

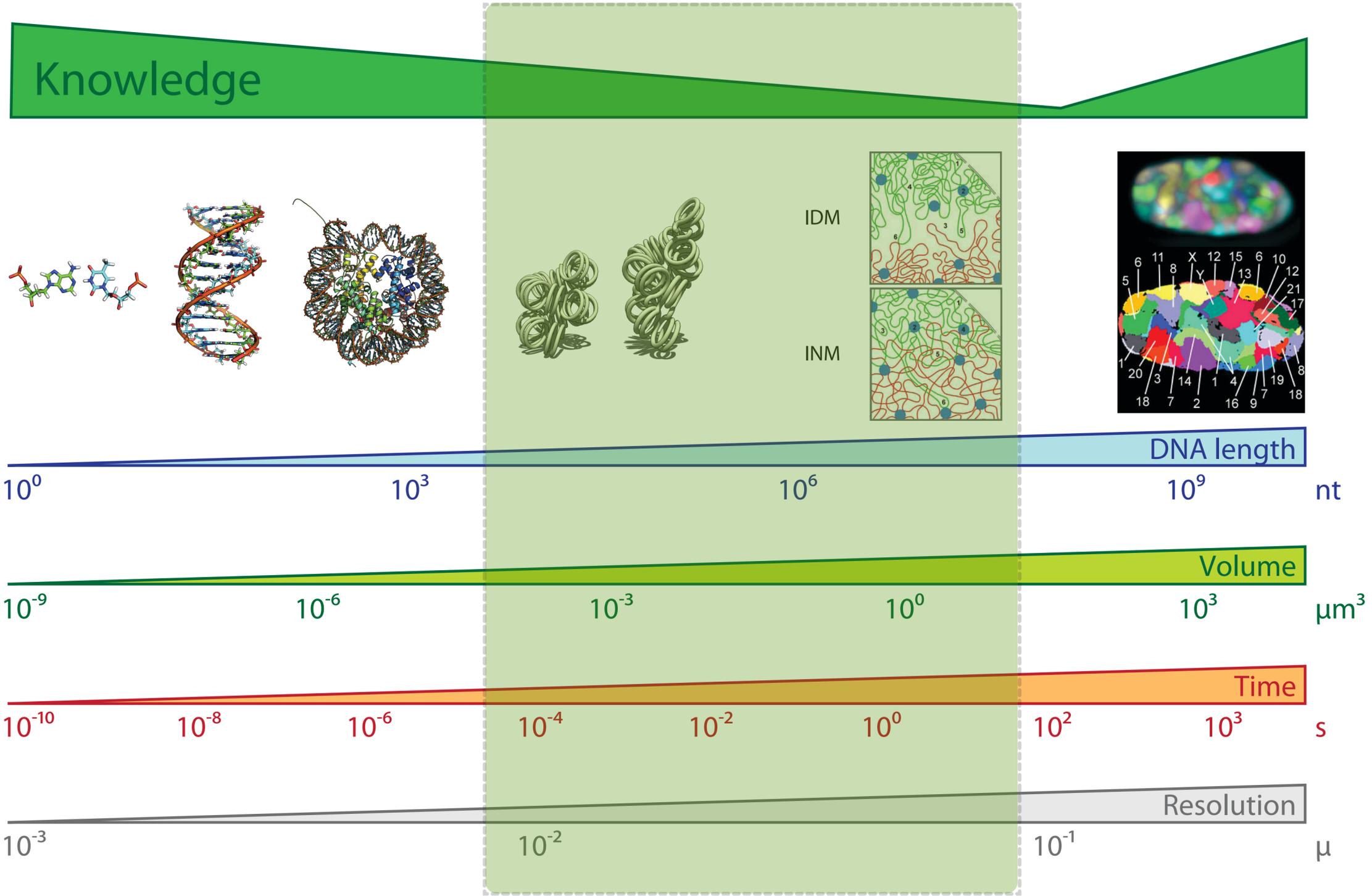
# Exploring the dimensions of the genome organization: 1D chromatin tracks and 2D interaction maps for generating 4D models

Marco Di Stefano

from Structural Genomics Group  
CNAG-CRG

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

# Resolution Gap



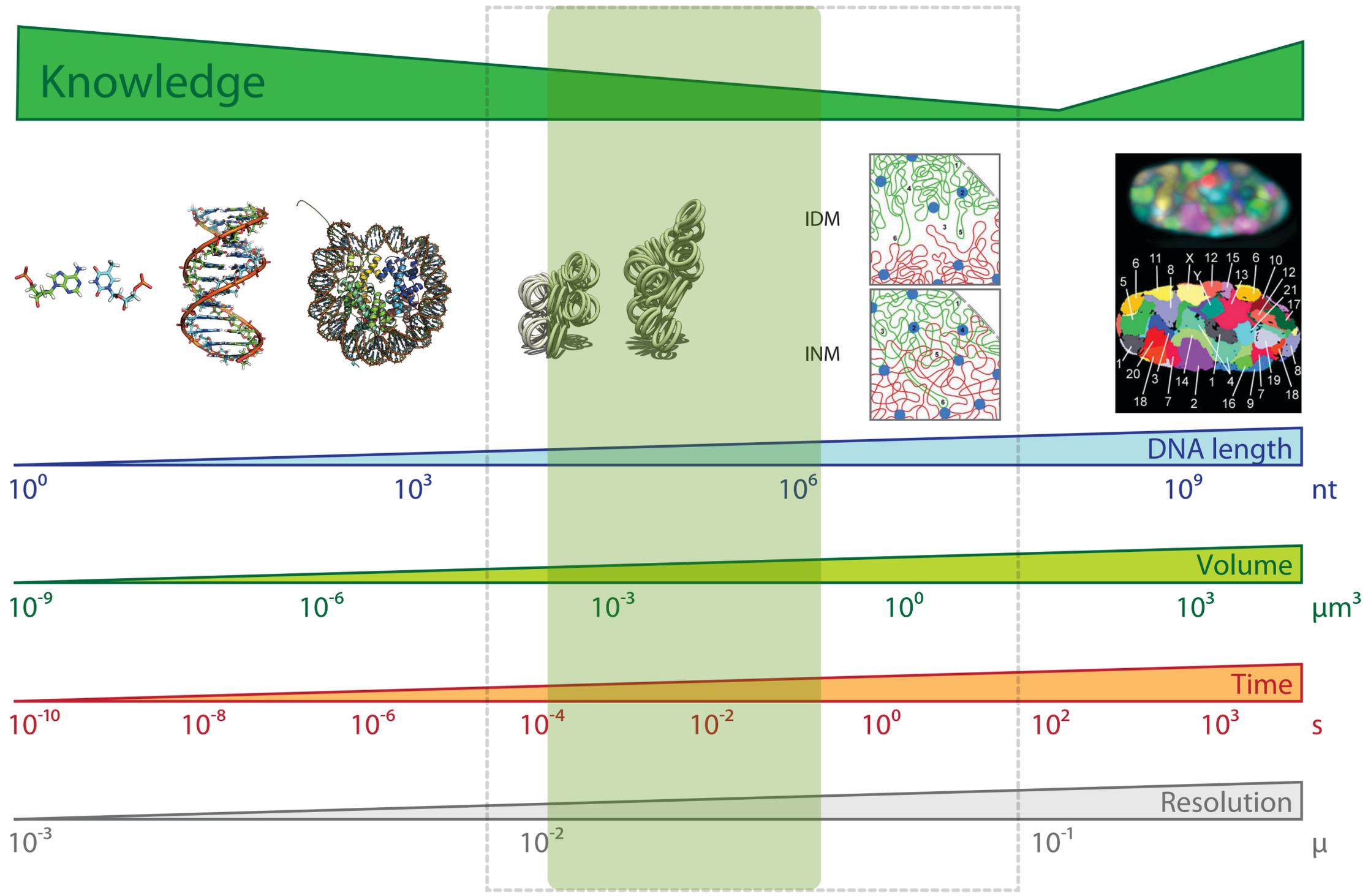
Adapted from: MA Marti-Renom & LA Mirny *PLoS Comput Biol* 2011.

# Resolution Gap



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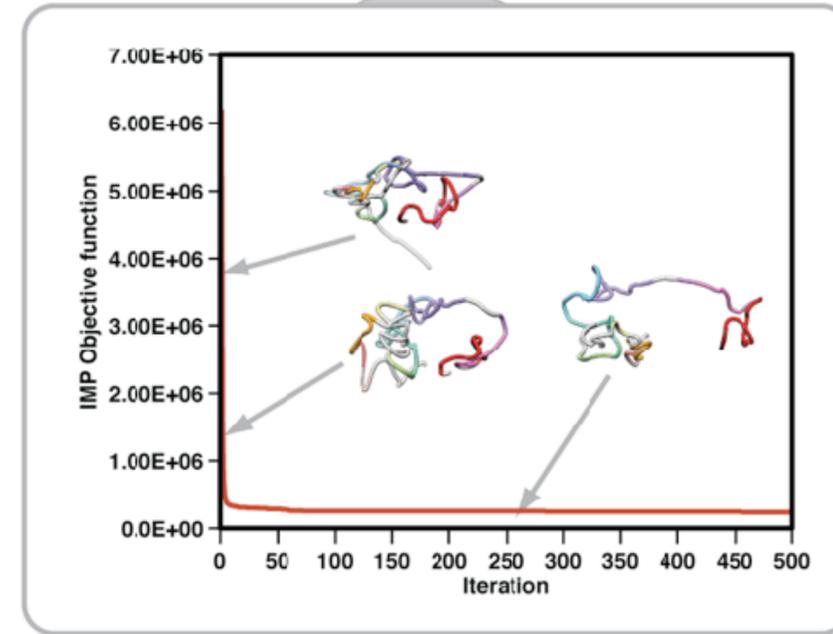
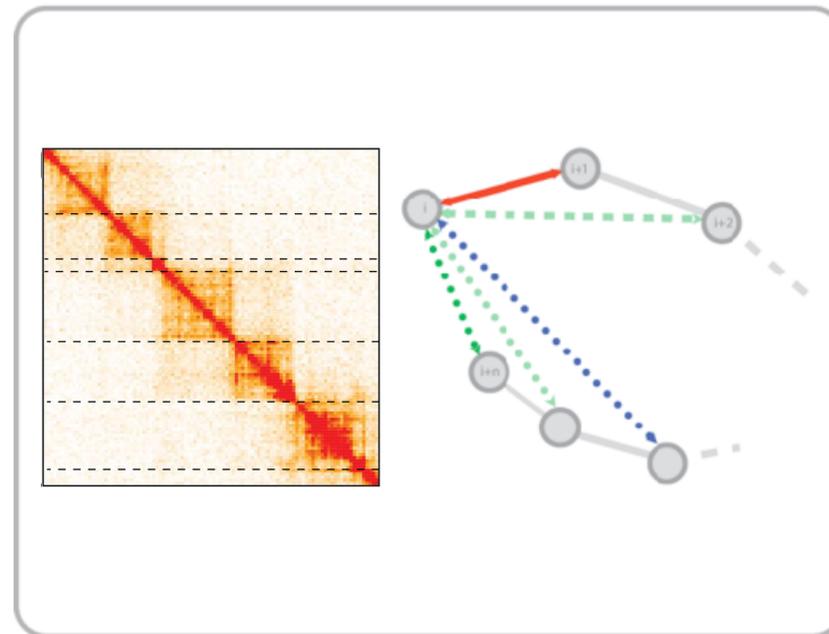
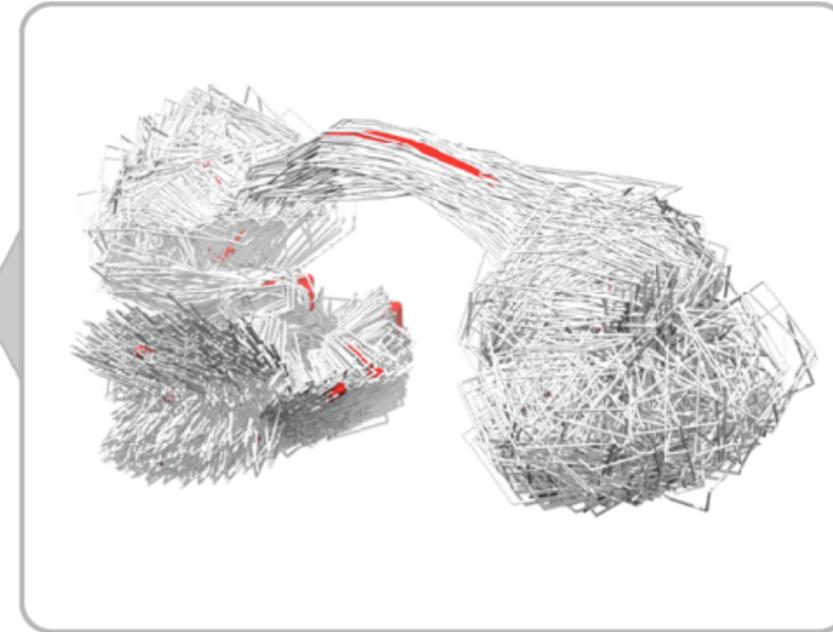
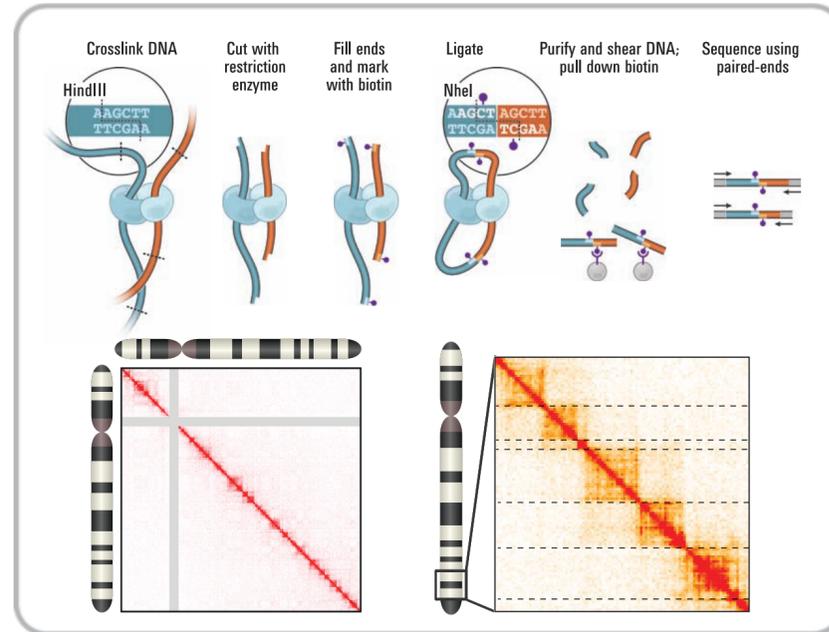
# Resolution Gap



Adapted from: MA Marti-Renom & LA Mirny *PLoS Comput Biol* 2011.

