

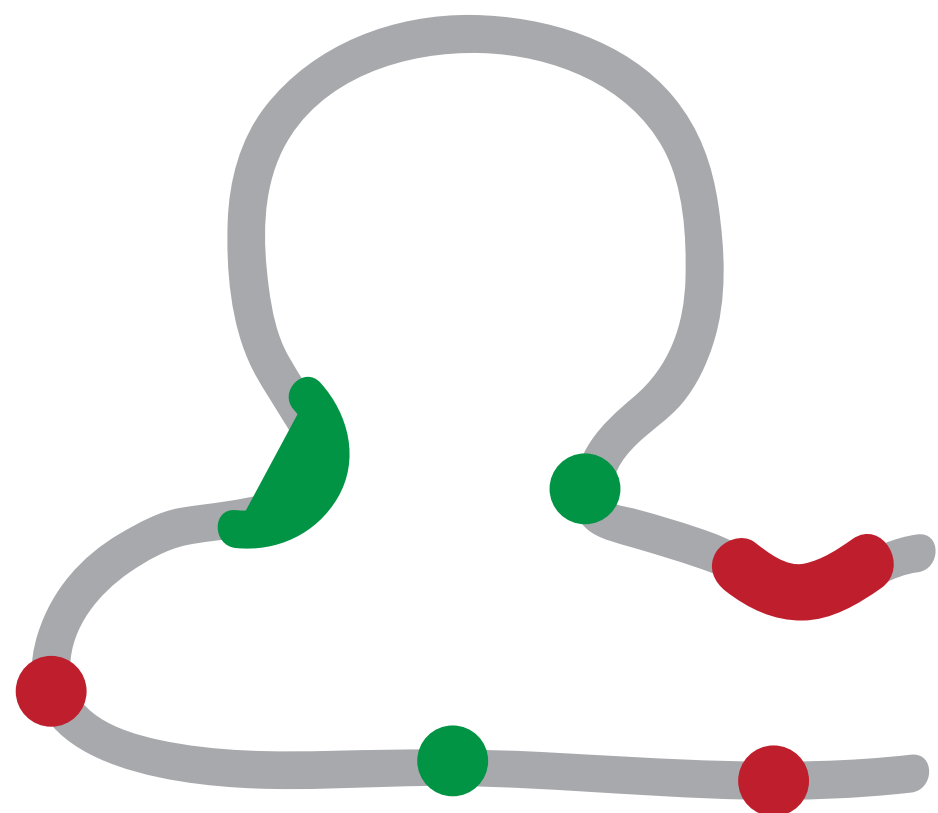
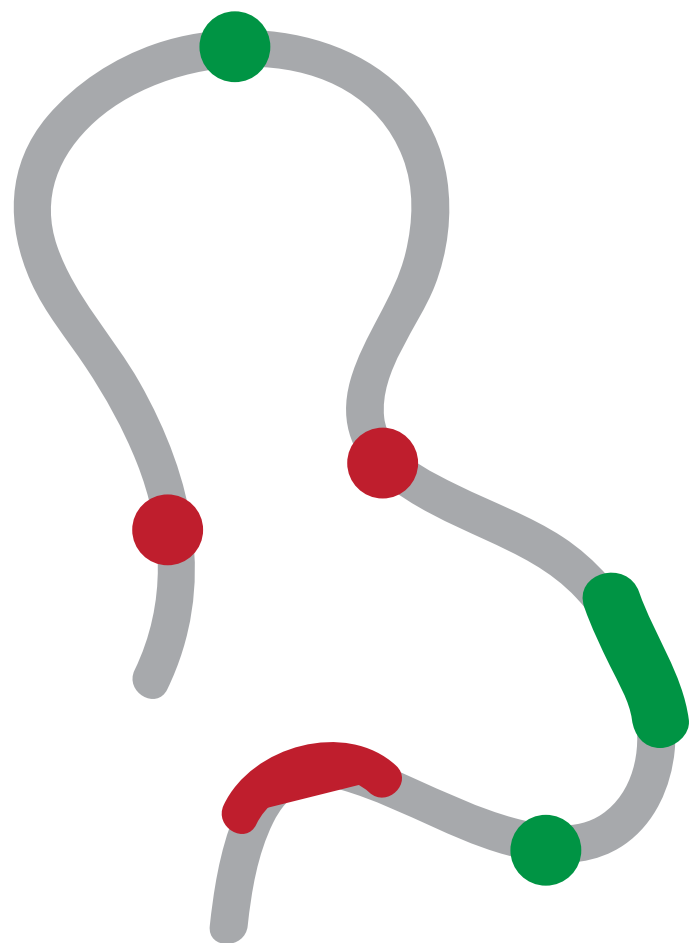
Exploring the time dependent structural rearrangements of SOX2 locus in mouse using the TADdyn tool

Marc A. Marti-Renom

Structural Genomics Group (ICREA, CNAG-CRG)

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

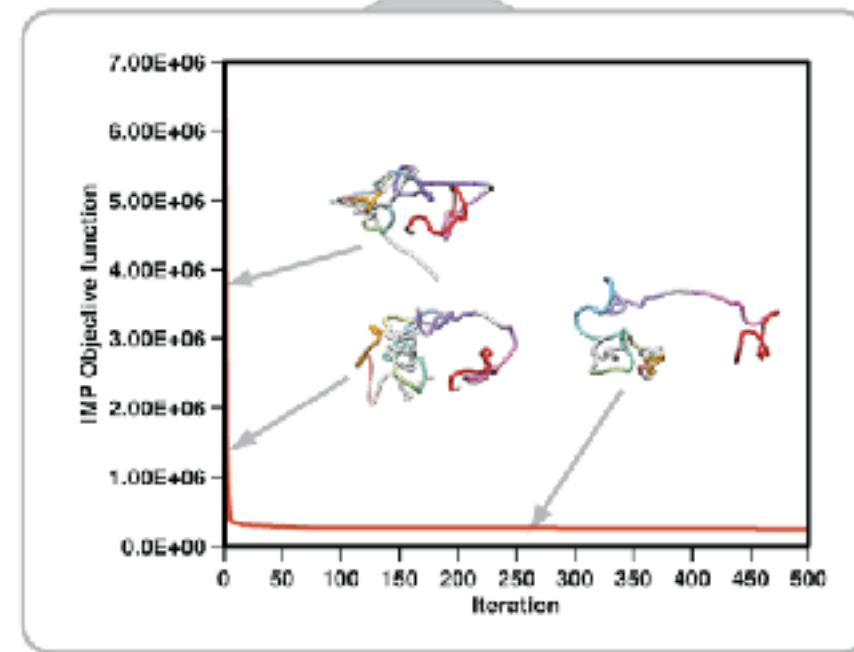
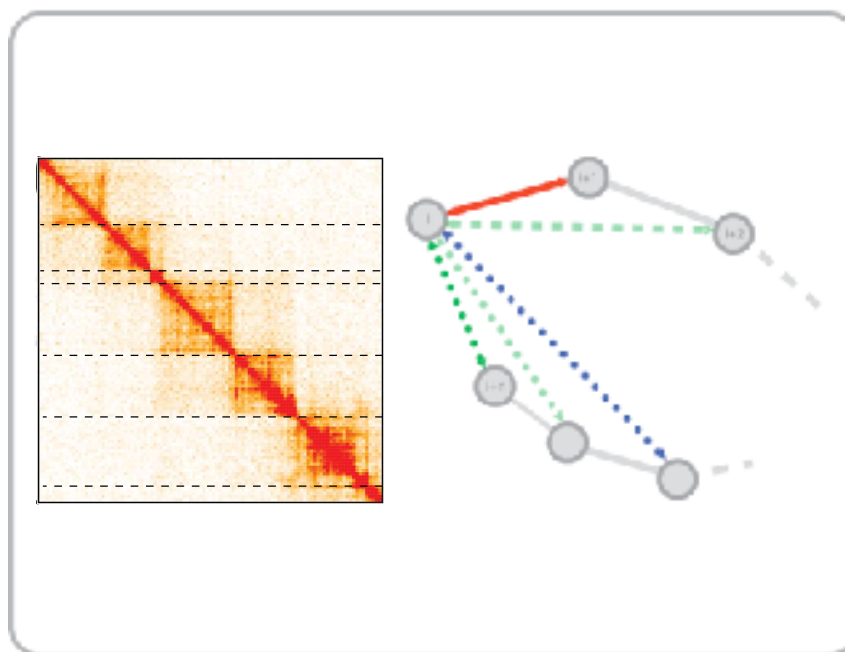
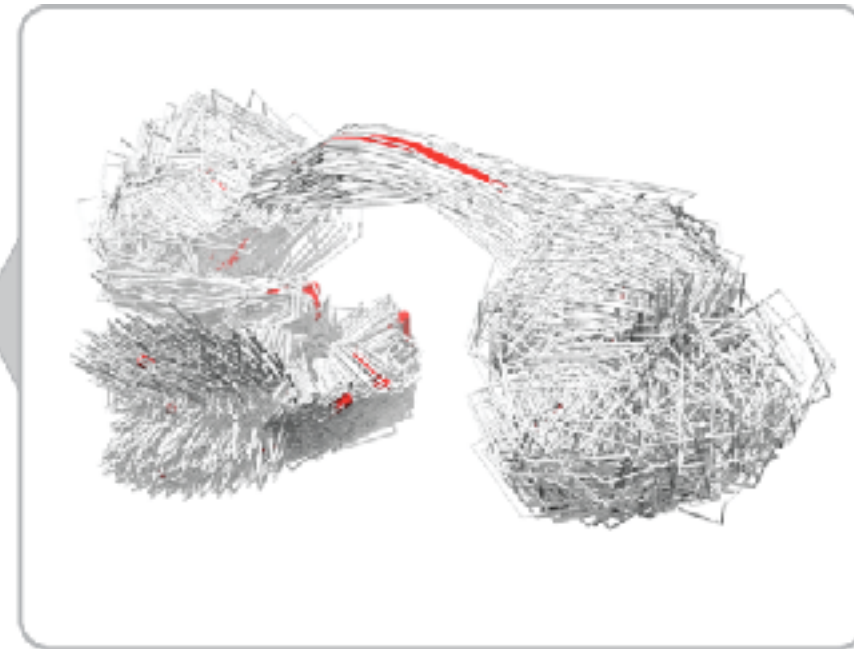
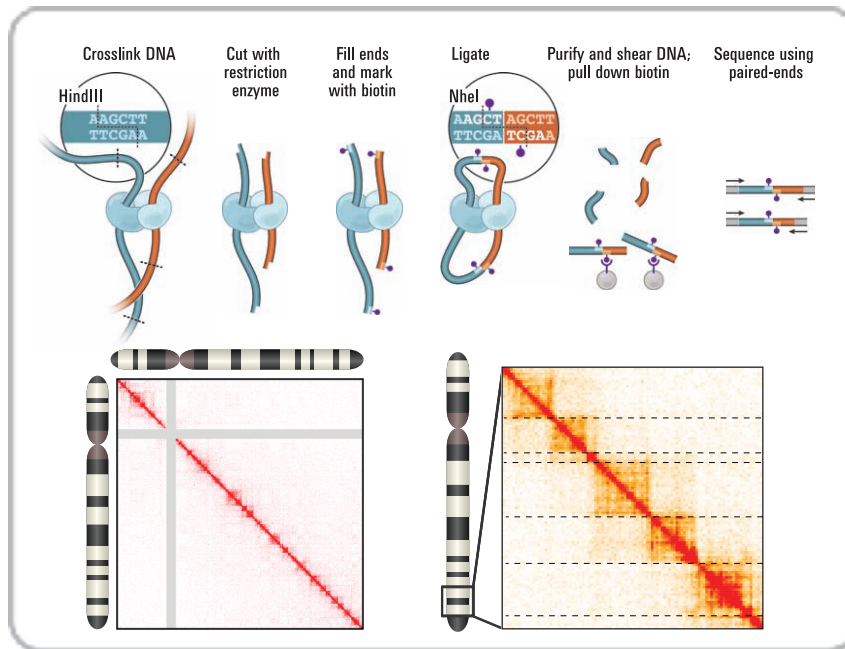
cnag **CRG**  **ICREA**



