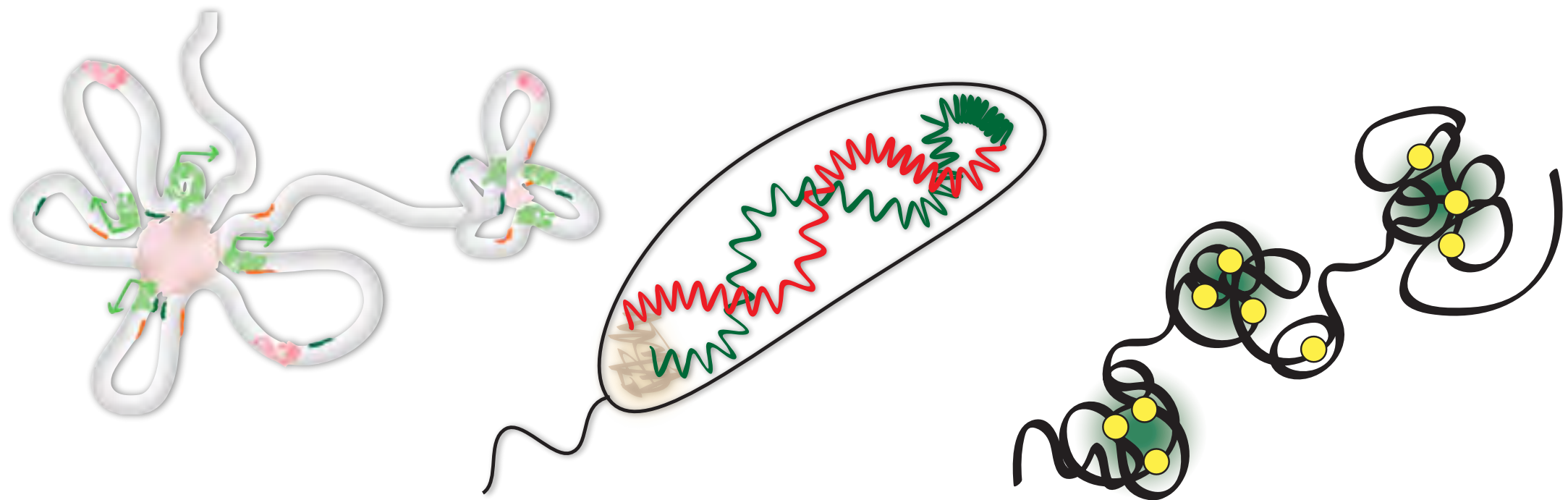
Hakim, O., & Misteli, T. (2012). SnapShot: Chromosome Confirmation Capture. Cell, 148(5), 1068–1068.e2.

Modeling 3D Genomes

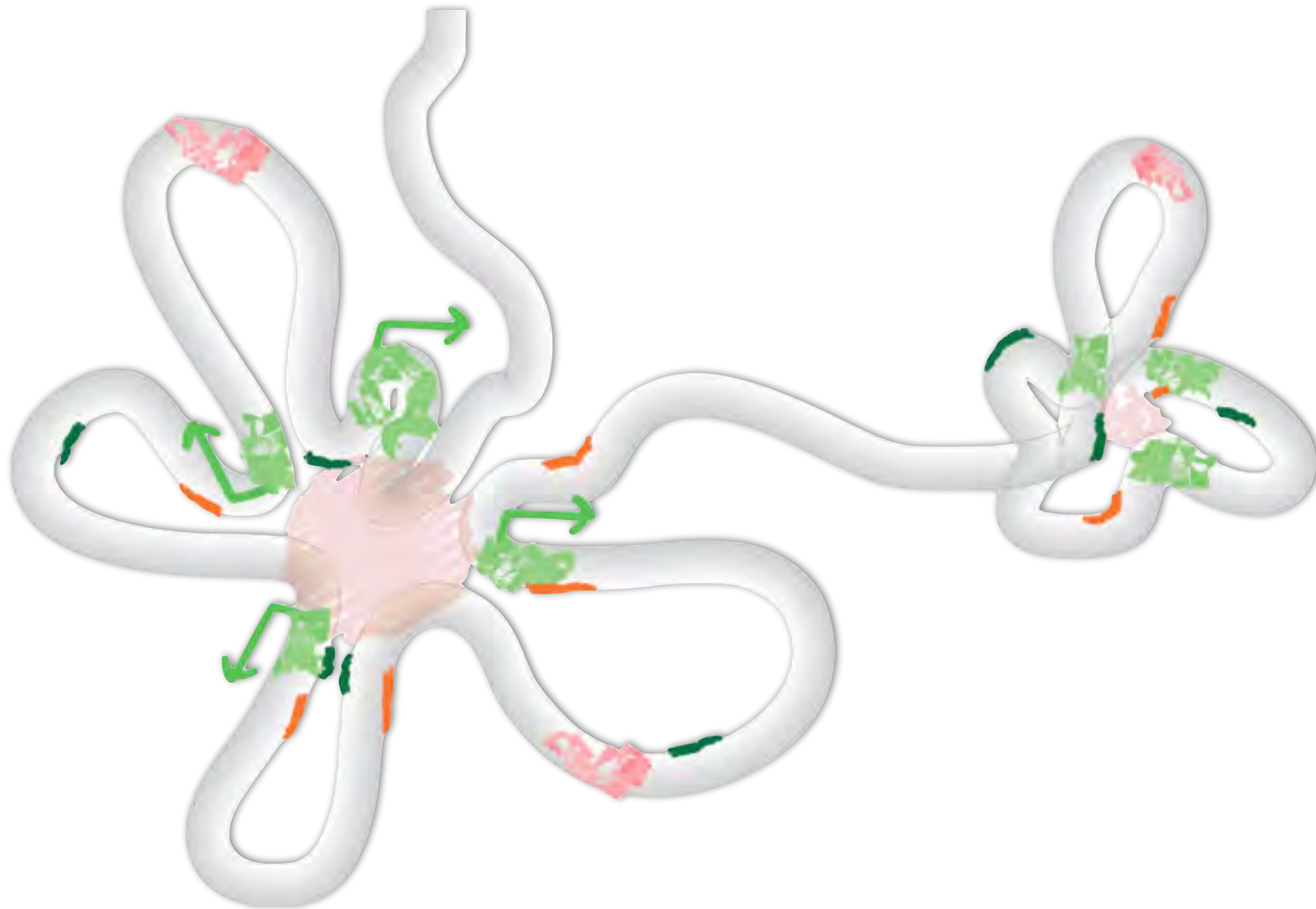
Baù, D. & Marti-Renom, M. A. Methods 58, 300–306 (2012).



Examples...



Human α -globin domain

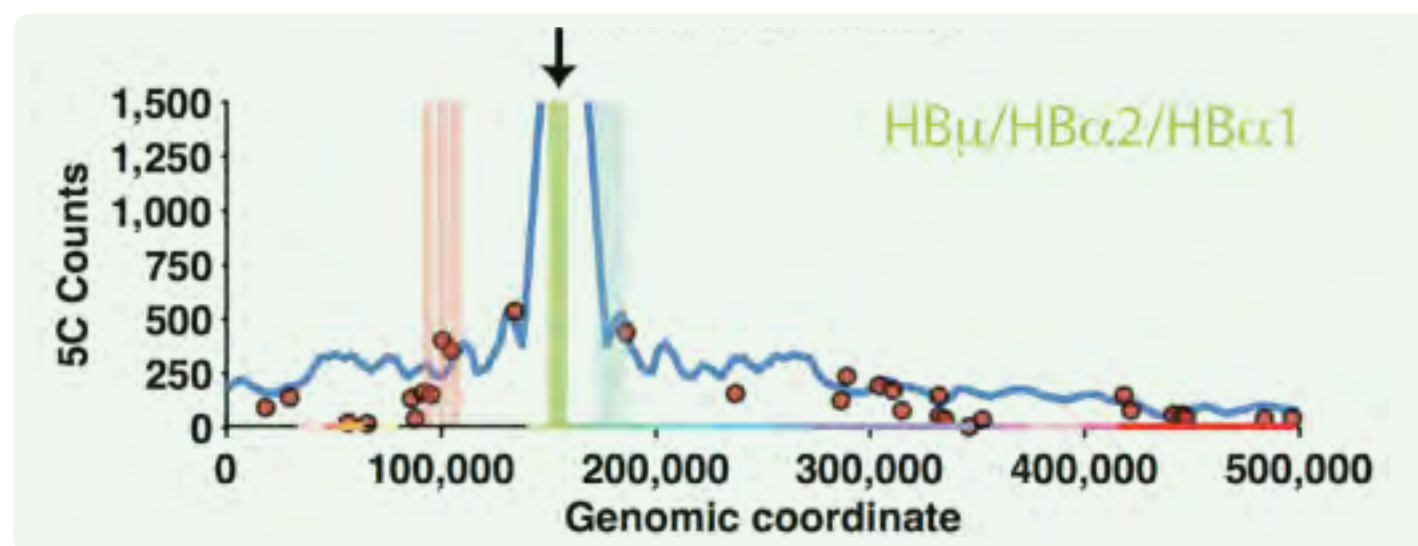
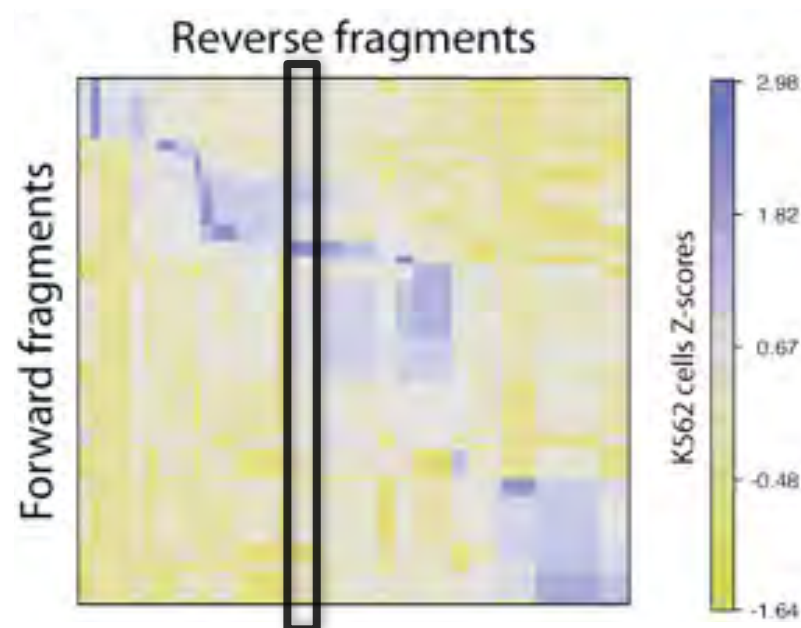


ENm008 genomic structure and environment



cnag **CRG**
Centre for Genomic Regulation

ENm008 genomic structure and environment



Representation

Harmonic

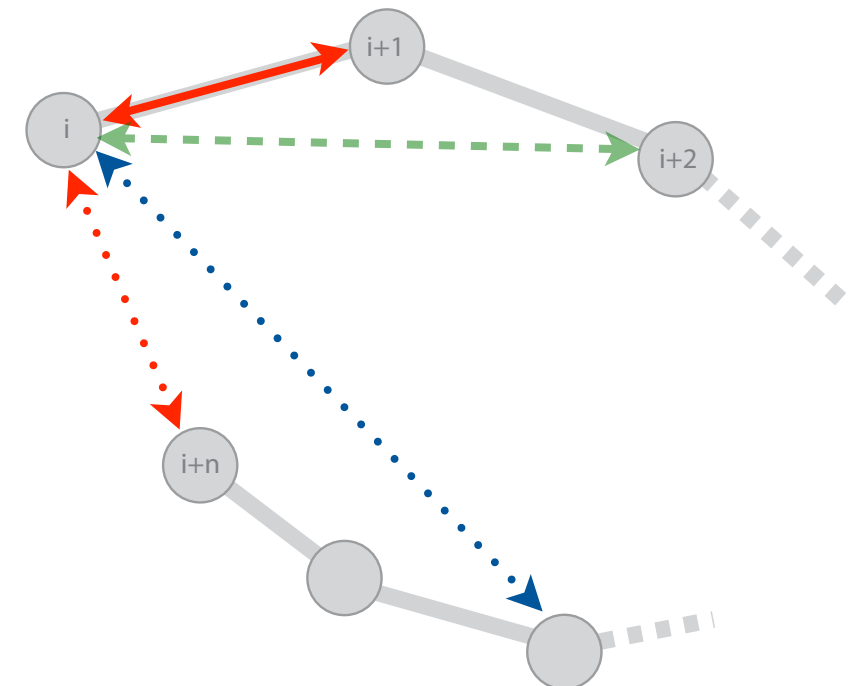
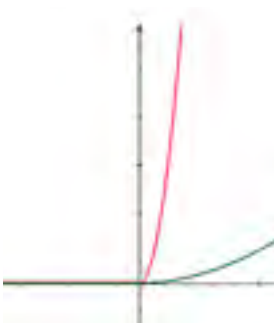
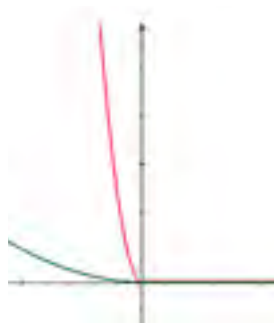
$$H_{i,j} = k(d_{i,j} - d_{i,j}^0)^2$$

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

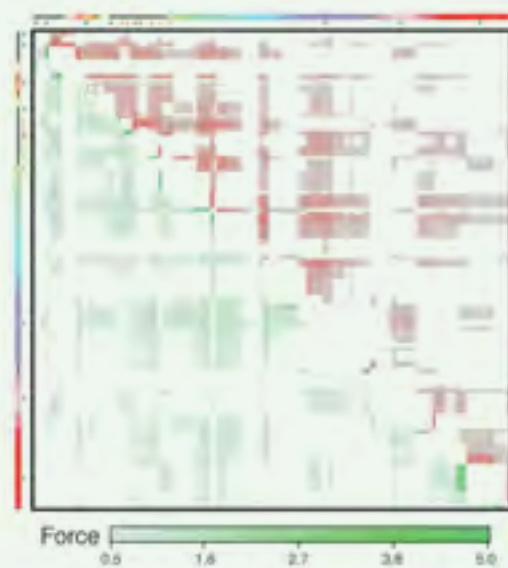
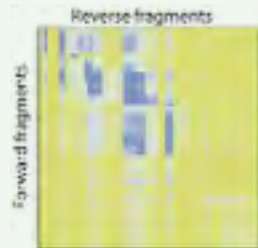
$$\begin{cases} \text{if } d_{i,j} \geq d_{i,j}^0; & ubH_{i,j} = k(d_{i,j} - d_{i,j}^0)^2 \\ \text{if } d_{i,j} < d_{i,j}^0; & ubH_{i,j} = 0 \end{cases}$$



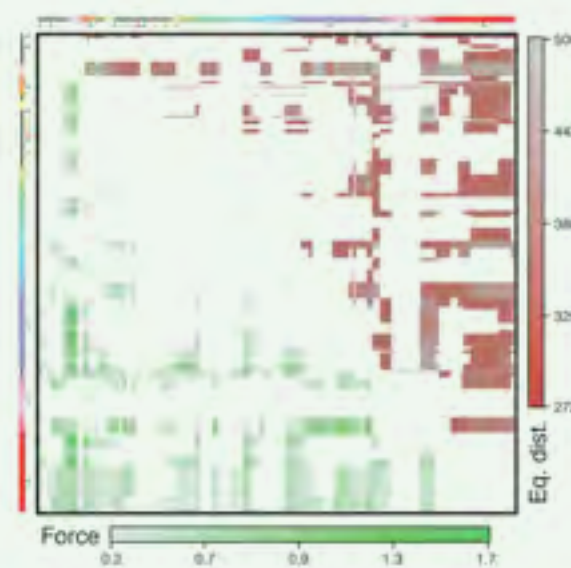
Scoring

GM12878

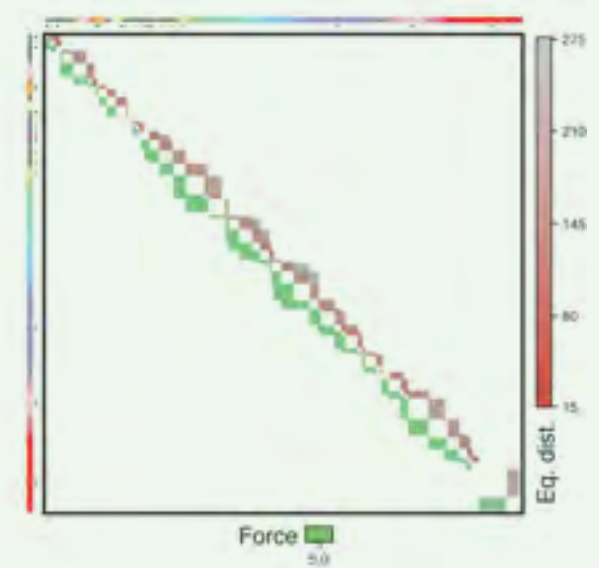
70 fragments
1,520 restraints



Harmonic



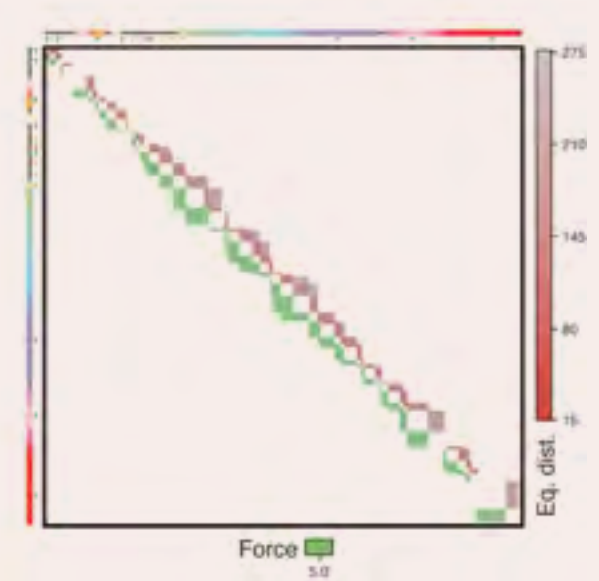
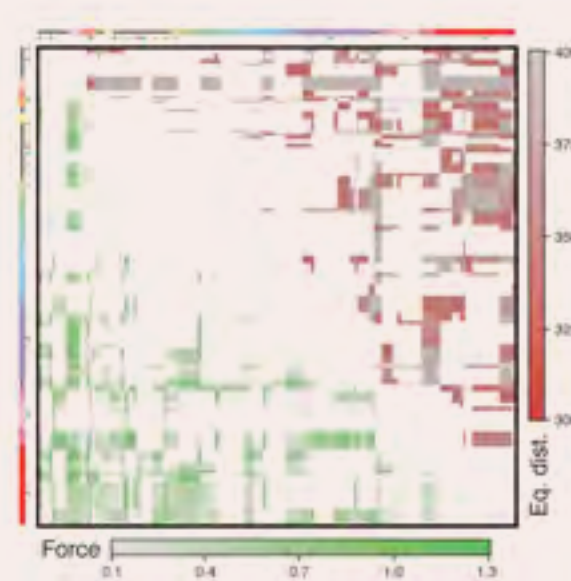
Harmonic Lower Bound



