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Universitair Medisch Centrum Rotterdam

Cohesin-dependent chromatin structures at a close view

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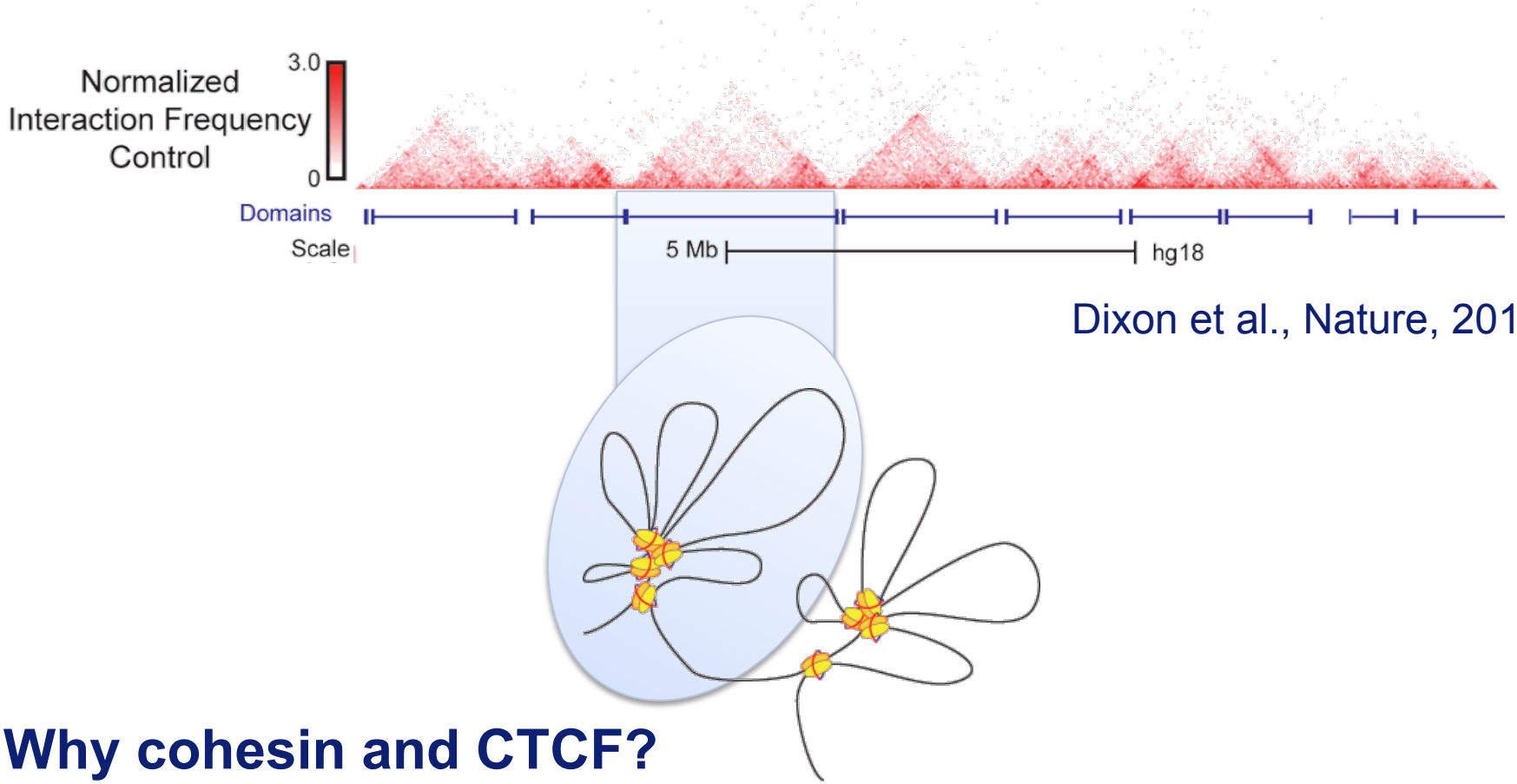
CSHL meeting August 2014

Which proteins shape chromatin architecture?

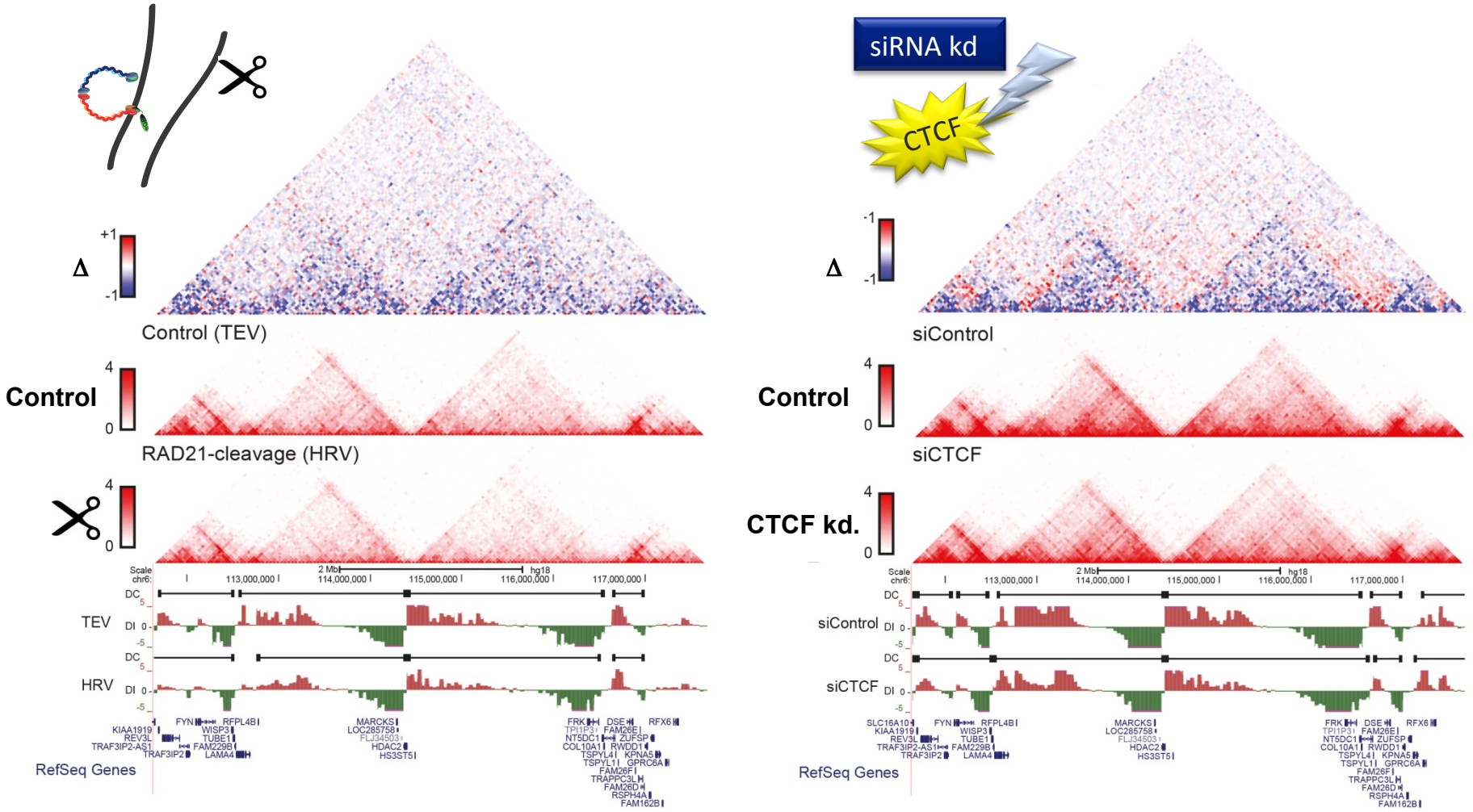


Dixon et al., Nature, 2012

Why cohesin and CTCF?

