



Photo by David Oliete - [www.davidoliête.com](http://www.davidoliете.com)

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

**Marc A. Martí-Renom**  
CNAG-CRG · ICREA

<http://marciuslab.org>  
<http://3DGenomes.org>  
<http://cnag.crg.eu>

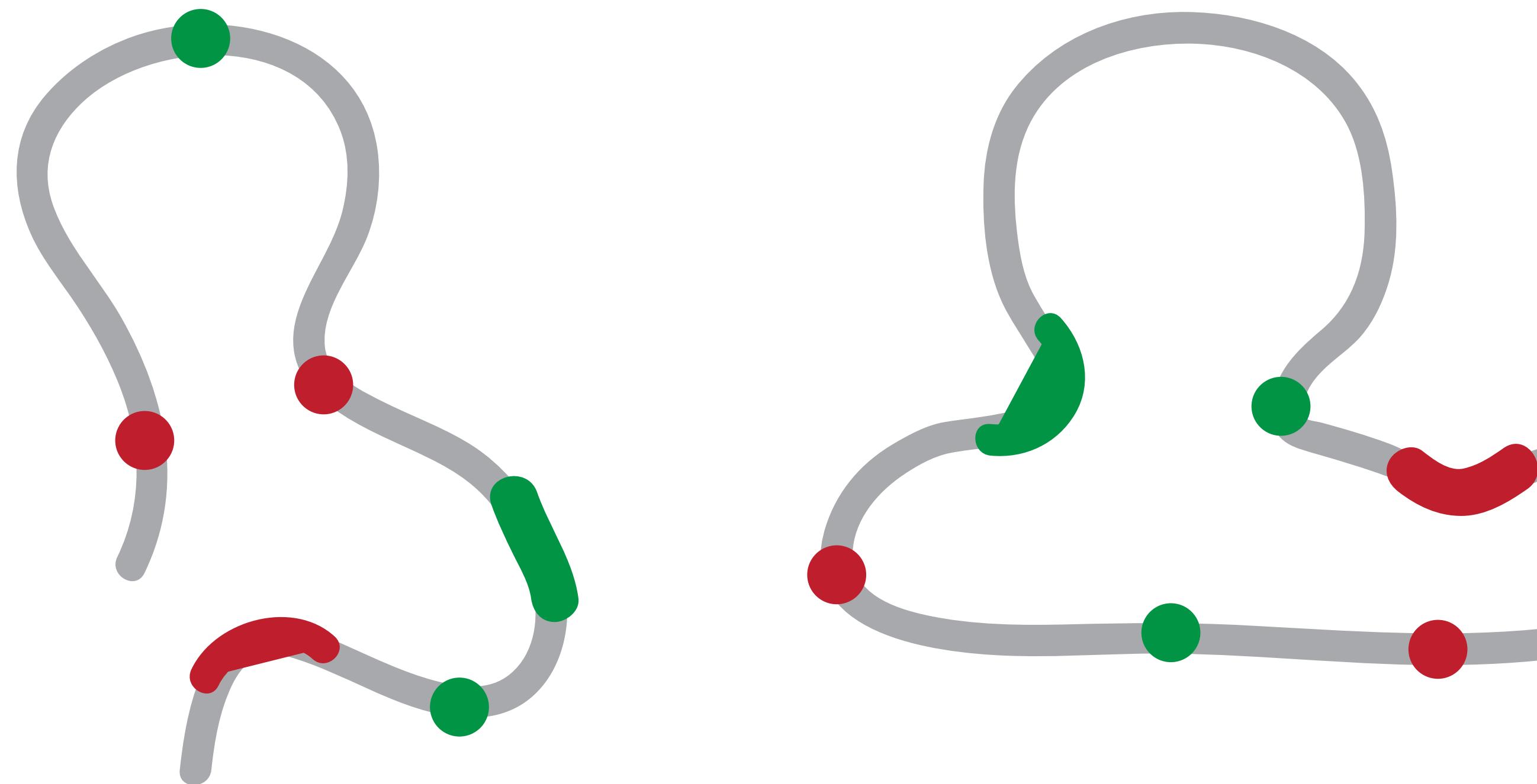
**cnag CRG** · ICREA

All you will see in the screen is here:

<http://marciuslab.org/www/presentations/>

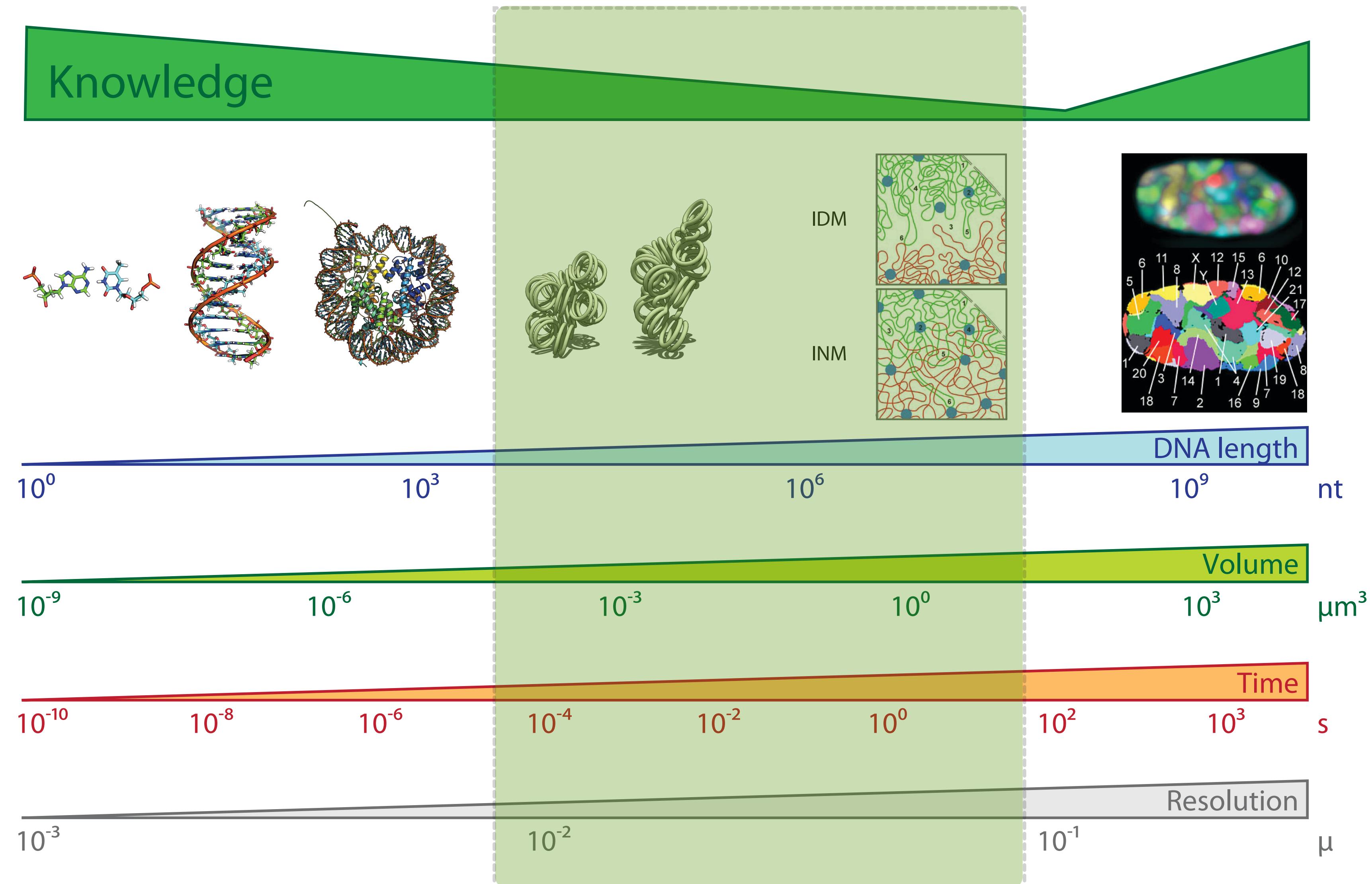
I encourage you to:

