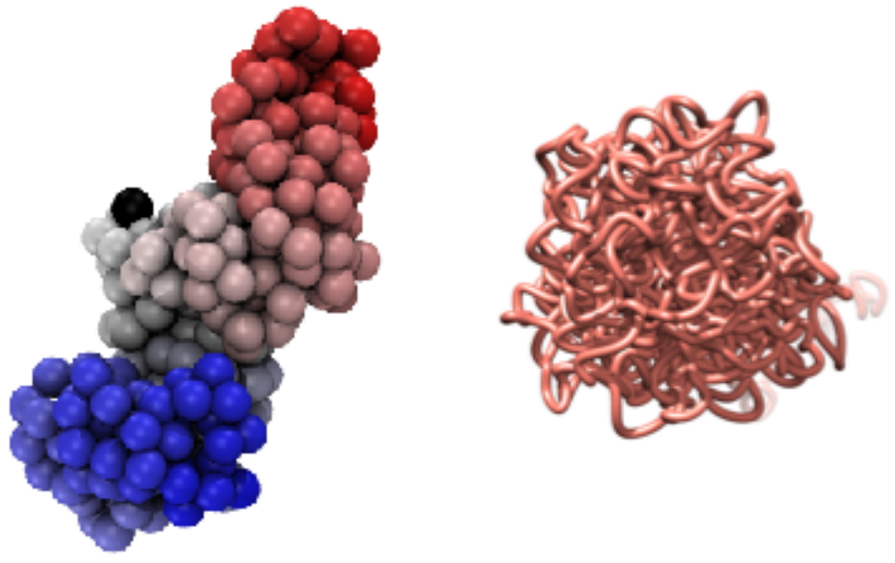
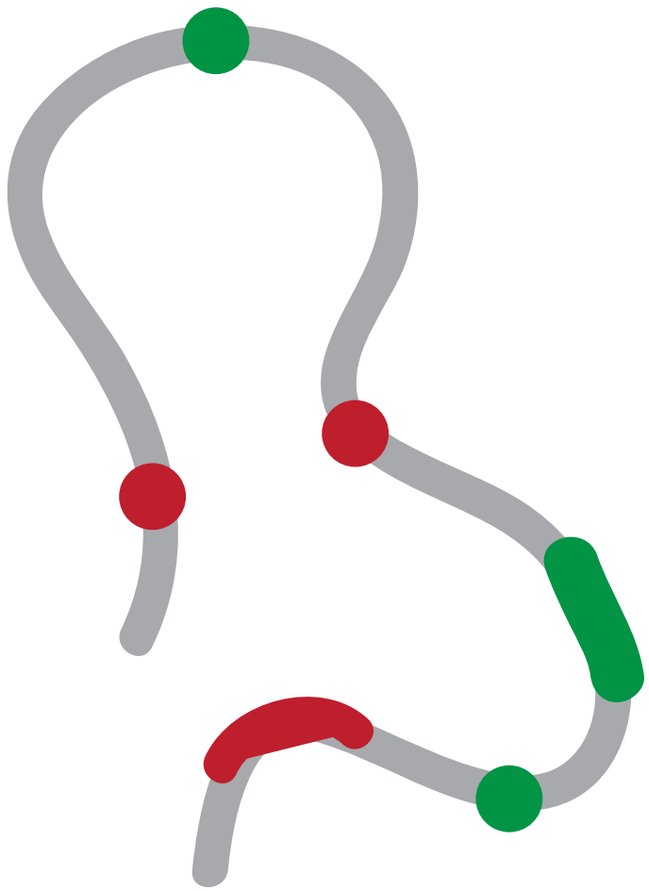
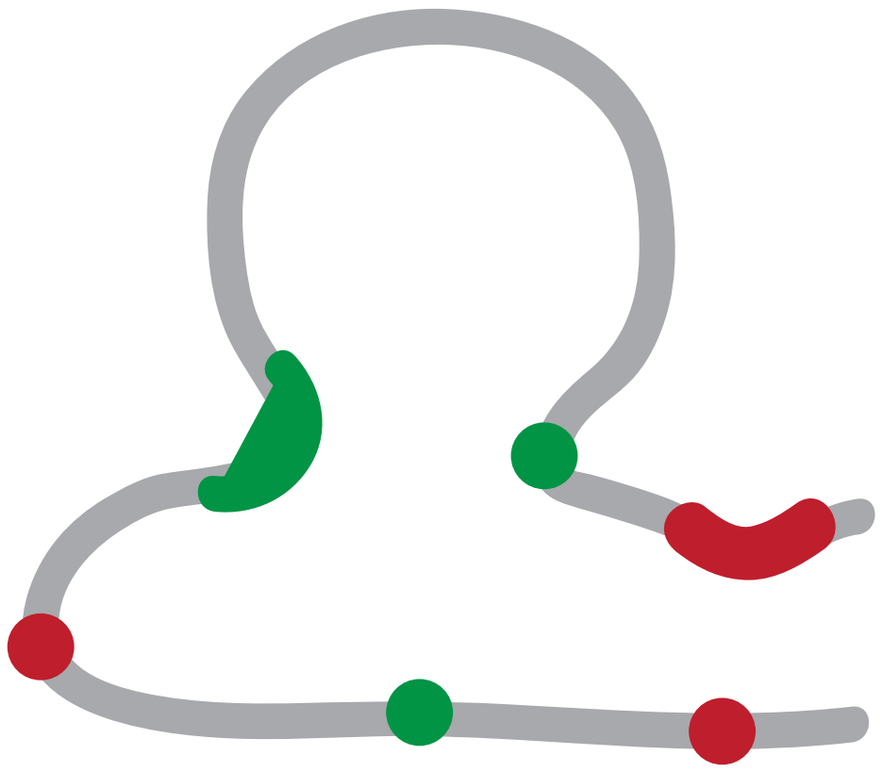
Genome structure dynamics using sparse interaction datasets

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



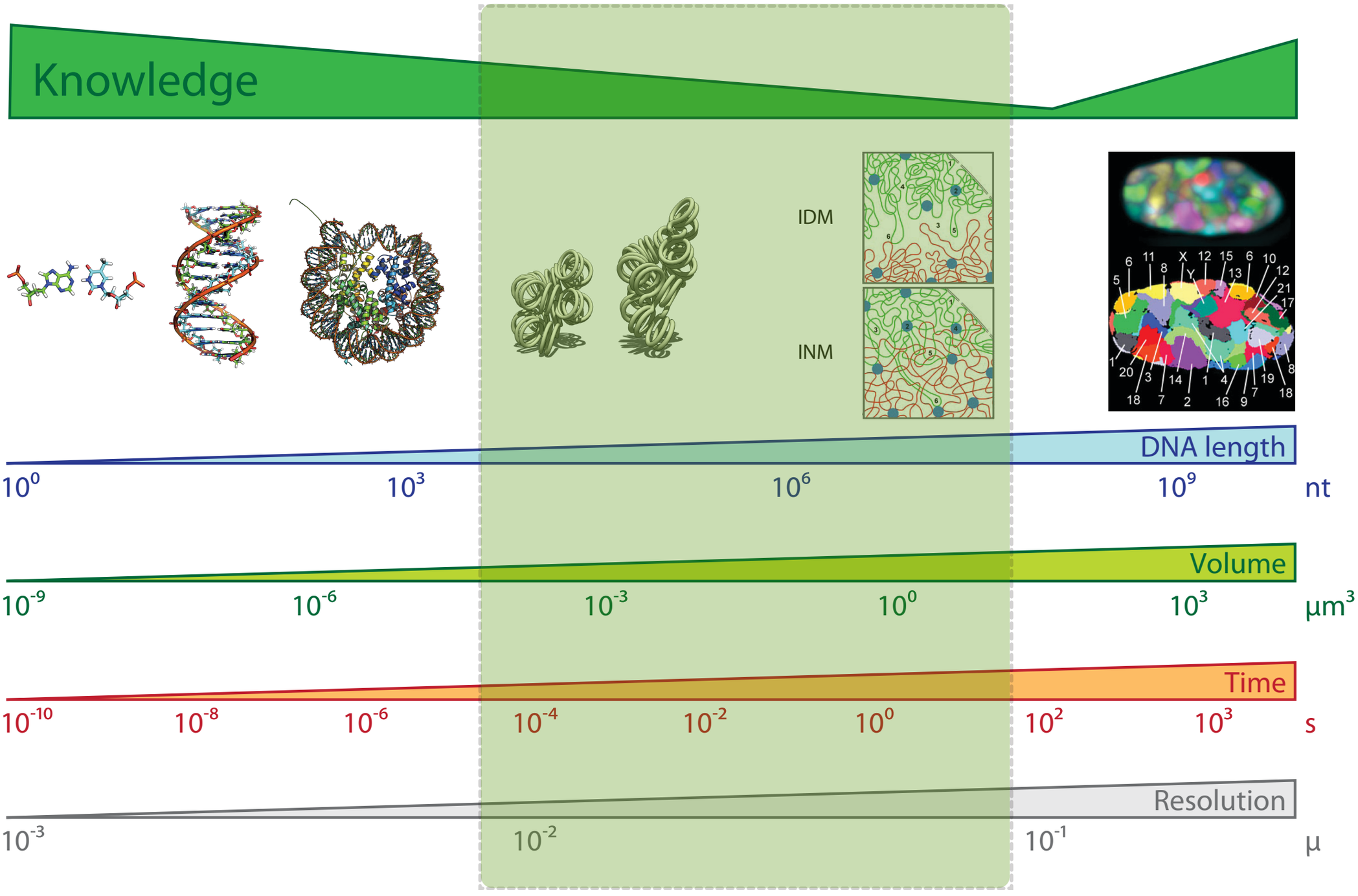
http://marciuslab.org
http://3DGenomes.org
http://cnag.crg.eu





Resolution Gap

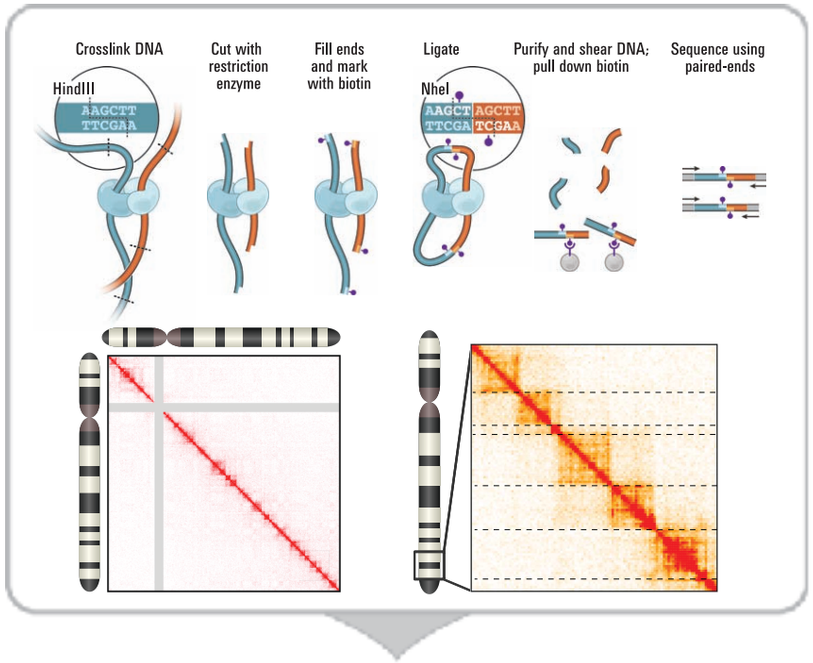
Marti-Renom, M. A. & Mirny, L. A. PLoS Comput Biol *7*, e1002125 (2011)

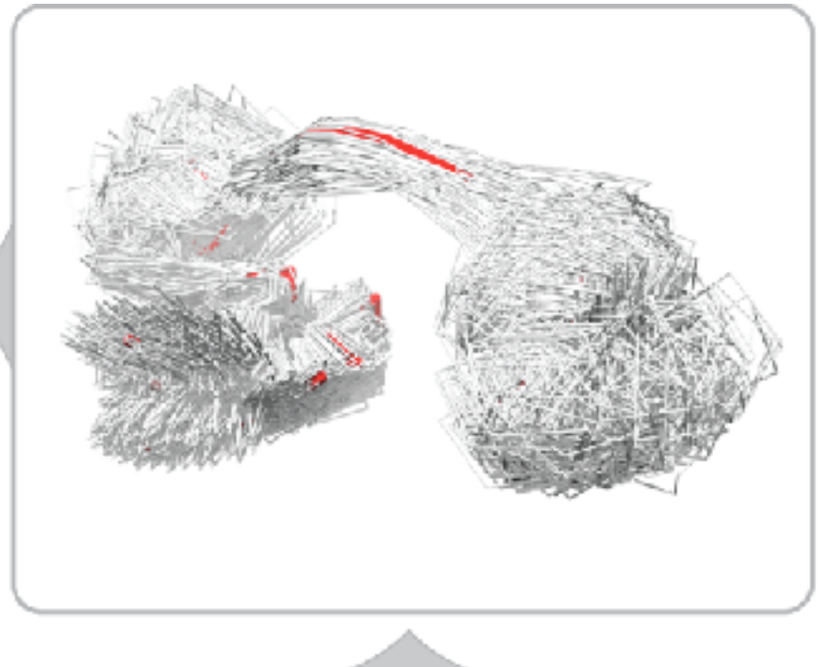


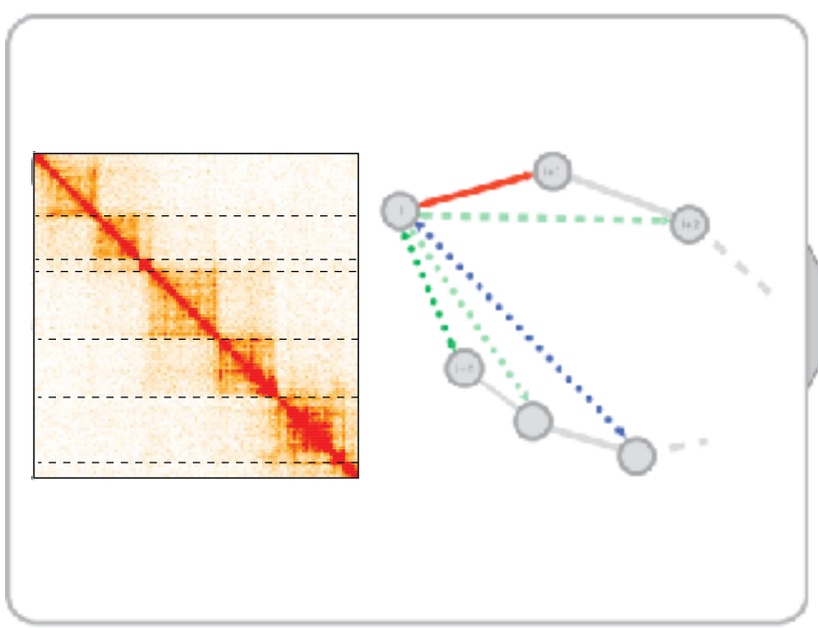
Hybrid Method

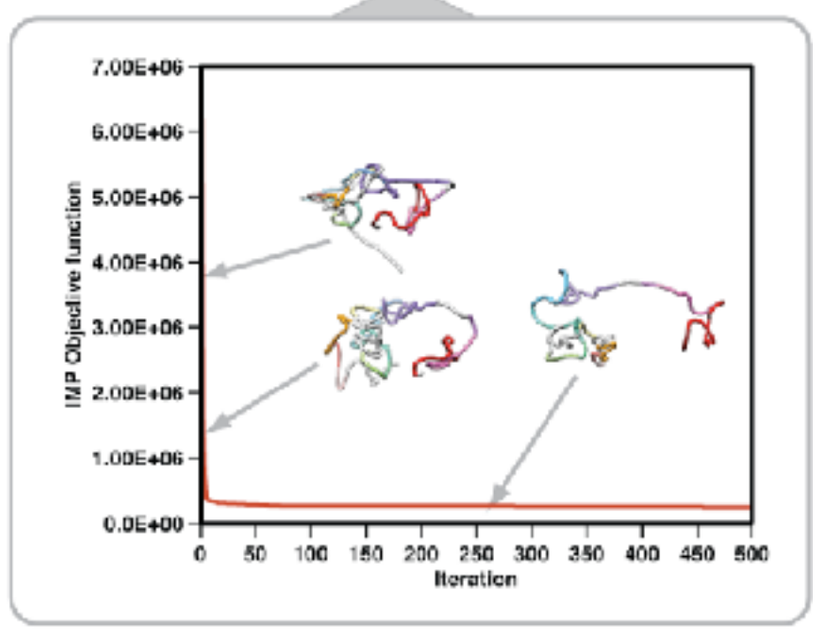
Baù, D. & Marti-Renom, M. A. Methods 58, 300–306 (2012).

Experiments





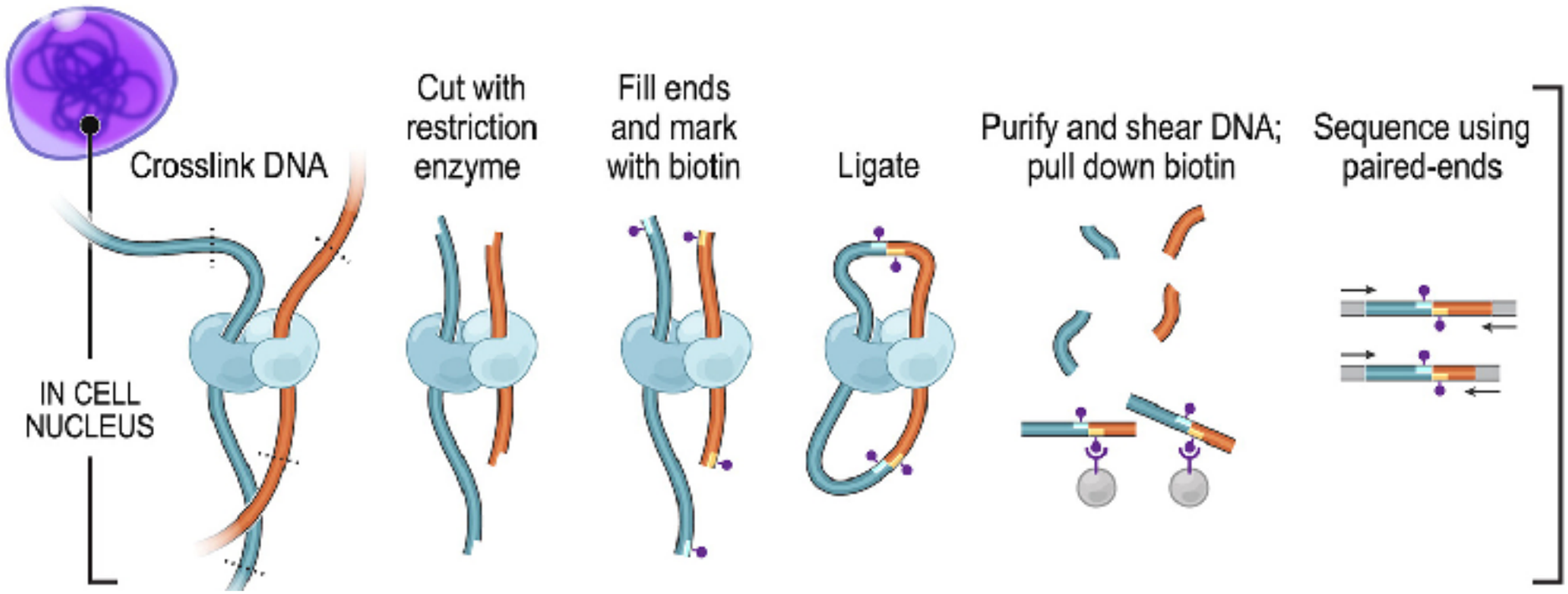


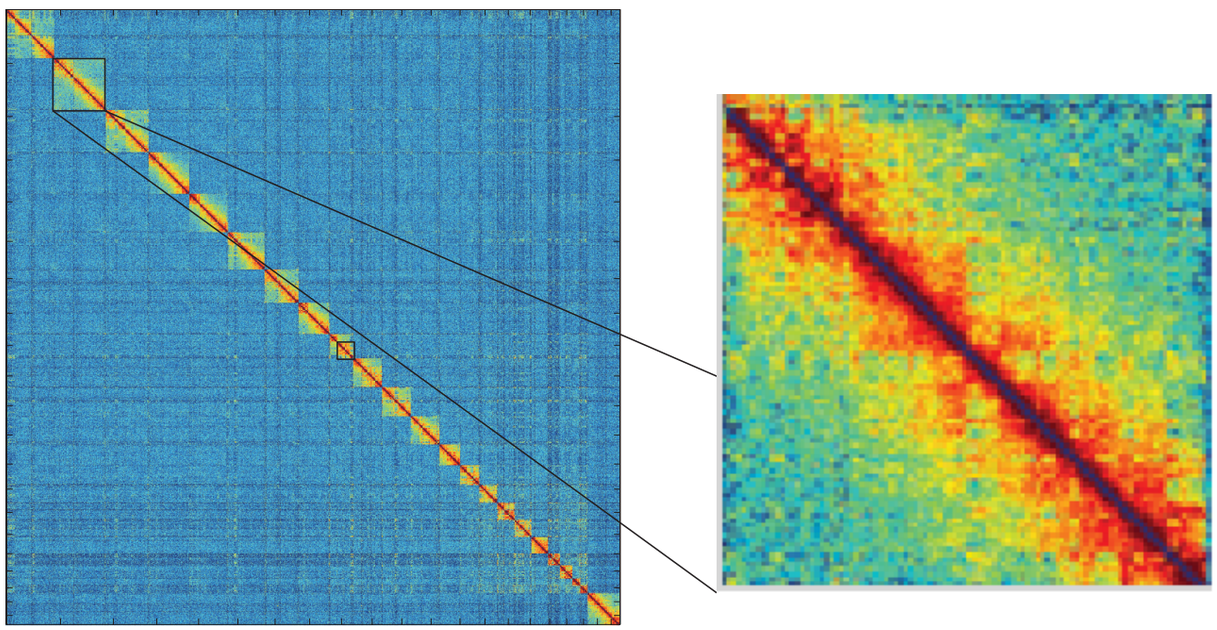


Computation

Chromosome Conformation Capture

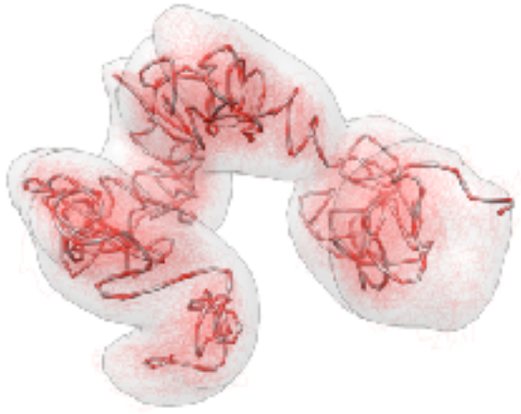
Dekker, J., Rippe, K., Dekker, M., & Kleckner, N. (2002). Science, 295(5558), 1306–1311.
Lieberman-Aiden, E., et al. (2009). Science, 326(5950), 289–293.

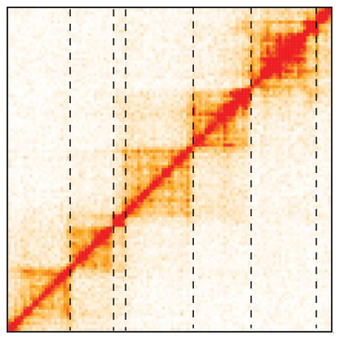




Restraint-based Modeling

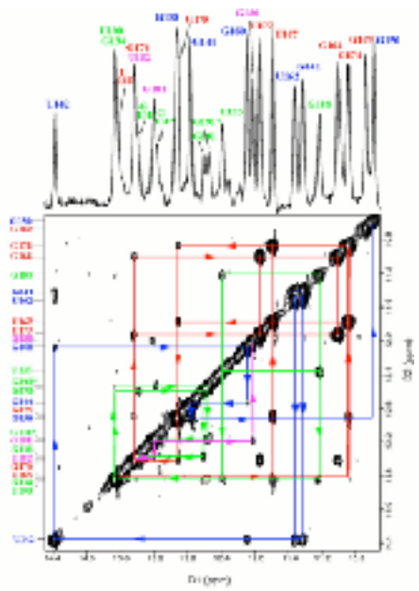
Baù, D. & Marti-Renom, M. A. Methods 58, 300–306 (2012).





