3DGenomics

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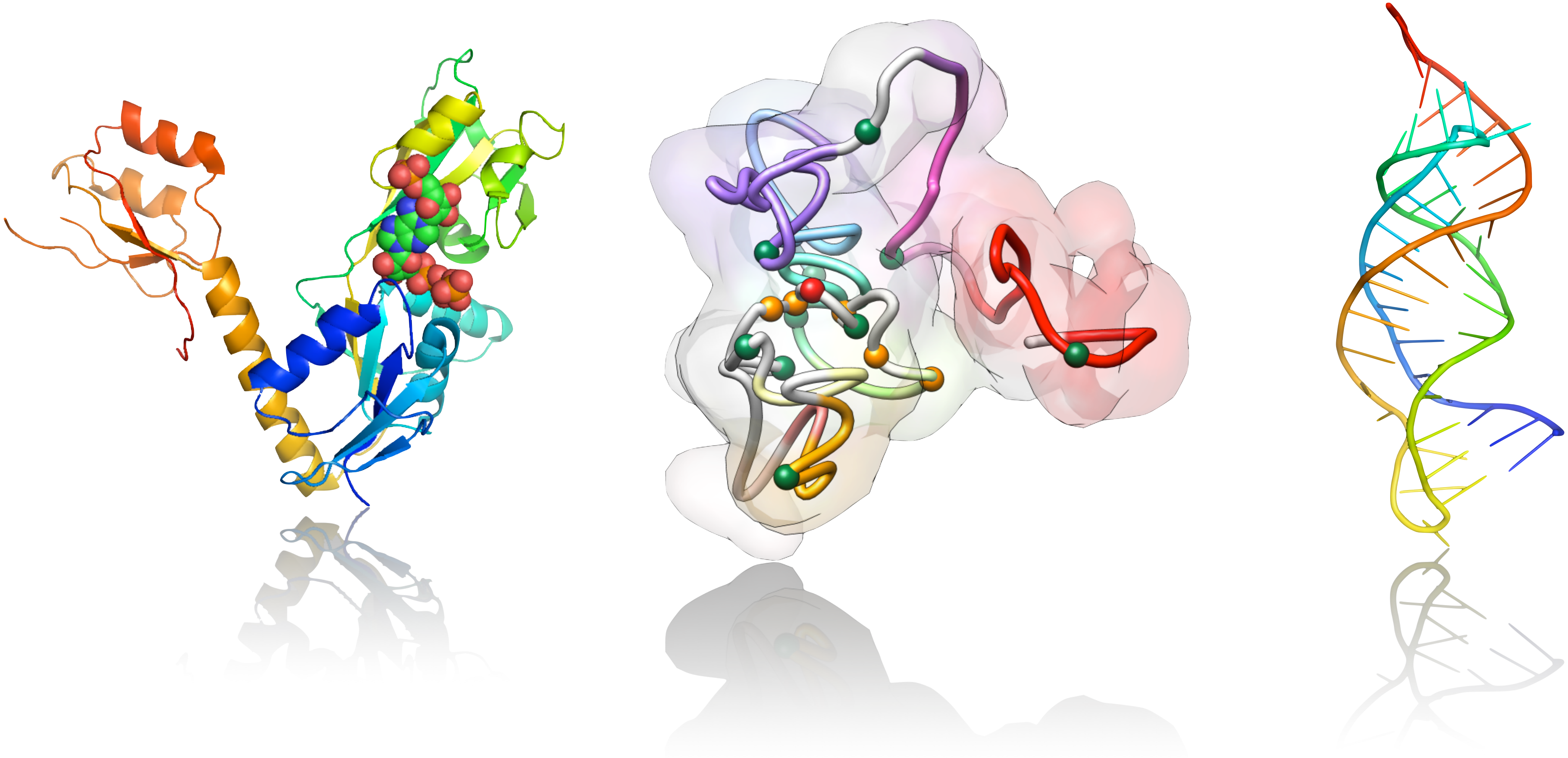
Structural Genomics Group
CNAG-CRG

