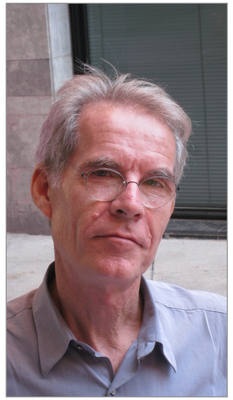
3D structural dynamics of the SOX2 locus activation

Marc A. Marti-Renom

CNAG-CRG · ICREA

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

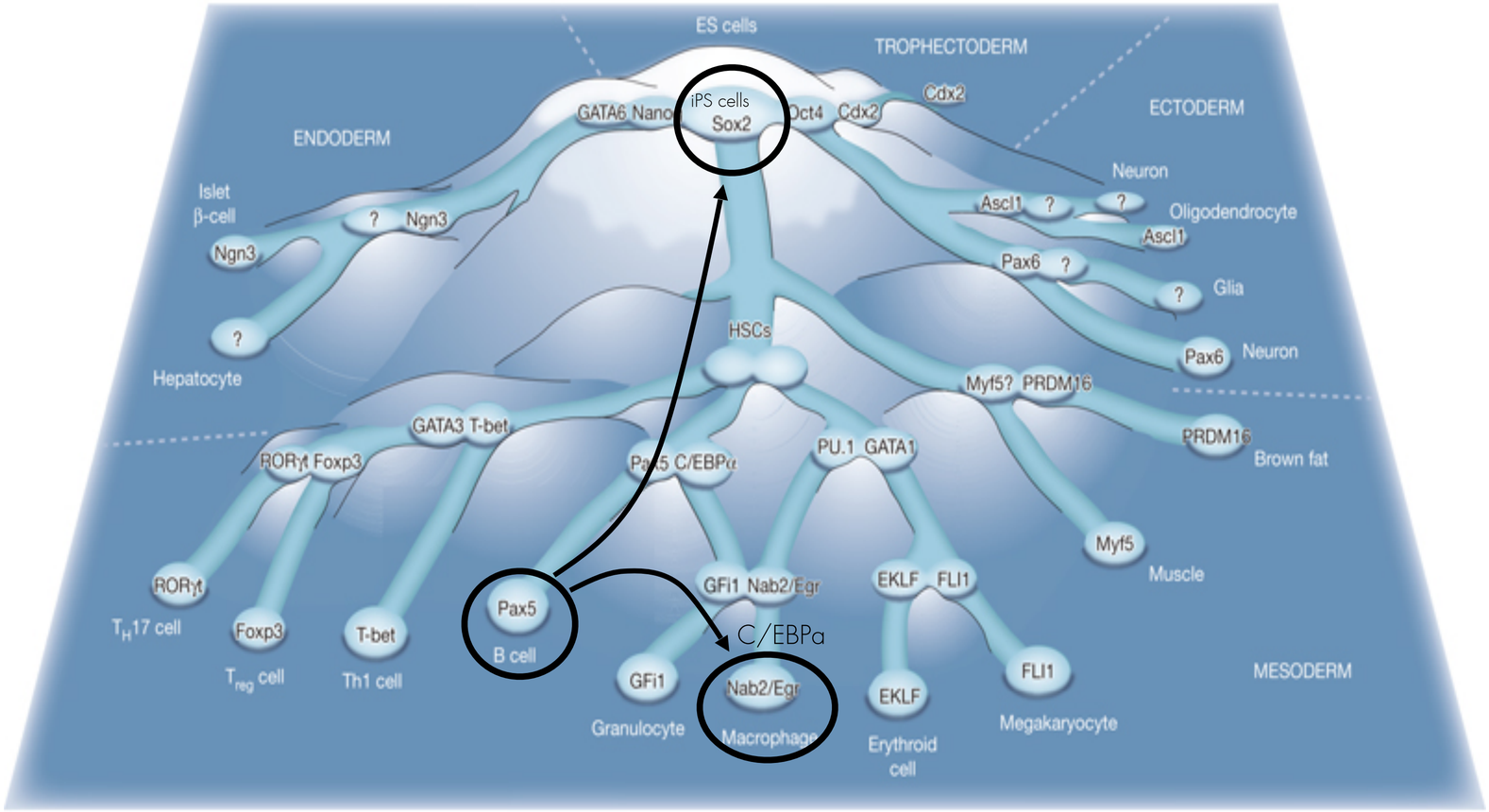
Marco di Stefano
CNAG-CRG



Ralph Stadhouders, Enrique Vidal & Thomas Graf
CRG

Transcription factors dictate cell fate

Graf & Enver (2009) Nature



Transcription factors (TFs) determine cell identity through gene regulation

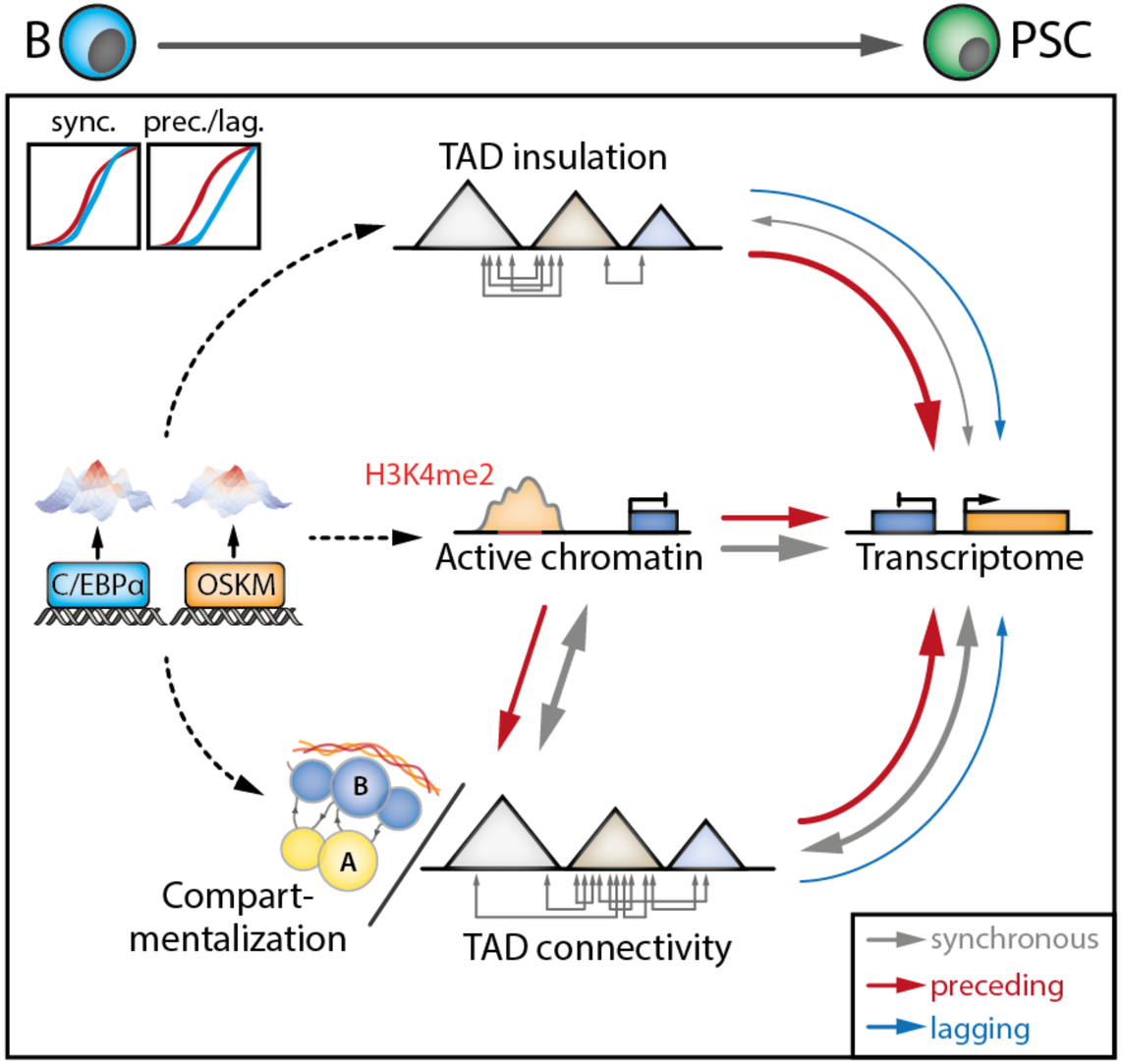
Normal 'forward' differentiation

Cell fates can be converted by enforced TF expression

Transdifferentiation or reprogramming

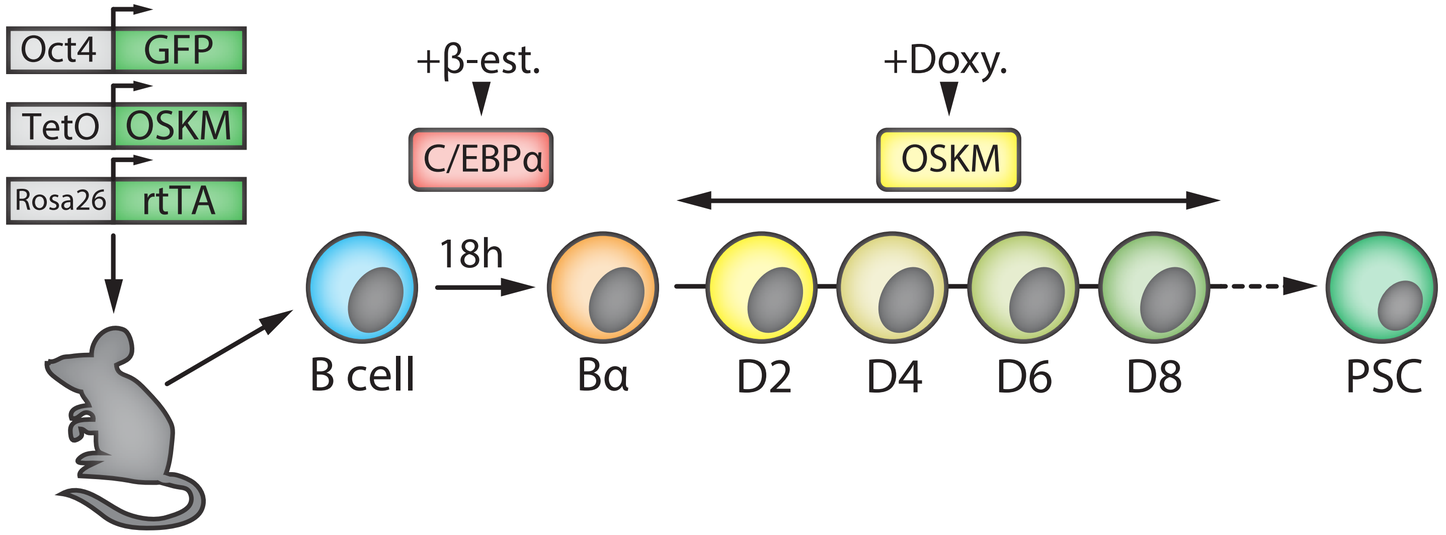
Interplay: topology, gene expression & chromatin

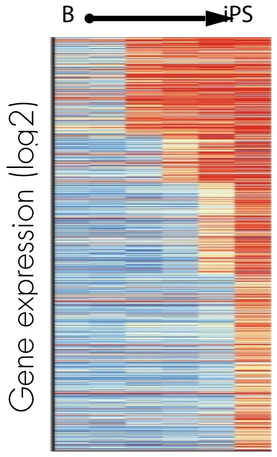
Stadhouders, R., Vidal, E. et al. (2018) Nature Genetics

