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

Marc A. Marti-Renom

CNAG-CRG · ICREA

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

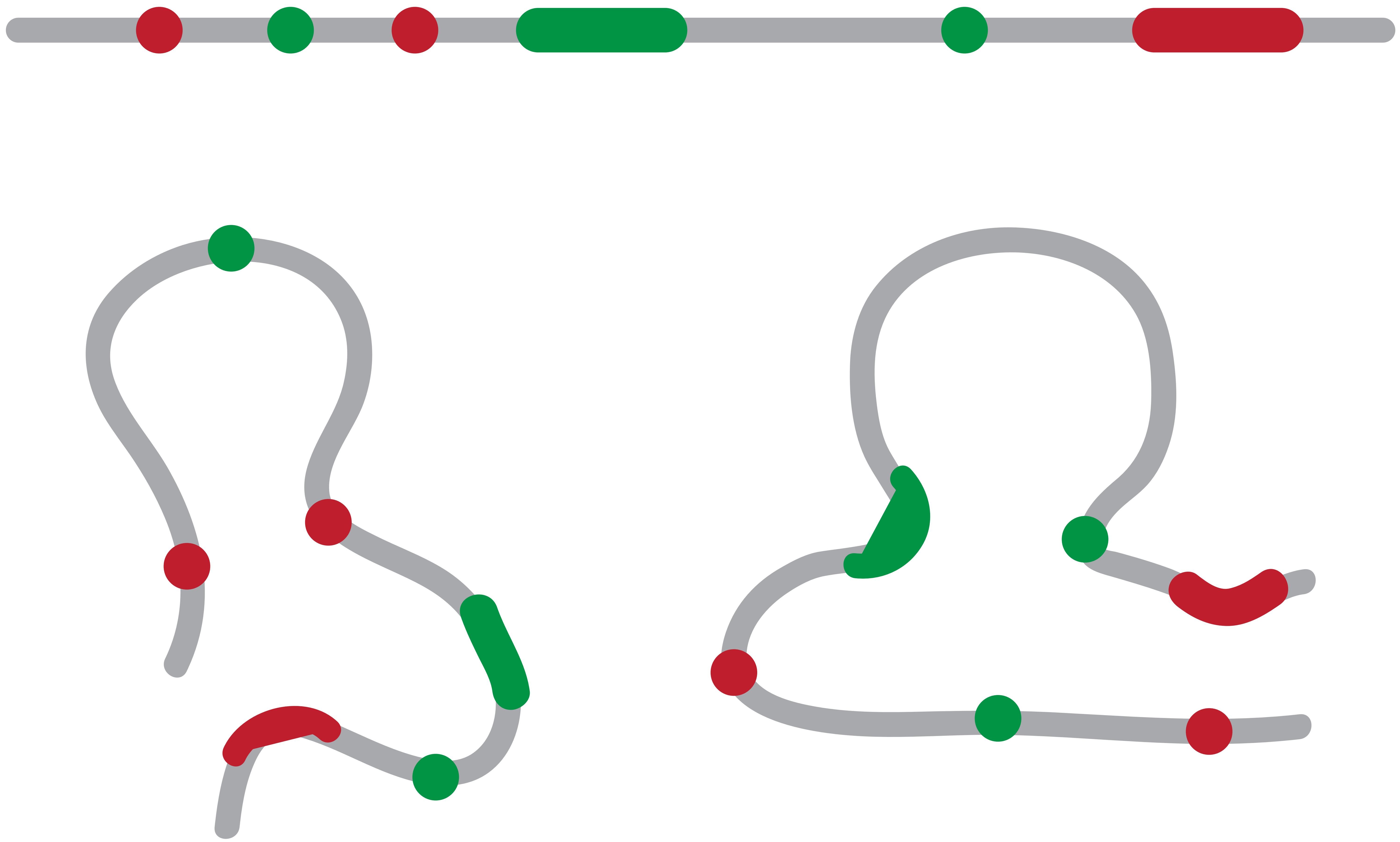
All you will see in the screen is here:

http://marciuslab.org/www/presentations/

I encourage you to:

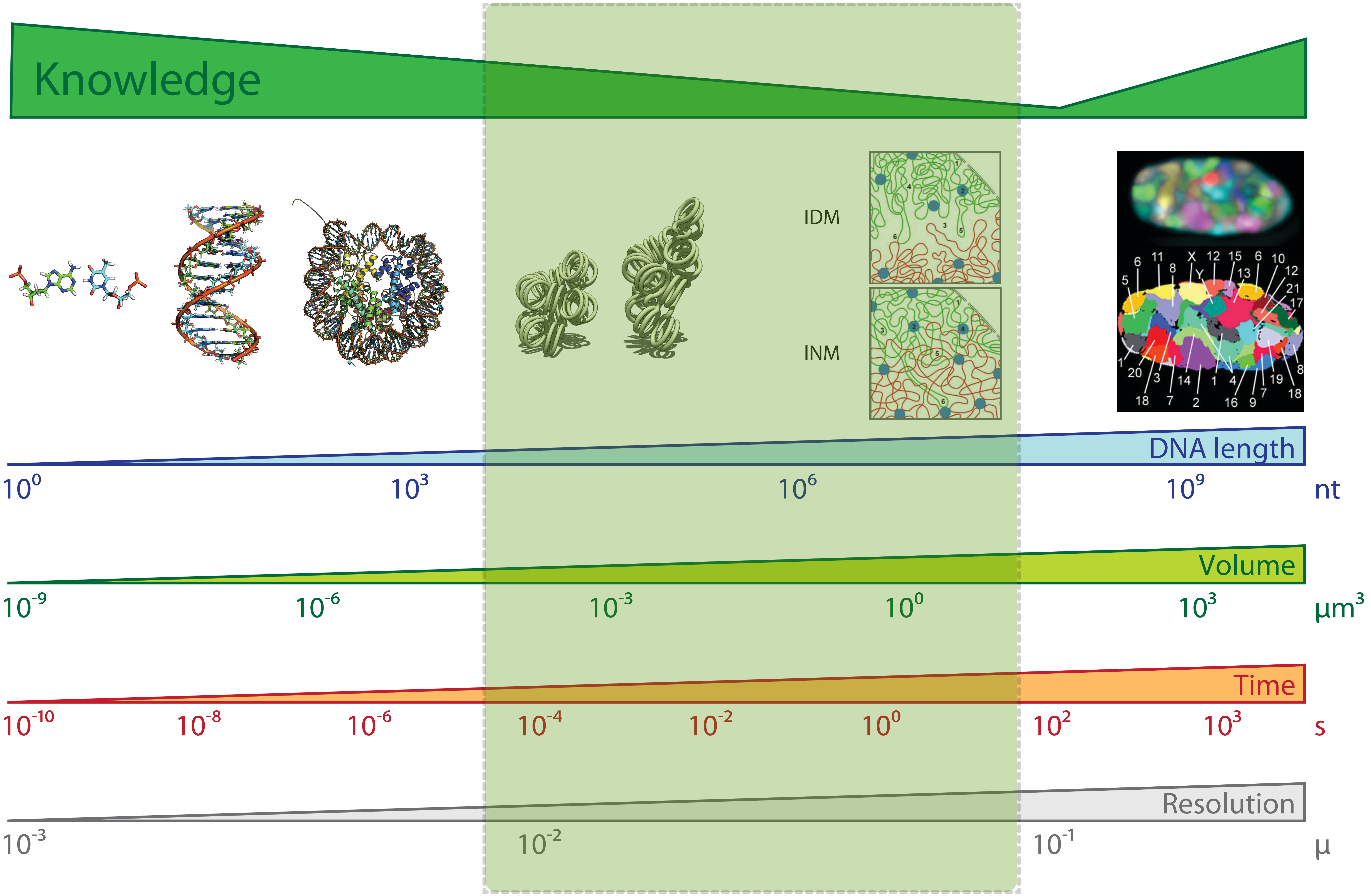
listen AND speak

not necessarily in this order... 😁



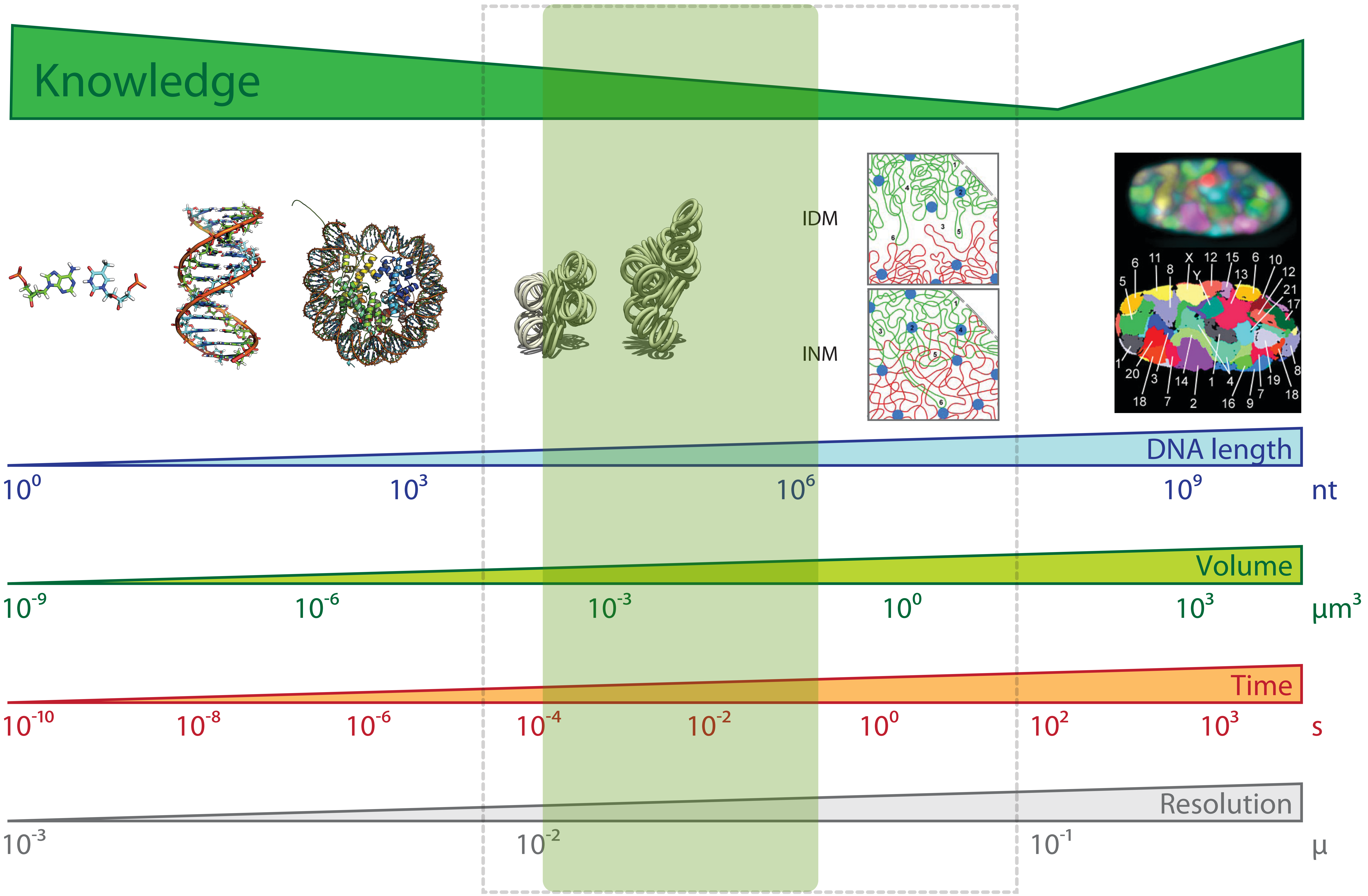
Resolution Gap

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



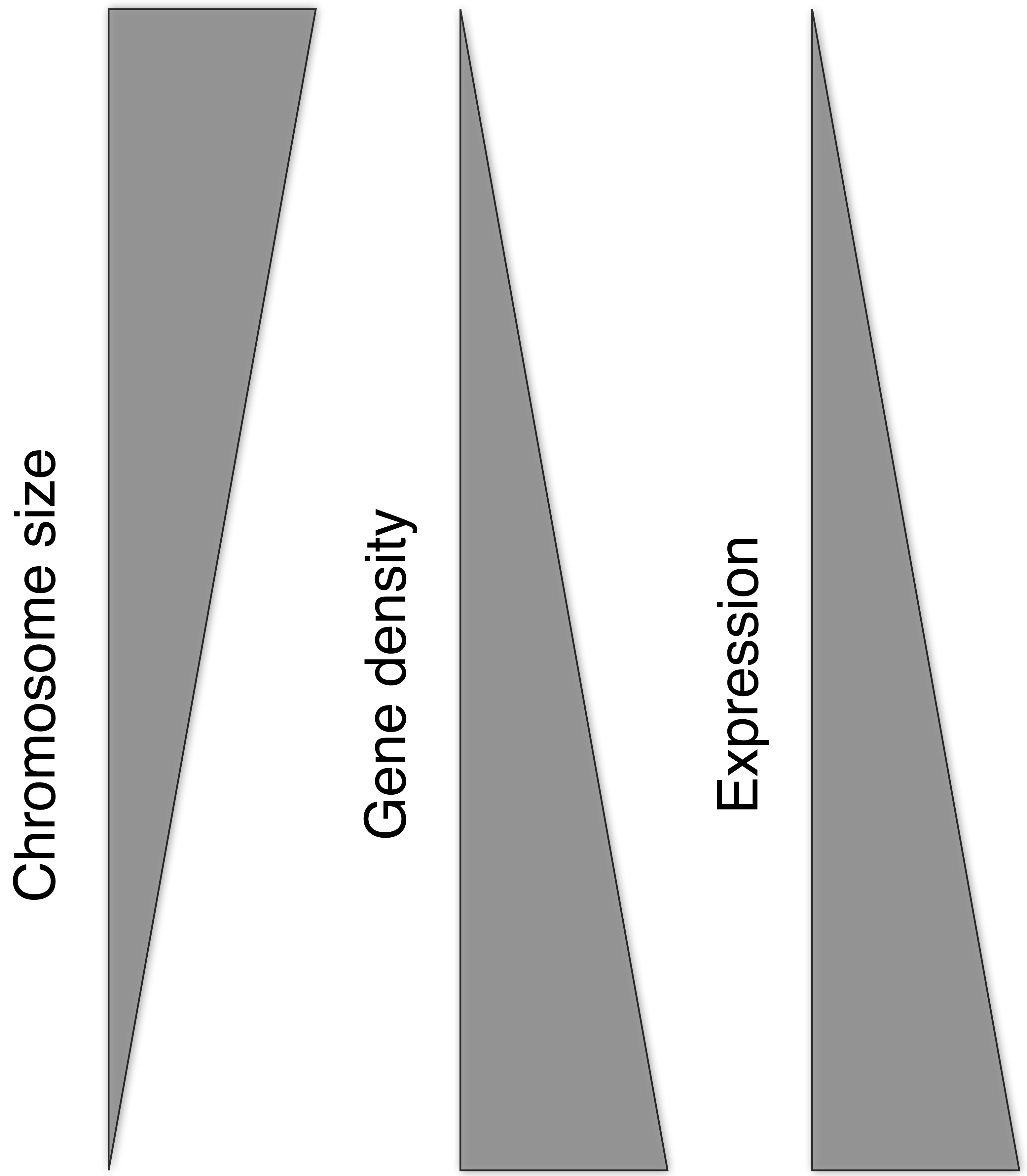
Resolution Gap

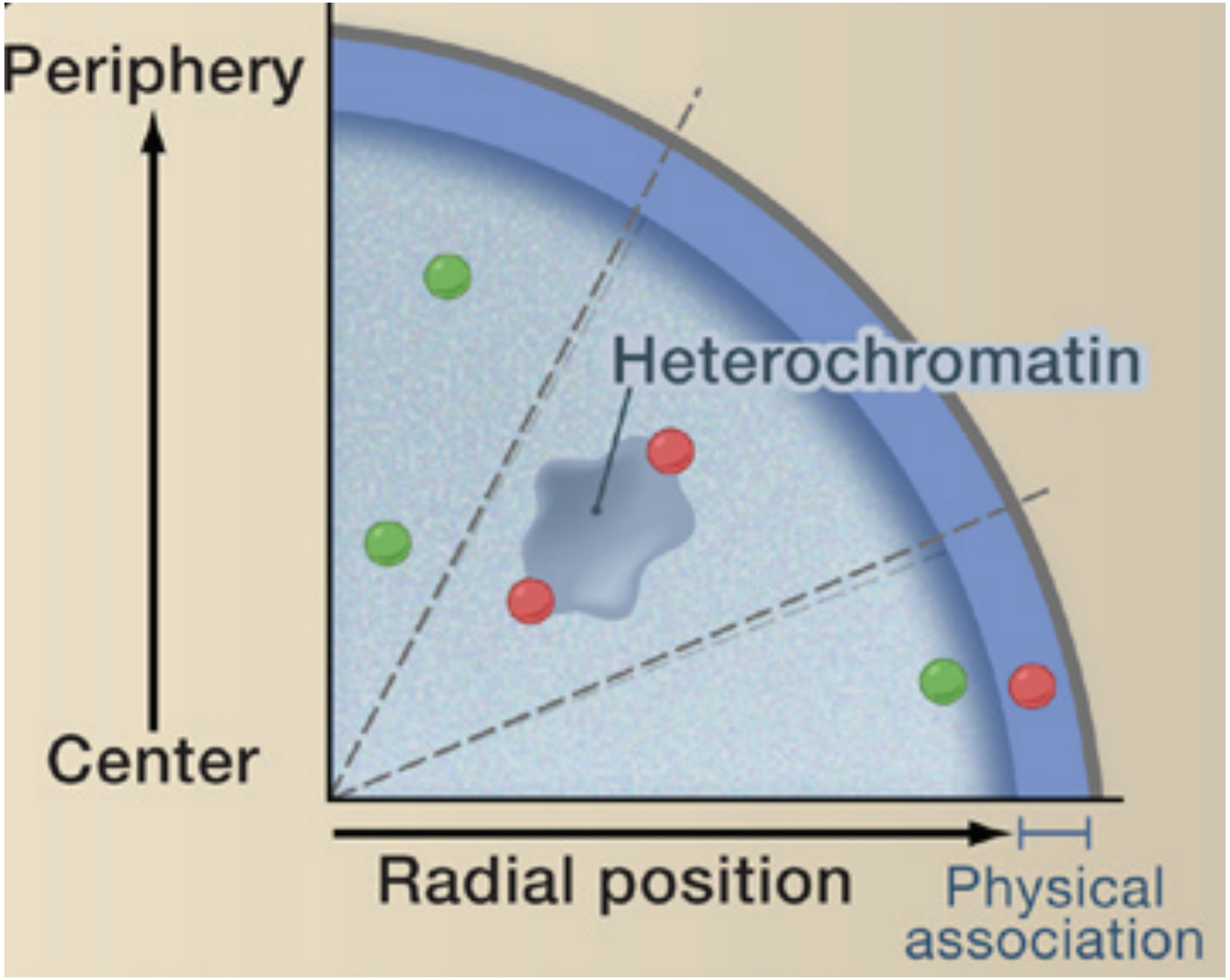
Marti-Renom, M. A. & Mirny, L. A. PLoS Comput Biol 7, e1002125 (2011)



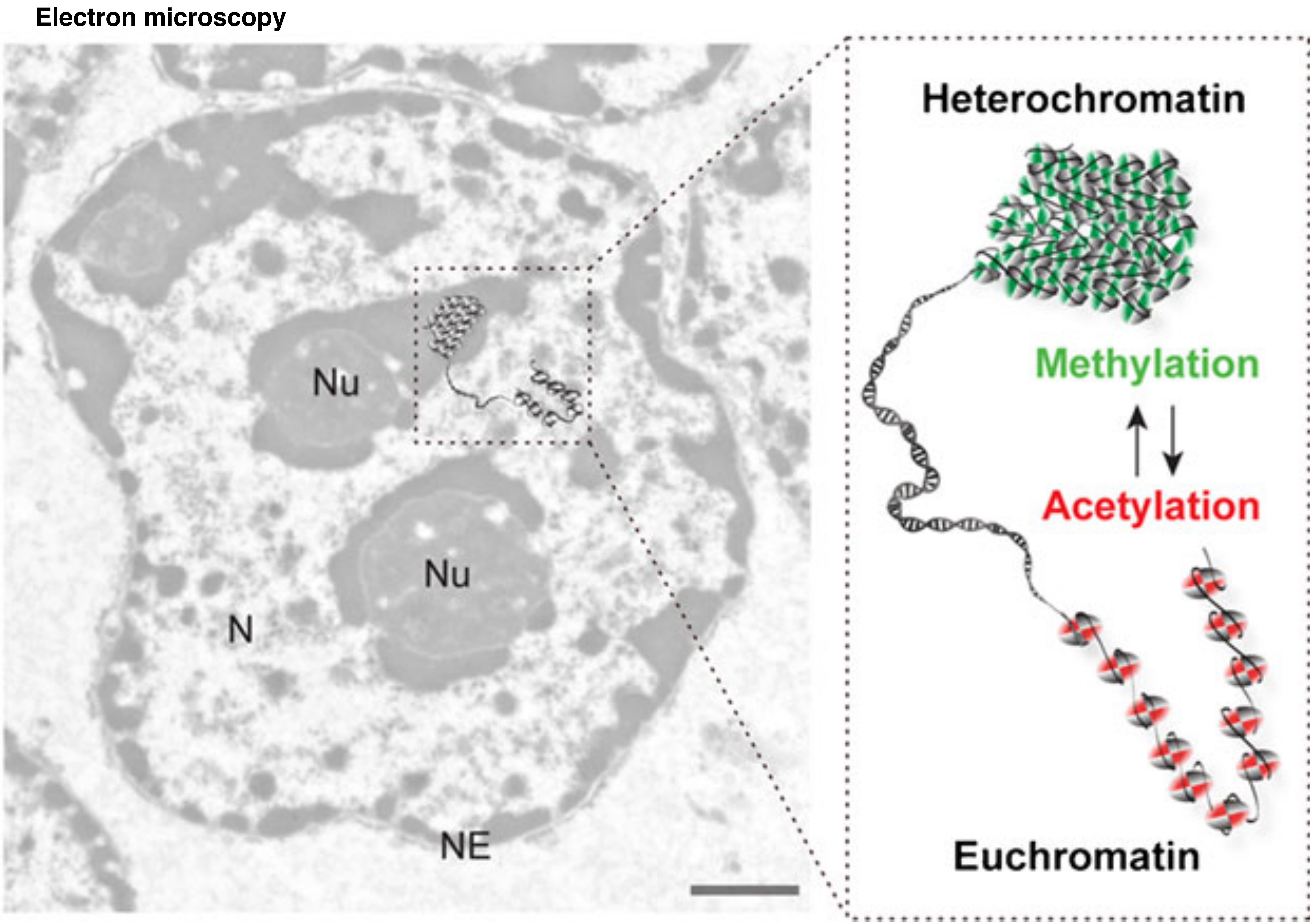
Level I: Radial genome organization

Takizawa, T., Meaburn, K. J. & Misteli, T. The meaning of gene positioning. Cell 135, 9–13 (2008).