Chromosome structure determination

3C-based data



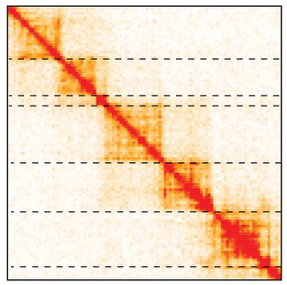
Biomolecular structure determination

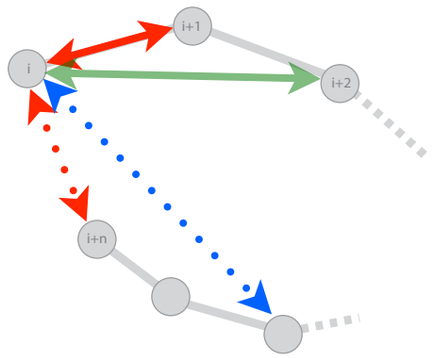
2D-NOESY data

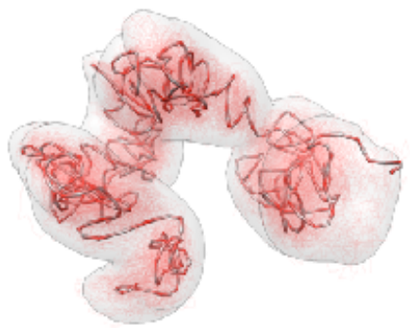
TADbit

http://3DGenomes.org

Serra, F., Baù, D. et al. PLOS CB (2017)







FastQ files to Maps

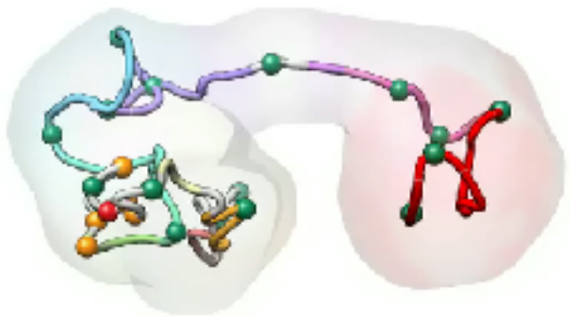
Map analysis

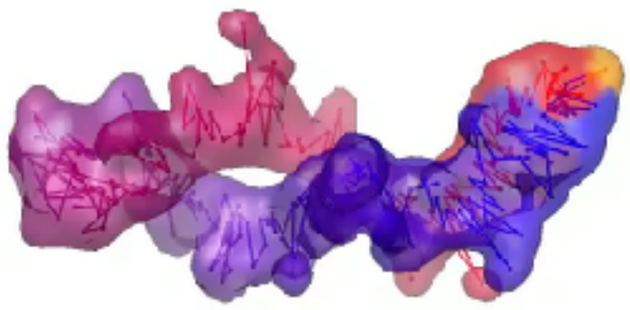
Model building

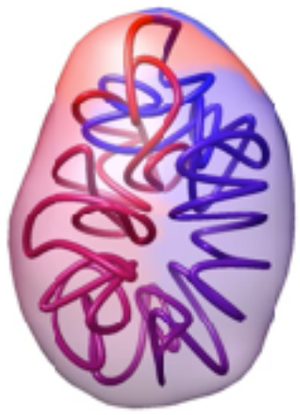
Model analysis

TADbit previous applications...

Baù, D. et al. Nat Struct Mol Biol (2011)
Umbarger, M. A. et al. Mol Cell (2011)
Le Dily, F. et al. Genes & Dev (2014)
Trussart M. et al. Nature Communication (2017)
Cattoni et al. Nature Communication (2017)
Stadhouders, R., Vidal, E. et al. Nature Genetics (2018)

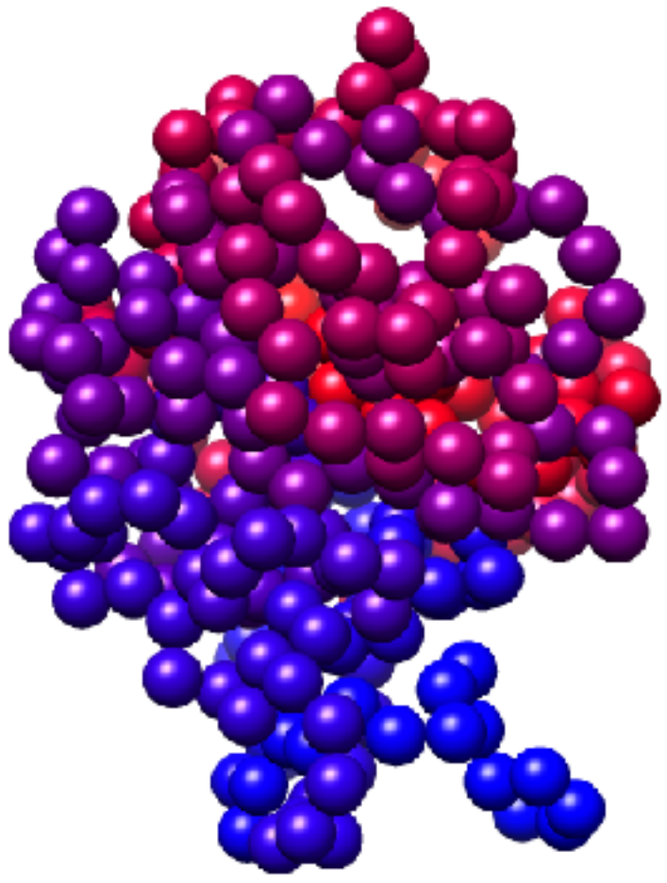






TADdyn. Dynamics of chromatin

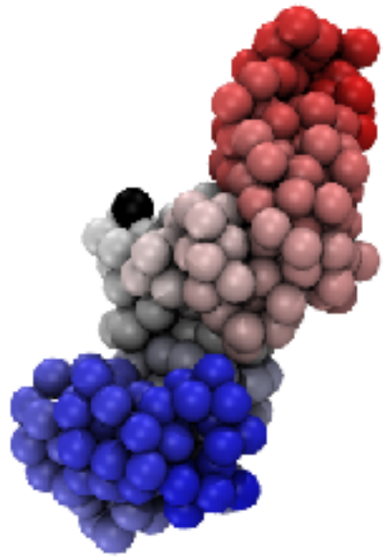
Marco Di Stefano



$$\mathcal{H}_{intra} = \sum_{i=1}^{N} U_{FENE}\,(i, i+1) + U_{br}(i, i+1, i+2) + \sum_{j=i+1}^{N} U_{LJ}(i, j)$$

Chain-connectivity interaction
Bending
Lennard-Jones Potential

Exploring the time dependent structural rearrangements of SOX2 locus during transdifferentiation

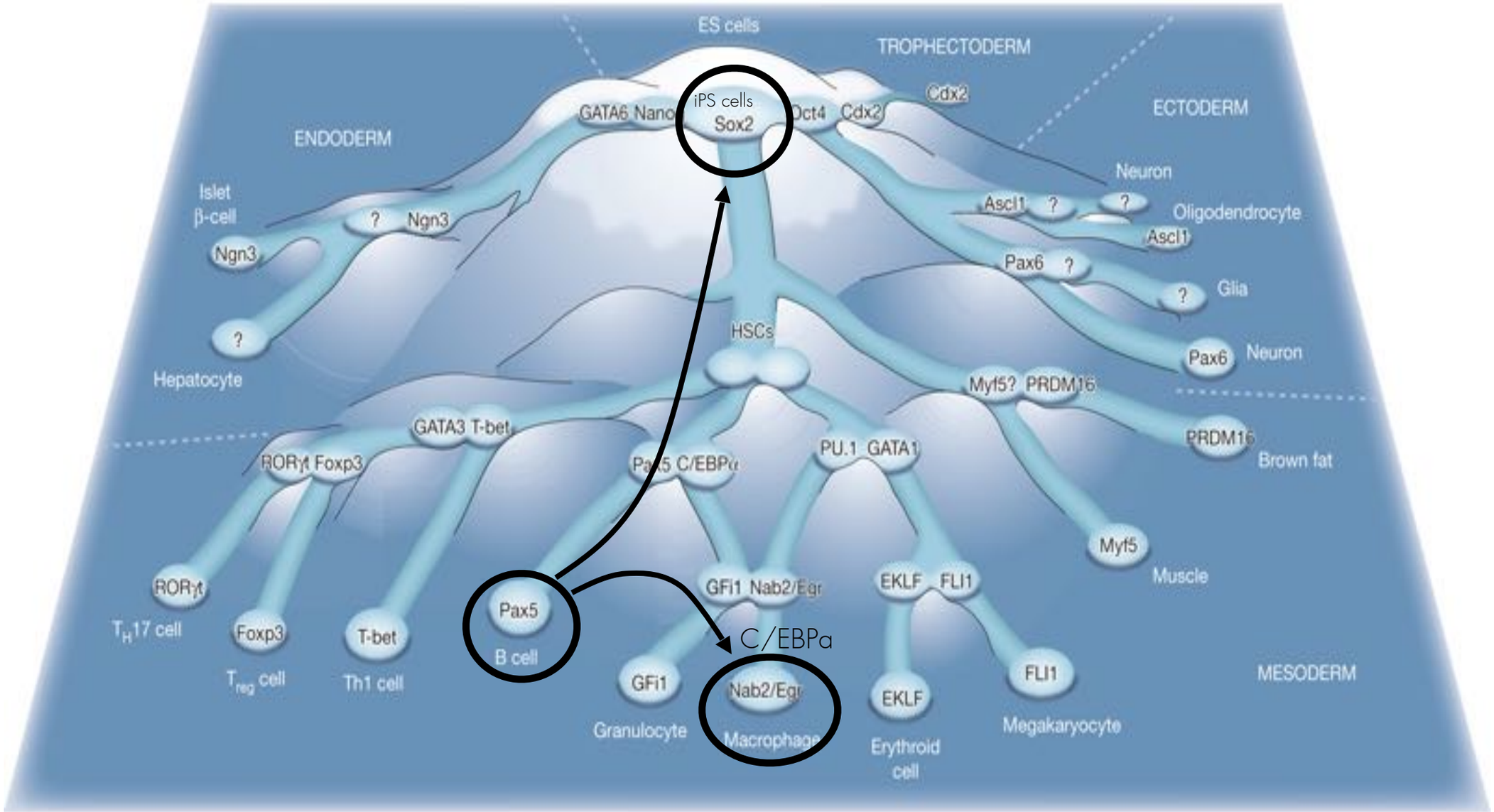


Stadhouders, R., Vidal, E. et al. (2018) Nature Genetics

Marco di Stefano

Transcription factors dictate cell fate

Graf & Enver (2009) Nature



Transcription factors (TFs) determine cell identity through gene regulation

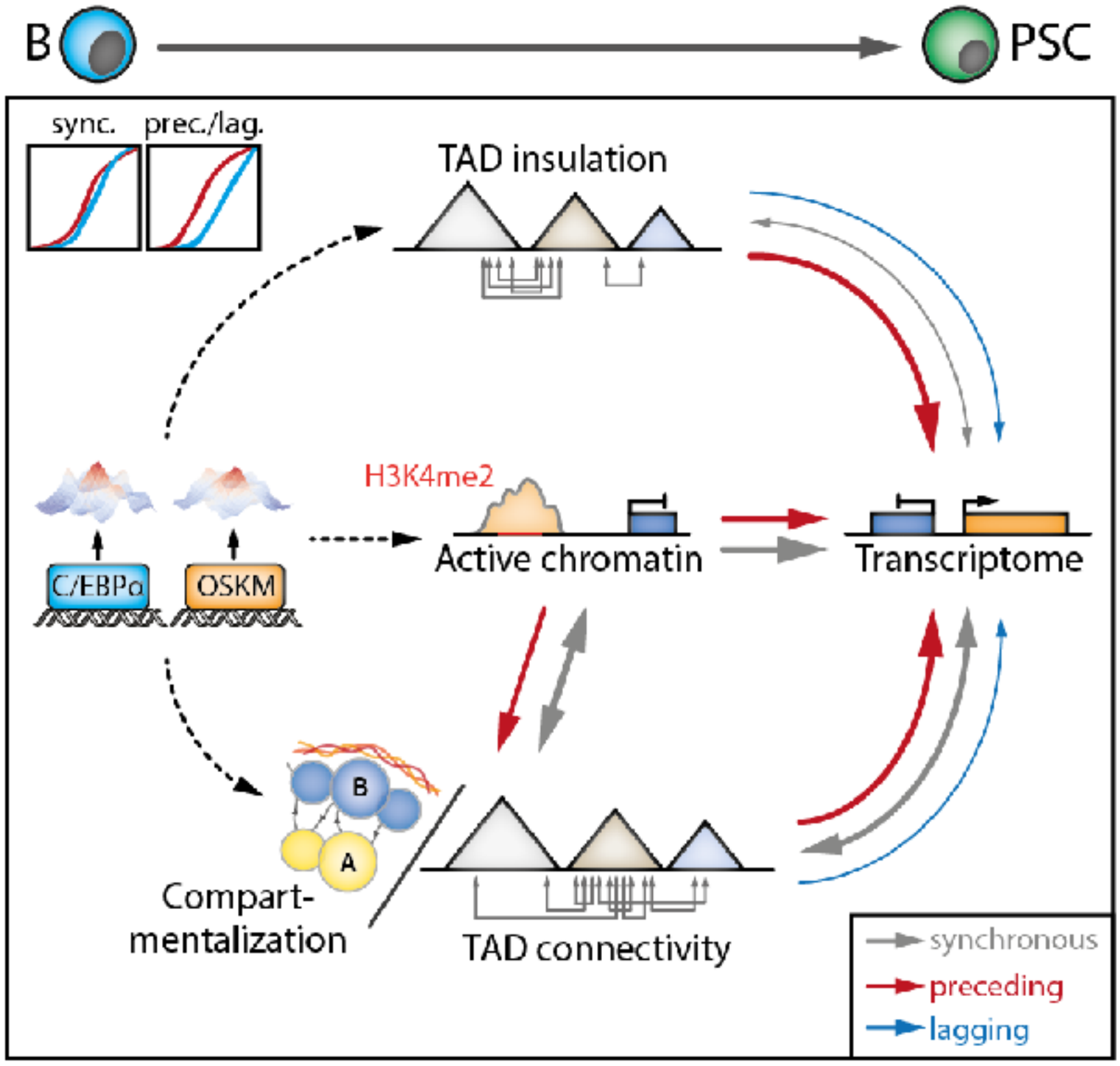
Normal 'forward' differentiation

Cell fates can be converted by enforced TF expression

Transdifferentiation or reprogramming

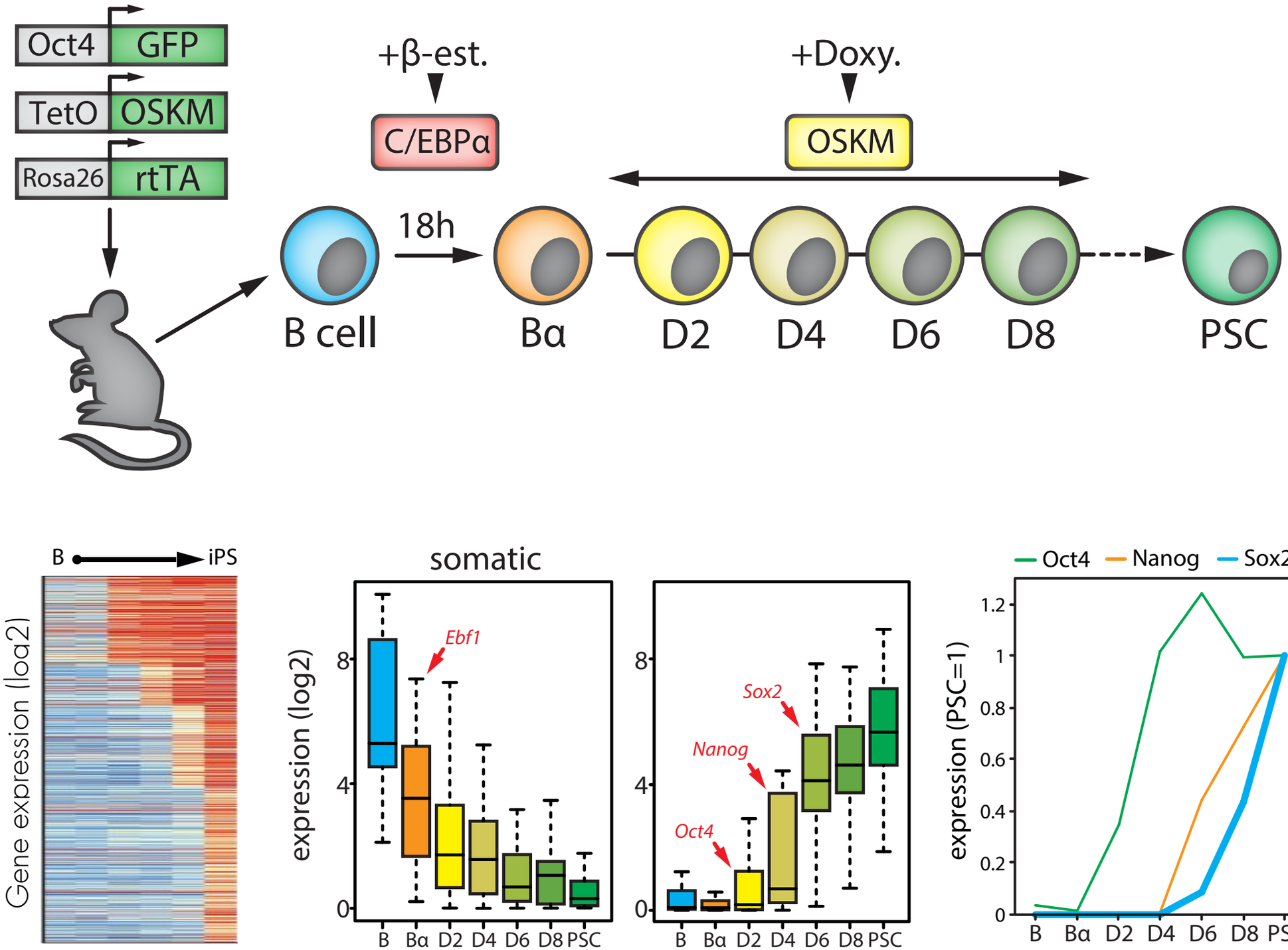
Interplay: topology, gene expression & chromatin

Stadhouders, R., Vidal, E. et al. (2018) Nature Genetics



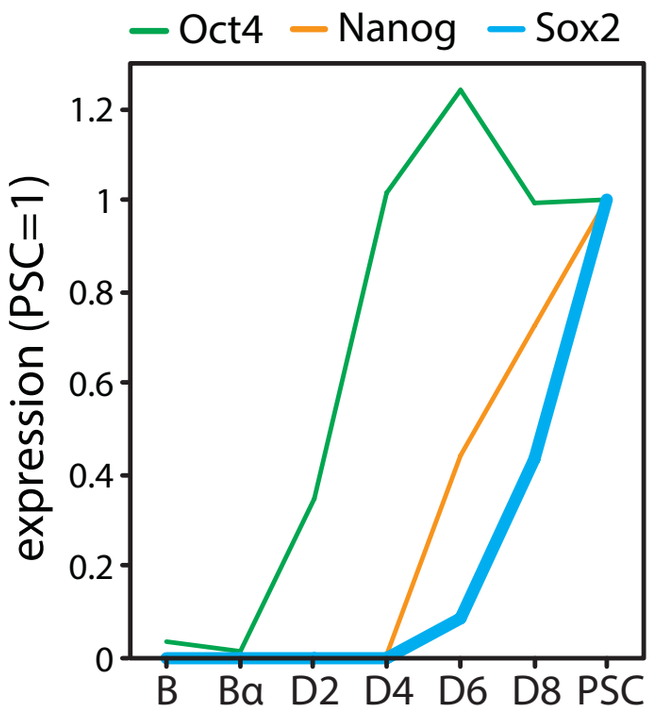
Reprogramming from B to PSC

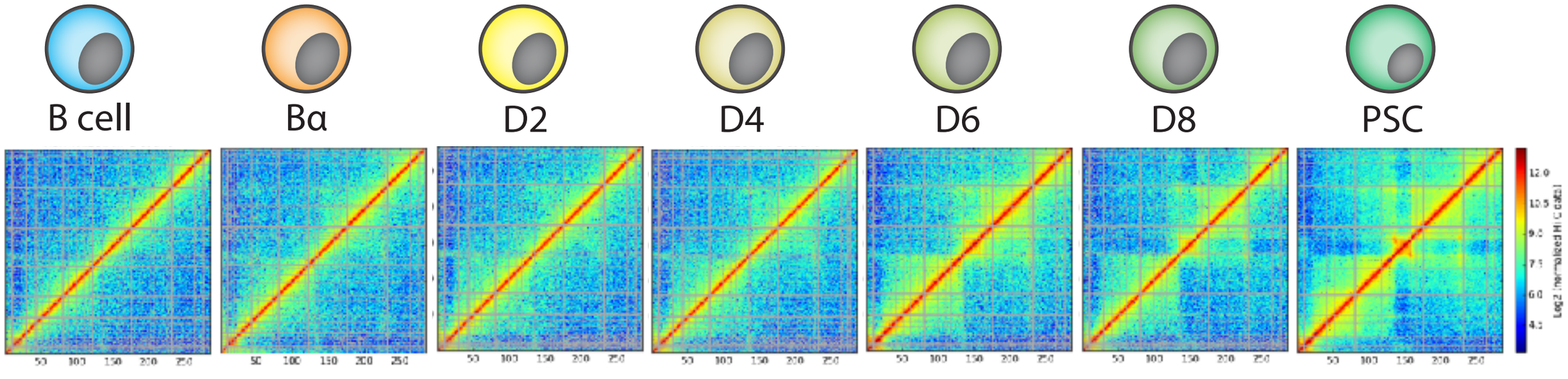
Stadhouders, R., Vidal, E. et al. (2018) Nature Genetics



Hi-C maps of reprogramming from B to PSC

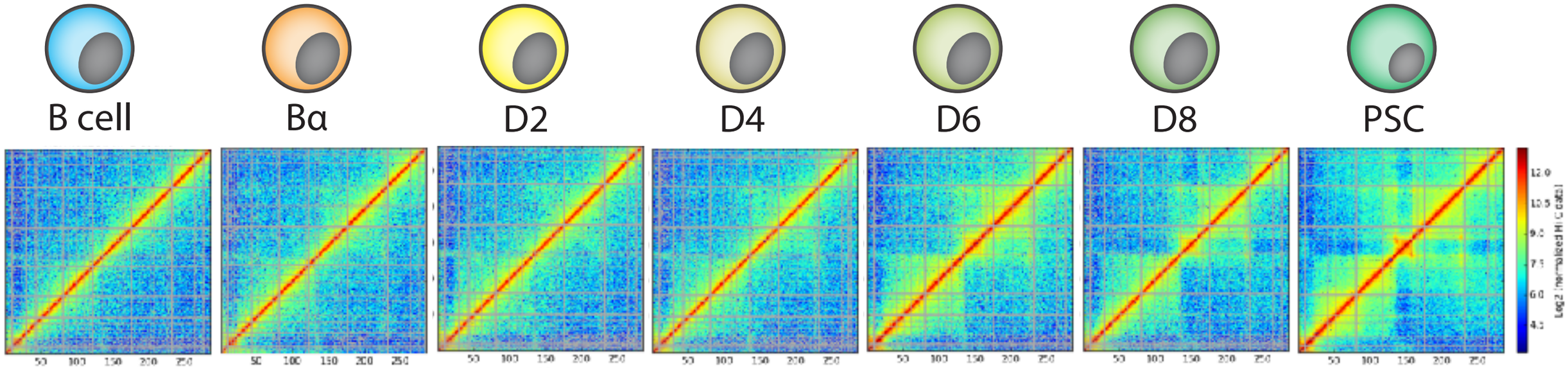
The SOX2 locus





Hi-C maps of reprogramming from B to PSC

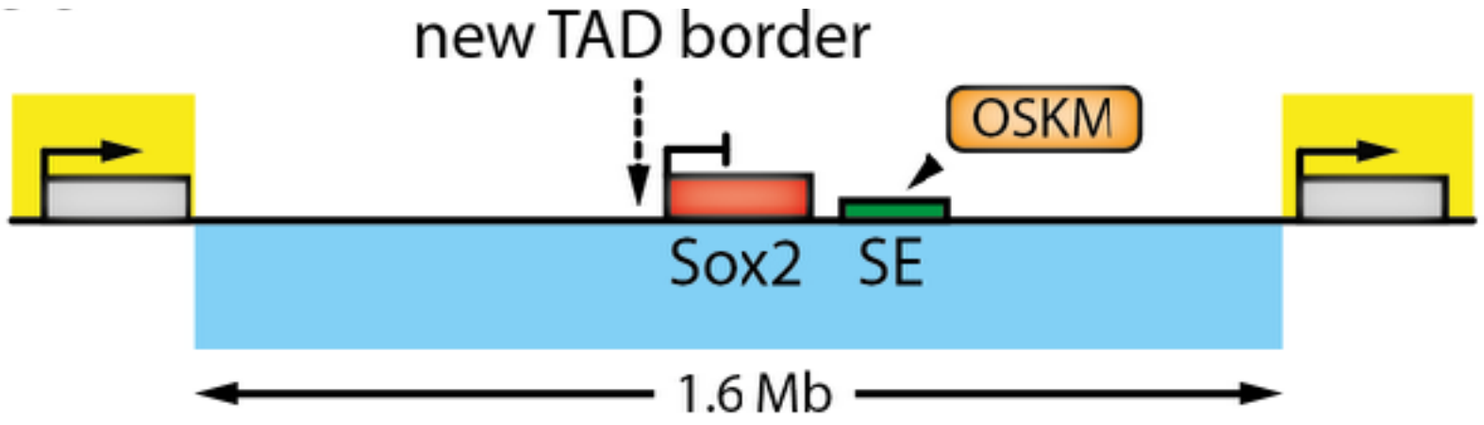
The SOX2 locus

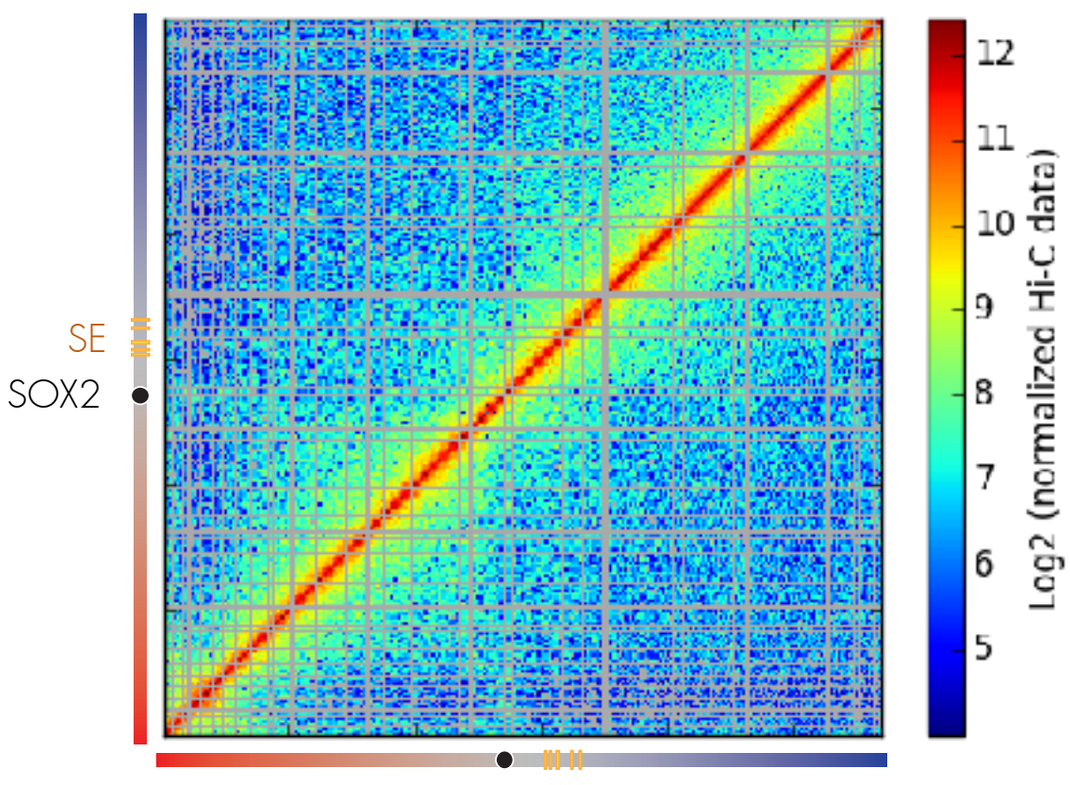


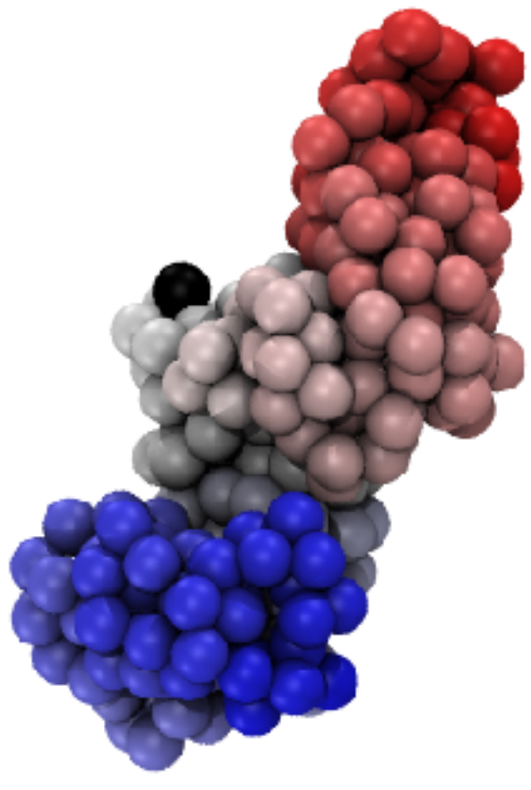
How does these structural rearrangements interplay with the transcription activity?

