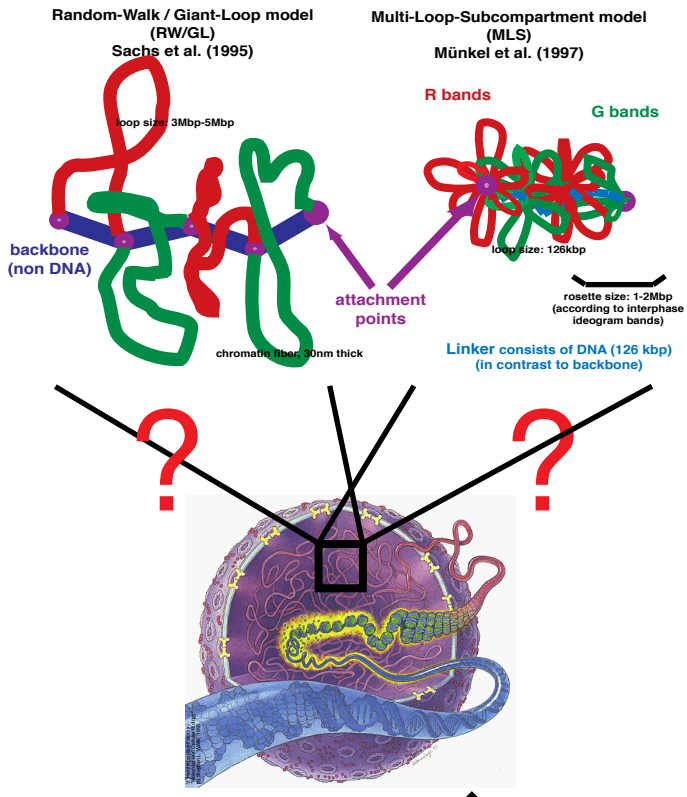
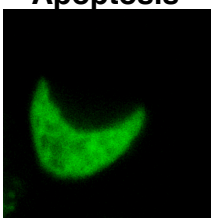
Three - Dimensional Organization of Chromosome Territories and the Human Cell Nucleus

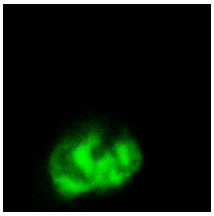
Tobias A. Knoch
and
Jörg Langowski

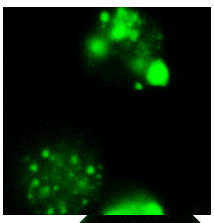
Biophysics of Macromolecules
DKFZ, Heidelberg



