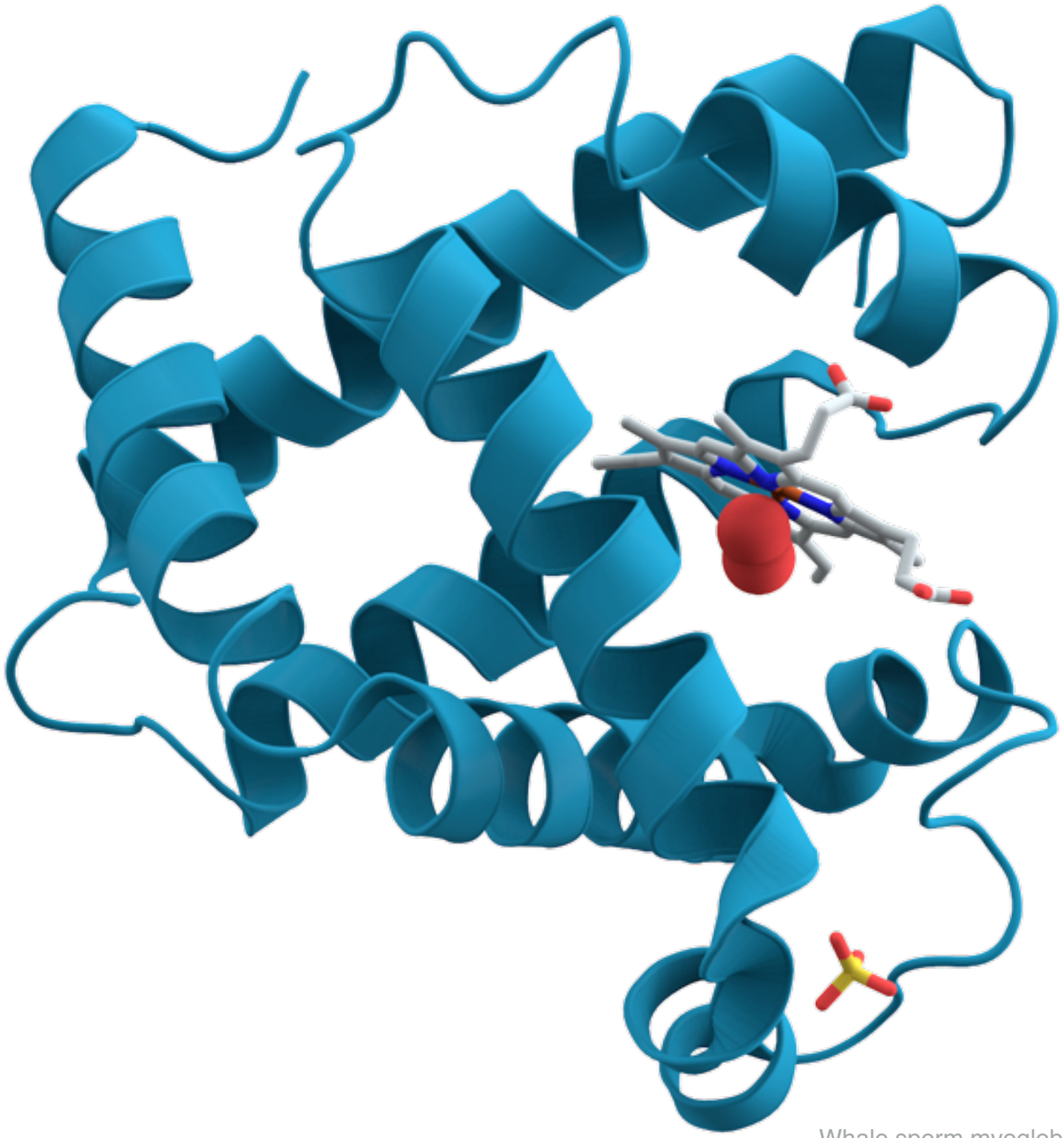
Structure determination of genomes and genomic domains by satisfaction of spatial restraints

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

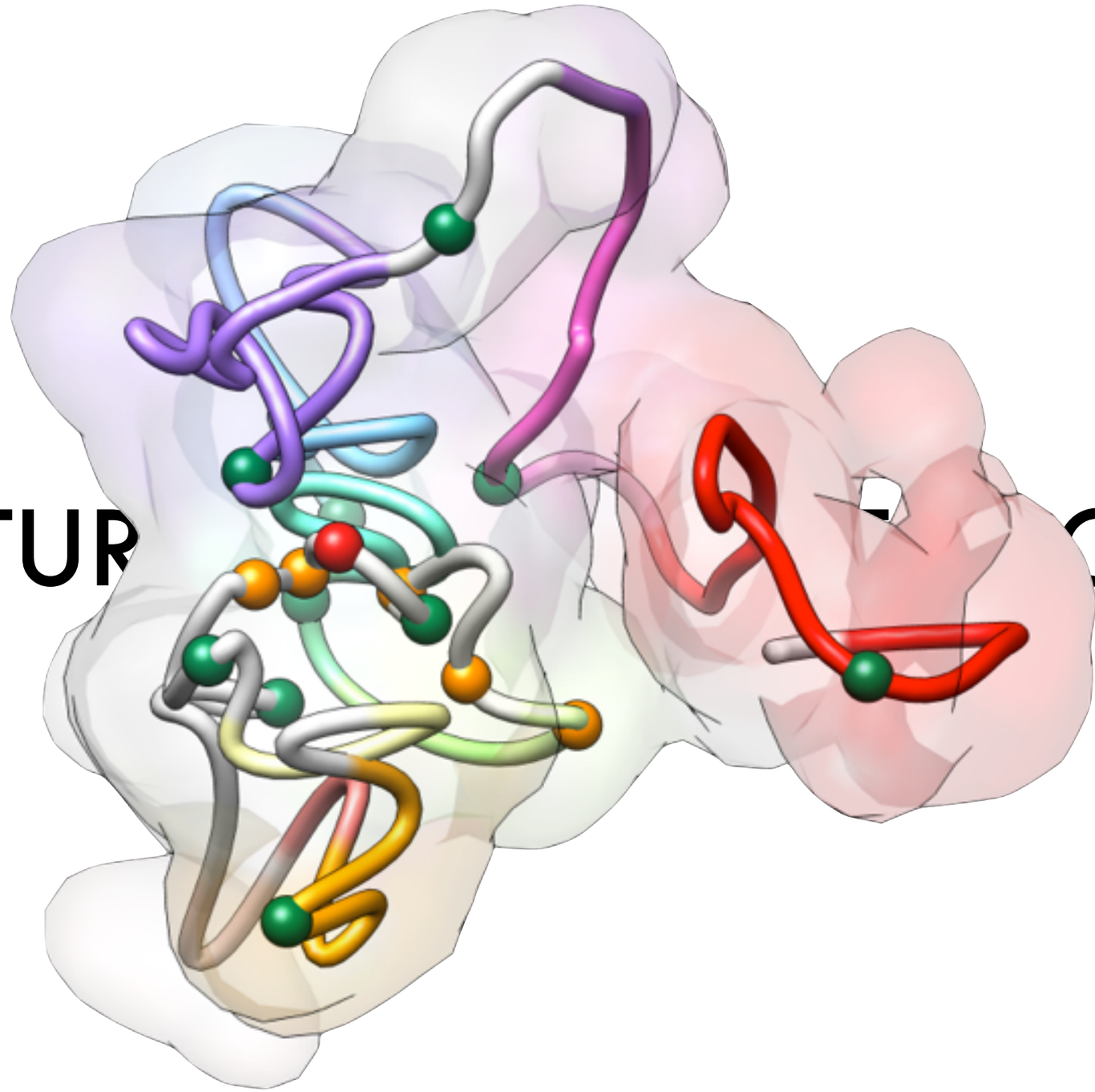
*iCrea
INSTITUCIÓ CATALANA DE RECERCA I ESTUDIS AVANÇATS

cnag CRG Centre for Genomic Regulation



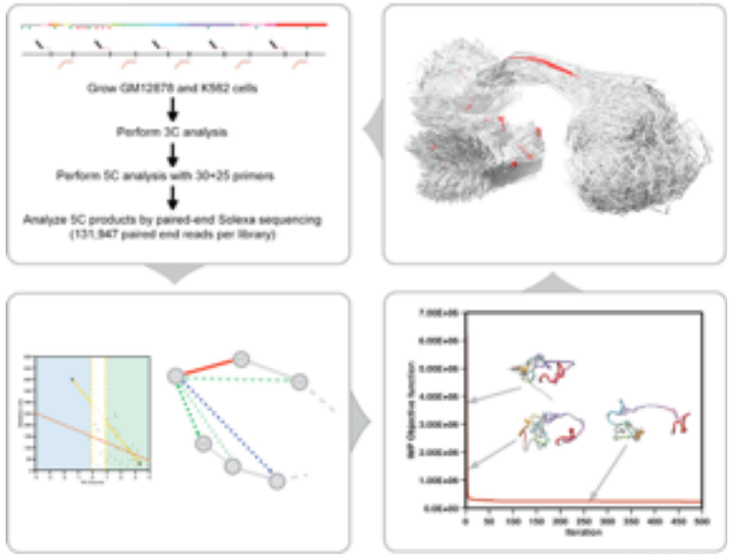
Whale sperm myoglobin structure (1960)

STRUCTUR CTION

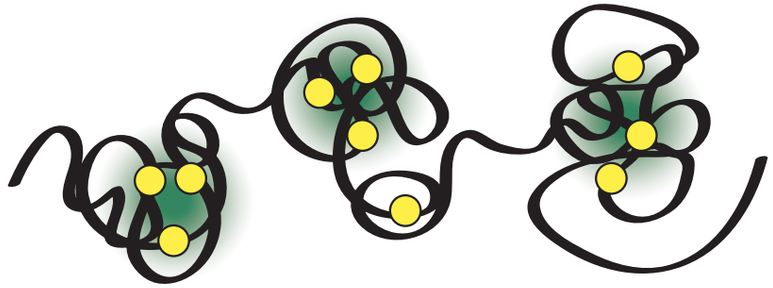


alpha-globin genomic domain structure (2011)

TADbit

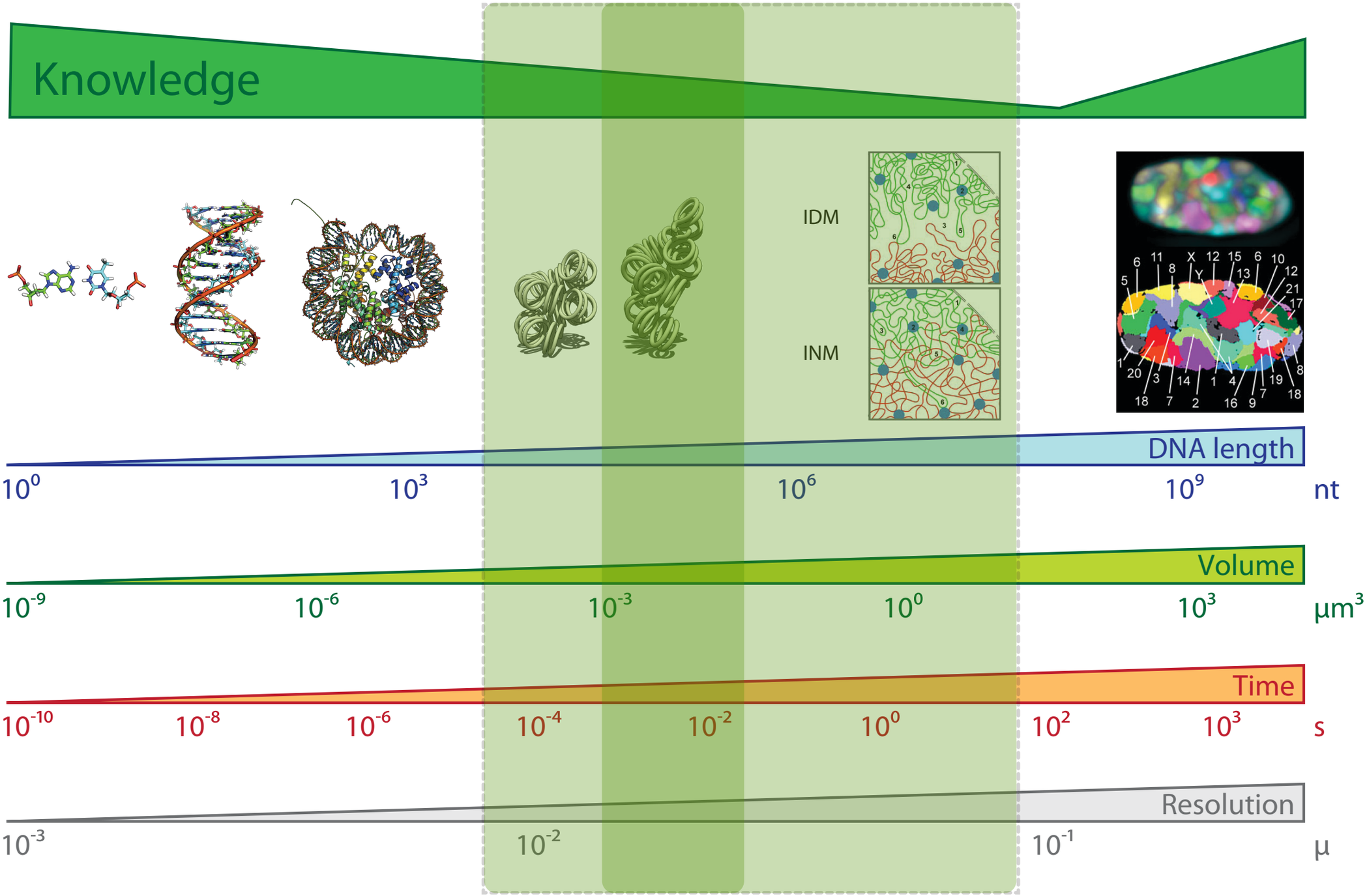

Grow GM12878 and K562 cells
Perform 3C analysis
Perform 5C analysis with 30+25 primers
Analyze 5C products by paired-end Solexa sequencing
(131,947 paired end reads per library)


Bud
parent cell



Resolution Gap

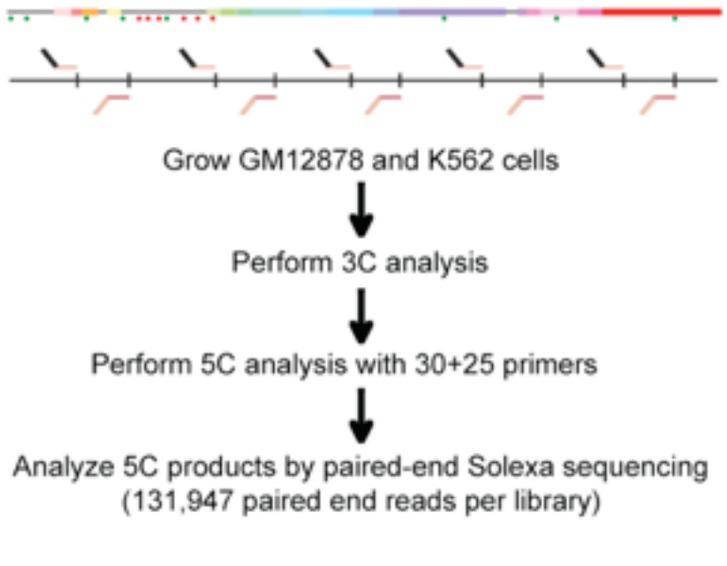
Marti-Renom, M. A. & Mirny, L. A. PLoS Comput Biol 7, e1002125 (2011)

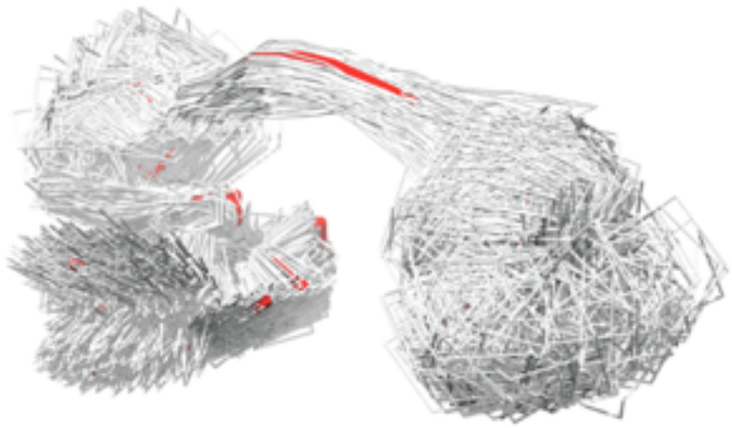


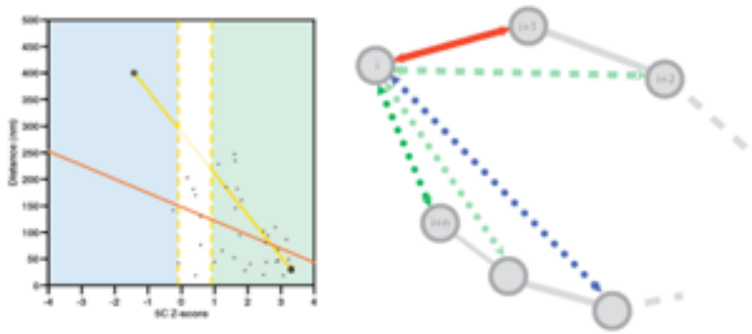
Hybrid Method

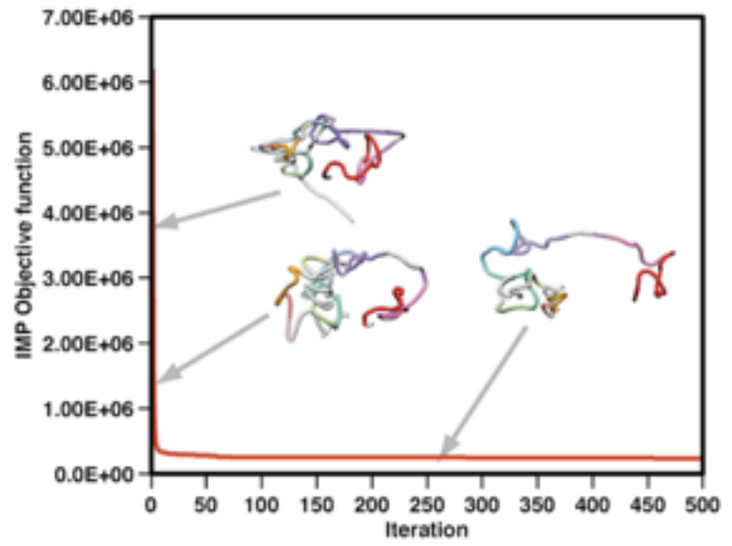
Baù, D. & Marti-Renom, M. A. Methods 58, 300–306 (2012).