ICREA

cnag CRG
Centre
for Genomic
Regulation

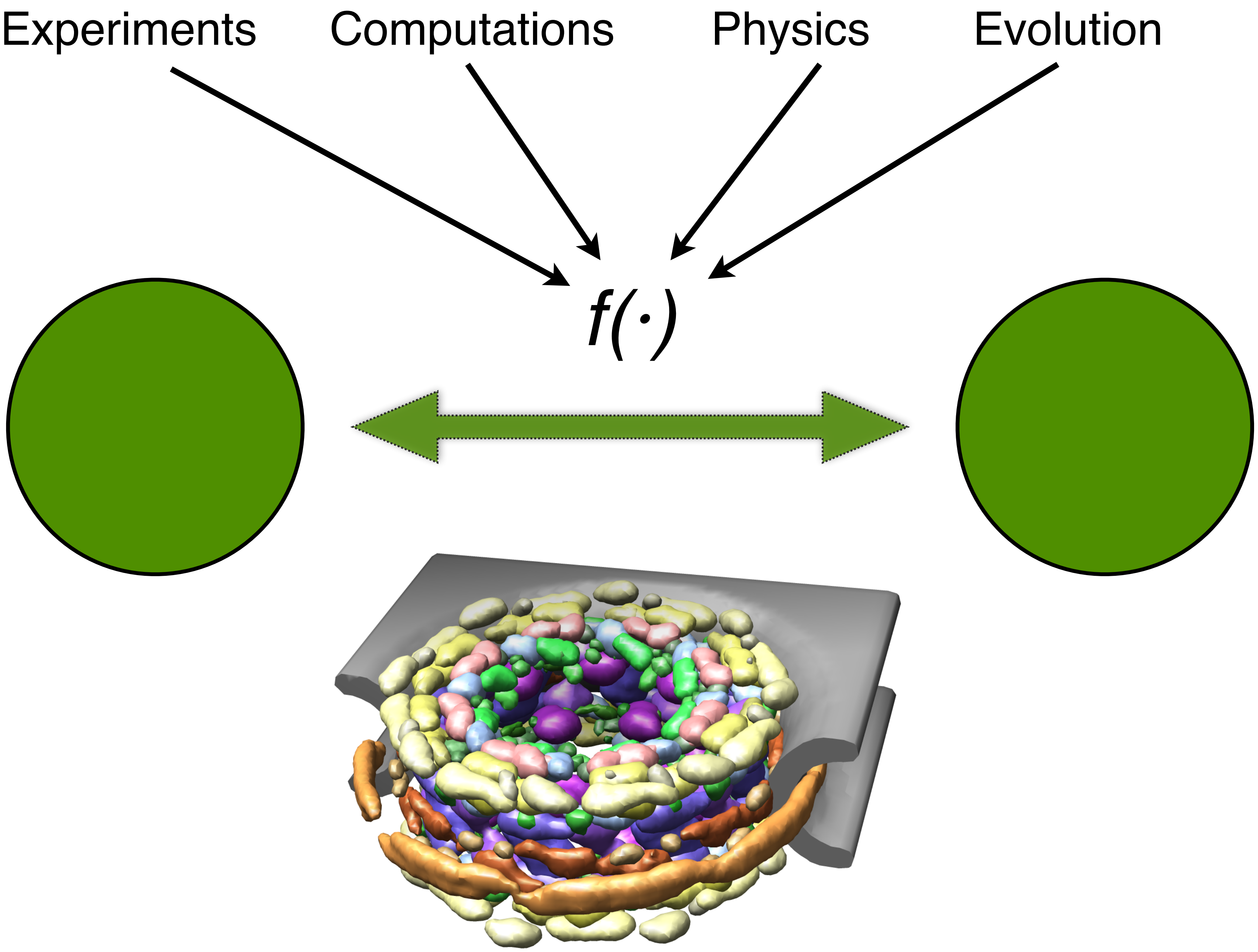
Structural Genomics Group

http://www.marciuslab.org



Integrative Modeling Platform

http://www.integrativemodeling.org



Experiments

Computations

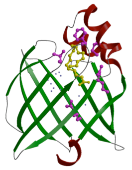
Physics

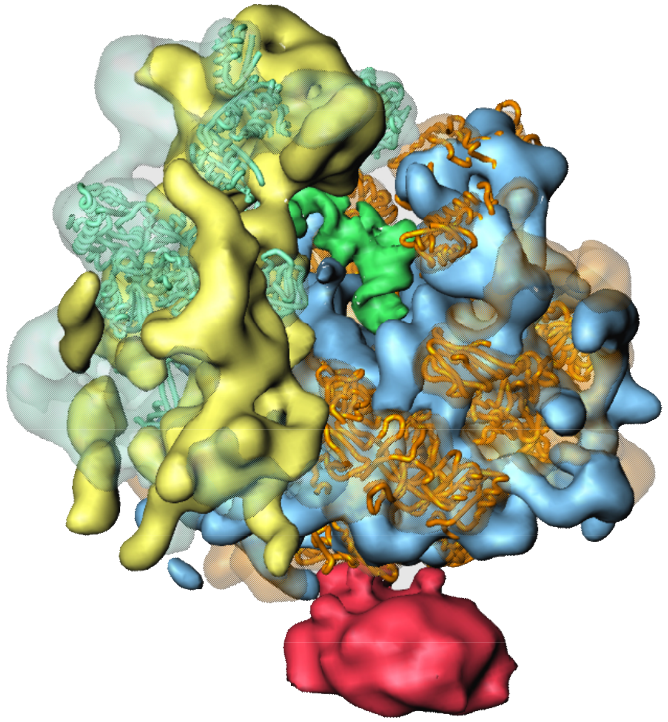
Evolution

