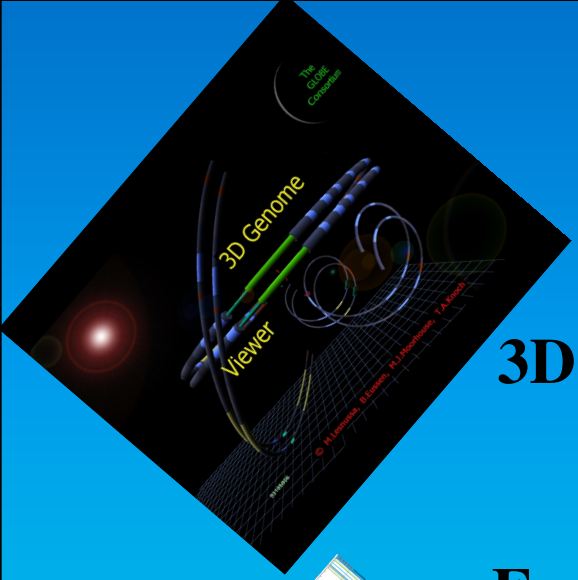
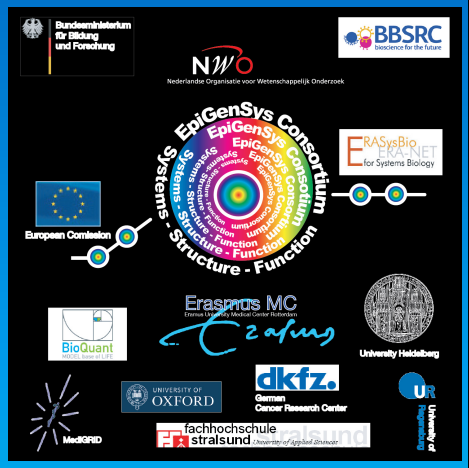
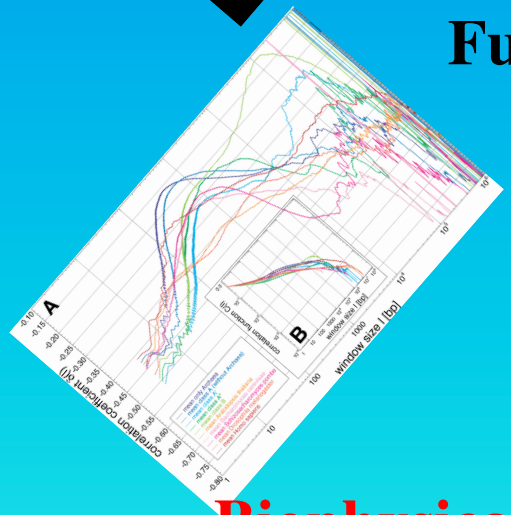
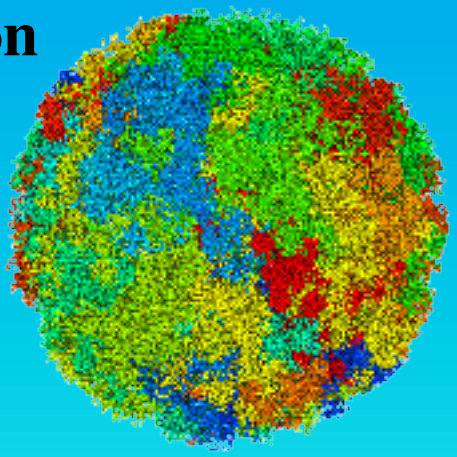




The Detailed 3D Multi-Loop Aggregate/Rosette Chromatin Architecture and Functional Dynamic Organization of the Human and Mouse Genomes





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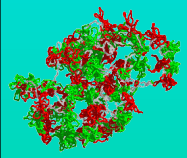
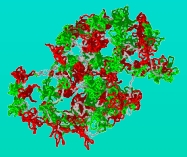
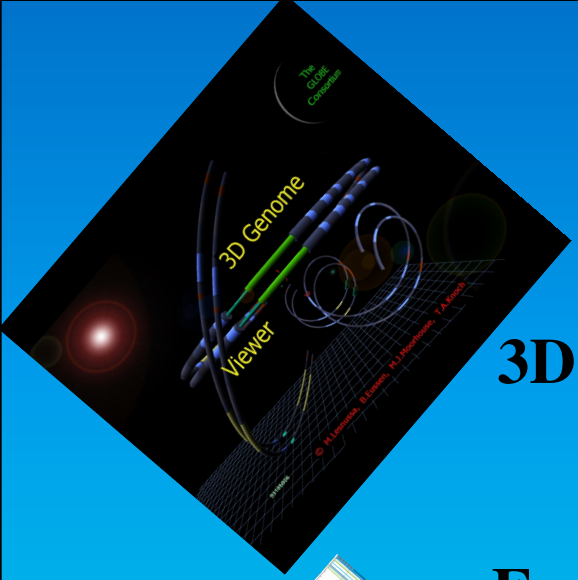
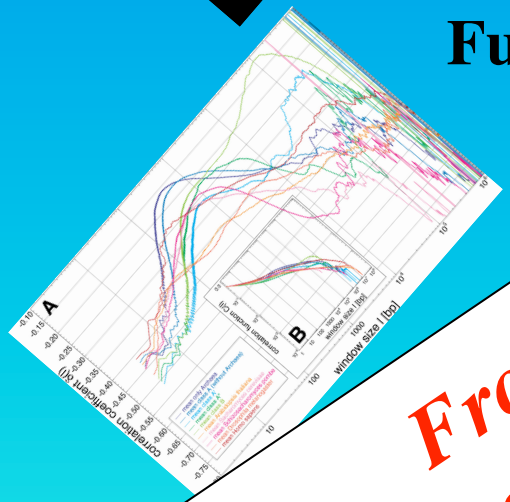


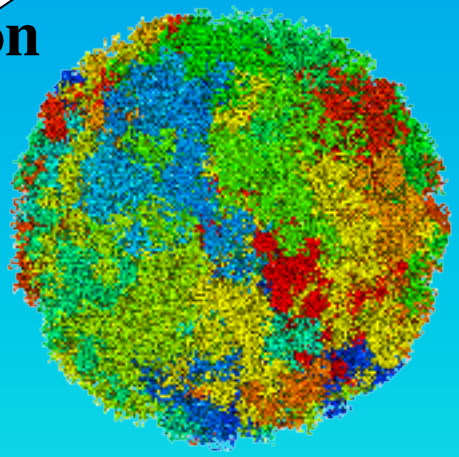




The Detailed 3D Multi-Loop Aggregate/P Chromatin Archite and Functional Dyn tion

Hum Genomes





From Sequence to Morphology: Towards a Holistic Understanding of Genomes!

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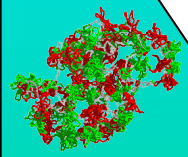
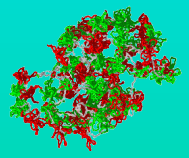
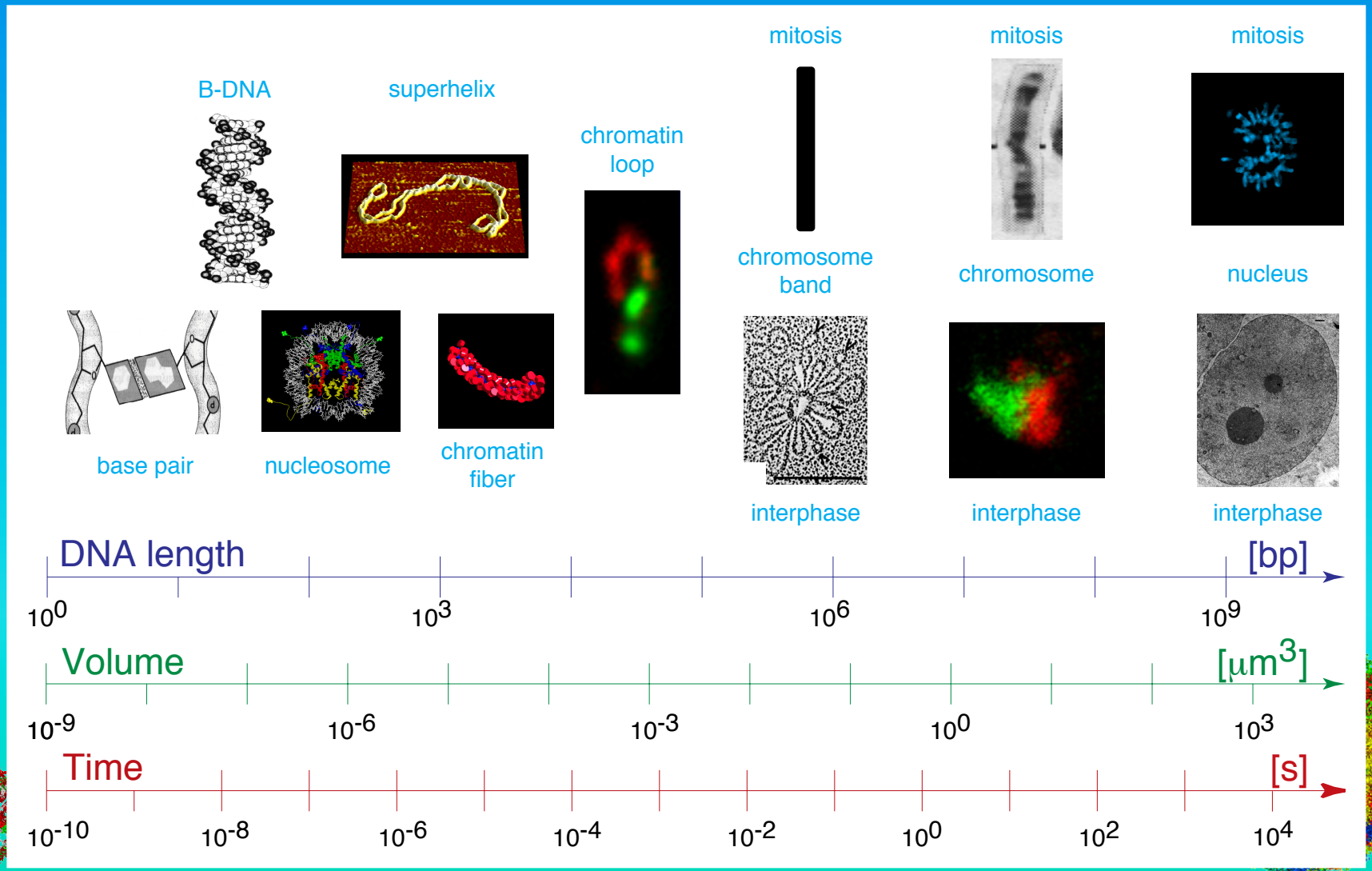




Dynamic and Hierarchical Genome Organization

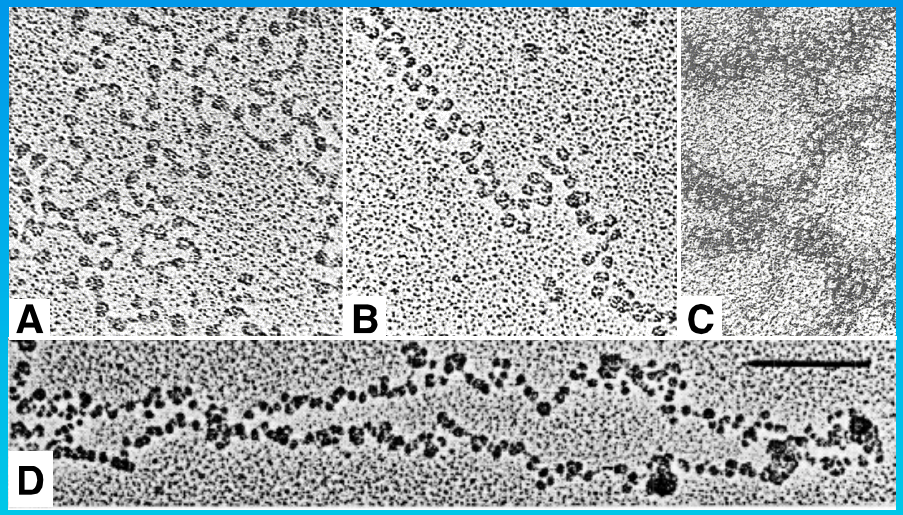
The different organization levels of genomes bridge several orders of magnitude concerning space and time. How all of these organization levels connect to processes like gene regulation, replication, embryogeneses, or cancer development is still unclear?



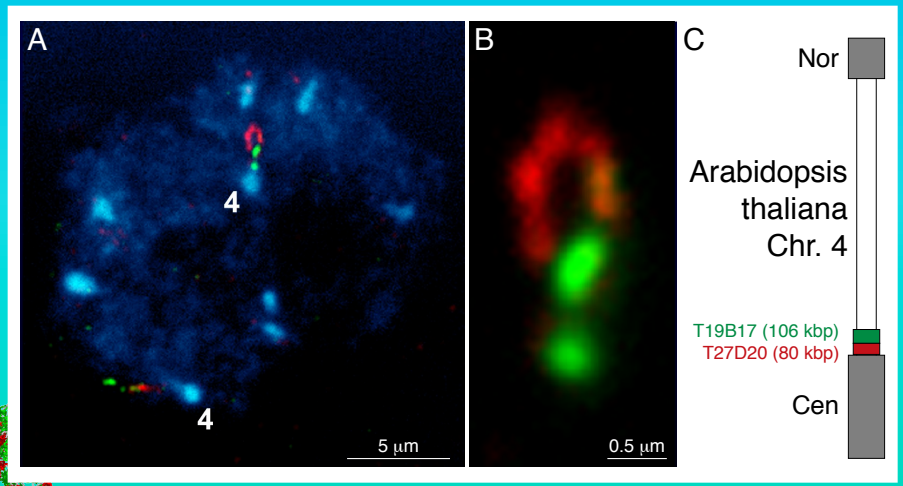
Chromatin Conformation and Higher-Order Topologies

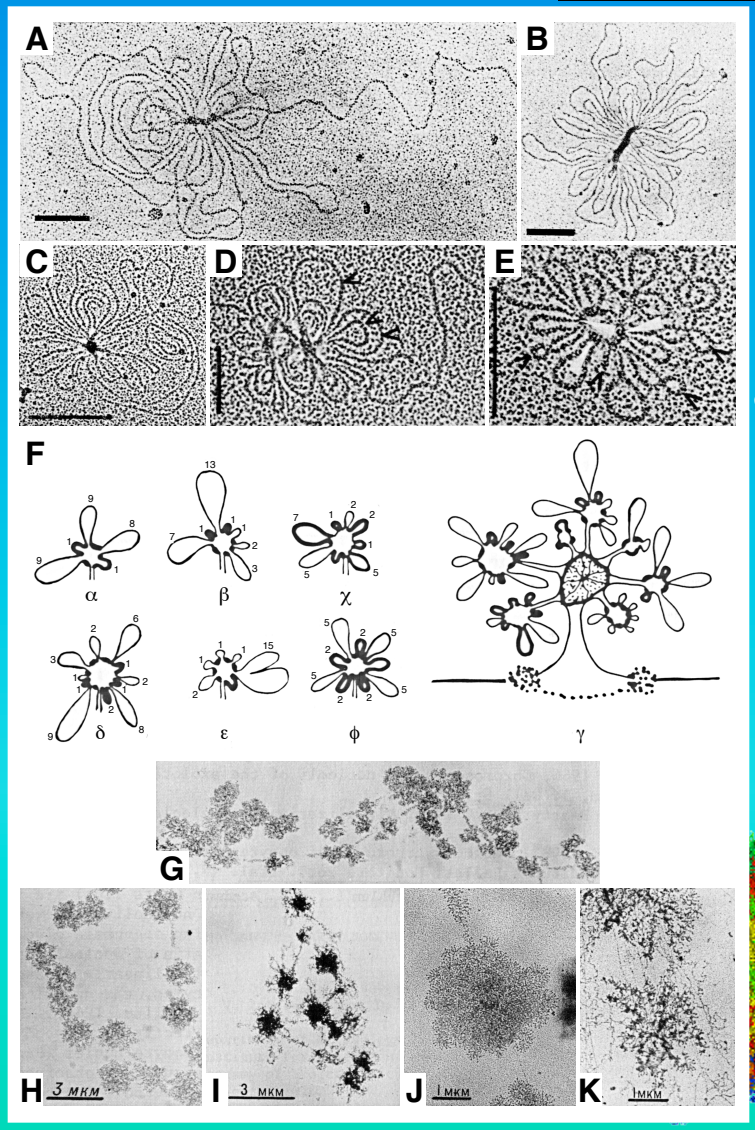
It becomes increasingly clearer, that the chromatin conformation is a random organization of nucleosomes, which depending on external or modification conditions has different condensation degrees, with a prevalence for the 30nm fiber with ~6nucleosomes per 11nm. This seems to make loops which further cluster to form aggregates more or less rosette-like which then constitute the chromosome.

A-C: Voet & Voet D: Reznik *et al.*



Courtesy P. Fransz, Amsterdam



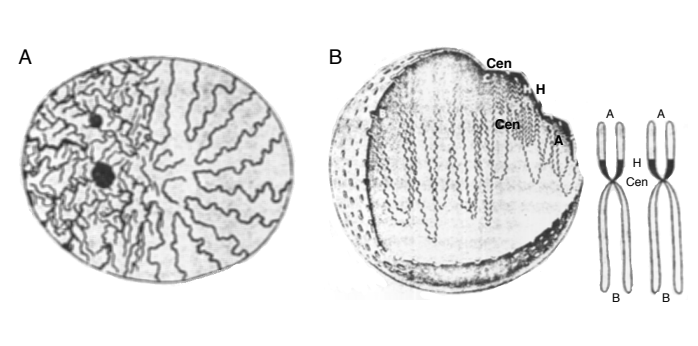


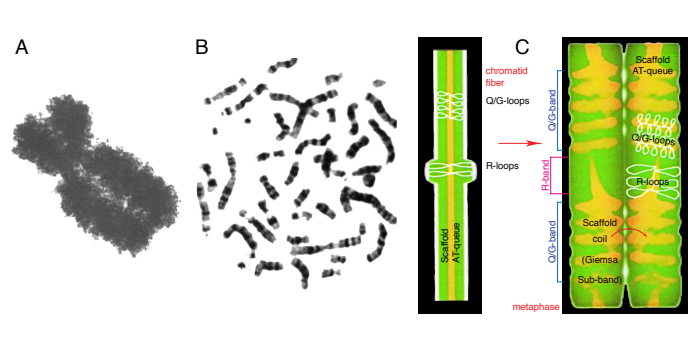
A, B: Avramova *et al.*; C: Salganik *et al.*; D-G:Frznik *et al.*; G-K: Tsvetkov & Parvenov.

Integral Models of Cell Nuclear Organization I

Already Rabl and Boveri were aware of the obvious fact that the organization of genomes has to be consistent from the sequence level to the morphology of the whole cell nucleus. Although they might be different in detail their common seem is recursive folding and clustering thereof with variation/ modification and dynamics accounting for different nuclear states and function.

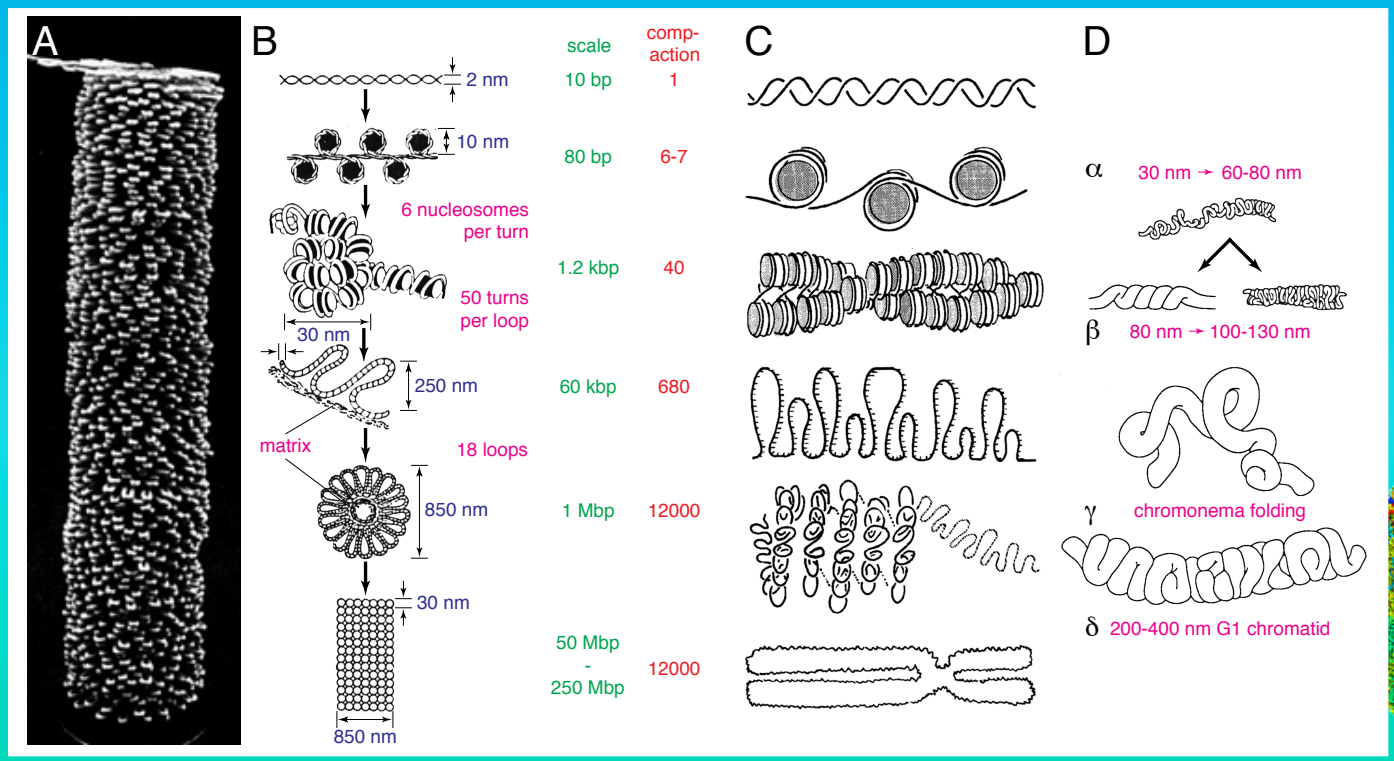
Rabl & Boveri

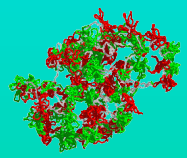


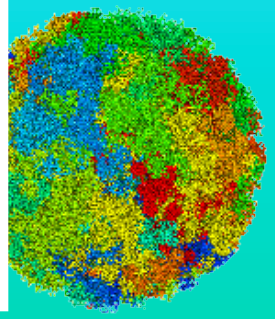


A: Bloom & Fawcett
B: Alberts *et al.*
C: Paulson & Laemmli

A, B: Pienta & Coffey; C: Alberts *et al.*; D: Belmont & Bruce

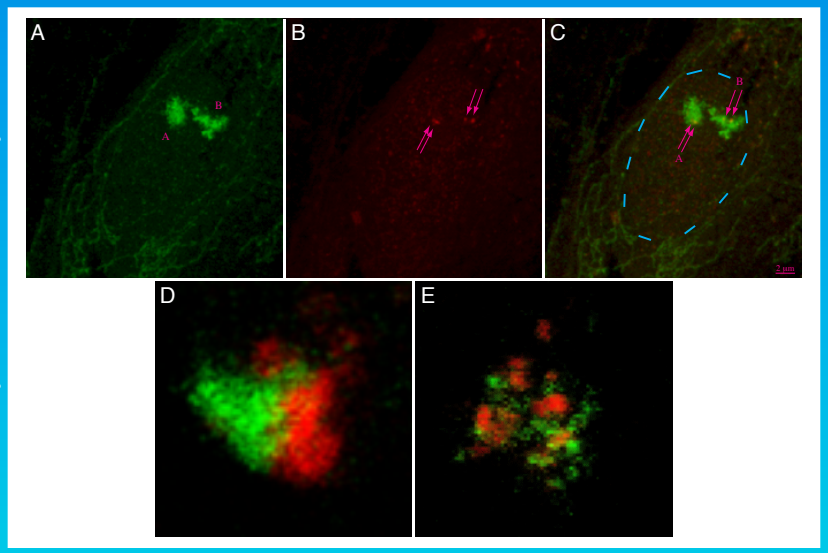




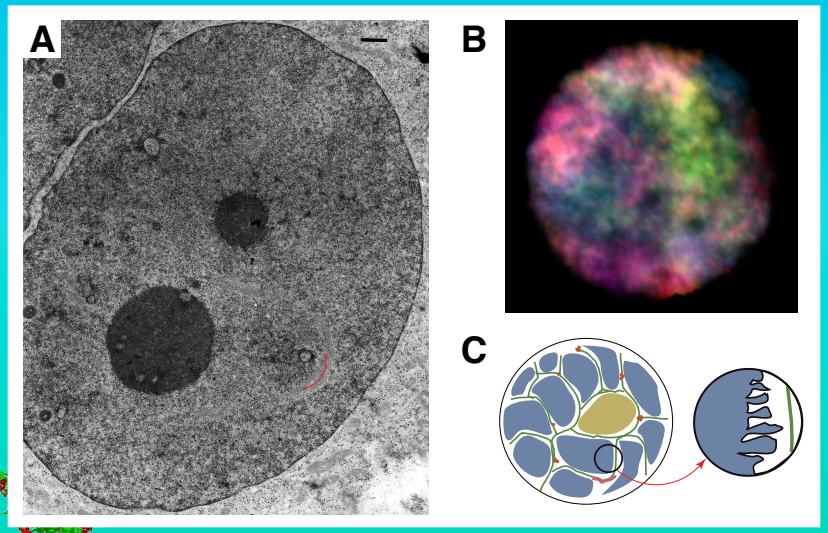


Integral Models of Cell Nuclear Organization

The biggest advantage of integral models is the again obvious and simple fact, that they allow the validation from the consistency of different levels of organization from the other levels. Thus, e.g. the so called Interchromosmal Domain Model can be ruled out by simple volumenous thought…