Experiments







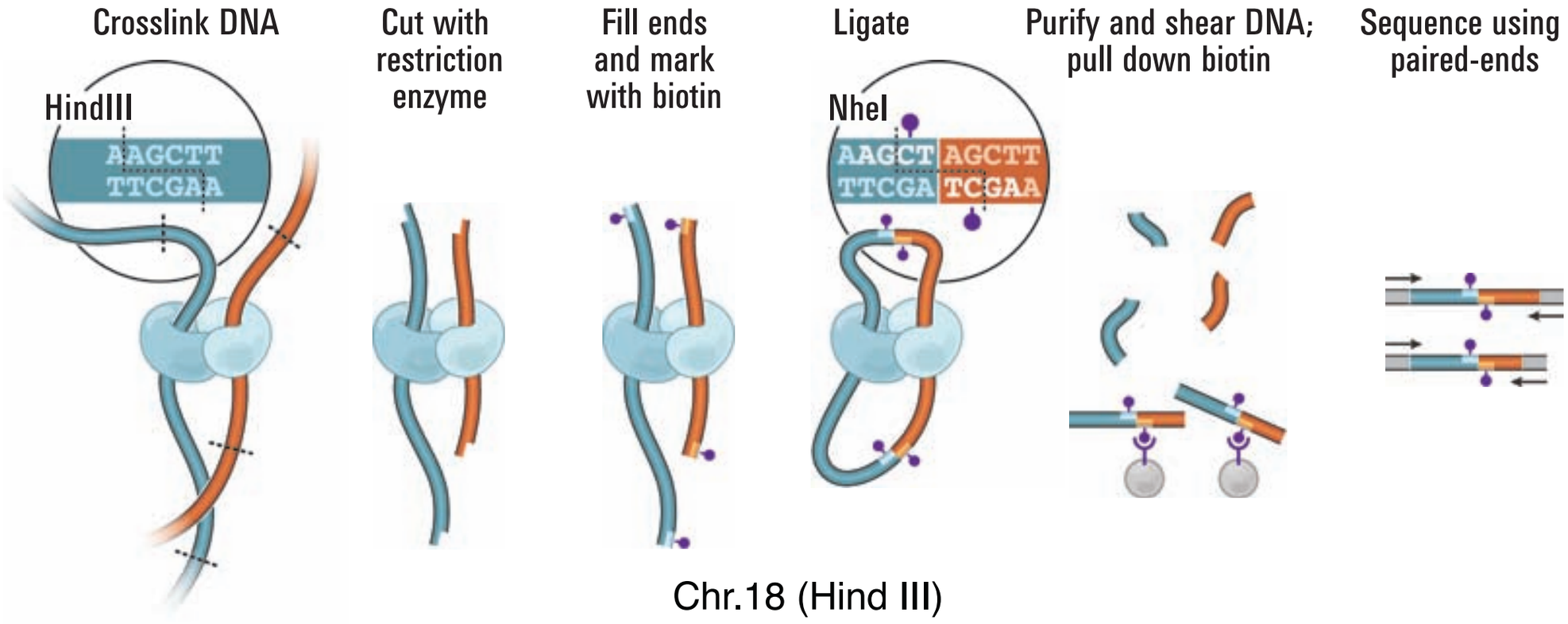


Computation

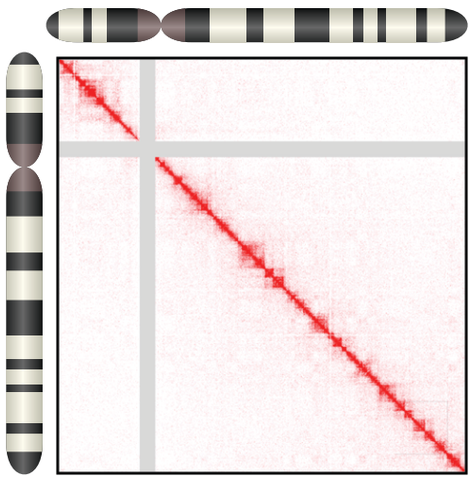
Hi-C technology

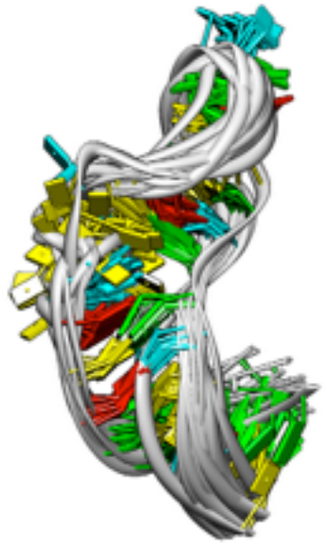
Lieberman-Aiden, E. et al. Science 326, 289–293 (2009).

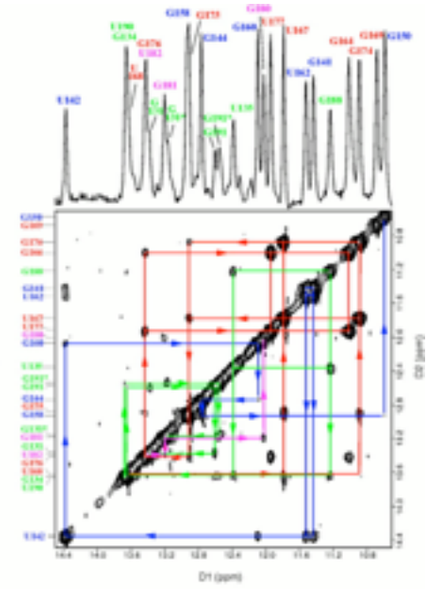
http://3dg.umassmed.edu



Chr.18 (Hind III)

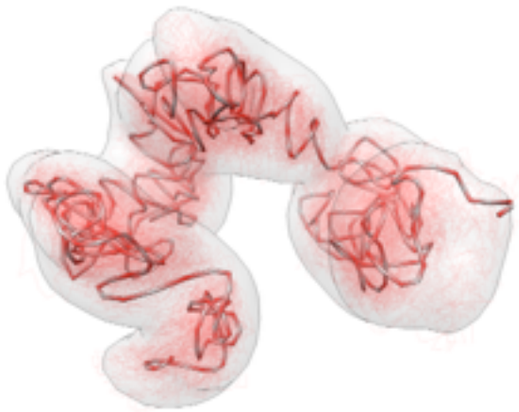


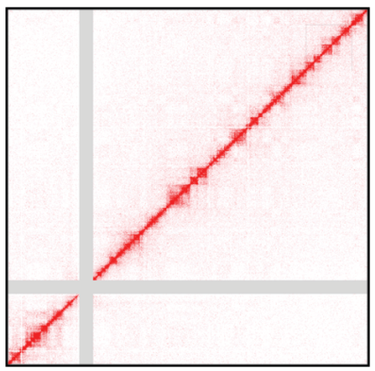




Biomolecular structure determination

2D-NOESY data

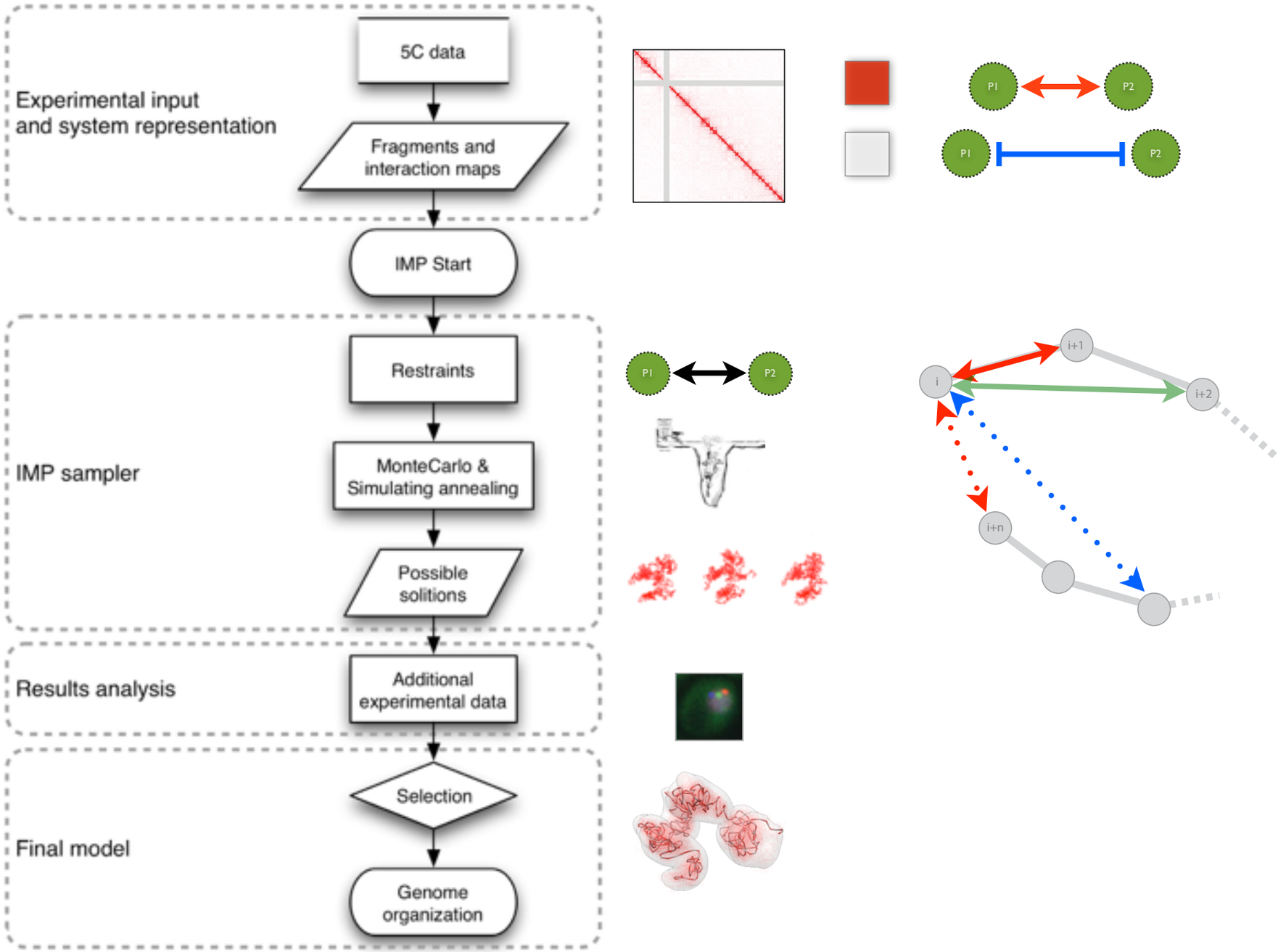




Chromosome structure determination

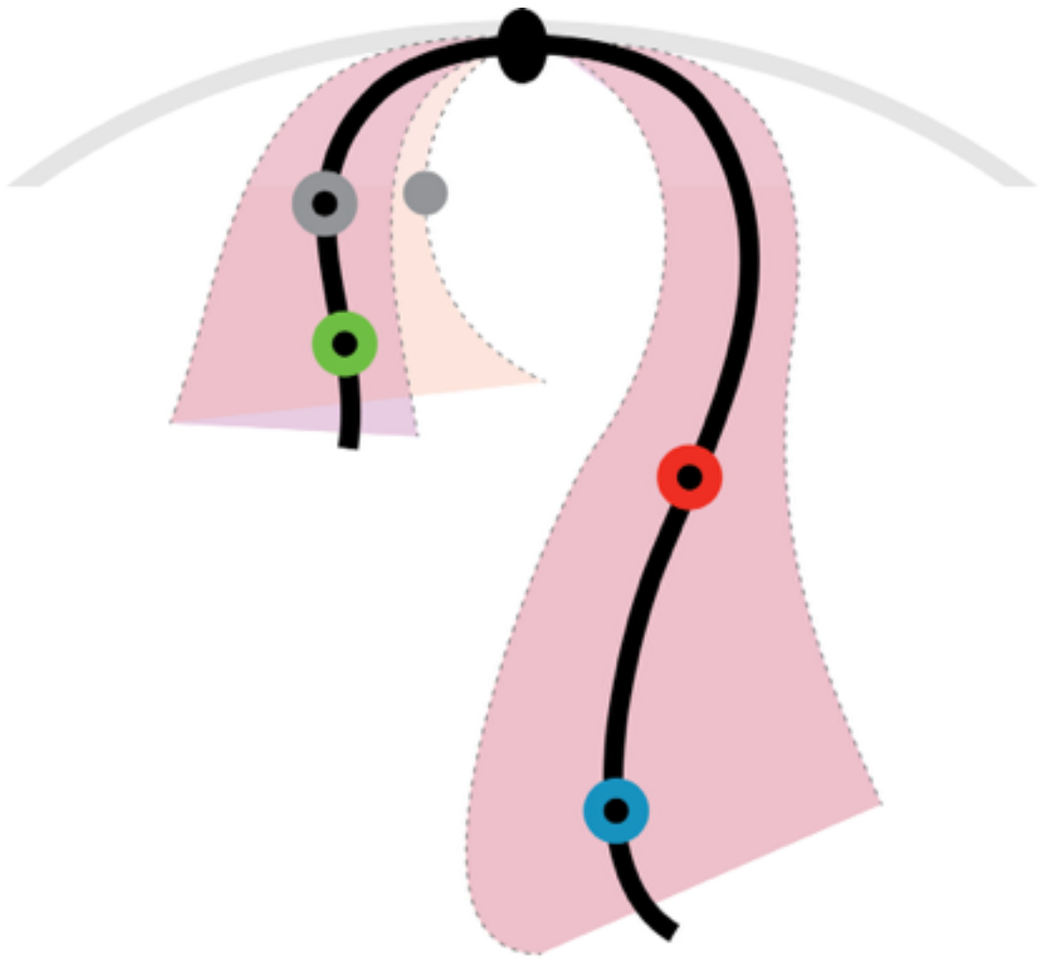
3C-based data

TADbit


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
P1
P2
P1
P2
P1
P2
i
i+1
i+2
i+n

TADbit

Mating-specific structure for yeast chrIII?

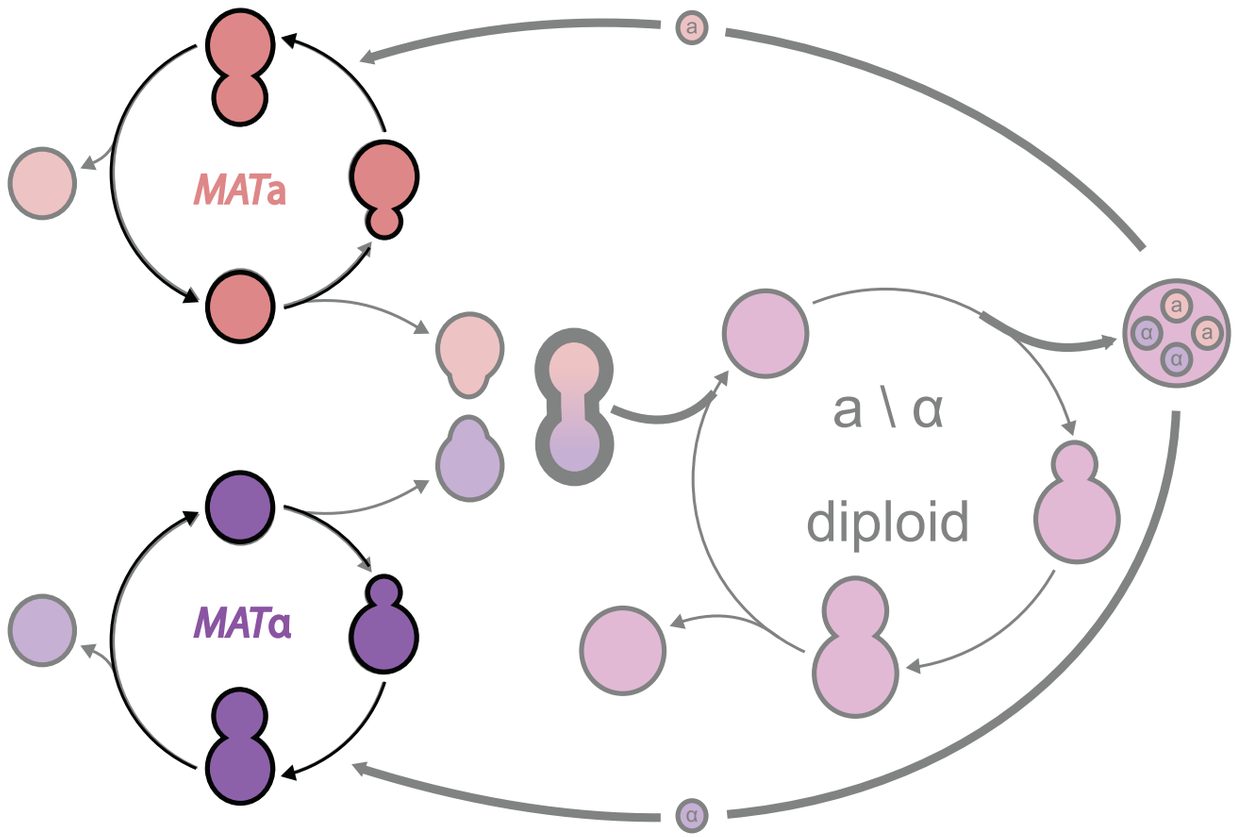


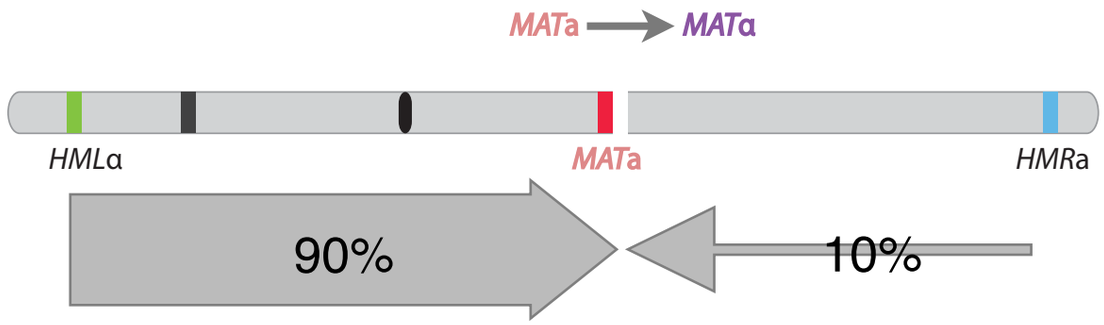
Jon-Matthew Belton
UMASS

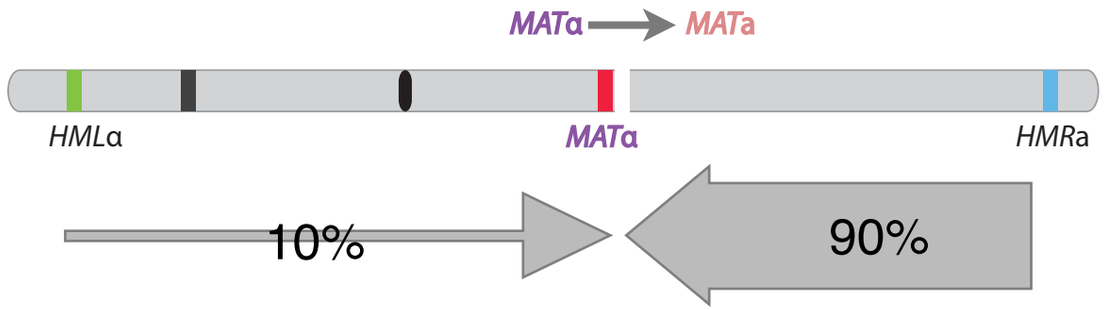
Davide Baù
CNAG/CRG

Job Dekker
Program in Systems Biology
Department of Biochemistry and Molecular Pharmacology
University of Massachusetts Medical School
Worcester, MA, USA

Kerstin Bystricky
Chromatin and gene expression
Laboratoire de Biologie Moléculaire Eucaryote - CNRS
Toulouse, France







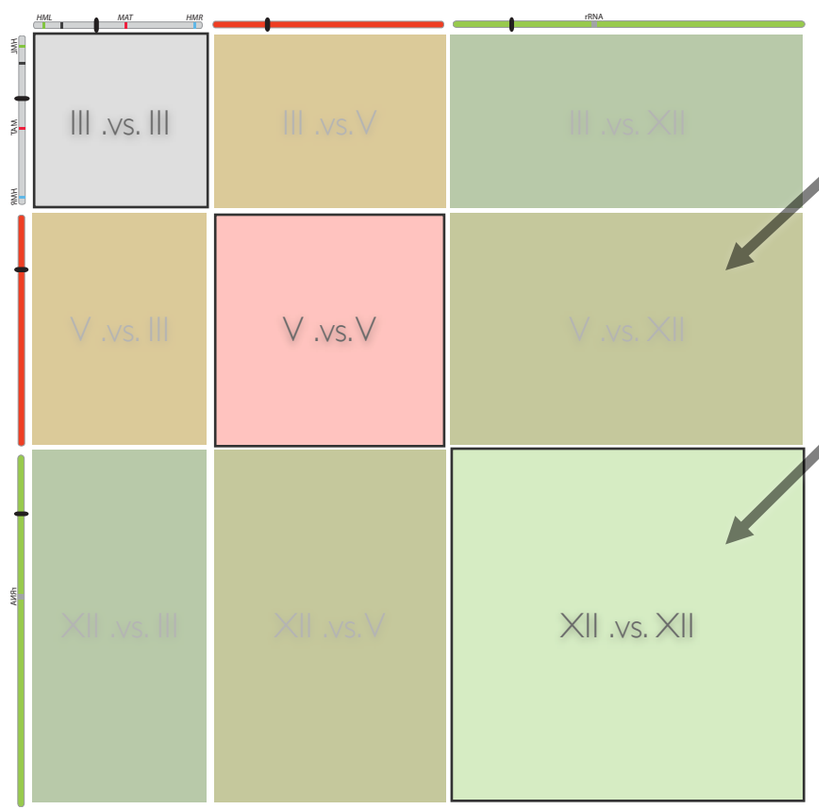
Wu, X. H., C. Wu, et al. Genetics (1997).

