



Photo by David Oliete - [www.davidoliête.com](http://www.davidoliете.com)

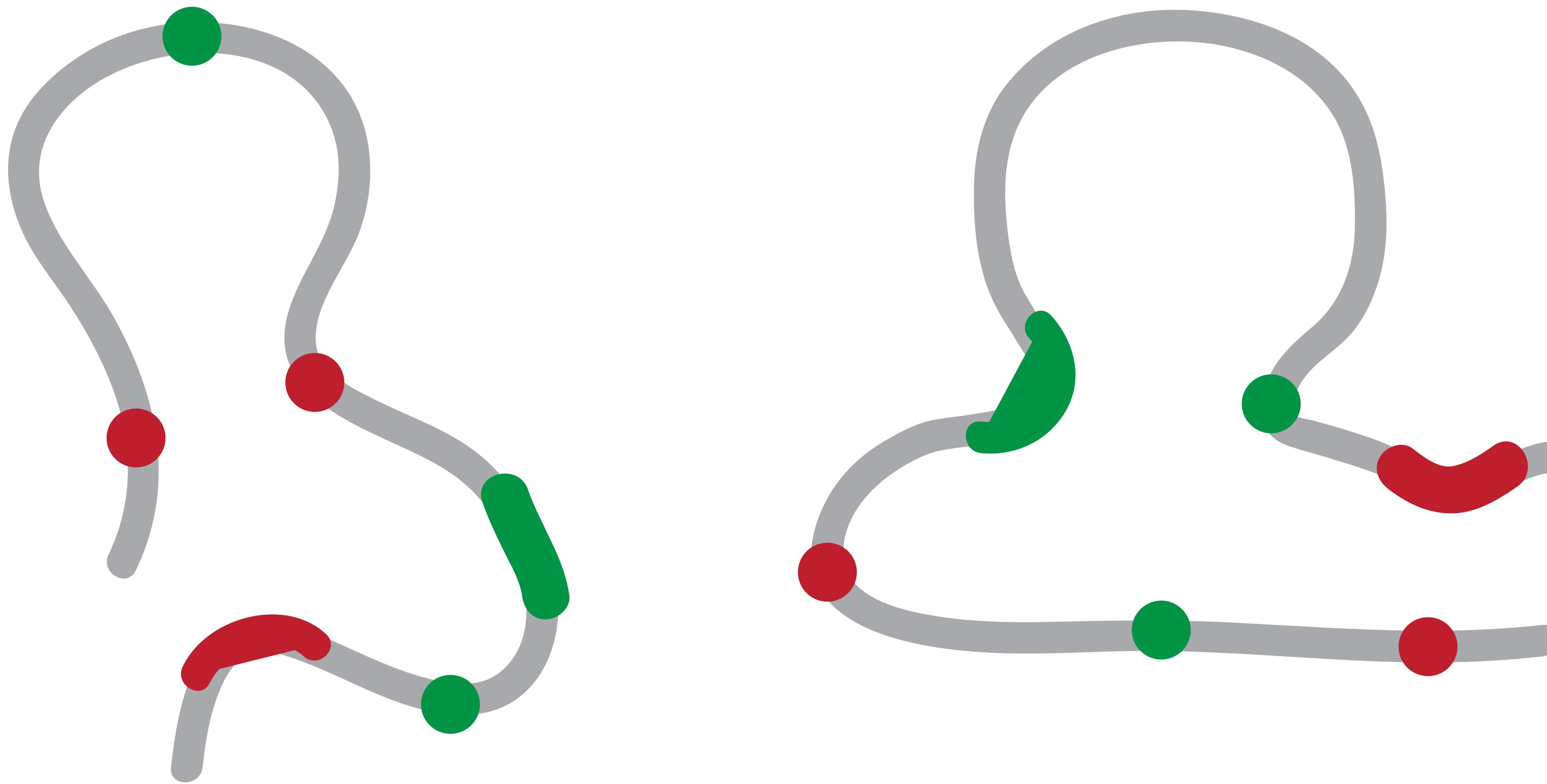
Structure determination of
genomes and genomic domains

Marc A. Martí-Renom
CNAG-CRG · ICREA

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

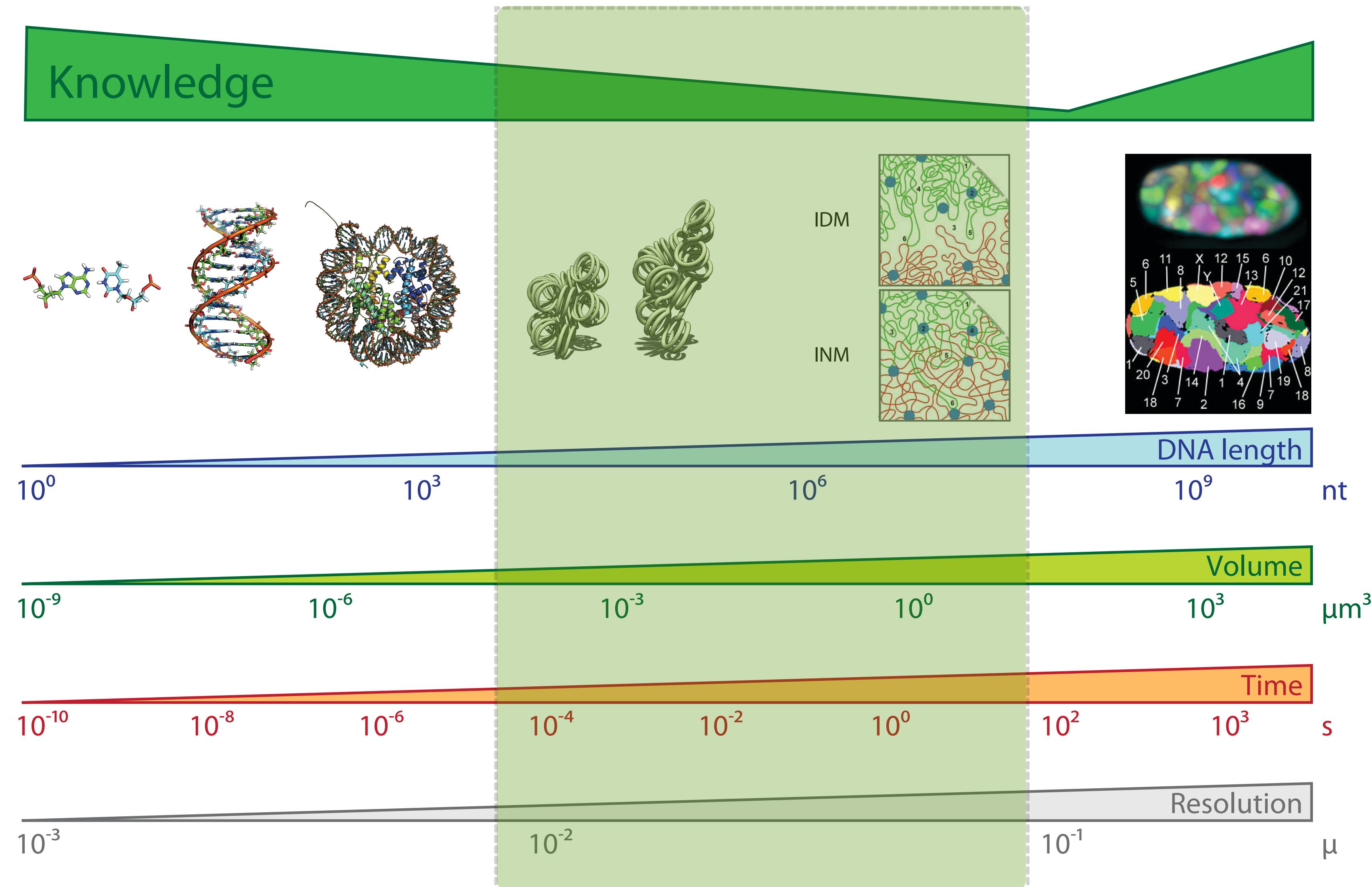


cnag CRG · ICREA



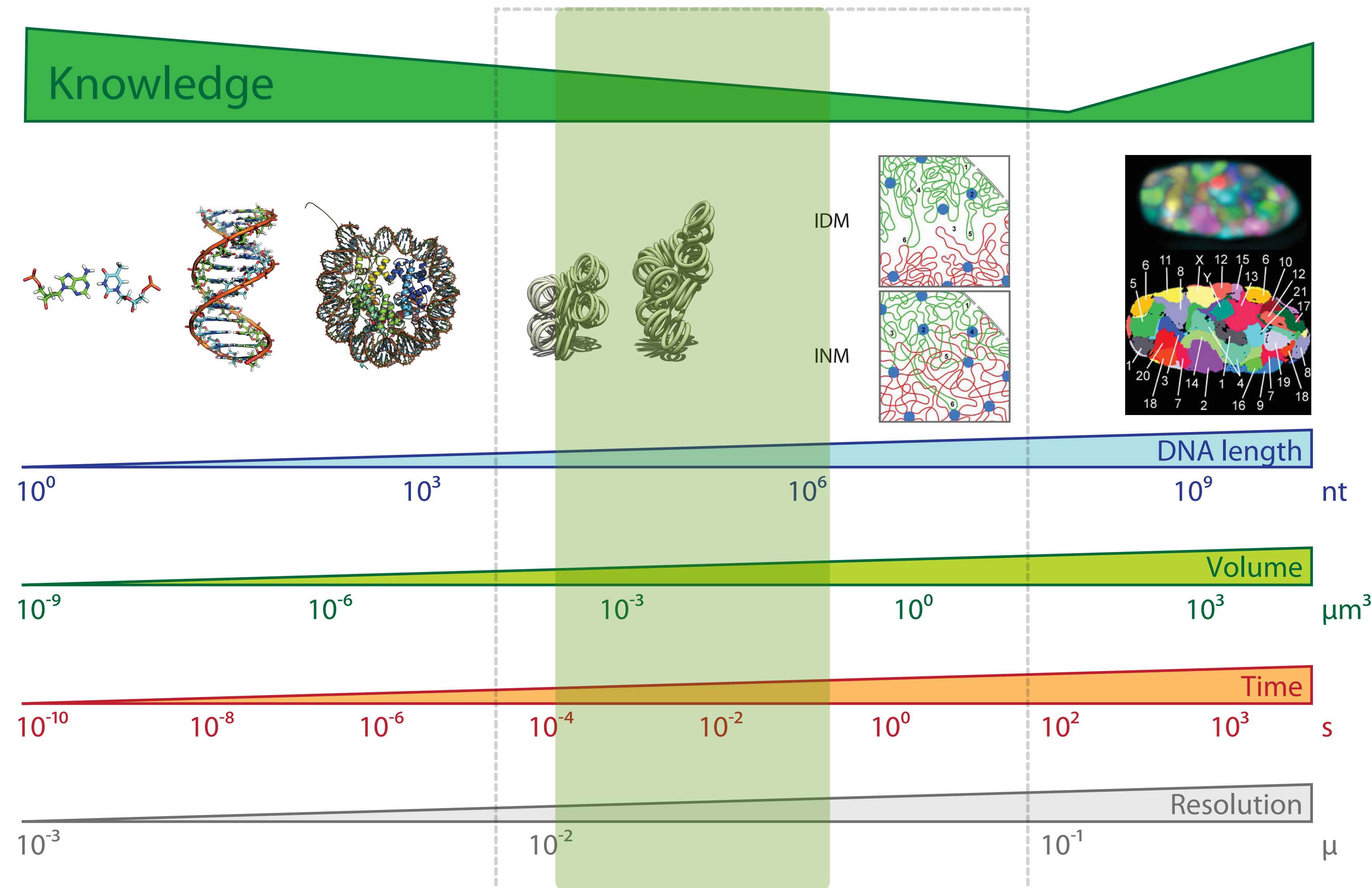
Resolution Gap

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



Resolution Gap

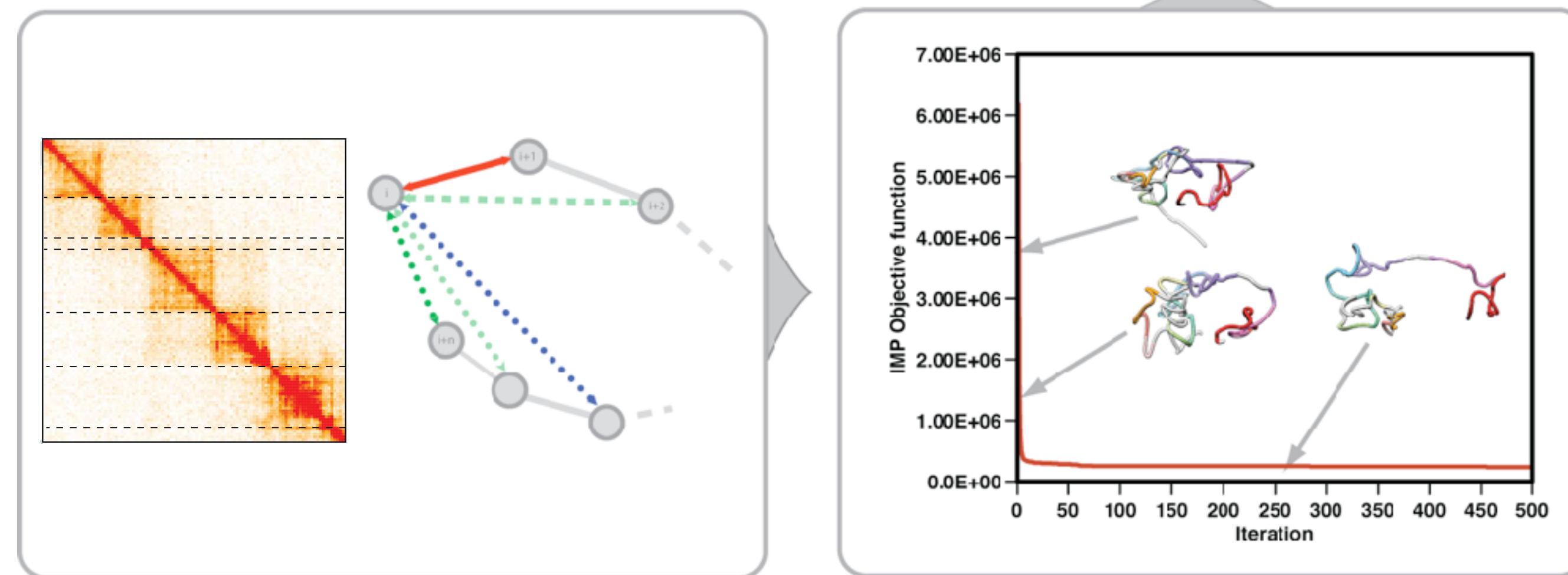
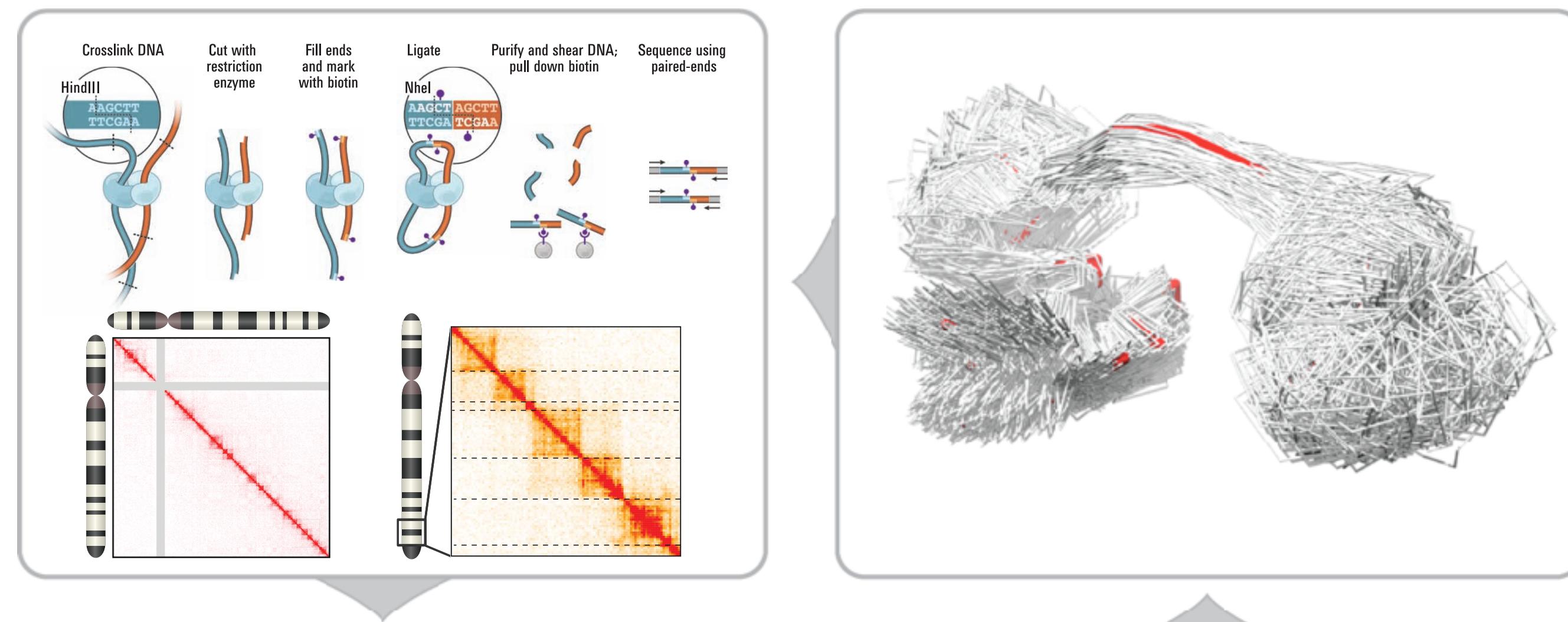
Marti-Renom, M. A. & Mirny, L. A. PLoS Comput Biol 7, e1002125 (2011)



