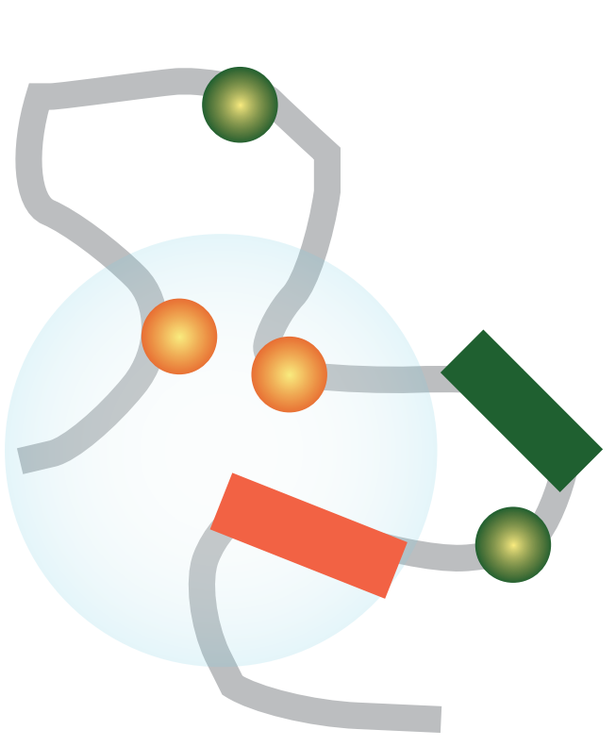
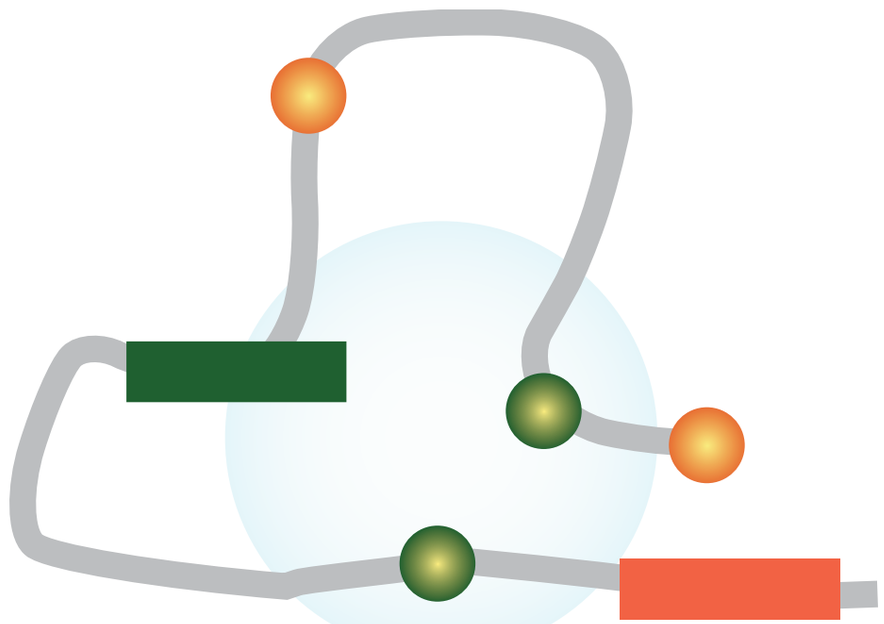
Structure determination of genomes and genomic domains by satisfaction of spatial restraints

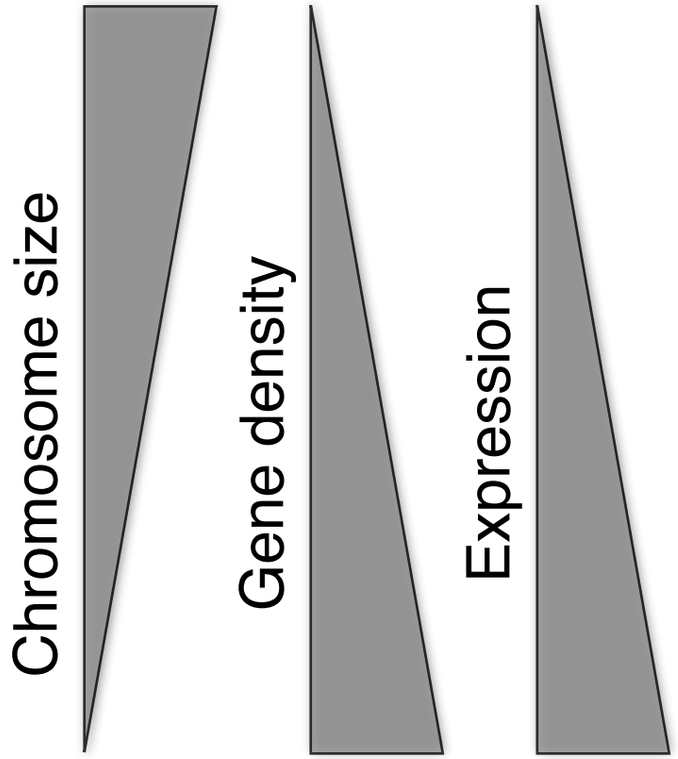
Marc A. Marti-Renom
Structural Genomics Group (CNAG-CRG)

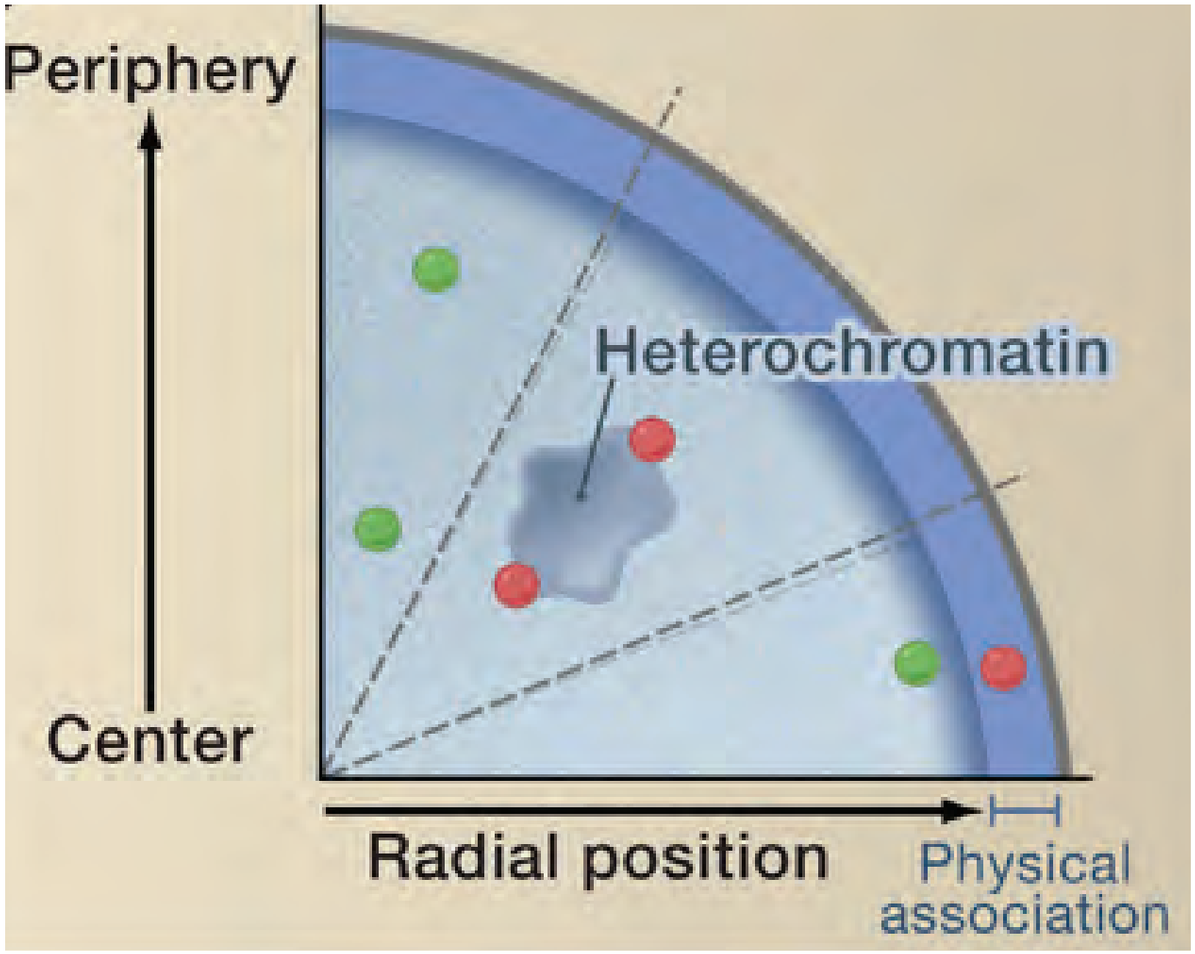




Complex genome organization

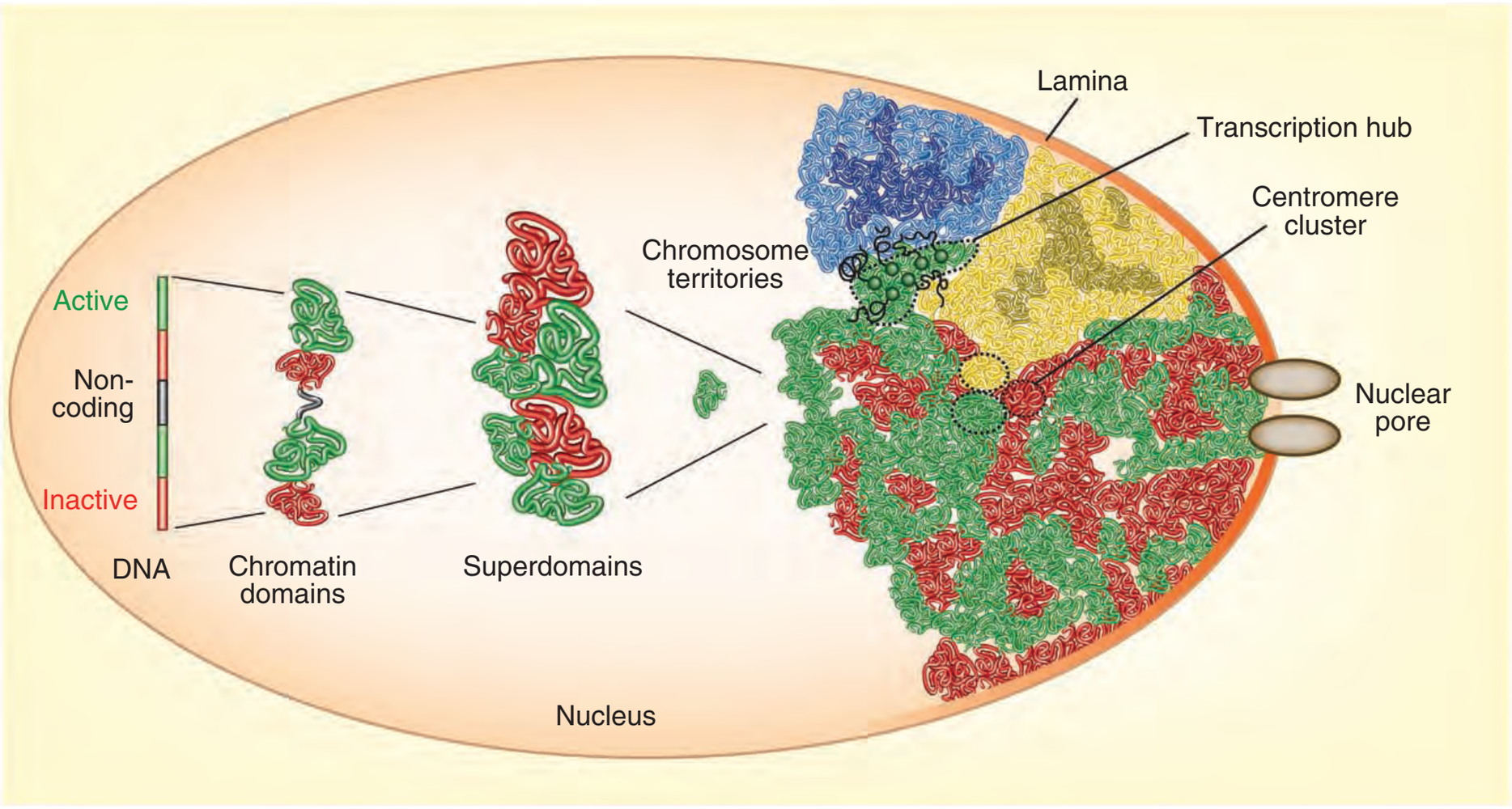
Takizawa, T., Meaburn, K. J. & Misteli, T. The meaning of gene positioning. Cell 135, 9–13 (2008).





