Dynamics of gene activation

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CNAG-CRG · ICREA

Nature Genetics (2018) 50 p238
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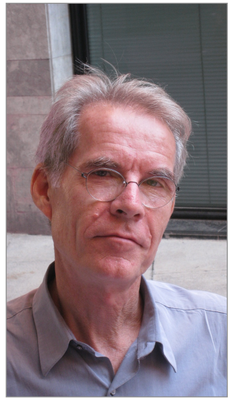
Marco di Stefano
CNAG-CRG

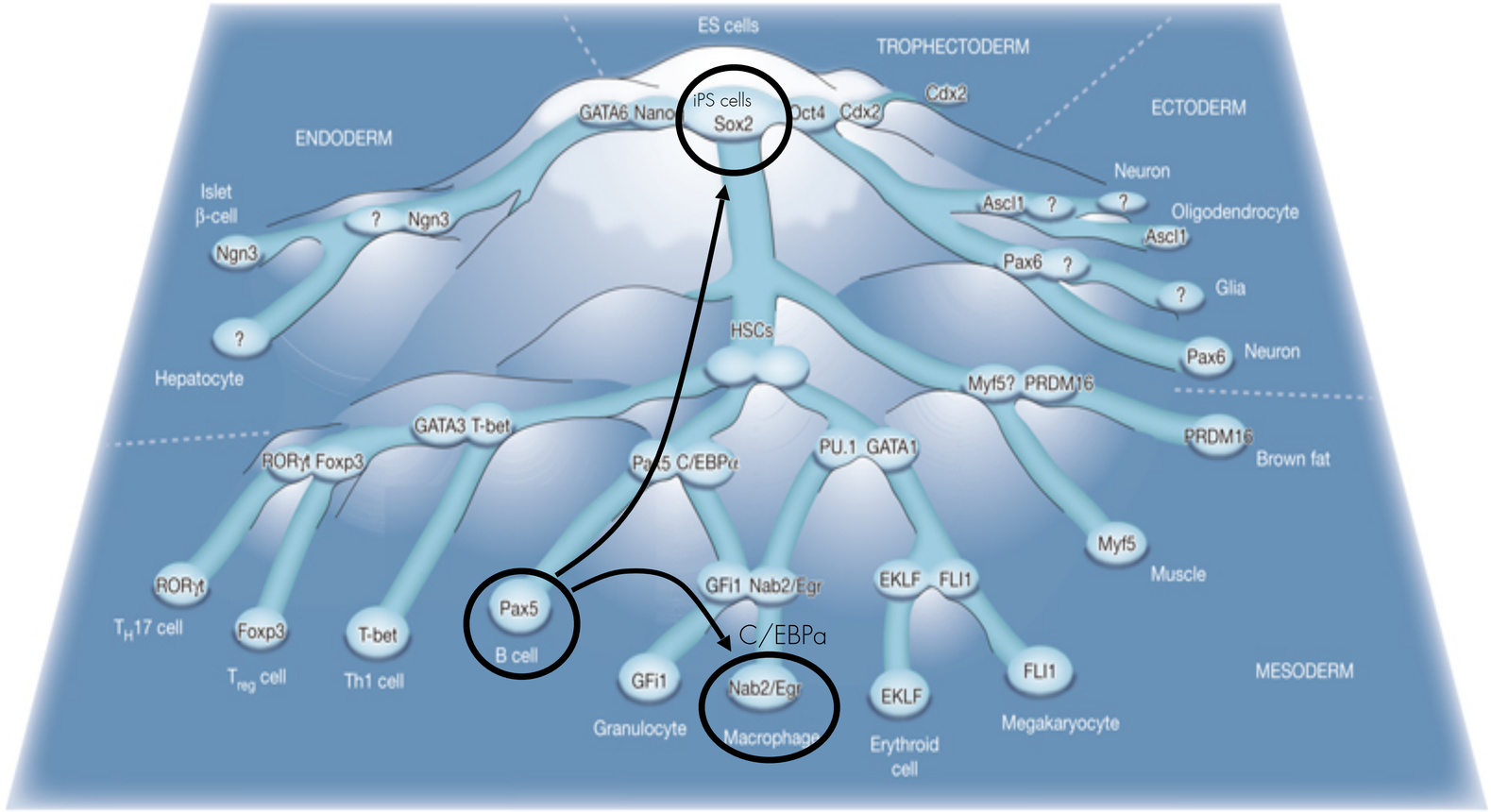




Ralph Stadhouders, Enrique Vidal & Thomas Graf
CRG

Transcription factors dictate cell fate

Graf & Enver (2009) Nature



Transcription factors (TFs) determine cell identity through gene regulation

Normal 'forward' differentiation

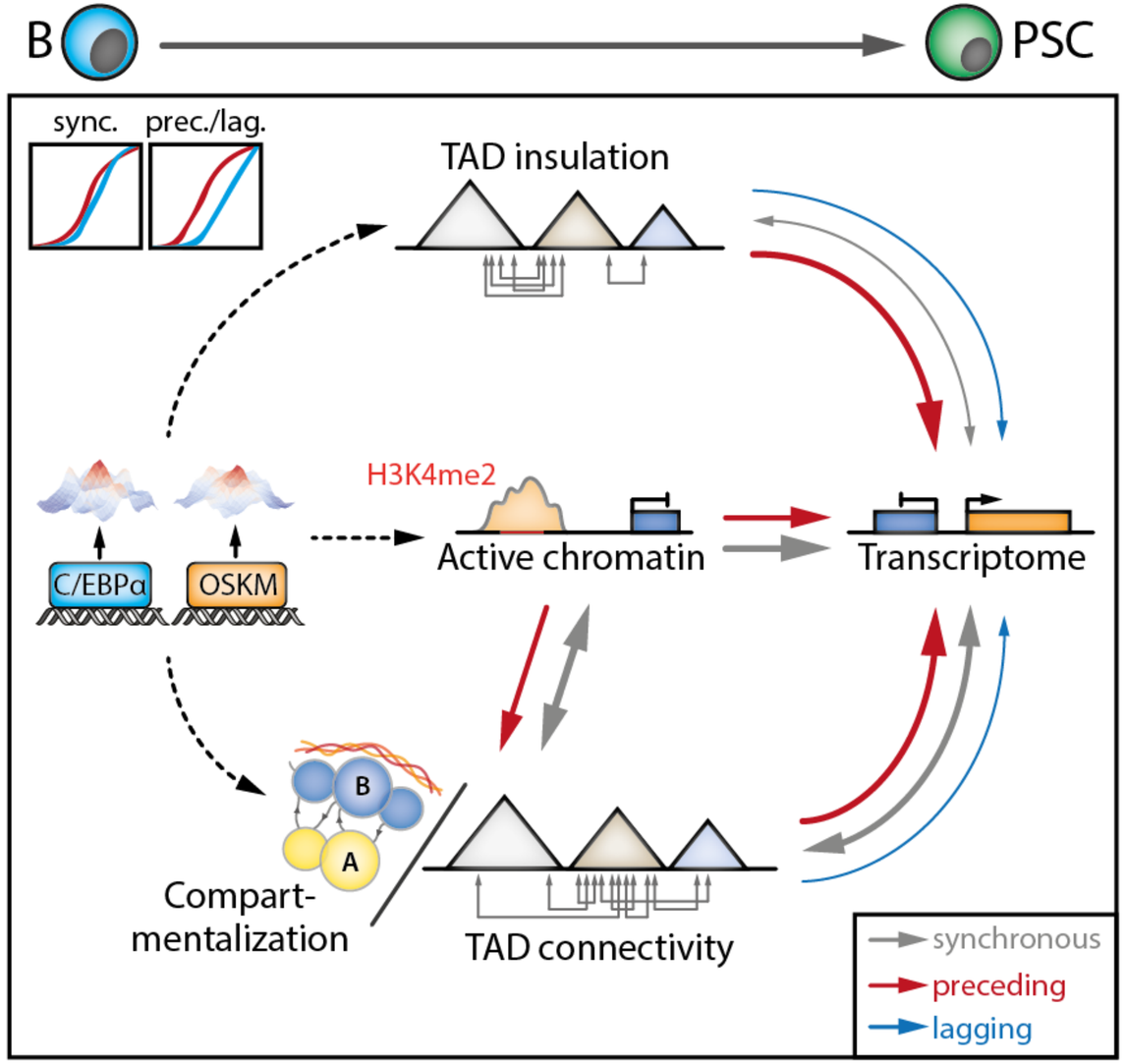
Cell fates can be converted by enforced TF expression

Transdifferentiation or reprogramming

Interplay: topology, gene expression & chromatin

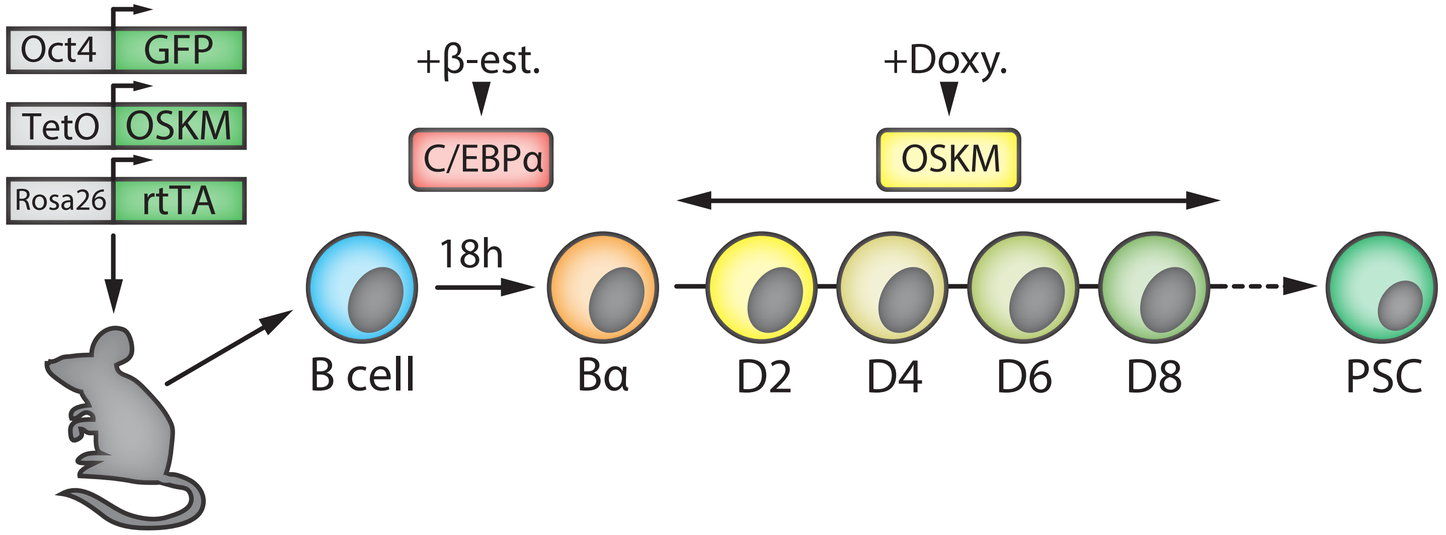
Graf & Enver (2009) Nature

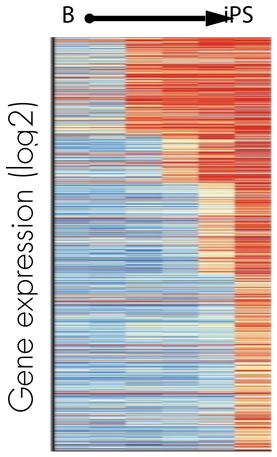
Stadhouders, R., Vidal, E. et al. (2018) Nature Genetics