$f(\cdot)$

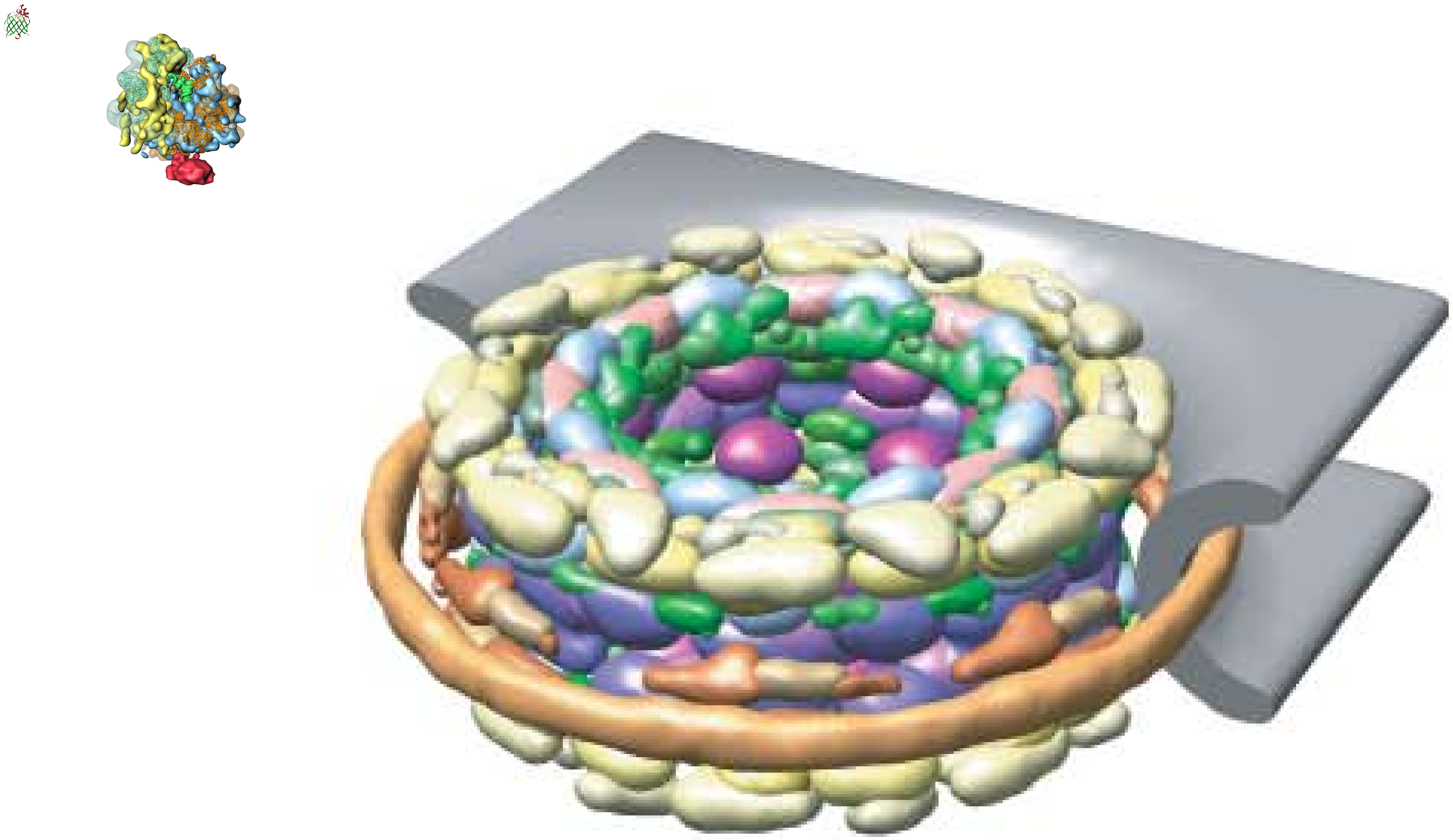
From: Russel, D. et al. PLOS Biology 10, e1001244 (2012).

Data Integration





Data Integration



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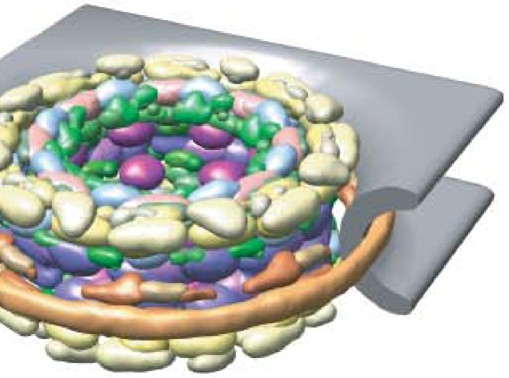
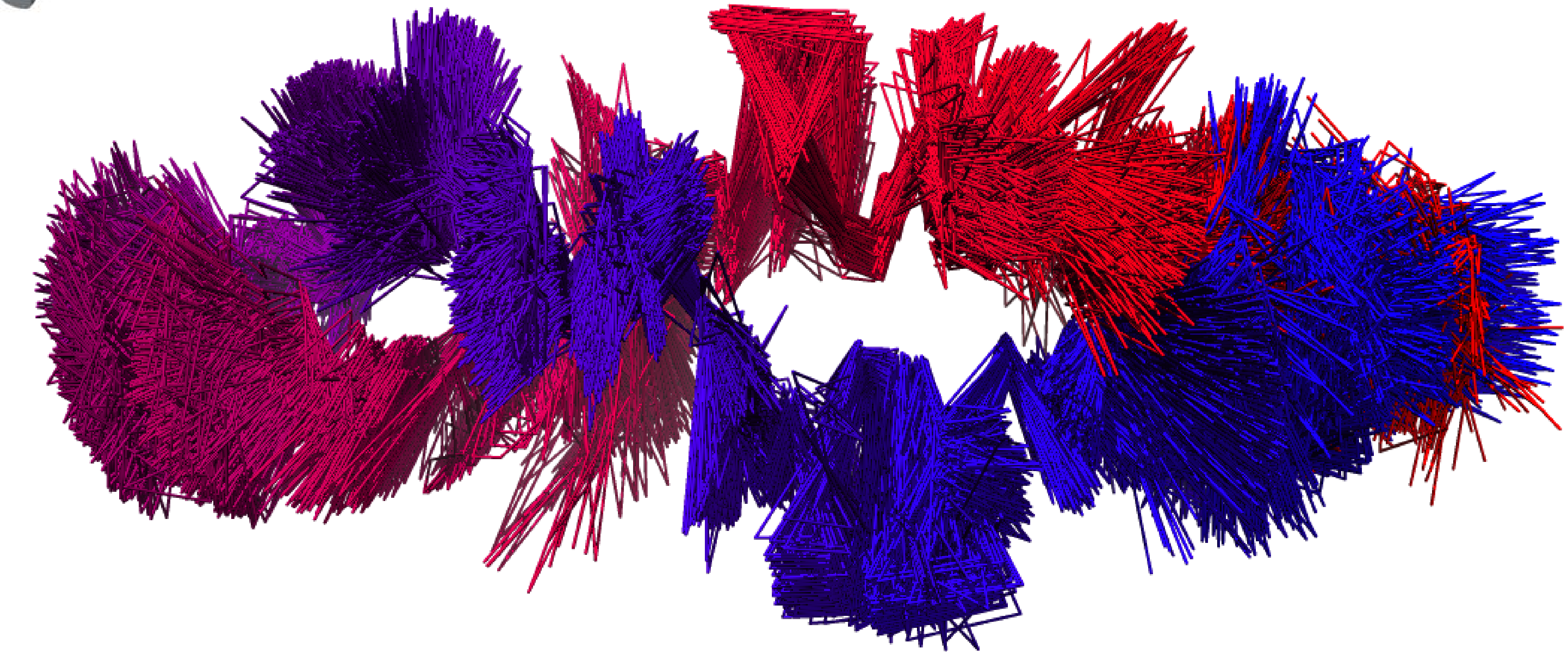
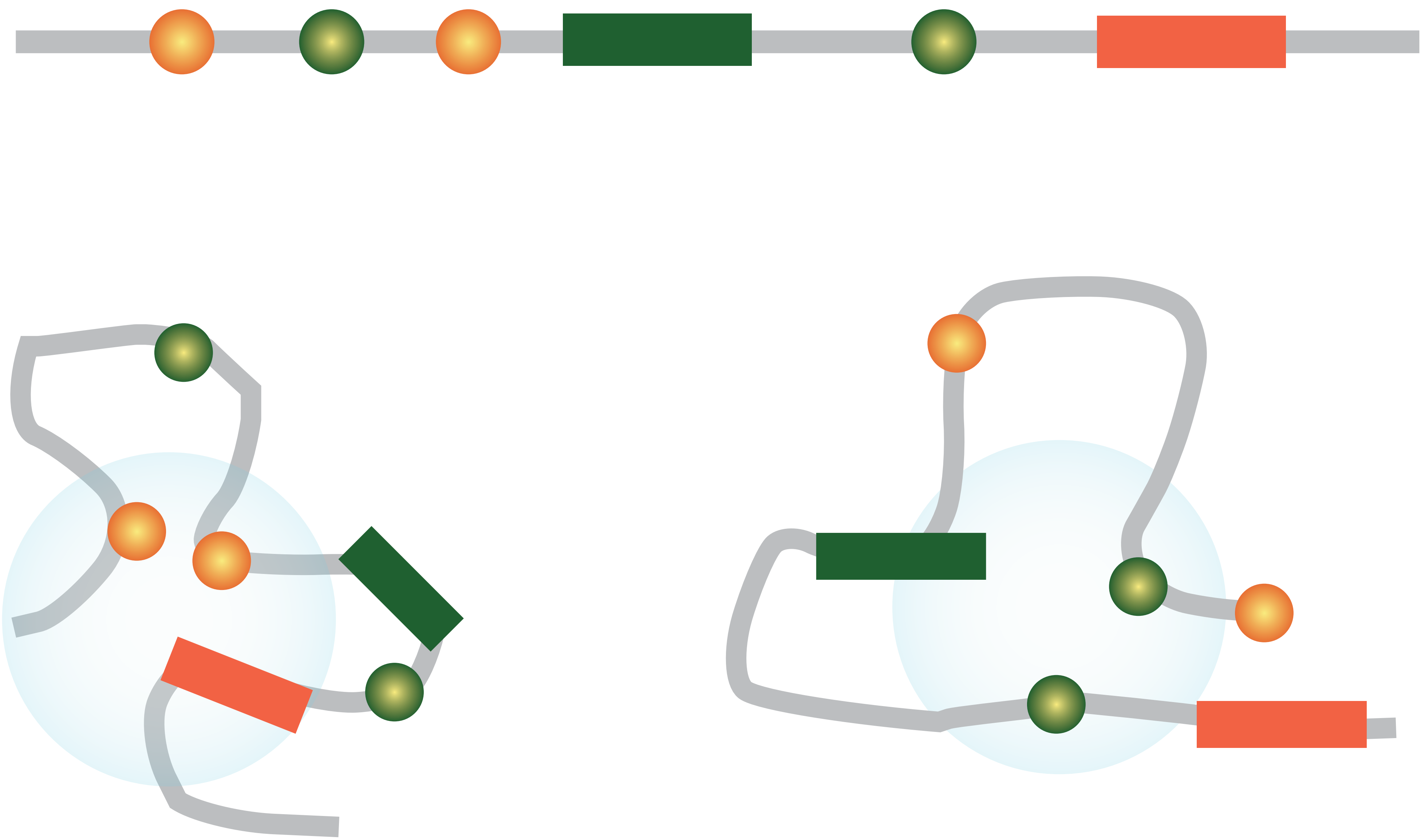


