Giacomo Cavalli

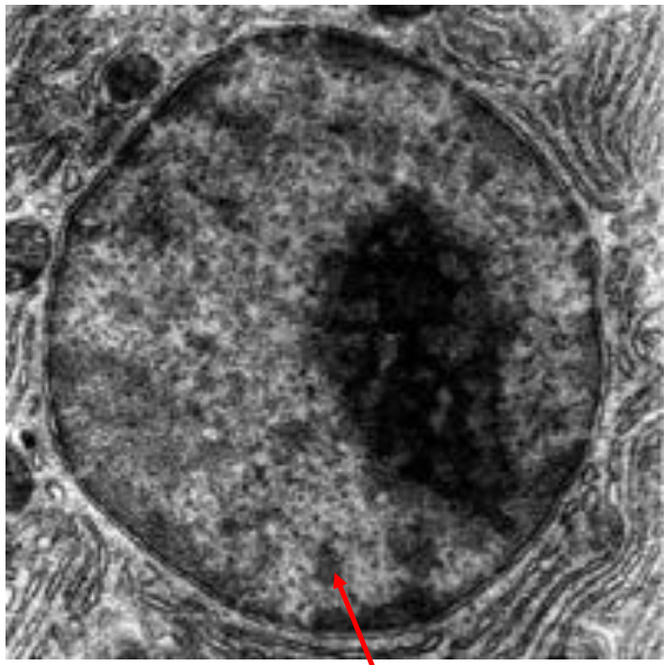
GDR DNA, Rencontres des Grands Causses, Millau, April 9, 2018

Physical characterization of Topologically Associating Domains (TADs)

Institute of Human Genetics
Montpellier France

INSTITUTE OF HUMAN GENETICS

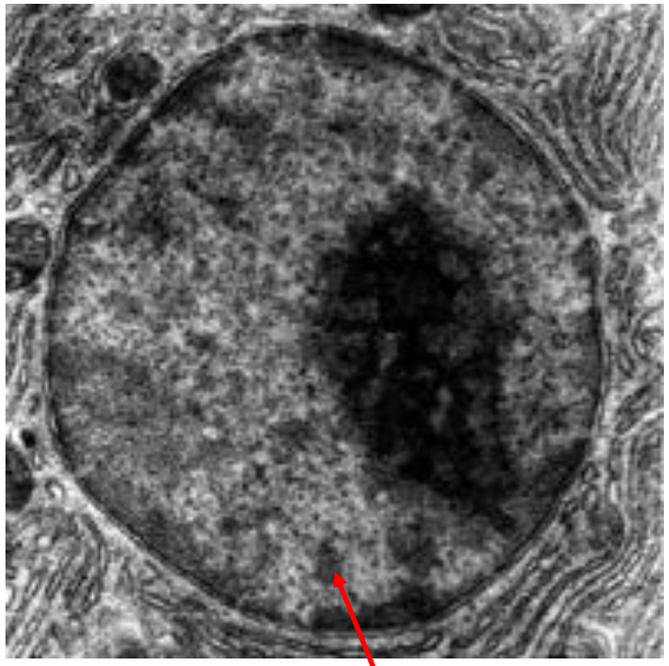
From linear genome to 3D chromosome folding



~10 µm

~2 meters
of DNA

From linear genome to 3D chromosome folding



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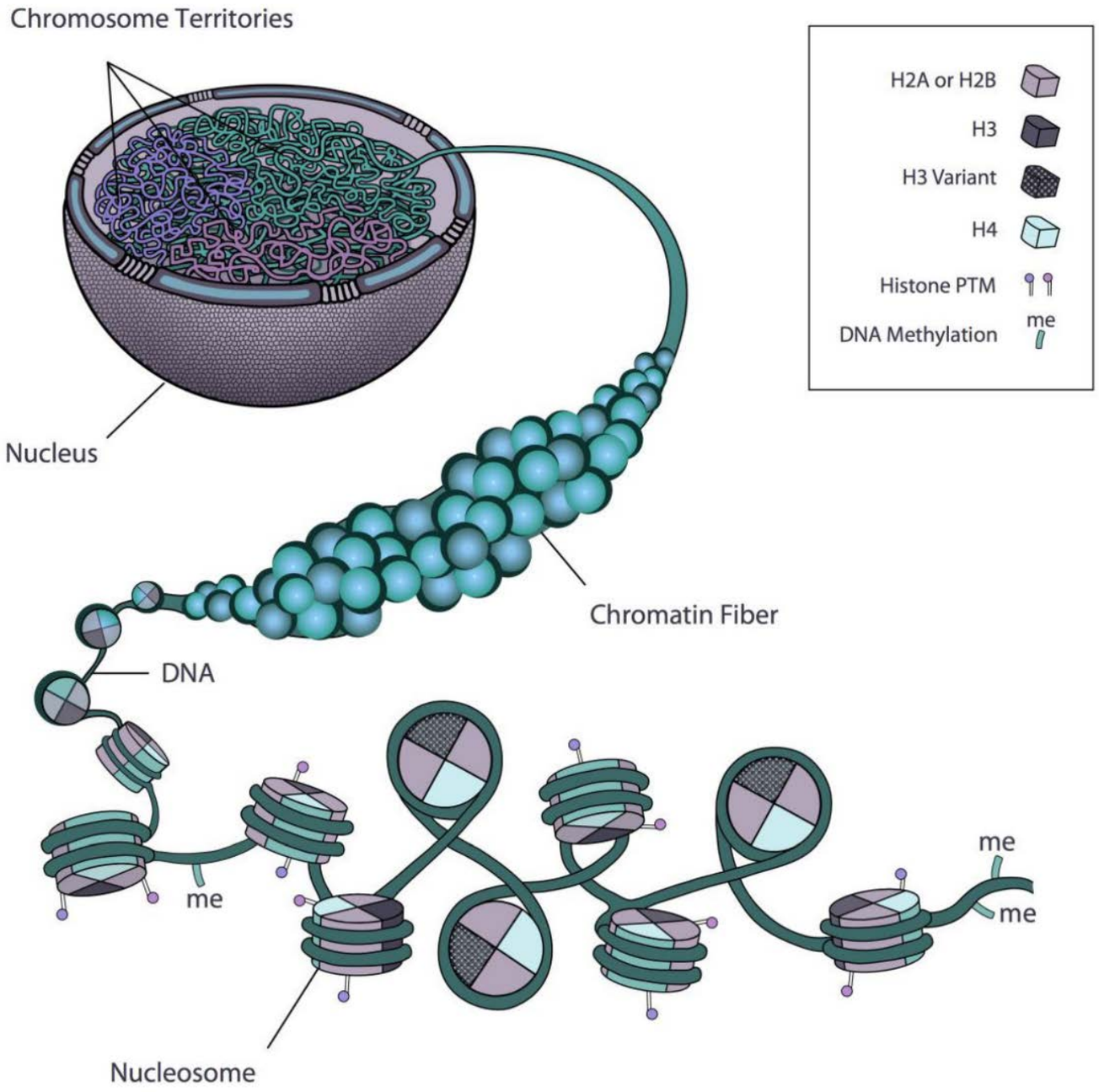
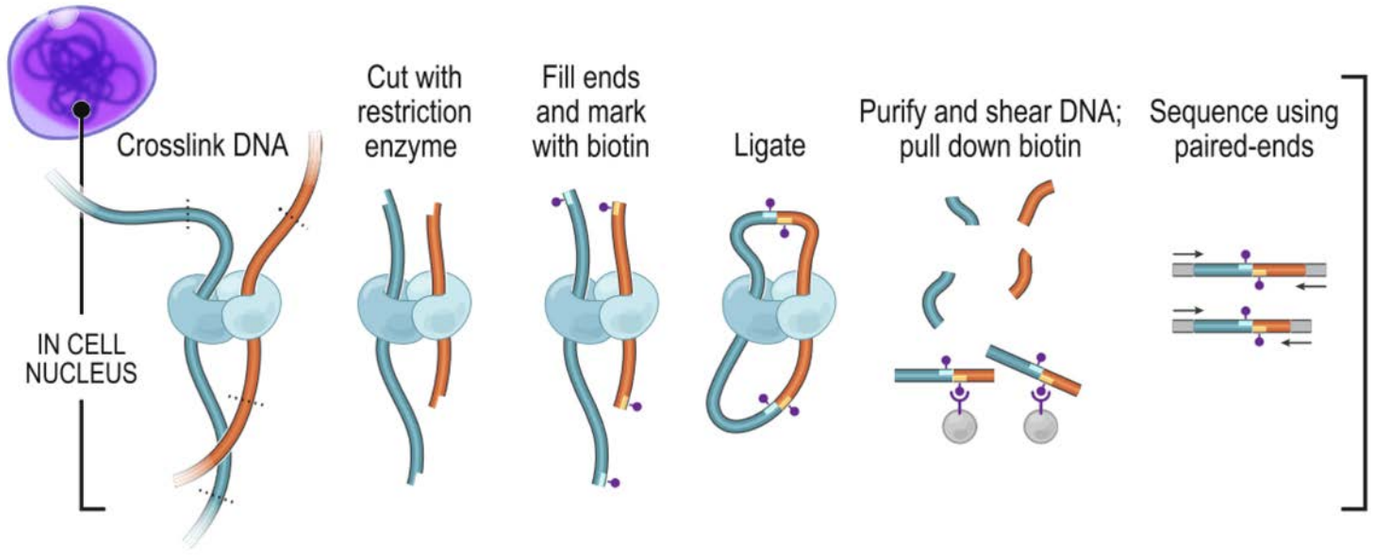


Rosa & Shaw, 2013

Chromosome Conformation Capture method



➡ Hi-C:
all vs all

Lieberman, *et al*, 2009
Rao, *et al*, 2014

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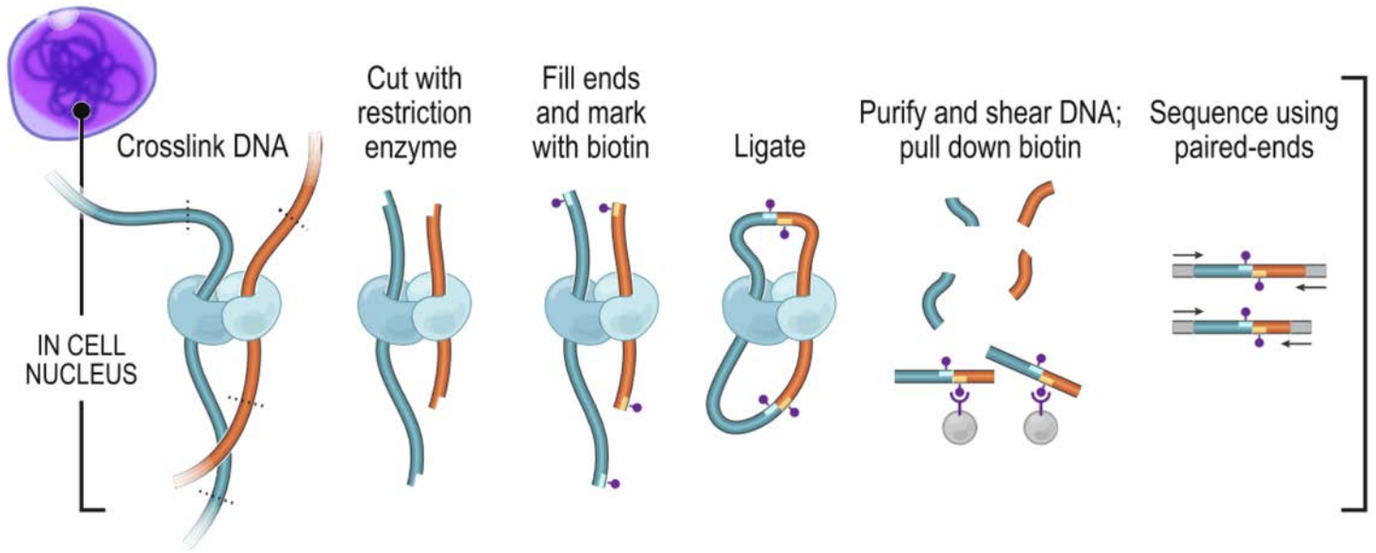

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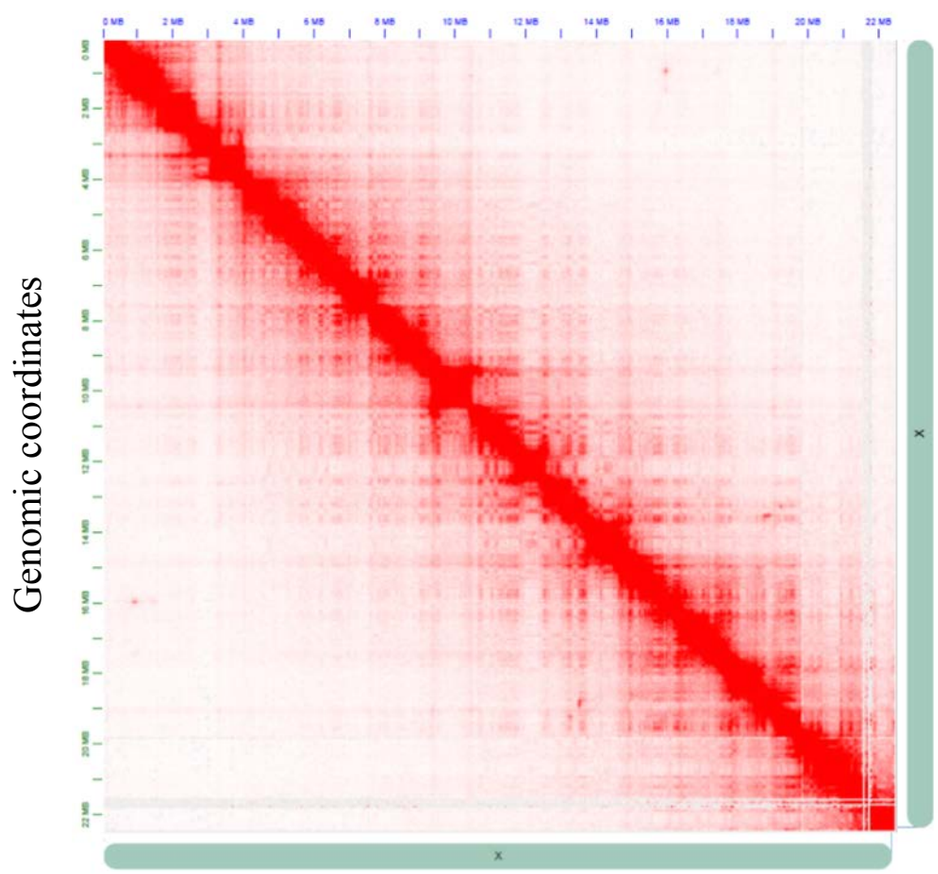

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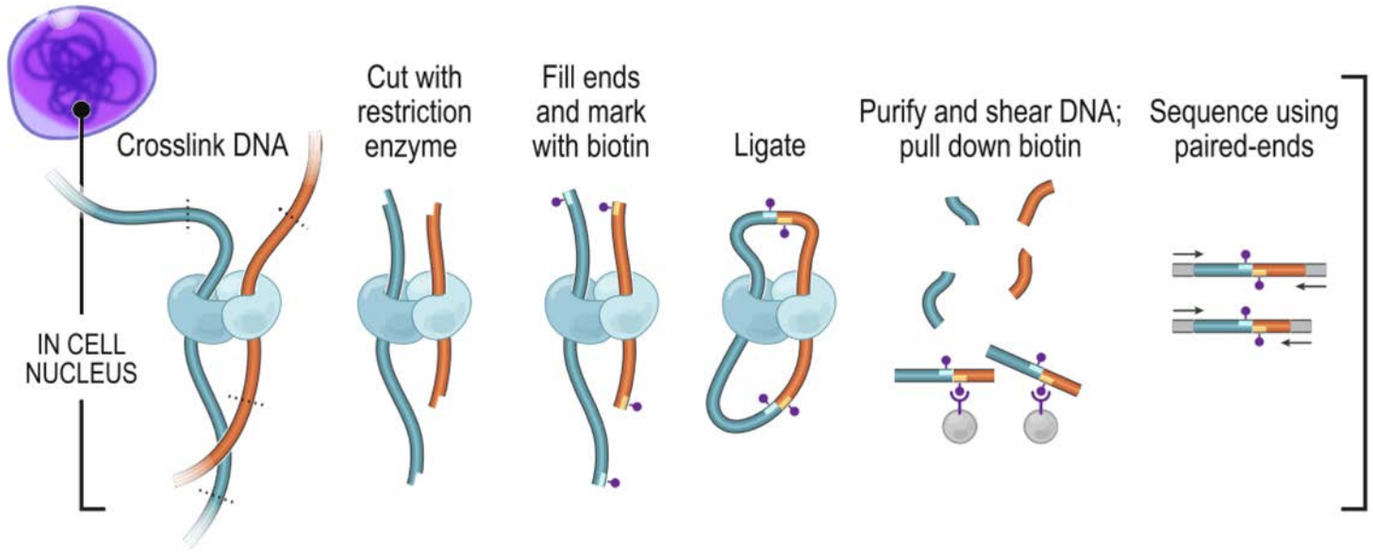