listen AND speak  
not necessarily in this order... 😊



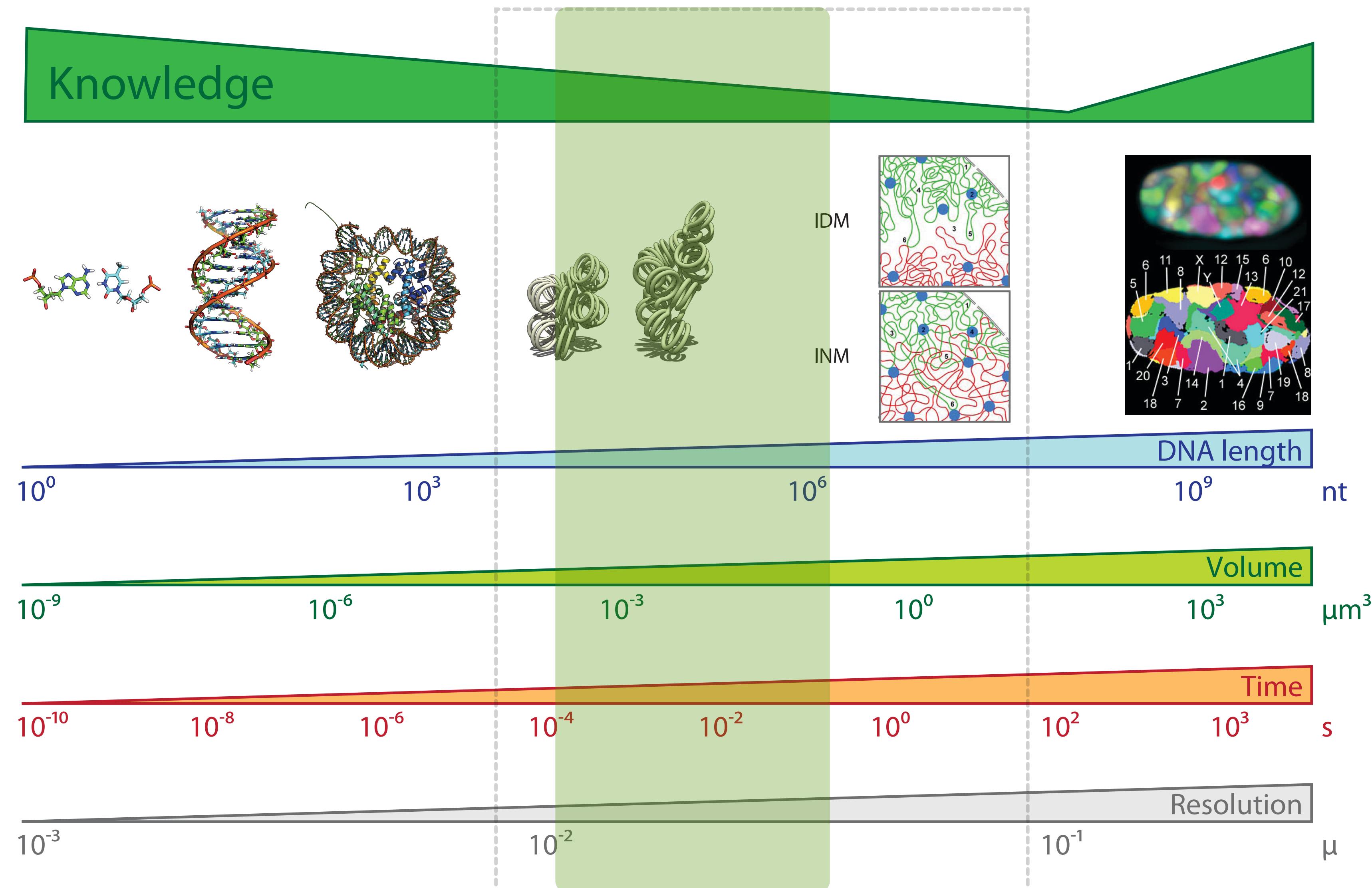
# Resolution Gap

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



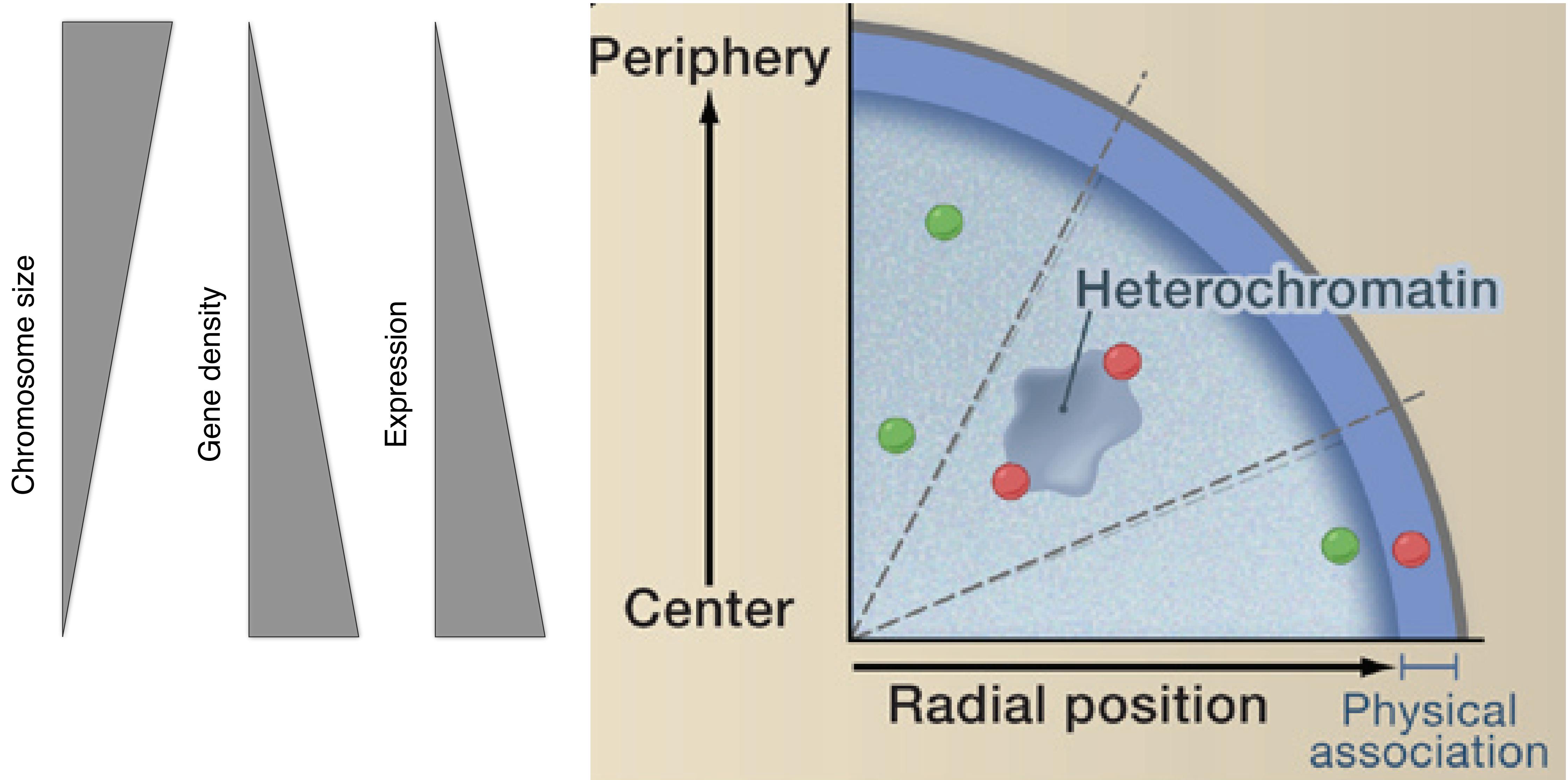
# Resolution Gap

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



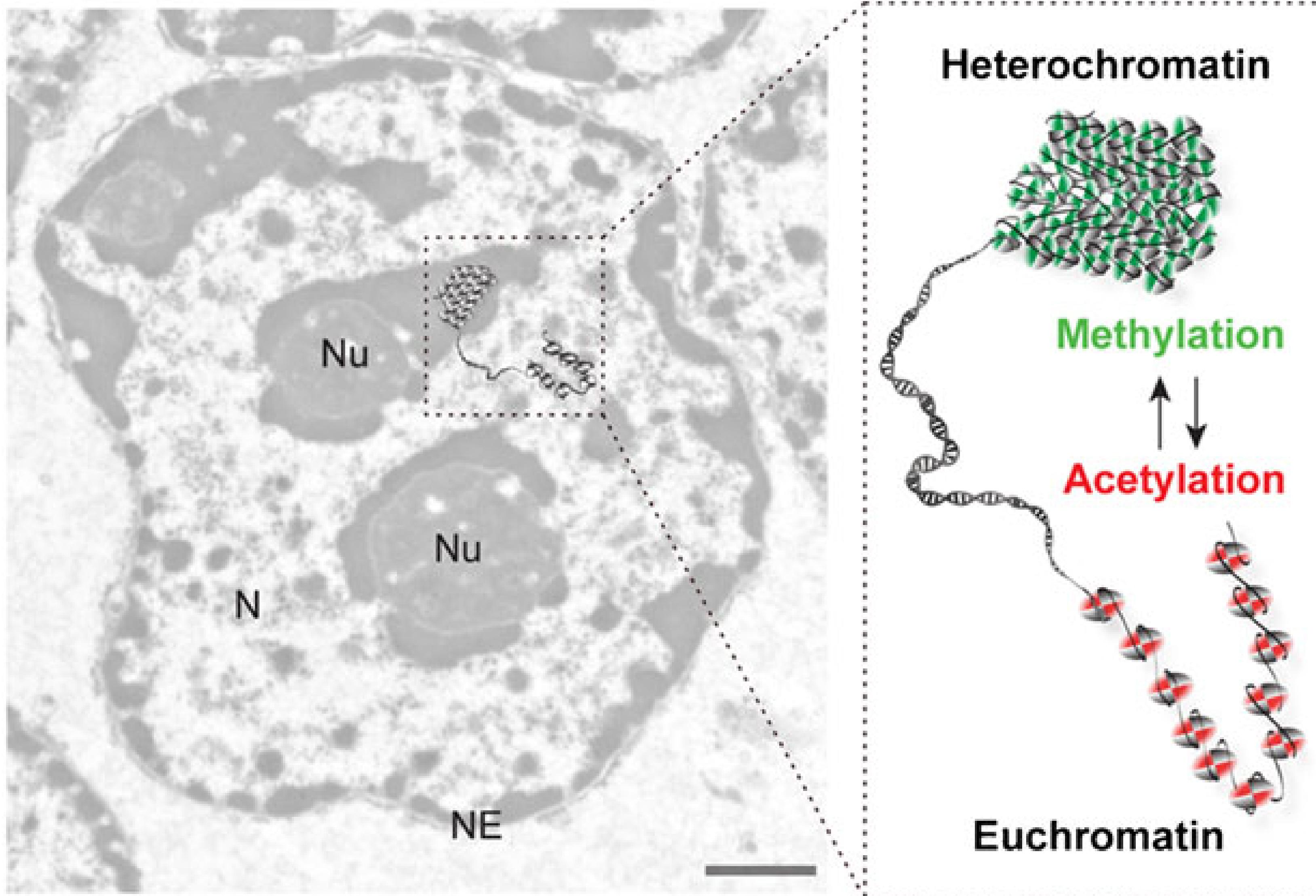
# Level I: Radial genome organization

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

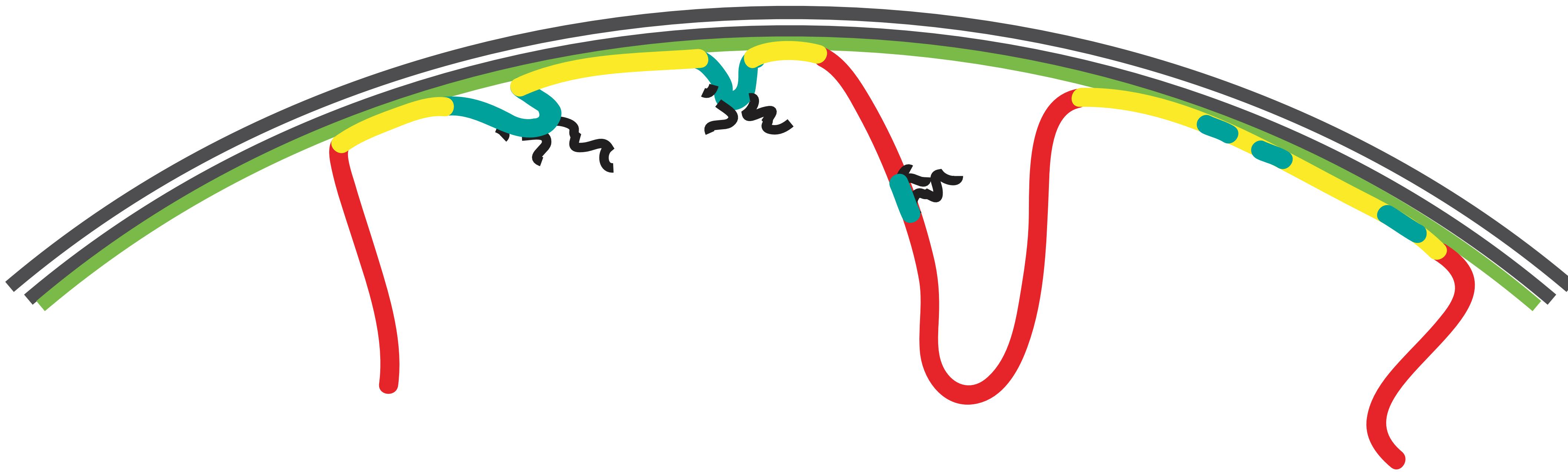


# Level II: Euchromatin vs heterochromatin

Electron microscopy



# Level III: Lamina-genome interactions

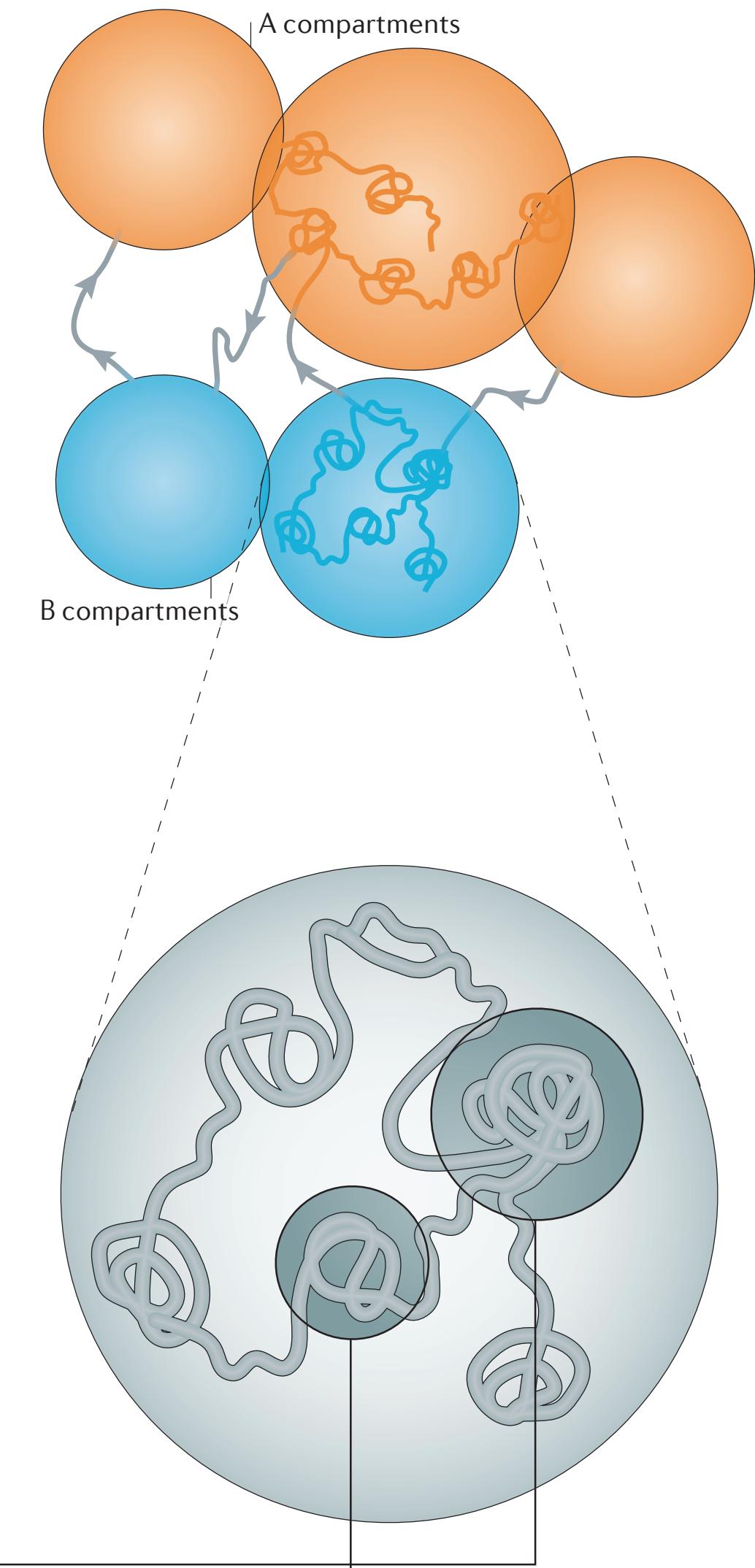
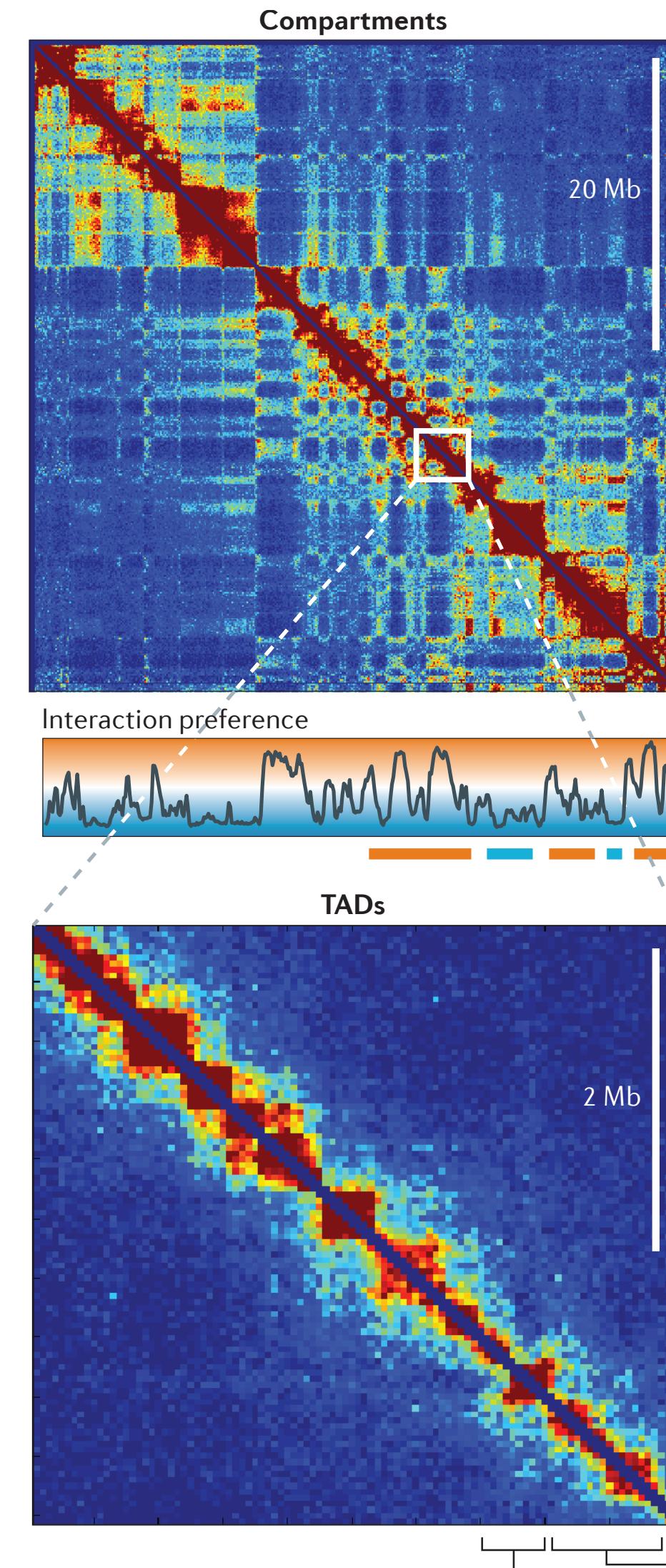
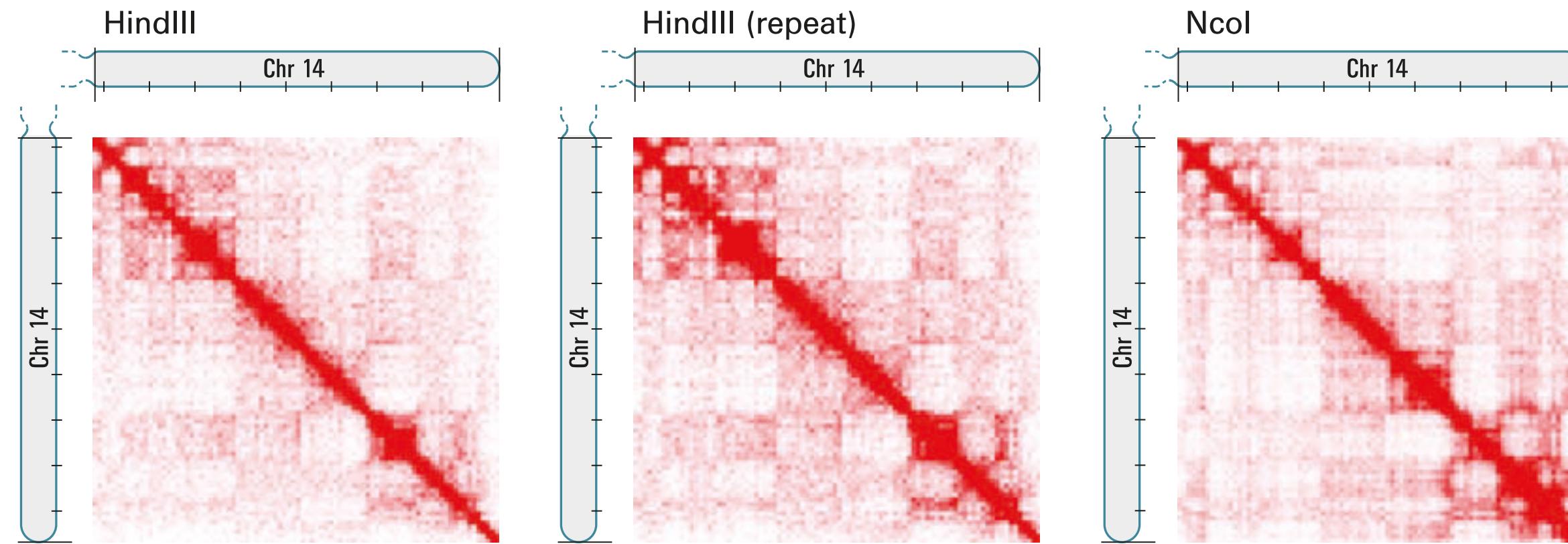
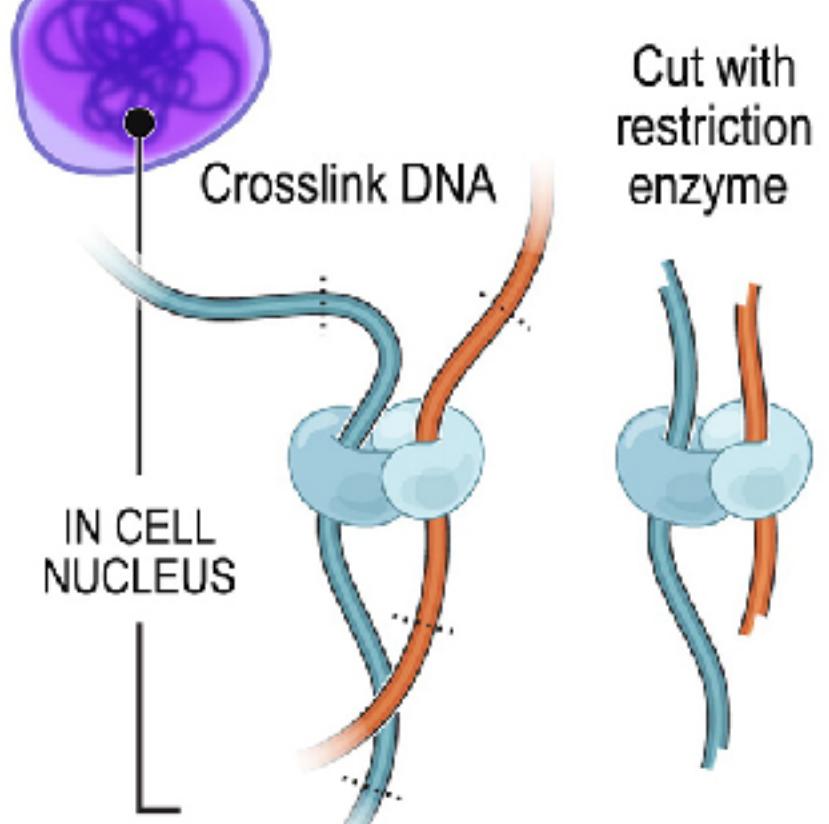


- nuclear membrane
- nuclear lamina
- internal chromatin (mostly active)
- lamina-associated domains (repressed)
- Genes
- mRNA

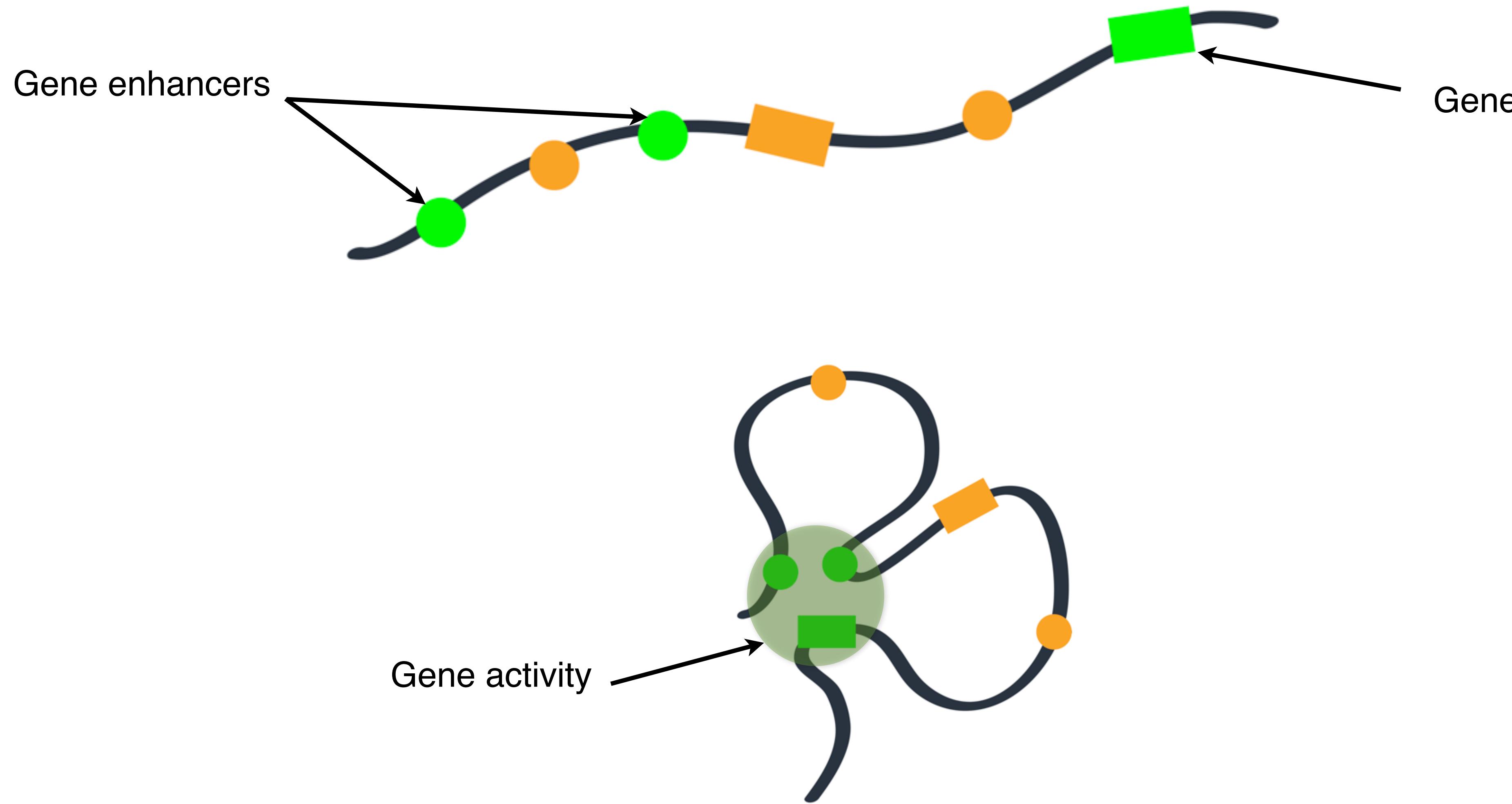
Adapted from Molecular Cell 38, 603-613, 2010

# Level IV: Higher-order organization

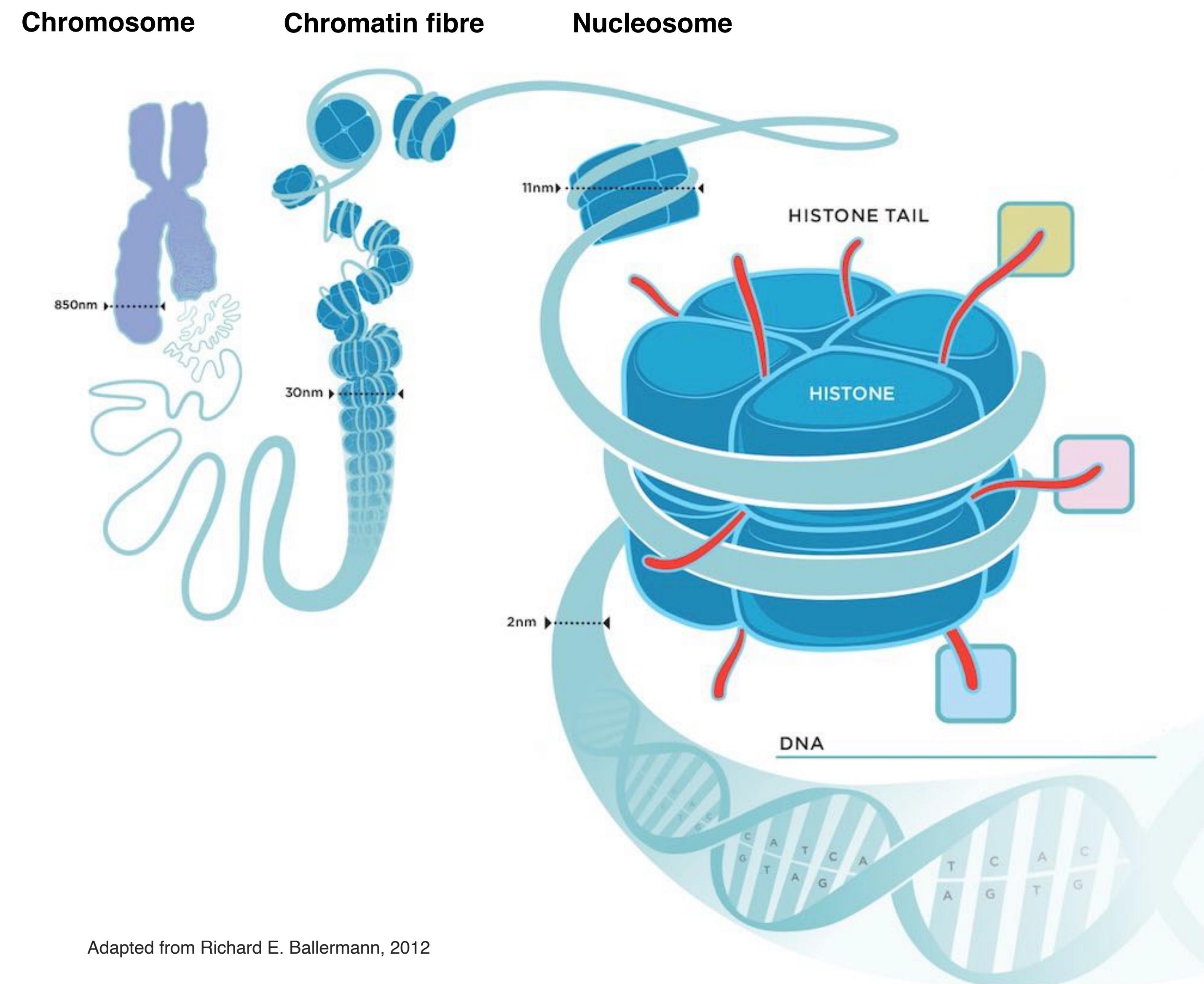
Dekker, J., Marti-Renom, M. A. & Mirny, L. A. Nat Rev Genet 14, 390–403 (2013).



## Level V: Chromatin loops



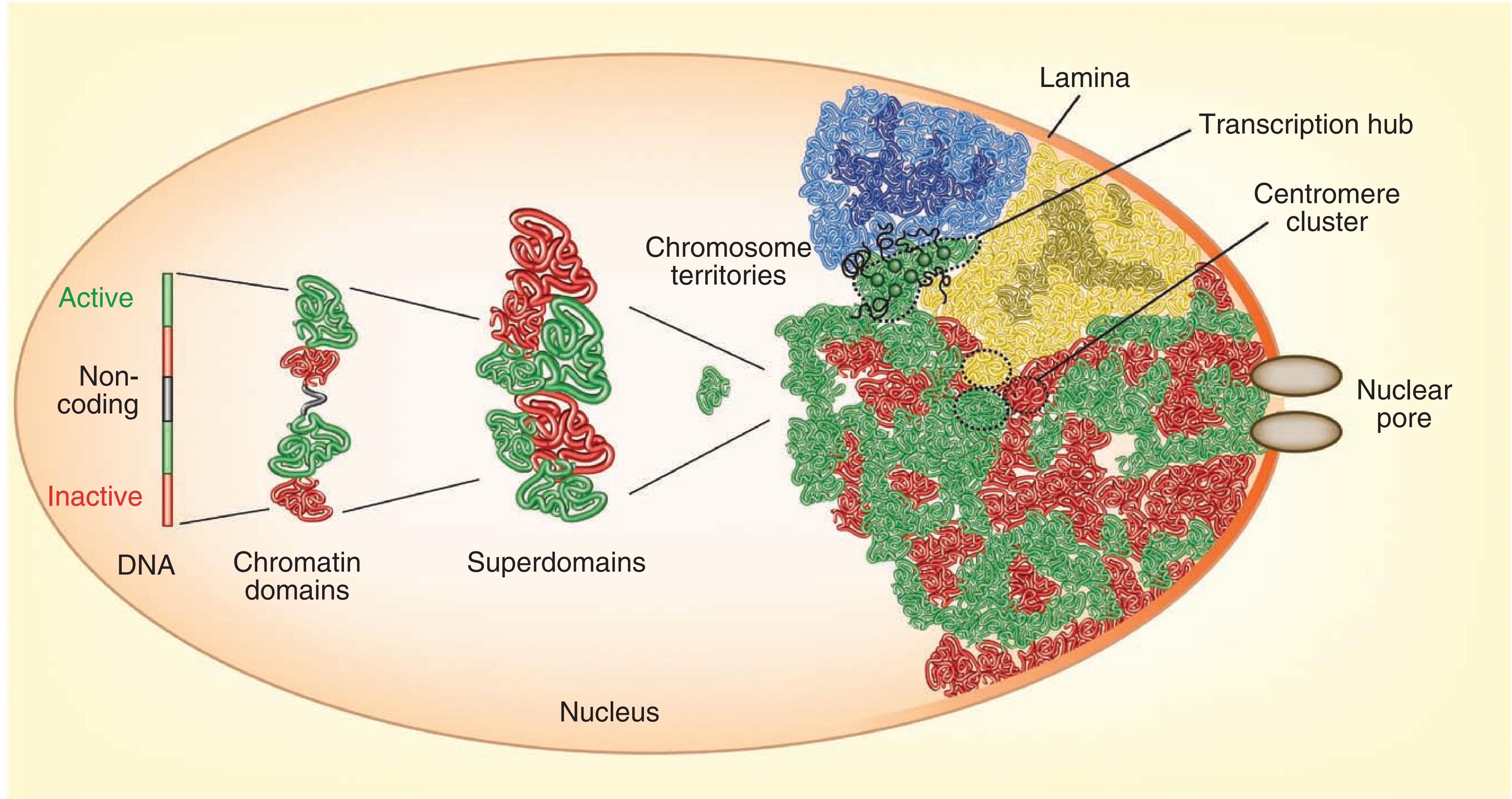
# Level VI: Nucleosome



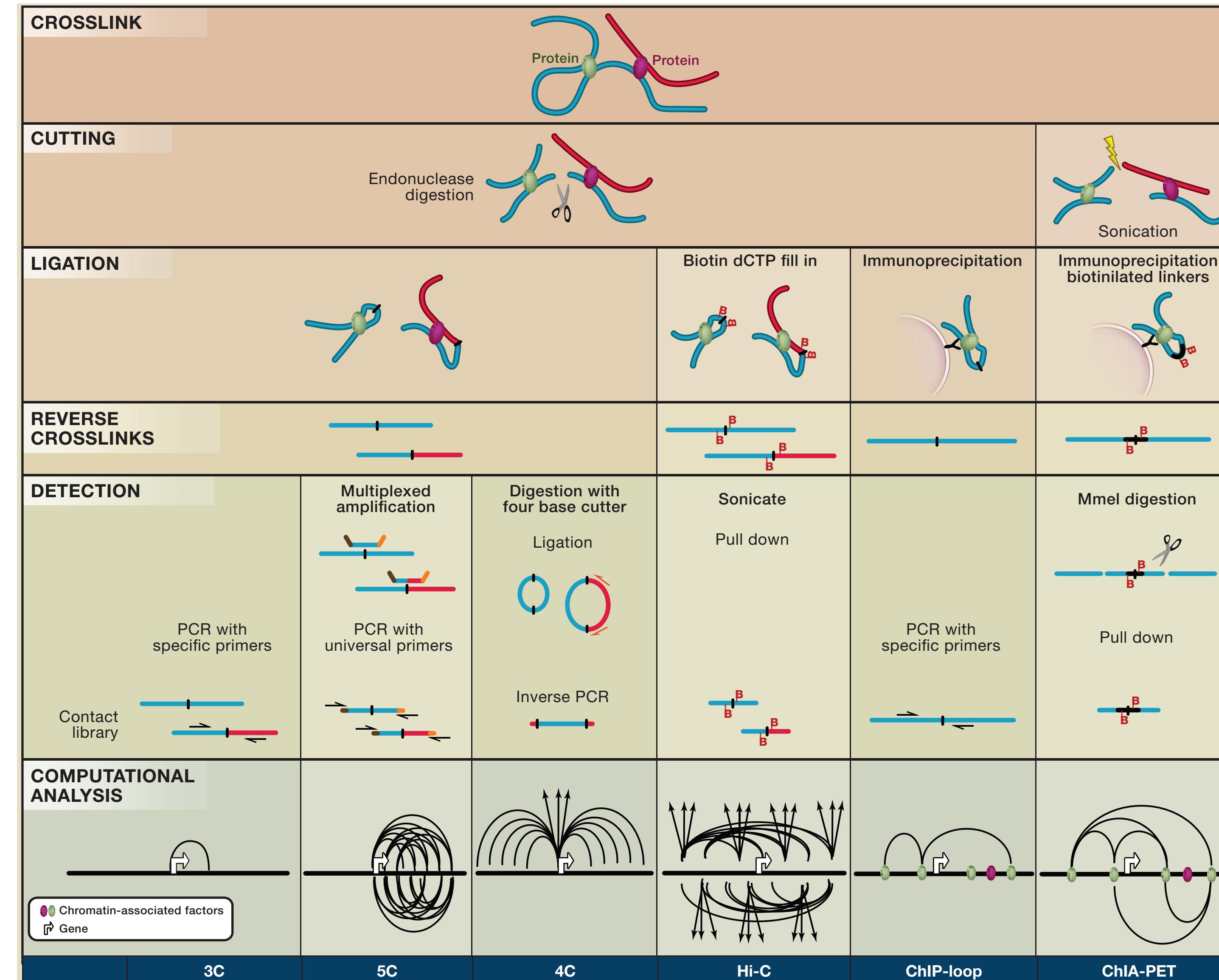
Adapted from Richard E. Ballermann, 2012

# Complex genome organization

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



# Chromosome Conformation Capture



## ARTICLE

doi:10.1038/nature12593

### Single-cell Hi-C reveals cell-to-cell variability in chromosome structure

Takashi Nagano<sup>1\*</sup>, Yaniv Lubling<sup>2\*</sup>, Tim J. Stevens<sup>3\*</sup>, Stefan Schoenfelder<sup>1</sup>, Eitan Yaffe<sup>2</sup>, Wendy Dean<sup>4</sup>, Ernest D. Lue<sup>3</sup>, Amos Tanay<sup>2</sup> & Peter Fraser<sup>1</sup>

## LETTER

doi:10.1038/nature20158

### Capturing pairwise and multi-way chromosomal conformations using chromosomal walks

Pedro Olivares-Chauvet<sup>1</sup>, Zohar Mukamel<sup>1</sup>, Aviezer Lifshitz<sup>1</sup>, Omer Schwartzman<sup>1</sup>, Noa Oded Elkayam<sup>1</sup>, Yaniv Lubling<sup>1</sup>, Gintaras Deikus<sup>2</sup>, Robert P. Sebra<sup>3</sup> & Amos Tanay<sup>1</sup>

nature  
genetics

ARTICLES

<https://doi.org/10.1038/s41588-018-0161-5>

### Enhancer hubs and loop collisions identified from single-allele topologies

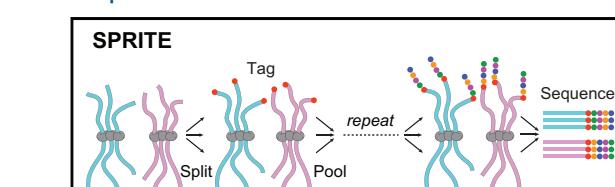
Amin Allahyar<sup>1,2</sup>, Carlo Vermeulen<sup>3,7</sup>, Britta A. M. Bouwman<sup>3</sup>, Peter H. L. Krijger<sup>3</sup>, Marjon J. A. M. Versteegen<sup>3</sup>, Geert Geenen<sup>3</sup>, Melissa van Kranenburg<sup>3</sup>, Mark Pieterse<sup>3</sup>, Roy Straver<sup>3,1</sup>, Judith H. I. Haarhuis<sup>4</sup>, Kees Jalink<sup>5</sup>, Hans Teunissen<sup>6</sup>, Ivo J. Renkens<sup>1</sup>, Wigard P. Kloosterman<sup>1</sup>, Benjamin D. Rowland<sup>1</sup>, Elzo de Wit<sup>6</sup>, Jeroen de Ridder<sup>3,\*</sup> and Wouter de Laat<sup>3\*</sup>