- Cohesin and CTCF colocalize and interact functionally
- Very abundant in mammalian genomes
- Both implicated in long-range interactions
- Cohesin/CTCF sites enrich at boundaries between topological domains

Hi-C after cohesin or CTCF depletion



Zuin, Dixon et al., PNAS, 2014

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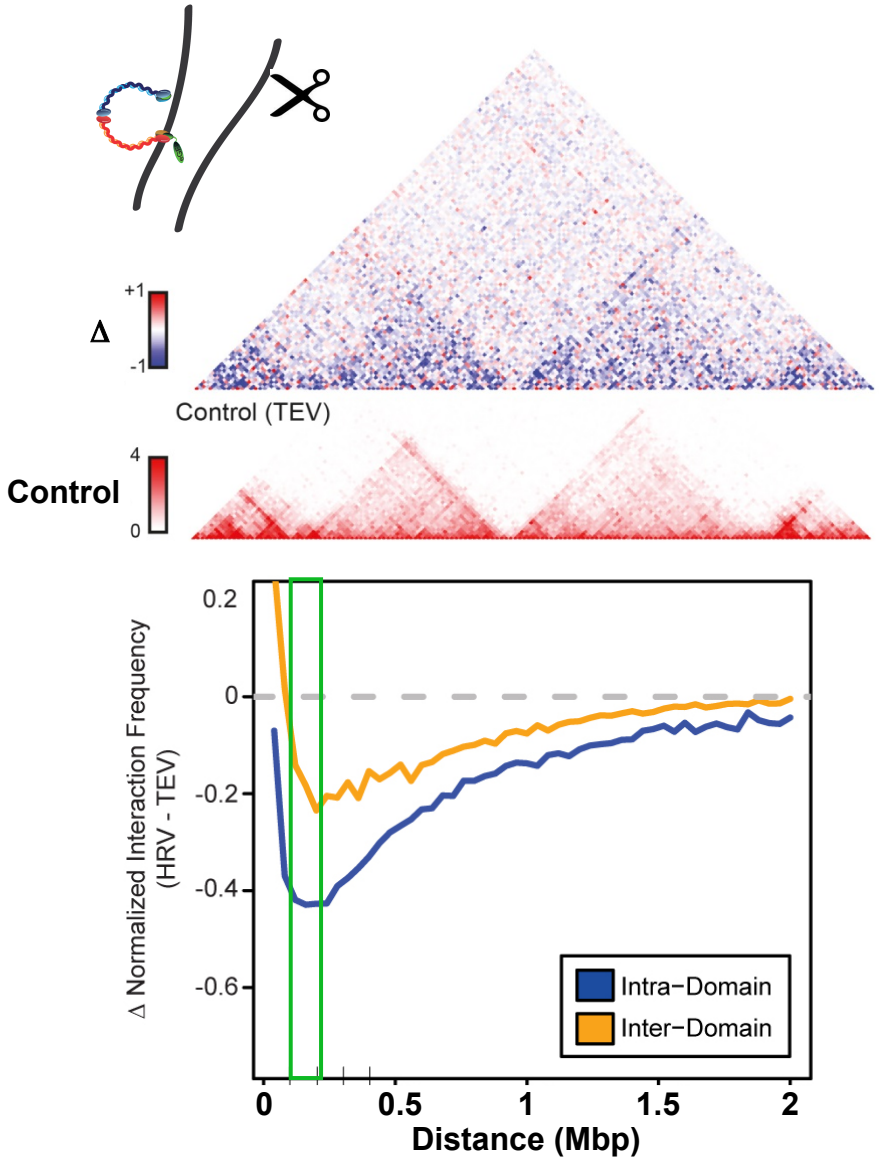
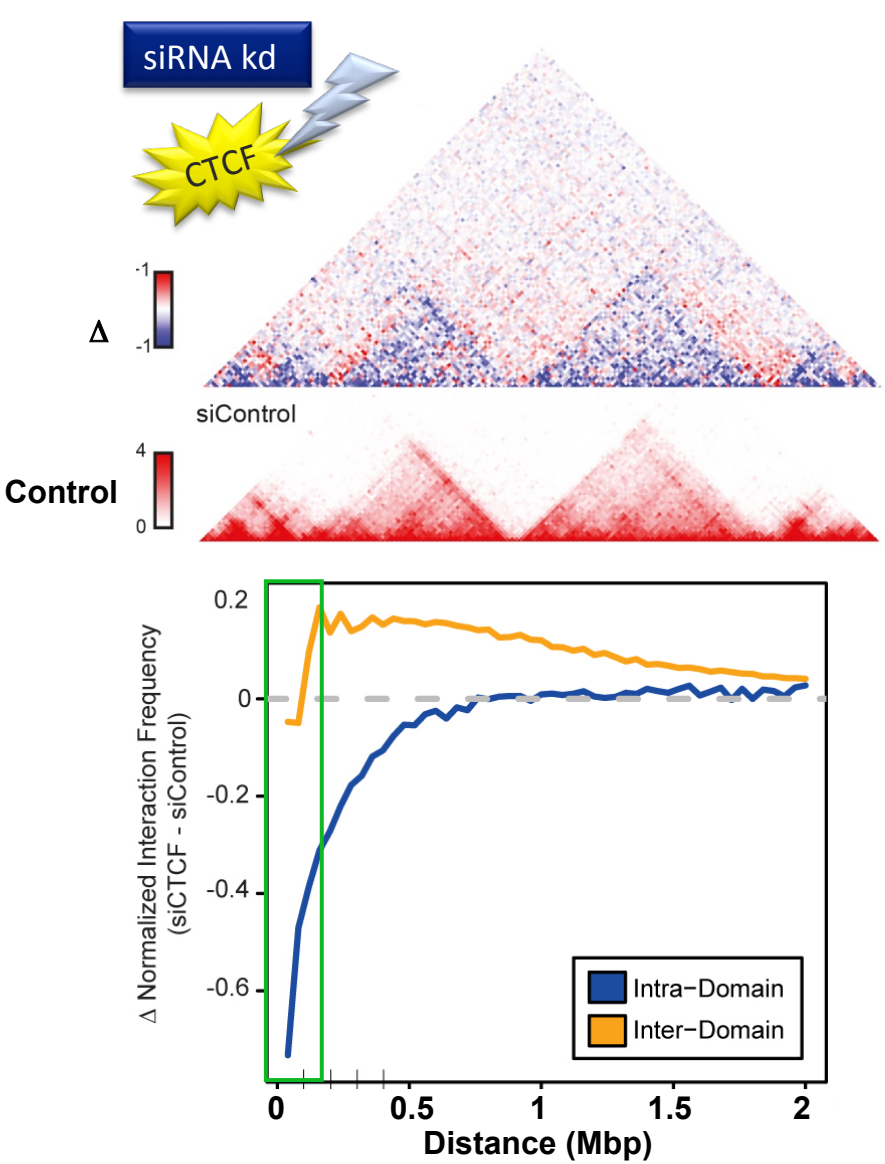
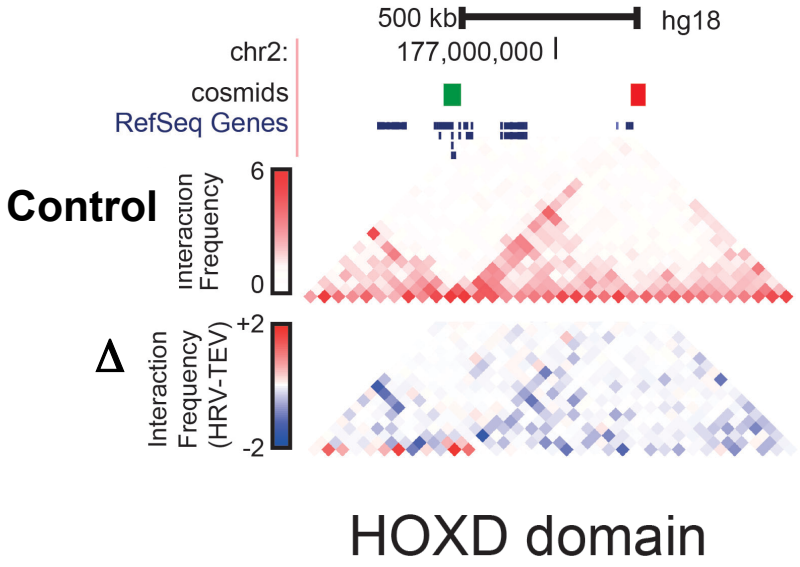
Hi-C after cohesin or CTCF depletion