Hybrid Method

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

Experiments

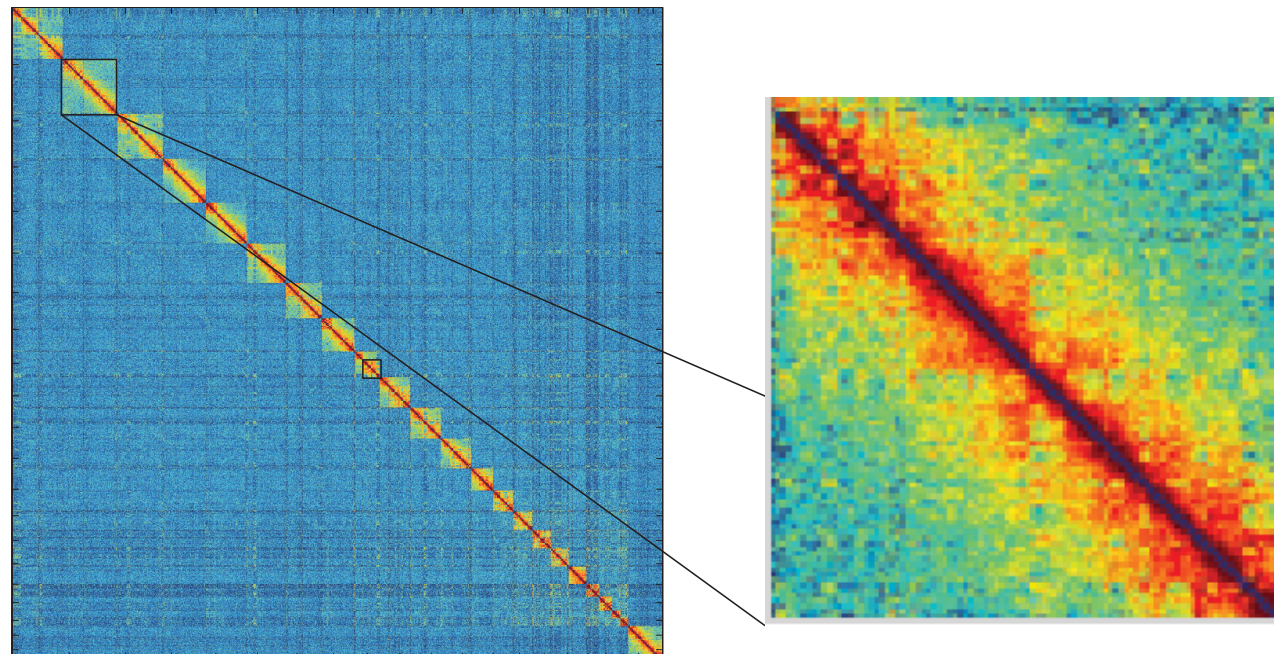
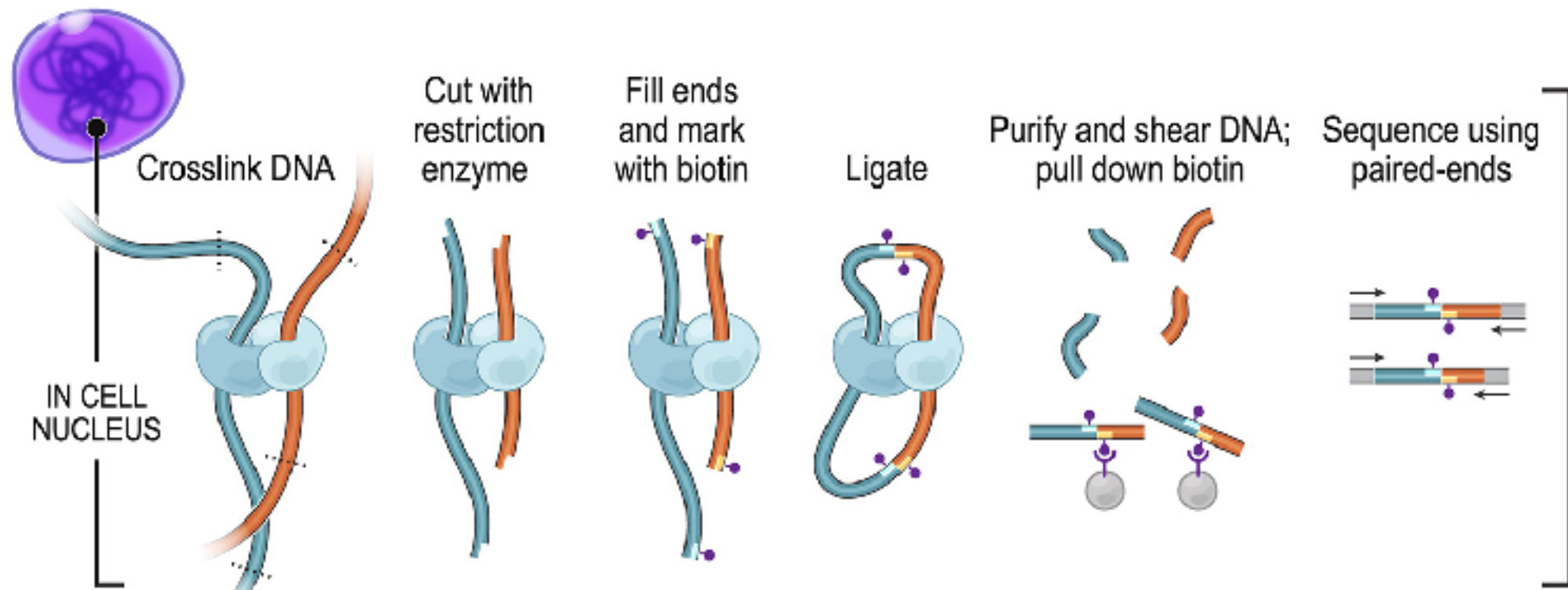


Computation

Chromosome Conformation Capture

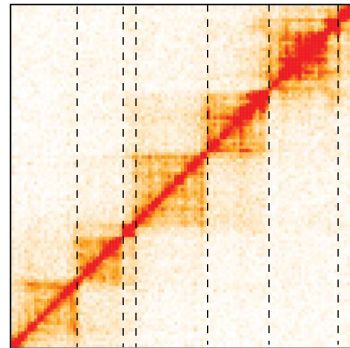
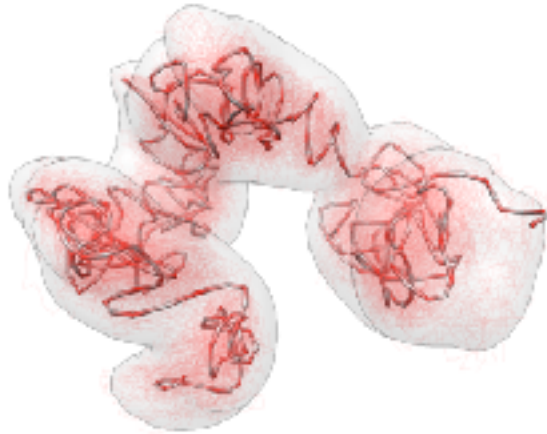
Dekker, J., Rippe, K., Dekker, M., & Kleckner, N. (2002). *Science*, 295(5558), 1306–1311.

Lieberman-Aiden, E., et al. (2009). *Science*, 326(5950), 289–293.



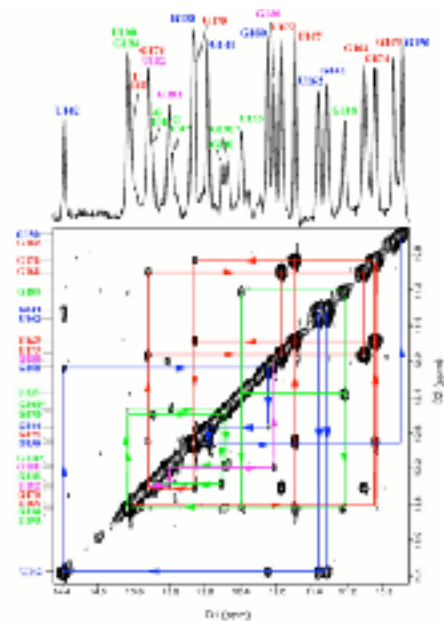
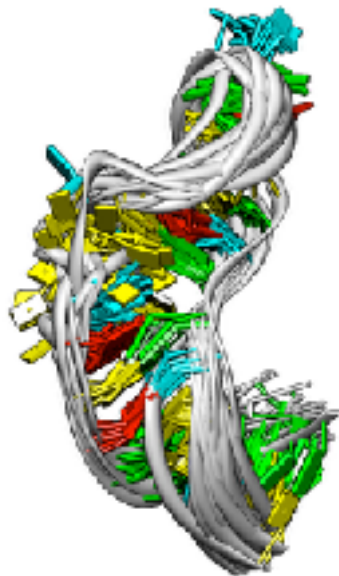
Restraint-based Modeling

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



Chromosome structure determination

3C-based data

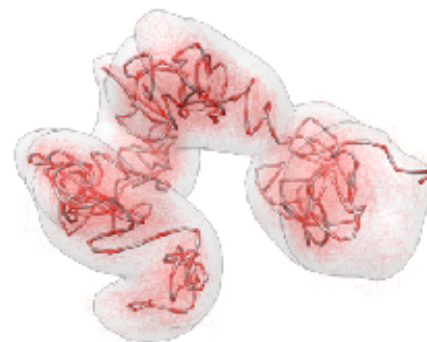
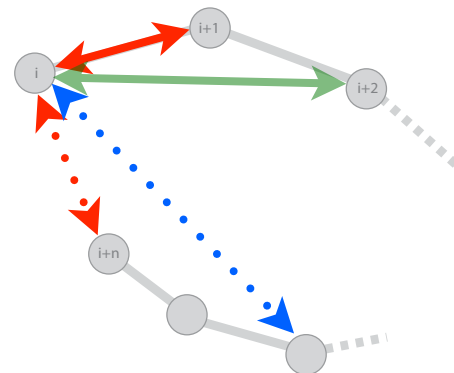
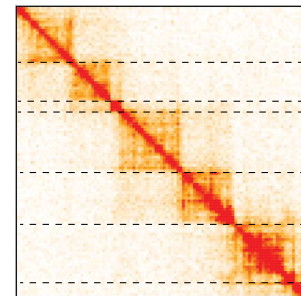


