

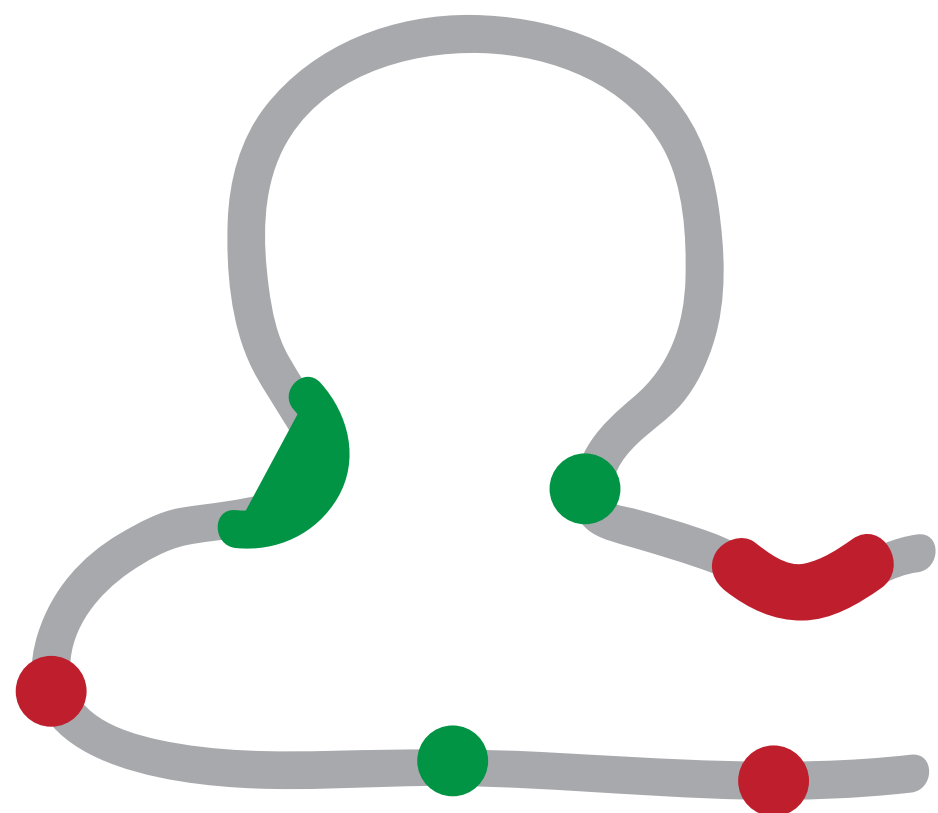
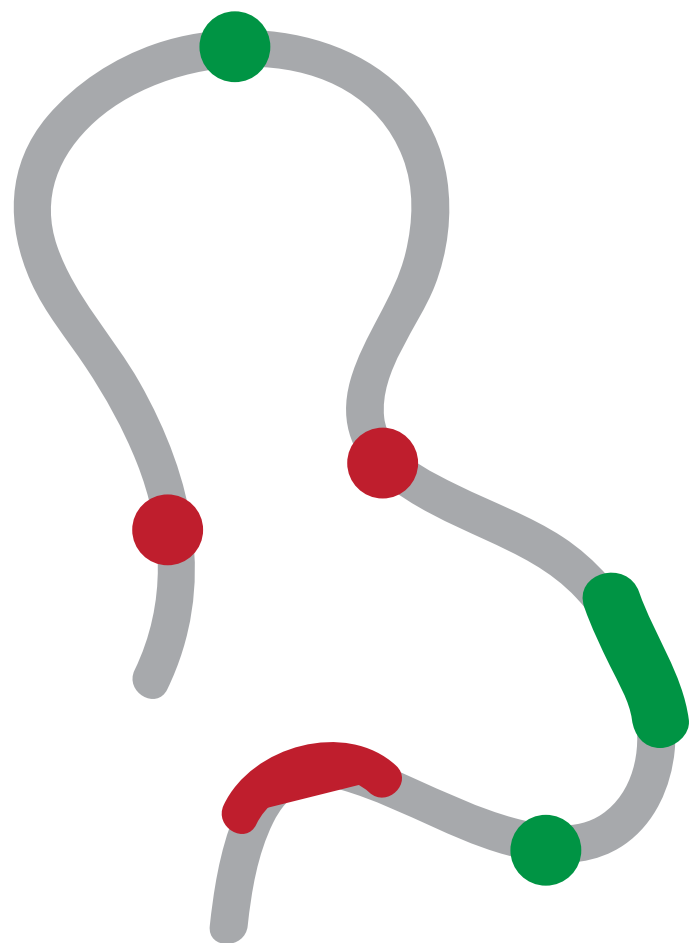
3D structural dynamics of the SOX2 locus activation

Marc A. Marti-Renom

Structural Genomics Group (ICREA, CNAG-CRG)

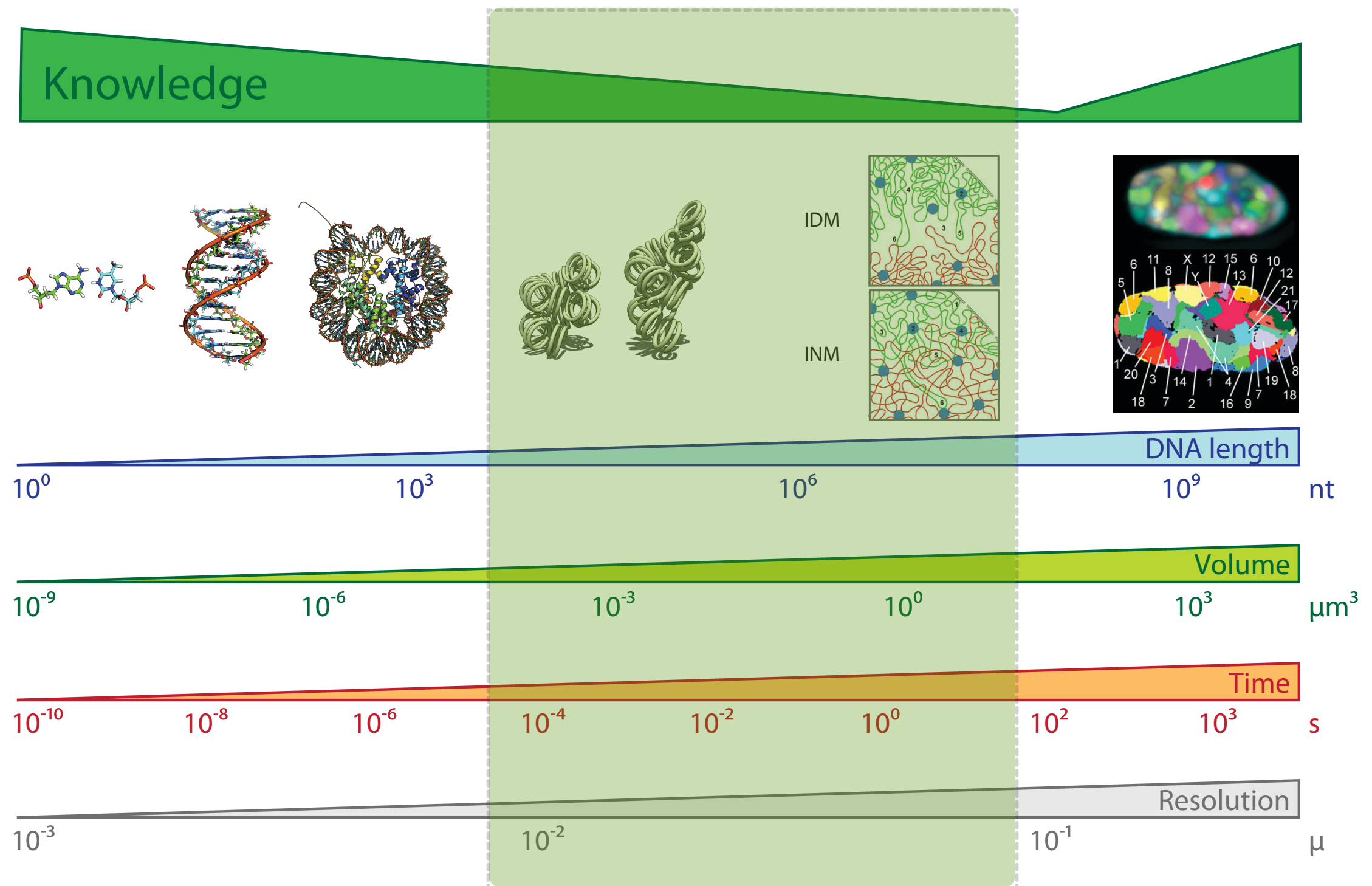
<http://marciuslab.org>
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<http://cnag.crg.eu>

cnag **CRG**   **ICREA**



Resolution Gap

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

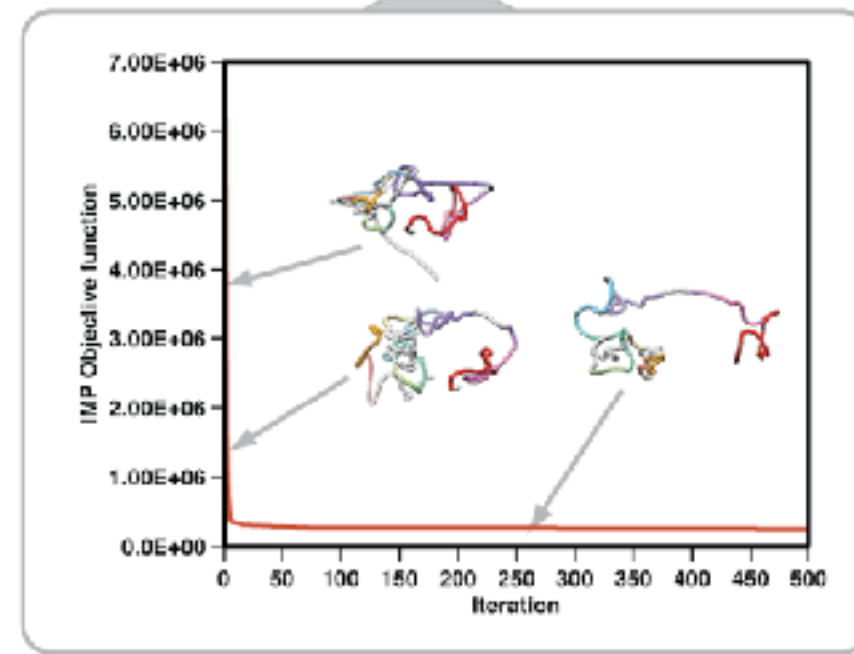
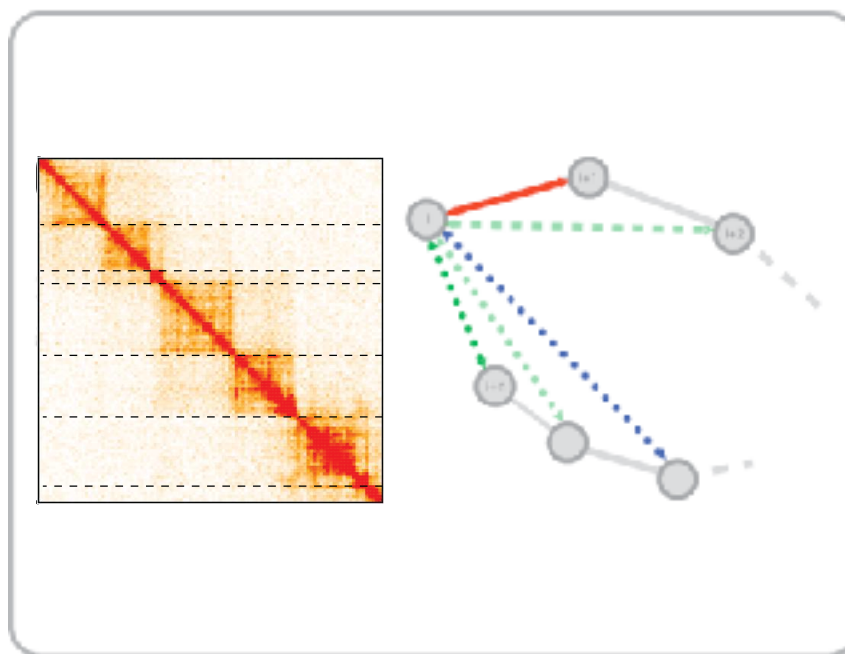
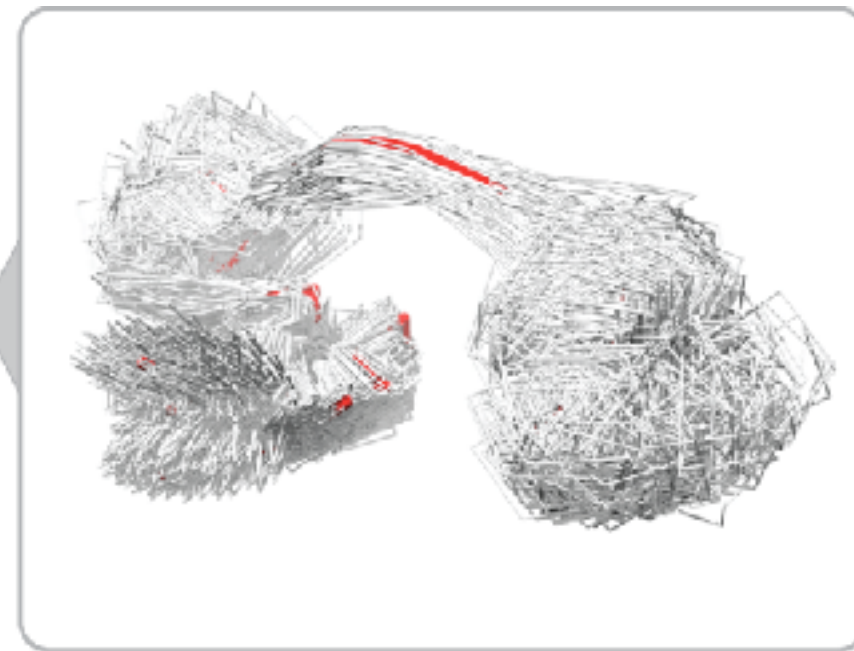
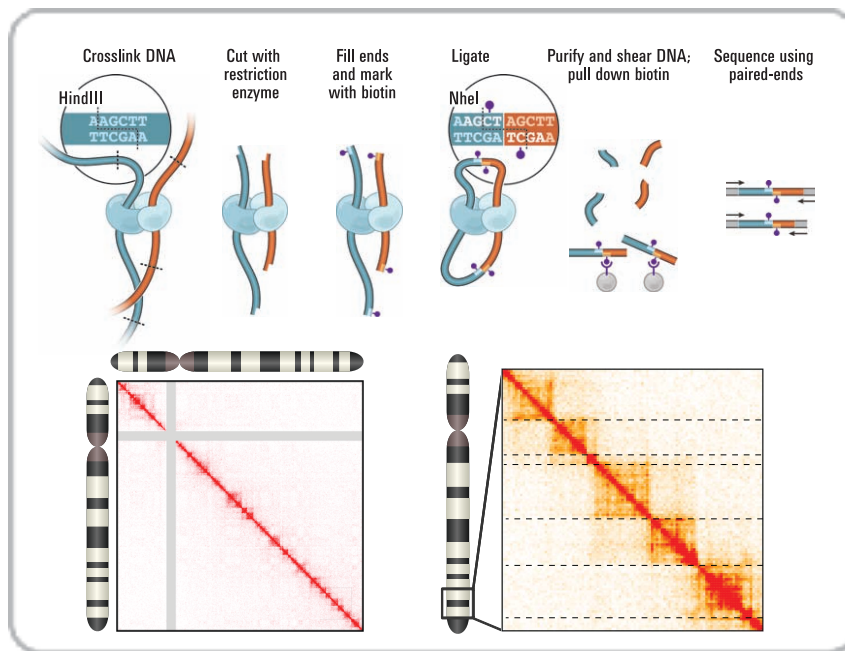