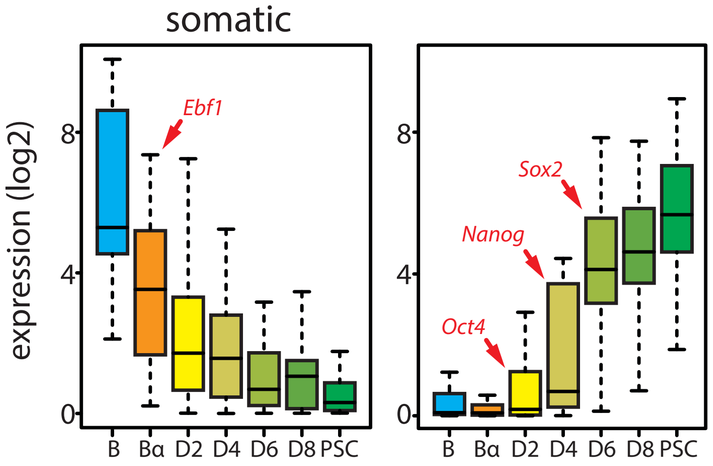


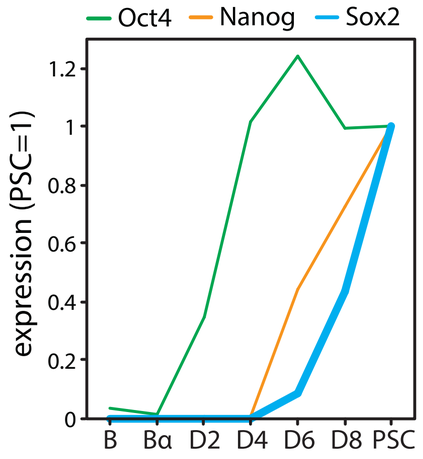
Reprogramming from B to PSC

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



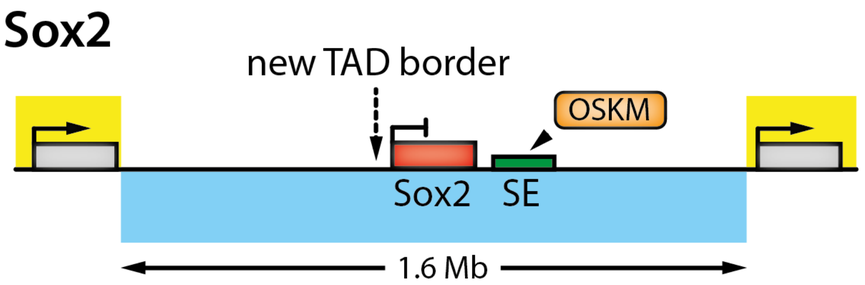


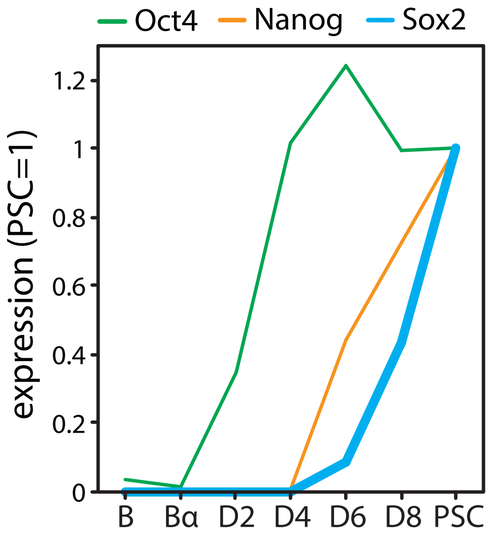


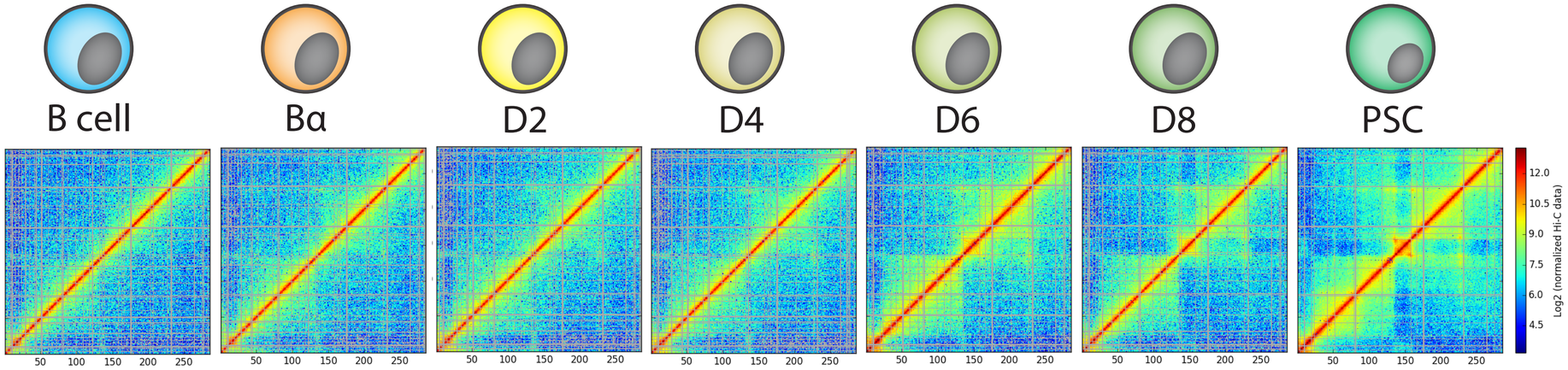


Hi-C maps of reprogramming from B to PSC

The SOX2 locus







Hi-C maps of reprogramming from B to PSC

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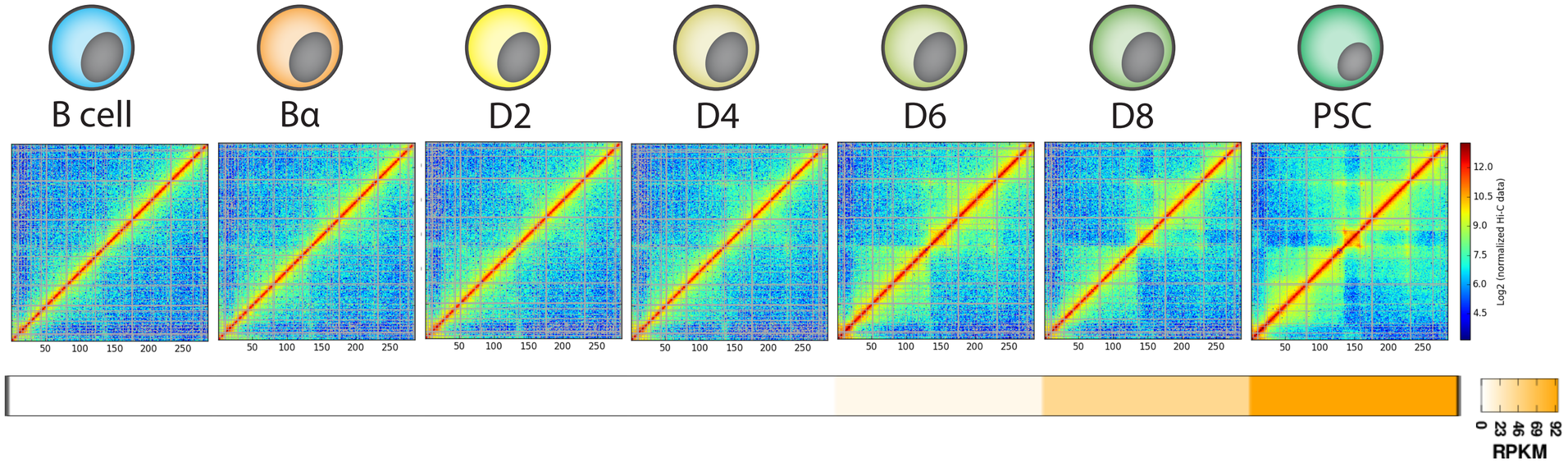
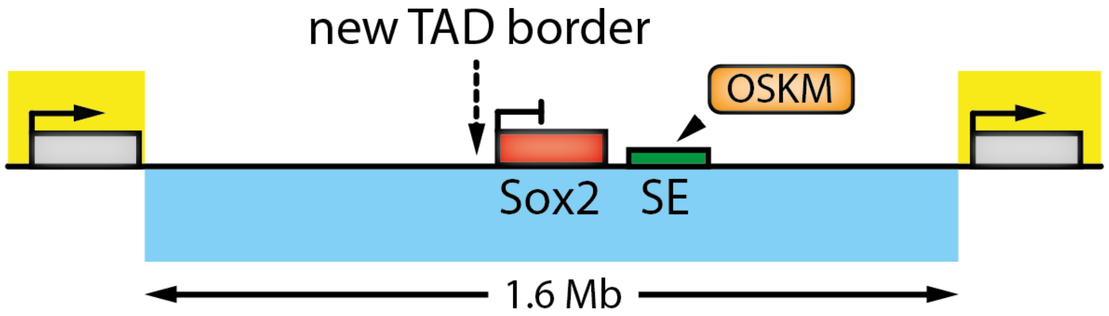
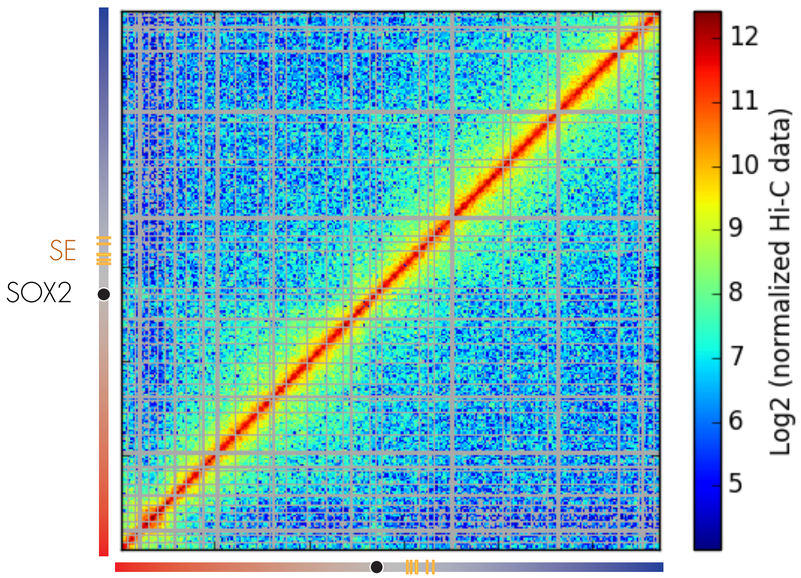


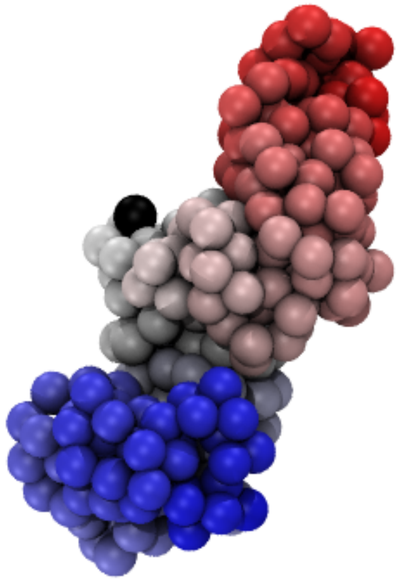
How does these structural rearrangements interplay with the transcription activity?