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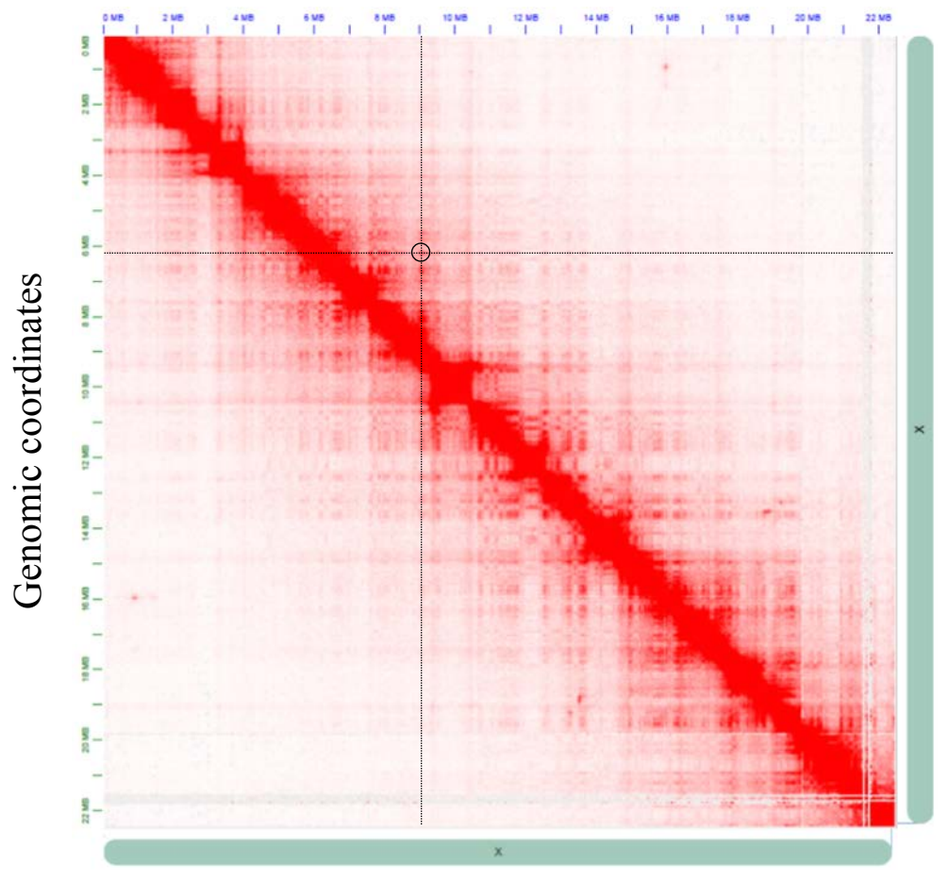

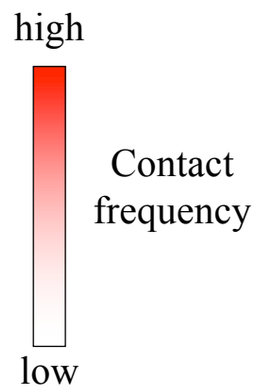

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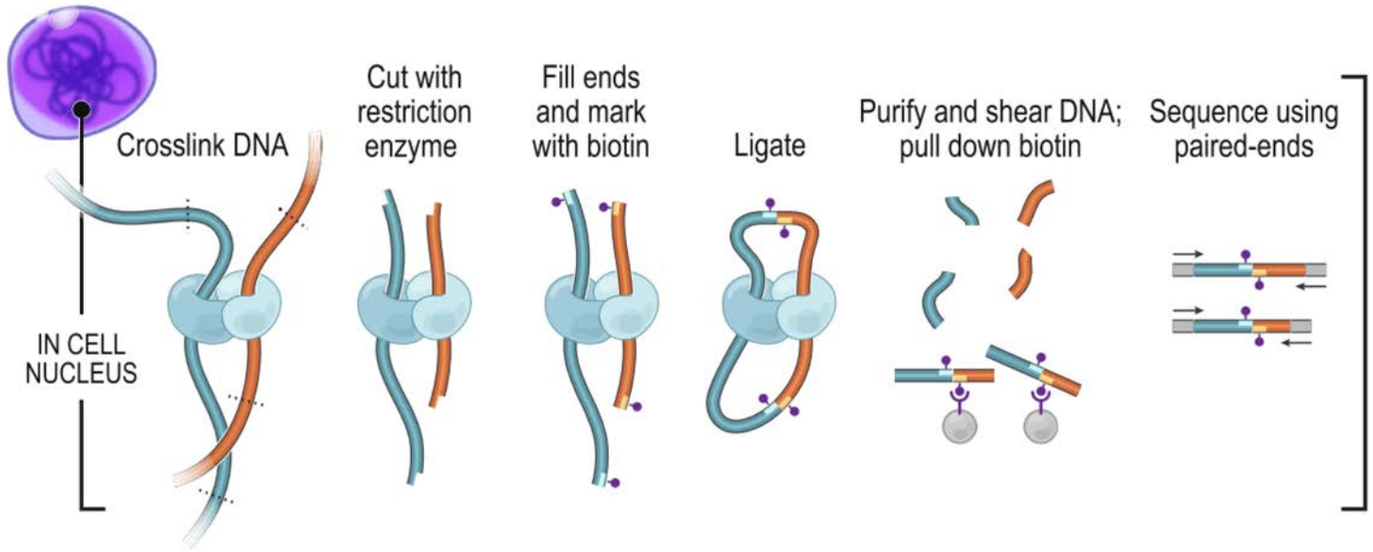

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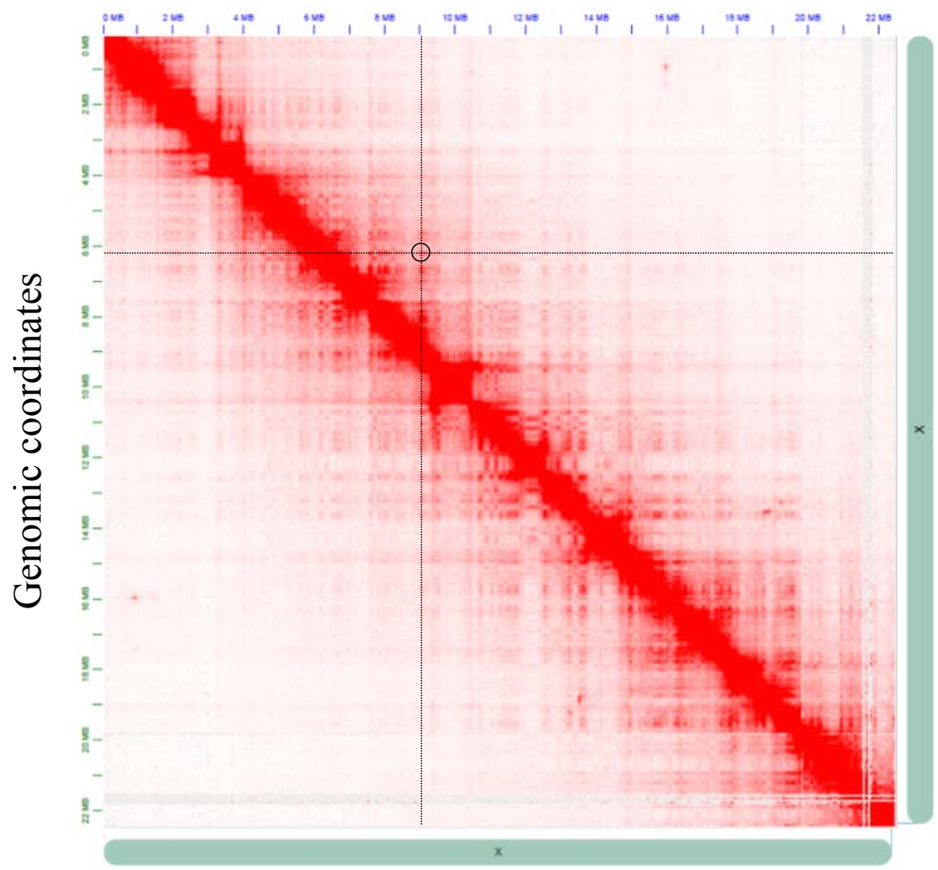
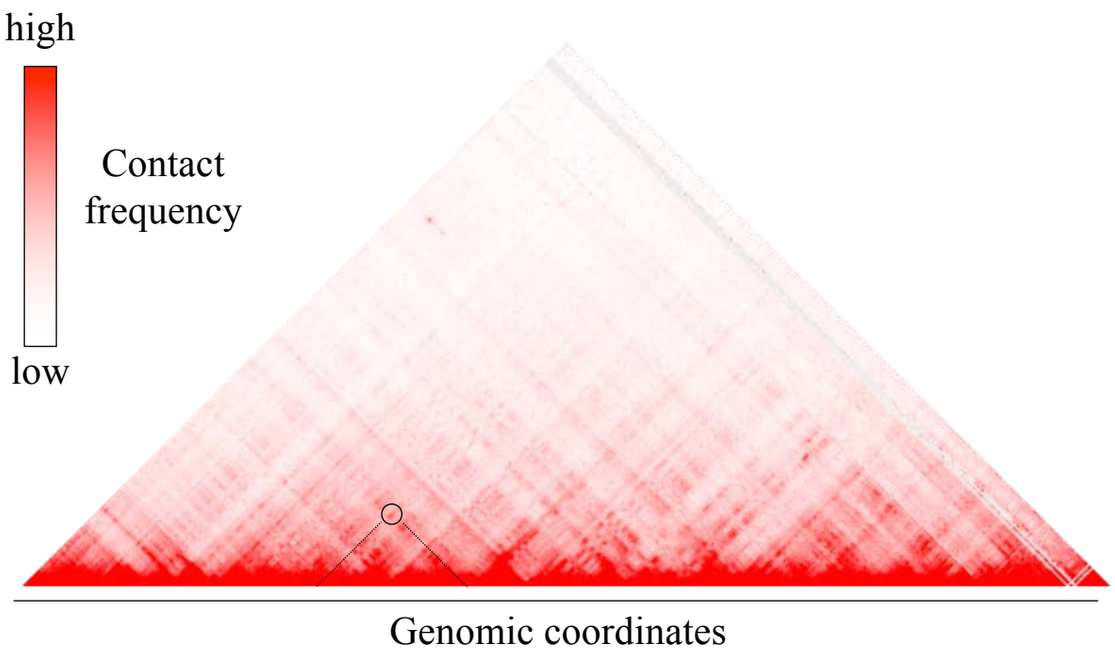
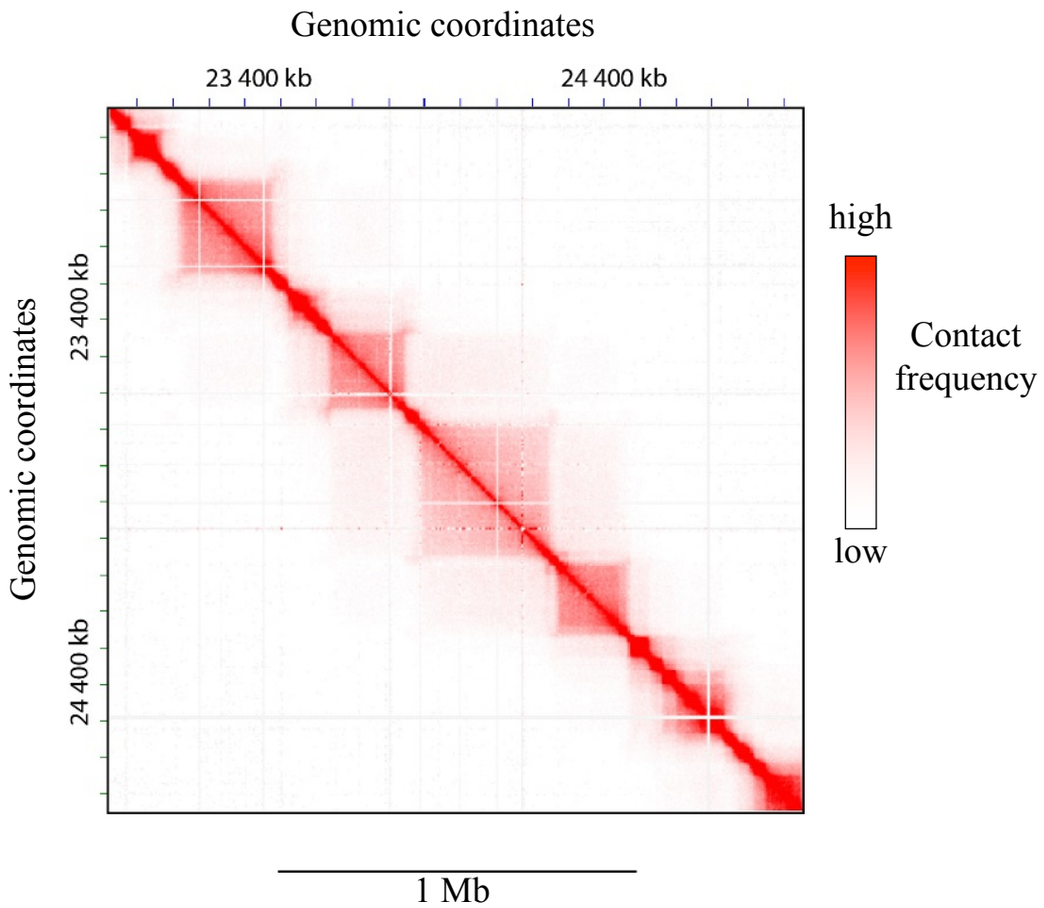




The « Topologically Associating Domains » (TADs)



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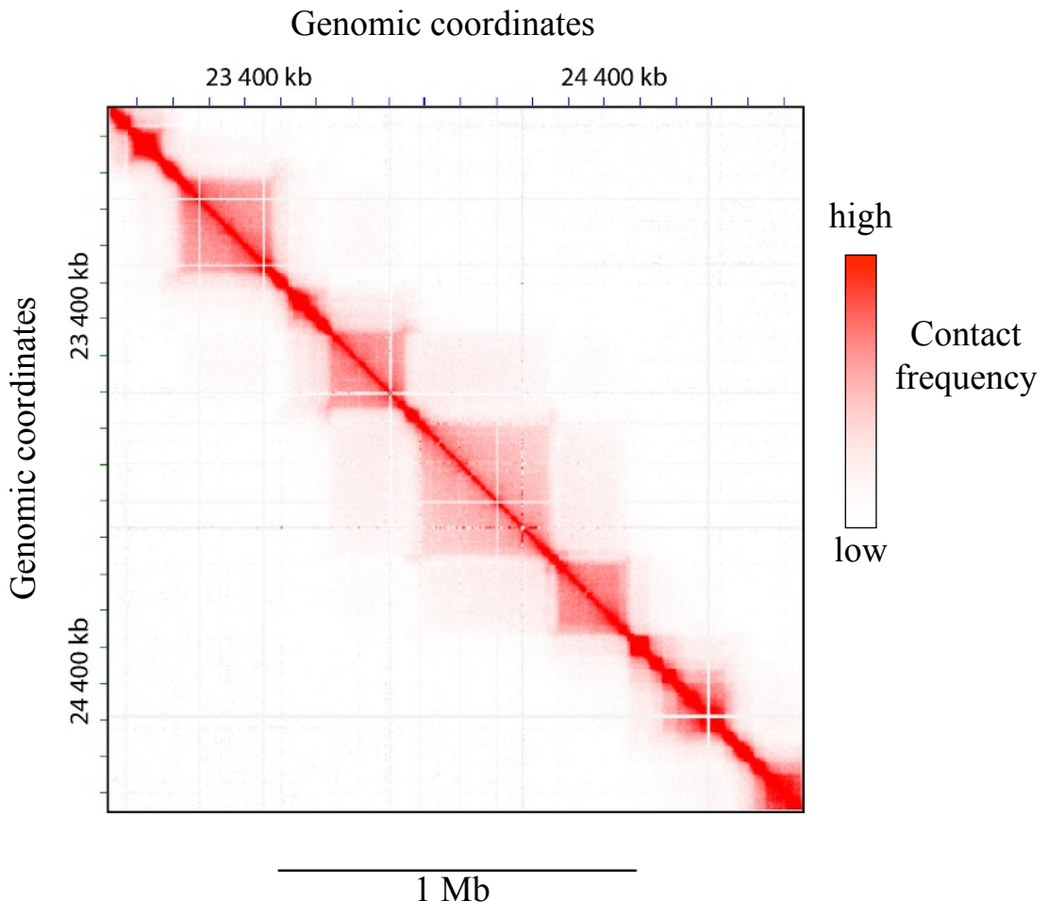
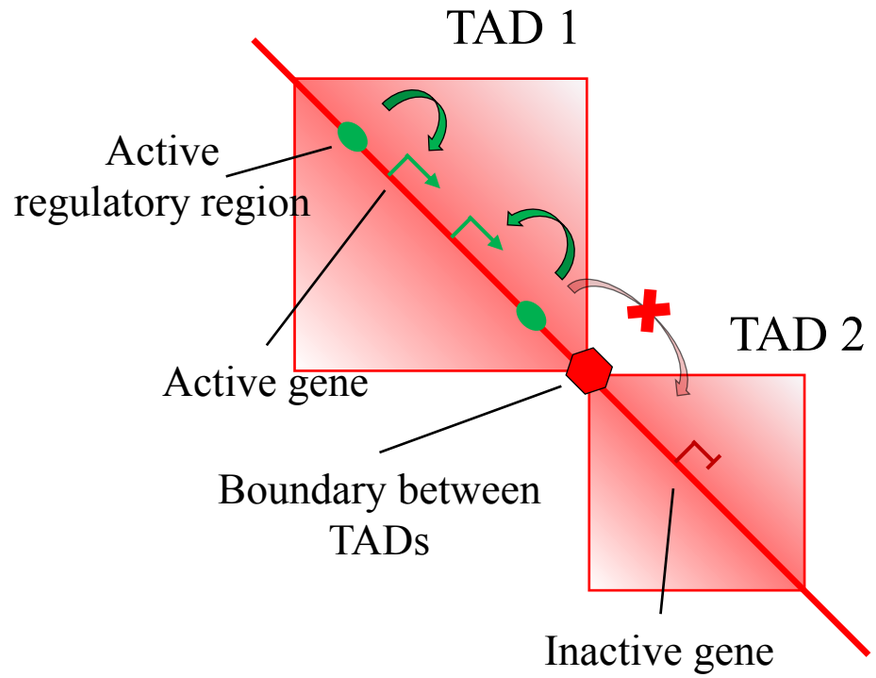