Hybrid Method

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

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

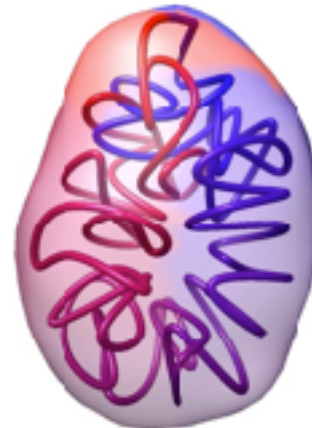
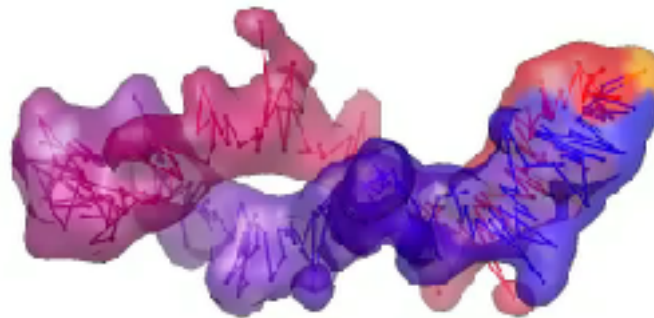
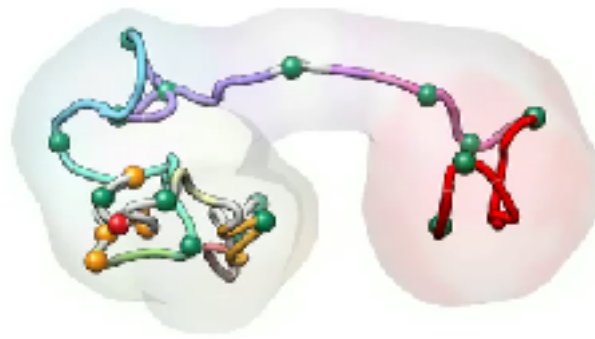
Experiments



Computation

TADbit previous applications...

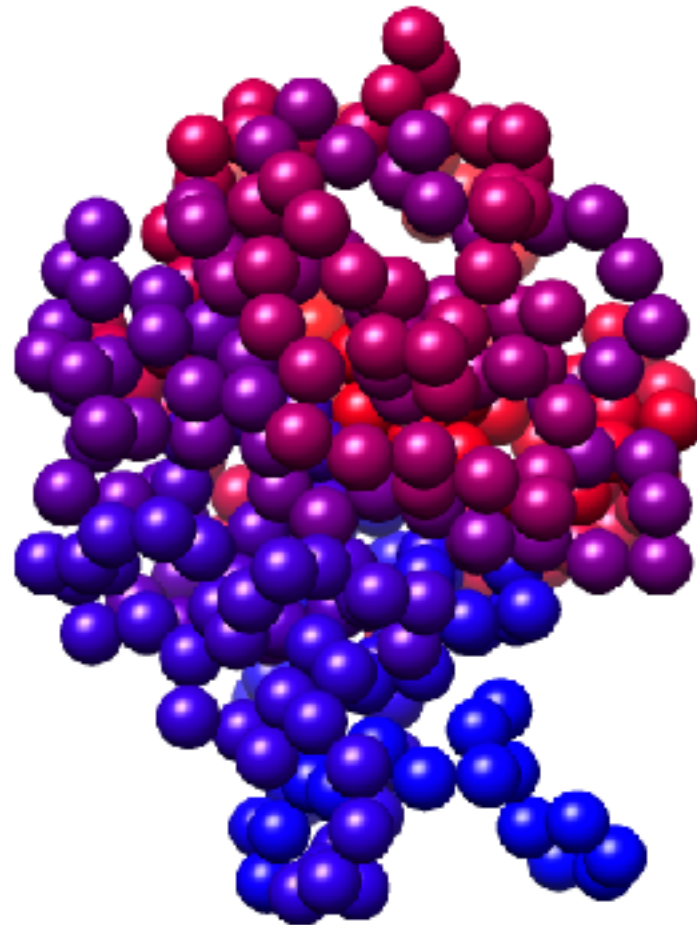
Baù, D. et al. Nat Struct Mol Biol (2011)
Umbarger, M. A. et al. Mol Cell (2011)
Le Dily, F. et al. Genes & Dev (2014)
Trussart M. et al. Nature Communication (2017)
Cattoni et al. Nature Communication (2017)
Stadhouders, R., Vidal, E. et al. Nature Genetics (2018)



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



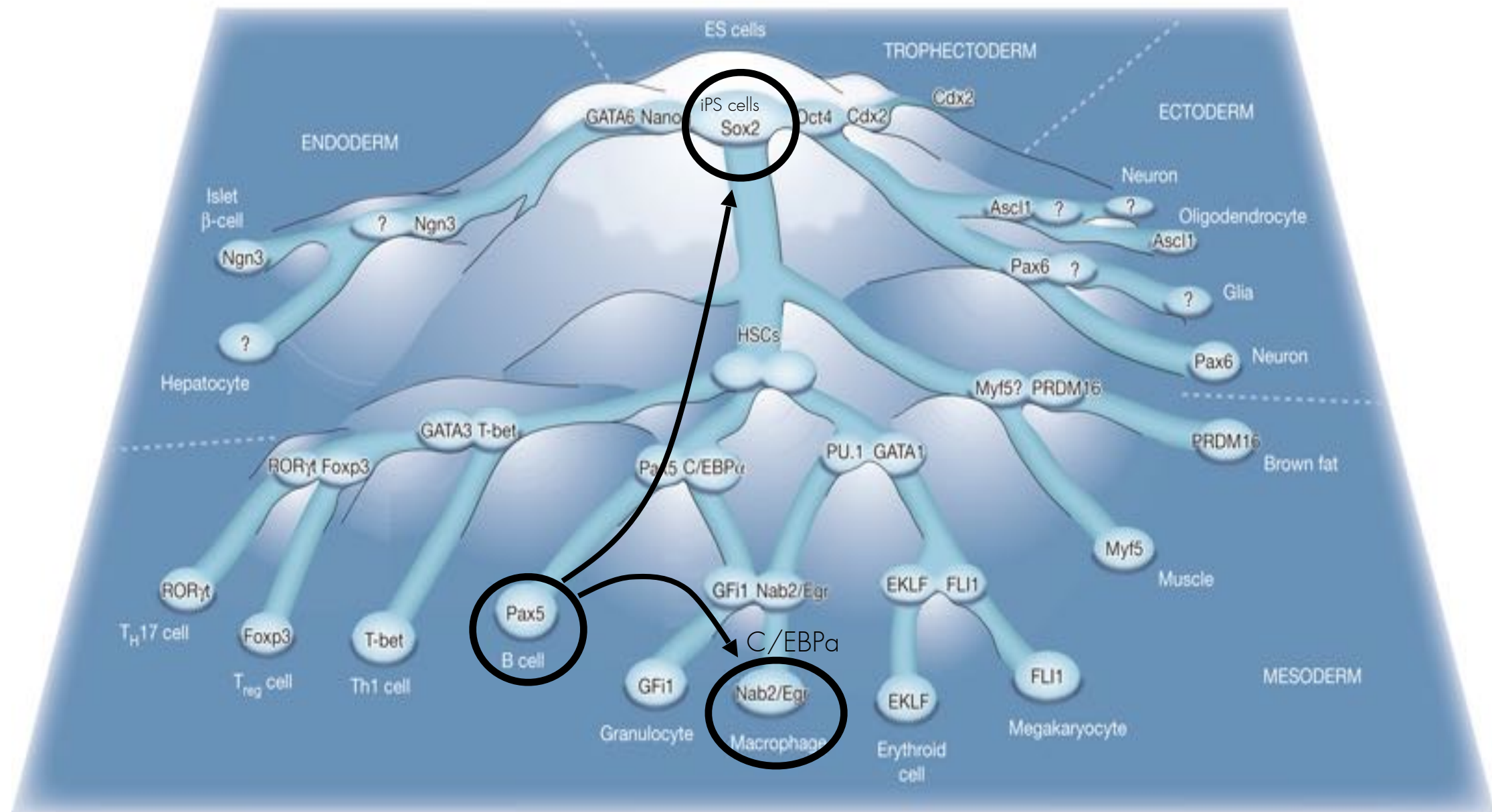
Stadhouders, R., Vidal, E. et al. (2018) Nature Genetics