Resource

## Cell

### Higher-Order Inter-chromosomal Hubs Shape 3D Genome Organization in the Nucleus

#### Graphical Abstract



Authors  
Sofia A. Quinodoz, Noah Ollikainen, Barbara Tabak, ..., Patrick McDonel, Manuel Garber, Mitchell Guttman  
Correspondence  
[mguttman@caltech.edu](mailto:mguttman@caltech.edu)

nature  
COMMUNICATIONS

## ARTICLE

DOI: 10.1038/s41467-018-06961-0 OPEN

### Chromatin conformation analysis of primary patient tissue using a low input Hi-C method

Noelia Diaz<sup>1</sup>, Kai Kruse<sup>1</sup>, Tabea Erdmann<sup>2</sup>, Annette M. Staiger<sup>3,4,5</sup>, German Ott<sup>3</sup>, Georg Lenz<sup>2</sup> & Juan M. Vaquerizas<sup>1</sup>

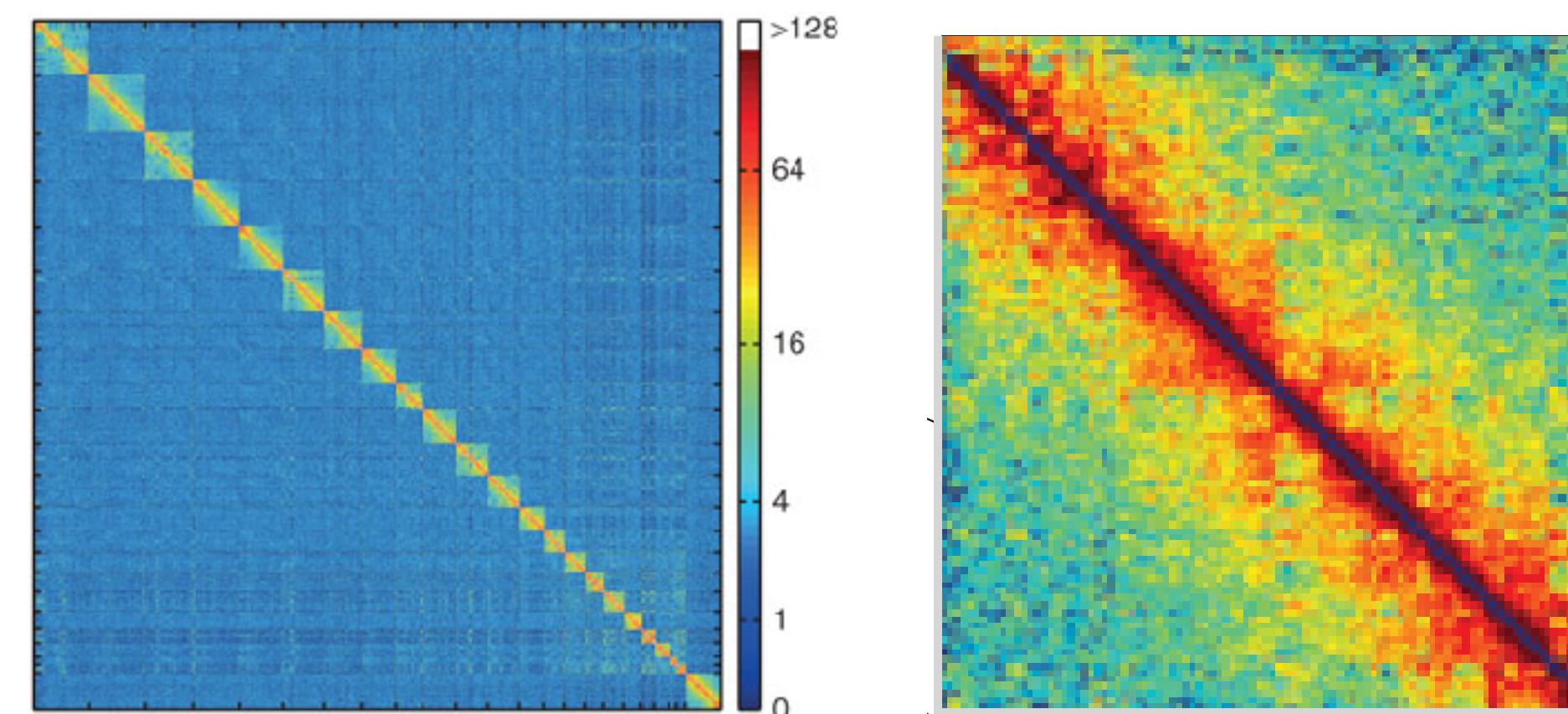
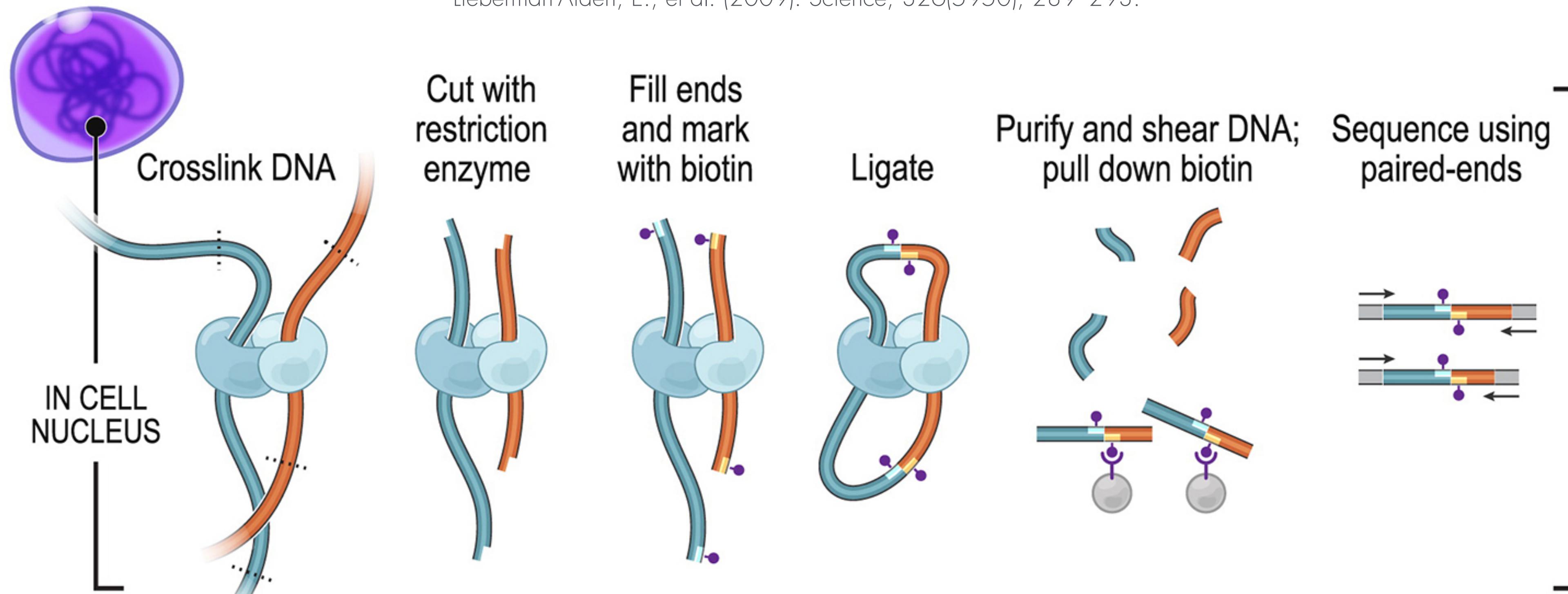
### Compartment-dependent chromatin interaction dynamics revealed by liquid chromatin Hi-C

Houda Belaghzal<sup>1</sup>, Tyler Borrman<sup>2</sup>, Andrew D. Stephens<sup>3</sup>, Denis L. Lafontaine<sup>1</sup>, Sergey V. Veney<sup>1</sup>, Zhiping Weng<sup>3</sup>, John F. Marko<sup>3,4</sup>, Job Dekker<sup>1,5,6#</sup>

# Chromosome Conformation Capture

Dekker, J., Rippe, K., Dekker, M., & Kleckner, N. (2002). Science, 295(5558), 1306–1311.

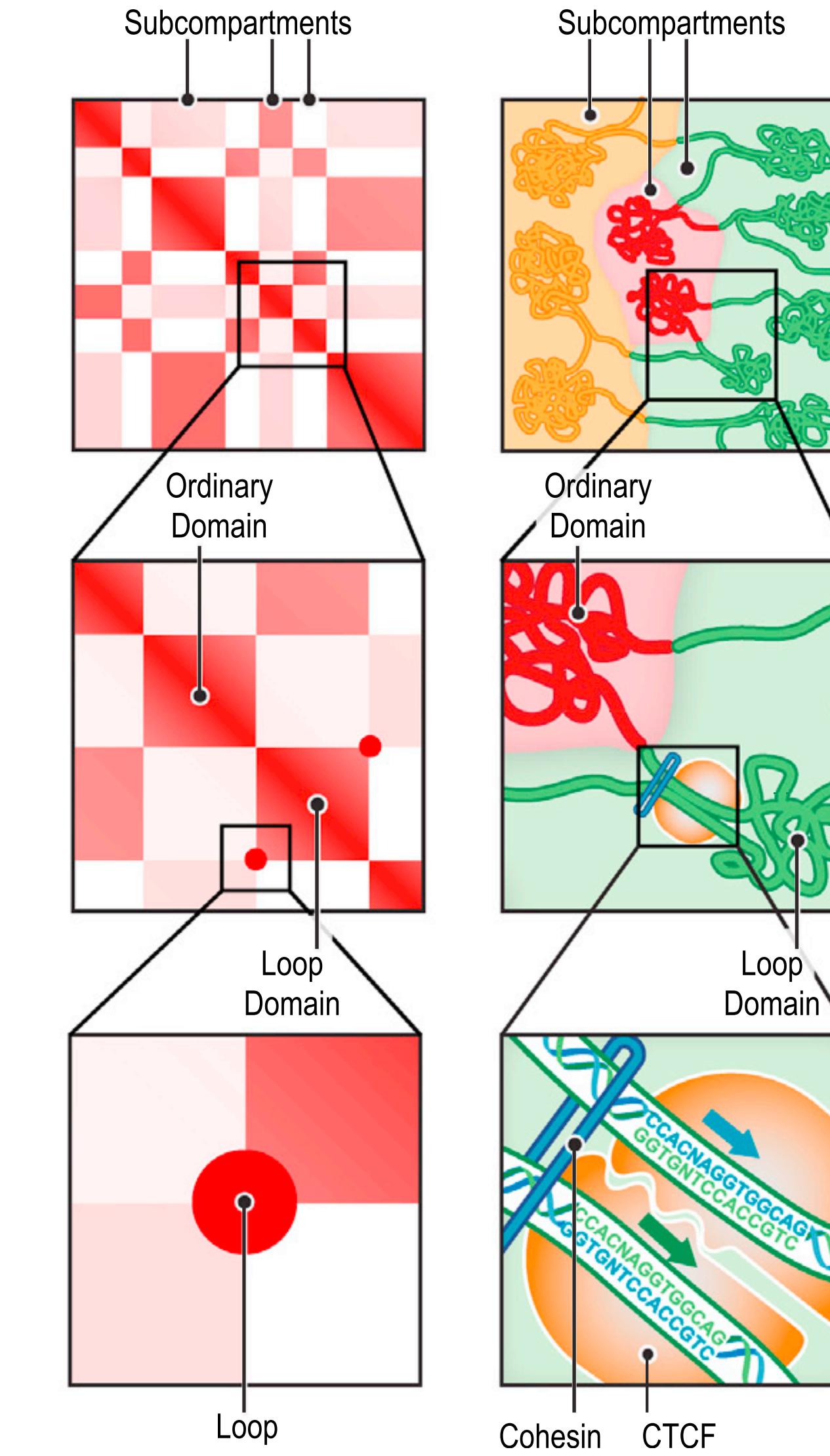
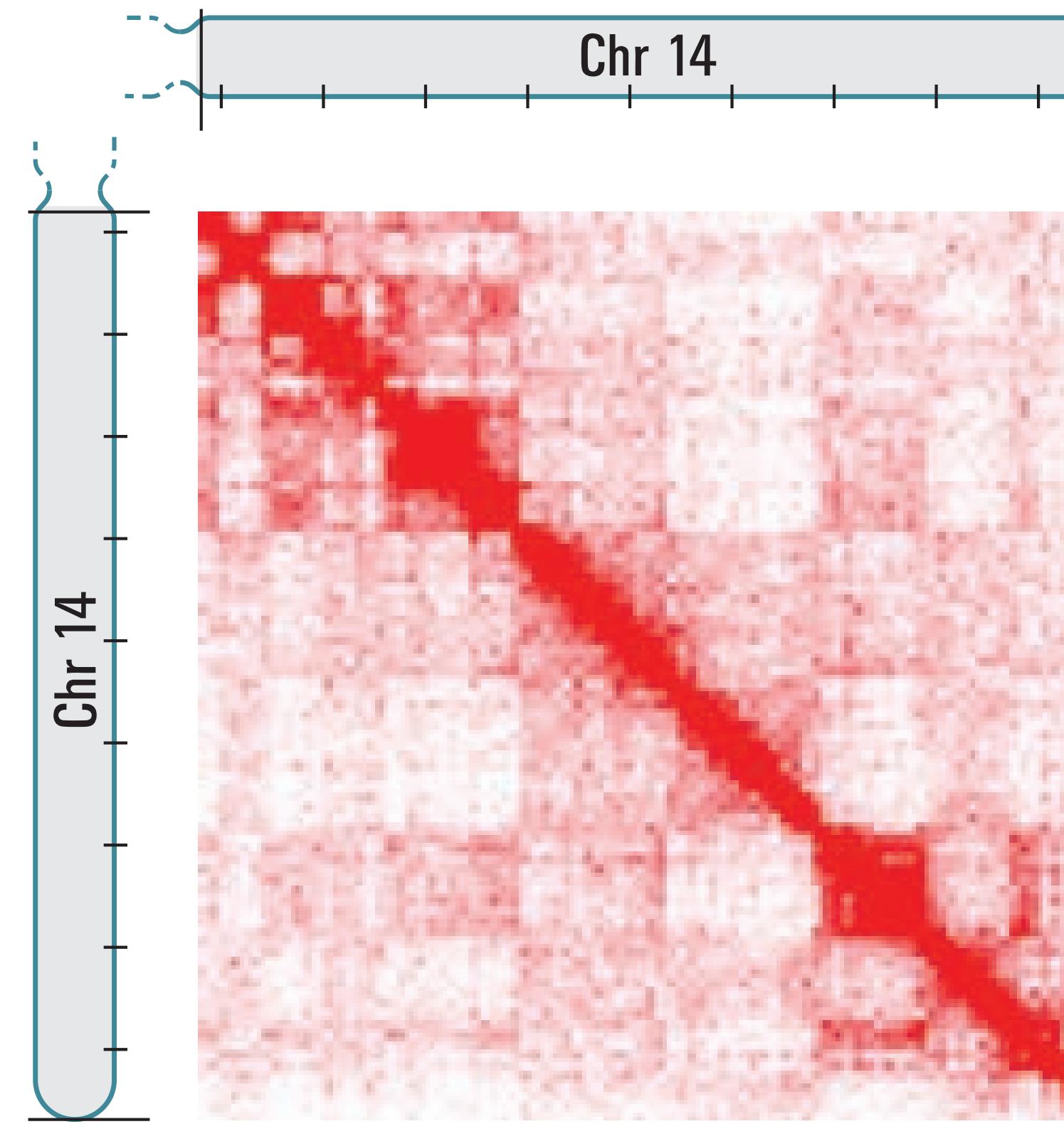
Lieberman-Aiden, E., et al. (2009). Science, 326(5950), 289–293.



# Hierarchical genome organisation

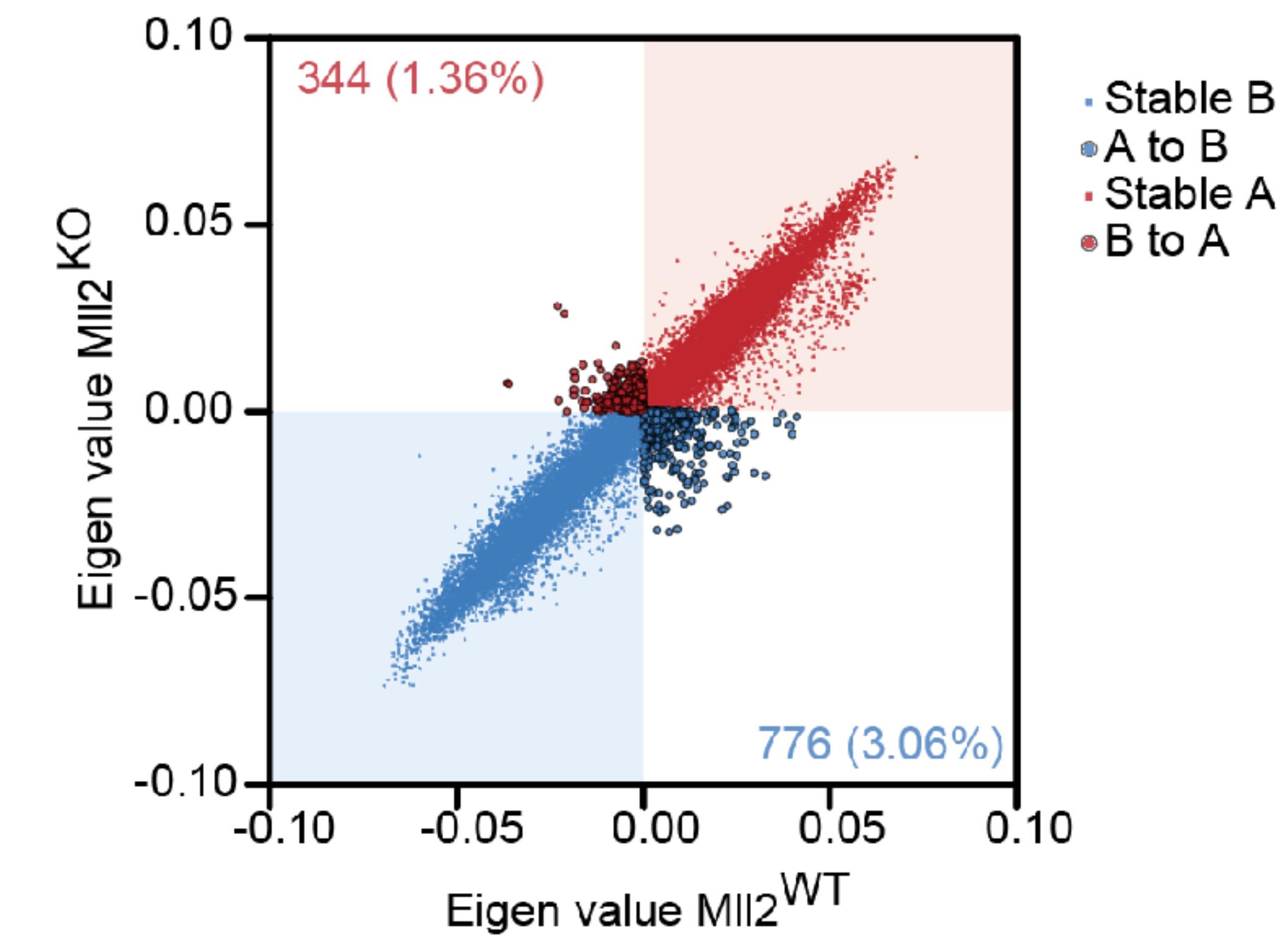
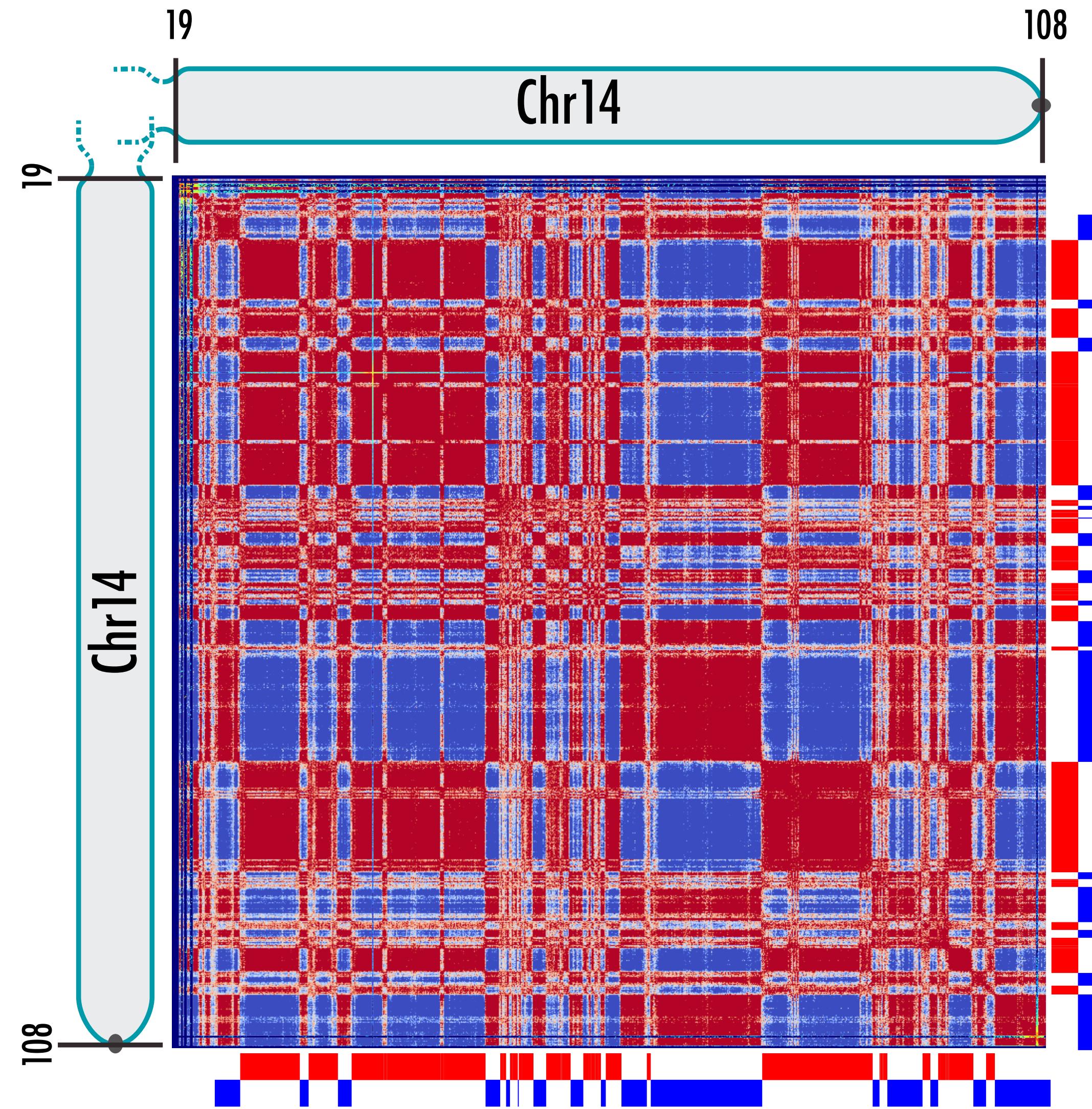
Lieberman-Aiden, E., et al. (2009). Science, 326(5950), 289–293.

Rao, S. S. P., et al. (2014). Cell, 1–29.