5C chromosome conformation

Chr. III - 317 kb: Mating Type Switching

Chr. V - 577 kb: Control

Chr. XII - 1 Mb: rDNA array



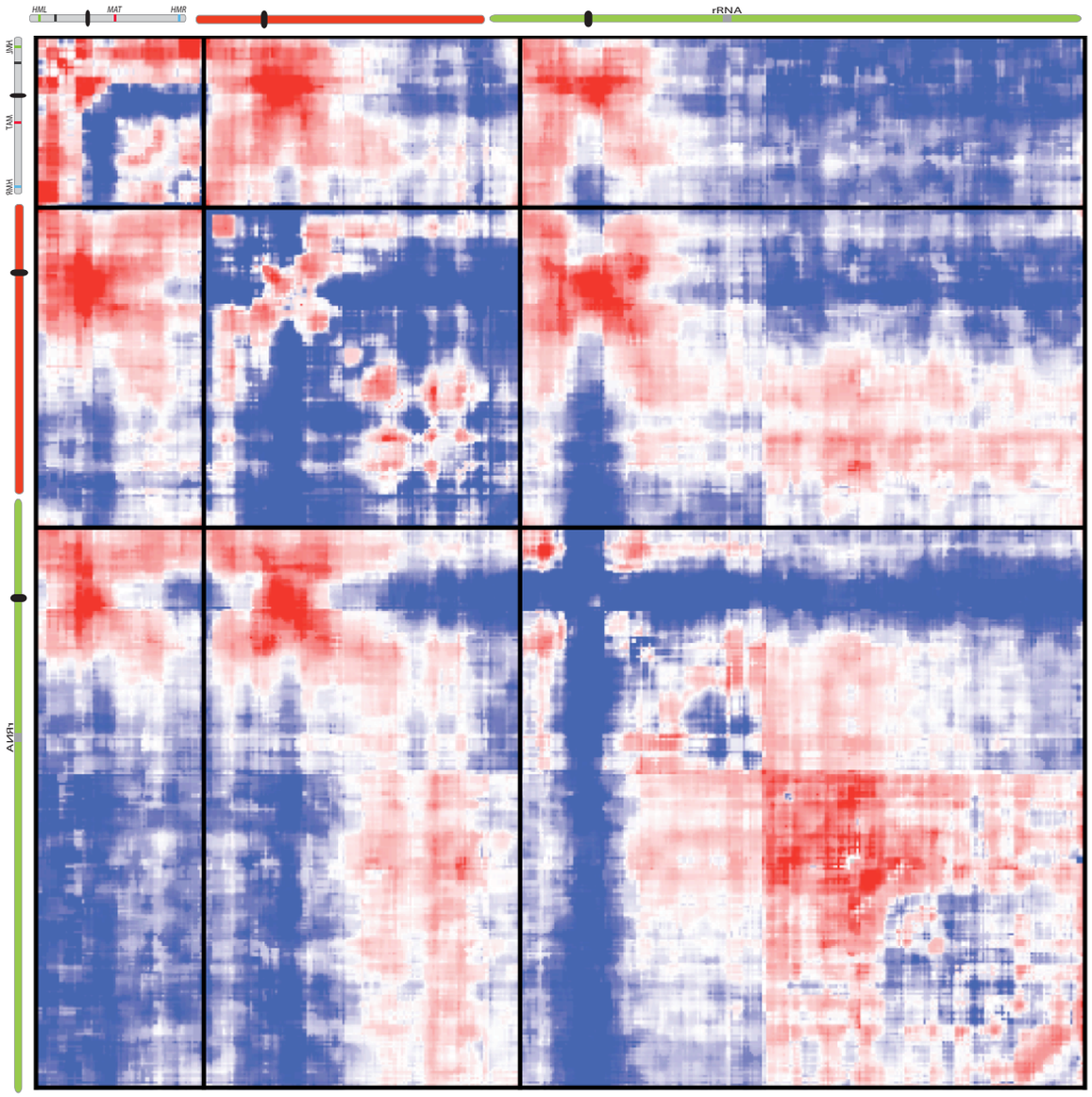
Interactions between chromosomes

Interactions within a chromosome

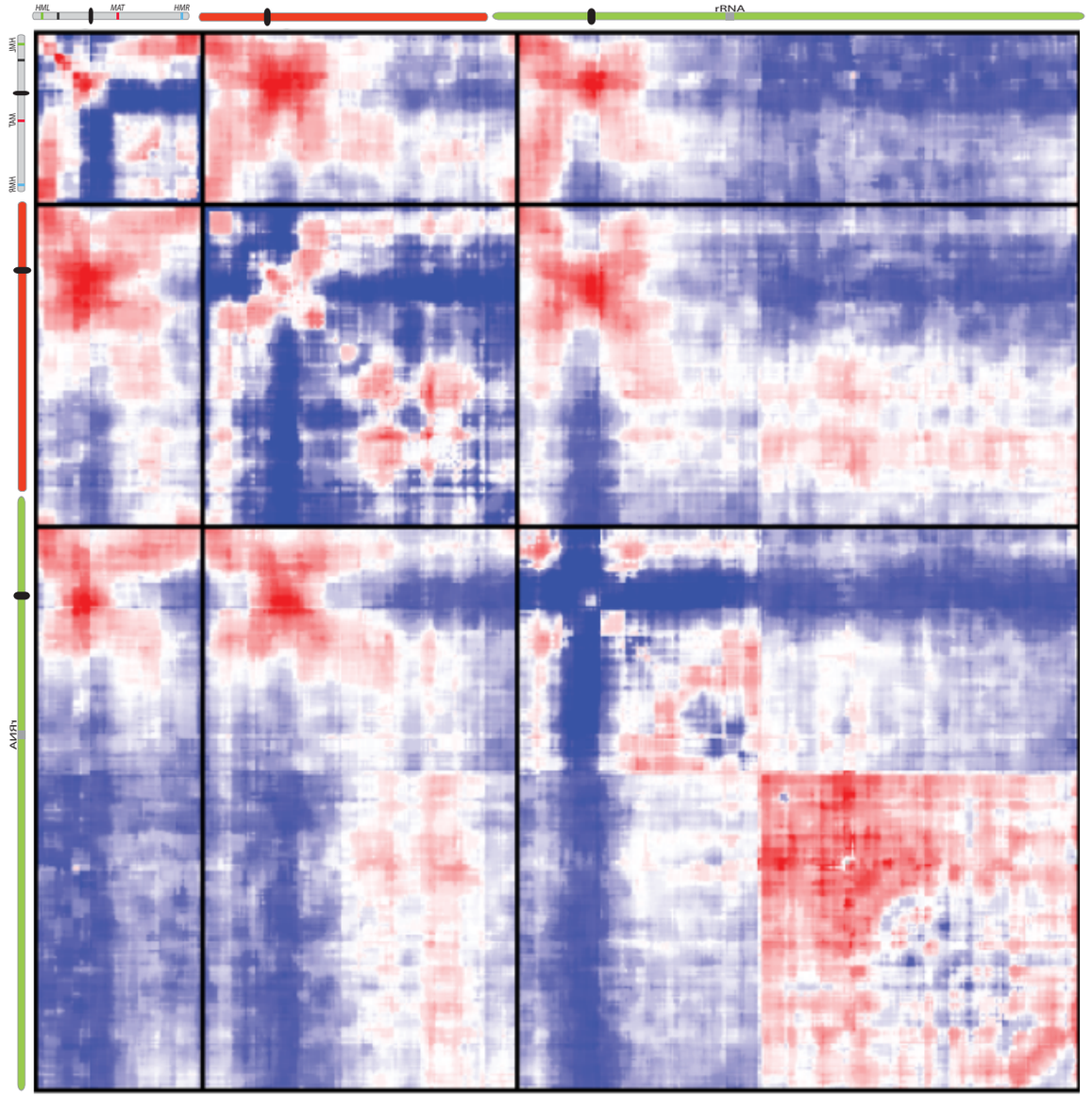
~100,000 possible interactions!

Global structure is *similar* between mating types

*MAT*a



*MAT*α

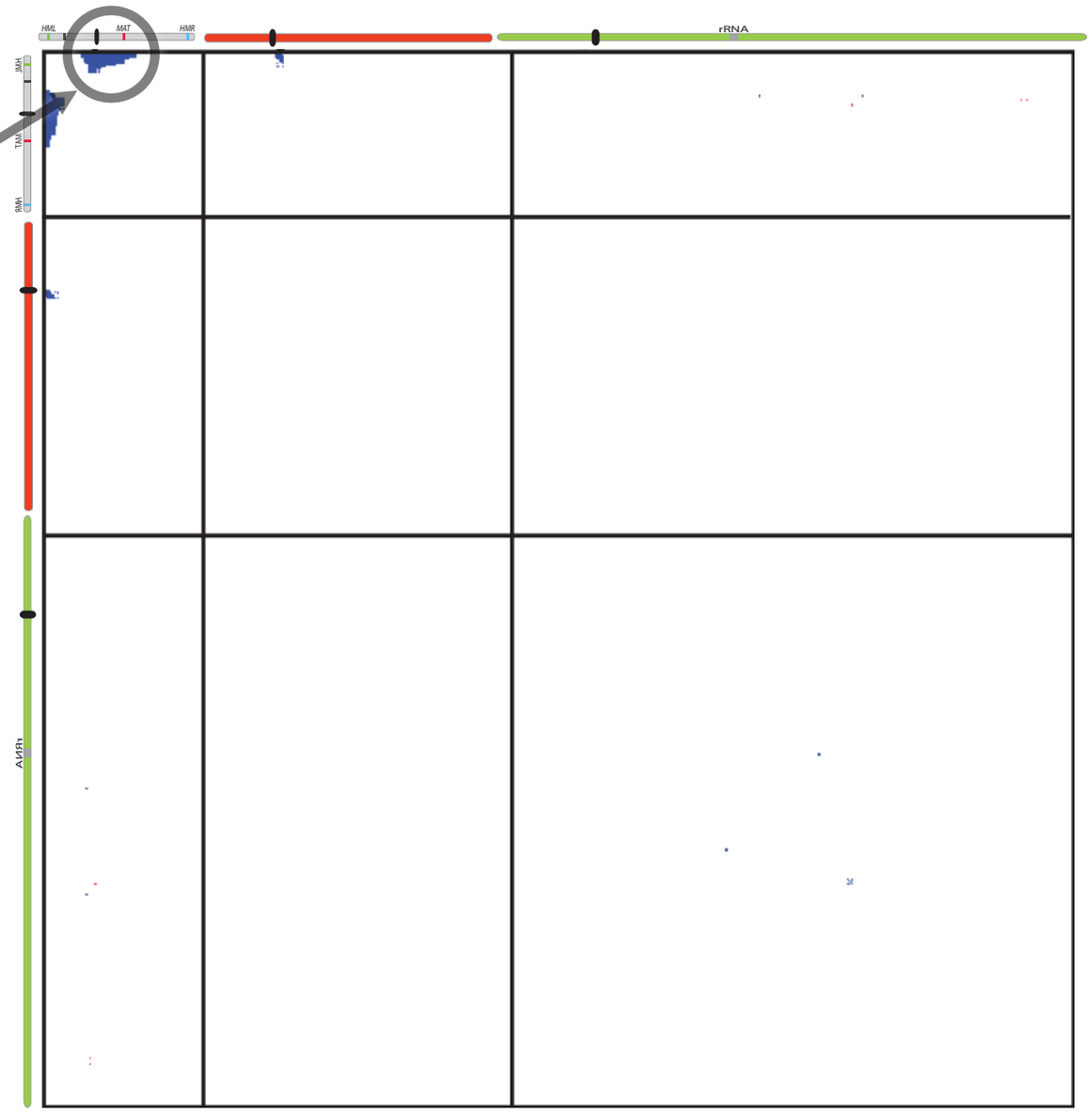


Difference in chromosome conformation

Log_2(*MAT*α / *MAT***a**)

= Enrichment of interaction in *MAT*α

= Enrichment of interaction in *MAT***a**



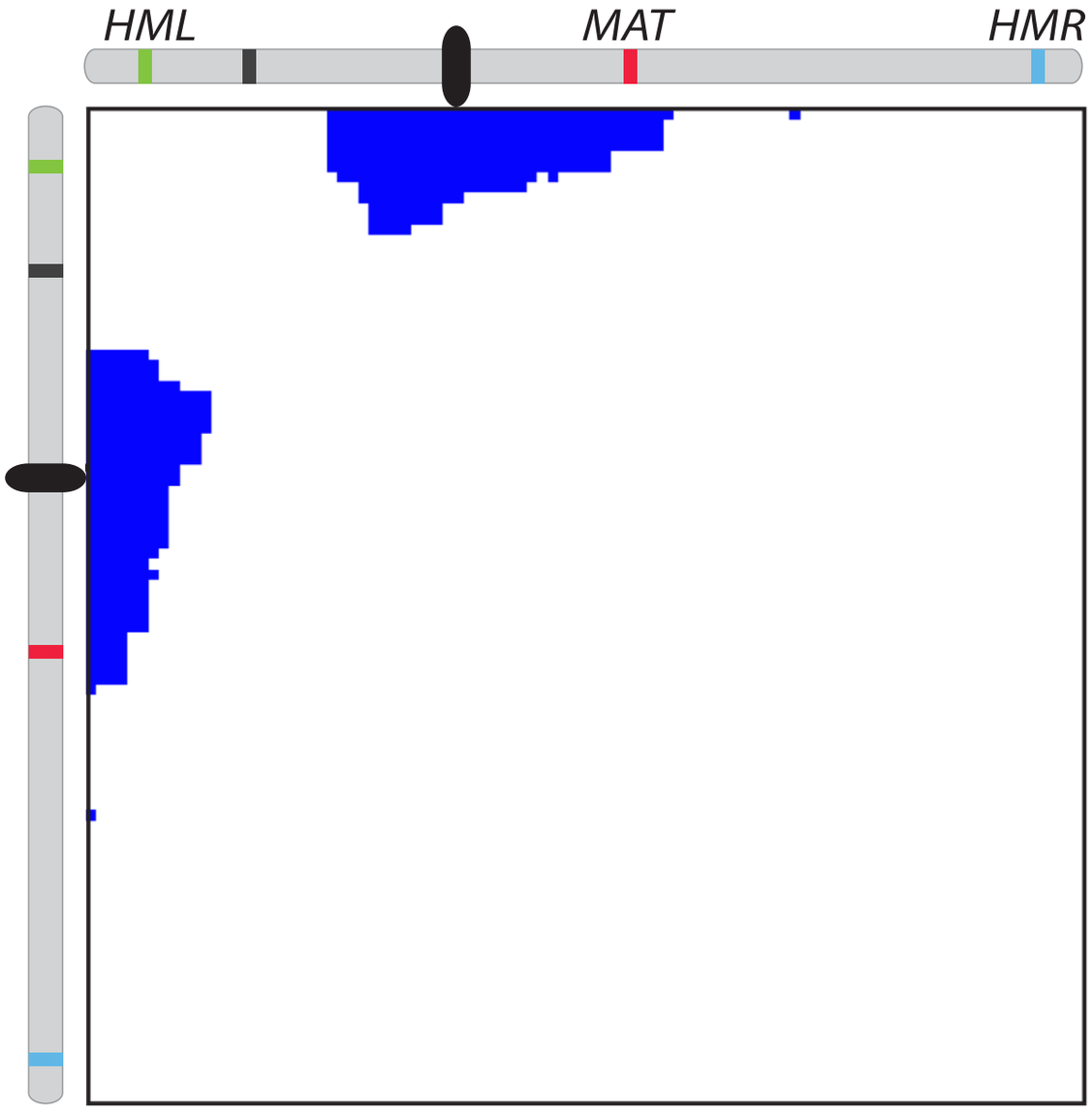
Only major difference in conformation is on chromosome III

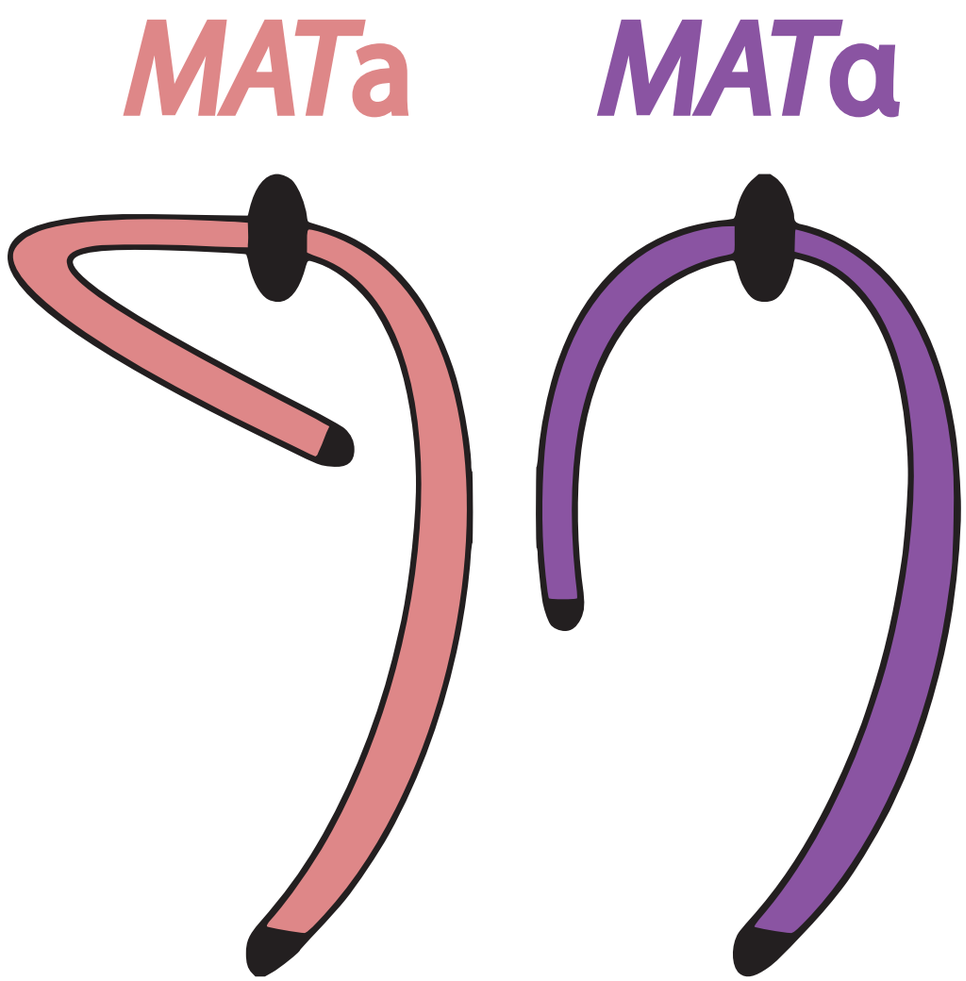
Difference in conformation of the left arm of chromosome III

Log_2(*MAT*α / *MAT***a**)