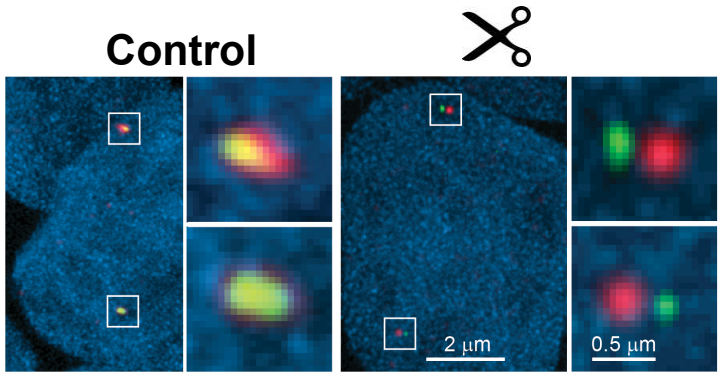


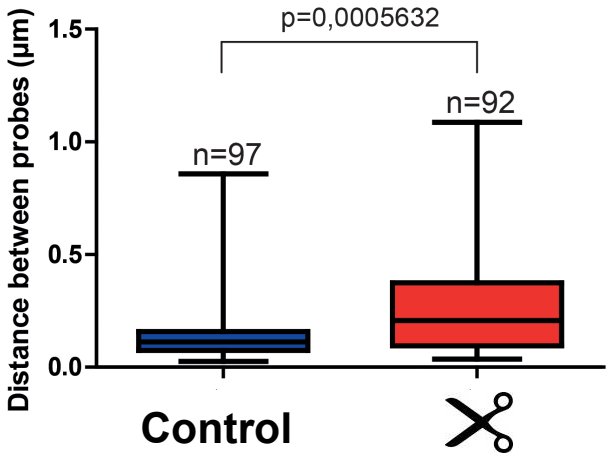
Cohesin cleavage increases distances at the HOXD domain

DNA FISH



HOXD domain





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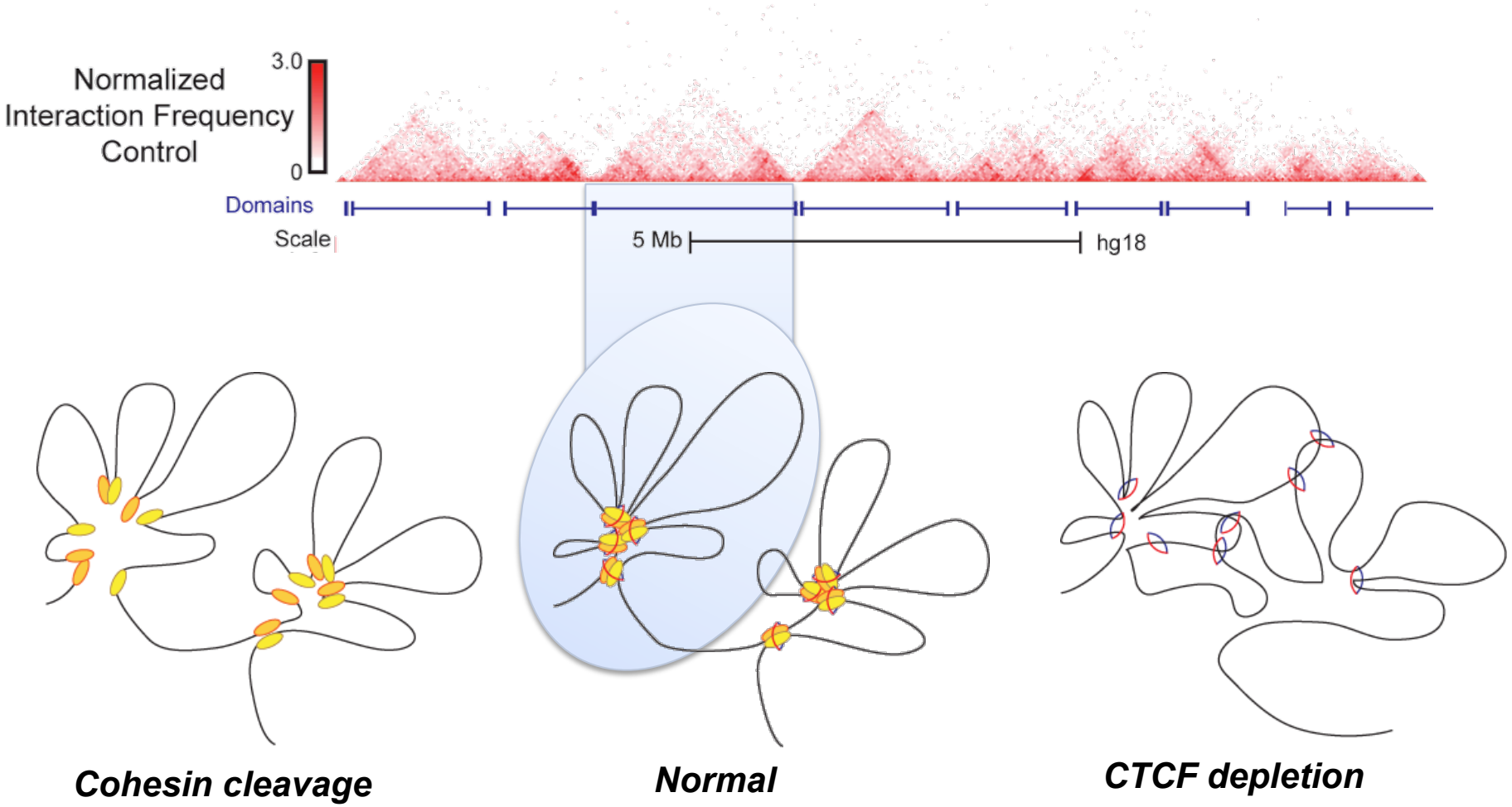
CTCF and cohesin contribute differently to TADs



