



Dynamics of gene activation

Marc A. Marti-Renom

CNAG-CRG . ICREA

Nature Genetics (2018) 50 p238

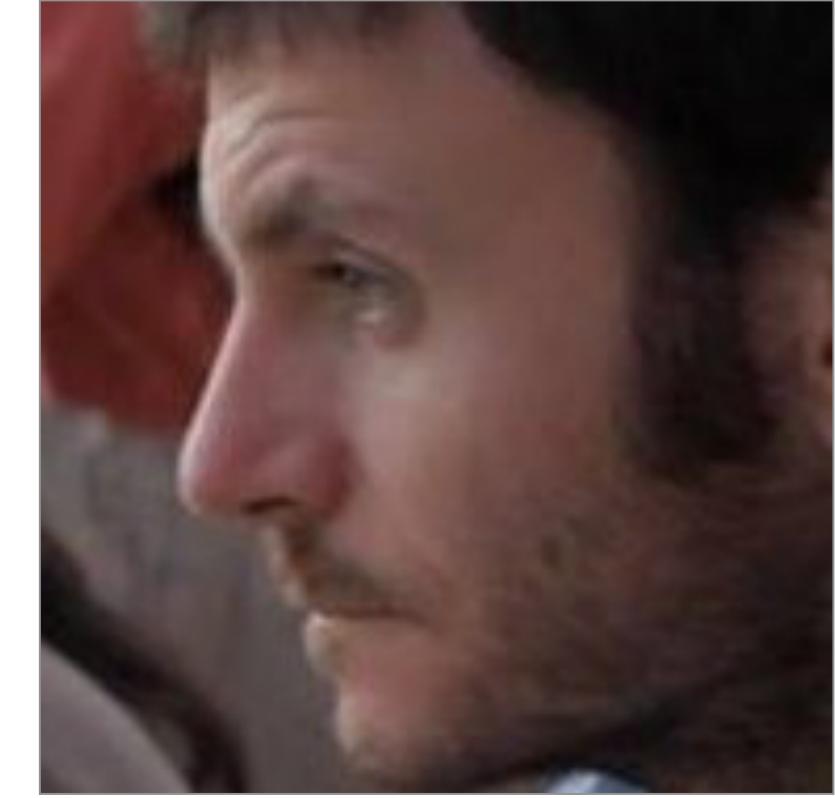
Nature Communications (2020) 11 p2564



Marco di Stefano
CNAG-CRG

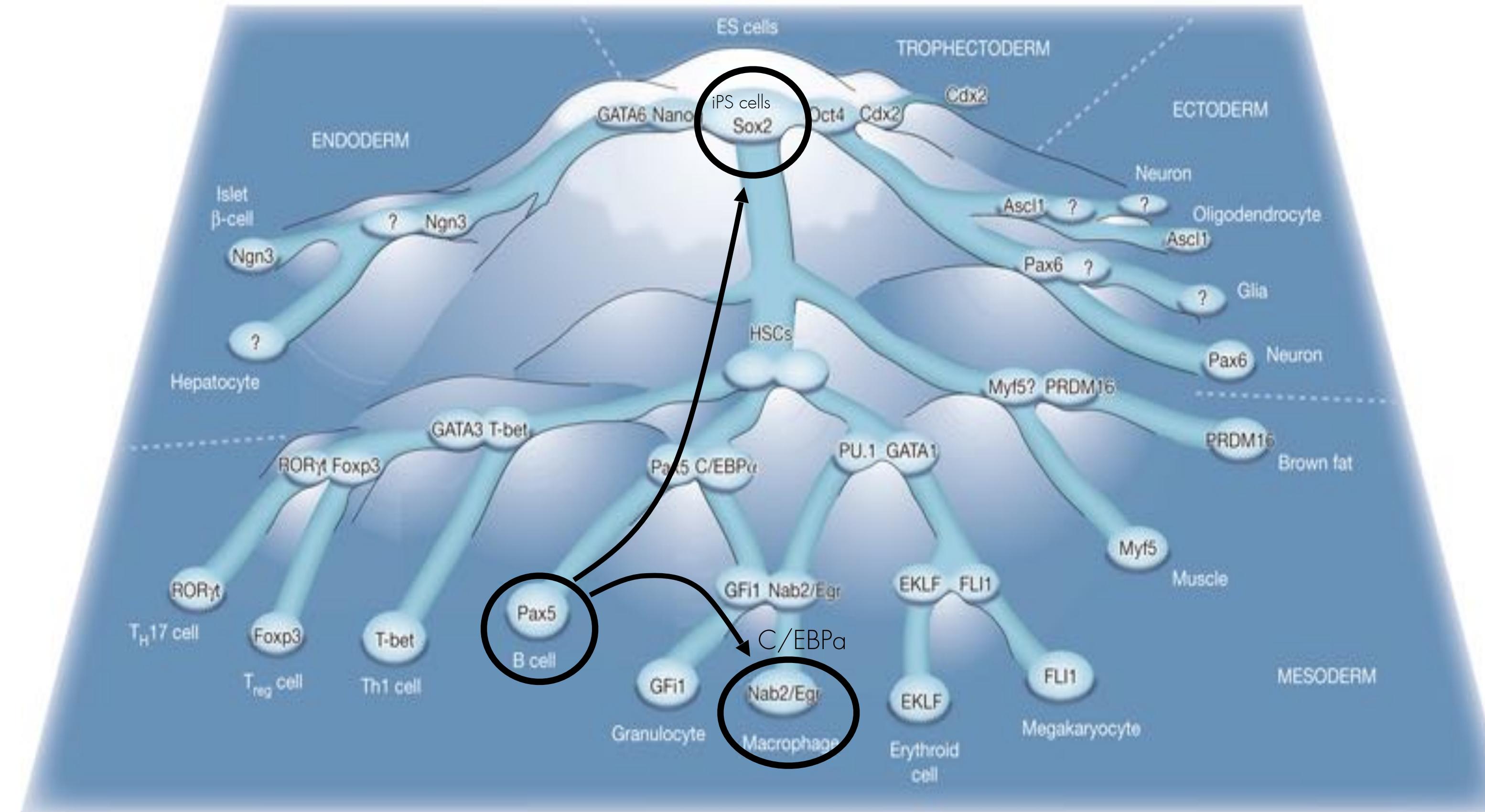


Ralph Stadhouders, Enrique Vidal & Thomas Graf
CRG



Transcription factors dictate cell fate

Graf & Enver (2009) Nature



Transcription factors (TFs) determine cell identity through gene regulation

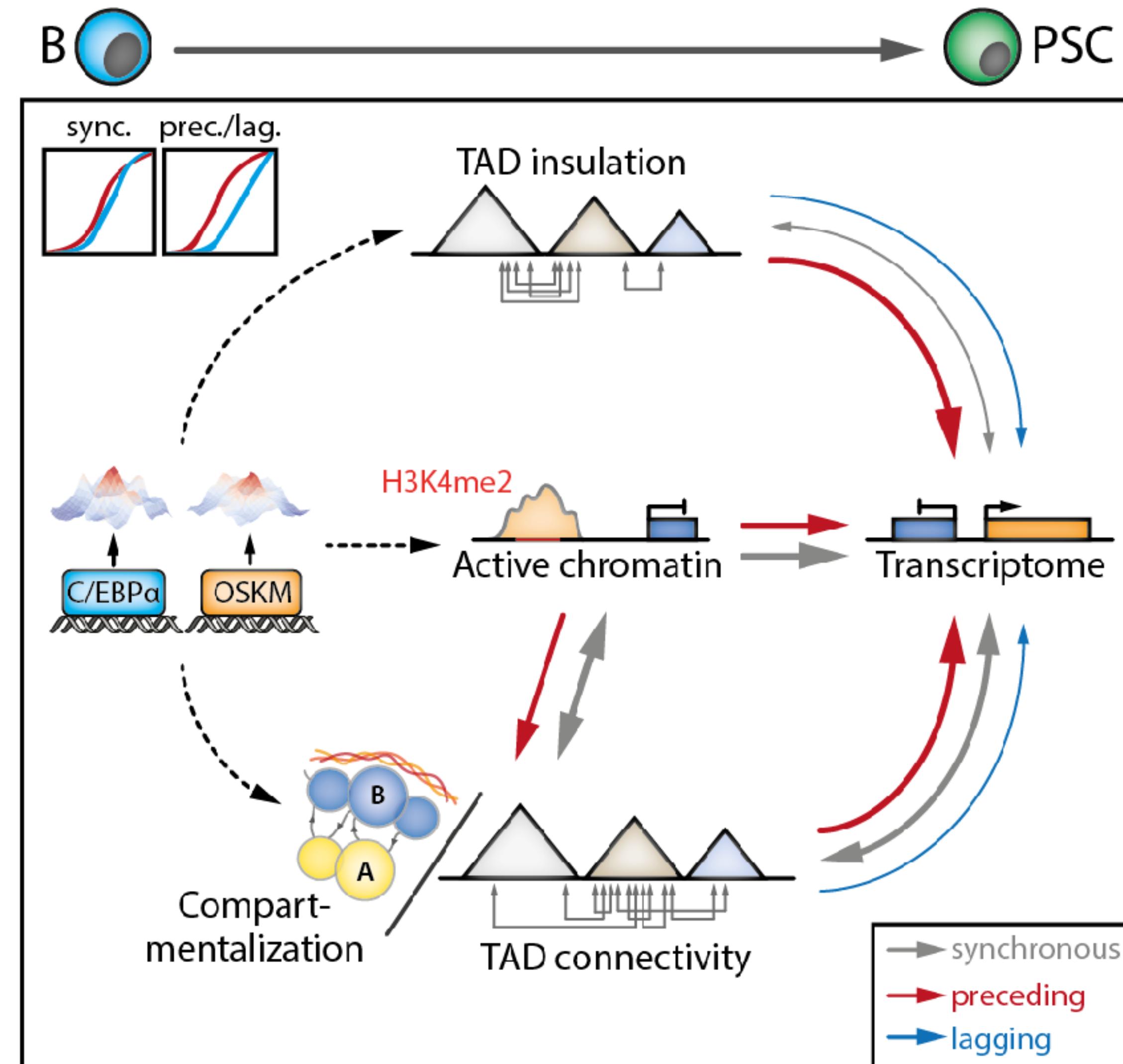
Normal 'forward' differentiation

Cell fates can be converted by enforced TF expression

Transdifferentiation or reprogramming

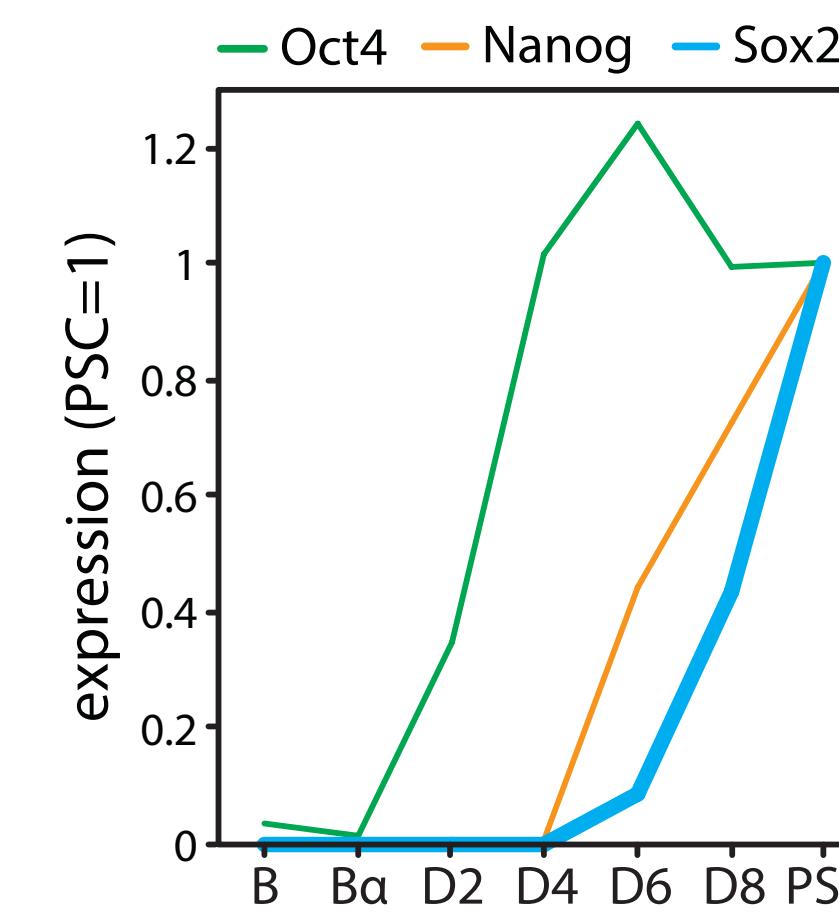
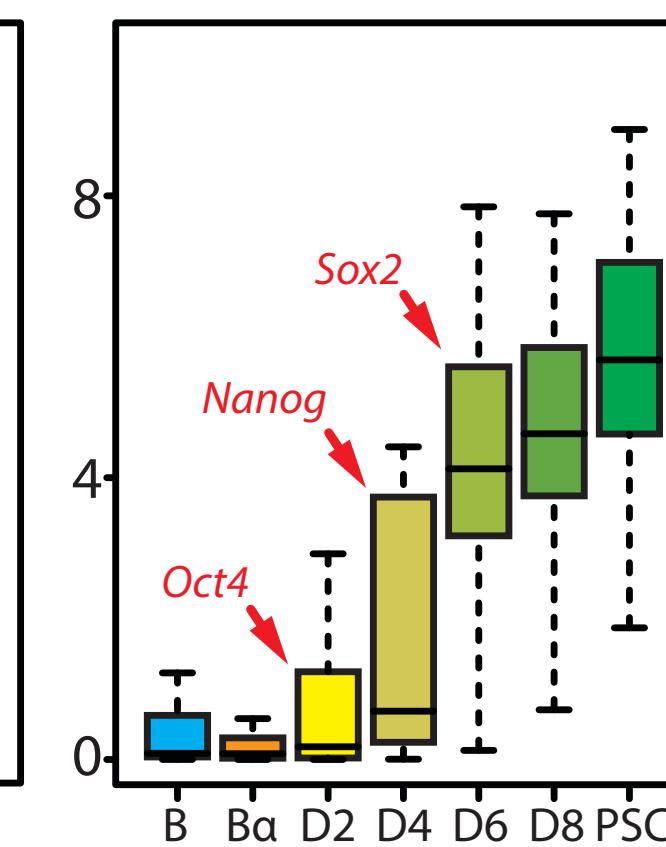
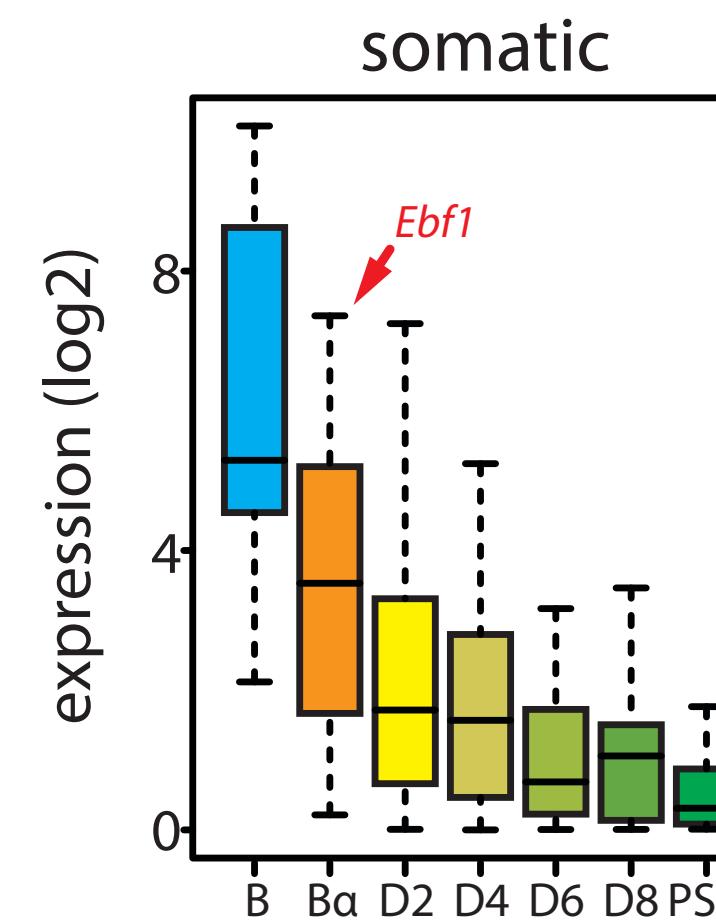
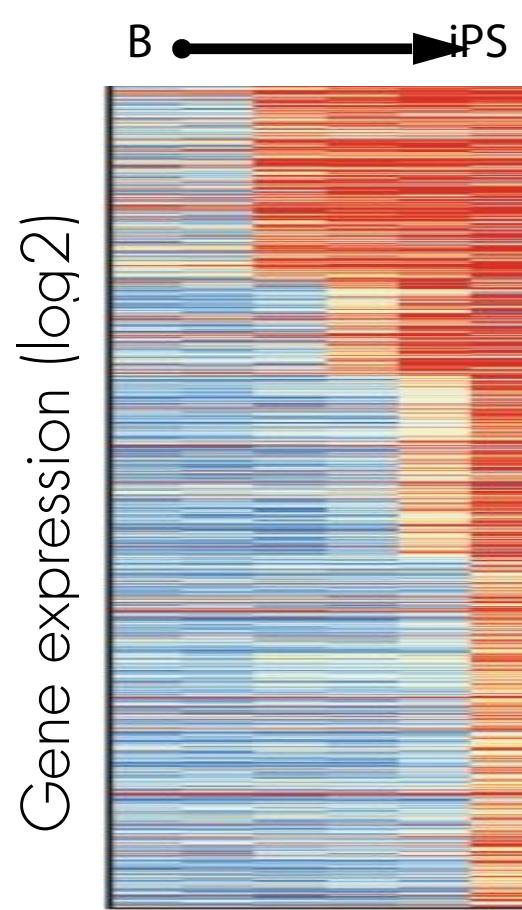
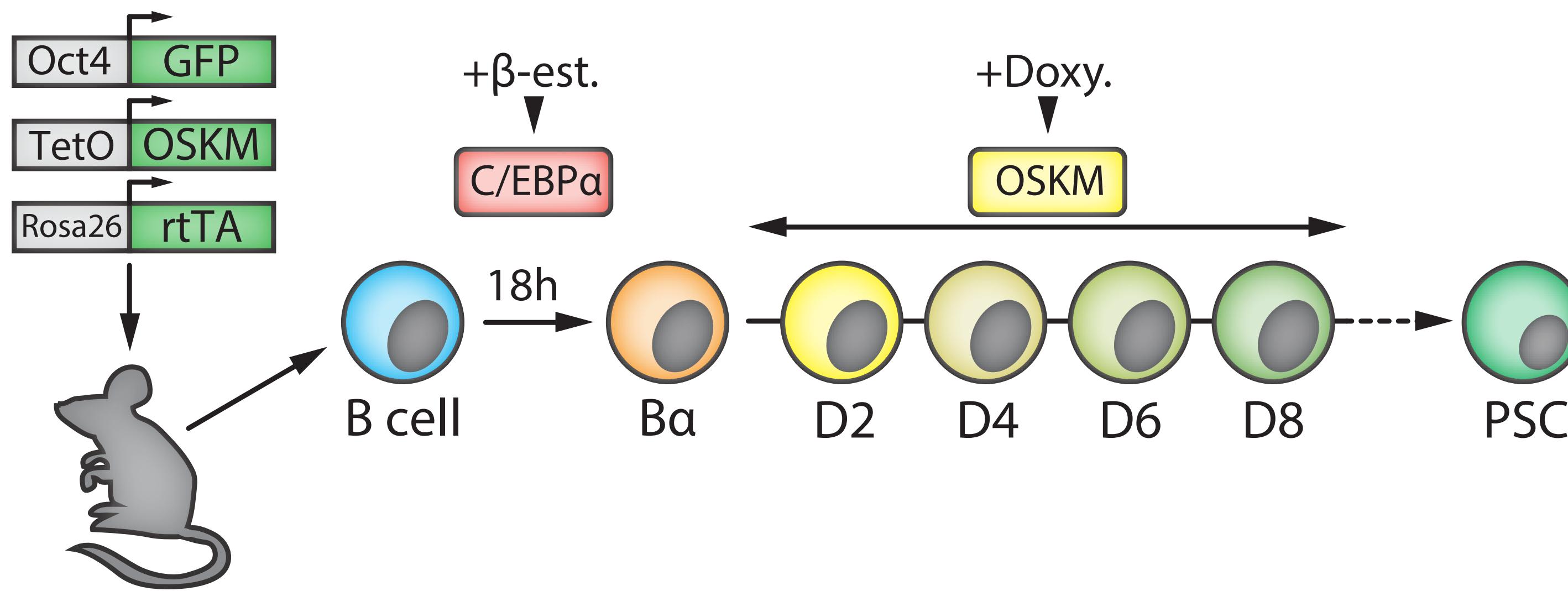
Interplay: topology, gene expression & chromatin

