Chromosome walking with super-resolution imaging and modeling

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http://3DGenomes.org
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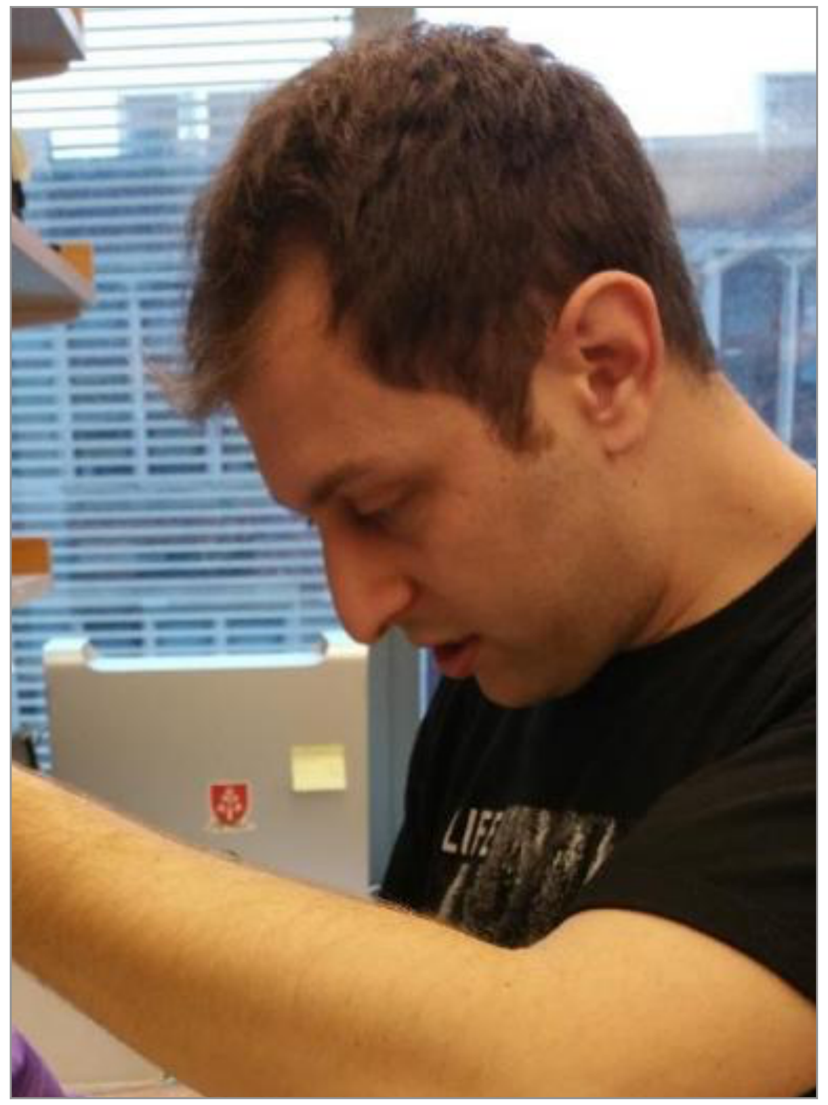
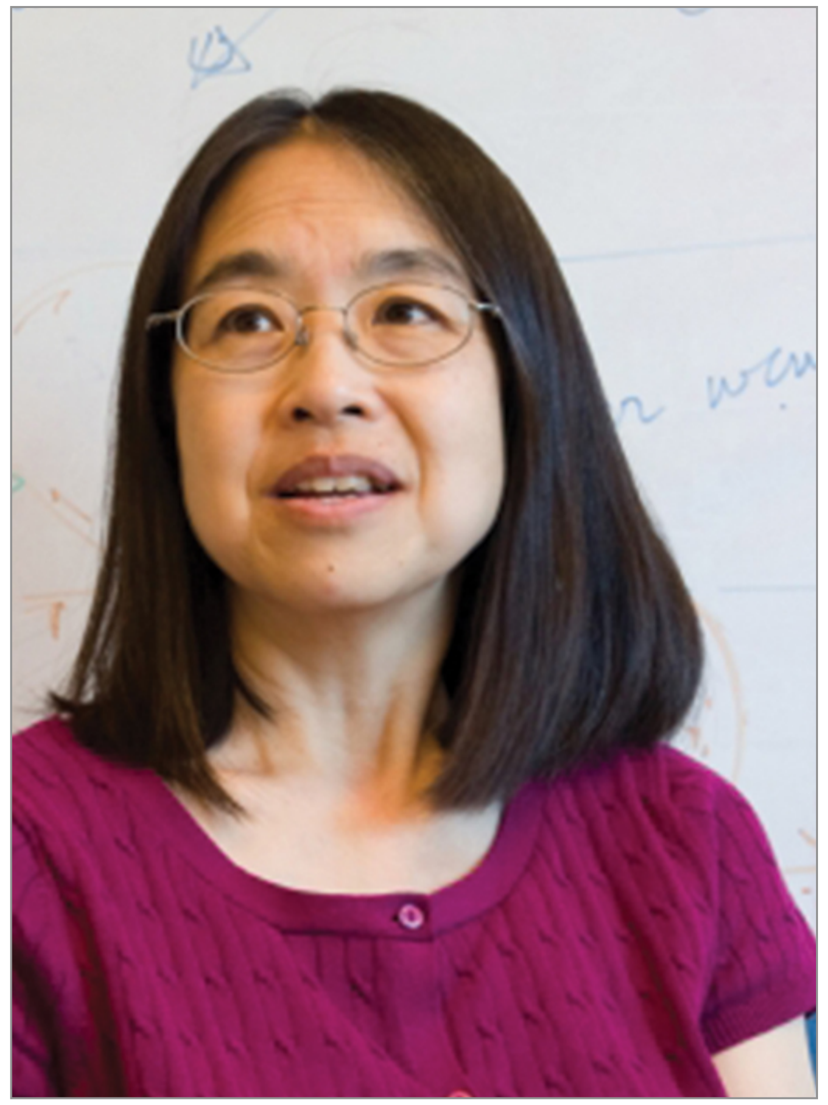