What are the main drivers of structural transitions?

TADbit modeling of SOX2 from B cells Hi-C







Optimal IMP parameters

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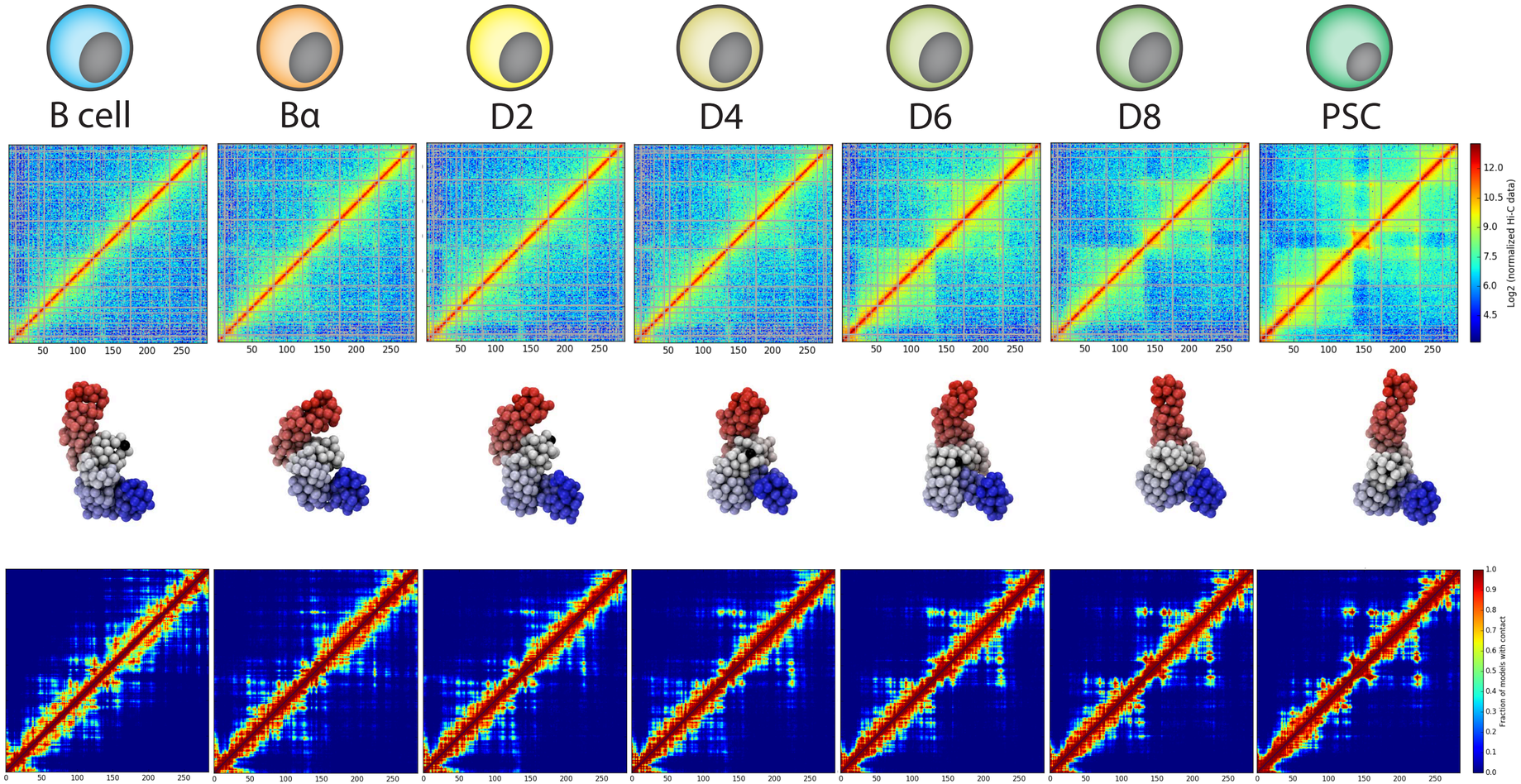
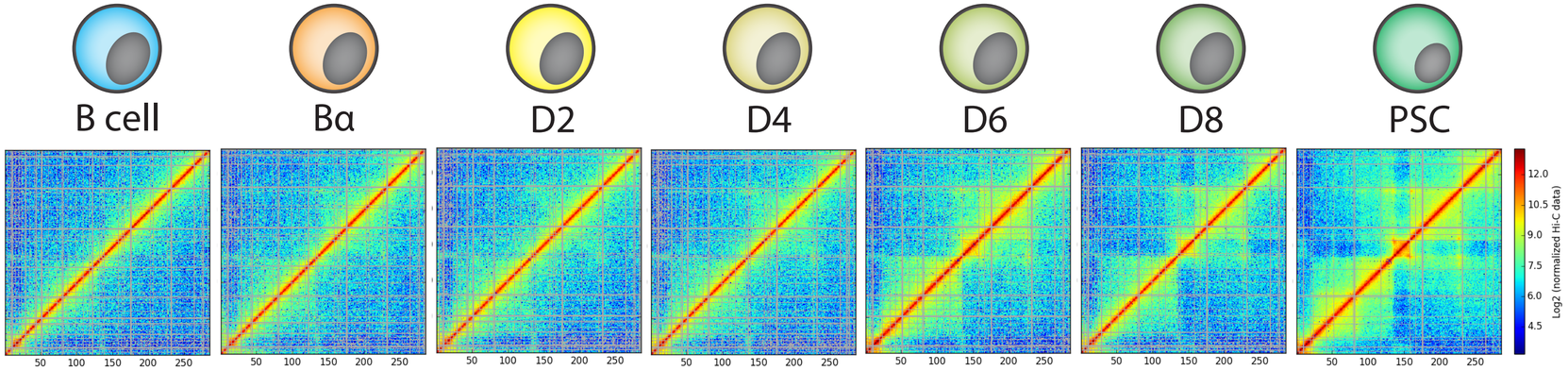
Models of reprogramming from B to PSC

The SOX2 locus



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

The SOX2 locus



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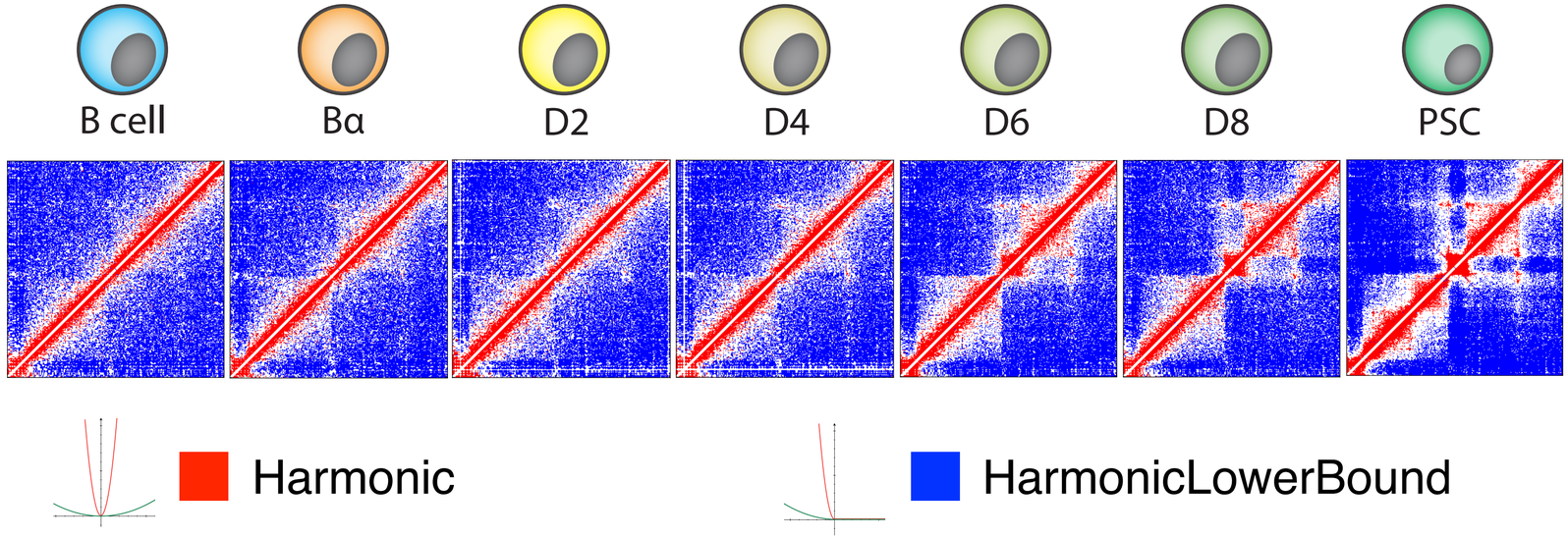

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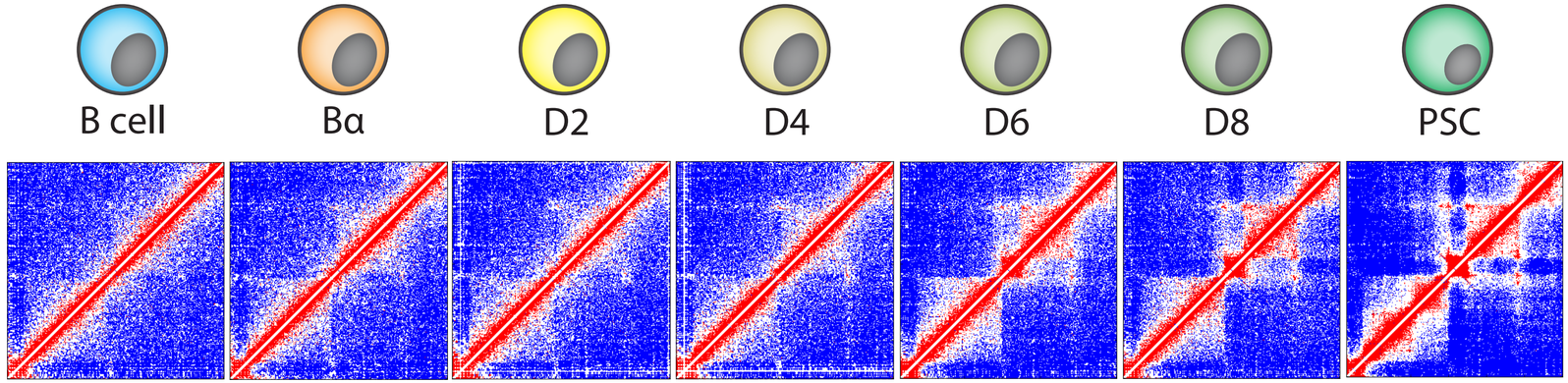
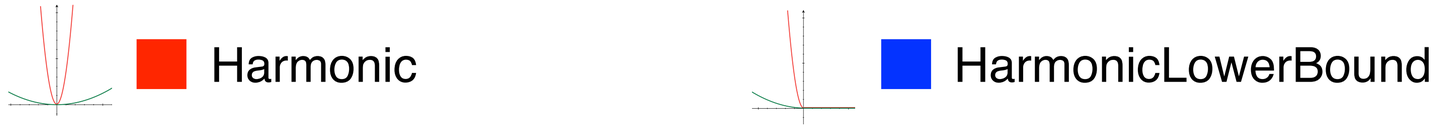
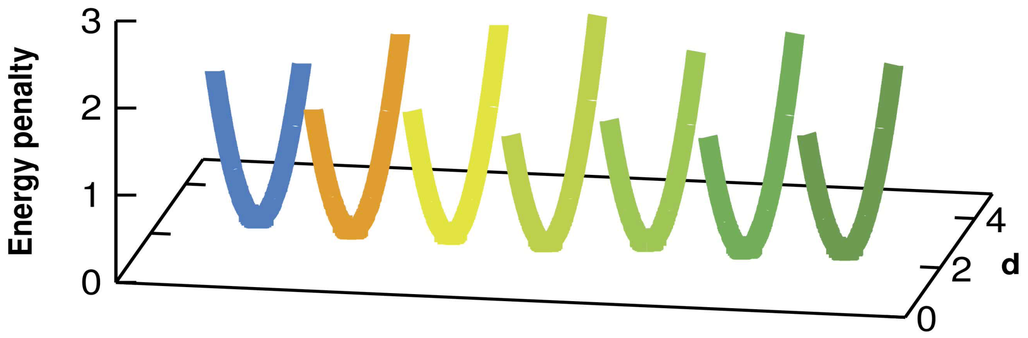