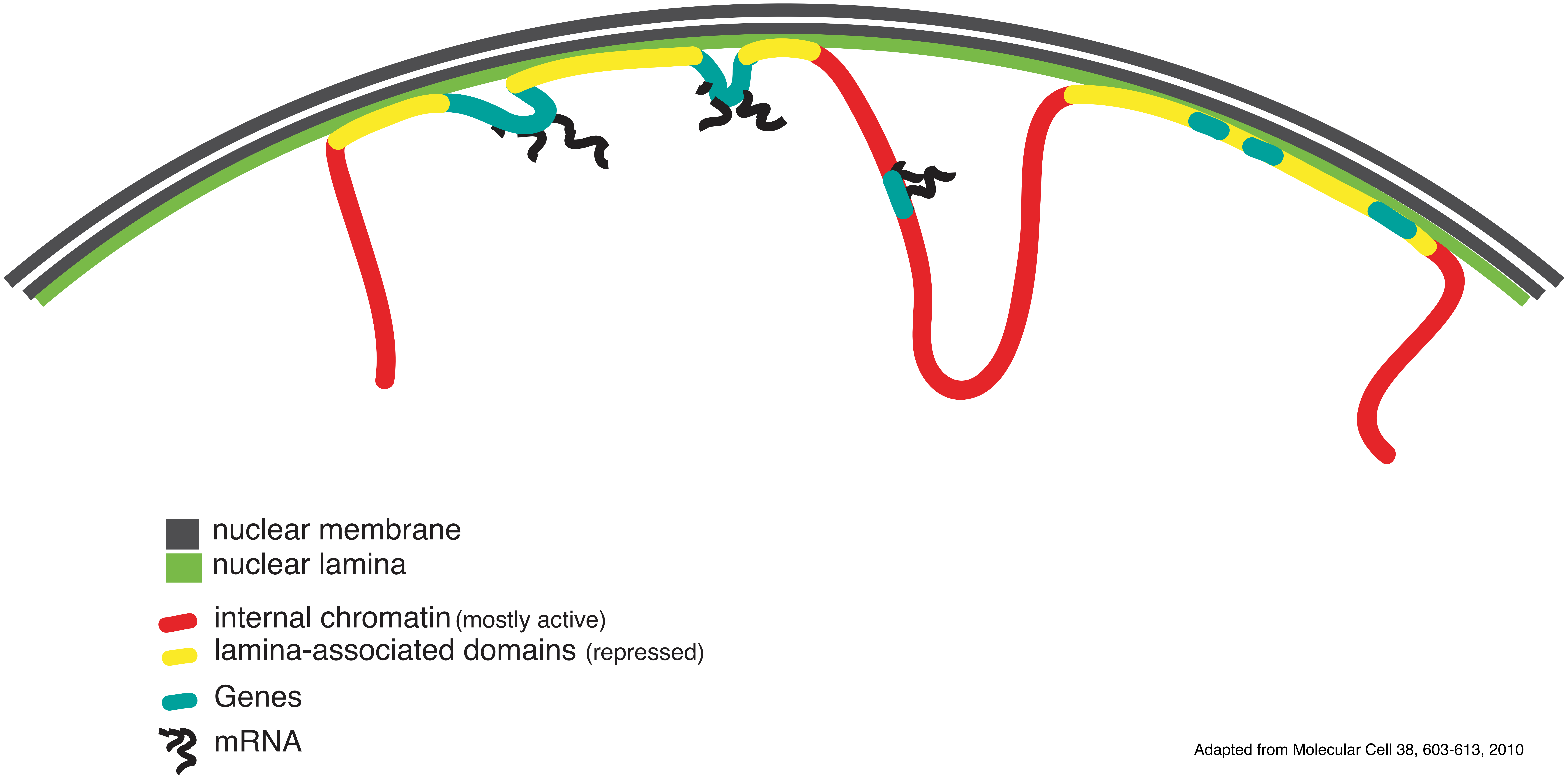




Level II: Euchromatin vs heterochromatin



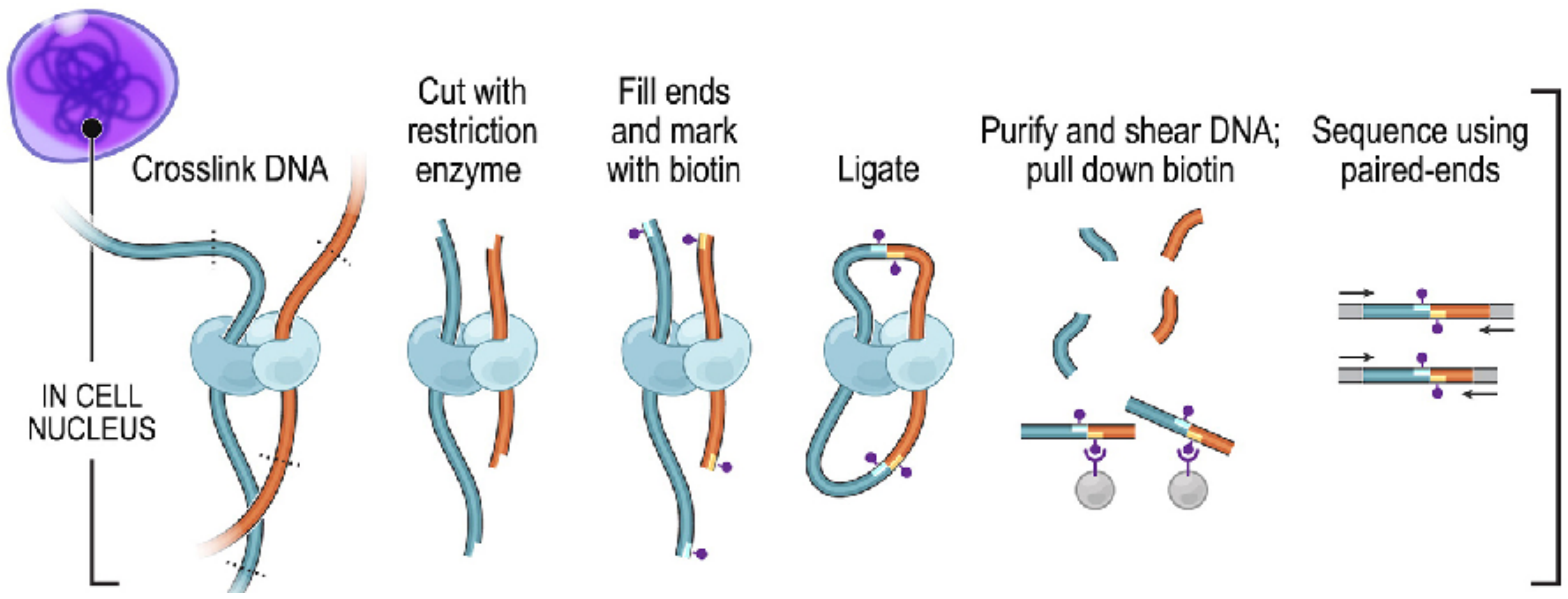
Level III: Lamina-genome interactions

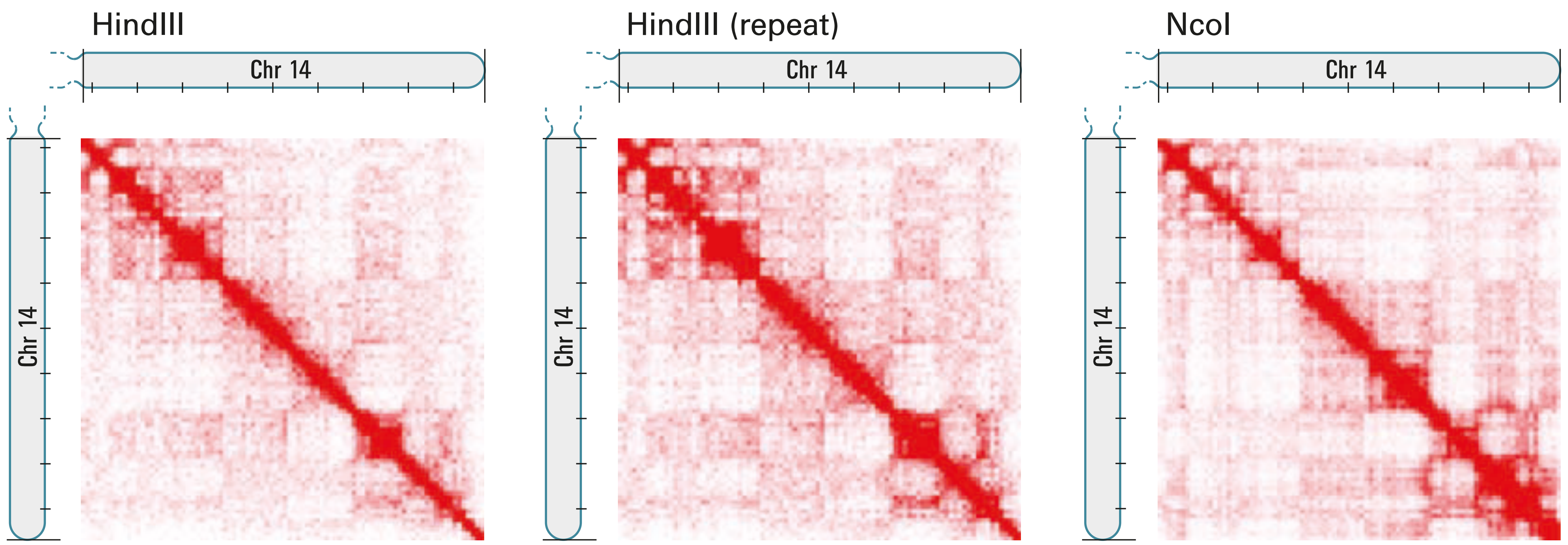


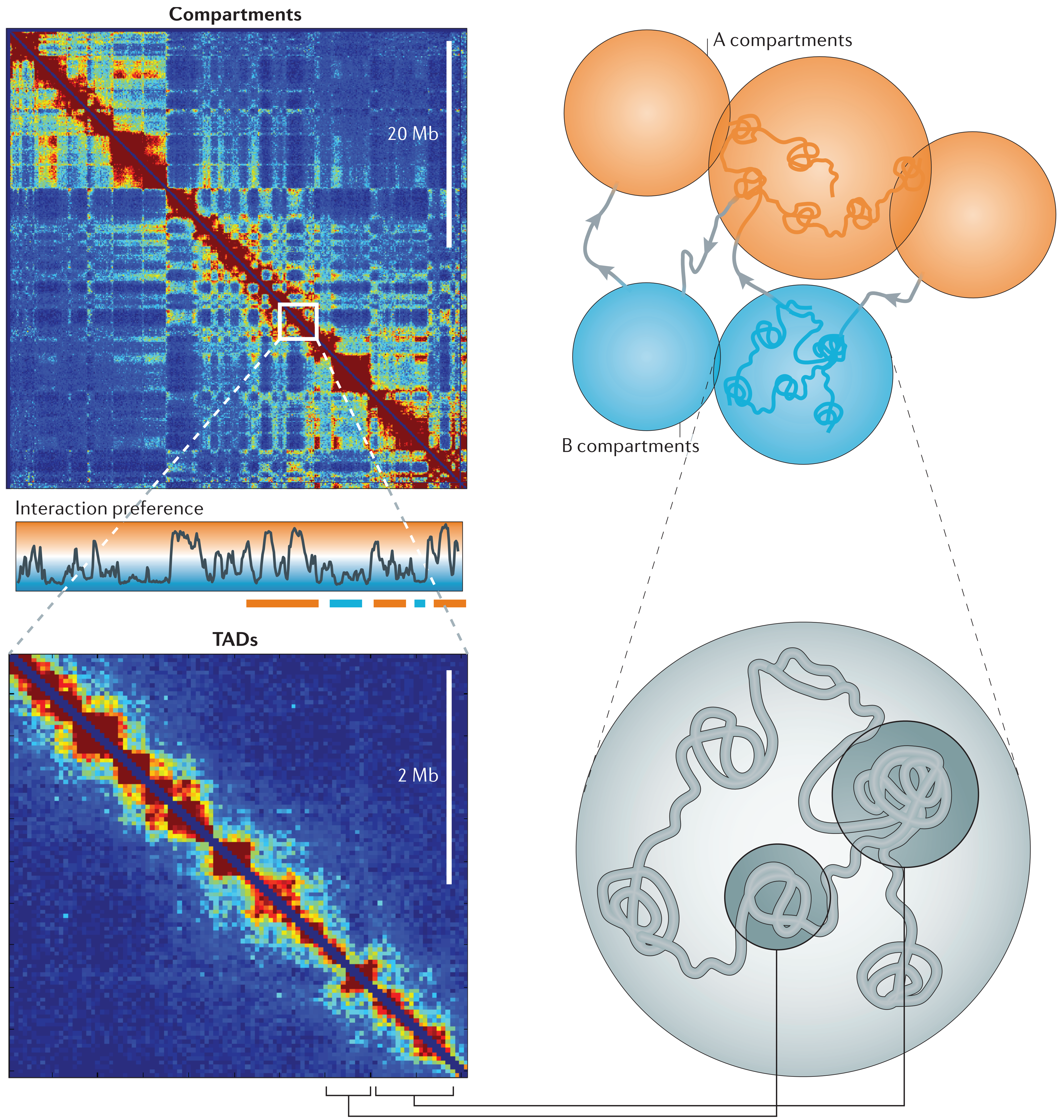
Adapted from Molecular Cell 38, 603-613, 2010

Level IV: Higher-order organization

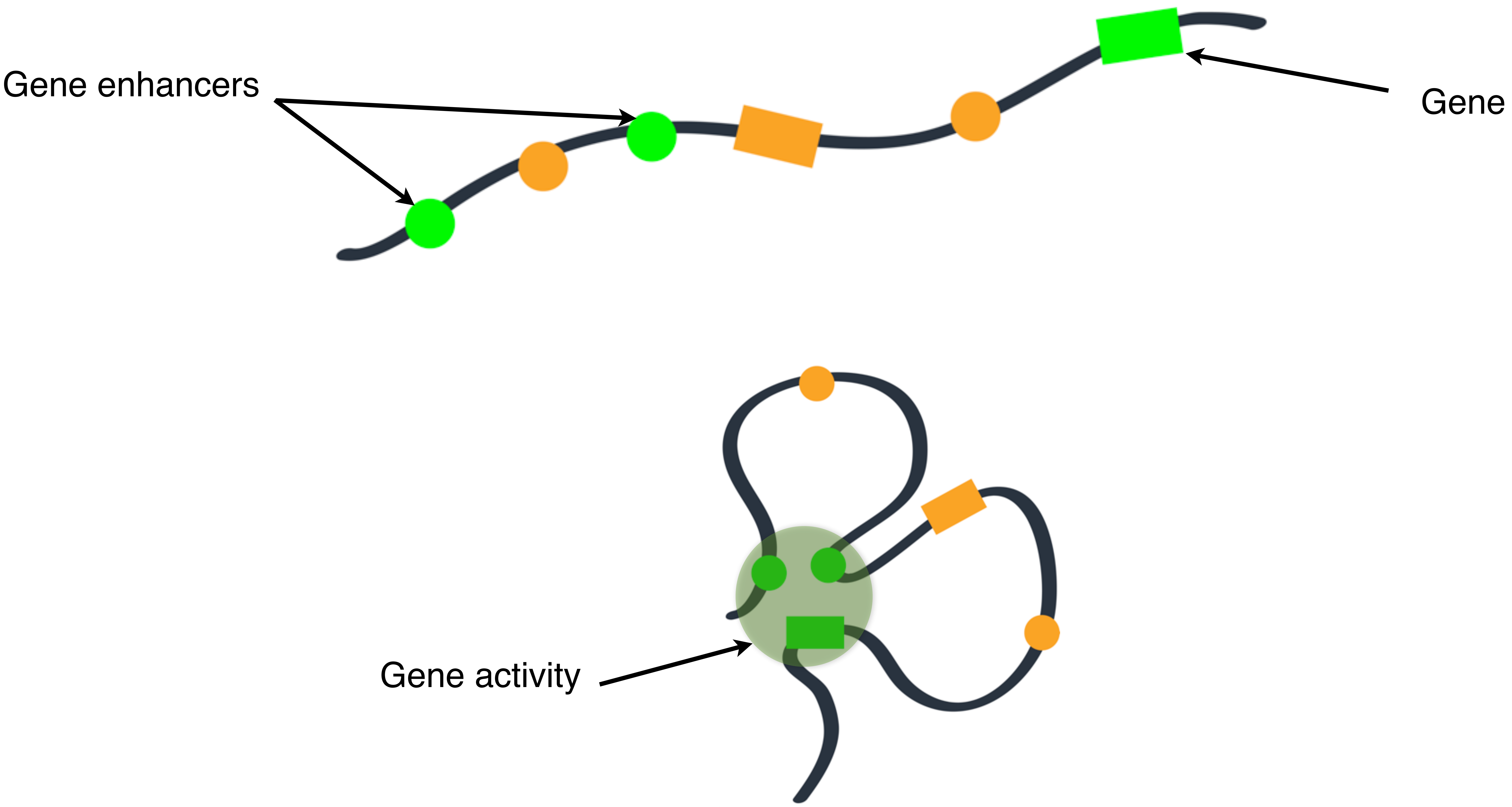
Dekker, J., Marti-Renom, M. A. & Mirny, L. A. Nat Rev Genet 14, 390–403 (2013).