= Enrichment of interaction in *MAT*α

= Enrichment of interaction in *MAT***a**





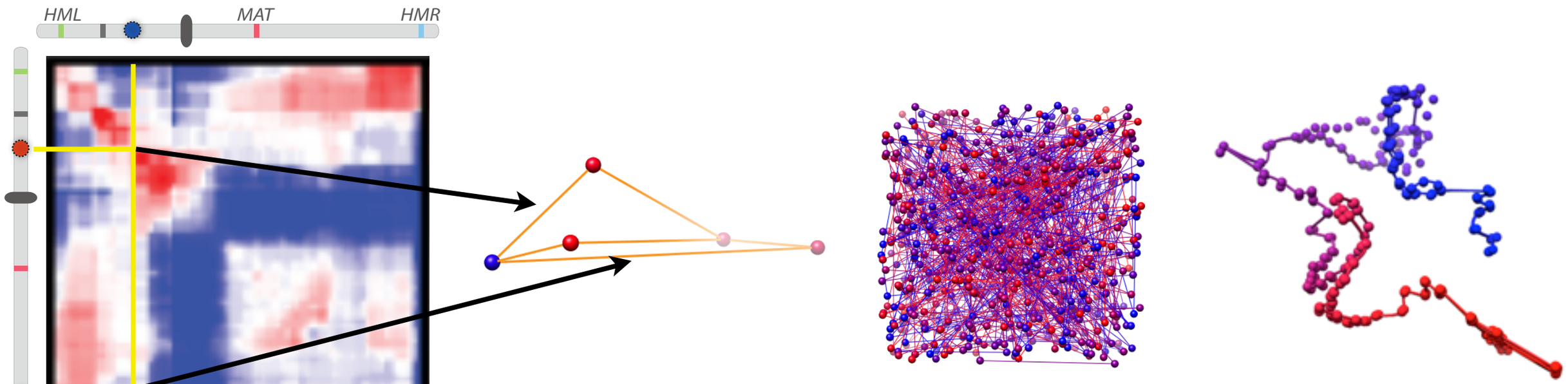
Average 3D models of ChrIII using IMP

5C Contact probabilities

5C data converted into distance restraints

Random initial organization

Fitting to distance constraints

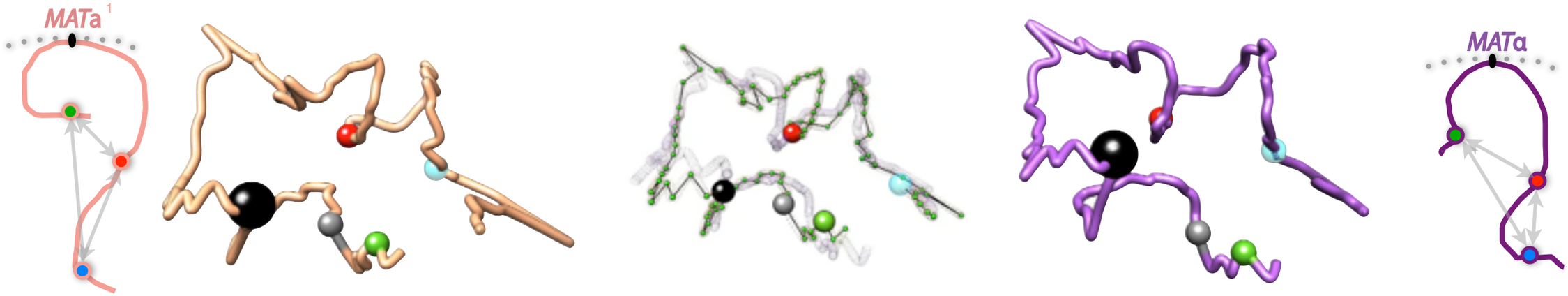


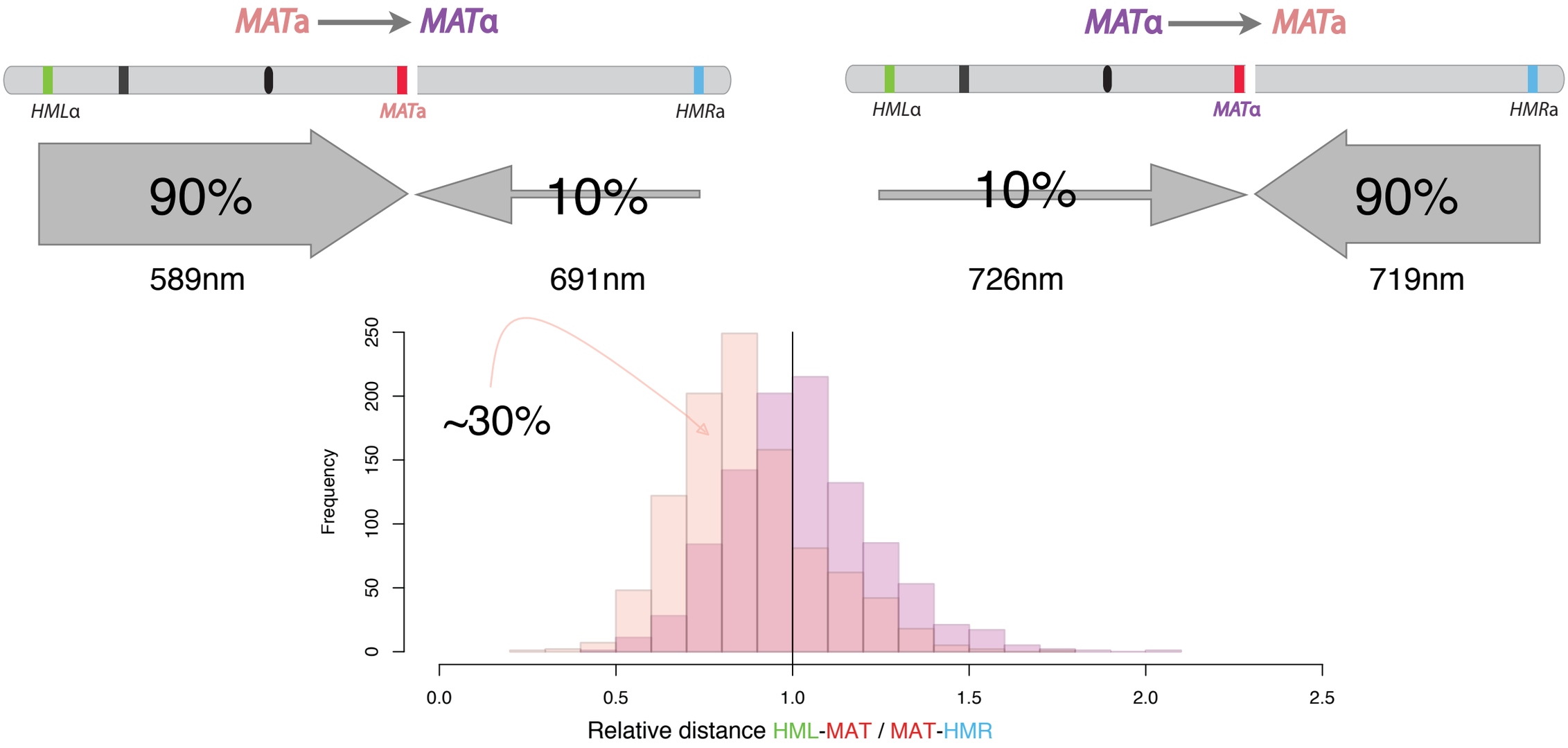
MATa

5,000 models
1,000 selected

MATα

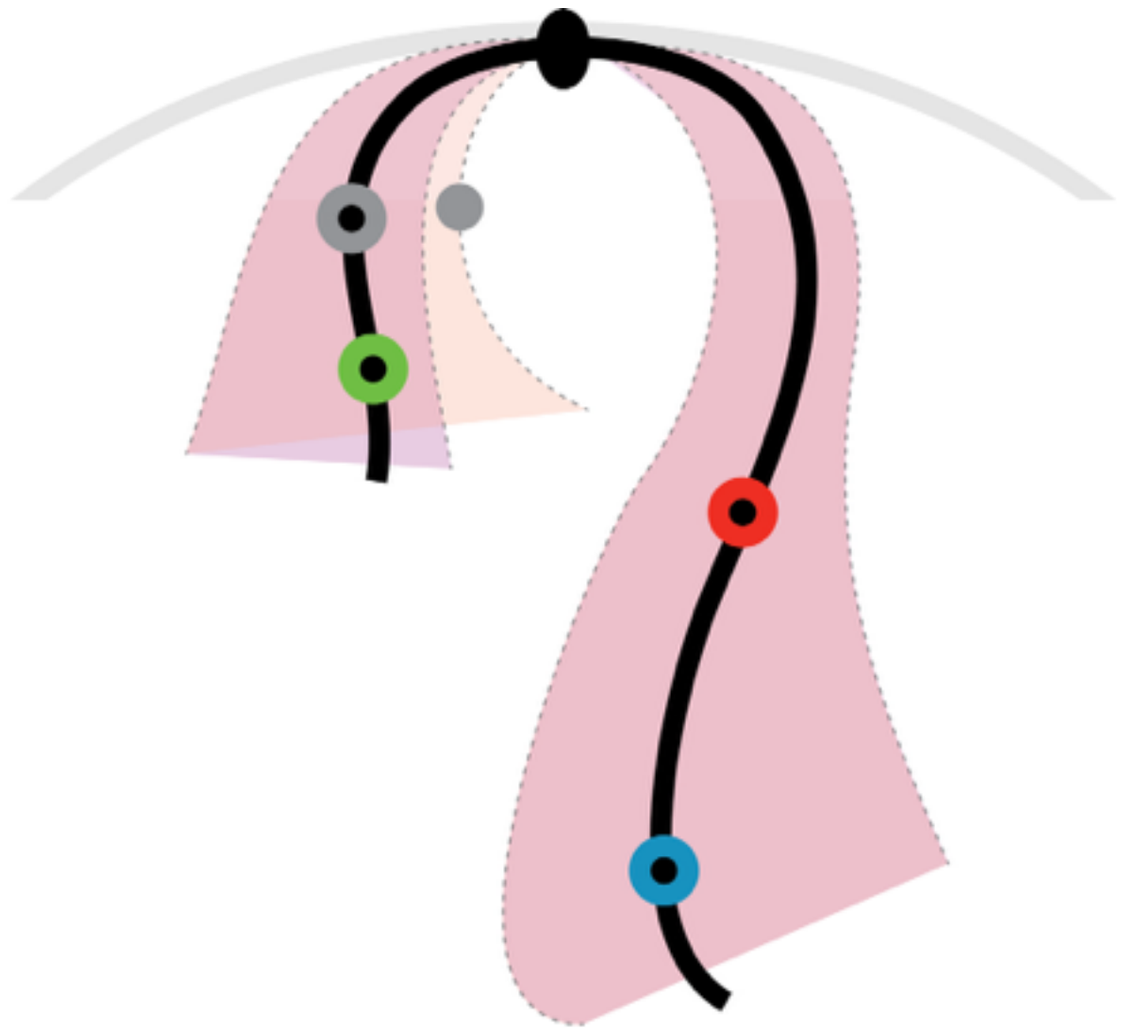
Mating type-specific conformation of chromosome III

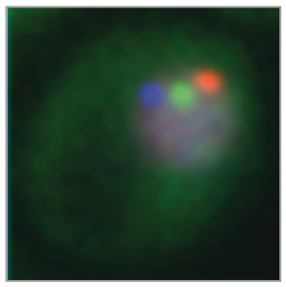


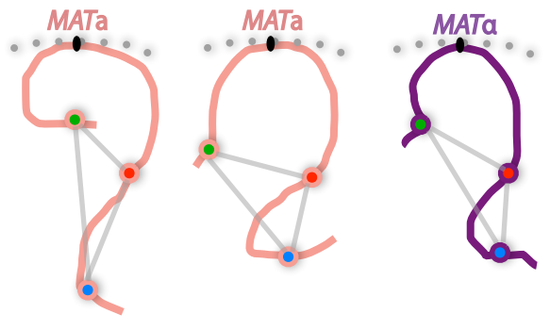


3D chrIII for mating in yeast

Sub-population in MATa responsible of mating-type recombination

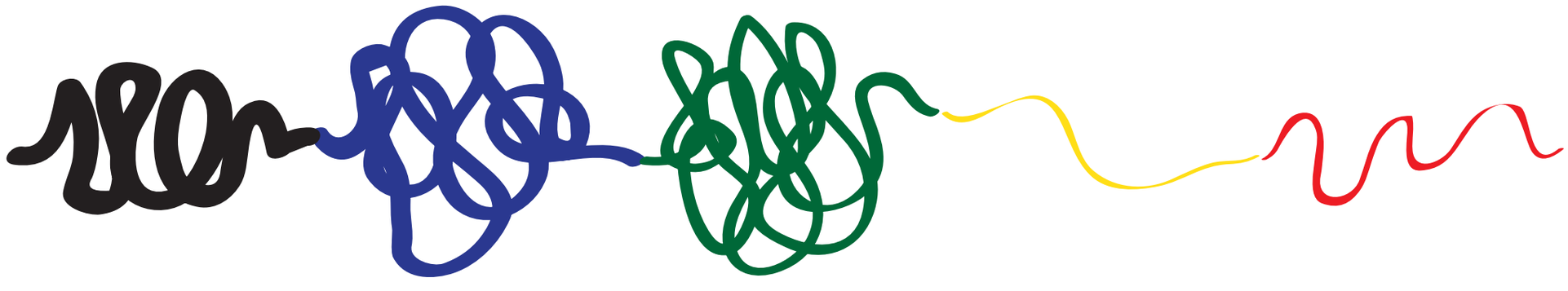






Imen Lassardi
LBME/CNRS

Structuring the COLORs of chromatin



Davide Baù

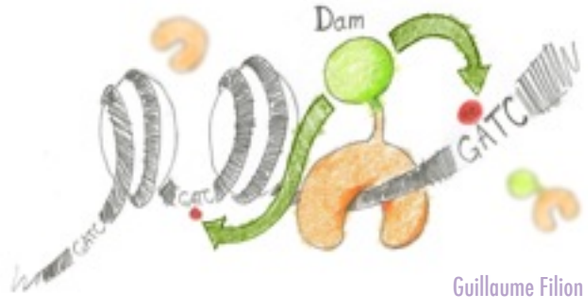
François Serra

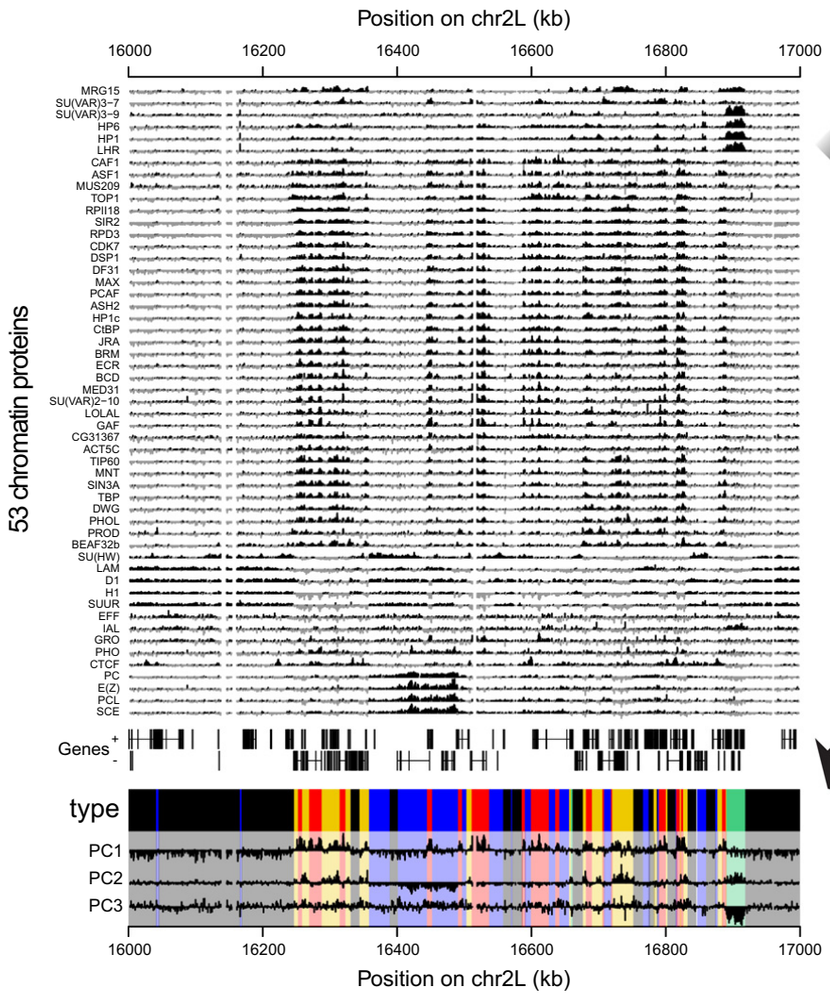
Guillaume Filion

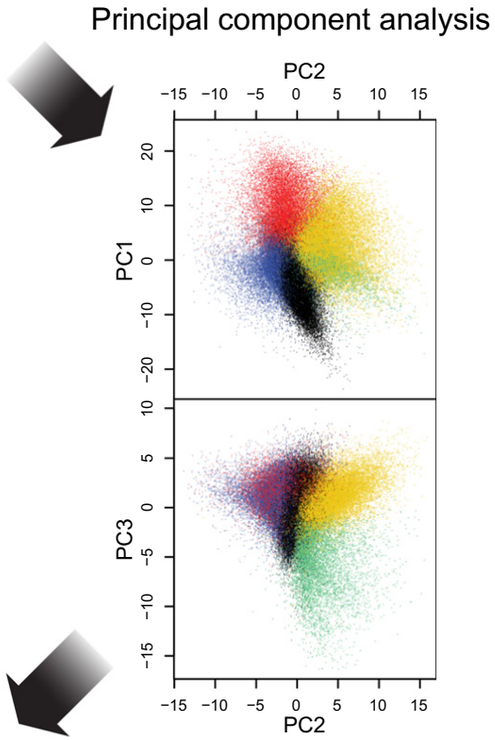
Gene Regulation, Stem Cells and Cancer
Centre de Regulació Genòmica
Barcelona, Spain

The COLORs

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







Hidden Markov model

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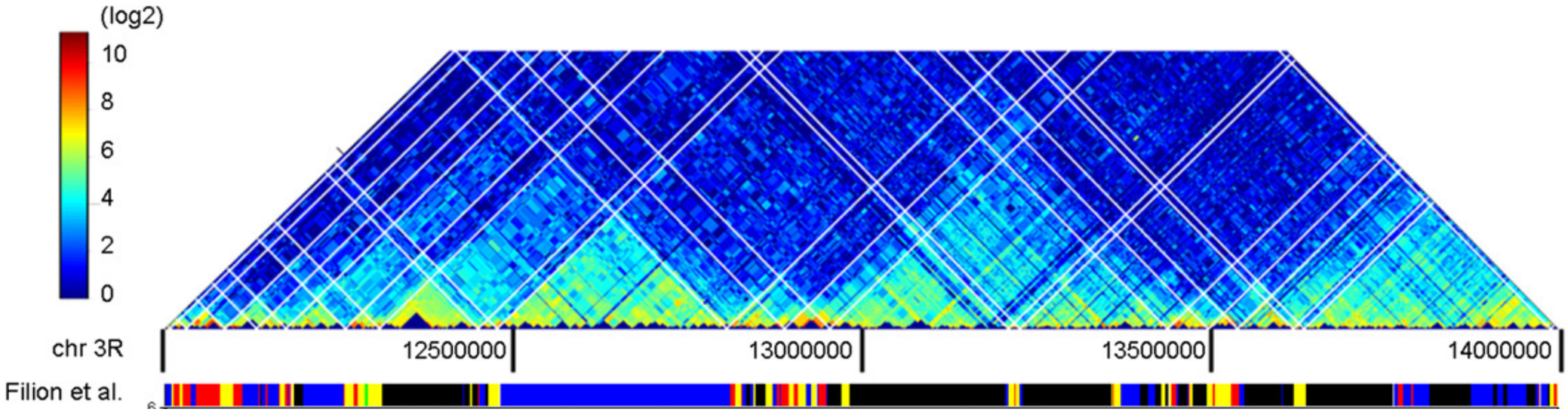
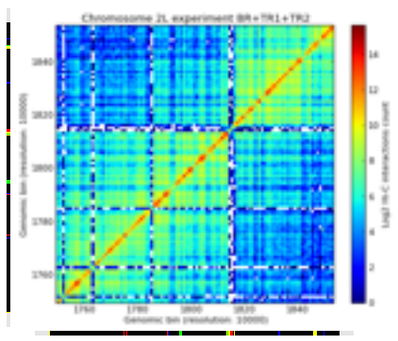
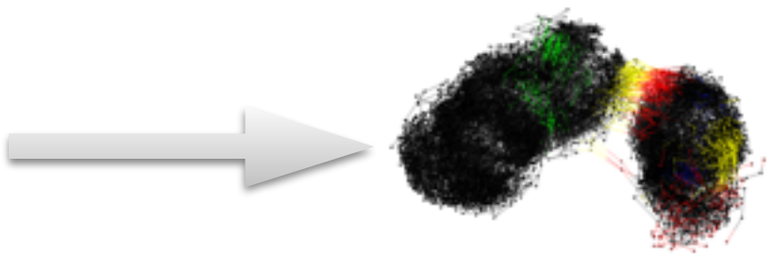
Functional COLORs