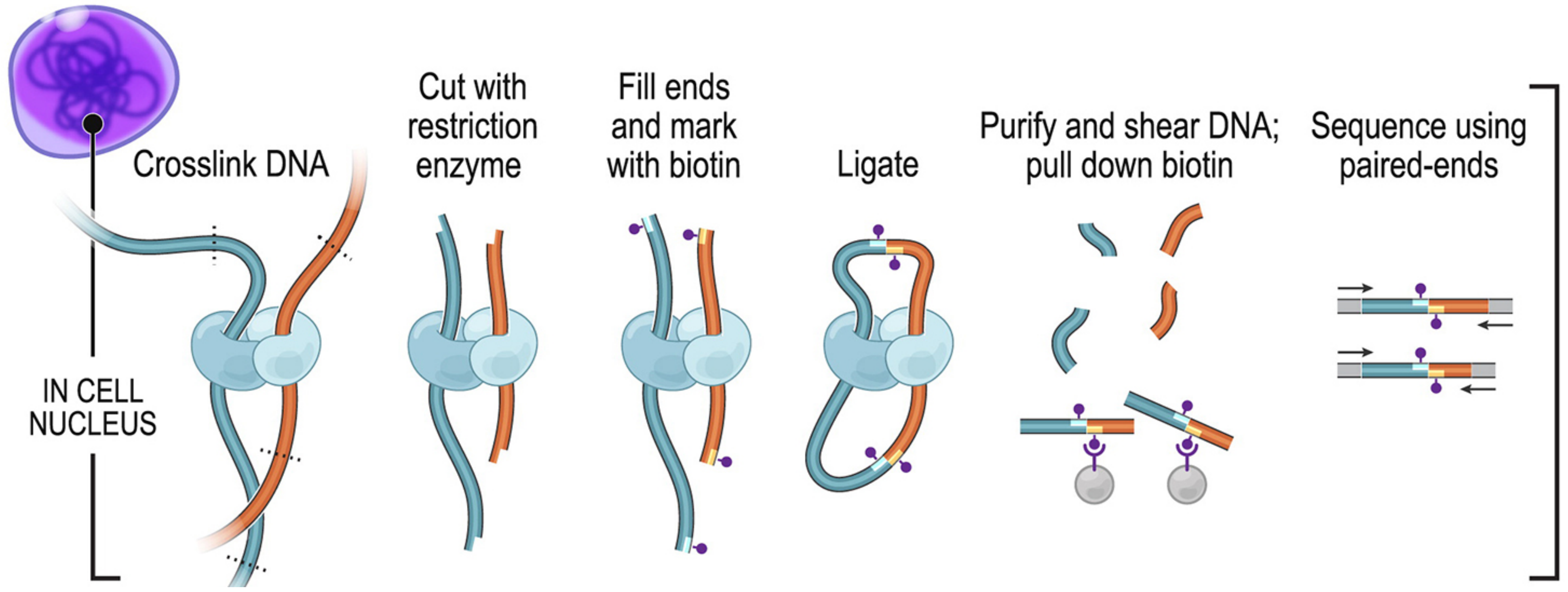
Guy Nir
Harvard Med School

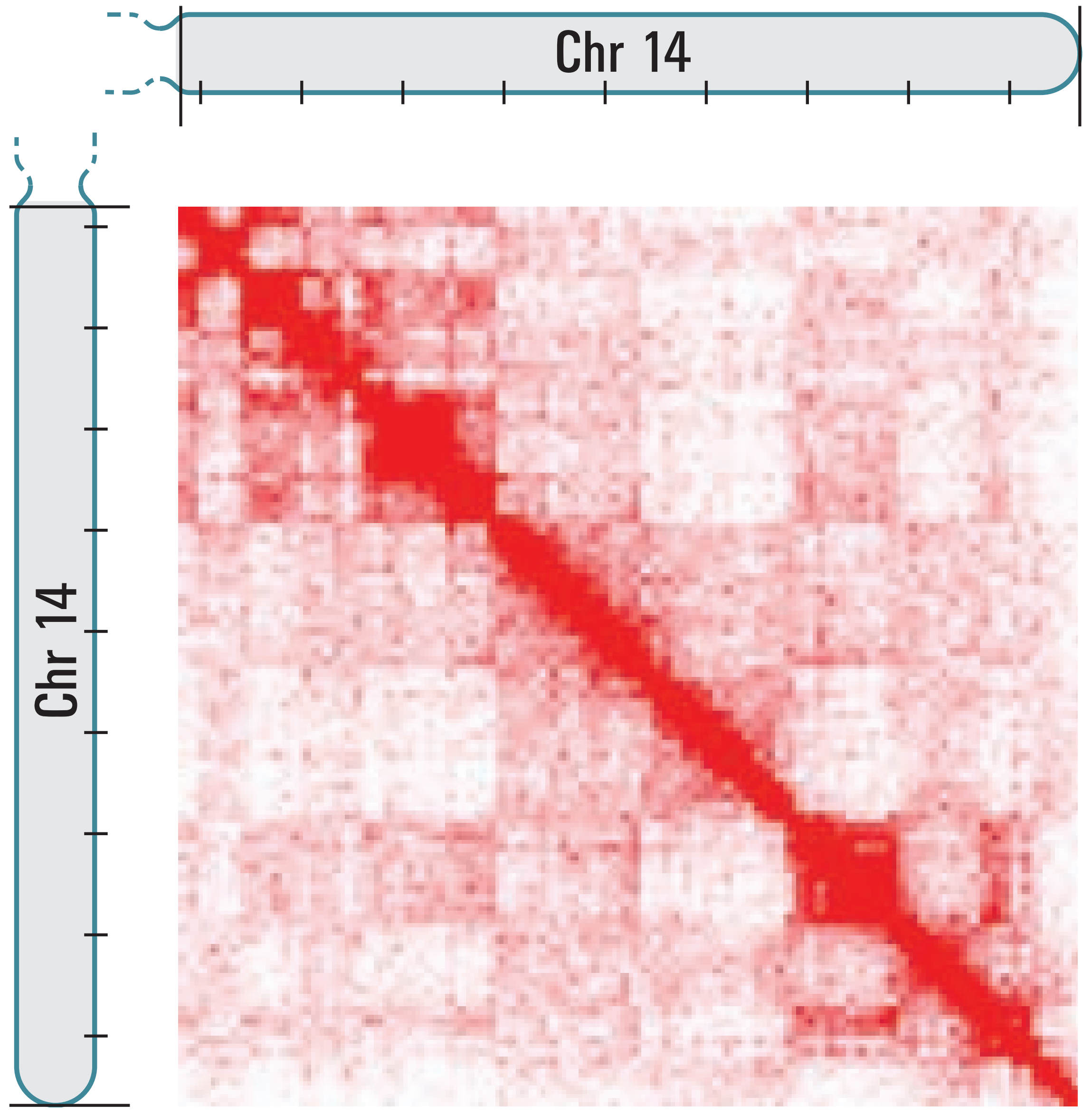


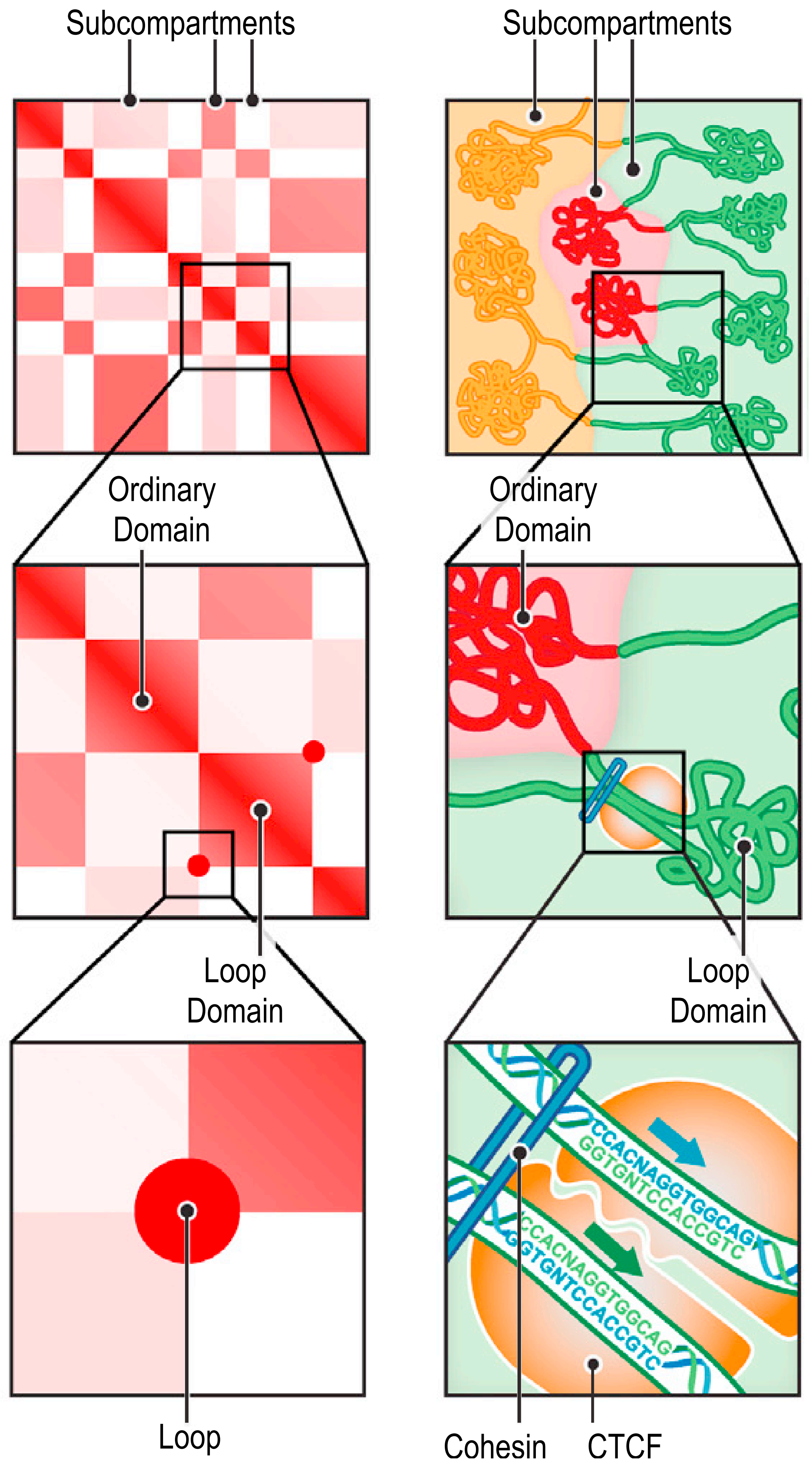
Ting Wu
Harvard Med School

Hierarchical genome organisation

Lieberman-Aiden, E., et al. (2009). Science, 326(5950), 289–293.
Rao, S. S. P., et al. (2014). Cell, 1–29.







Can we walk the chromatin path in the nucleus?

by

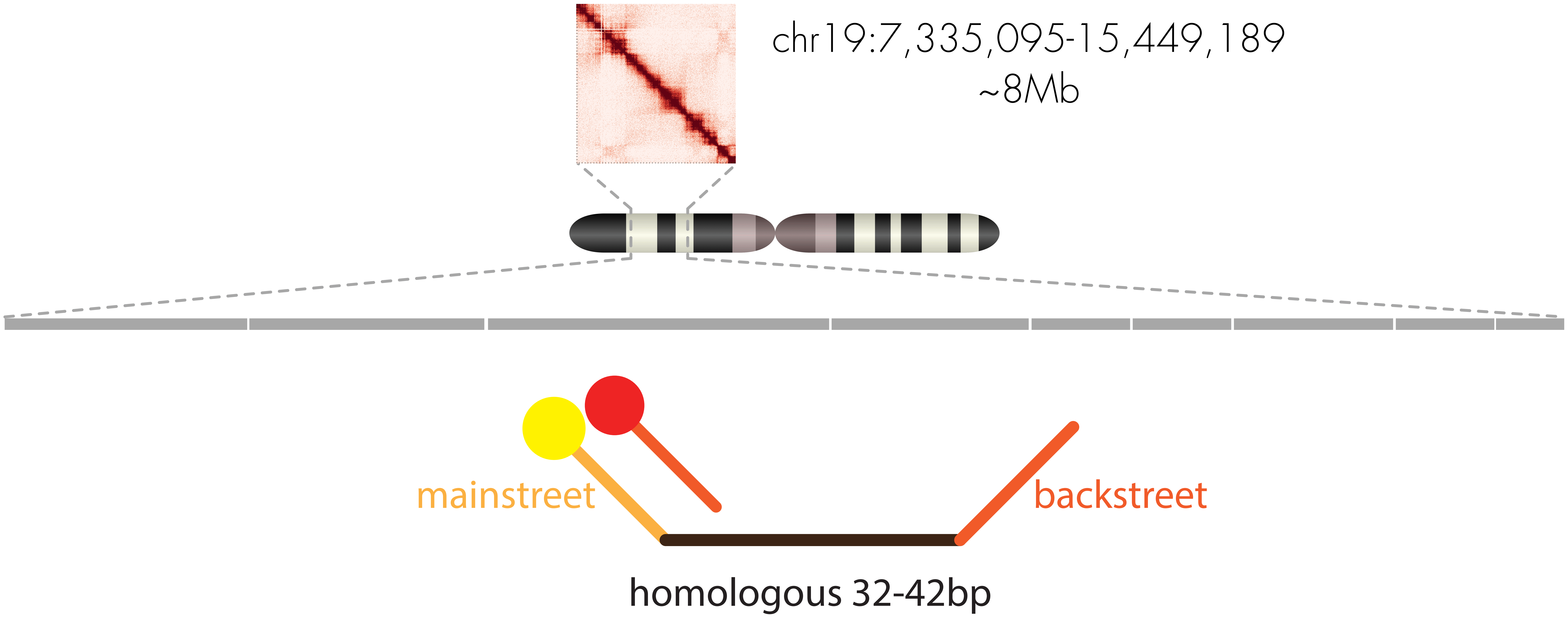
Integrating imaging and Hi-C maps with modeling.

by developing a method for

Oligopaint-based modeling of genomes (IMGR)

High-resolution imaging

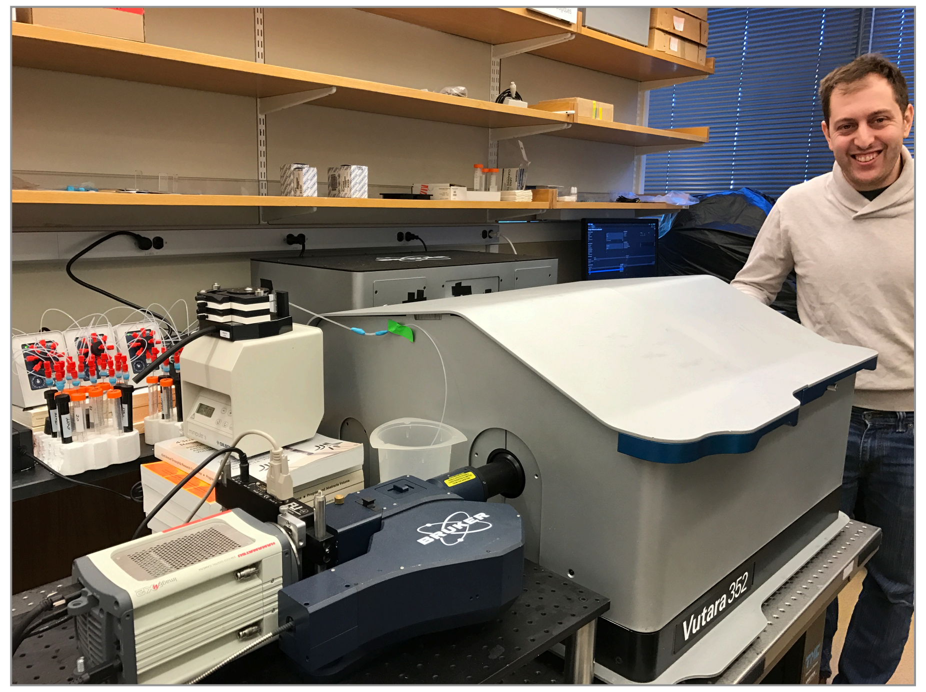
Tracing chromosomes with OligoSTORM & fluidics cycles in PGP1 cells



Beliveau et al. Nat. Comm. 2015

High-resolution imaging

Tracing chromosomes with OligoSTORM & fluidics cycles in PGP1 cells



Guy Nir Harvard Med School

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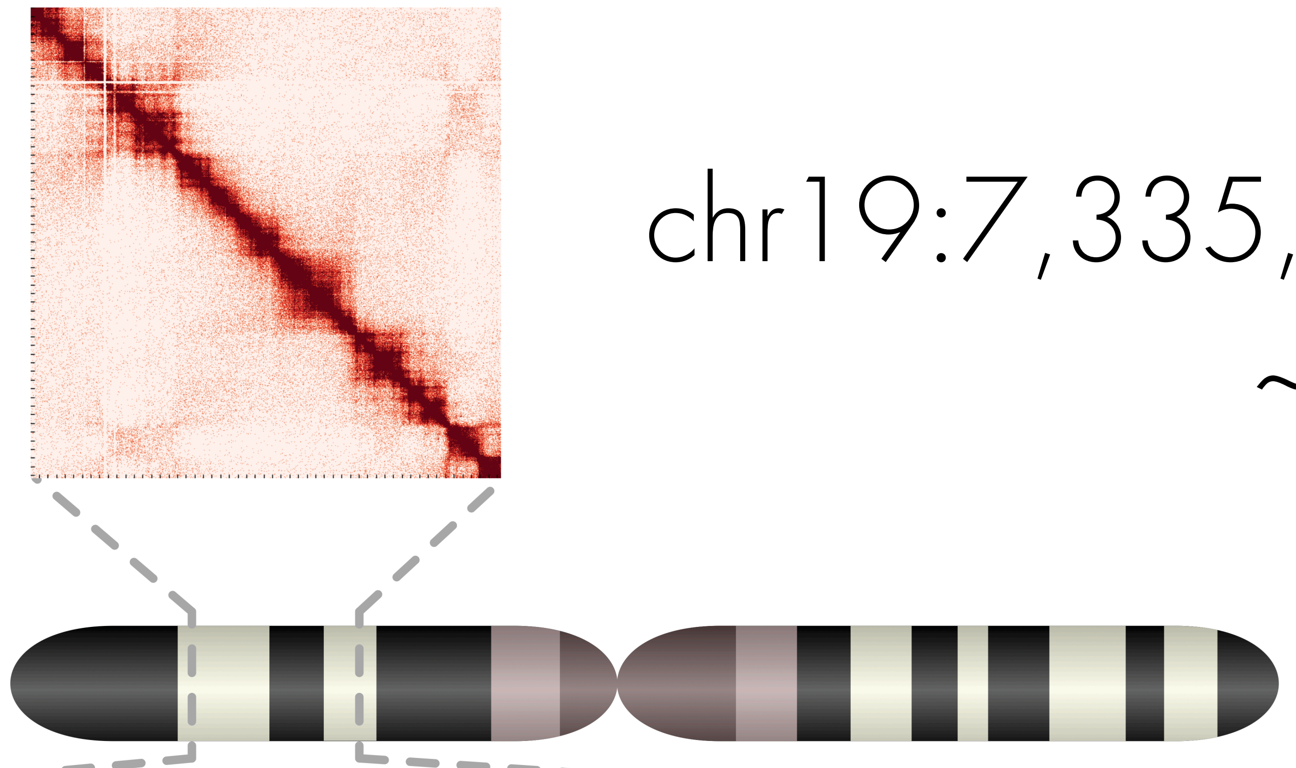
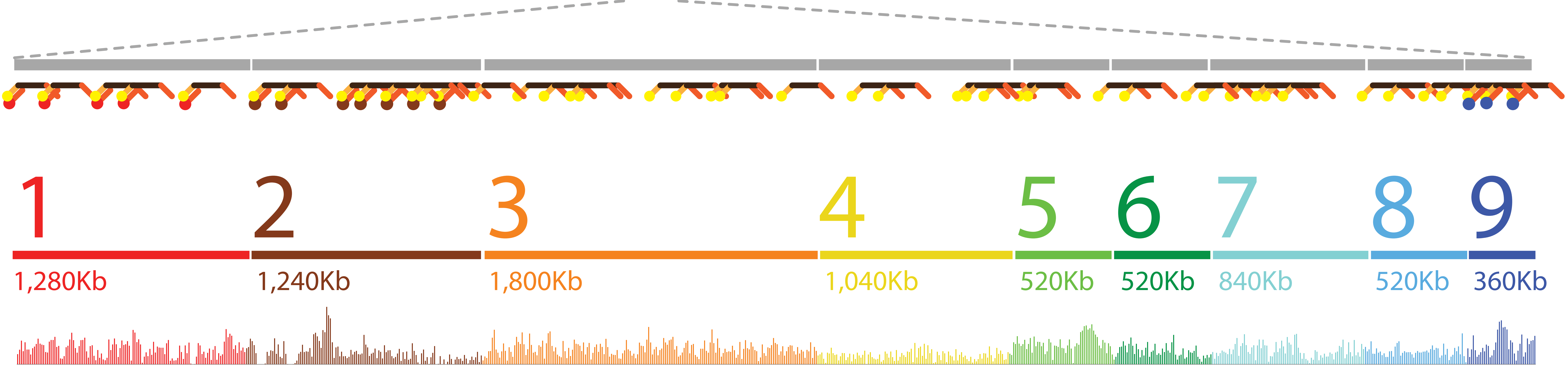
Jeff Stuckey Bruker
John Schreiner Zero Epsilon
Steve Callahan Zero Epsilon