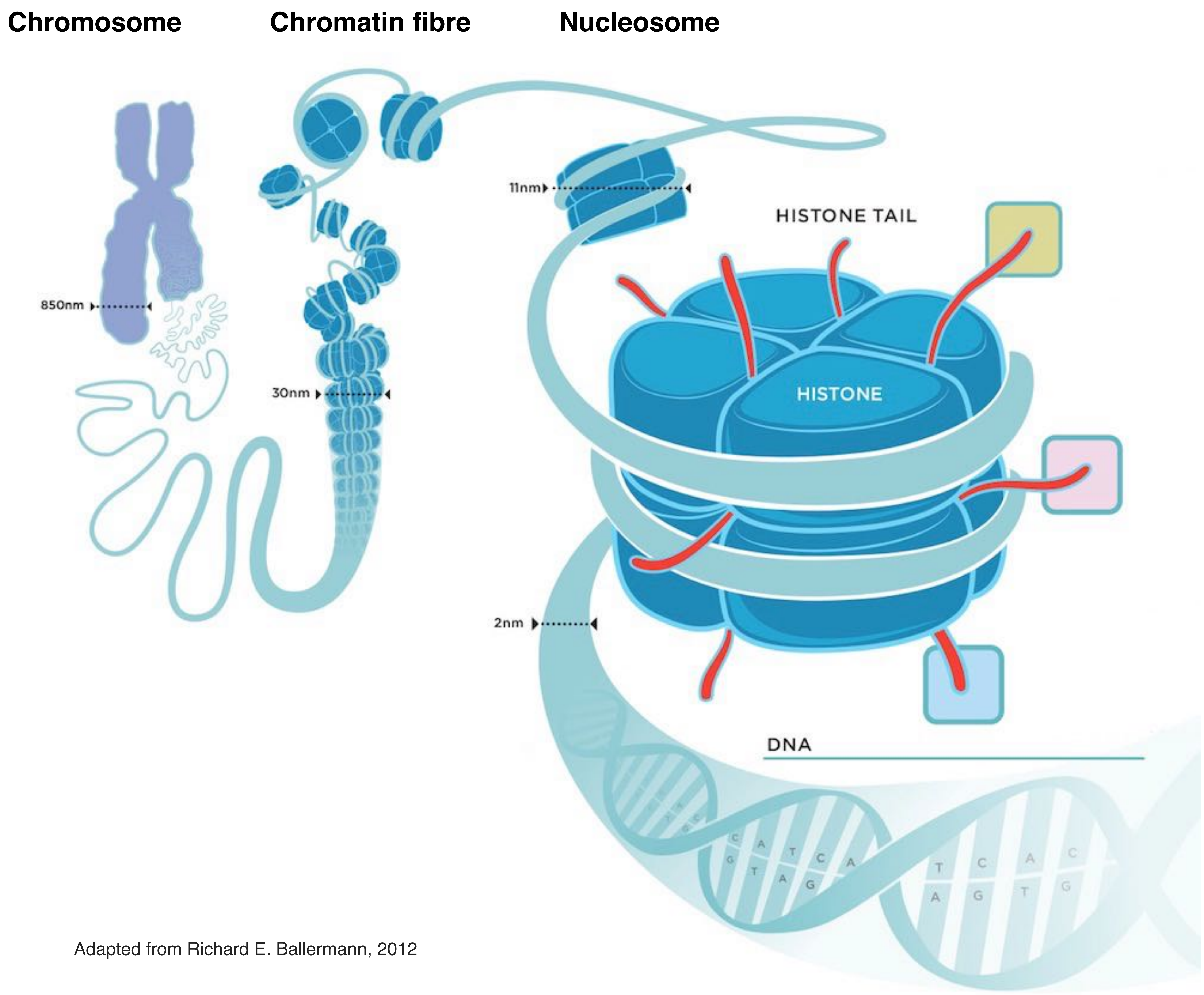




Level V: Chromatin loops



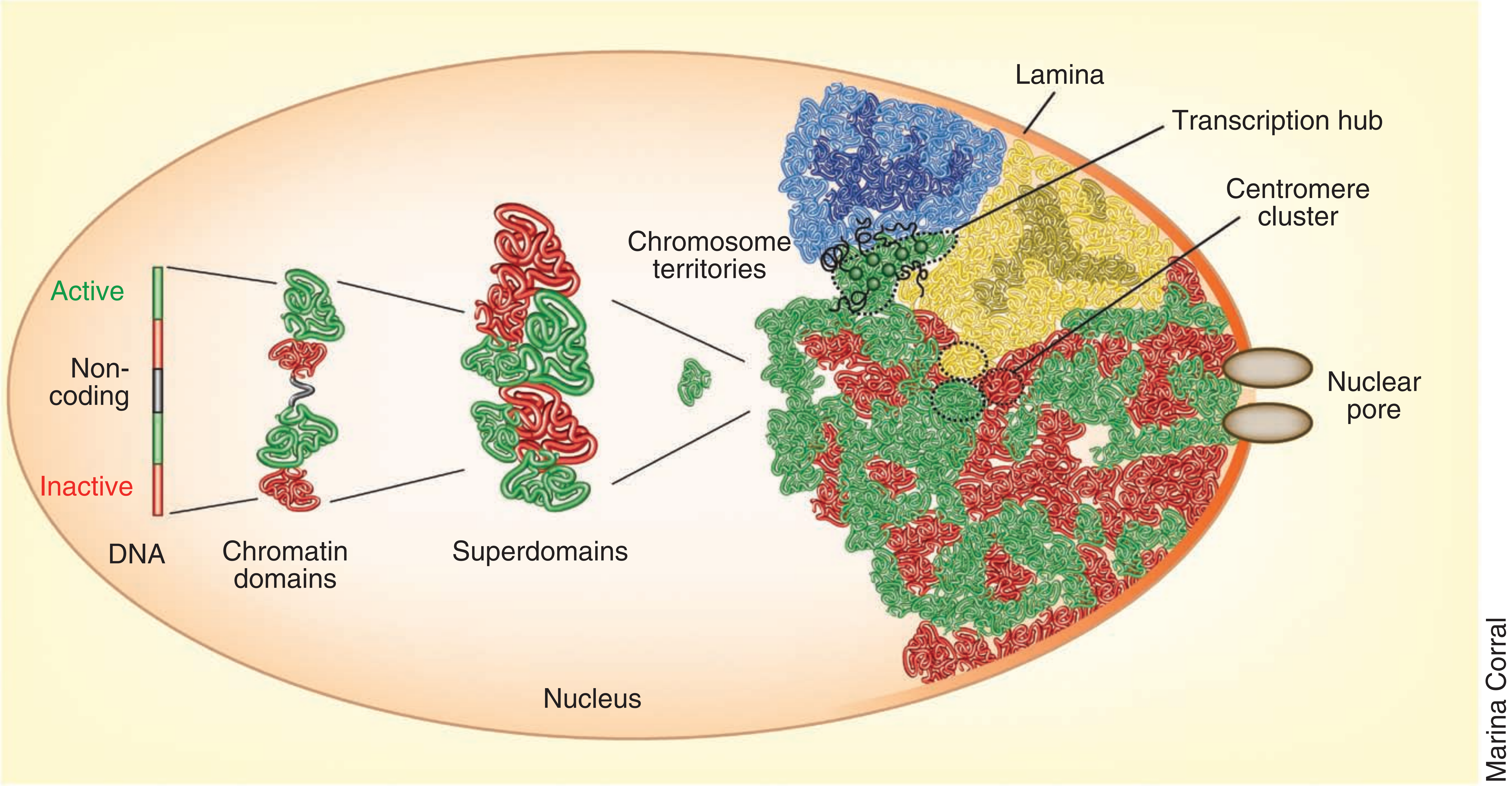
Level VI: Nucleosome



Adapted from Richard E. Ballermann, 2012

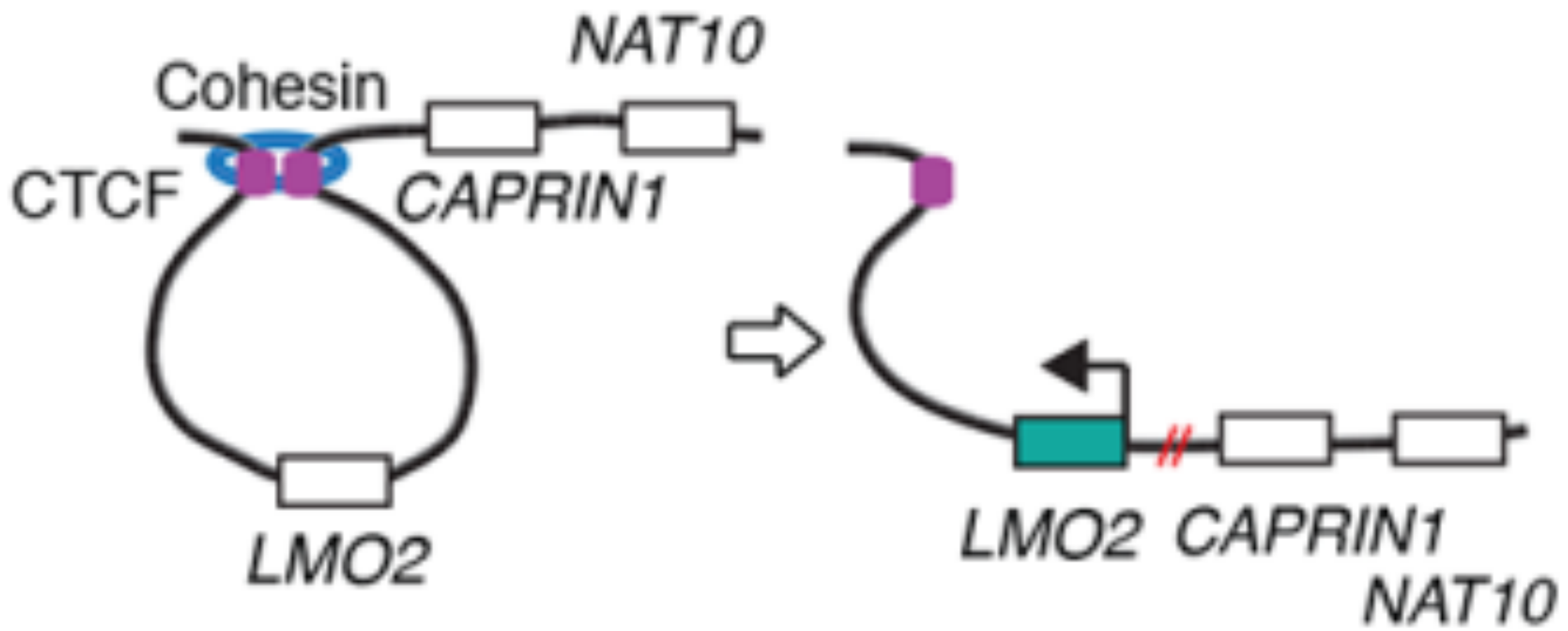
Complex genome organization

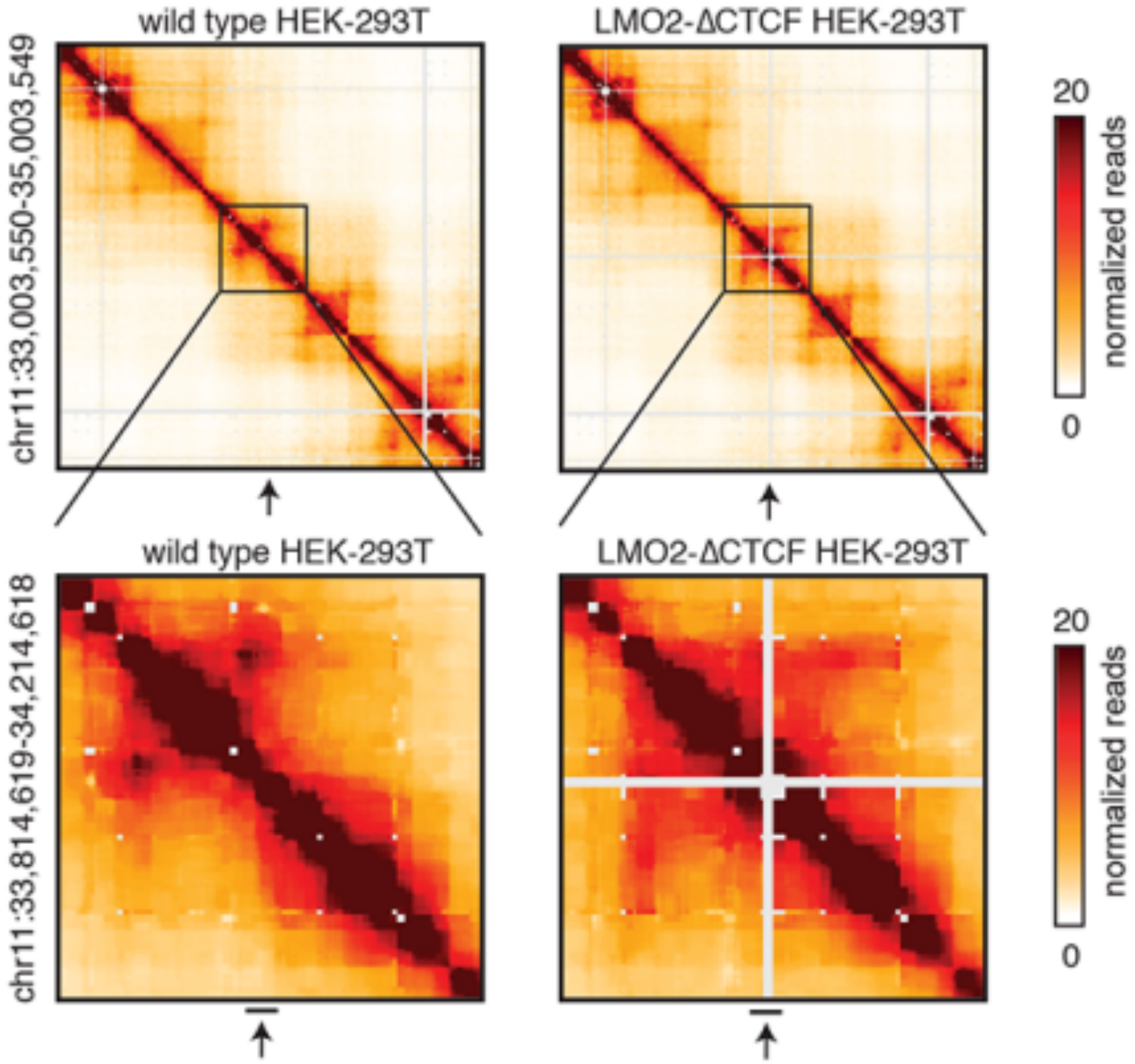
Cavalli, G. & Misteli, T. Functional implications of genome topology. Nat Struct Mol Biol 20, 290–299 (2013).



TADs are functional units

Hnisz, D., et al. (2016). Science





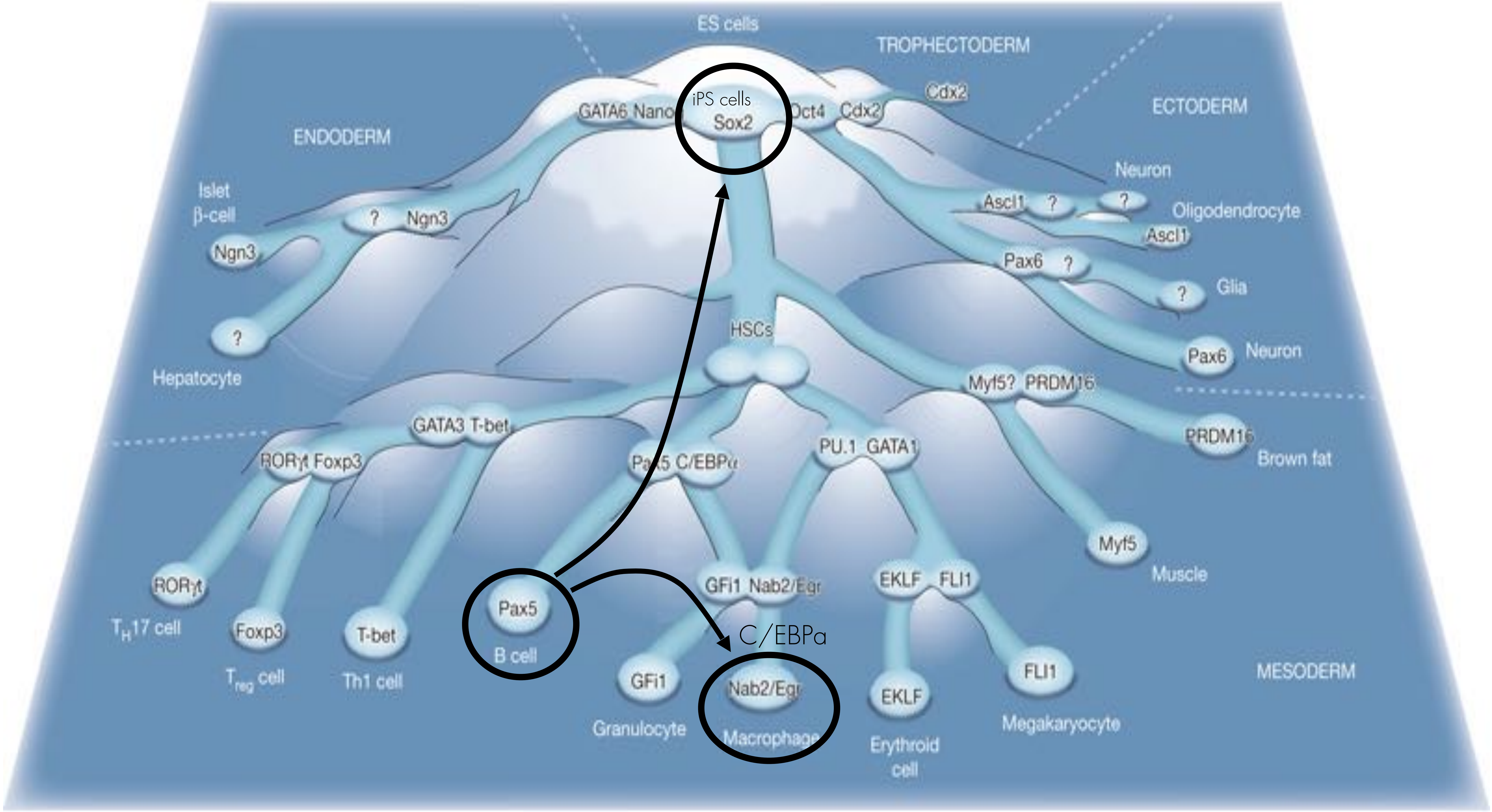
Dynamics of gene activation


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

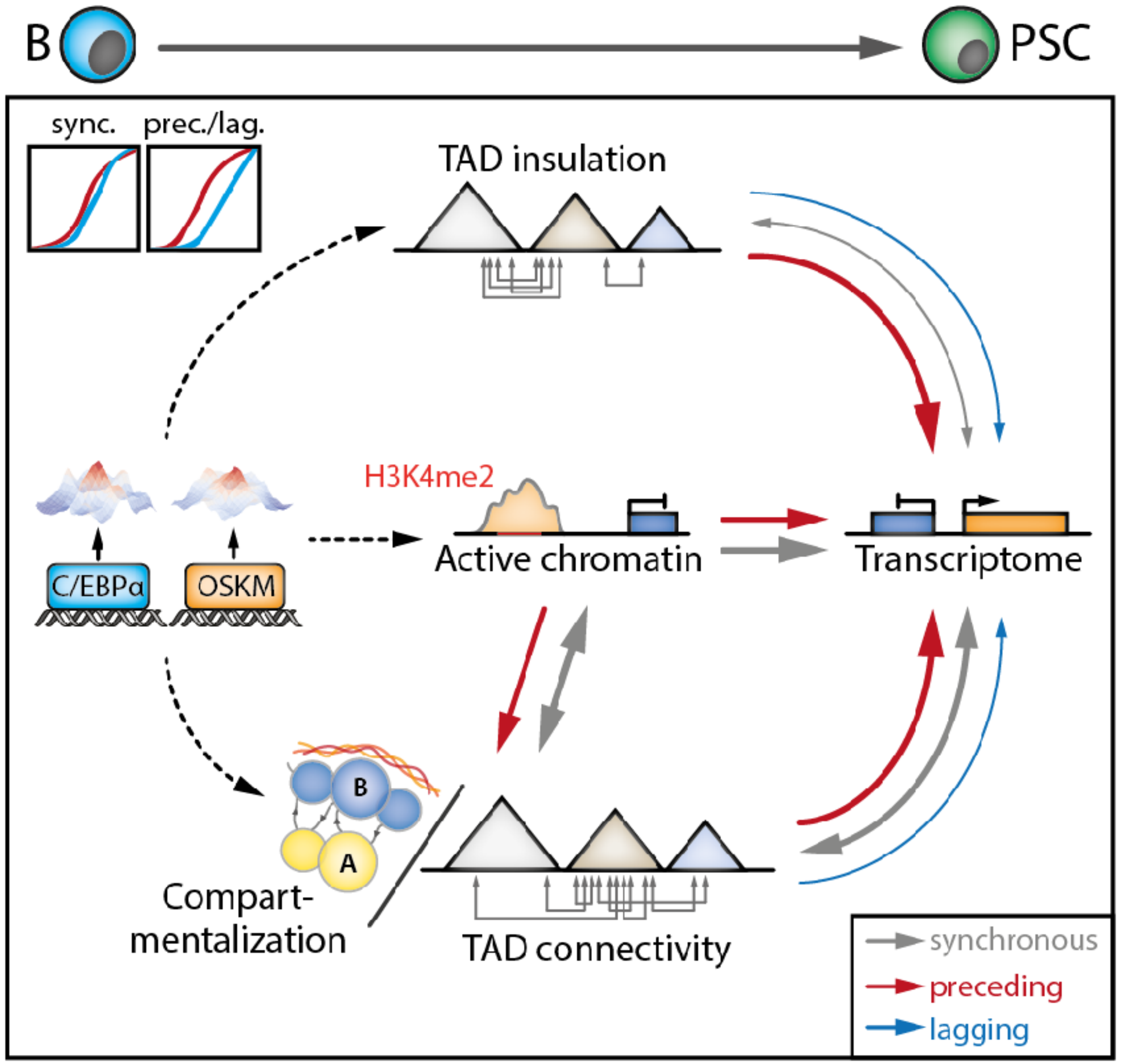
Normal 'forward' differentiation

Cell fates can be converted by enforced TF expression

Transdifferentiation or reprogramming

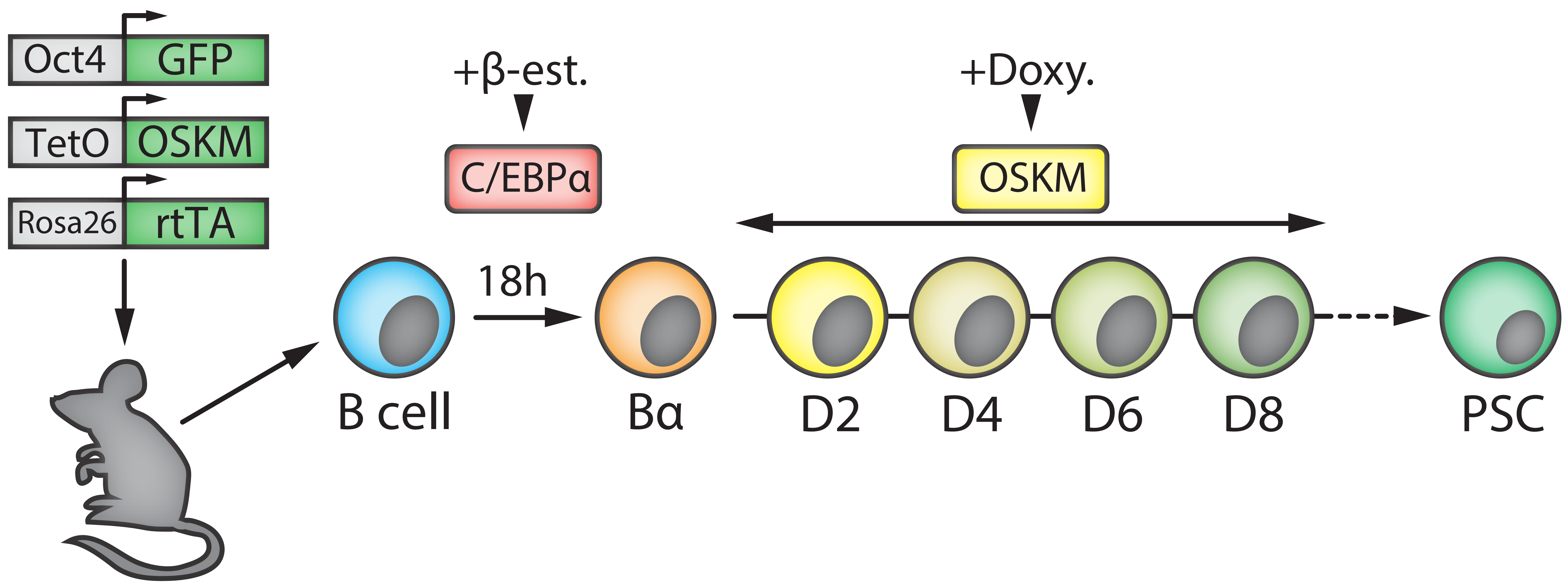
Interplay: topology, gene expression & chromatin

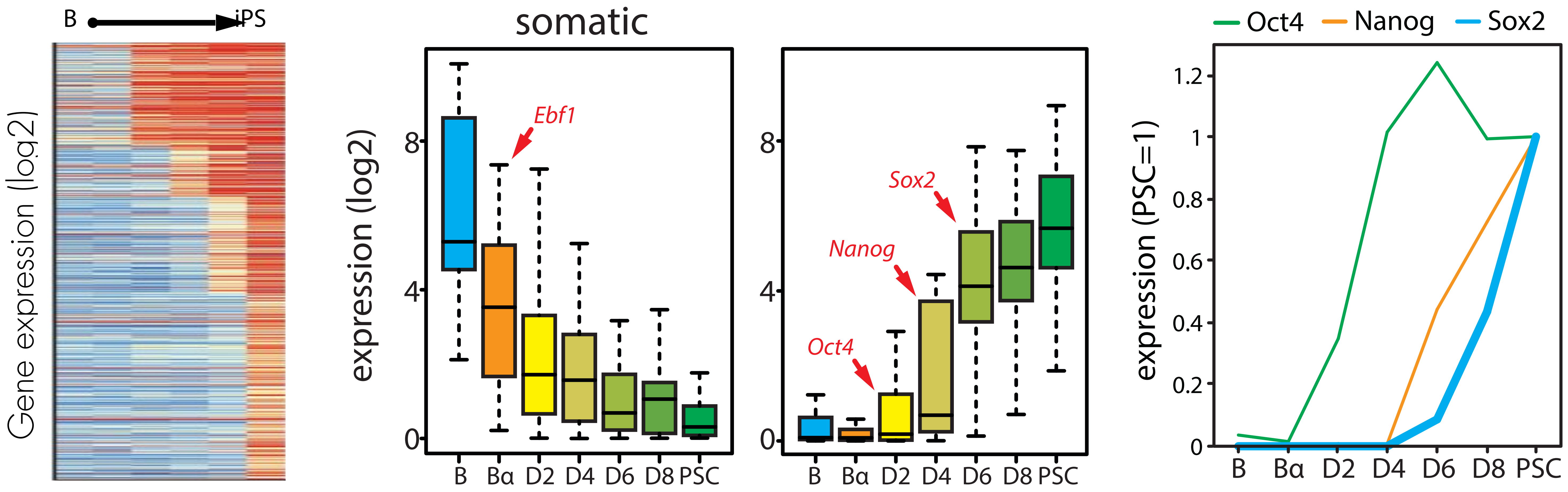
Stadhouders, R., Vidal, E. et al. (2018) Nature Genetics



Reprogramming from B to PSC

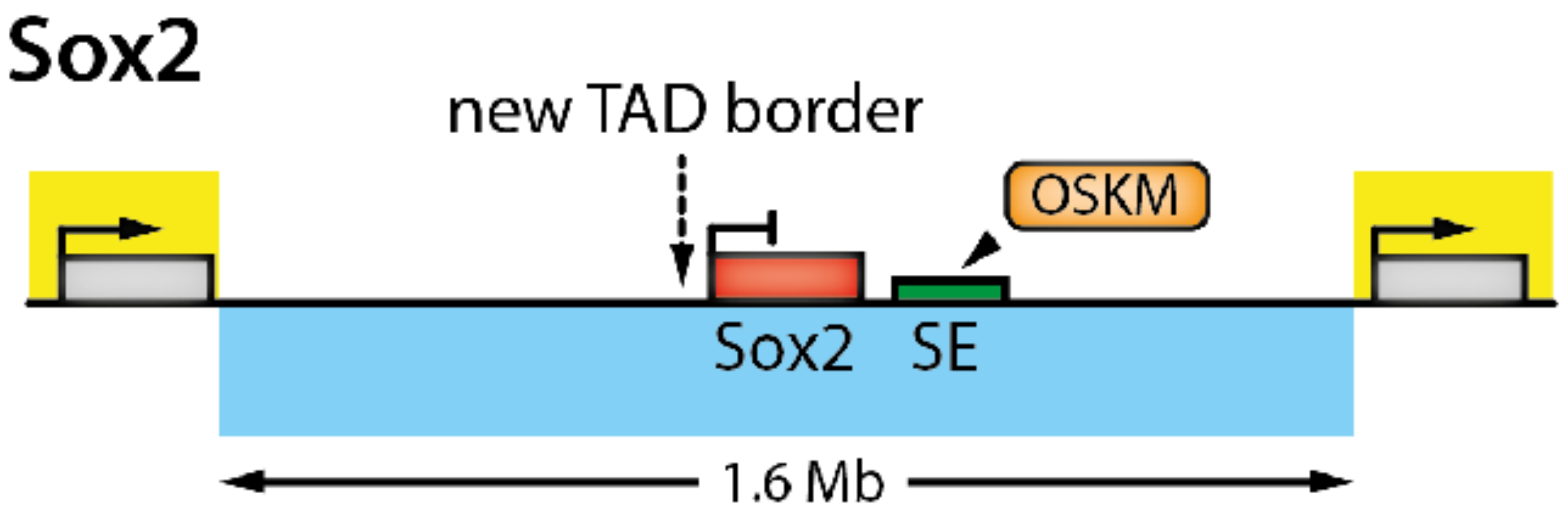
Stadhouders, R., Vidal, E. et al. (2018) Nature Genetics

