



Chromosome walking with super-resolution imaging and modeling

Marc A. Marti-Renom

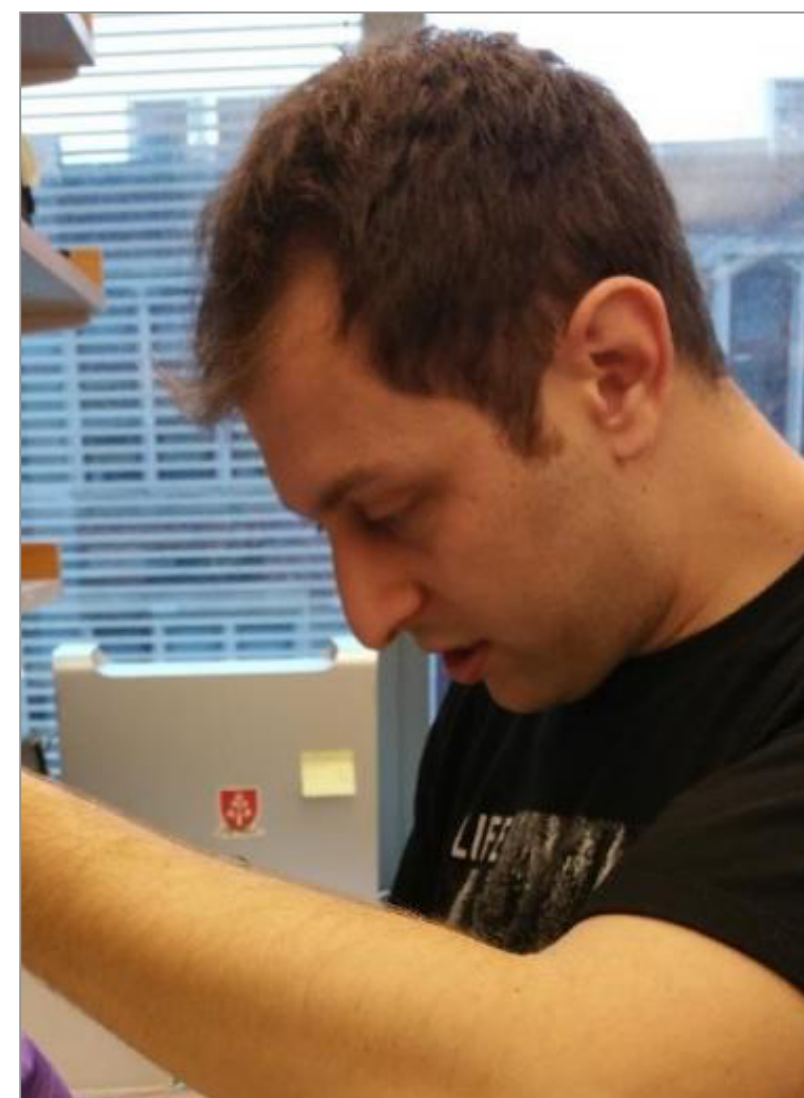
CNAG-CRG · ICREA

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

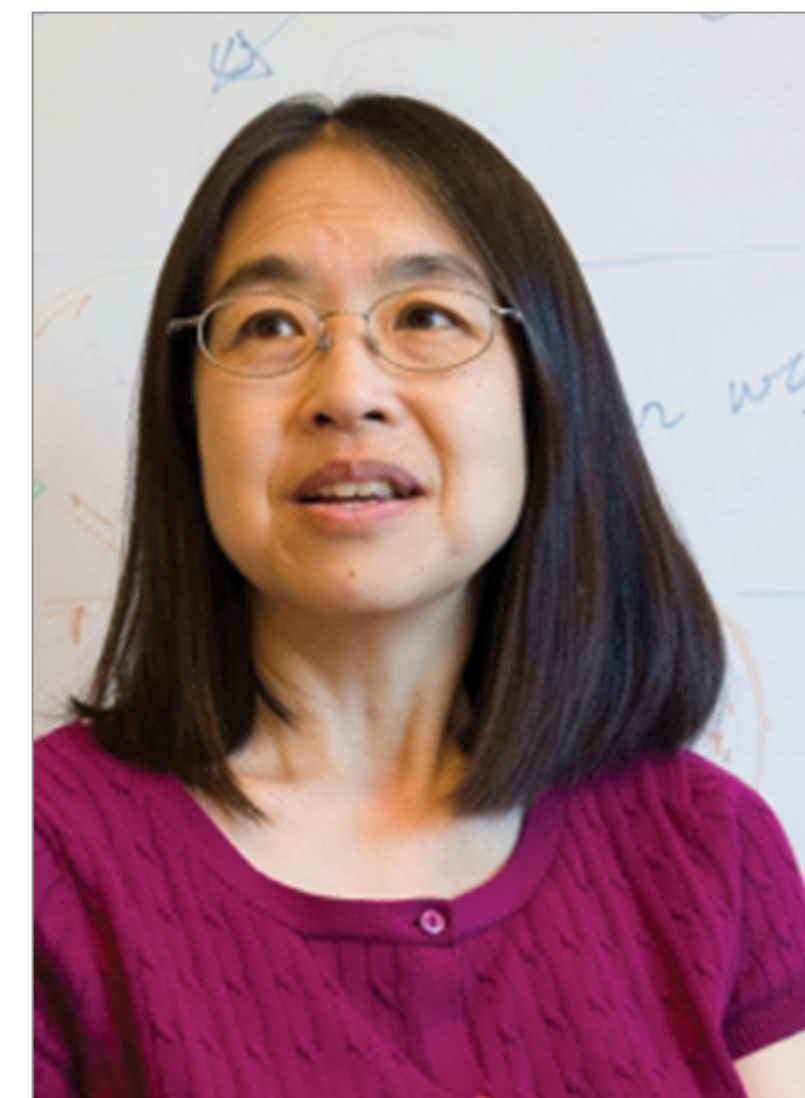
cnag CRG[®] ICREA



Irene Farabella
CNAG-CRG



Guy Nir
Harvard Med School



Ting Wu
Harvard Med School

Can we walk the chromatin path in the nucleus?

by

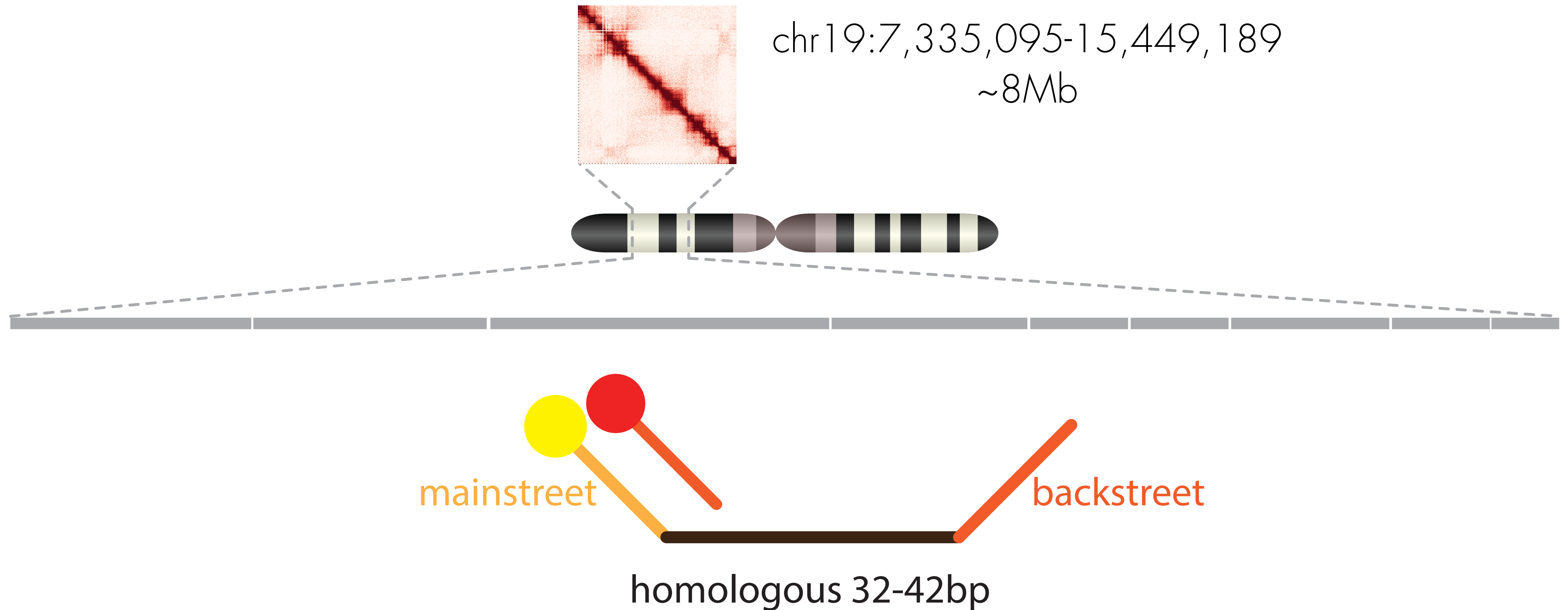
Integrating imaging and Hi-C maps with modeling.