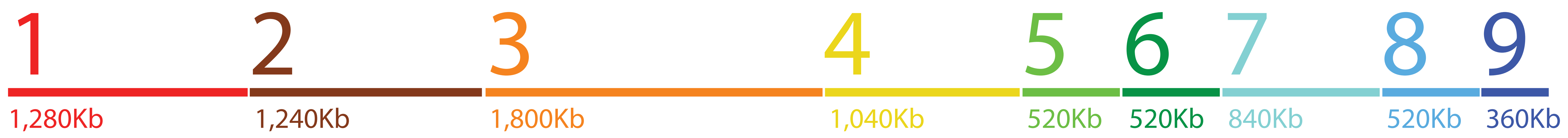


chr19:7,335,095-15,449,189
~8Mb



High-resolution imaging

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

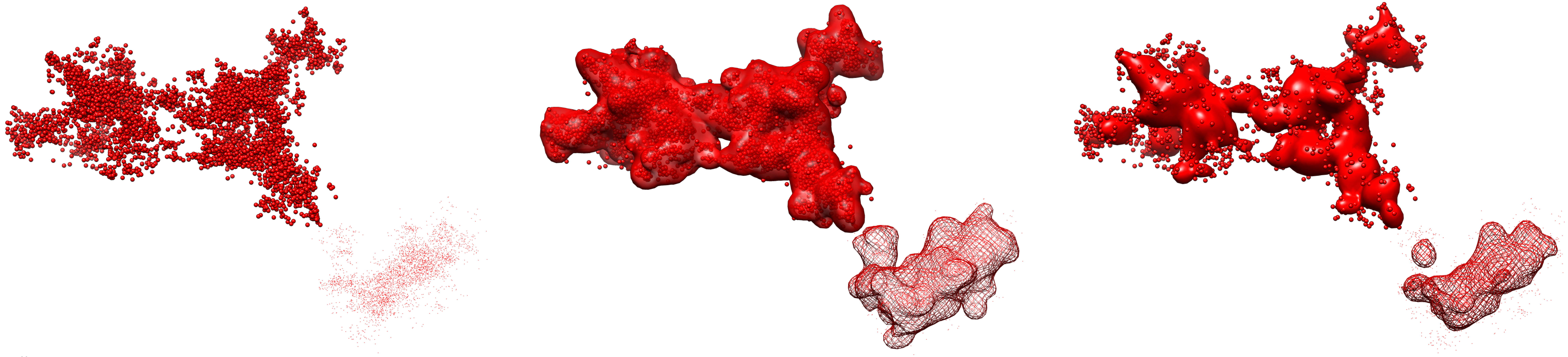


Cell-02

High-resolution imaging

XYZ points convolution into a density map

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

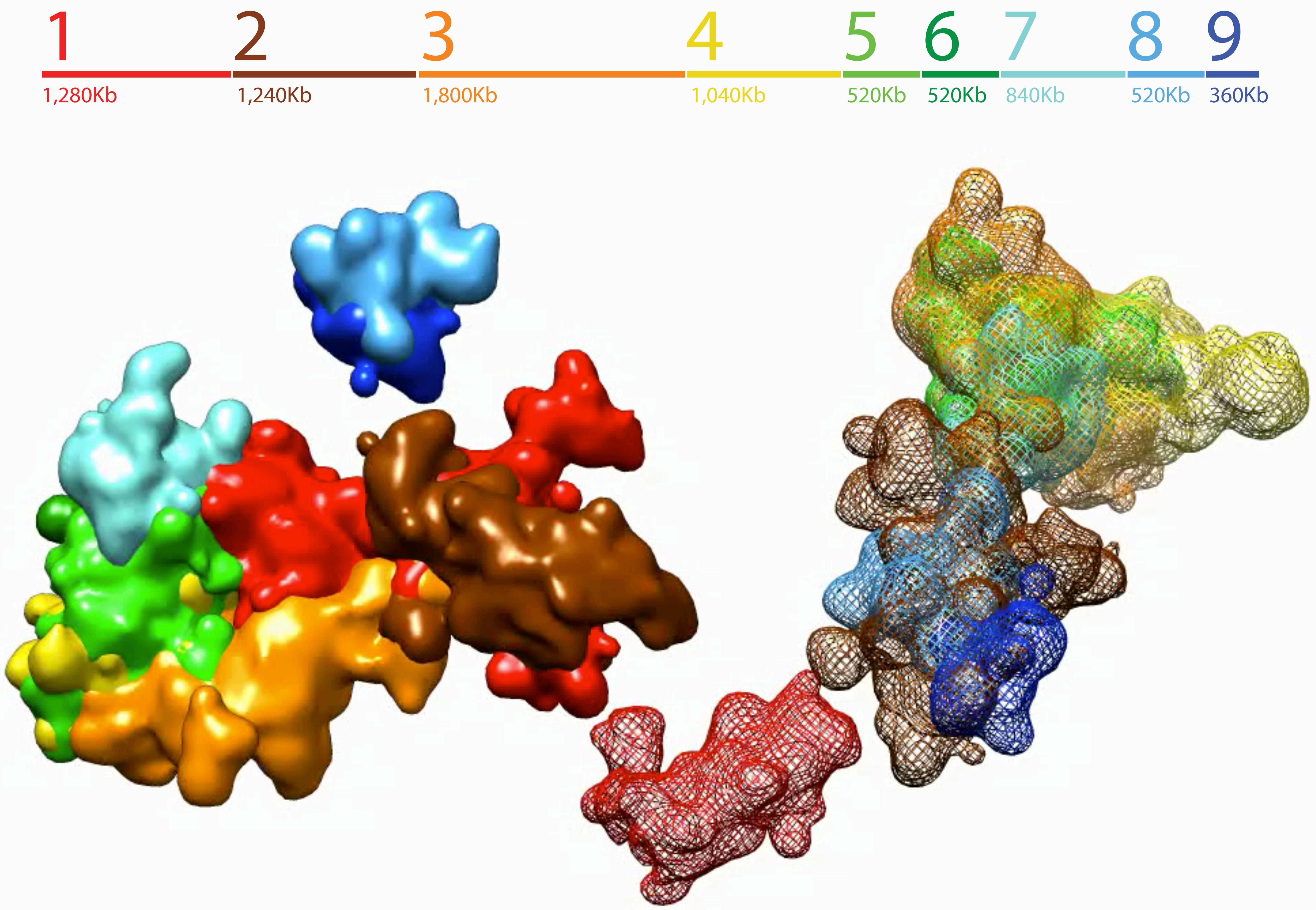


Cell-02 · Segment 1

Farabella et al, J Appl Crystallogr. 2015

Density maps

Cell-02 · Density map @ 50nm

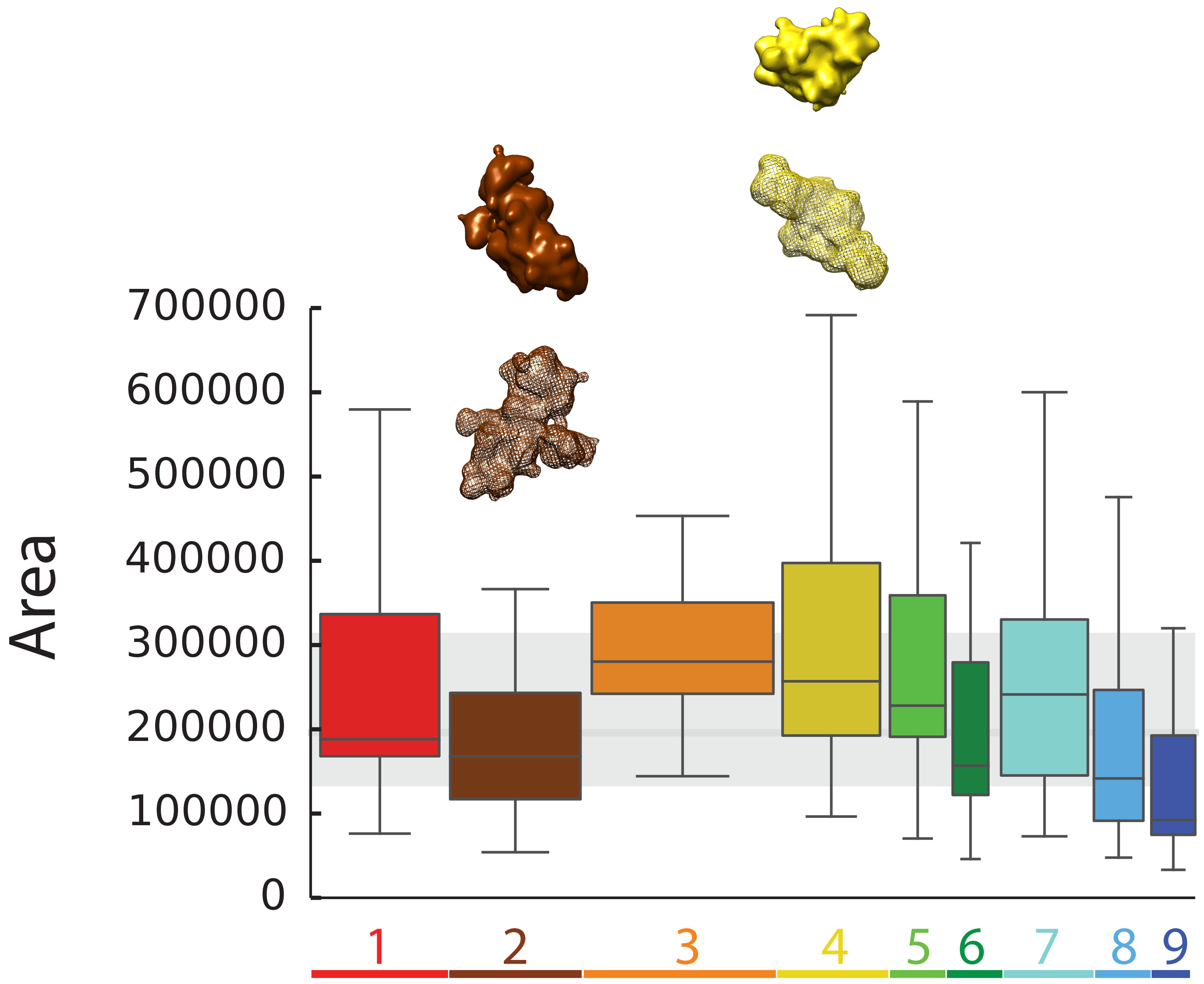


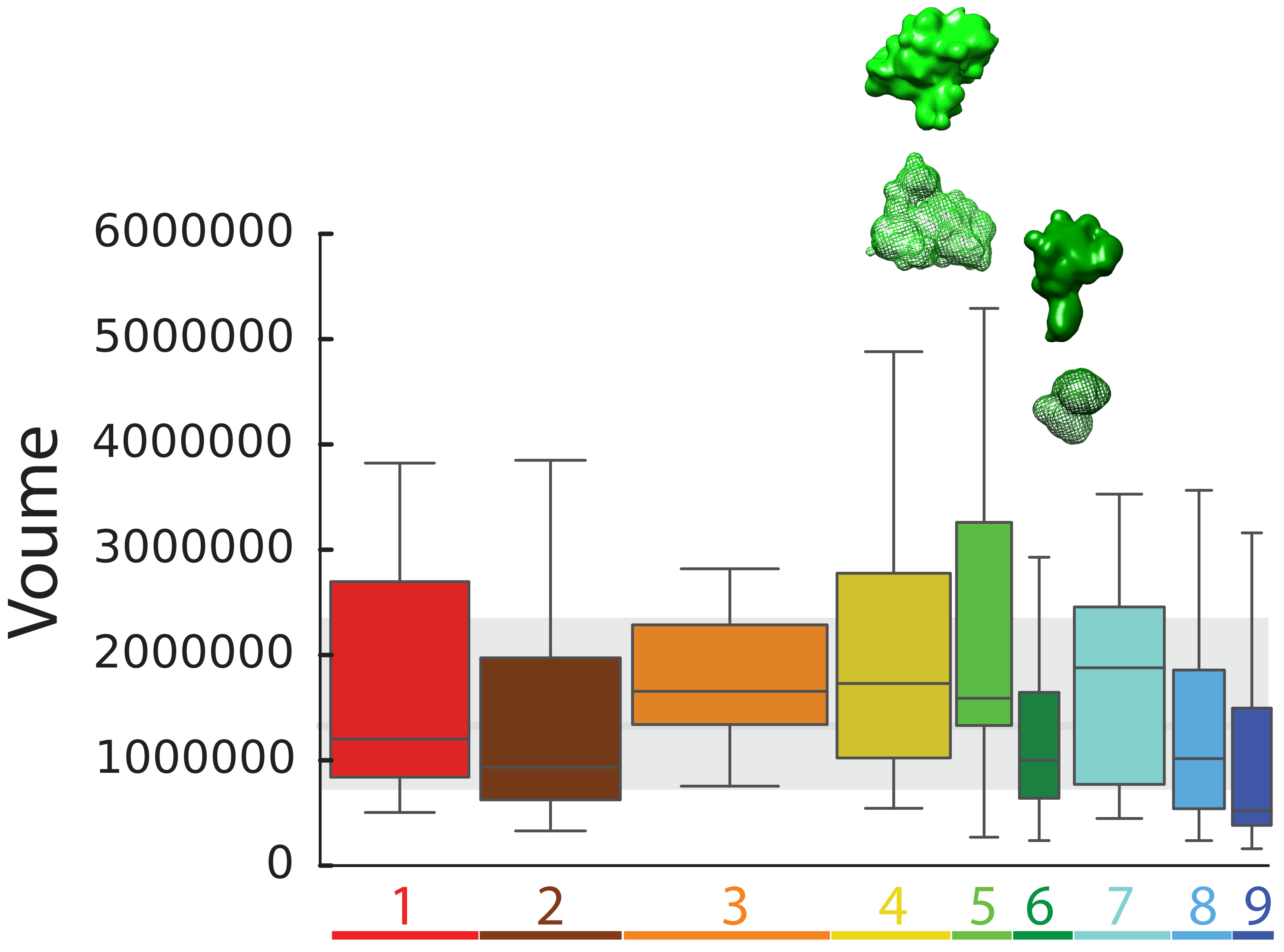
Area (nm^2)
Volume (nm^3)
Sphericity
Overlap (%)
Distance (nm)