Hybrid Method

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

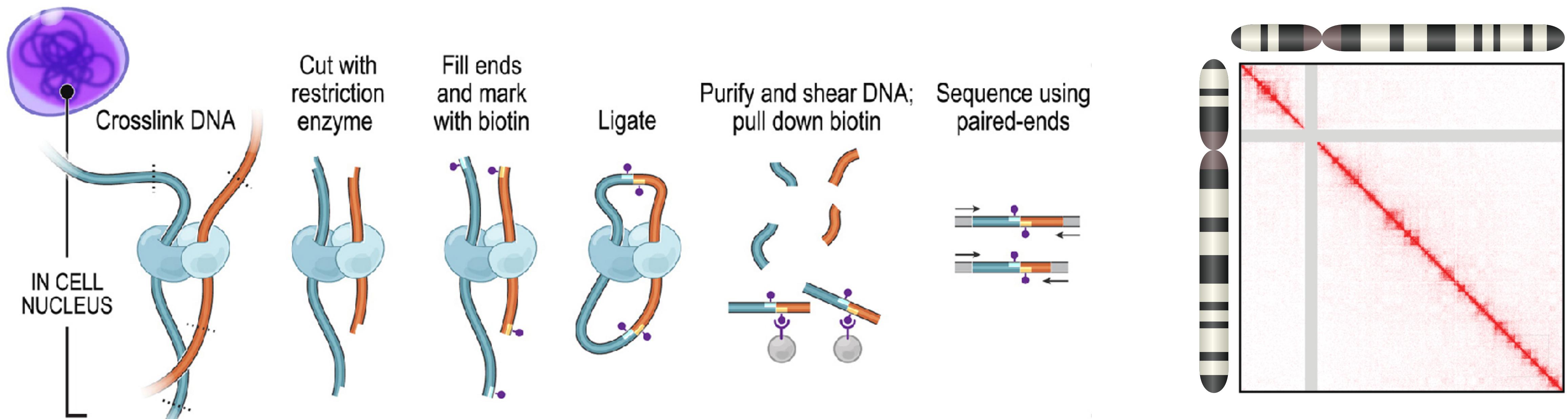
Experiments



Computation

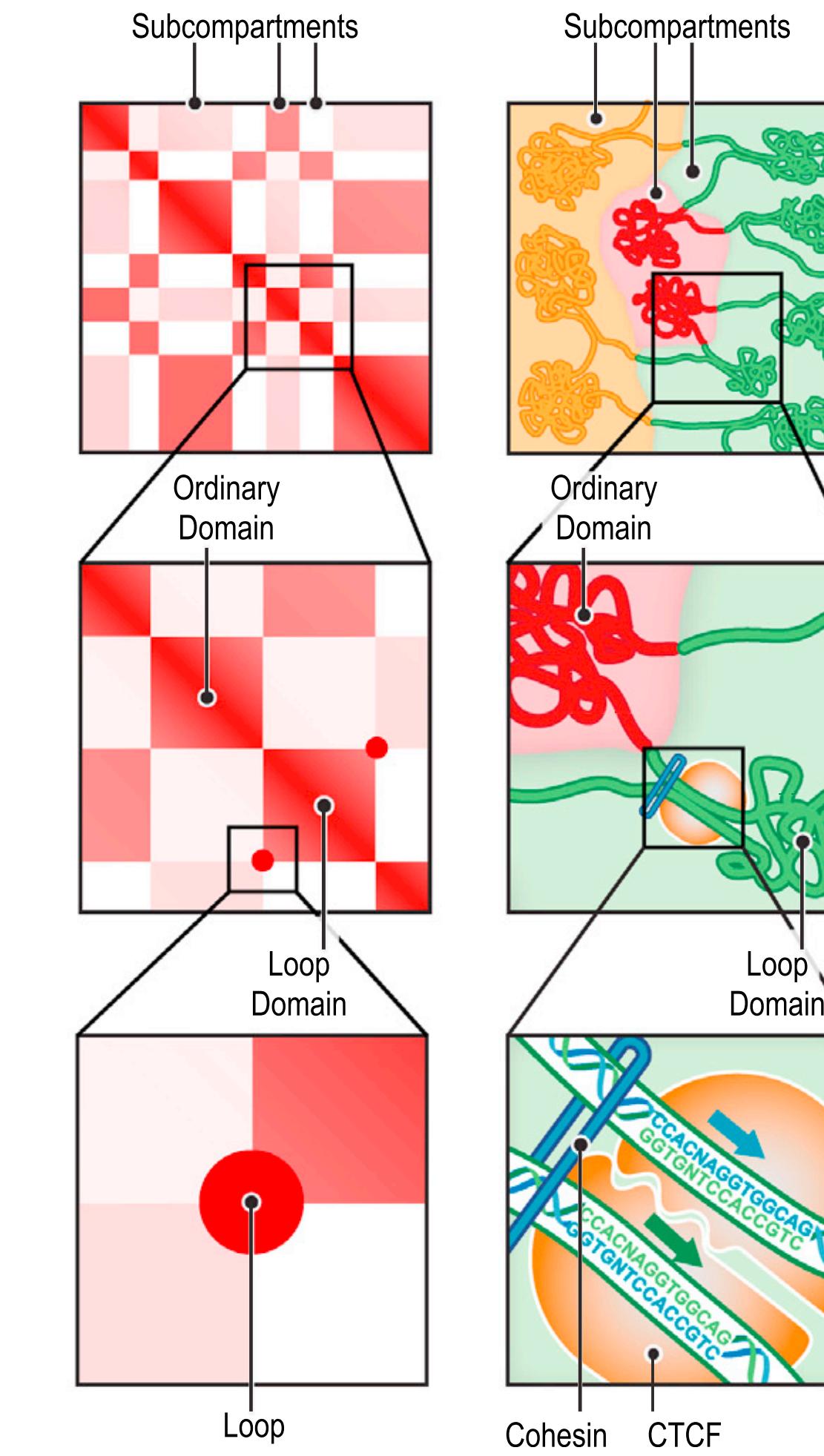
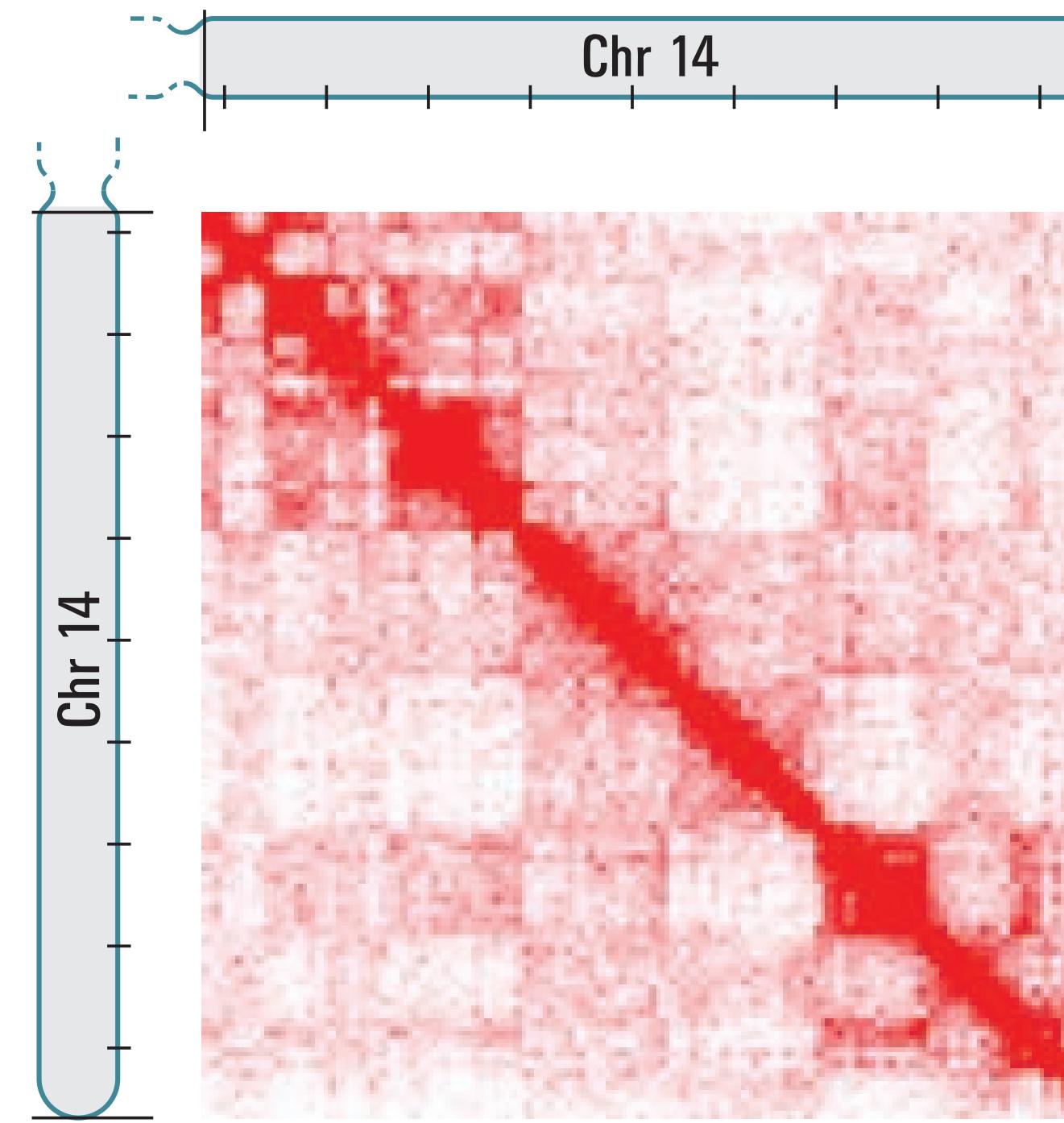
Chromosome Conformation Capture

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.



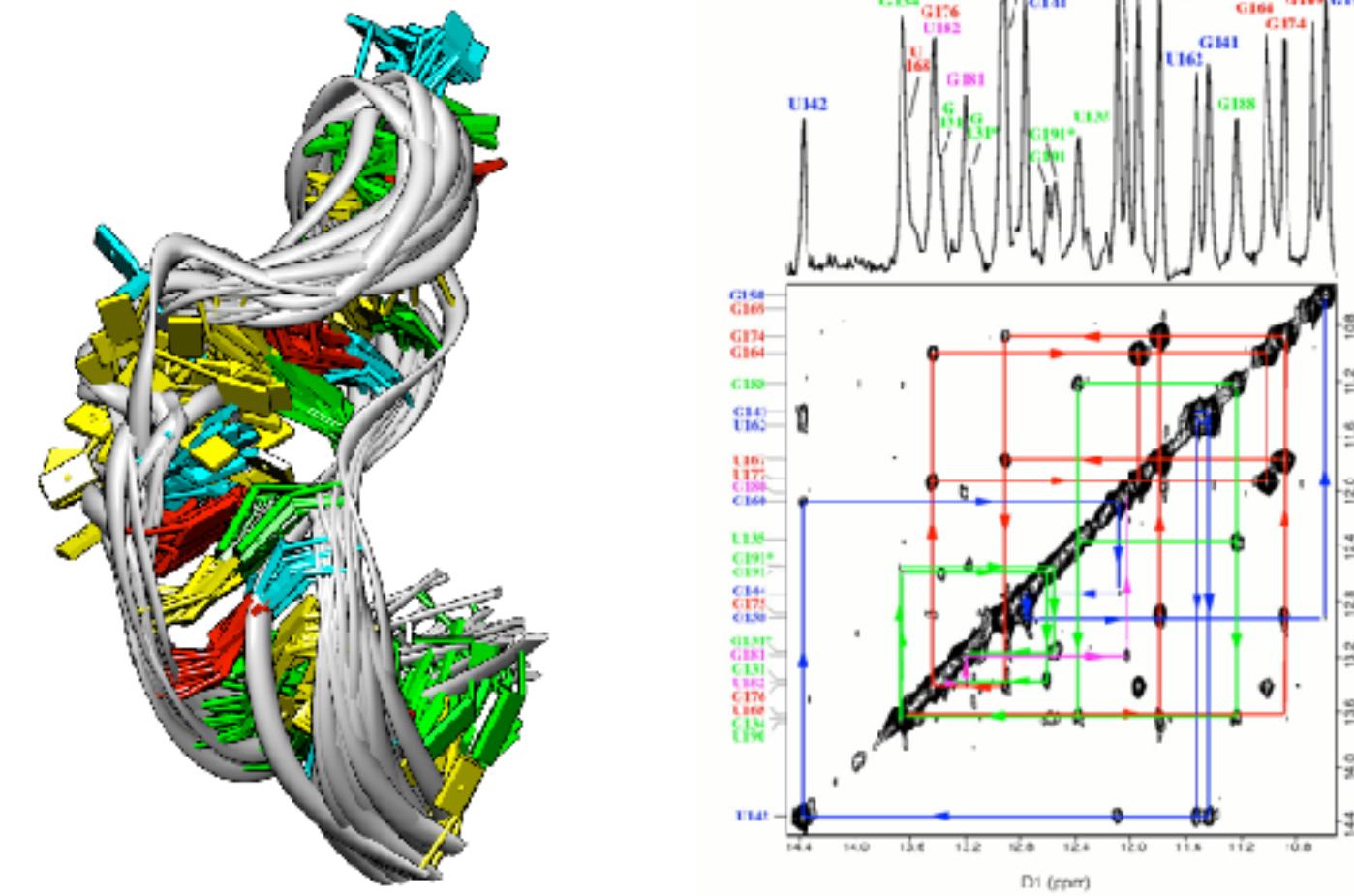
Hierarchical genome organisation

Lieberman-Aiden, E., et al. (2009). Science, 326(5950), 289–293.
Rao, S. S. P., et al. (2014). Cell, 1–29.

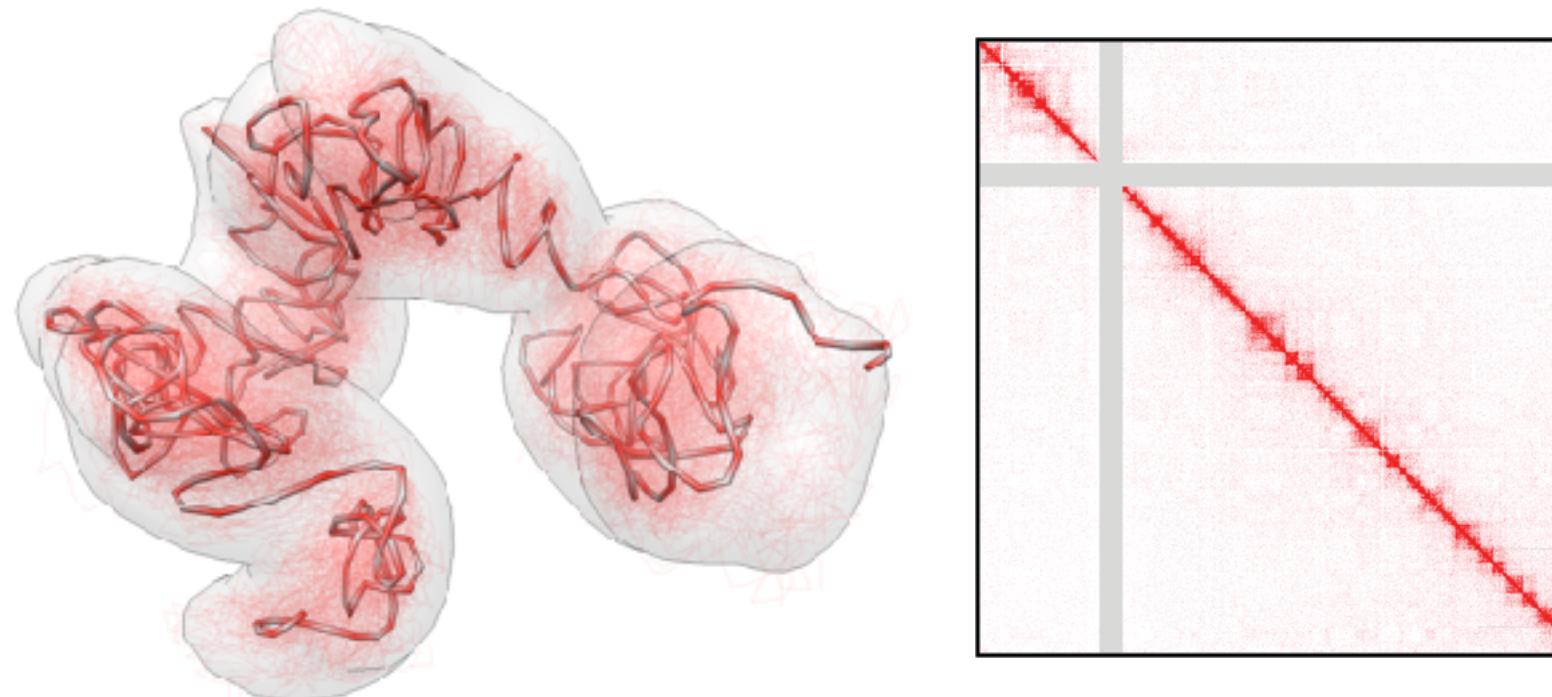


Restraint-based Modeling

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



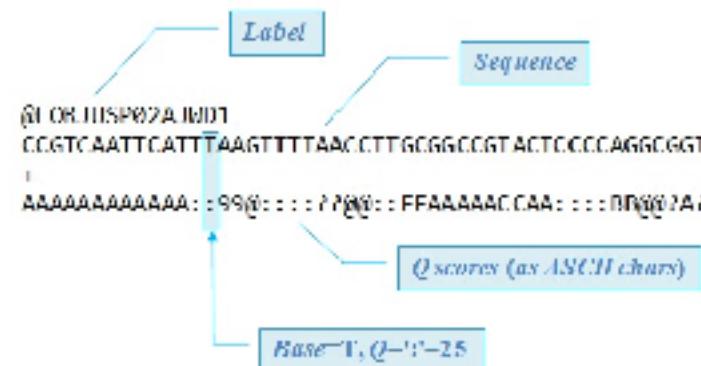
Biomolecular structure determination
2D-NOESY data



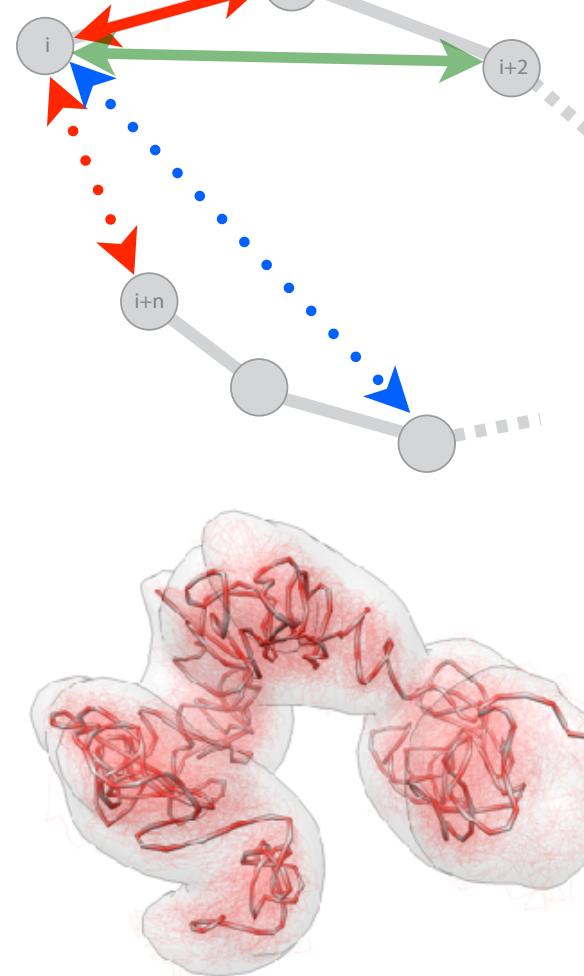
Chromosome structure determination
3C-based data



<http://3DGenomes.org>



FastQ files to Maps

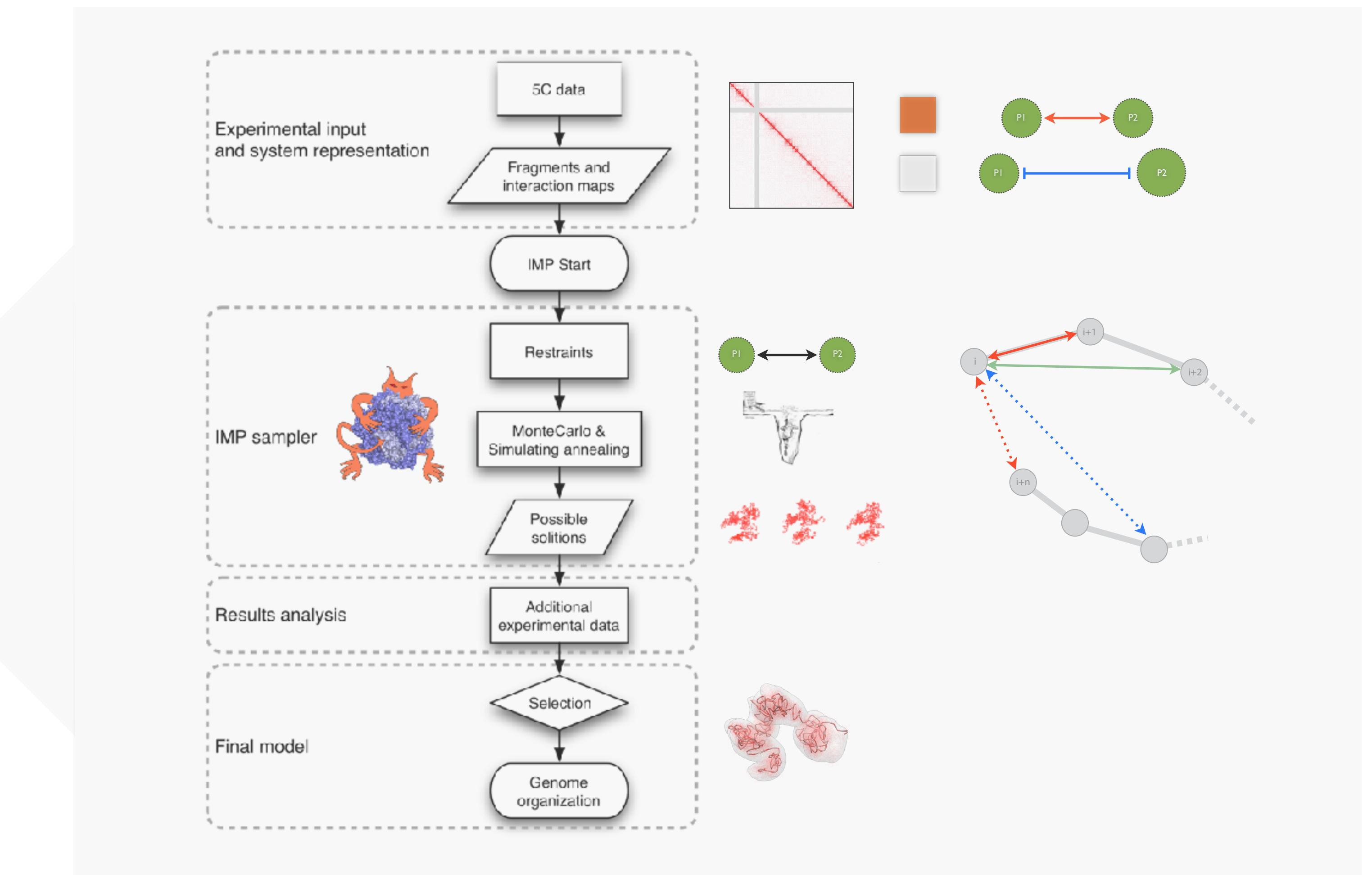


Model building

Model analysis

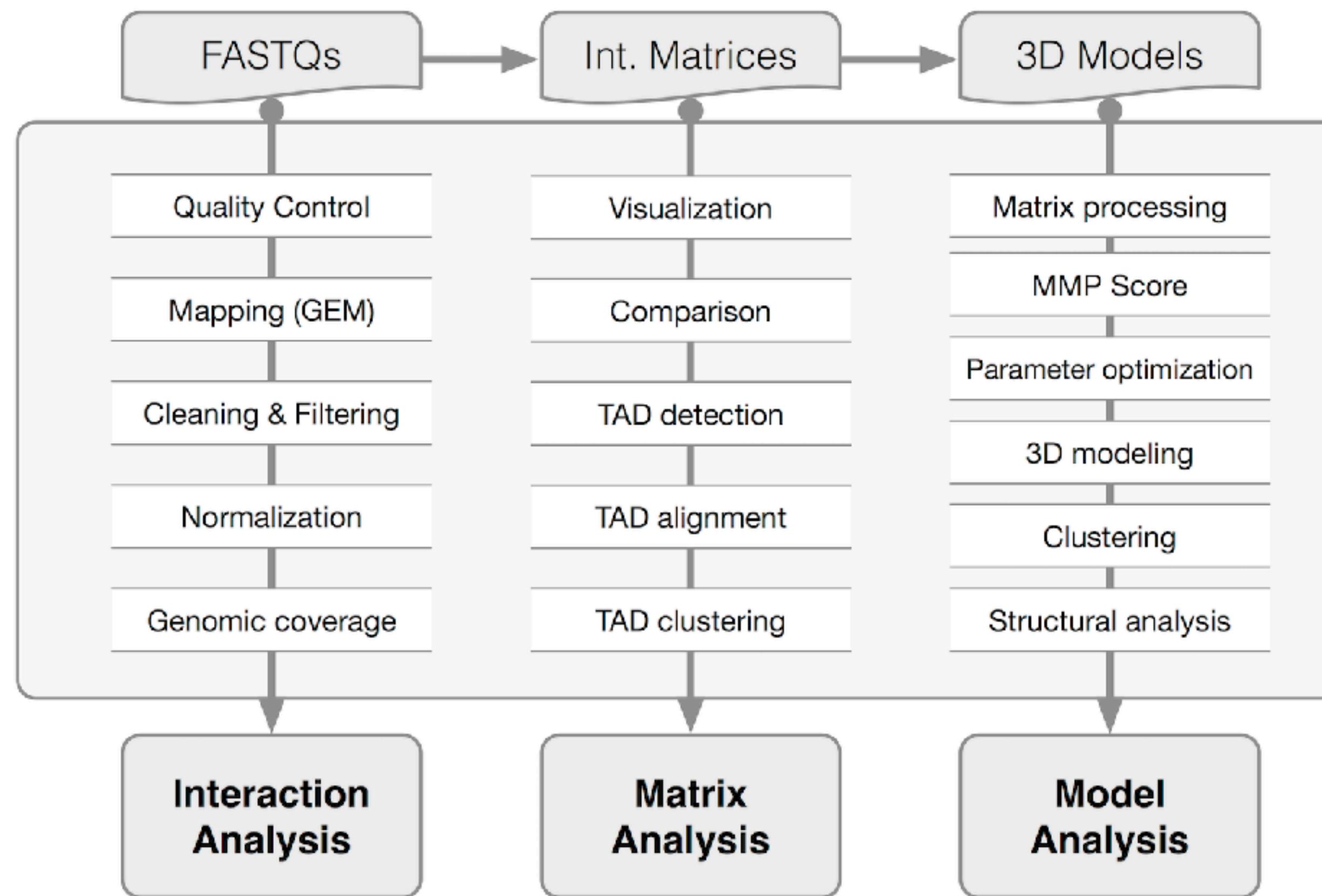
Map analysis

FastQ files to Maps





Serra, Baù, et al. (2017). PLOS CompBio



- 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)
- Belton, J.M. et al. Cell Reports (2015)
- Trussart M. et al. Nature Communication (2017)
- Cattoni, D. et al. Nature Communication (2017)
- Stadhouders R. et al. Nature Genetics (2018)
- Kojic, A., Cuadrado, A. et al. Nat Struct Mol Biol (2018)
- Beekman R. et al. Nature Medicine (2018)
- Mas, G. et al. Nature Genetics (2018)
- Pascual-Reguant, L. et al. Nature Communication (2018)
- Nir, Farabella, Perez-Estrada, et al. PLOS Genetics (2018)
- Cuadrado, Giménez-Llorente et al. Cell Reports (2019)
- Vara et al. Cell Reports (2019)
- Miguel-Escalada et al. Nature Genetics (2019)
- Morf et al. Nature Biotechnology (2019)
- Di Stefano et al. Genetics (2020)

Nature Structural & Molecular Biology, 25(9), 766-777, 2018
Cell, 173(7), 1796-1809.e17, 2018
Structure, 26(6), 894-904.e2, 2018
Genome Research, 29(1), 29-39, 2019
Genome Research, 29(1), gr.238527.118, 2019
Cell Systems 9, 1–13.e1–e6, 2019
Nature Communications, 10(1), 5355, 2019
BMC Biology, 17(1), 55, 2019
Molecular Cell, 2019
Cell Systems, 9(5), 446-458.e6, 2019



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3D structural dynamics of the SOX2 locus activation

