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

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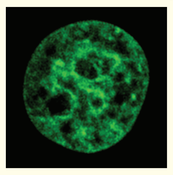
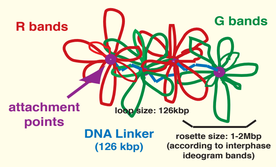
INTRODUCTION

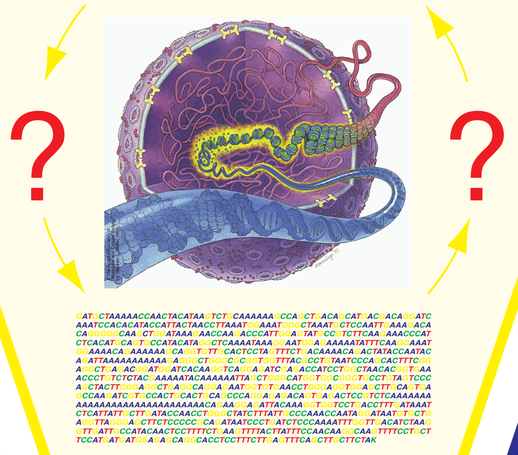
The dynamic 3D chromatin architecture of genomes and the obvious co-evolutionary connection to its function – the storage and expression of genetic information – is still, after ~170 years of concentrated research, one of the central issues of our time. By integration of experiments and simulations ranging from the DNA sequence to the nuclear morphology we show here an interdisciplinary approach leading to the final determination of the three-dimensional organization and dynamics of the human genome.

Nuclear chromatin morphology by histone H2A-YFP *in vivo* labelling



Multi-Loop-Subcompartment (MLS) model of chromatin folding (Knoch *et al.*, 1998, 2002)





T2C

Selective high-resolution high-throughput chromosome interaction capture (T2C) is used to map all interactions (everything-with-everything) in specific genetic regions (Fig. 1). From the interaction matrices visually or algorithmically, the compaction of the chromatin quasi-fibre, chromatin loops and their arrangement into loop aggregates/rosettes, as well as their interlinkage can be determined. The resulting architecture can also be derived by polymer physical means and simulations can be done. T2C shows a consensus structure bridging cell types and functional states with only minor variations, again only in agreement with MLS-model like architectures even at very high resolution (Fig. 2).

Fig. 1A & 1B: T2C interaction maps with logarithmic and rainbow coloured frequency range of the human IGF (A) and the β-Globin (B) loci in different cell types with annotated architectures and the derived and simulated architecture.

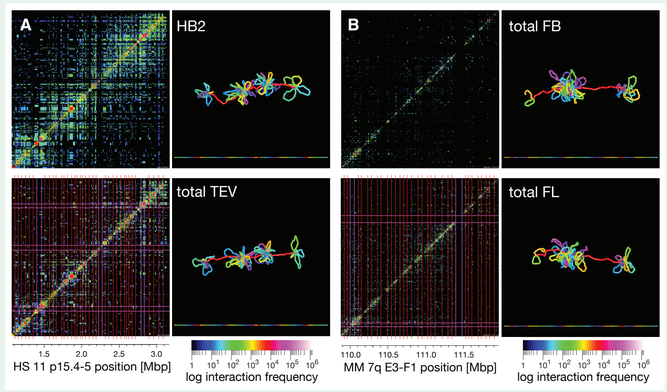
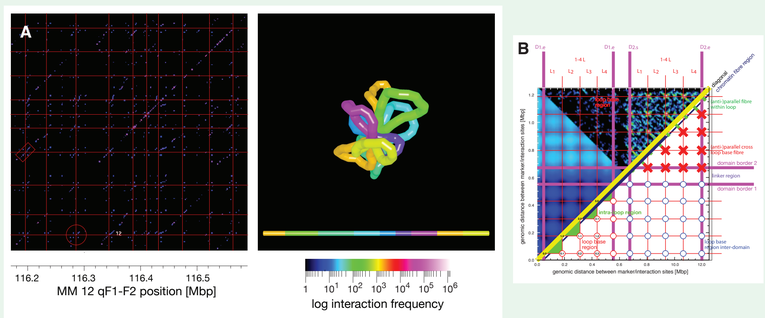


Fig. 2A & 2B: At highest molecular resolution in the mouse IGH locus the limit of the "genomic" uncertainty principle and statistical mechanics is reached and shows in detail the folding of subchromosomal domains which again can be simulated (A). Again there is agreement with an MLS model like chromatin architecture even in the finest details (B).