TADs are functional genome units



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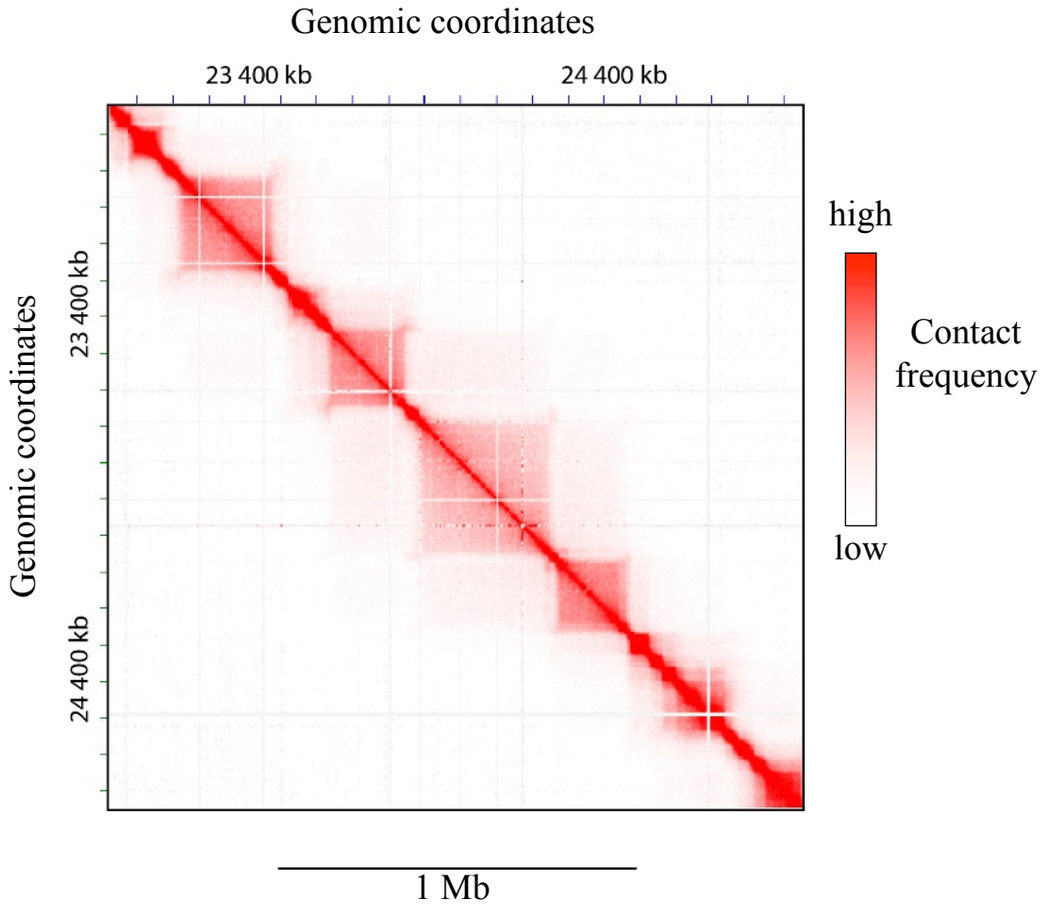

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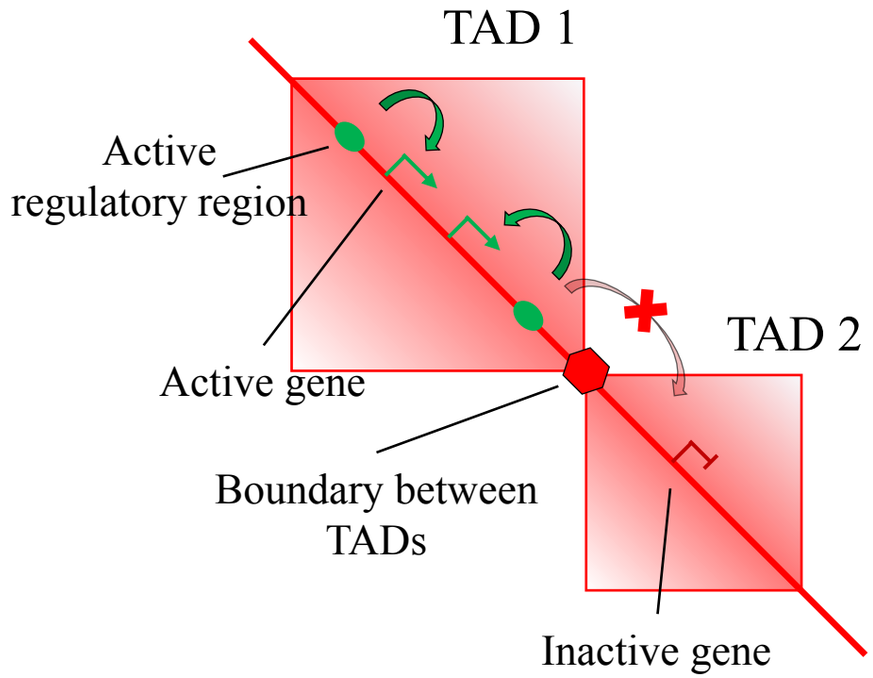


Are TADs structural chromosomal units?

Investigating the physical nature of TADs

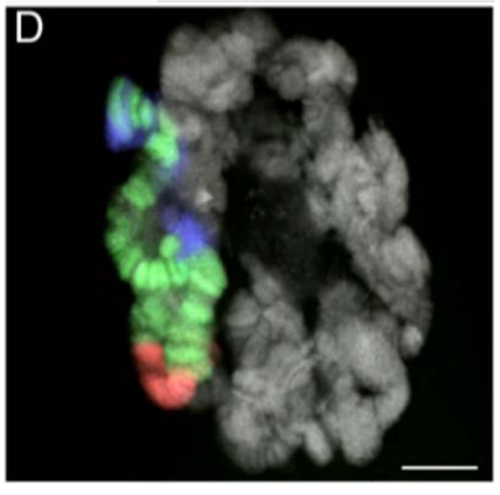
Quentin Szabo

Marcelo Nollamnn
CBS, Montpellier

Daniel Jost
TIMC-IMAG, Grenoble

Fluorescent in Situ Hybridization (FISH) using Oligopaints and 3D-Structured Illumination Microscopy (3D-SIM)

Beliveau, *et al*, 2012
Beliveau, *et al*, 2015



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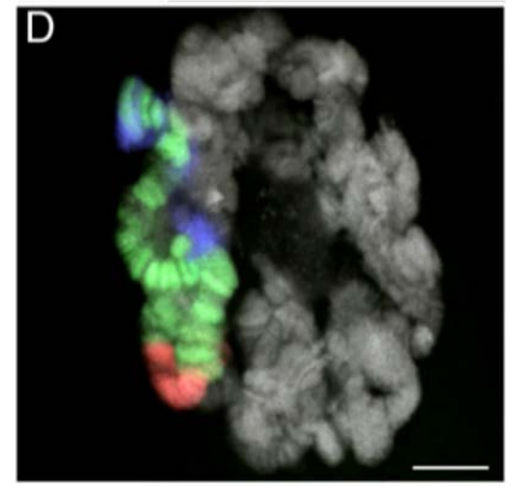
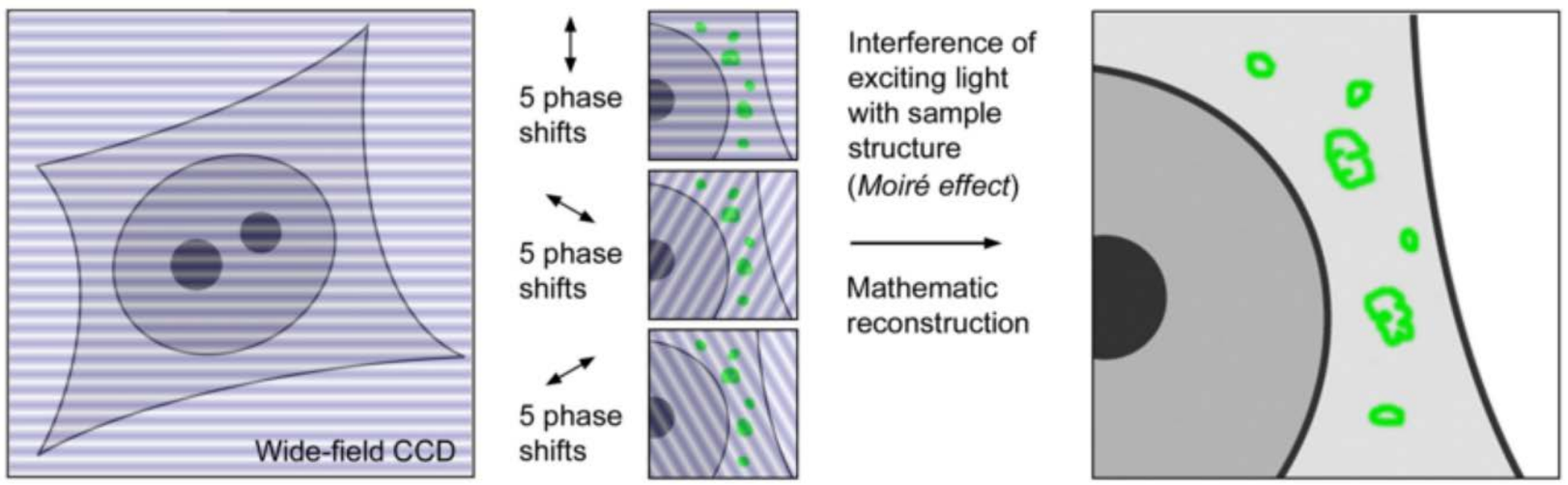
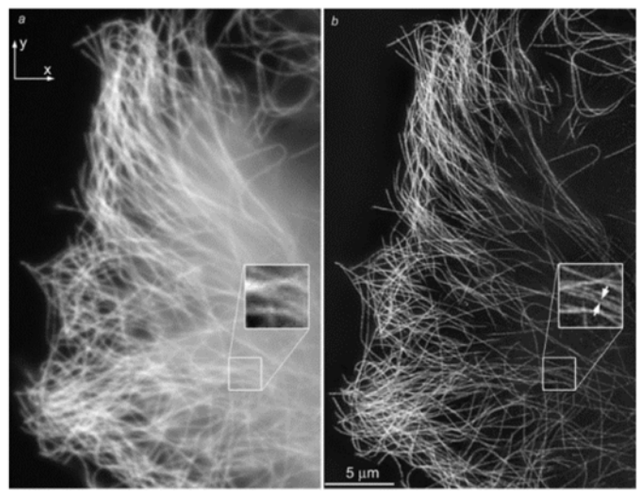