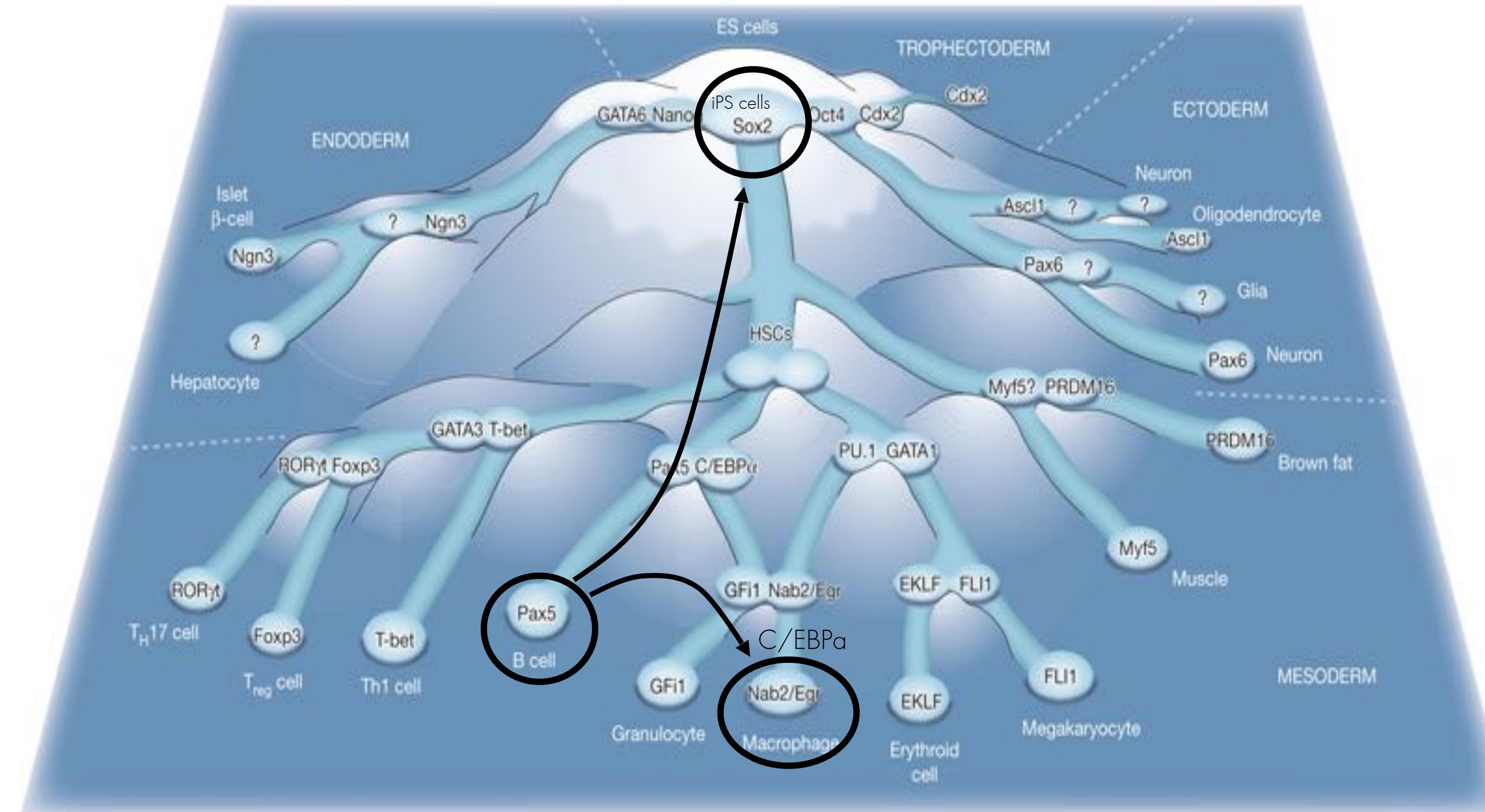


**Marco di Stefano
Ralph Stadhouders**
with Graf Lab (CRG, Barcelona)

Nature Genetics (2018) 50 238–249 & BioRxived

Transcription factors dictate cell fate

Graf & Enver (2009) Nature

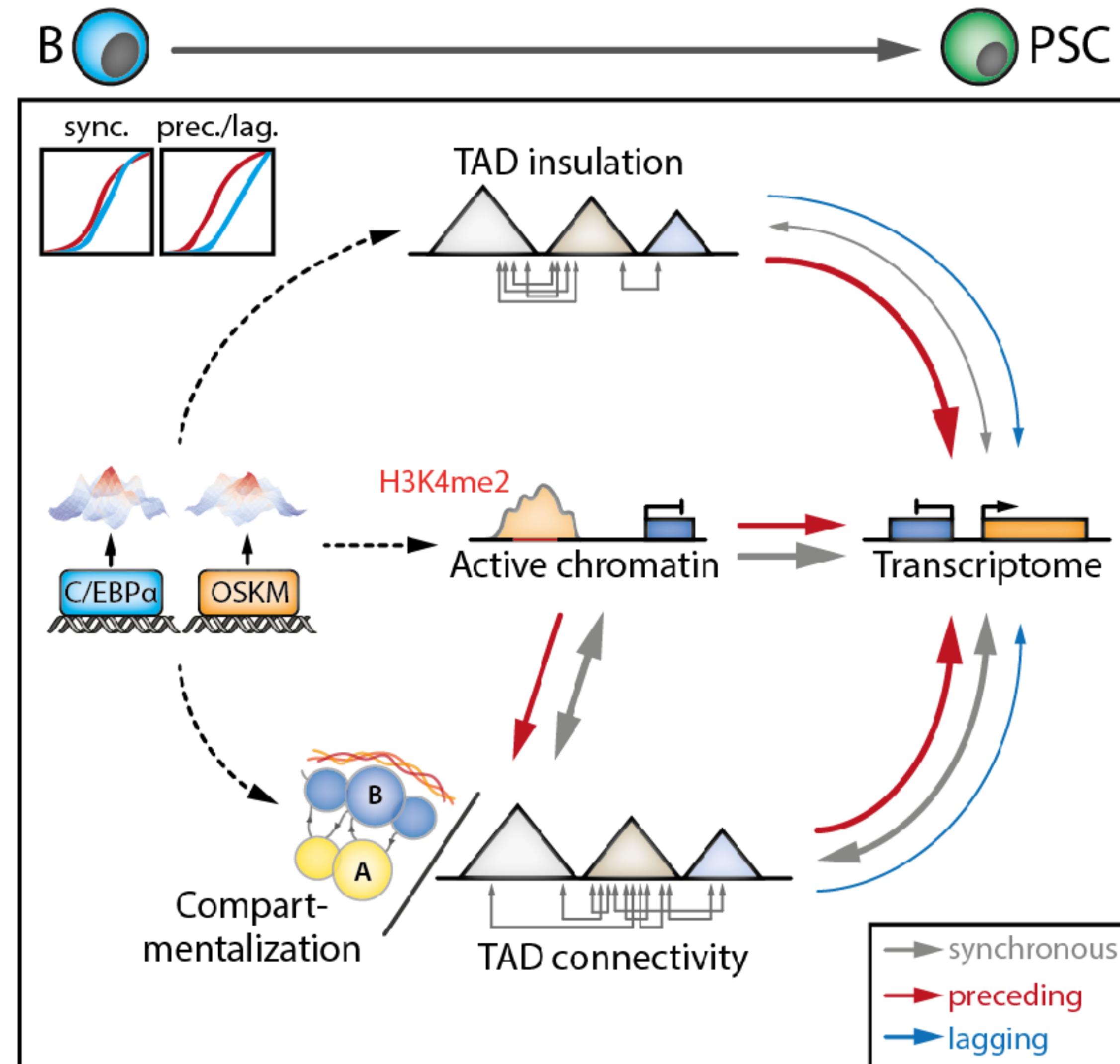


Transcription factors (TFs) determine cell identity through gene regulation
Normal 'forward' differentiation

Cell fates can be converted by enforced TF expression
Transdifferentiation or reprogramming

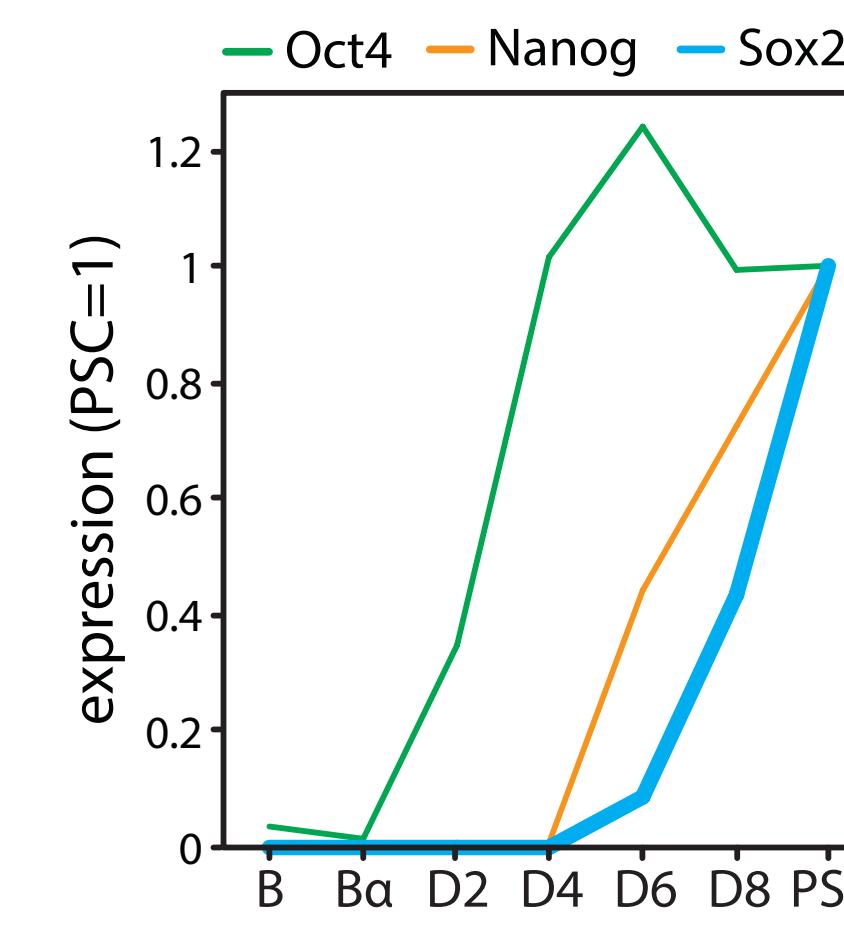
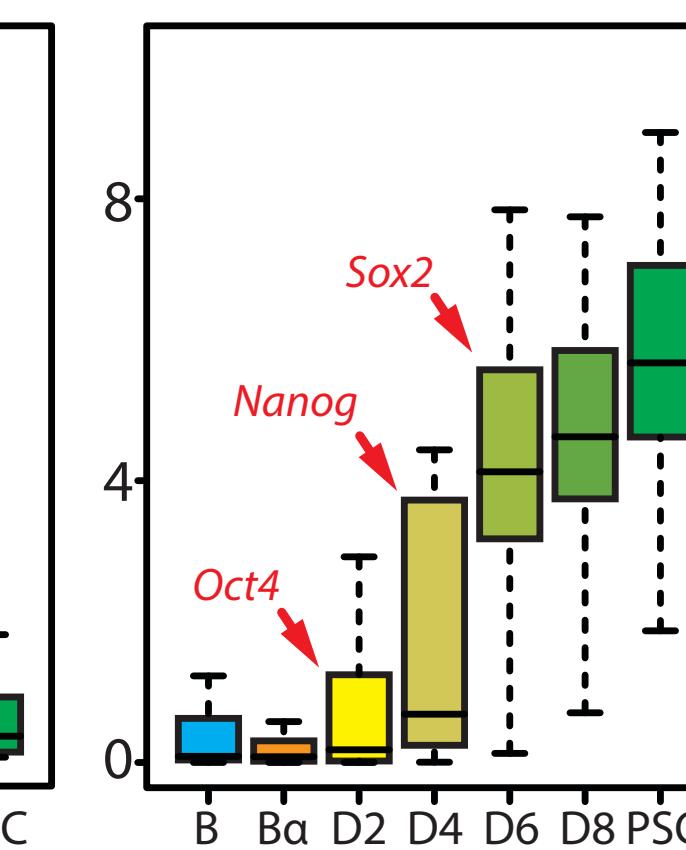
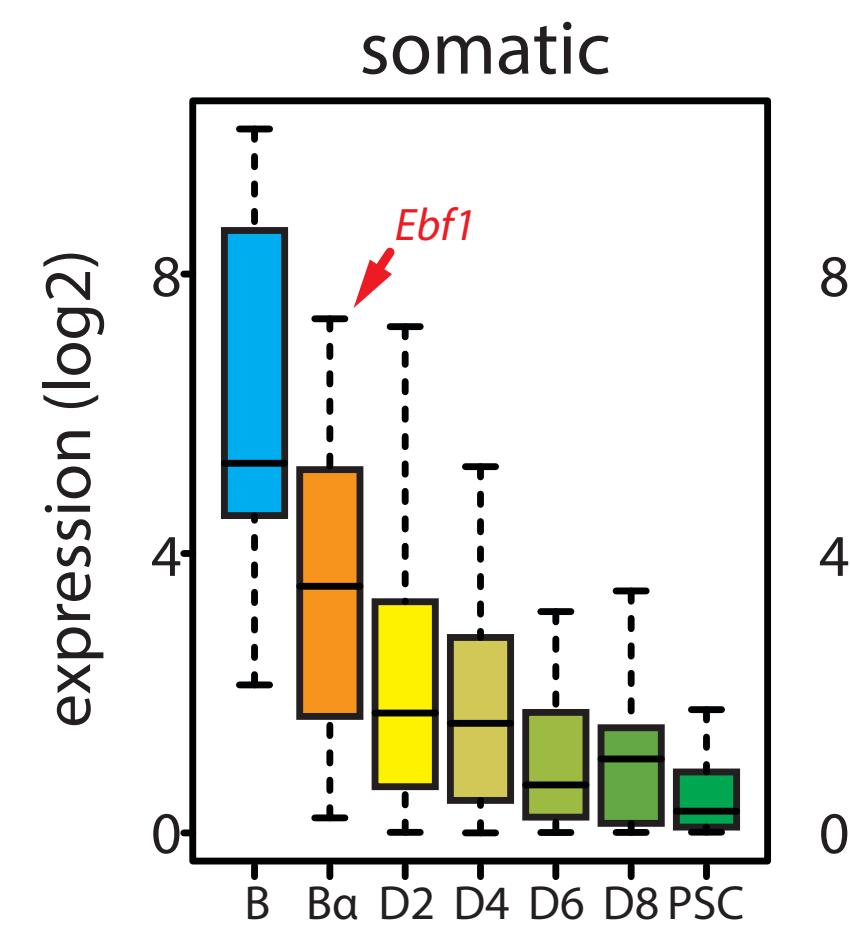
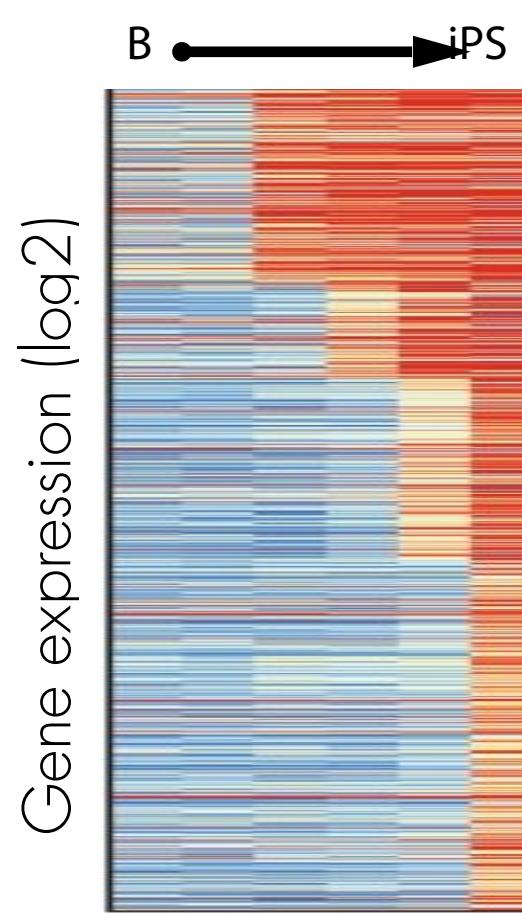
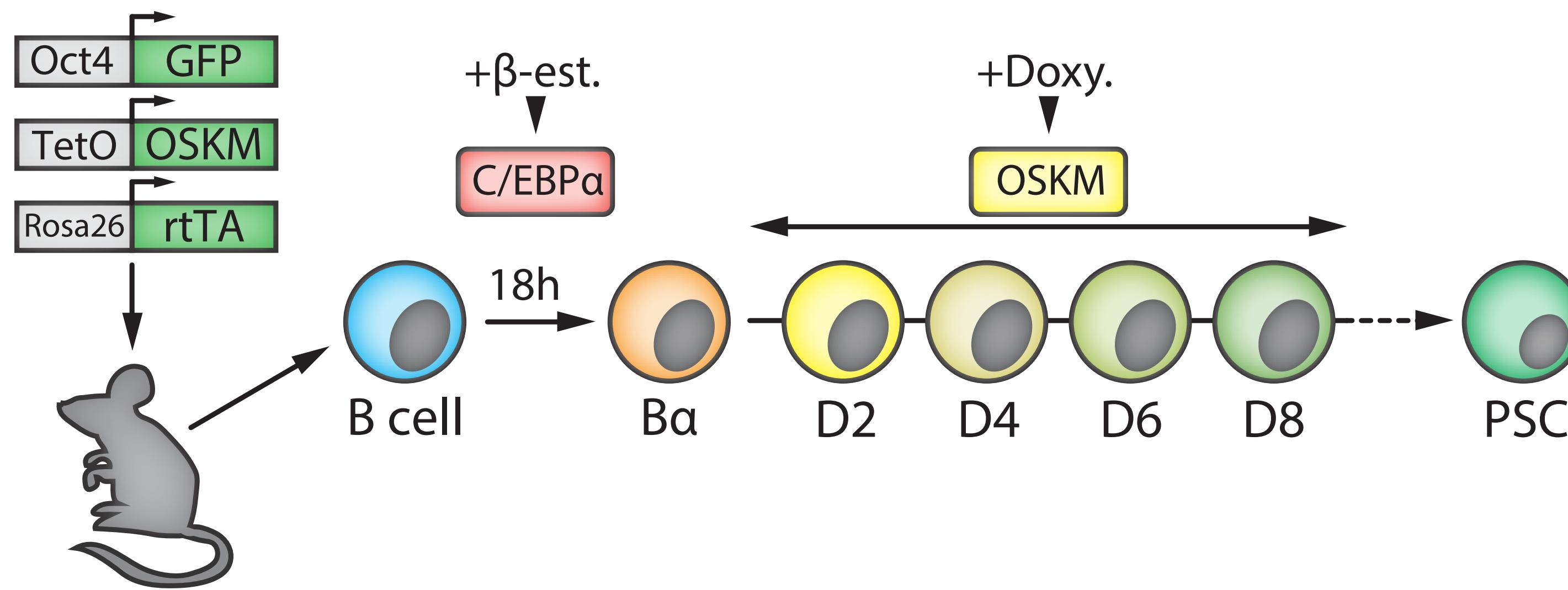
Interplay: topology, gene expression & chromatin

Graf & Enver (2009) Nature
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

Sox2

new TAD border

Sox2 SE

1.6 Mb

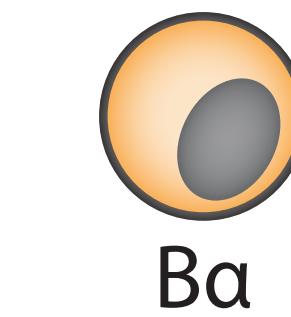
Oct4 — Nanog — Sox2

expression (PSC=1)

B Ba D2 D4 D6 D8 PSC



B cell



Ba



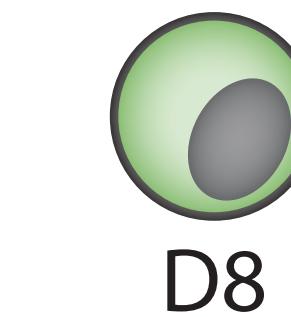
D2



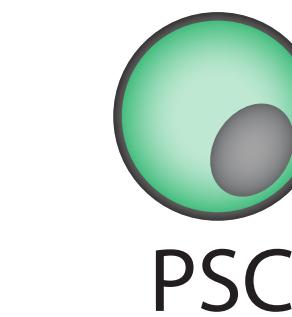
D4



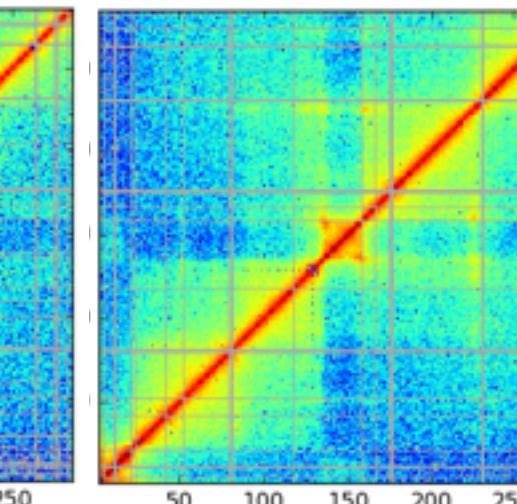
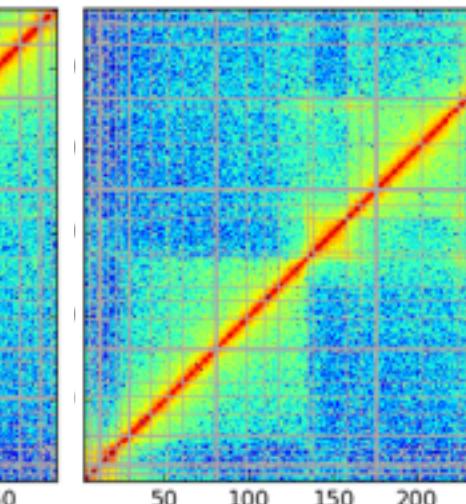
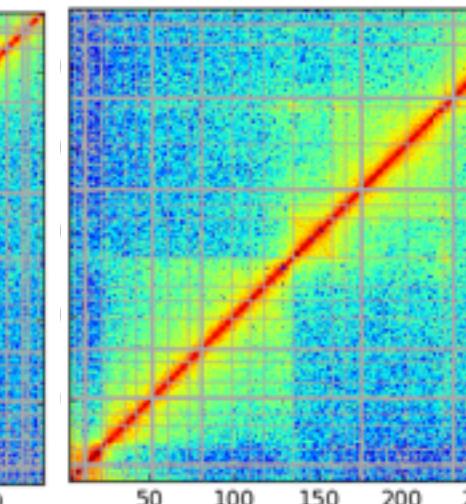
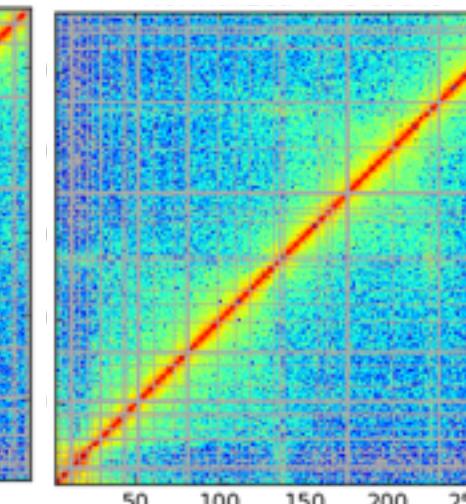
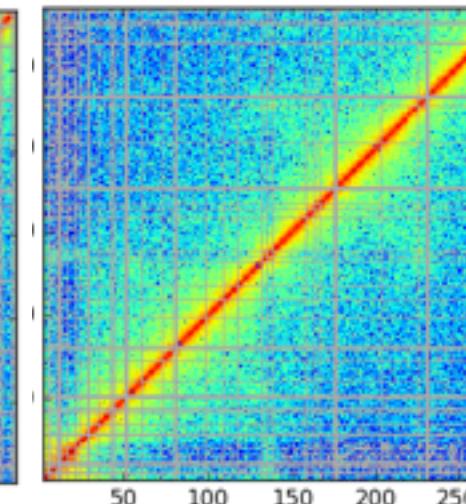
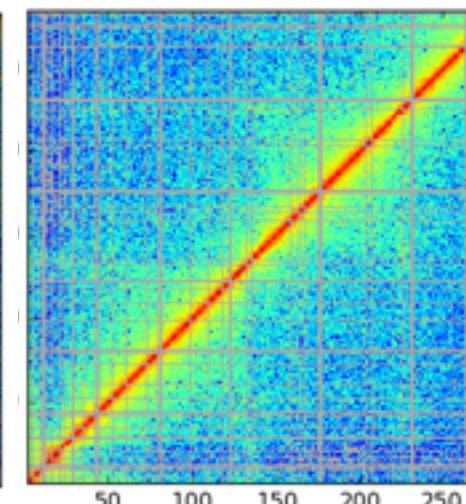
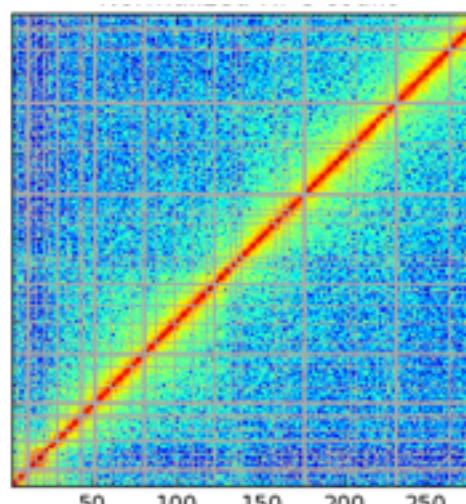
D6