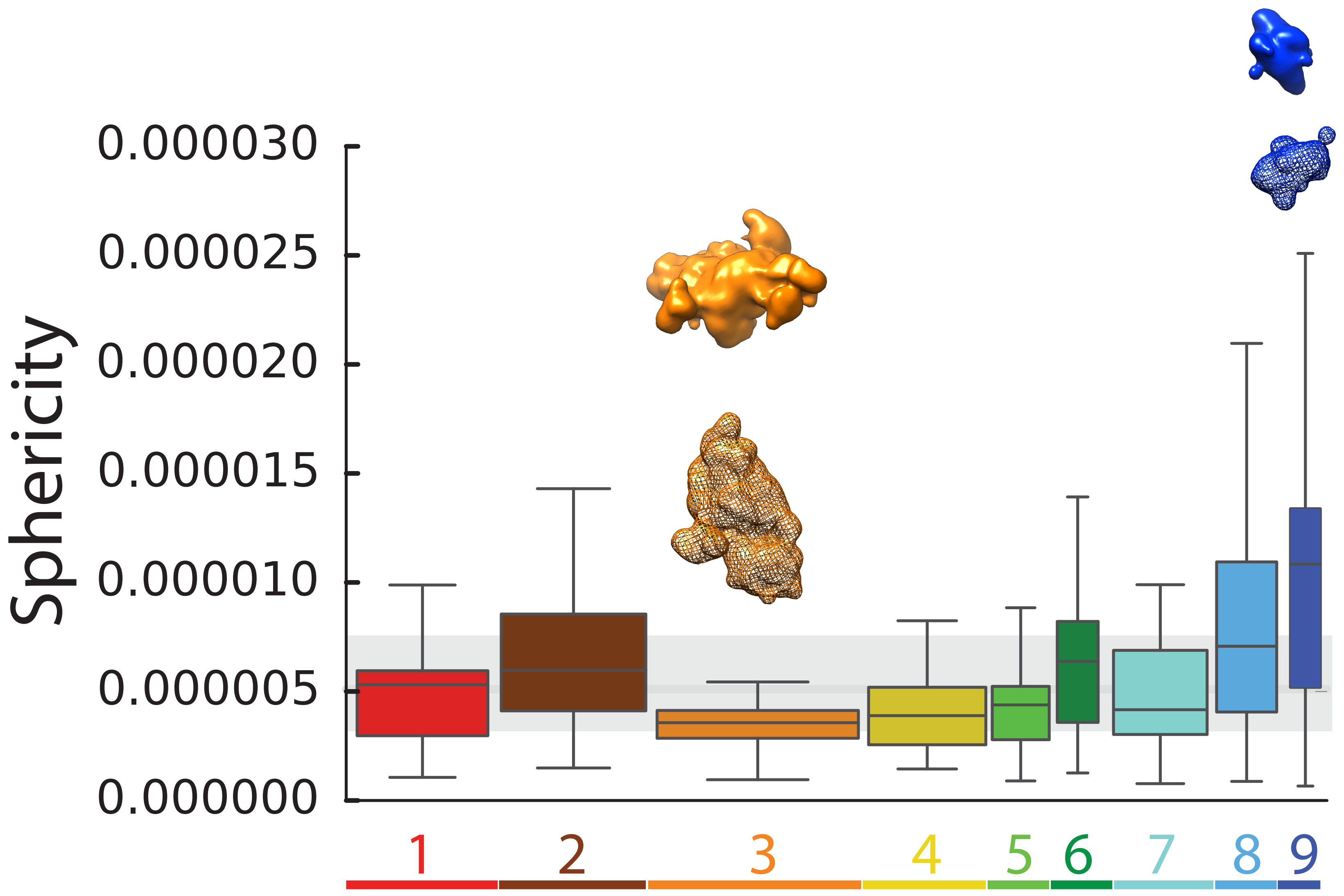
Farabella et al, J Appl Crystallogr. 2015