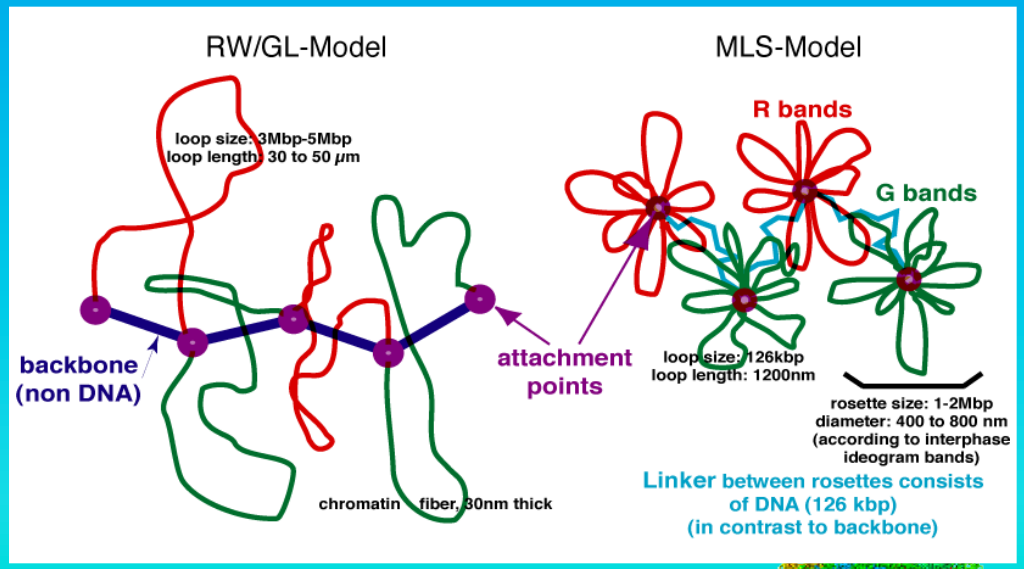


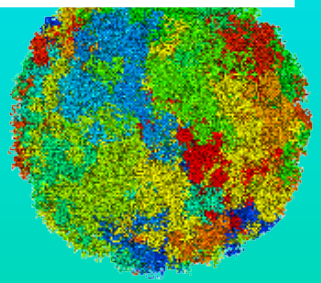
D: courtesy S. Dietzel; E: courtesy D. Zink



A: courtesy K. Richter; B: courtesy K. Greulich-Bode

Random-Walk/Giant-Loop Multi-Loop-Subcompatment Model





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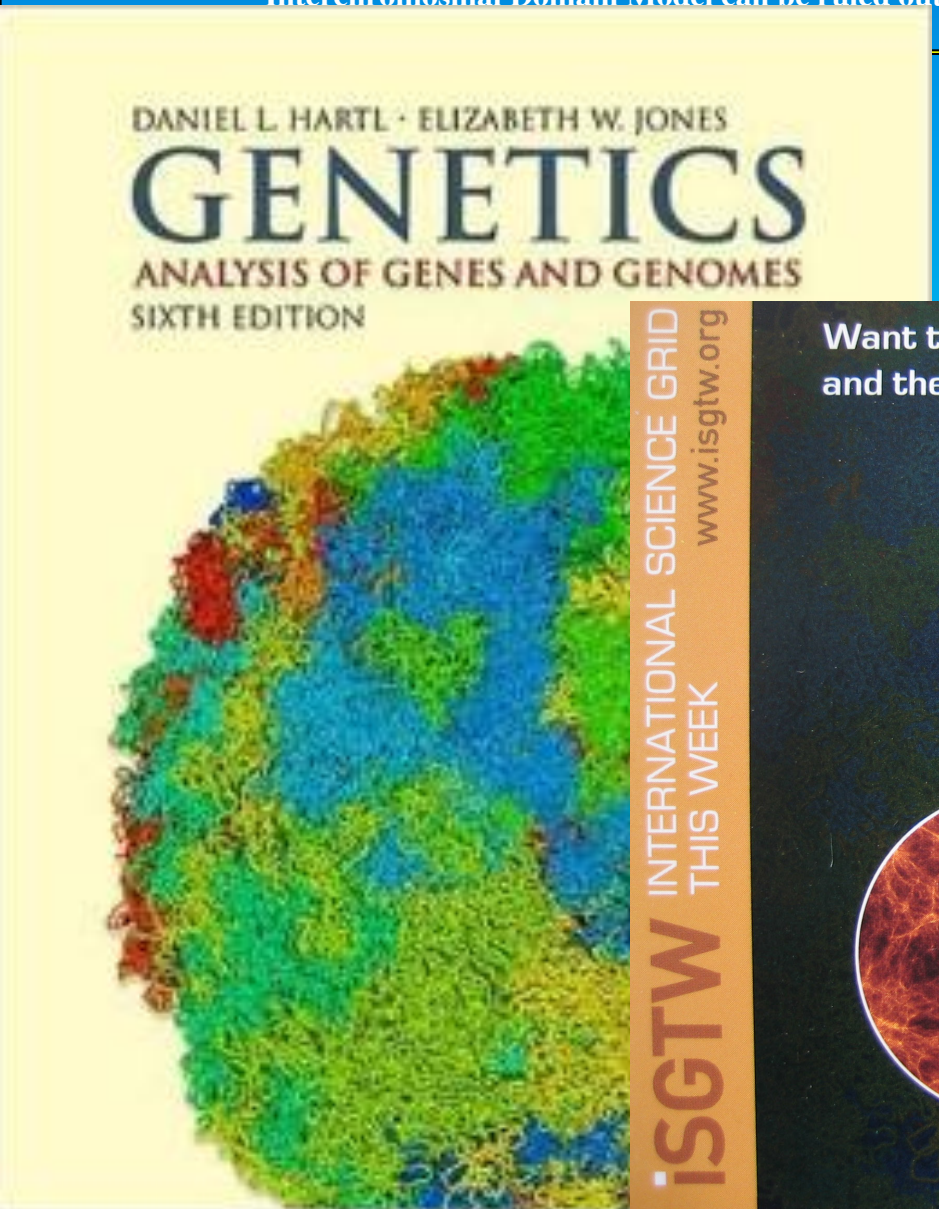
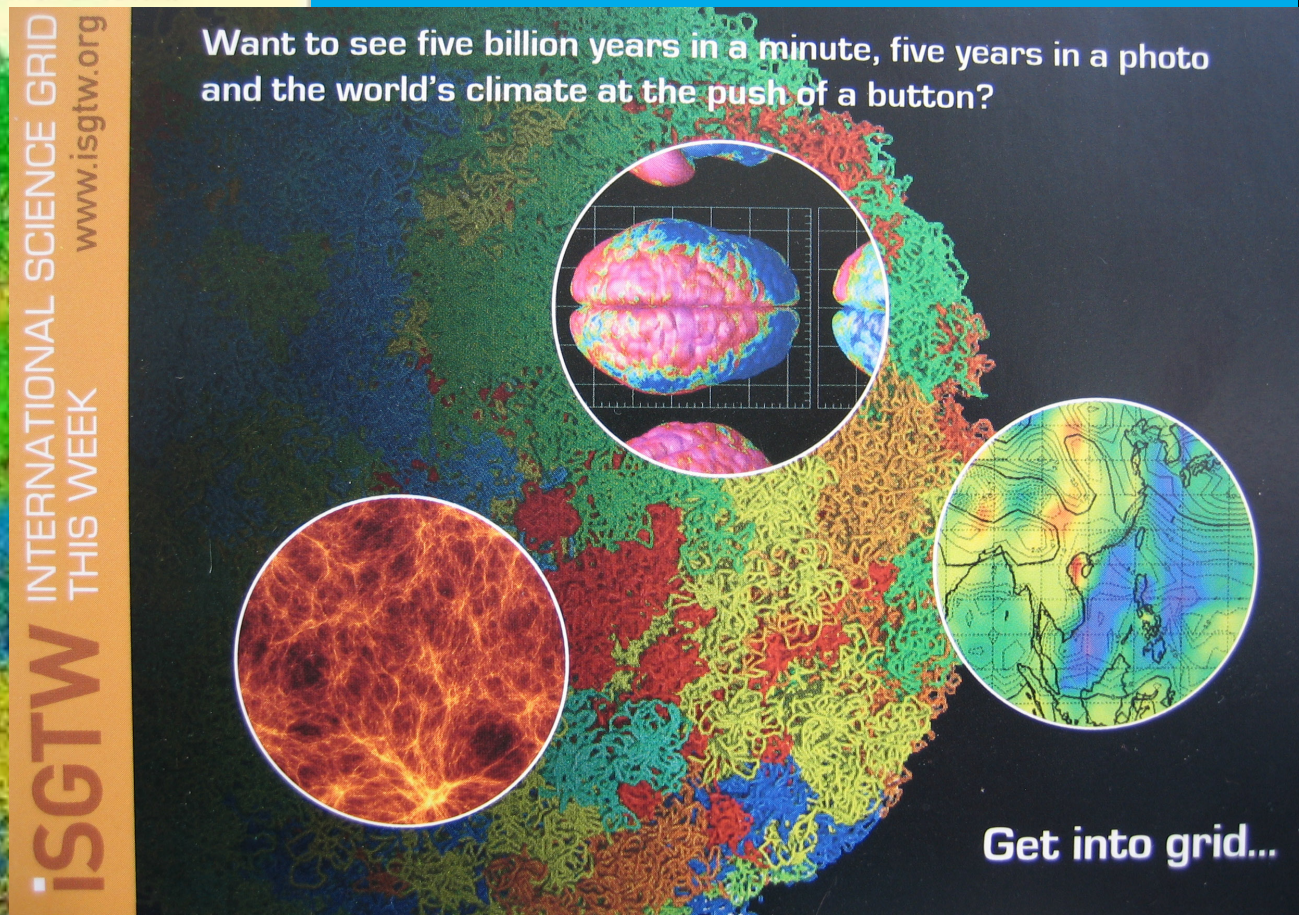
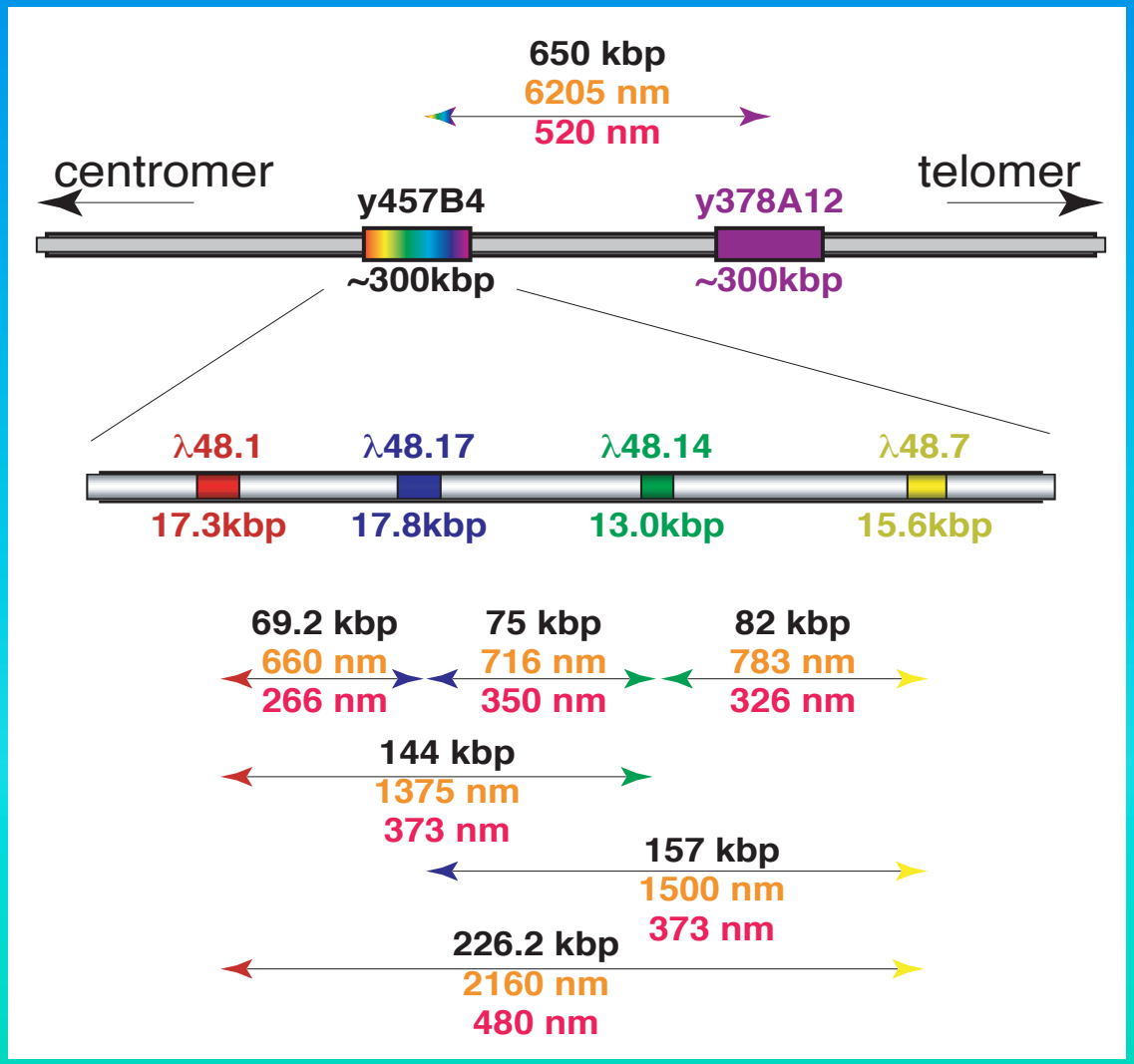
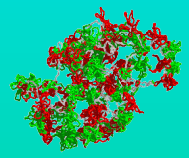


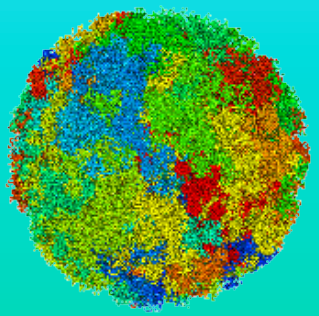


3D Architecture of the Prader-Willi Region

Fluorescence *in situ* hybridization with various protocols of small probes within the Prader-Willi region combined with spectral precision distance confocal laser scanning microscopy and comparison with large-scale computer simulations shows a Multi-Loop Subcompartiment organization of the Prader-Willi region.







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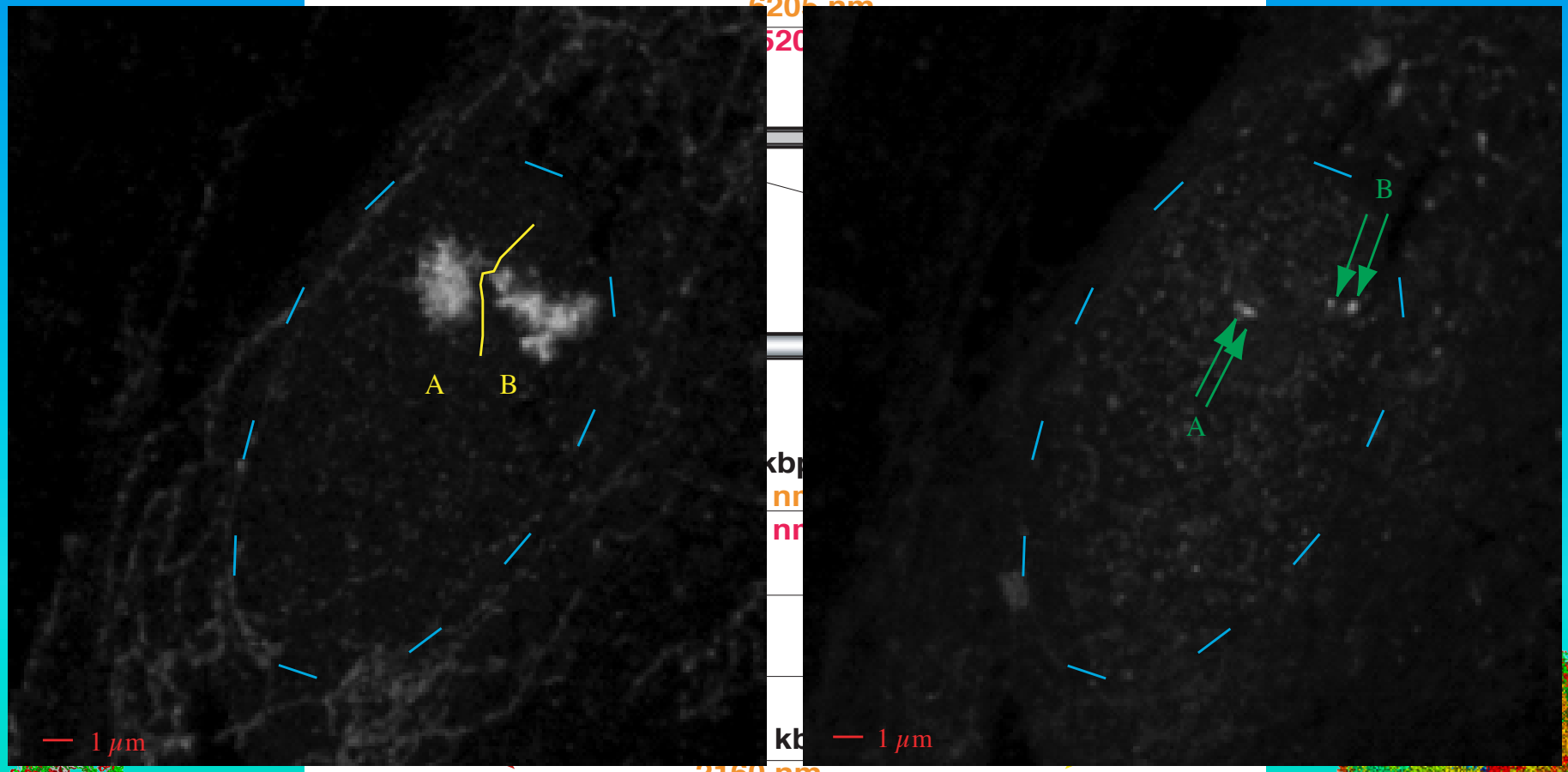

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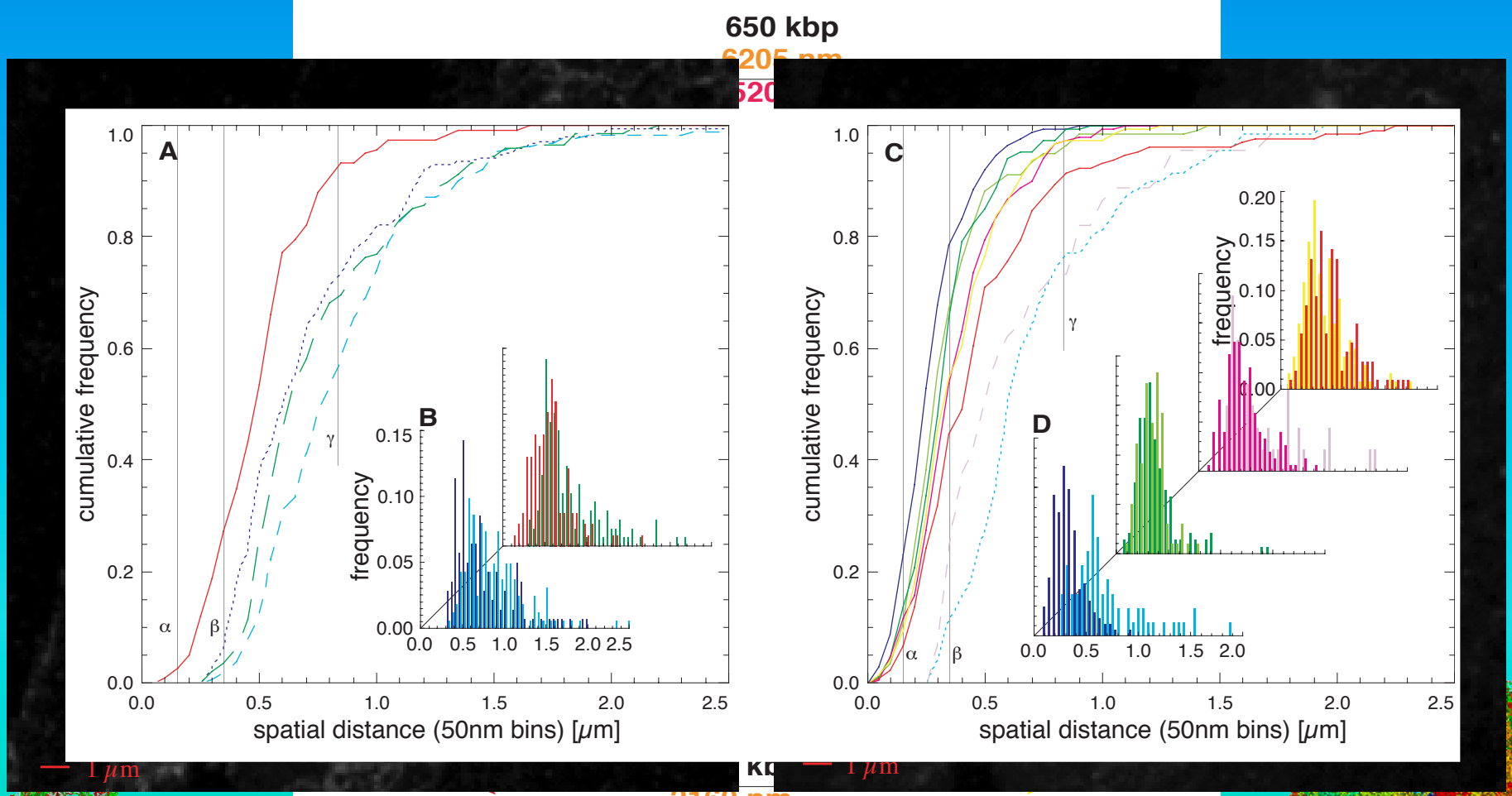

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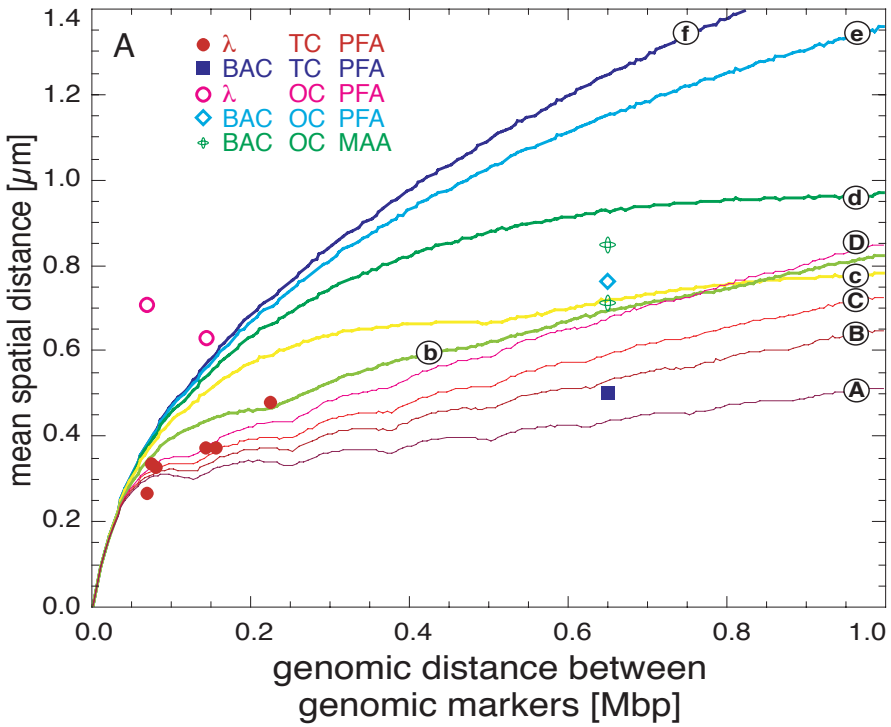
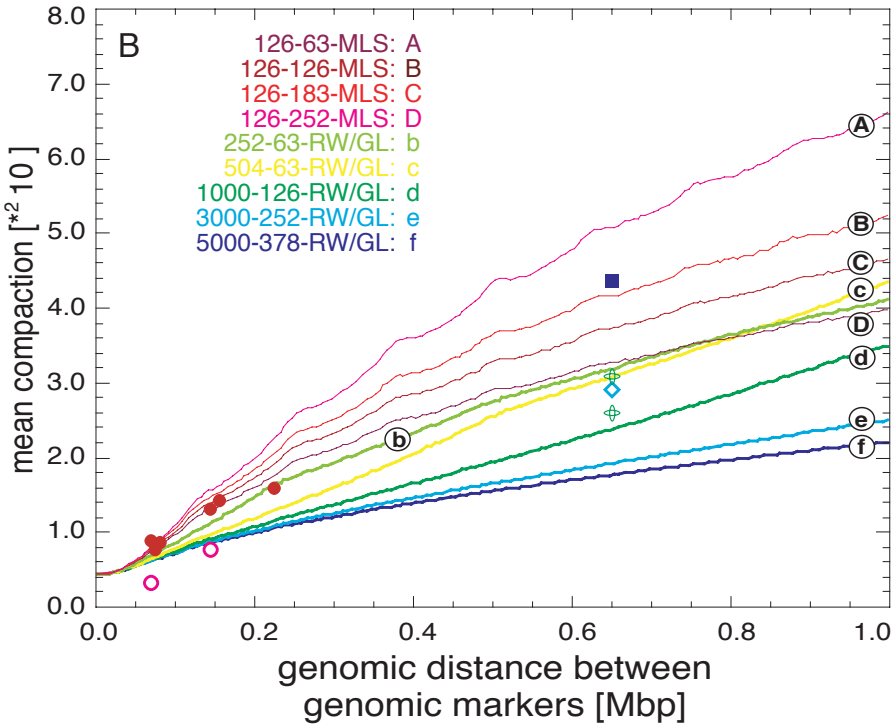
650 kbp