What are the main drivers of structural transitions?

TADbit modeling of SOX2 from B cells Hi-C





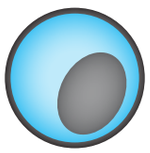


Optimal IMP parameters

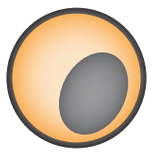
lowfreq=0 , upfreq=1 , maxdist=200nm, dcutoff=125nm, particle size=50nm (5kb)

Models of reprogramming from B to PSC

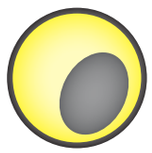
The SOX2 locus



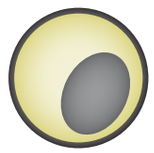
B cell



Bα

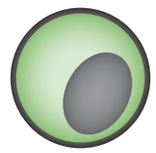


D2

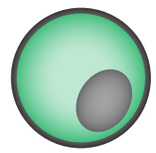


D4

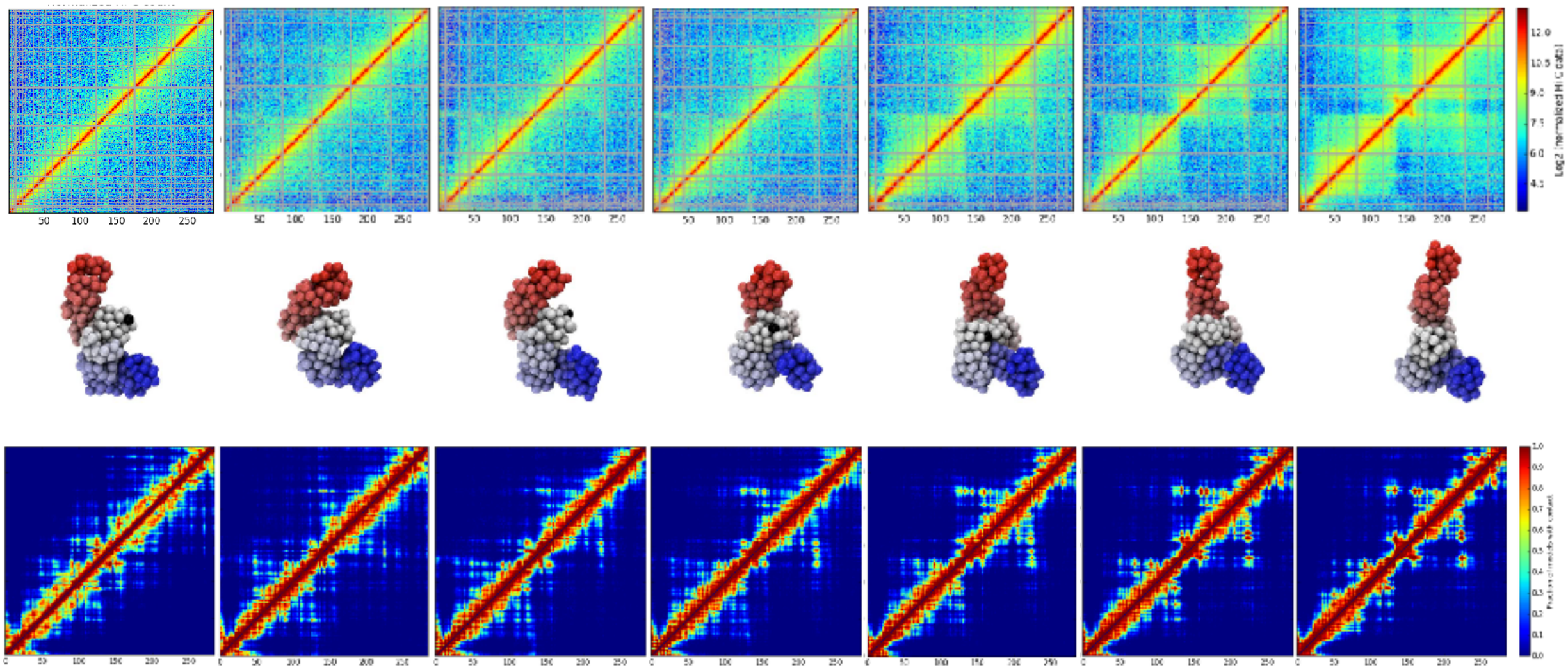
D6



D8

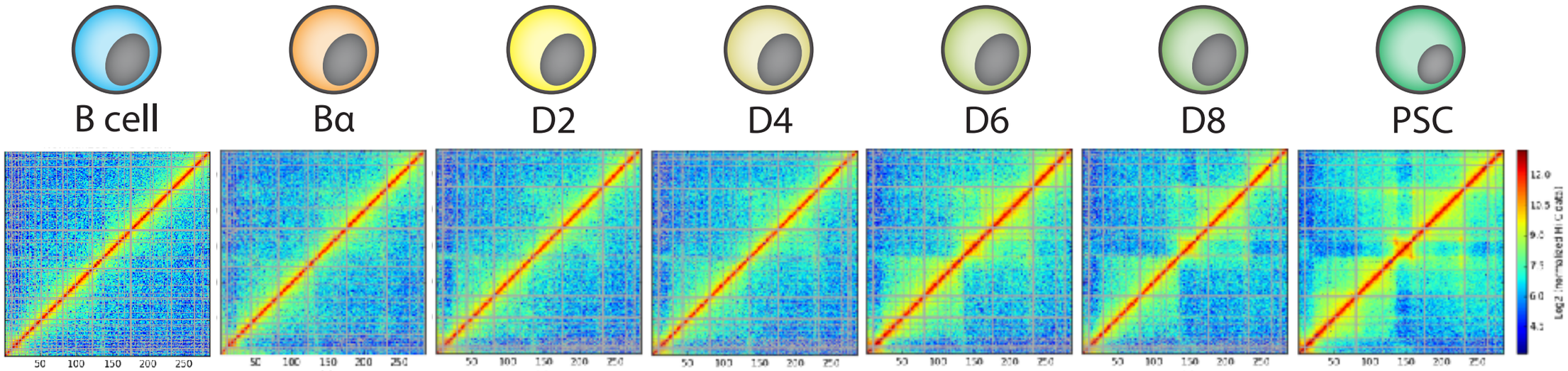


PSC



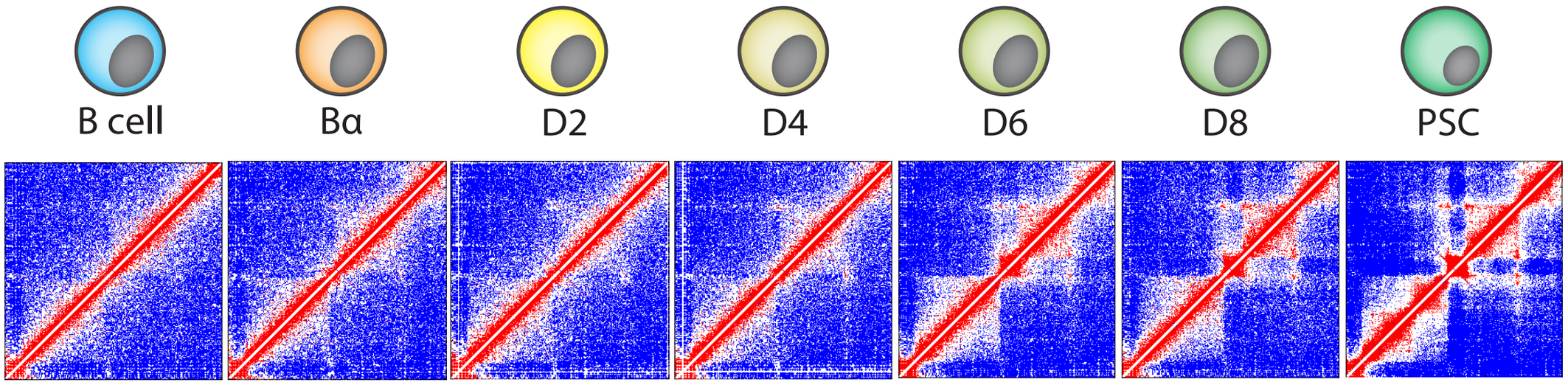
TADdyn: from time-series Hi-C maps to dynamic restraints

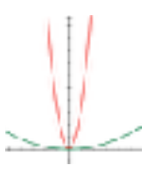
The SOX2 locus



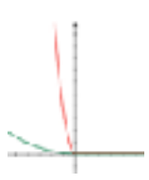
TADdyn: from time-series Hi-C maps to dynamic restraints

The SOX2 locus





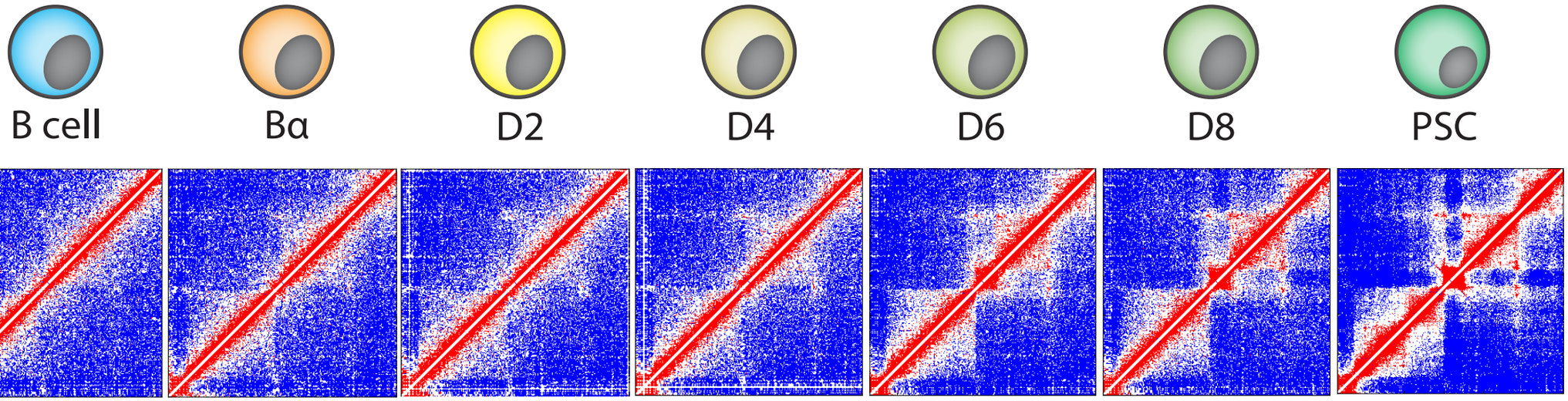
Harmonic

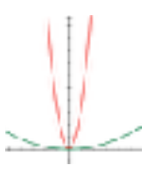


HarmonicLowerBound

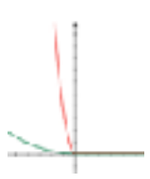
TADdyn: from time-series Hi-C maps to dynamic restraints

The SOX2 locus

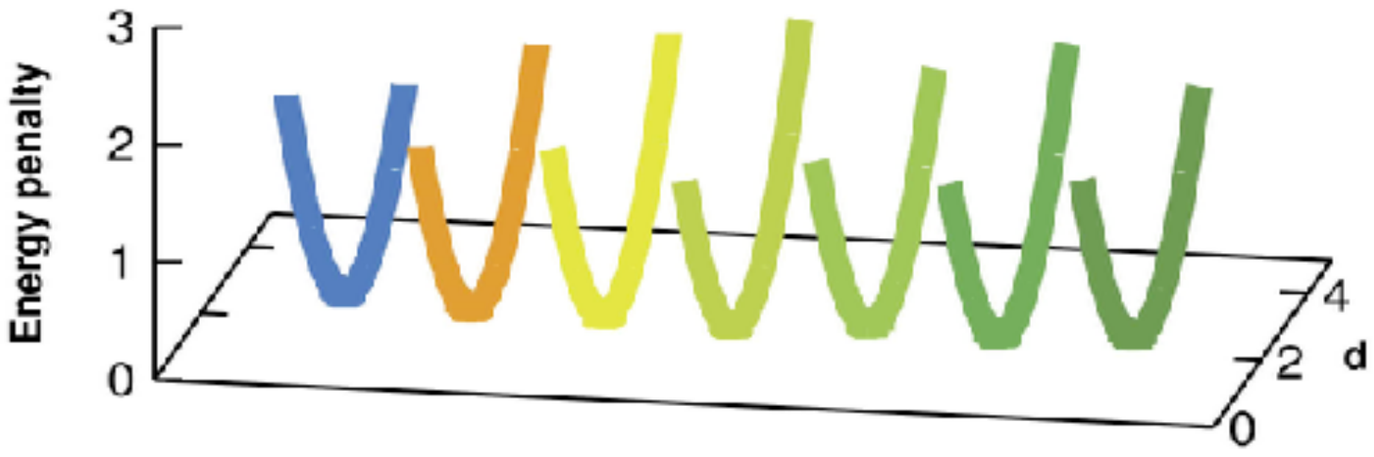




Harmonic



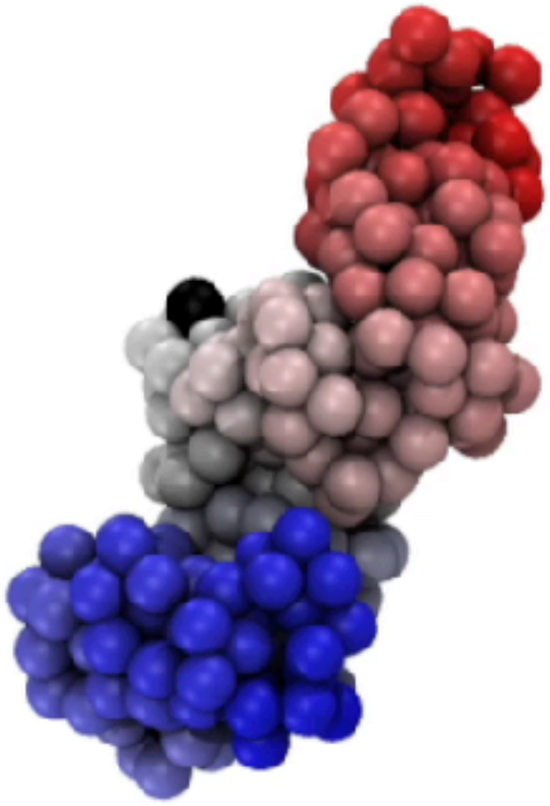
HarmonicLowerBound

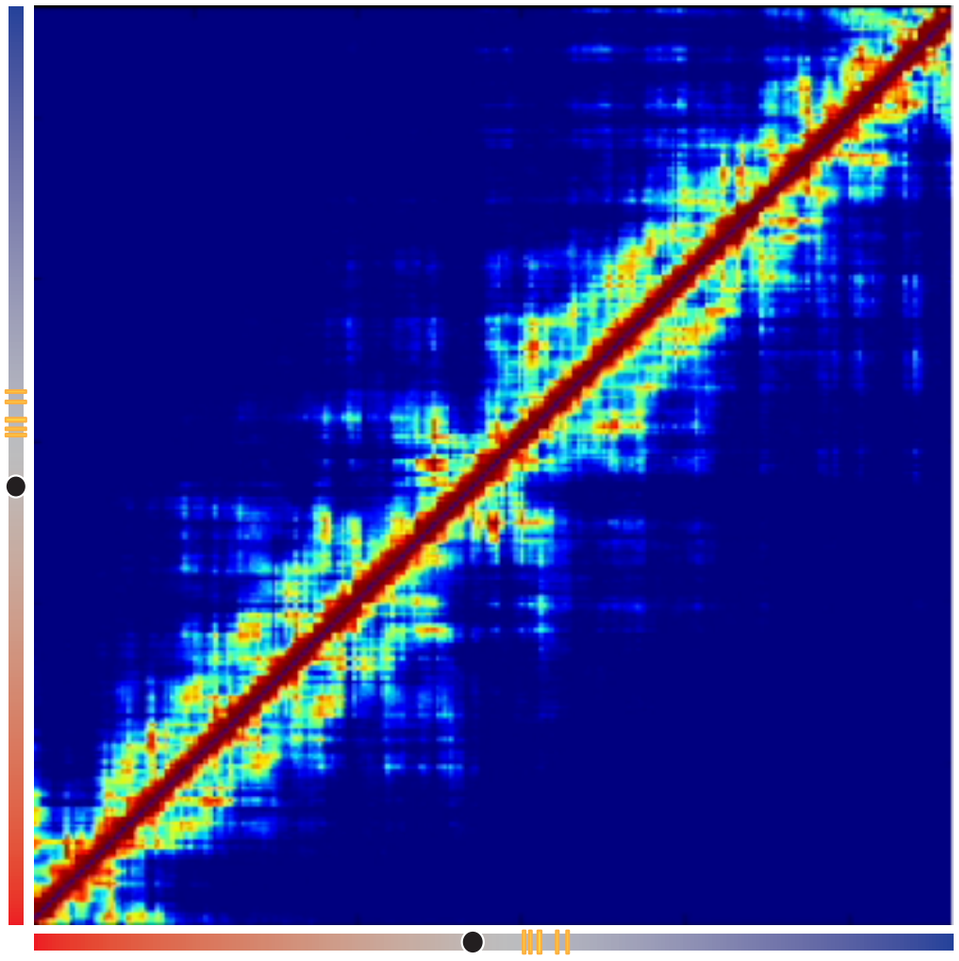


Transition	Stable	Vanishing	Raising
B -> Bα	18,612	6,984	7,290
Bα -> D2	18,512	7,390	6,687
D2 -> D4	18,369	6,830	6,893
D4 -> D6	18,971	6,291	7,289
D6 -> D8	20,167	6,093	6,250
D8 -> ES	20,679	5,738	6,173

SOX2 locus structural changes from B to PSC

Contacts





SOX2 locus structural changes from B to PSC

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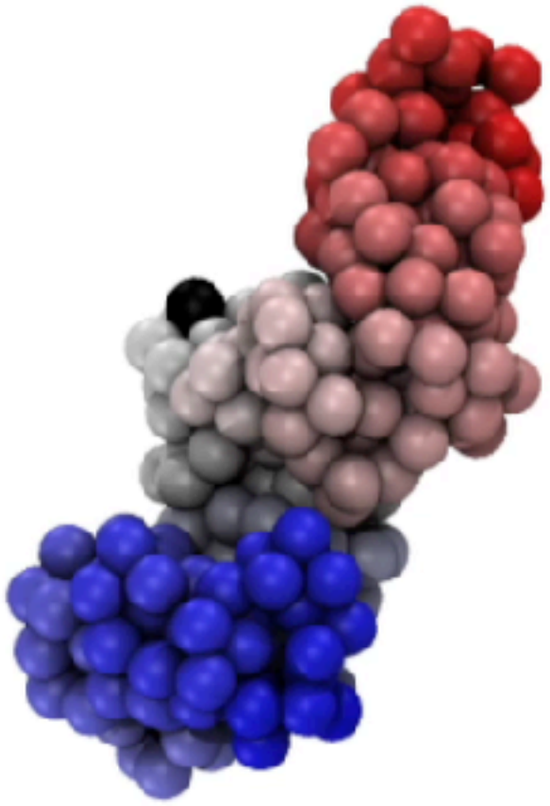
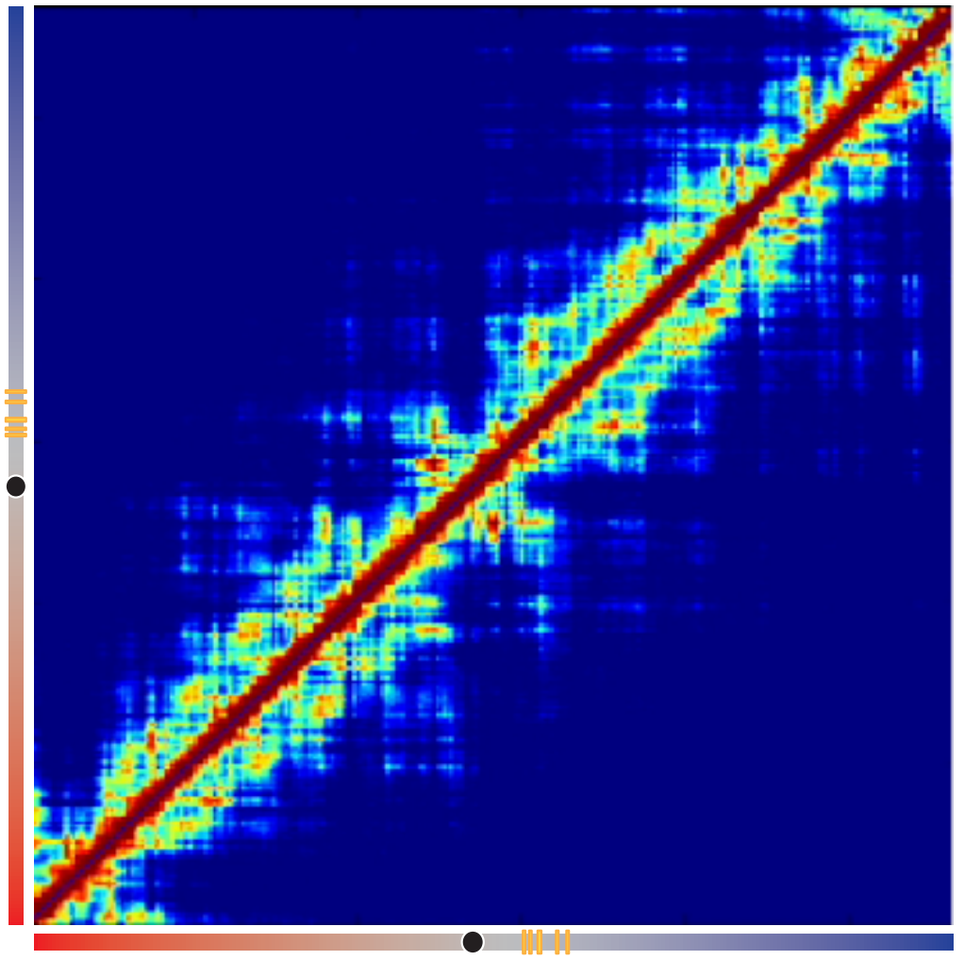
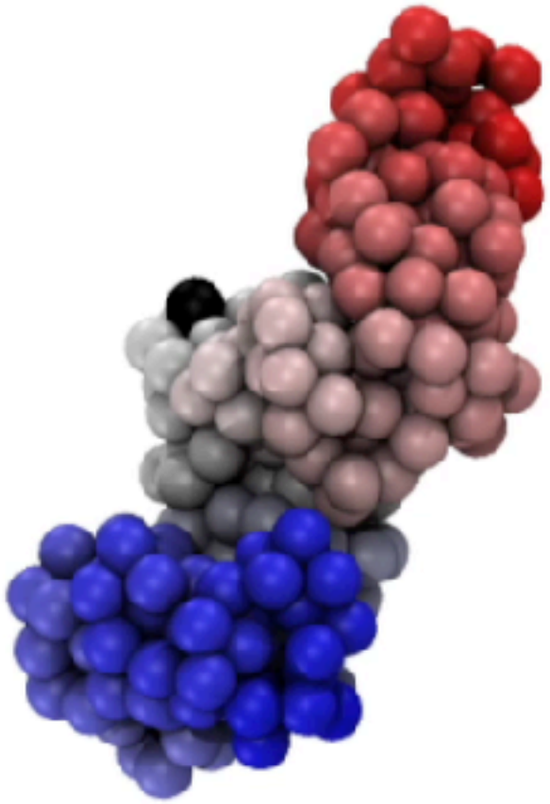
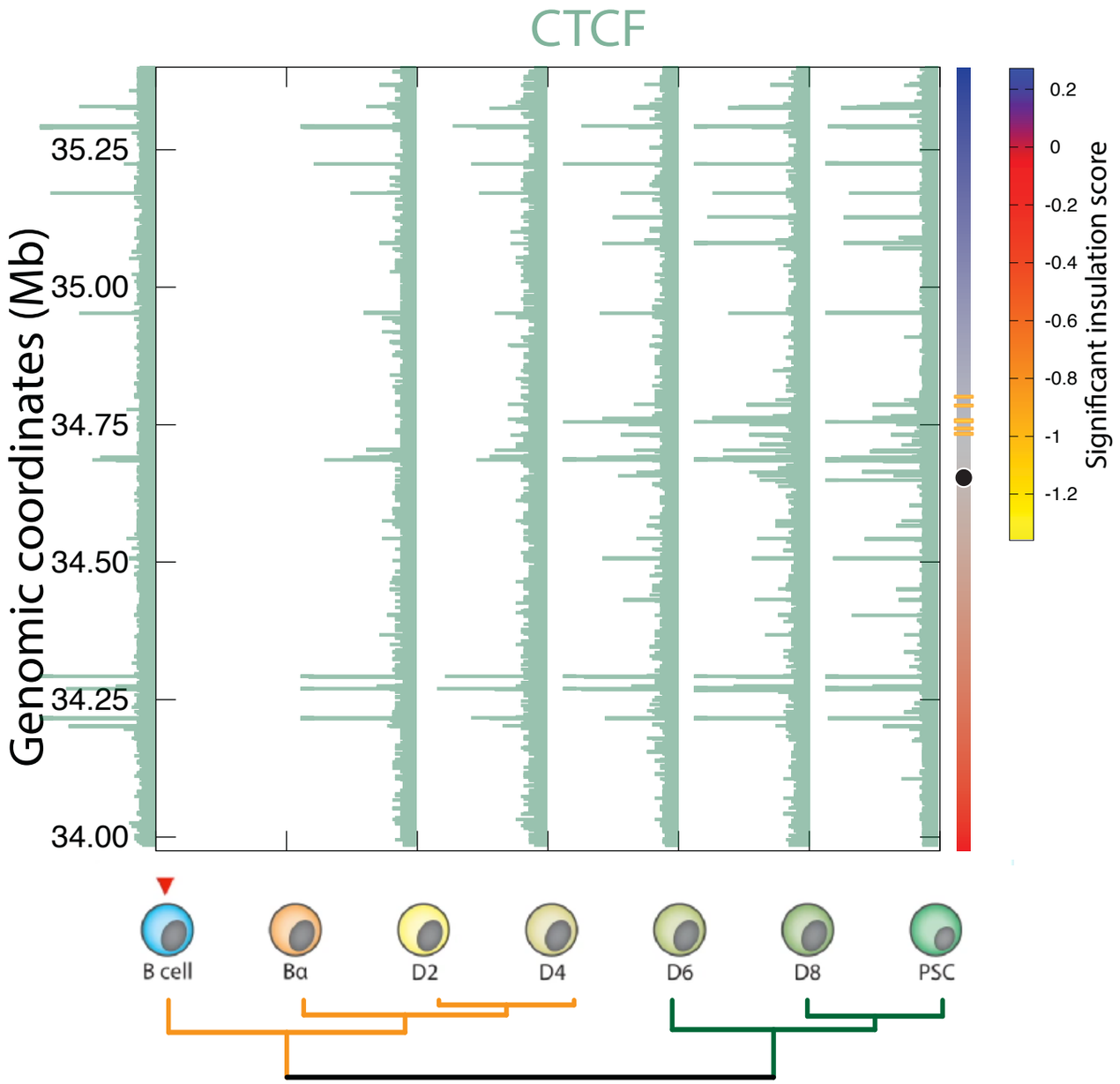