Graf & Enver (2009) Nature
Stadhouders, R., Vidal, E. et al. (2018) Nature Genetics



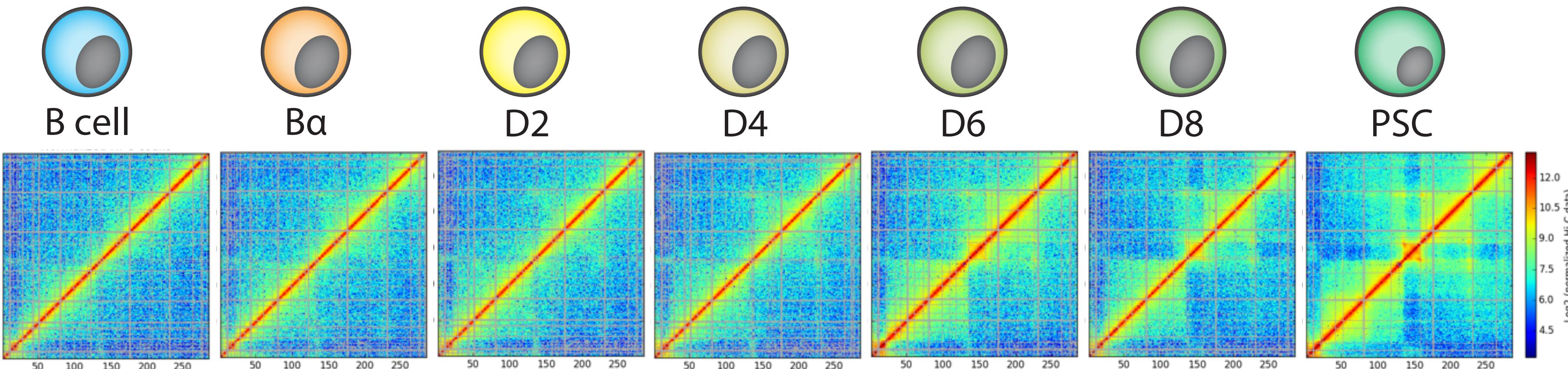
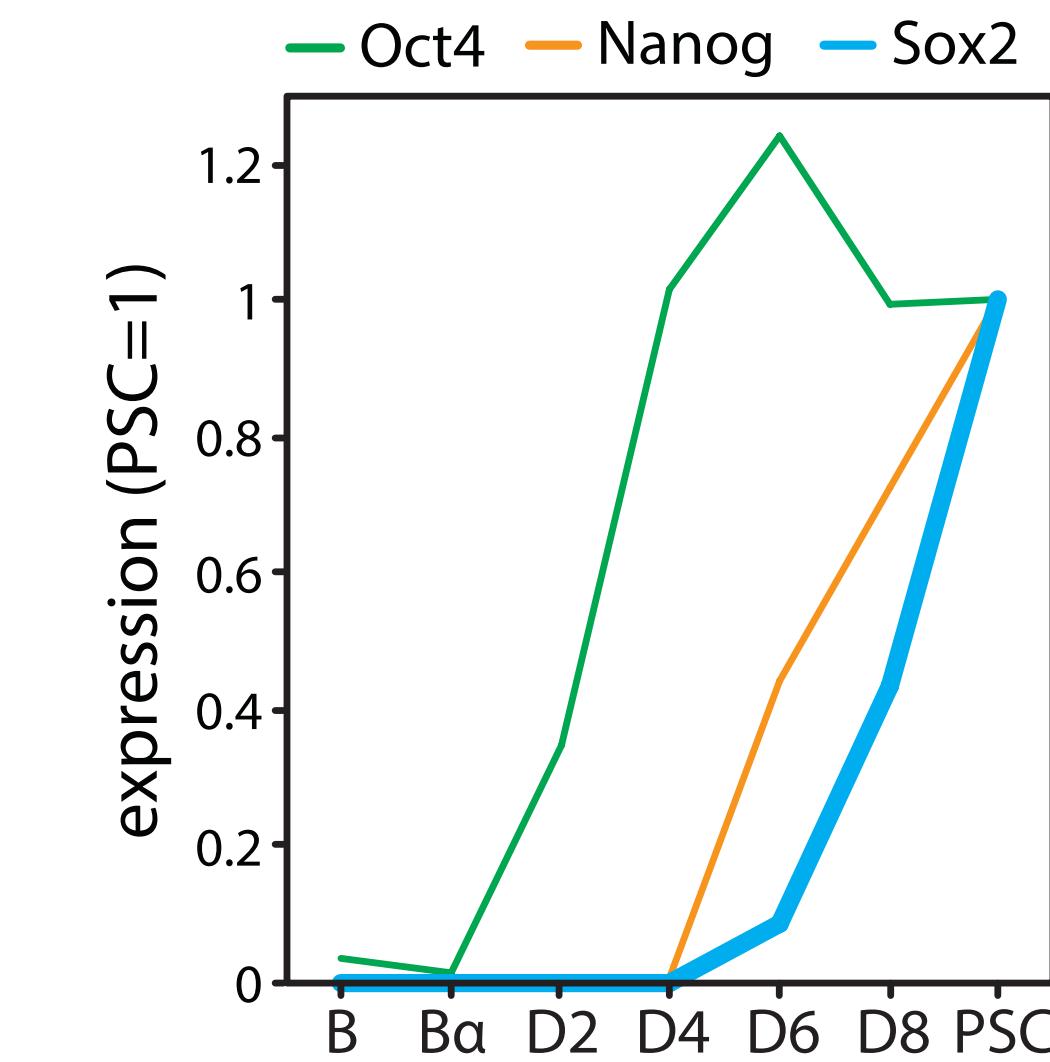
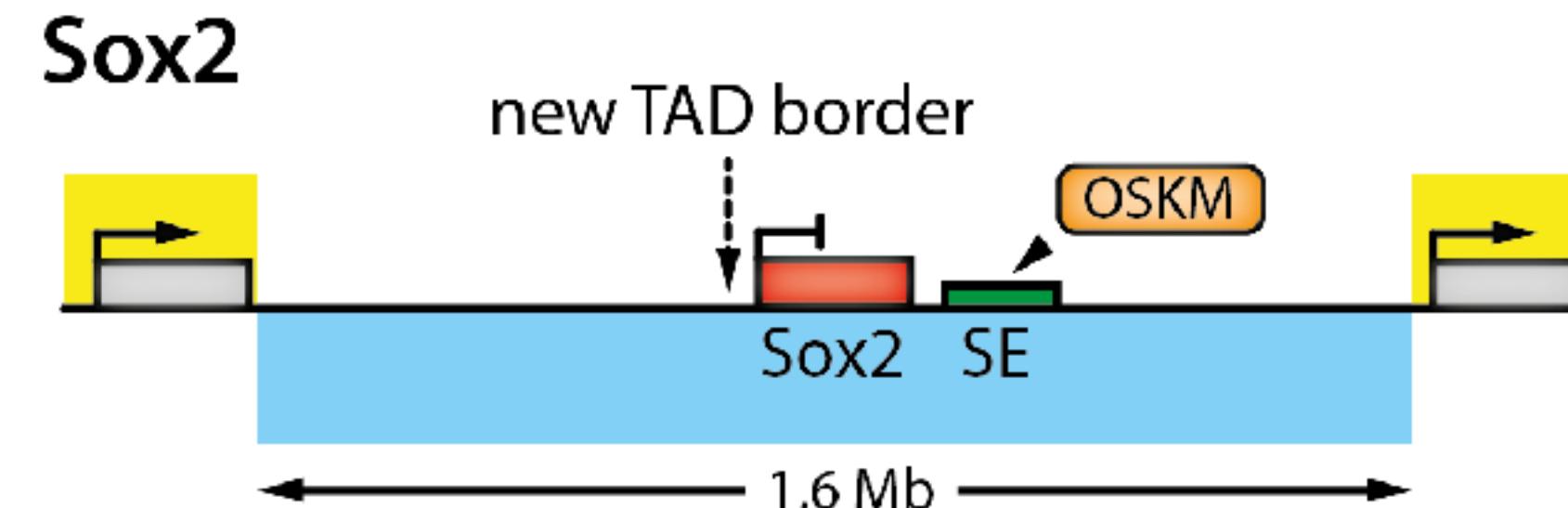
Reprogramming from B to PSC

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



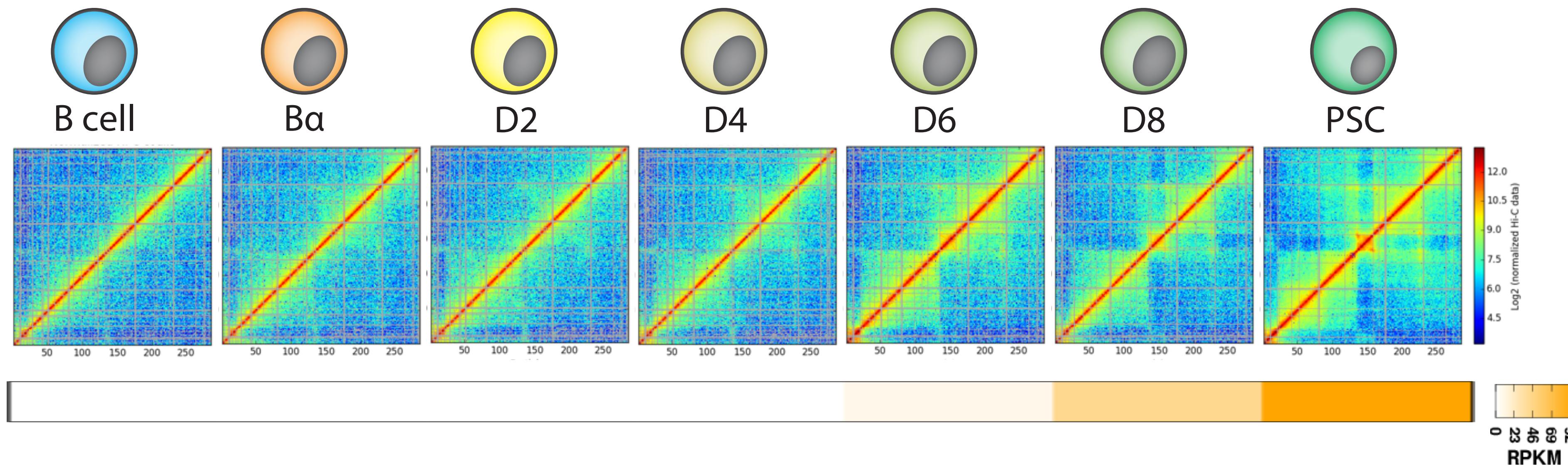
Hi-C maps of reprogramming from B to PSC

The SOX2 locus



Hi-C maps of reprogramming from B to PSC

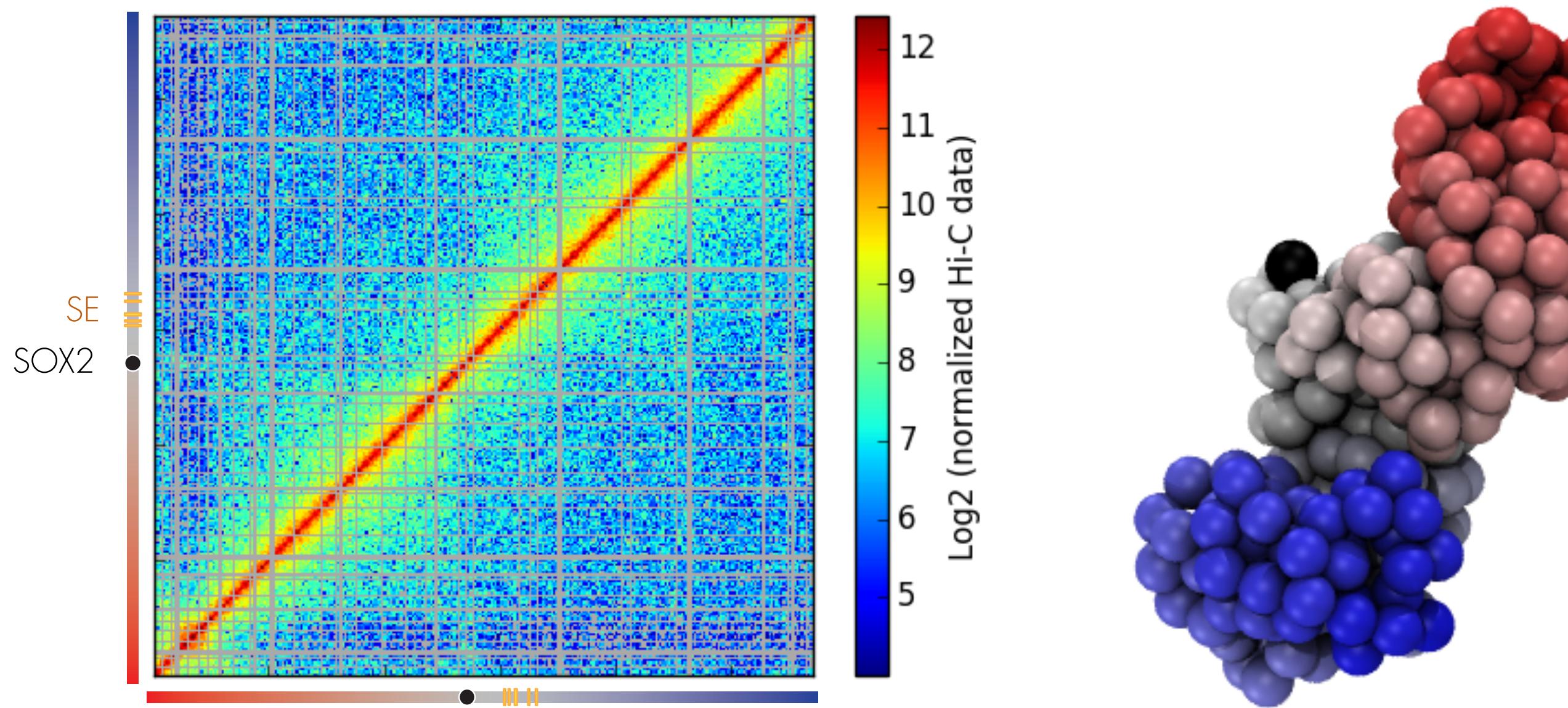
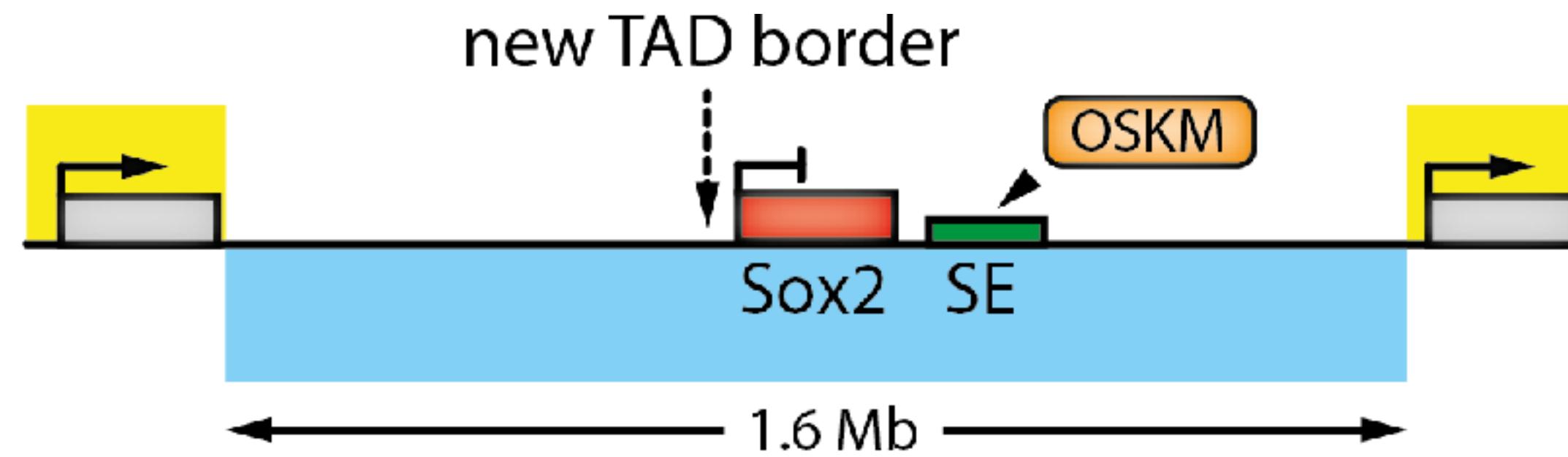
The SOX2 locus



How does these structural rearrangements interplay with the transcription activity?

What are the main drivers of structural transitions?