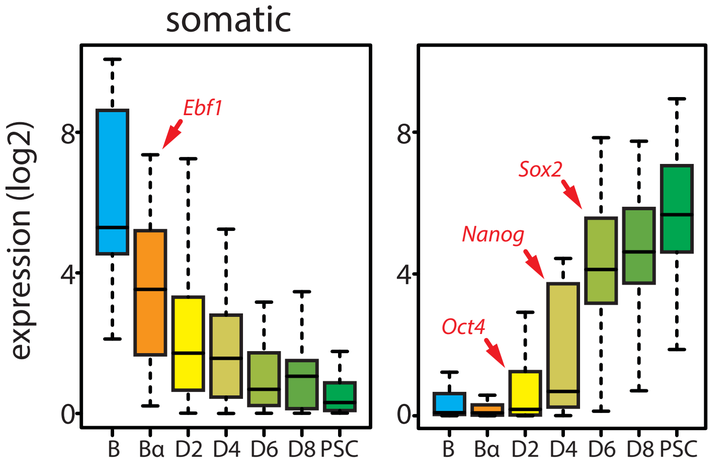


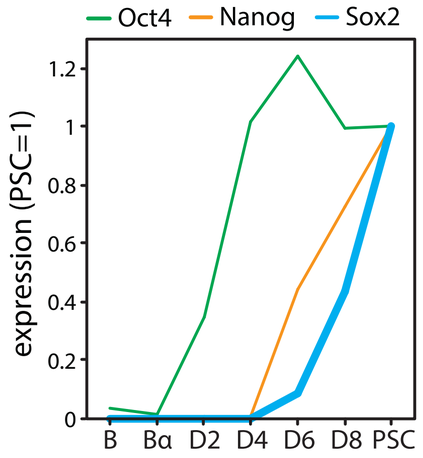
Reprogramming from B to PSC

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



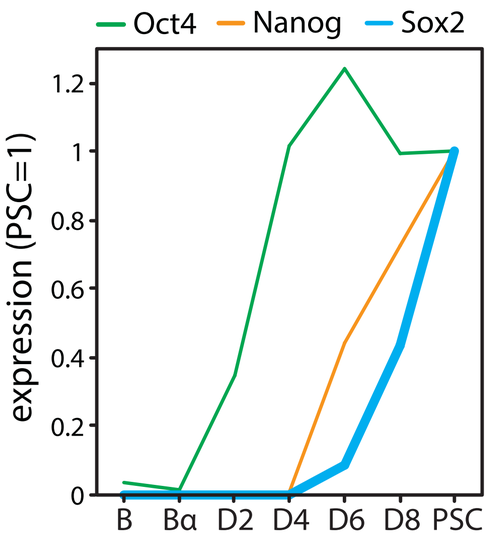


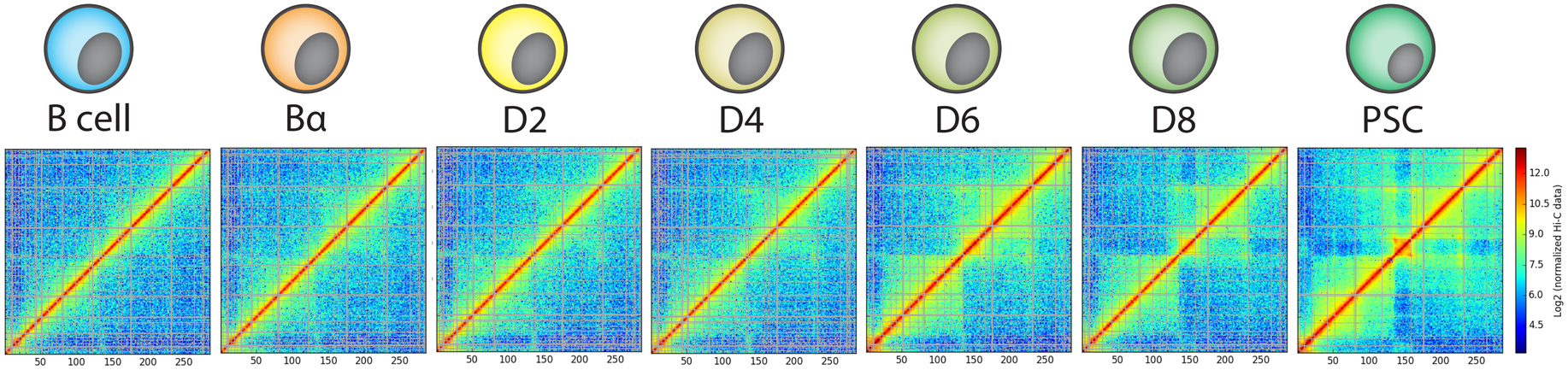




Hi-C maps of reprogramming from B to PSC

The SOX2 locus





Hi-C maps of reprogramming from B to PSC

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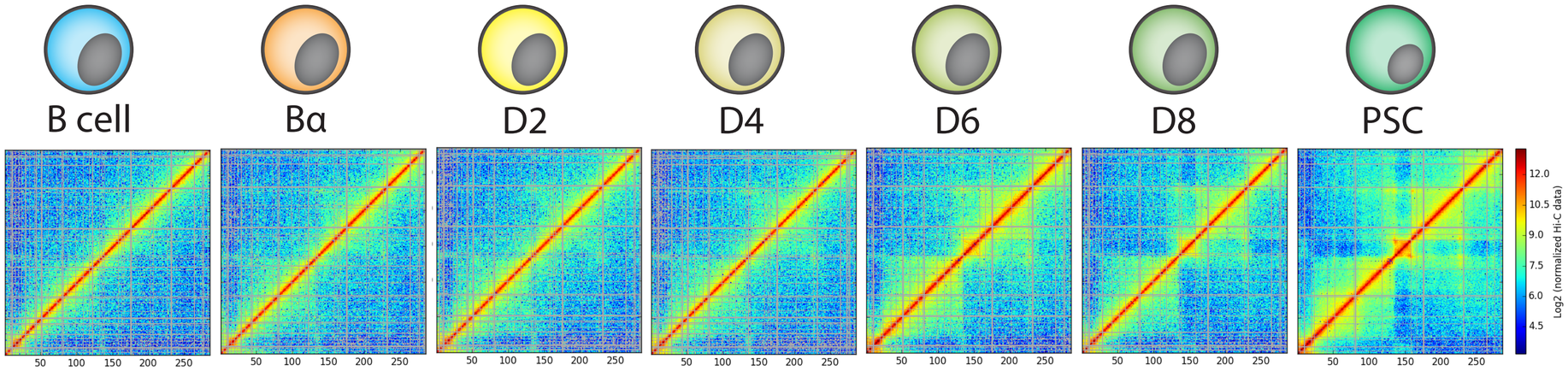
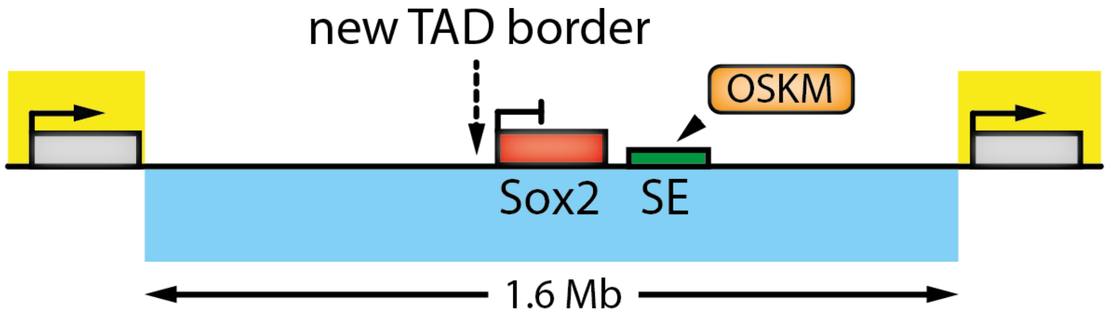
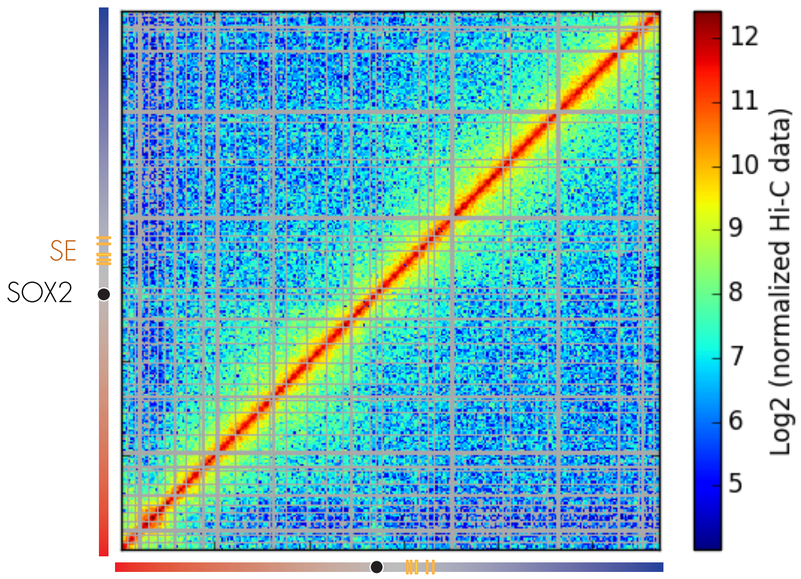


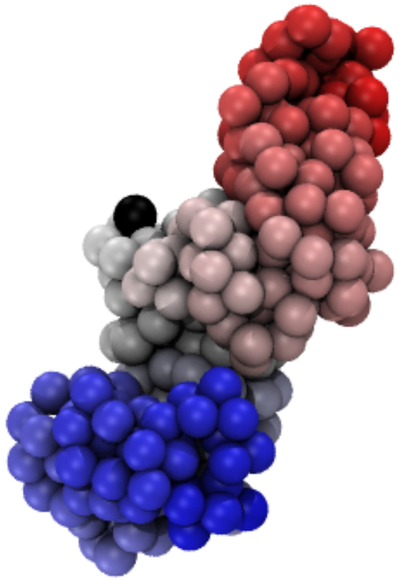
How does these structural rearrangements interplay with the transcription activity?

What are the main drivers of structural transitions?

