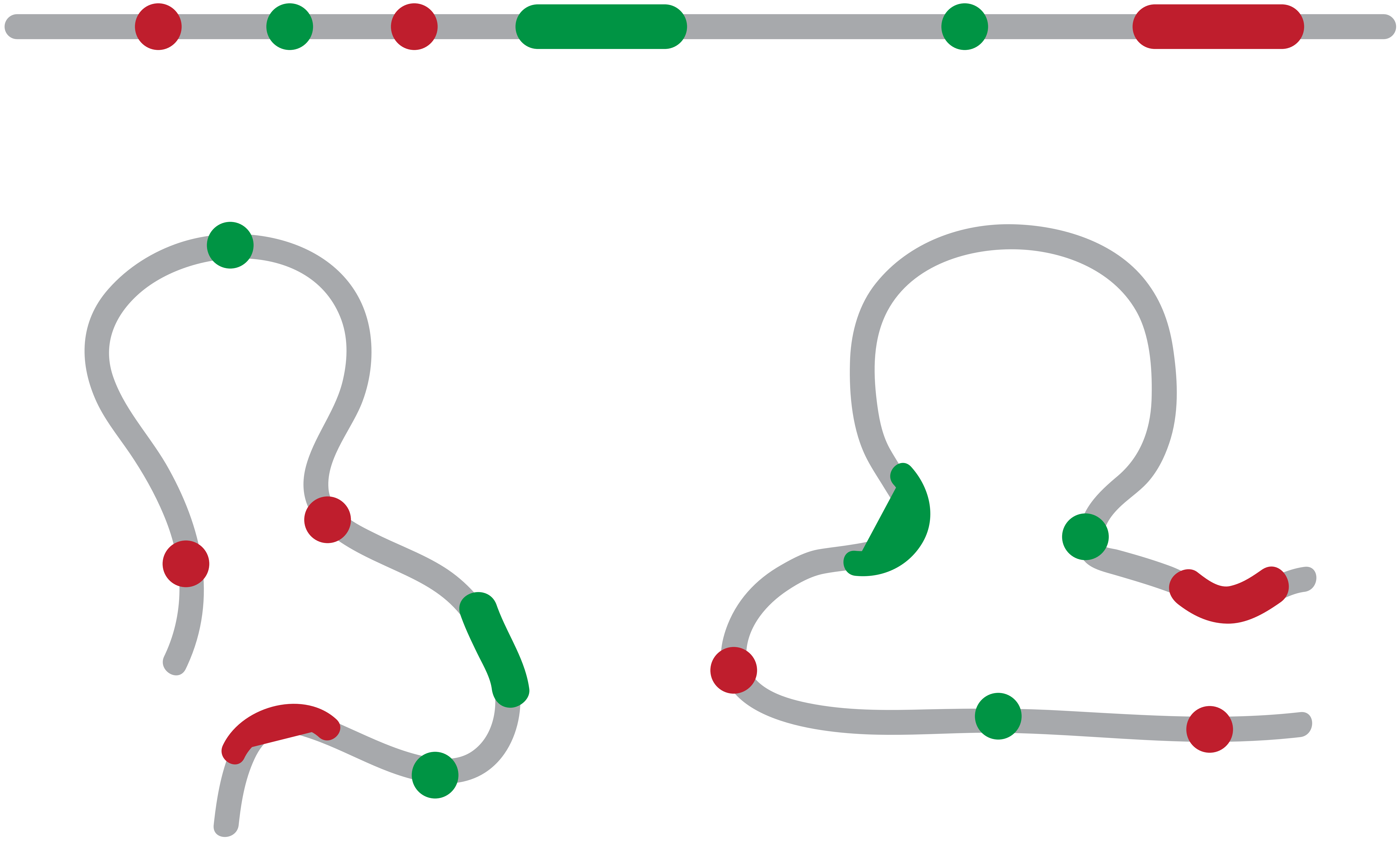

Photo by David Oliete - www.davidoliete.com

Structure determination of genomes and genomic domains by satisfaction of spatial restraints

Marc A. Marti-Renom

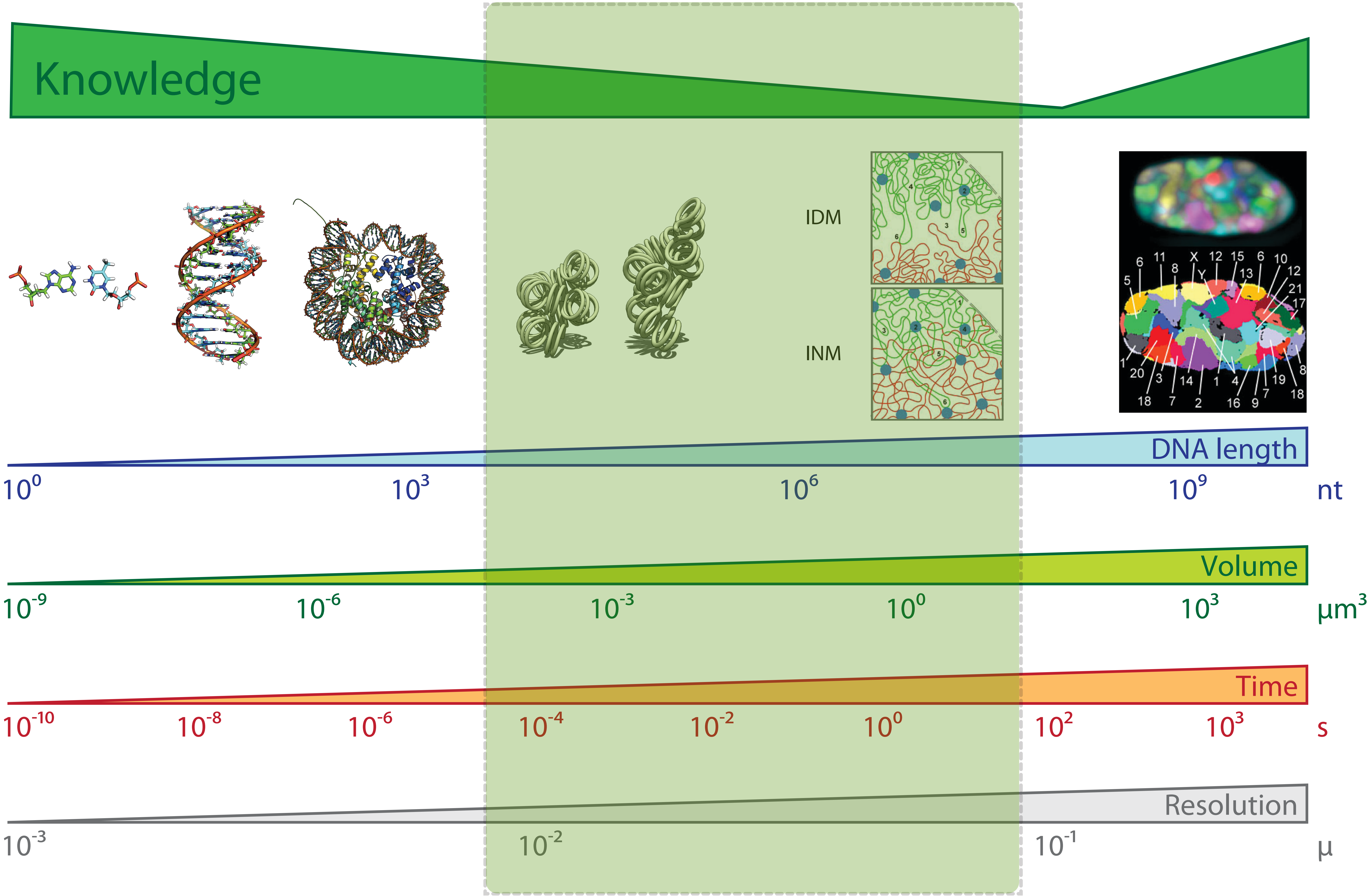
CNAG-CRG · ICREA

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



Resolution Gap

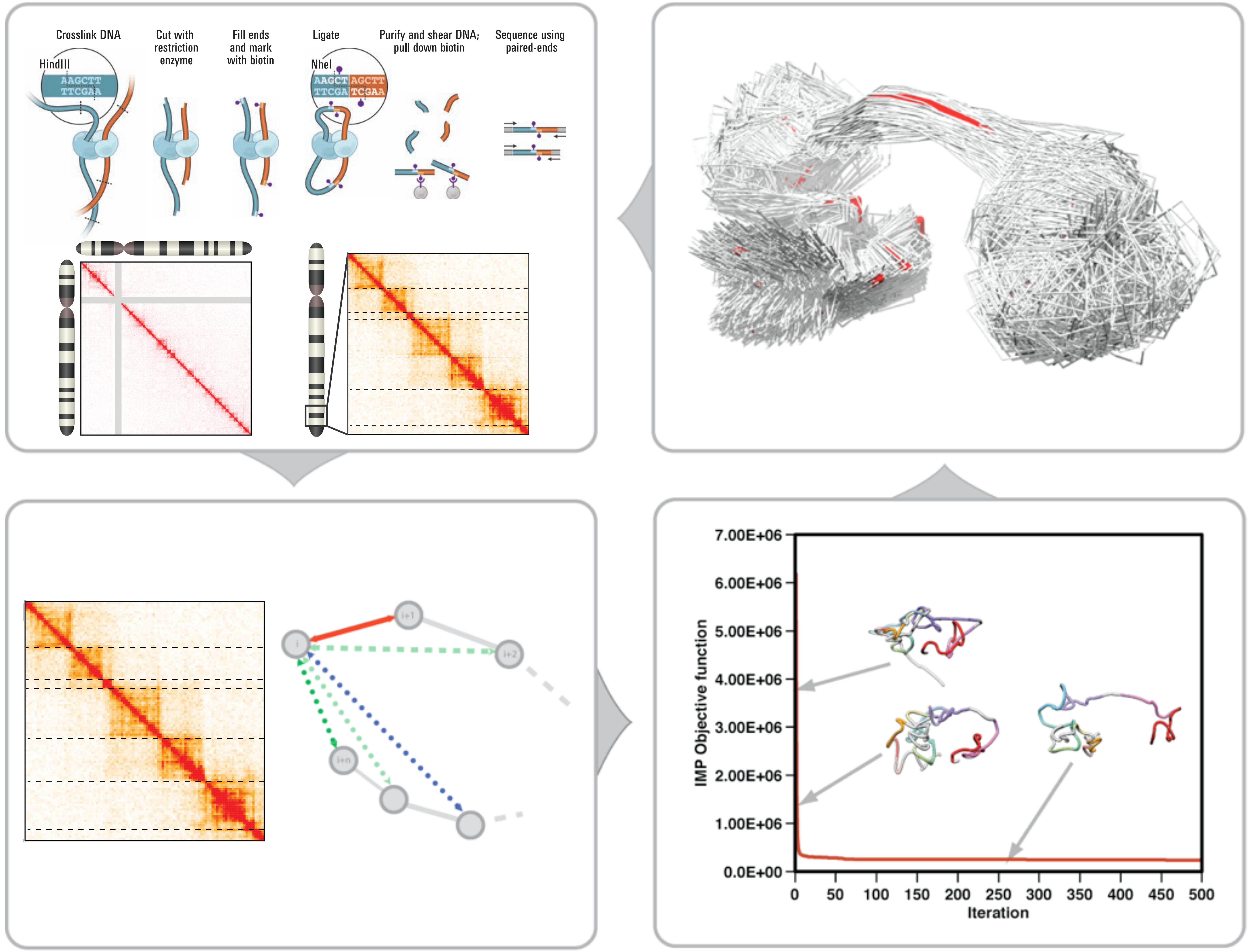
Marti-Renom, M. A. & Mirny, L. A. PLoS Comput Biol 7, e1002125 (2011)



Hybrid Method

Baù, D. & Marti-Renom, M. A. Methods 58, 300–306 (2012).

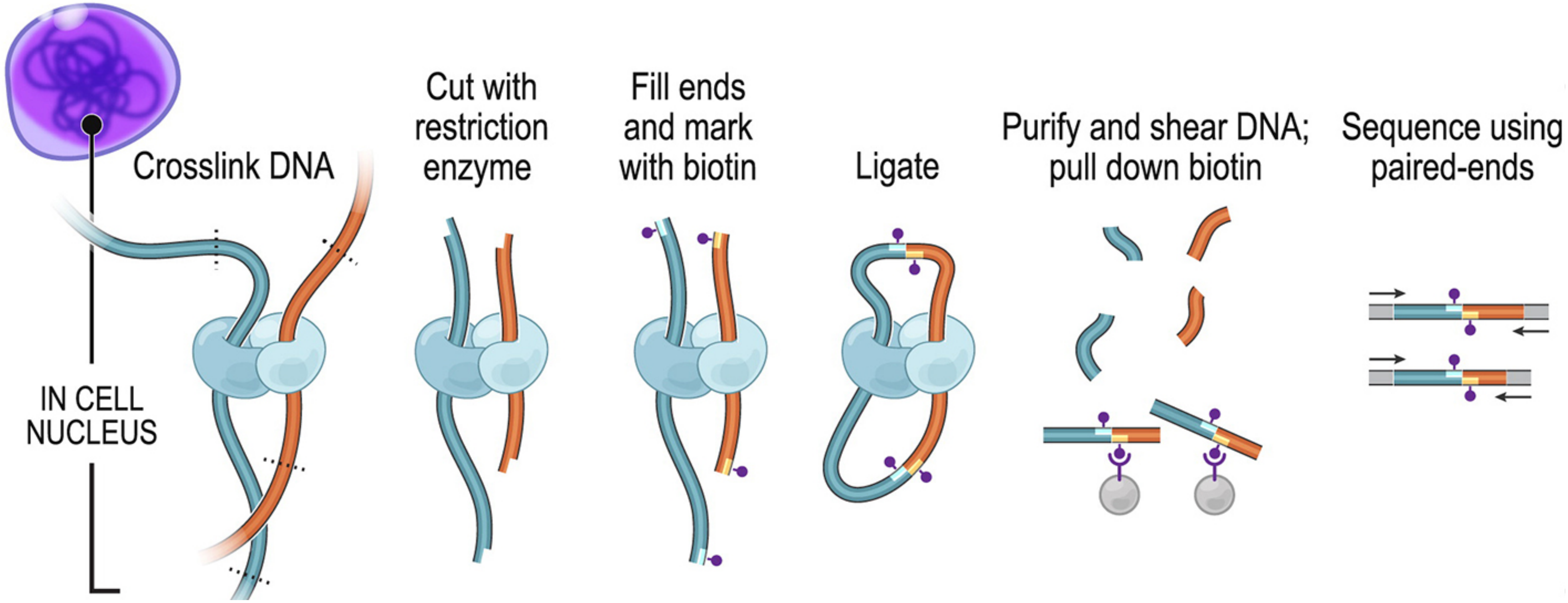
Experiments

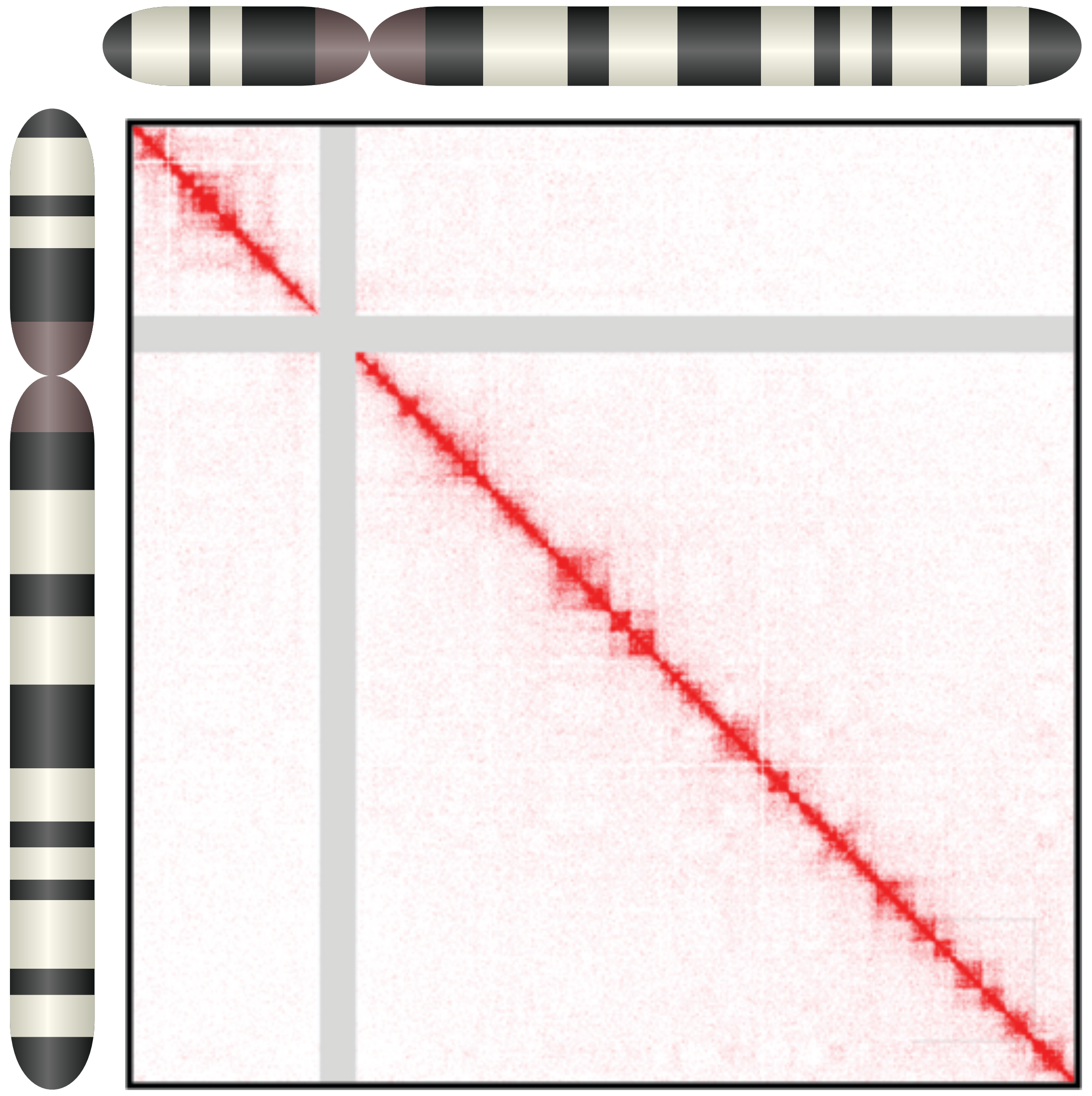


Computation

Chromosome Conformation Capture

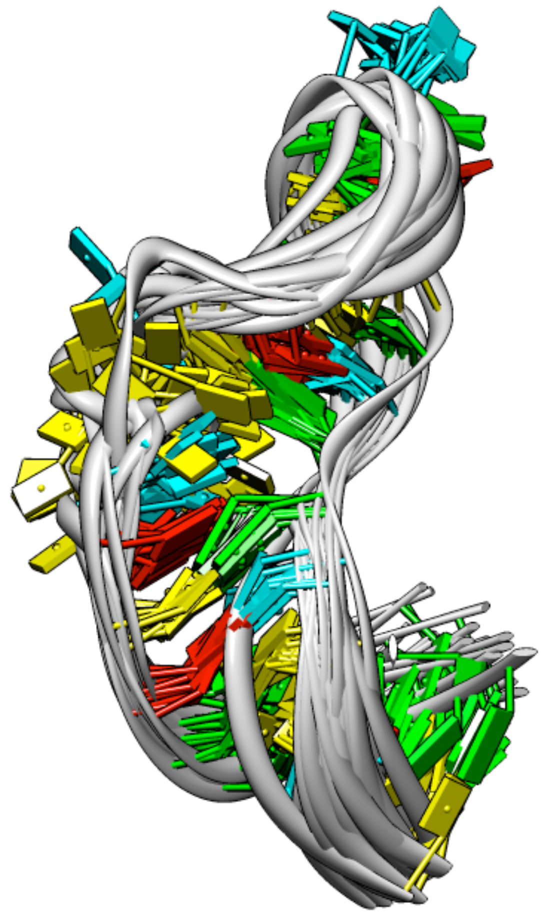
Dekker, J., Rippe, K., Dekker, M., & Kleckner, N. (2002). Science, 295(5558), 1306–1311.
Lieberman-Aiden, E., et al. (2009). Science, 326(5950), 289–293.

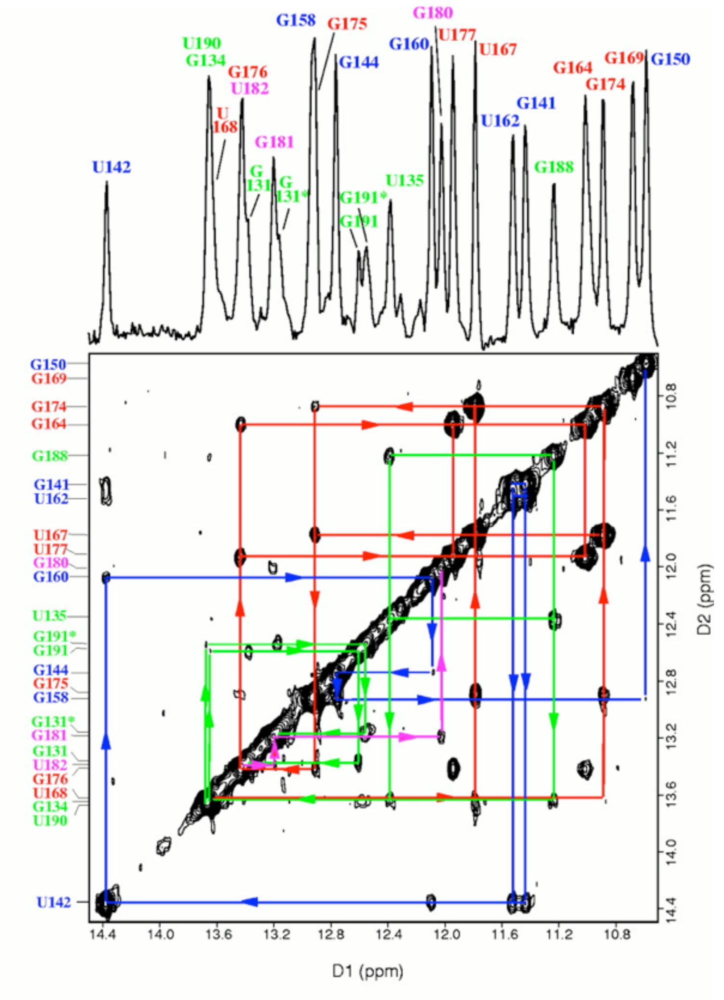




Restraint-based Modeling

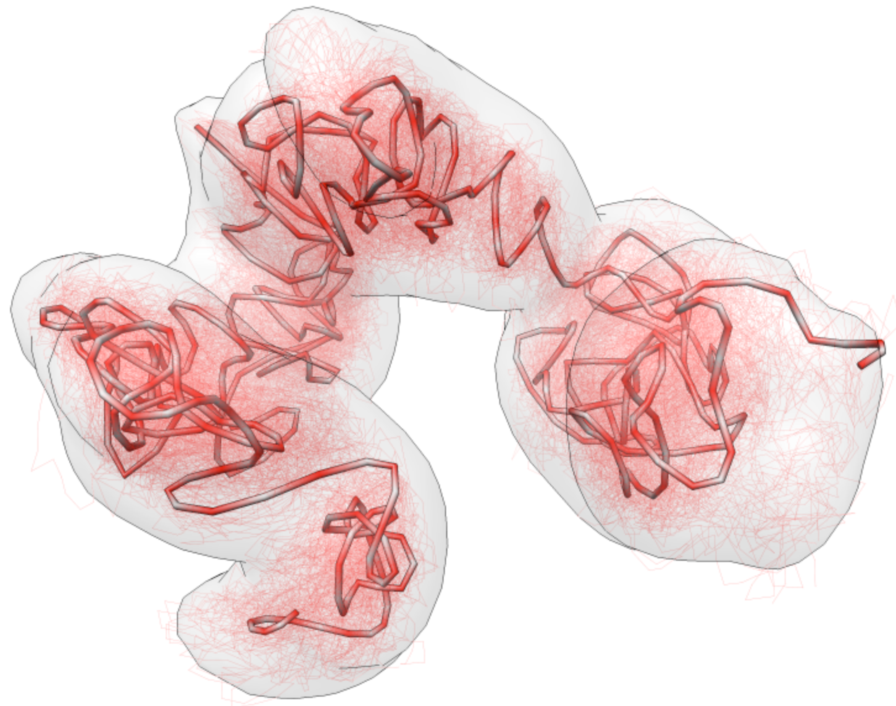
Baù, D. & Marti-Renom, M. A. Methods 58, 300–306 (2012).