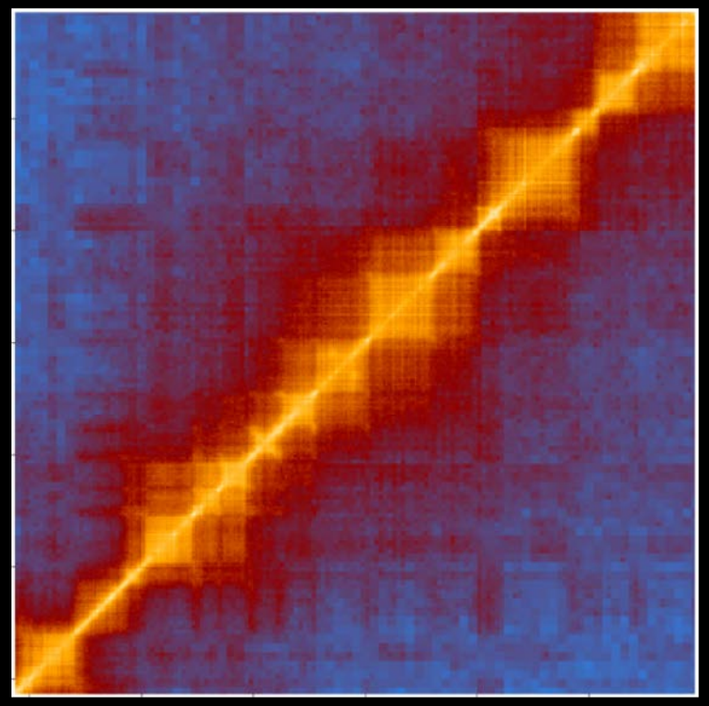


Schermelleh, Heintzmann and Leonhardt, 2010

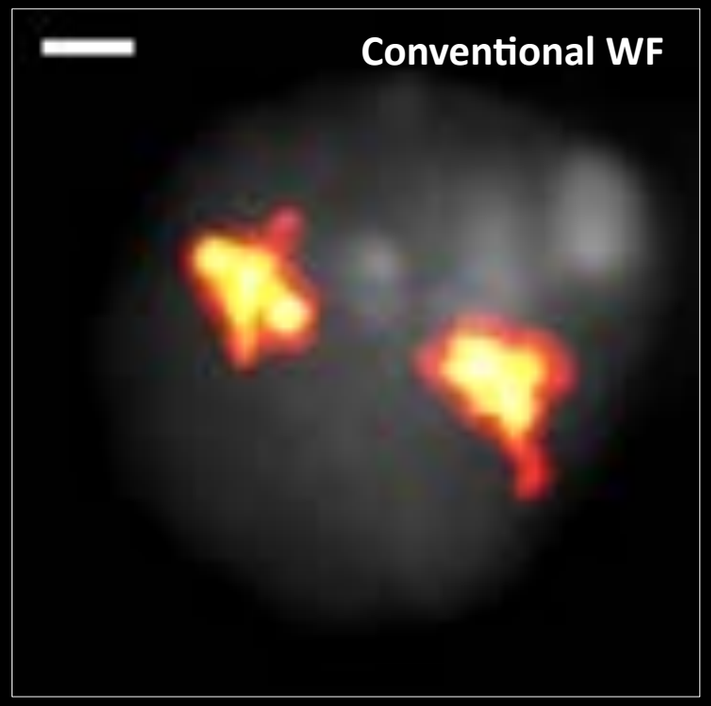


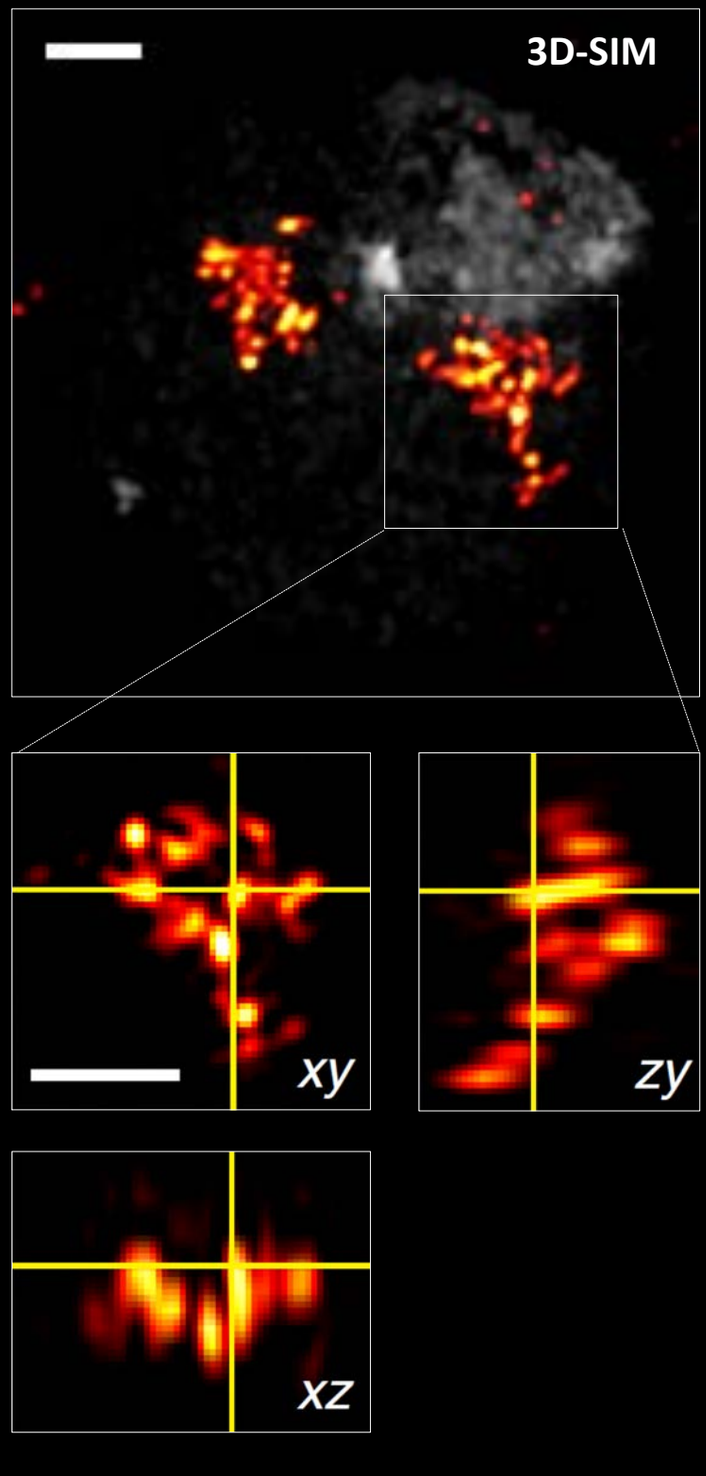
Gustafsson, *et al*, 2008

3D-SIM super-resolution imaging reveals chromatin nano-structures

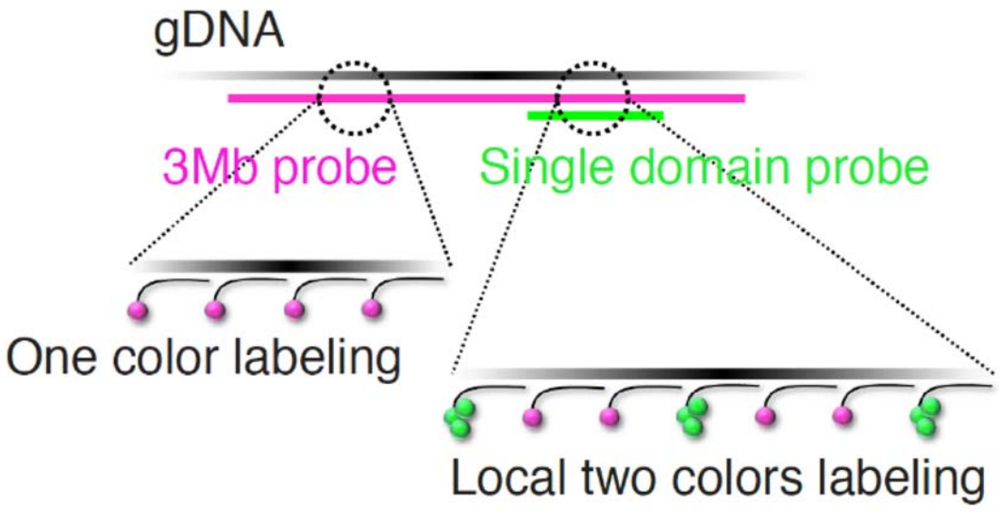


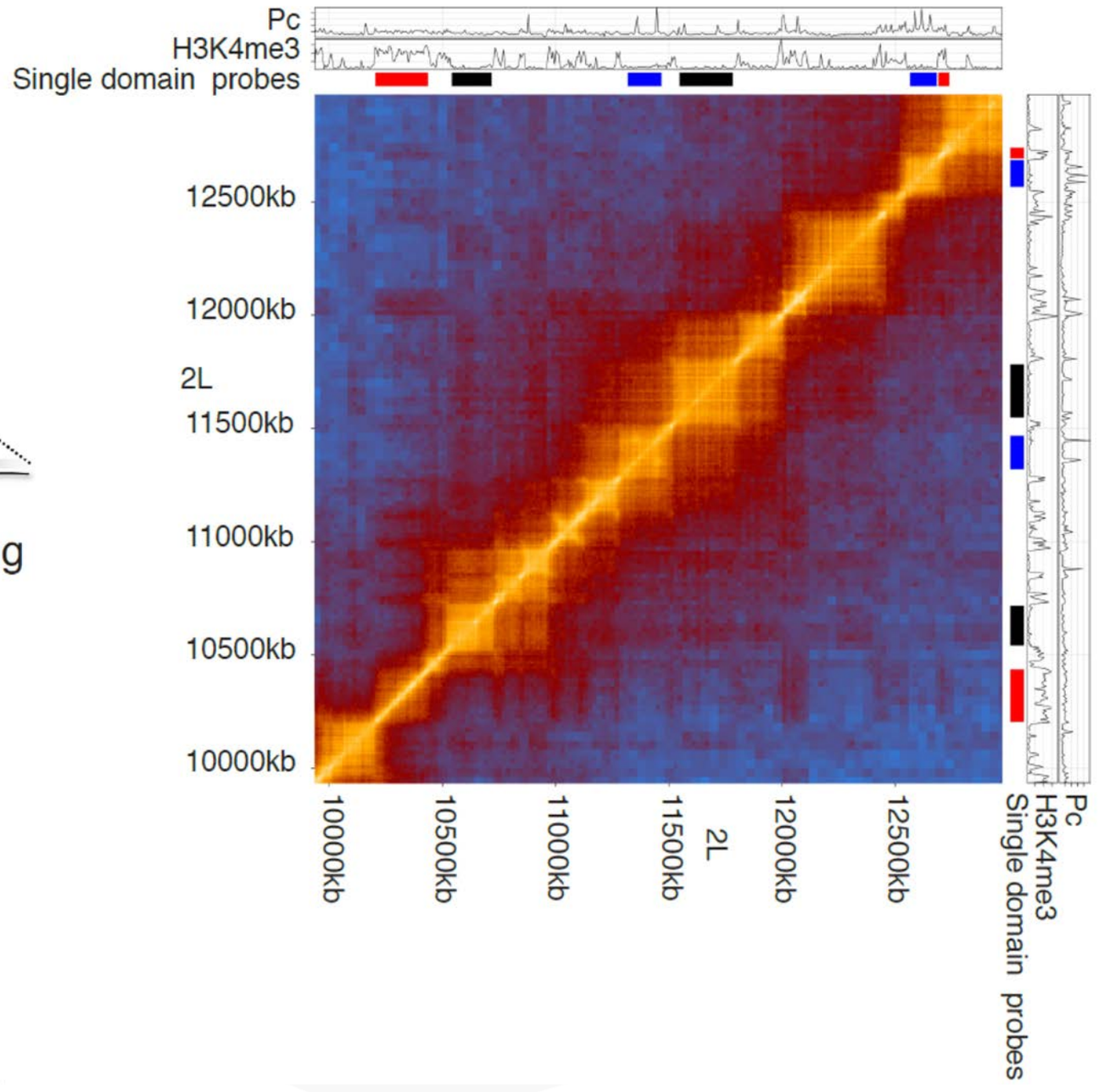
36 000 oligos homogeneously covering 3 Mb (12 oligos/kb)



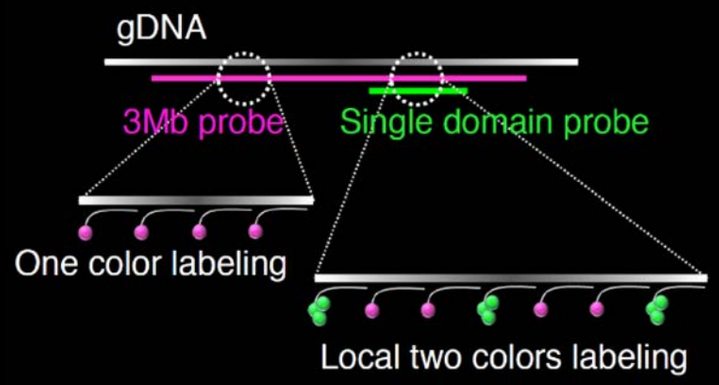


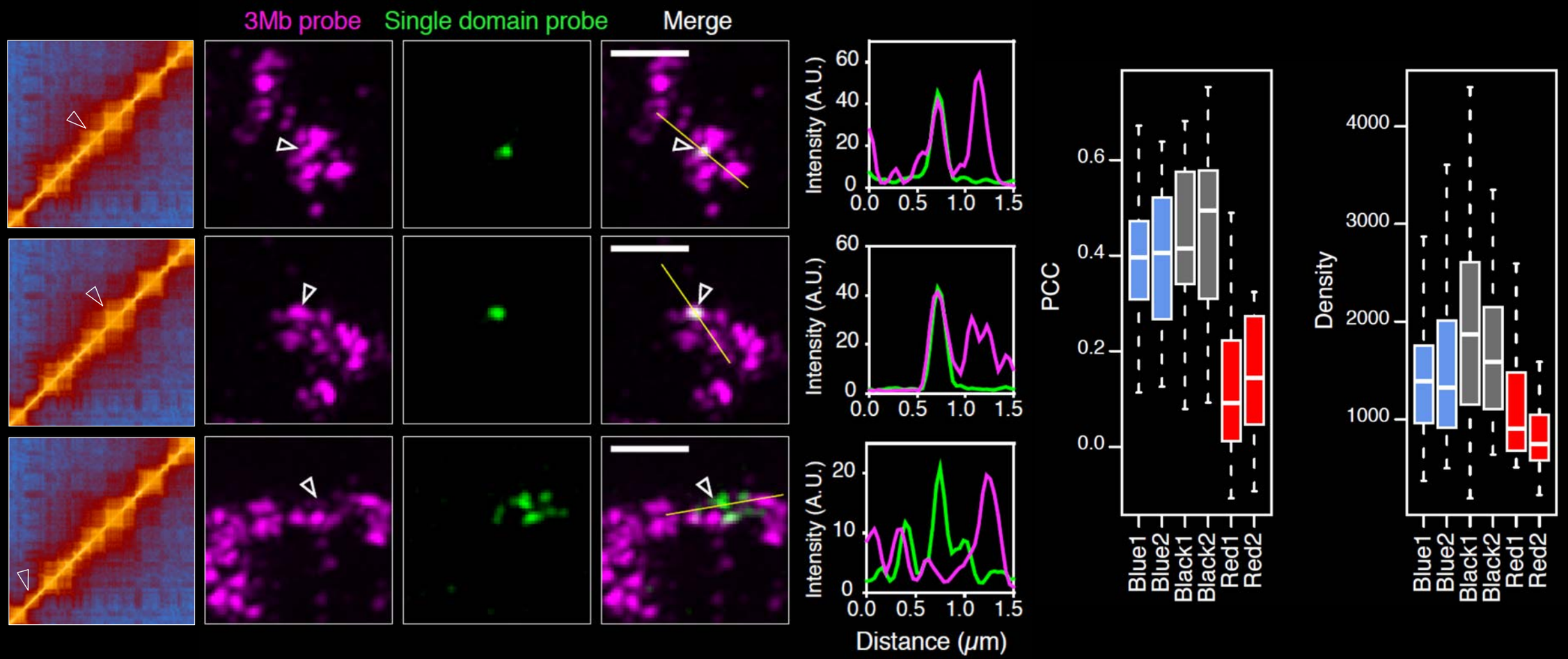
Dual FISH labeling of the chromatin





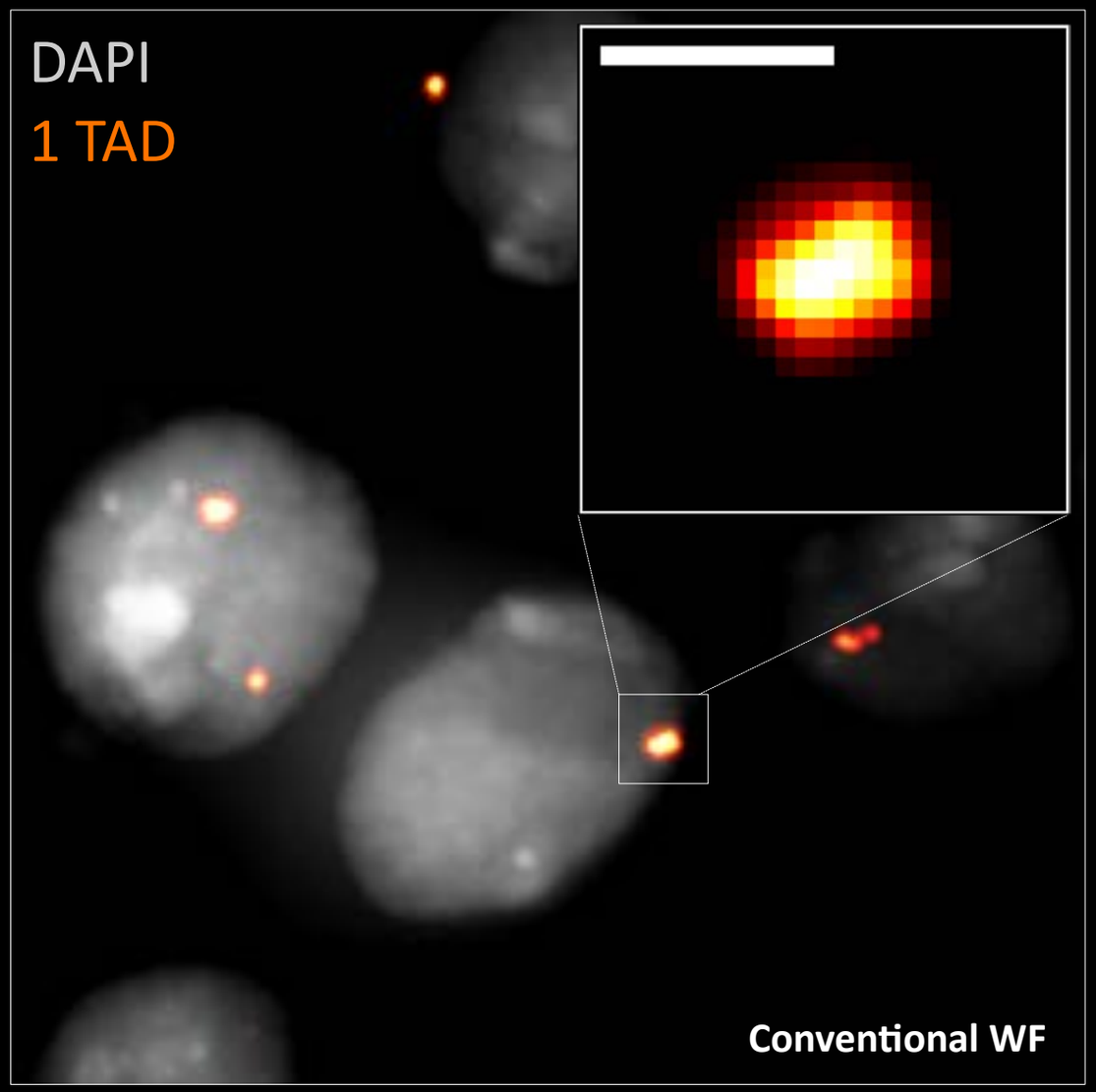
Changes in local chromatin compaction correspond to changes in chromatin state