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







50 ~1Mb regions
10 for each color

Structural COLORs

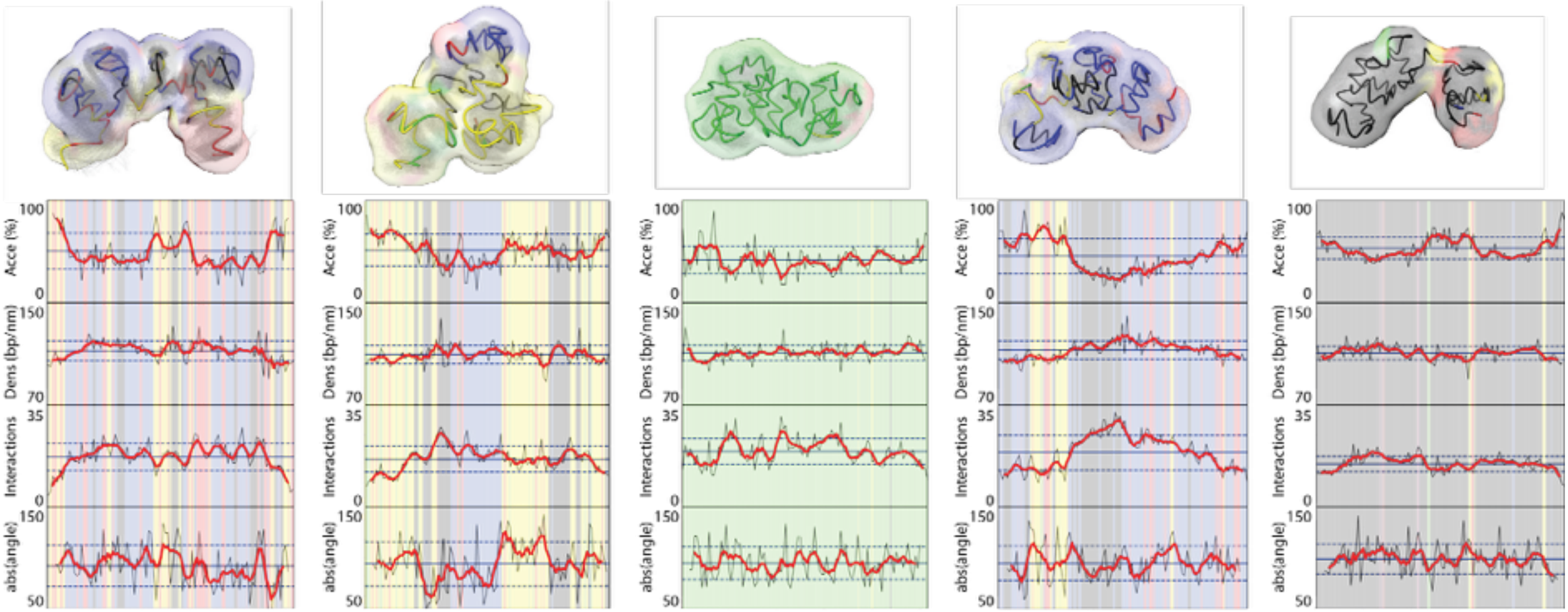
RED dense region
3L:10610000-11630000
23.0% 17.8% 0% 42.8% 16.3%

YELLOW dense region
X:15590000-16600000
6.4% 43.5% 7.5% 18.9% 23.6%

GREEN dense region
2R:510000-1530000
0.1% 1.0% 98.3% 0% 0%

BLUE dense region
X:2340000-3370000
12.7% 11.3% 1.1% 50.6% 23.3%

BLACK dense region
2L:17500000-18530000
2.0% 2.4% 1.6% 2.0% 92.0%



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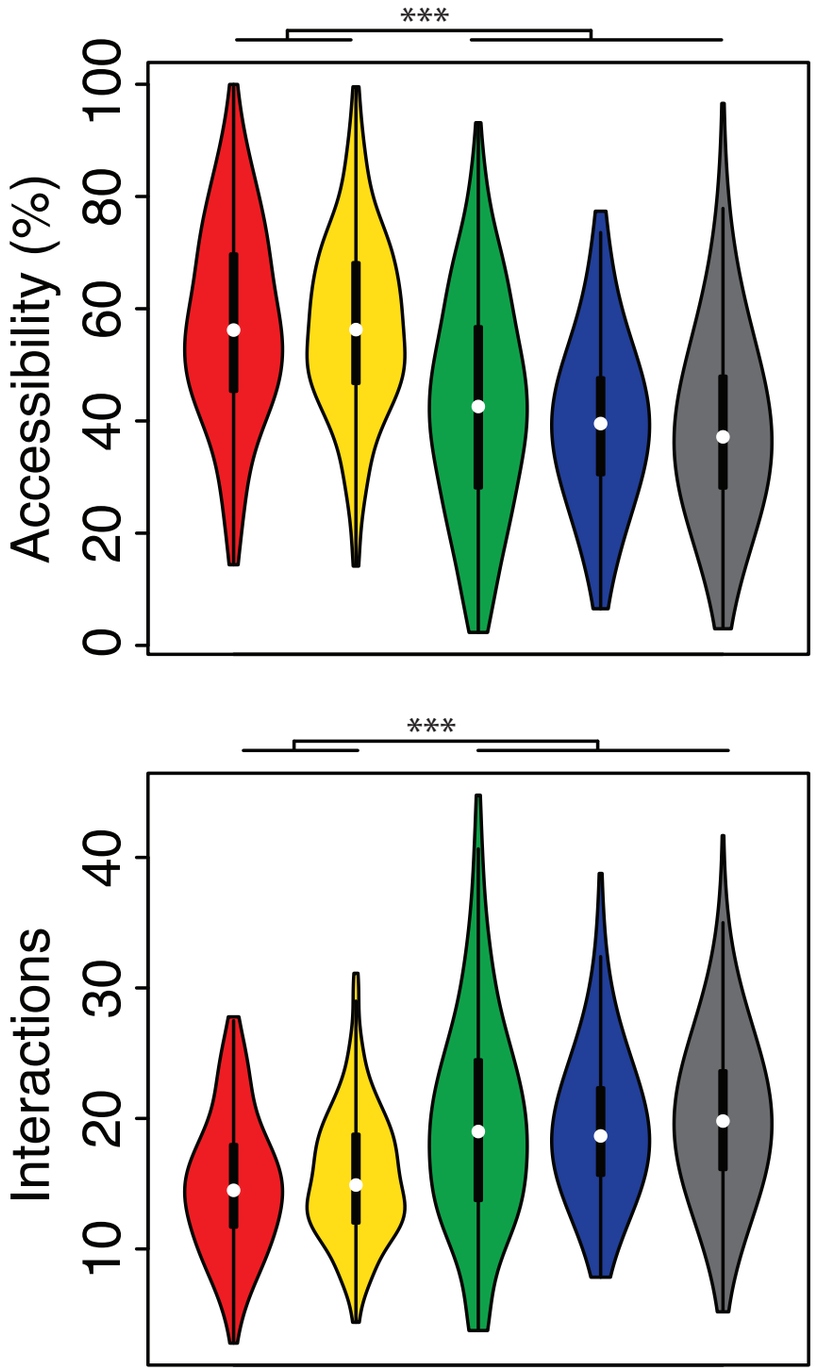
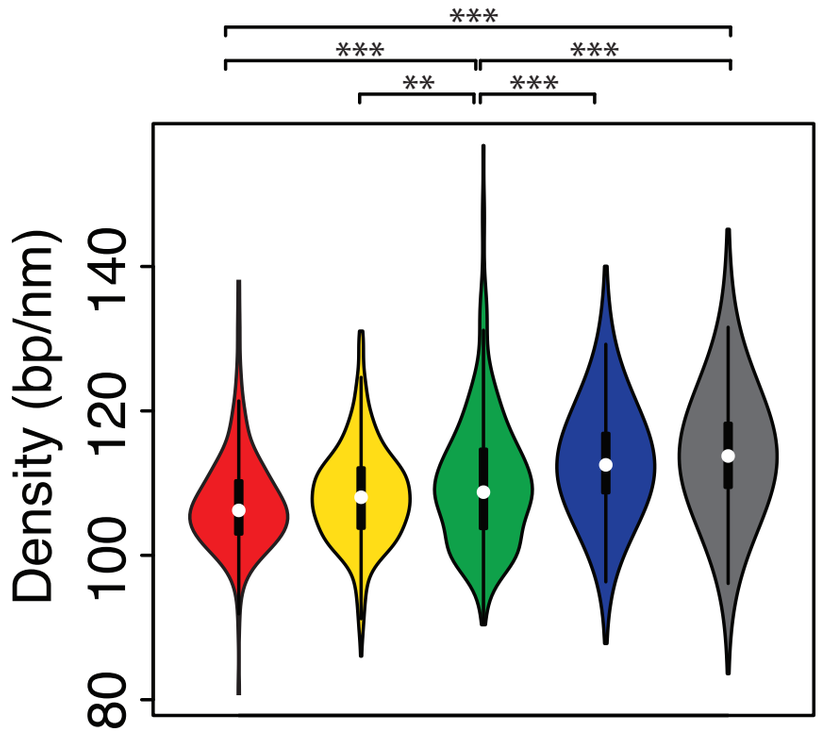
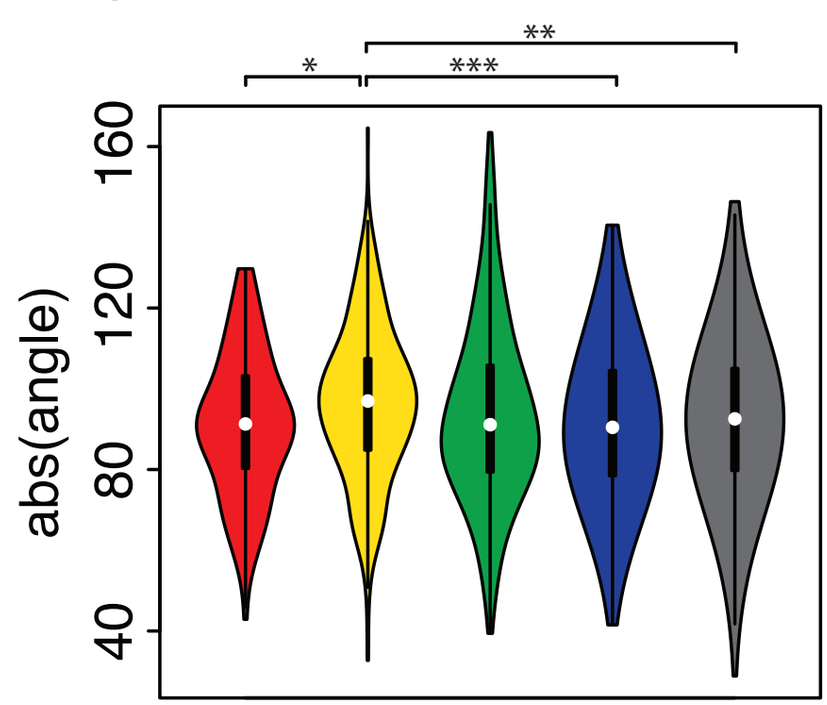
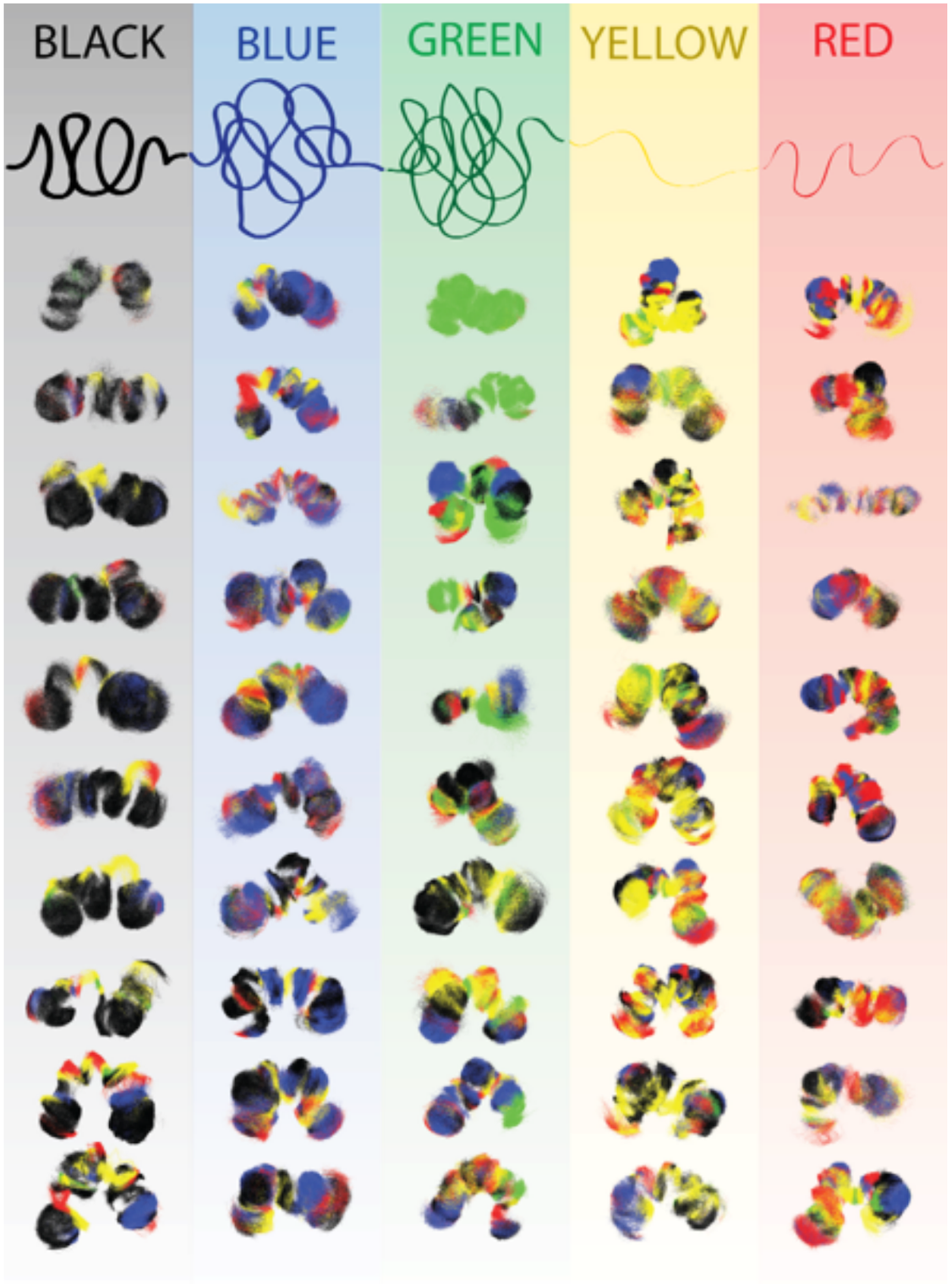
Structural COLORs

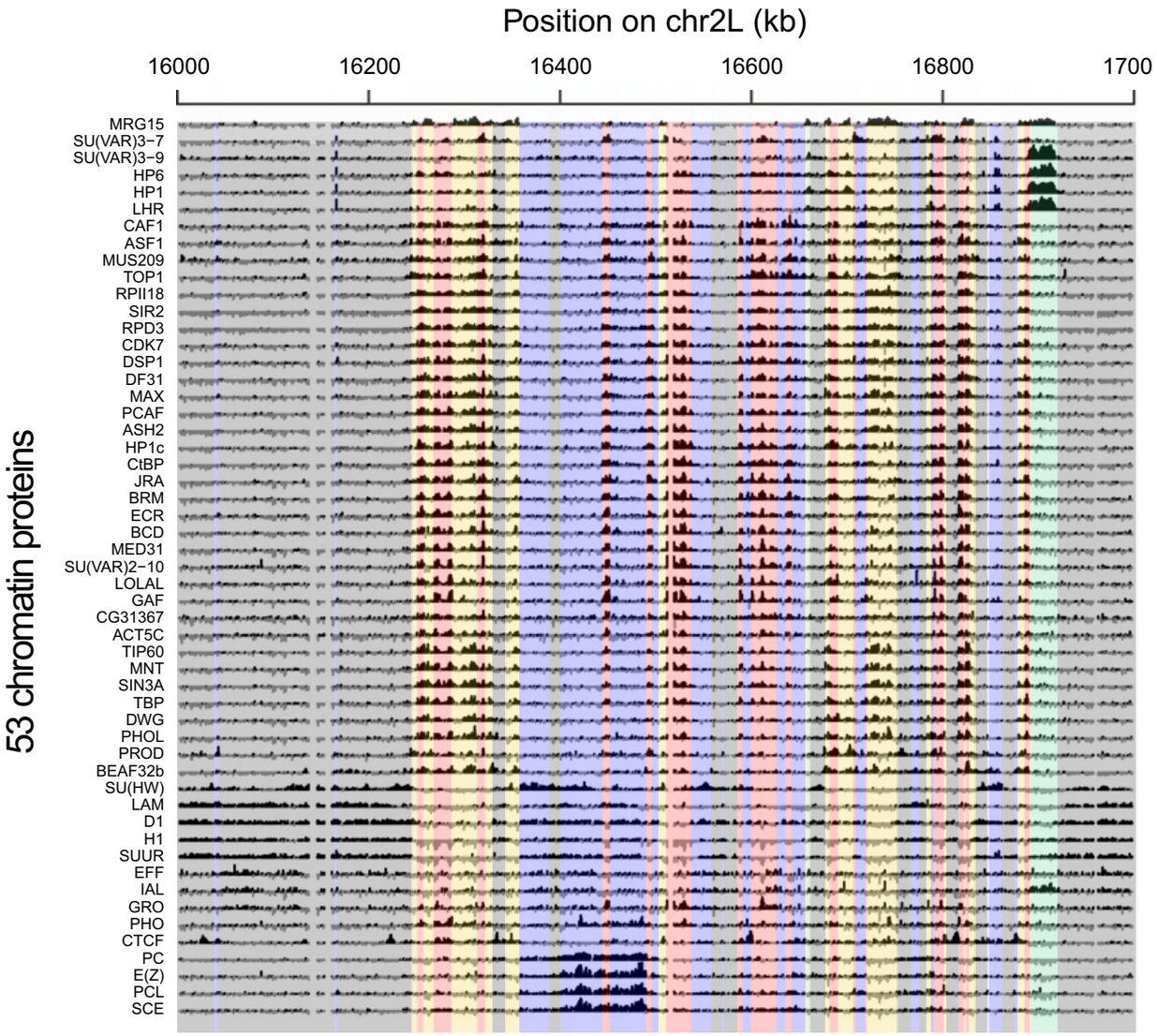






Structural COLORs





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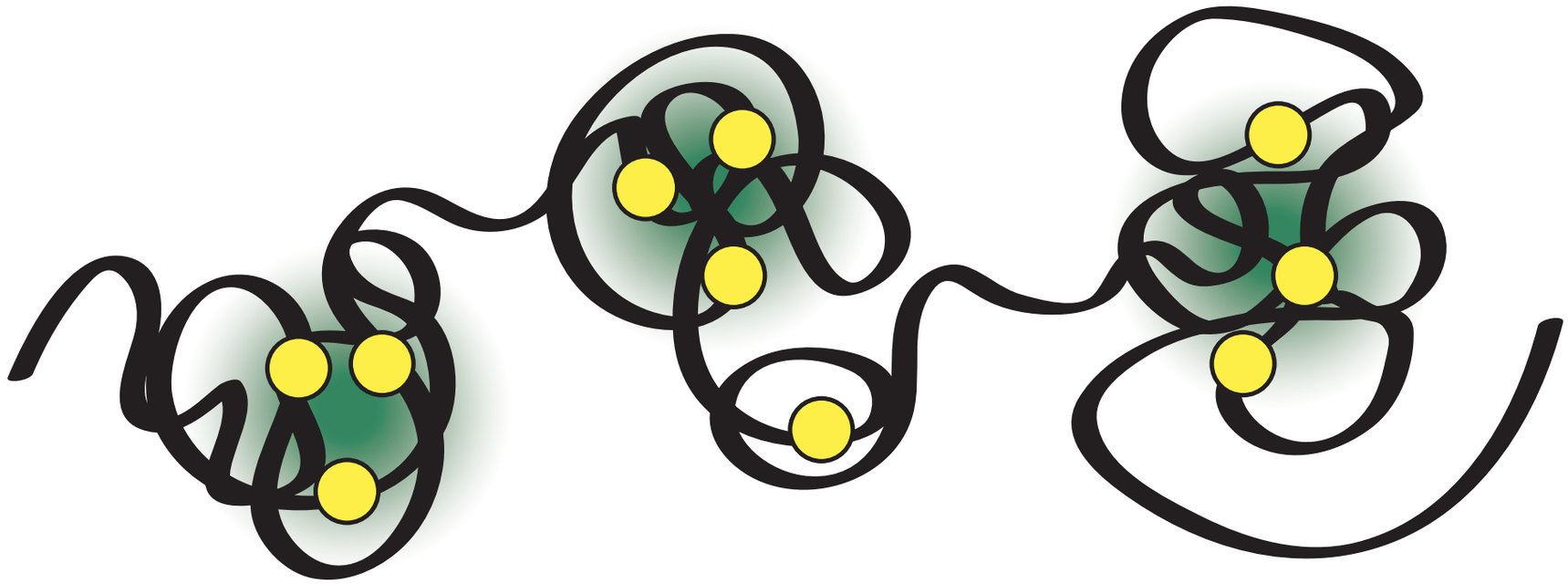
On TADs and hormones