Complex genome organization

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

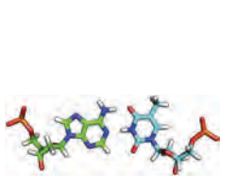


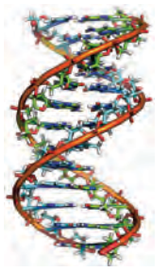
Marina Corral

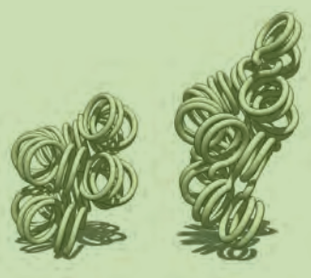
Resolution Gap

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

Knowledge

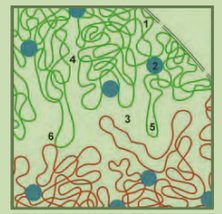


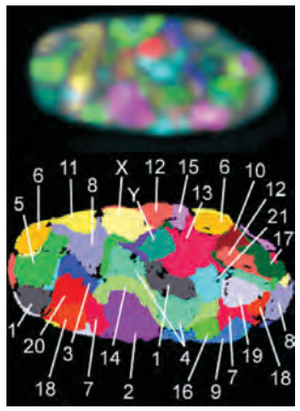




IDM

INM





DNA length

10^0 10^3 10^6 10^9 nt

Volume

10^{-9} 10^{-6} 10^{-3} 10^0 10^3 μm^3

Time

10^{-10} 10^{-8} 10^{-6} 10^{-4} 10^{-2} 10^0 10^2 10^3 s

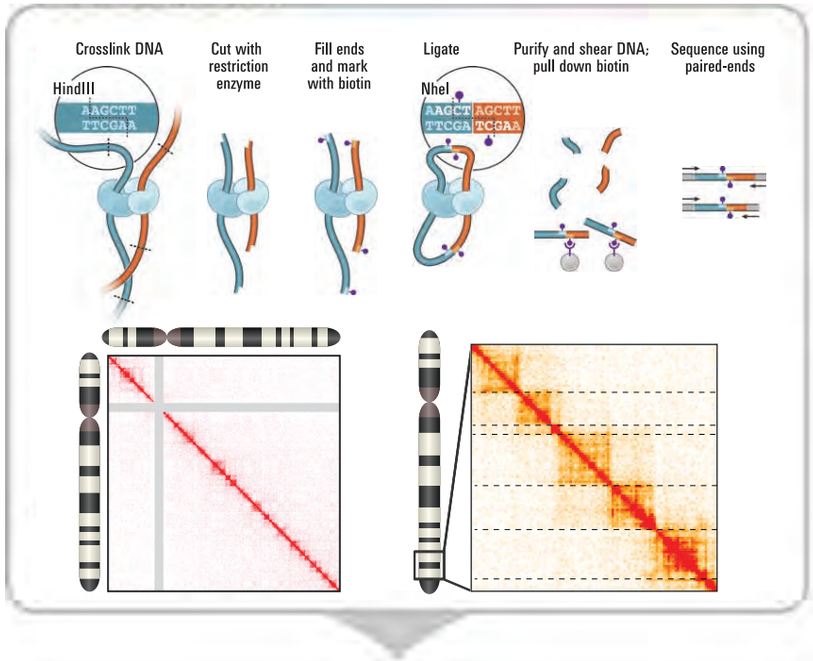
Resolution

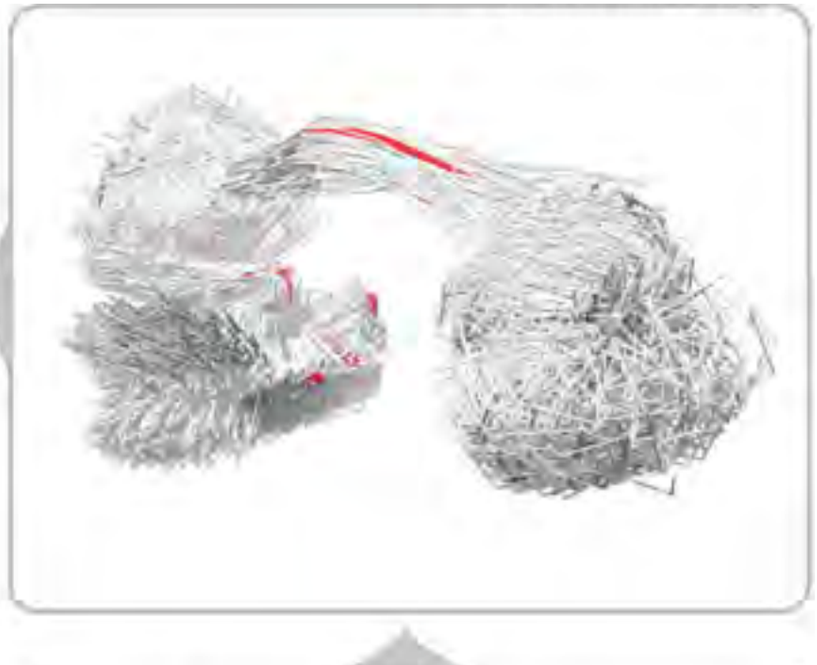
10^{-3} 10^{-2} 10^{-1} μ

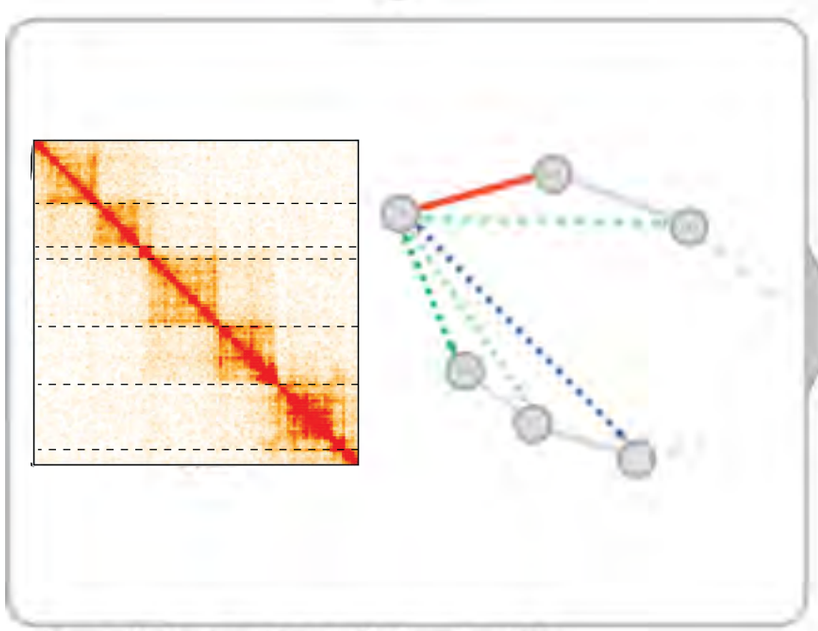
Hybrid Method

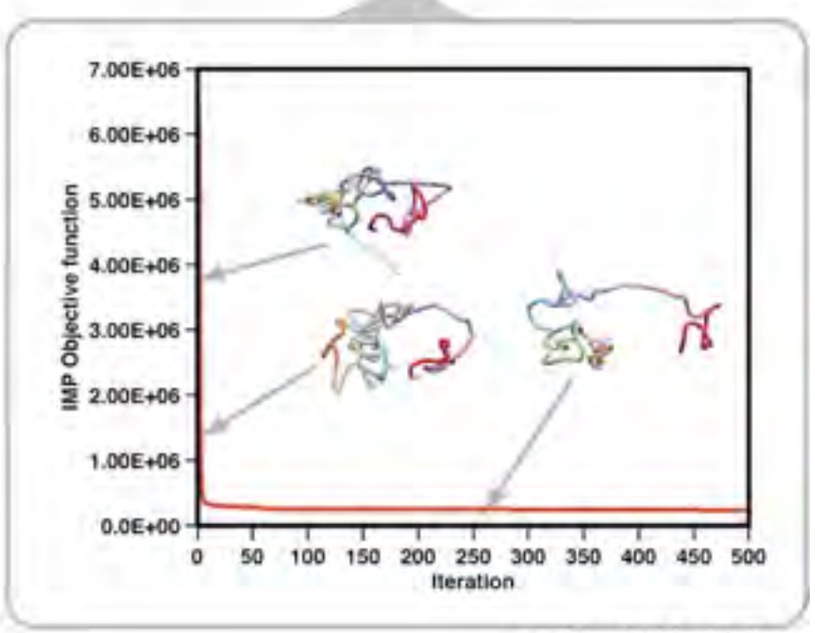
Baù, D. & Marti-Renom, M. A. Methods 58, 300–306 (2012).