SIMULATION

For the prediction of experiments we simulated various models of human interphase chromosome 15 with Monte Carlo and Brownian Dynamics methods. The chromatin fiber was modelled as a flexible polymer fiber. Only stretching, bending and excluded volume interactions are considered. Chromosomes are further confined by a spherical potential representing the surrounding chromosomes or the nuclear membrane. Only the MLS model leads to clearly distinct functional and dynamic subcompartments in agreement with experiments (Fig. 8B & 1A) in contrast to the RW/GL models where big loops are intermingling freely and featureless (Fig. 8C & 8D).

Fig. 8A: Starting configuration with the form and size of a metaphase chromosome.

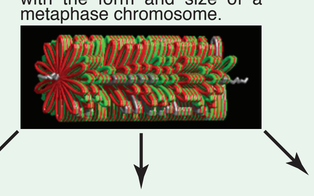


Fig. 8B: MLS model with 126 kbp loops and linkers.

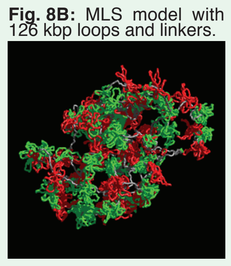


Fig. 8C: RW/GL model with 126 kbp loops.

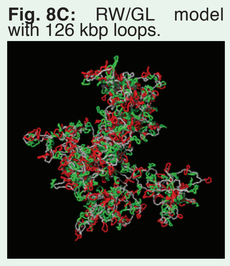


Fig. 8D: RW/GL model with 5 Mbp loops.

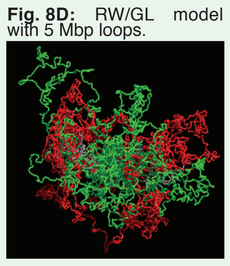
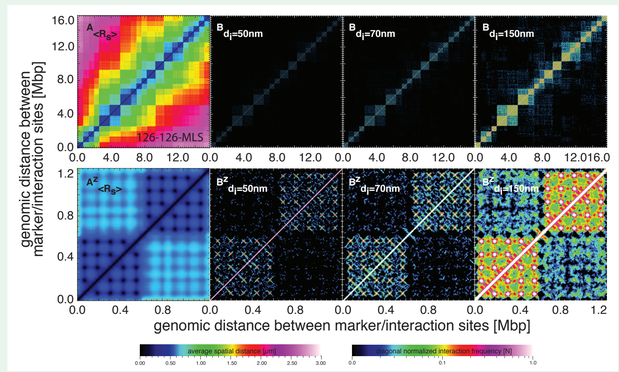


Fig. 9A & 9B: 2D distance average spatial distance and simulated interaction frequency maps for three different interaction radii. Only the MLS model represents the architecture found by T2C to a very detailed degree.



CONCLUSION

With a novel selective high-throughput high-resolution chromosomal interaction capture (T2C), the limit of the "genomic" uncertainty principle and statistical mechanics is reached revealing the existence of a chromatin quasi- fibre, folding into loops, which form loop aggregates/ rosettes connected by a linker. A consensus architecture exists between with only small but obviously significant fuctional differences. Spatial distances using FISH and comparison to polymere simulations agree only with a rosette-like architecture of chromosomes as proposed by the MLS model. The scaling of T2C interactions, spatial distances, simulations, and the DNA sequence organization itself, all show the same fine-structured multi-scaling behaveour, again only in agreement with an MLS model being tightly entangled with the DNA sequence. Consequently, we finally open the path to detailed architectural "sequencing" of genomes in a systems genomics manner at the limit of the "genomic" uncertainty principle and statistical mechanics with fundamental importance for diagnostis and treatment.

FISH IGH DYNAMICS

By 3D-FISH and a novel epifluorescent Spectral Precision Distance Microscopy approach, combined with a comparison to computer simulations (Fig. 8), the spatial organization was approached in diffrent functional states resulting in functional depending spatial distance distributions as function of genetic separation (Fig. 3), which agree best with an MLS model with loops and linkers of ~80 to 150 kbp (Fig. 4B) as well as very obvious functional architectures after trilateration (Fig. 4B & 4C). This agrees with the fine-structured multi-scaling of the DNA sequence (Fig. 5), the nuclear morphology *in vivo*, as well as interaction maps generated by chromosomal conformation capture combined with our novel selective interaction capture (T2C) .