SOX2 locus structural changes from B to PSC

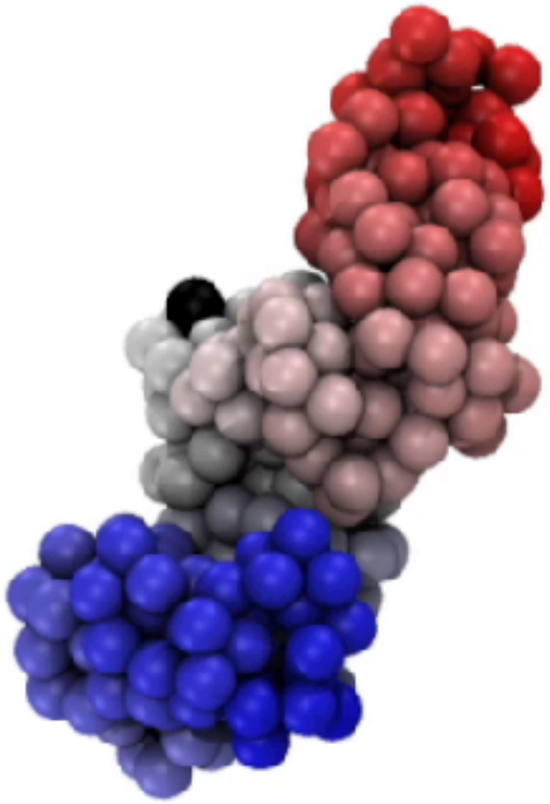
TAD borders

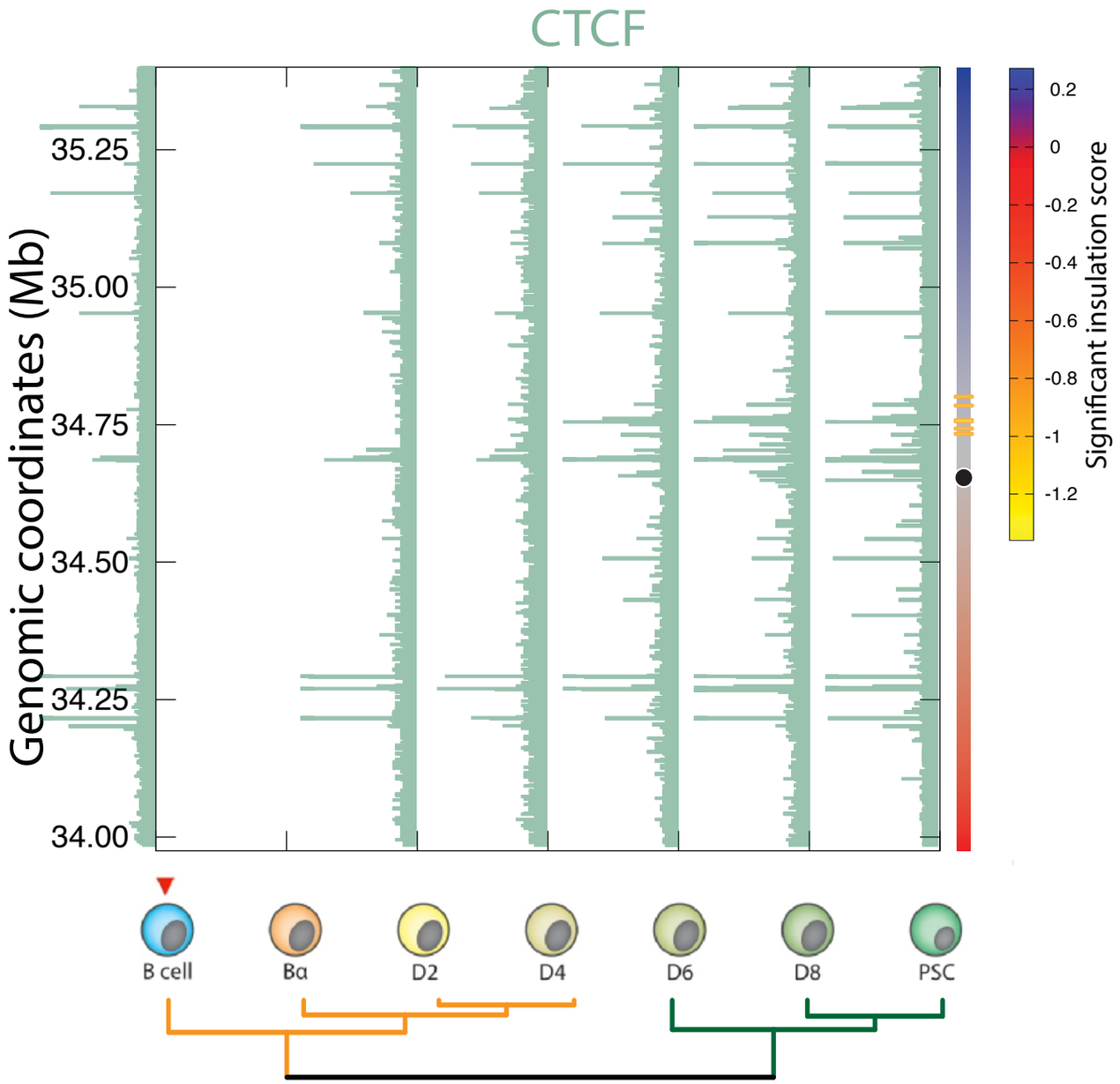




SOX2 locus structural changes from B to PSC

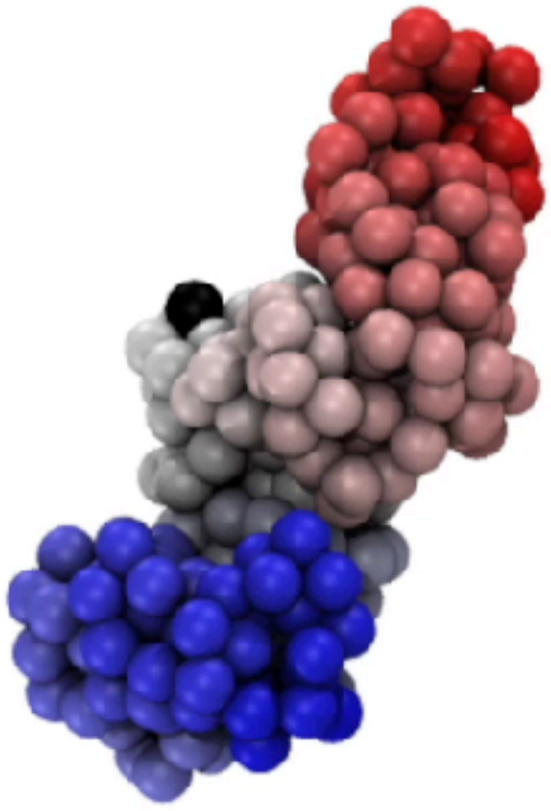
TAD borders

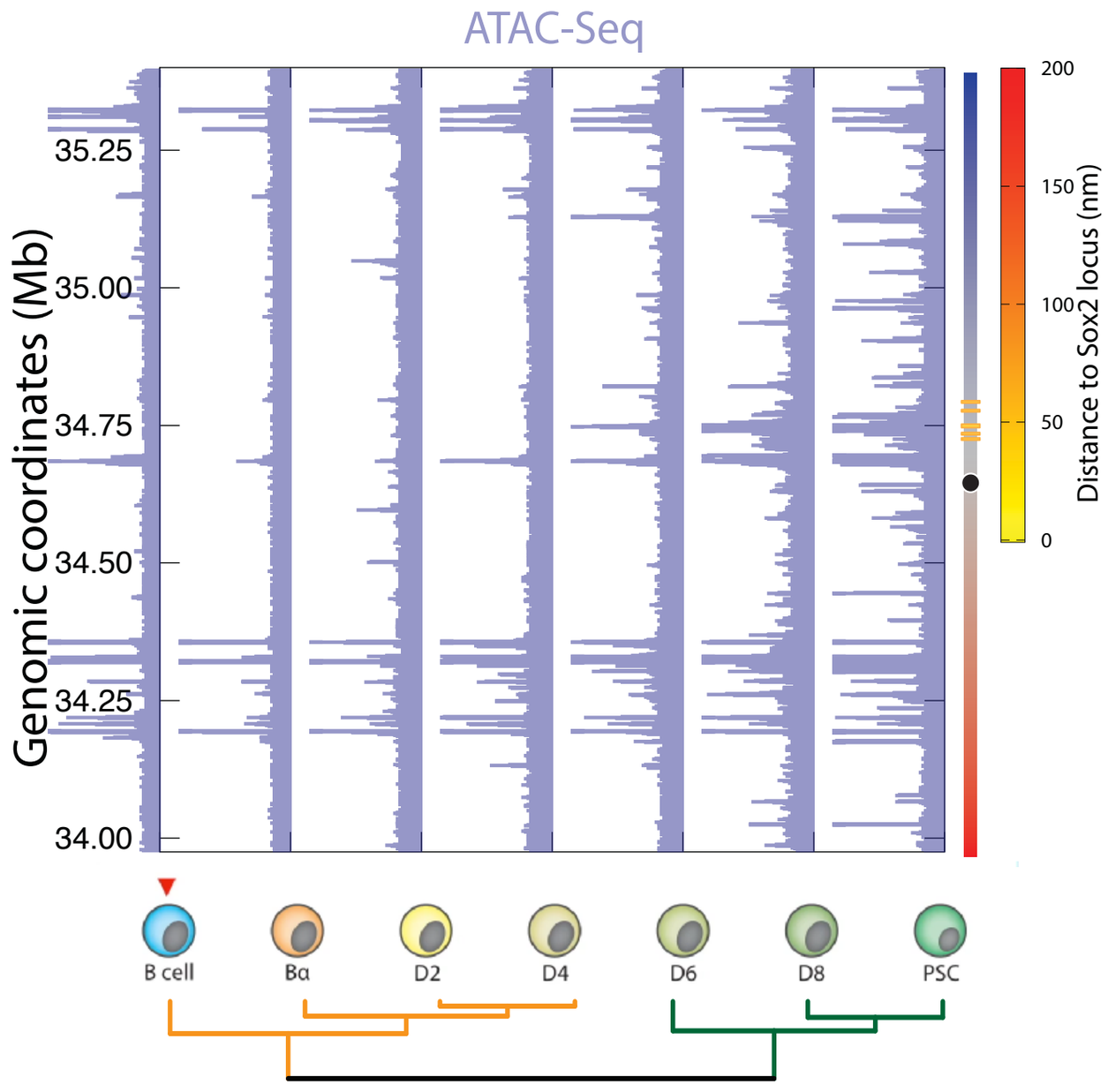




SOX2 locus structural changes from B to PSC

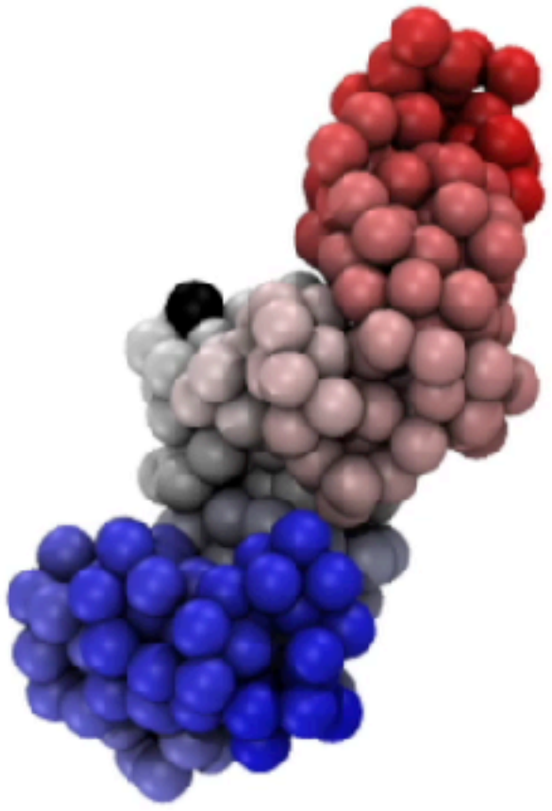
Distance to regulatory elements

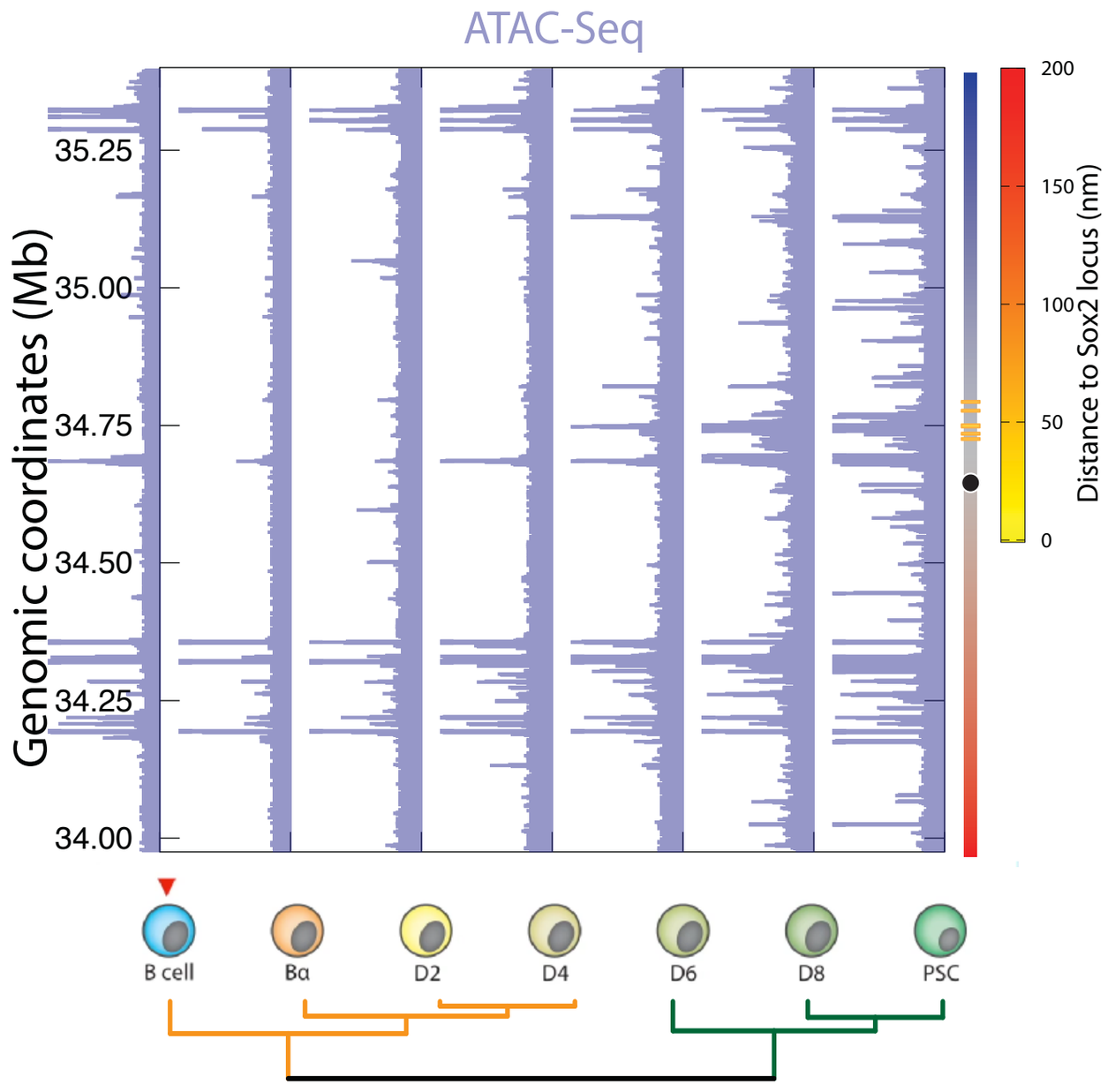




SOX2 locus structural changes from B to PSC

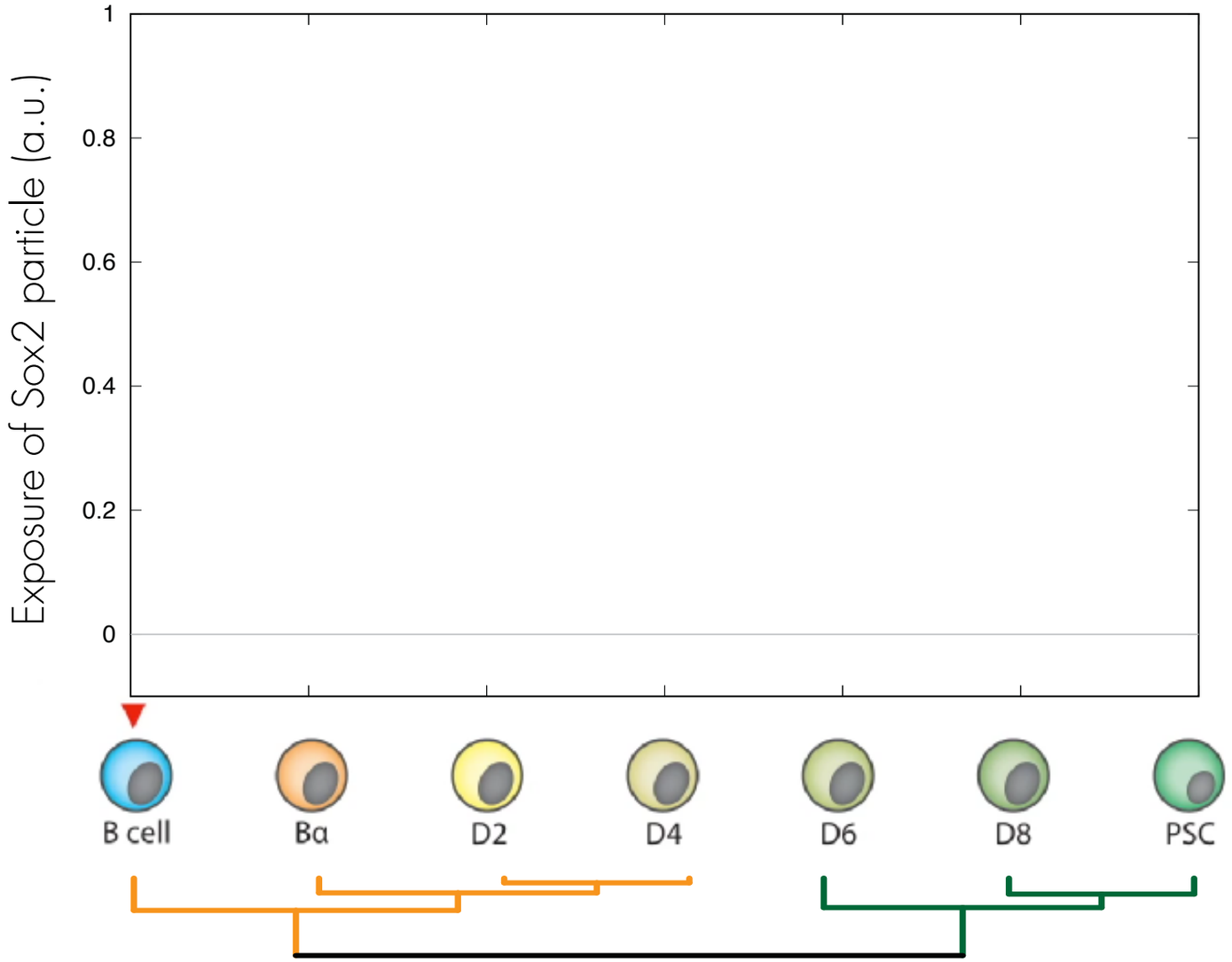
Distance to regulatory elements





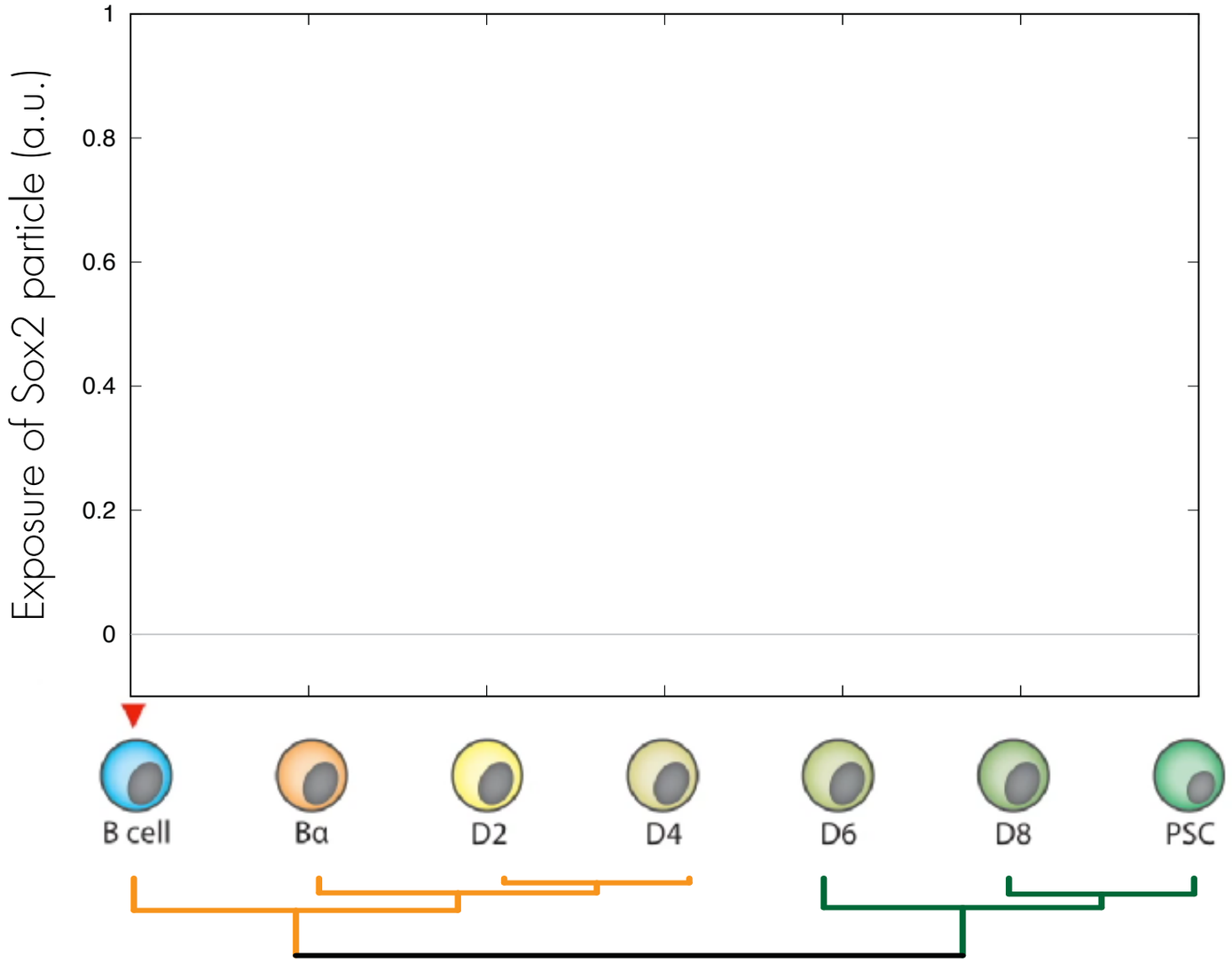
SOX2 locus structural changes from B to PSC