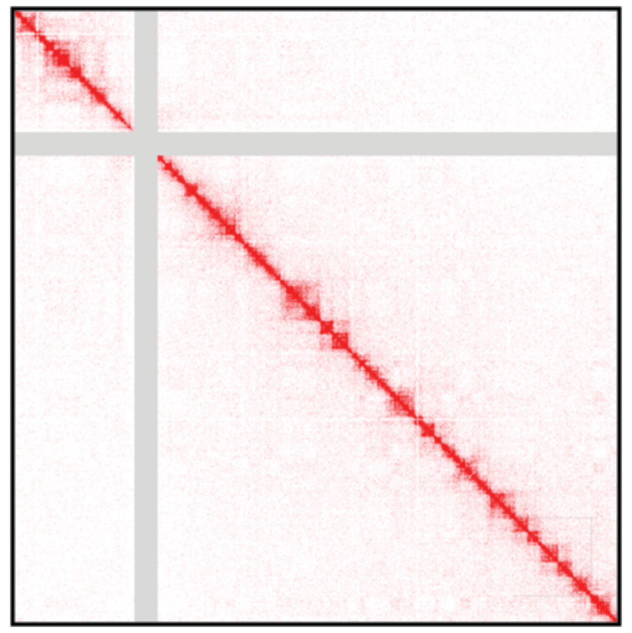




Biomolecular structure determination

2D-NOESY data



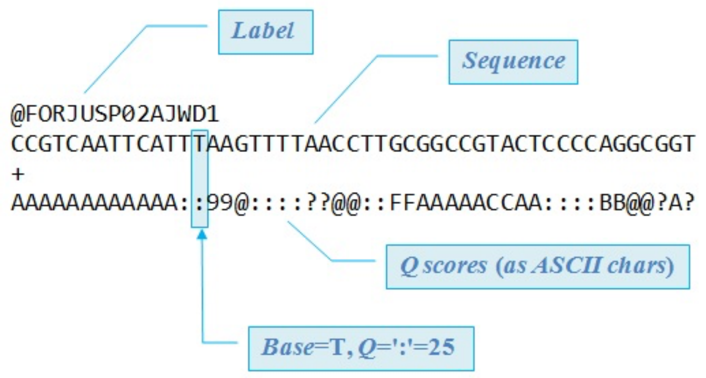


Chromosome structure determination

3C-based data

TADbit

http://3DGenomes.org



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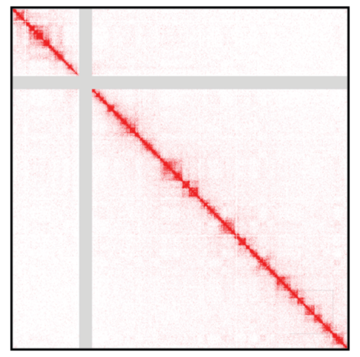
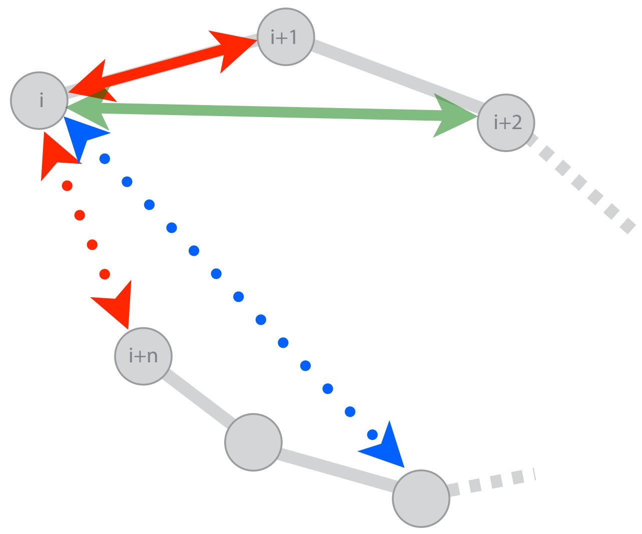
+
AAAAAAAAAAAA::99@::::??@@::FFAAAAACCAA::::BB@@?A?
```

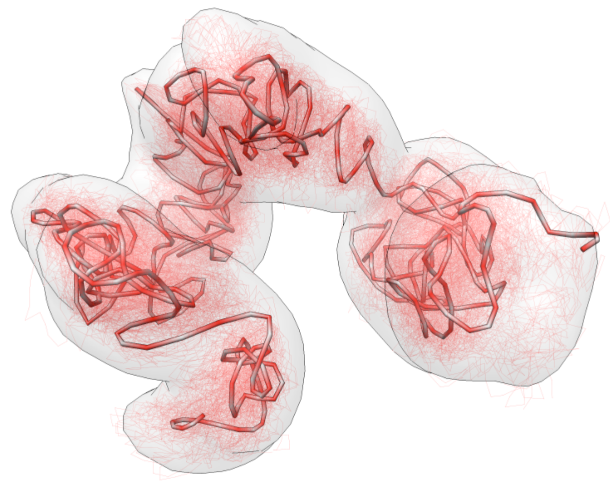
FastQ files to Maps



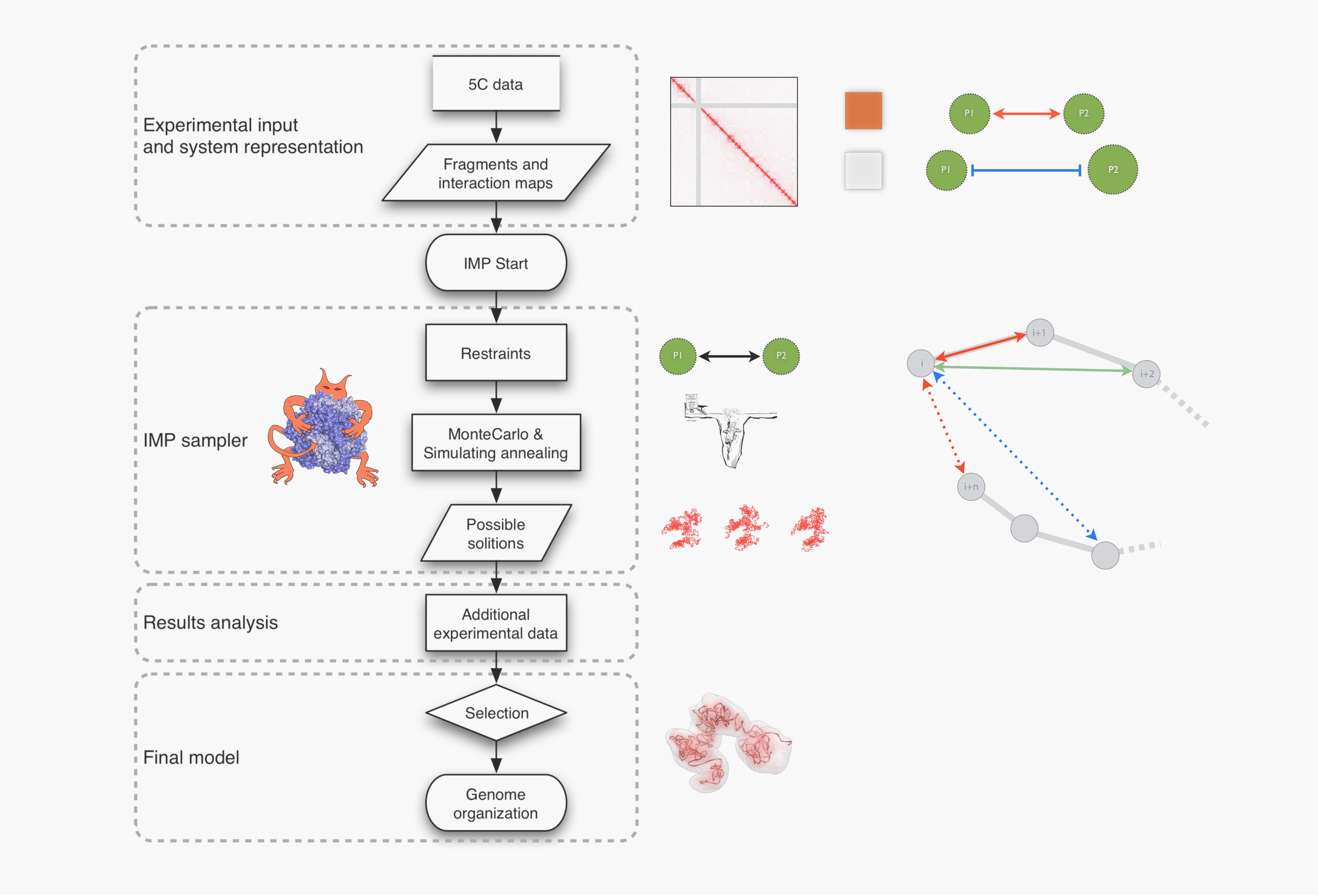
Map analysis



Model building



Model analysis



Experimental input
and system representation

5C data

Fragments and
interaction maps

IMP Start

IMP sampler

Restraints

MonteCarlo &
Simulating annealing

Possible
solitions

Results analysis

Additional
experimental data

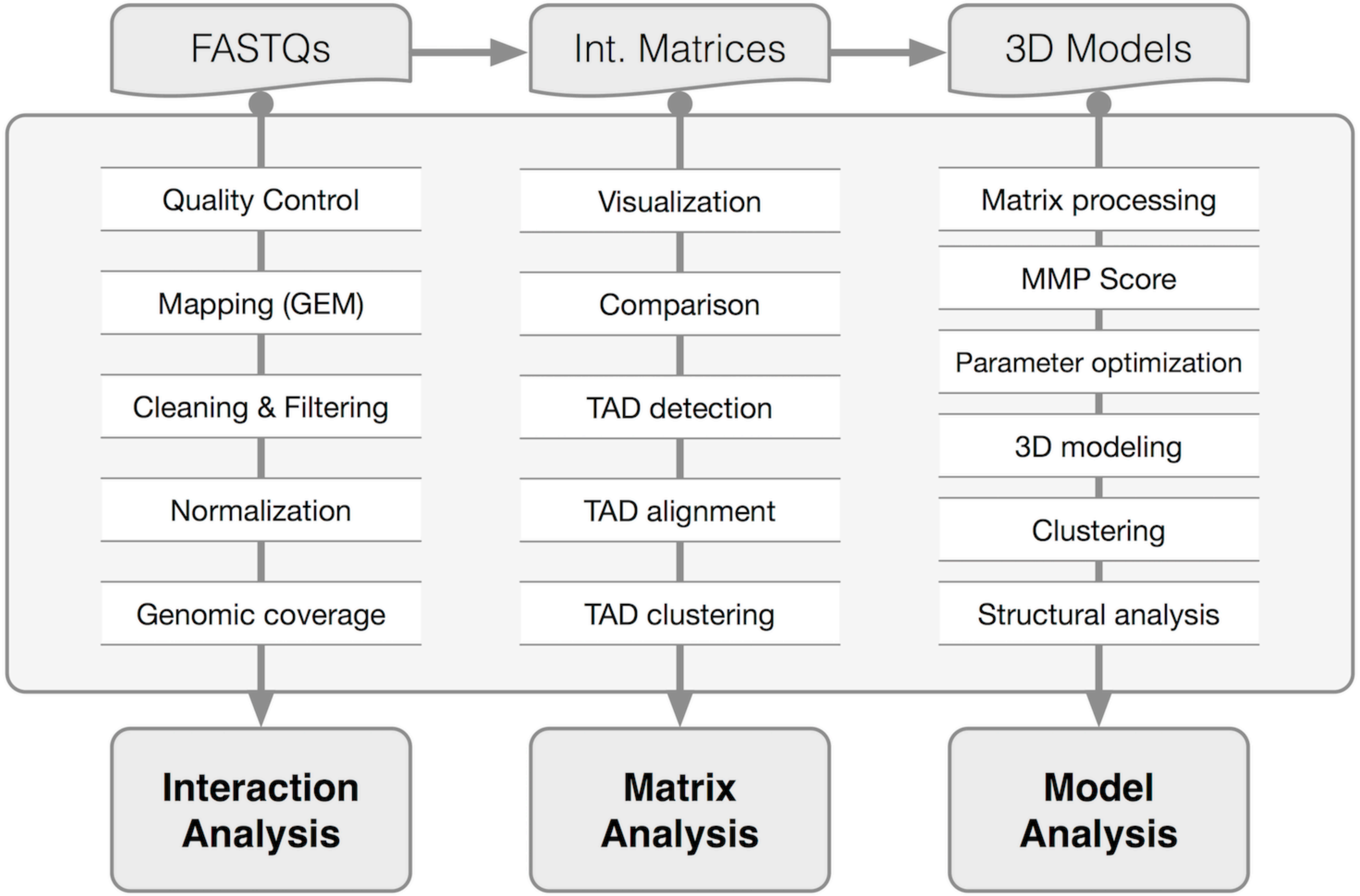
Selection

Final model

Genome
organization

TADbit

Serra, Baù, et al. (2017). PLOS CompBio



- Baù, D. et al. Nat Struct Mol Biol (2011)
- Umbarger, M. A. et al. Mol Cell (2011)
- Le Dily, F. et al. Genes & Dev (2014)
- Belton, J.M. et al. Cell Reports (2015)
- Trussart M. et al. Nature Communication (2017)
- Cattoni, D. et al. Nature Communication (2017)
- Stadhouders R. et al. Nature Genetics (2018)
- Kojic, A., Cuadrado, A. et al. Nat Struct Mol Biol (2018)
- Beekman R. et al. Nature Medicine (2018)
- Mas, G. et al. Nature Genetics (2018)
- Pascual-Reguant, L. et al. Nature Comm. (2018)

Nature Structural & Molecular Biology, 25(9), 766-777, 2018