Experiments





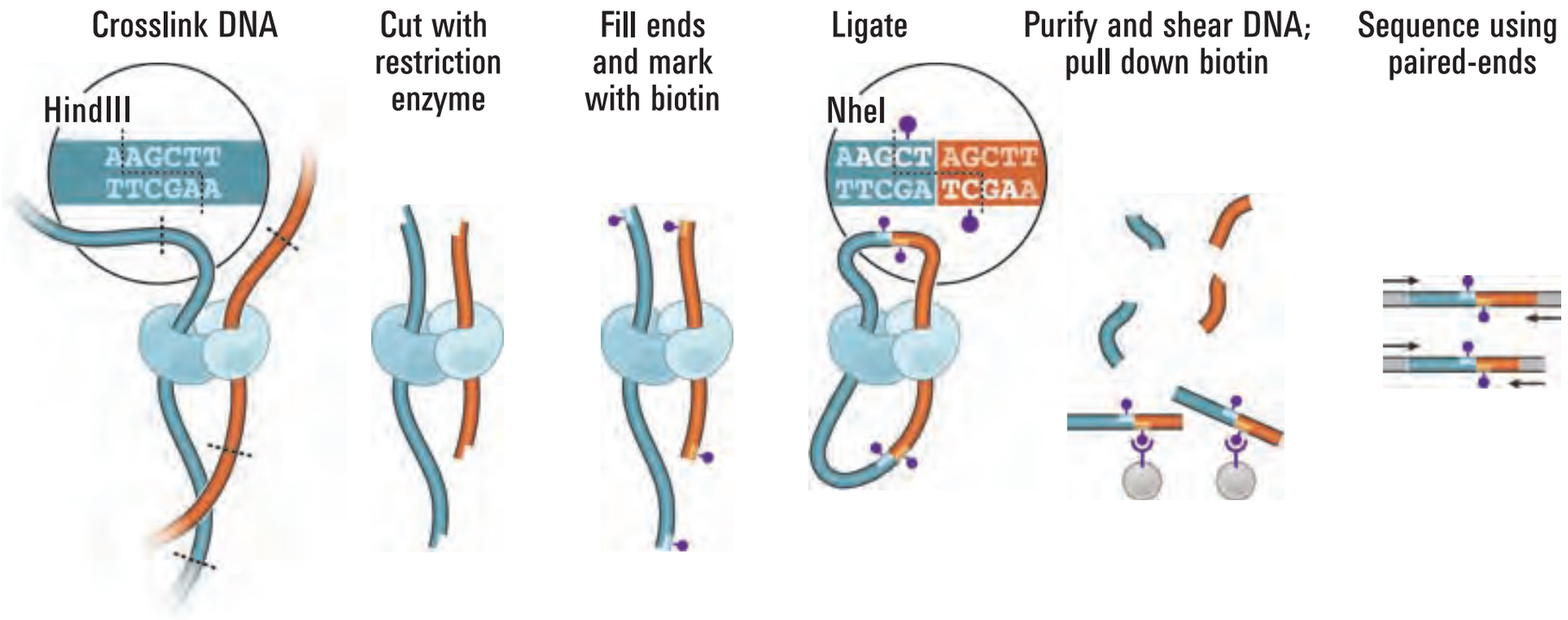




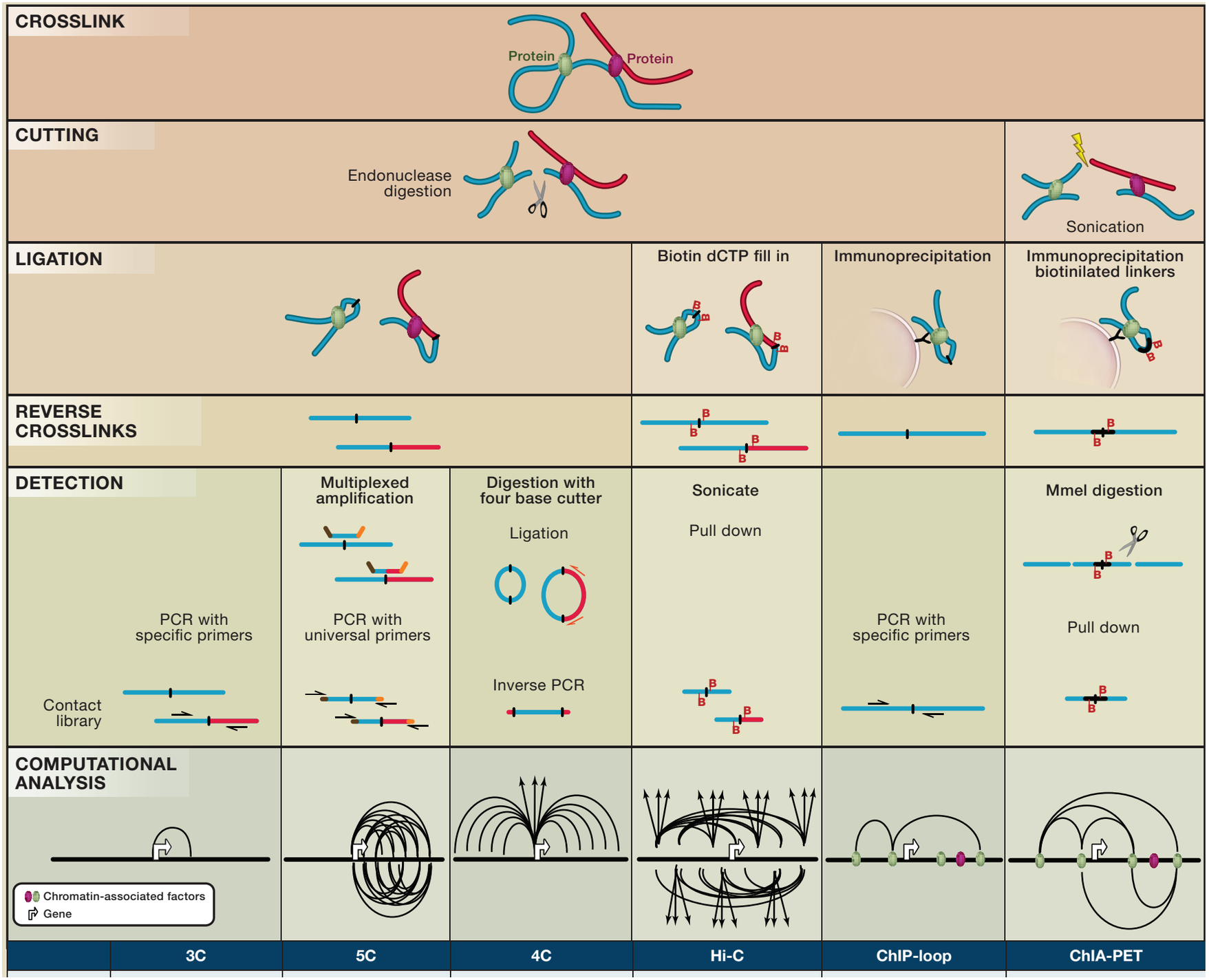
Computation

Chromosome Conformation Capture

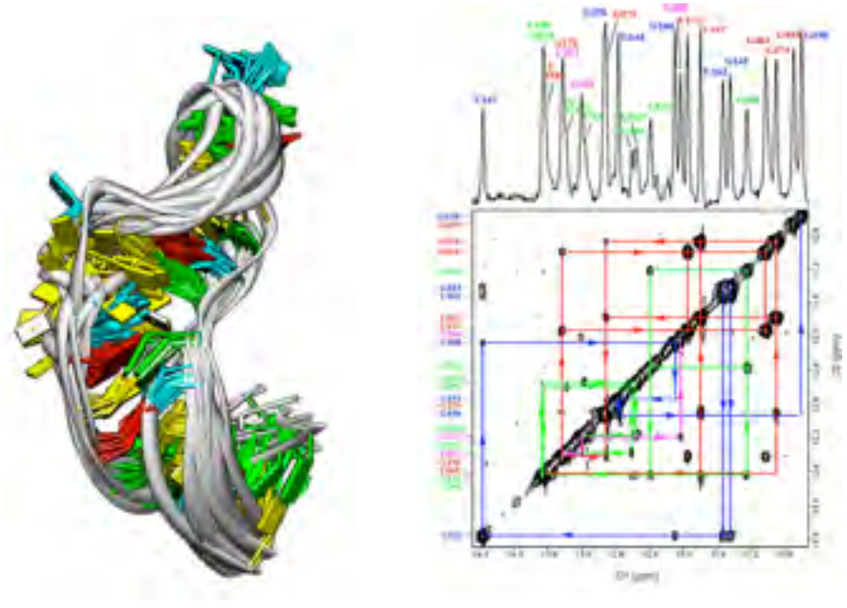
Dekker, J., Rippe, K., Dekker, M., & Kleckner, N. (2002). Science, 295(5558), 1306–1311.
Lieberman-Aiden, E., et al. (2009). Science, 326(5950), 289–293.



Chromosome Conformation Capture

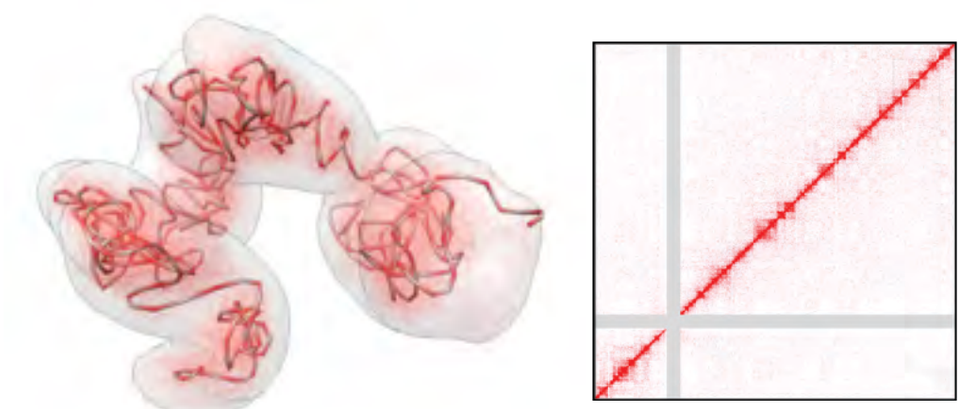


Structure determination by satisfaction of spatial restraints



Biomolecular structure determination

2D-NOESY data

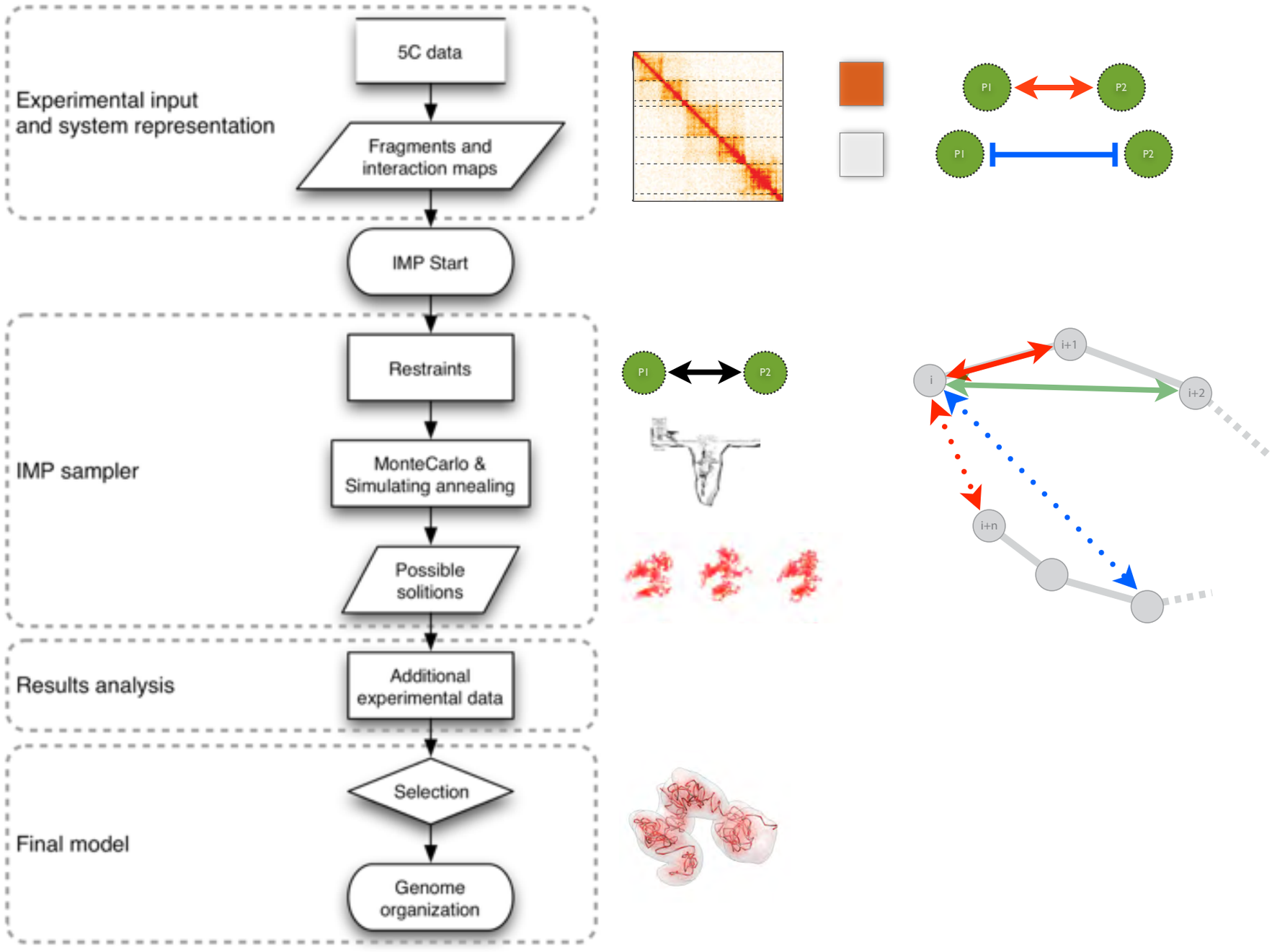


Chromosome structure determination

3C-based data

TADbit

http://3DGenomes.org



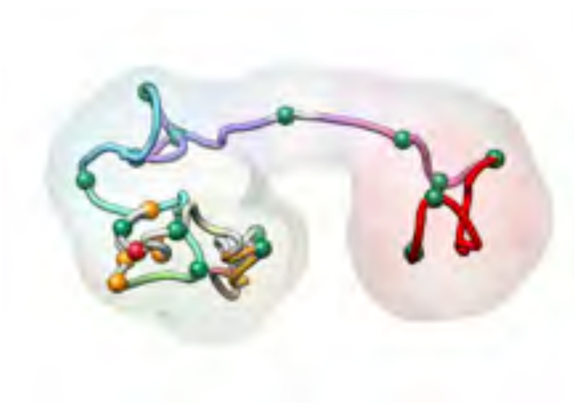
TADbit previous applications...