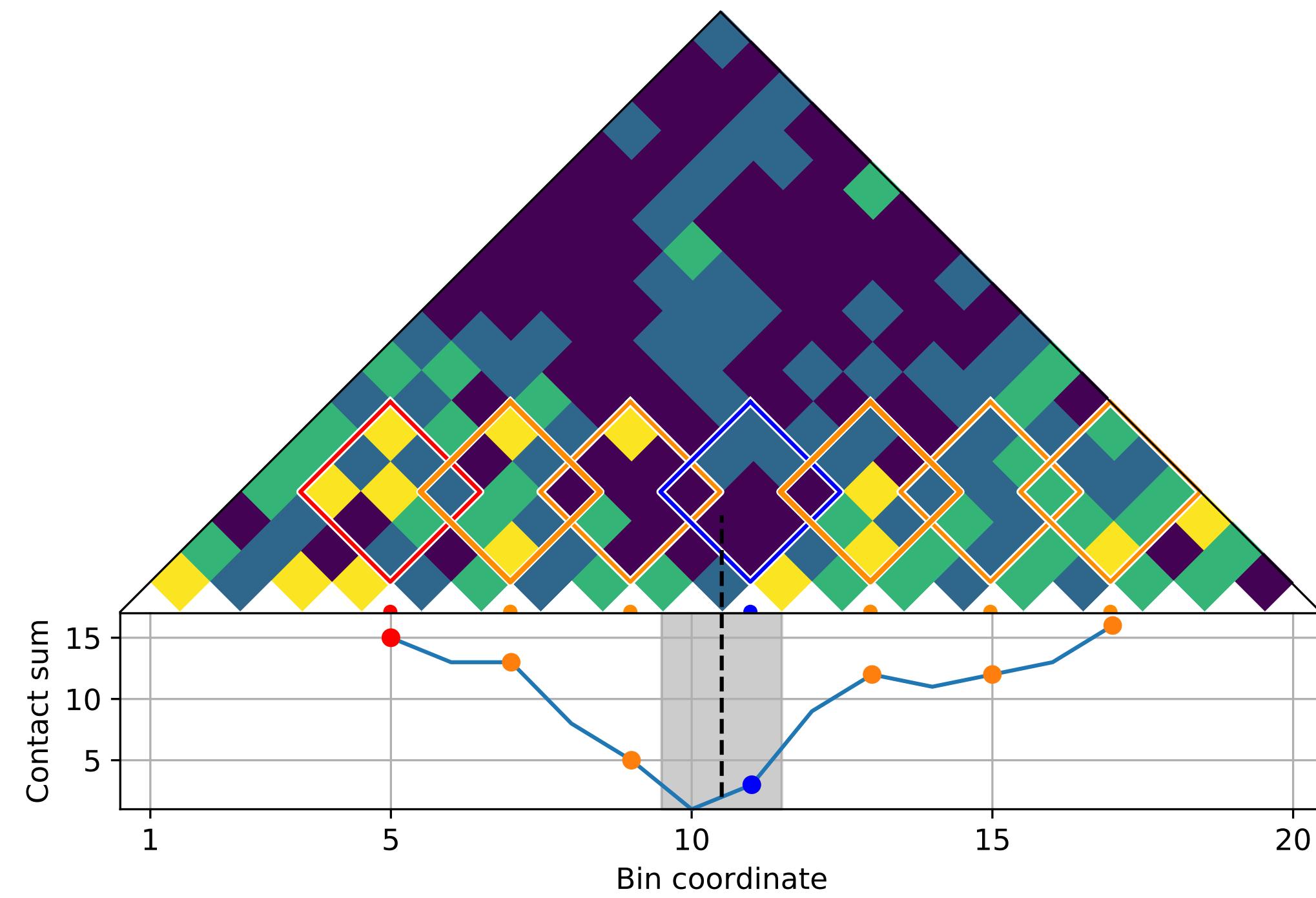
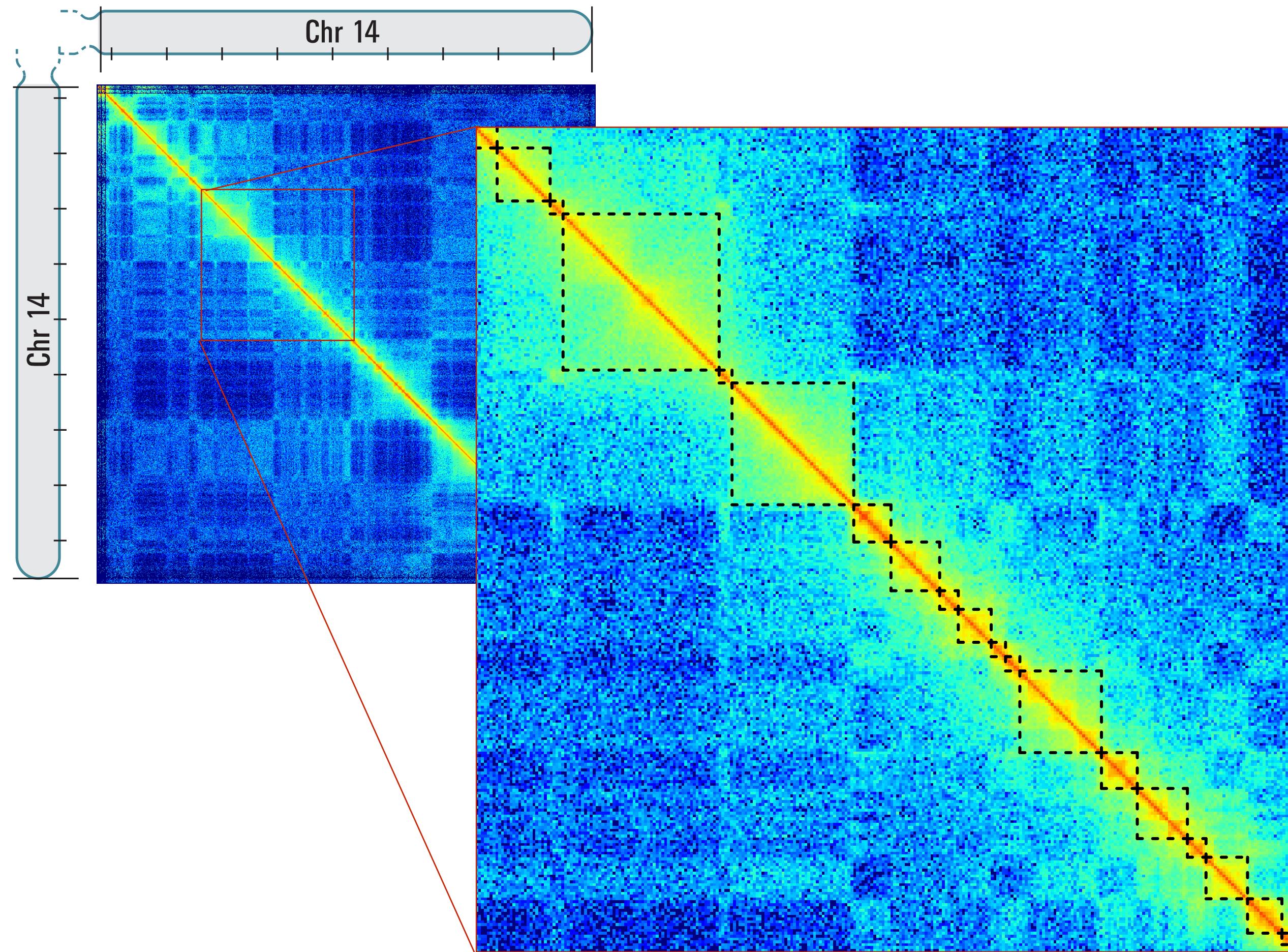
# A/B Compartiment

# Chromosome 14



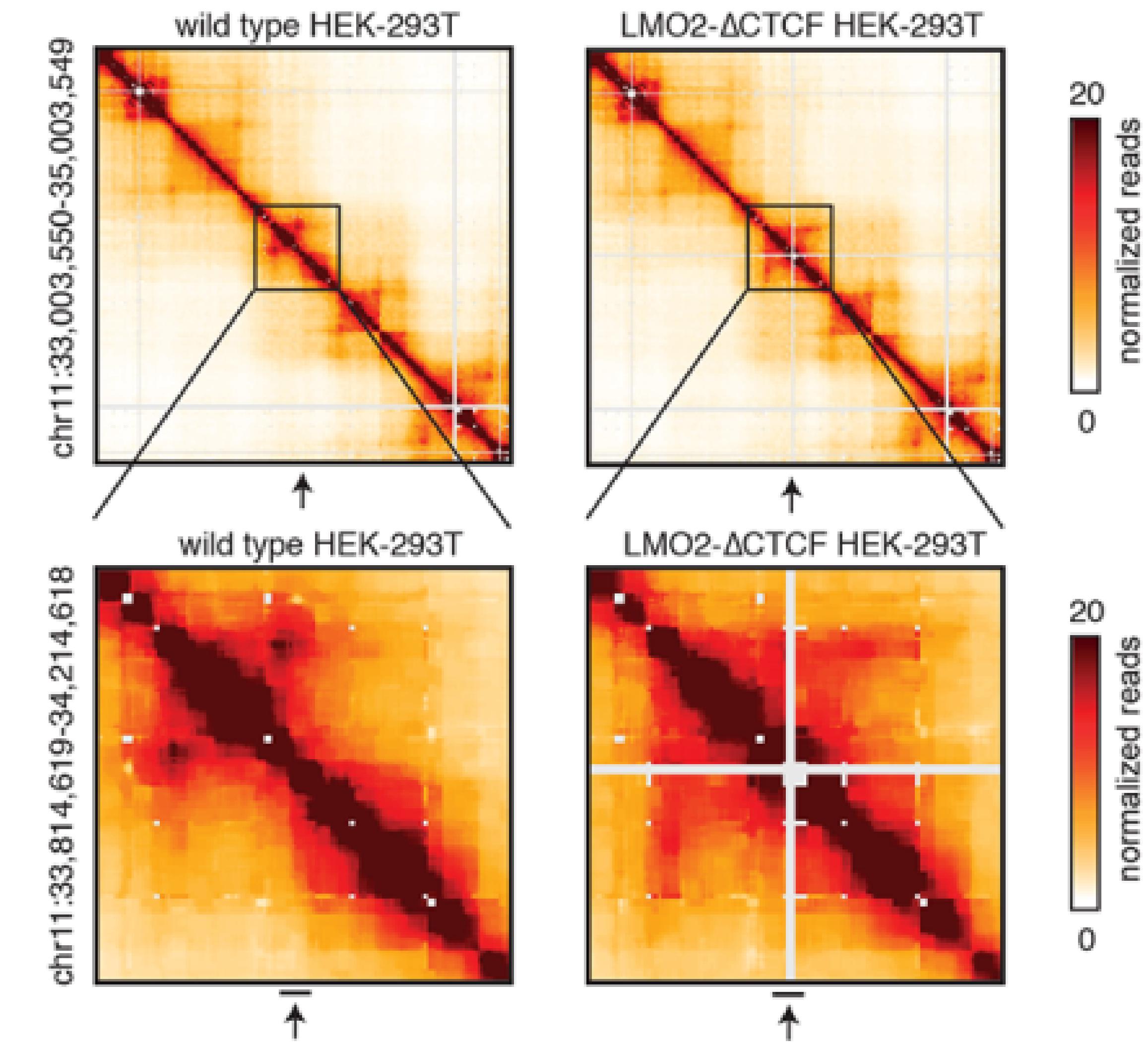
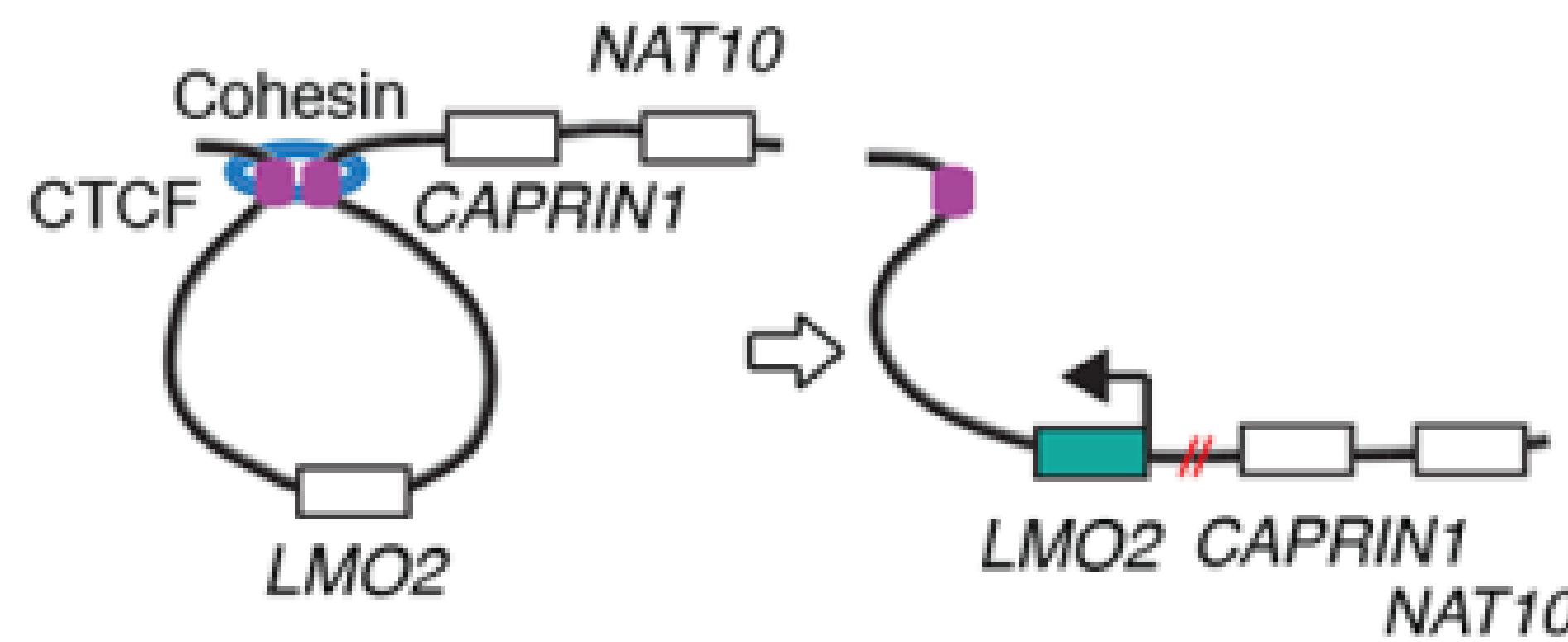
# TADs

## Chromosome 14



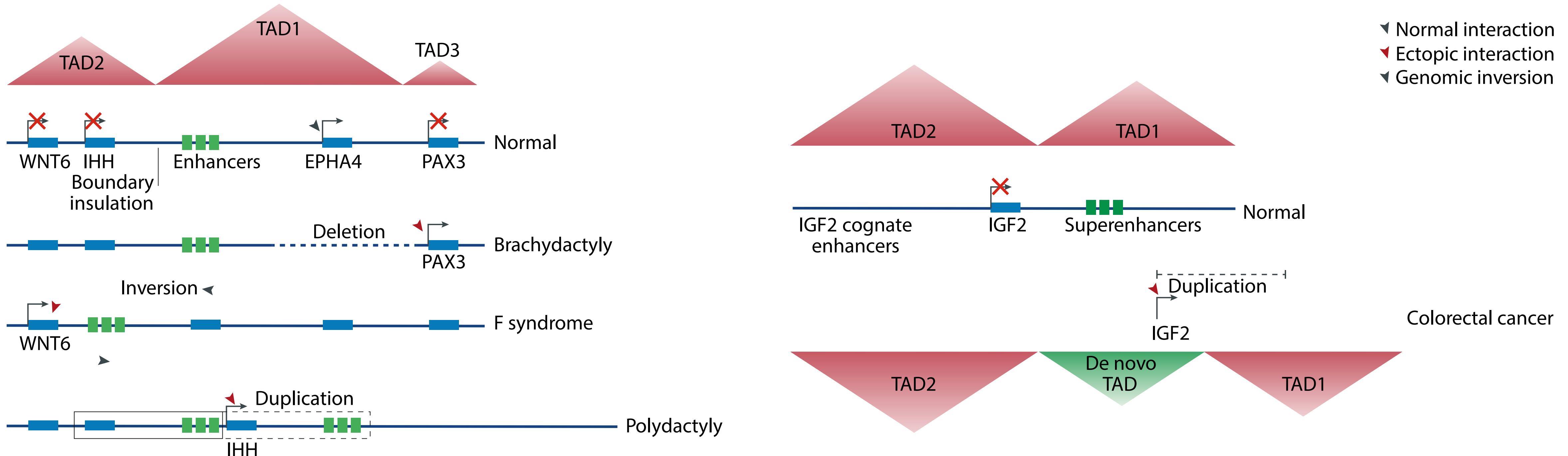
# TADs are functional units

Hnisz, D., et al. (2016). Science



# TADs are functional units

Figure adapted from Hui Zheng and Wei Xie. *Nature Reviews Molecular Cell Biology* (2019)

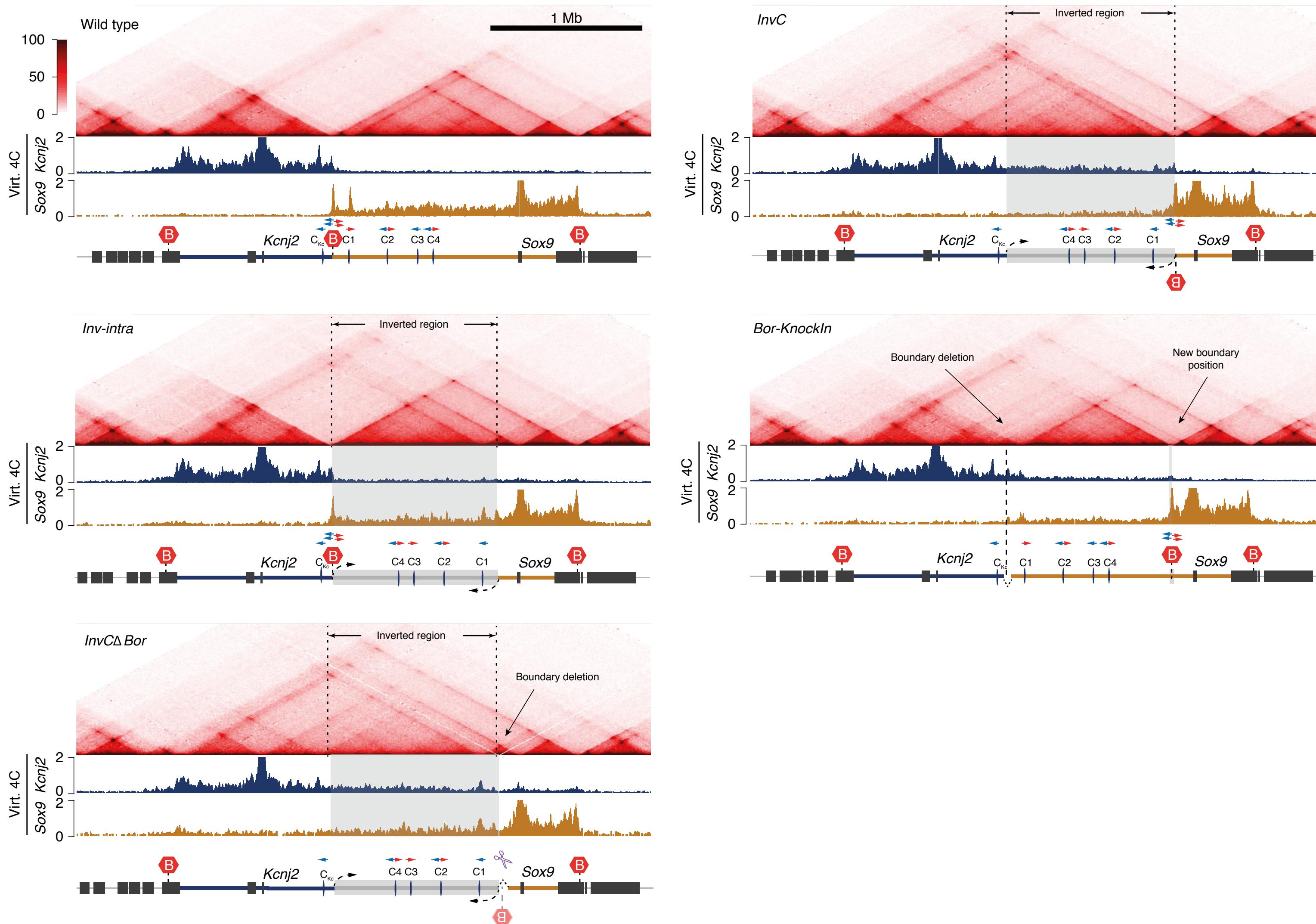


Lupianez, D. G. et al. *Cell* 161, 1012–1025 (2015)

Flavahan, W. A. et al. *Nature* 529, 110–114 (2016).

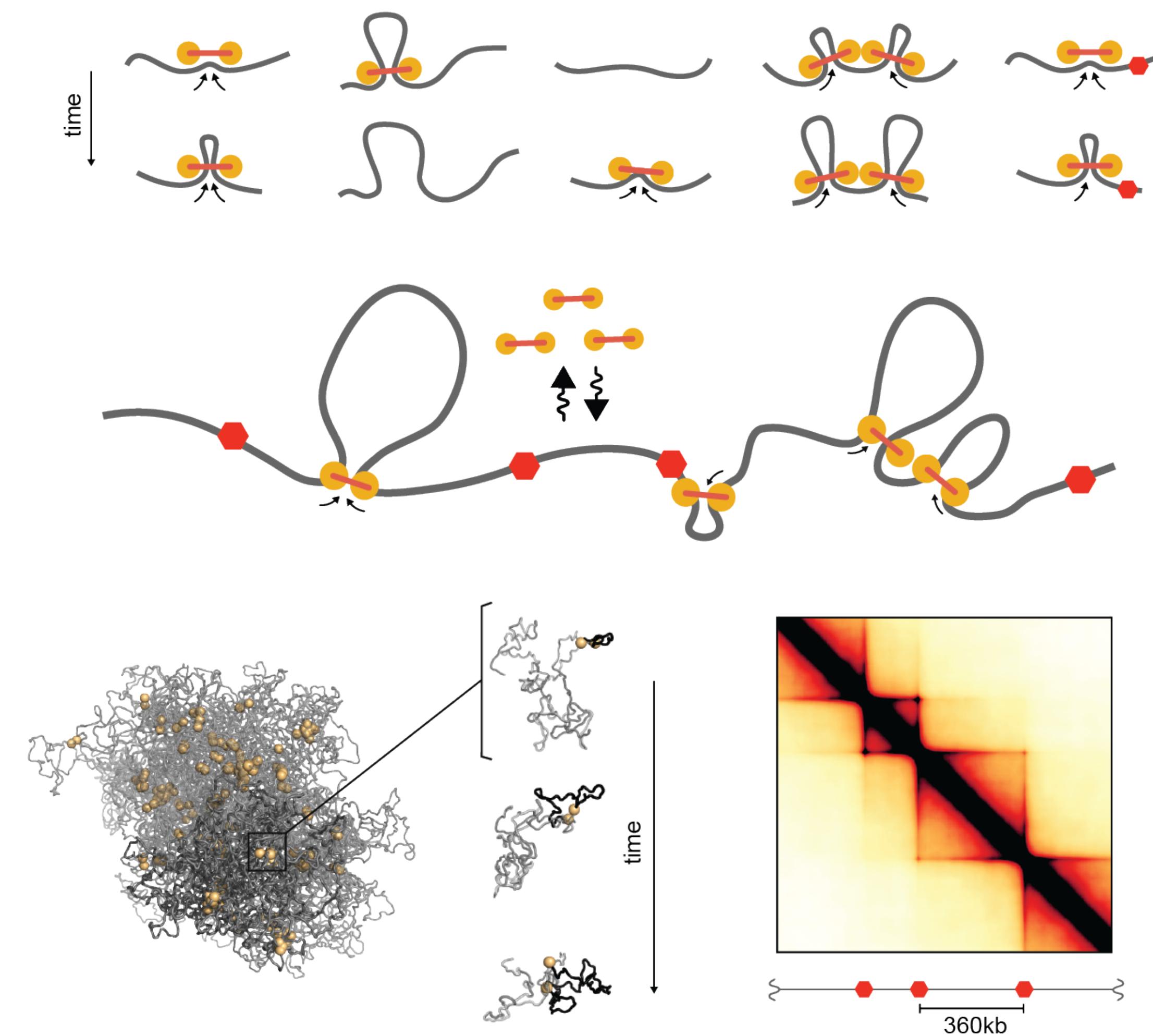
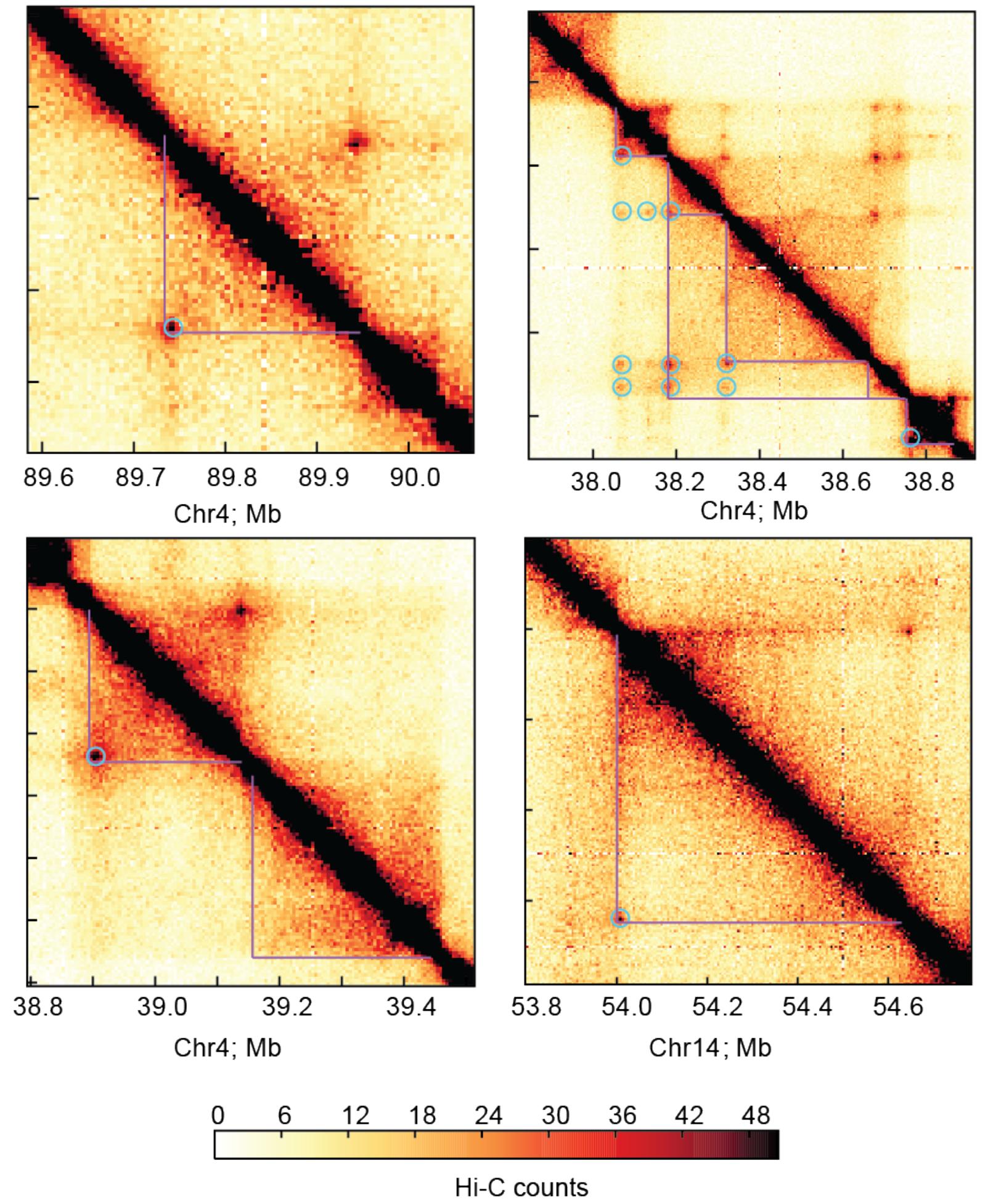
# TADs are functional units

