

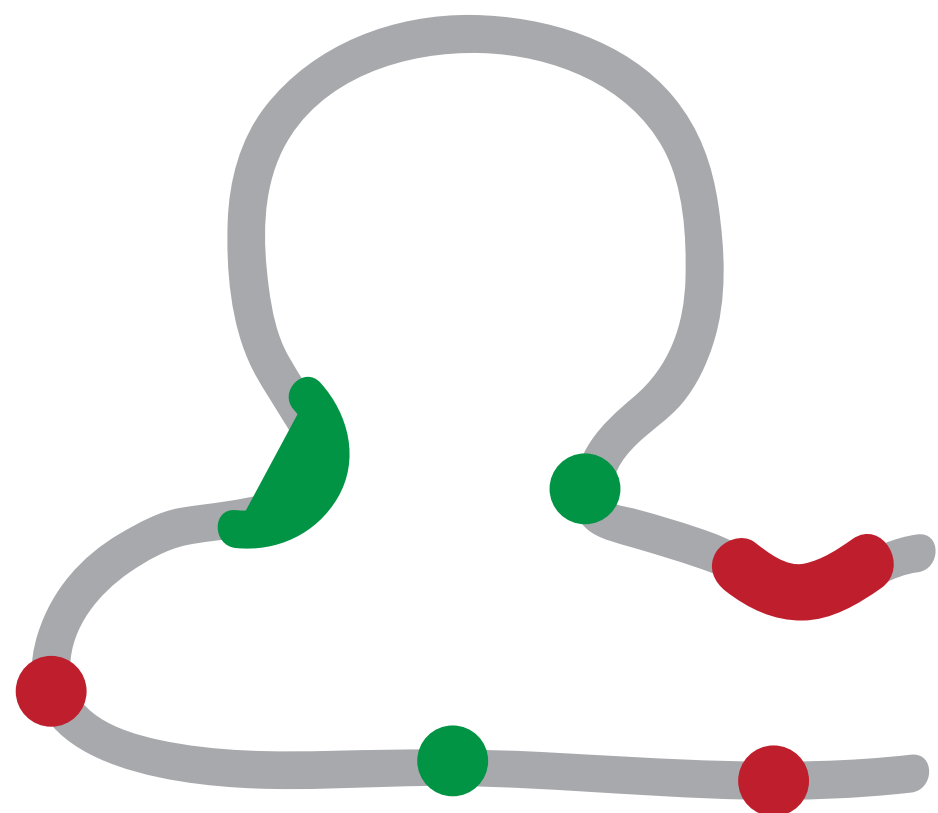
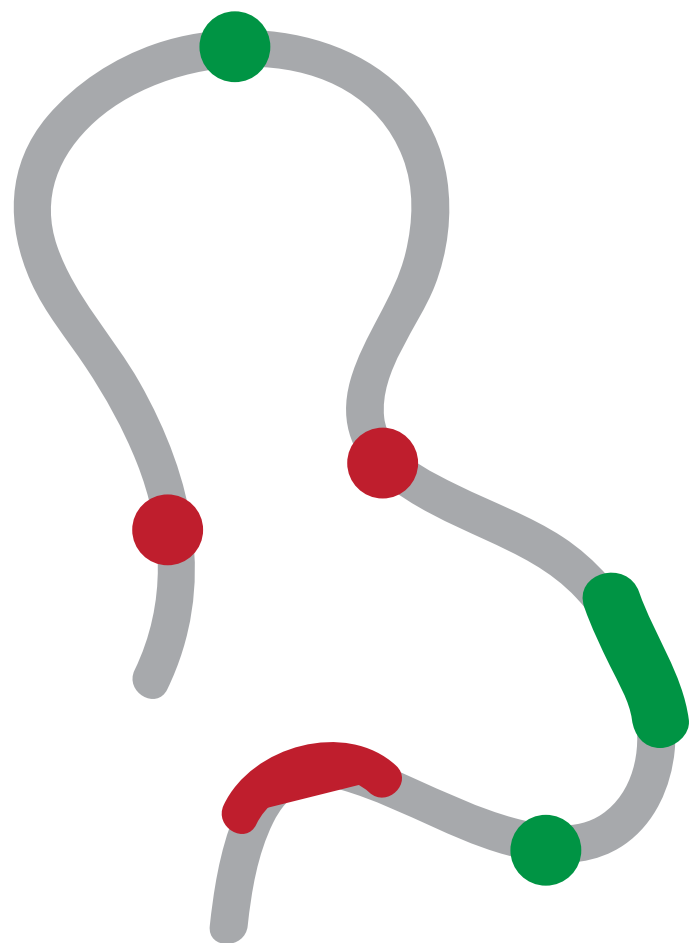
Exploring the time dependent structural rearrangements of SOX2 locus during transdifferentiation

Marc A. Marti-Renom

Structural Genomics Group (ICREA, CNAG-CRG)

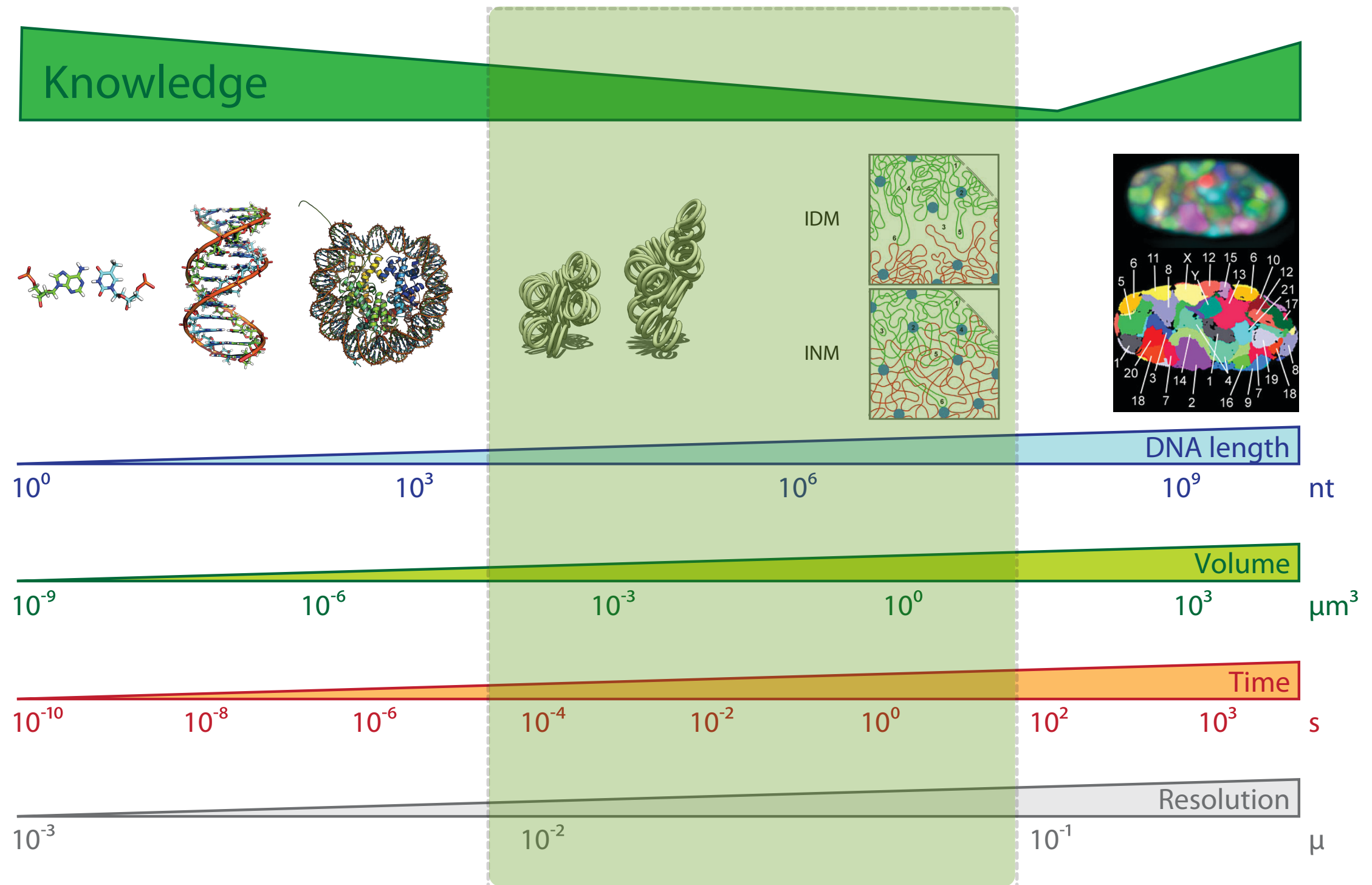
<http://marciuslab.org>
<http://3DGenomes.org>
<http://cnag.crg.eu>

cnag **CRG**   **ICREA**



Resolution Gap

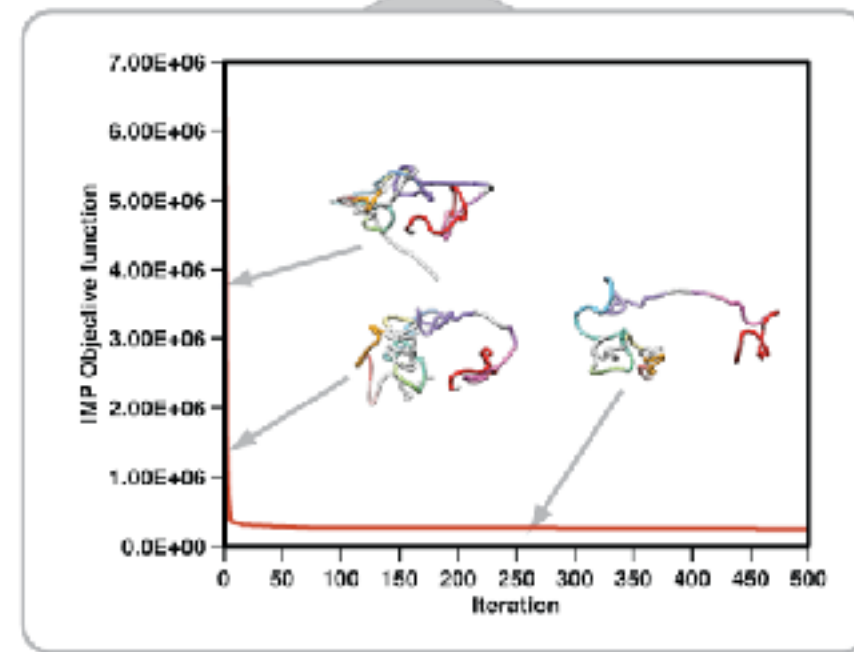
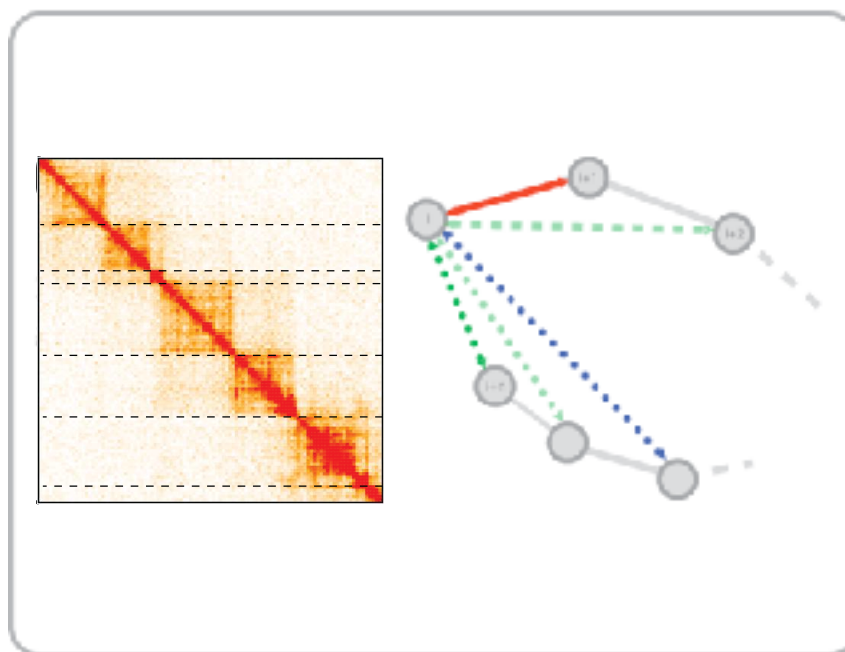
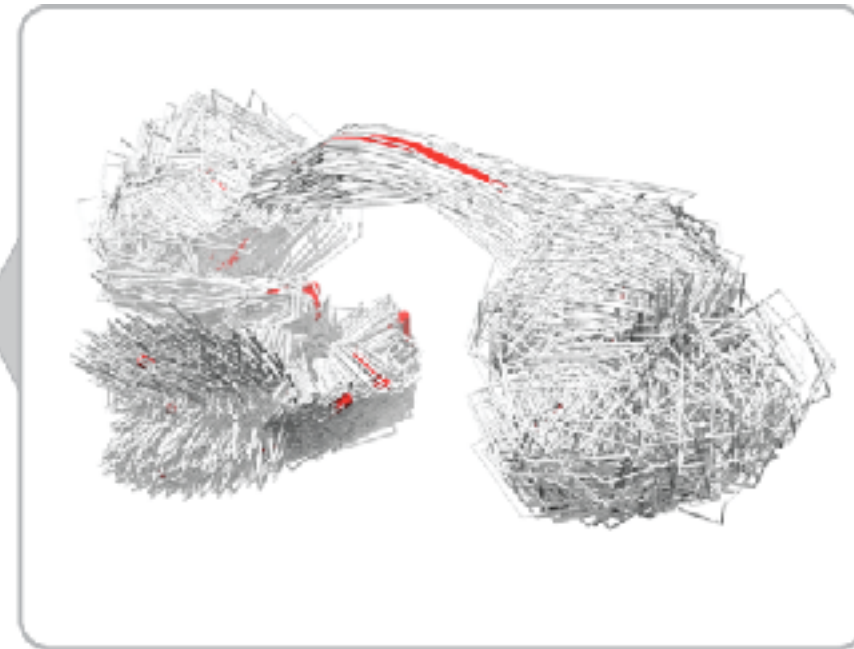
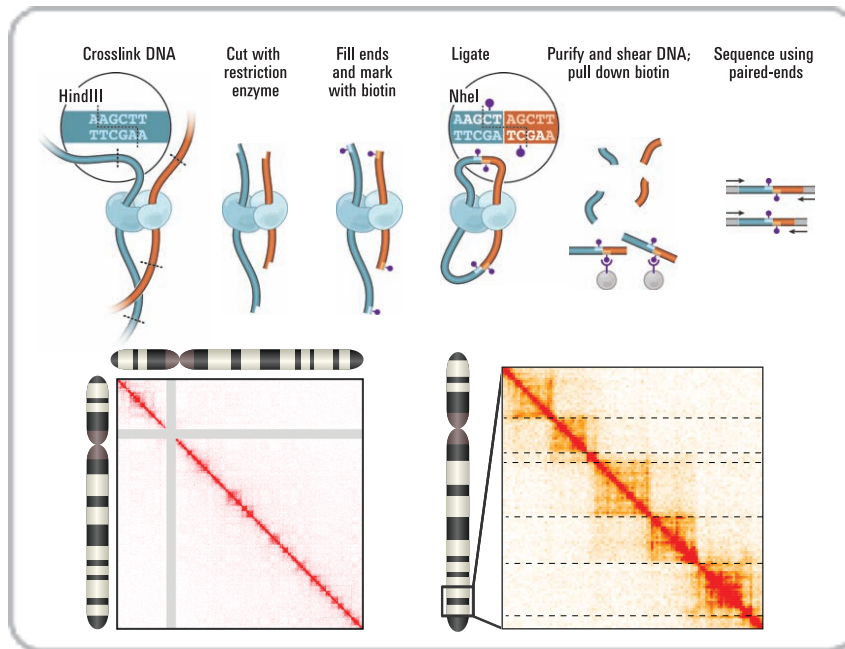
Marti-Renom, M. A. & Mirny, L. A. PLoS Comput Biol 7, e1002125 (2011)



Hybrid Method

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

Experiments

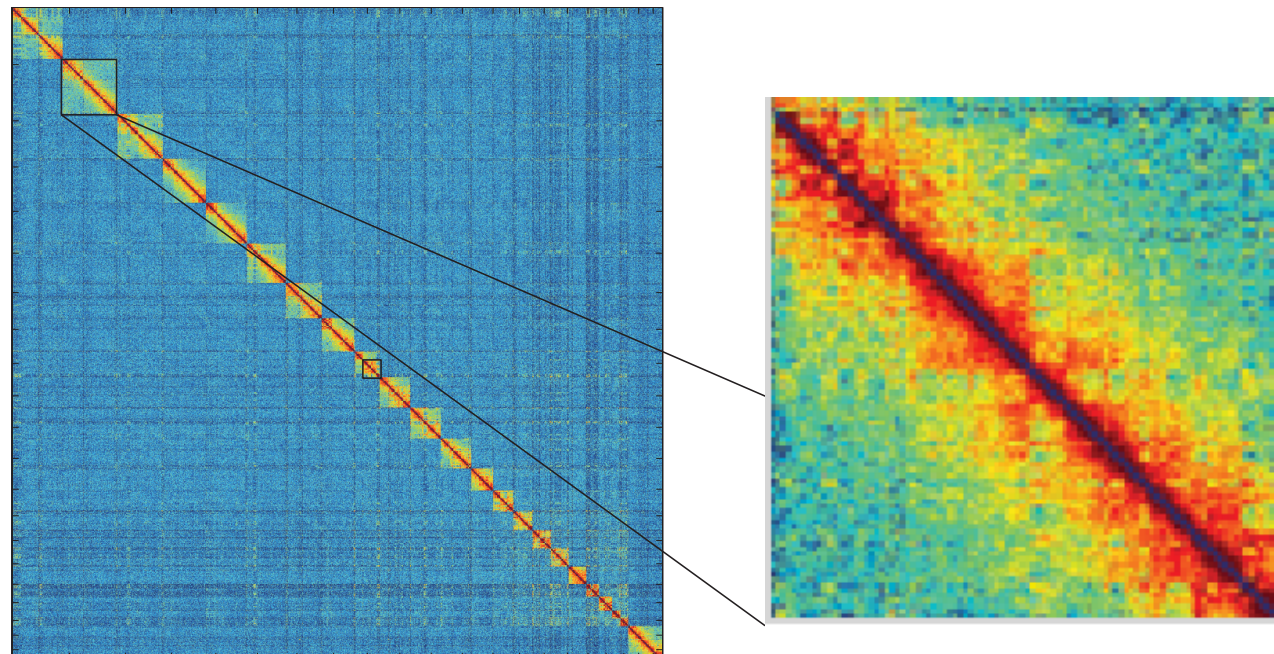
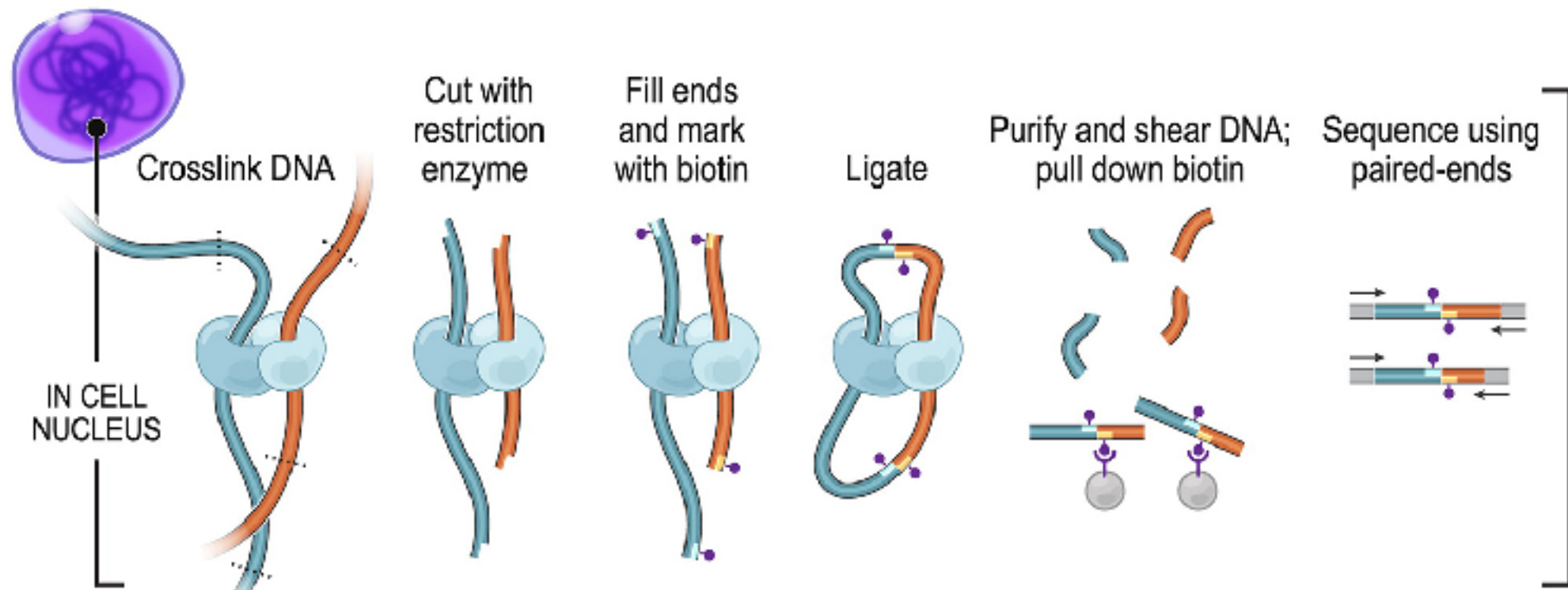