François Serra

Davide Baù

François le Dily

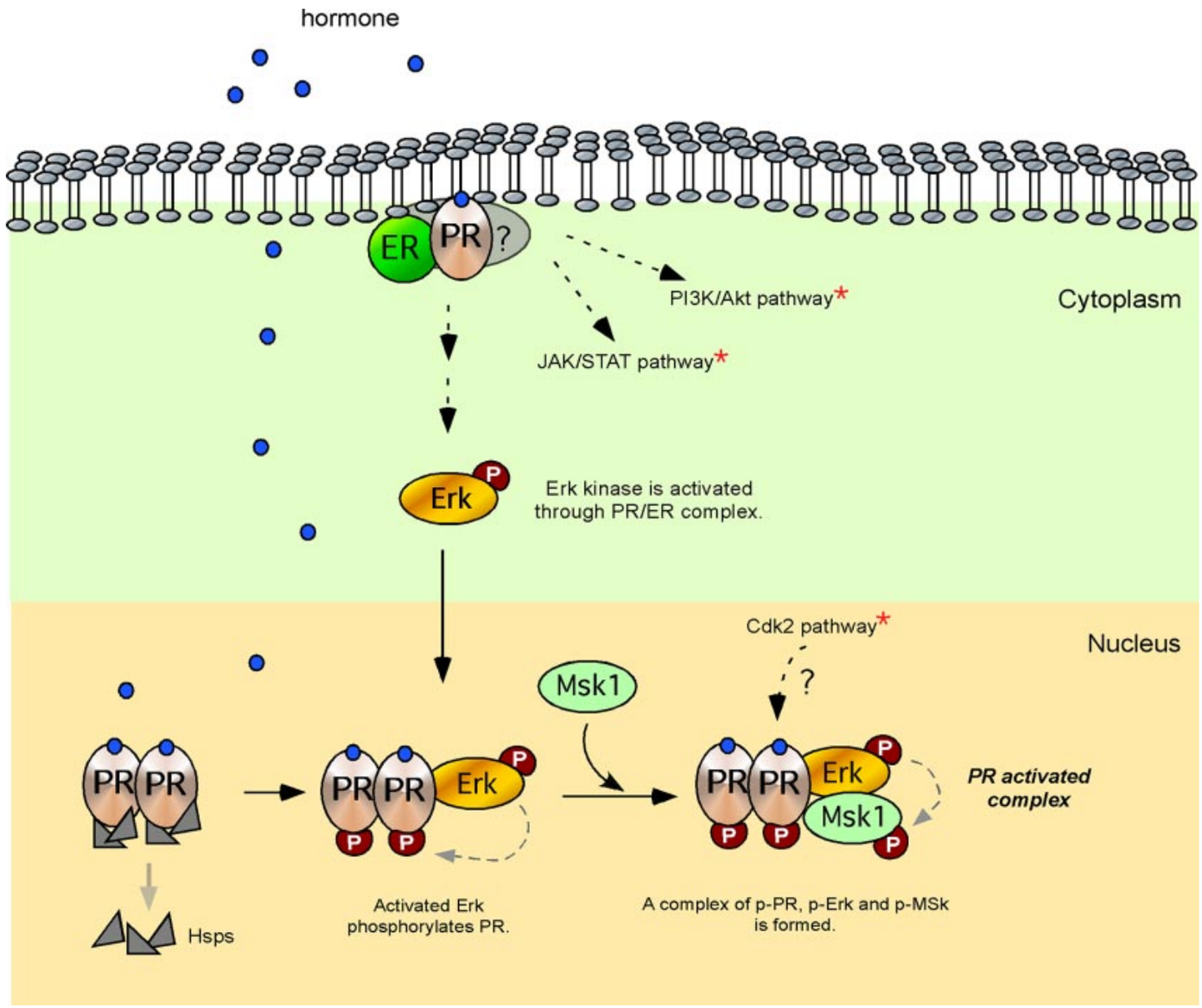
Miguel Beato & Guillaume Filion

Gene Regulation, Stem Cells and Cancer

Centre de Regulació Genòmica

Barcelona, Spain

Progesterone-regulated transcription in breast cancer



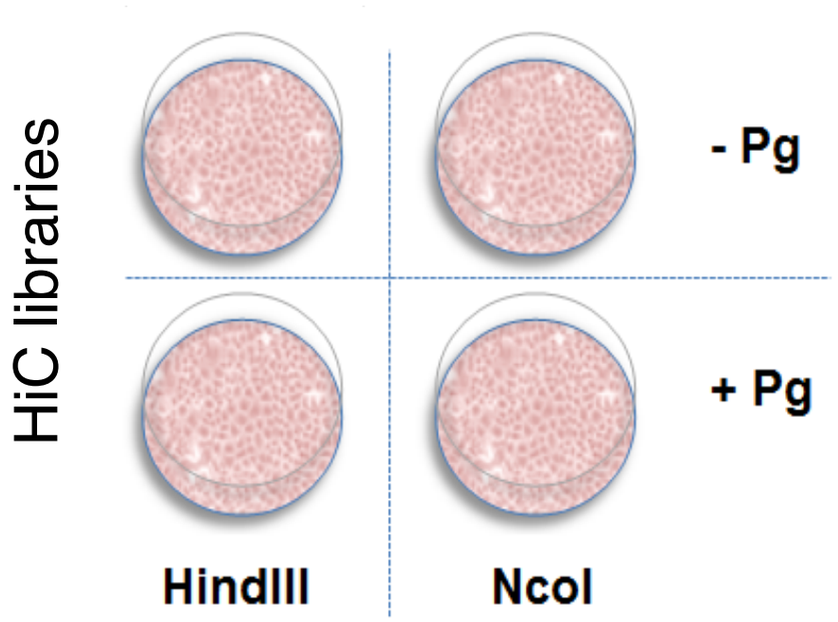
Vicent *et al* 2011, Wright *et al* 2012, Ballare *et al* 2012

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

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

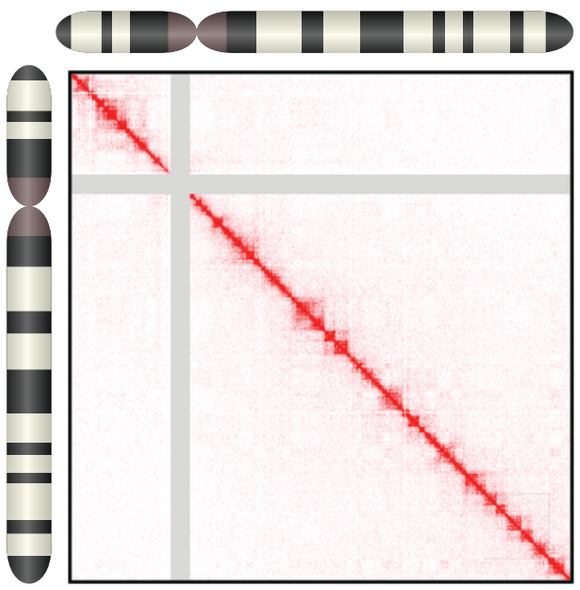
Regulation in 3D?

Experimental design

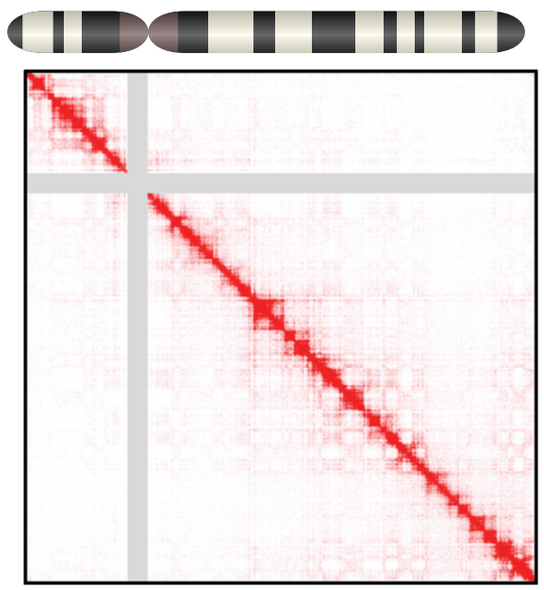


ChIP-Seq
RNA-Seq
Hi-C

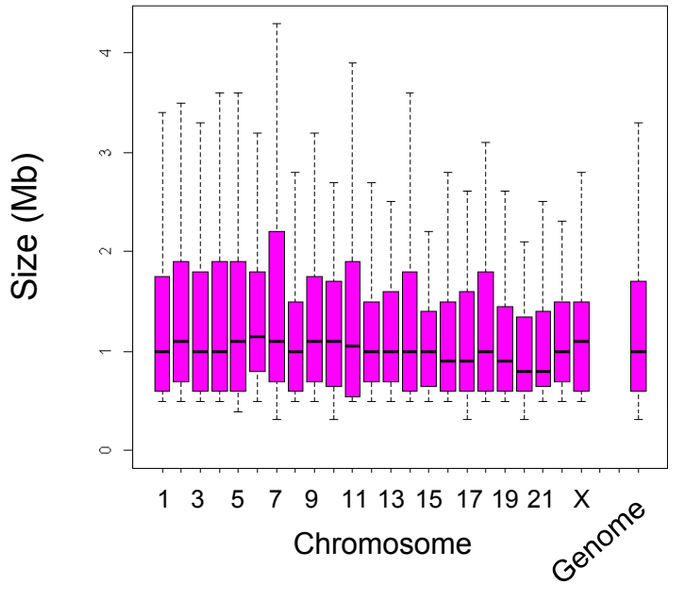
Chr.18 (Hind III)



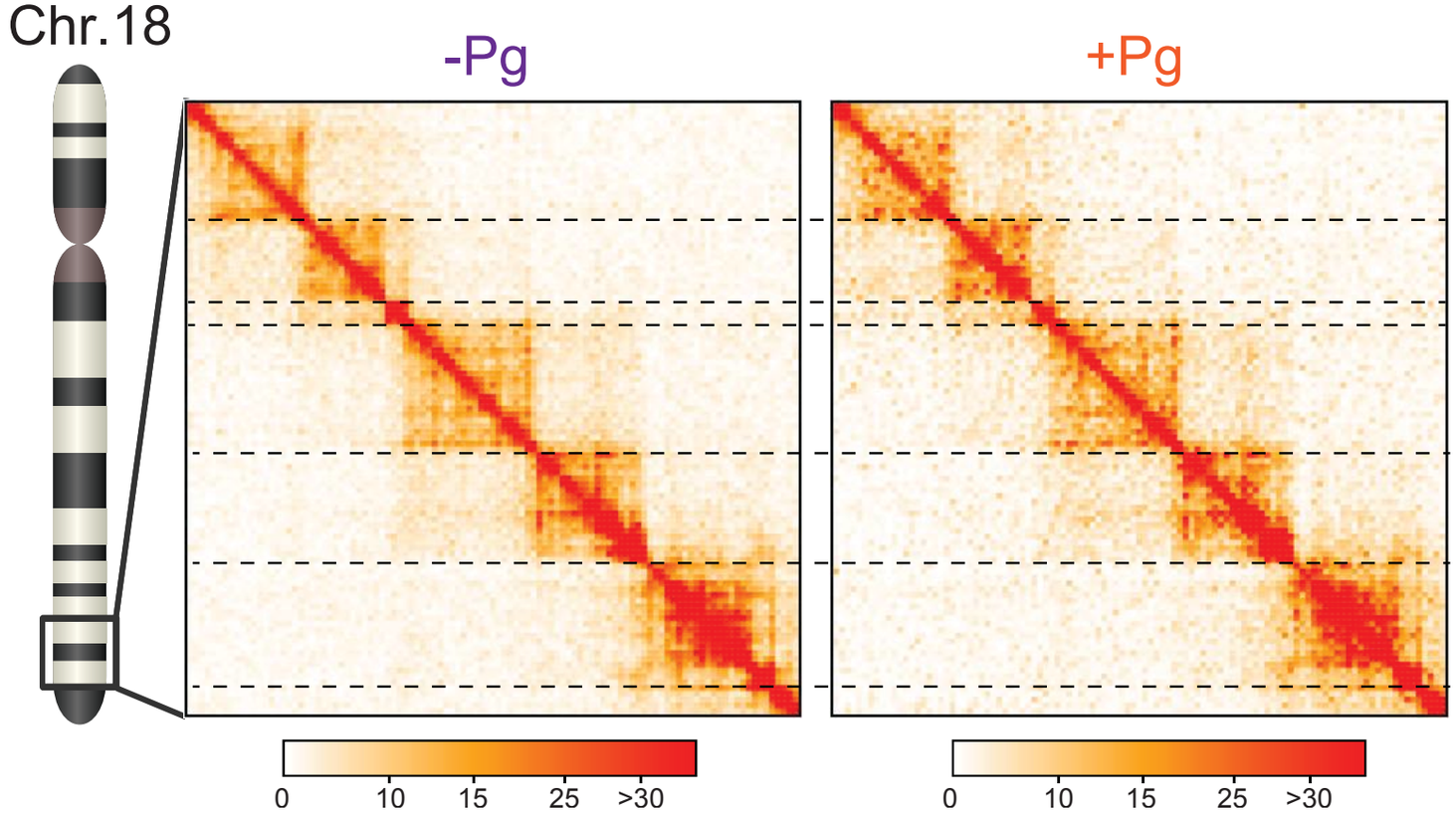
Chr.18 (NcoI)

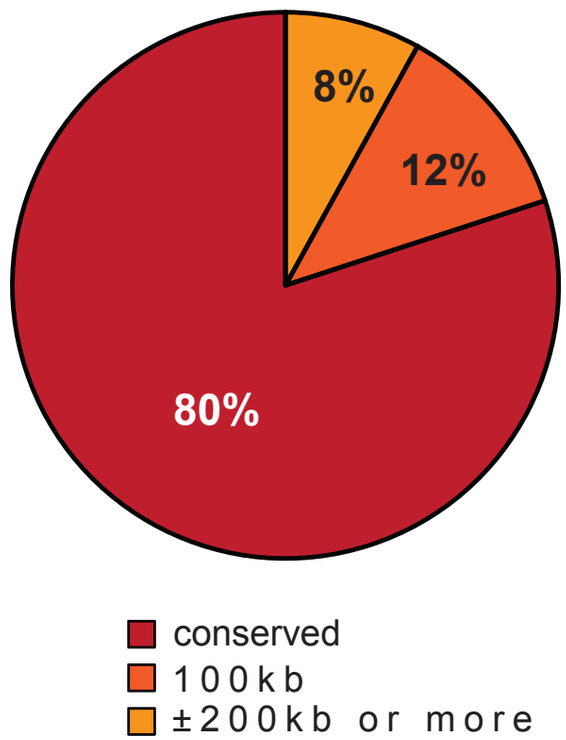


Are there TADs? how robust?