6205 nm





2160 nm

480 nm

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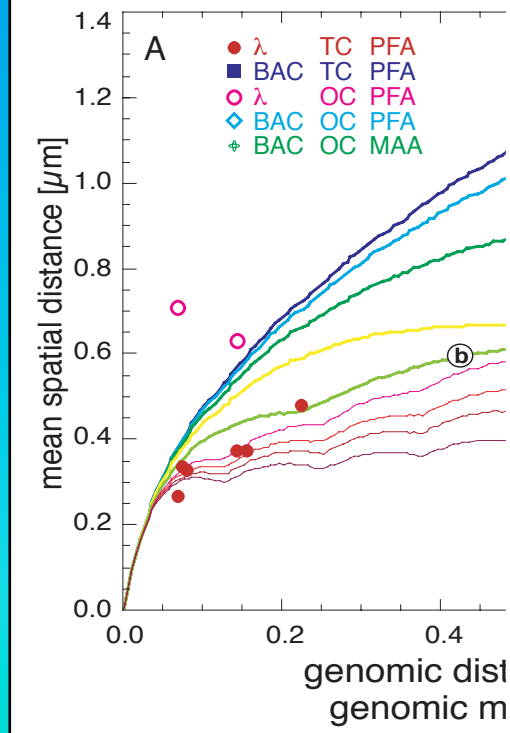
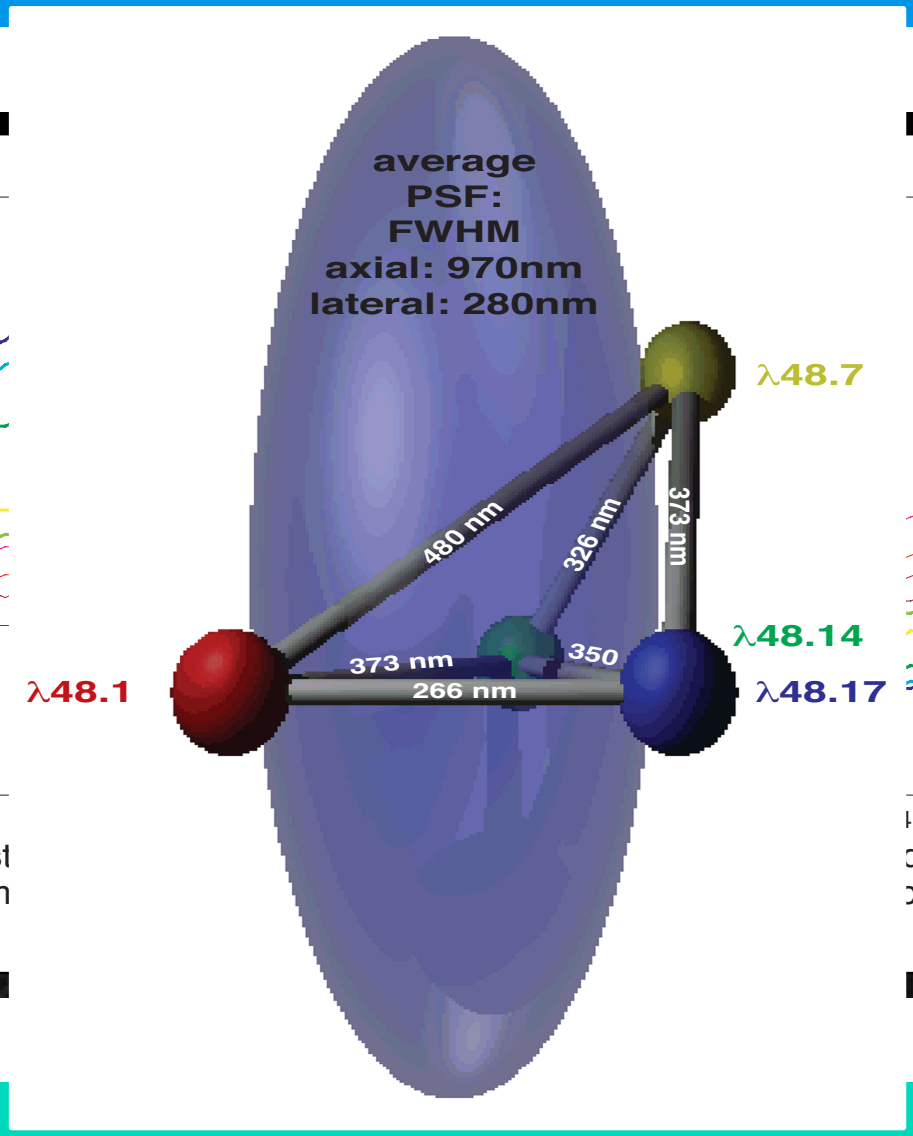
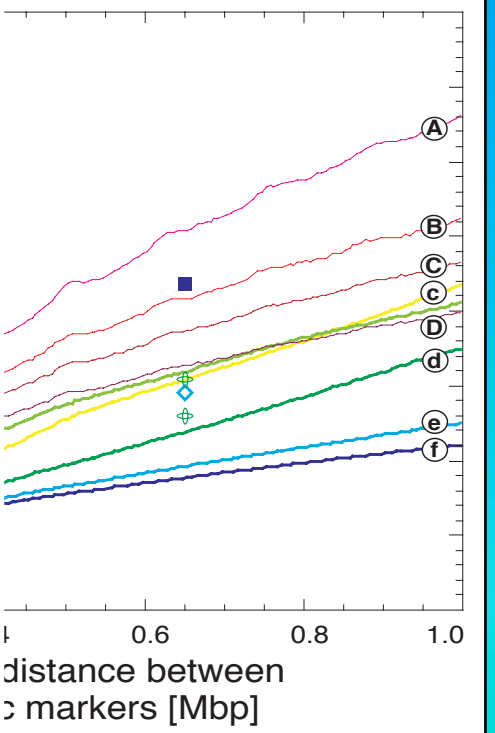
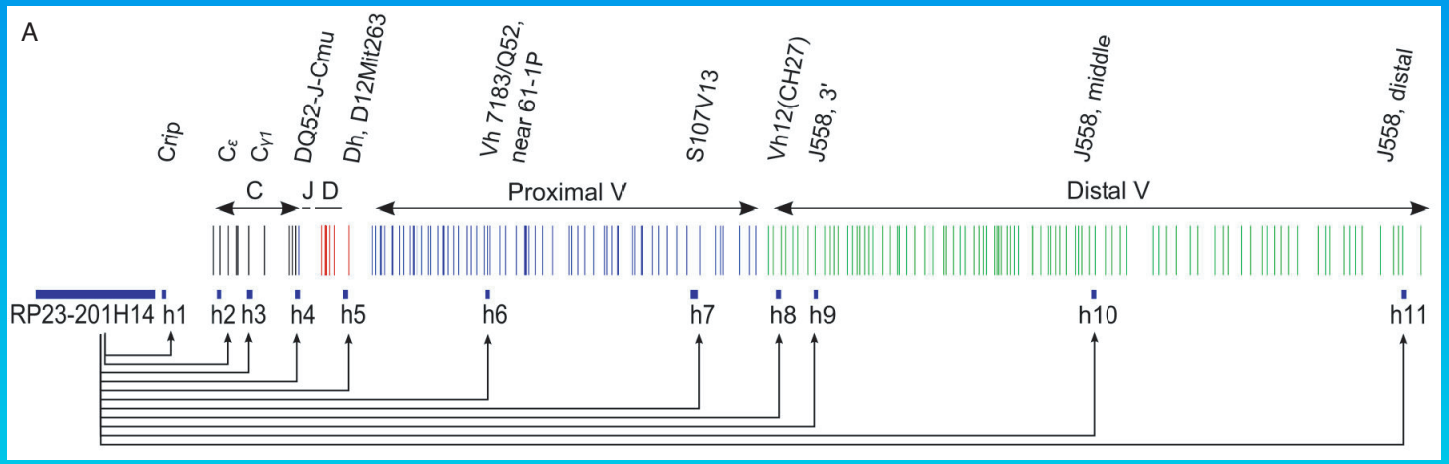


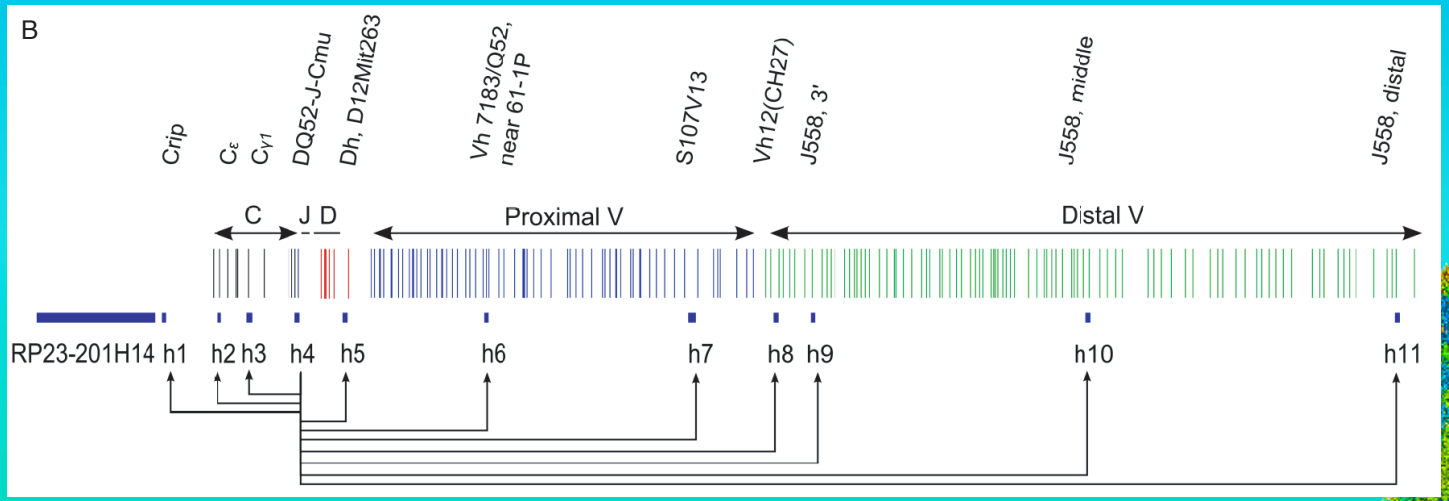


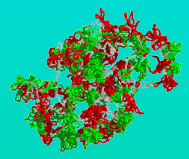


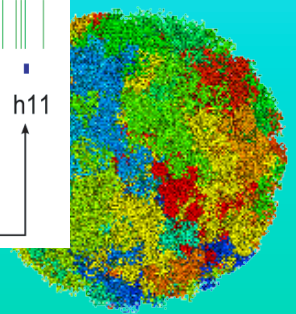
3D Archticture & Function of the IgH Locus

Fluorescence *in situ* hybridization of the IgH locus combined with spectral precision distance epifluorescence microscopy, analytical trilateration and comparison with computer simulations shows again a Multi-Loop Subcompartiment organization of the IgH locus with functional relevant distances.









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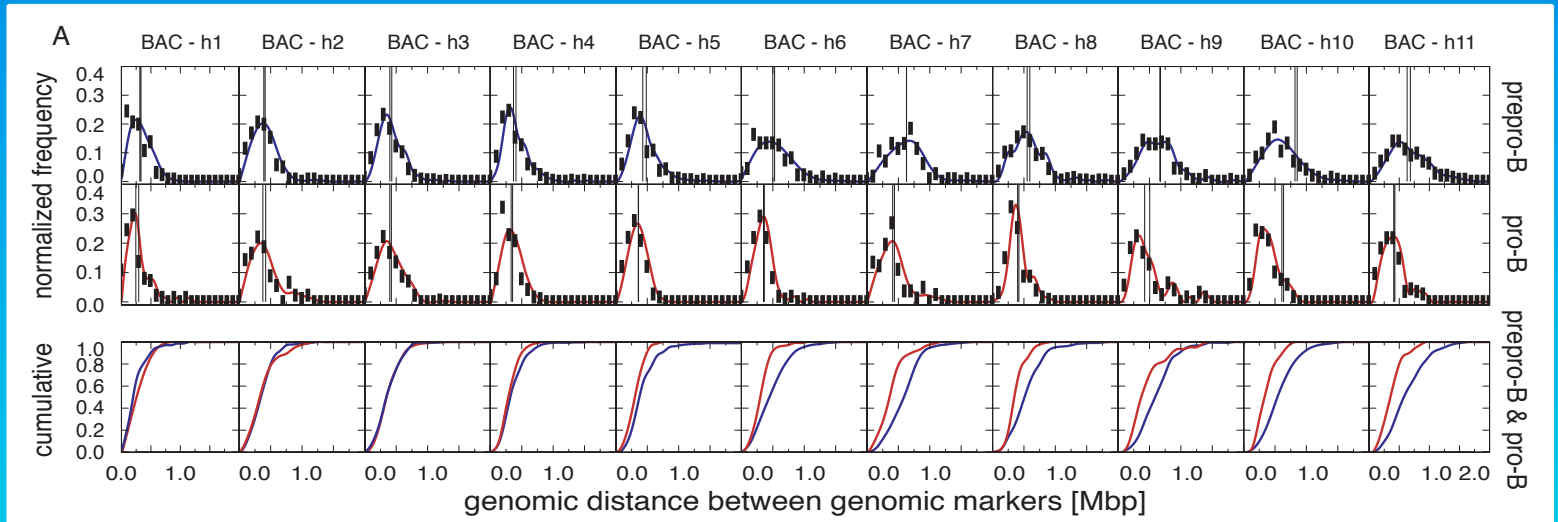

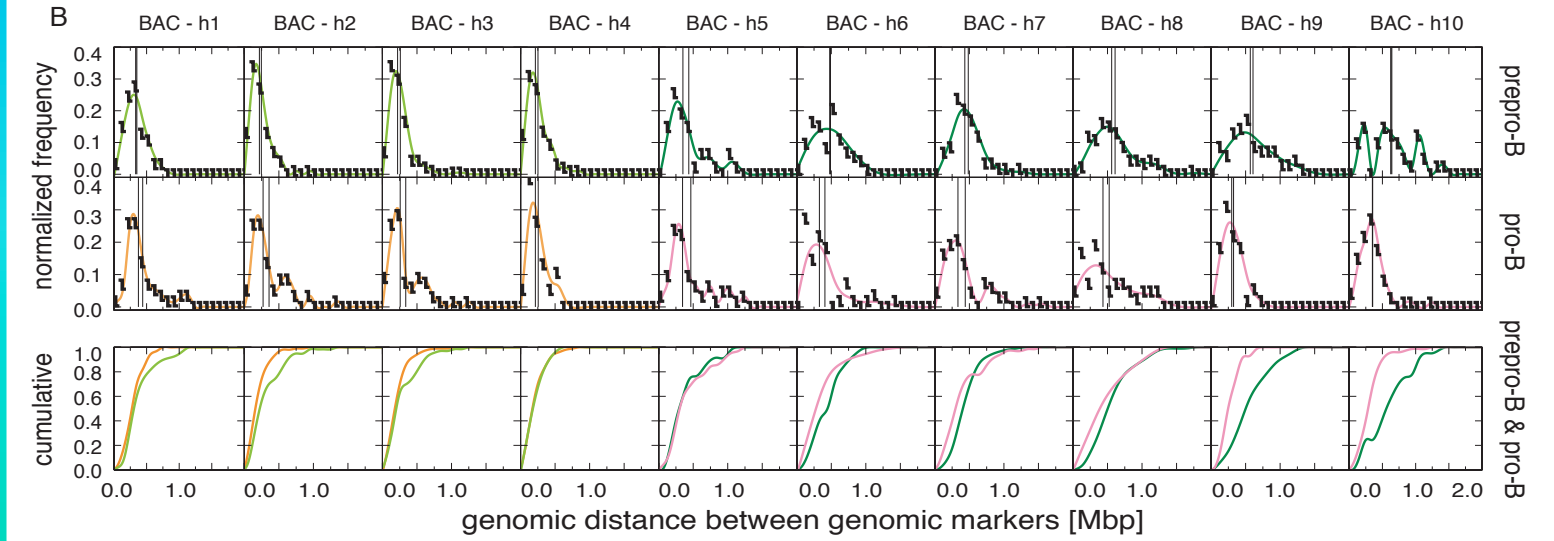

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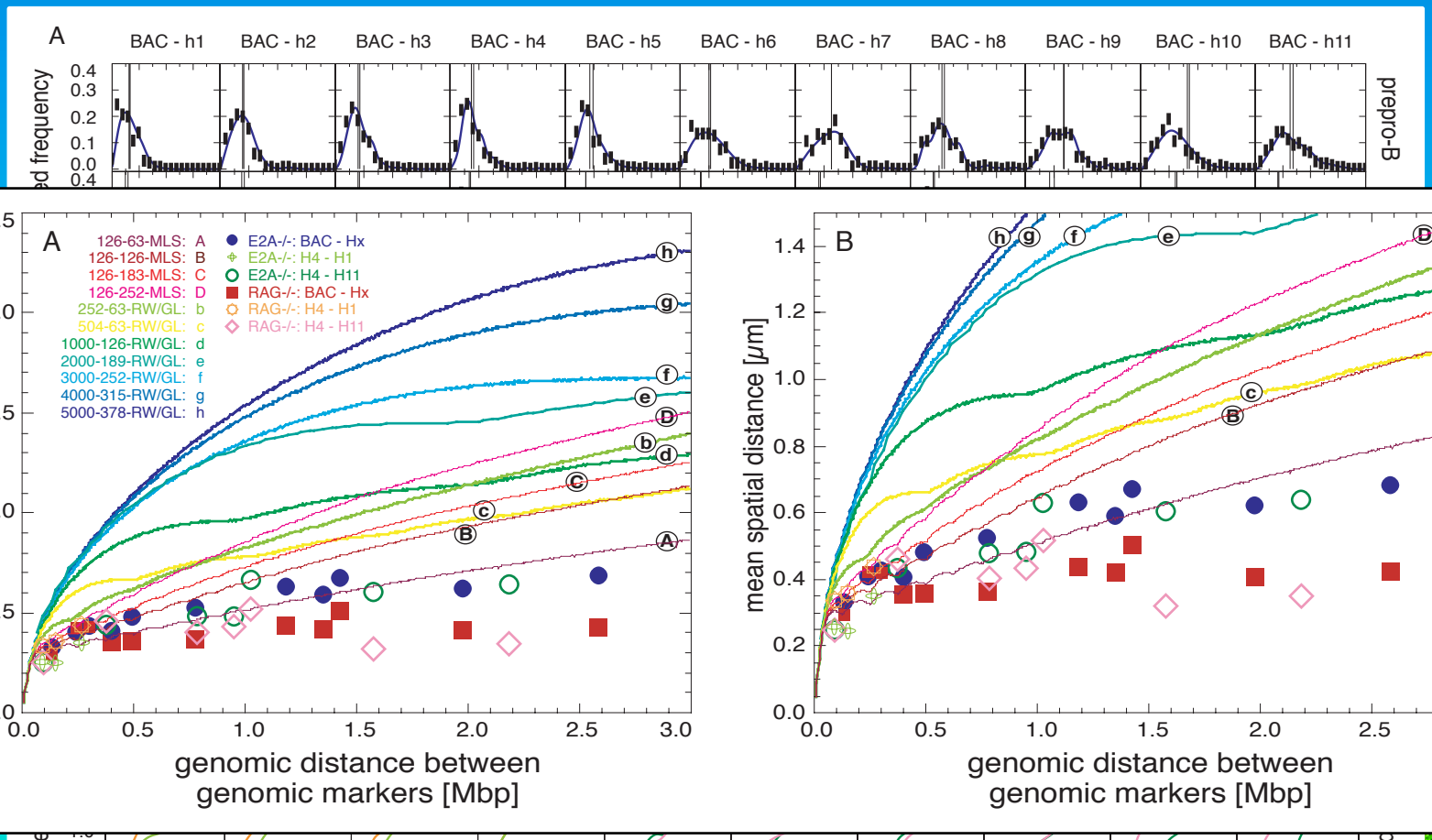