Cell, 173(7), 1796-1809.e17, 2018
Structure, 26(6), 894-904.e2, 2018
Genome Research, 29(1), 29-39, 2019
Genome Research, 29(1), gr.238527.118, 2019


Photo by David Oliete - www.davidoliete.com

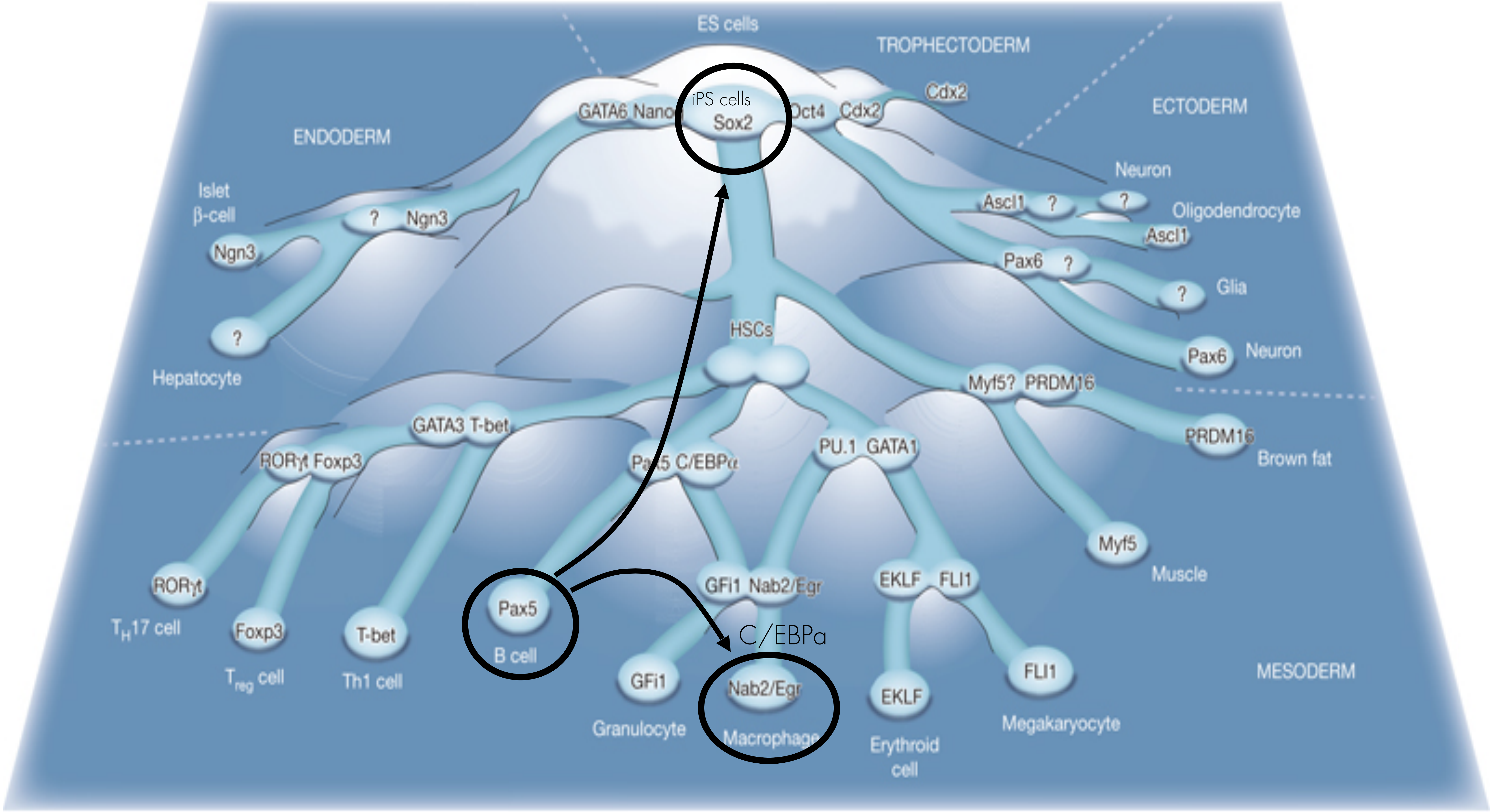
3D structural dynamics of the SOX2 locus activation

Marco di Stefano
Ralph Stadhouders
with Graf Lab (CRG, Barcelona)

Nature Genetics (2018) 50 238–249 & unpublished

Transcription factors dictate cell fate

Graf & Enver (2009) Nature



Transcription factors (TFs) determine cell identity through gene regulation

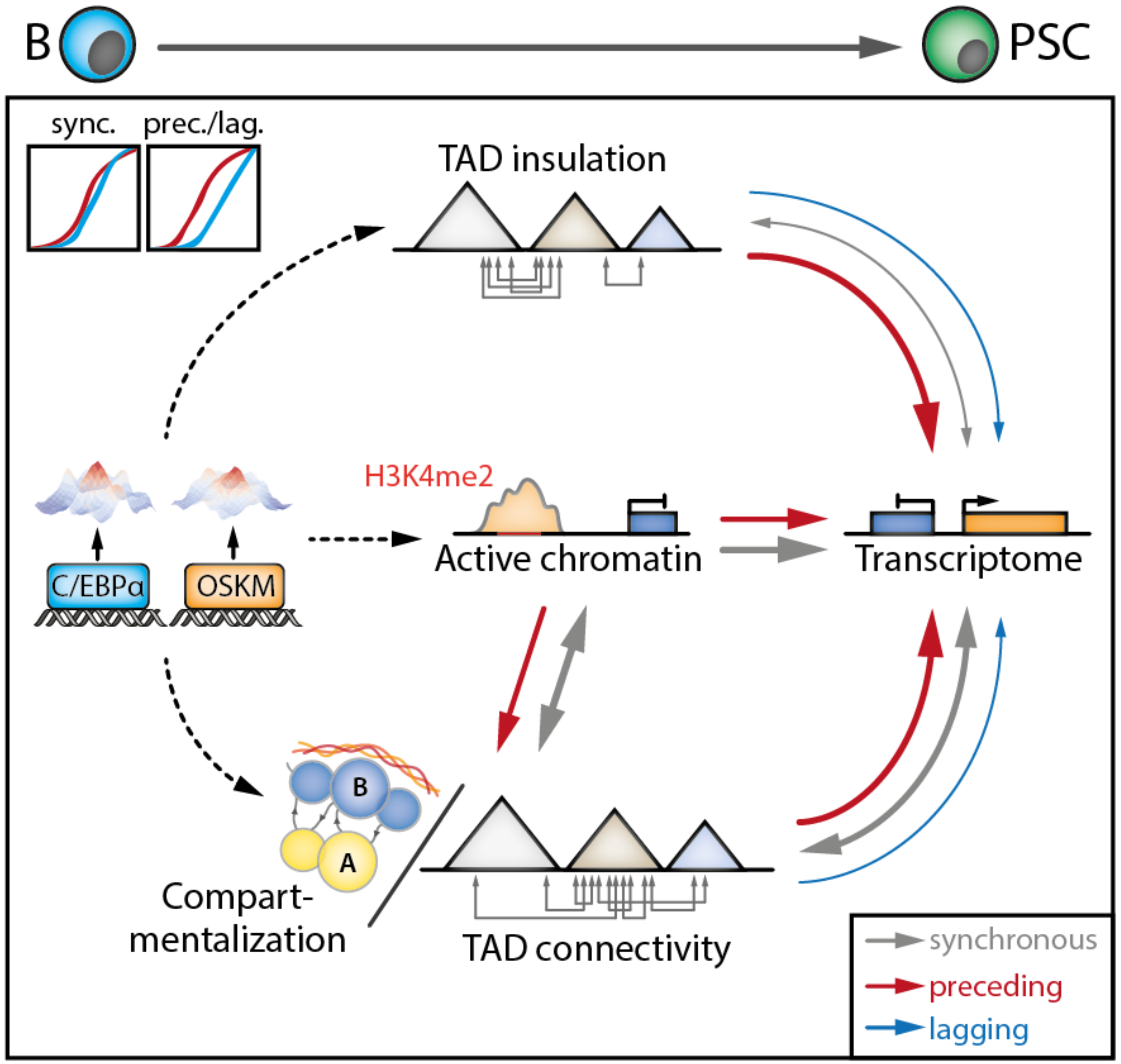
Normal 'forward' differentiation

Cell fates can be converted by enforced TF expression

Transdifferentiation or reprogramming

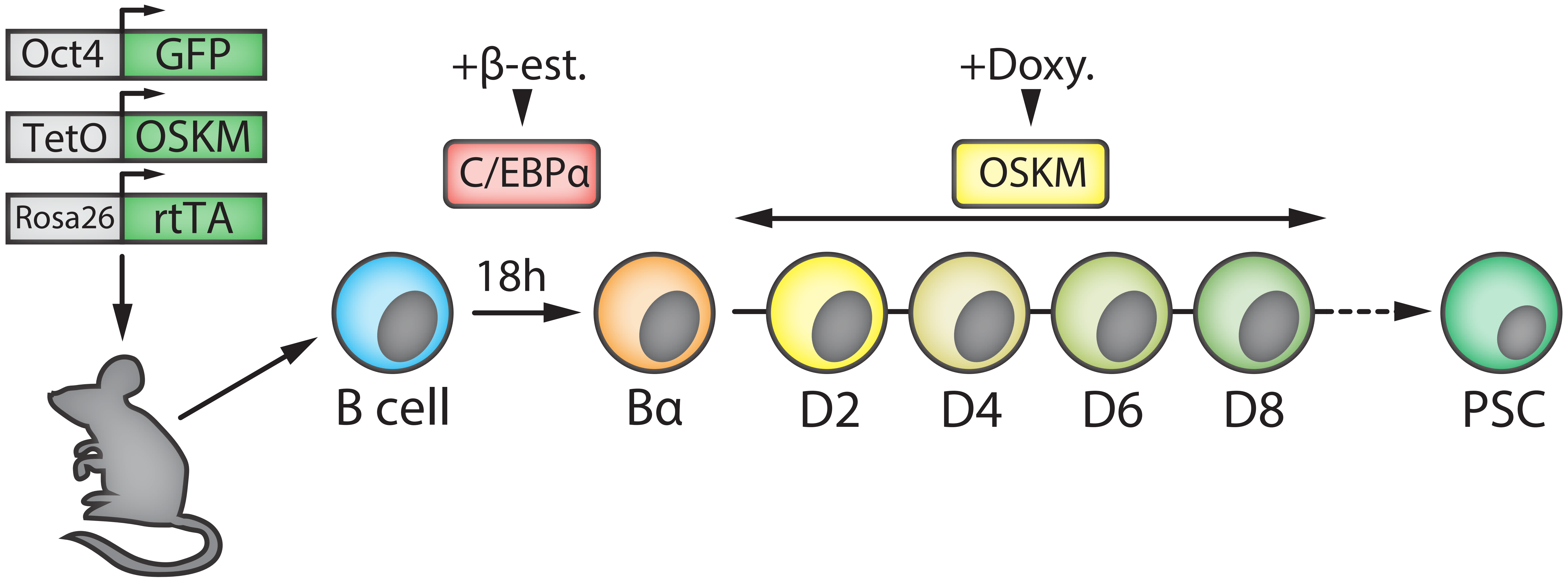
Interplay: topology, gene expression & chromatin

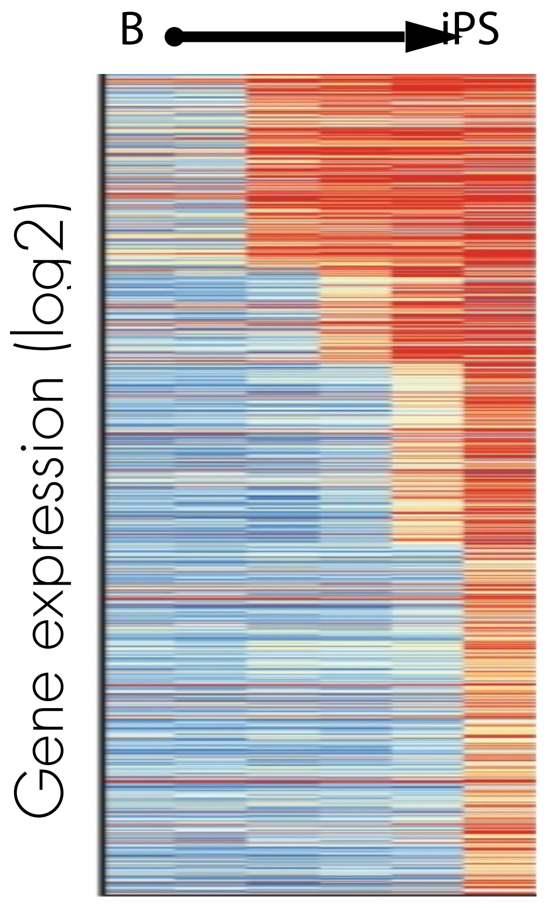
Stadhouders, R., Vidal, E. et al. (2018) Nature Genetics

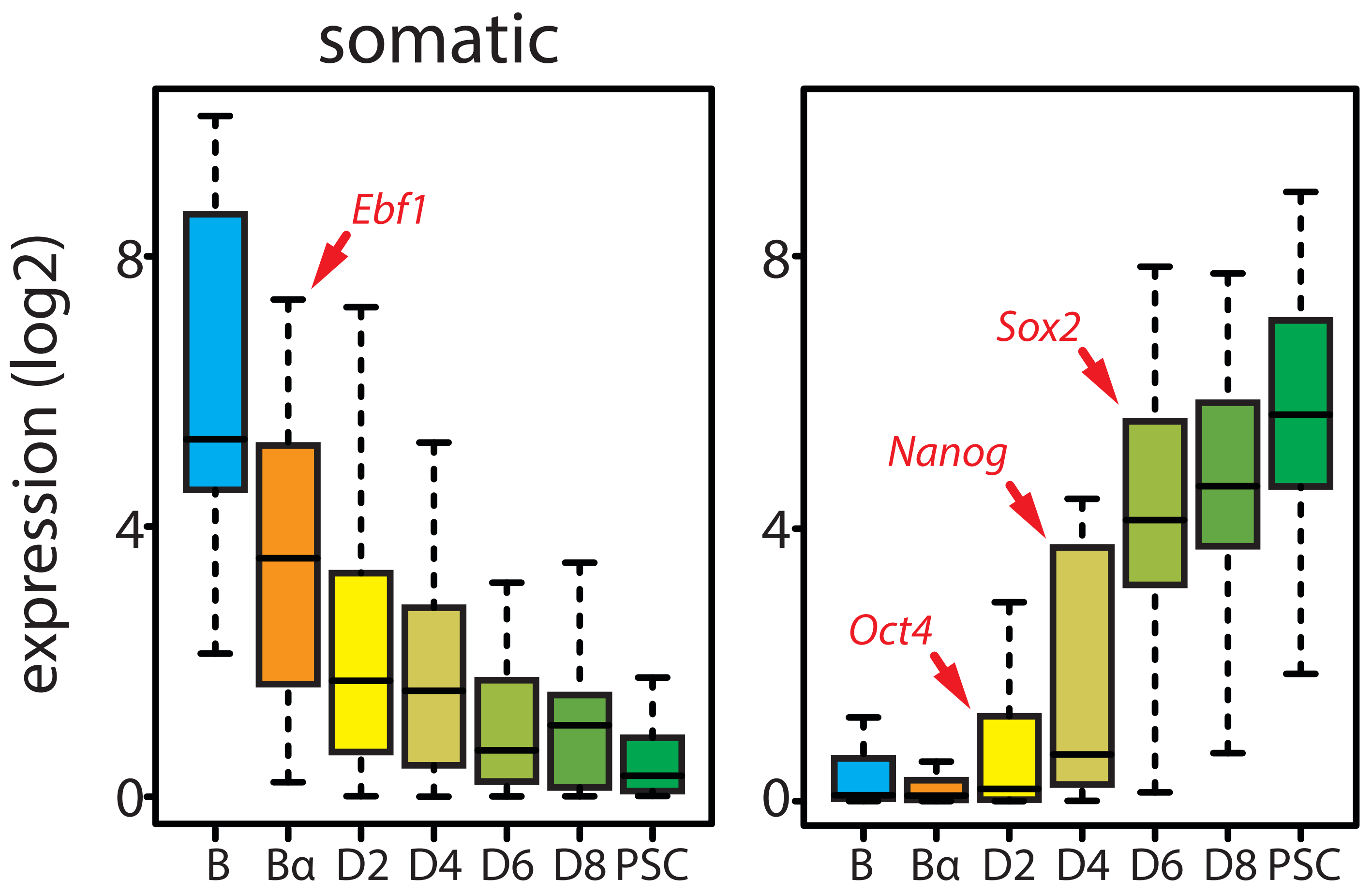


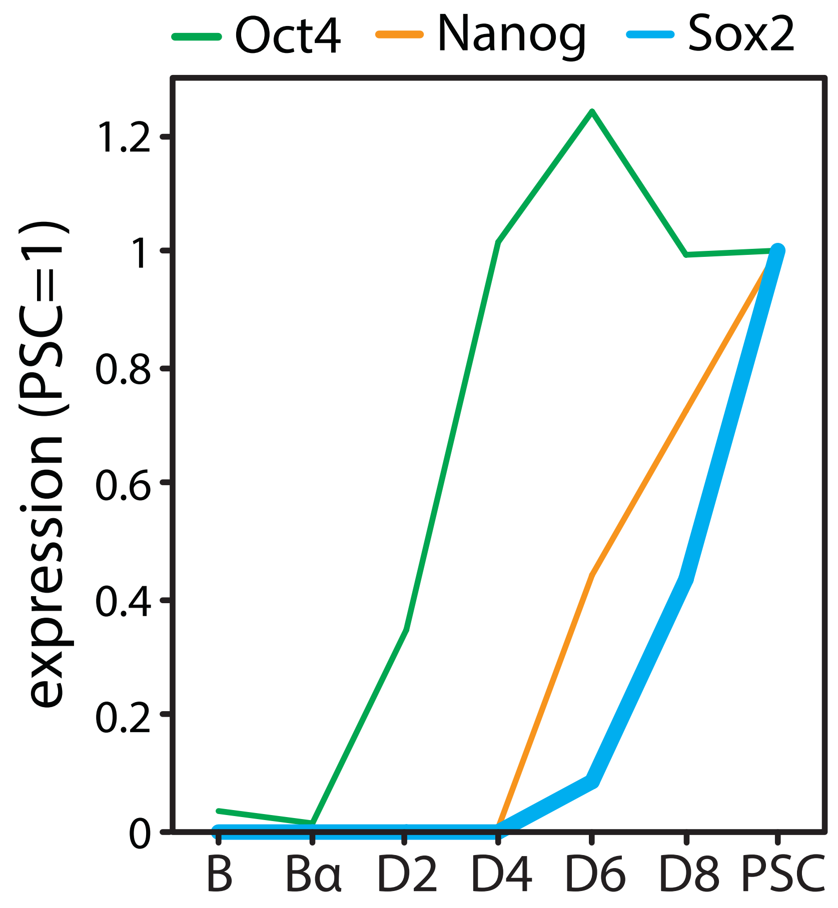
Reprogramming from B to PSC

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



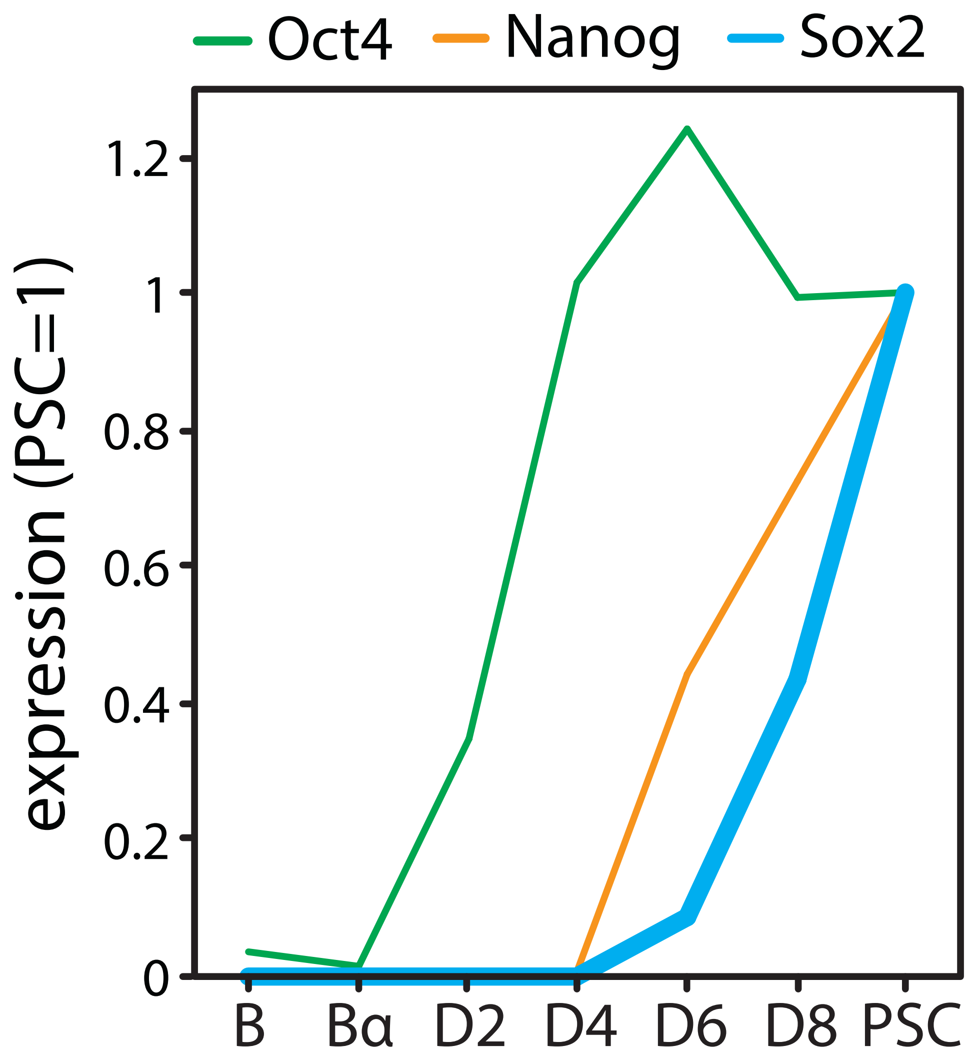


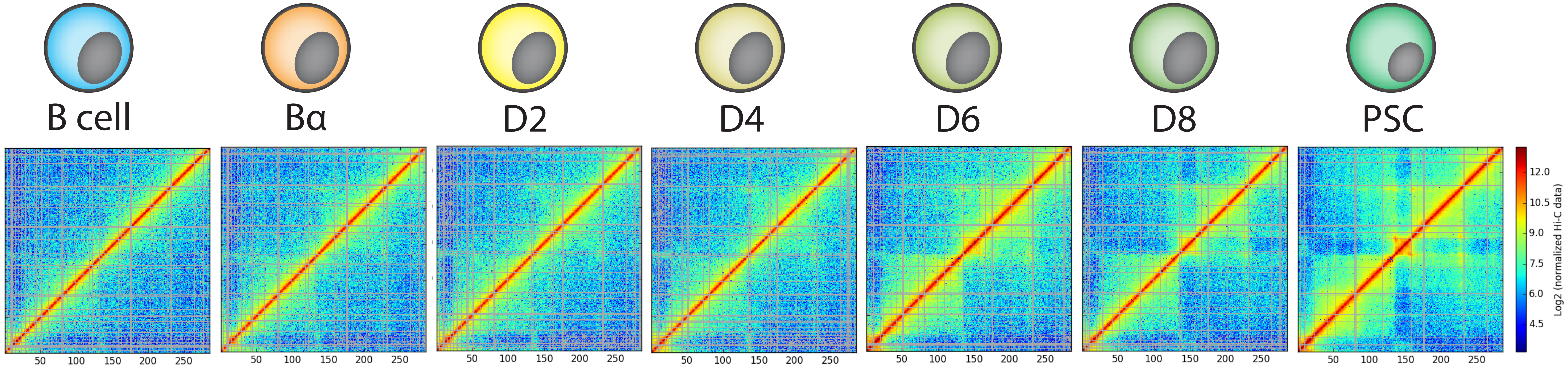




Hi-C maps of reprogramming from B to PSC

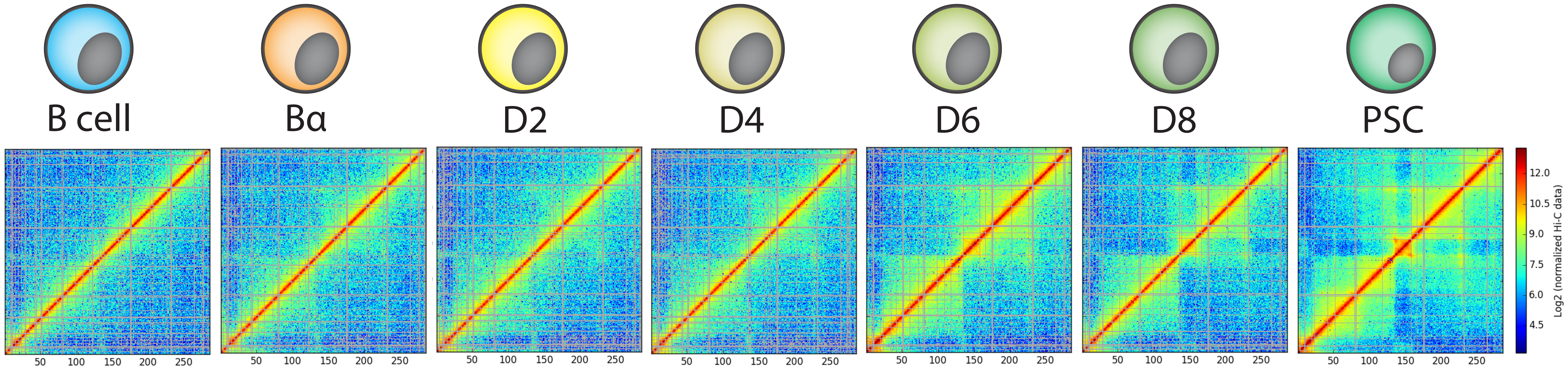
The SOX2 locus





Hi-C maps of reprogramming from B to PSC

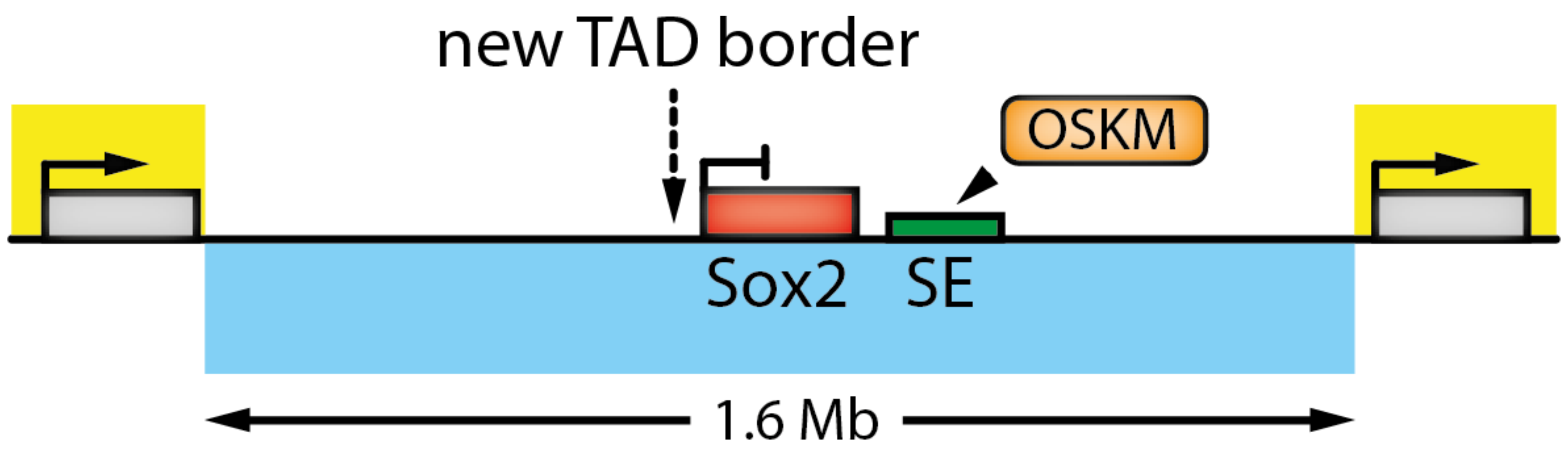
The SOX2 locus

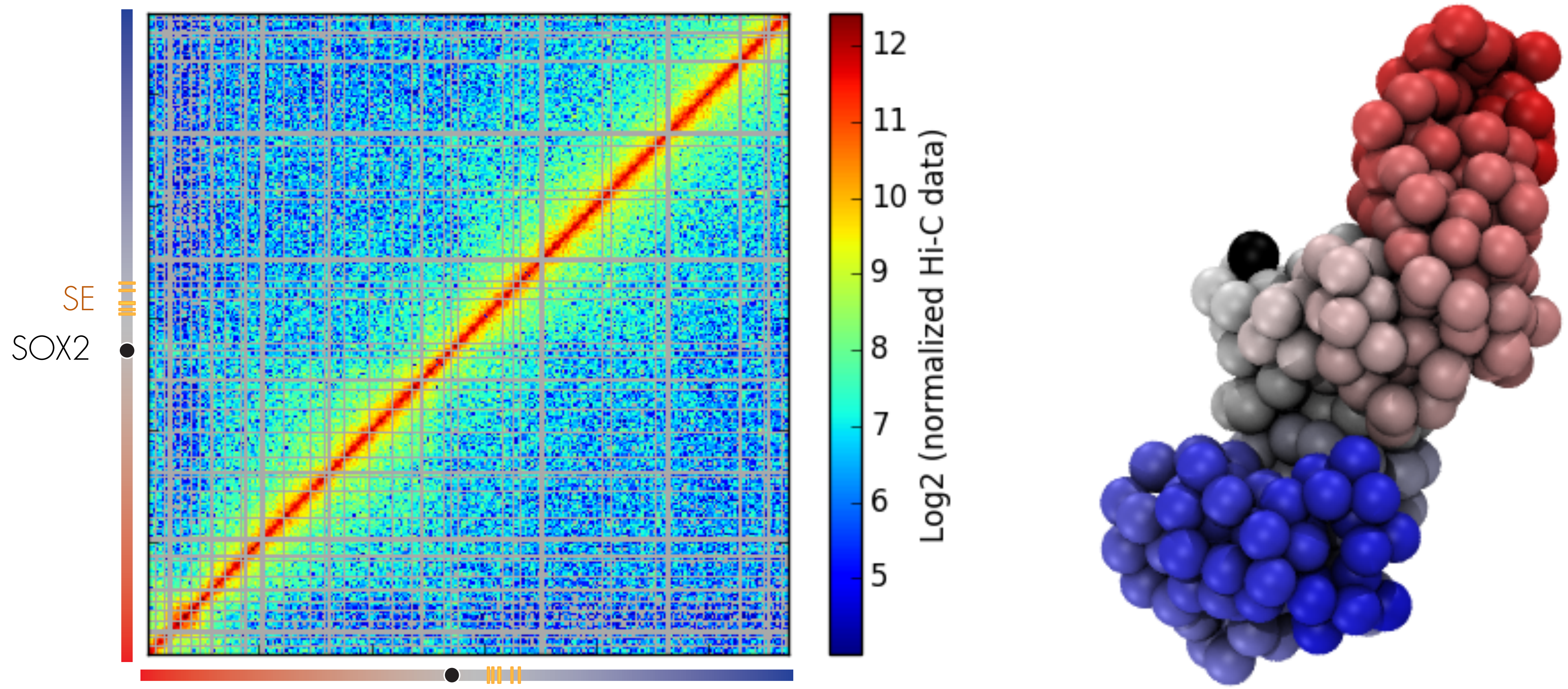


How does these structural rearrangements interplay with the transcription activity?