by developing a method for

Oligopaint-based modeling of genomes

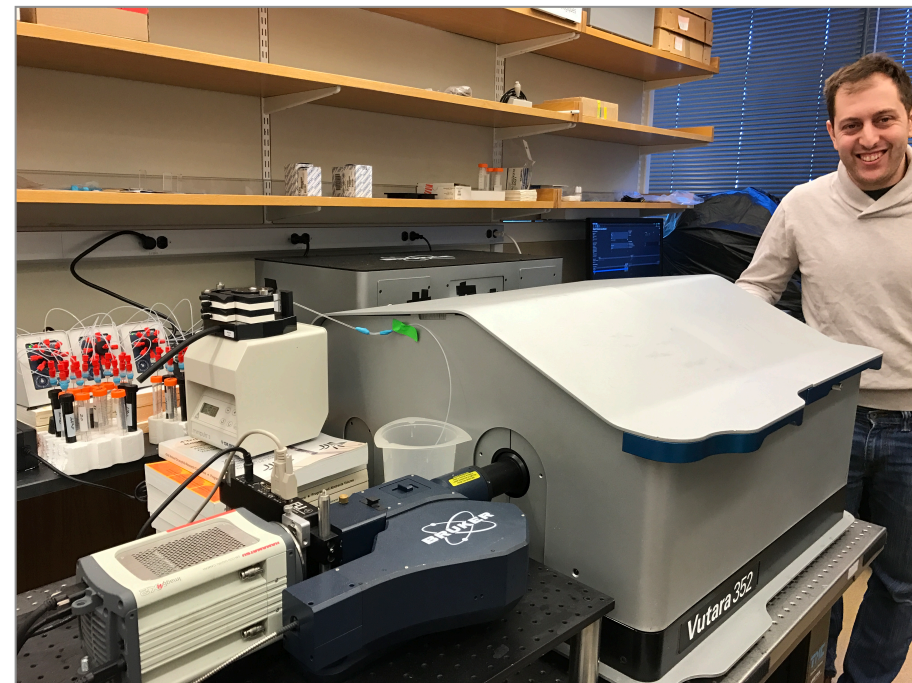
High-resolution imaging

Tracing chromosomes with OligoSTORM & fluidics cycles in PGP1 cells



High-resolution imaging

Tracing chromosomes with OligoSTORM & fluidics cycles in PGP1 cells



Guy Nir Harvard Med School

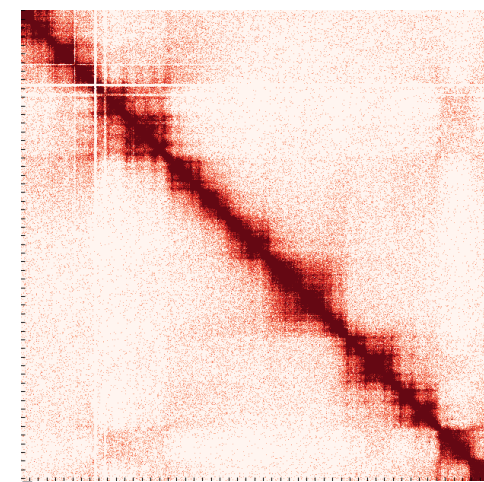
Bodgan Bintu Harvard

Carl Ebeling Bruker

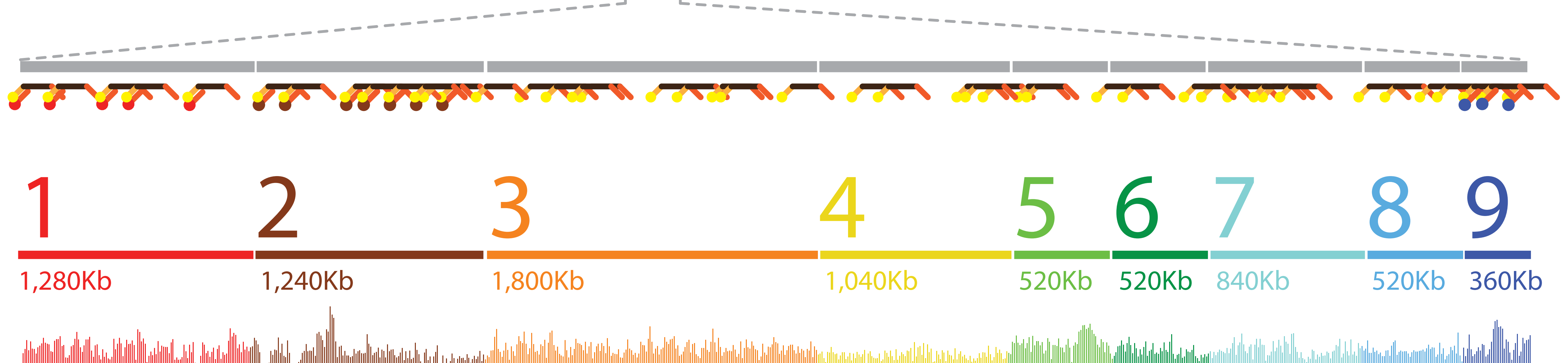
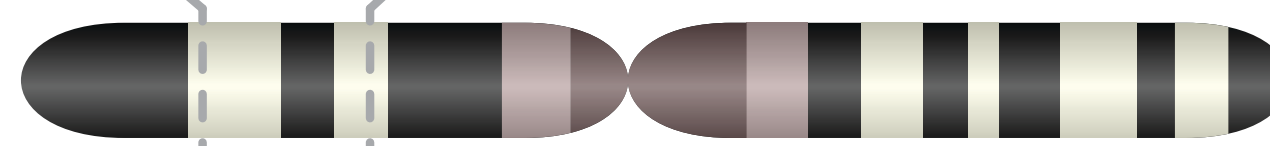
Jeff Stuckey Bruker

John Schreiner Zero Epsilon

Steve Callahan Zero Epsilon

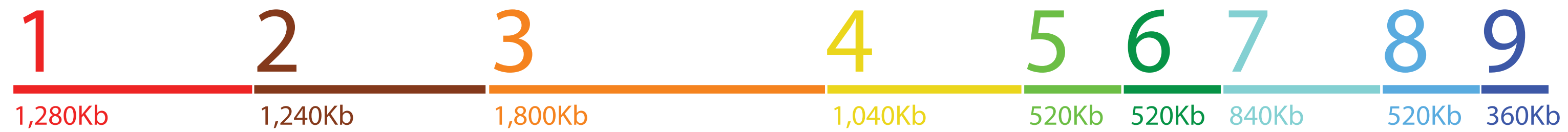


chr19:7,335,095-15,449,189
~8Mb



High-resolution imaging

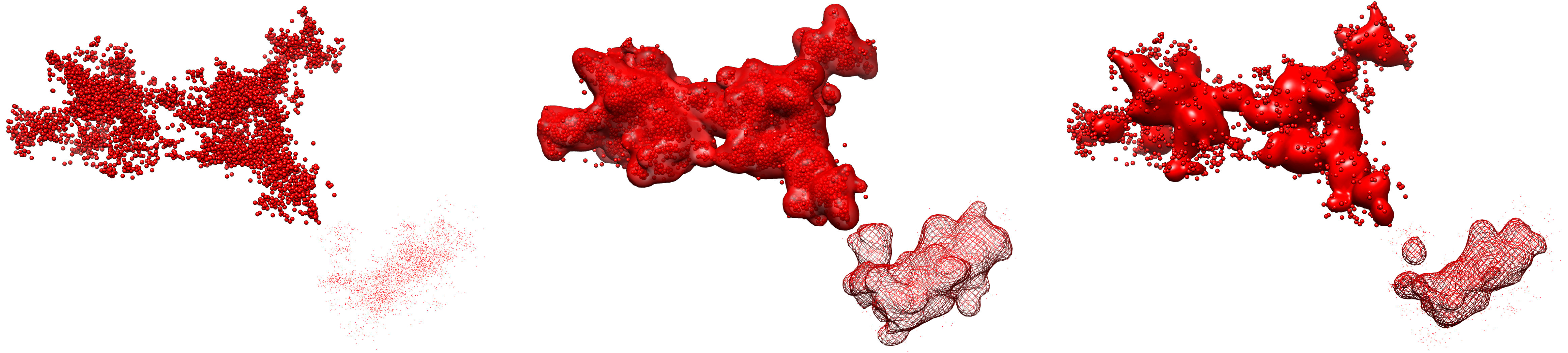
Tracing chr19:7,335,095-15,449,189 ~8Mb



High-resolution imaging

XYZ points convolution into a density map

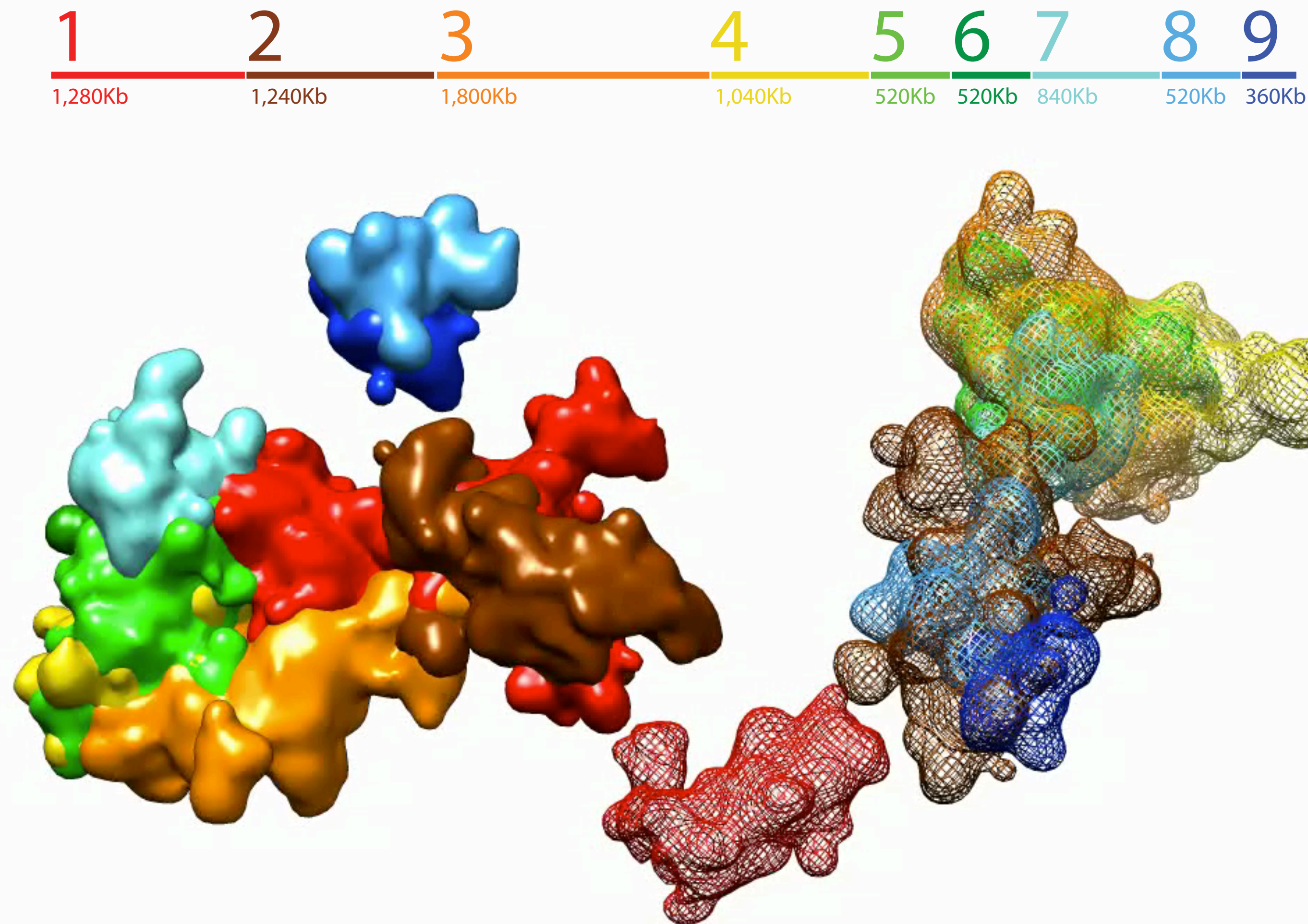
$$\rho(x, y, z) = \sum_N \frac{Z_N}{(\sigma\sqrt{2\pi})^3} e^{-\frac{(x-x_n)^2 + (y-y_n)^2 + (z-z_n)^2}{2\sigma^2}}$$



Cell-02 · Segment 1

Density maps

Cell-02 · Density map @ 50nm



Area (nm²)

Volume (nm³)

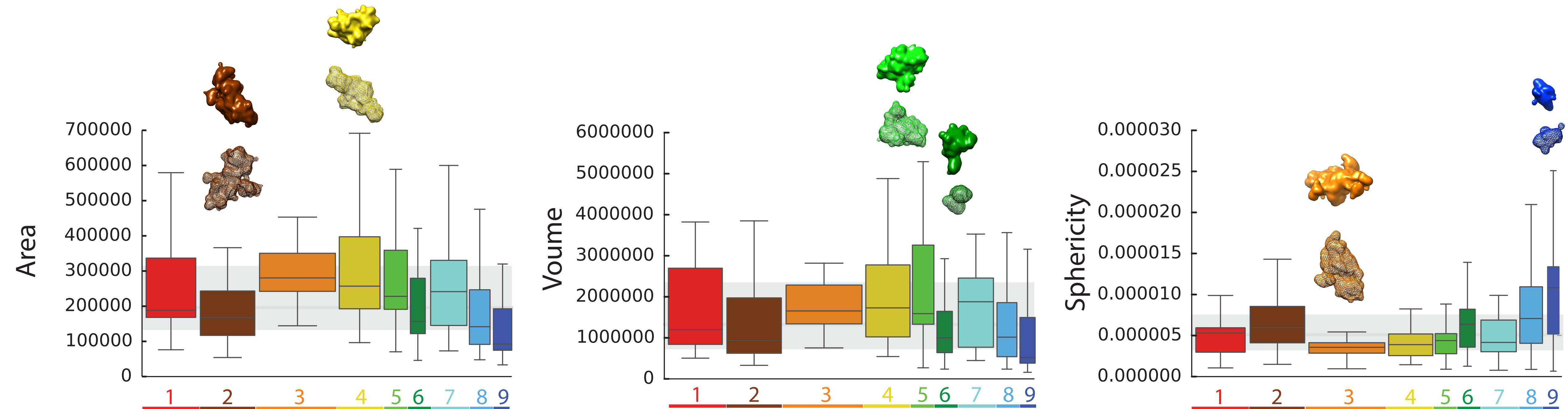
Sphericity

Overlap (%)

Distance (nm)

