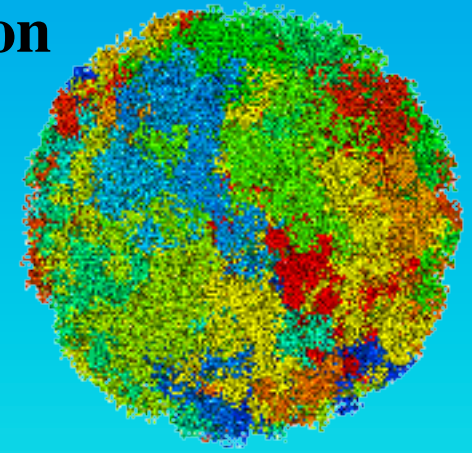
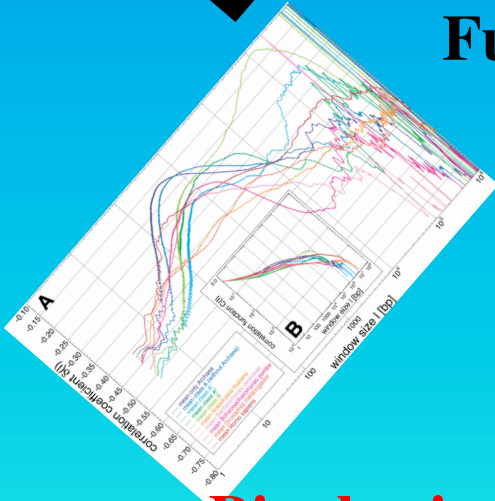


The Detailed 3D Multi-Loop Aggregate/Rosette Chromatin Architecture and Functional Dynamic Organization of the Human and Mouse Genomes

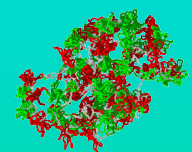
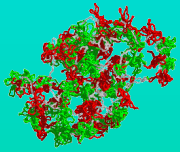


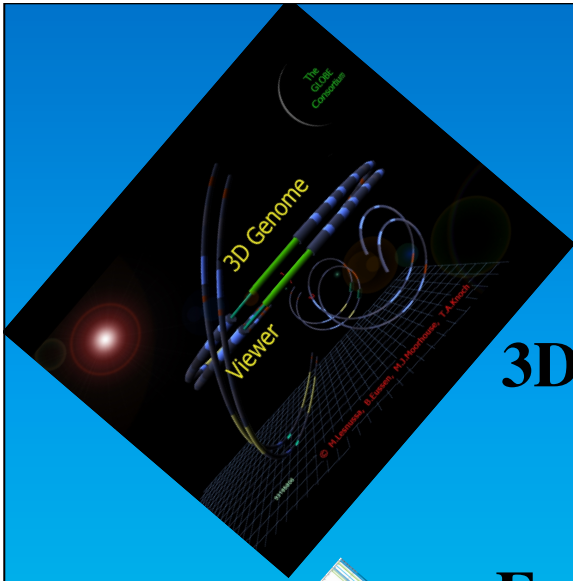
Tobias A. Knoch

Biophysical Genomics & Erasmus Computing Grid

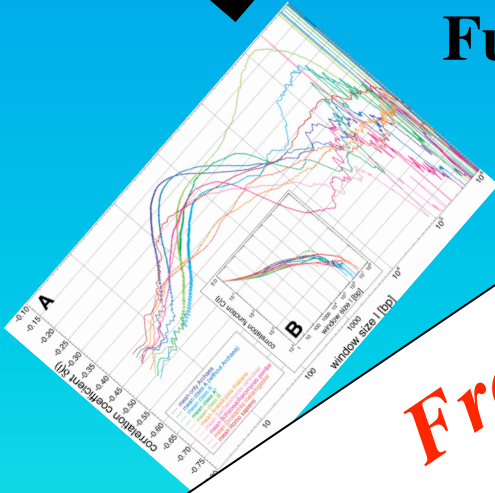
Erasmus Medical Center

TA.Knoch@taknoch.org

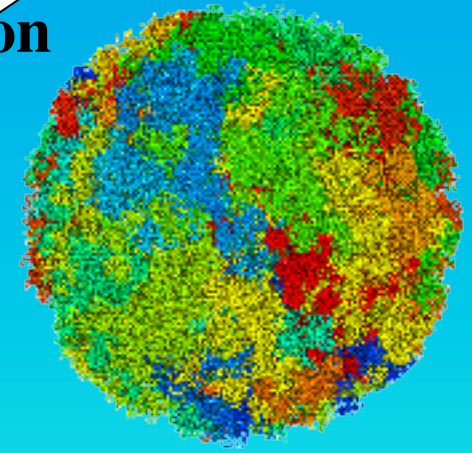




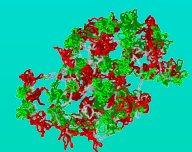
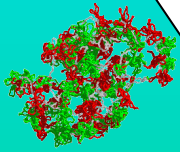
The Detailed 3D Multi-Loop Aggregate/ Chromatin Architecture and Functional Dynamics Human and Mouse Genomes



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

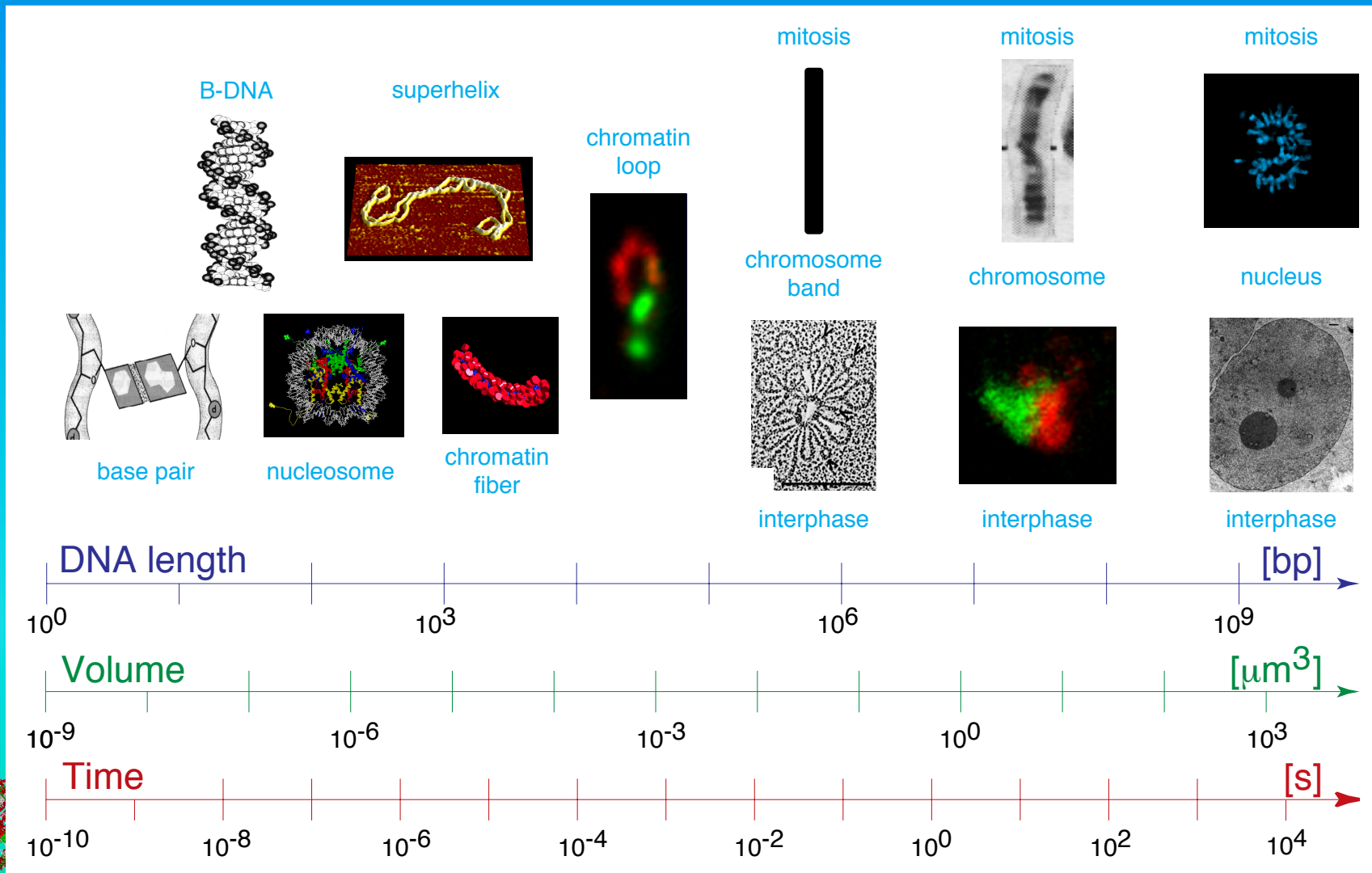
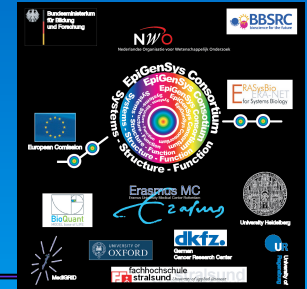


Dr. Tobias A. Knoch
Genomics & Erasmus Computing Grid
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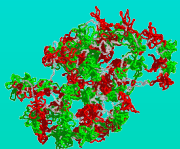
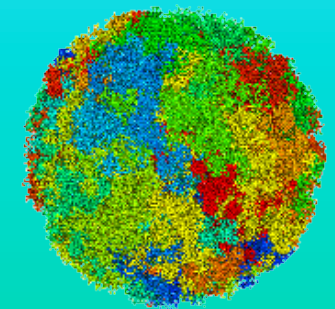
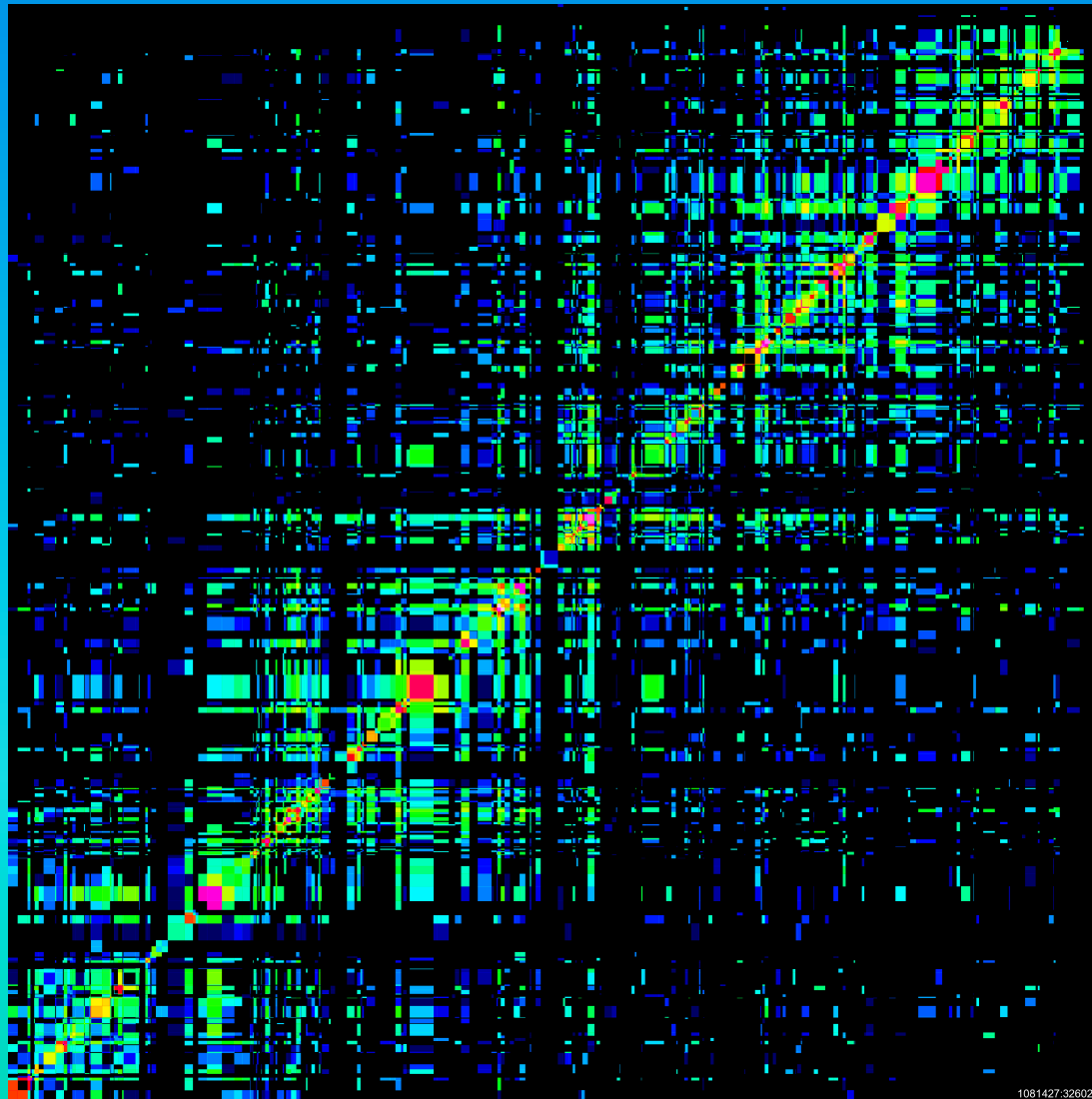
Dynamic and Hierarchical Genome Organization