D8



PSC

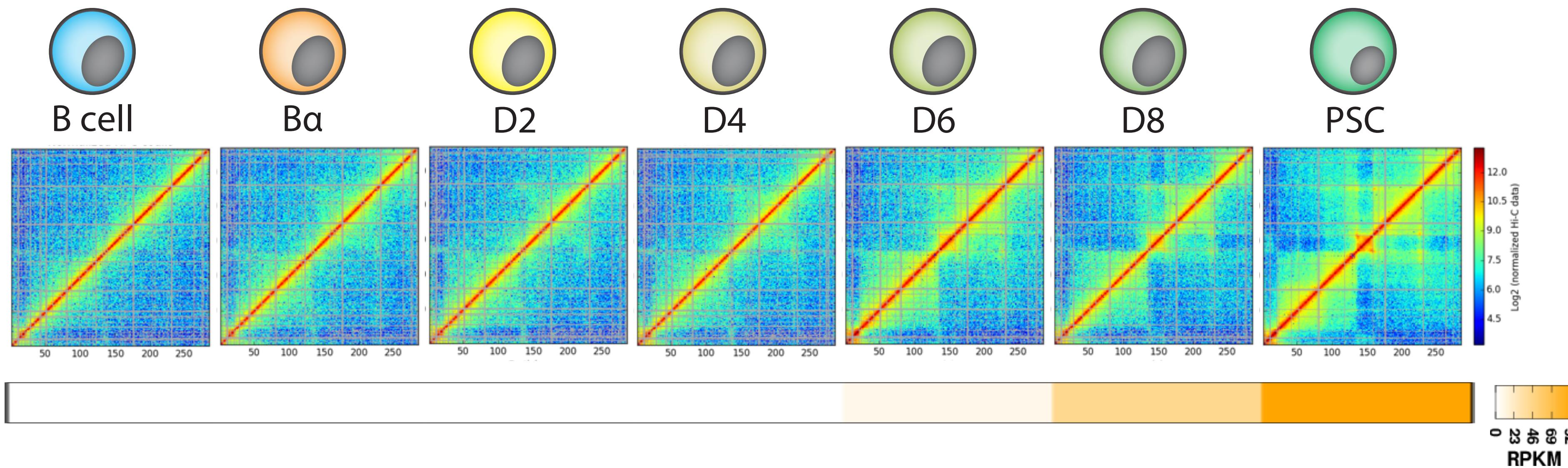


Log₂ (normalized Hi-C data)

12.0
10.5
9.0
7.5
6.0
4.5

Hi-C maps of reprogramming from B to PSC

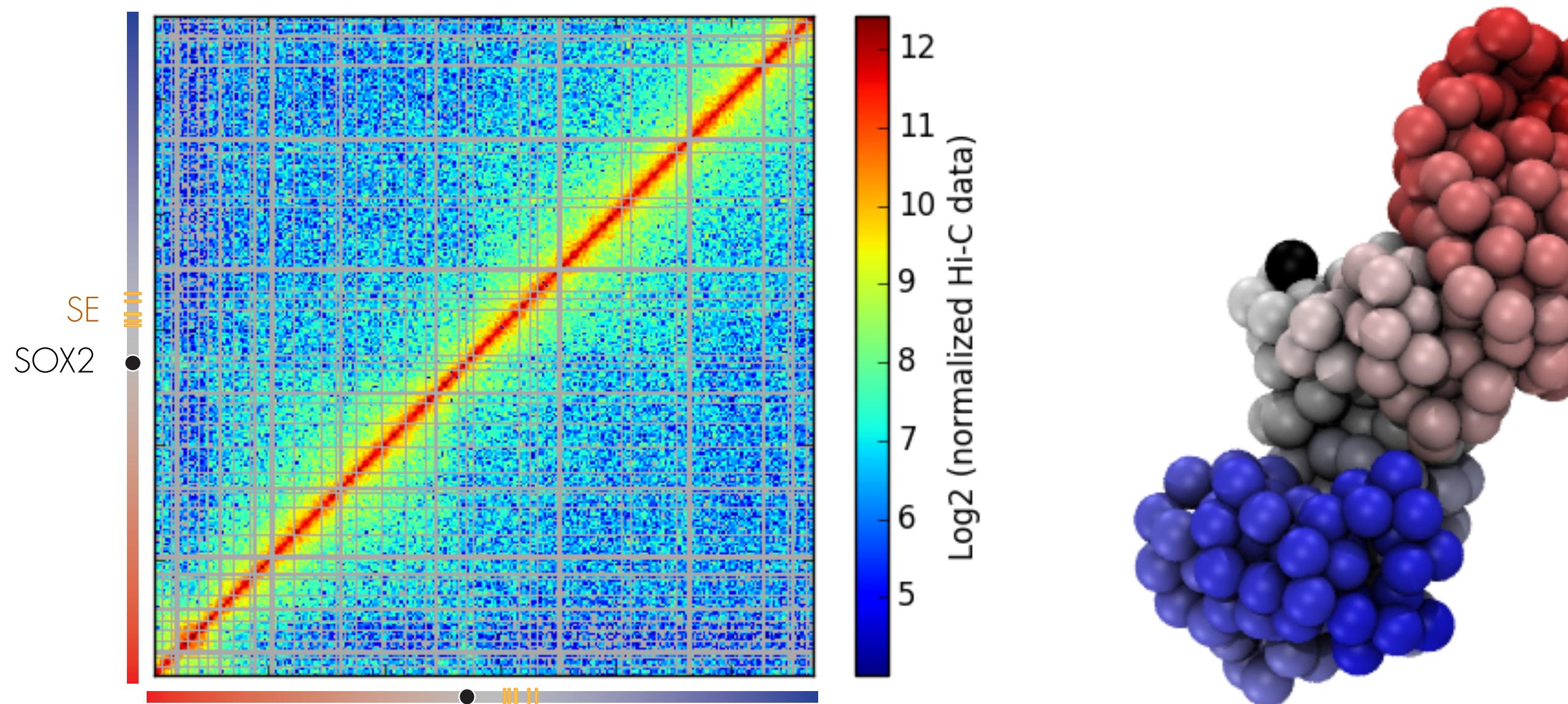
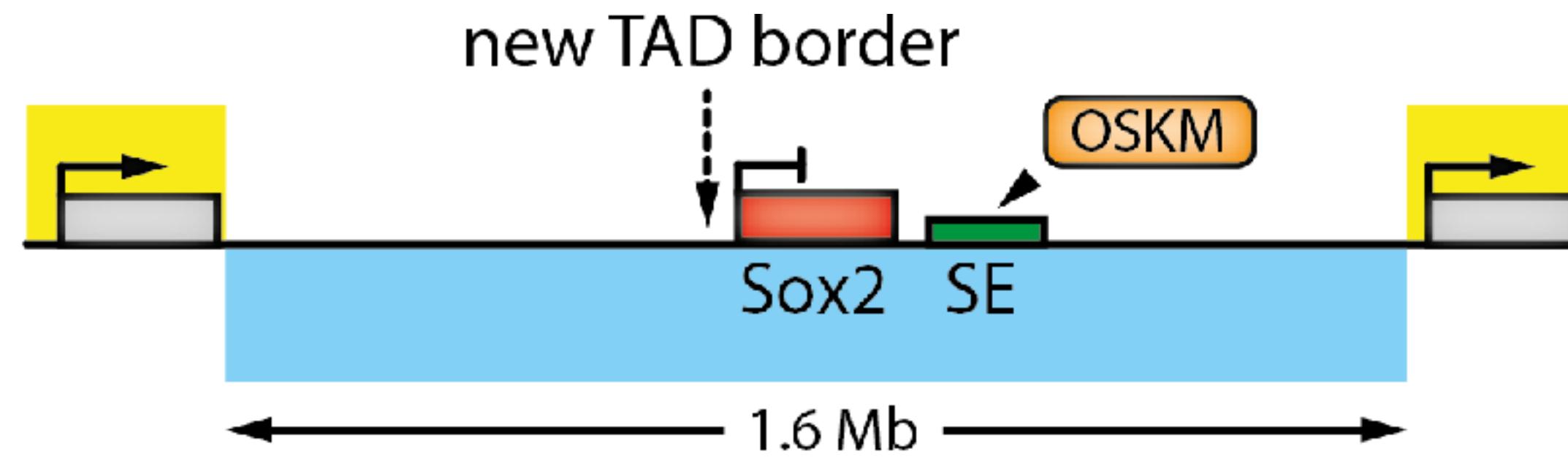
The SOX2 locus



How does these structural rearrangements interplay with the transcription activity?

What are the main drivers of structural transitions?

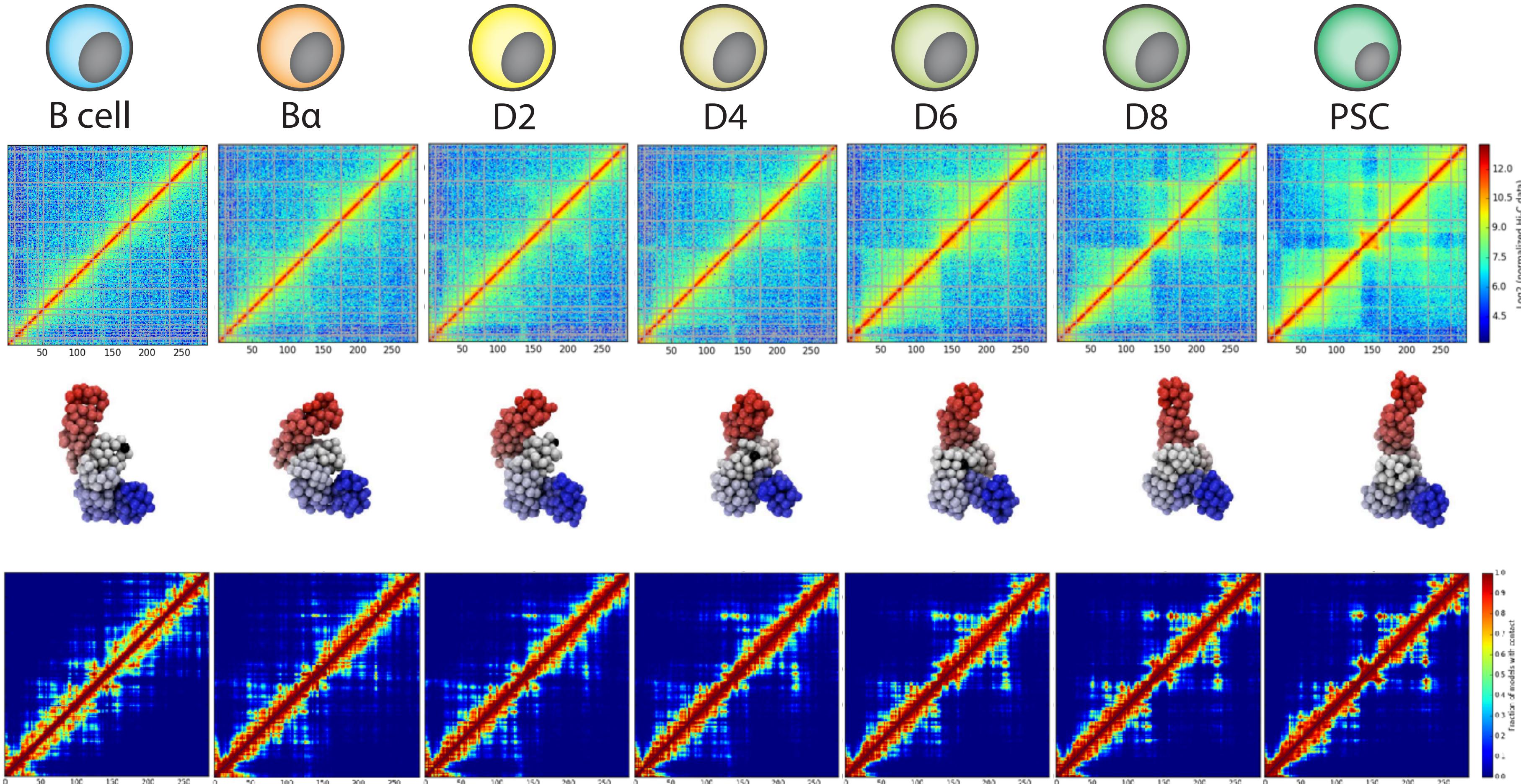
TADbit modeling of SOX2 from B cells Hi-C



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

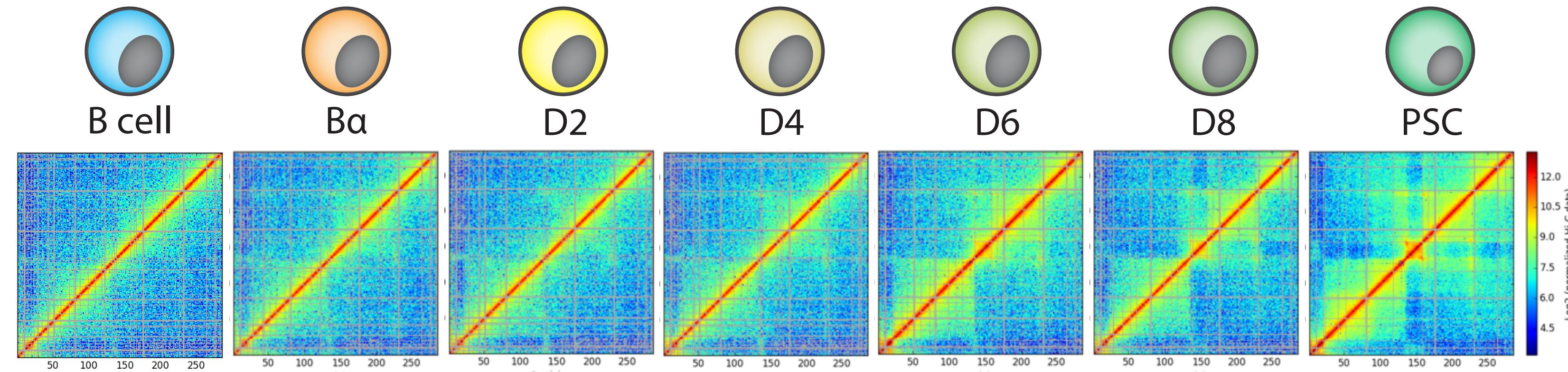
Models of reprogramming from B to PSC

The SOX2 locus



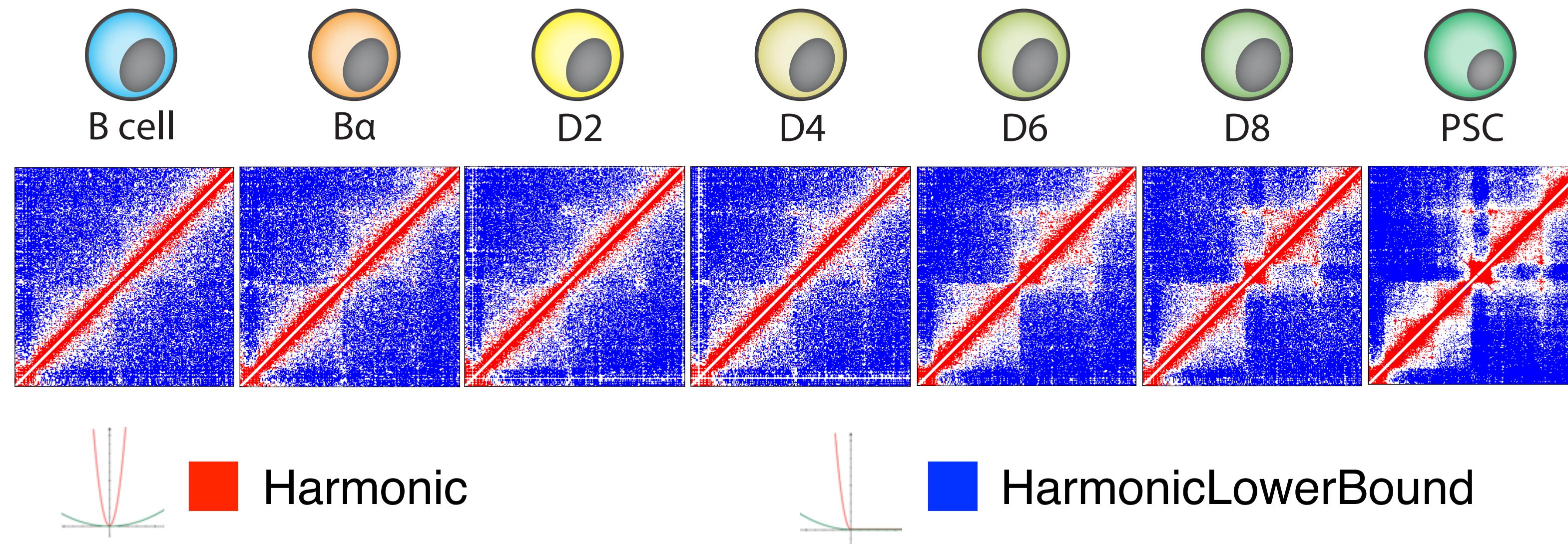
TADdyn: from time-series Hi-C maps to dynamic restraints

The SOX2 locus



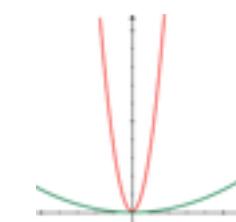
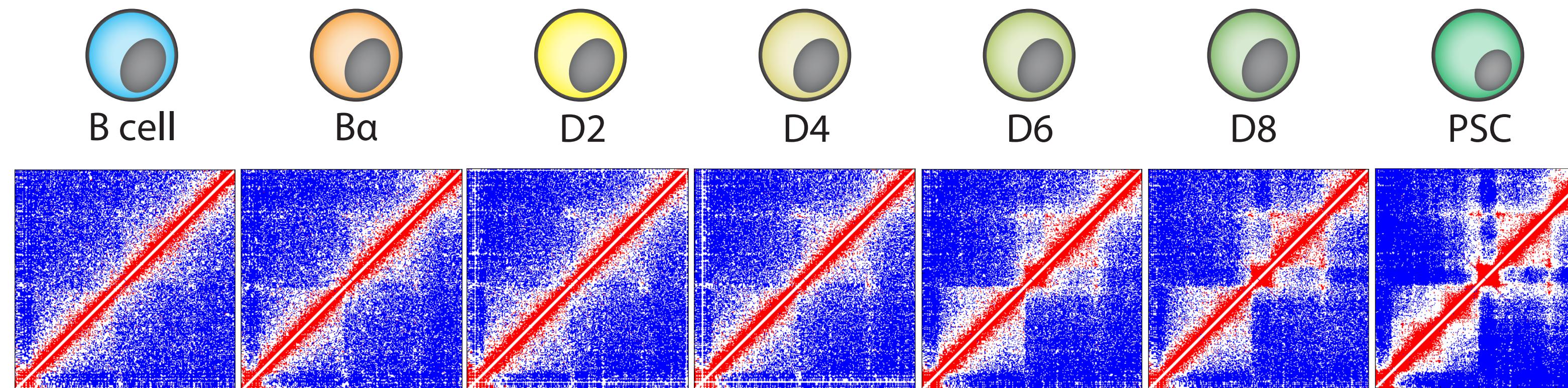
TADdyn: from time-series Hi-C maps to dynamic restraints