Structural exposure



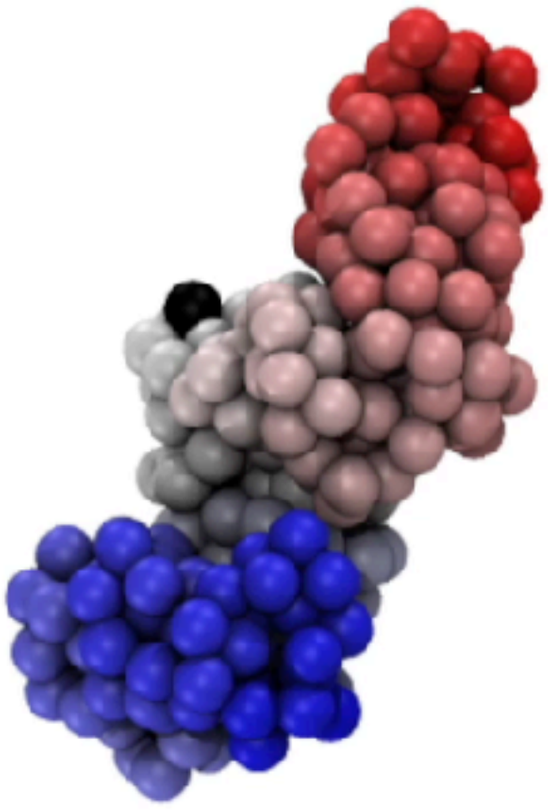
SOX2 locus structural changes from B to PSC

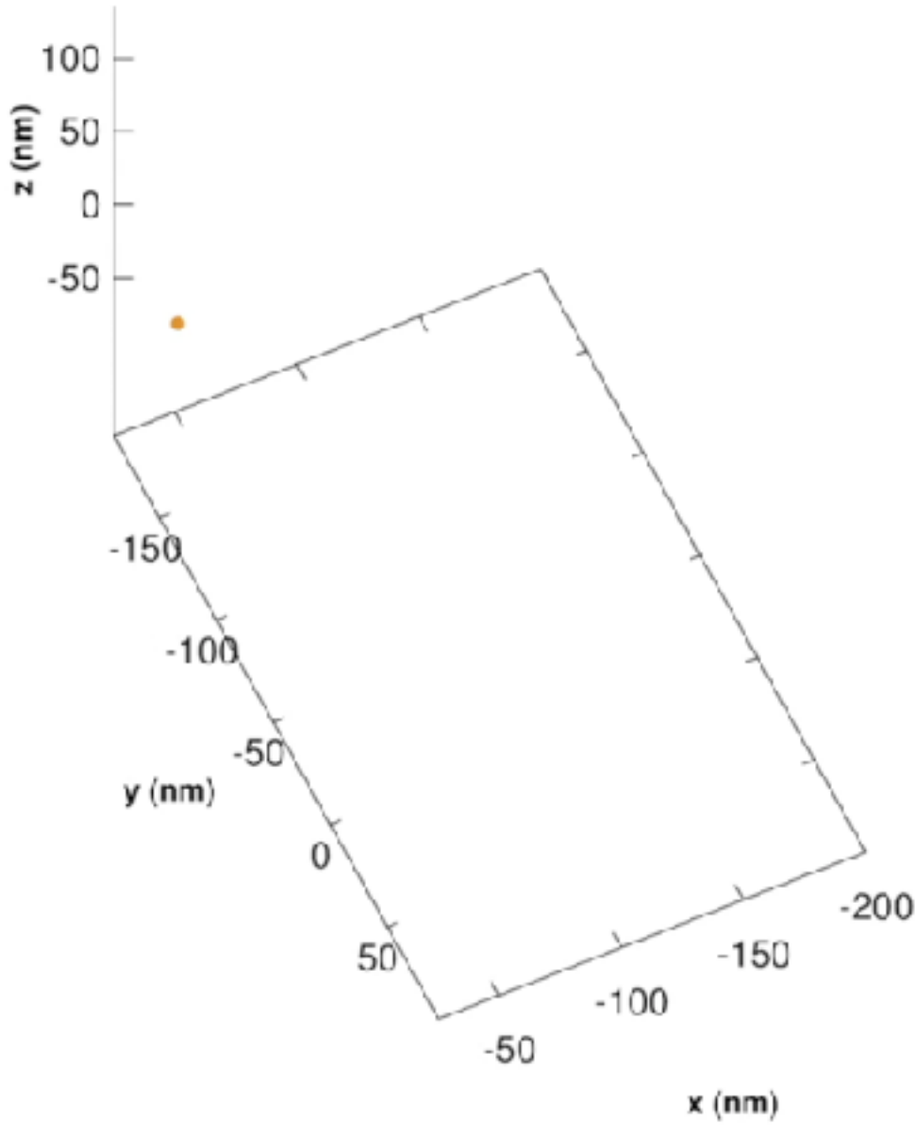
Structural exposure

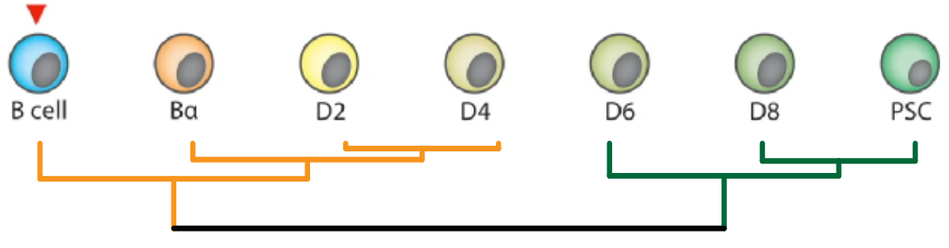


SOX2 locus dynamics changes from B to PSC

SOX2 displacement

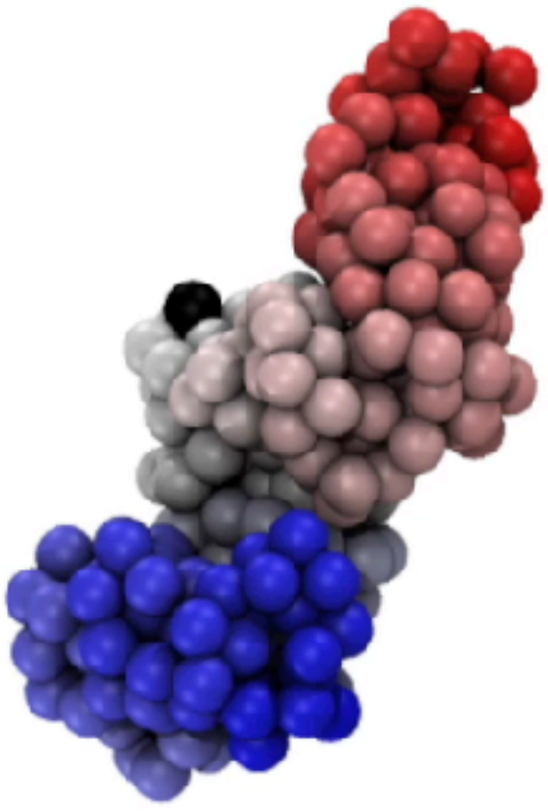


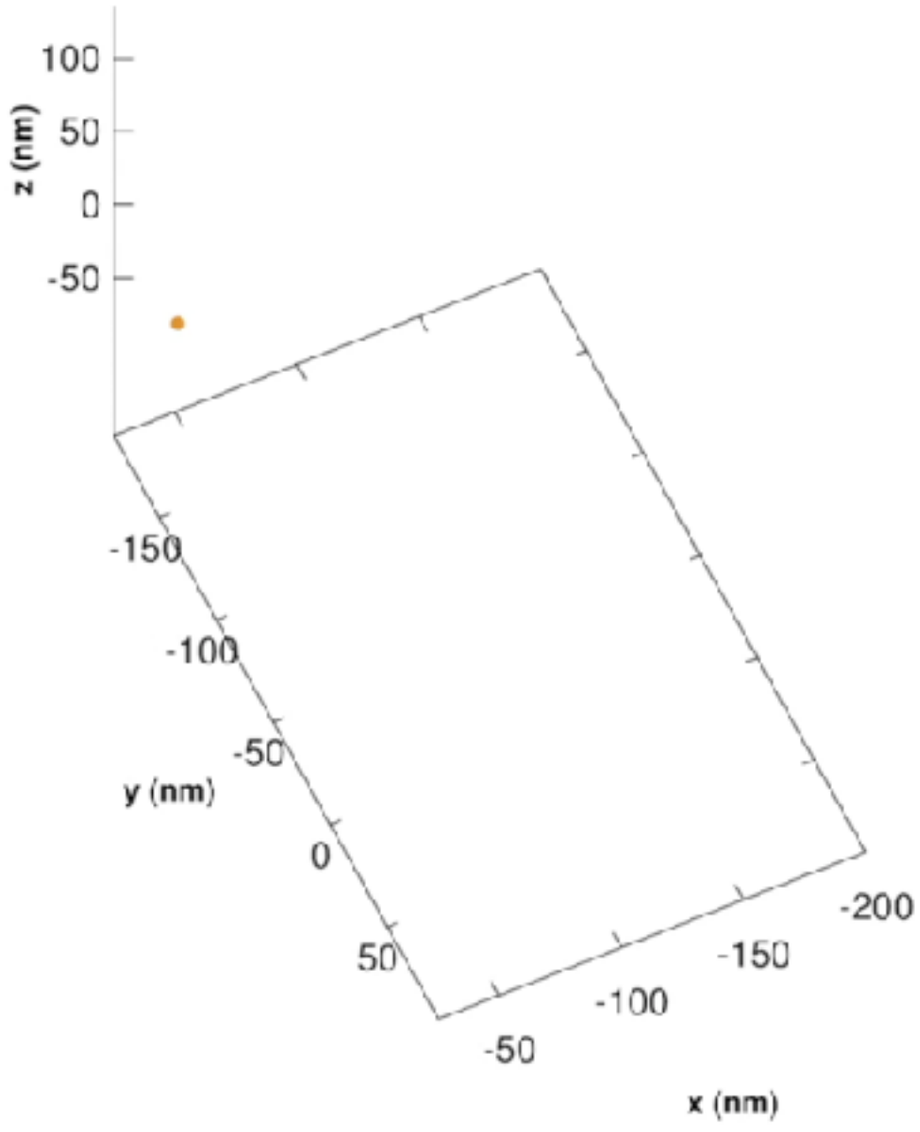


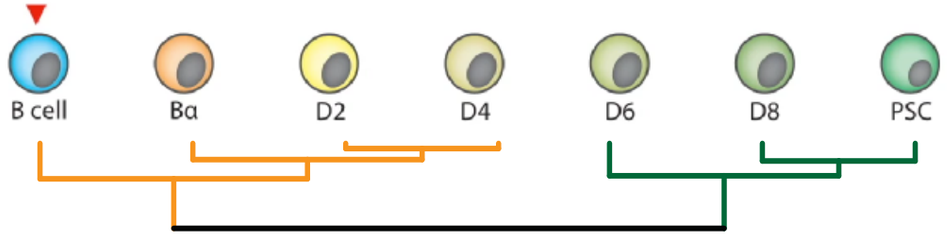


SOX2 locus dynamics changes from B to PSC

SOX2 displacement

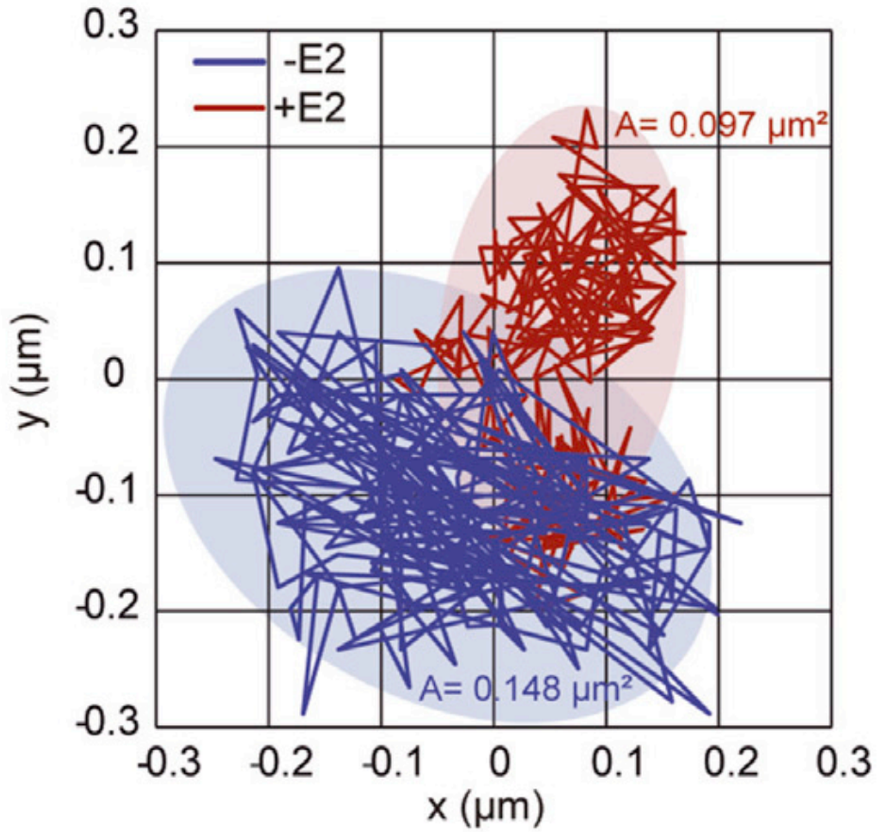


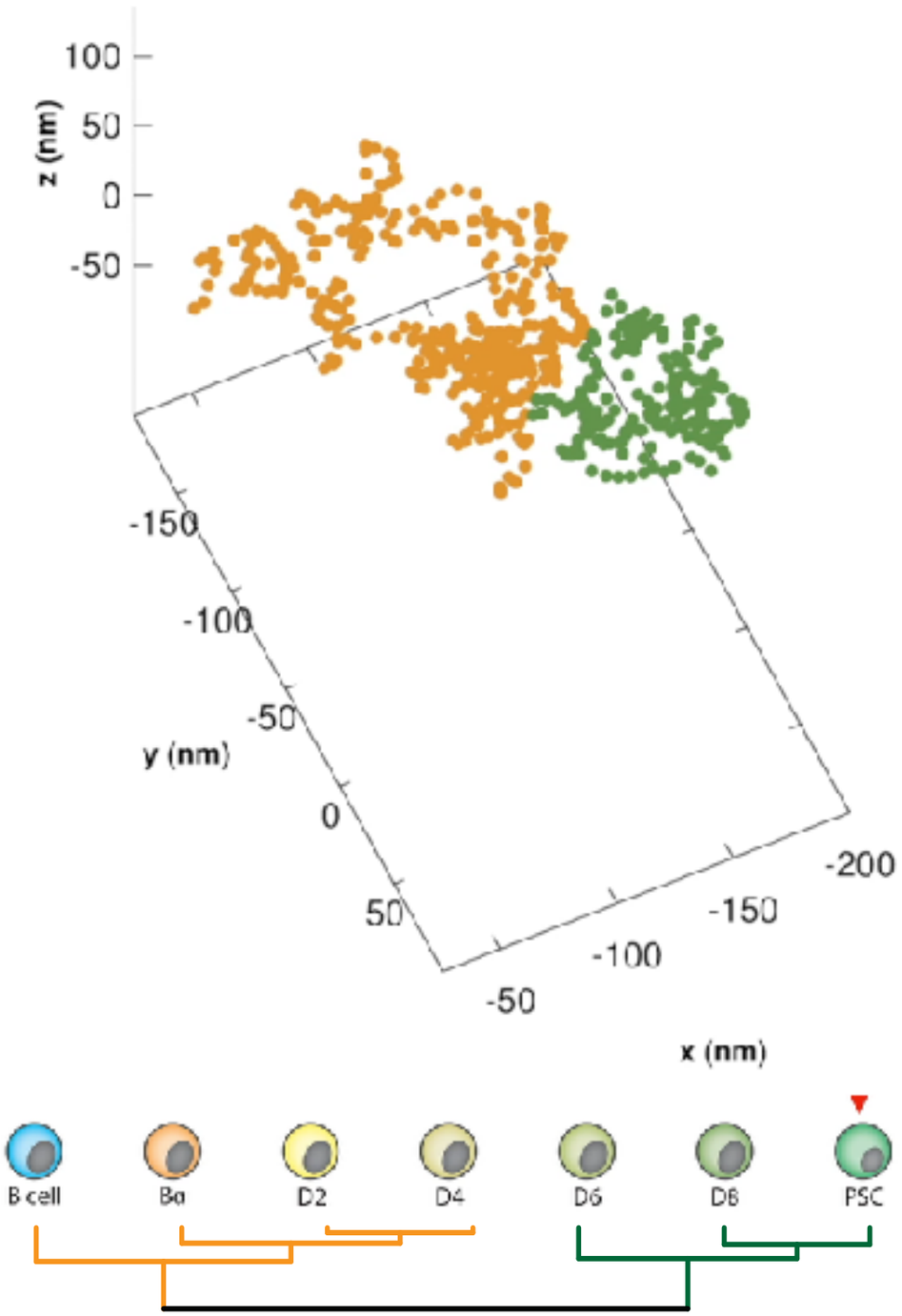




SOX2 locus dynamics changes from B to PSC

SOX2 displacement

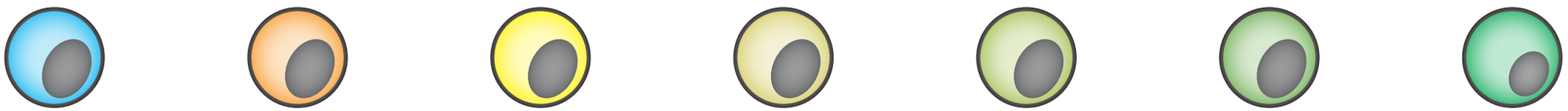




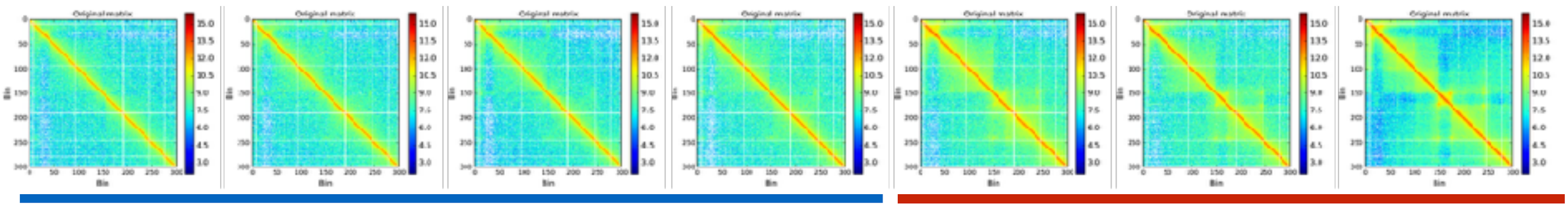
Two dimensional trajectories and area explored over 50s of the CCND1 locus recored before -E2 and after +E2 activation.

Germier ,T., et al, Blophys J. 113, 1383–1394 (2017).