Despang, et al. (2019). Nature Genetics 51, 1263–1271 (2019)



# Loop-extrusion as a TAD forming mechanism

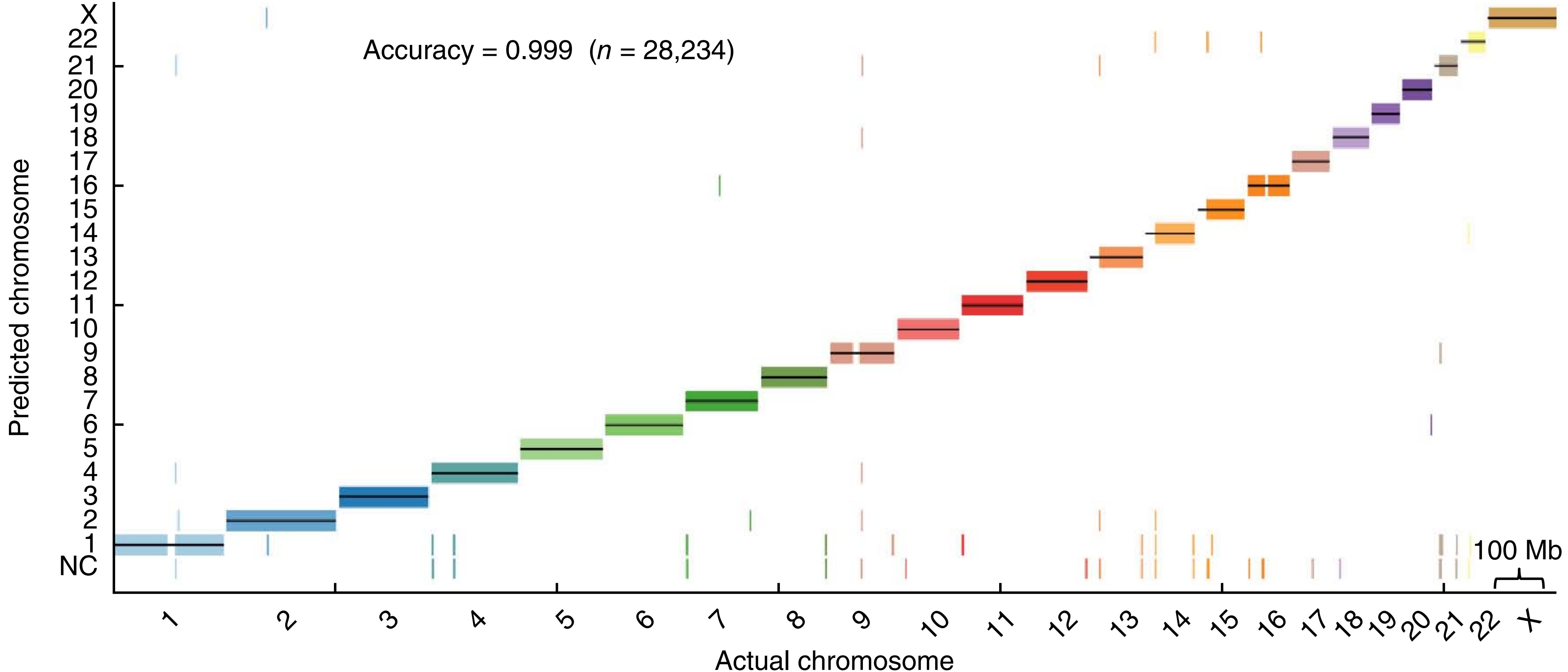
Fudenberg, G., Imakaev, M., Lu, C., Goloborodko, A., Abdennur, N., & Mirny, L. A. (2018).  
Cold Spring Harb Symp Quant Biol 2017. 82: 45-55



**SIDE EFFECTS**

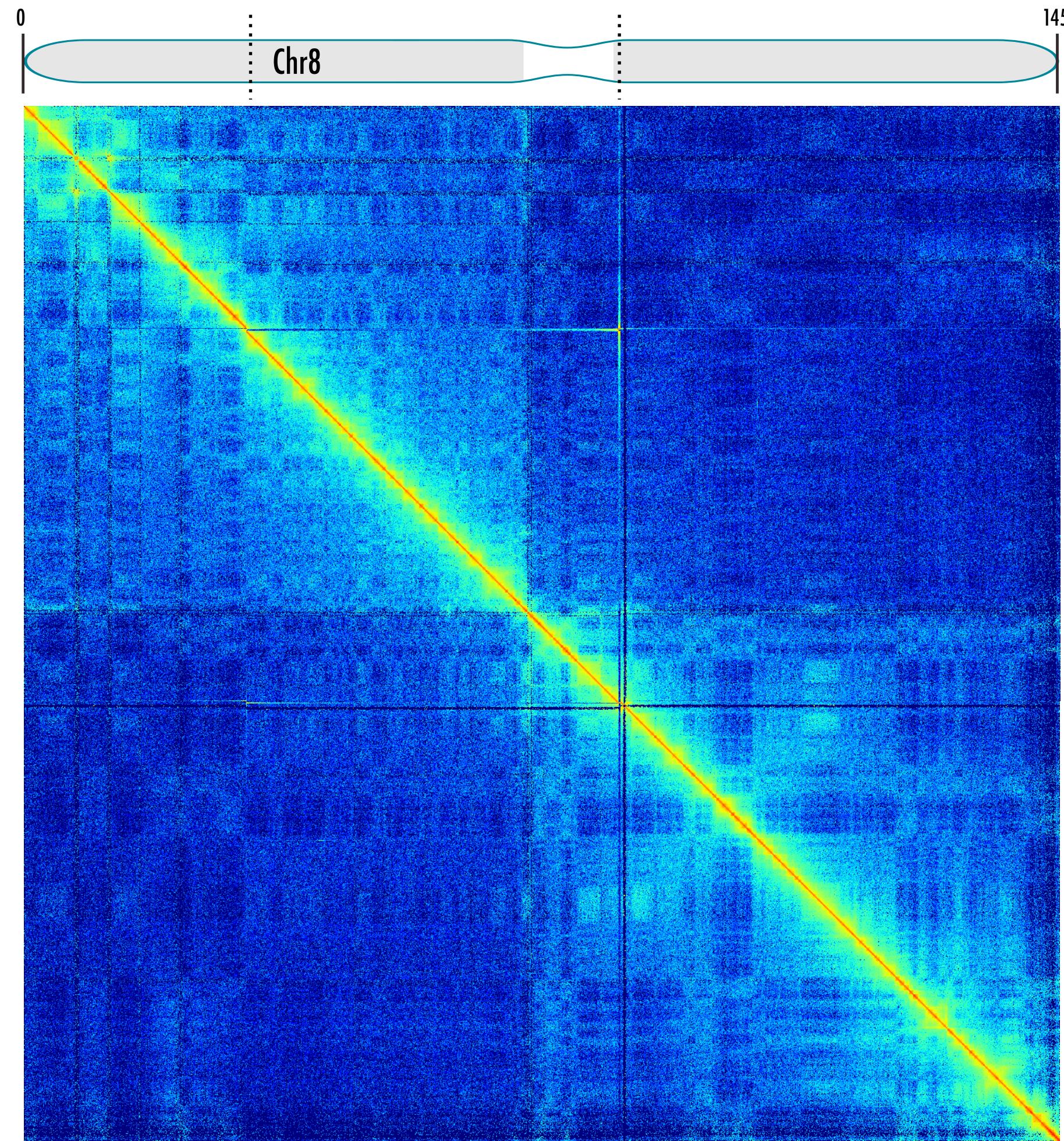
# Hi-C for de-novo assembly

Kaplan, N., & Dekker, J. (2013). Nature Biotechnology, 31(12), 1143–1147.

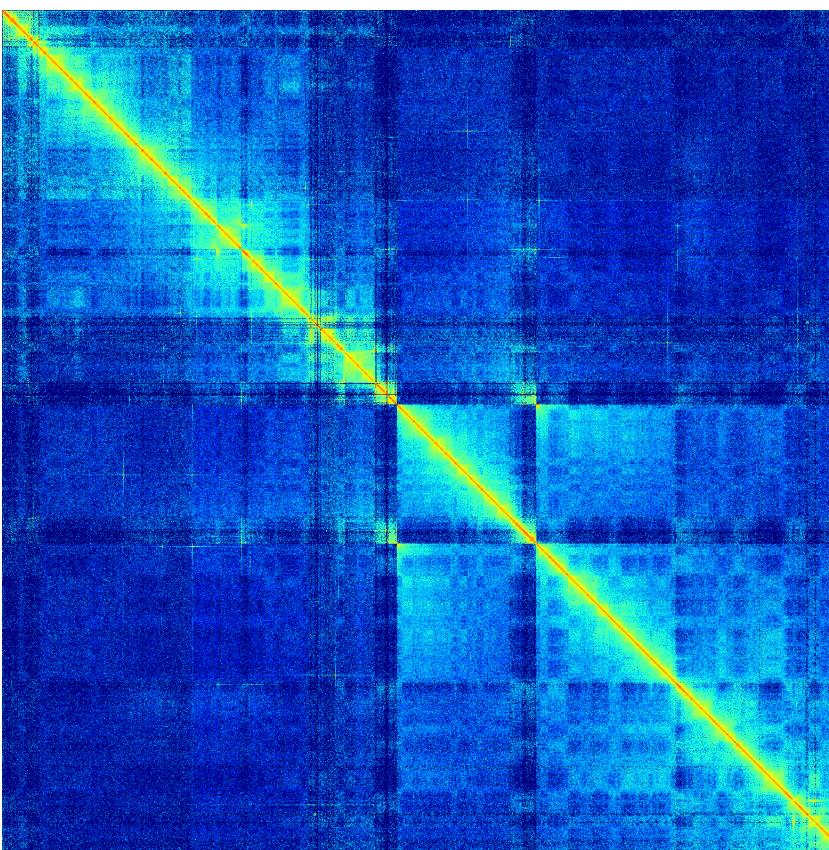


# Assembly error detection

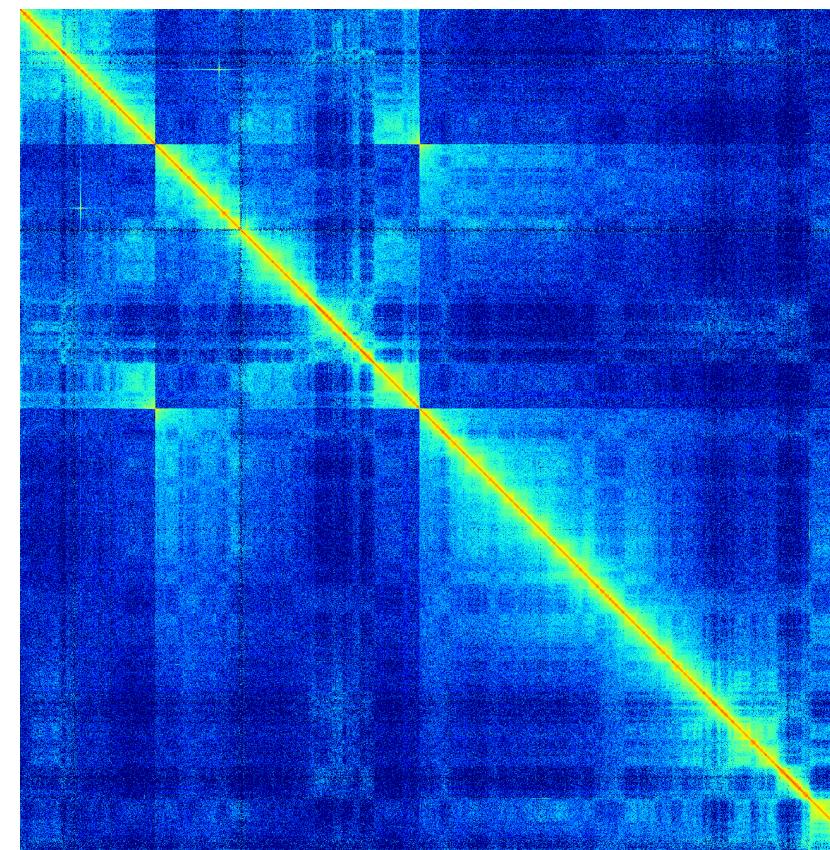
Chromosome 8 Gorilla



Chr 7



Chr 12

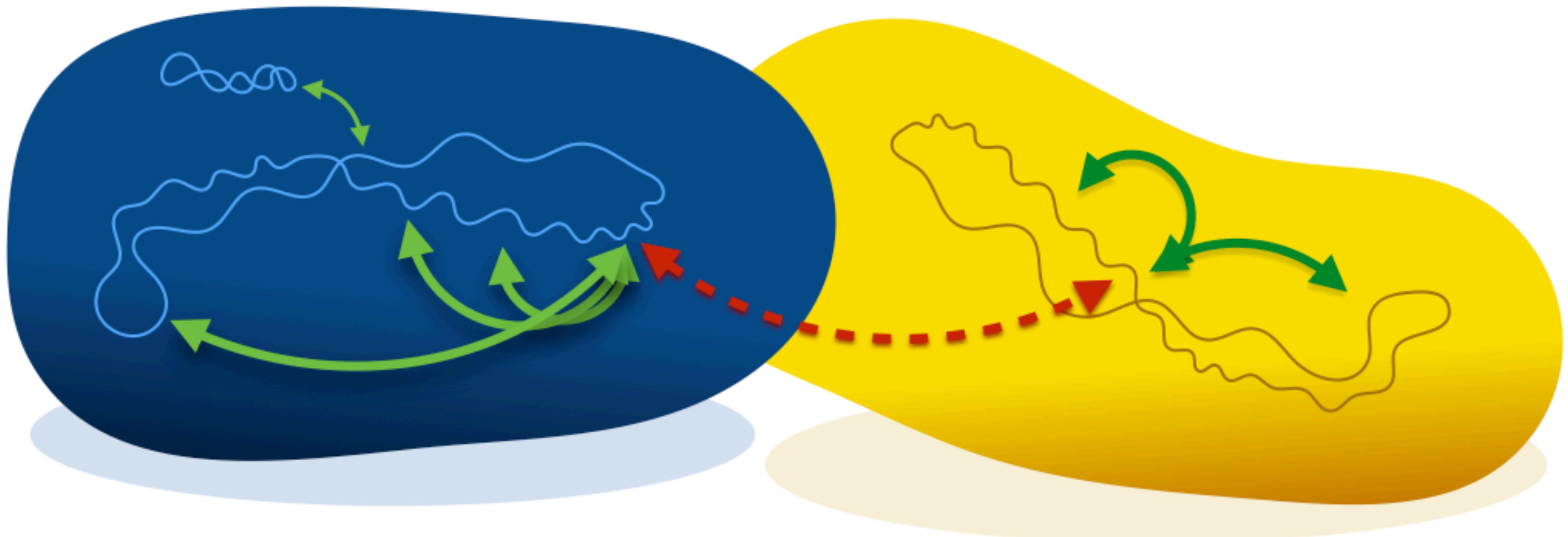


GGO8 has an inversion of the region corresponding to HSA8:30.0-86.9Mb  
Aylwyn Scally (Department of Genetics, University of Cambridge)

# Hi-C for meta genomics

Beitel, C. W., Froenicke, L., Lang, J. M., Korf, I. F., Michelmore, R. W., Eisen, J. A., & Darling, A. E. (2014). Strain- and plasmid-level deconvolution of a synthetic metagenome by sequencing proximity ligation products. doi:10.7287/peerj.preprints.260v1

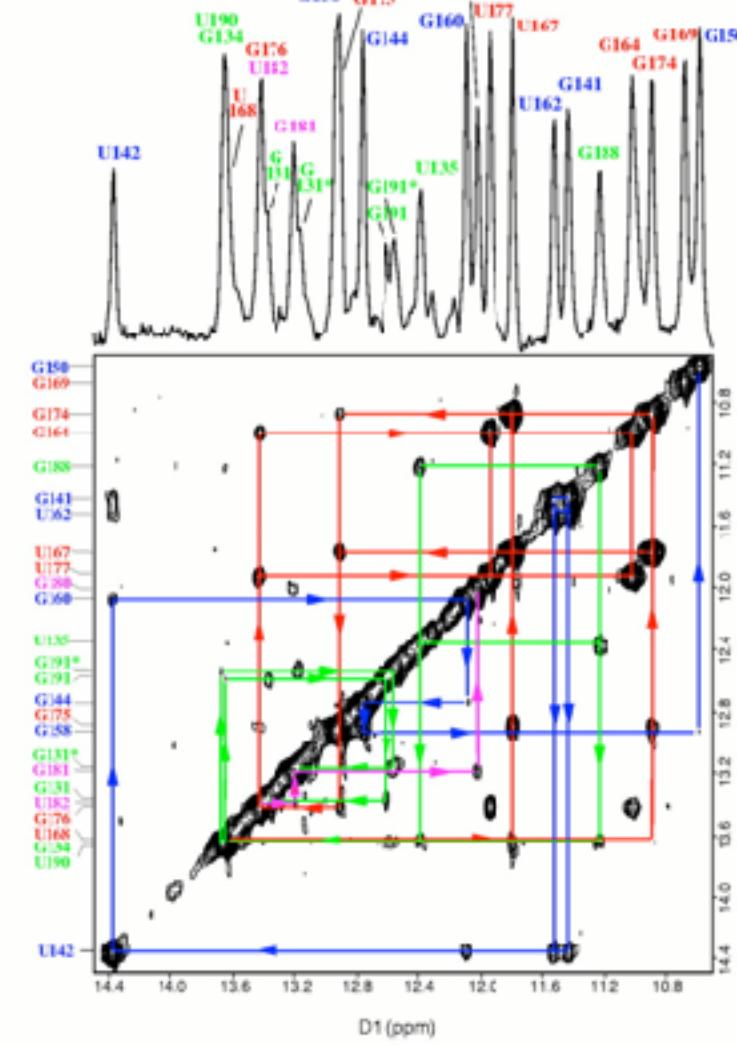
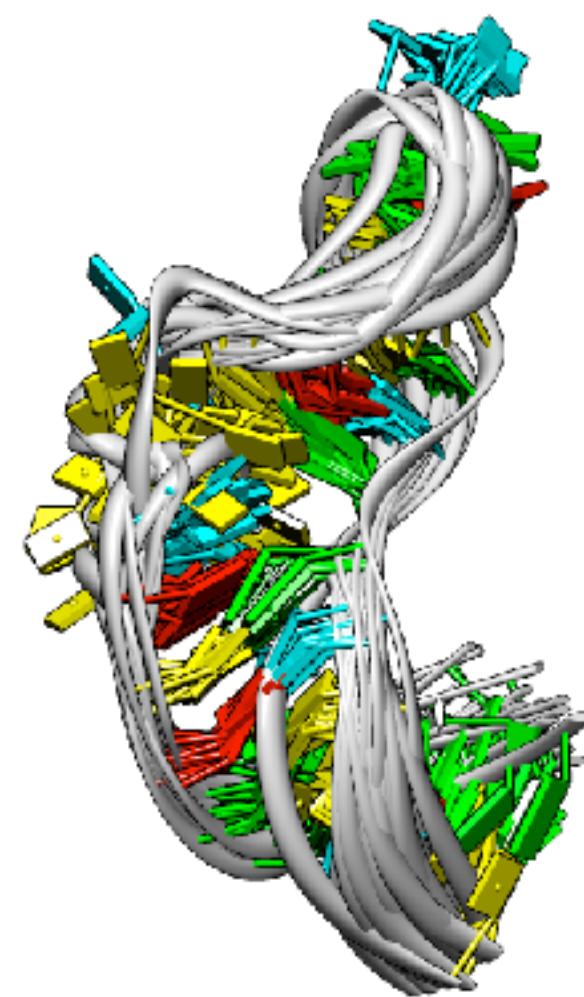
Romain Koszul





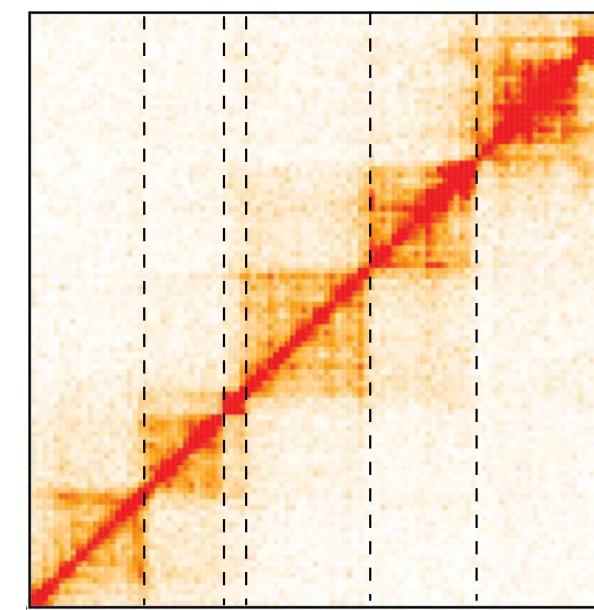
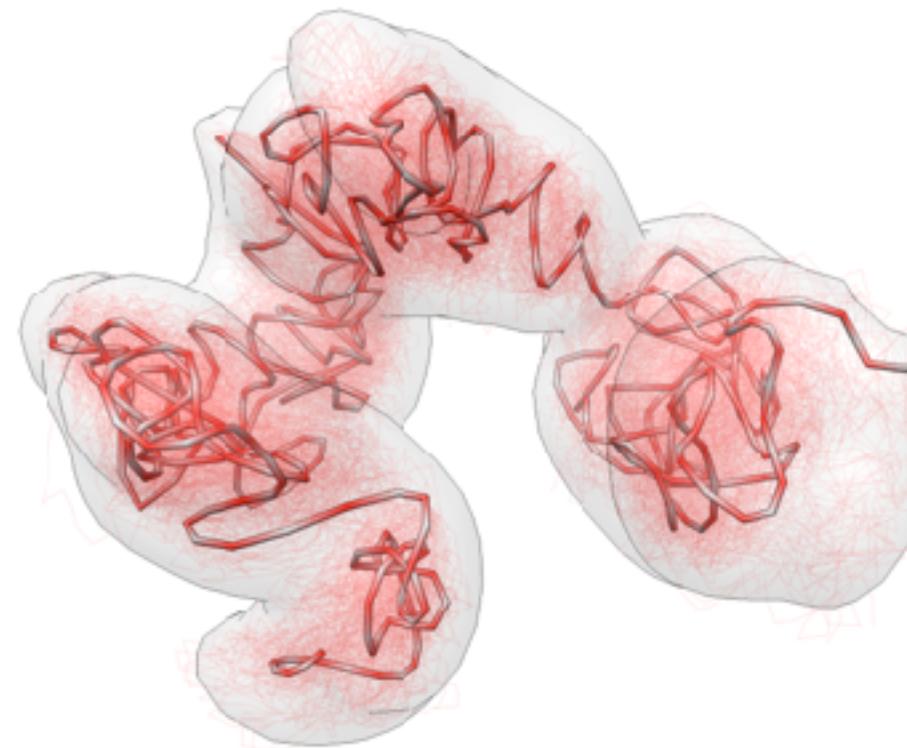
# Restraint-based Modeling

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



# Biomolecular structure determination

## 2D-NOESY data



# Chromosome structure determination 3C-based data

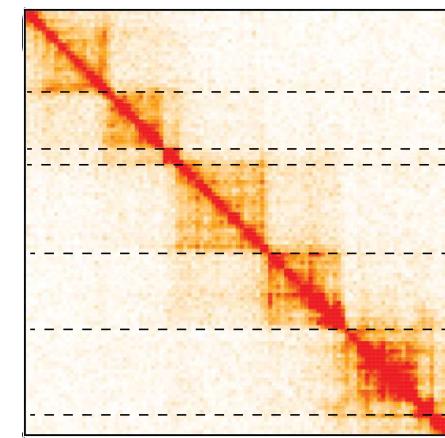


<http://3DGenomes.org>

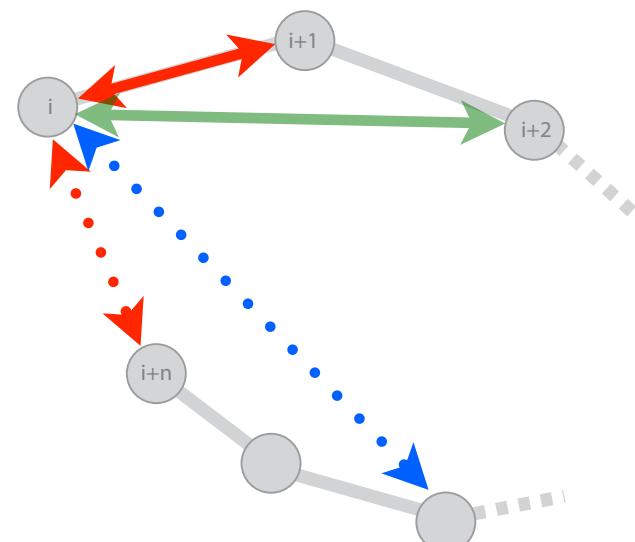
Serra, F., Baù, D. et al. PLOS CB (2017)