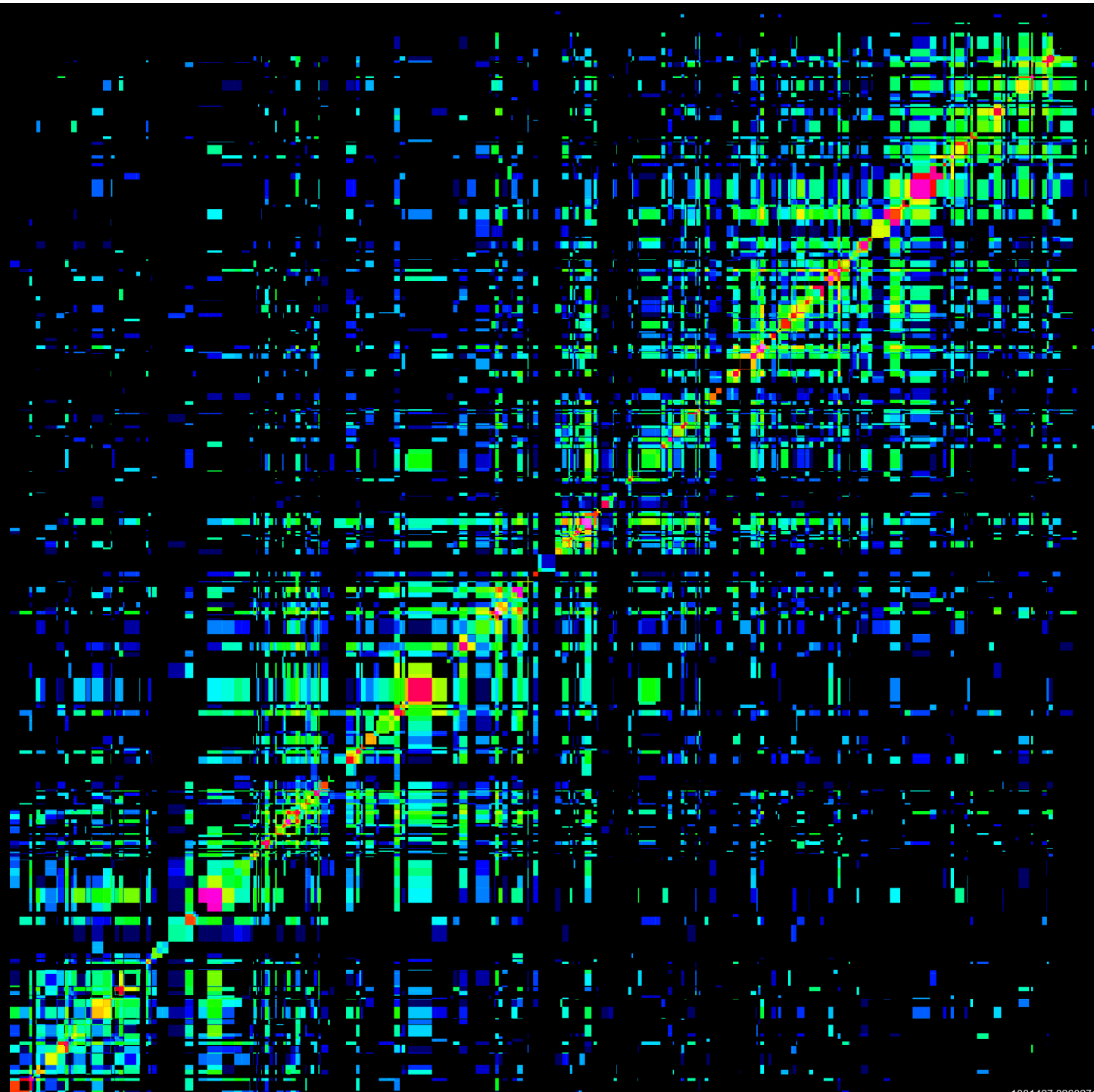
The different organization levels of genomes bridge several orders of magnitude concerning space and time. How all of these organization levels connect to processes like gene regulation, replication, embryogenesis, or cancer development is still unclear?



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.

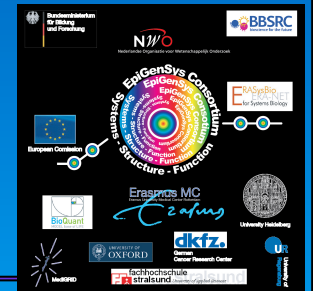




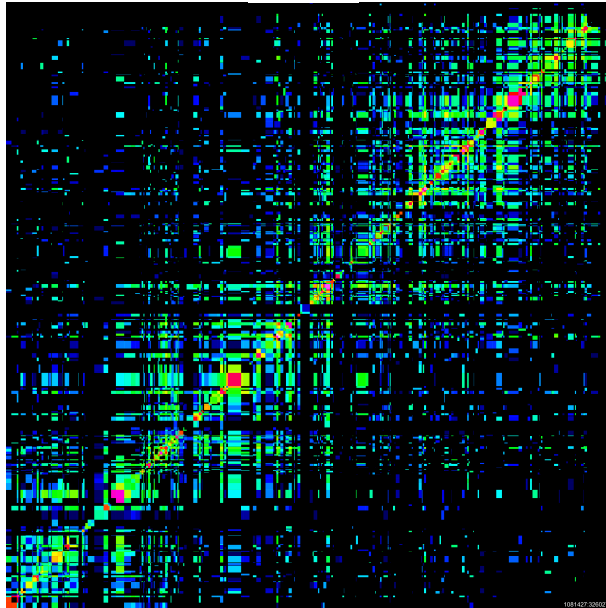
We Reached the Level of the Genomic Uncertainty Principle!
The Conformation of Chromatin and the 3D Architecture
can be derived with Tremendous Resolution !

Stable Consensus Architecture of Genomes

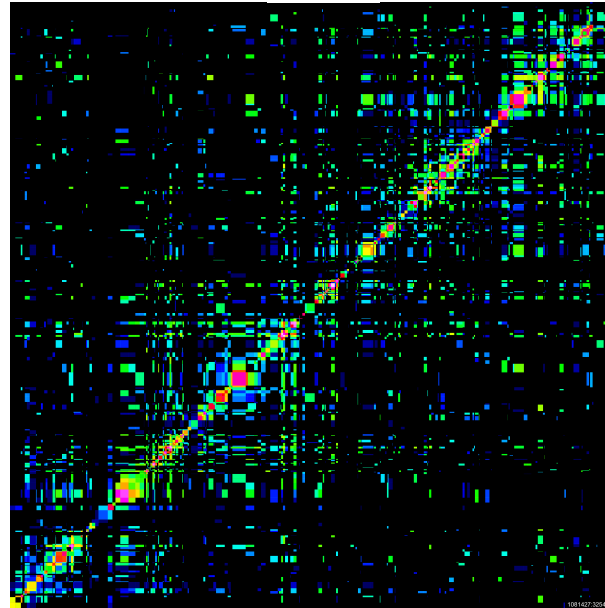
Due to the high signal-to-noise ratio of T2C reaching 5-6 orders of magnitude interaction maps reveal definitely an extremely high degree of similarity between different species, cell types, or functional states, thus functional differences are variation of a stable theme persisting through the cell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



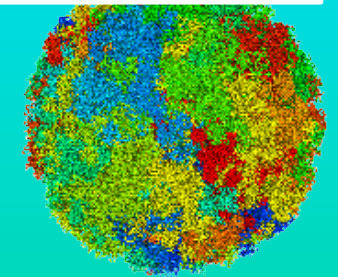
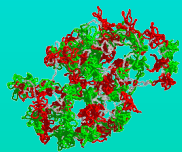
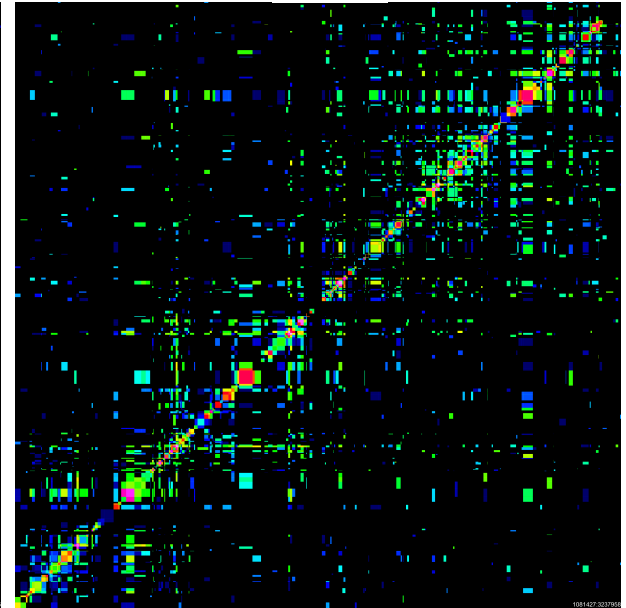
HB2