TADbit modeling of SOX2 from B cells Hi-C





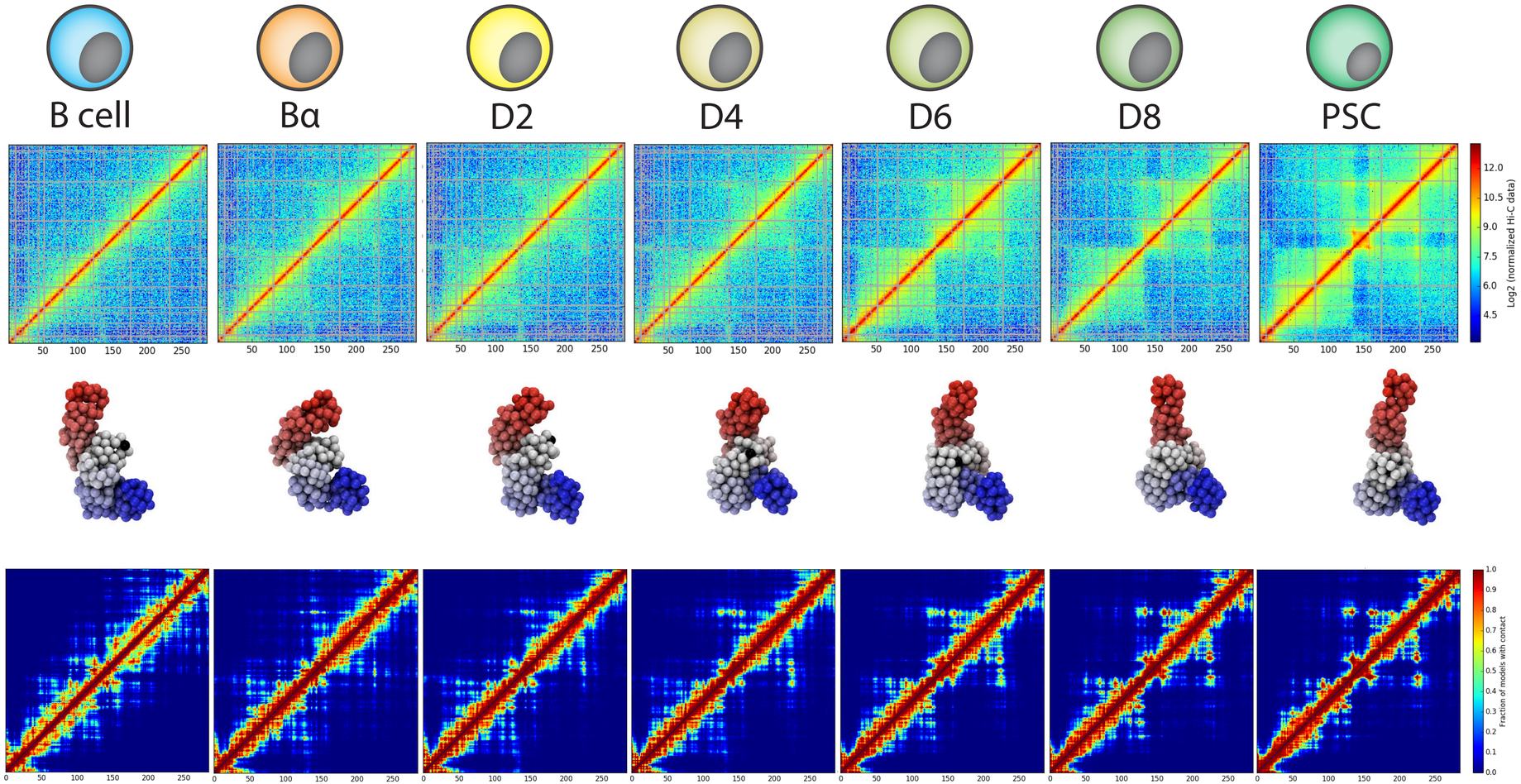


Optimal IMP parameters

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

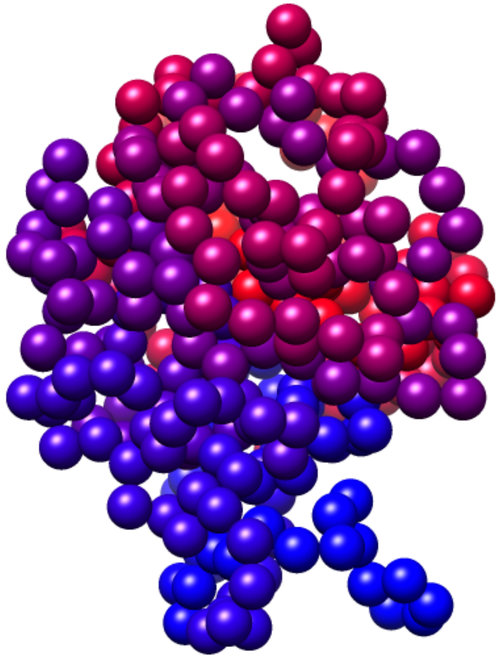
Models of reprogramming from B to PSC

The SOX2 locus



TADdyn. Dynamics of chromatin

Marco Di Stefano

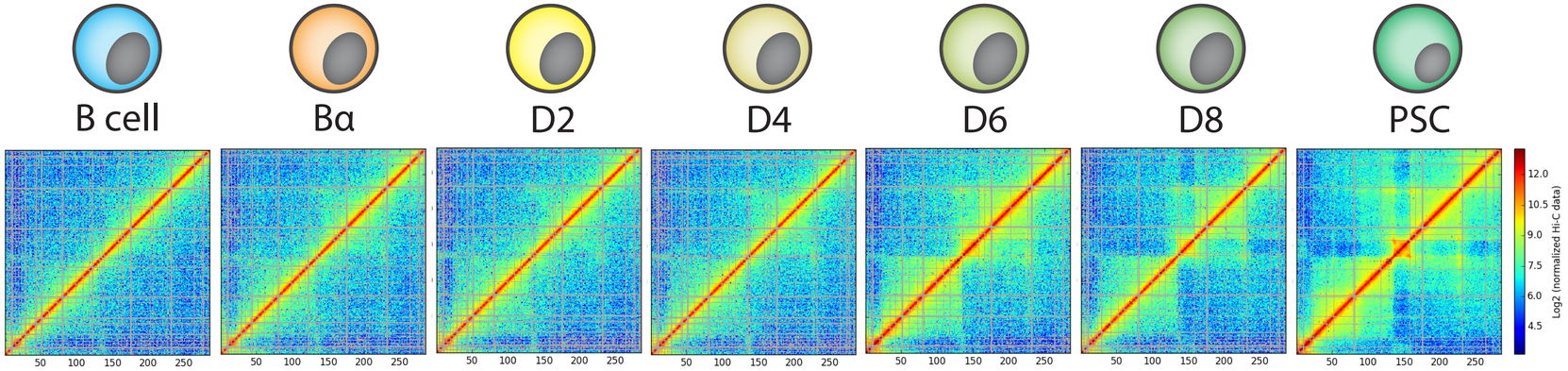


$$\mathcal{H}_{intra} = \sum_{i=1}^{N} U_{FENE}(i, i+1) + U_{br}(i, i+1, i+2) + \sum_{j=i+1}^{N} U_{LJ}(i, j)$$

Chain-connectivity interaction
Bending
Lennard-Jones Potential

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

The SOX2 locus



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

