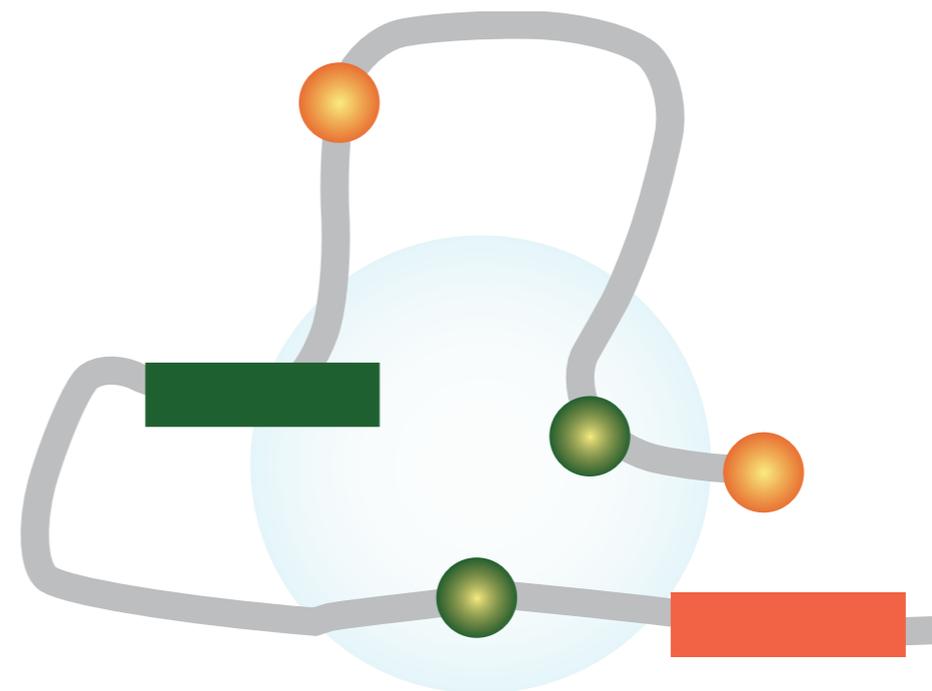
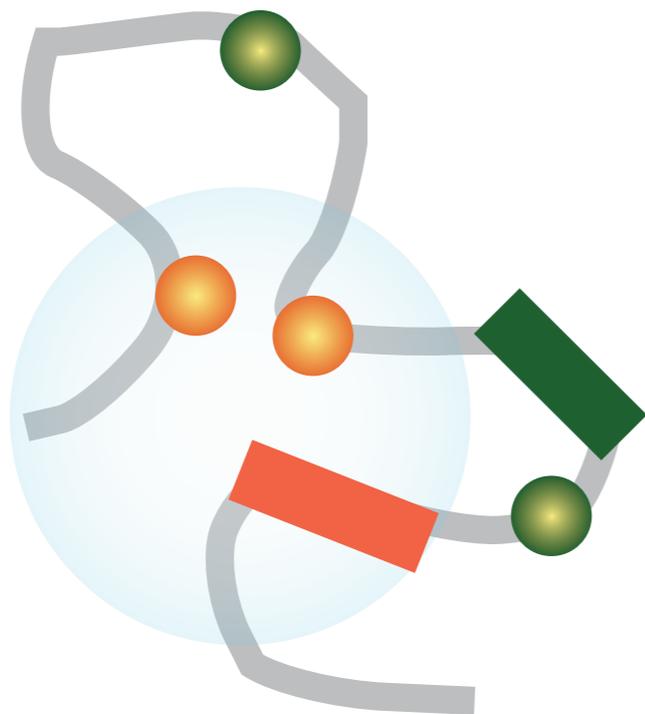


3D genomes

Marc A. Martí-Renom

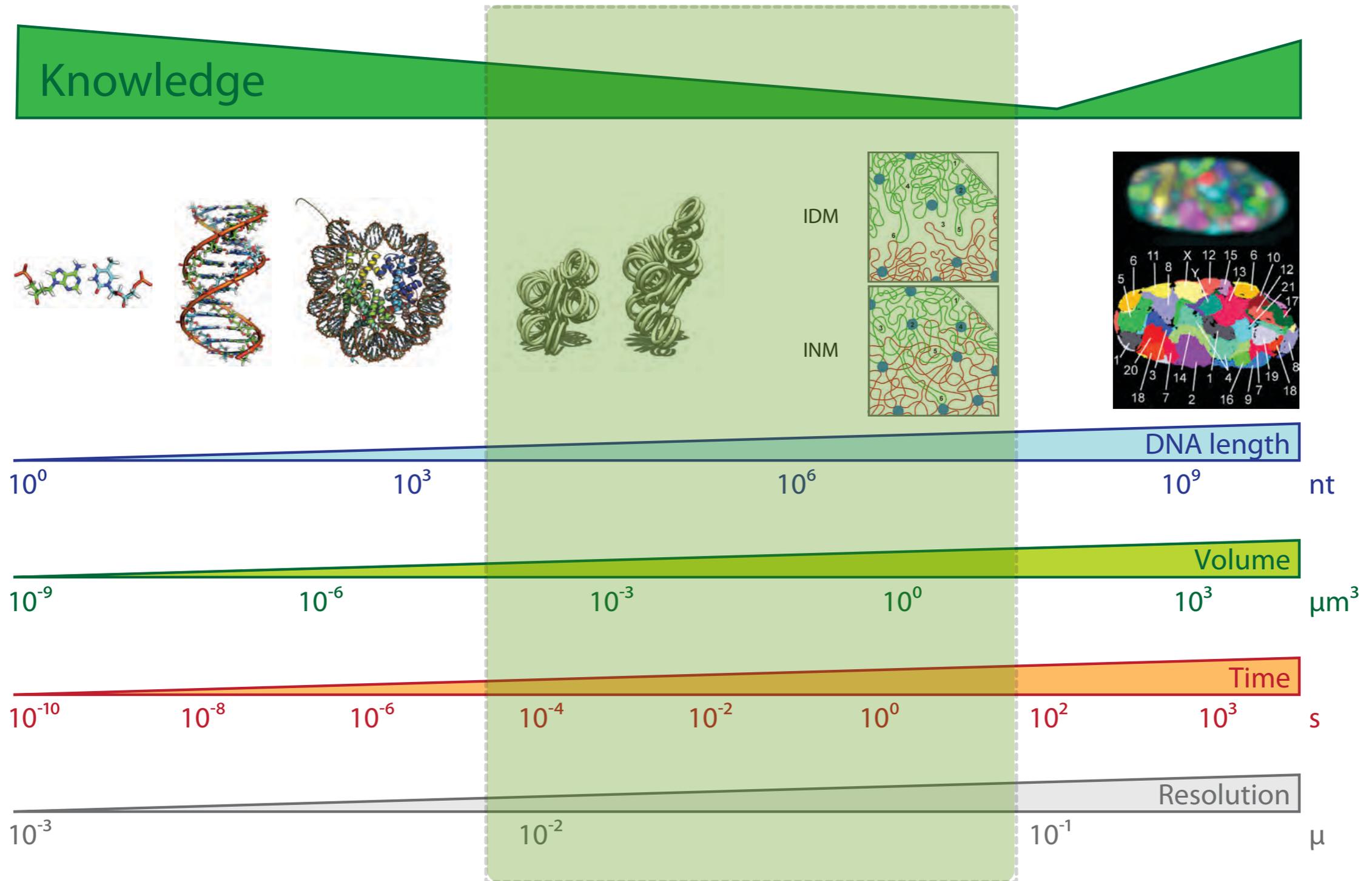
Genome Biology Group (CNAG)
Structural Genomics Group (CRG)

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



Resolution Gap

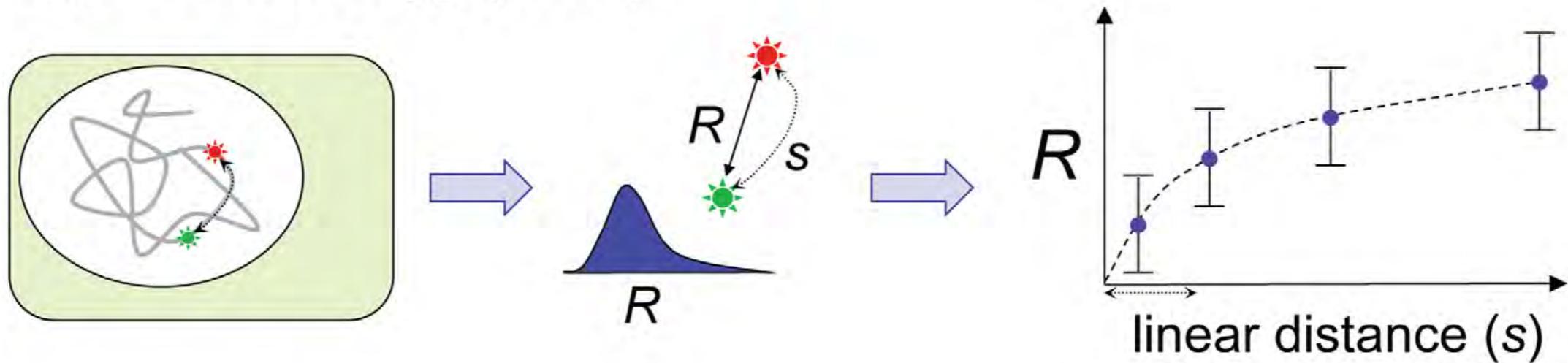
Marti-Renom, M. A. & Mirny, L. A. PLoS Comput Biol 7, e1002125 (2011)



