

Chromosome walking with super-resolution imaging and modeling

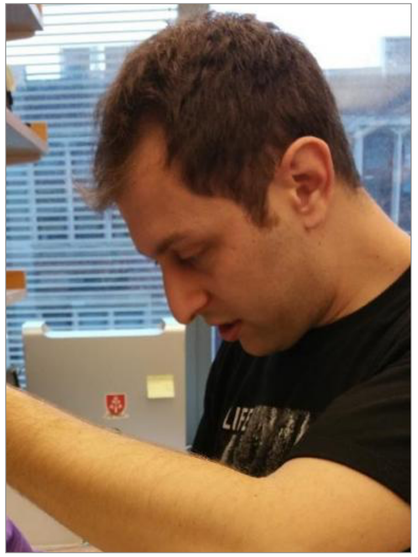
Marc A. Marti-Renom
CNAG-CRG · ICREA

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http://cnag.crg.eu

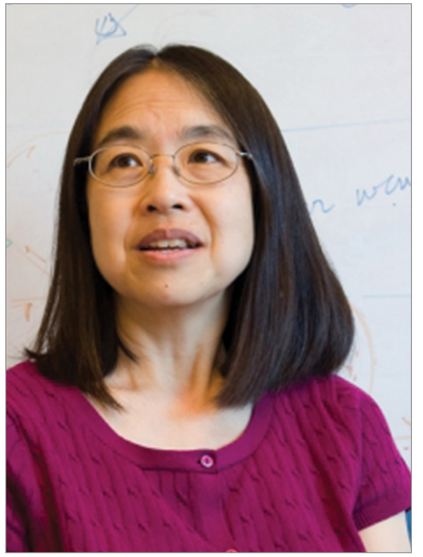
cnag CRG ICREA



Irene Farabella
CNAG-CRG



Guy Nir
Harvard Med School



Ting Wu
Harvard Med School

Can we walk the chromatin path in the nucleus?

by

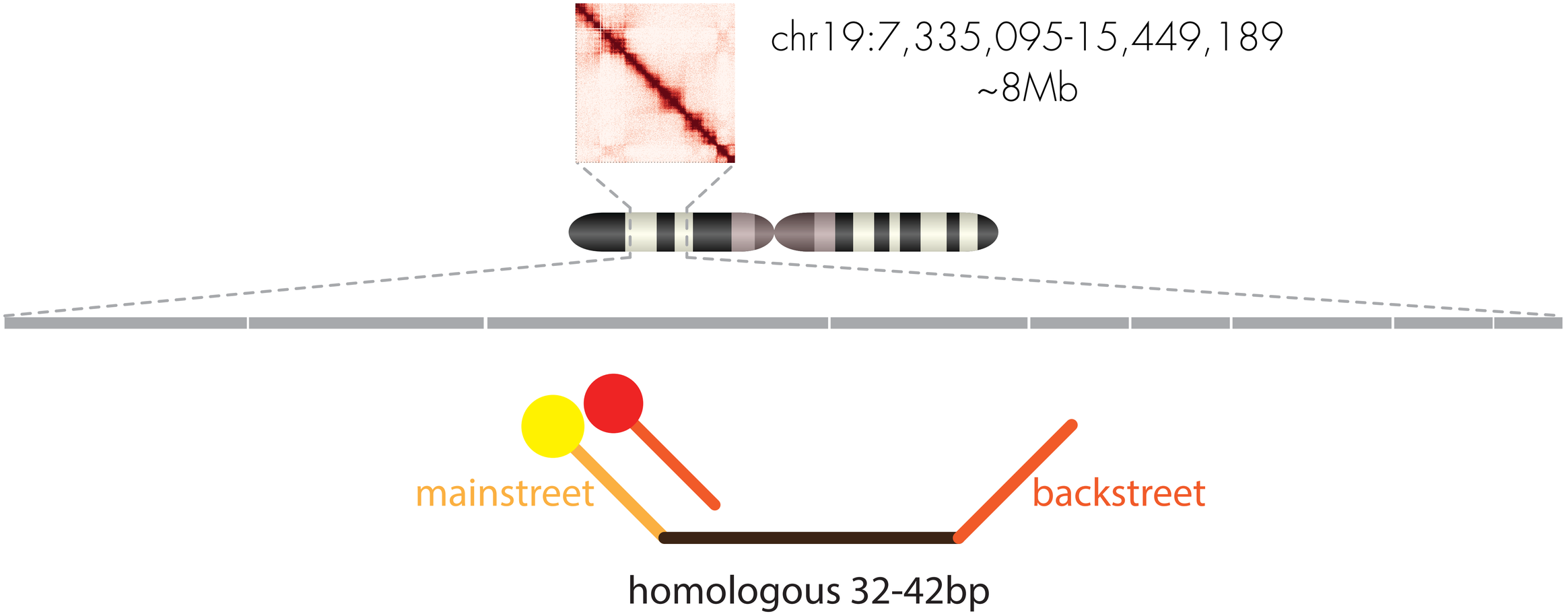
Integrating imaging and Hi-C maps with modeling.

by developing a method for

Oligopaint-based modeling of genomes

High-resolution imaging

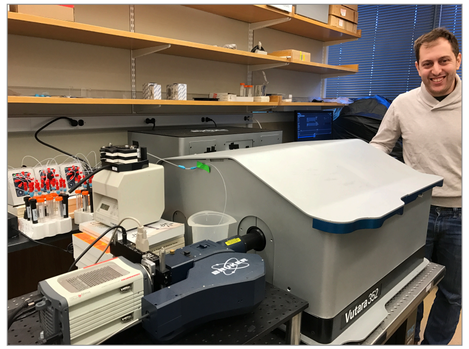
Tracing chromosomes with OligoSTORM & fluidics cycles in PGP1 cells



Beliveau et al. Nat. Comm. 2015

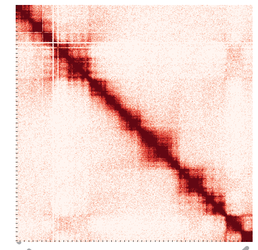
High-resolution imaging

Tracing chromosomes with OligoSTORM & fluidics cycles in PGP1 cells

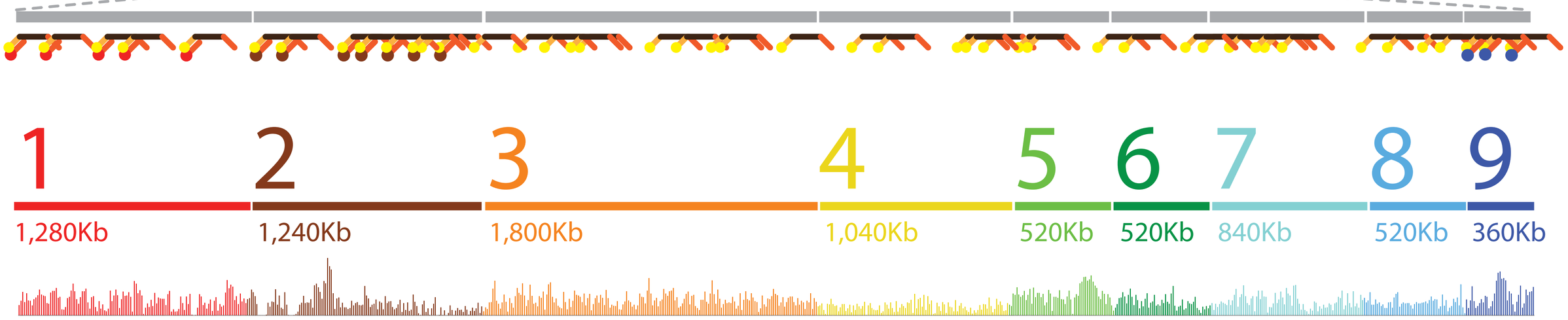


Guy Nir Harvard Med School

Bodgan Bintu Harvard
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Jeff Stuckey Bruker
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Steve Callahan Zero Epsilon