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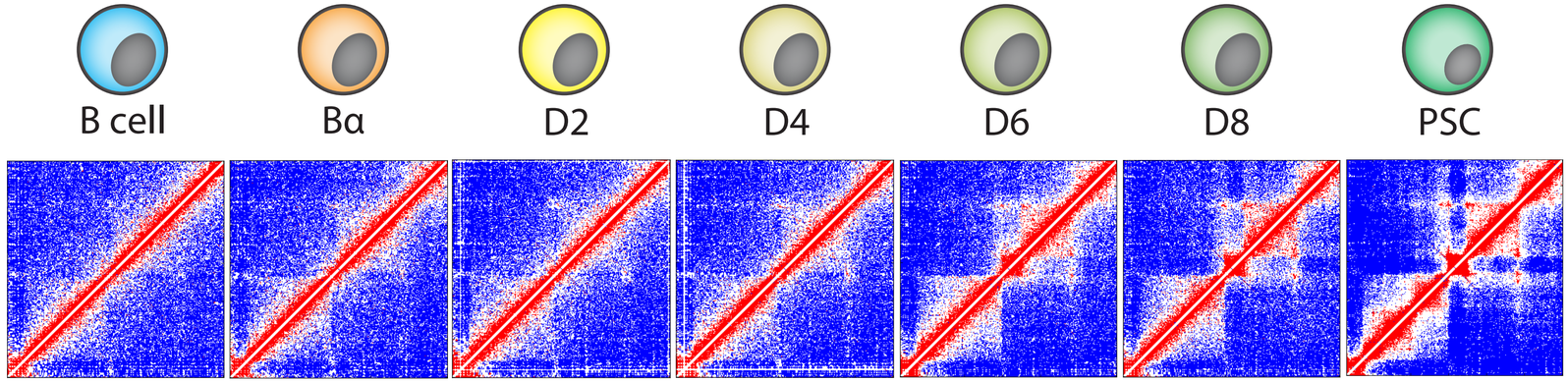
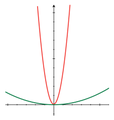
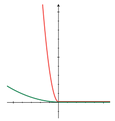




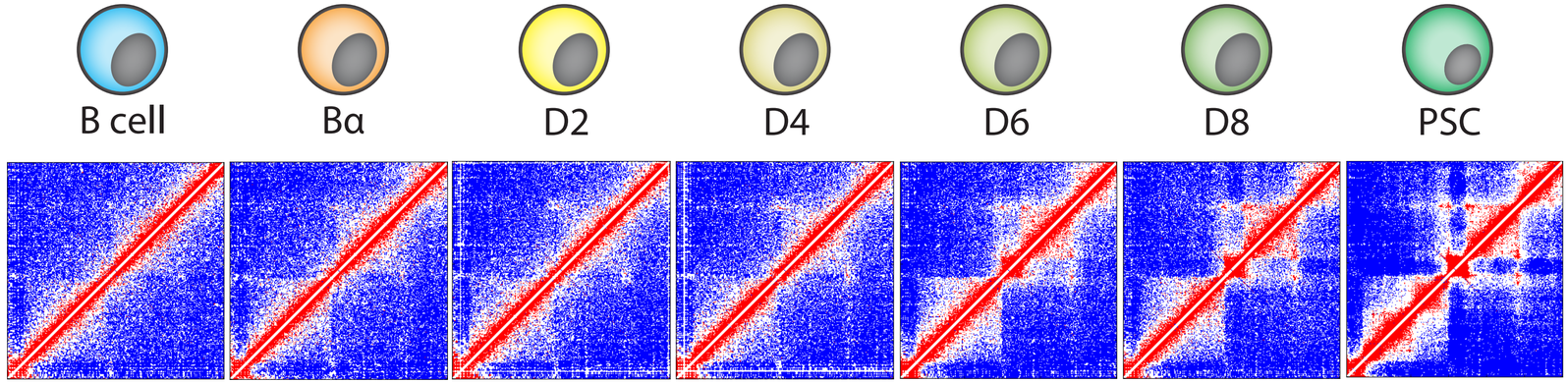
Harmonic

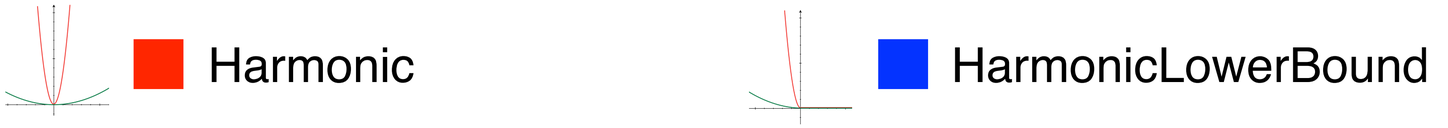


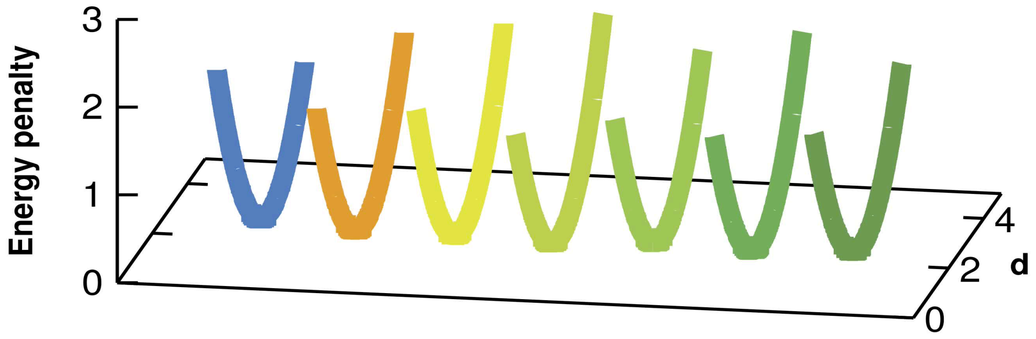
HarmonicLowerBound

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

The SOX2 locus



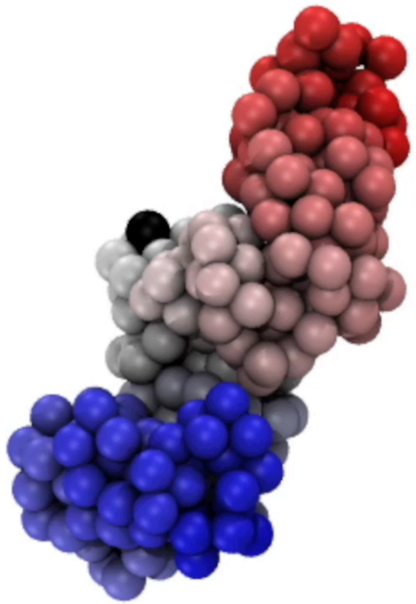


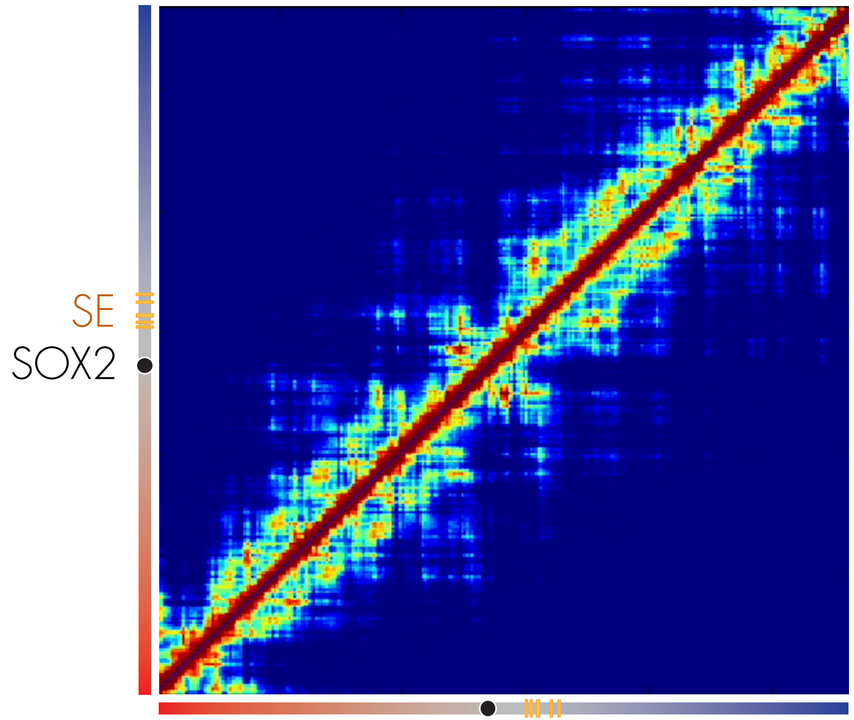


Transition	Stable	Vanishing	Raising
B -> Bα	18,612	6,984	7,290
Bα -> D2	18,512	7,390	6,687
D2 -> D4	18,369	6,830	6,893
D4 -> D6	18,971	6,291	7,289
D6 -> D8	20,167	6,093	6,250
D8 -> ES	20,679	5,738	6,173