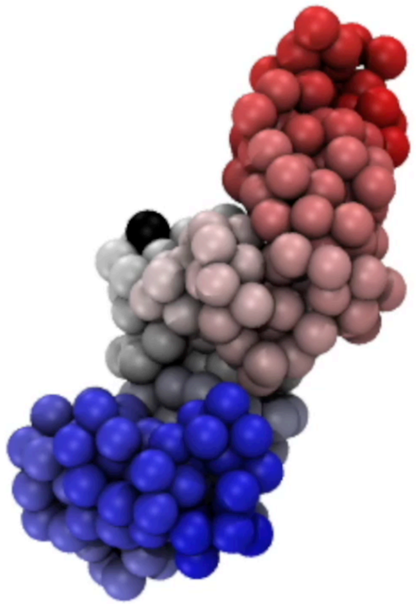


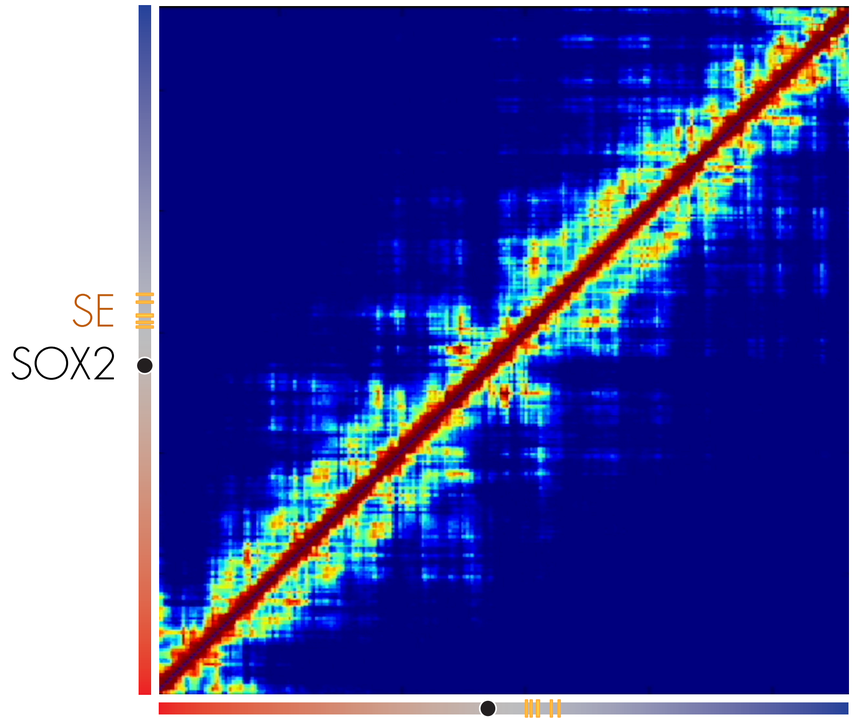


Transition	Stable	Vanishing	Raising
B -> Bα	18,612	6,984	7,290
Bα -> D2	18,512	7,390	6,687
D2 -> D4	18,369	6,830	6,893
D4 -> D6	18,971	6,291	7,289
D6 -> D8	20,167	6,093	6,250
D8 -> ES	20,679	5,738	6,173

SOX2 locus structural changes from B to PSC

Contacts





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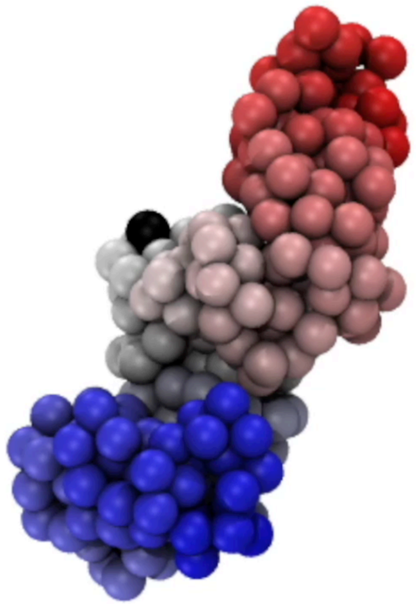
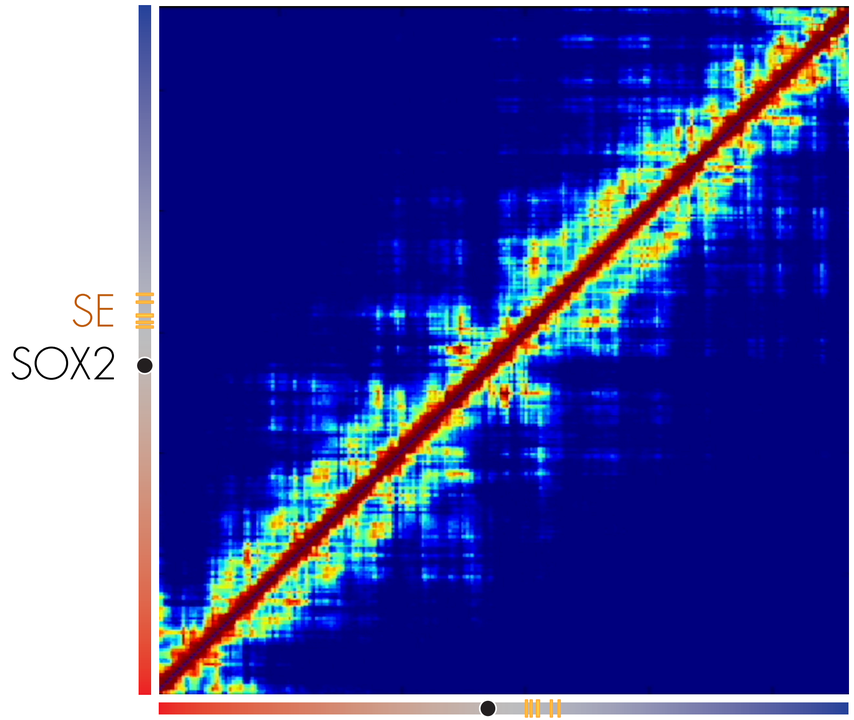
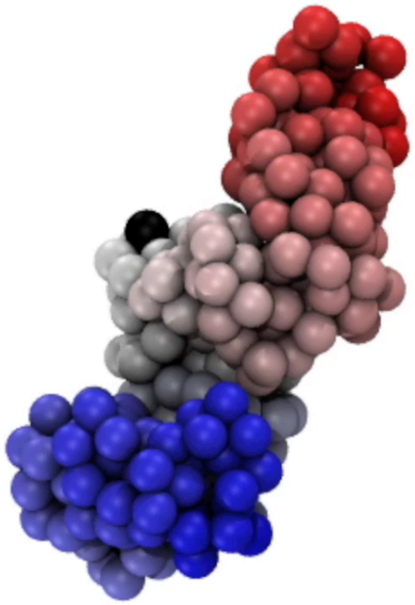
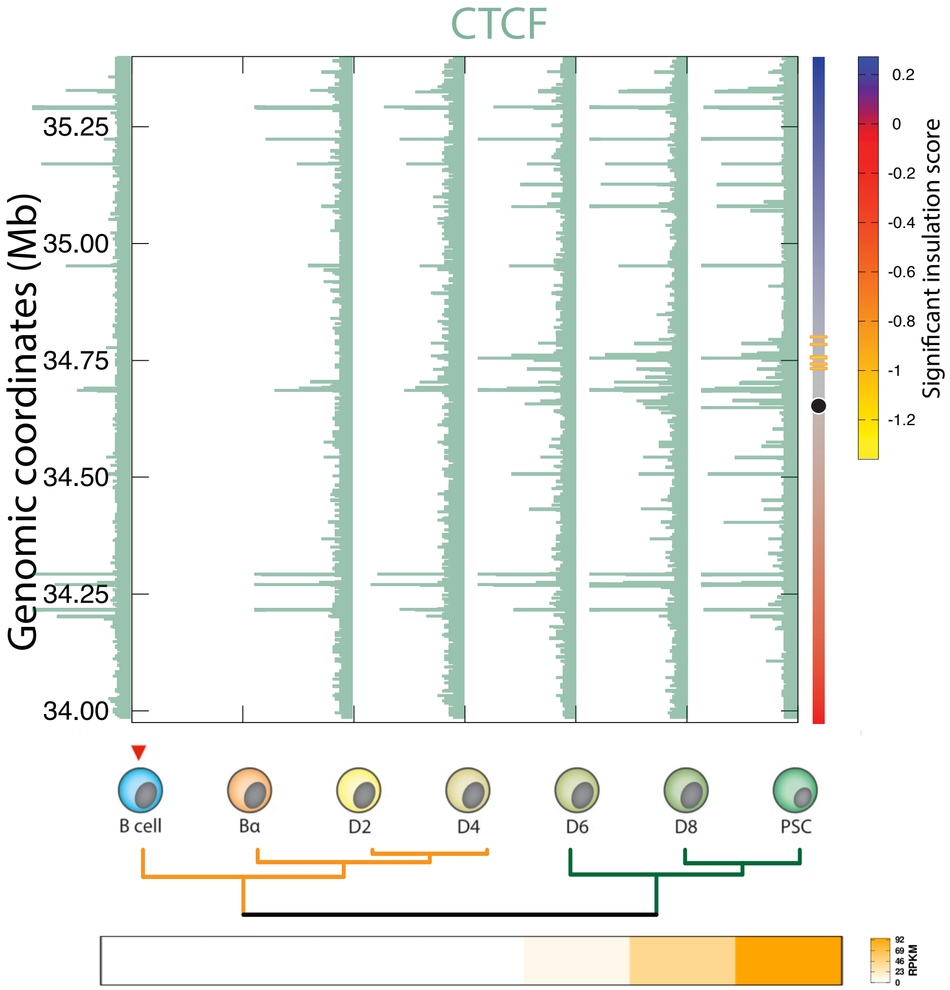