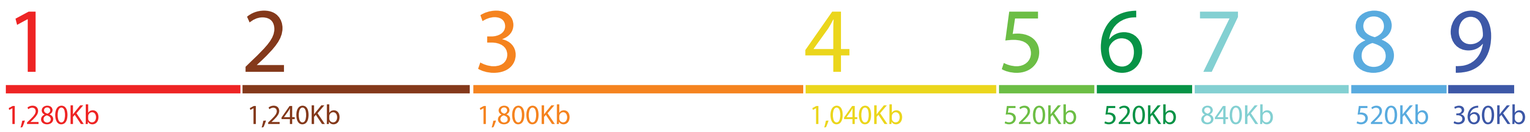


chr19:7,335,095-15,449,189
~8Mb



High-resolution imaging

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

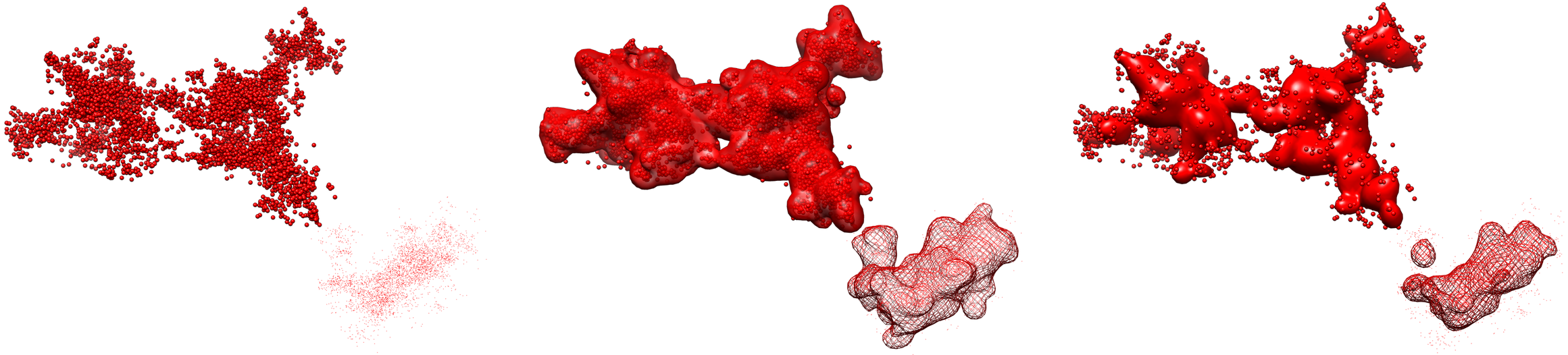


Cell-02

High-resolution imaging

XYZ points convolution into a density map

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

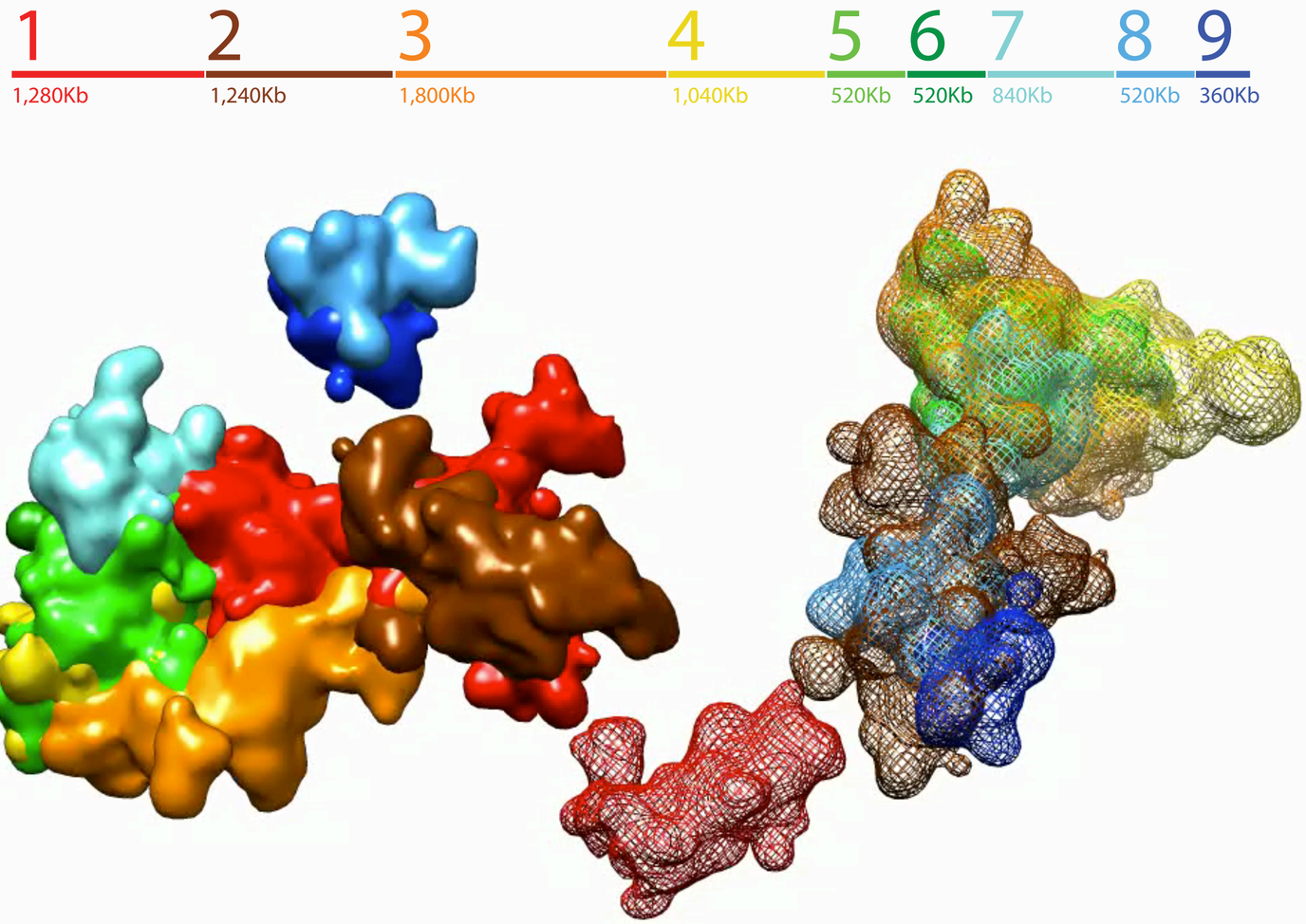