Biomolecular structure determination
2D-NOESY data



<http://3DGenomes.org>

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



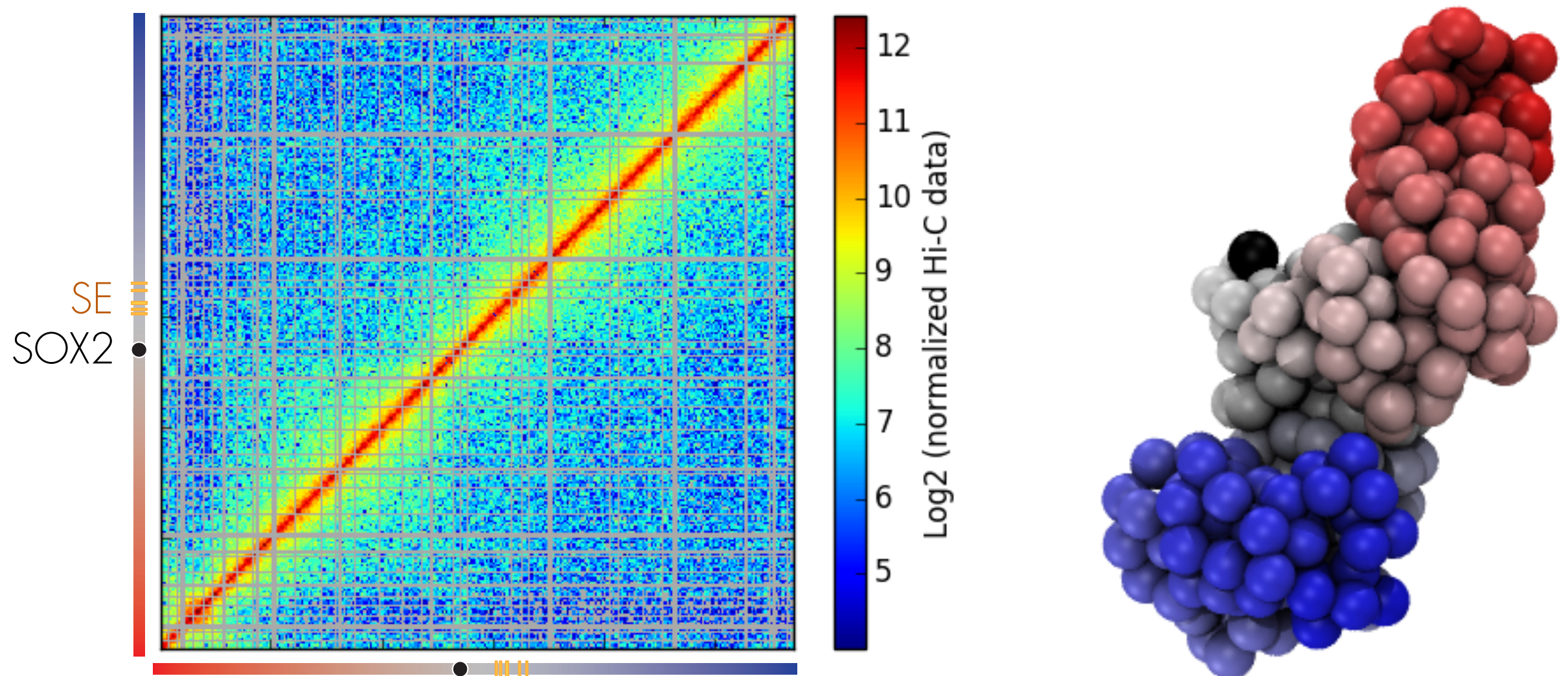
FastQ files to Maps

Map analysis

Model building

Model analysis

TADbit modeling of SOX2 from B cells Hi-C

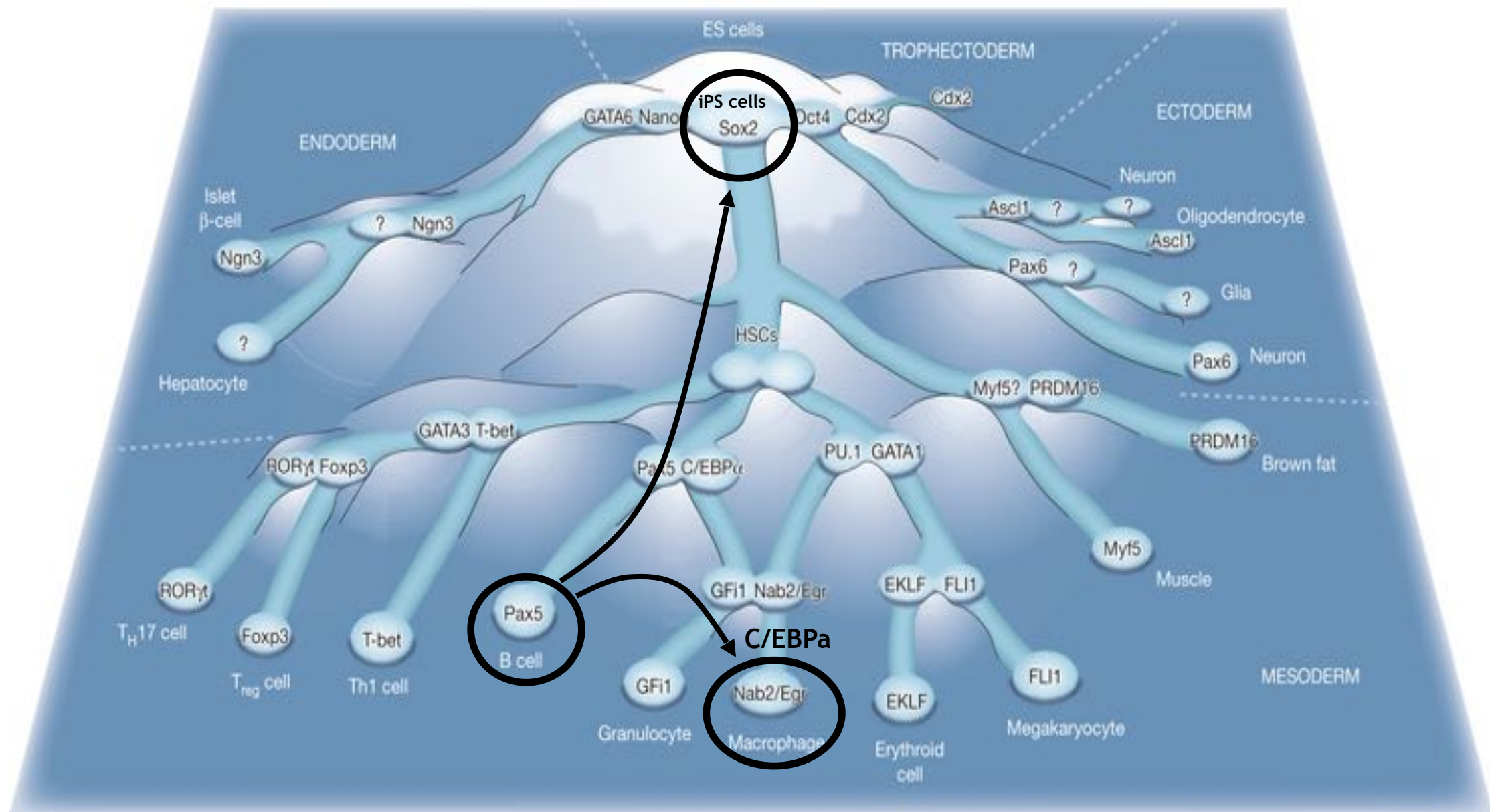


Optimal IMP parameters

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

Transcription factors dictate cell fate

Graf & Enver (2009) Nature



Transcription factors (TFs) determine cell identity through gene regulation

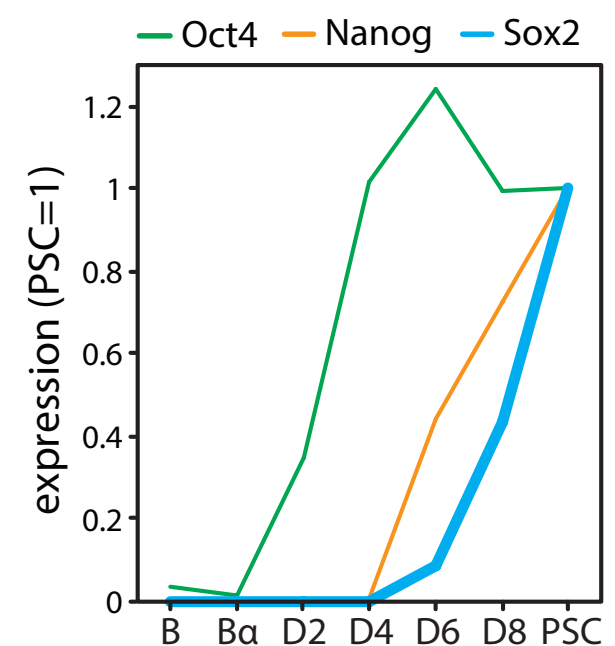
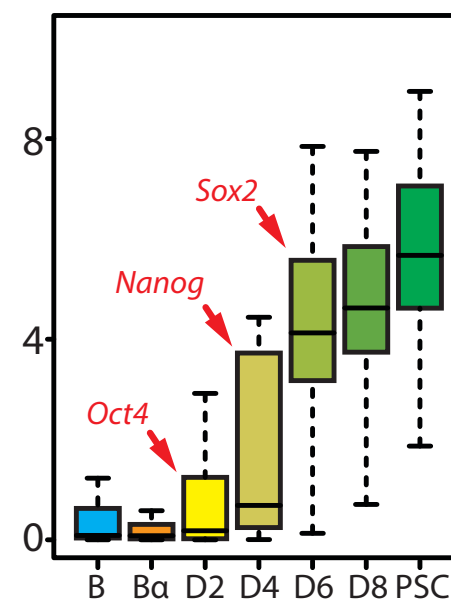
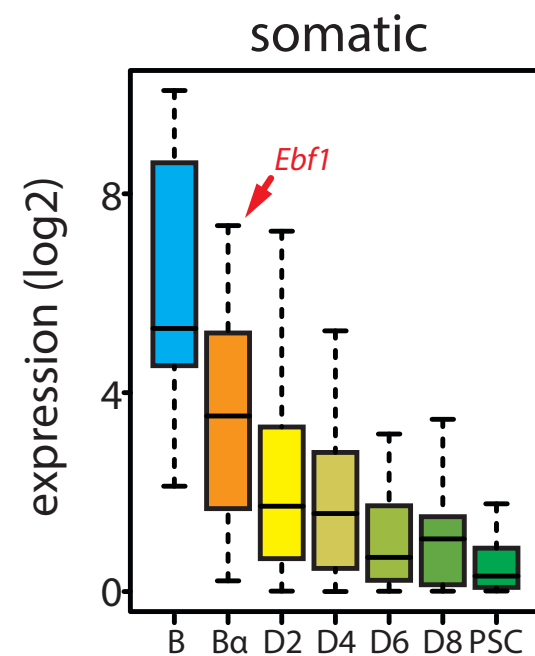
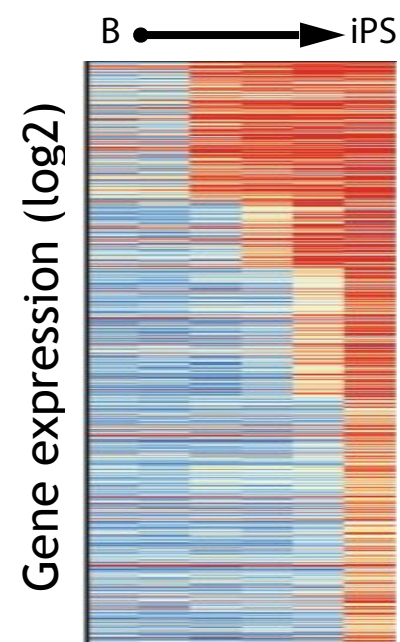
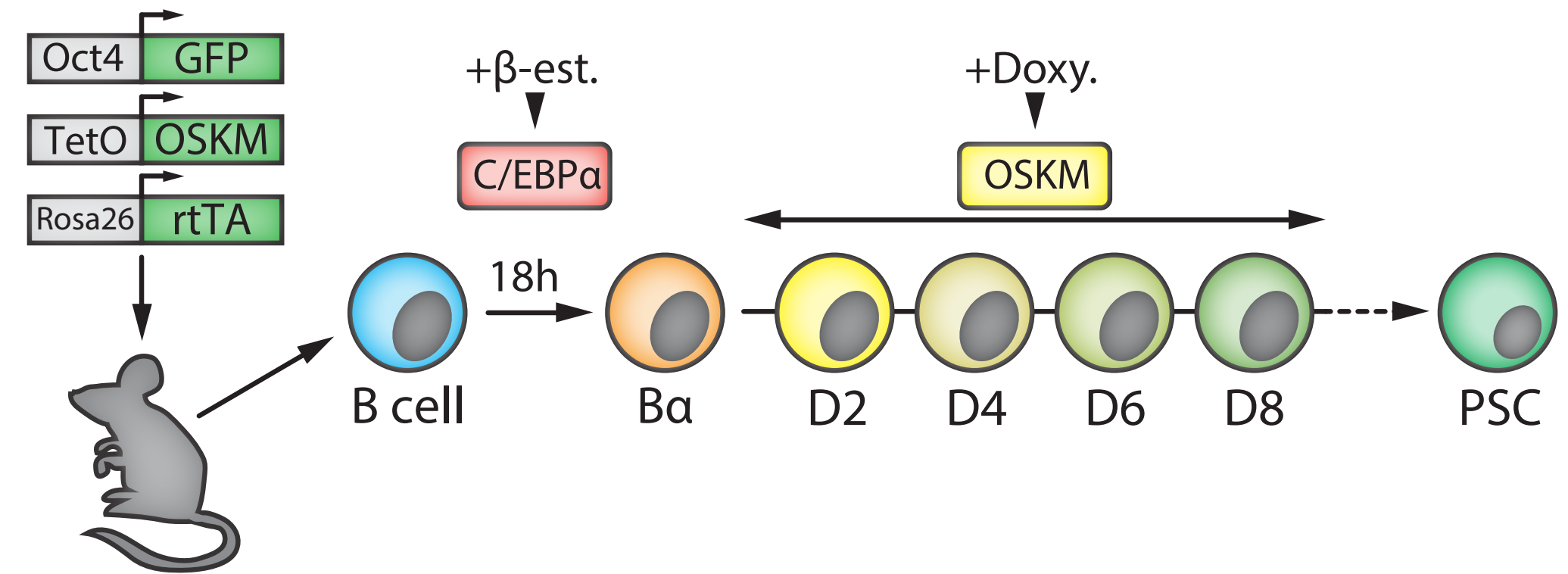
Normal 'forward' differentiation

Cell fates can be converted by enforced TF expression

Transdifferentiation or reprogramming

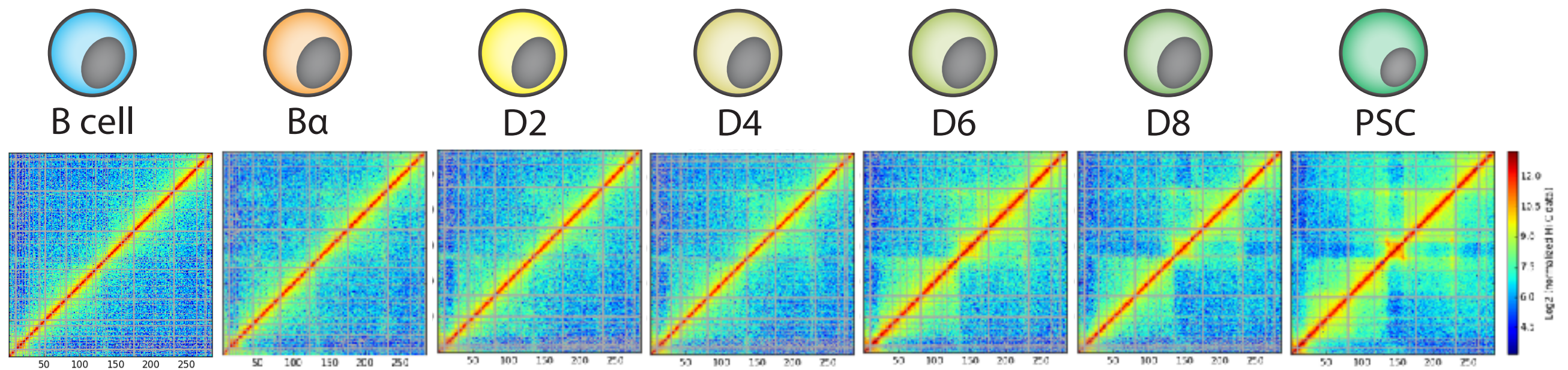
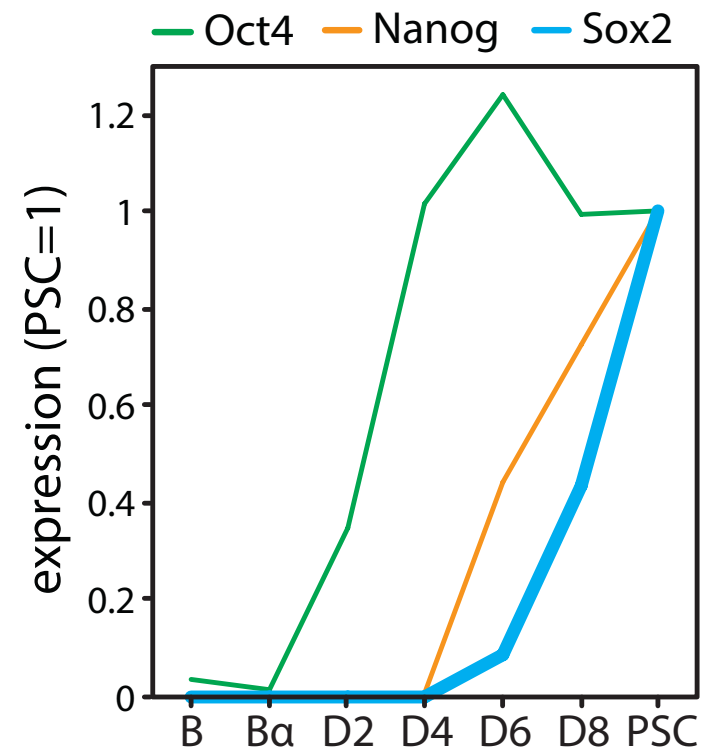
Reprogramming from B to PSC

Stadhouders, R., Vidal, E. et al. (2017) Nature Genetics, in press.