SOX2 locus structural changes from B to PSC

TAD borders





SOX2 locus structural changes from B to PSC

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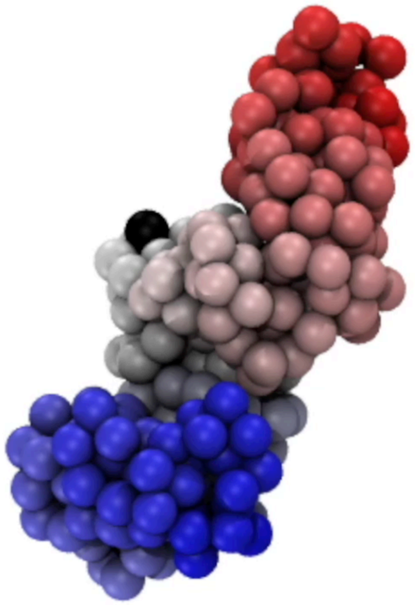
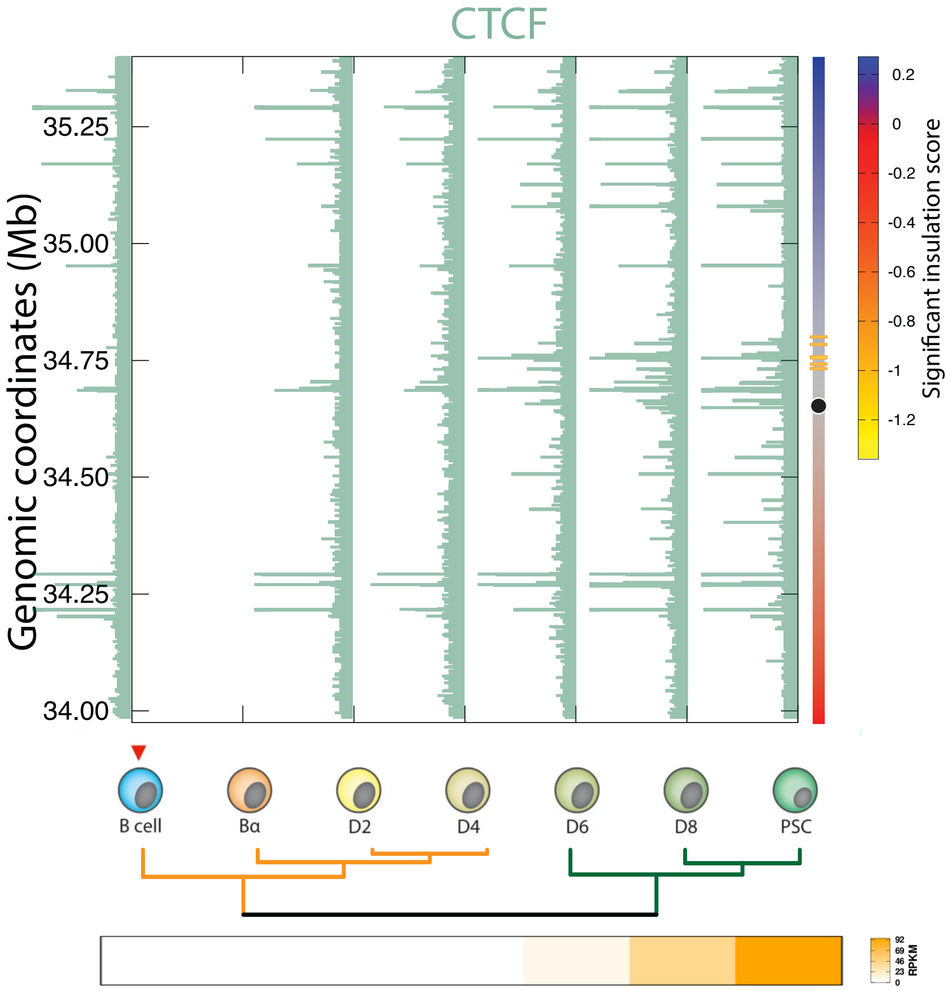
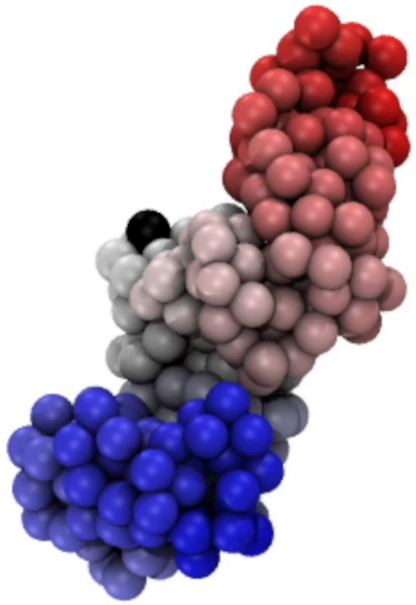
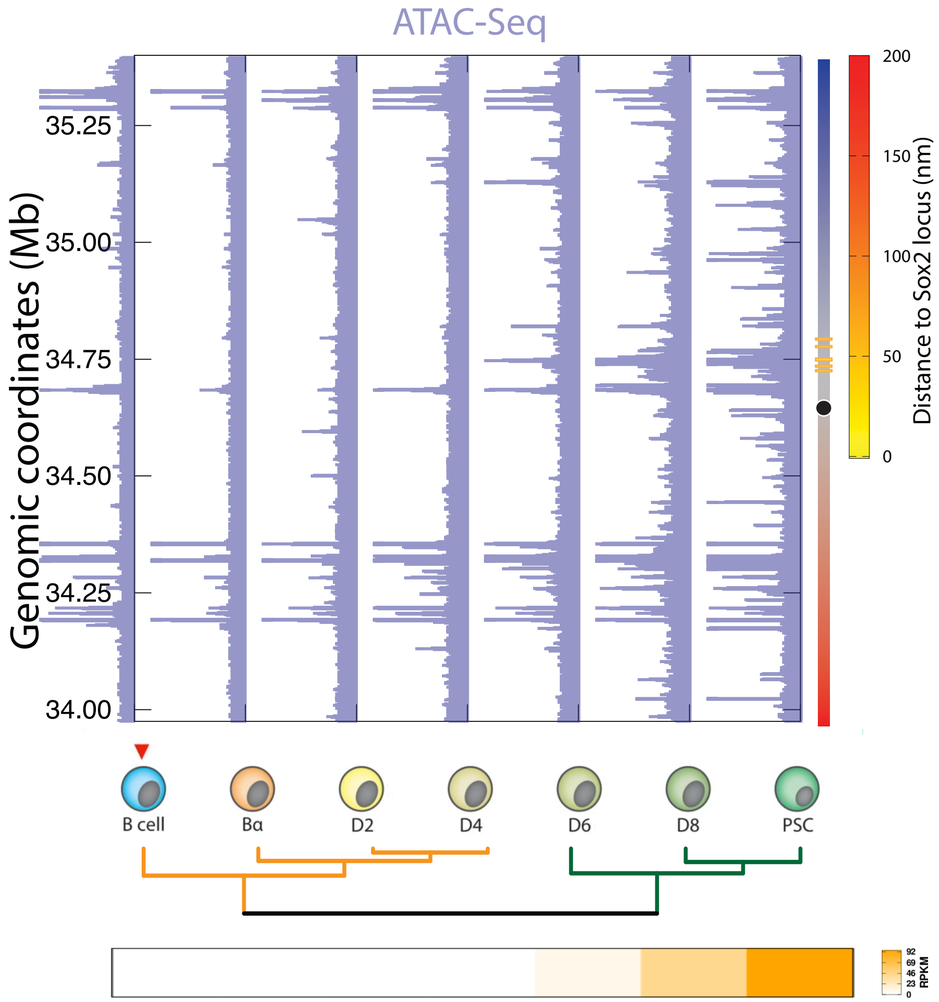