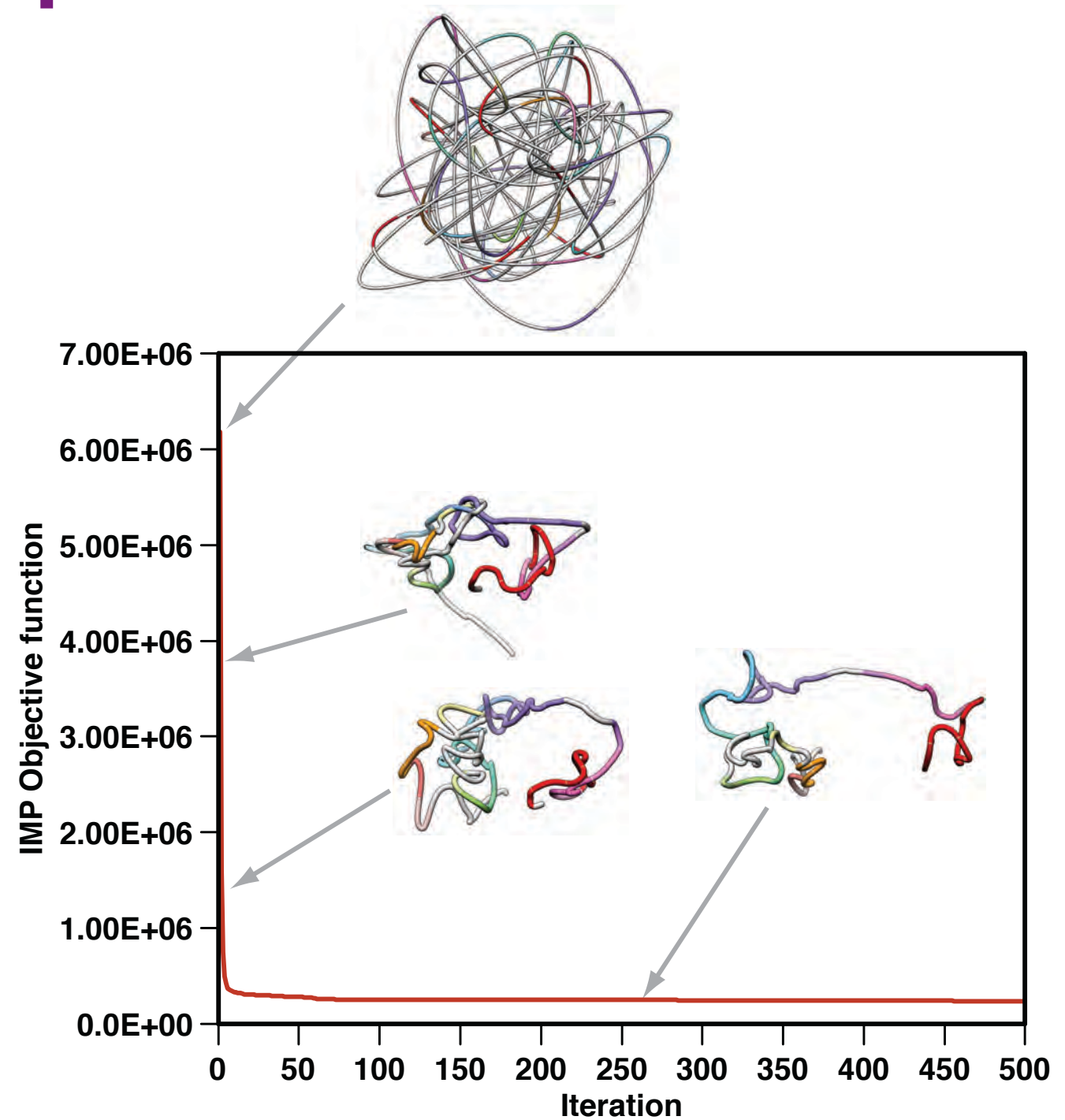
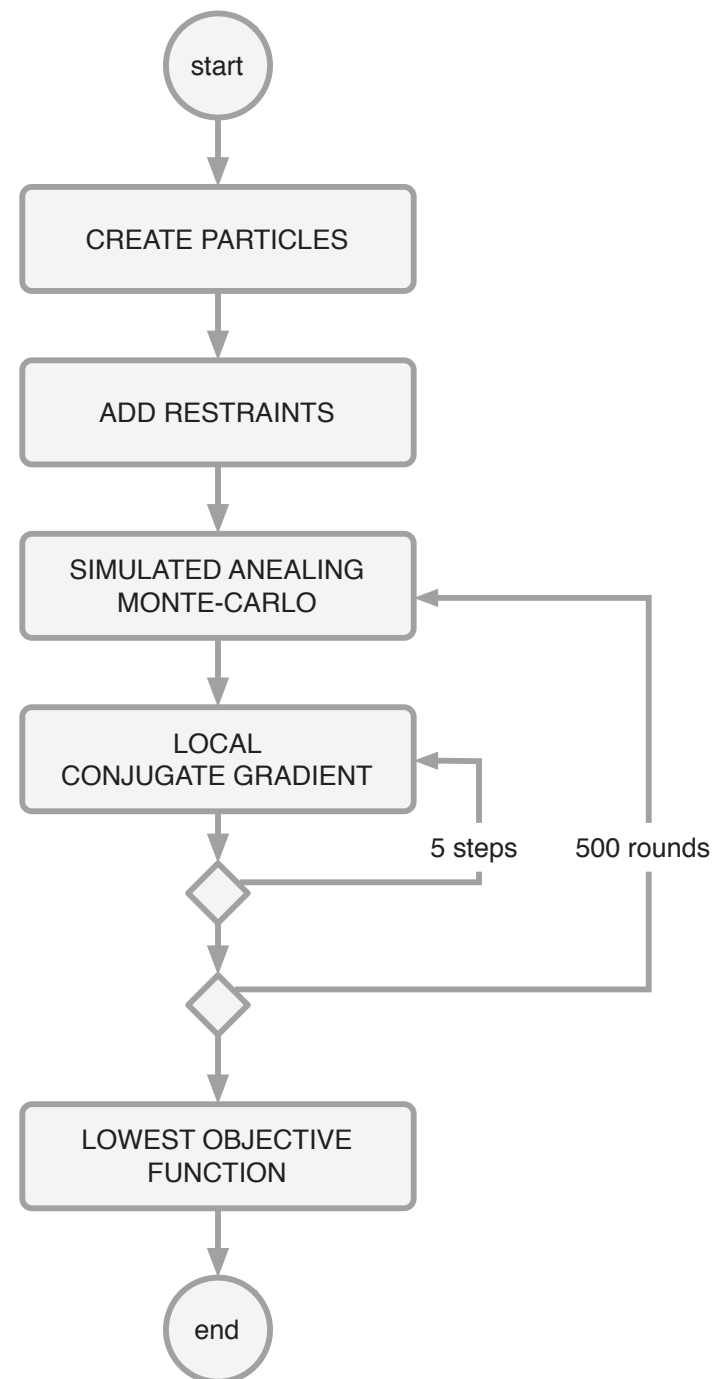
Harmonic Upper Bound

K562

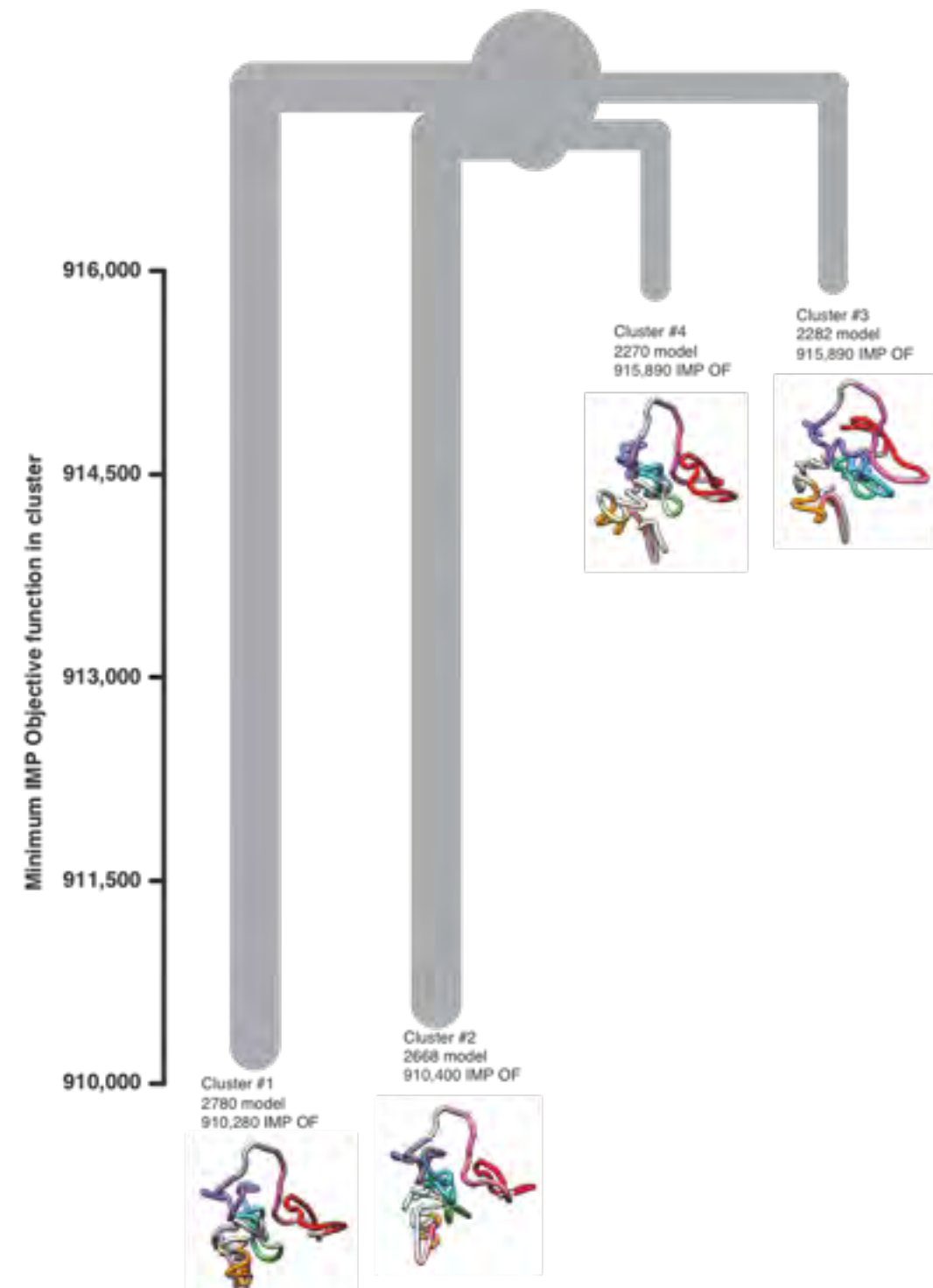
70 fragments
1,049 restraints



Optimization

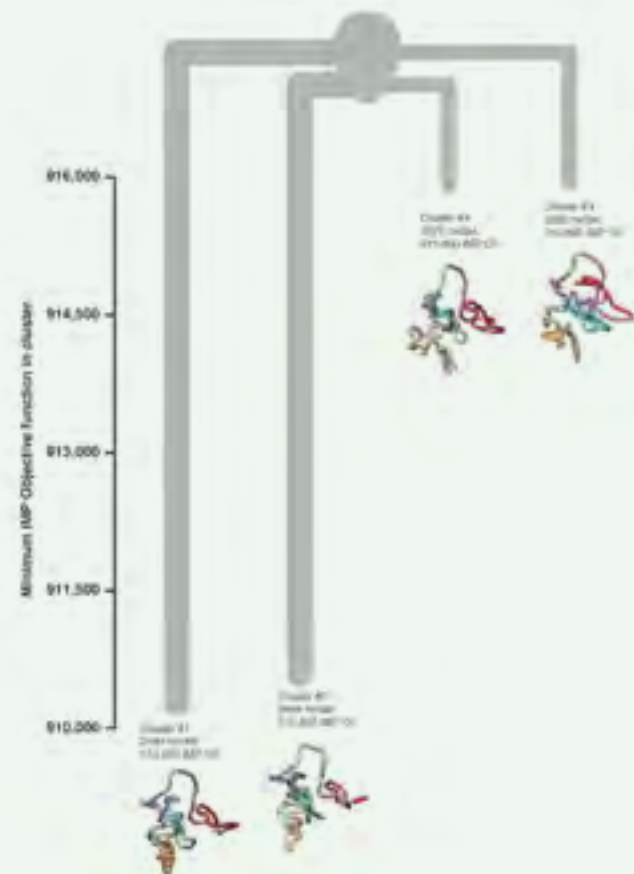
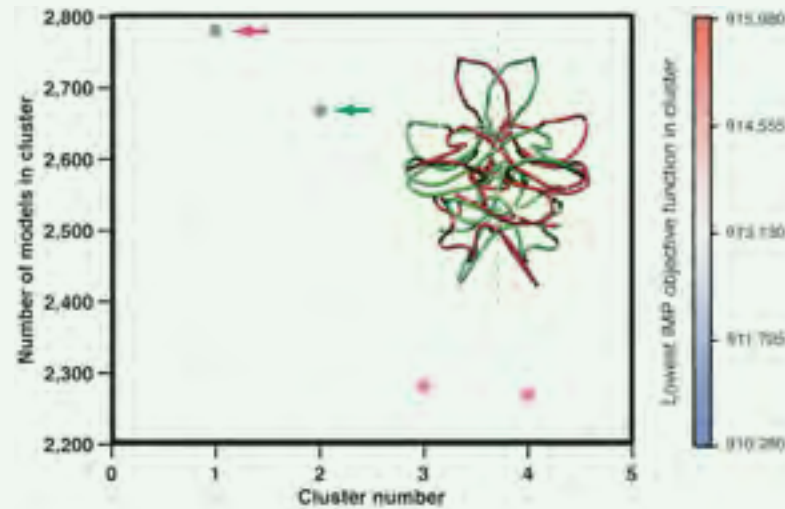


Clustering

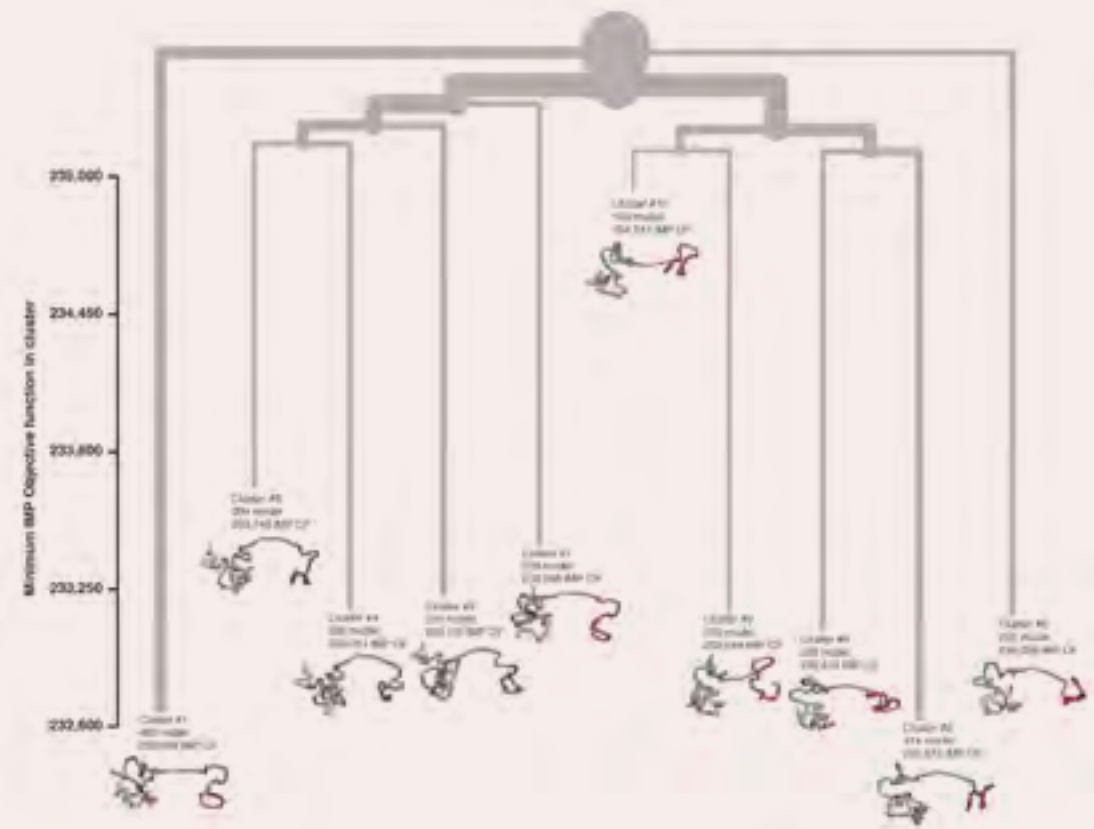
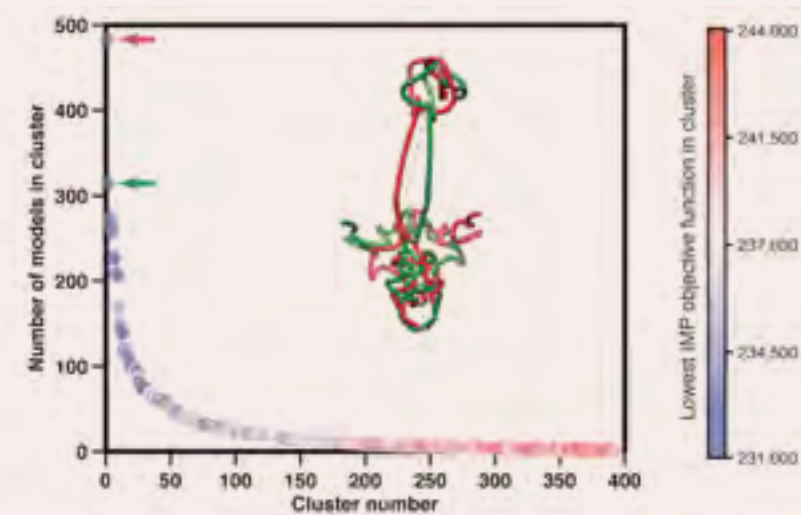