Marco di Stefano

Transcription factors dictate cell fate

Graf & Enver (2009) Nature



Transcription factors (TFs) determine cell identity through gene regulation

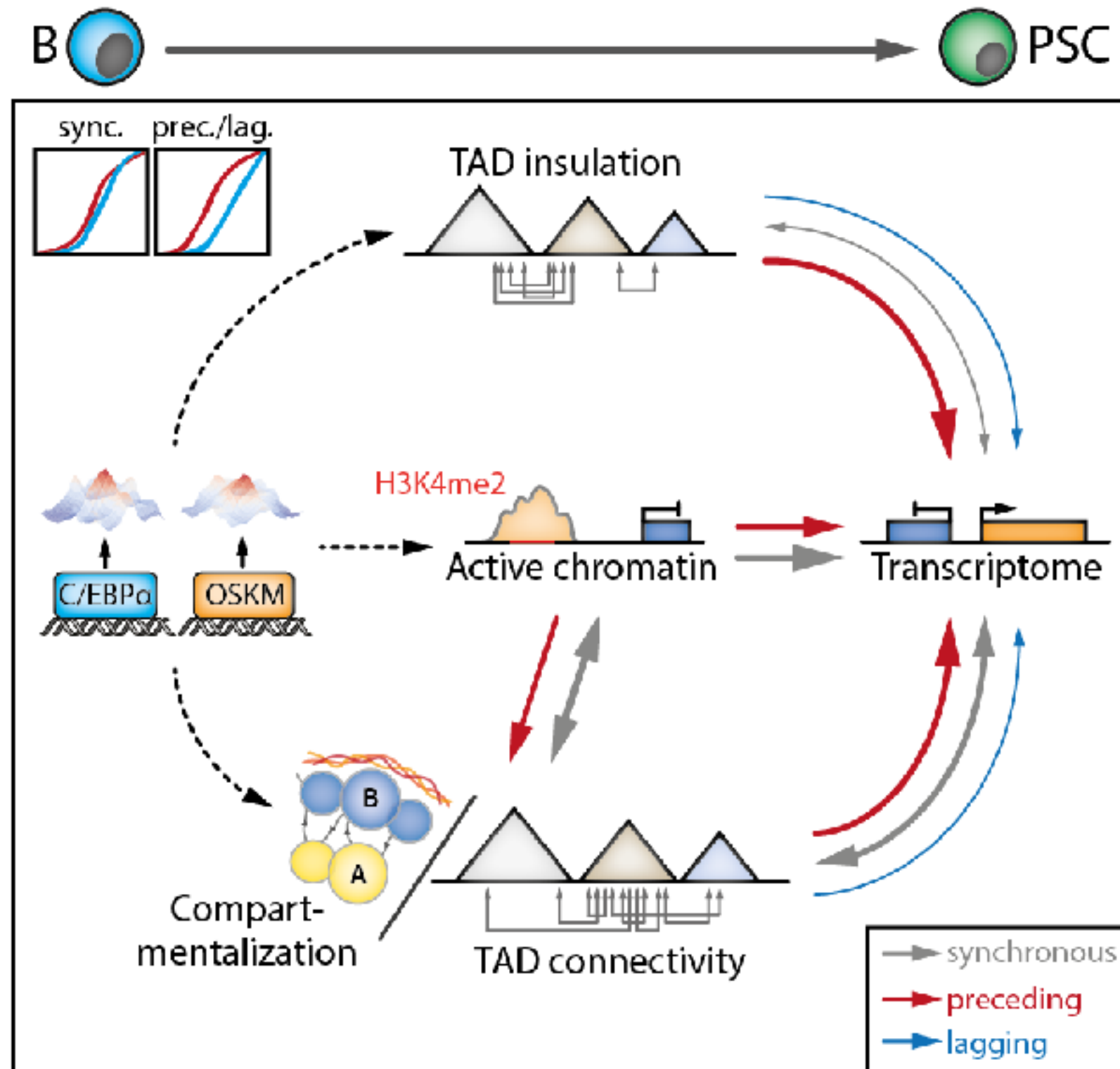
Normal 'forward' differentiation

Cell fates can be converted by enforced TF expression

Transdifferentiation or reprogramming

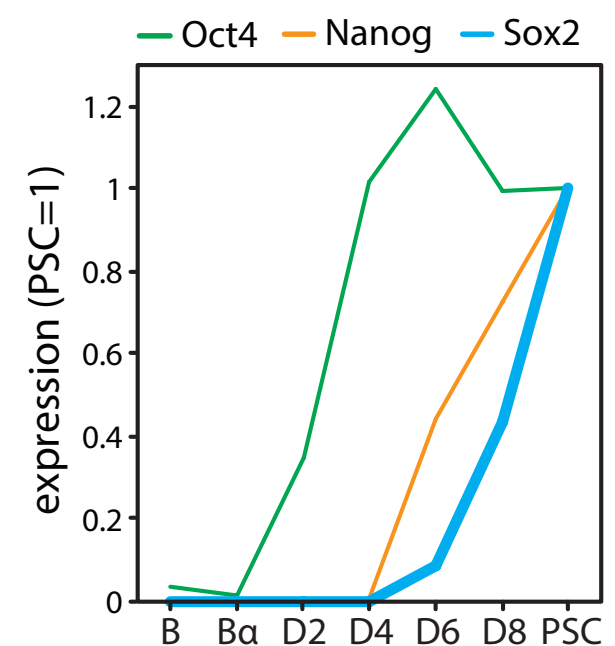
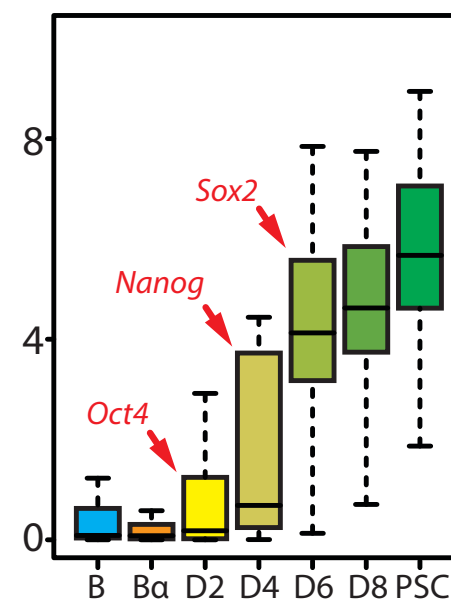
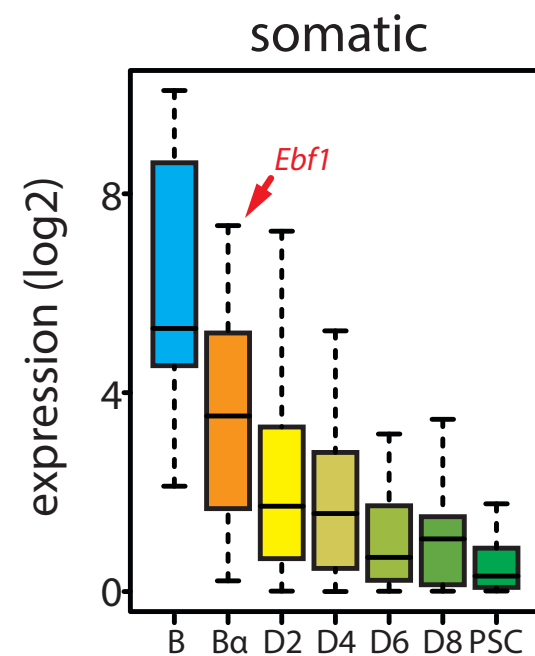
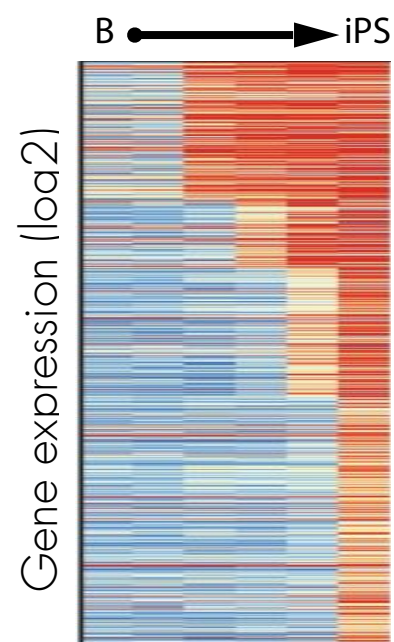
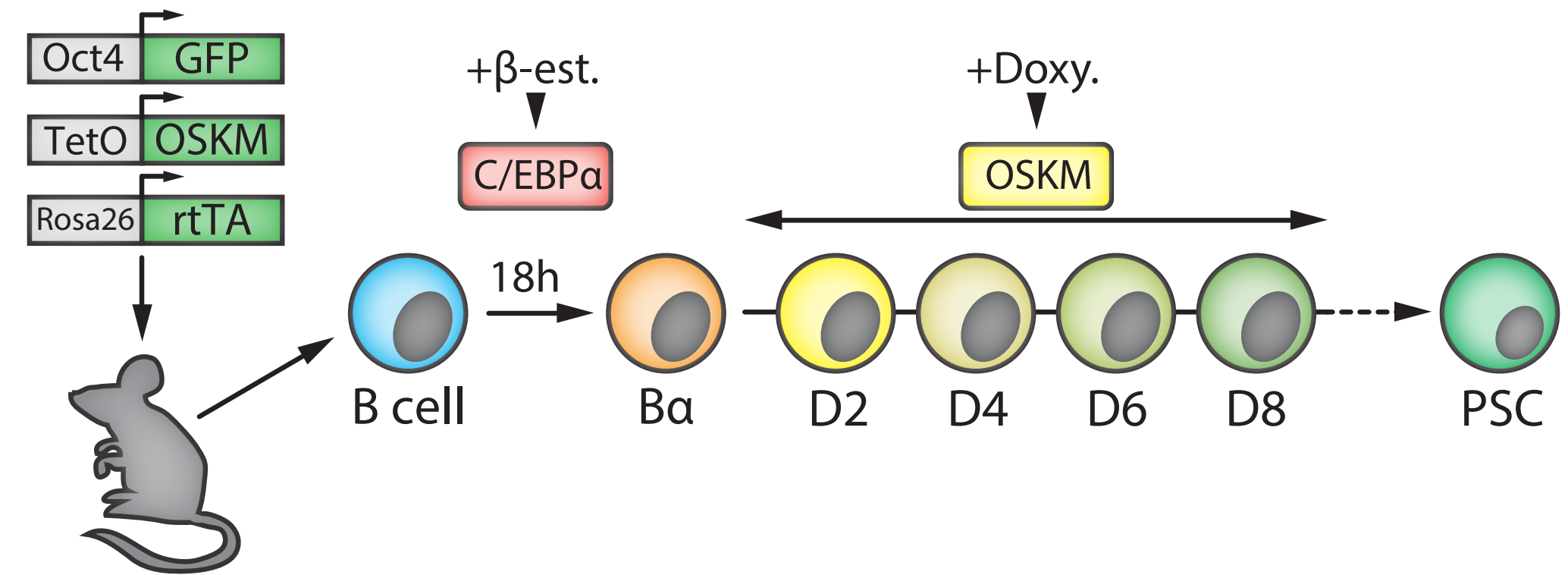
Interplay: topology, gene expression & chromatin

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



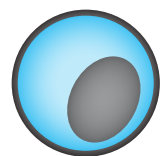
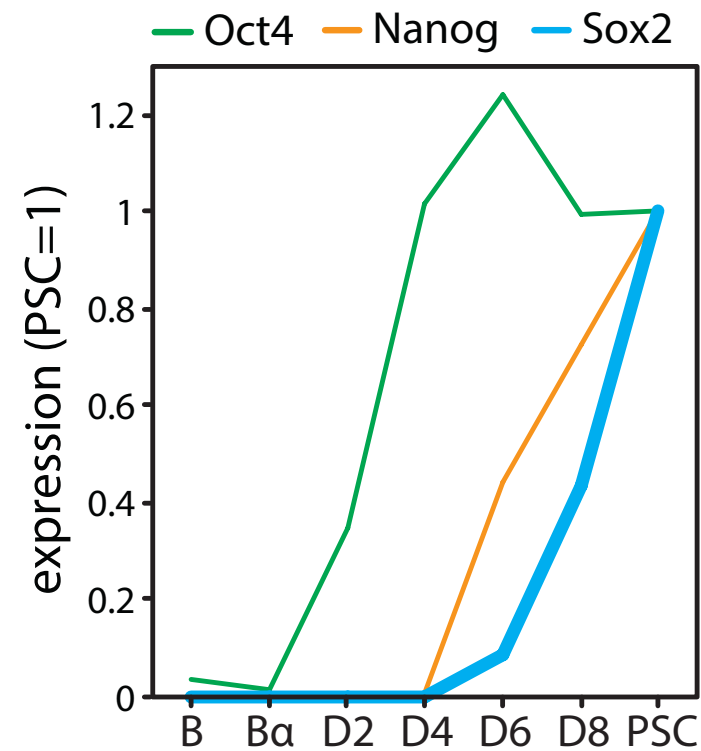
Reprogramming from B to PSC