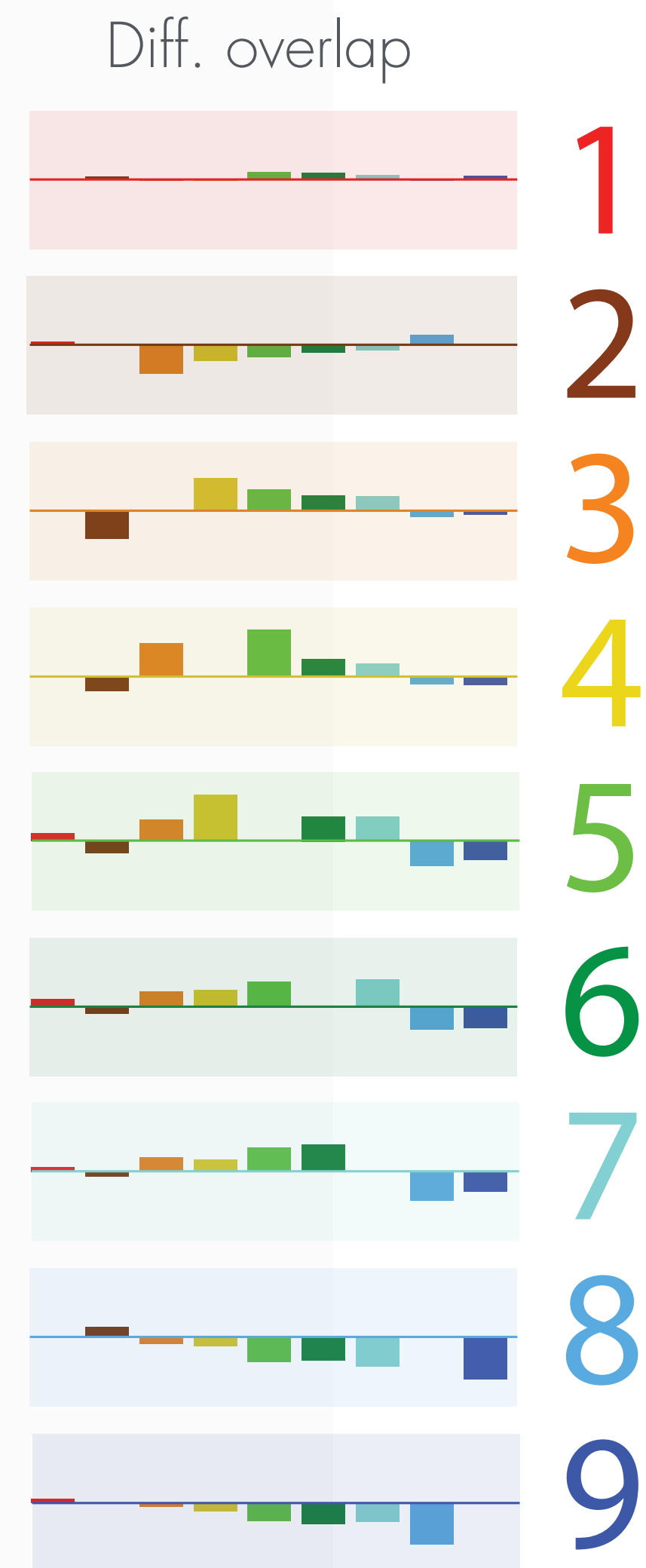
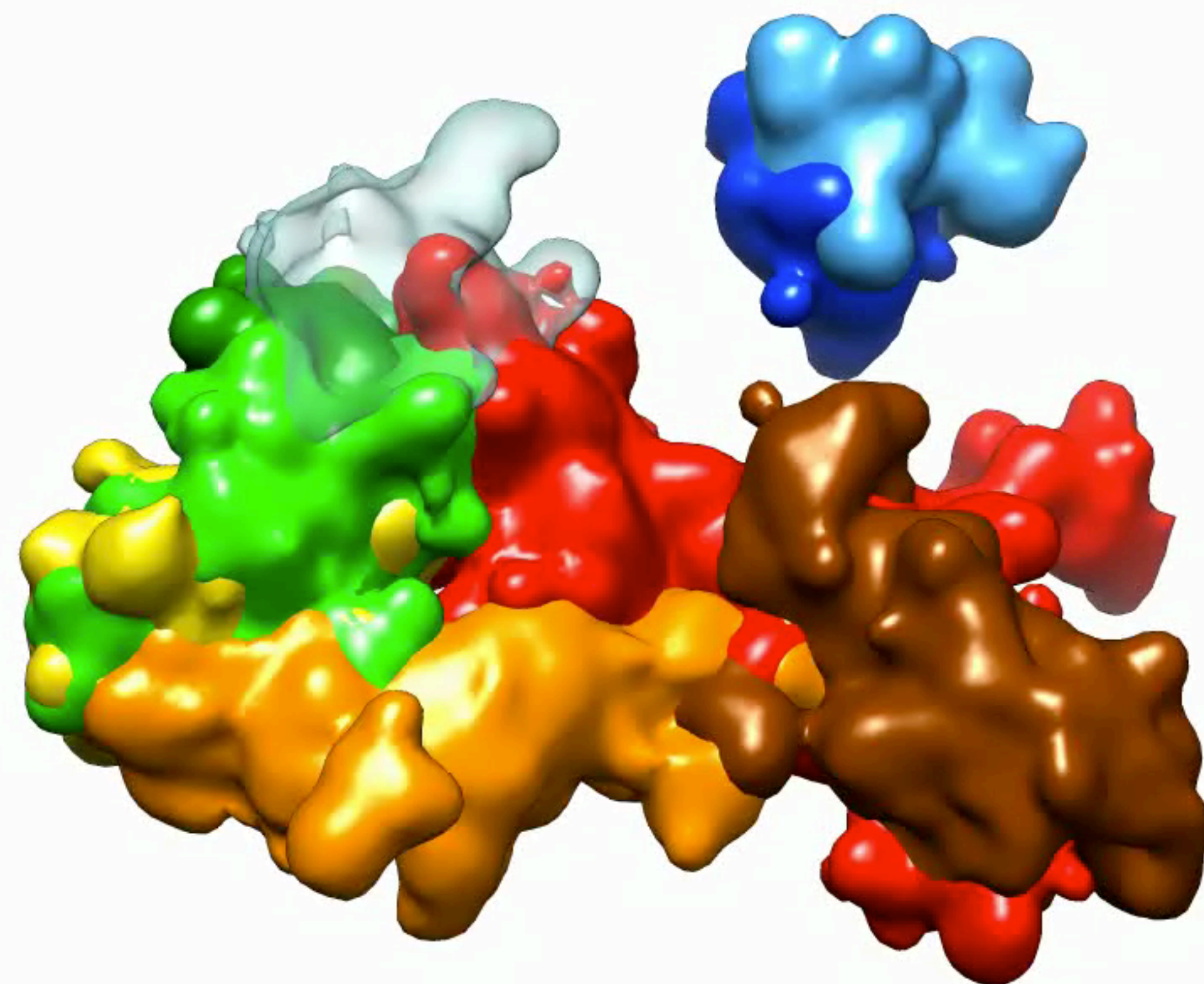
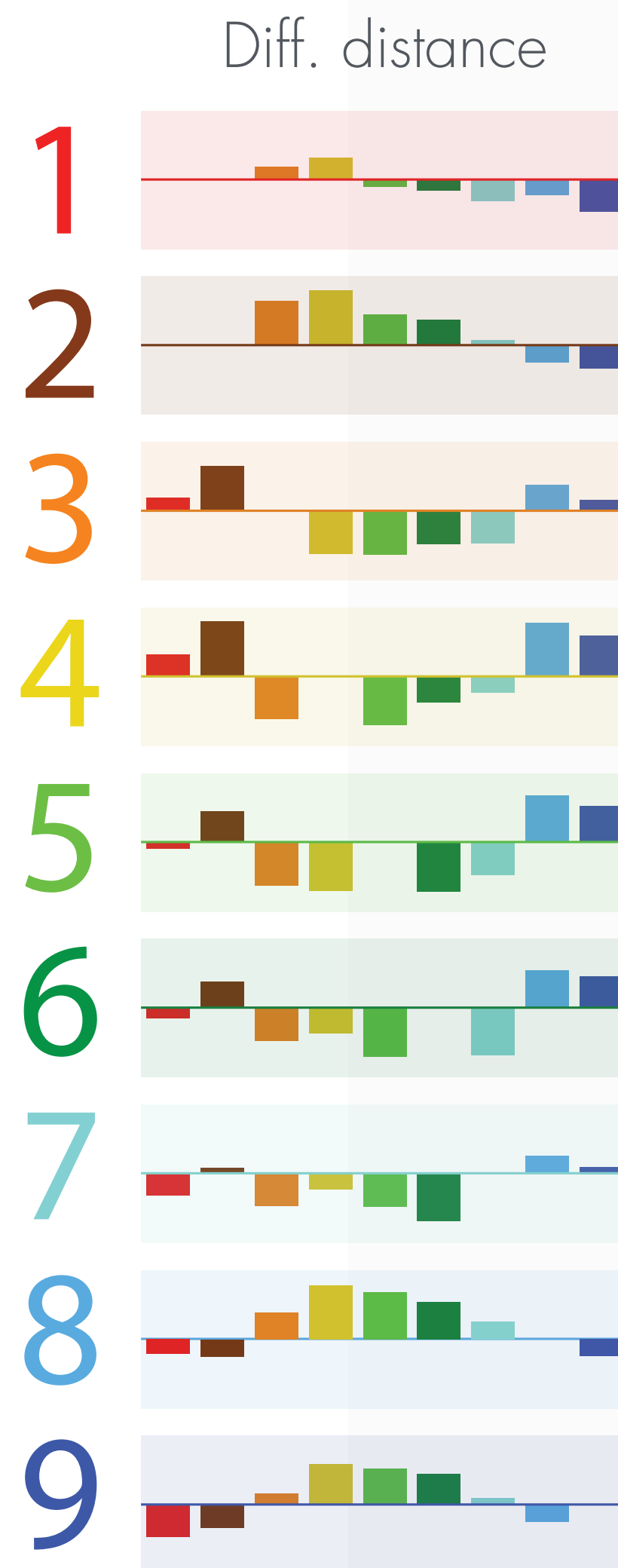
Structural features