# TADbit: Hybrid Method

## Experiments

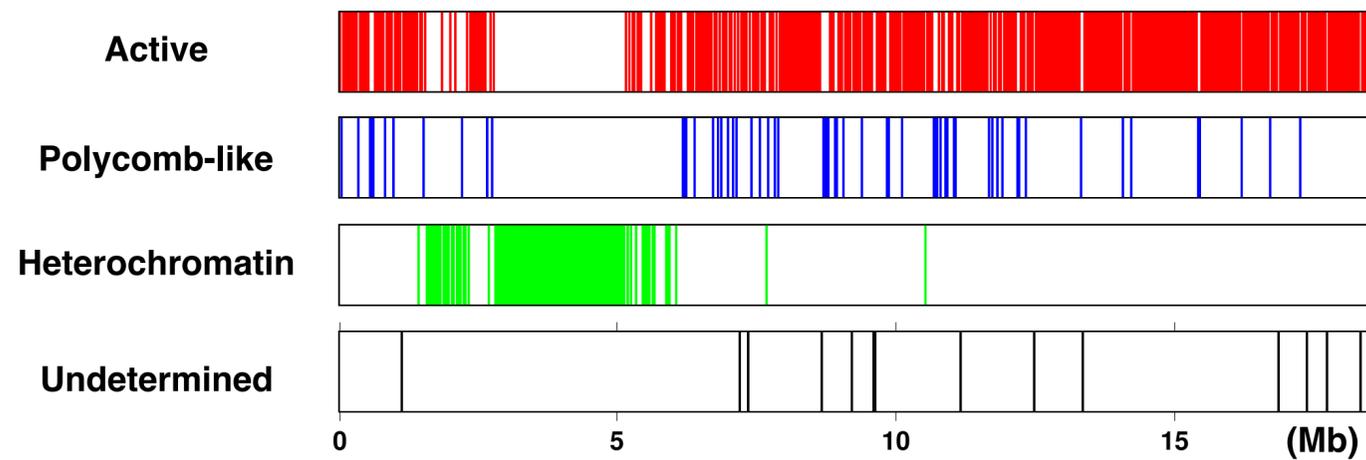


## Computation

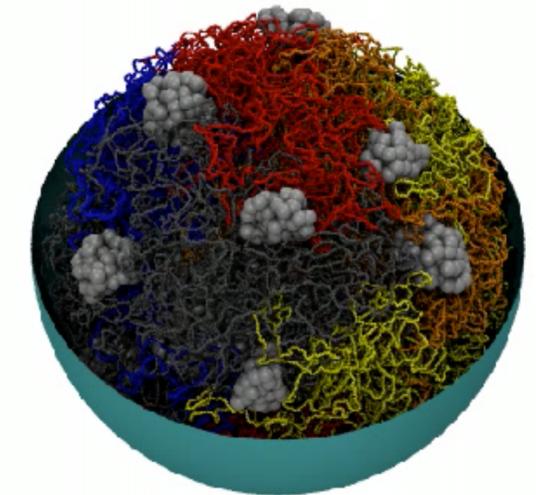
D Baù and MA Marti-Renom *Methods* 2012; F Serra, D Baù and MA Marti-Renom *PLoS Comp Biol* 2017; MDS and MA Marti-Renom, *Restraint-Based Modeling of Genomes and Genomic Domains* 2019.