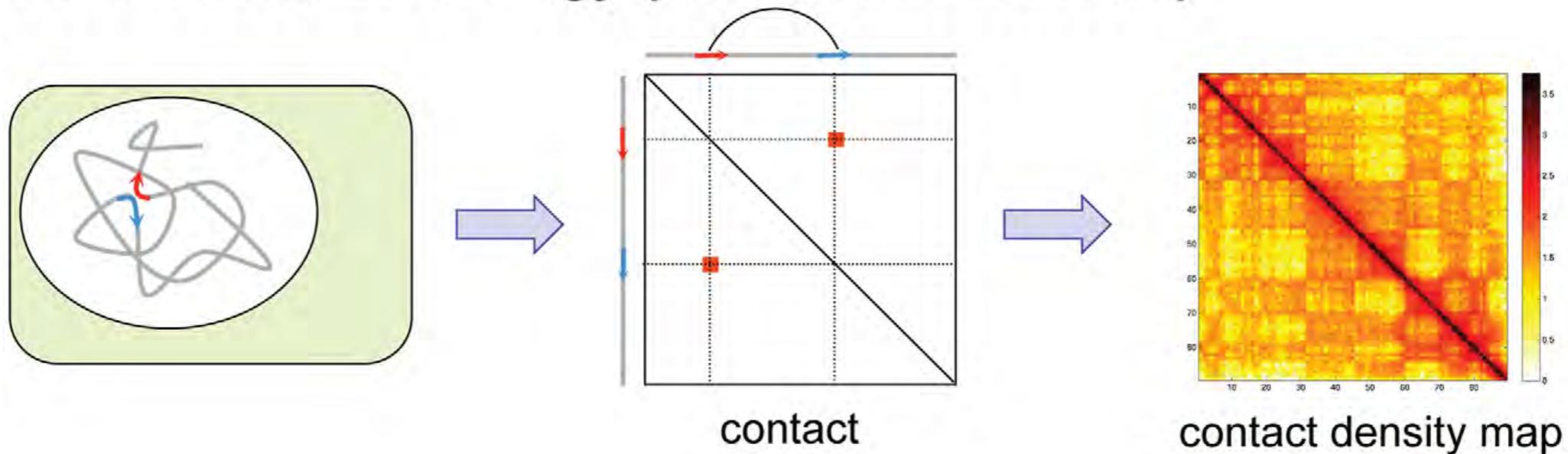
Resolution Gap

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

Light microscopy (FISH)

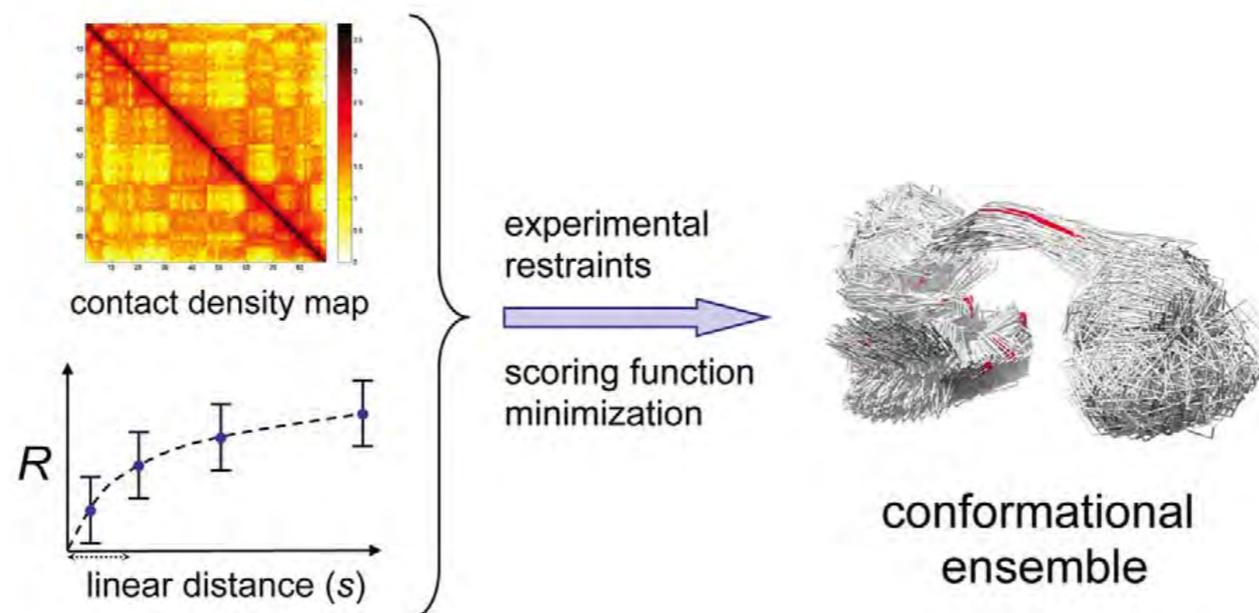
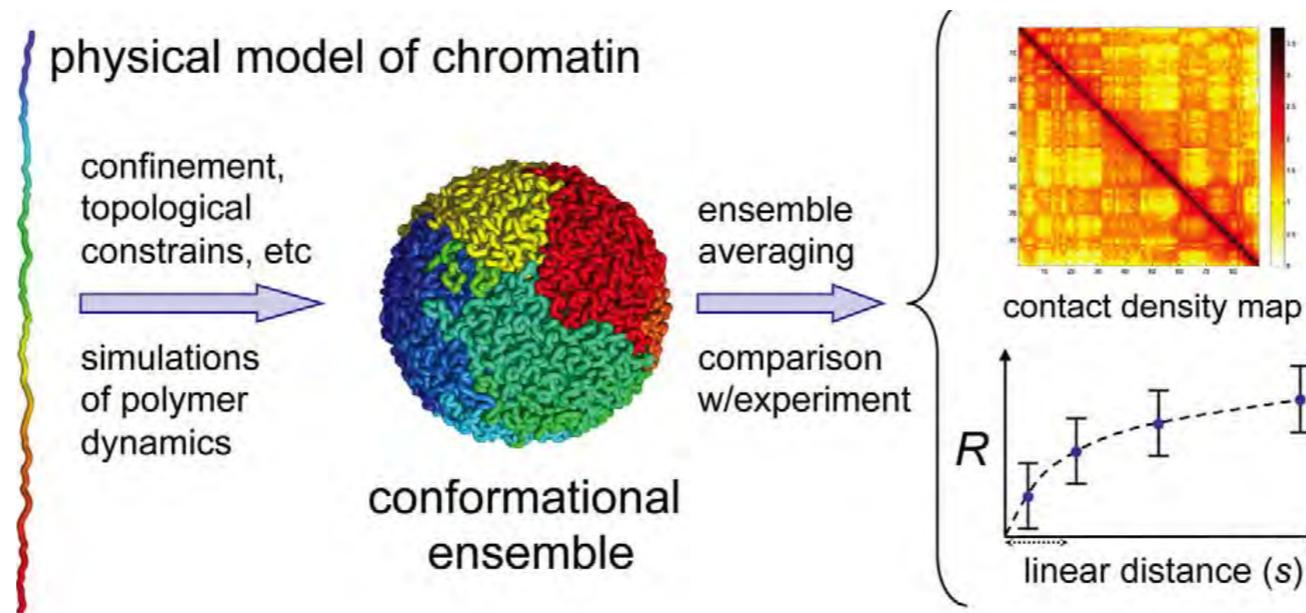


Cell/molecular biology (3C-based methods)



Resolution Gap

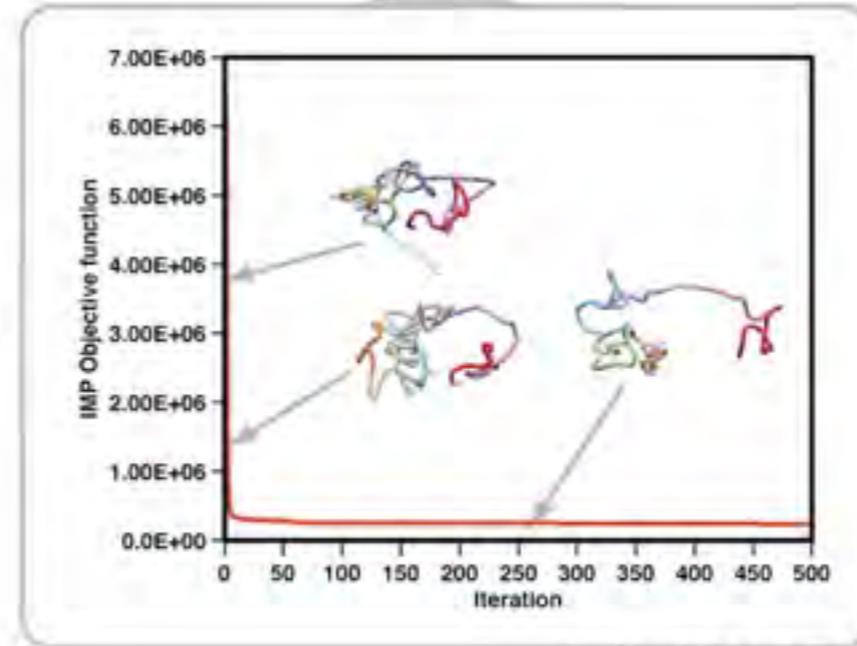
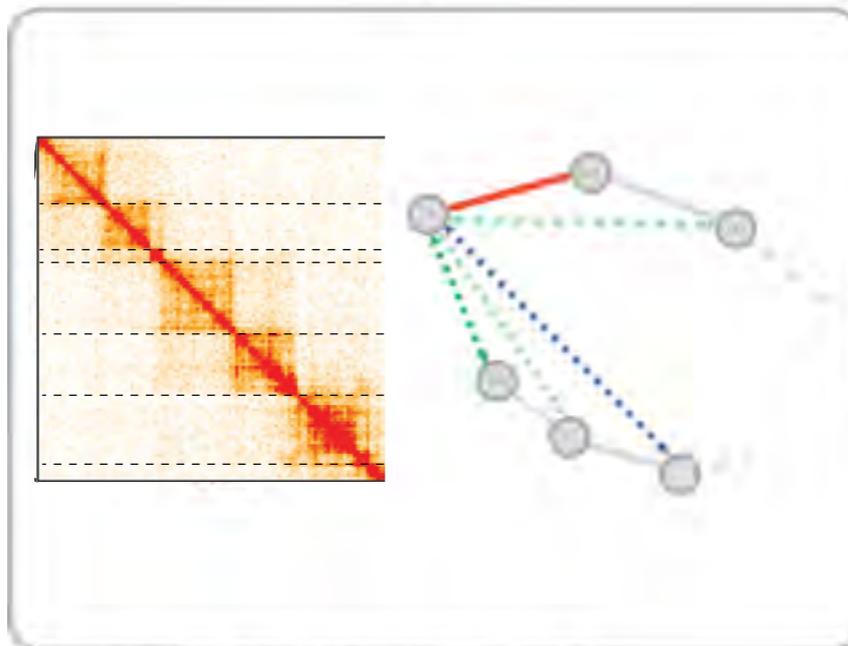
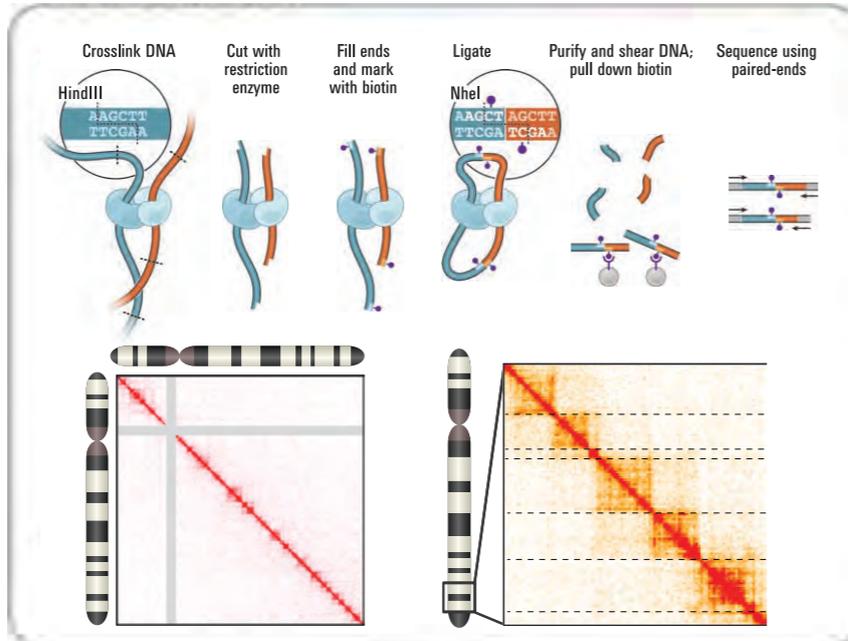
Marti-Renom, M. A. & Mirny, L. A. PLoS Comput Biol 7, e1002125 (2011)