Computation

Chromosome Conformation Capture

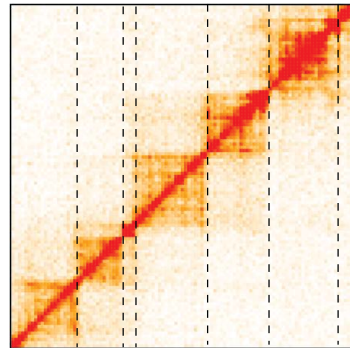
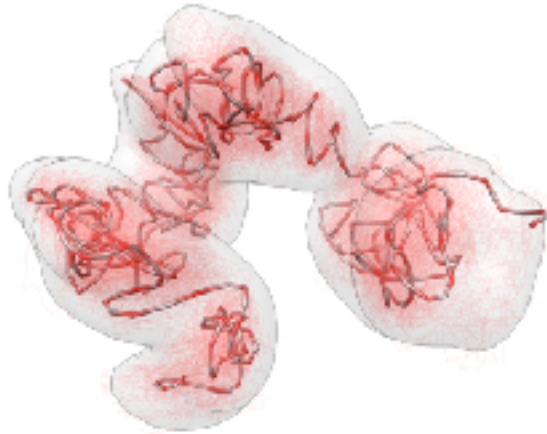
Dekker, J., Rippe, K., Dekker, M., & Kleckner, N. (2002). *Science*, 295(5558), 1306–1311.

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

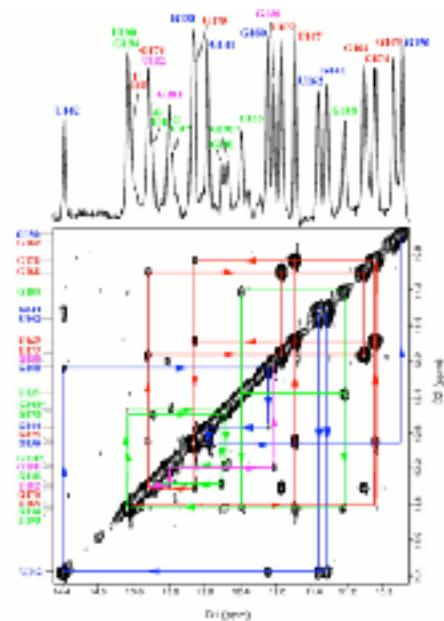
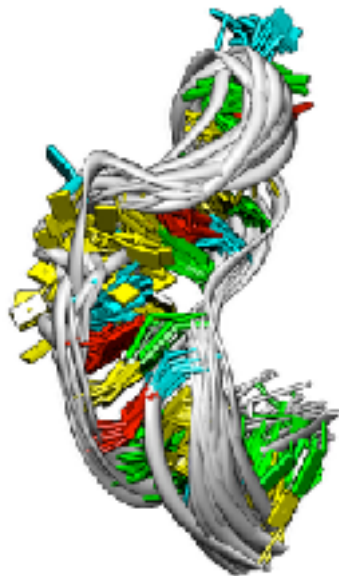


Restraint-based Modeling

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



Chromosome structure determination
3C-based data

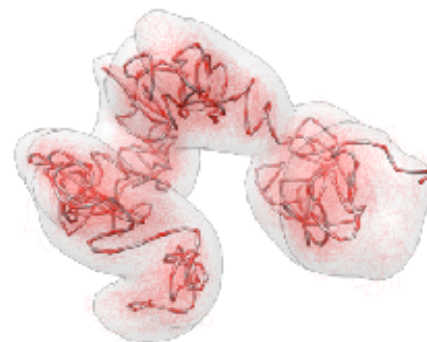
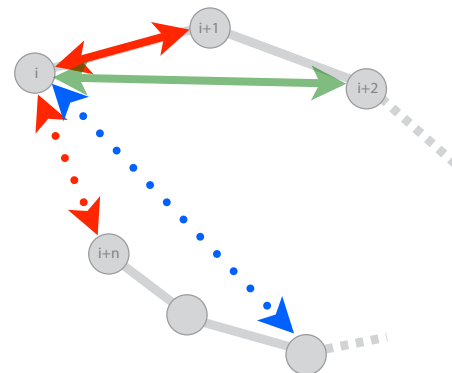
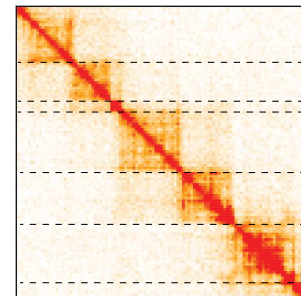
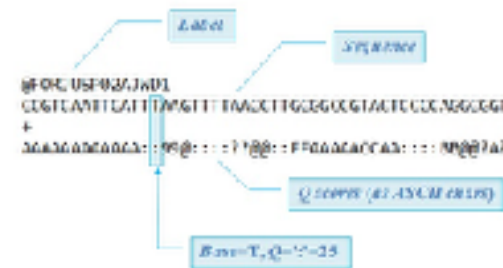


Biomolecular structure determination
2D-NOESY data



<http://3DGenomes.org>

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



FastQ files to Maps

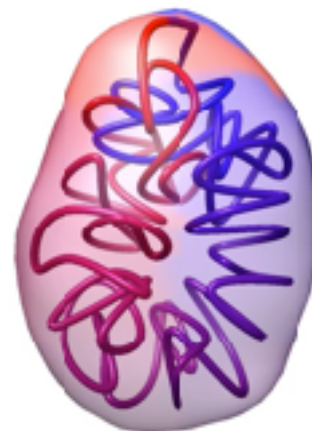
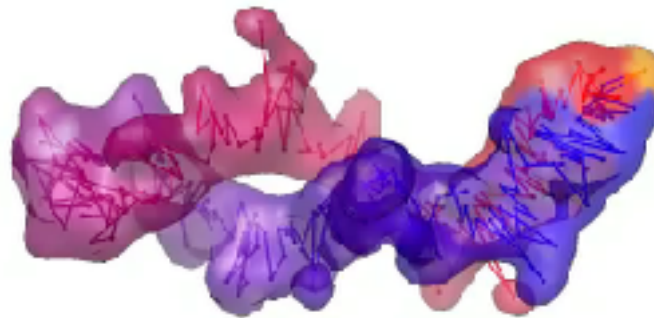
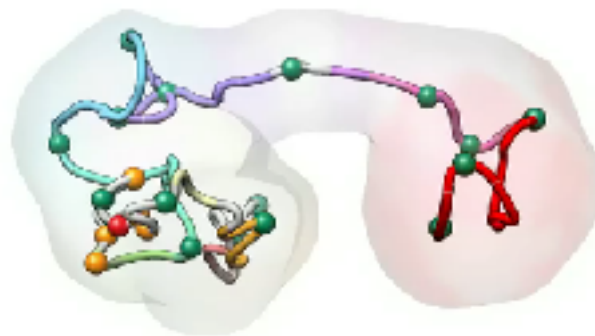
Map analysis

Model building

Model analysis

TADbit 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)



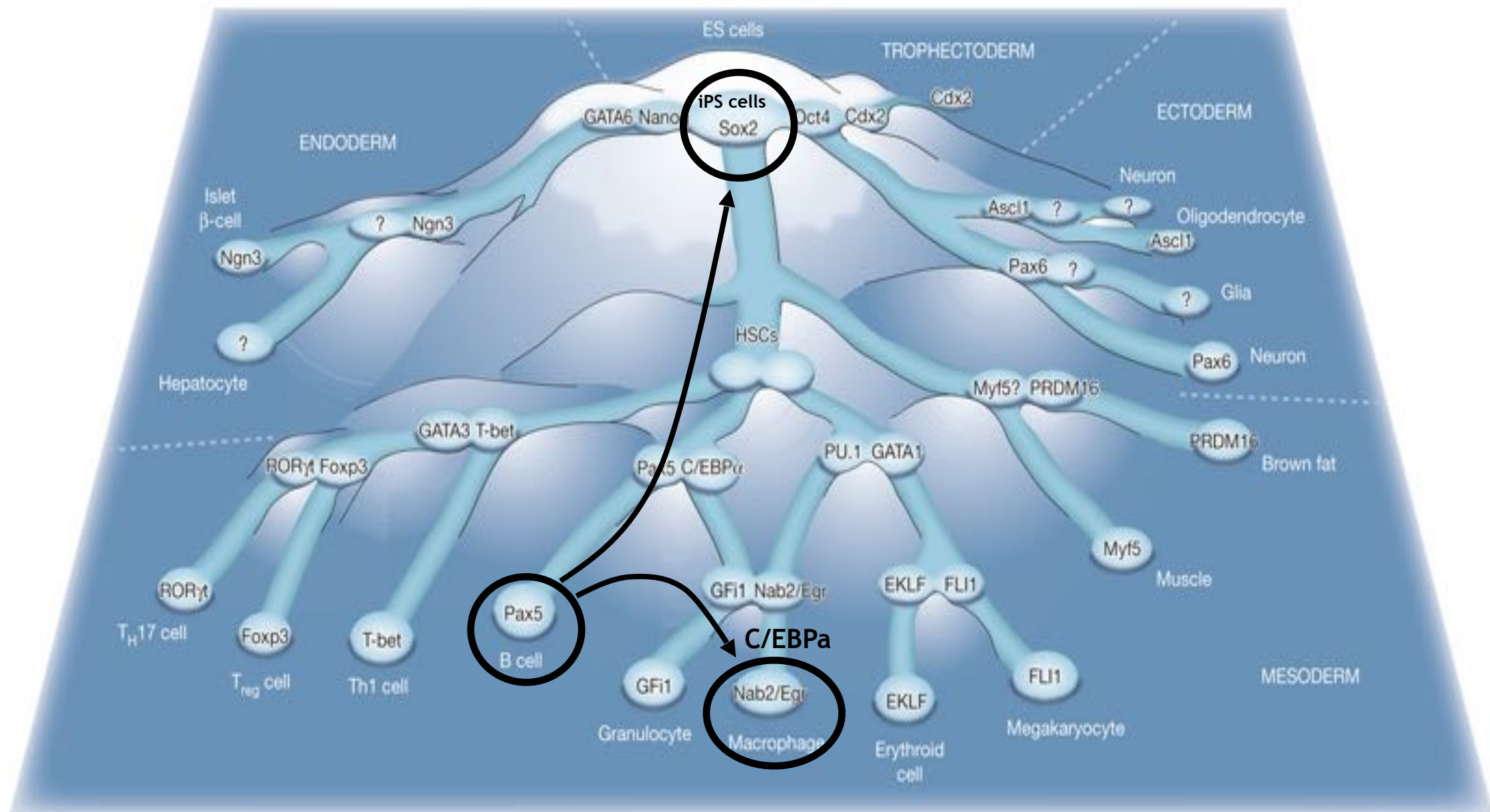
Interplay: topology, gene expression & chromatin