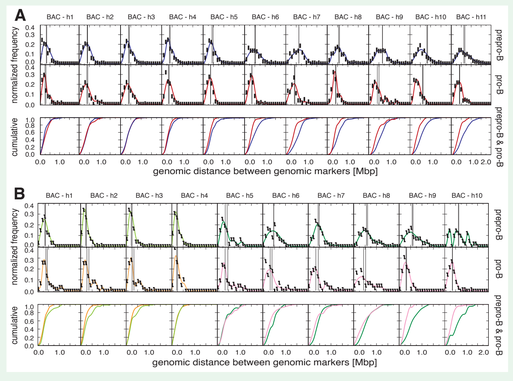
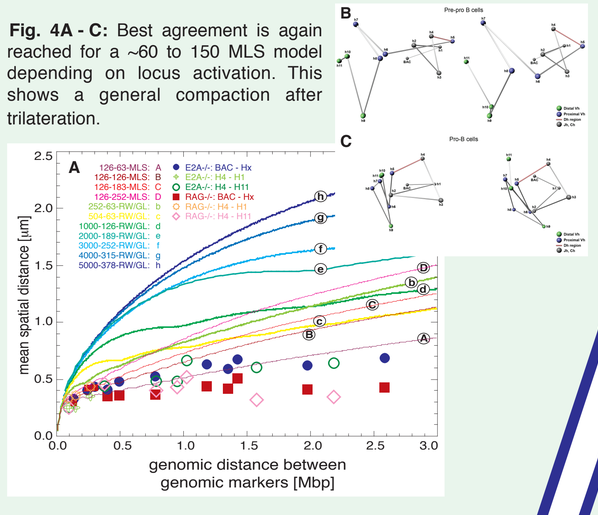


Fig. 3A & 3B: Activation of the IgH locus leads to compaction and clear differences in the dynamic behaveour depending on the local invironment.

Fig. 4A - C: Best agreement is again reached for a ~60 to 150 MLS model depending on locus activation. This shows a general compaction after trilateration.



DNA Sequence Correlations

Correlation analysis of completely sequenced genomes reveals fine-structured multi-scaling long-range correlations which are linked to the three-dimensional genome organization (Fig. 5). The general multi-scaling behaviour is due to a block organization and the fine-structure is attributable to the codon usage and to nucleosomal binding. Computer generated random sequences agree with these results. Mutation by sequence reshuffling destroyed all correlations. Trees constructed from the species specific correlation behaviour were as expected for Eukarya (Fig. 6) and led to a new classification system for Archaea and Bacteria (Fig. 7).

Fig. 5: Comparison of the average correlation behaviour of Eukarya, Archaea and Bacteria classes.

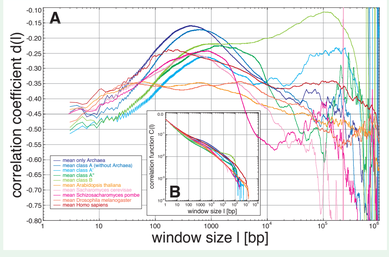


Fig. 6: Tree of Eukarya.

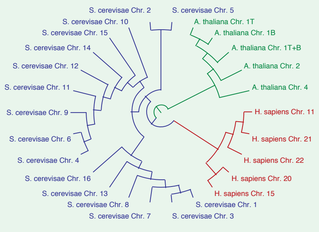
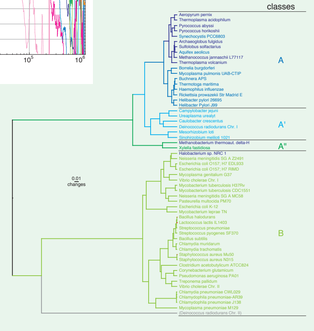


Fig. 7: Tree of Archaea & Bacteria.



SCALING ANALYSIS

Scaling analysis is especially suited to quantify the unordered and non-euclidean chromatin distribution of the nucleus. The dynamic behaviour of the chromatin structure and the diffusion of particles in the nucleus are also closely connected to the scaling behaveour. Scaling analyses of T2C data show a fine-structured multi-scaling behaveour revealing in detail the nucleosomal structure, besides corresponding to the formation of a chromatin quasi-fibre with a density of 5±1n/11nm and an average persistence length L_p of ~70-150nm, folded into 40-100kbp loops, forming loop aggregates/rosettes connected by a linker (Fig. 10A & 11). The scaling behaveour only agrees with the scaling of MLS-model like chromosomal architectures (Fig. 10B).