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



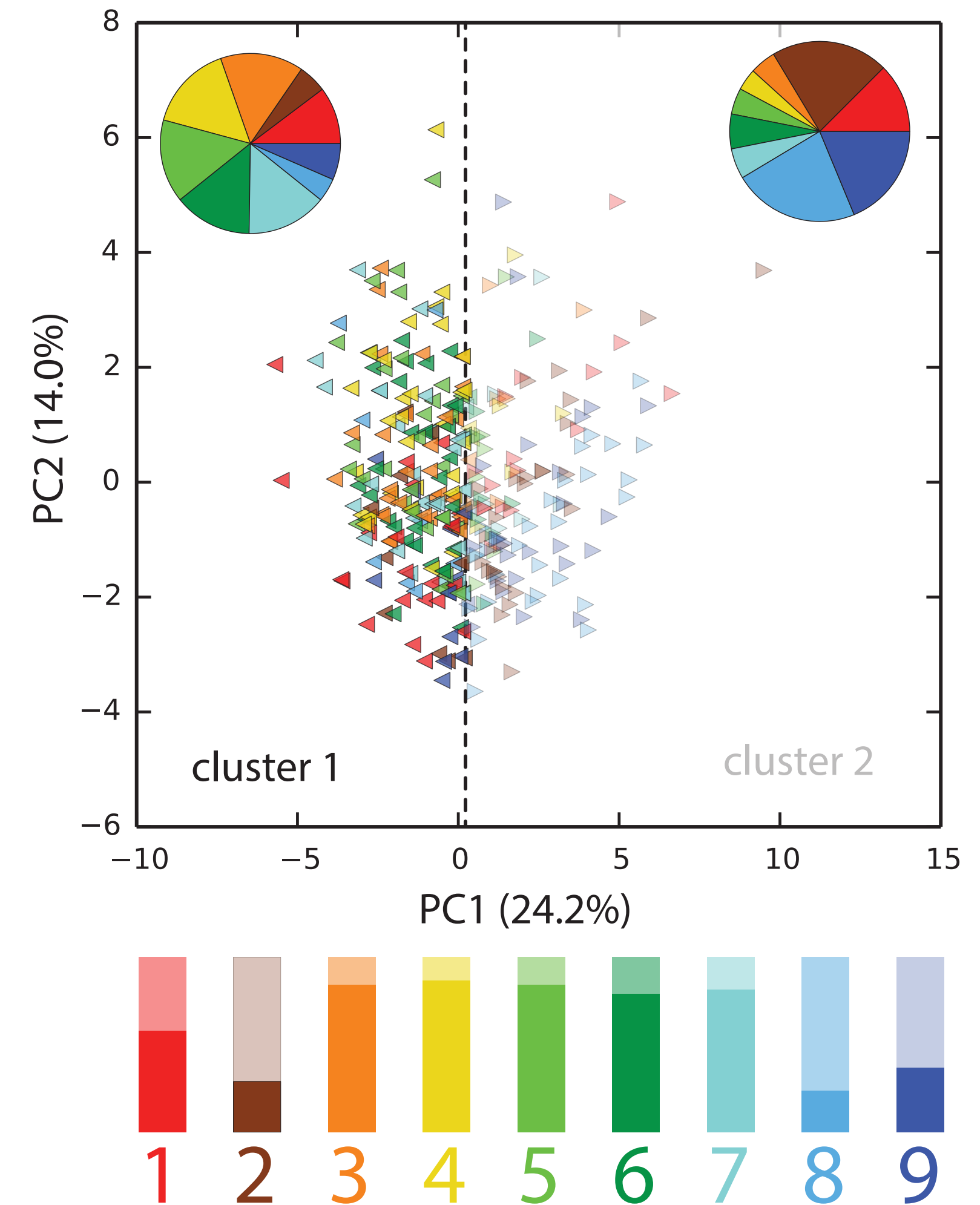
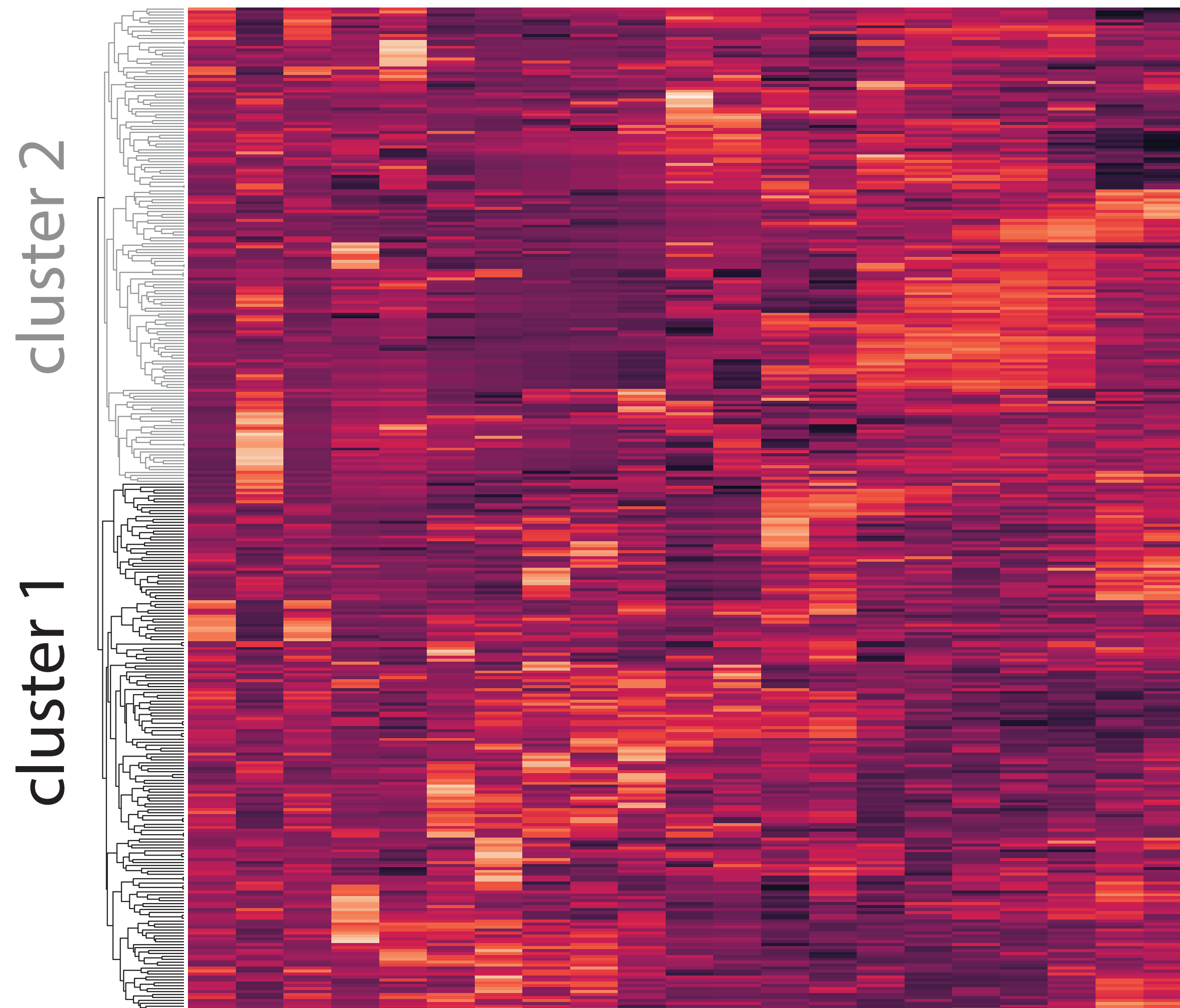
Spatial arrangement

Distance and overlap of 19 cells each with 2 homologous resolved



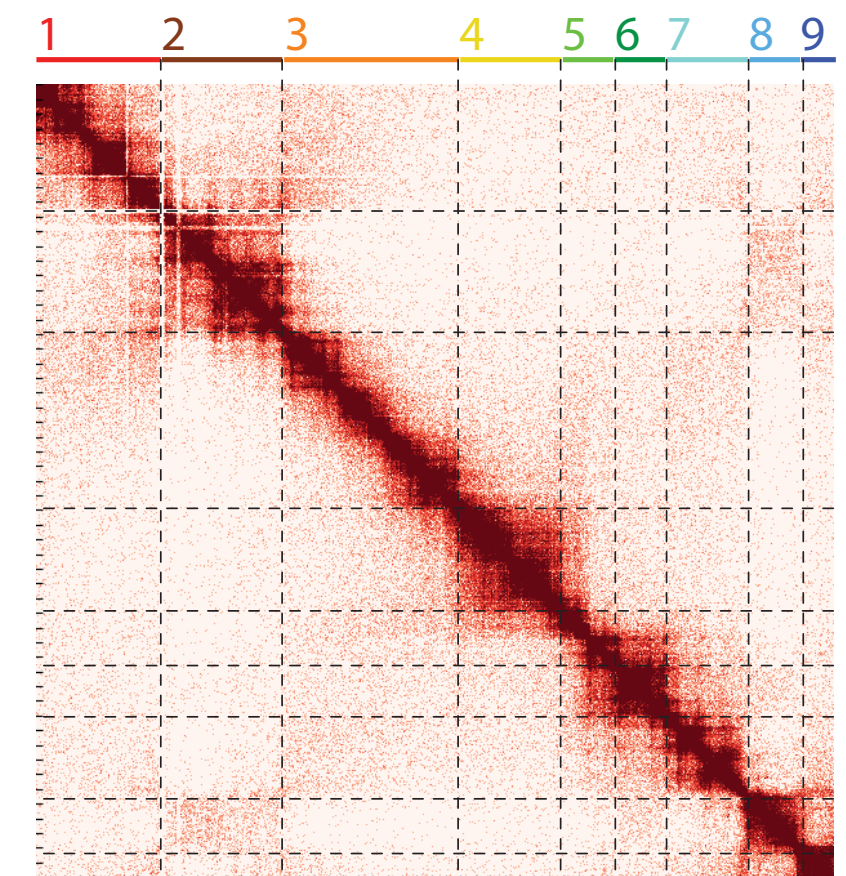
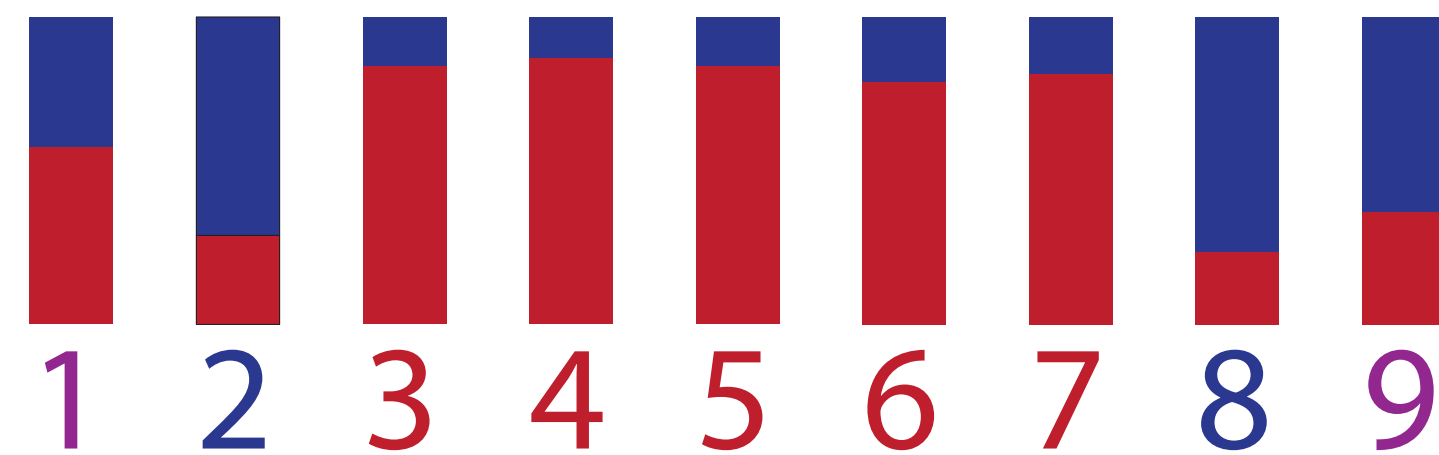
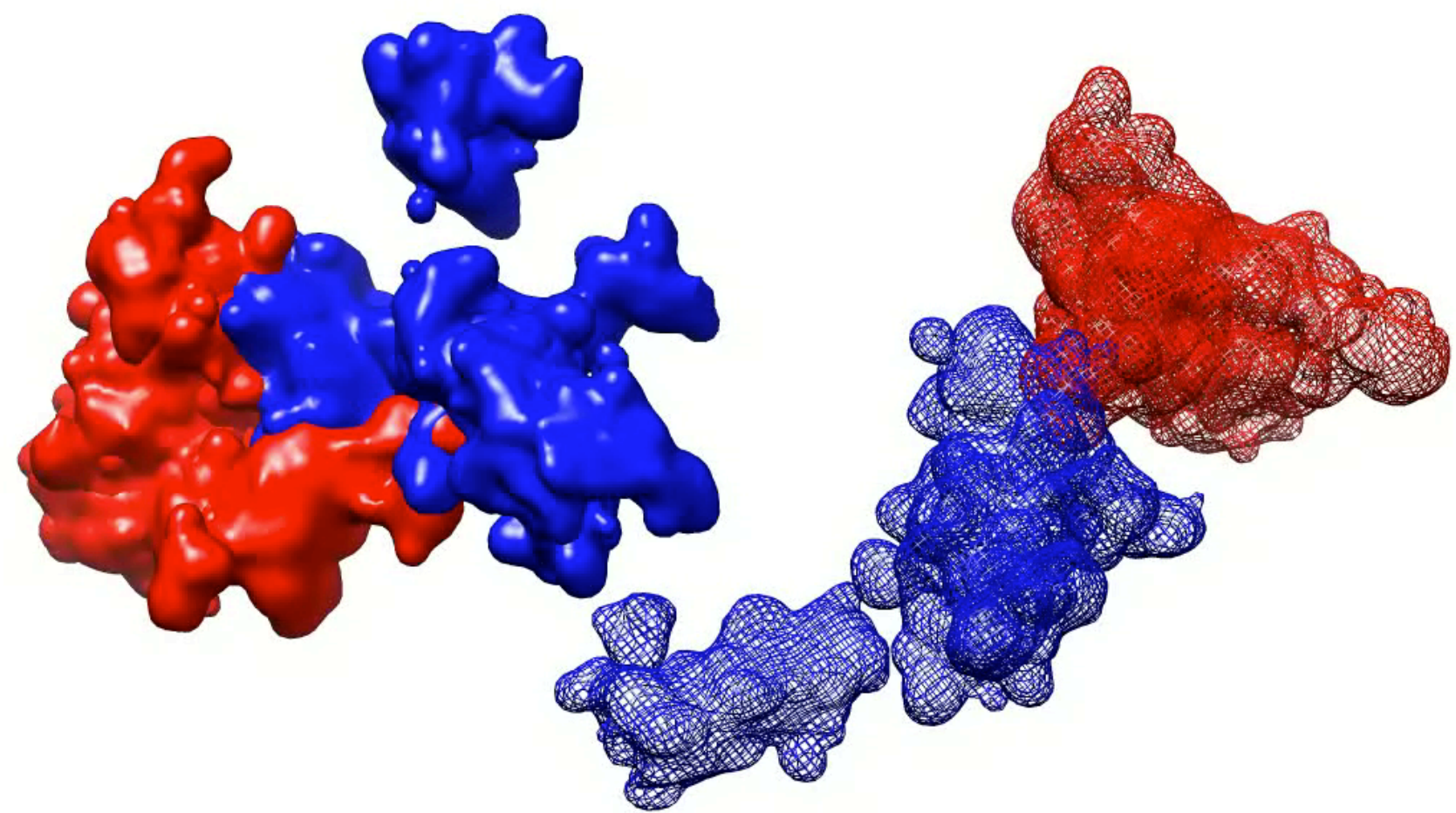
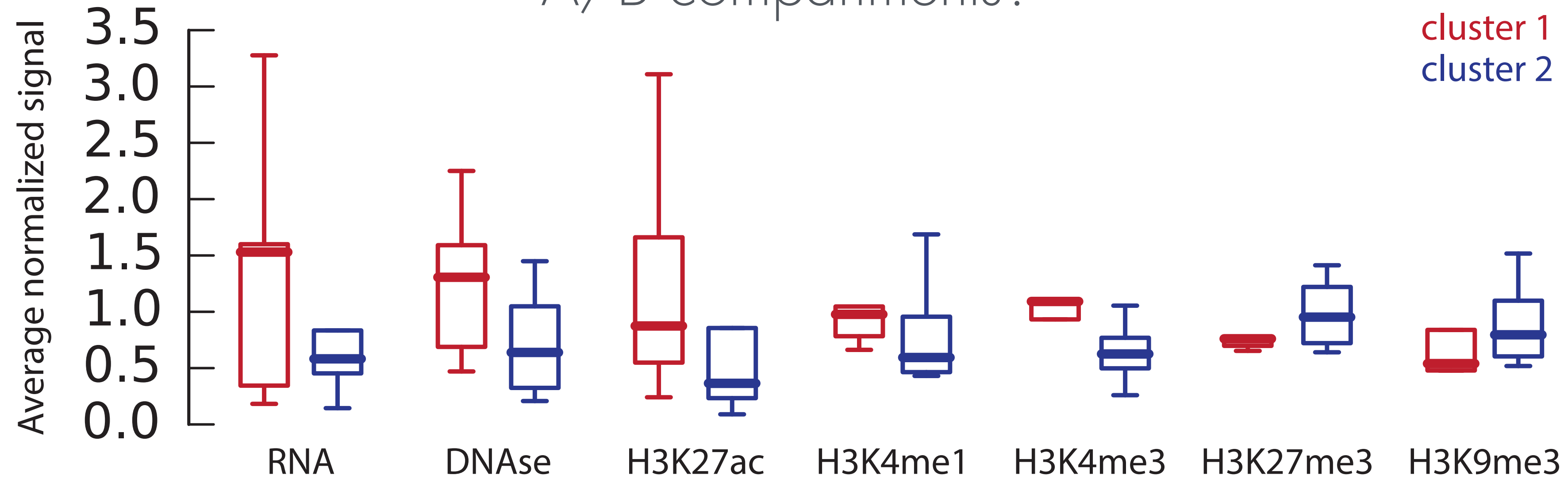
Structural clustering