# Novel developments in hybrid methods

## 1D epigenetic tracks



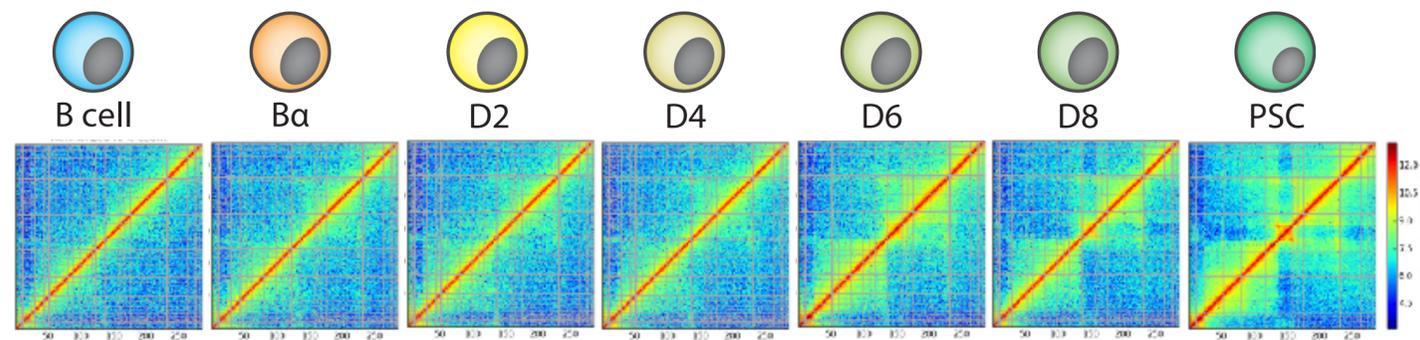
## 3D genome-wide models



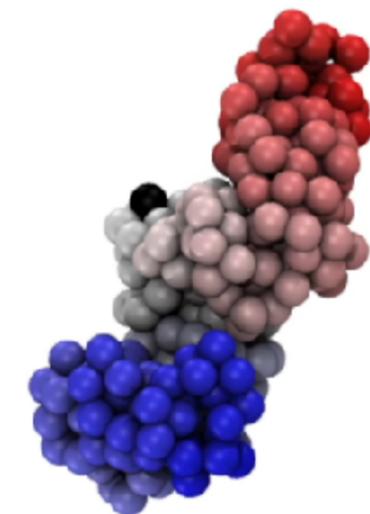
**TADphys**

**Polymer model**  
**Molecular dynamics**

## 2D Hi-C interaction maps over time



## 4D gene-specific models



**TADdyn**

# Dynamics of gene expression

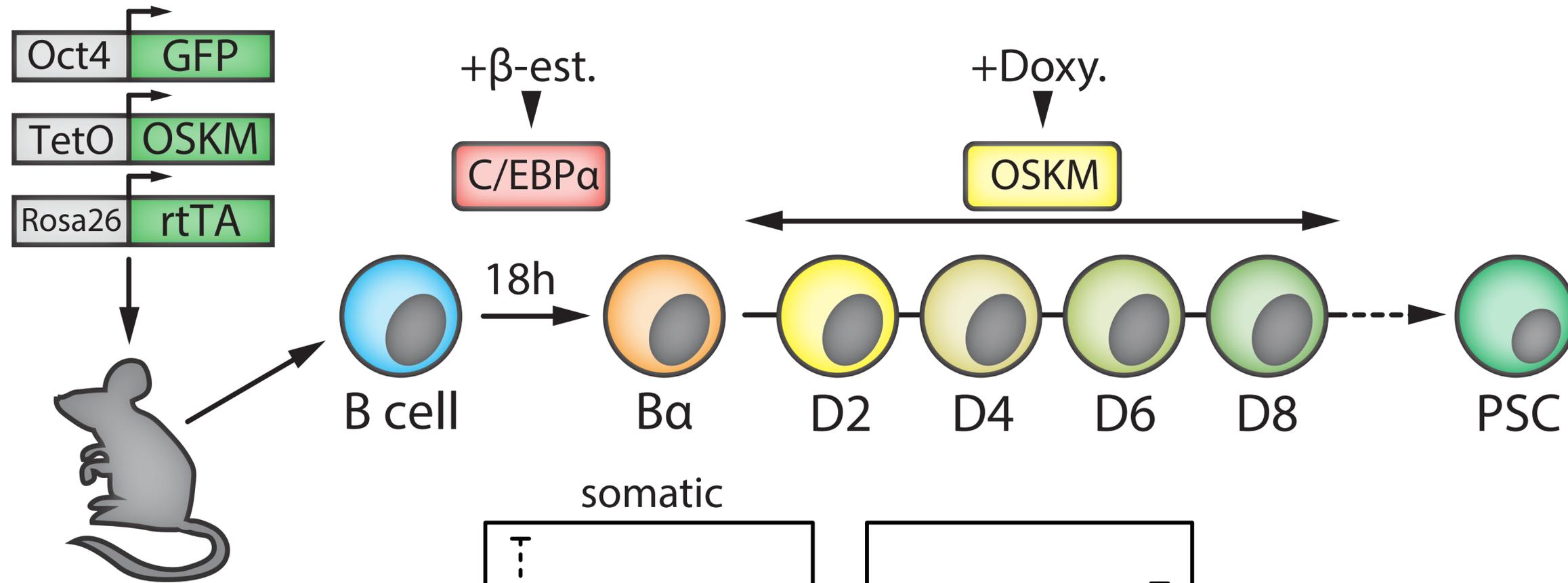


T Graf  
**CRG**

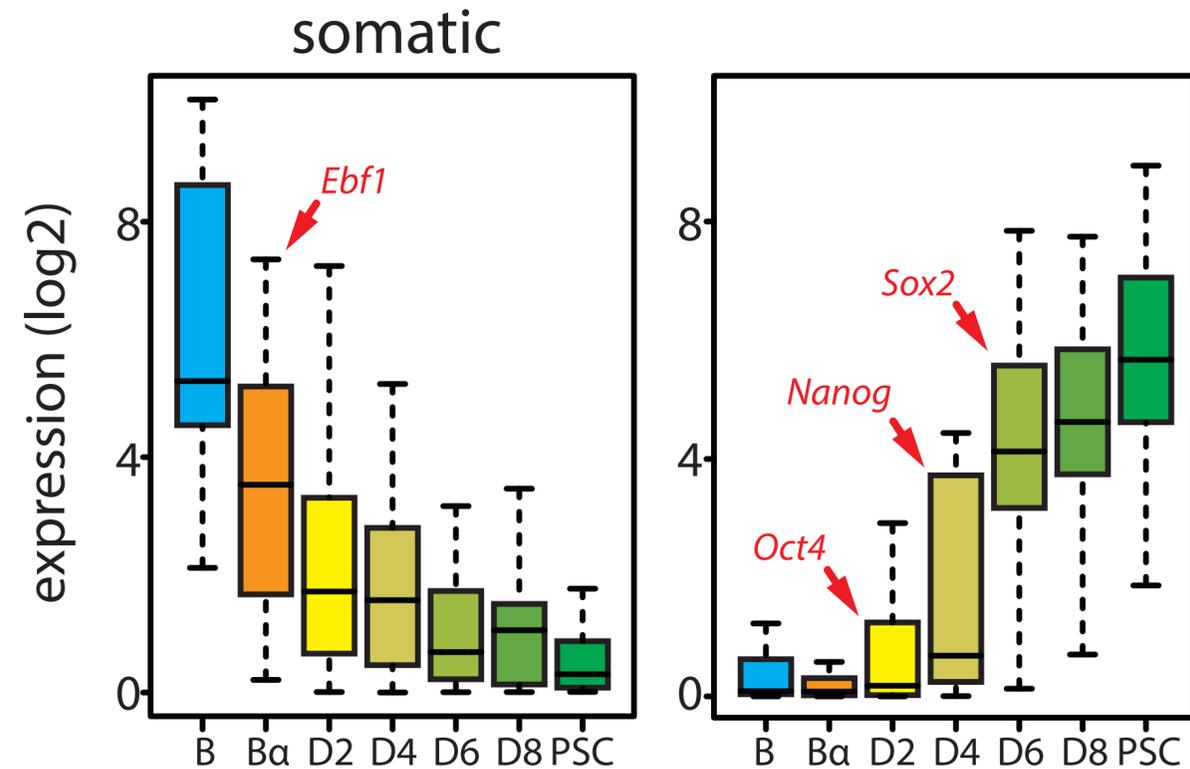


MA Marti-Renom  
**CRG**

# Reprogramming from B to PSC

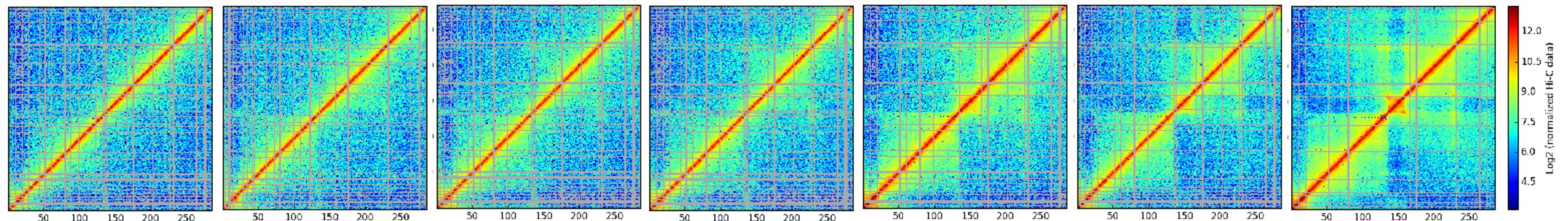
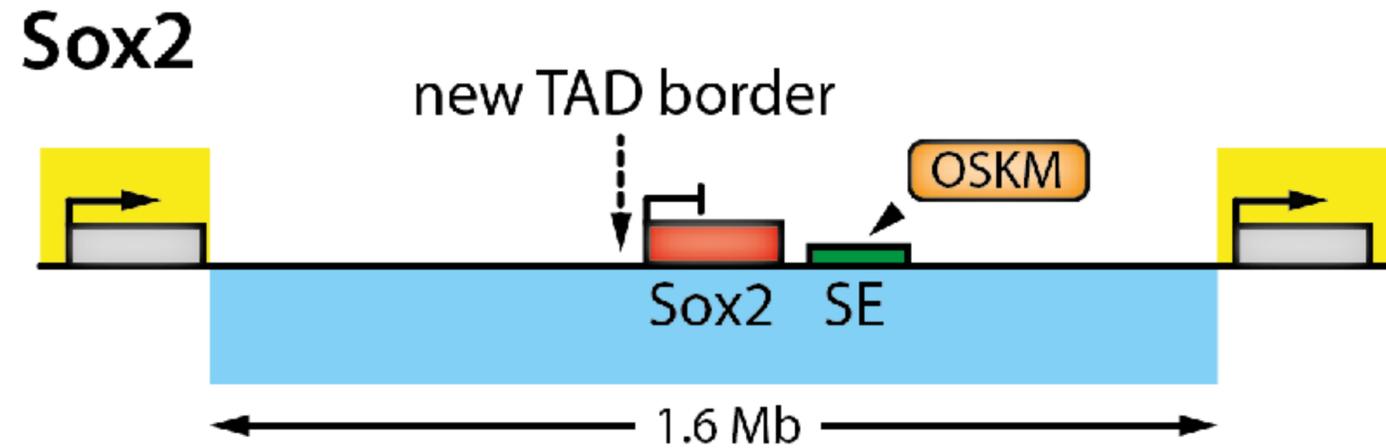
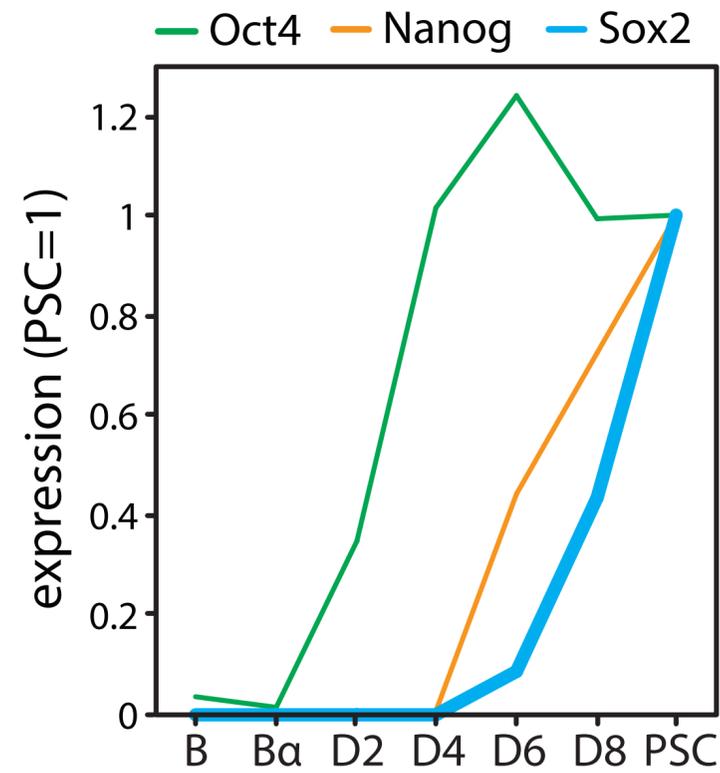


R Stadhouders  
CRG



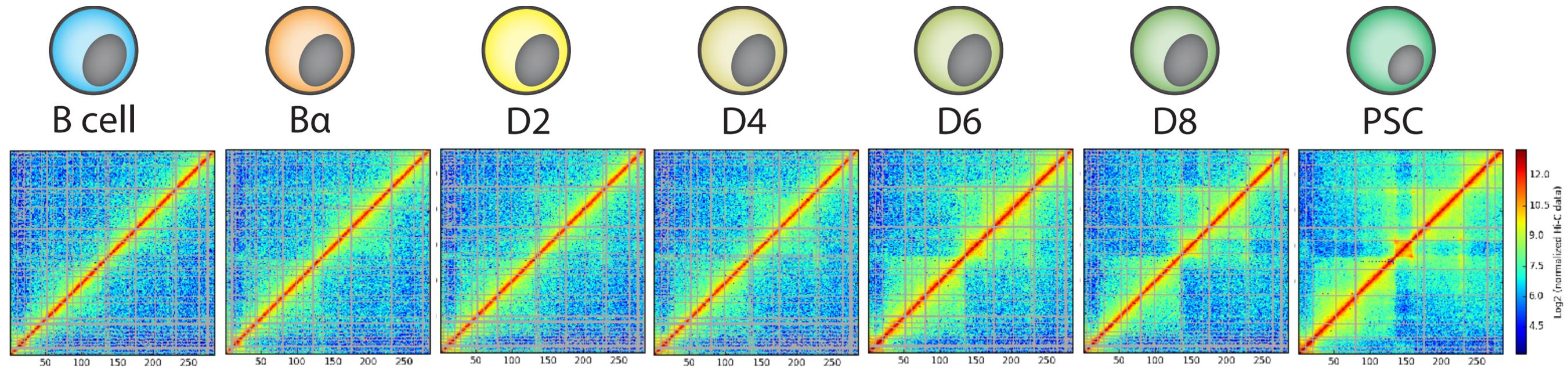
Mouse strain development: B Di Stefano...T Graf *Nat. Cell Biol.* 2016.  
Expression data: R Stadhouders, E Vidal...T Graf *Nature Genet.* 2018.

# Hi-C maps of reprogramming from B to PSC



*In situ* Hi-C data: R Stadhouders, E Vidal...T Graf Nat. Genet. 2018.

# Hi-C maps of reprogramming from B to PSC

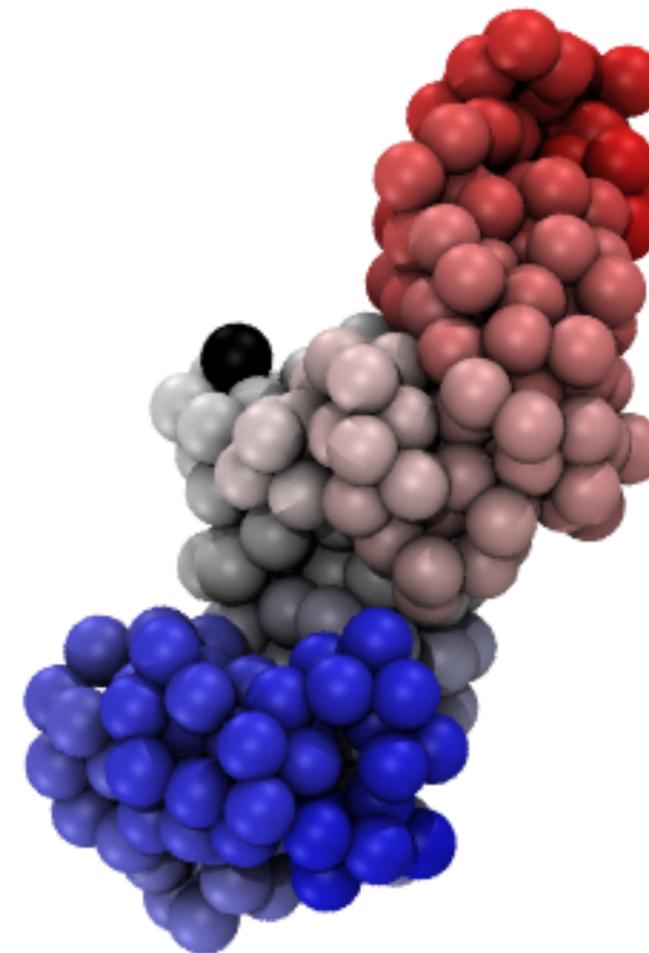
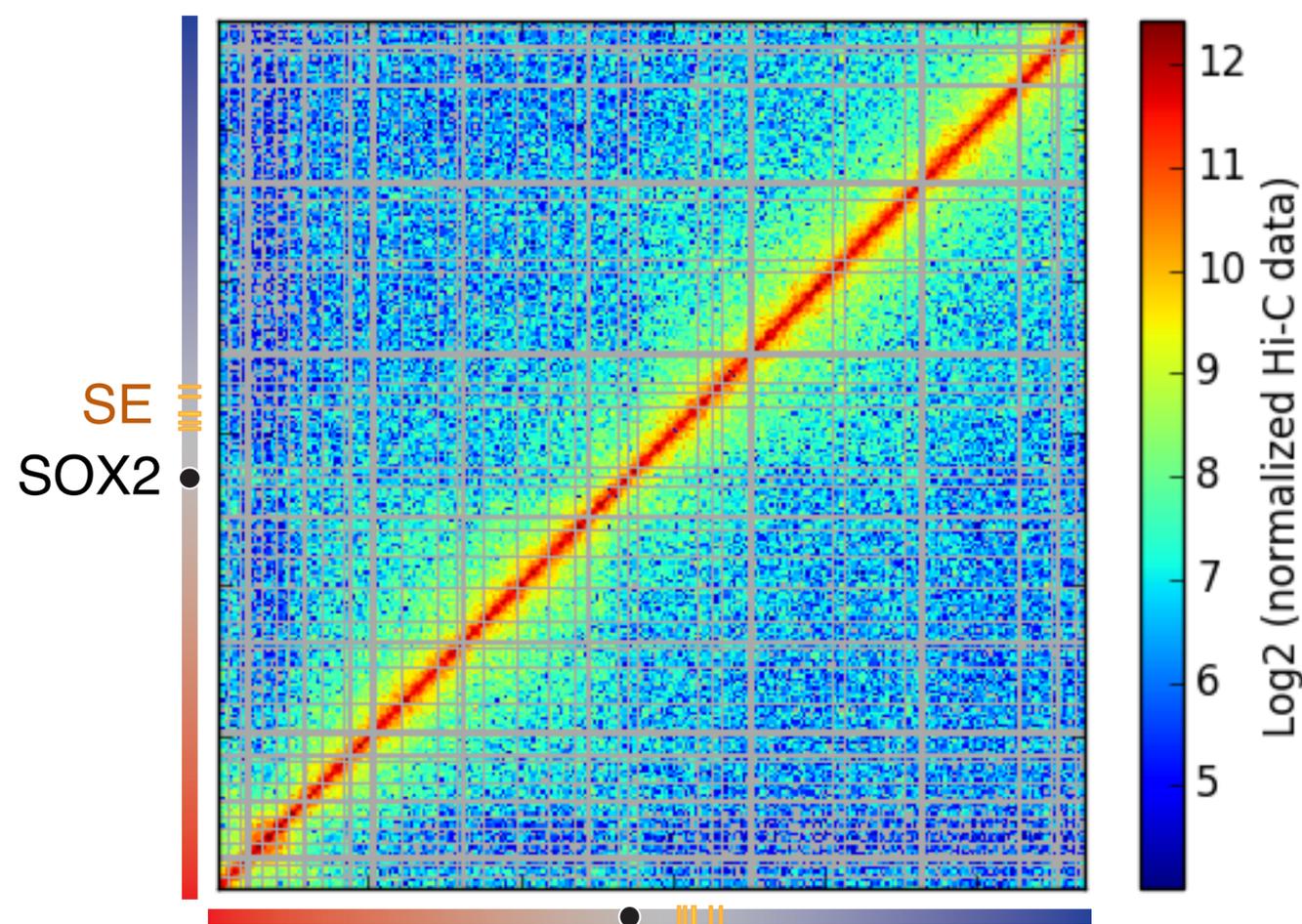


How do these structural rearrangements interplay with the transcription activity?

What are the main drivers of structural transitions?

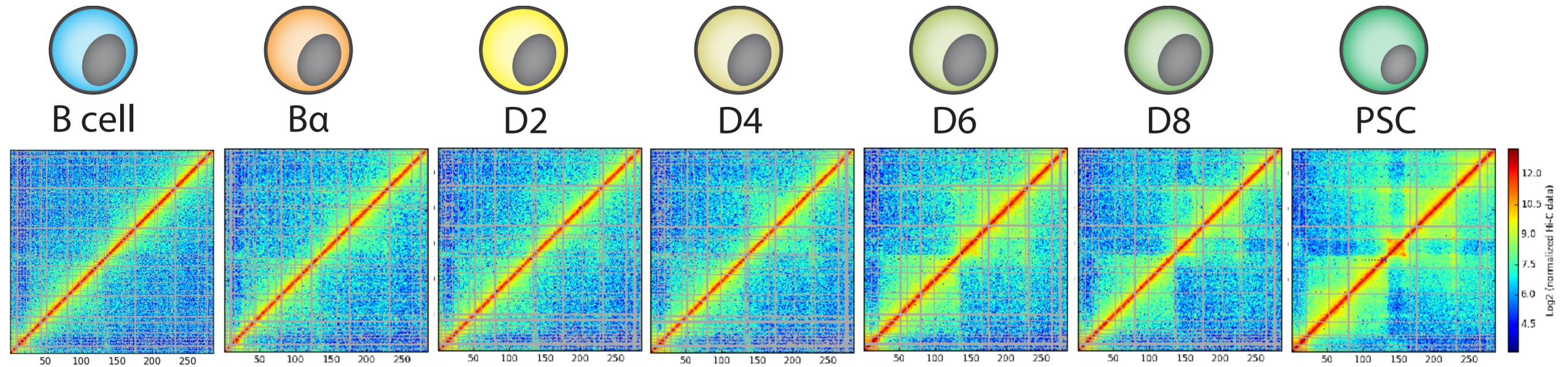
We use Hi-C data and steered molecular dynamics simulations of coarse-grained chromatin models to study the structural transitions

# TADdyn modelling: initial conformations



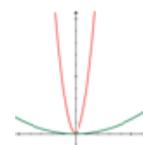
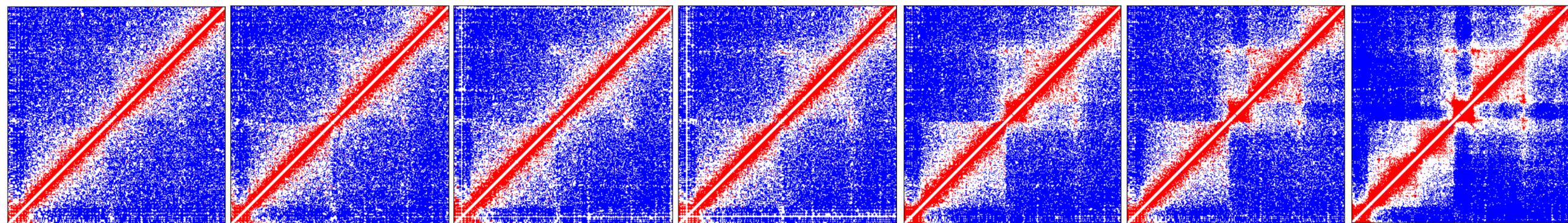
Optimal TADbit parameters  
lowfreq=0, upfreq=1, maxdist=200nm, dcutoff=125nm,  
particle size=50nm (5kb)