Not just one solution

GM12878



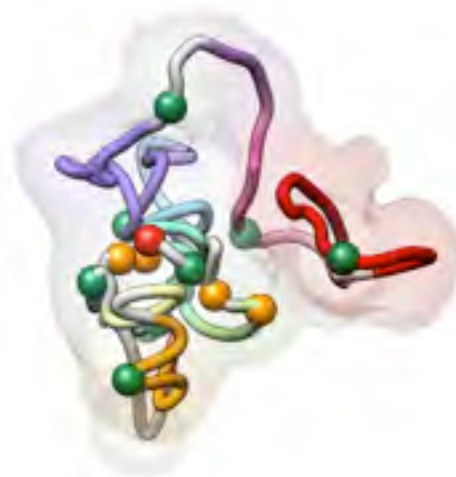
K562



Regulatory Requirements

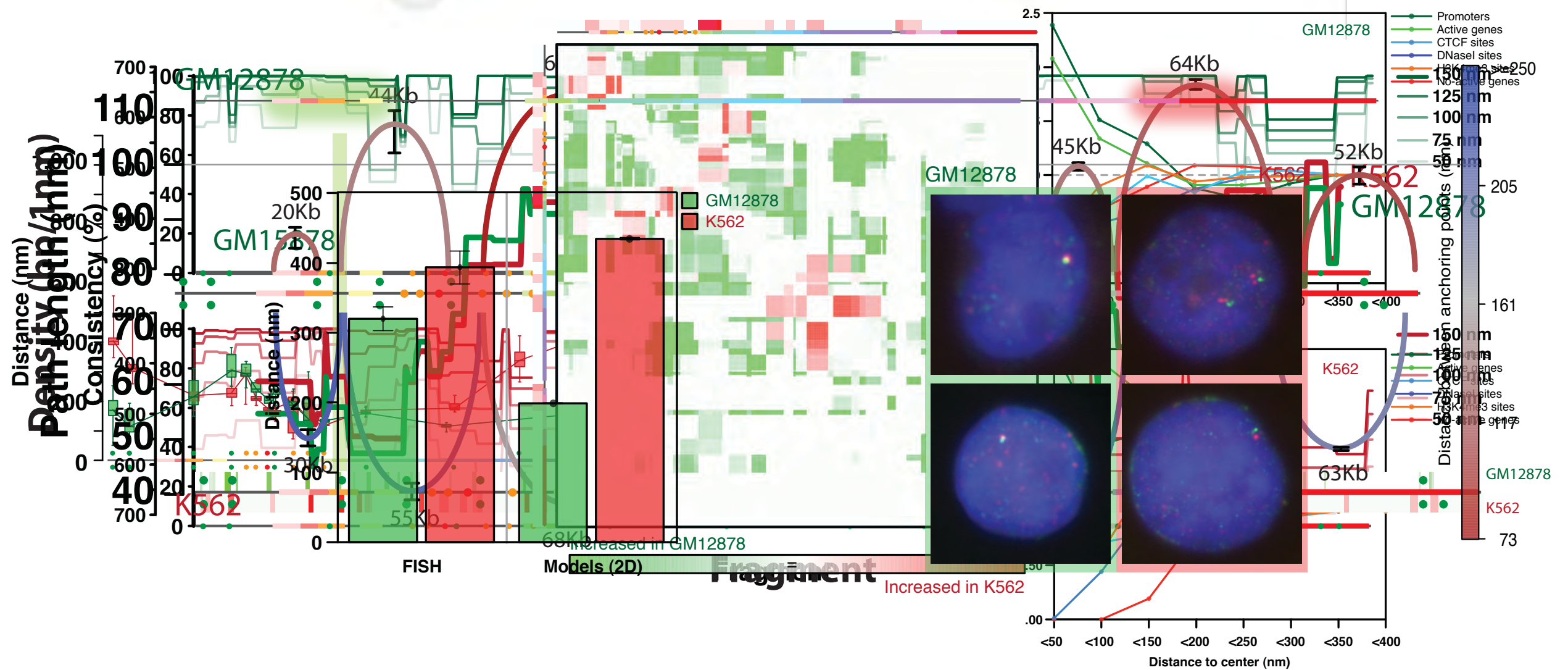
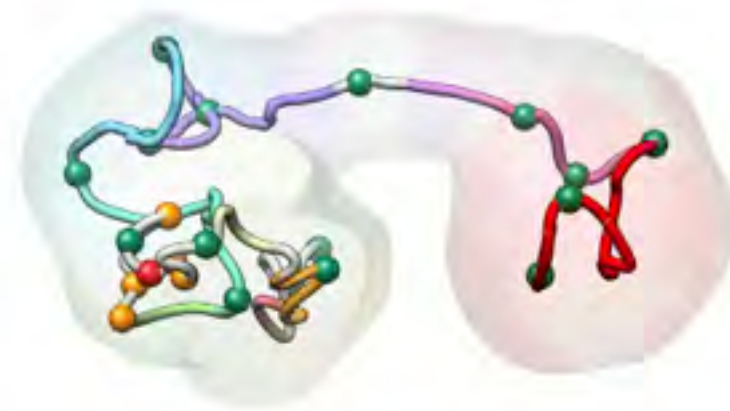
GM 12878

Cluster #1
2780 model

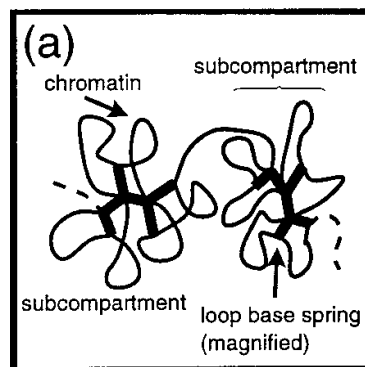
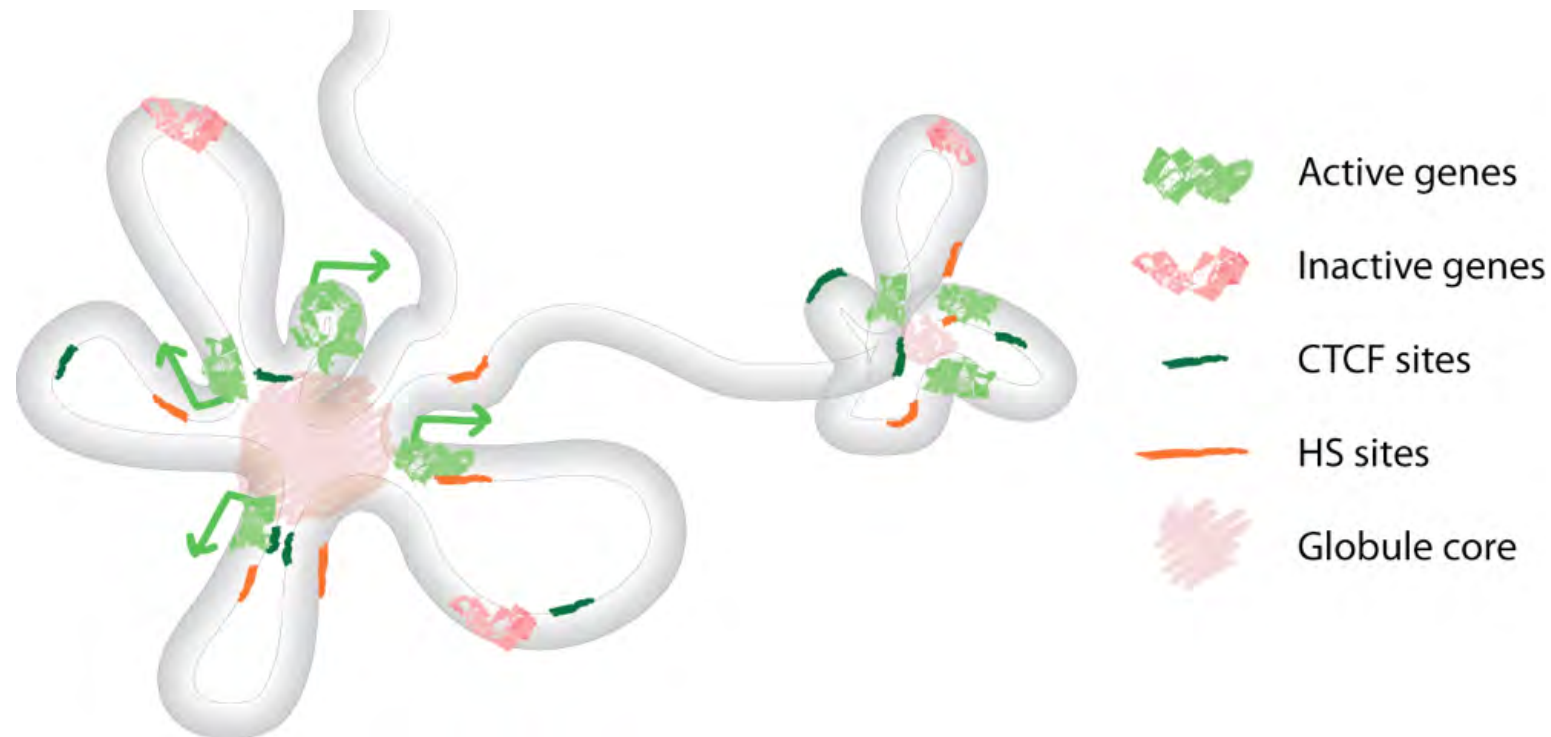


K562

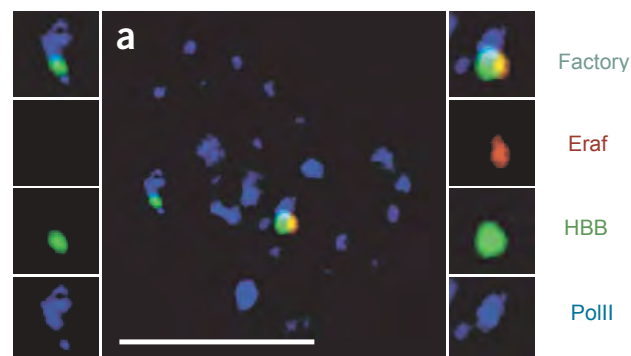
Cluster #2
314 model



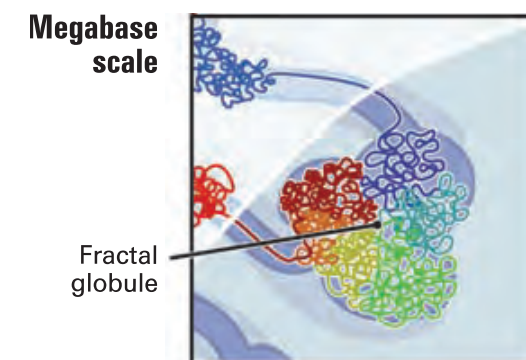
The “Chromatin Globule” model



Münkel et al. JMB (1999)



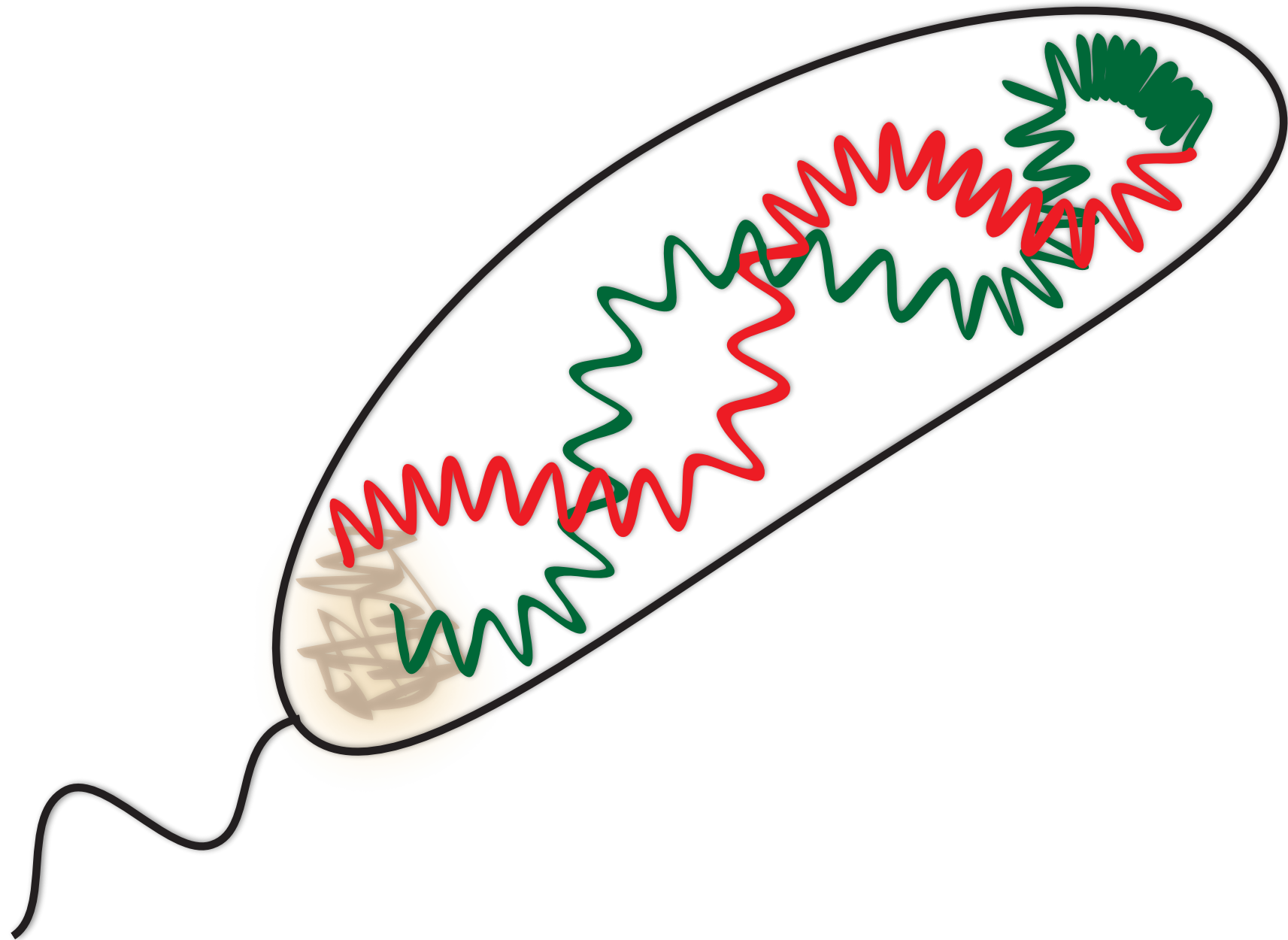
Osborne et al. Nat Genet (2004)



Lieberman-Aiden et al. Science (2009)

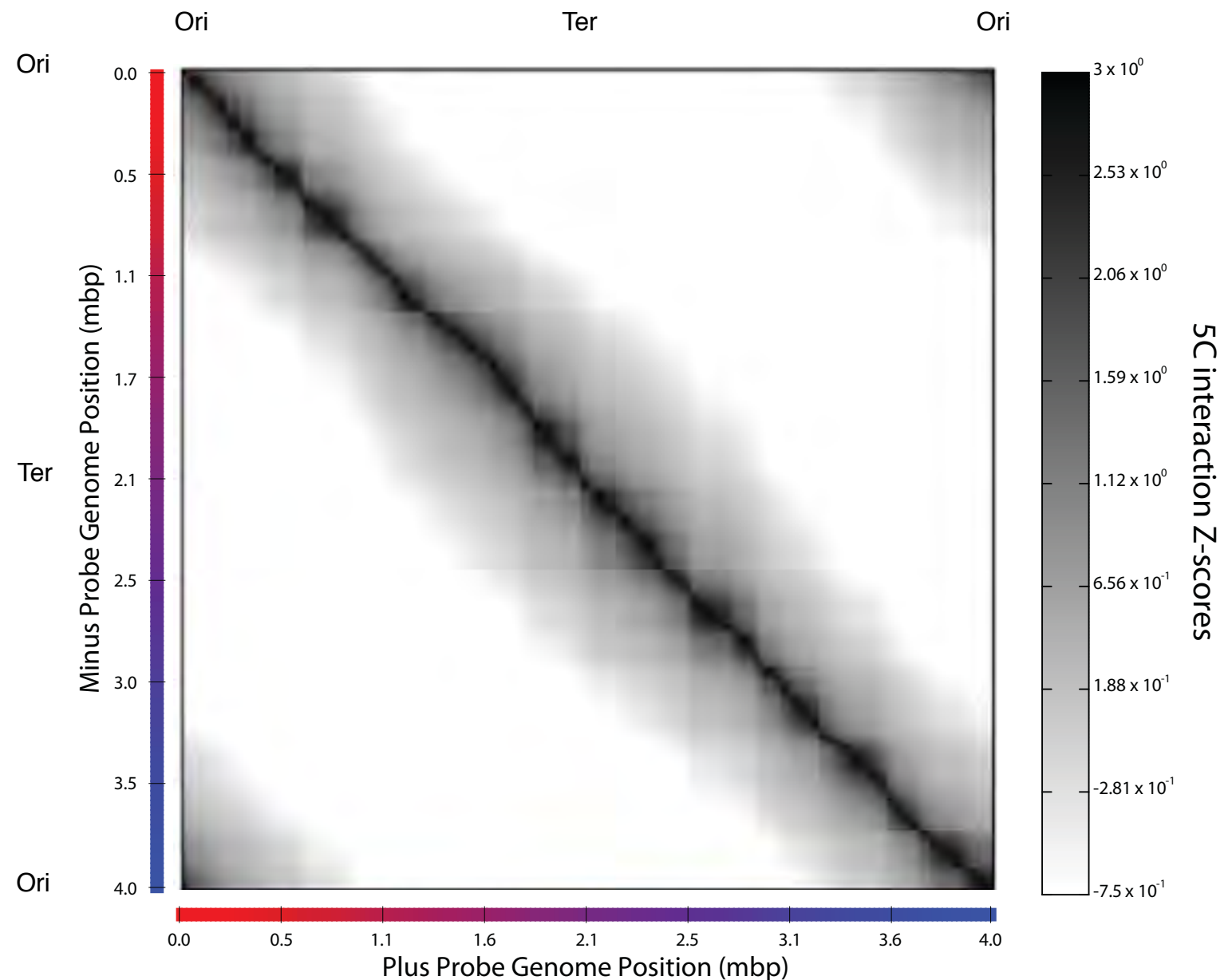
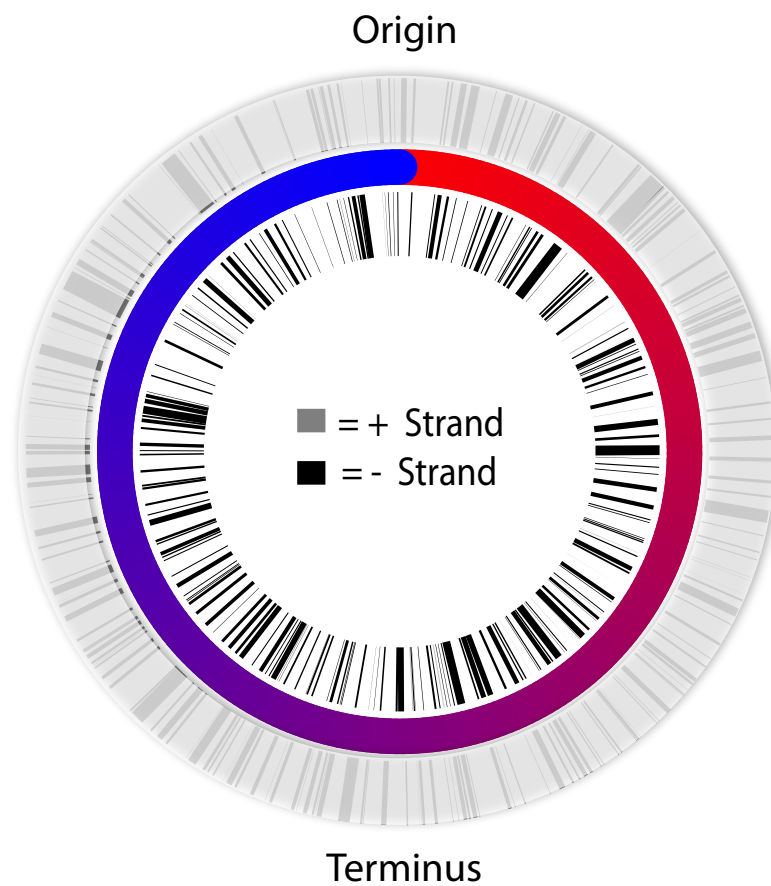
D. Baù et al. Nat Struct Mol Biol (2011) 18:107-14
A. Sanyal et al. Current Opinion in Cell Biology (2011) 23:325–33.