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

Transcription factors dictate cell fate

Graf & Enver (2009) Nature



Transcription factors (TFs) determine cell identity through gene regulation

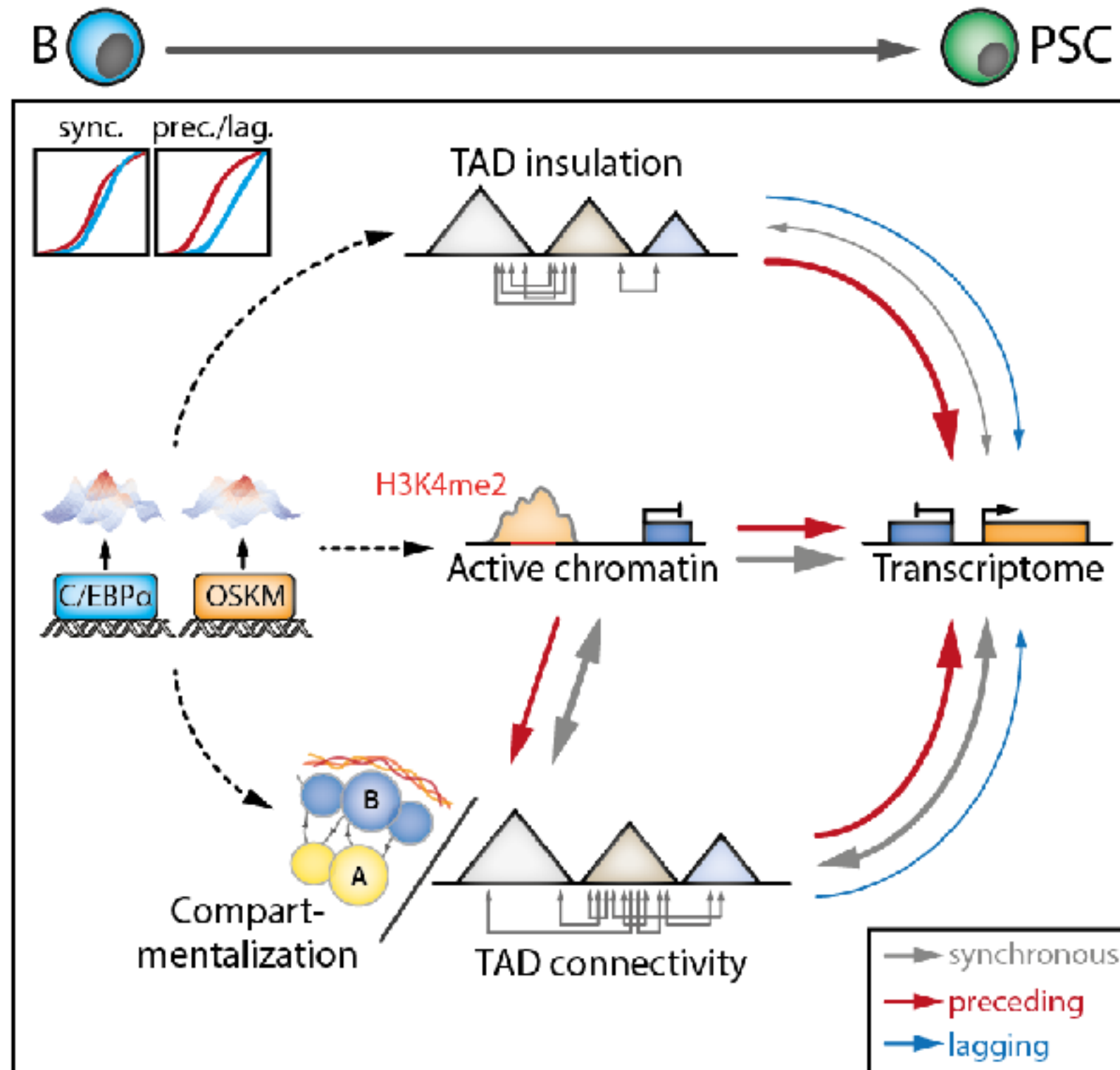
Normal 'forward' differentiation

Cell fates can be converted by enforced TF expression

Transdifferentiation or reprogramming

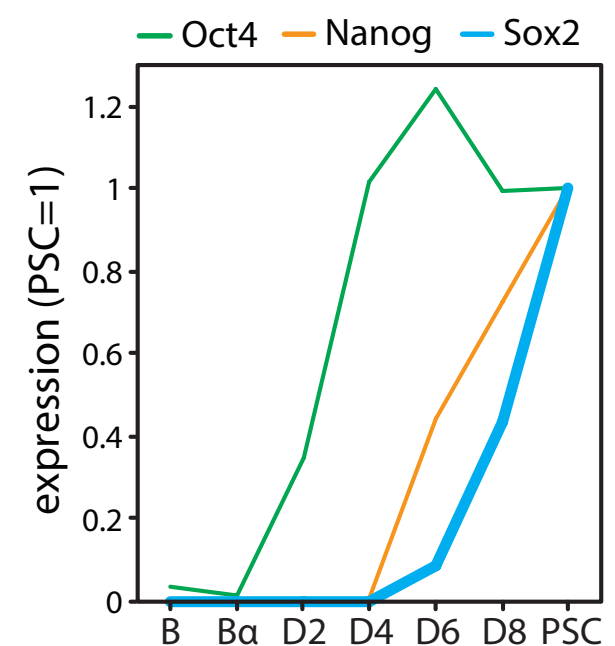
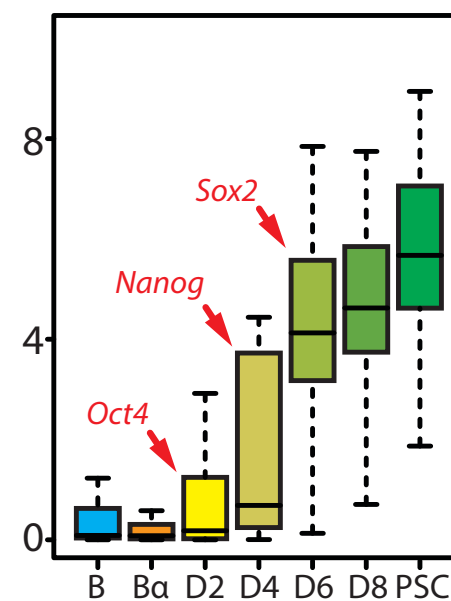
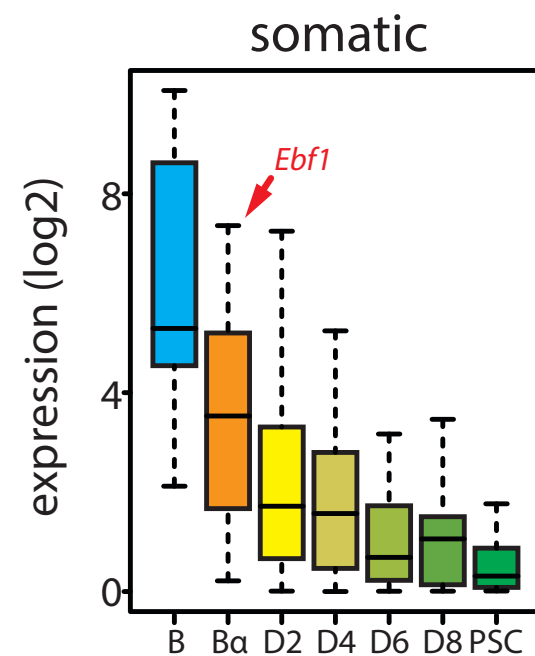
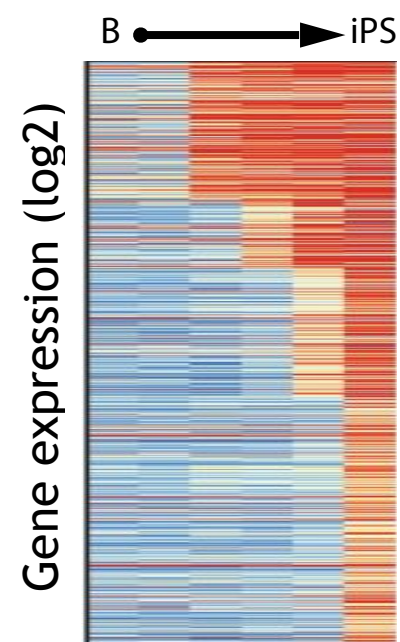
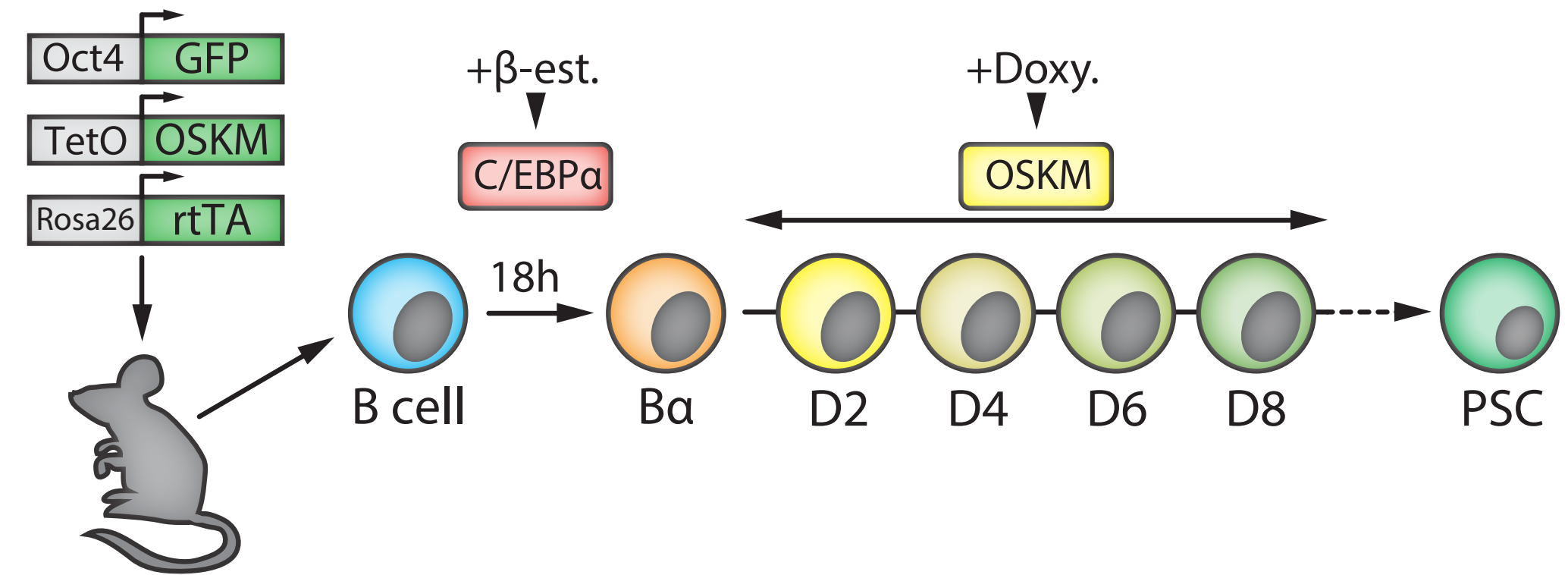
Interplay: topology, gene expression & chromatin

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



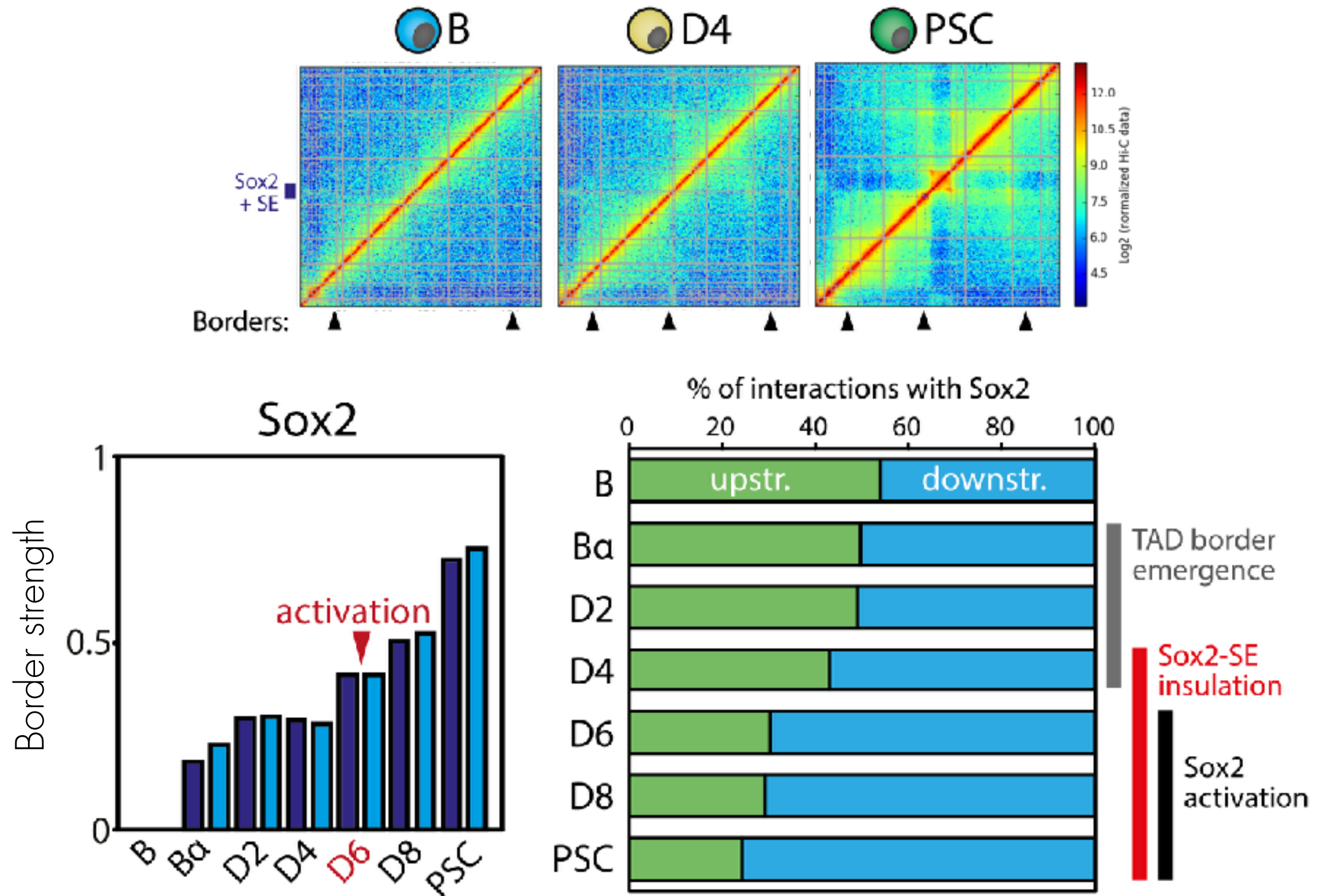
Reprogramming from B to PSC

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

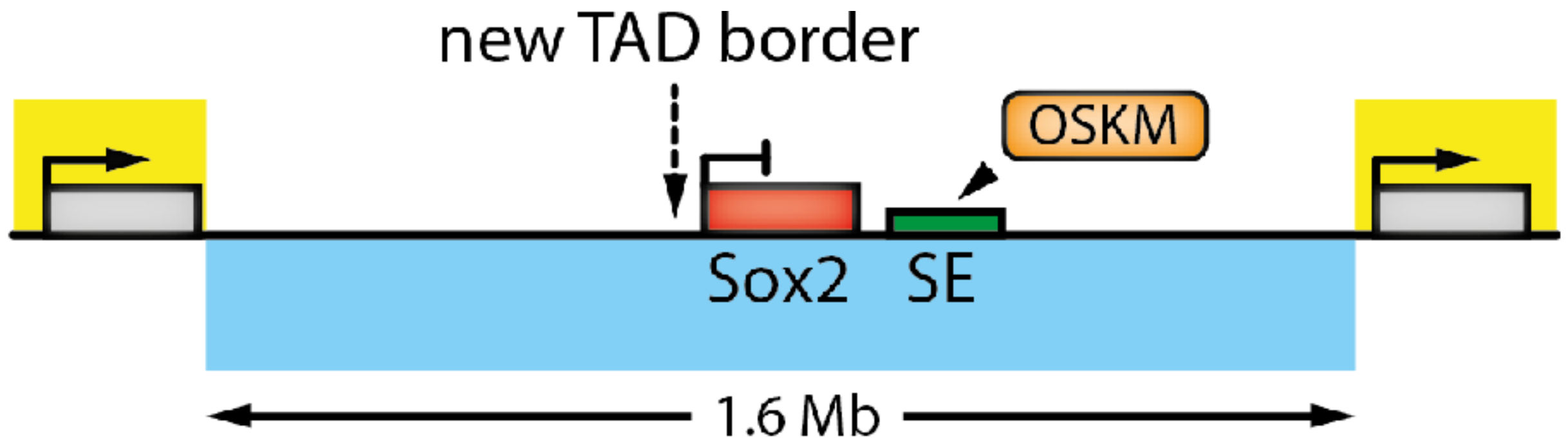


Birth of a TAD border upstream of Sox2

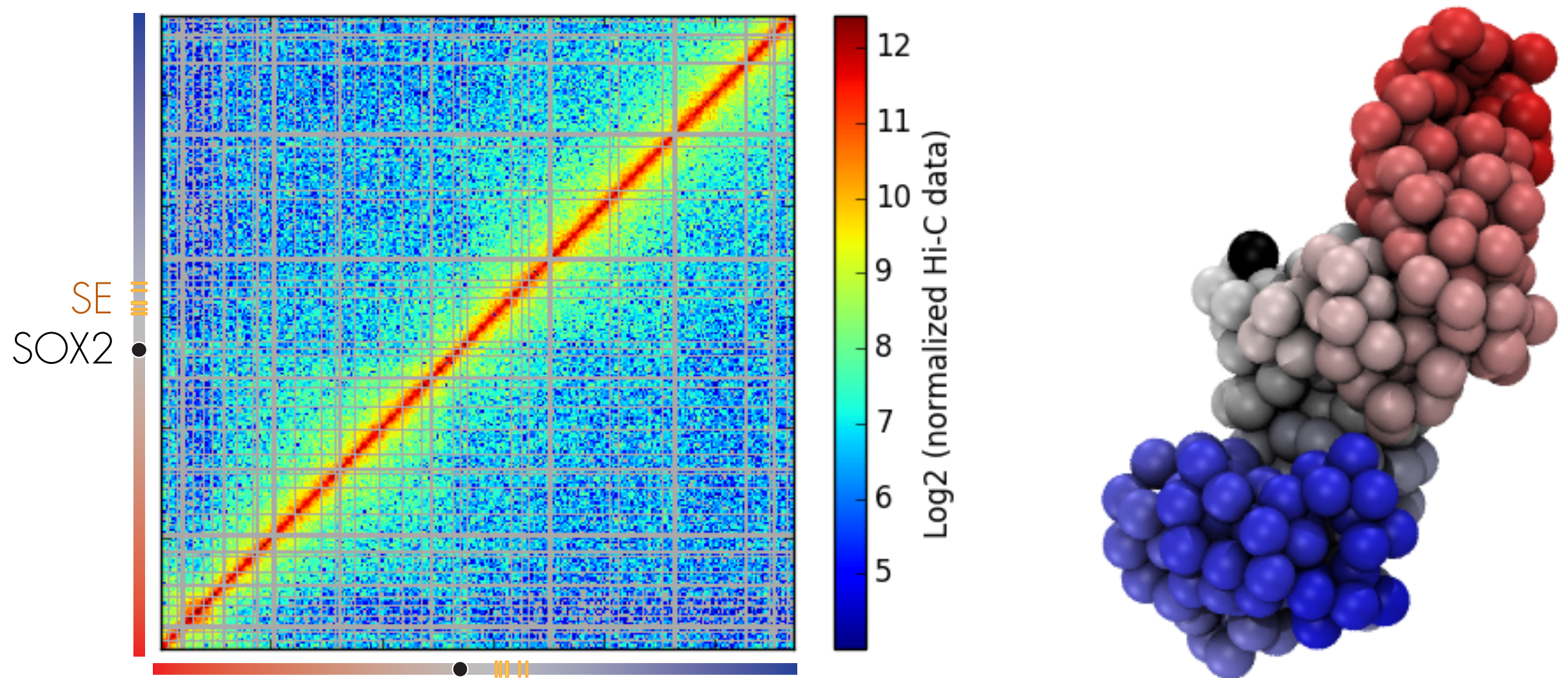
Stadhouders, R., Vidal, E. et al. (2017) Nature Genetics, in press.



Sox2 overall topological changes



TADbit modeling of SOX2 from B cells Hi-C

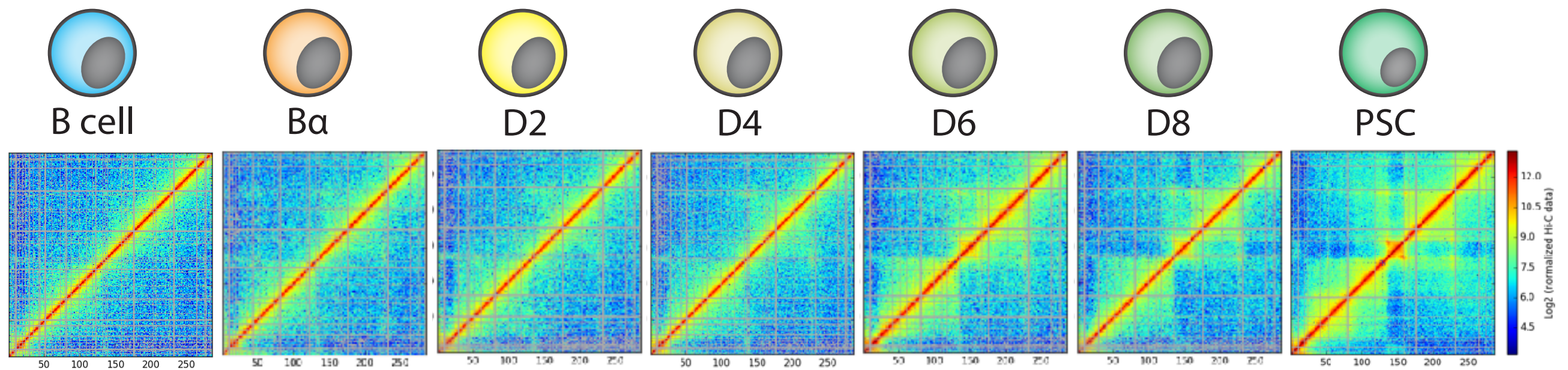
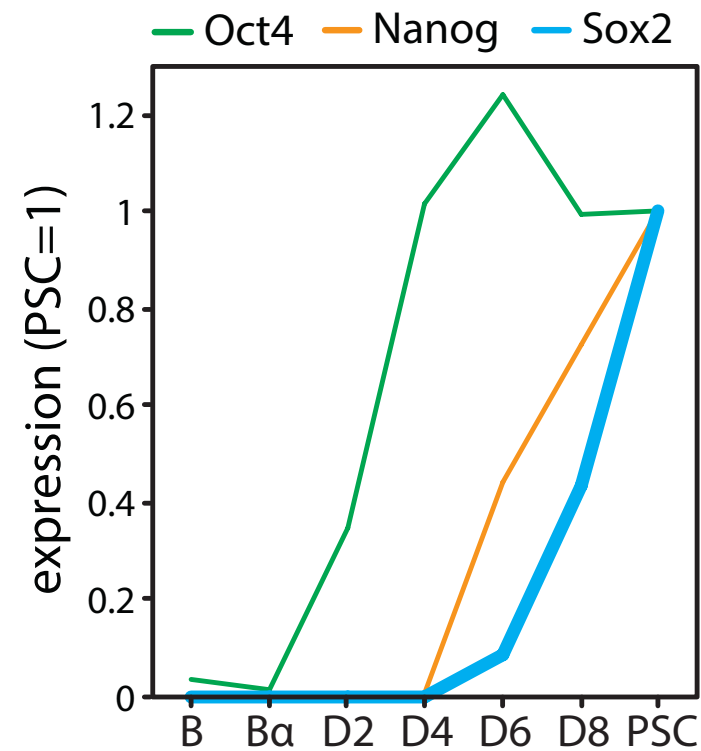


Optimal IMP parameters

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

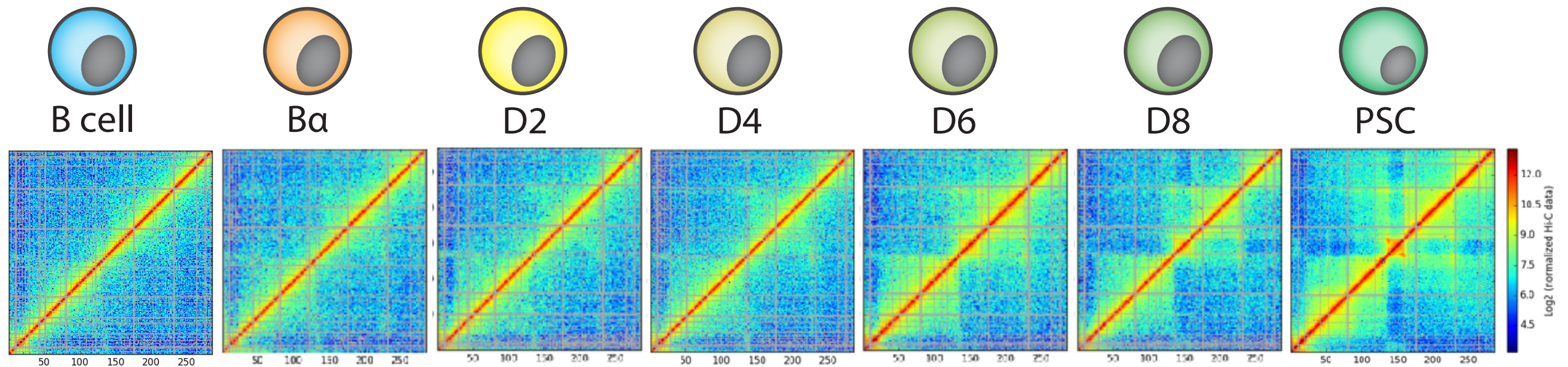
Hi-C maps of reprogramming from B to PSC