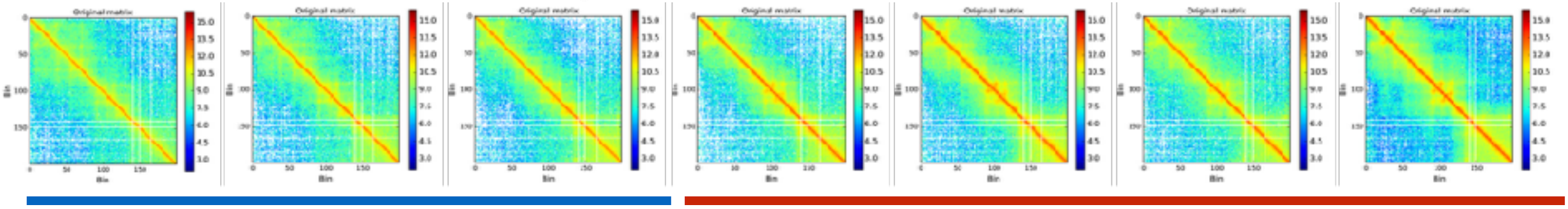
Other regions…



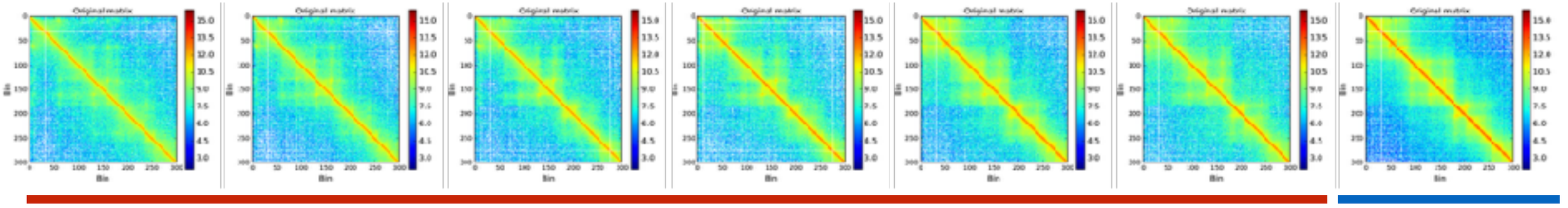
Sox2 chr3:34649995-34652460



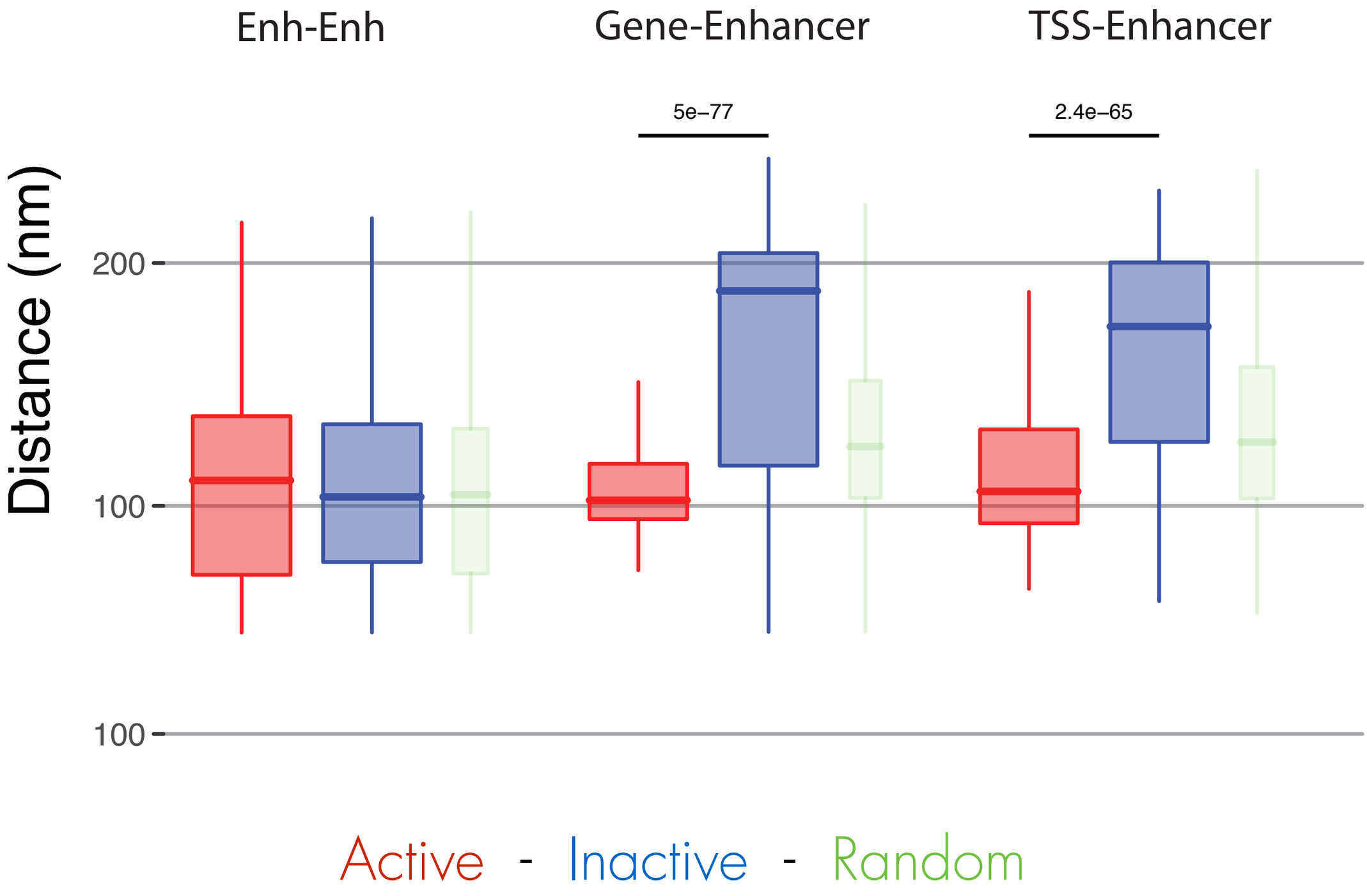
Nanog chr6:122707565-122714633



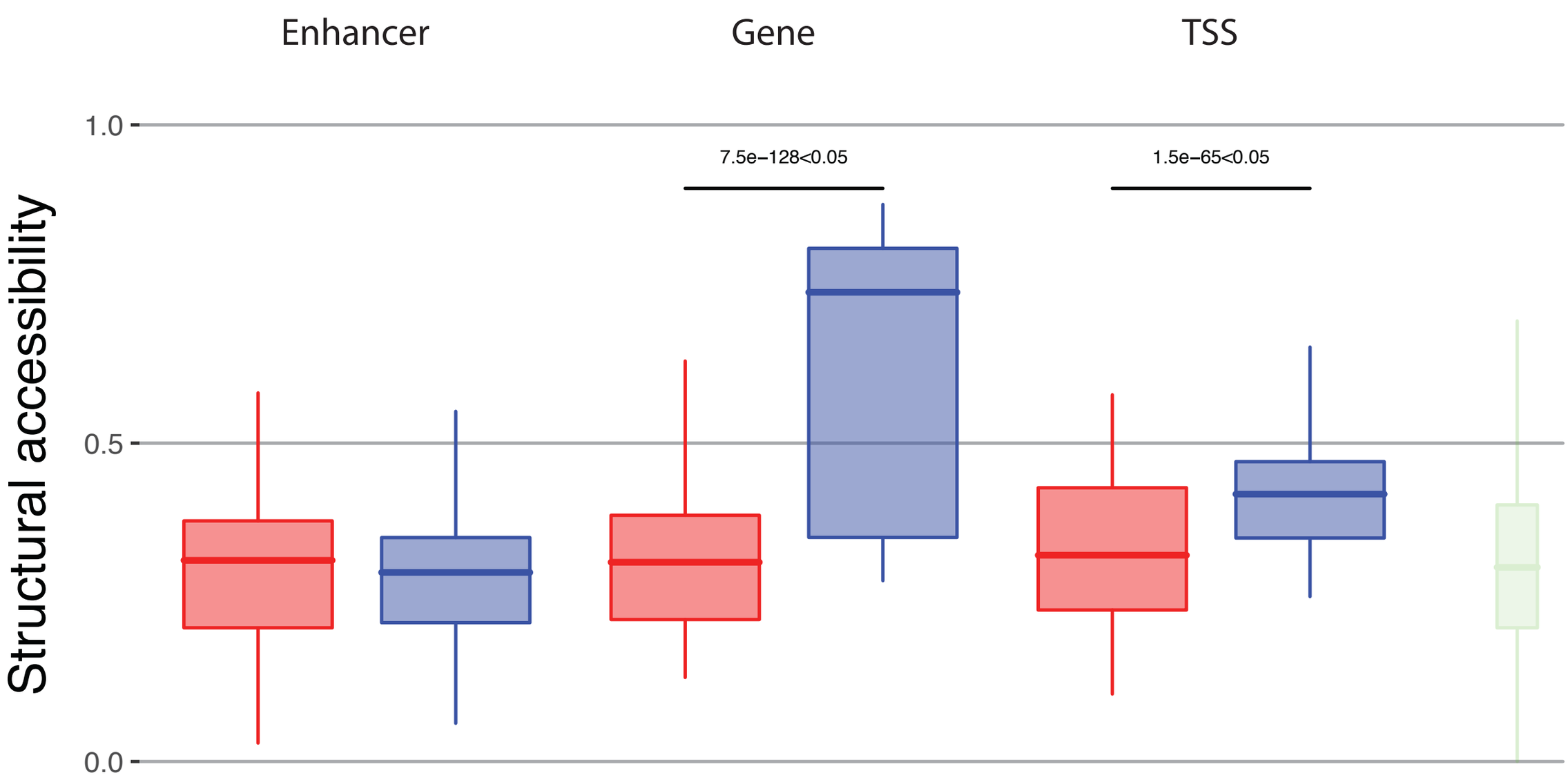
CEBPa chr7:35119293-35121931



Distance to enhancers

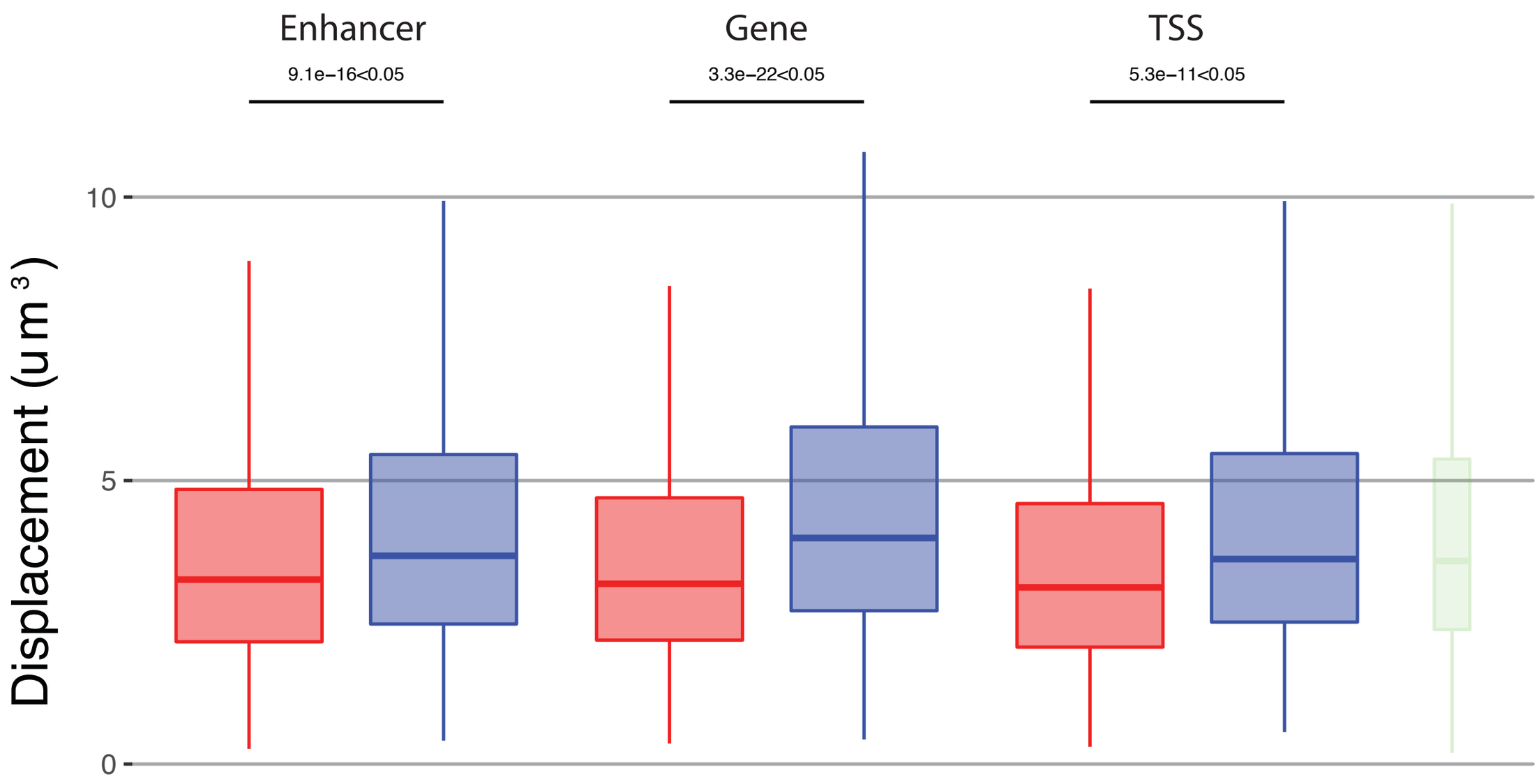


Accessibility



Active - Inactive - Random

Displacement



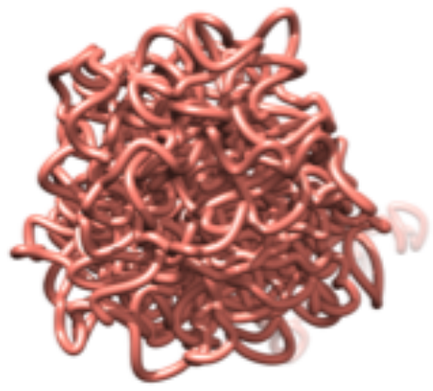
Active - Inactive - Random

A "cage" model for transcriptional activation

stpRNAs, a new type of structural RNAs?

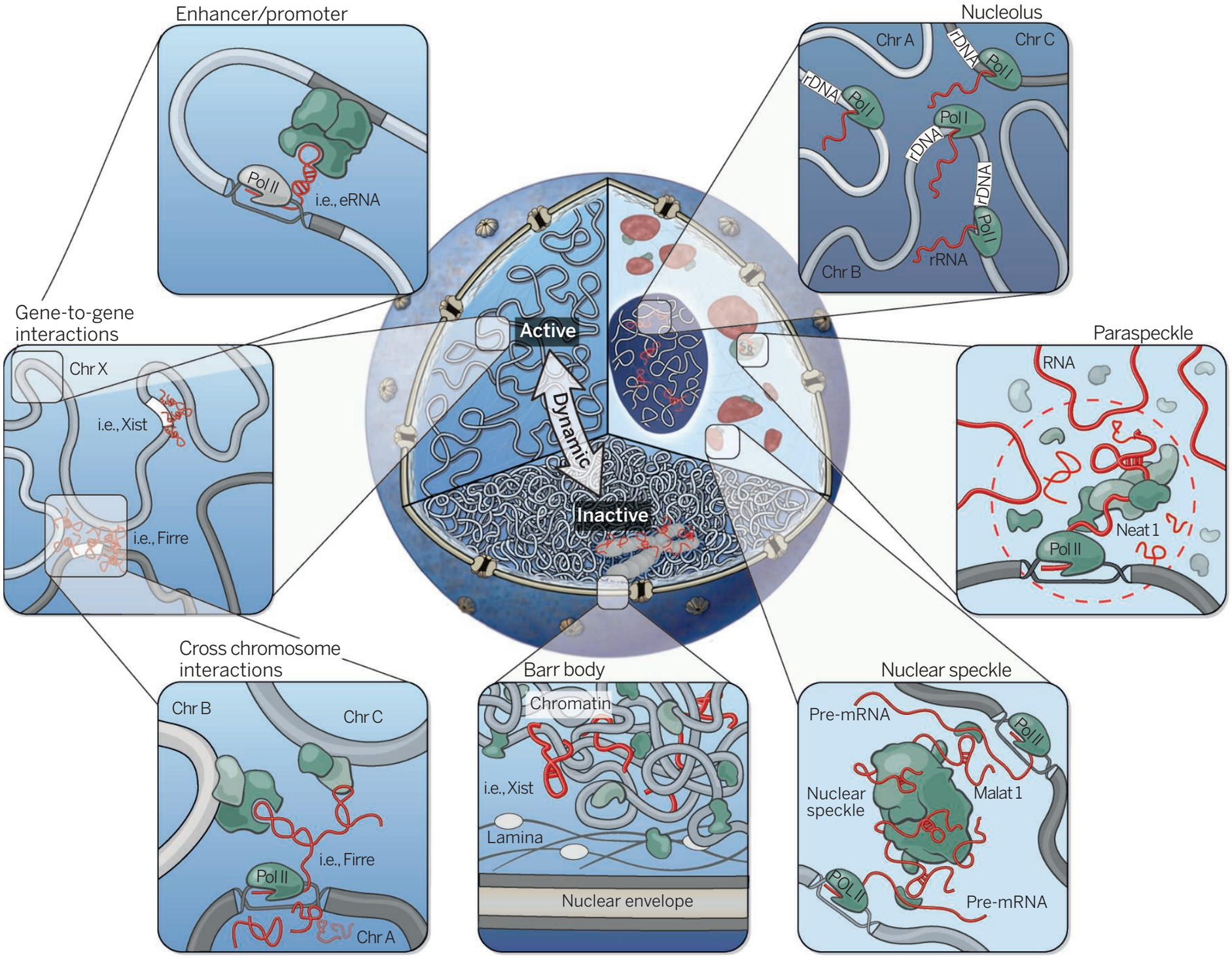
Irene Farabella

Marco di Stefano

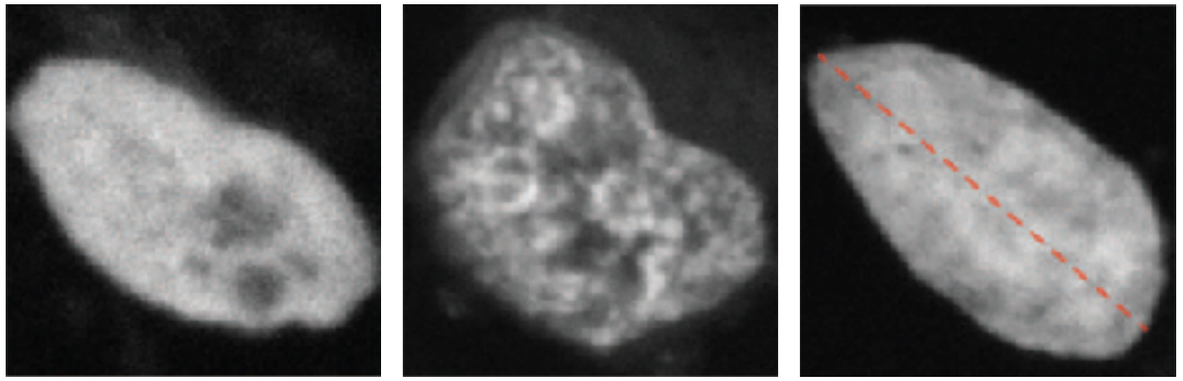


RNA, nuclear organisation dynamics and architecture

Rinn and Guttman, Science; 345(6202):1240–1241 (2014)

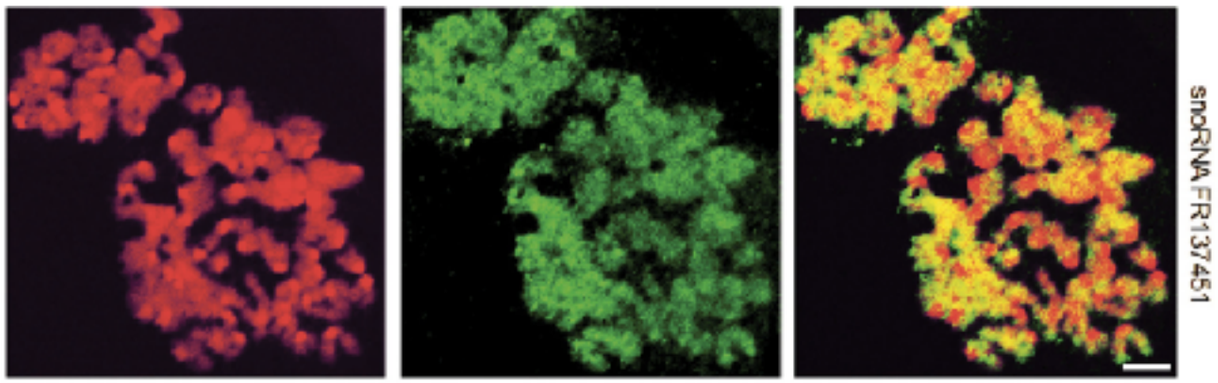


RNA, nuclear organisation dynamics and architecture



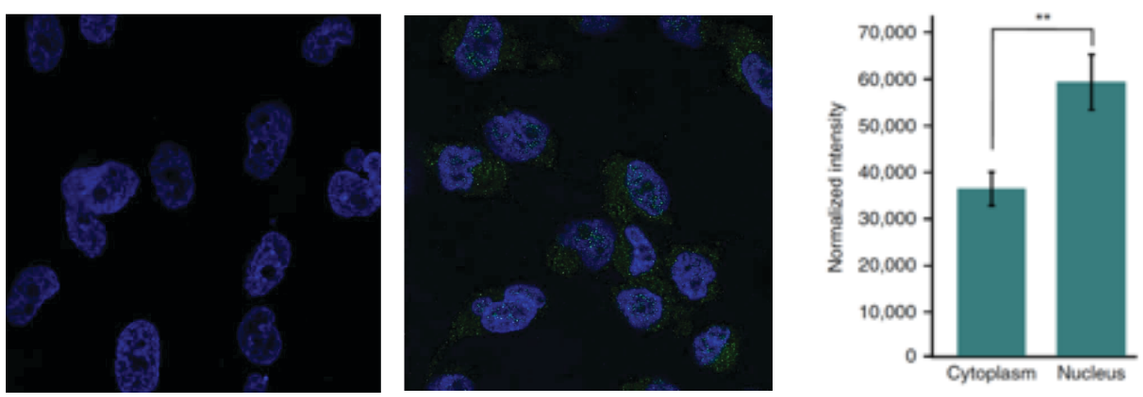
Chromatin-interlinking lncRNAs

Adapted from: Caudron-Herger et al., Nucleus ;2(5):410-24 (2011)



Mitotic chromosome-associated RNAs

Adapted from: Meng et al., Nucleic Acids Res. ;44(10):4934-46 (2016)



RNA-DNA triplex *in vivo* and *in vitro*

Adapted from: Mondal et al. Nat Commun. 6:7743 (2015)

Are there lncRNAs that act as global architectural factor for chromatin organisation?

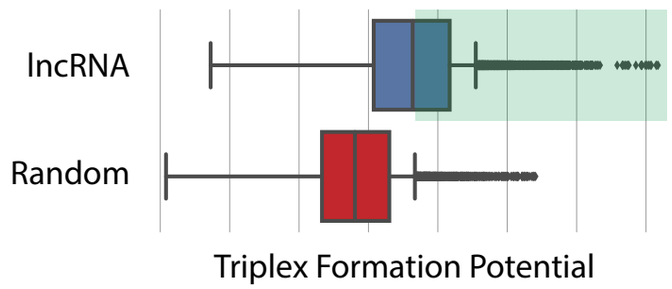
Hypothesis: such lncRNA may interact with DNA through triplex formation.

lncRNA selection

GENCODE v19 mapped of GRCh37
lncRNA genes 13,870

K562 & GM12878
Nuclear localisation
>=1 RPKM in both replica and in both cells line

≥2 exons
>200 nt length
nuclear in K562 & GM12878



Triplex forming lncRNA enriched

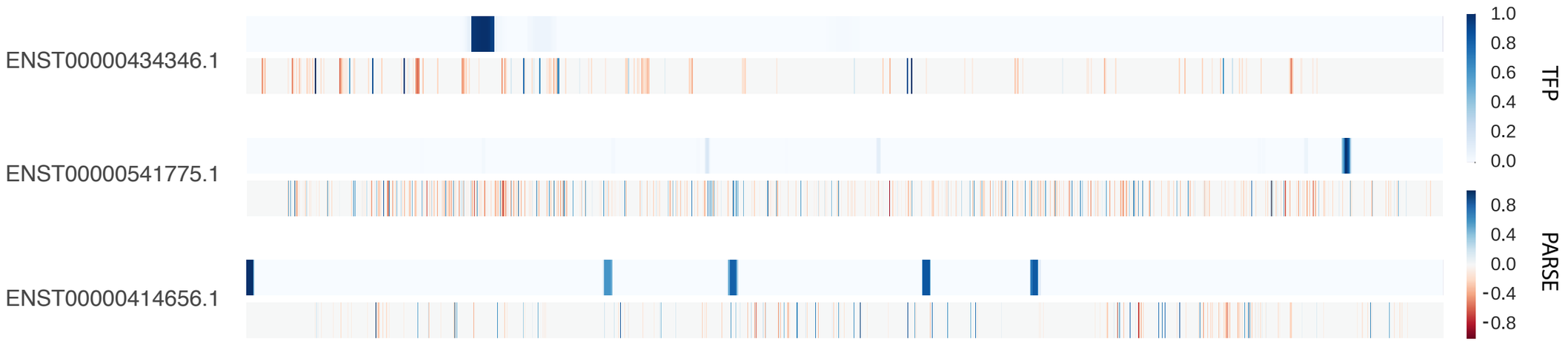
set of 339 lncRNAs

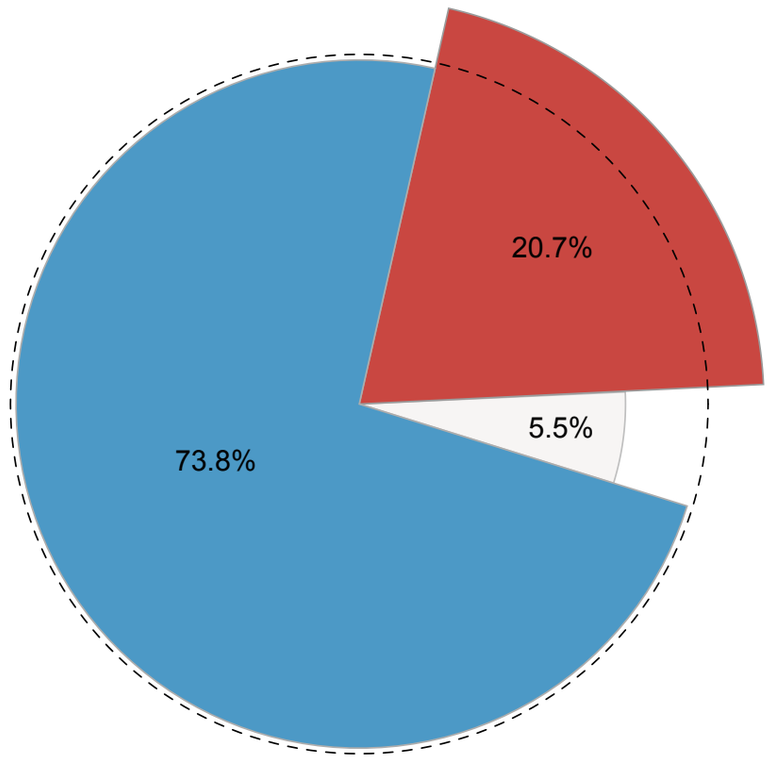
RNA-Seq expression using
GEM split mapper & Flux capacitor
Marc Dabad & Anna Esteve (CNAG-CRG)

TFO/PARSE lncRNA profiles

127 triplex forming lncRNA

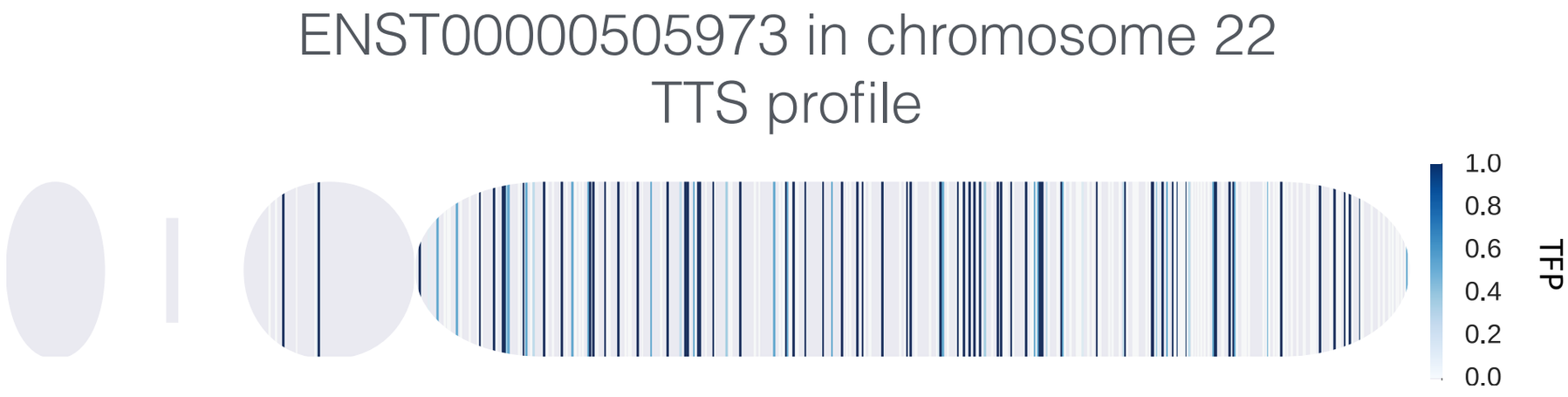
with Secondary Structure information based on PARSE