Hybrid Method

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

Experiments



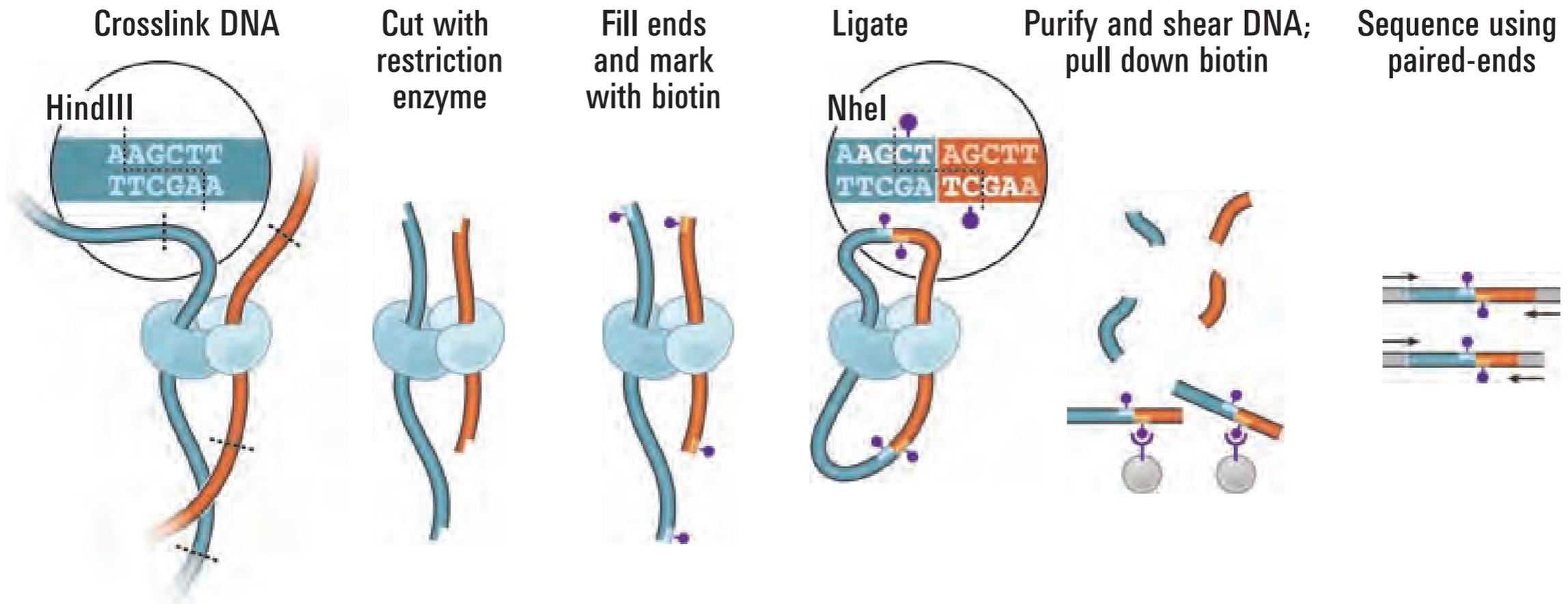
Computation

3C-based technologies

Dekker et al. (2002). *Science* 295:1306–1311.

Lieberman-Aiden, et al. (2009). *Science* 326:289–293.

Rao et al. (2014). *Cell*, 1–29

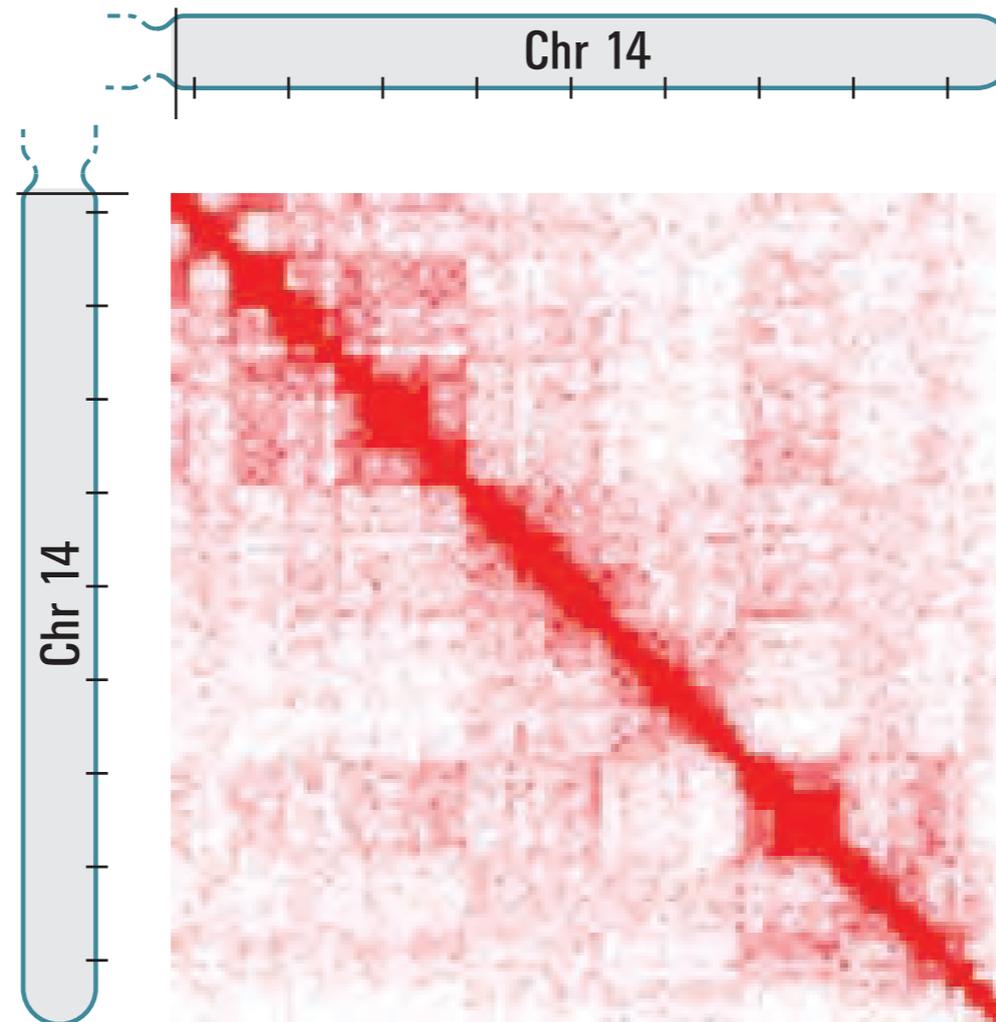
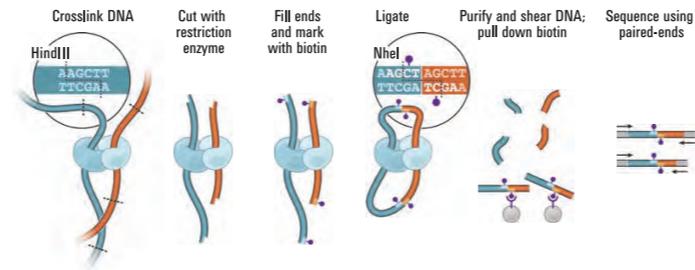


3C-based technologies

Dekker et al. (2002). *Science* 295:1306–1311.

Lieberman-Aiden, et al. (2009). *Science* 326:289–293.

