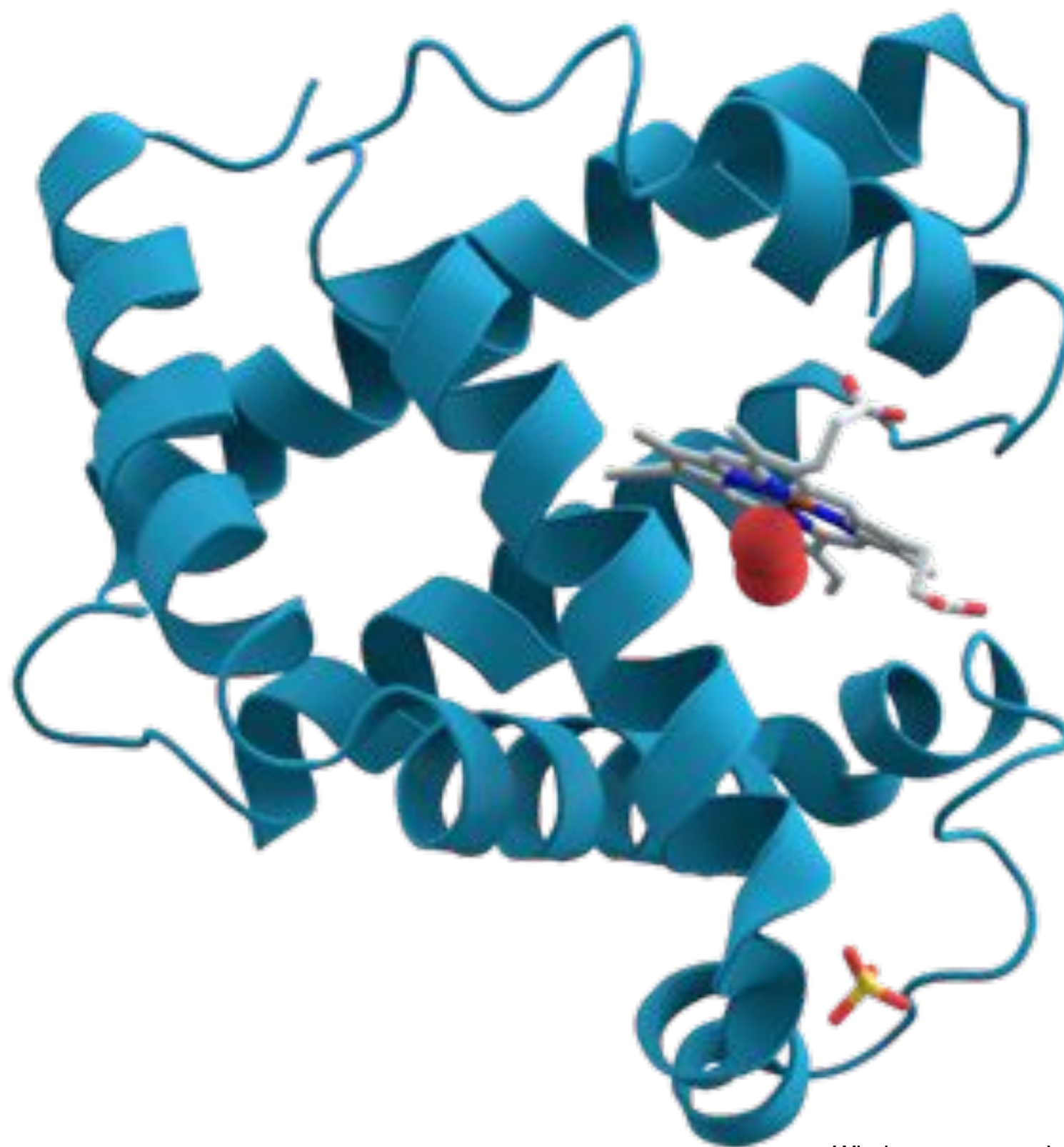


Structure determination of genomes and genomic domains by satisfaction of spatial restraints

Marc A. Marti-Renom

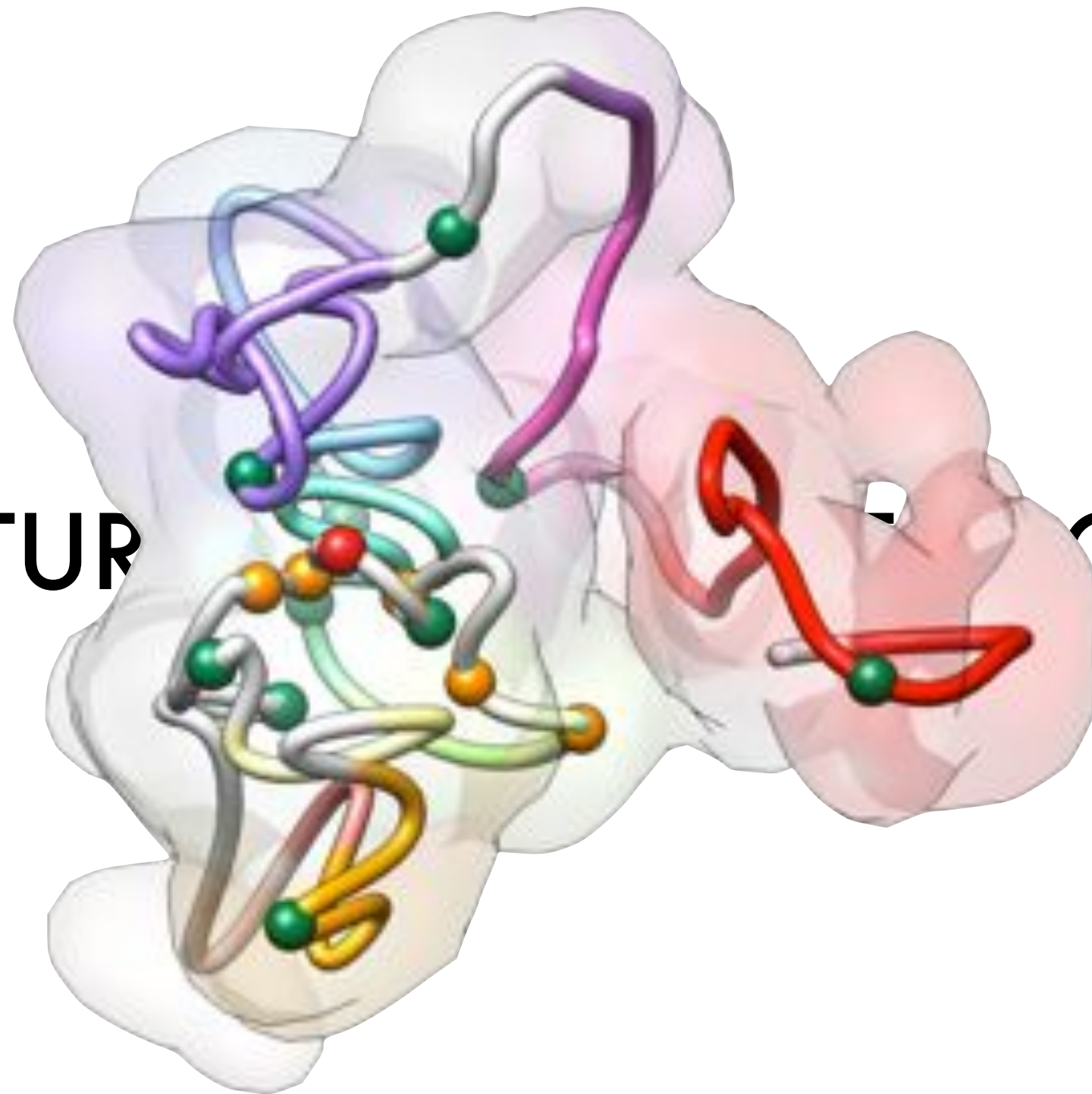
Genome Biology Group (CNAG)
Structural Genomics Group (CRG)

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



Whale sperm myoglobin structure (1960)

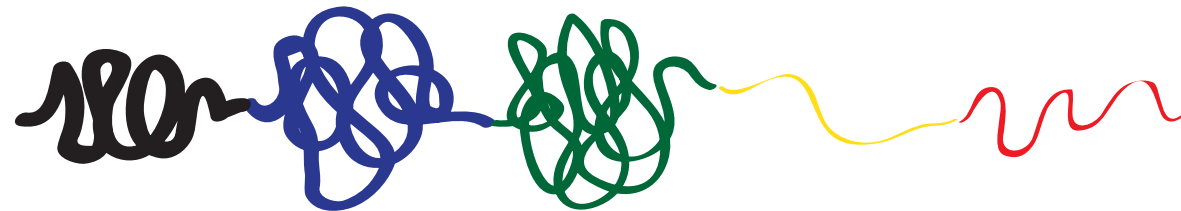
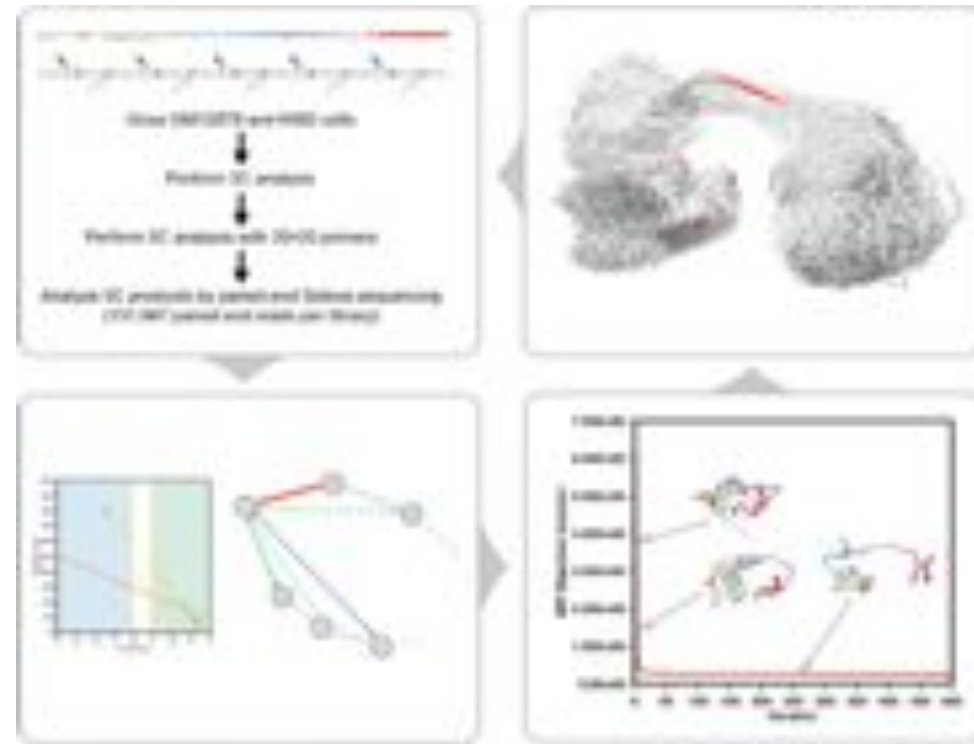
STRUCTURE



FUNCTION

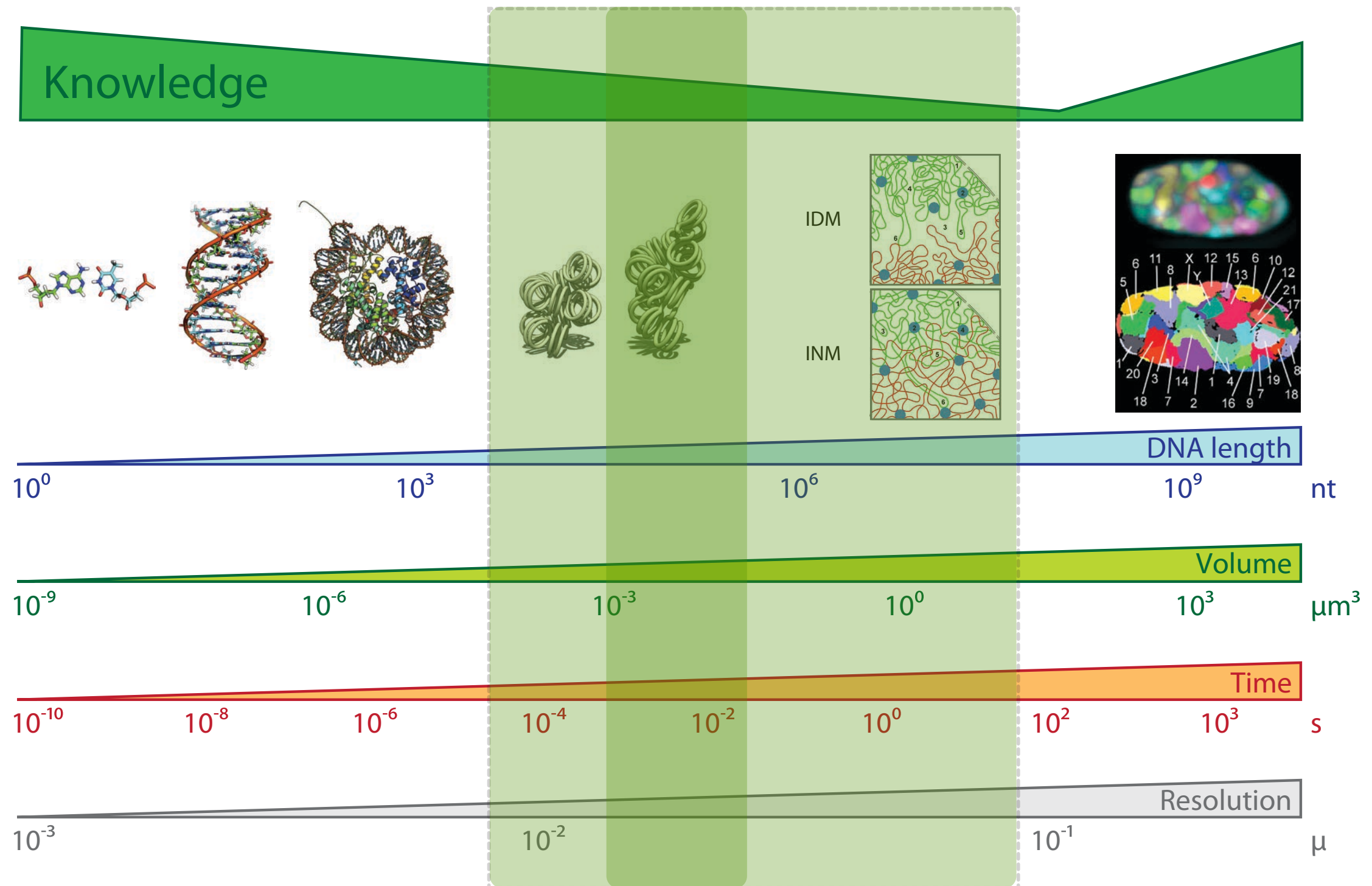
alpha-globin genomic domain structure (2011)

