Approaching the Three-Dimensional Intra/Inter Chromosomal Architectural and Dynamic Organization of the Human Genome

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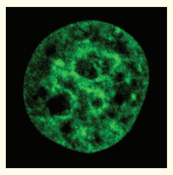
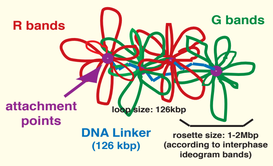
INTRODUCTION

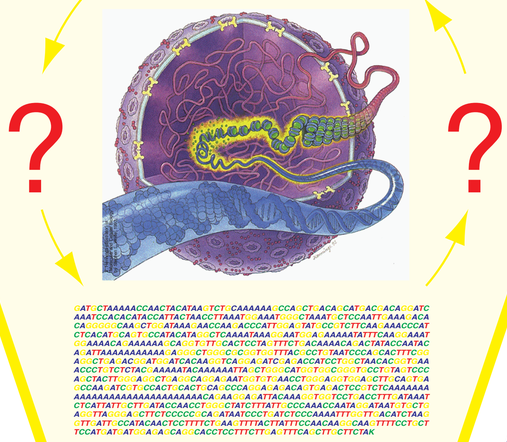
Despite the successful linear sequencing of the genome its three dimensional structure is widely unknown although its importance for gene regulation and replication. By integration of experiments and simulations ranging from the DNA sequence to the nuclear morphology we show here an interdisciplinary approach leading to the 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)





PWS REGION

Fluorescence *in situ* hybridization (FISH) is used for the specific marking of chromosome arms (Fig. 1A) and pairs of small chromosomal DNA regions (Fig. 1B). The labelling is visualized with confocal laser scanning microscopy followed by image reconstruction. Chromosome arms show only small overlap and globular substructures, as predicted by the MLS-model (Fig. 1A & 9A). A comparison between simulated and measured spatial distances between genomic regions as function of their genomic distances results in a good agreement with the MLS-model having loop sizes of arround 80 to 150 kbp and linker sizes between 63 kbp and 126 kbp (Fig. 2A) and a defined 3D space (Fig. 2B).

Fig. 1A & 1B: FISH-images of a territory painting of chromosome 15 (A) and genomic markers YAC-48 and YAC60 (B) with a genomic separation of 1.0 Mbp in interphase of fibroblast cells.

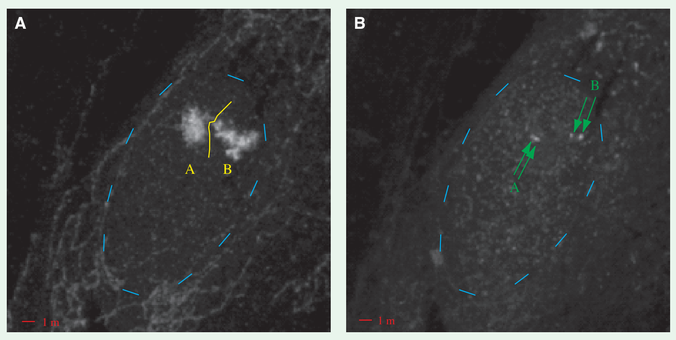
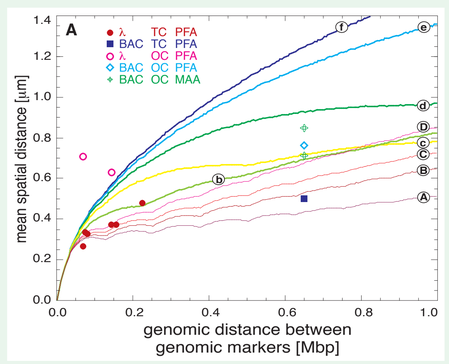


Fig. 2A & 2B: Comparison of the RW/GL- and the MLS-model with experimentally determined interphase distances agrees best with an MLS model of ~80 to 150 kbp loop aggregates separated by also ~60 to 126 kbp linkrs (A). Trilateration of the distances leads clearly to the same conclusion of a compact looped structure (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.

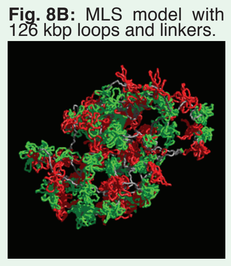


Fig. 8C: RW/GL model with 126 kbp loops.