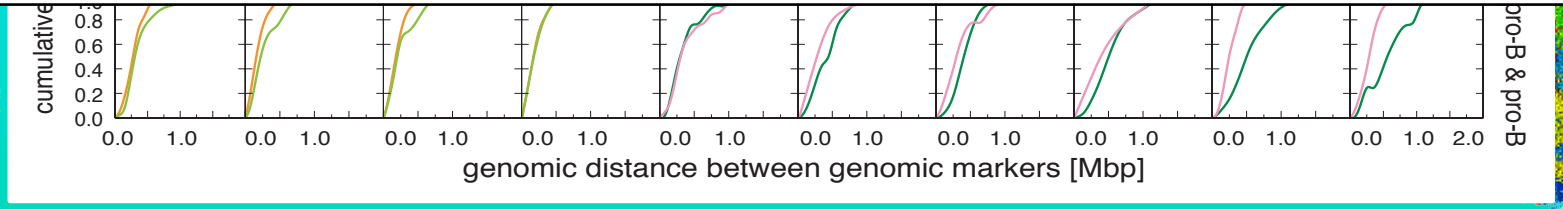

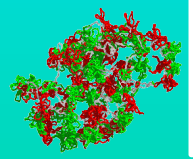

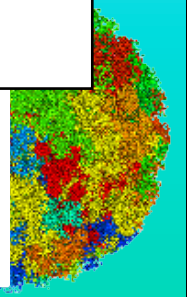

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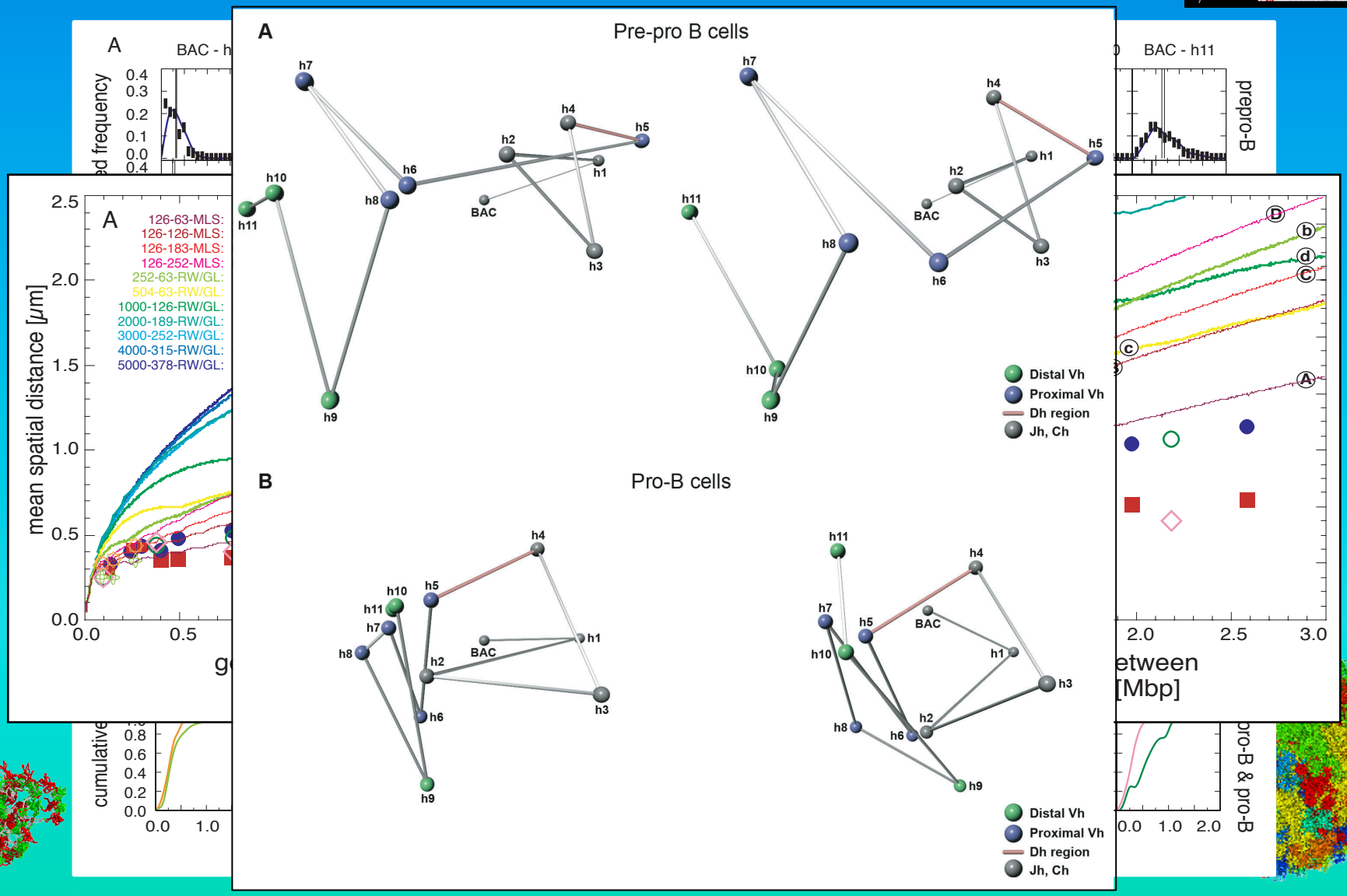
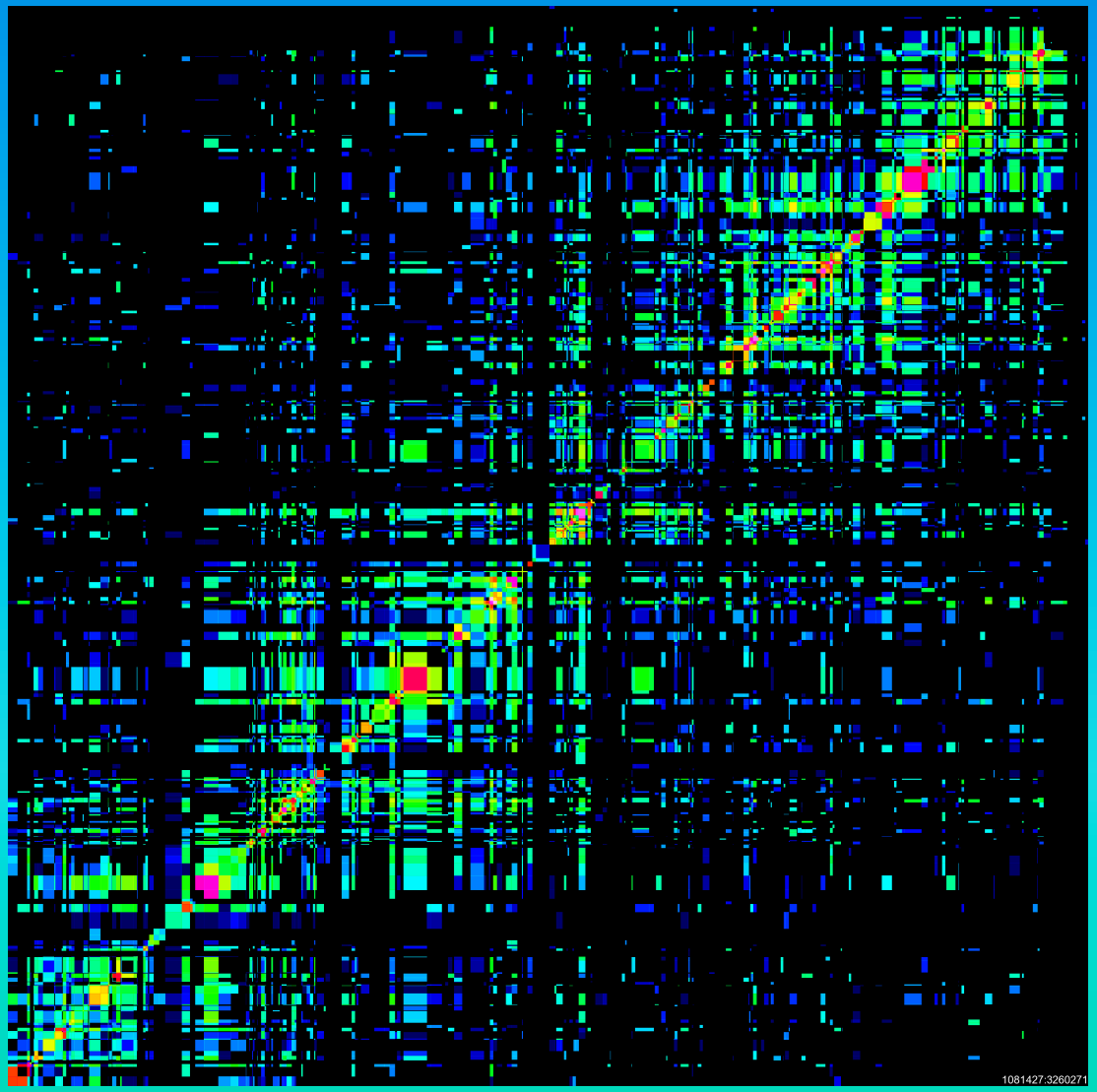
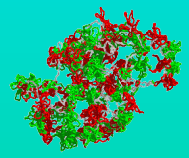


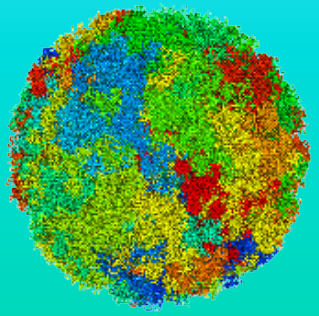
Selective Chromosome Interaction Capture (T2C)

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. T2C reaches the limit of the "genomic" uncertainty principle and statistical mechanics.



HS IGF locus
~2.1 Mbp





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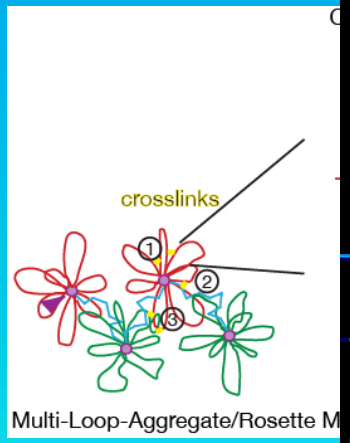
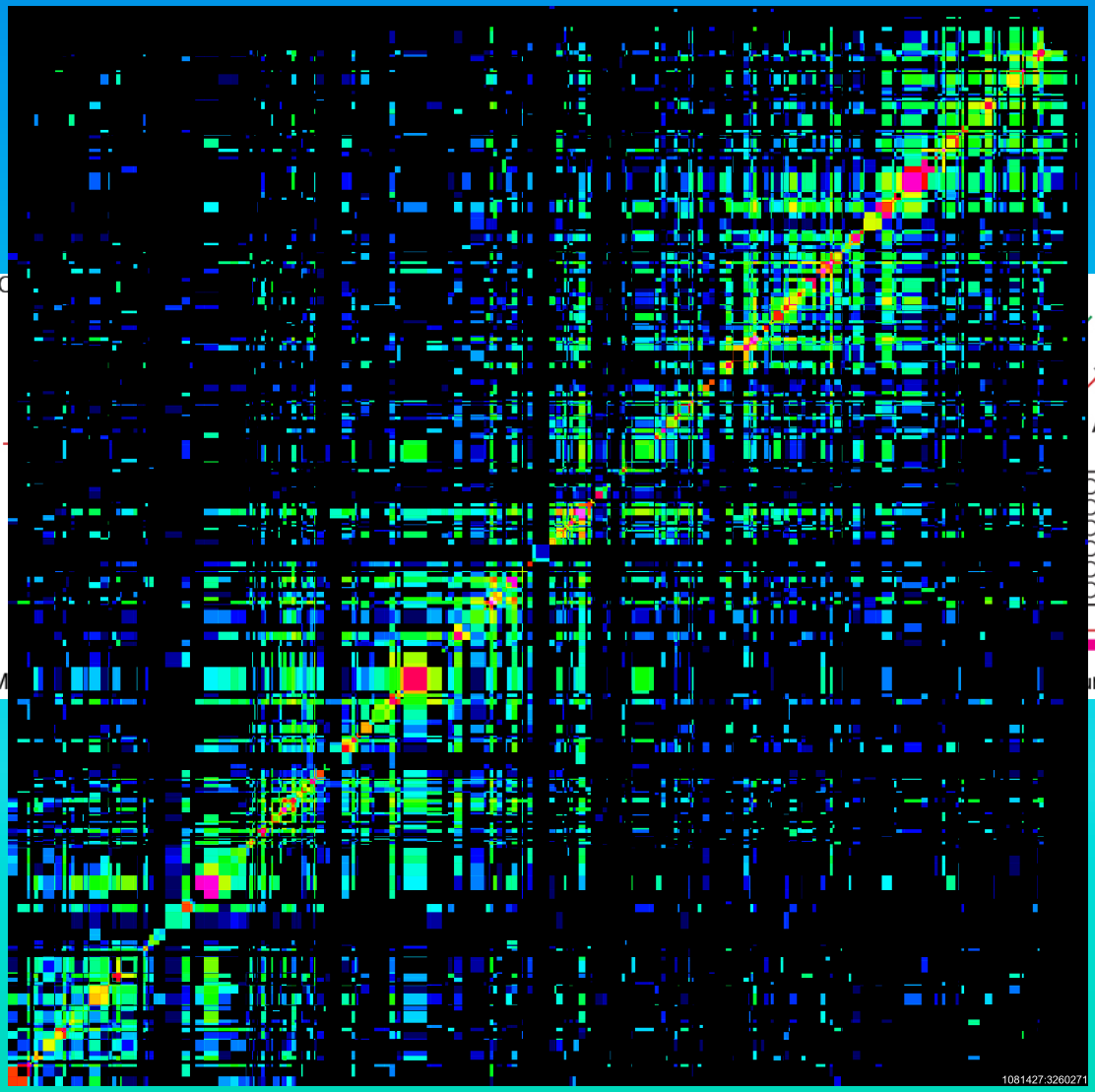
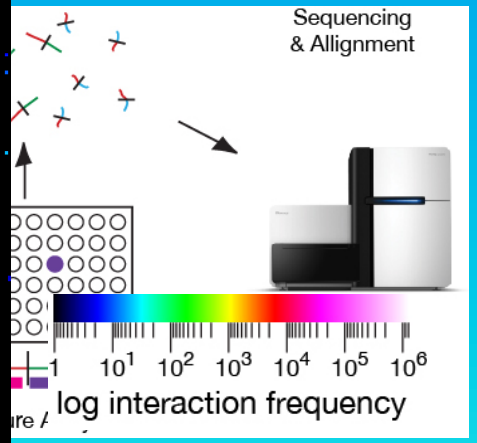
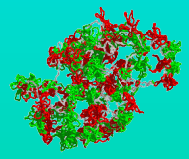
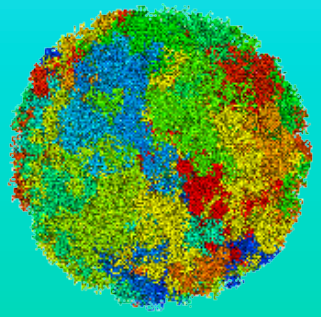


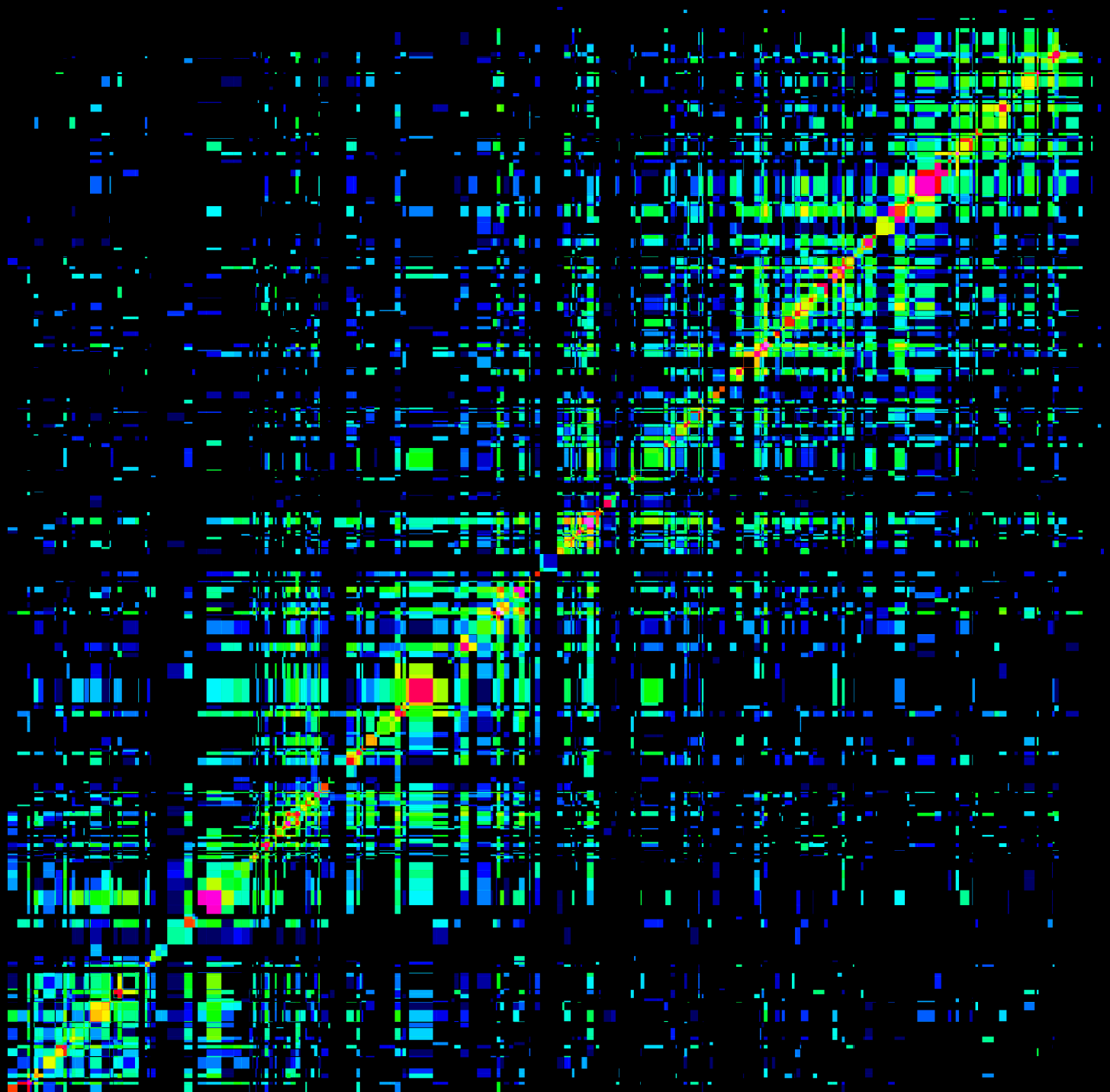




HS IGF locus
~2.1 Mbp



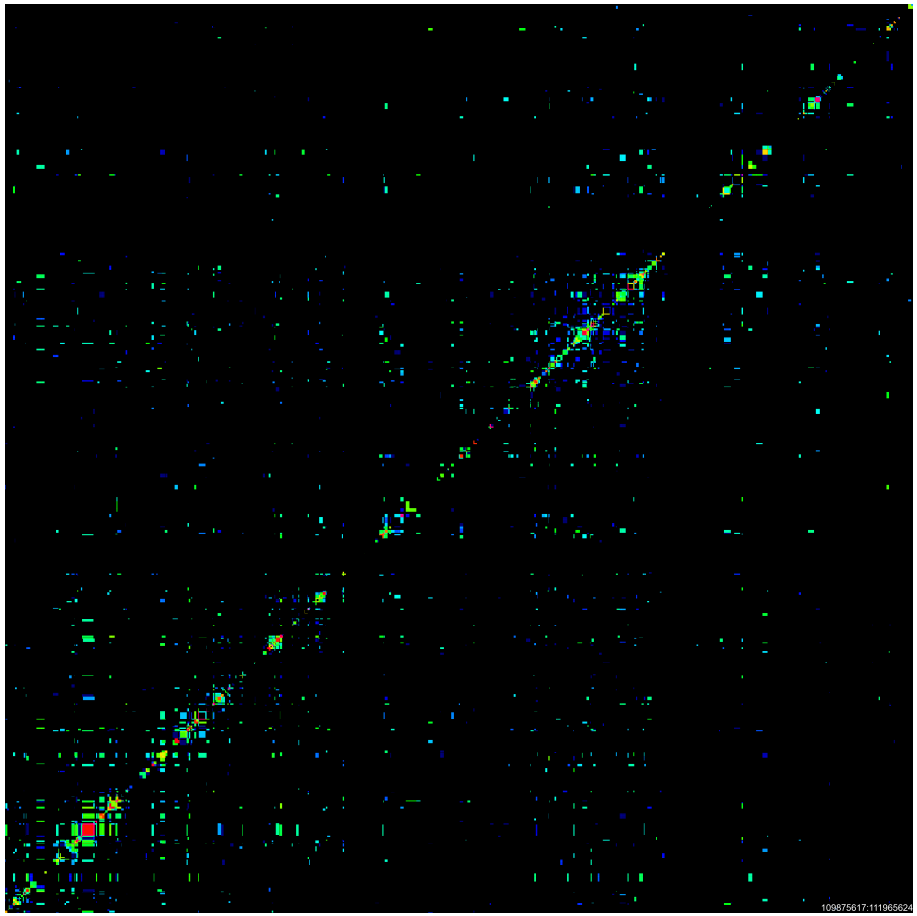




Stable Consensus Architecture of Genomes

Due to the high signal-to-noise ratio of T2C reaching 5-6 orders of magnitude interaction maps reveal definitely an extremely high degree of similarity between different species, cell types, or functional states, thus functional differences are variation of a stable theme persisting through the cell cycle

Fetal Brain (inactive β-Globin)



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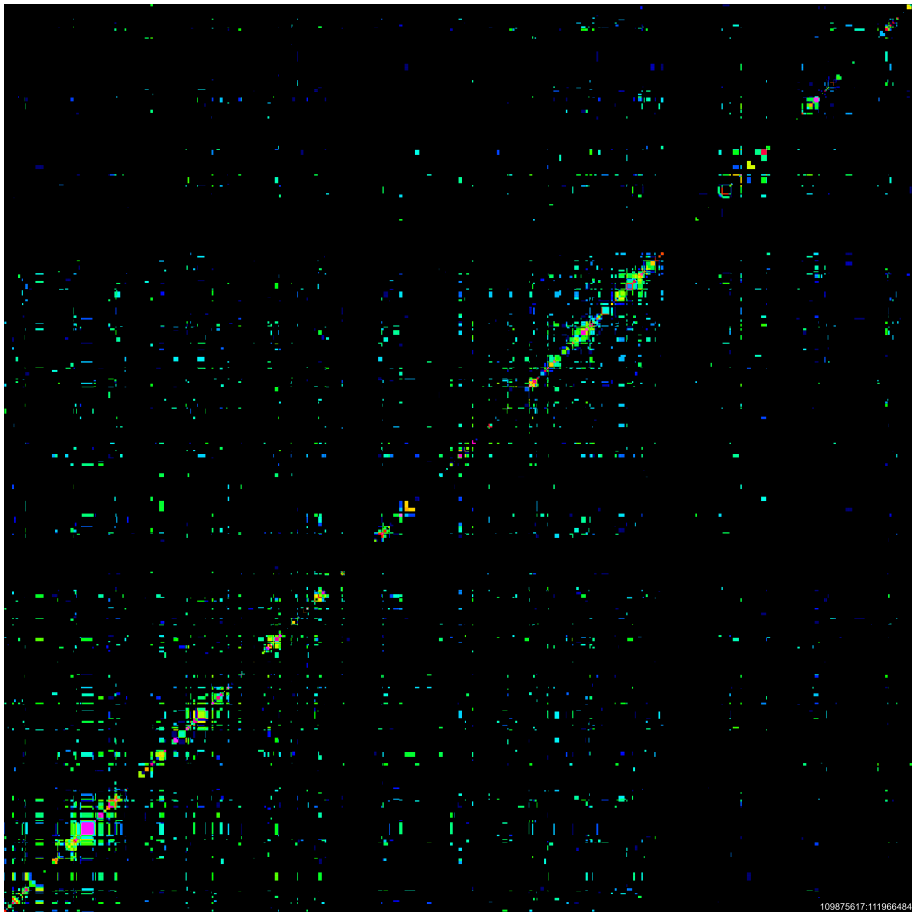

MM β-Globin 2.1 Mbp

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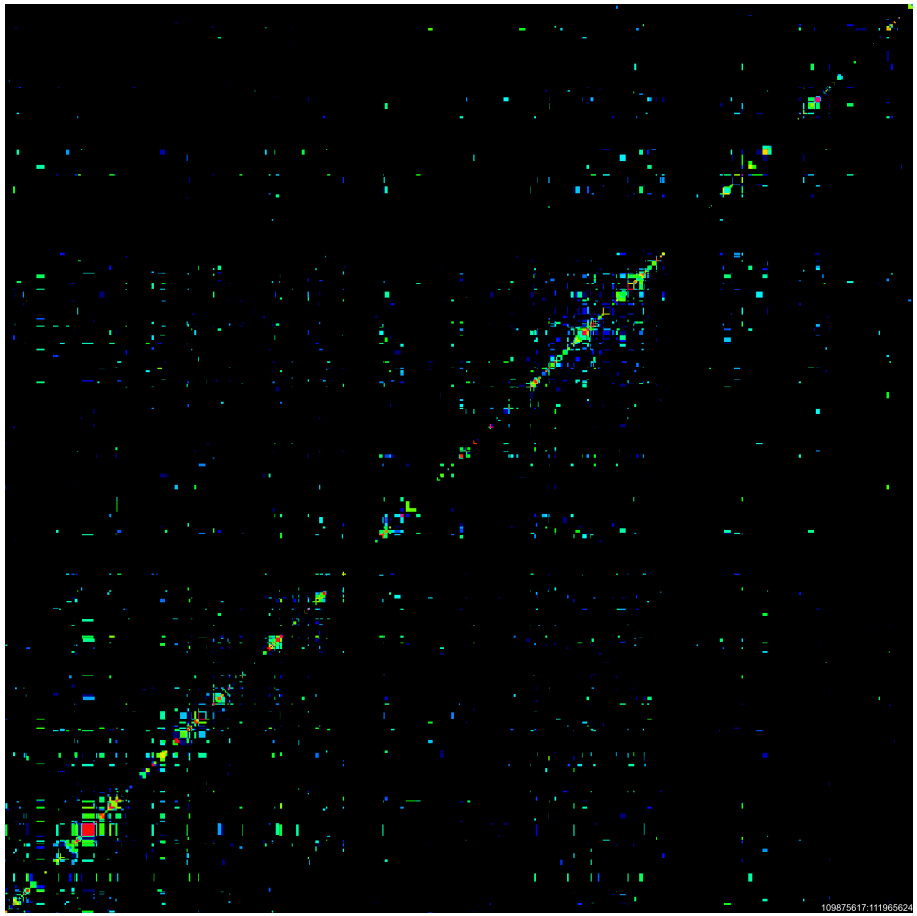

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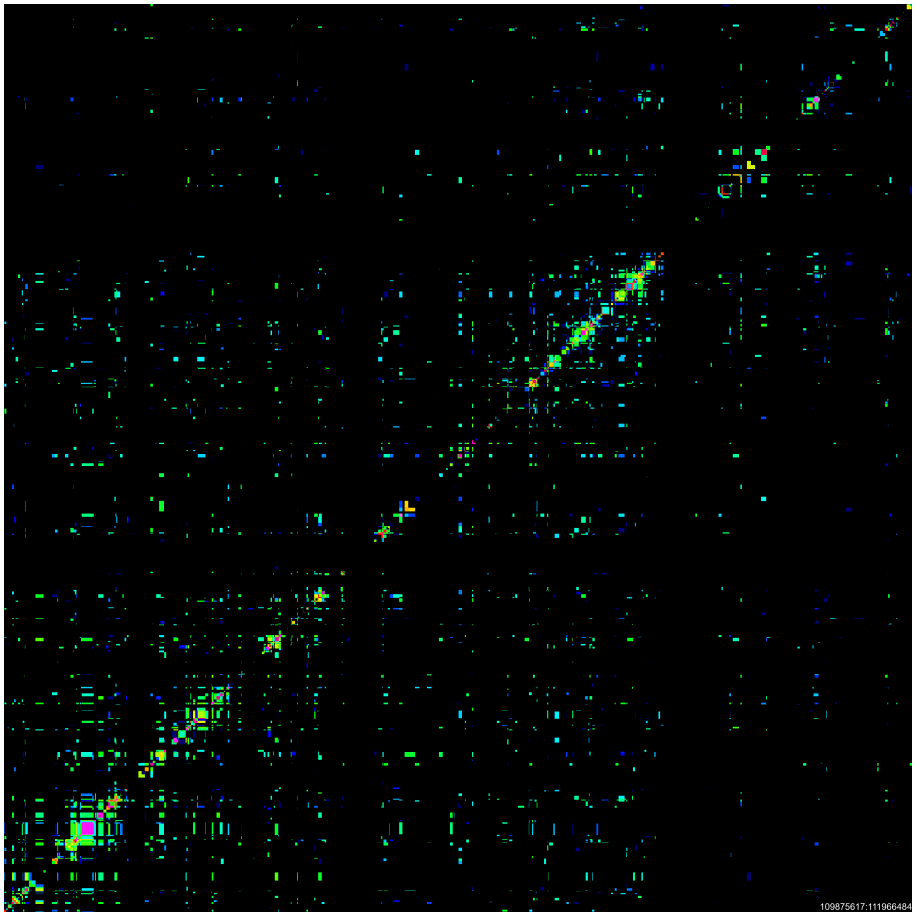