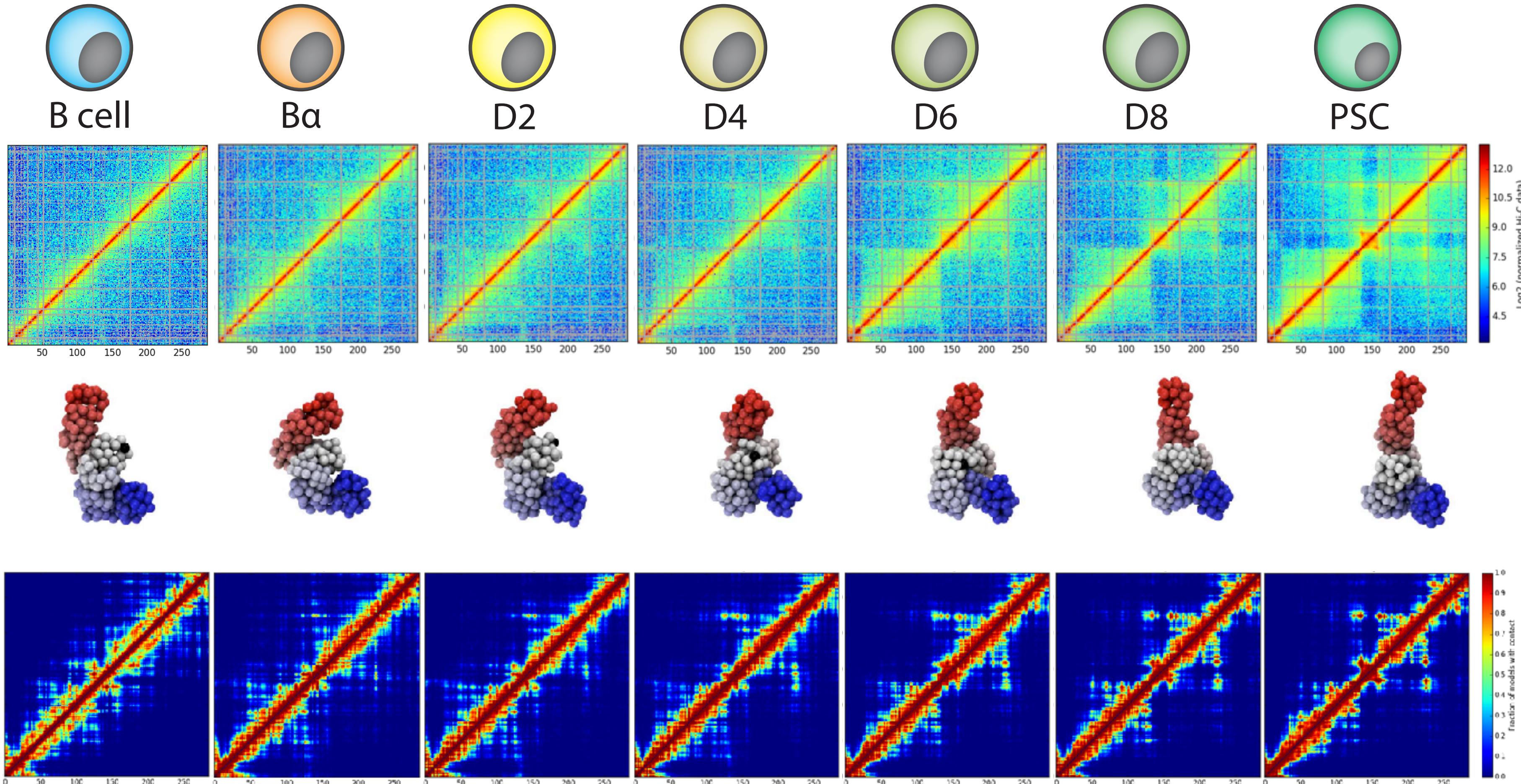
TADbit modeling of SOX2 from B cells Hi-C



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

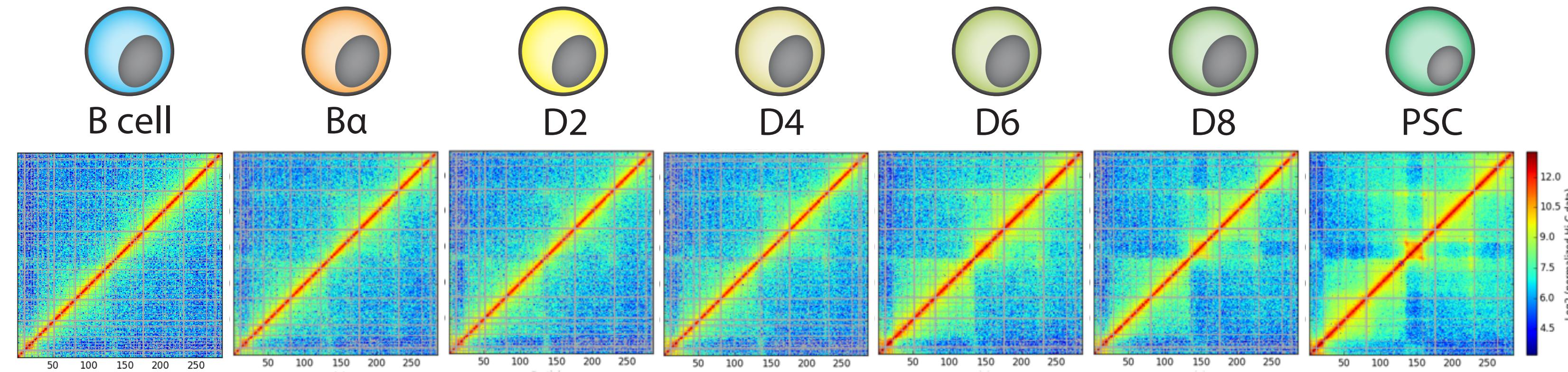
Models of reprogramming from B to PSC

The SOX2 locus



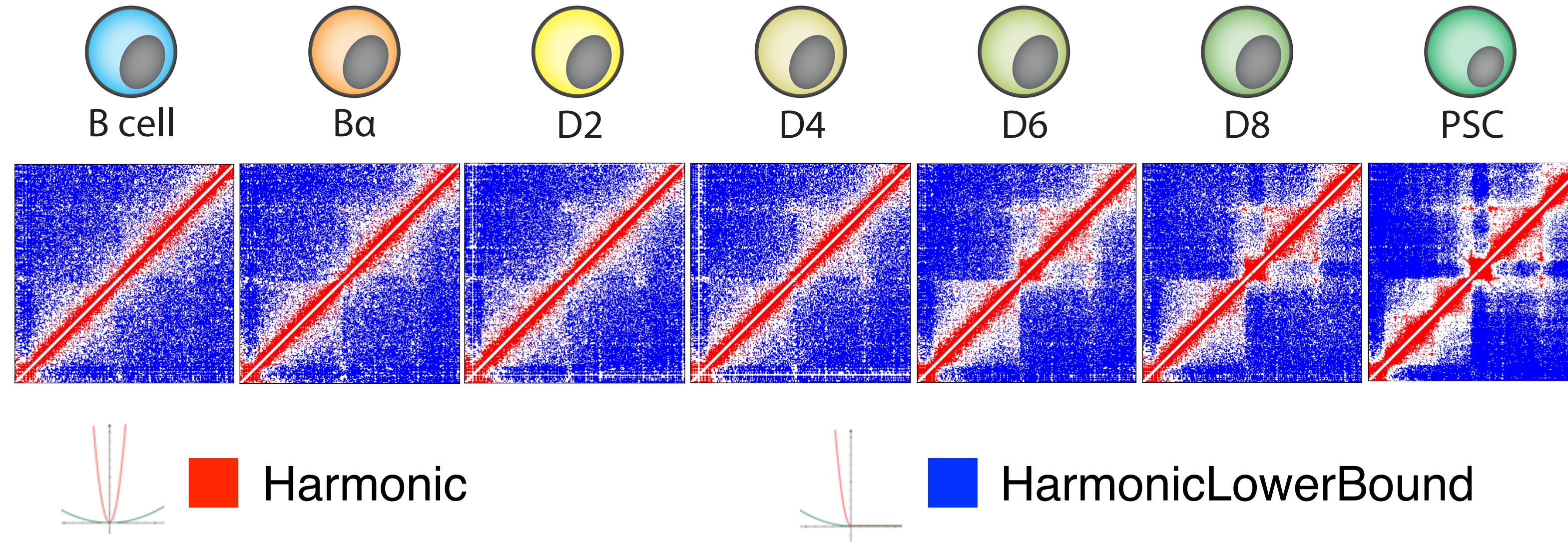
TADdyn: from time-series Hi-C maps to dynamic restraints

The SOX2 locus



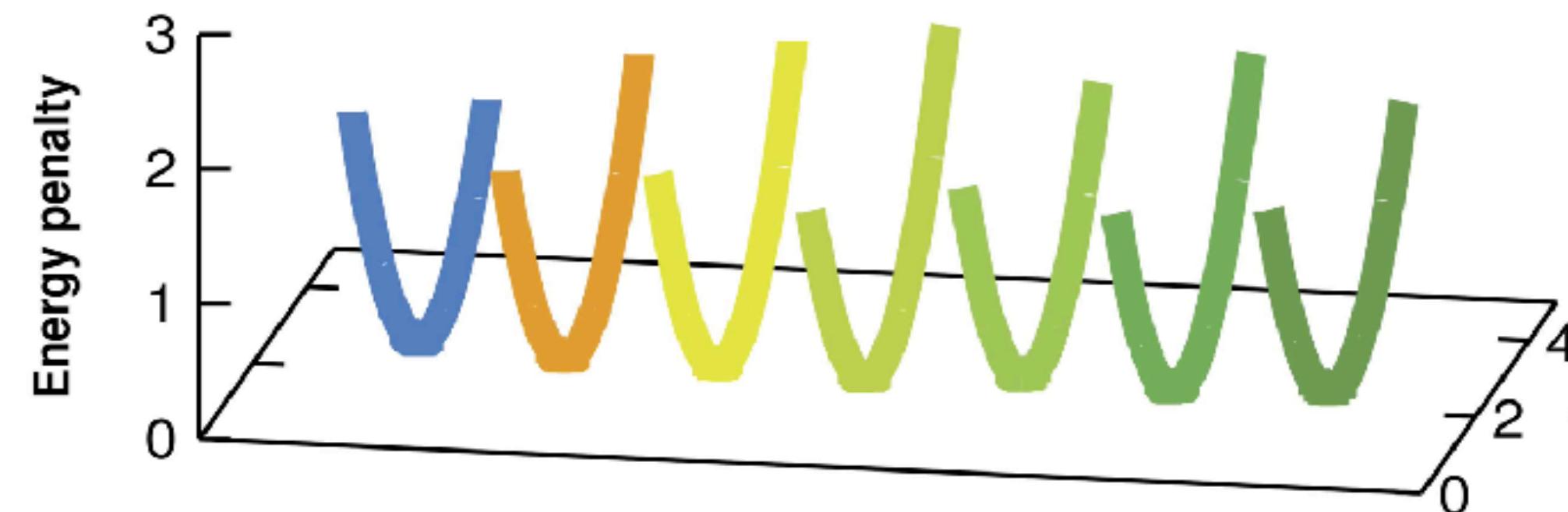
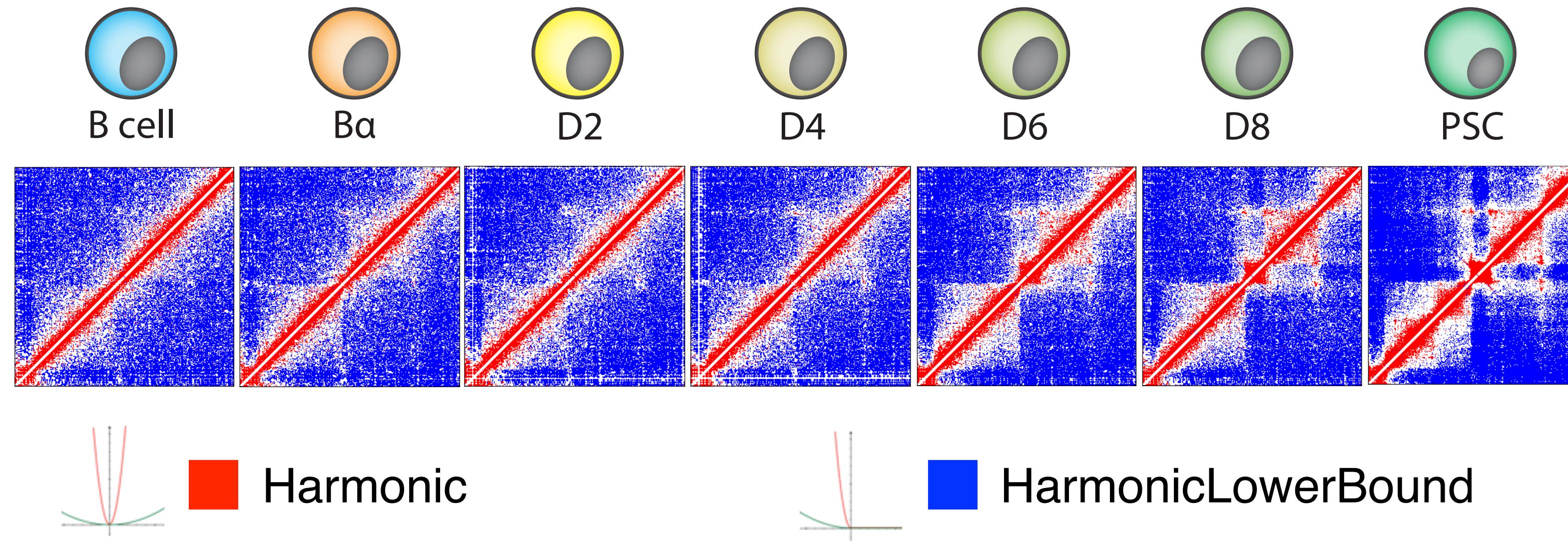
TADdyn: from time-series Hi-C maps to dynamic restraints

The SOX2 locus



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

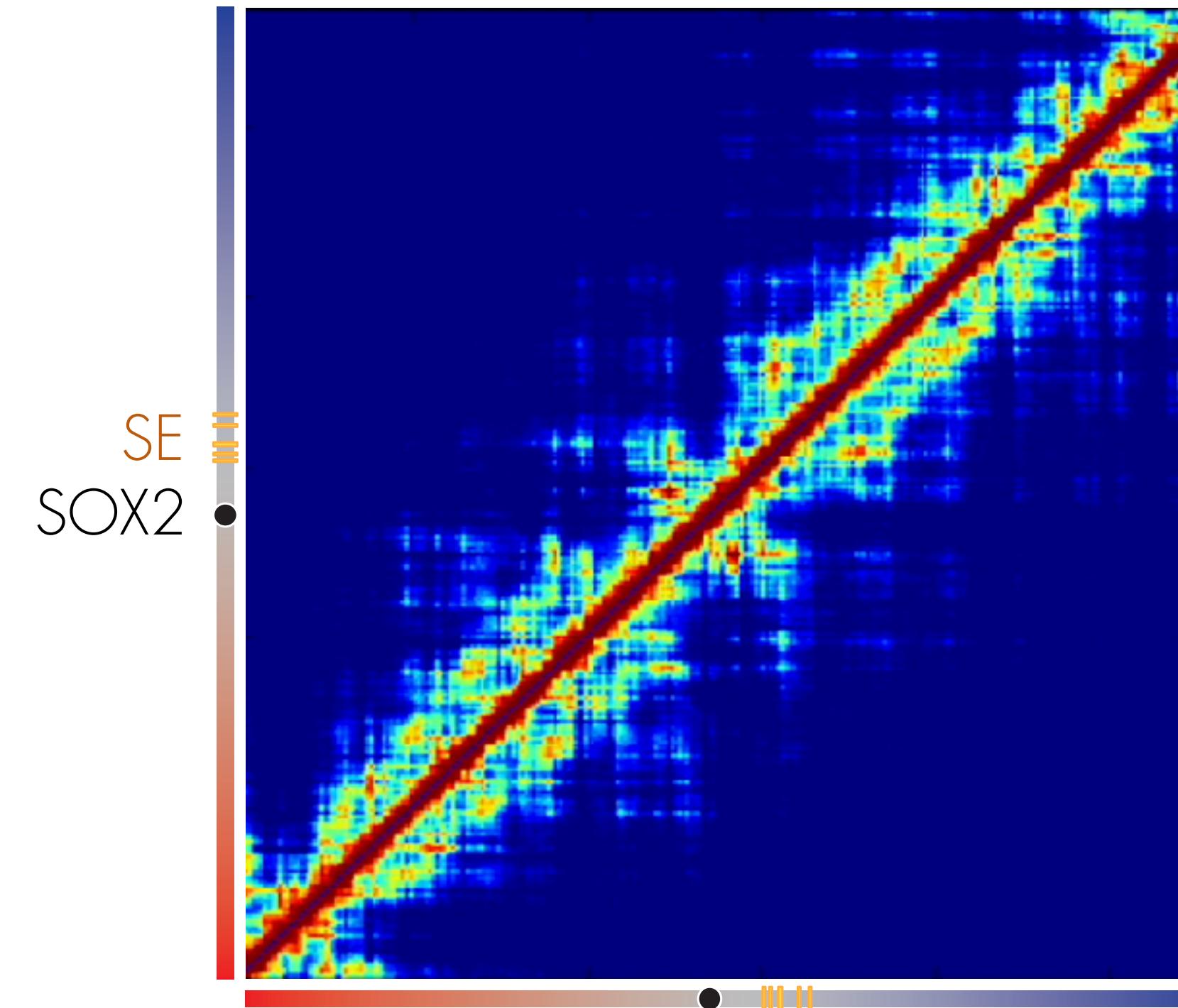
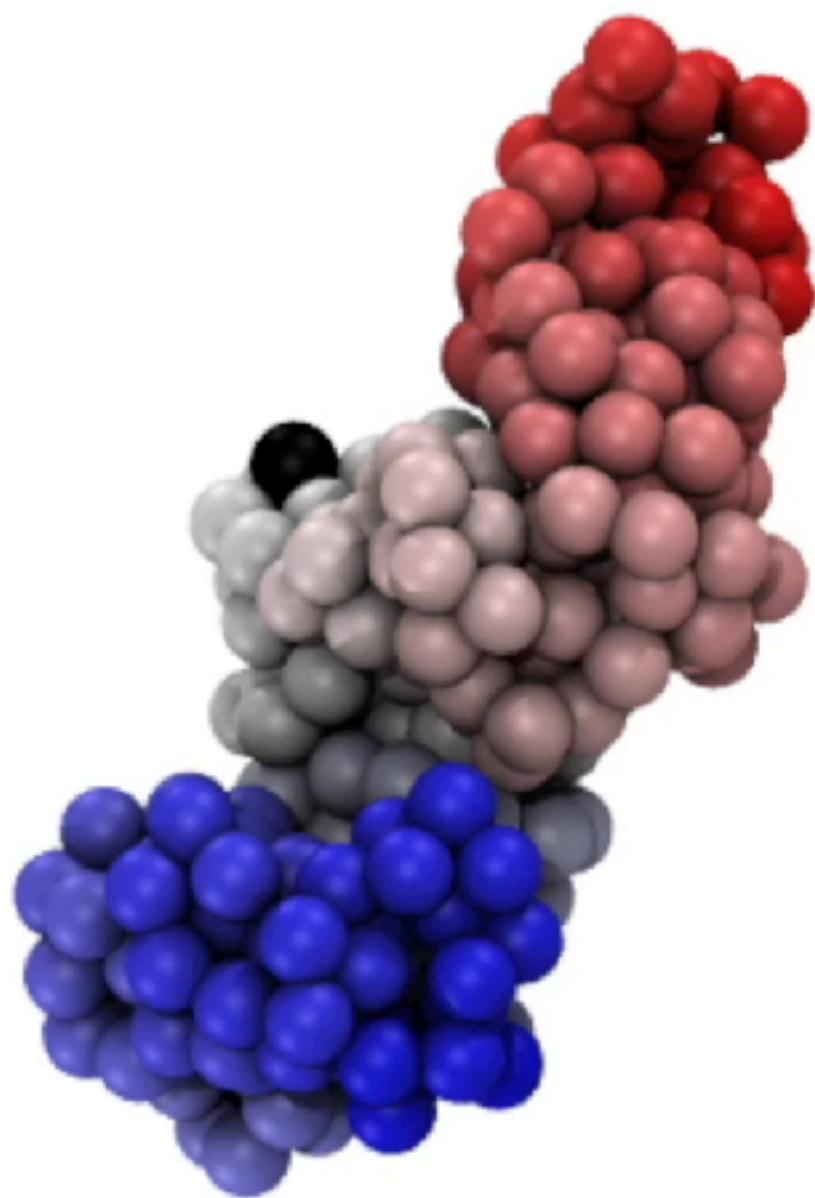
The SOX2 locus