Rao et al. (2014). *Cell*, 1–29

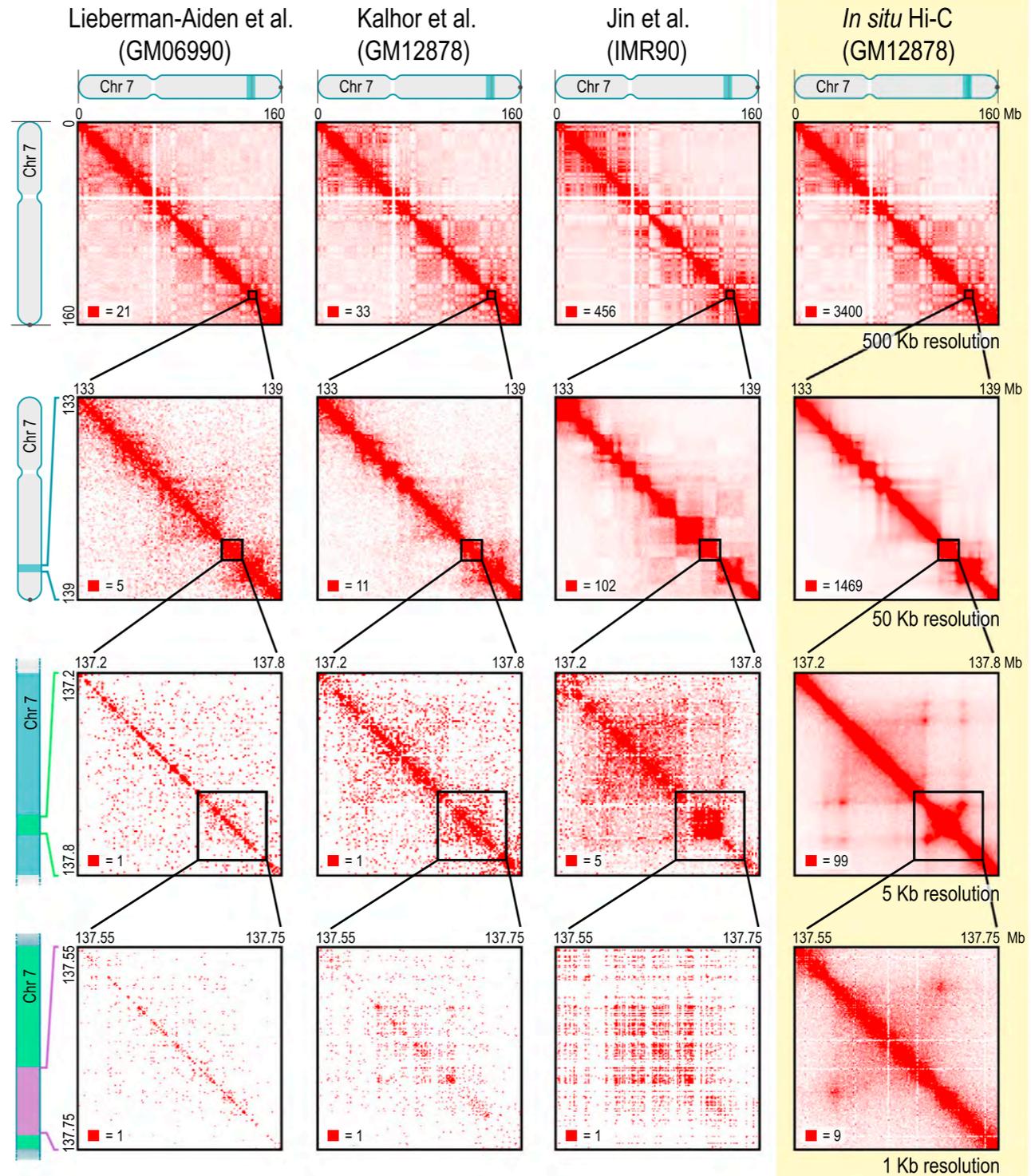
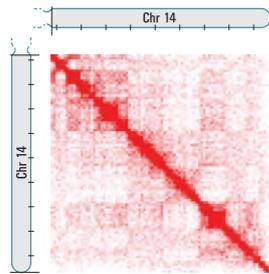
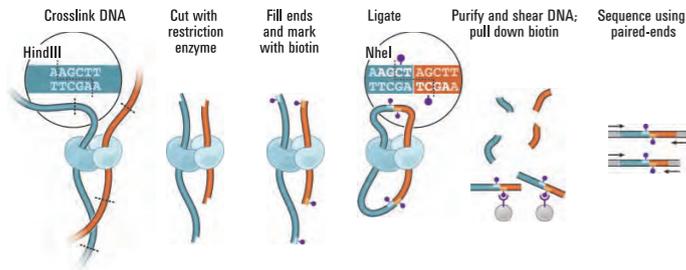


3C-based technologies

Dekker et al. (2002). *Science* 295:1306–1311.

Lieberman-Aiden, et al. (2009). *Science* 326:289–293.

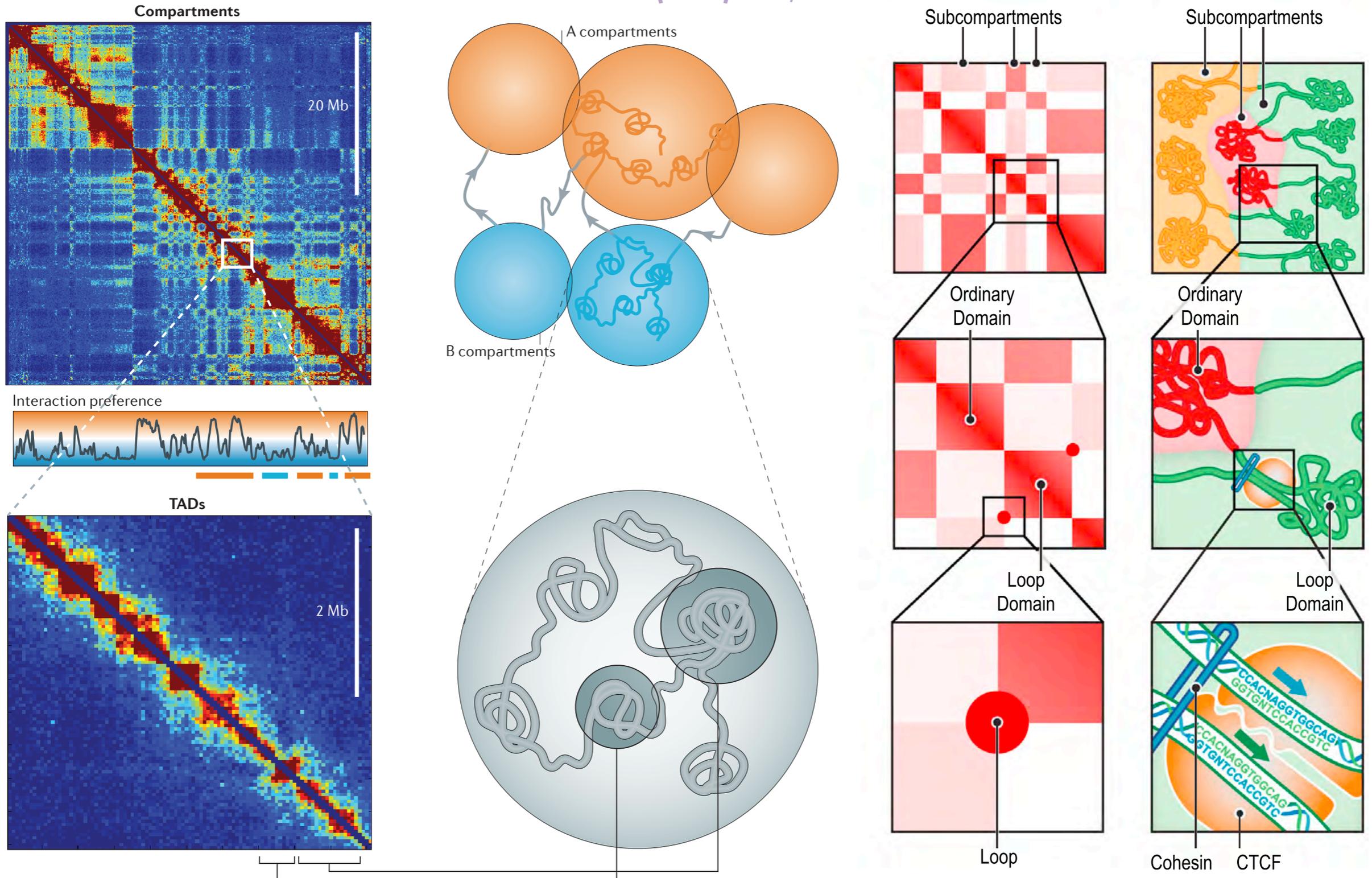
Rao et al. (2014). *Cell*, 1–29



What we know...

Lieberman-Aiden, et al. (2009). *Science* 326:289–293.