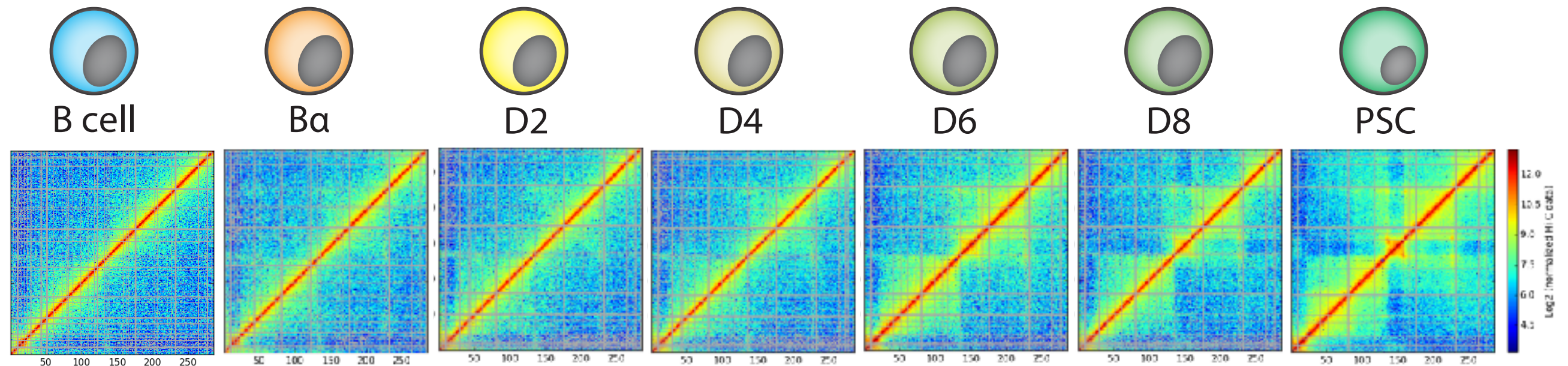
Hi-C maps of reprogramming from B to PSC

The SOX2 locus



Hi-C maps of reprogramming from B to PSC

The SOX2 locus

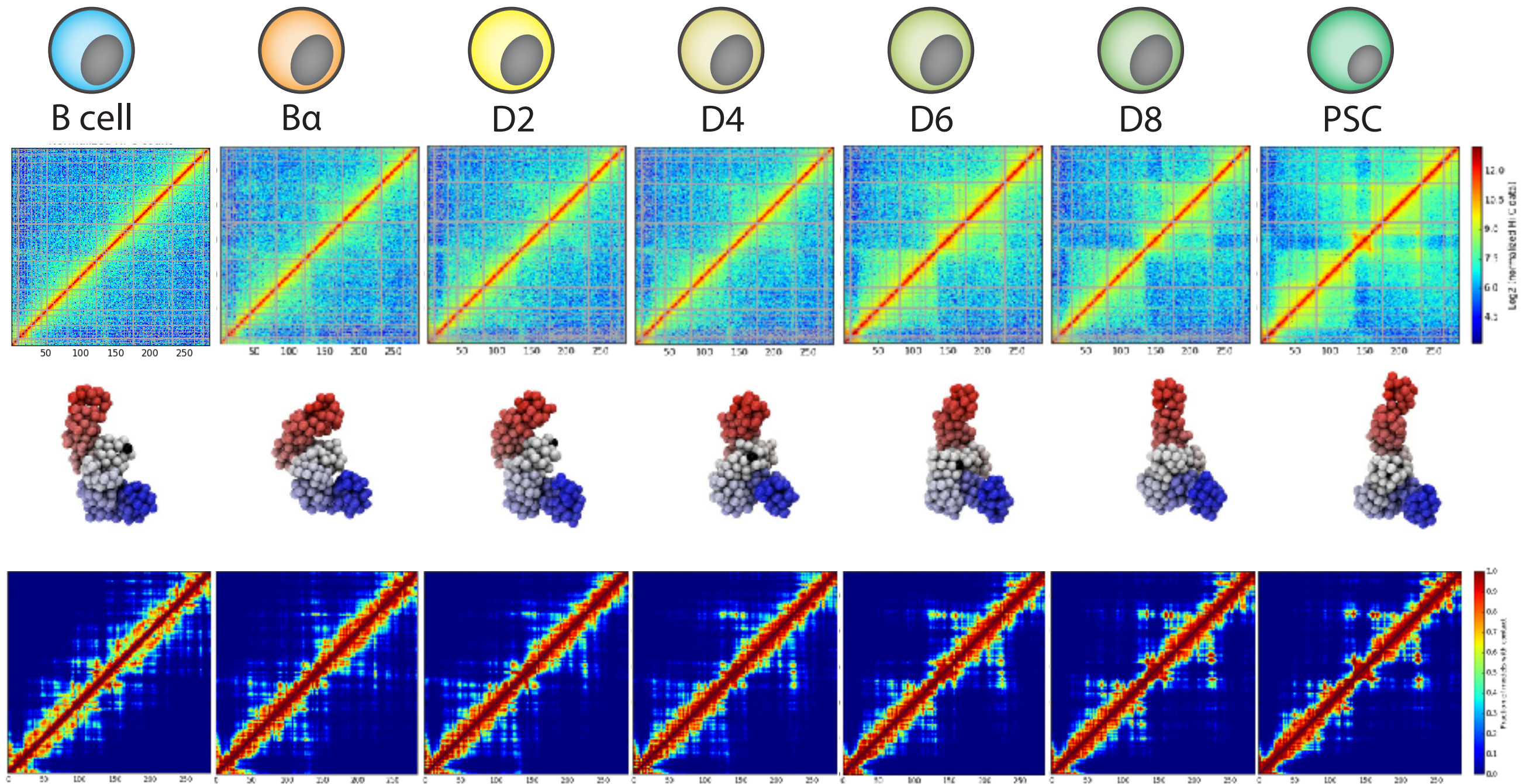


How does these structural rearrangements interplay with the transcription activity?

What are the main drivers of structural transitions?

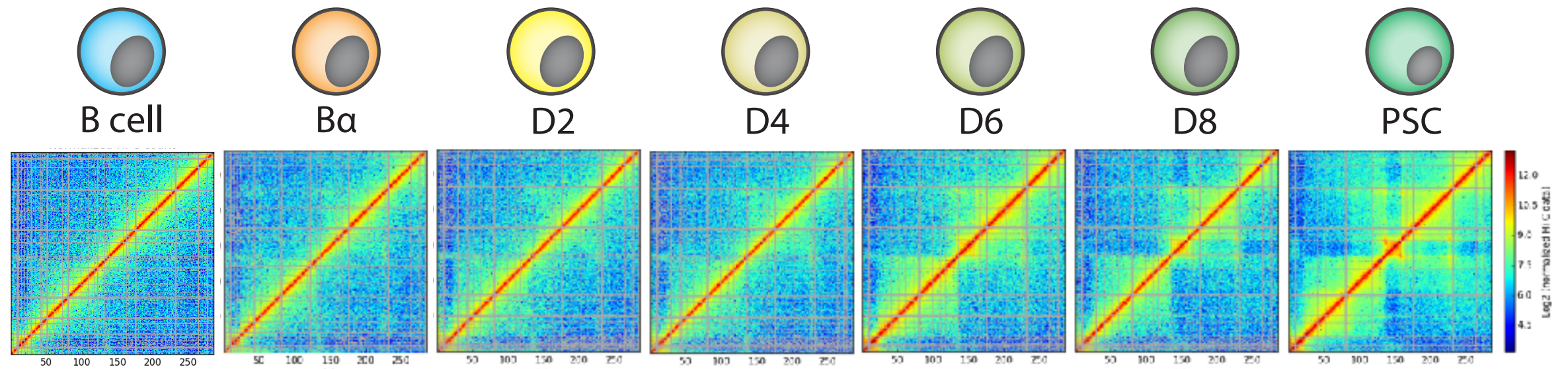
Models of reprogramming from B to PSC

The SOX2 locus



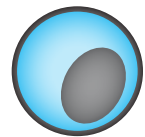
TADdyn: from time-series Hi-C maps to dynamic restraints

The SOX2 locus

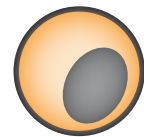


TADdyn: from time-series Hi-C maps to dynamic restraints

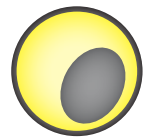
The SOX2 locus



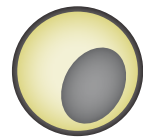
B cell



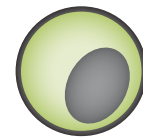
Bα



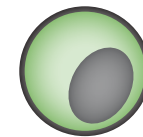
D2



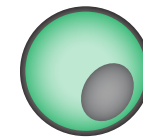
D4



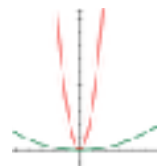
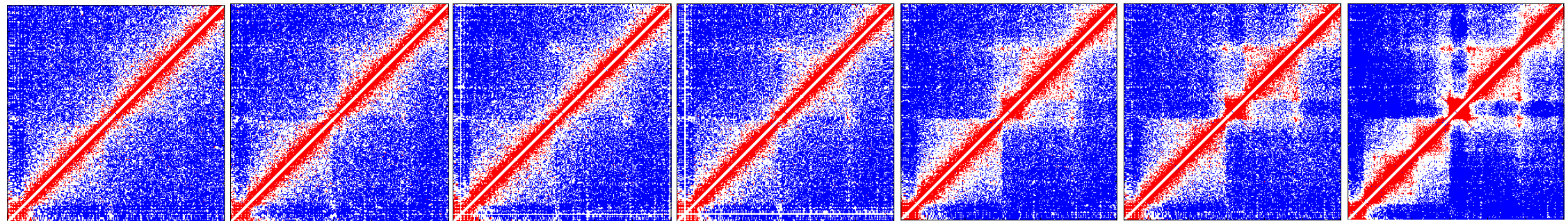
D6



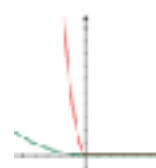
D8



PSC



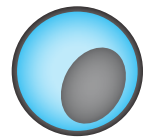
Harmonic



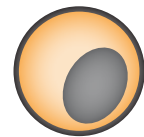
HarmonicLowerBound

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

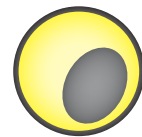
The SOX2 locus



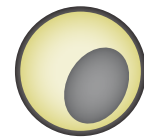
B cell



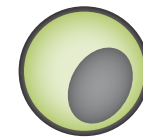
B α



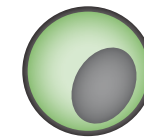
D2



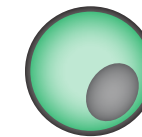
D4



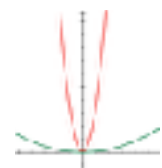
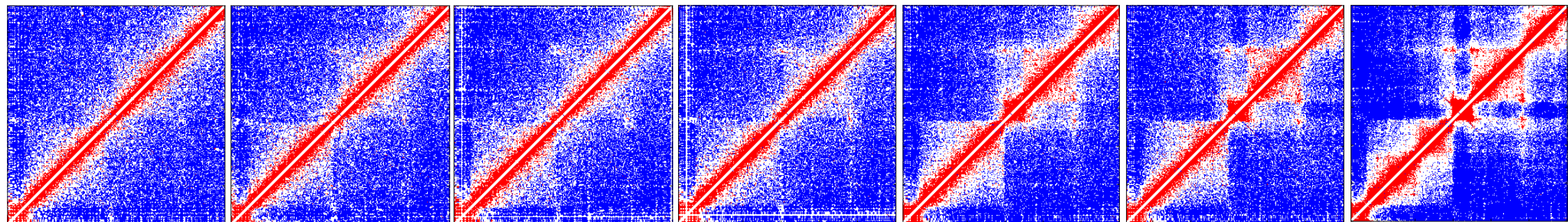
D6