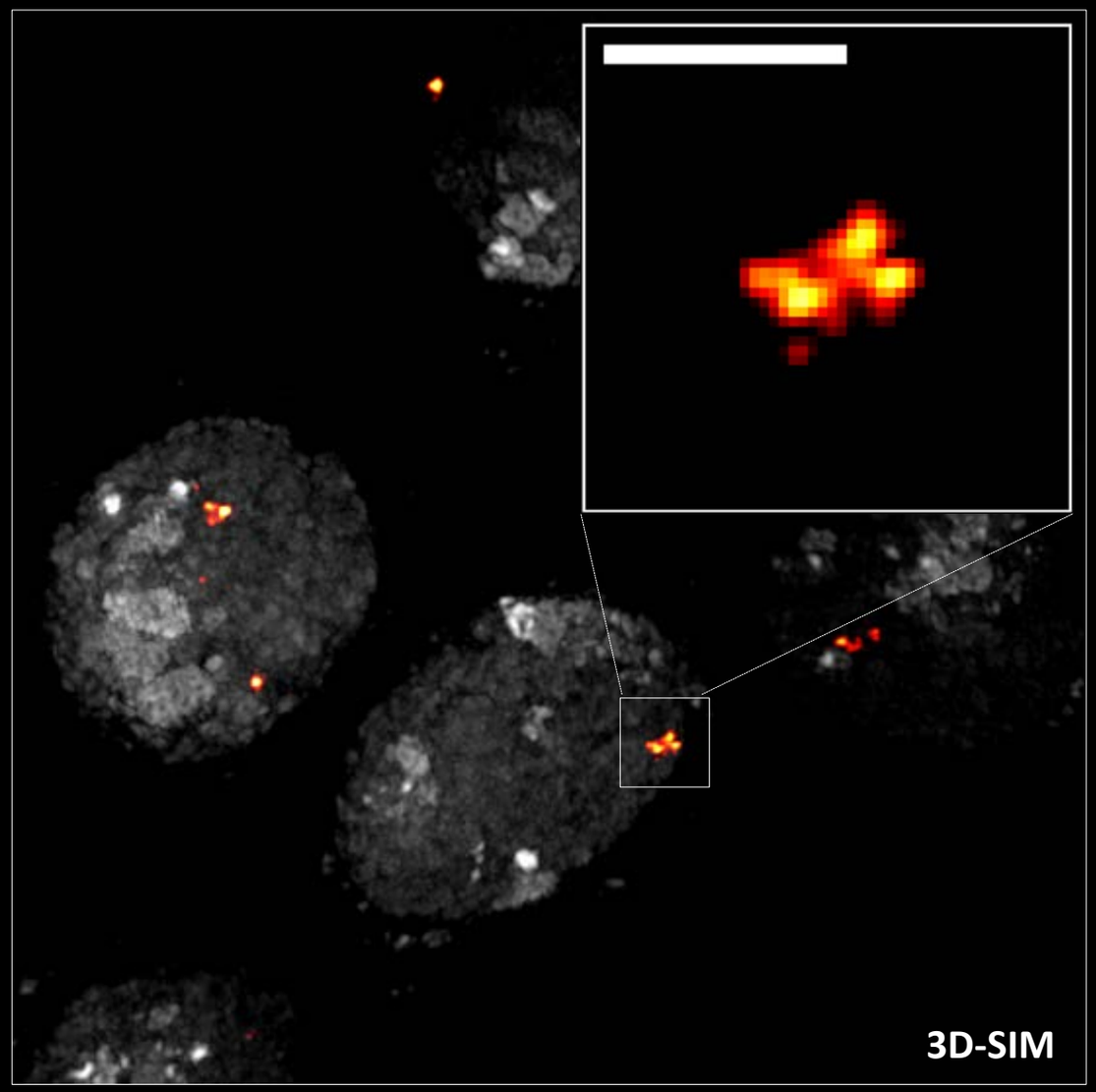




The nature of homologous pairing in *Drosophila*

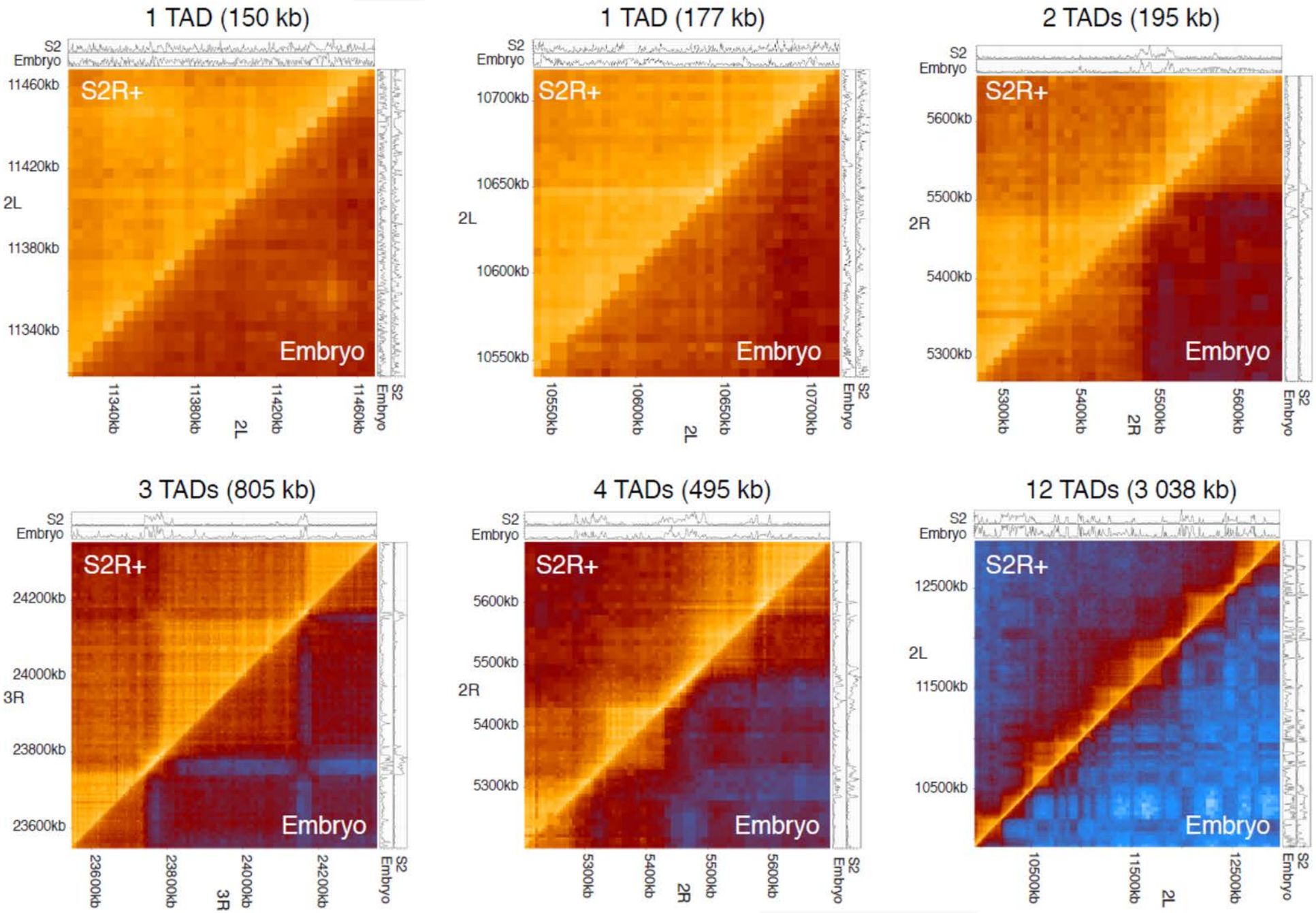
Tetraploid S2R+ cells



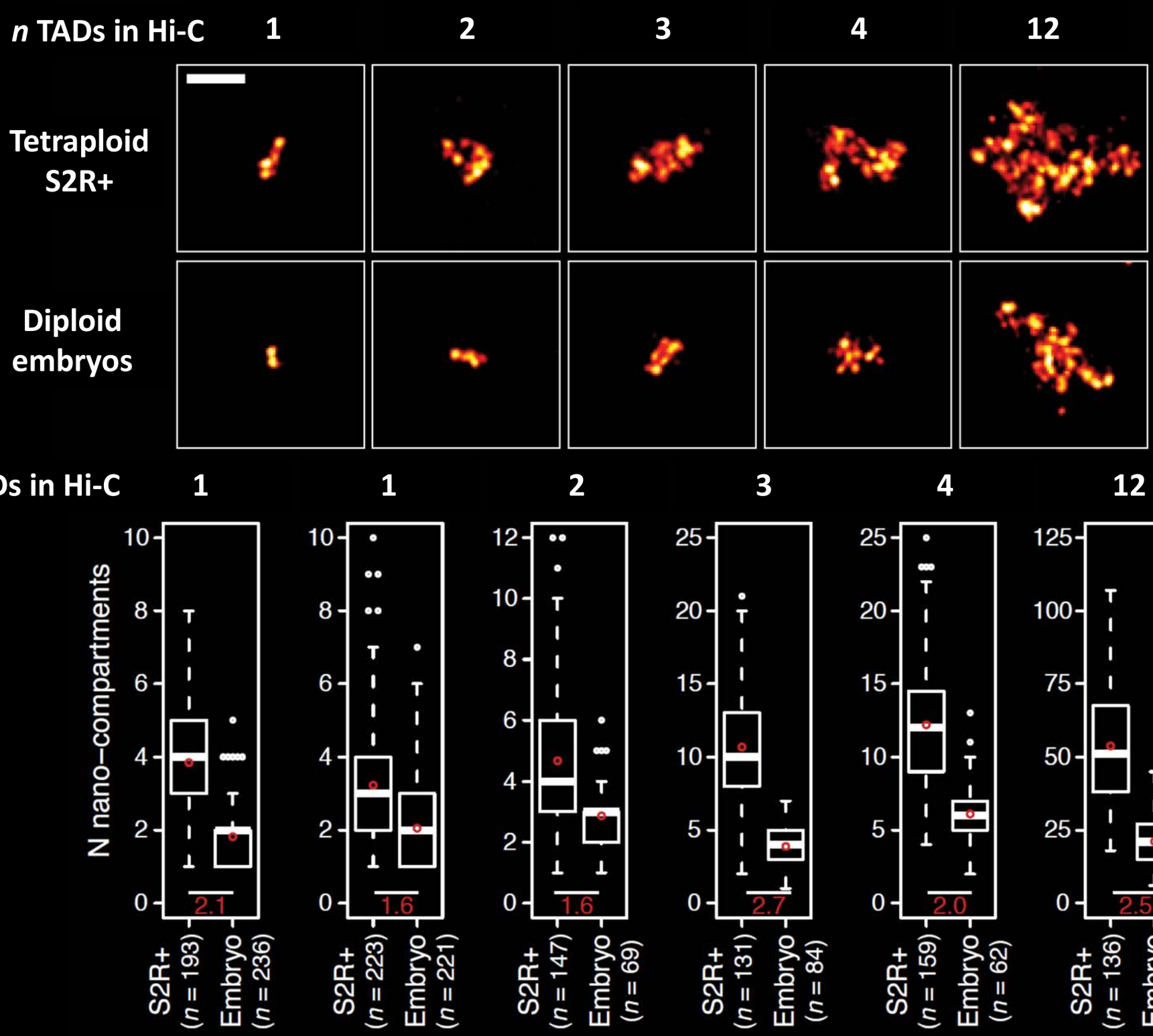


Counting nano-compartments in tetraploid vs diploid cells

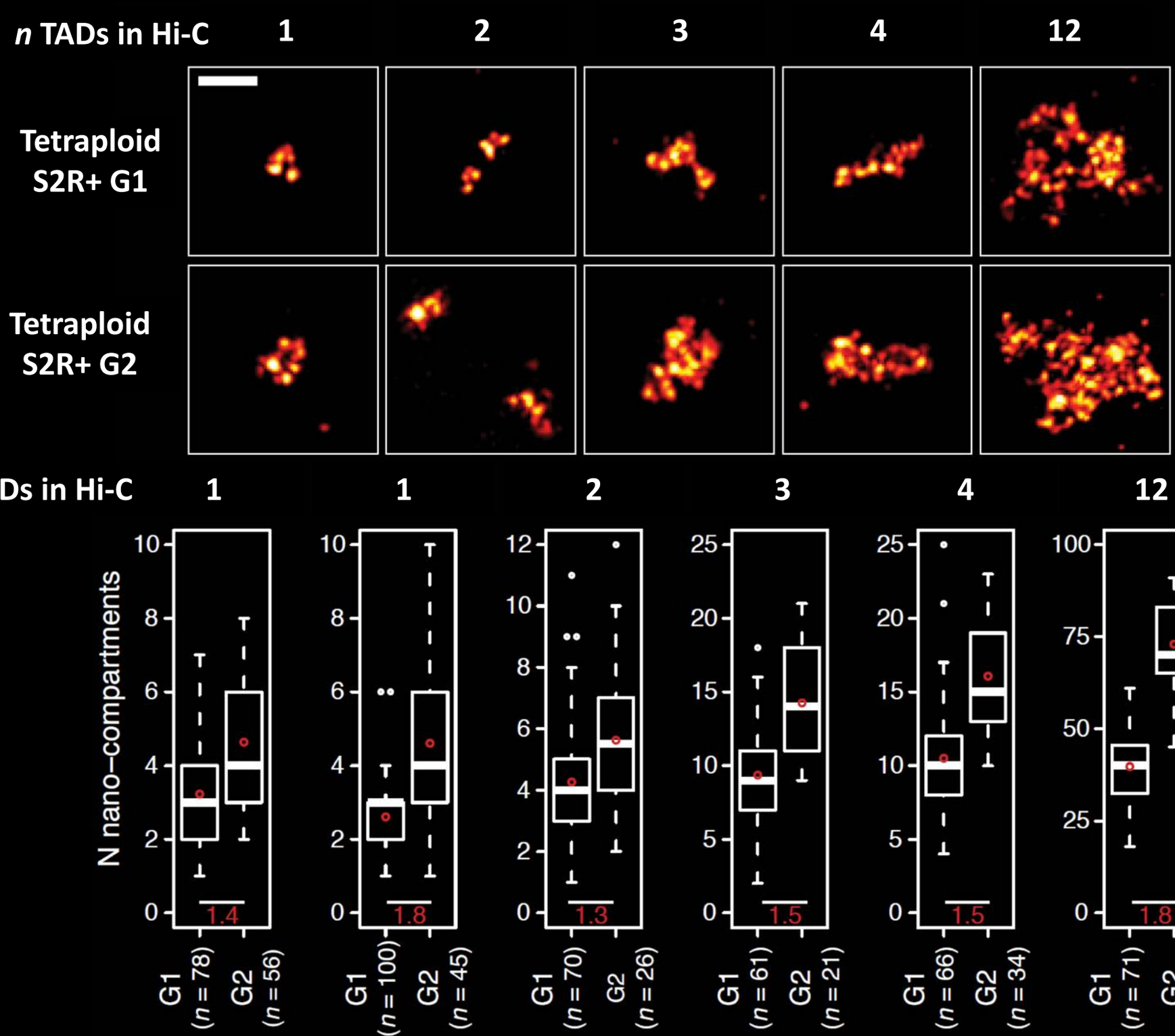
Oligopaint target regions



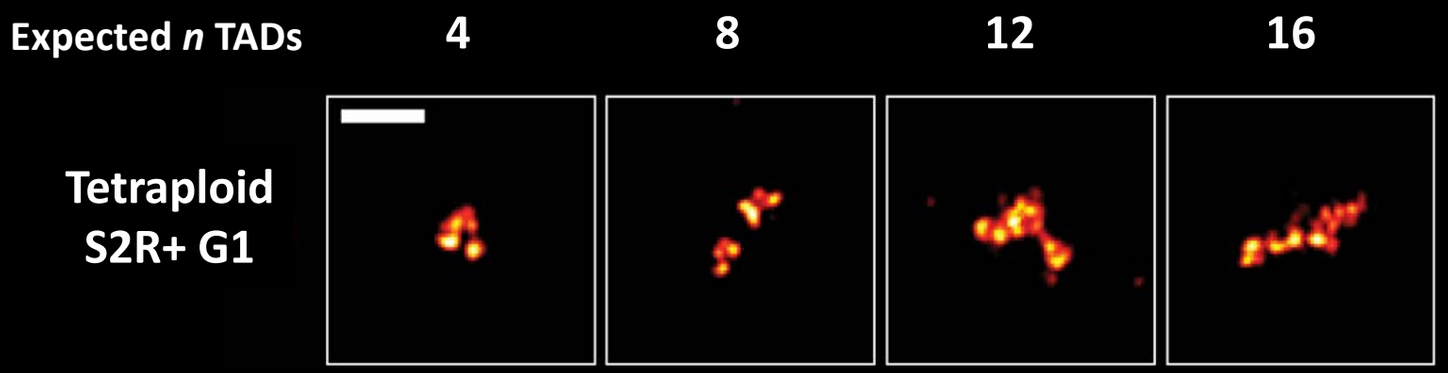
Resolution of non intermingled homologous TADs