TADbit



Resolution Gap

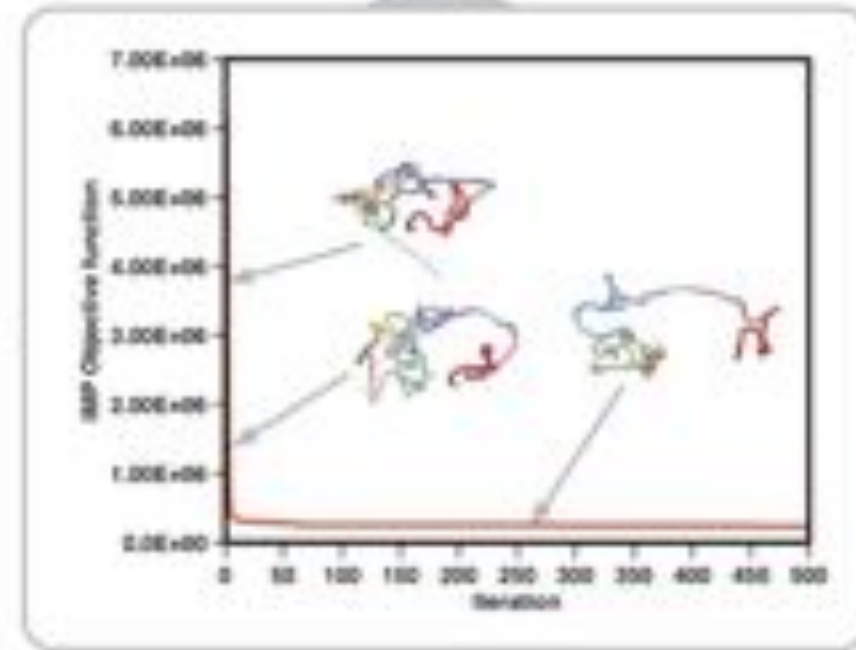
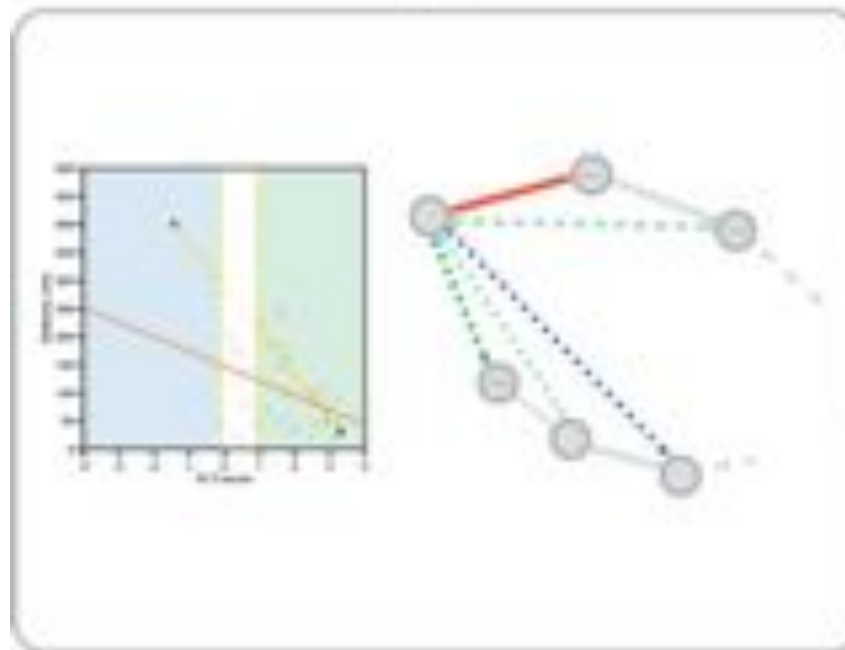
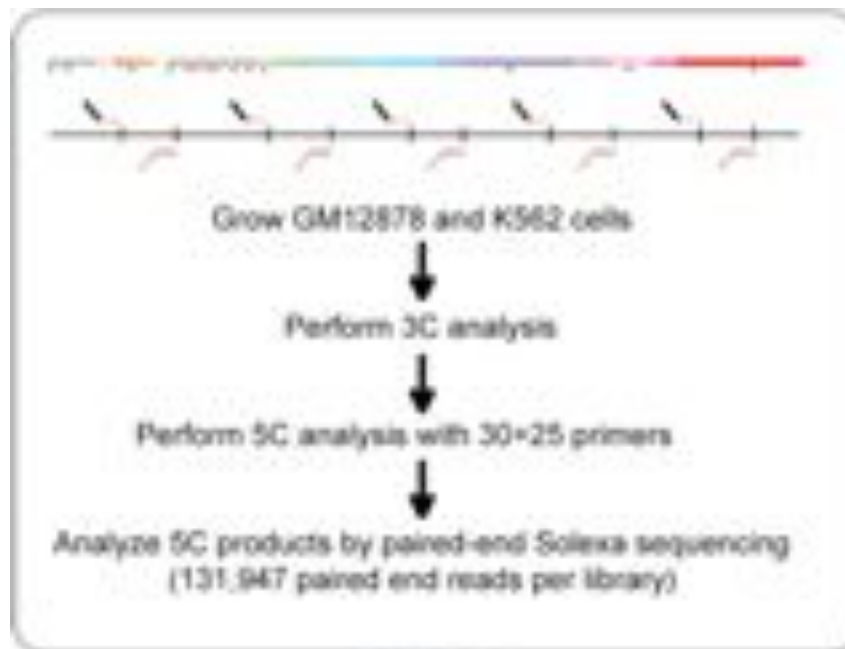
Marti-Renom, M. A. & Mirny, L. A. PLoS Comput Biol 7, e1002125 (2011)



Hybrid Method

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

Experiments



Computation

Hi-C technology

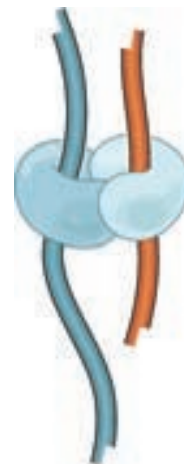
Lieberman-Aiden, E. et al. Science 326, 289–293 (2009).

<http://3dg.umassmed.edu>

Crosslink DNA



Cut with restriction enzyme



Fill ends and mark with biotin



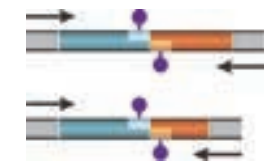
Ligate



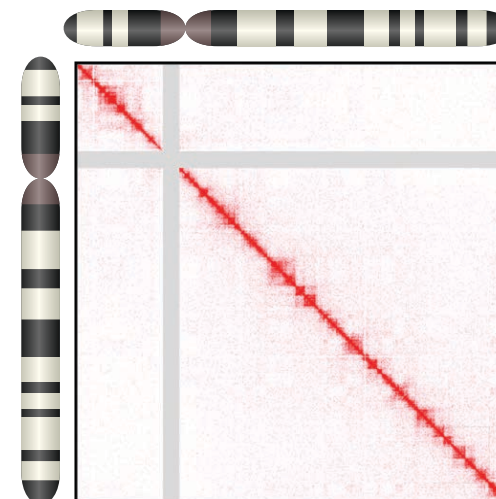
Purify and shear DNA; pull down biotin

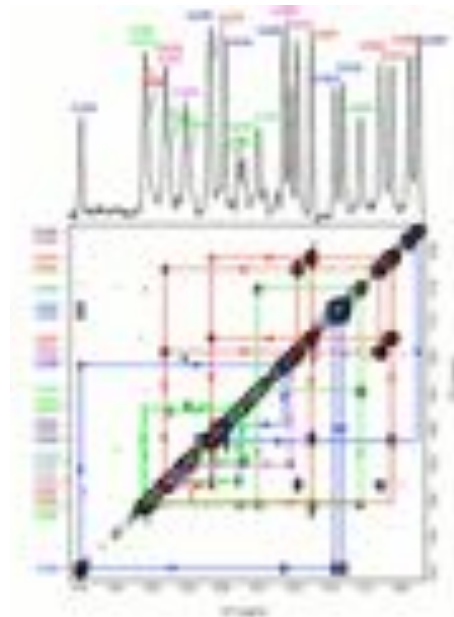


Sequence using paired-ends

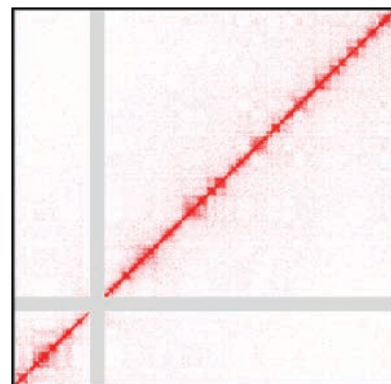
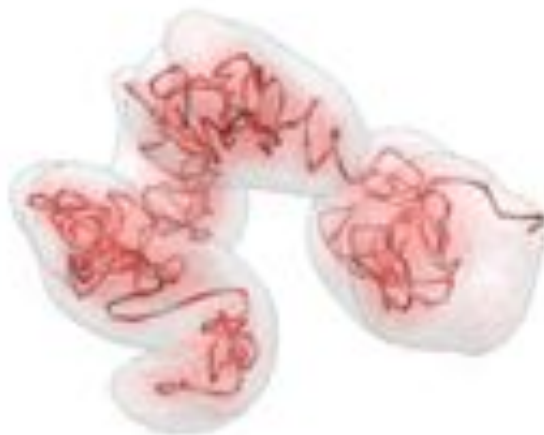


Chr.18 (Hind III)