The SOX2 locus

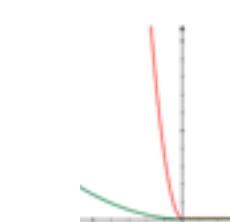


TADdyn: from time-series Hi-C maps to dynamic restraints

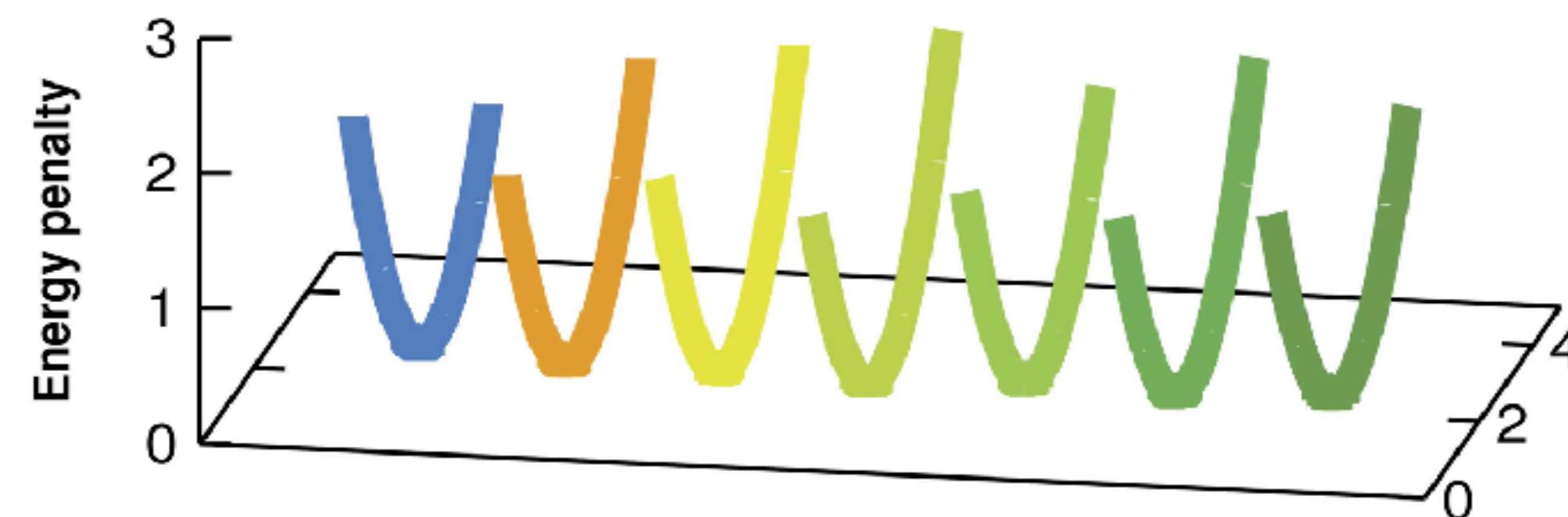
The SOX2 locus



Harmonic



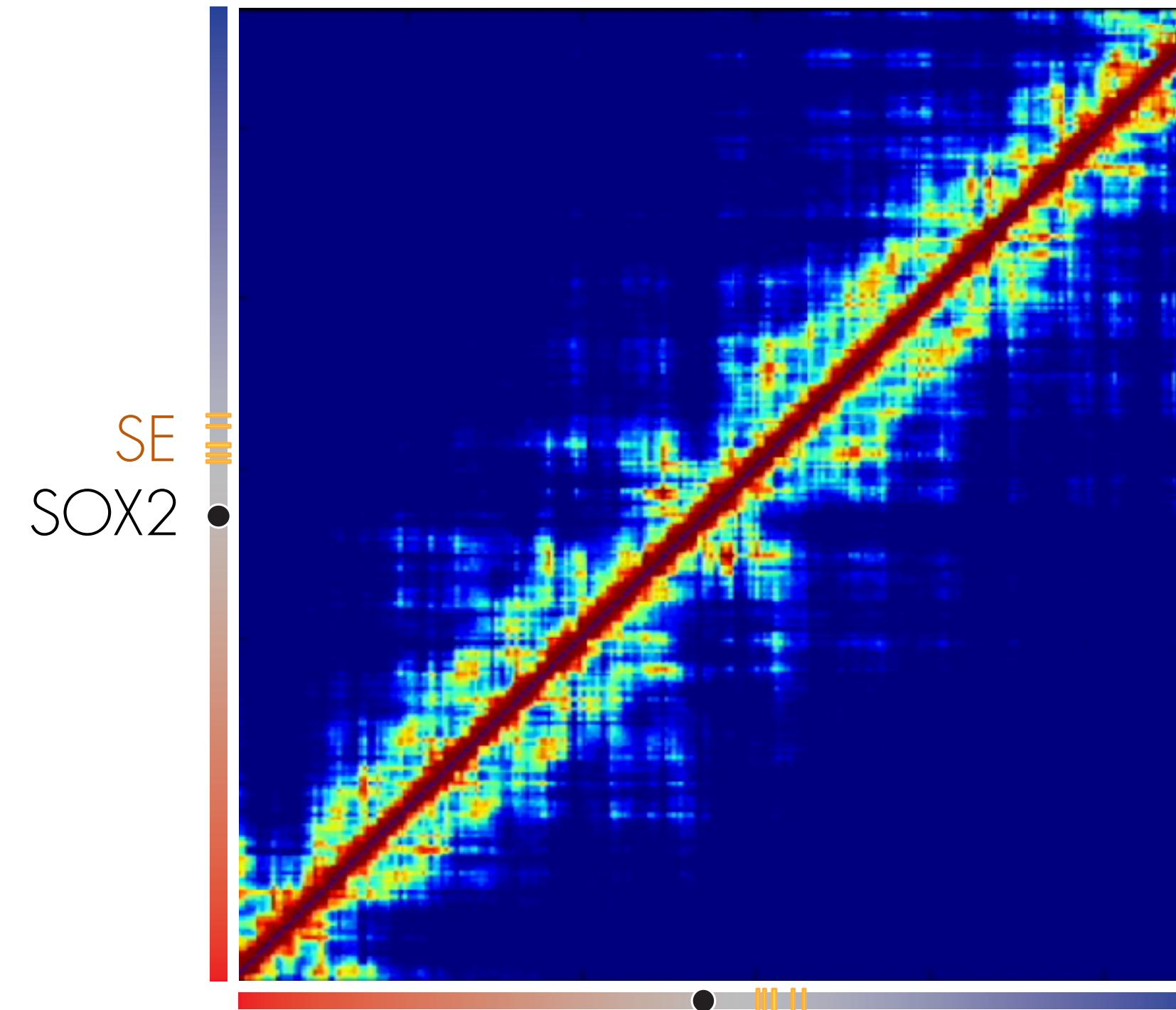
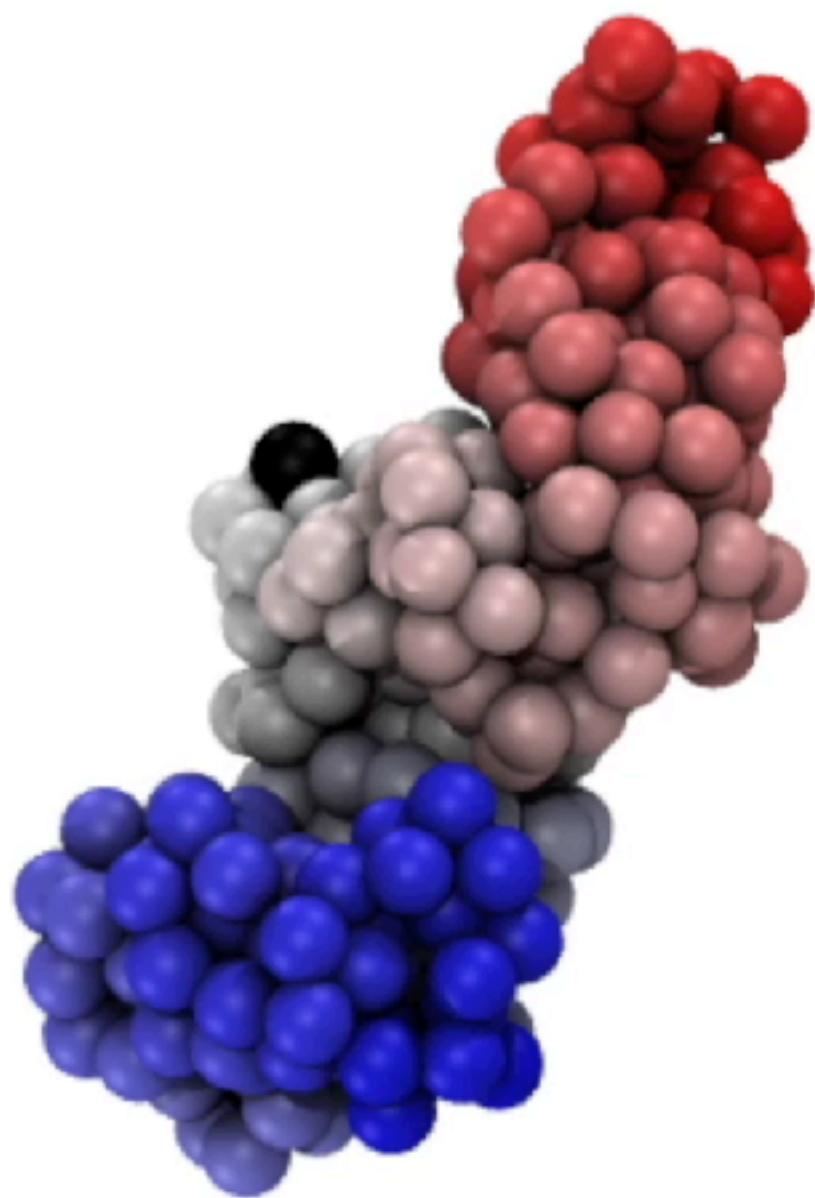
HarmonicLowerBound



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

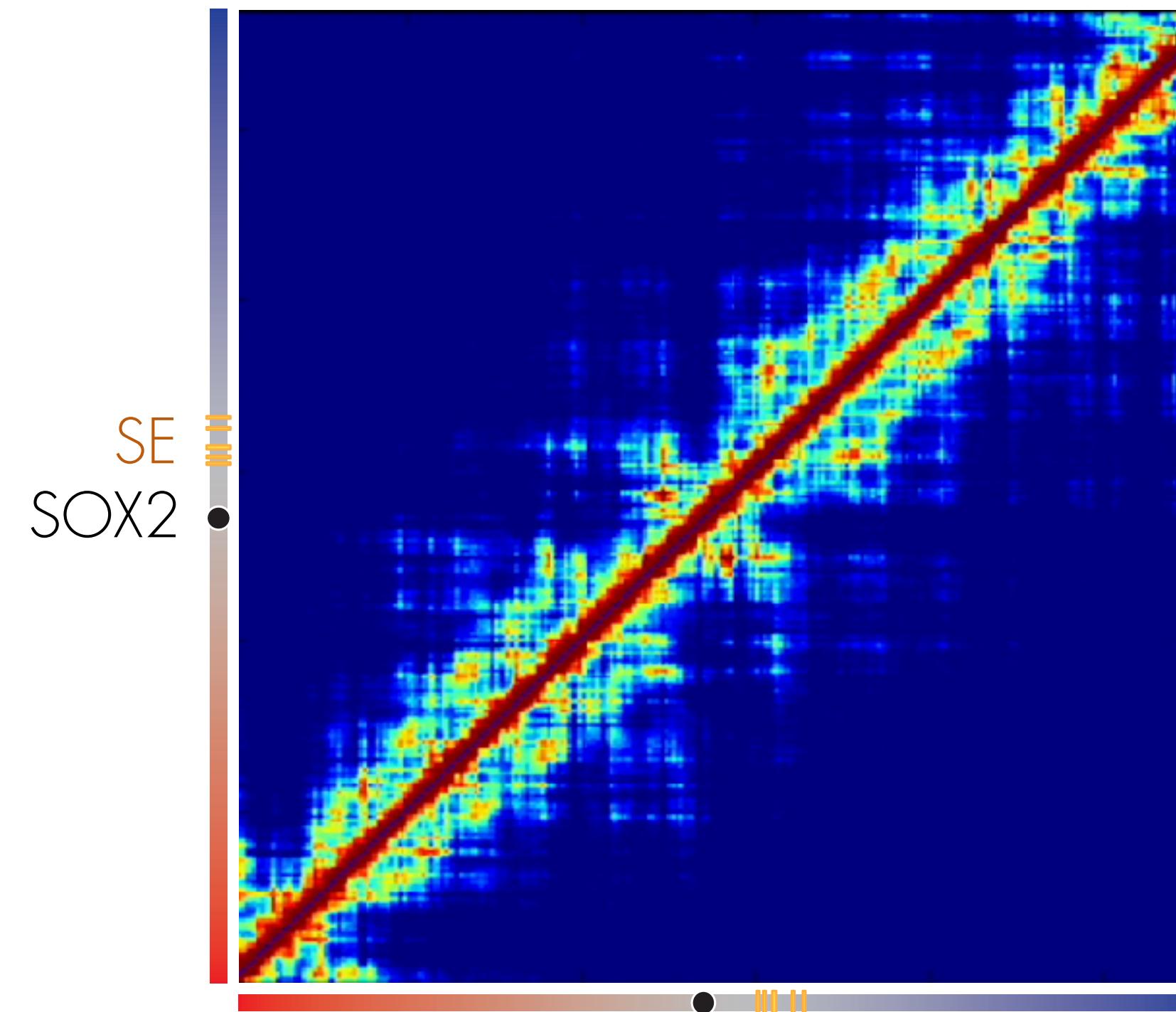
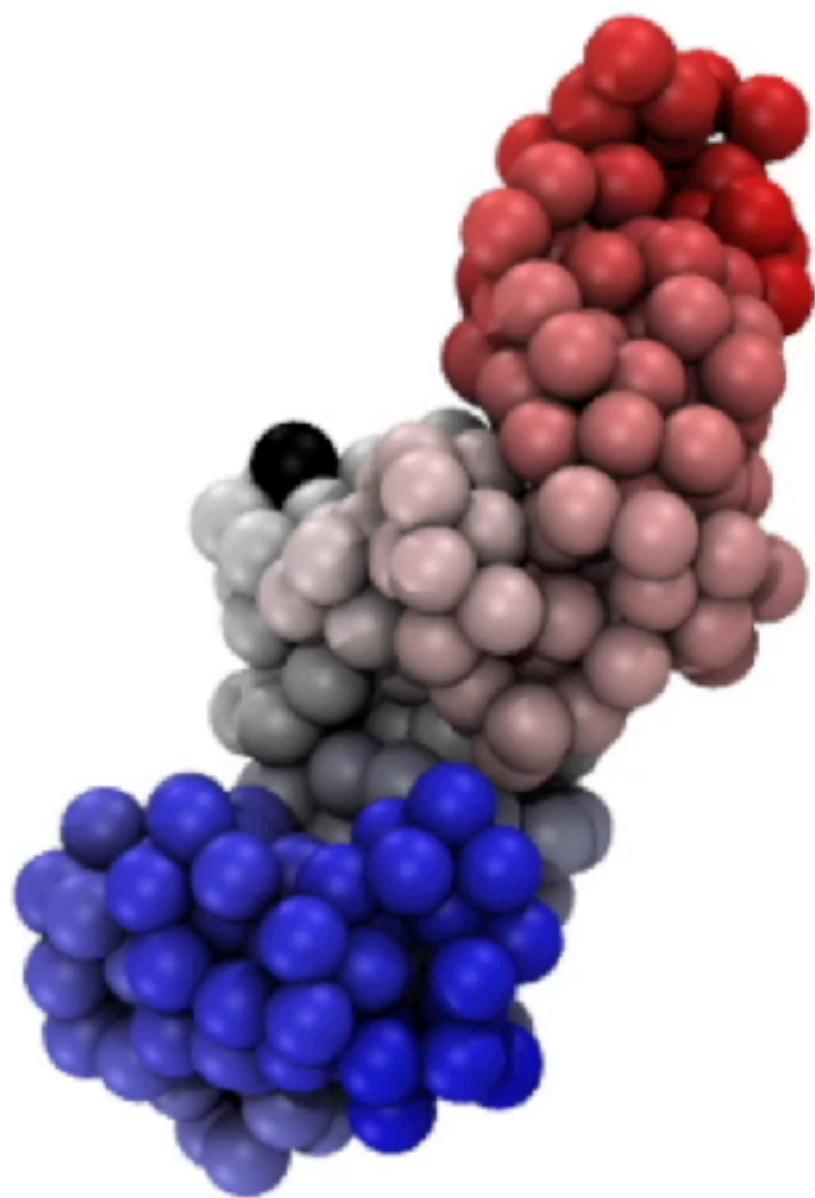
SOX2 locus structural changes from B to PSC

Contacts



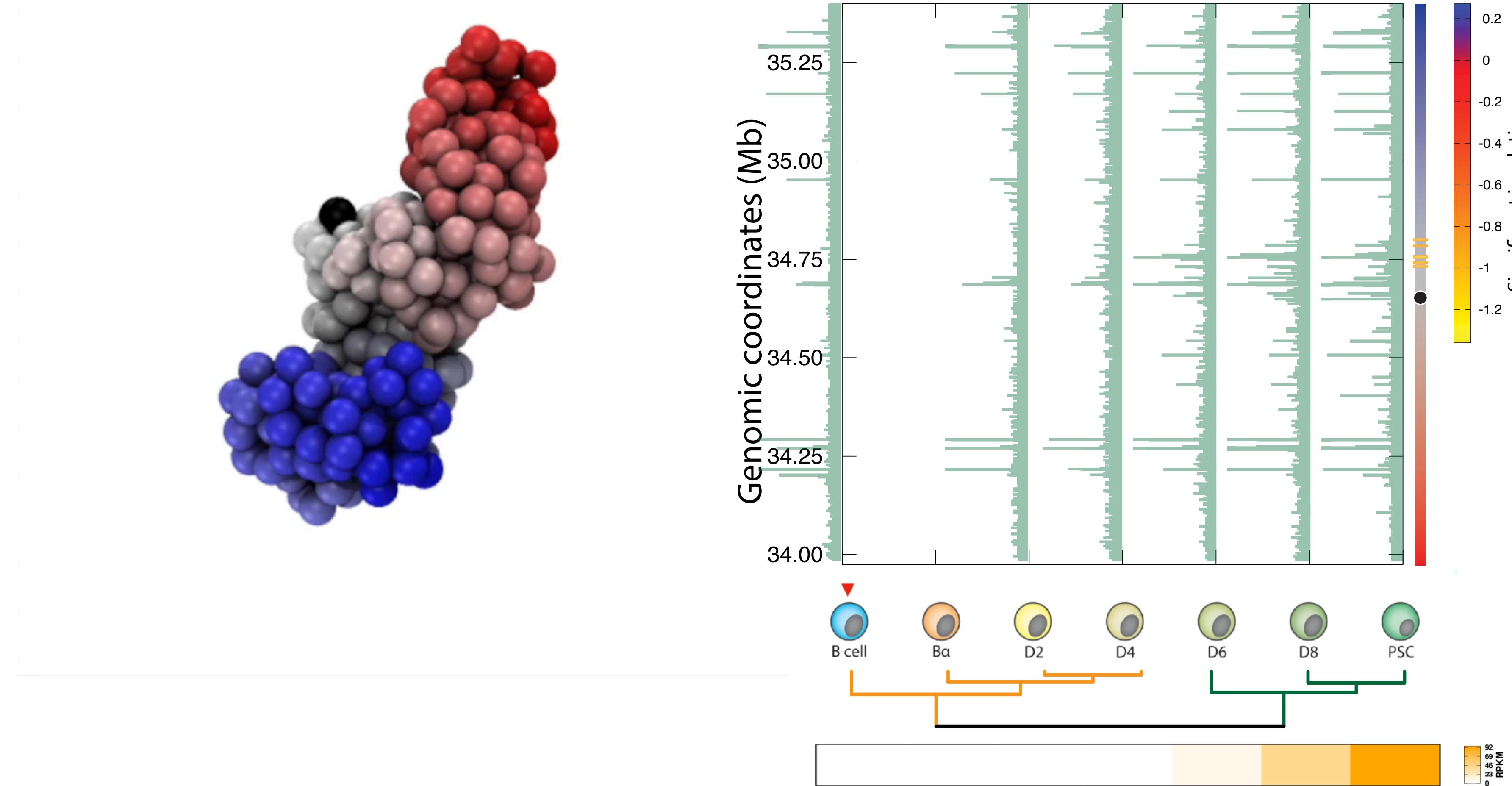
SOX2 locus structural changes from B to PSC

Contacts



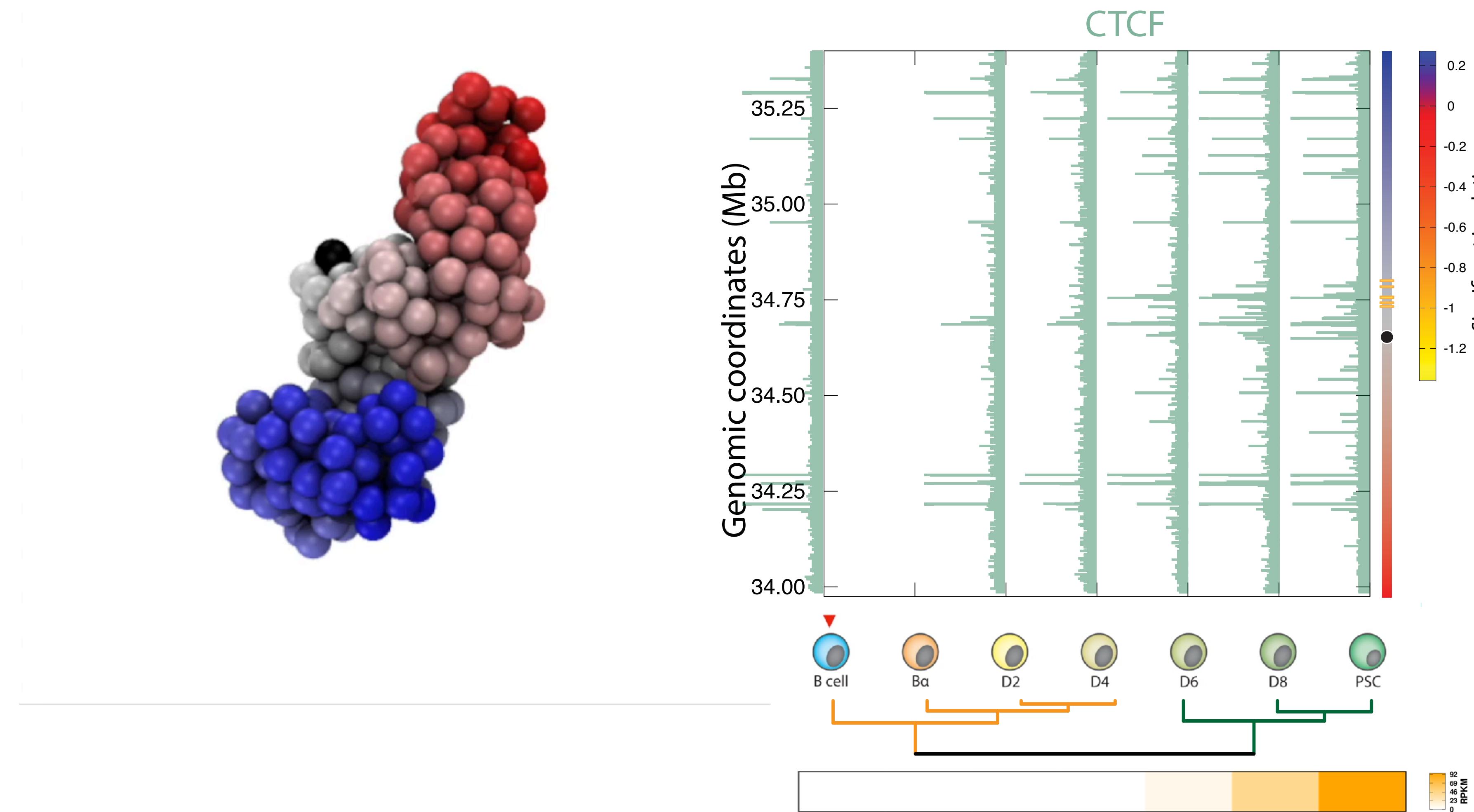
SOX2 locus structural changes from B to PSC