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

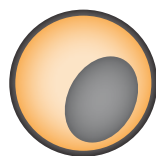


Hi-C maps of reprogramming from B to PSC

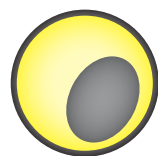
The SOX2 locus



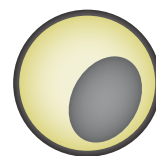
B cell



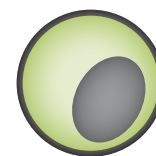
Bα



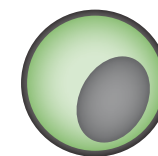
D2



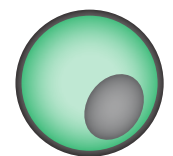
D4



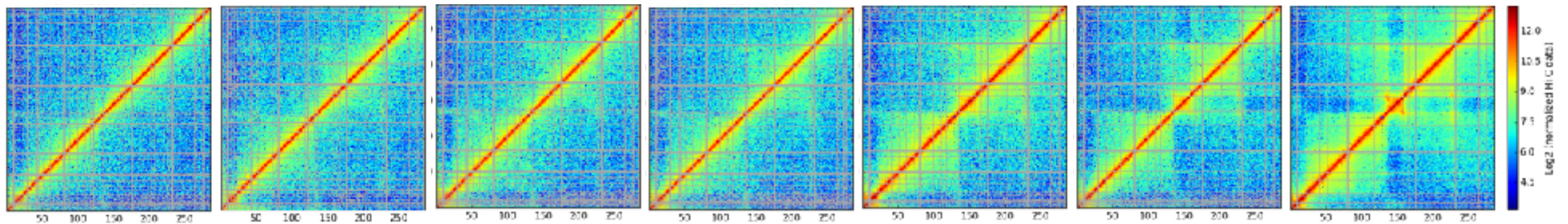
D6



D8

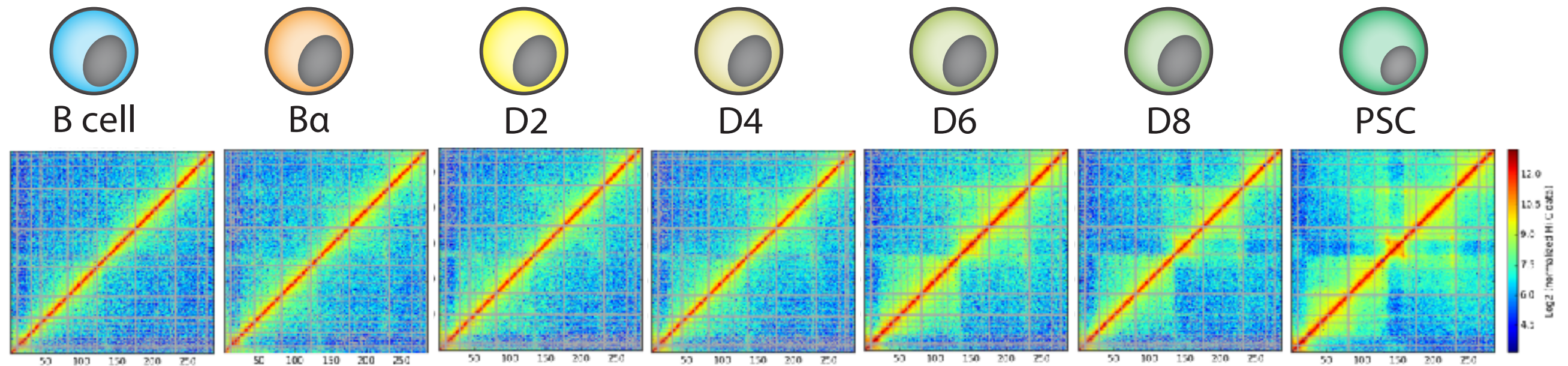


PSC



Hi-C maps of reprogramming from B to PSC

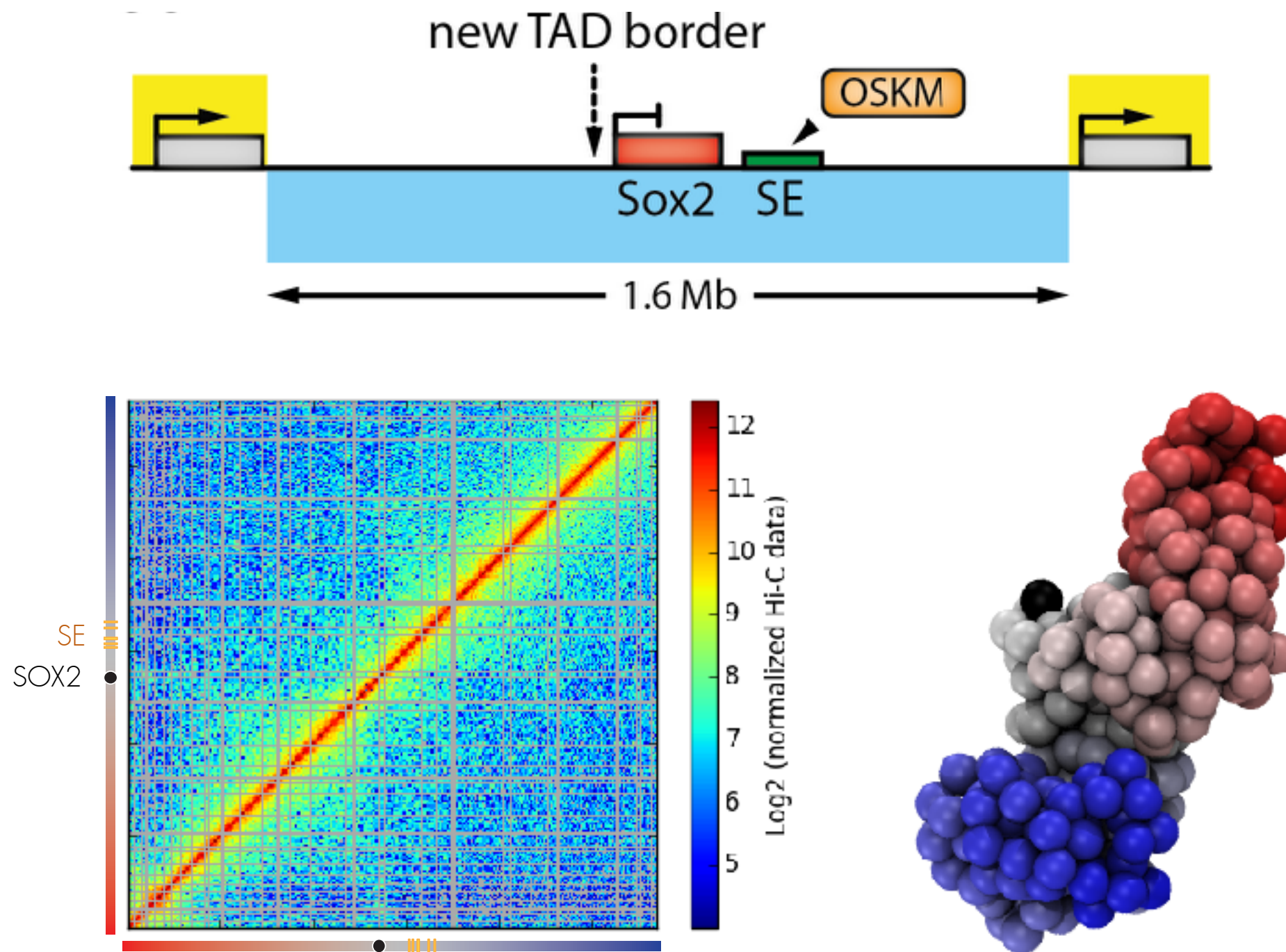
The SOX2 locus



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

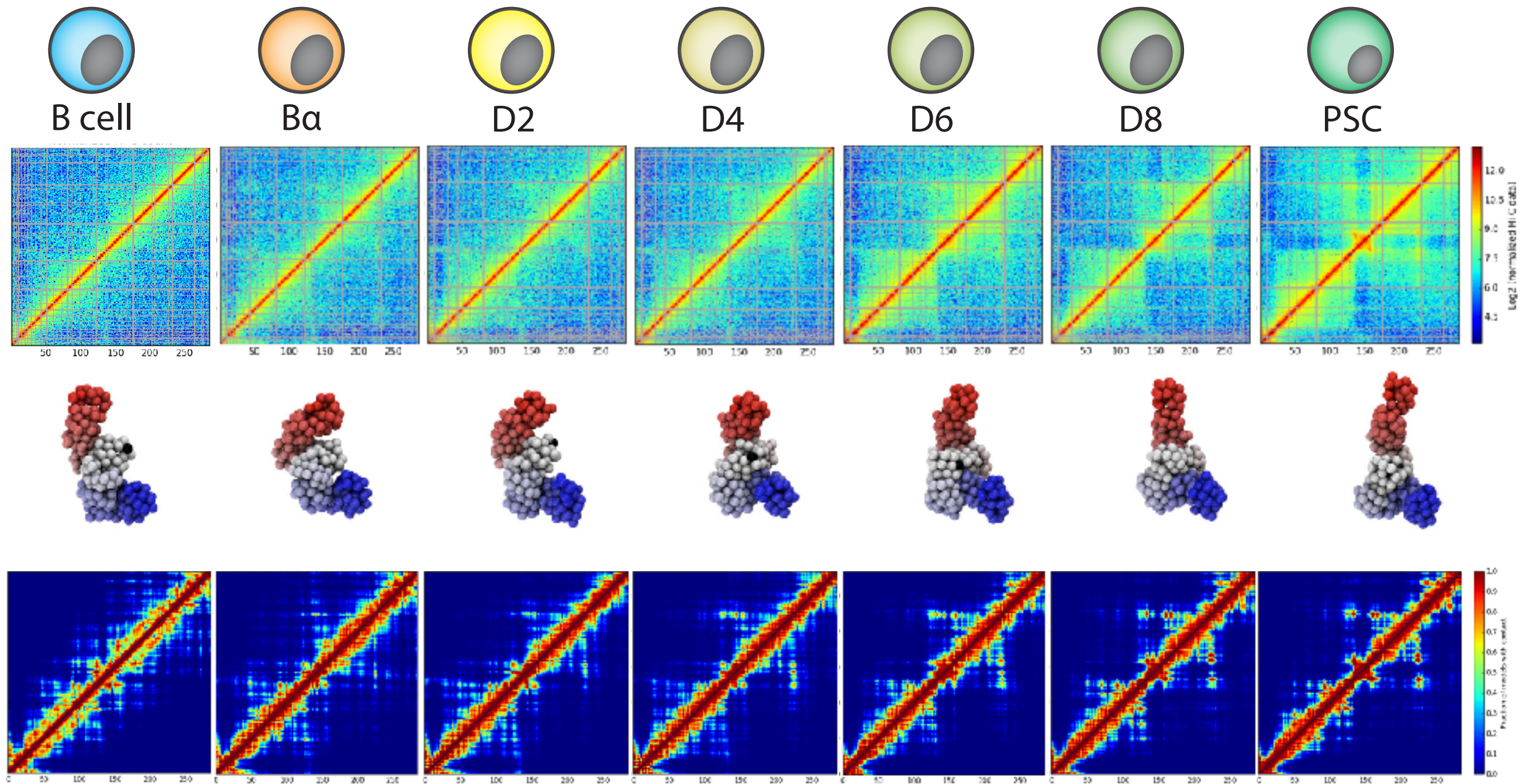


Optimal IMP parameters

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

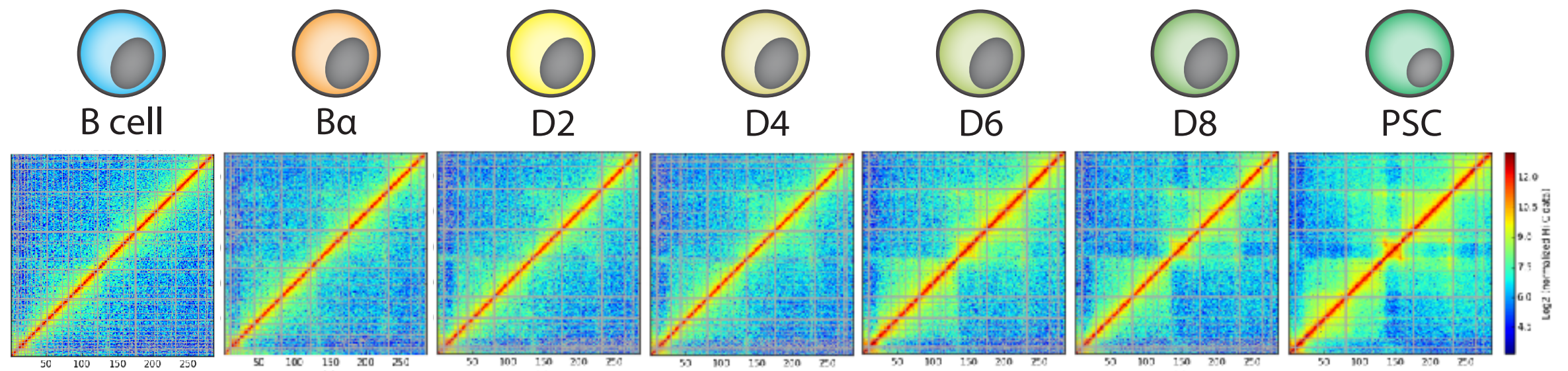
Models of reprogramming from B to PSC

The SOX2 locus



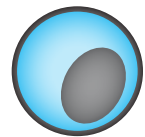
TADdyn: from time-series Hi-C maps to dynamic restraints

The SOX2 locus

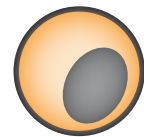


TADdyn: from time-series Hi-C maps to dynamic restraints

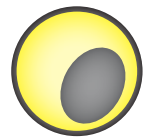
The SOX2 locus



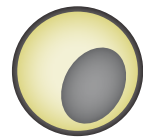
B cell



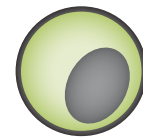
Bα



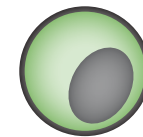
D2



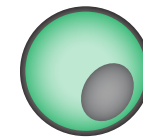
D4



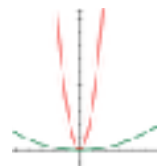
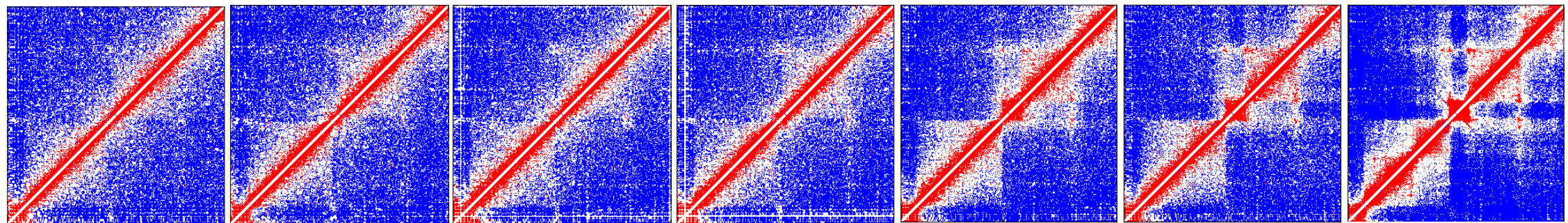
D6



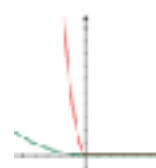
D8



PSC



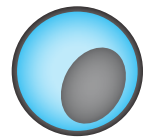
Harmonic



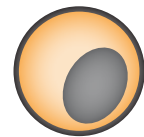
HarmonicLowerBound

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

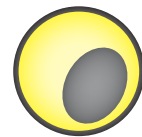
The SOX2 locus



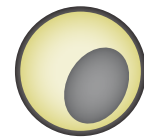
B cell



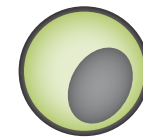
B α



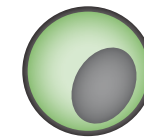
D2



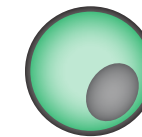
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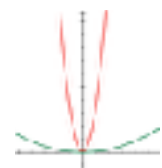
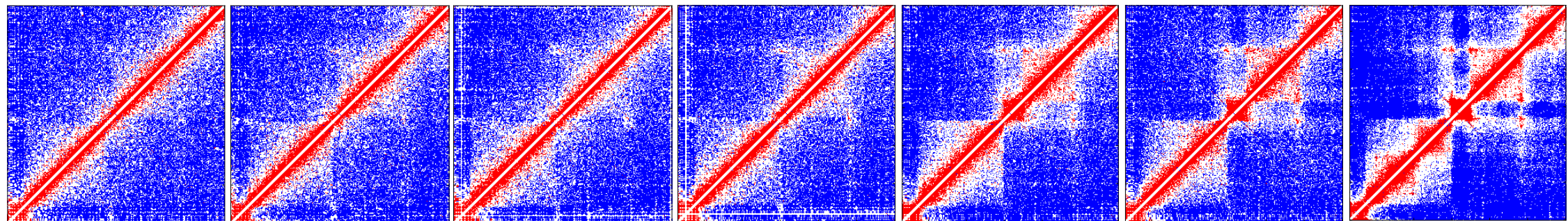
D6