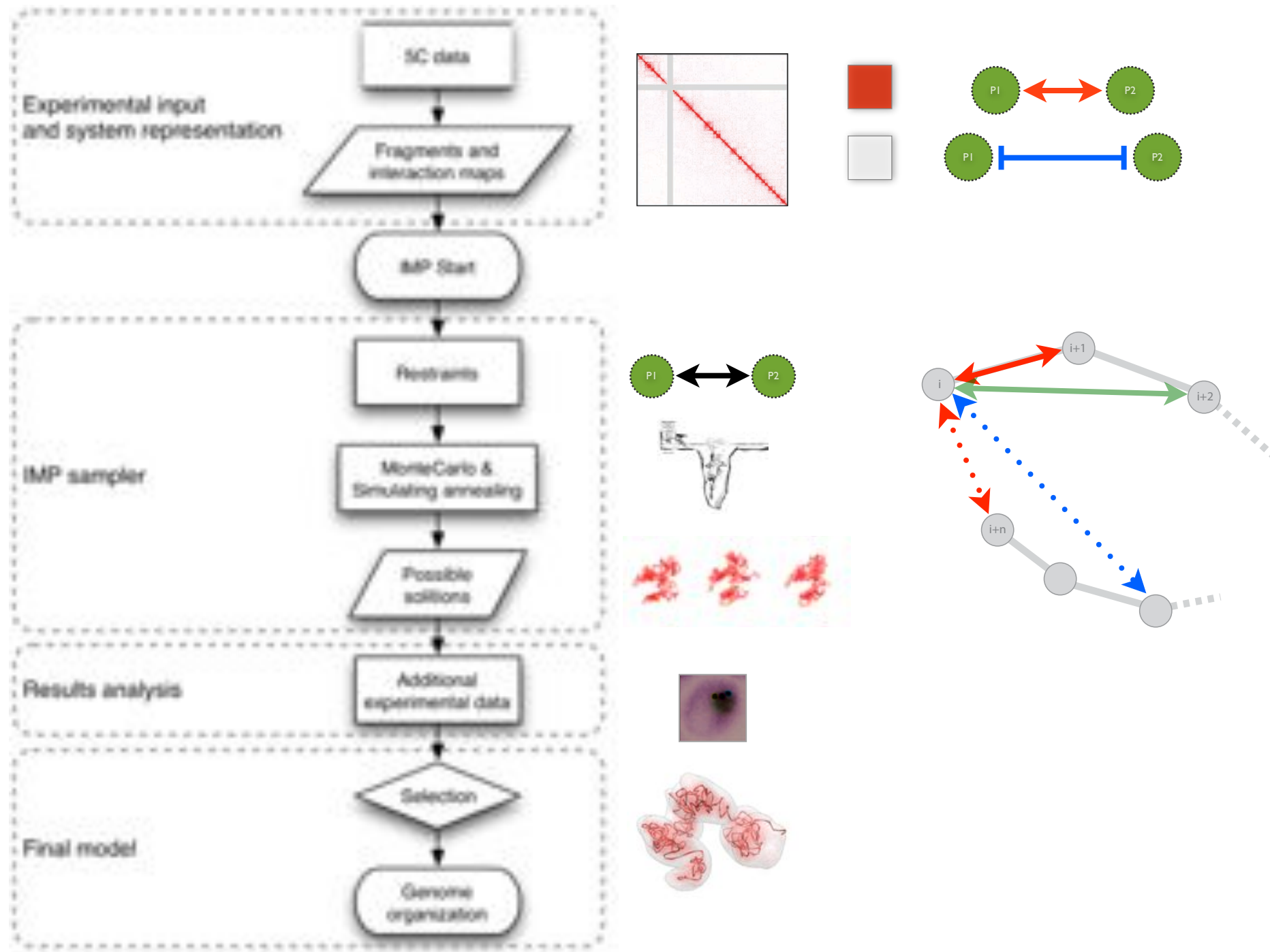


Biomolecular structure determination
2D-NOESY data



Chromosome structure determination
3C-based data

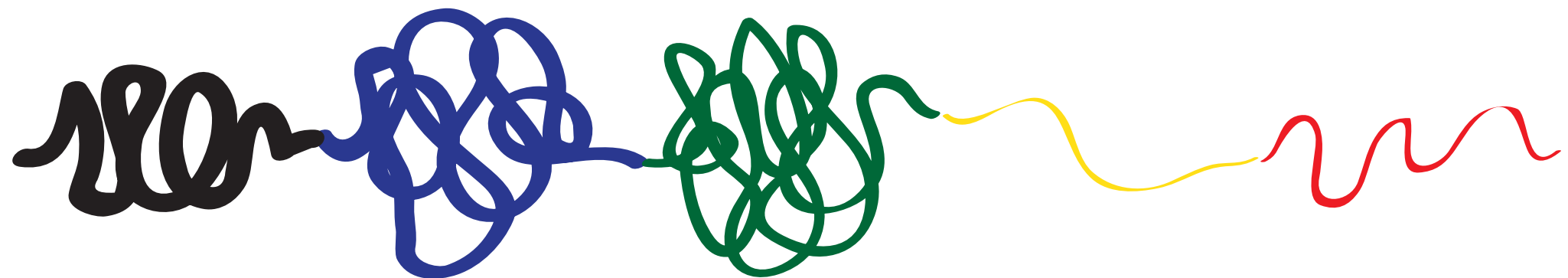
TADbit



TADbit



Structuring the **COLORs** of chromatin



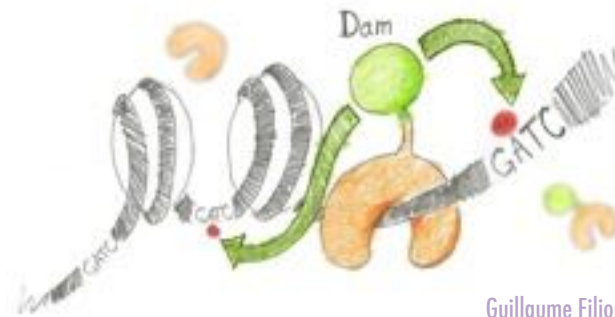
Davide Baù



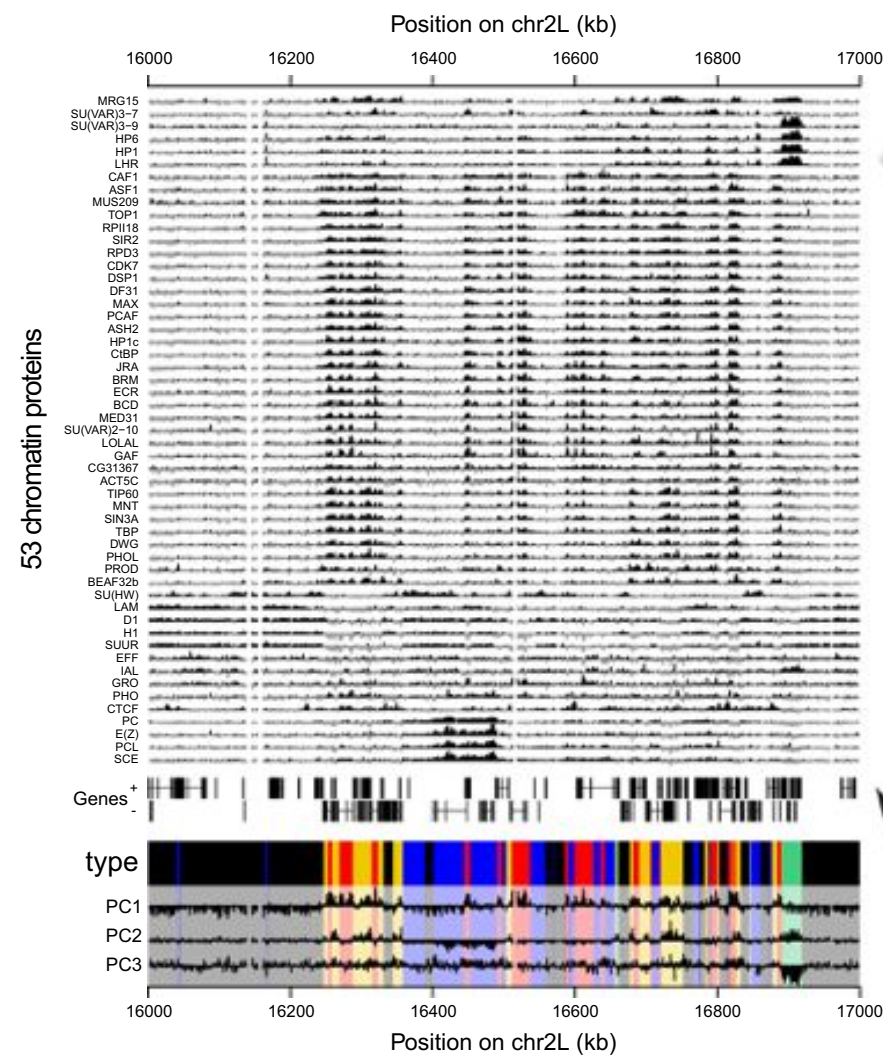
François Serra

The COLOrS

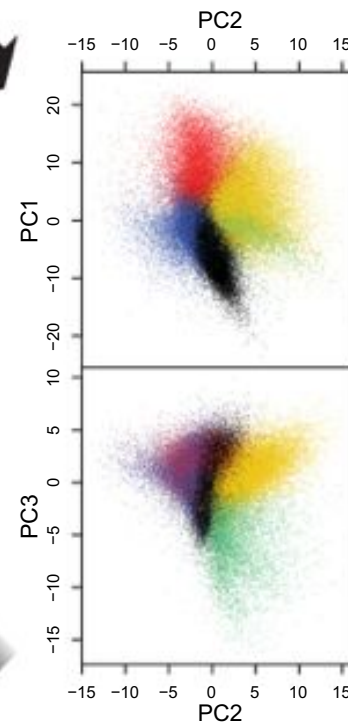
Filion et al. (2010). Cell, 143(2), 212-224.



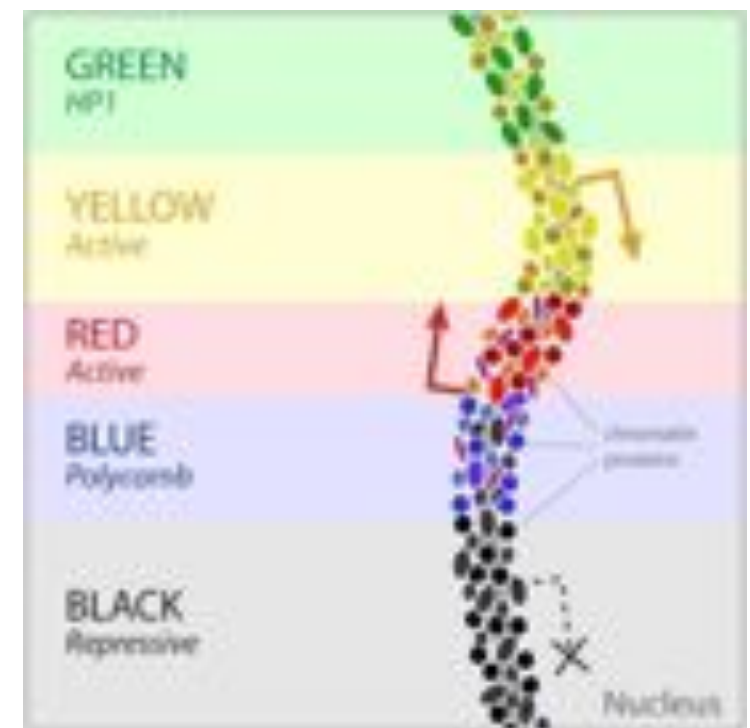
Guillaume Filion



Principal component analysis

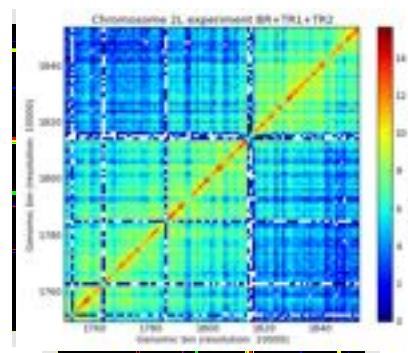
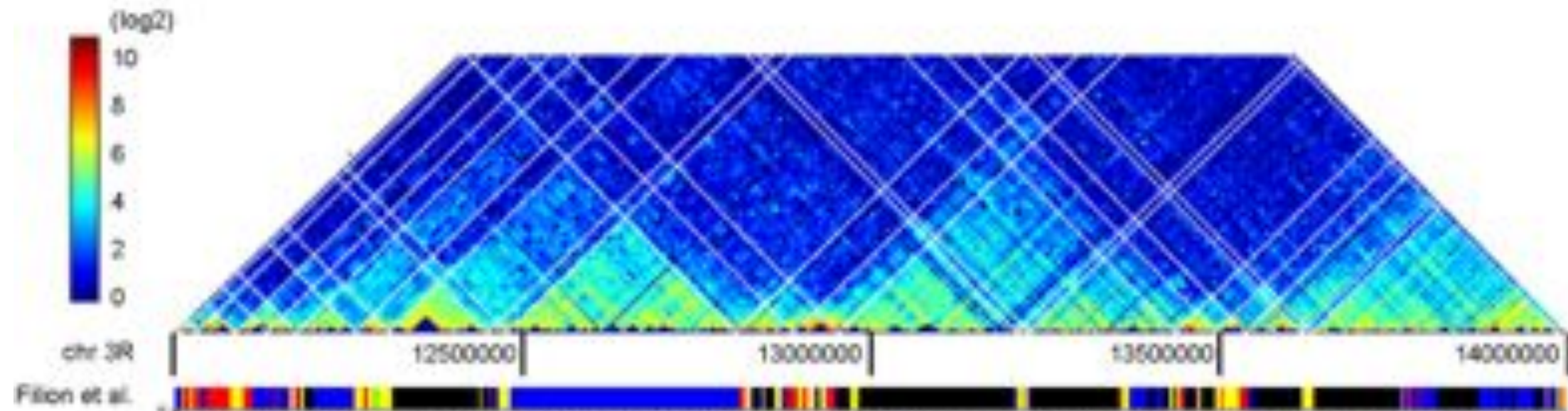


Hidden Markov model



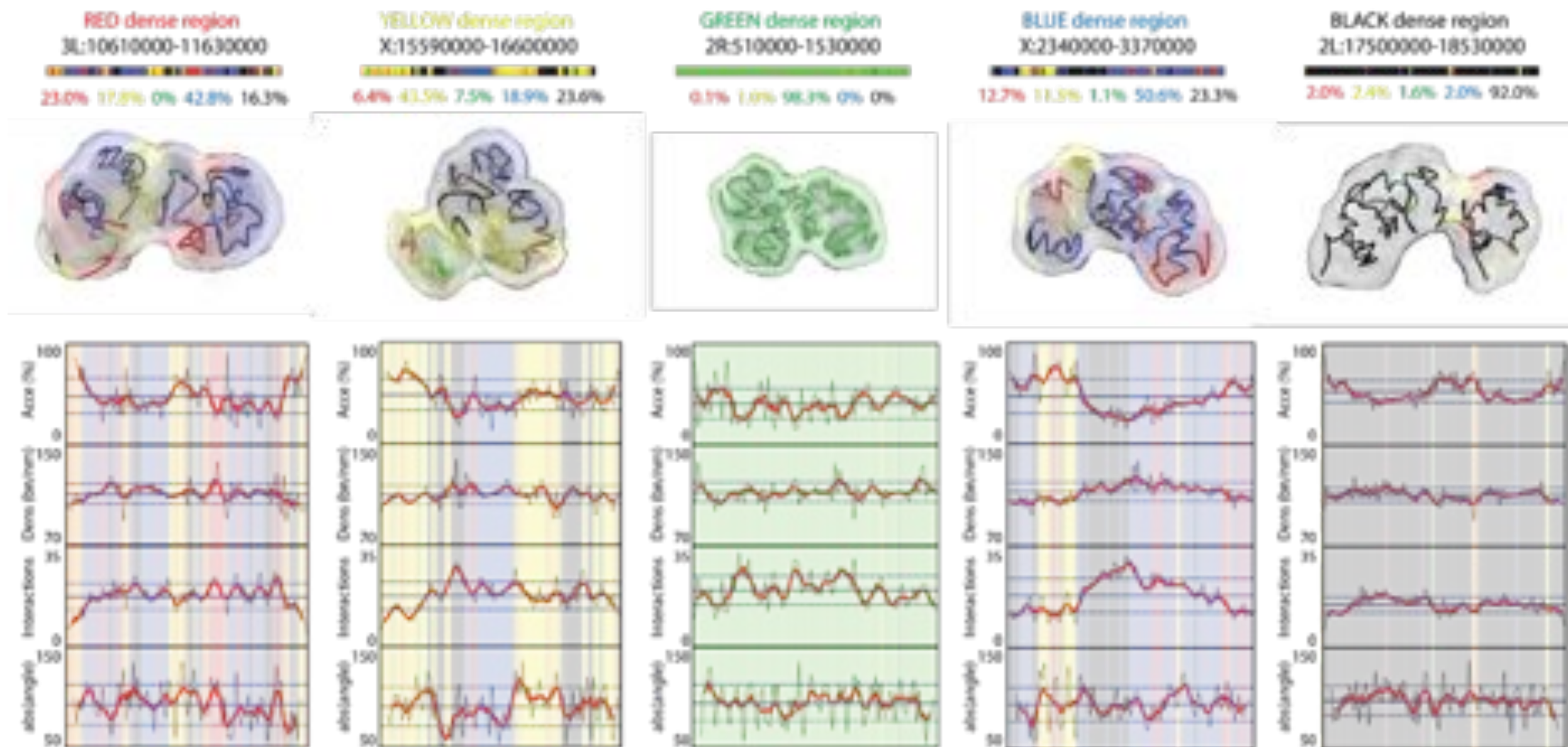
Functional COLORs

Hou et al. (2012). Molecular Cell, 48(3), 471–484.