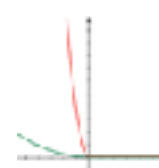
D8



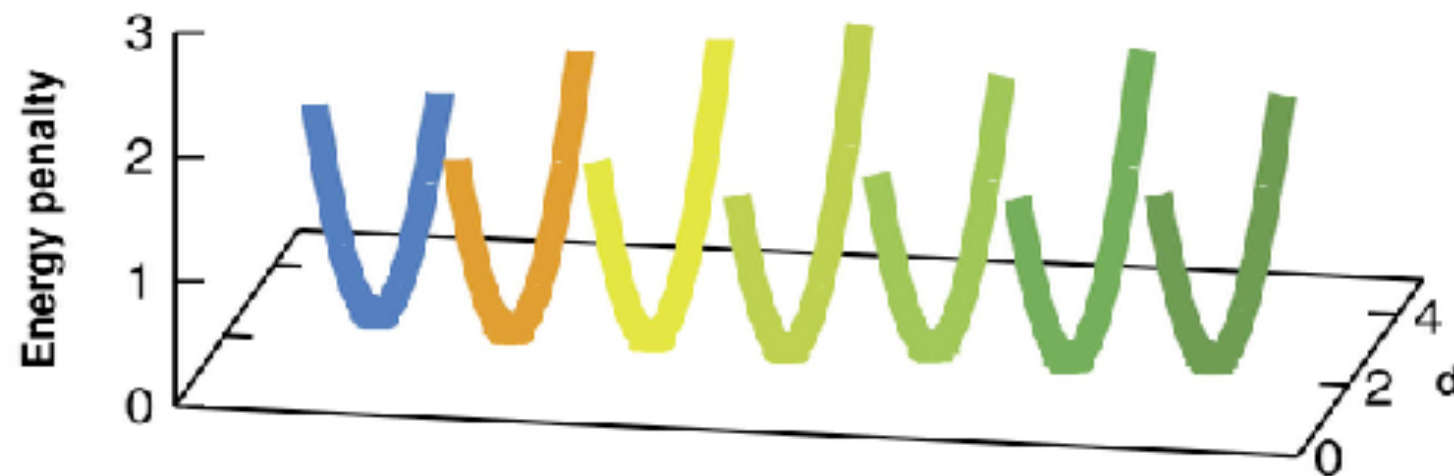
PSC



■ Harmonic



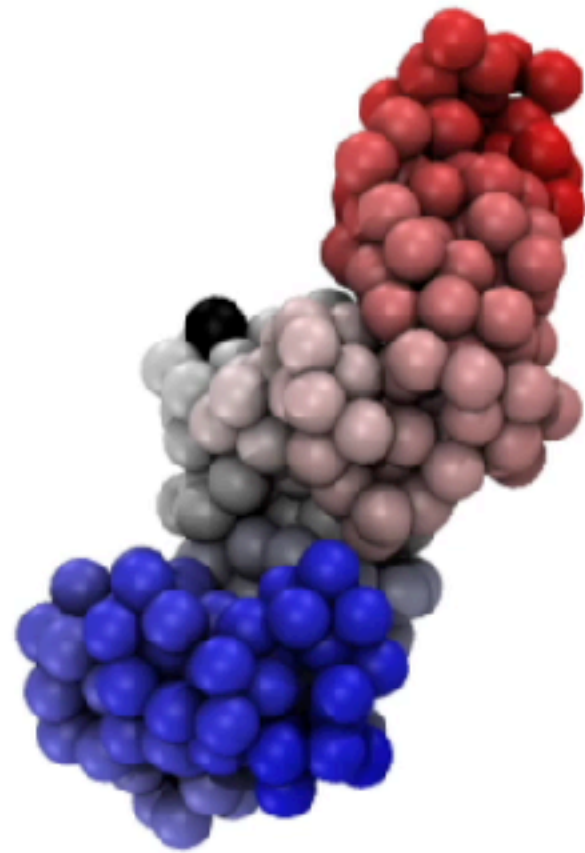
■ HarmonicLowerBound



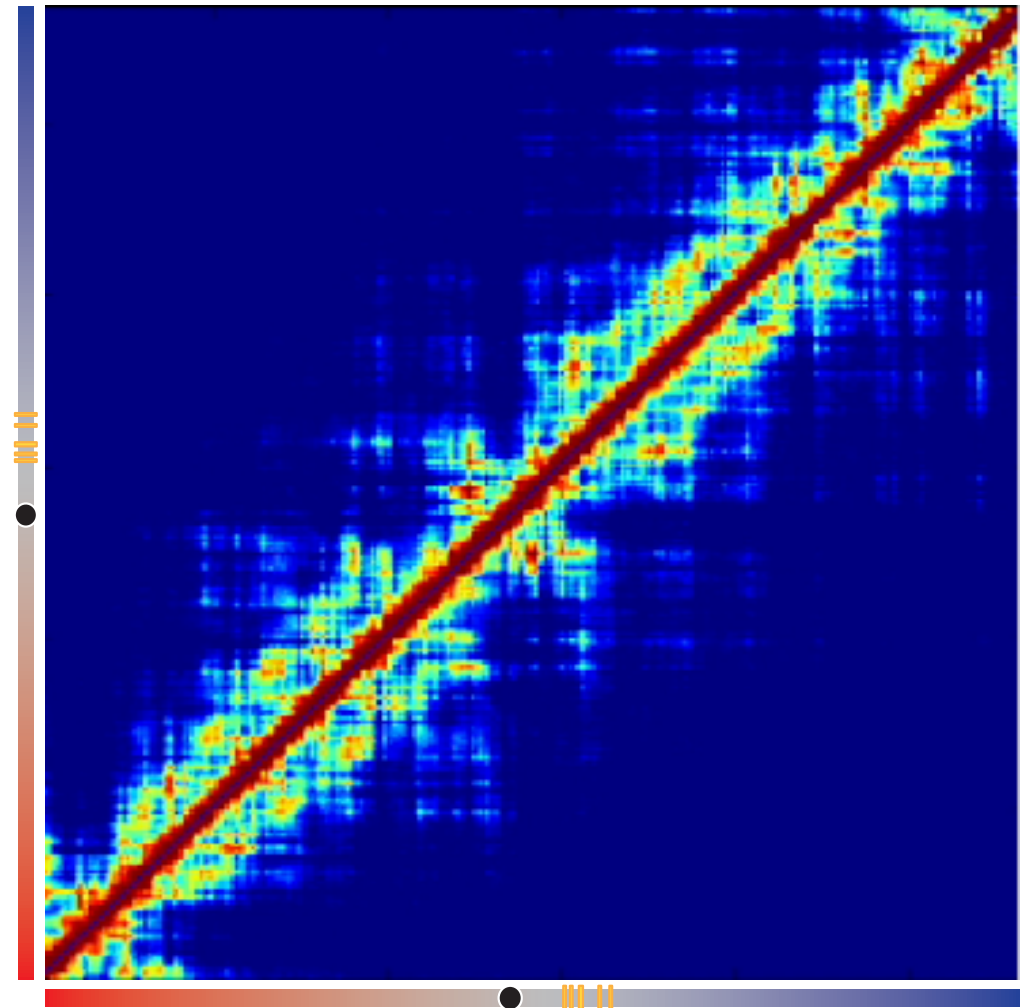
Transition	Stable	Vanishing	Raising
B → B α	18,612	6,984	7,290
B α → D2	18,512	7,390	6,687
D2 → D4	18,369	6,830	6,893
D4 → D6	18,971	6,291	7,289
D6 → D8	20,167	6,093	6,250
D8 → ES	20,679	5,738	6,173

SOX2 locus structural changes from B to PSC

Contacts

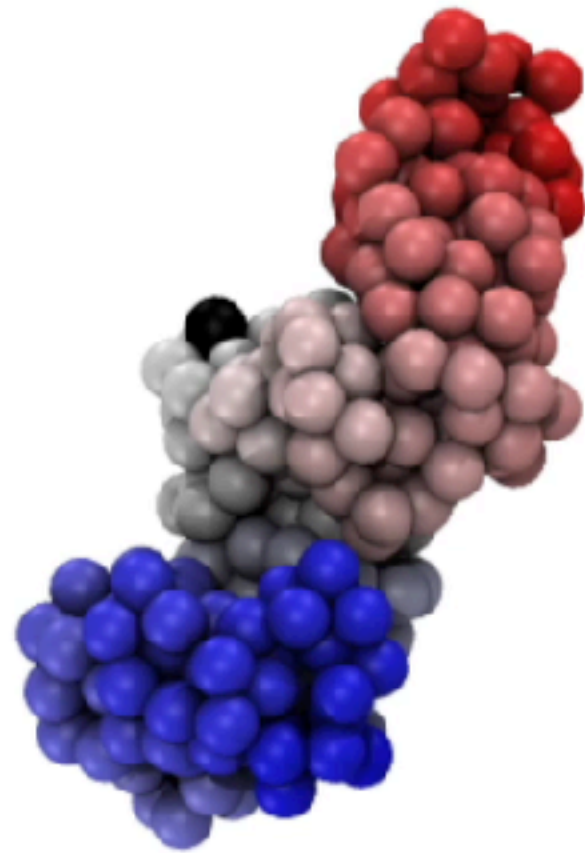


SE
SOX2

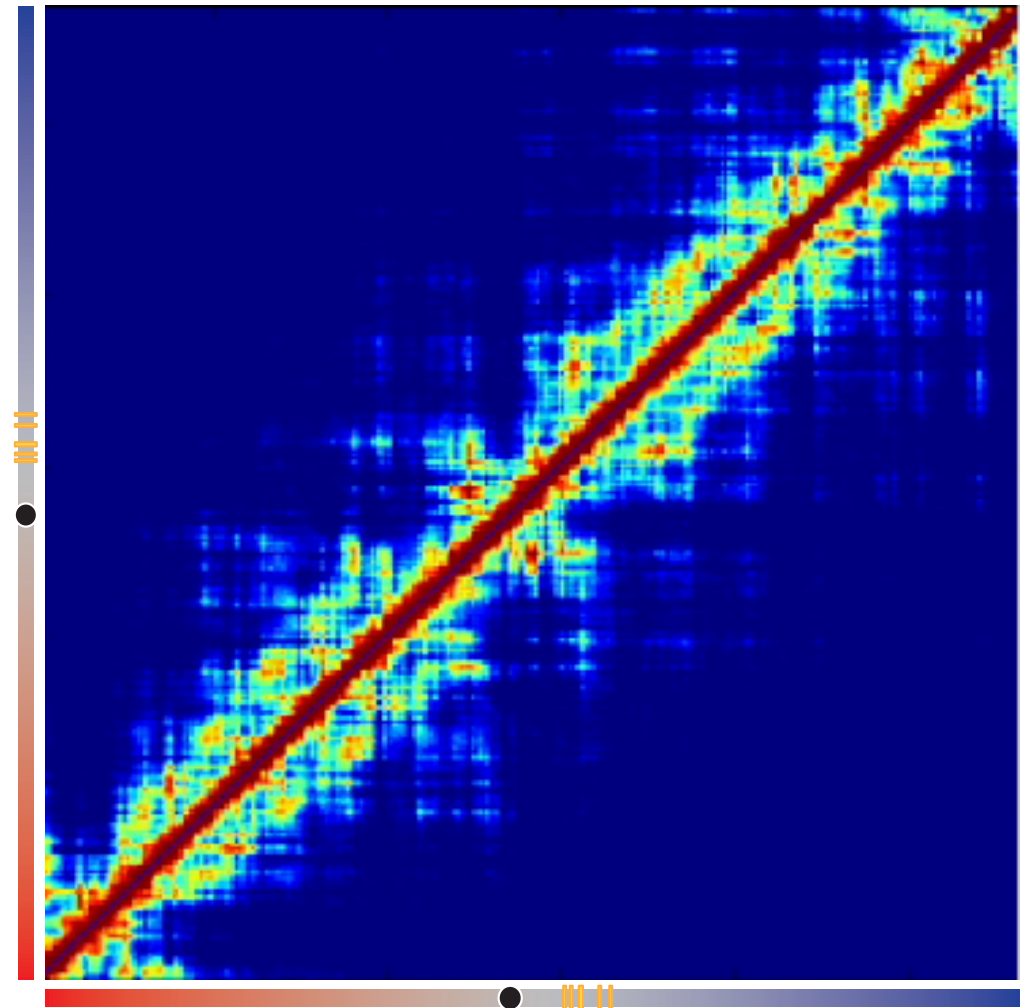


SOX2 locus structural changes from B to PSC

Contacts

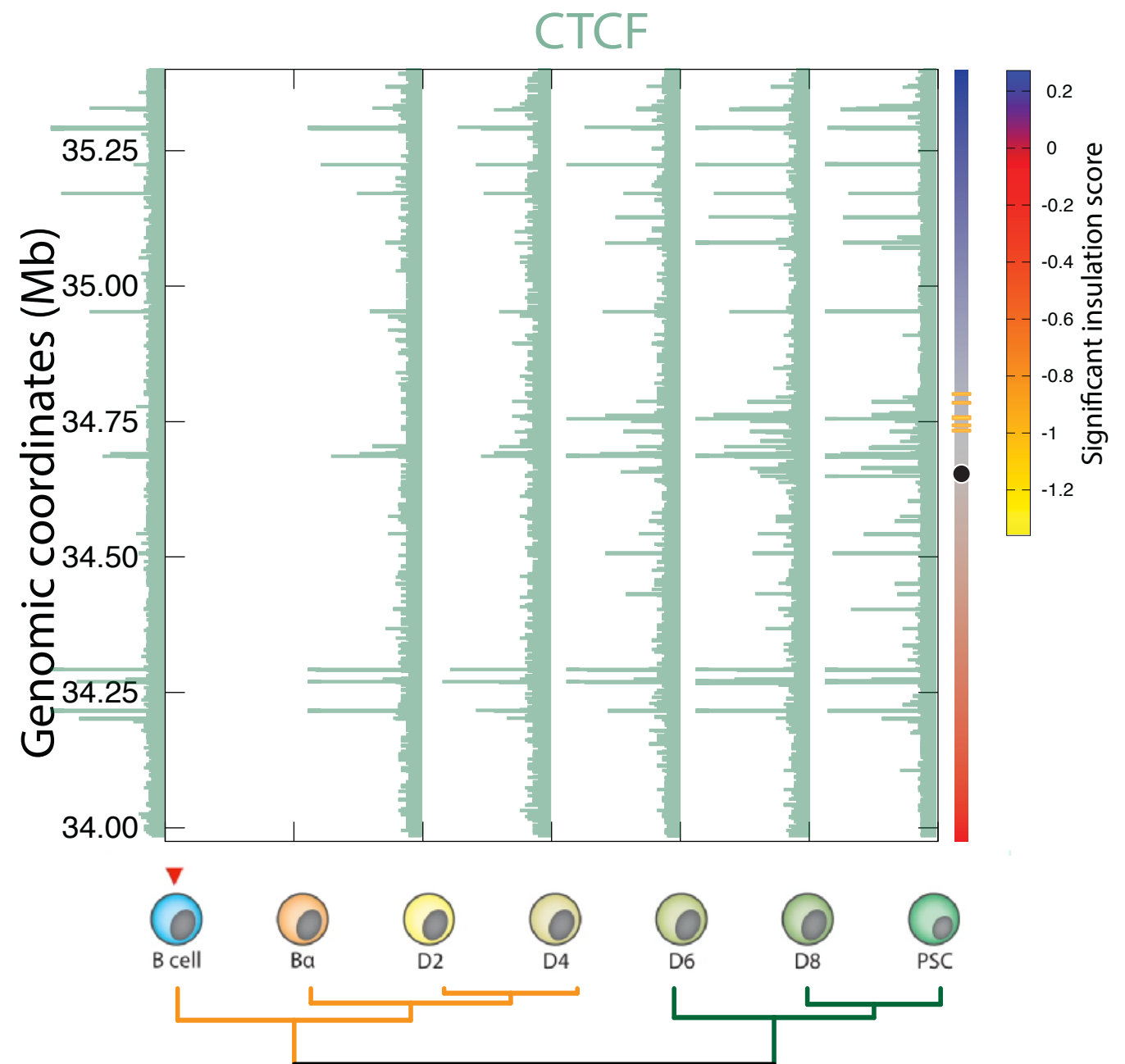
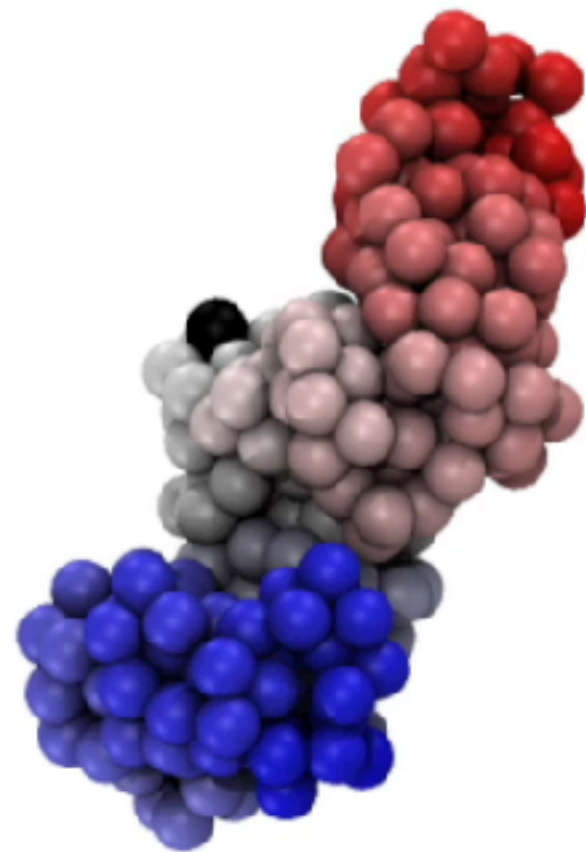


