

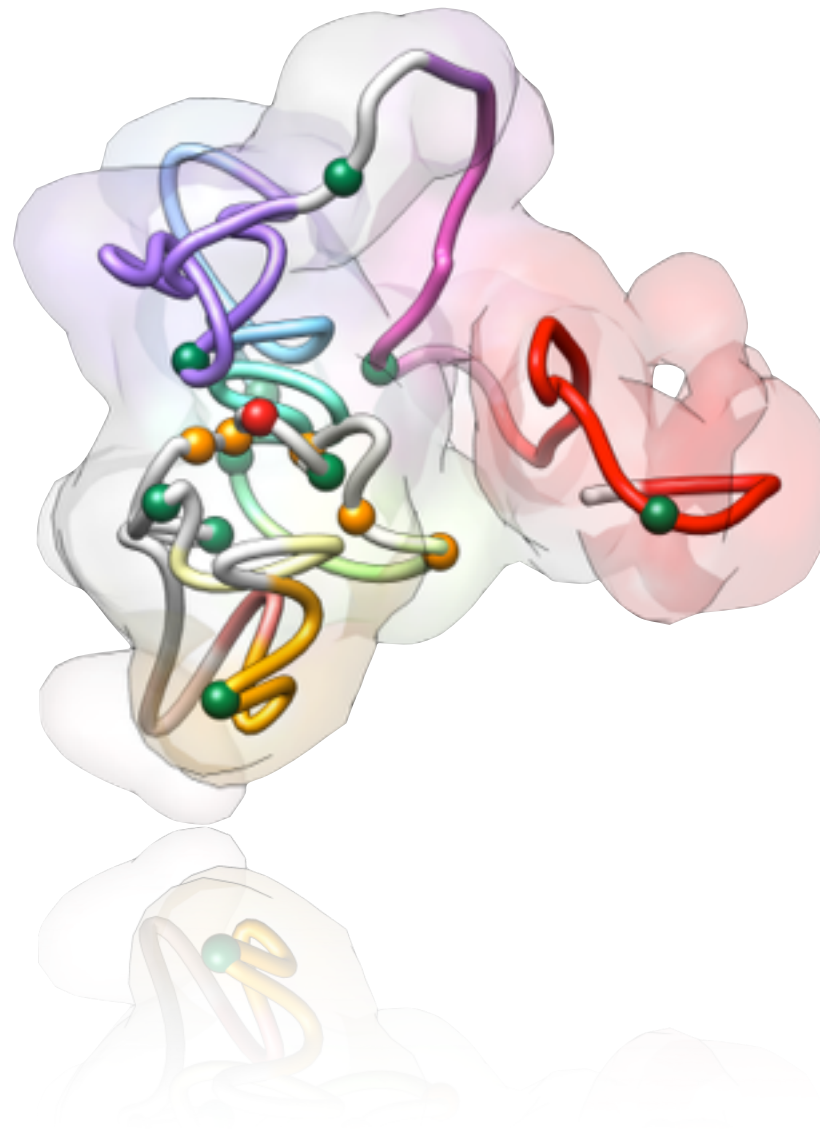
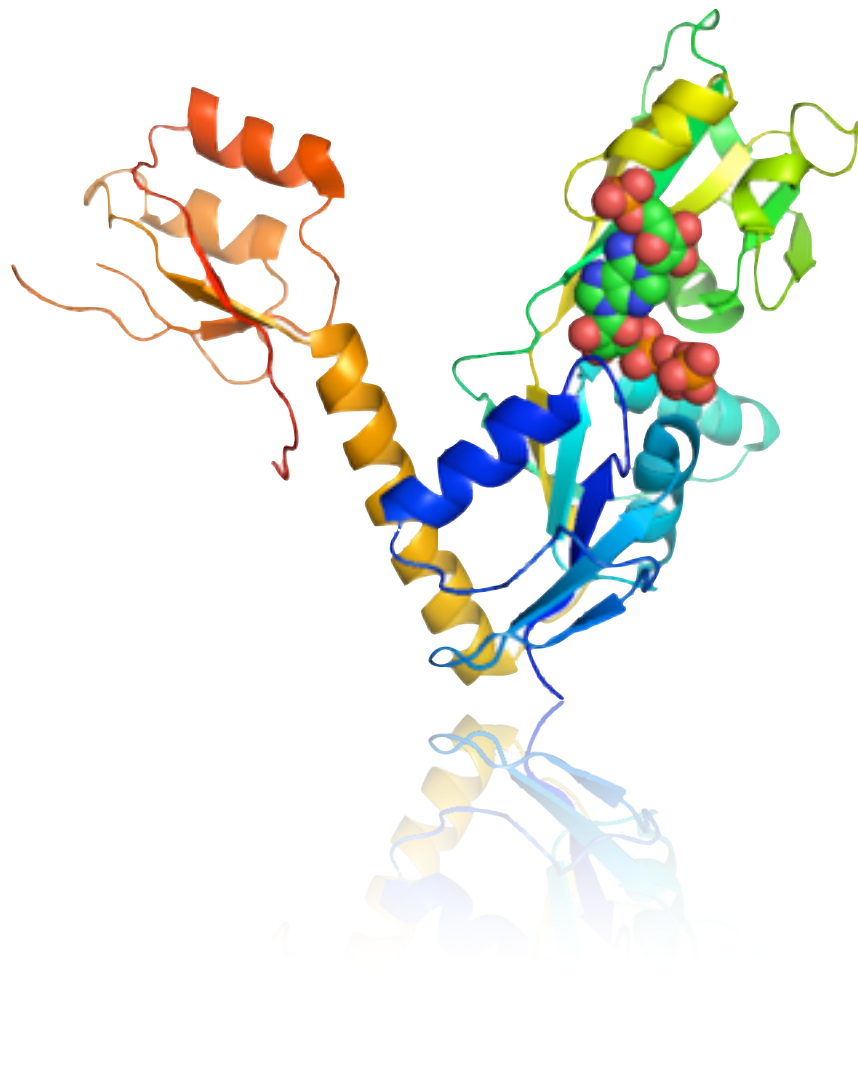
# Structure determination of genomes and genomic domains by satisfaction of spatial restraints

**Marc A. Marti-Renom**

*Structural Genomics Group (CNAG-CRG)*

# Structural Genomics Group

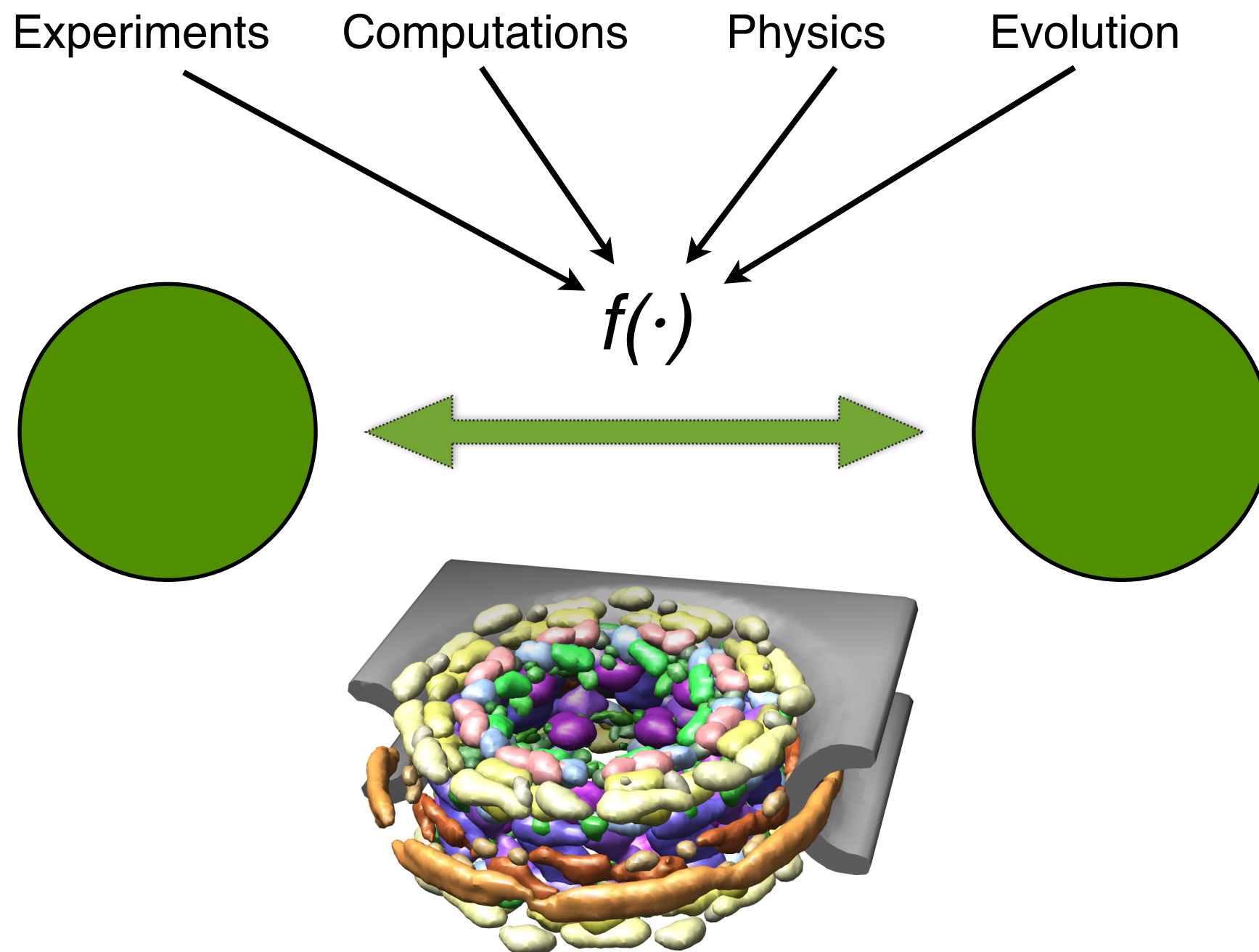
<http://www.marciuslab.org>



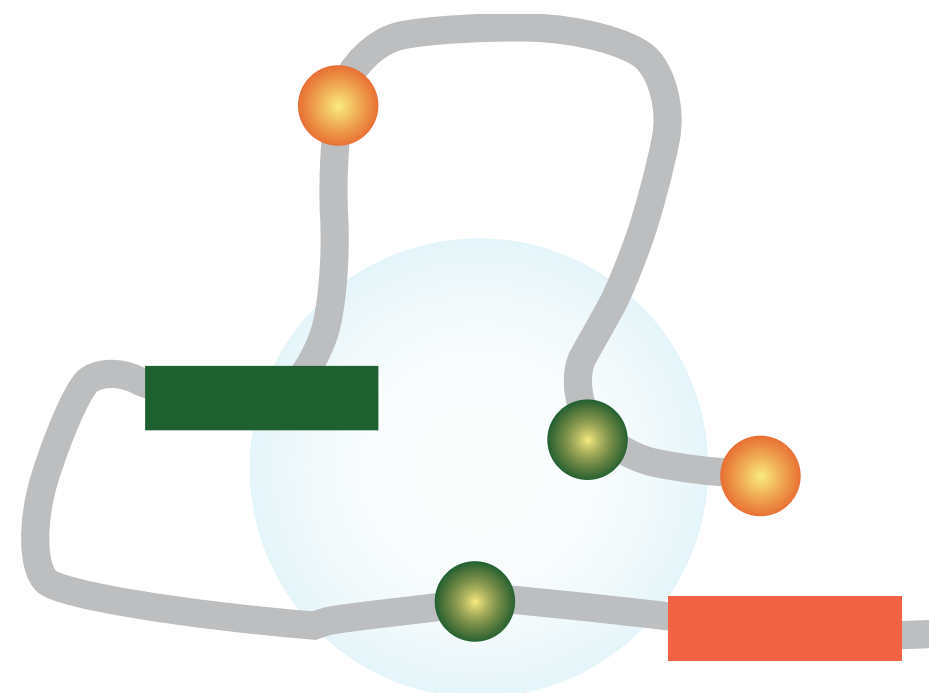
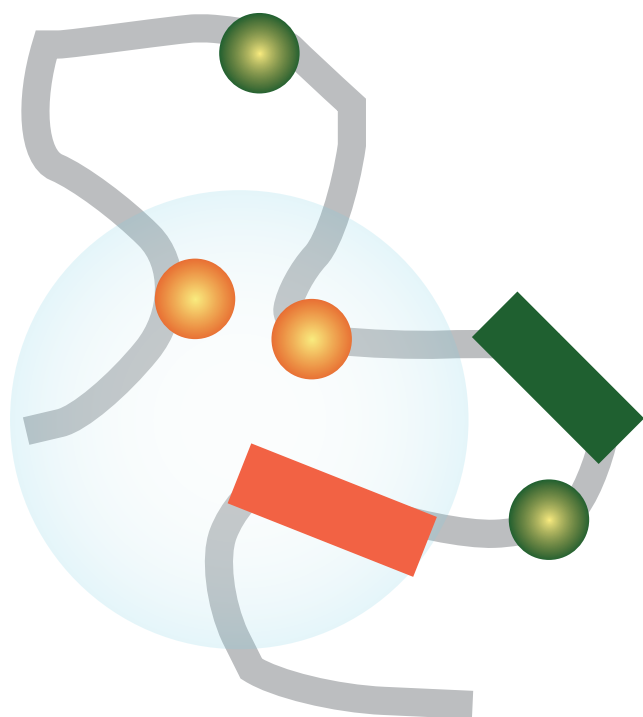