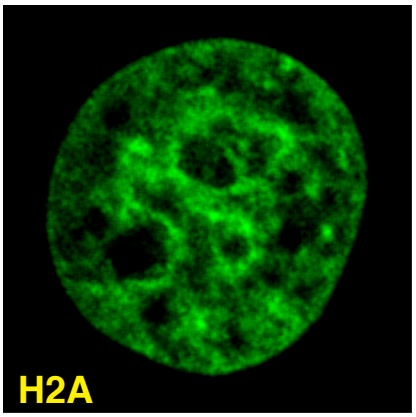
Apoptosis



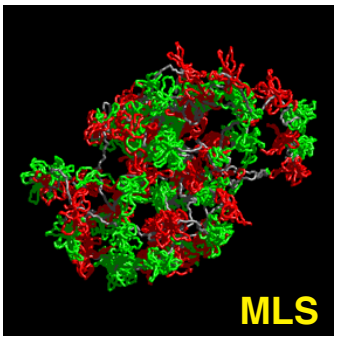


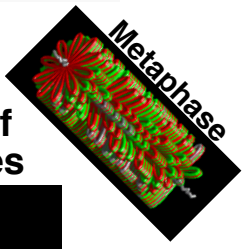


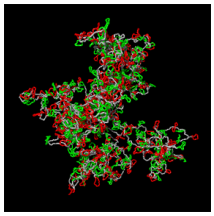
Chromatin Labeling in vivo

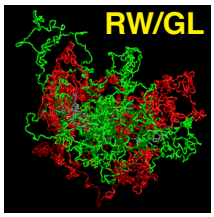


Simulation of Chromosomes

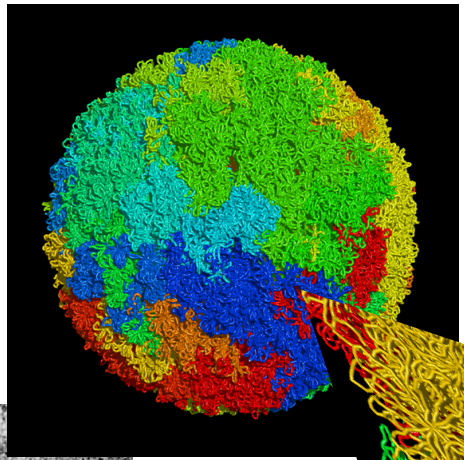


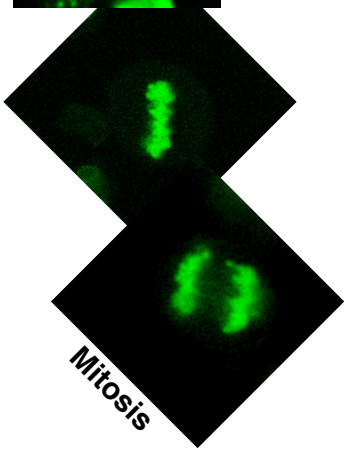


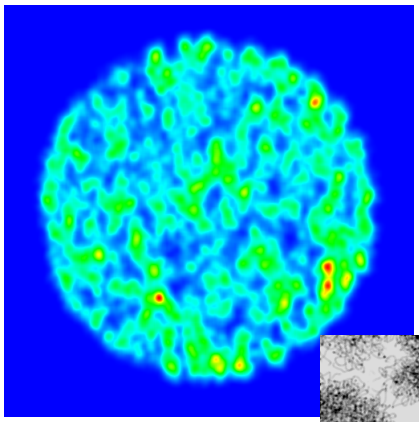




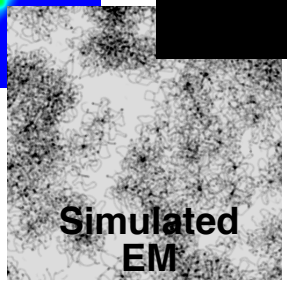
Simulation of Nuclei



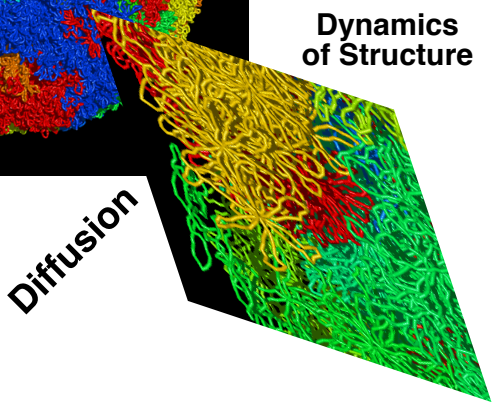




Simulated Confocal Image

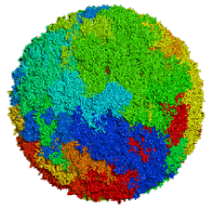


Dynamics of Structure



Comparison between simulated parameters and experiments:

A Multi-Loop-Subcompartment (MLS) like model is favoured !



Tobias A. Knoch

Measurement Categories	Measurements	Simulation Chrom.	Simulation Nucleus	Result
Distances:	- Genetic Markers	++	++	~ MLS
	- Ensemble of Markers	++	++	?
	- Consecutiv Subcomp.	+	++	nd
	- Pair Correlation of Subcomp.	~	++	MLS
Density:	- Radial Density Subcomp.	+	++	nd
	- Radial Density Chromosome	+	++	nd
Overlap:	- Subcompartment	~	++	MLS
	- Chromosomes	~	++	MLS
Destruction:	- DNA Fragment Distribution	++	++	MLS
Fractal Analysis:	- Chromatin Backbone	++	++	nd
	- Chromatin Distribution (Territory + Nucleus)	(~/- -)	(++/++)	nd / ?
Dynamics:	- Subcompartment	- -	++	?
	- Chromosome	- -	++	?
Diffusion:	- Static Diffusion	- -	++	~ ?
	- Dynamic Diffusion	- -	++	~ ?
Imaging:	- Confocal Section	+	++	~ MLS
	- EM Section	+	++	~

Three-Dimensional Organization of Chromosome Territories and the Human Cell Nucleus:

Comparison between simulated Parameters and Experiments

Knoch, T. A.

Three-dimensional organization of chromosome territories and the human cell nucleus. *SBD*, Heidelberg, Germany, October, 2000.

Abstract

Despite the successful linear sequencing of the human genome its three-dimensional structure is widely unknown, although it is important for gene regulation and replication. For a long time the interphase nucleus has been viewed as a 'spaghetti soup' of DNA without much internal structure, except during cell division. Only recently has it become apparent that chromosomes occupy distinct 'territories' also in interphase. Two models for the detailed folding of the 30 nm chromatin fiber within these territories are under debate: In the Random-Walk/Giant-Loop-model big loops of 3 to 5 Mbp are attached to a non-DNA backbone. In the Multi-Loop-Subcompartment (MLS) model loops of around 120 kbp are forming rosettes, which are also interconnected by the chromatin fiber. Here we show with a comparison between simulations and experiments an interdisciplinary approach leading to a determination of the three-dimensional organization of the human genome:

For the predictions of experiments various models of human interphase chromosomes and the whole cell nucleus were simulated with Monte Carlo and Brownian Dynamics methods. Only the MLS-model leads to the formation of non-overlapping chromosome territories and distinct functional and dynamic subcompartments in agreement with experiments. Fluorescernce in situ hybridization is used for the specific marking of chromosome arms and pairs of small chromosomal DNA regions. The labeling is visualized with confocal laser scanning microscopy followed by image reconstruction procedures. Chromosome arms show only small overlap and globular substructures as predicted by the MLS-model. The spatial distances between pairs of genomic markers as function of their genomic separation result in a MLS-model with loop and linker sizes around 126 kbp. With the development of GFP-fusion-proteins it is possible to study the chromatin distribution and dynamics resulting from cell cycle, treatment by chemicals or radiation in vivo. The chromatin distributions are similar to those found in the simulation of whole cell nuclei of the MLS-model. Fractal analysis is especially suited to quantify the unordered and non-euklidean chromatin distribution of the nucleus. The dynamic behaveour of the chromatin structure and the diffusion of particles in the nucleus are also closely connected to the fractal dimension. Fractal analysis of the simulations reveal the multi-fractality of chromosomes. First fractal analysis of chromatin distributions in vivo result in significant differences for different morphologies and might favour a MLS-model-like chromatin distribution. Simulations of fragment distributions based on double strand breakage after carbon-ion irradiation differ in different models. Here again a comparison with experiments favours a MLS-model.

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 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 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, Brownian Dynamics, Monte Carlo, fluorescence in situ hybridization, confocal laser scanning microscopy, fluorescence correlation spectroscopy, super resolution microscopy, spatial precision distance microscopy, autofluorescent proteins, CFP, GFP, YFP, DsRed, fusionprotein, in vivo labelling.

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