SOX2 locus structural changes from B to PSC

Contacts





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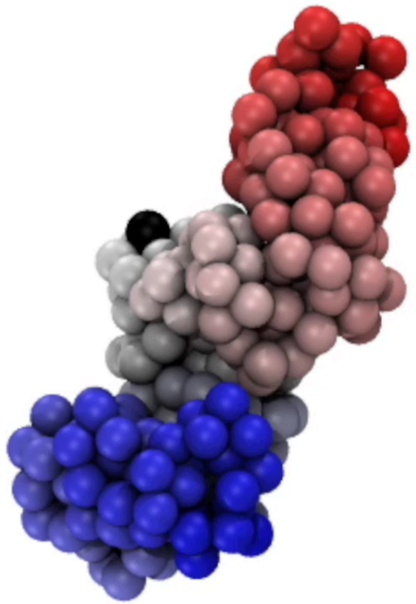
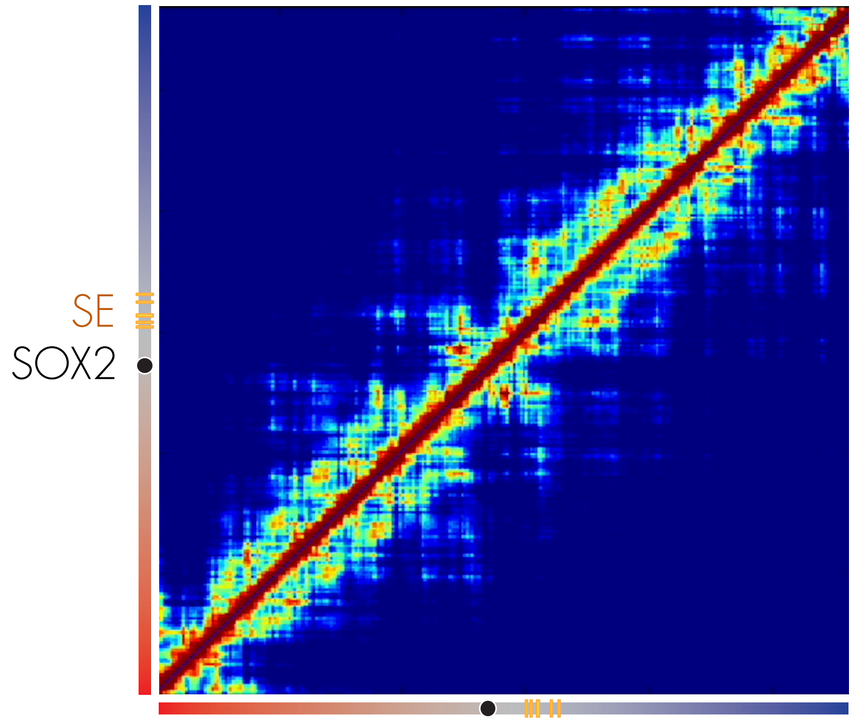
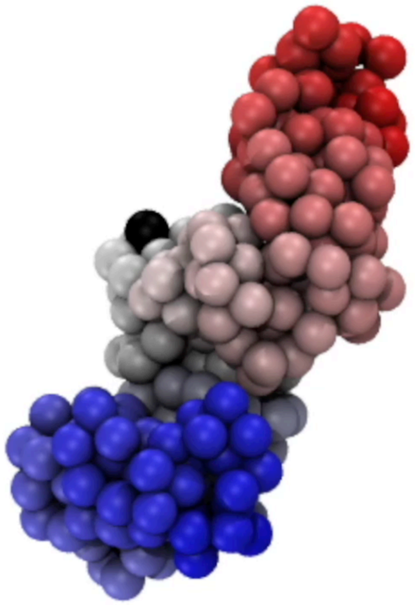
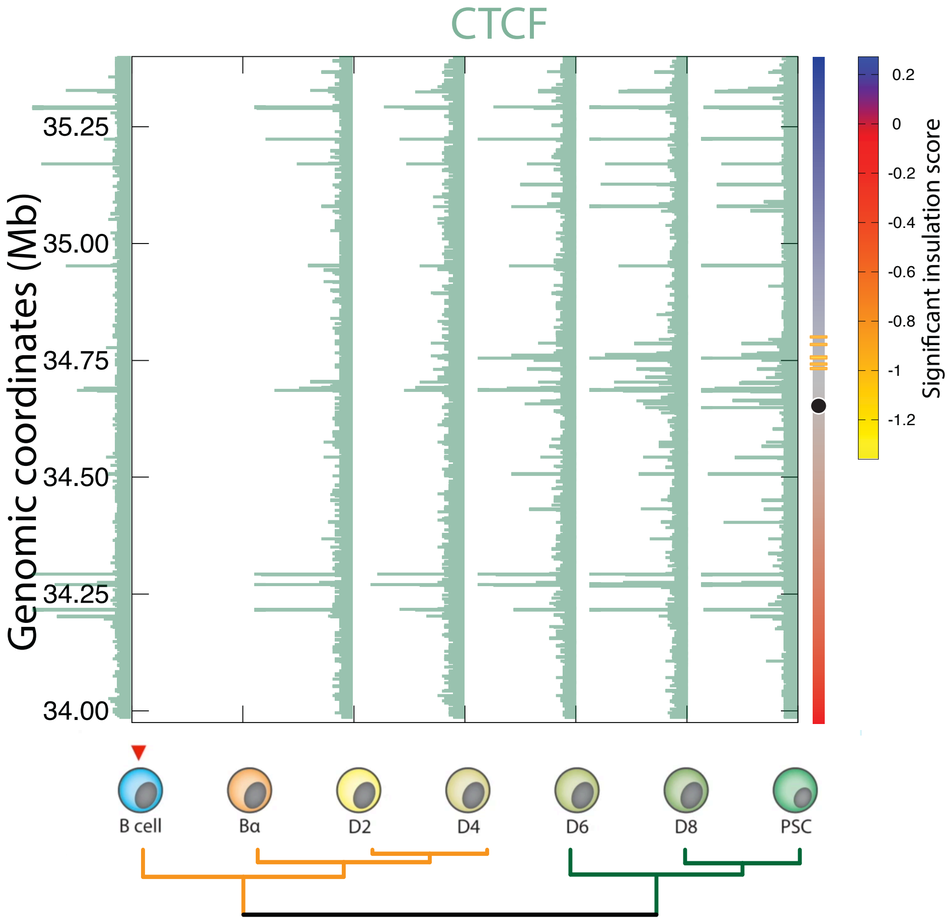