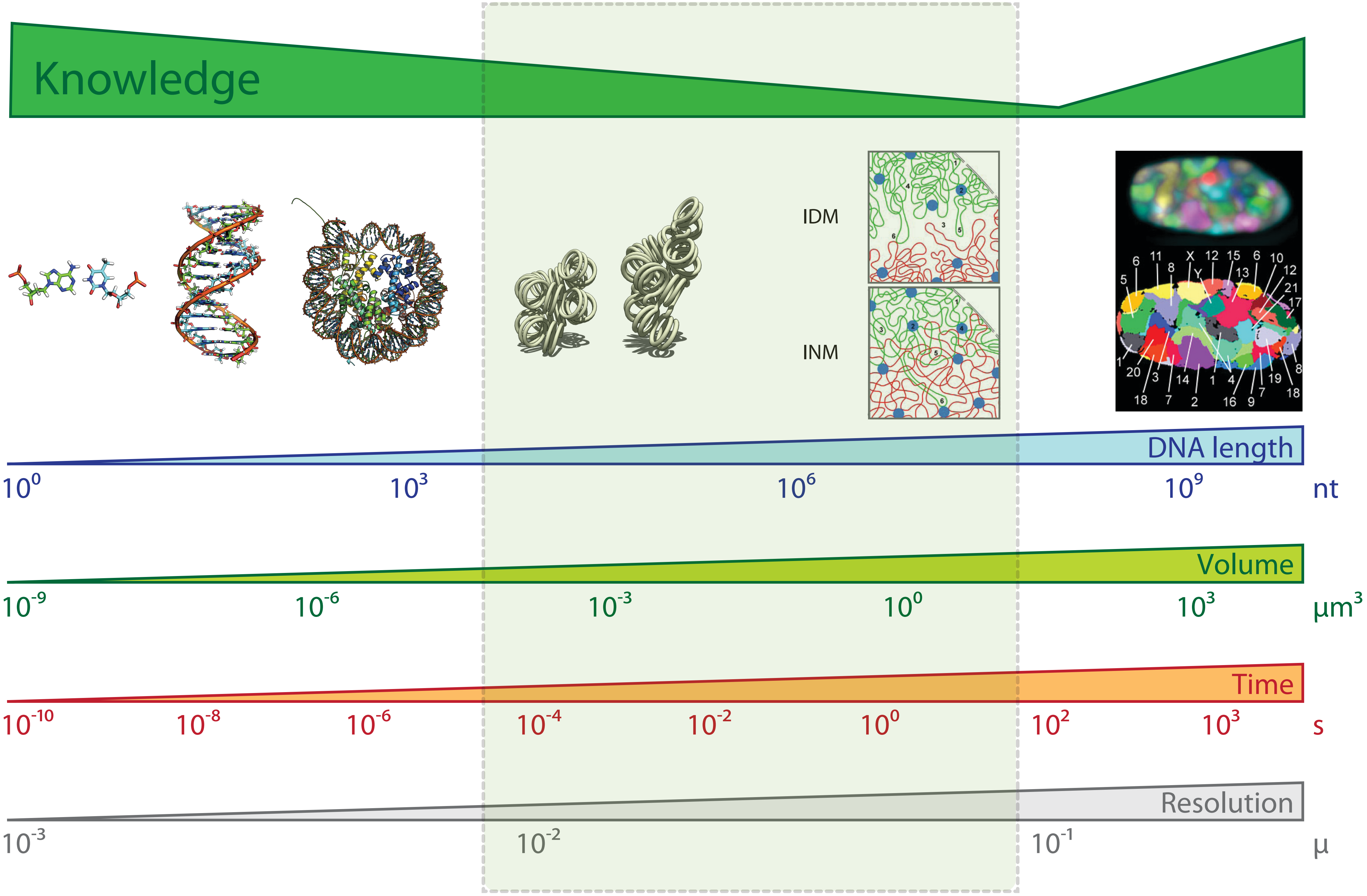


Complex genome organization



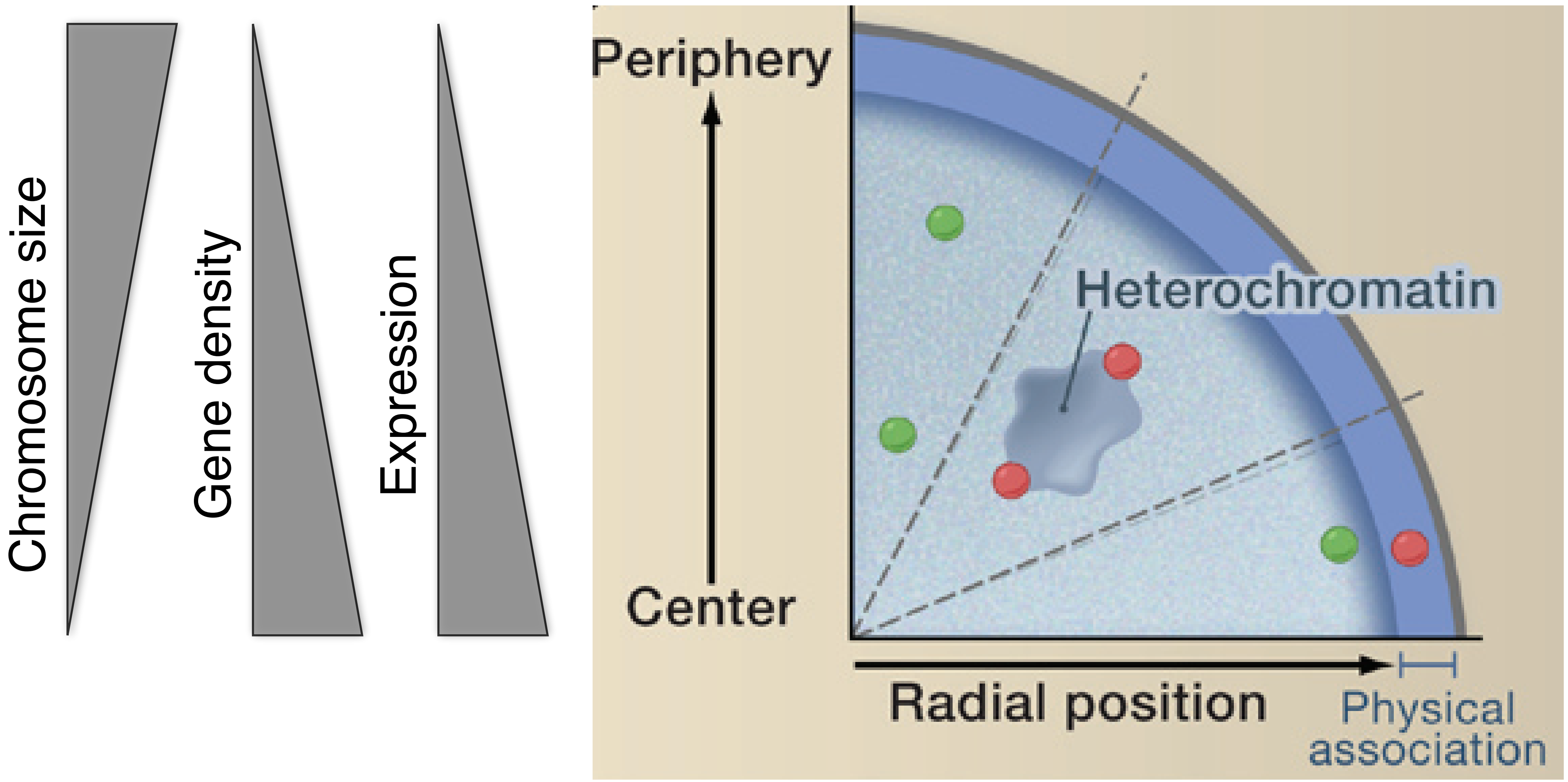
Resolution Gap

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

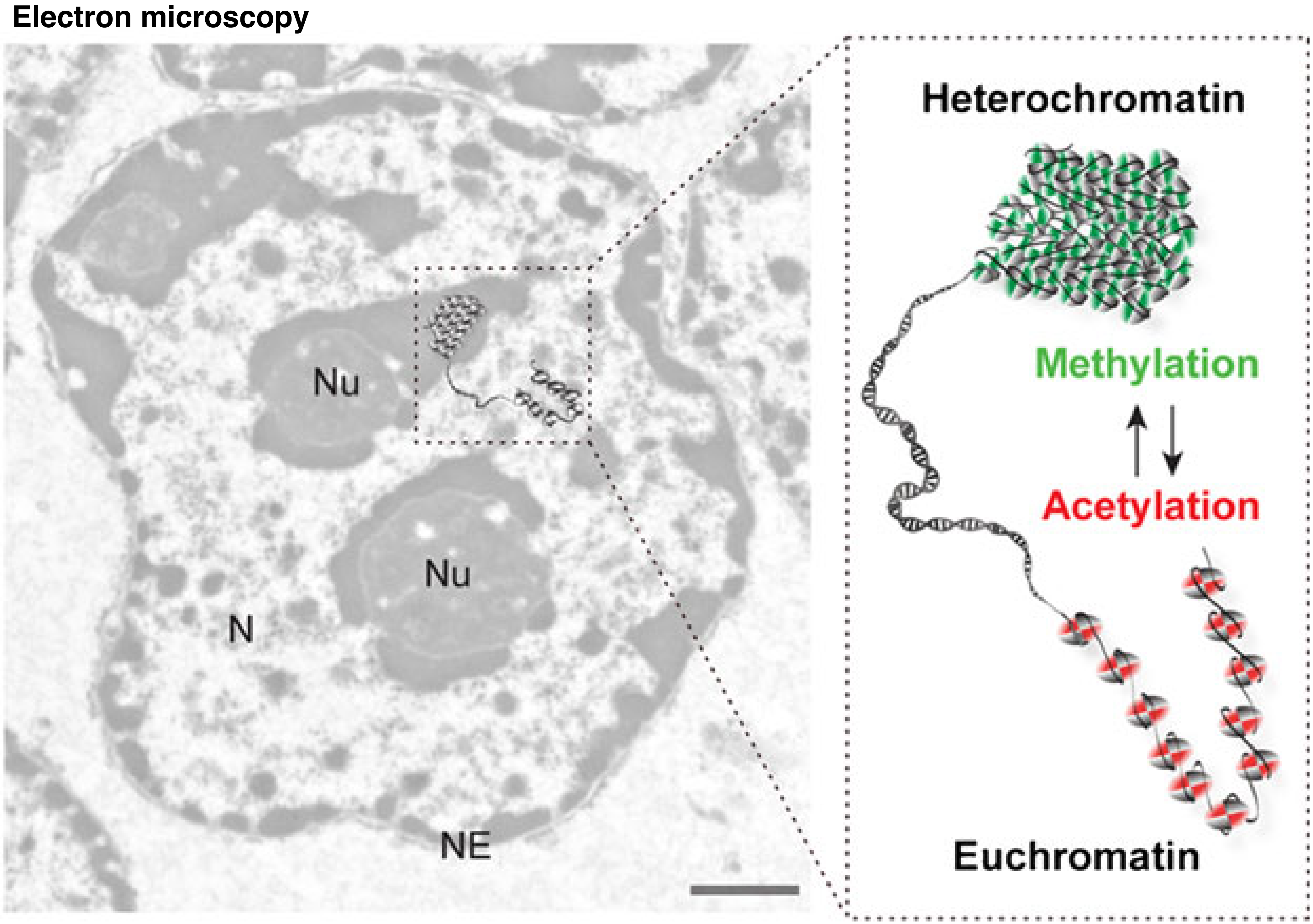


Level I: Radial genome organization

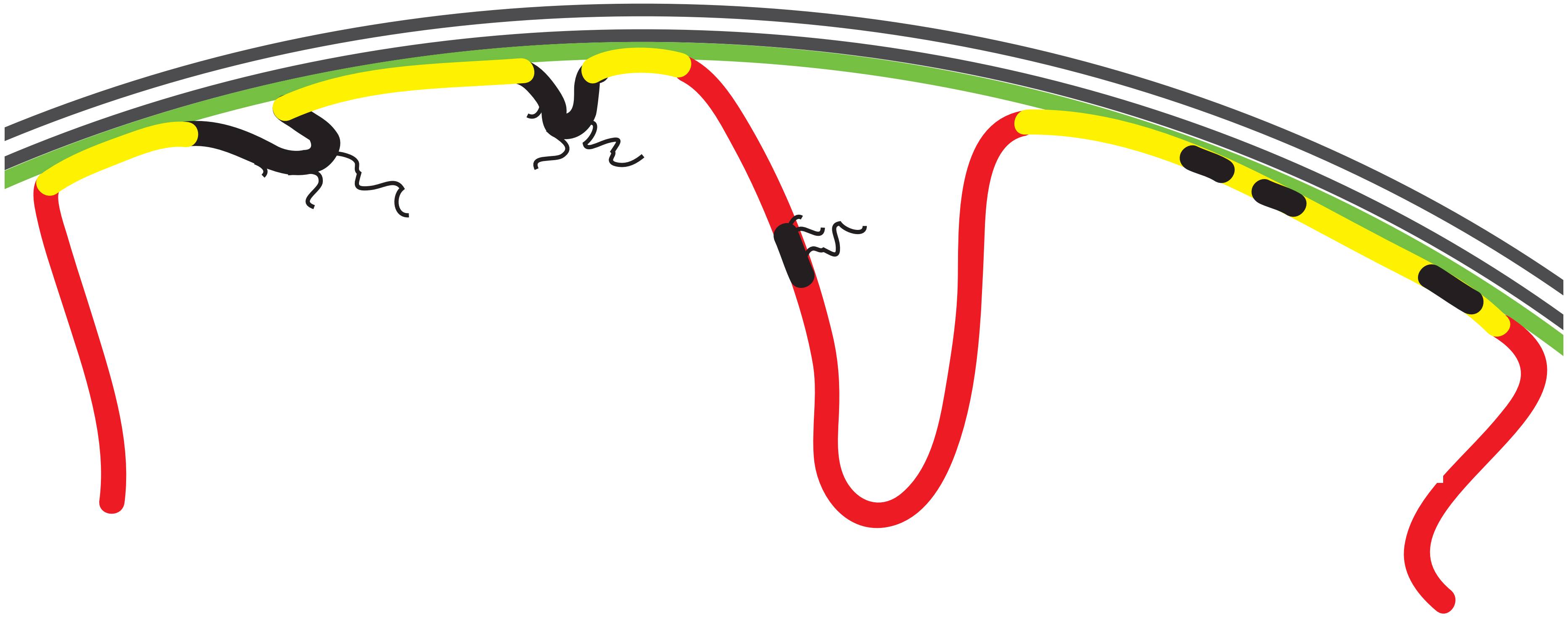
Takizawa, T., Meaburn, K. J. & Misteli, T. The meaning of gene positioning. Cell 135, 9–13 (2008).