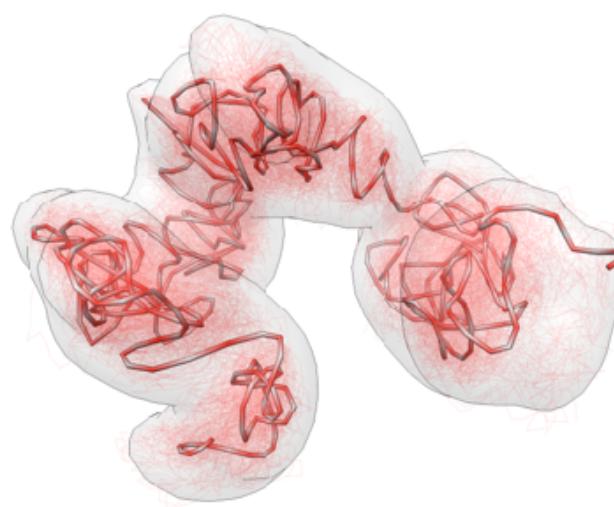
## FastQ files to Maps



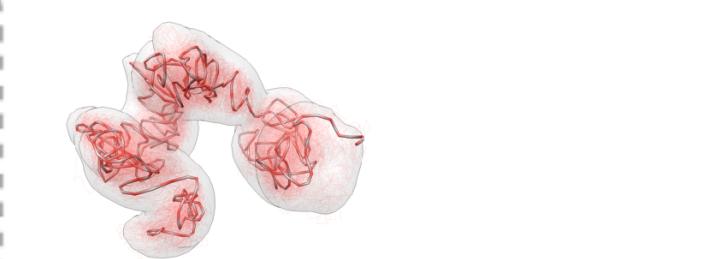
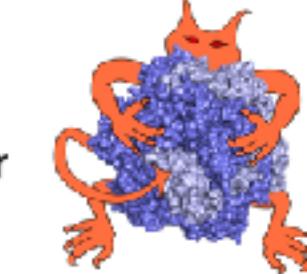
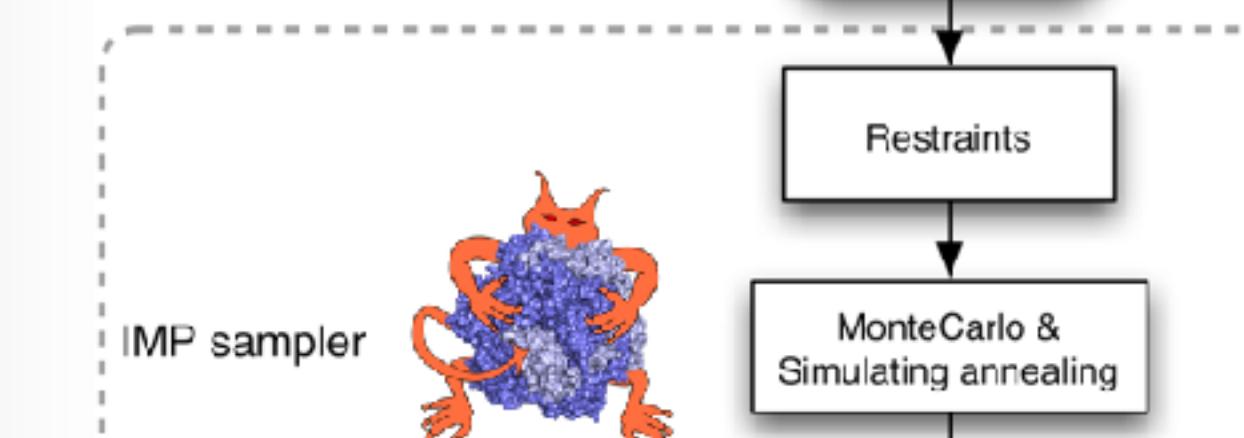
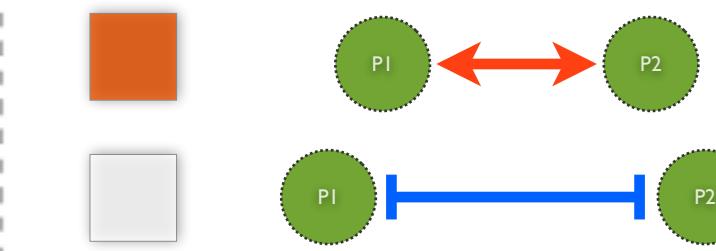
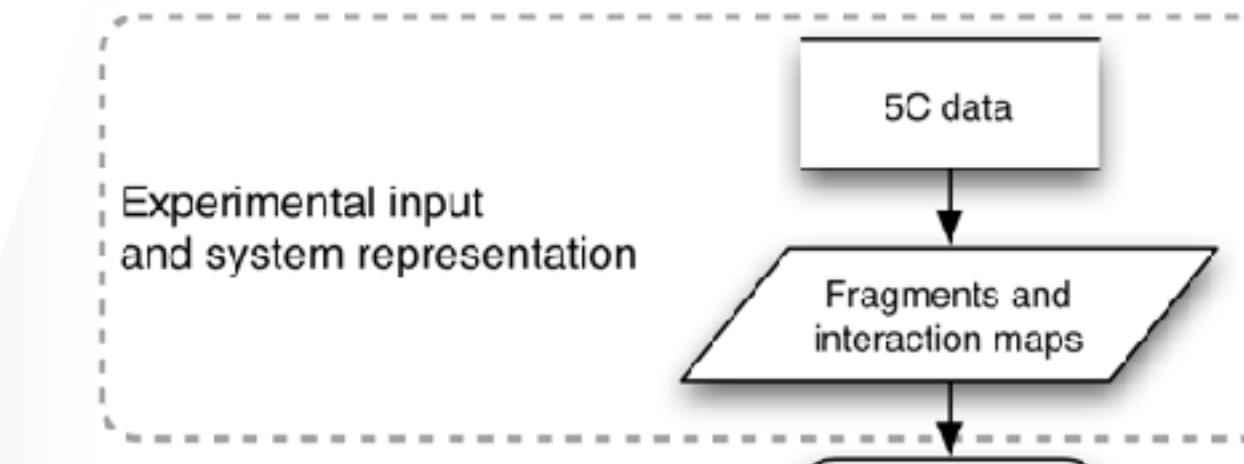
## Map analysis



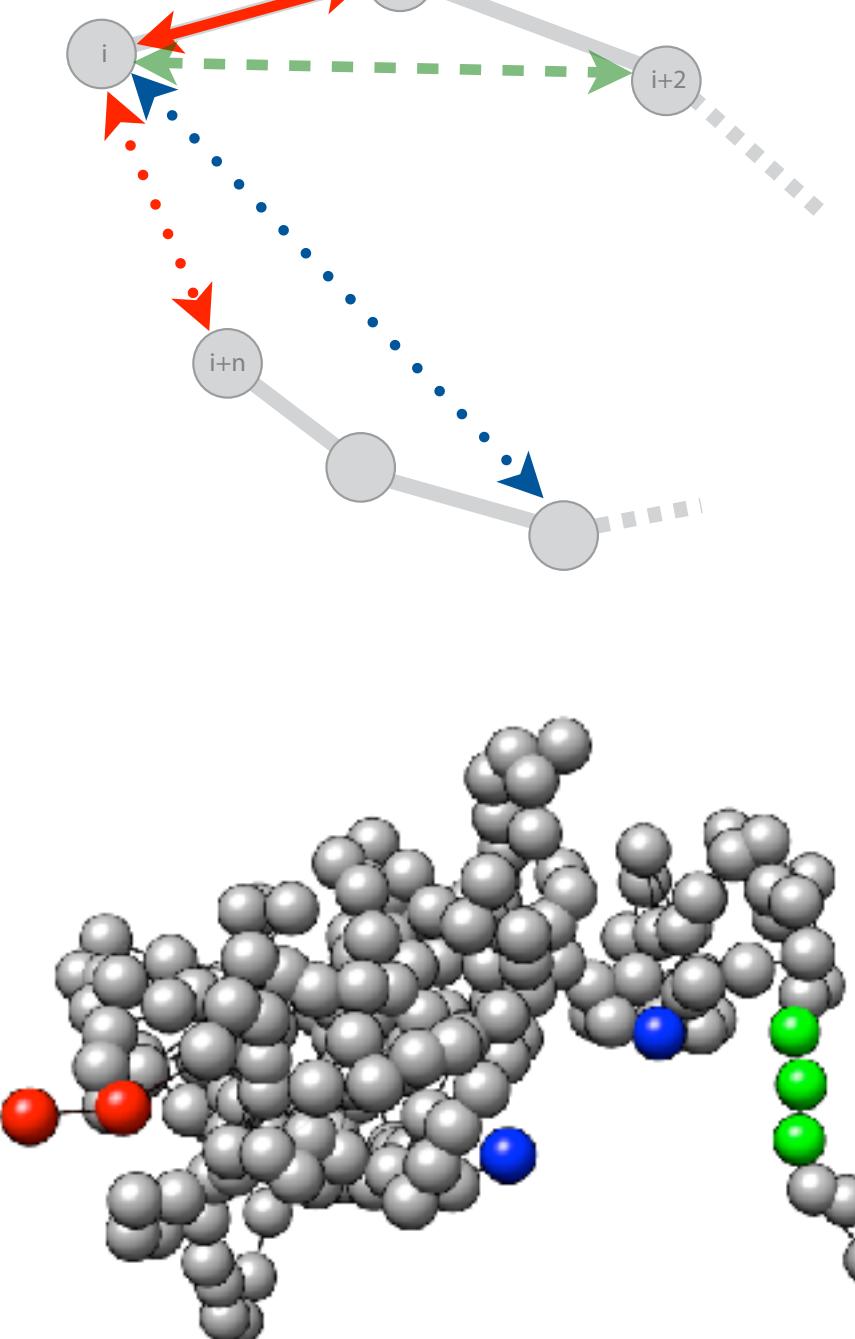
## Model building



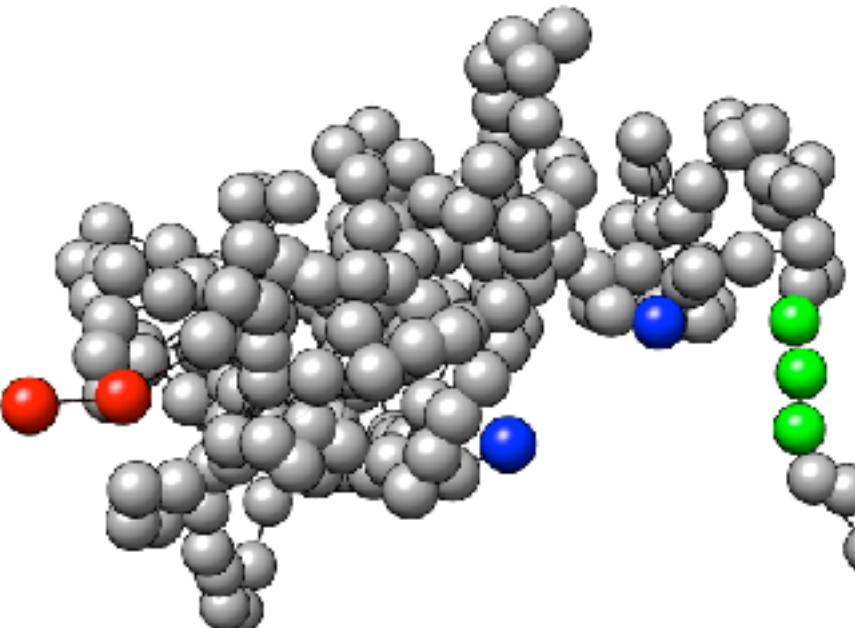
## Model analysis



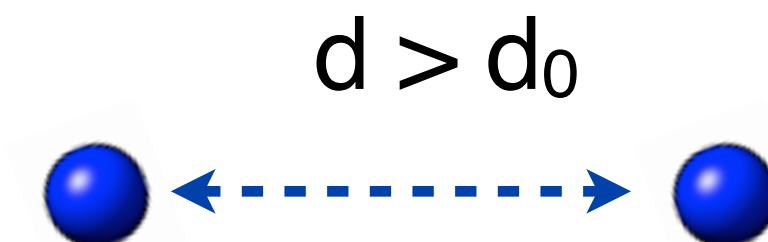
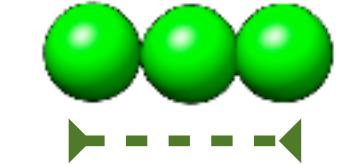
# Model representation and scoring



$$d = d_0$$

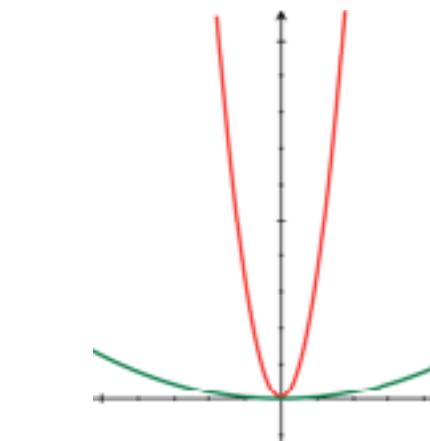


$$d < d_0$$



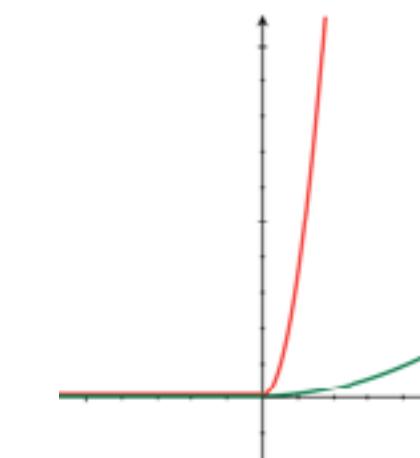
Harmonic

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



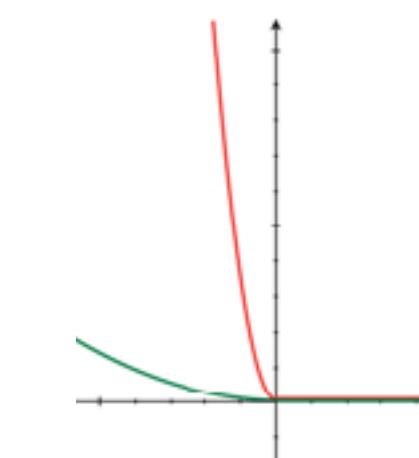
Harmonic Upper Bound

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

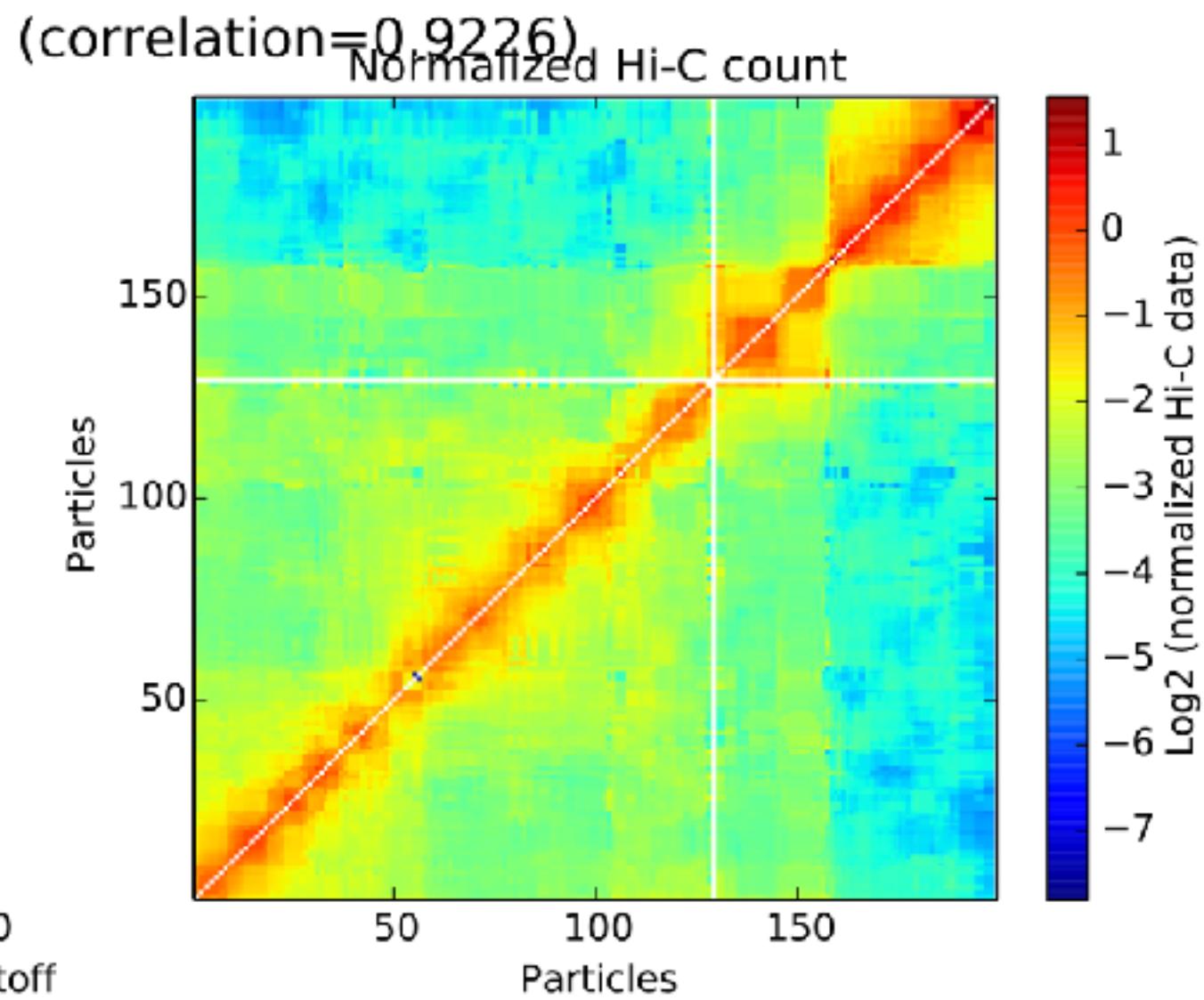
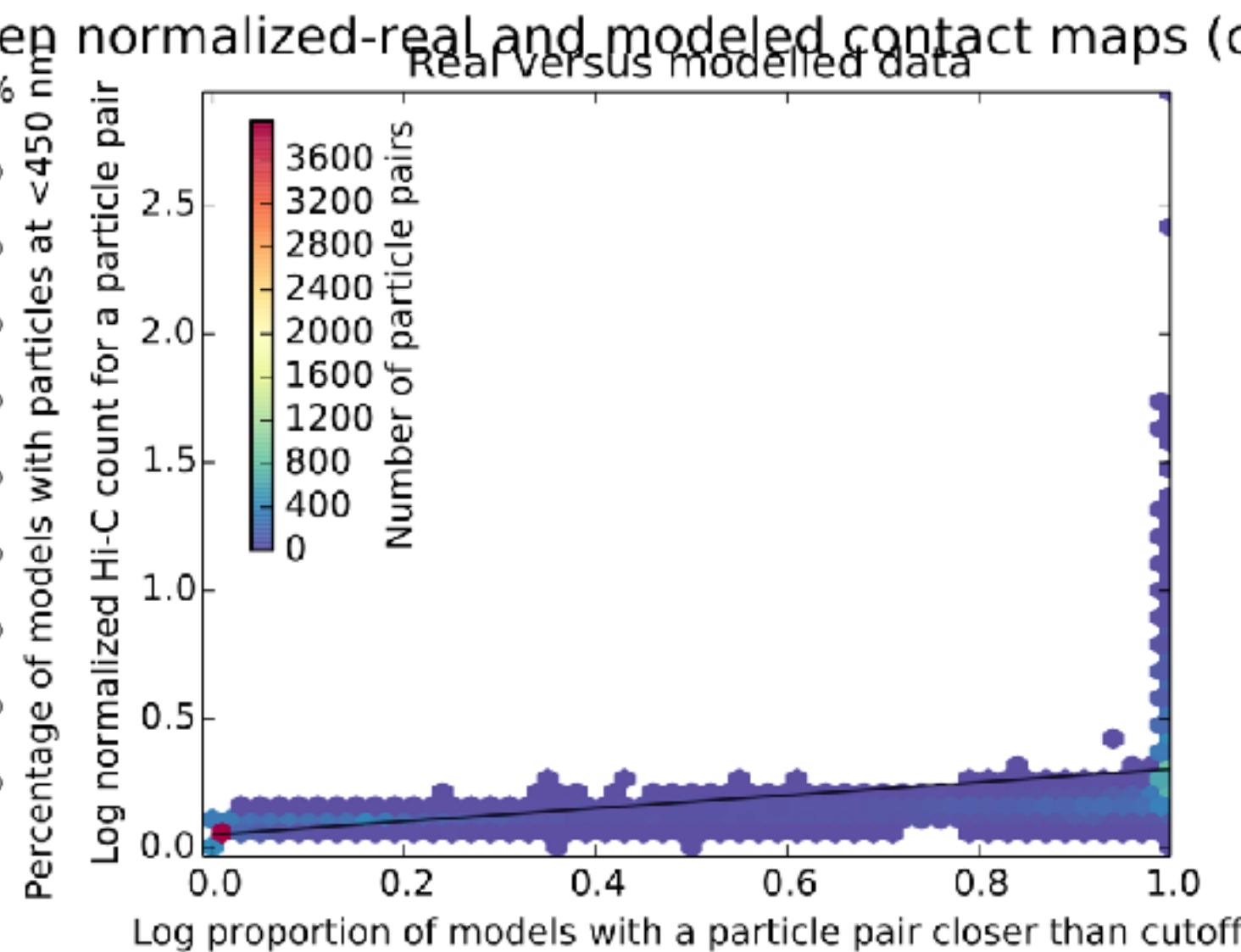
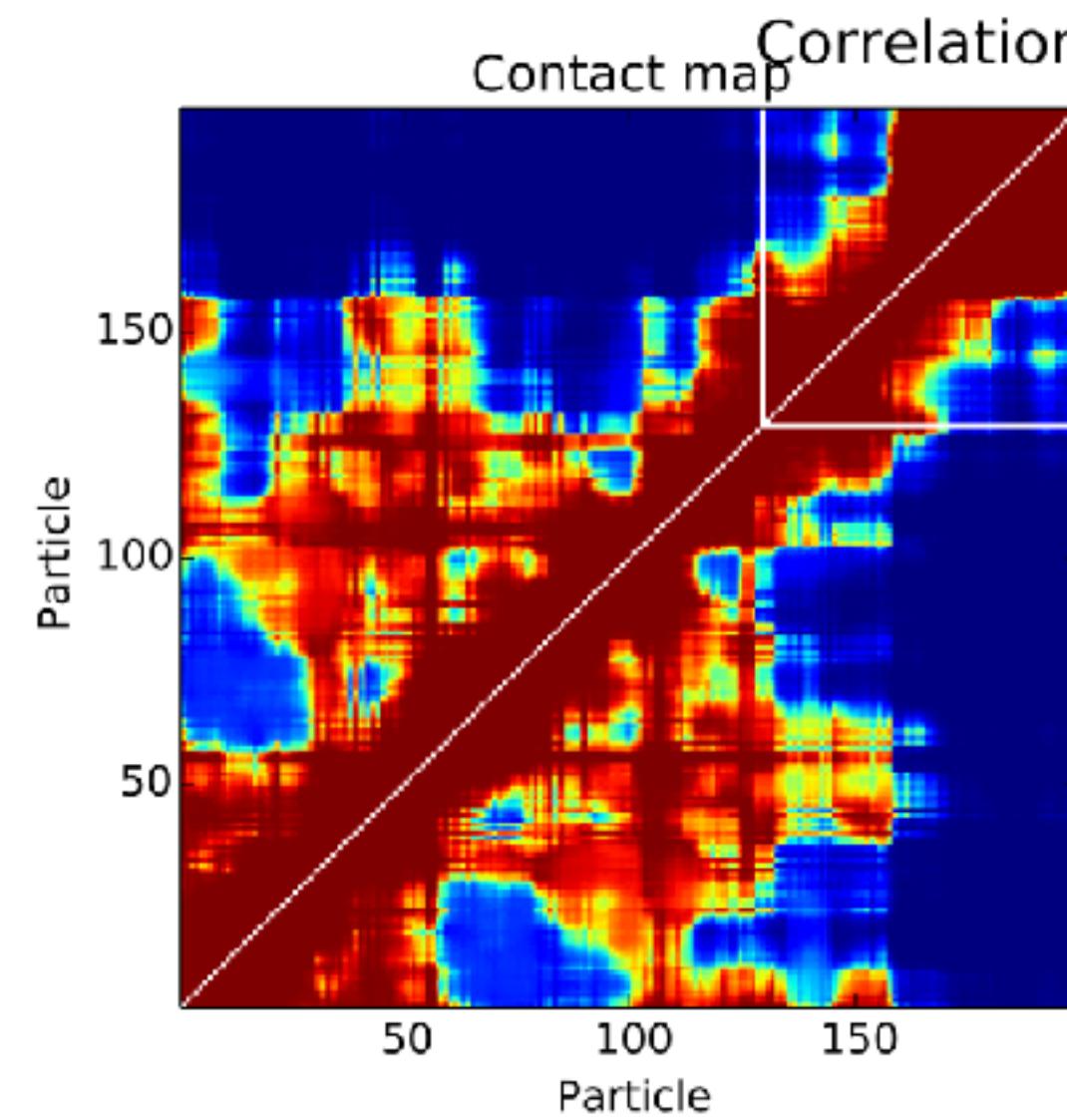
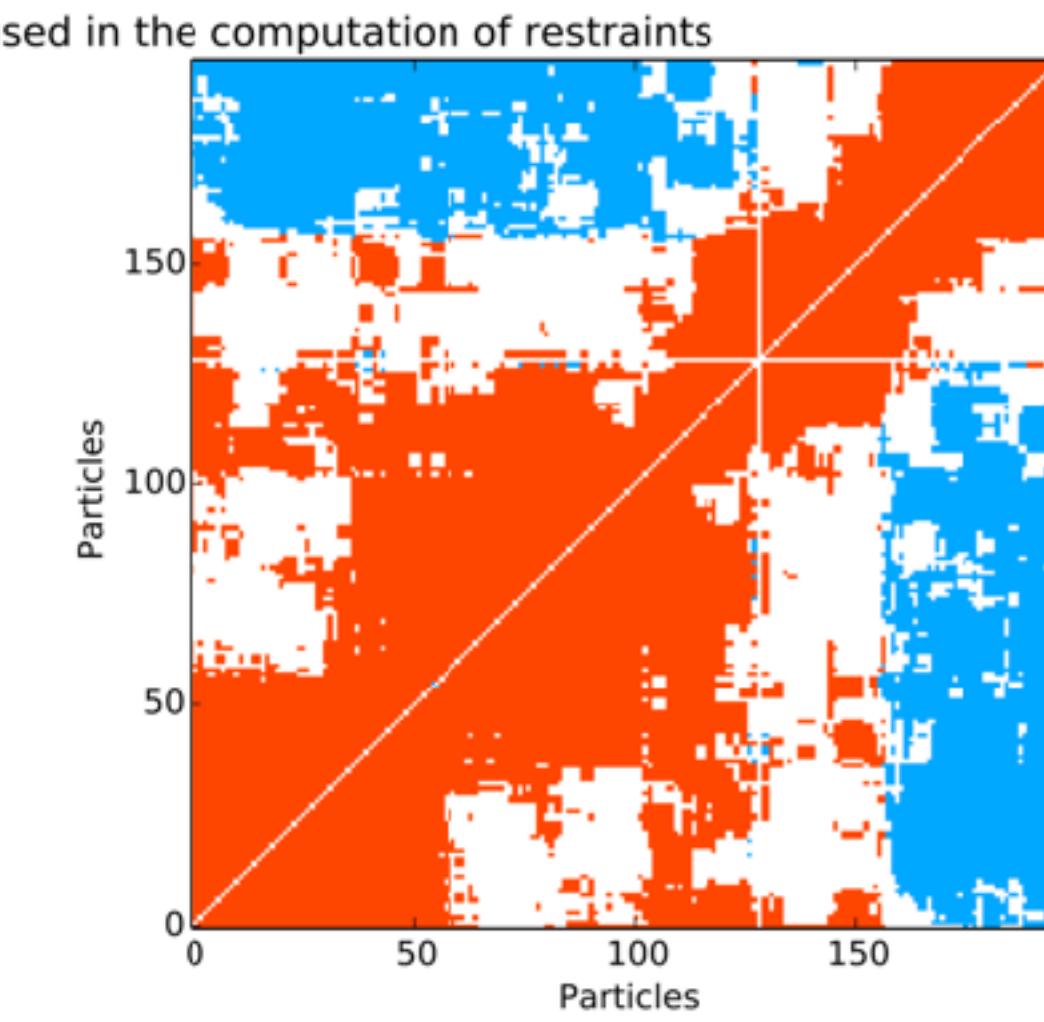
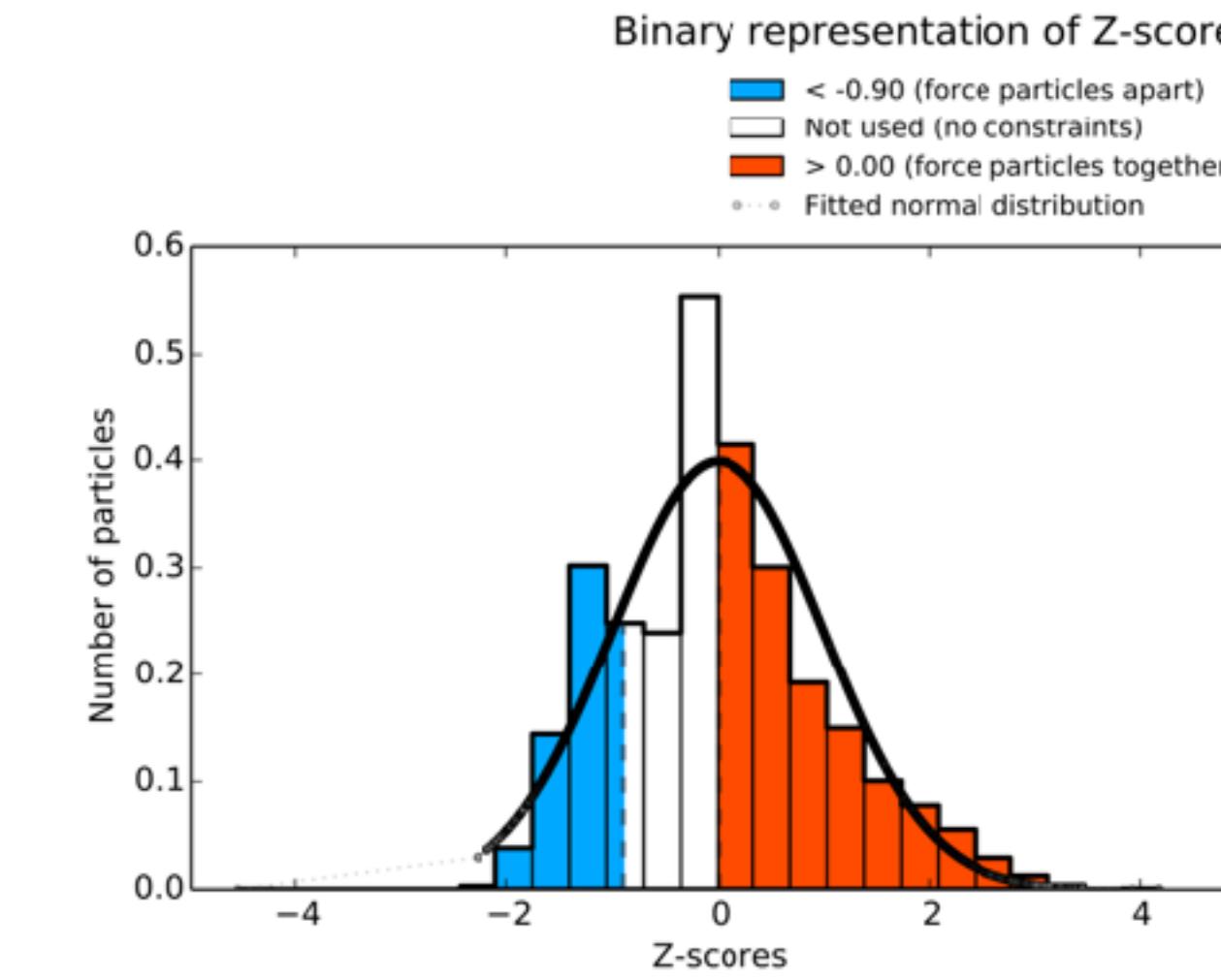
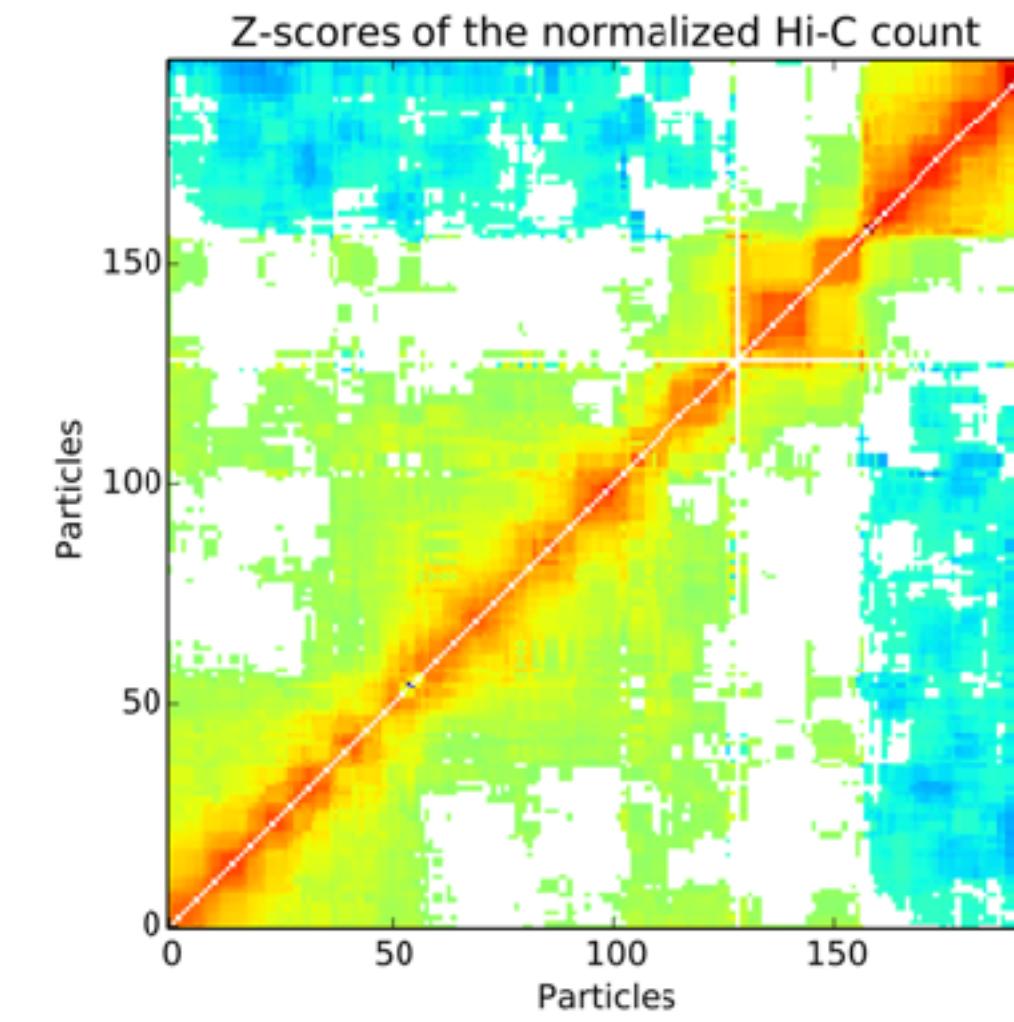