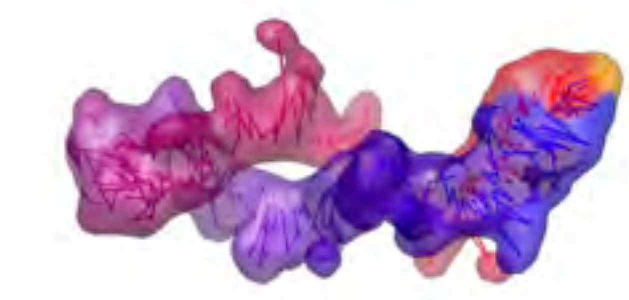
Baù, D. et al. Nat Struct Mol Biol (2011).
Umbarger, M. A. et al. Mol Cell (2011).

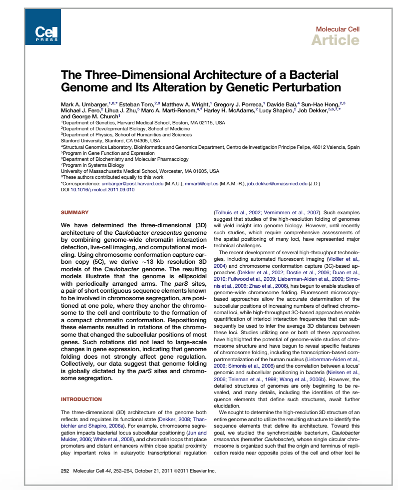

TECHNICAL REPORTS

nature structural & molecular biology

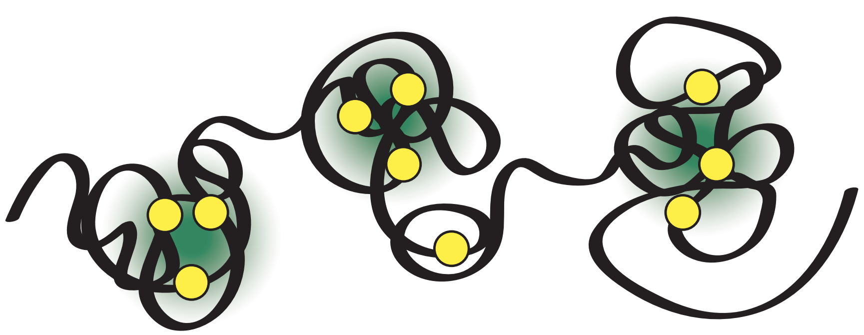
The three-dimensional folding of the α-globin gene domain reveals formation of chromatin globules






Molecular Cell
Article

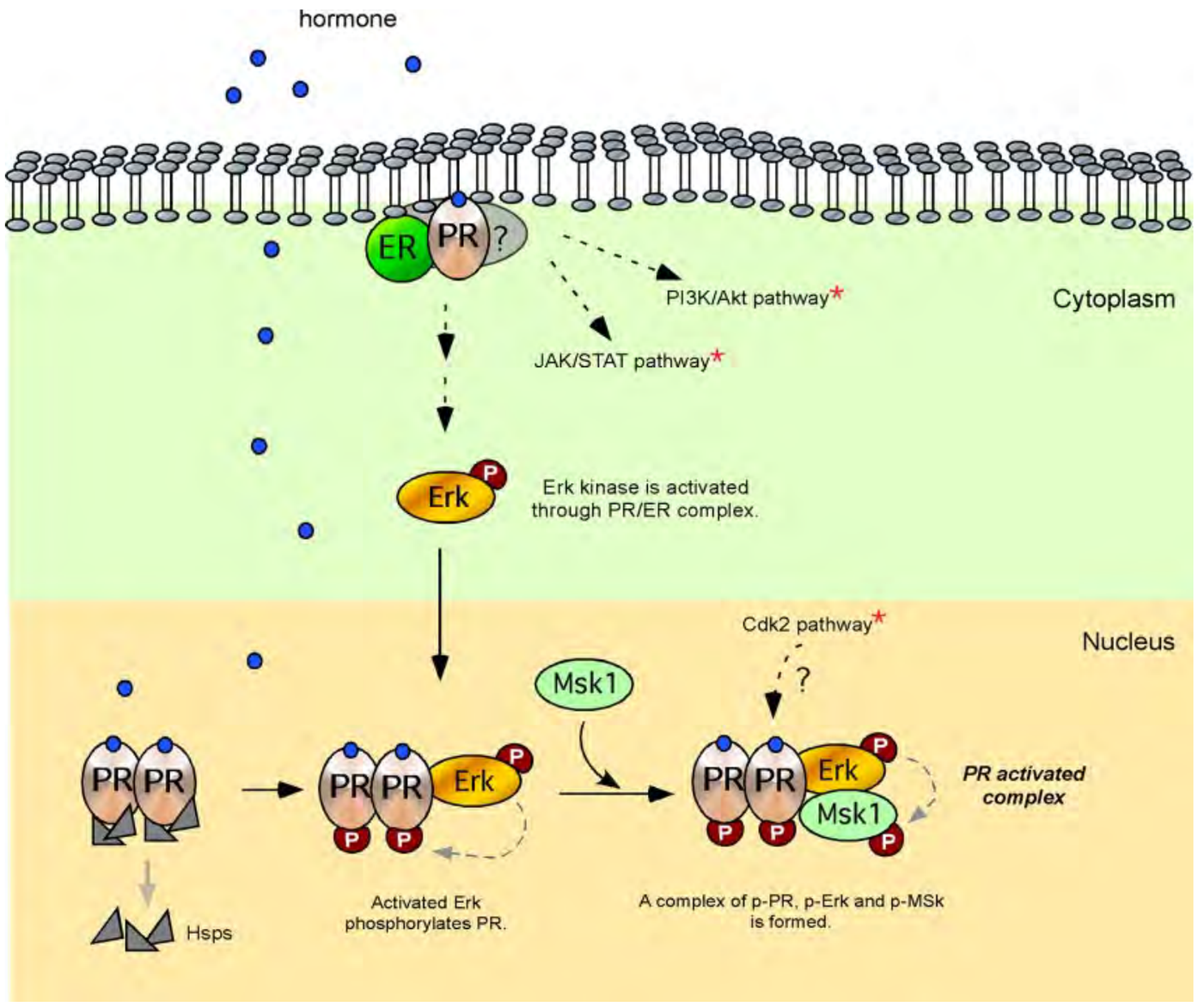
The Three-Dimensional Architecture of a Bacterial Genome and Its Alteration by Genetic Perturbation



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

François Le Dily *et al.* Genes and Development (2014)

Progesterone-regulated transcription in breast cancer



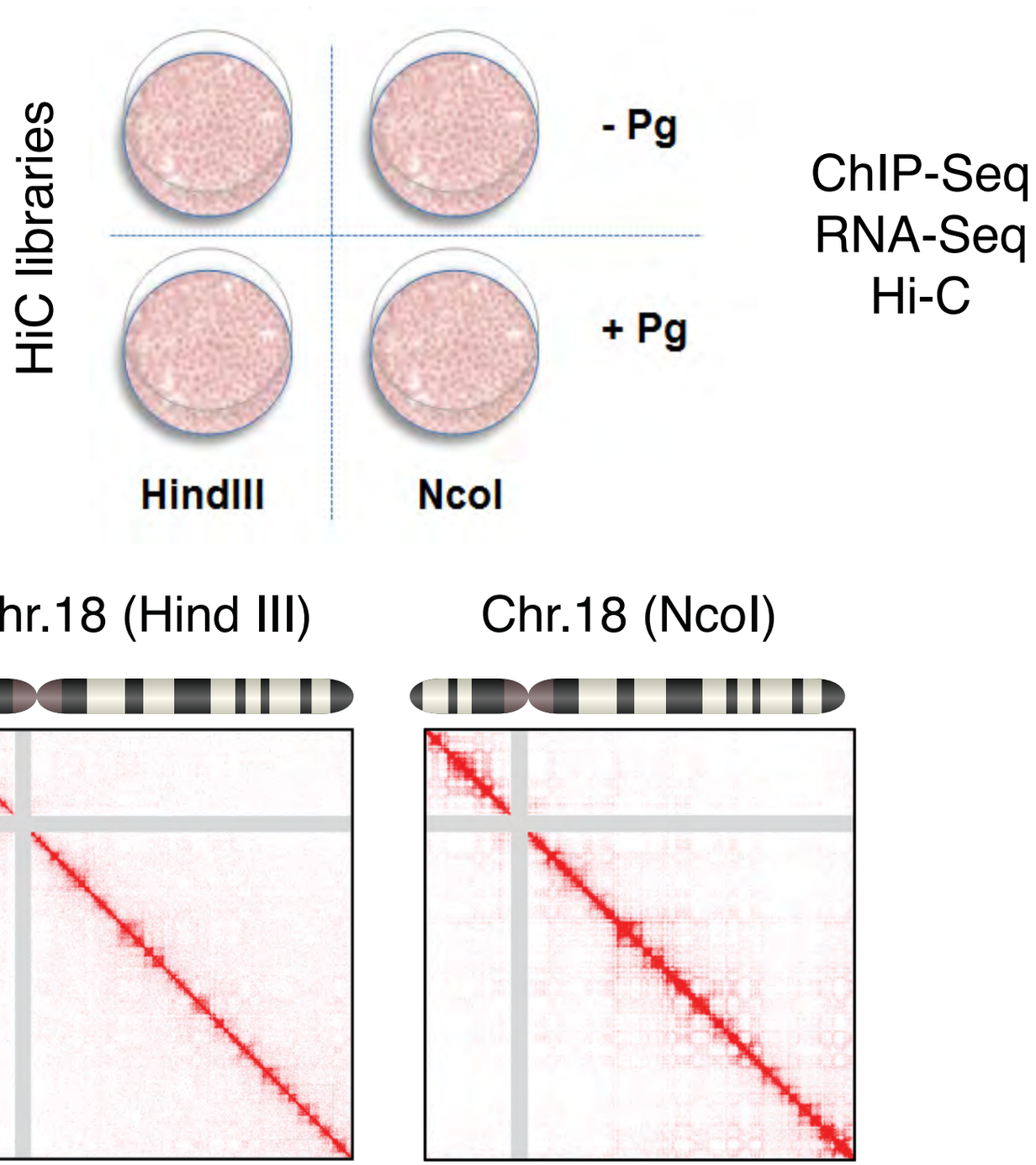
Vicent *et al* 2011, Wright *et al* 2012, Ballare *et al* 2012

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

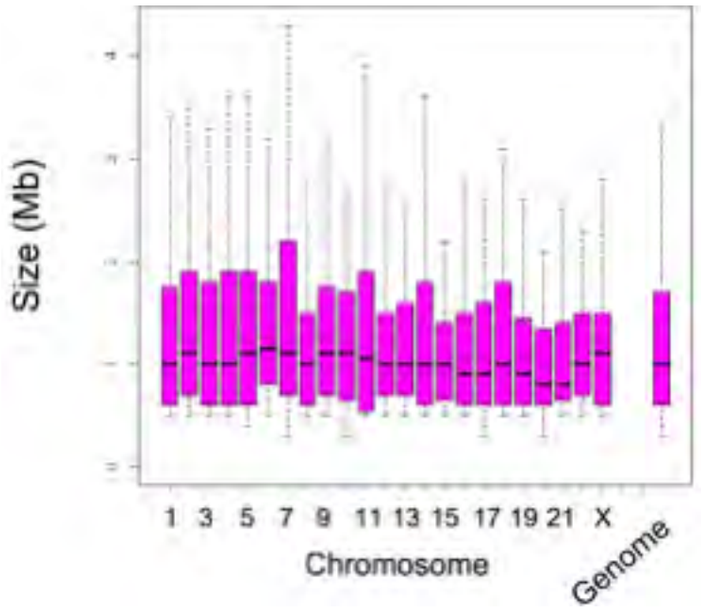
> 2,000 genes **Down**-regulated

Regulation in 3D?