The SOX2 locus



Hi-C maps of reprogramming from B to PSC

The SOX2 locus

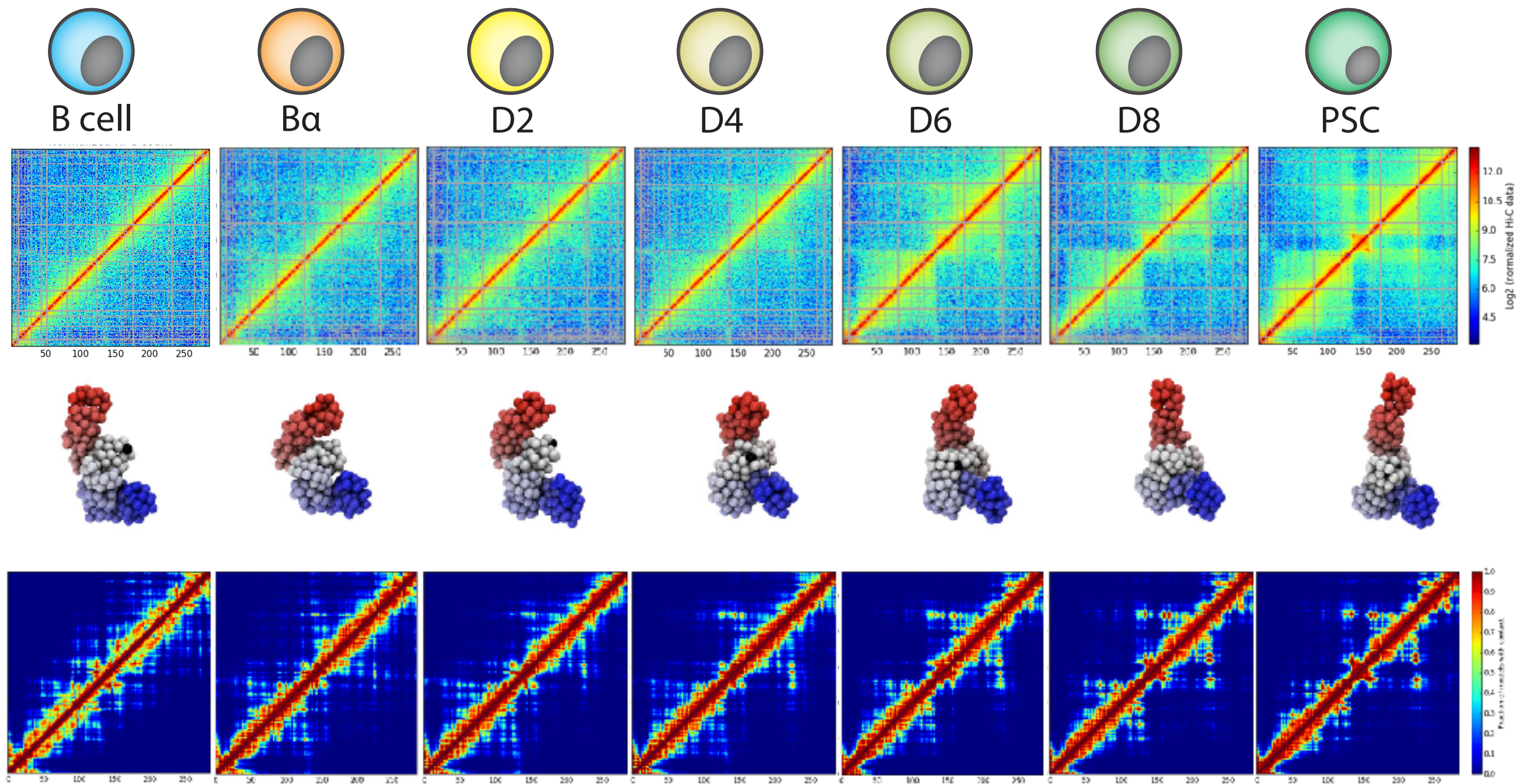


How do these structural rearrangements interplay with the transcription activity?

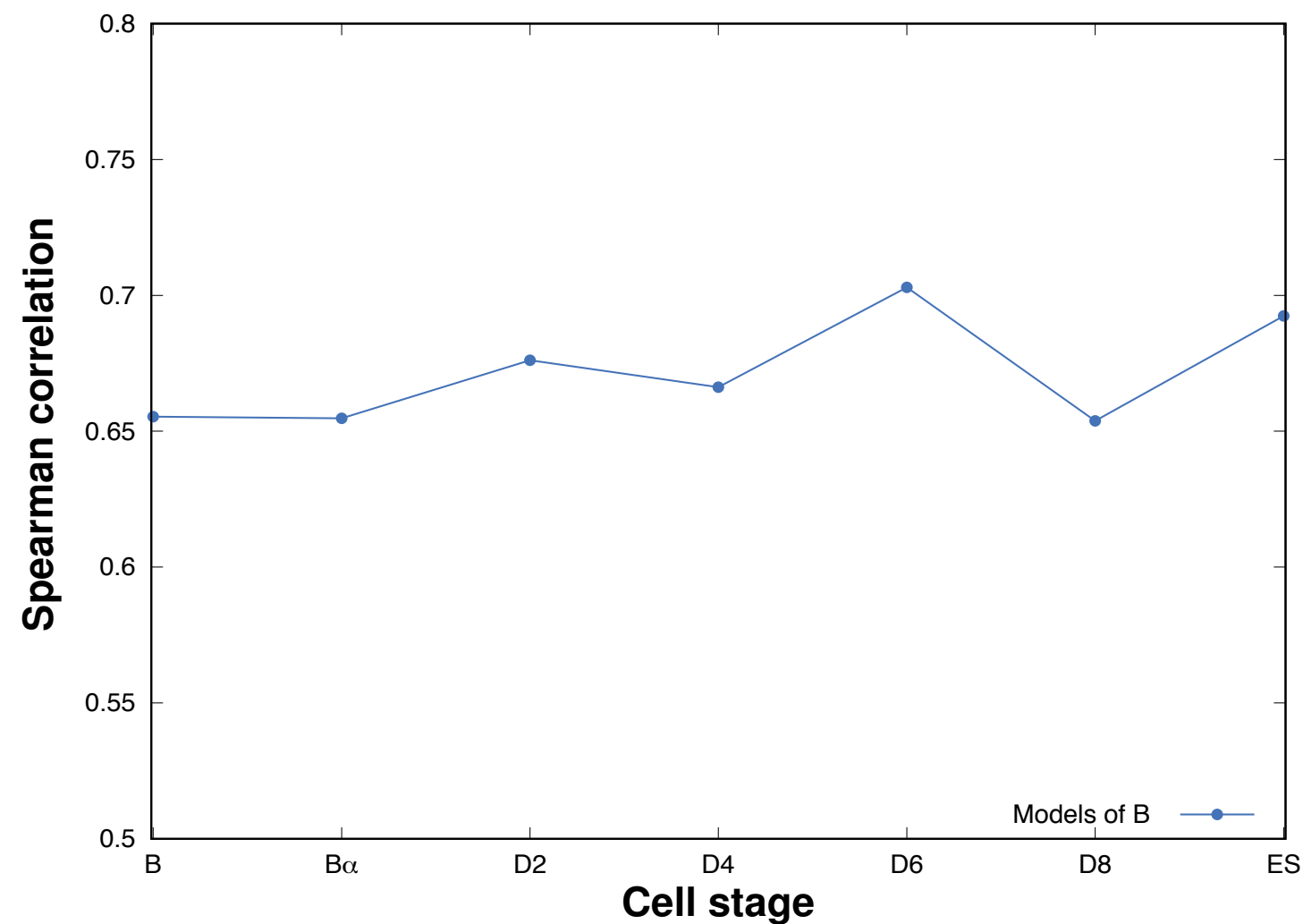
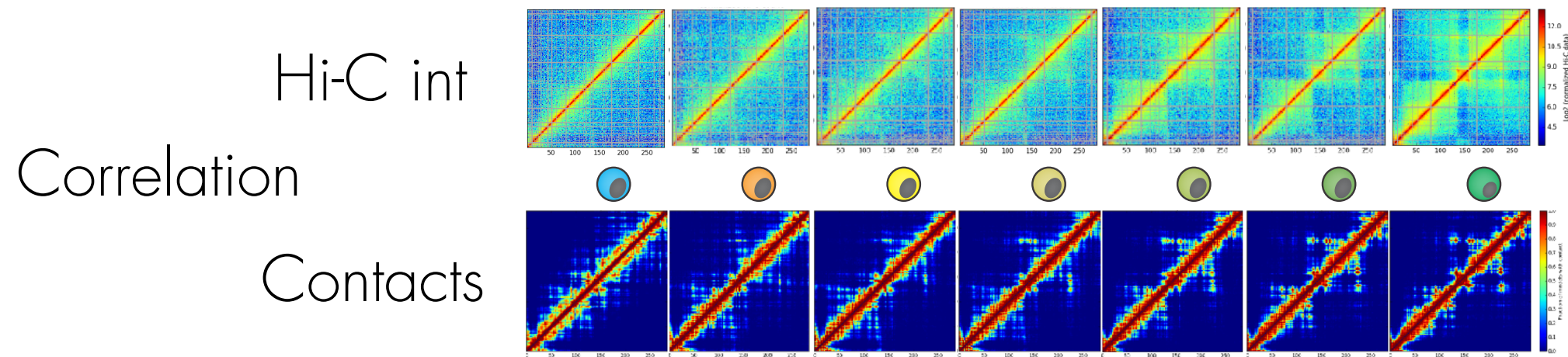
What are the main drivers of structural transitions?

Models of reprogramming from B to PSC

The SOX2 locus

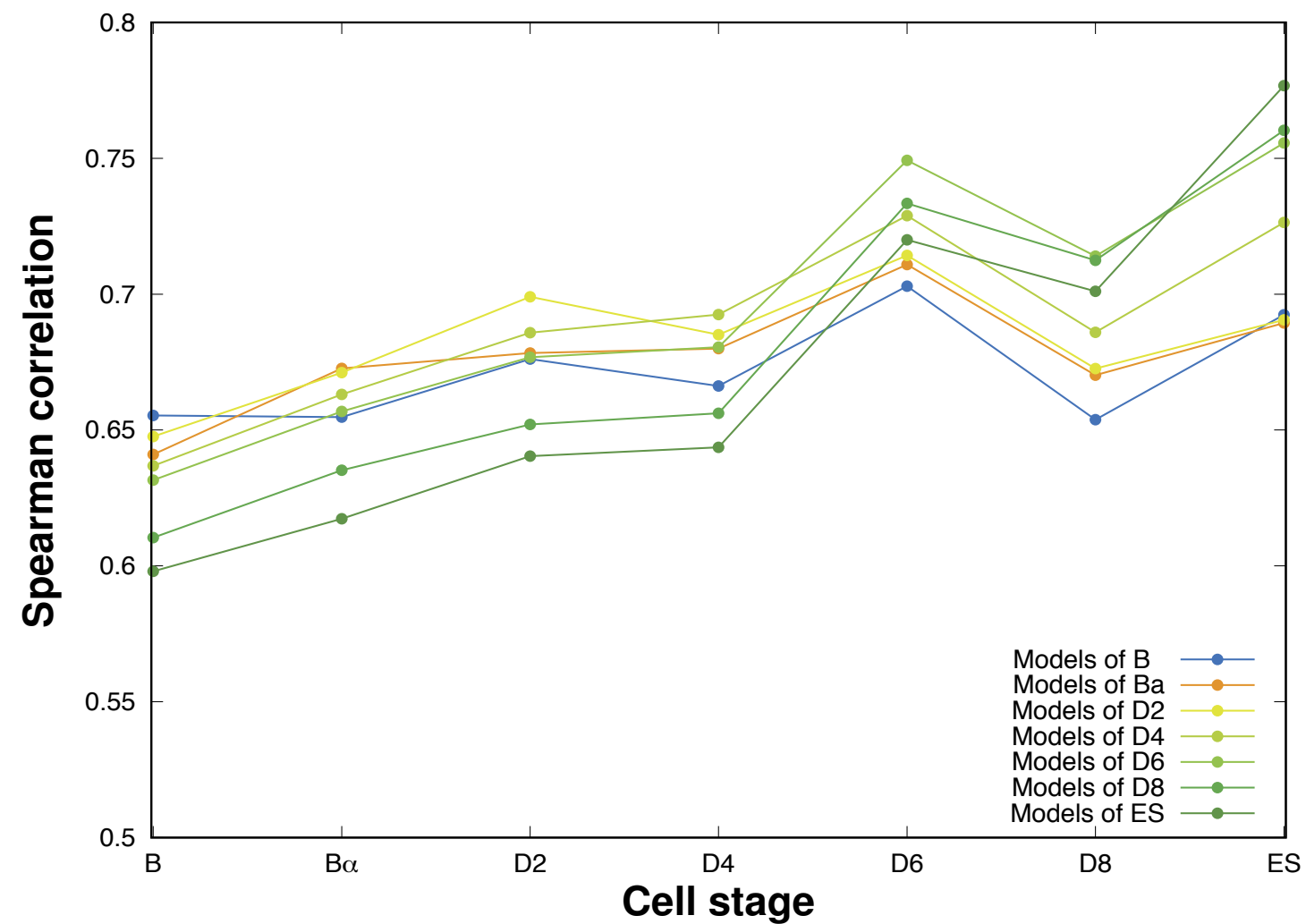
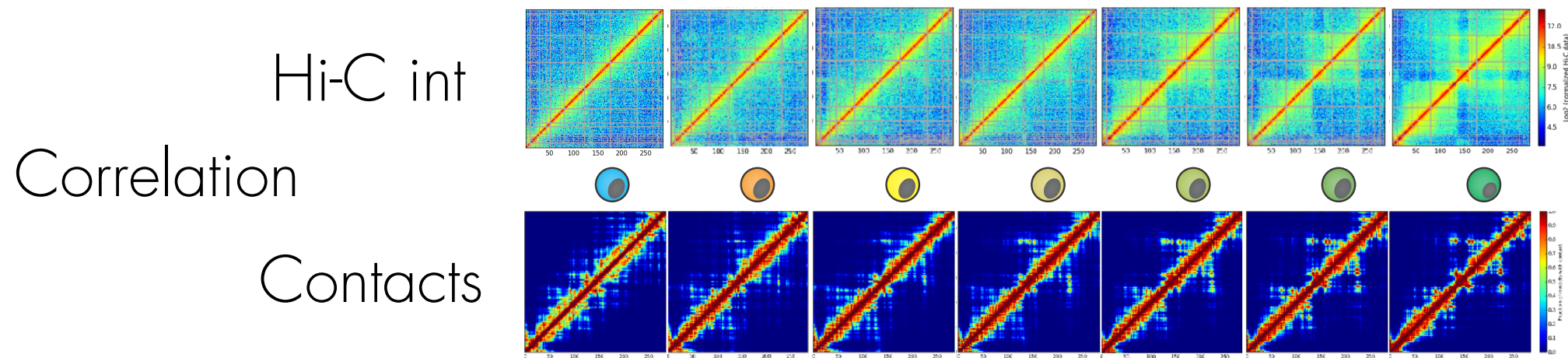


Model assessment

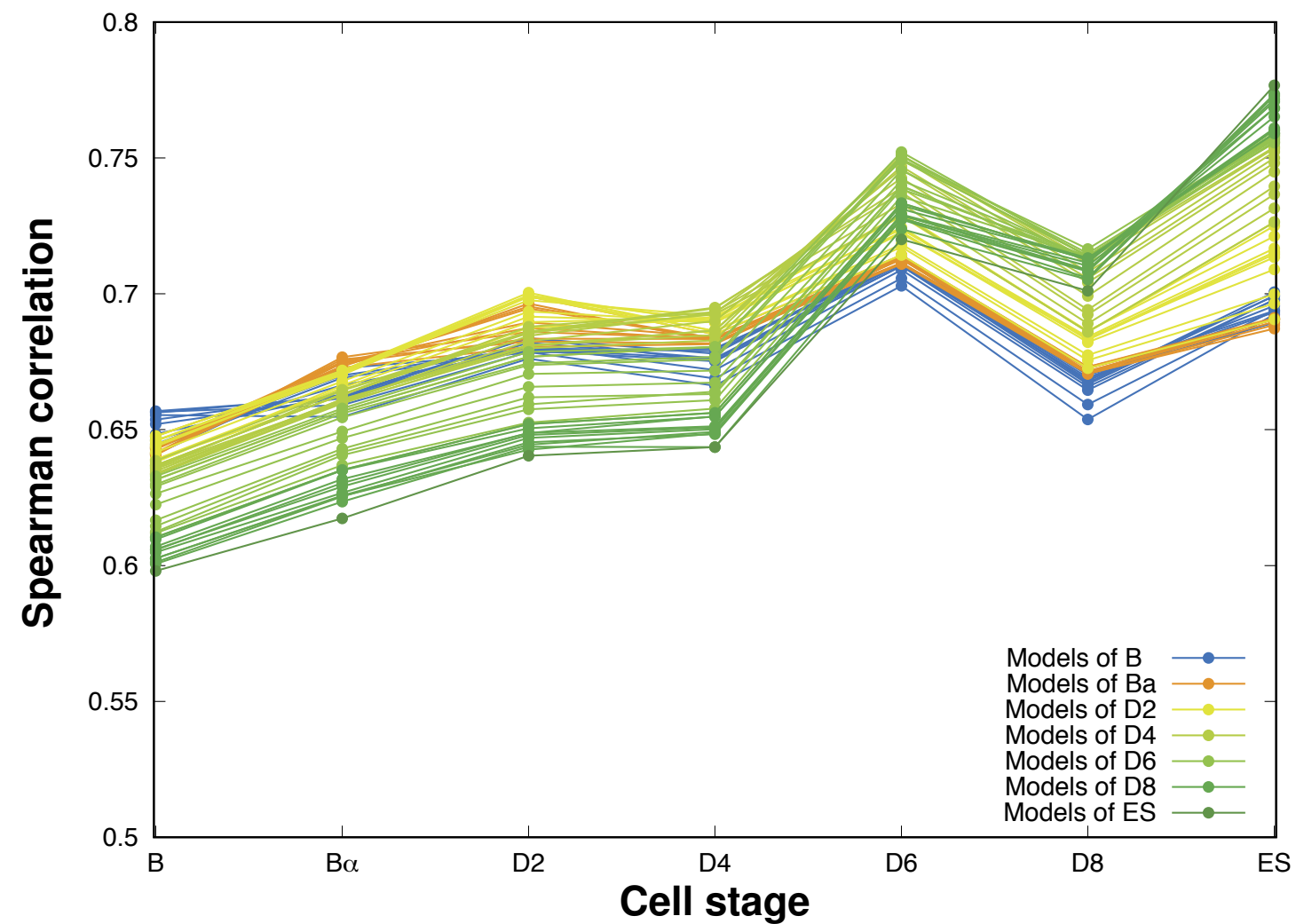
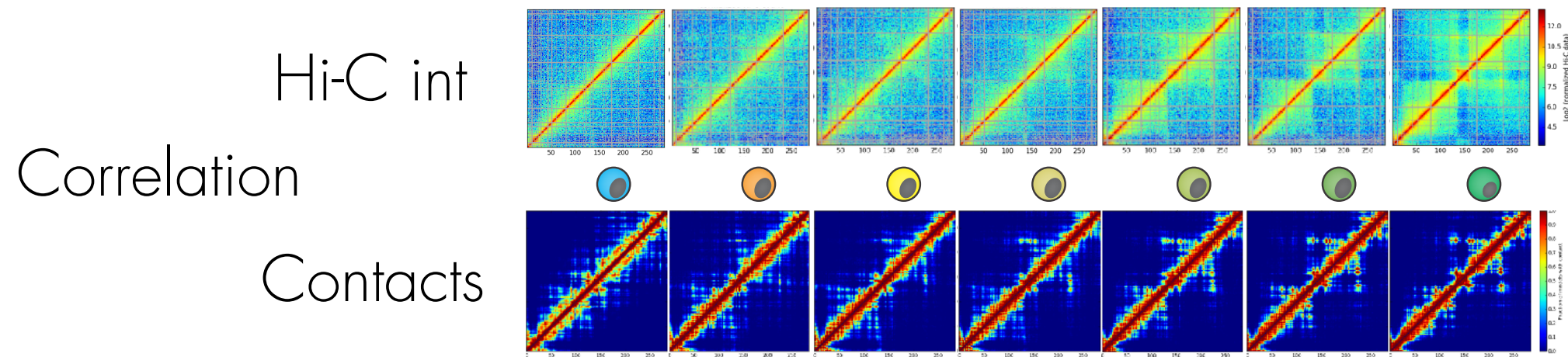