TEV

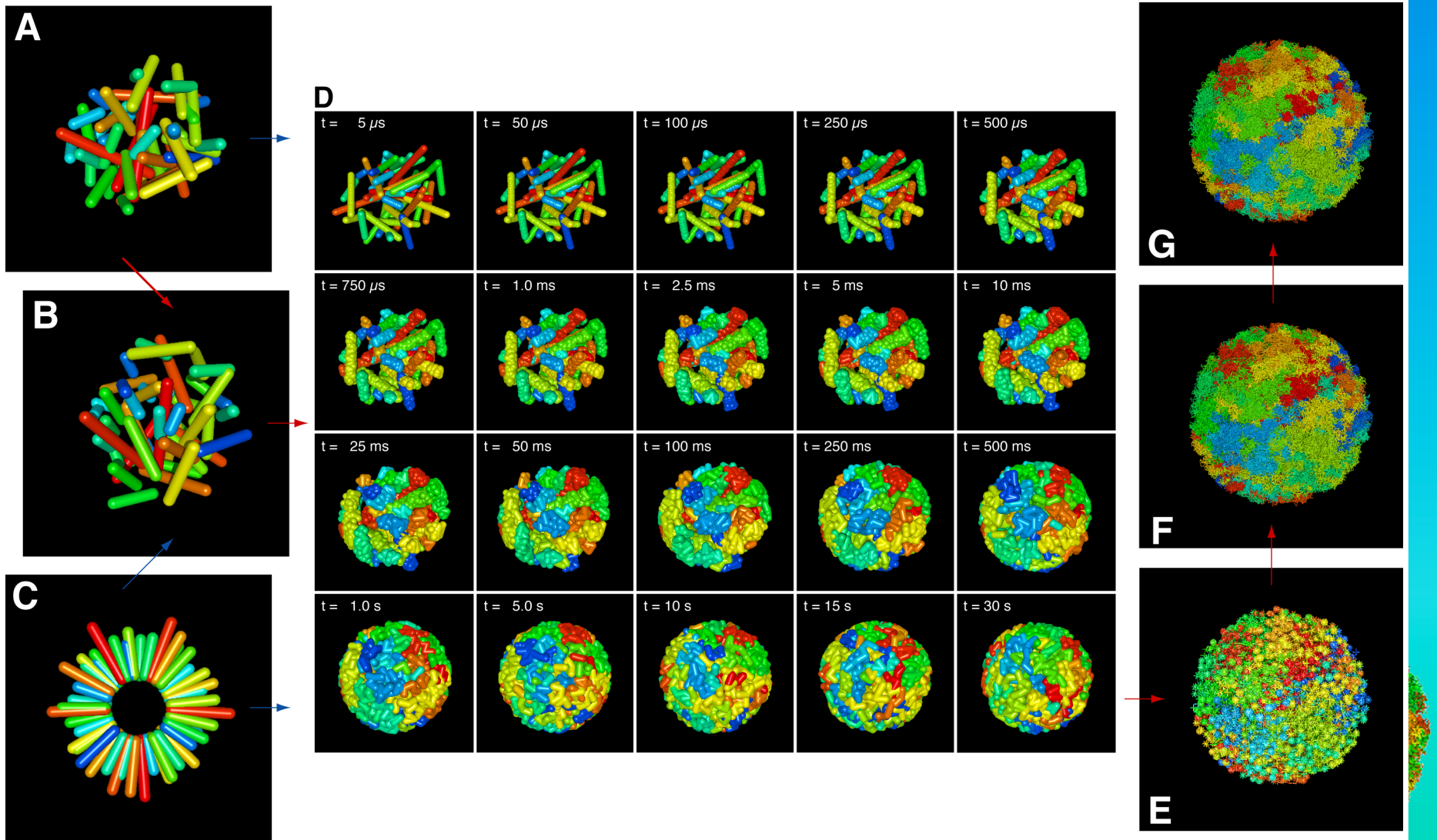
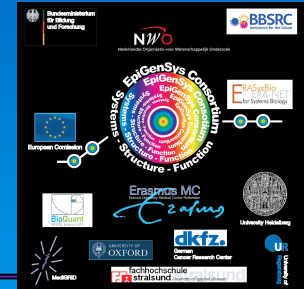


HRV



Simulation of Chromosomes & Nuclei

By parallel super-computer simulations using novel Monte Carlo and Brownian Dynamics approaches simulate chromosomes and whole nuclei with unprecedented resolution, resulting in novel predictions for the detailed folding of the chromatin fiber with corresponding impact on the experimental evaluation.

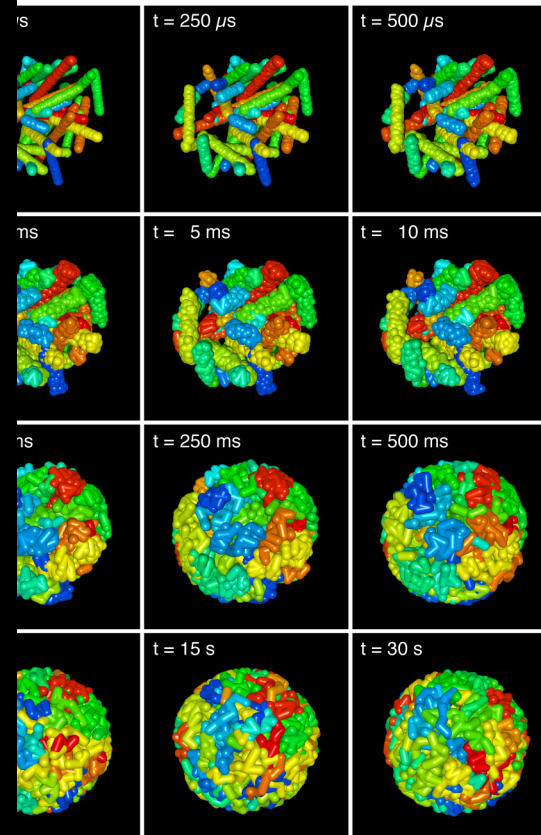
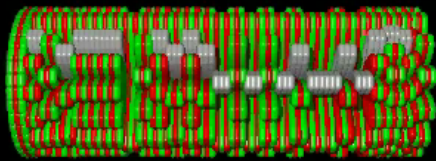


Simulation of Chromosomes & Nuclei

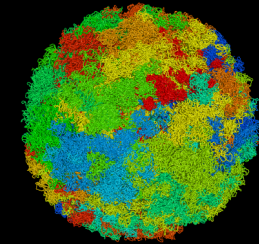
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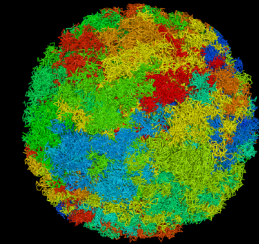
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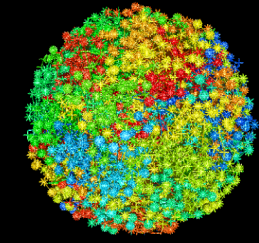
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F

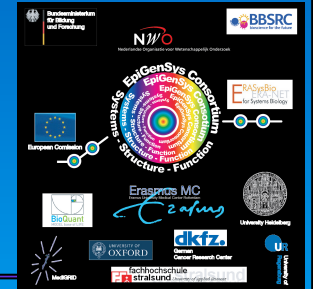


E

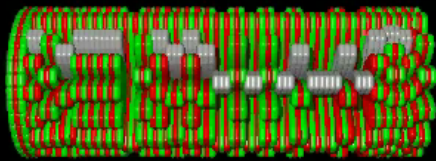


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A



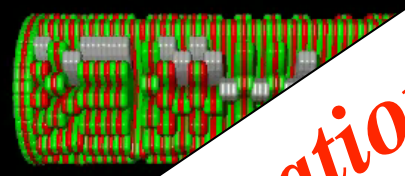
E

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A

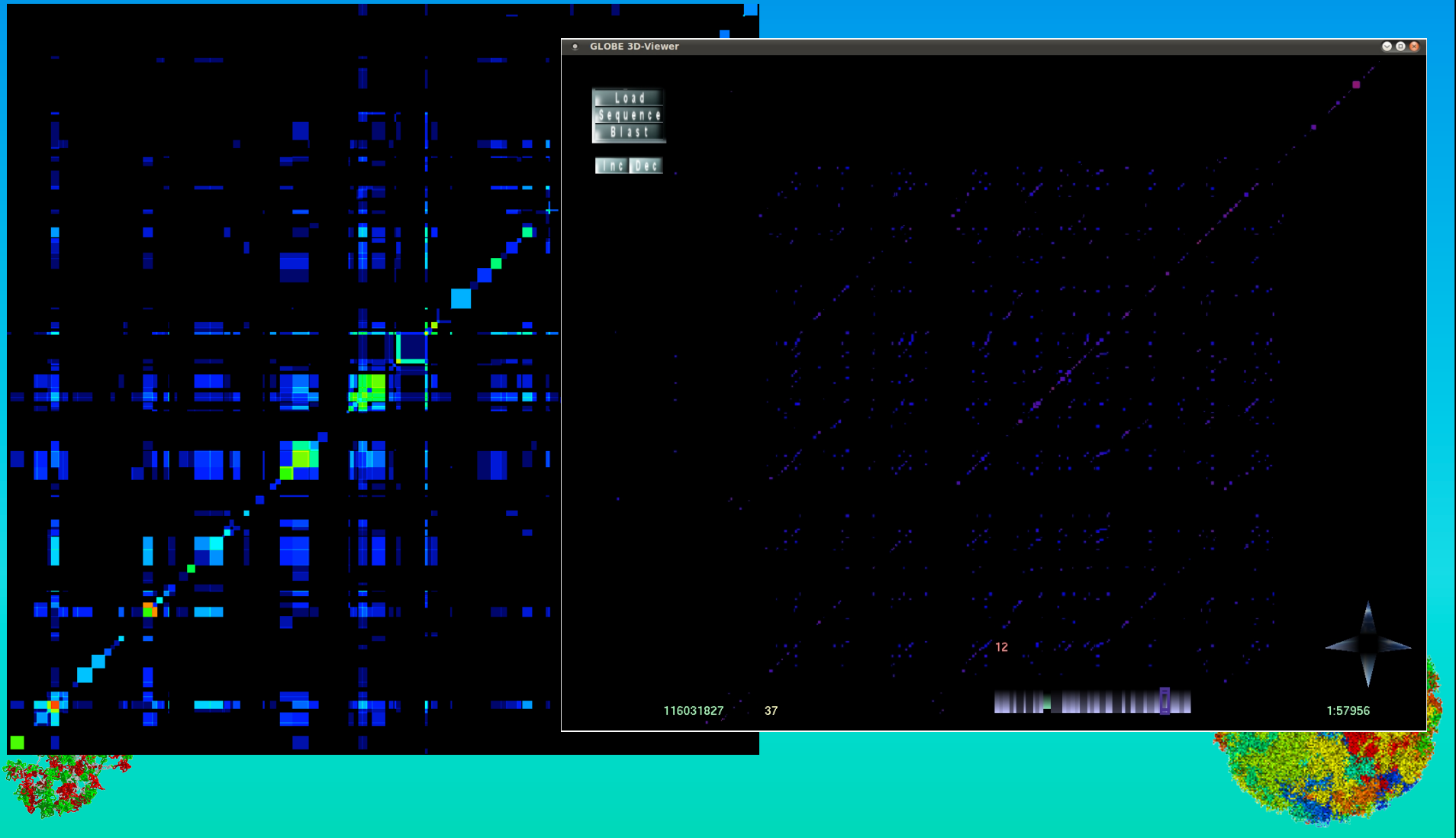


E

**The Combination of Modelling and Experiment
Reveals the Chromosomal Architecture !**

Fine Structure of Loop Aggregates/Rosettes

Depending on the resolution, the loops within a domain and 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 $\sim 6\text{kbp}$ and these form the core.