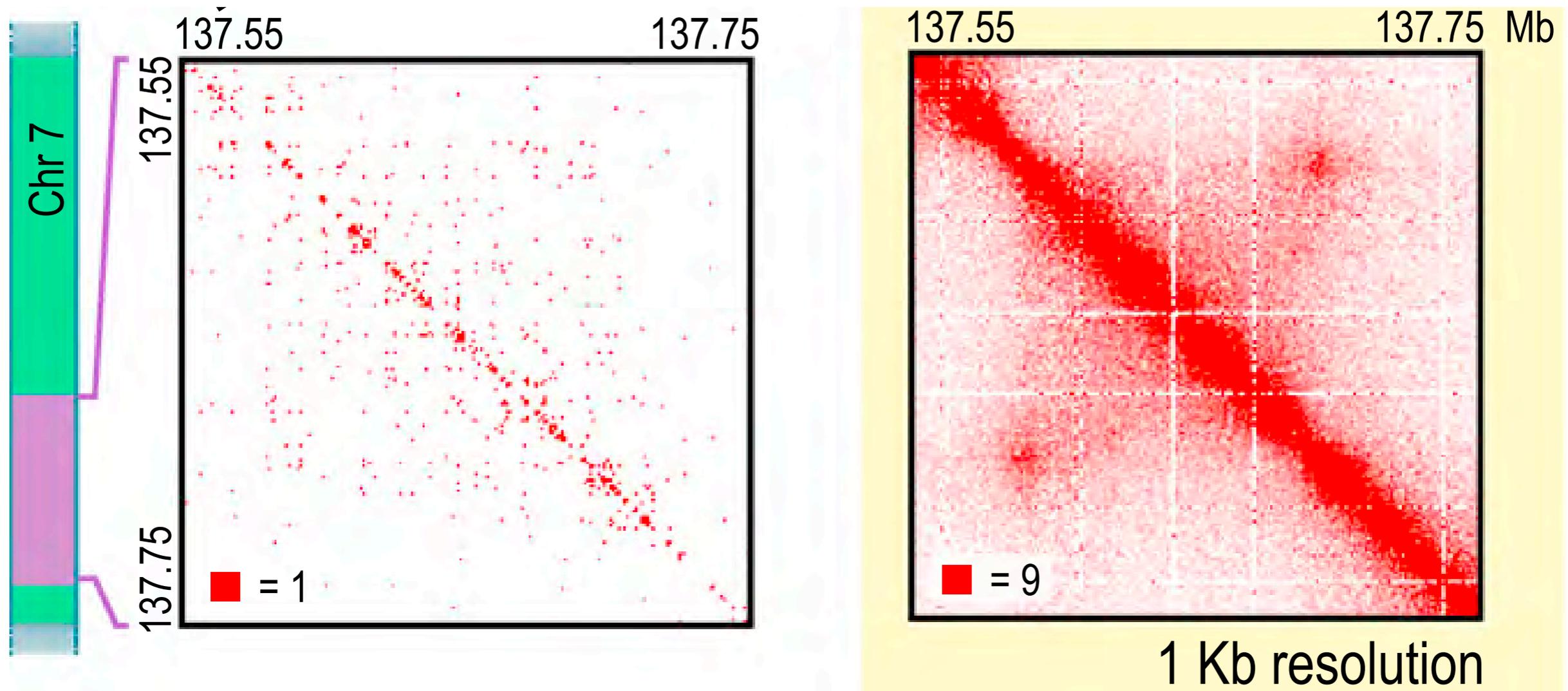
Rao et al. (2014). *Cell*, 1–29



from 100Kb to 1Kb

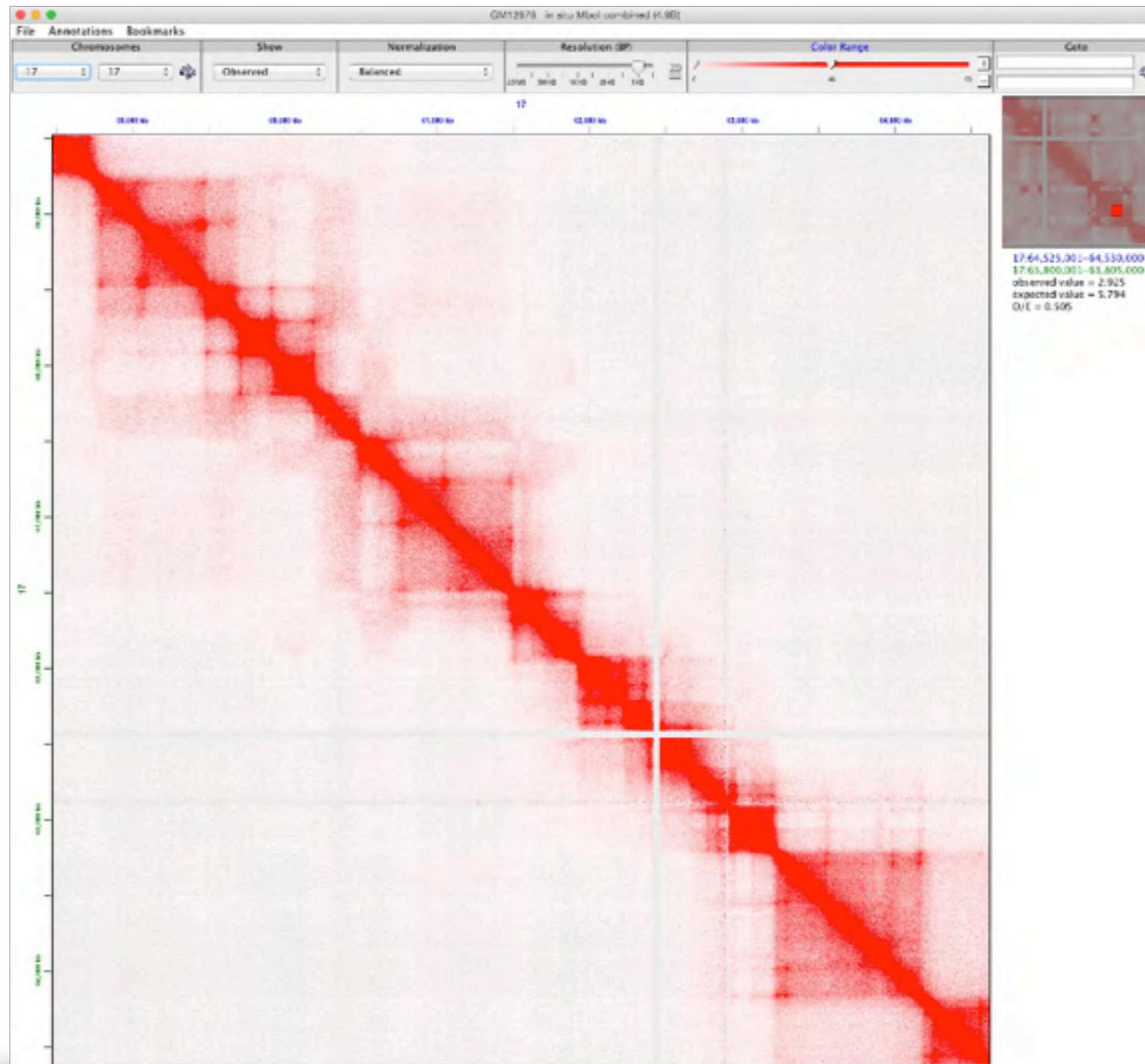
Lieberman-Aiden, et al. (2009). Science 326:289–293.

Rao et al. (2014). Cell, 1–29

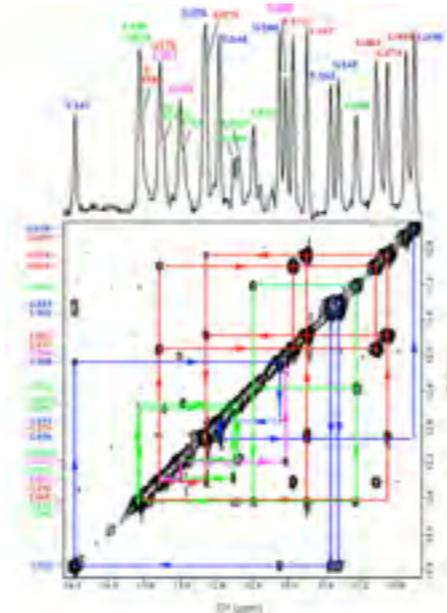


JuiceBox

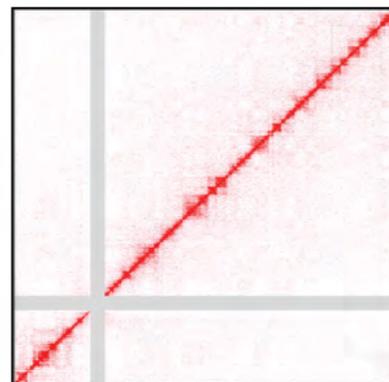
<http://www.aidenlab.org/juicebox/>



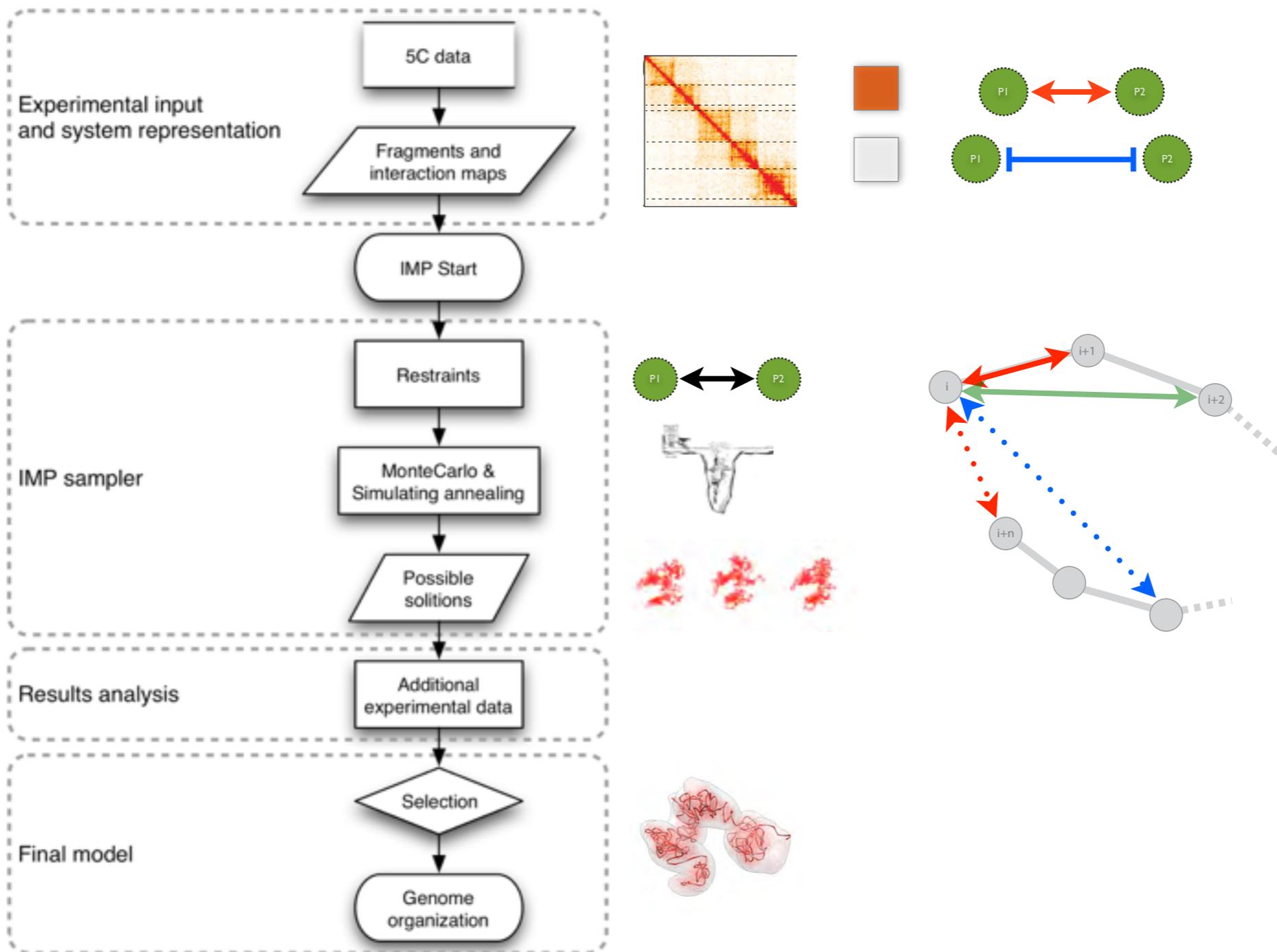




Biomolecular structure determination 2D-NOESY data



Chromosome structure determination 3C-based data



TADbit previous applications...