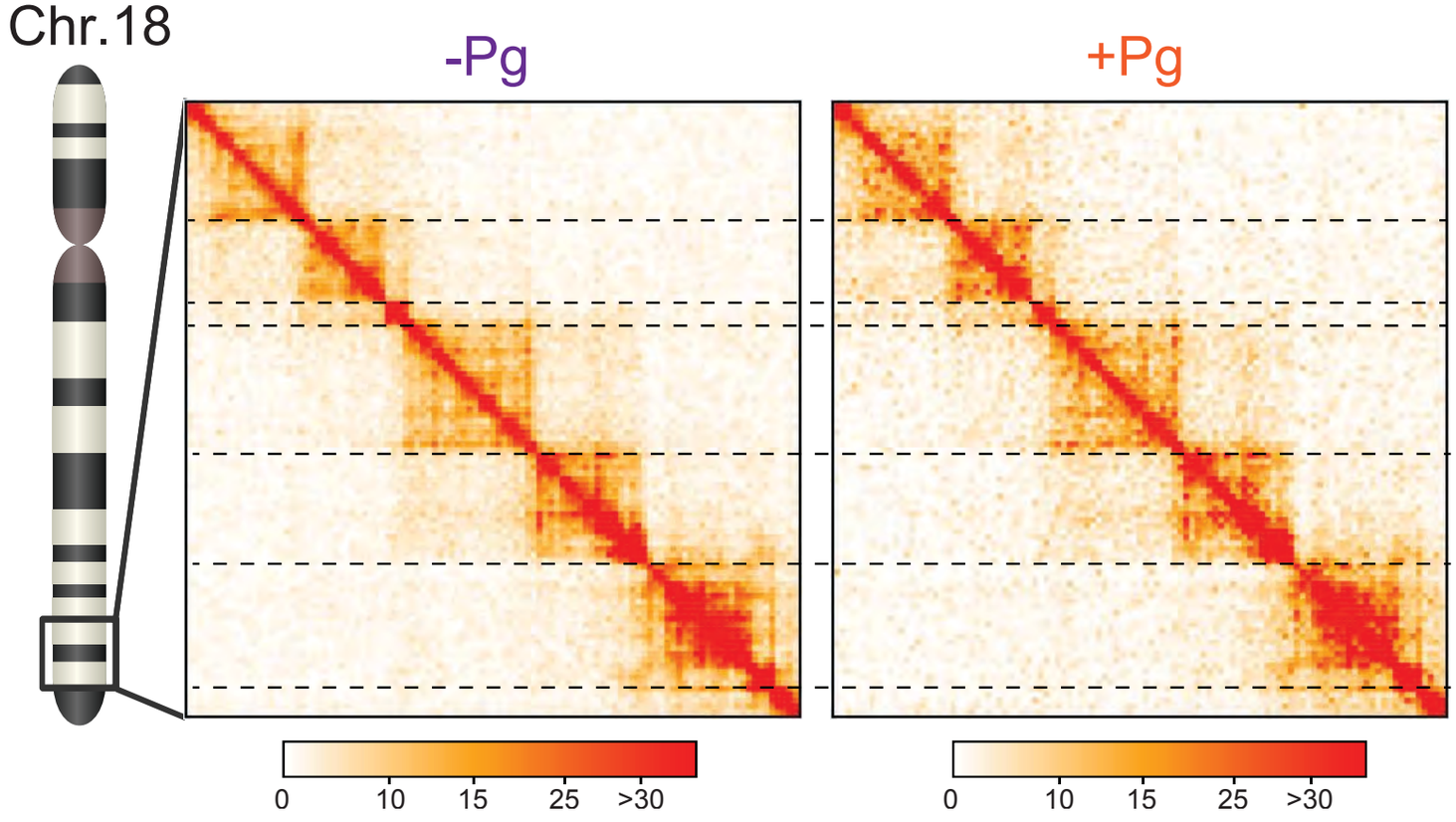
Experimental design

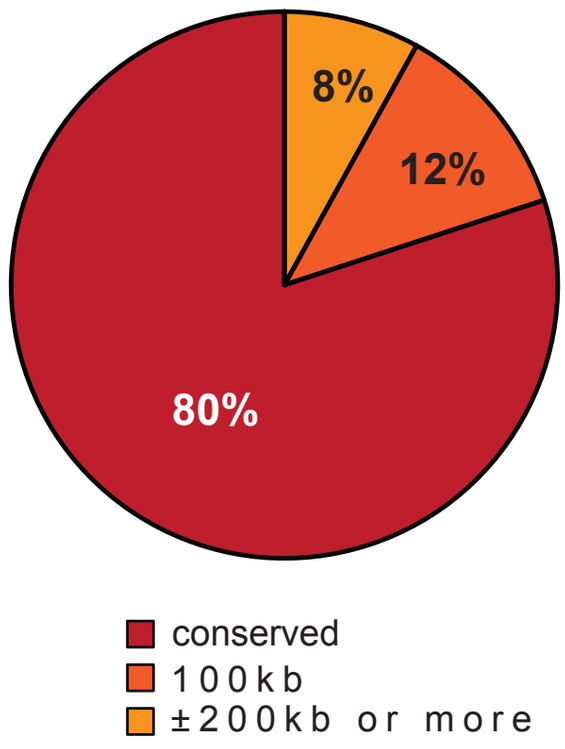


Are there TADs? how robust?