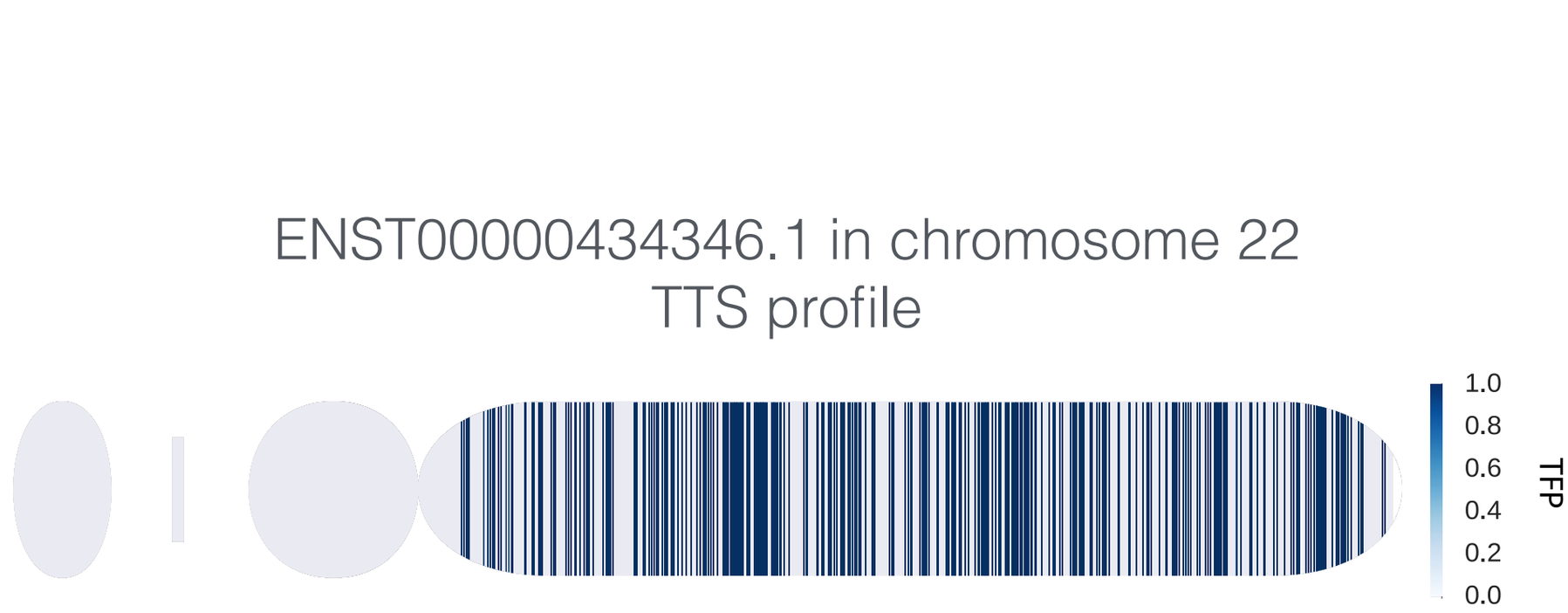




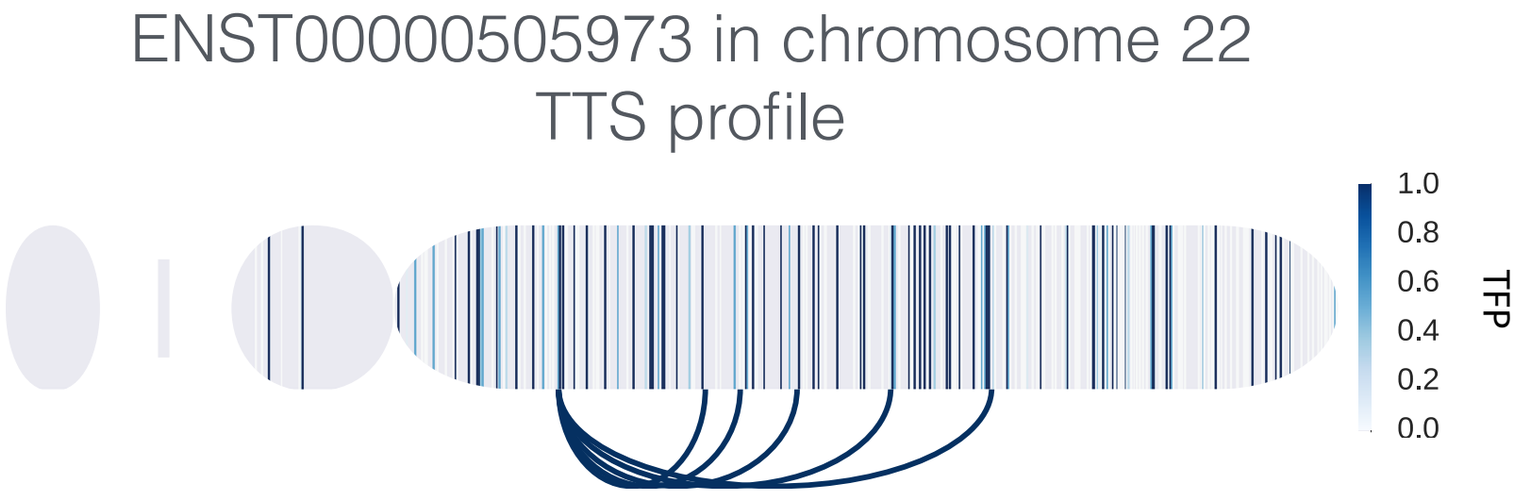
Data from: Wan et al., Nature 505, 706–709 (2014)

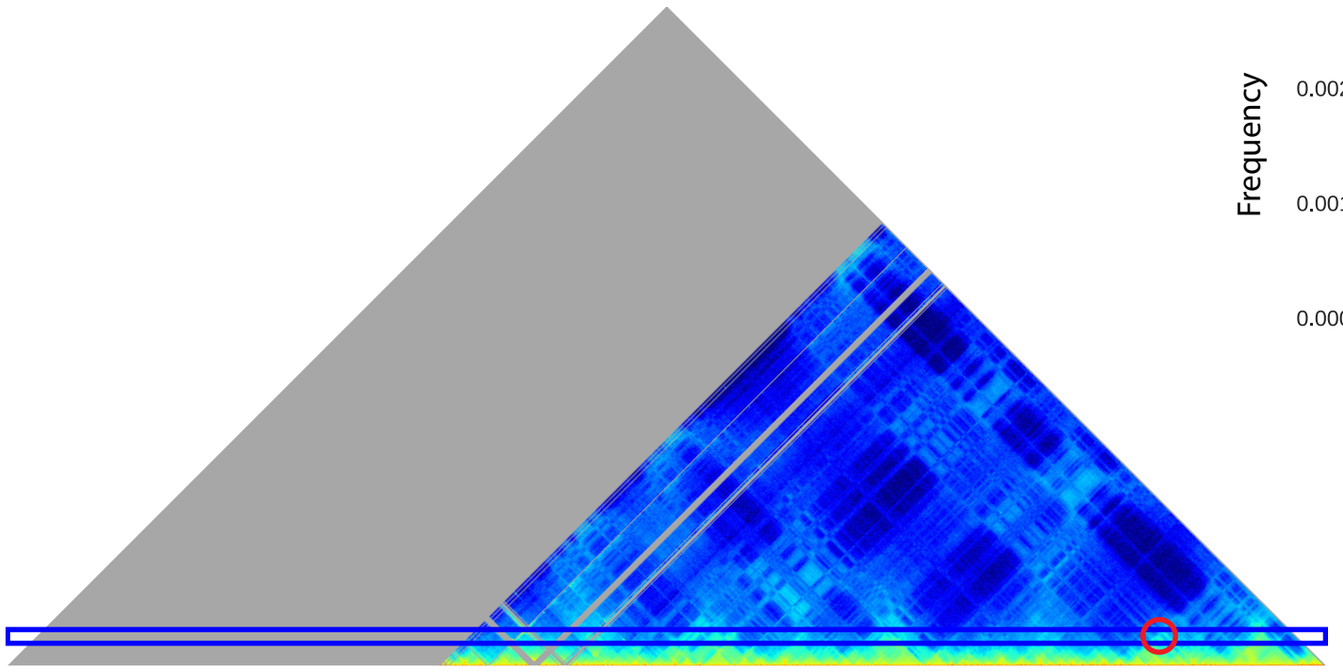
TTS profile on Chromosome

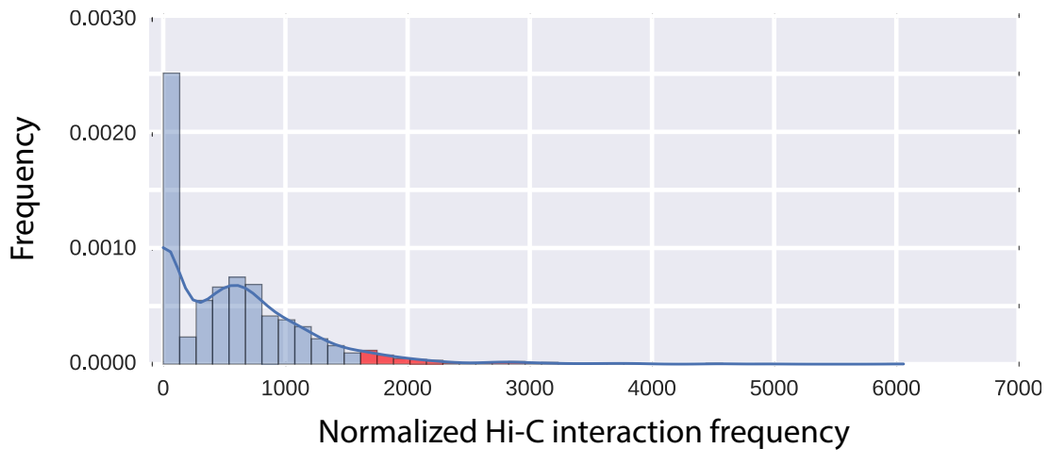




3D Co-localisation of loci



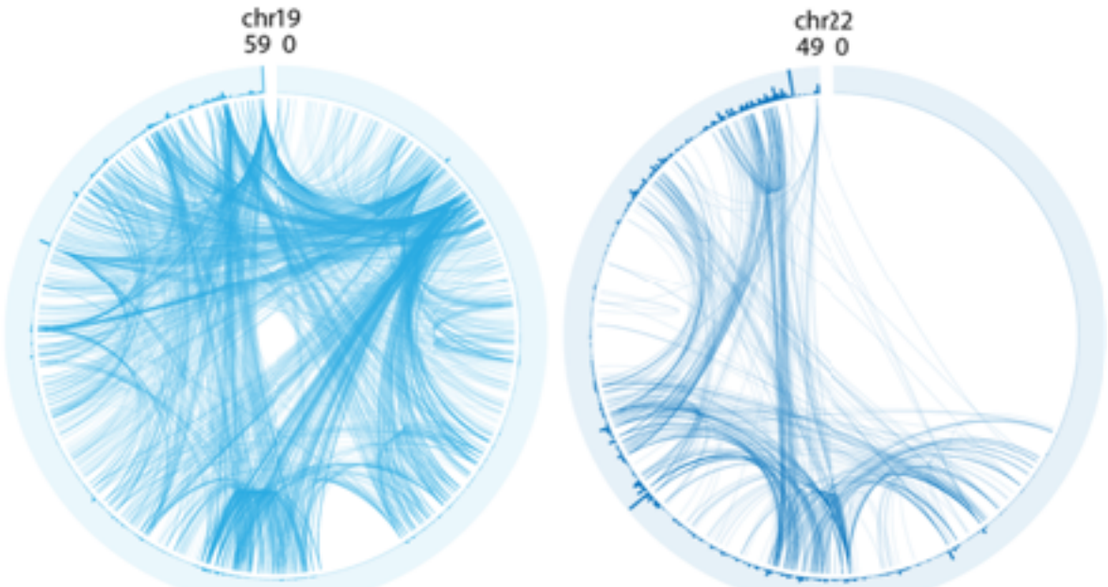




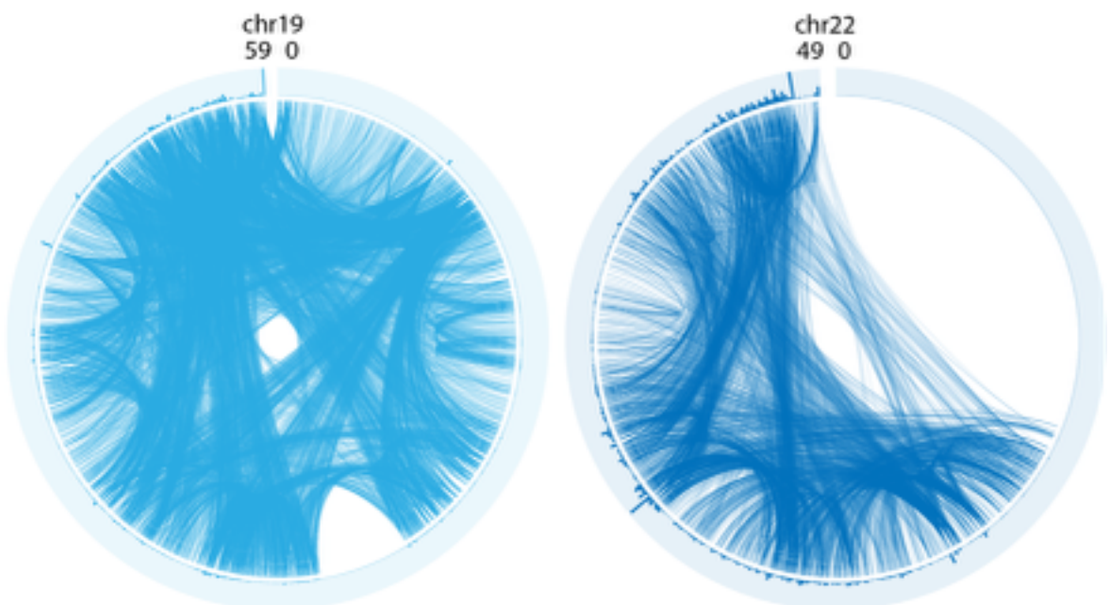
$$S = log_2\left(\frac{CTTS_d^{obs}}{CTTS_d^{exp}}\right)$$

Enriched Co-localised TTS site

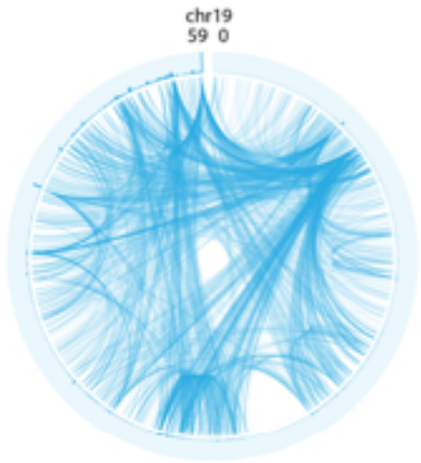
ENST00000434346.1



ENST00000541775.1



TADdyn modeling



Steered Molecular Dynamics
PLUMED/LAMMPS
with distance dependent harmonic restraints

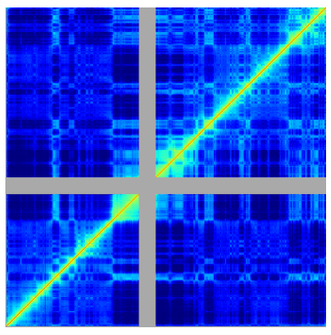
Kremer and Grest 1991

Structure Population

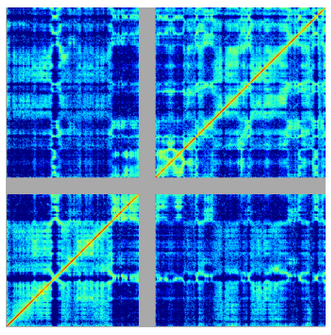
1,000 replicas using 10% of the initial set of retrains

Marco Di Stefano

HiC experiment
(Rao @50kb)

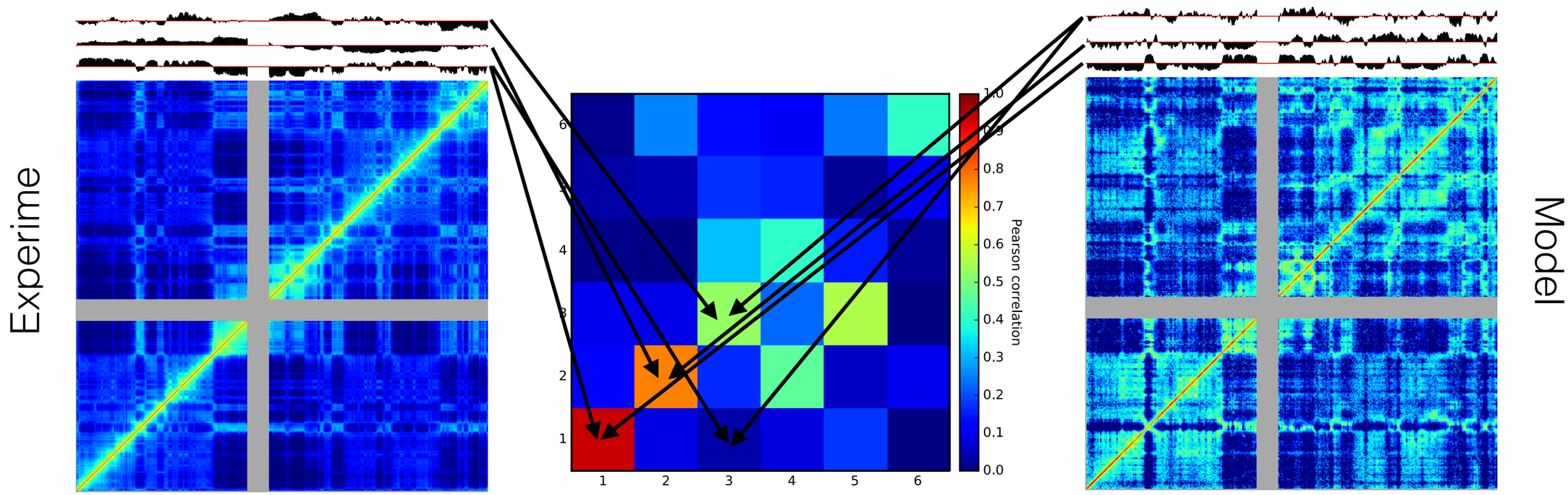


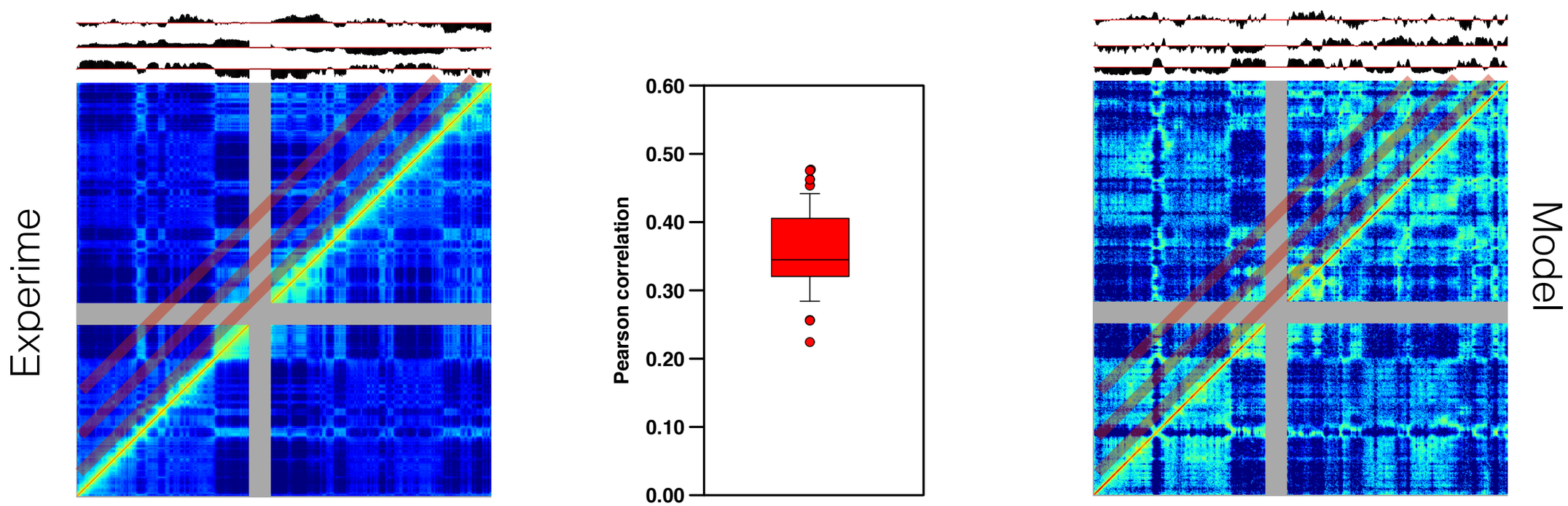
Predicted from
Structure population



Benchmark measures

Eigen vector correlation & Diagonal cross correlation

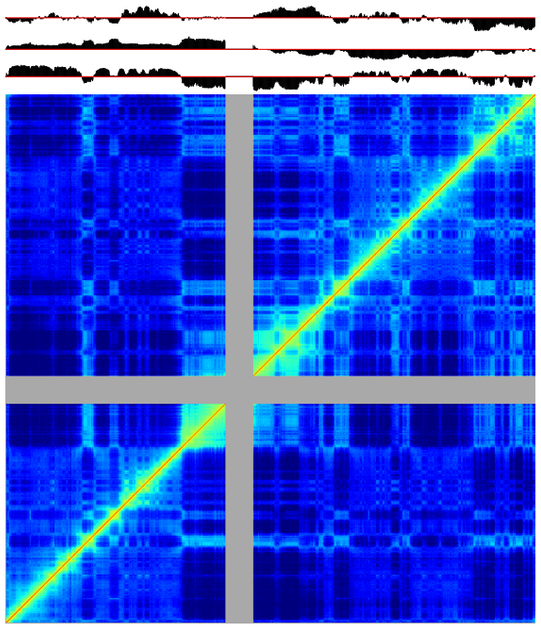




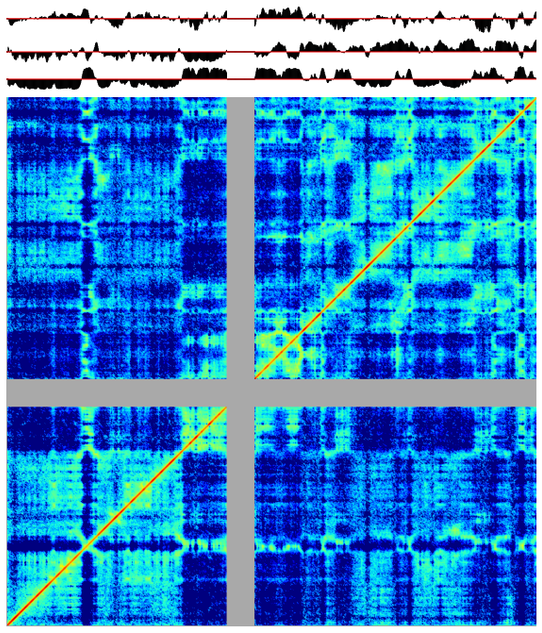
ENST00000434346.1 TTS in Chr19

total of 3,039 restraints over 620,899 possible (0.5%)