SOX2 locus structural changes from B to PSC

Distance to regulatory elements





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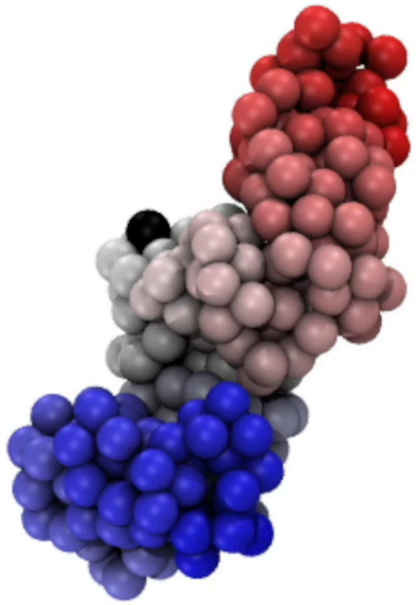
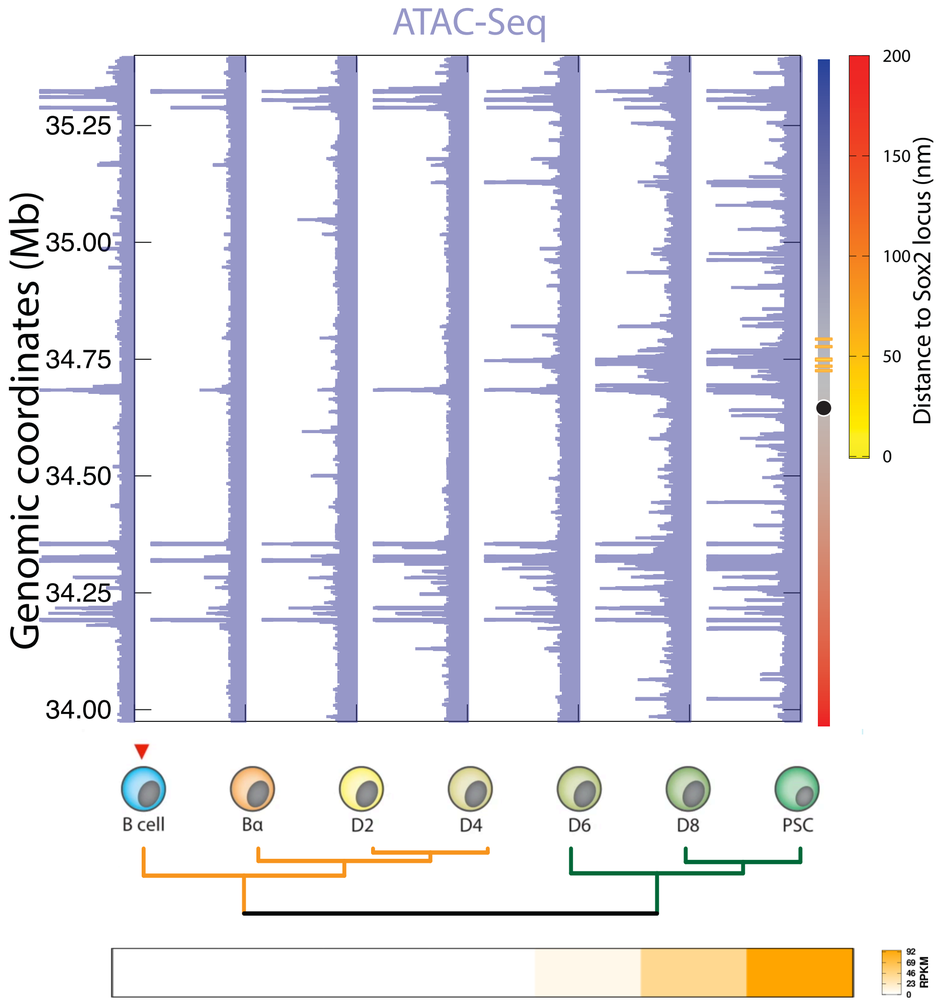
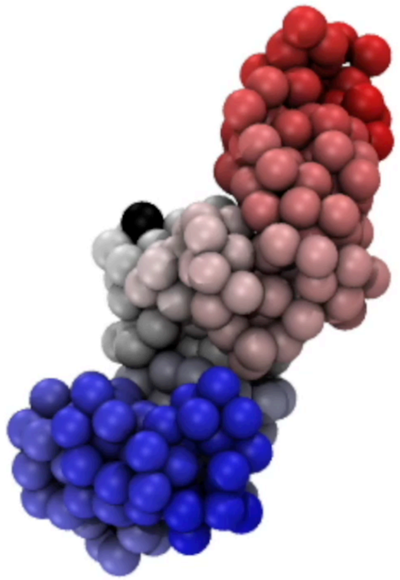
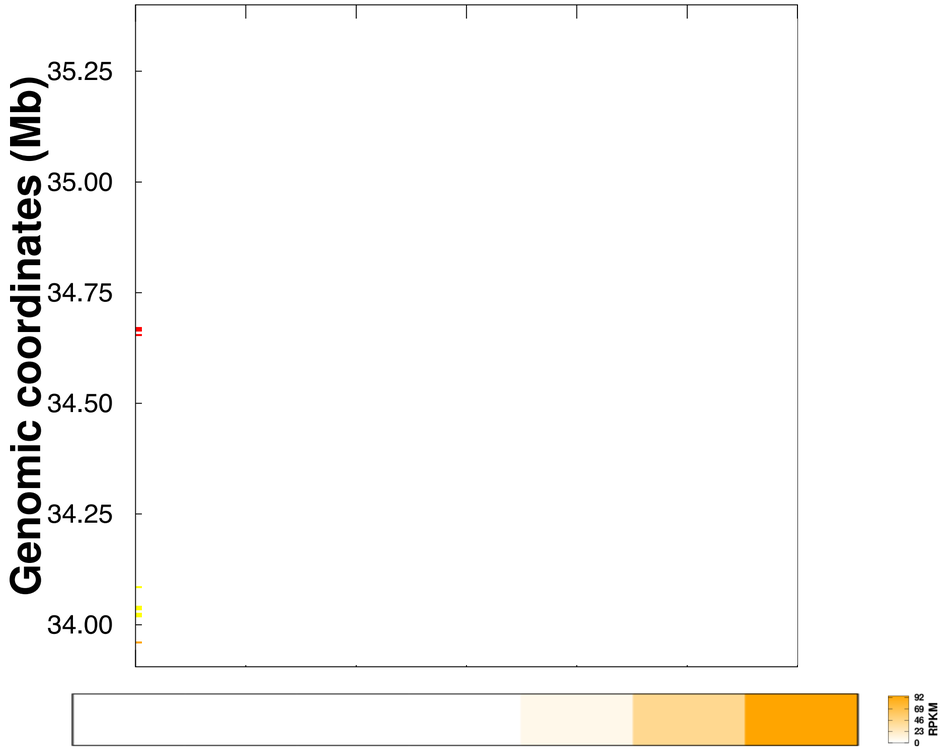