# Integrative Modeling Platform

<http://www.integrativemodeling.org>



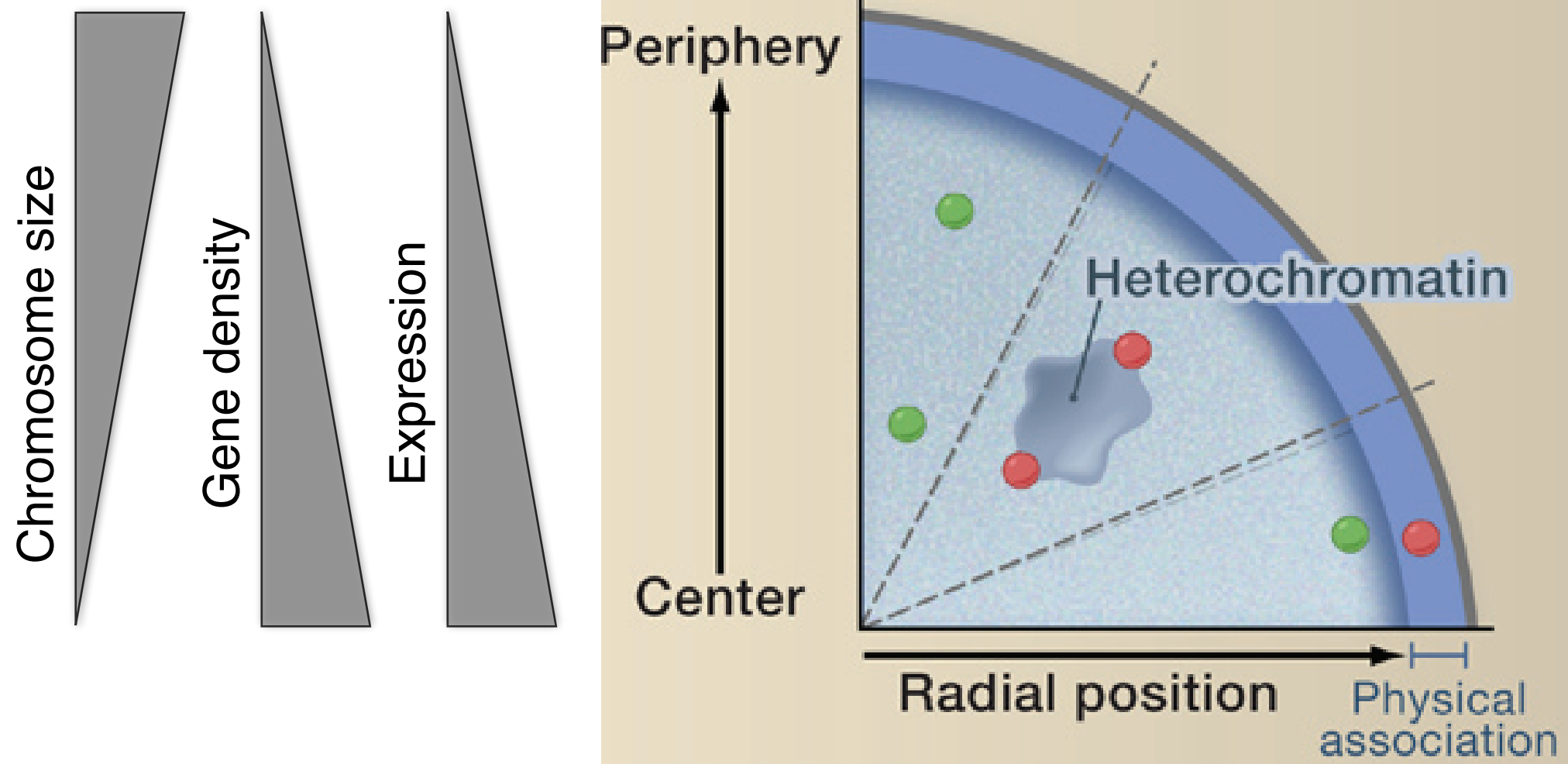
From: Russel, D. et al. PLOS Biology 10, e1001244 (2012).





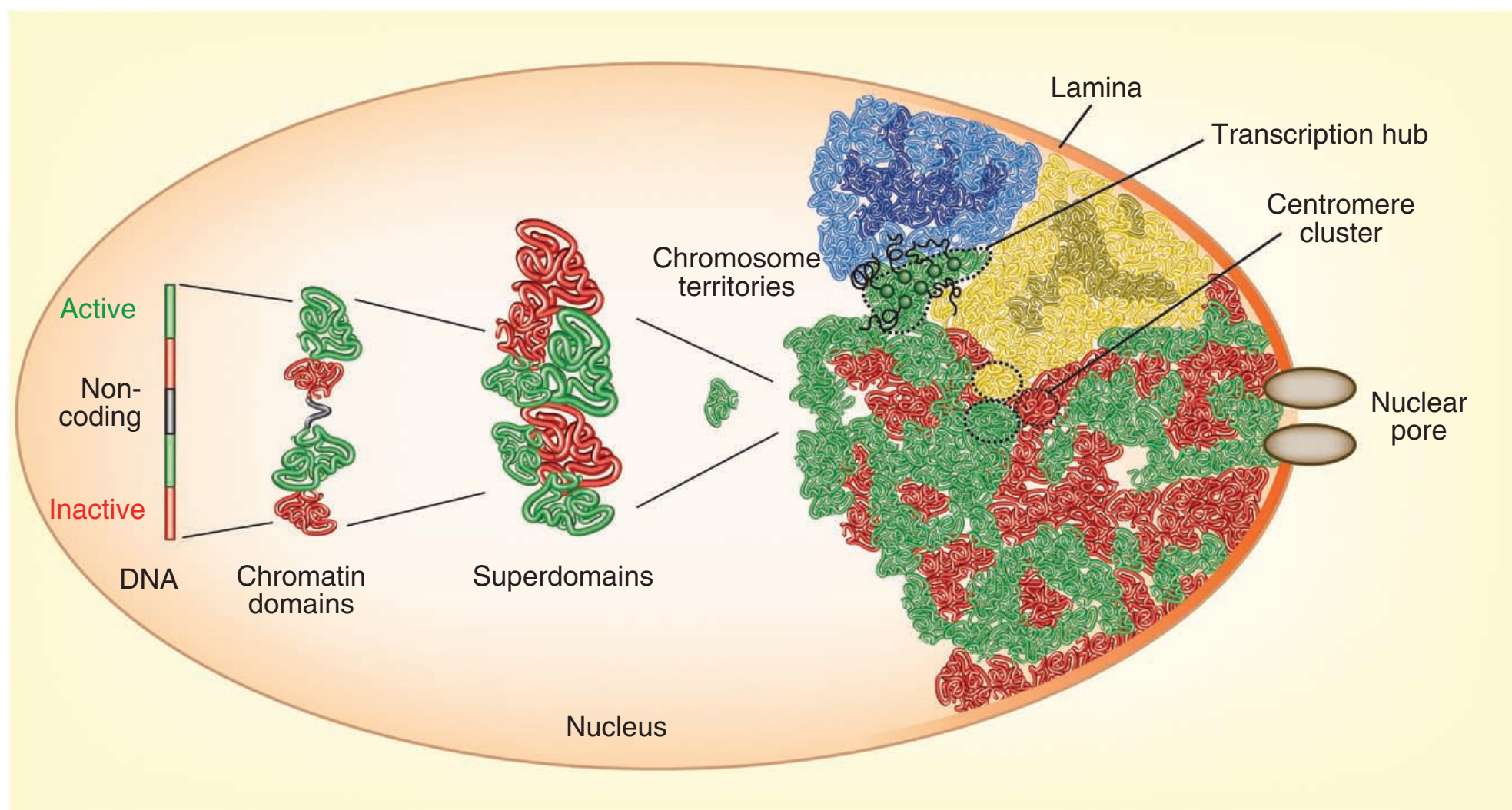
# Complex genome organization

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).