Try to use reproducibility score!
IN HiC-Spector! compare the first 20
eigenvectors

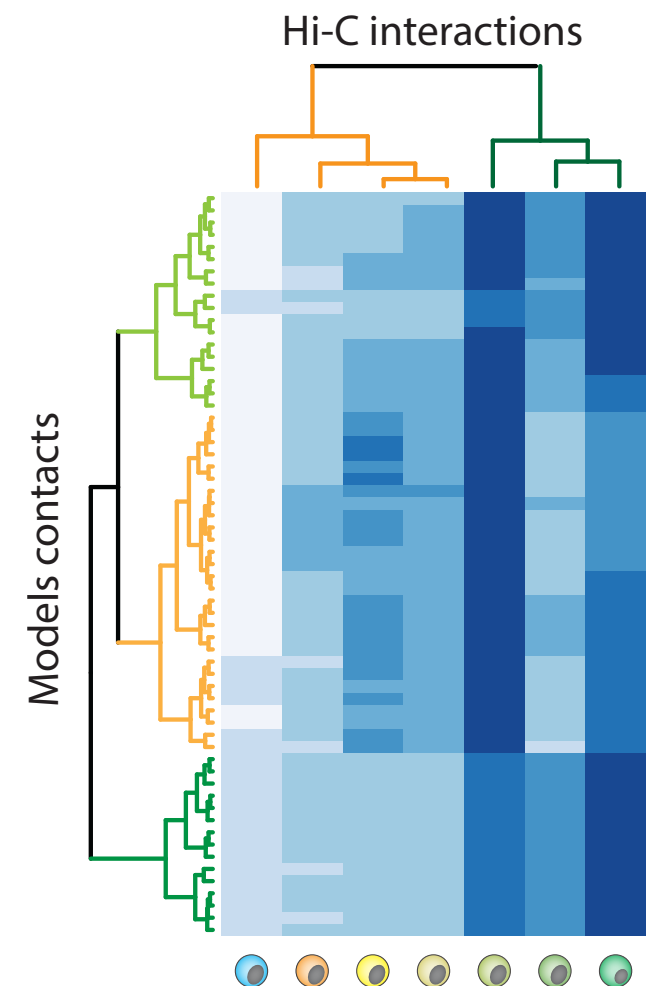
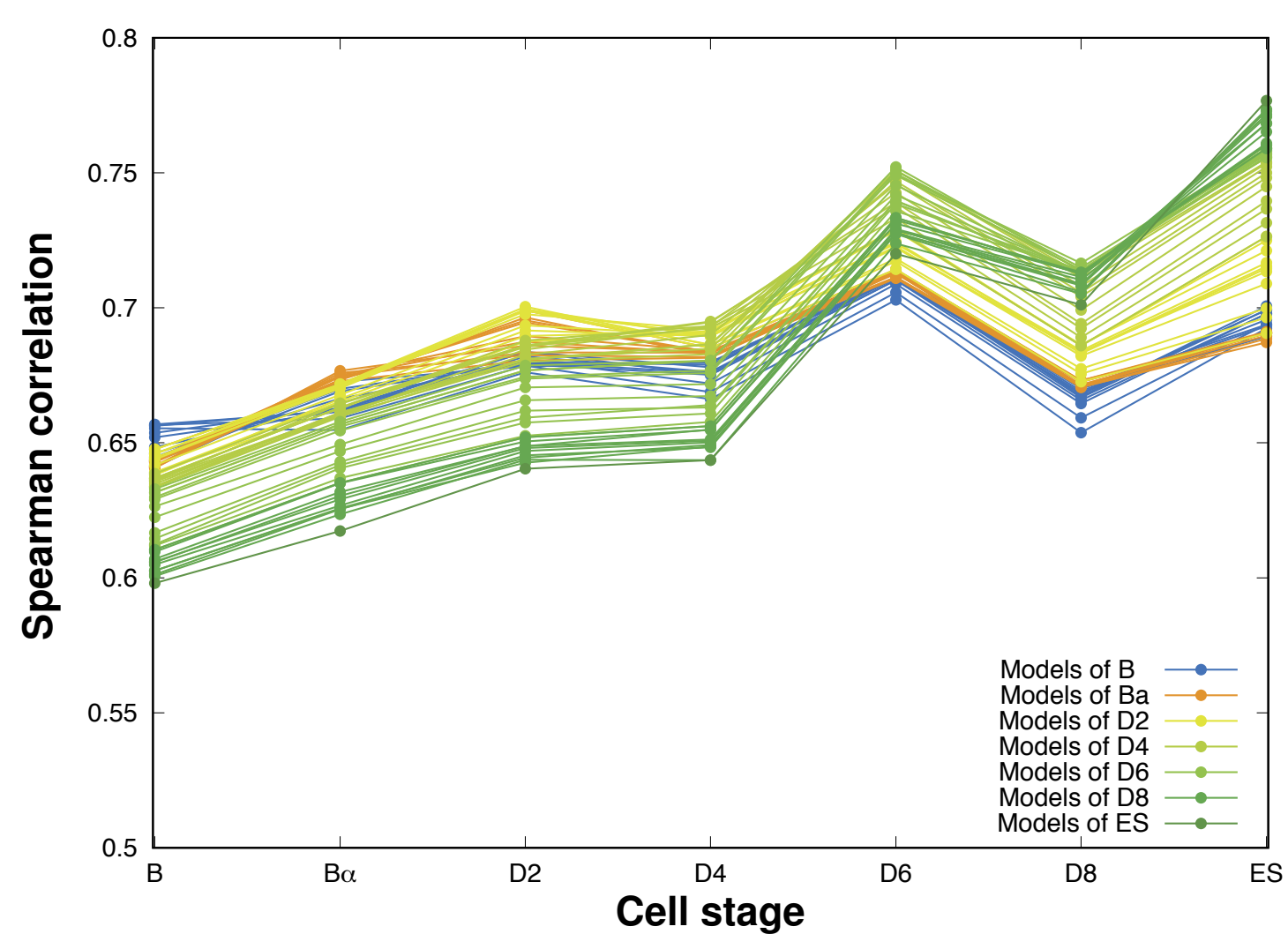
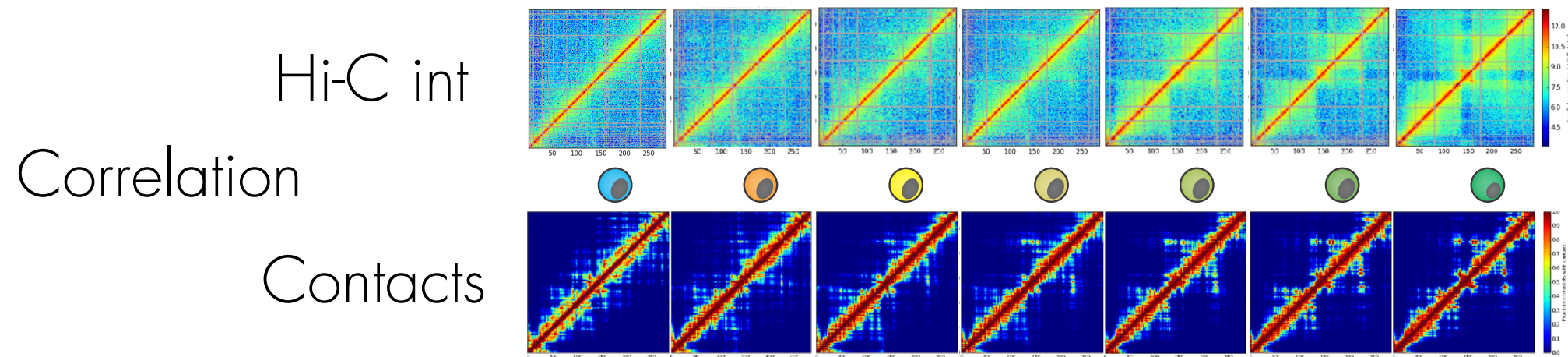
Model assessment



Model assessment

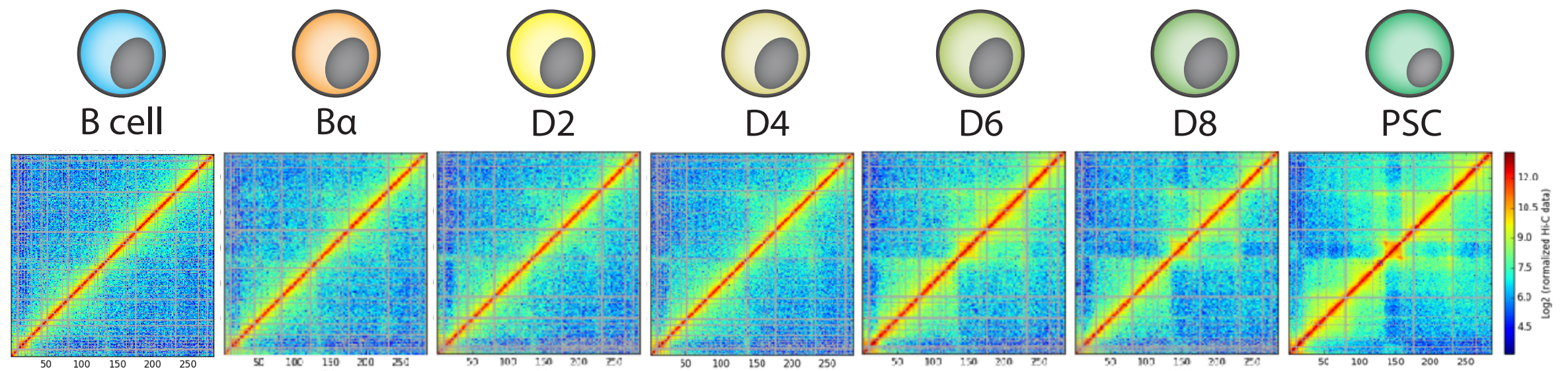


Model assessment



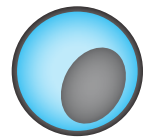
TADdyn: from time-series Hi-C maps to dynamic restraints

The SOX2 locus

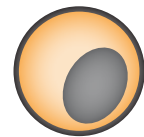


TADdyn: from time-series Hi-C maps to dynamic restraints

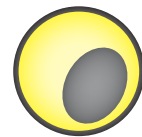
The SOX2 locus



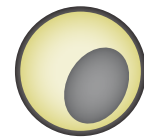
B cell



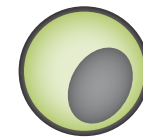
Bα



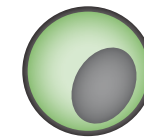
D2



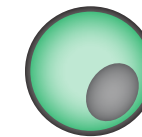
D4



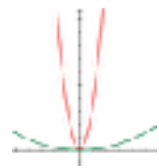
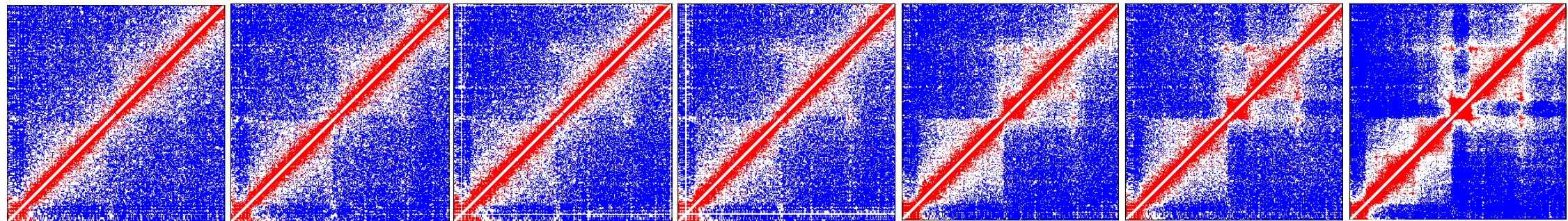
D6



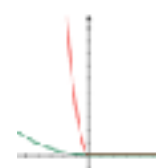
D8



PSC



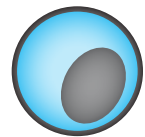
Harmonic



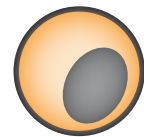
HarmonicLowerBound

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

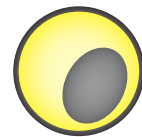
The SOX2 locus



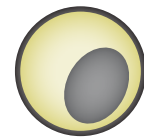
B cell



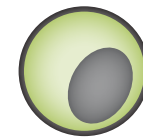
B α



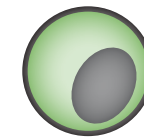
D2



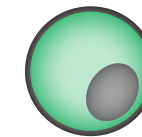
D4



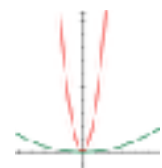
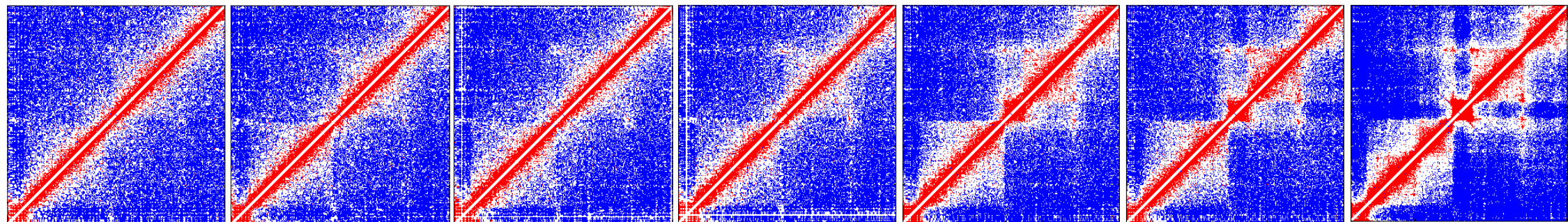
D6



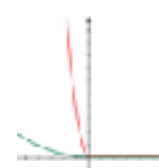
D8



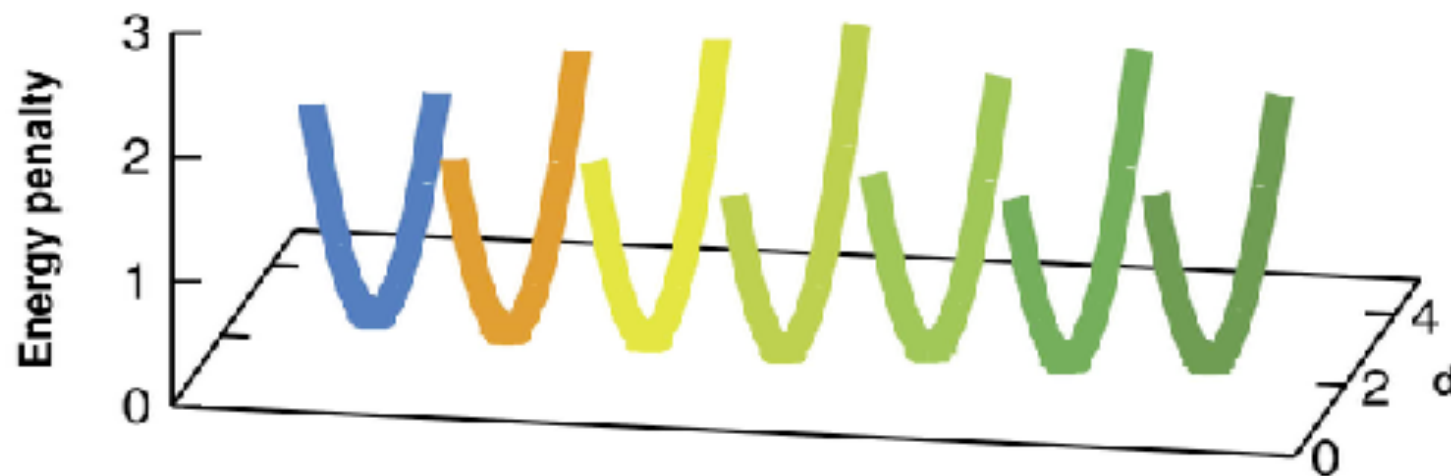
PSC



■ Harmonic



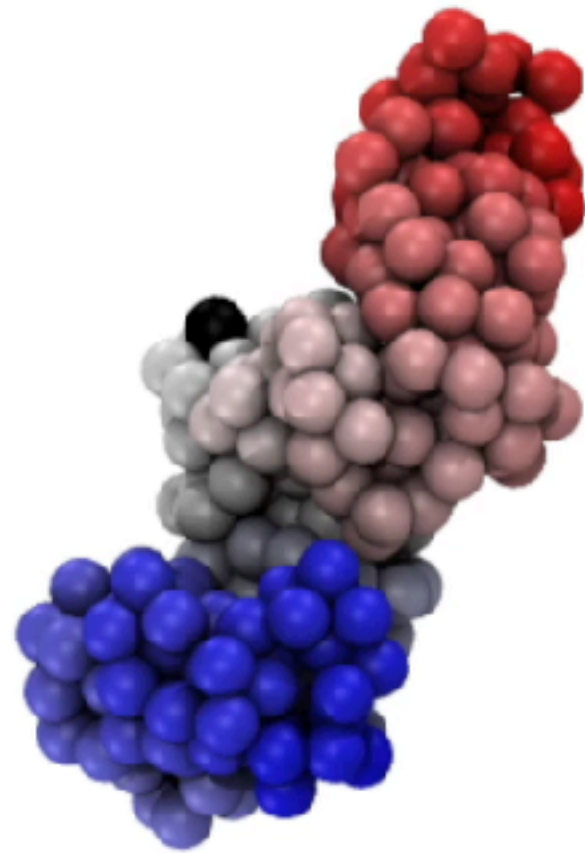
■ HarmonicLowerBound



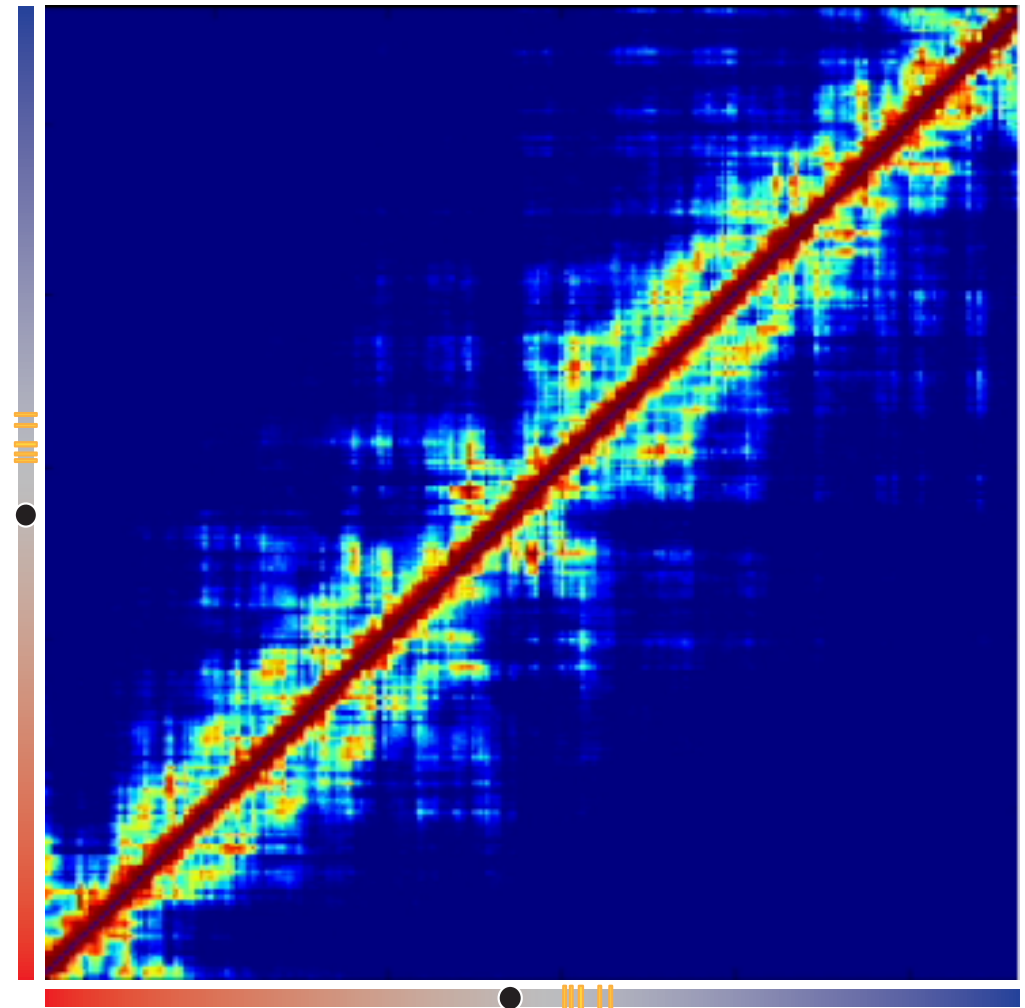
Transition	Stable	Vanishing	Raising
B → B α	18,612	6,984	7,290
B α → D2	18,512	7,390	6,687
D2 → D4	18,369	6,830	6,893
D4 → D6	18,971	6,291	7,289
D6 → D8	20,167	6,093	6,250
D8 → ES	20,679	5,738	6,173