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

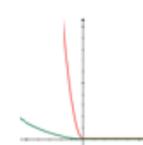


Optimal TADbit parameters

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

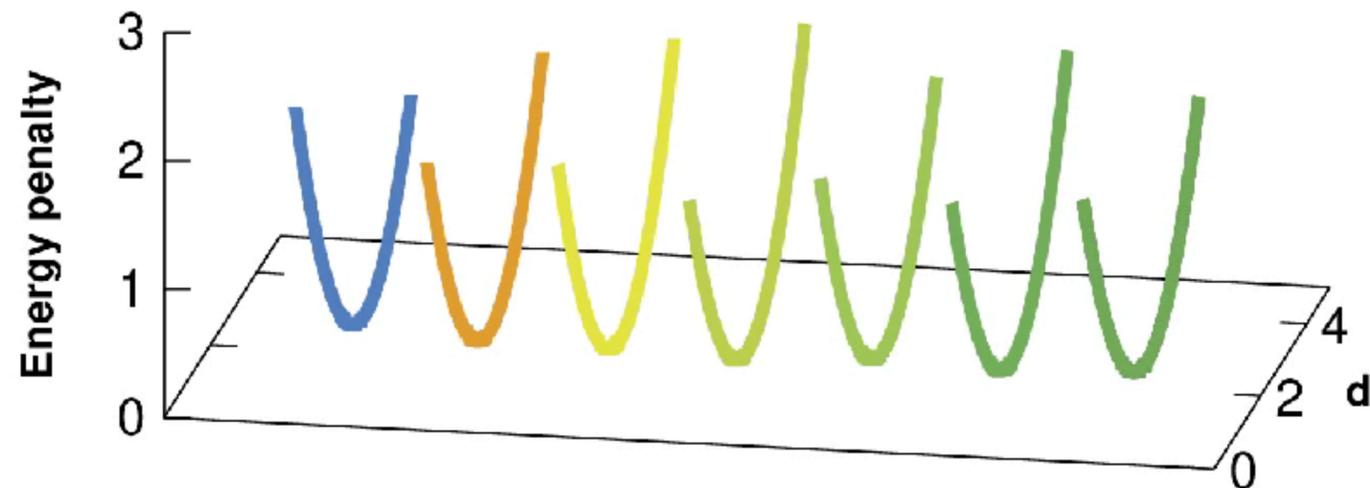
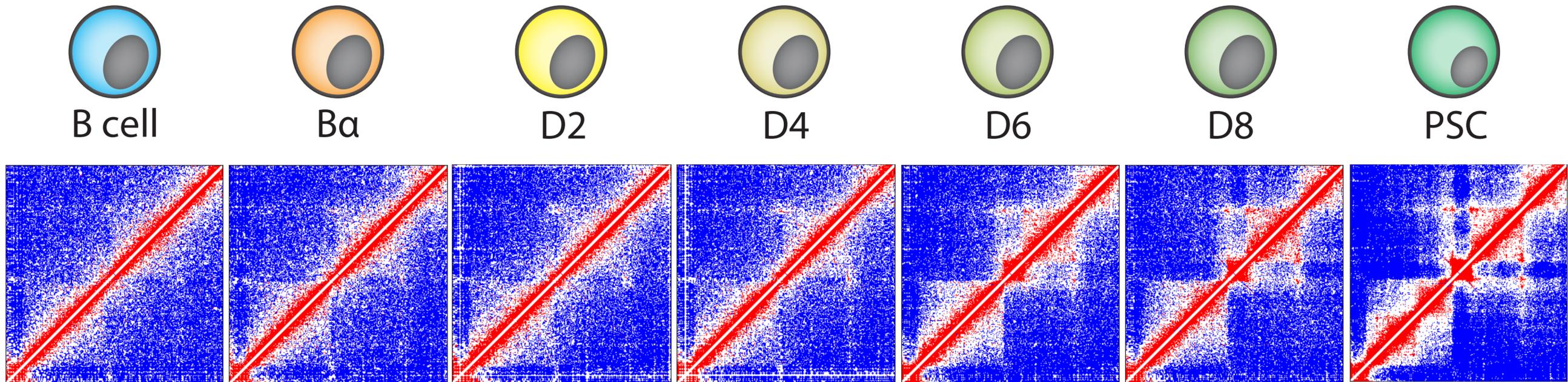


Harmonic

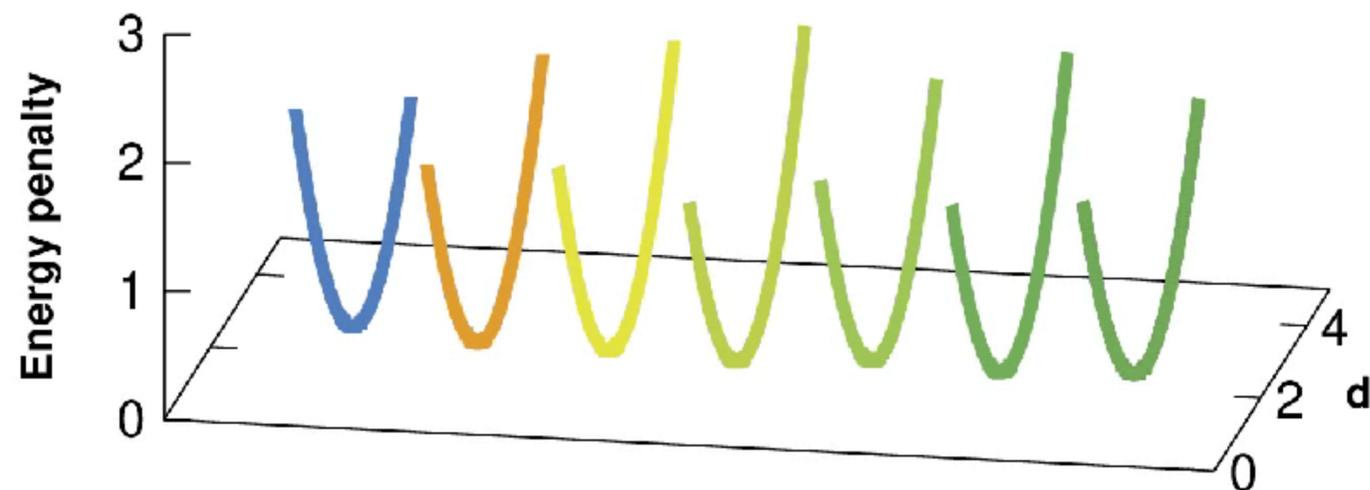
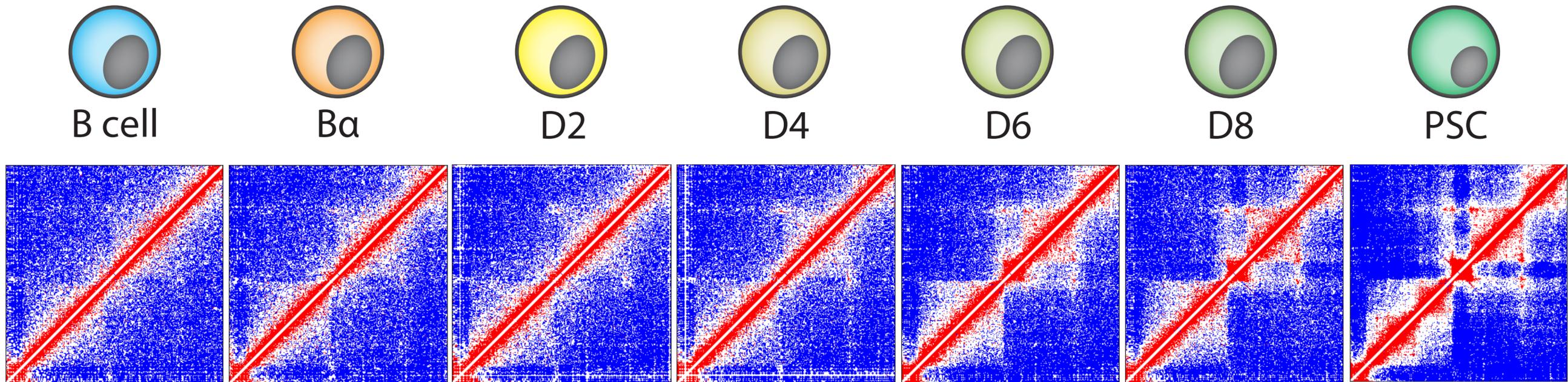


HarmonicLowerBound

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



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

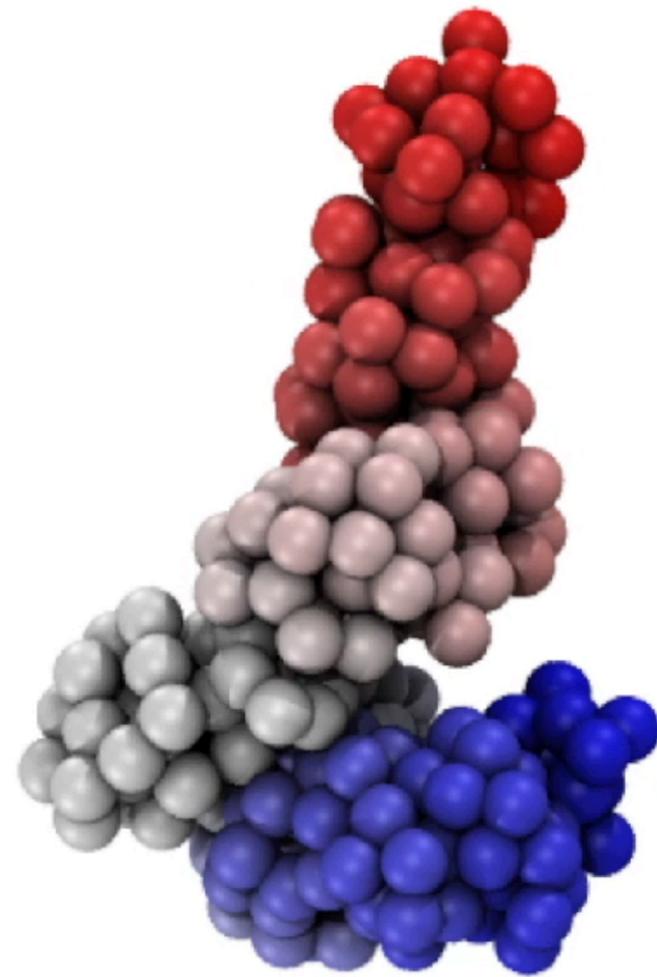


Number of *Harmonics*

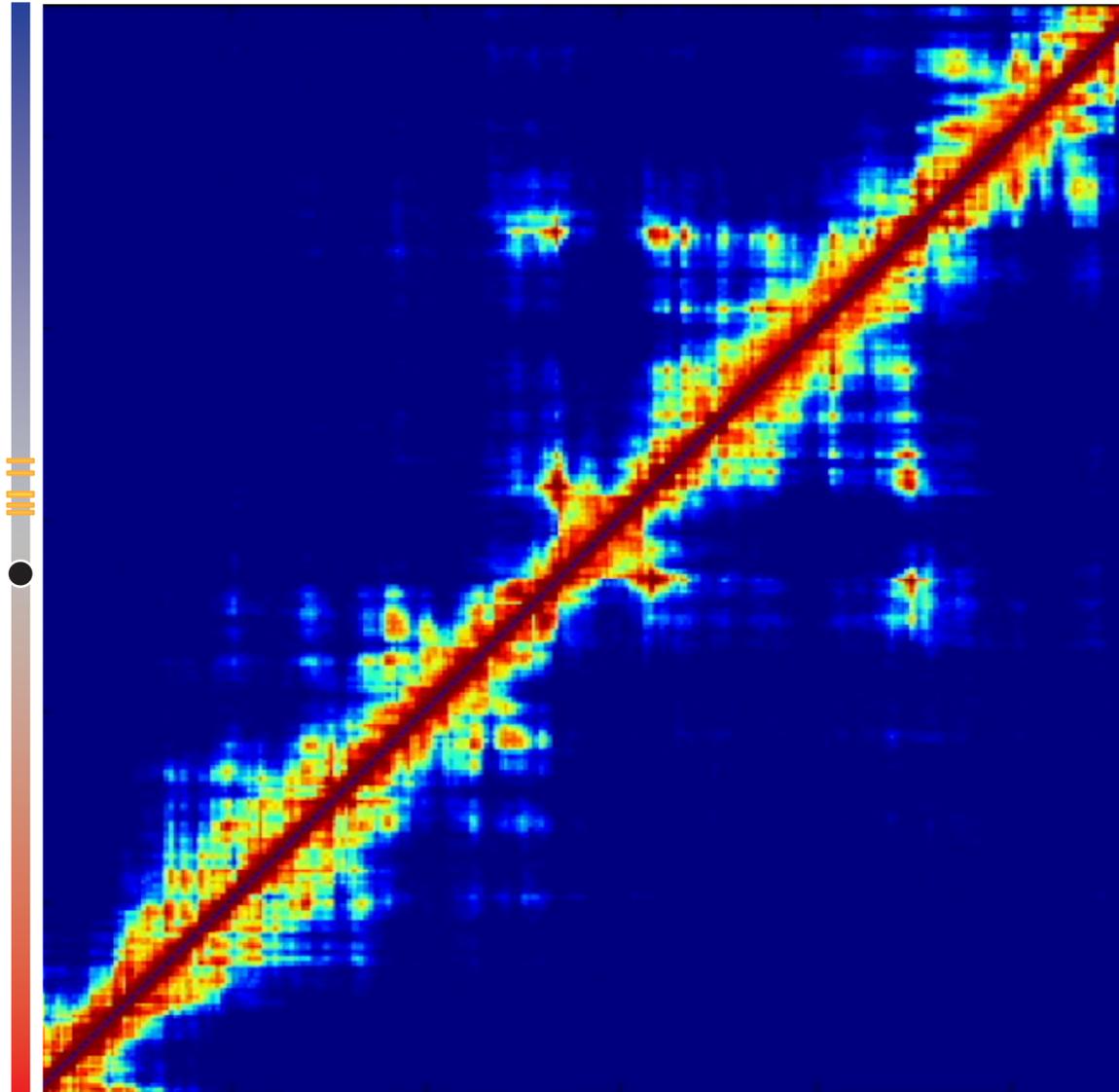
Transition	Stable	Vanishing	Raising
<b>B -&gt; B<math>\alpha</math></b>	3.271	1.575	1.730
<b>B<math>\alpha</math> -&gt; D2</b>	3.386	1.615	1.597
<b>D2 -&gt; D4</b>	3.473	1.510	1.488
<b>D4 -&gt; D6</b>	3.704	1.257	1.766
<b>D6 -&gt; D8</b>	3.890	1.580	1.432
<b>D8 -&gt; ES</b>	3.989	1.333	1.592