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



Cluster properties

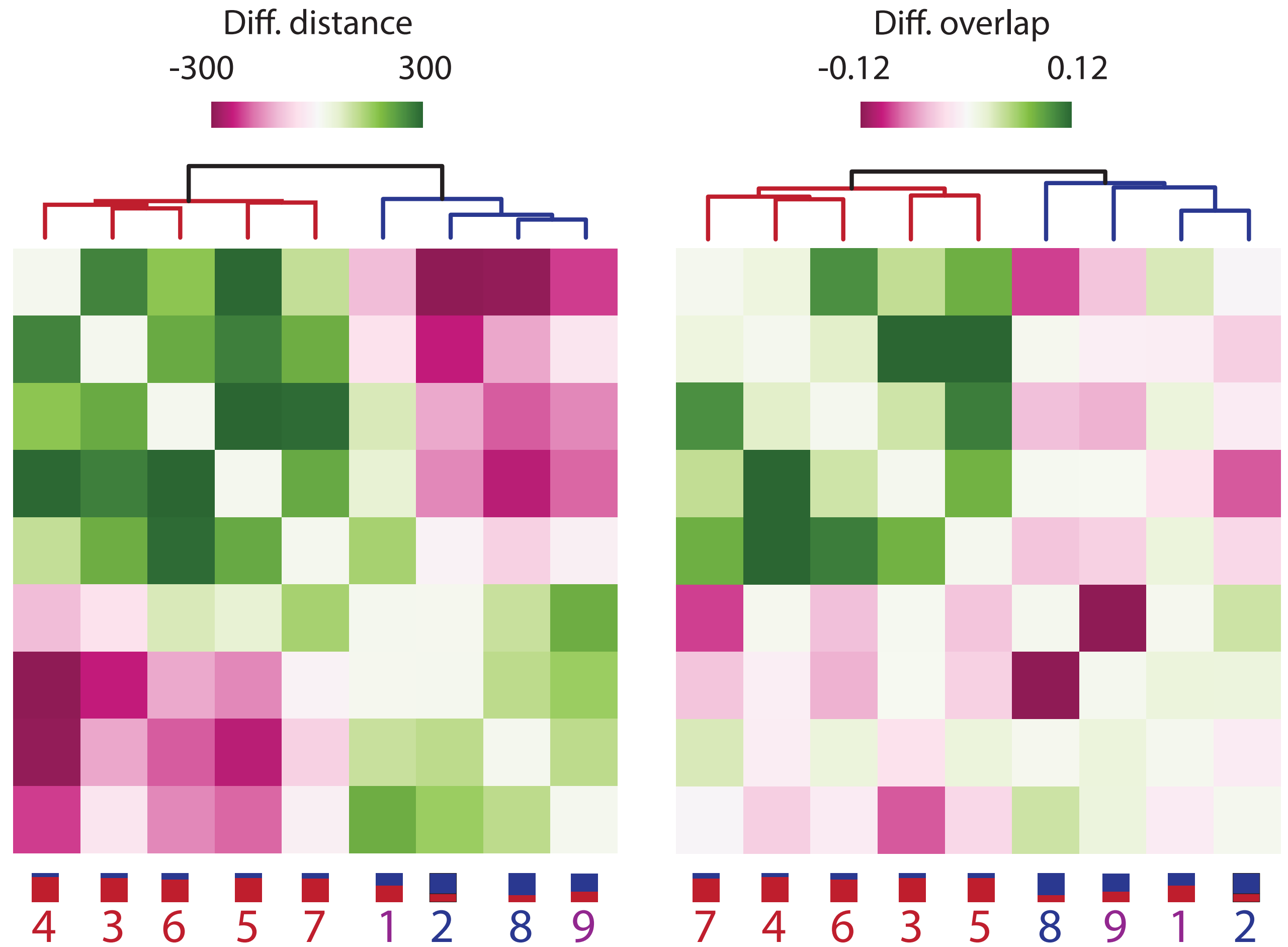
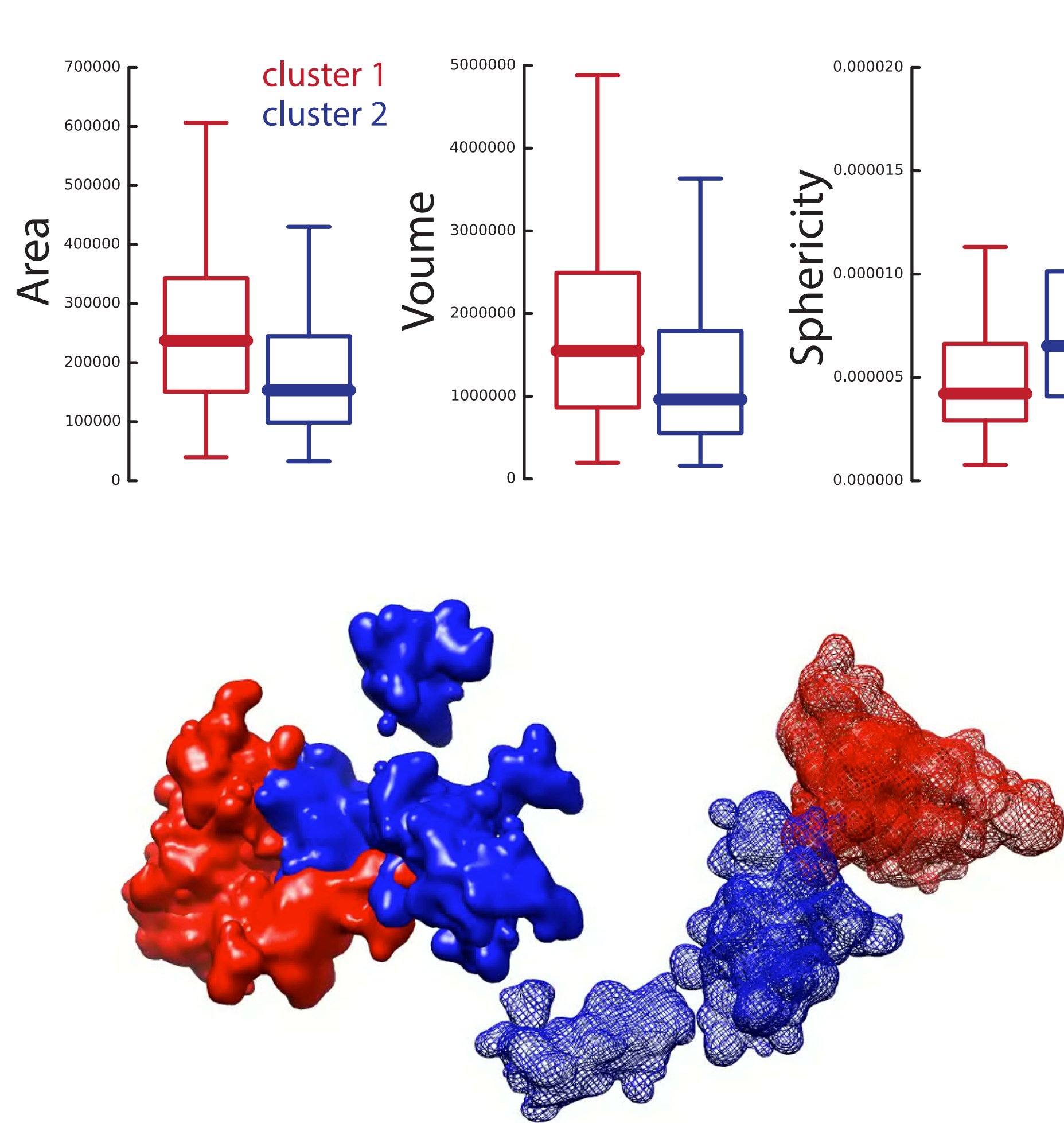
A/B compartments?



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

A/B compartment properties

A/B compartment properties



Can we walk the chromatin path in the nucleus?