SOX2 locus structural changes from B to PSC

Contacts

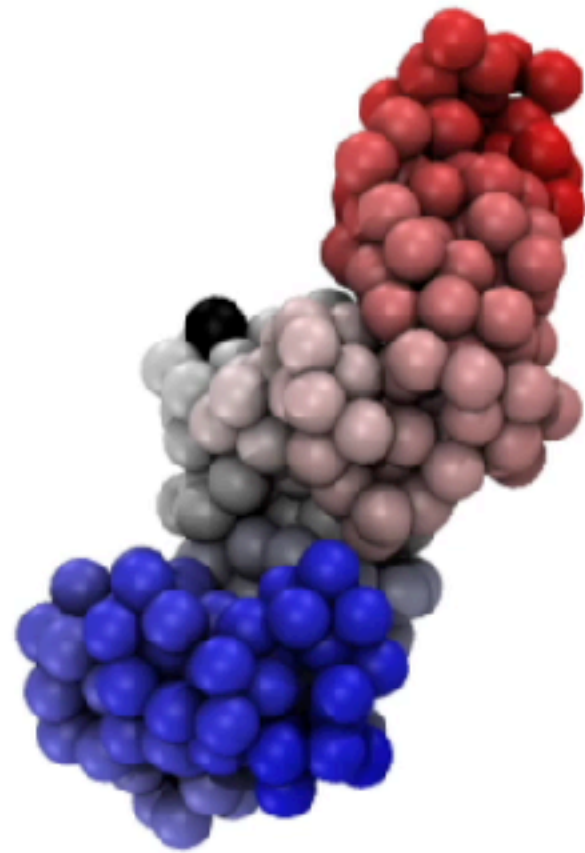


SE
SOX2

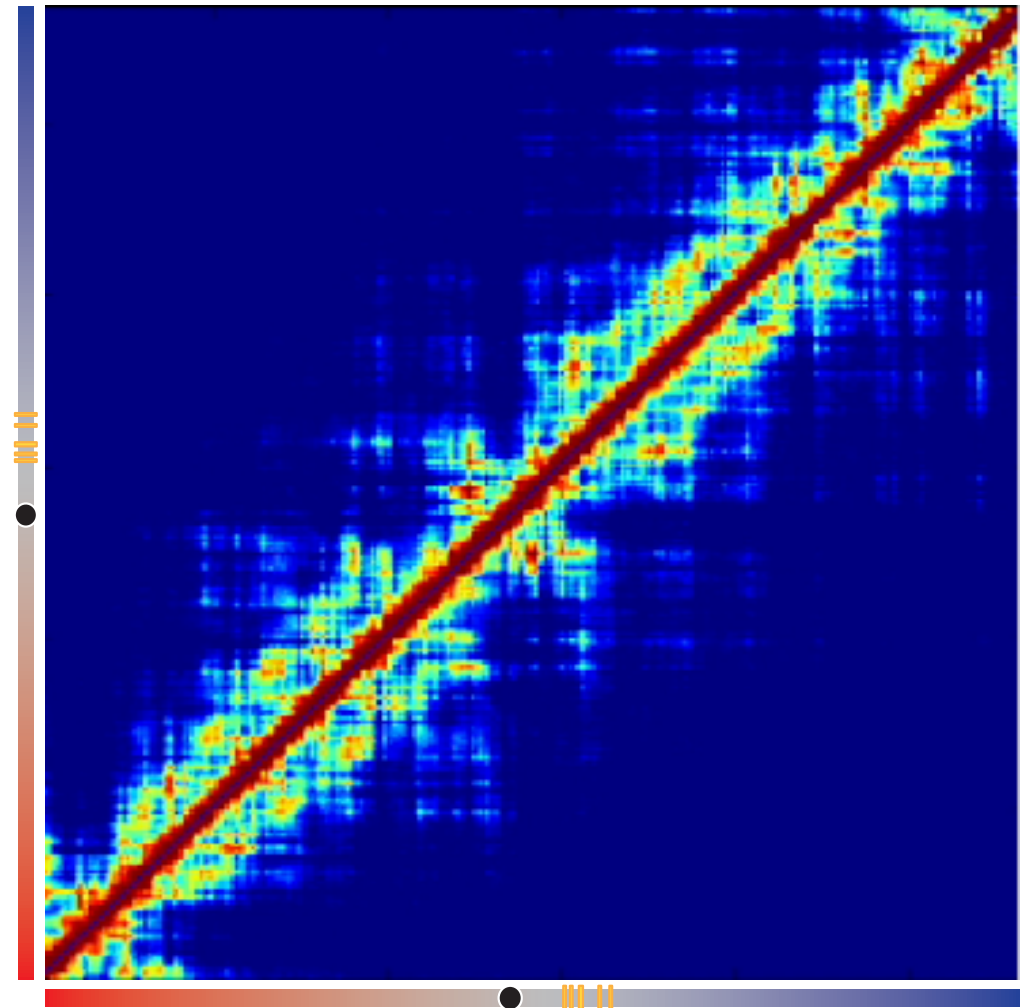


SOX2 locus structural changes from B to PSC

Contacts

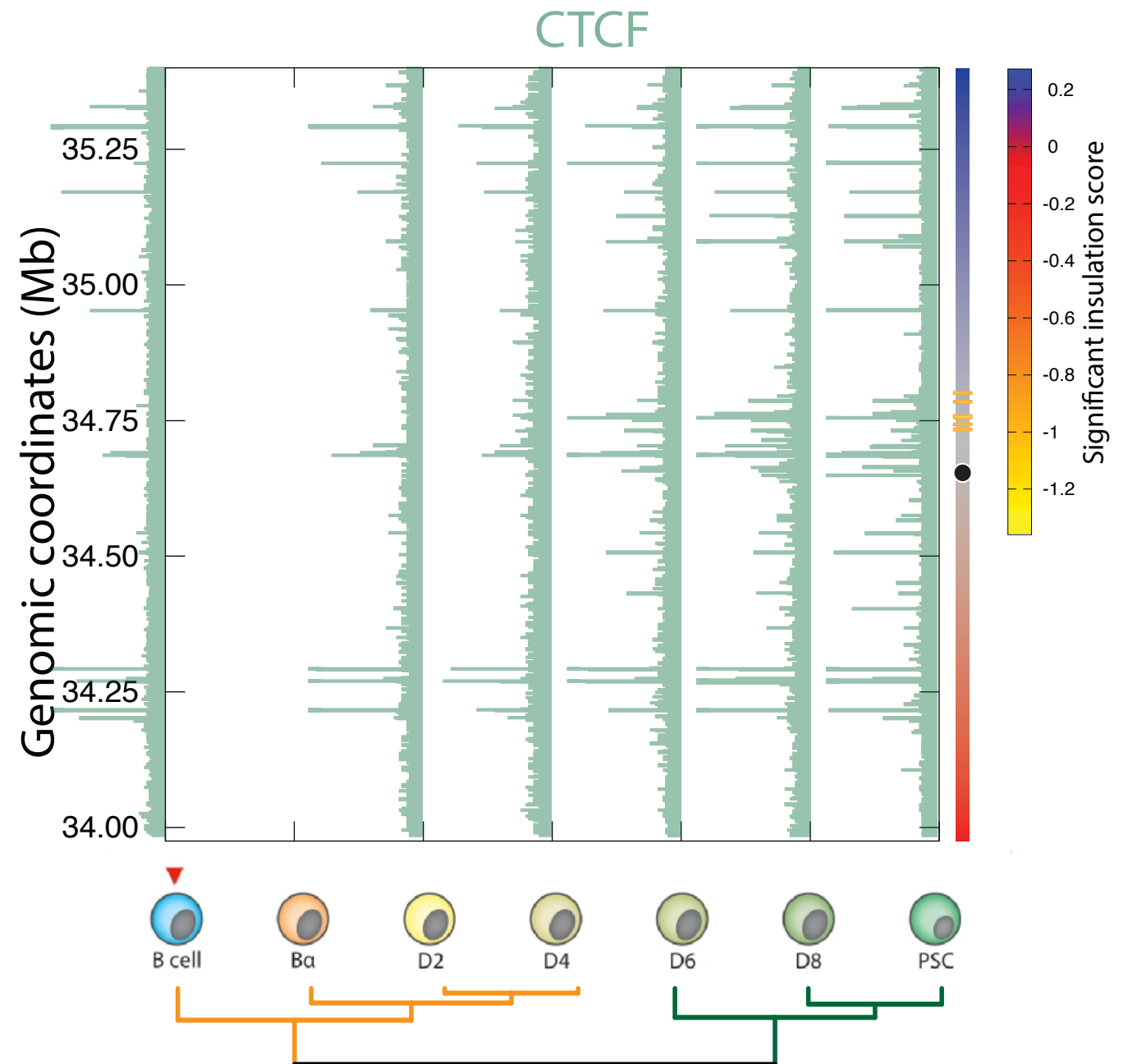
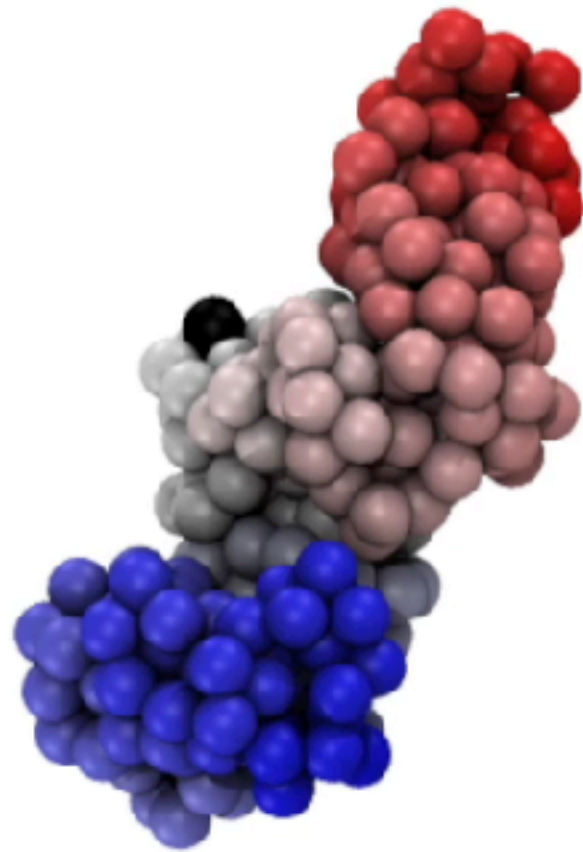


SE
SOX2



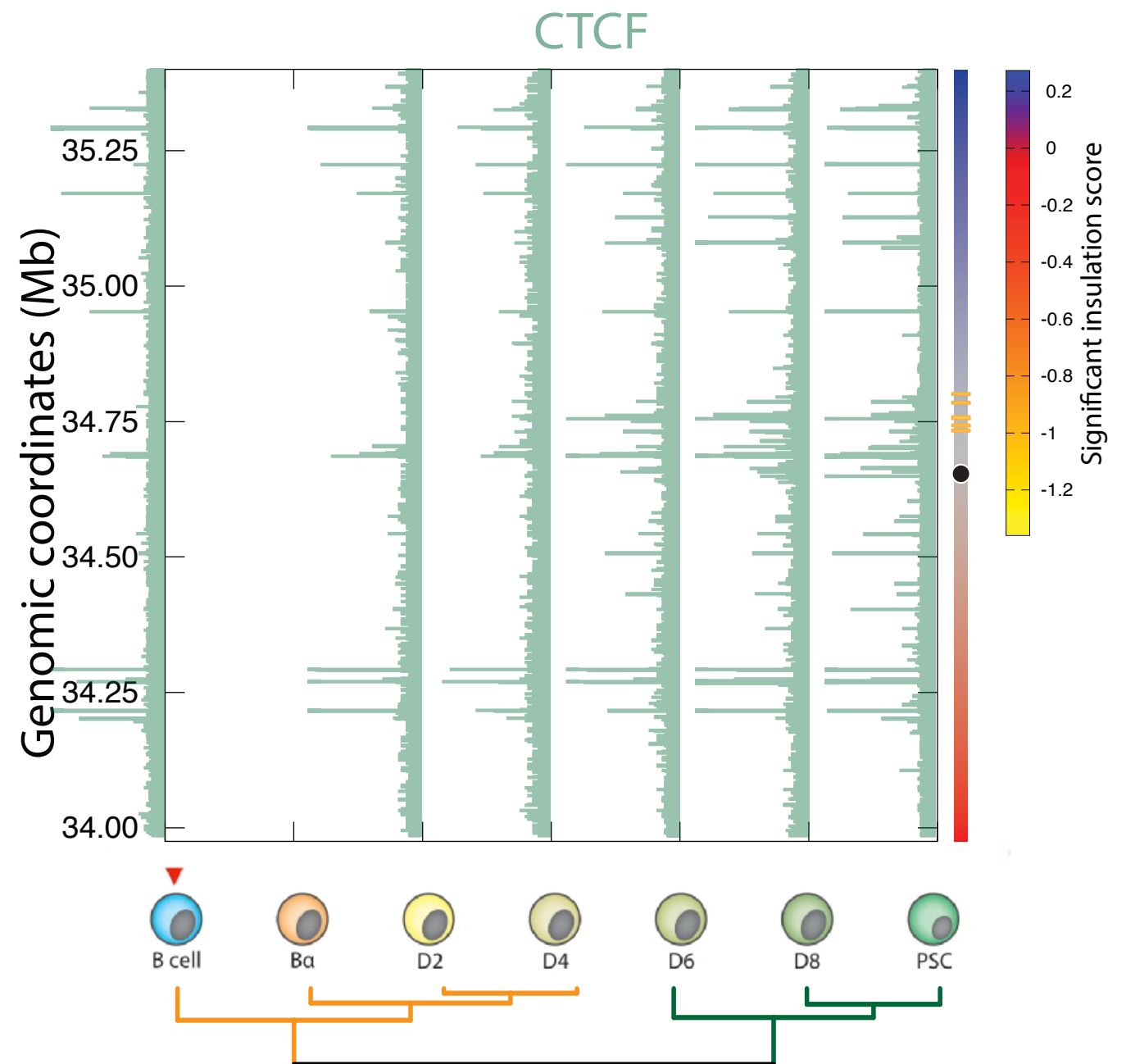
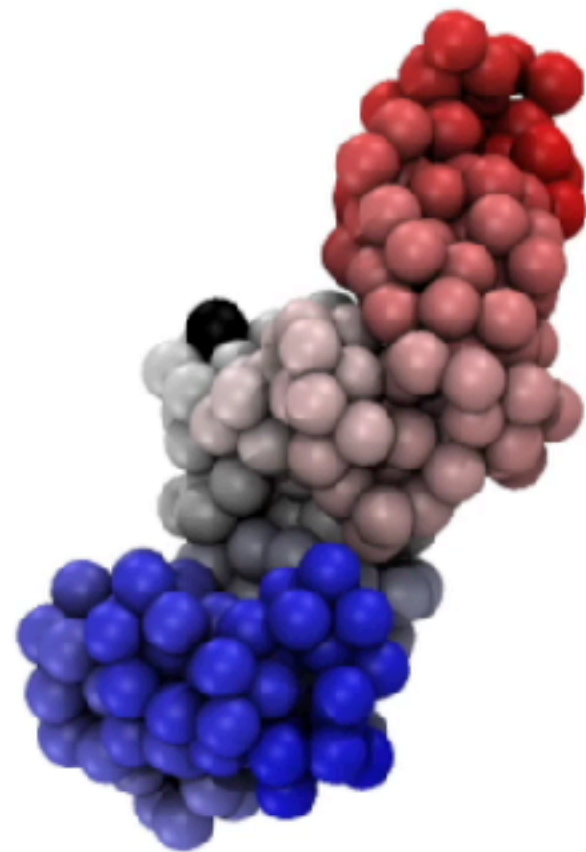
SOX2 locus structural changes from B to PSC