SOX2 locus structural changes from B to PSC

Chromatin Activity

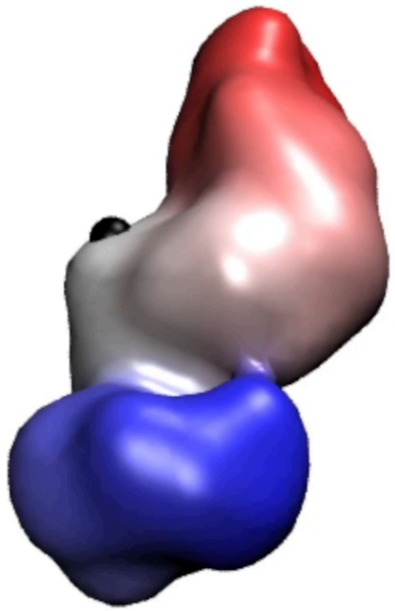


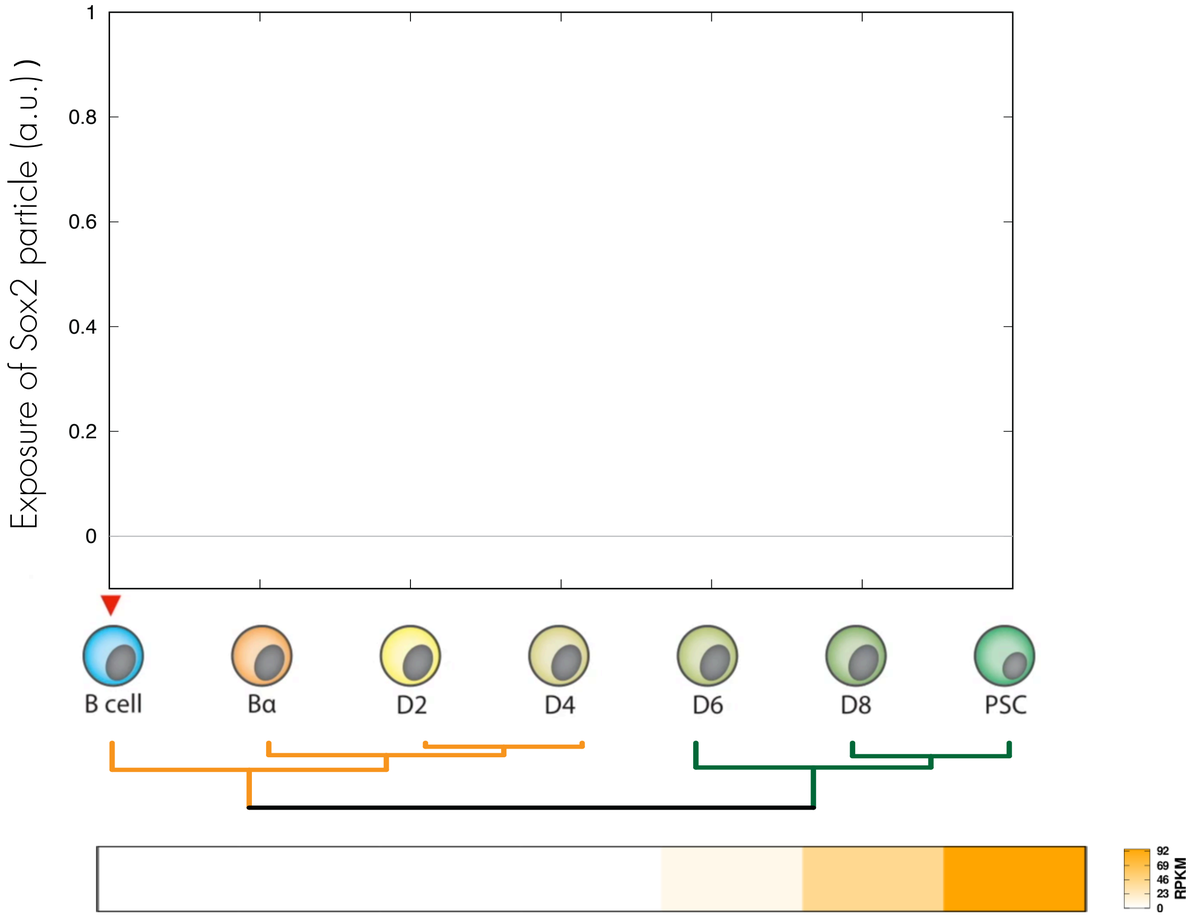


	B	Ba	D2	D4	D6	D8	PSC
A	9	6	7	13	13	22	48
AP	4	1	4	4	4	13	23
APD	3	1	1	1	4	10	15

SOX2 locus structural changes from B to PSC

Structural exposure





SOX2 locus structural changes from B to PSC

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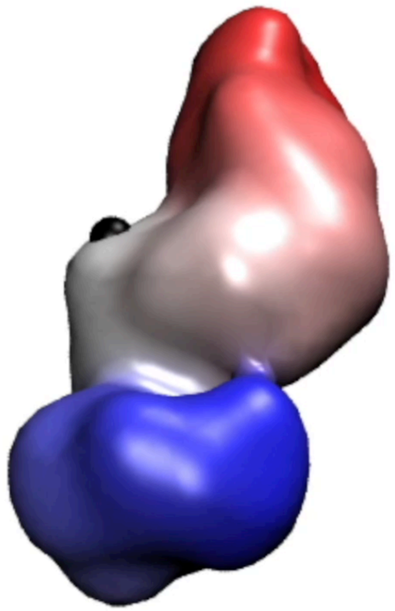
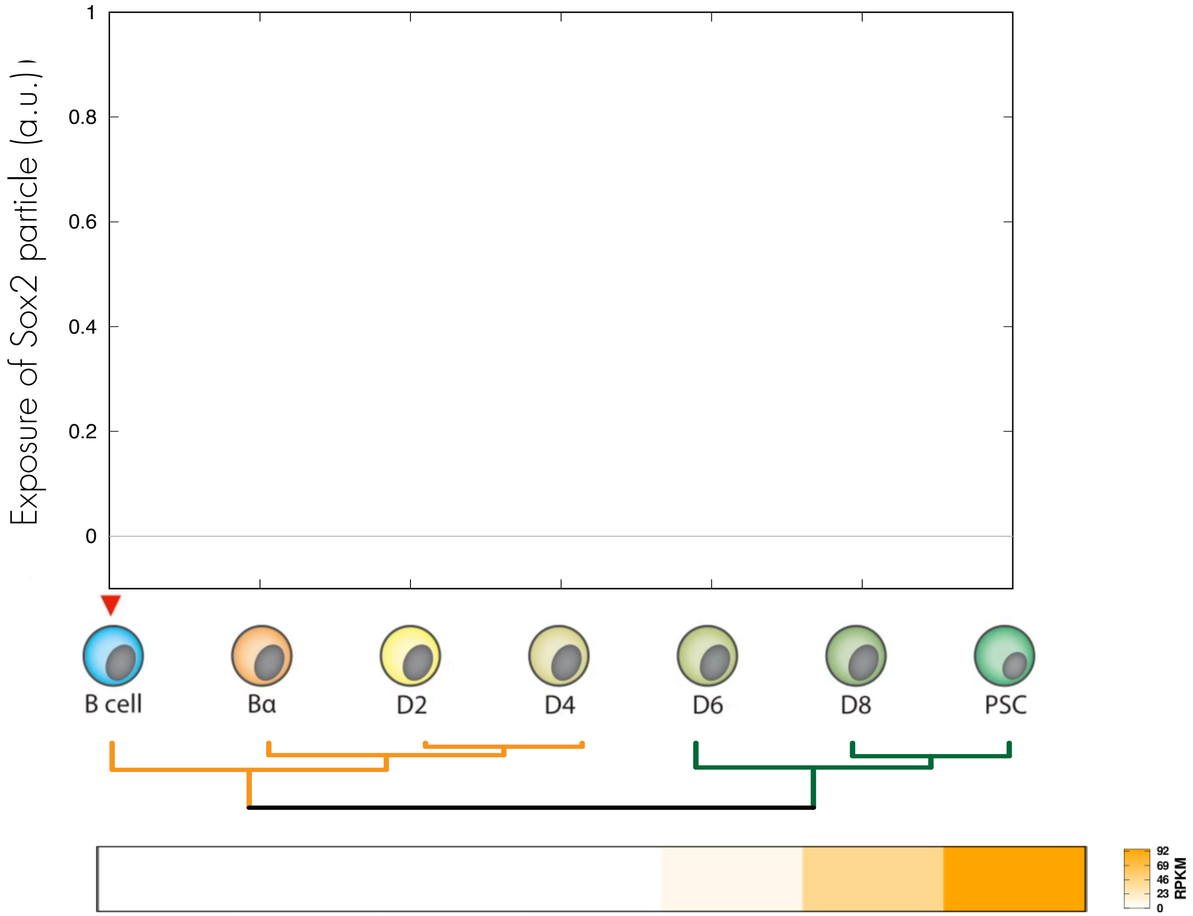
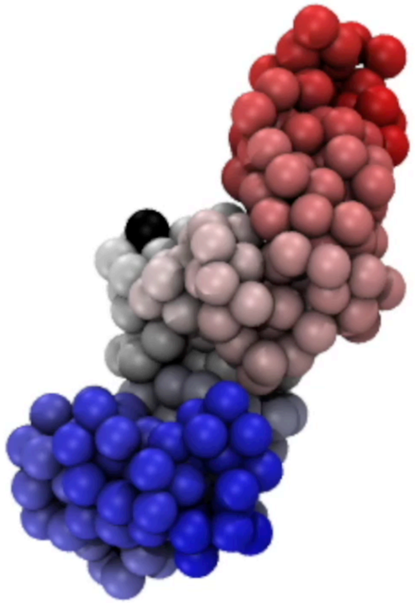
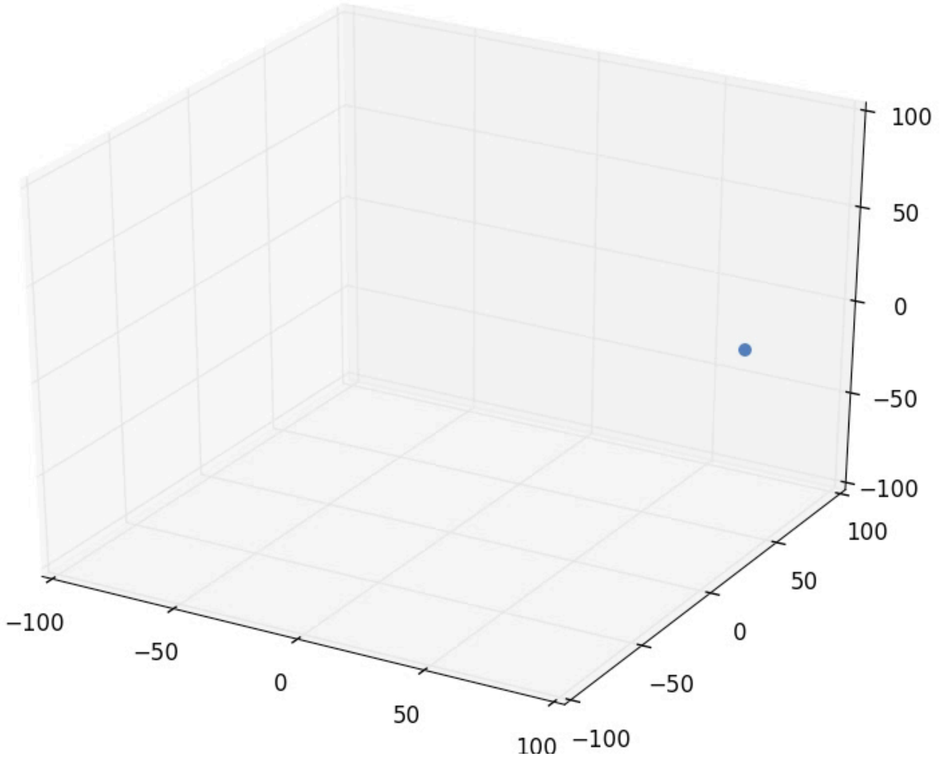


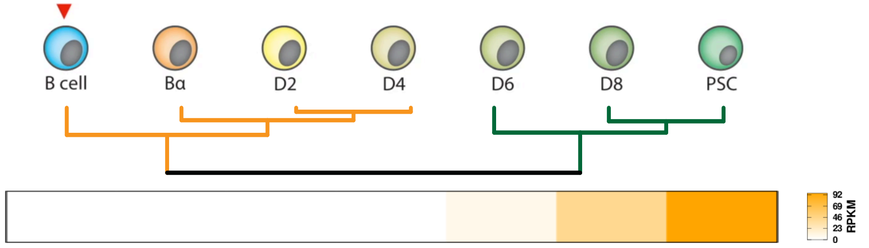


SOX2 locus dynamics changes from B to PSC

SOX2 displacement

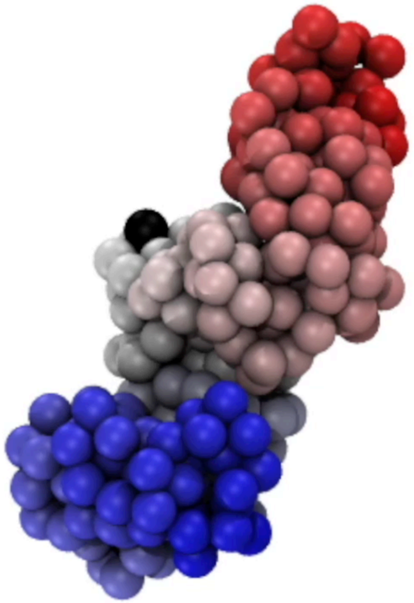


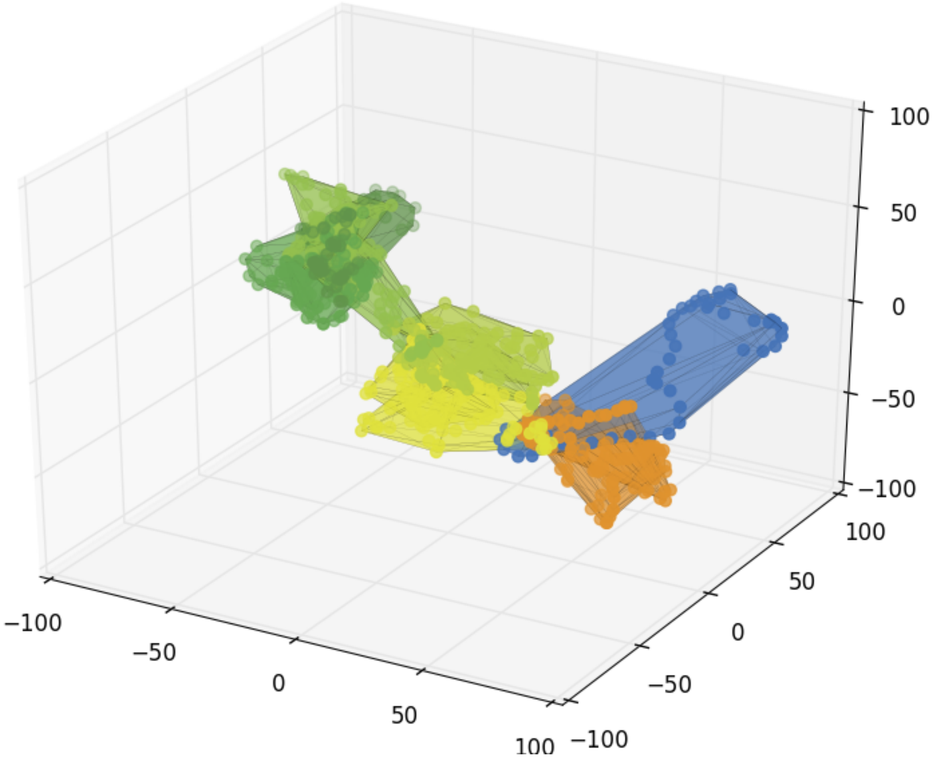


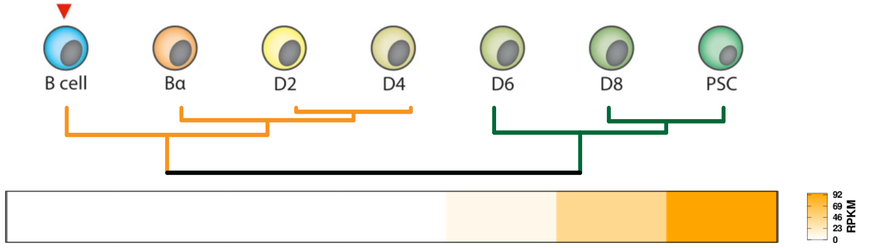


SOX2 locus dynamics changes from B to PSC

SOX2 displacement

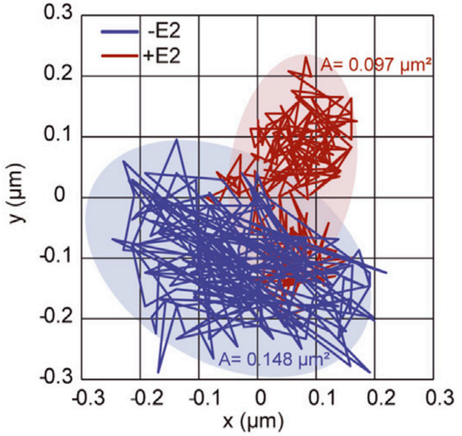






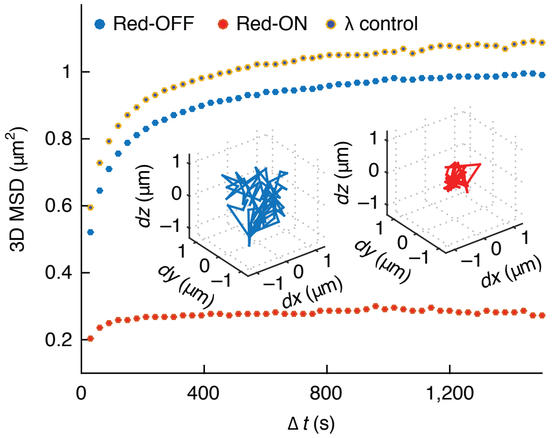
SOX2 locus dynamics changes from B to PSC