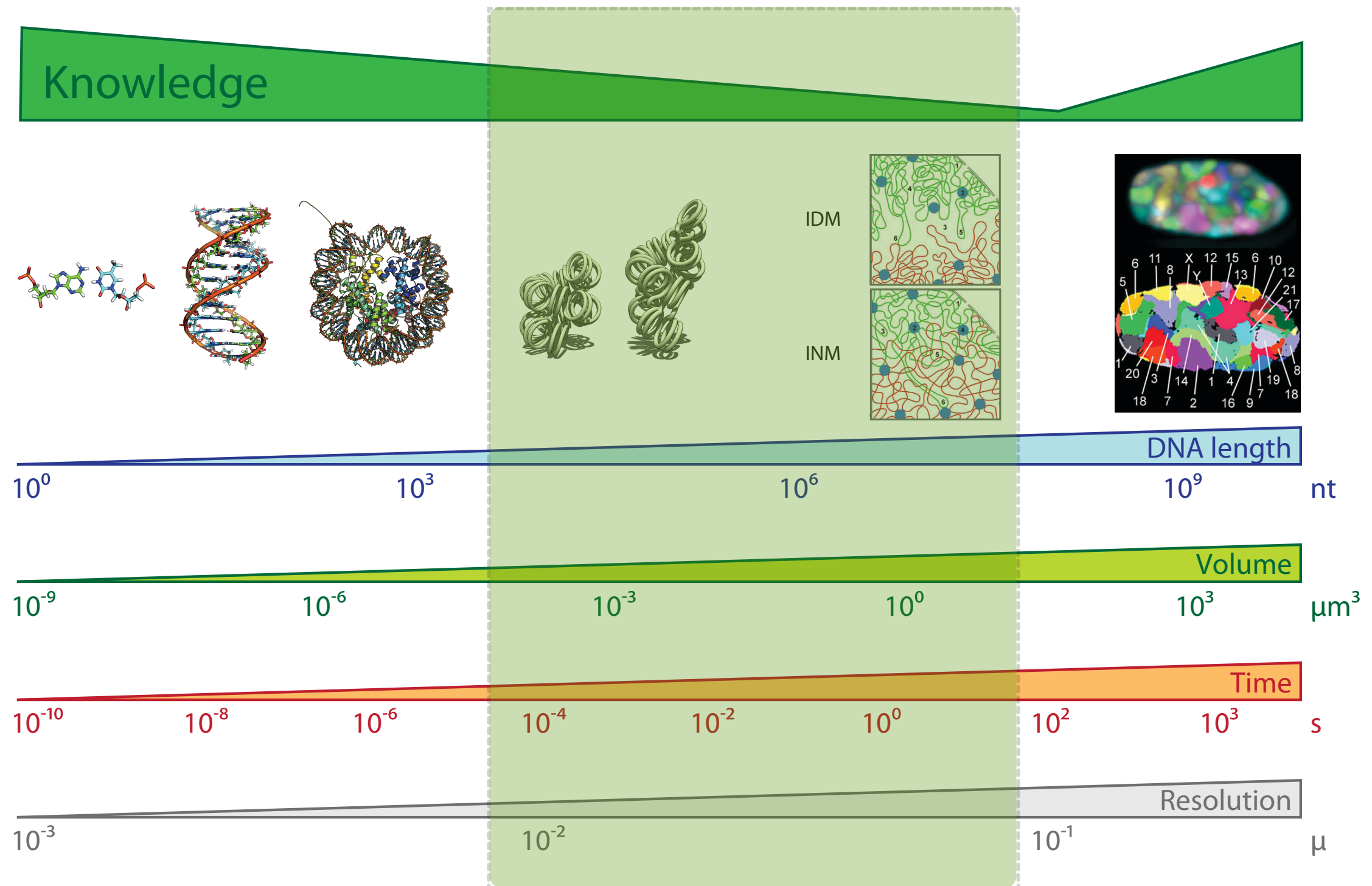


Marina Corral



# Resolution Gap

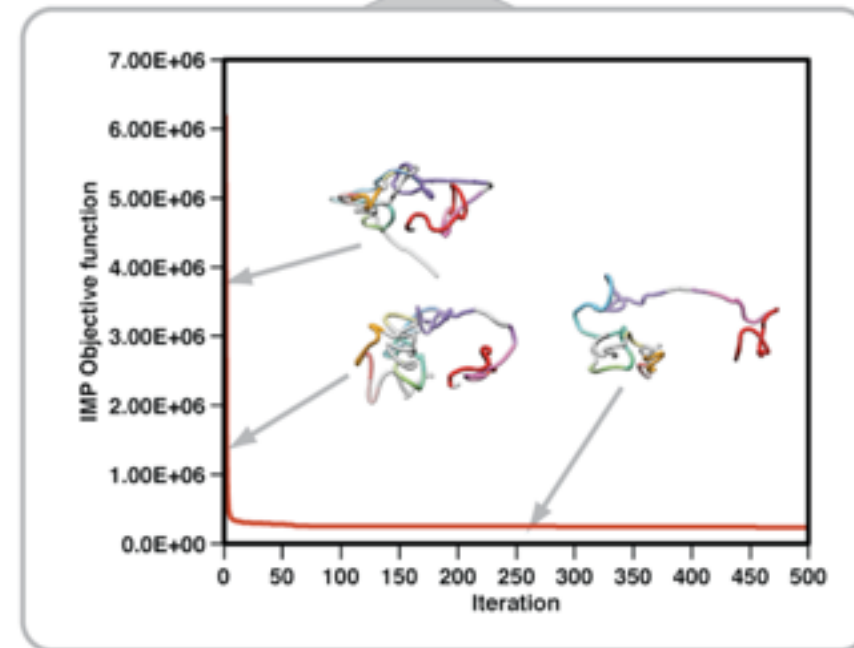
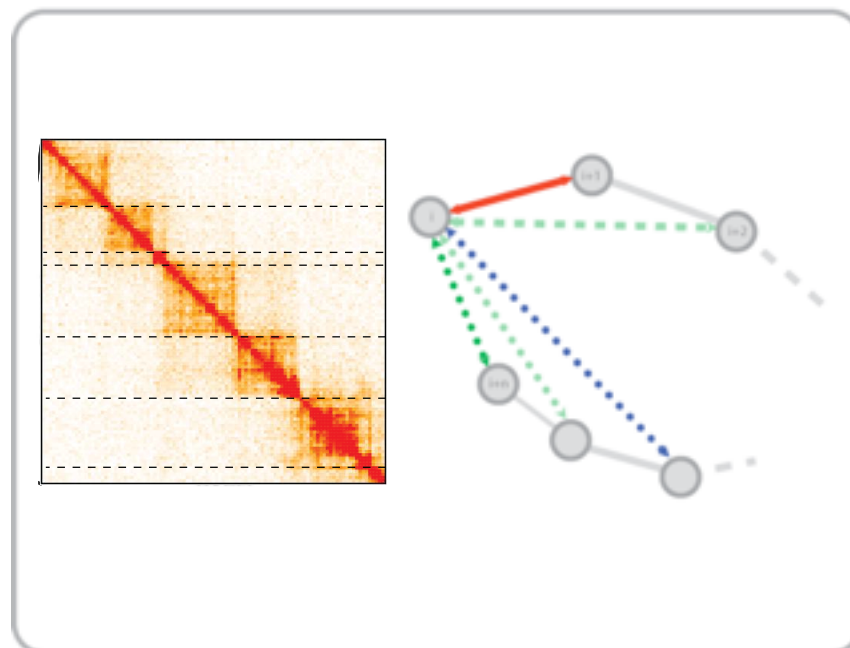
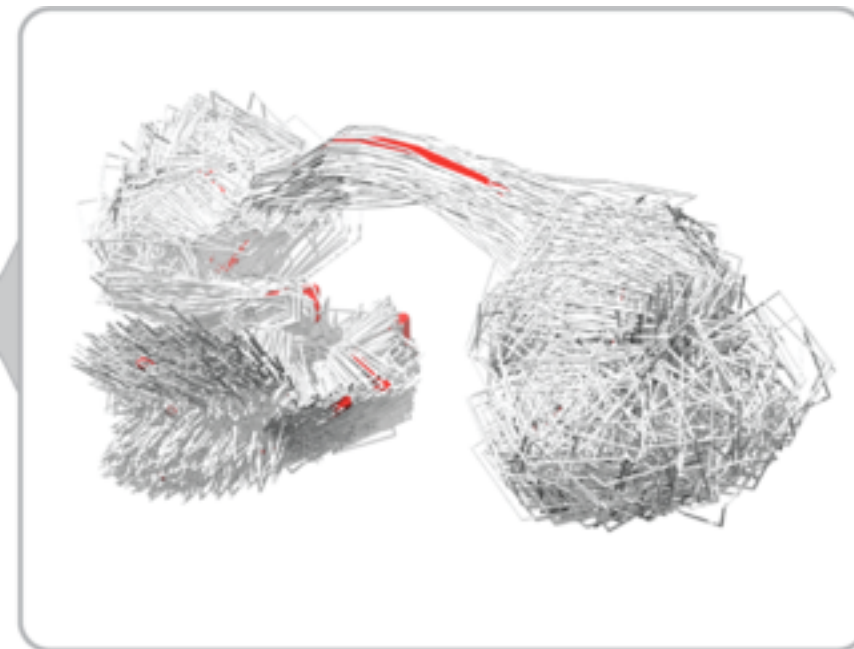
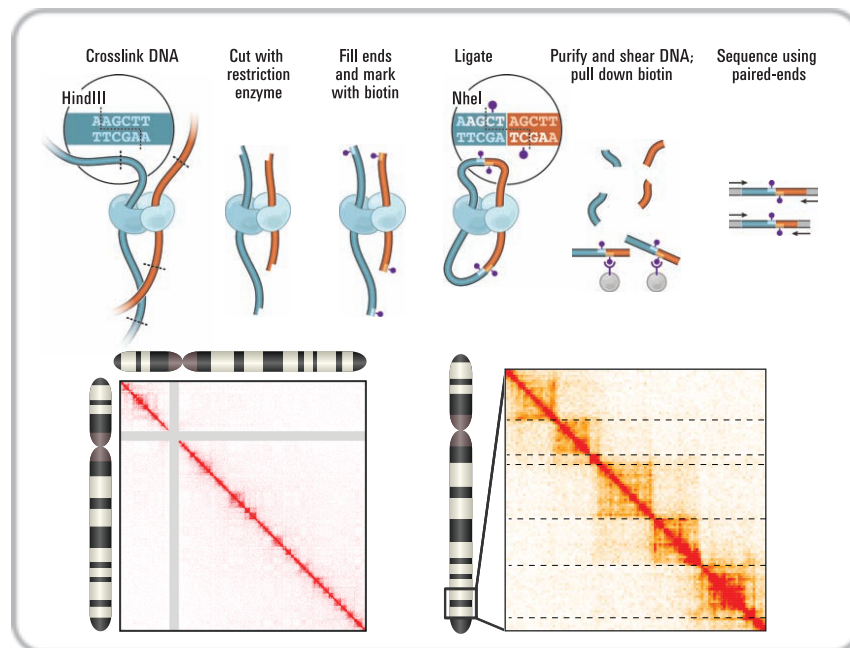
Marti-Renom, M. A. & Mirny, L. A. PLoS Comput Biol 7, e1002125 (2011)



# Hybrid Method

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

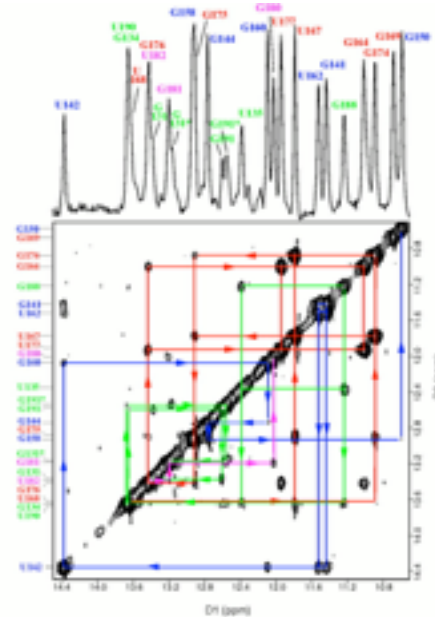
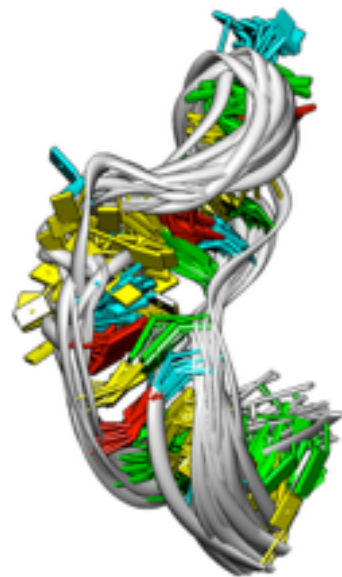
## Experiments



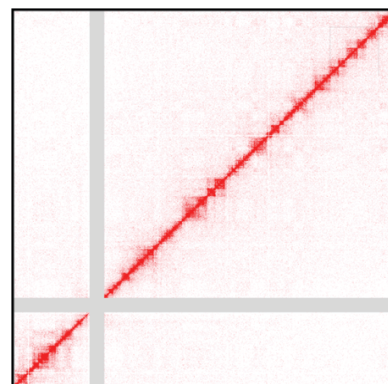
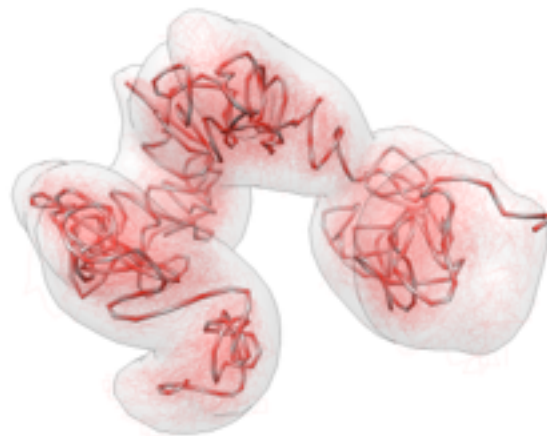
## Computation



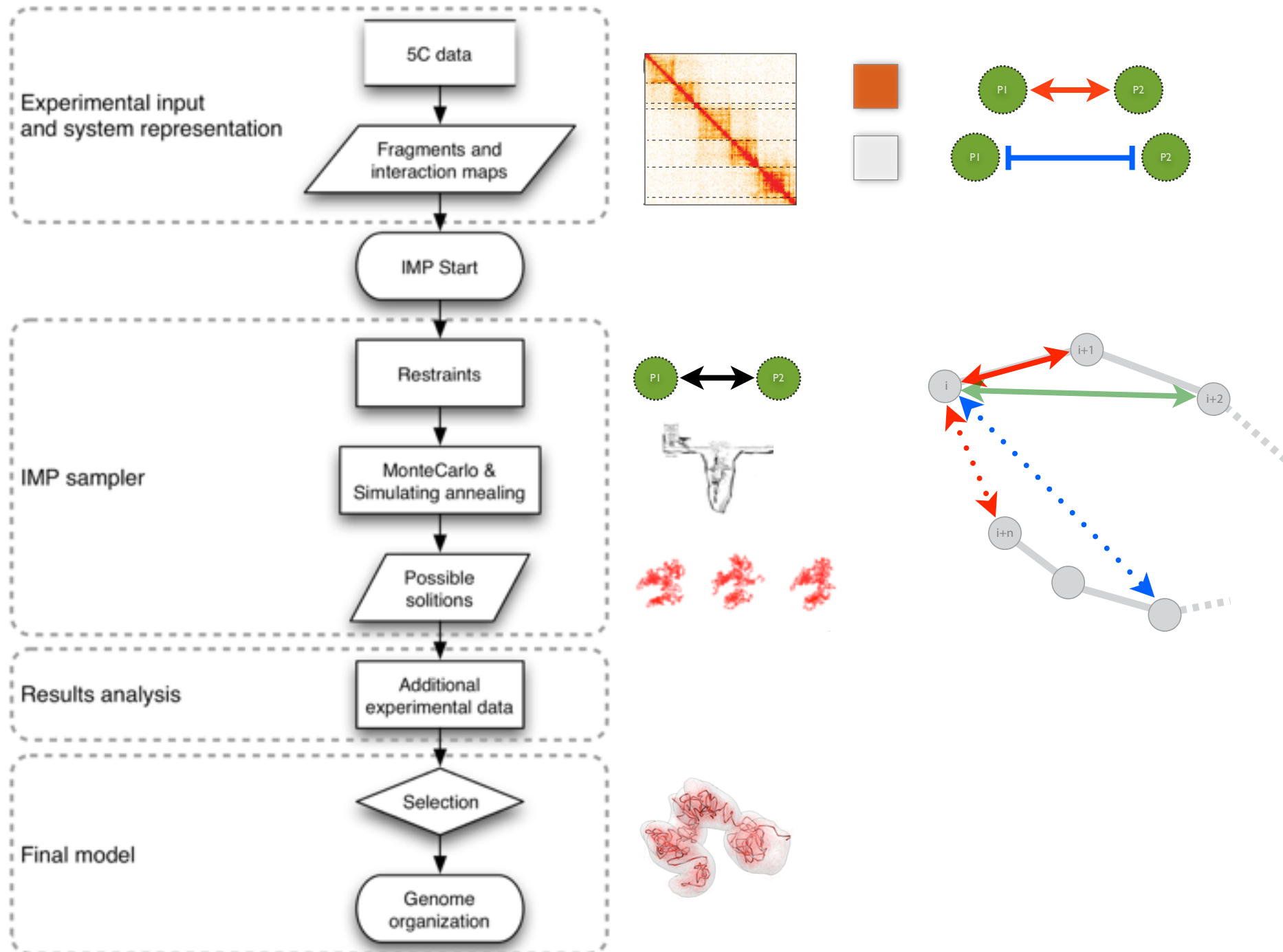
# Structure determination by satisfaction of spatial restraints



Biomolecular structure determination  
2D-NOESY data



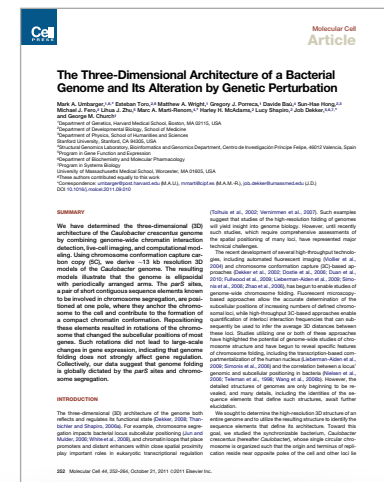
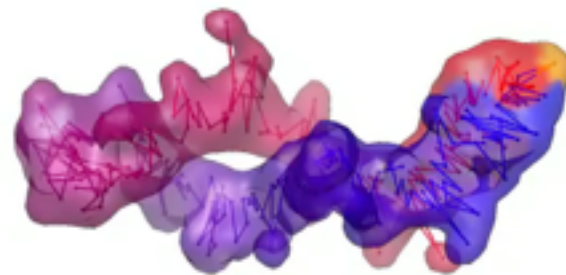
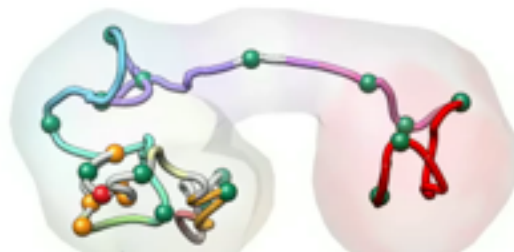
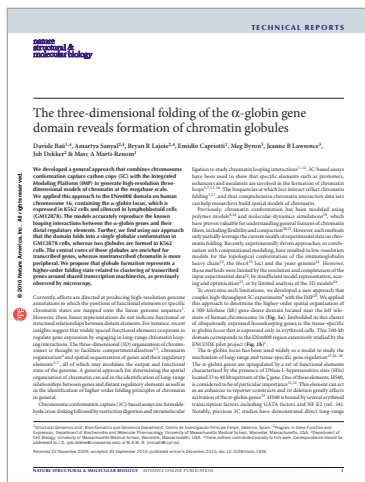
Chromosome structure determination  
3C-based data