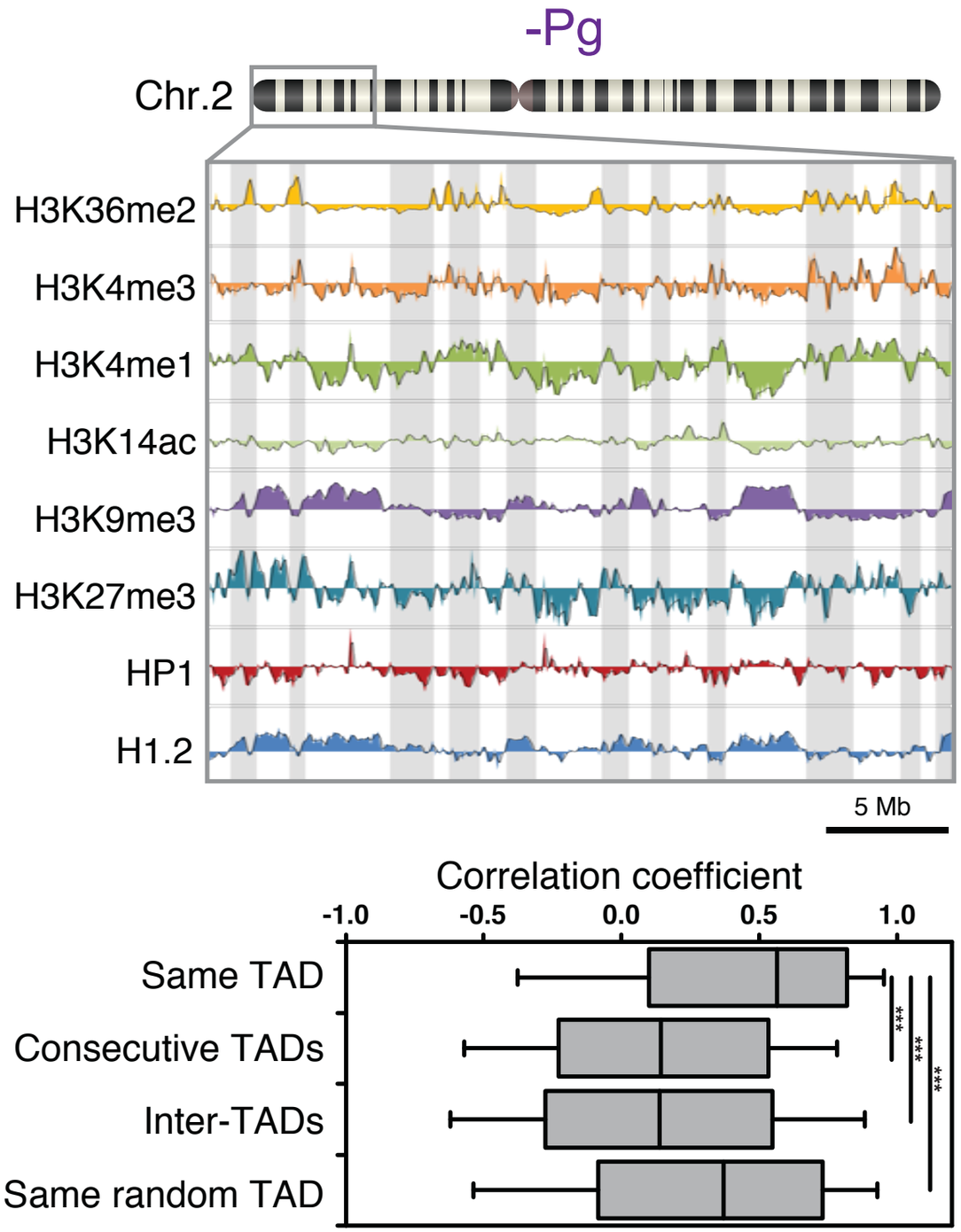


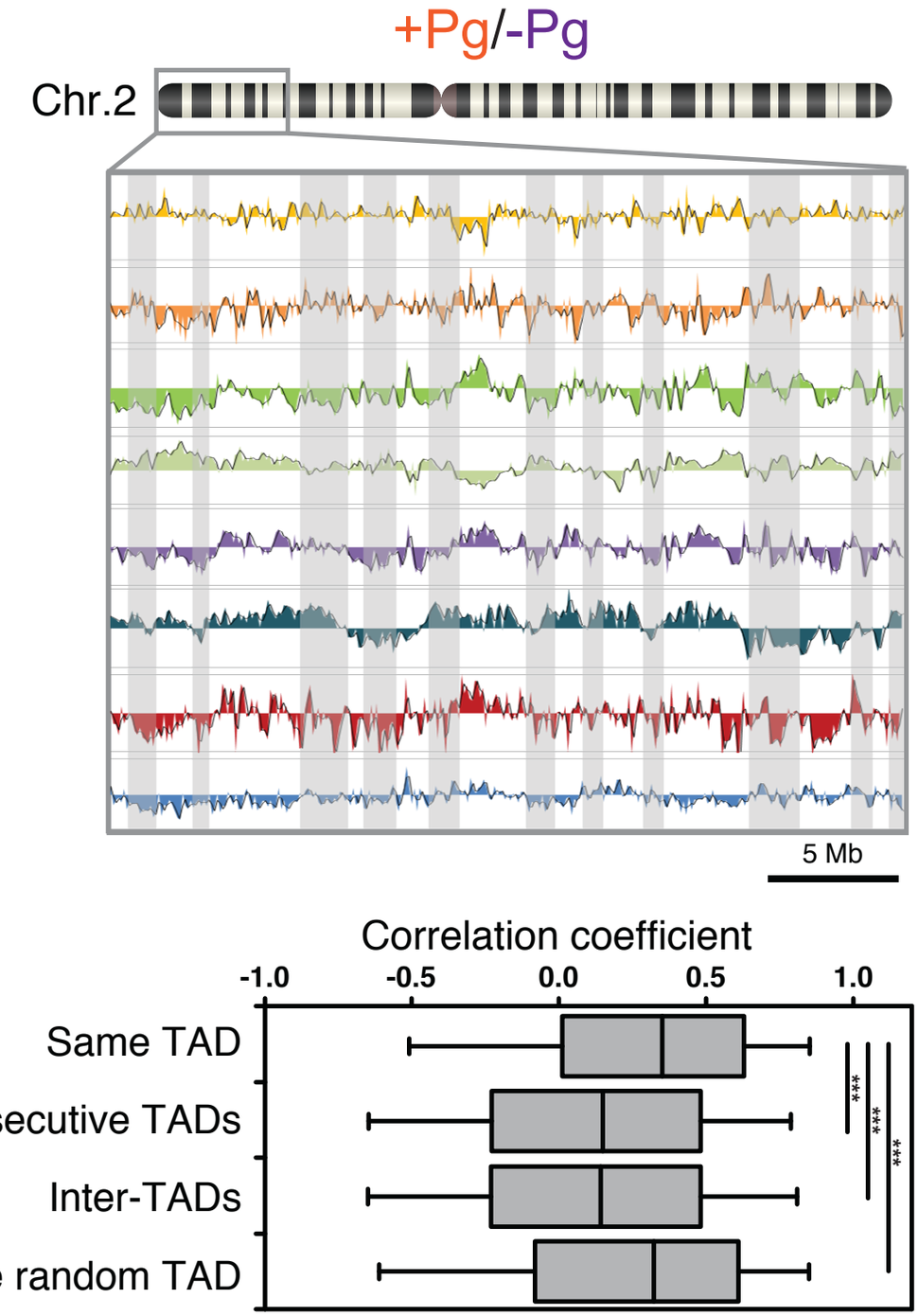
>2,000 detected TADs



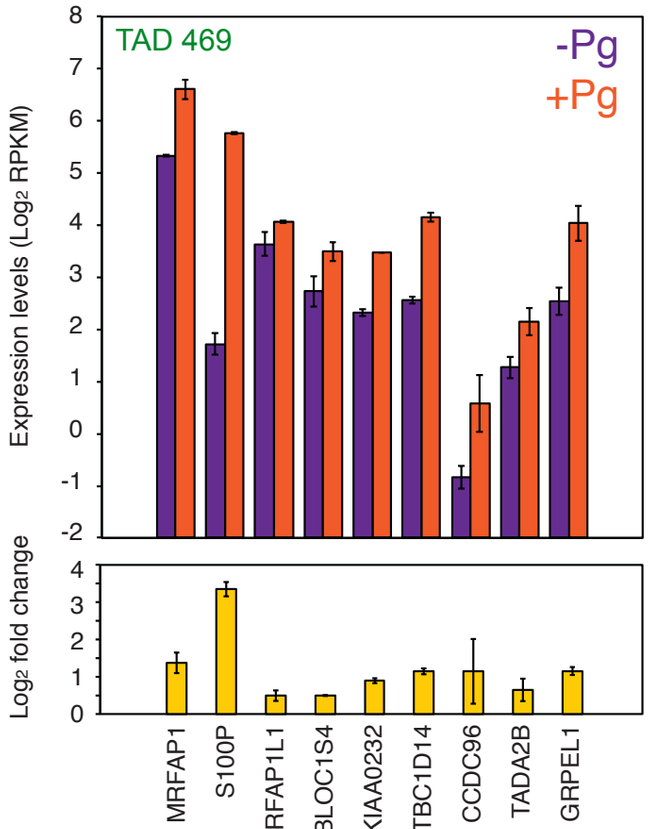


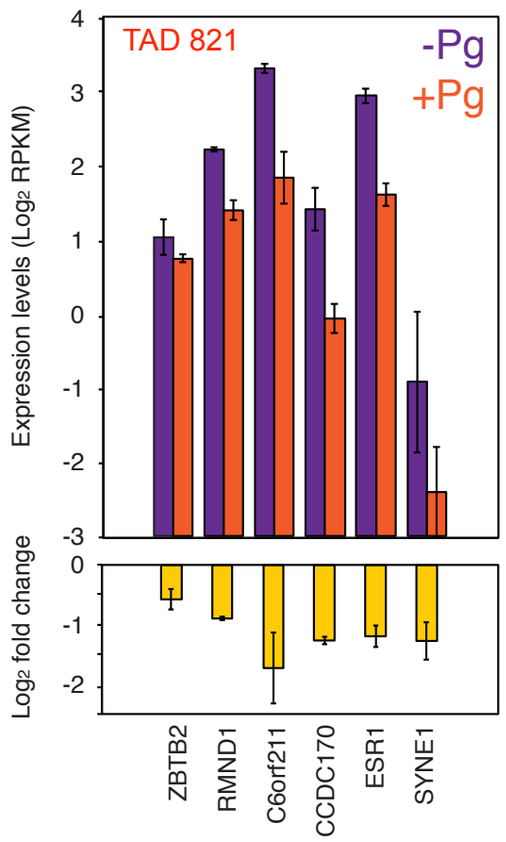
Are TADs homogeneous?

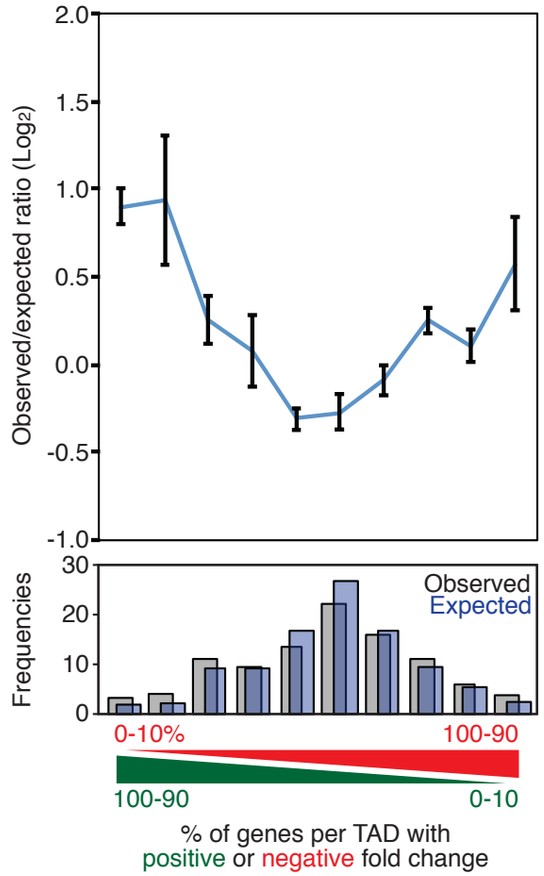




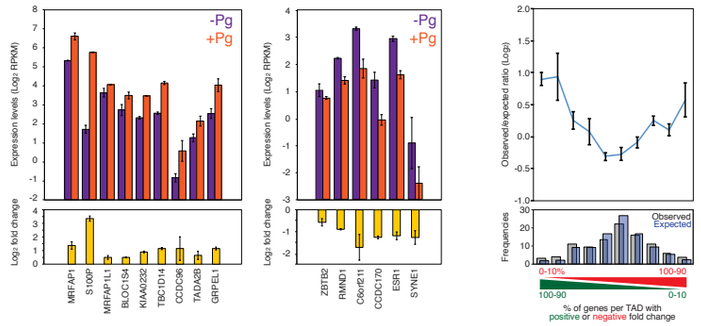
Do TADs respond differently to Pg treatment?



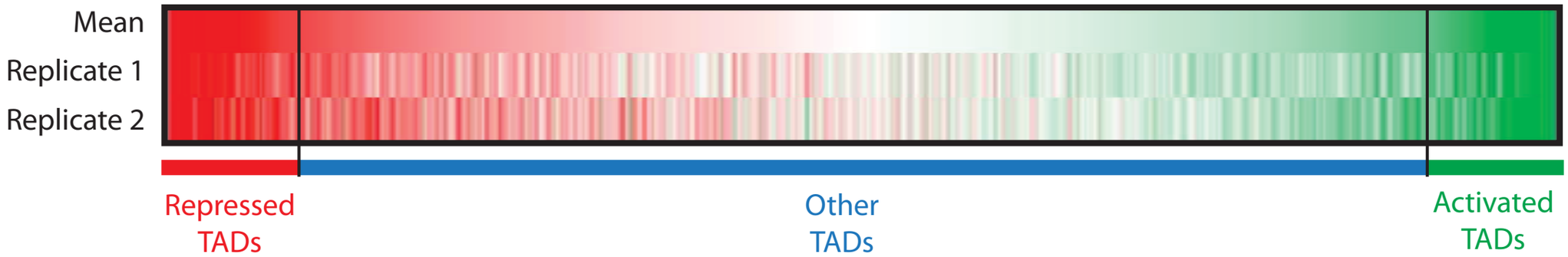


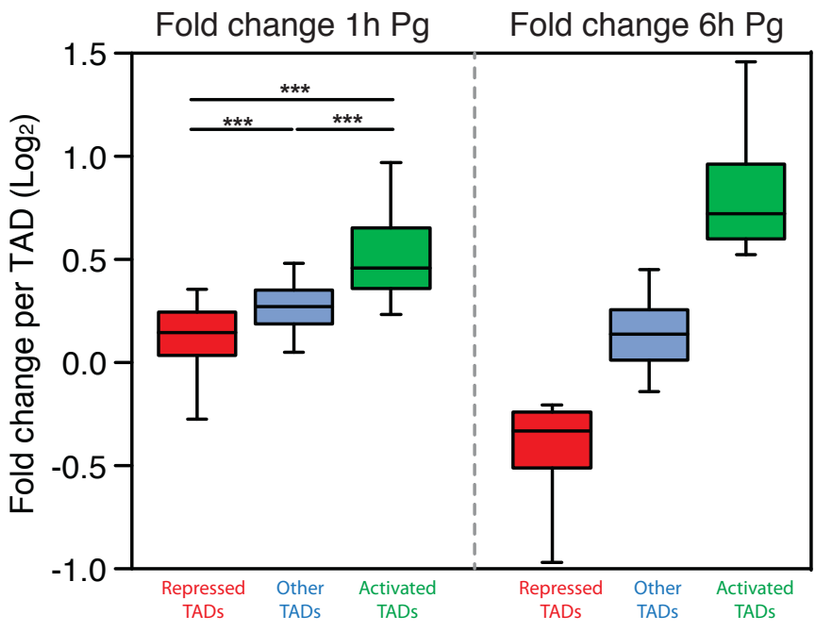


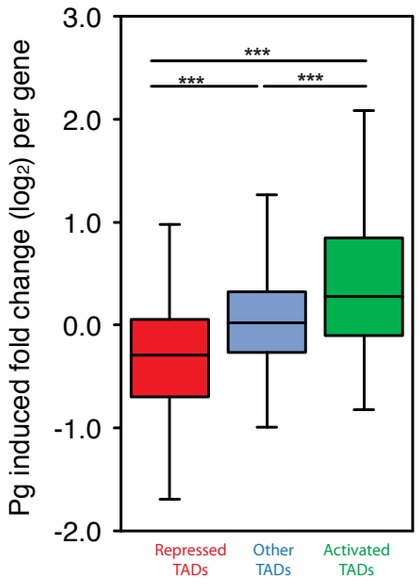
Do TADs respond differently to Pg treatment?

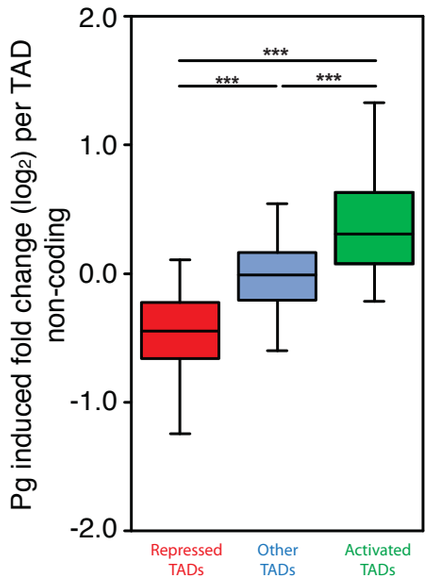


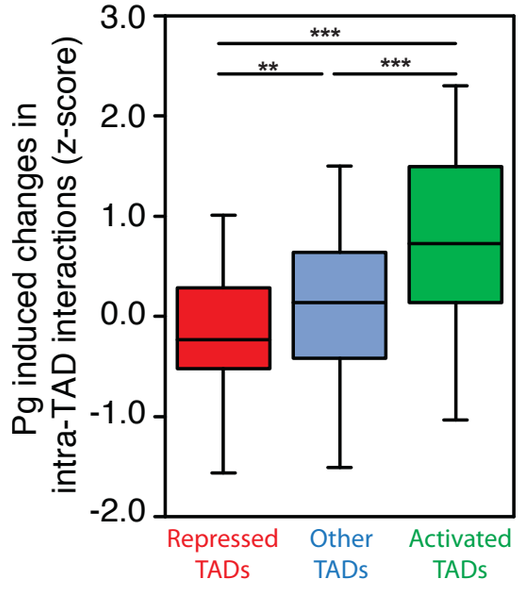
Pg induced fold change per TAD (6h)



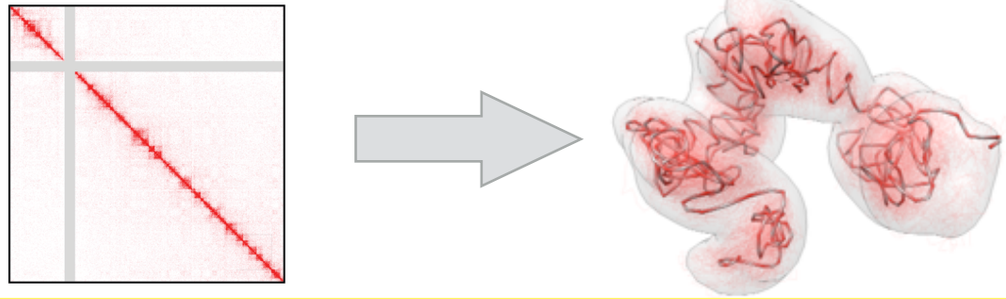




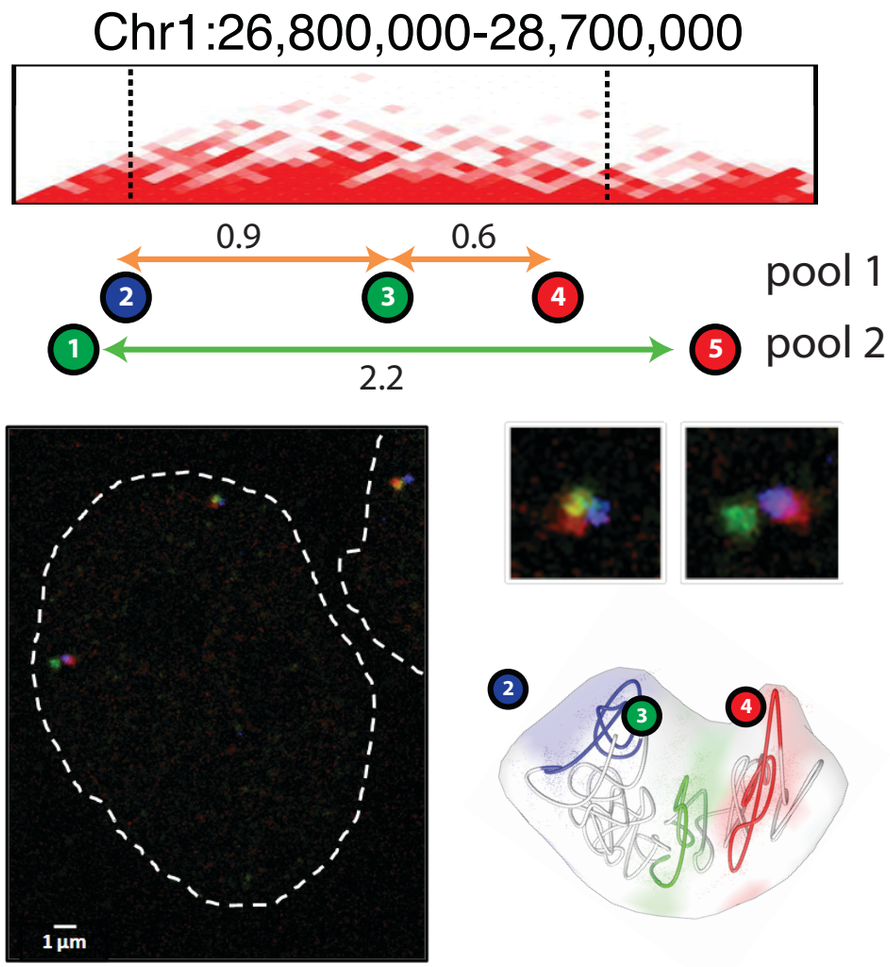


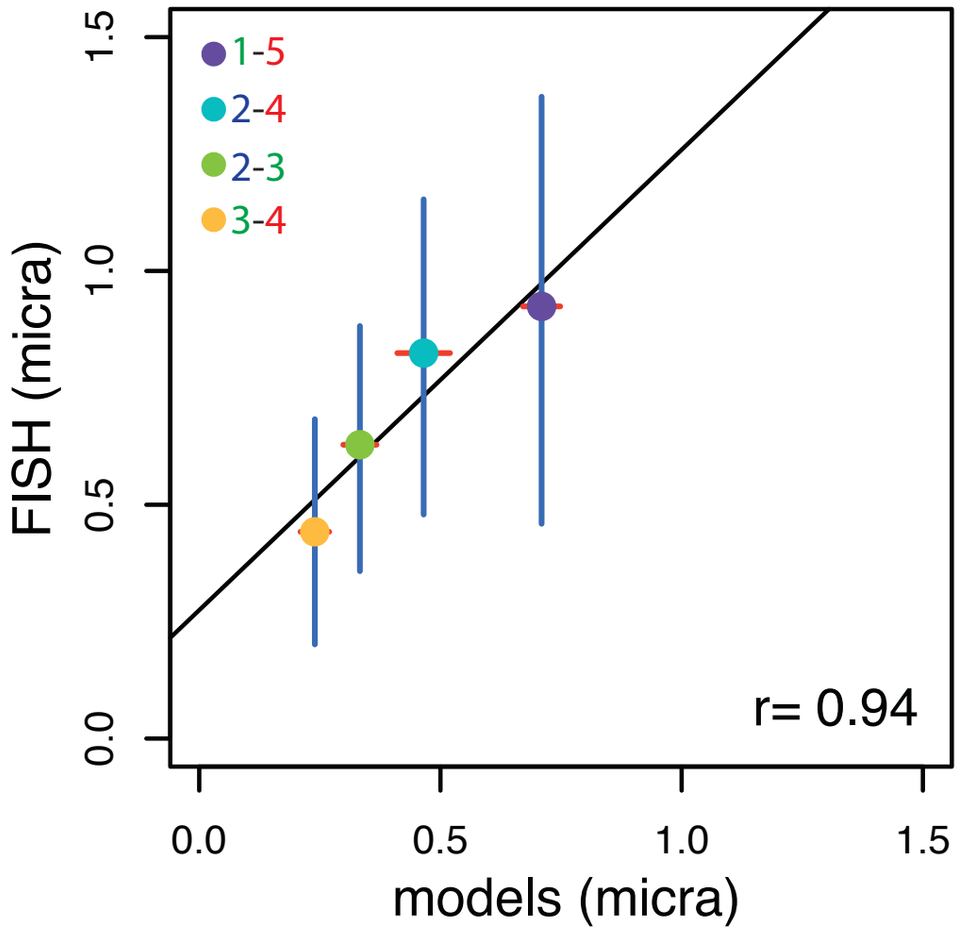


Modeling 3D TADs



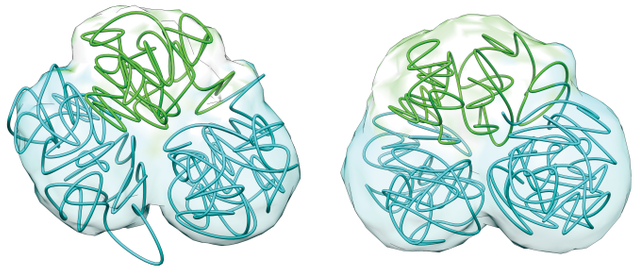
61 genomic regions containing 209 TADs covering 267Mb



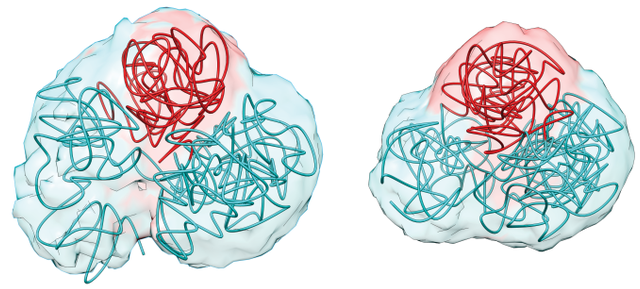


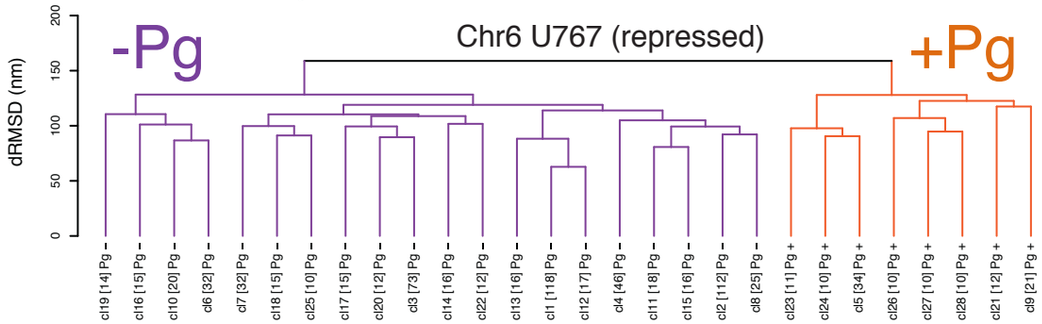
How TADs respond structurally to Pg?