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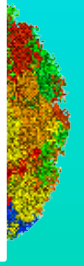
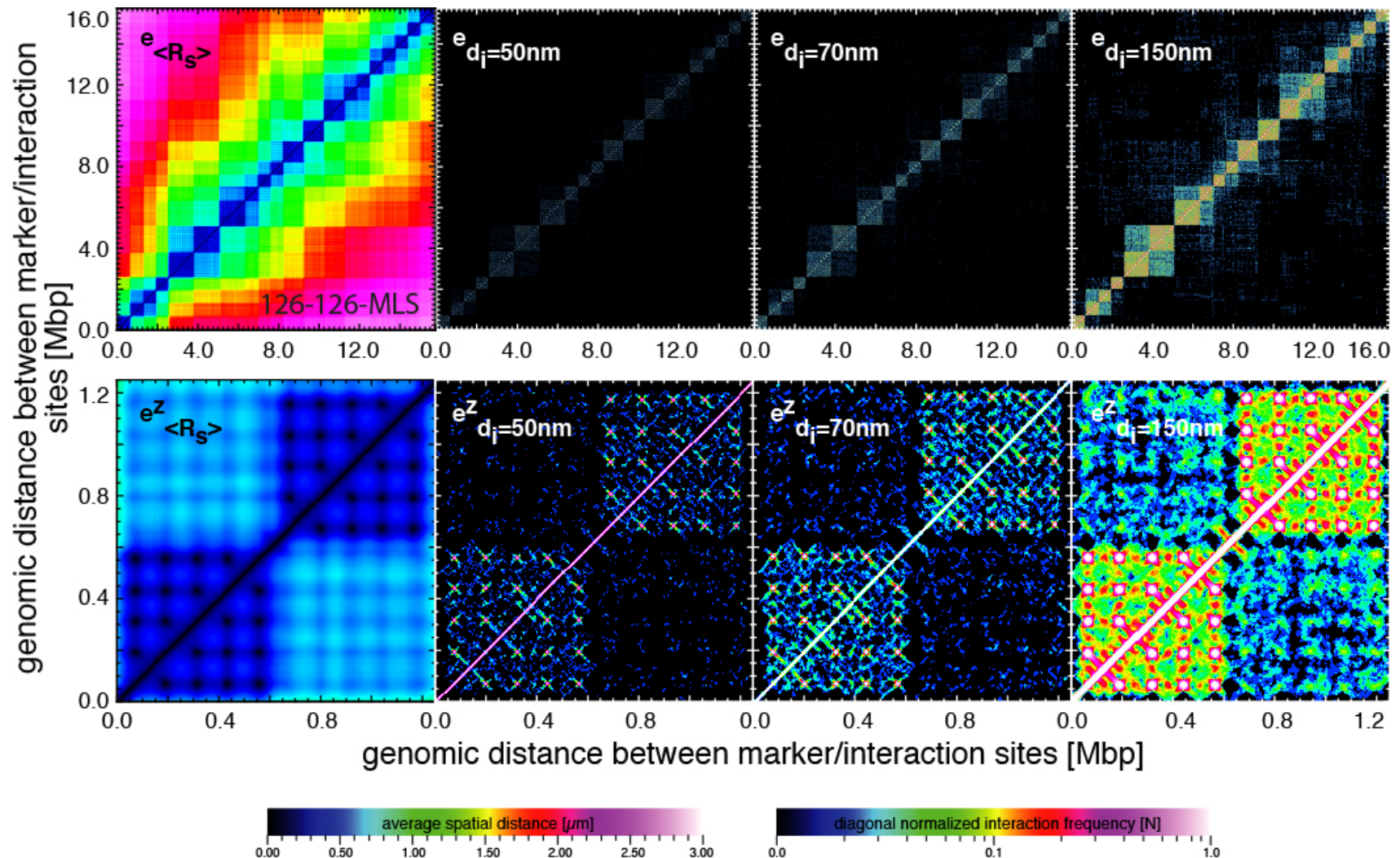
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The Rosalind Franklin Images!
The 3D Architecture of Chromosomes can be Directly Derived Visually !!!

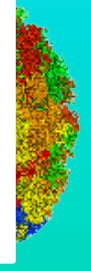
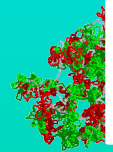
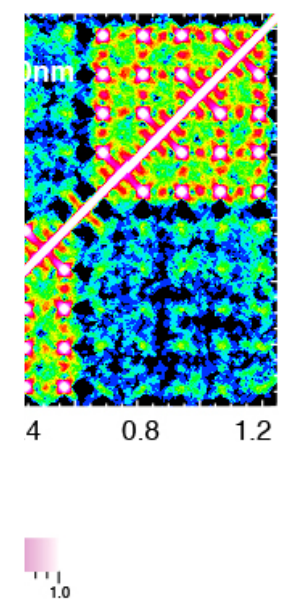
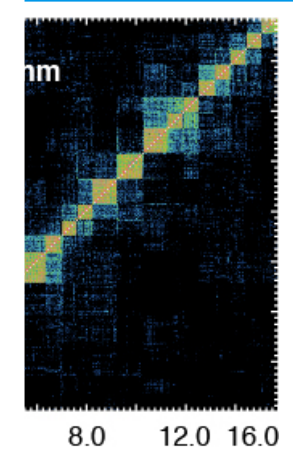
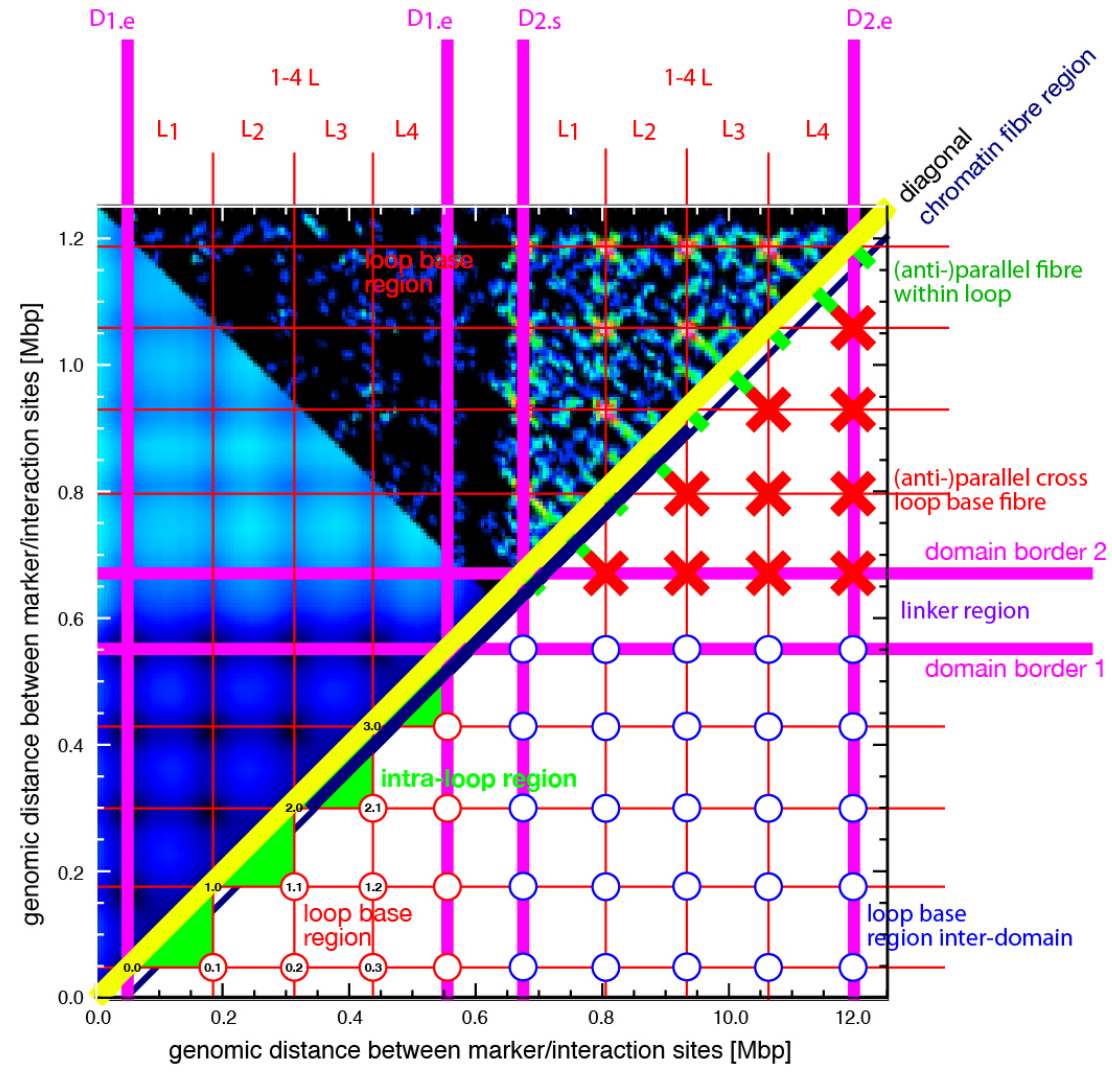
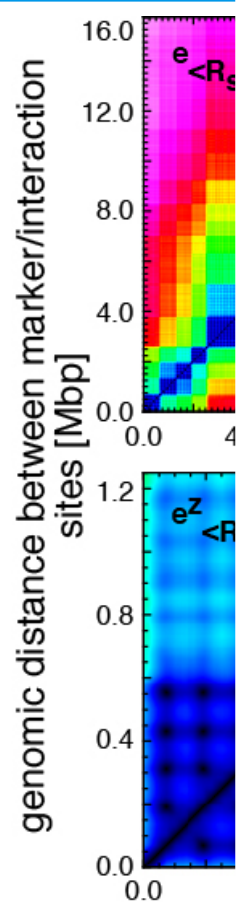
Simulated Interaction Maps

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.