Cell-02 · Segment 1

Farabella et al, J Appl Crystallogr. 2015

Density maps

Cell-02 · Density map @ 50nm

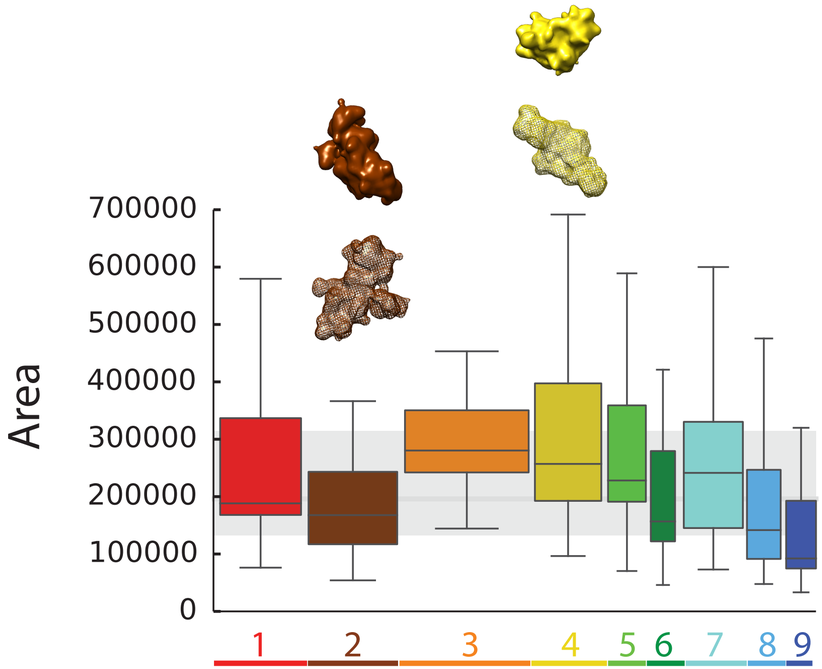


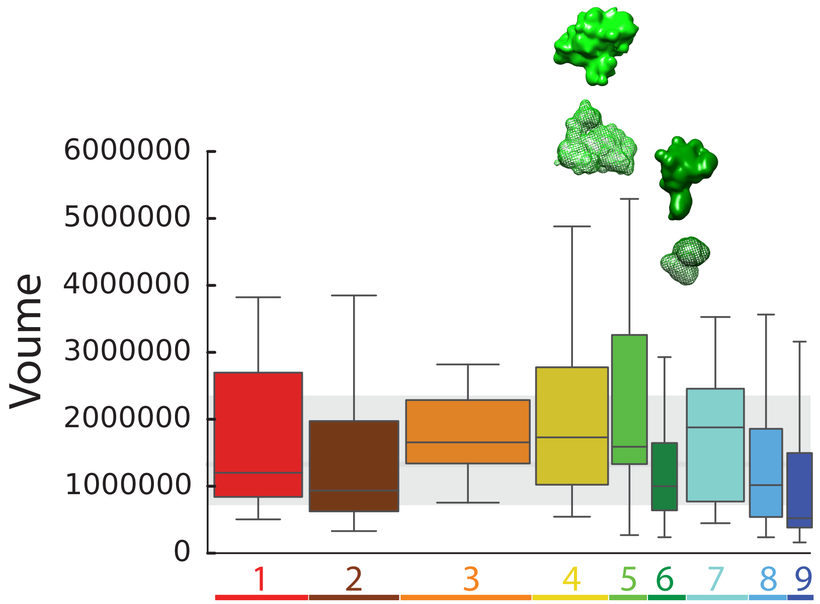
Area (nm^2)
Volume (nm^3)
Sphericity
Overlap (%)
Distance (nm)

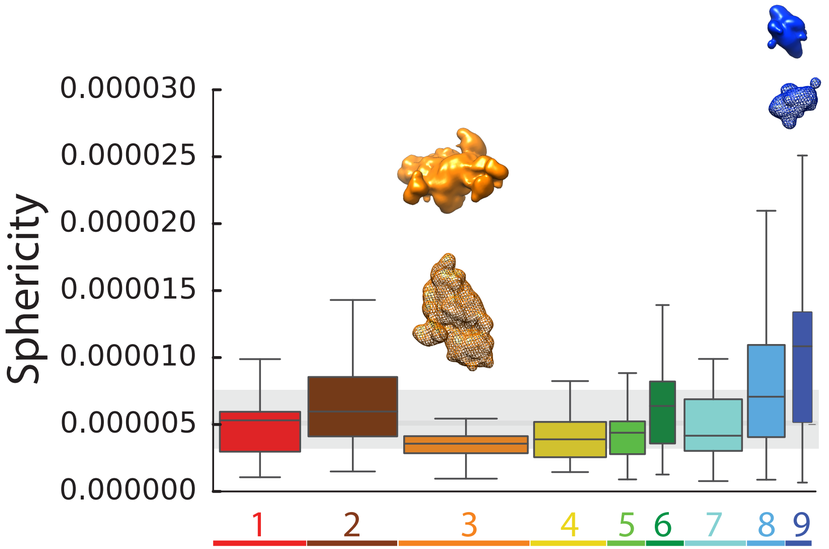
Farabella et al, J Appl Crystallogr. 2015