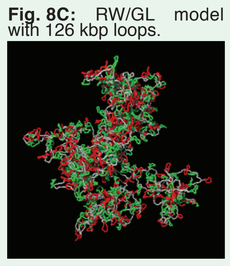


Fig. 8D: RW/GL model with 5 Mbp loops.

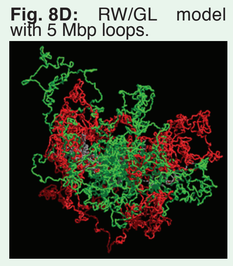
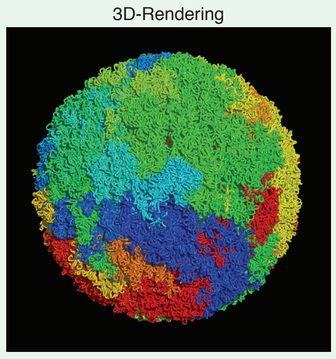
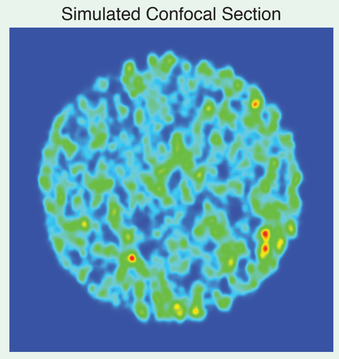


Fig. 9A & 9B: Simulation of a human interphase nucleus containing all 46 chromosomes with 1,200,000 polymer segments. The MLS-model leads to the formation of distinct and non-overlapping chromosome territories.

3D-Rendering



Simulated Confocal Section



CONCLUSION

Simulations of chromsomes and the whole cell nucleus show that only the MLS-model leads to the formation of non-overlapping chromosome territories and distinct functional and dynamic sub-compartments. Spatial distances between FISH labeled pairs of genomic markers as function of their genomic distance agrees with an MLS-model with loop sizes of ~80 to 150 kbp and linker sizes of 60 to 126 kbp. This is true for both the PWS as well as the IgH loci with clear functional dependences both concerning the 3D architecture as well as its dynamics. This is also in agreement with the *in vivo* morphology as visualized by Histone-GFP and the interaction mapping by chromosome conformation capture combined with high-throughput sequencing. Completely sequenced genomes show fine-structured multi-scaling long-range correlations favouring again an MLS like model. Consequently, genomes show a three-dimensional as well as sequential organization of high complexity, which is closely related to each other in a systems biology/medical co-evolutionarily developed holistic entity.

IgH LOCUS DYNAMICS

The Immunoglobin Heavy-Chain locus has a complex organization. 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 distance distributions (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 novel high-throughput sequencing techniques.

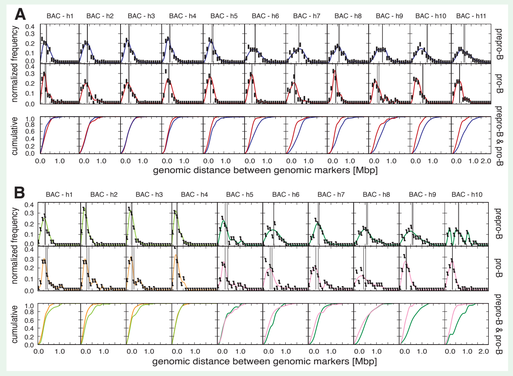


Fig. 3A & 3B: Activation of the IgH locus leads to compaction and clear differences in the dynamic behaveour depending on the local invironment.

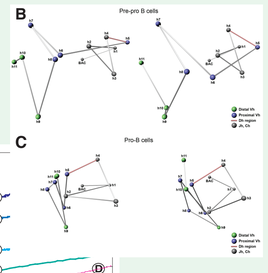
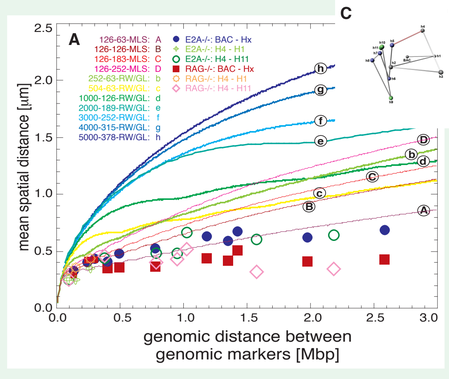


Fig. 4A - C: Best agreement is again reached for a ~60 to 150 MLS model depending on locus activation. This shows a general compaction after trilateration.