What are the main drivers of structural transitions?

TADbit modeling of SOX2 from B cells Hi-C



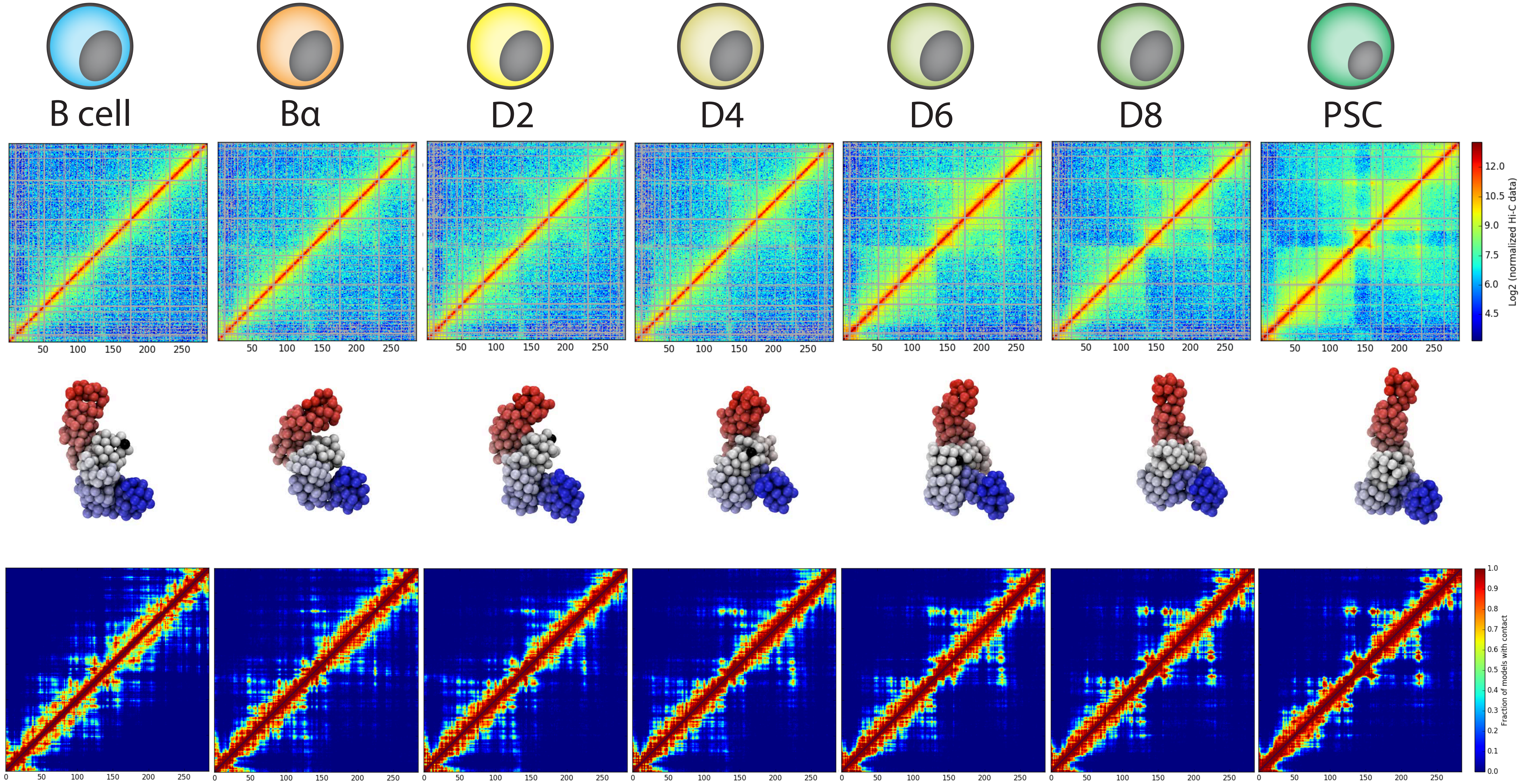


Optimal IMP parameters

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

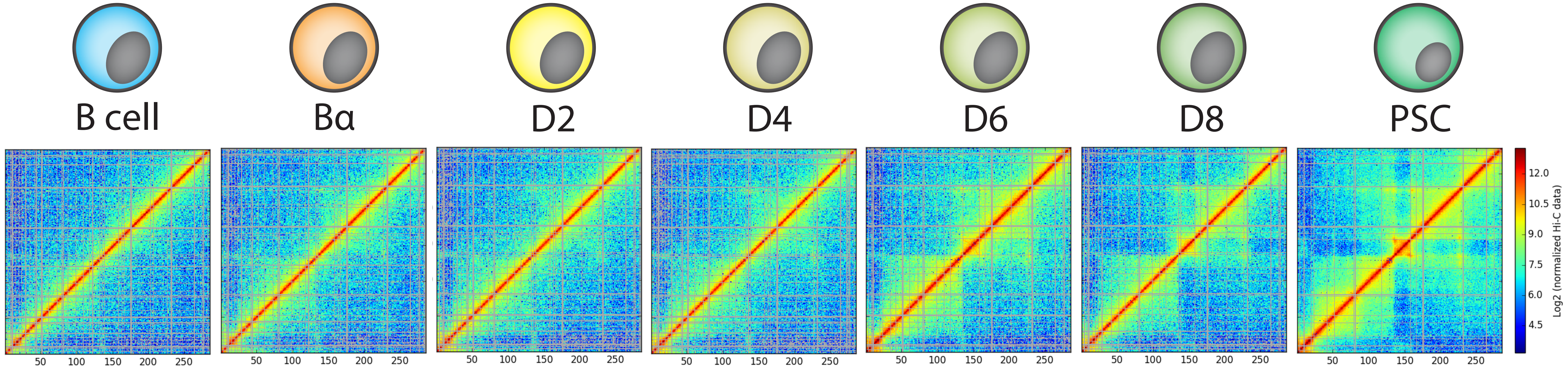
Models of reprogramming from B to PSC

The SOX2 locus



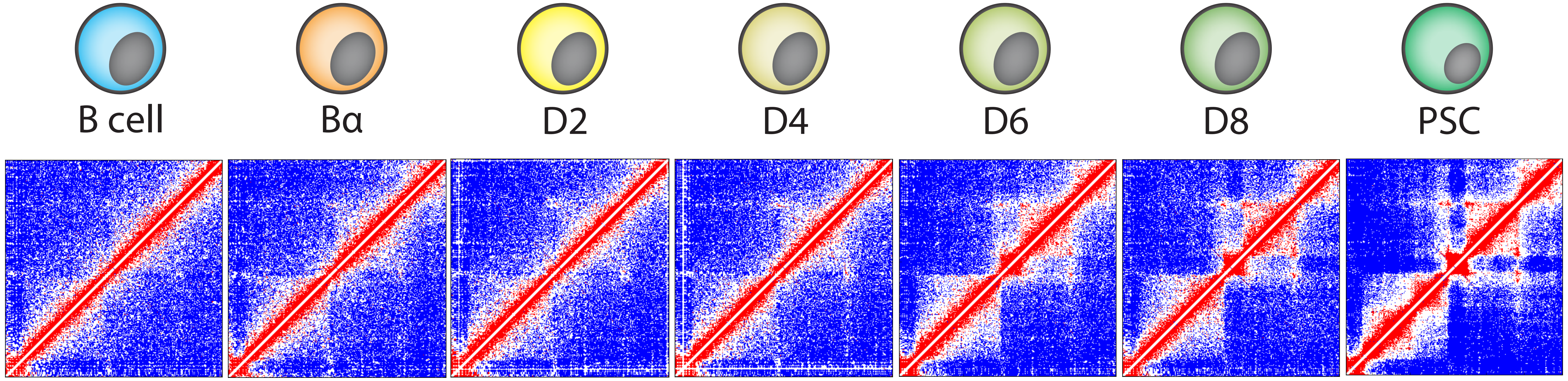
TADdyn: from time-series Hi-C maps to dynamic restraints

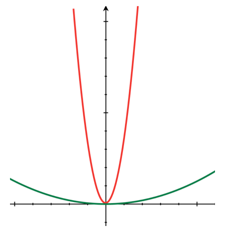
The SOX2 locus



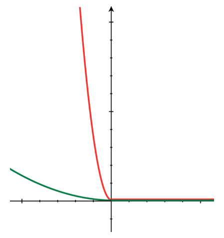
TADdyn: from time-series Hi-C maps to dynamic restraints

The SOX2 locus





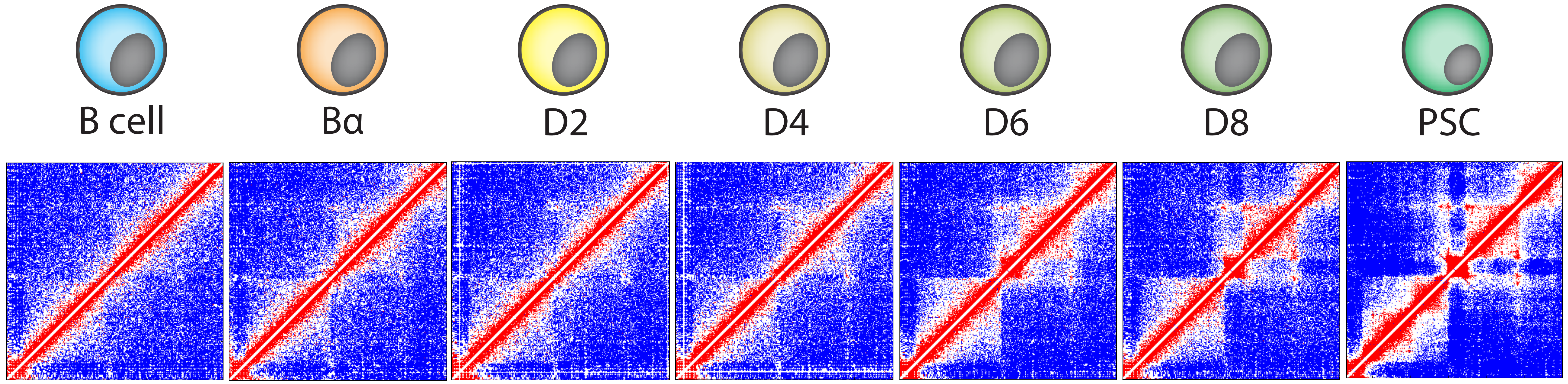
🟥 Harmonic

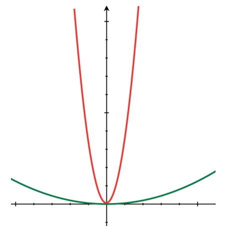


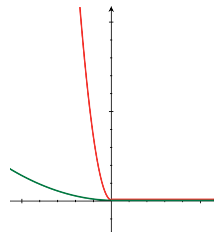
🟦 HarmonicLowerBound

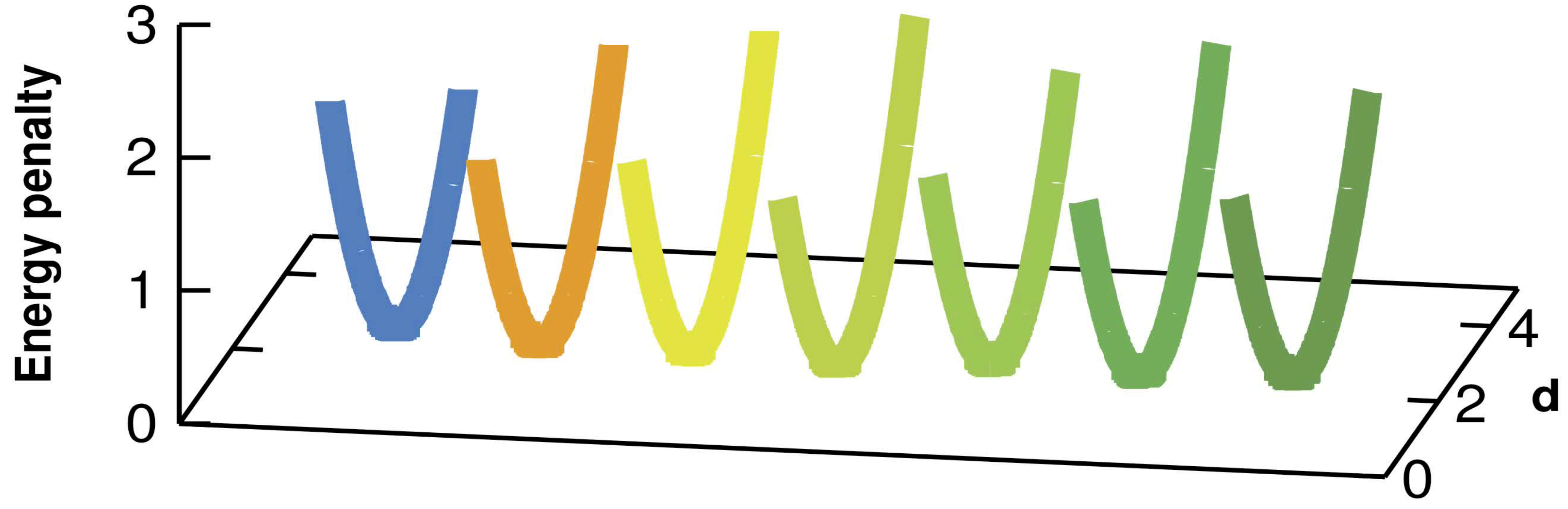
TADdyn: from time-series Hi-C maps to dynamic restraints

The SOX2 locus



 🟥 Harmonic

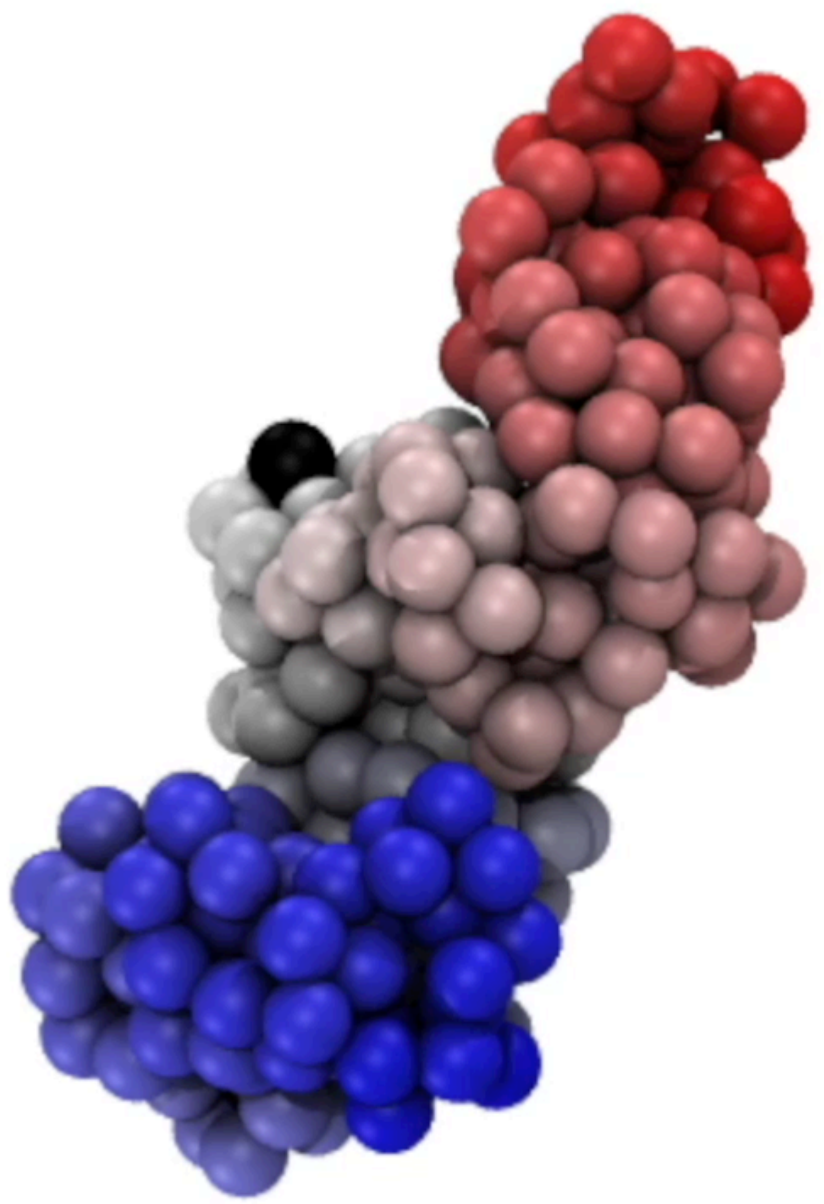
 🟦 HarmonicLowerBound

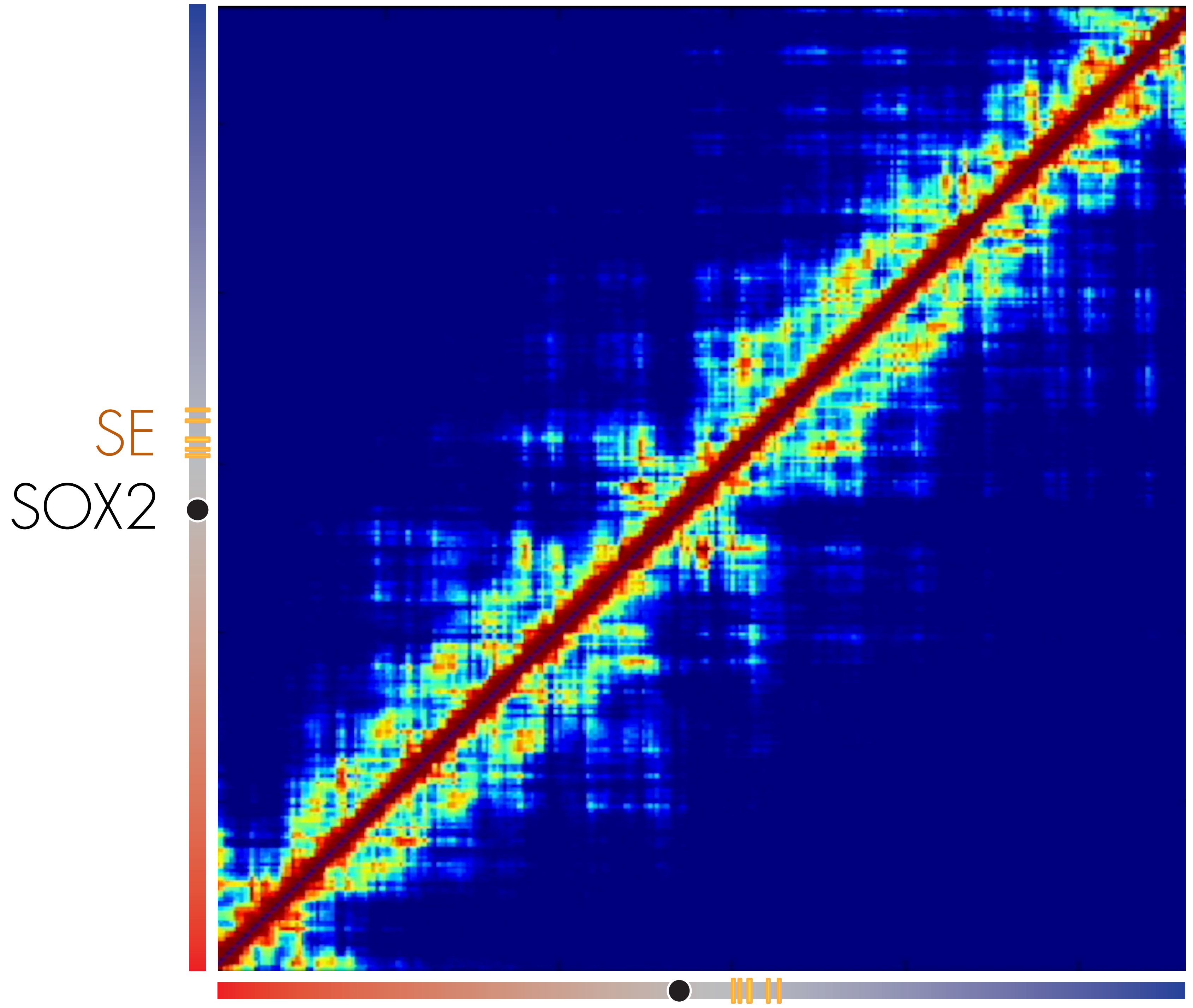


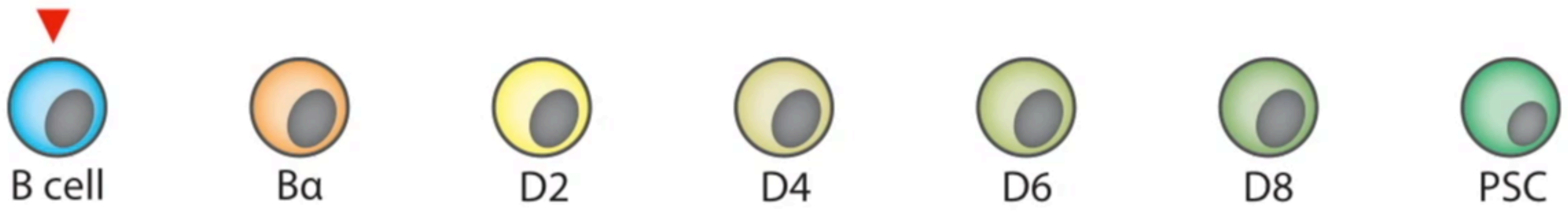
Transition	Stable	Vanishing	Raising
B -> Bα	18,612	6,984	7,290
Bα -> D2	18,512	7,390	6,687
D2 -> D4	18,369	6,830	6,893
D4 -> D6	18,971	6,291	7,289
D6 -> D8	20,167	6,093	6,250
D8 -> ES	20,679	5,738	6,173

SOX2 locus structural changes from B to PSC

Contacts

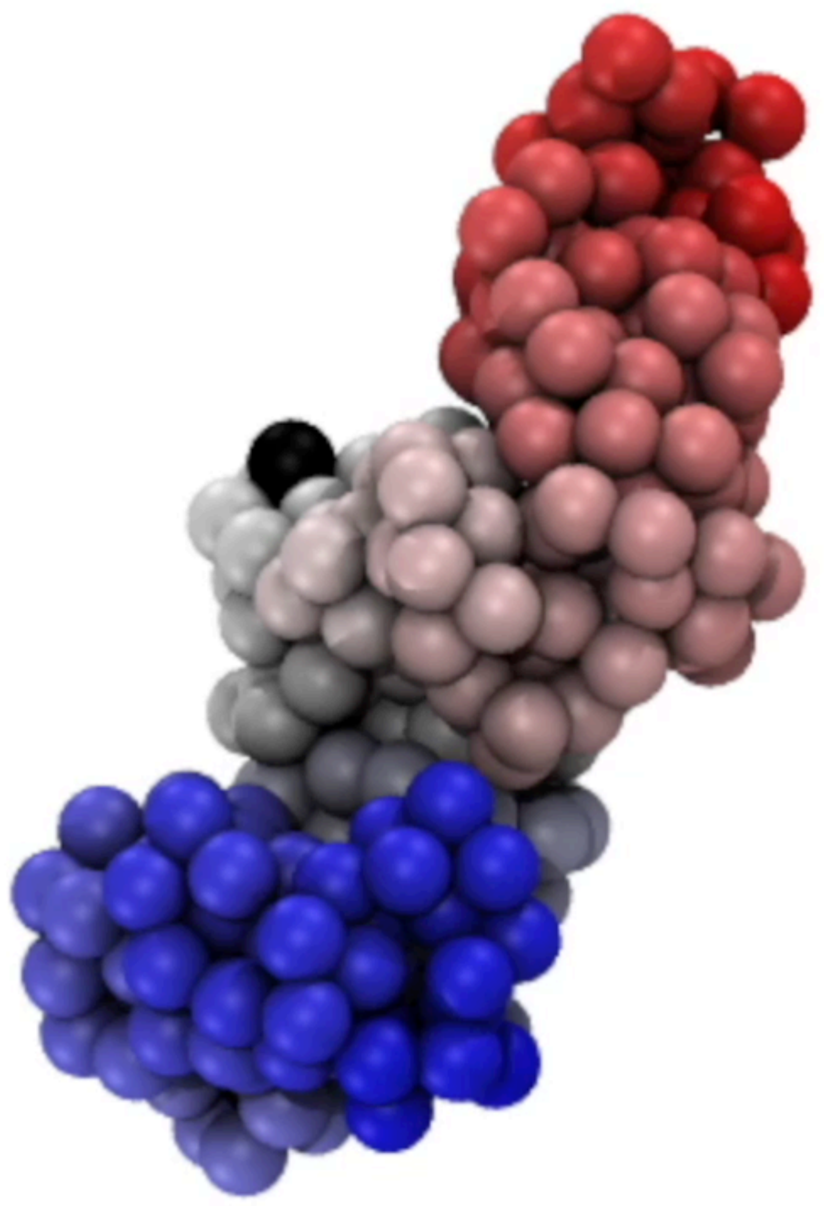


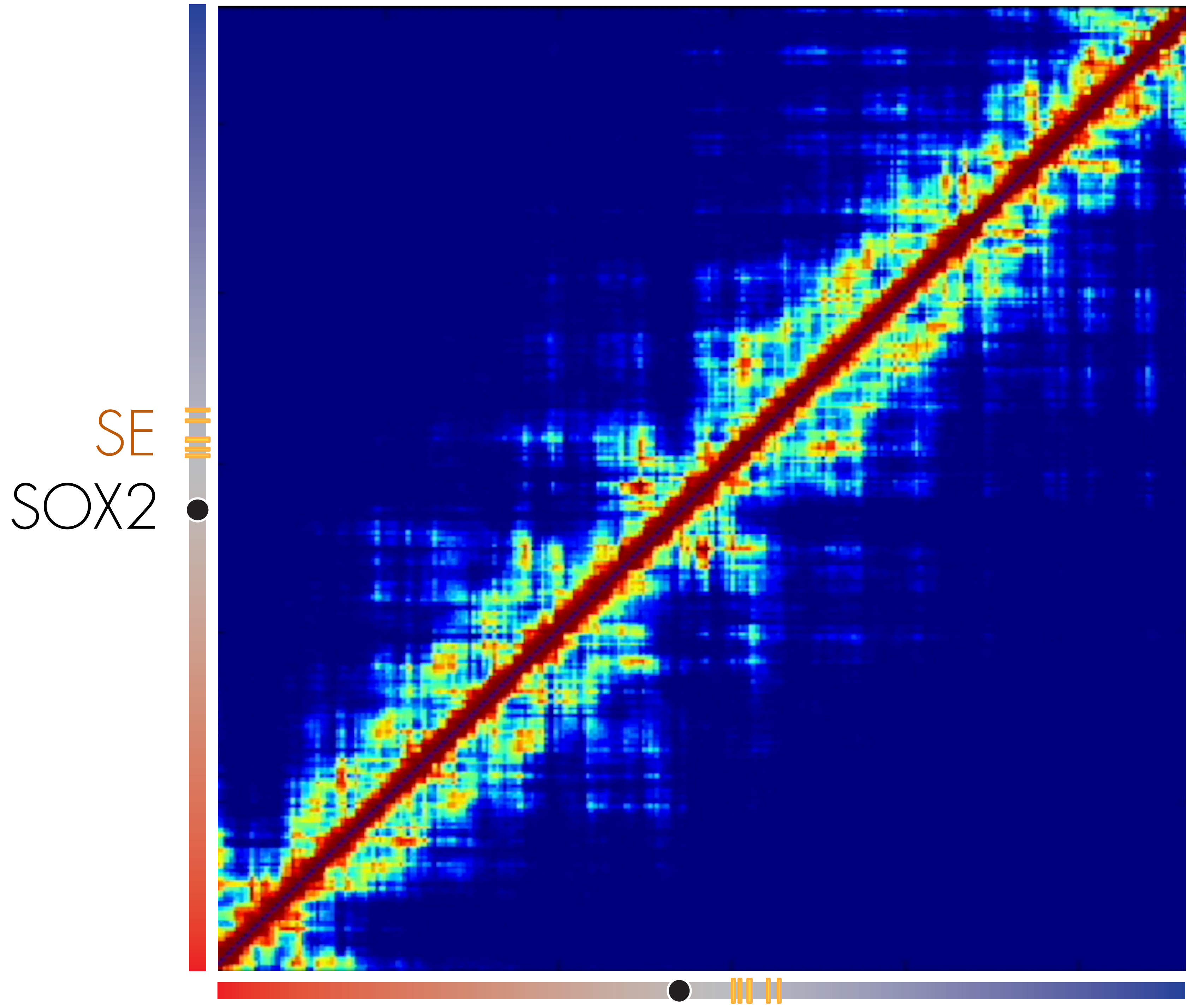




SOX2 locus structural changes from B to PSC

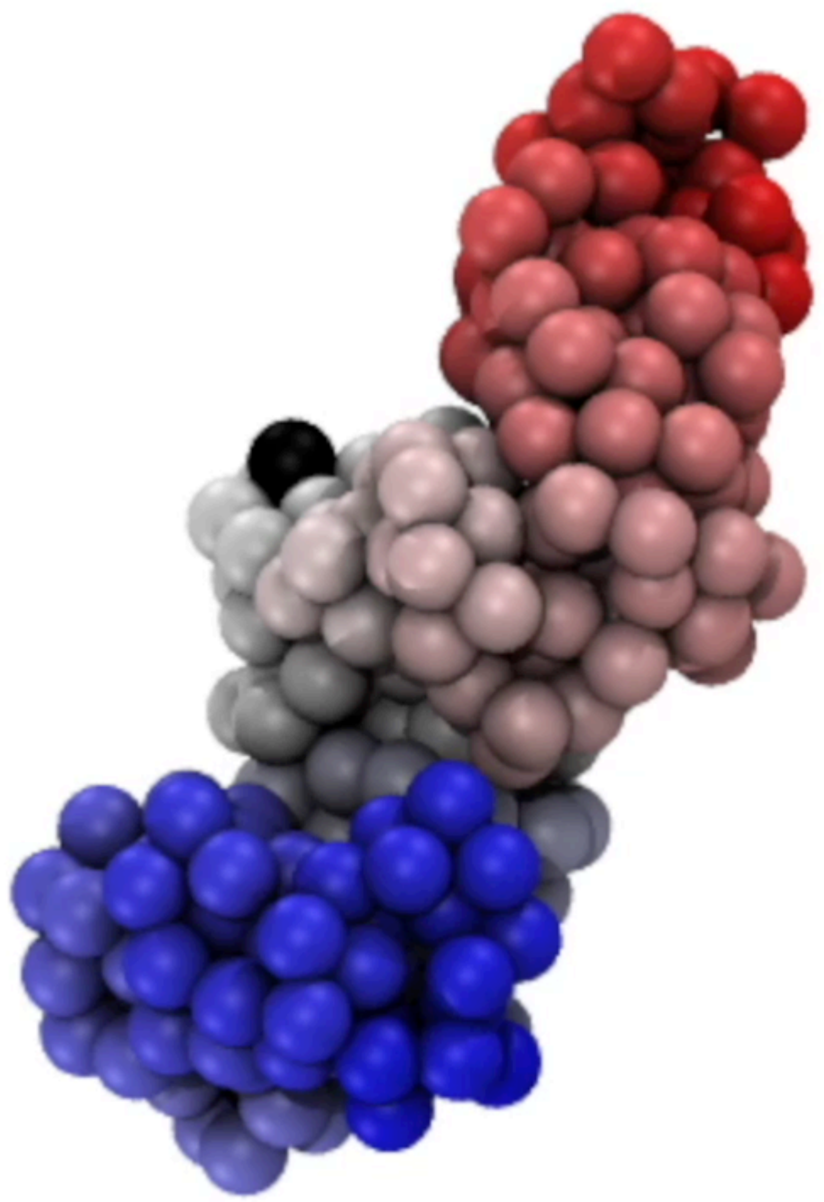
Contacts

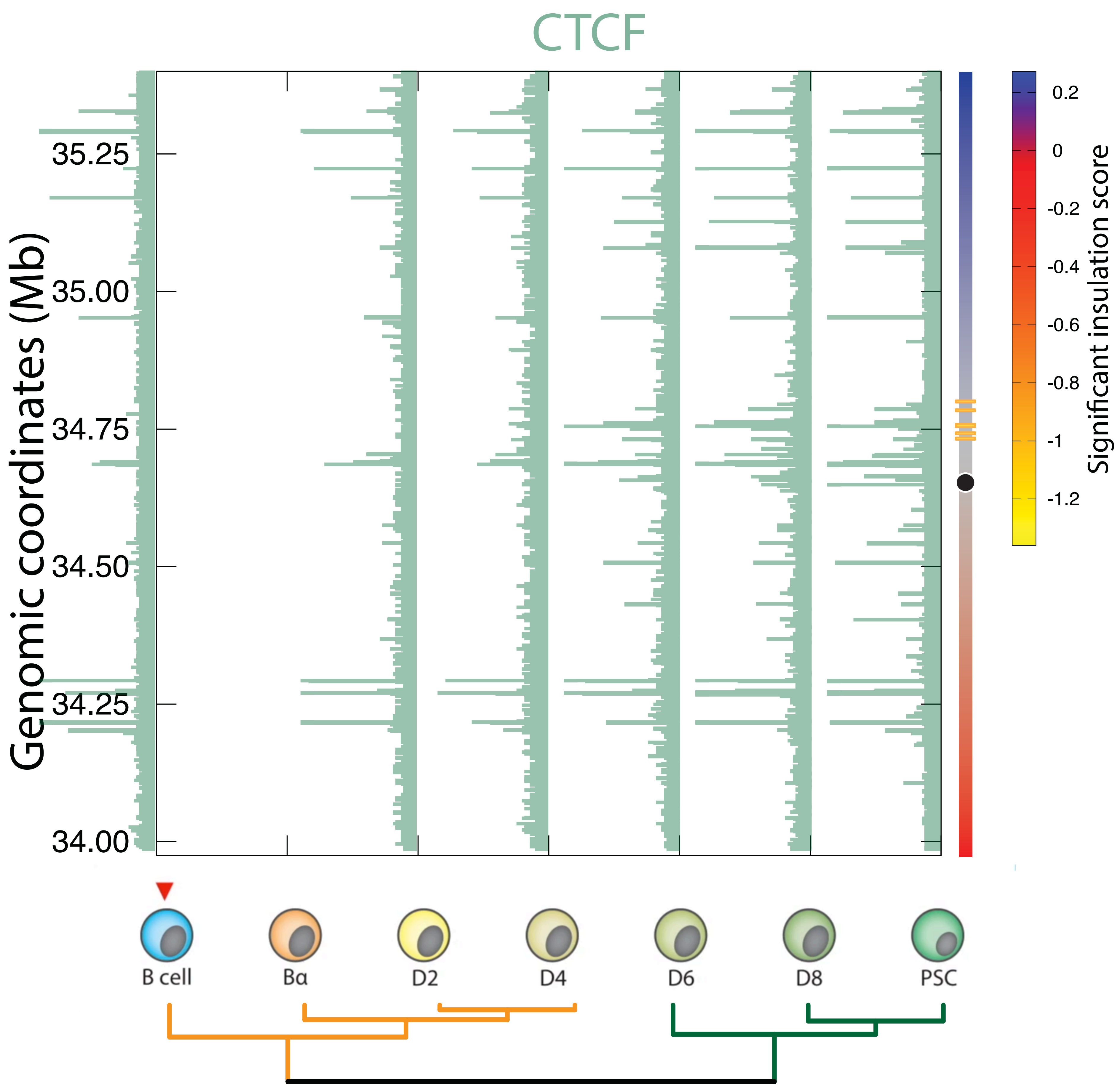