SE
SOX2



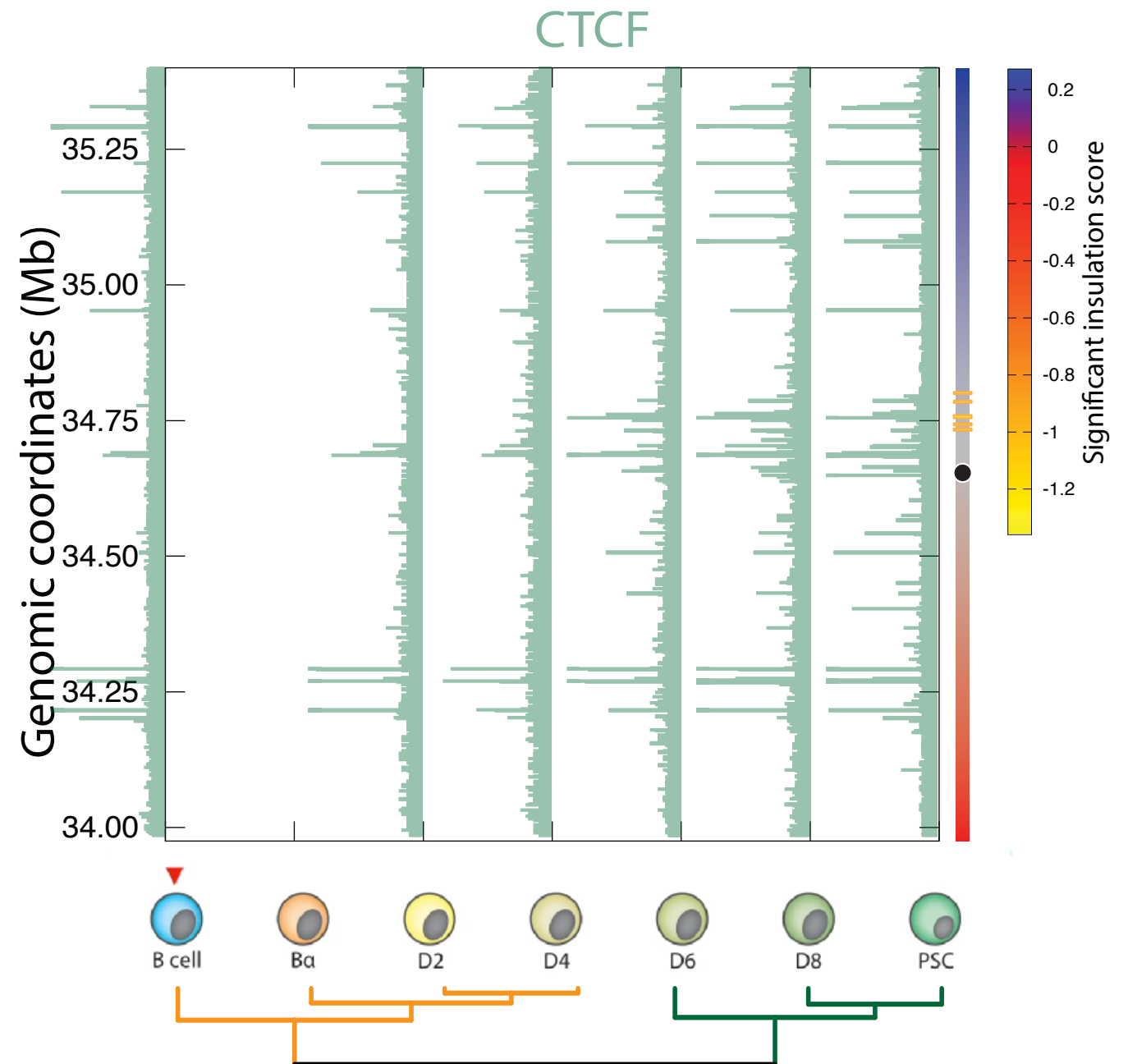
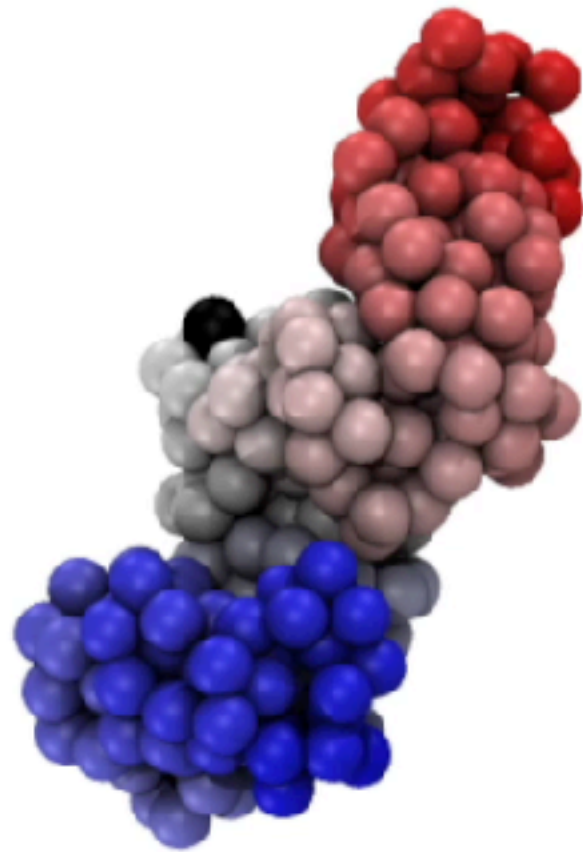
SOX2 locus structural changes from B to PSC

TAD borders



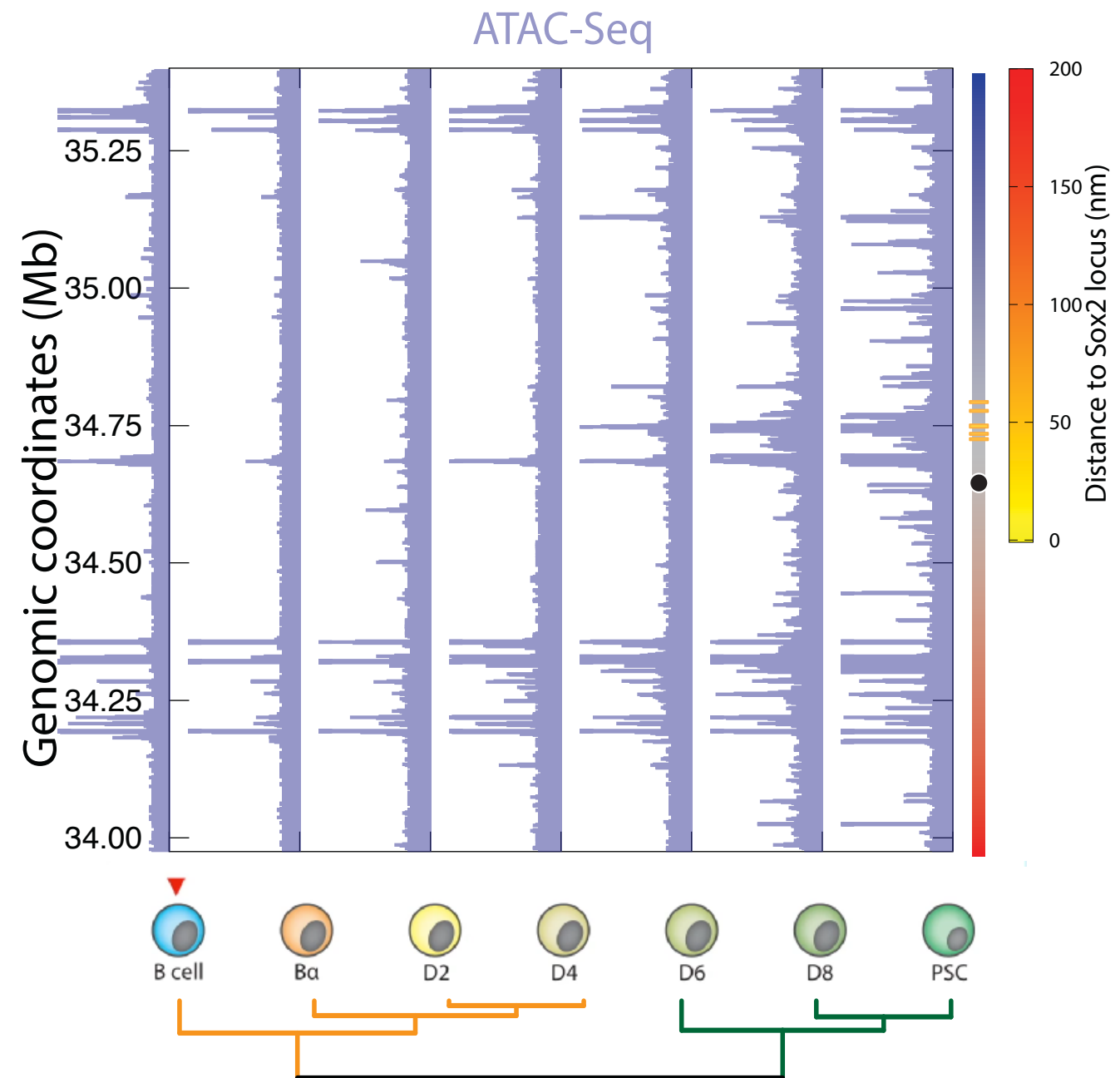
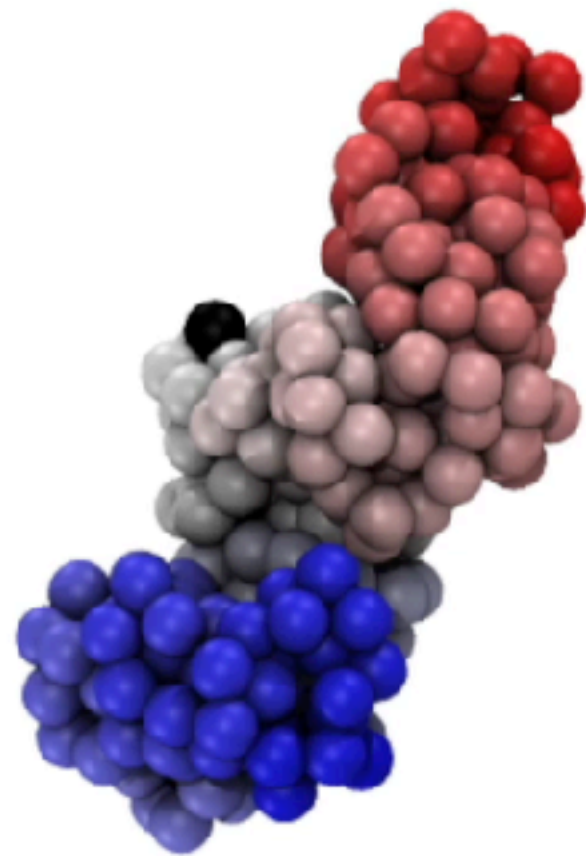
SOX2 locus structural changes from B to PSC

TAD borders



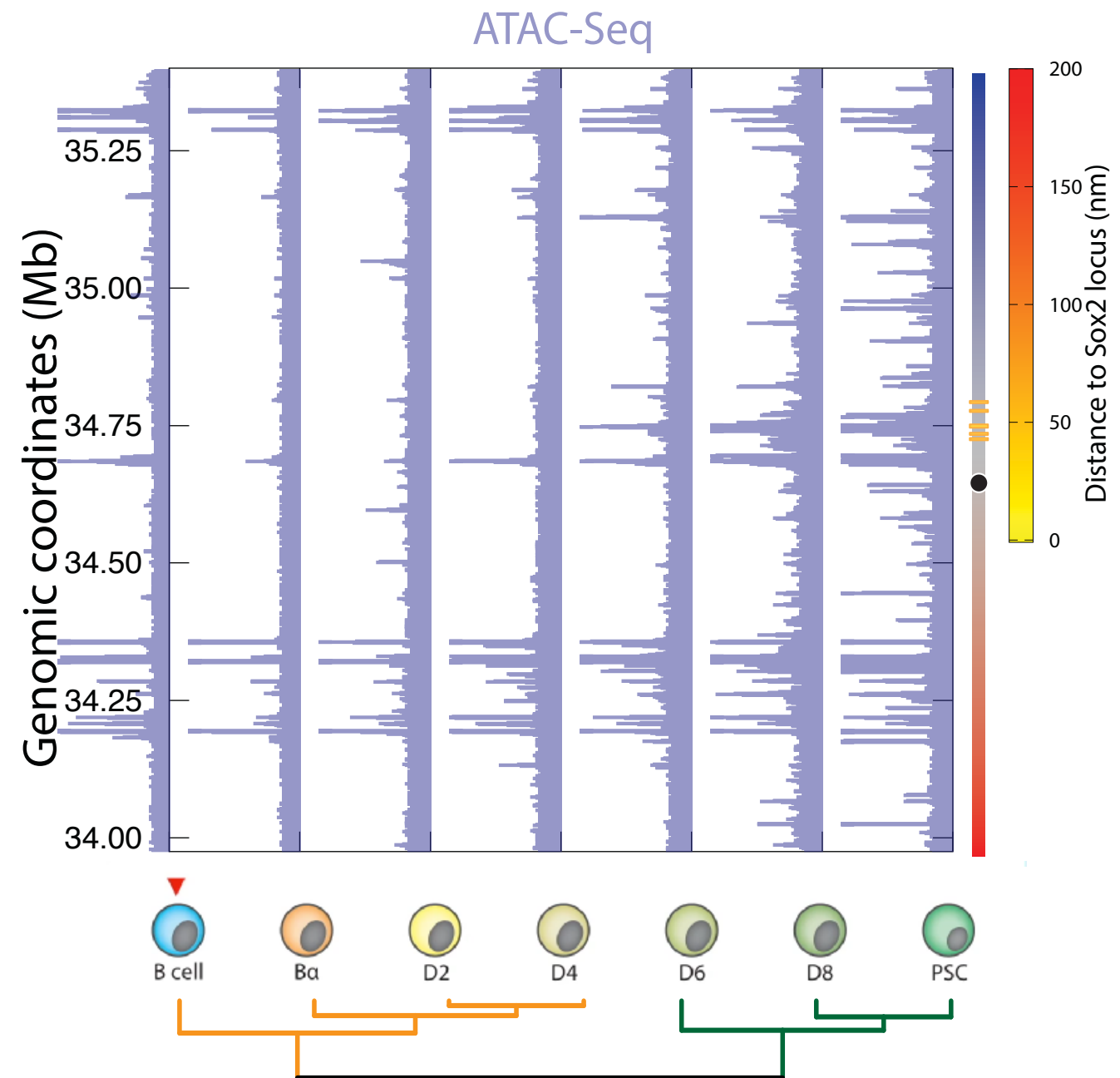
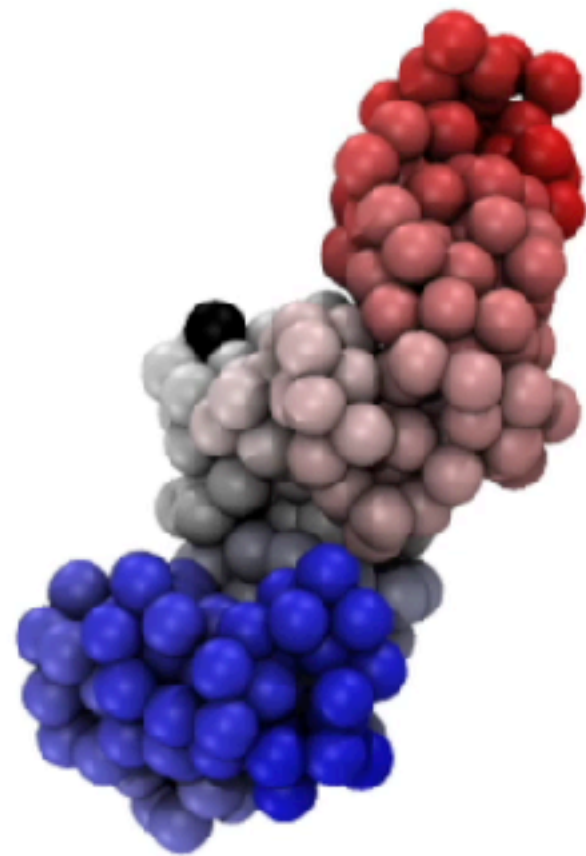
SOX2 locus structural changes from B to PSC