Baù, D. et al. Nat Struct Mol Biol (2011).
 Umbarger, M. A. et al. Mol Cell (2011).
 Le Dily, F. et al. Genes & Dev (2014)

TECHNICAL REPORTS

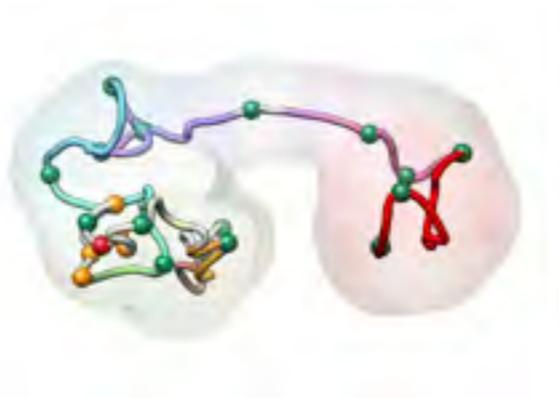
The three-dimensional folding of the α -globin gene domain reveals formation of chromatin globules

David Baù¹, Amara Sanyal¹, Bryan R. Lajtha¹, Emilio Caporaso¹, Meg Ryan¹, James R. Loman¹, Job Dekker¹, & Marc A. Marziani¹

Abstract
 We developed a general approach that combines chromosome conformation capture (3C) with the topological associating domain (TAD) to generate high-resolution three-dimensional maps of chromatin in the presence of the α -globin gene. We applied this approach to the α -globin gene on human chromosome 16, revealing the α -globin locus, which is organized in 10 TADs and is highly compartmentalized. Our results unexpectedly revealed the presence of long-range interactions between the α -globin gene and the β -globin gene, which are known to be highly compartmentalized. We propose that global interactions represent a higher-order folding state related to clustering of topologically associated domain (TAD) interactions, as previously observed by microscopy.

Introduction
 Chromatin structure is essential for the regulation of gene expression. Chromatin is organized into topologically associating domains (TADs), which are regions of high internal interactions. TADs are thought to facilitate compartmentalization of chromatin, all of which may regulate the expression of genes in a cell-specific manner. A general approach for describing the spatial organization of chromatin can aid in the identification of long-range interactions between genes and distal regulatory elements, as well as in the identification of higher-order folding principles of chromatin. An understanding of spatial organization and global interactions in chromatin conformation capture (3C) has become an essential tool for studying chromatin organization and gene regulation.

Results
 We developed a general approach that combines chromosome conformation capture (3C) with the topological associating domain (TAD) to generate high-resolution three-dimensional maps of chromatin in the presence of the α -globin gene. We applied this approach to the α -globin gene on human chromosome 16, revealing the α -globin locus, which is organized in 10 TADs and is highly compartmentalized. Our results unexpectedly revealed the presence of long-range interactions between the α -globin gene and the β -globin gene, which are known to be highly compartmentalized. We propose that global interactions represent a higher-order folding state related to clustering of topologically associated domain (TAD) interactions, as previously observed by microscopy.



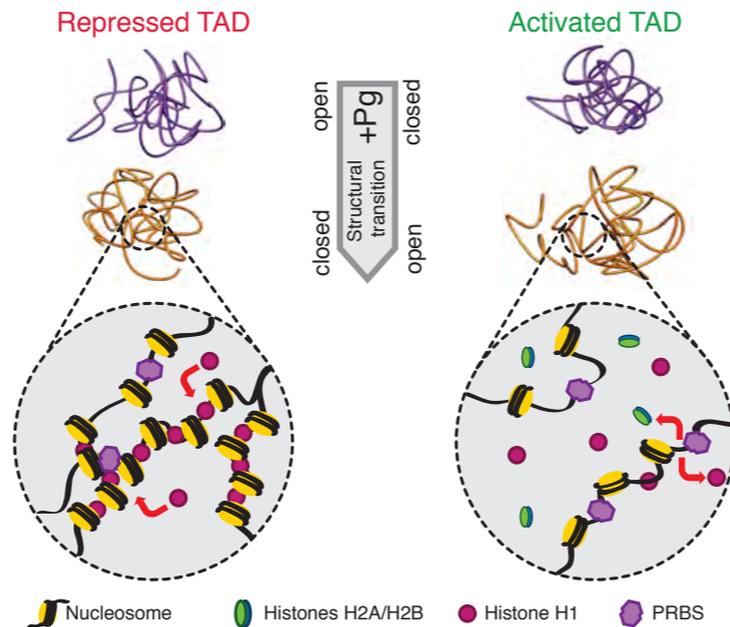
Molecular Cell Article

The Three-Dimensional Architecture of a Bacterial Genome and Its Alteration by Genetic Perturbation

Mark A. Umbarger^{1,2}, Kaitlyn M. Heston^{1,2}, Matthew A. Wright¹, Gregory J. Parnis¹, David Baù¹, Benjamin Heston^{1,2}, Matthew J. Parnis^{1,2}, John J. Zhu¹, Marc A. Matheson¹, Harry T. McKeown¹, Lutz Engerer¹, Job Dekker^{1,3}, & Charles M. Chang^{1,2}

Abstract
 We have determined the three-dimensional (3D) architecture of the Caulobacter crescentum genome by combining chromosome conformation capture (Hi-C) with chromosome conformation capture (Hi-C) and chromosome conformation capture (Hi-C) based on Hi-C. We show that the 3D architecture of the genome is organized into a series of topologically associating domains (TADs) and that the genome is highly compartmentalized. We show that the 3D architecture of the genome is altered by genetic perturbations, including deletions and insertions, and that these alterations are associated with changes in gene expression.

Introduction
 The three-dimensional (3D) architecture of the genome both within and between its functional units (genes, TADs, TADs, and TADs) is essential for the regulation of gene expression. We used Hi-C to determine the 3D architecture of the genome and to identify the interactions that define its architecture. To test our model, we used the topological associating domain (TAD) approach to identify the interactions that define its architecture. We show that the 3D architecture of the genome is altered by genetic perturbations, including deletions and insertions, and that these alterations are associated with changes in gene expression.

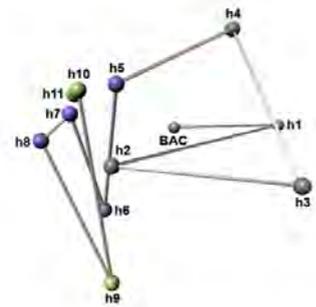


Distinct structural transitions of chromatin topological domains correlate with coordinated hormone-induced gene regulation

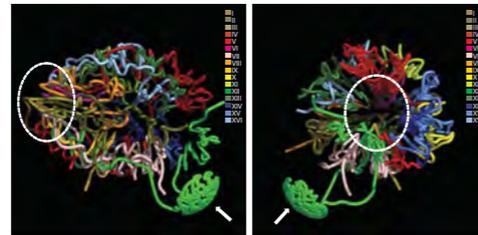
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Visualizing 3D Genomes

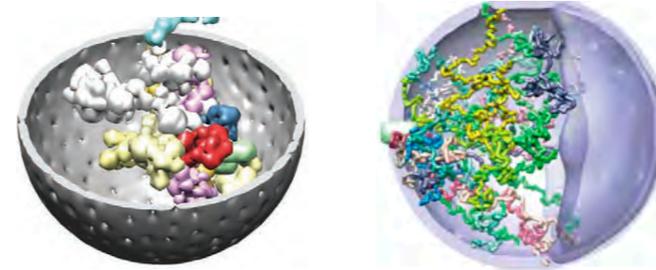
Jhunjunwala (2008) Cell



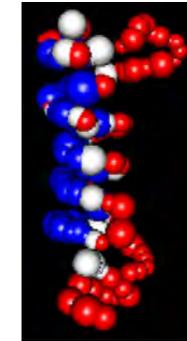
Duan (2010) Nature



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

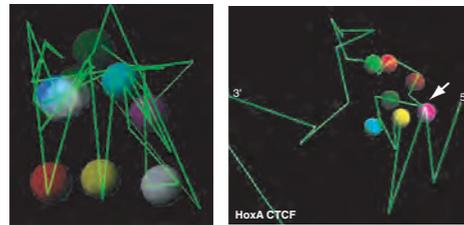


Hu (2013) PLoS Computational Biology

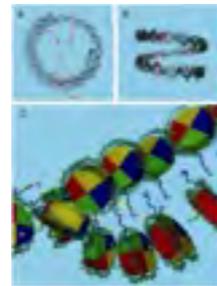


2008

2014



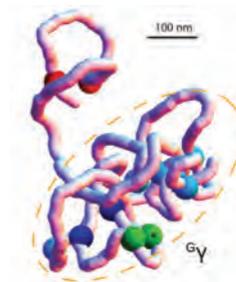
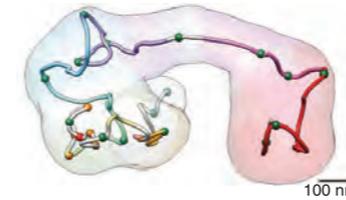
Fraser (2009) Genome Biology
Ferraiuolo (2010) Nucleic Acids Research