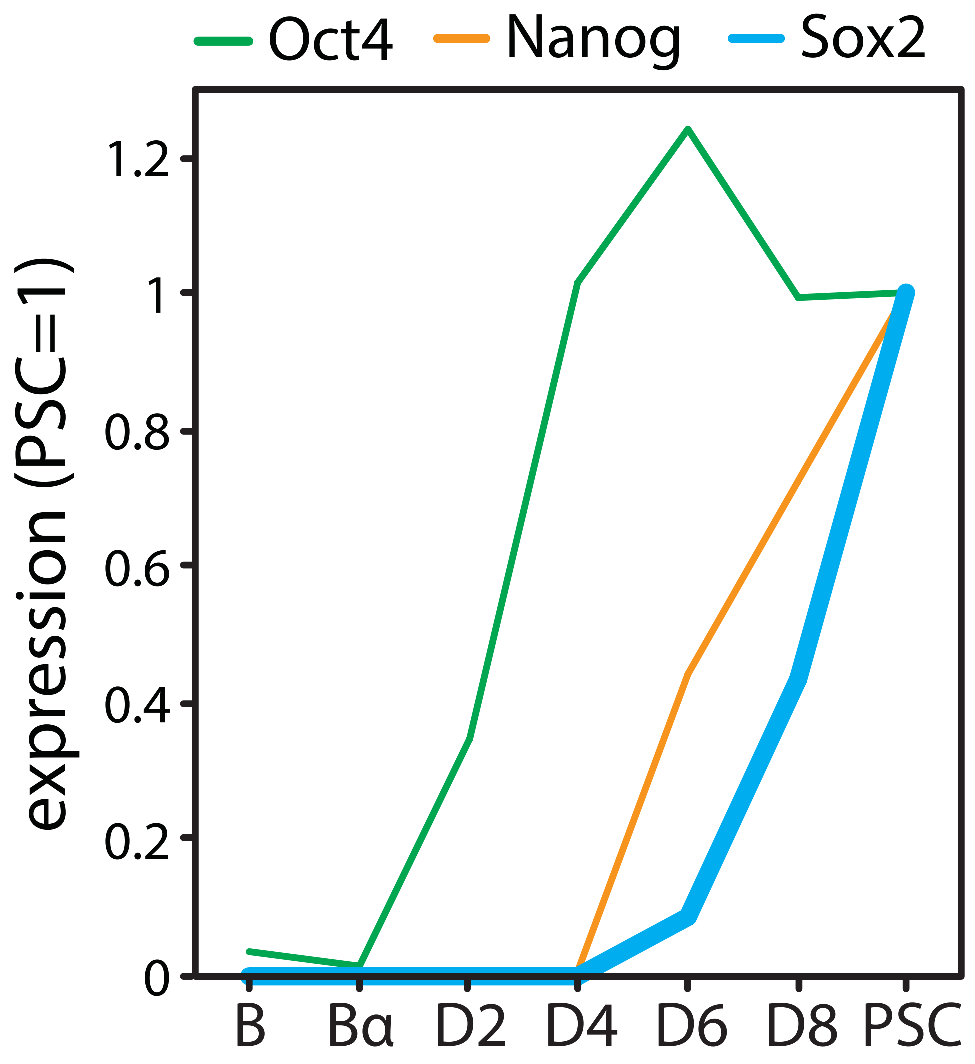


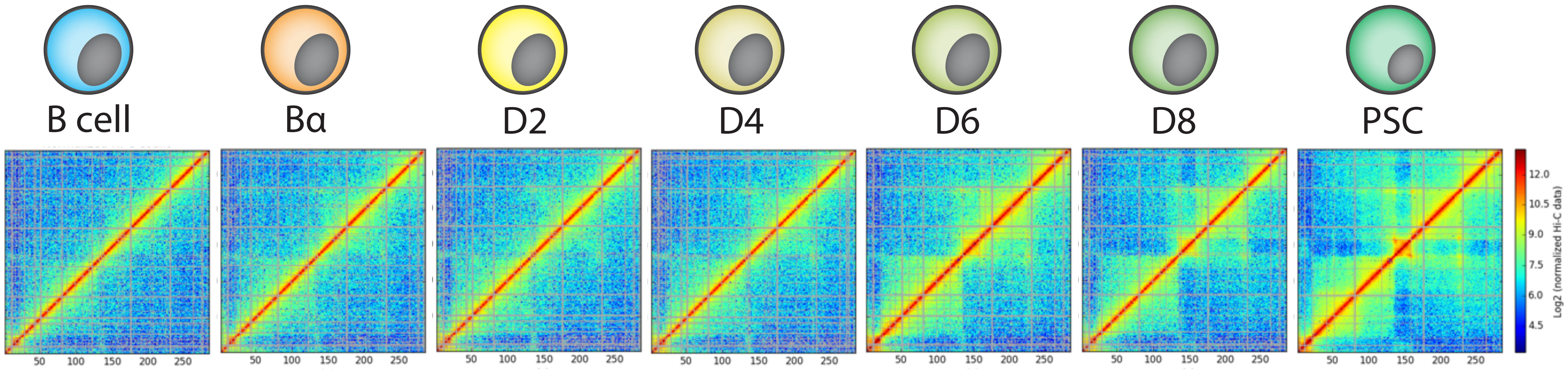


Hi-C maps of reprogramming from B to PSC

The SOX2 locus

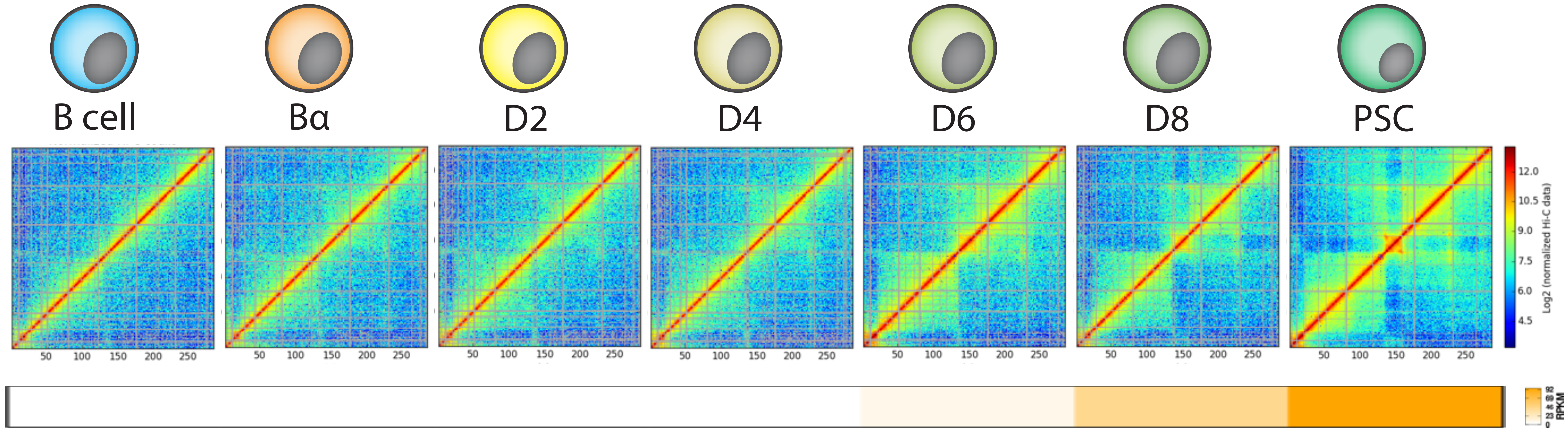






Hi-C maps of reprogramming from B to PSC

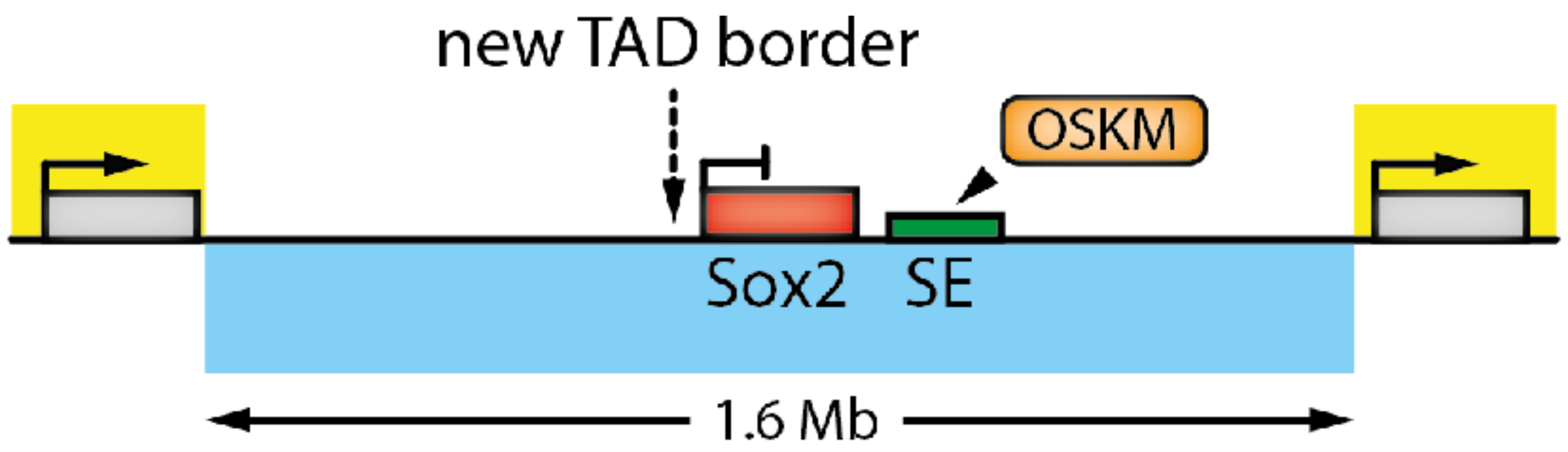
The SOX2 locus

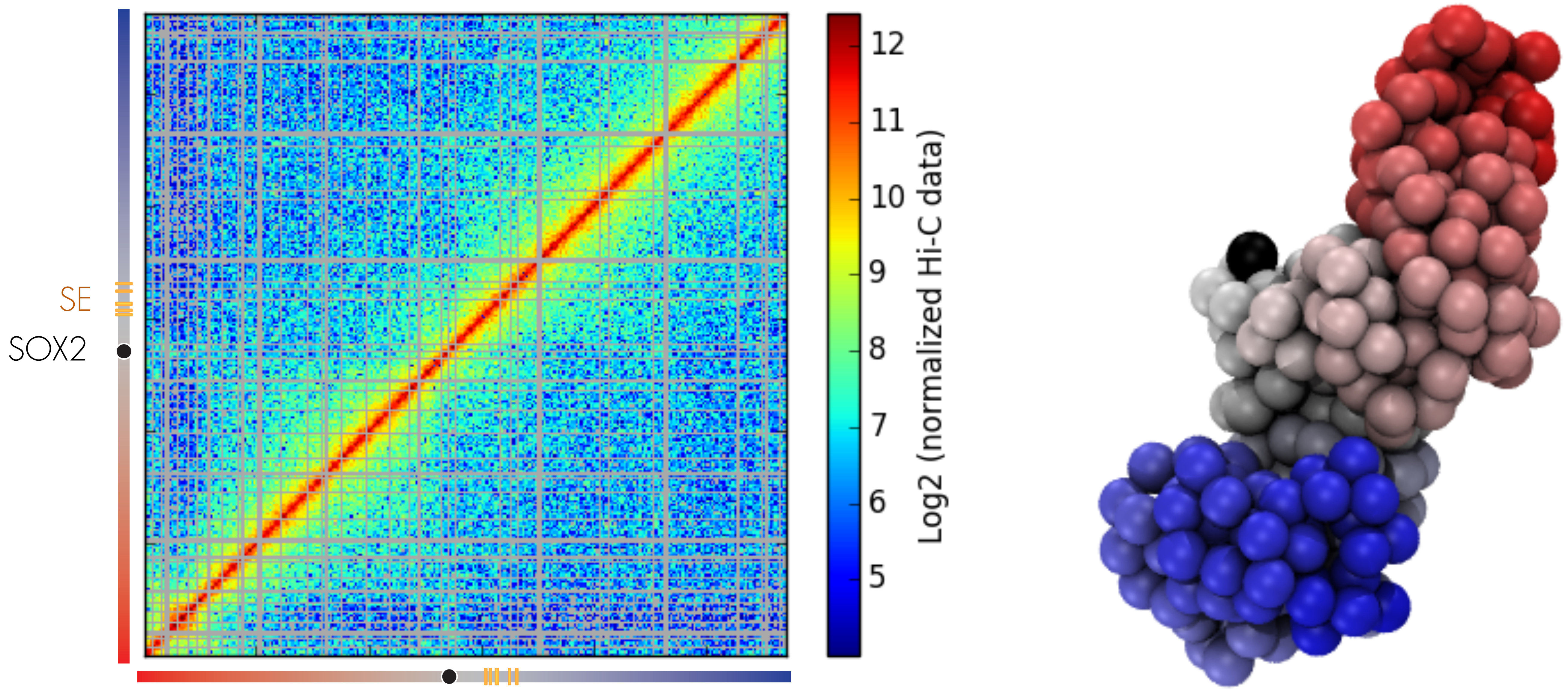


How does these structural rearrangements interplay with the transcription activity?

What are the main drivers of structural transitions?

TADbit modeling of SOX2 from B cells Hi-C



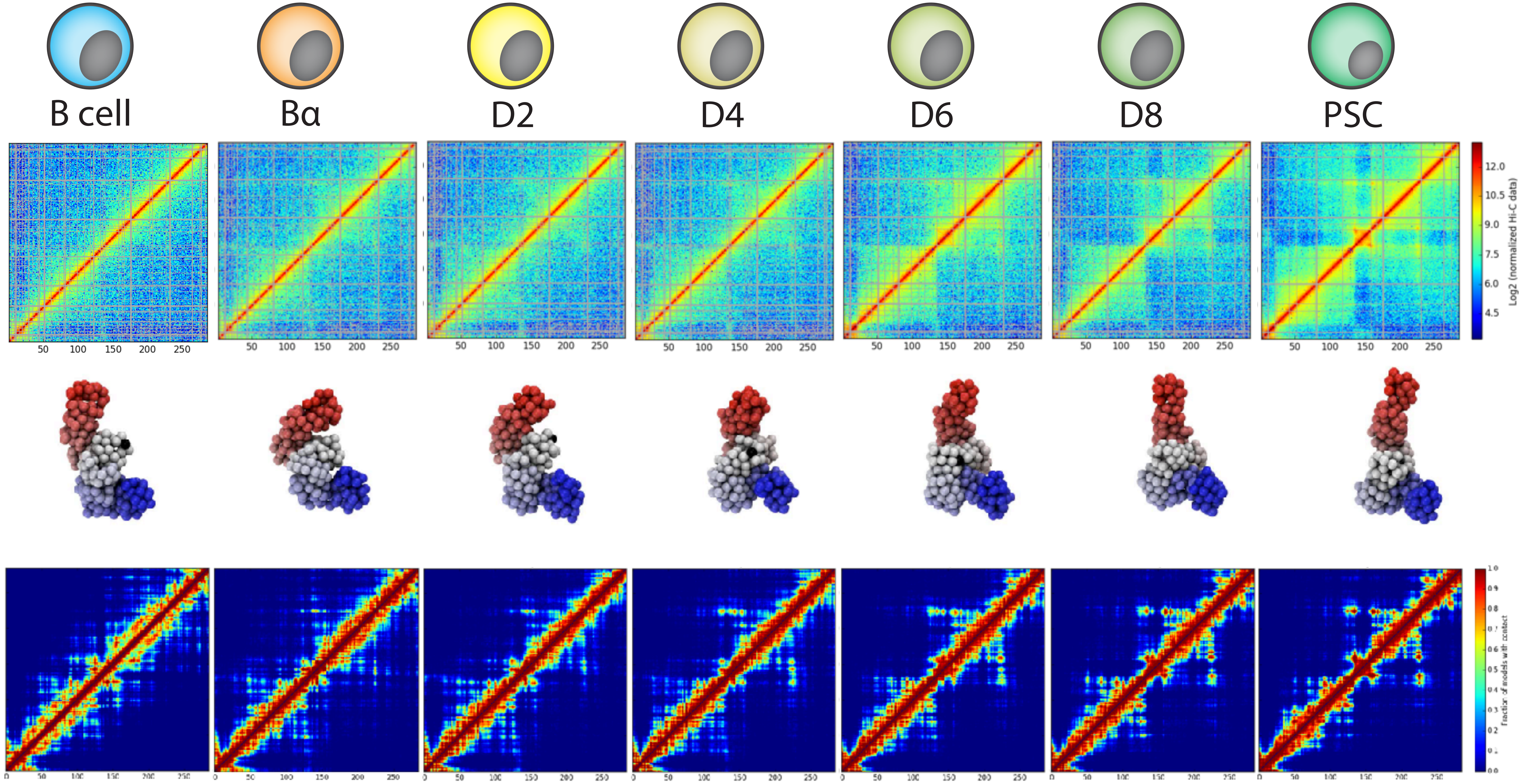


Optimal IMP parameters

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

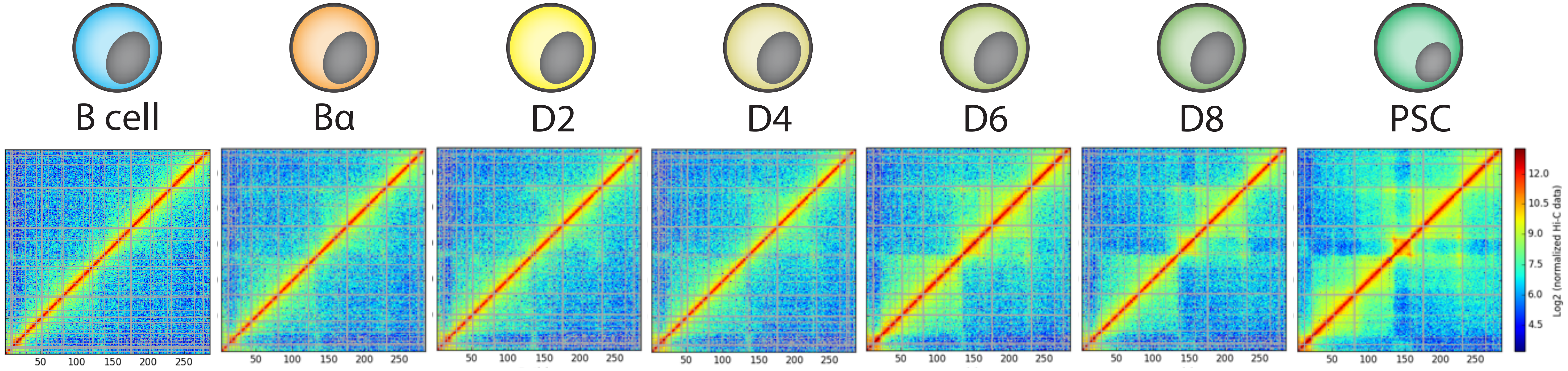
Models of reprogramming from B to PSC

The SOX2 locus



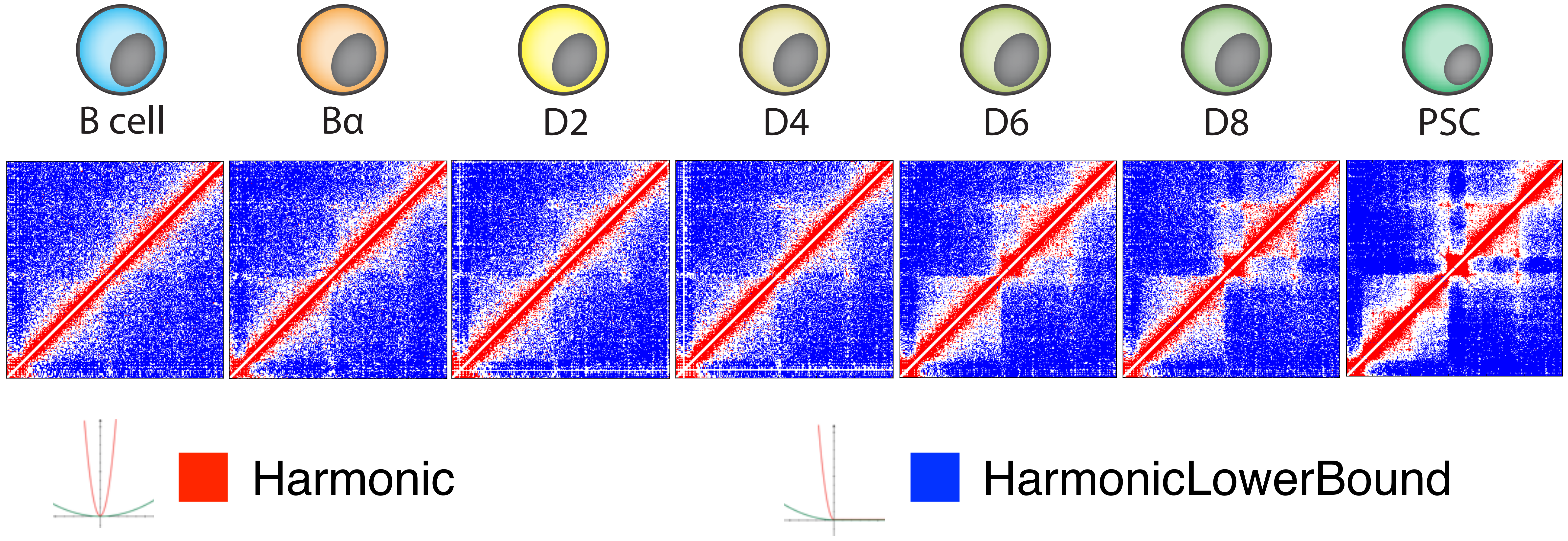
TADdyn: from time-series Hi-C maps to dynamic restraints