Caulobacter crescentus genome



The 3D architecture of *Caulobacter Crescentus*

4,016,942 bp & 3,767 genes

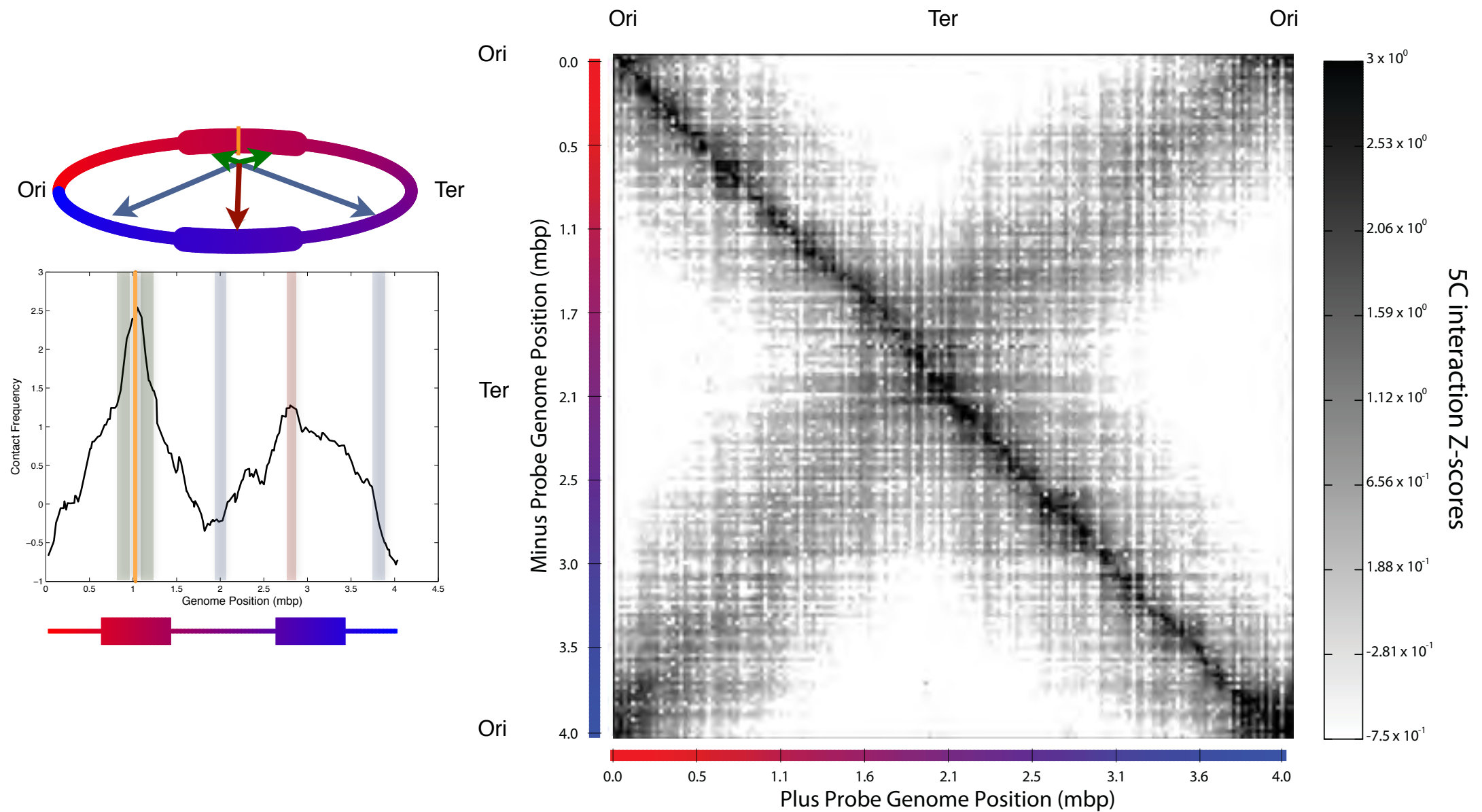
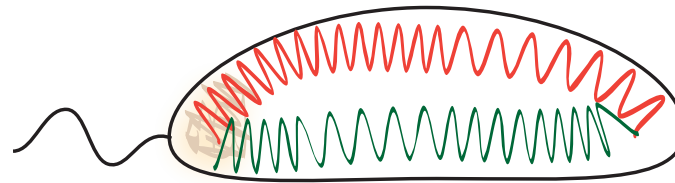


169 5C primers on + strand
170 5C primers on - strand
28,730 chromatin interactions

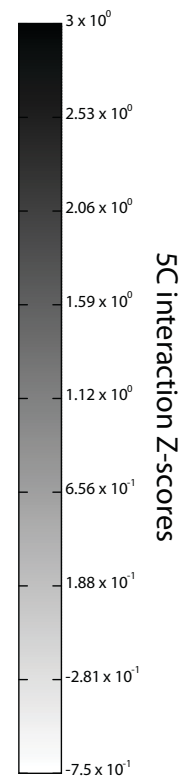
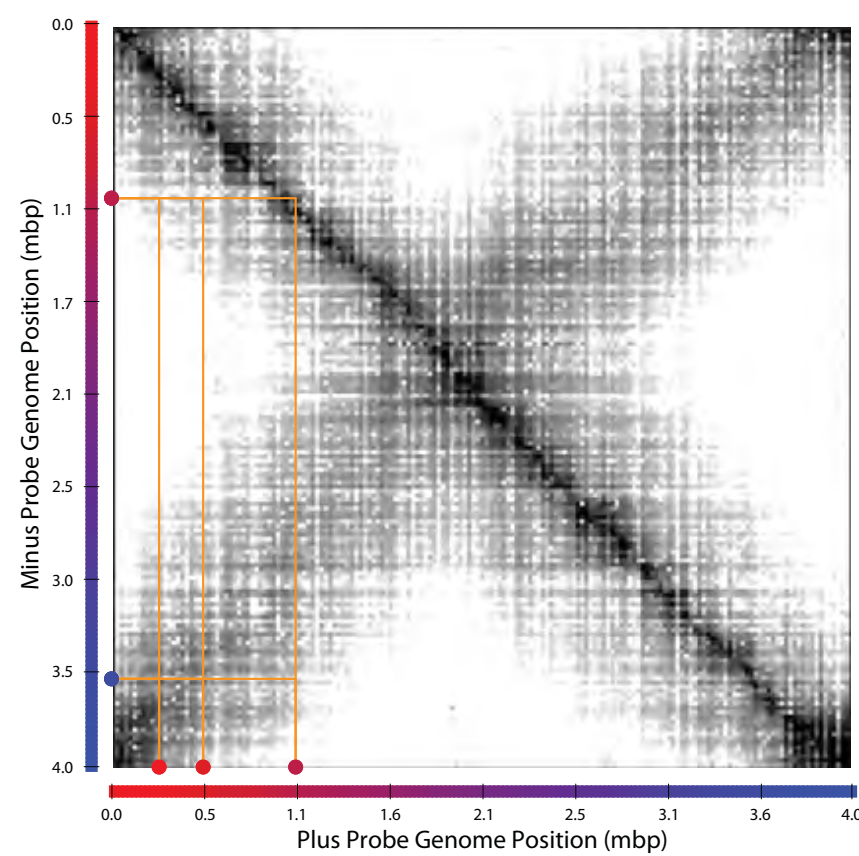
~13Kb

5C interaction matrix

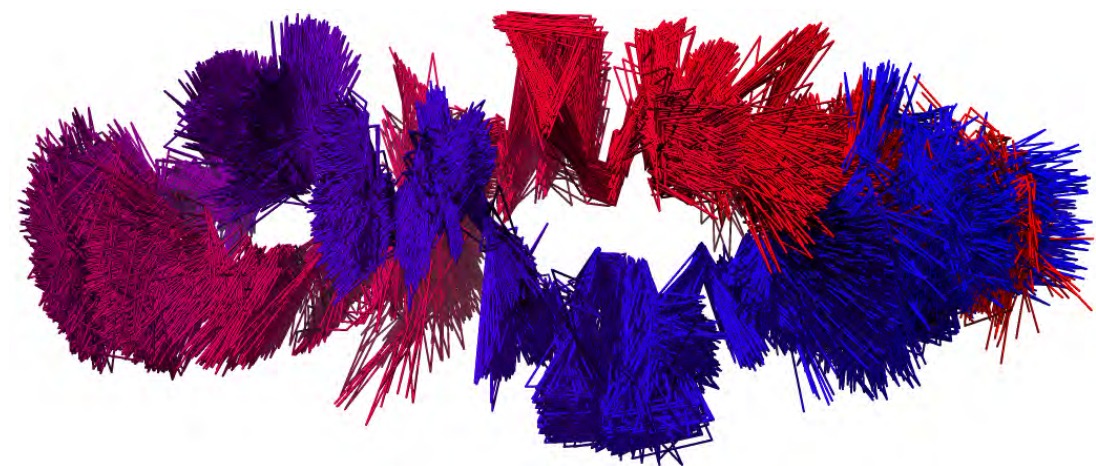
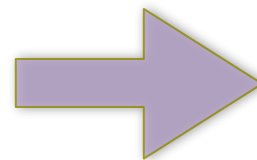
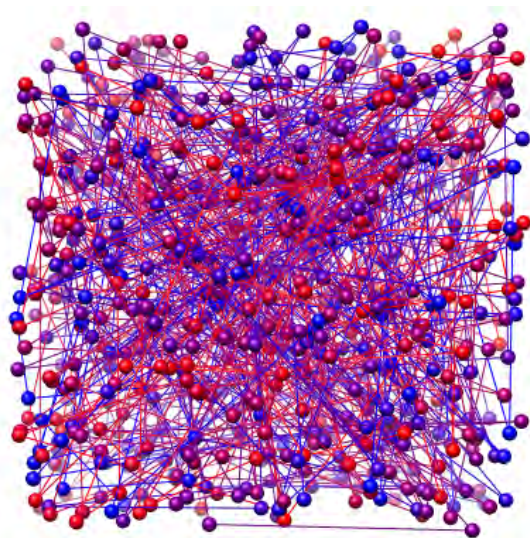
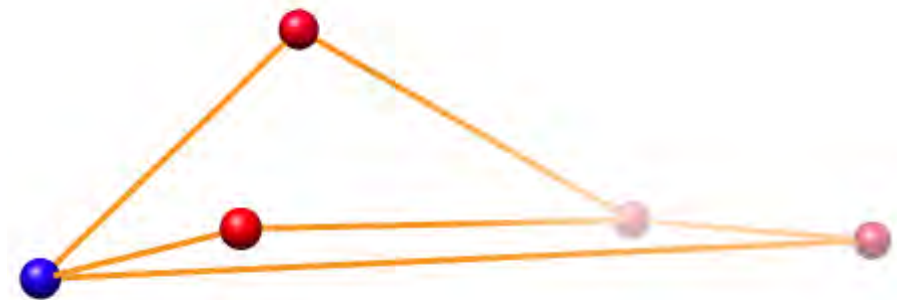
ELLIPSOID for *Caulobacter crescentus*