Asbury (2010) BMC Bioinformatics



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



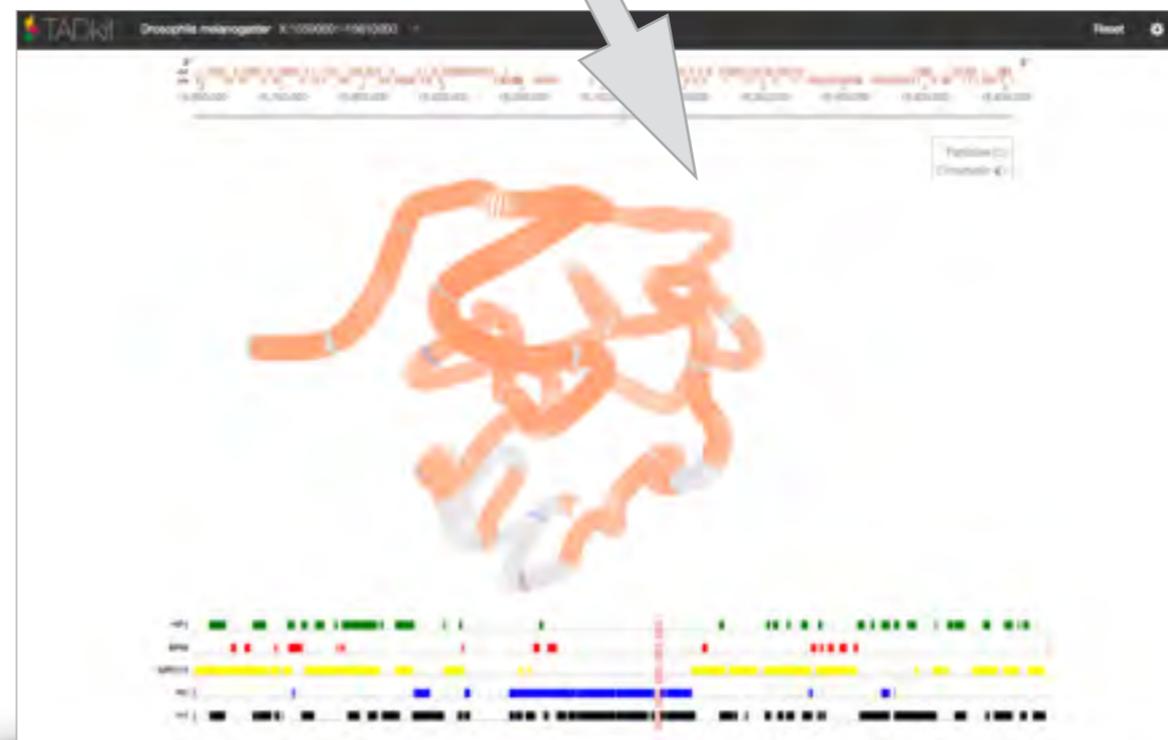
Junier (2012) Nucleic Acids Research

Diversity of representations
NO LINK to 1D and 2D data

<http://3DGenomes.org>

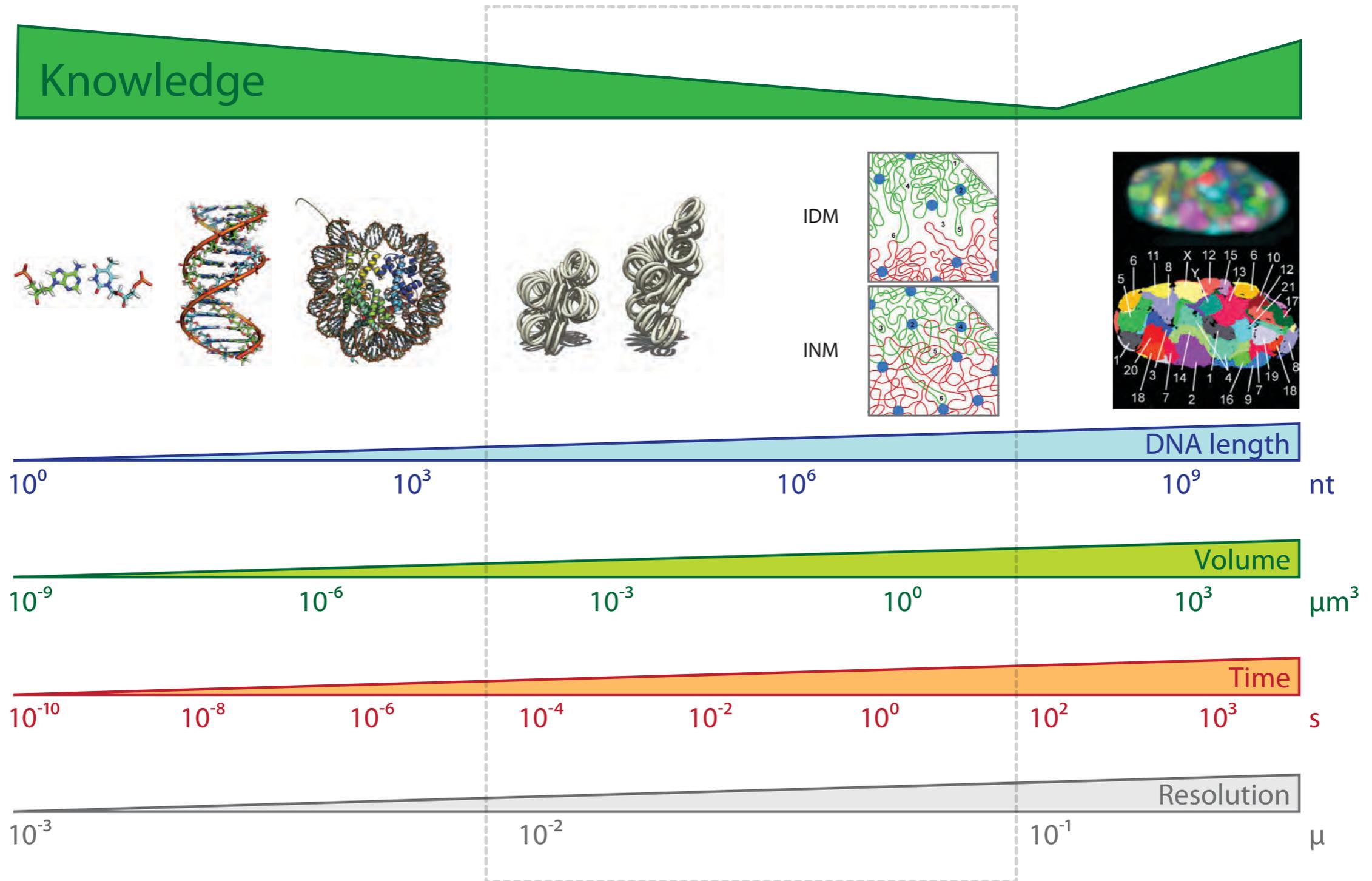


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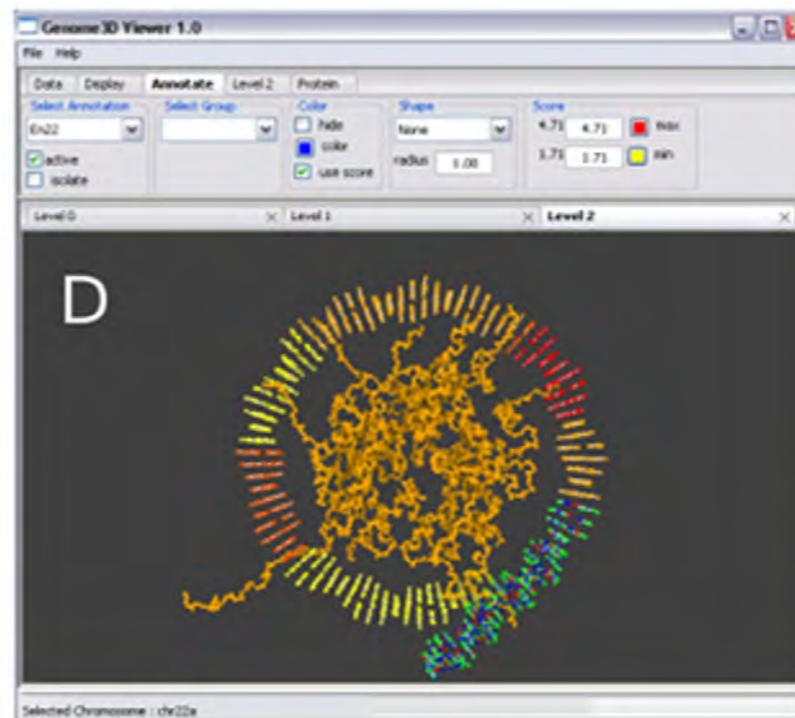
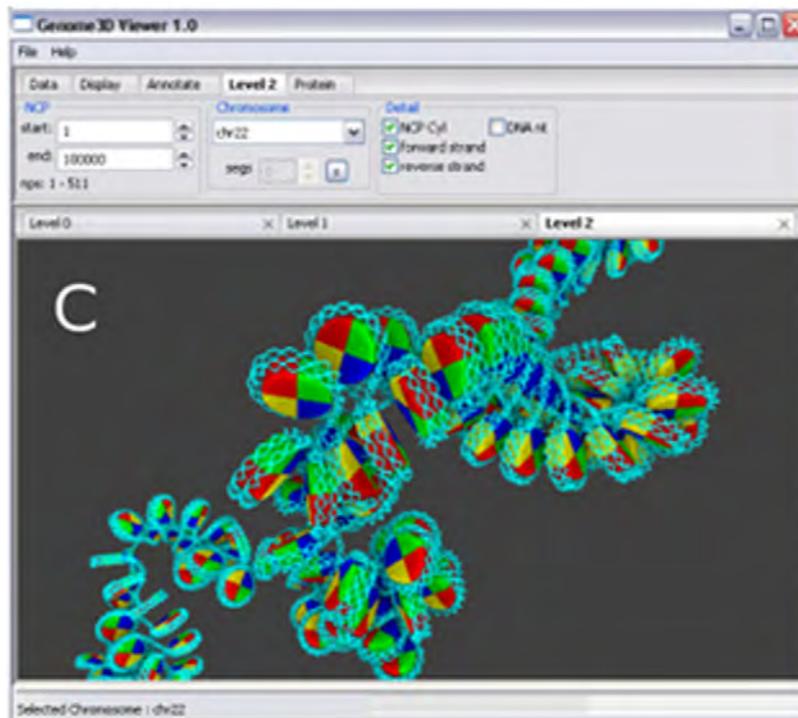
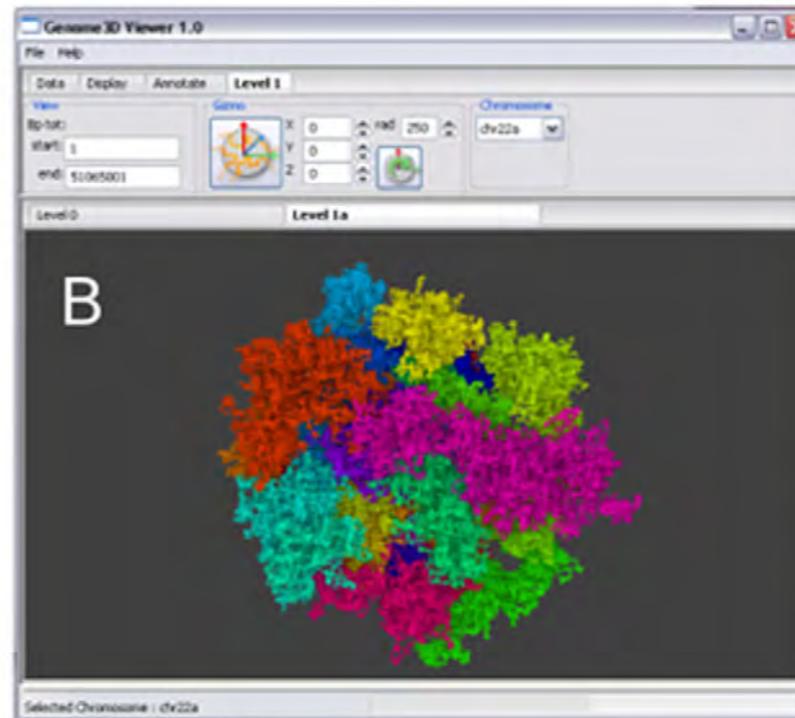
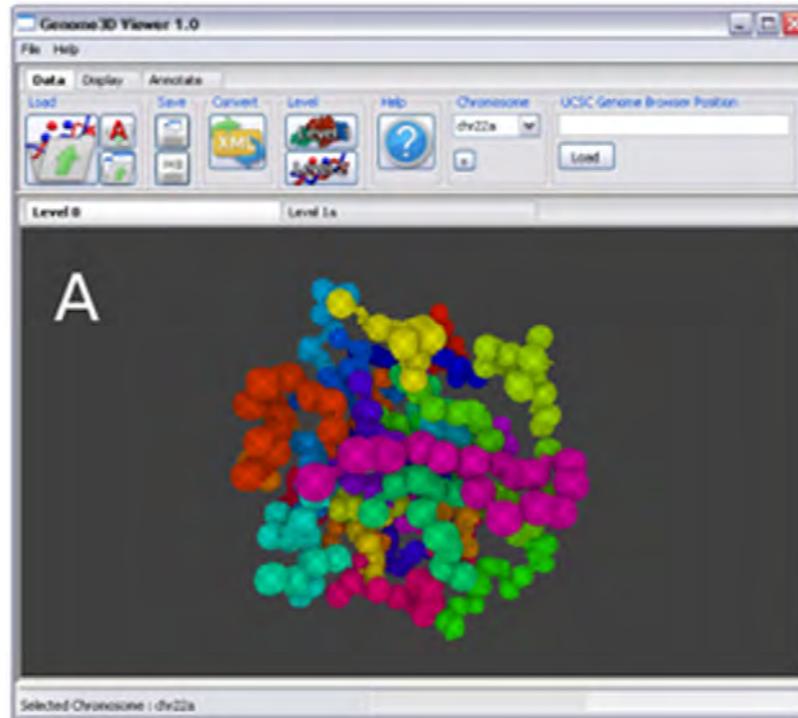
Scale aware?