# TADbit previous applications...

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

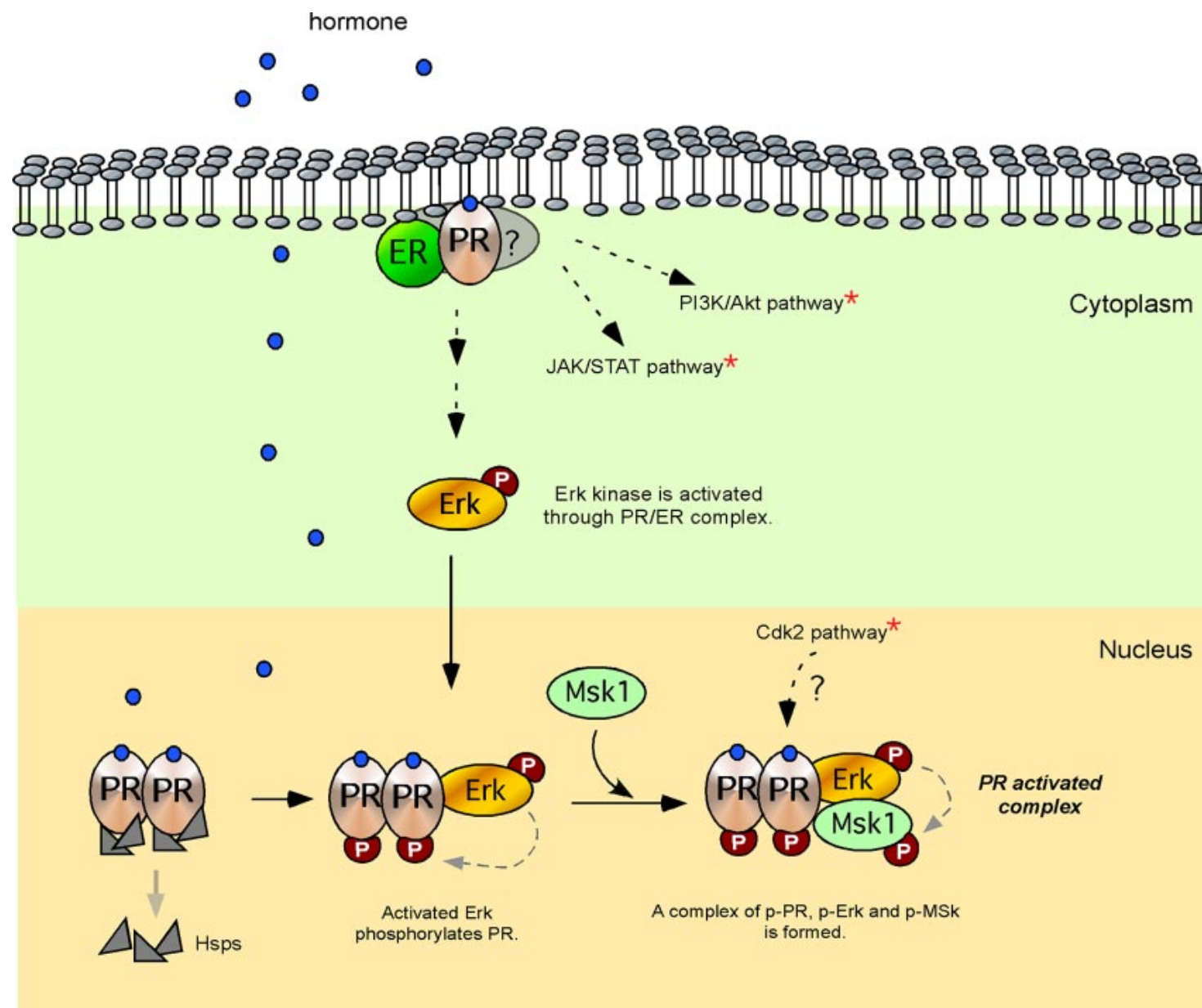


## Distinct structural transitions of chromatin topological domains correlate with coordinated hormone-induced gene regulation

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



# Progesterone-regulated transcription in breast cancer

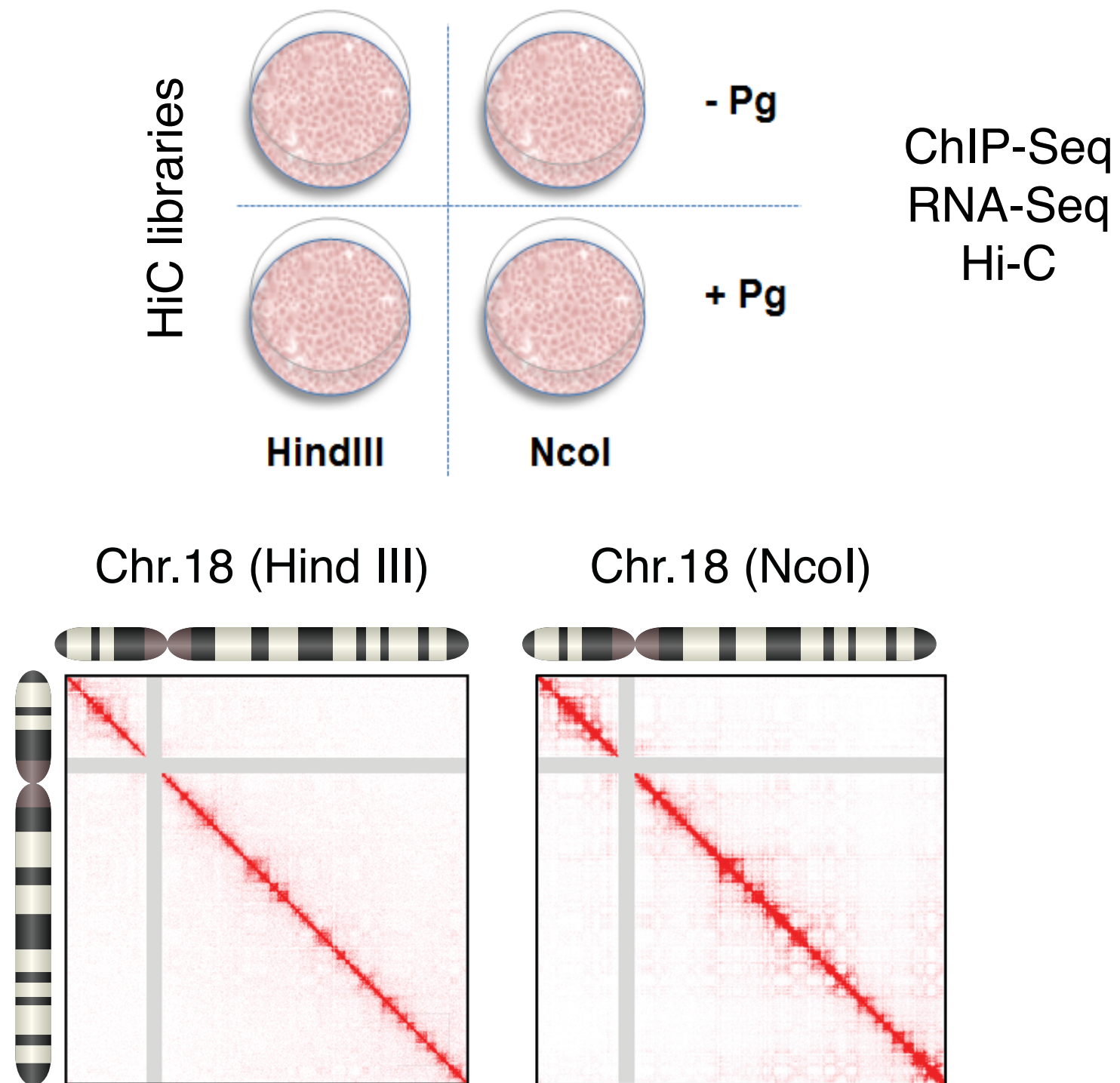


> 2,000 genes **Up**-regulated  
> 2,000 genes **Down**-regulated

**Regulation in 3D?**

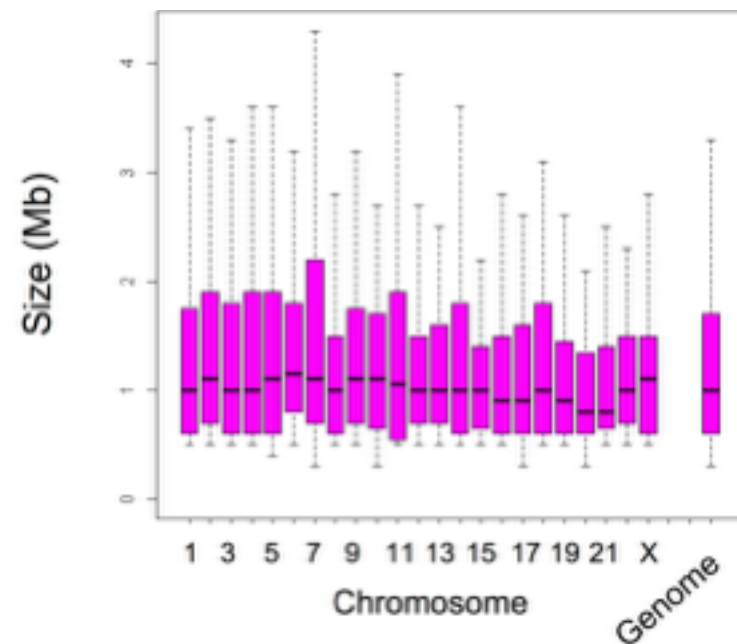
Vicent *et al* 2011, Wright *et al* 2012, Ballare *et al* 2012

# Experimental design





# Are there TADs? how robust?



>2,000 detected TADs

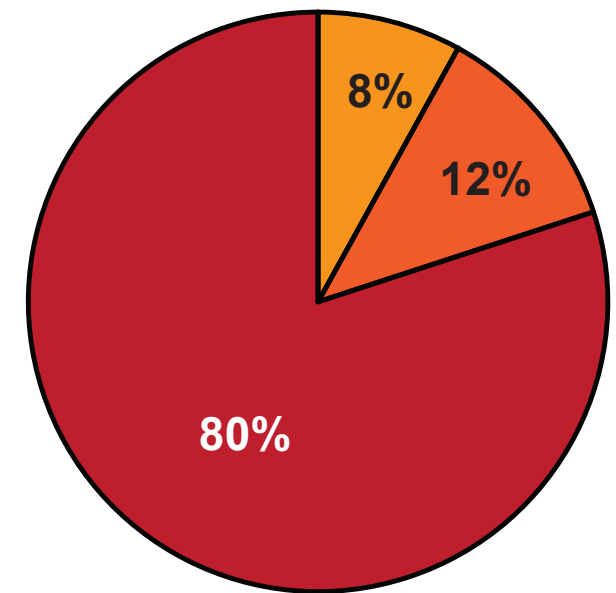
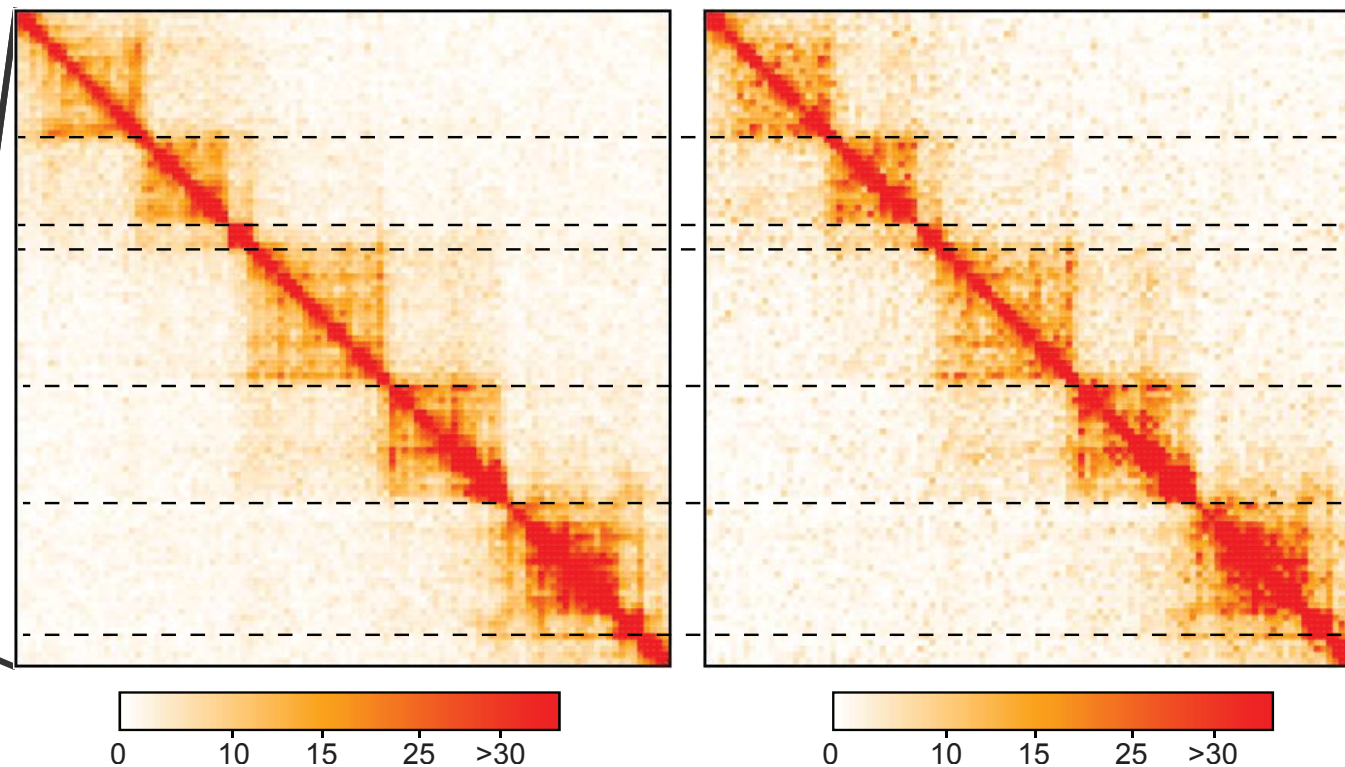