Structural features

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



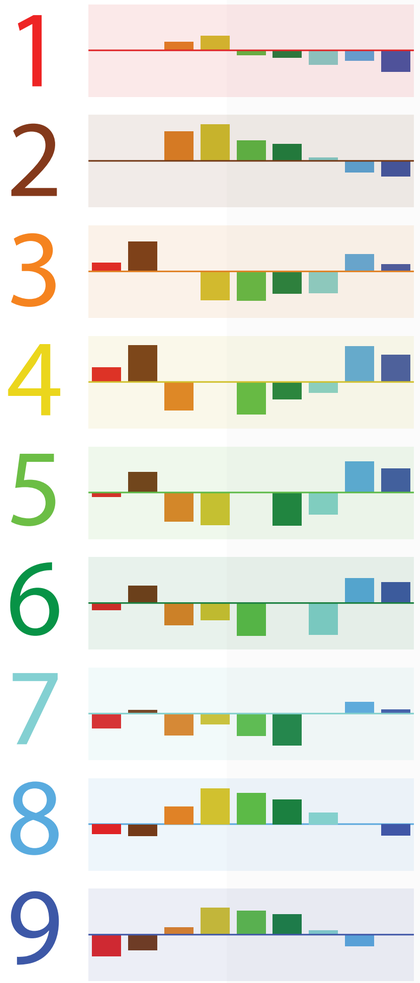


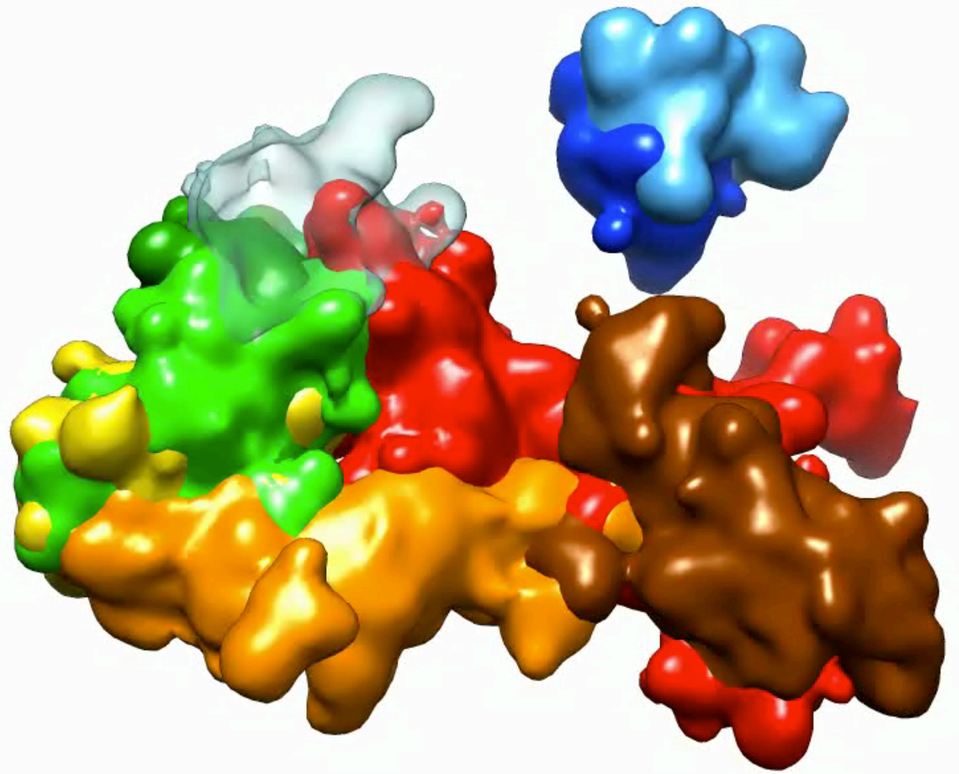


Spatial arrangement

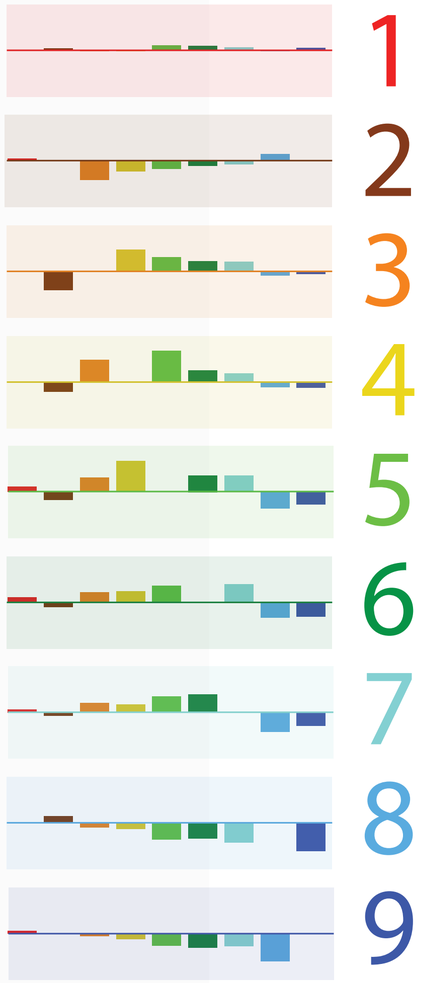
Distance and overlap of 19 cells each with 2 homologous resolved