The SOX2 locus



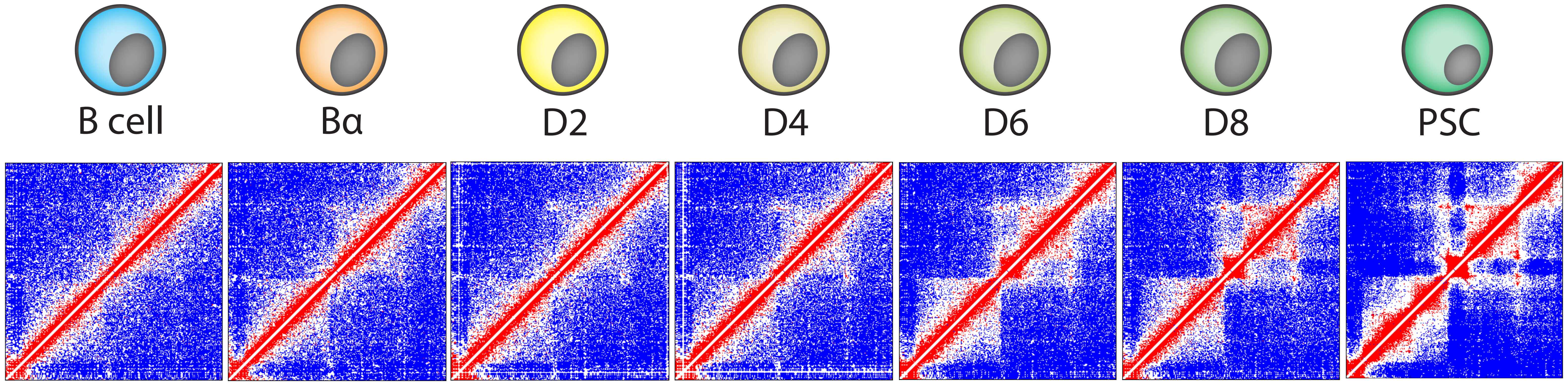
TADdyn: from time-series Hi-C maps to dynamic restraints

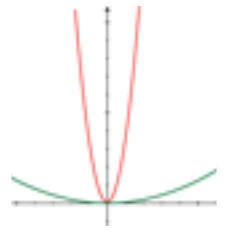
The SOX2 locus

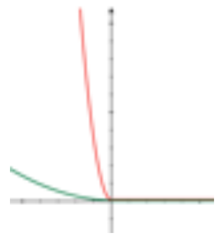


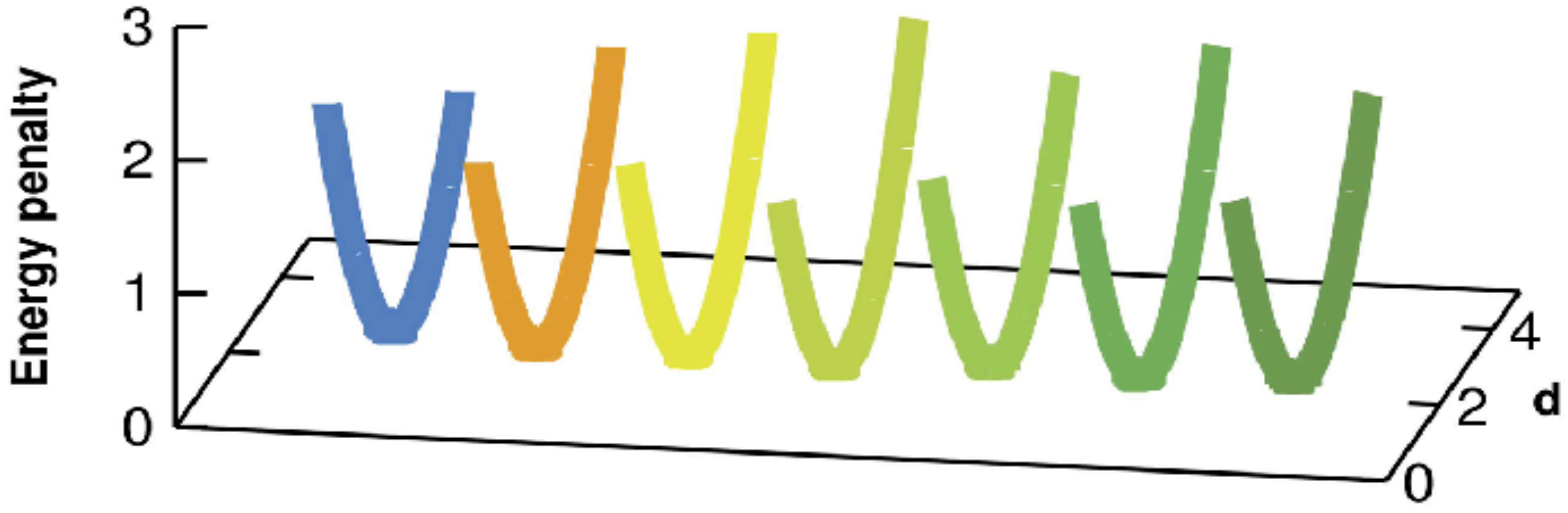
TADdyn: from time-series Hi-C maps to dynamic restraints

The SOX2 locus




Harmonic

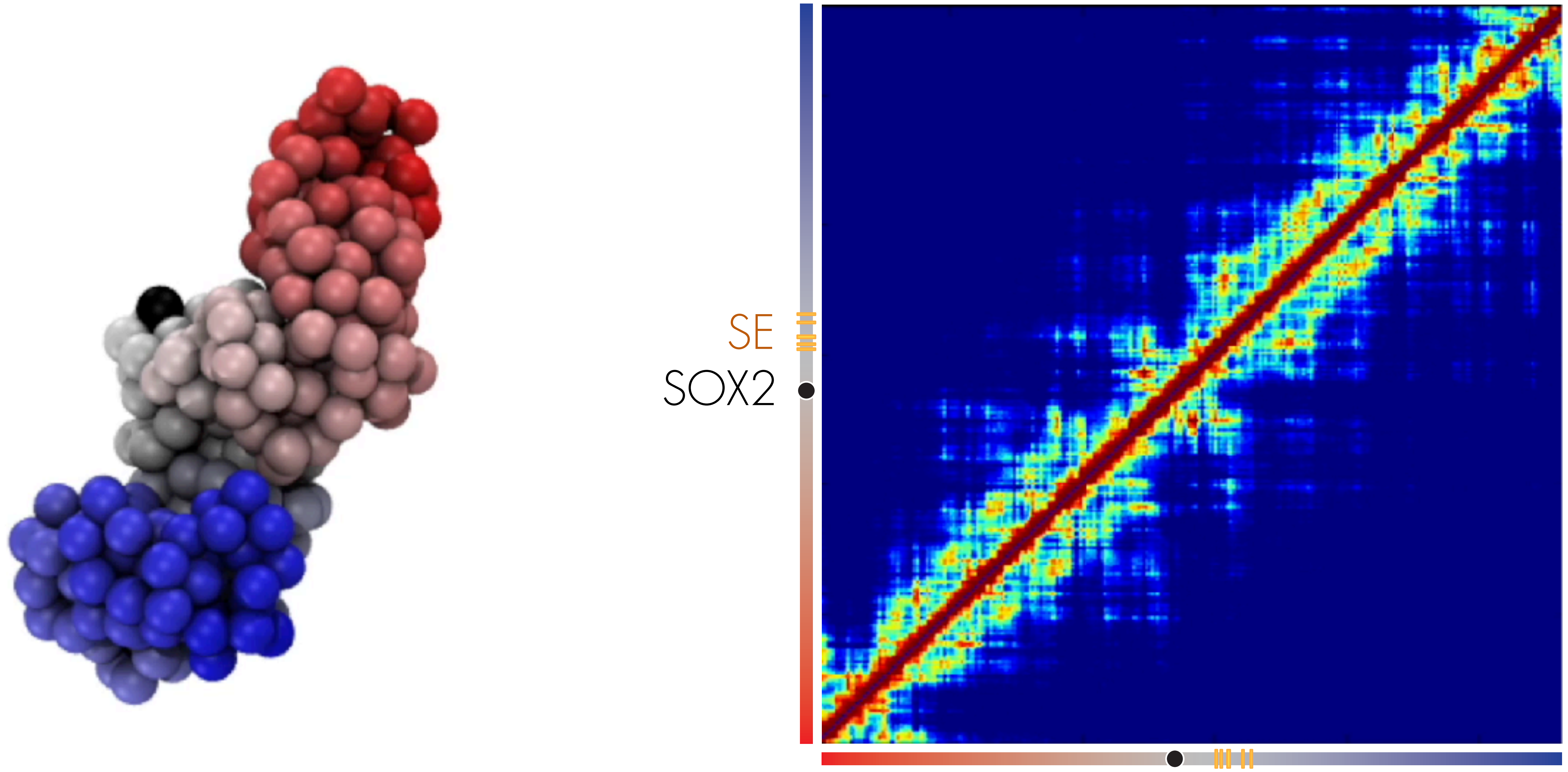

HarmonicLowerBound



Transition	Stable	Vanishing	Raising
B -> 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

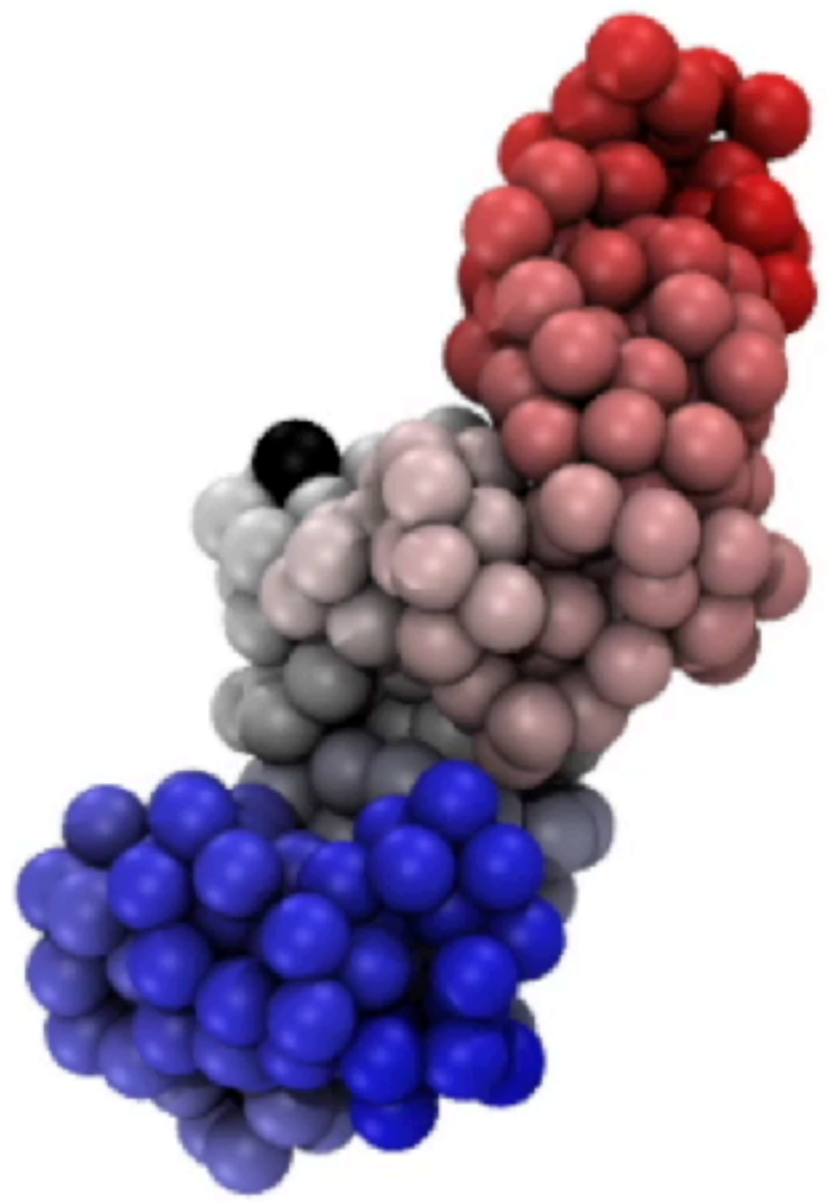
SOX2 locus structural changes from B to PSC