Level II: Euchromatin vs heterochromatin



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

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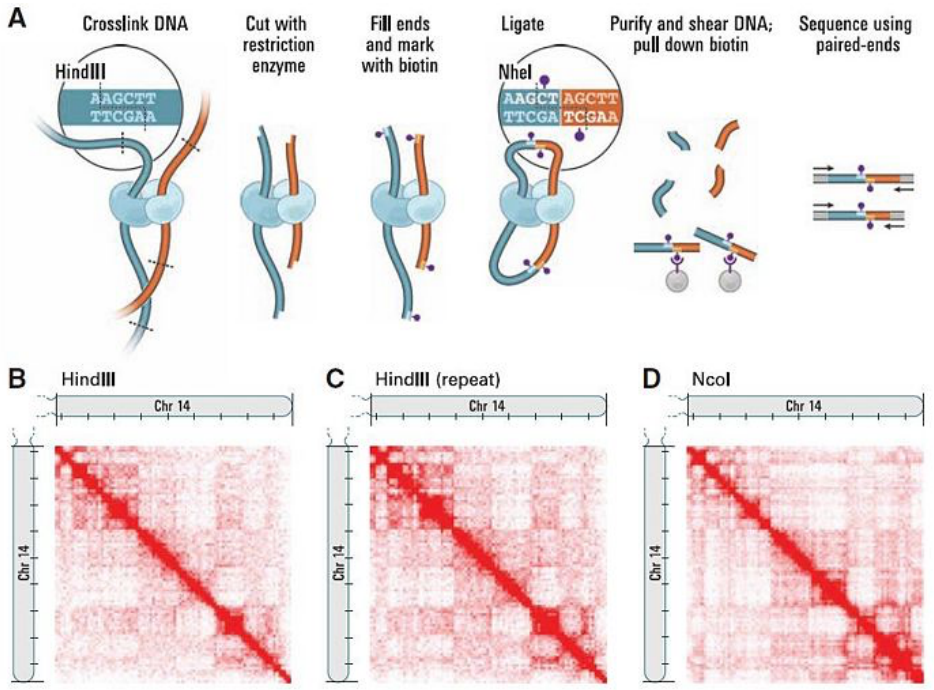
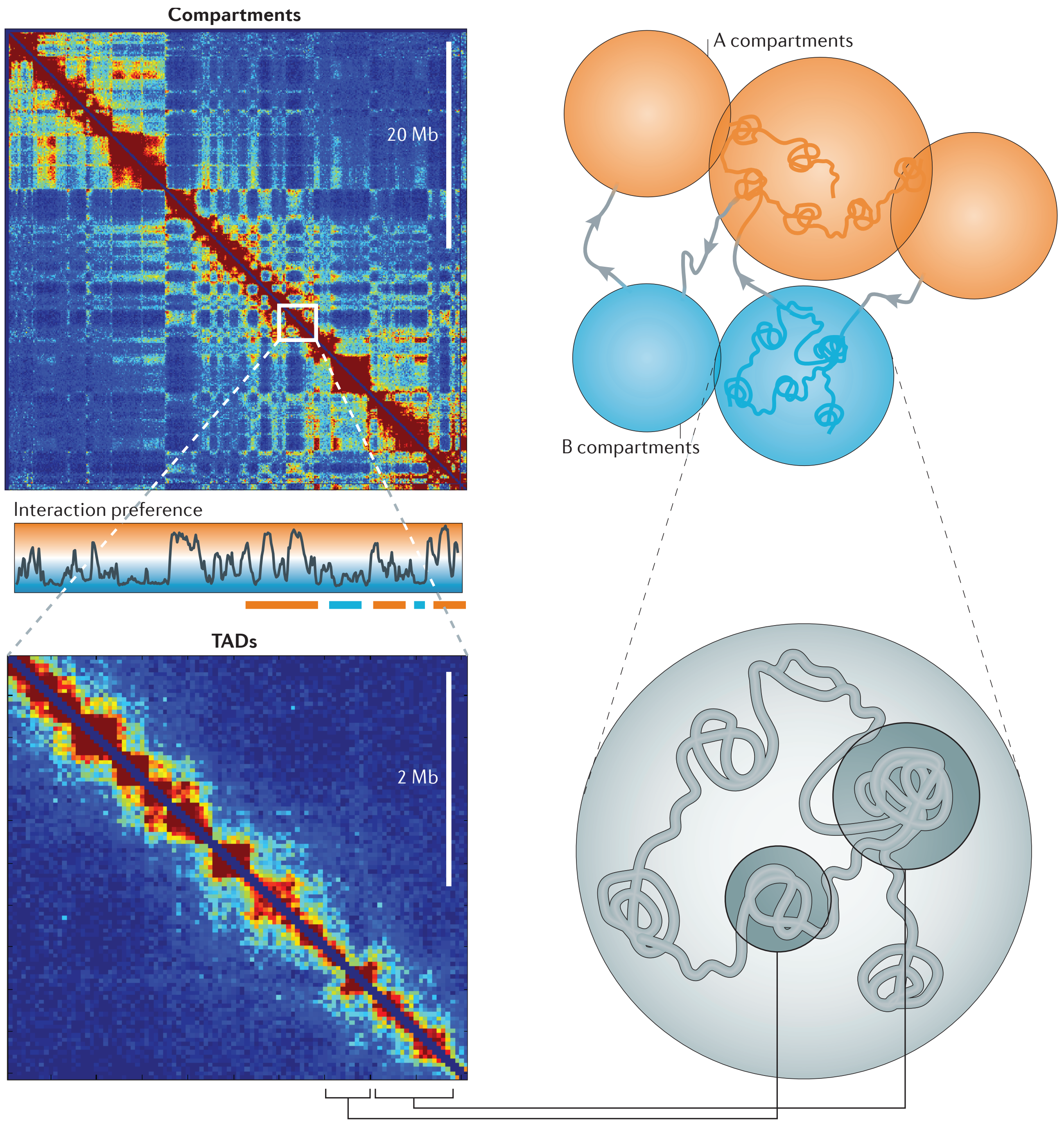
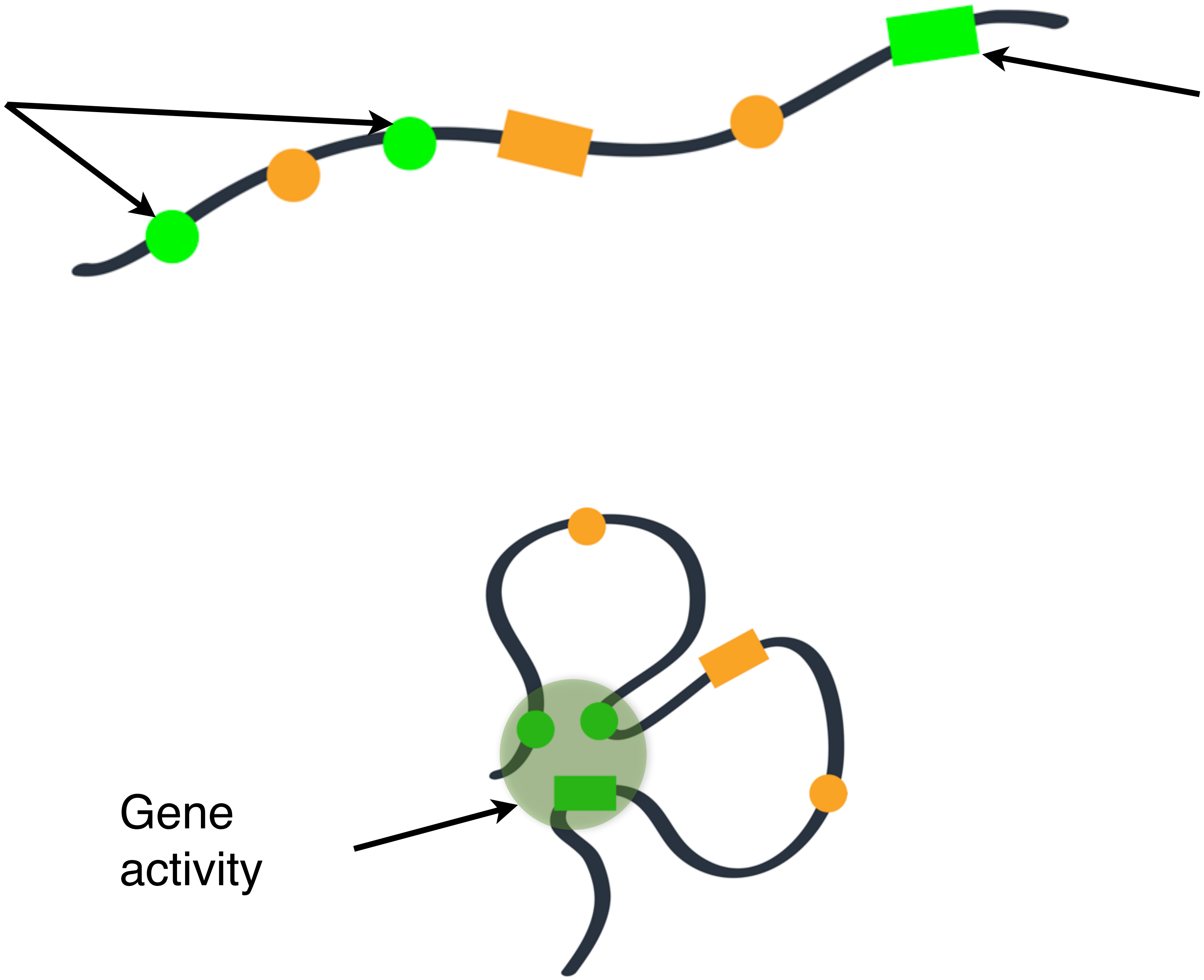
Level IV: Higher-order organization

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).