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

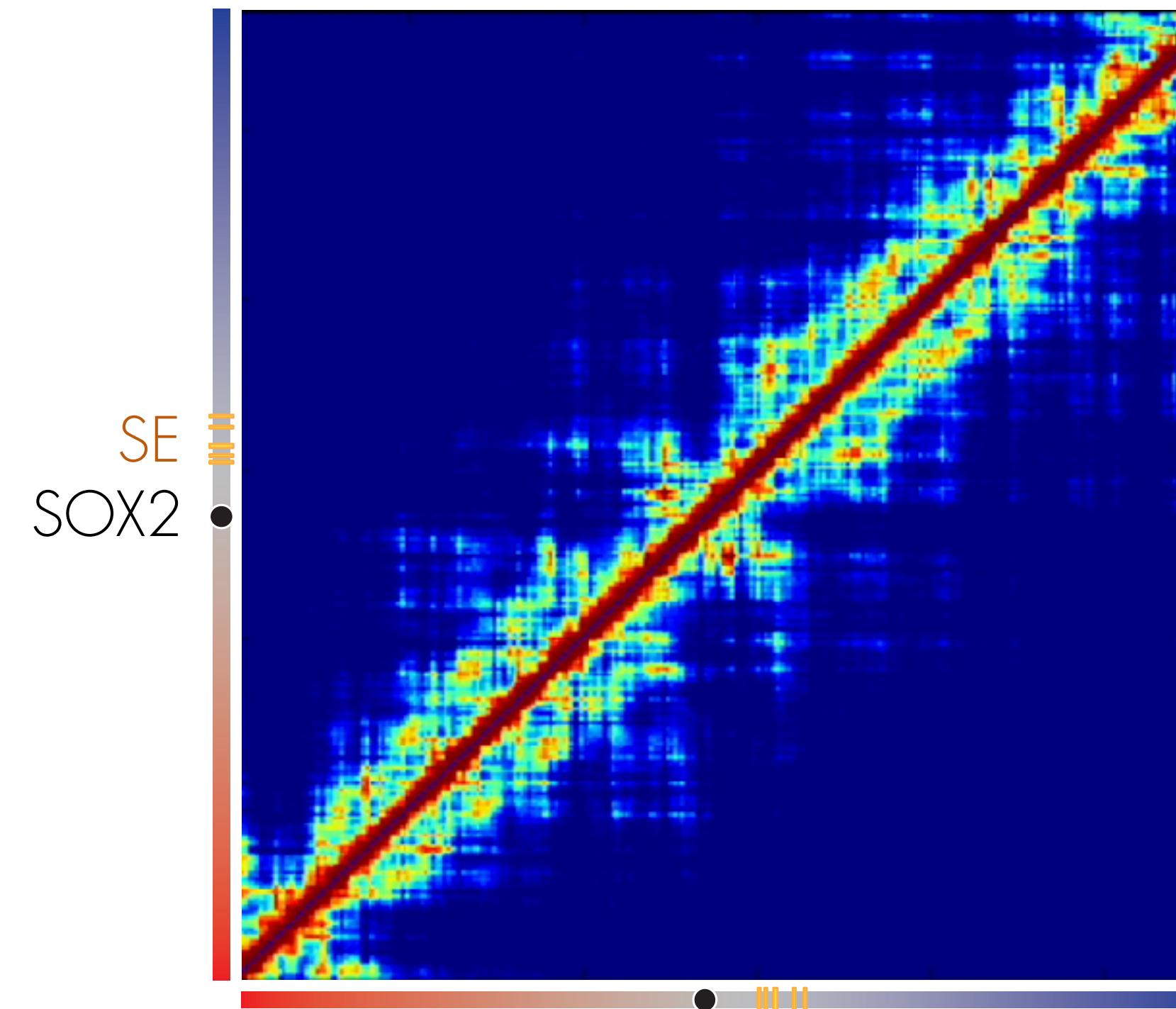
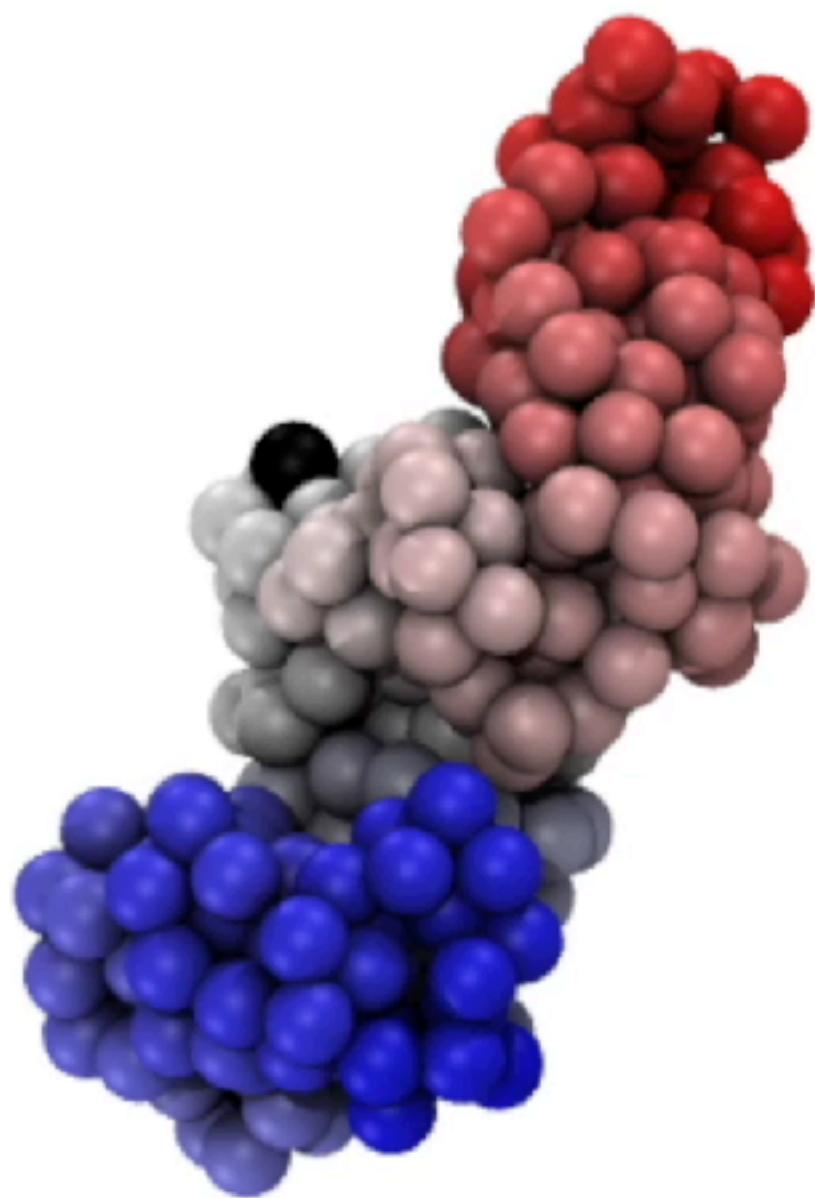
SOX2 locus structural changes from B to PSC

Contacts



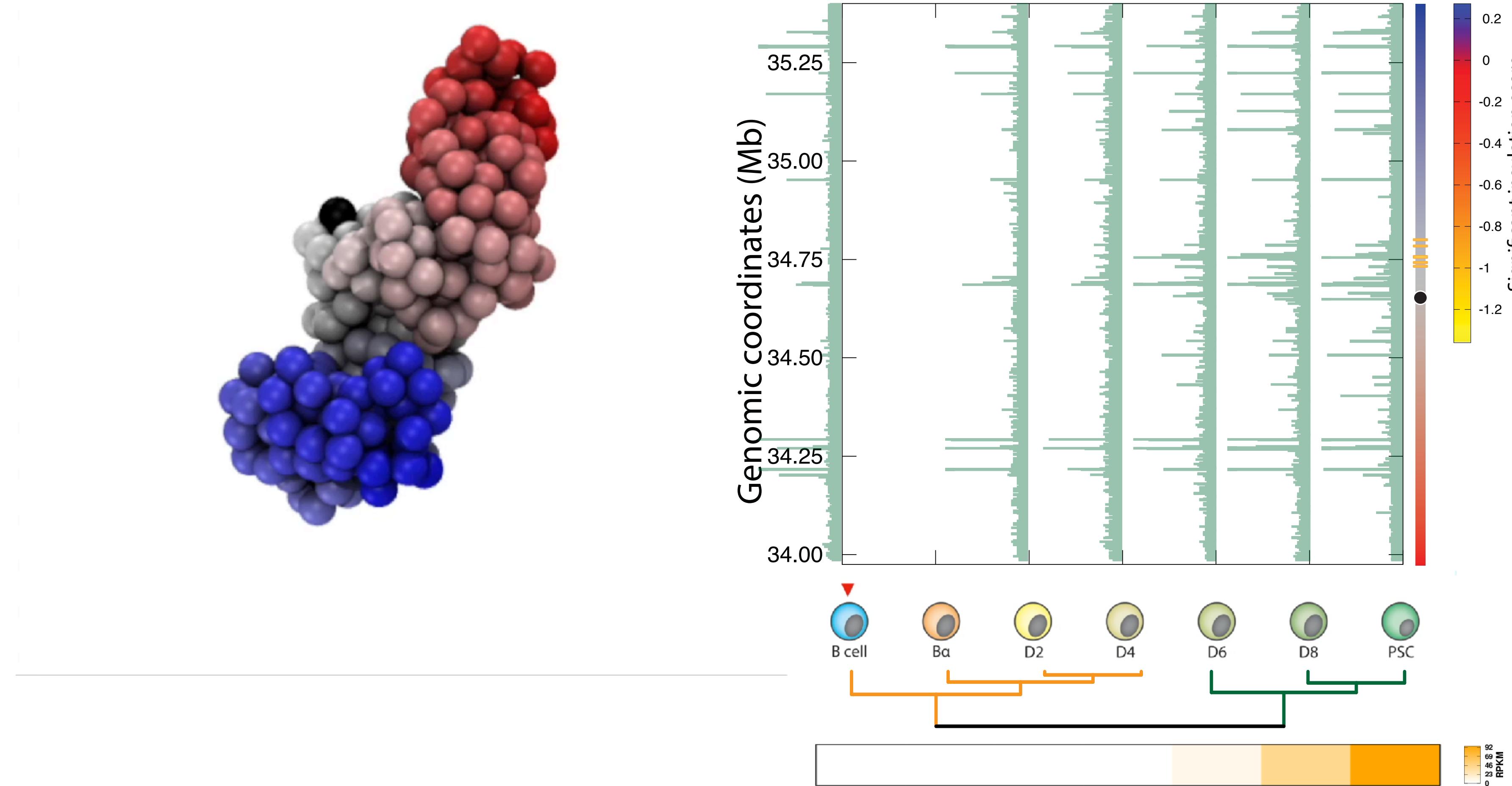
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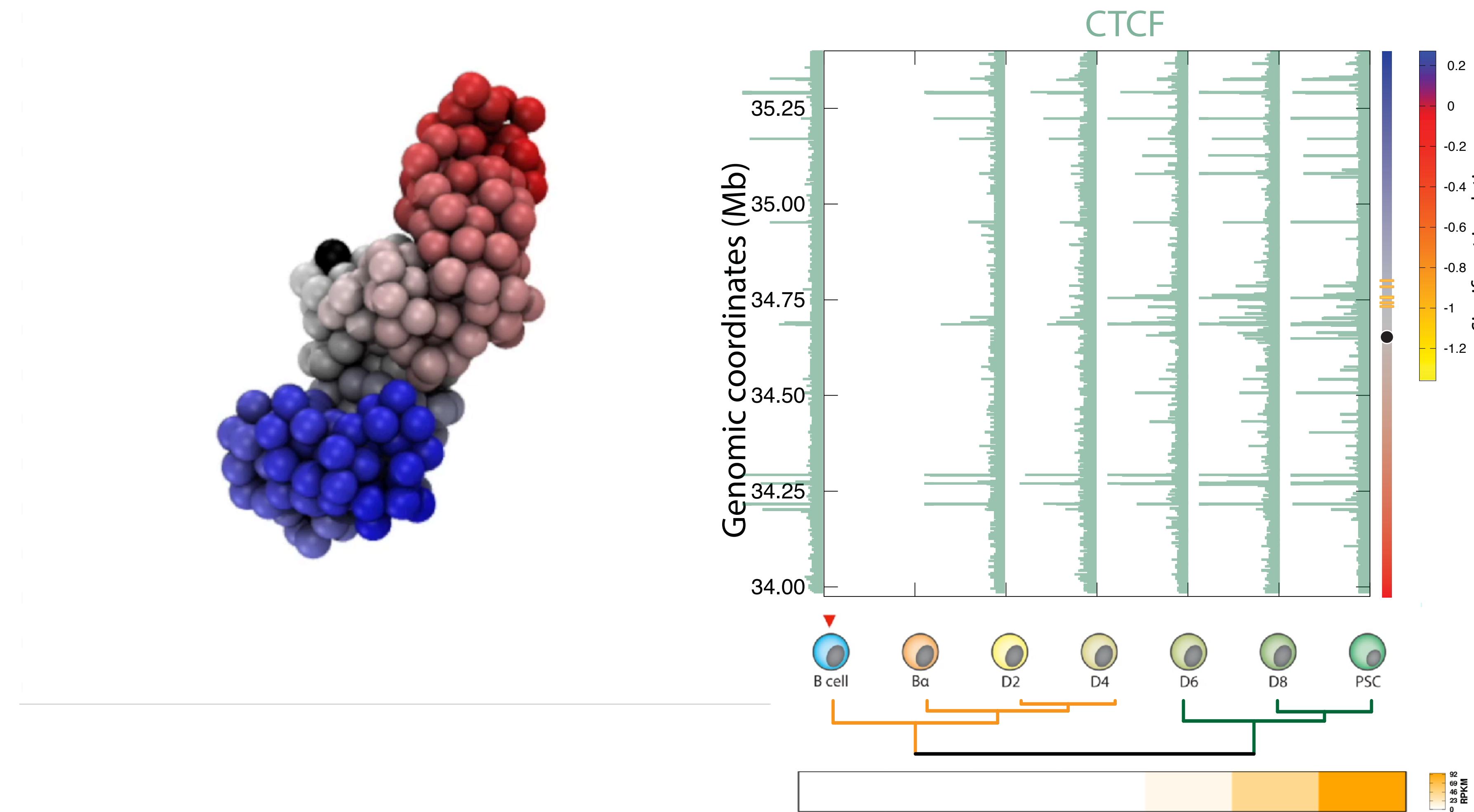
SOX2 locus structural changes from B to PSC