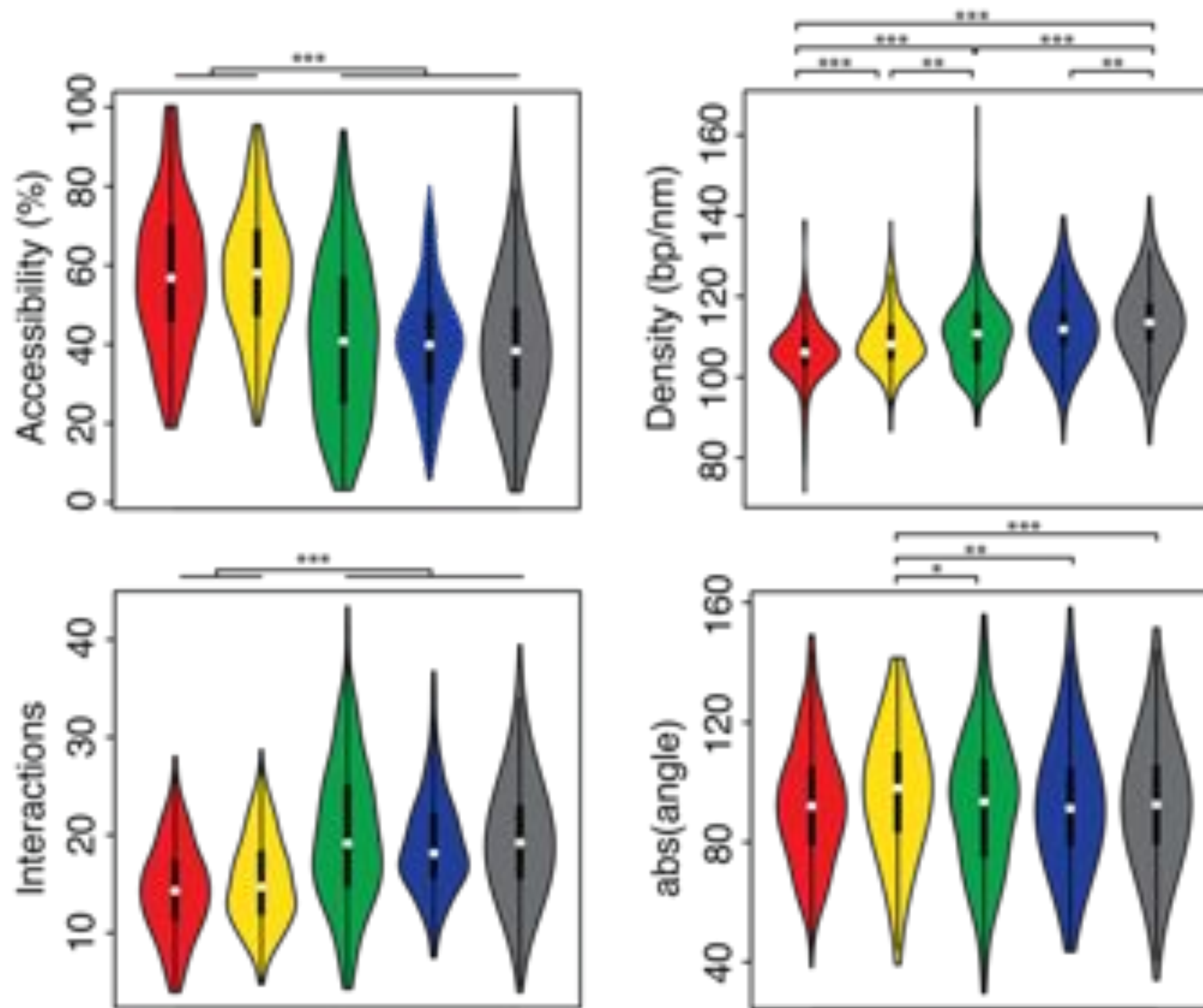


50 ~1Mb regions
10 for each color

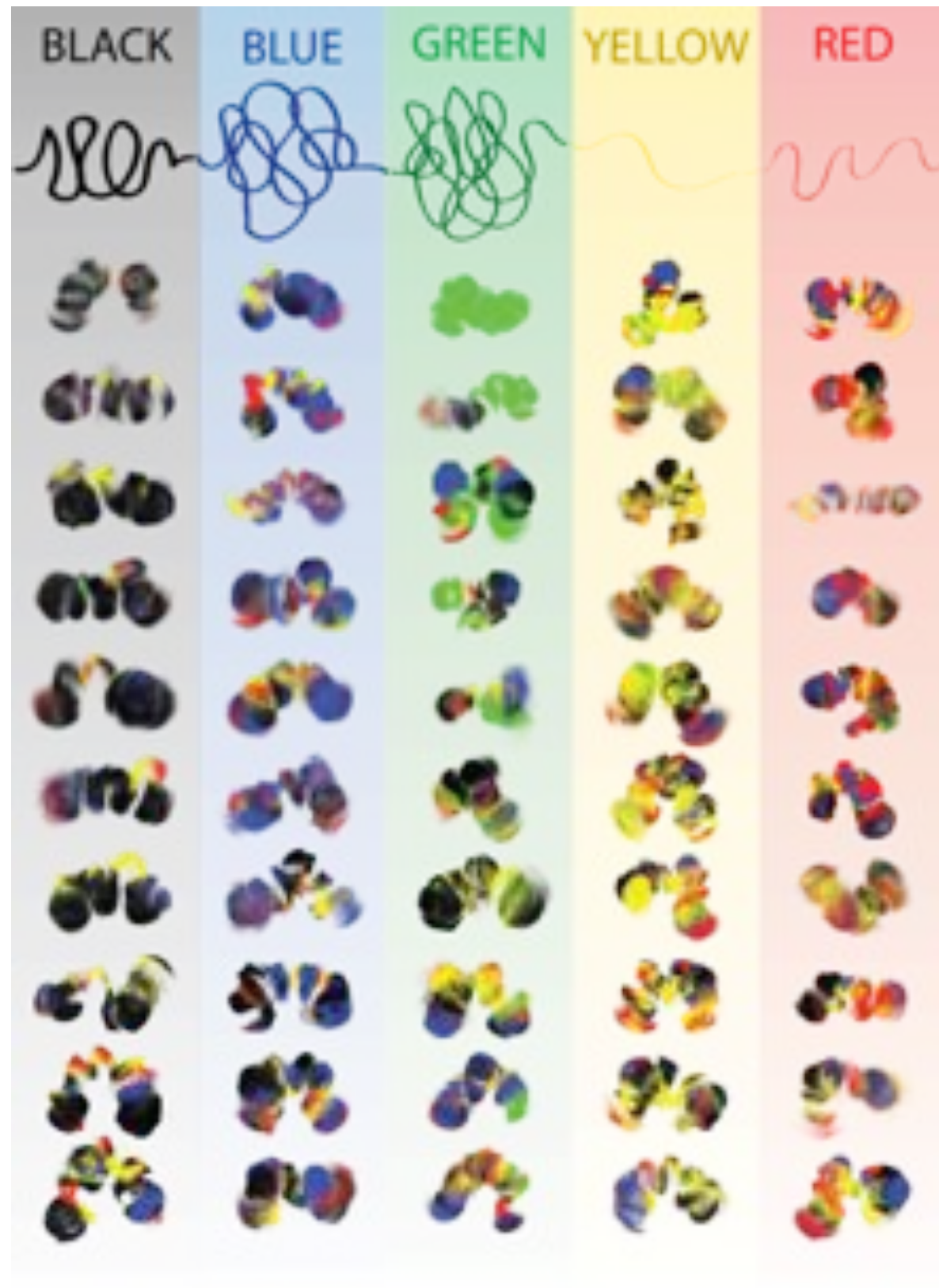
Structural COLOrS



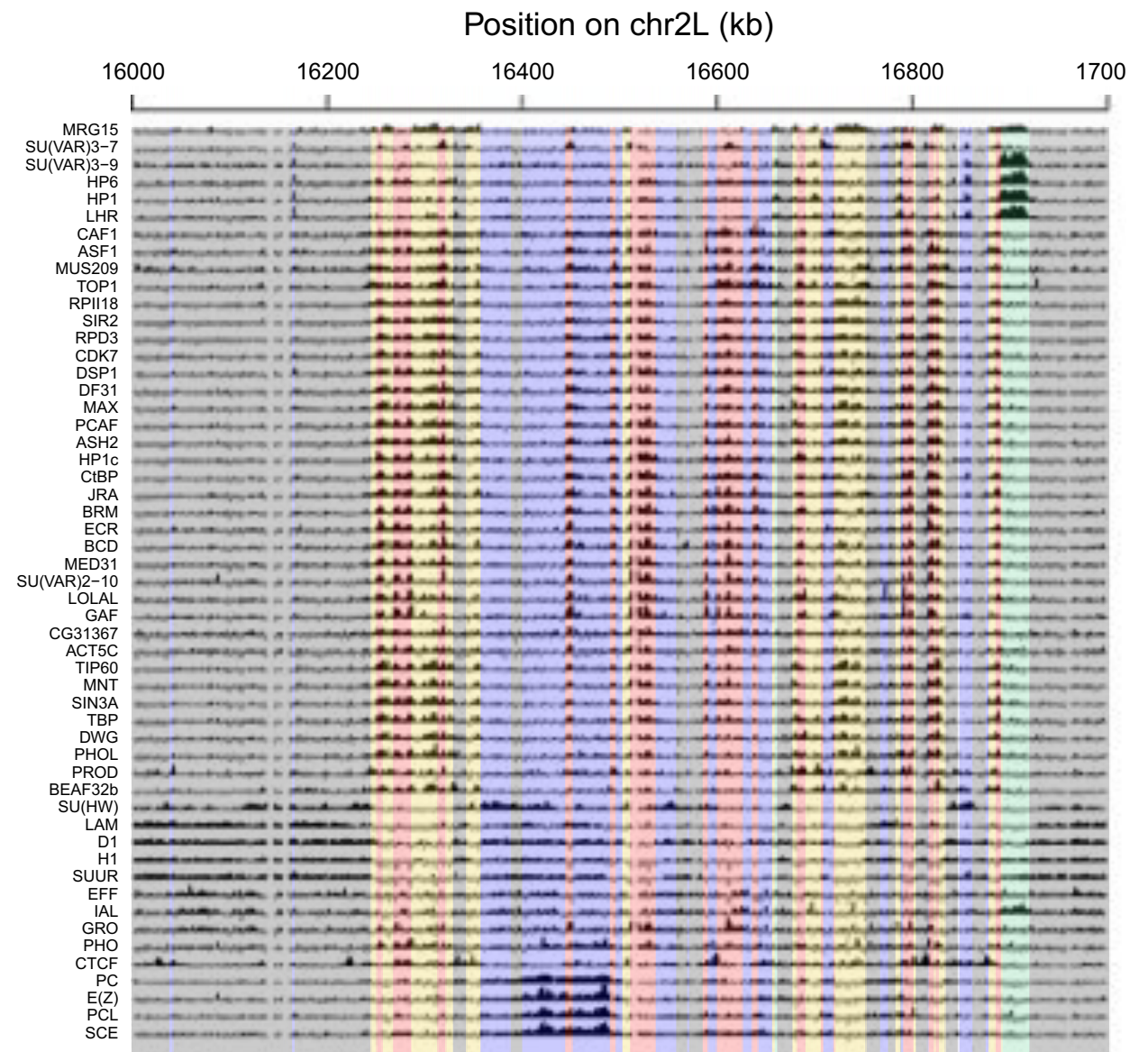
Structural COLOrS



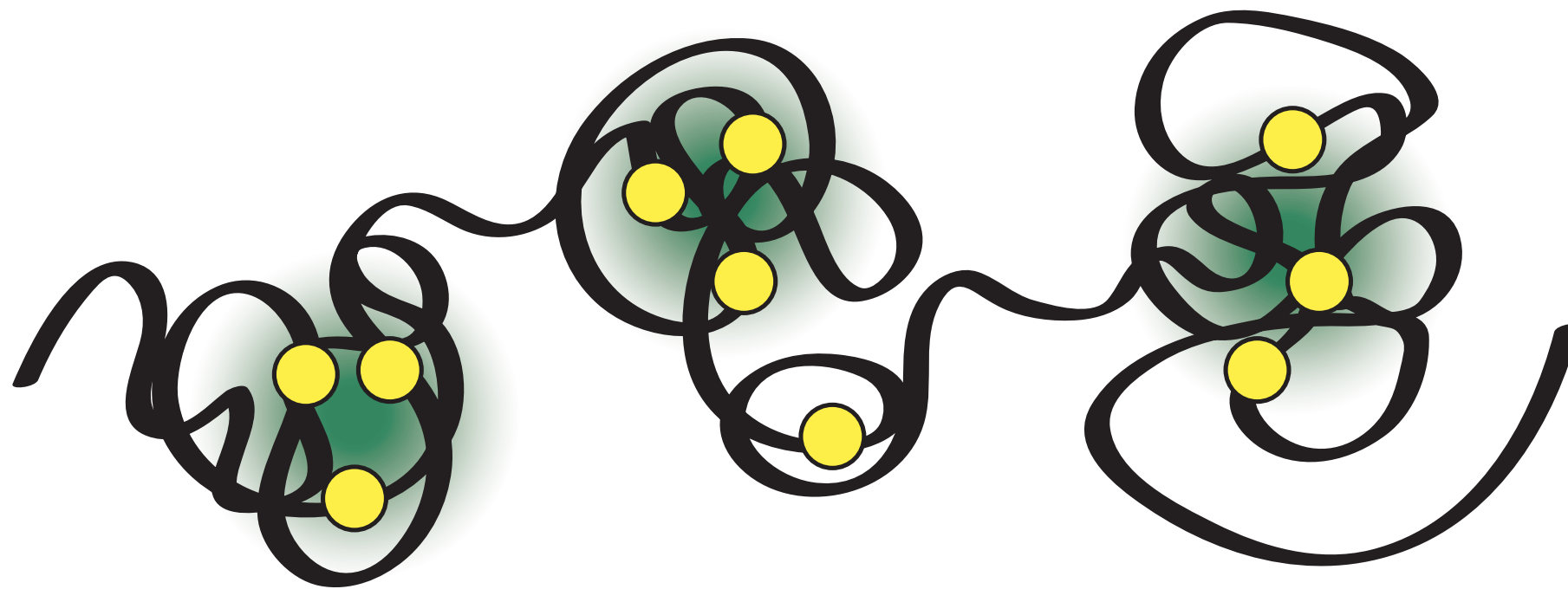
Structural COLOrS



53 chromatin proteins



On TADs and hormones



François le Dily

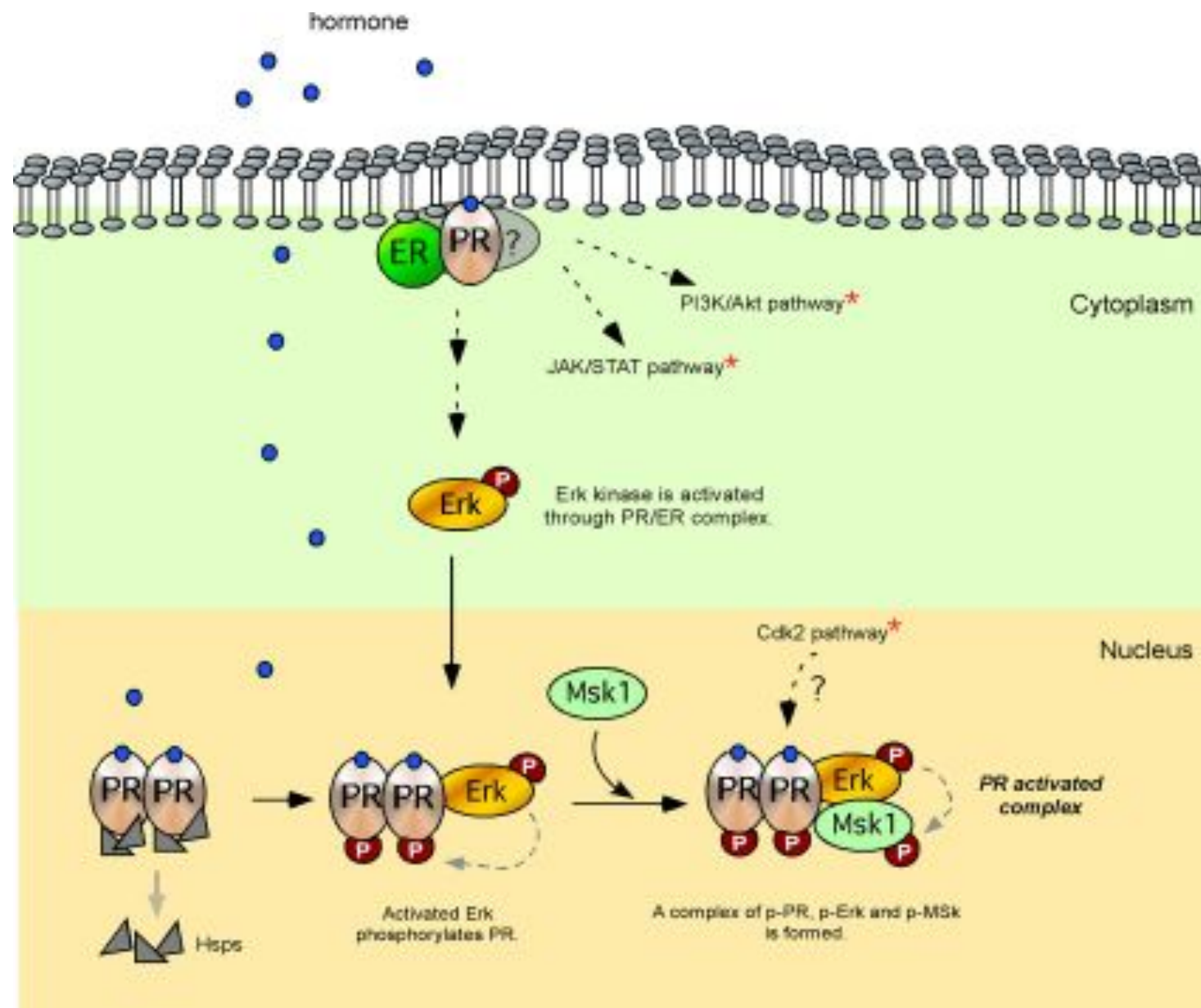


Davide Baù



François Serra

Progesterone-regulated transcription in breast cancer



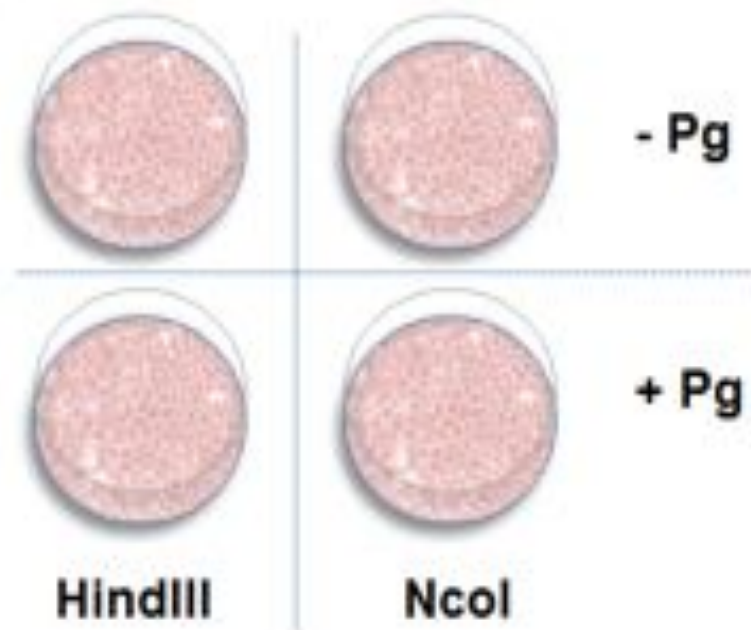
> 2,000 genes **Up**-regulated
> 2,000 genes **Down**-regulated

Regulation in 3D?