Structural features

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

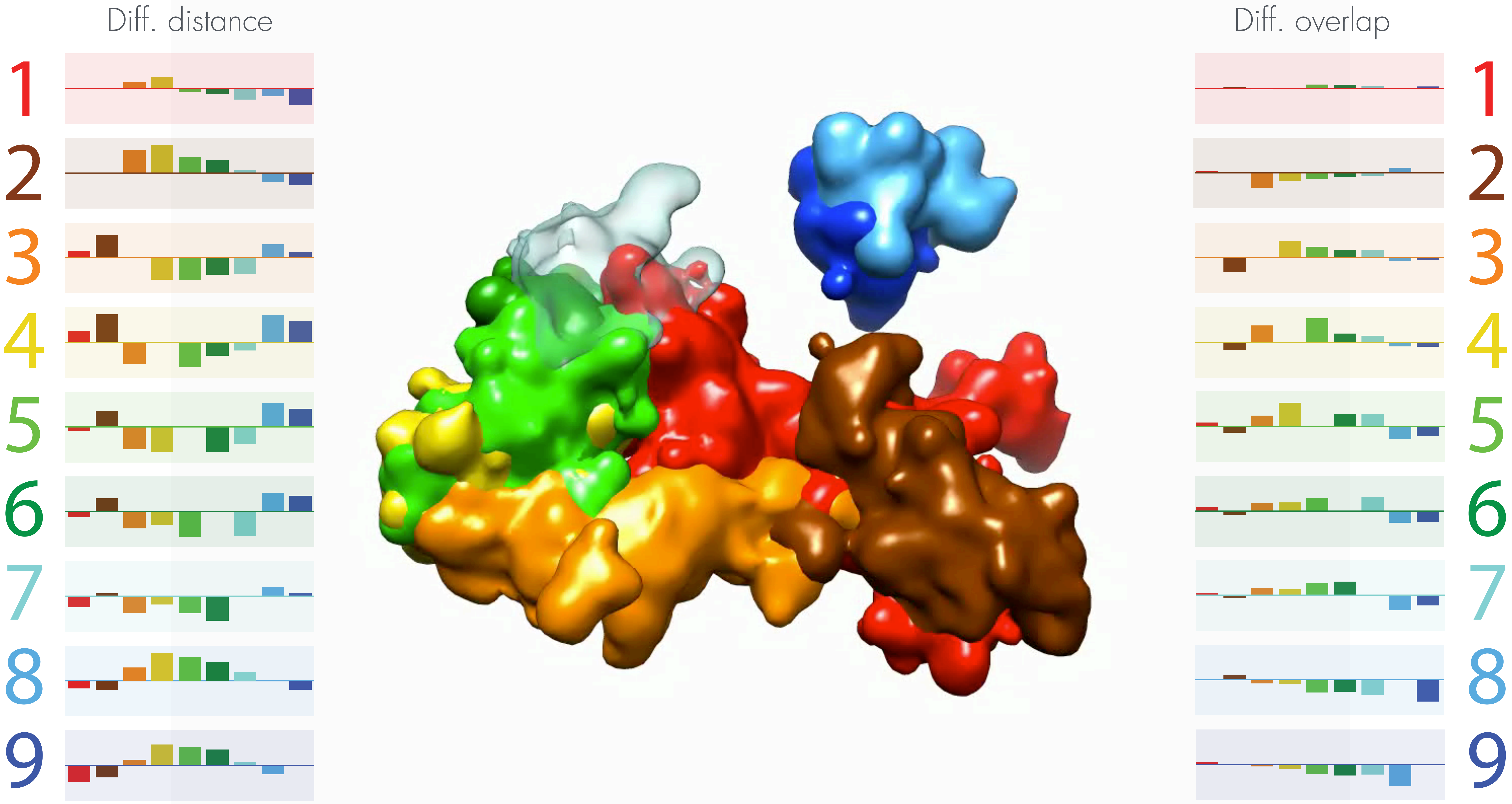






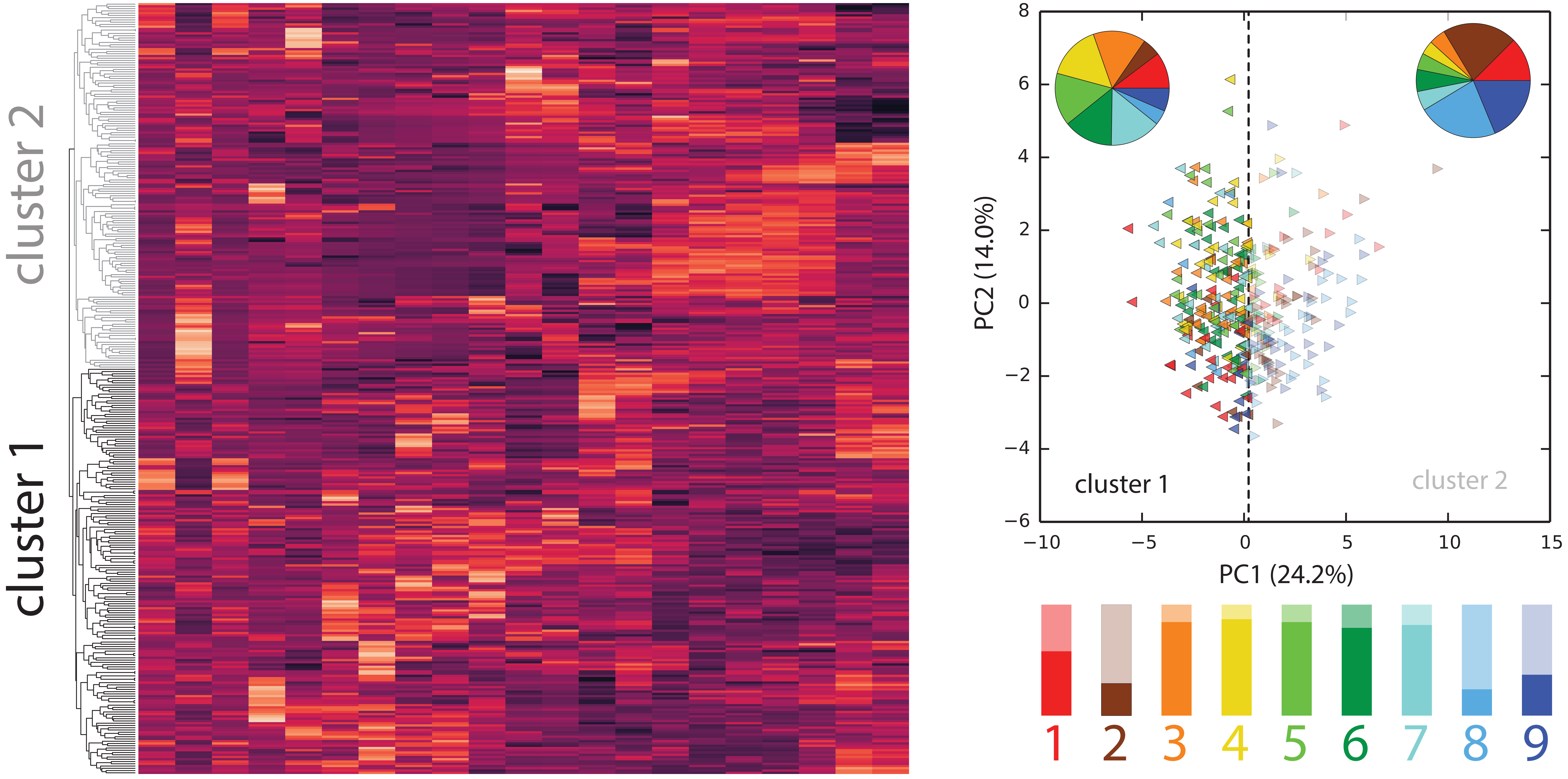
Spatial arrangement

Distance and overlap of 19 cells each with 2 homologous resolved



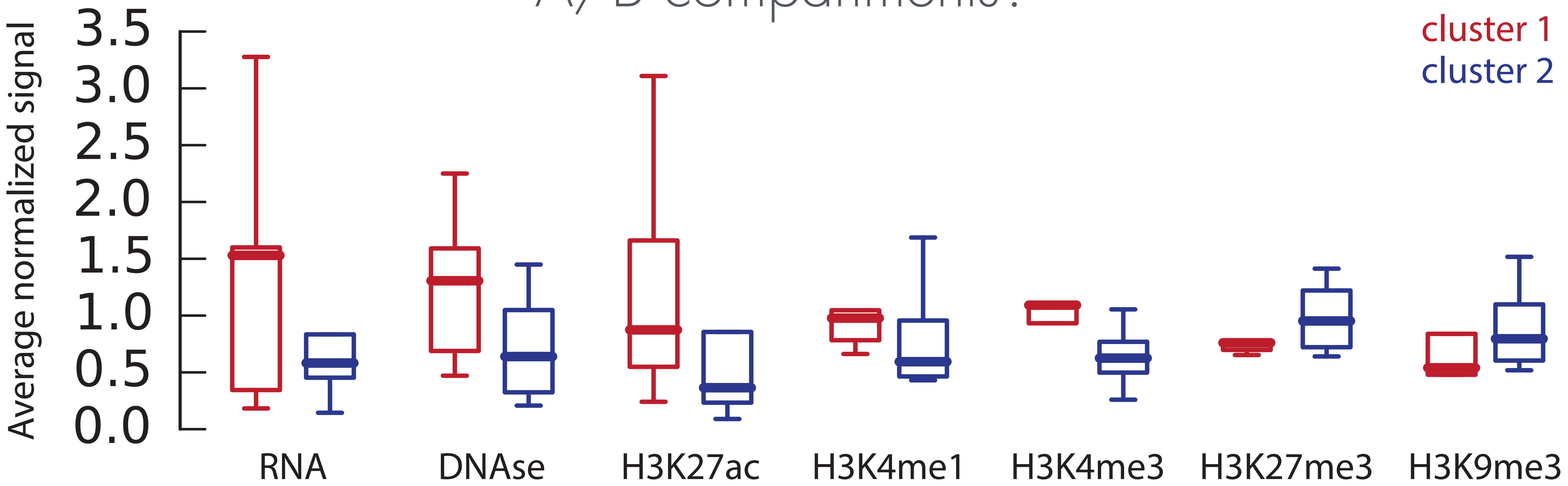
Structural clustering

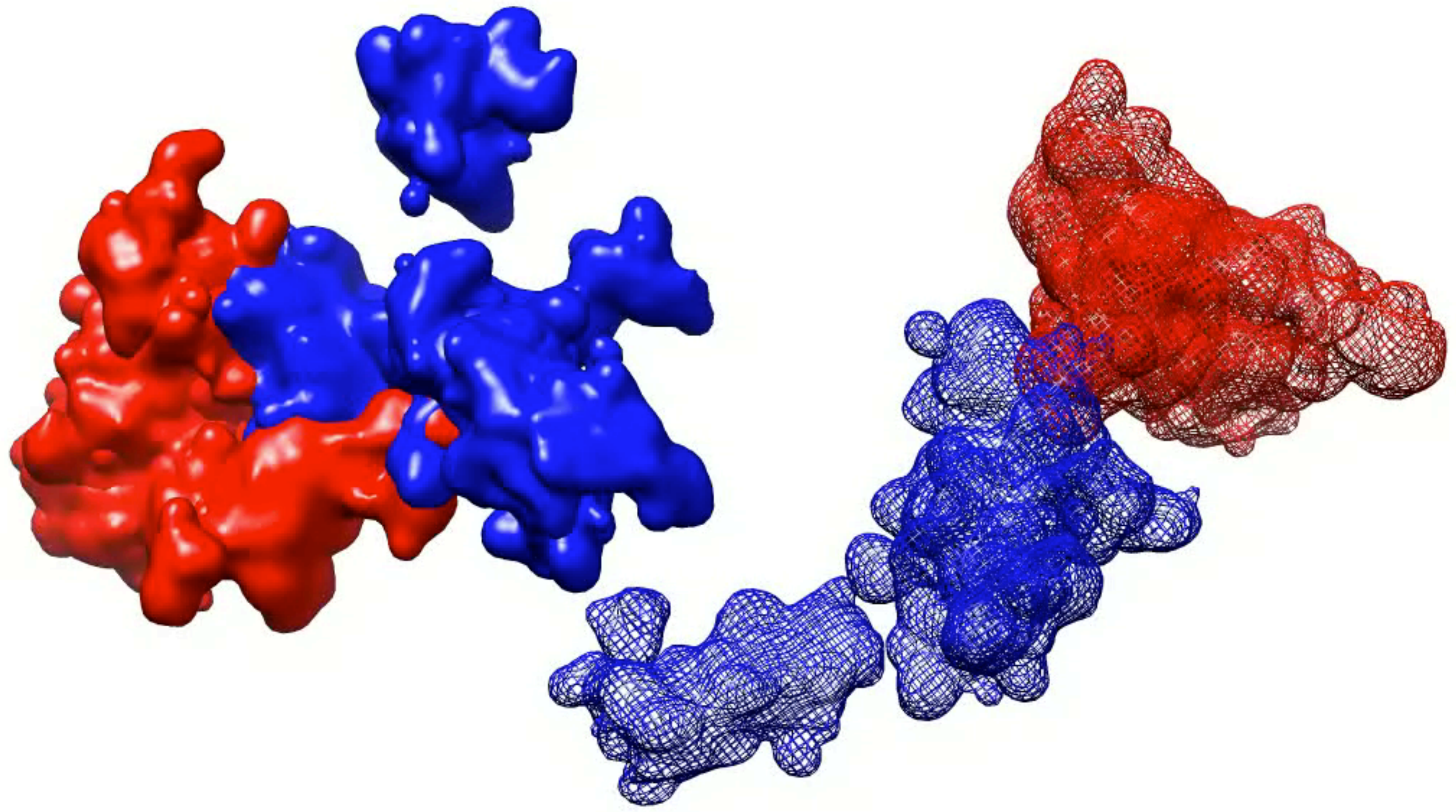
19 cells each with 2 homologous and 9 segments each (342)

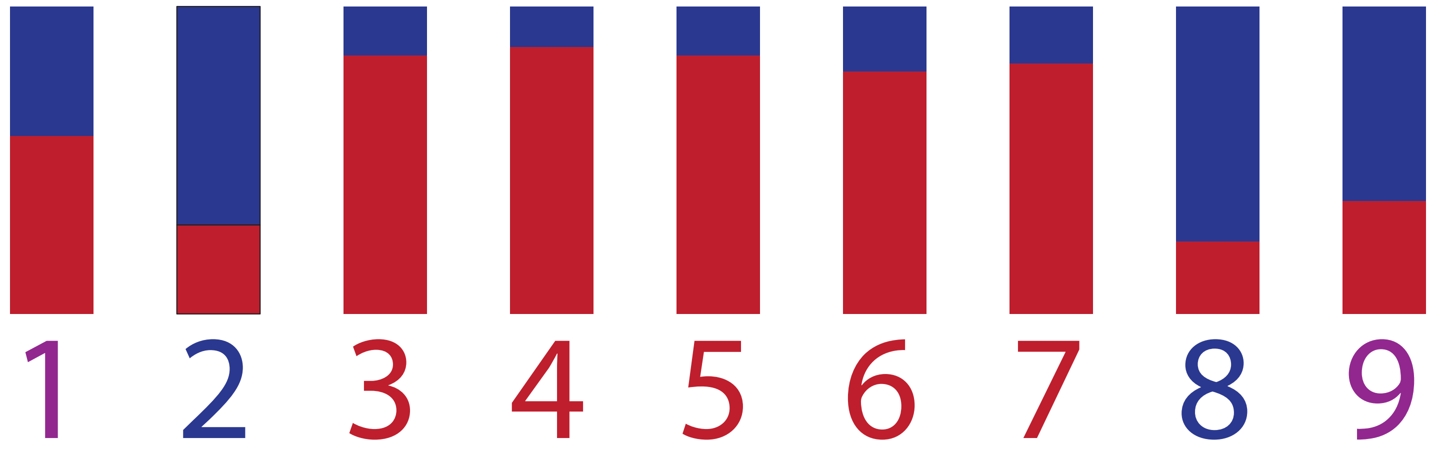


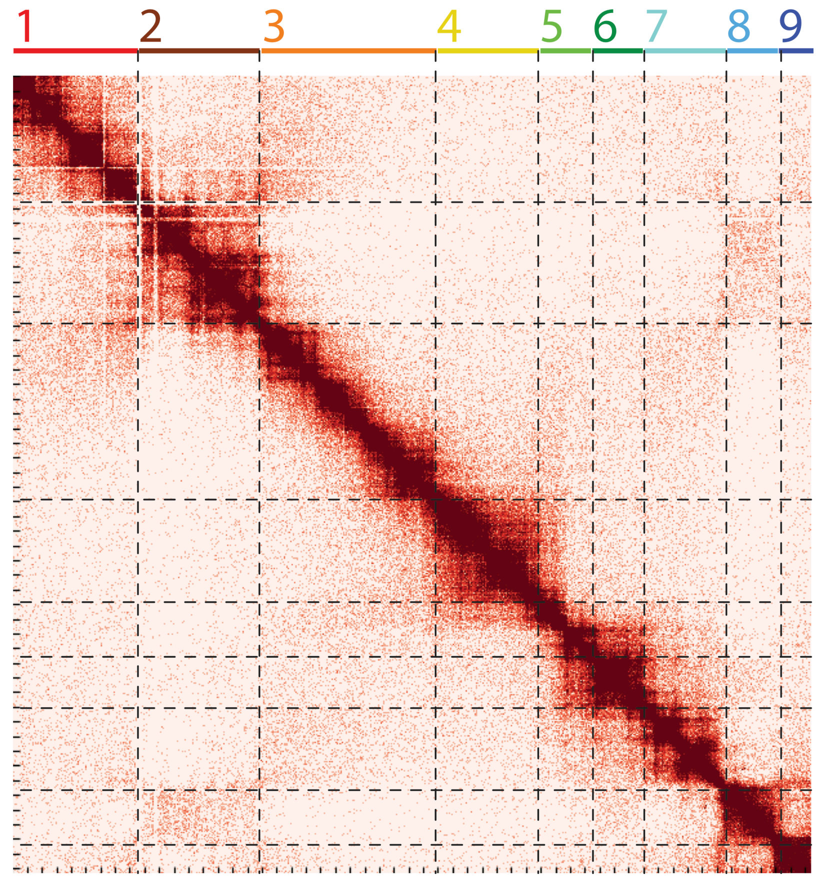
Cluster properties

A/B compartments?