TAD borders



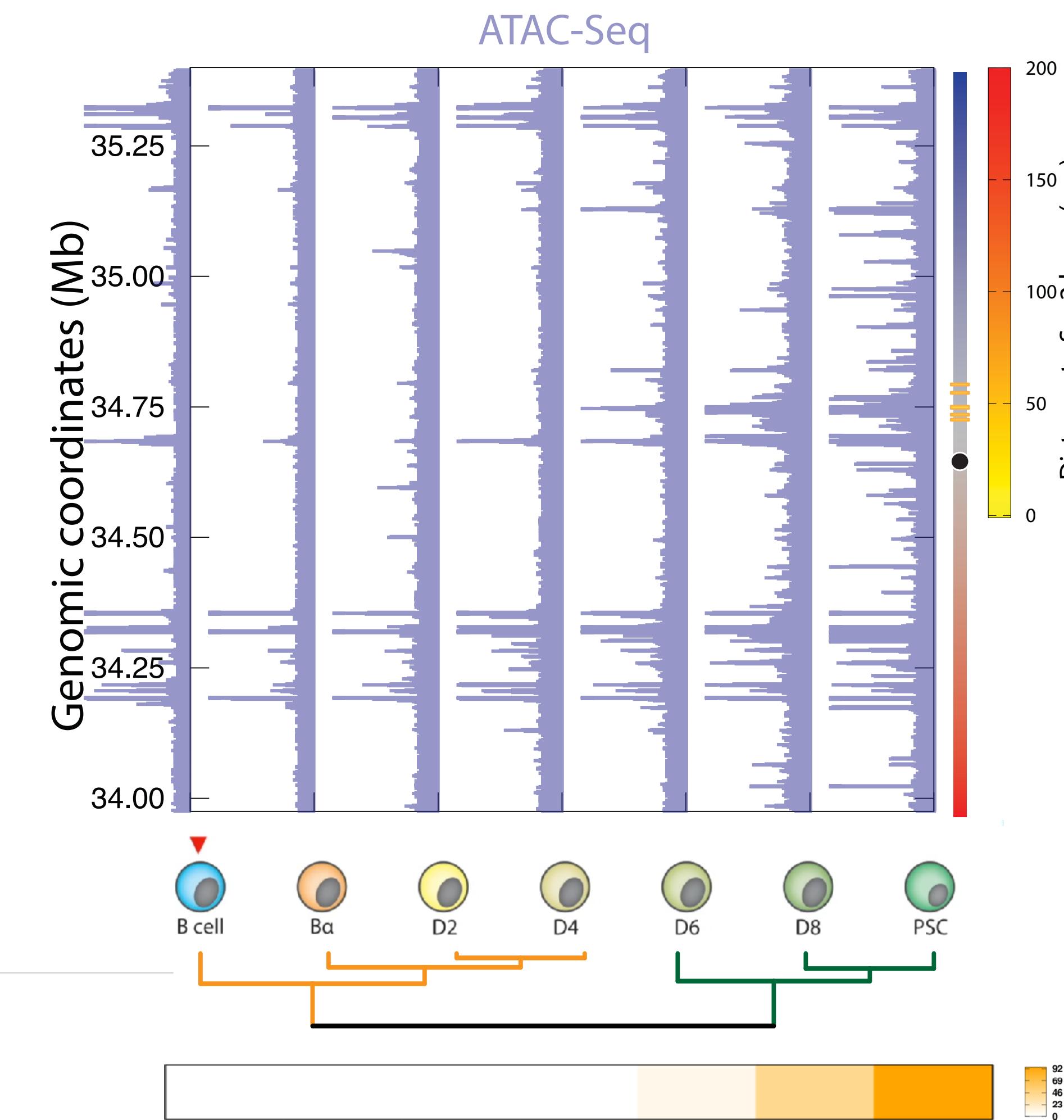
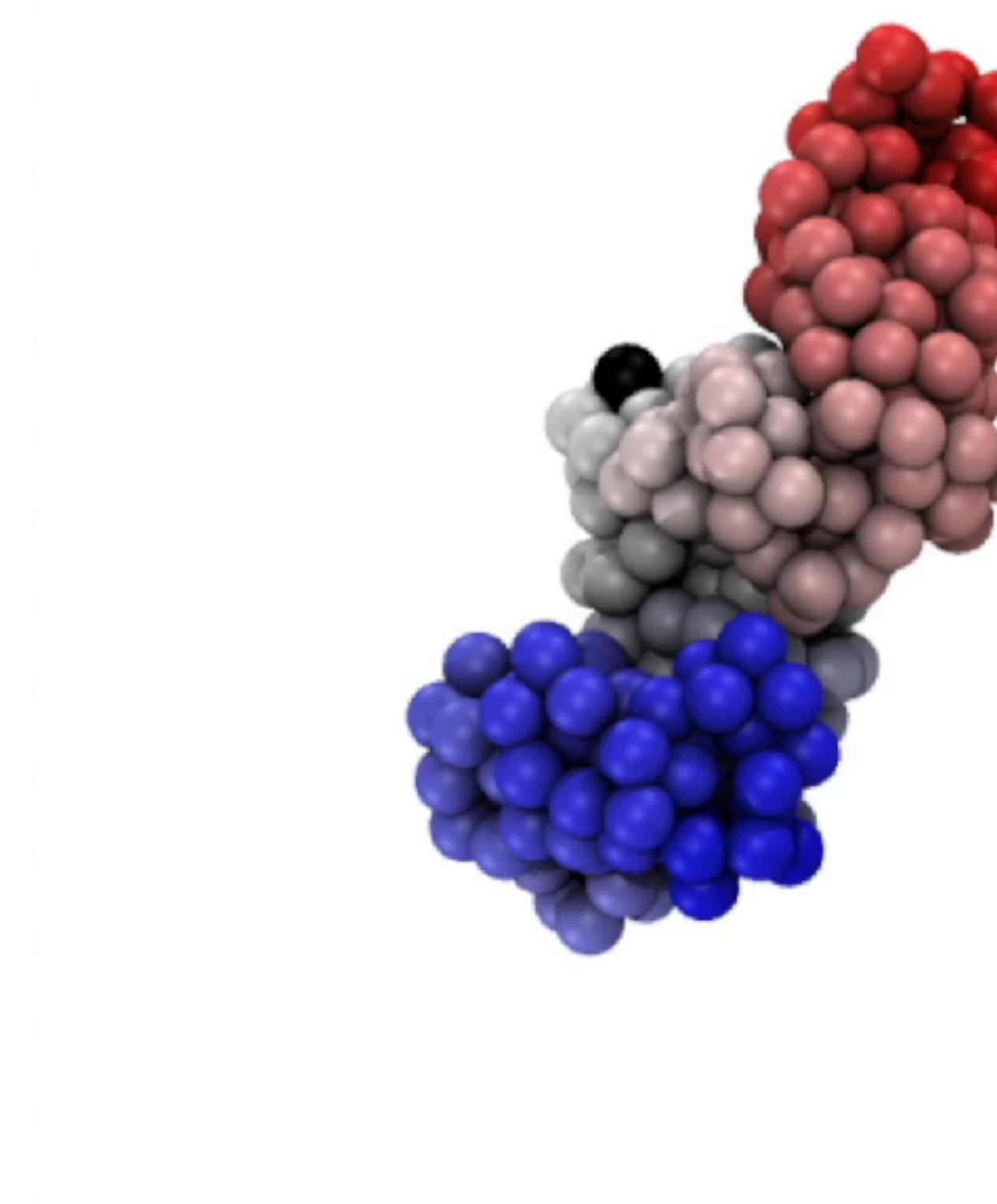
SOX2 locus structural changes from B to PSC

TAD borders



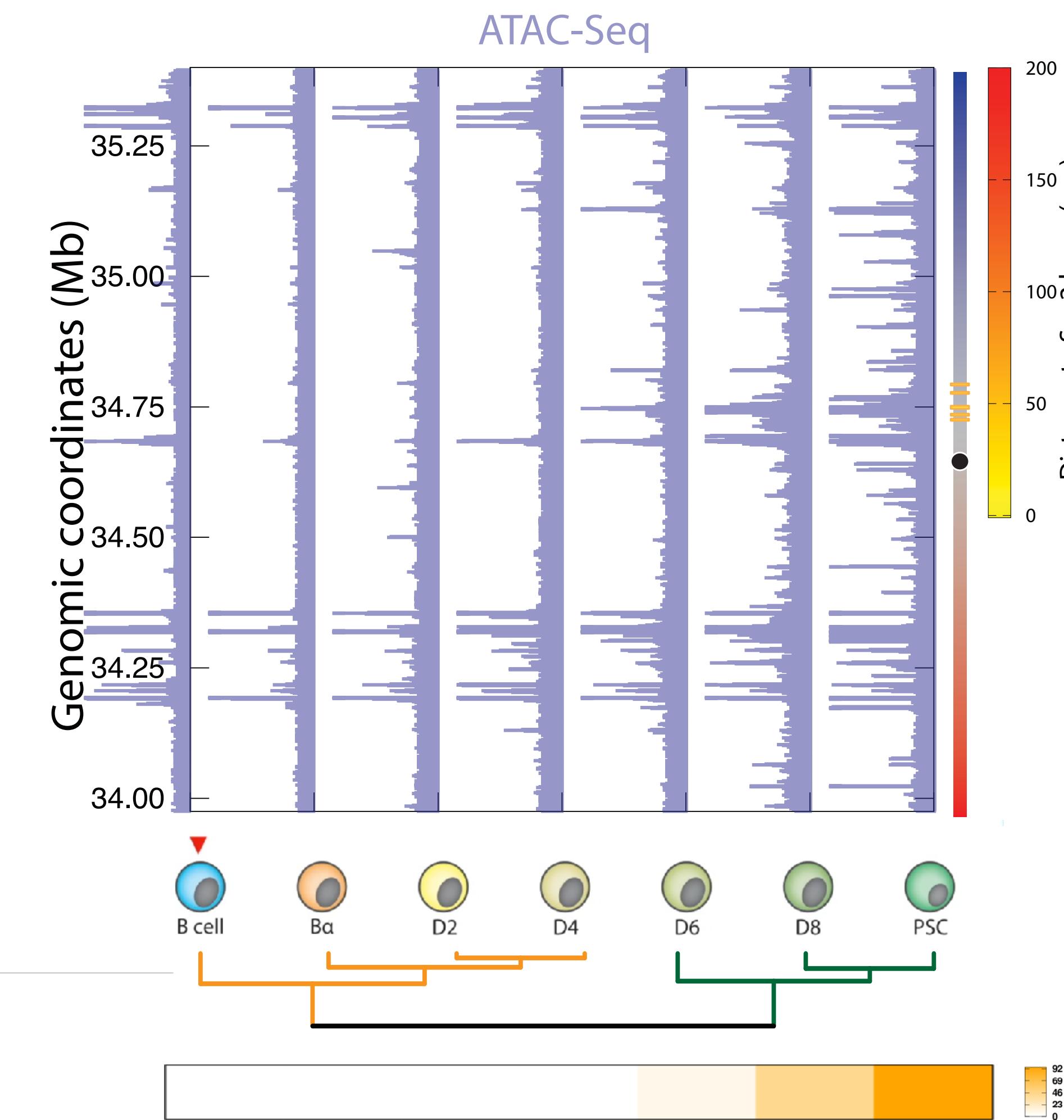
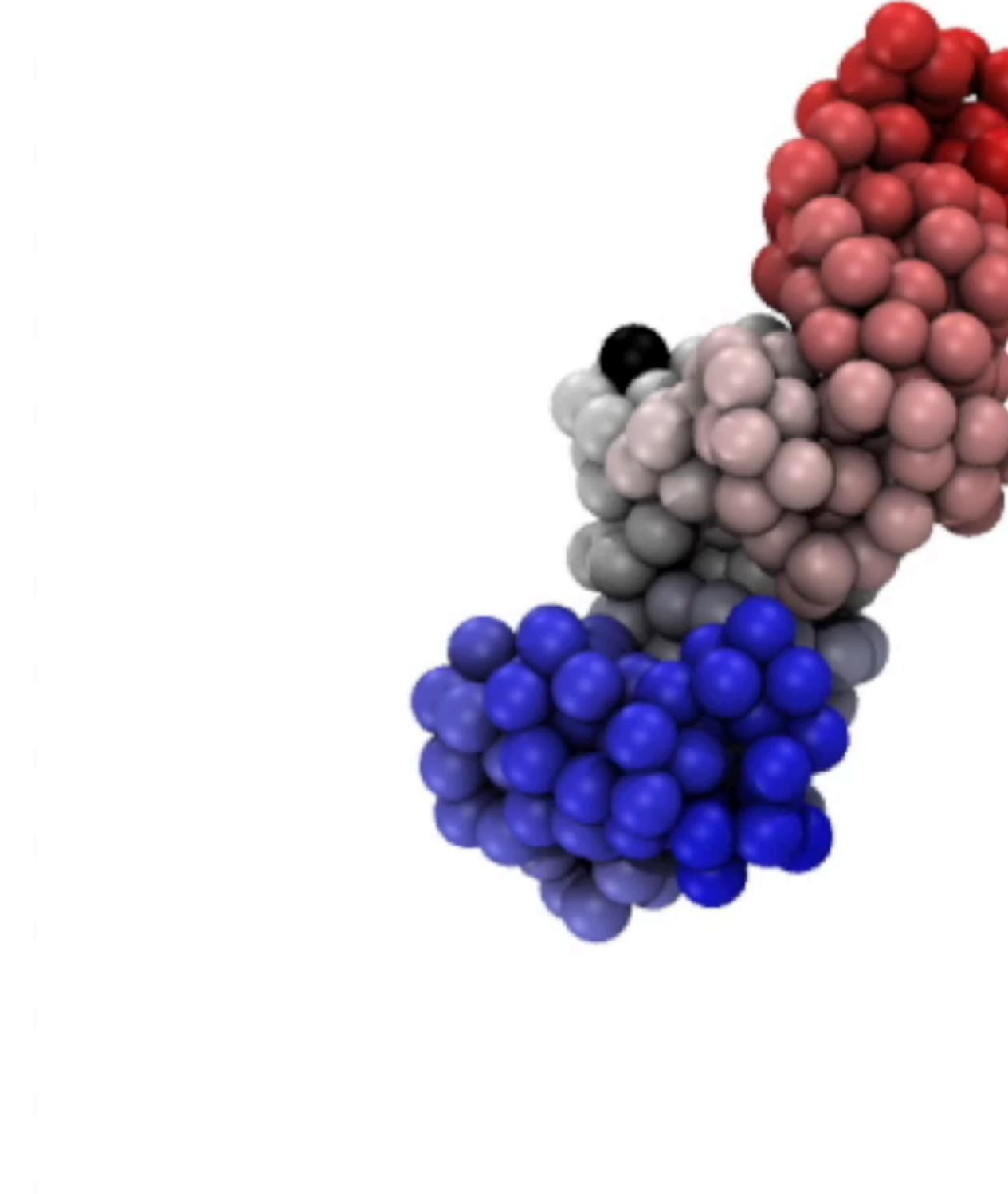
SOX2 locus structural changes from B to PSC

Distance to regulatory elements



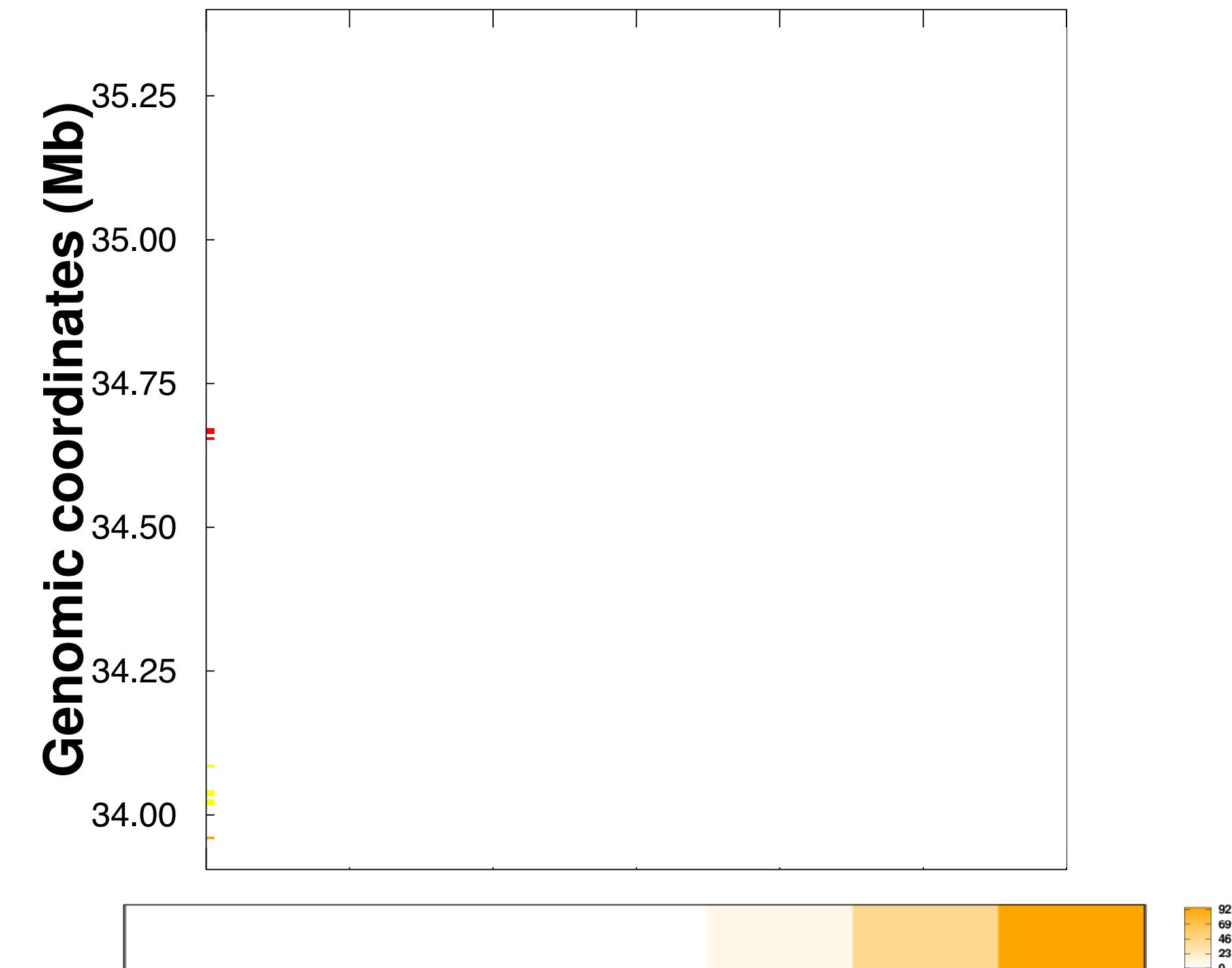
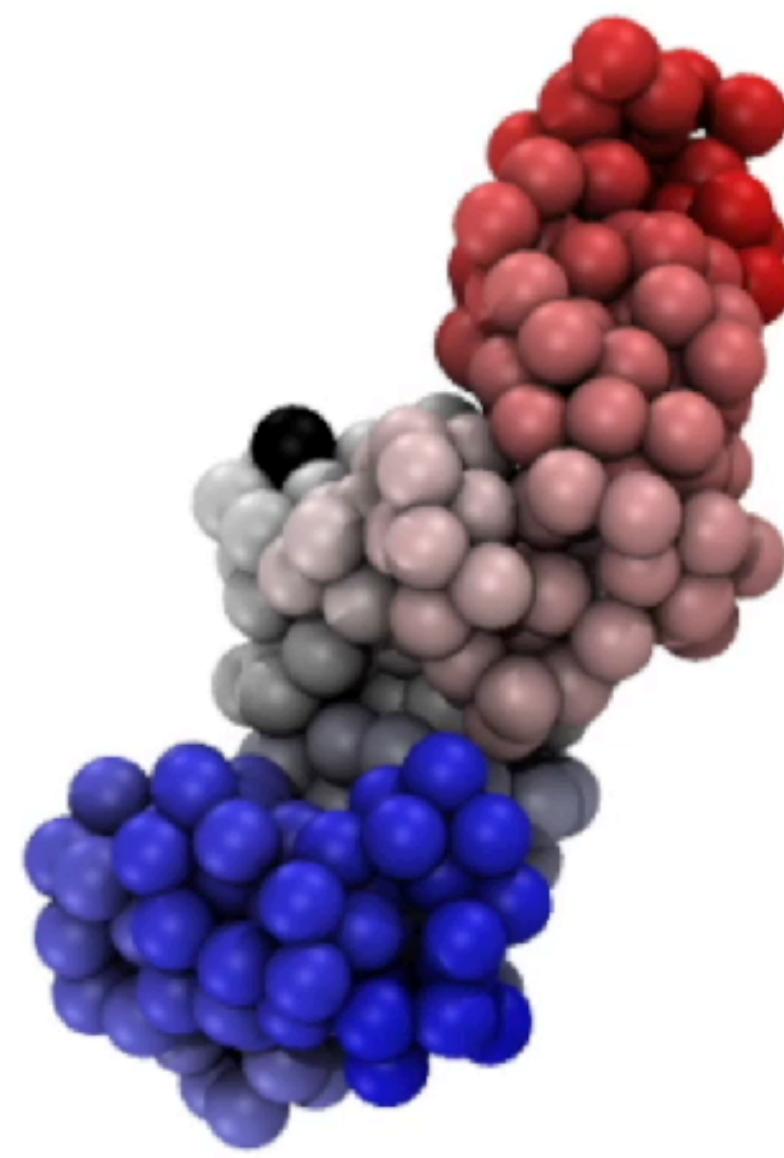
SOX2 locus structural changes from B to PSC

Distance to regulatory elements



SOX2 locus structural changes from B to PSC

Chromatin Activity

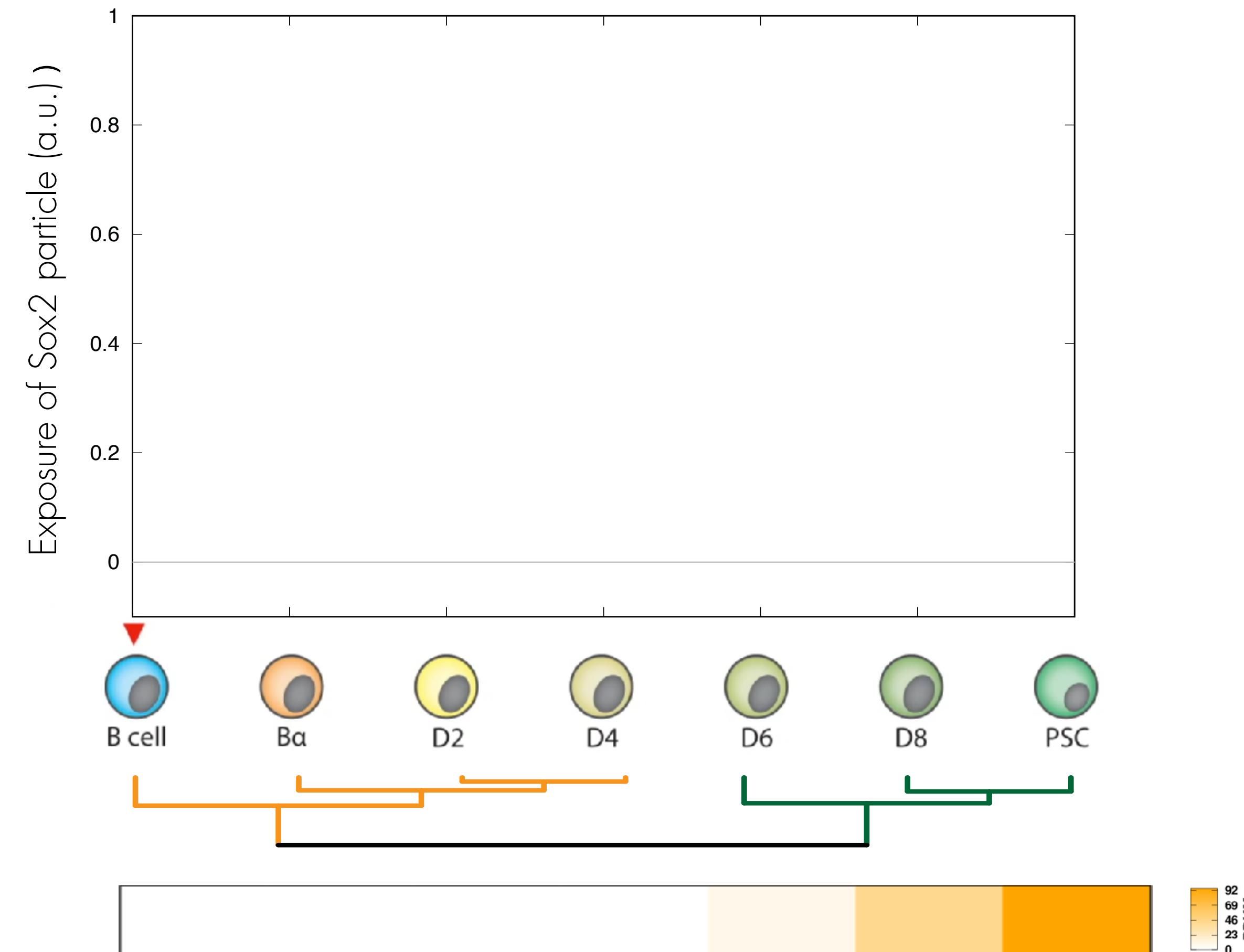
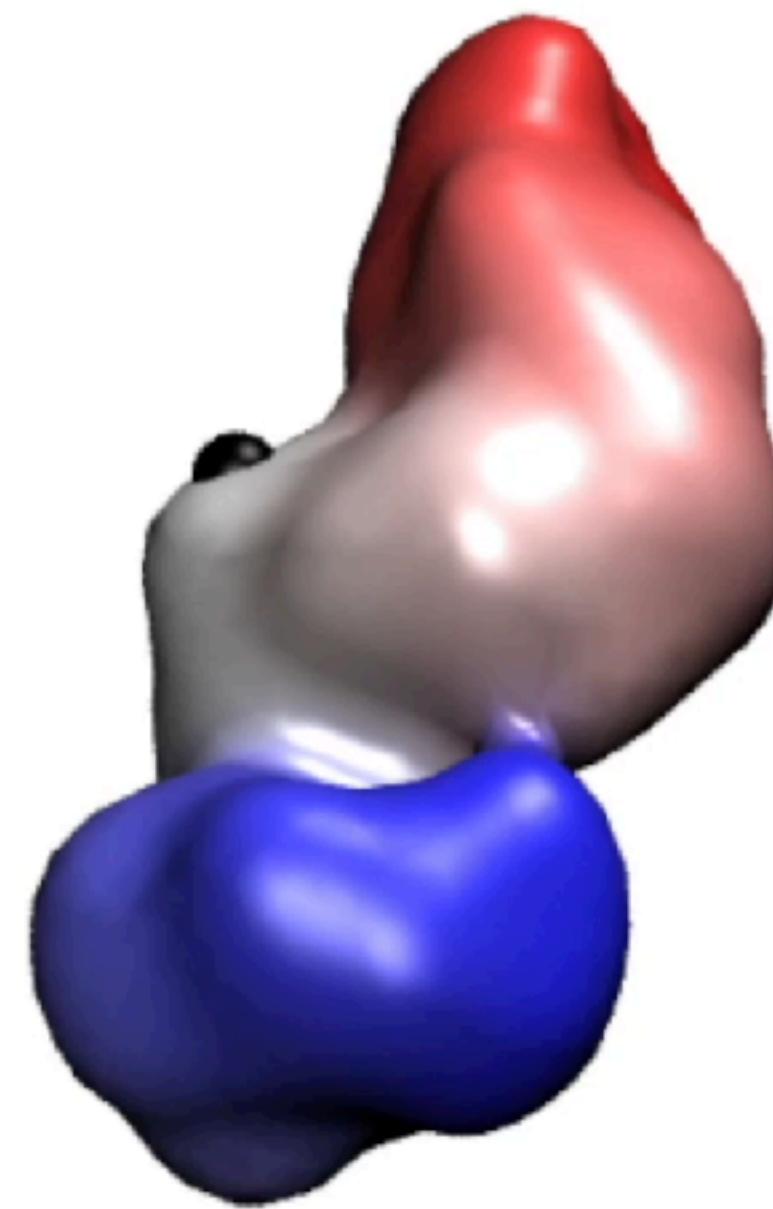