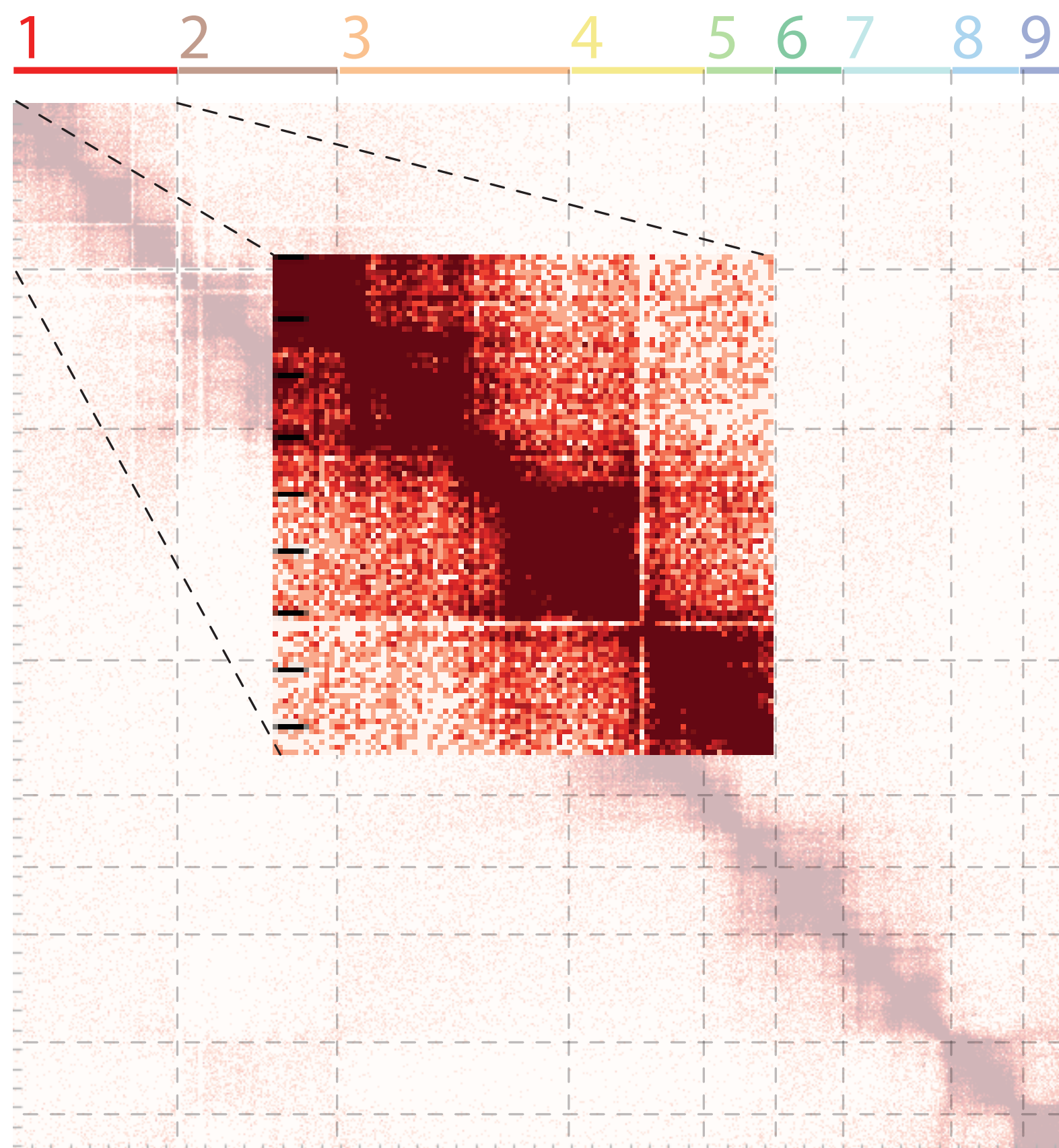
YES!

Can we increase the resolution of our data?

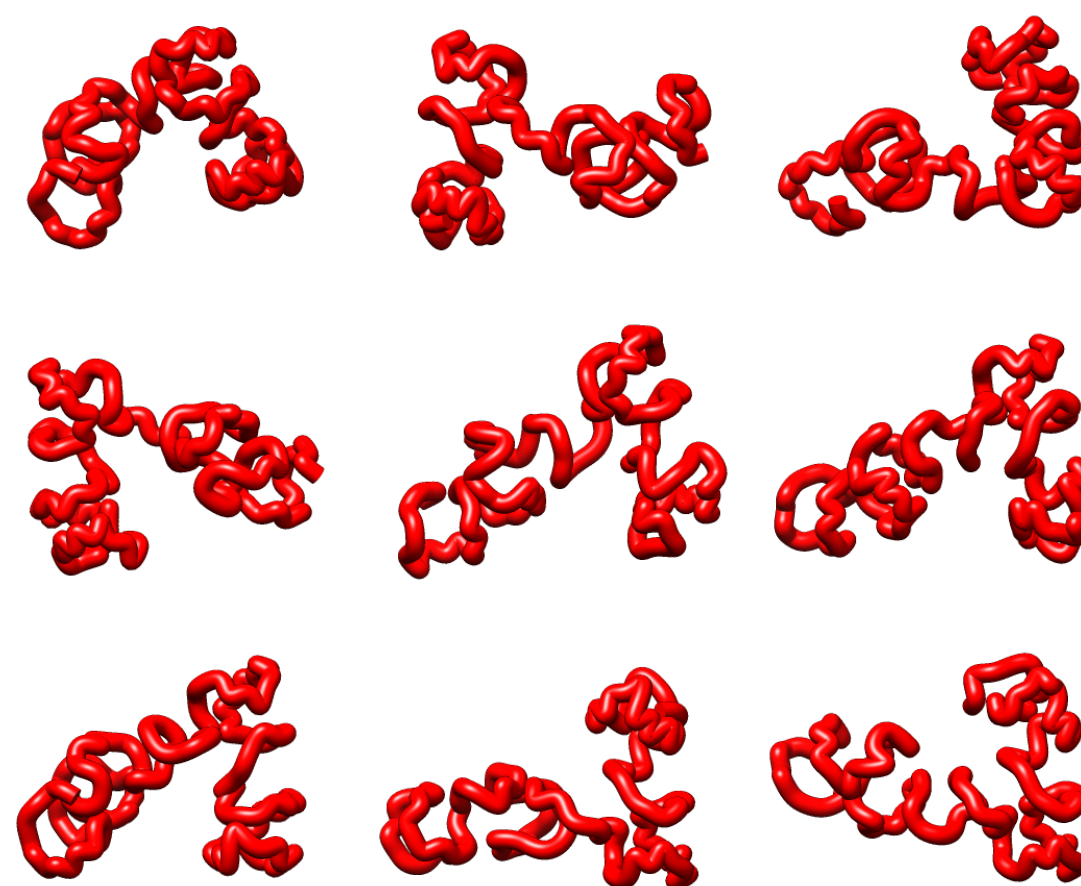
by fitting 3D models based on Hi-C interaction maps

Increasing resolution

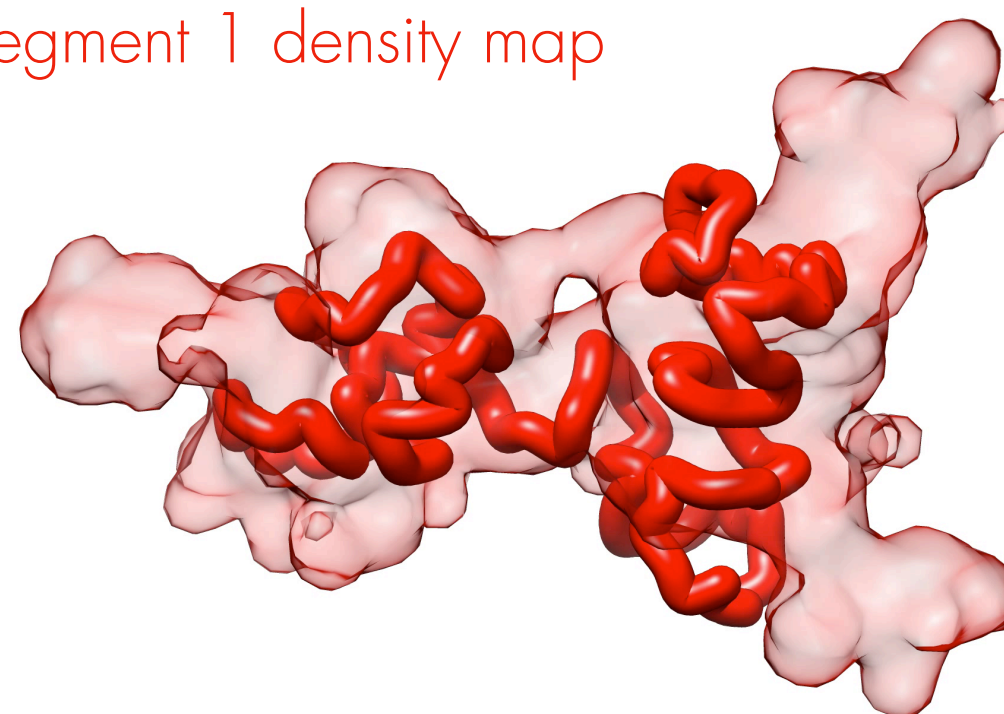
Rigid body fitting 3D structures based on Hi-C data