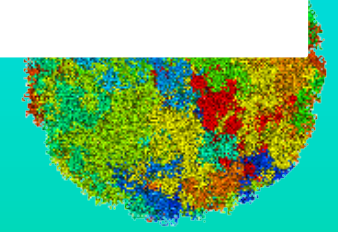
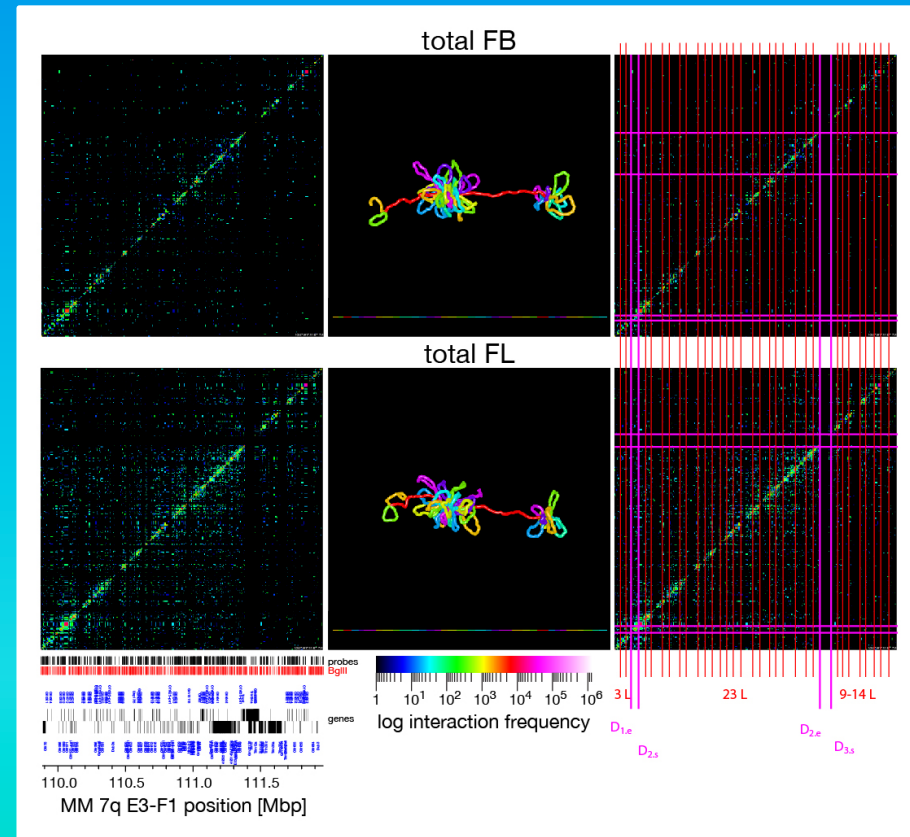
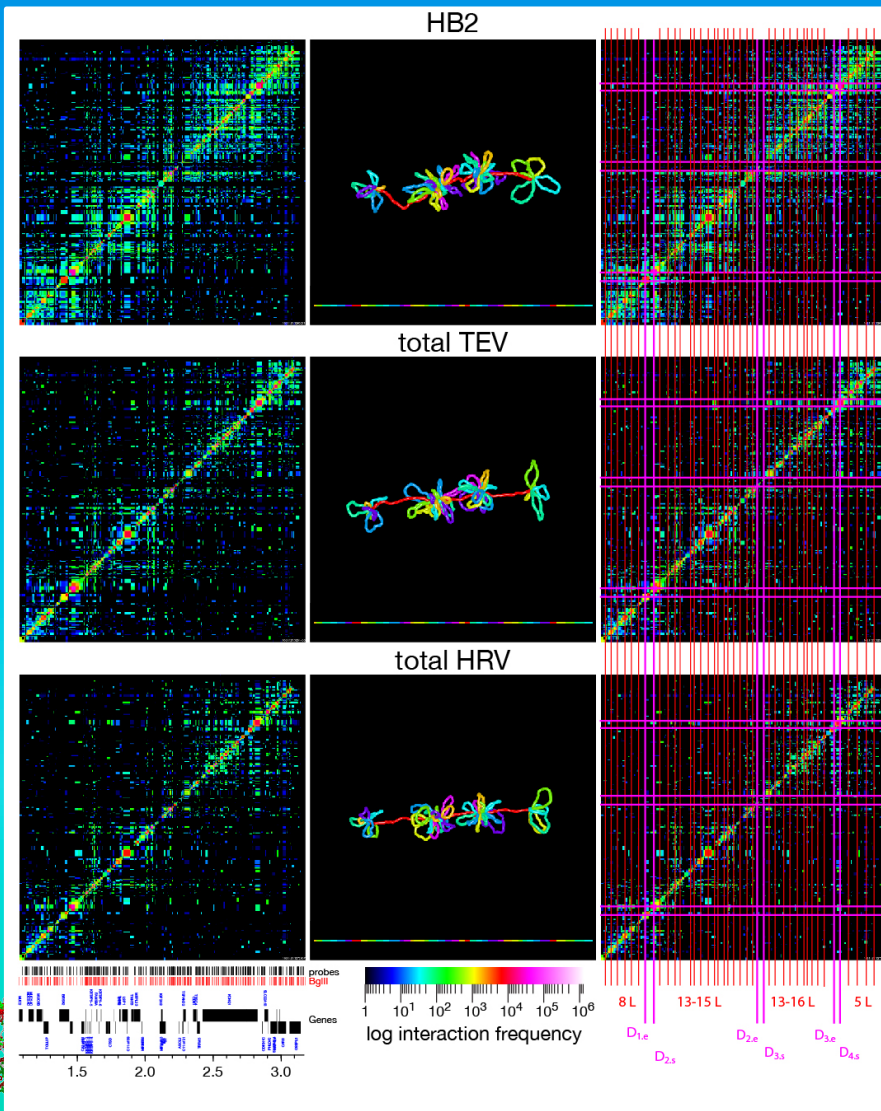
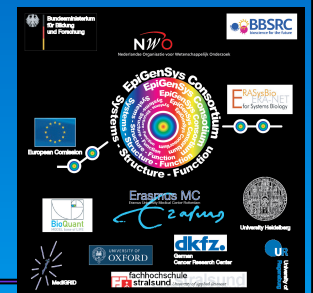
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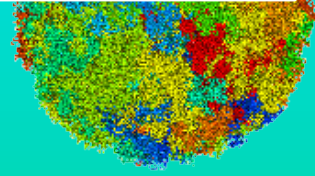
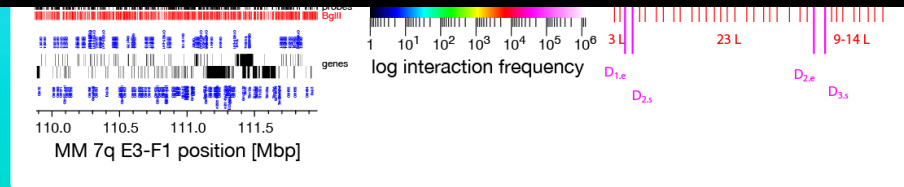
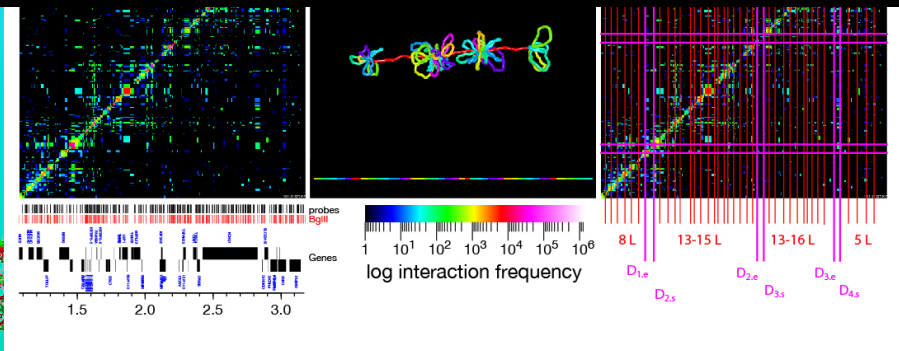
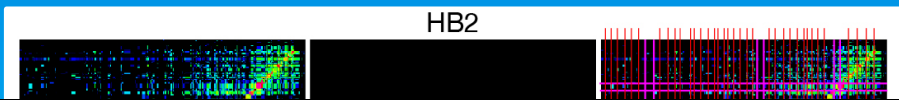
Variation of a Consensus Architecture Scheme

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.



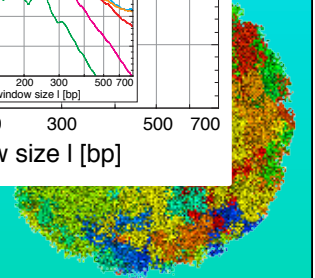
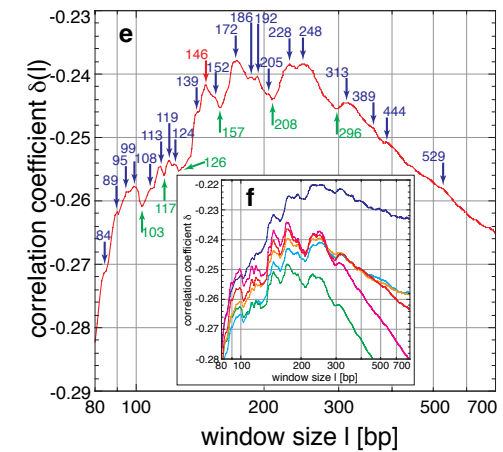
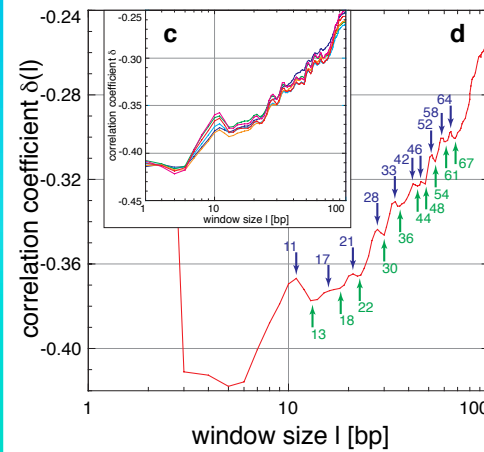
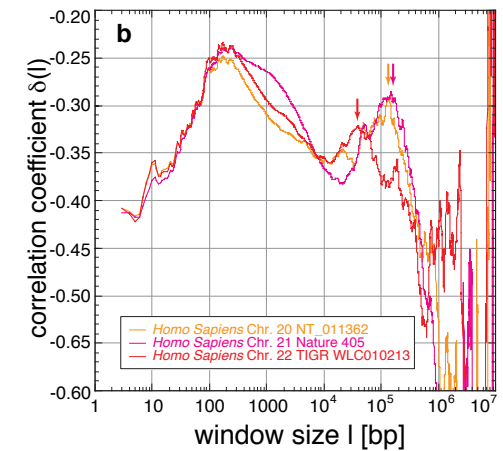
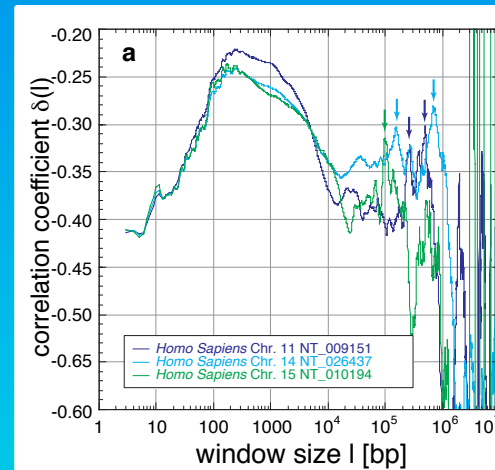
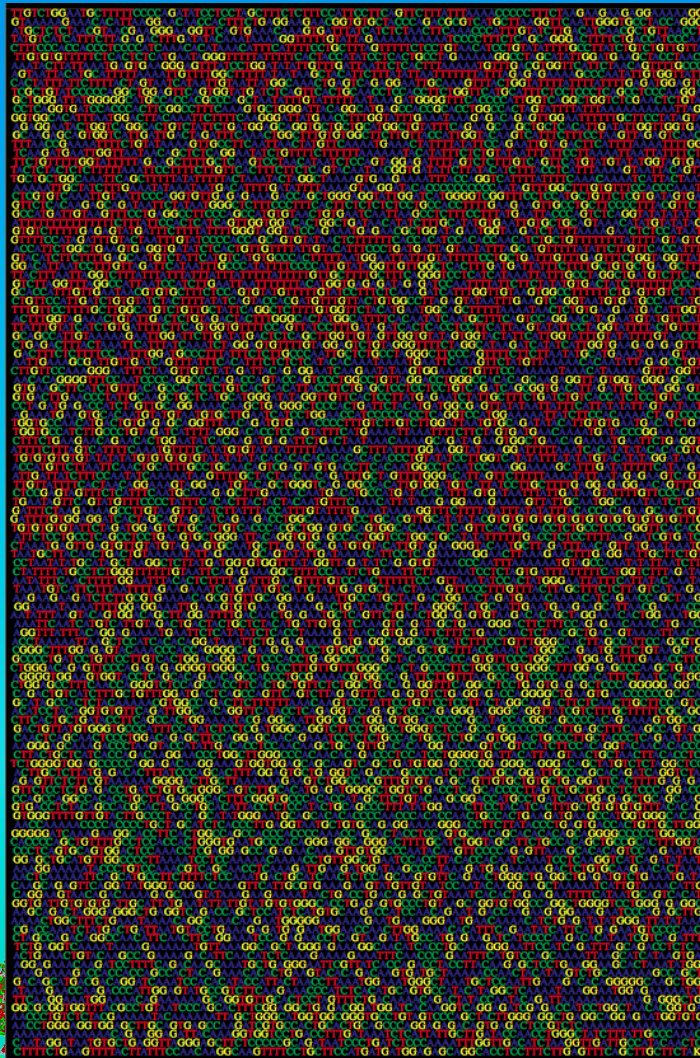
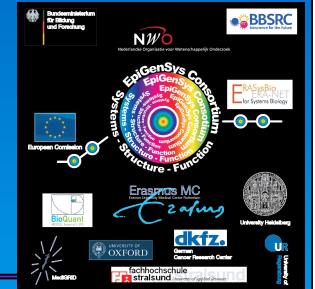
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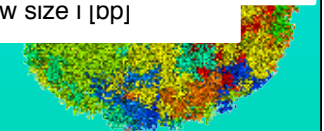
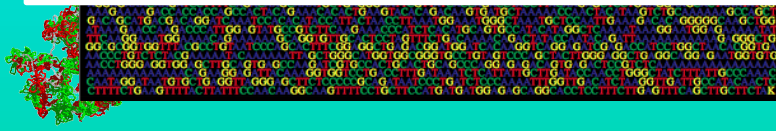
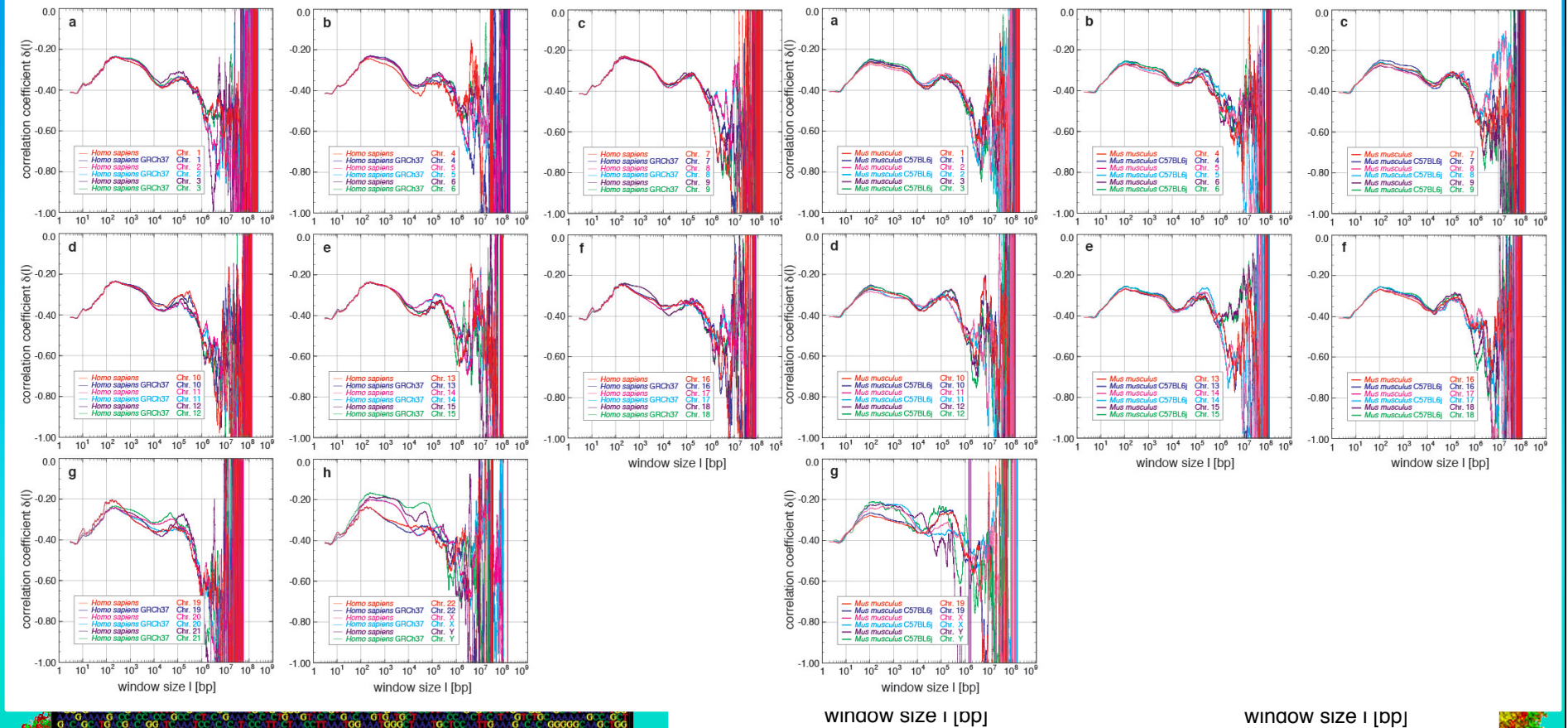
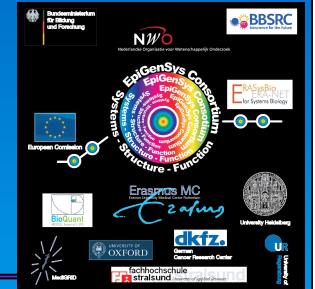
Nucleosomal Positioning Prediction