Diff. distance



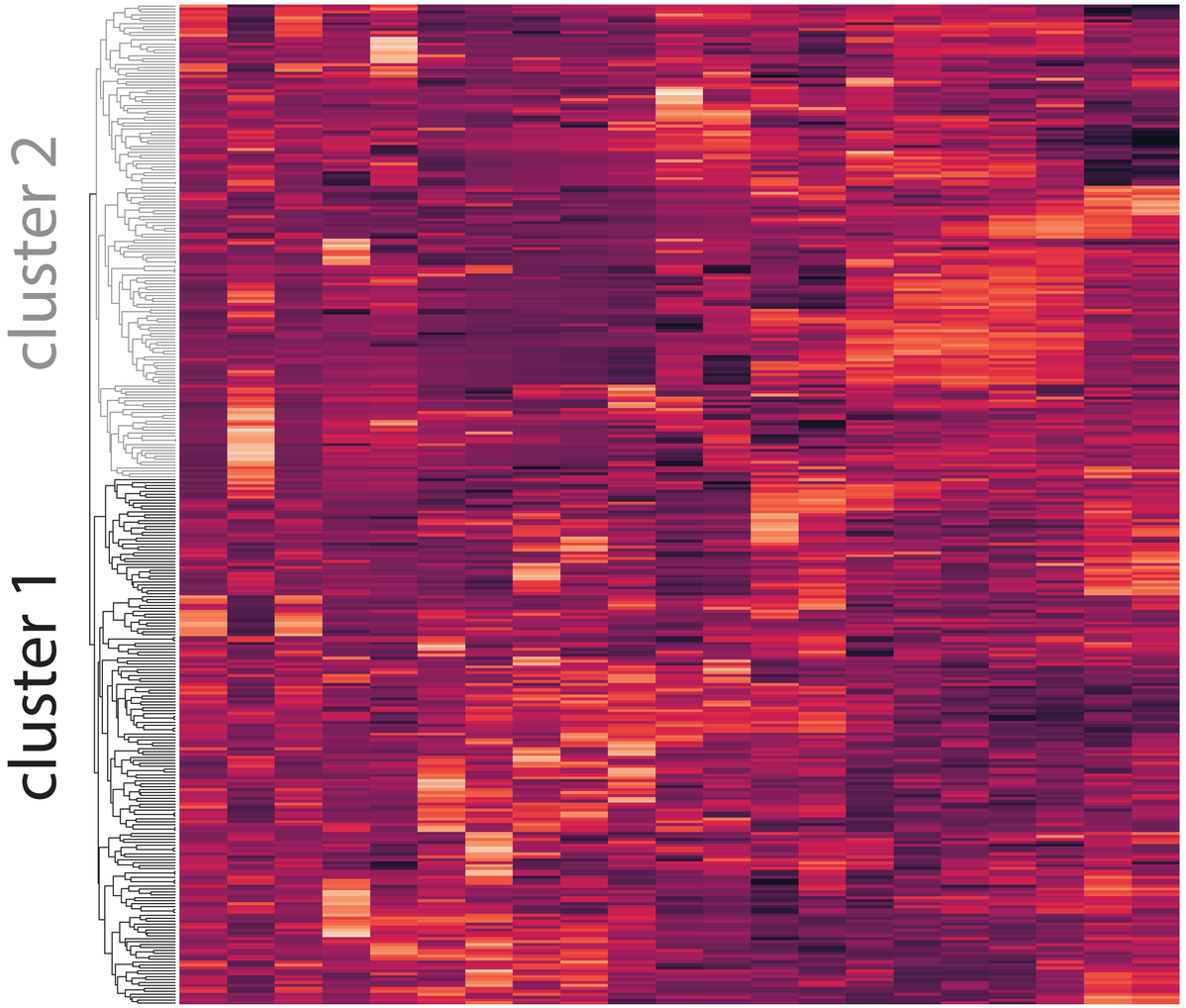


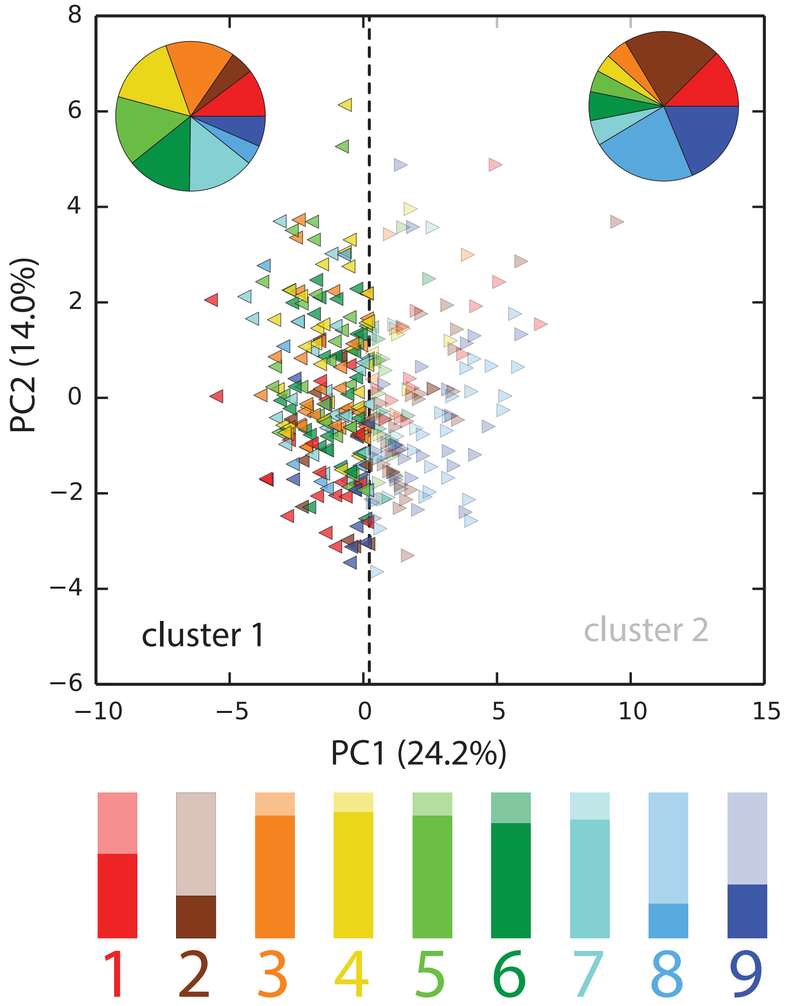
Diff. overlap



Structural clustering

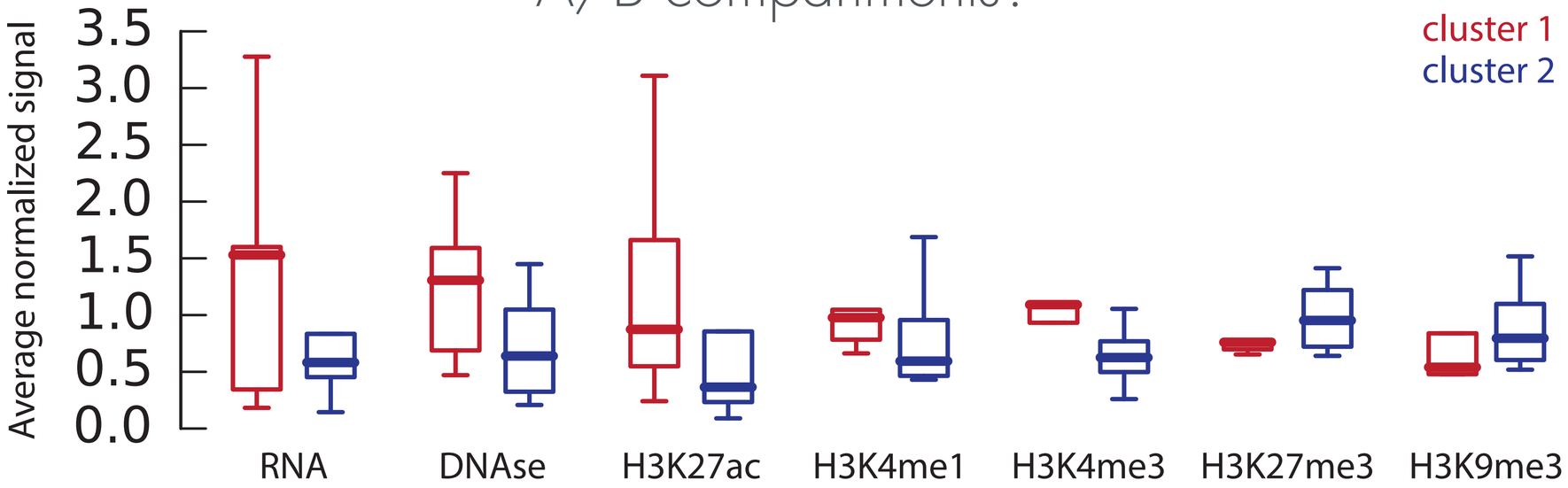
19 cells each with 2 homologous and 9 segments each (342)

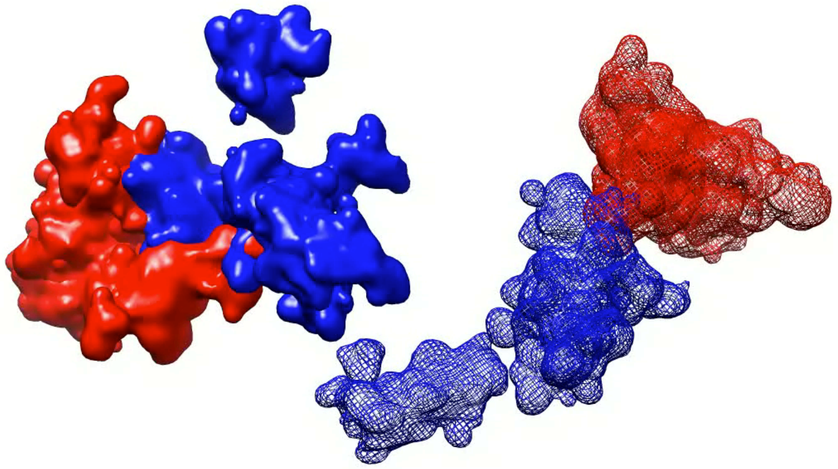


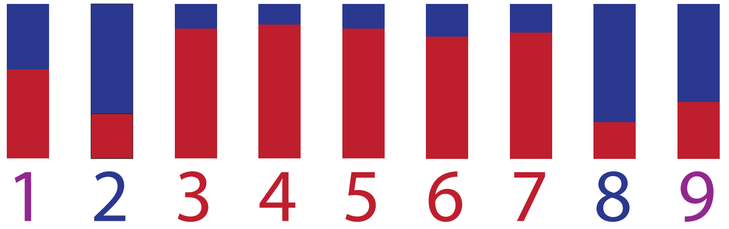


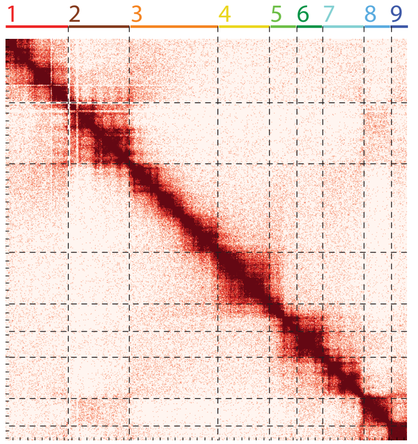
Cluster properties

A/B compartments?