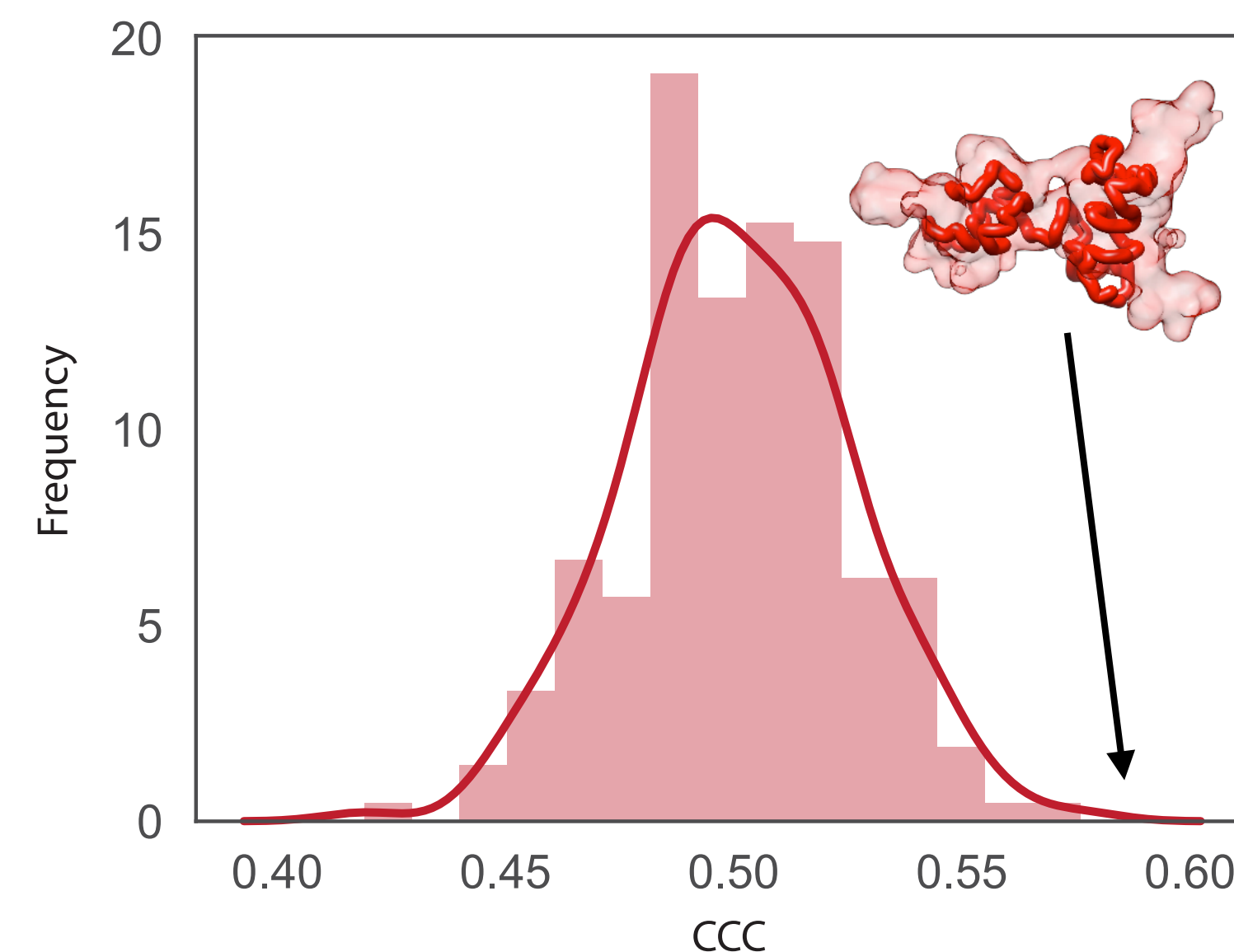
Segment 1 3D models



Segment 1 density map

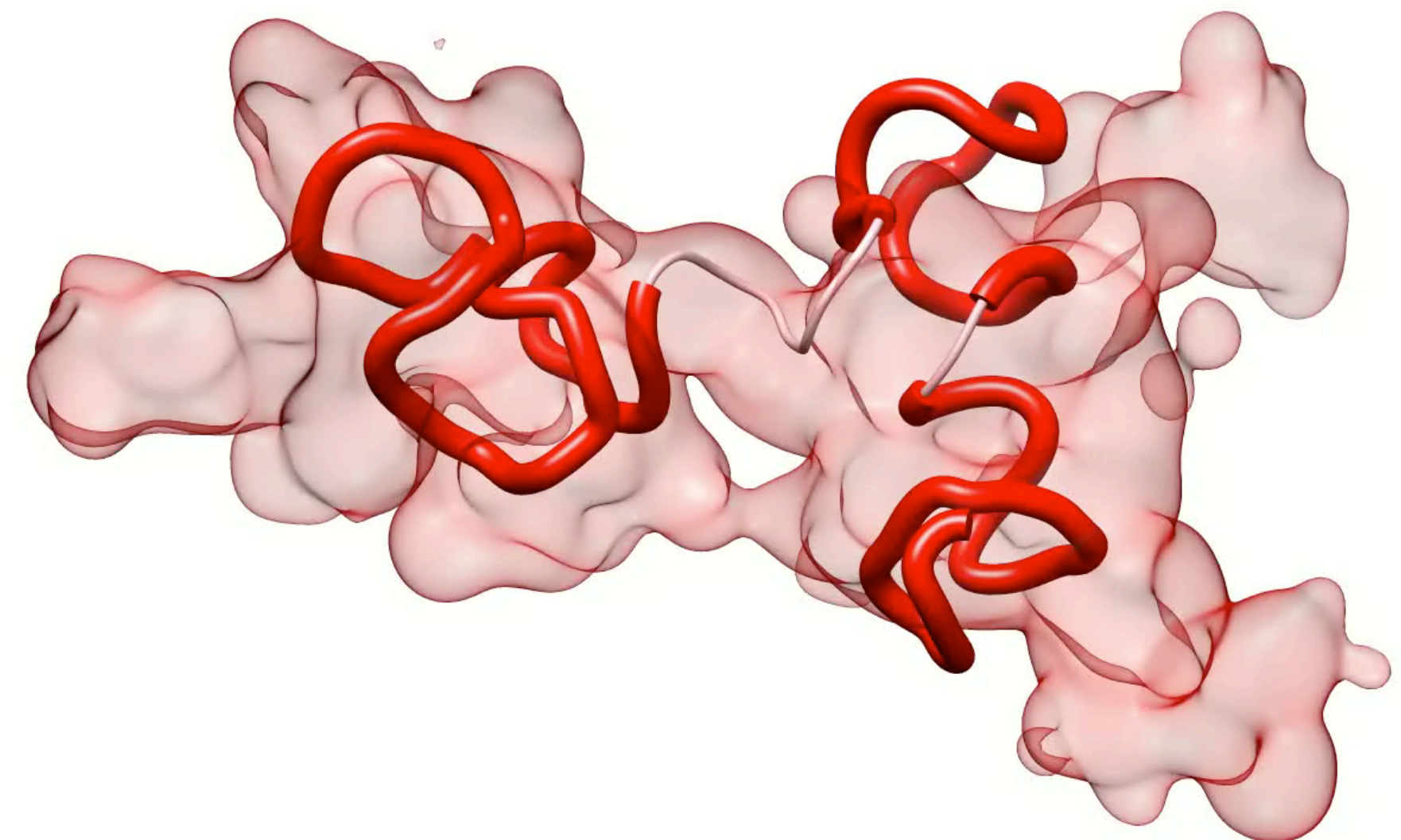
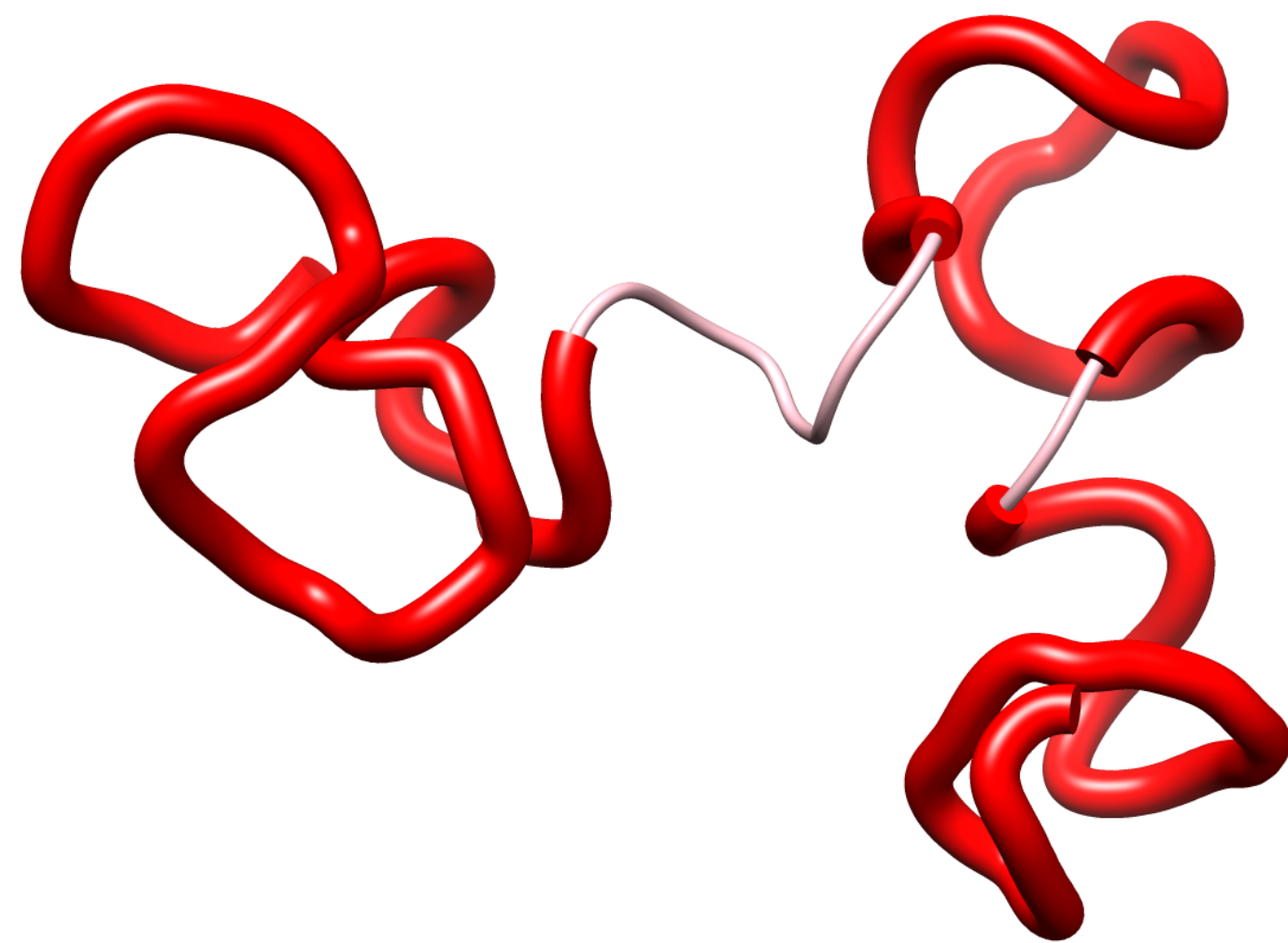
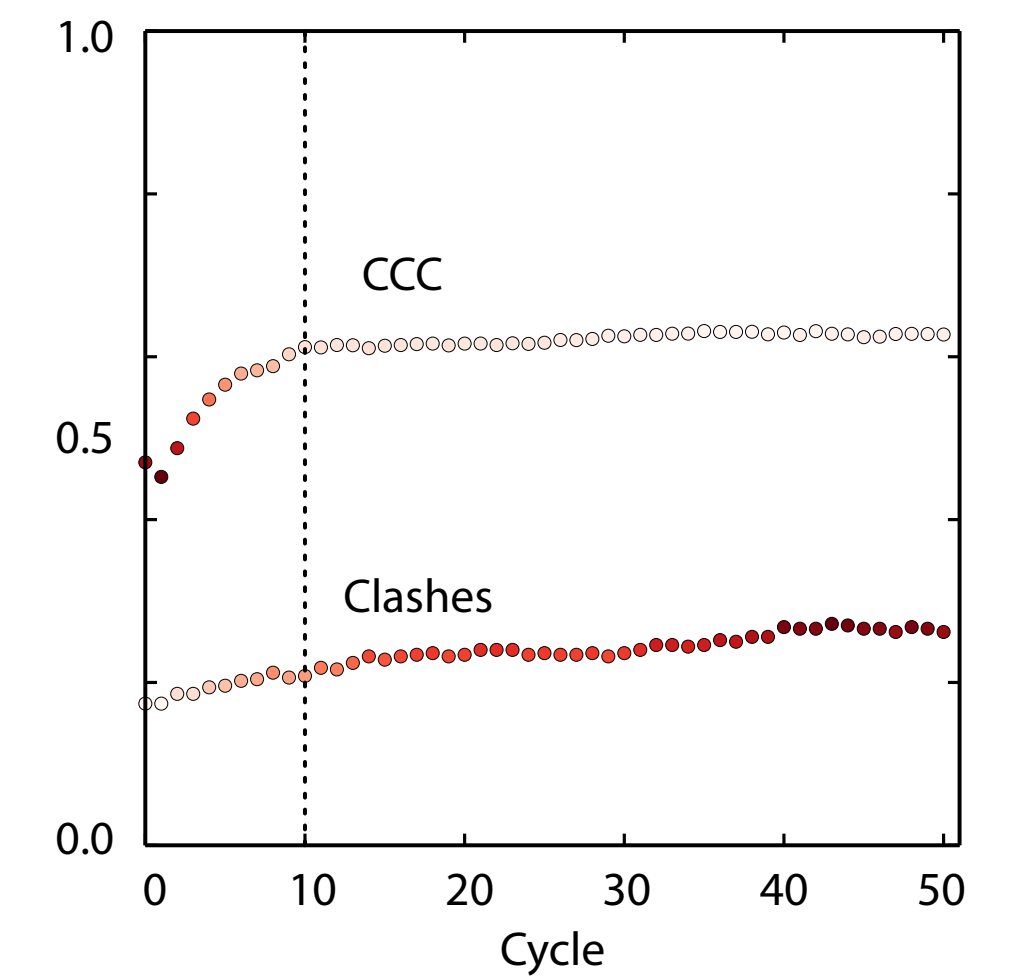
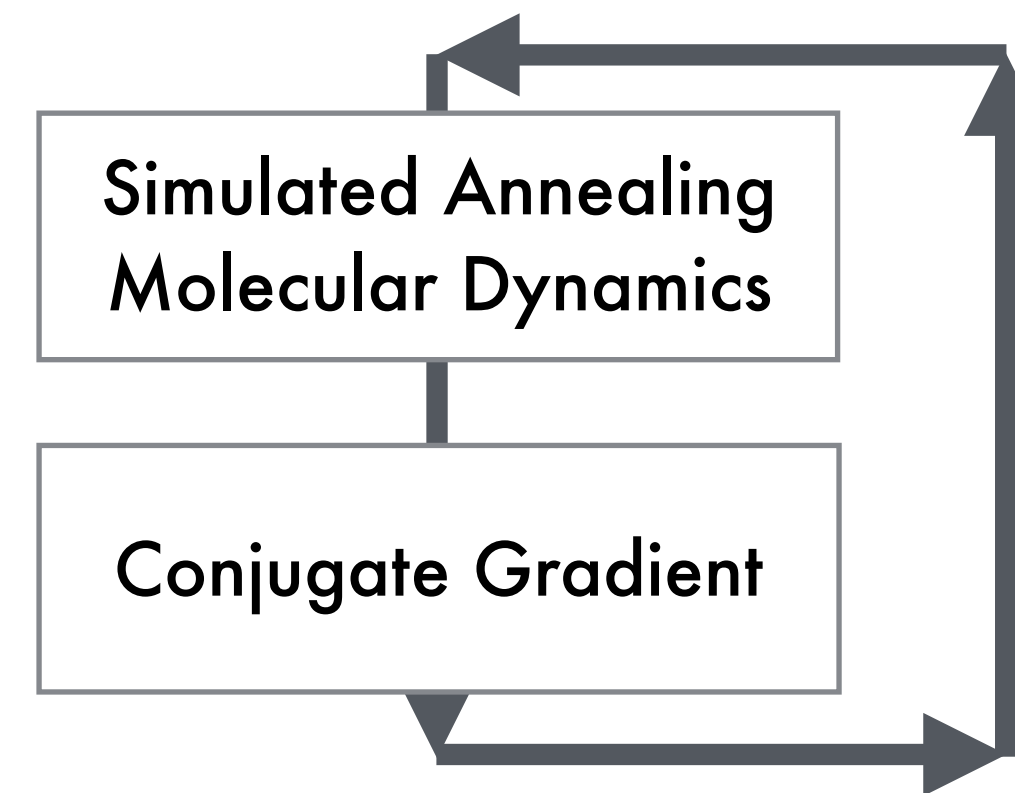
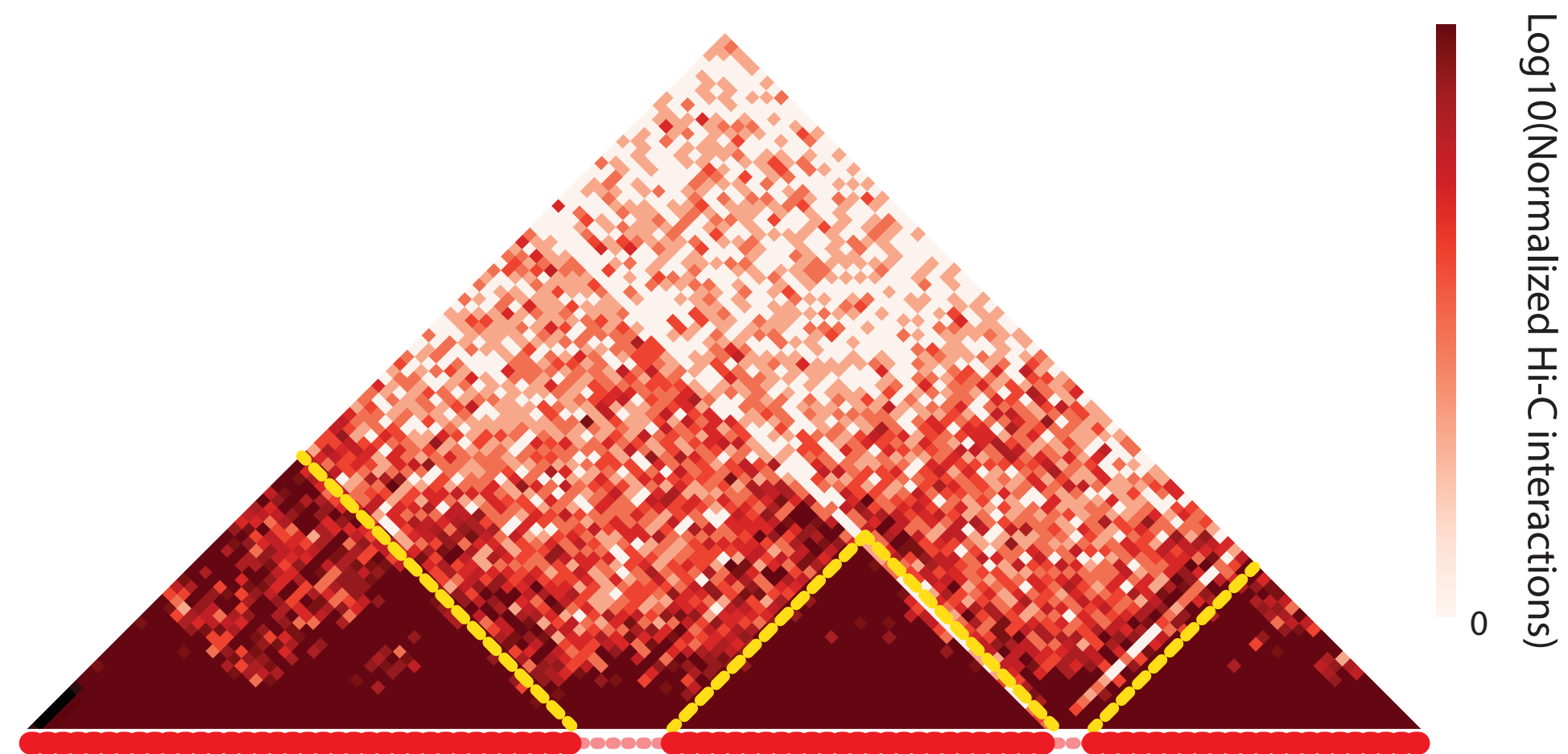