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

Experimental design

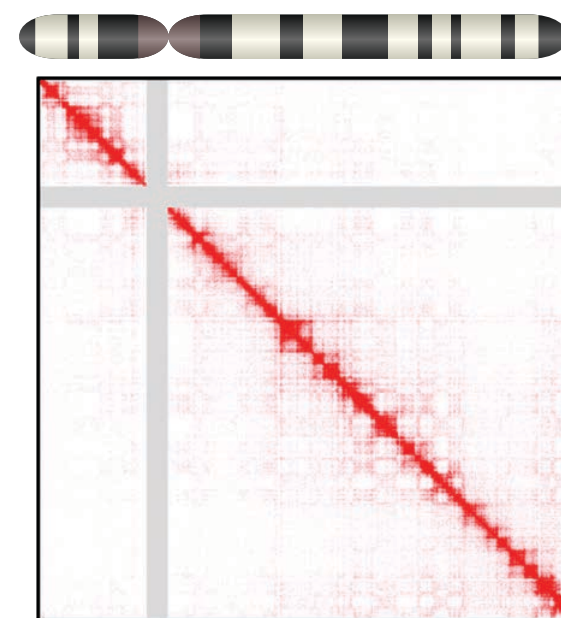
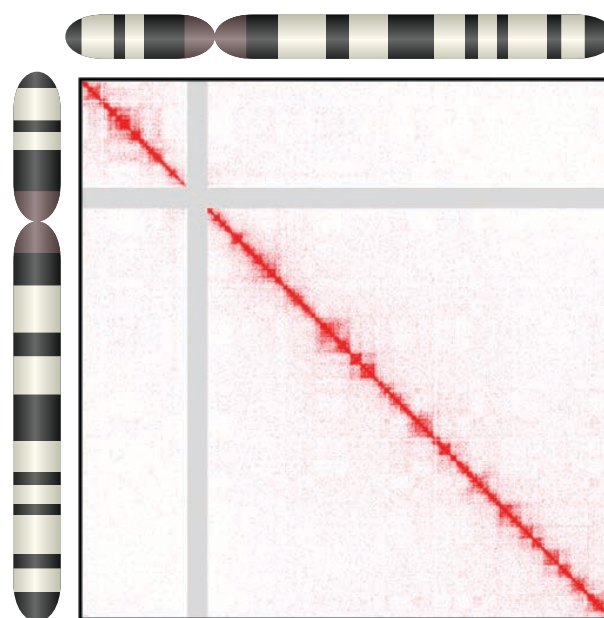
HiC libraries



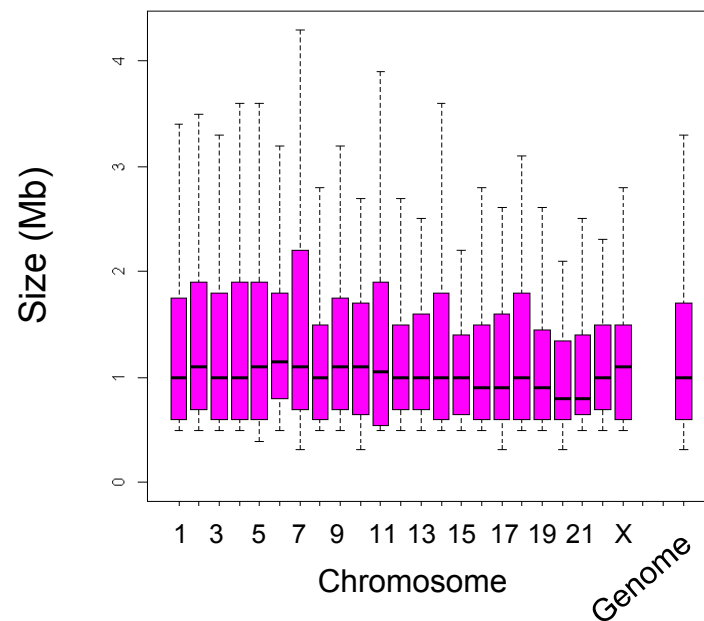
ChIP-Seq
RNA-Seq
Hi-C

Chr.18 (Hind III)

Chr.18 (NcoI)



Are there TADs? how robust?

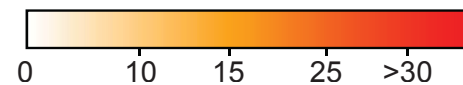
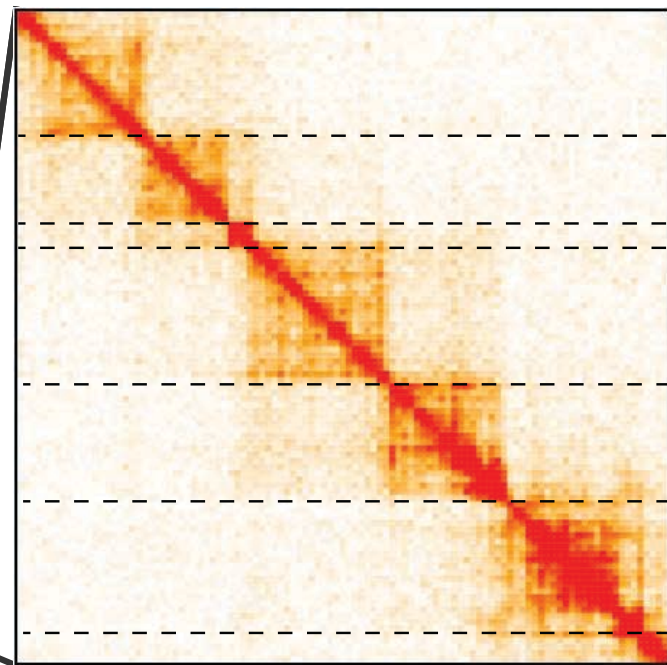


>2,000 detected TADs

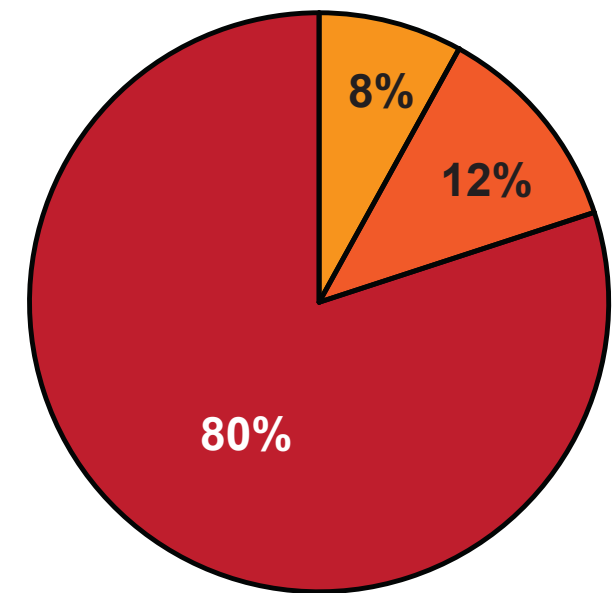
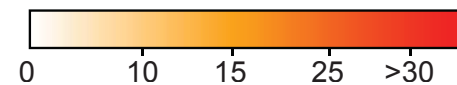
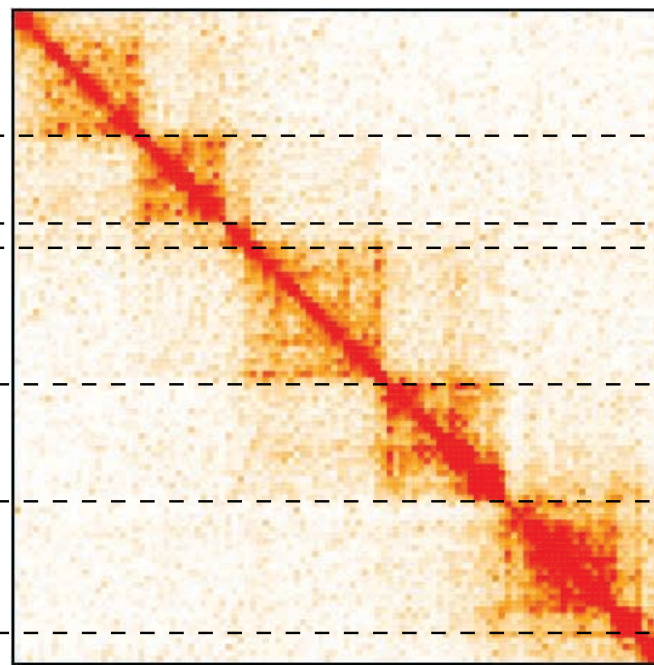
Chr.18



-Pg

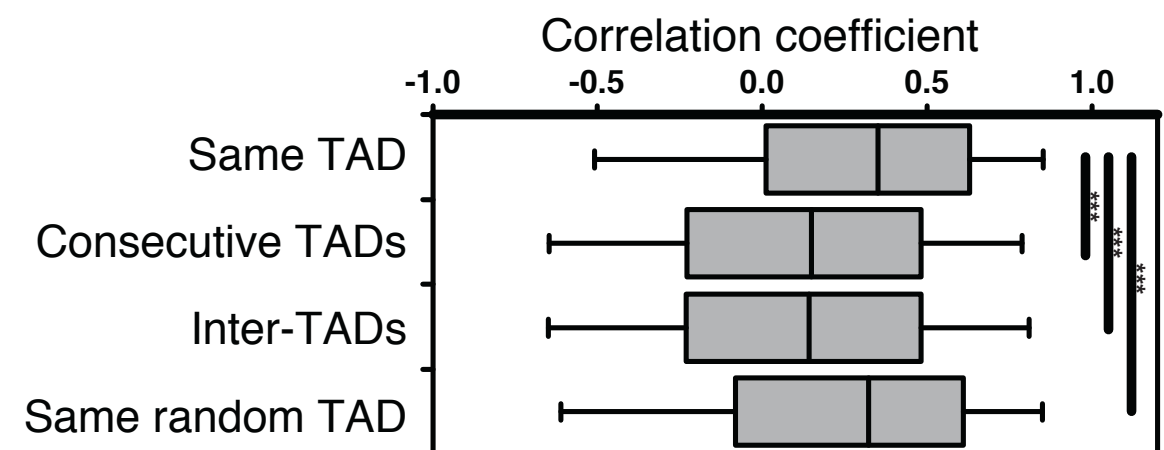
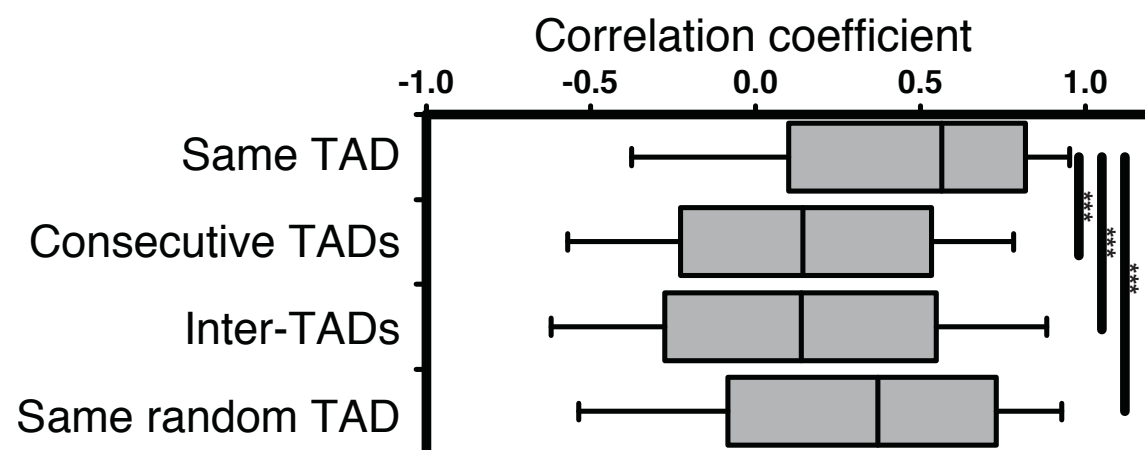
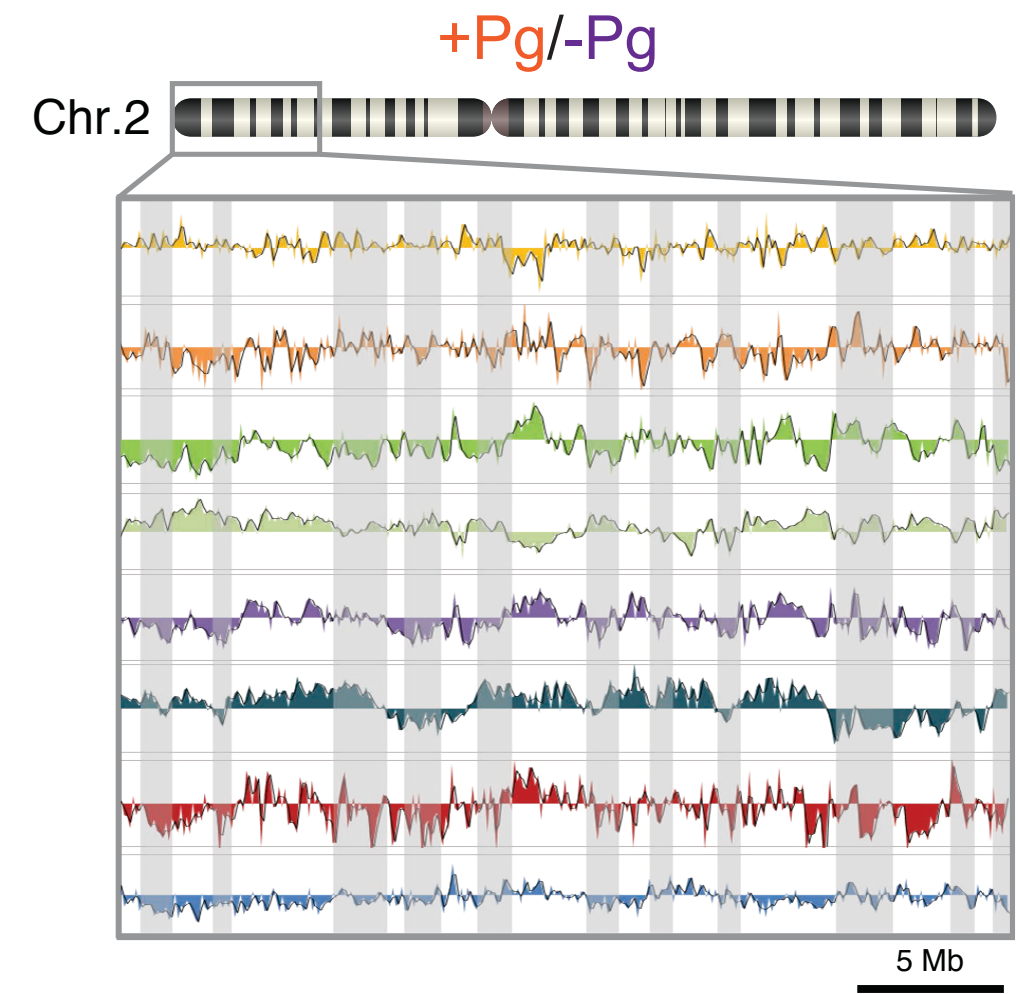
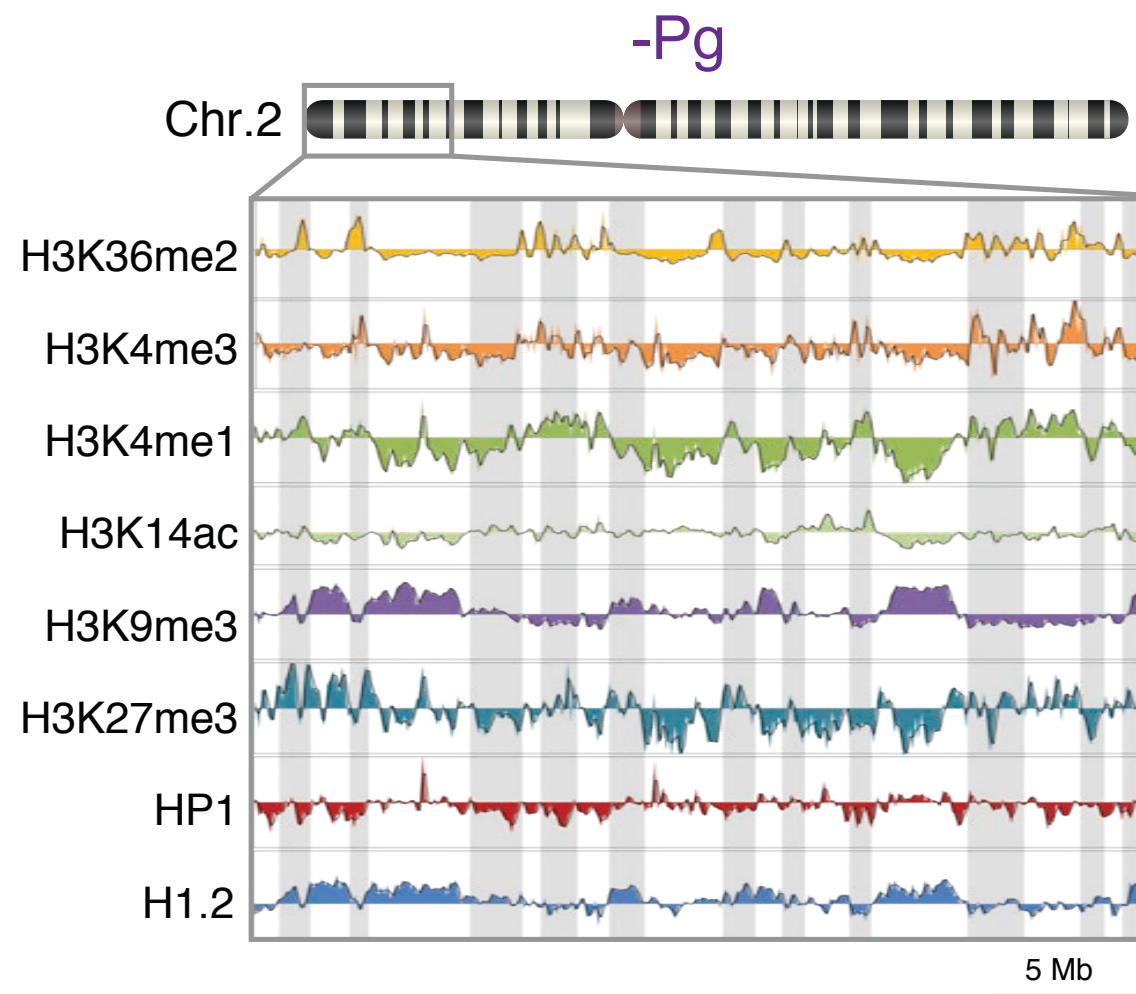