SOX2 locus structural changes from B to PSC

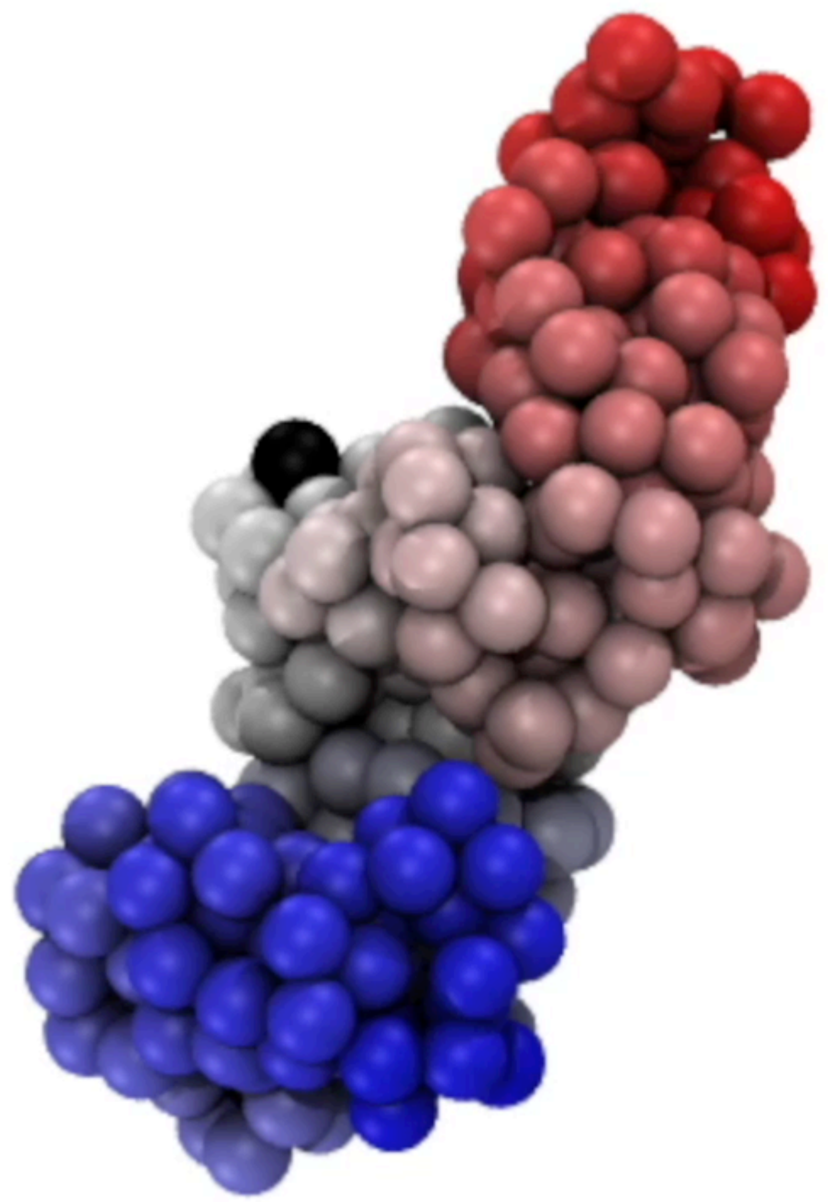
TAD borders

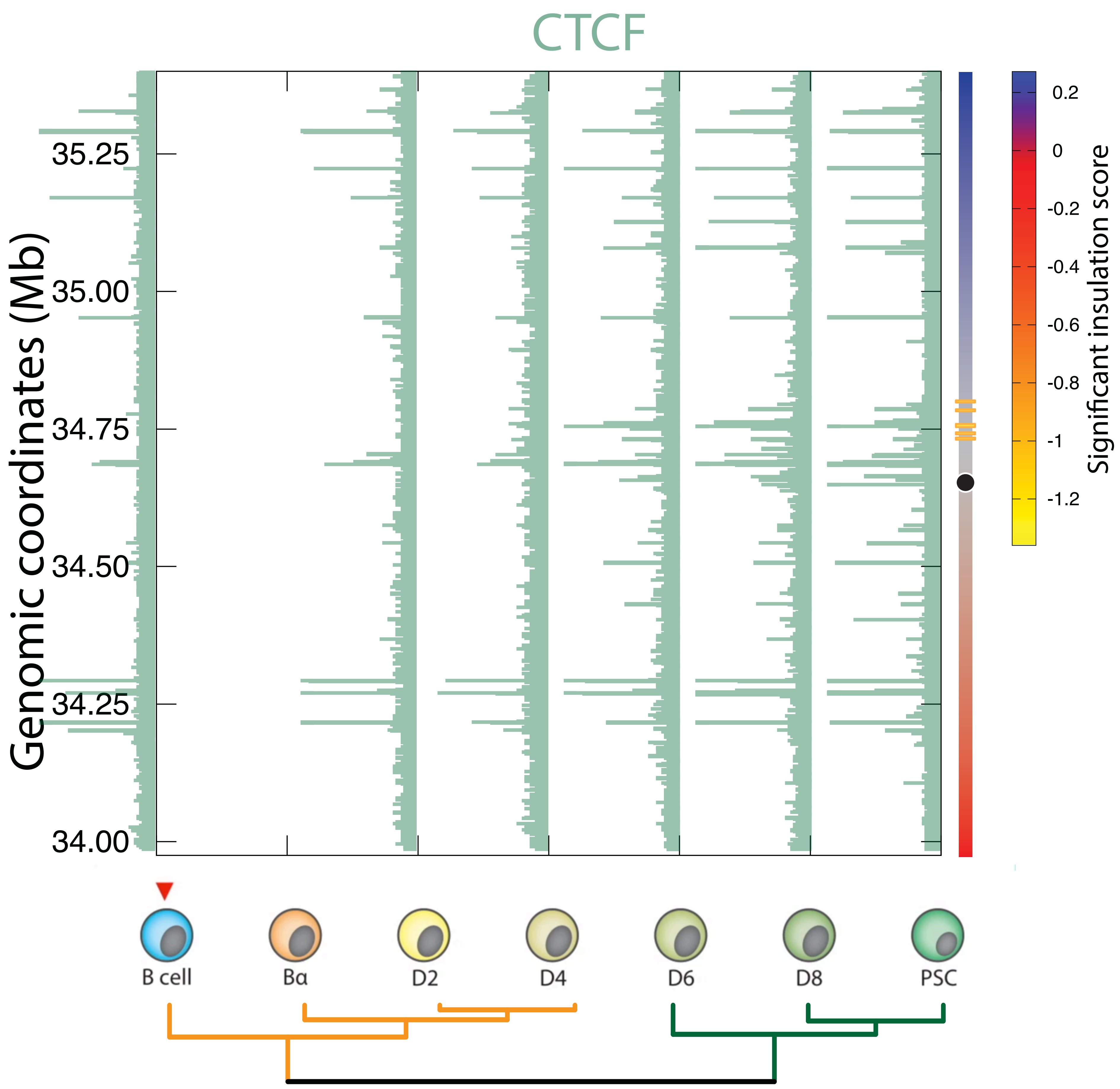




SOX2 locus structural changes from B to PSC

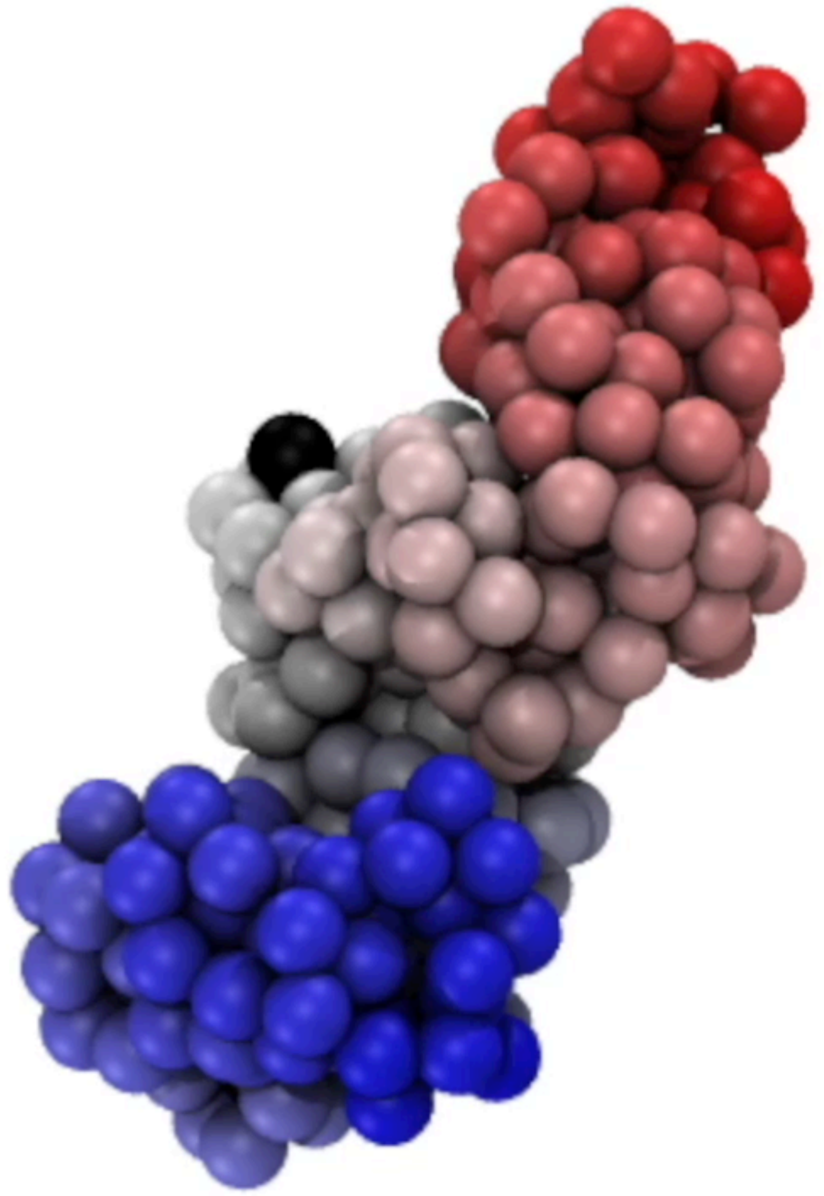
TAD borders

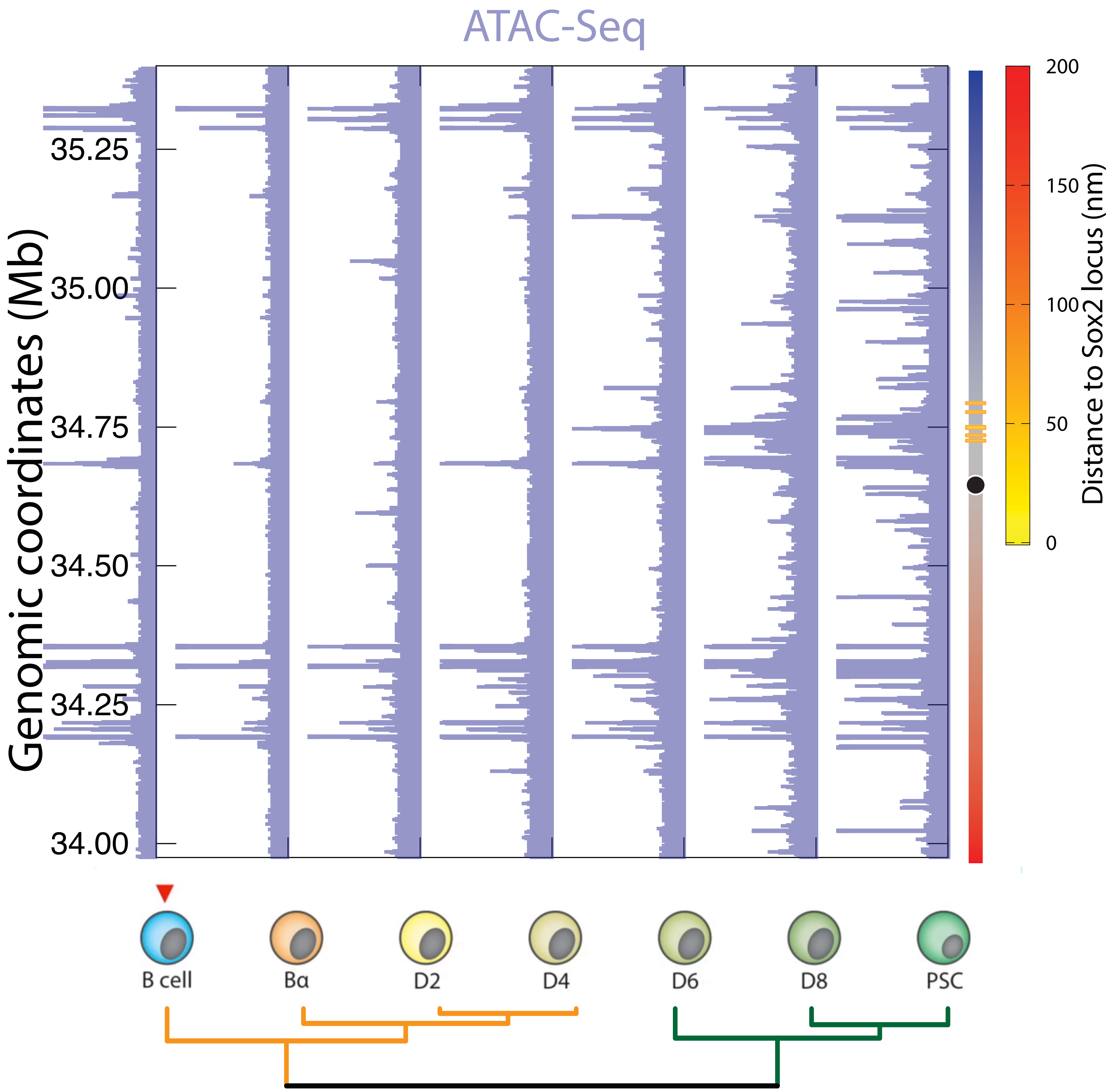




SOX2 locus structural changes from B to PSC

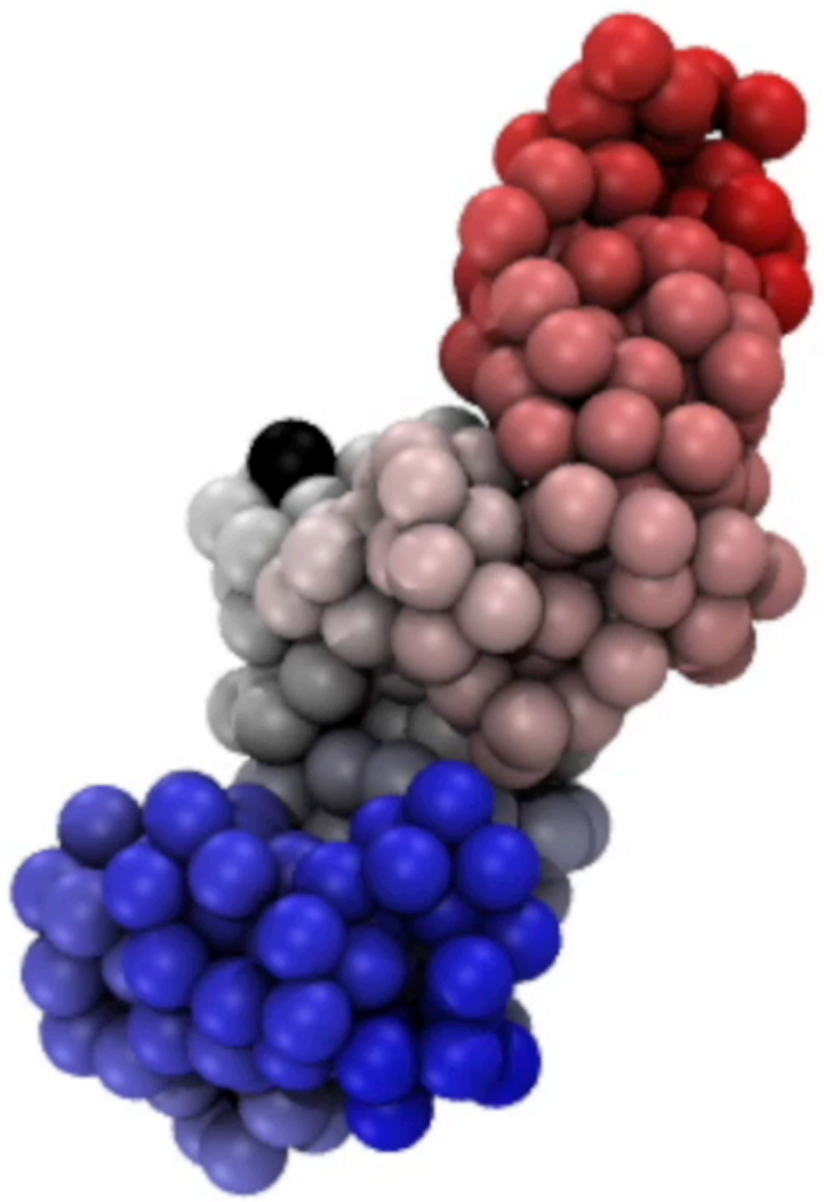
Distance to regulatory elements

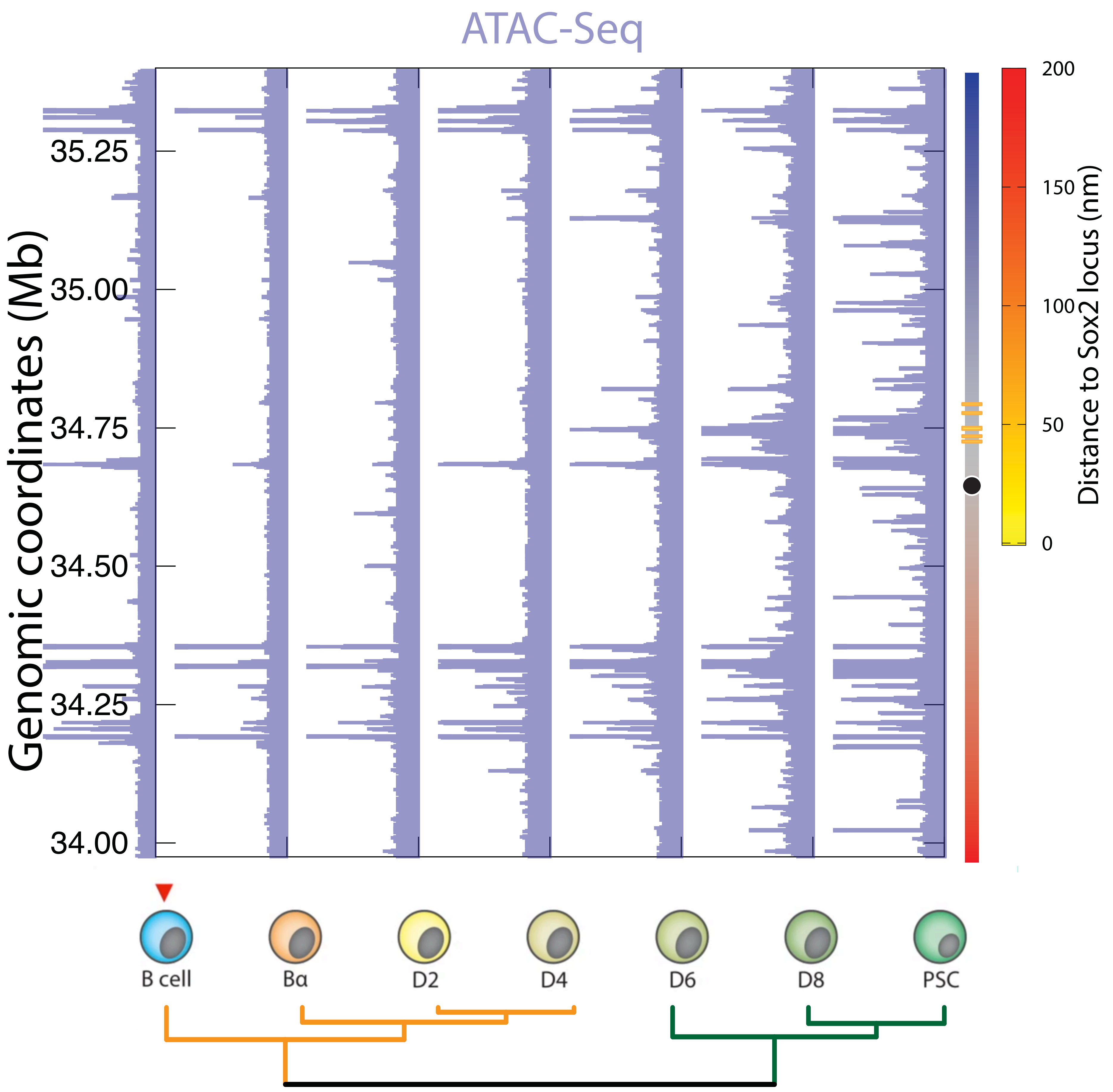




SOX2 locus structural changes from B to PSC

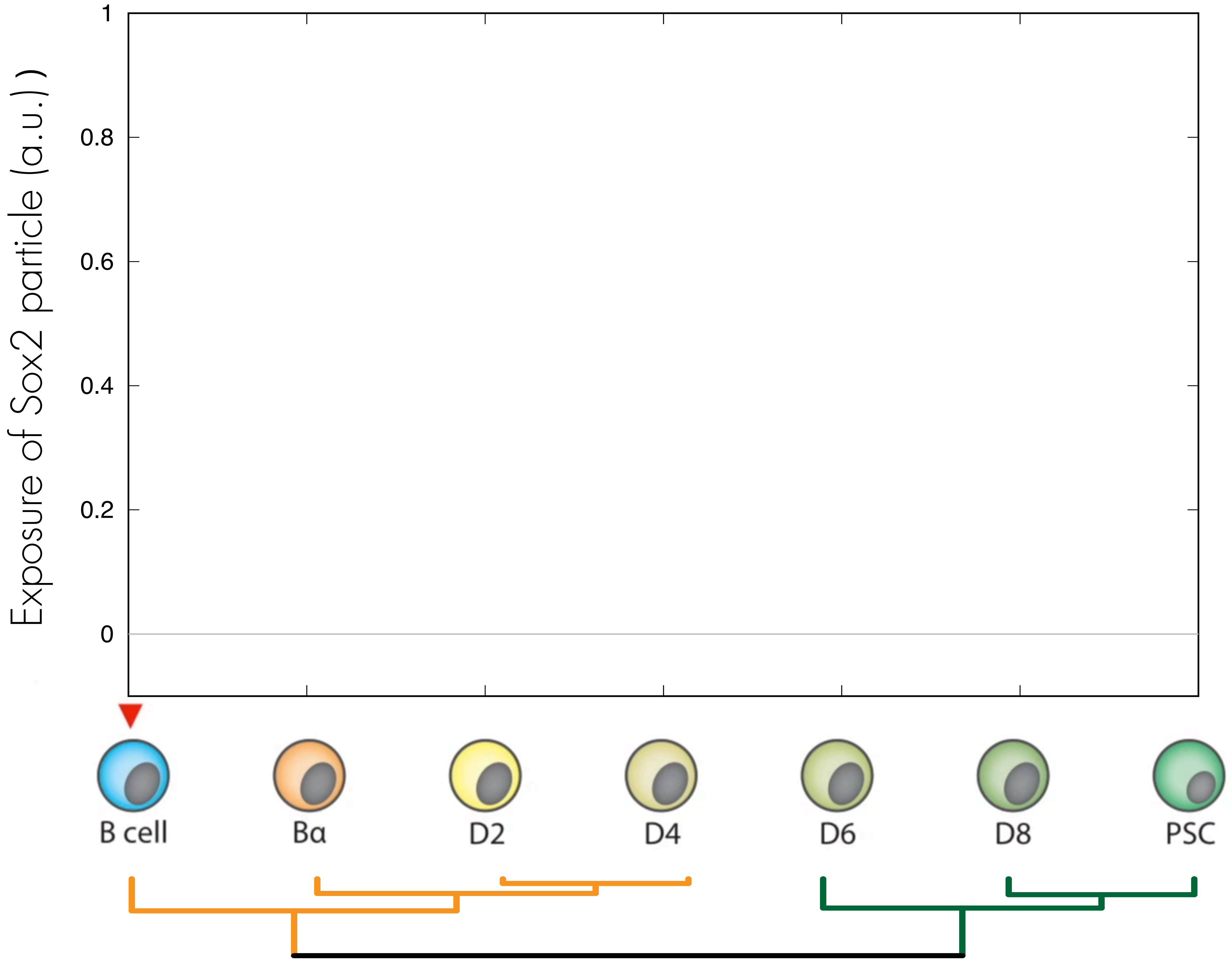
Distance to regulatory elements





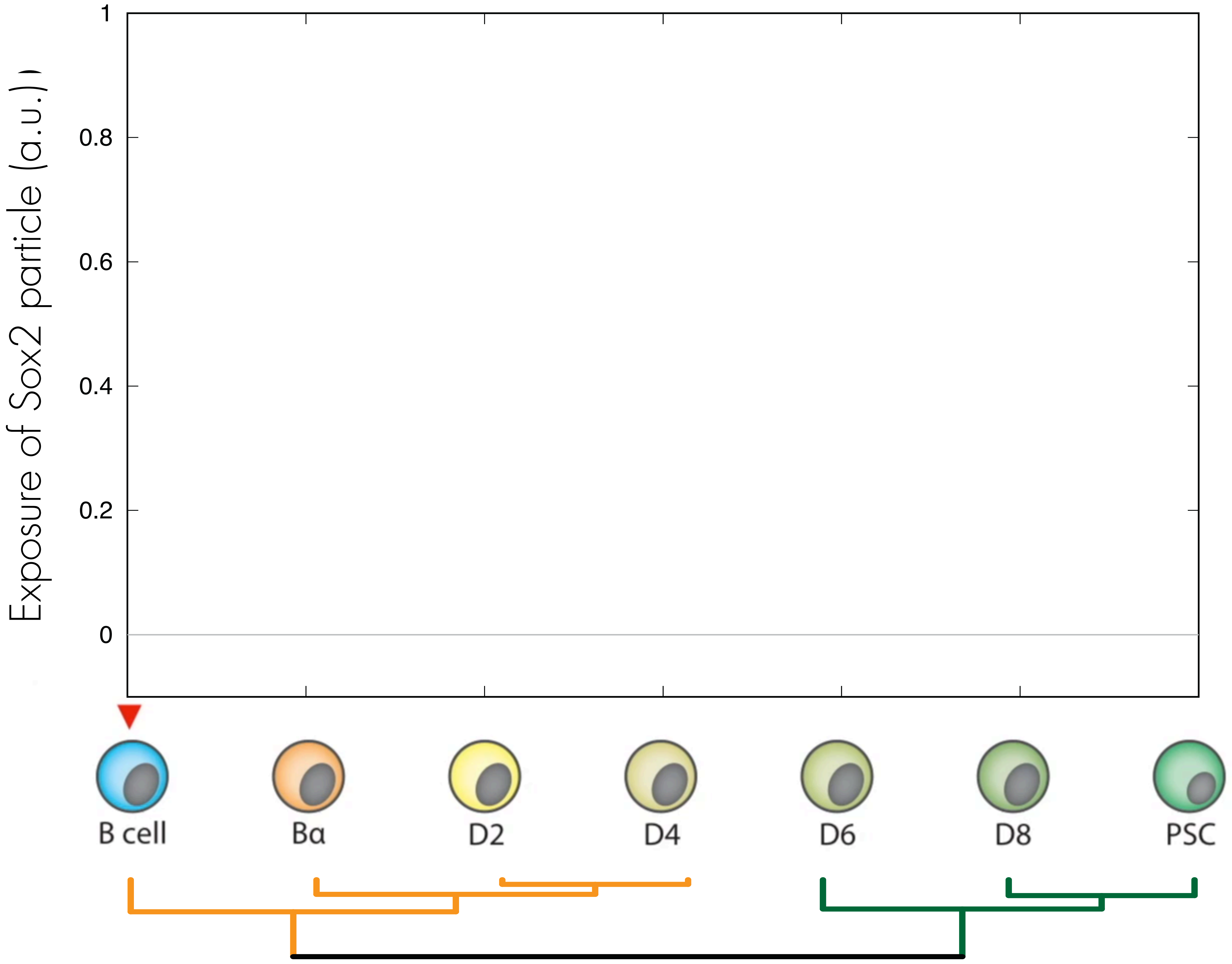
SOX2 locus structural changes from B to PSC

Structural exposure



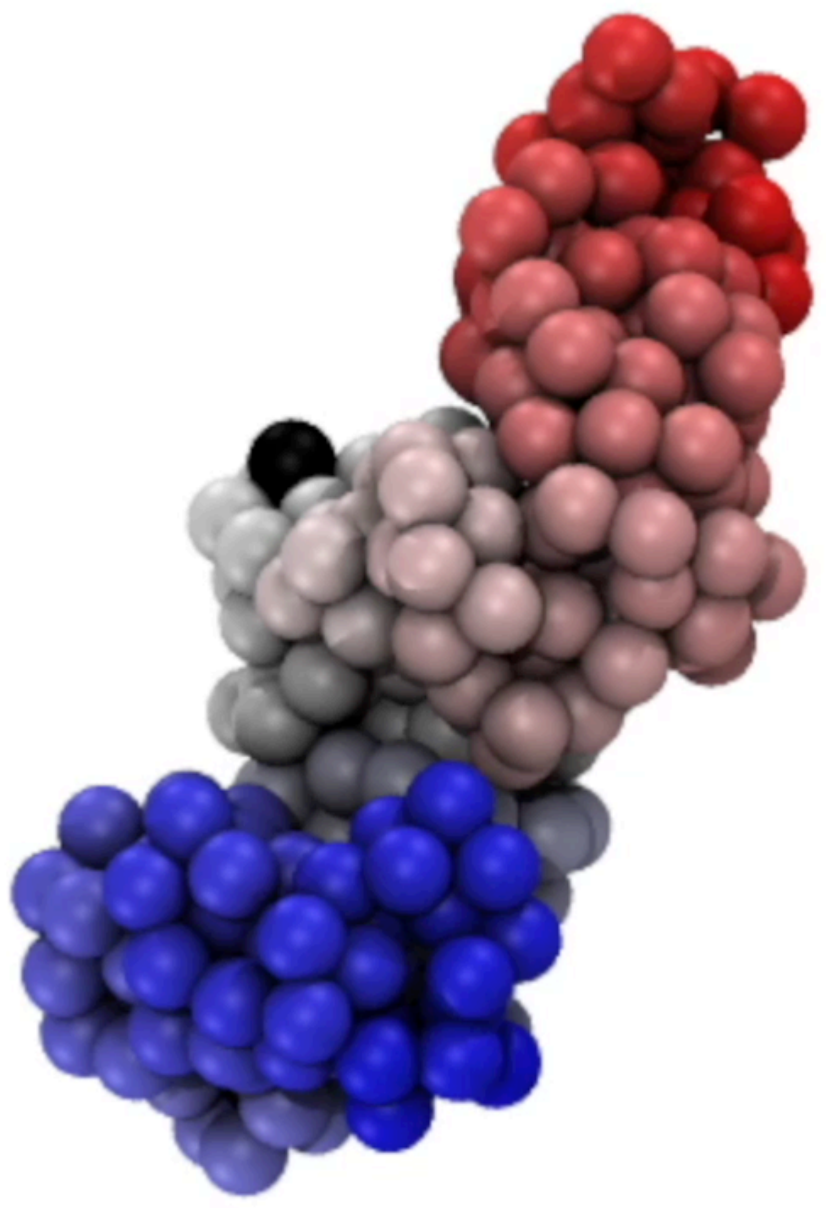
SOX2 locus structural changes from B to PSC

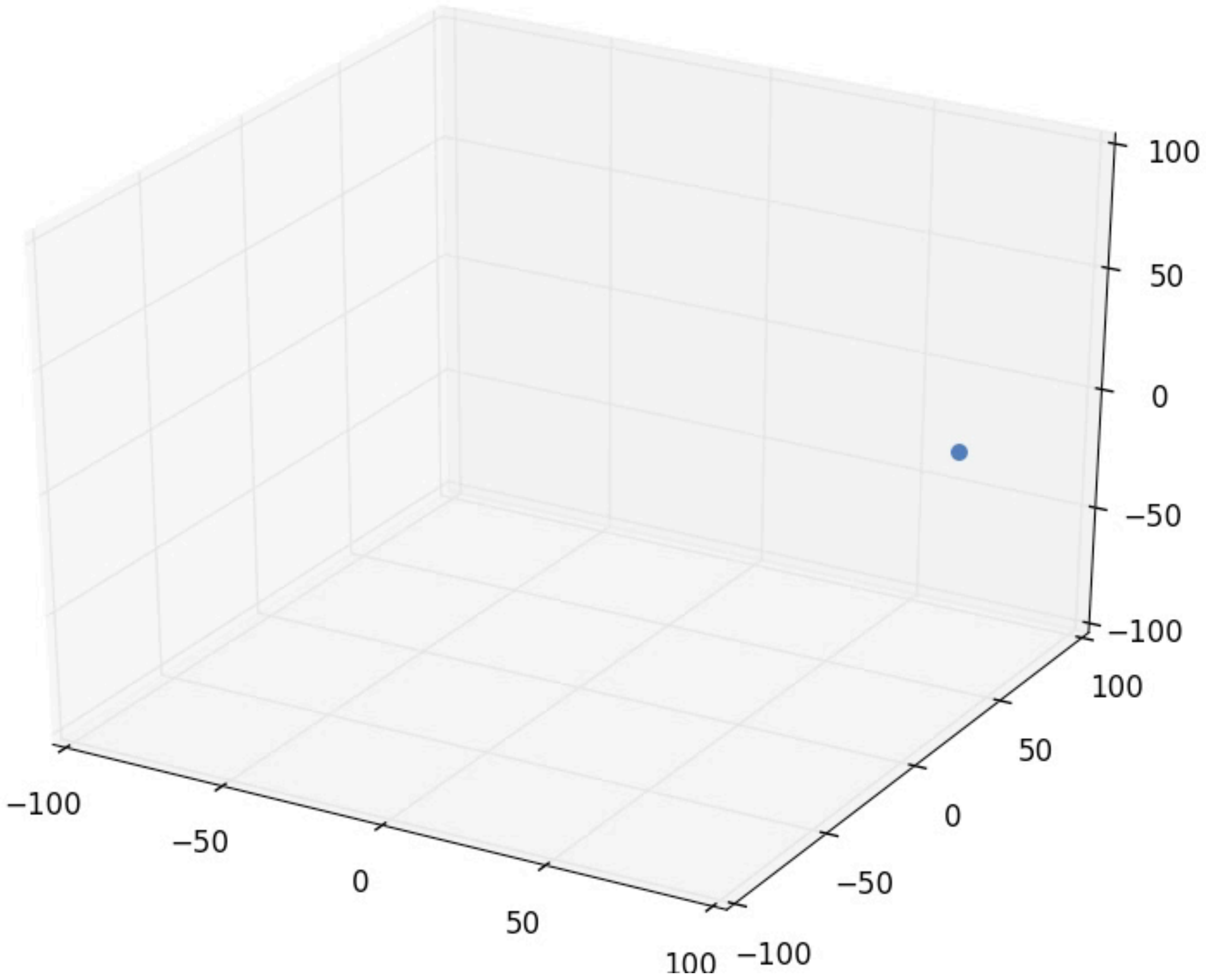
Structural exposure

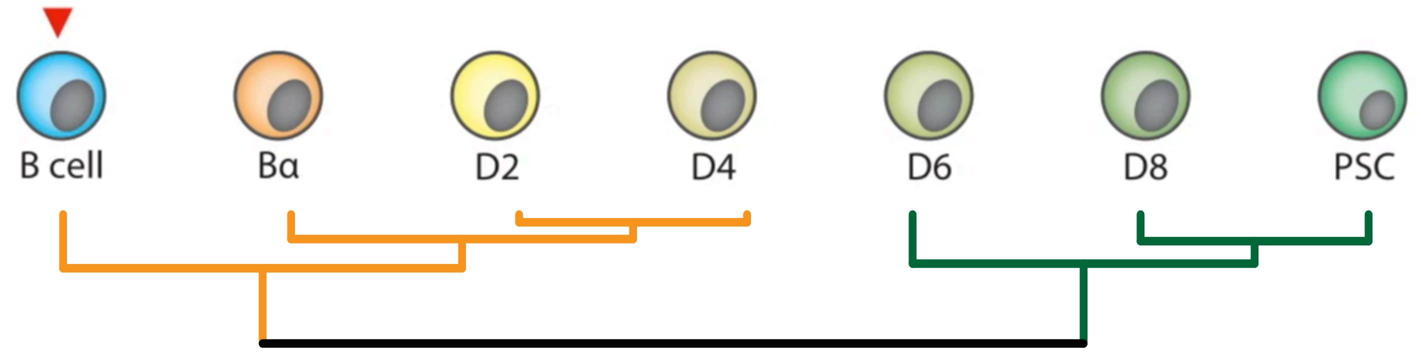


SOX2 locus dynamics changes from B to PSC

SOX2 displacement

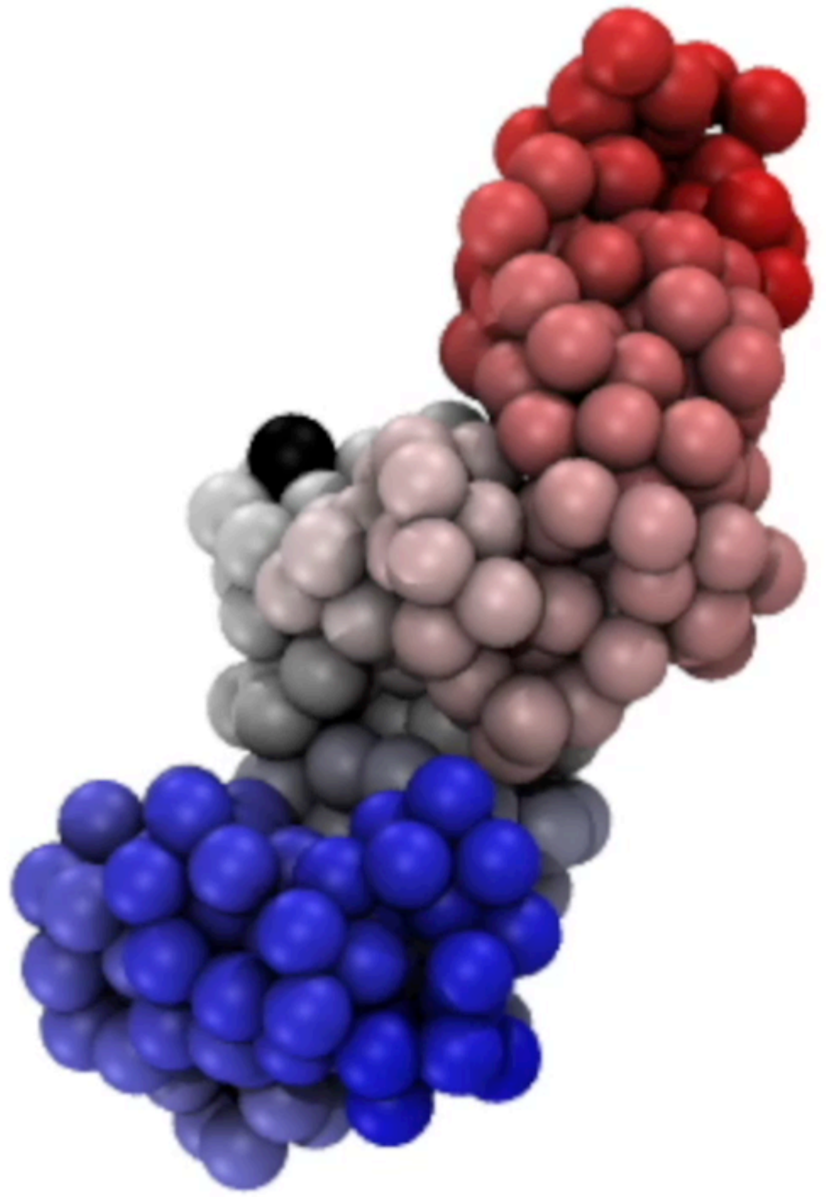


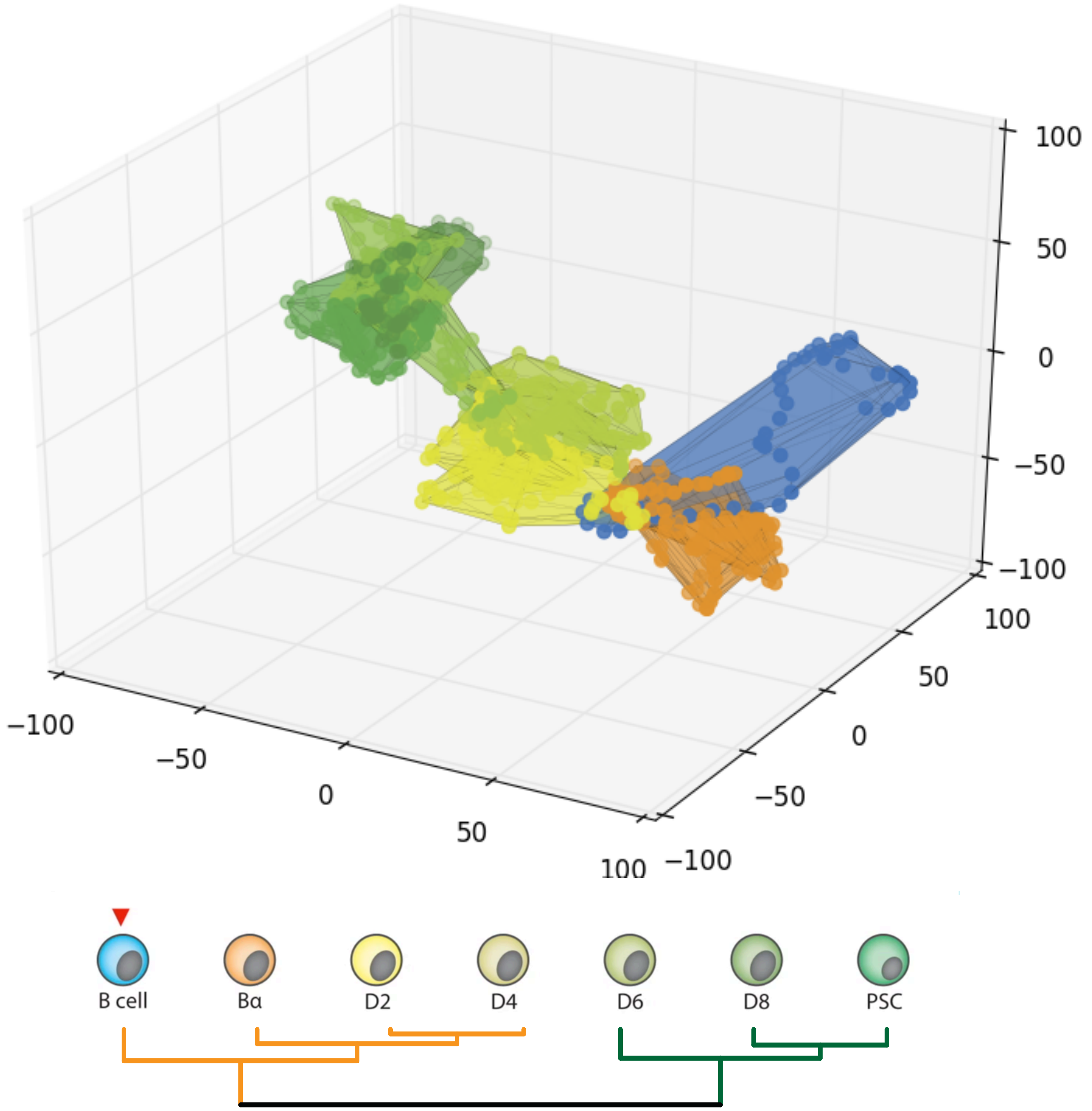




SOX2 locus dynamics changes from B to PSC

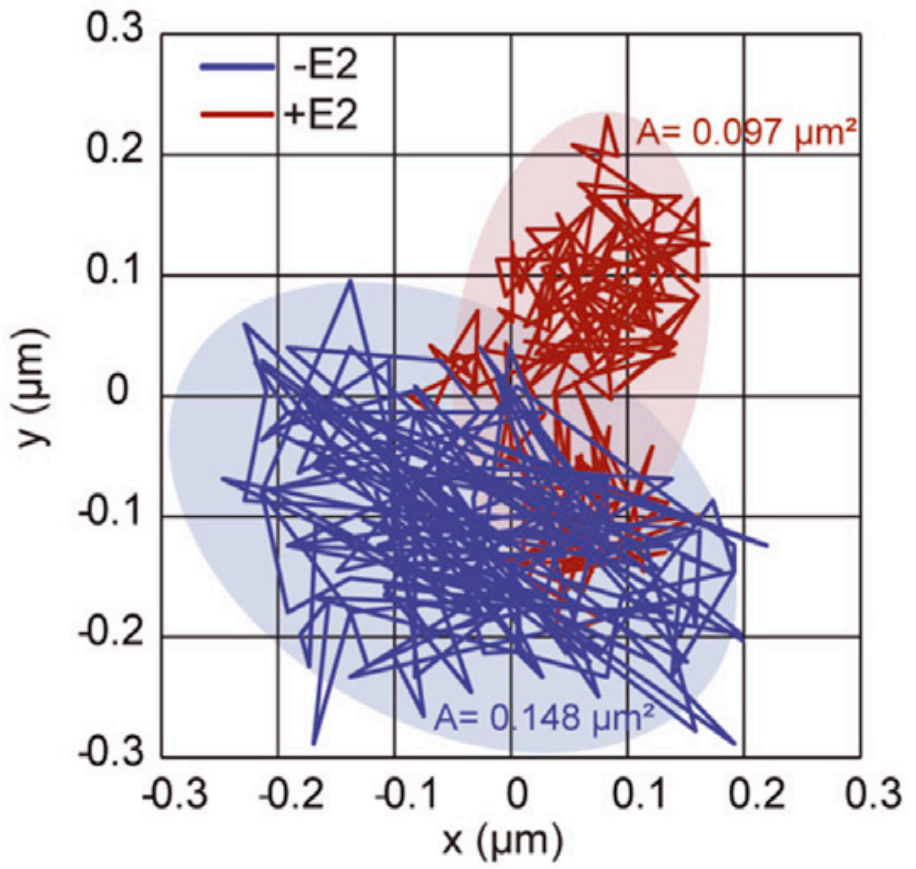
SOX2 displacement





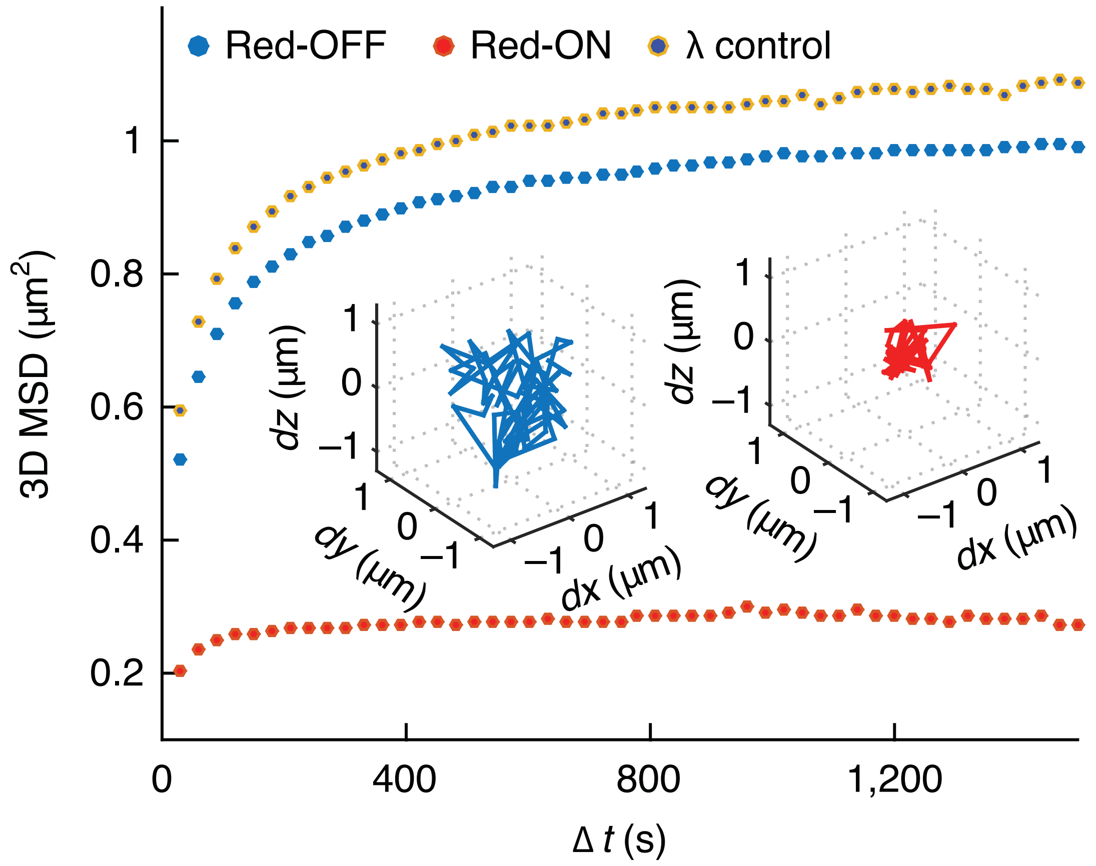
SOX2 locus dynamics changes from B to PSC

SOX2 displacement



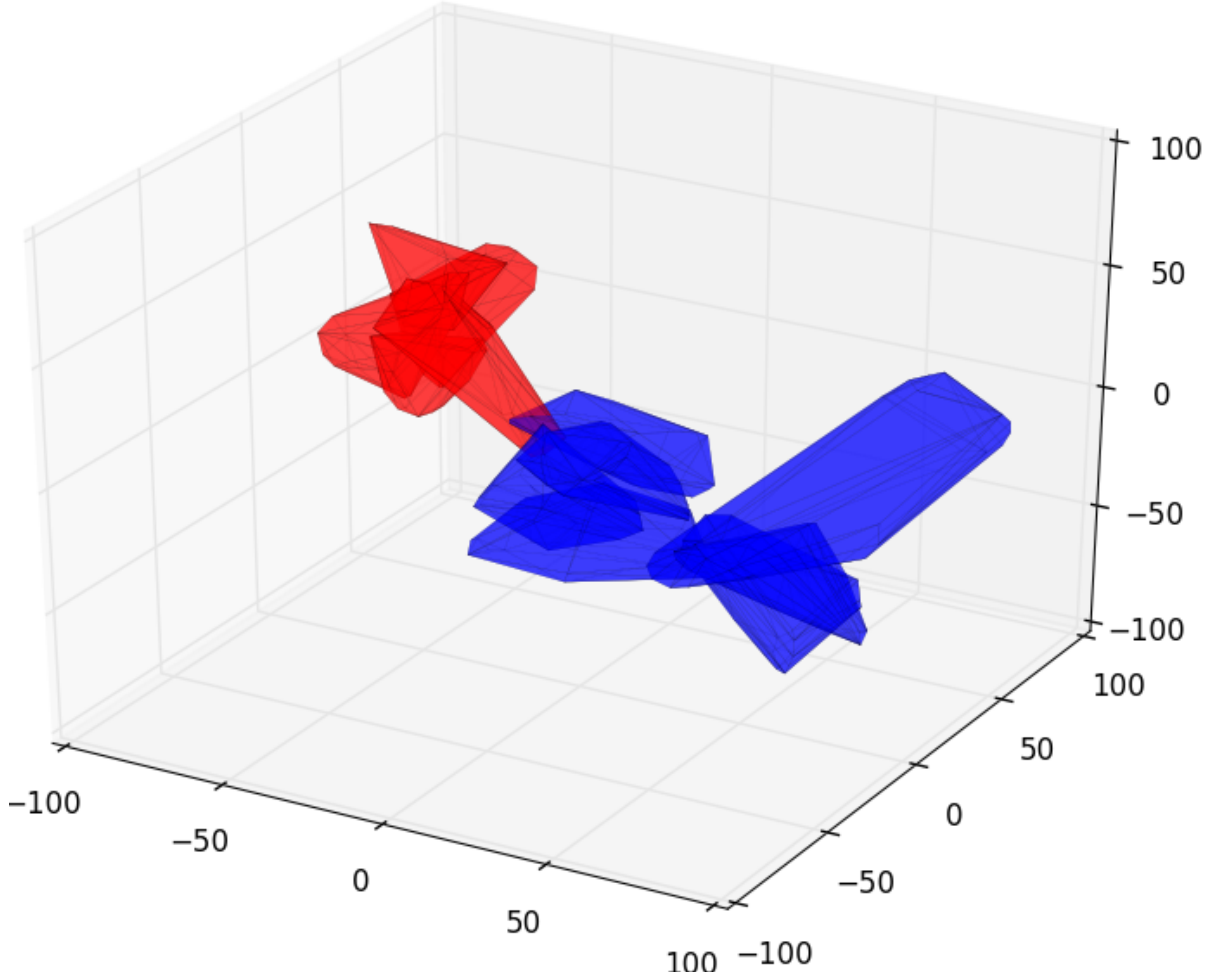
Two dimensional trajectories and area explored over 50s of the CCND1 locus recored before -E2 and after +E2 activation.

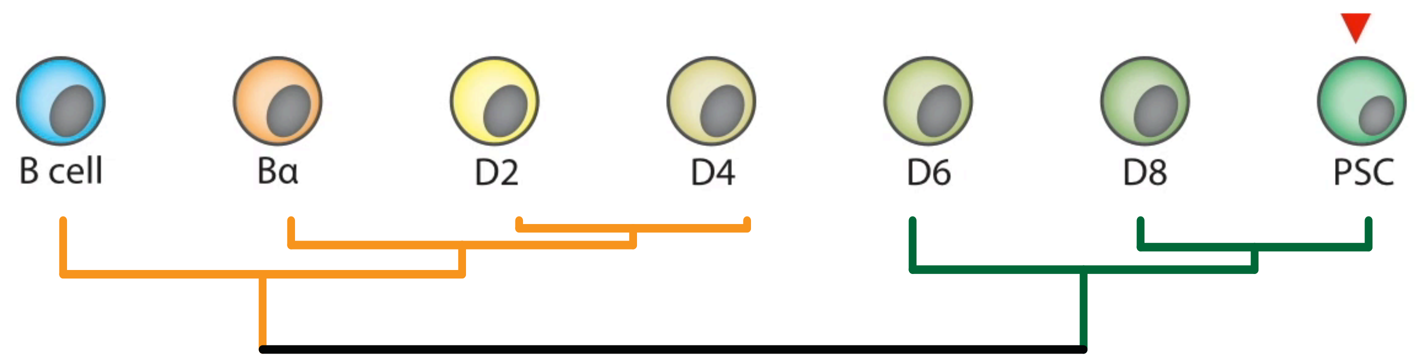
Germier ,T., et al, (2017) Blophys J.



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