TAD borders



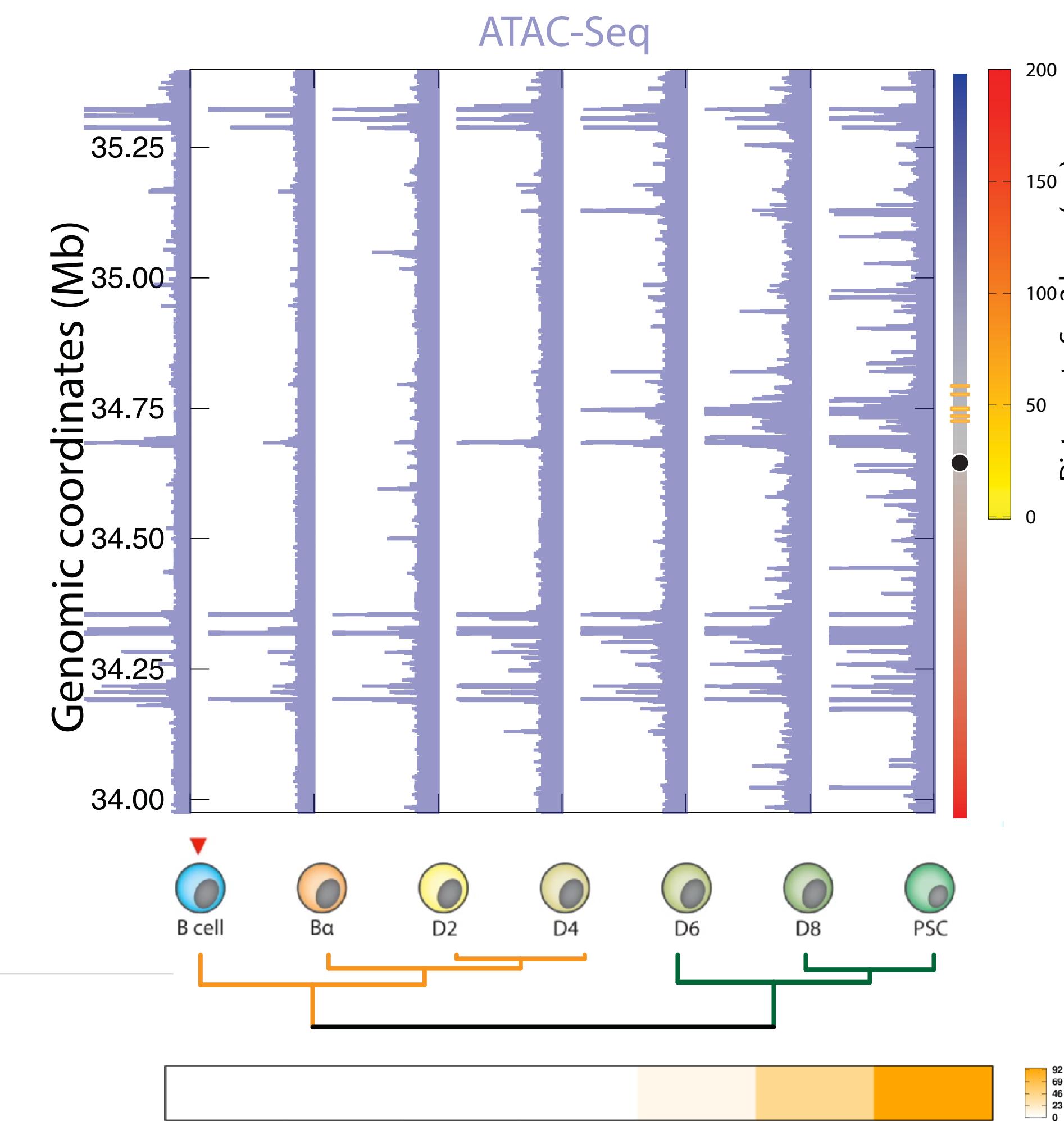
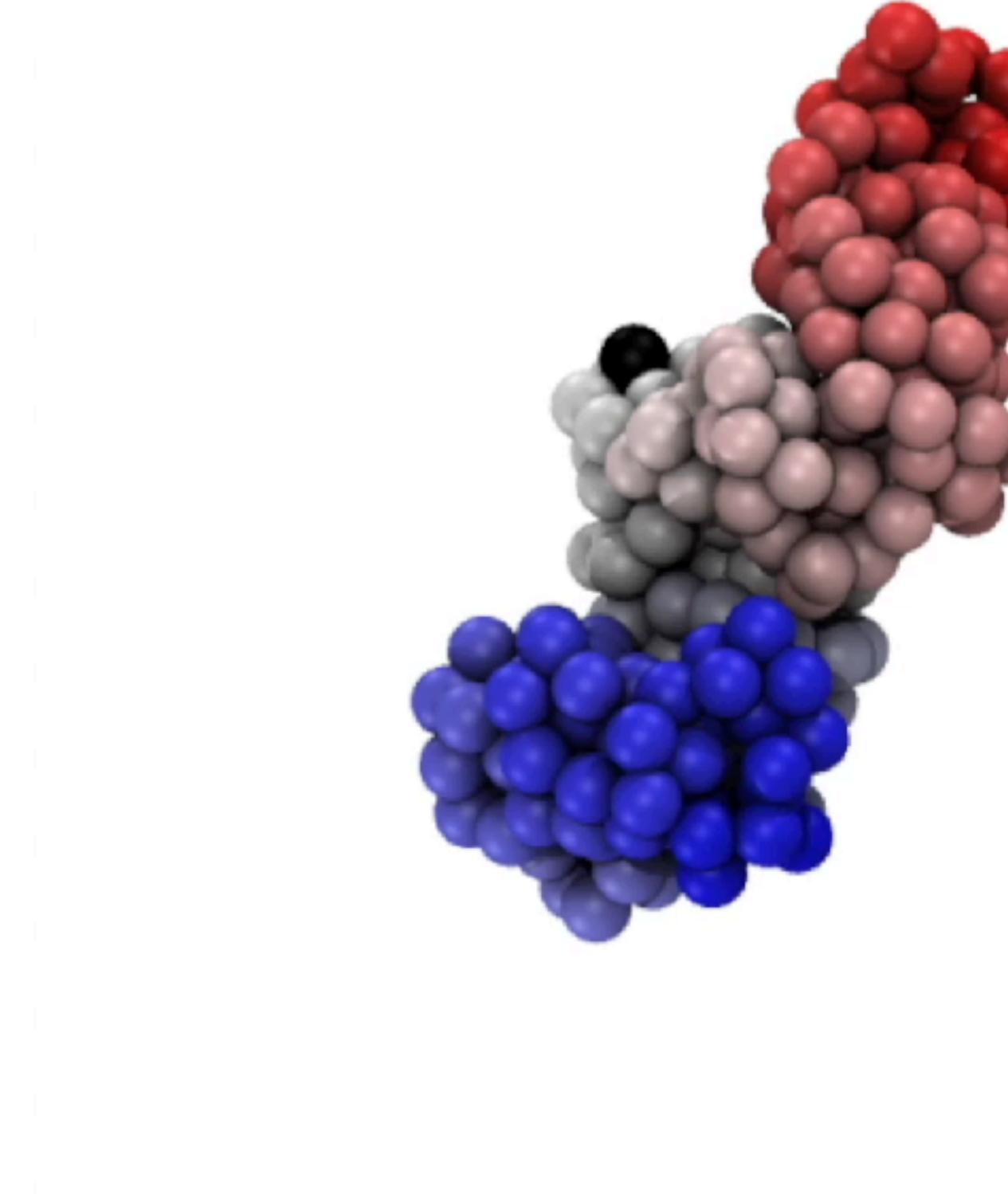
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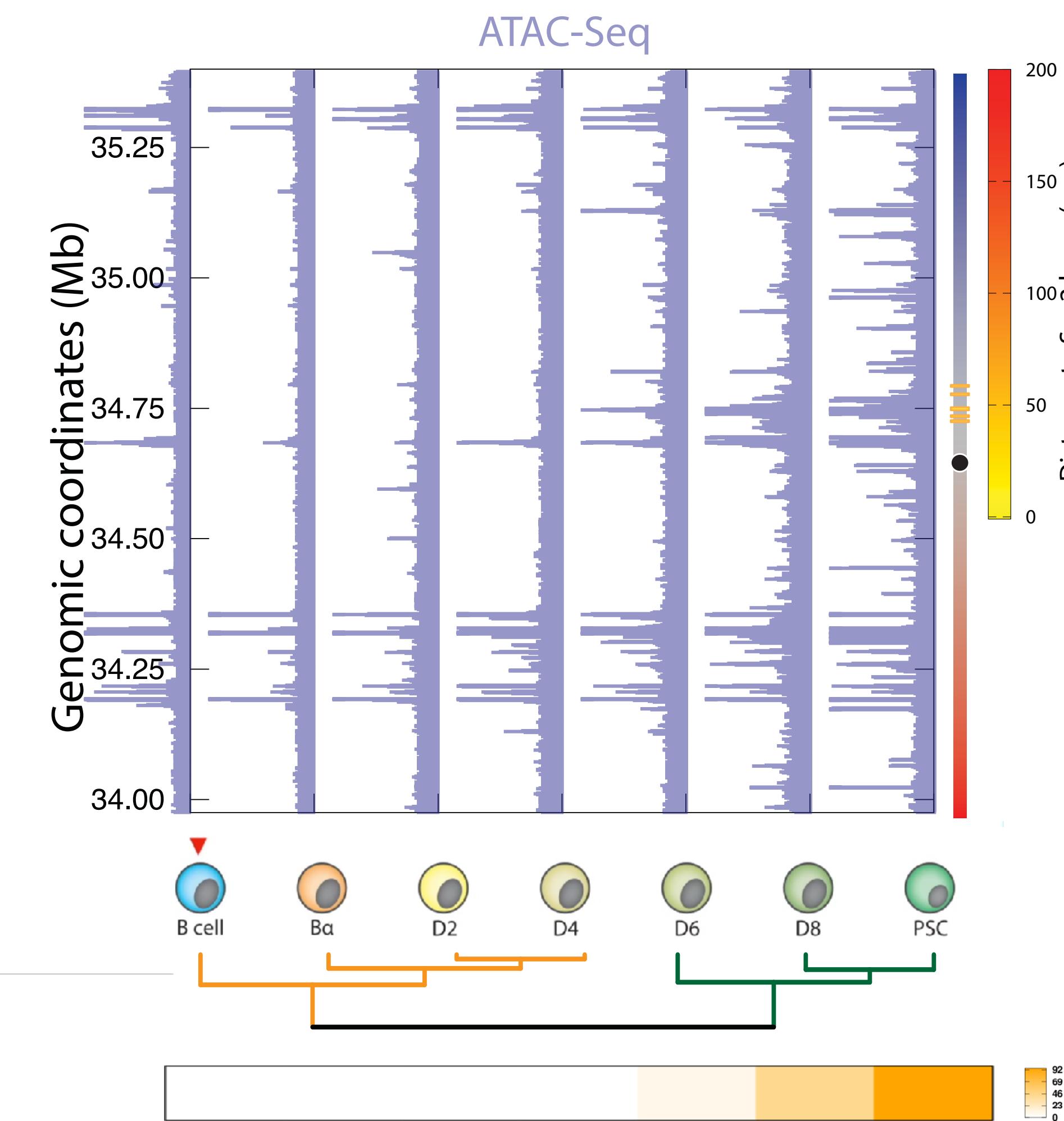
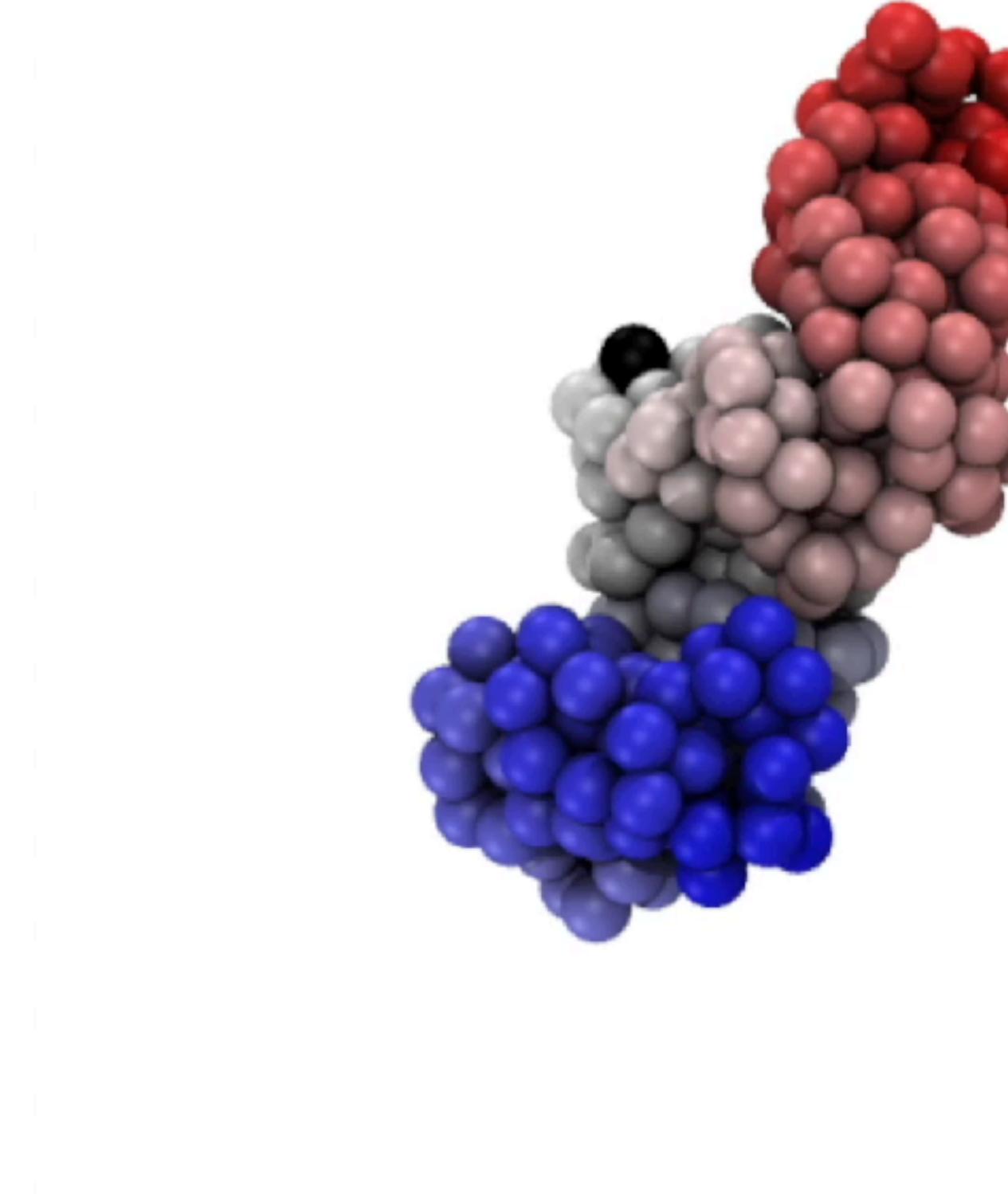
SOX2 locus structural changes from B to PSC

Distance to regulatory elements



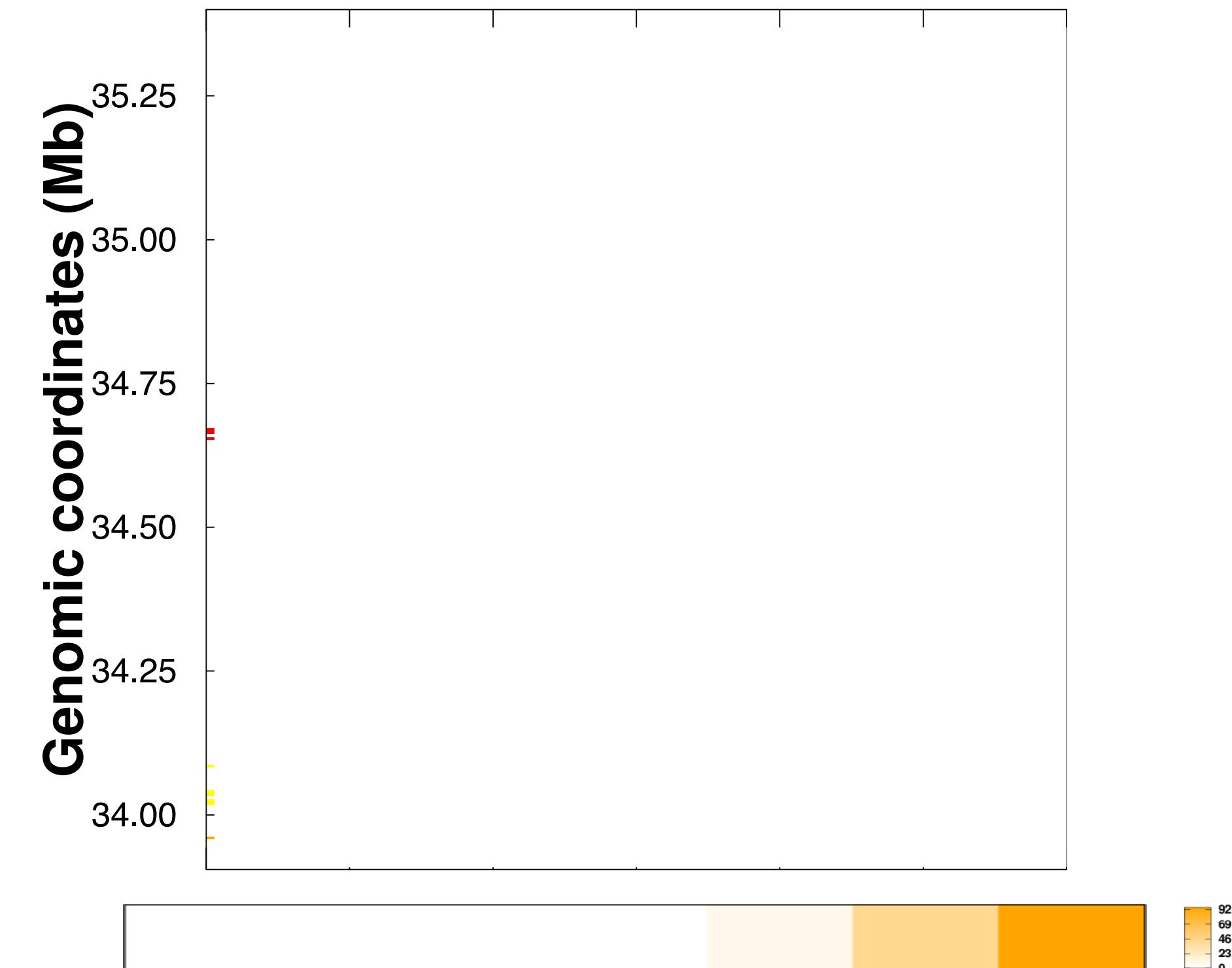
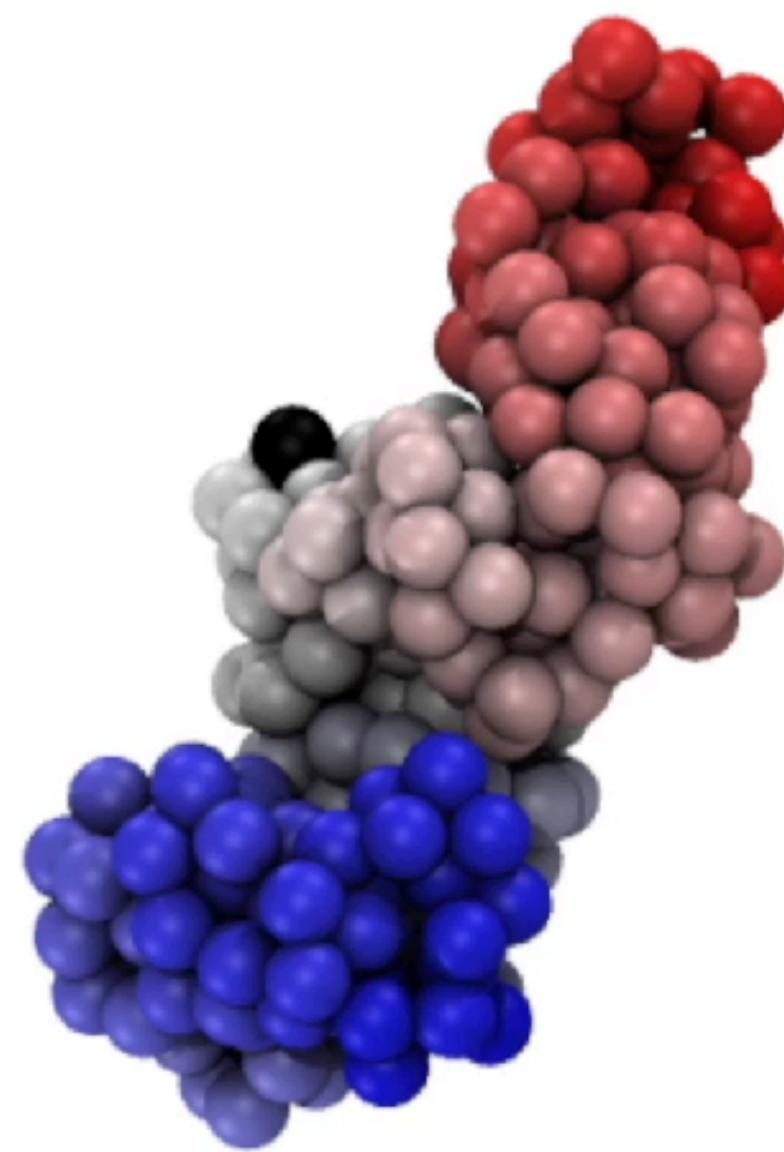
SOX2 locus structural changes from B to PSC