+Pg

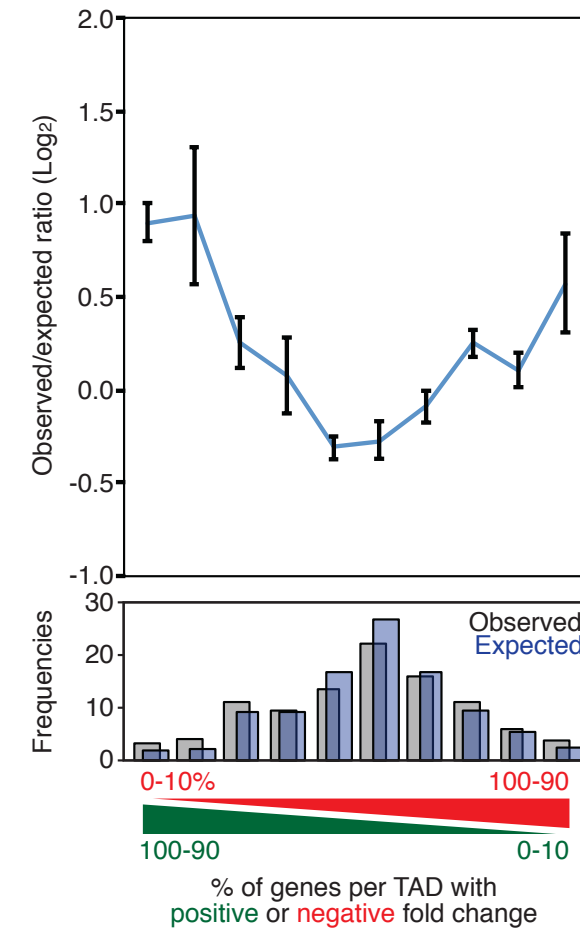
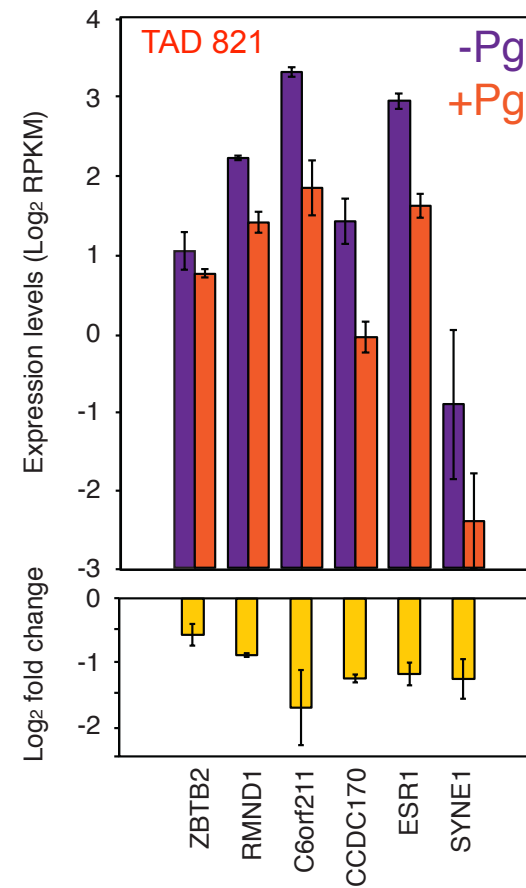
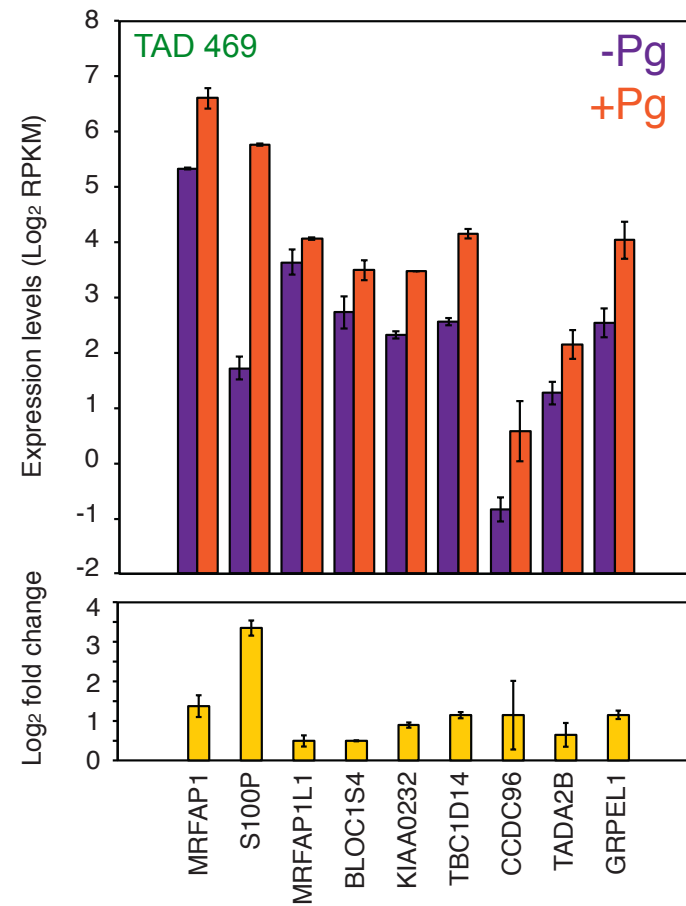


■ conserved
■ 100 kb
■ ±200 kb or more

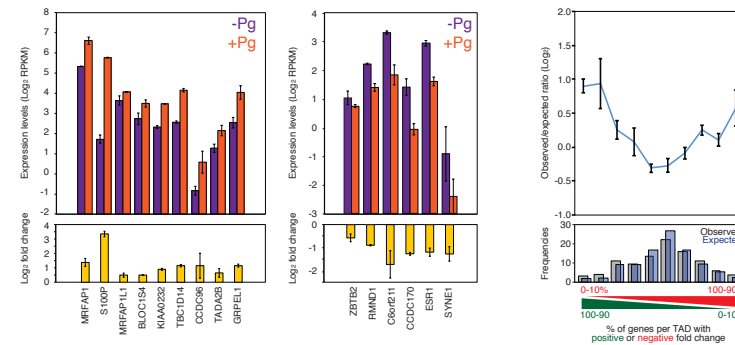
Are TADs homogeneous?



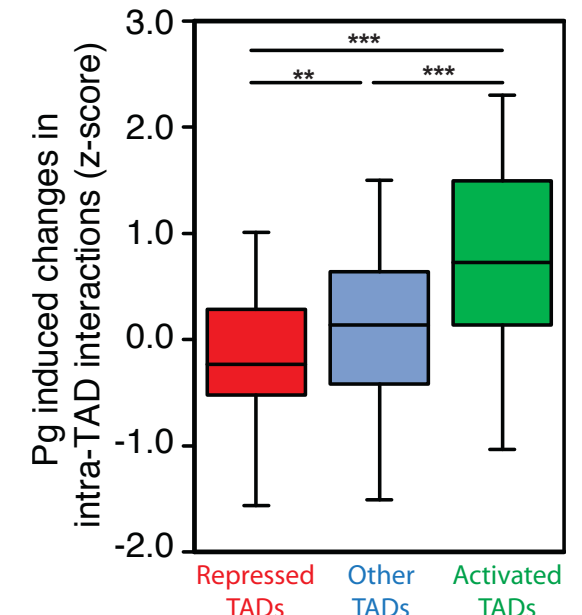
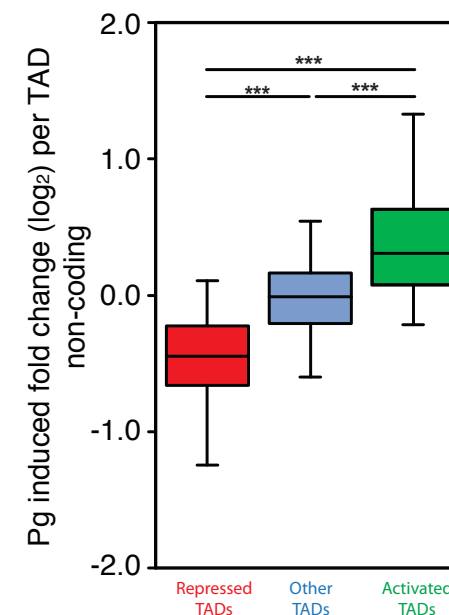
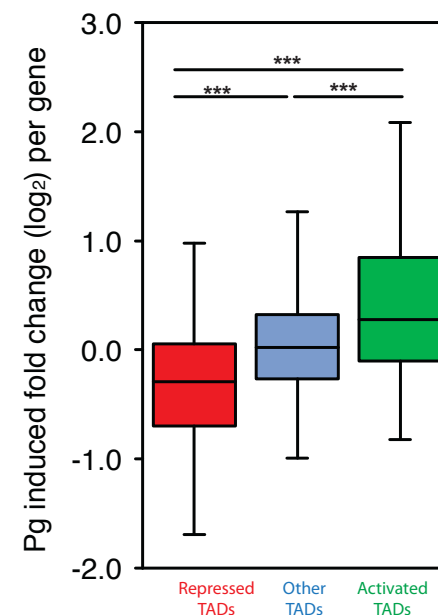
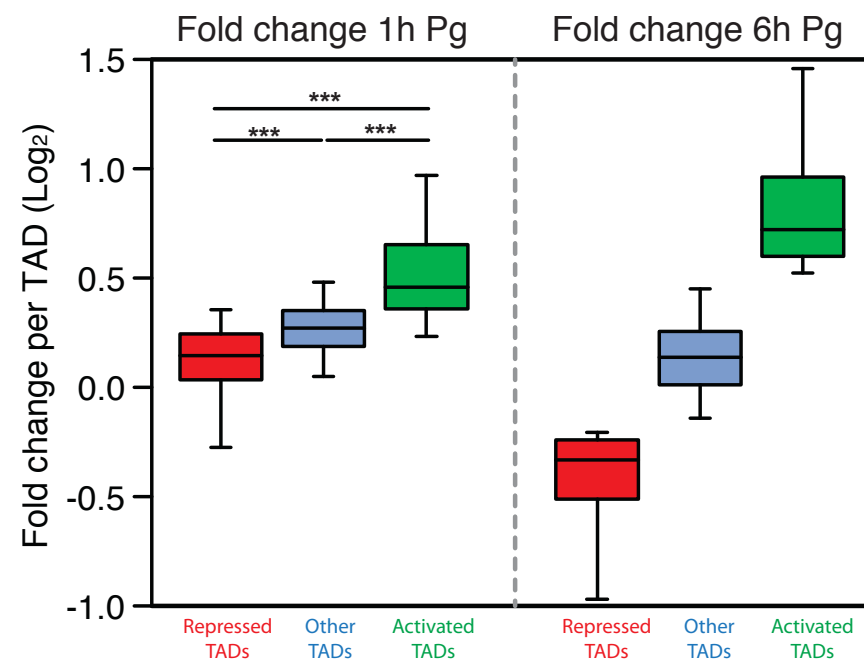
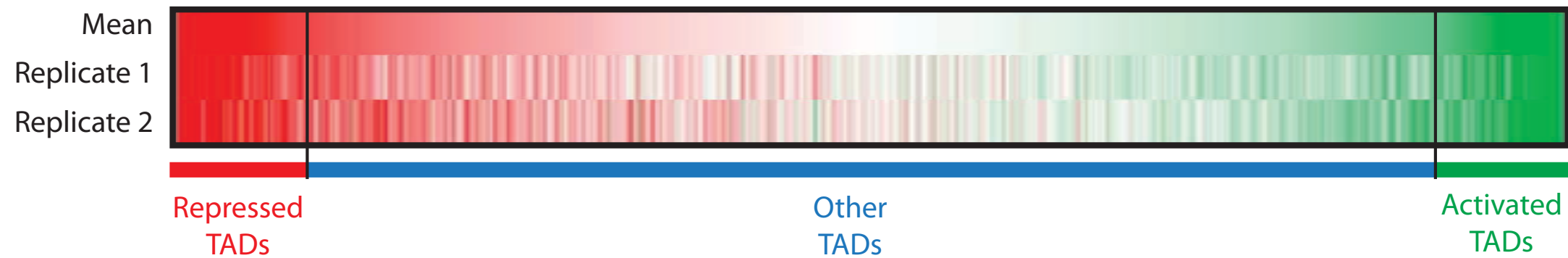
Do TADs respond differently to Pg treatment?