TAD borders



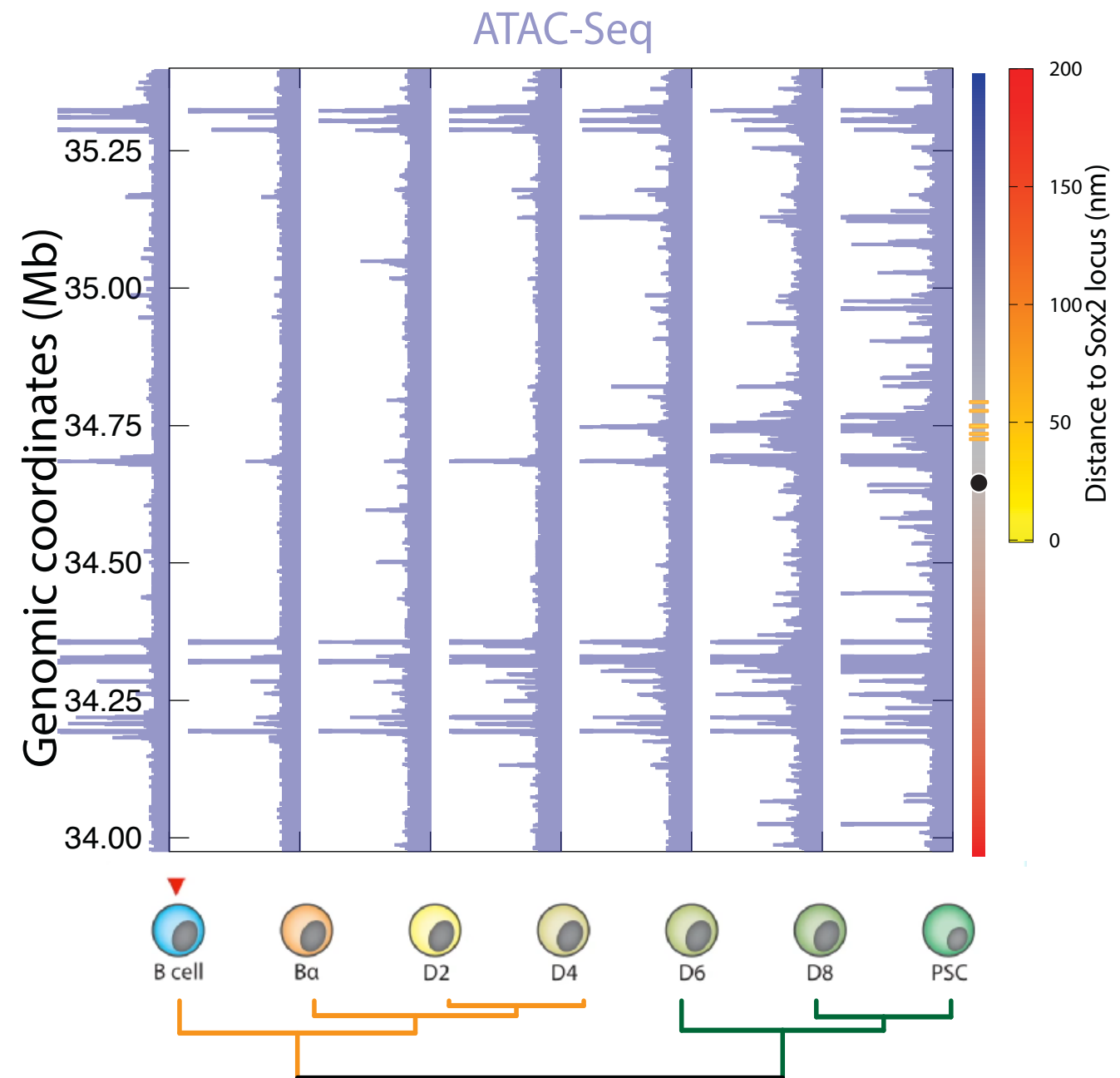
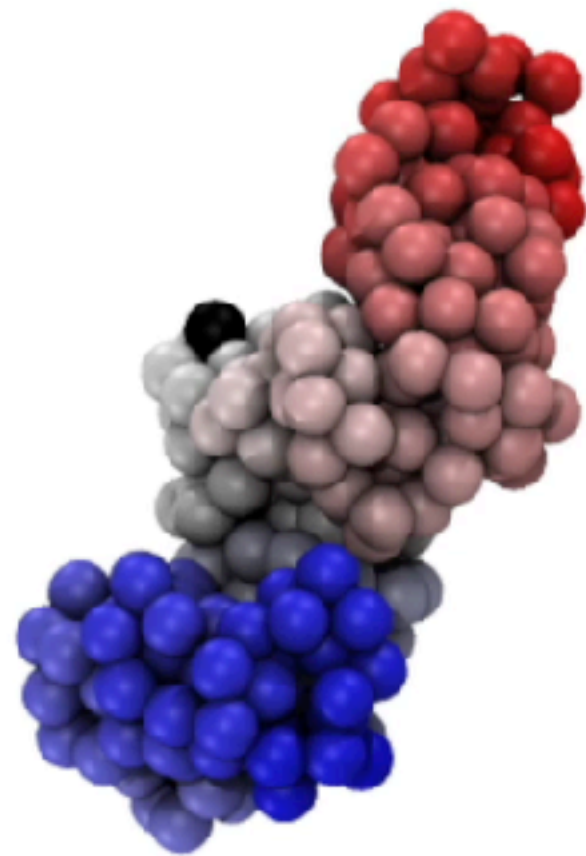
SOX2 locus structural changes from B to PSC

TAD borders



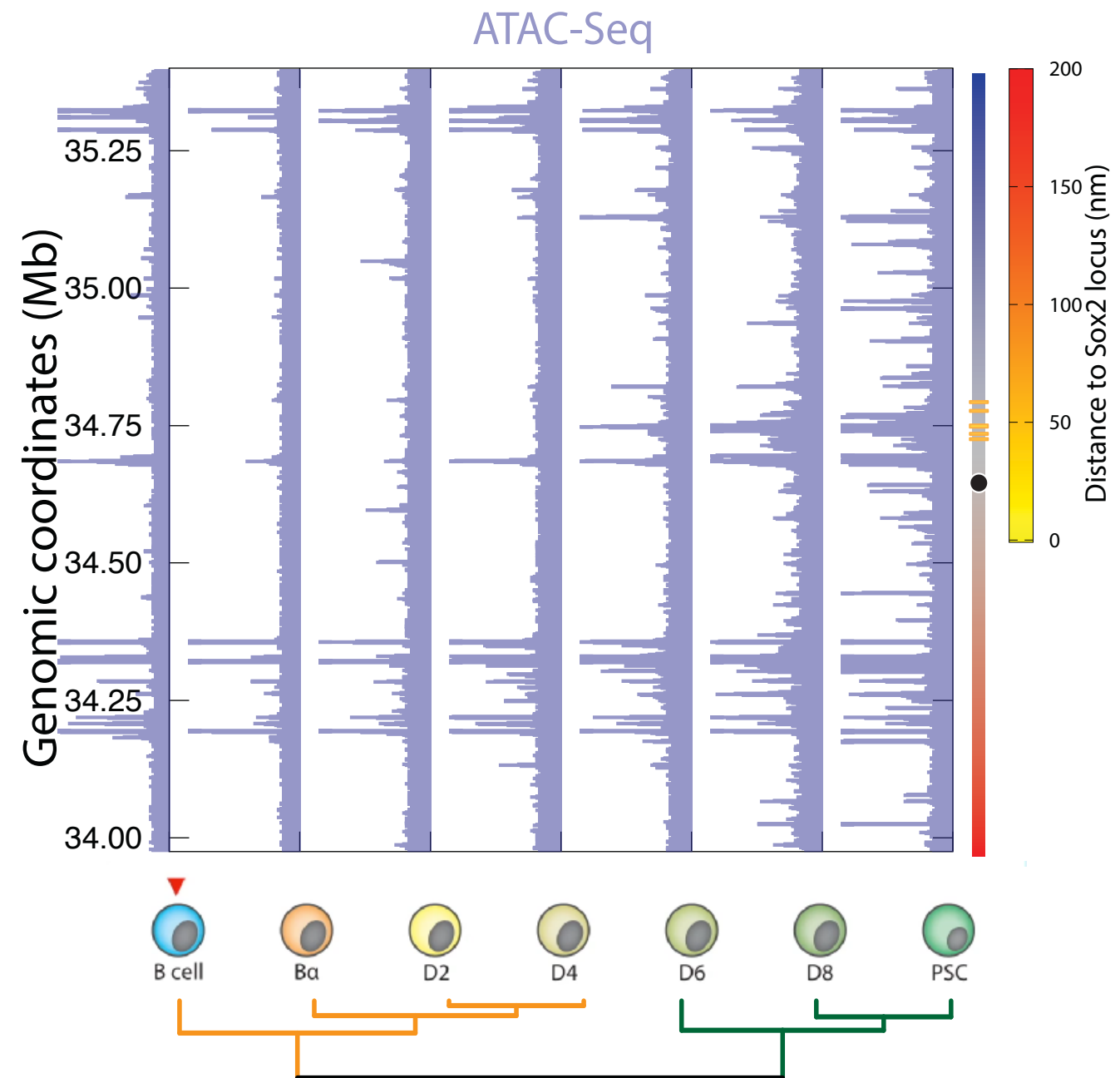
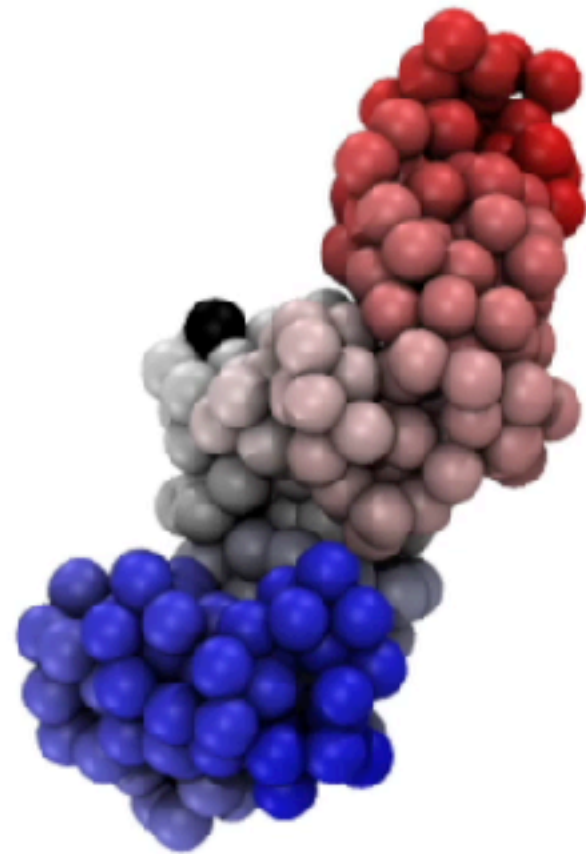
SOX2 locus structural changes from B to PSC

Distance to regulatory elements



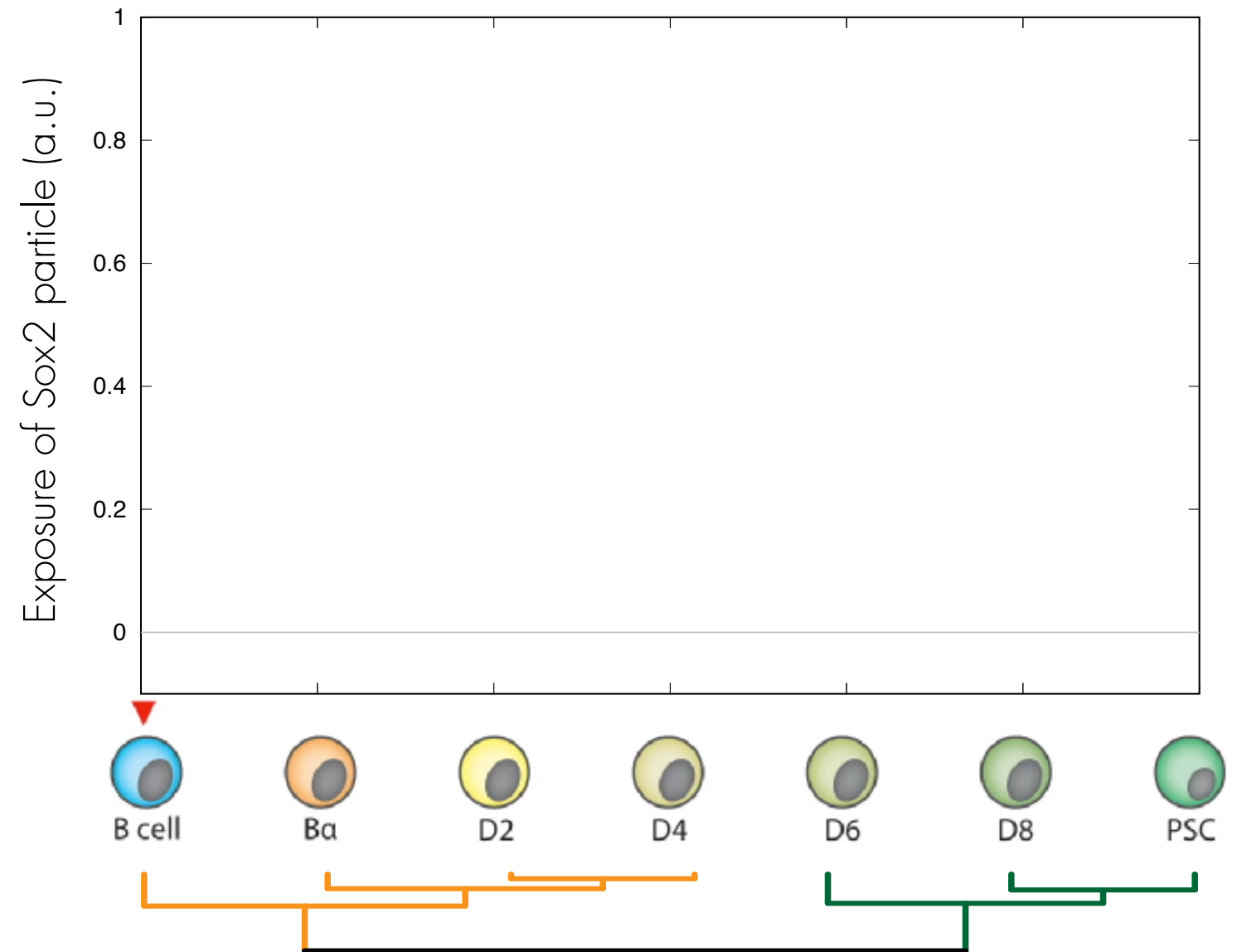
SOX2 locus structural changes from B to PSC

Distance to regulatory elements



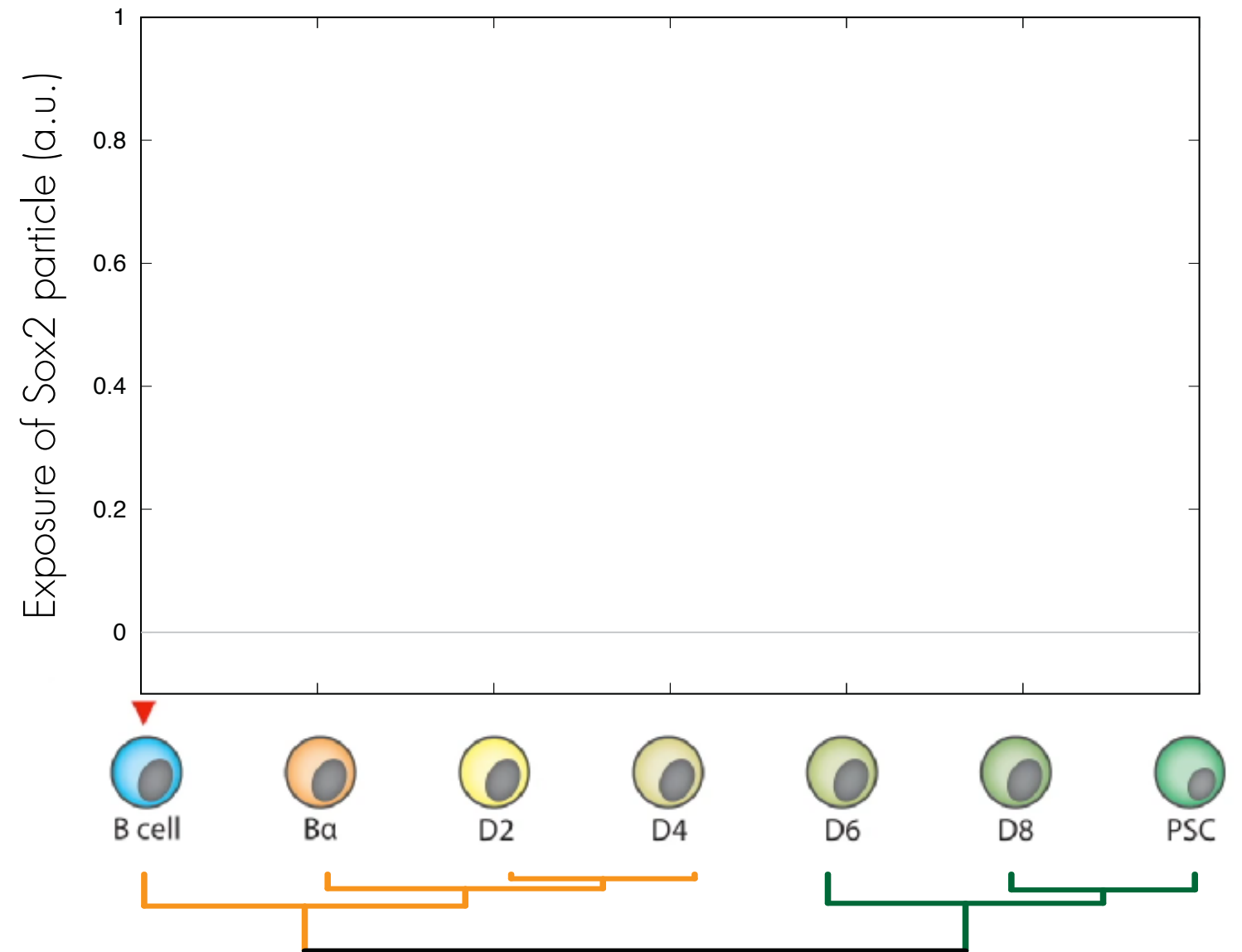
SOX2 locus structural changes from B to PSC

Structural exposure



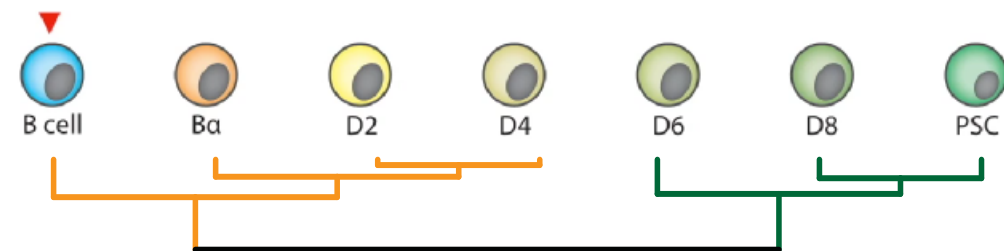
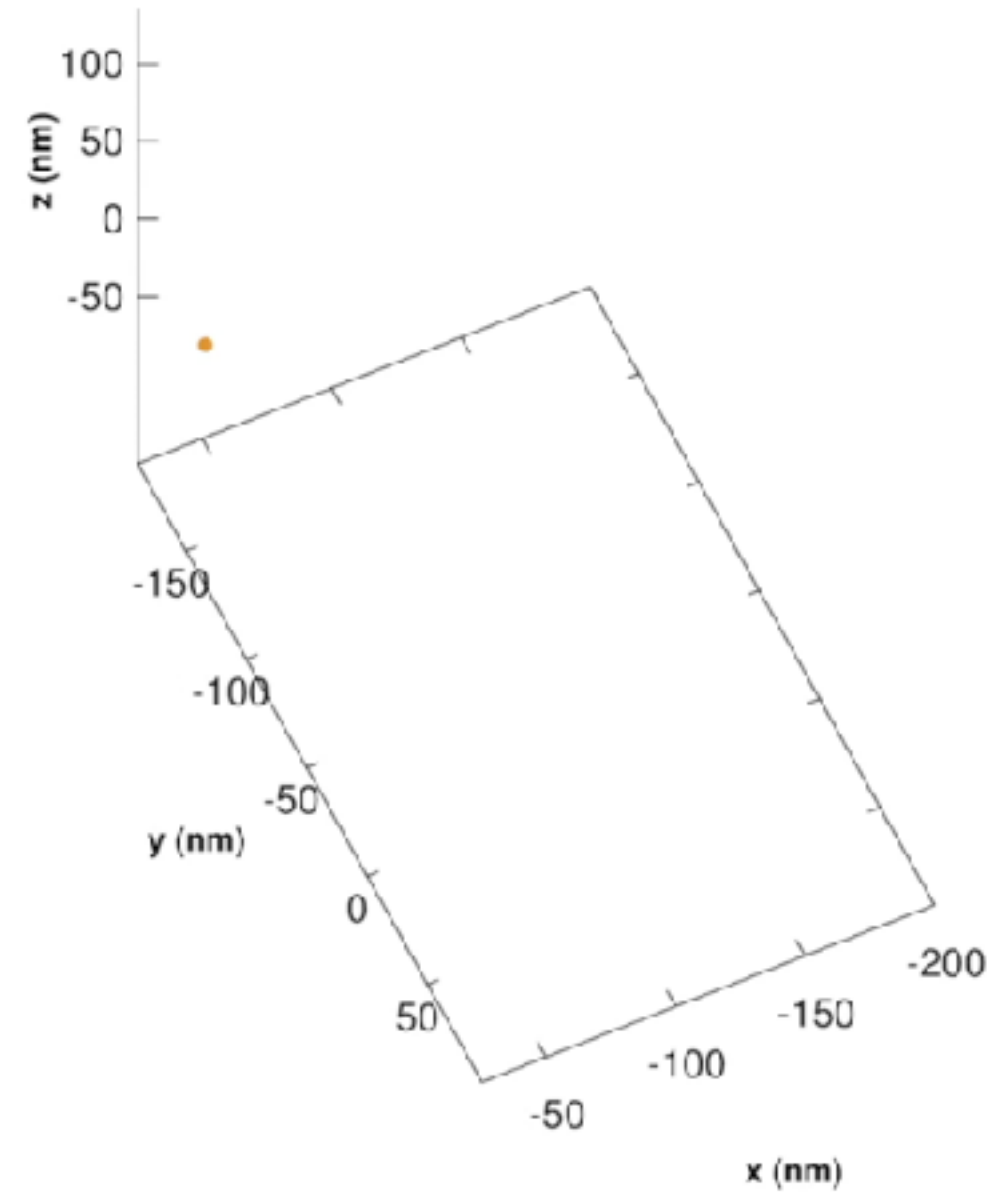
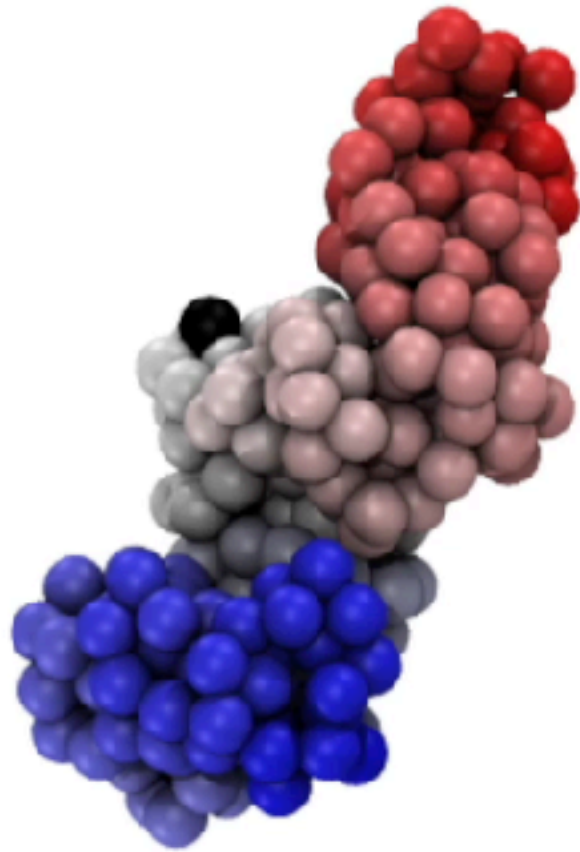
SOX2 locus structural changes from B to PSC