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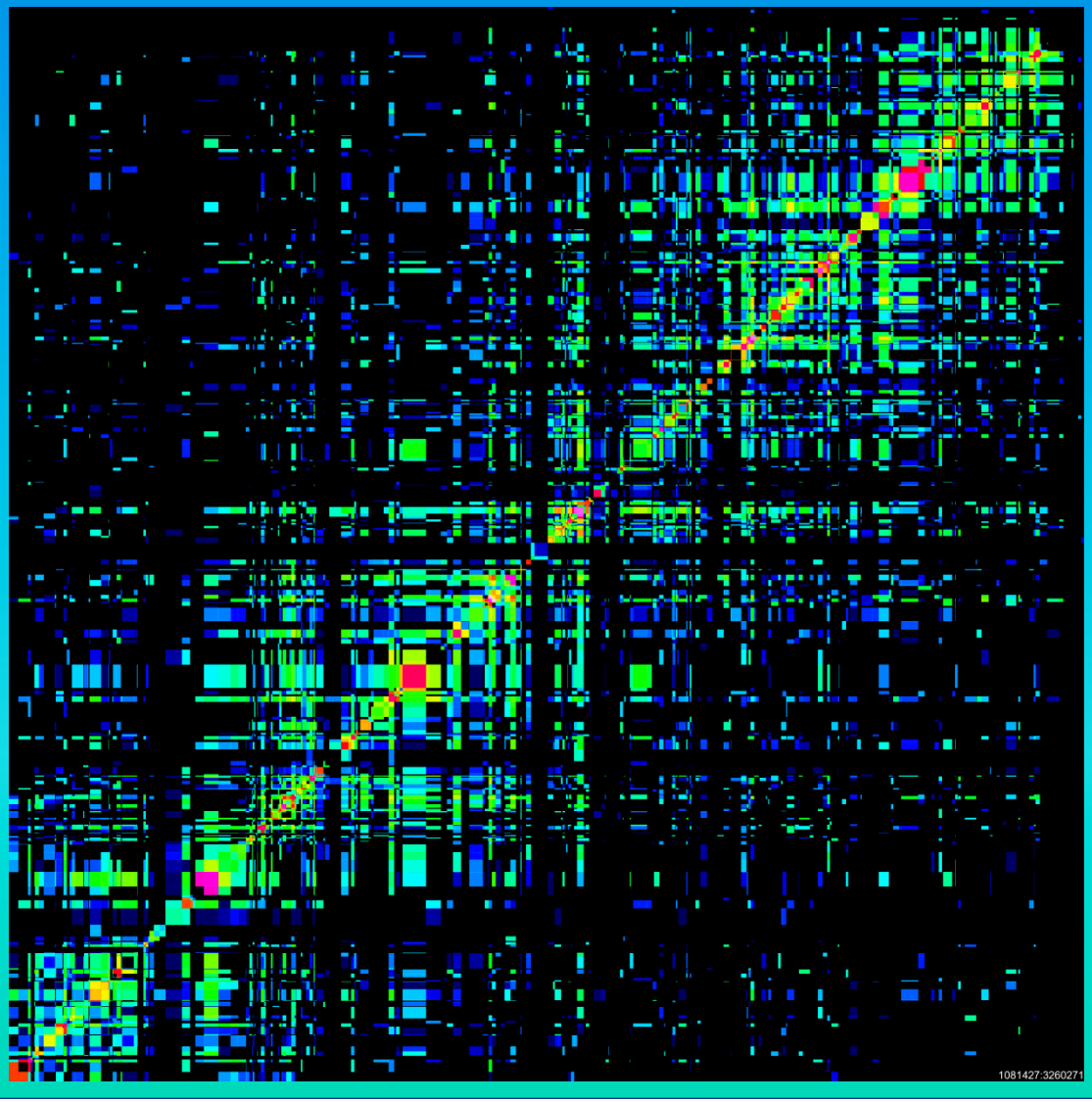
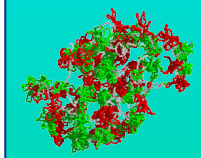
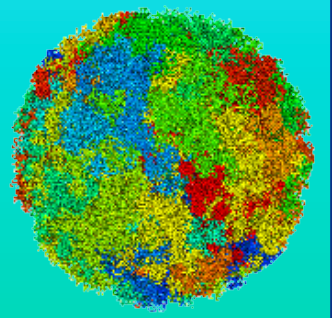
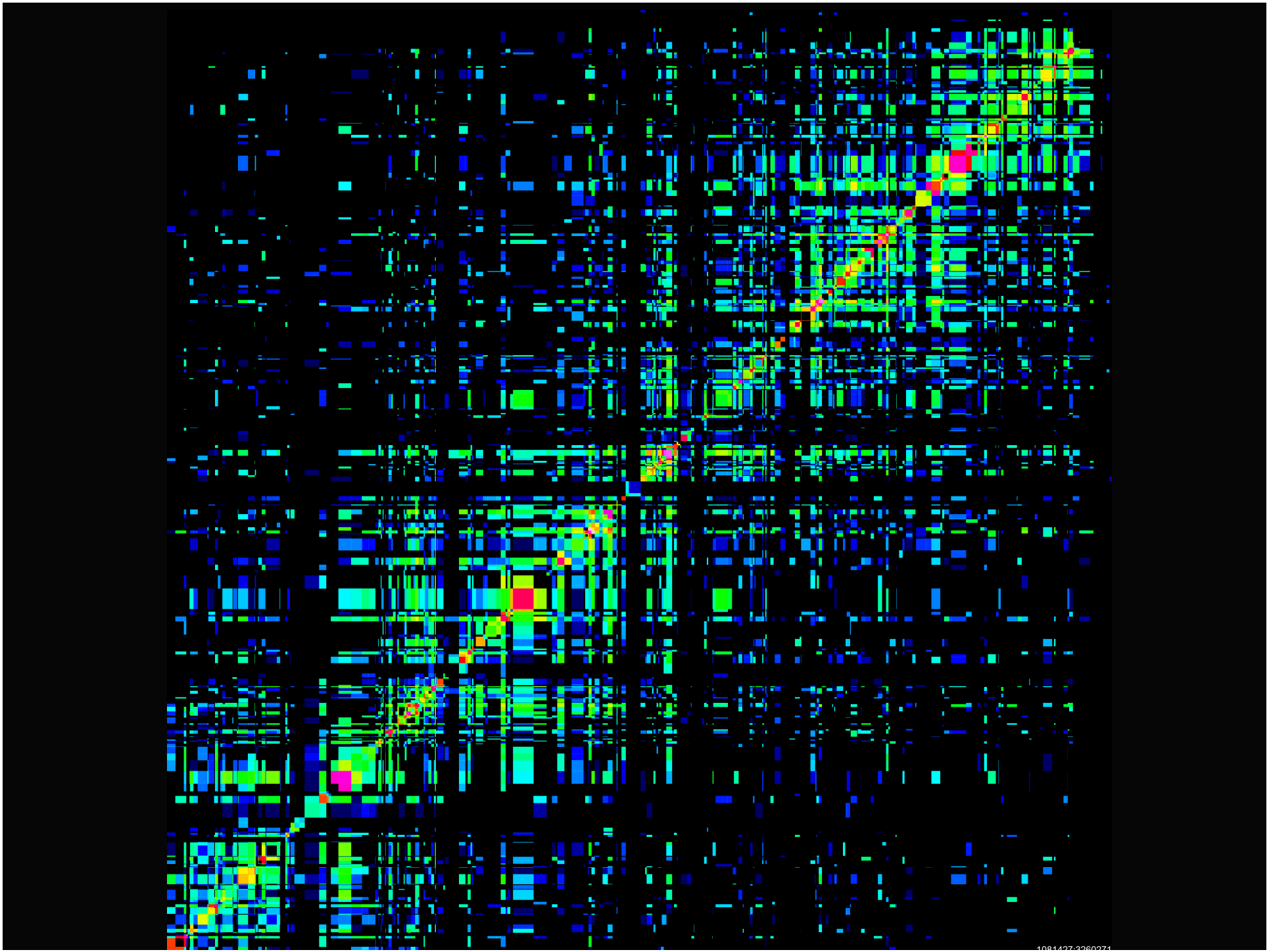
Selective Chromosome Interaction Capture (T2C)

T2C is a novel selective high-resolution high-throughput chromosome interaction capture, in which the relation between, region size, resolution, interaction frequency range, and sequencing depth can be designed towards the goal of the experiment.