A "hit-and-stick" model for transcriptional activation

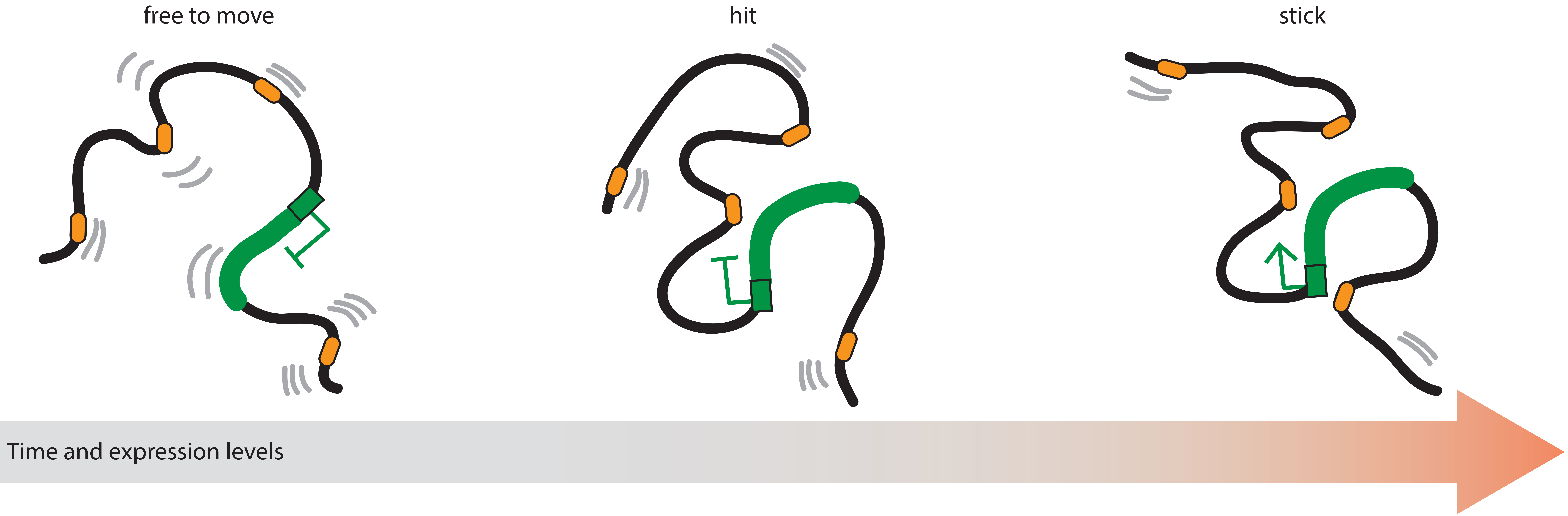



Photo by David Oliete - www.davidoliete.com

Chromosome walking with super-resolution imaging and modeling

Irene Farabella
Guy Nir
Cynthia Perez-Estrada
with Wu Lab (HMS, Boston) & Aiden Lab (UT, Texas)

PLOS Genetics (2018) 14(12) e1007872

Can we walk the chromatin path in the nucleus?

by

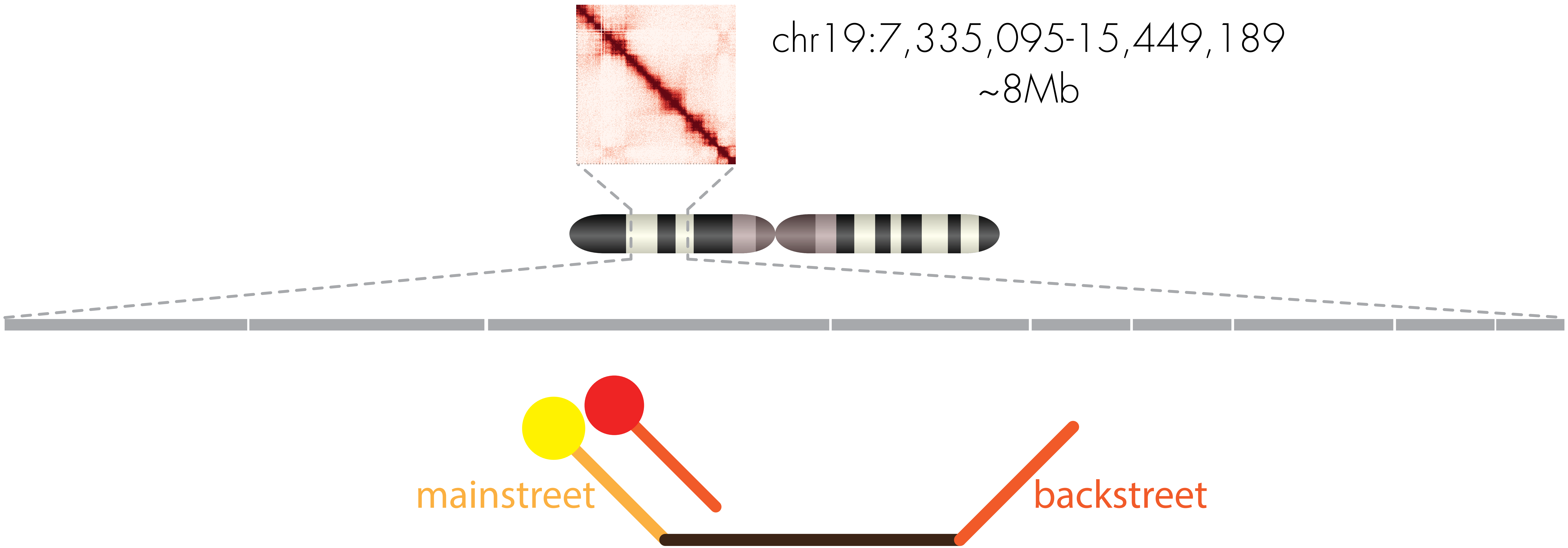
Integrating imaging and Hi-C maps with modeling.

by developing a method for

Oligopaint-based modeling of genomes

High-resolution imaging

Tracing chromosomes with OligoSTORM & fluidics cycles in PGP1 cells

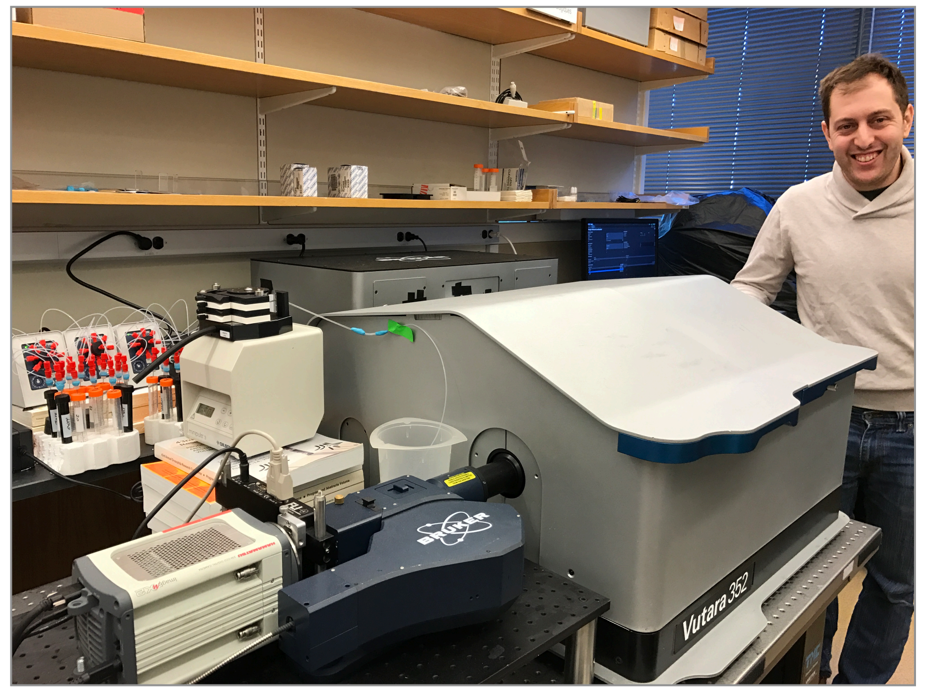


homologous 32-42bp

Beliveau et al. Nat. Comm. 2015

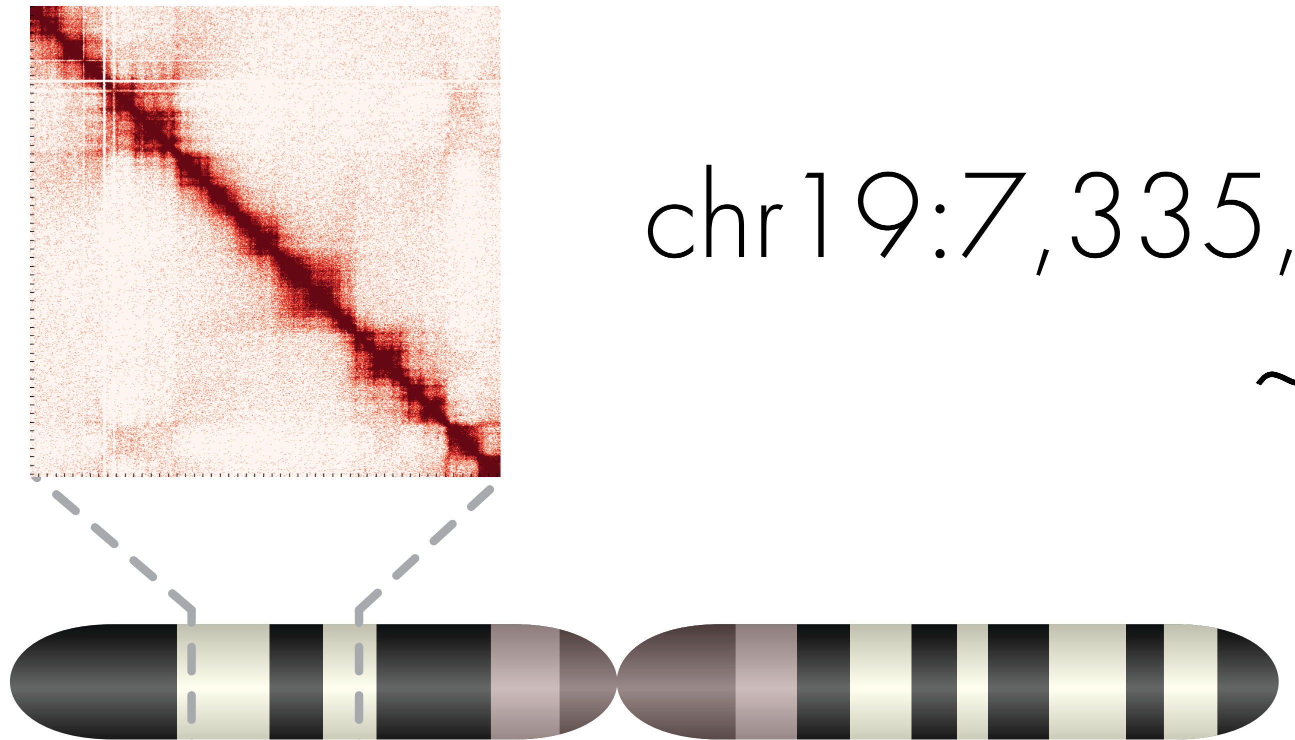
High-resolution imaging

Tracing chromosomes with OligoSTORM & fluidics cycles in PGP1 cells

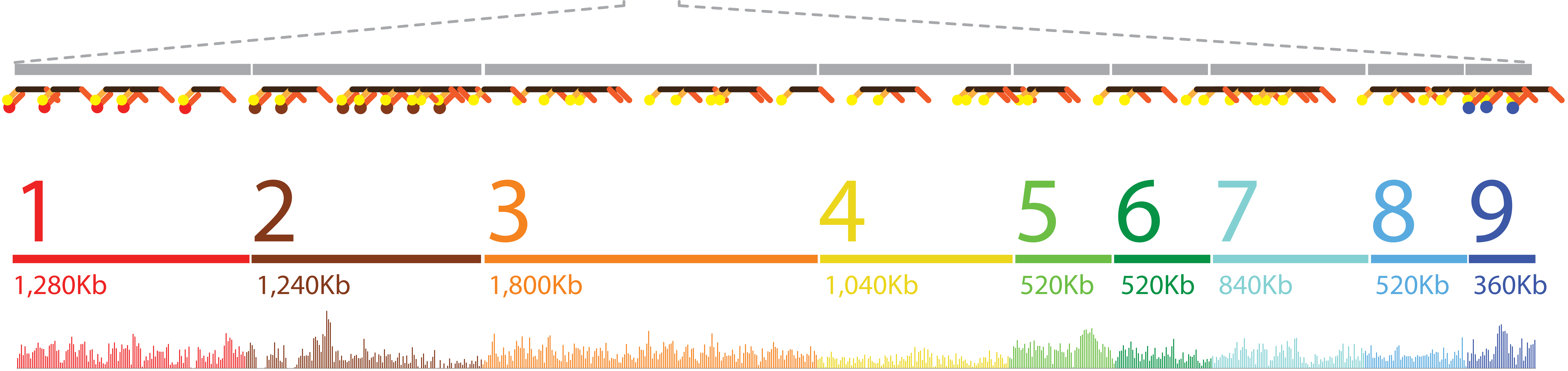


Guy Nir Harvard Med School

Bodgan Bintu Harvard
Carl Ebeling Bruker
Jeff Stuckey Bruker
John Schreiner Zero Epsilon
Steve Callahan Zero Epsilon

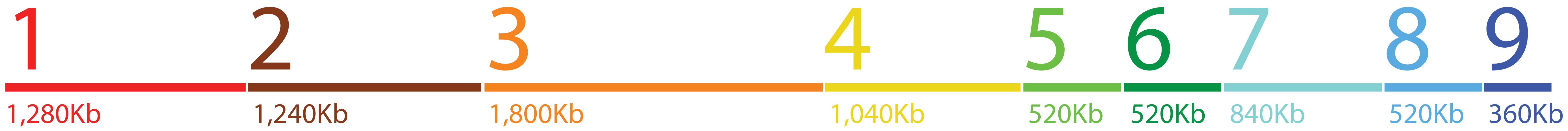


chr19:7,335,095-15,449,189
~8Mb



High-resolution imaging

Tracing chr19:7,335,095-15,449,189 ~8Mb



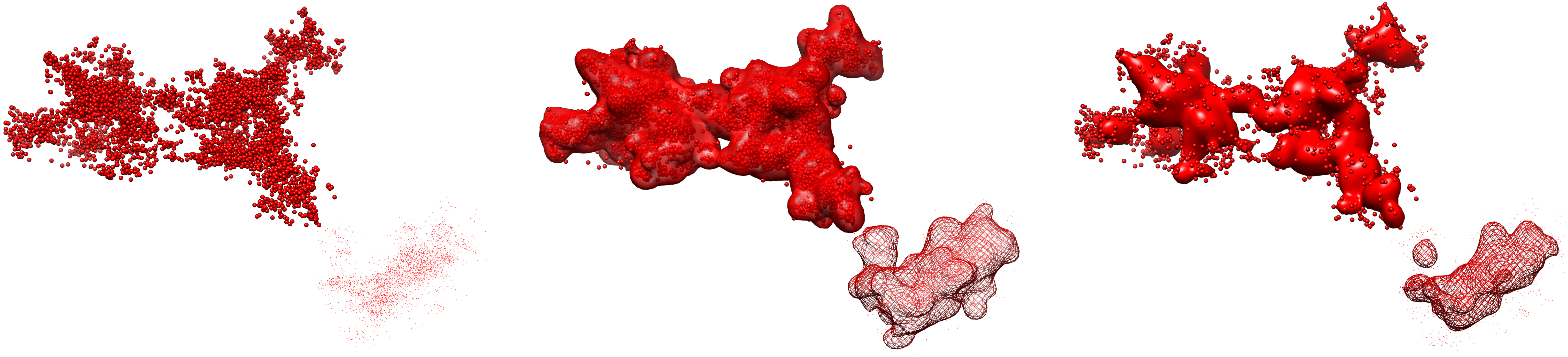
1	2	3	4	5	6	7	8	9
1,280Kb	1,240Kb	1,800Kb	1,040Kb	520Kb	520Kb	840Kb	520Kb	360Kb

Cell-02

High-resolution imaging

XYZ points convolution into a density map

$$\rho(x,y,z) = \sum_{N} \frac{Z_N}{\left(\sigma\sqrt{2\pi}\right)^3} e^{-\frac{(x-x_n)^2+(y-y_n)^2+(z-z_n)^2}{2\sigma^2}}$$