SOX2 locus structural changes from B to PSC

TAD borders





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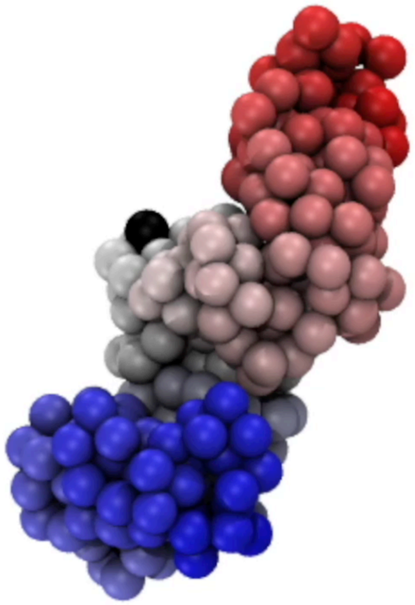
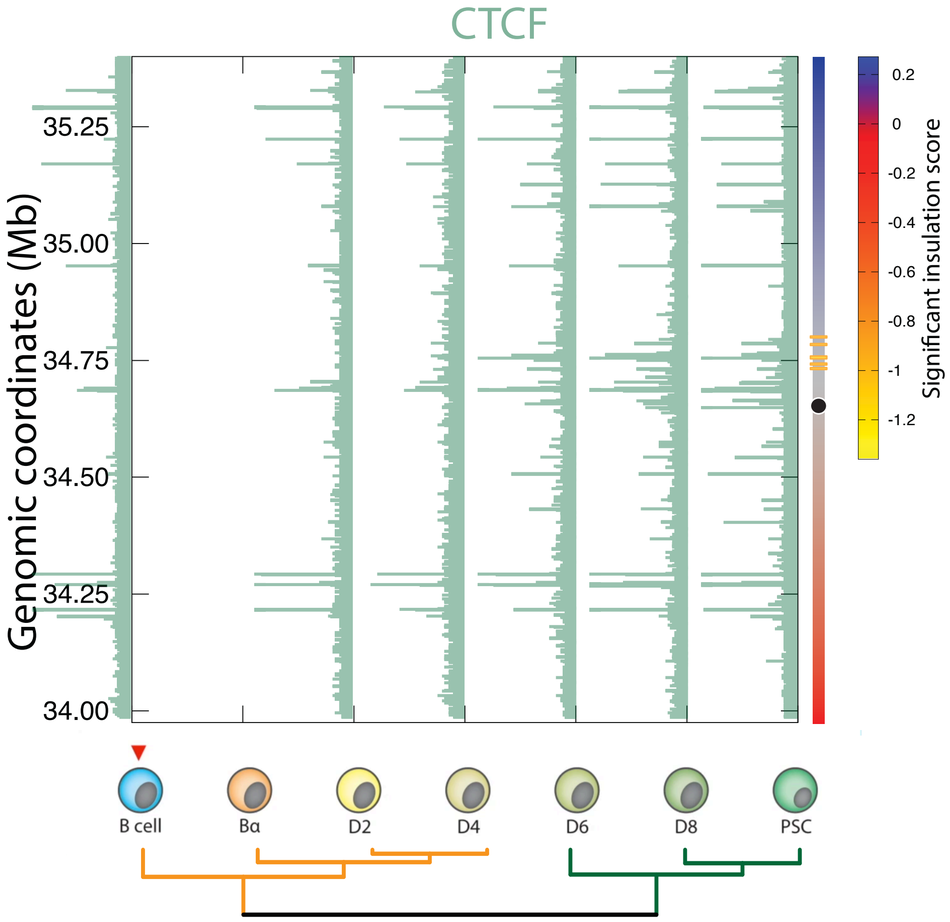
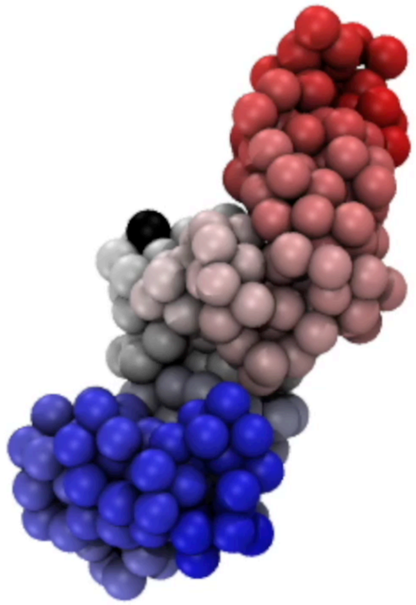
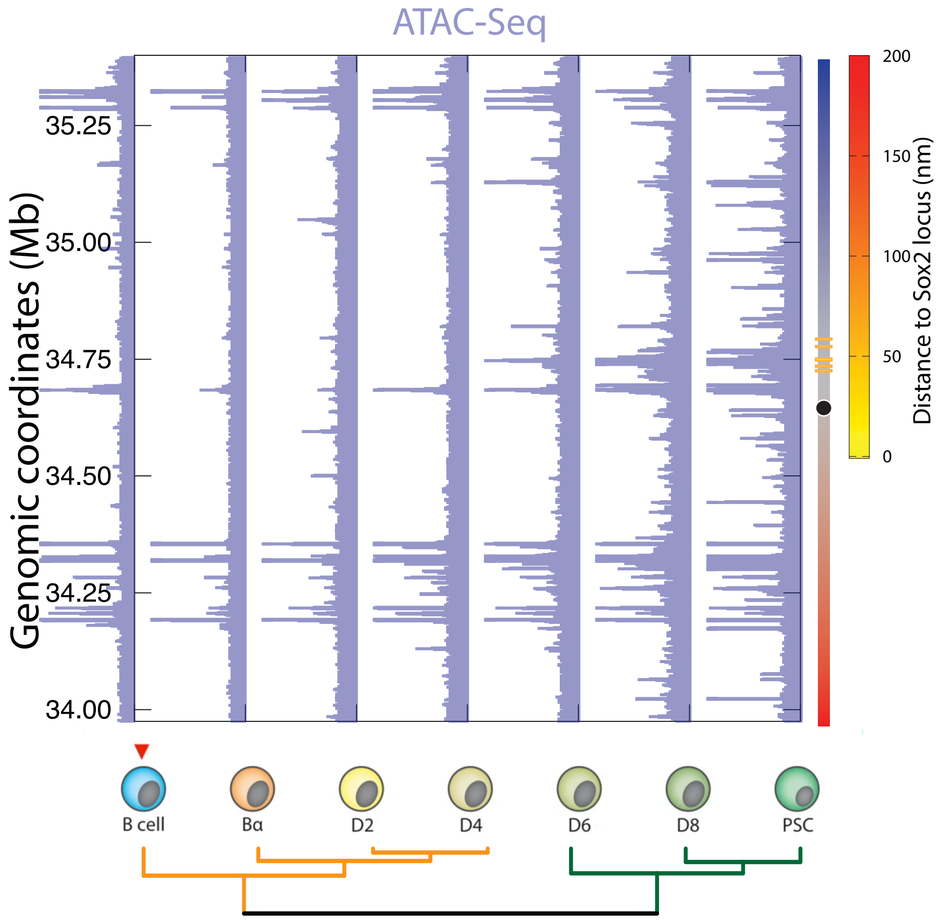