# SOX2 locus structural changes from B to PSC

Contacts



SE  
SOX2



B cell



Ba



D2



D4



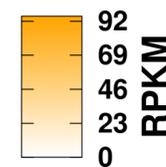
D6



D8

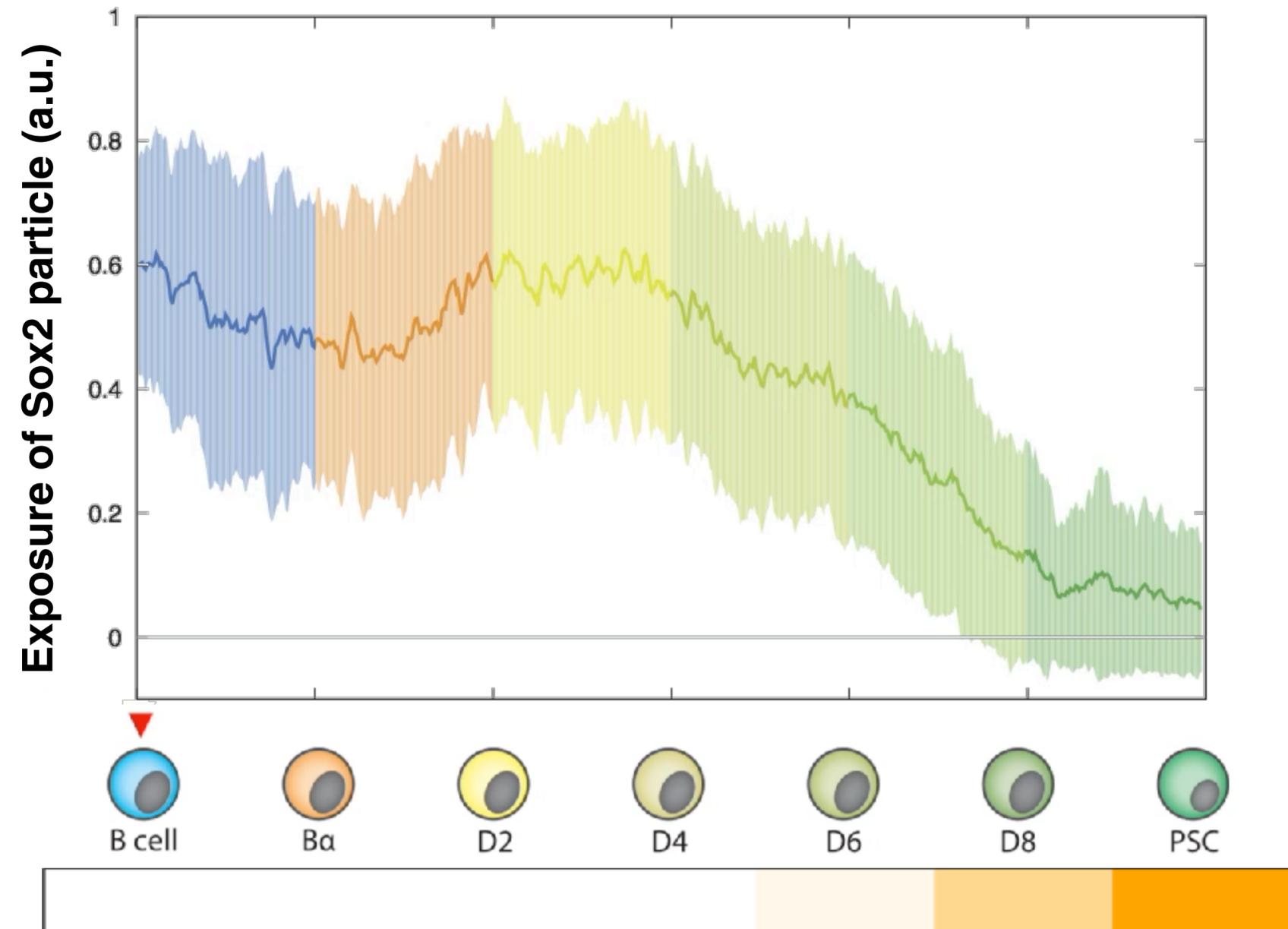
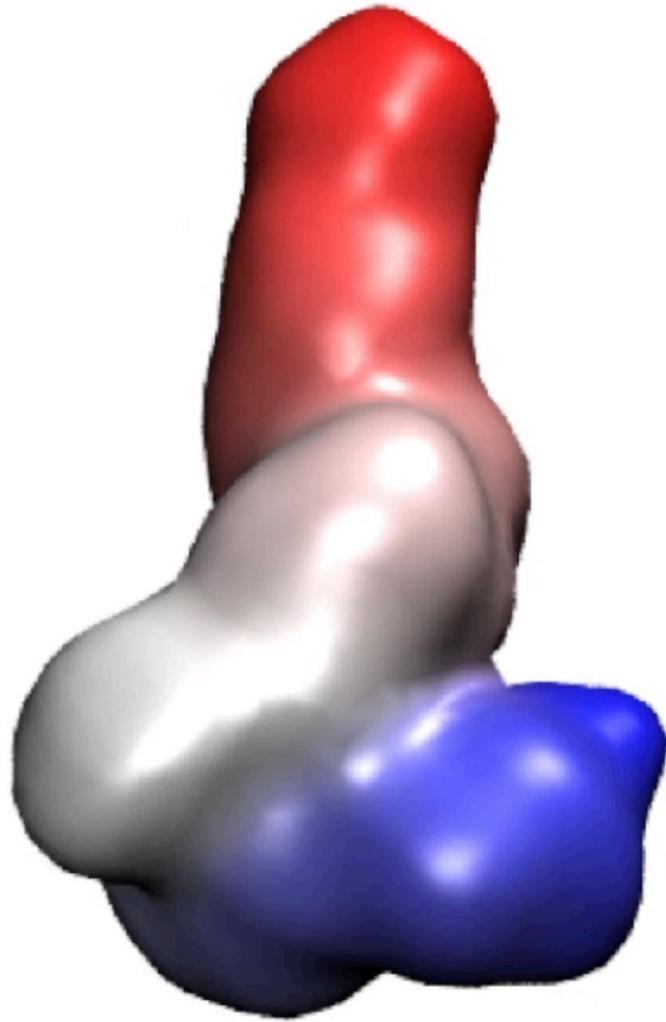


PSC



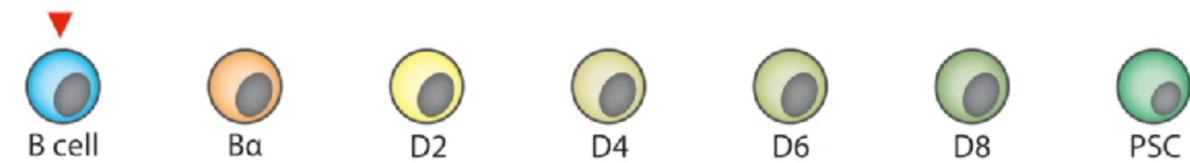
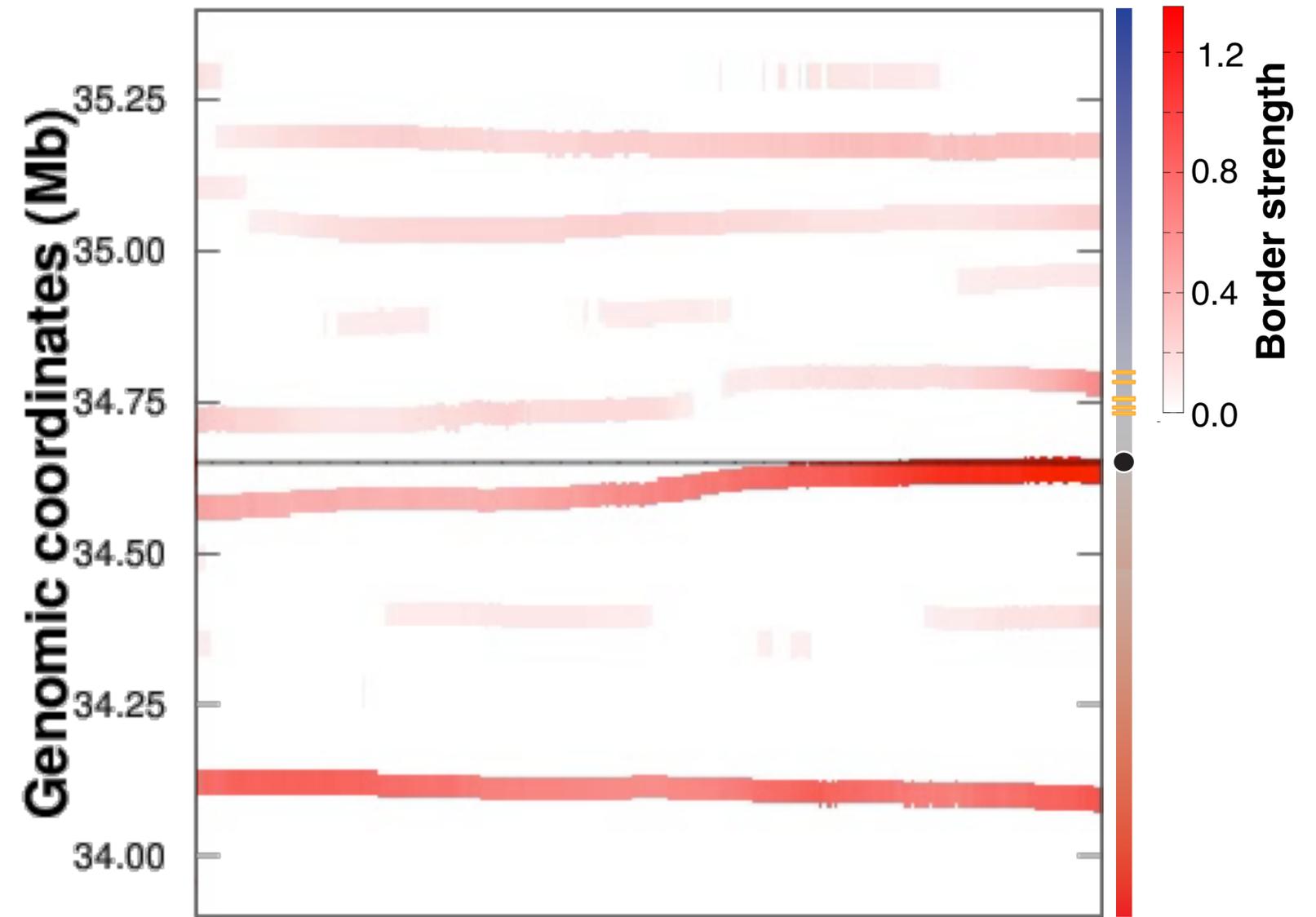
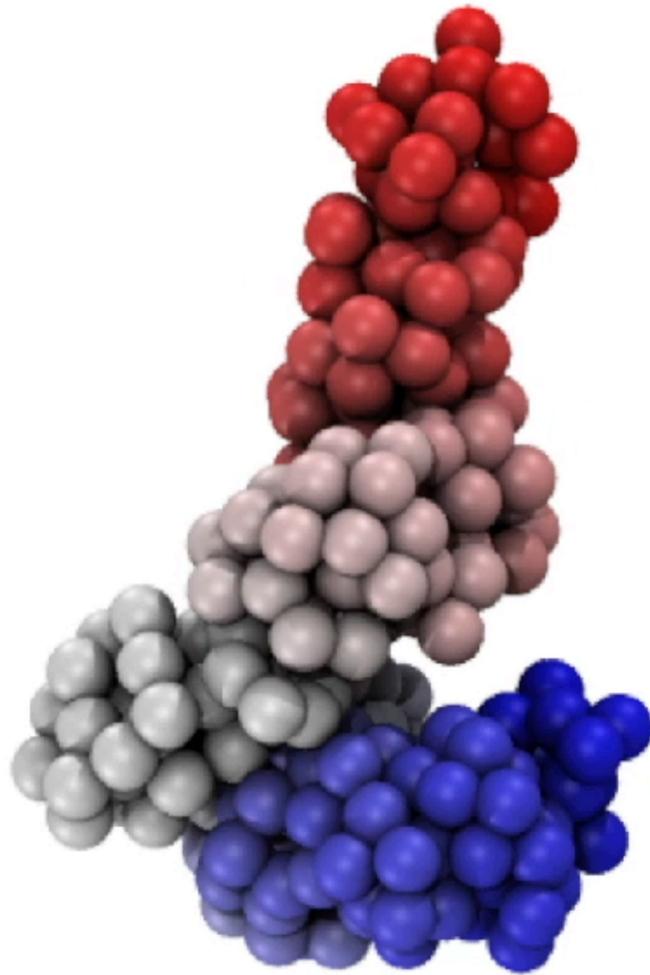
# SOX2 locus structural changes from B to PSC