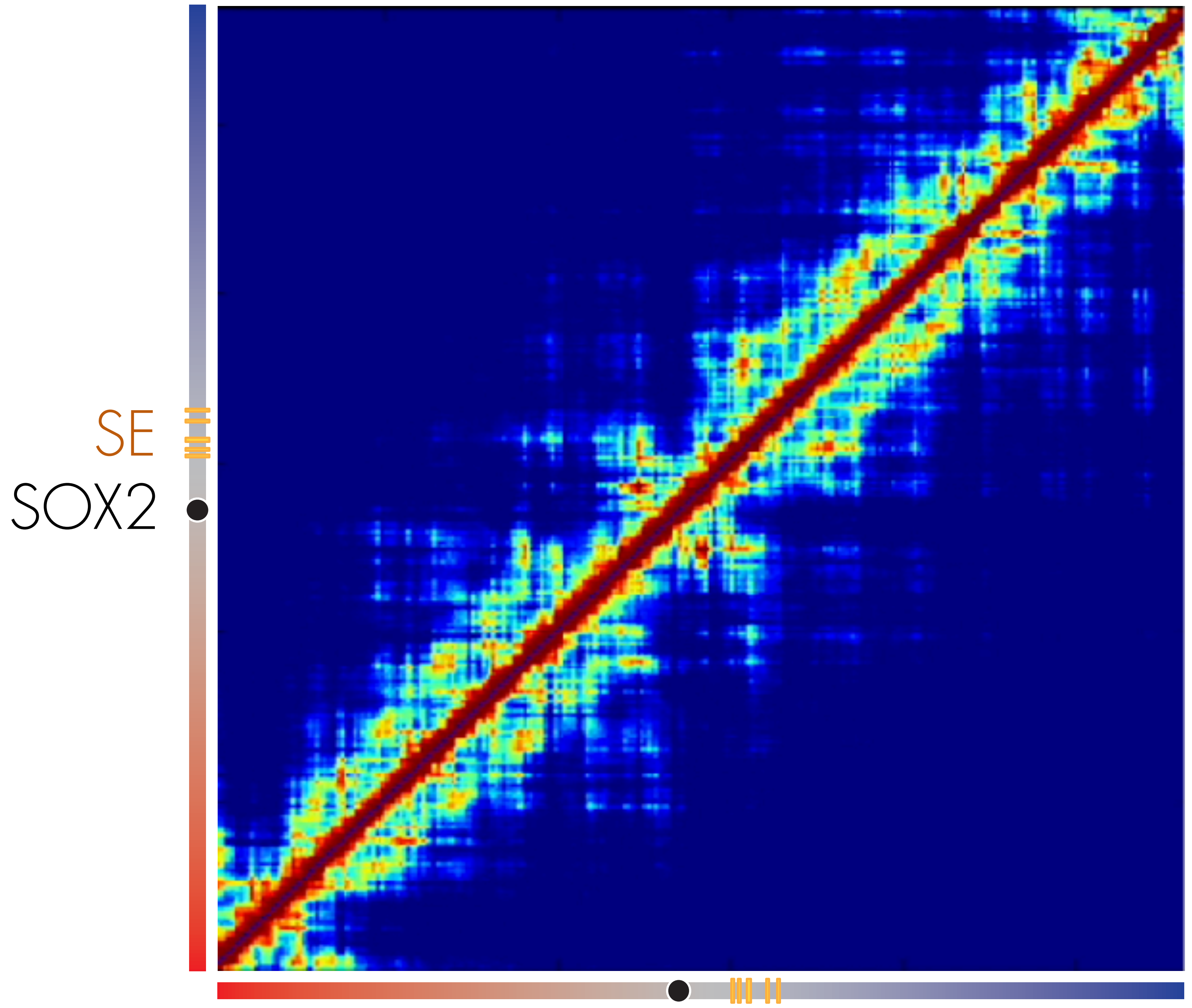
Contacts



SOX2 locus structural changes from B to PSC

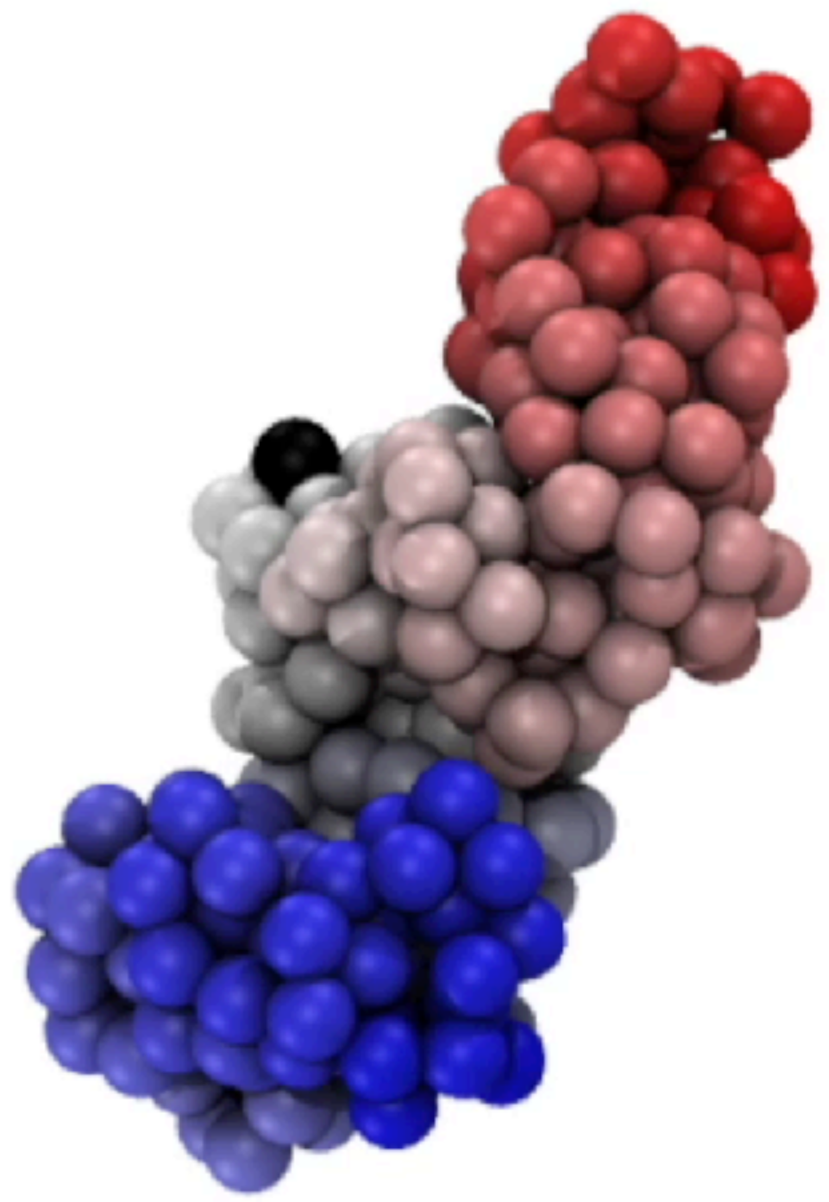
Contacts

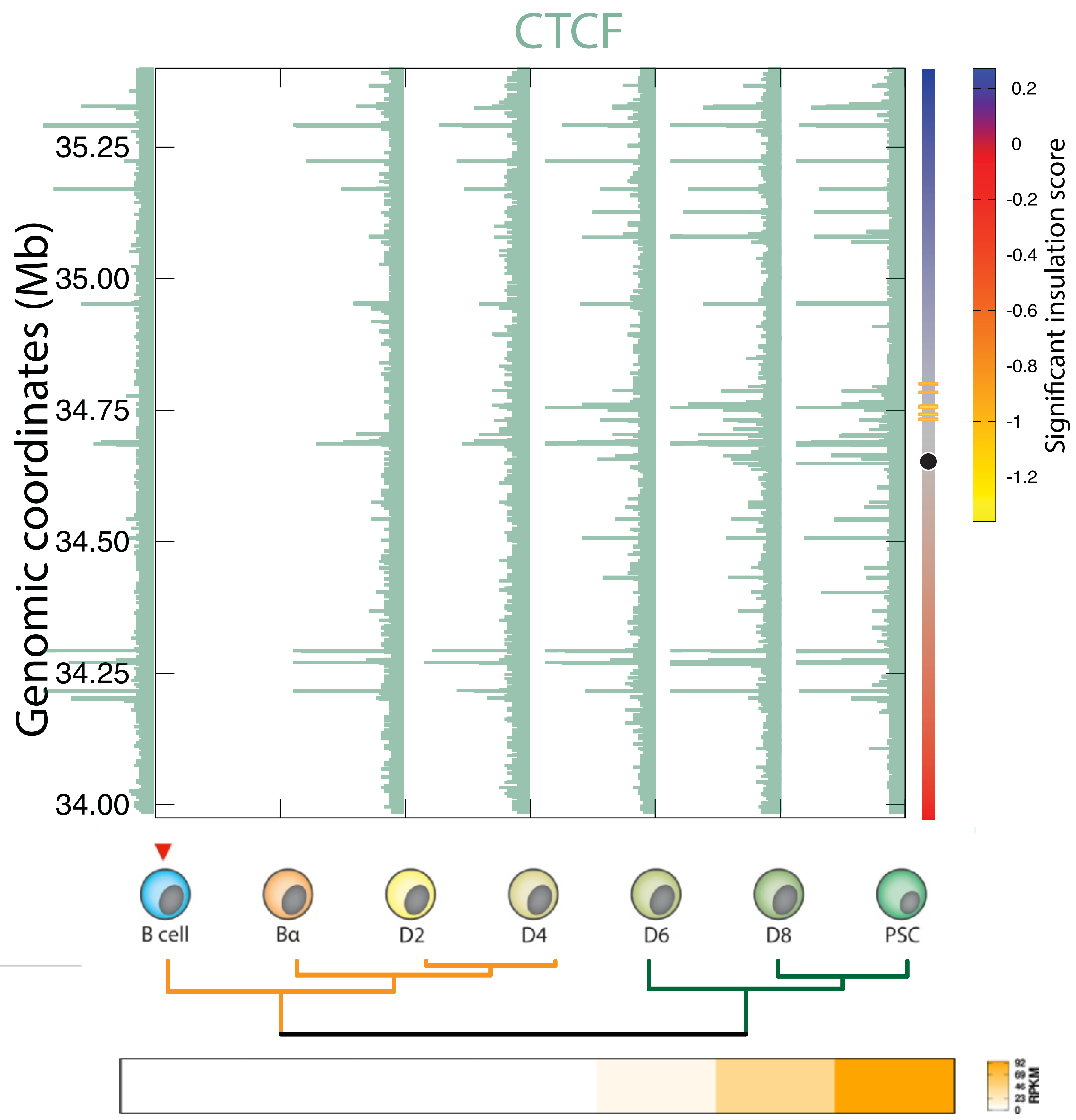




SOX2 locus structural changes from B to PSC

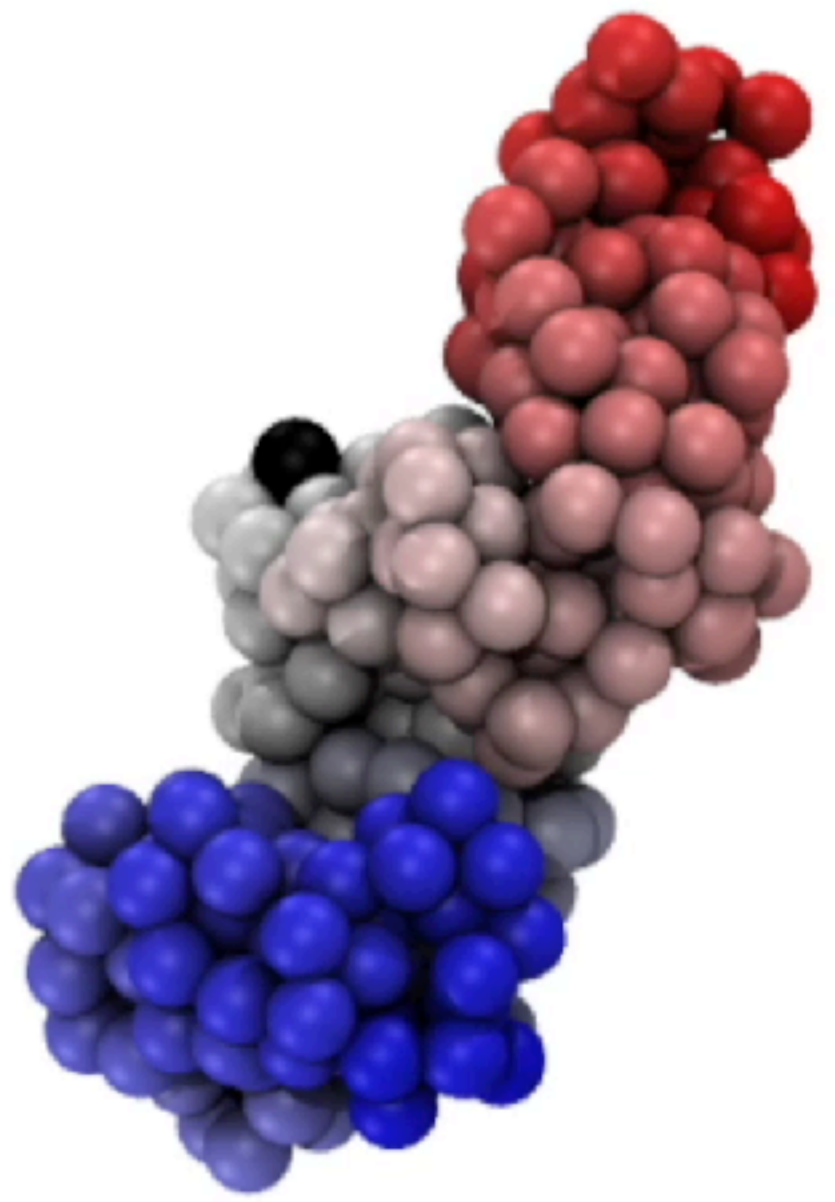
TAD borders

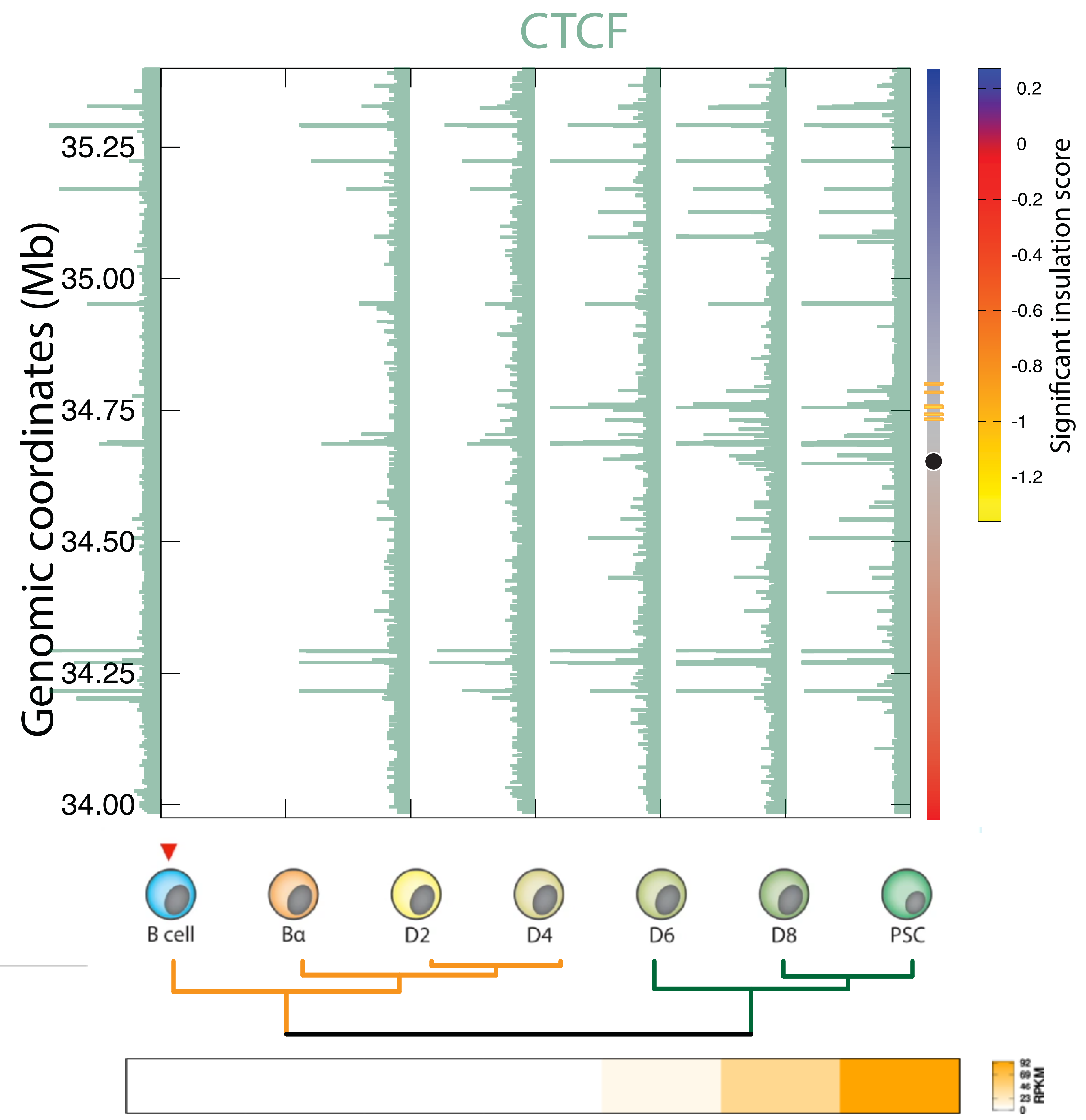




SOX2 locus structural changes from B to PSC

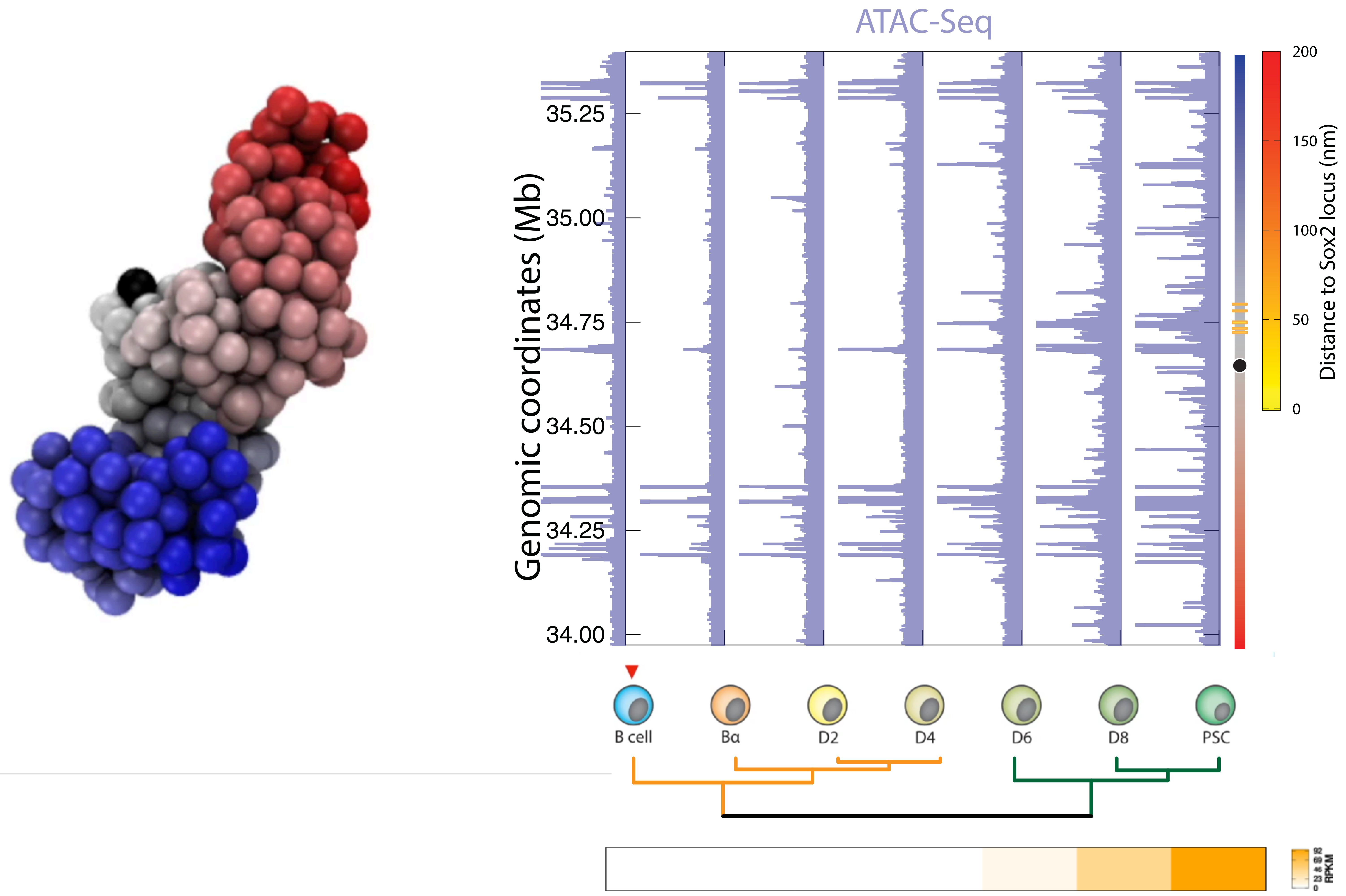
TAD borders





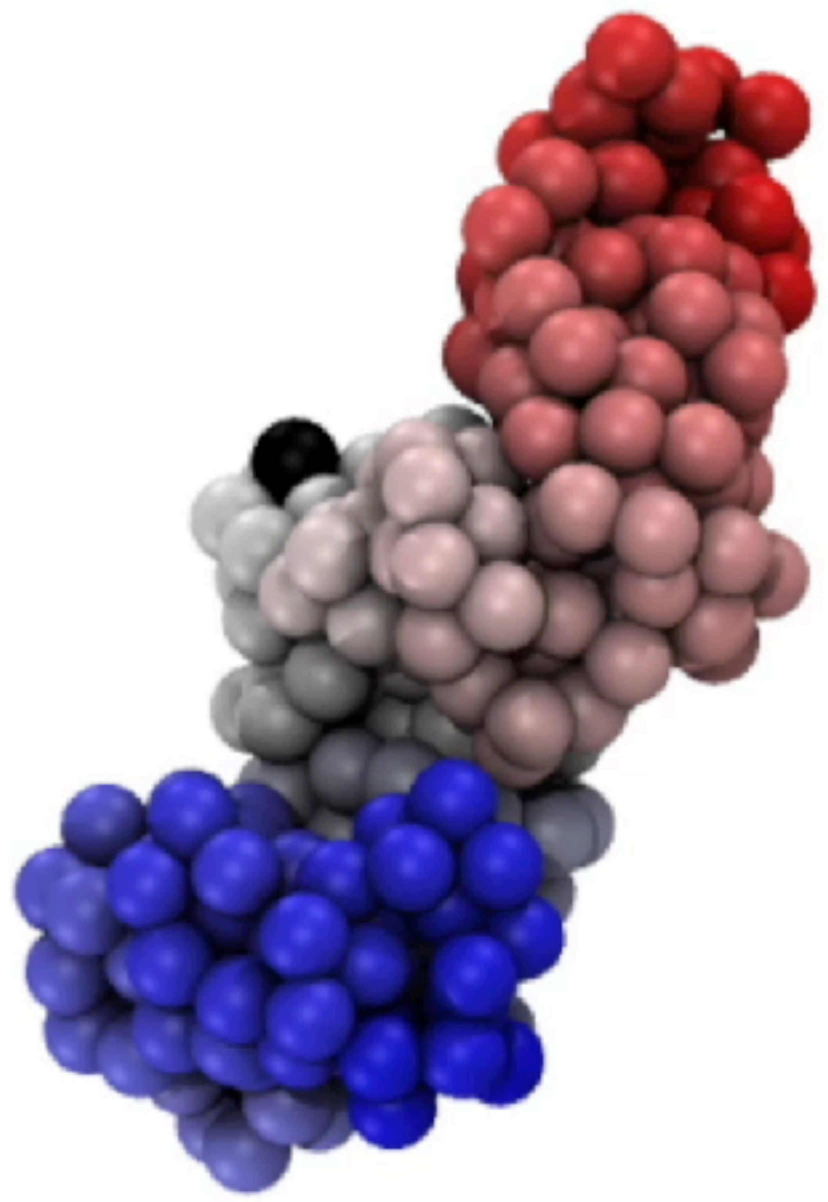
SOX2 locus structural changes from B to PSC