Chr.18



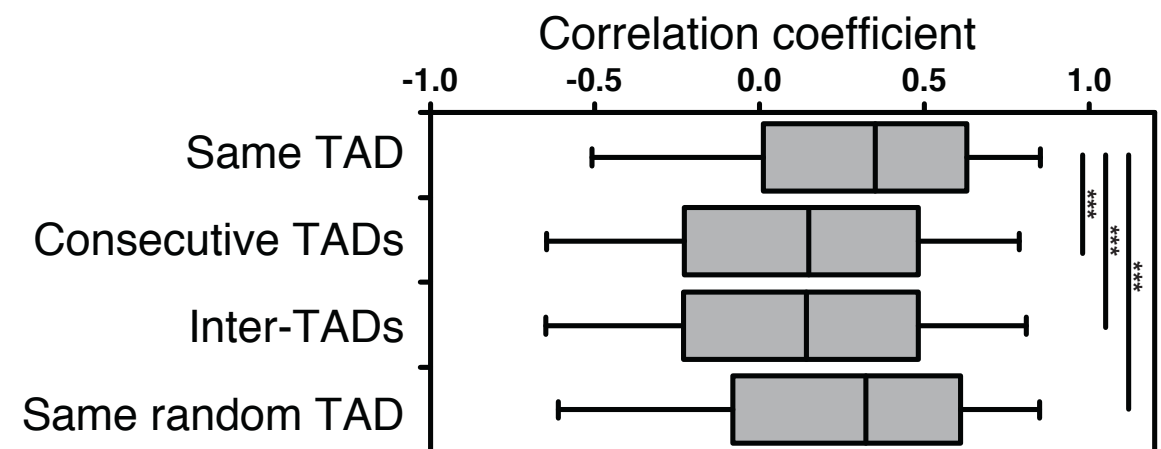
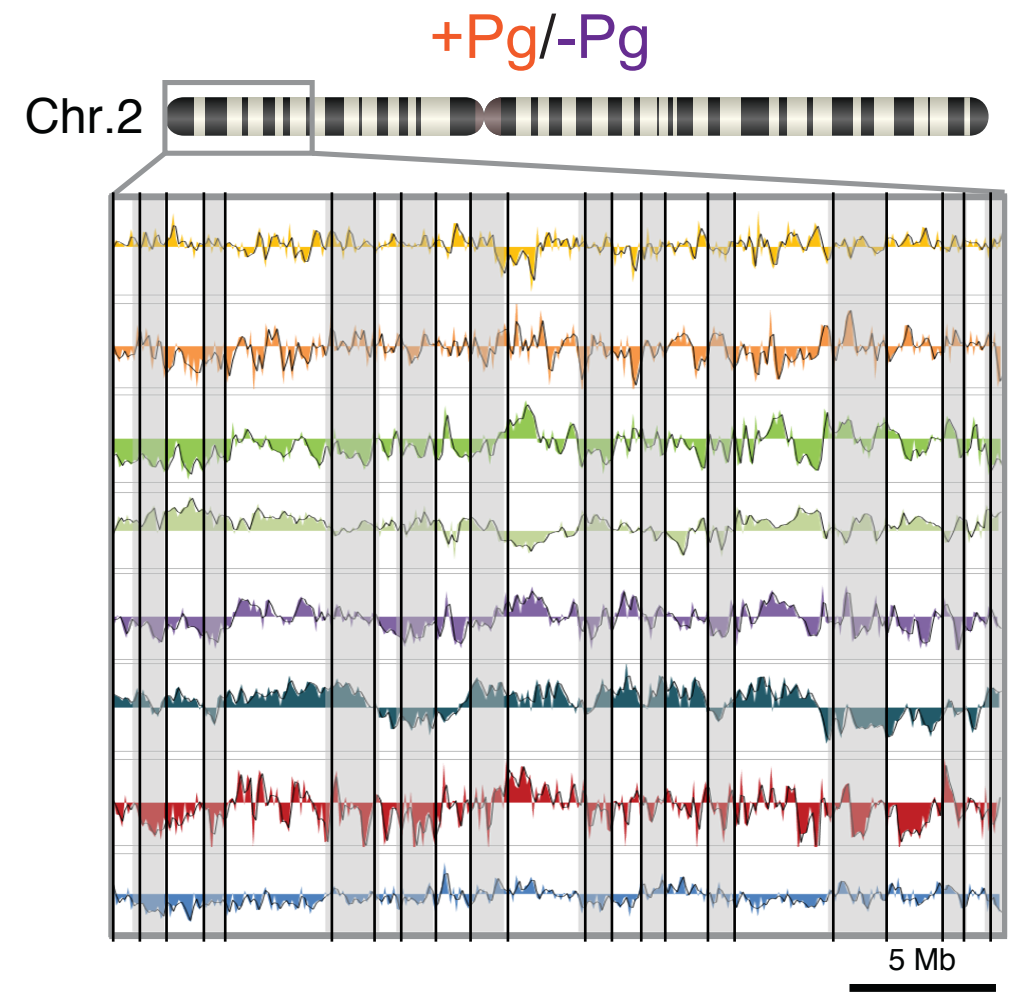
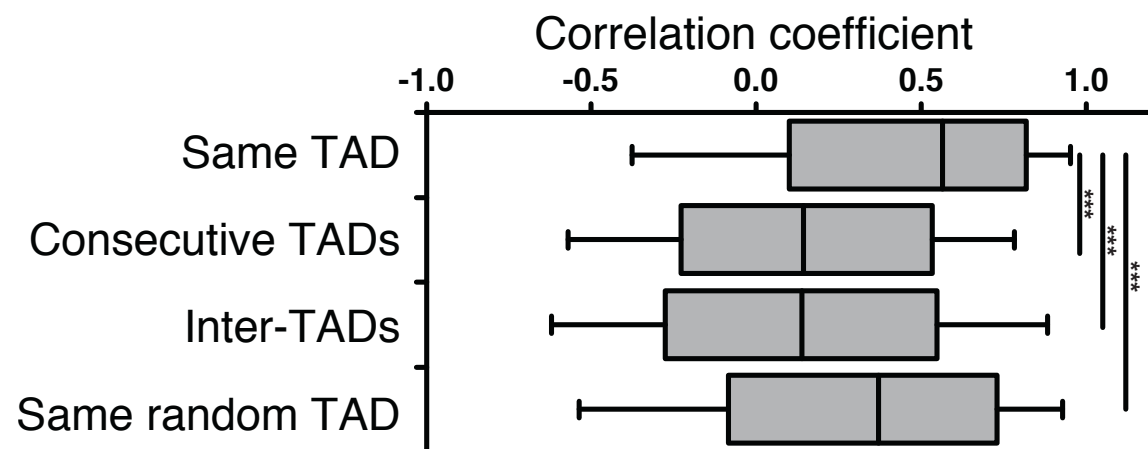
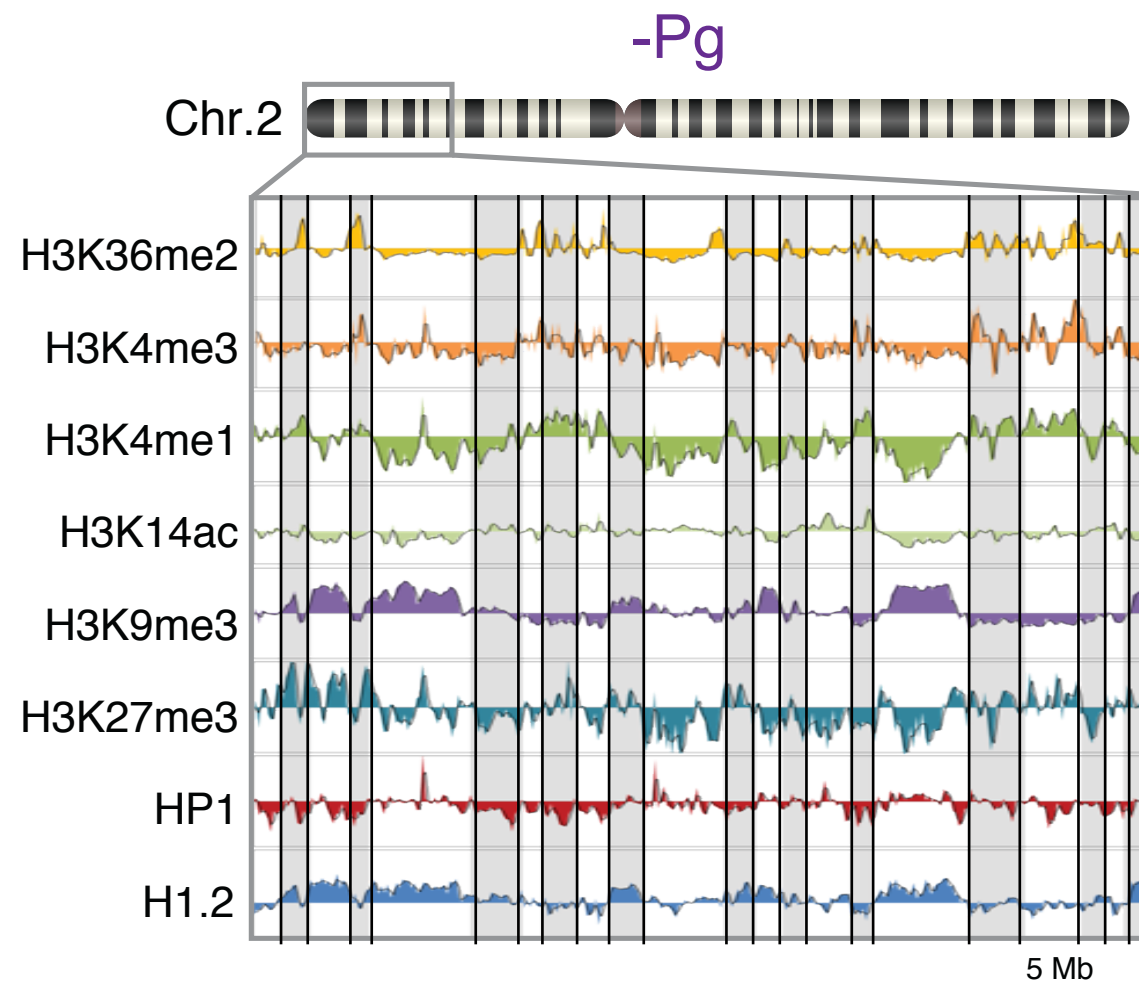
-Pg