Fig. 10A & 10B: The human IGF and mouse β-Globin loci show in the human HB2, TEV/HRV, as well as mouse fetal brain (FB) and liver (FL) cell lines all the same fine-structured multi-scaling behaveours leading to loci specific consensus architectures, agreeing only with an MLS-model like chromosome organization.

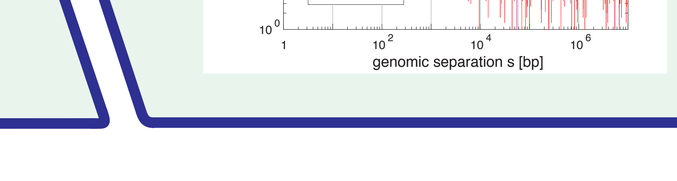
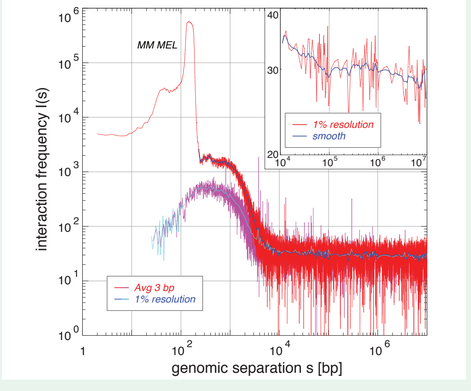


Fig. 11: With a single base pair resolution at the limit of the "genomic" uncertainty principle and statistical mechanics, the scaling behaveour reveals not only the structure of the nucleosome, but also describes the formation of the chromatin quasi-fibre, its average density, as well as average dynamic properties with unprecedented detail, besides showing the loop aggregate/rosette architecture again.



The Results and Functional Meaning

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Detailed 3D Multi-Loop Aggregate/Rosette Chromatin Architecture

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Functional Dynamic Organization of the Human and Mouse Genomes

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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 debated after ~170 years. With a systems genomics approach combining a novel selective high-throughput chromosomal interaction capture (T2C) with quantitative polymer simulations and scaling analysis of architecture and DNA sequence, we determined and cross-proved the final architecture of genomes with unprecedented molecular resolution and dynamic range from single base pairs to entire chromosomes: for a variety of genetic loci of different species, cell type, cell cycle, functional states and system distortion a chromatin quasi-fibre exists with 5±1 nucleosome per 11 nm, which folds into stable(!) 40-100 kbp loops forming stable(!) aggregates/rosettes which are connected by a ~50 kbp chromatin linker. Modifications on all these organizational levels are variations of the aforementioned scheme. Beyond, functional variations on various levels are reflected also on others. Spatial isotropy breaking is also found. Polymer simulations using Monte Carlo and Brownian dynamics approaches confirm this and predict and explain additional experimental findings. Beyond, a novel fluorescence correlation spectroscopy (FCS) approach combined with analytical polymer models measures the architectural dynamics *in vivo* in the entire genome and agrees with the before mentioned conclusion using completely independent means. System distortions are reflected in the corresponding variations as well. Beyond, we find a fine-structured multi-scaling behaviour of both the architecture and the DNA sequence, showing for the first time directly the tight entanglement between architecture and sequence. All this agrees with the outcome of a synopsis e.g. with previous spatial distance measurement studies, *in vivo* morphology of entire cell nuclei, or electron microscopy of chromosome spreading studies, as well as the heuristics of the field in the last 170 years. This now complete architecture and dynamics of these genomes has fundamental consequences for the entire system of the storage and expression of genetic information as well as for its investigation in general: E.g. this architecture, its dynamics, and accessibility balance stability and flexibility ensuring genome integrity and variation enabling gene expression/regulation by self-organization of (in)active units already in proximity. Thus, both the T2C and FCS approaches open the door to "architectural and dynamic sequencing" of genomes at a resolution where a genome mechanics with corresponding uncertainty principles applies. Consequently, this will lead now to a detailed understanding of genomes with fundamental new insights and huge novel perspectives for diagnosis, treatment and genome engineering efforts in the future.

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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.

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simultaneous co-transfections. *Dissertation*, Ruperto-Carola University, Heidelberg, Germany, and TAK†Press, Tobias A. Knoch, Mannheim, Germany, ISBN 3-00-009959-X and ISBN 978-3-00-009959-5 (soft cover, 3rd ed.), ISBN 3-00-009960-3 and ISBN 978-3-00-009960-1 (hard cover, 3rd ed.), ISBN 3-00-035856-9 and ISBN 978-3-00-010685-9 (DVD, 3rd ed.) 2002.

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