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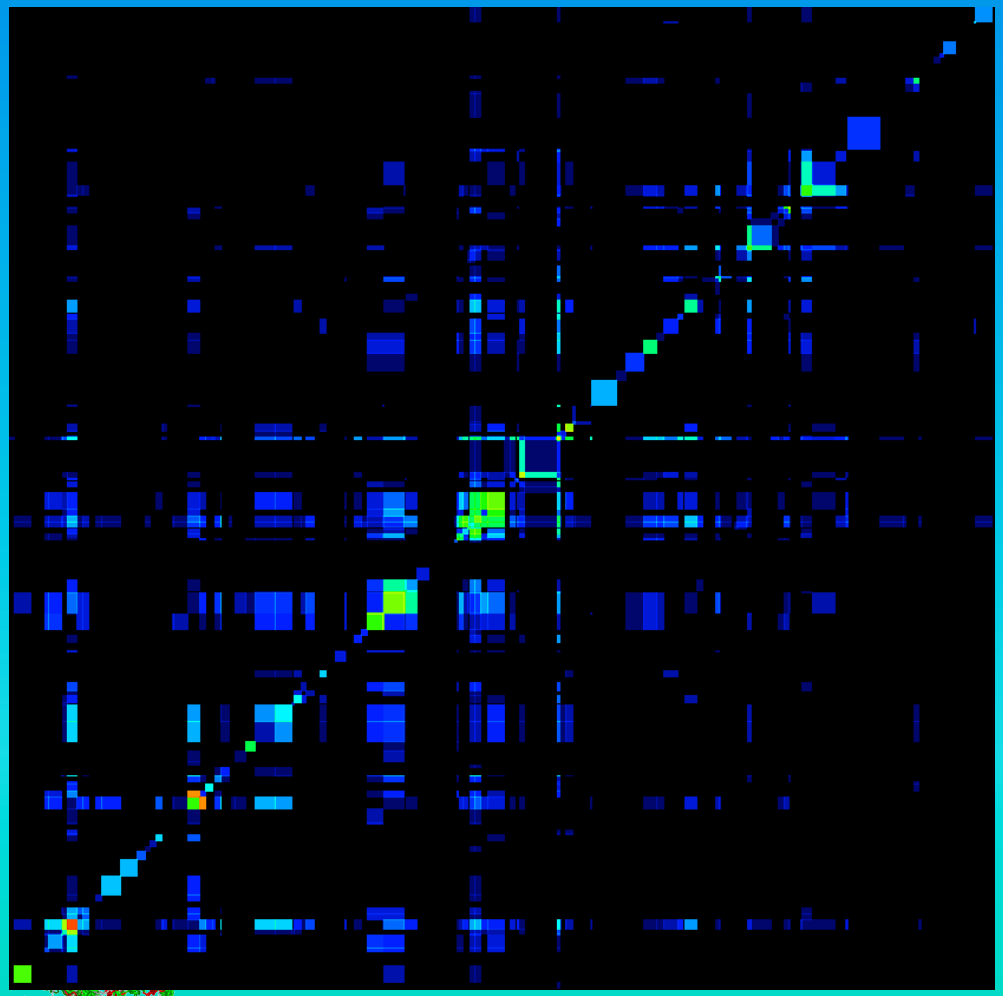
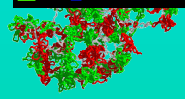
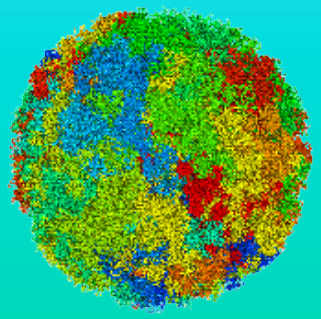
Fine Structure of Loop Aggregates/Rosettes

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.



~ 400 kbp





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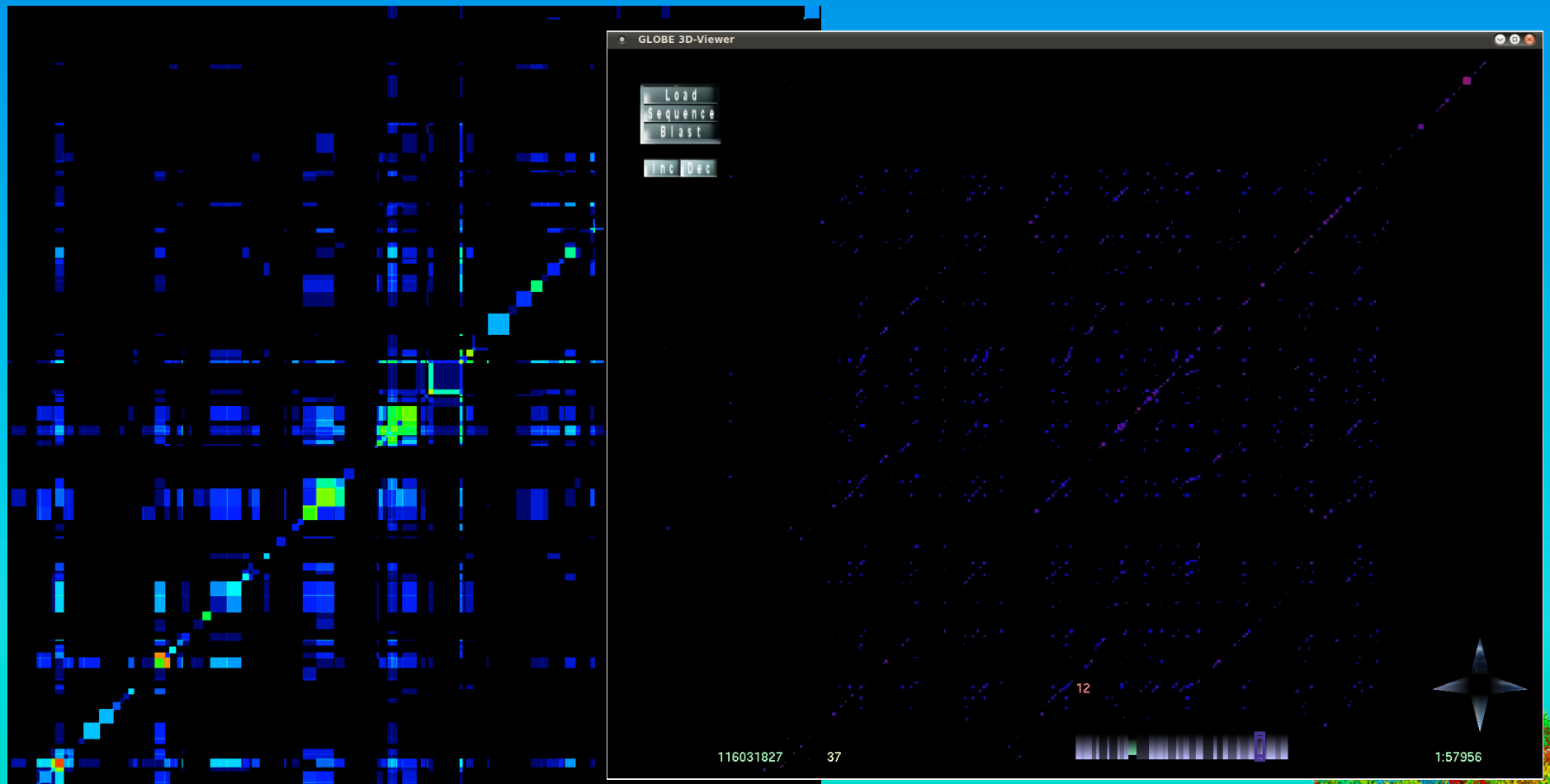

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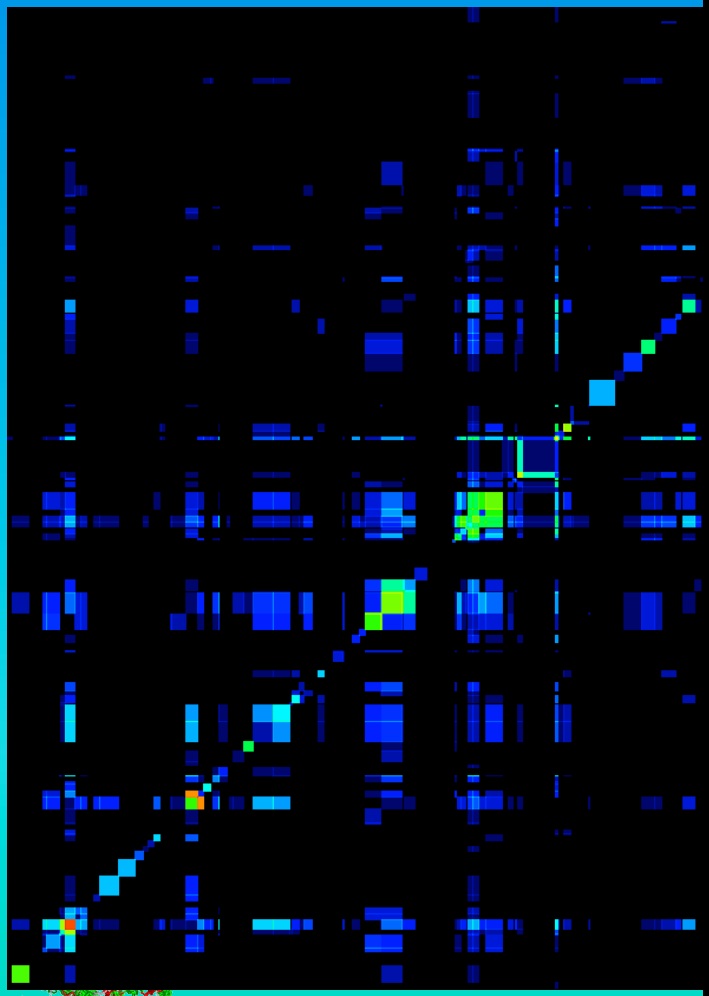
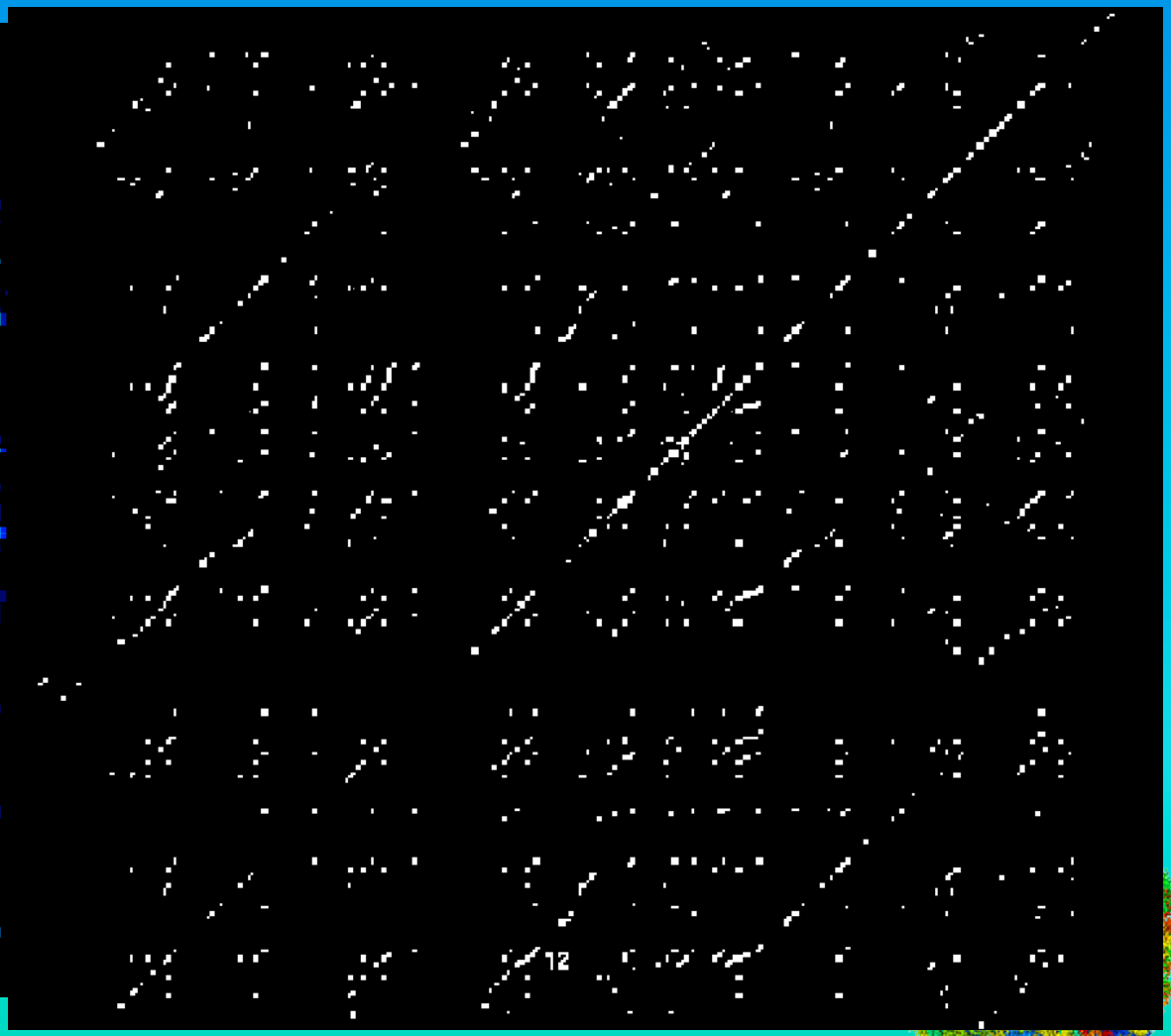


~ 400 kbp



~ 380 kbp

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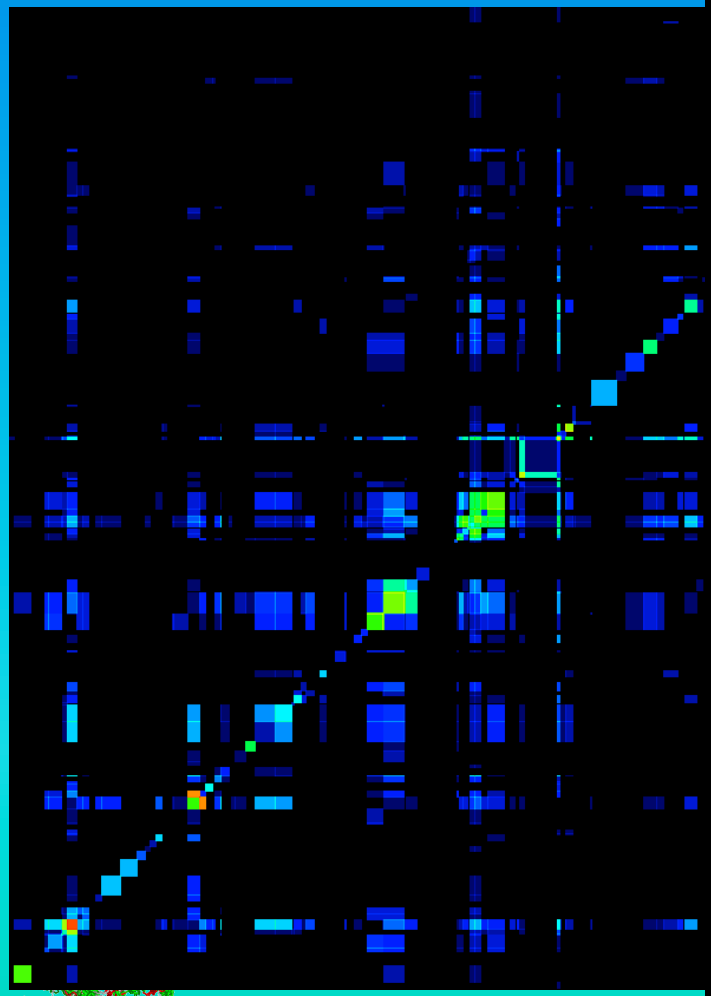
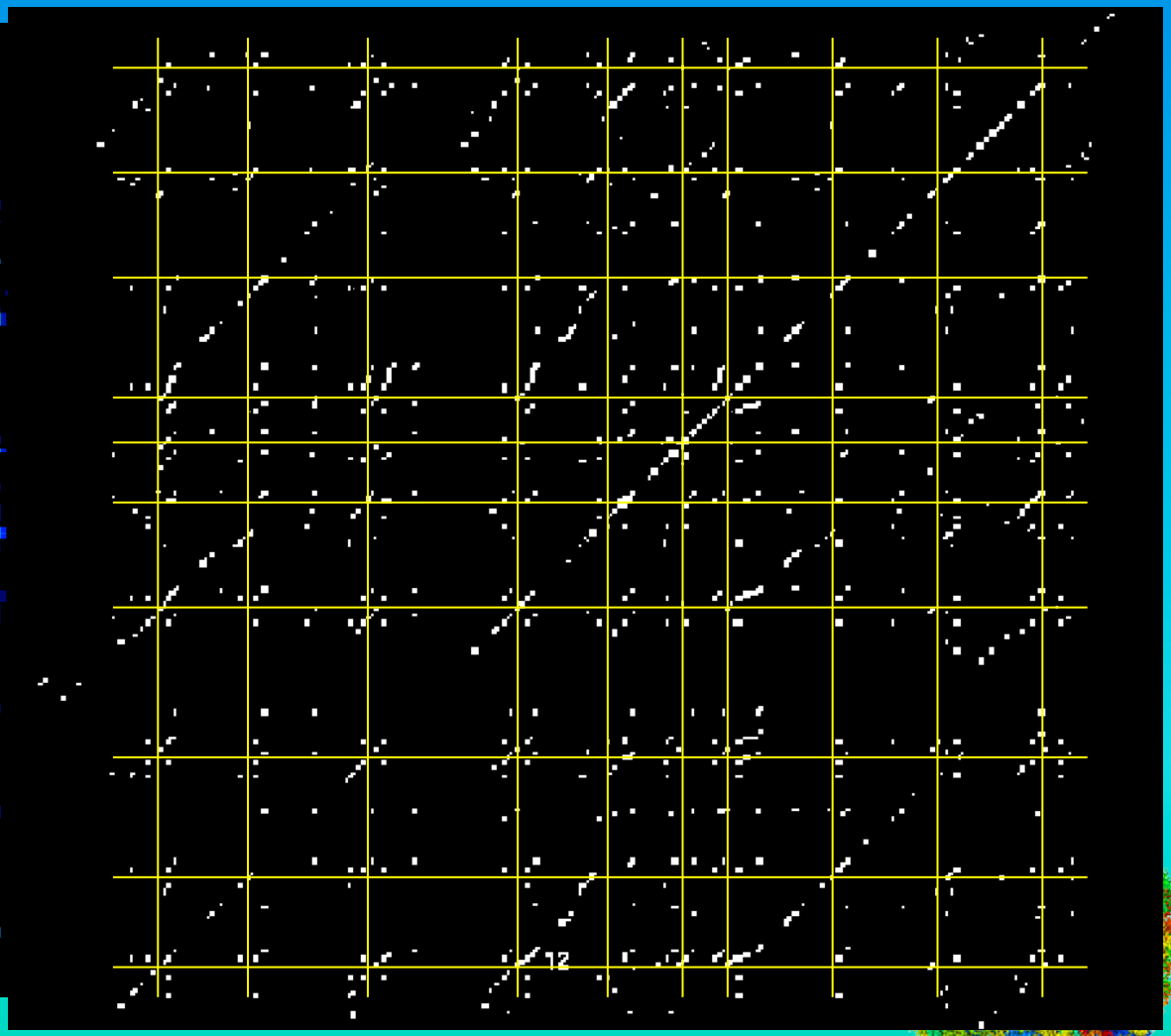


~ 400 kbp



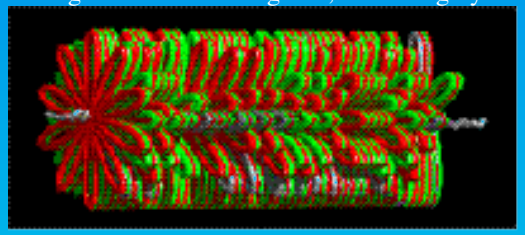
~ 380 kbp

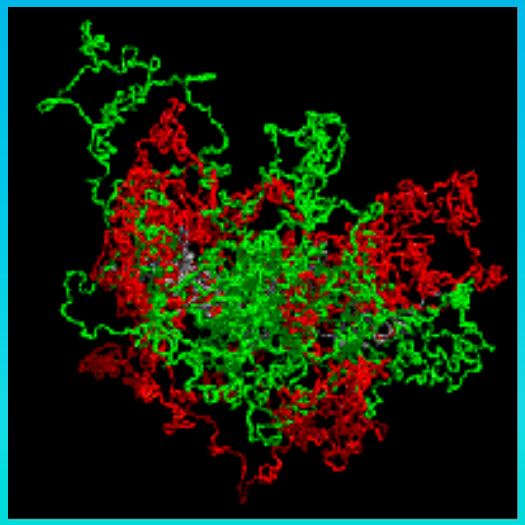
Simulation of Single Chromosomes

The 30 nm chromatin fiber is modeled as a polymer chain with stretching, bending, and excluded volume interactions. Monte Carlo and Brownian Dynamic methods lead to thermodynamical equilibrium configurations.

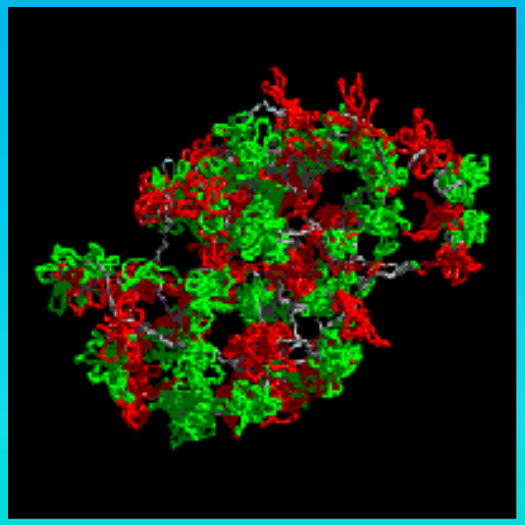
All models form chromosome territories with big voids and different chromatin morphologies. Experimental territory and subcompartment diameters agree best with an MLS model with 80 to 120 kbp loops and linkers.

Metaphase starting configuration with ideogram bands in red/green, linker in grey.

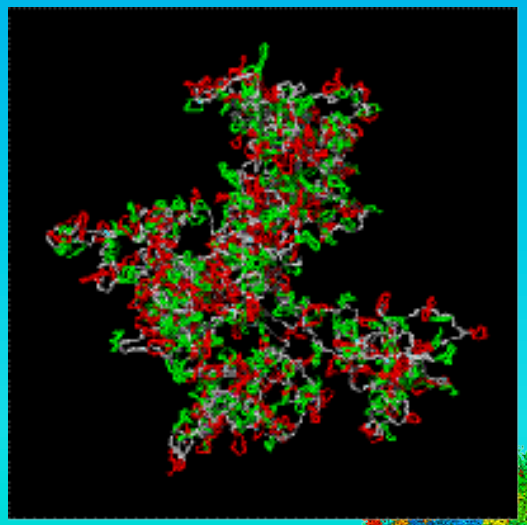




RW/GL model, loop size 5 Mbp, after ~80.000 MC and 1000 relaxing BD steps. Large loops intermingle freely and reach out of the chromsome territory, thus forming no distinct features like in MLS model.



MLS model, loop size 126kbp, linker size 126 kbp, after ~50.000 MC and 1000 relaxing BD steps. Here rosettes form subcompartments as separated organizational and dynamic entities.



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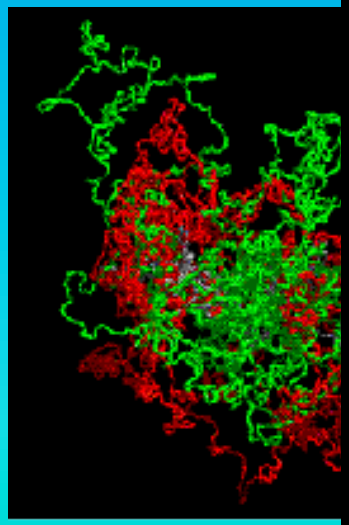
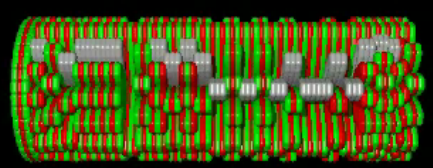


RW/GL model, loop size [redacted] ~80.000 MC and 1000 relaxing BD steps. Large loops intermingle freely and reach out of the chromsome territory, thus forming no distinct features like in MLS model.