Structural exposure



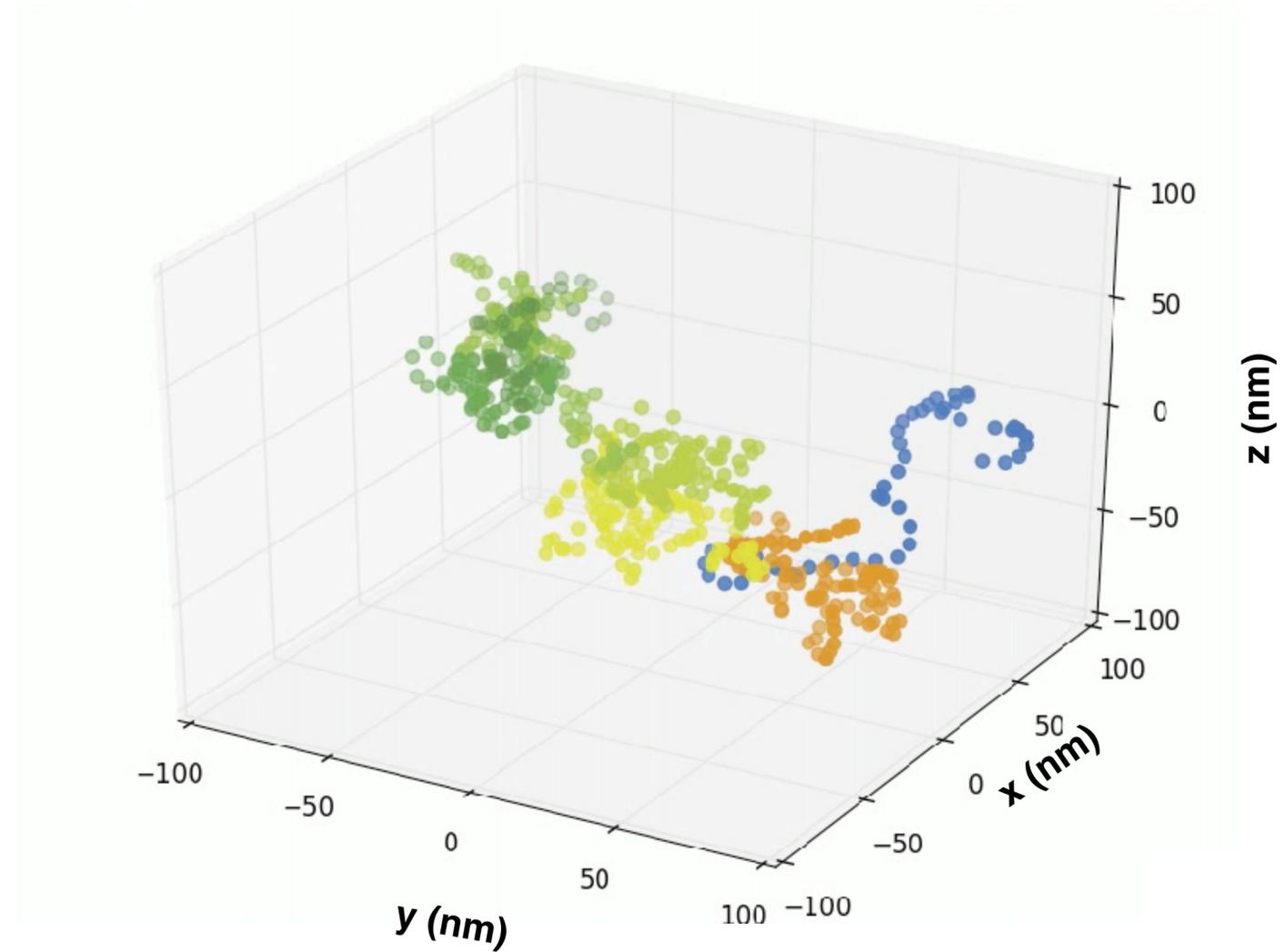
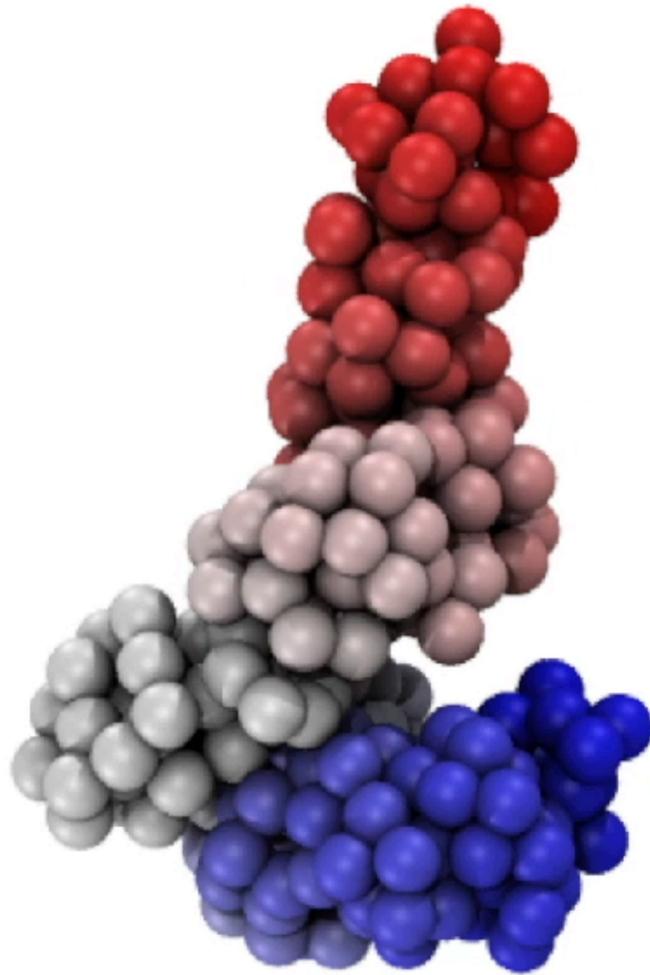
# SOX2 locus structural changes from B to PSC

Domain borders



# SOX2 locus structural changes from B to PSC

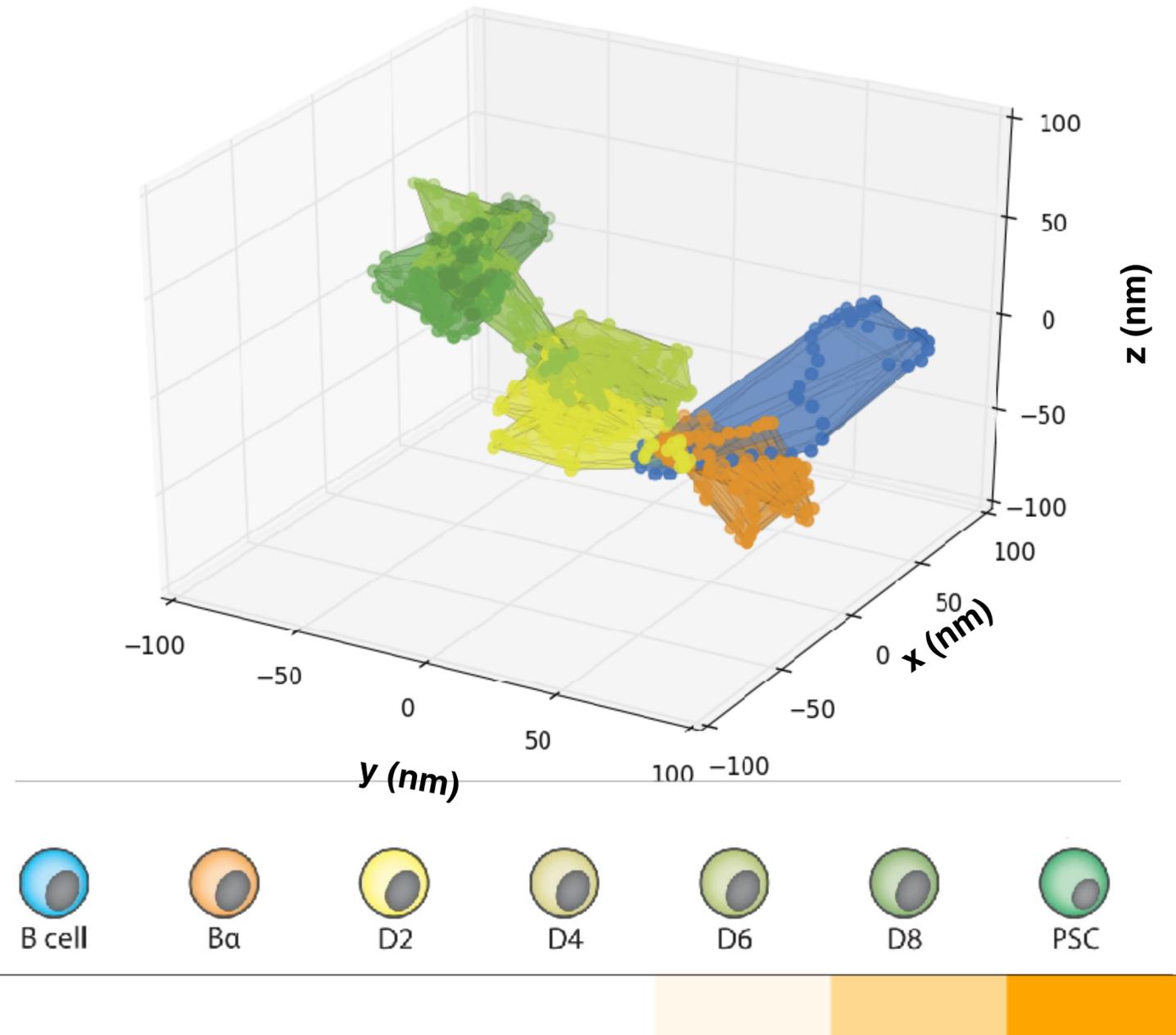
Displacement of the TSS



TSS particle positions during the TADdyn dynamics

# SOX2 locus structural changes from B to PSC

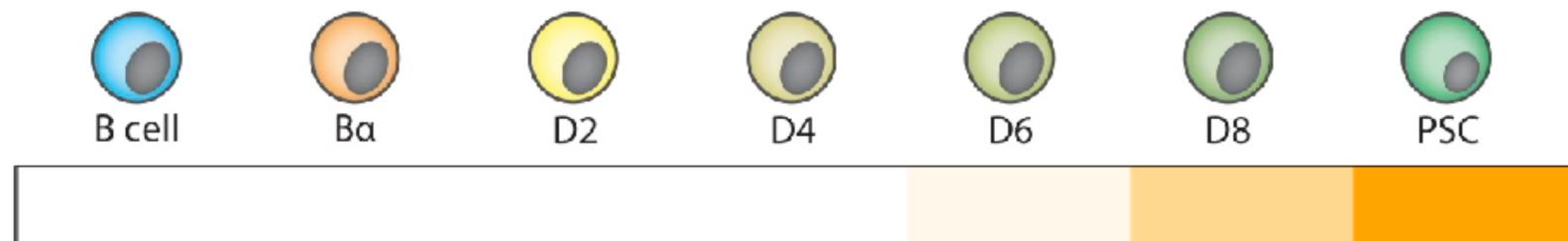
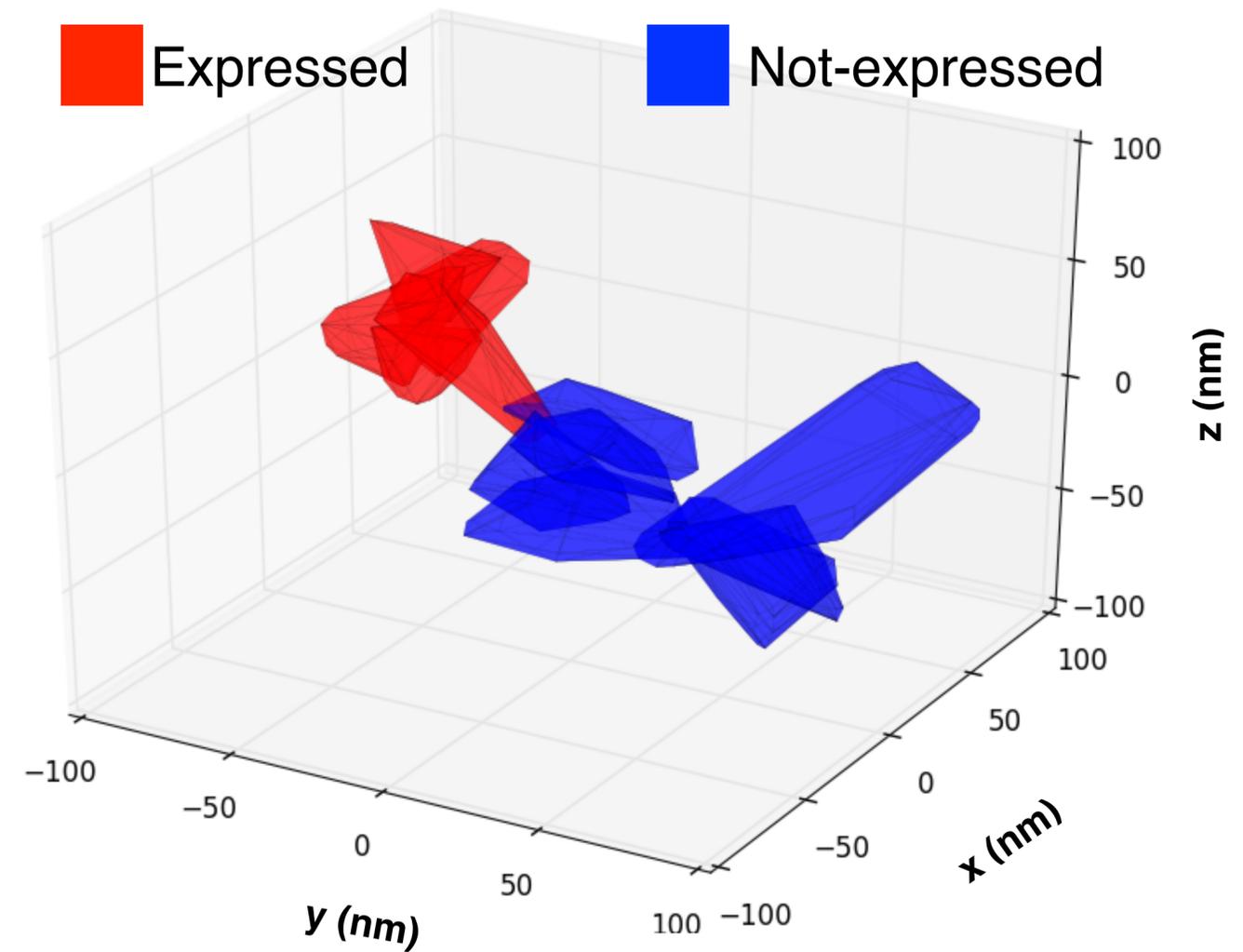
Displacement of the TSS



We divided the trajectory in groups of 50 time steps, and compute the convex hull volume of these groups of points.