Distance to regulatory elements



SOX2 locus structural changes from B to PSC

Chromatin Activity

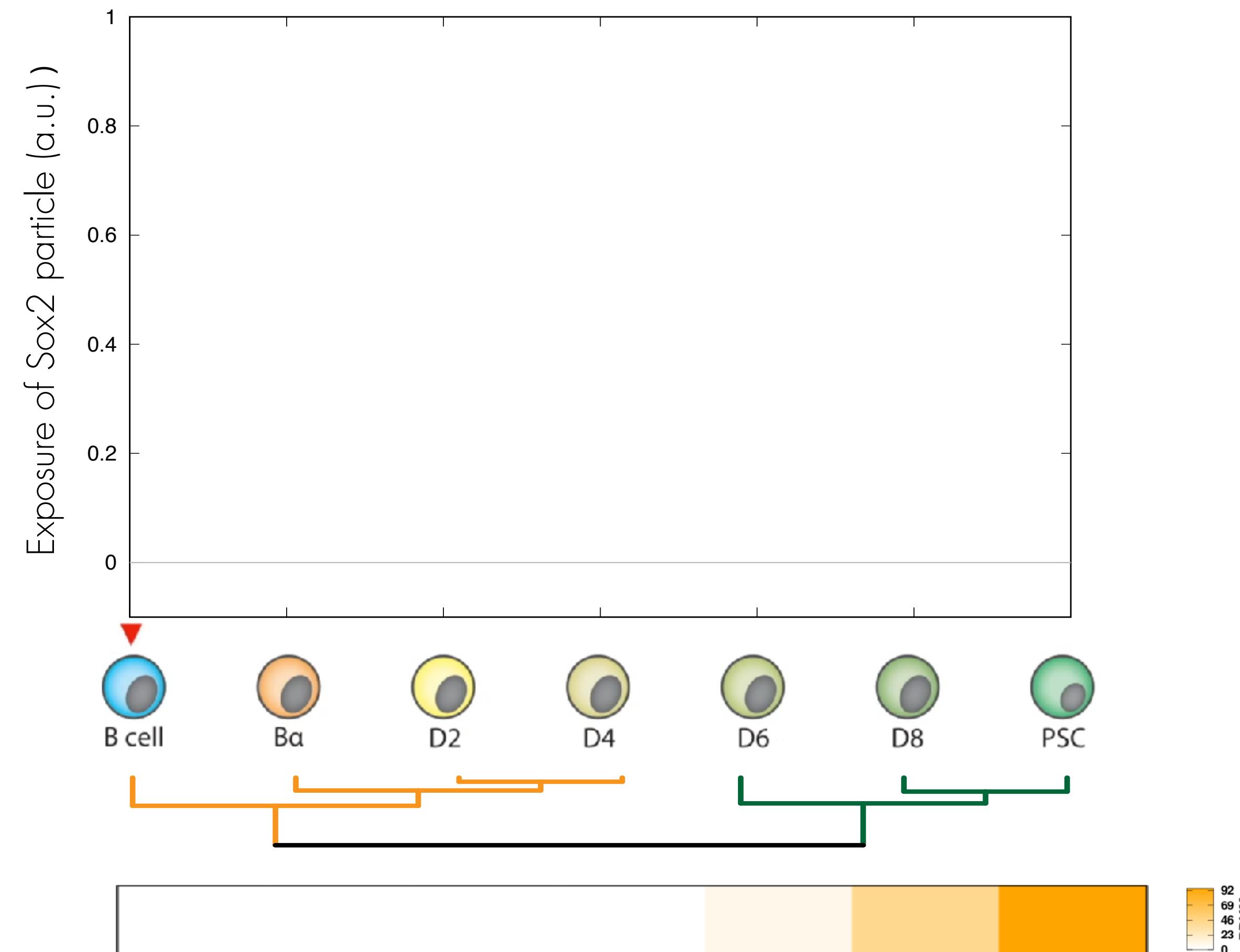
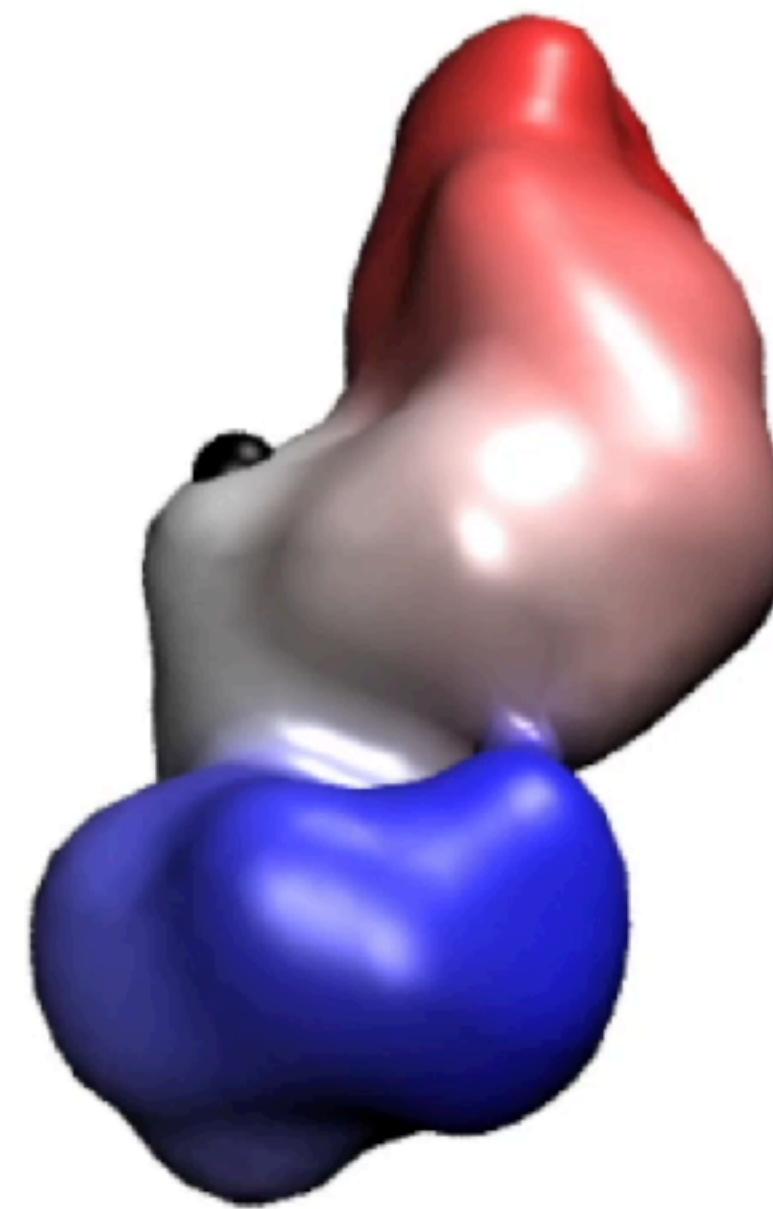


	B	Ba	D2	D4	D6	D8	PSC
A	9	6	7	13	13	22	48
AP	4	1	4	4	4	13	23
APD	3	1	1	1	4	10	15



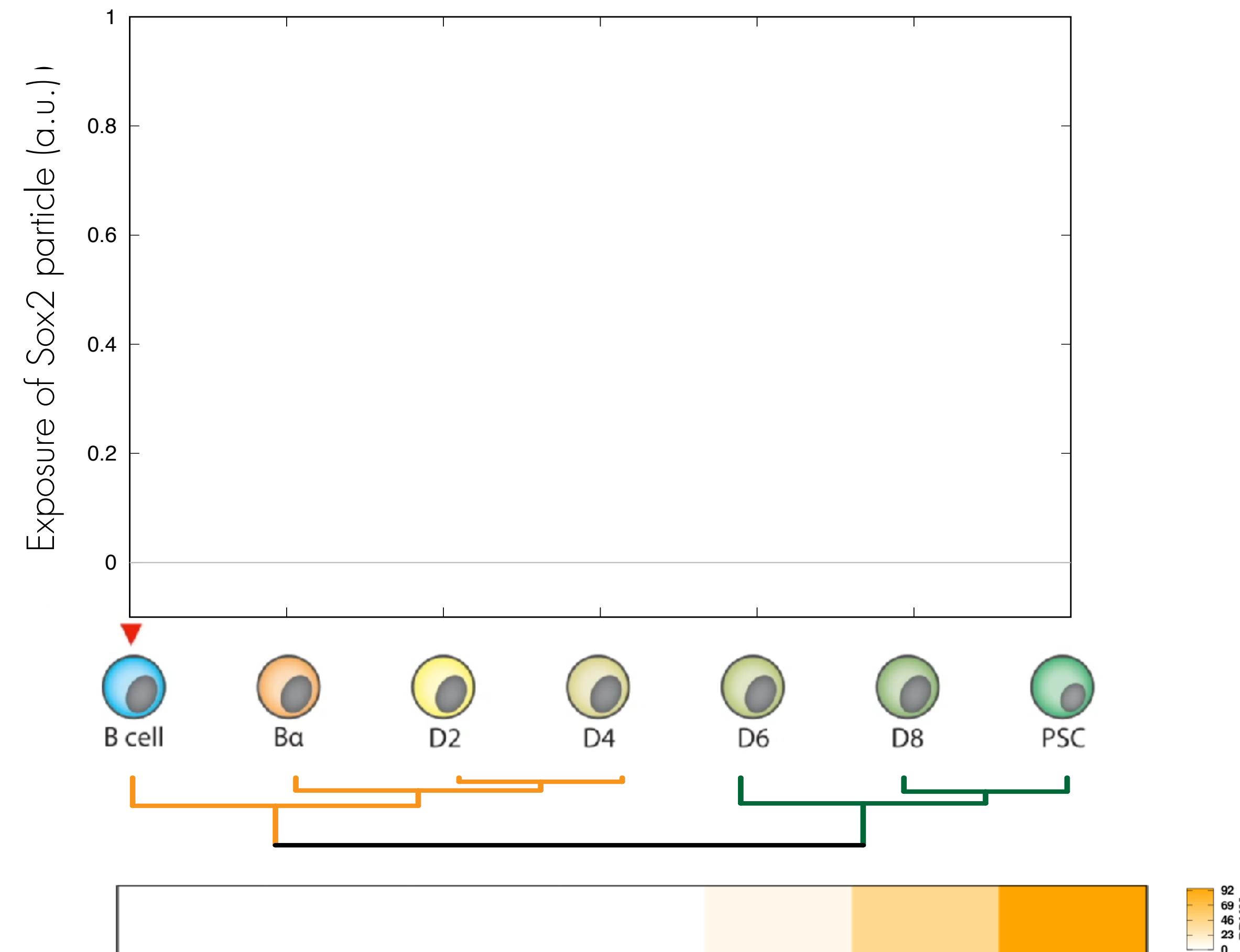
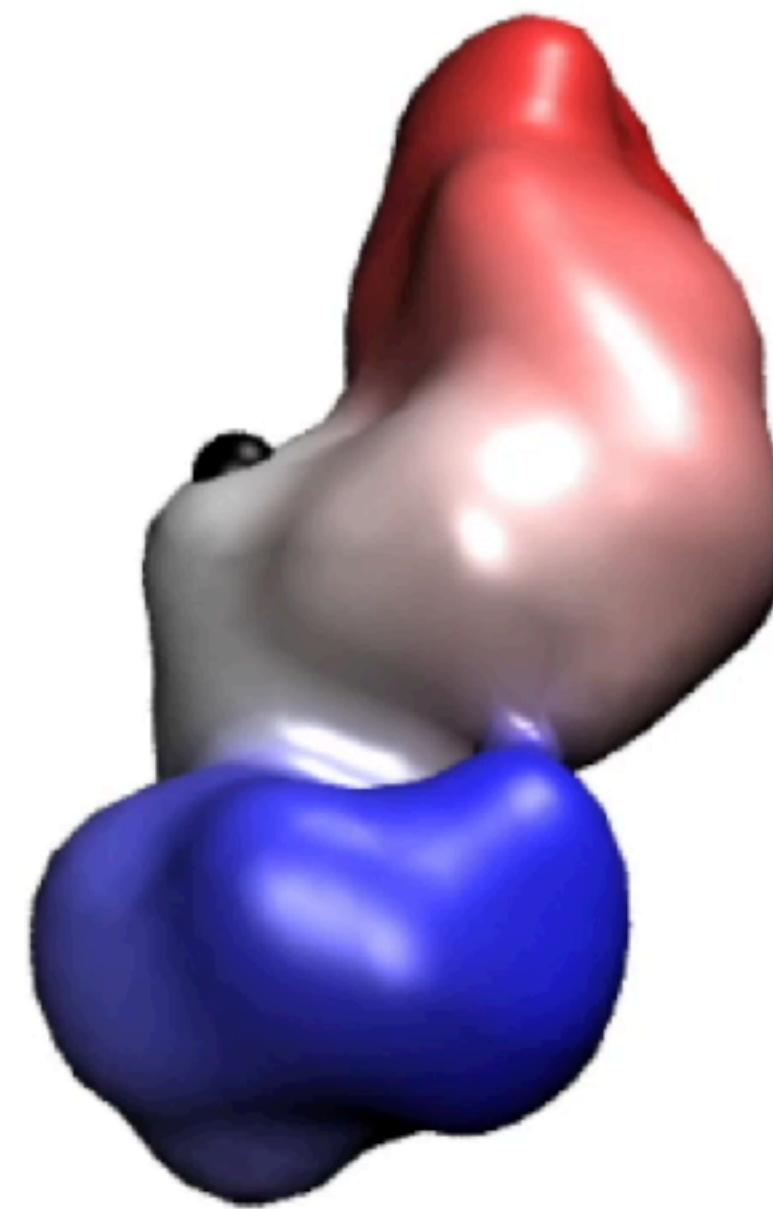
SOX2 locus structural changes from B to PSC

Structural exposure



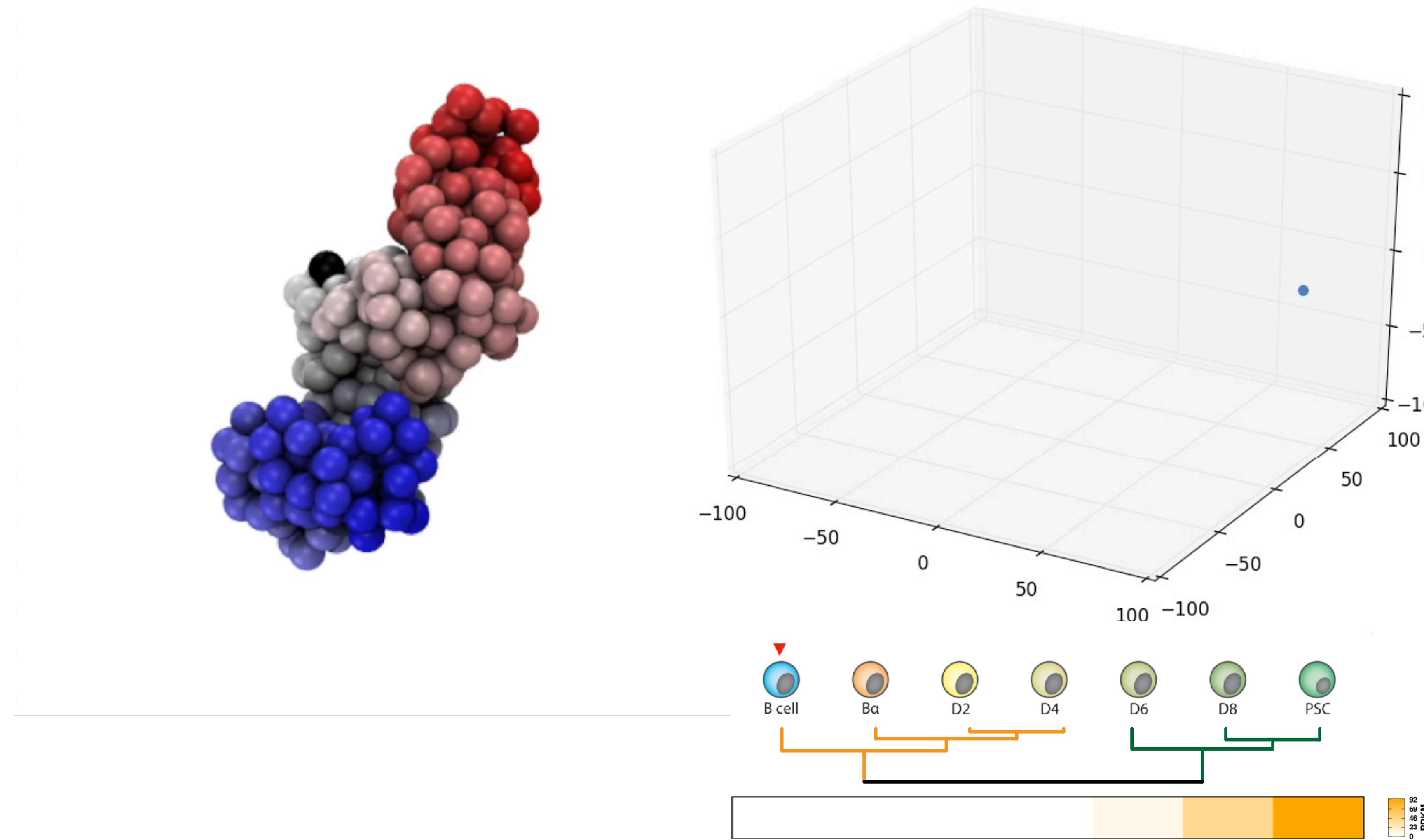
SOX2 locus structural changes from B to PSC

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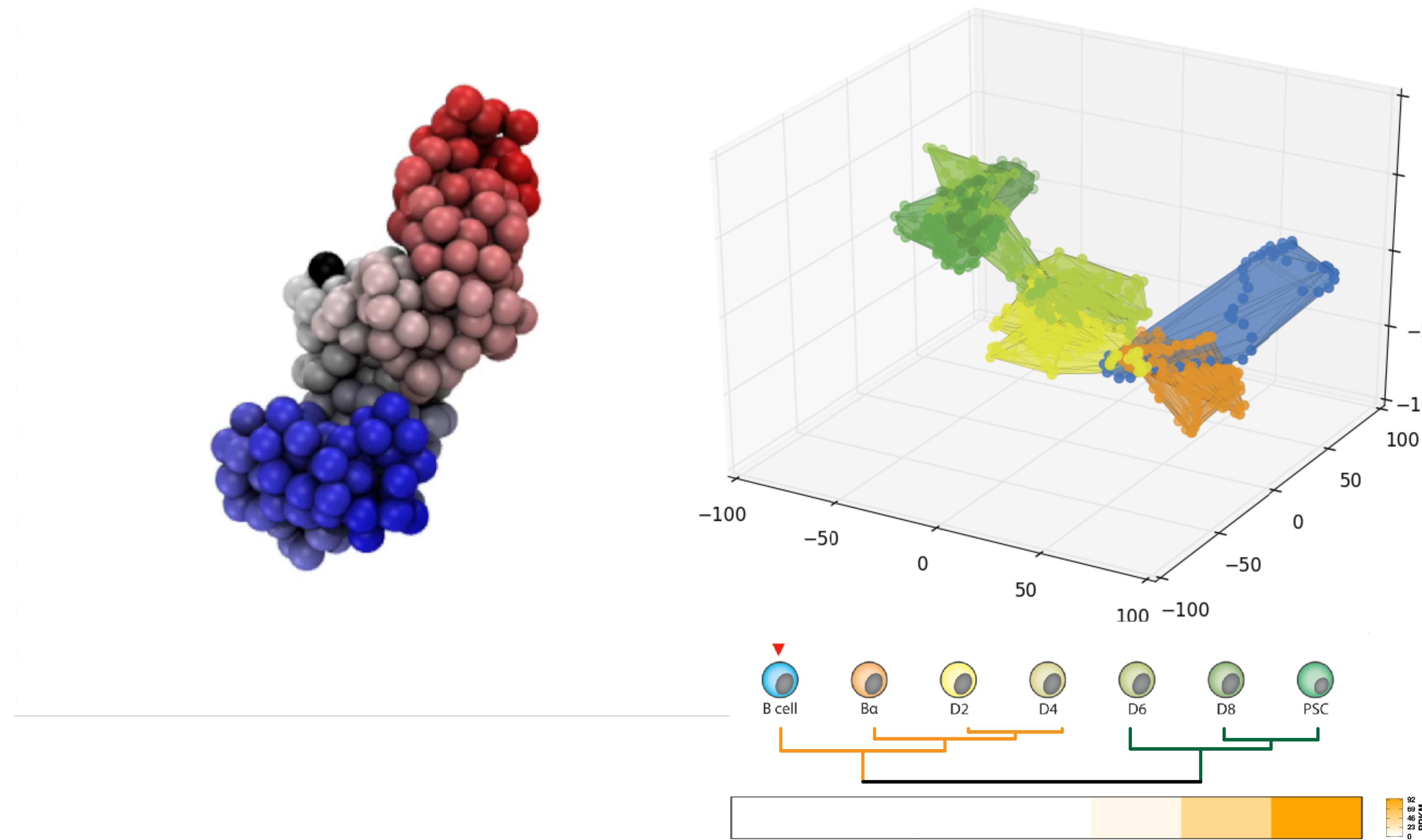
SOX2 locus dynamics changes from B to PSC