The DNA sequence is analyzed by the most simplest scaling analysis to find unprejudiced patterns as e.g. nucleosome positions as well as chromatin loops and rosettes. The analysis is done using our grid infrastructures and here especially our volunteer grid.



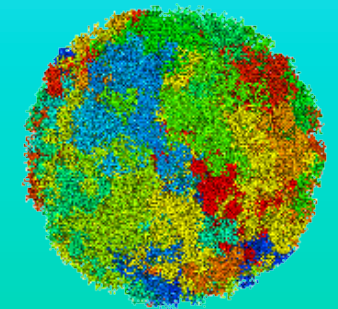
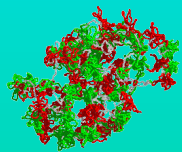
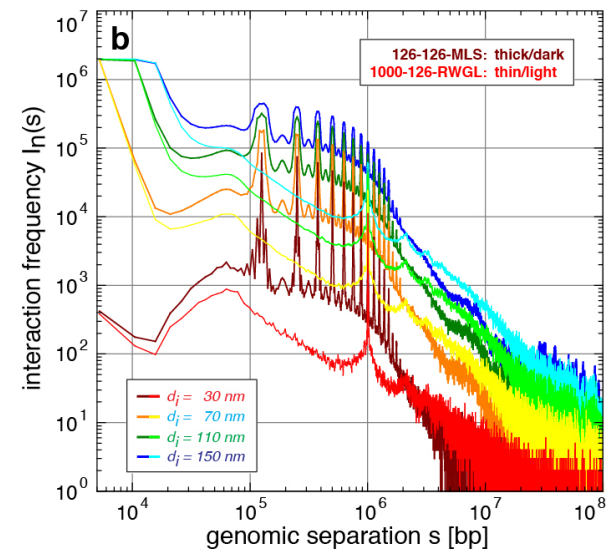
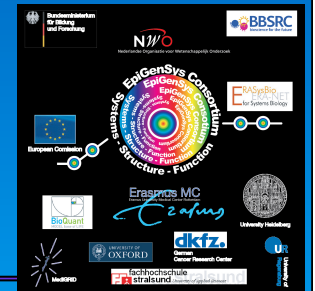
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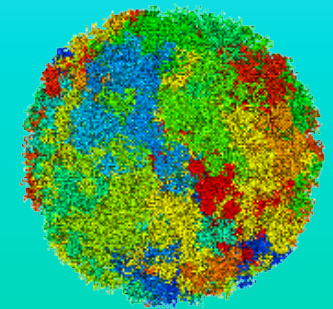
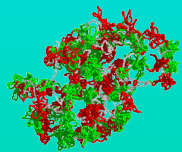
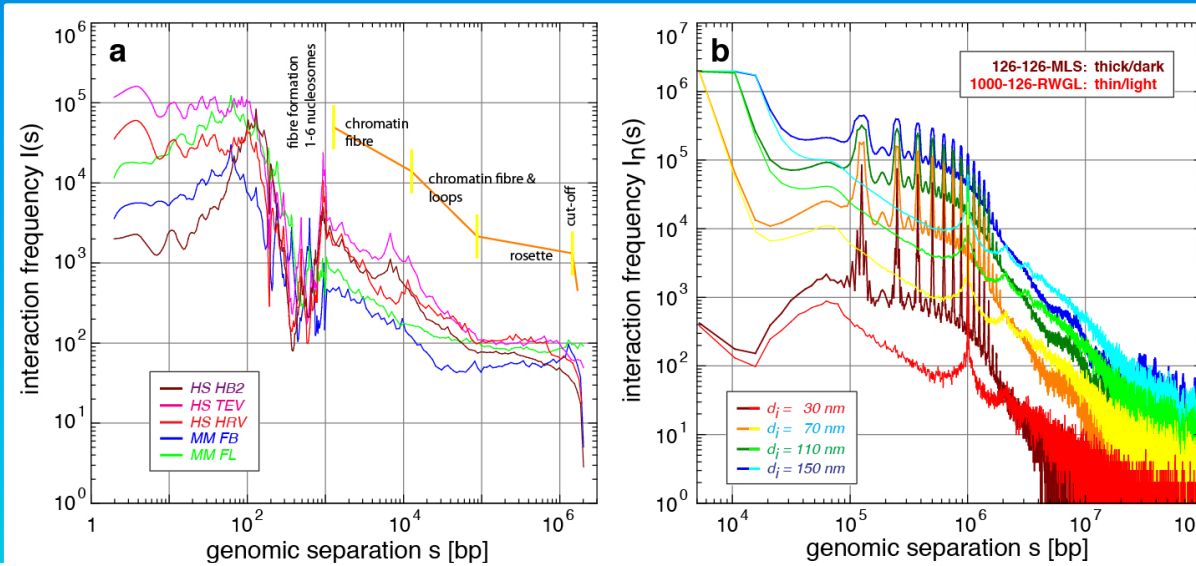
Scaling Analysis

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.