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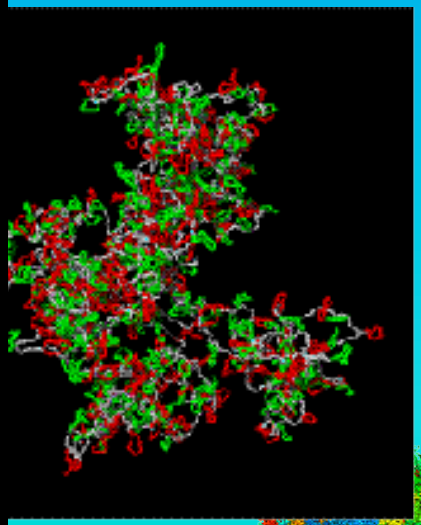

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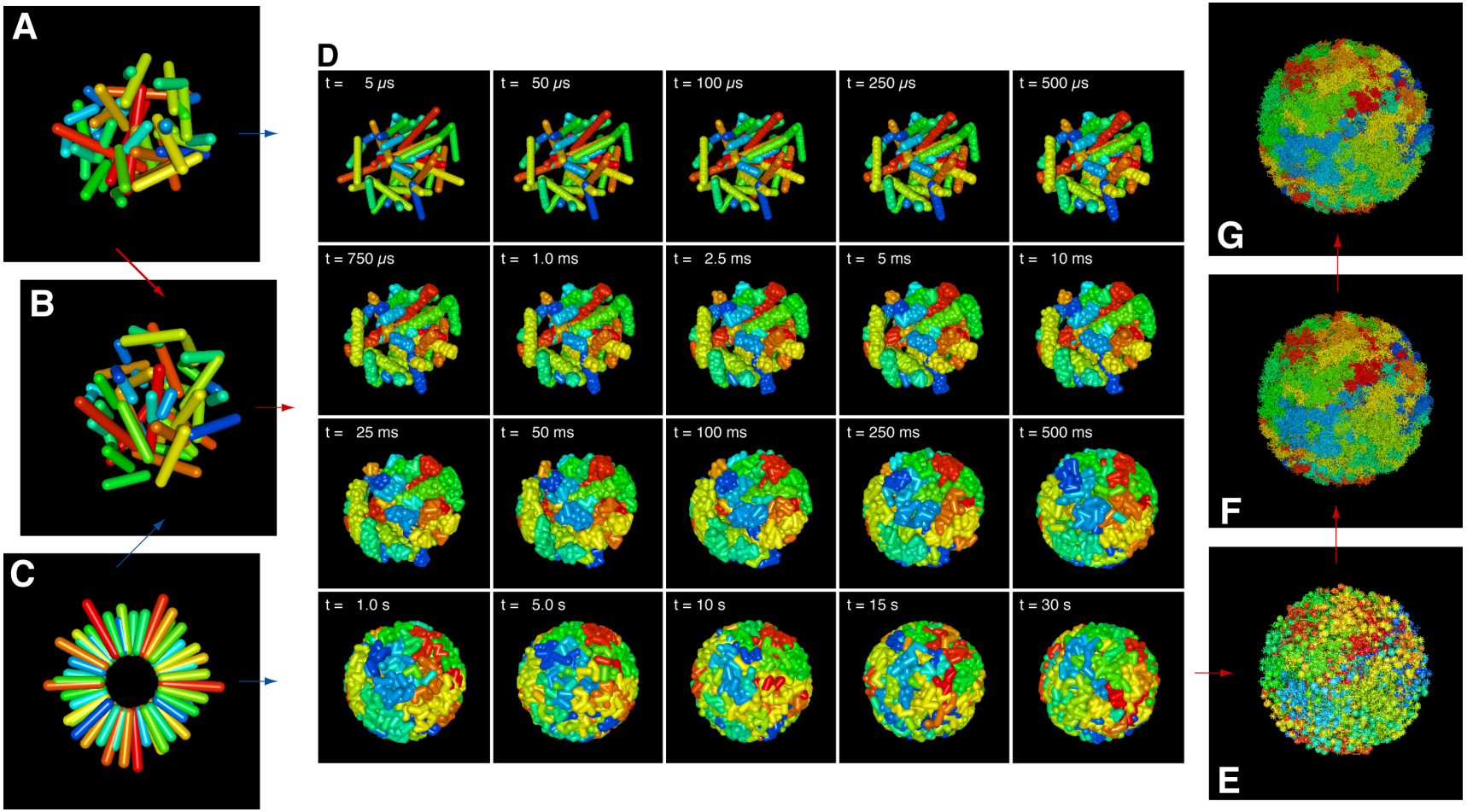
Simulation of Whole Nuclei with all 46 Chromosomes

Starting with some metaphase arrangement of cylindrical chromosomes, interphase nuclei with a 30 nm fiber resolution and at thermodynamical equilibrium are created in 4 steps using simulated annealing and Brownian Dynamics methods with stretching, bending, excluded volume and a spherical boundary interactions.

The chromosome territory position depends on their metaphase position and is reasonably stable.



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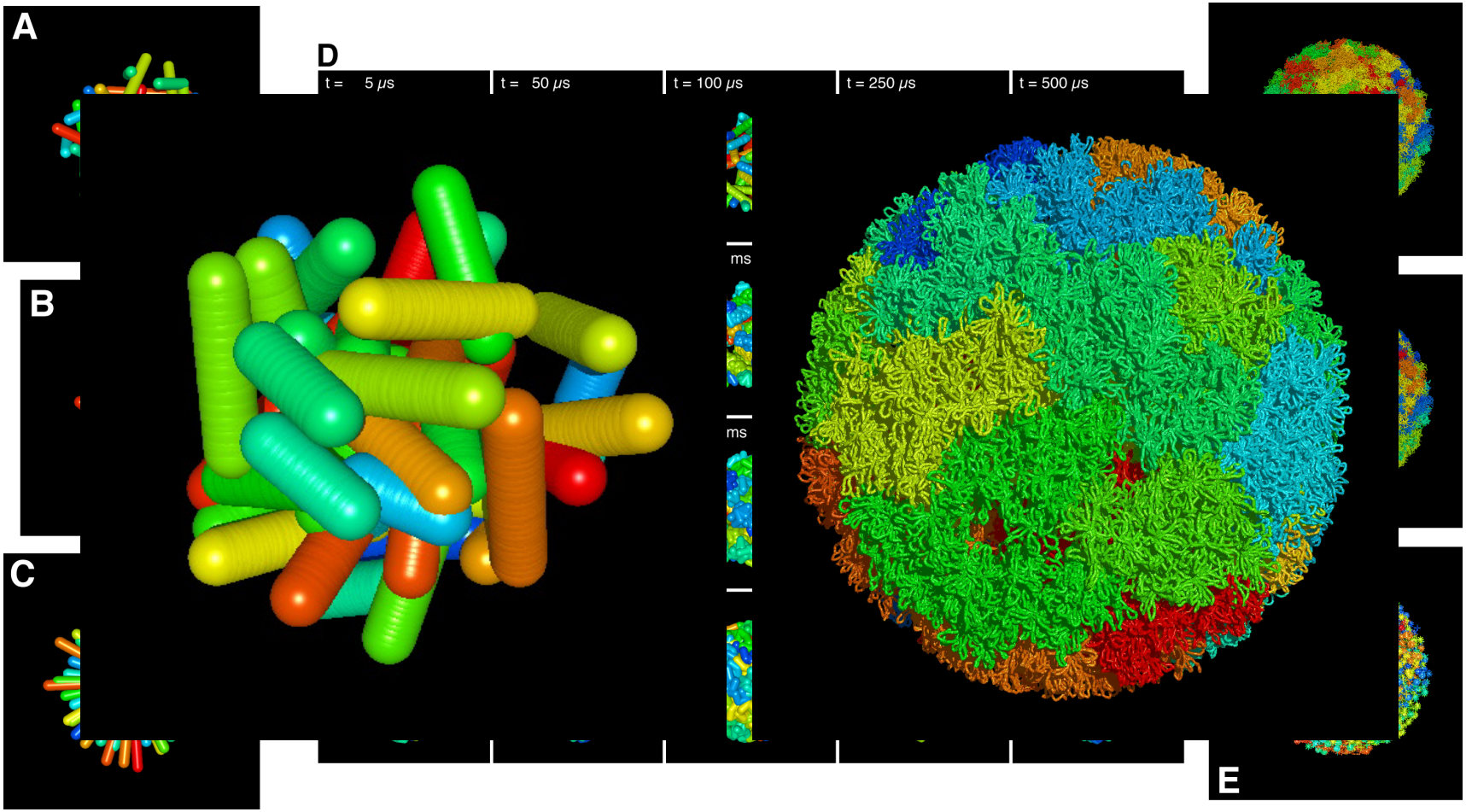
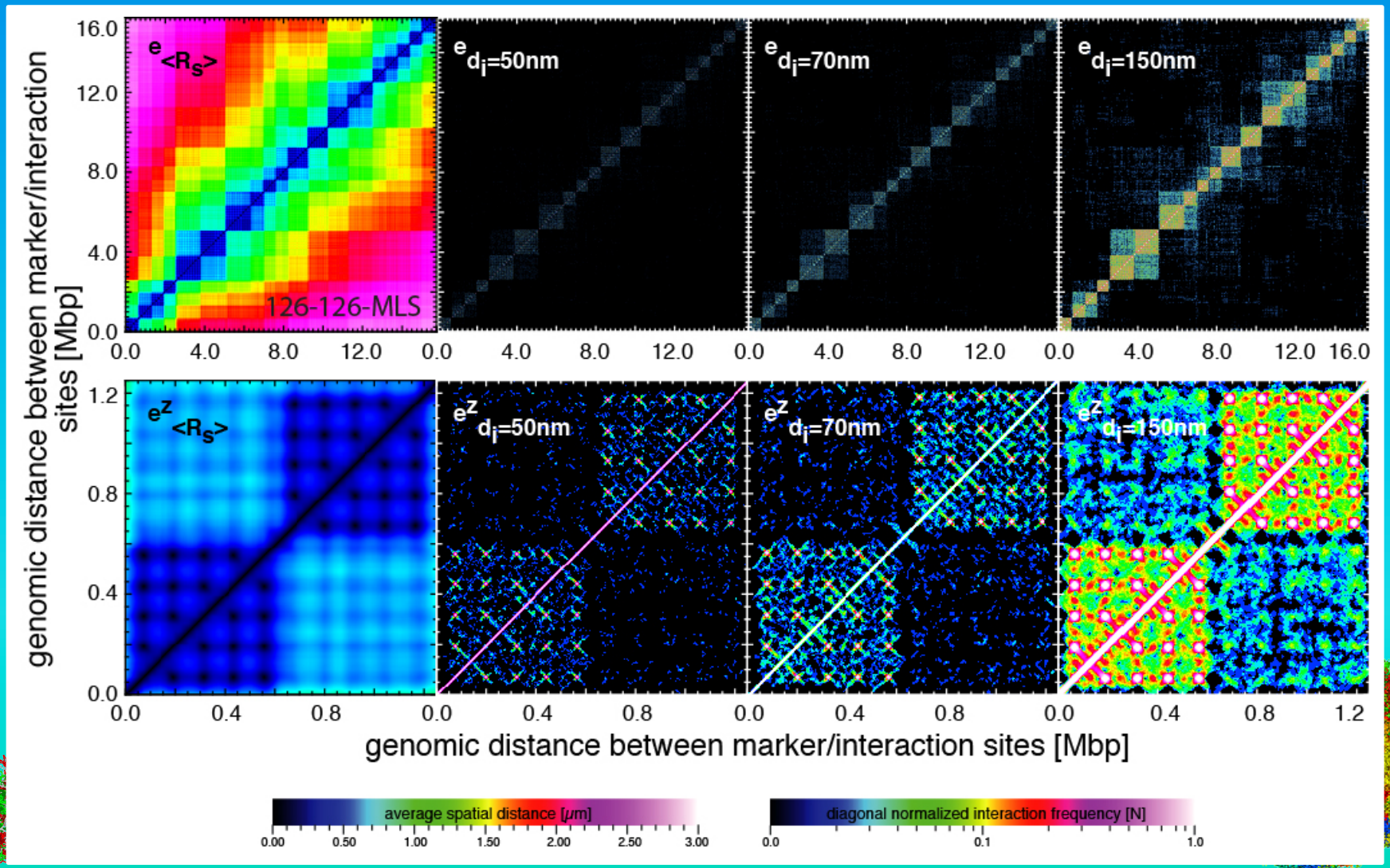


Simulated Interaction Maps

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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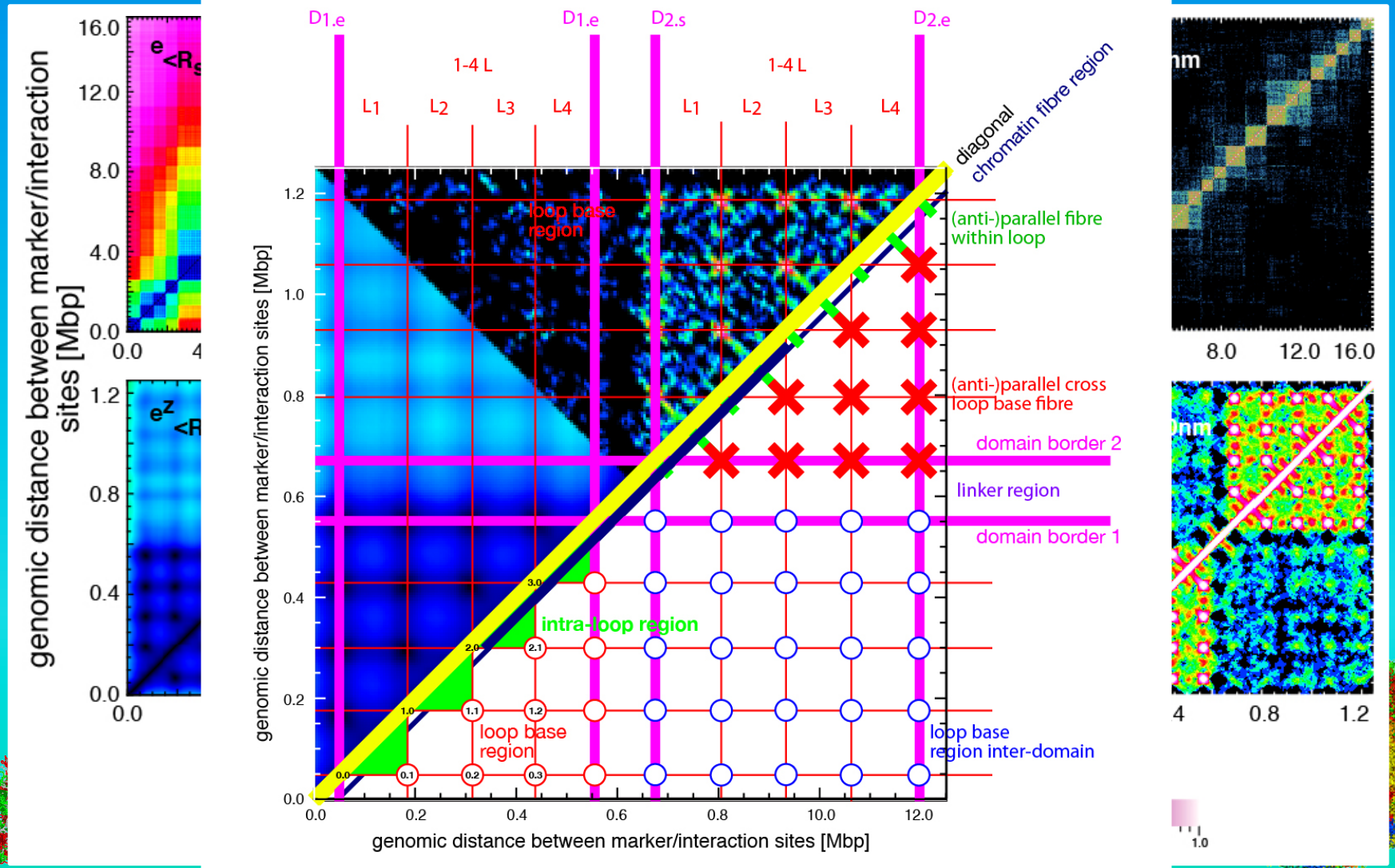
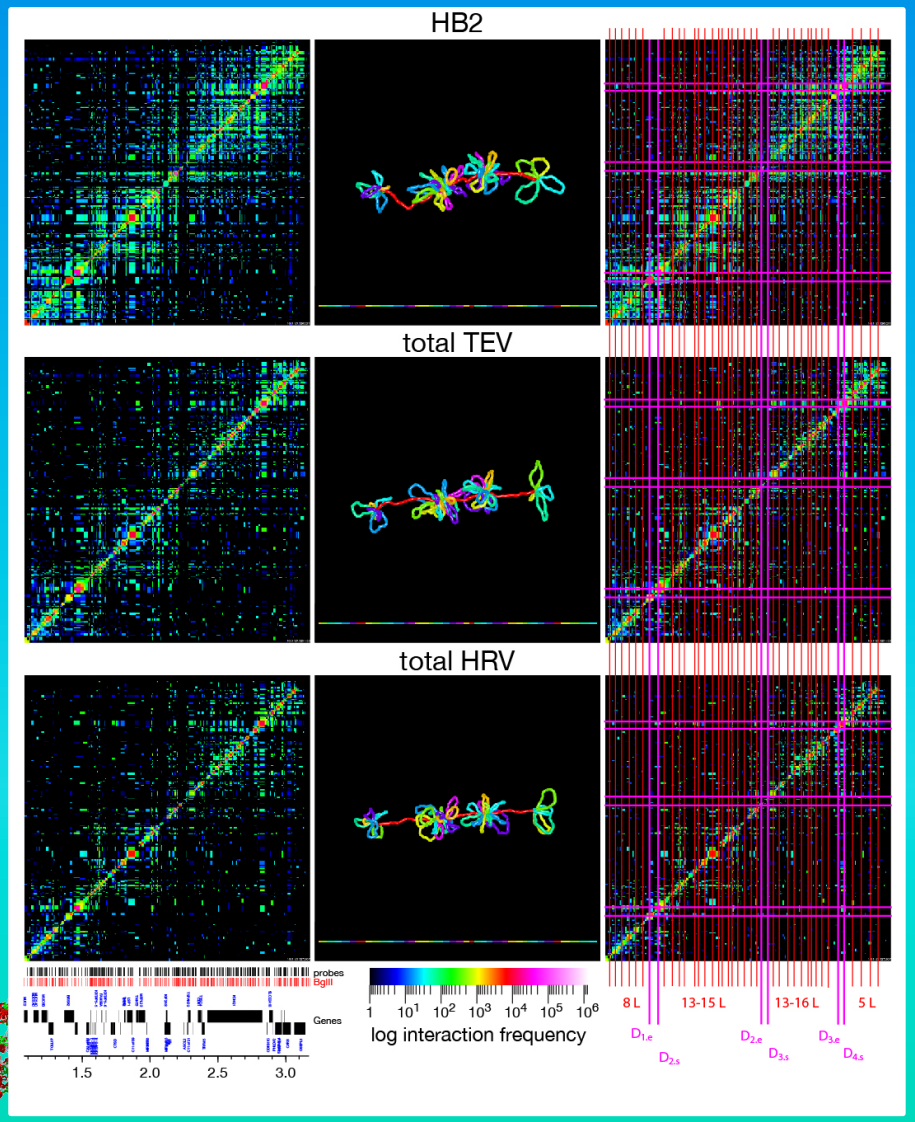
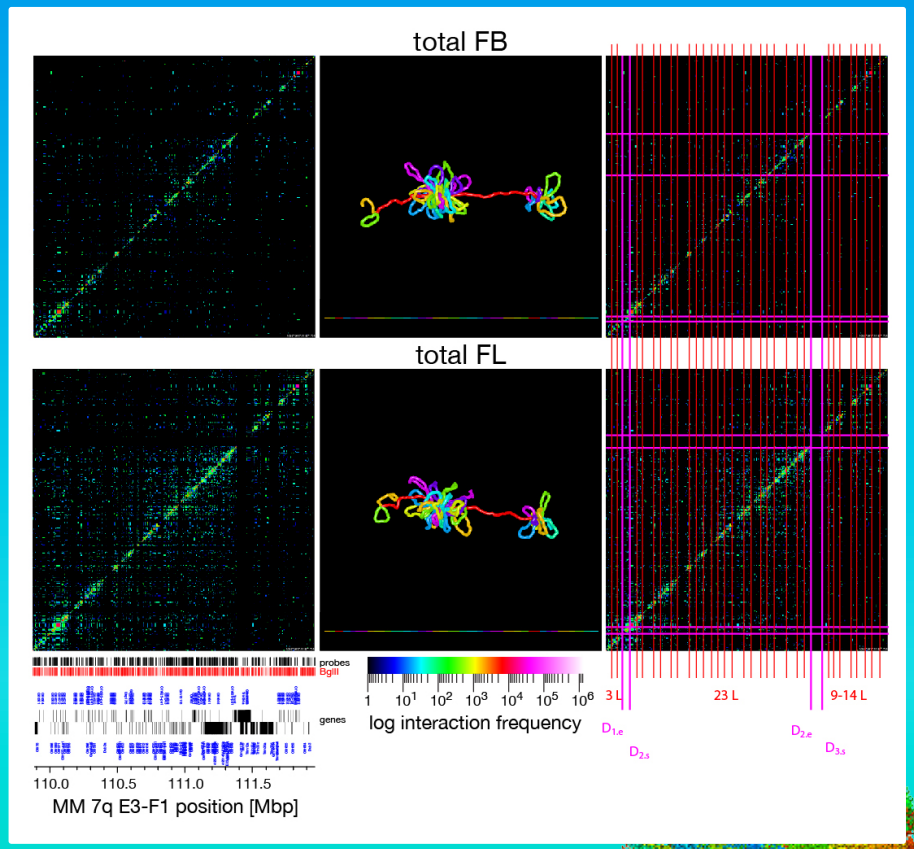


Variation of a Consensus Architecture Scheme

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.