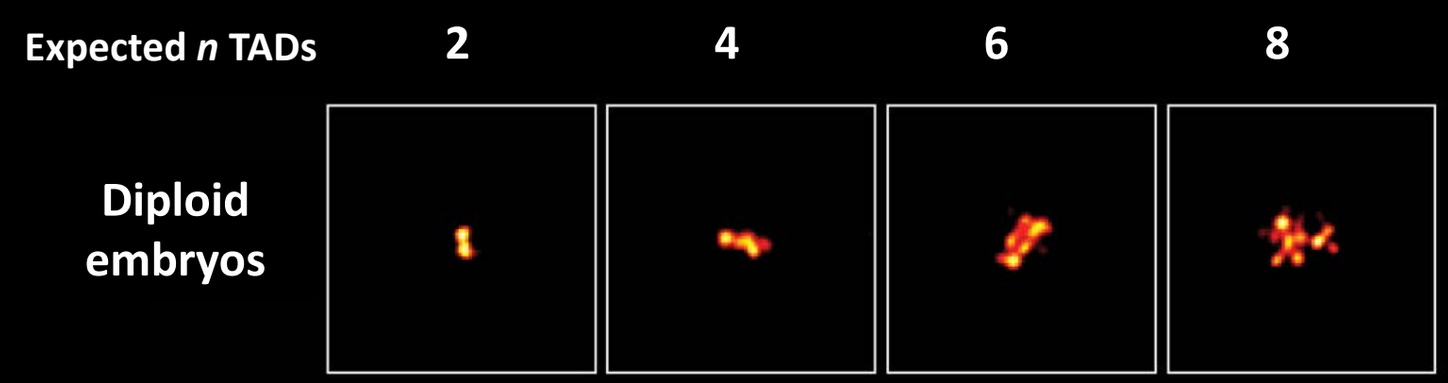


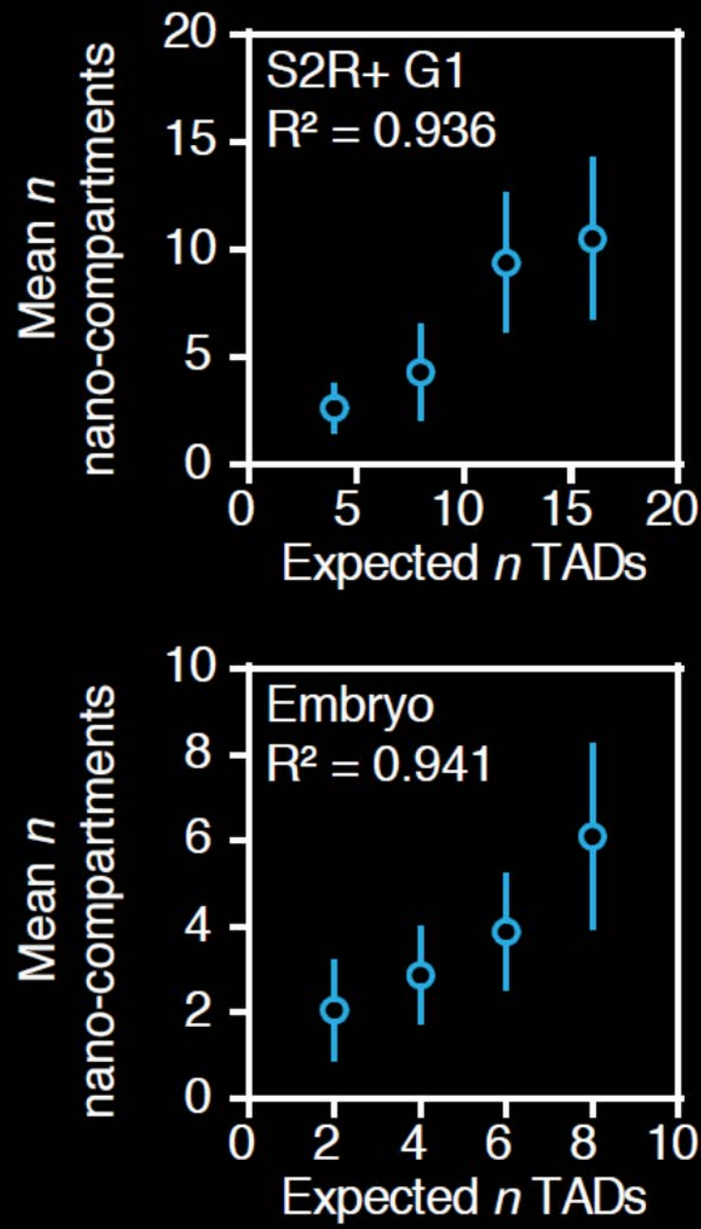
Resolution of non intermingled sister chromatids



Correlation between the number of nano-compartments and the expected number of TADs

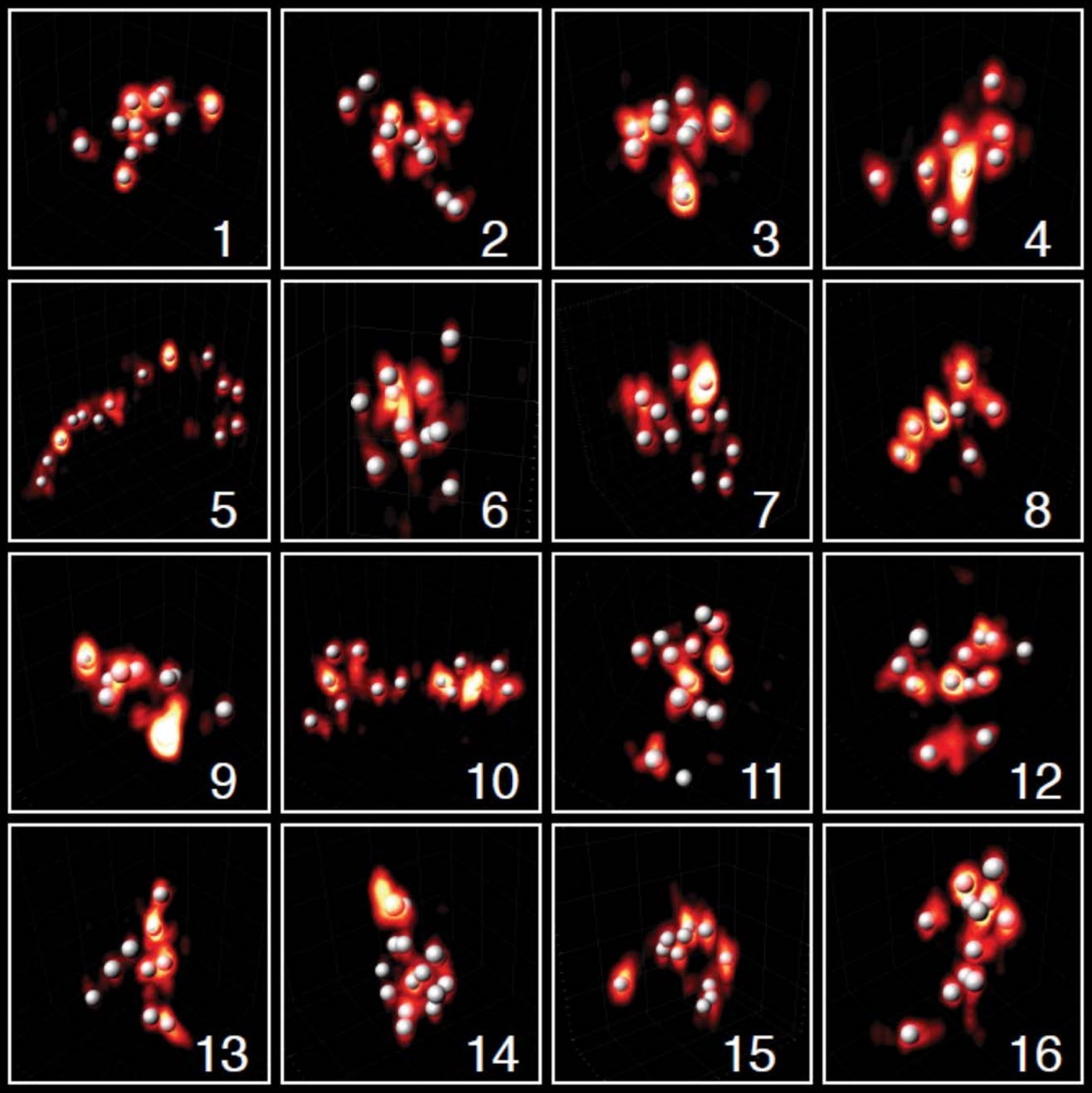


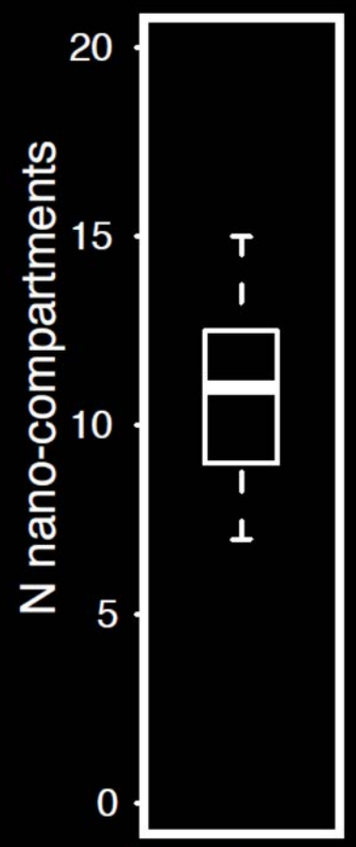


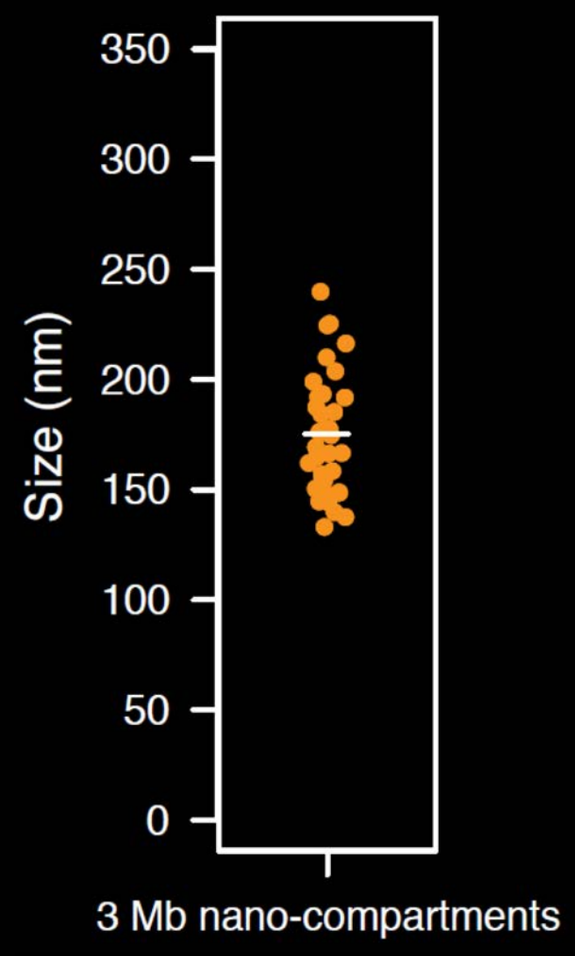


Dynamic 3D organization of TADs within single chromosome copies

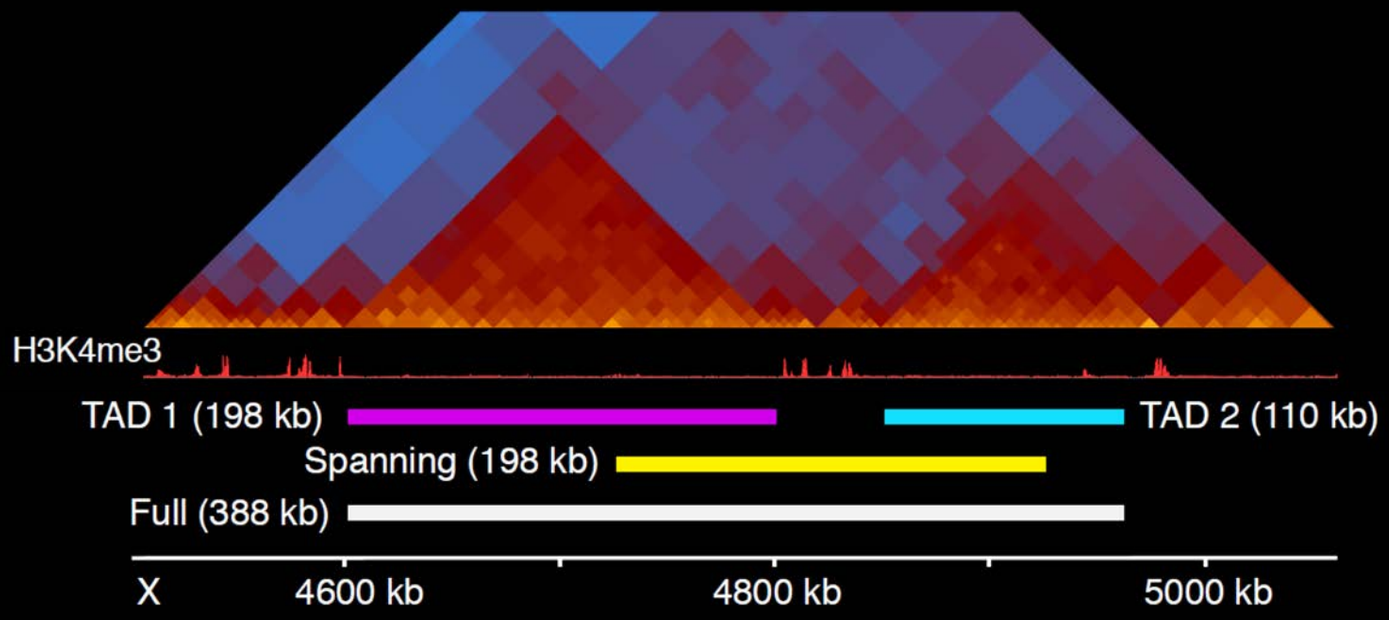
Single unpaired unique chromosome copies (3Mb labeling)

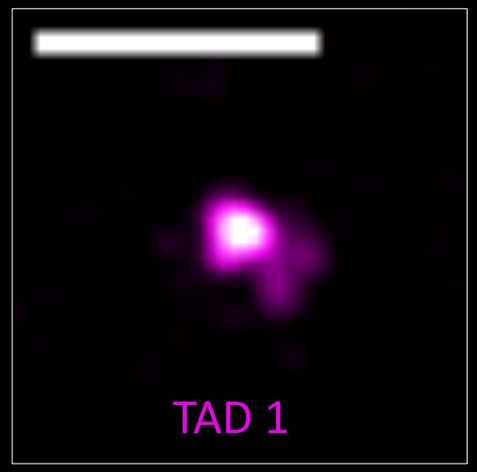


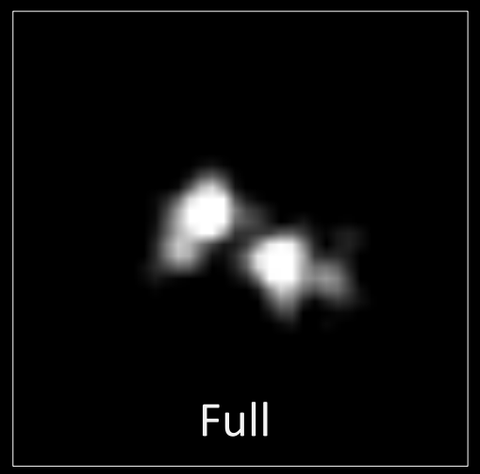


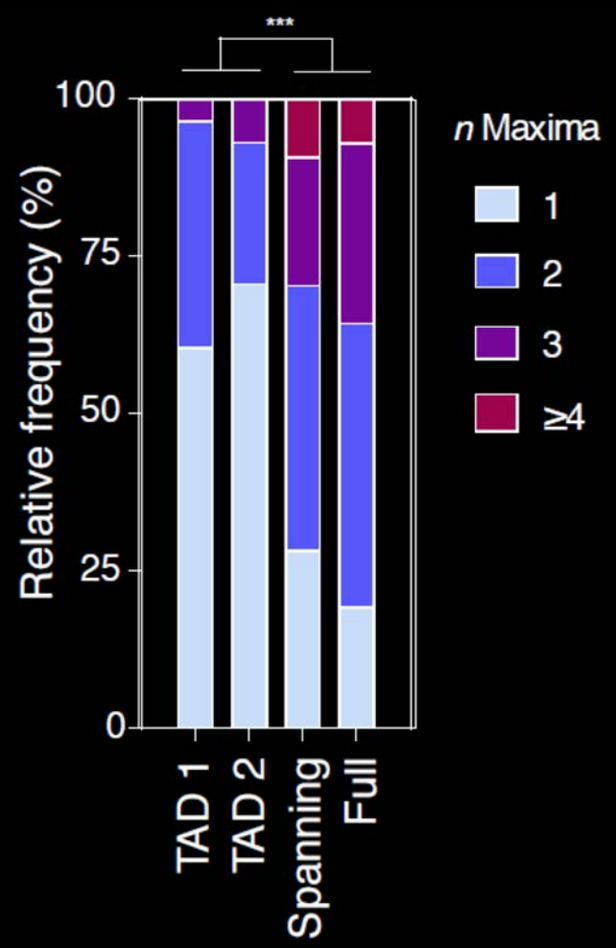


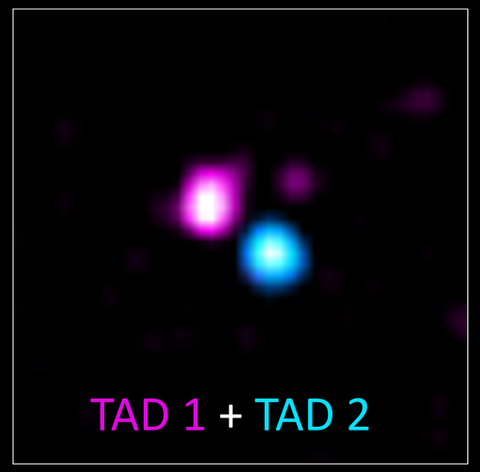
Single-cell analysis of haploid chromosome reveals that repressed TADs form 3D discrete chromosomal units