+Pg

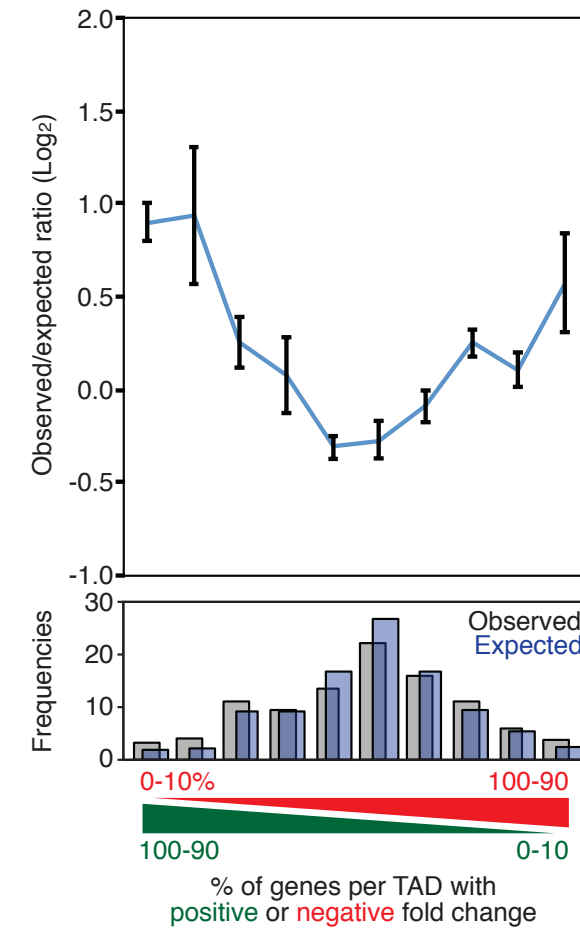
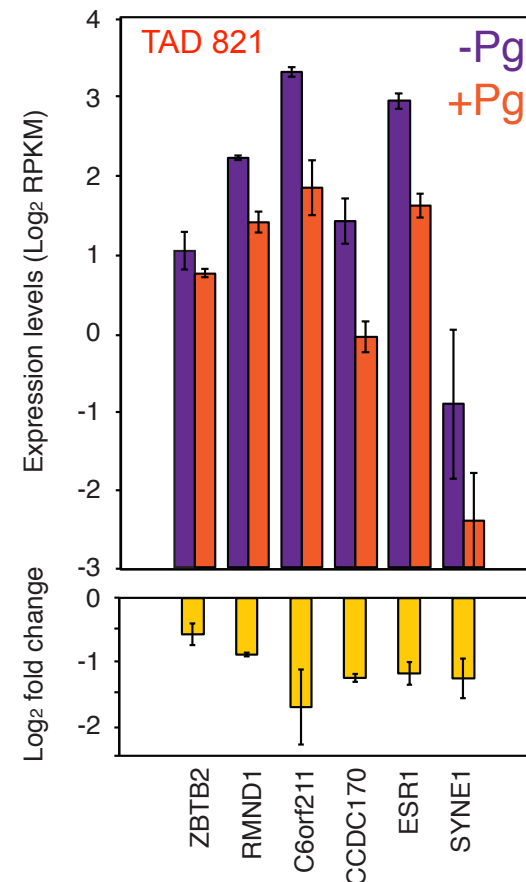
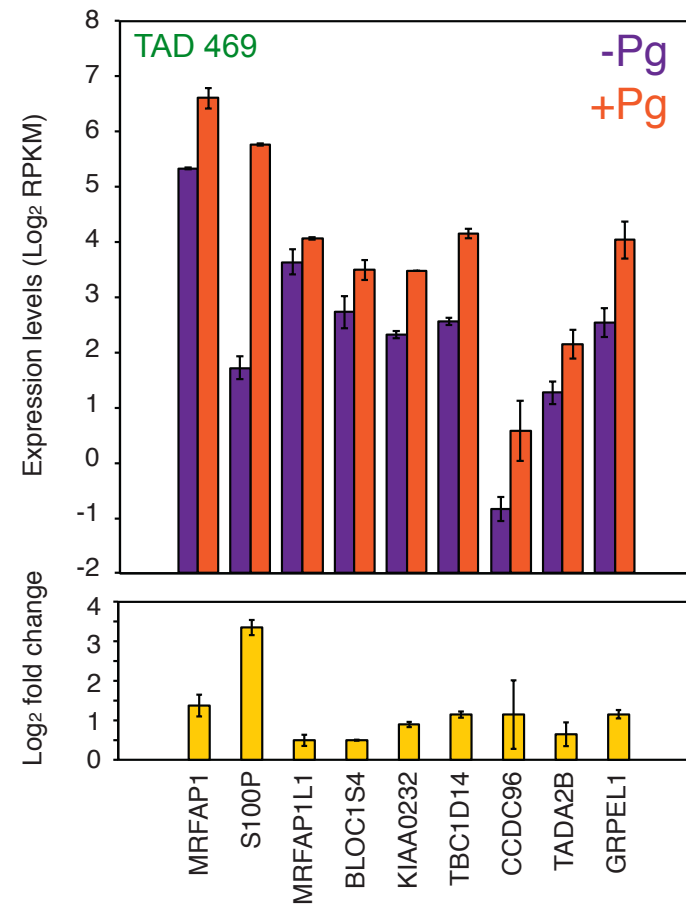


■ conserved  
■ 100 kb  
■ ±200 kb or more

# Are TADs homogeneous?

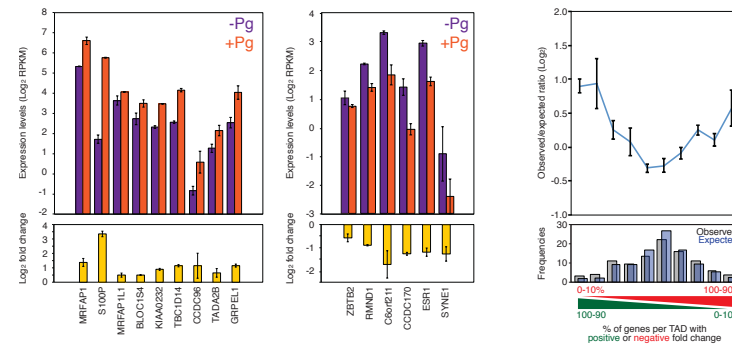


# Do TADs respond differently to Pg treatment?

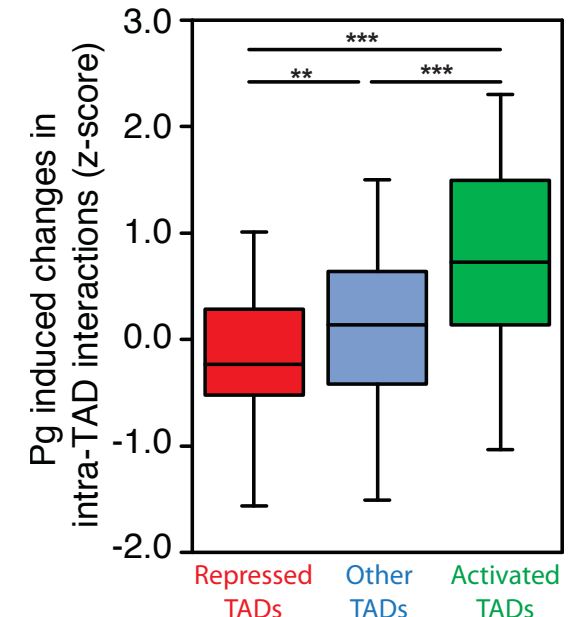
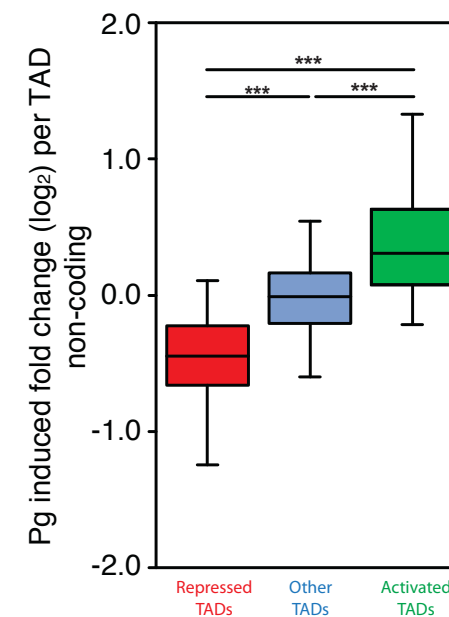
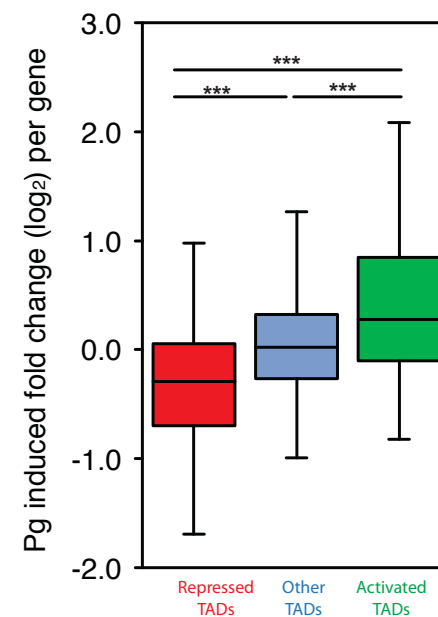
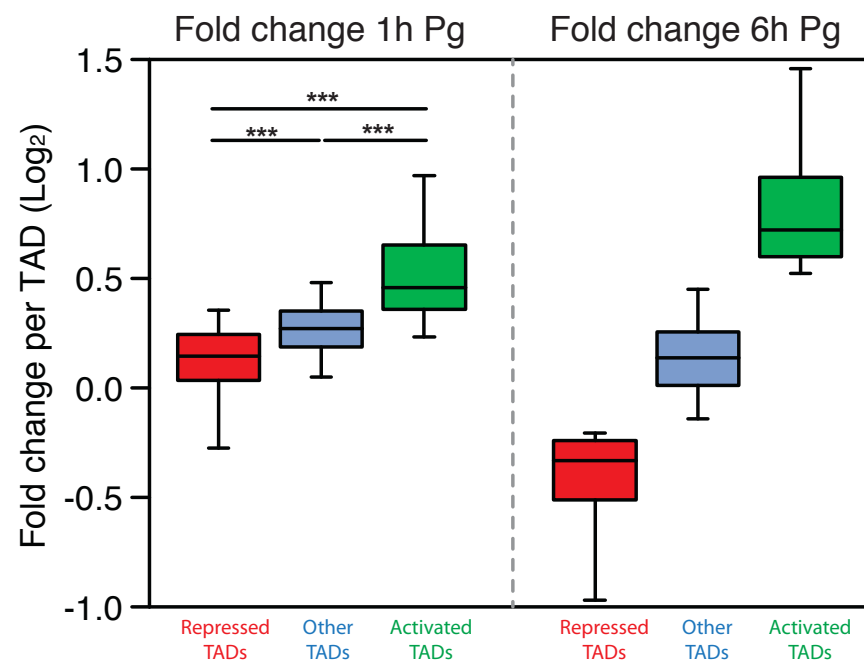




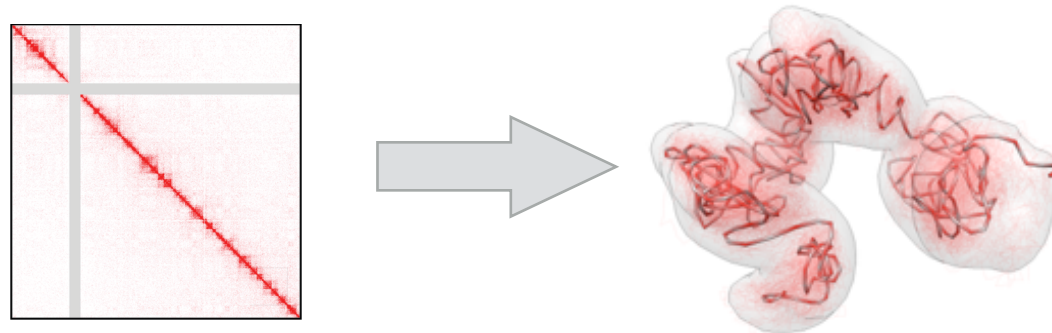
# Do TADs respond differently to Pg treatment?



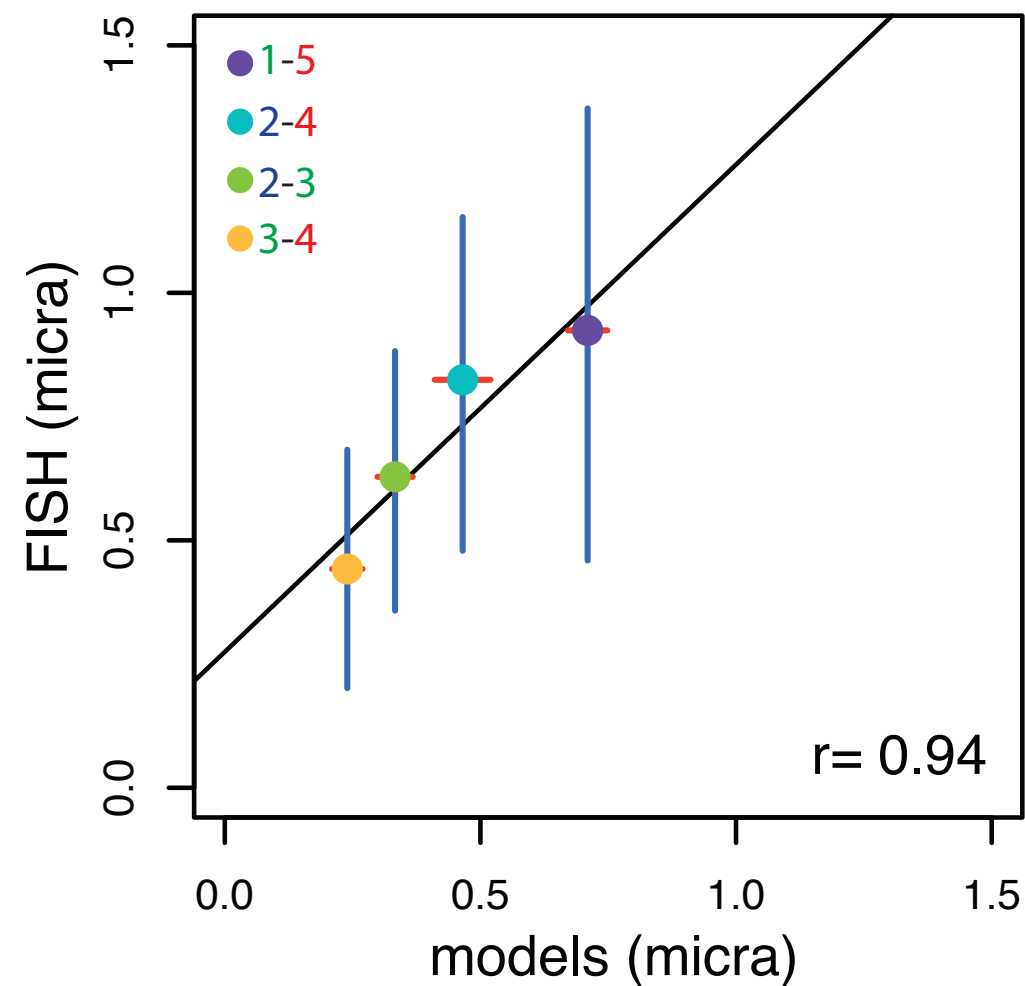
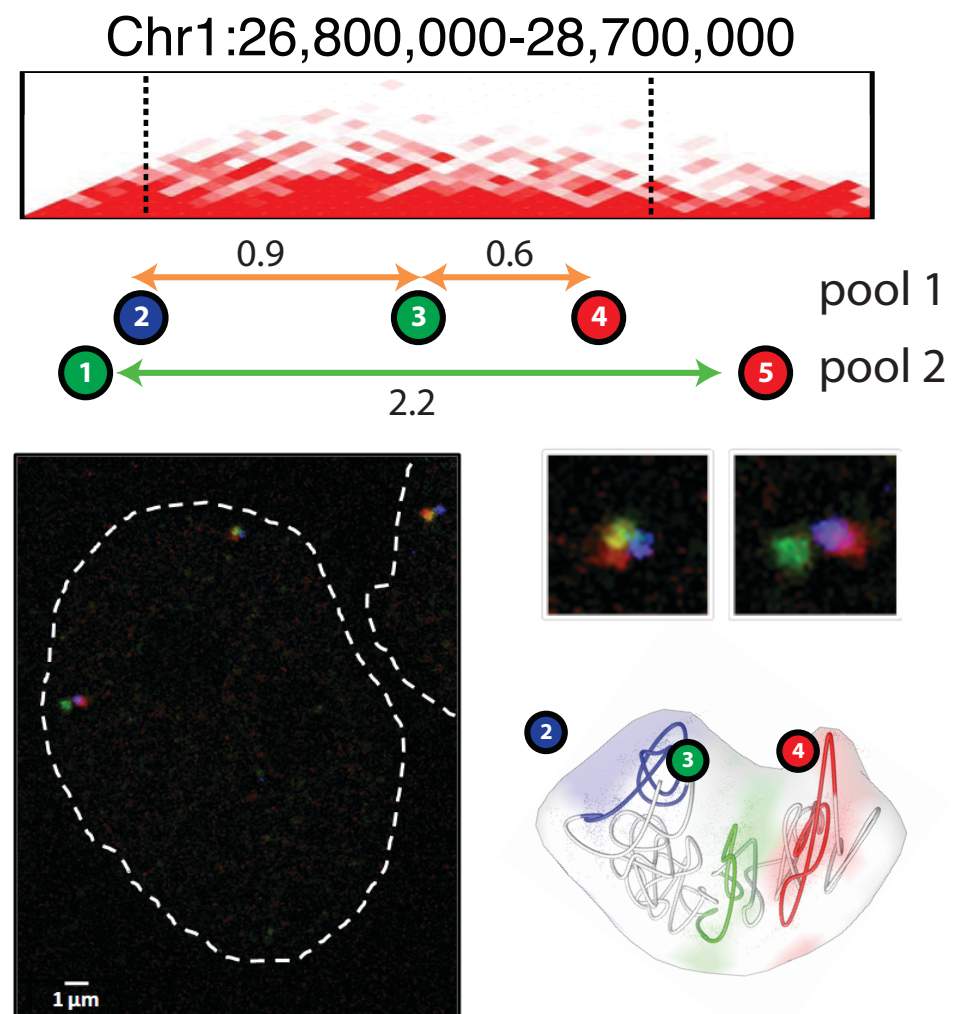
Pg induced fold change per TAD (6h)