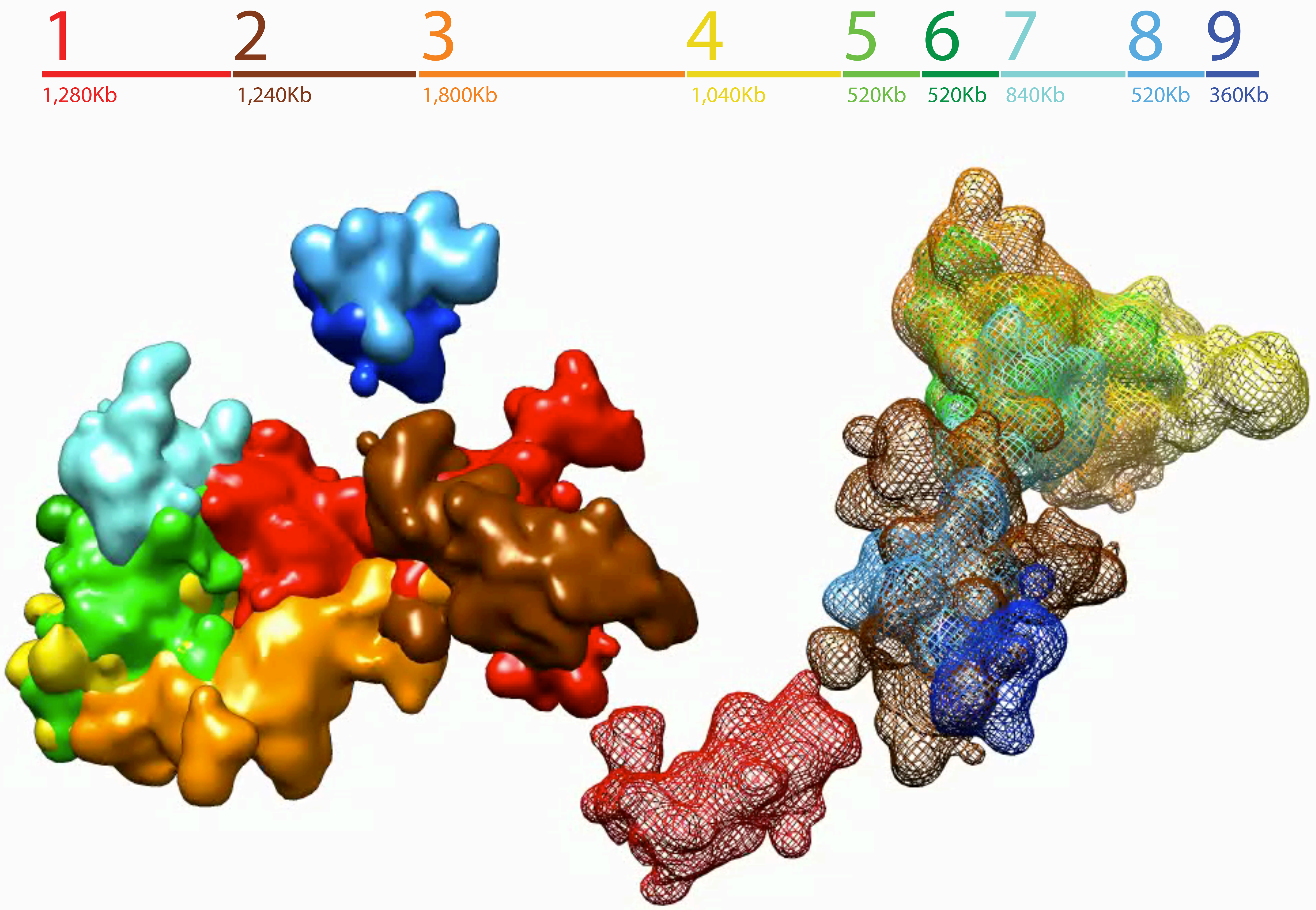


Cell-02 · Segment 1

Farabella et al, J Appl Crystallogr. 2015

Density maps

Cell-02 · Density map @ 50nm

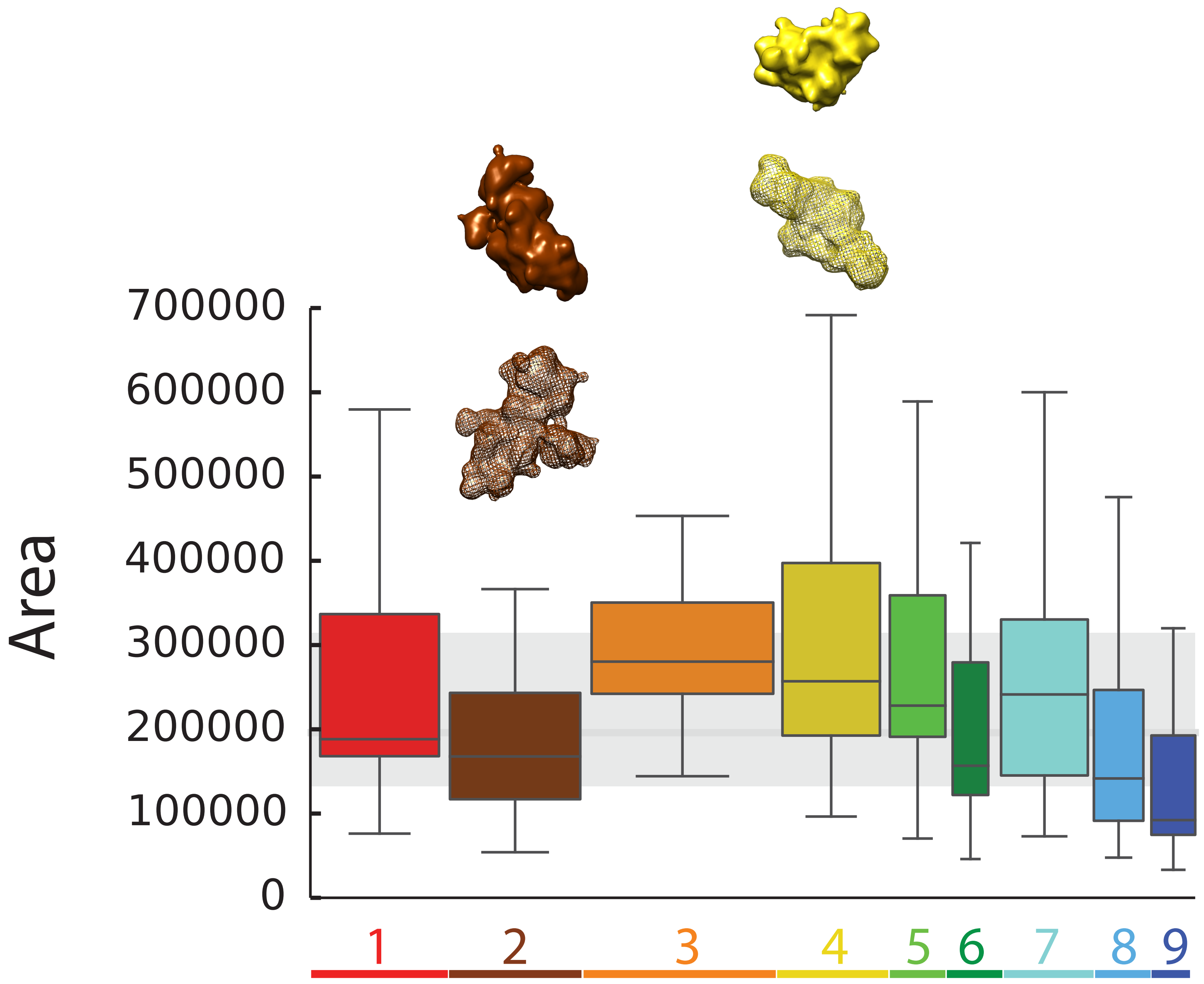


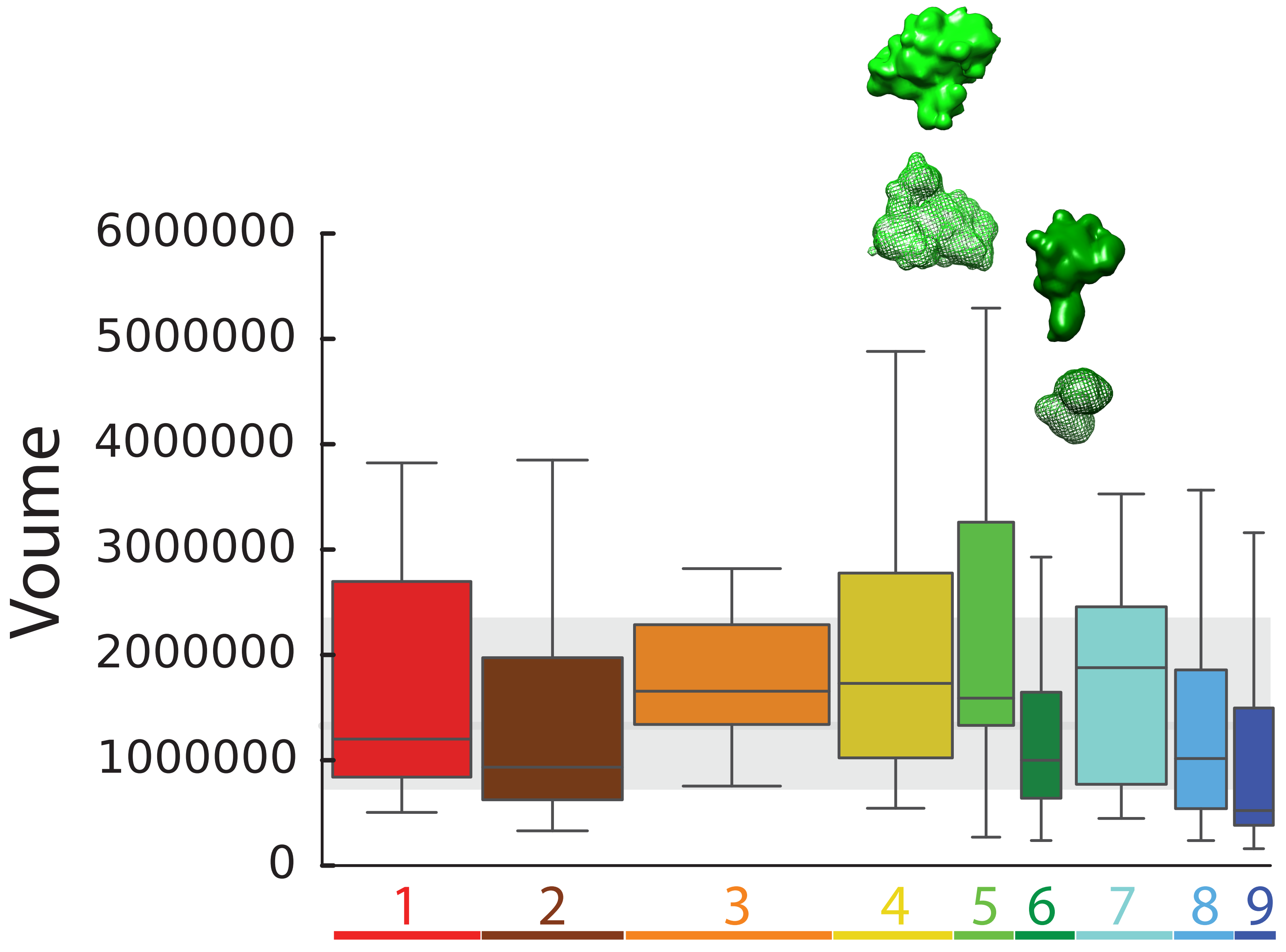
Area (nm^2)
Volume (nm^3)
Sphericity
Overlap (%)
Distance (nm)

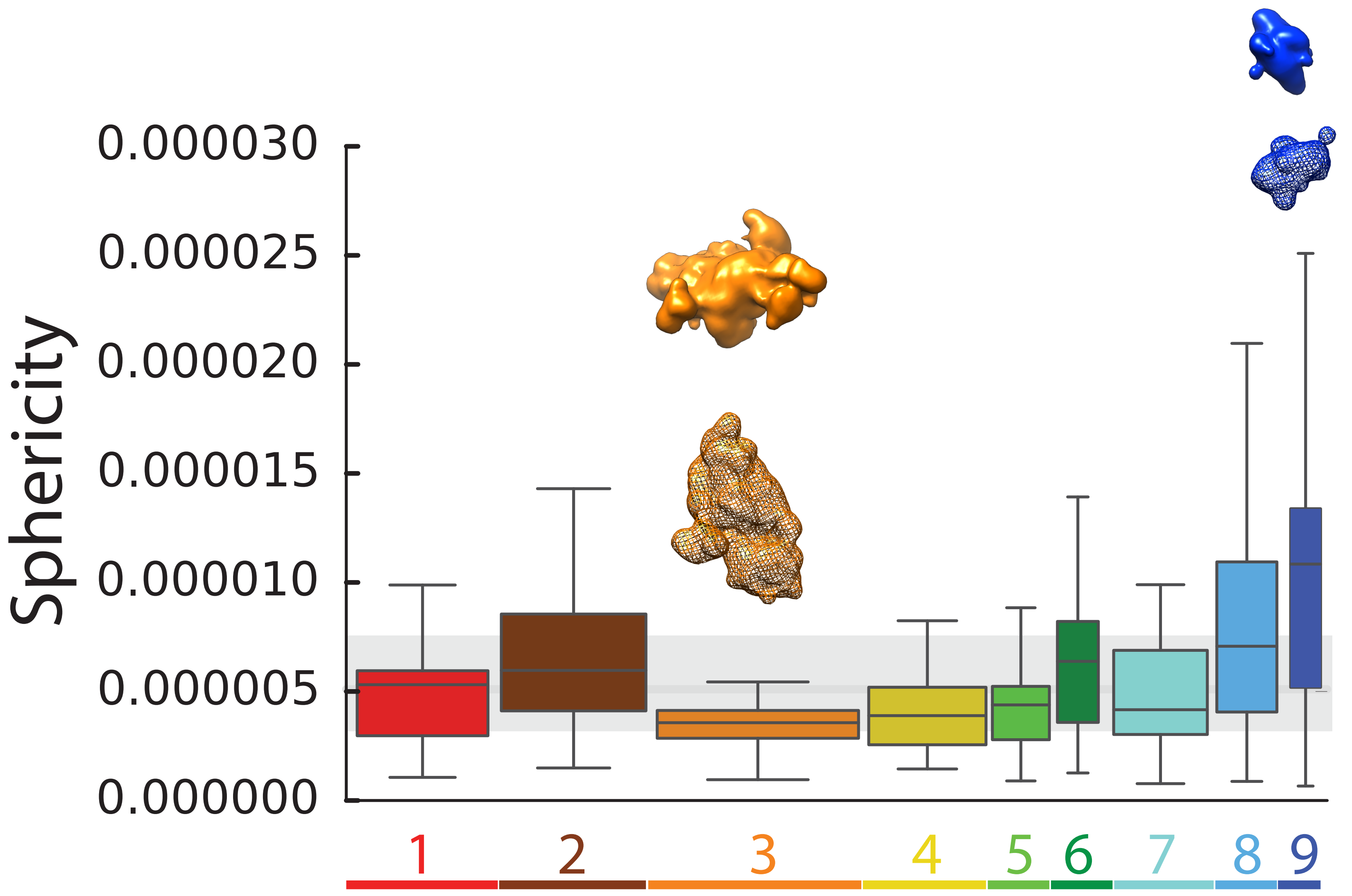
Farabella et al, J Appl Crystallogr. 2015

Structural features

Area, Volume and Sphericity of 19 cells each with 2 homologous resolved

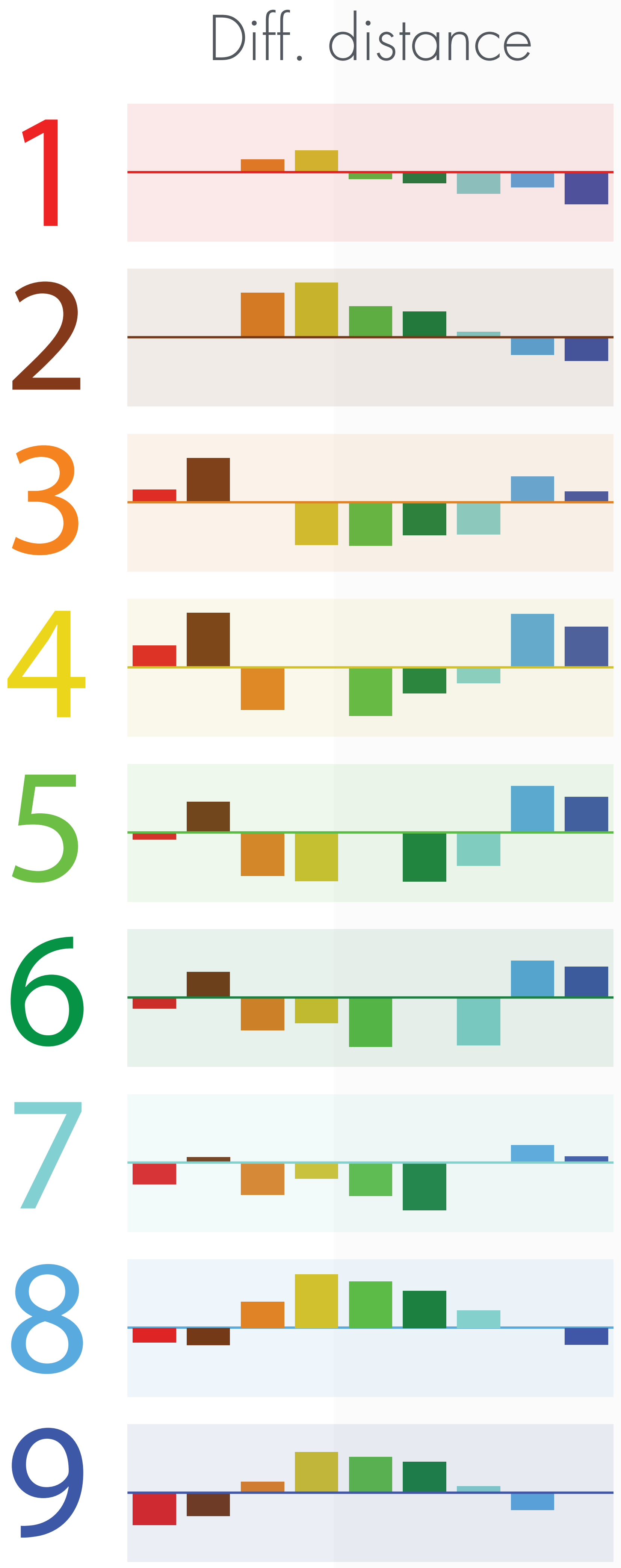


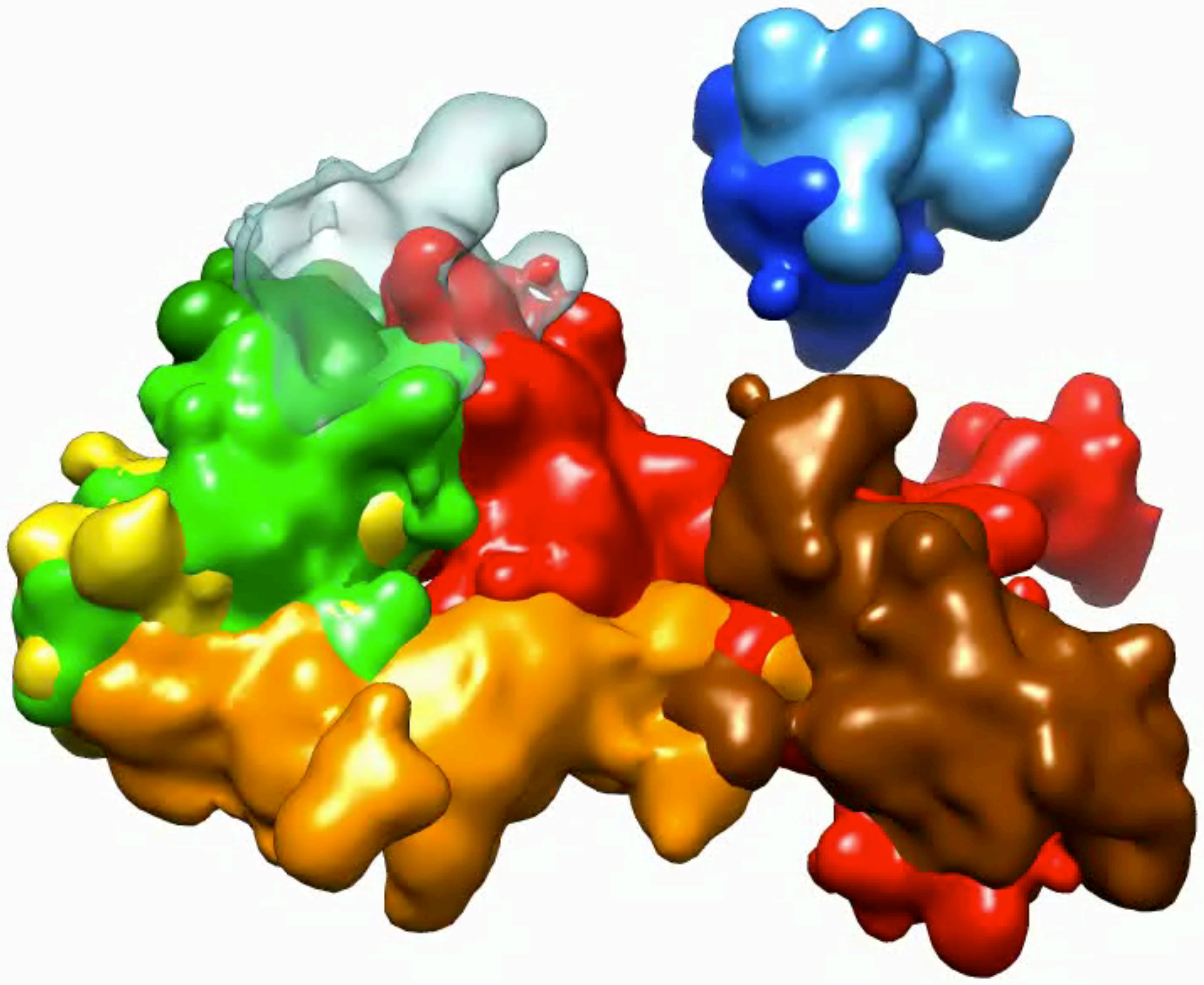


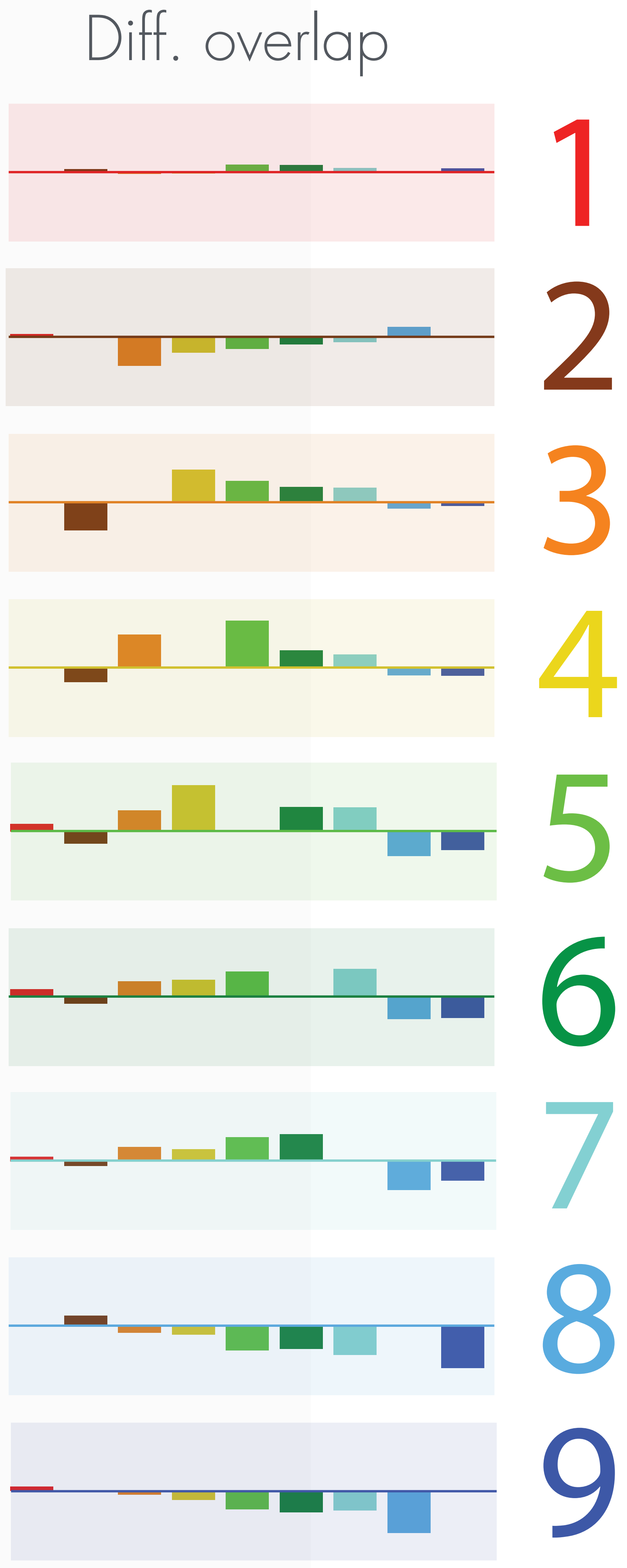


Spatial arrangement

Distance and overlap of 19 cells each with 2 homologous resolved

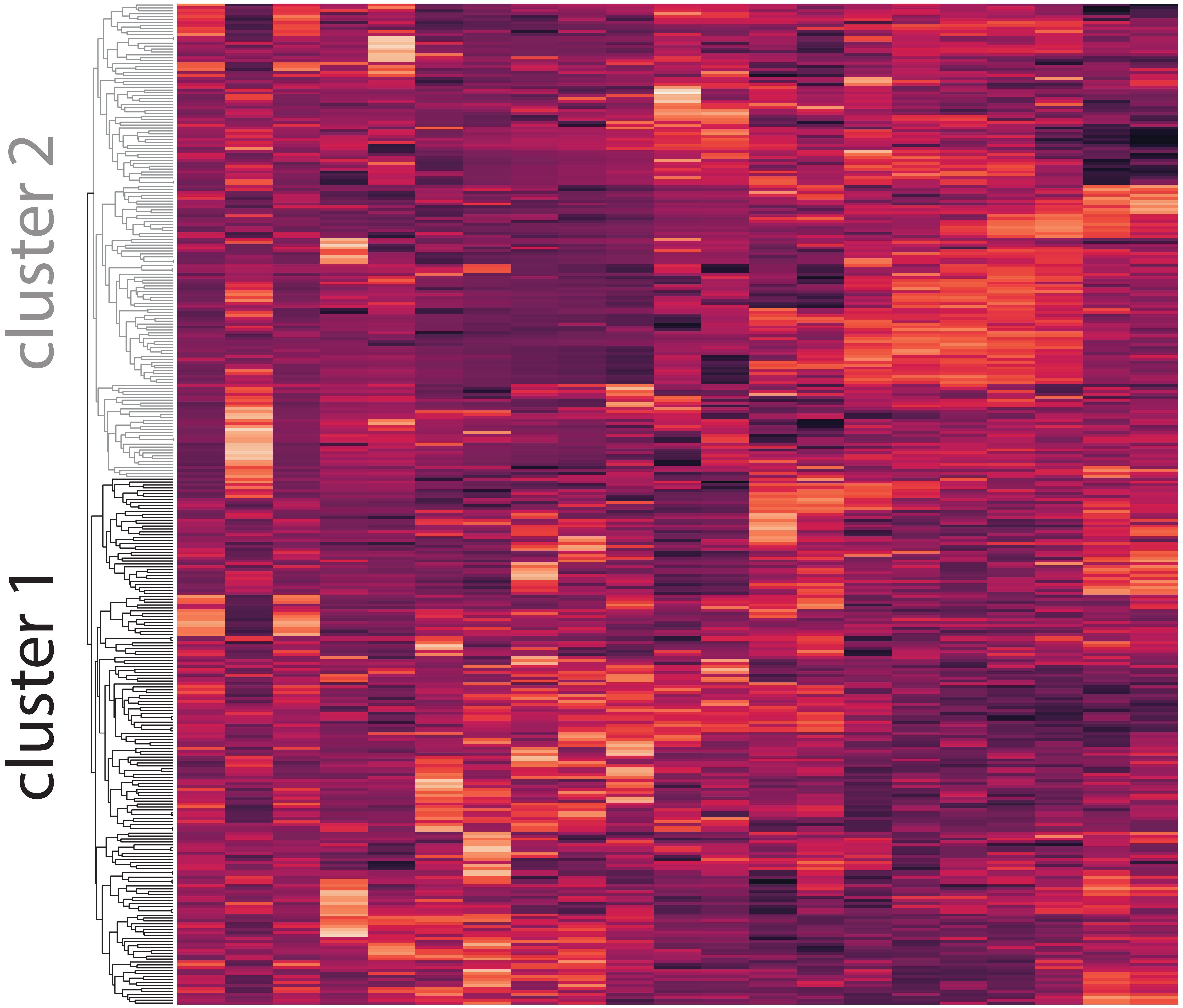


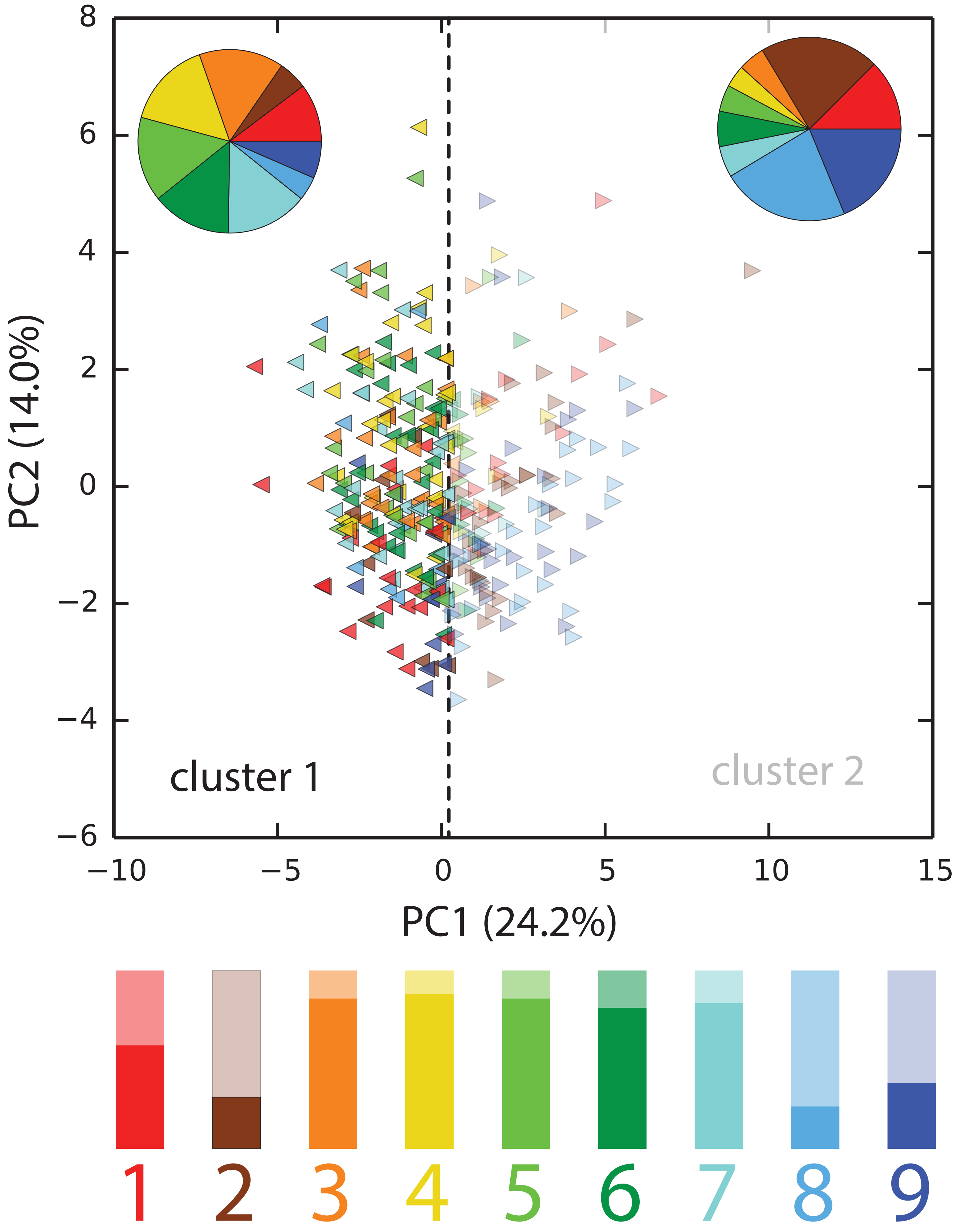




Structural clustering

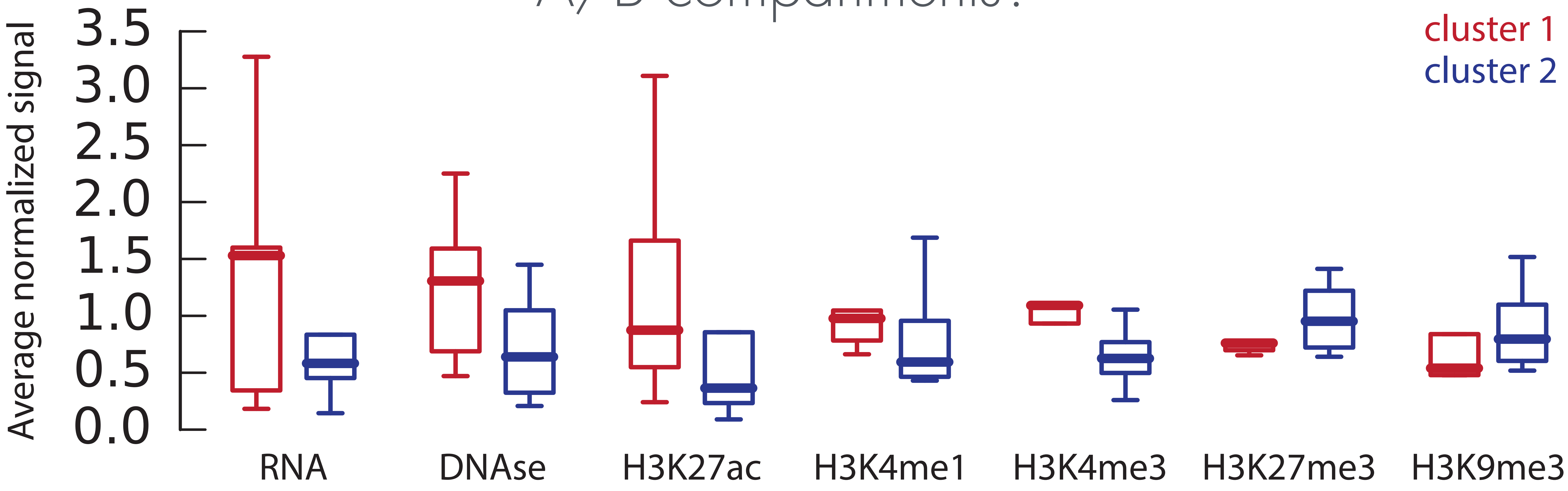
19 cells each with 2 homologous and 9 segments each (342)

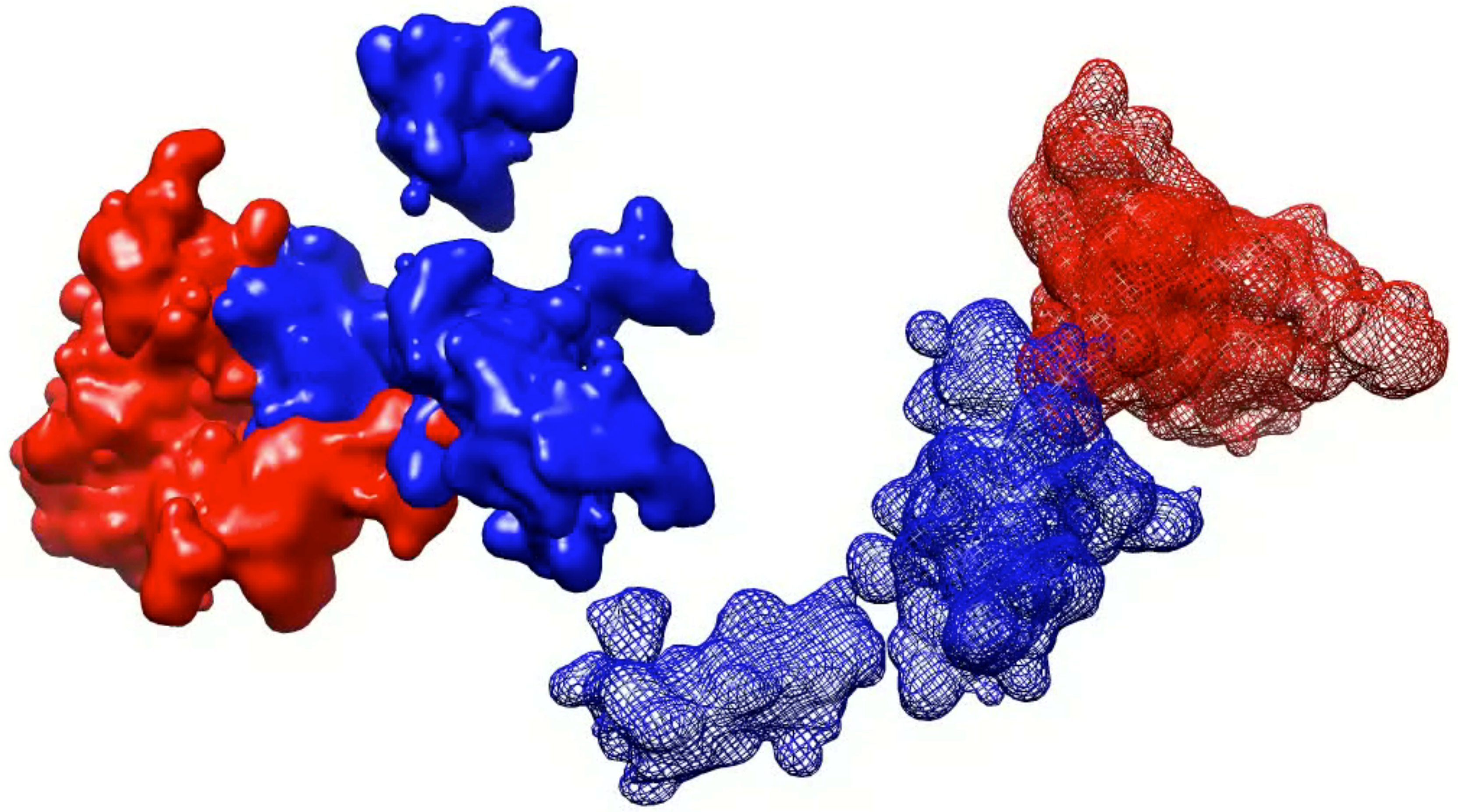


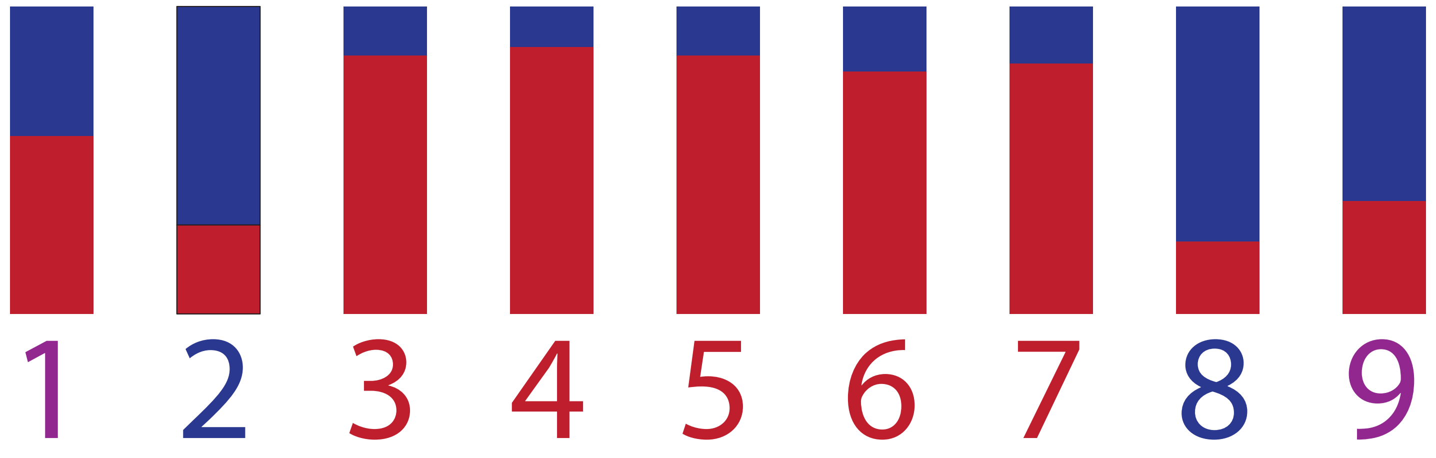


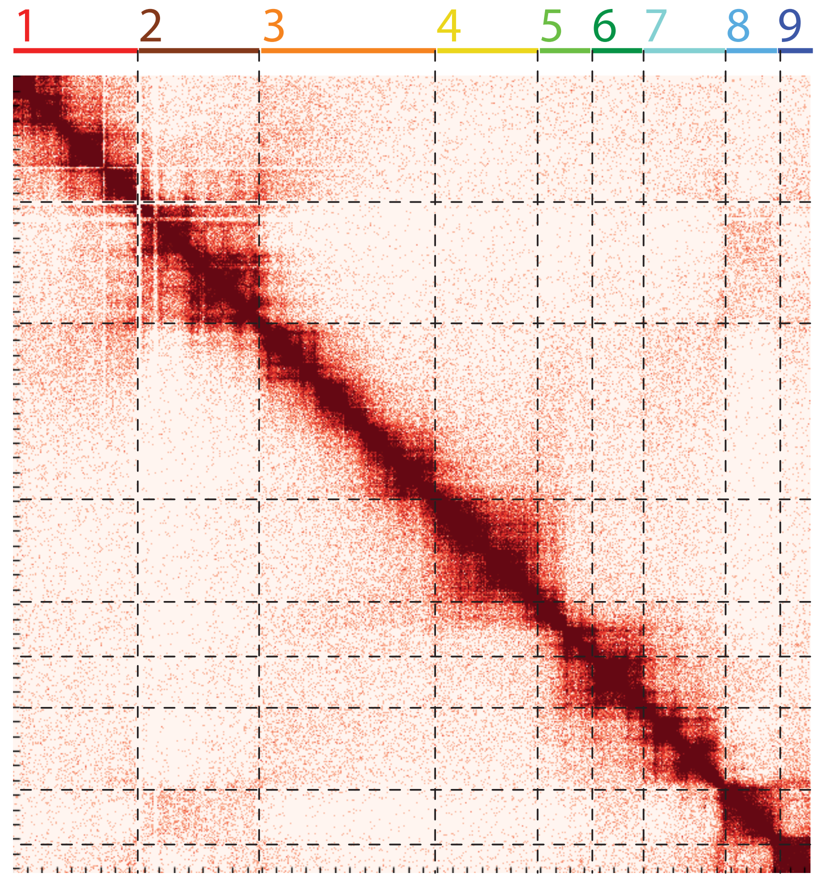
Cluster properties

A/B compartments?





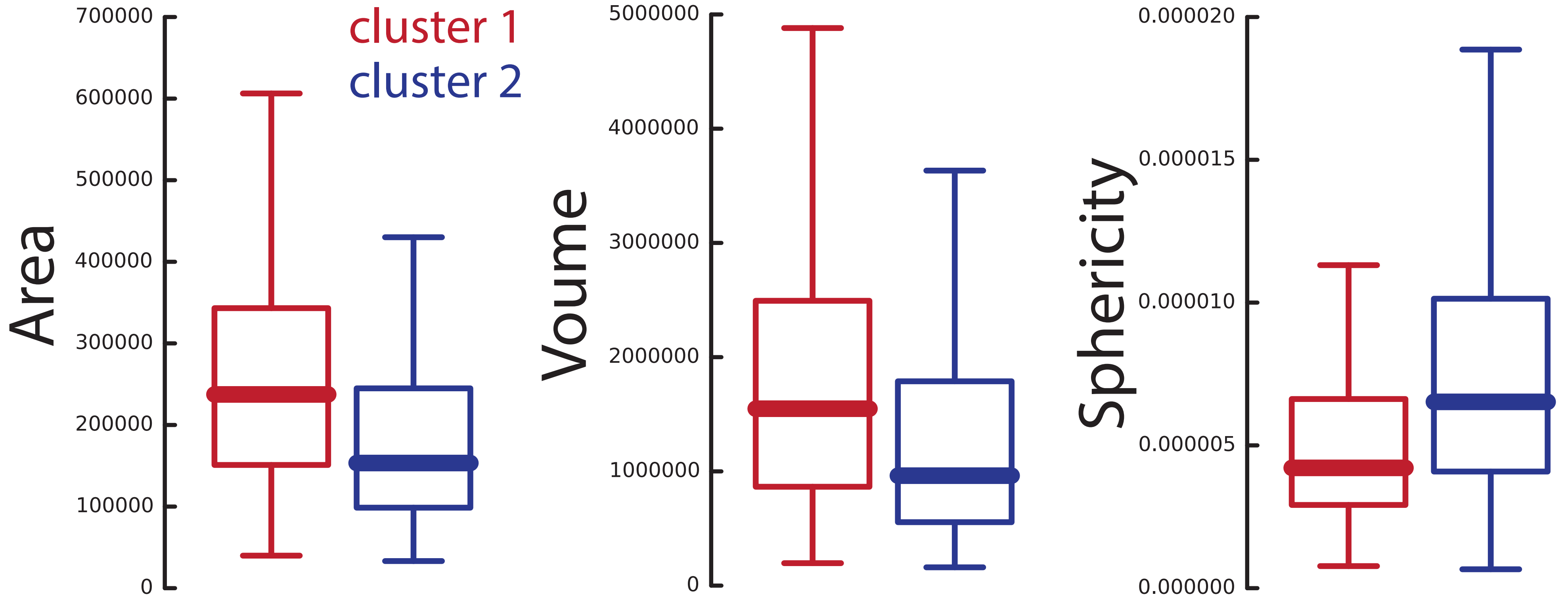


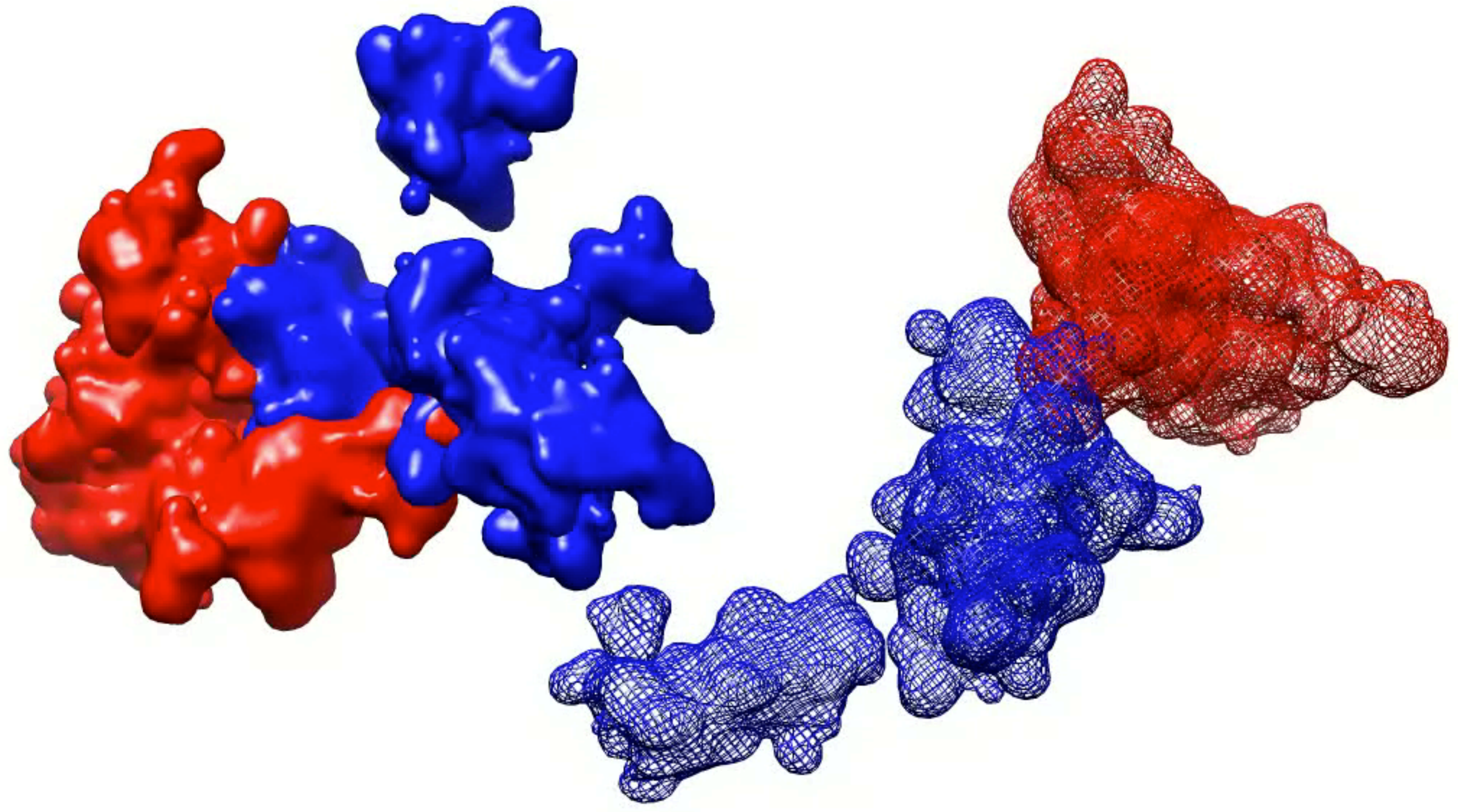


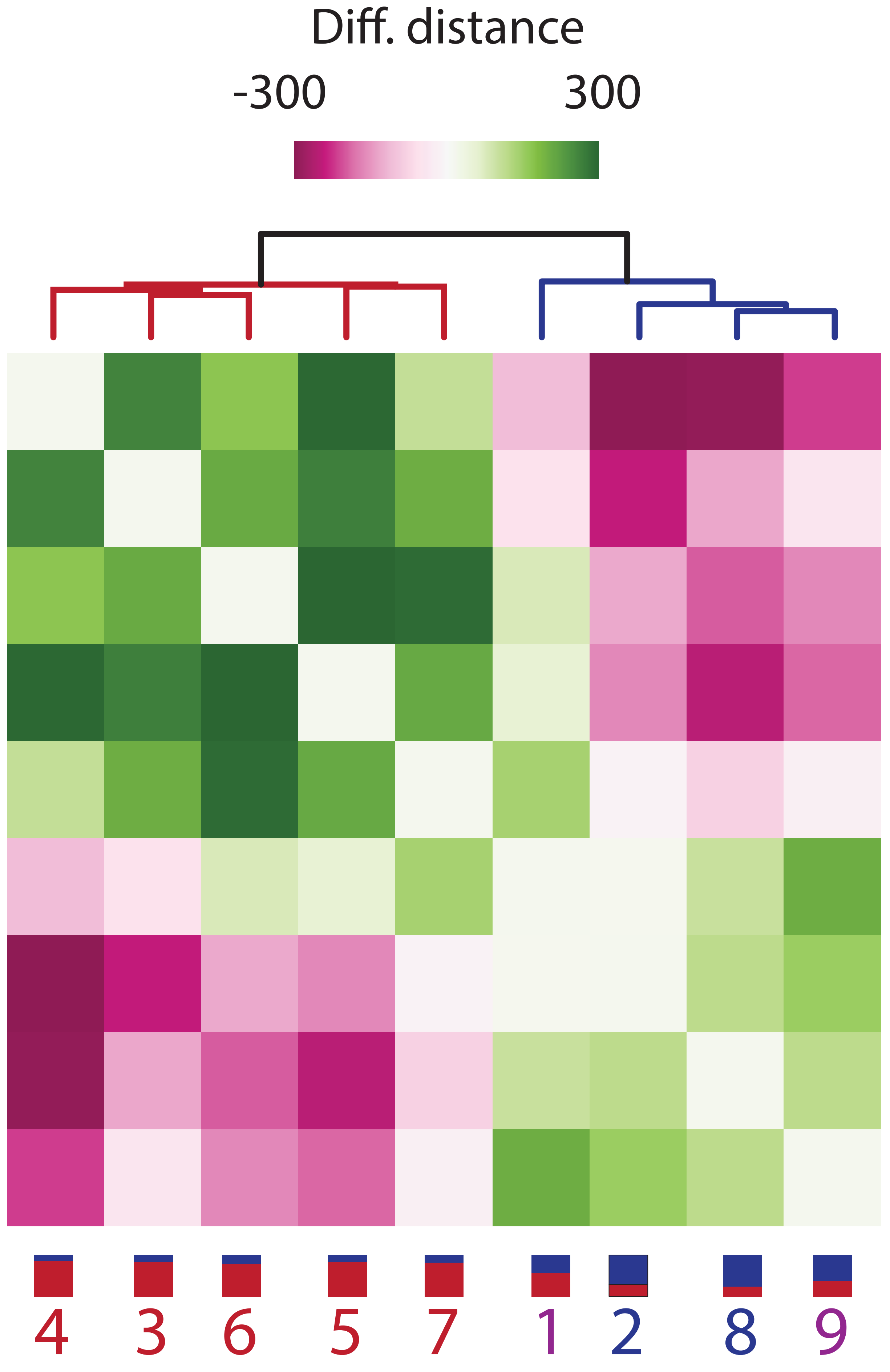
PGP1 ChIP-seq and Hi-C data from ENCODE and Lieberman-Aiden Lab, respectively

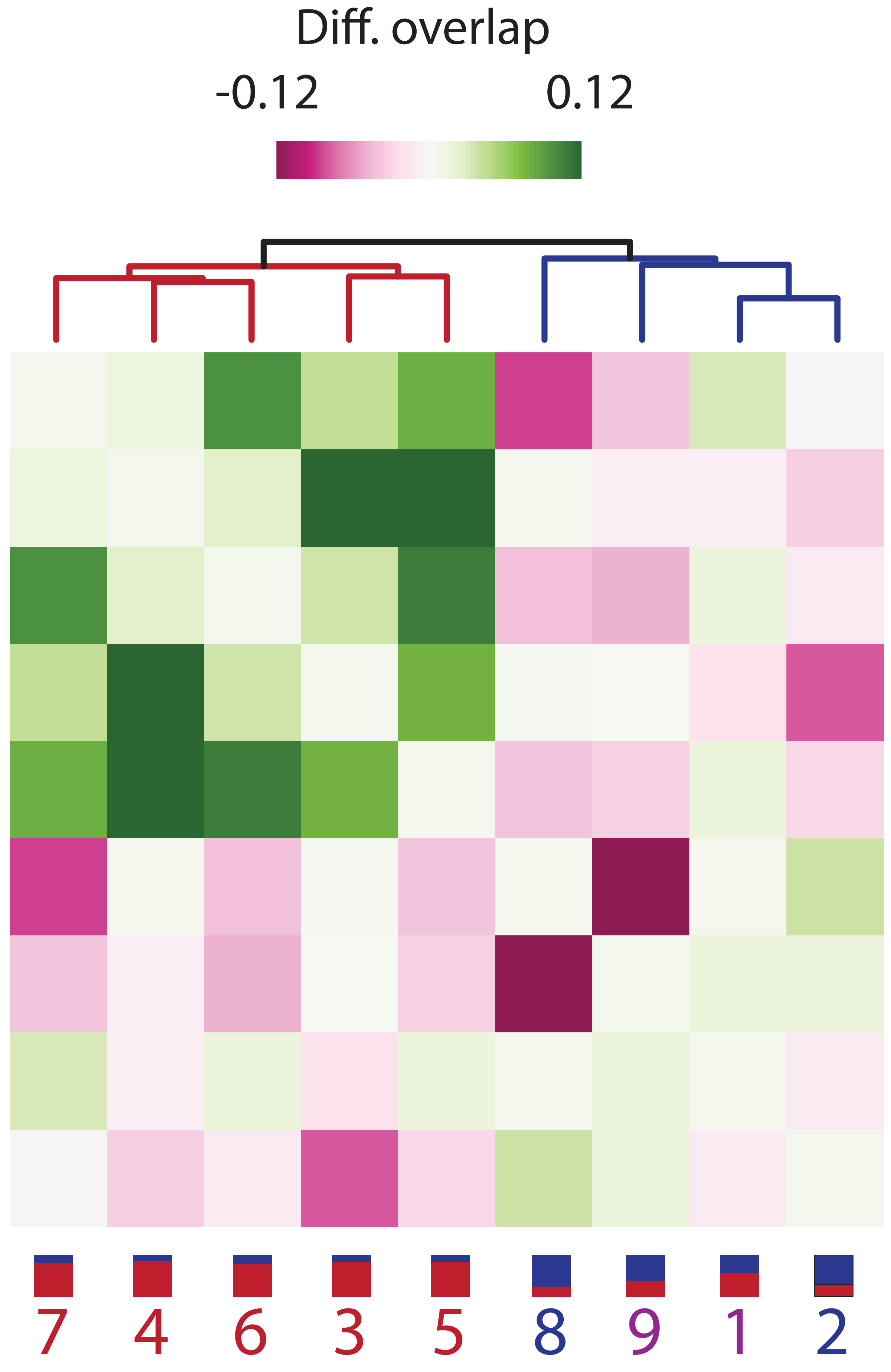
Cluster properties

A/B compartment properties









Can we walk the chromatin path in the nucleus?

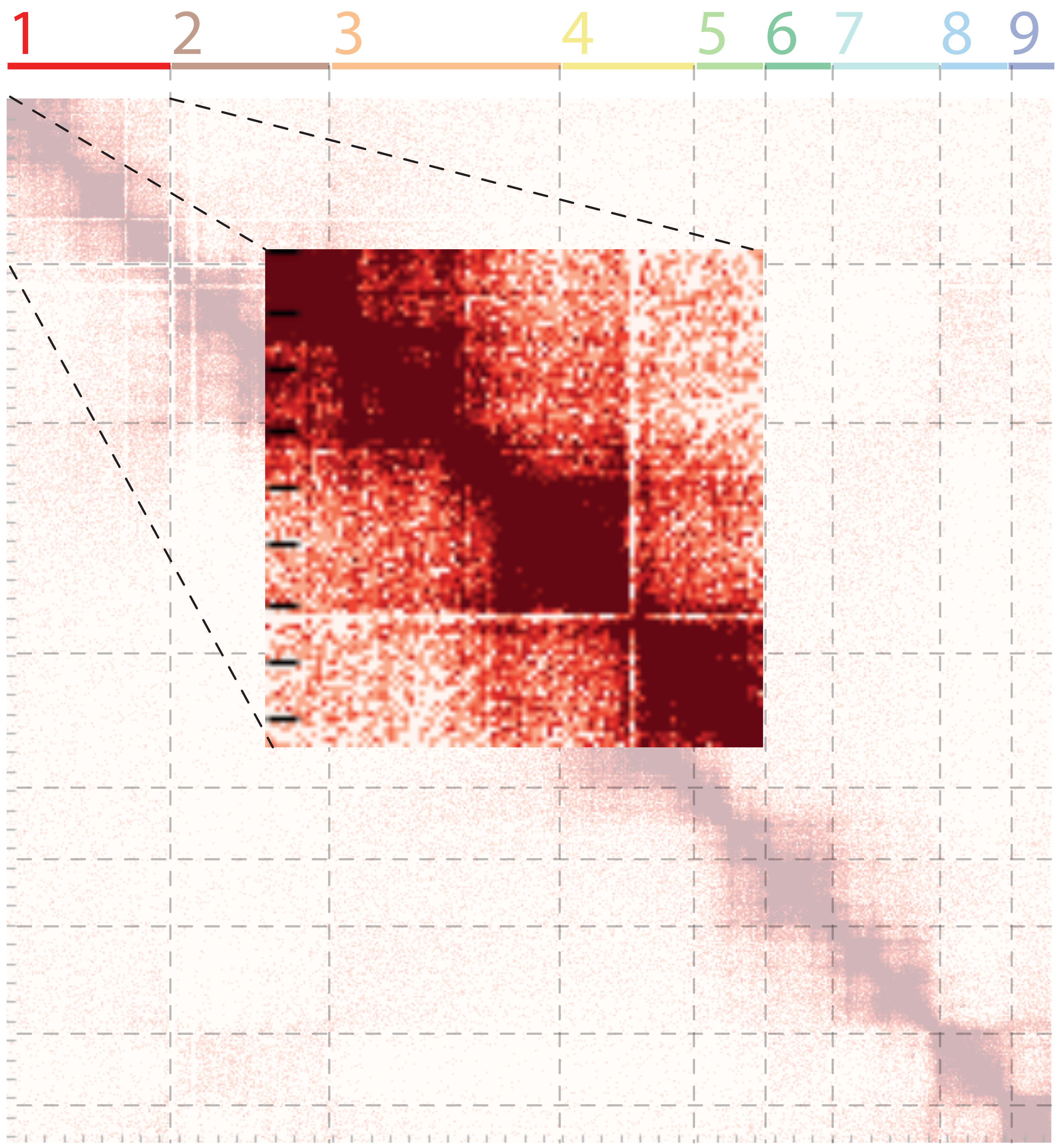
YES!