	B	Ba	D2	D4	D6	D8	PSC
A	9	6	7	13	13	22	48
AP	4	1	4	4	4	13	23
APD	3	1	1	1	4	10	15



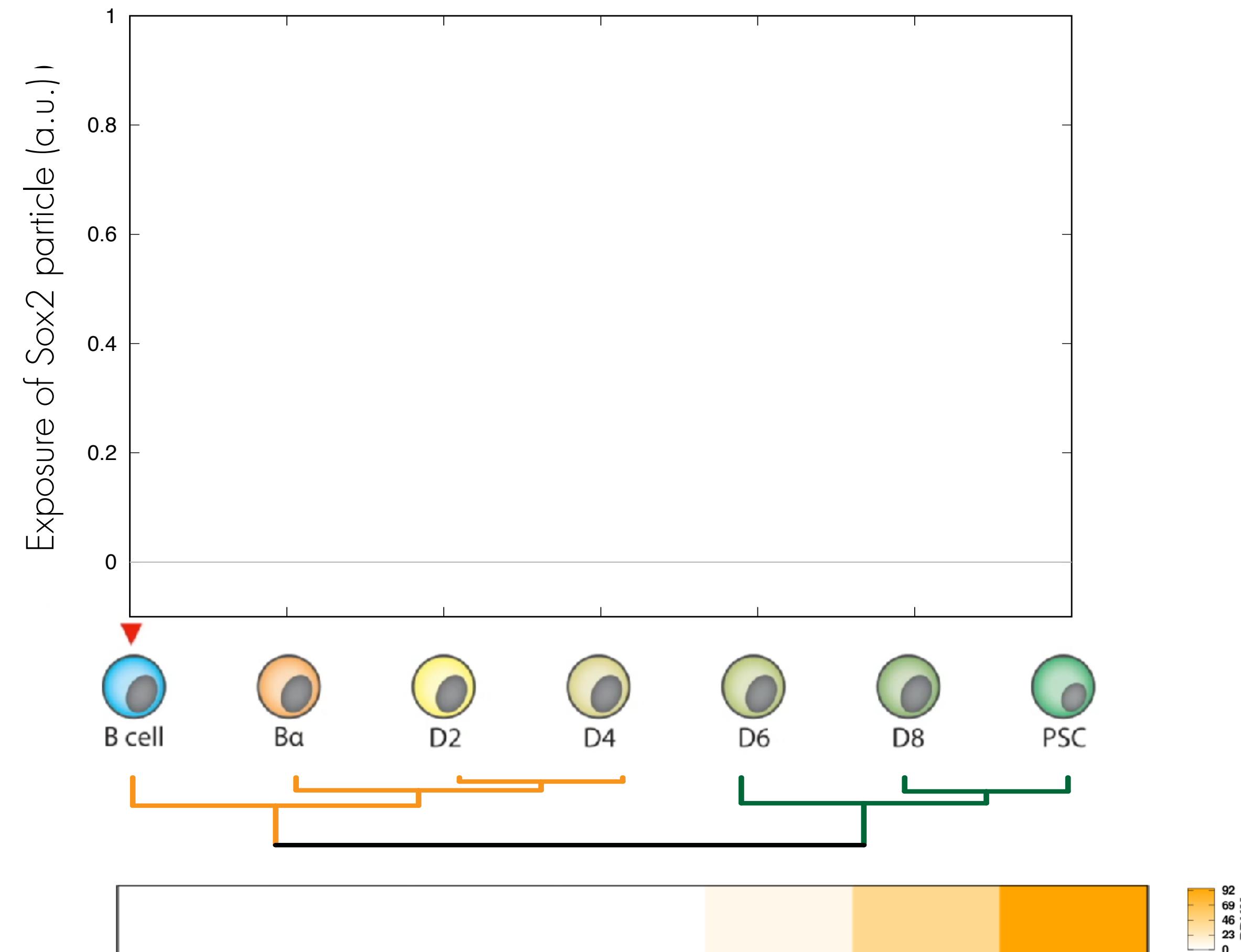
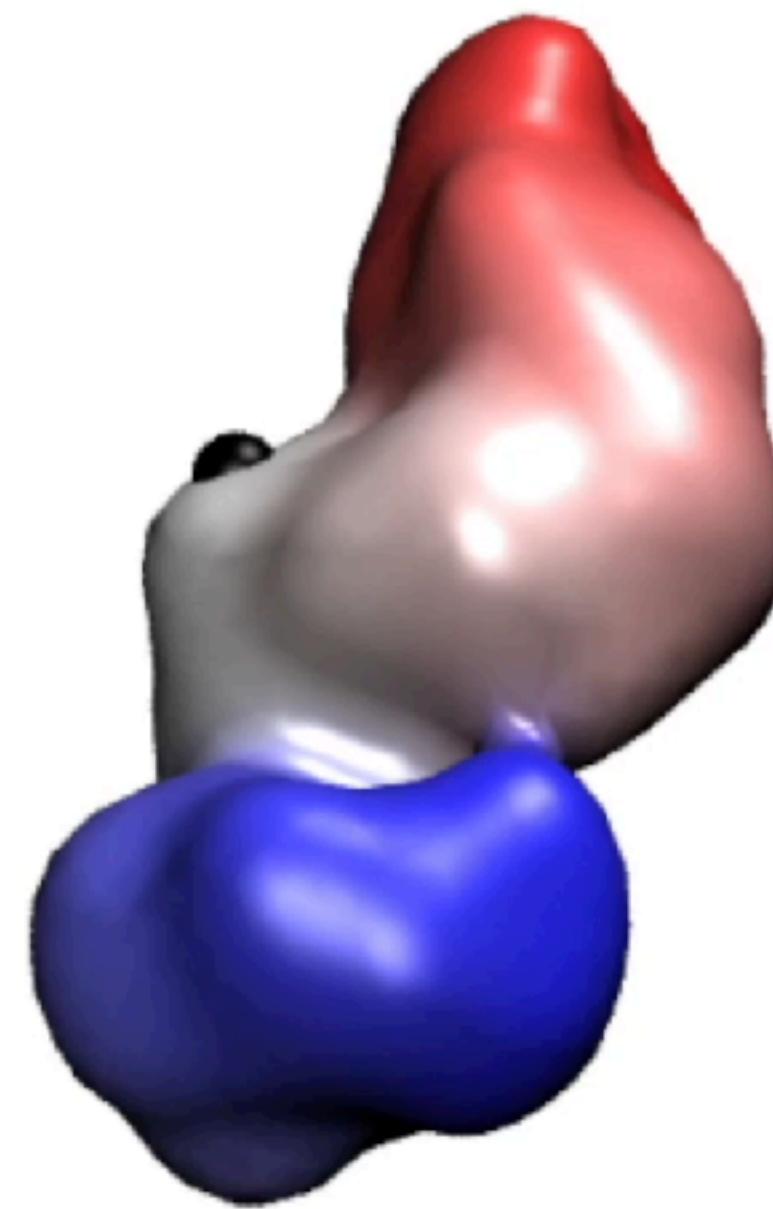
SOX2 locus structural changes from B to PSC

Structural exposure



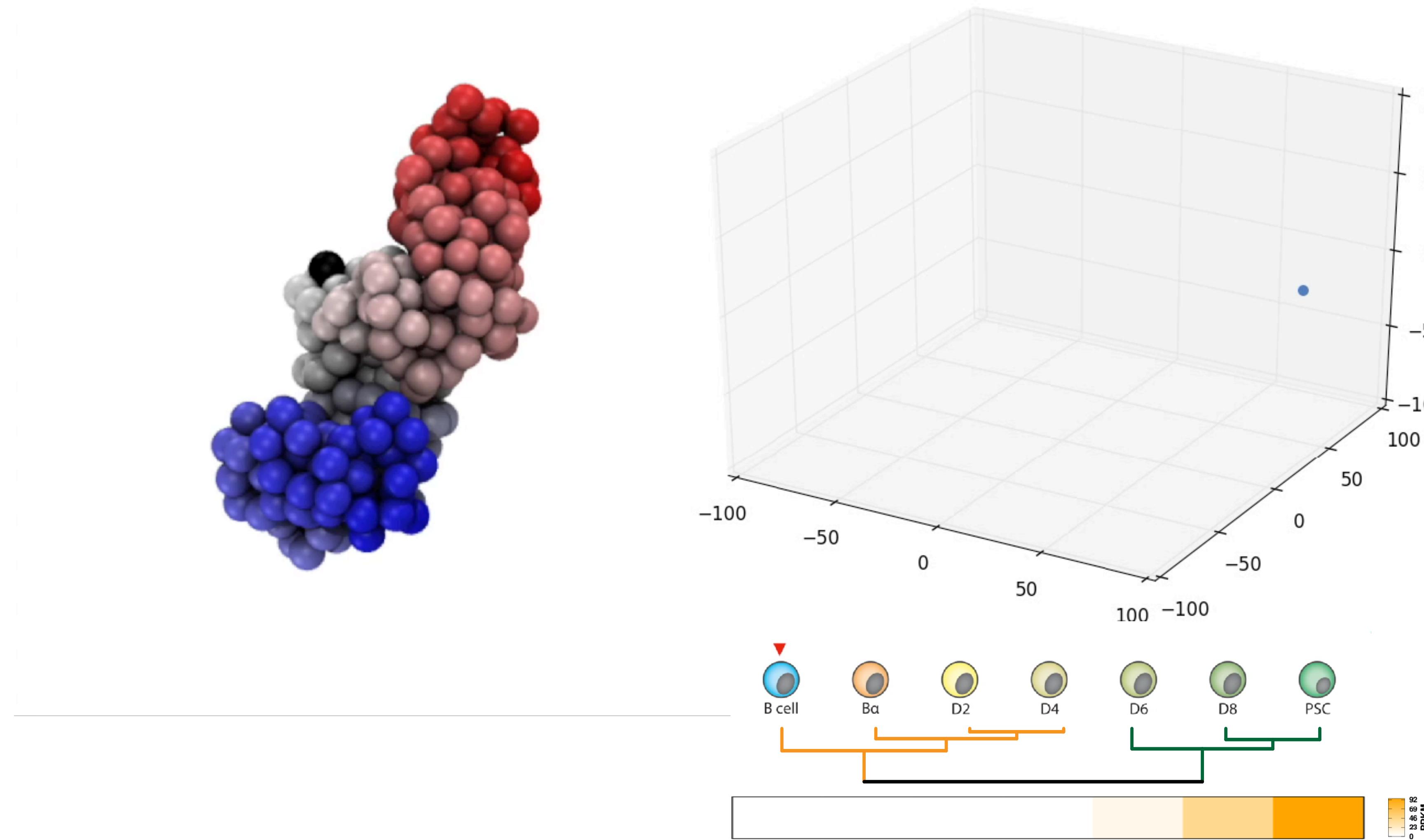
SOX2 locus structural changes from B to PSC

Structural exposure



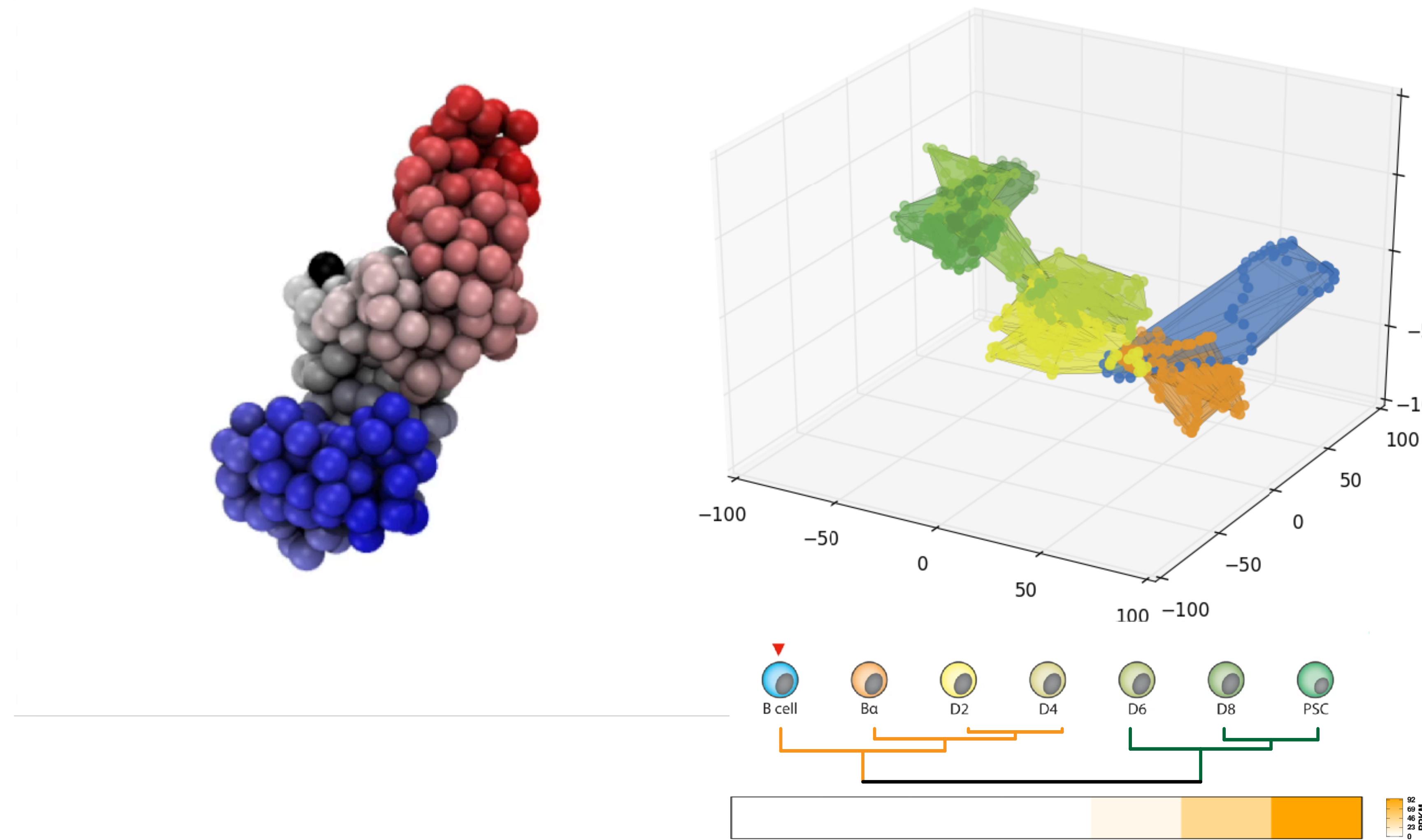
SOX2 locus dynamics changes from B to PSC

SOX2 displacement



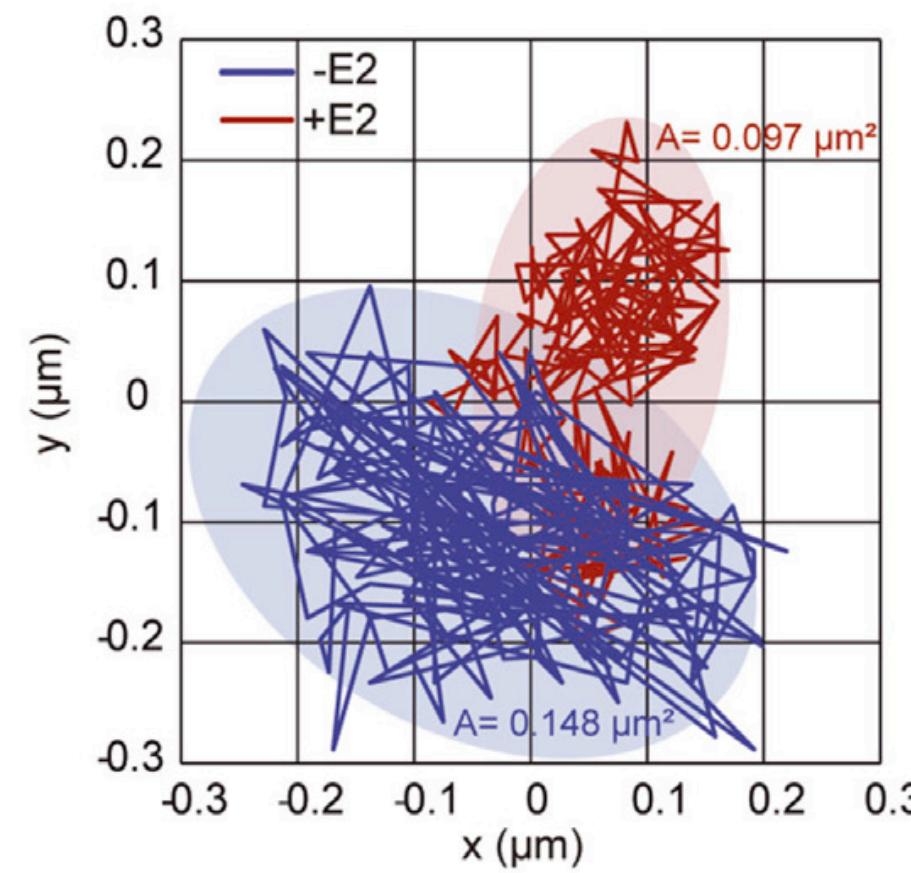
SOX2 locus dynamics changes from B to PSC

SOX2 displacement



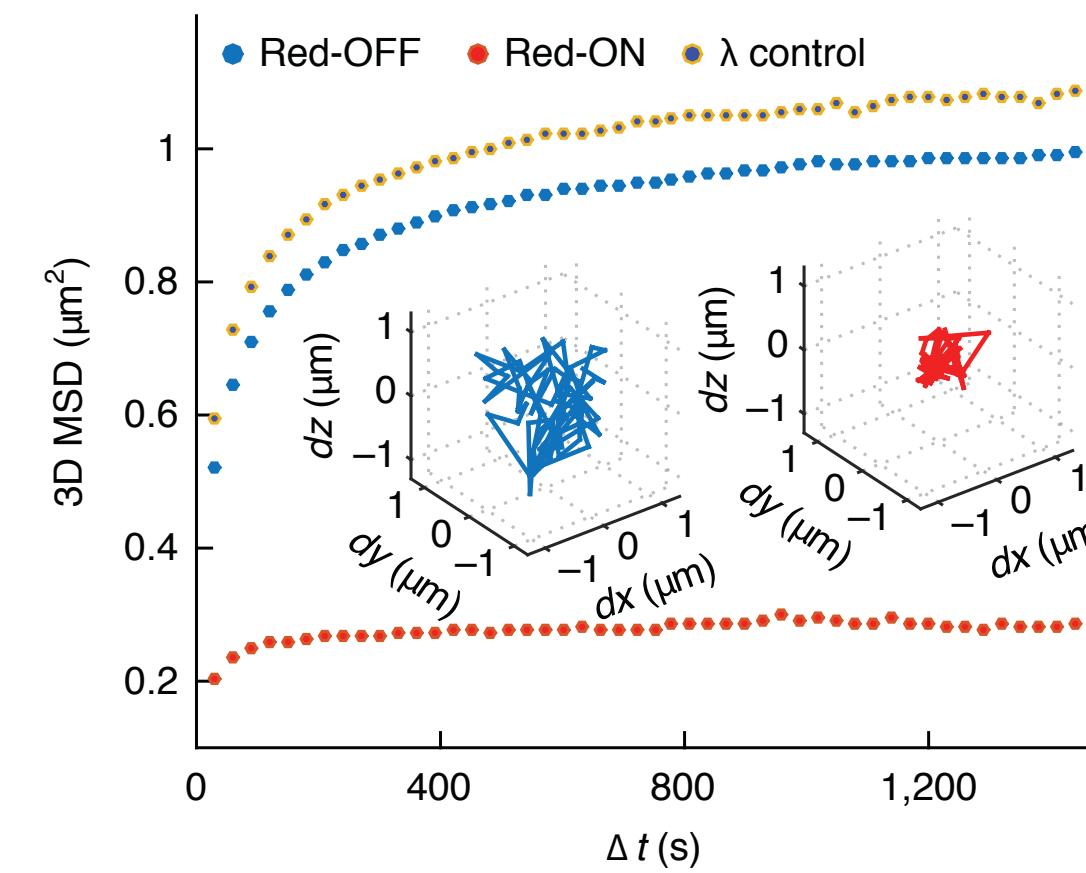
SOX2 locus dynamics changes from B to PSC