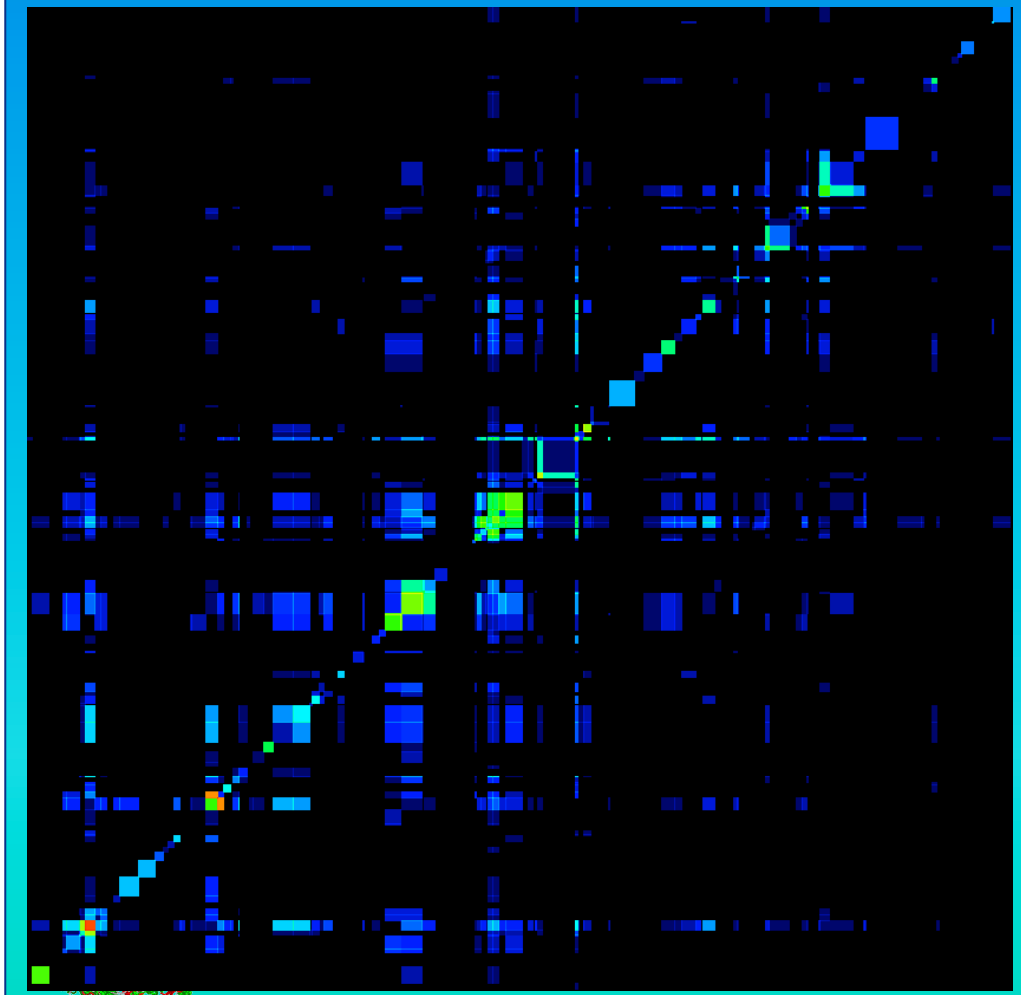


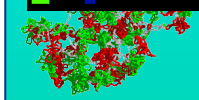


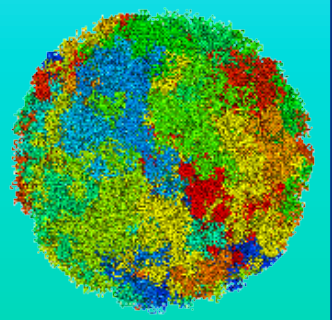


Fine Structure of Loop Aggregates/Rosettes

Depending on the resolution, the loops within a domain an their arrangement in loop aggregates/ rosettes can be shown as well as the details of how the loops are organized at their base as well as their aggregated rosette core: parallel loop fibres exist at the loop base with ~6kbp and these form the core.







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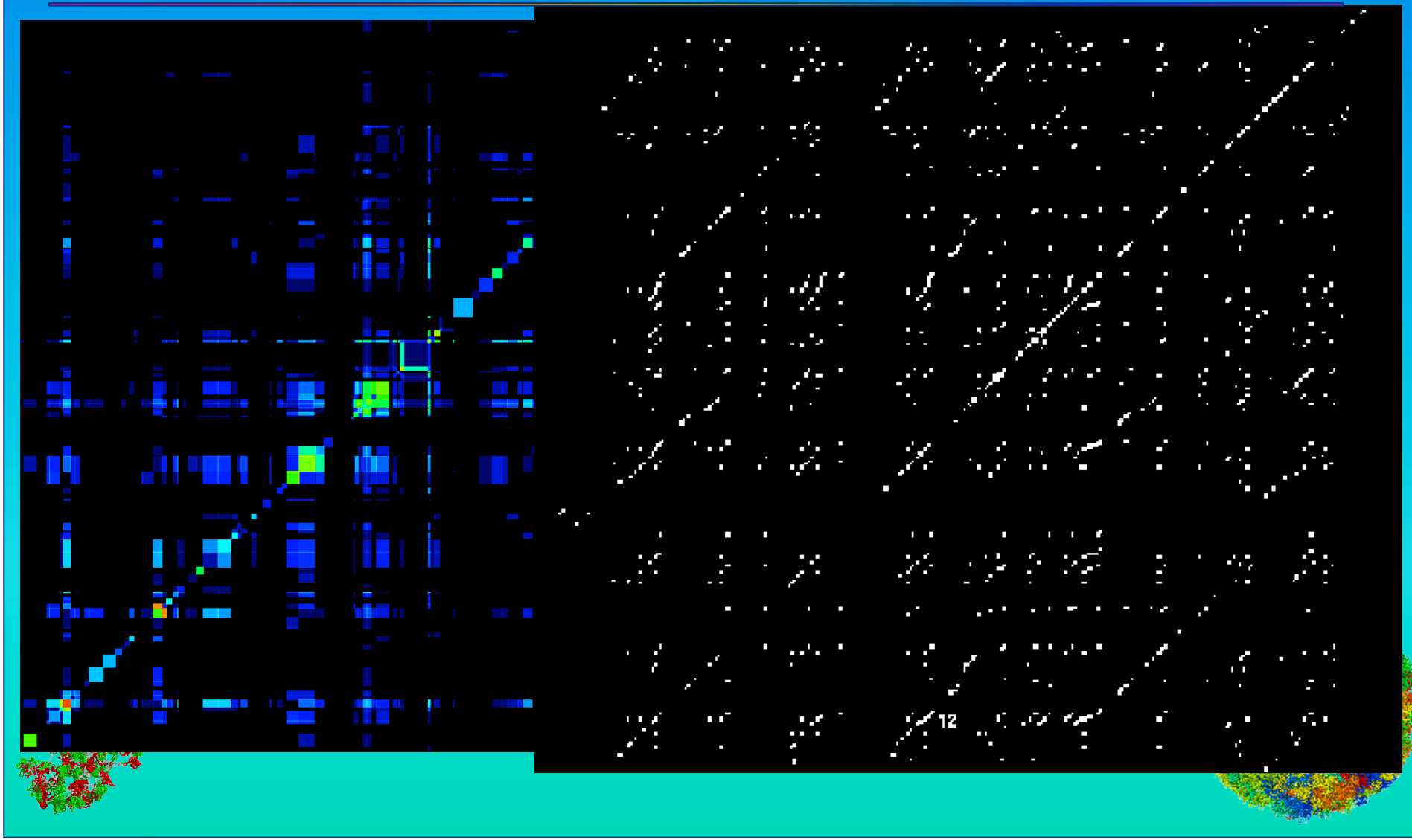
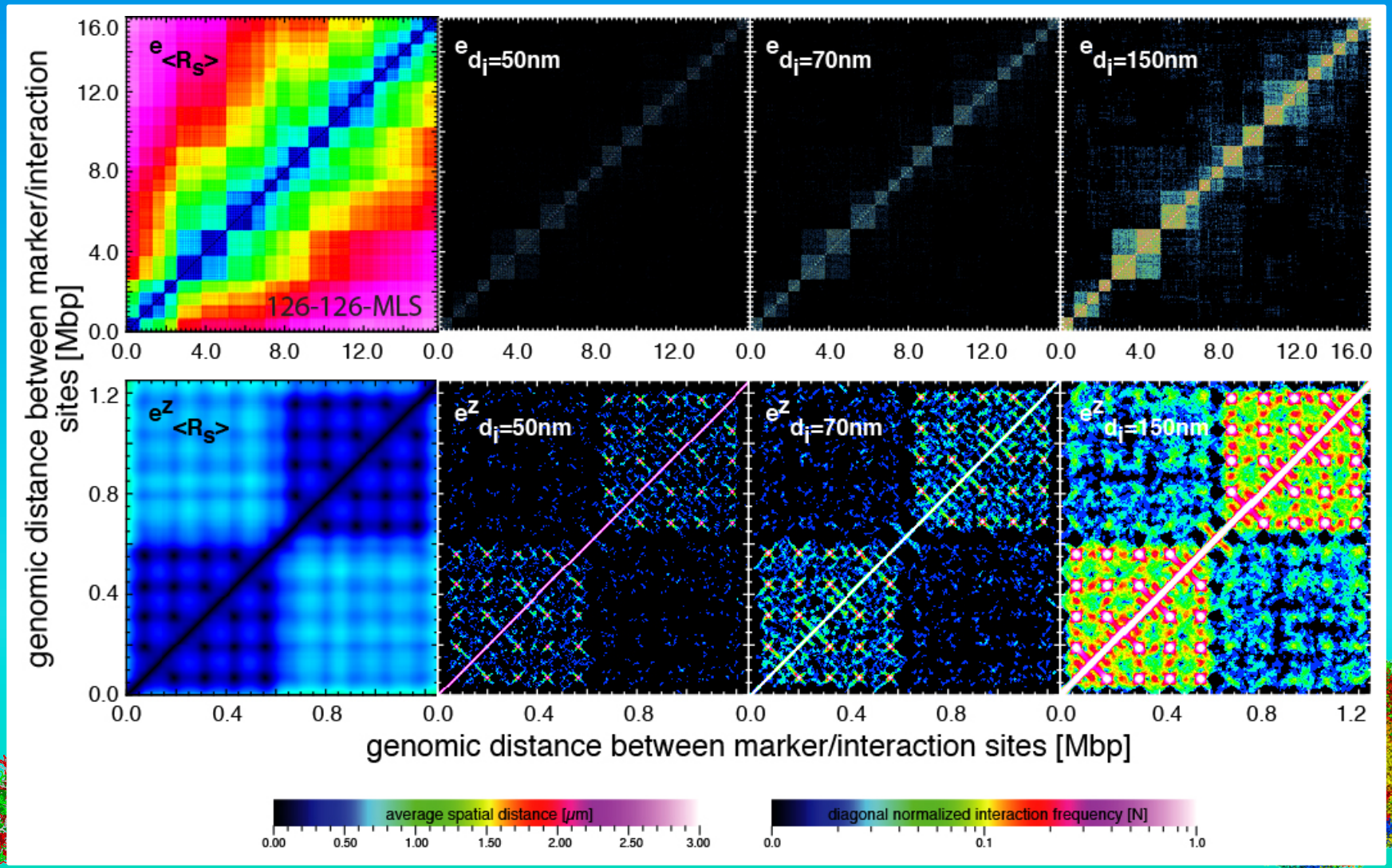


Simulated Interaction Maps

Simulated spatial distance maps as well as simulated interaction maps result in the representation of every parameter variation, and also exhibit the fine-structure describing the loop base as well as rosette core. Thus from the quasi-fibre to the entire chromosome the architecture can be understood in detail.