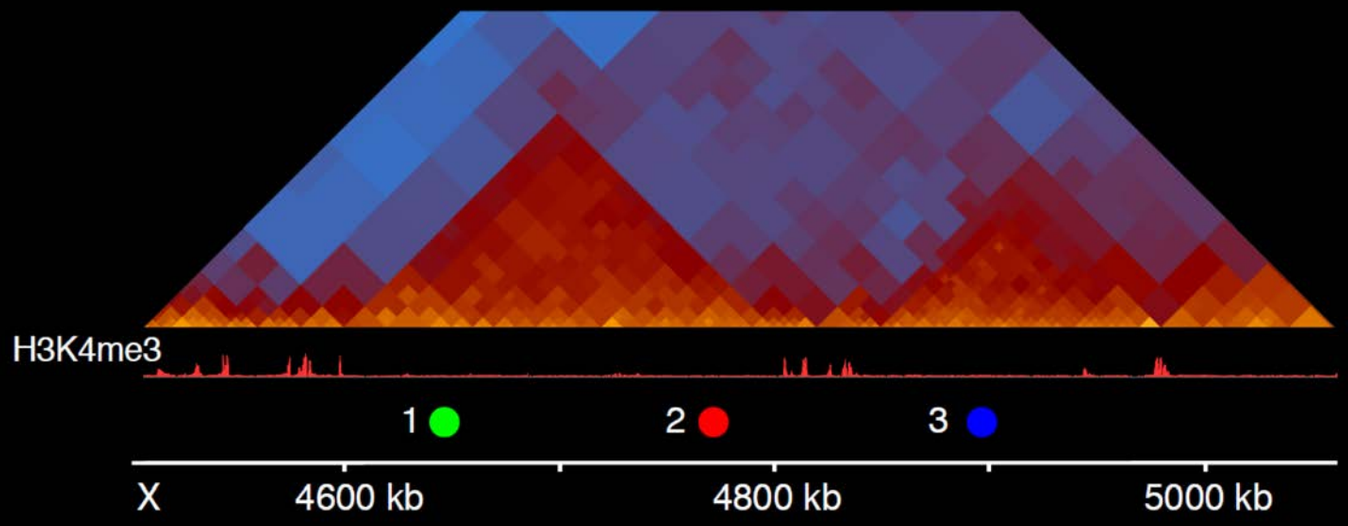


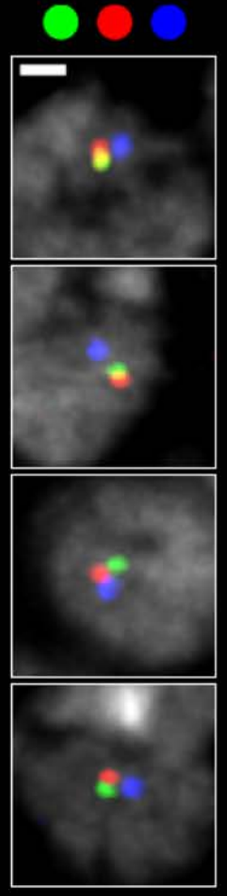


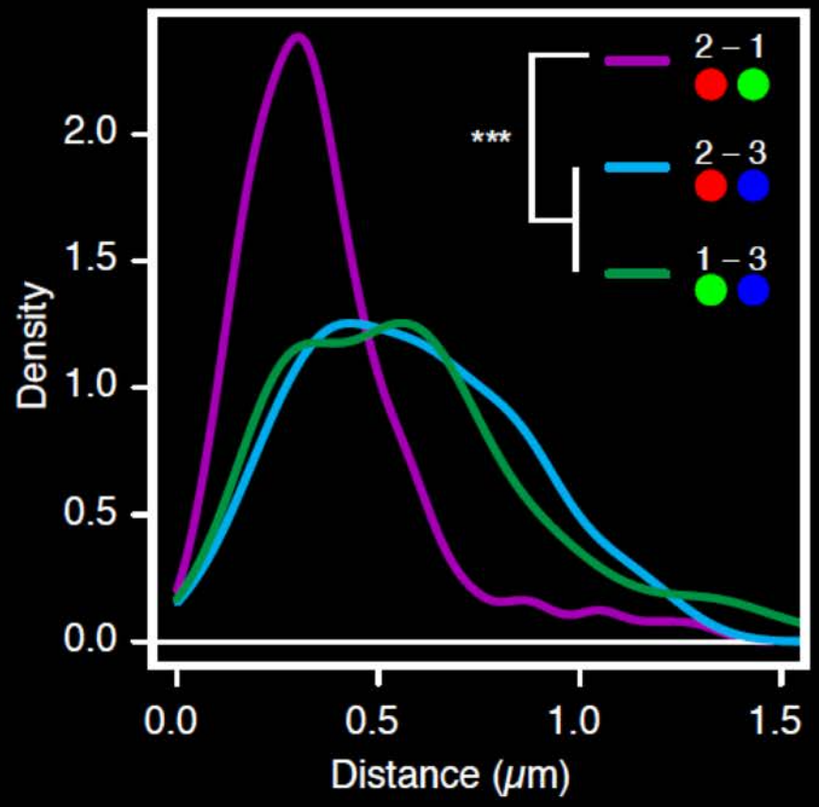
No contacts in 68% of the cells

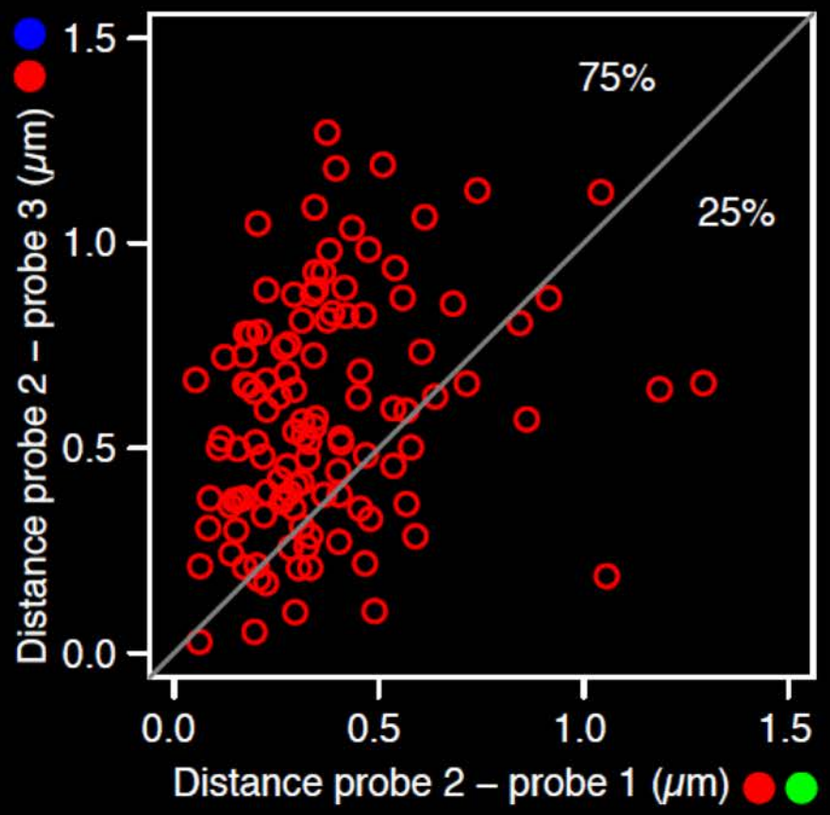
Less than 10% of volume overlap in 84% of the cells

Single-cell analysis of haploid chromosome reveals consistent TAD-based compartmentalization



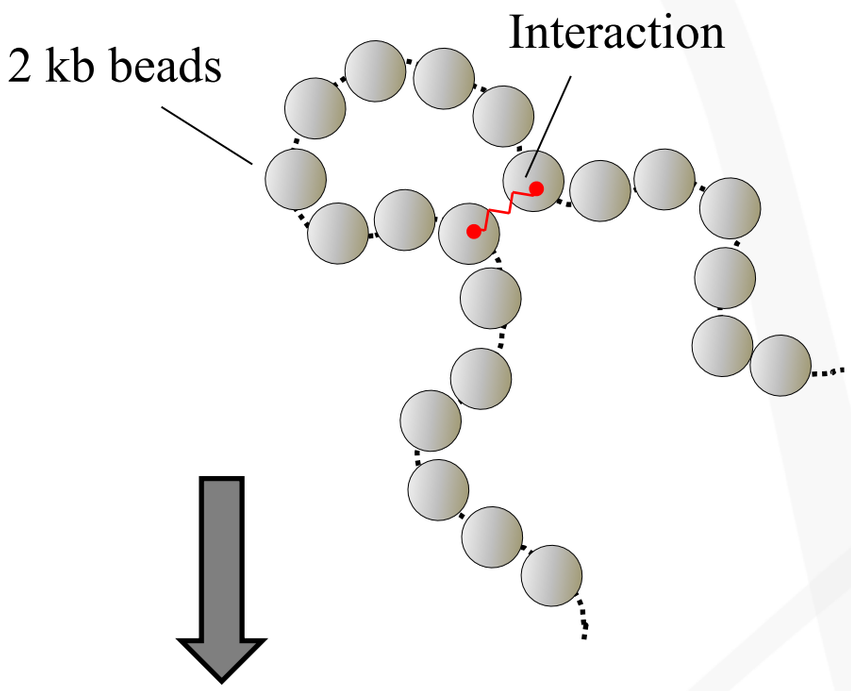






Polymer modeling of the chromatin fiber

Polymer model of the region of interest



Optimize
interaction potentials

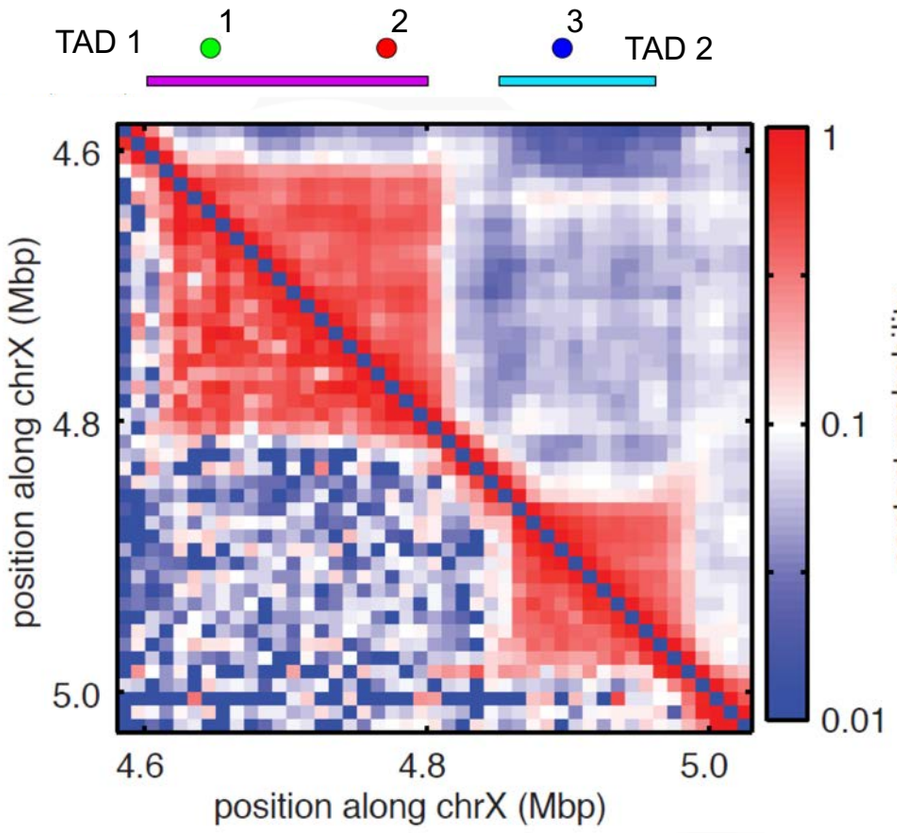
Simulate ensemble of
different configurations

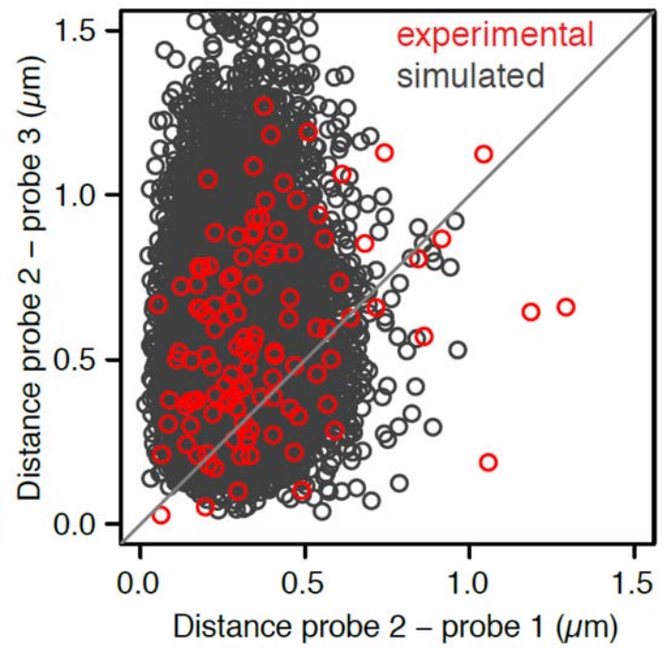
Simulated
contact map

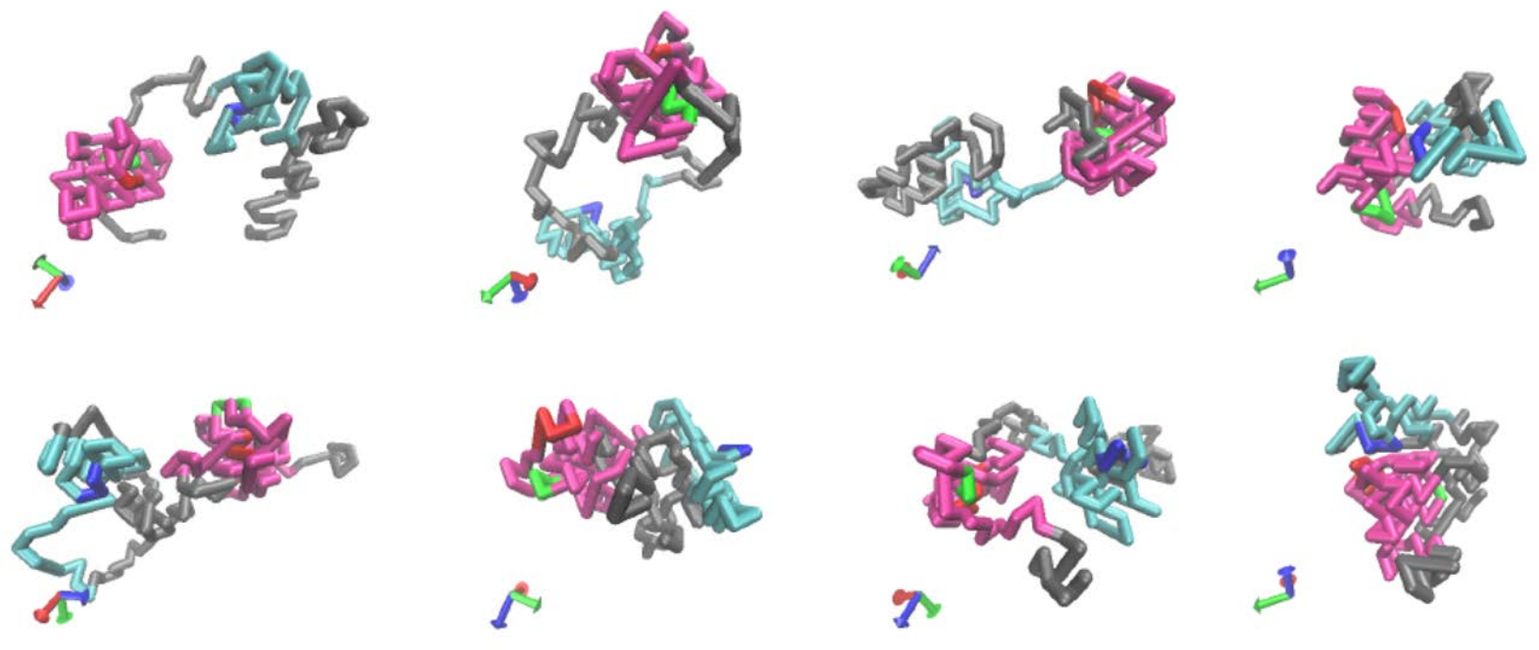
Compare with
experimental
Hi-C map

Adapted from Giorgetti, *et al*, 2015

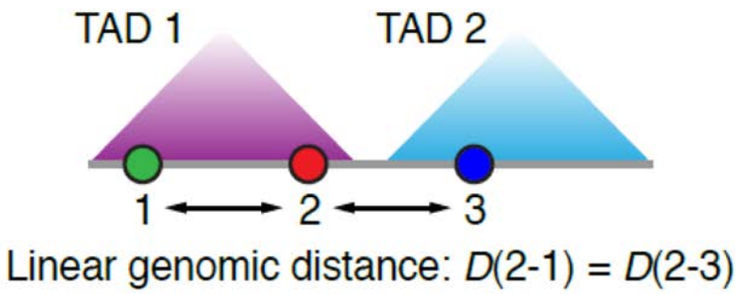
Polymer modeling recapitulates the TAD-based chromatin compartmentaliztion