SOX2 locus structural changes from B to PSC

Distance to regulatory elements





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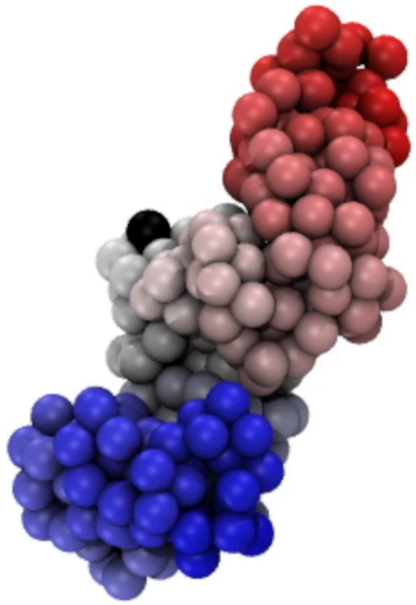
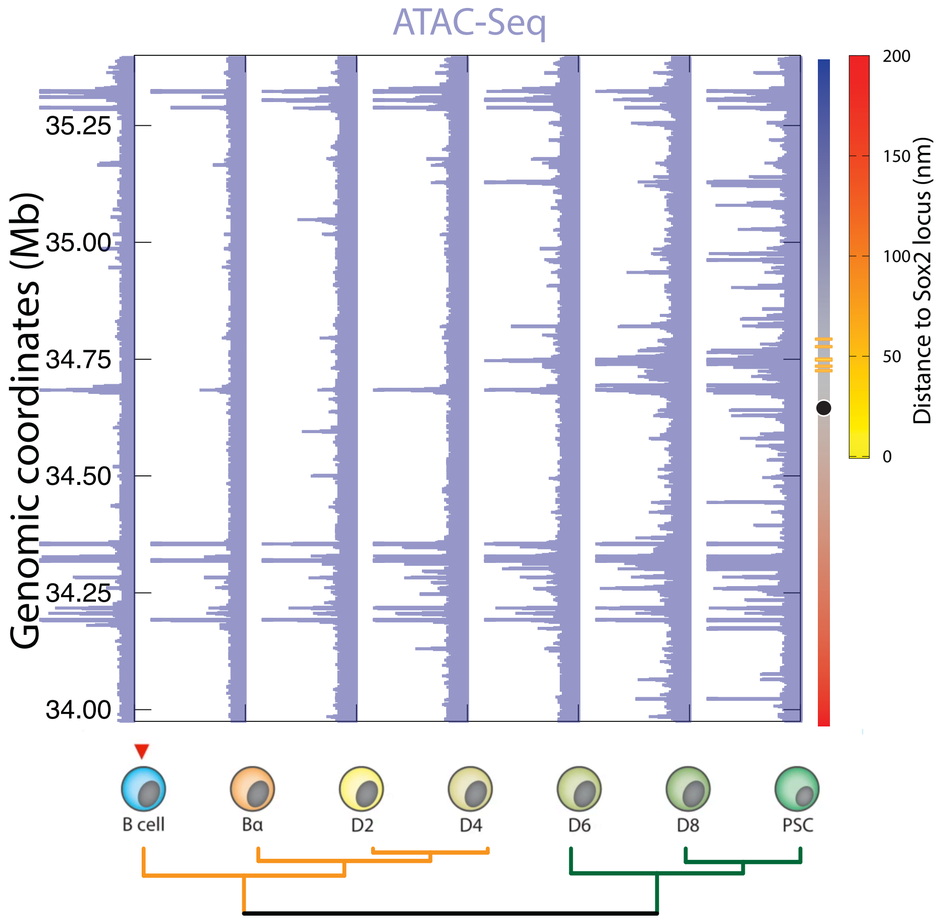
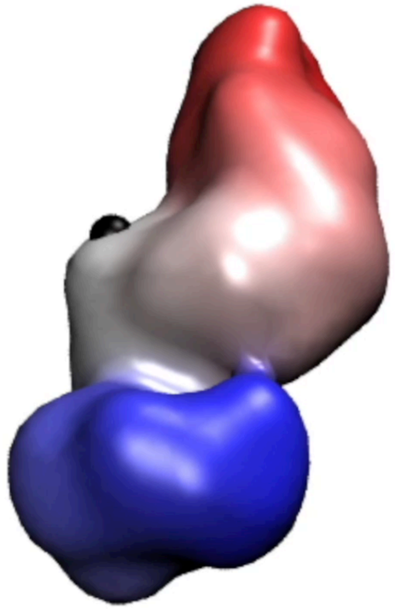
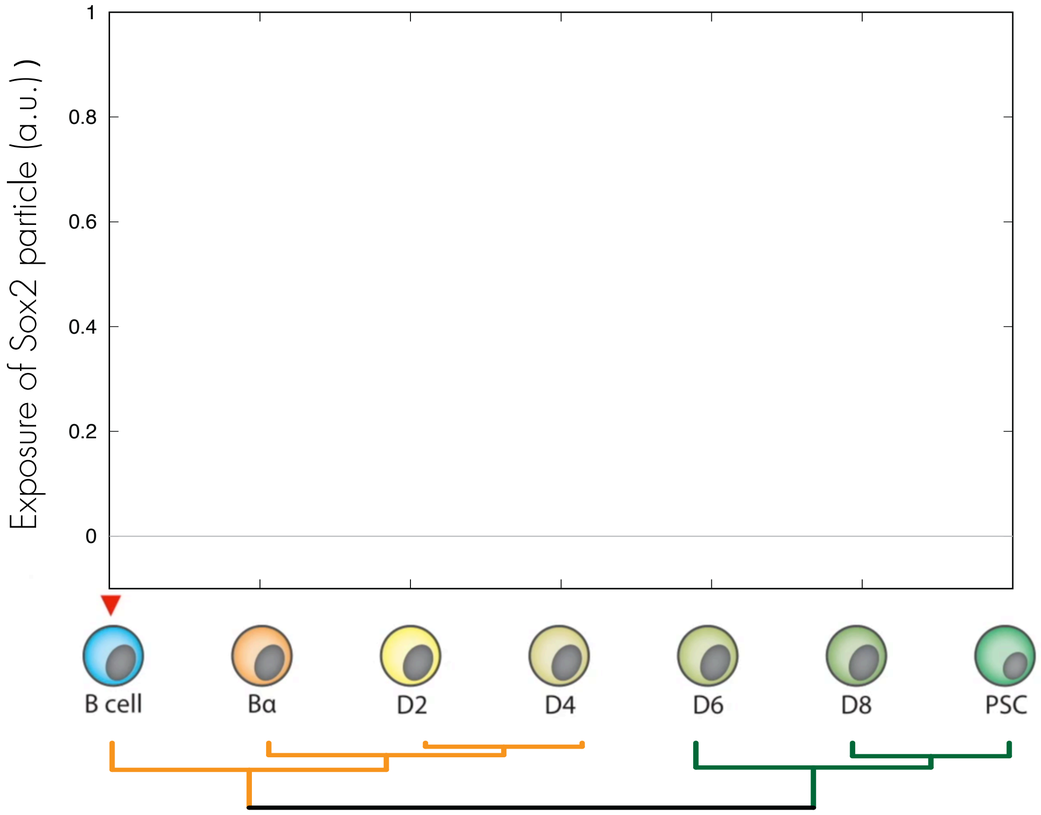




SOX2 locus structural changes from B to PSC

Structural exposure





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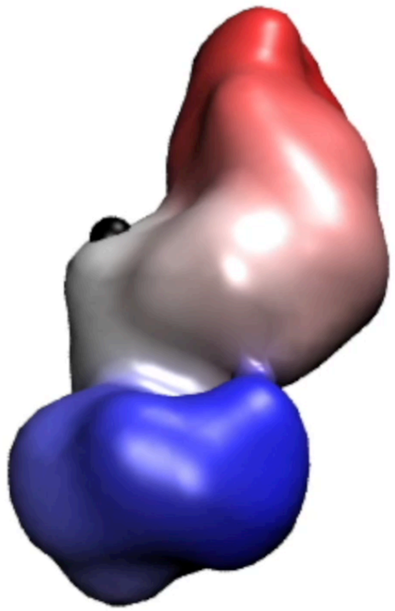
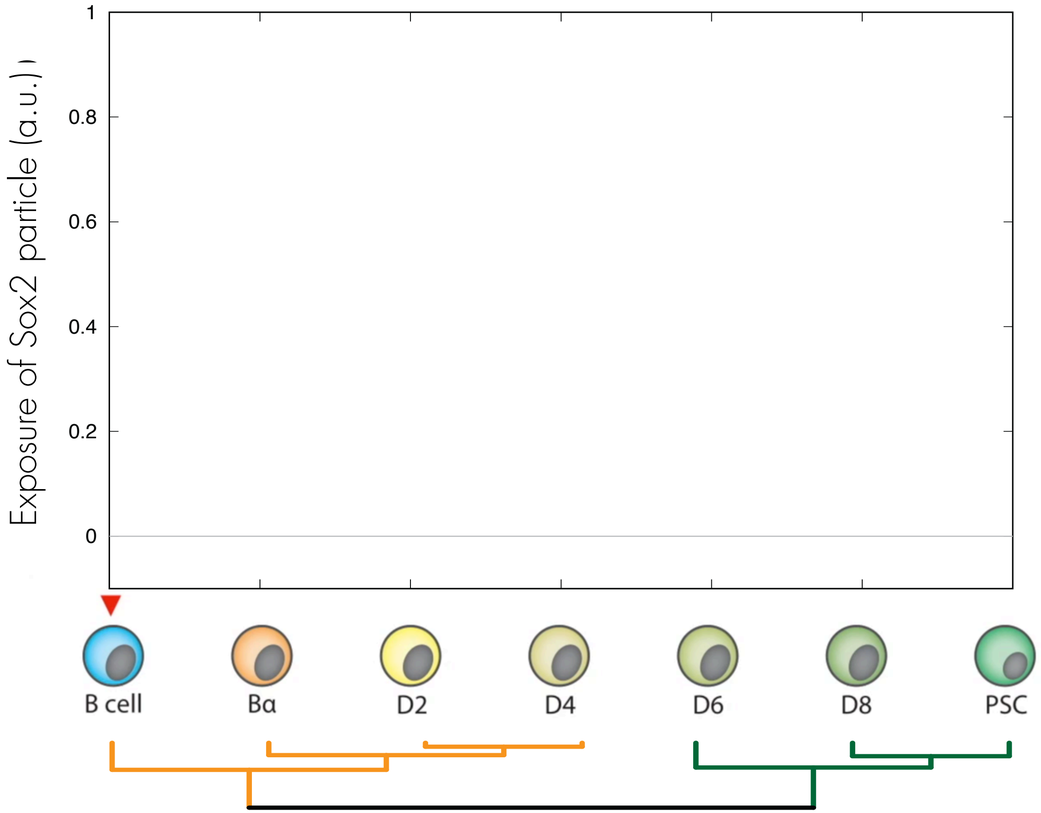
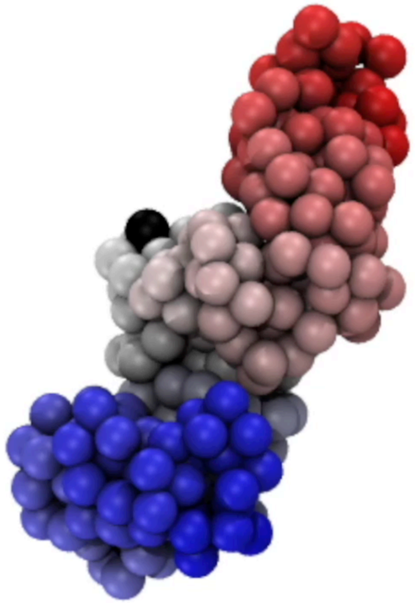
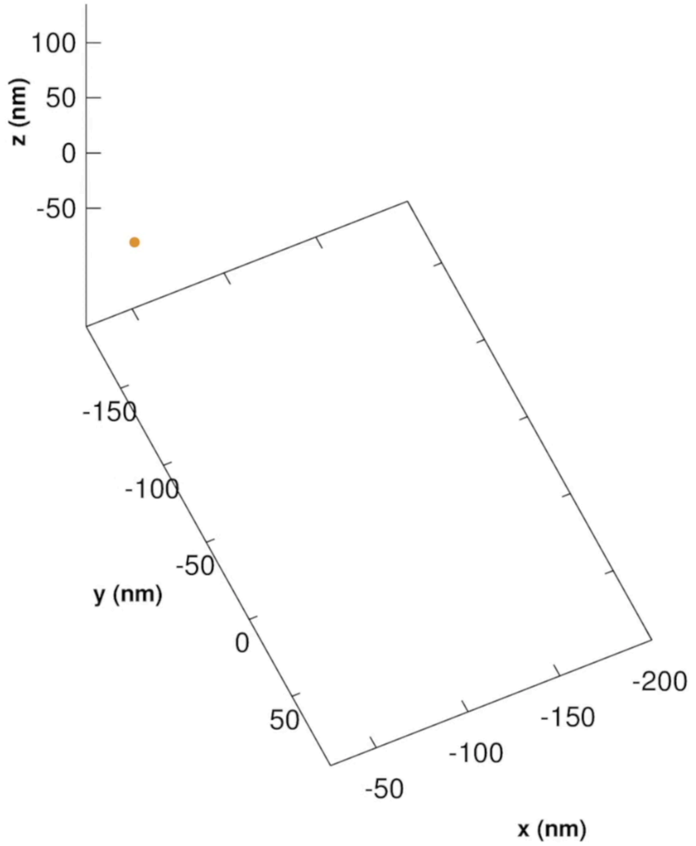