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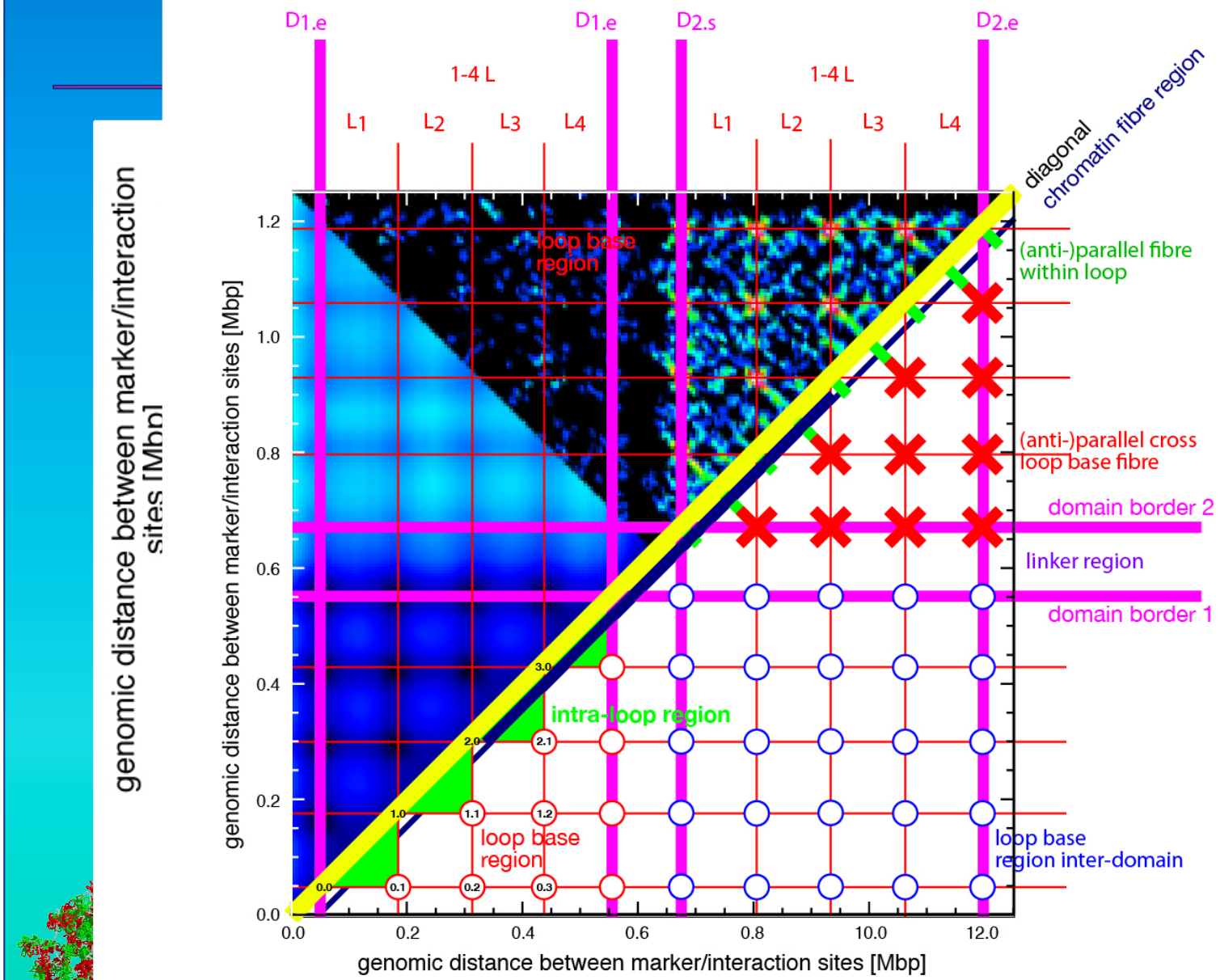
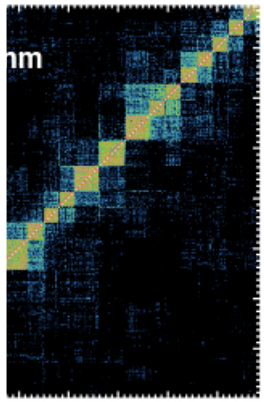
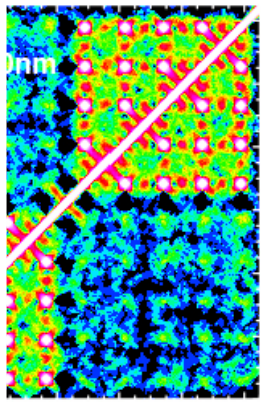