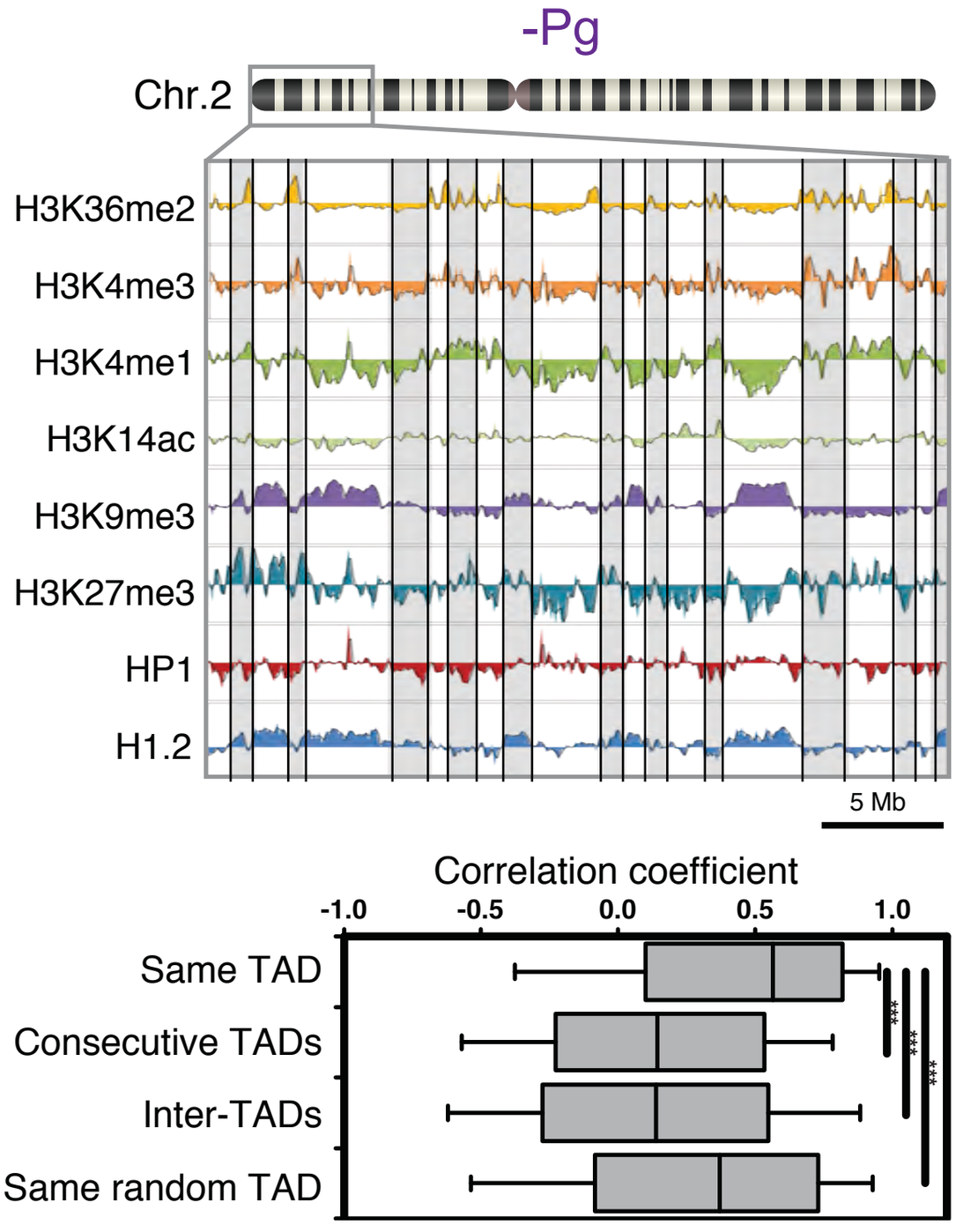


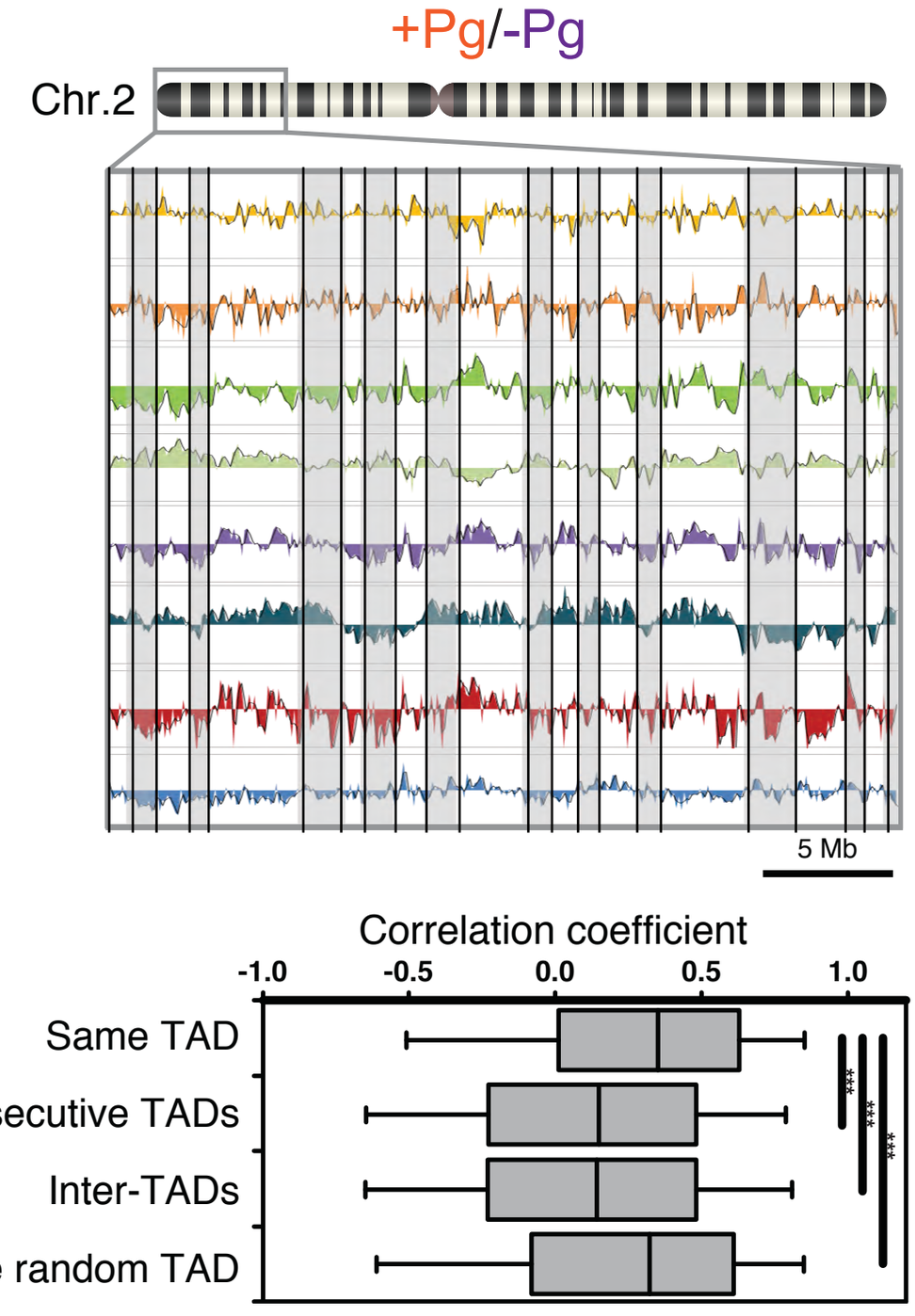
>2,000 detected TADs



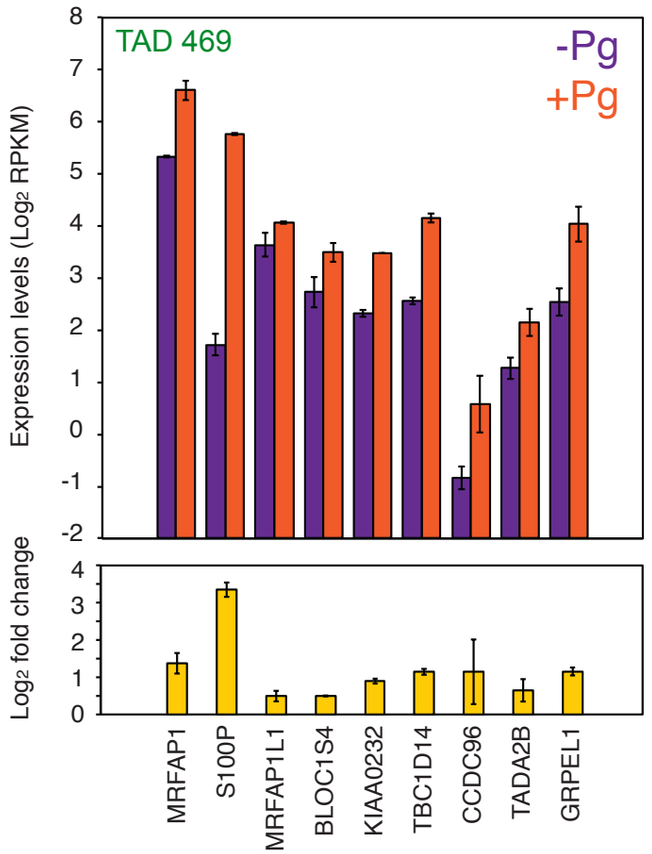


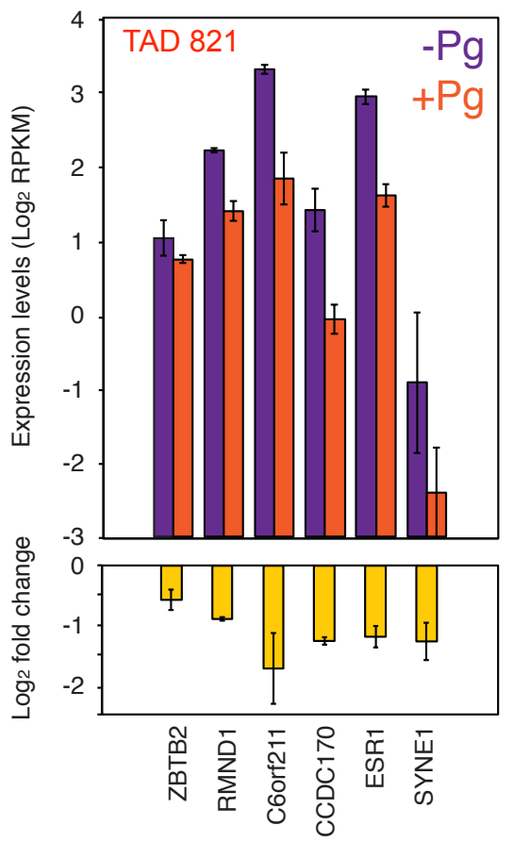
Are TADs homogeneous?

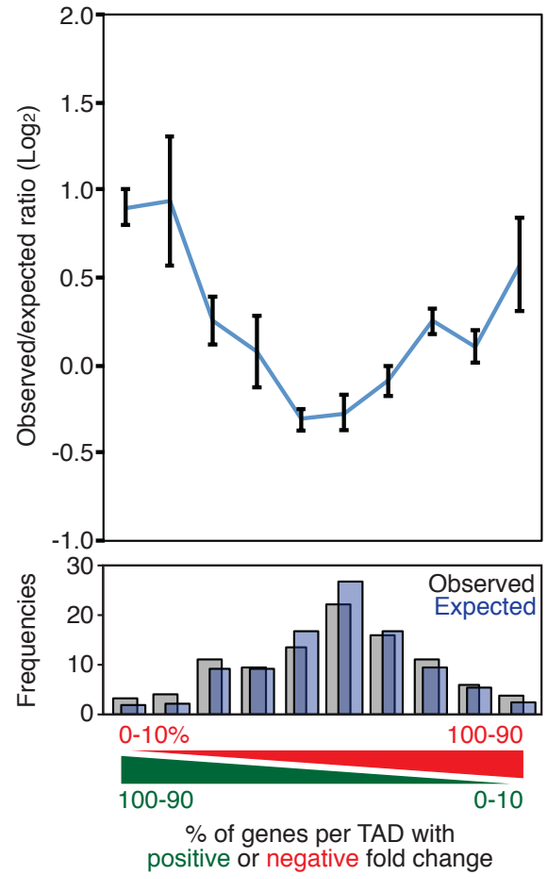




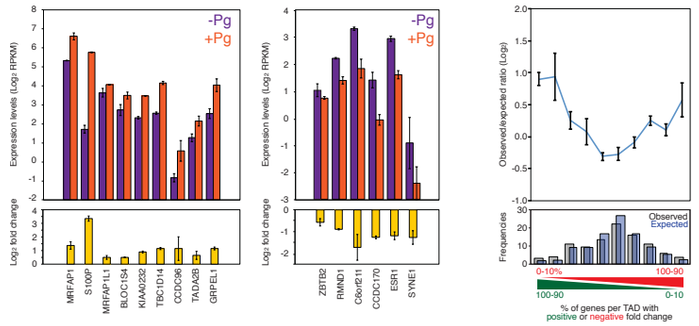
Do TADs respond differently to Pg treatment?



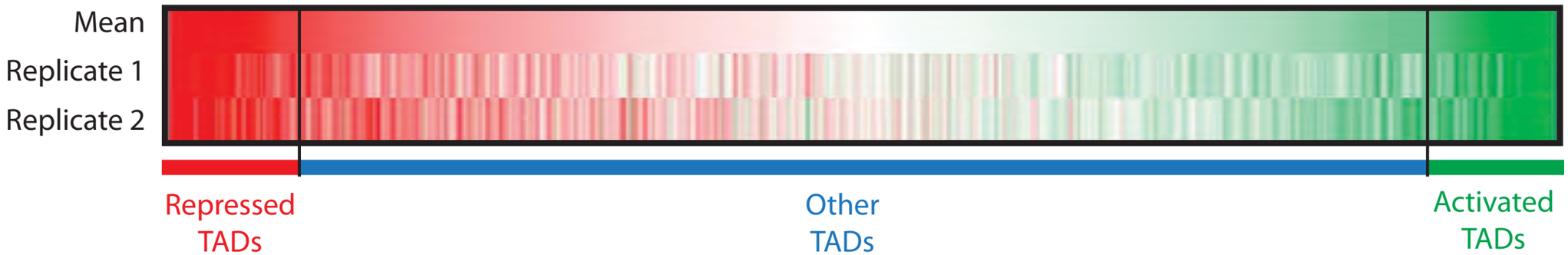




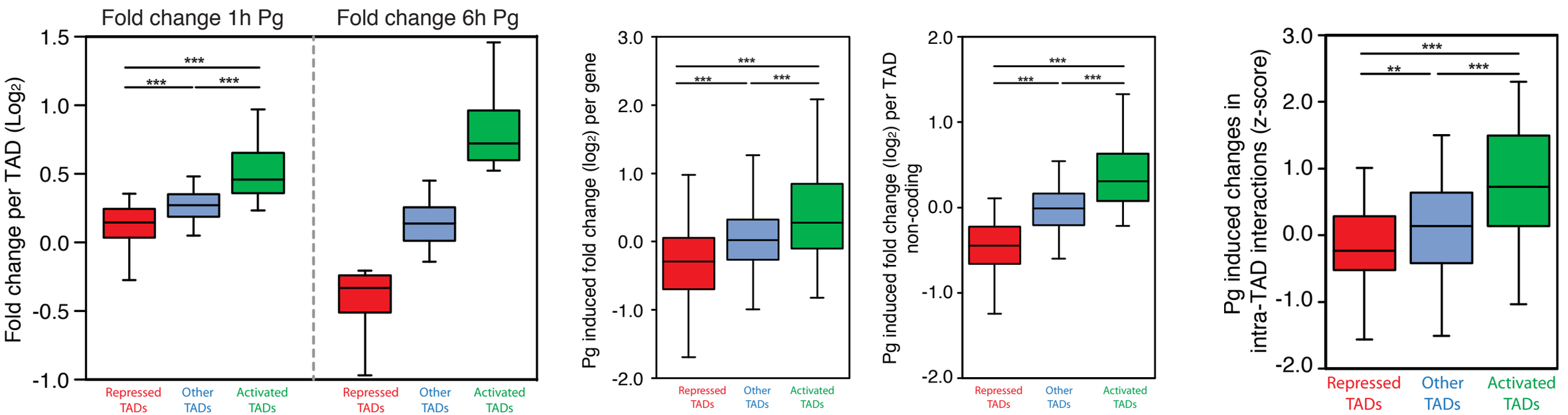
Do TADs respond differently to Pg treatment?



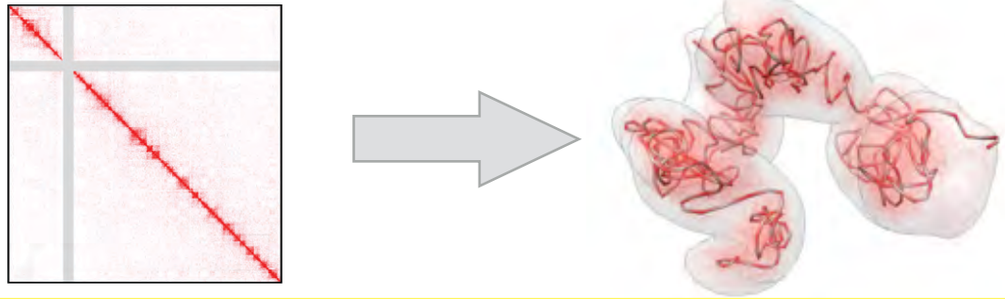
Pg induced fold change per TAD (6h)



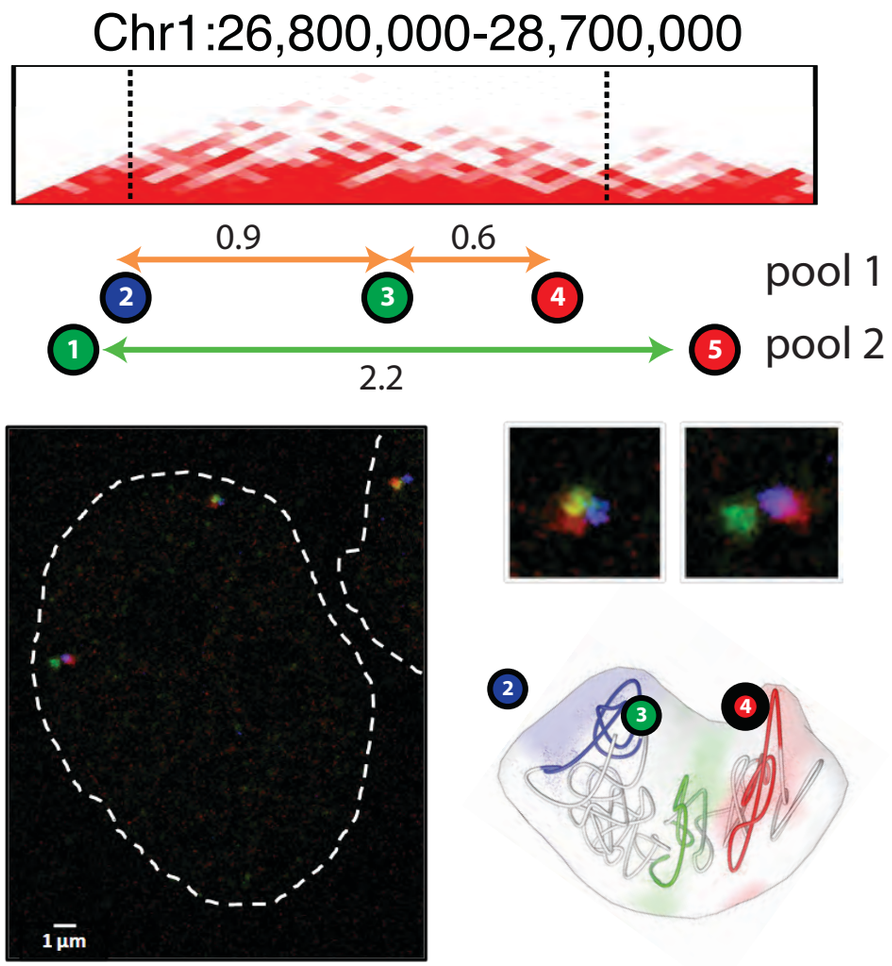
Repressed TADs | Other TADs | Activated TADs