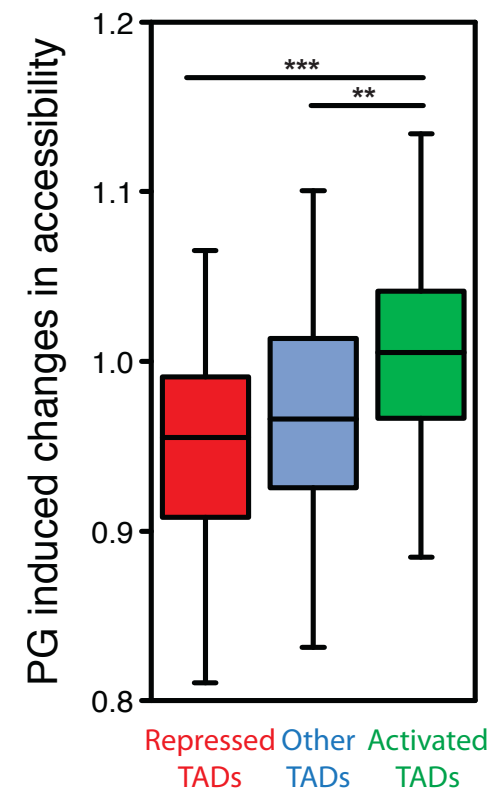
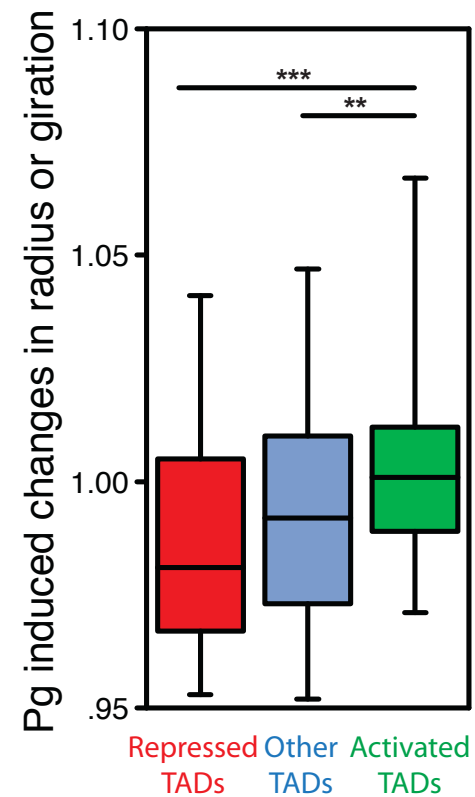
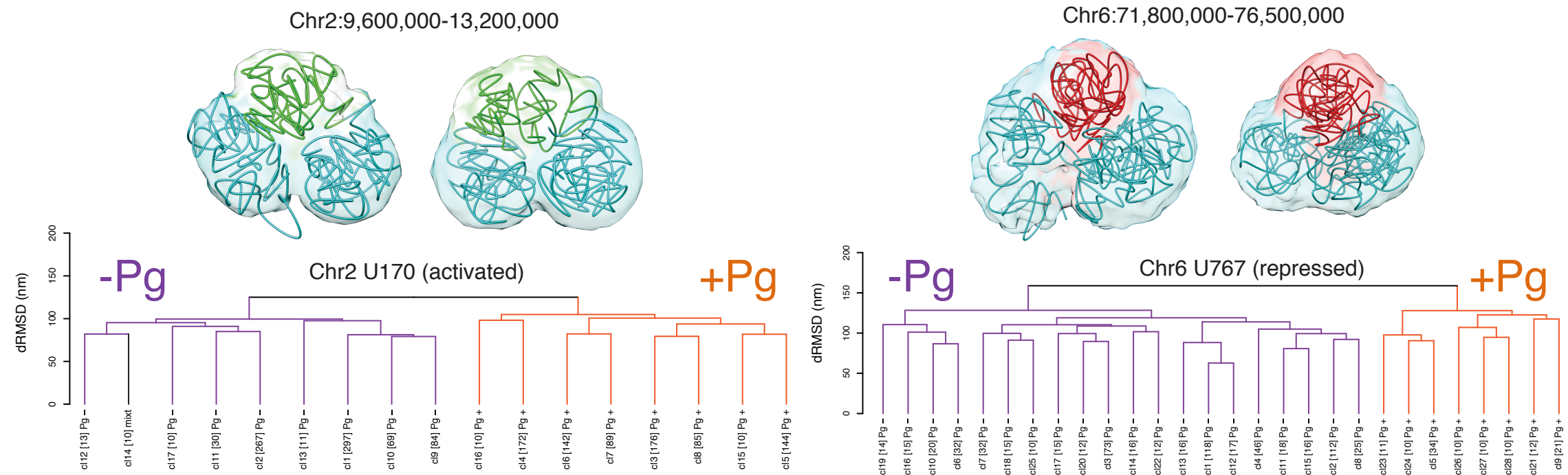
# Modeling 3D TADs



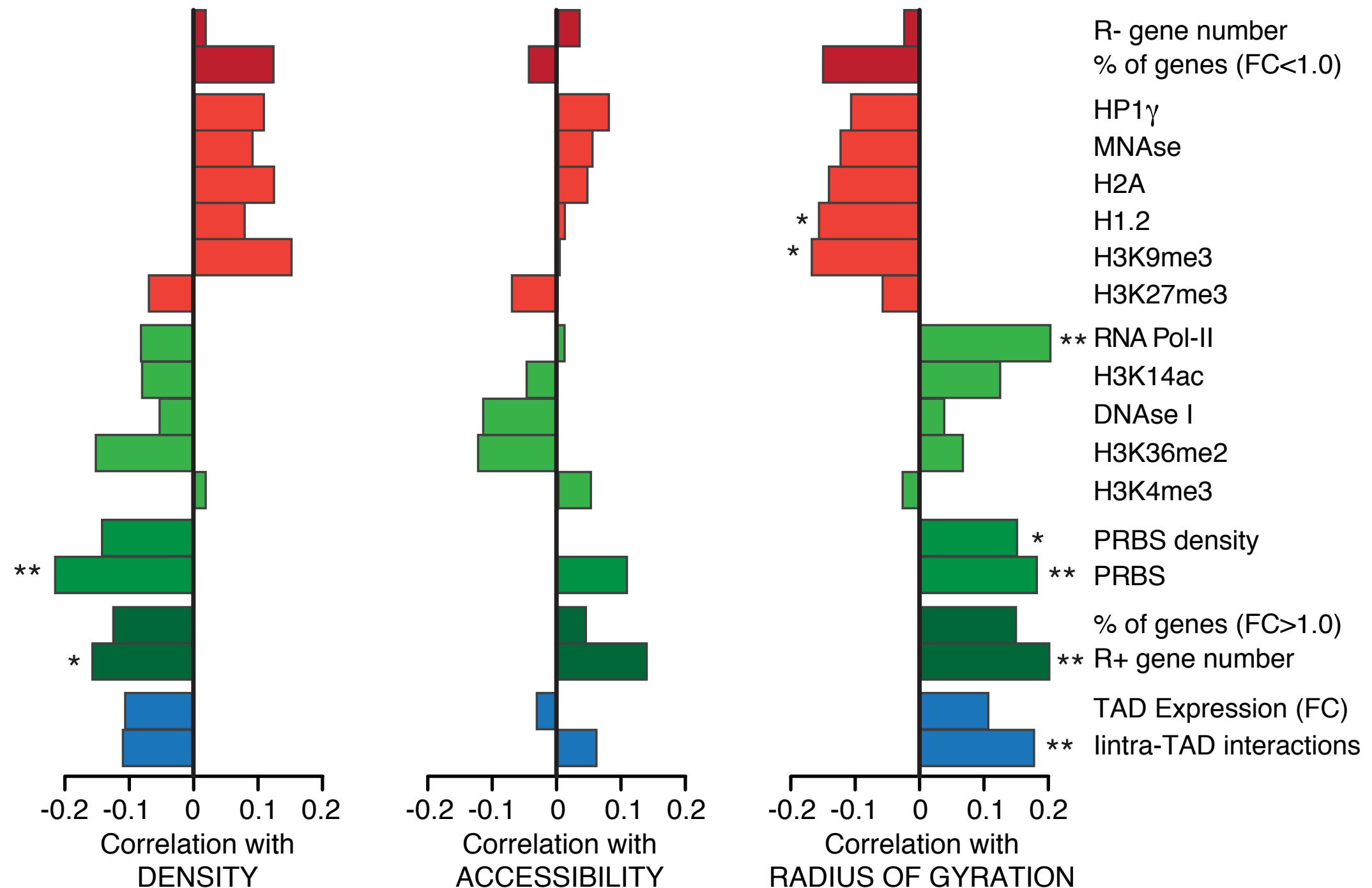
61 genomic regions containing 209 TADs covering 267Mb