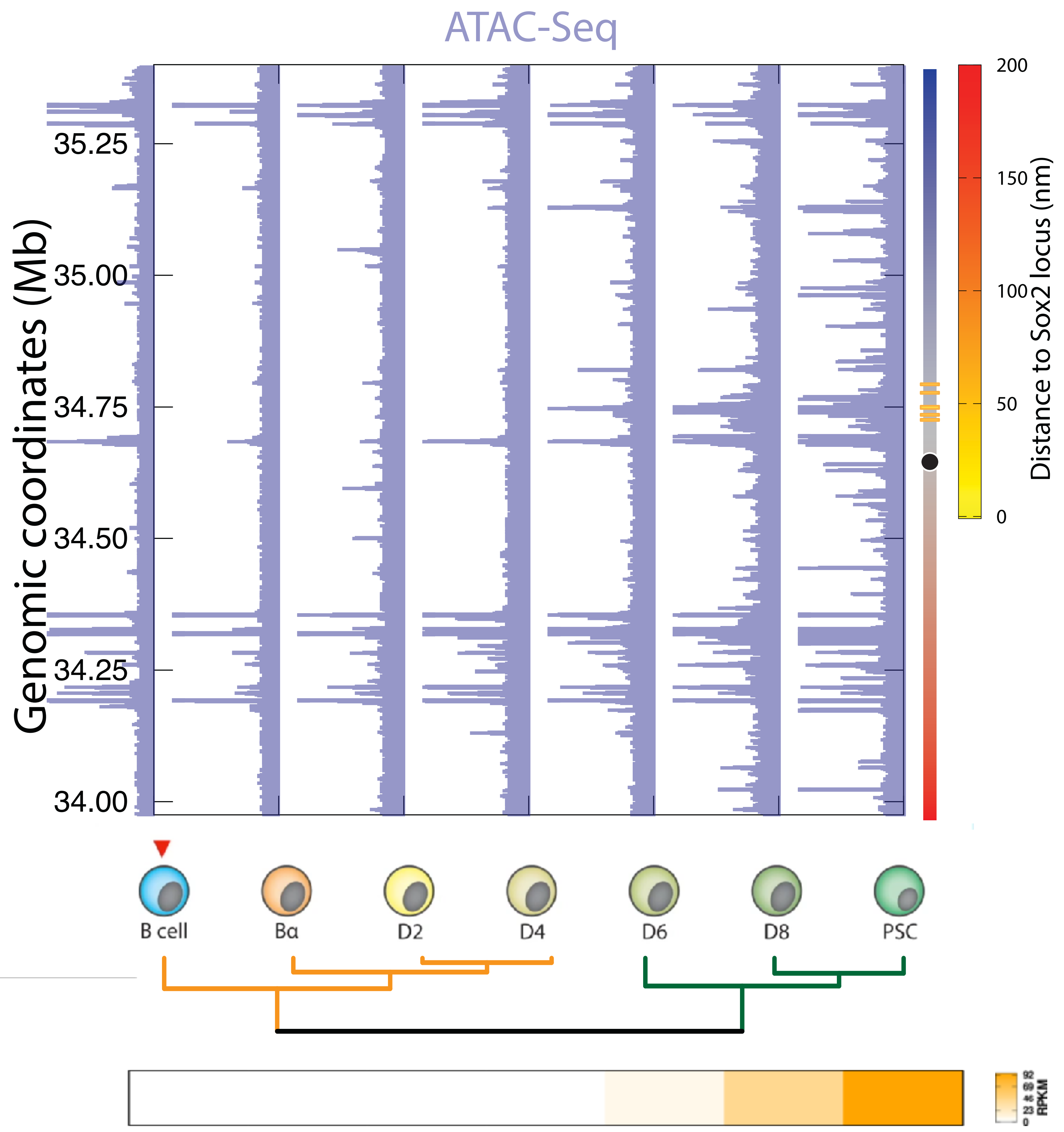
Distance to regulatory elements



SOX2 locus structural changes from B to PSC

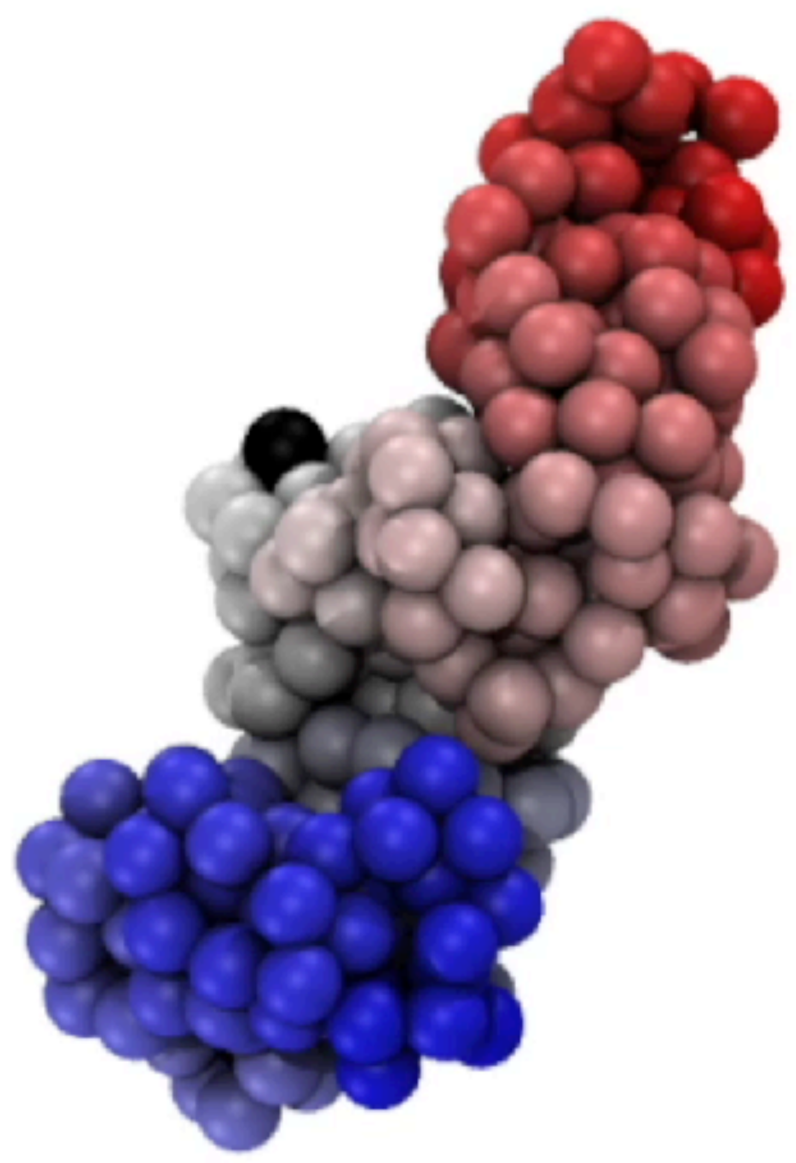
Distance to regulatory elements

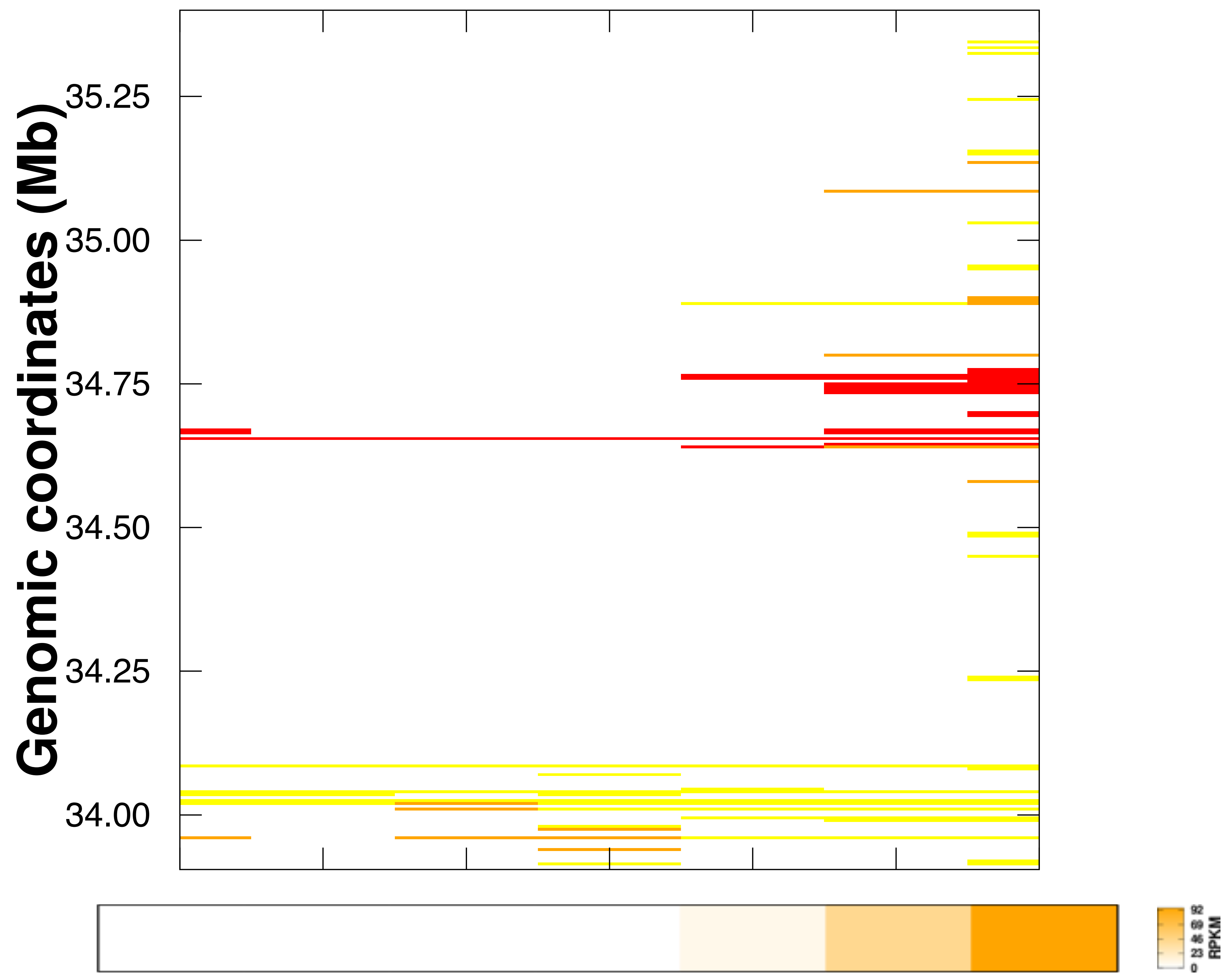




SOX2 locus structural changes from B to PSC

Chromatin Activity

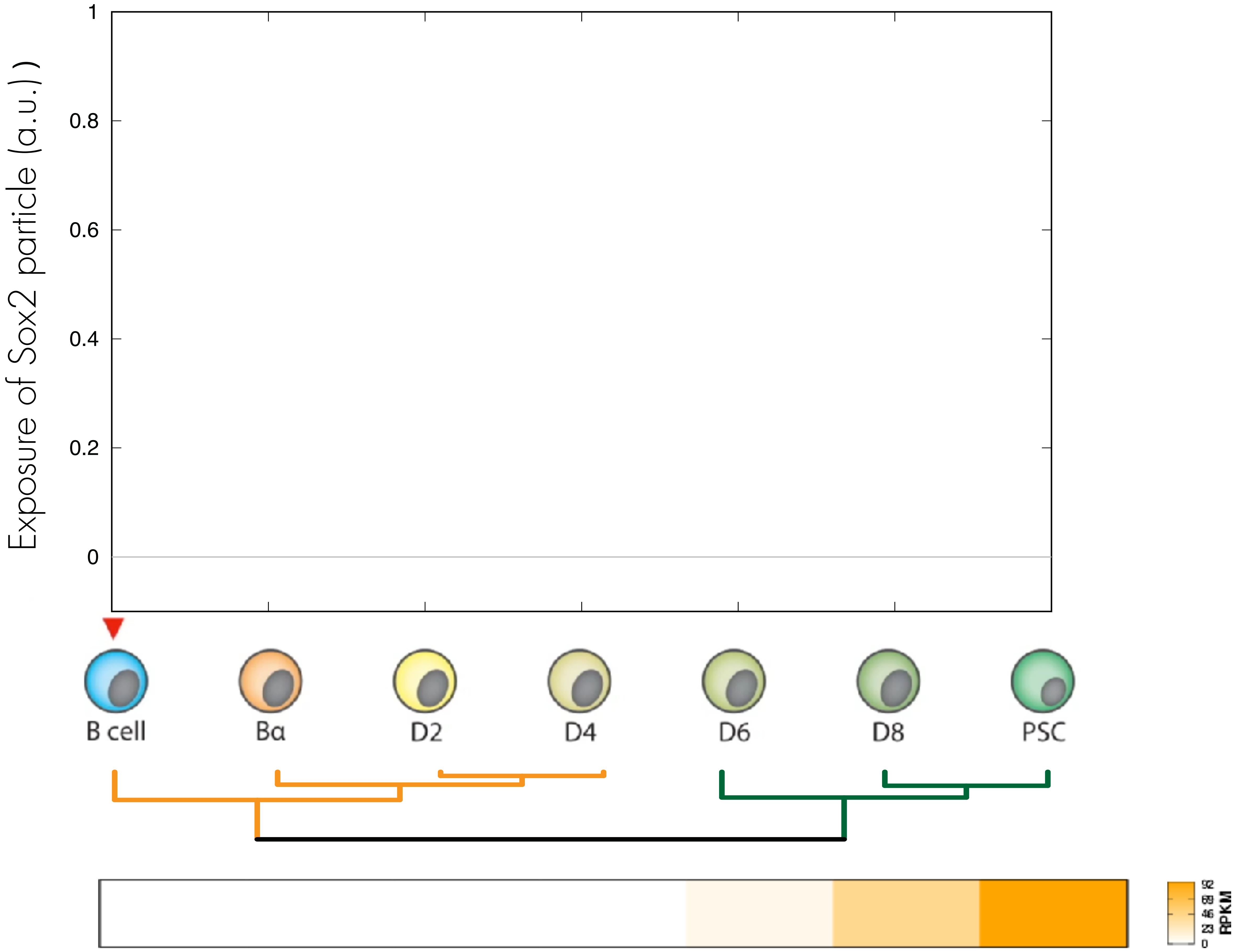




	B	Ba	D2	D4	D6	D8	PSC
A	9	6	7	13	13	22	48
AP	4	1	4	4	4	13	23
APD	3	1	1	1	4	10	15

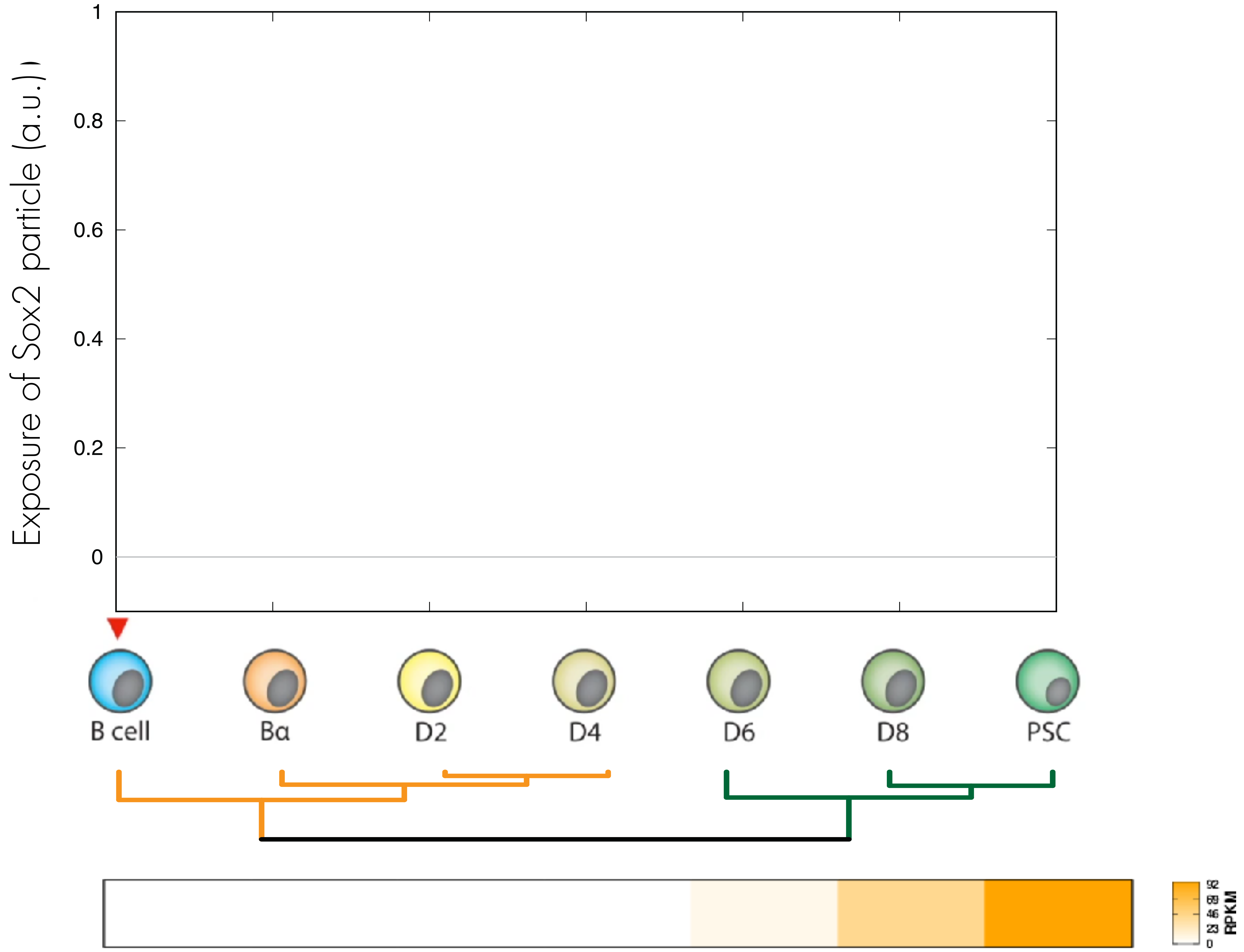
SOX2 locus structural changes from B to PSC

Structural exposure



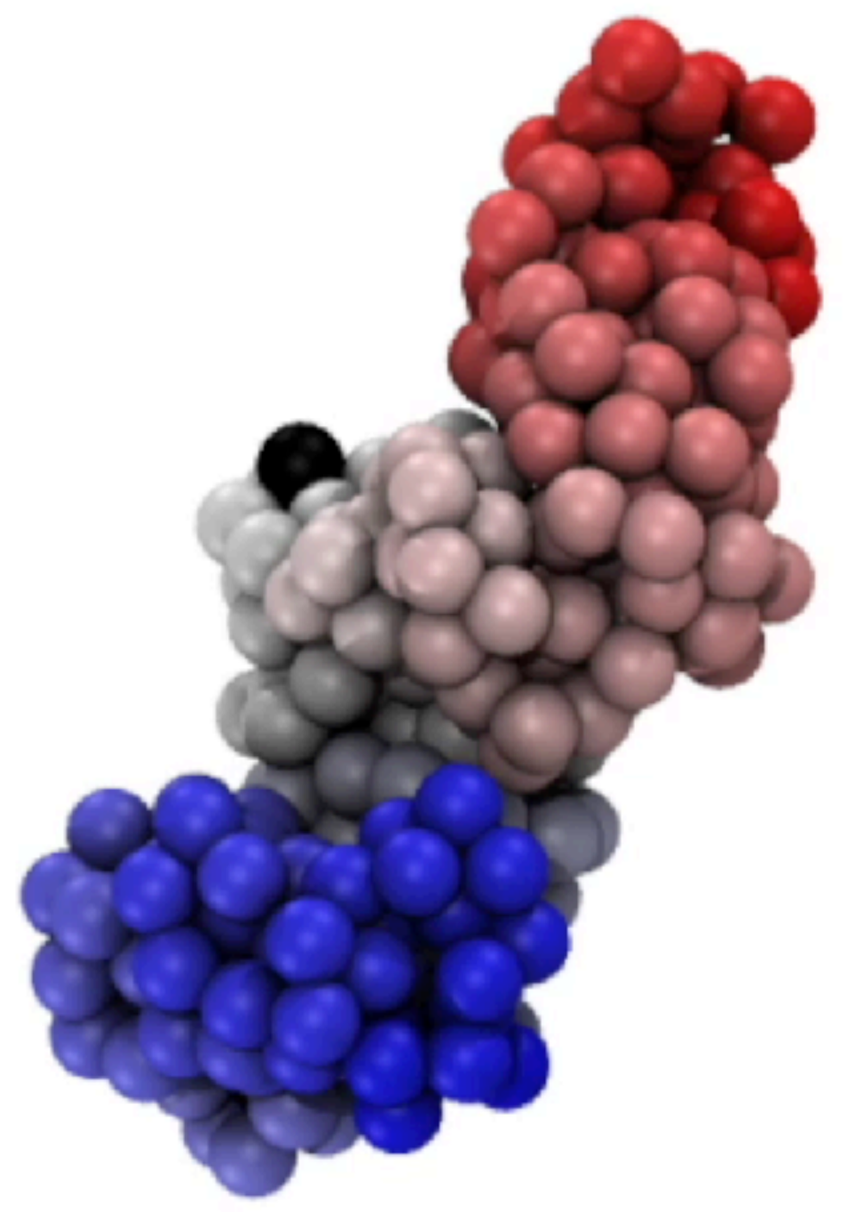
SOX2 locus structural changes from B to PSC