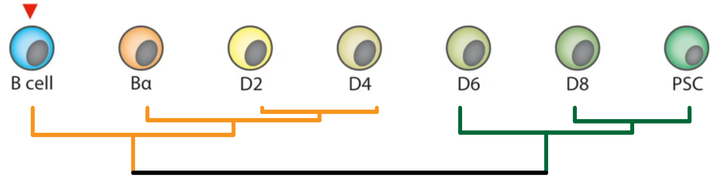


SOX2 locus dynamics changes from B to PSC

SOX2 displacement

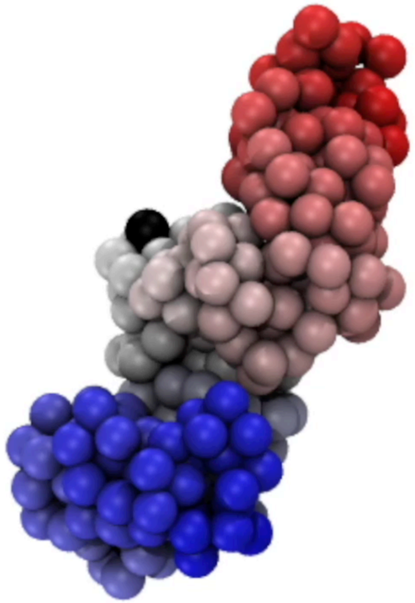


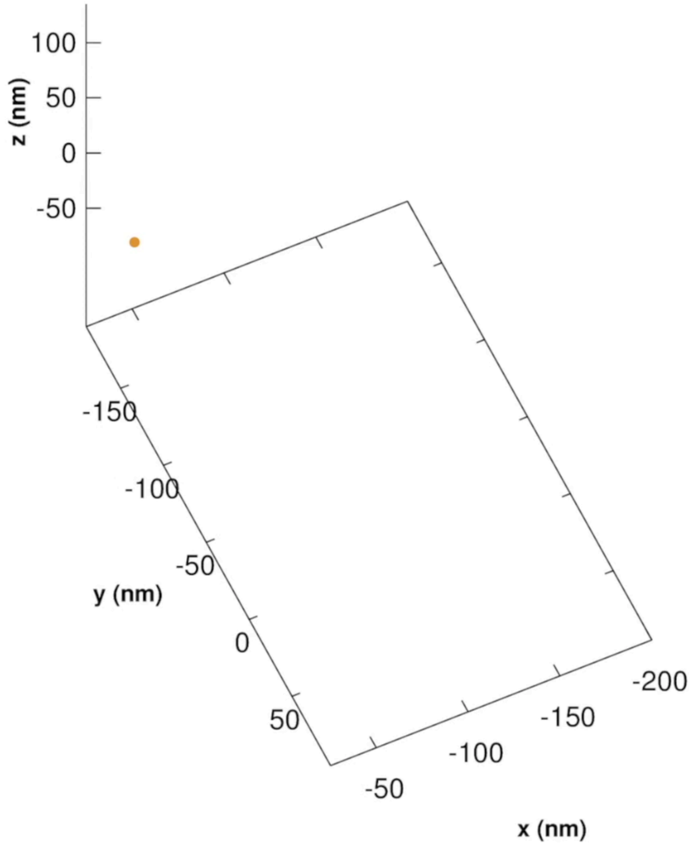


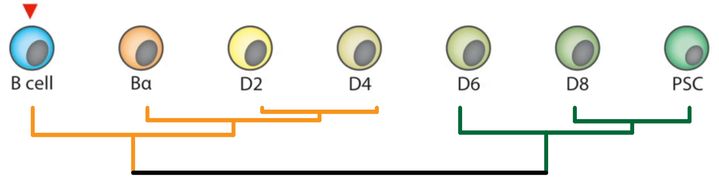


SOX2 locus dynamics changes from B to PSC

SOX2 displacement

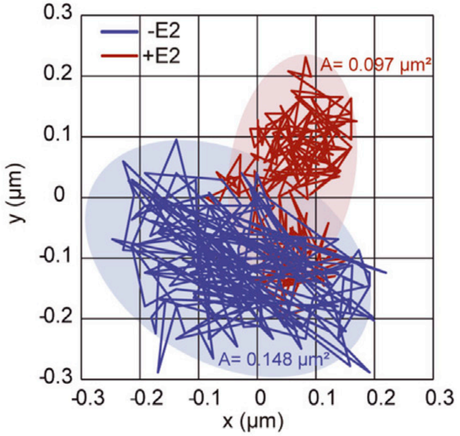






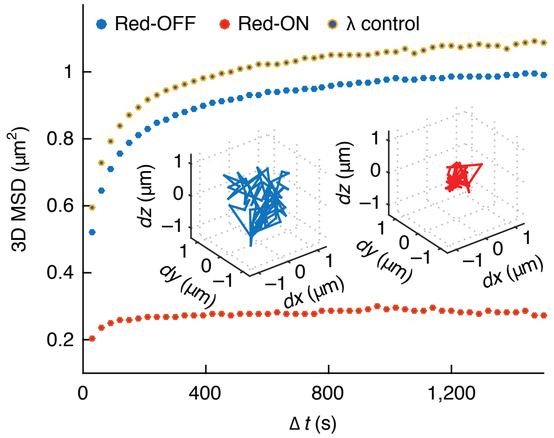
SOX2 locus dynamics changes from B to PSC

SOX2 displacement



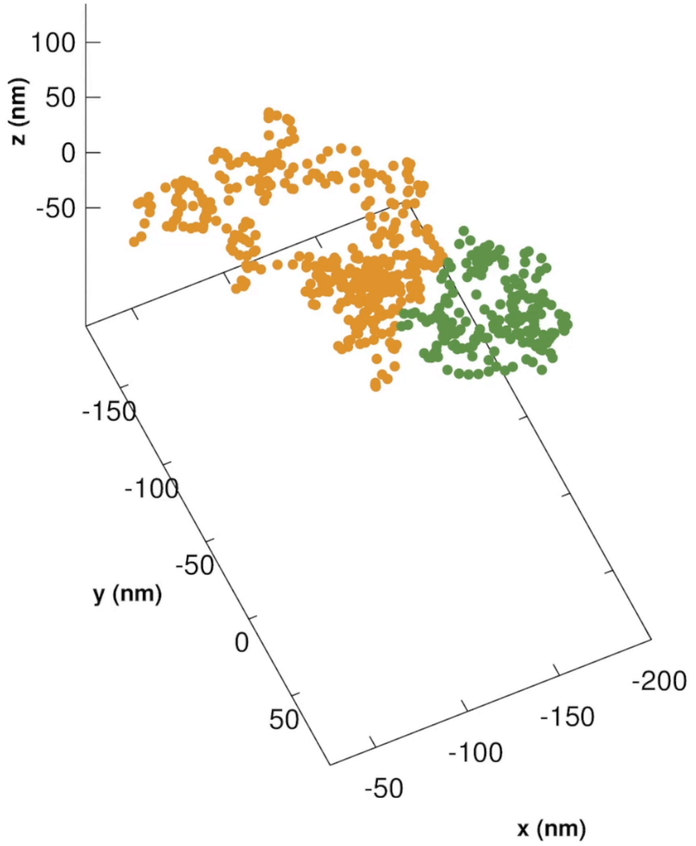
Two dimensional trajectories and area explored over 50s of the CCND1 locus recored before -E2 and after +E2 activation.

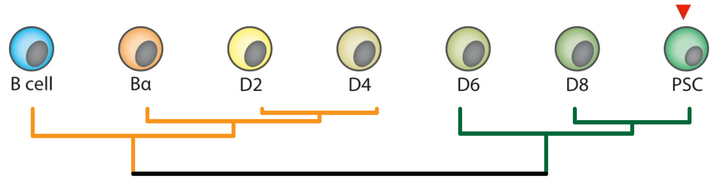
Germier ,T., et al, (2017) Biophys J.



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





TITLE: Live-Cell Imaging Reveals Enhancer-dependent *Sox2* Transcription in the Absence of Enhancer Proximity

AUTHOR NAMES AND AFFILIATIONS: Jeffrey M. Alexander[1], Juan Guan[2], Bo Huang[2,3,4], Stavros Lomvardas[5,6], Orion D. Weiner[1,3*]

A “cage” model for transcriptional activation