Distance to regulatory elements



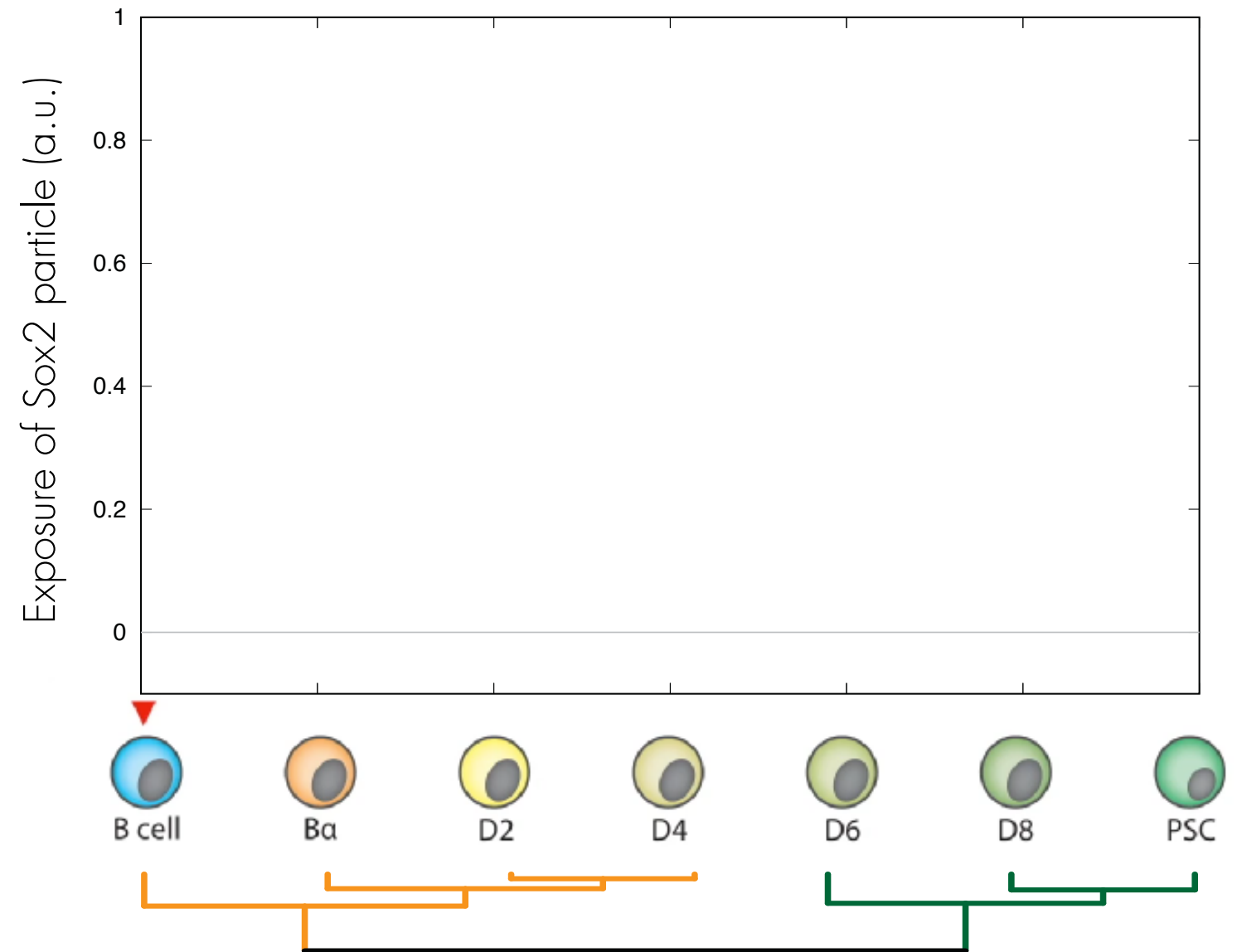
SOX2 locus structural changes from B to PSC

Distance to regulatory elements



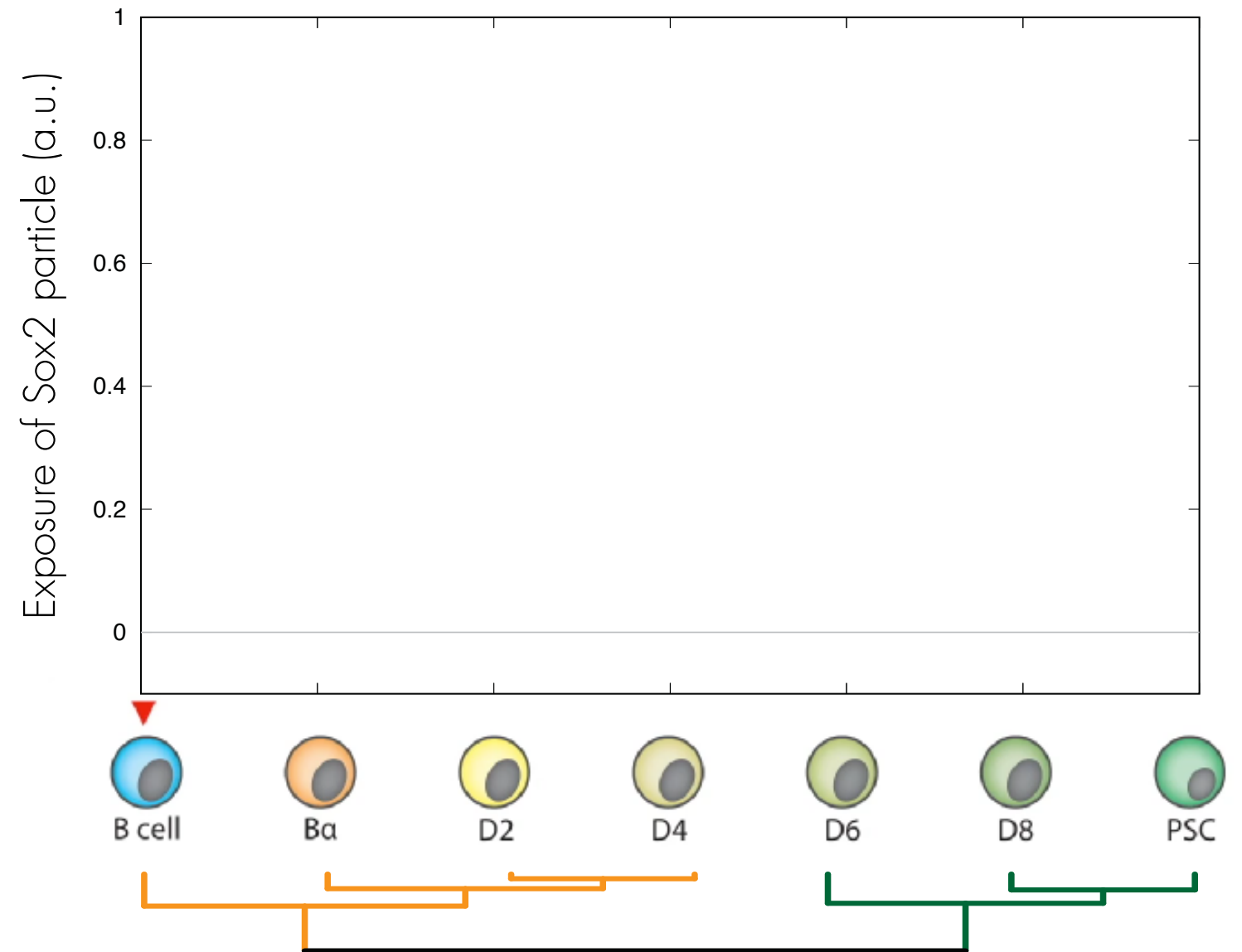
SOX2 locus structural changes from B to PSC

Structural exposure



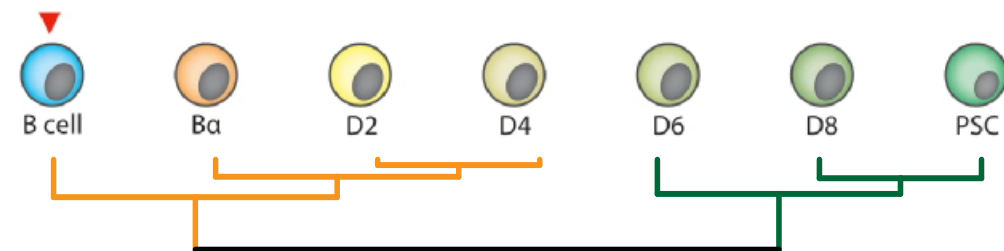
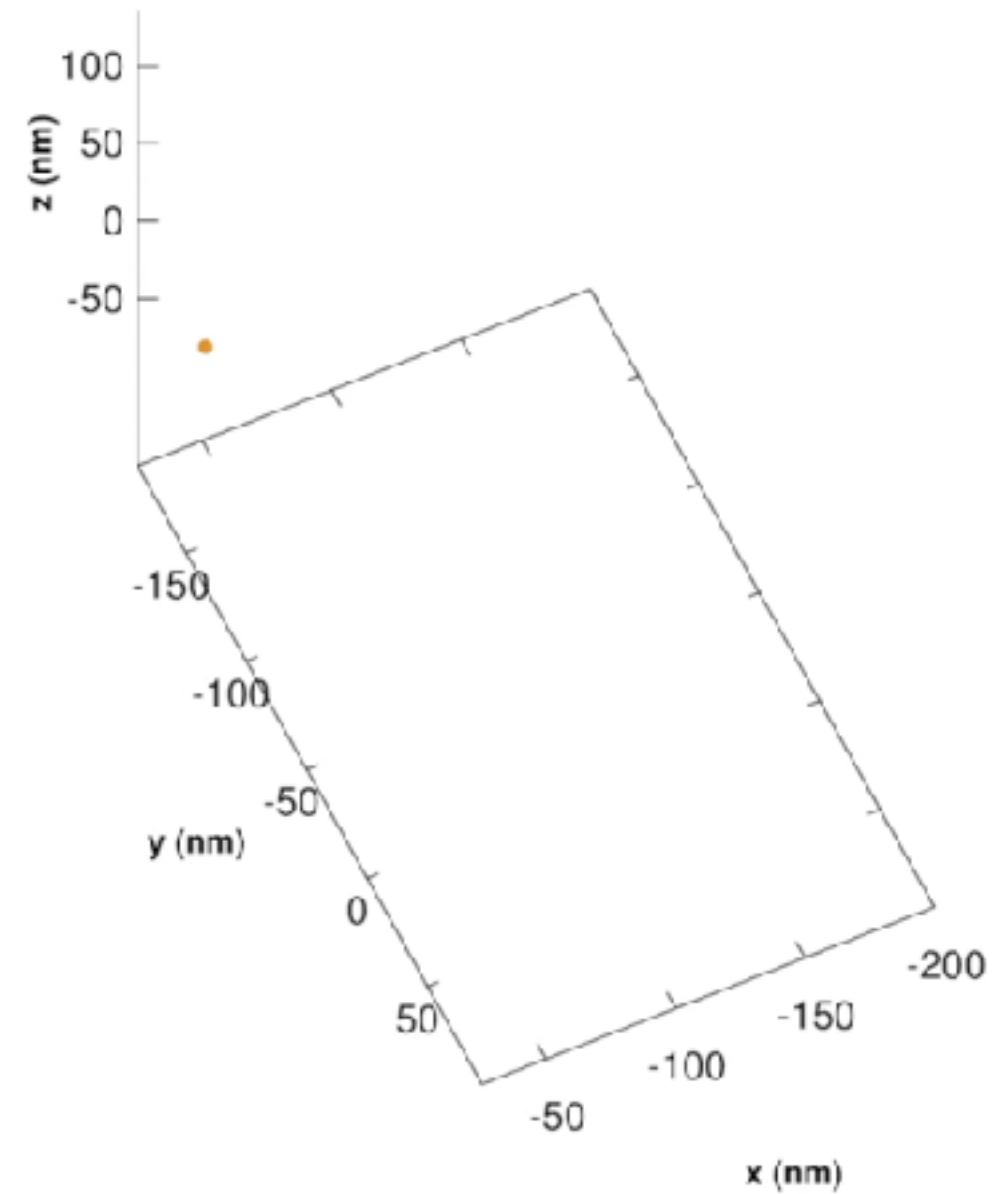
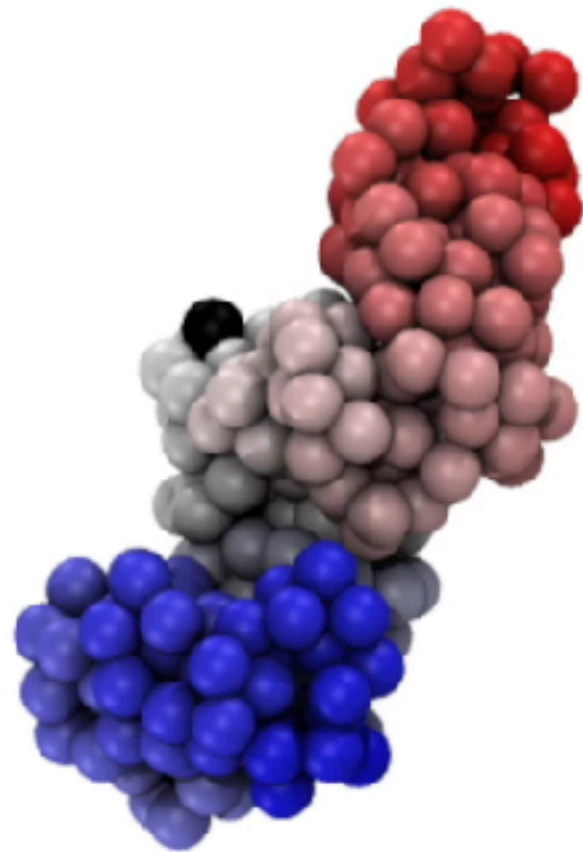
SOX2 locus structural changes from B to PSC