Harmonic Lower Bound

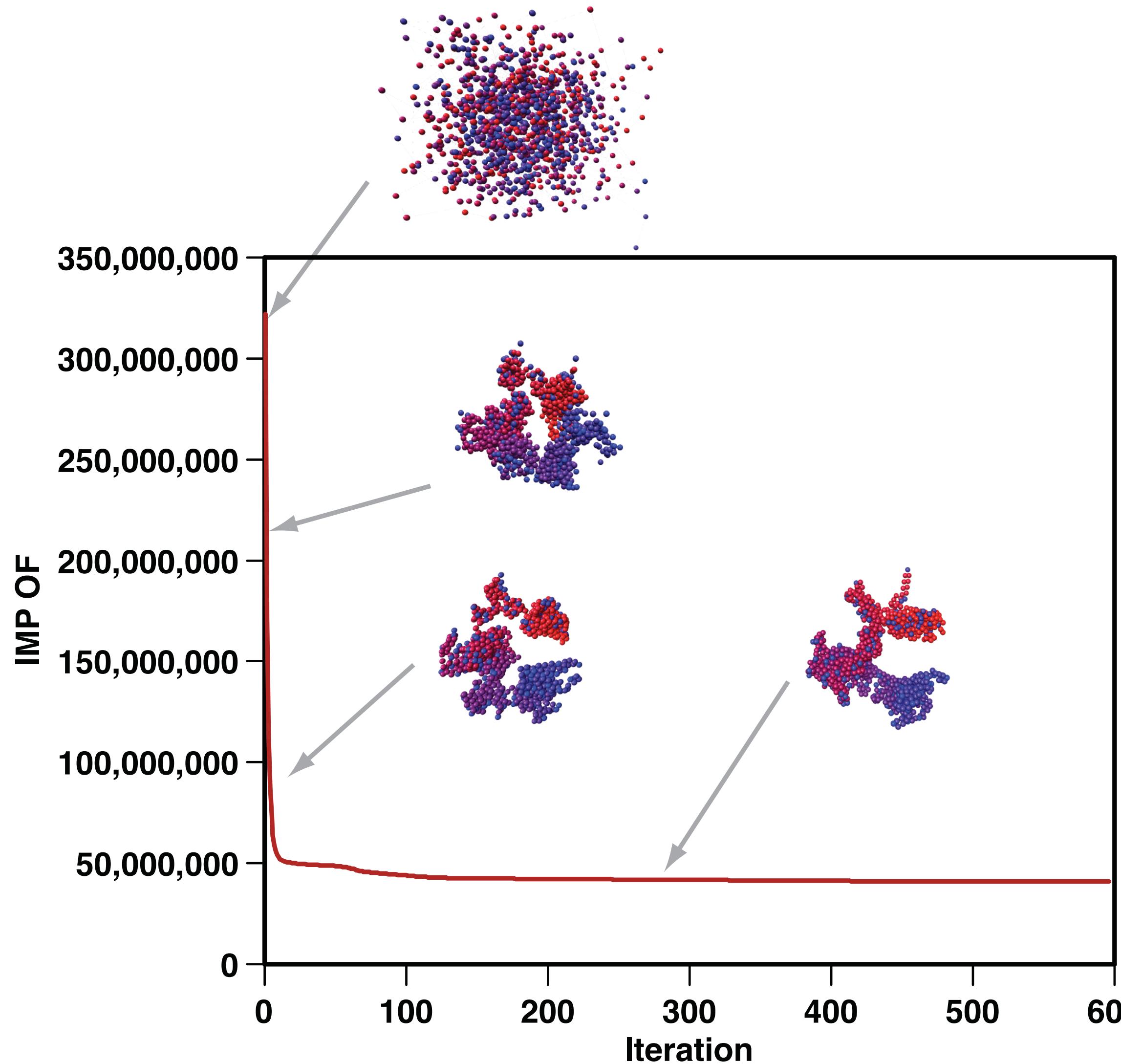
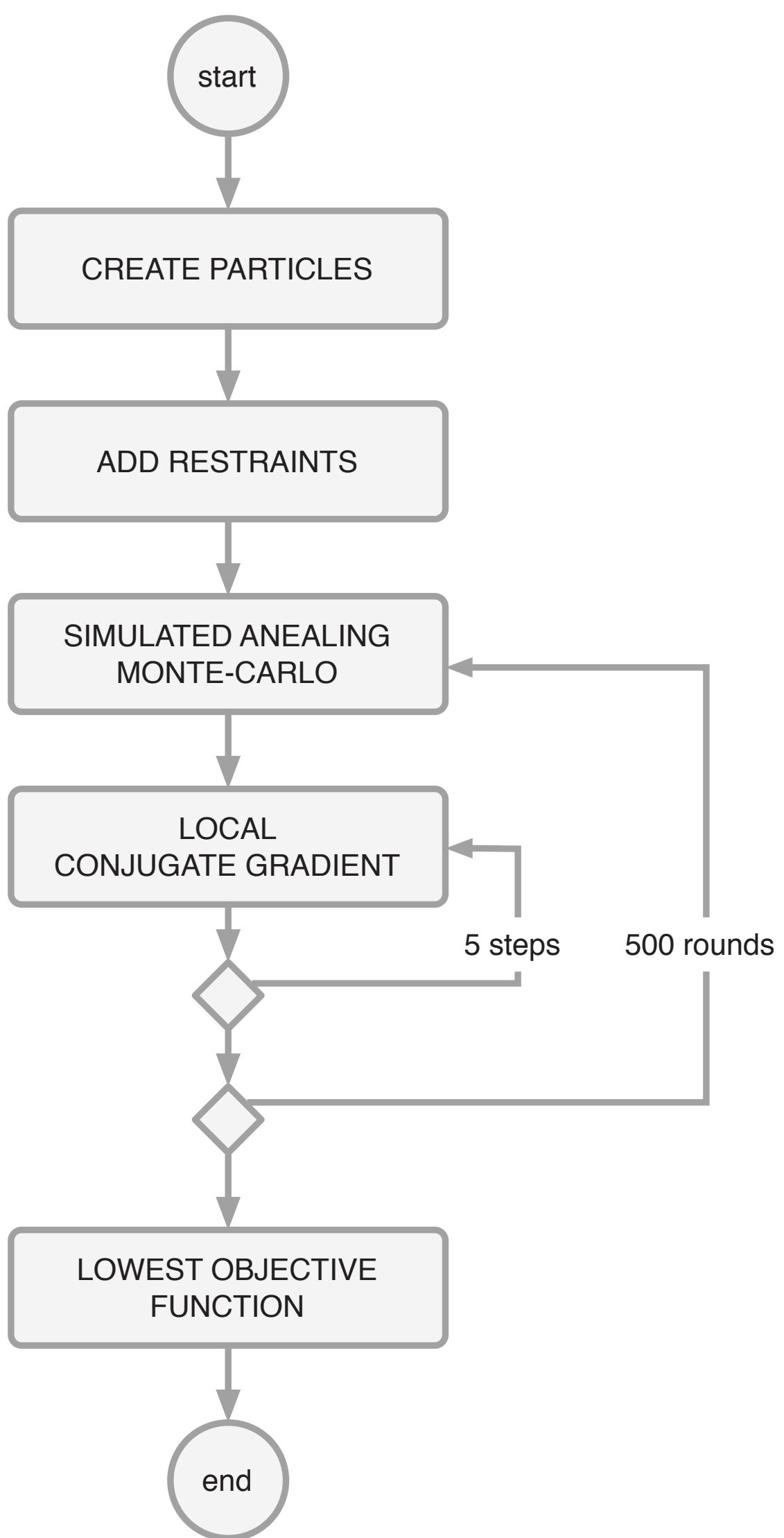
$$\begin{cases} \text{if } d_{i,j} \leq d_{i,j}^0; & lbH_{i,j} = k(d_{i,j} - d_{i,j}^0)^2 \\ \text{if } d_{i,j} > d_{i,j}^0; & lbH_{i,j} = 0 \end{cases}$$



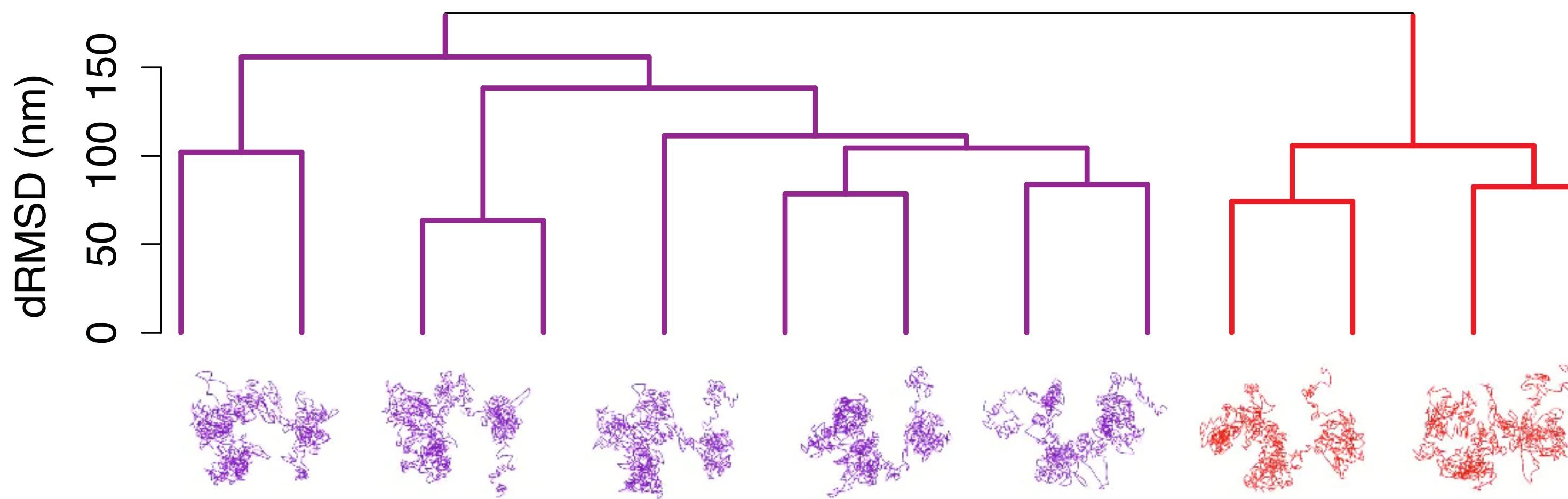
# Parameter optimization



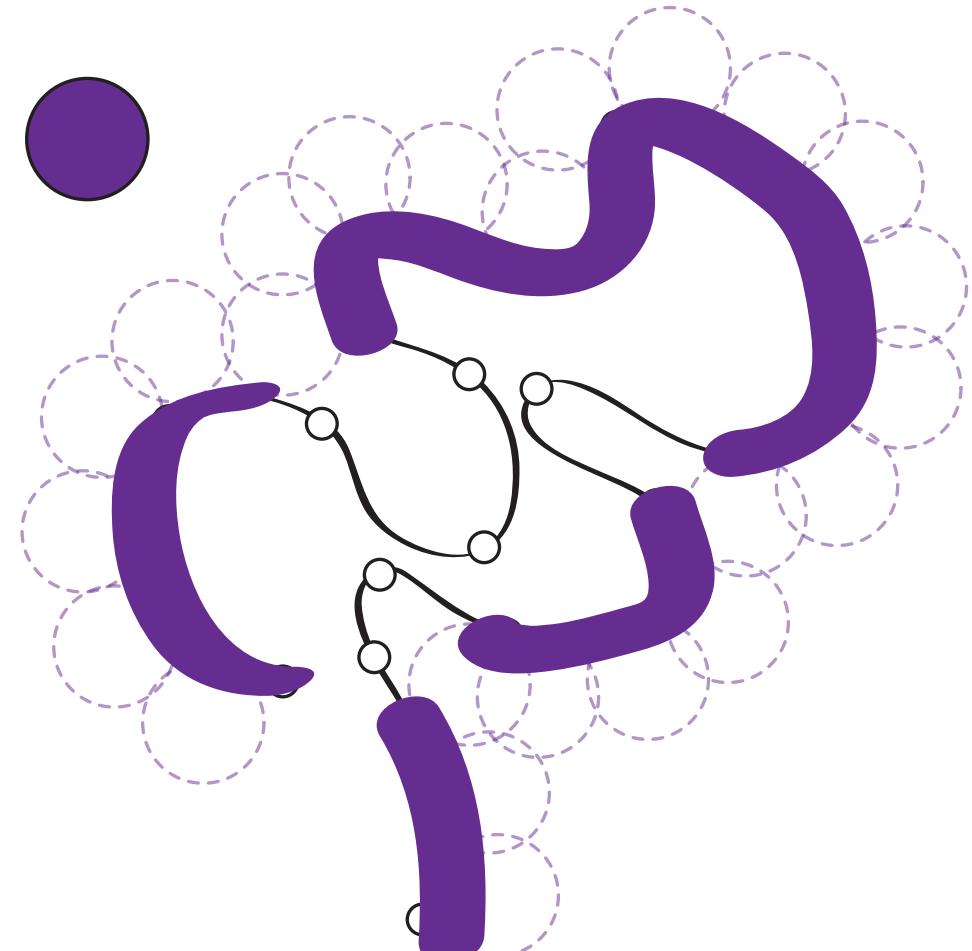
# Optimization of the scoring function



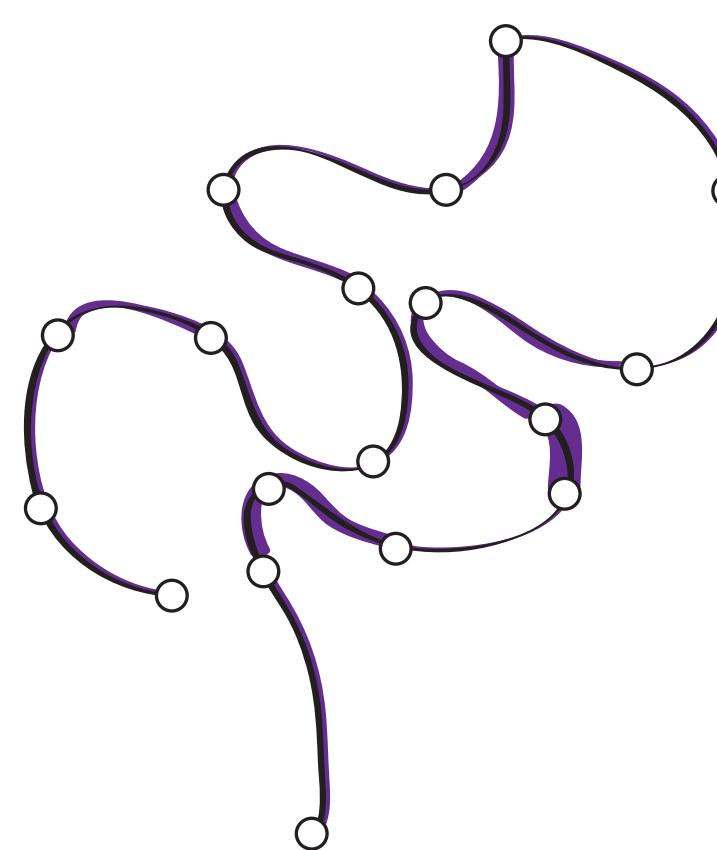
# Model analysis: clustering and structural features