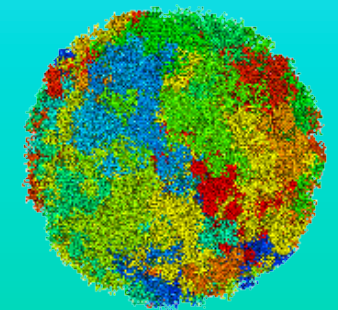
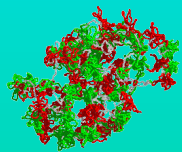
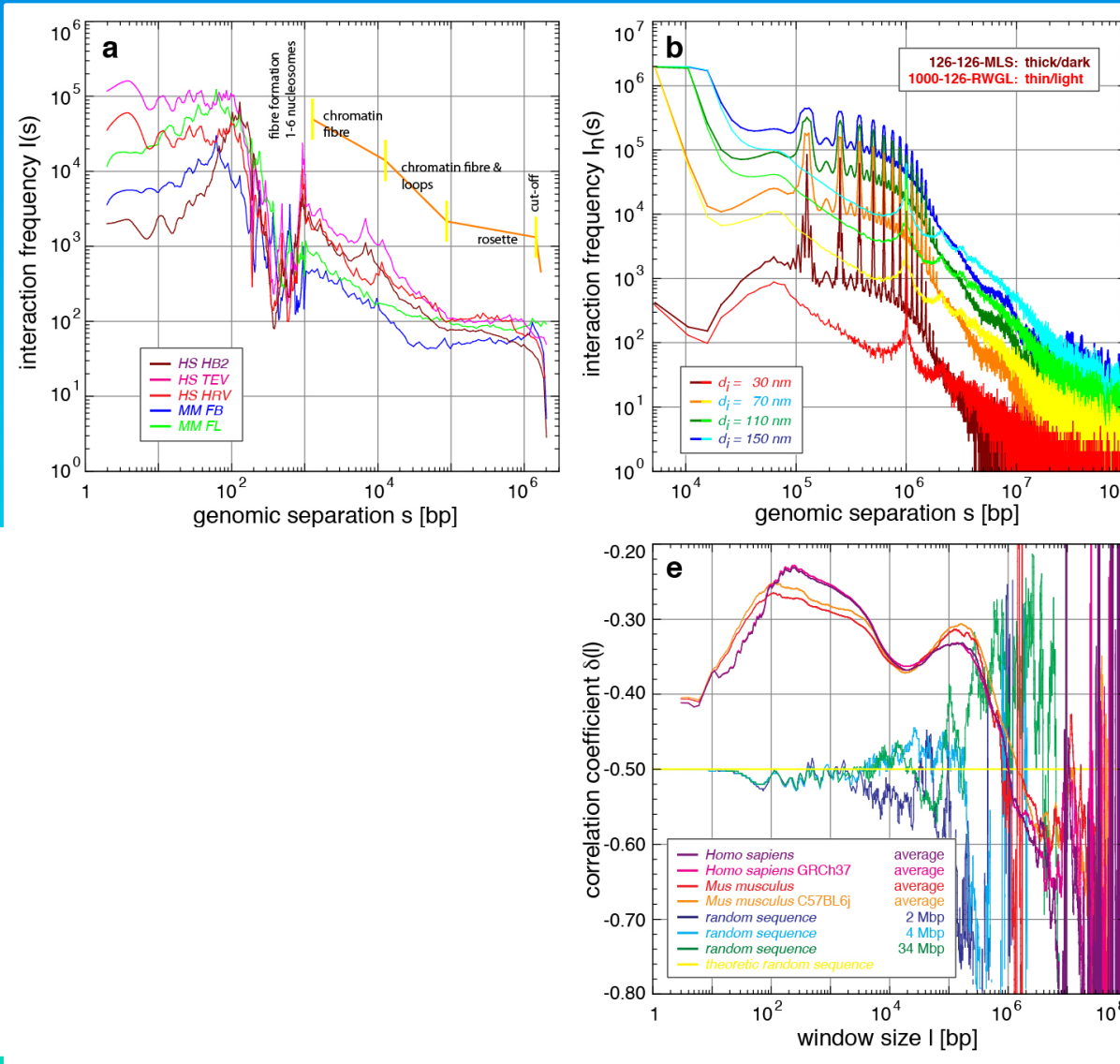
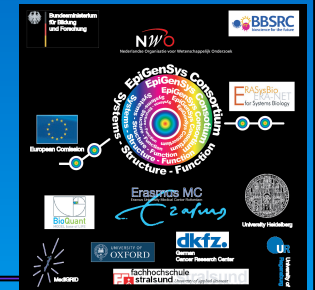
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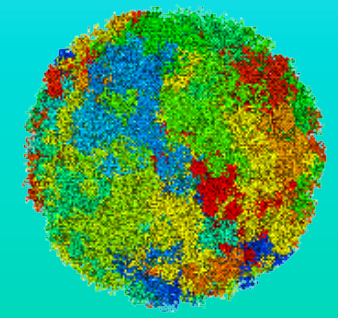
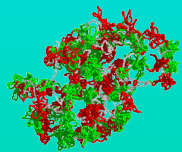
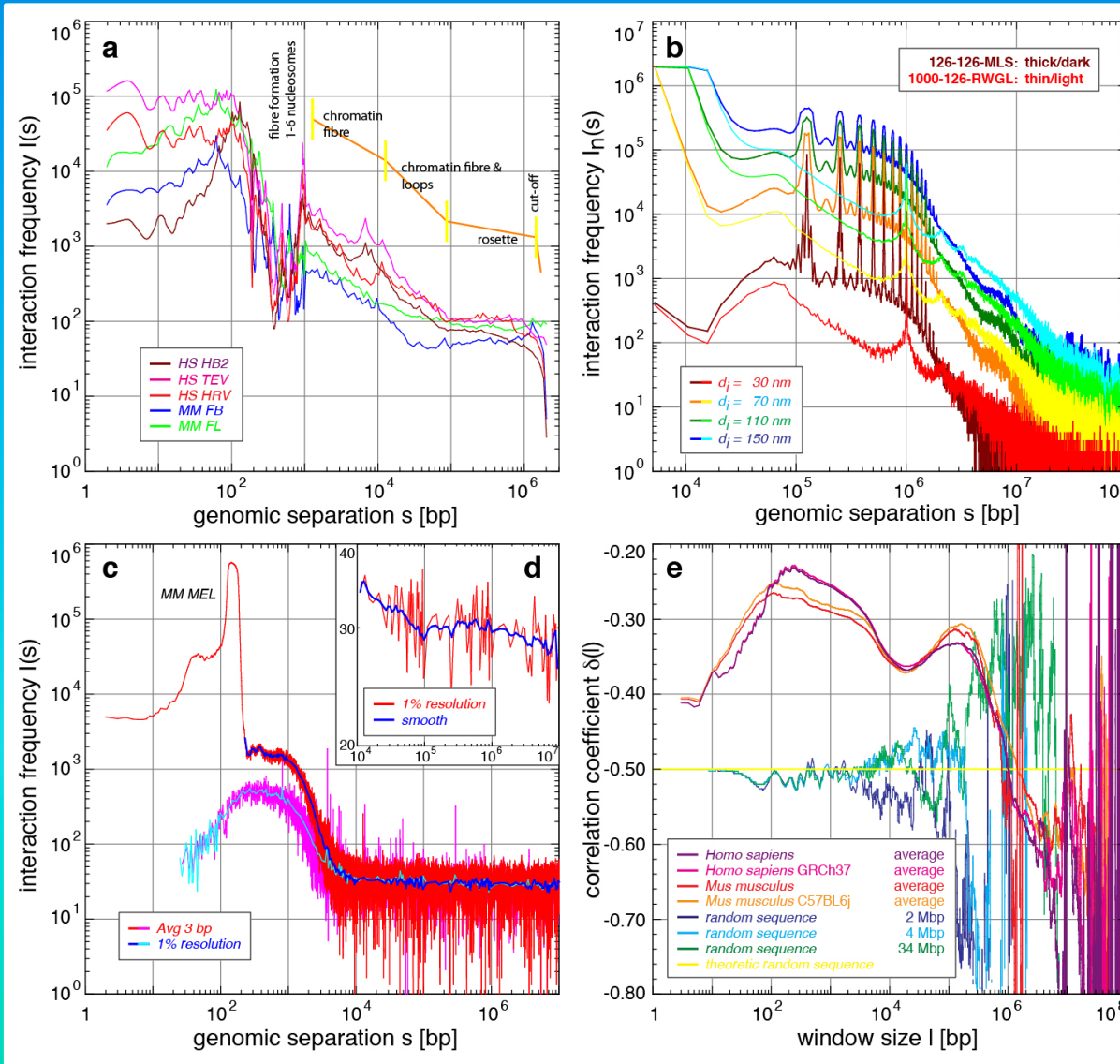
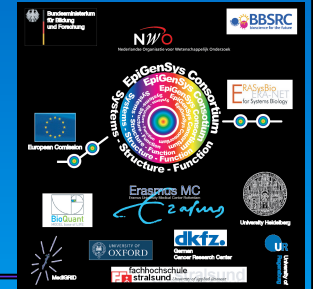
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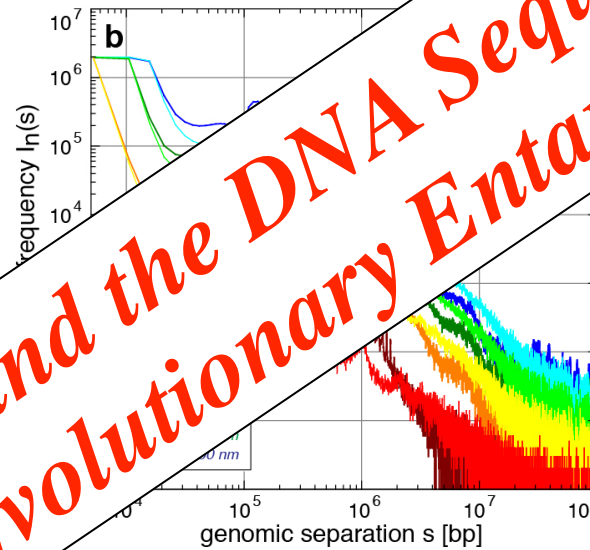
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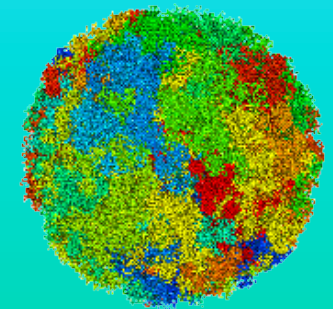


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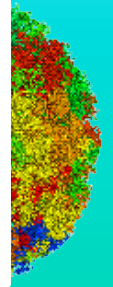
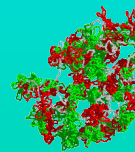
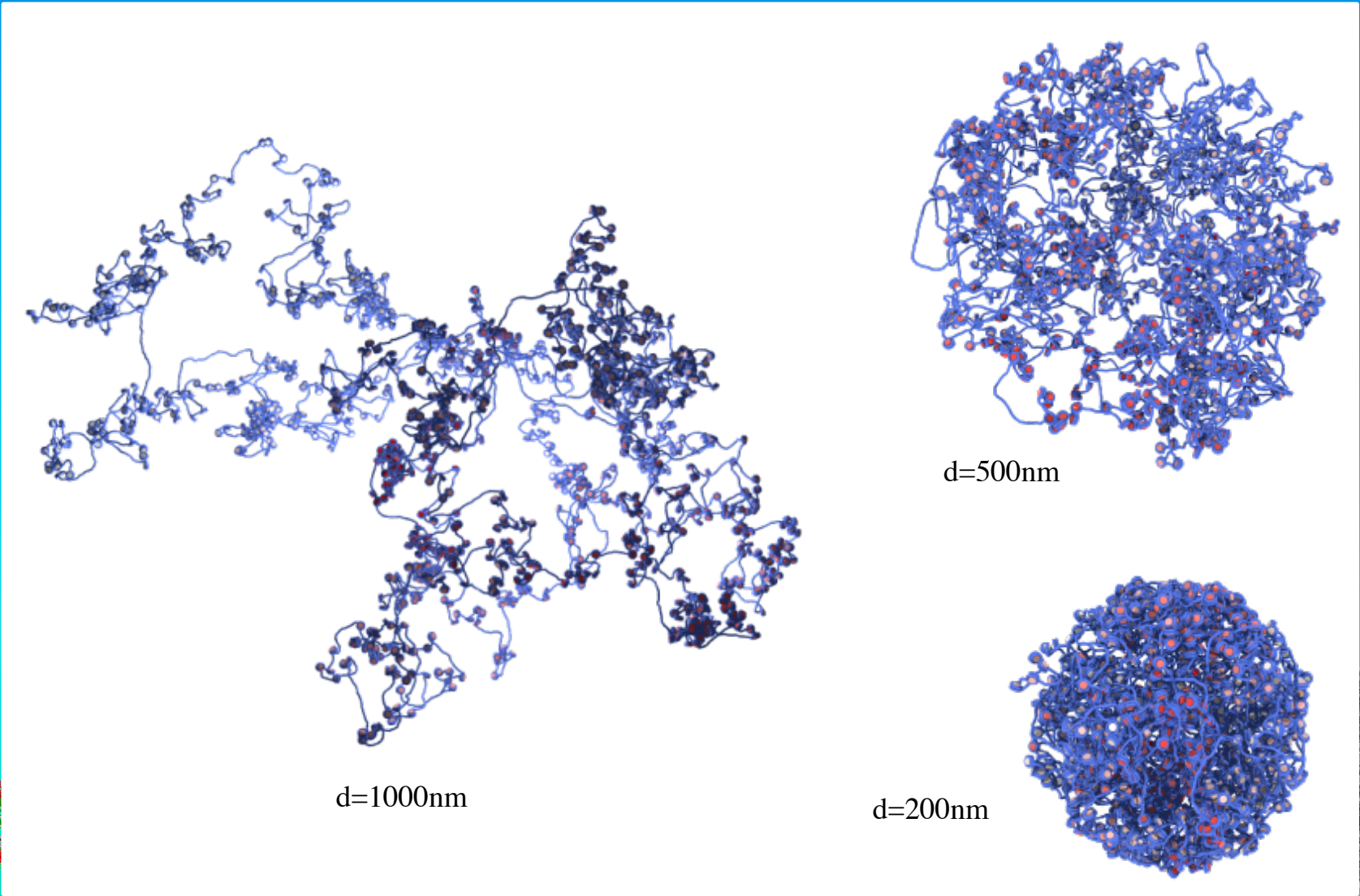


The 3D Architecture and the DNA Sequence Organization are Evolutionary Entangled!