Can we increase the resolution of our data?

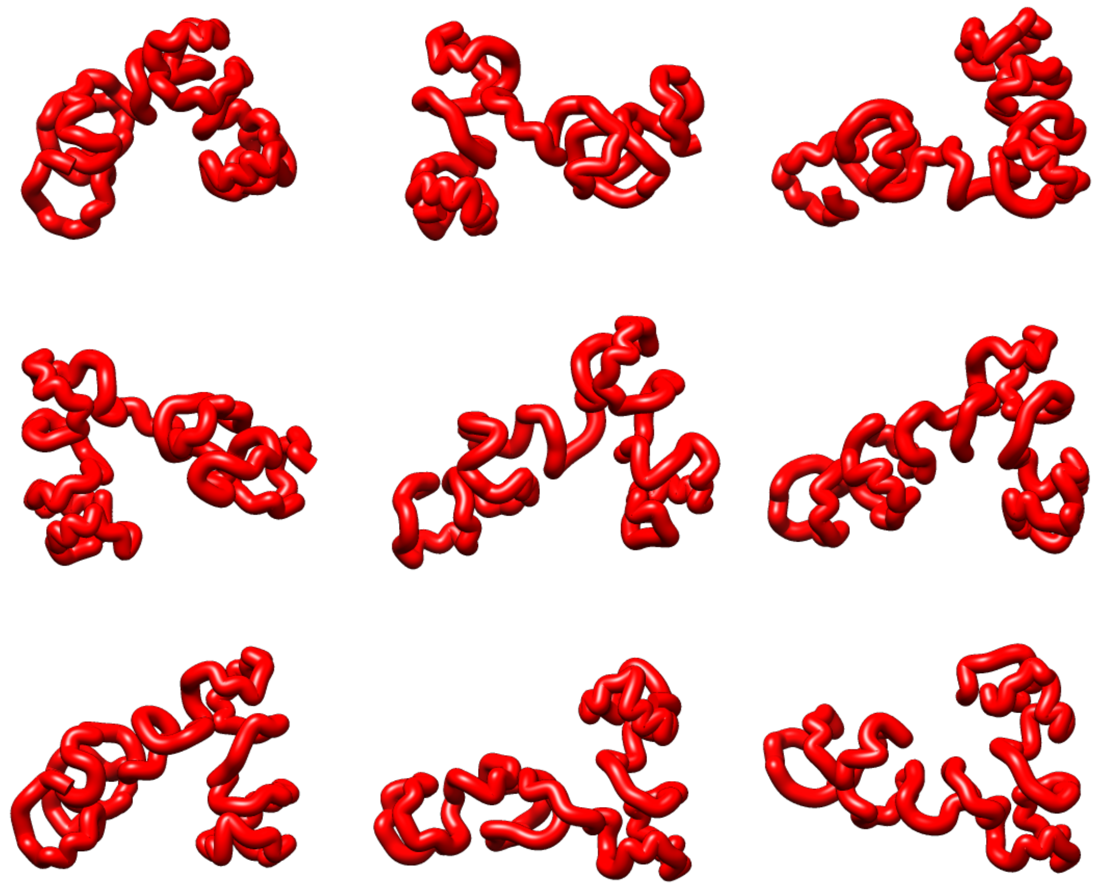
by fitting 3D models based on Hi-C interaction maps

Increasing resolution

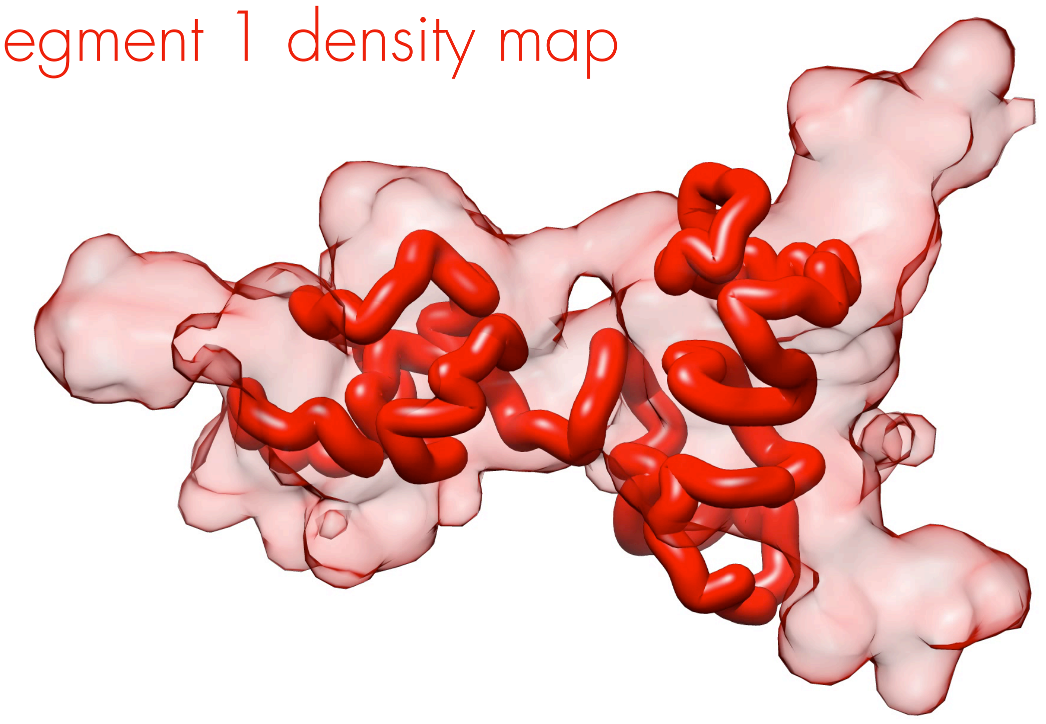
Rigid body fitting 3D structures based on Hi-C data



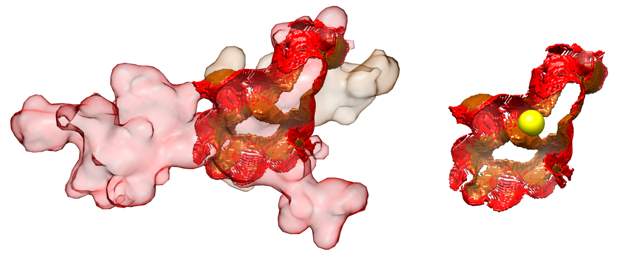
Segment 1 3D models



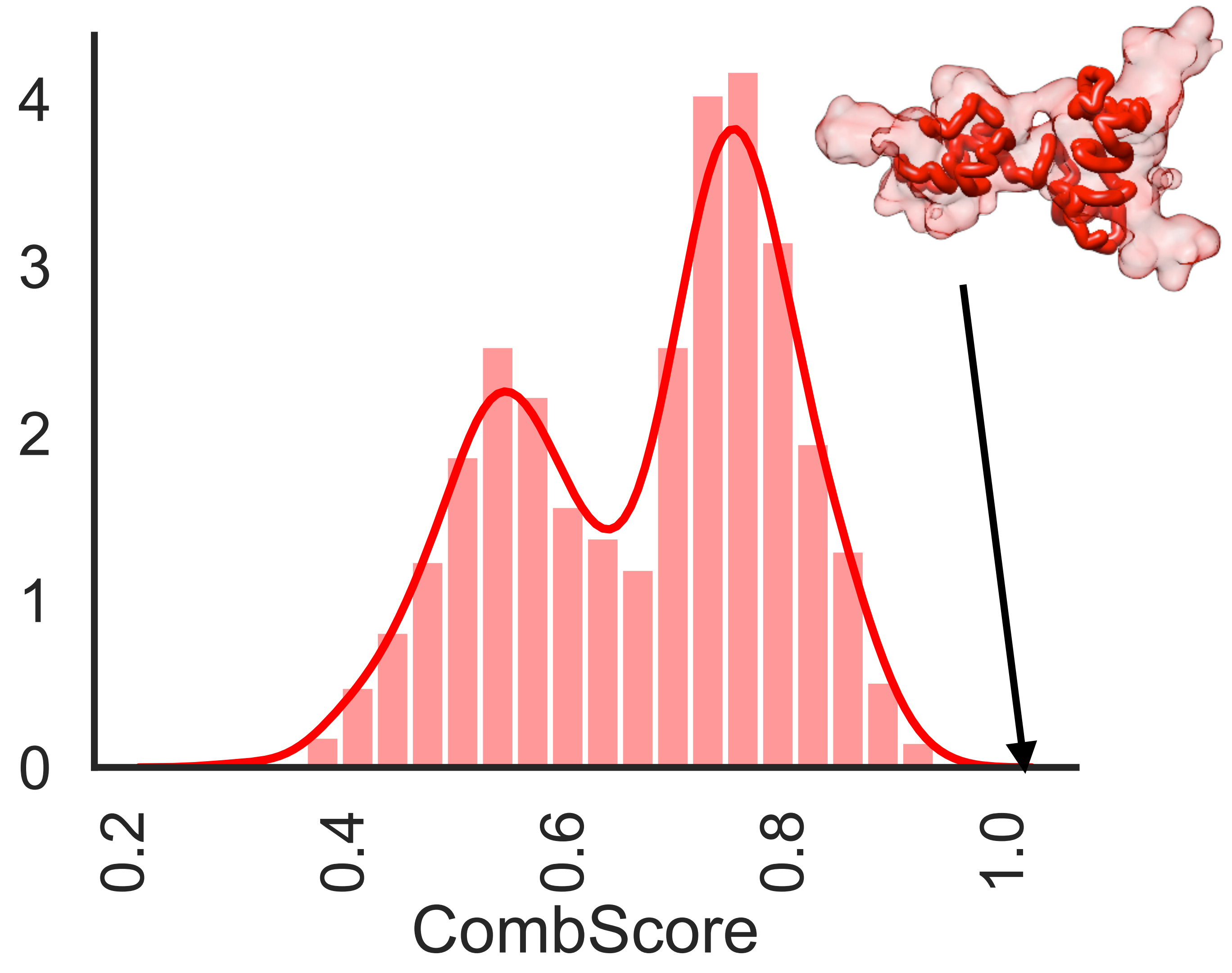
Segment 1 density map



$$\mathrm{ConS} = 1 - \frac{d_{P,COM}}{\max\left(d_{P,COM}\right)}$$



$$CCC = \frac{\sum_{i=1}^{M}\left[\rho_i^{EM} - \bar{\rho}^{EM}\right]\left[\rho_i^{P} - \bar{\rho}^{P}\right]}{\sqrt{\sum_{i=1}^{M}\left[\rho_i^{EM} - \bar{\rho}^{EM}\right]^2 \sum_{i=1}^{M}\left[\rho_i^{P} - \bar{\rho}^{P}\right]^2}}$$

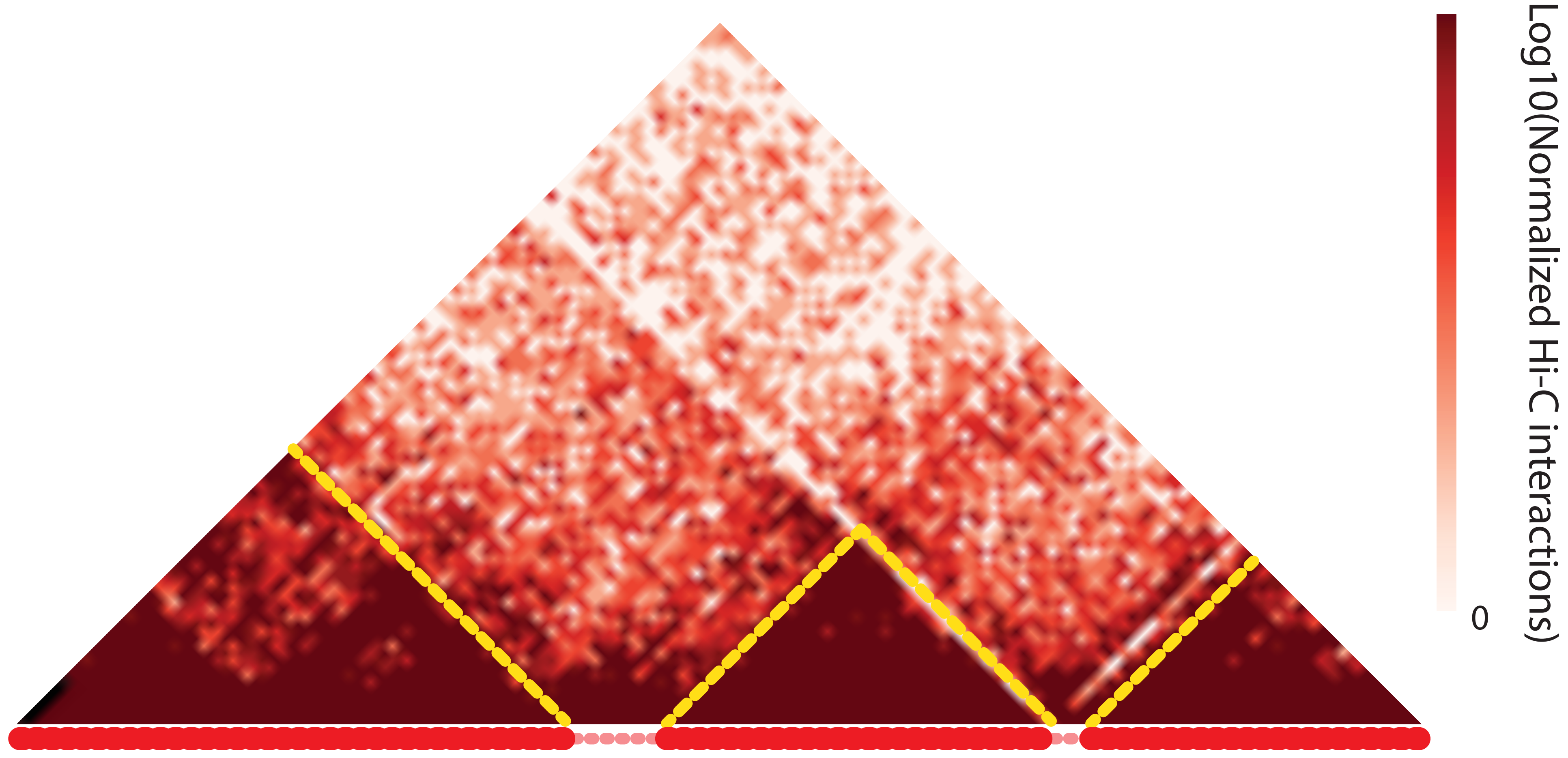


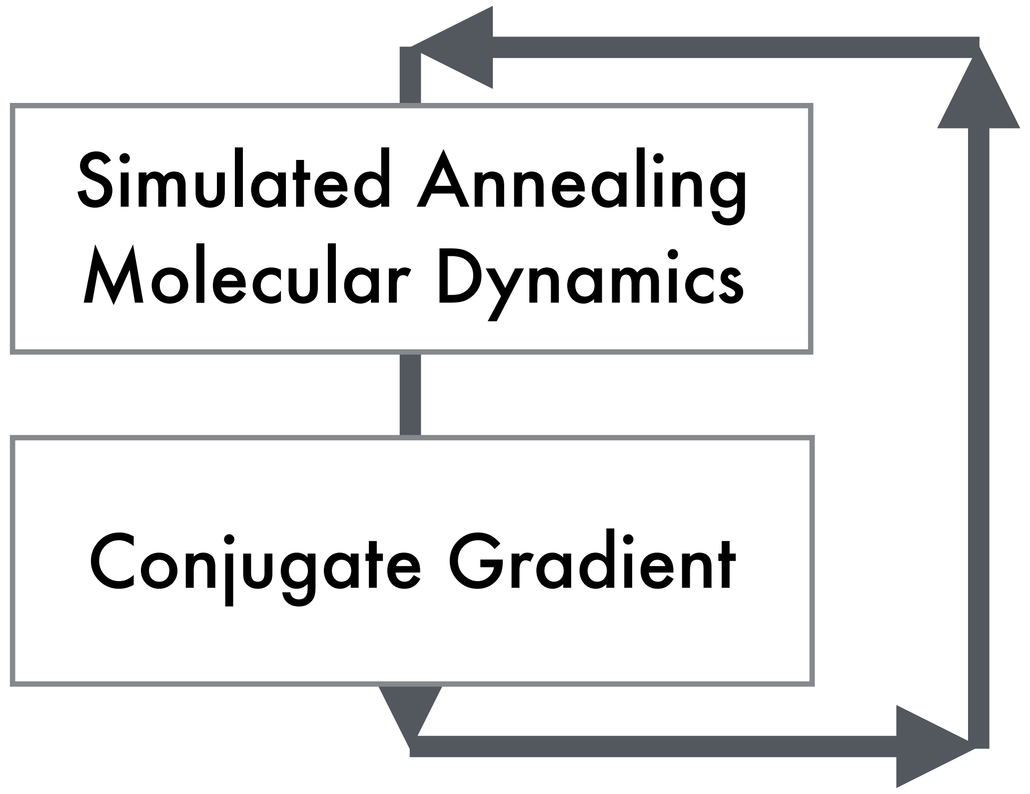
TADbit Serra, Baù, et al. PLOS CB 2017
http://www.3DGenomes.org

Farabella et al, J Appl Crystallogr. 2015
Roseman, 2000; Wriggers & Chacon, Structure 2001

Increasing resolution

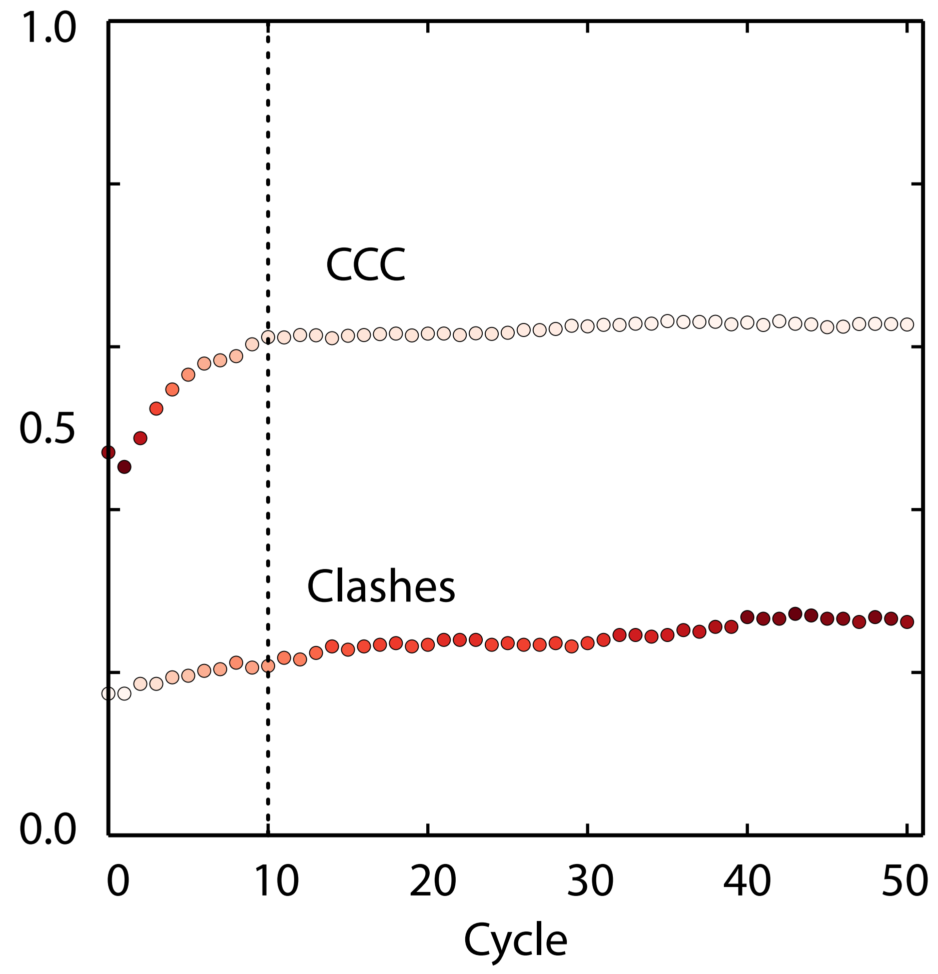
Flexible fitting 3D structures based on Hi-C data

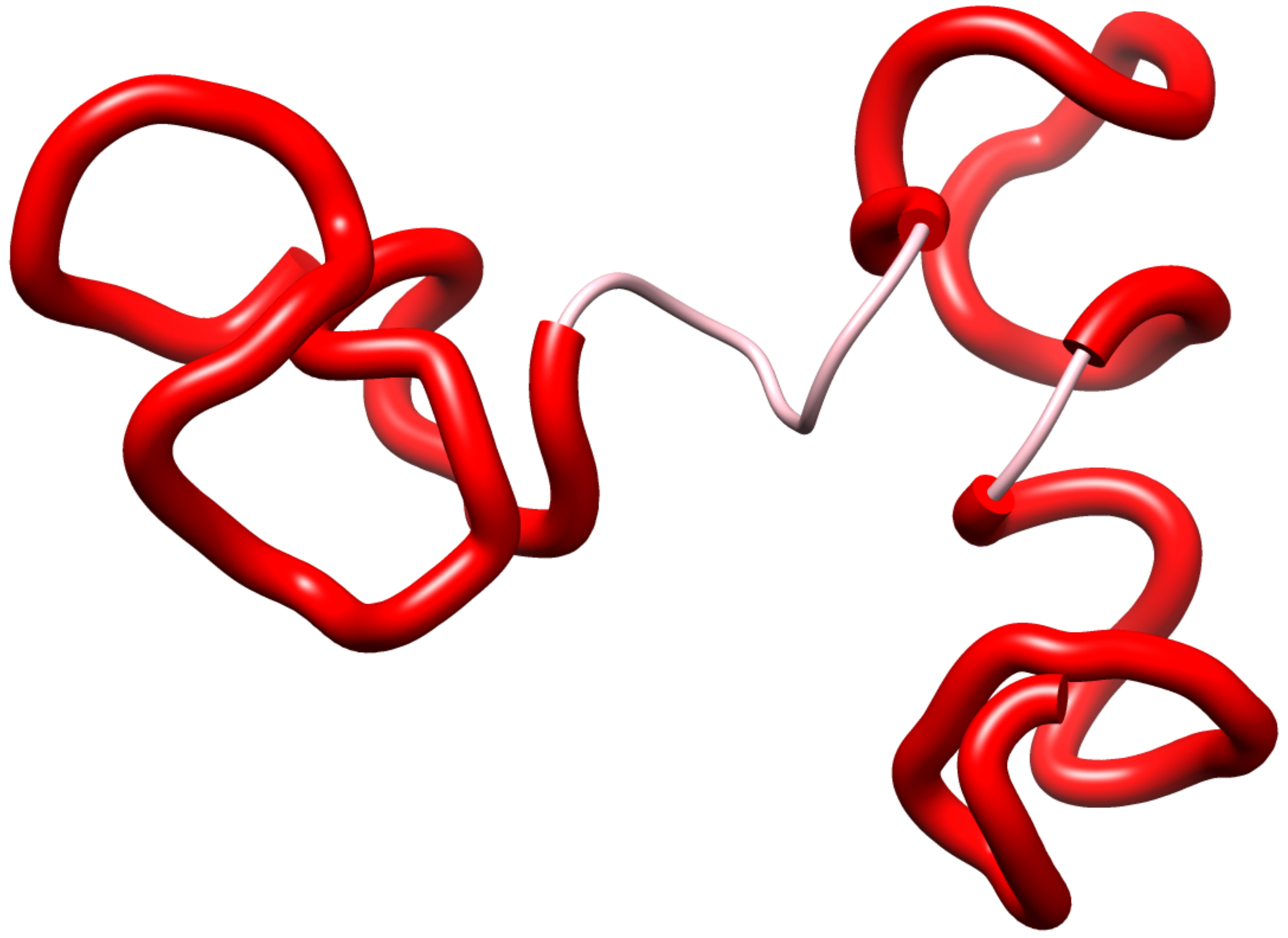


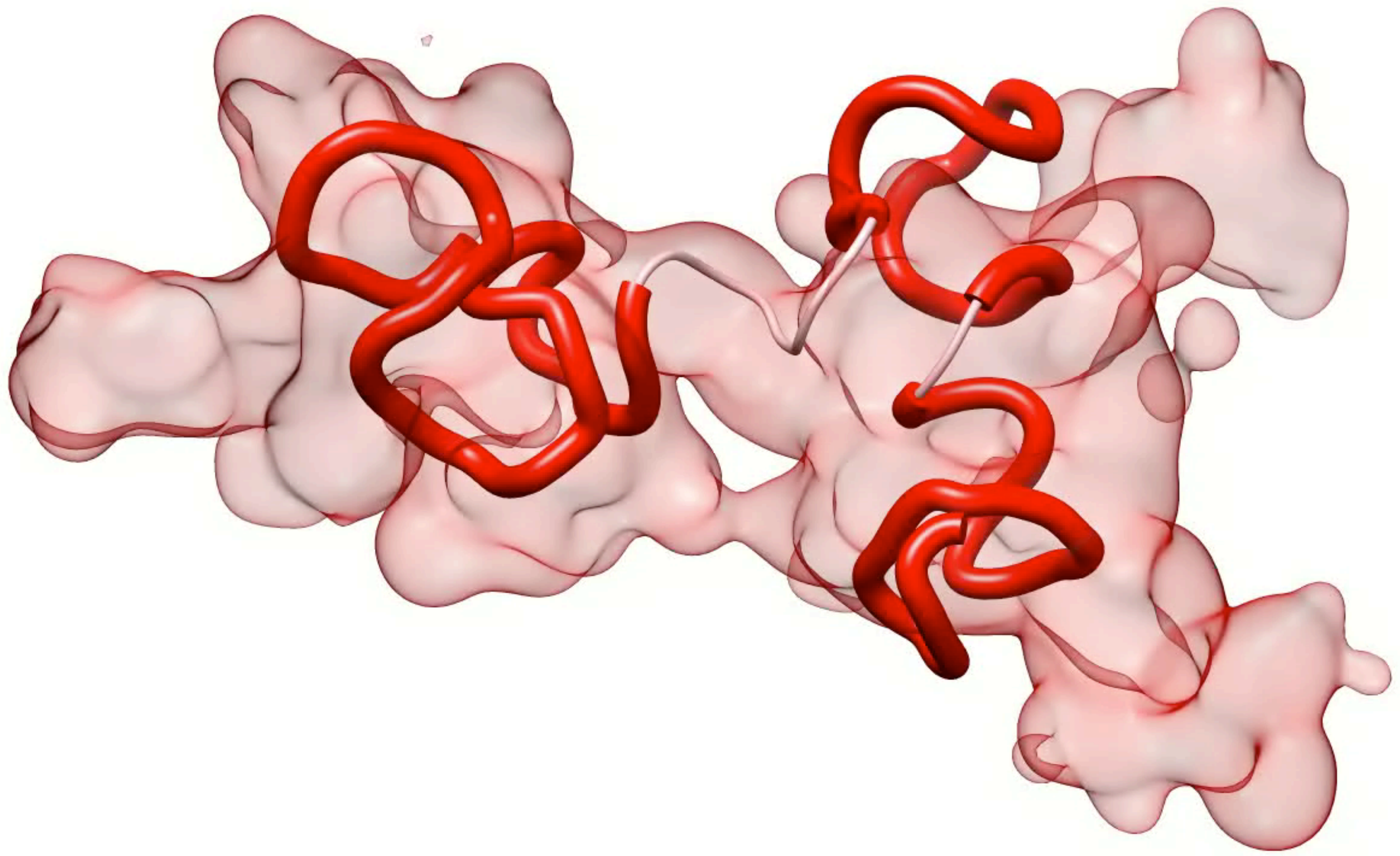


Simulated Annealing Molecular Dynamics

Conjugate Gradient







Increasing resolution

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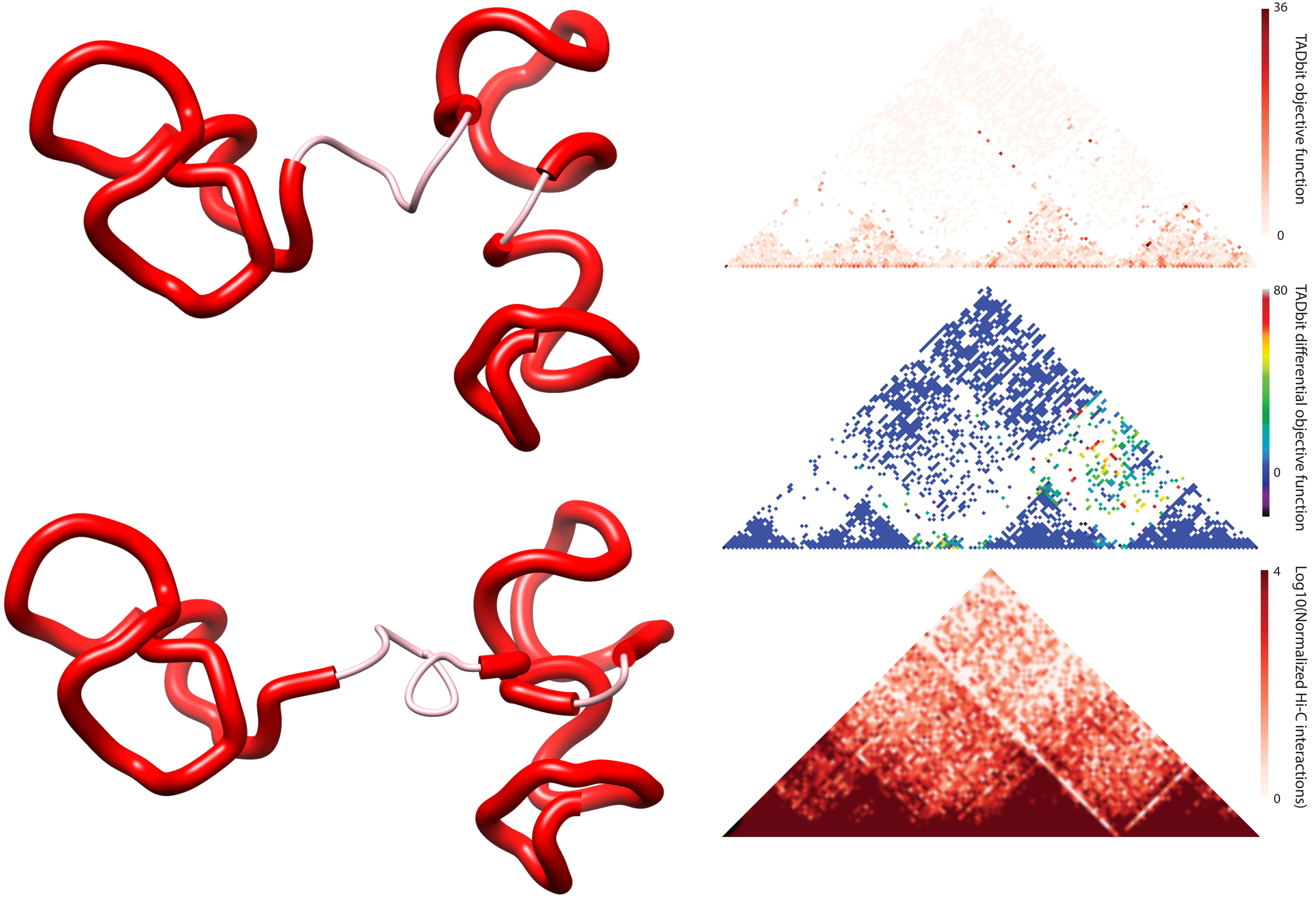
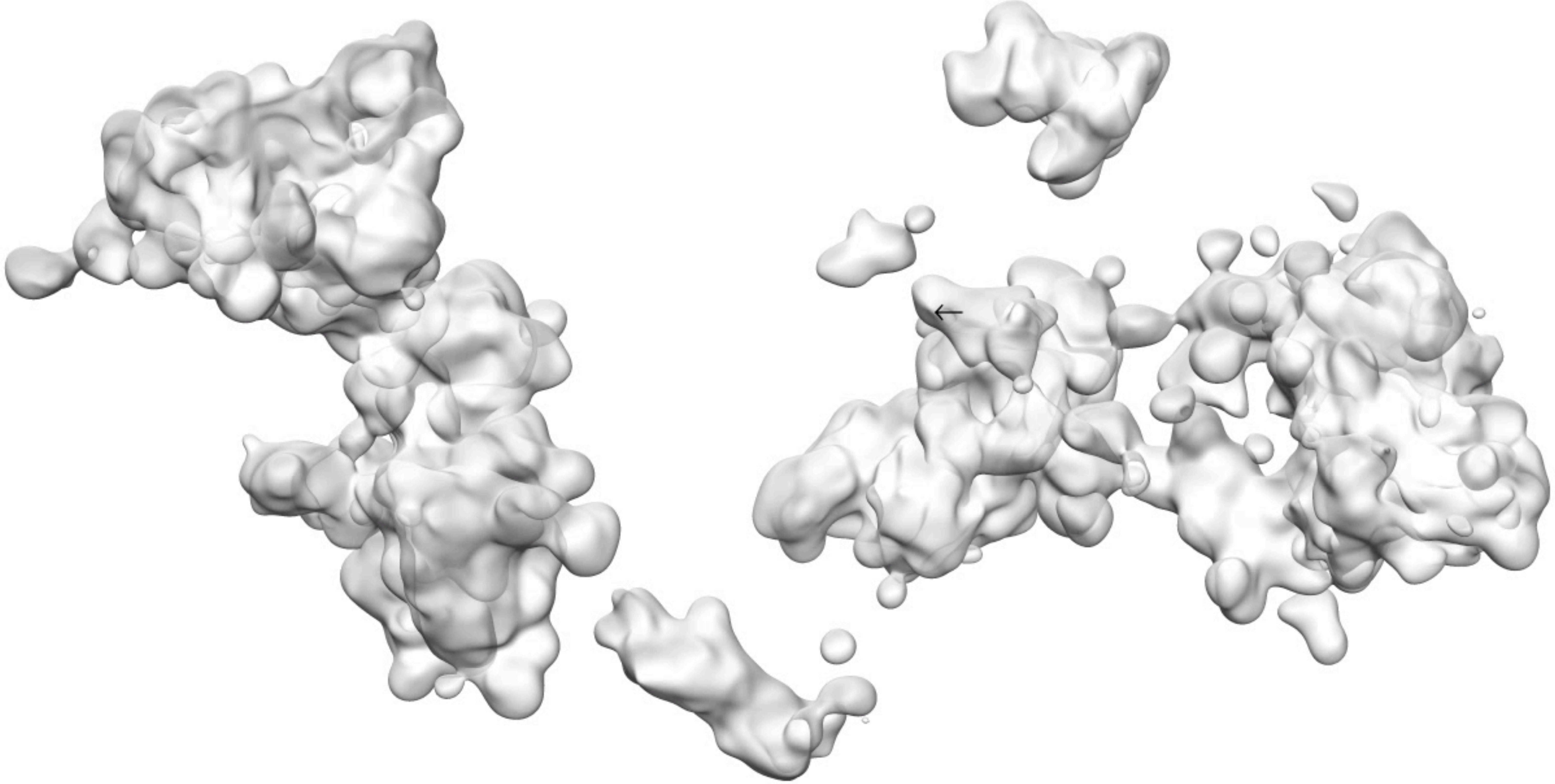


Chromosome walking path @10Kb resolution



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

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