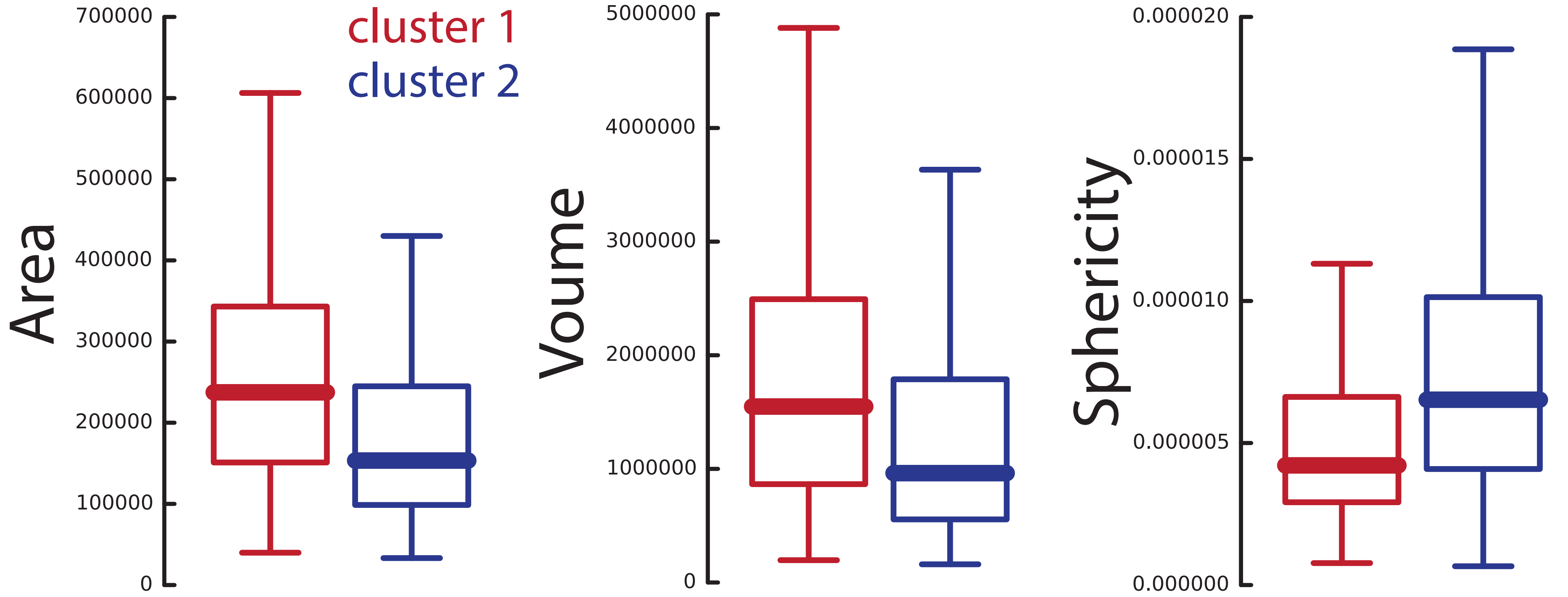


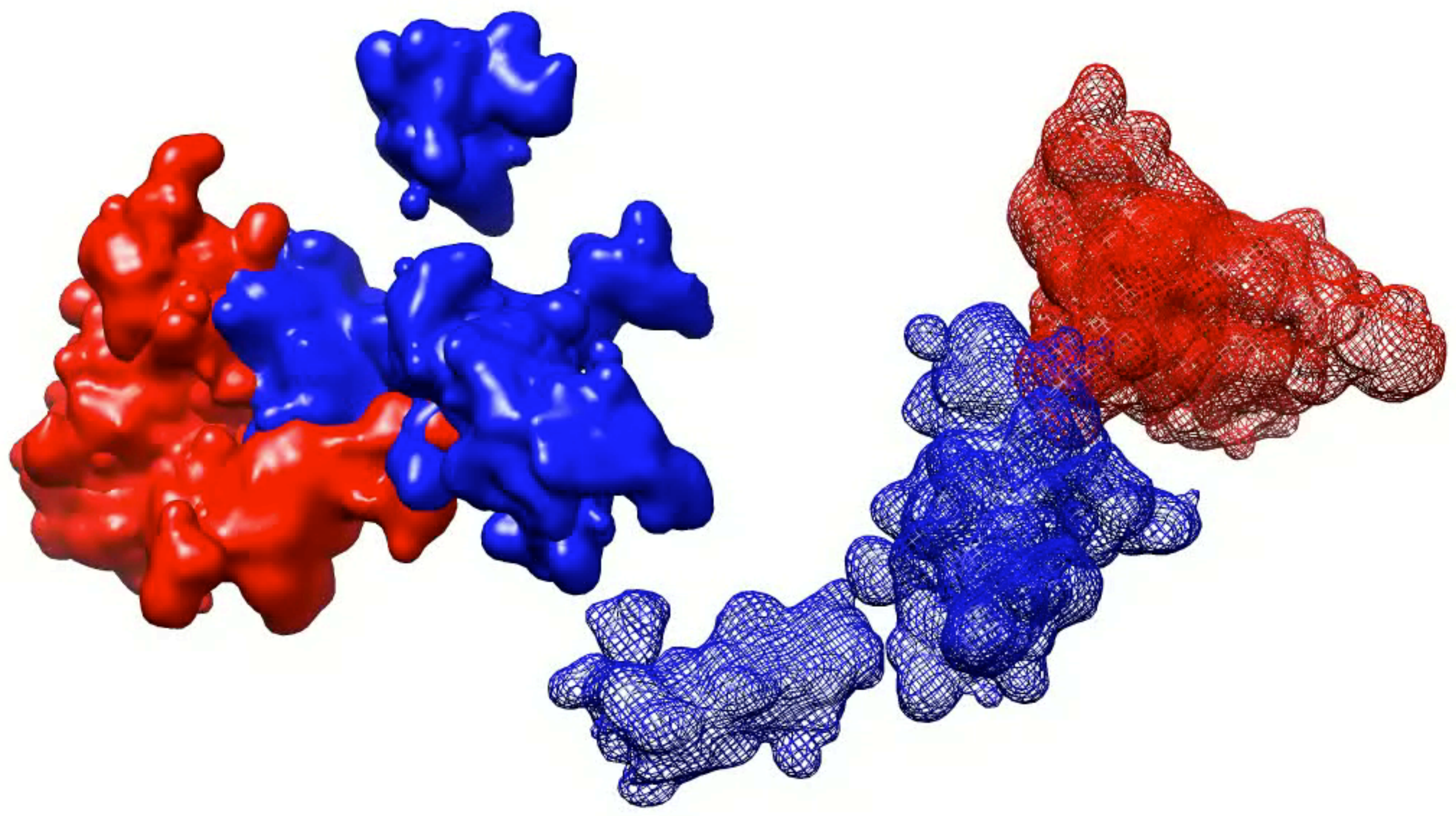


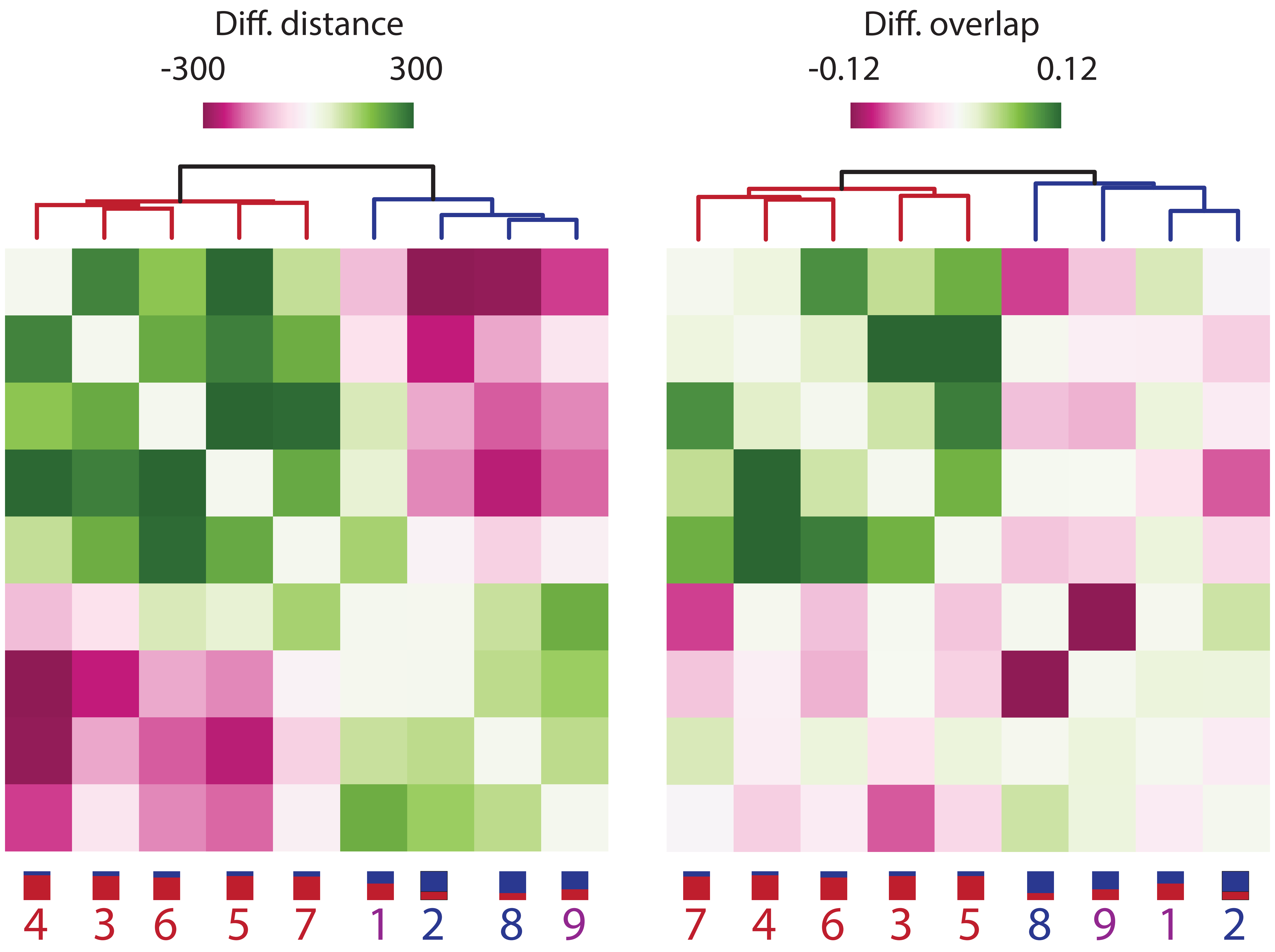
PGP1 ChIP-seq and Hi-C data from ENCODE and Lieberman-Aiden Lab, respectively

Cluster properties

A/B compartment properties







Can we walk the chromatin path in the nucleus?

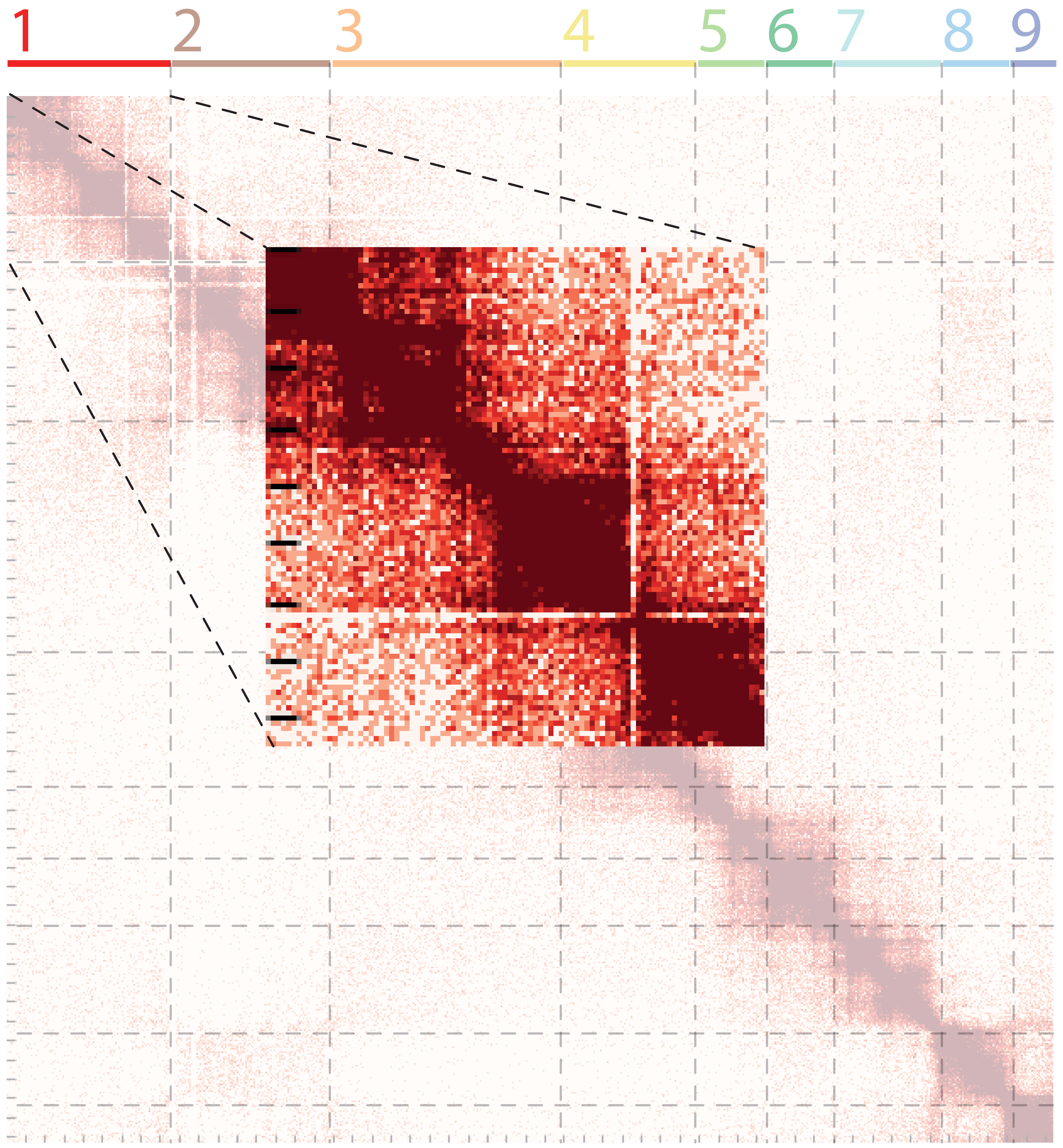
YES!

Can we increase the resolution of our data?

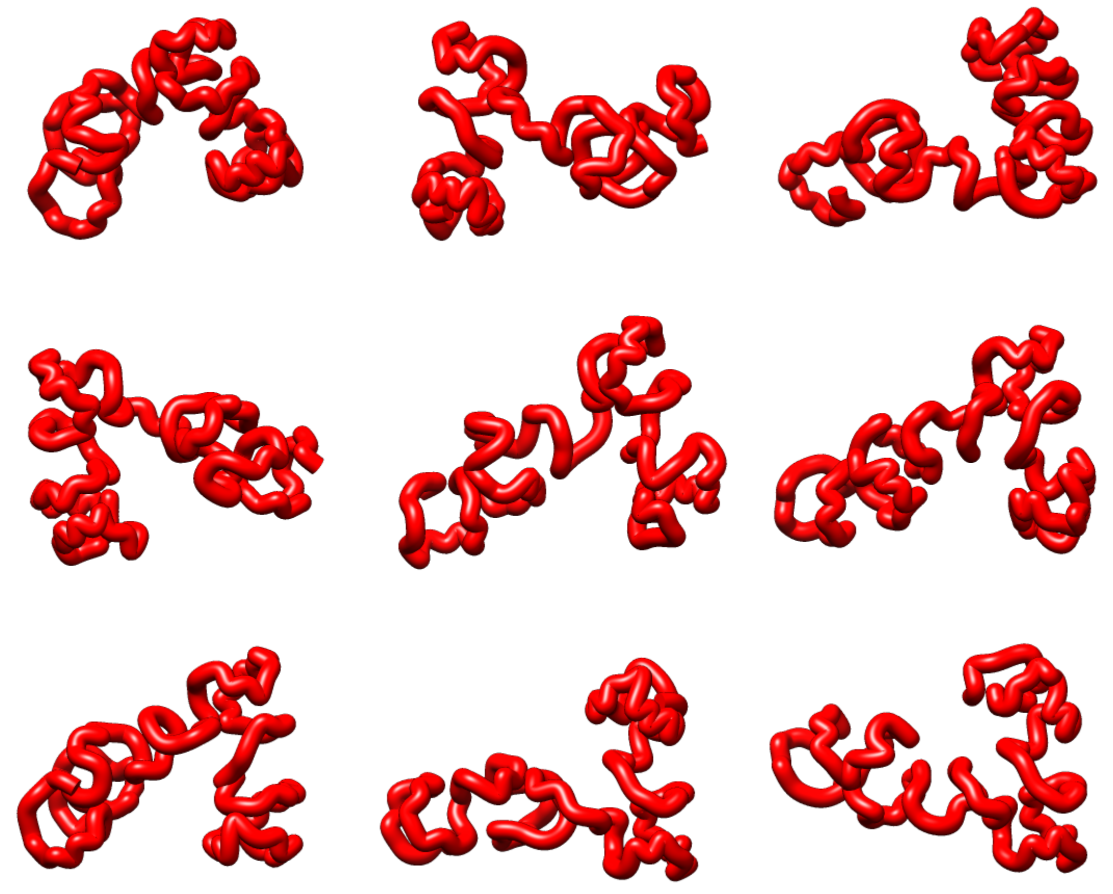
by fitting 3D models based on Hi-C interaction maps

Increasing resolution

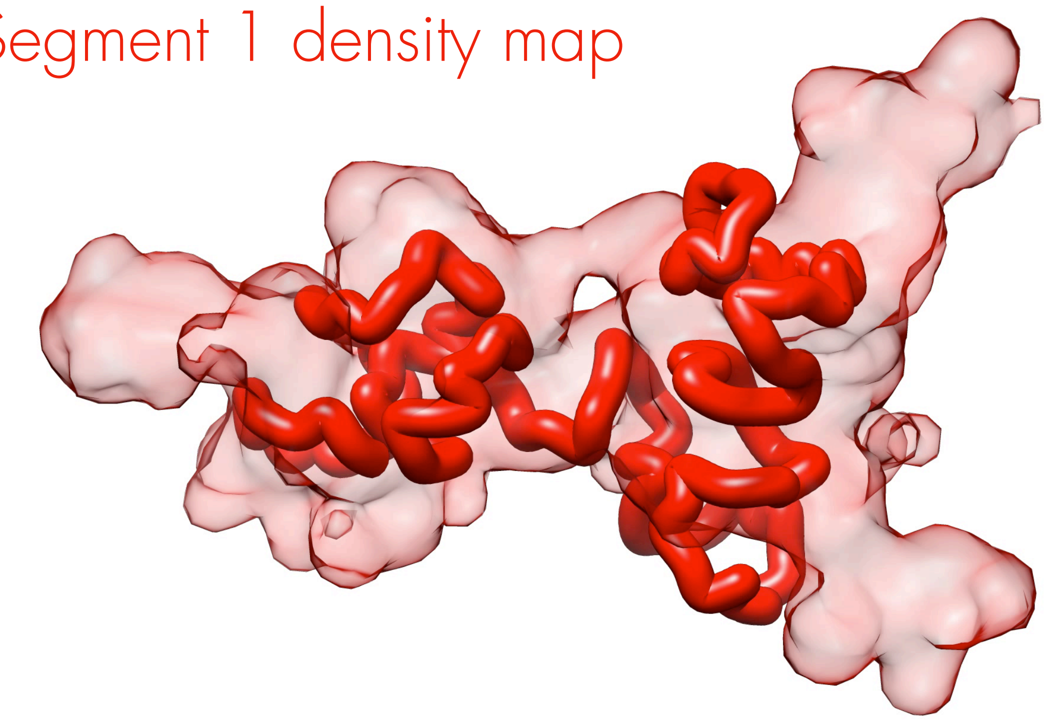
Rigid body fitting 3D structures based on Hi-C data