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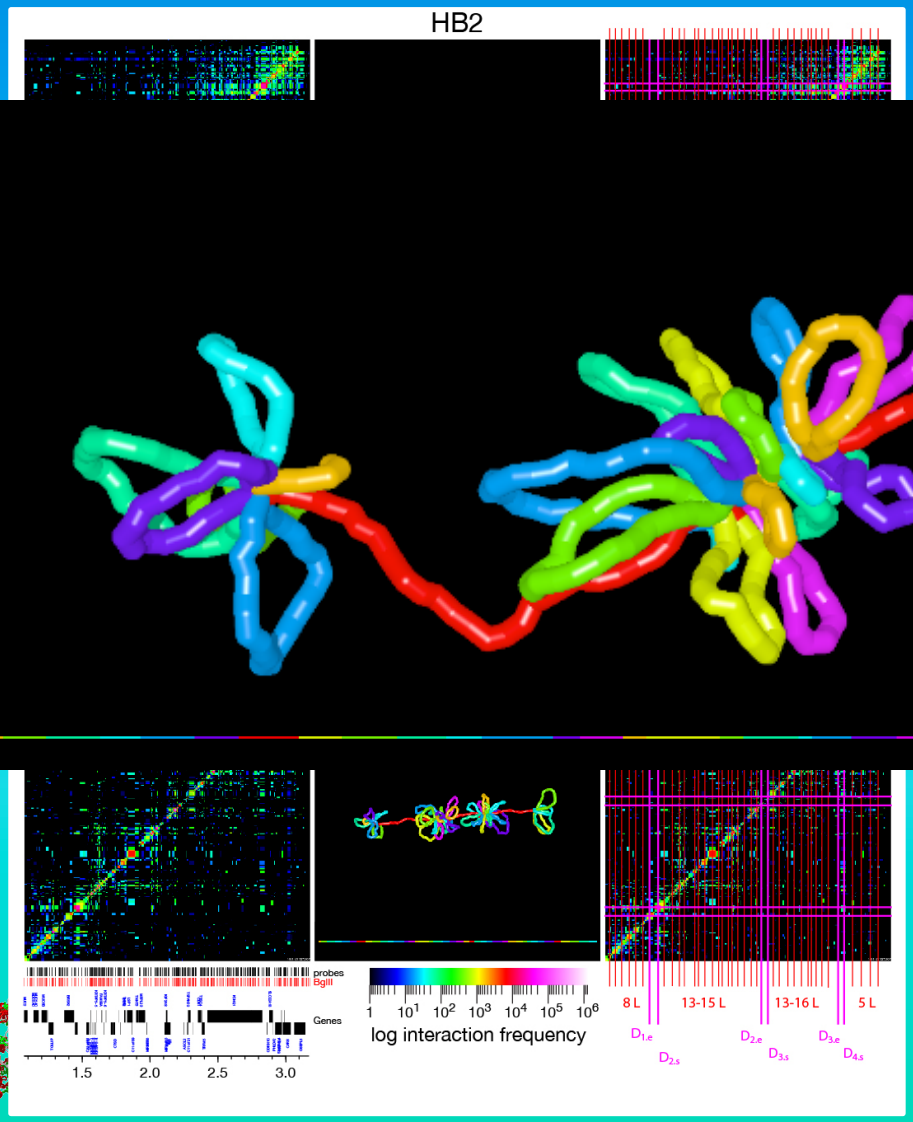

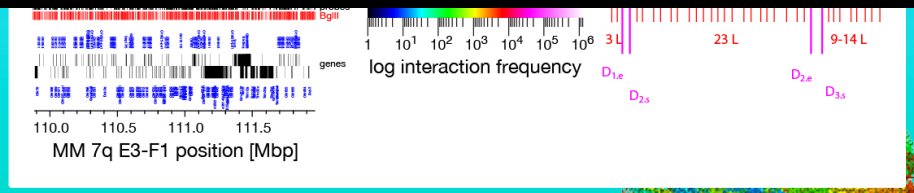

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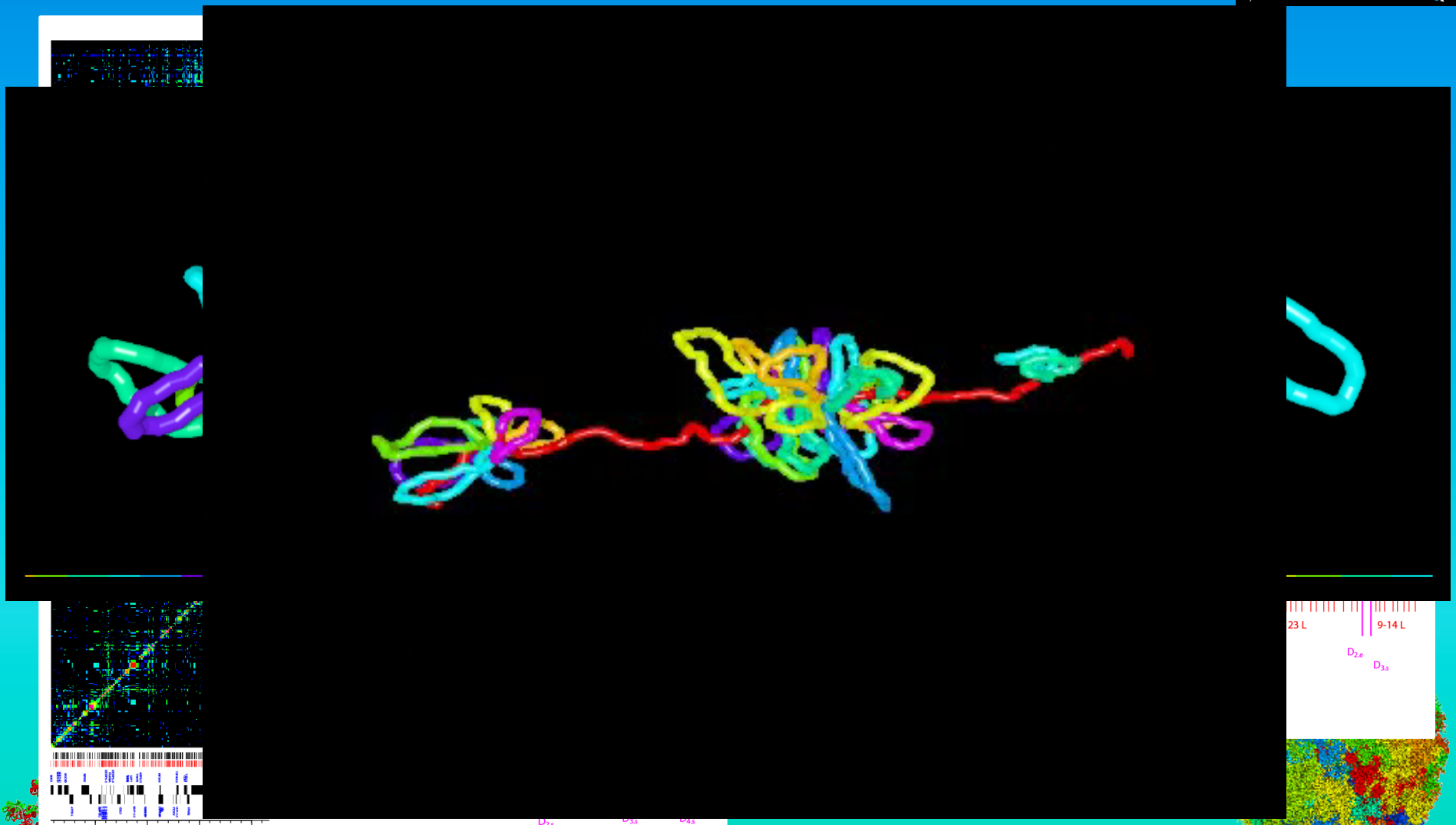
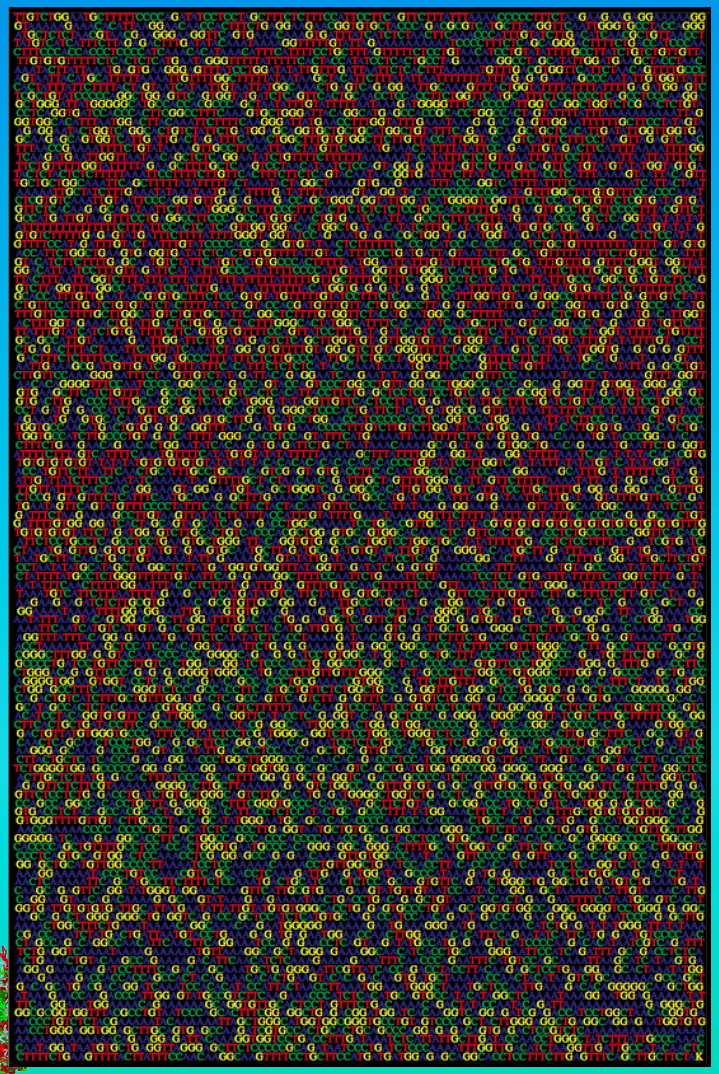
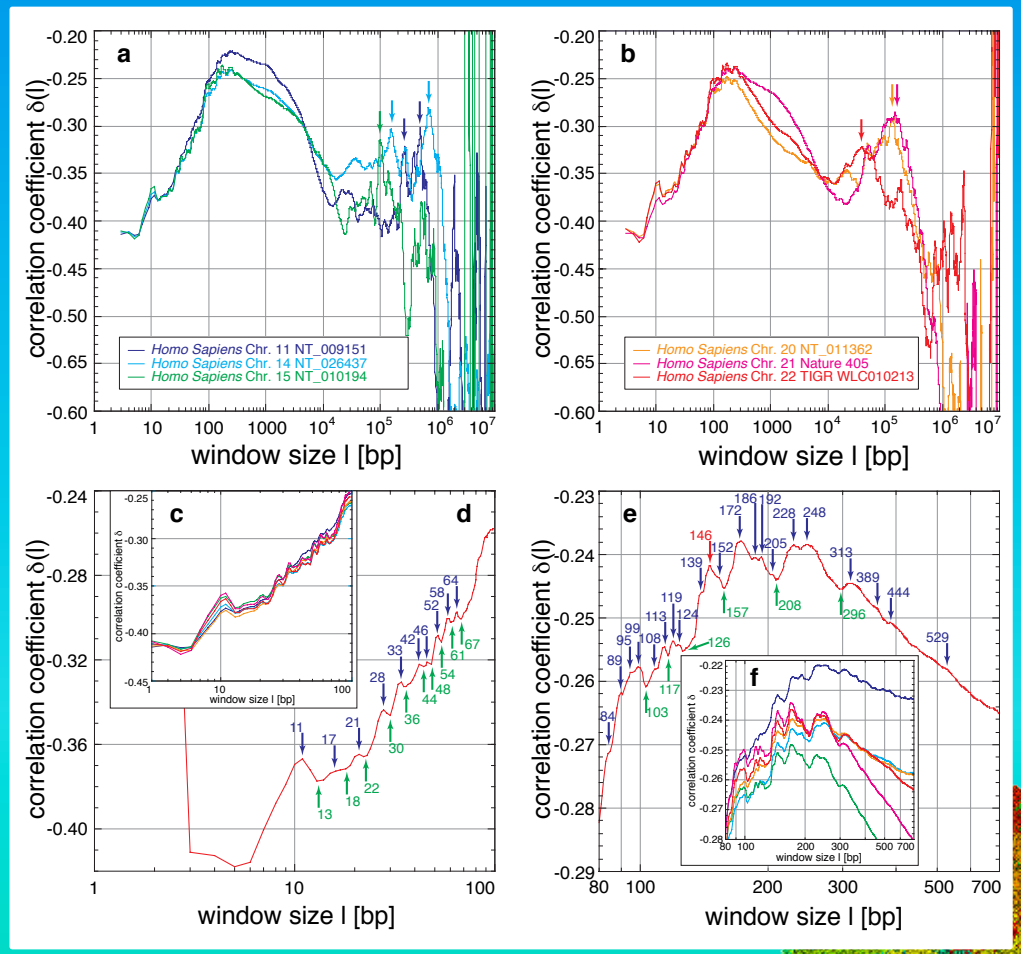


DNA Sequence Organization

Determination of the concentration fluctuation function $C(l)$ and its local slope the correlation coefficient $\delta(l)$ are an indication for the i) degree of long-rang scaling behaveour, ii) general multi-scaling, and iii) fine-structure features, which all are connected to all levels of genome organization and especially also the three-dimensional genome architecture.





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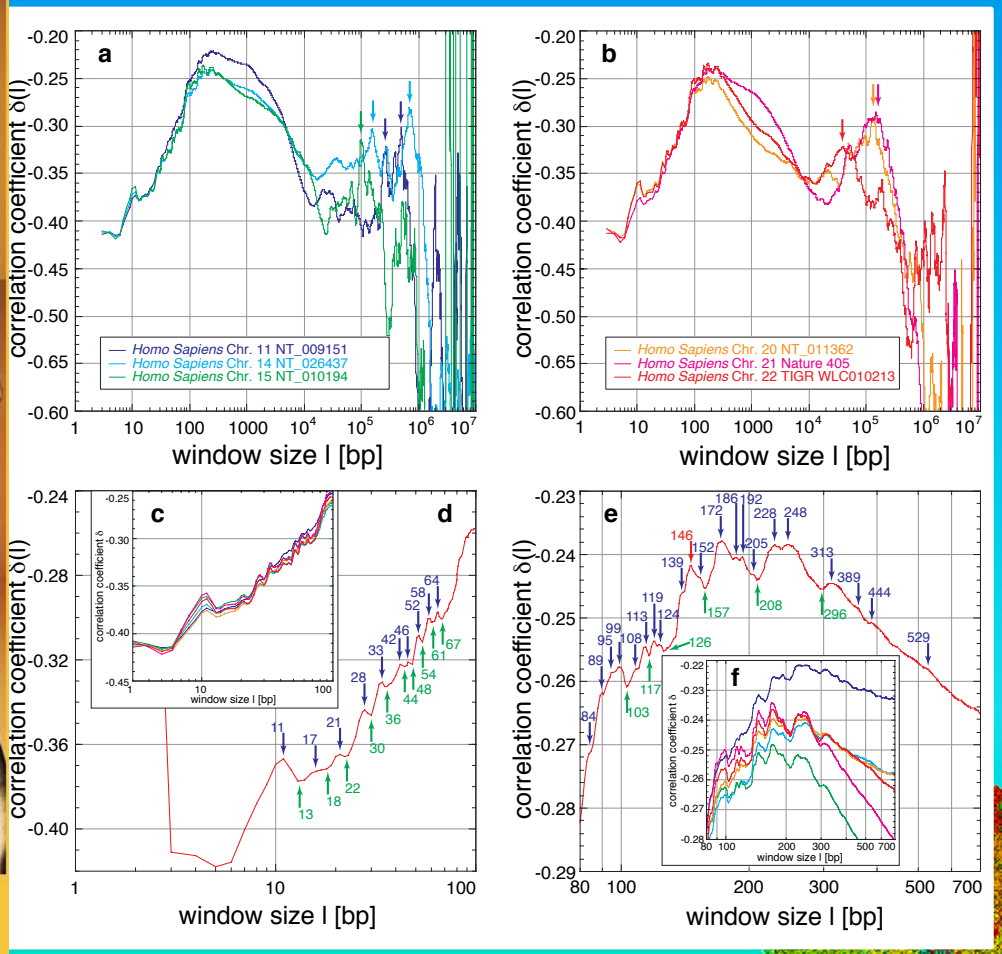

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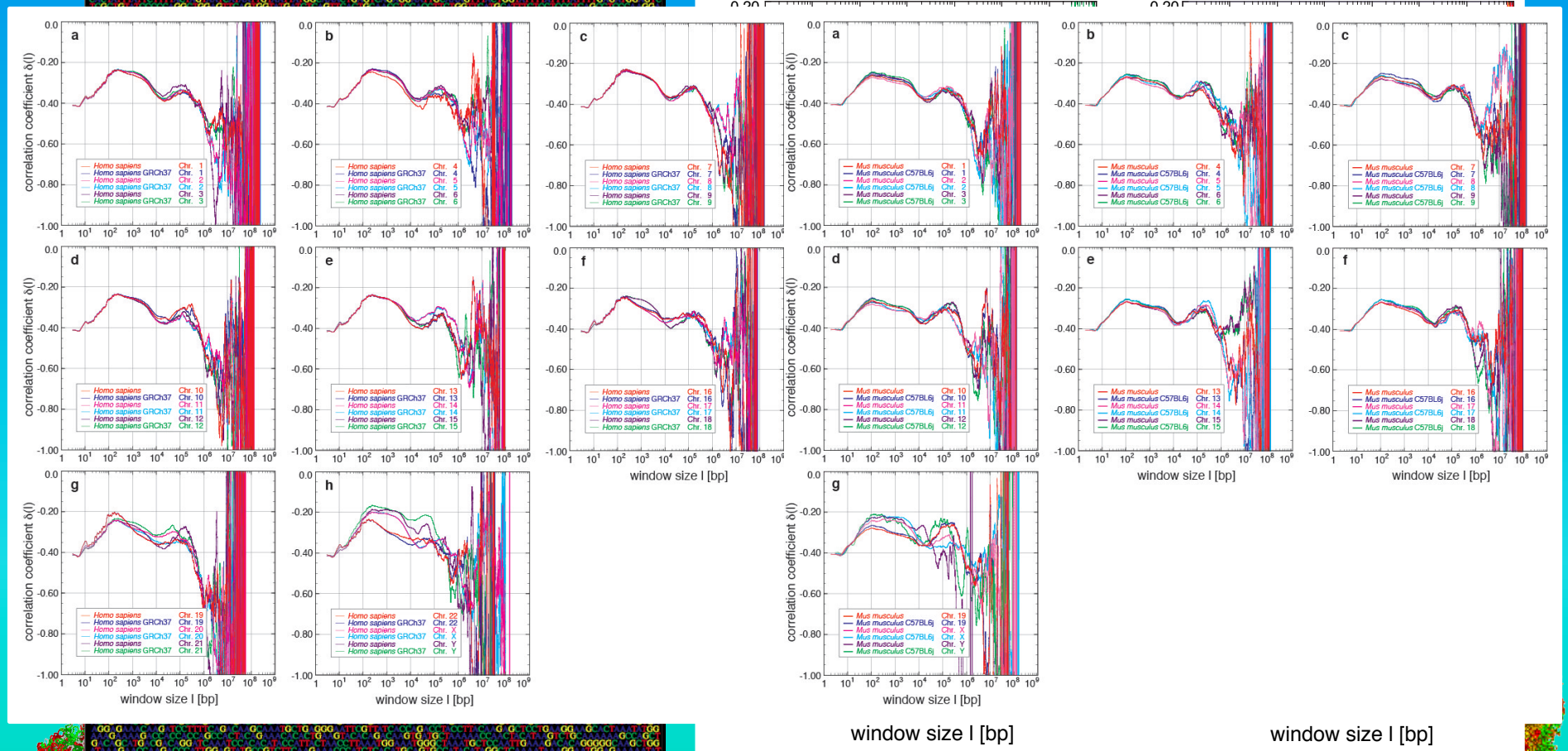
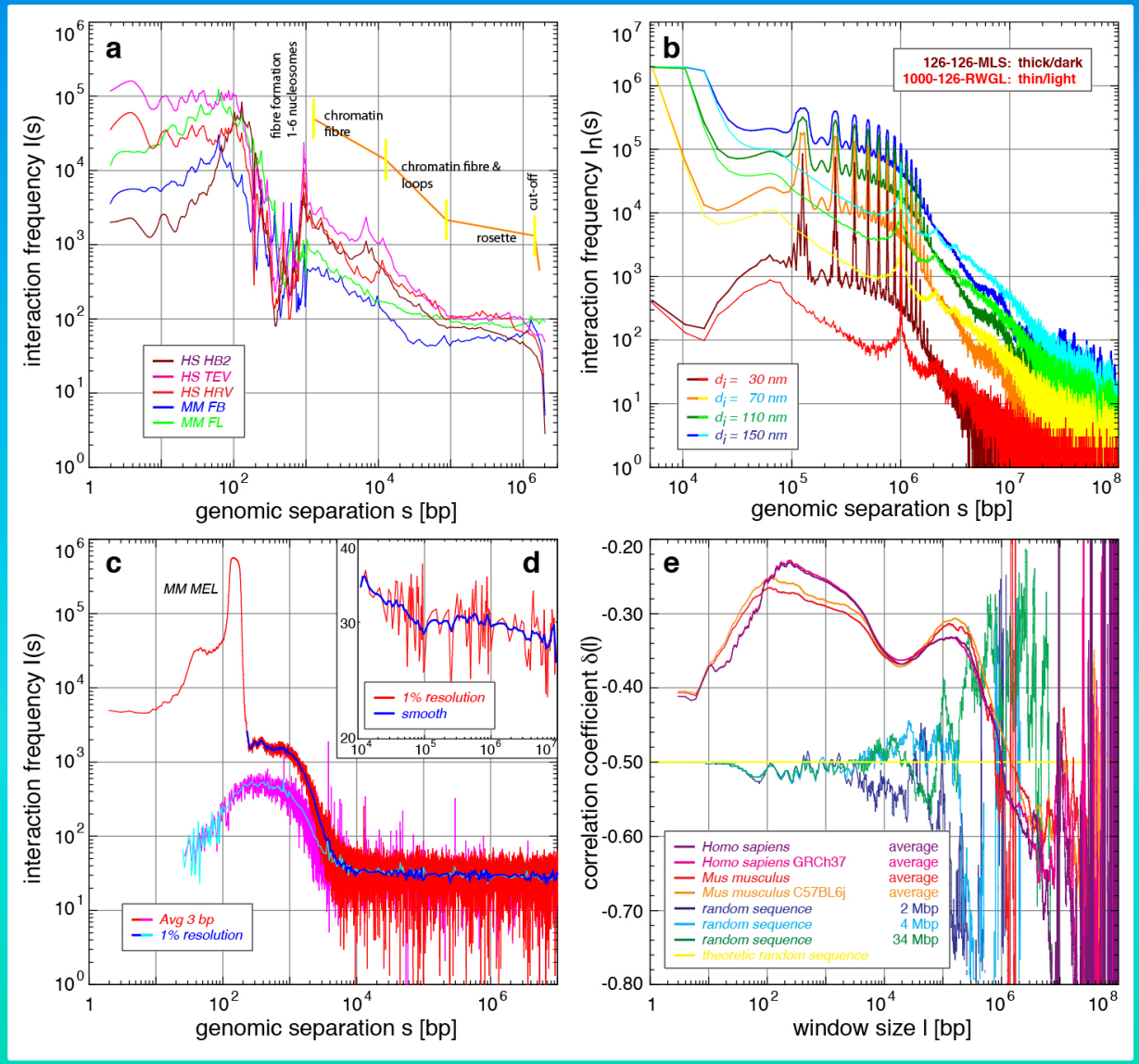
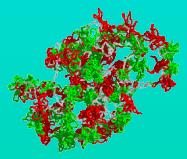
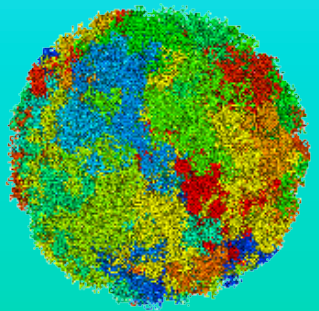


Scaling Analysis

Scaling analysis show again the entire bandwidth of architectural effects in an aggregated manner. Beyond, they show the scale bridging of the structures and the evolutionary holistic entanglement between the 3D architecture and the DNA sequence organization itself.







From Fiber Topology to Nuclear Morphology

Chromosome territories form in the RW/GL and the MLS model. However, only the MLS model leads distinct subcompartments and low chromosome and subcompartment overlap. Best agreement is reached for an MLS model with 80 to 120 kbp loops and linkers in nuclei with 8 to 10 μm diameter.

The simulated nuclear morphology reflects the chromosome fiber topology of different models in detail.

rendering

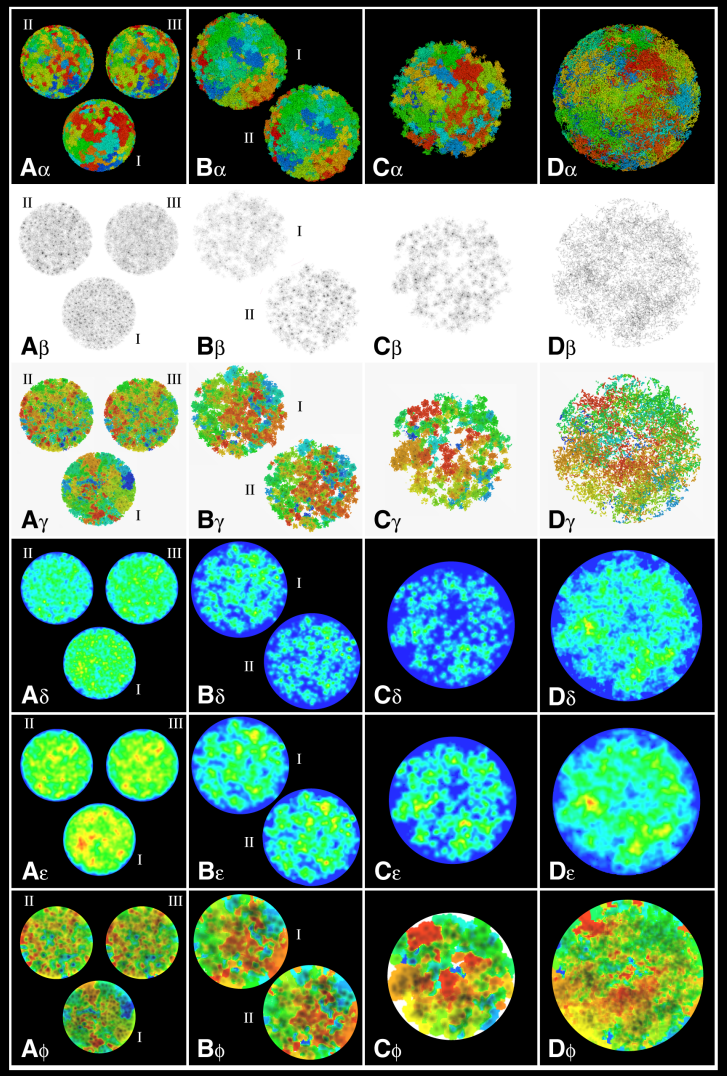
electron microscopy

electron microscopy territory painting

confocal microscopy
100x objective, theoretic resolution

confocal microscopy
63x objective, real resolution

confocal microscopy
territory painting

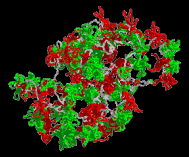


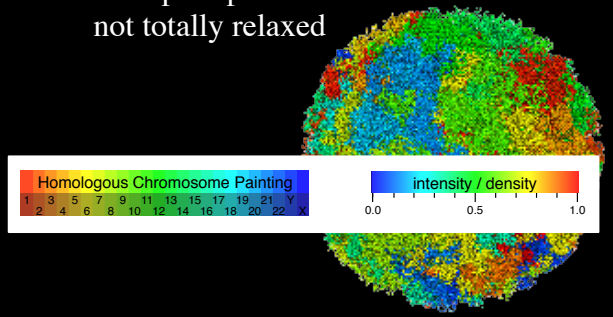
A: MLS in 6 μm nucleus
I: 63 kbp loops, 63 kbp linkers
II: 63 kbp loops, 252 kbp linkers
III: 126 kbp loops, 252 kbp linkers

B: MLS in 8 μm nucleus
I: 126 kbp loops, 126 kbp linkers
II: 84 kbp loops, 126 kbp linkers

C: MLS in 10 μm nucleus
126 kbp loops, 126 kbp linker,
not totally relaxed

D: RW/GL in 12 μm nucleus
5 Mbp loops
not totally relaxed





In vivo Morphology & Chromatin Distribution

The stable expression of fusions between histones and autofluorescent proteins and the integration into nucleosomes allows the minimal invasive investigation of the structure and dynamics of chromatin.