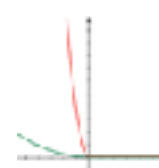
D8



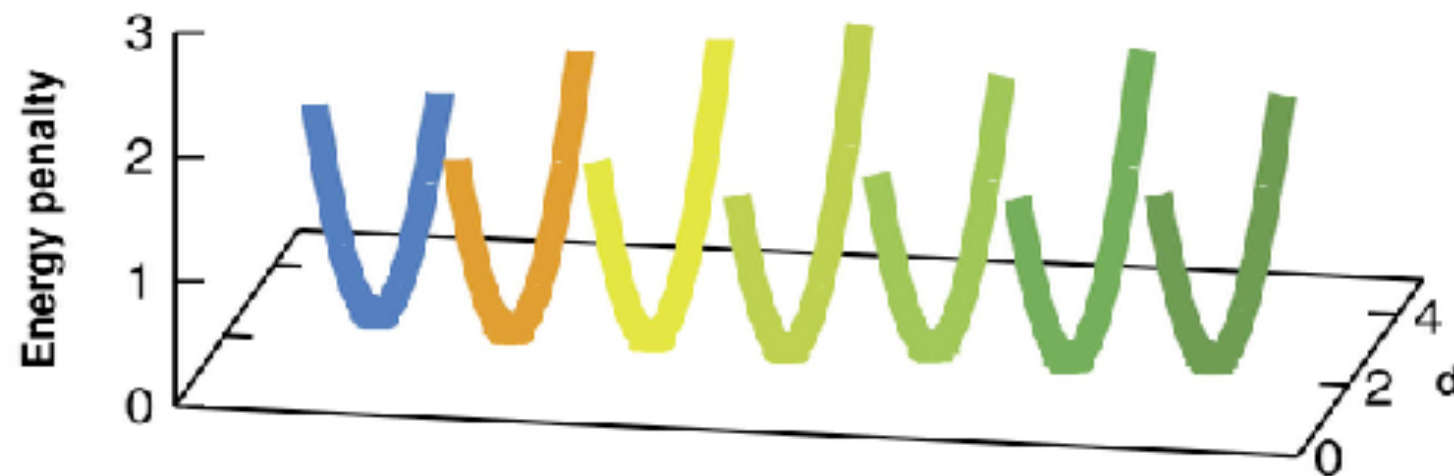
PSC



Harmonic



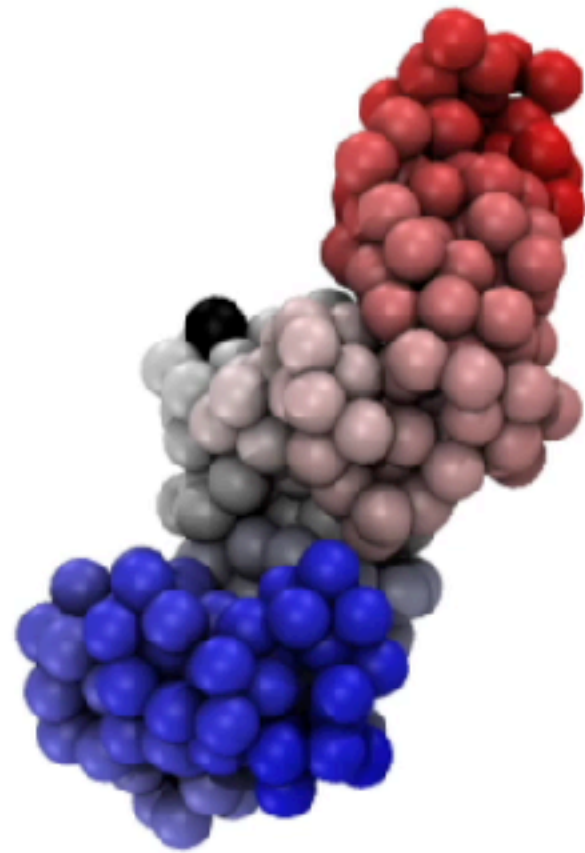
HarmonicLowerBound



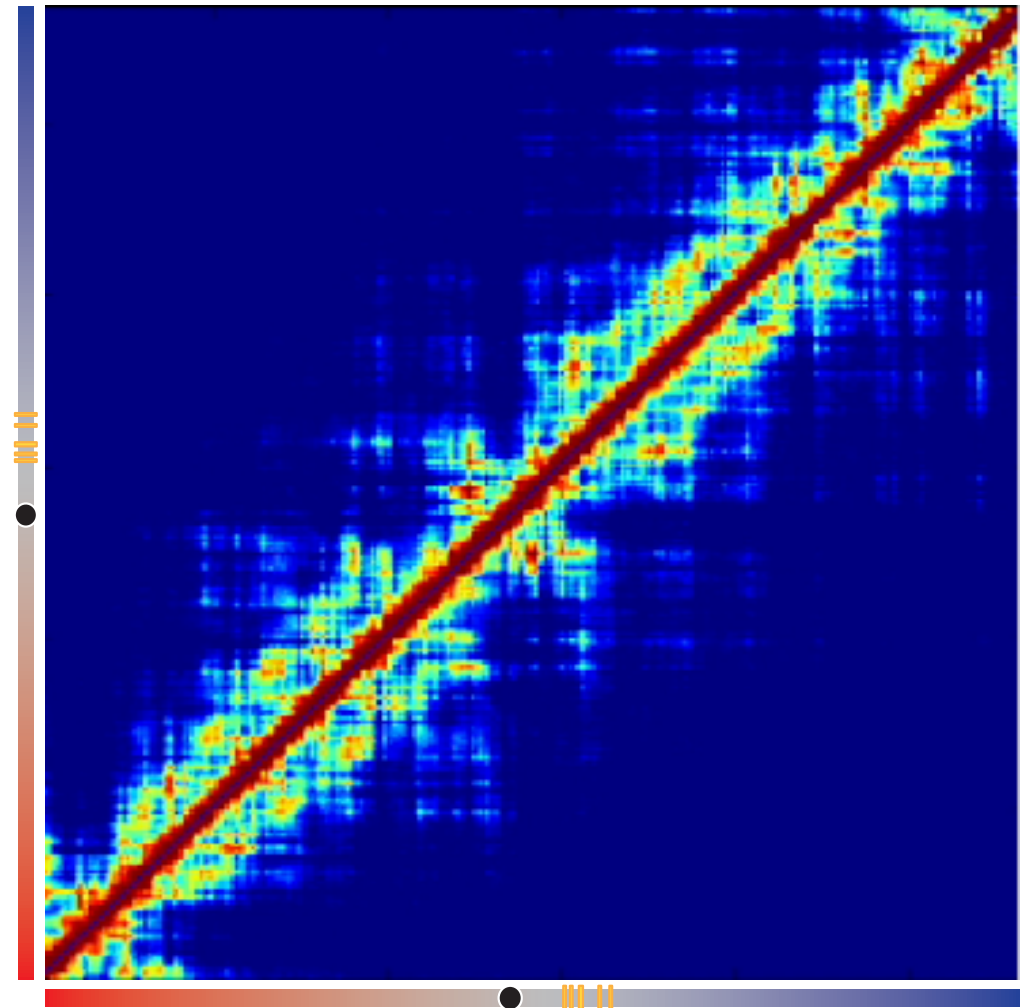
Transition	Stable	Vanishing	Raising
B → B α	18,612	6,984	7,290
B α → D2	18,512	7,390	6,687
D2 → D4	18,369	6,830	6,893
D4 → D6	18,971	6,291	7,289
D6 → D8	20,167	6,093	6,250
D8 → ES	20,679	5,738	6,173

SOX2 locus structural changes from B to PSC

Contacts

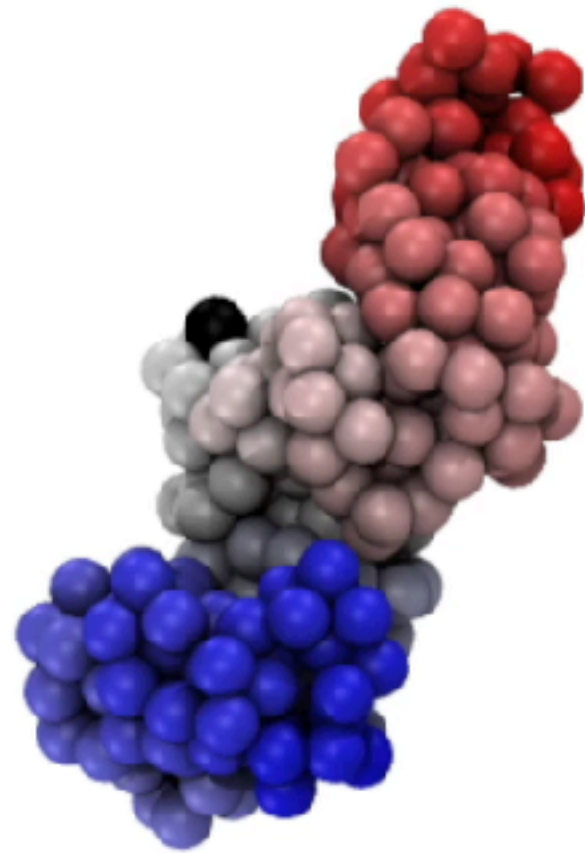


SE
SOX2

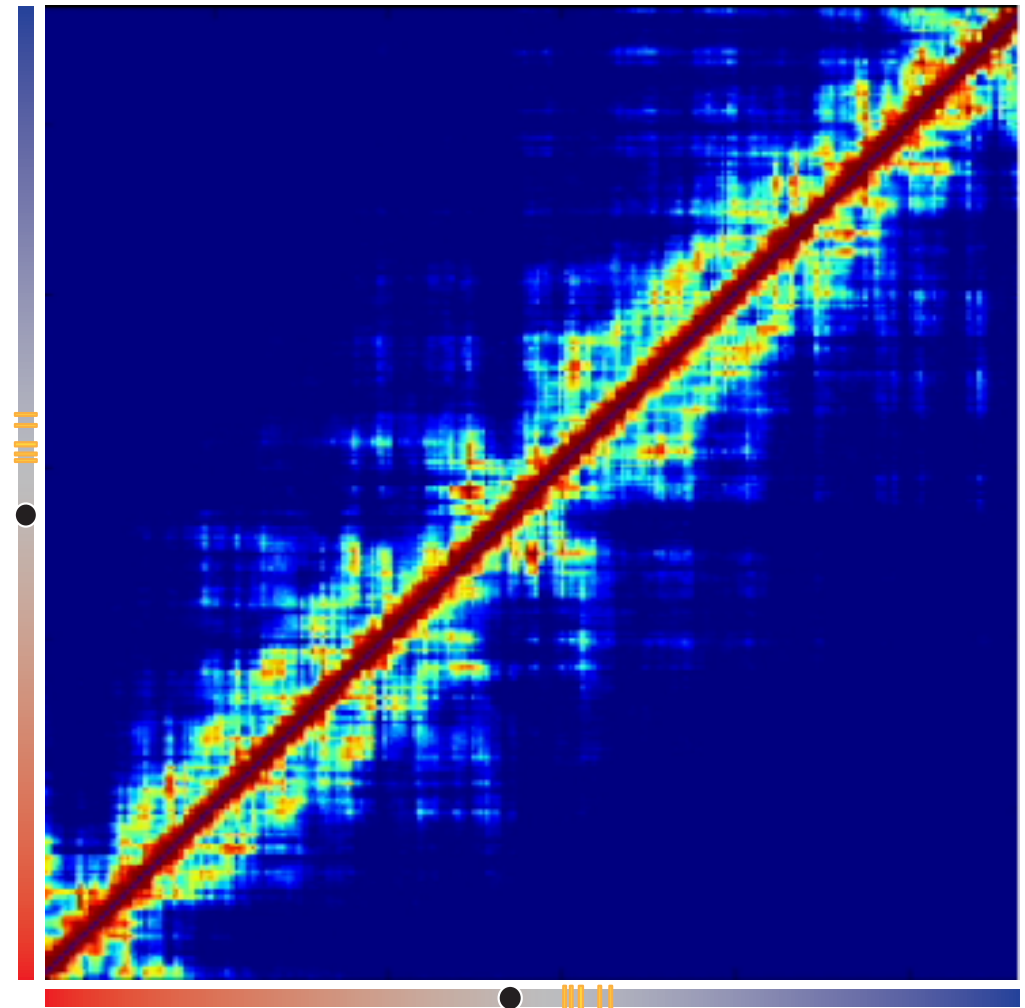


SOX2 locus structural changes from B to PSC

Contacts

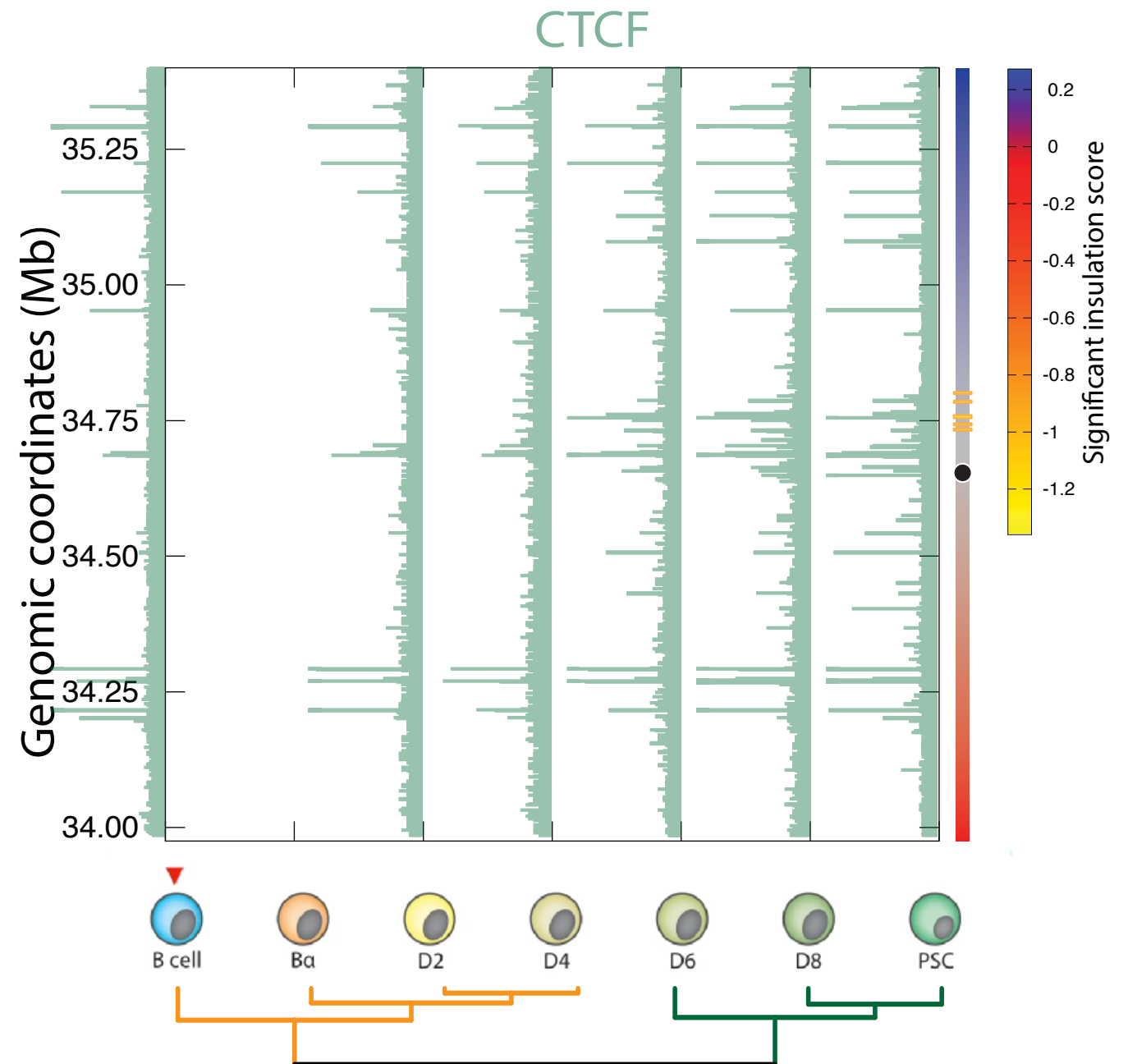
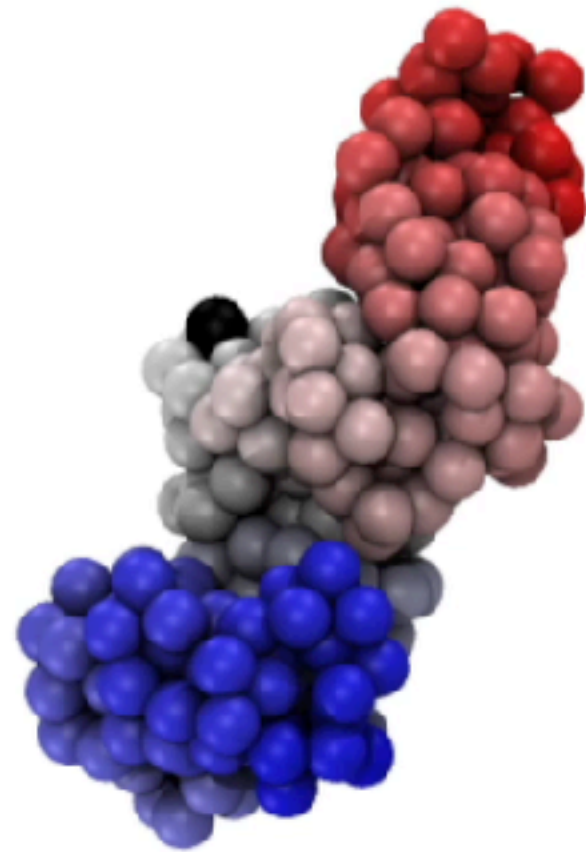


