

Dynamics of gene activation

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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

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



Interplay: topology, gene expression & chromatin

Hi-C maps of reprogramming from B to PSC The SOX2 locus





Hi-C maps of reprogramming from B to PSC The SOX2 locus



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- How does these structural rearrangements interplay with the transcription activity?
 - What are the main drivers of structural transitions?



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

TADbit modeling of SOX2 from B cells Hi-C





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



Energy penalty

Transition	Stable	Vanishing	Raising	
Β -> Β α	18,612	6,984	7,290	
Β 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





















SOX2 locus structural changes from B to PSC Contacts





















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 Chromatin Activity







	В	Ba	D2	D4	D6	D8	PSC
А	9	6	7	13	13	22	48
AP	4]	4	4	4	13	23
APD	3]]]	4	10	15
	B cell	Βα	D2	D4	0 D6	D8	PSC















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 recored before -E2 and after +E2 activation.

Germier ,T., et al, (2017) Blophys 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





Dynamics of gene activation Trends in ~20 loci





Time and expression levels

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



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In collaboration with Ralph Stadhouders, Enrique Vidal, and Thomas Graf.

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