3D model building with the 5C + IMP approach



339 mers



Genome organization in *Caulobacter crescentus*

Arms are helical

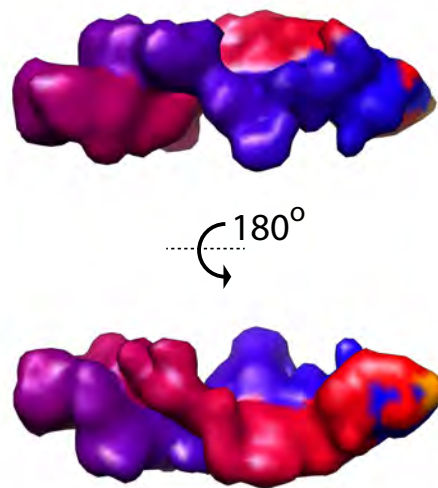
Resolution

dif site 47 ± 17 Kb from Ter

Centromer-like

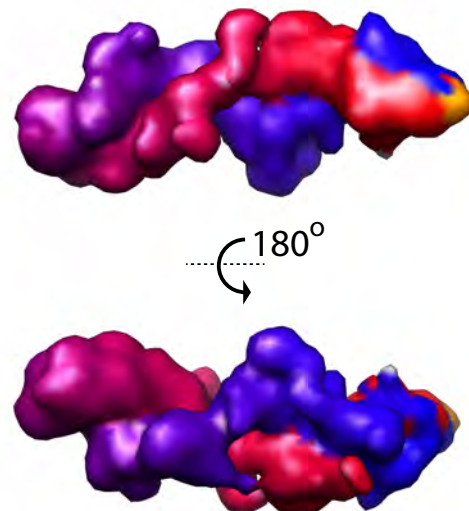
parS sites 25 ± 17 Kb from Ori

Cluster 1



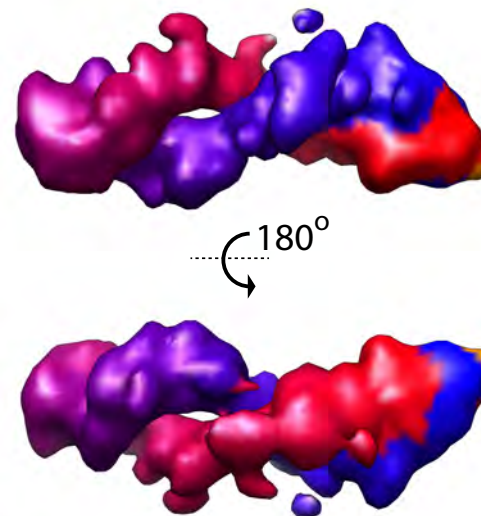
500 nm

Cluster 2



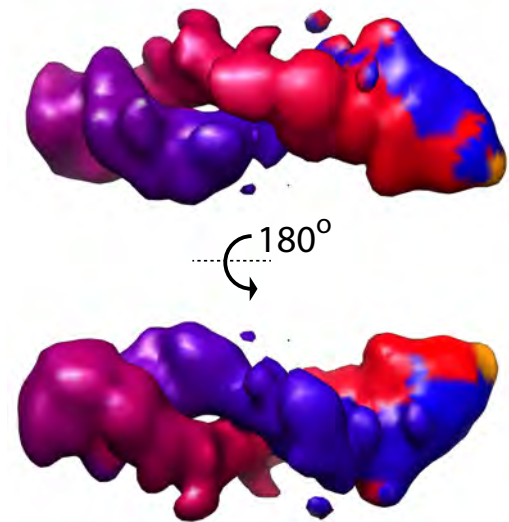
500 nm

Cluster 3



500 nm

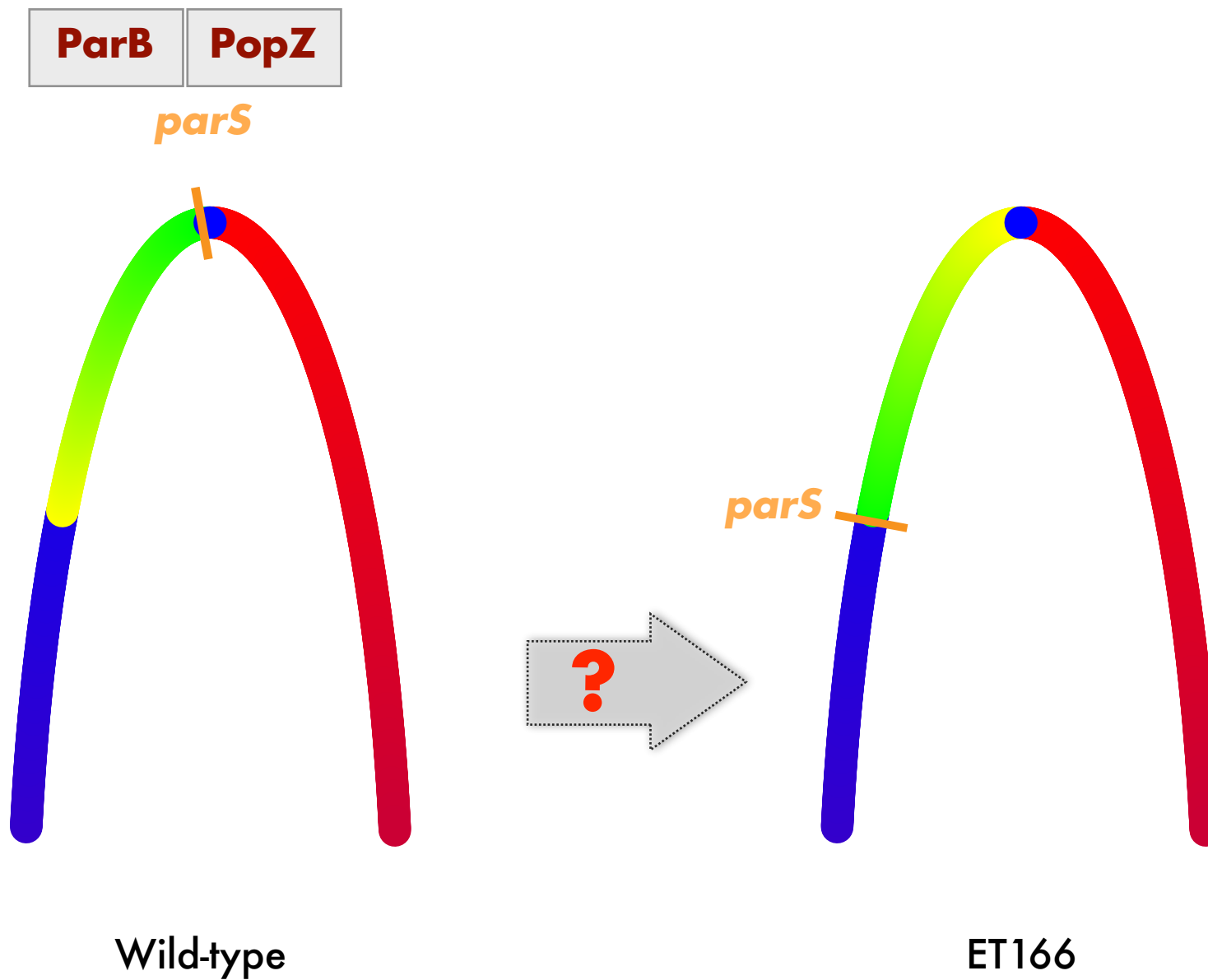
Cluster 4



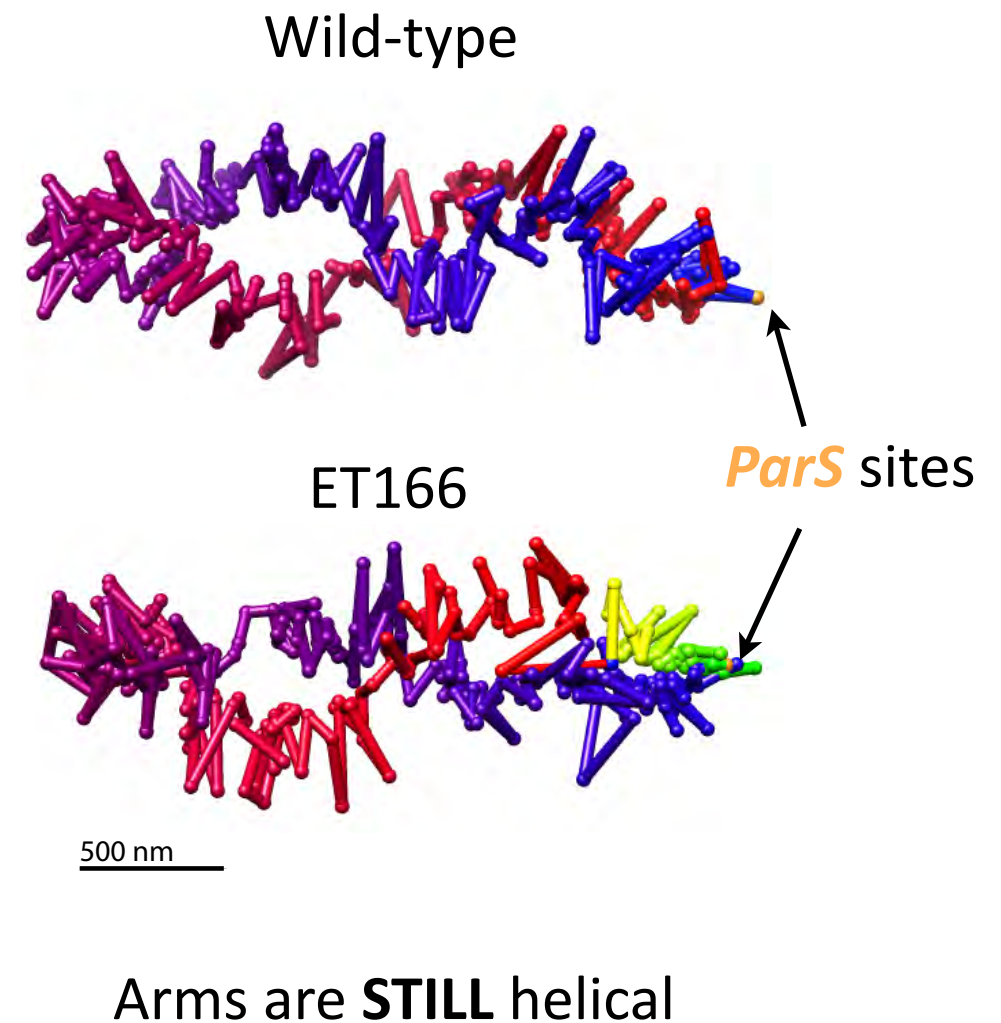
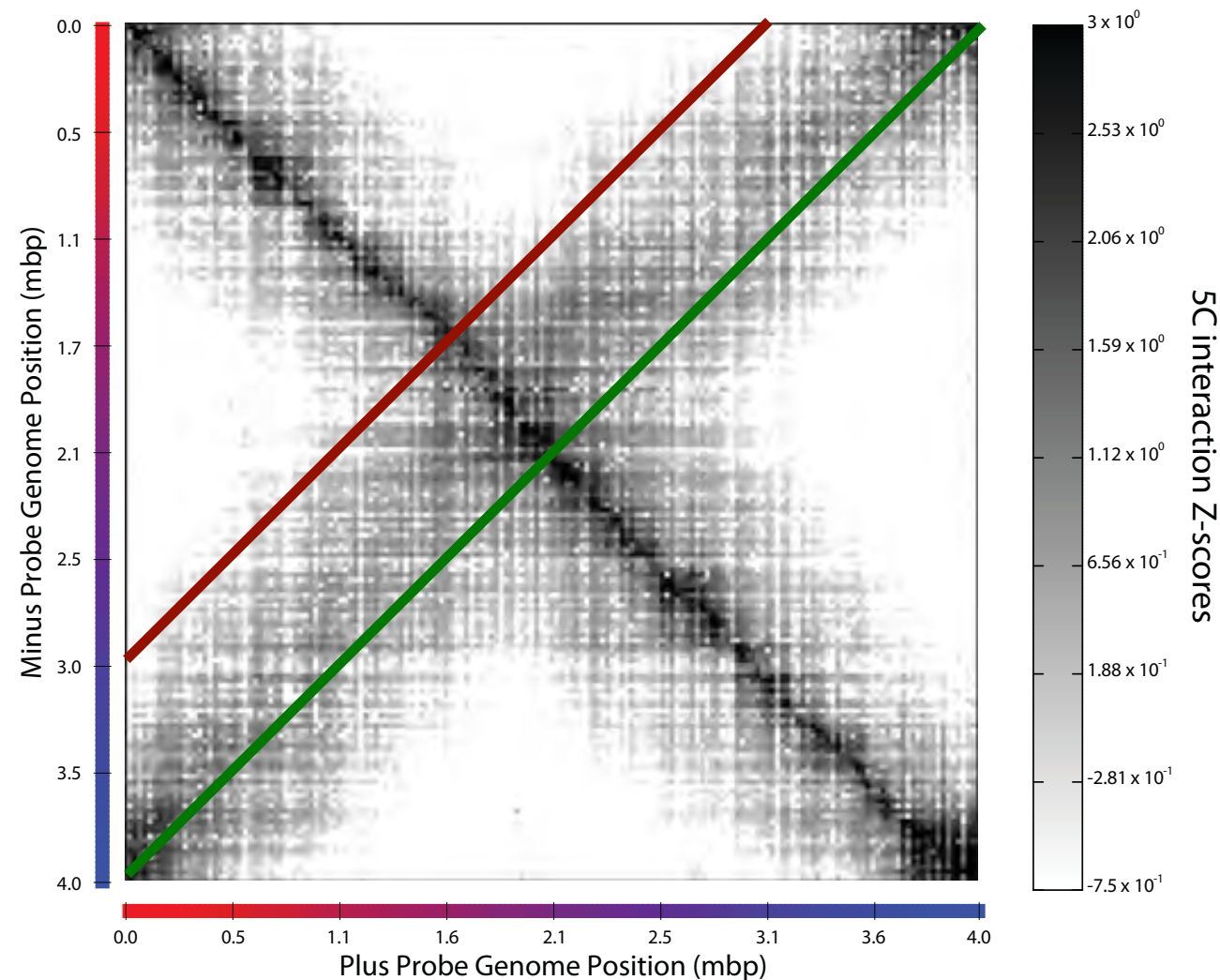
500 nm

MIRRORS!

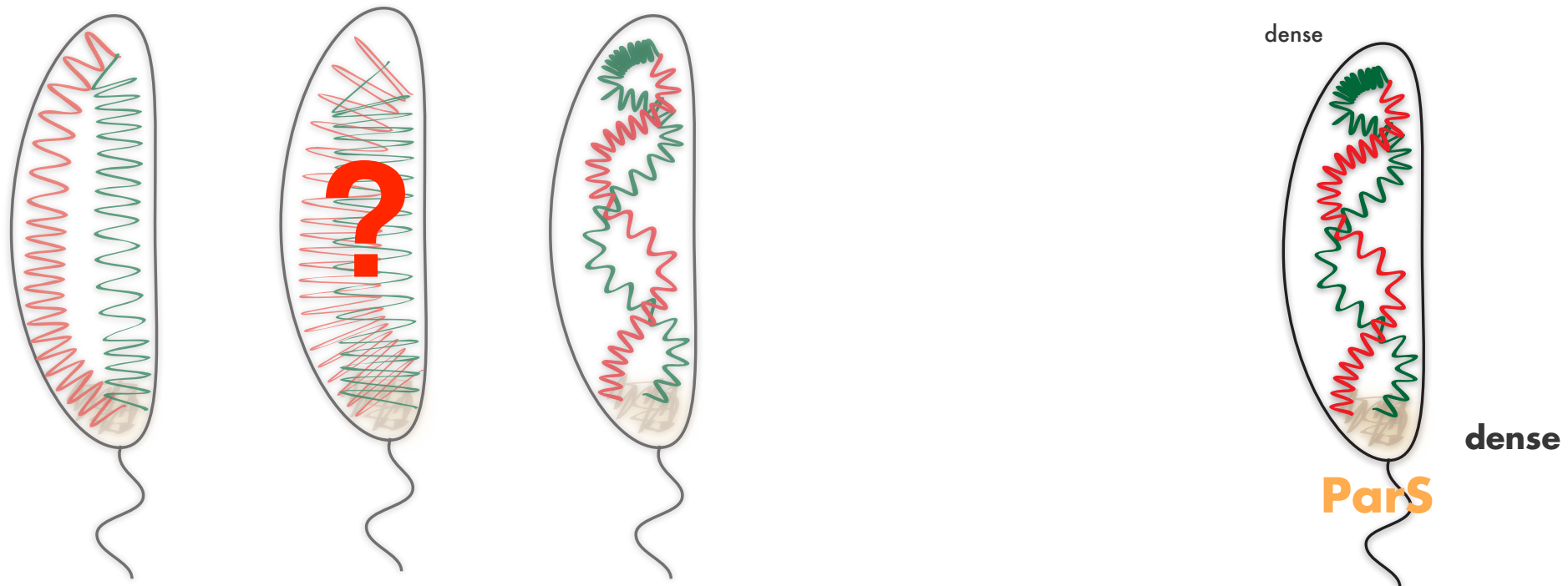
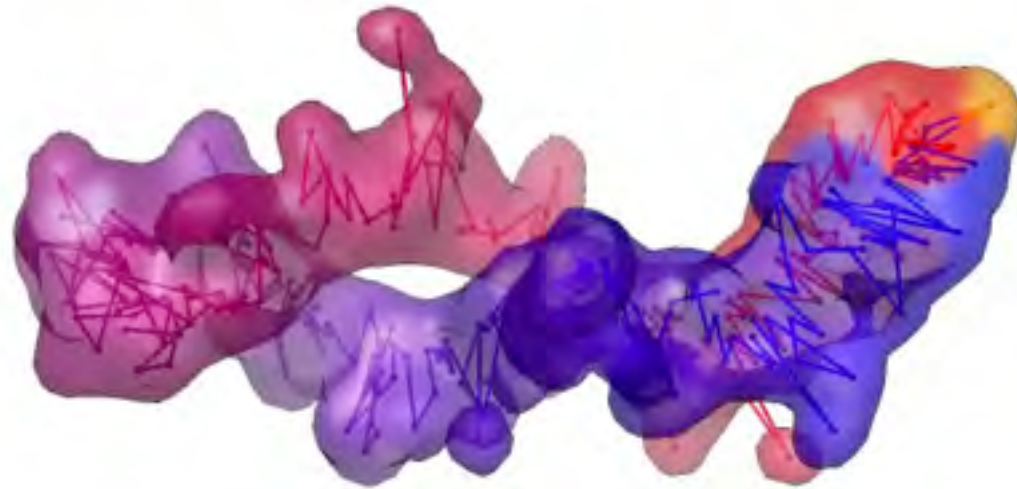
Moving the **parS** sites 400 Kb away from Ori



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



Genome architecture in *Caulobacter*

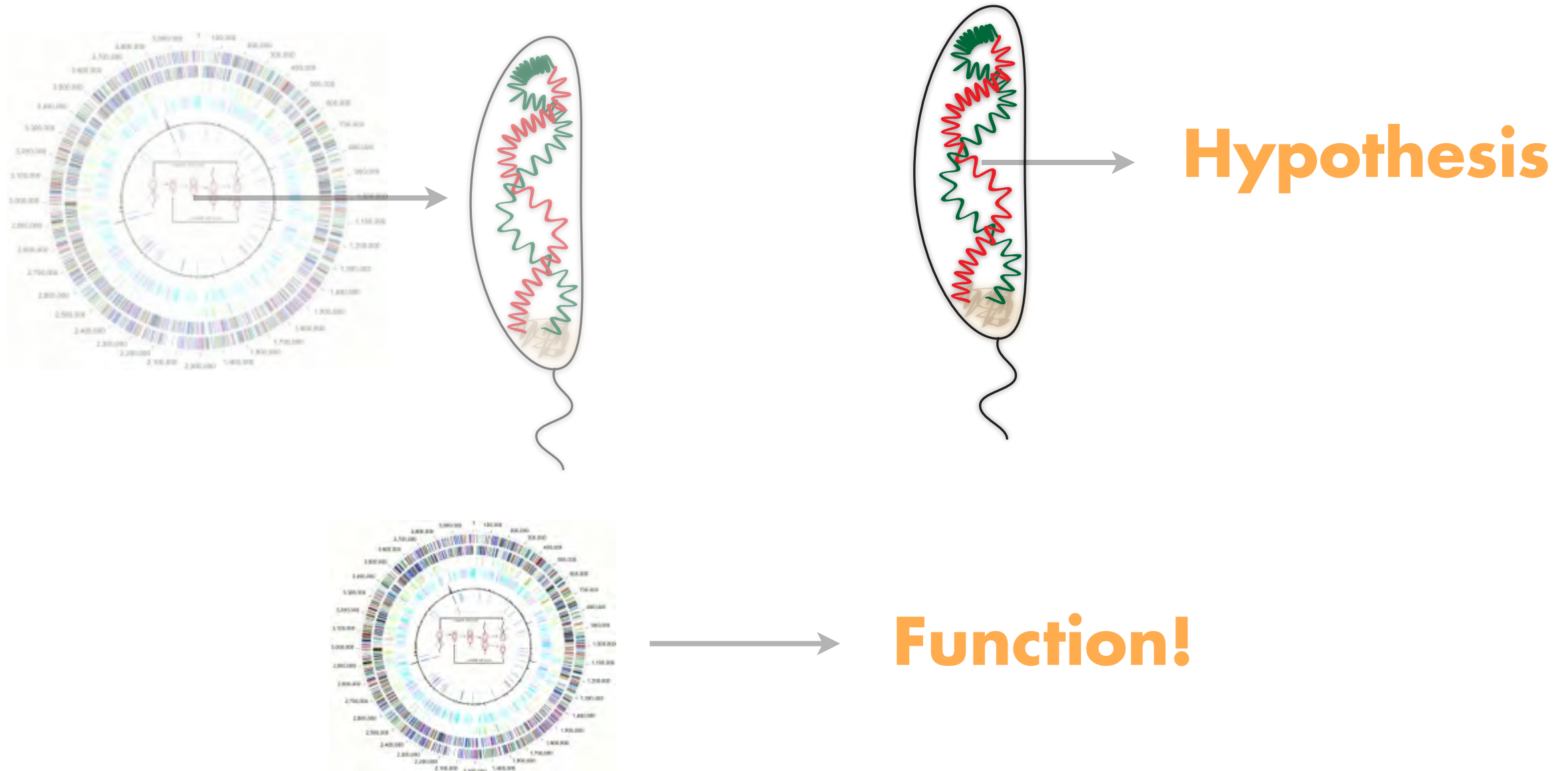


M.A. Umbarger, et al. *Molecular Cell* (2011) 44:252–264

From Sequence to Function

5C + IMP

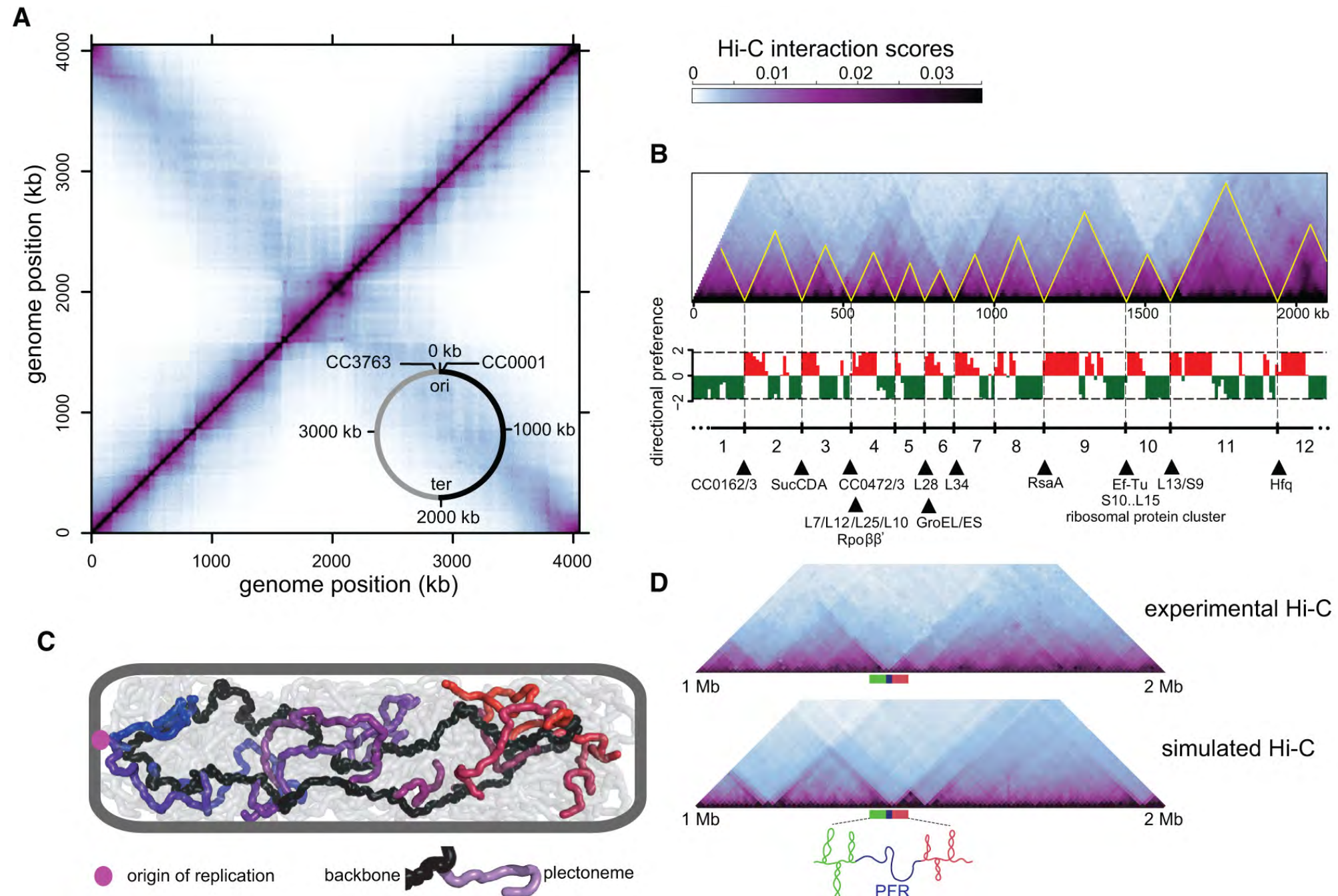
Technology



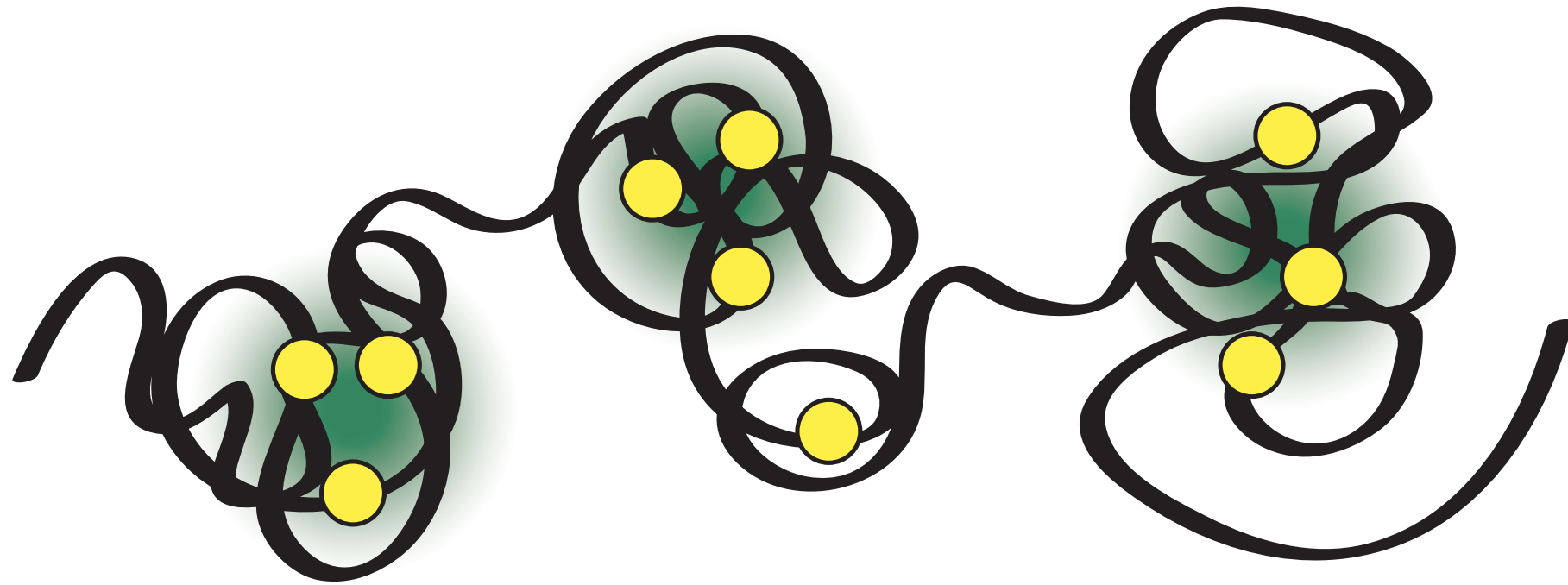
D. Baù and M.A. Marti-Renom Chromosome Res (2011) 19:25-35.