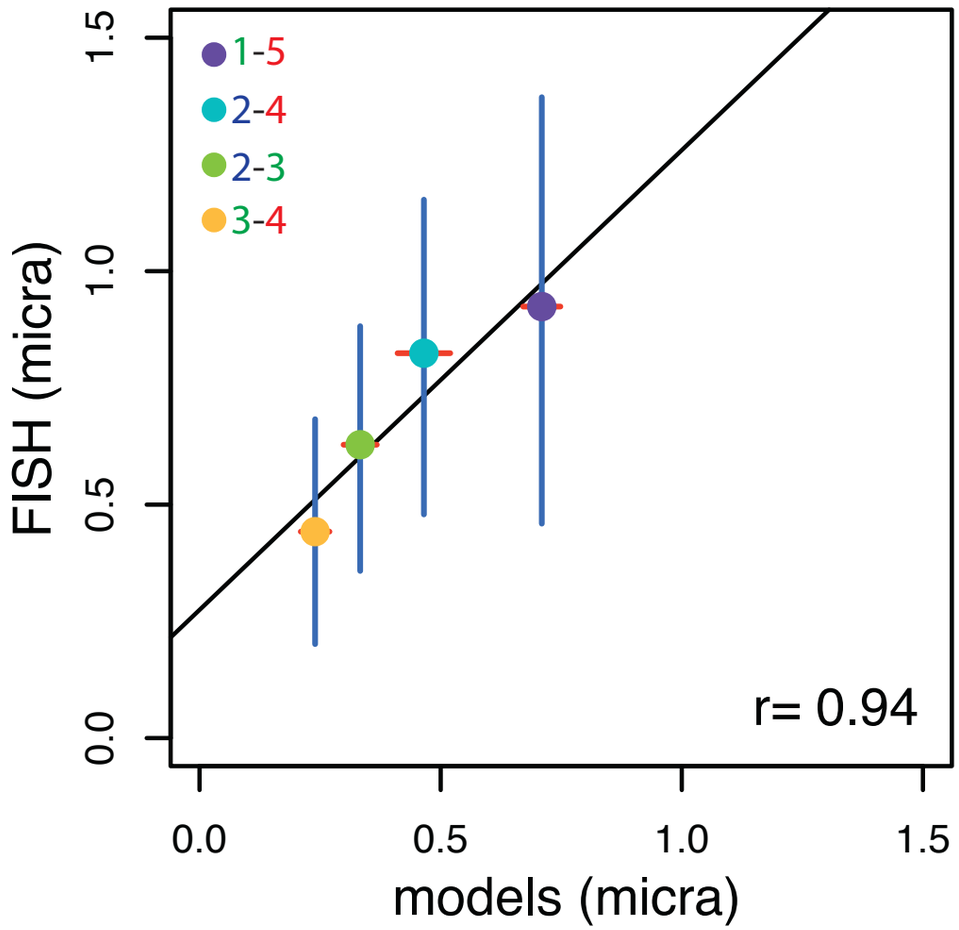


Modeling 3D TADs



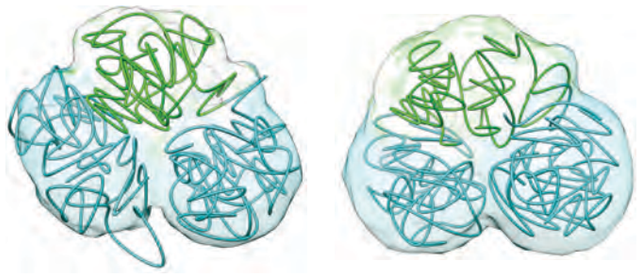
61 genomic regions containing 209 TADs covering 267Mb



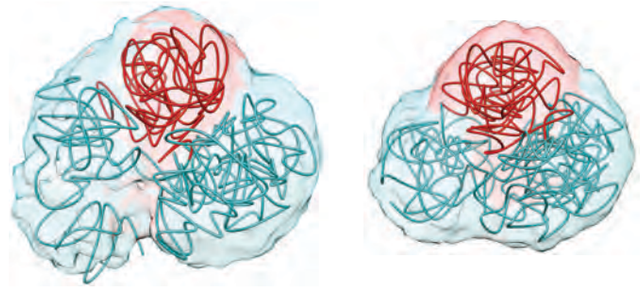


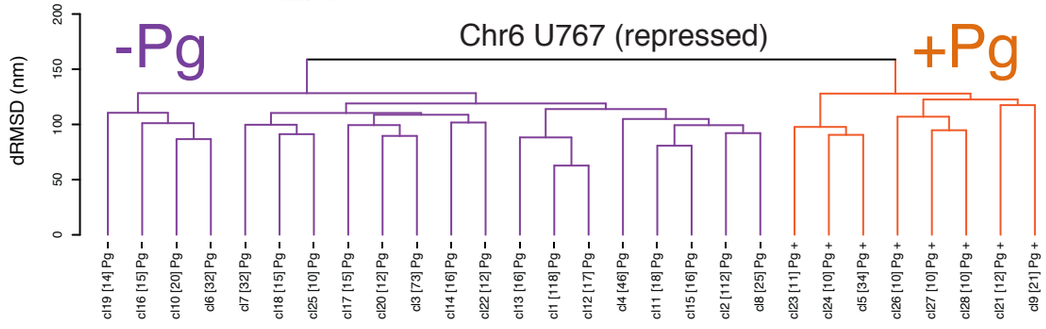
How TADs respond structurally to Pg?