SOX2 displacement



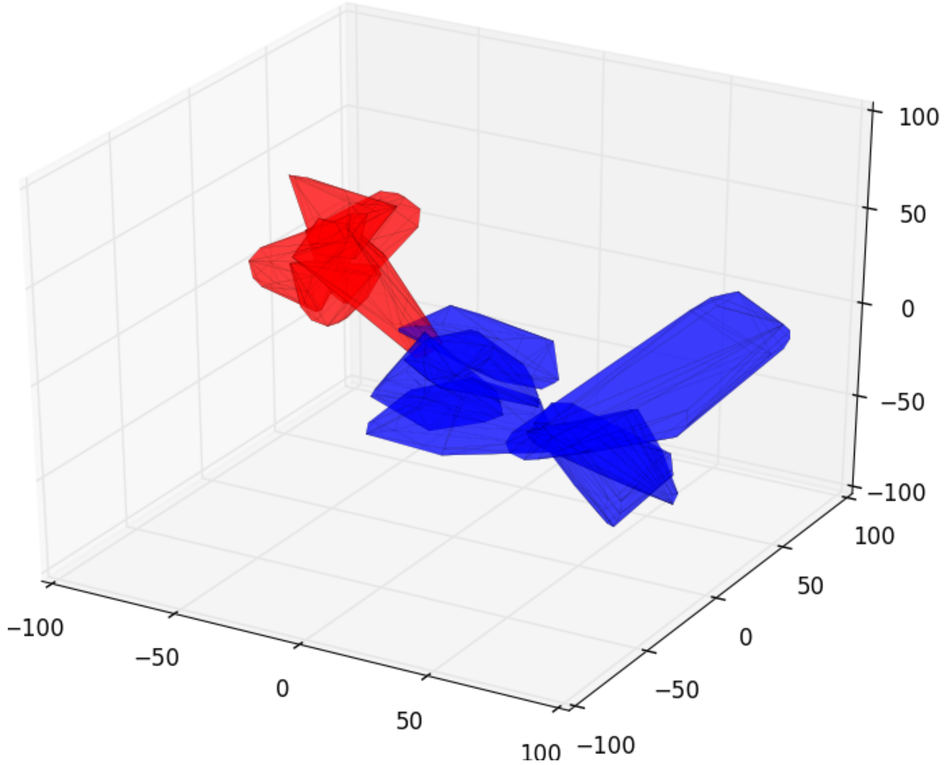
Two dimensional trajectories and area explored over 50s of the CCND1 locus recored before -E2 and after +E2 activation.

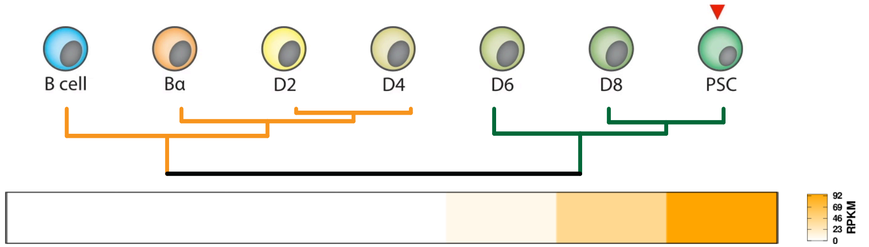
Germier ,T., et al, (2017) Biophys J.



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

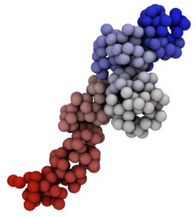
Chen ,T., et al, (2018) Nat. Genetics

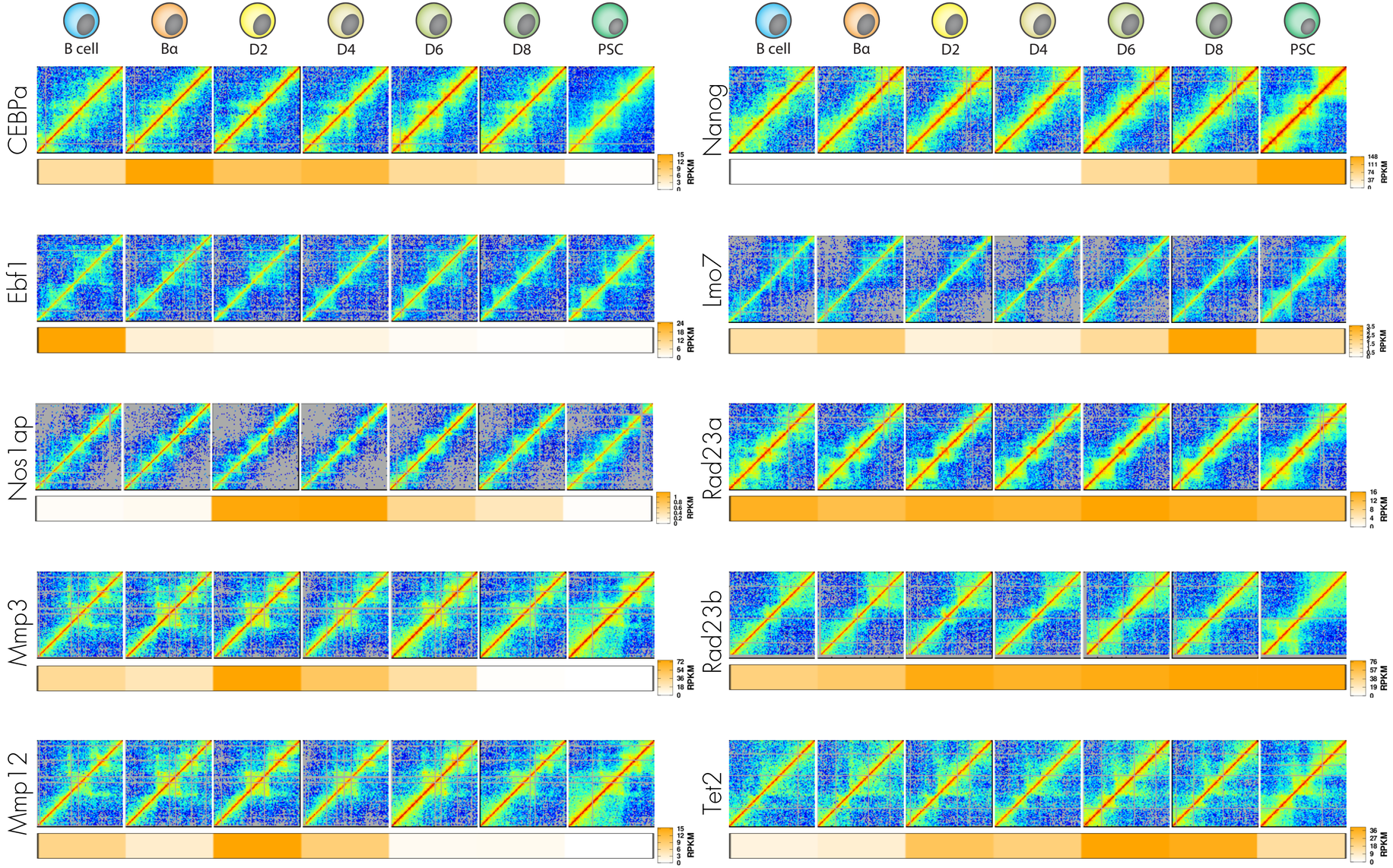




Structural changes from B to PSC

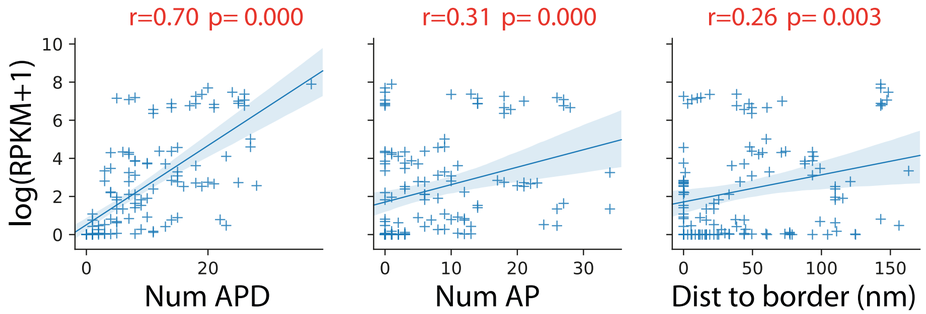
Other 21 loci

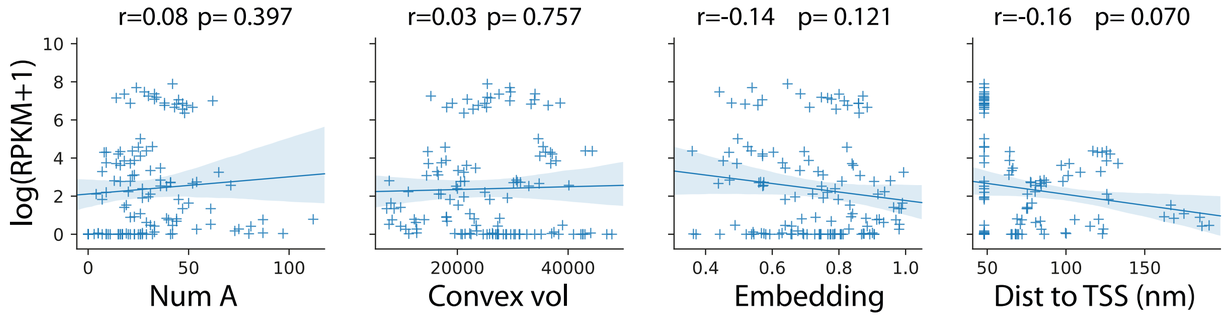


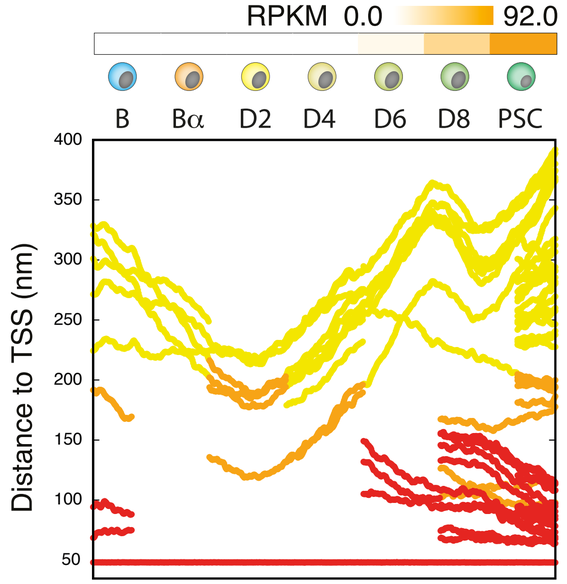


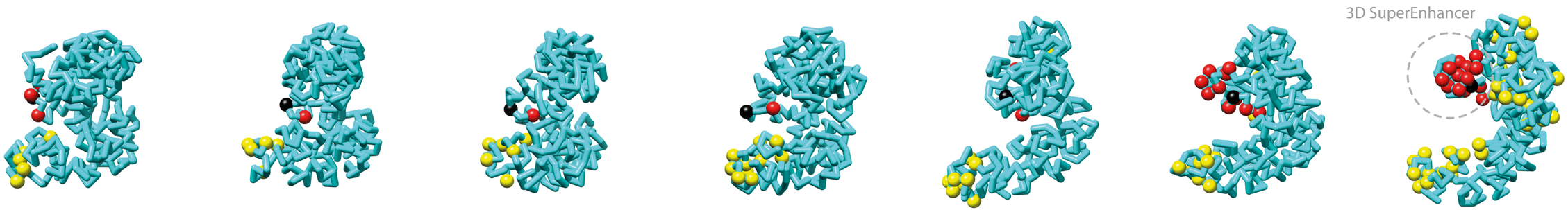
Dynamics of gene activation

Trends in 21 loci









Time and expression levels

Dynamics of gene activation

3D enhancer hubs