$$CCC = \frac{\sum_{i=1}^M [\rho_i^{EM} - \bar{\rho}^{EM}] [\rho_i^P - \bar{\rho}^P]}{\sqrt{\sum_{i=1}^M [\rho_i^{EM} - \bar{\rho}^{EM}]^2 \sum_{i=1}^M [\rho_i^P - \bar{\rho}^P]^2}}$$



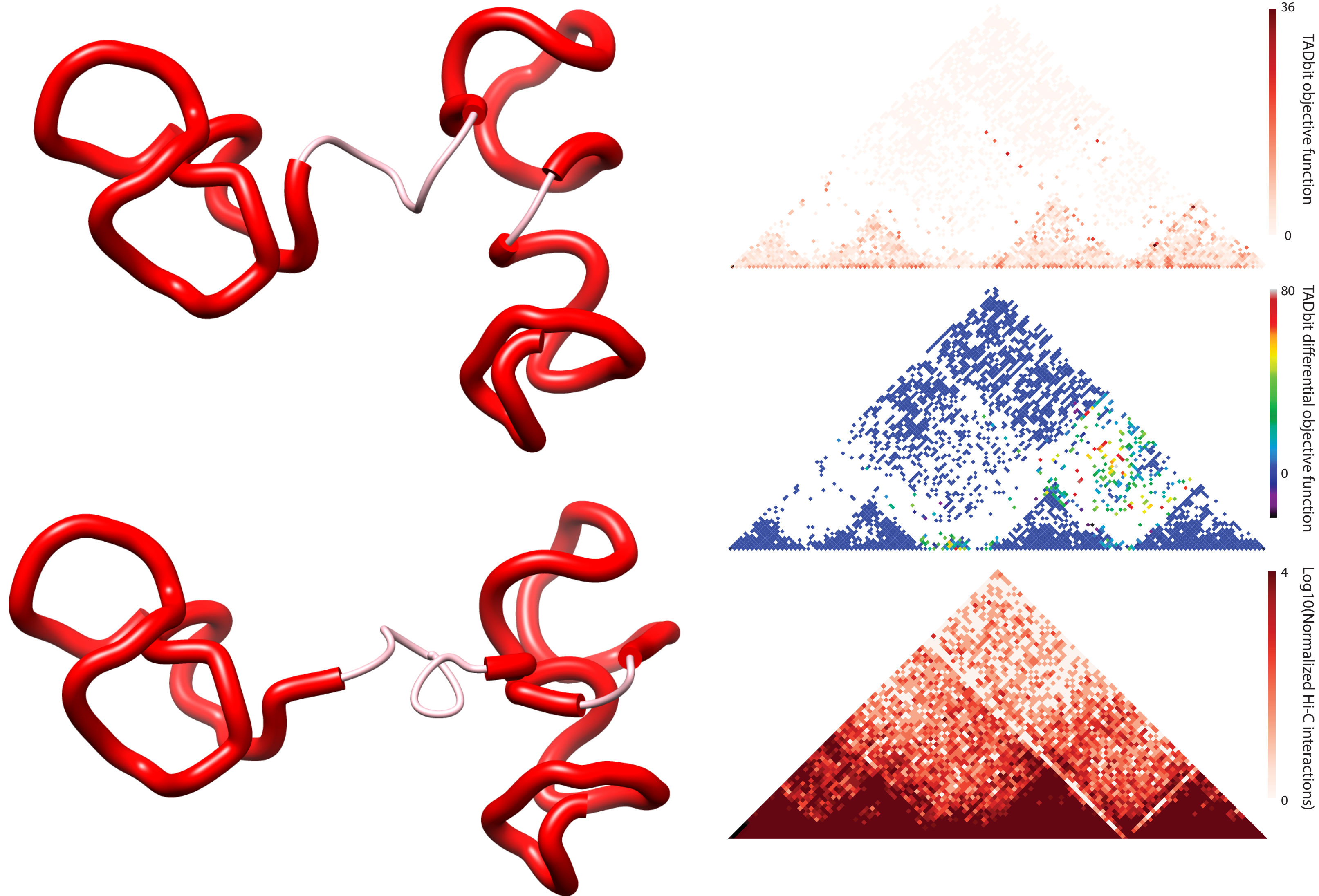
Increasing resolution

Flexible fitting 3D structures based on Hi-C data

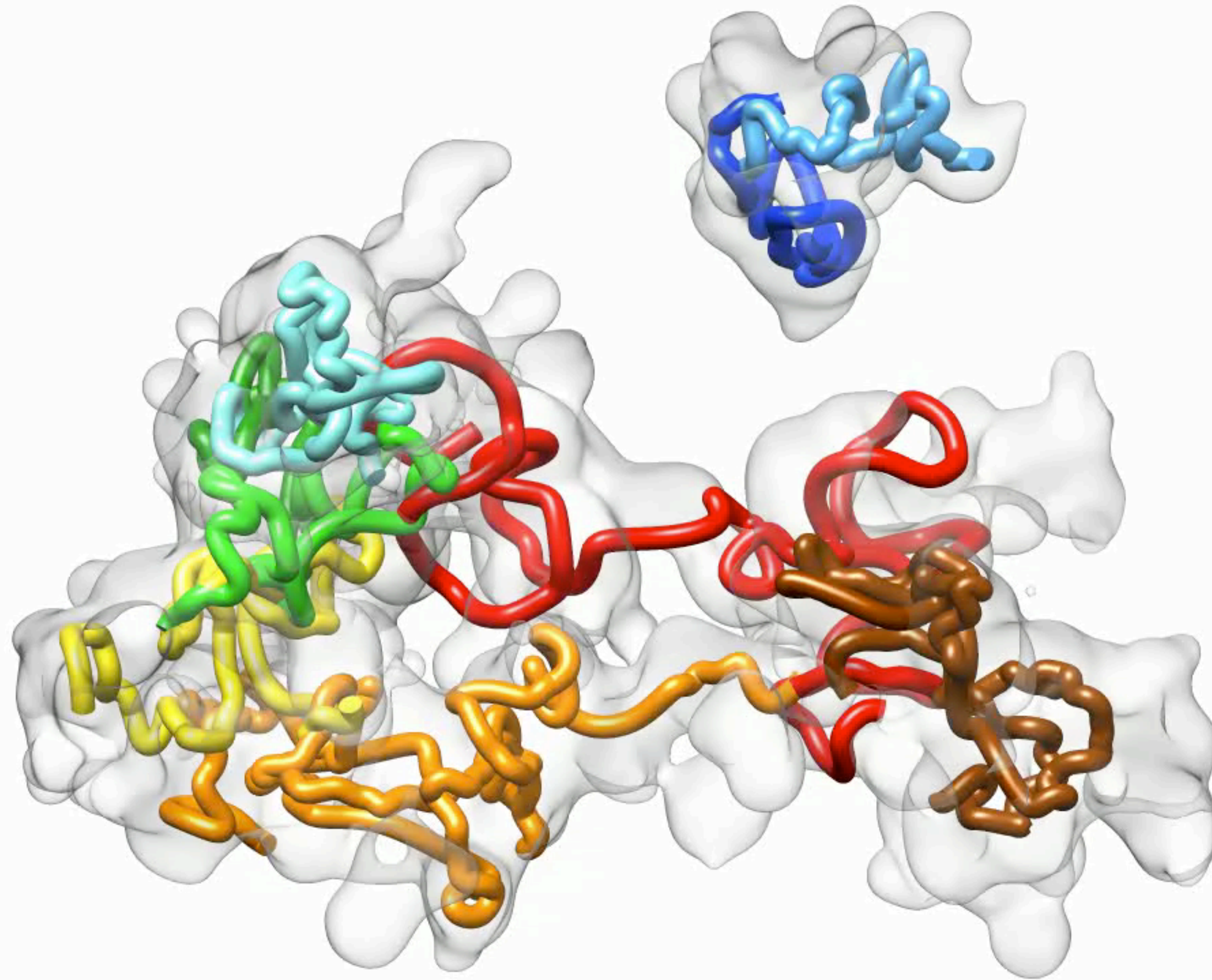


Increasing resolution

Flexible fitting 3D structures based on Hi-C data



Chromosome walking path @10Kb resolution



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