SOX2 displacement



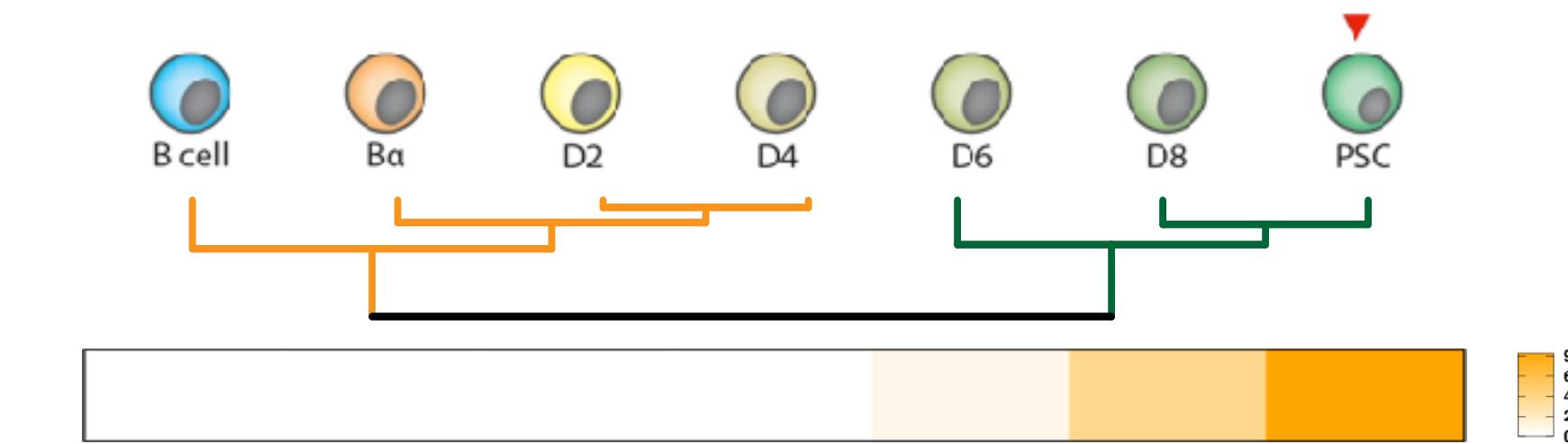
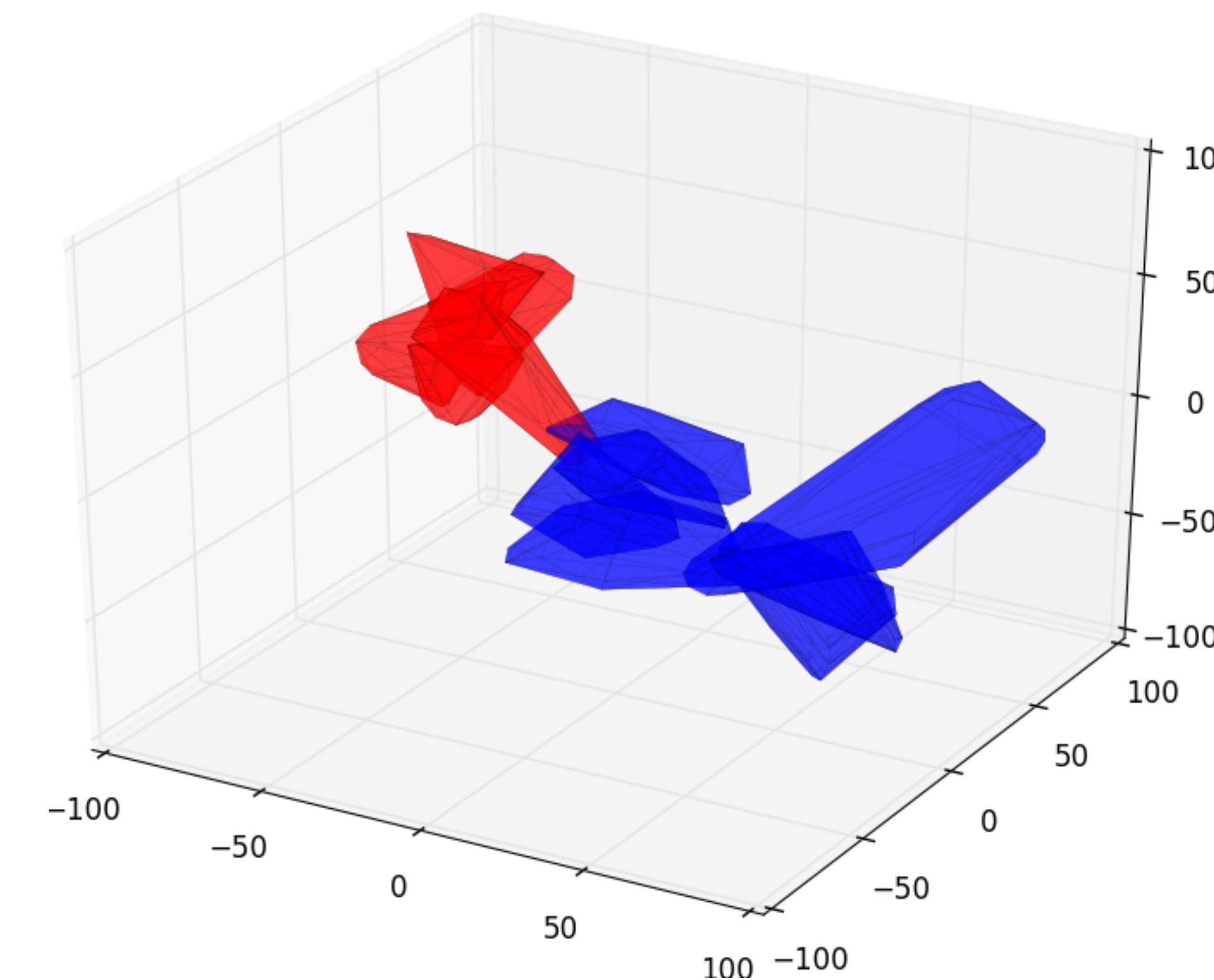
Two dimensional trajectories and area explored over 50s of the CCND1 locus recorded before -E2 and after +E2 activation.

Germier ,T., et al, (2017) Biophys J.



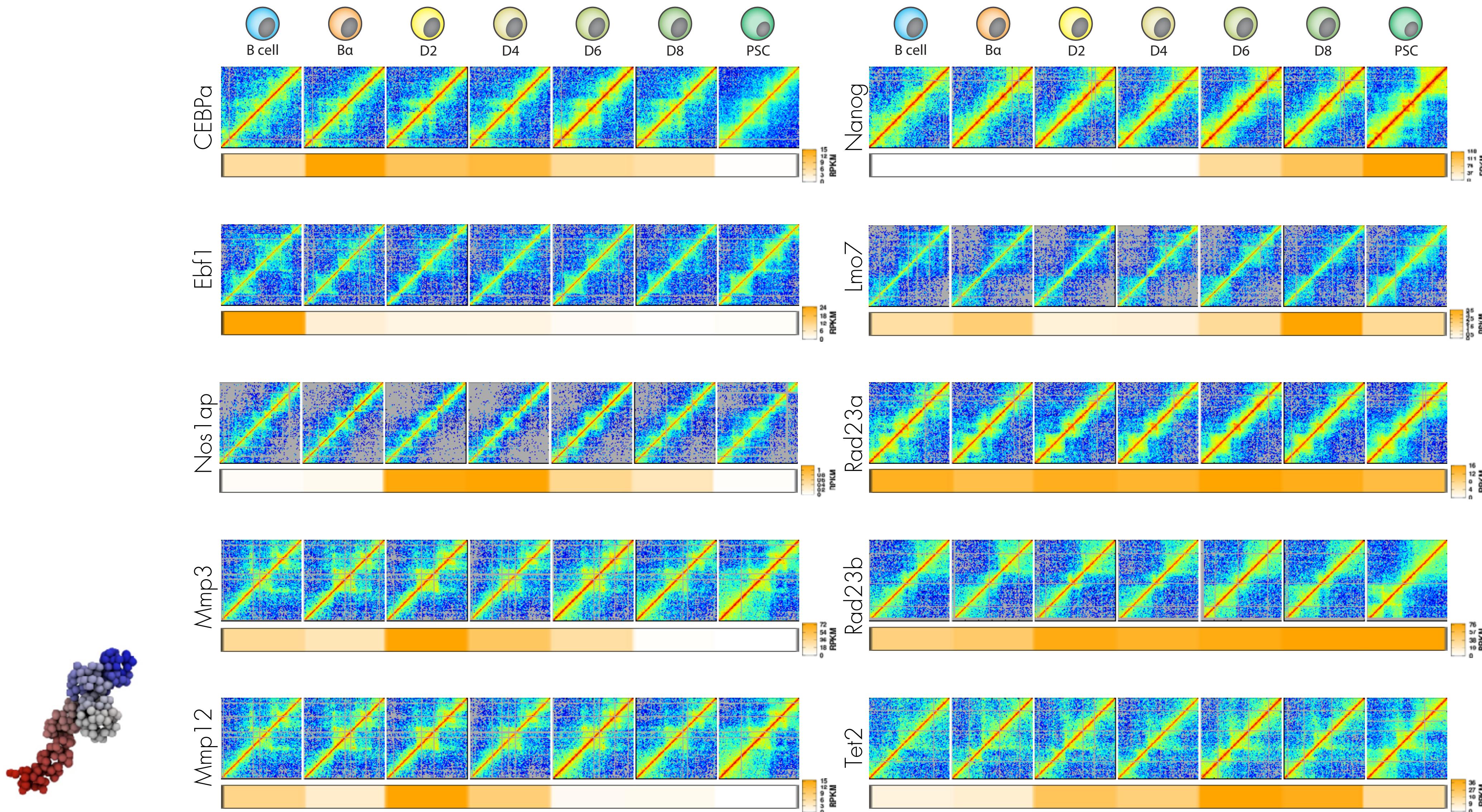
Transcription affects the 3D topology of the enhancer-promoted enhancing its temporal stability and is associated with further spatial compaction.

Chen ,T., et al, (2018) Nat. Genetics



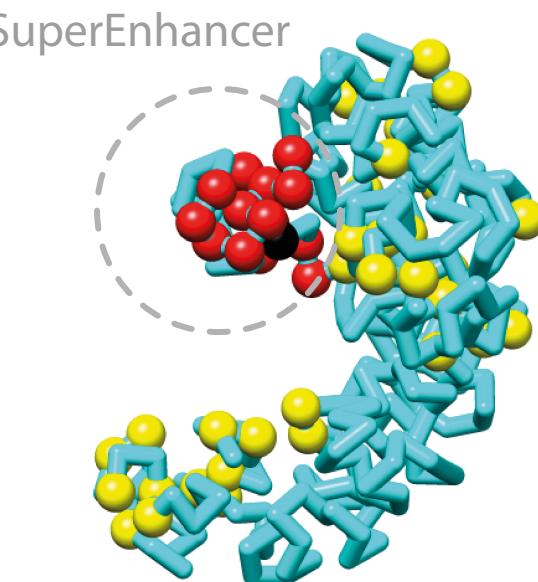
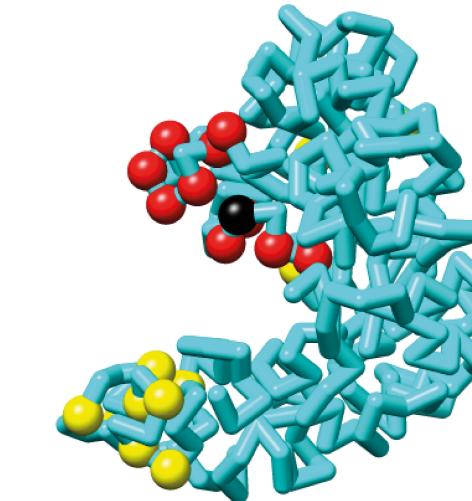
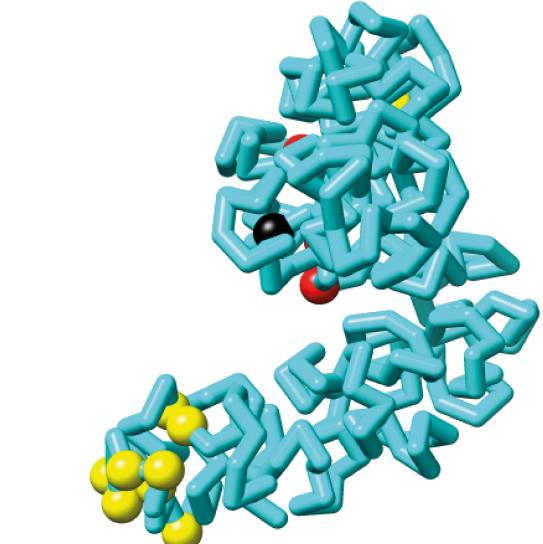
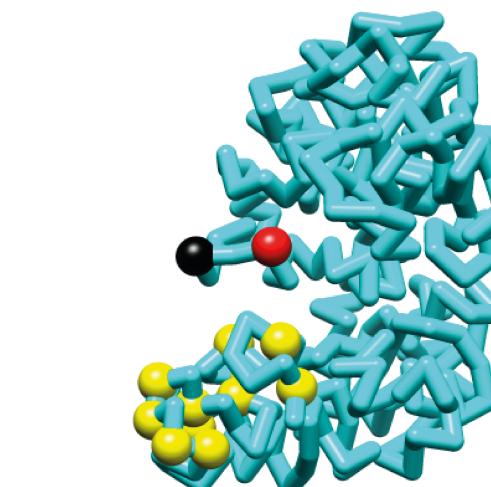
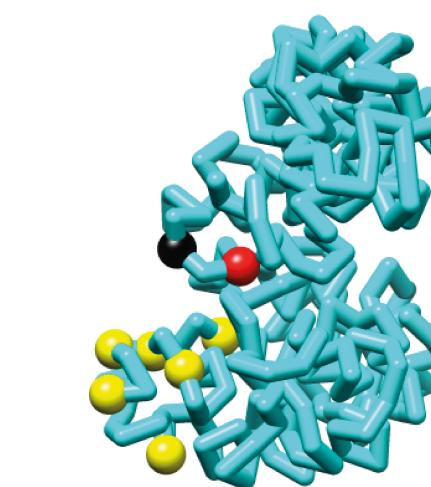
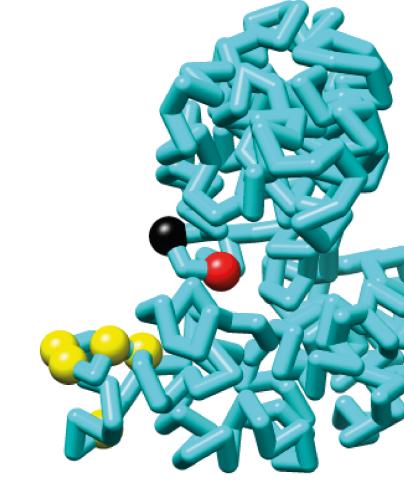
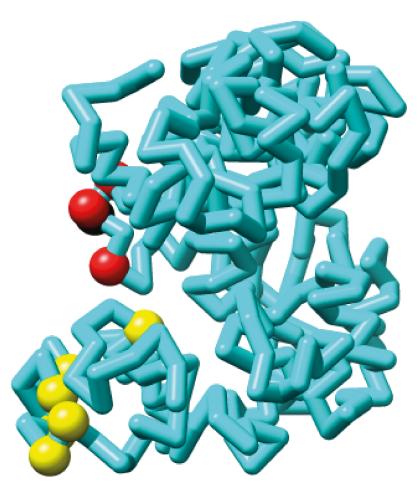
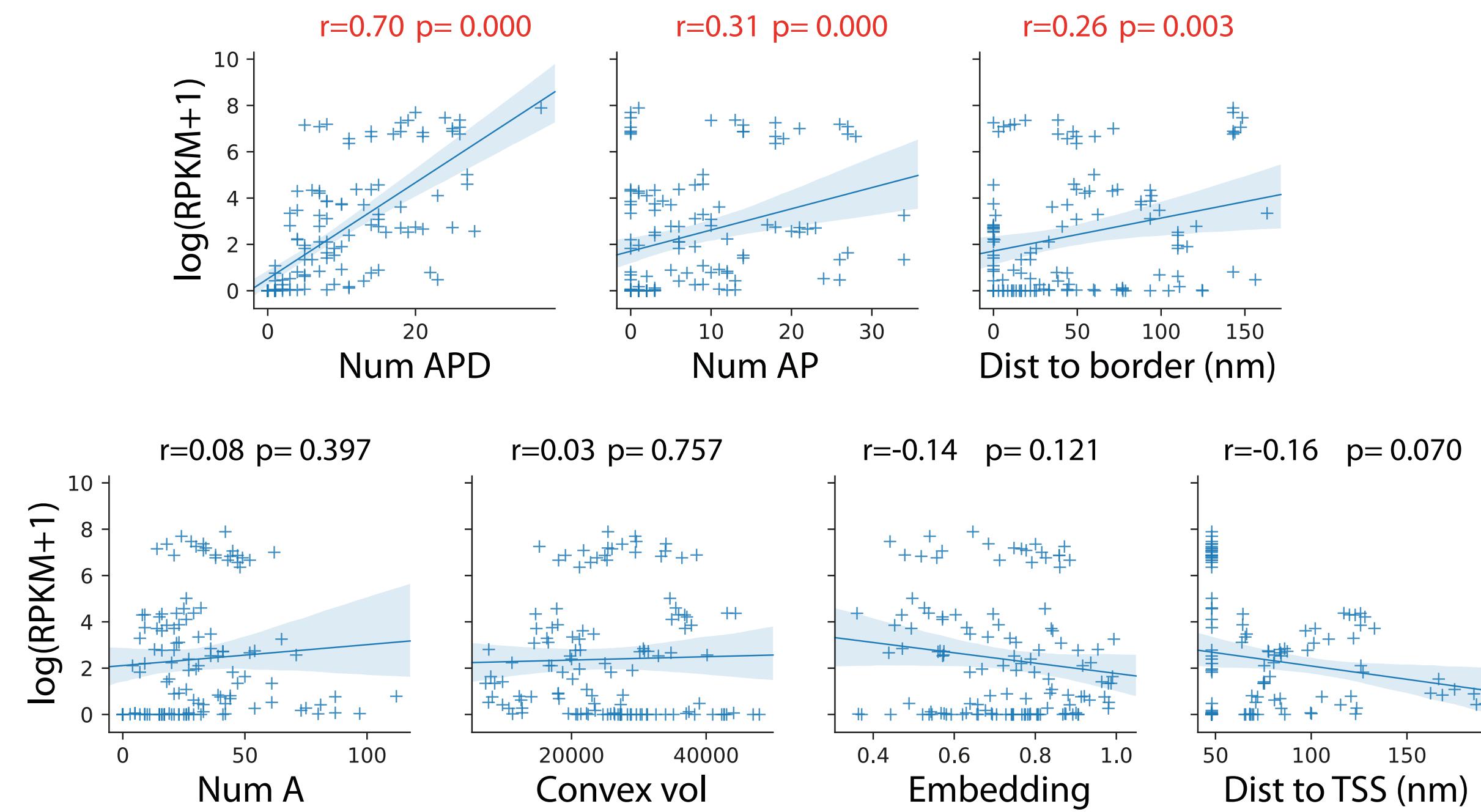
Structural changes from B to PSC

Other 21 loci

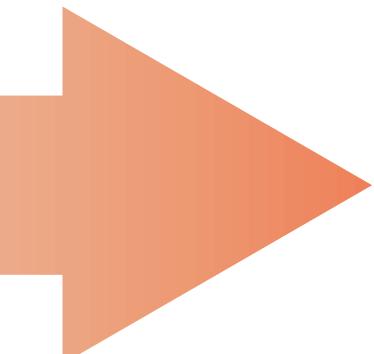


Dynamics of gene activation

Trends in 21 loci

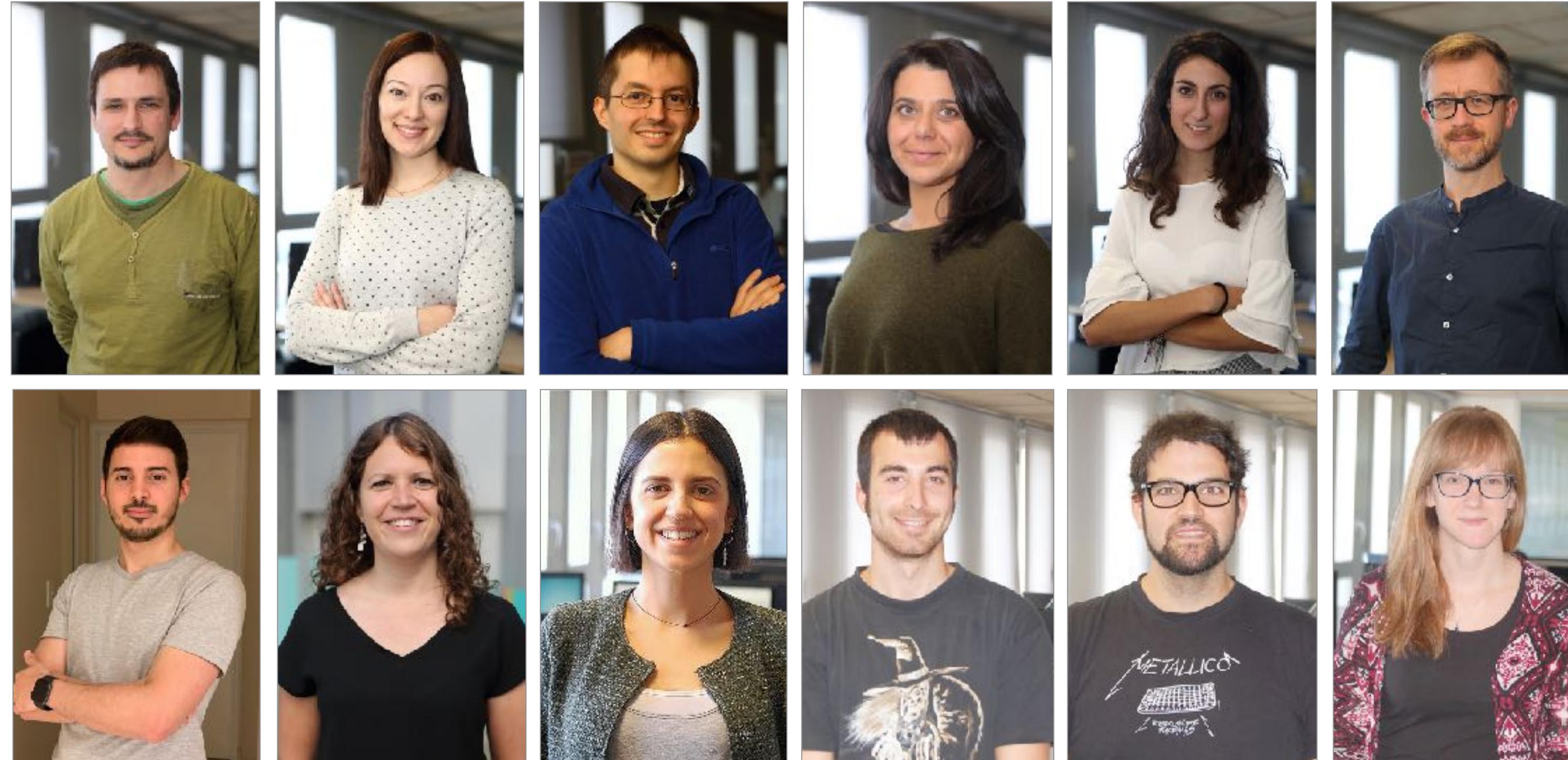


Time and expression levels





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