Do TADs respond differently to Pg treatment?



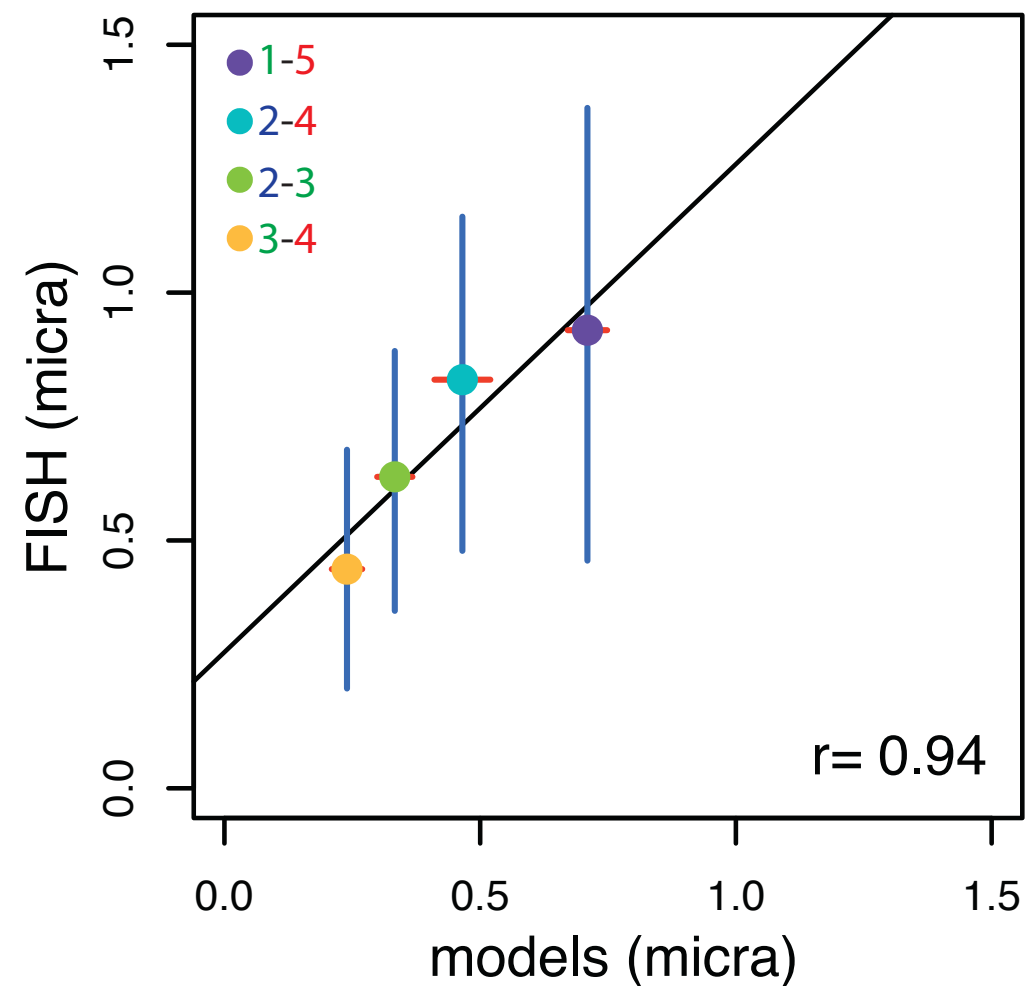
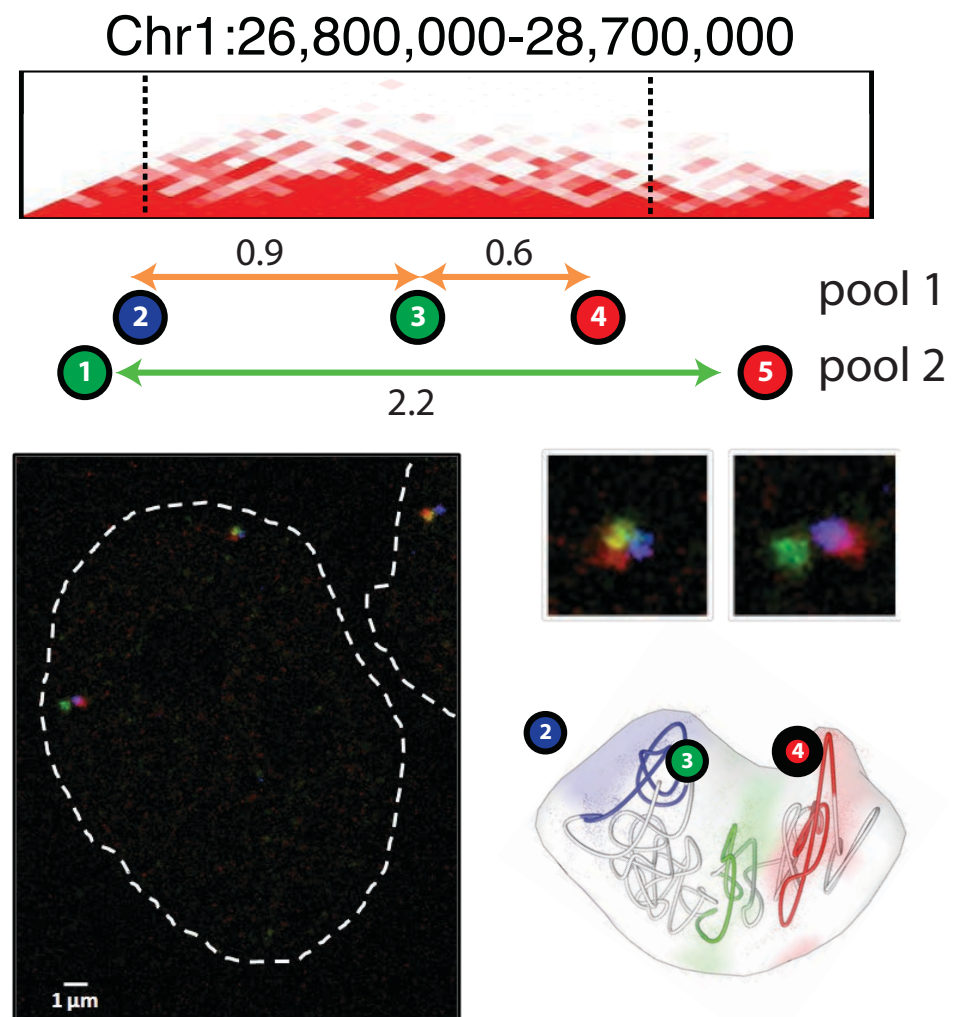
Pg induced fold change per TAD (6h)



Modeling 3D TADs

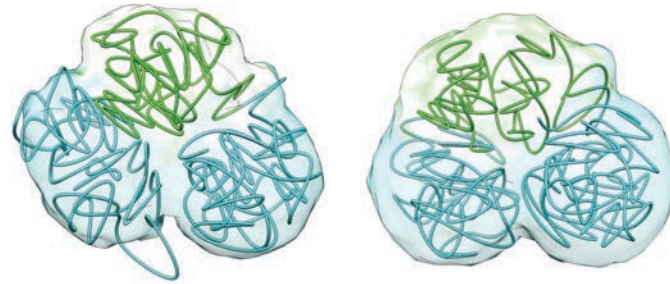


61 genomic regions containing 209 TADs covering 267Mb

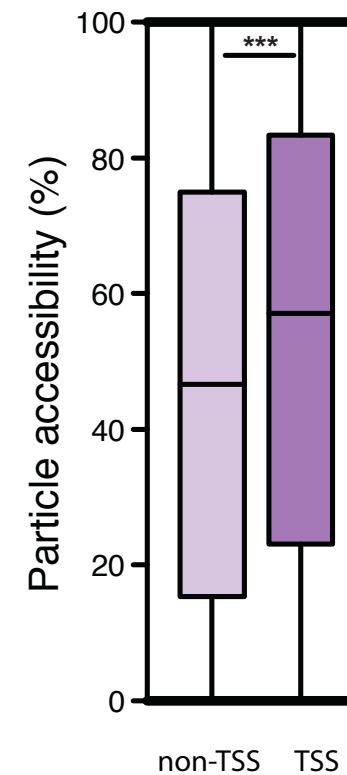
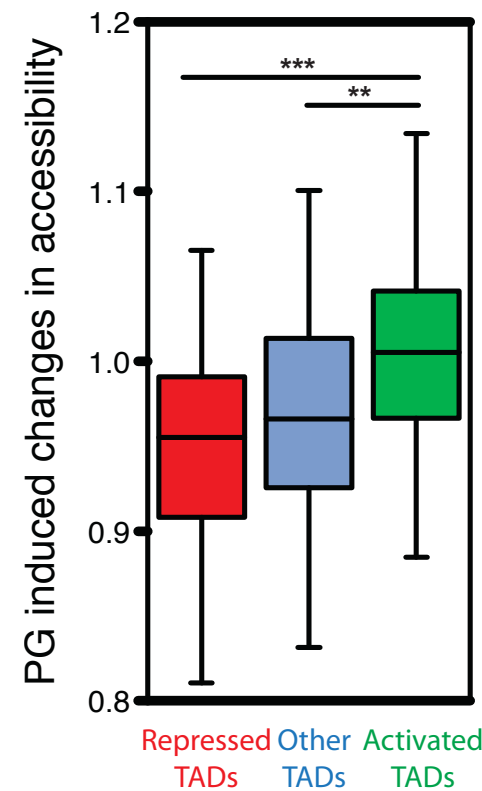
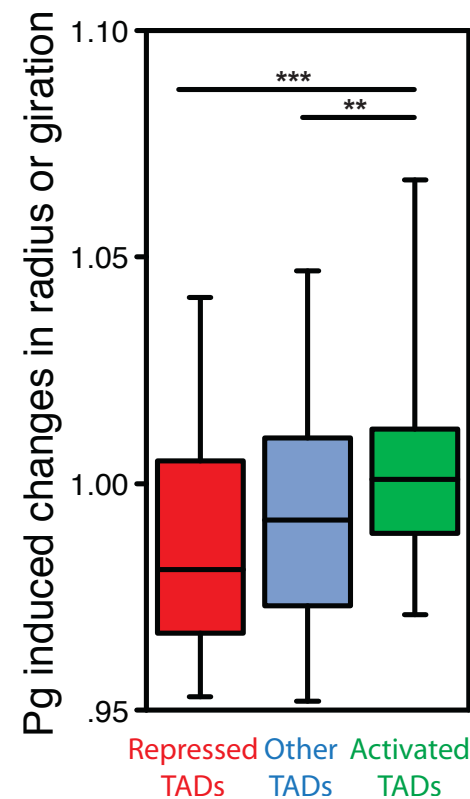
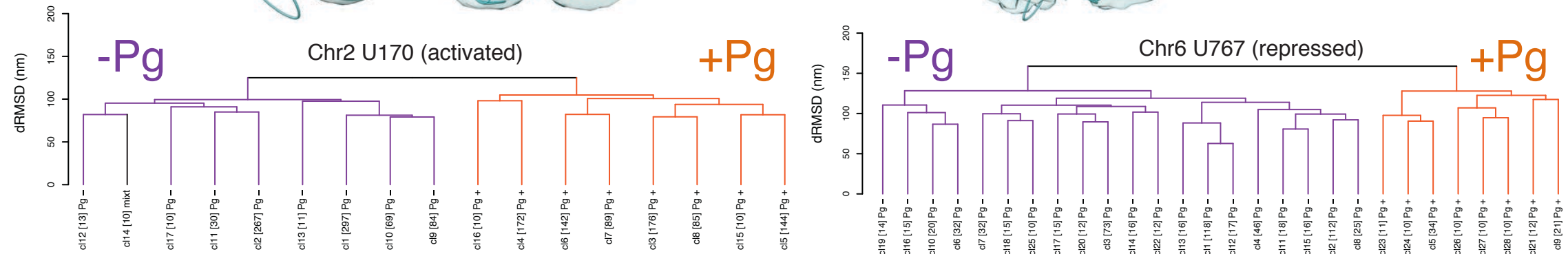
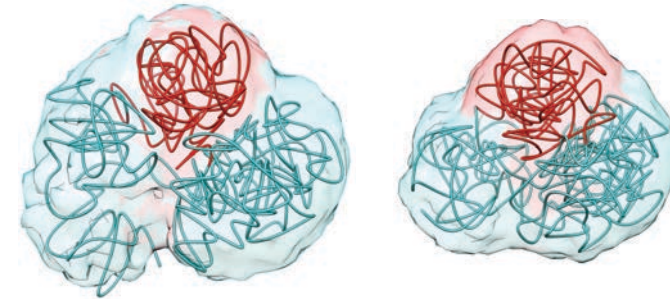


How TADs respond structurally to Pg?