Asbury (2010). BMC Bioinformatics, 11:444-7



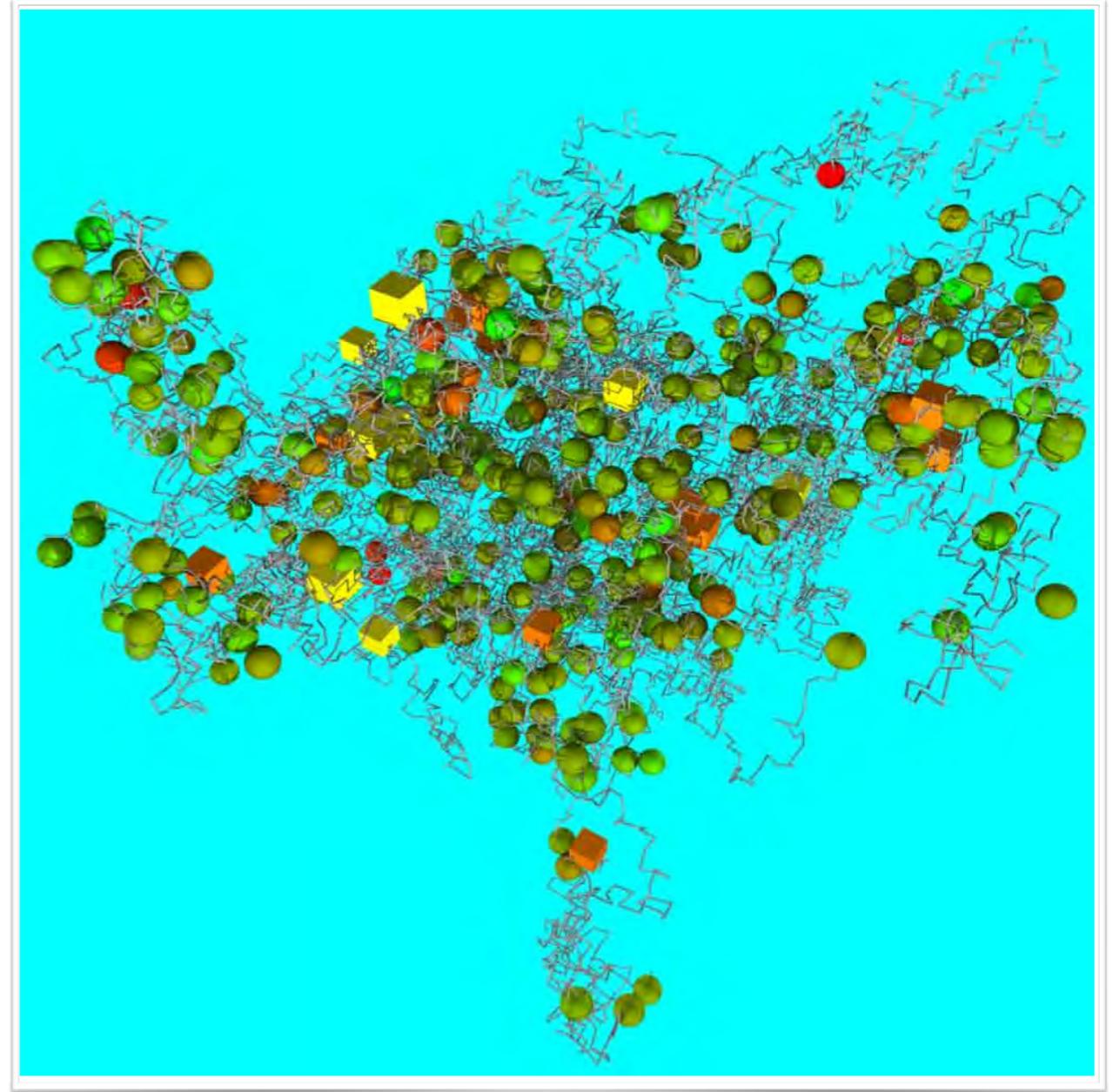
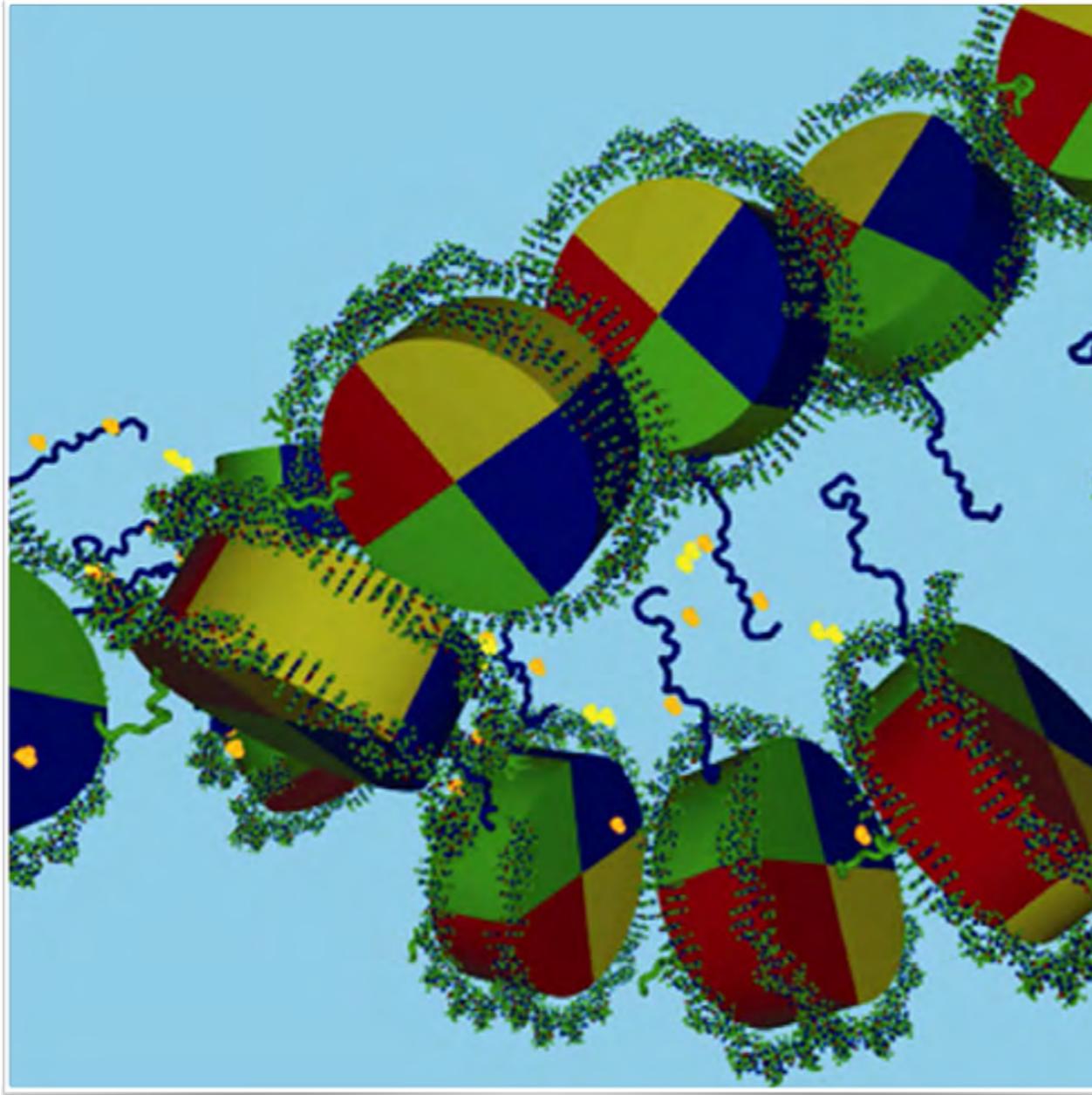
Genome3D

<http://www.genome3d.org>



Genome3D

<http://www.genome3d.org>



3:00-4:00PM

Tool 1. Juicebox

by Neva C. Durand and Jim Robinson

Juicebox is a Google map-like visualization software package for Hi-C data.

4:00-5:00PM

Tool 2. TADkit

by Mike Goodstadt and Marc A. Marti-Renom

TADkit is a web application for viewing and exploring spatial conformations of genomes in relation to their linear sequence and epigenetic state.

3:00-4:00PM

Tool 3. Genome3D

by W. Jim Zheng and Jijun Tang

Genome 3D is the first model-view framework of eukaryotic genomes enabling the integration and visualization of genomic and epigenomic data in the 3D space.