# SOX2 locus structural changes from B to PSC

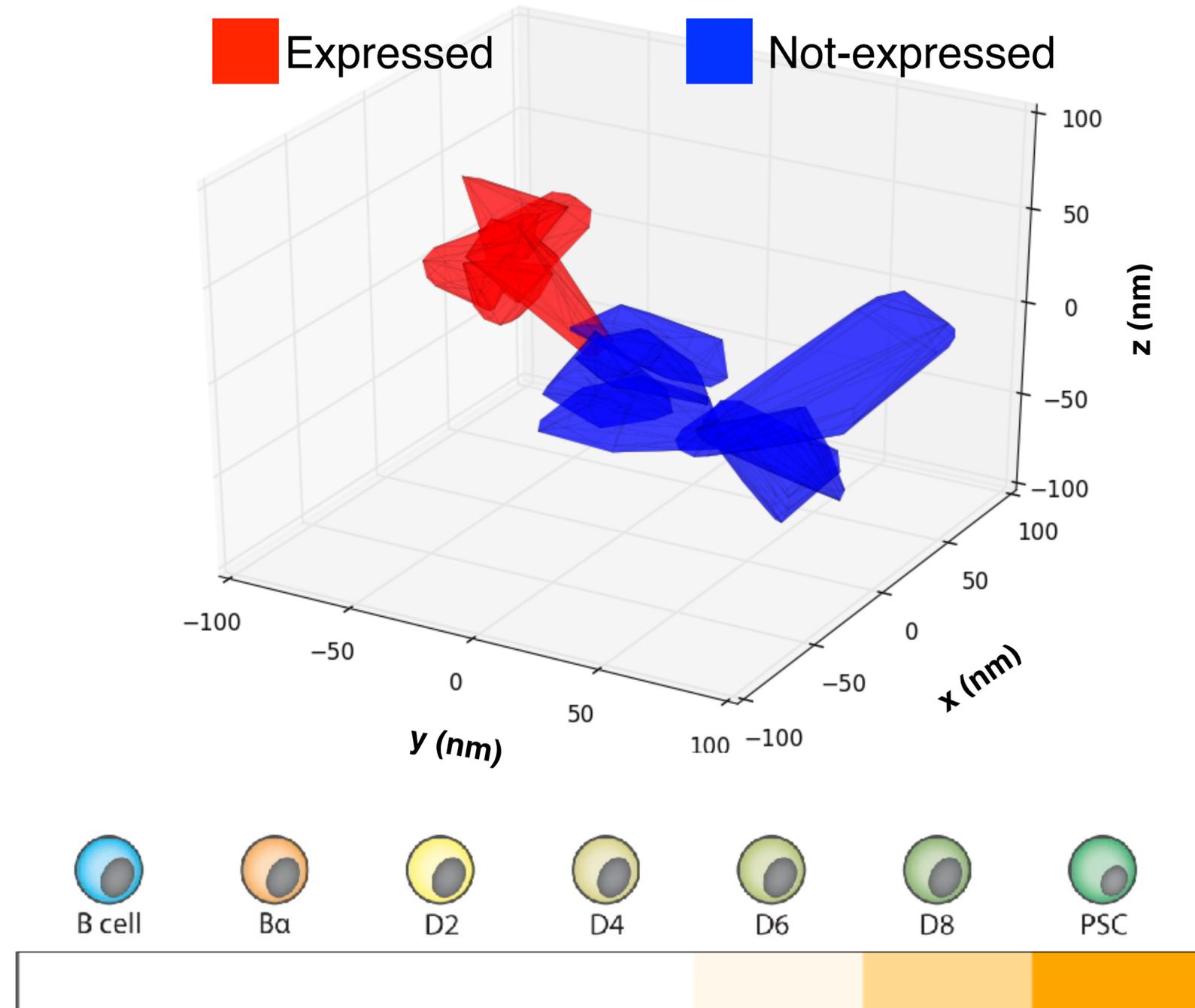
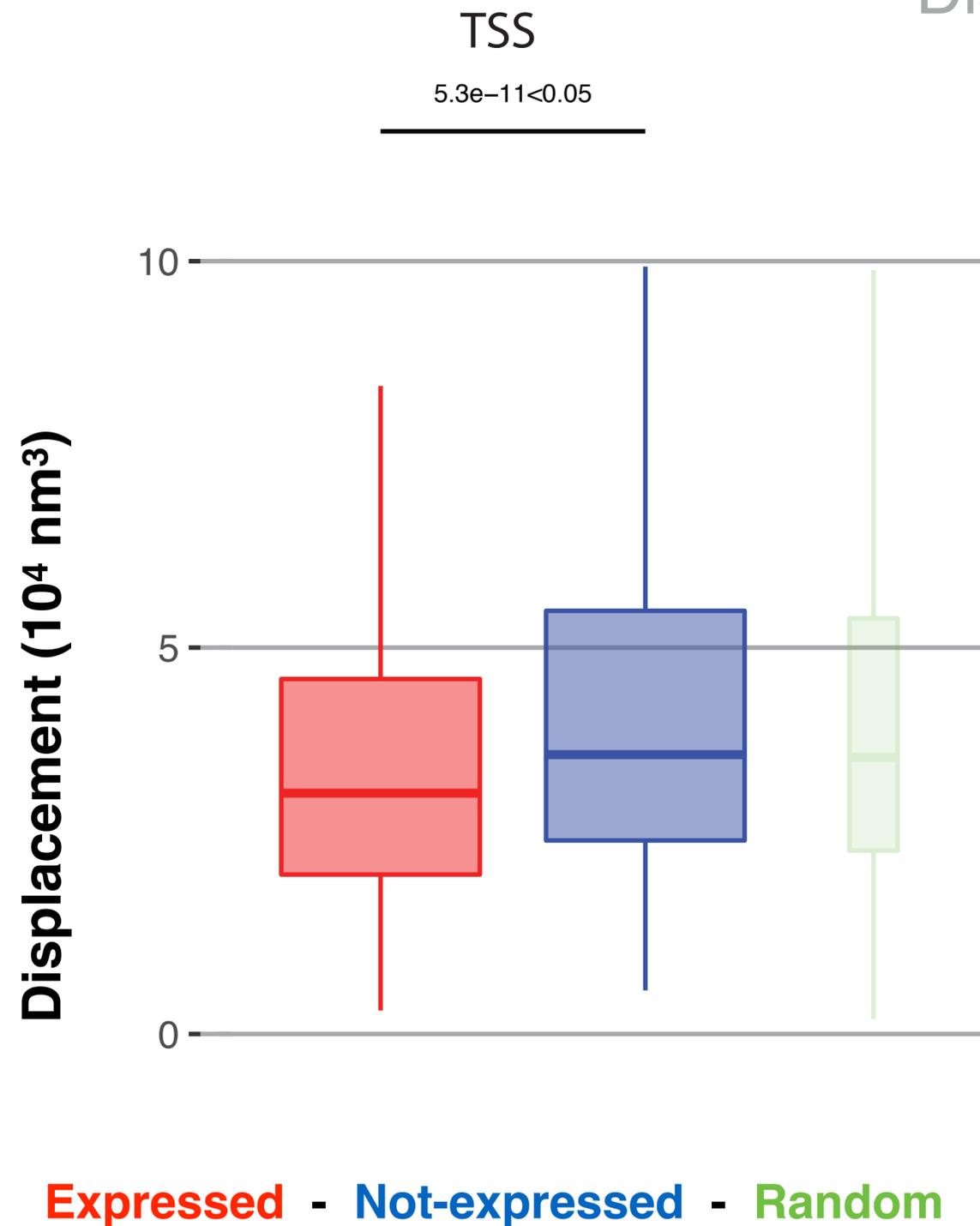
Displacement of the TSS



The trajectories are divided between the expressed (red) and not-expressed (blue) stages.

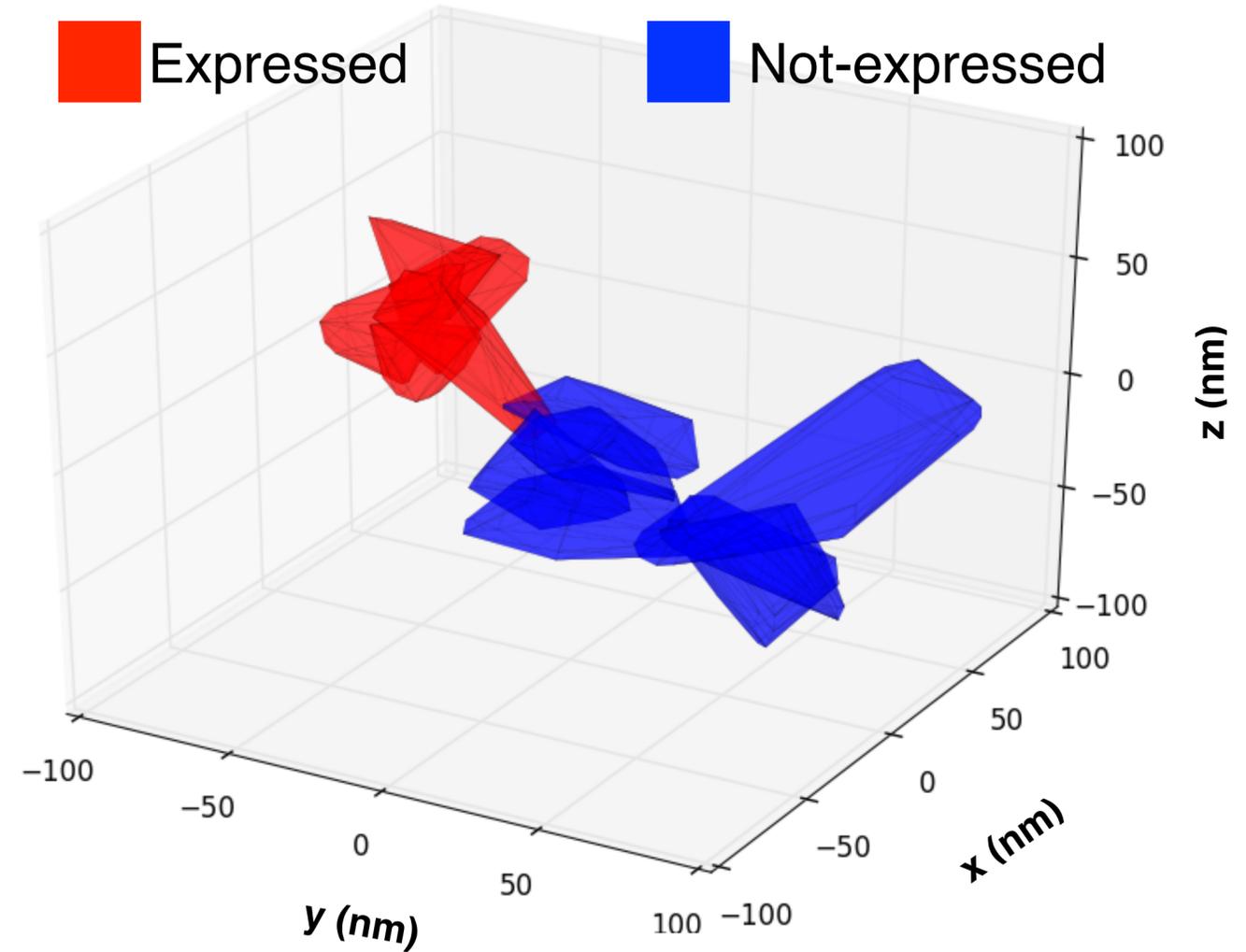
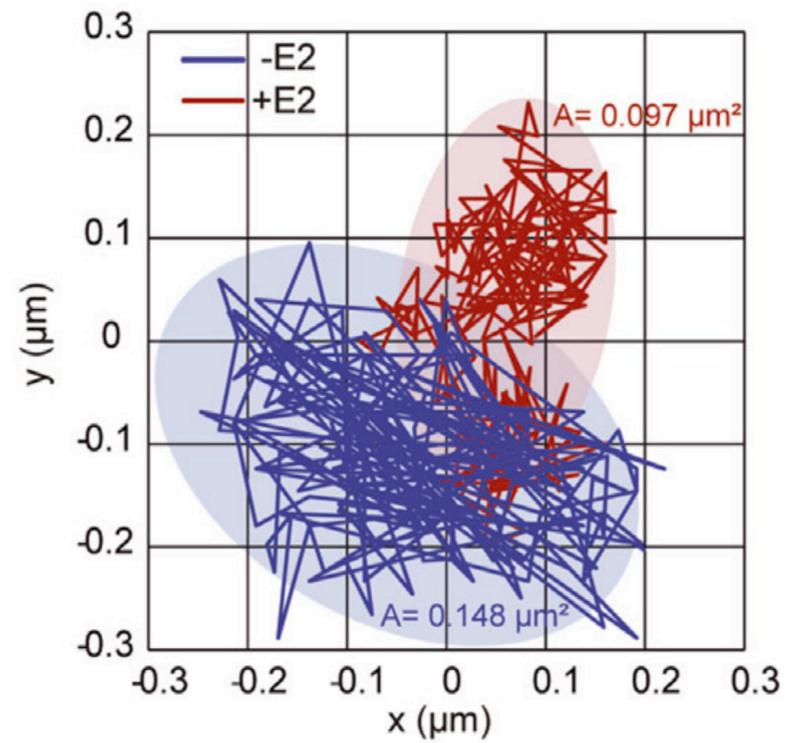
# SOX2 locus structural changes from B to PSC