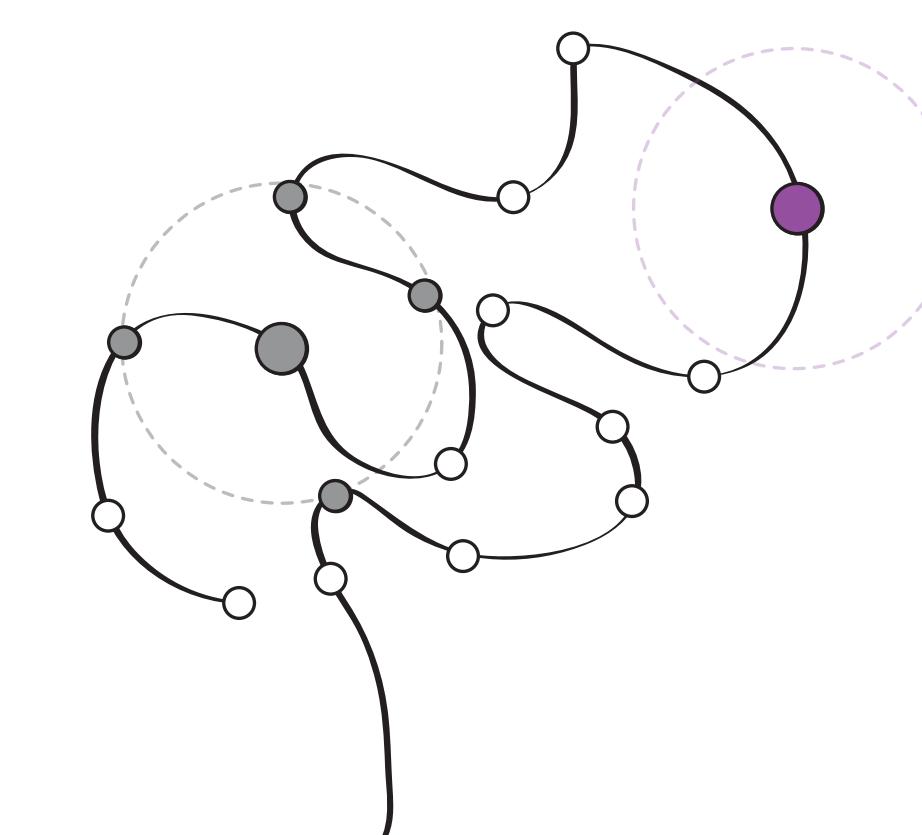
Accessibility (%)



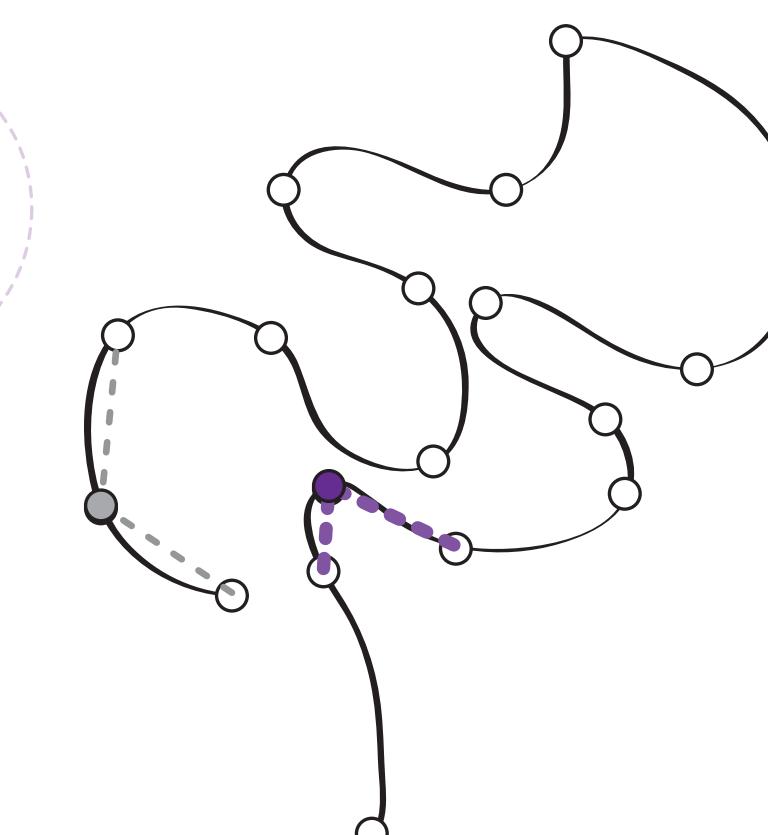
Density (bp/nm)



Interactions

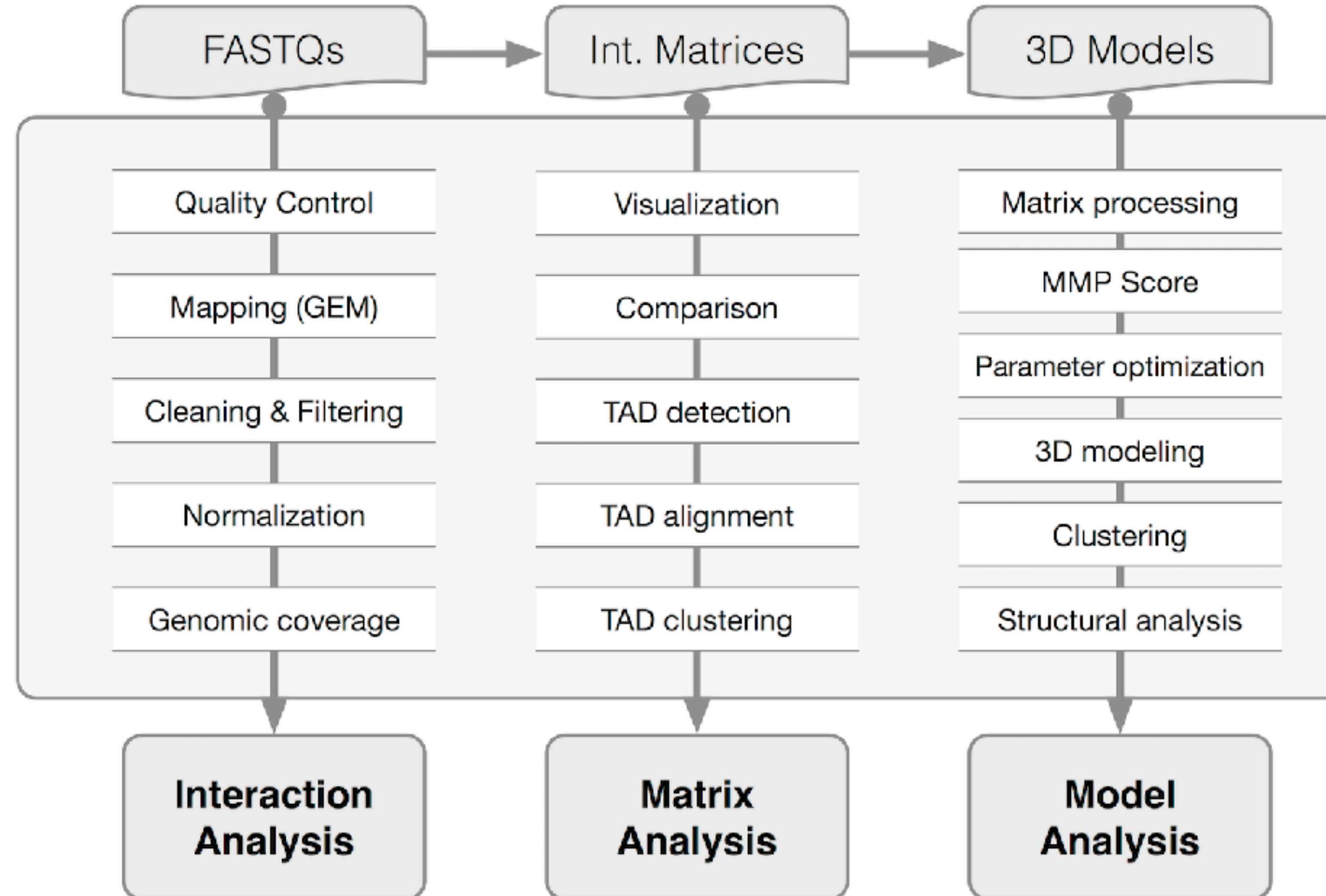


Angle





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# DISCLAIMER — Many alternatives

Tool	Short-read aligner(s)	Mapping improvement	Read filtering	Read-pair filtering	Normalization	Visualization	Confidence estimation	Implementation language(s)
HiCUP [46]	Bowtie/Bowtie2	Pre-truncation	✓	✓	—	—	—	Perl, R
Hiclib [47]	Bowtie2	Iterative	✓ <sup>a</sup>	✓	Matrix balancing	✓	—	Python
HiC-inspector [131]	Bowtie	—	✓	✓	—	✓	—	Perl, R
HIPPIE [132]	STAR	✓ <sup>b</sup>	✓	✓	—	—	—	Python, Perl, R
HiC-Box [133]	Bowtie2	—	✓	✓	Matrix balancing	✓	—	Python
HiCdat [122]	Subread	— <sup>c</sup>	✓	✓	Three options <sup>d</sup>	✓	—	C++, R
HiC-Pro [134]	Bowtie2	Trimming	✓	✓	Matrix balancing	—	—	Python, R
TADbit [120]	GEM	Iterative	✓	✓	Matrix balancing	✓	—	Python
HOMER [62]	—	—	✓	✓	Two options <sup>e</sup>	✓	✓	Perl, R, Java
Hicpipe [54]	—	—	—	—	Explicit-factor	—	—	Perl, R, C++
HiBrowse [69]	—	—	—	—	—	✓	✓	Web-based
Hi-Corrector [57]	—	—	—	—	Matrix balancing	—	—	ANSI C
GOTHiC [135]	—	—	✓	✓	—	—	✓	R
HiTC [121]	—	—	—	—	Two options <sup>f</sup>	✓	✓	R
chromoR [59]	—	—	—	—	Variance stabilization	—	—	R
HiFive [136]	—	—	✓	✓	Three options <sup>g</sup>	✓	—	Python
Fit-Hi-C [20]	—	—	—	—	—	✓	✓	Python

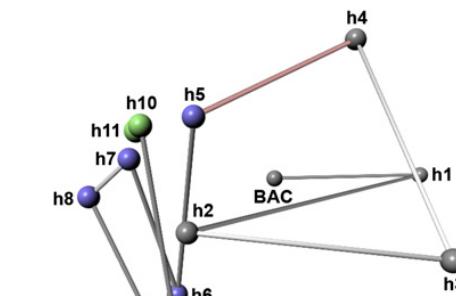
# DISCLAIMER — Many alternatives

Method *available online	Representation	Scoring					Sampling	Models		
			U <sub>3C</sub>		U <sub>Biol</sub>	U <sub>Phys</sub>				
			F <sub>y</sub> → D <sub>y</sub> conversion	Functional form						
ChromSDE* [37]	Points	$D_{ij} = \begin{cases} \left(\frac{1}{F_{ij}}\right)^x & \text{if } F_{ij} > 0 \\ \infty & \text{if } F_{ij} = 0 \end{cases}$ $\alpha$ is optimized		$\sum_{(i,j) D_{ij} < \infty} \frac{(r_{ij}^2 - D_{ij}^2)}{D_{ij}} - \lambda \sum_{(i,j)} r_{ij}^2$ where $\lambda$ is set to 0.01	N/A	N/A	Deterministic semidefinite programming to find the coordinates	Consensus		
ShRec3D* [38]	Points	$D_{ij} = \begin{cases} \left(\frac{1}{F'_{ij}}\right)^x & \text{if } F'_{ij} > 0 \\ \frac{N^2}{\sum_{ij} F'_{ij}} & \text{if } F'_{ij} = 0 \end{cases}$ $F'_{ij}$ is the original $F_{ij}$ corrected to satisfy all triangular inequalities with the shortest path reconstruction		N/A	N/A	N/A	Deterministic transformations of $D_{ij}$ into coordinates	Consensus		
TADbit* [43]	Spheres	$D_{ij} \propto \begin{cases} \alpha F_{ij} + \beta & \text{if } F_{ij} < \gamma' \text{ or } F_{ij} > \gamma \\ \frac{s_i + s_j}{2} & \text{if }  i-j  = 1 \end{cases}$ $\alpha$ and $\beta$ are estimated from the max and the min $F_{ij}$ , from the optimized max distance and from the resolution. $\gamma' < \gamma$ are optimized too. $s_i$ is the radius of particle $i$		$\sum_{(i,j)} k_{ij}(r_{ij} - D_{ij})^2$ where $k_{ij} = 5$ if $ i-j  = 1$ or proportional to $F_{ij}$ otherwise	Yes	U <sub>ext</sub> and U <sub>bond</sub> have harmonic forms	Monte Carlo (MC) sampling with Simulated annealing and Metropolis scheme			
BACH* [45]	Points	$D_{ij} \propto \frac{B_i B_j}{F_{ij}}$ . The biases $B_i$ and $B_j$ and $\alpha$ are optimized		$b_{ij} D_{ij}^{1/2} + c_{ij} \log(D_{ij})$ where $b_{ij}$ and $c_{ij}$ are optimized parameters	No	No	Sequential importance and Gibbs sampling with hybrid MC and adaptive rejection	Population		
Giorgetti et al. [40]	Spheres	Particles interact with pair-wise well potentials of depths $B_{ij}$ and contact radius $a$ , which is larger than a hard-core radius and smaller than a maximum contact radius. The parameters are optimized over all the population of models			No	N/A	MC sampling with metropolis scheme	Population		
Duan et al. [41]	Spheres	$\overline{F_{ i-j }} = \frac{\sum_{k=1}^{N- i-j } F_{ i,k+ i-j }}{N- i-j }$ is the average of $F_{ij}$ at genomic distance $ i-j $ expressed in kb. $D_{ij} = \overline{F_{ i-j }} \times 7.7 \times  i-j $ assuming that $\approx 1$ kb maps onto 7.7 nm	$\sum_{(i,j)} (r_{ij} - D_{ij})^2$	Yes	U <sub>ext</sub> and U <sub>bond</sub> have harmonic forms	Interior-point gradient-based method	Resampling			
MCMC5C* [49]	Points	$D_{ij} \propto \frac{1}{F_{ij}}$ where $\alpha$ is optimized		$\sum_{(i,j)} (F_{ij} - r_{ij}^{-1/\alpha})^2$	N/A	N/A	MC sampling with Markov chain based algorithm	Resampling		
PASTIS* [47]	Points	$D_{ij} \propto \frac{1}{F_{ij}}$ where $\alpha$ is optimized		$b_{ij} D_{ij}^{1/2} + c_{ij} \log(D_{ij})$ where $b_{ij}$ and $c_{ij}$ are optimized parameters	No	No	Interior point and isotonic regression algorithms	Resampling		
Meluzzi and Arya [48]	Spheres	$\sum_{(i,j)} k_{ij} r_{ij}^2$ where $k_{ij}$ are adjusted such that the contact probabilities computed on the models match the $F_{ij}$			No	U <sub>ext</sub> is a pure repulsive LJ potential. U <sub>bond</sub> and U <sub>bend</sub> have harmonic forms	Brownian dynamics	Resampling		
AutoChrom3D* [44]	Points	$D_{ij} \propto \begin{cases} \alpha F_{ij} + \beta & \text{if } F_{\min} < F_{ij} < F_{\gamma} \\ \alpha' F_{ij} + \beta' & \text{if } F_{\gamma} < F_{ij} < F_{\max} \end{cases}$ where $F_{\min}$ ( $F_{\max}$ ) are the min(max) of $F_{ij}$ . The parameters $(\alpha, \beta)$ , $(\alpha', \beta')$ and $F_{\gamma}$ are found using the nuclear size, the resolution and the decay of $F_{ij}$ with $ i-j $	$\sum_{(i,j)} \frac{(r_{ij} - D_{ij})^2}{D_{ij}^2}$	Yes	N/A	Non-linear constrained	Consensus			
Kalhor et al. [14]	Spheres	$D_{ij} = R_{\text{contact}}$ to enforce the pair contact, if the normalized contact frequency $F_{ij}$ is higher than 0.25. Otherwise the contact is not enforced		$\sum_{\text{models}} \sum_{(i,j)} k_{ij}(r_{ij} - D_{ij})^2$ where $k_{ij}$ is different for pairs of particles, on different chromosomes, on the same chromosome, or connected	Yes	U <sub>ext</sub> and U <sub>bond</sub> have harmonic forms	Conjugate gradients sampling with Simulated annealing scheme	Population		

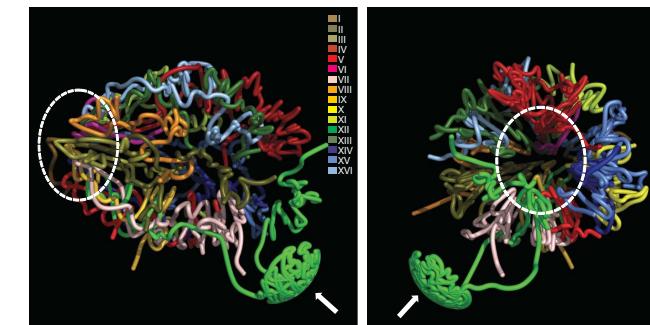
\* These methods are publicly available.

# Are the models correct?

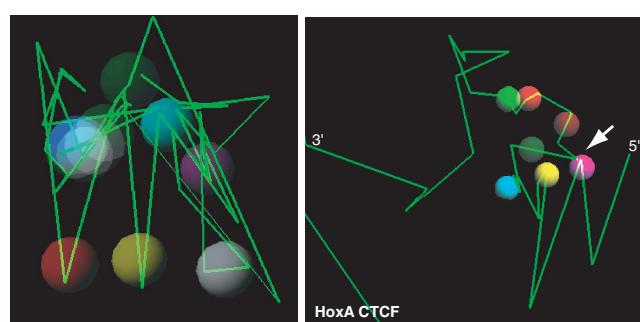
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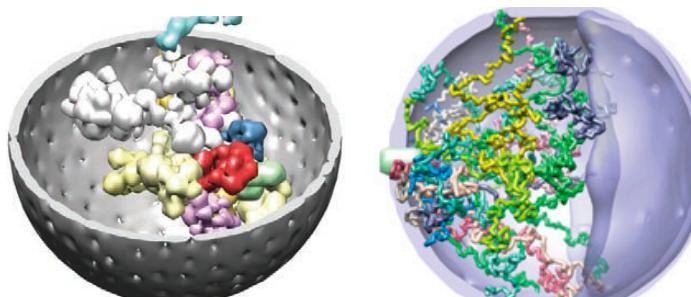
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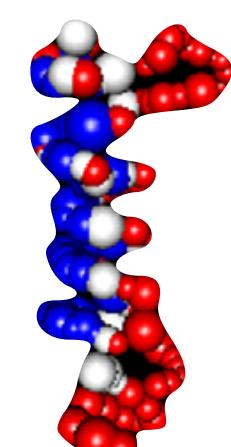
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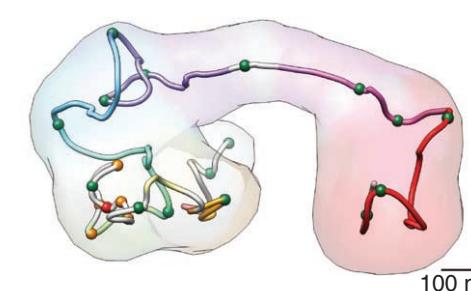
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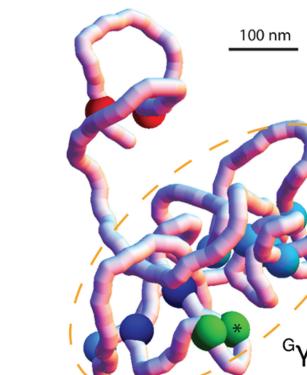
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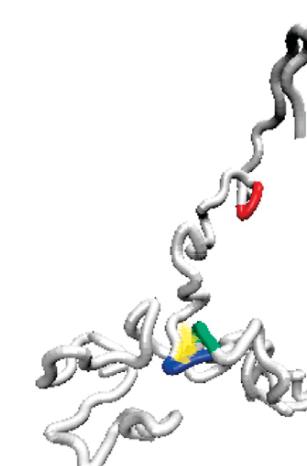
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## Assessing the limits of restraint-based 3D modeling of genomes and genomic domains

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### ABSTRACT

Restraint-based modeling of genomes has been recently explored with the advent of Chromosome Conformation Capture (3C-based) experiments. We previously developed a reconstruction method to resolve the 3D architecture of both prokaryotic and eukaryotic genomes using 3C-based data. These models were congruent with fluorescent imaging validation. However, the limits of such methods have not systematically been assessed. Here we propose the first evaluation of a mean-field restraint-based reconstruction of genomes by considering diverse chromosome architectures and different levels of data noise and structural variability. The results show that: first, current scoring functions for 3D reconstruction correlate with the accuracy of the models; second, reconstructed models are robust to noise but sensitive to structural variability; third, the local structure organization of genomes, such as Topologically Associating Domains, results in more accurate models; fourth, to a certain extent, the models capture the intrinsic structural variability in the input matrices and fifth, the accuracy of the models can be *a priori* predicted by analyzing the properties of the interaction matrices. In summary, our work provides a systematic analysis of the limitations of a mean-field restraint-based method, which could be taken into consideration in further development of methods as well as their applications.

### INTRODUCTION

Recent studies of the three-dimensional (3D) conformation of genomes are revealing insights into the organization and the regulation of biological processes, such as gene

expression regulation and replication (1–6). The advent of the so-called Chromosome Conformation Capture (3C) assays (7), which allowed identifying chromatin-looping interactions between pairs of loci, helped deciphering some of the key elements organizing the genomes. High-throughput derivations of genome-wide 3C-based assays were established with Hi-C technologies (8) for an unbiased identification of chromatin interactions. The resulting genome interaction matrices from Hi-C experiments have been extensively used for computationally analyzing the organization of genomes and genomic domains (5). In particular, a significant number of new approaches for modeling the 3D organization of genomes have recently flourished (9–14). The main goal of such approaches is to provide an accurate 3D representation of the bi-dimensional interaction matrices, which can then be more easily explored to extract biological insights. One type of methods for building 3D models from interaction matrices relies on the existence of a limited number of conformational states in the cell. Such methods are regarded as mean-field approaches and are able to capture, to a certain degree, the structural variability around these mean structures (15).

We recently developed a mean-field method for modeling 3D structures of genomes and genomic domains based on 3C interaction data (9). Our approach, called TADbit, was developed around the Integrative Modeling Platform (IMP, <http://integrativemodeling.org>), a general framework for restraint-based modeling of 3D bio-molecular structures (16). Briefly, our method uses chromatin interaction frequencies derived from experiments as a proxy of spatial proximity between the ligation products of the 3C libraries. Two fragments of DNA that interact with high frequency are dynamically placed close in space in our models while two fragments that do not interact as often will be kept apart. Our method has been successfully applied to model the structures of genomes and genomic domains in eukaryote and prokaryote organisms (17–19). In all of our studies, the final models were partially validated by assessing their

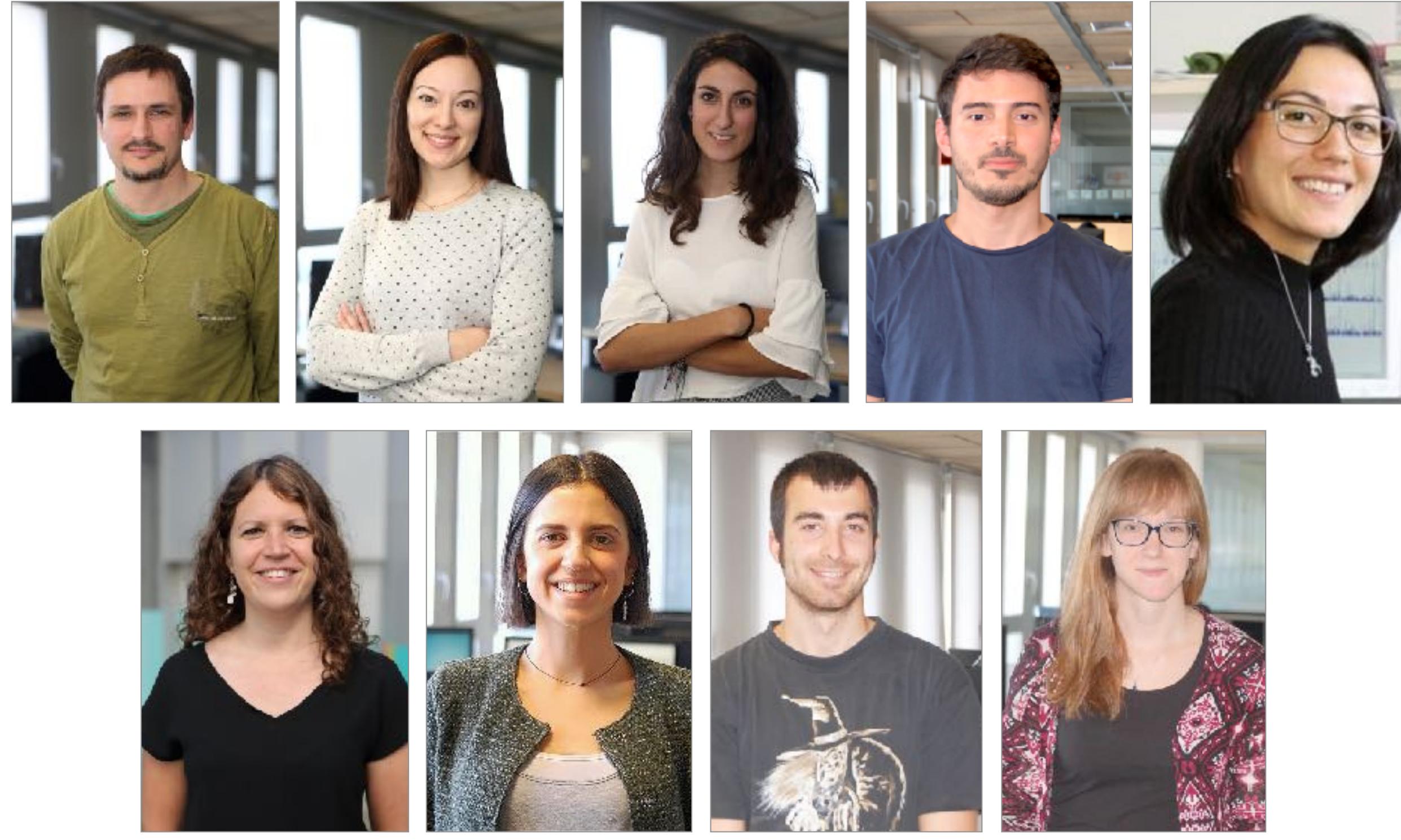
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