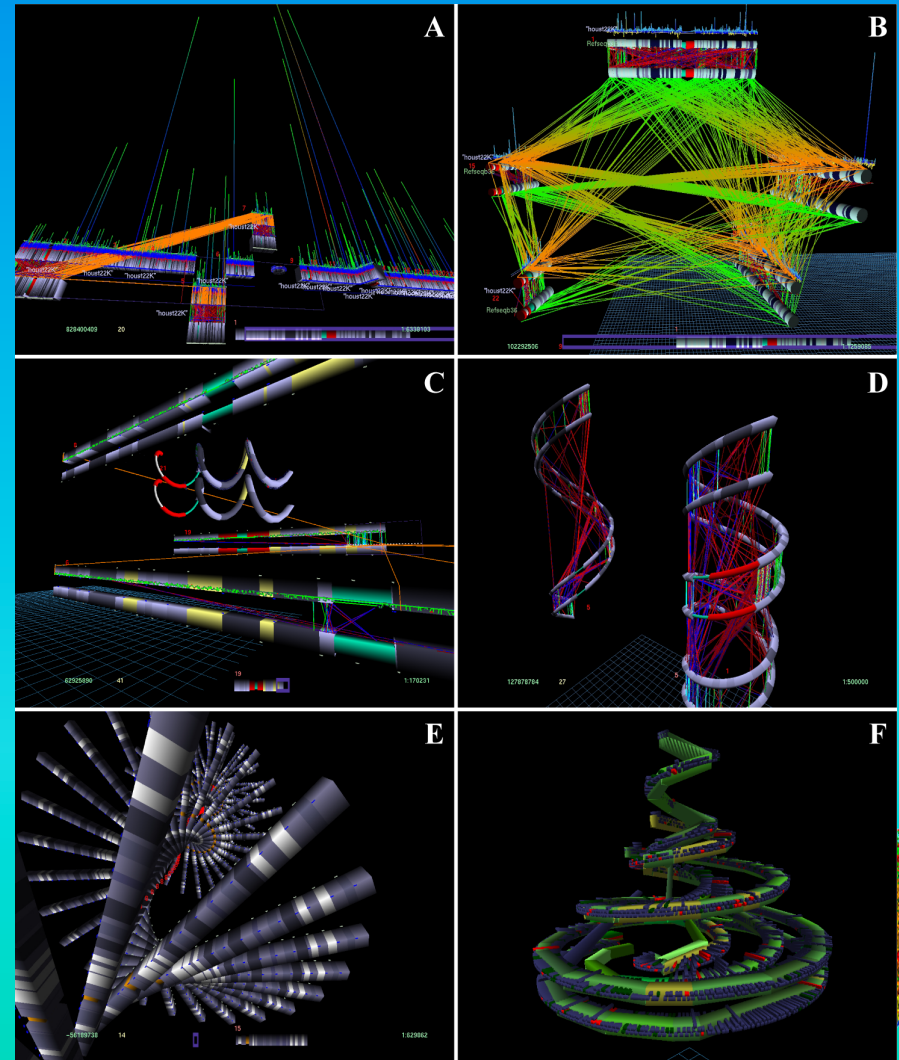
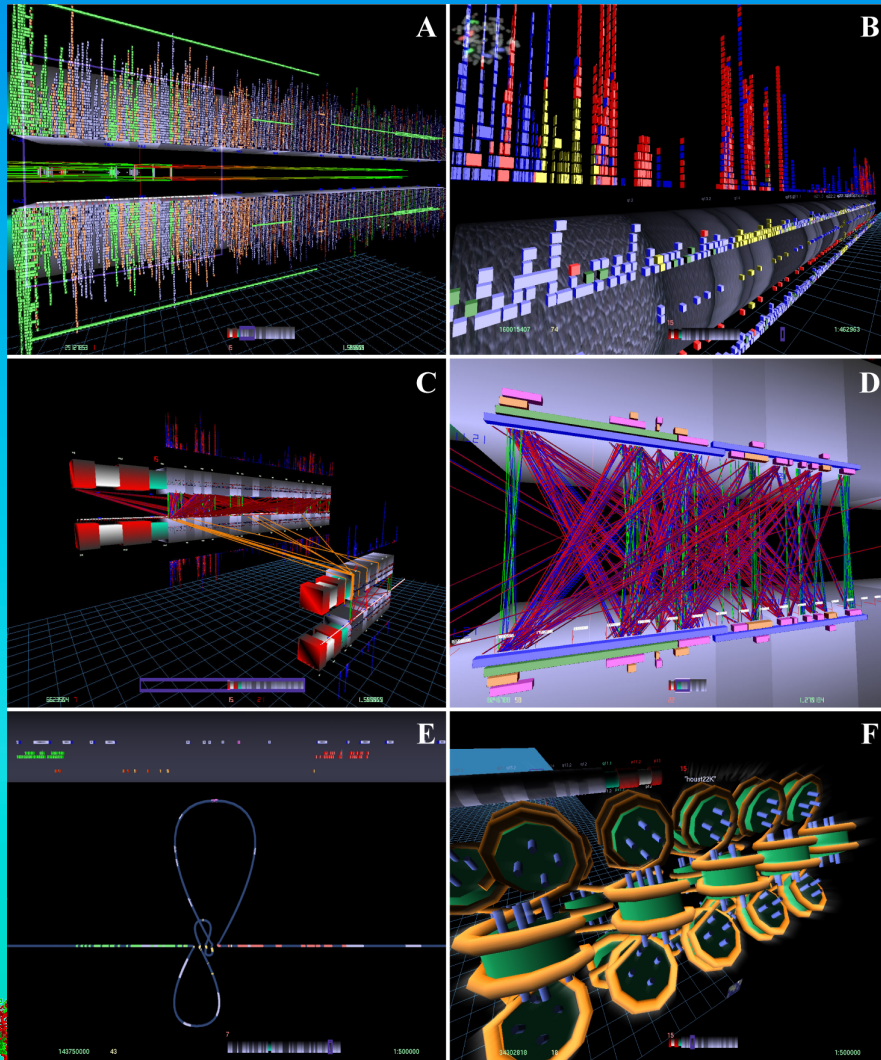
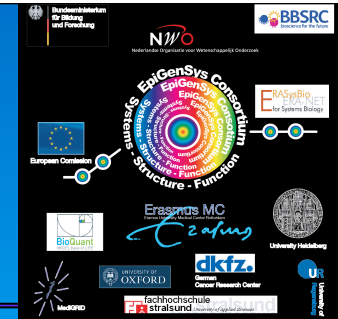
Simulation of Nucleosomes & Chromatin

The position of nucleosomes influence greatly the structure of chromatin fibers done on super-computers. Here a dedicated workflow is applied, with which overlapping nucleosome populations can be analyzed and the best positioning of nucleosomes by Monte Carlo simulated annealing can be achieved. For an actual locus in a spherical confinement then a 3D independent nucleosome fibre conformation can be simulated.



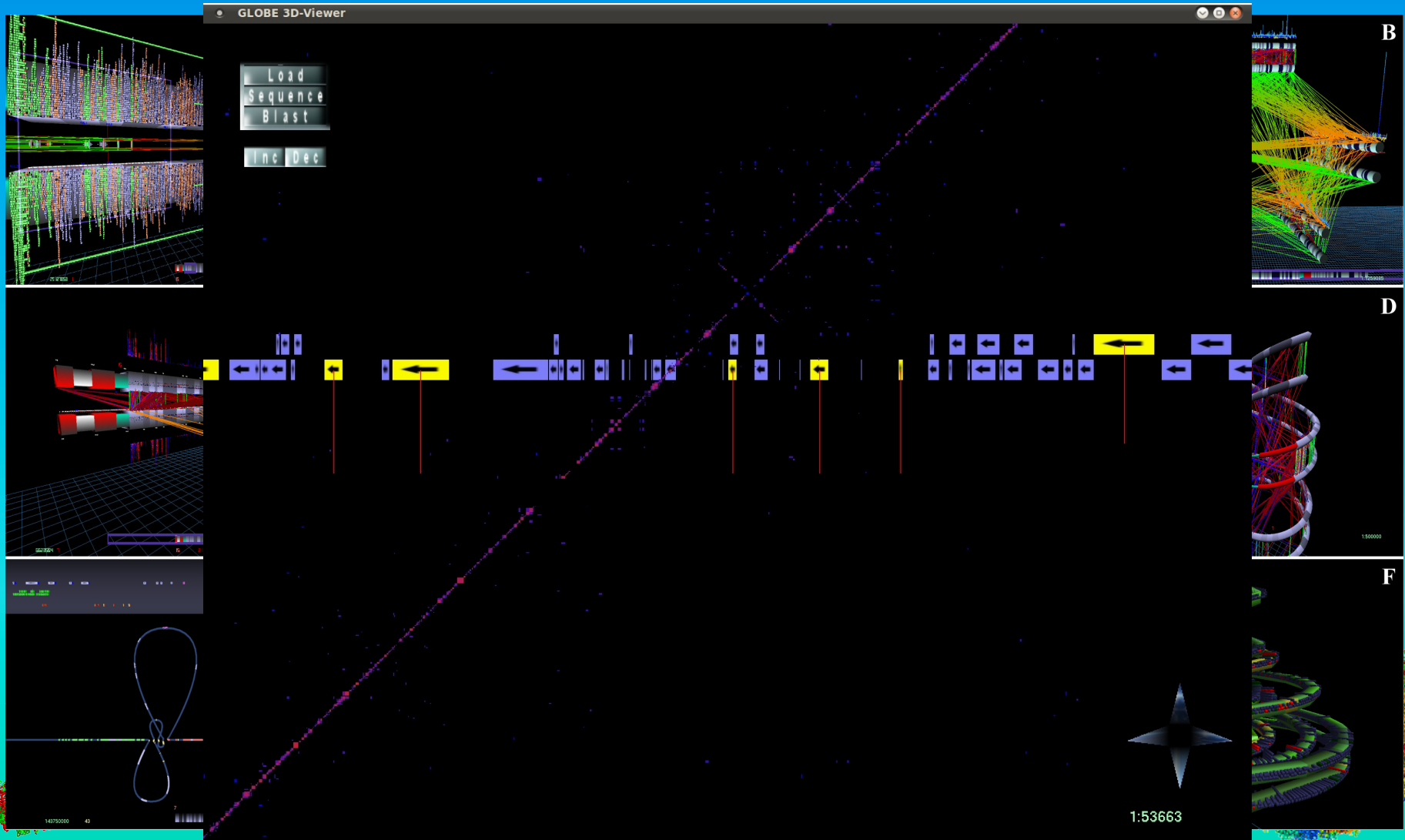
Systems Biological Result Integration via the GLOBE 3D Genome Platform

All results will be integrated using our GLOBE 3D Genome Platform, established for analysis, manipulation and understanding of multi-dimensional complex genome wide data. Thus in reiterative cycles between experiments and simulations a systems biological/medical genome model will be achieved.



Systems Biological Result Integration via the GLOBE 3D Genome Platform

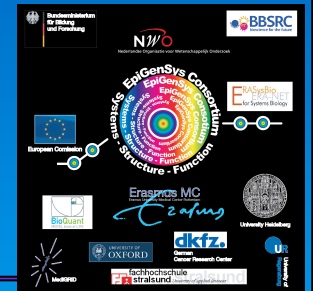
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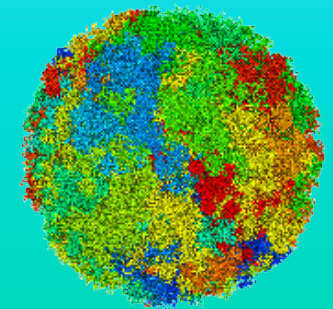
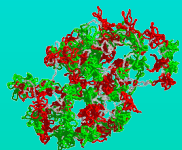
Nick Kepper
Michael Lesnussa
Anis Abuseiris
A.M. Ali Imam

Malte Wachsmuth
Gero Wedemann

Petros Kolovos
Jessica Zuin

Christel E. M. Kockx
Rutger W. W. Brouwer
Harmen J. G. van de Werken
Wilfred F. J. van Ijken

Kerstin S. Wendt
Frank G. Grosveld



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

Knoch, T. A.,

Kepper, N., Lesnussa, M., Abuseiris, A., Wachsmuth, M., Kolovos, P., Zuin, J., van den
Werken, H. J. G., Wendt, K. S. & Grosveld, F. G.

Nuclear Organization and Function, Cold Spring Harbor Laboratory, Cold Spring Harbor,
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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 of concentrated research, one of the central issues of our time. With a systems genomics combination of S2C and FCS together with analytical and simulated polymer models as well as scaling analysis it is now possible to gain insights into the architecture and dynamics with unprecedented detail. S2C is a novel superior selective high-throughput high-resolution chromosomal interaction capture of all physical genomic interactions (S2C) which has great advantages since it allows to reach an optimal combination of resolution, interaction frequency range, and multiplexability, at unprecedented signal-to-noise ratio of multiple orders of magnitude. With a novel FCS approach it is possible to determine the relaxation of local concentration fluctuations of the chromatin fibre and derive based on an analytical polymer model the relation between average persistence length, mass density and chromatin architecture. Whereas S2C measures architectural parameters, the FCS approach allows to measure *in vivo* the dynamics of the architecture. As common ground polymer simulations using Monte Carlo and Brownian Dynamics approaches round-off both techniques in detail. In combination both approaches reach agreement concerning the 3D architecture and dynamics of genomes in detail as well as in the general scaling of genomes which yields the same scaling properties derived from the DNA base pair sequence organization itself. Consequently, this finally opens the path to detailed architectural and dynamic sequencing of genomes in a systems genomic manner which is of fundamental importance for genome understanding in perspective as far as diagnosis and treatment.

Corresponding author email contact: TA.Knoch@taknoch.org

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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