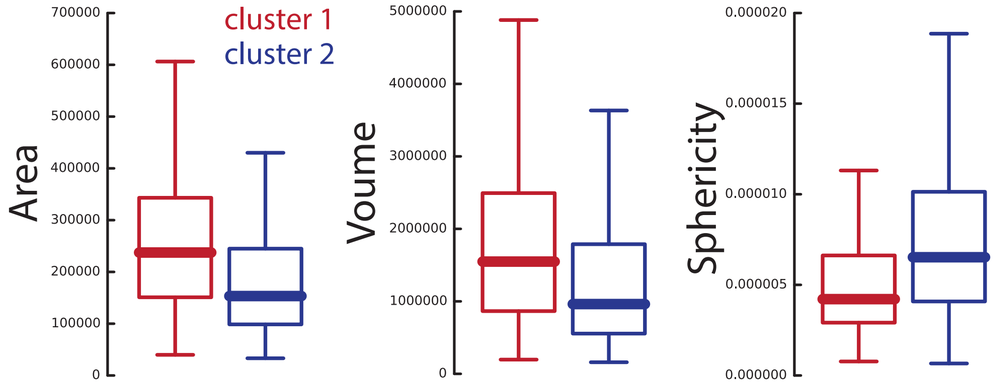


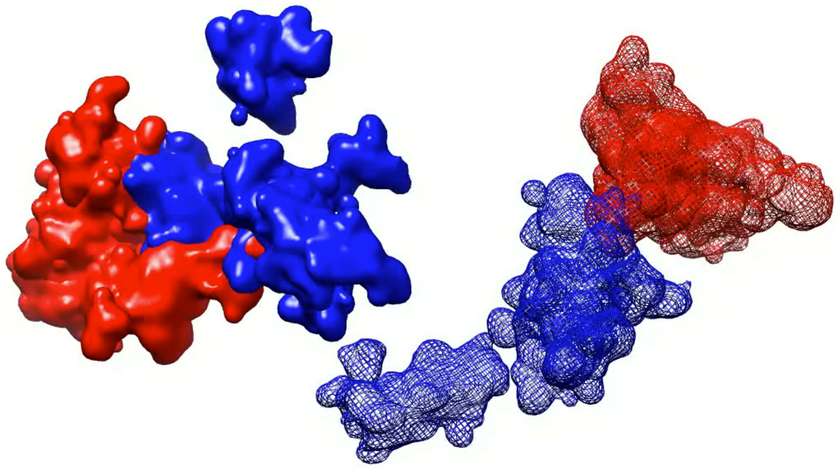


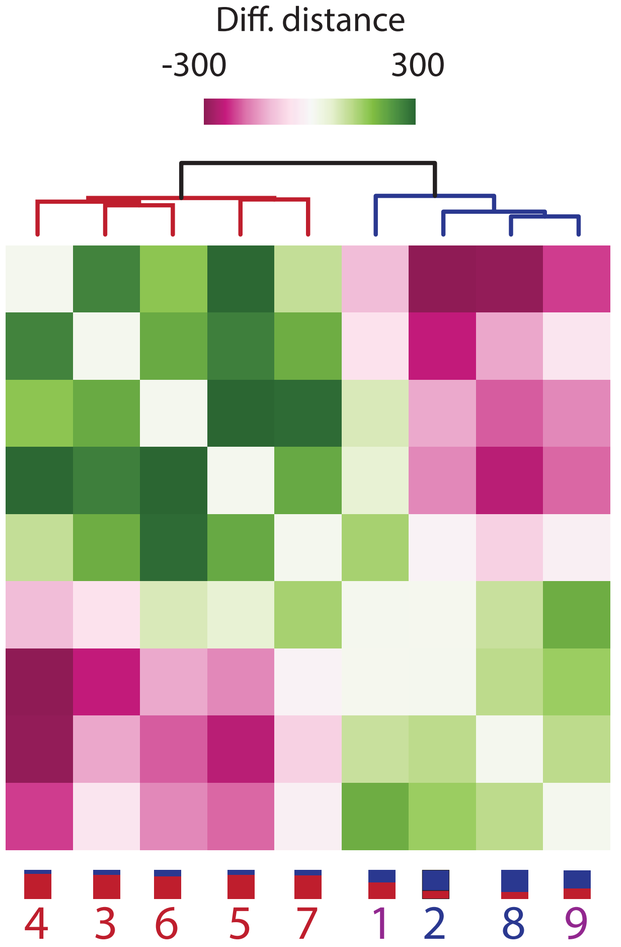
PGP1 ChIP-seq and Hi-C data from ENCODE and Lieberman-Aiden Lab, respectively

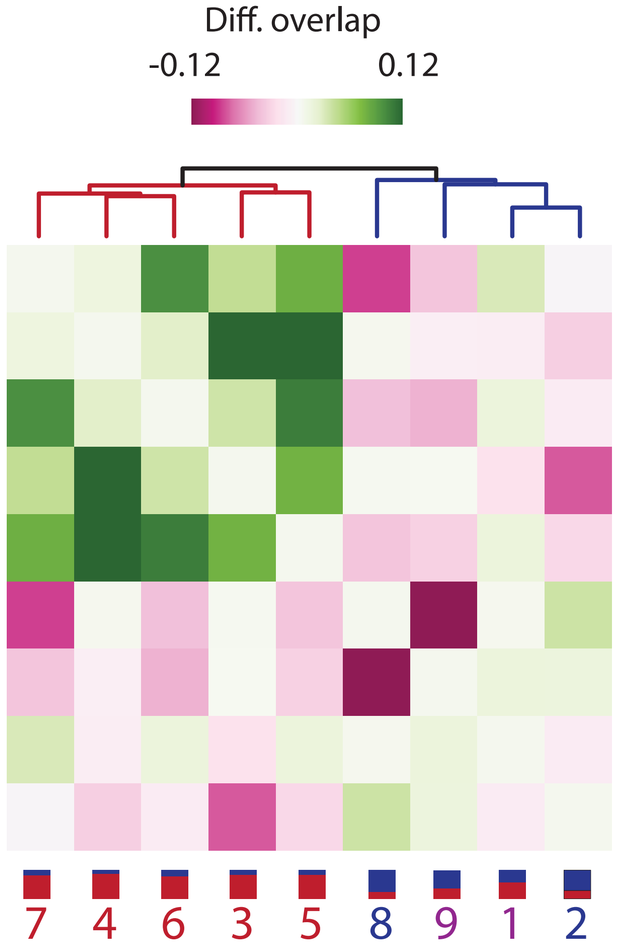
Cluster properties

A/B compartment properties









Can we walk the chromatin path in the nucleus?

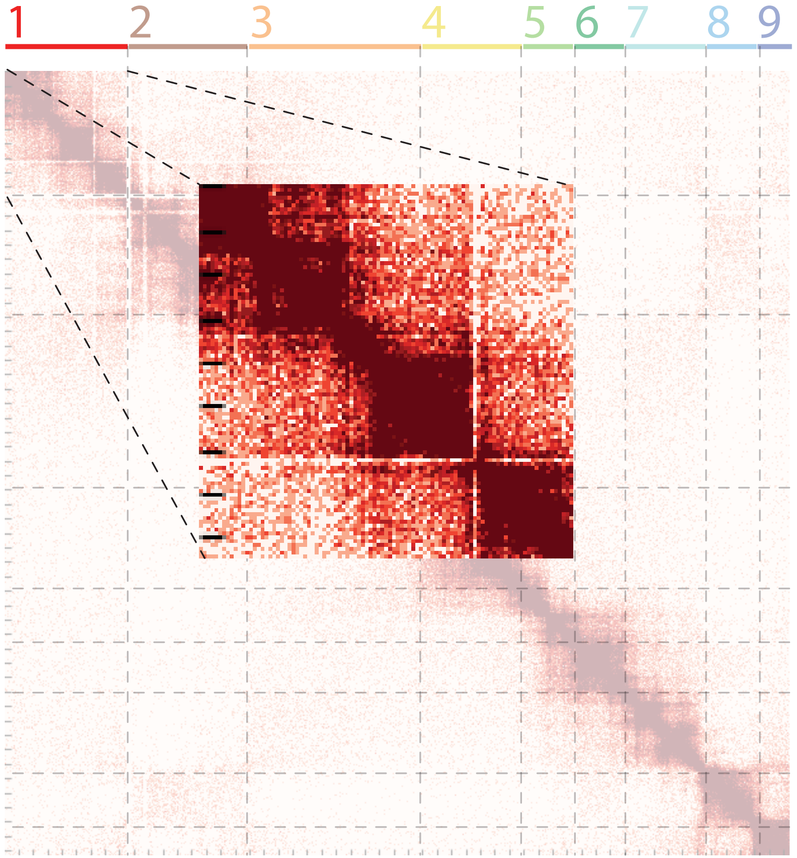
YES!

Can we increase the resolution of our data?