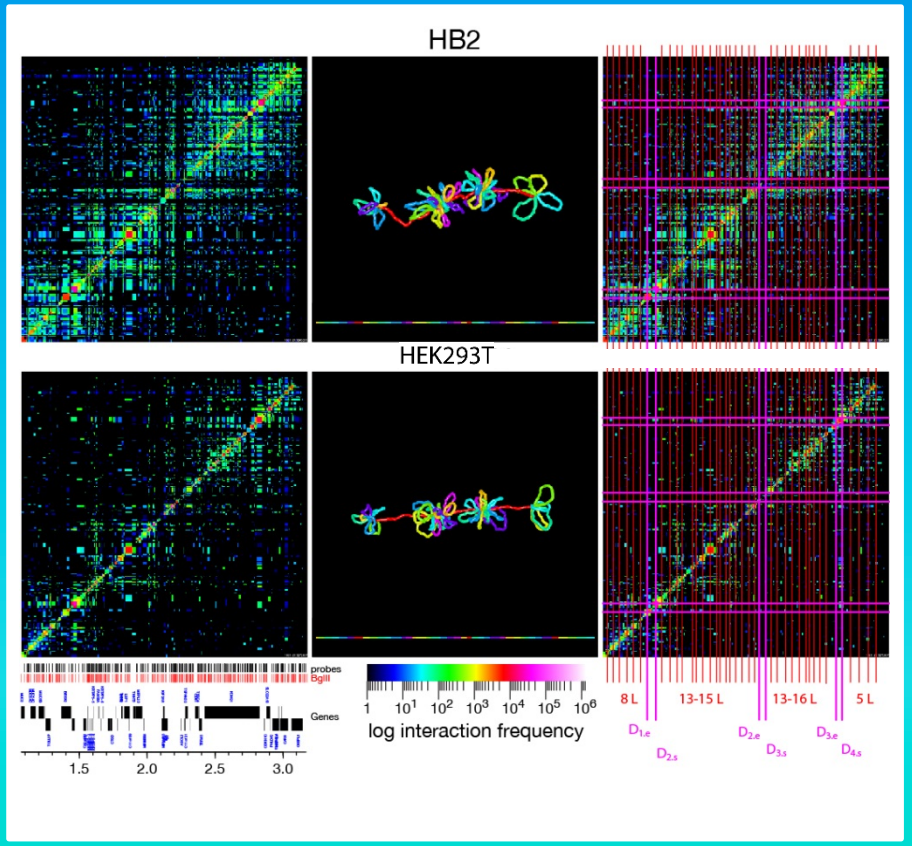




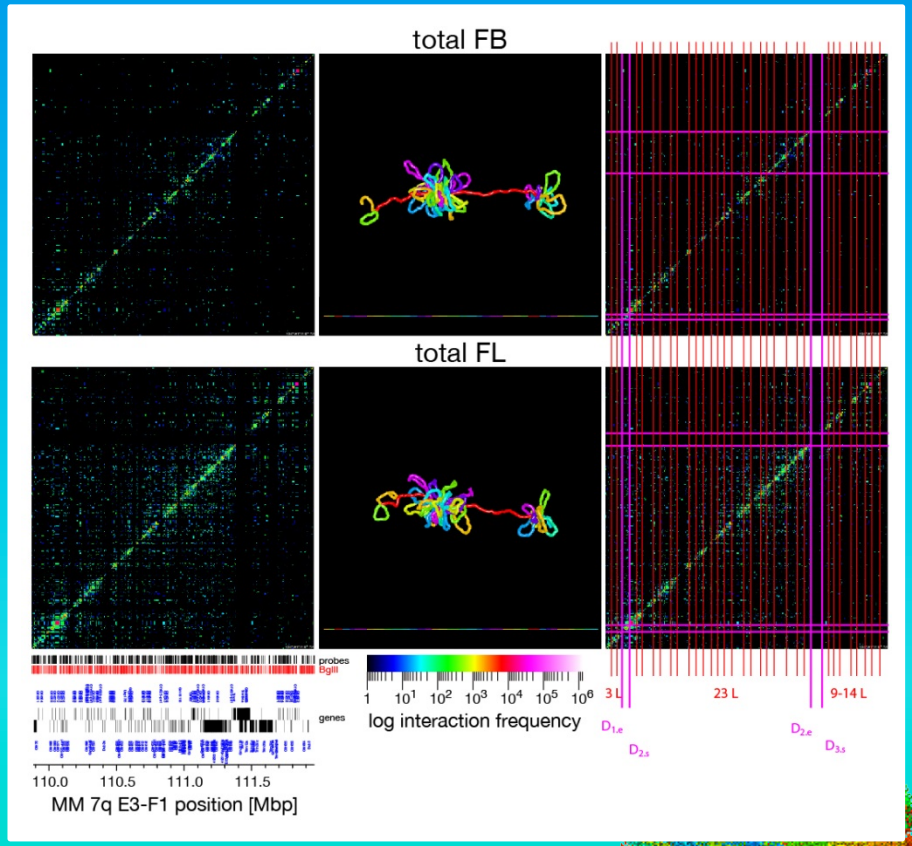
Variation of a Consensus Architecture Scheme

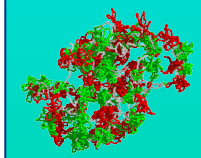
The difference between different cell types, functional states or even species is minor despite depending on the region. From this, the chromatin fibre conformation, loop position, and their association into loop aggregates/ rosettes can be derived, simulated by polymer models and finally visualized.

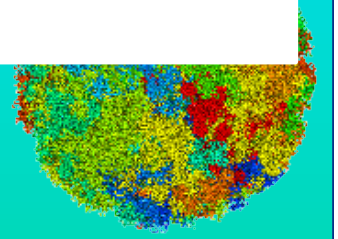
HUMAN



MOUSE







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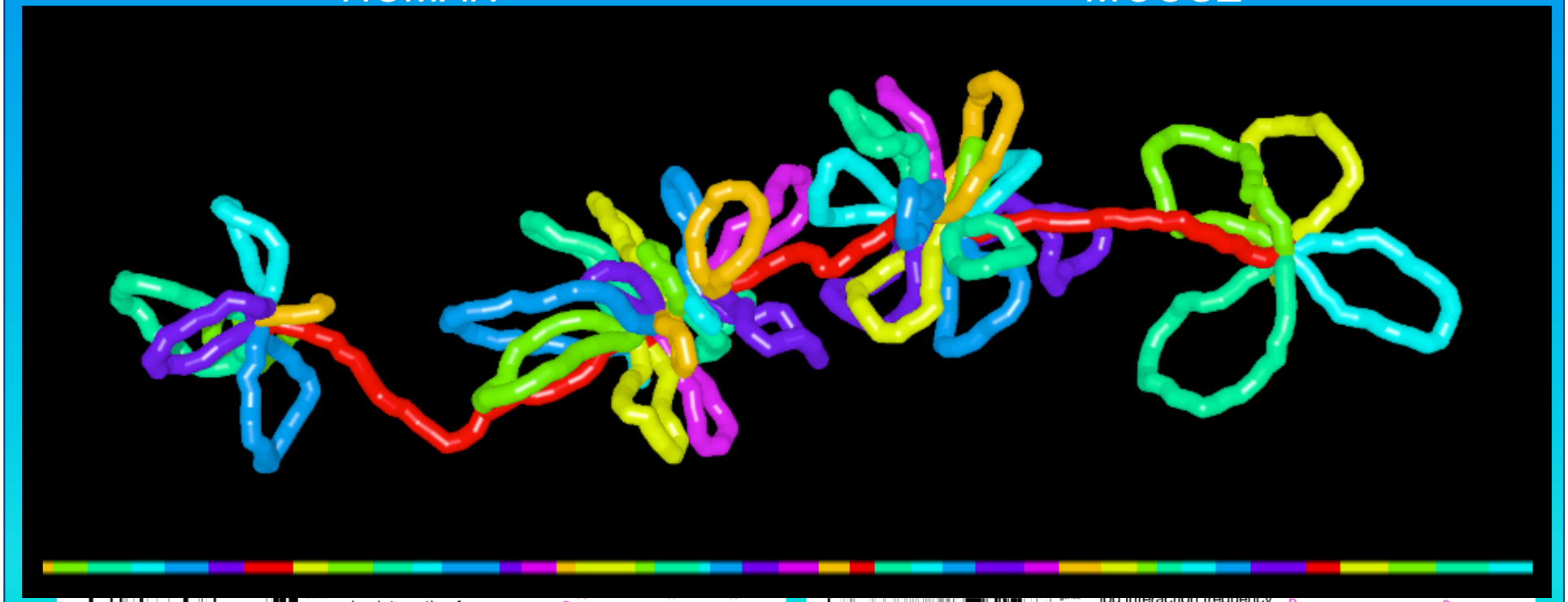
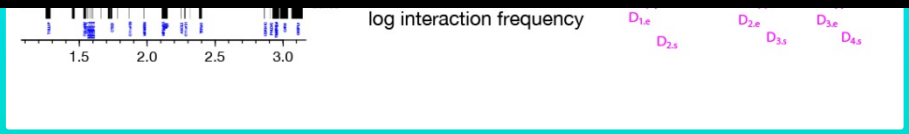
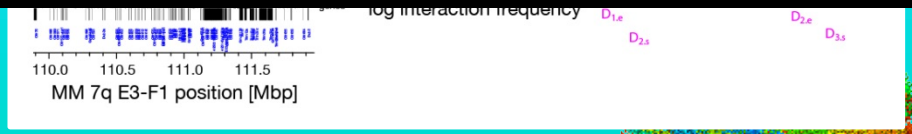
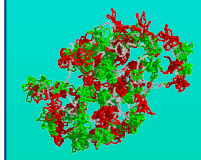
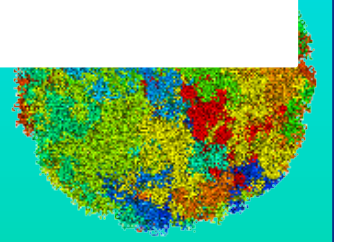