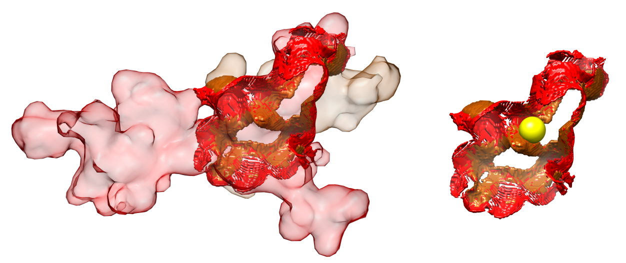
Segment 1 3D models



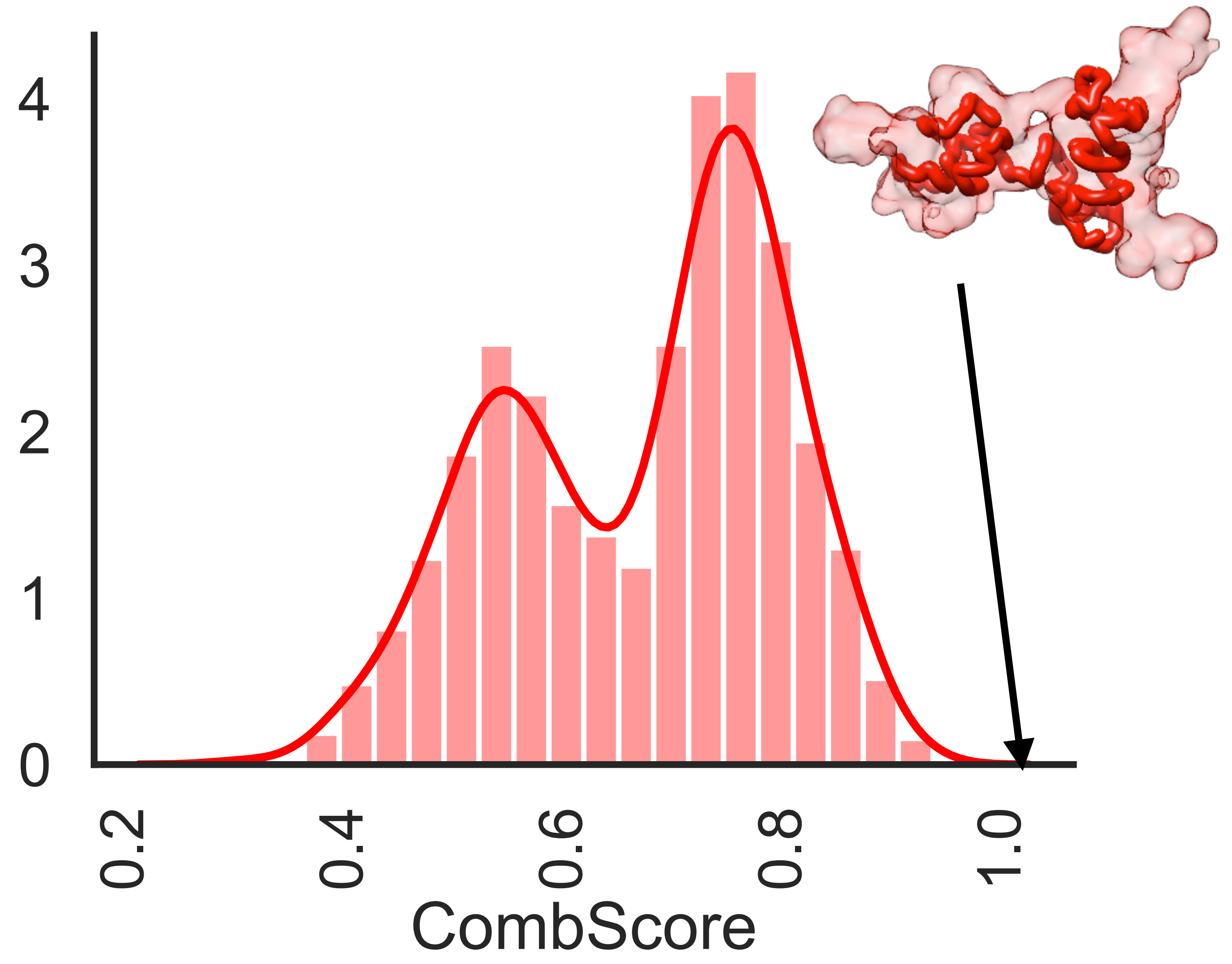
Segment 1 density map



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



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

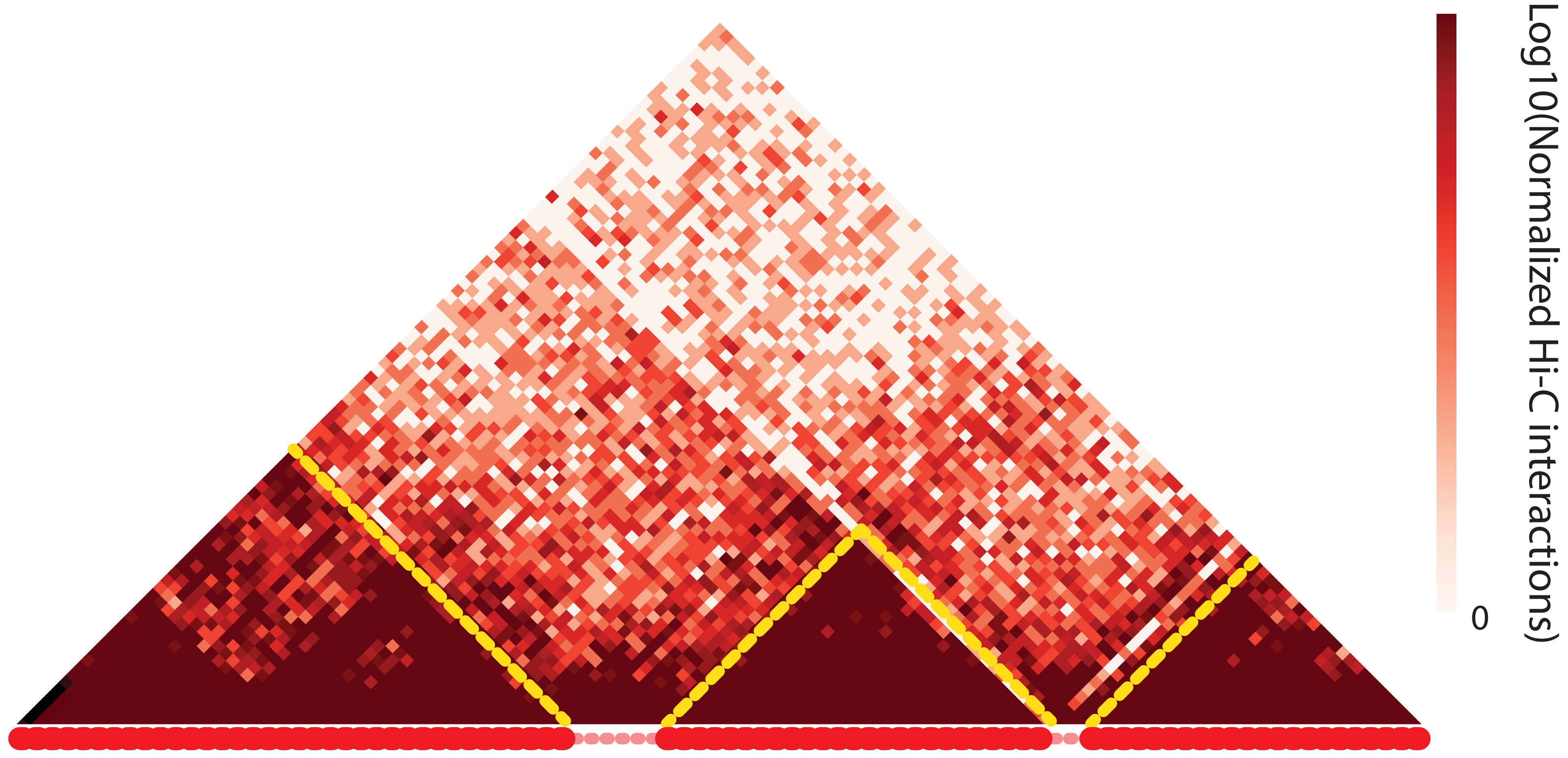


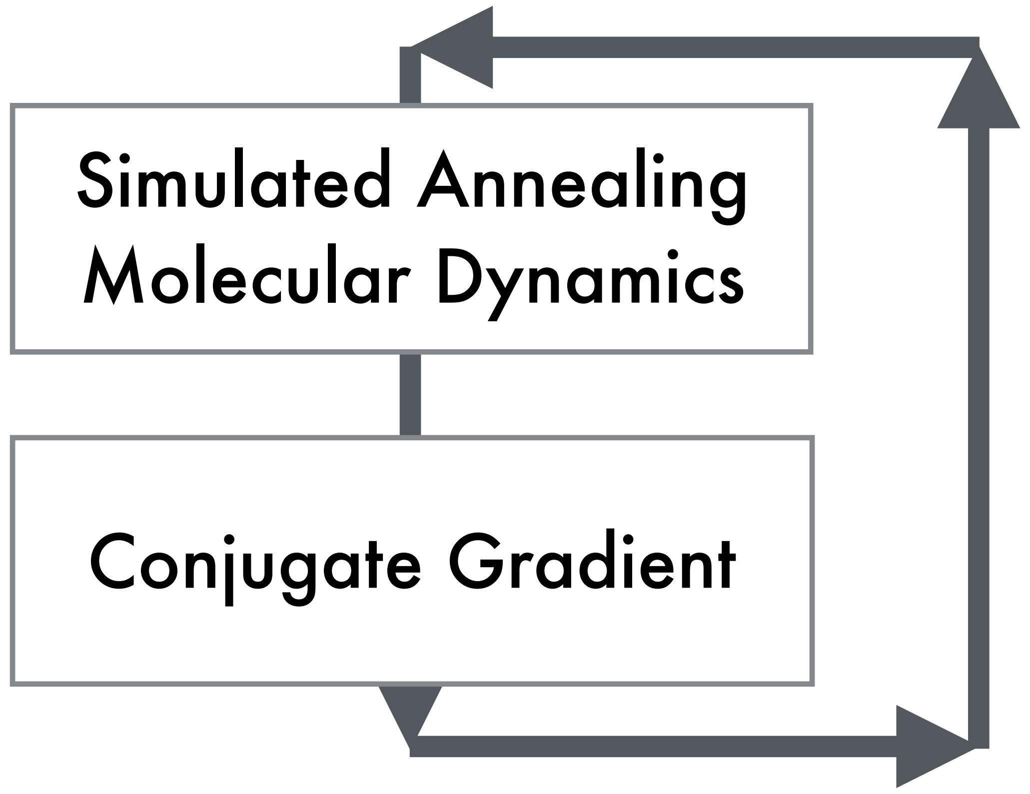
TADbit Serra, Baù, et al. PLOS CB 2017
http://www.3DGenomes.org

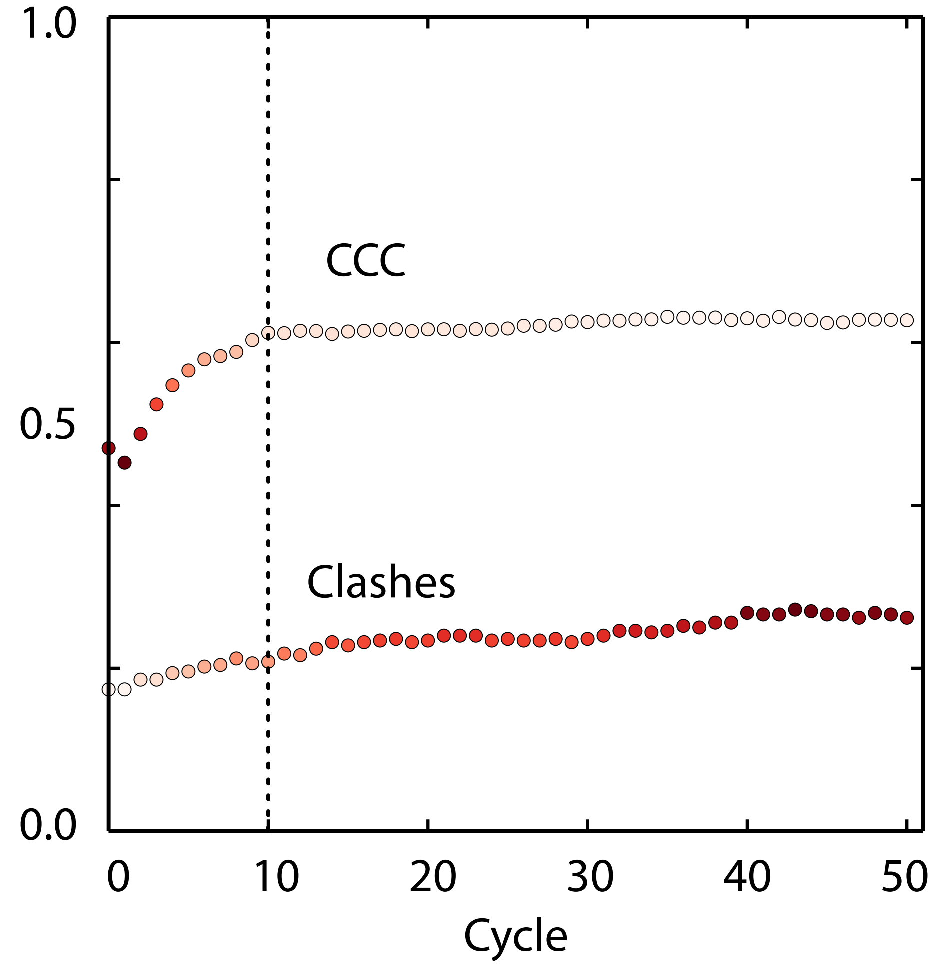
Farabella et al, J Appl Crystallogr. 2015
Roseman, 2000; Wriggers & Chacon, Structure 2001