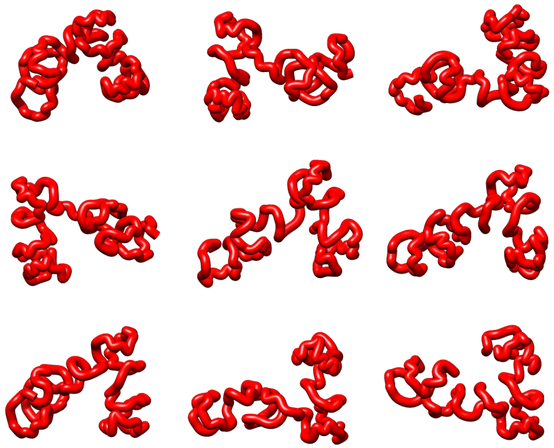
by fitting 3D models based on Hi-C interaction maps

Increasing resolution

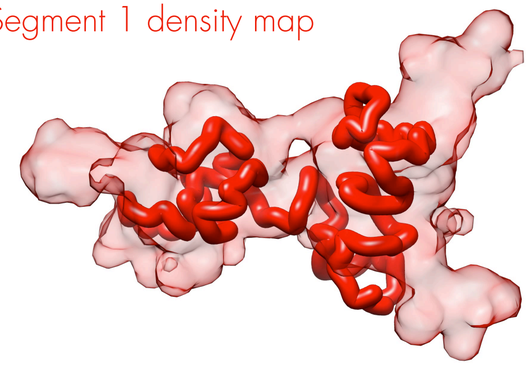
Rigid body fitting 3D structures based on Hi-C data



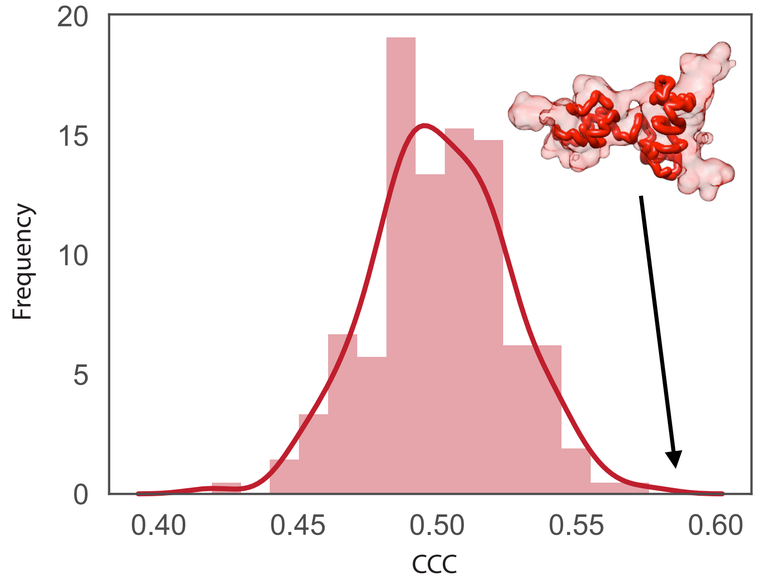
Segment 1 3D models



Segment 1 density map



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



TADbit

Serra, Baù, et al. PLOS CB 2017

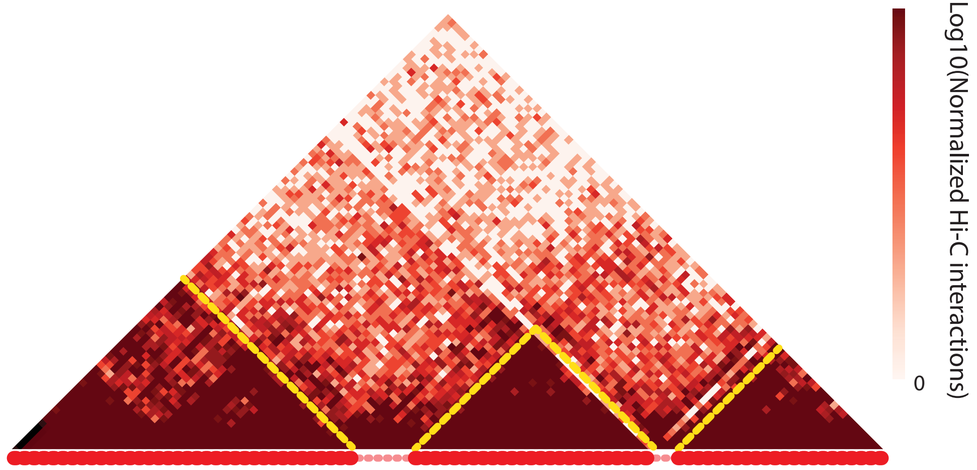
http://www.3DGenomes.org

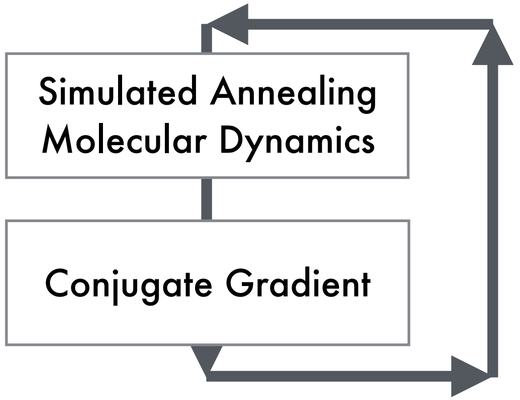
Farabella et al, J Appl Crystallogr. 2015

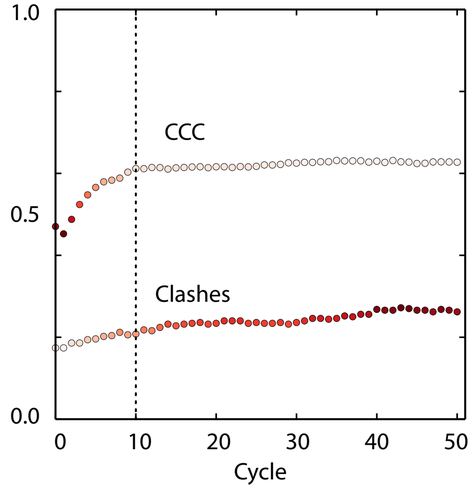
Roseman, 2000; Wriggers & Chacon, Structure 2001

Increasing resolution

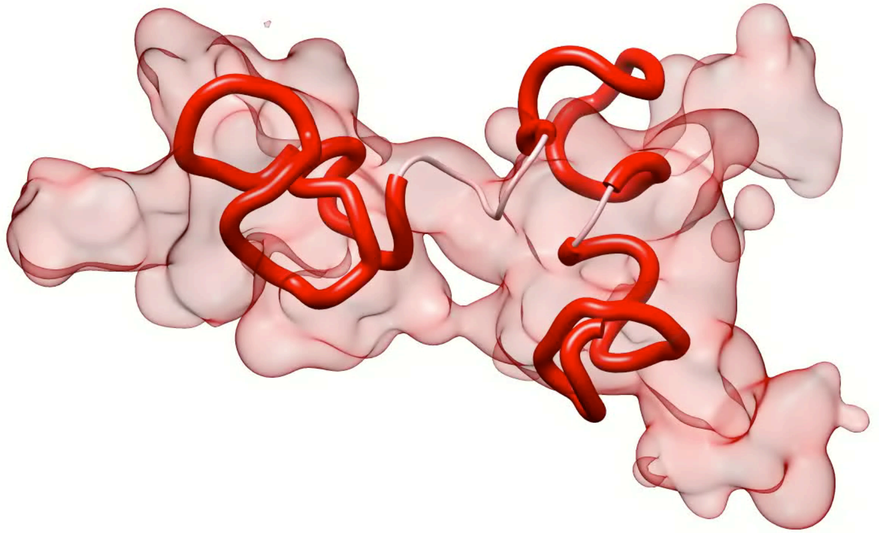
Flexible fitting 3D structures based on Hi-C data