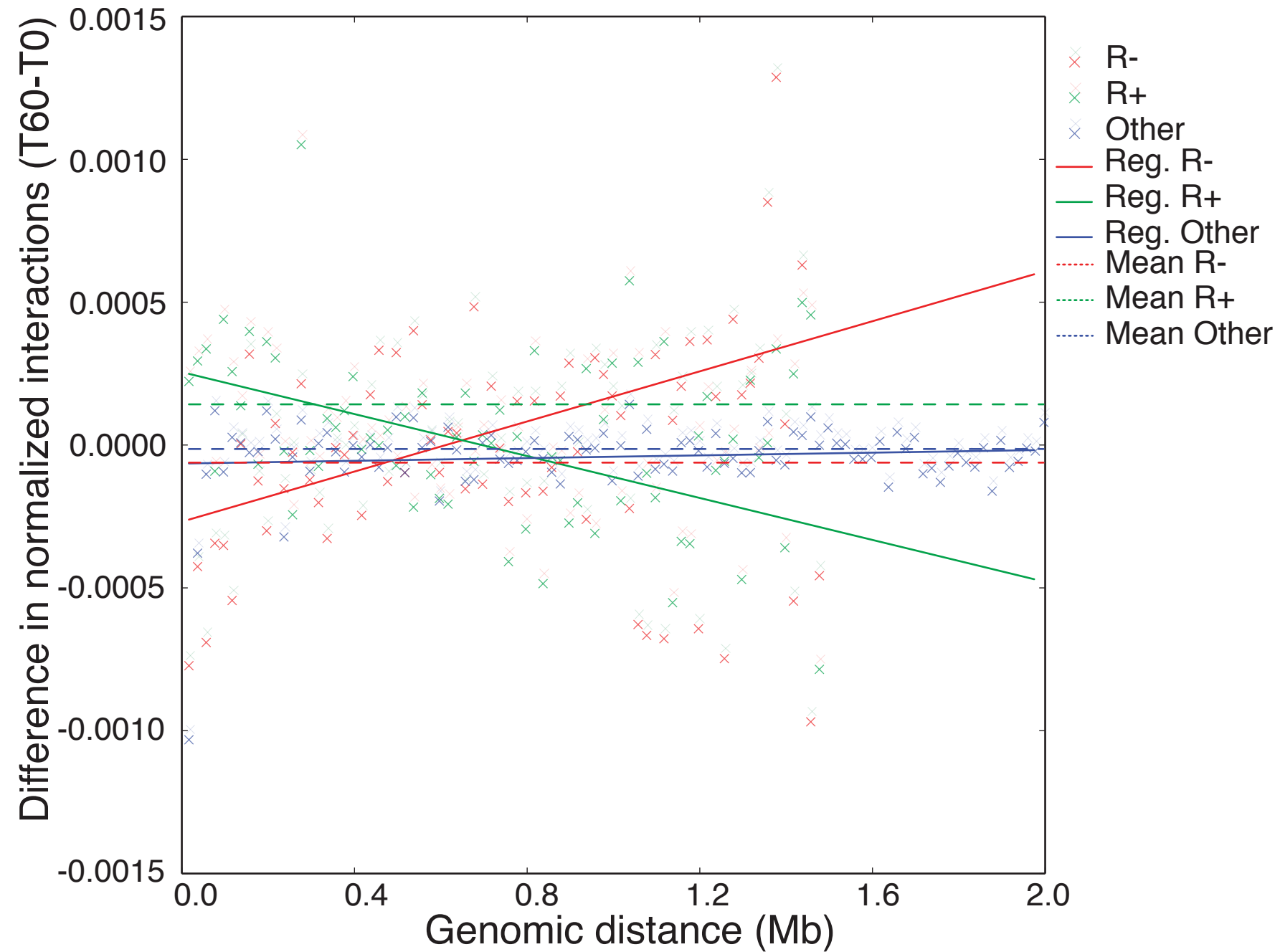
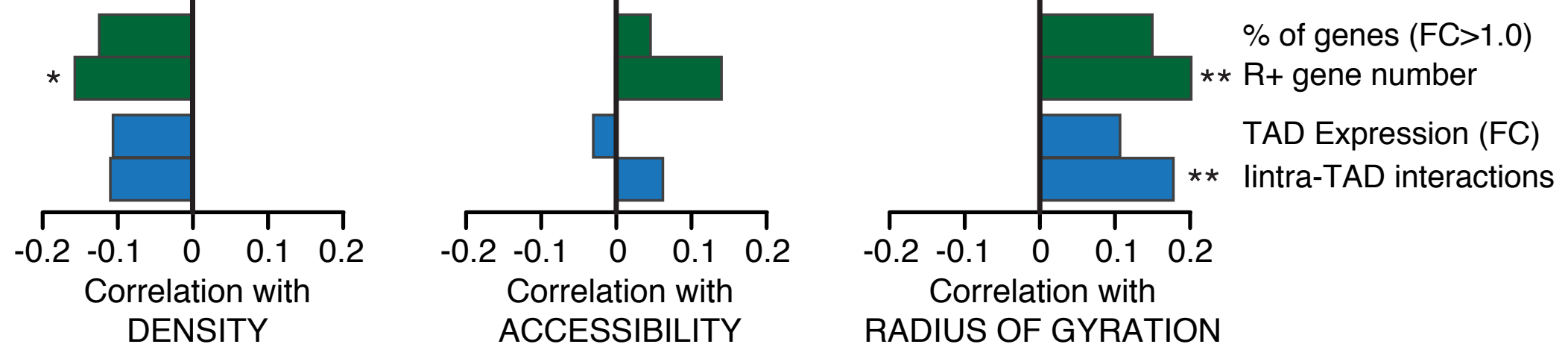
# How TADs respond structurally to Pg?



# How TADs respond structurally to Pg?



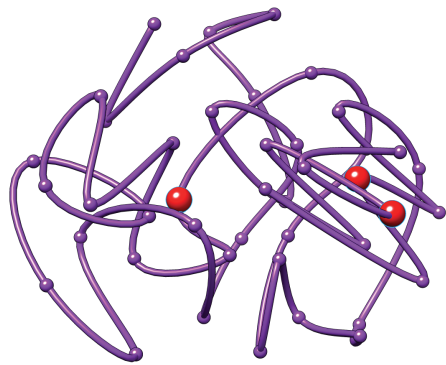




# Model for TAD regulation

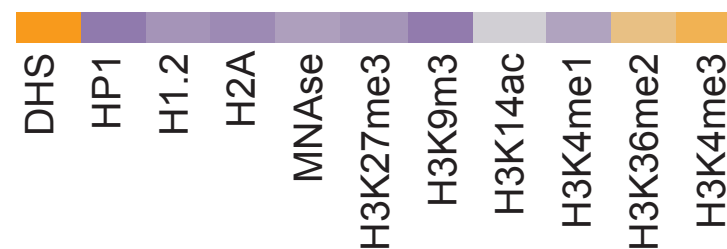
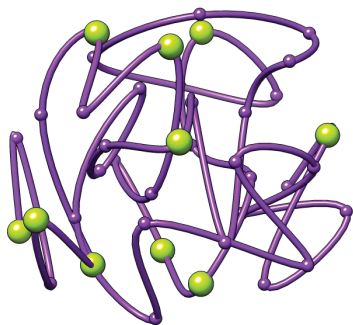
## Repressed TAD

chr1 U41

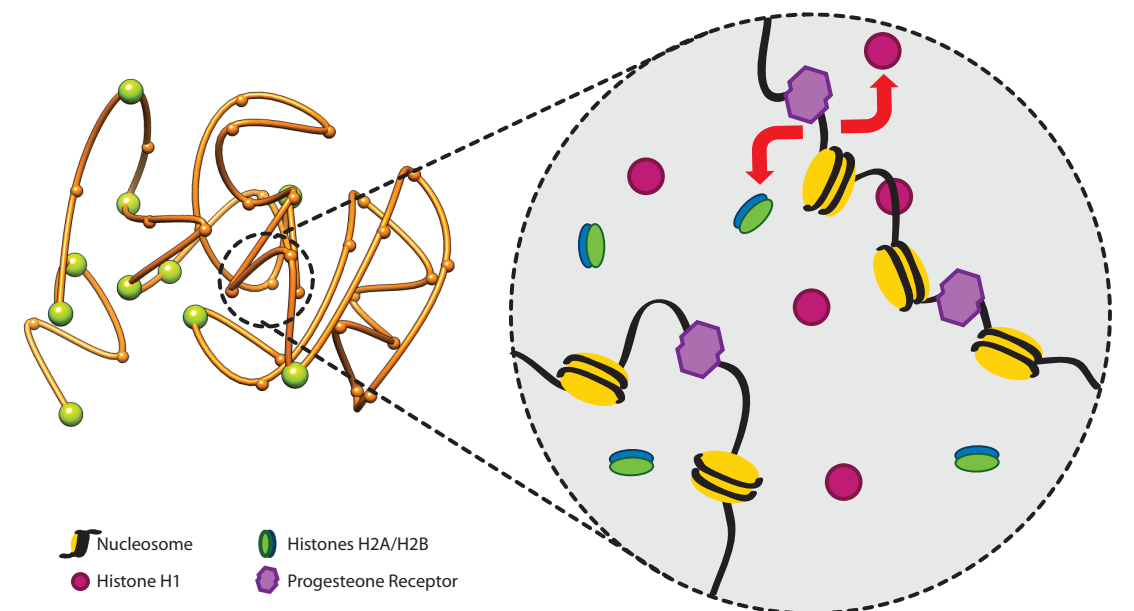
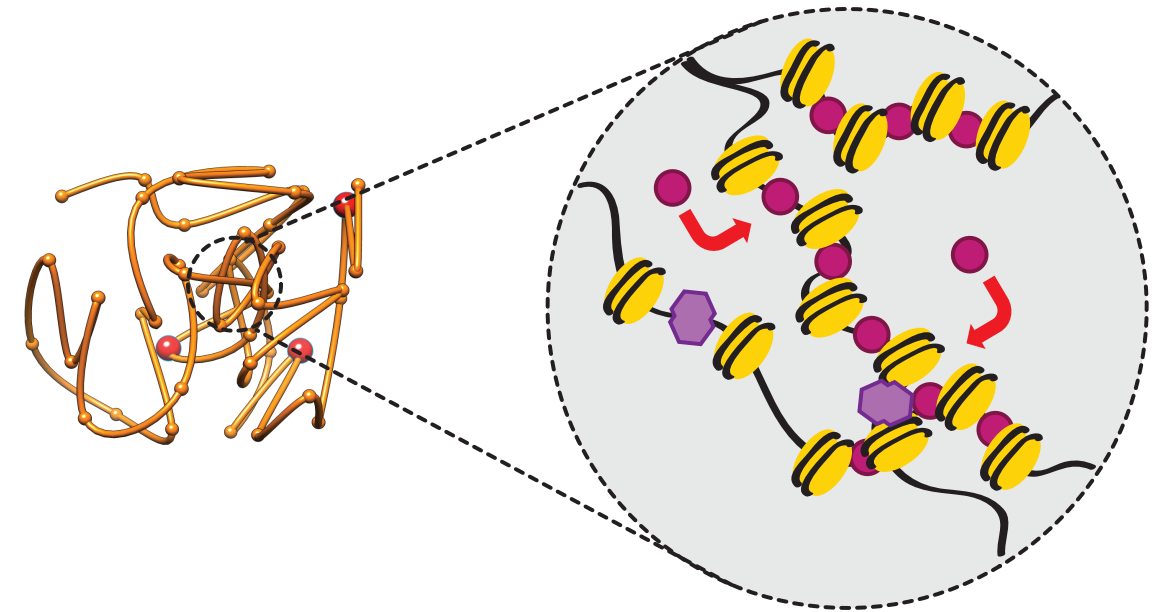


## Activated TAD

chr2 U207



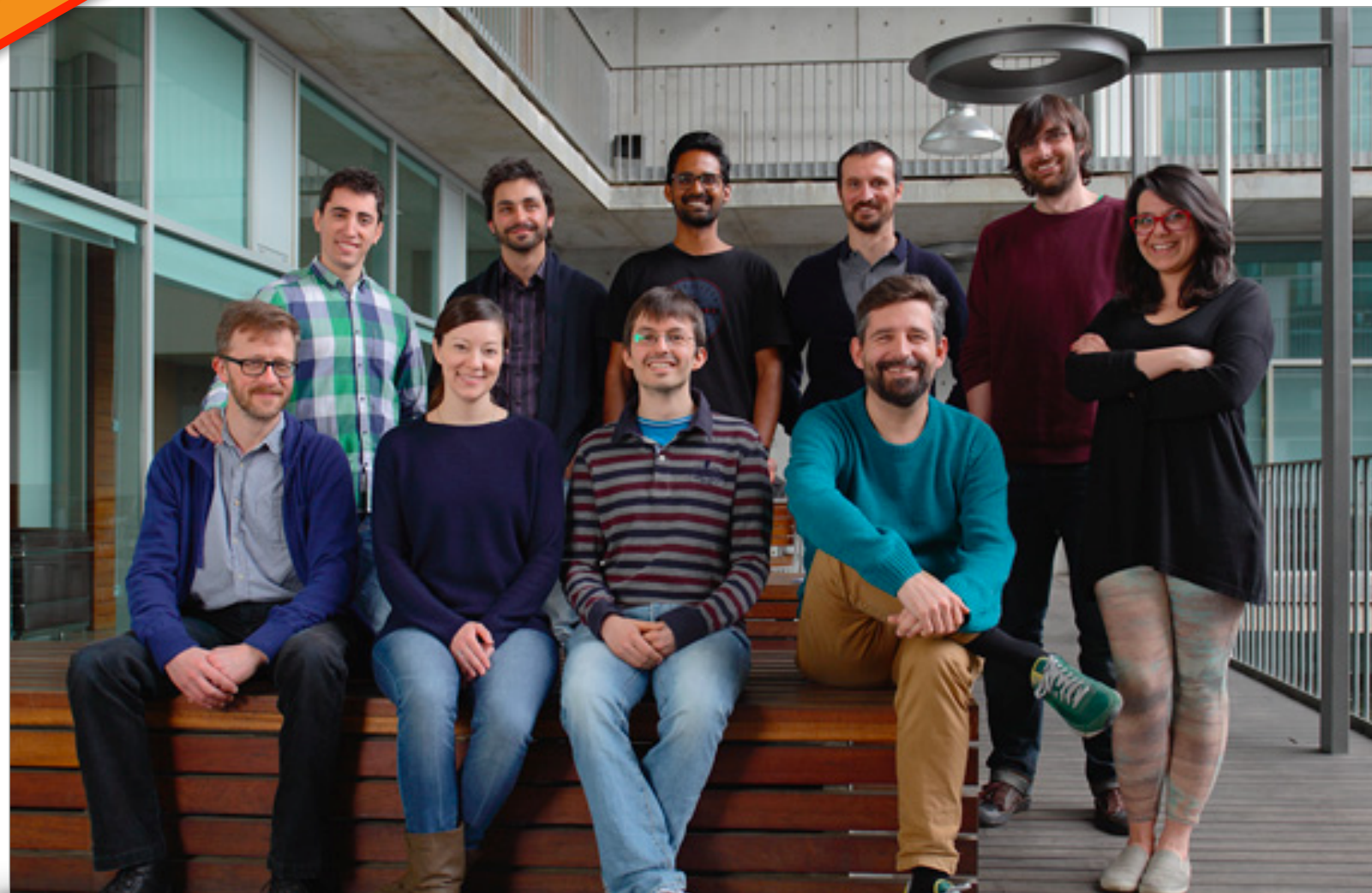
Structural transition  
**+Pg**



 Nucleosome  
 Histone H1  
 Histones H2A/H2B  
 Progesterone Receptor

Open positions soon!

# Acknowledgments



François le Dily  
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<http://cnag.crg.cat>