SE
SOX2



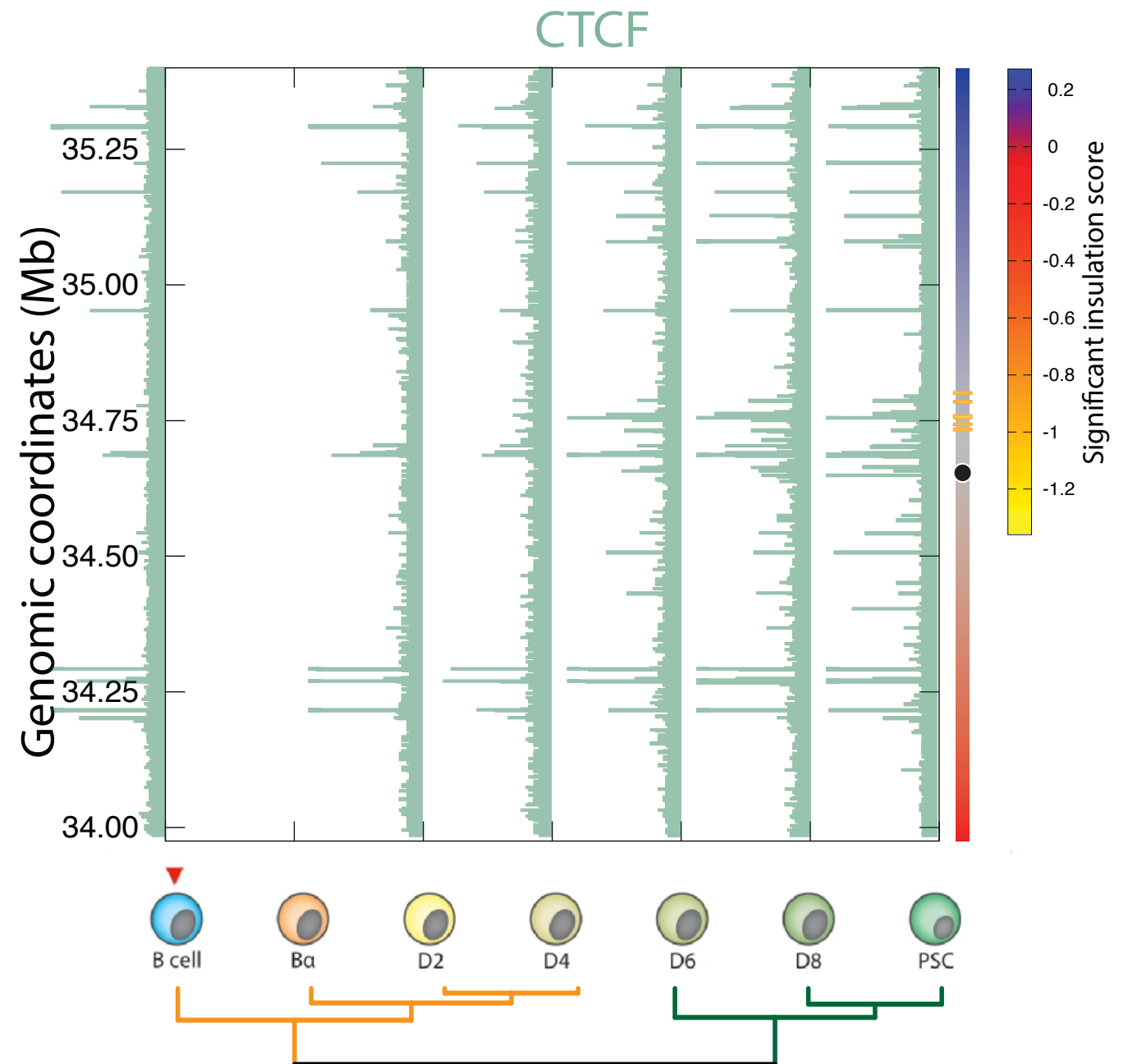
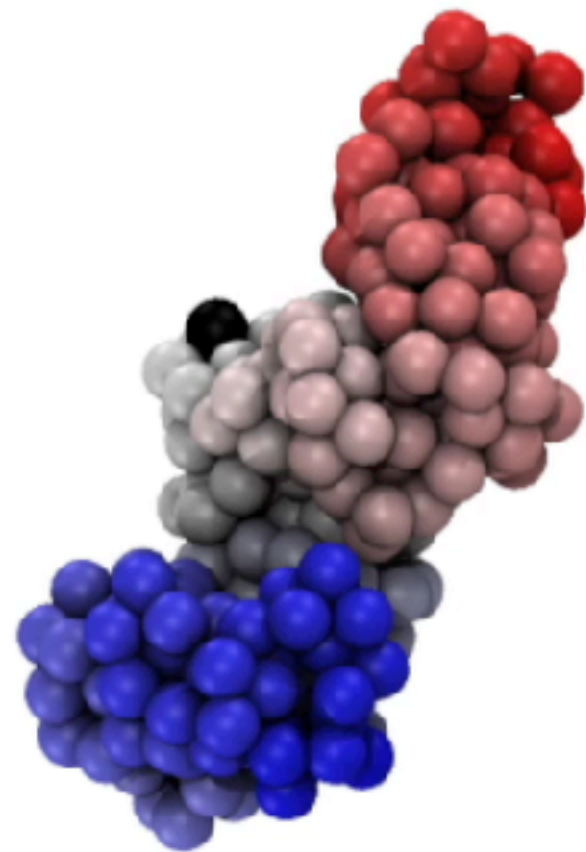
SOX2 locus structural changes from B to PSC

TAD borders



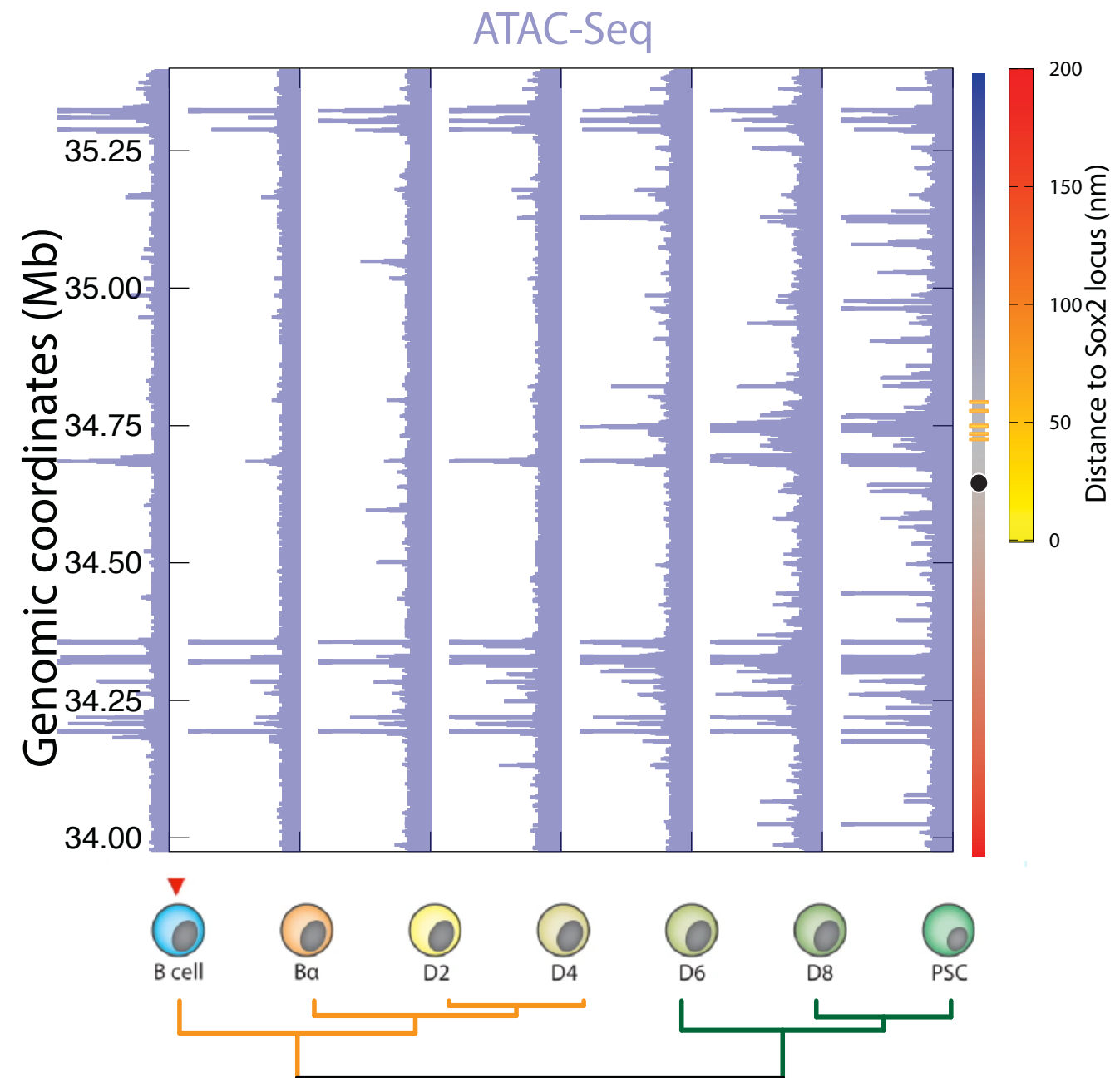
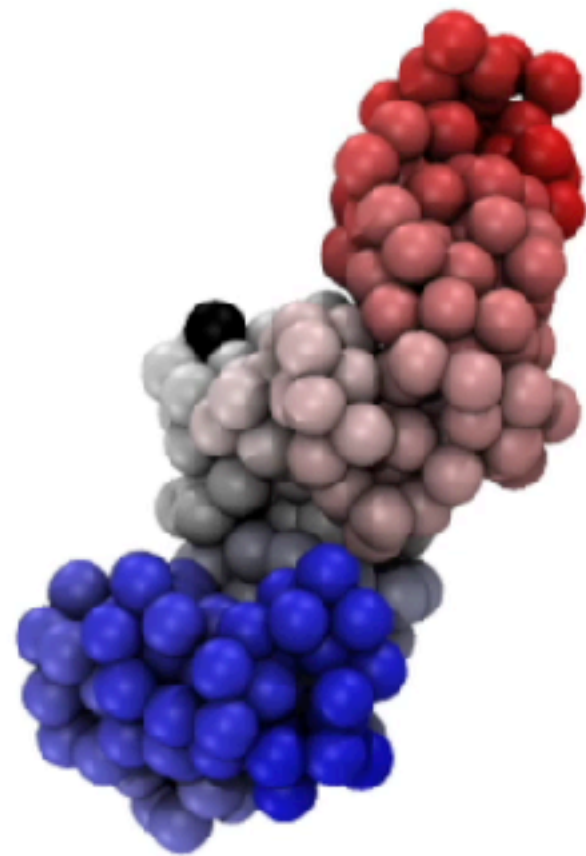
SOX2 locus structural changes from B to PSC

TAD borders



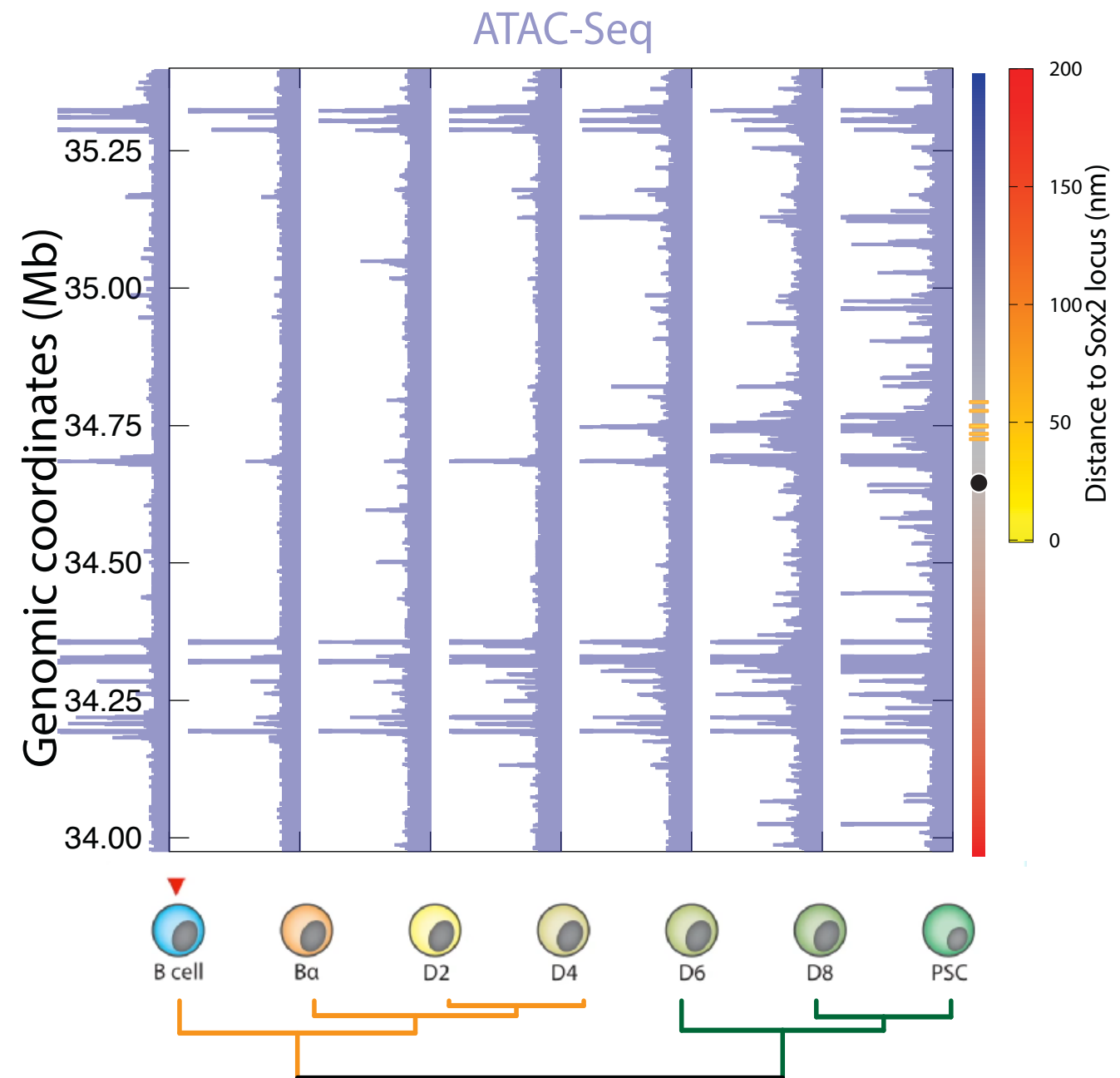
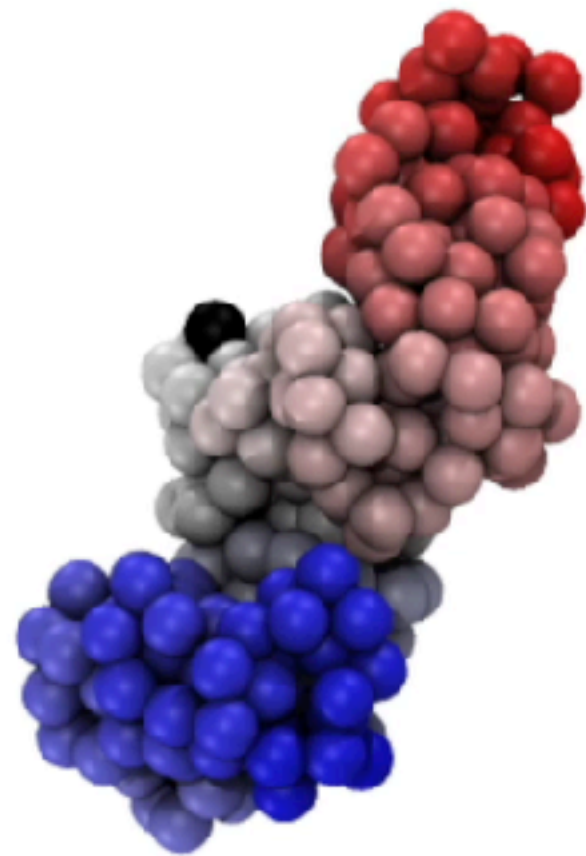
SOX2 locus structural changes from B to PSC