SOX2 displacement



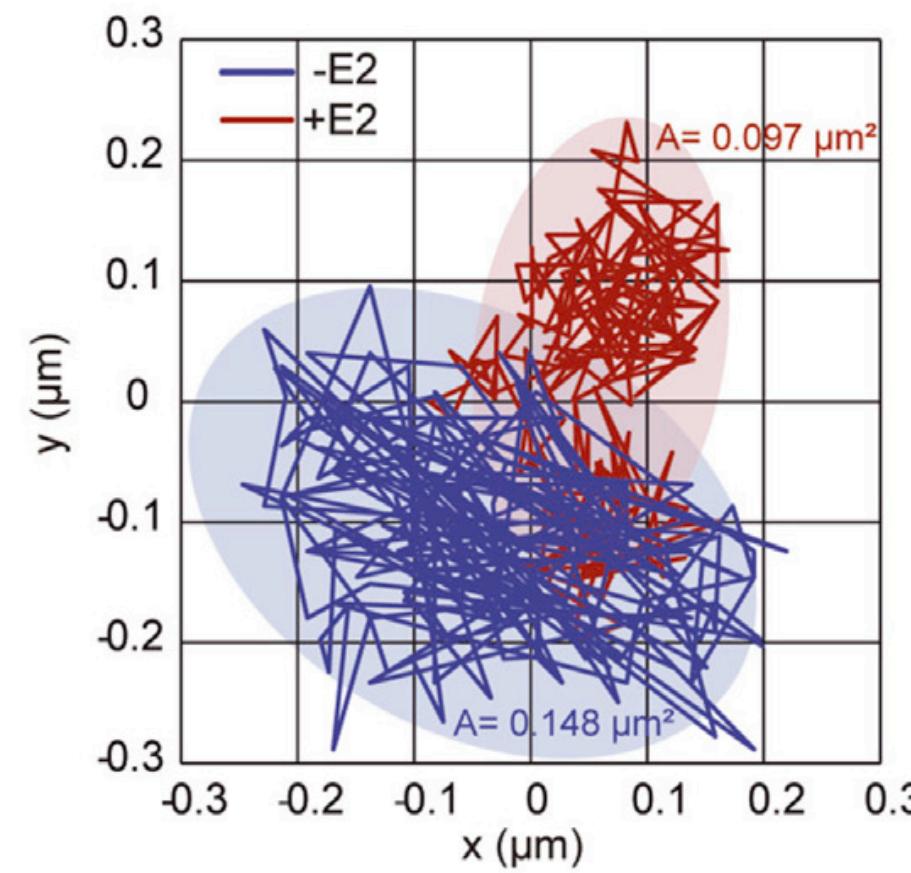
SOX2 locus dynamics changes from B to PSC

SOX2 displacement



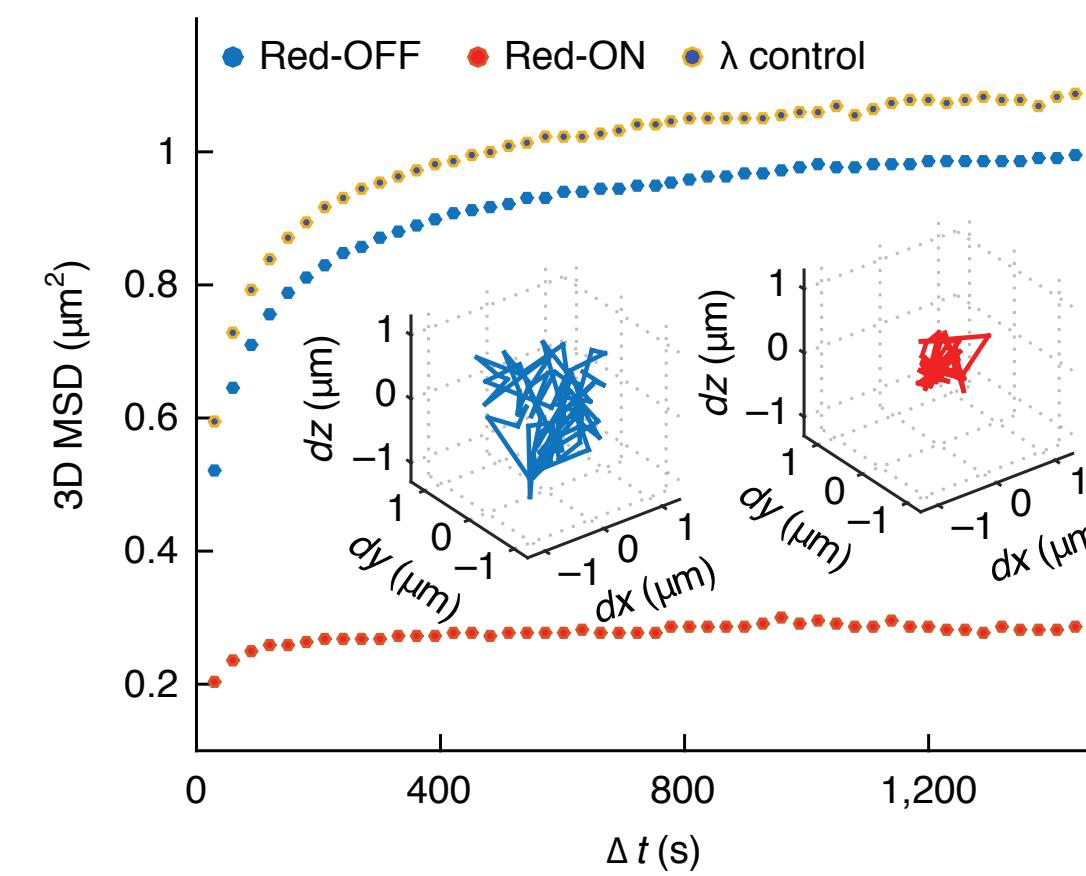
SOX2 locus dynamics changes from B to PSC

SOX2 displacement



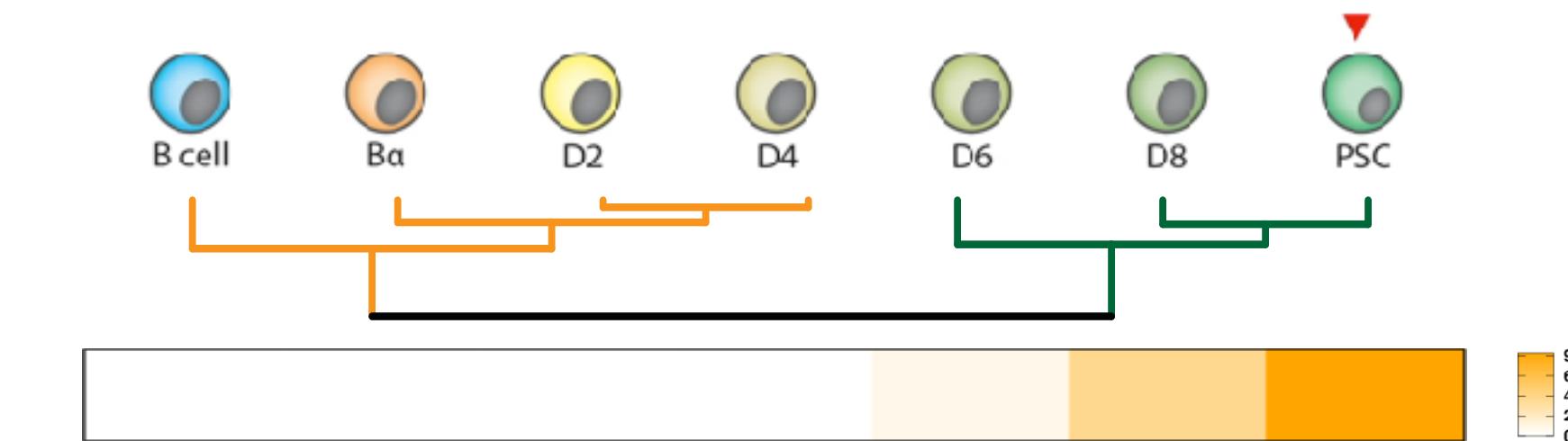
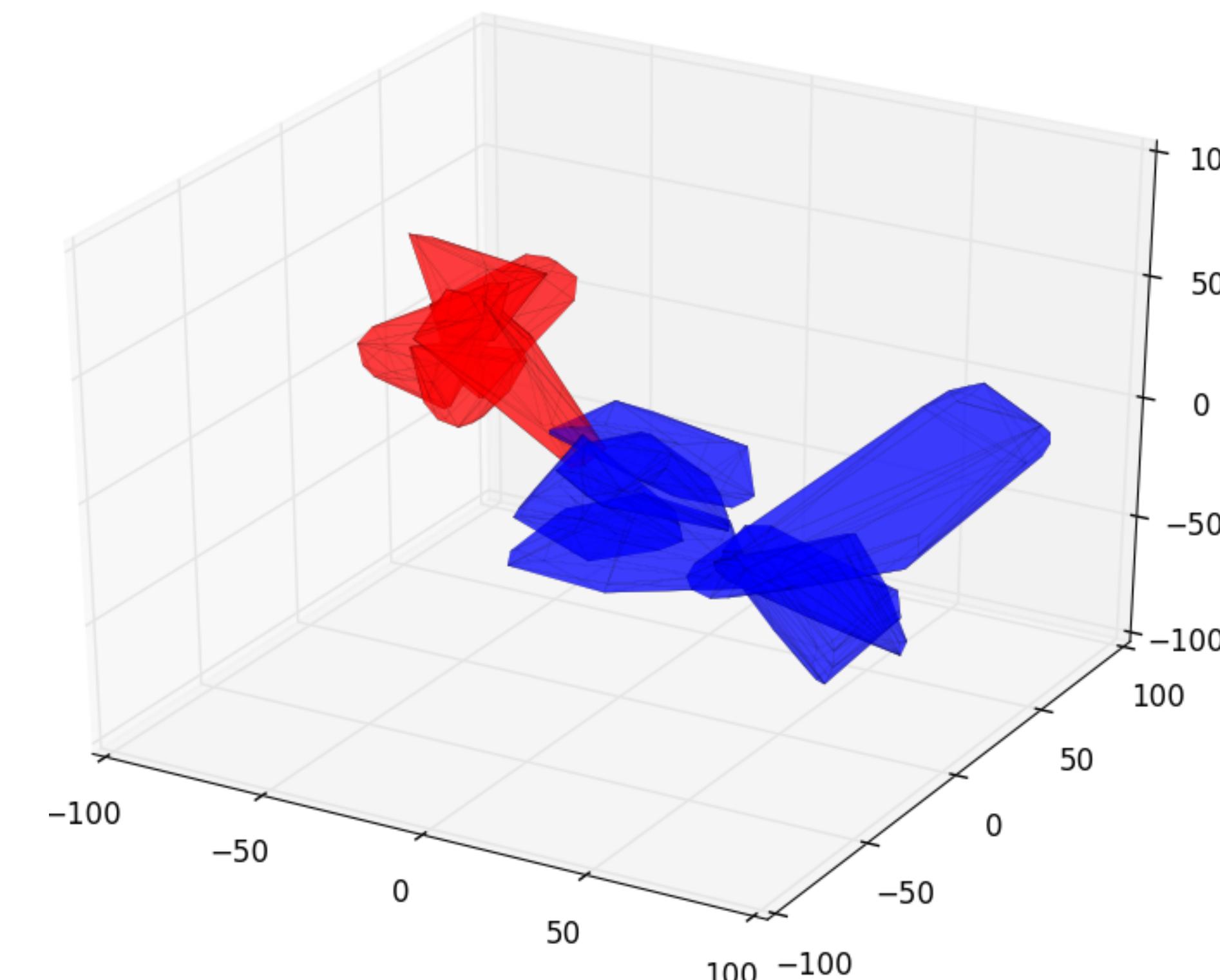
Two dimensional trajectories and area explored over 50s of the CCND1 locus recorded before -E2 and after +E2 activation.

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



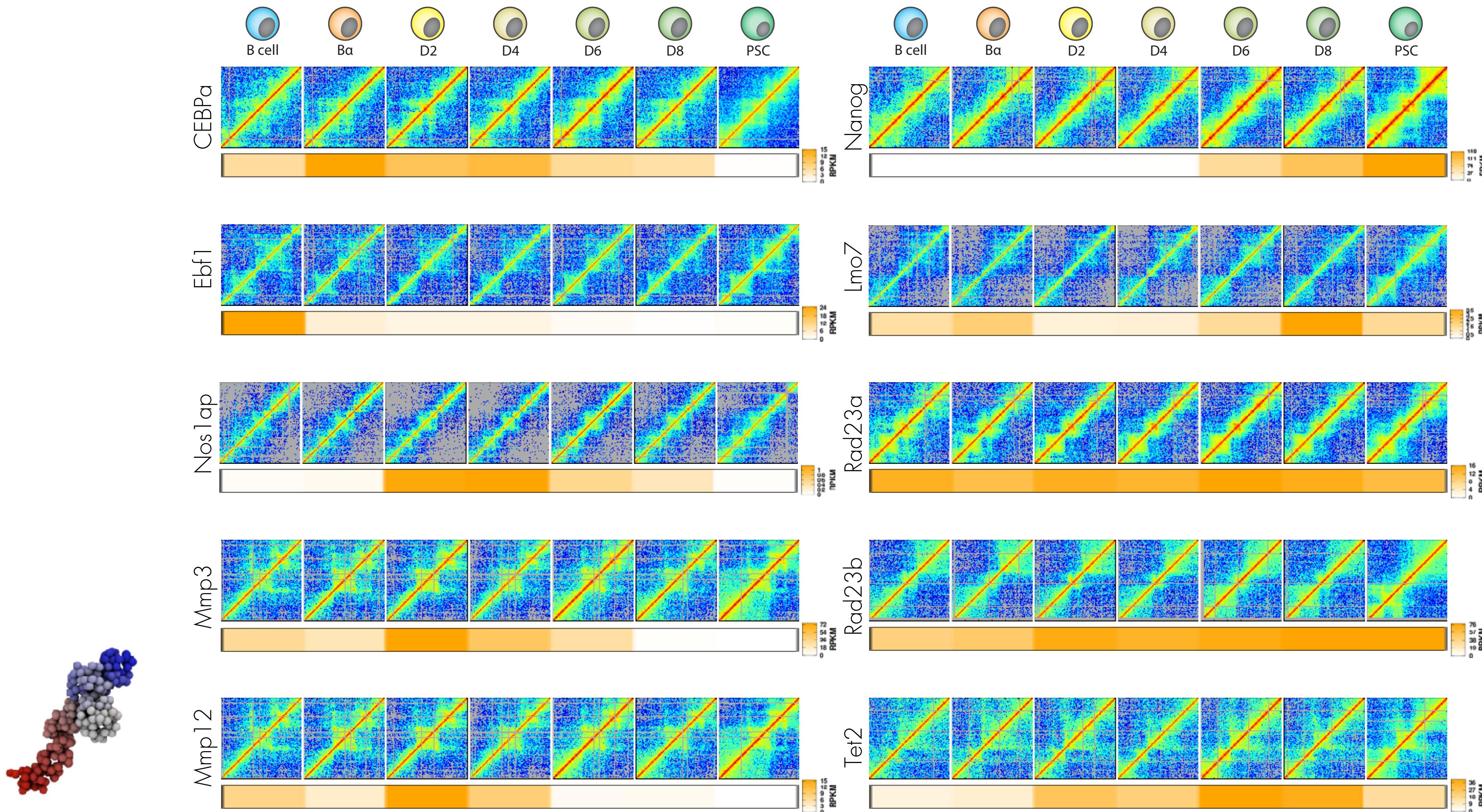
Transcription affects the 3D topology of the enhancer-promoted enhancing its temporal stability and is associated with further spatial compaction.