The clustered morphology in detail favour an MLS like chromatin topology.

HeLa, H2A-YFP

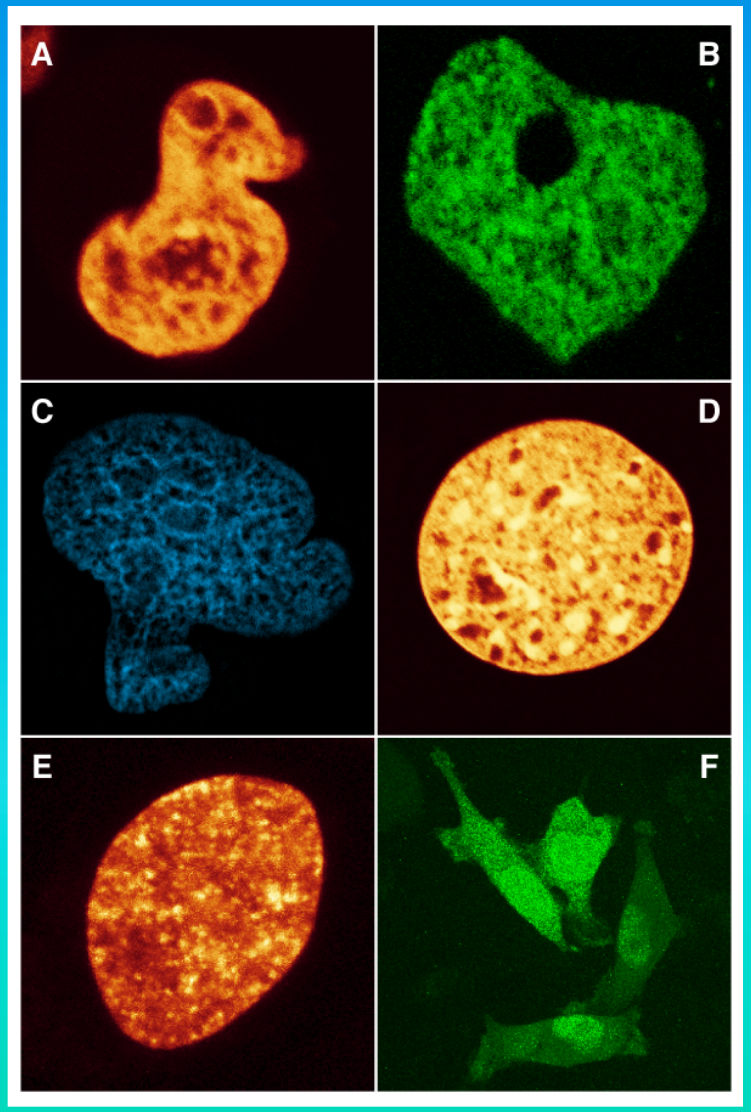
Cos7, H1.0-GFP

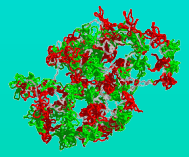
LCLC 103H, H2A-CFP

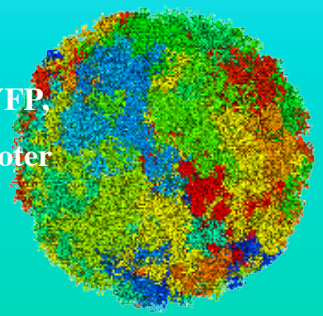
ID13, H2A-YFP

HeLa, mH2A1.2-YFP

HeLa, H2A-YFP, natural promoter







In Vivo Dynamics and 3D architecture

Counting nucleosomes in living cells with n spectroscopy (FCS) and
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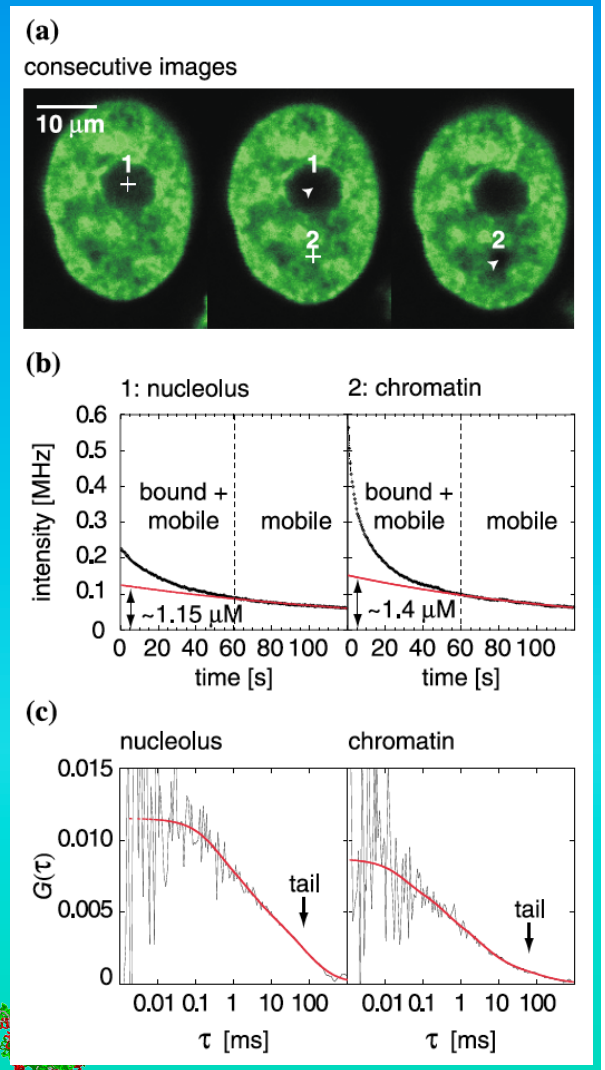

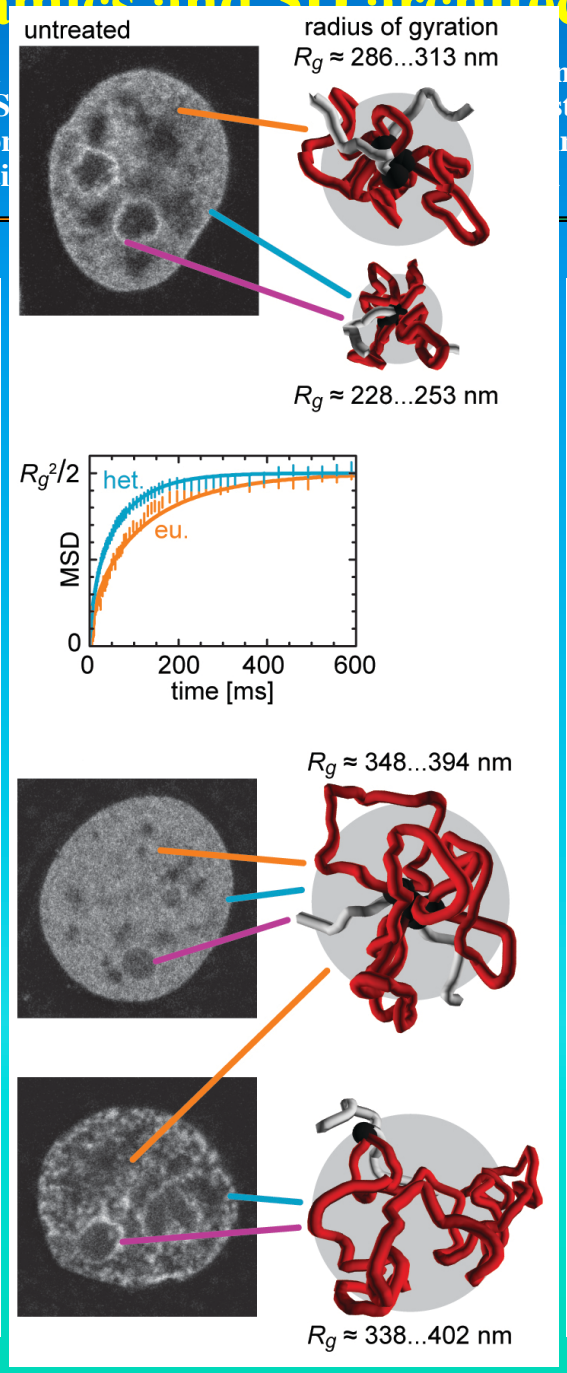

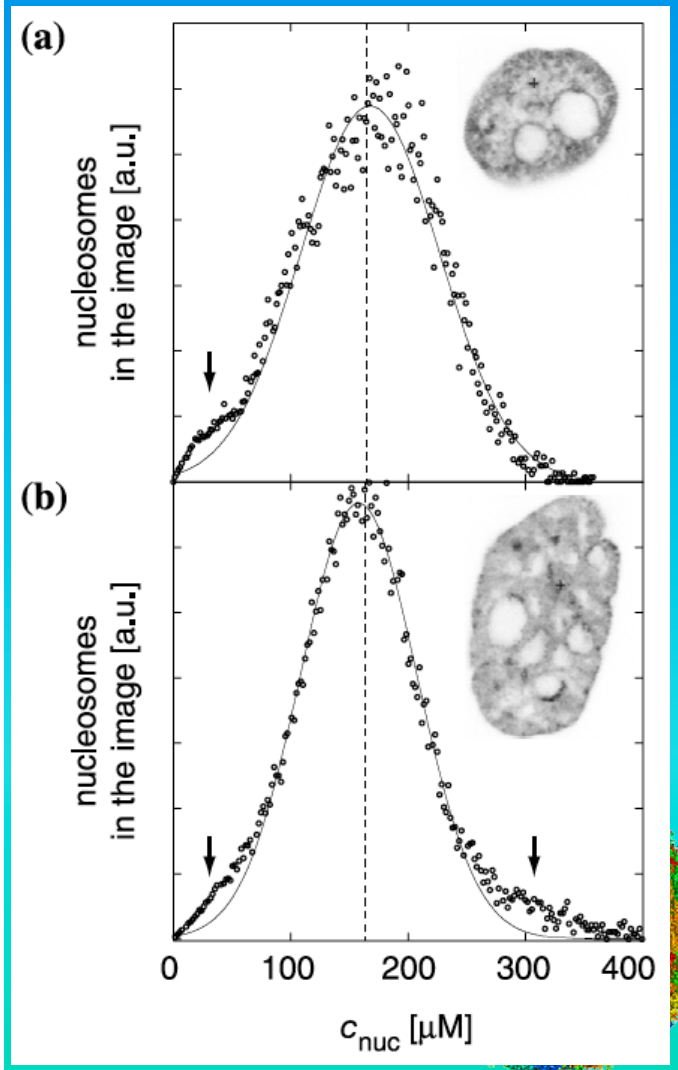

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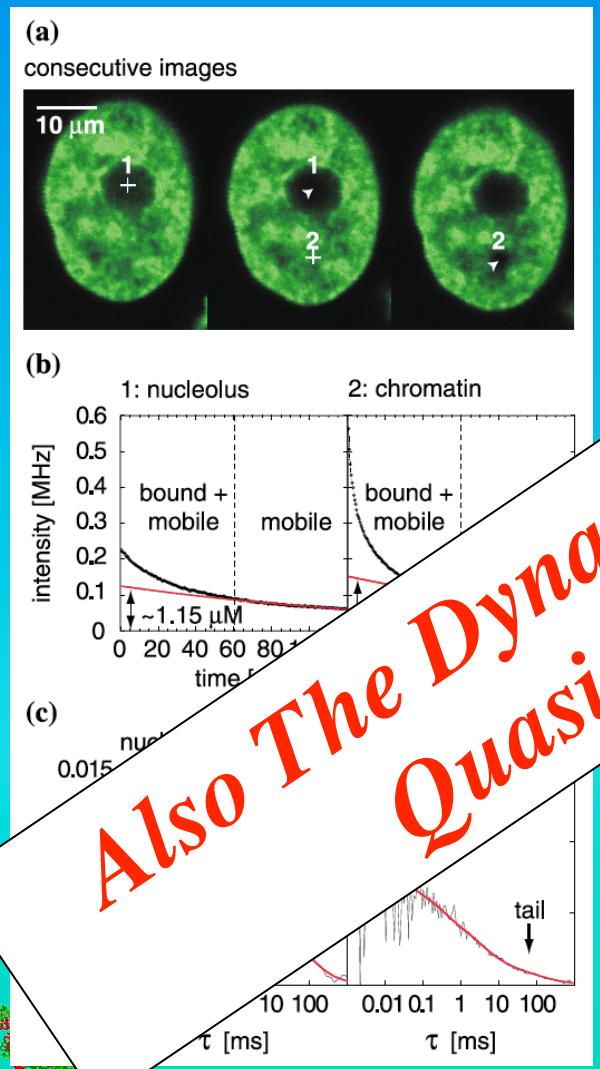
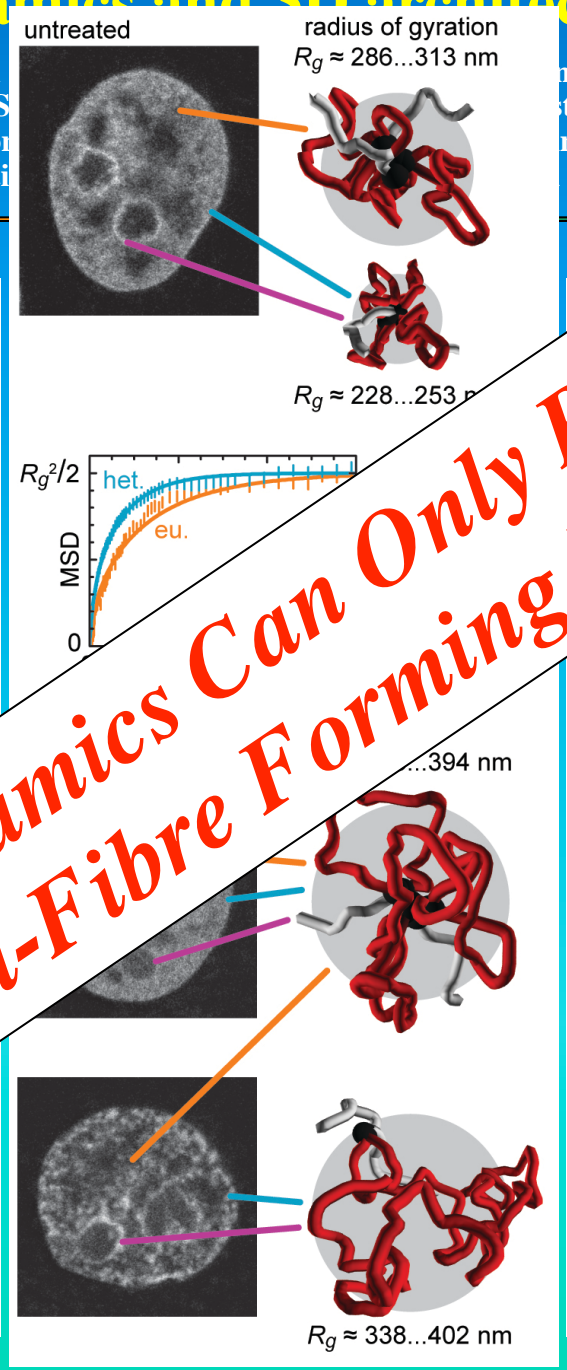
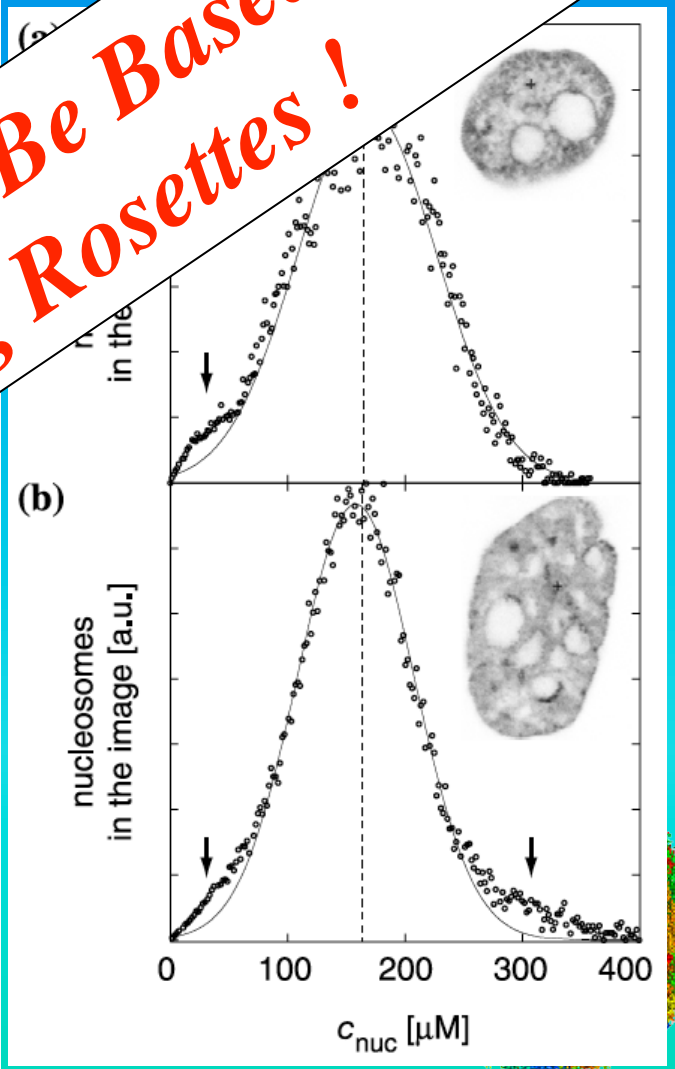






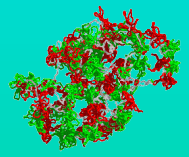
Also The Dynamics Can Only Be Based On A Quasi-Fibre Forming Rosettes !

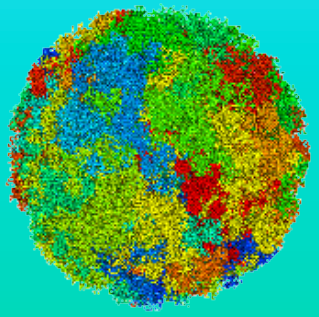
Conclusion

The compacted chromatin quasi-fibre, folds into loop-aggregates connected by a linker !

Every structural level of nuclear organization including its dynamics is connected and represented in all the other levels in a holistic systems genomics manner.

- **The 3D genomes architecture consists of chromatin quasi-fibres (5±1 nuc. / 11 nm, L_p of 80-120 nm), forming stable loop aggregates/rosettes (~40-100 kbp loops, ~60 kbp linkers).**
- **The dynamics of genomes follows the 3D genome architecture in detail and determines in an inseparable entanglement with the architecture genome function.**
- **From the single base pair to the entire cell nucleus, all genomic levels represent all other levels and by modification a code is present and used to store genetic information.**
- **Genomes have a consensus organization with only small variation from the basic theme on each compaction level of the genome and these small variations determine genome function.**
- **Genome organization and function cannot be determined or understood from a single organizational level but only in a holistic systems genomics manner integrating all parts of the system.**
- **The genome behaves on the basis of a genomic statistical mechanics with a genomic uncertainty principle attached !**





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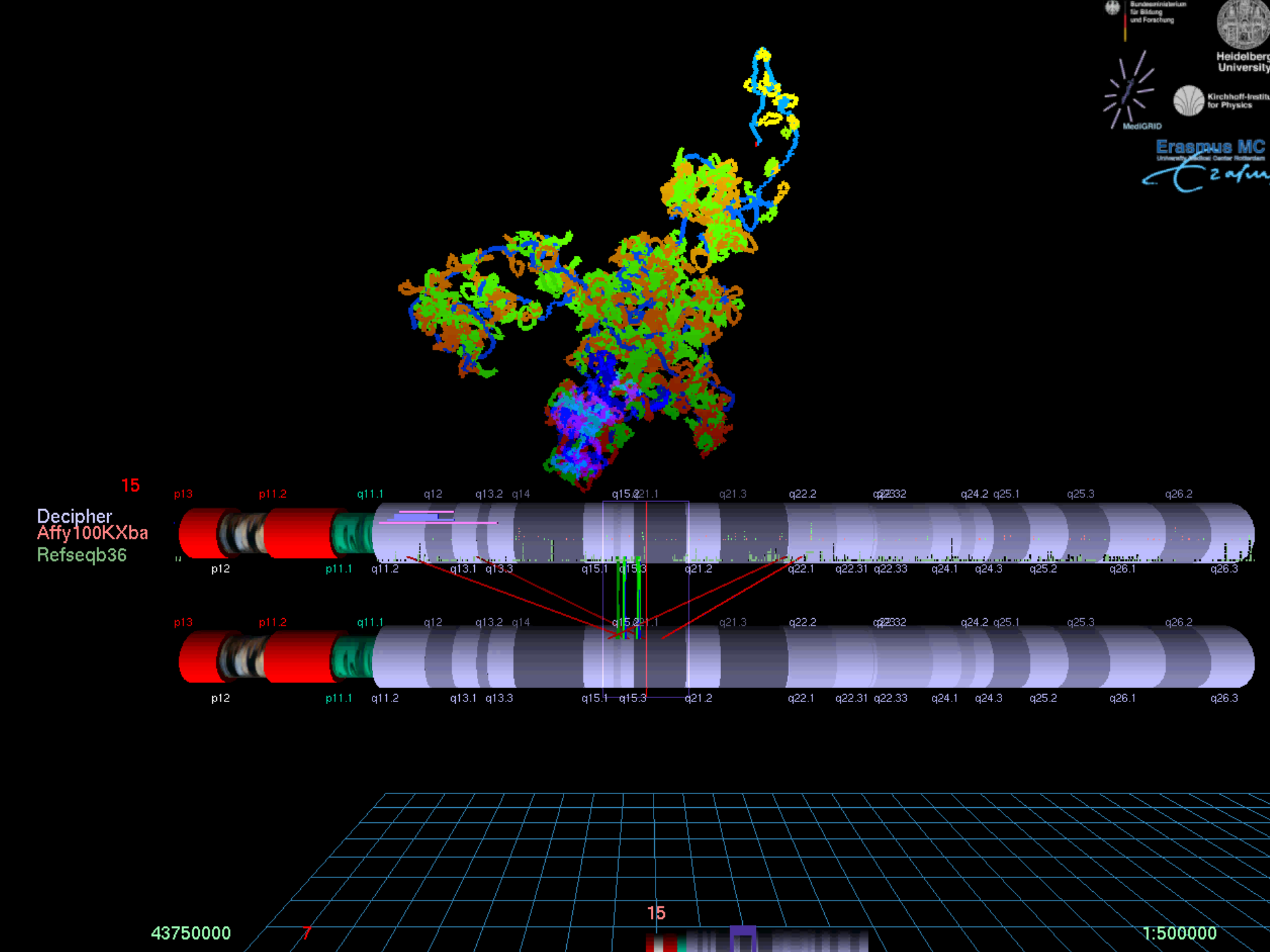
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The
Detailed 3D Multi-Loop Aggregate/Rosette Chromatin Architecture
and
Functional Dynamic Organization
of the
Human and Mouse Genome

Knoch, T. A.

Genome Regulation in 3D, Weizmann Institute, Rehovo, Israel, 28th – 30th June, 2015.

Abstract

The dynamic three-dimensional chromatin architecture of genomes and the obvious co-evolutionary connection to its function – the storage and expression of genetic information – is still, after ~170 years, a central question of current research. With a systems genomics approach using a novel selective high-throughput chromosomal interaction capture (T2C) technique together with quantitative polymer simulations and scaling analysis of genomic structures and the DNA sequence, we determined the architecture of genomes with unprecedented molecular resolution and dynamic range from single base pair entire chromosomes. Polymer simulations using Monte Carlo and Brownian dynamics approaches confirm T2C results and allow to predict and to explain additional experimental findings. This agrees also with novel dynamics information from fluorescence correlation spectroscopy (FCS) analysis of chromatin relaxations *in vivo*. Beyond, we find a fine-structured multi-scaling behaviour of both the architecture and the DNA sequence, which shows for the first time the tight entanglement between architecture and sequence. Since, T2C allows reaching an optimal combination of resolution, interaction frequency range, multiplexing, and an unseen signal-to-noise ratio at molecular resolution this, hence, opens the door to architectural sequencing of genomes. Additionally, we have reached the level of genome statistical mechanics with corresponding uncertainty principles. Hence, we determined the three-dimensional architecture and dynamics of genomes for the first time in a consistent system genomics manner from several angles which are all in agreement as well as additionally also with the heuristics of the research of the last 170 years. This will lead to a detailed understanding of genomes with fundamental new insights and huge novel perspectives for diagnosis, treatment, and genome engineering.

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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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