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.

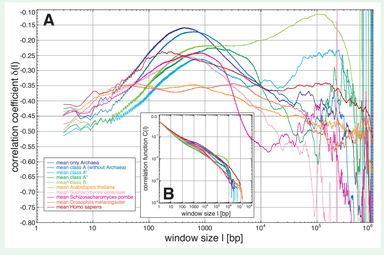


Fig. 6: Tree of Eukarya.

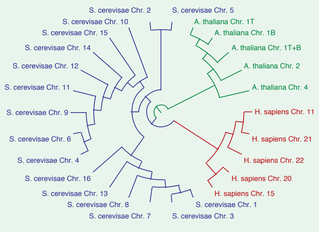
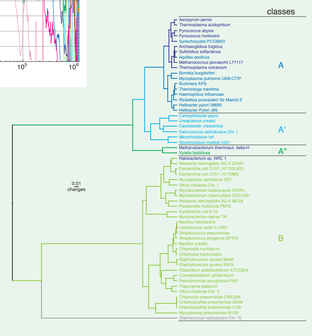


Fig. 7: Tree of Archaea & Bacteria.

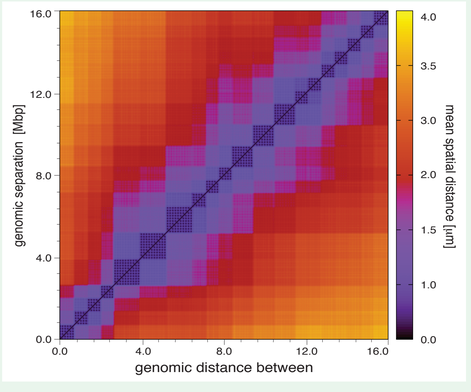


INTERACTION MAPPING

The complete description of the three-dimensional organization is given by the complete map of interaction probabilities between every genomic location to each other, which is the inverse of the complete map of spatial distances between every genomic location to each other. This can be obtained by a novel chromosome conformation capture combined with high-throughput sequencing technique or high-throughput multi-colour FISH methods. Whereas the first gives the averages, the second also results in the attached distribution. Simulation of these maps again lead to best agreement with experiments for MLS models and shows the details of the loop, aggregate and chromosomal arrangement in their functional context.

Fig. 10A & 10B: Complete spatial distance maps between genomic loci to each other in a region of ~16Mbp with a resolution of 5.2 kbp shows clearly the loop size, structure and arrangement of RW/GL models (A: Fig. 8C; B: 8D) including their distribution along the chromosome. This clearly is different compared to all experimental evidences.

Fig. 11: Complete spatial distance maps between genomic loci to each other in a region of ~16Mbp with a resolution of 5.2 kbp of an MLS model with loops and linkers of 126kbp (Fig: 8B) shows clearly the loop size, structure and arrangement within the chromosome including their variation. This is in agreement with experimental data from various sources.



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Abstract

Genomes are tremendous co-evolutionary holistic systems for molecular storage, processing and fabrication of information. Their system-biological complexity remains, however, still largely mysterious, despite the huge advances in the understanding of the general sequential, three-dimensional and regulatory organization. With the development of the *GLOBE 3D Genome Platform* we have created a completely novel grid based virtual "paper" tool and in fact the first systems biological/medical genome browser integrating the holistic complexity of genomes in a single easy comprehensible way, which is used in WP1-5. Based on a detailed study of biophysical and IT requirements, every architectural level from sequence to morphology of one or several genomes can be approached in a real (WP1-3) and in a simulated symbolic representation (WP4) simultaneously and navigated by continuous scale-free zooming within a three-dimensional OpenGL and grid driven environment. In principle several multi-dimensional data sets can be visualized, customized in terms of arrangement, shape, colour, and texture etc. as well as accessed and annotated individually or in groups using internal or external data bases/facilities. Hence, the GLOBE 3D Genome Platform is an example of a grid based approach towards a virtual holistic desktop for system biological/medical genomic work combining the three fundamental distributed resources: i) visual data representation, ii) data access and management, and iii) data analysis and creation.

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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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