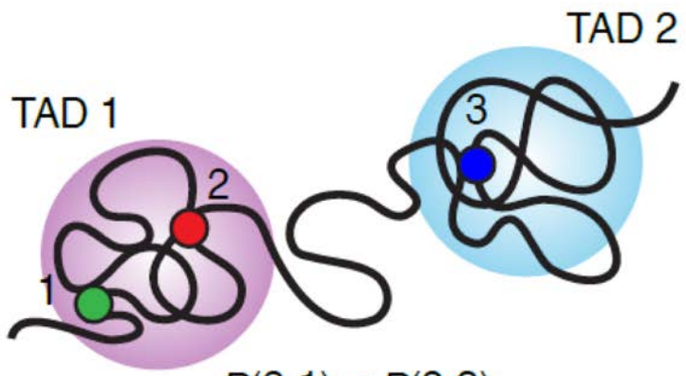
The relative TAD positioning can explain shorter *inter* versus *intra*-TAD distances



Linear genomic distance: *D*(2-1) = *D*(2-3)

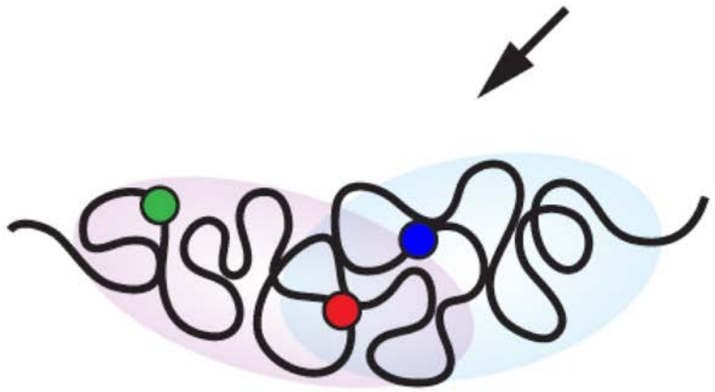
3D distance scenarios:

75 % of the cells

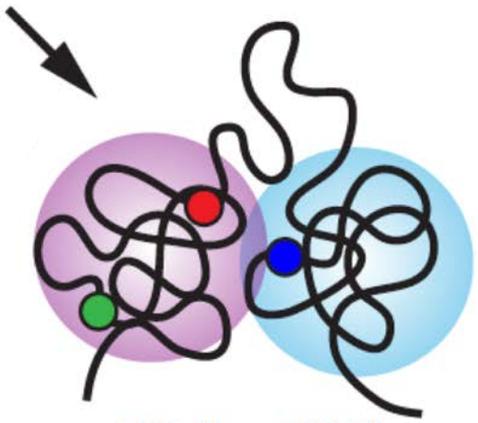


D(2-1) < *D*(2-3)

25 %



D(2-1) > *D*(2-3)



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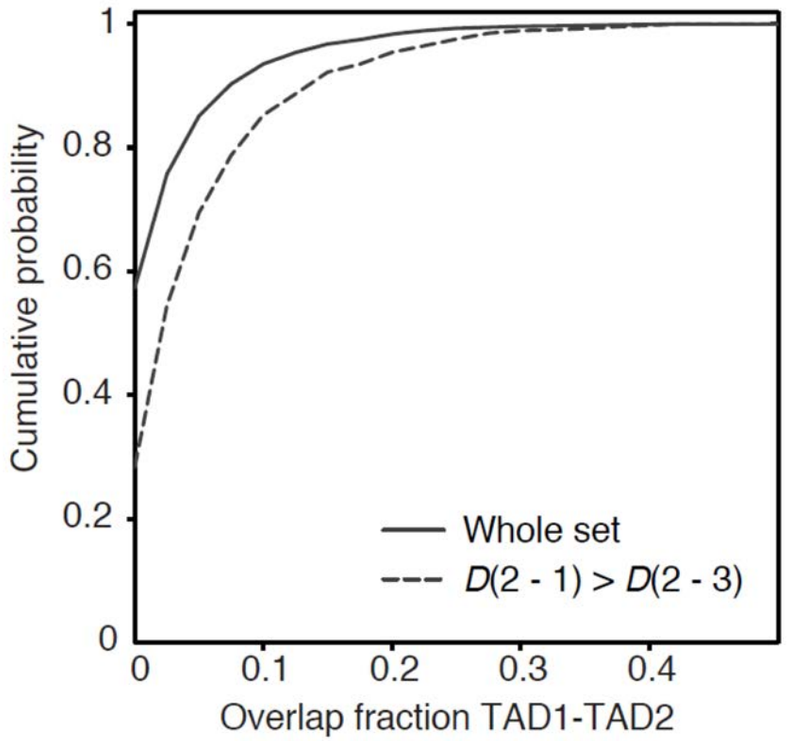


Conclusions

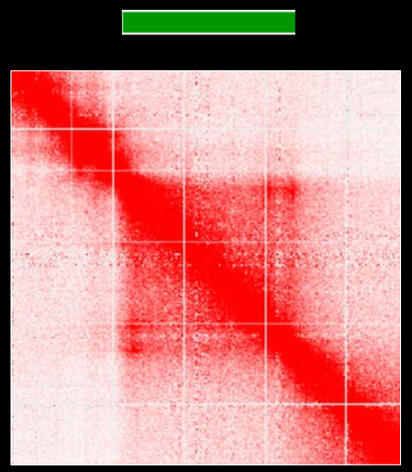
Chromatin is organized in a series of discrete nano-compartments

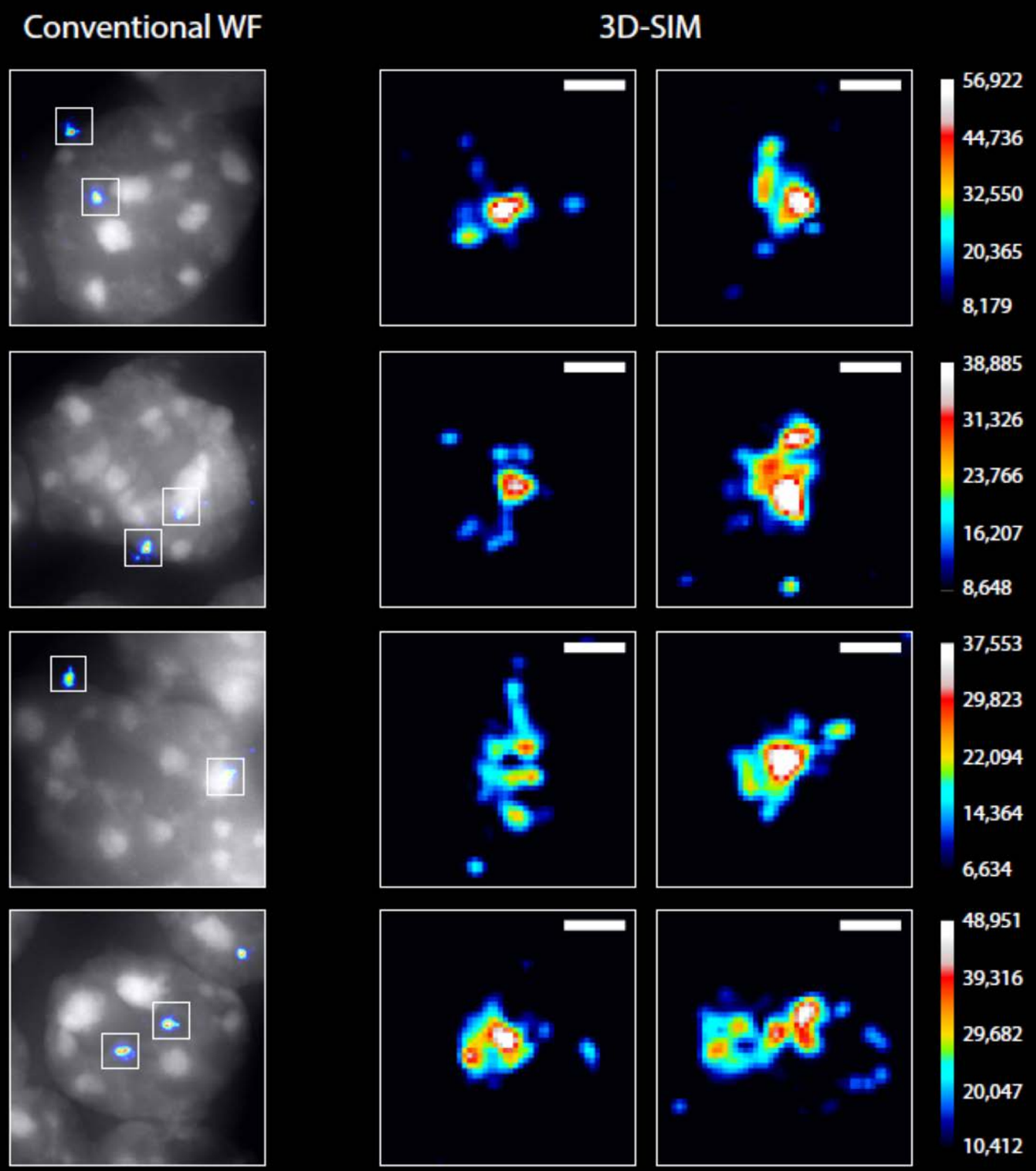
Nano-compartments correspond to repressed TADs, which are interspersed with decondensed active chromatin

Repressed TADs form structural and physical chromosomal units in individual cells, with dynamic *cis* and *trans* contact events

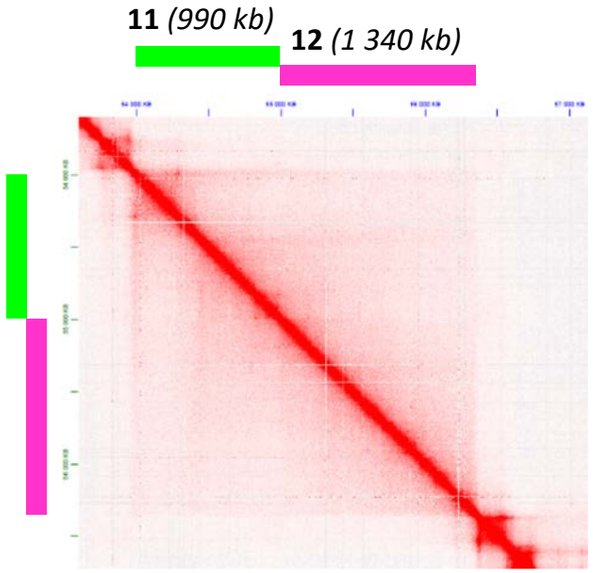
Szabo *et al*. Science Advances, 2018

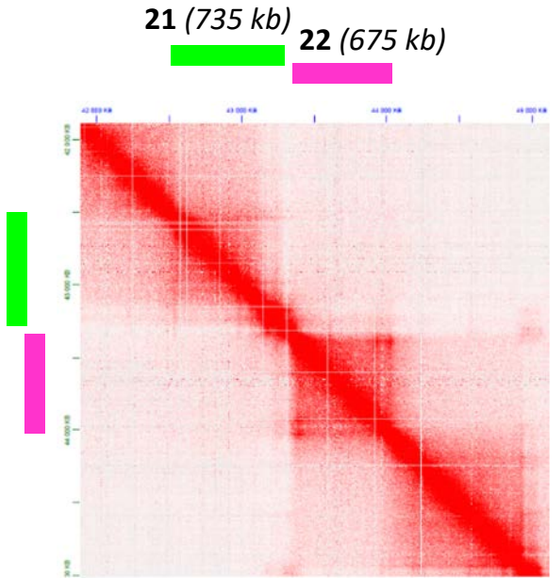
Outlook: understanding TAD dynamics in mammals

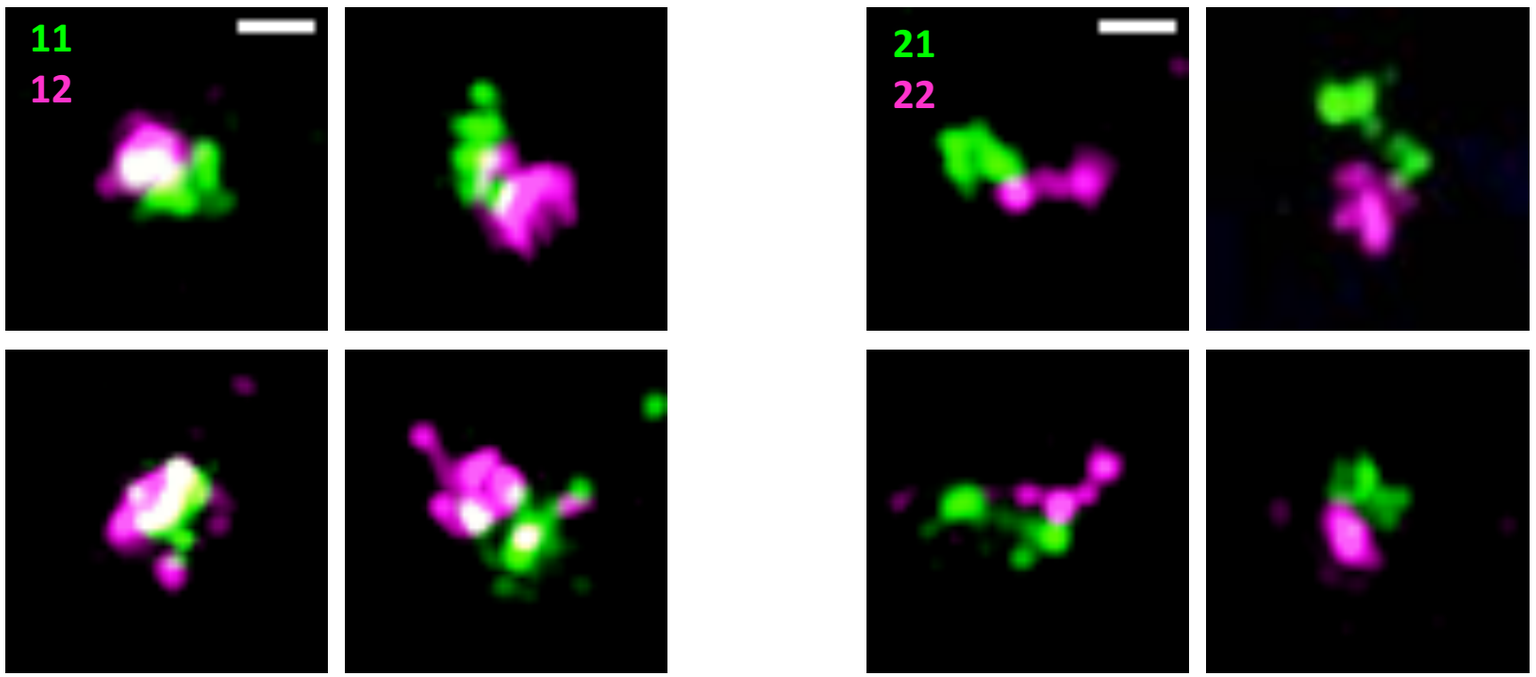


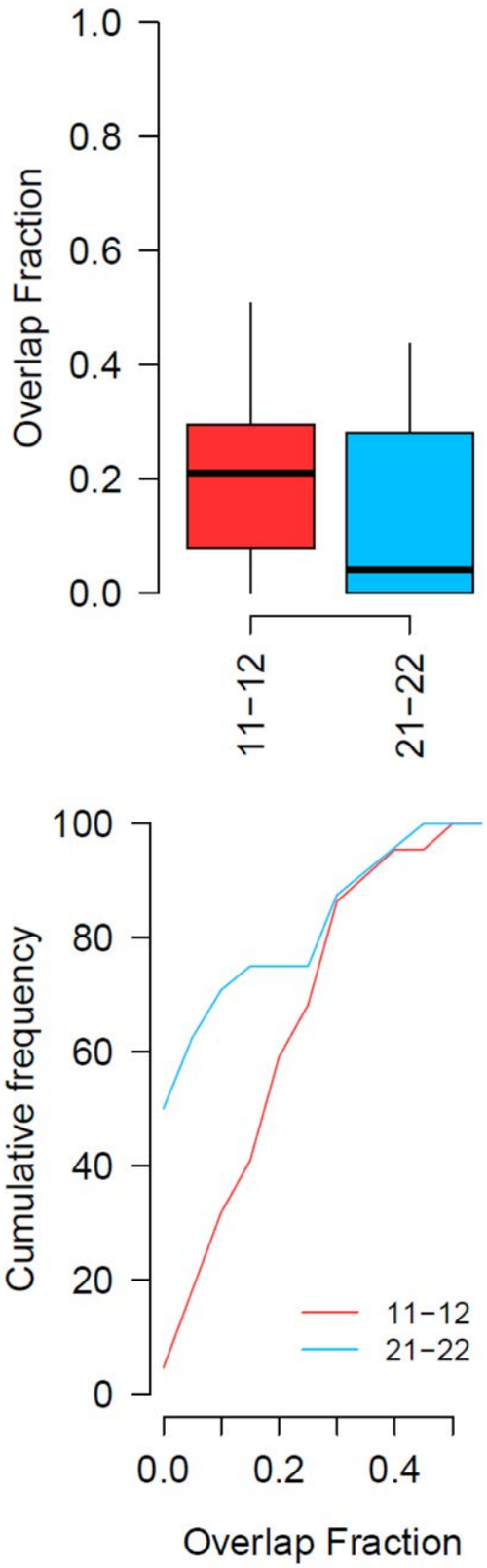


Outlook: understanding TAD dynamics in mammals









Scale bars: 500 nm

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