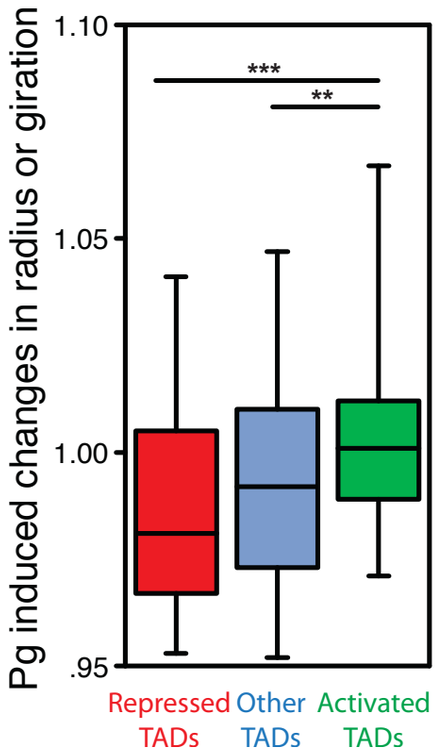
Chr2:9,600,000-13,200,000

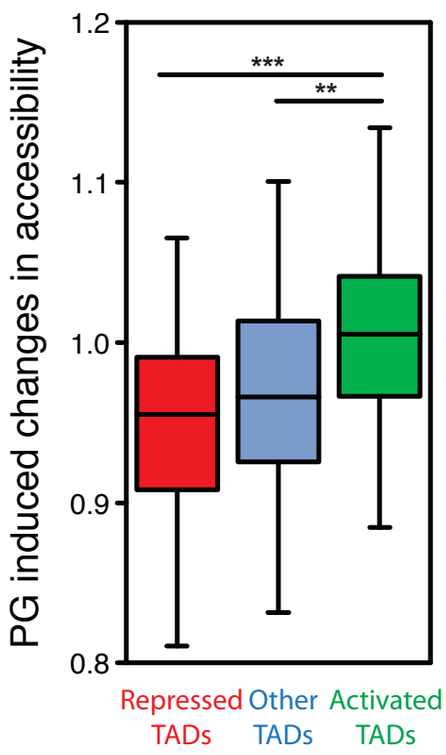


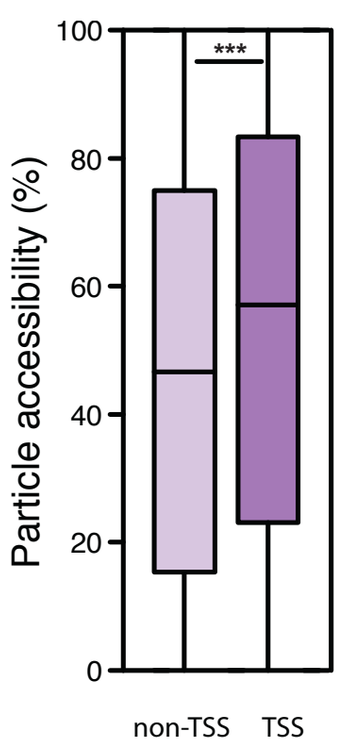
Chr6:71,800,000-76,500,000









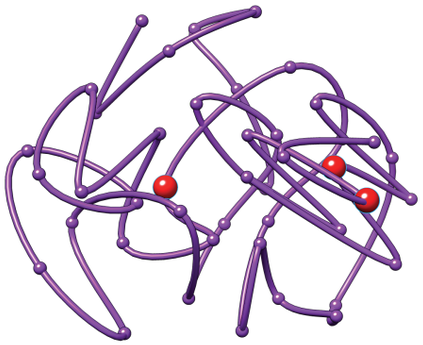


cnag CRG Centre for Genomic Regulation

Model for TAD regulation

Repressed TAD

chr1 U41

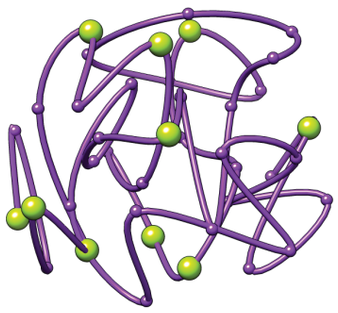


DHS HP1 H1.2 H2A MNAse H3K27me3 H3K9m3 H3K14ac H3K4me1 H3K36me2 H3K4me3

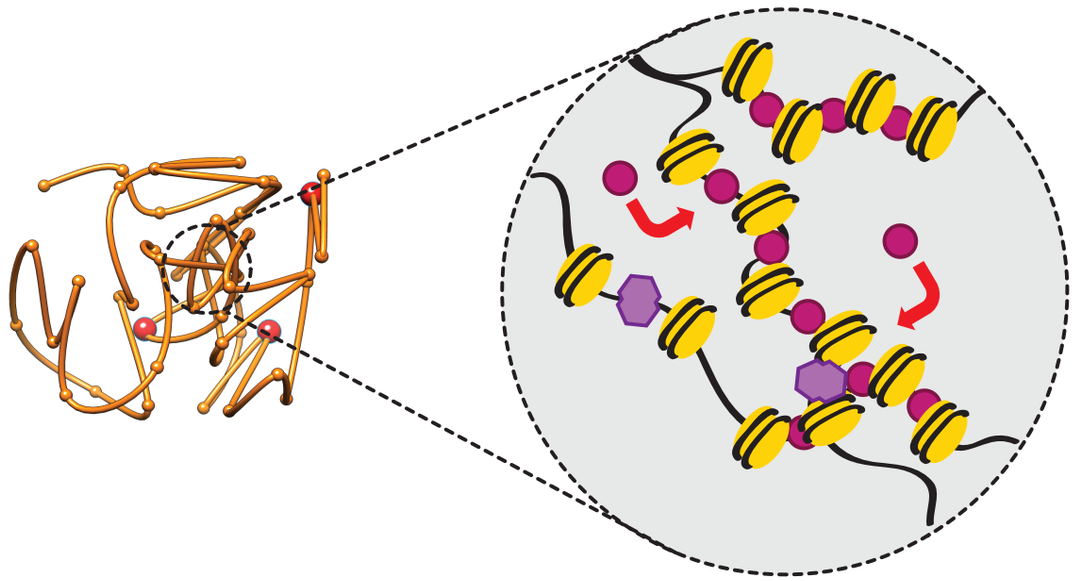
Structural transition **+Pg**

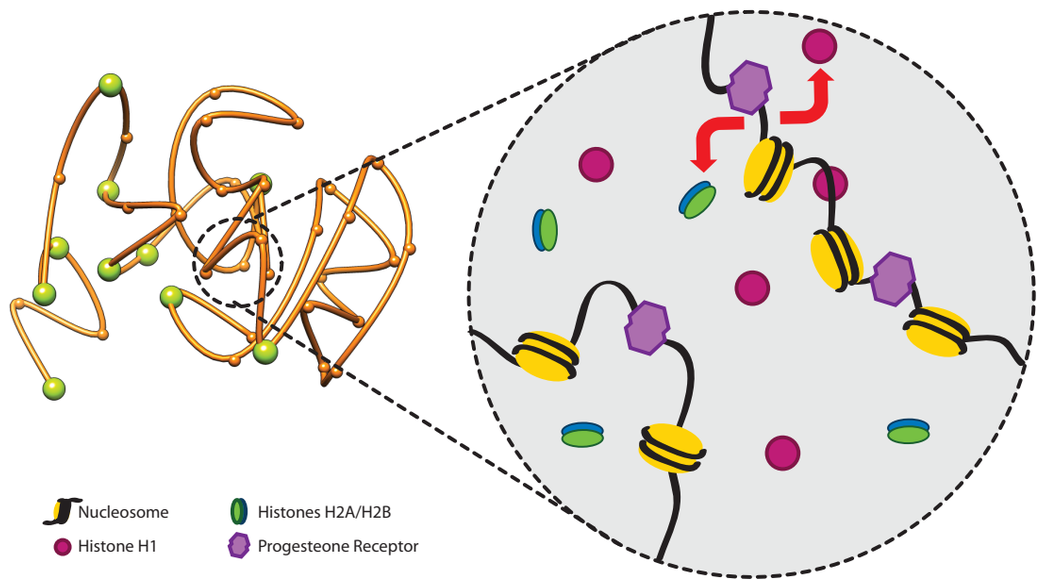
Activated TAD

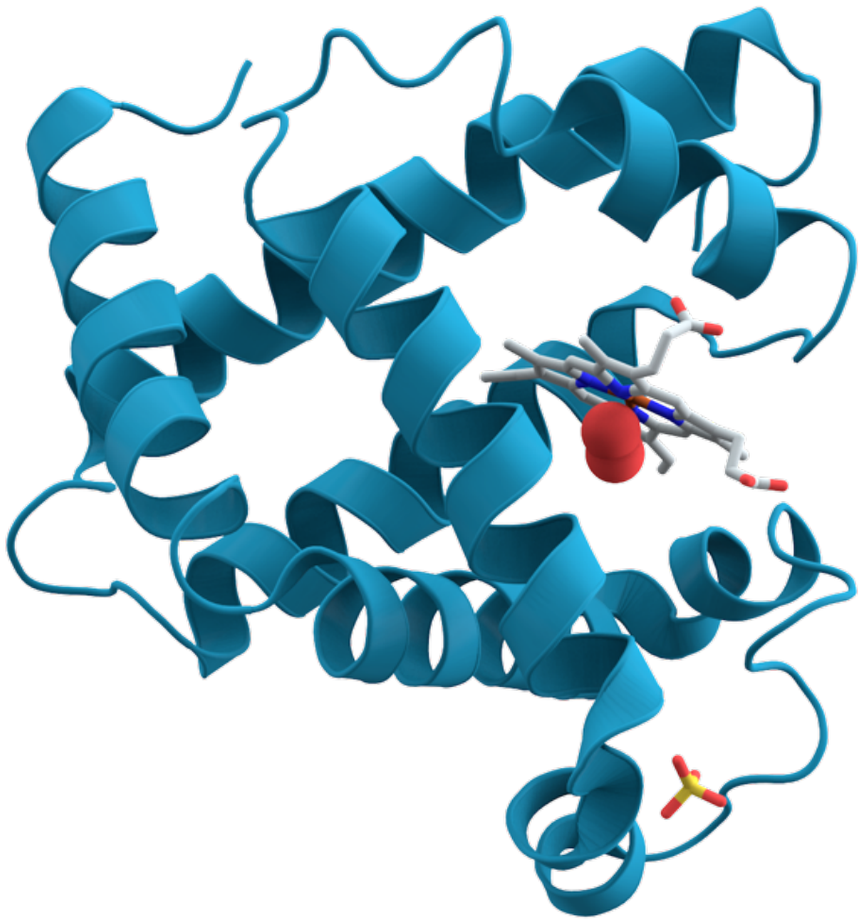
chr2 U207

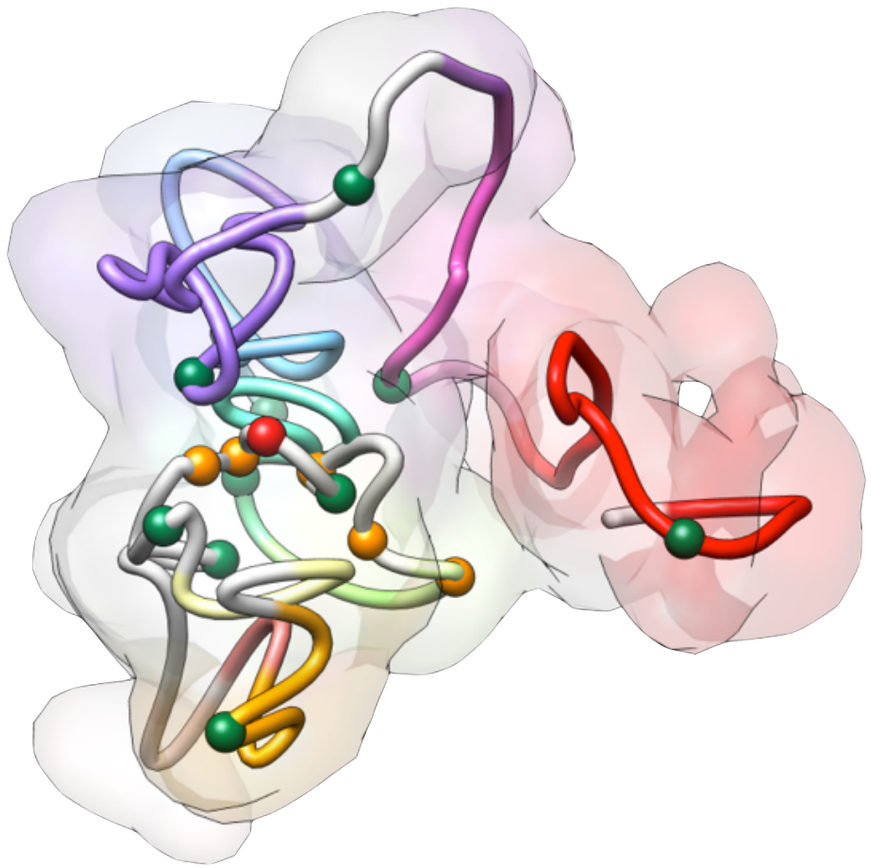


DHS HP1 H1.2 H2A MNAse H3K27me3 H3K9m3 H3K14ac H3K4me1 H3K36me2 H3K4me3



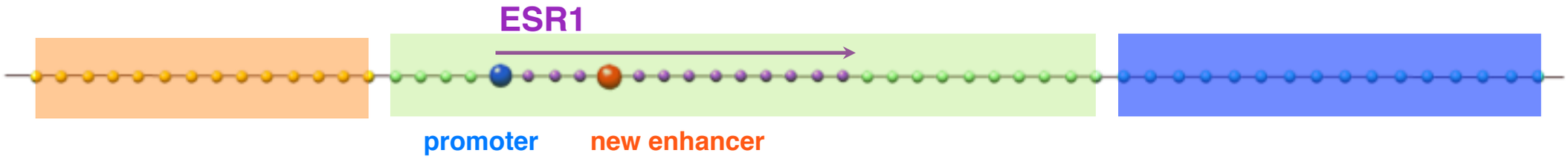


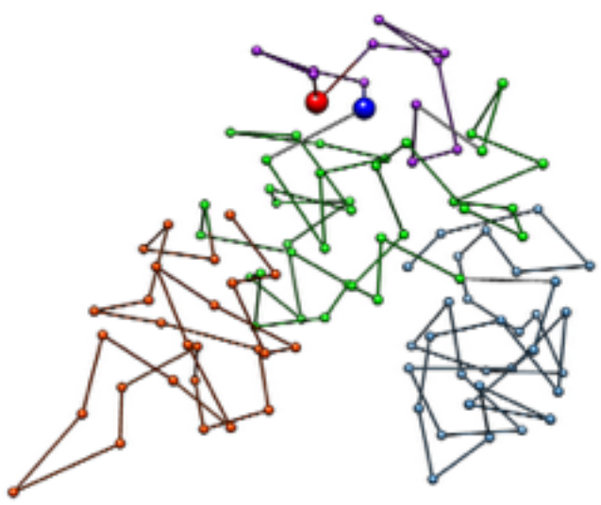




STRUCTURE ⟷ FUNCTION

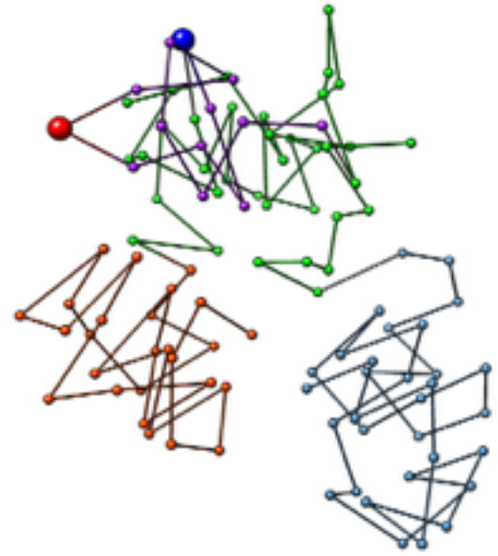
Structure >> Function!

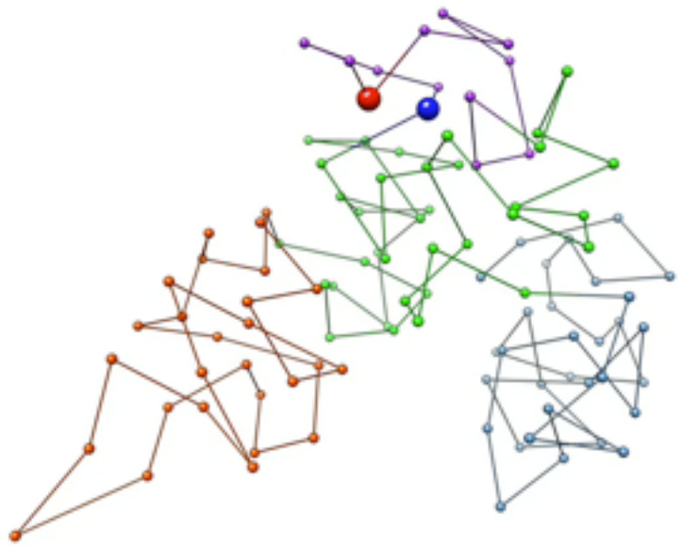




+Pg

represses
ESR1 gene





Open positions soon
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Job Dekker
Program in Systems Biology
Department of Biochemistry and Molecular Pharmacology
University of Massachusetts Medical School
Worcester, MA, USA

Kerstin Bystricky
Chromatin and gene expression
Laboratoire de Biologie Moléculaire Eucaryote - CNRS
Toulouse, France

Miguel Beato & Guillaume Filion
Gene Regulation, Stem Cells and Cancer
Centre de Regulació Genòmica
Barcelona, Spain

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