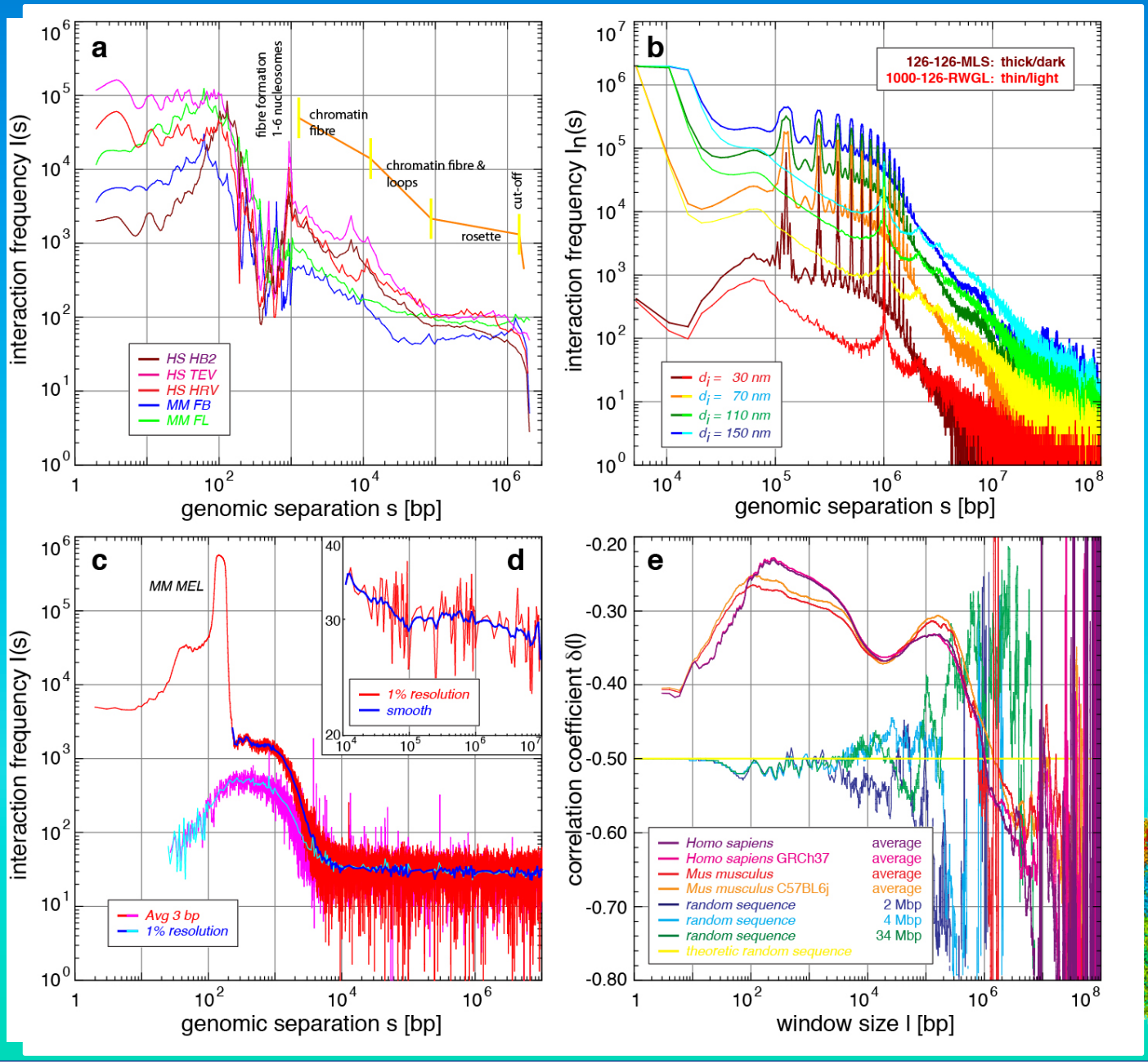








Scaling Analysis



Acknowledgments

Cohesin and Chromatin Structure,
Department of Cell Biology, Erasmus MC

Jessica Zuin

Michael van der Reijden

Department of Biomics, Erasmus MC

Wilfred van IJcken

Christel Kockx

Rutger Brouwer

Hi-C

Ludwig Institute for Cancer Research,
La Jolla, California

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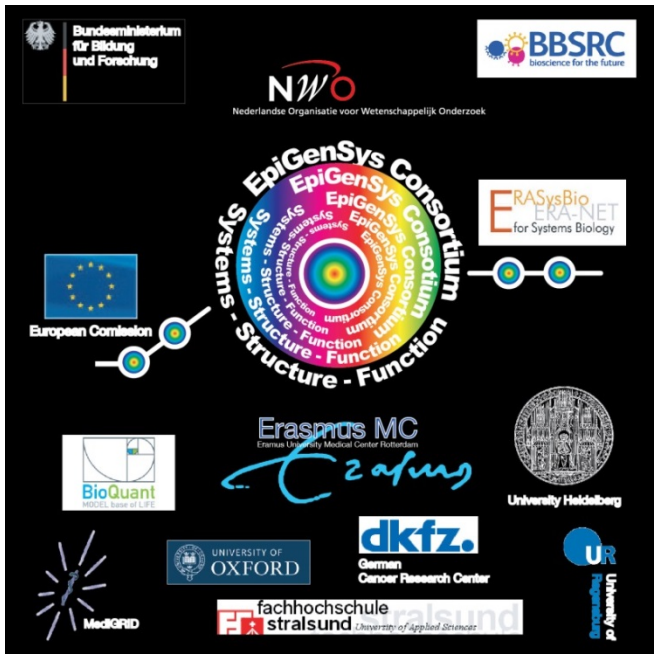

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Cohesin-Dependent Chromatin Structure at a Close View

Zuin, J., van den Werken, H. J. G., Kolovos, P., Brouwer, R. W. W., Kockx, C. E. M., van IJcken, W. F. J., Grosveld, F. G.,
&
Knoch, T. A. & Wendt, K. S.

Nuclear Organization and Function, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA, 19th – 23rd August, 2014.

Abstract

The cohesin complex is an important factor for the three-dimensional organization of chromatin. Hi-C studies have shown that chromatin loops cluster together into topological domains. Recently, we and others have used Hi-C to show how topological domains and subdomains change when the cohesin complex is depleted. Our study showed that topological domains are altered after cohesin depletion but not disrupted. However, the current resolution of Hi-C (40kb) is not sufficient to yield information about the inside of TADs, for instance which long range contacts are affected in particular and which regions remain unaffected, are only interactions involving cohesin sites affected and how does the chromatin fibre rearrange without cohesin. To address these question we have studied a 2.1 Mb region on the human chromosome 11 using our novel T2C technique which allows to generate a Hi-C type dataset at restriction fragment resolution (2-6 kb). Our selected region contains two topological domains and two imprinted gene clusters, H19/IGF2 and KCNQ1/KCNQ1OT1. We have generated T2C maps for two different cell types, a breast endothelial cell line and HEK293T cells, and also for cells where the cohesin complex was destroyed in interphase by proteolytic cleavage of its RAD21 subunit. We will present our results addressing the aforementioned questions. Further we have also reinvestigated previously published data concerning the interactions and potential co-regulation between the imprinted gene clusters and their imprinted control regions.

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Keywords:

Genome, genomics, genome organization, genome architecture, structural sequencing, architectural sequencing, systems genomics, coevolution, holistic genetics, genome mechanics, genome statistical mechanics, genomic uncertainty principle, multilism genotype-phenotype, genome function, genetics, gene regulation, replication, transcription, repair, homologous recombination, simultaneous co-transfection, cell division, mitosis, metaphase, interphase, cell nucleus, nuclear structure, nuclear organization, chromatin density distribution, nuclear morphology, chromosome territories, subchromosomal domains, chromatin loop aggregates, chromatin rosettes, chromatin loops, chromatin quasi fibre, chromatin density, persistence length, spatial distance measurement, histones, H1.0, H2A, H2B, H3, H4, mH2A1.2, DNA sequence, complete sequenced genomes, molecular transport, obstructed diffusion, anomalous diffusion, percolation, long-range correlations, fractal analysis, scaling analysis, exact yard-stick dimension, box-counting dimension, lacunarity dimension, local nuclear

dimension, nuclear diffuseness, parallel super computing, grid computing, volunteer computing, polymer model, analytic mathematical model, Brownian Dynamics, Monte Carlo, fluorescence *in situ* hybridization (FISH), targeted chromatin capture (T2C) confocal laser scanning microscopy, fluorescence correlation spectroscopy, spatial precision distance microscopy, super-resolution microscopy, two dimensional fluorescence correlations spectroscopy (2D-FCS) auto-fluorescent proteins, CFP, GFP, YFP, DsRed, fusion protein, *in vivo* labelling, information browser, visual data base access, holistic viewing system, integrative data management, extreme visualization, three-dimensional virtual environment, virtual paper tool, human ecology, e-human grid ecology, society, social systems, e-social challenge, inverse tragedy of the commons, grid phenomenon, micro-sociality, macro-sociality, autopoietic tragedy of social sub-systems, micro subsystems, macro subsystems, micro operationality, macro operationality, grid psychology micro riskmanagement, macro riskmanagement.

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