Distance to regulatory elements



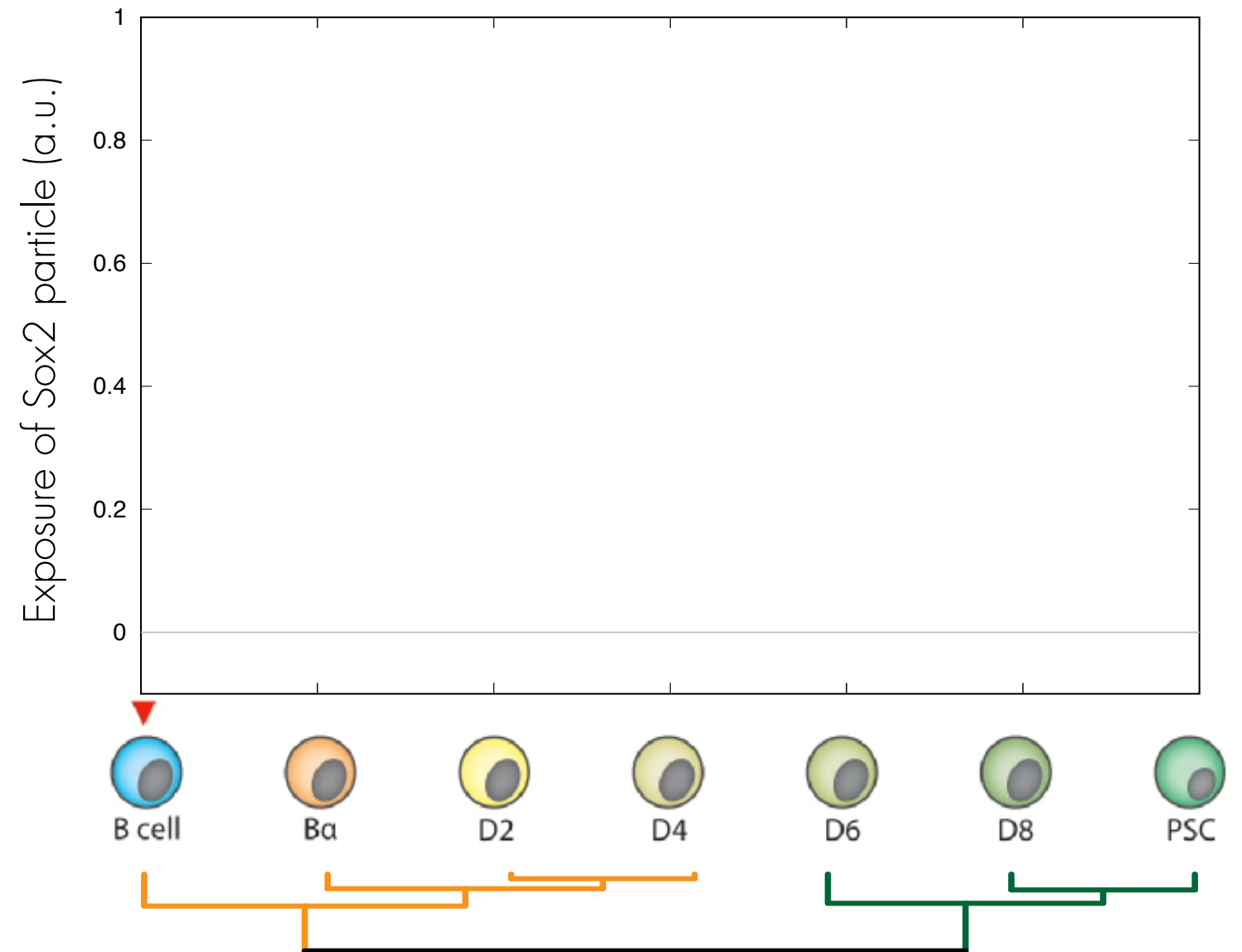
SOX2 locus structural changes from B to PSC

Distance to regulatory elements



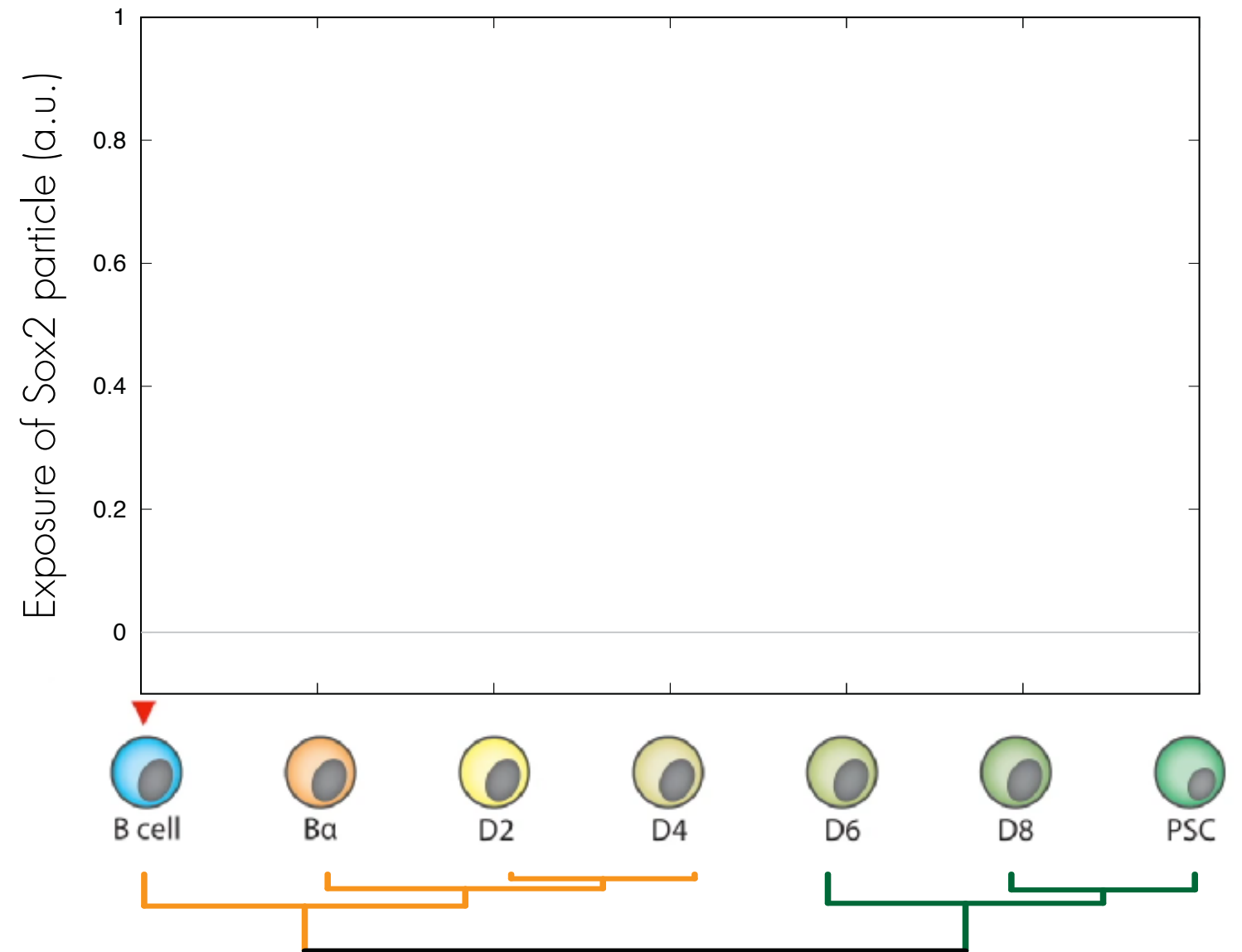
SOX2 locus structural changes from B to PSC

Structural exposure



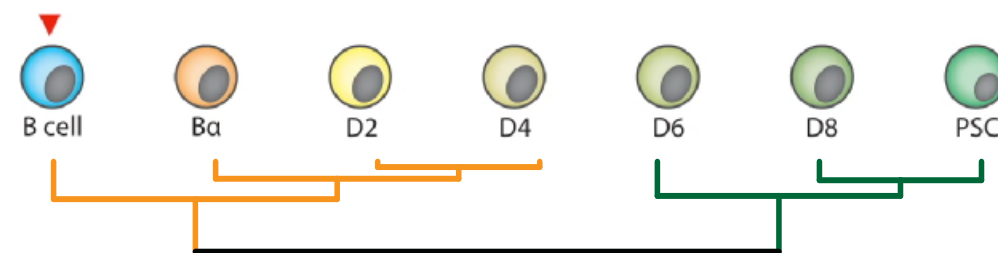
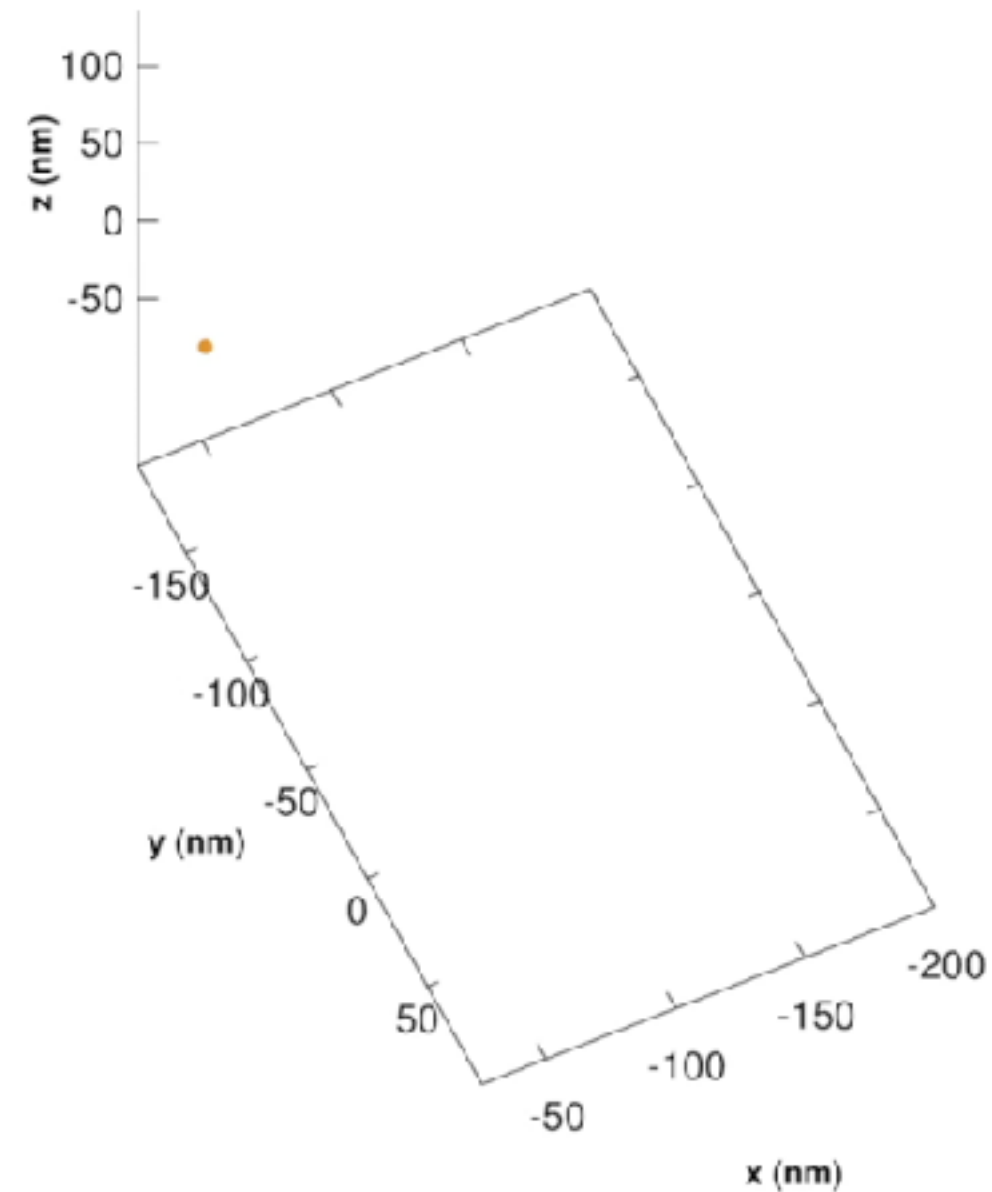
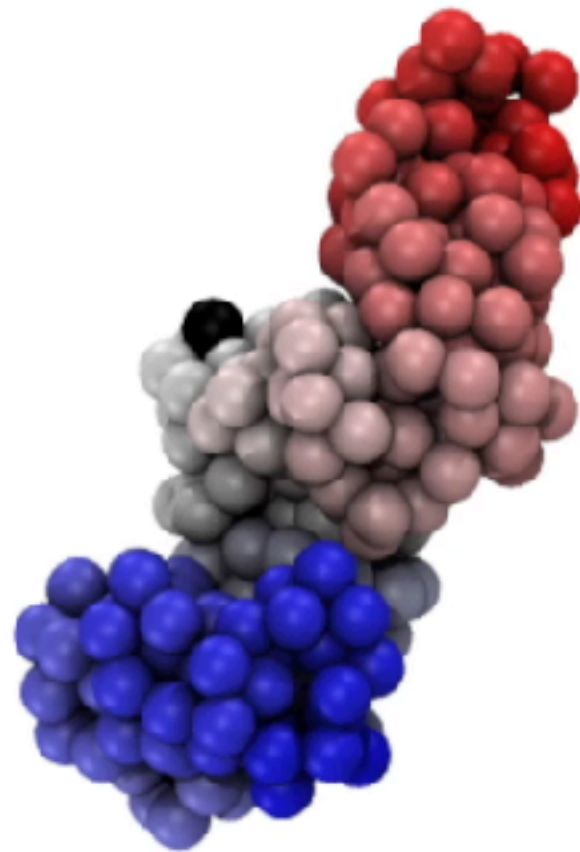
SOX2 locus structural changes from B to PSC