Level V: Chromatin loops



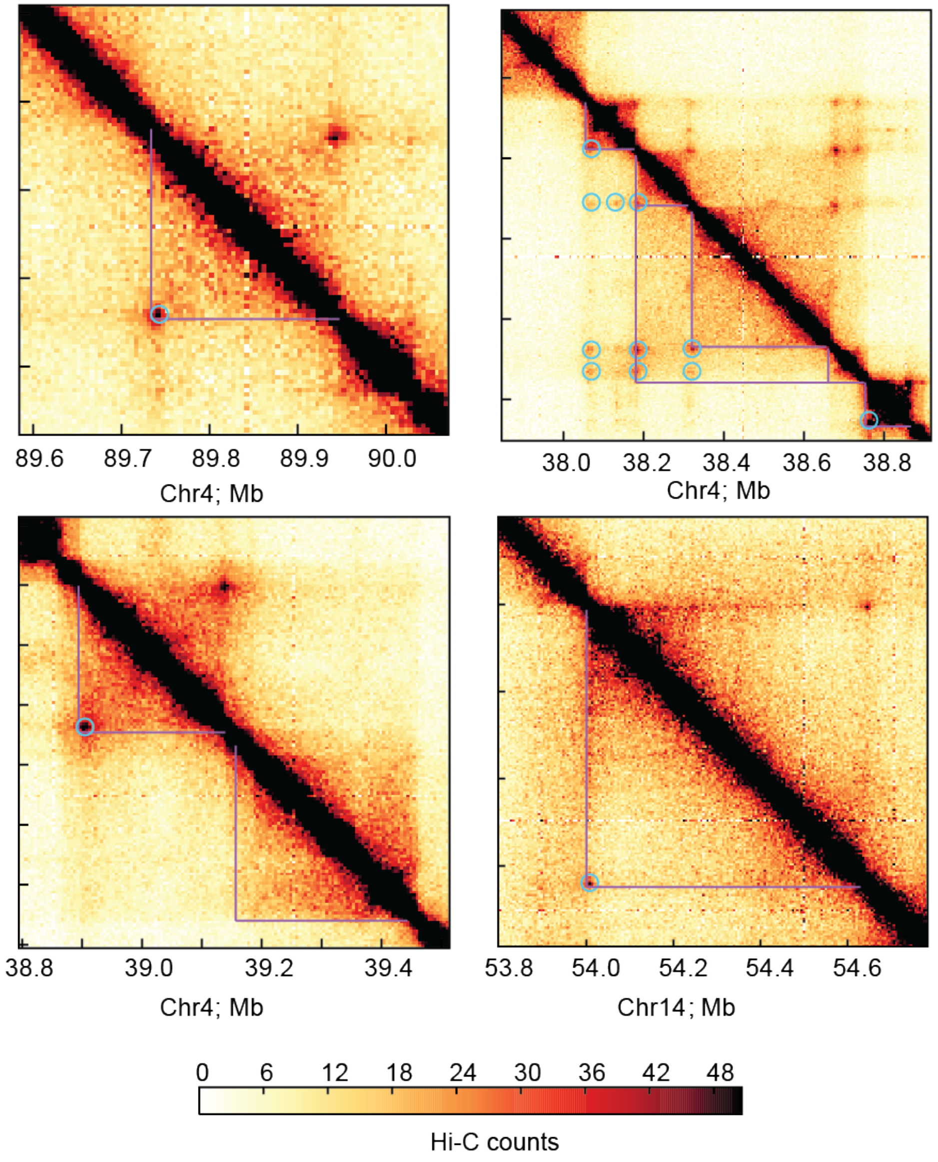
Gene
enhancers

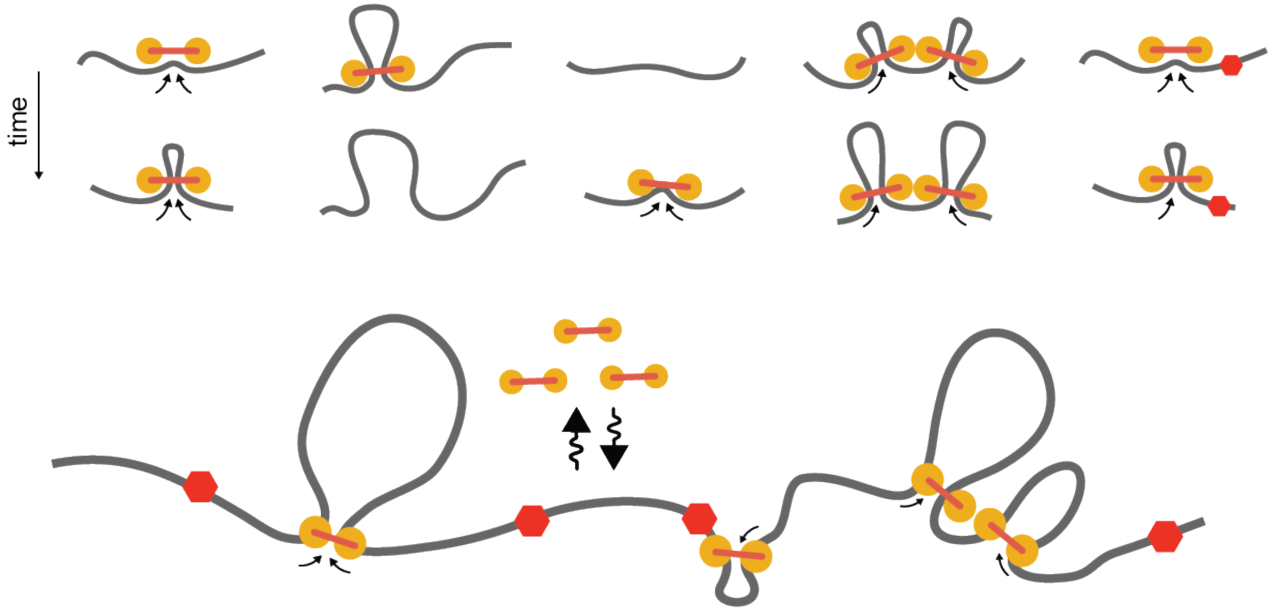
Gene

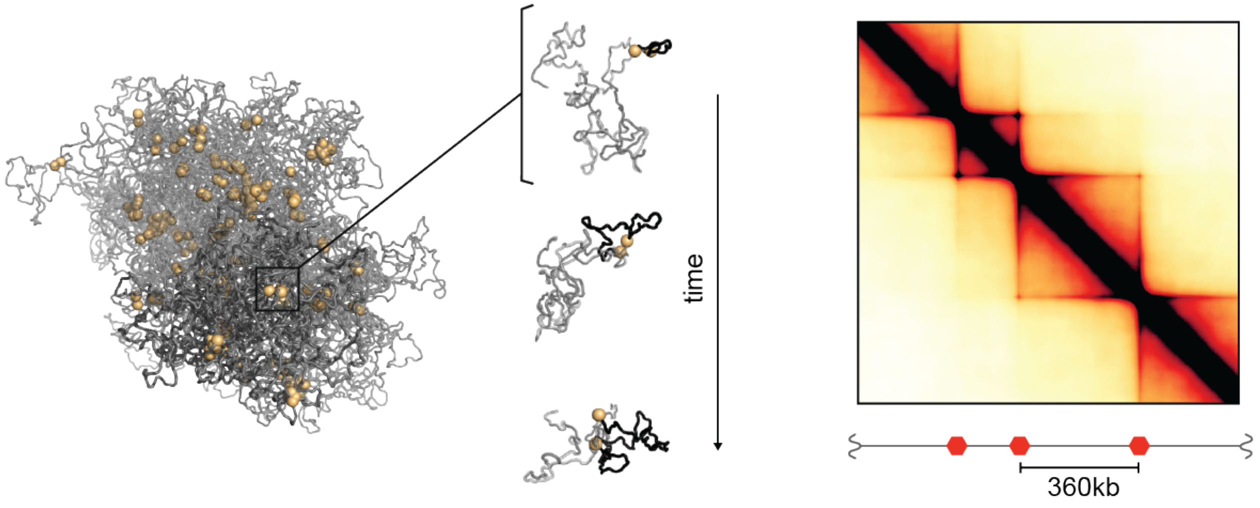
Gene
activity

Level V: Loop-extrusion as a driving force

Fudenberg, G., Imakaev, M., Lu, C., Goloborodko, A., Abdennur, N., & Mirny, L. A. (2015). Formation of Chromosomal Domains by Loop Extrusion. bioRxiv.

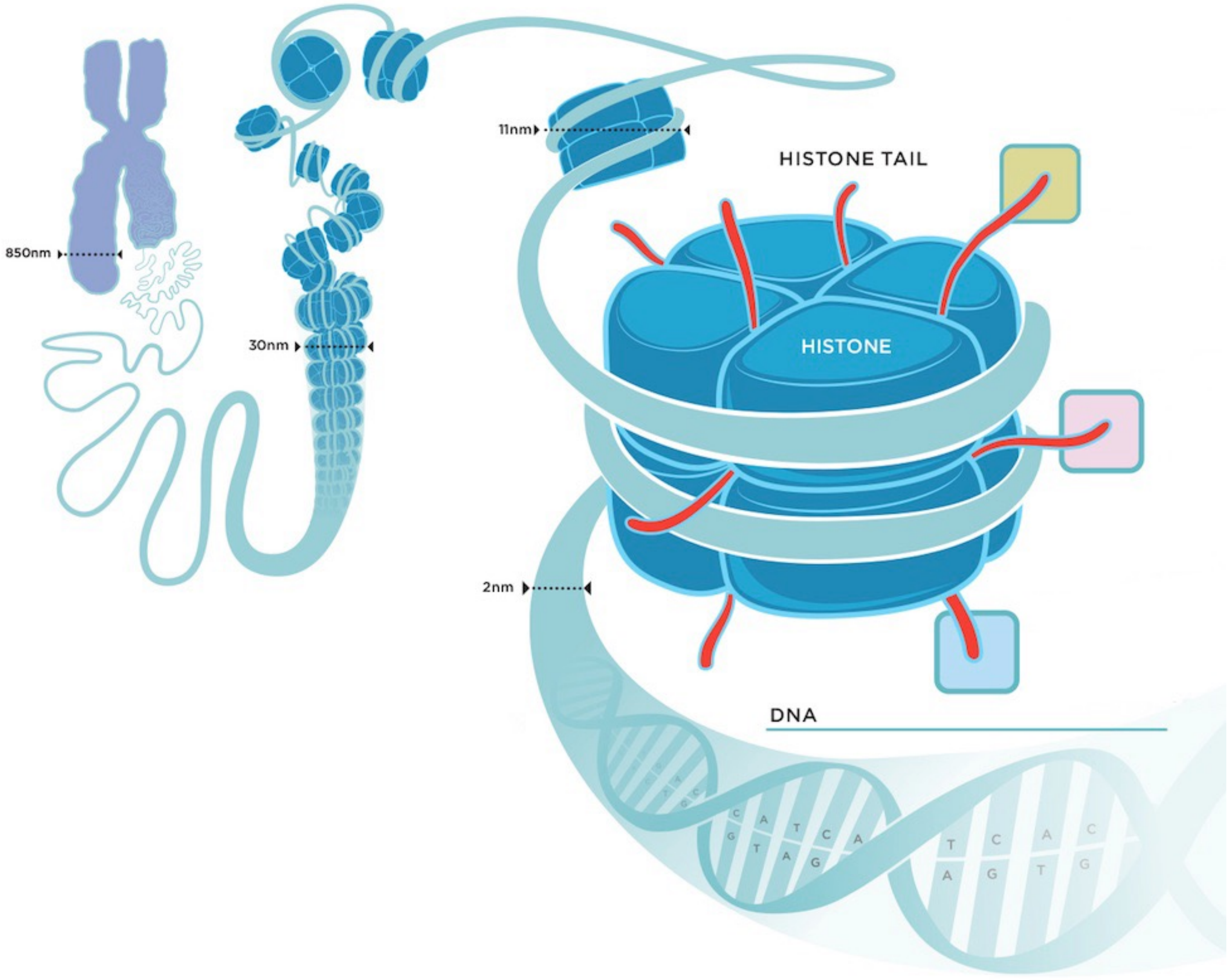






Level VI: Nucleosome

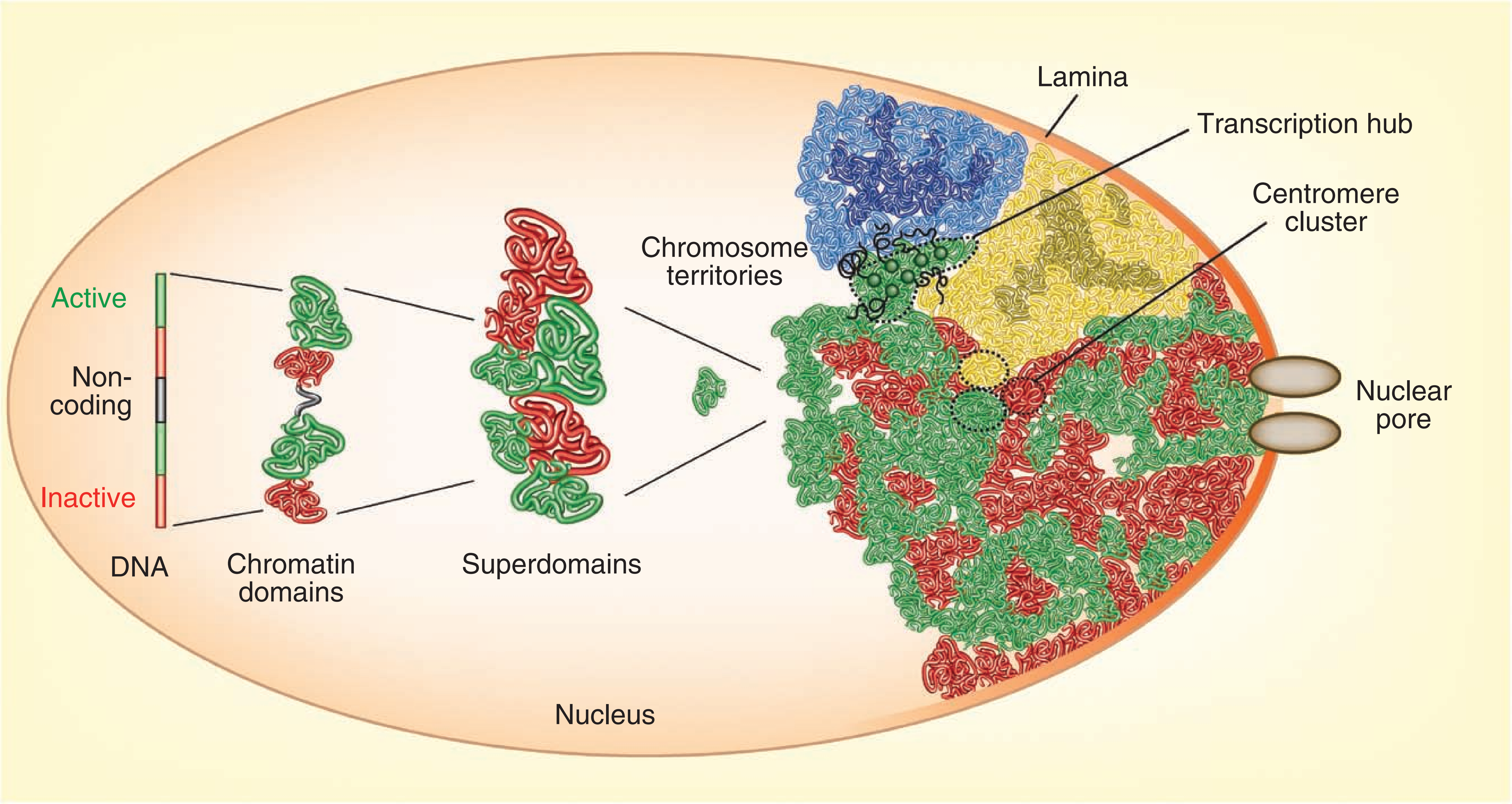
Chromosome **Chromatin fibre** **Nucleosome**