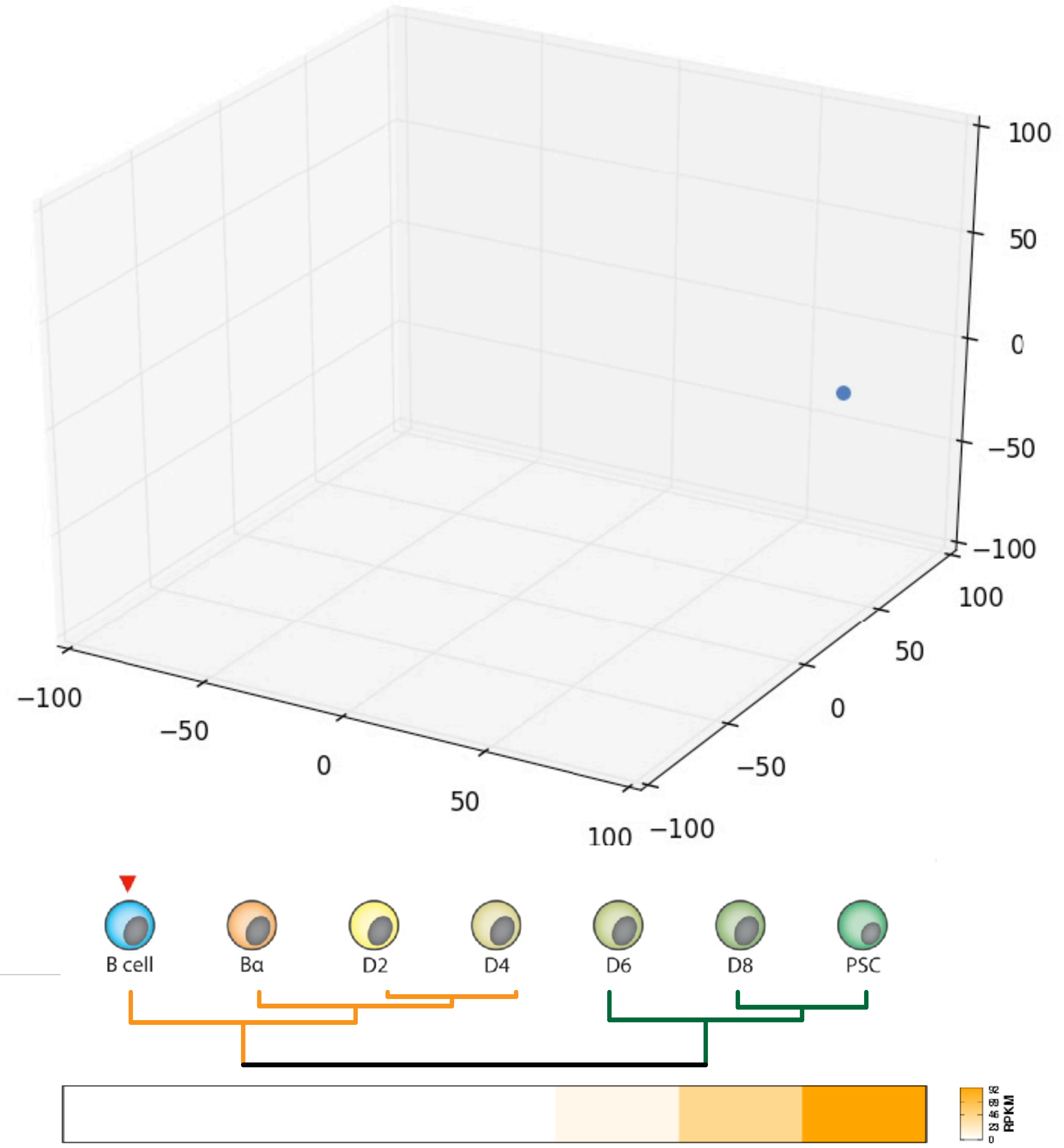
Structural exposure



SOX2 locus dynamics changes from B to PSC

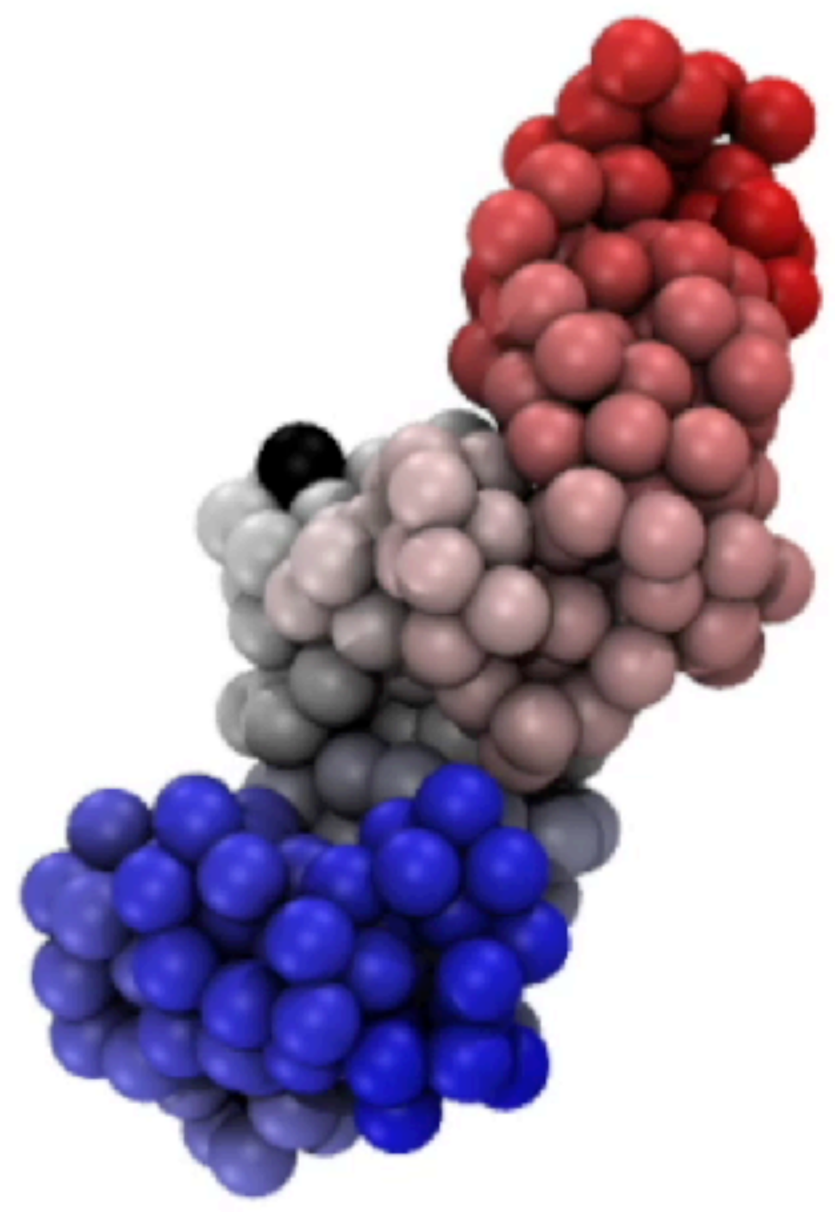
SOX2 displacement

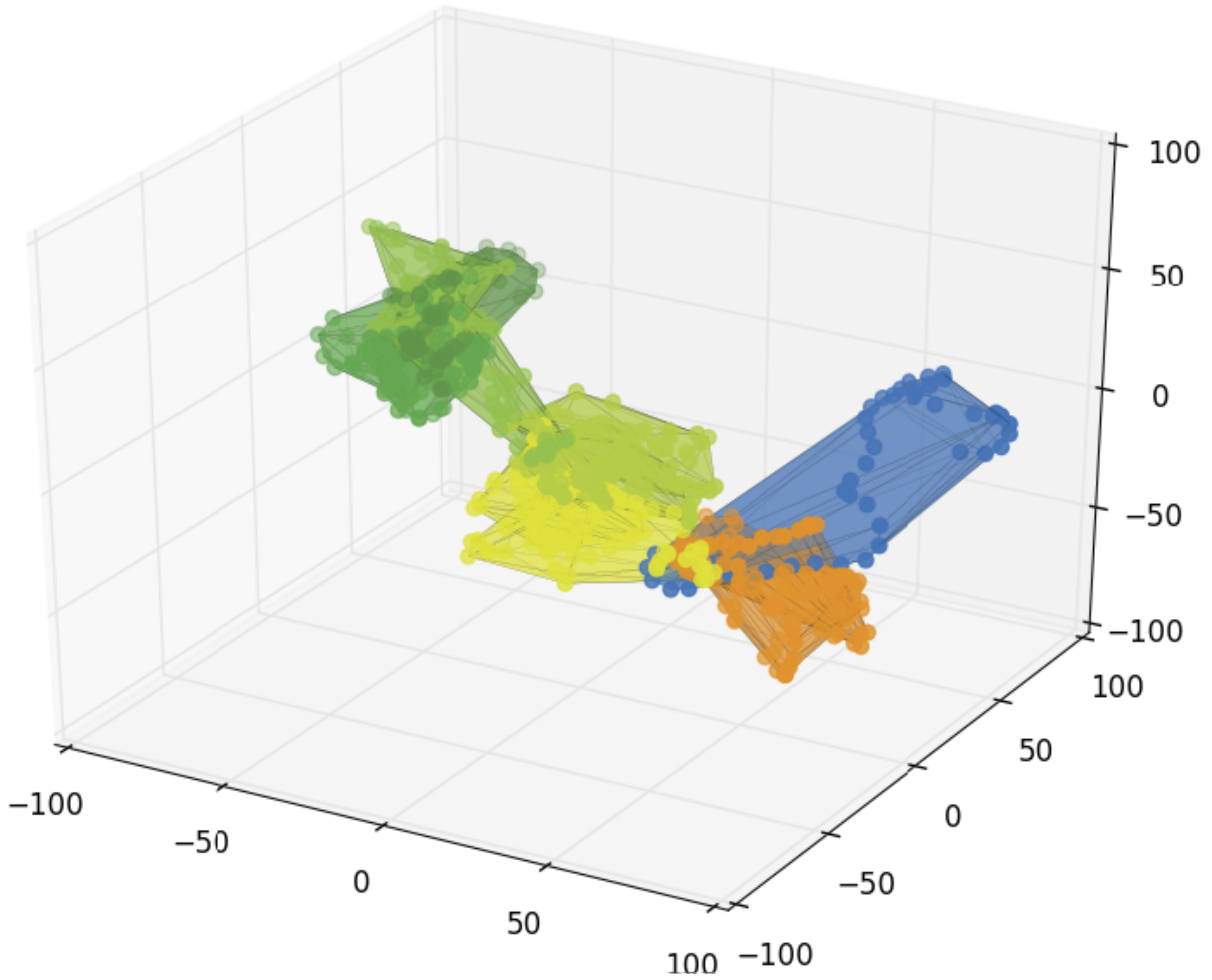


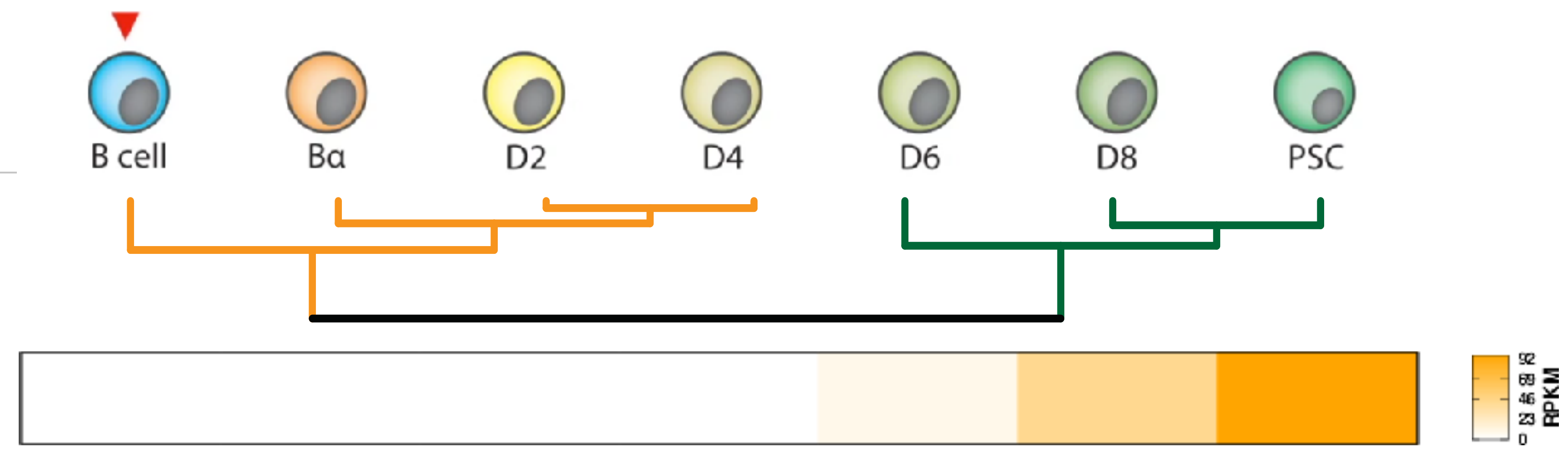


SOX2 locus dynamics changes from B to PSC

SOX2 displacement

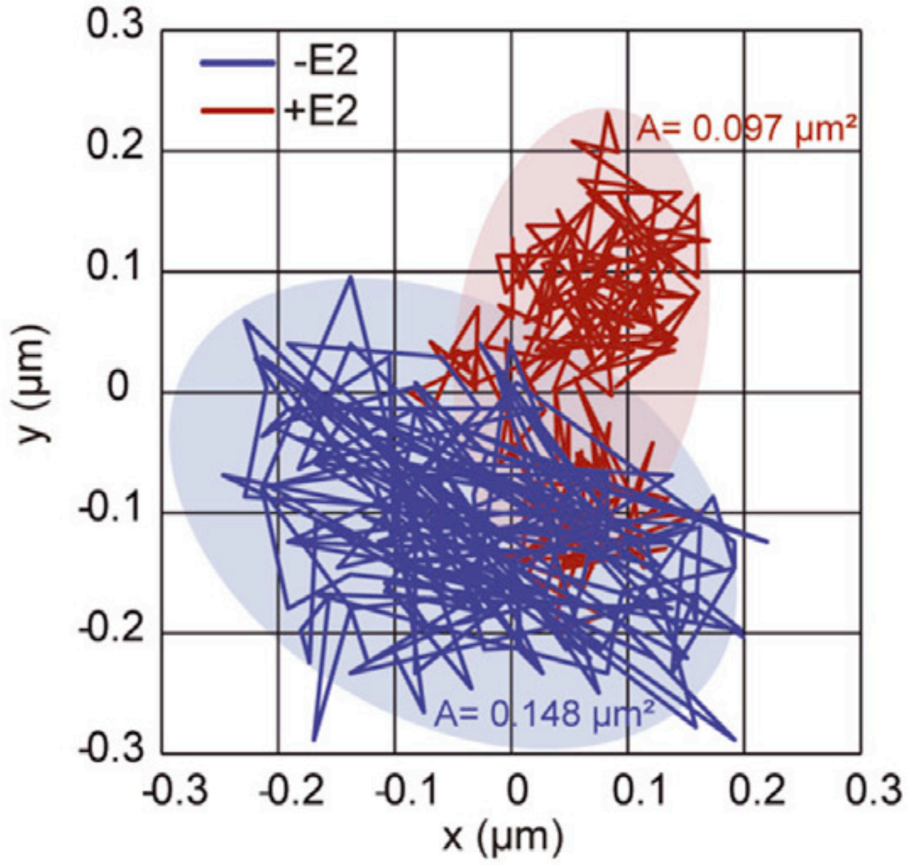






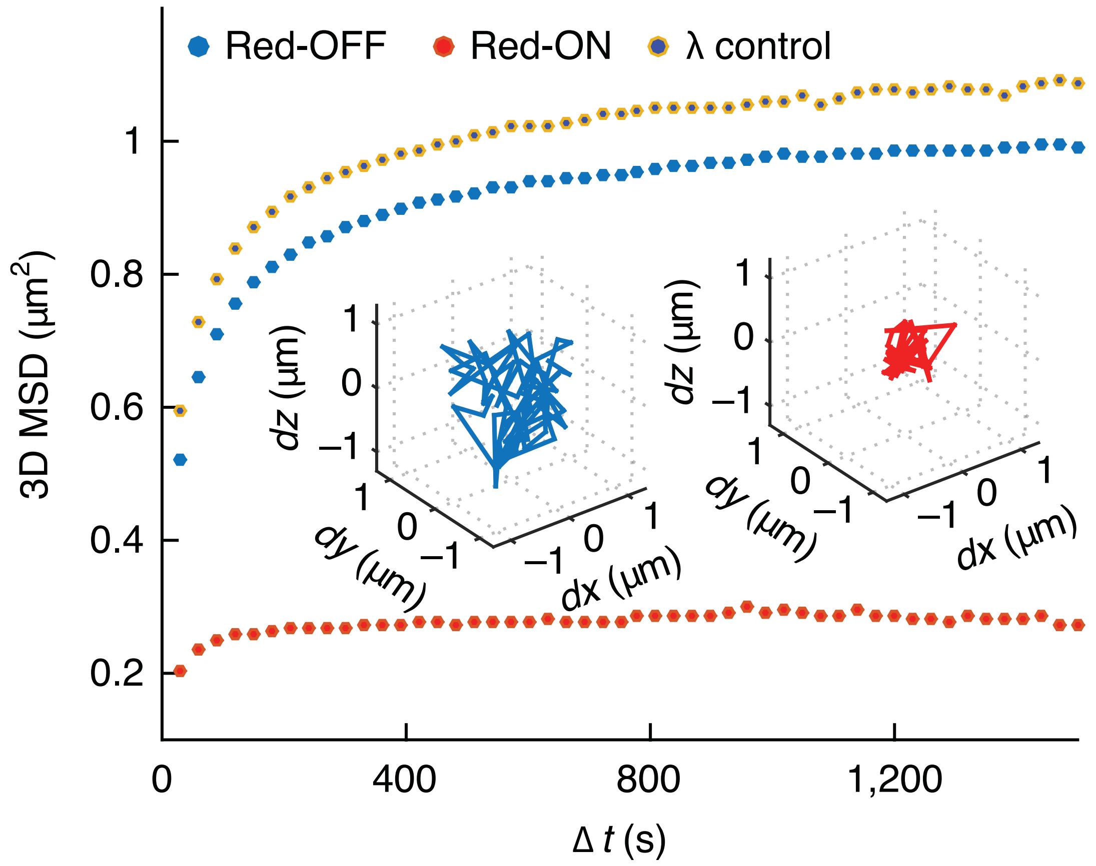
SOX2 locus dynamics changes from B to PSC

SOX2 displacement



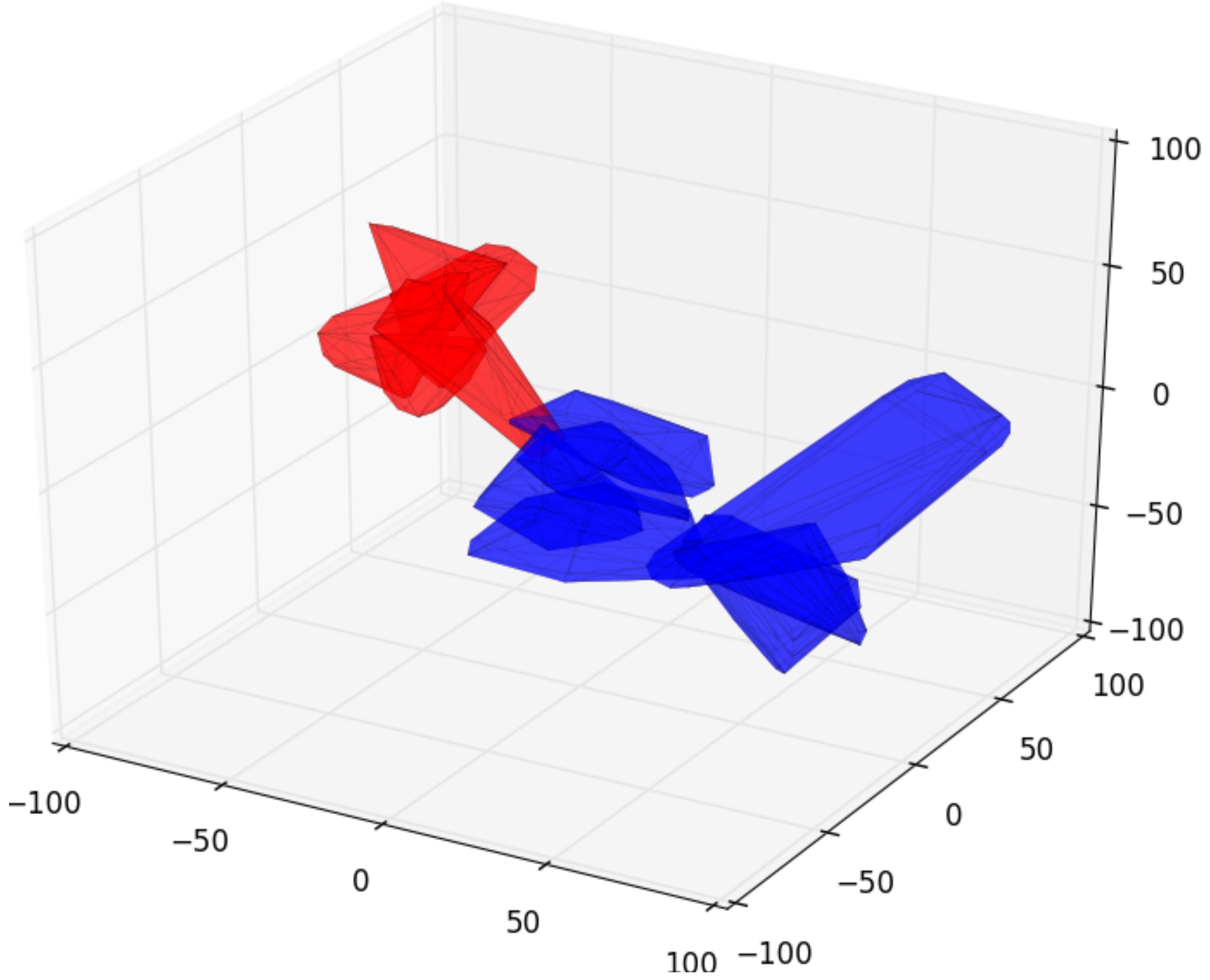
Two dimensional trajectories and area explored over 50s of the CCND1 locus recored before -E2 and after +E2 activation.

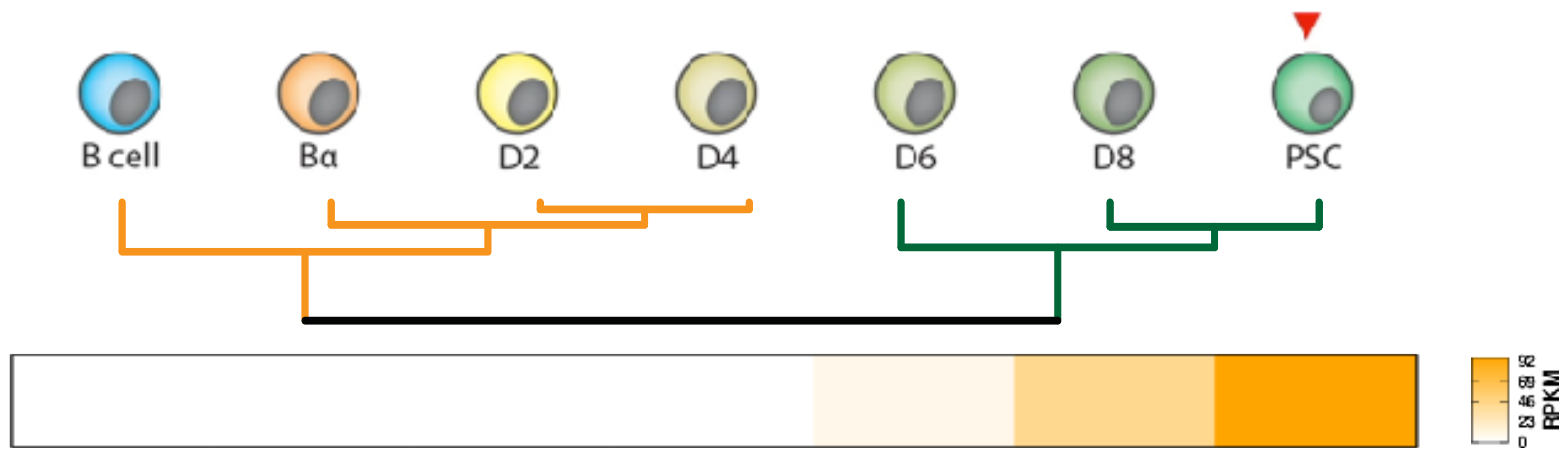
Germier ,T., et al, (2017) Blophys J.



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

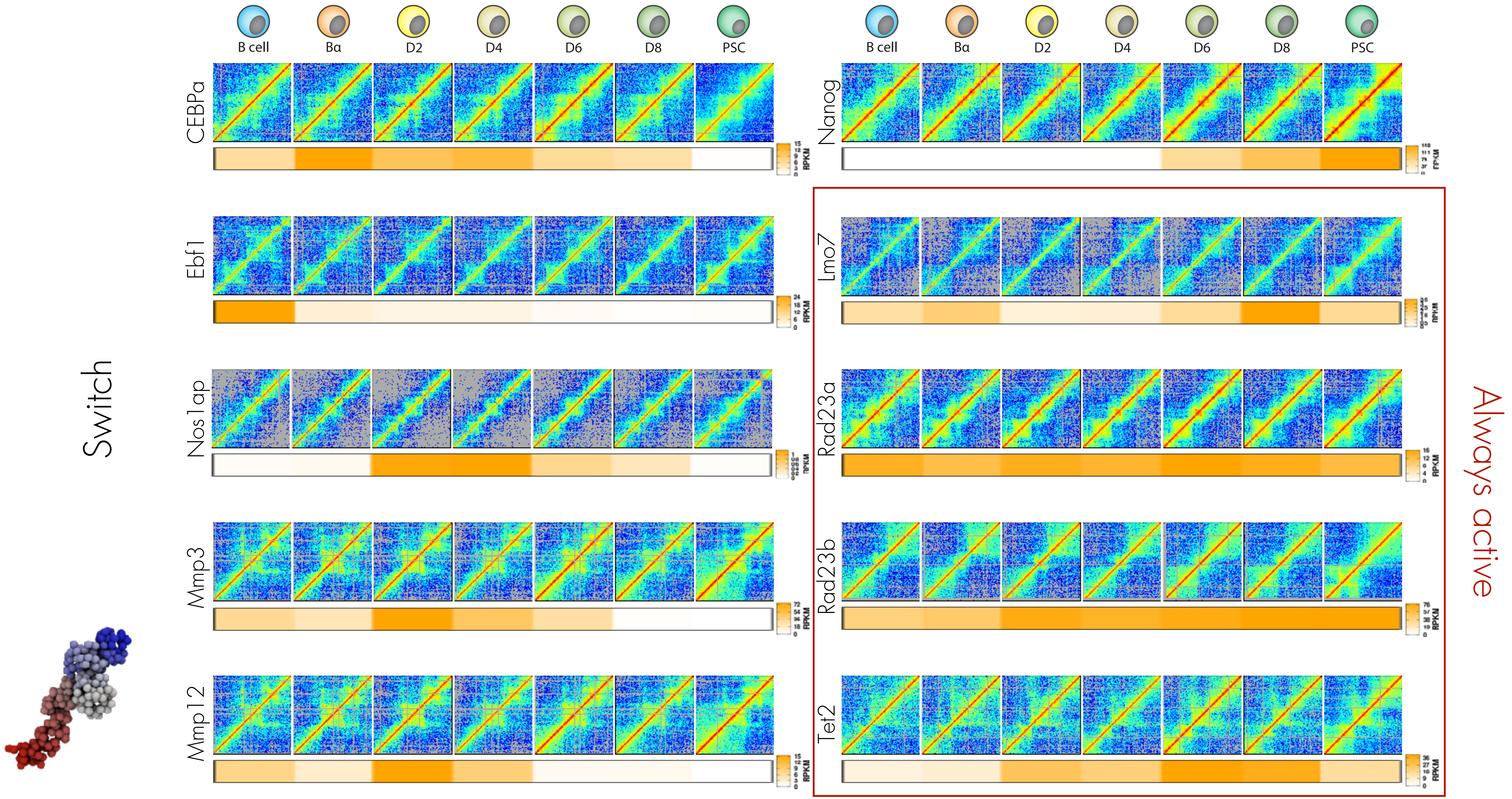
Chen ,T., et al, (2018) Nat. Genetics





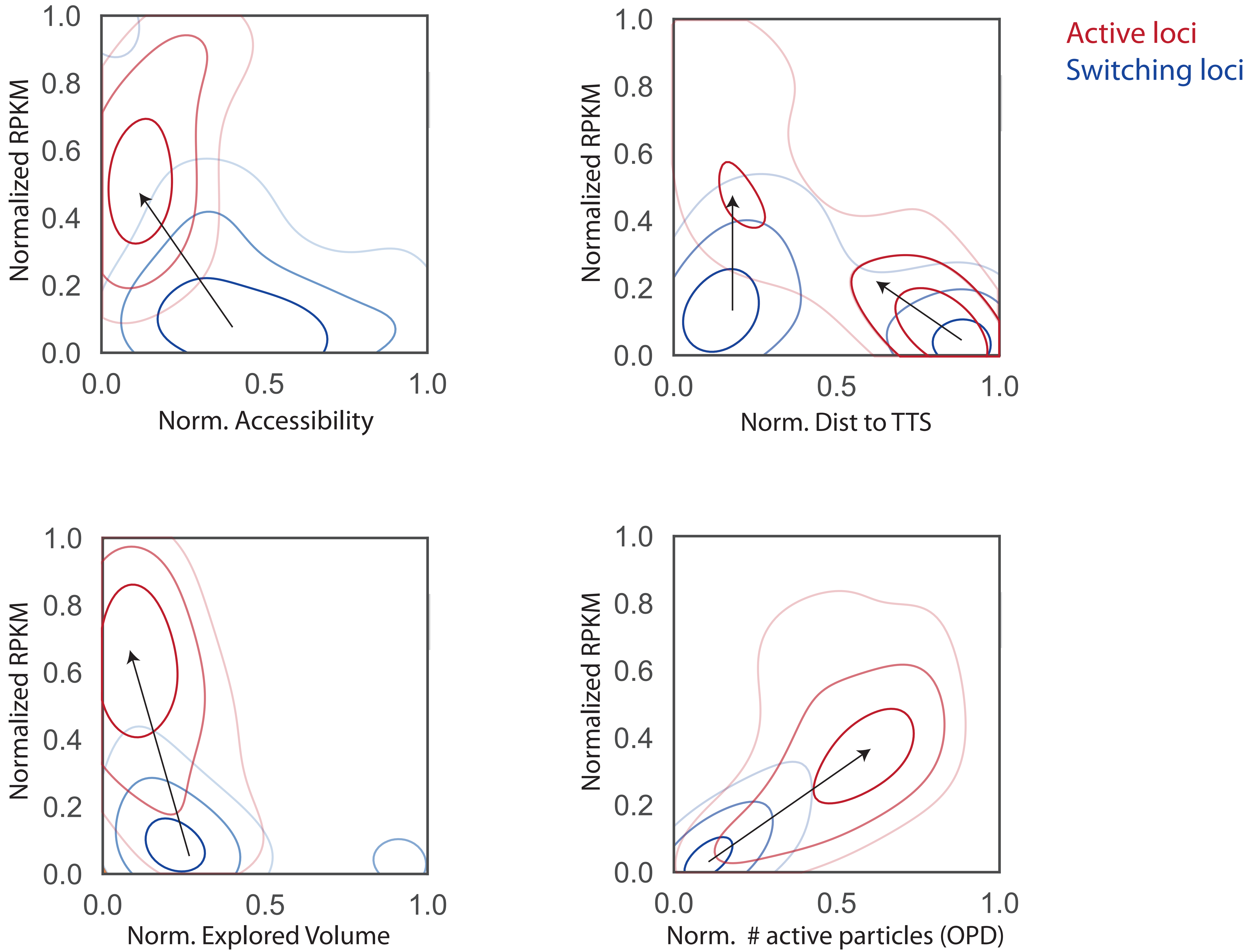
Structural changes from B to PSC

Other 10 loci

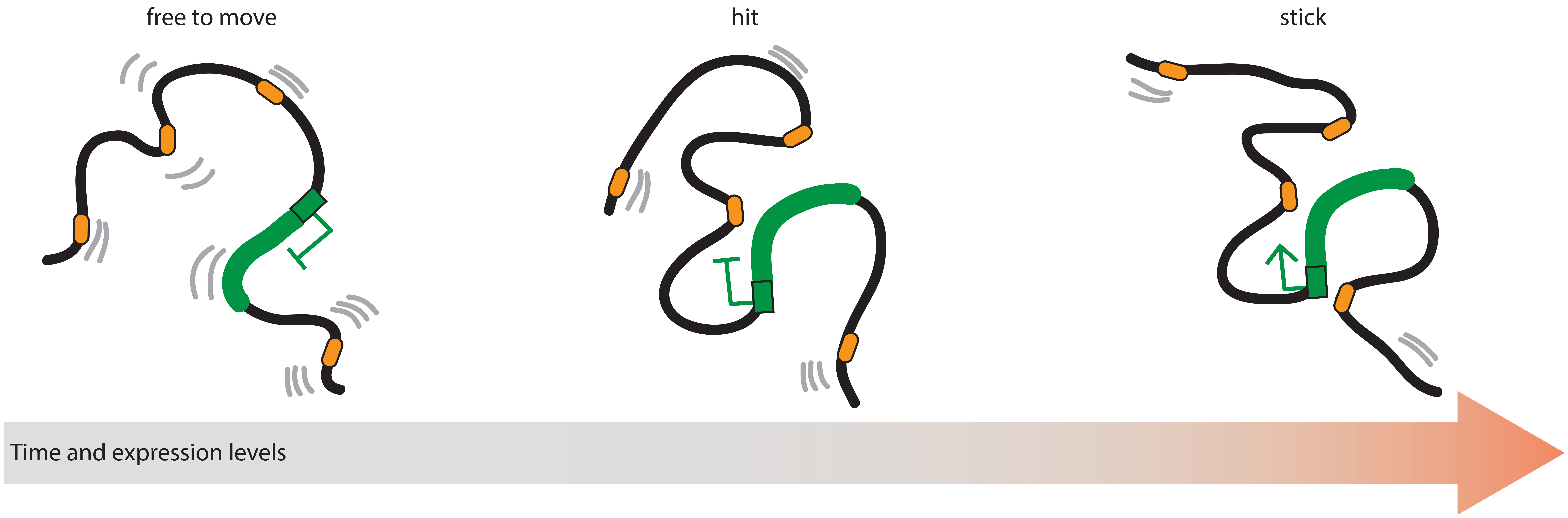


Dynamics of gene activation

Trends in all 11 loci



A "hit-and-stick" model for gene activation



http://marciuslab.org
http://3DGenomes.org

@marciuslab
@mamartirenom

David Castillo
Yasmina Cuartero
Marco Di Stefano
Irene Farabella
Silvia Galan
Mike Goodstadt
Maria Marti-Marimon
Francesca Mugianesi
Julen Mendieta
Juan Rodriguez
Paula Soler
Aleksandra Sparavier

.: Our current sponsors :.