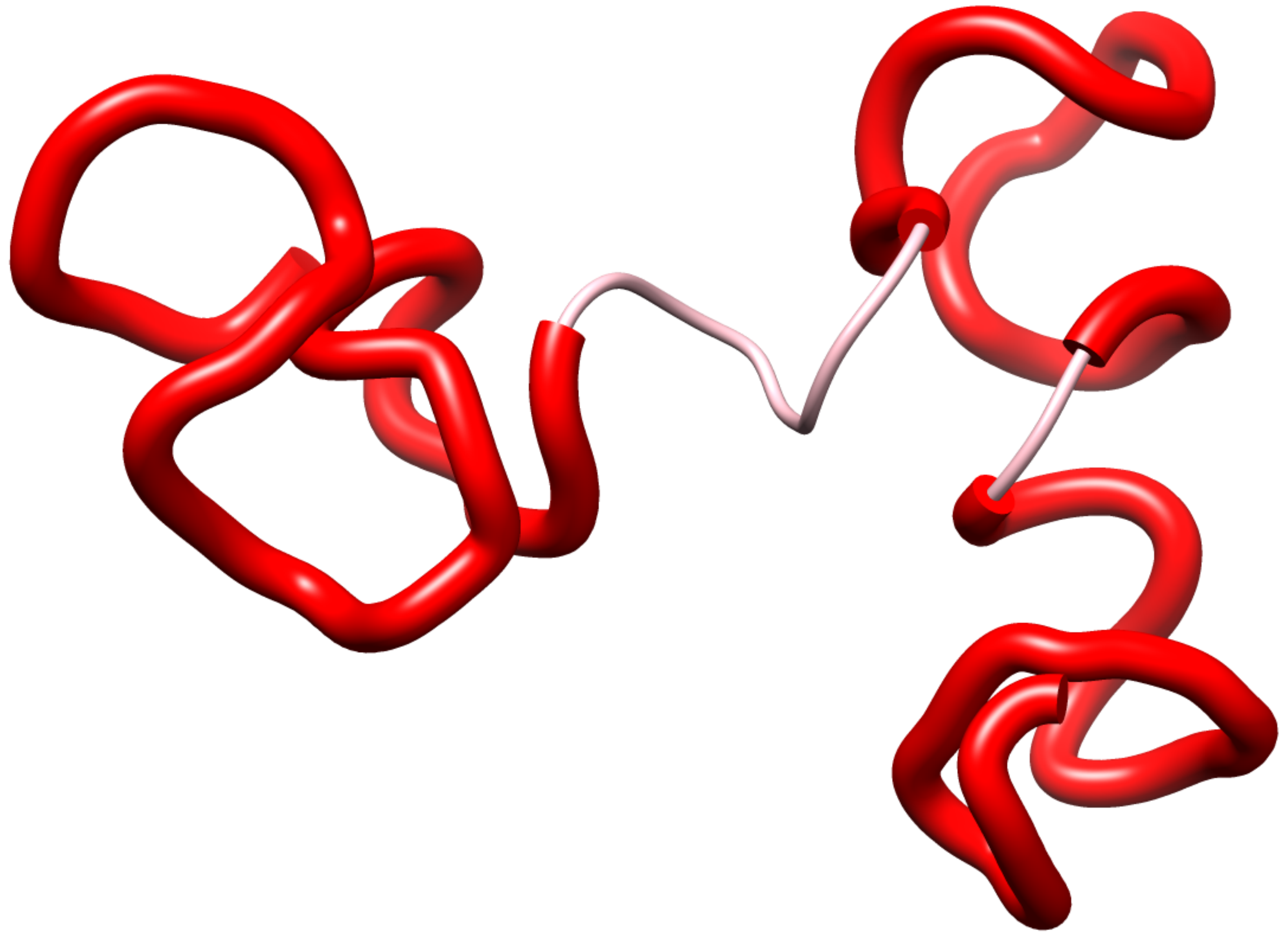
Increasing resolution

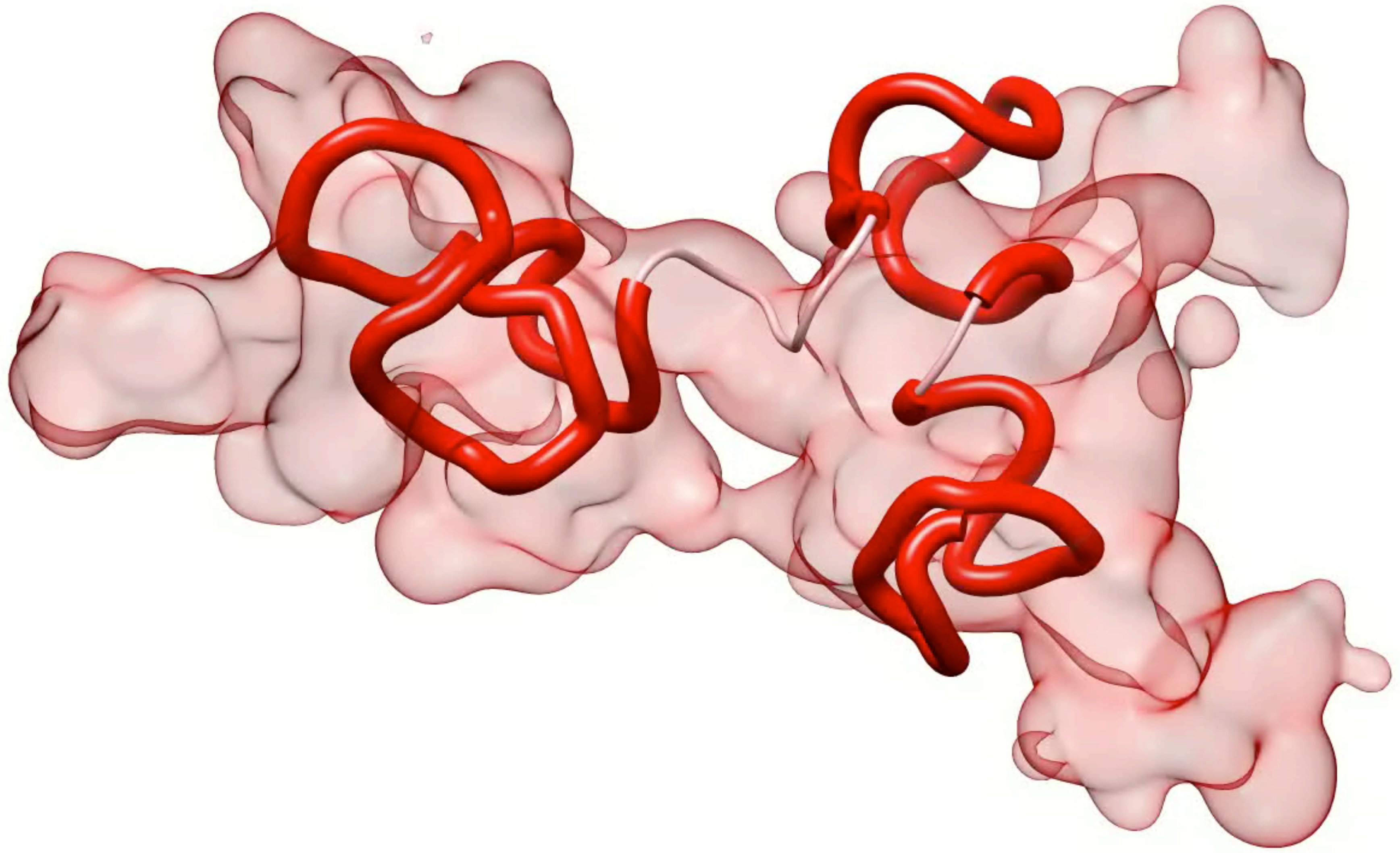
Flexible fitting 3D structures based on Hi-C data











Increasing resolution

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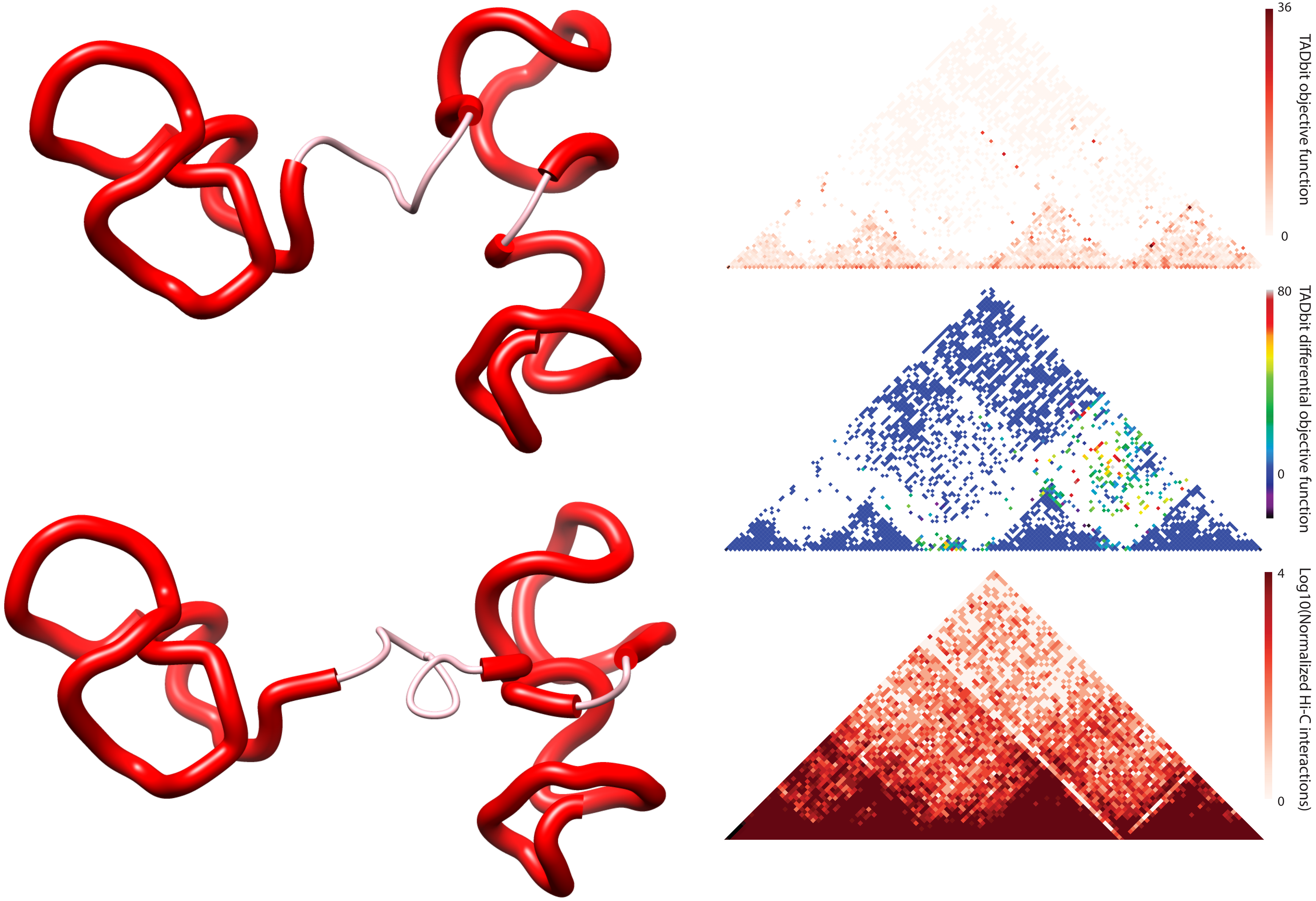
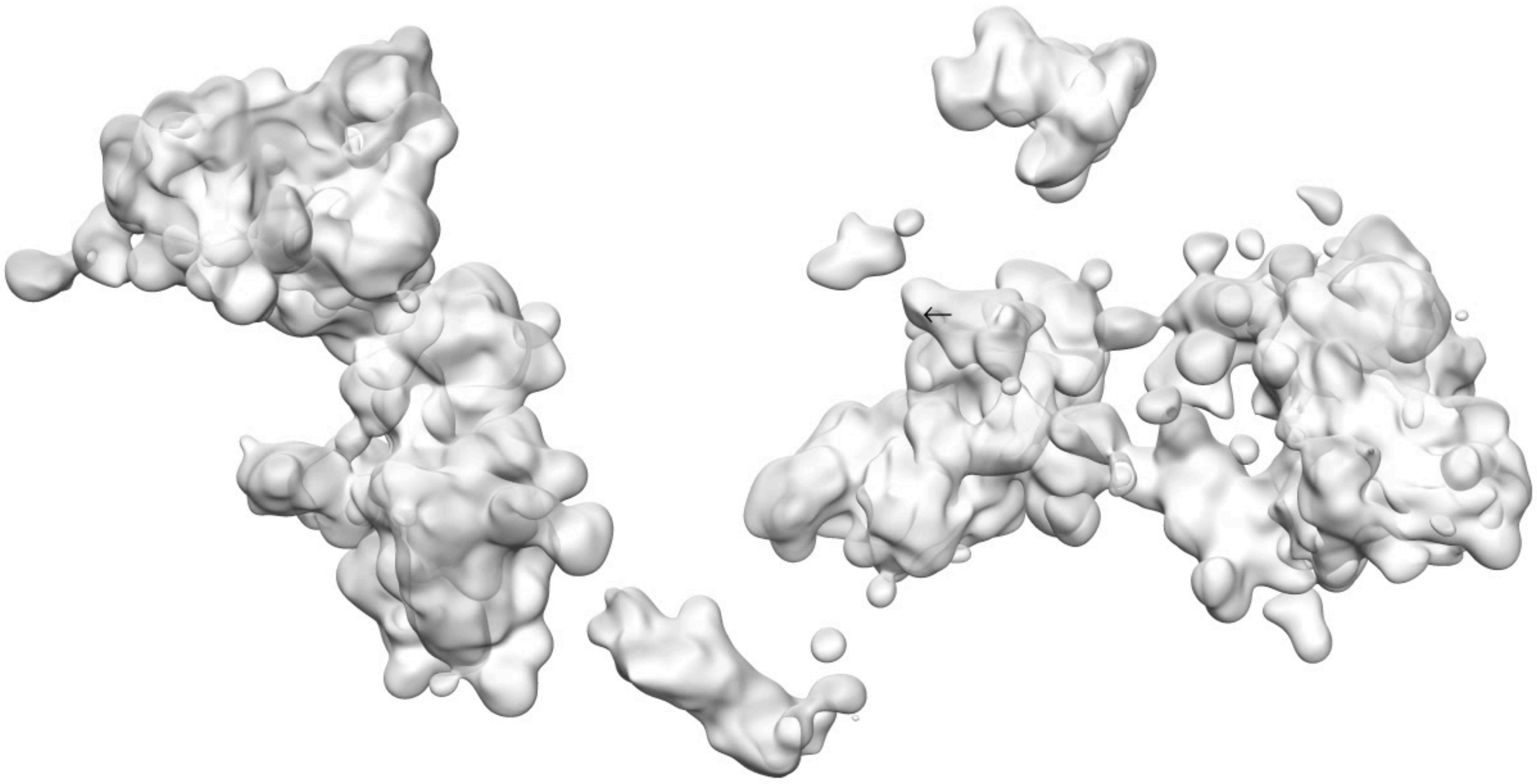


Chromosome walking path @10Kb resolution



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