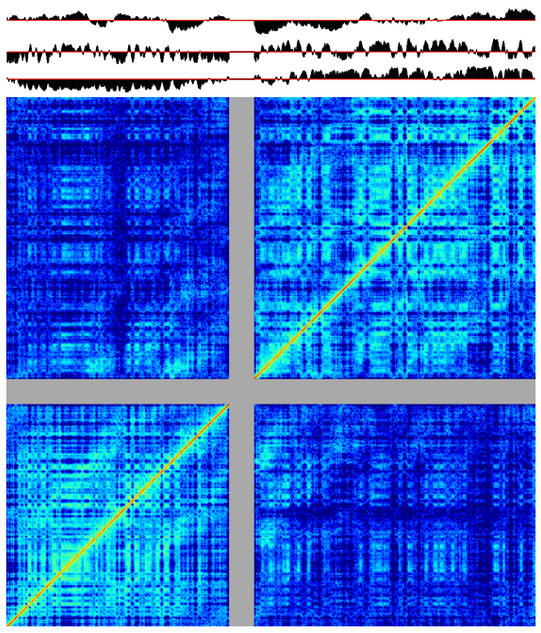
HiC experiment



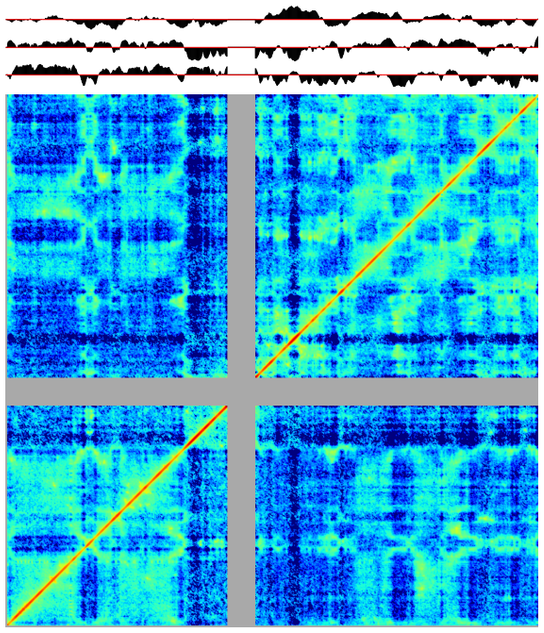
cTTS

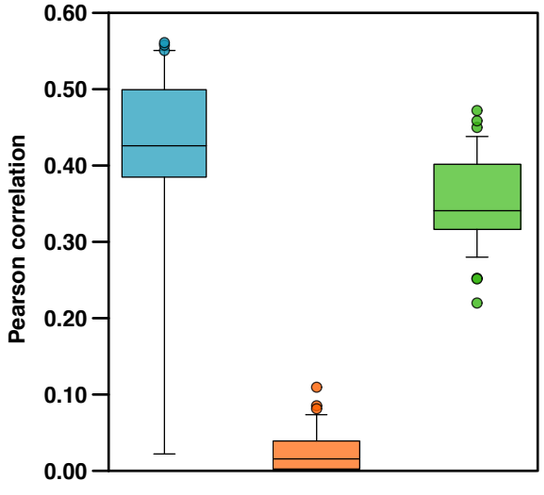


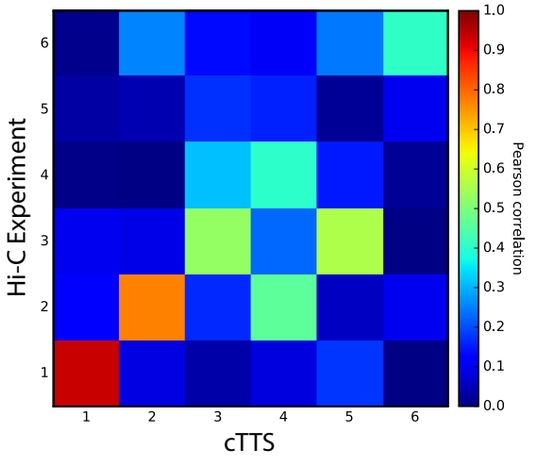
Random

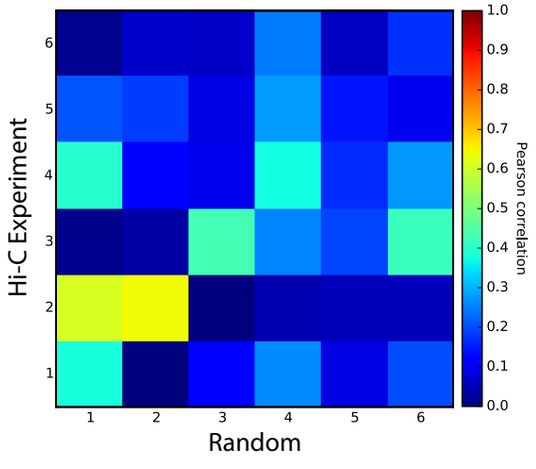


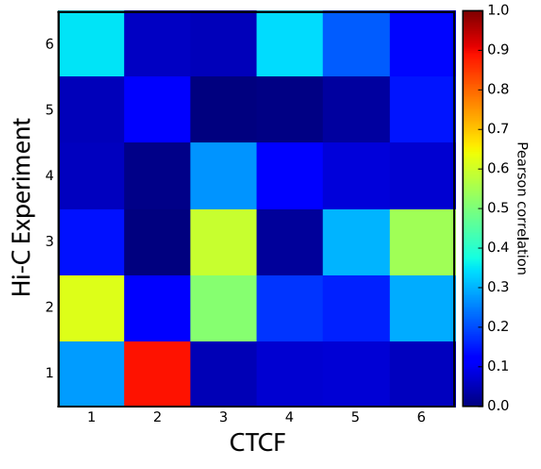
CTCF





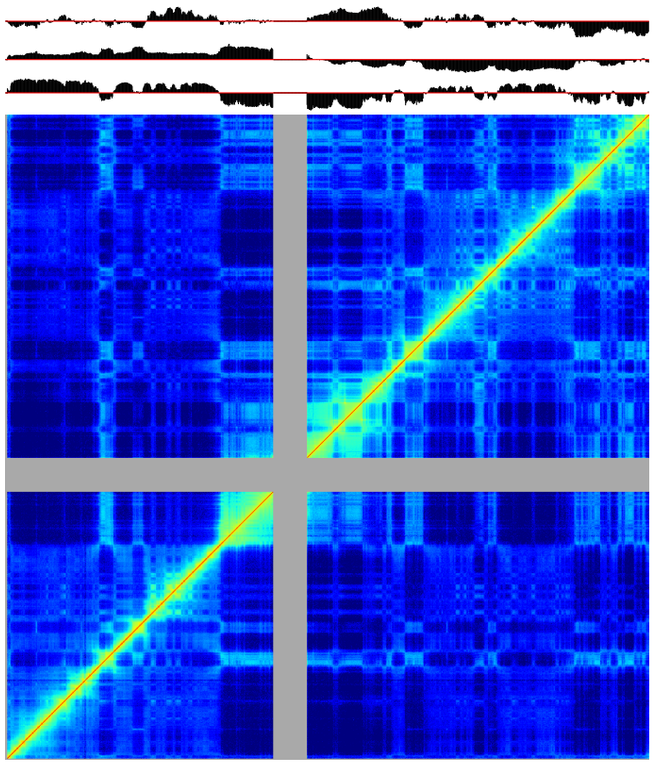


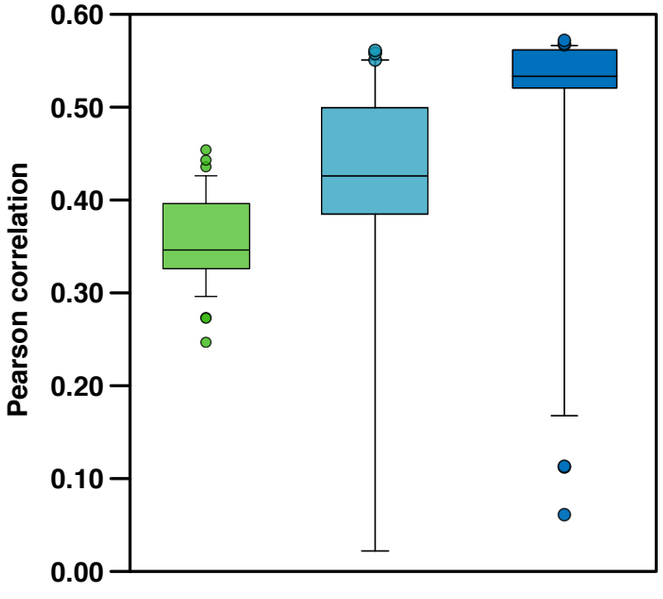




Other stpRNA TTS in Chr19

HiC experiment





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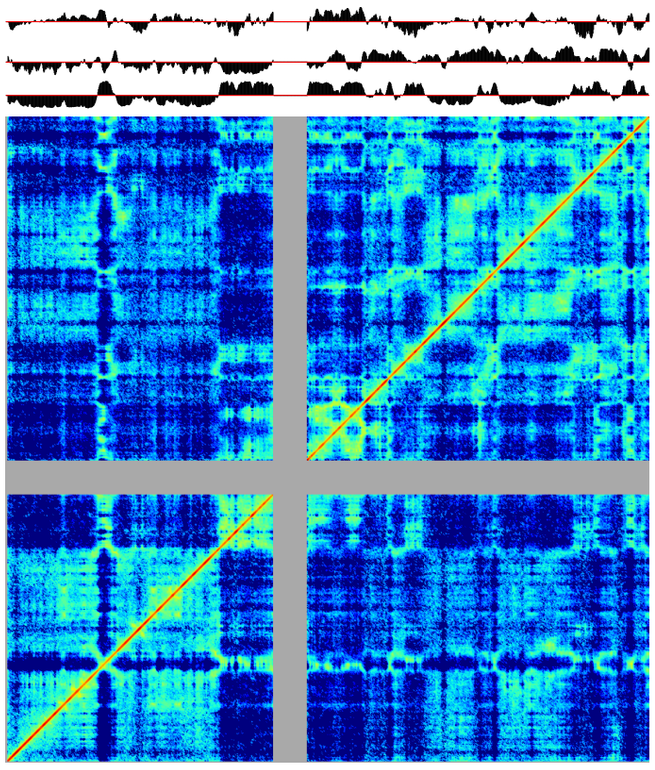

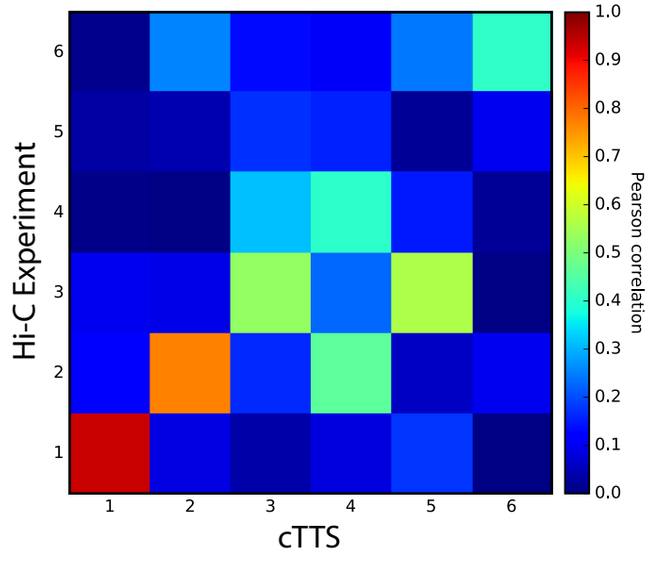

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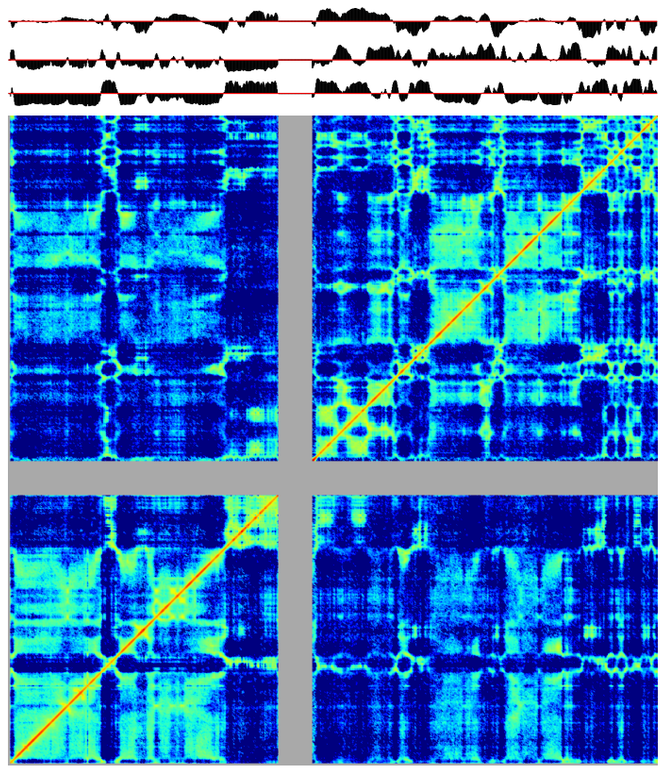
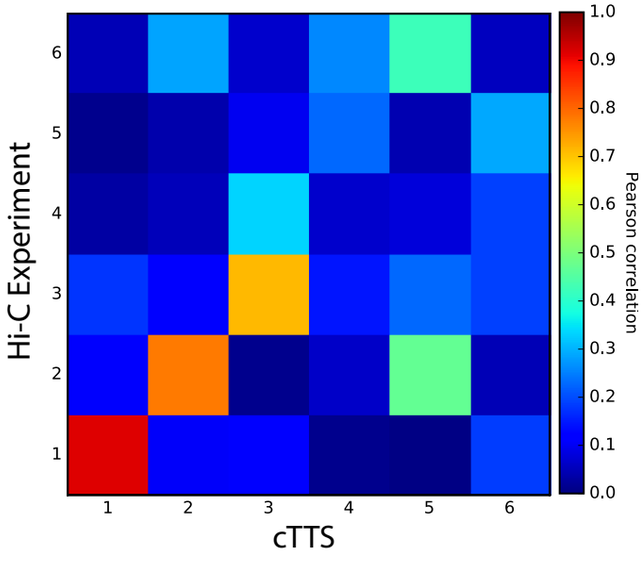
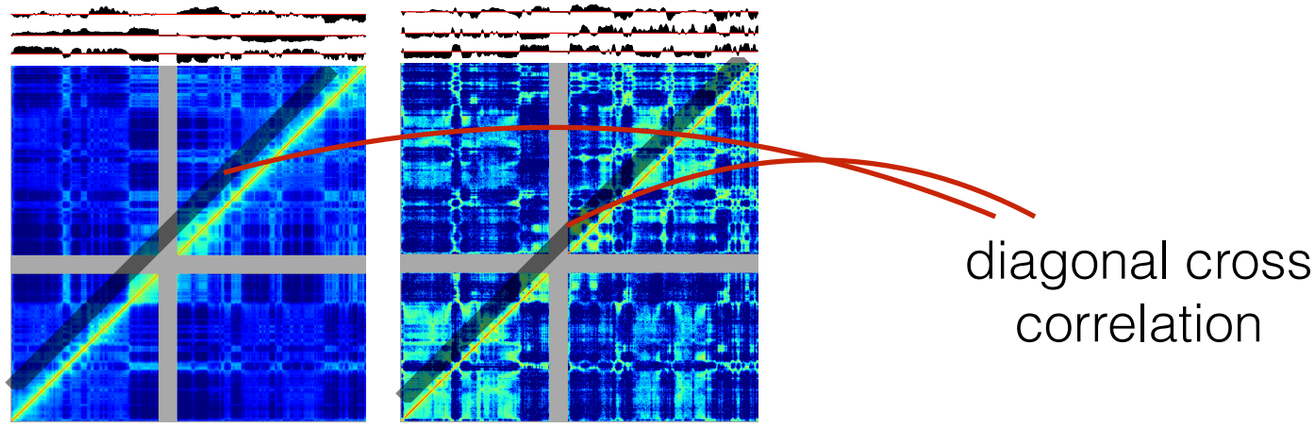
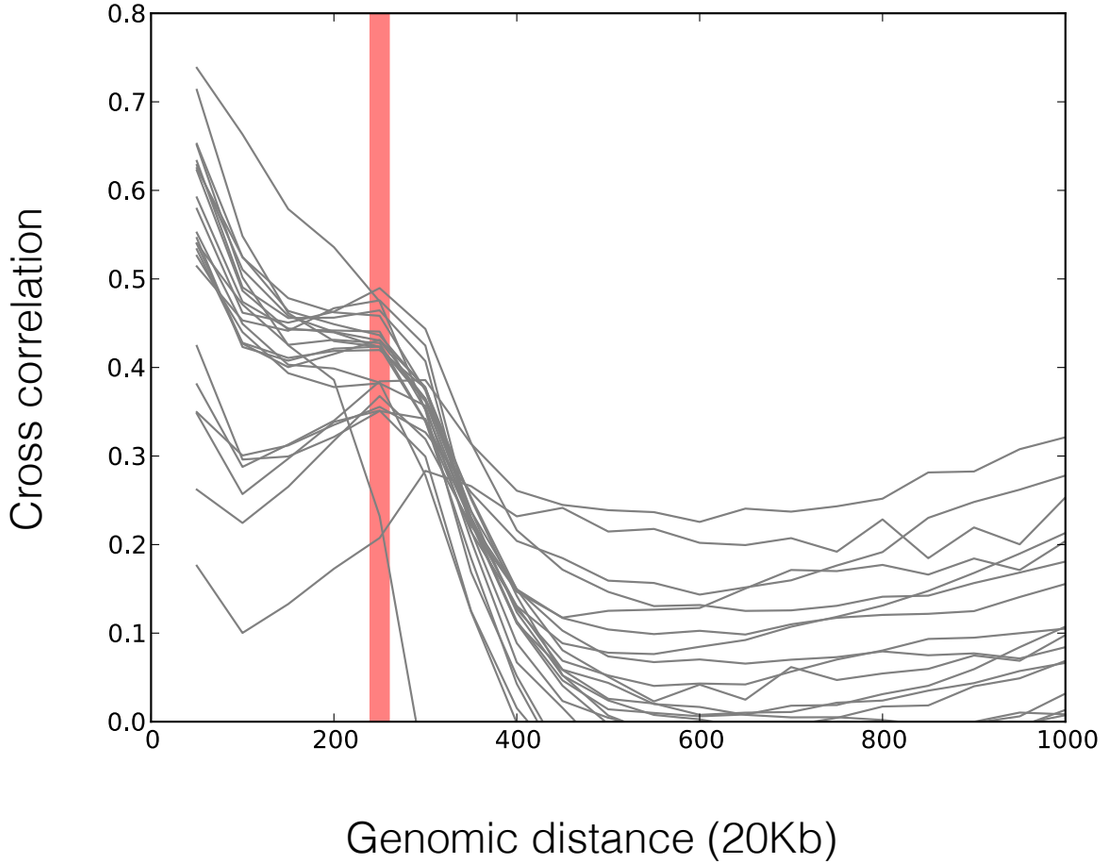




RNA & nuclear architecture



CTCF



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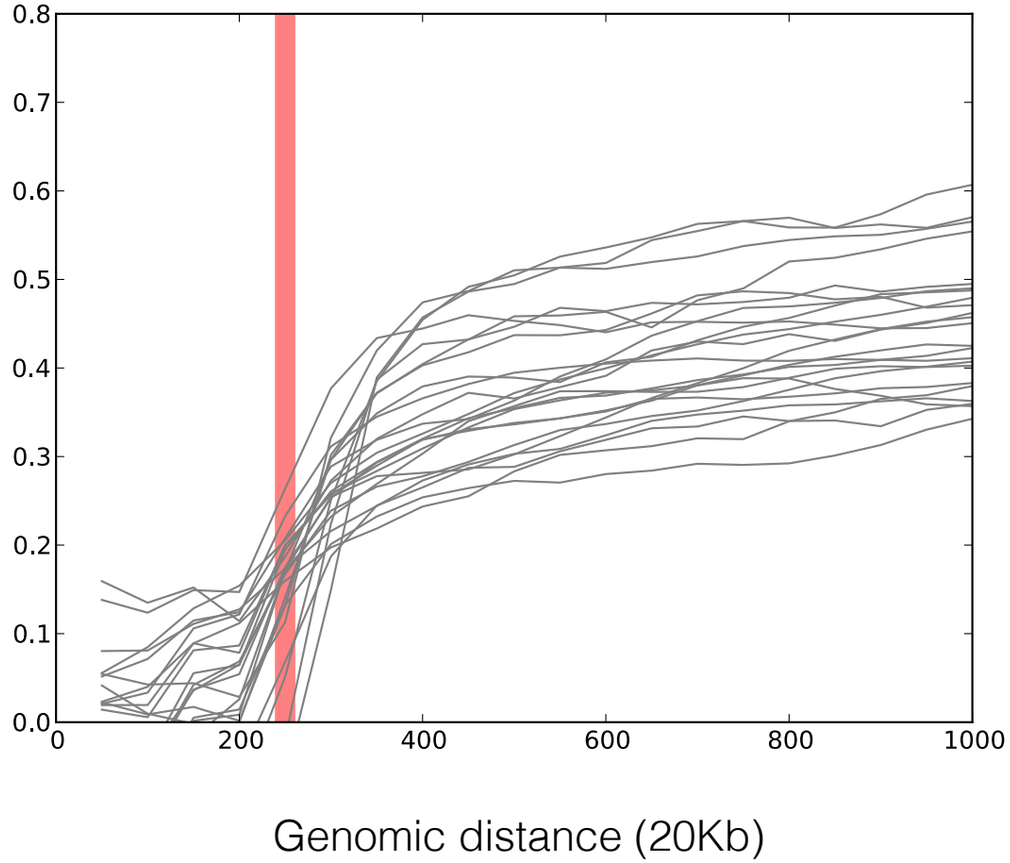
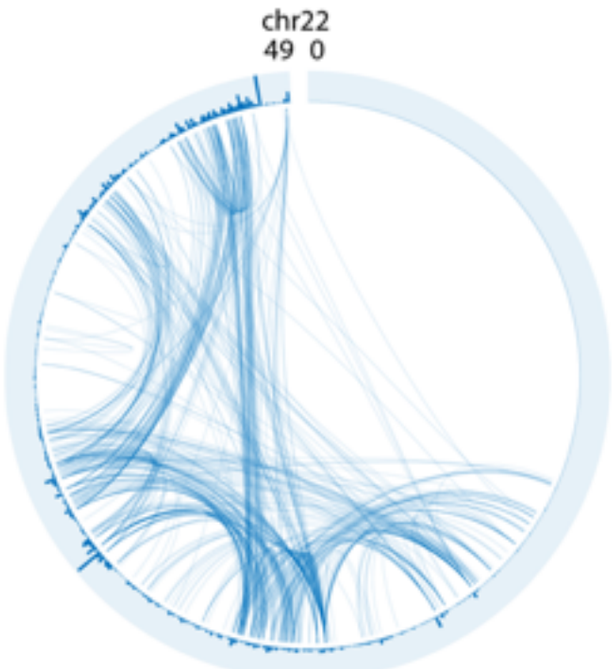
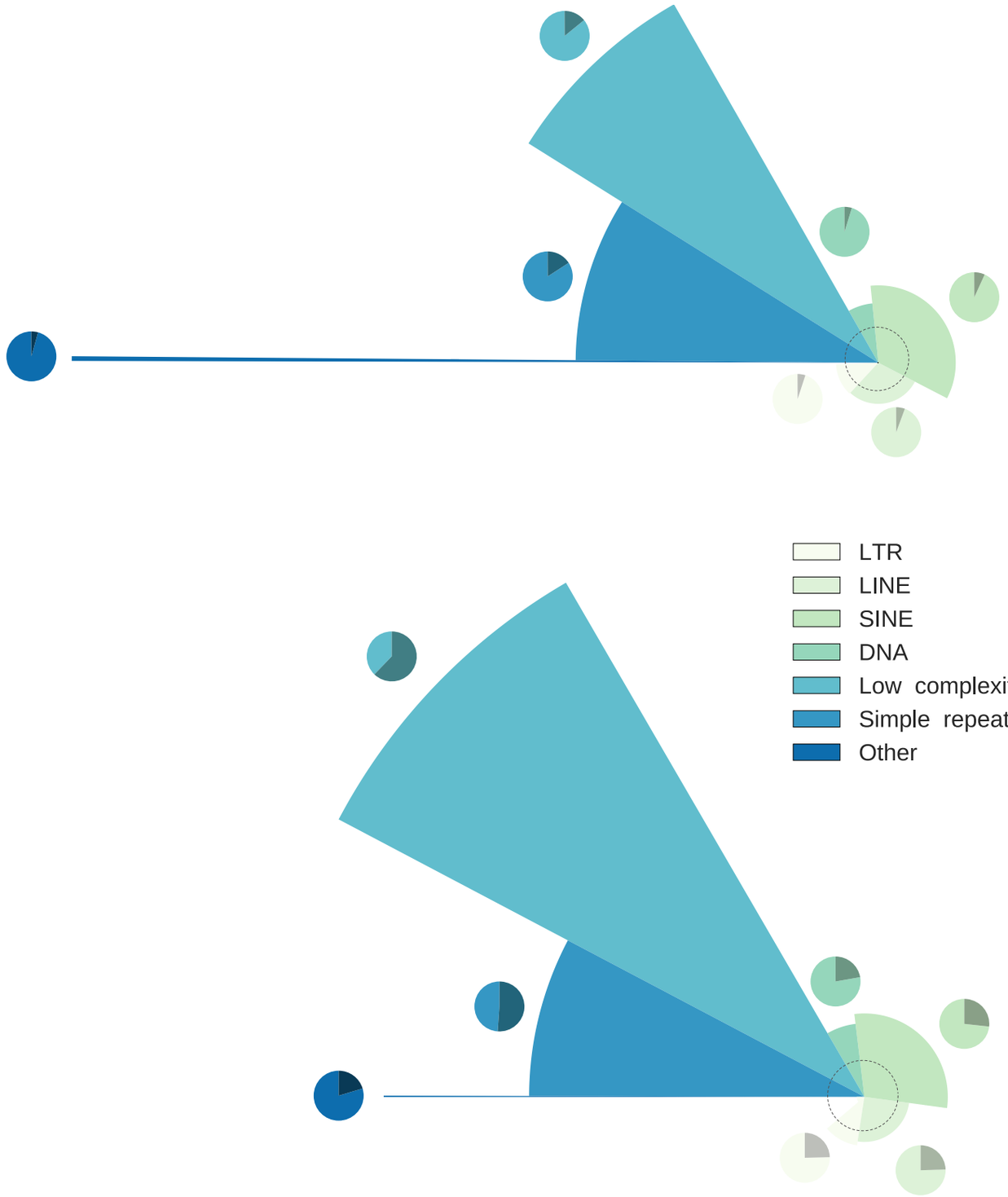


TTS and repetitive elements

ENST00000434346.1





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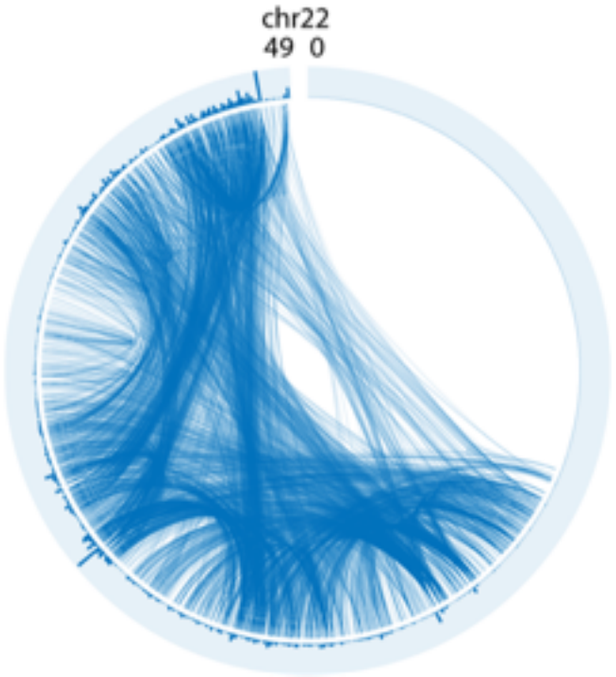

Staple RNA to hold DNA?

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

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