Structural exposure



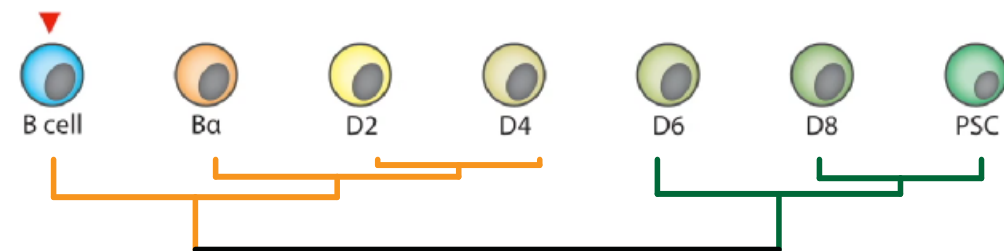
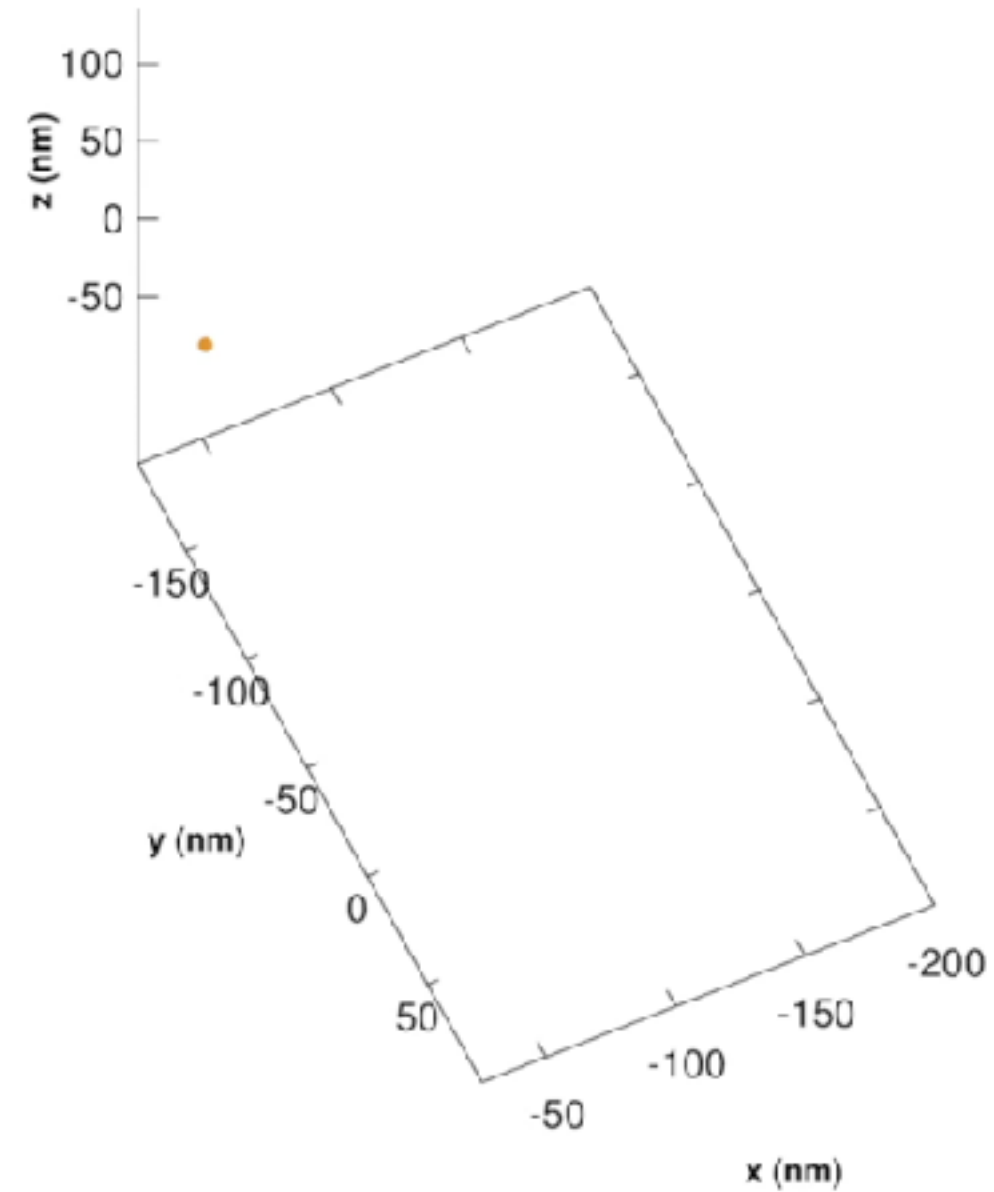
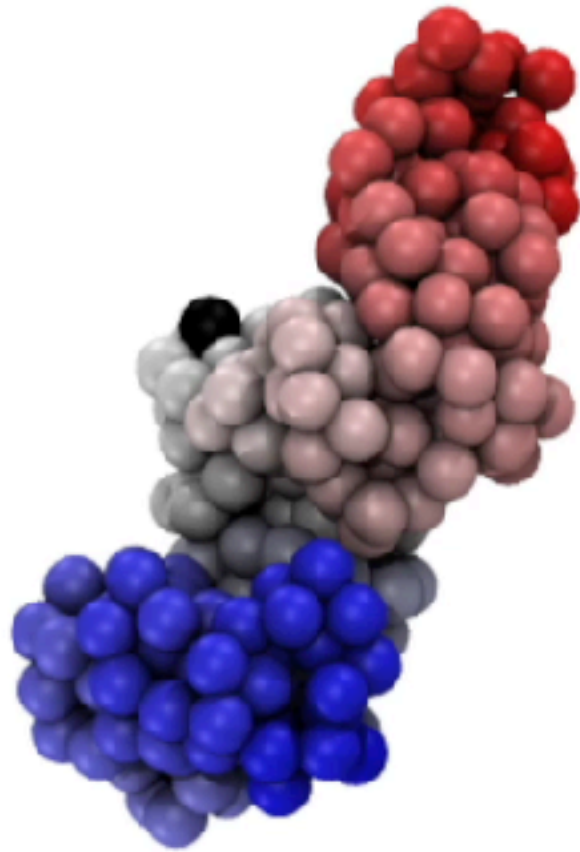
SOX2 locus dynamics changes from B to PSC

SOX2 displacement



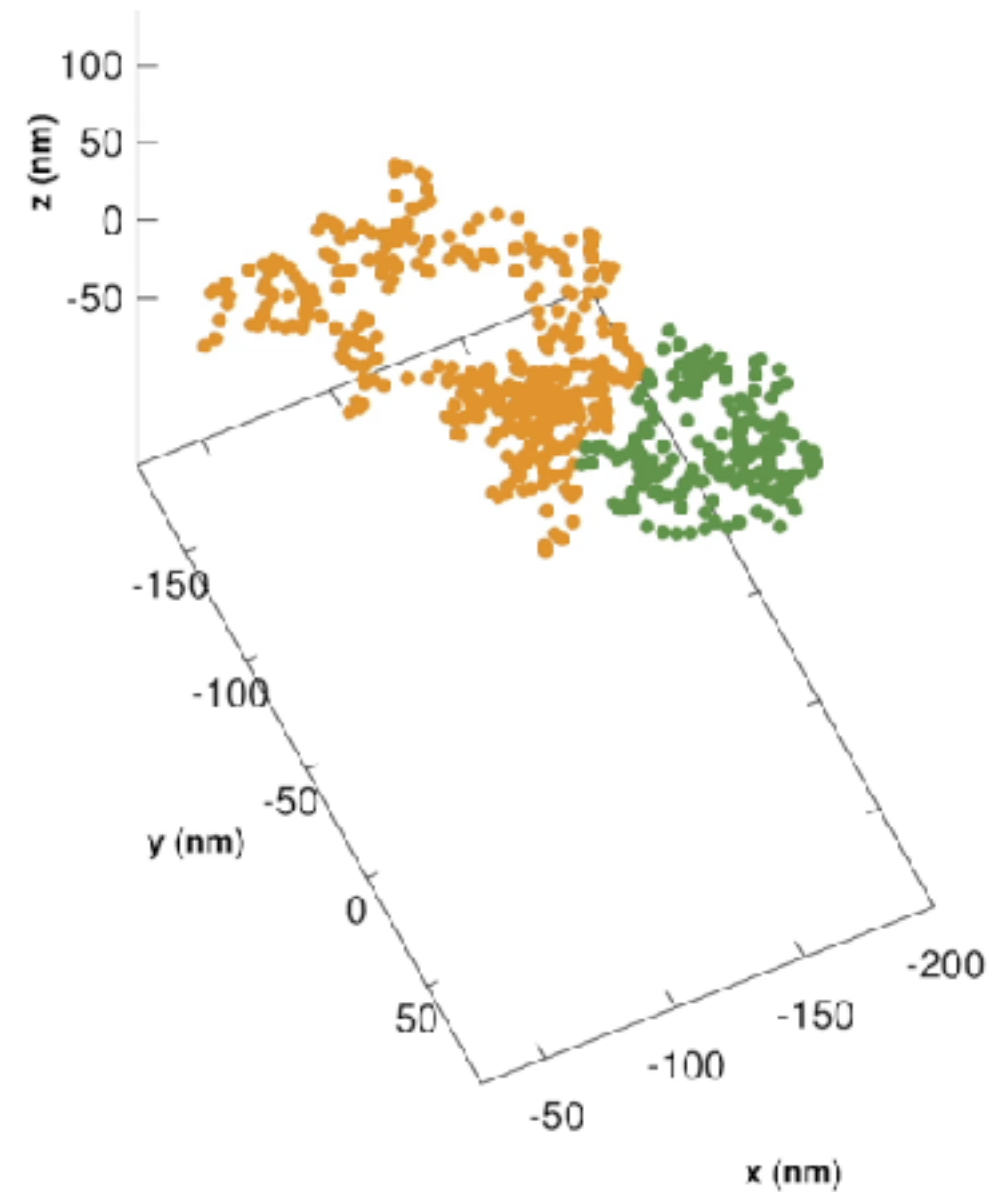
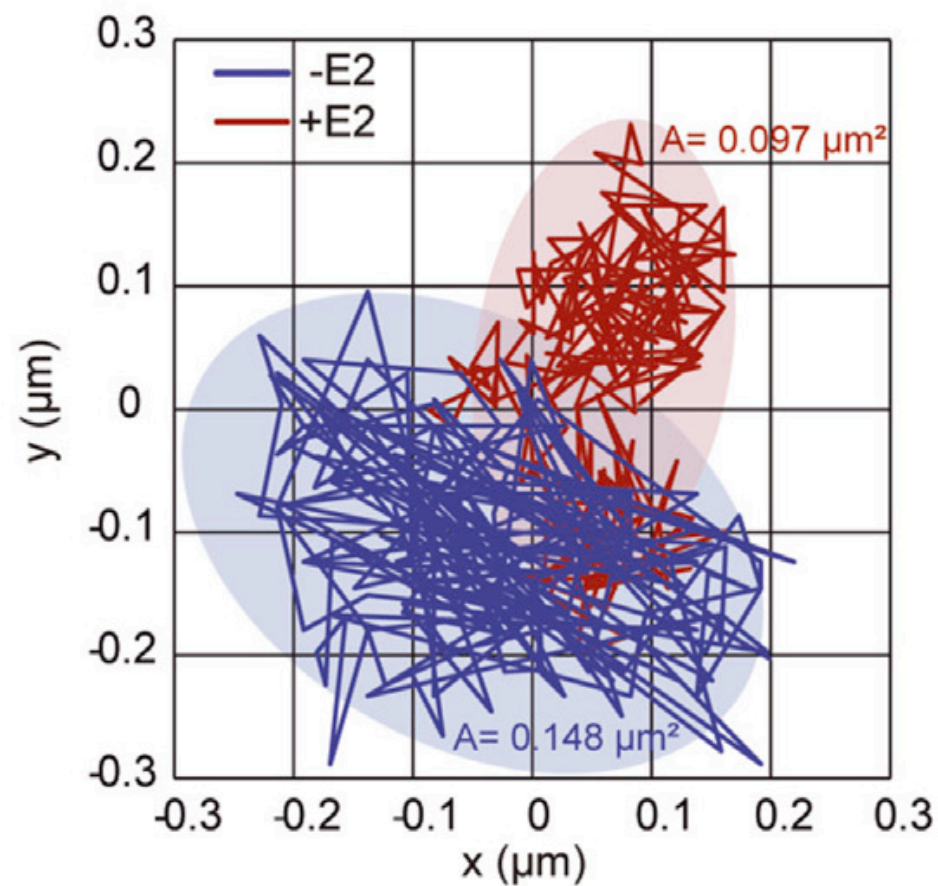
SOX2 locus dynamics changes from B to PSC

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

The Sox2 transcriptional activation is preceded by major structural rearrangements involving the formation of a small “cage” domain.



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

cnag

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Centre for Genomic Regulation

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