Bacteria has also TADs (CIDs)

Le, T. B. K., Imakaev, M. V., Mirny, L. A., & Laub, M. T. (2013). High-Resolution Mapping of the Spatial Organization of a Bacterial Chromosome. *Science* (New York, NY), 1242059



On TADs and hormones

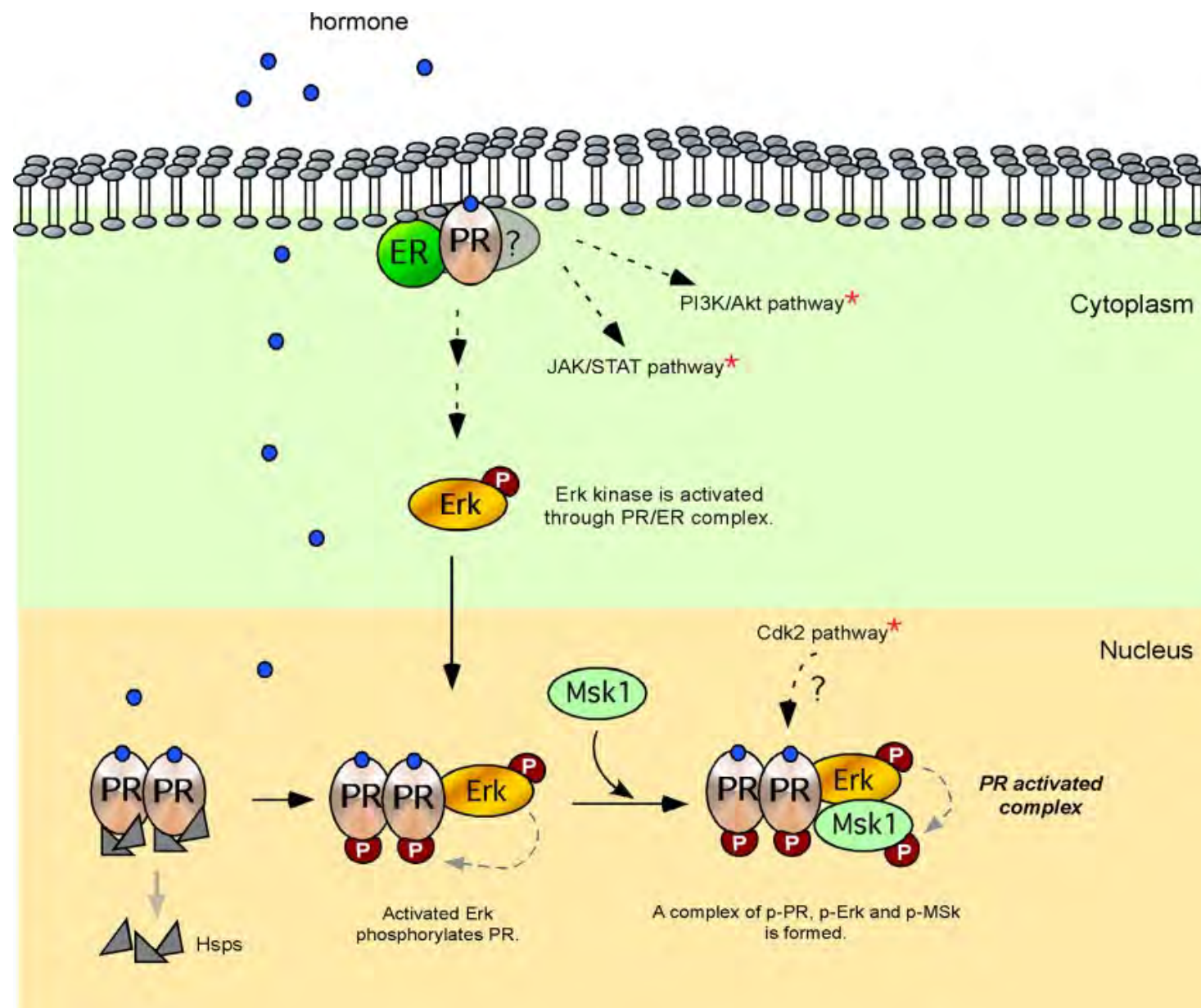


Davide Baù



François le Dily

Progesterone-regulated transcription in breast cancer

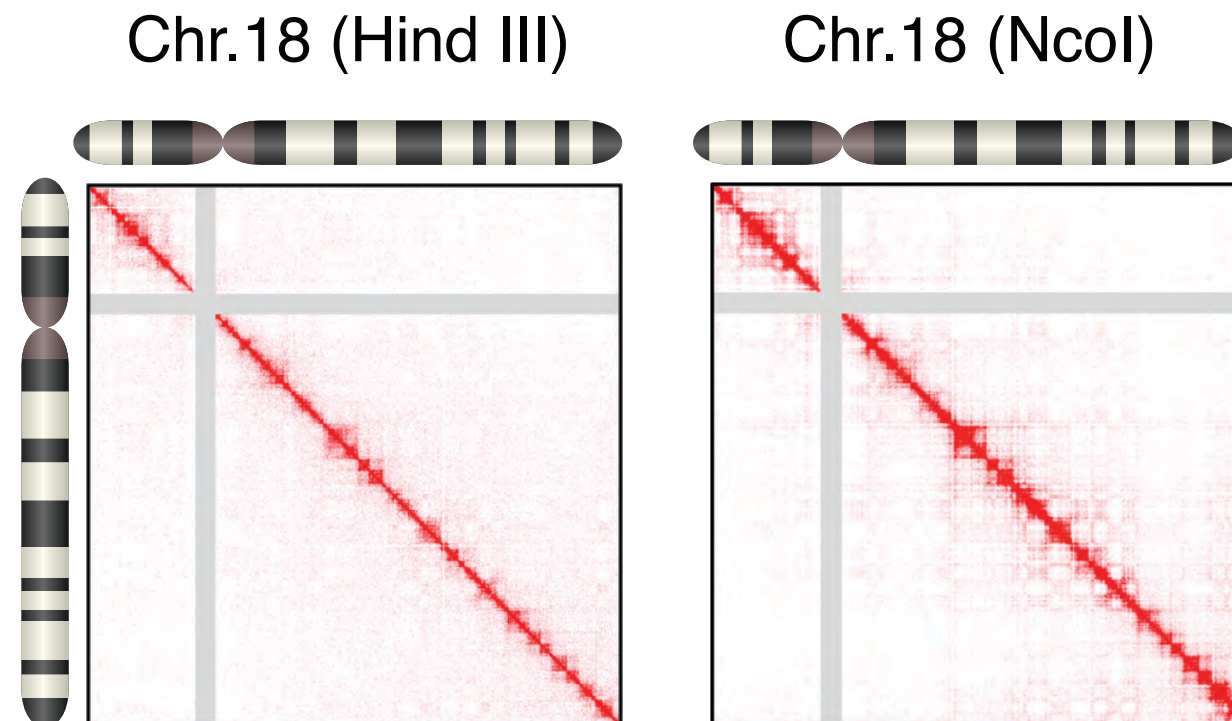
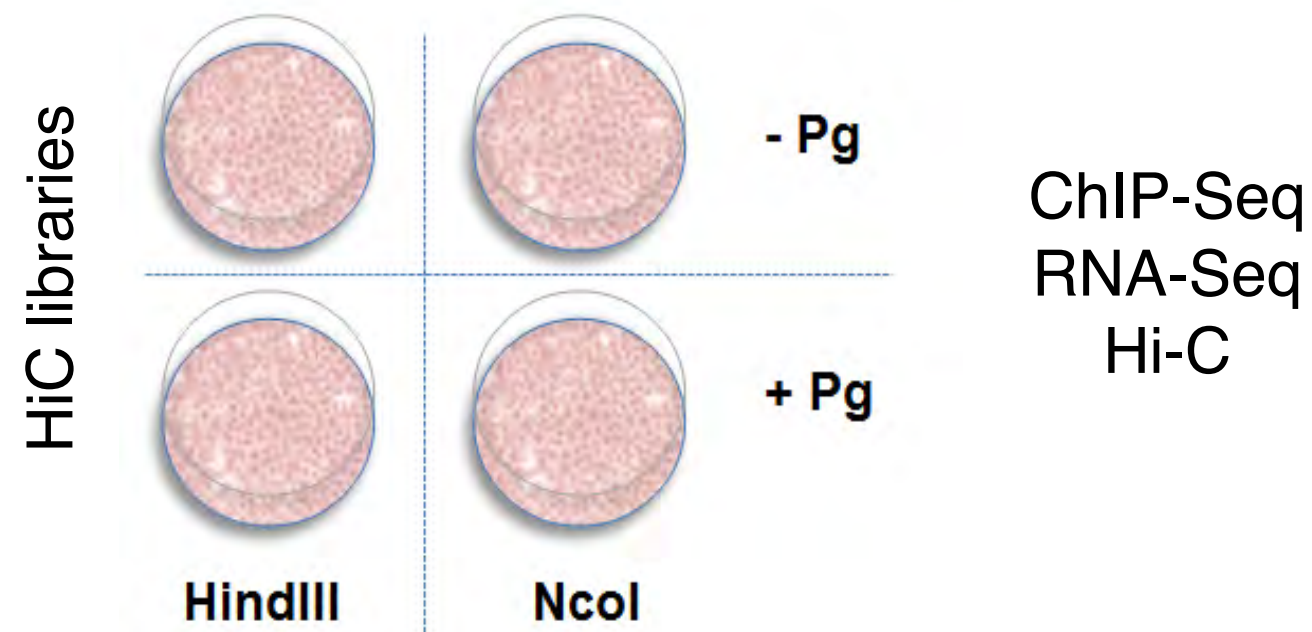


> 2,000 genes **Up**-regulated
> 2,000 genes **Down**-regulated

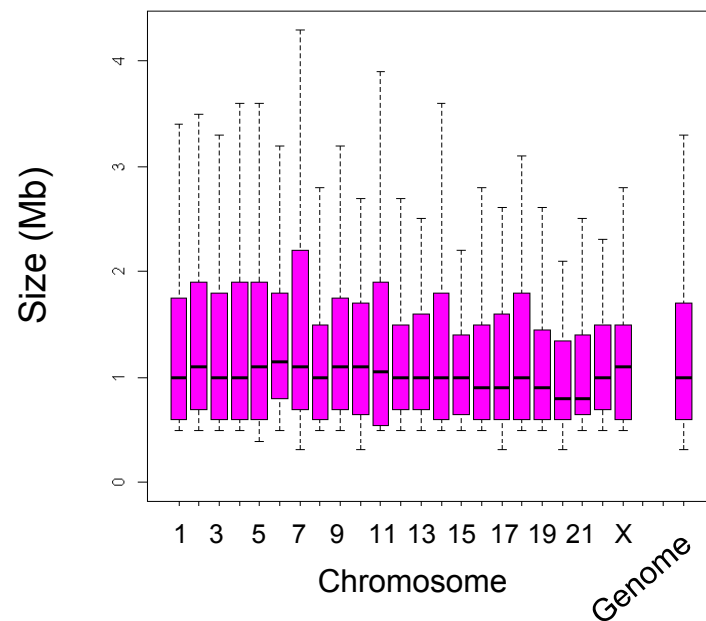
Regulation in 3D?

Vicent *et al* 2011, Wright *et al* 2012, Ballare *et al* 2012

Experimental design



Are there TADs? how robust?

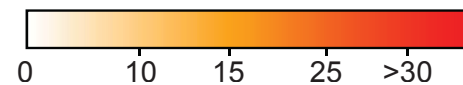
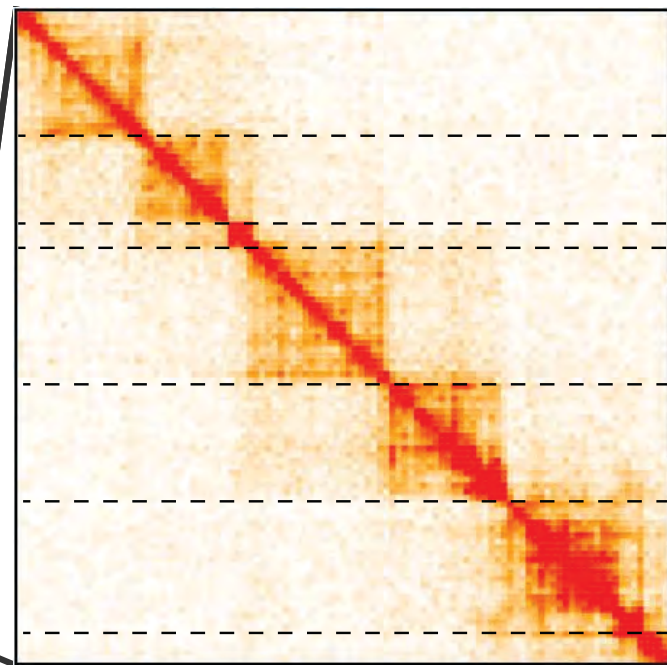


>2,000 detected TADs

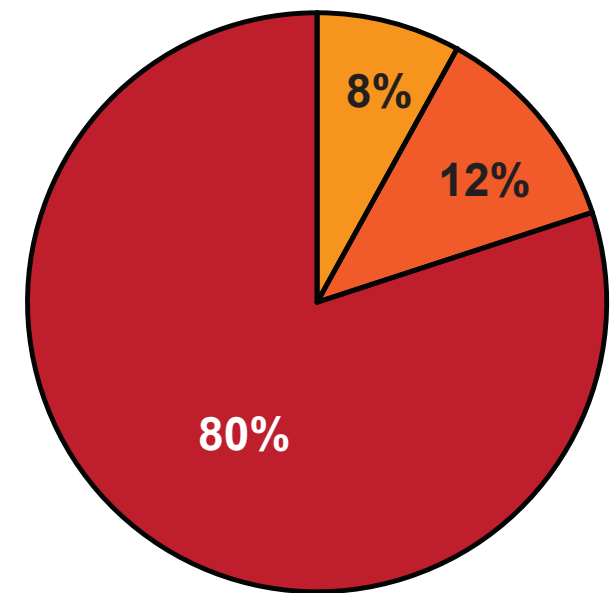
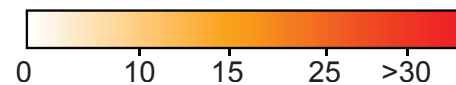
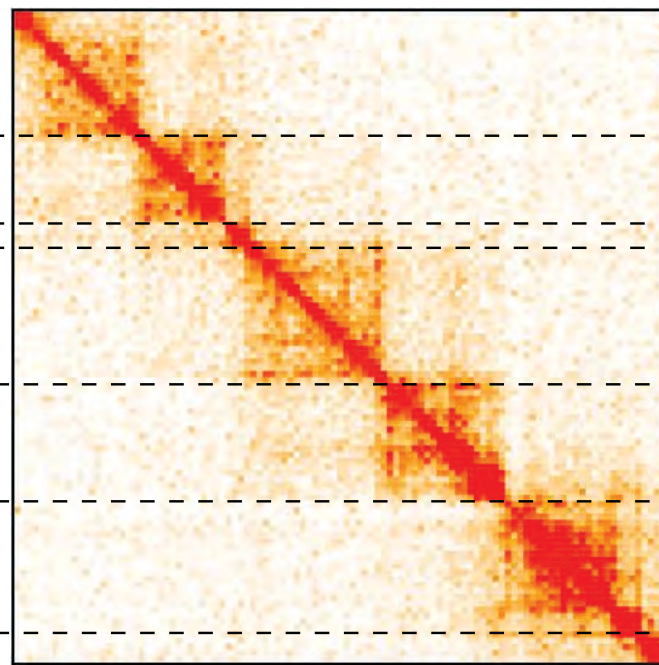
Chr.18



-Pg

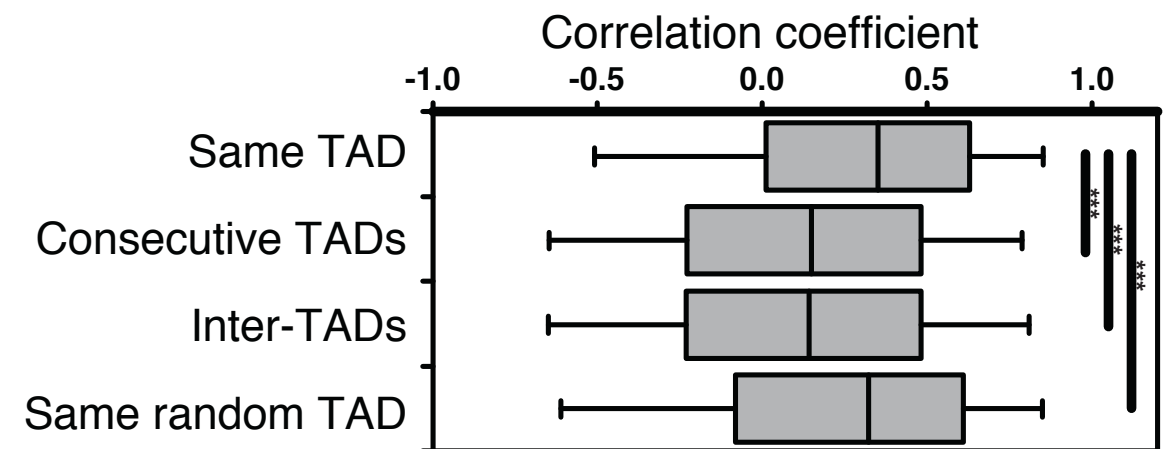
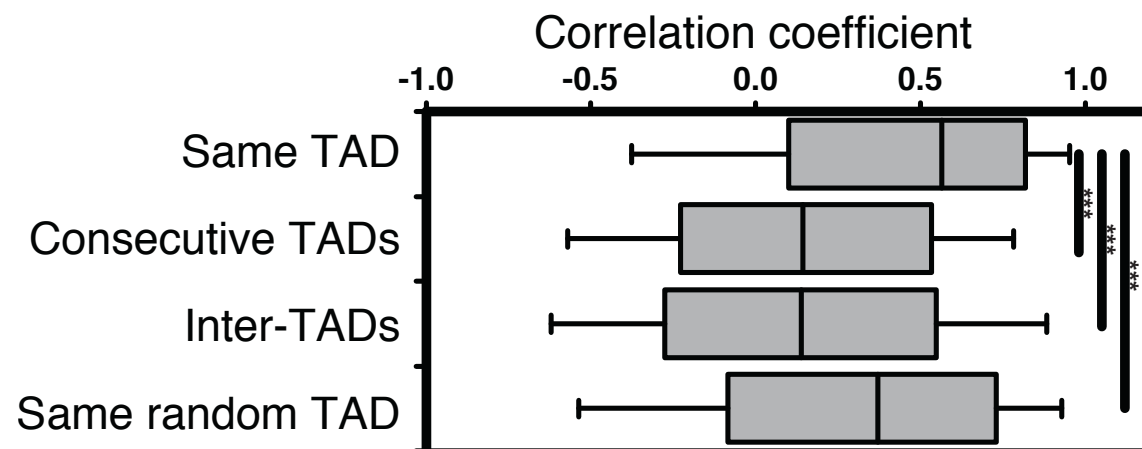
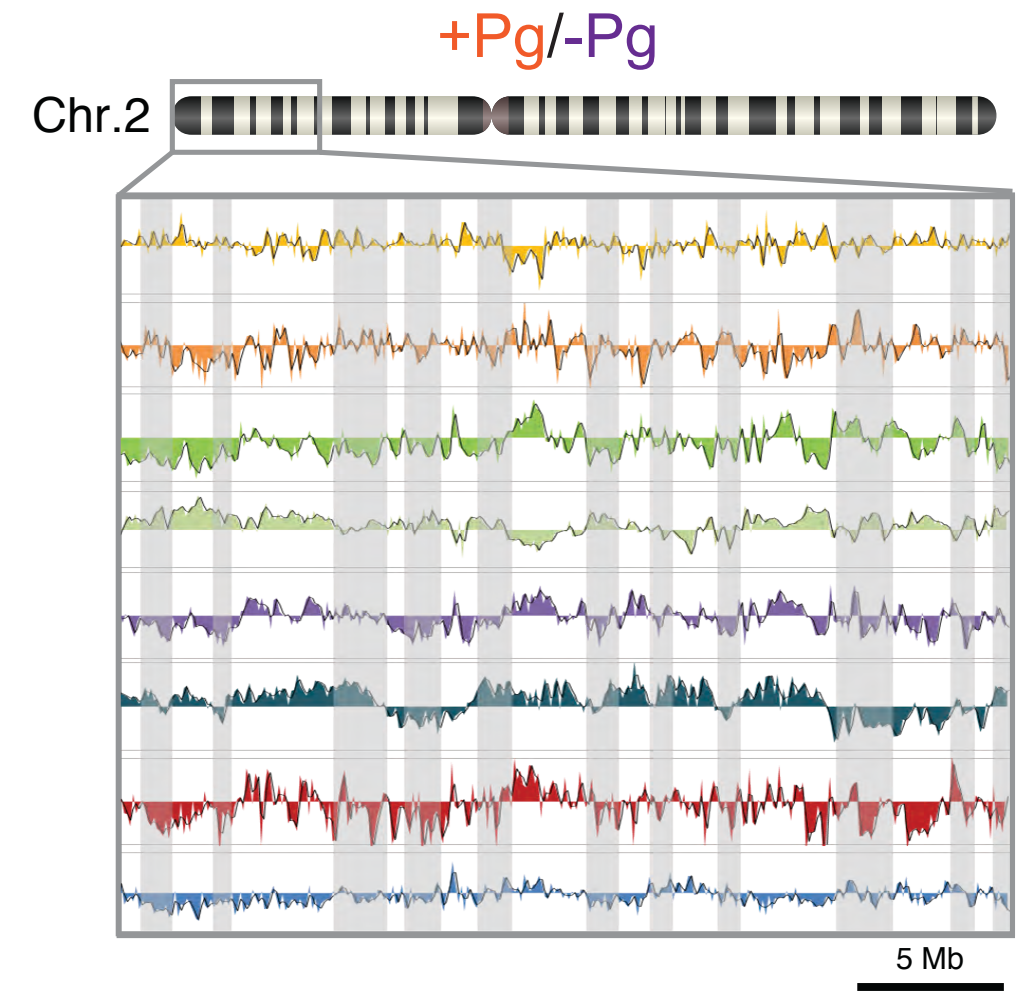
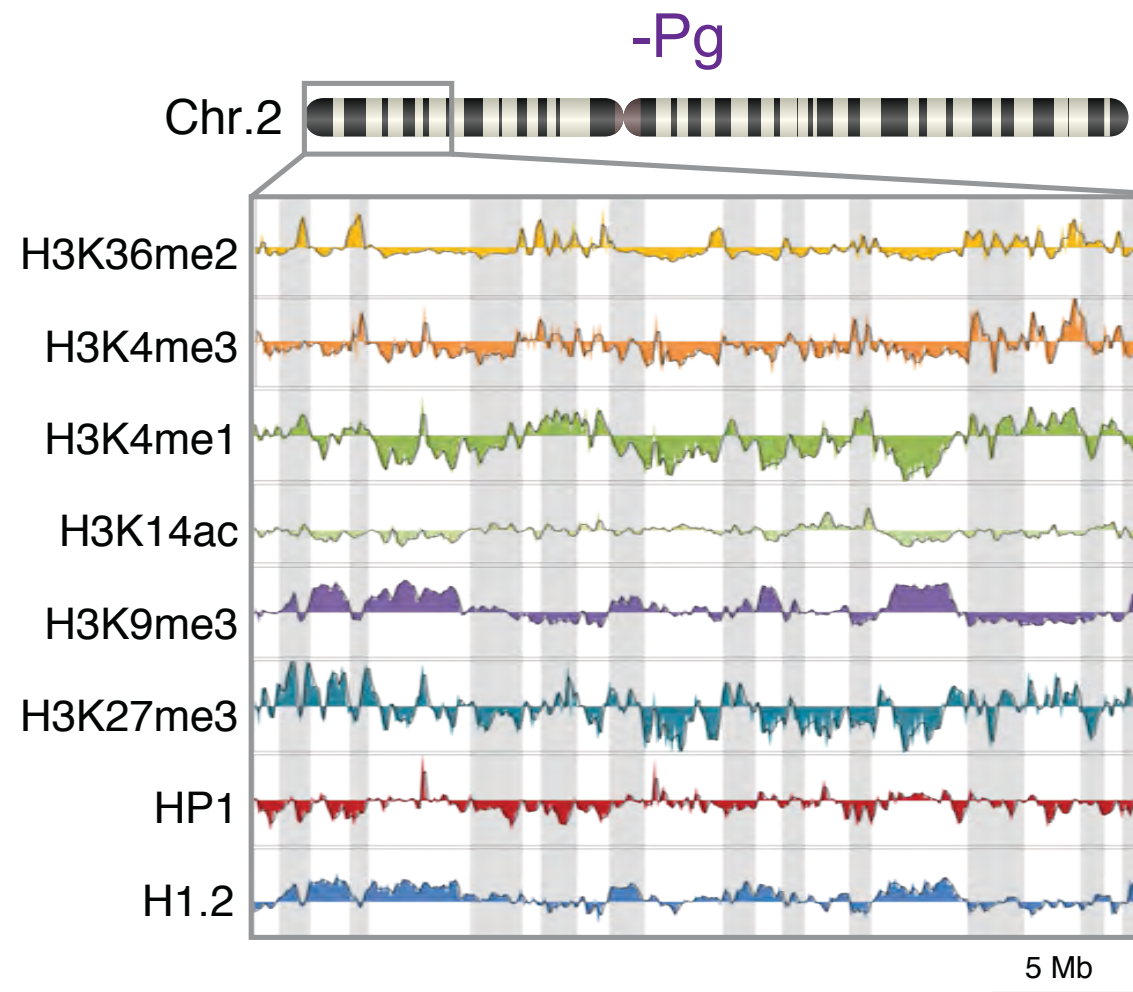