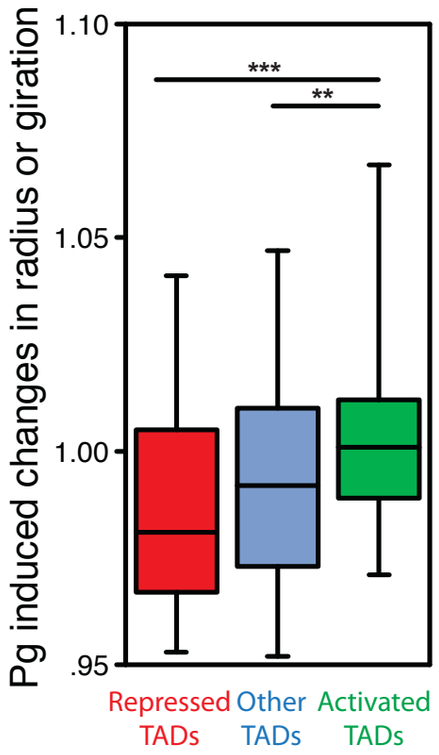
Chr2:9,600,000-13,200,000

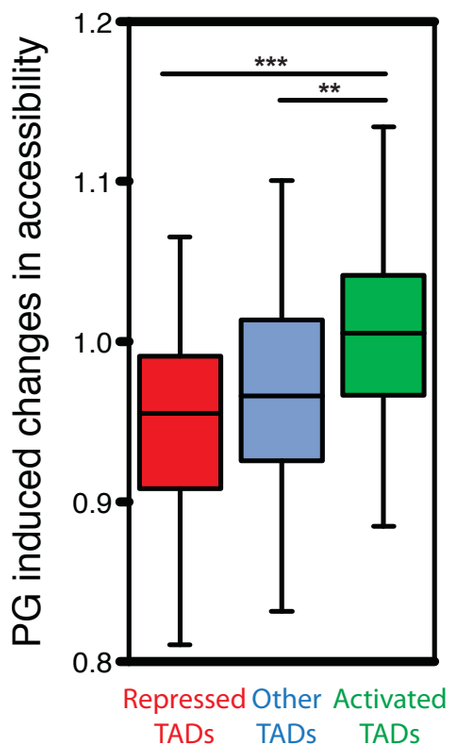


Chr6:71,800,000-76,500,000

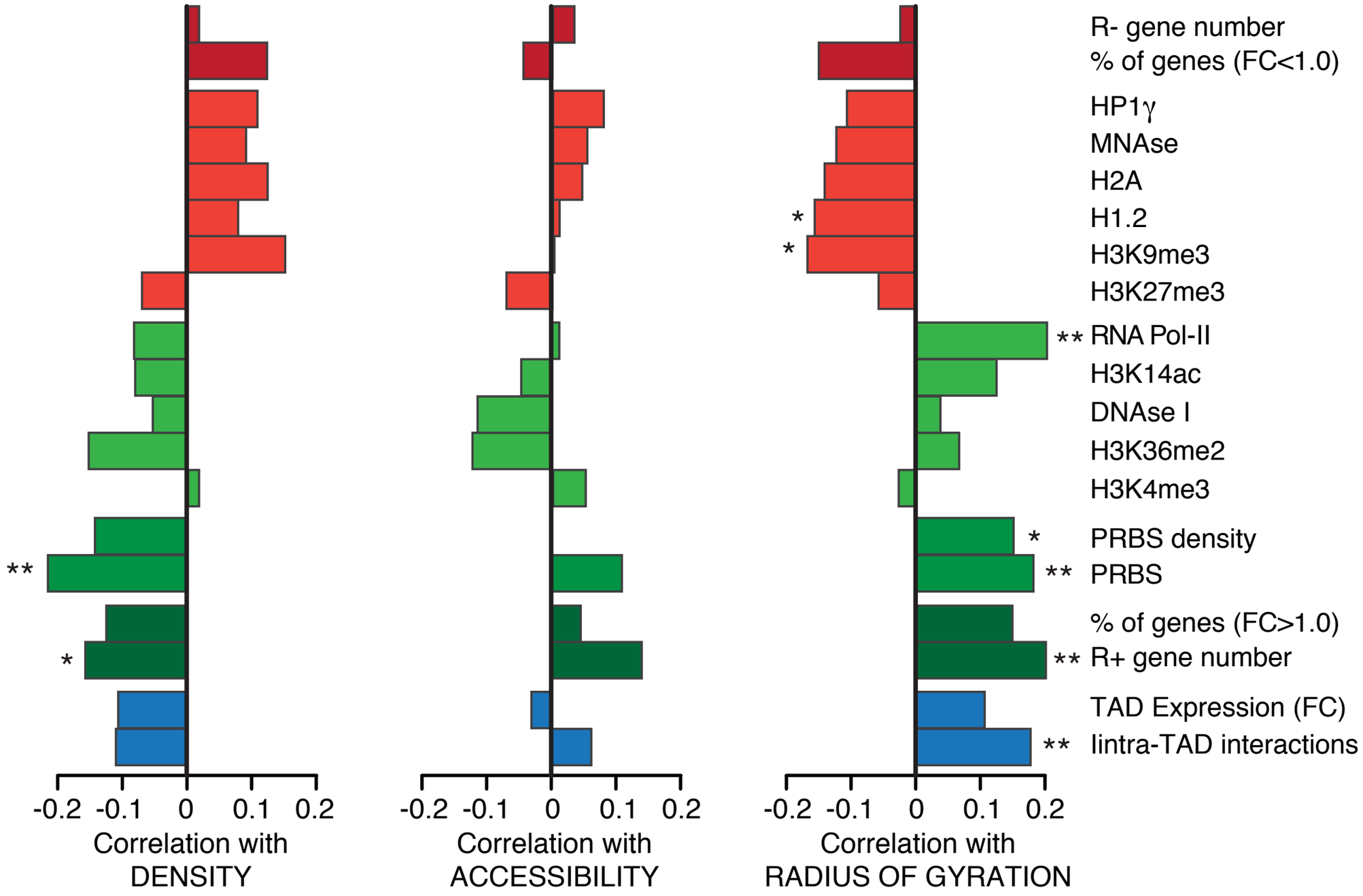


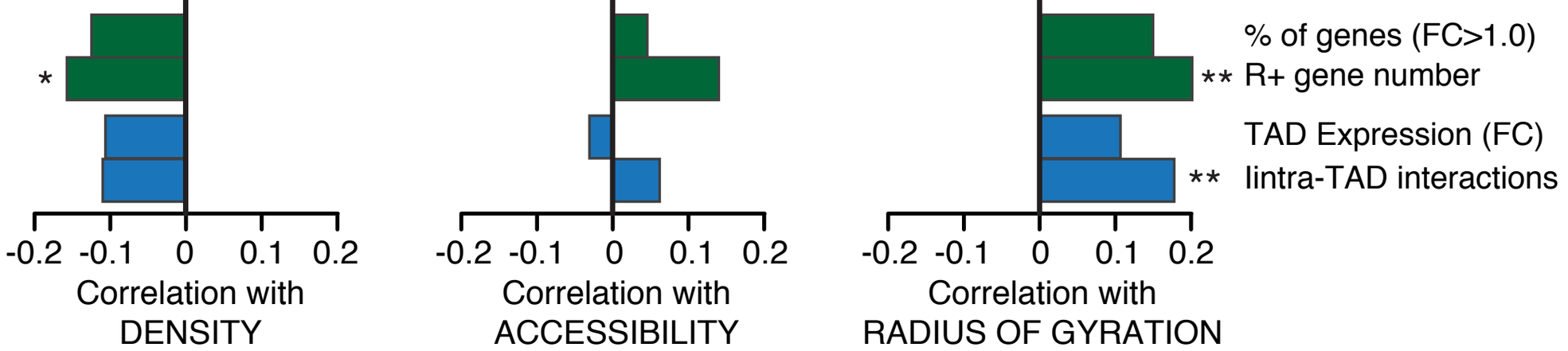


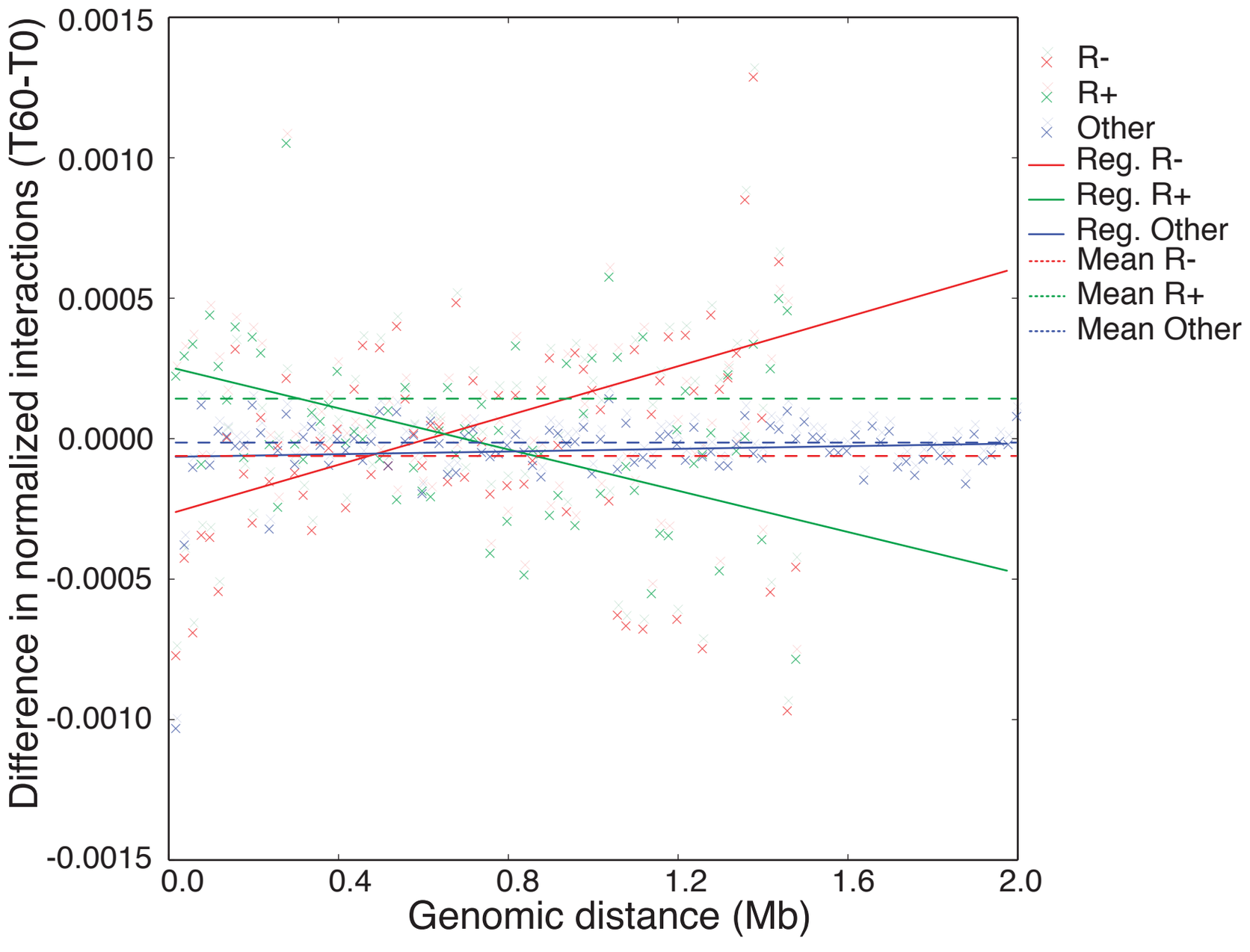




How TADs respond structurally to Pg?



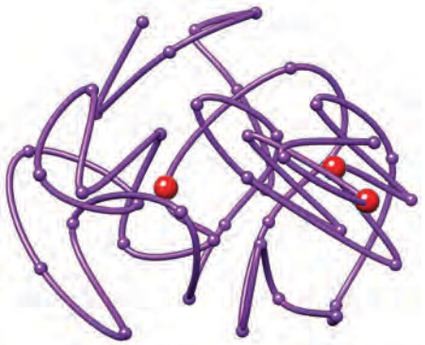

% of genes (FC>1.0)
R+ gene number
TAD Expression (FC)
lintra-TAD interactions
*
**
**
-0.2 -0.1 0 0.1 0.2
Correlation with
DENSITY
Correlation with
ACCESSIBILITY
Correlation with
RADIUS OF GYRATION

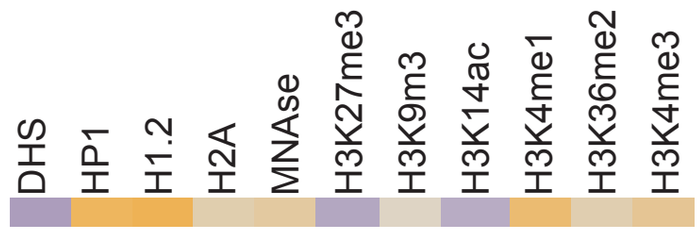

Difference in normalized interactions (T60-T0)
0.0015
0.0010
0.0005
0.0000
-0.0005
-0.0010
-0.0015
0.0
0.4
0.8
1.2
1.6
2.0
Genomic distance (Mb)
R-
R+
Other
Reg. R-
Reg. R+
Reg. Other
Mean R-
Mean R+
Mean Other

Model for TAD regulation

Repressed TAD

chr1 U41

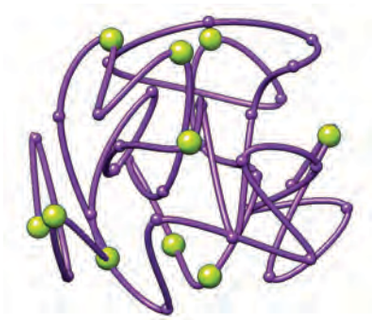


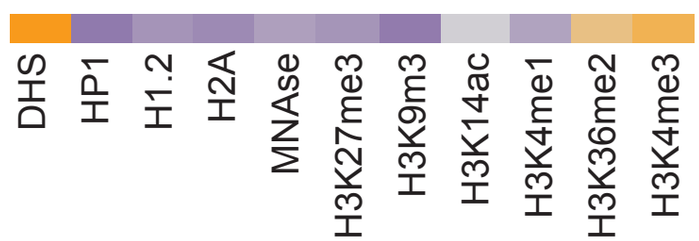


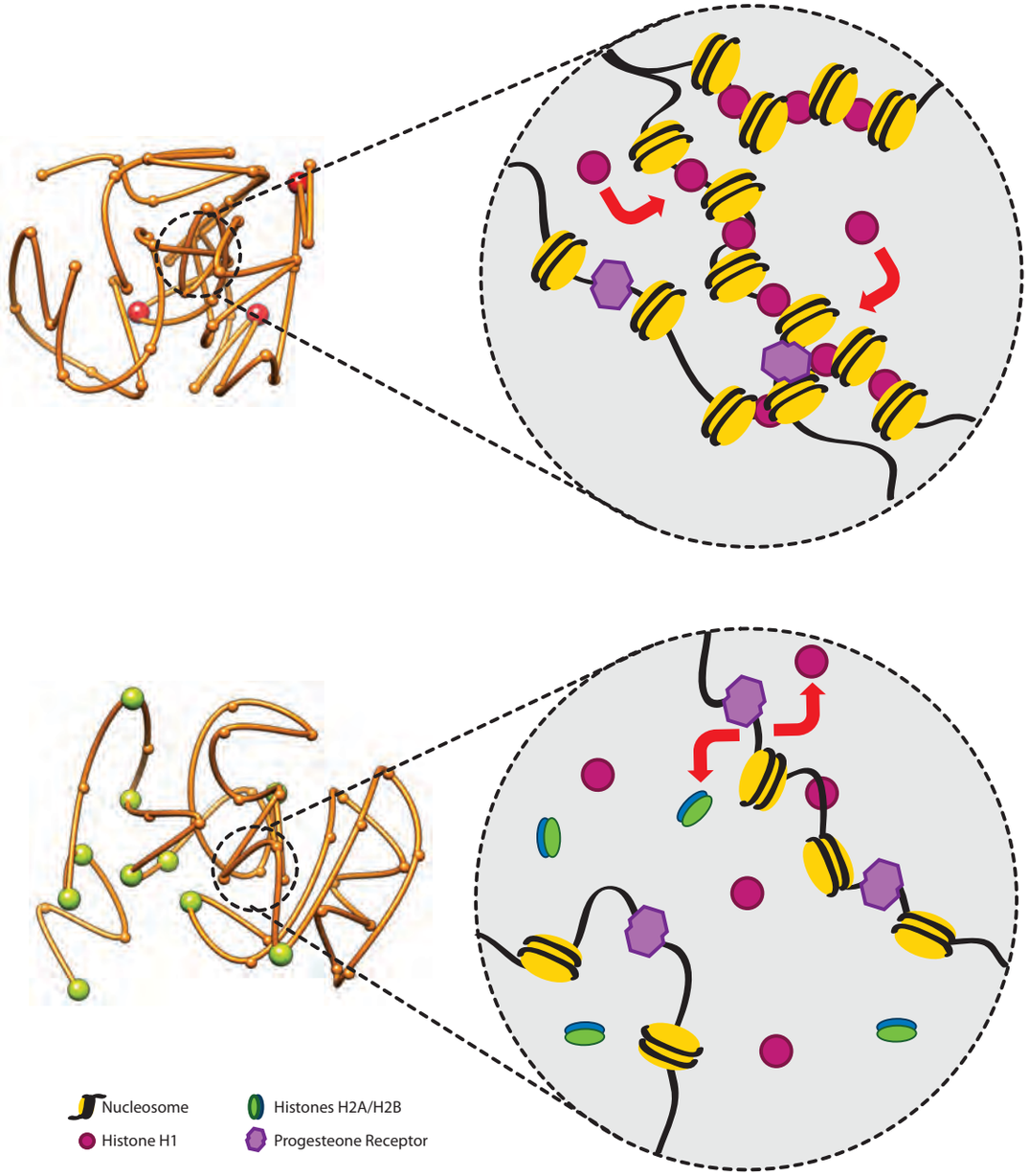
Structural transition **+Pg**

Activated TAD

chr2 U207







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Toulouse, France

Miguel Beato & Guillaume Filion
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Barcelona, Spain

http://marciuslab.org
http://3DGenomes.org
http://cnag.crg.cat

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