Structural exposure



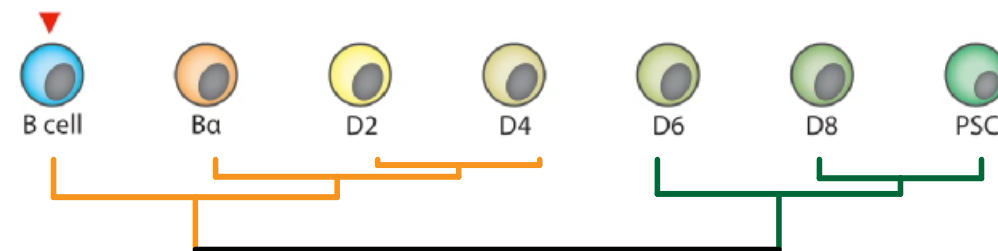
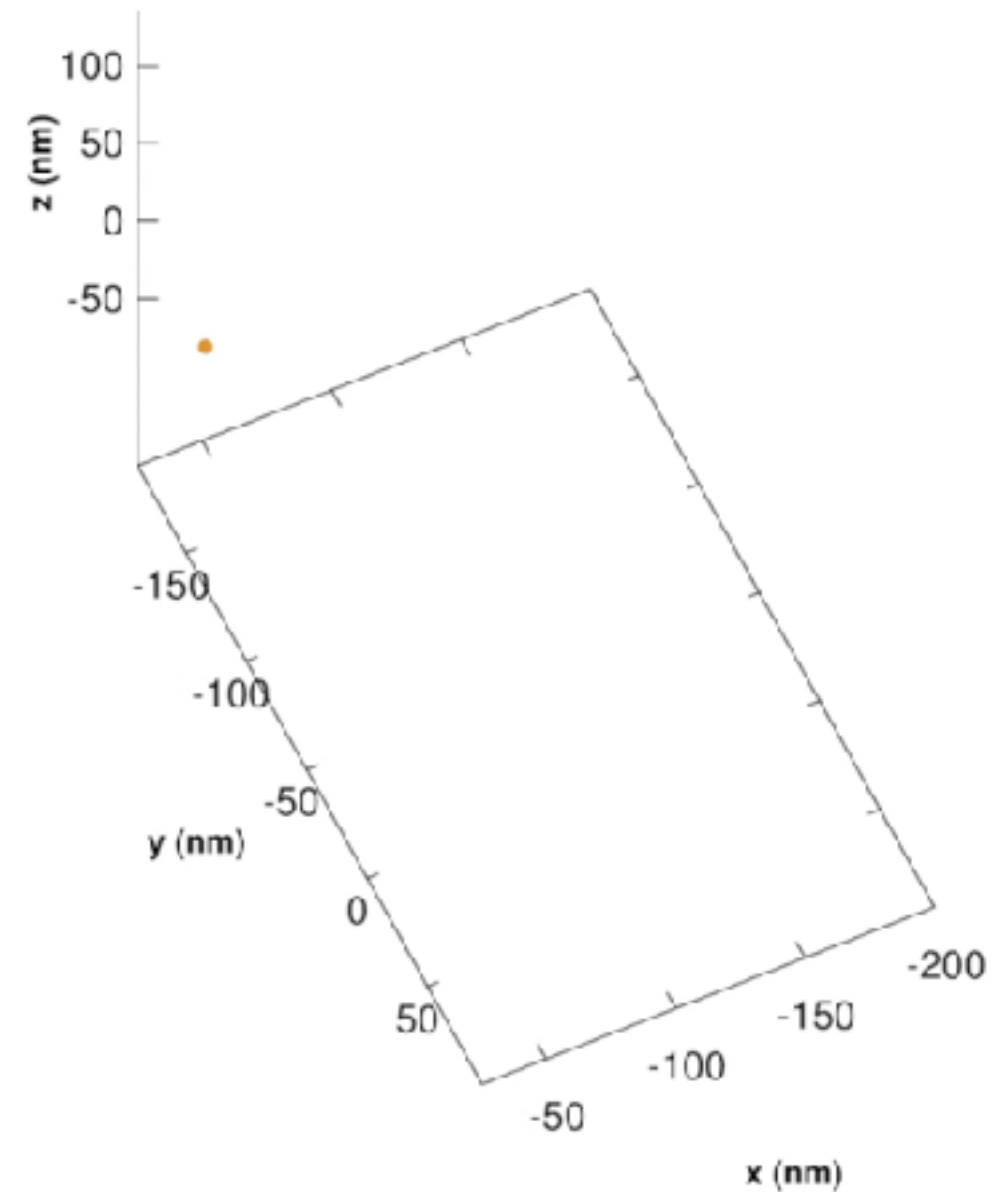
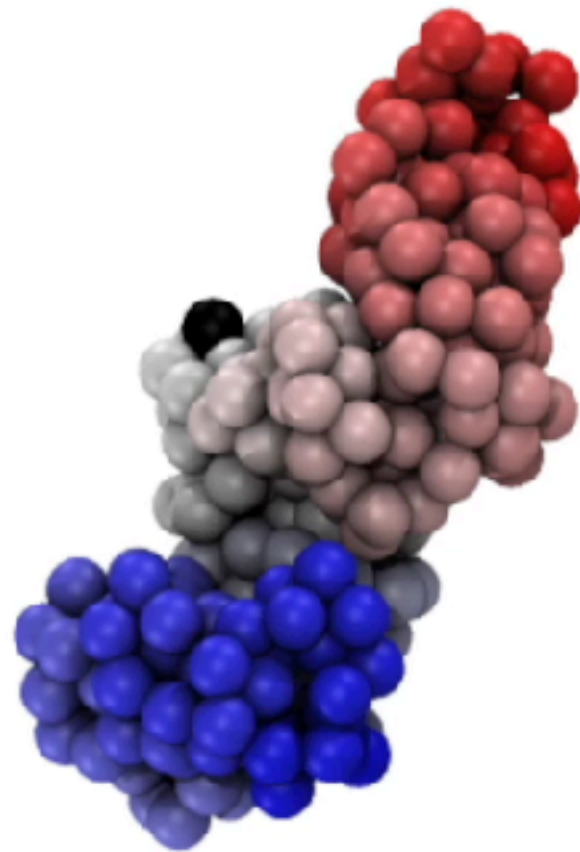
SOX2 locus dynamics changes from B to PSC

SOX2 displacement



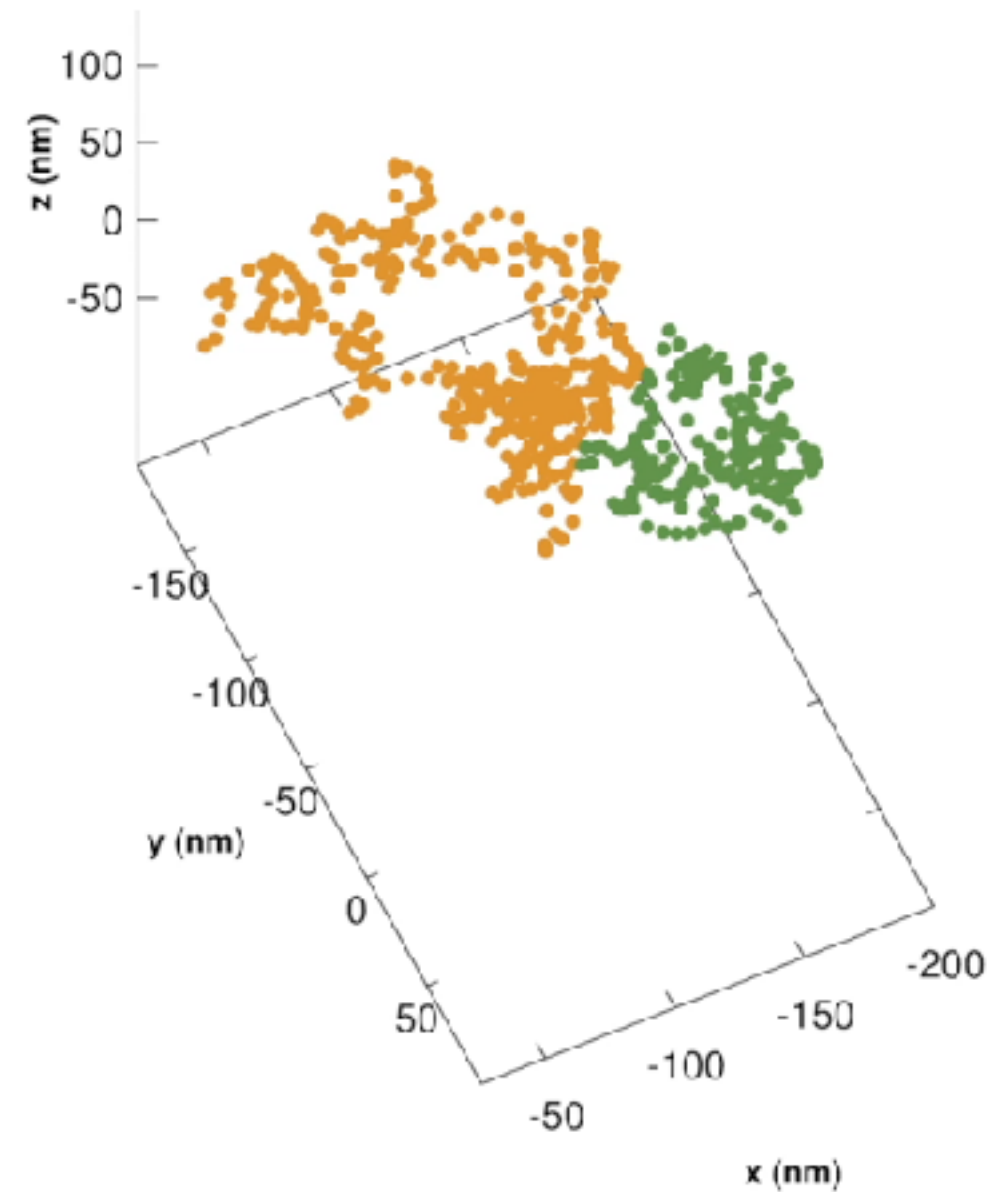
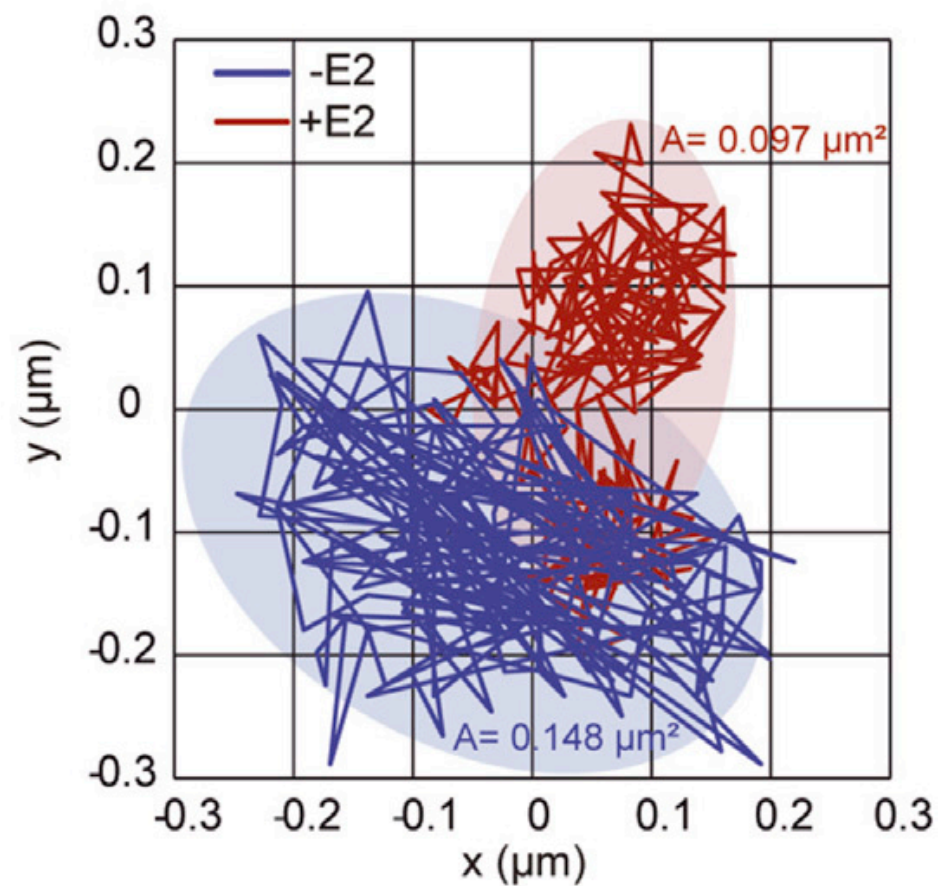
SOX2 locus dynamics changes from B to PSC

SOX2 displacement



SOX2 locus dynamics changes from B to PSC

SOX2 displacement



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

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



A “cage” model for transcriptional activation



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

cnag

CRG
Centre for Genomic Regulation

ICREA



Marco Di Stefano

David Castillo
Yasmina Cuartero
Irene Farabella
Silvia Galan
Mike Goodstadt
Francesca Mugianesi
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