Adapted from Richard E. Ballermann, 2012

Complex genome organization

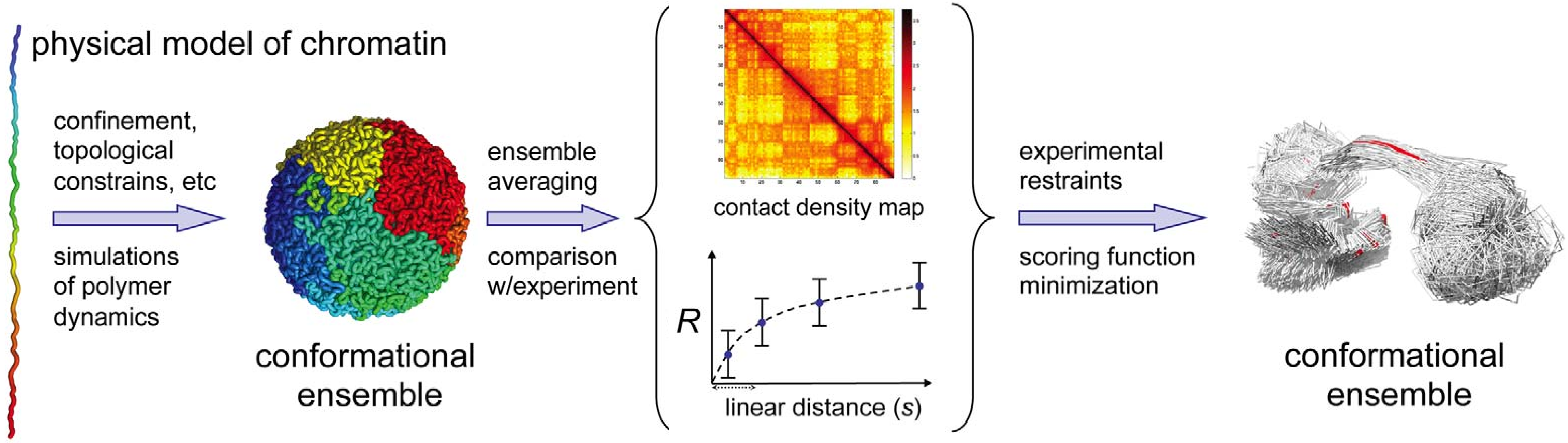
Cavalli, G. & Misteli, T. Functional implications of genome topology. Nat Struct Mol Biol 20, 290–299 (2013).



Marina Corral

Modeling Genomes

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



physical model of chromatin

confinement, topological constrains, etc

simulations of polymer dynamics

conformational ensemble

ensemble averaging

comparison w/experiment

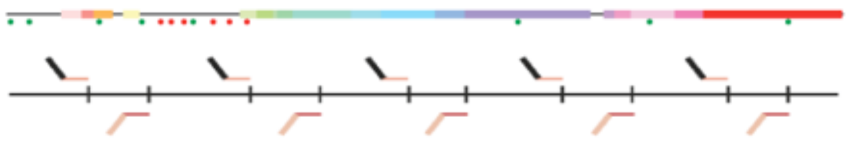
contact density map

experimental restraints

scoring function minimization

conformational ensemble

Experiments



Grow GM12878 and K562 cells

↓

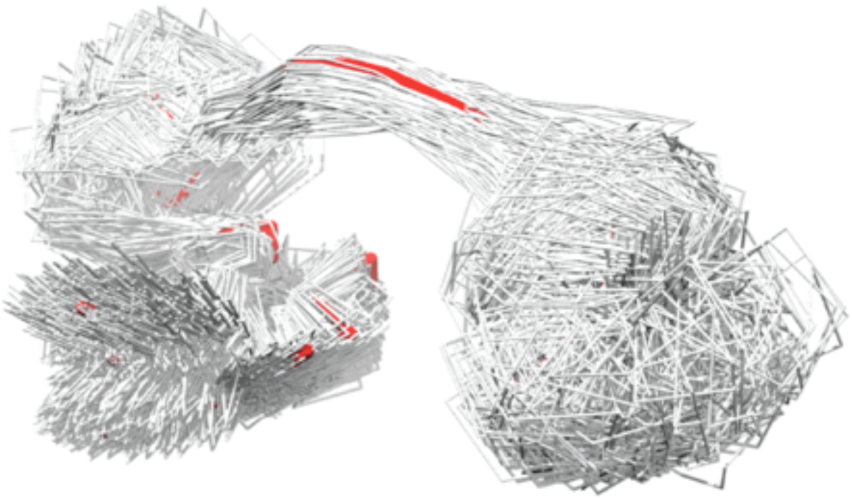
Perform 3C analysis

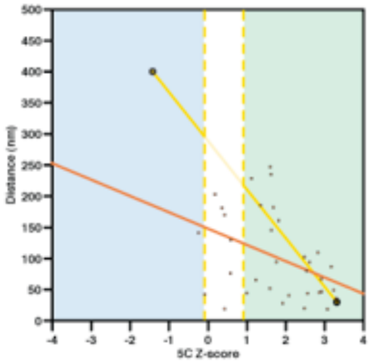
↓

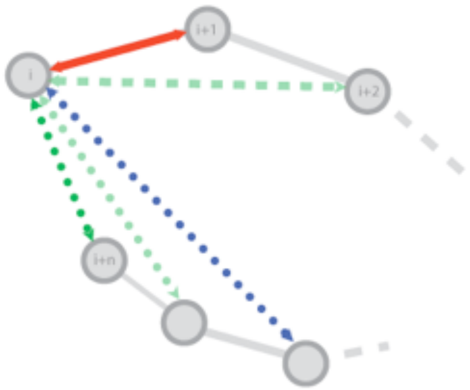
Perform 5C analysis with 30+25 primers

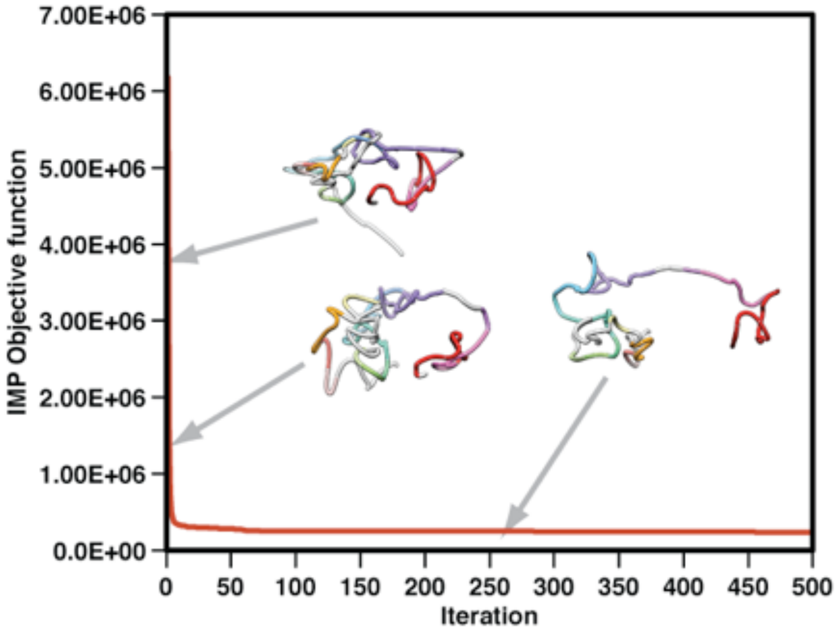
↓

Analyze 5C products by paired-end Solexa sequencing
(131,947 paired end reads per library)