Displacement of the TSS

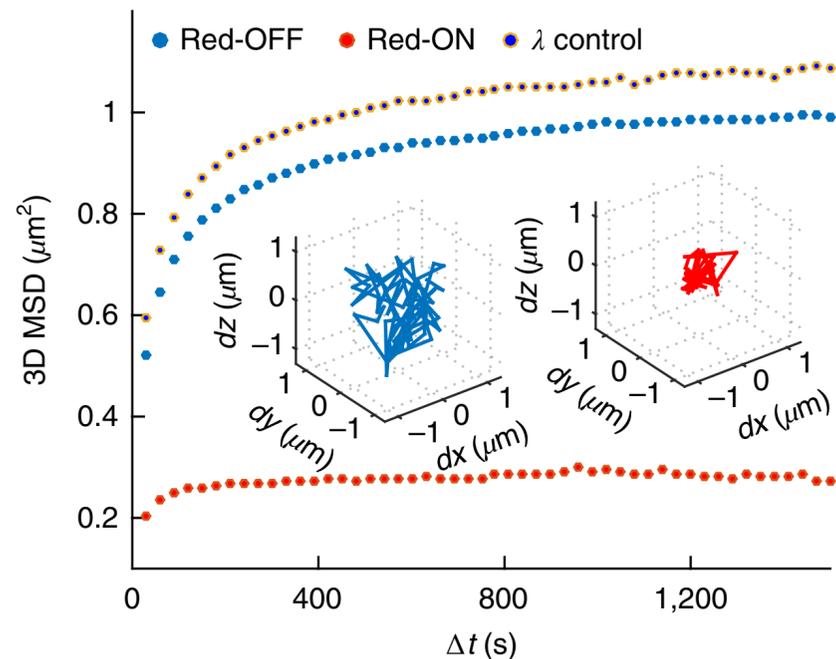


# SOX2 locus structural changes from B to PSC

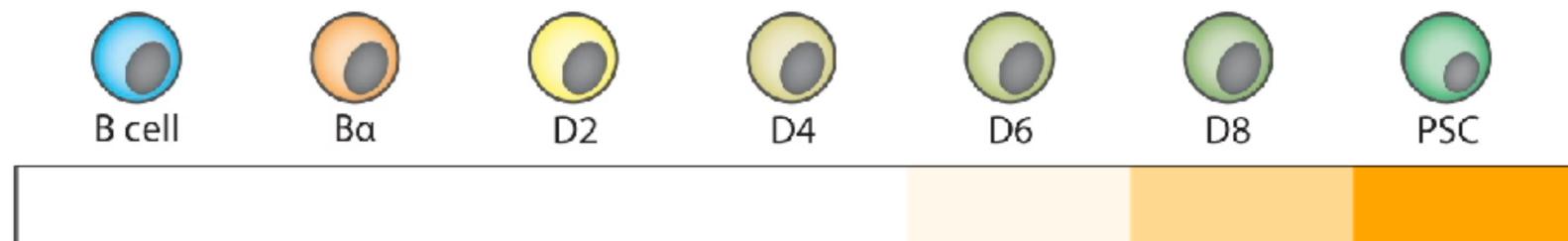
Displacement of the TSS



T Germier & K Bystricky *Biophys J* 2017

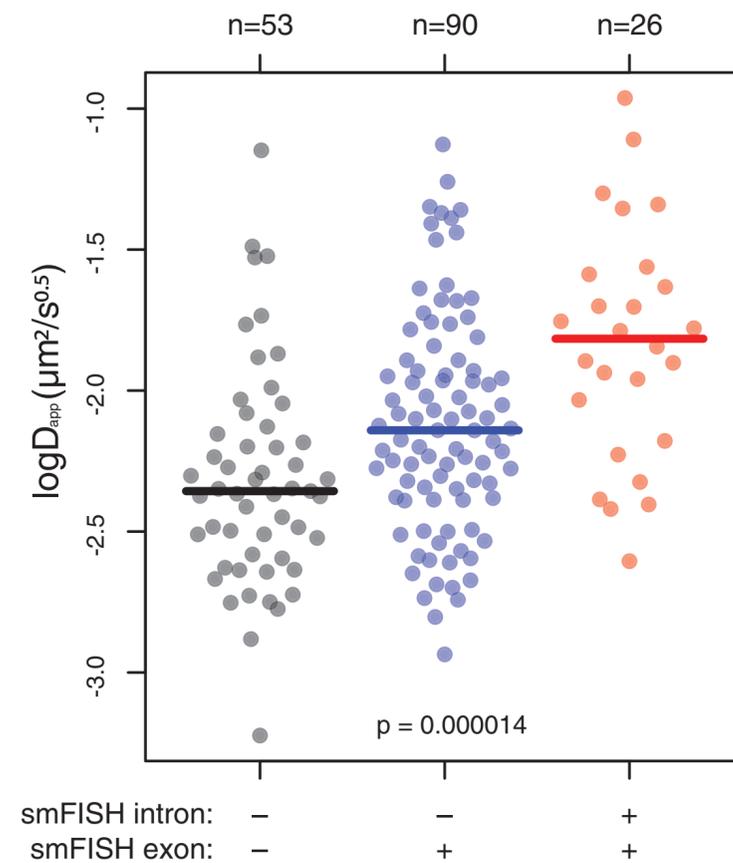


H Chen & T Gregor *Nat Genet* 2018

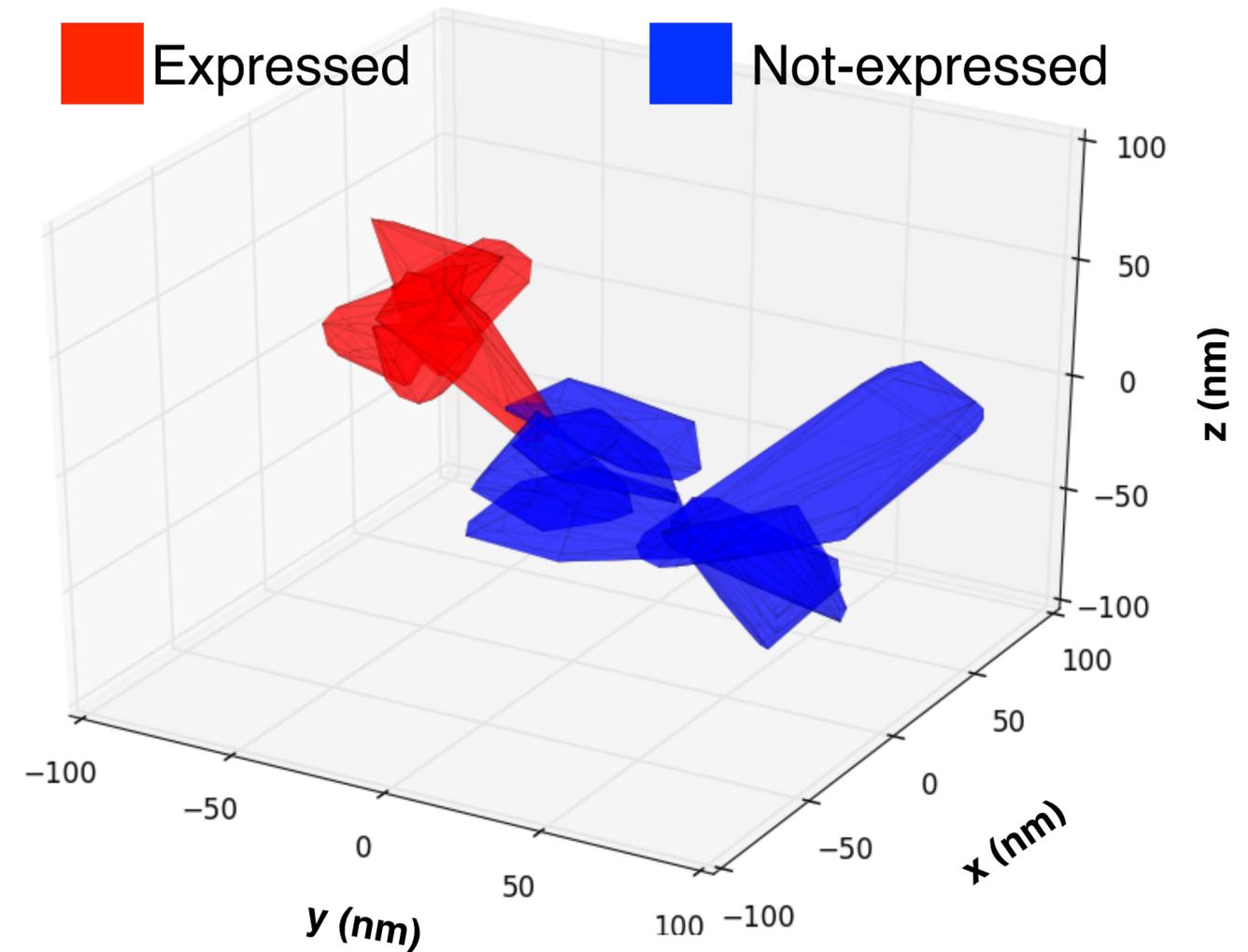


# SOX2 locus structural changes from B to PSC

Displacement of the TSS



Scale bars, 5 μm. **(B)** Mobility of the *Fgf5* enhancer correlates with nascent transcription of the *Fgf5* locus at the single-cell level. Cells were binned into three groups according to the transcription status of the *Fgf5* locus, as measured by multiplexed smFISH and indicated at the bottom. Individual dots represent apparent anomalous diffusion coefficients extracted from the corresponding live-imaging tMSD data. Statistical significance is supported



## The take home message of Part 2

- TADdyn models show structural transition of the SOX2 region from an *inactive* state before D4 to an *active* state after D6.
- TADdyn dynamics shows that the gene activation is favoured by the formation of a spatial *cage* accommodating the TSS its super-enhancer region.
- Once engaged by open/active regions, the gene is transcribed and its dynamics is spatially confined.

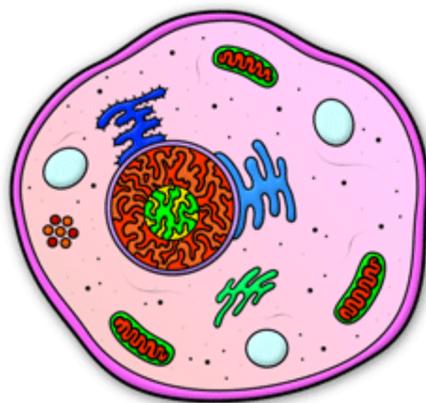
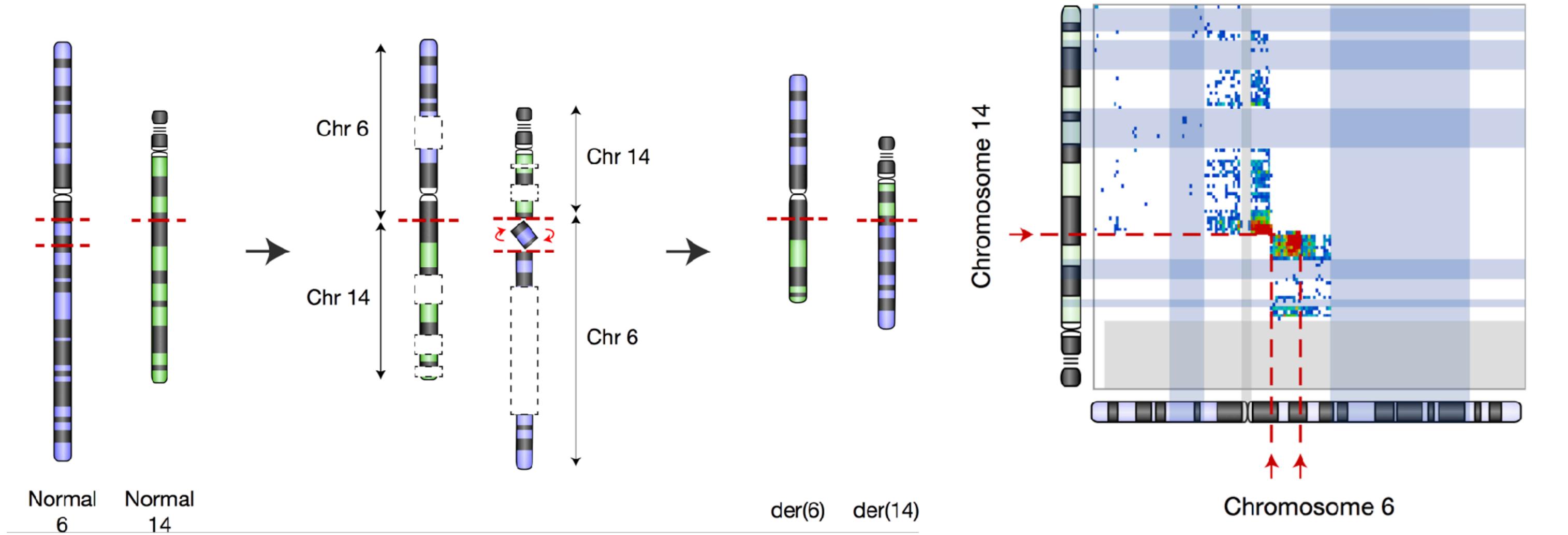


# Citizen Science project



-  Genigma.app
-  #Genigma3D
-  @Genigma

# Annotating translocations in cancer cells



HEK293

T47D

HAP1

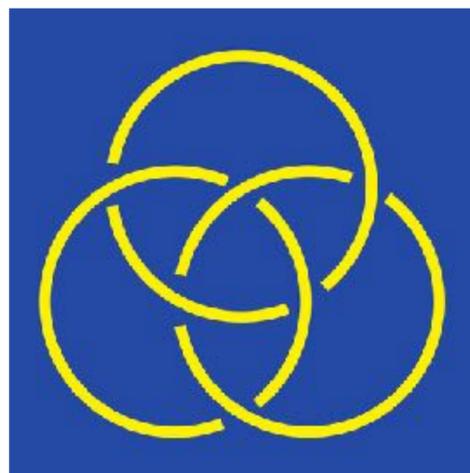
# Genigma: Why citizens?



# The App prototype

# Thanks for listening!

Marc A. Marti-Renom  
David Castillo  
Yasmina Cuartero  
Irene Farabella  
Silvia Galan  
Mike Goodstadt  
Rodrigo Jara  
Francesca Mugianesi  
Julen Mendieta  
Juan Rodriguez  
Maria Marti-Marimon  
Paula Soler  
Aleksandra Sparavier



D Jost  
ENS de Lyon



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CRG