+Pg

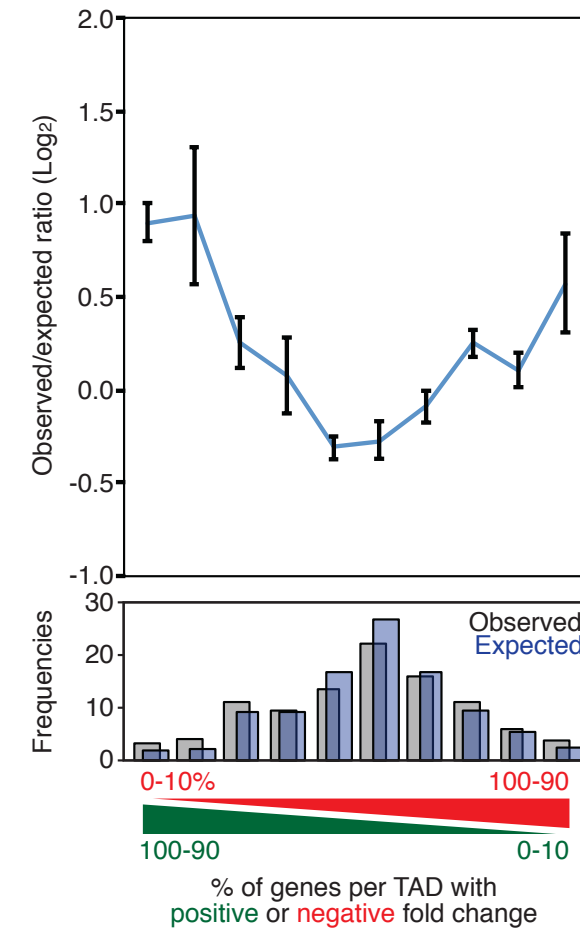
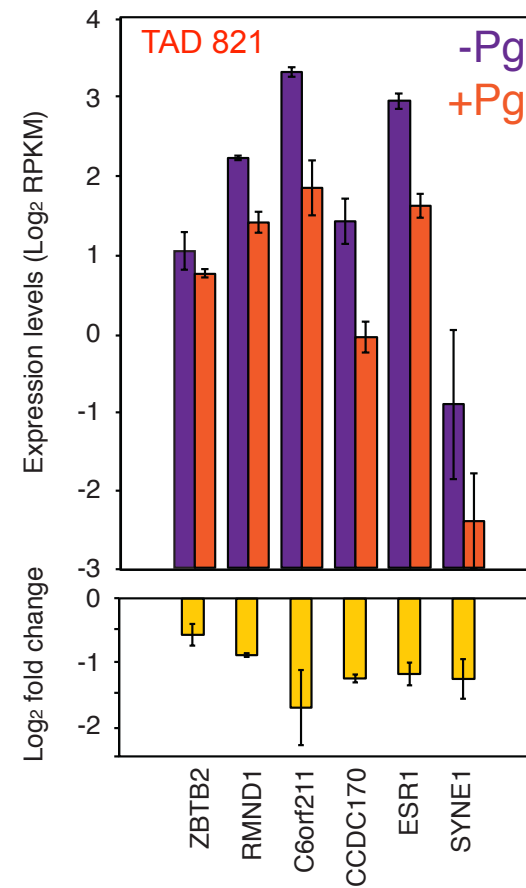
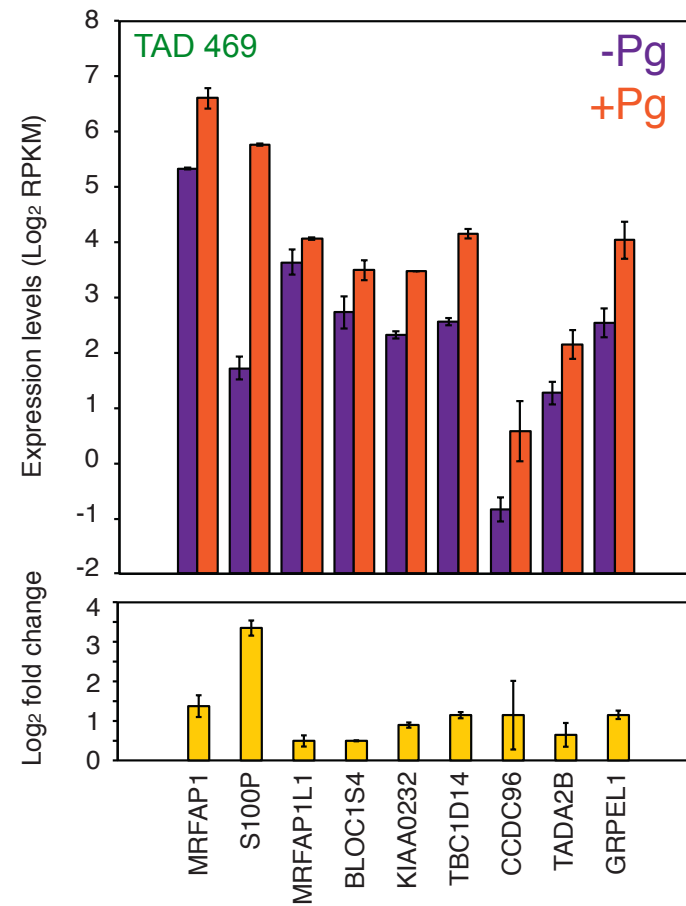


conserved
100 kb
±200 kb or more

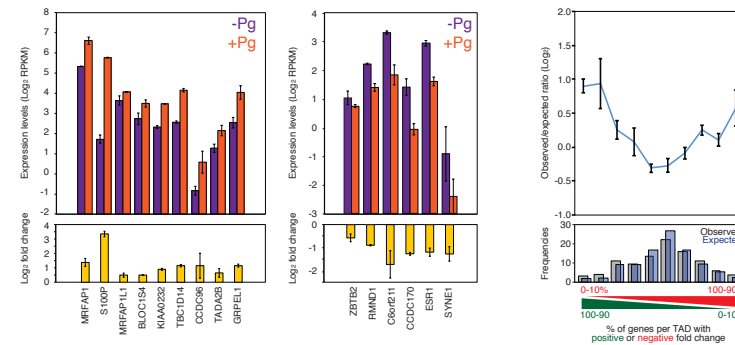
Are TADs homogeneous?



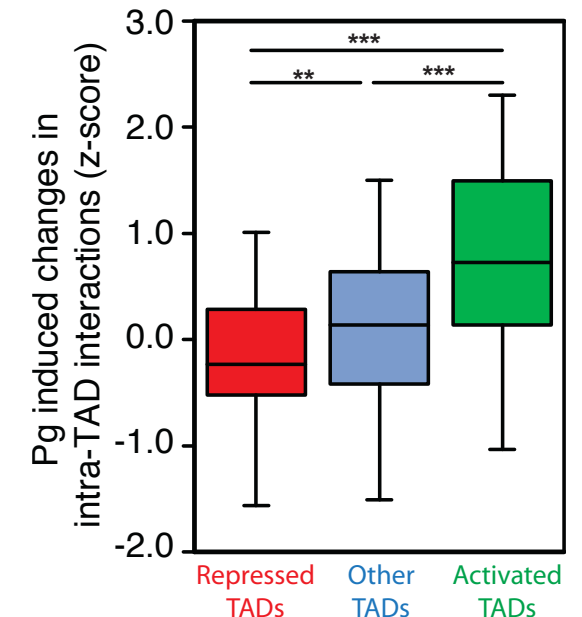
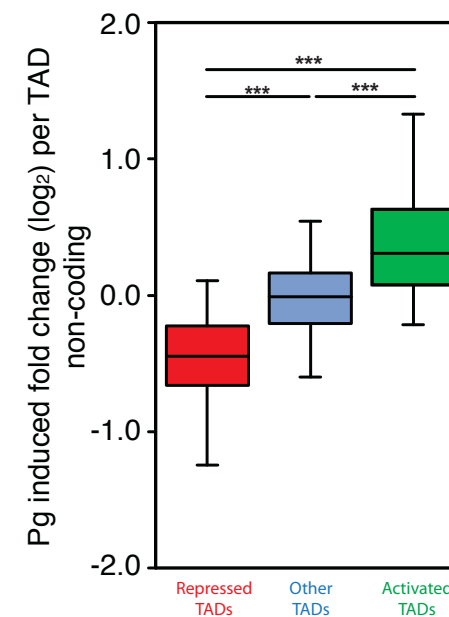
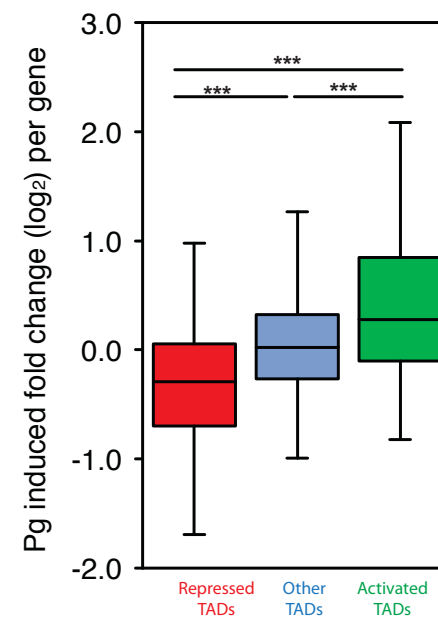
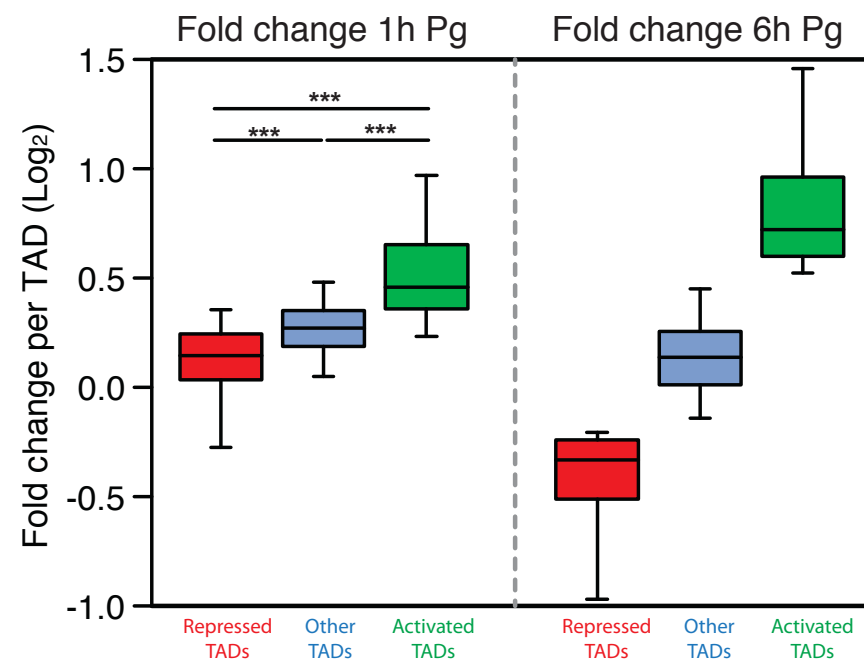
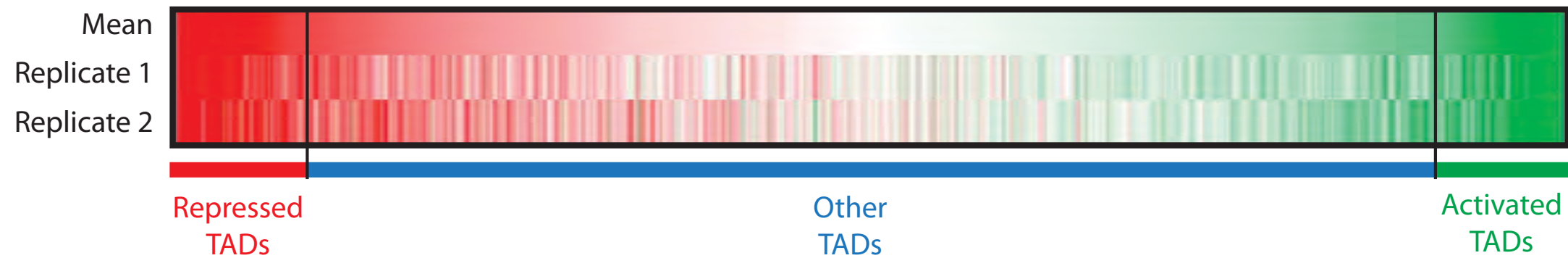
Do TADs respond differently to Pg treatment?



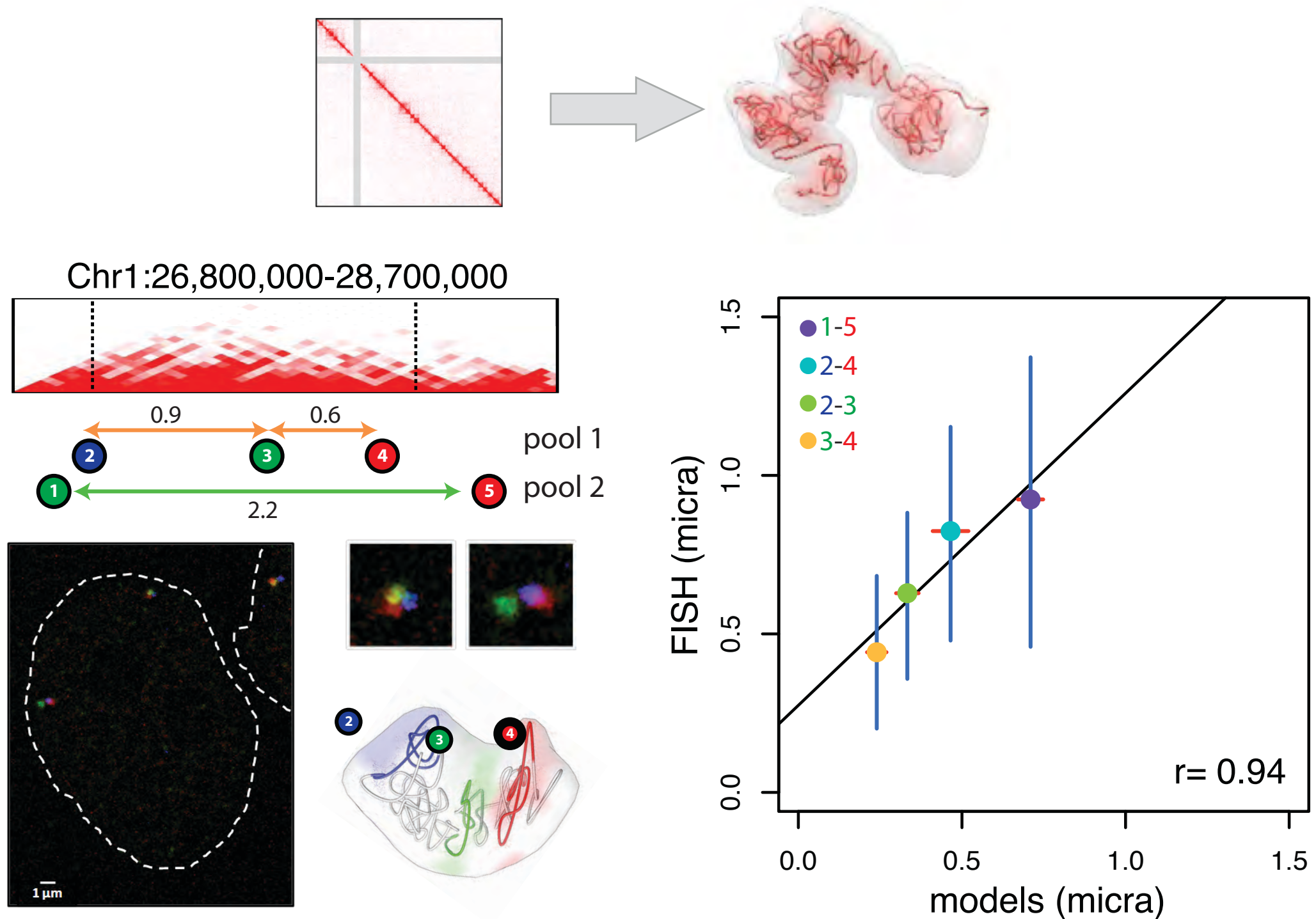
Do TADs respond differently to Pg treatment?