Structural exposure



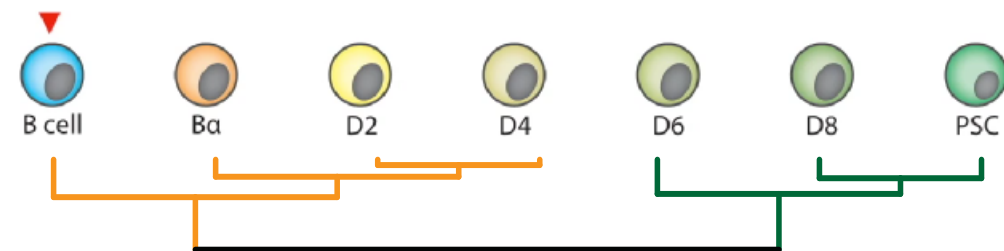
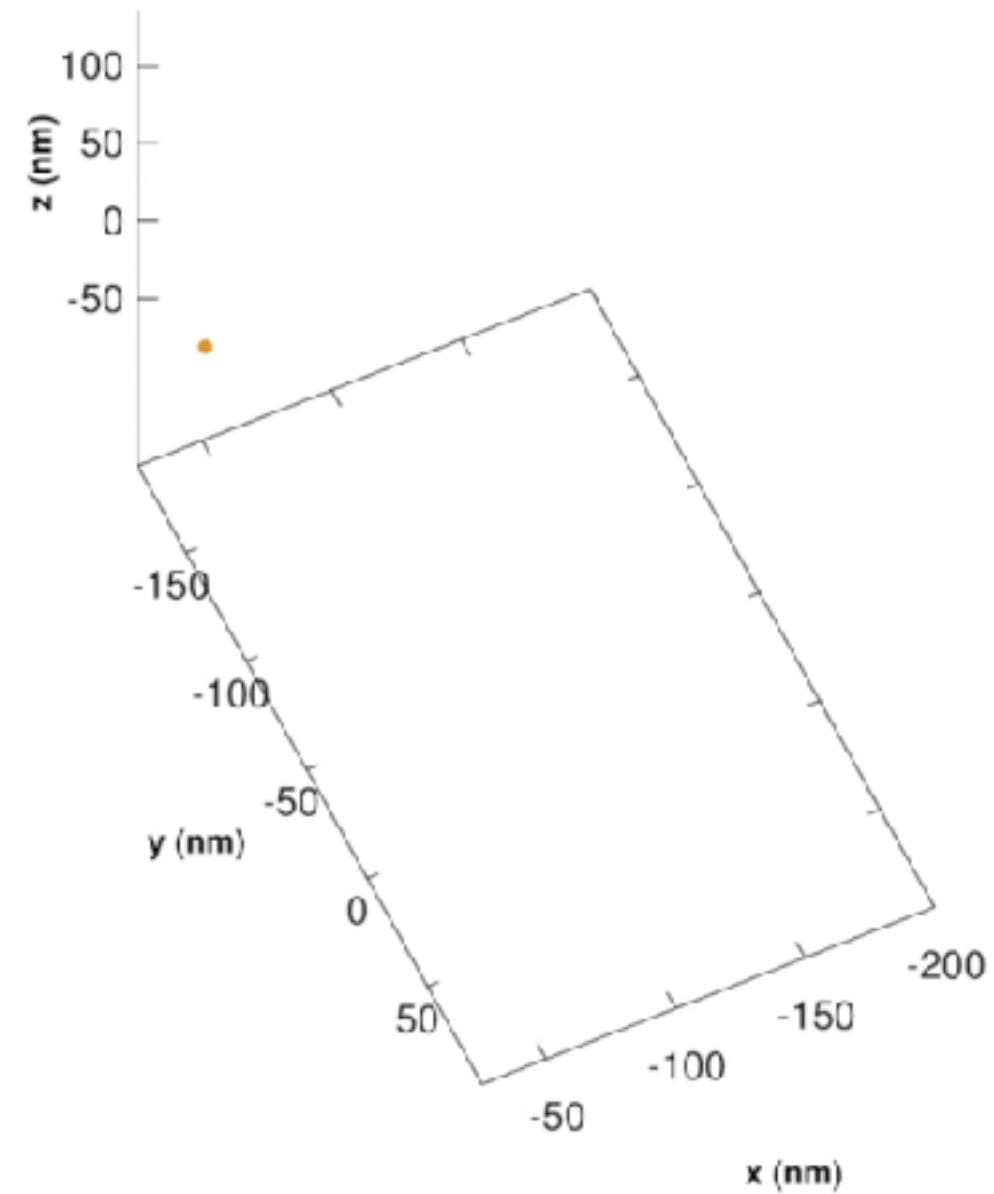
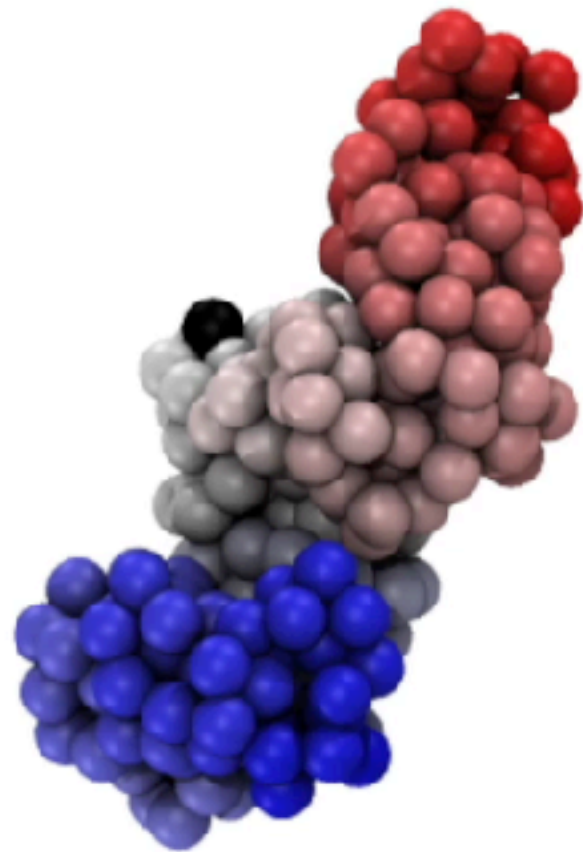
SOX2 locus dynamics changes from B to PSC

SOX2 displacement



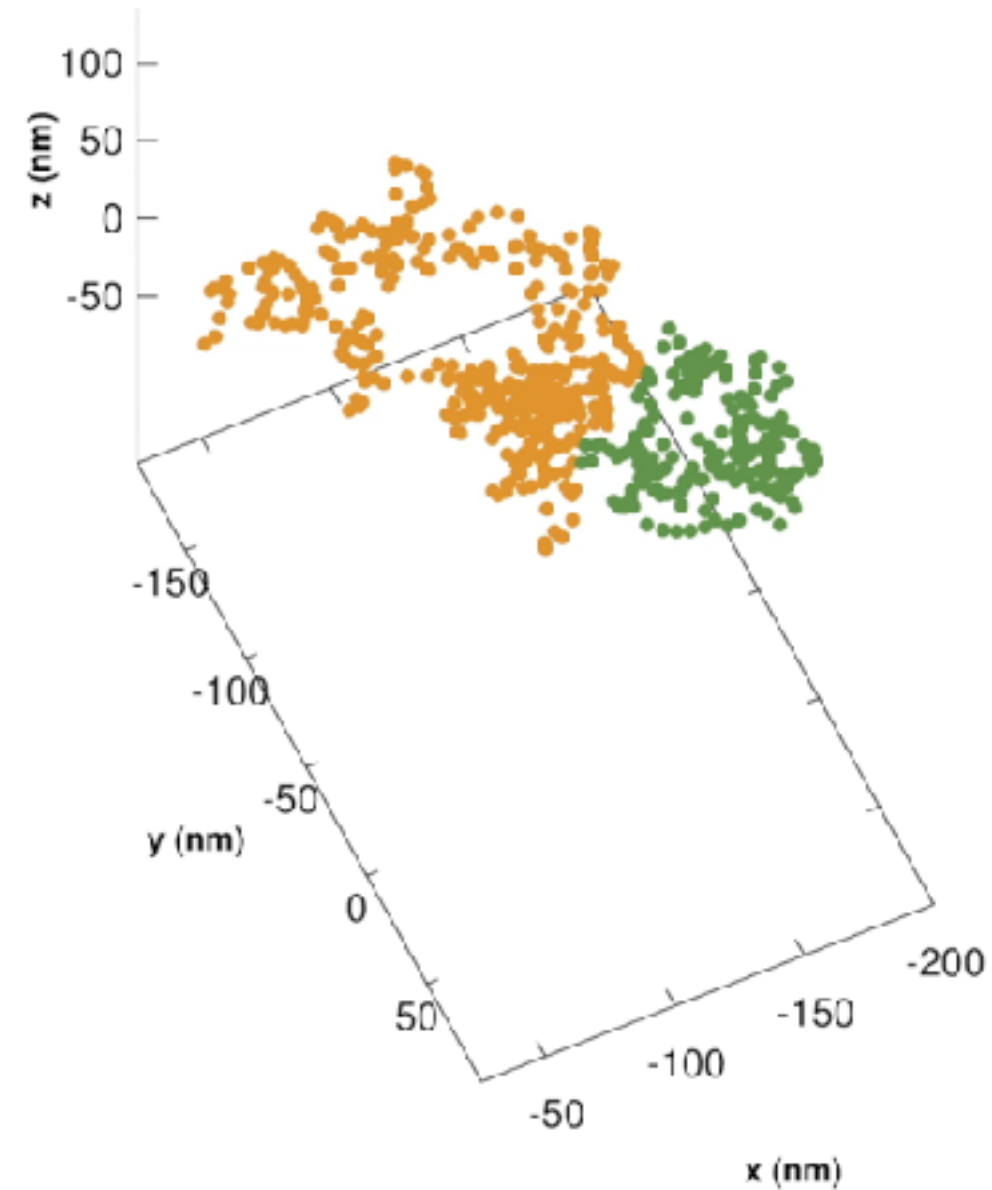
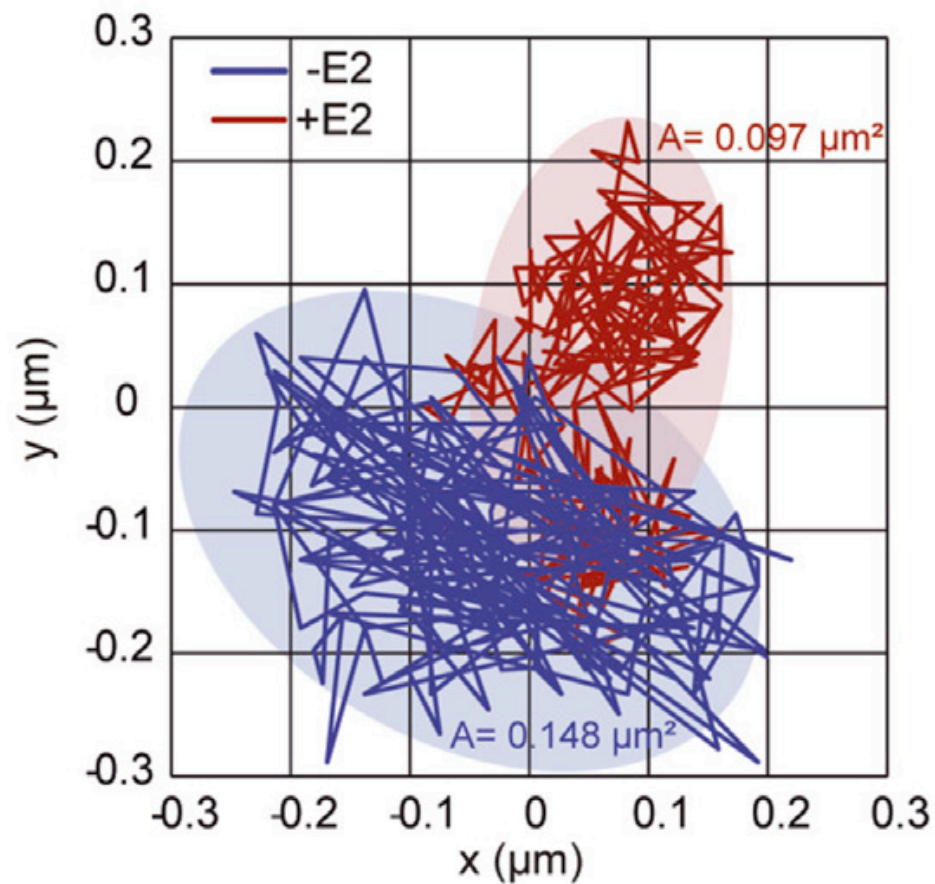
SOX2 locus dynamics changes from B to PSC

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).



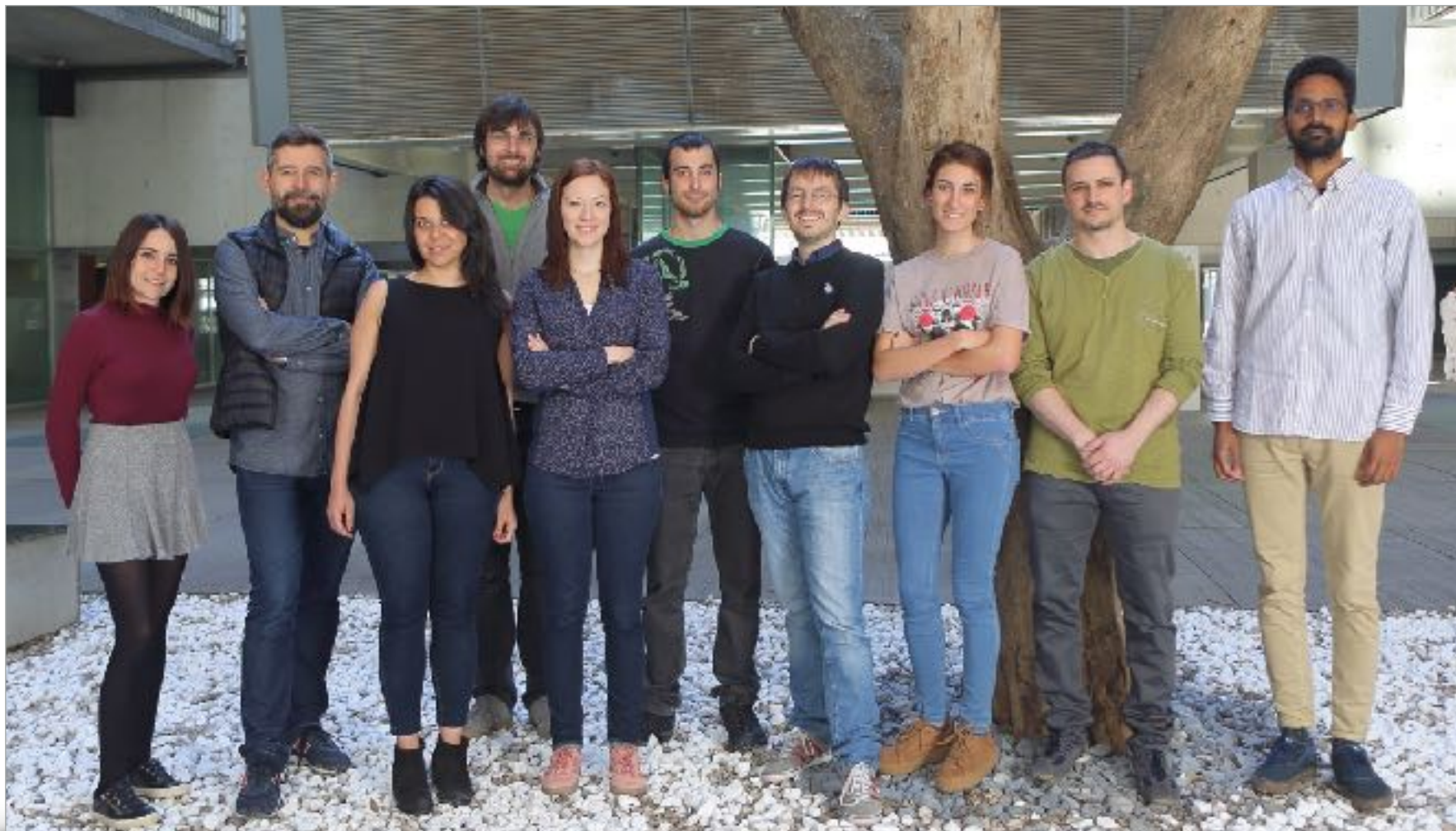
A “cage” model for transcriptional activation

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



<http://marciuslab.org>
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Marco Di Stefano

David Castillo
Yasmina Cuartero
Irene Farabella
Silvia Galan
Mike Goodstadt
Francesca Mugianesi
Julen Mendieta
Juan Rodriguez
François Serra
Paula Soler
Aleksandra Sparavier
Yannick Spill

In collaboration with Ralph Stadhouders (Erasmus MC) and Thomas Graf (CRG)

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