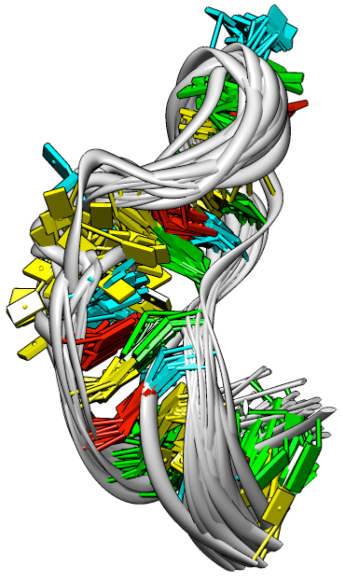


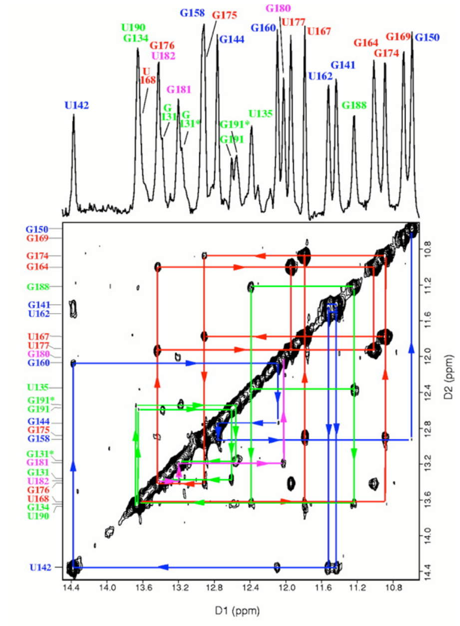




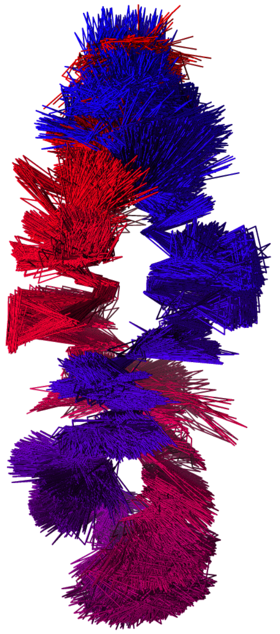


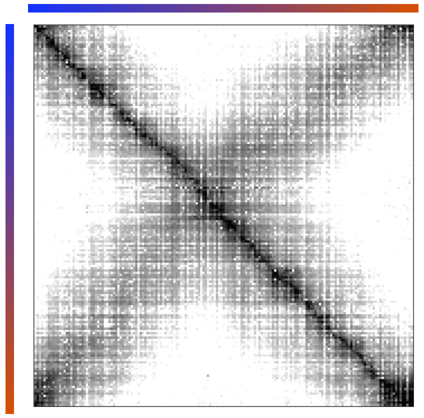
Computation





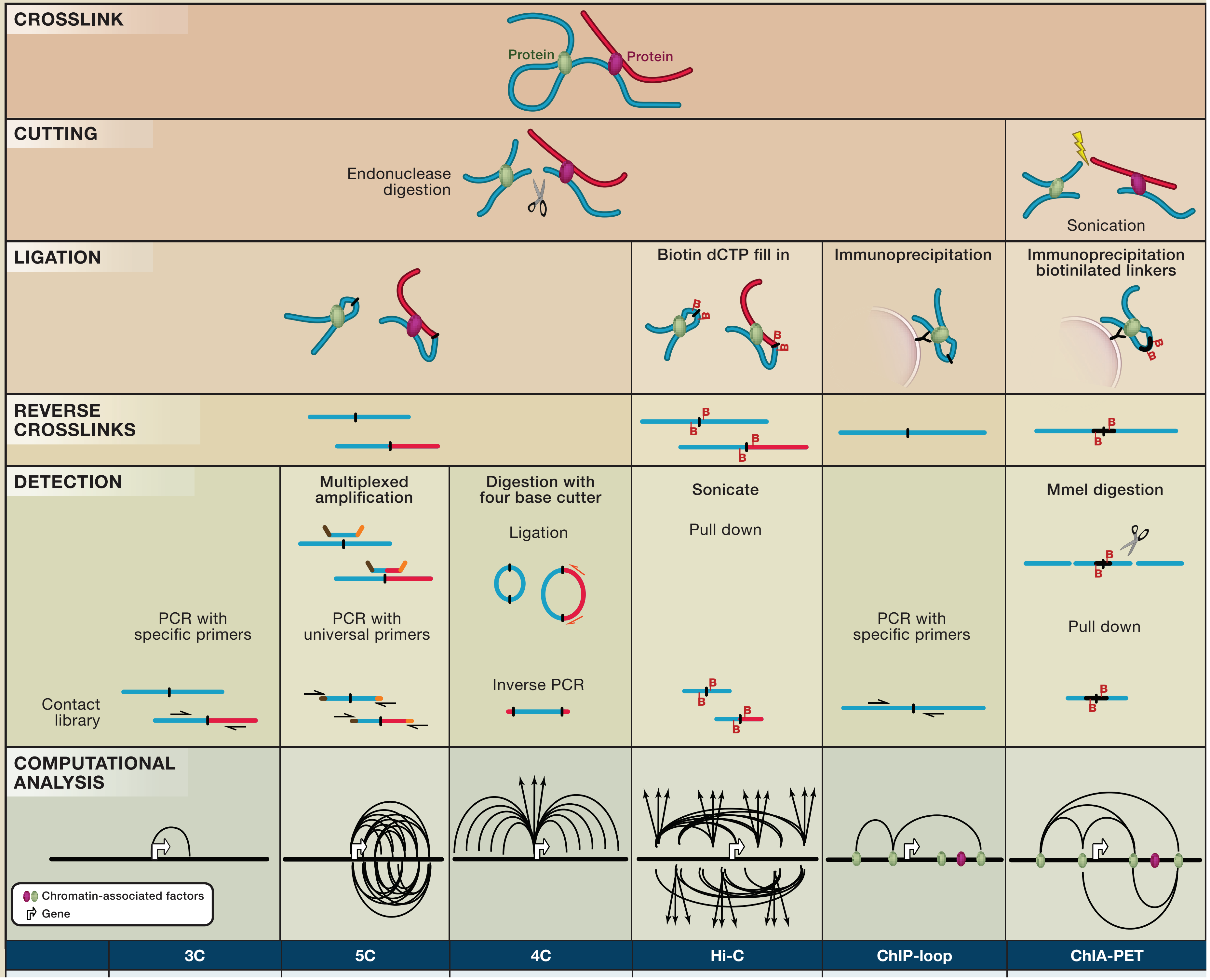
Biomolecular structure determination
2D-NOESY data





Chromosome structure determination
5C data

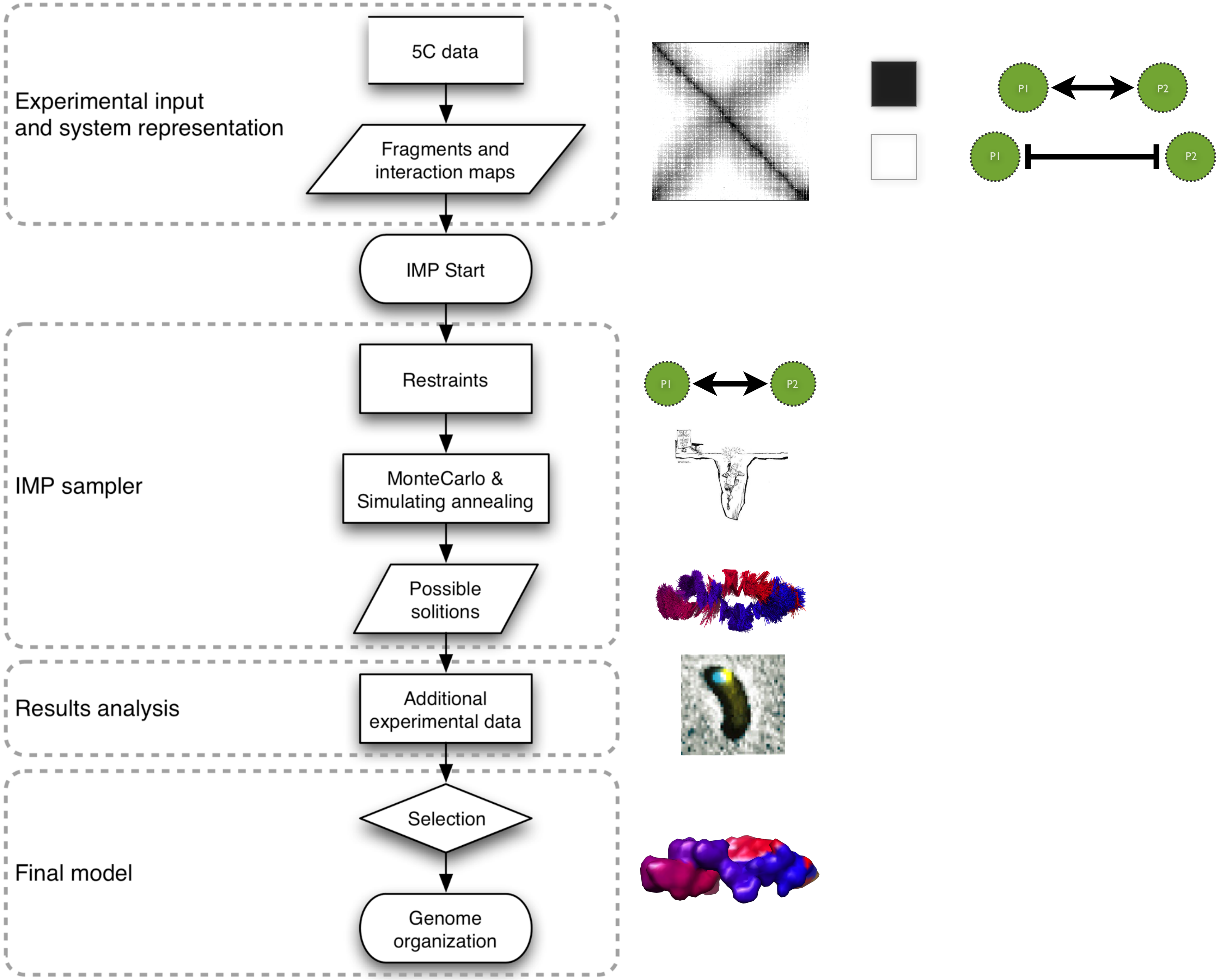
Chromosome Conformation Capture



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

Modeling 3D Genomes

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



Experimental input and system representation

5C data

Fragments and interaction maps

IMP Start

IMP sampler

Restraints

MonteCarlo & Simulating annealing

Possible solitions

Results analysis

Additional experimental data

Final model

Selection

Genome organization

Example of 3D Genome