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



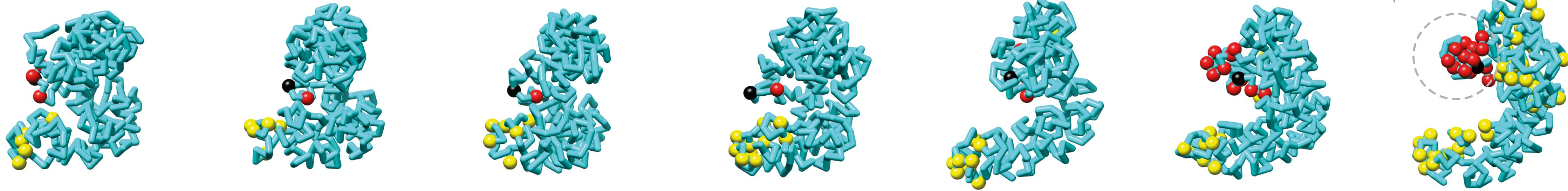
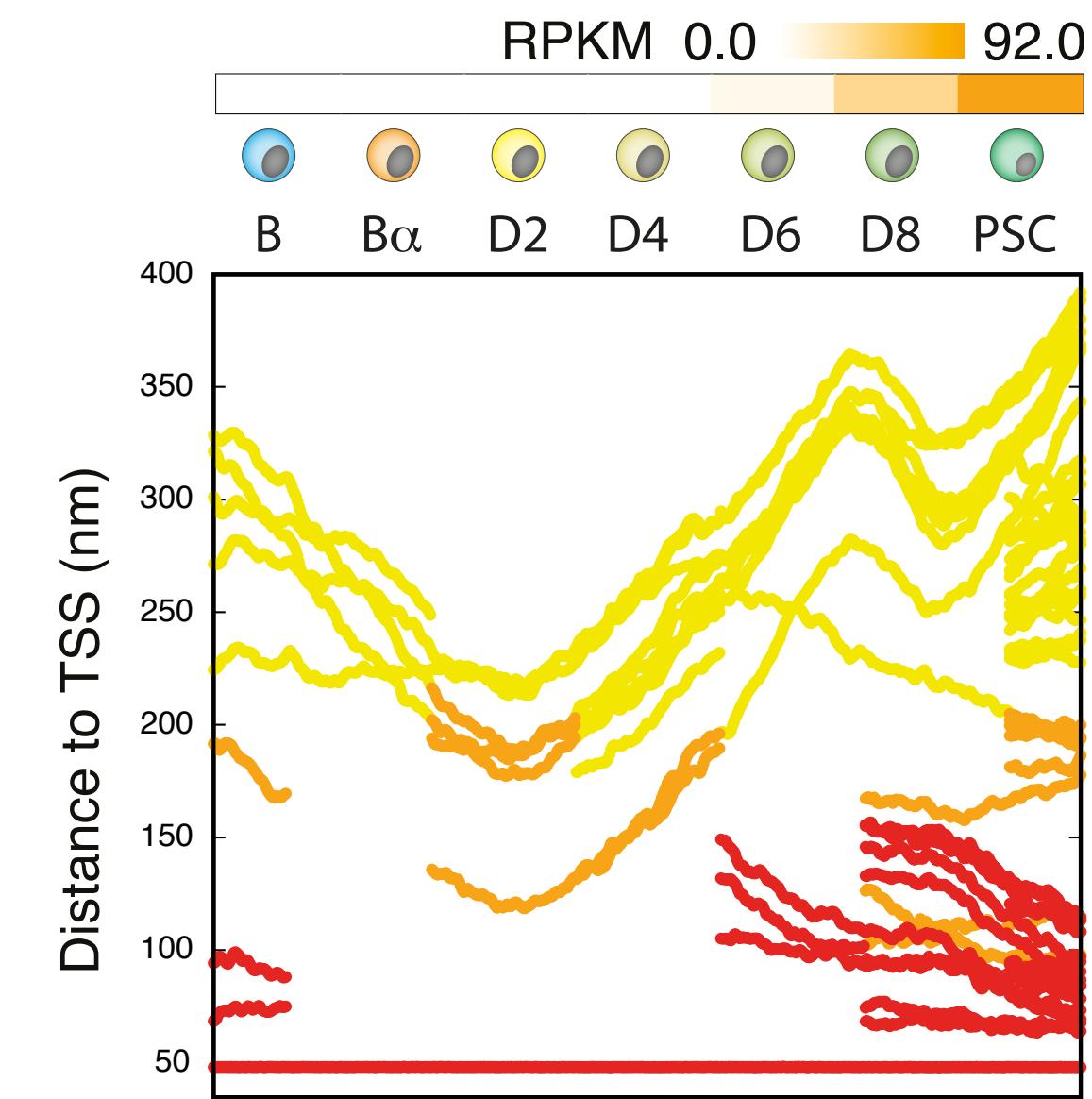
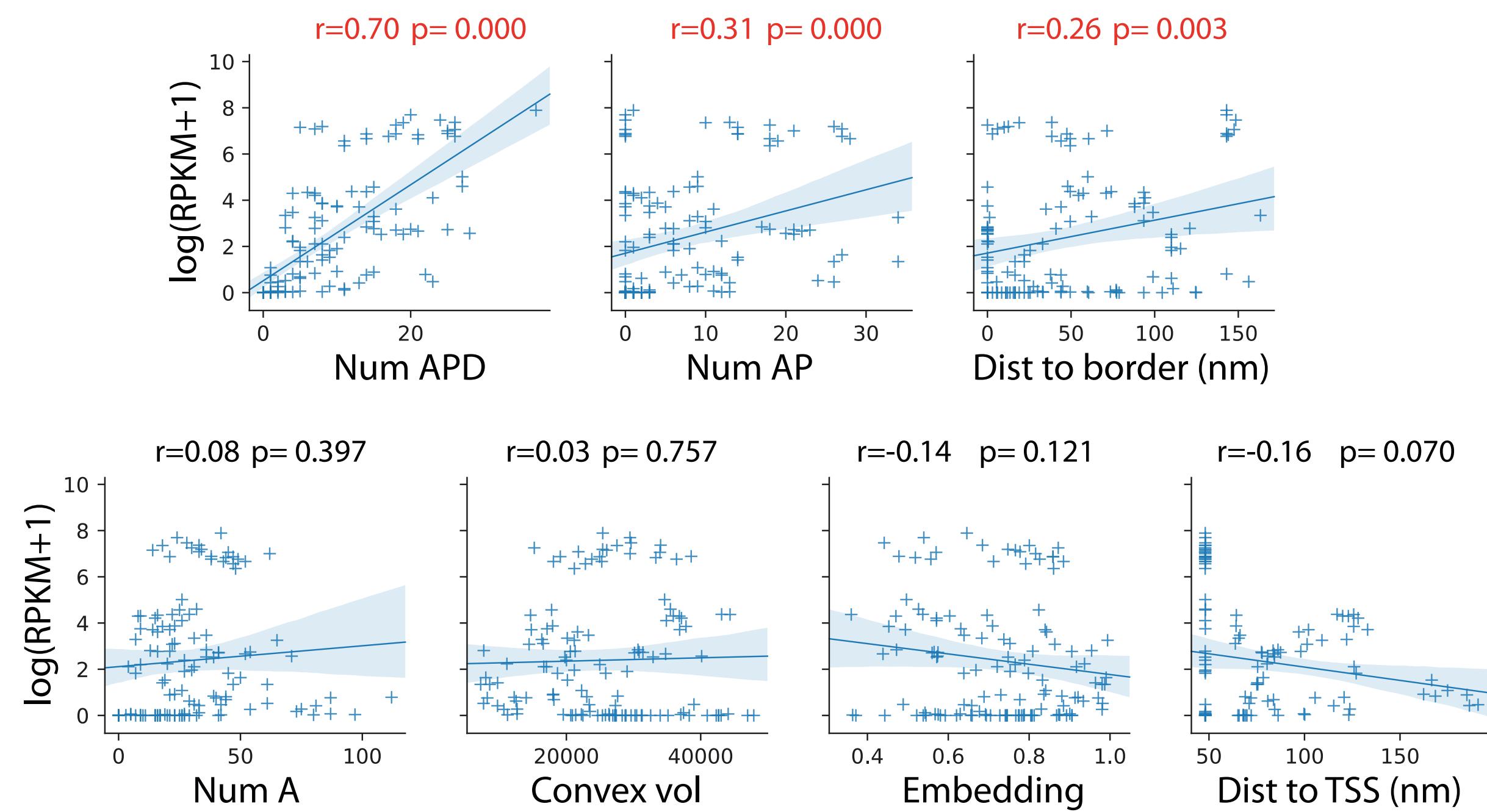
Structural changes from B to PSC

Other 21 loci



Dynamics of gene activation

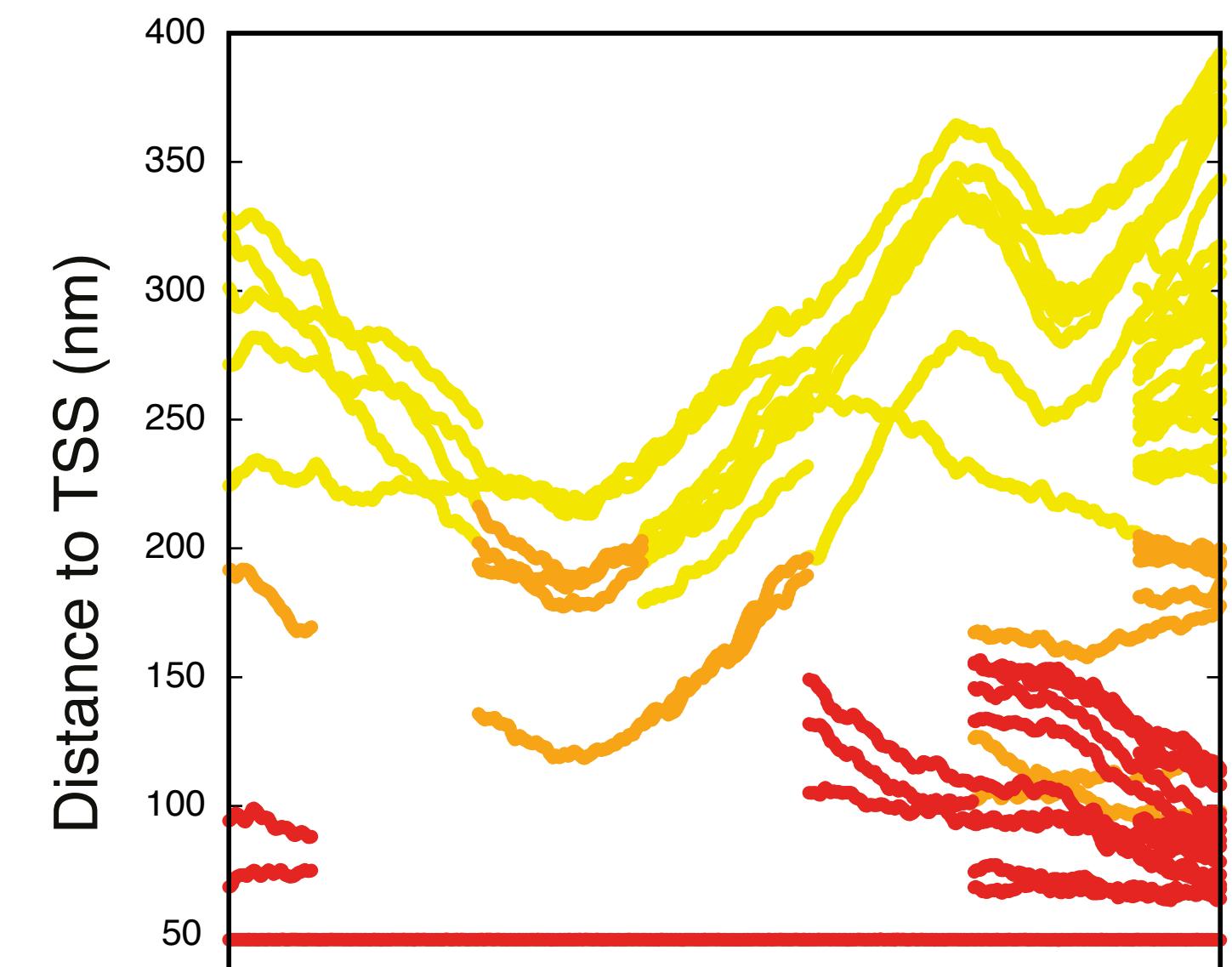
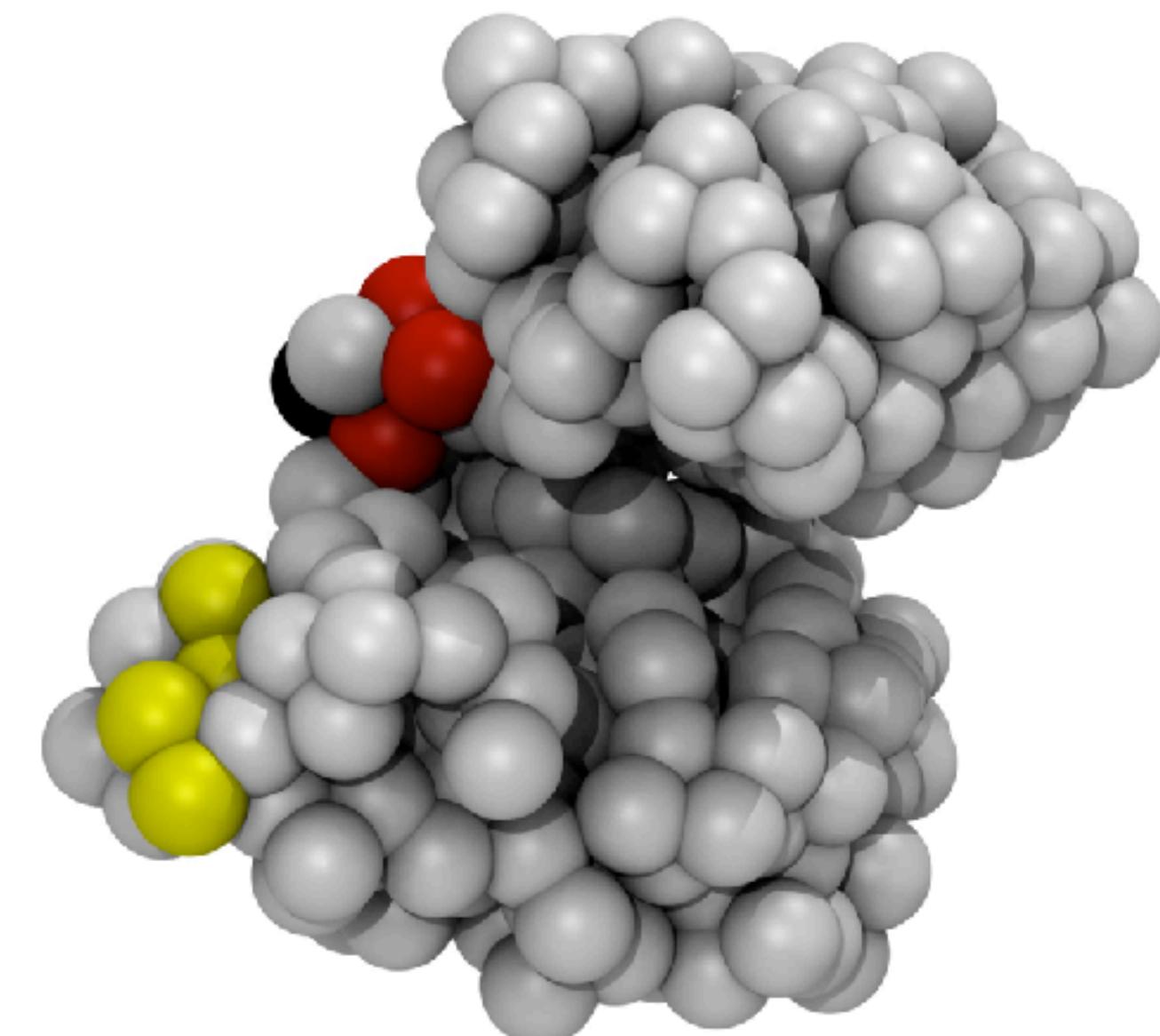
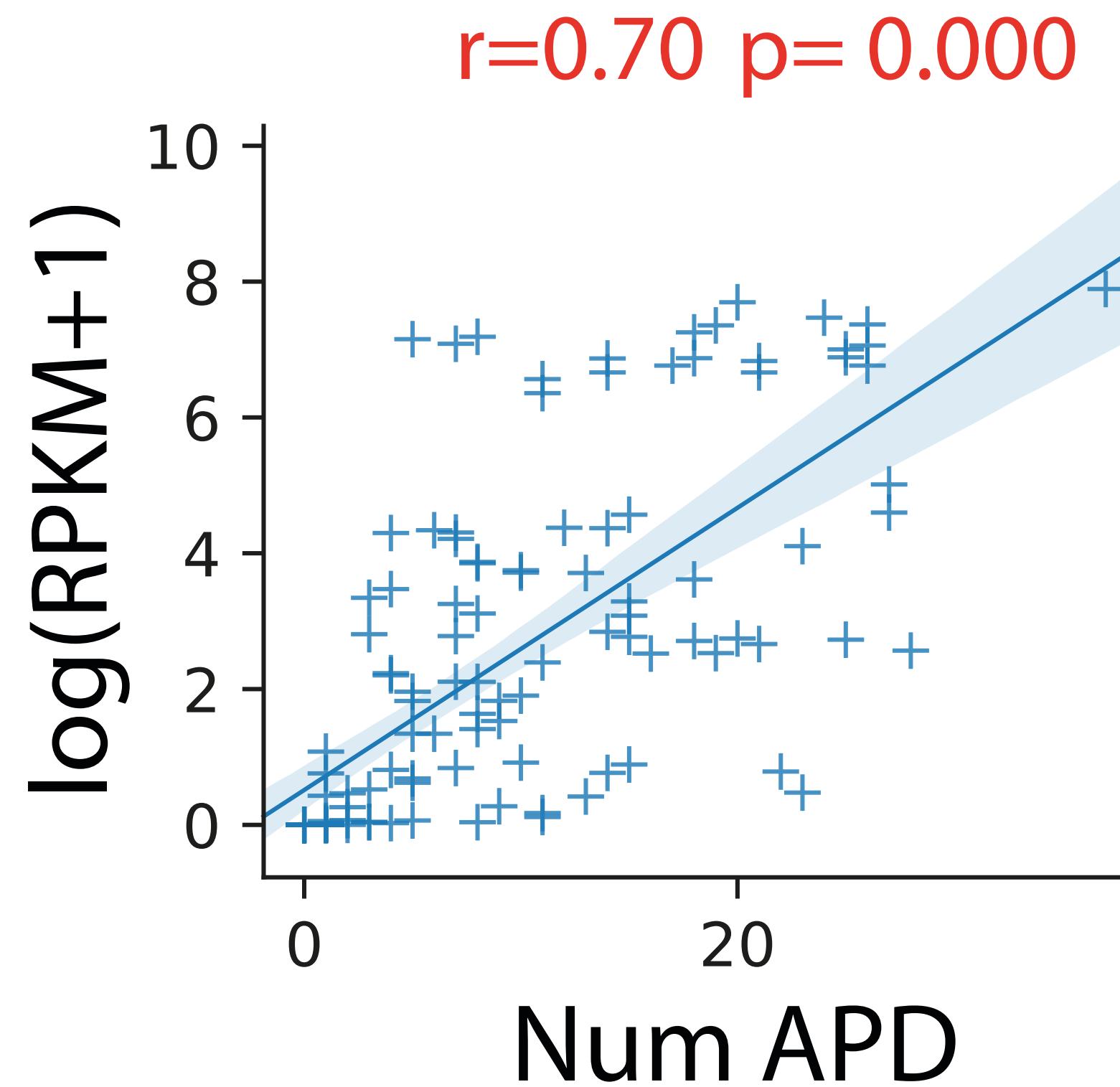
Trends in 21 loci



Time and expression levels

Dynamics of gene activation

3D enhancer hubs



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

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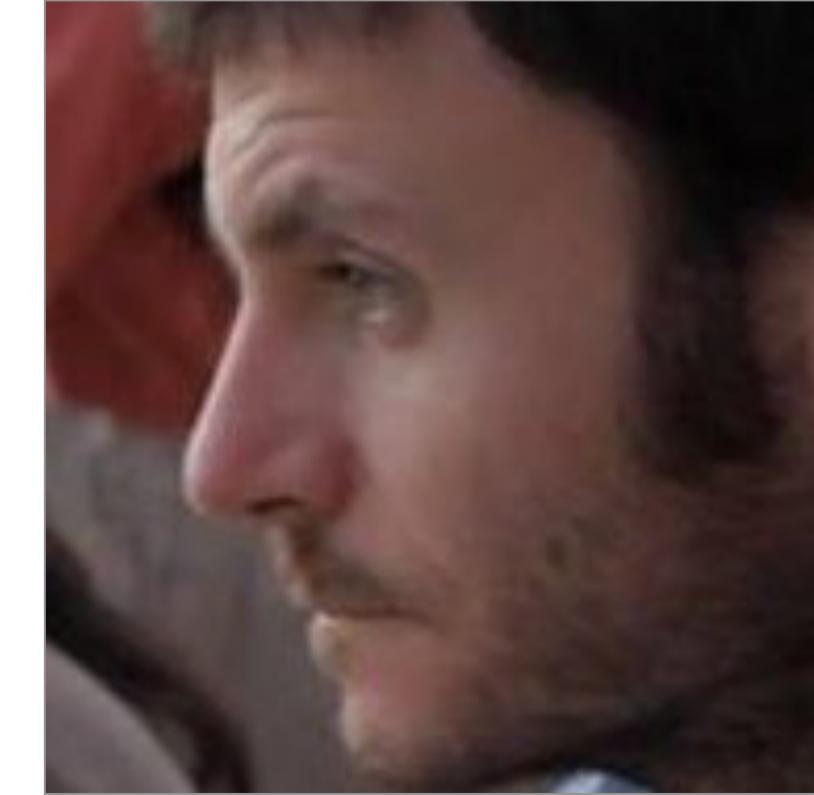
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