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



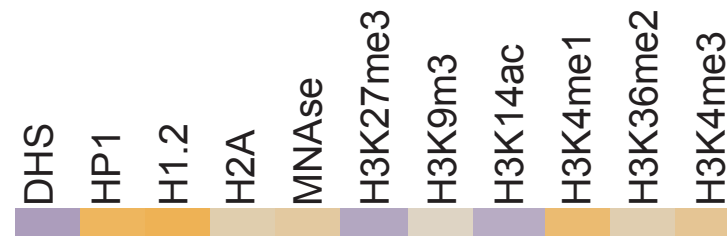
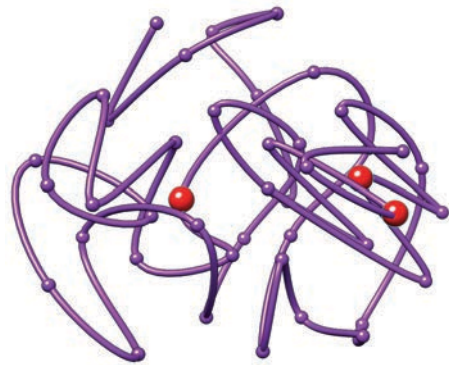
Chr6:71,800,000-76,500,000



Model for TAD regulation

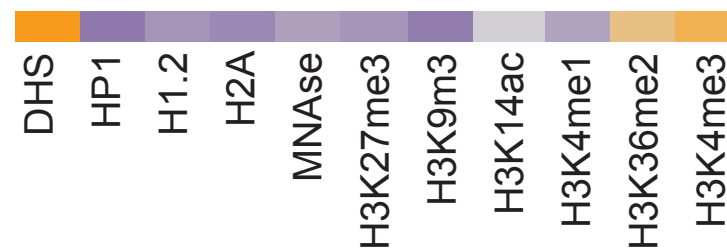
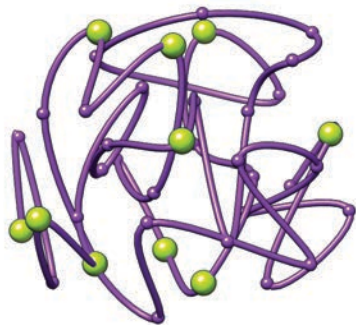
Repressed TAD

chr1 U41

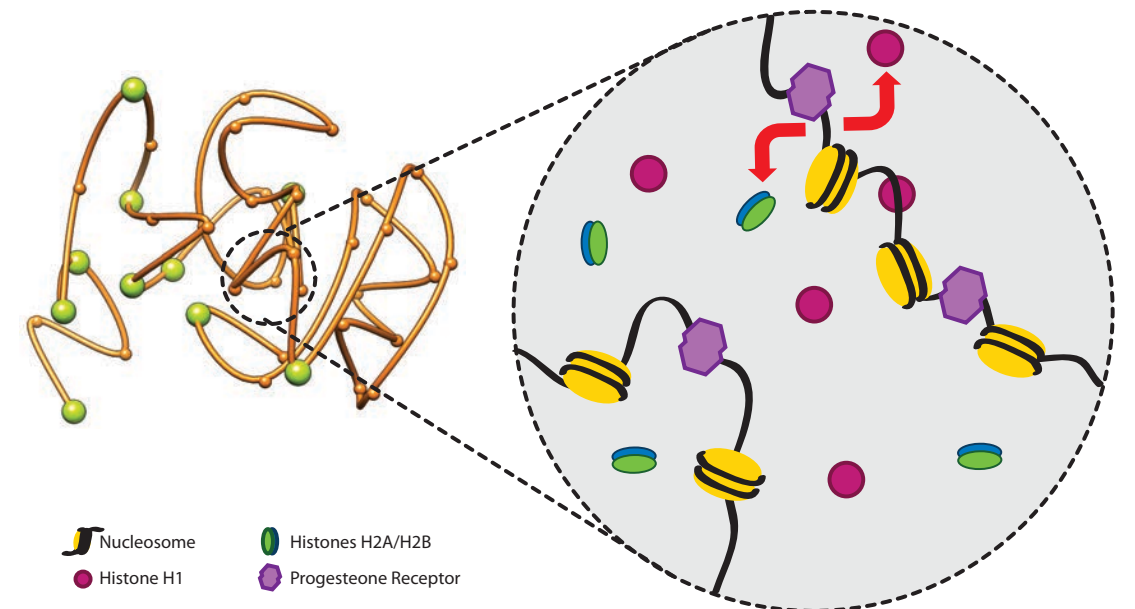
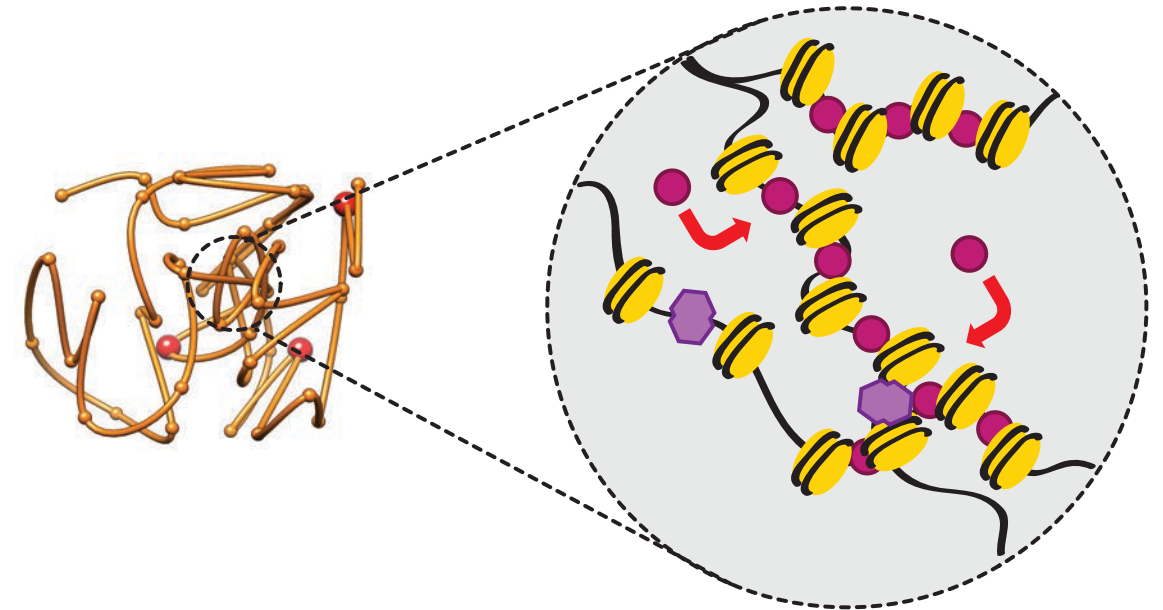


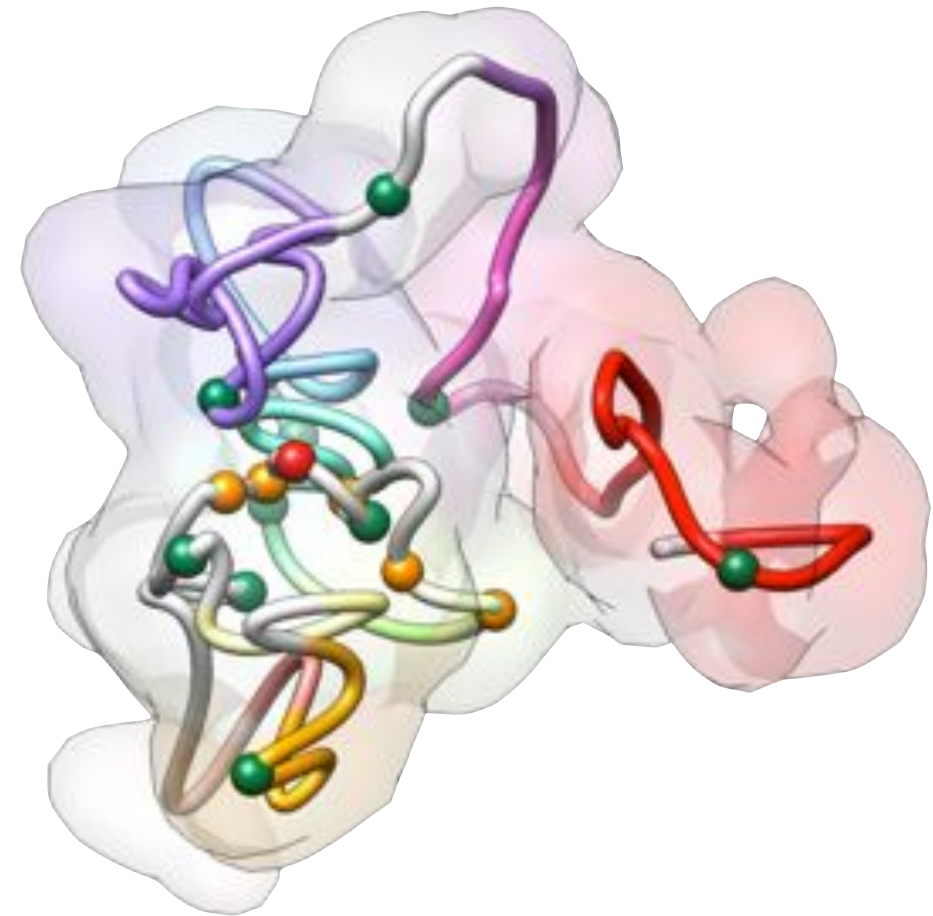
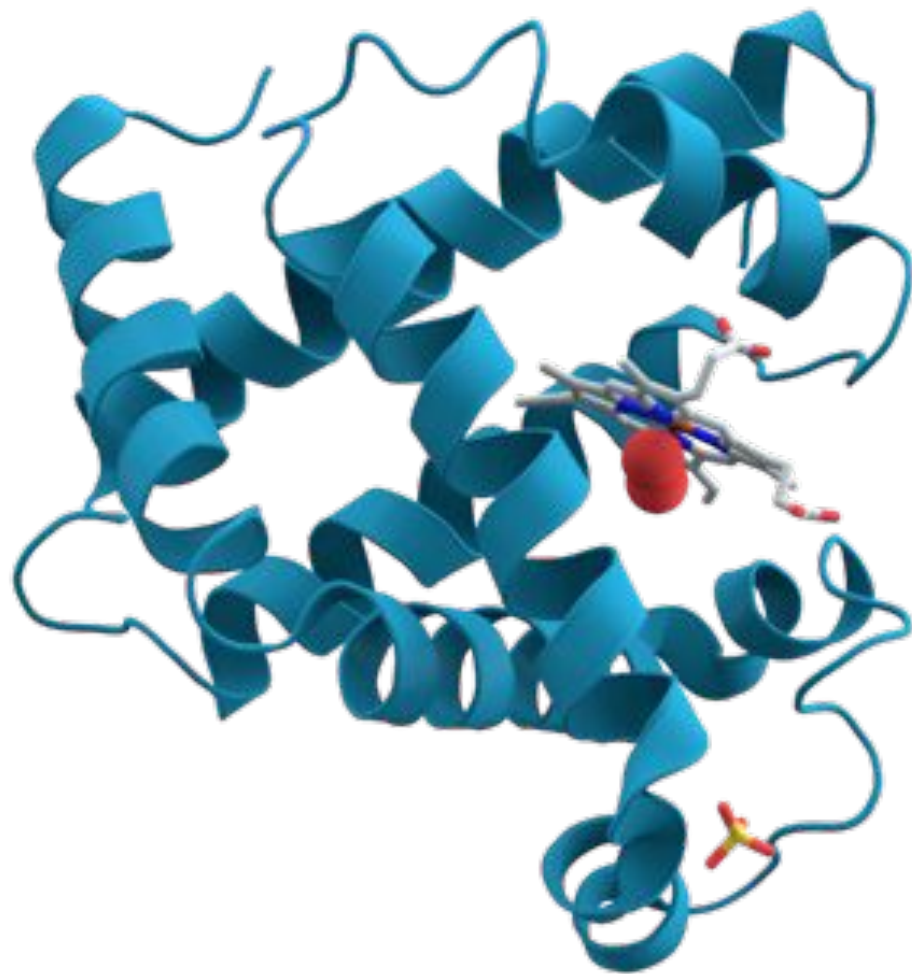
Activated TAD


chr2 U207



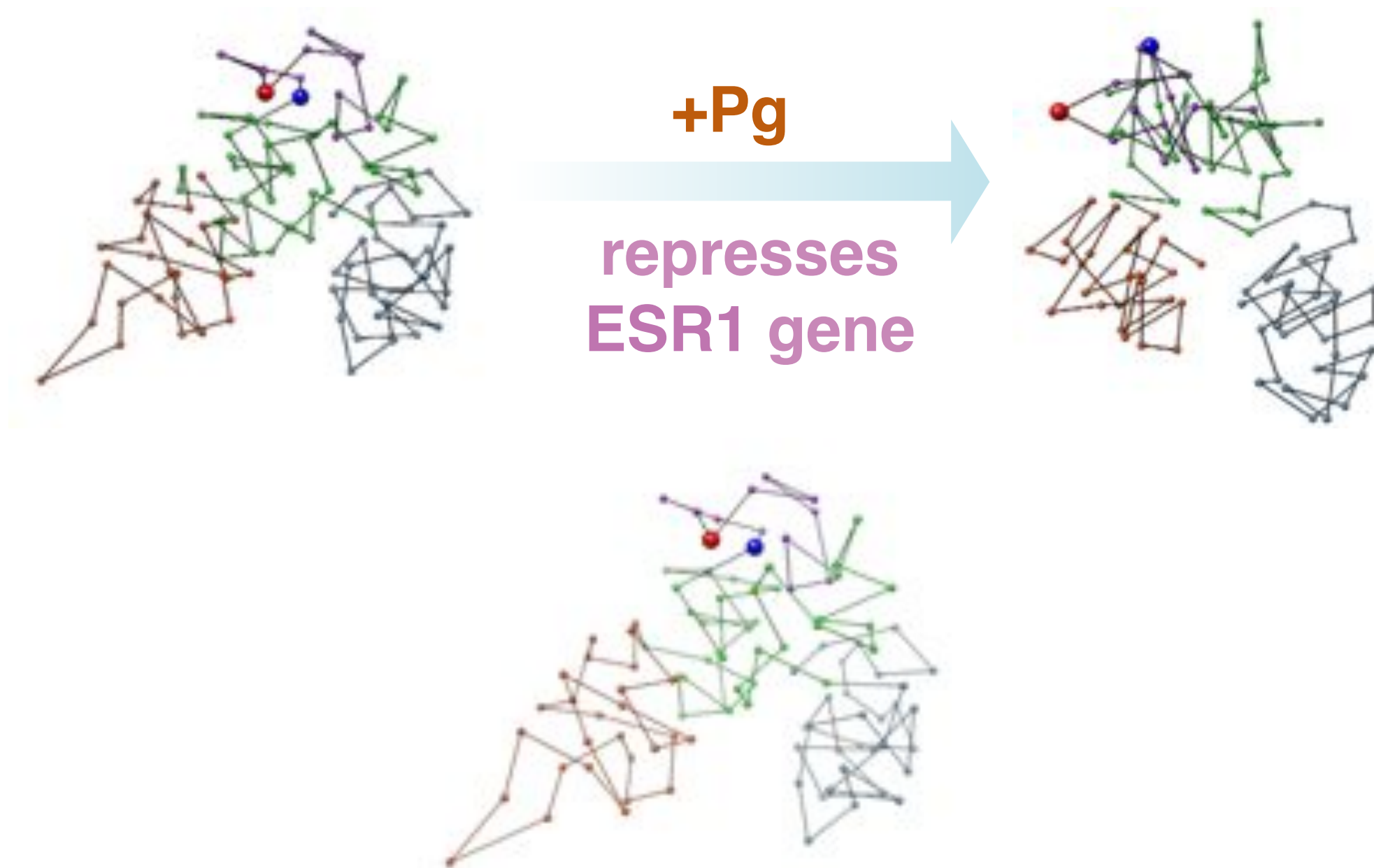
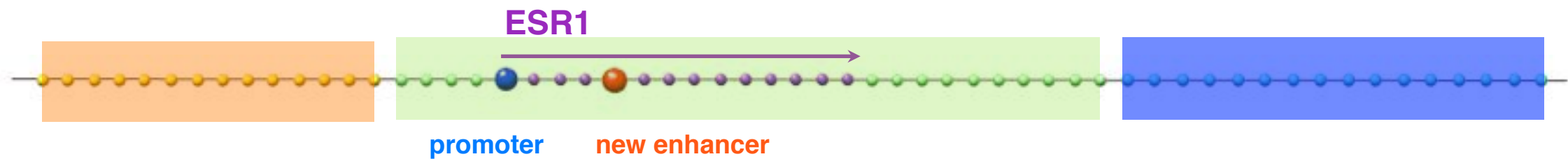
Structural transition
+Pg





STRUCTURE  **FUNCTION**

Structure >> Function!





Open positions soon
<http://marciuslab.org>

Acknowledgments



Davide Baù
François le Dily
François Serra

David Dufour
Mike Goodstadt
Gireesh Bogu
Francisco Martínez-Jiménez

Miguel Beato & Guillaume Filion

Gene Regulation, Stem Cells and Cancer
Centre de Regulació Genòmica
Barcelona, Spain

<http://marciuslab.org>
<http://cnag.cat> · <http://crg.cat>



cnag



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