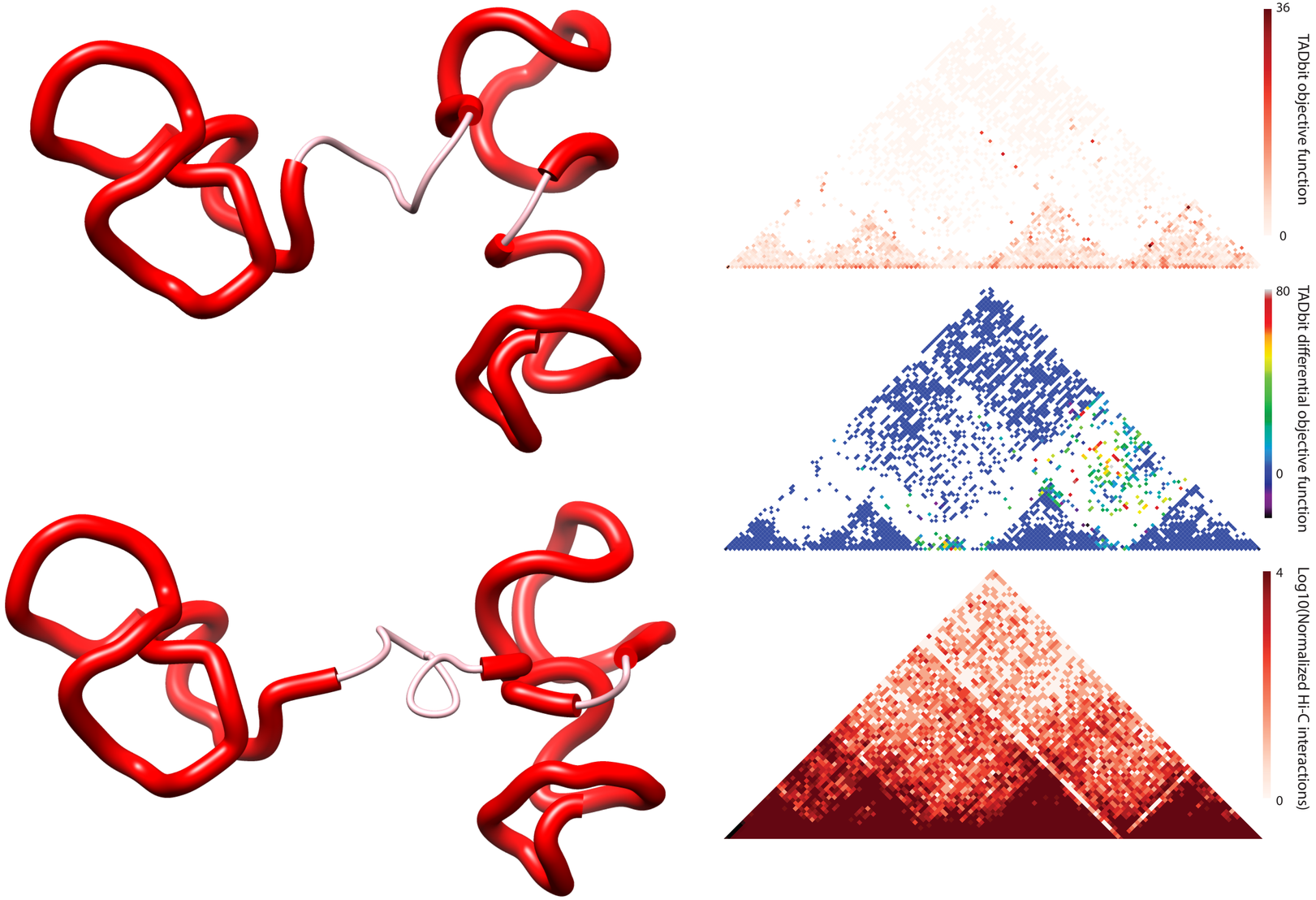




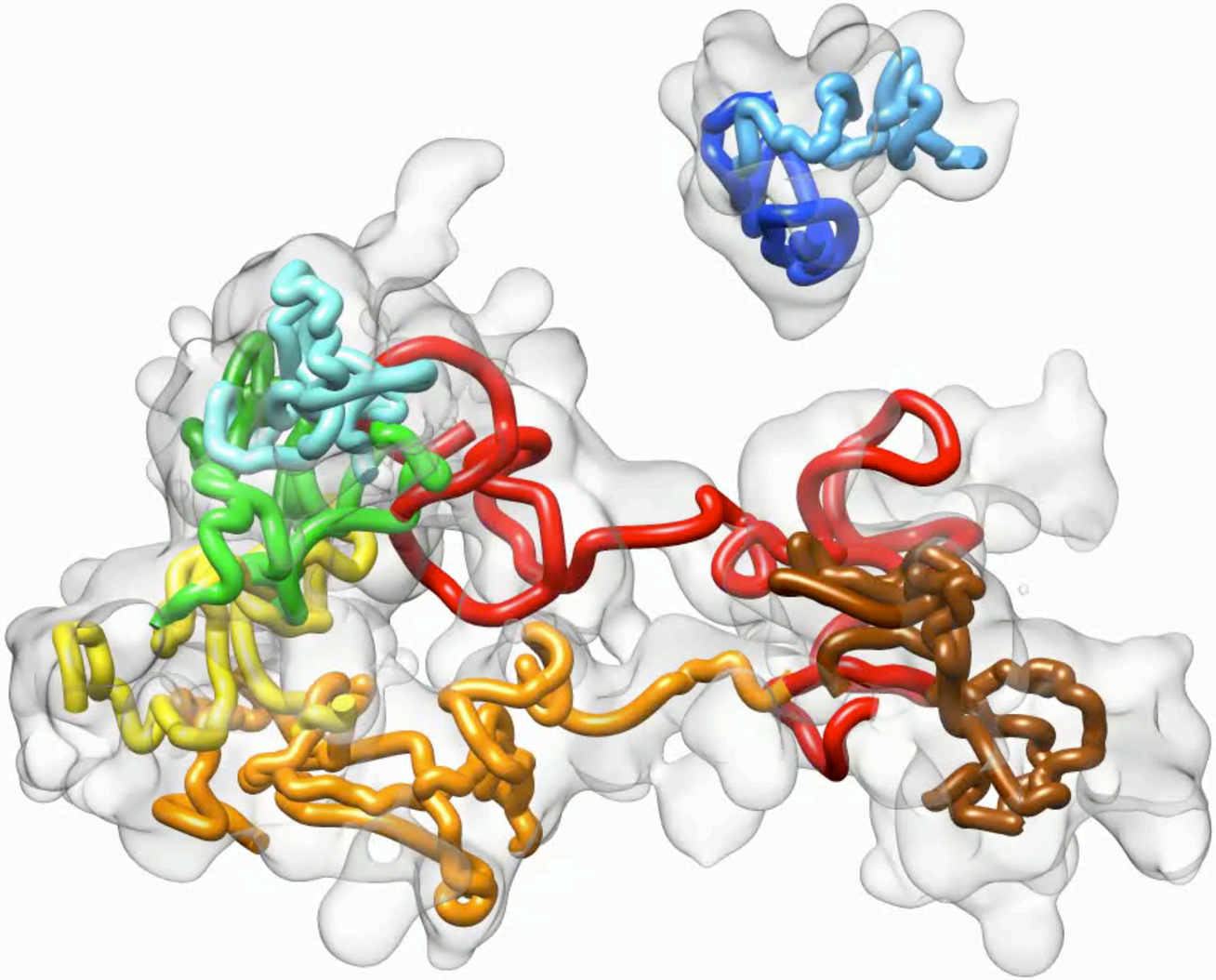


Increasing resolution

Flexible fitting 3D structures based on Hi-C data



Chromosome walking path @10Kb resolution



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This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 813327