Pg induced fold change per TAD (6h)



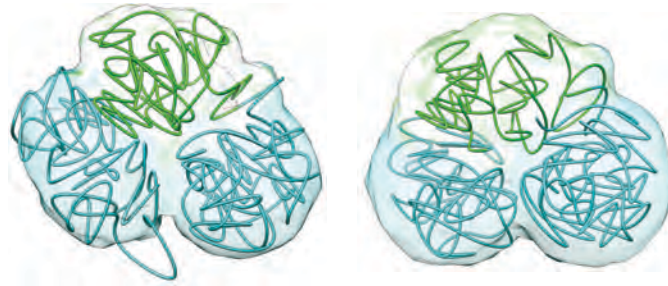
Modeling 3D TADs



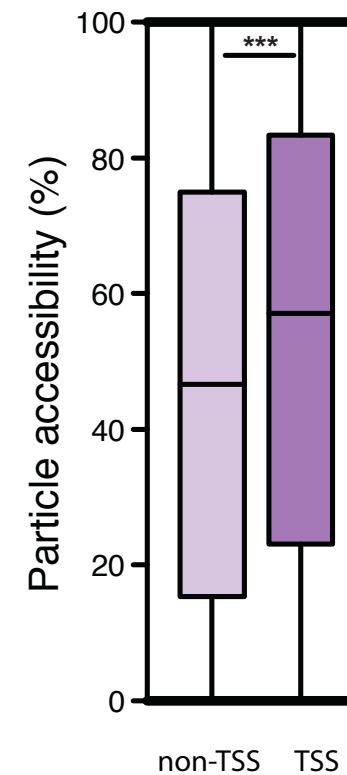
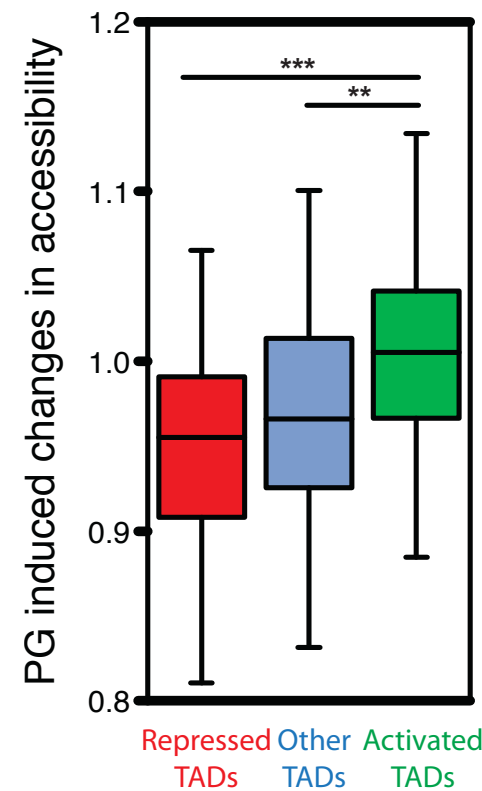
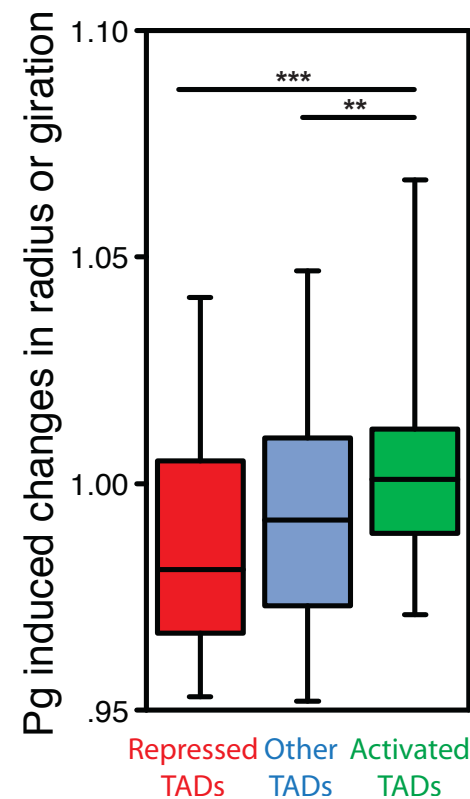
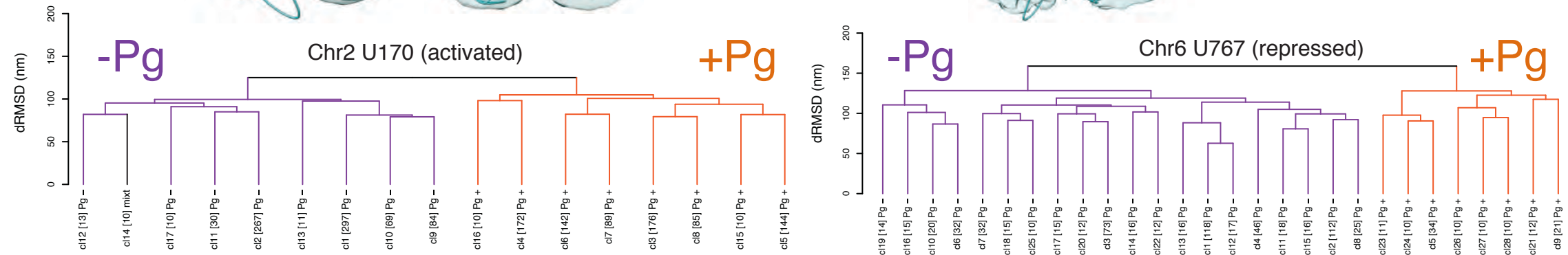
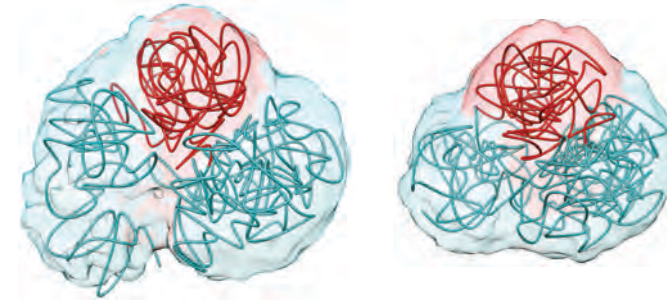
61 genomic regions containing 209 TADs covering 267Mb

How TADs respond structurally to Pg?

Chr2:9,600,000-13,200,000



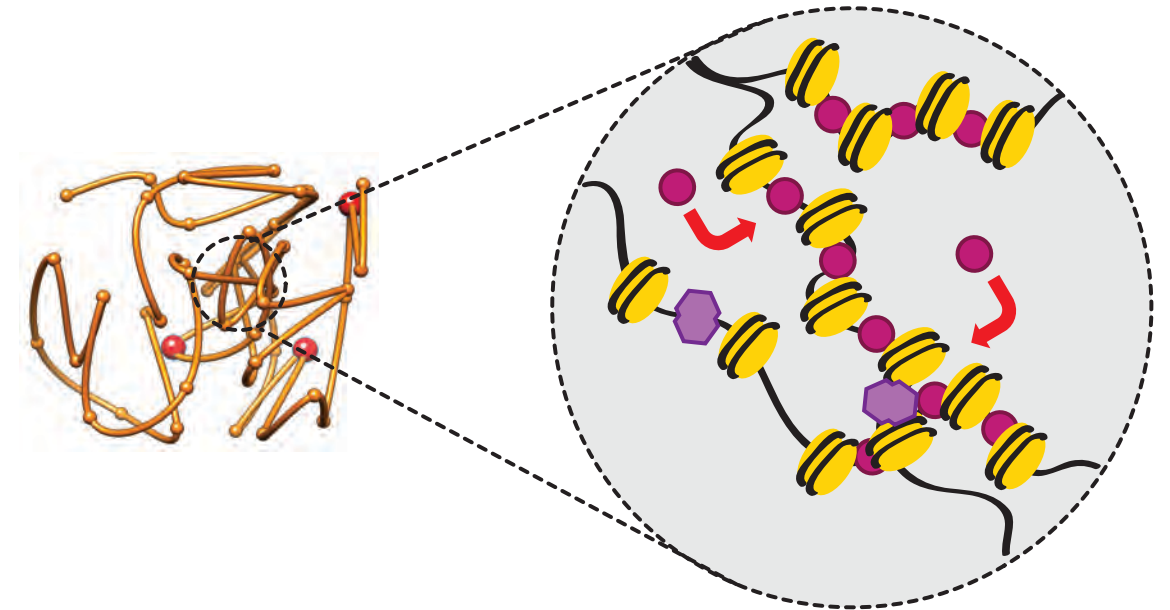
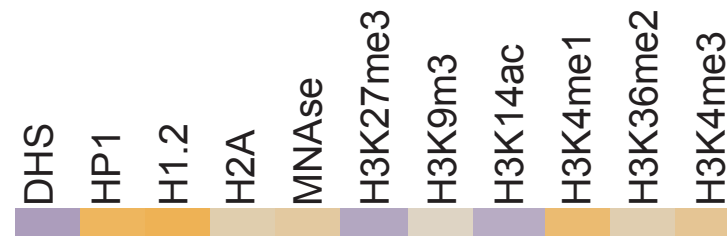
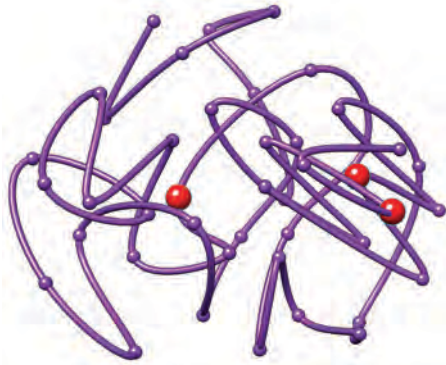
Chr6:71,800,000-76,500,000



Model for TAD regulation

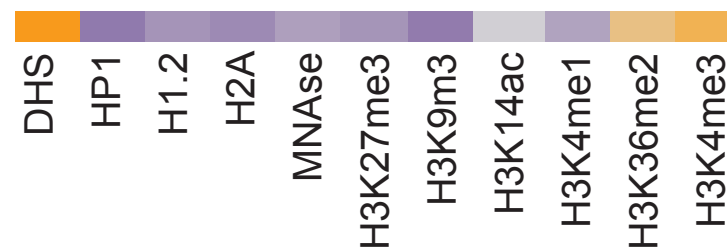
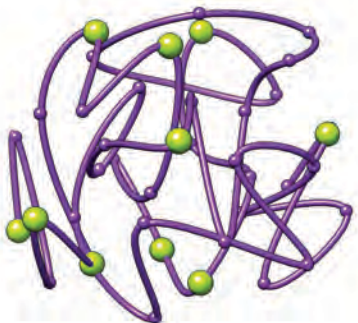
Repressed TAD

chr1 U41

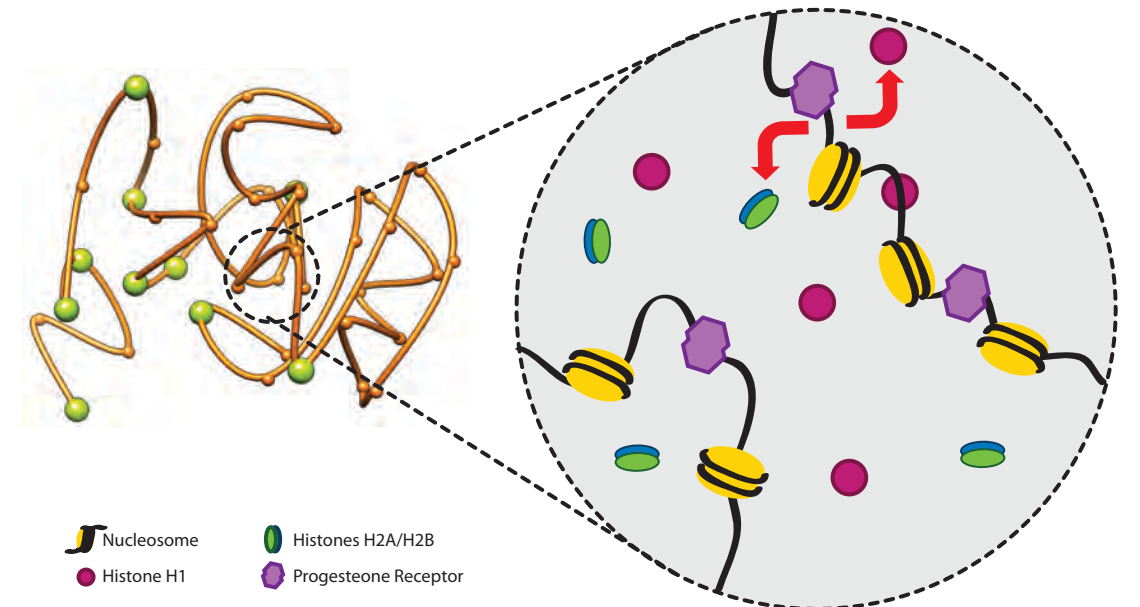


Activated TAD

chr2 U207



Structural transition
+Pg



 Nucleosome
 Histone H1
 Histones H2A/H2B
 Progesterone Receptor

PLoS CB Outlook

Marti-Renom MA, Mirny LA (2011) PLoS Comput Biol 7(7): e1002125.

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PLOS COMPUTATIONAL BIOLOGY

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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Editor: Philip E. Bourne, University of California San Diego, United States of America

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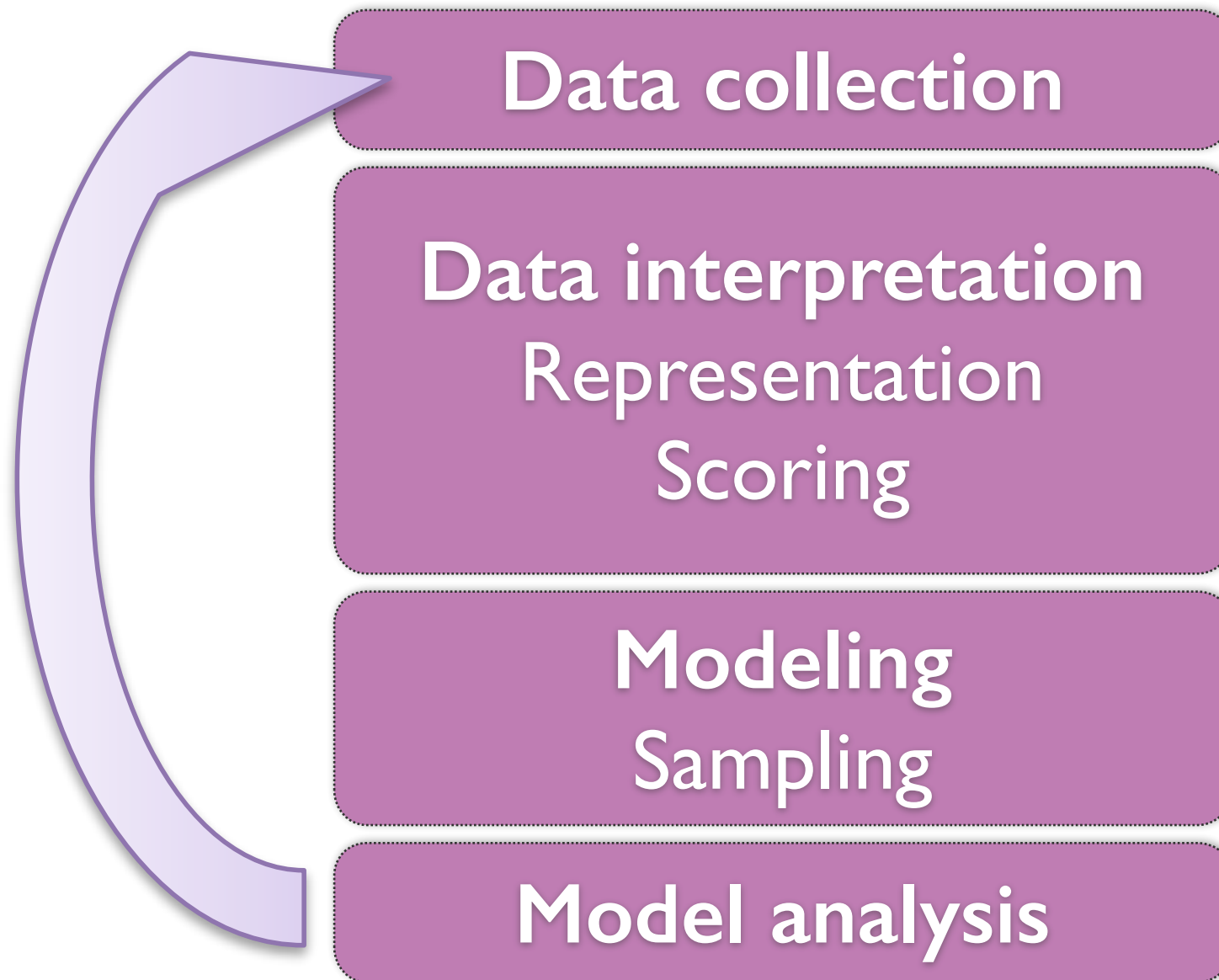
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MURRE
Cell (2008) 133:265-79

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

David Doolittle¹, Robert L. Jorgensen², David M. Jorgensen³, David M. Jorgensen⁴, David M. Jorgensen⁵, David M. Jorgensen⁶, David M. Jorgensen⁷, David M. Jorgensen⁸, David M. Jorgensen⁹, David M. Jorgensen¹⁰, David M. Jorgensen¹¹, David M. Jorgensen¹², David M. Jorgensen¹³, David M. Jorgensen¹⁴, David M. Jorgensen¹⁵, David M. Jorgensen¹⁶, David M. Jorgensen¹⁷, David M. Jorgensen¹⁸, David M. Jorgensen¹⁹, David M. Jorgensen²⁰, David M. Jorgensen²¹, David M. Jorgensen²², David M. Jorgensen²³, David M. Jorgensen²⁴, David M. Jorgensen²⁵, David M. Jorgensen²⁶, David M. Jorgensen²⁷, David M. Jorgensen²⁸, David M. Jorgensen²⁹, David M. Jorgensen³⁰, David M. Jorgensen³¹, David M. Jorgensen³², David M. Jorgensen³³, David M. Jorgensen³⁴, David M. Jorgensen³⁵, David M. Jorgensen³⁶, David M. Jorgensen³⁷, David M. Jorgensen³⁸, David M. Jorgensen³⁹, David M. Jorgensen⁴⁰, David M. Jorgensen⁴¹, David M. Jorgensen⁴², David M. Jorgensen⁴³, David M. Jorgensen⁴⁴, David M. Jorgensen⁴⁵, David M. 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