Simulation of Radiation-Induced Damage Distribution to Evaluate Models for Higher-Order Chromosome Organization

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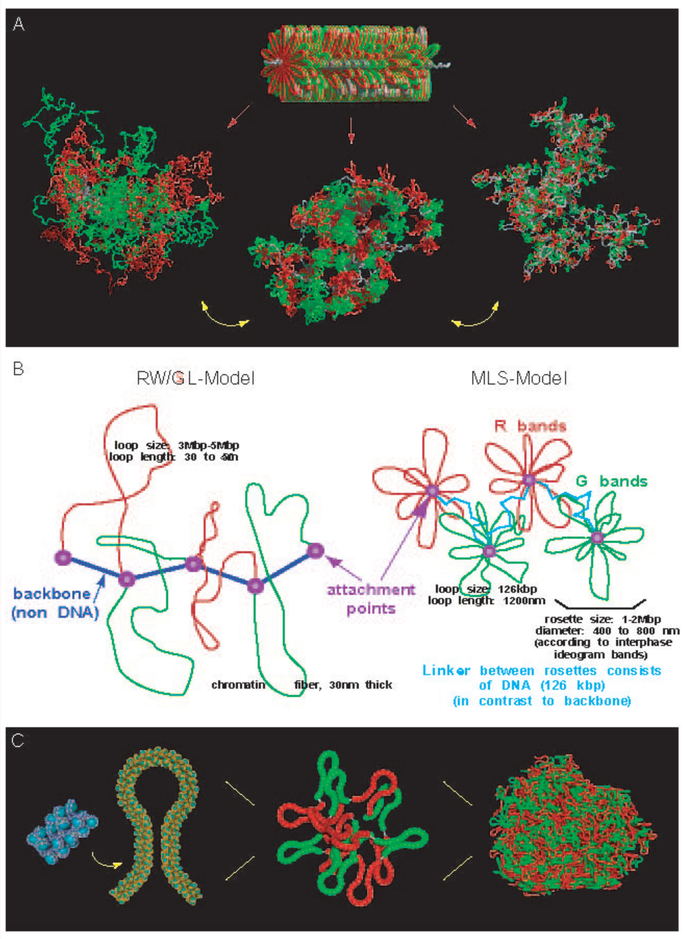
The Chromosome Models



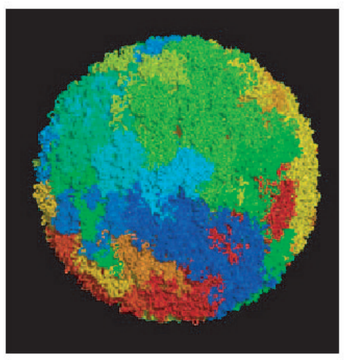
Simulation of the Random Walk/Giant Loop (RWGL; Sachs et al. 1995) chromosome model (A β, B left) und of the Multi-Loop Subcompartment (MLS; Münkel and Langowski 1998) chromosome model (A γ, B right), in each case starting from a metaphase-like configuration (A α).

In the RWGL-model, Mbp-sized chromatin loops are attached to a non-DNA backbone which follows a random walk. In the MLS-model, about 10 loops of 120 kbp form rosette-like subcompartments which are connected by small linker segments.

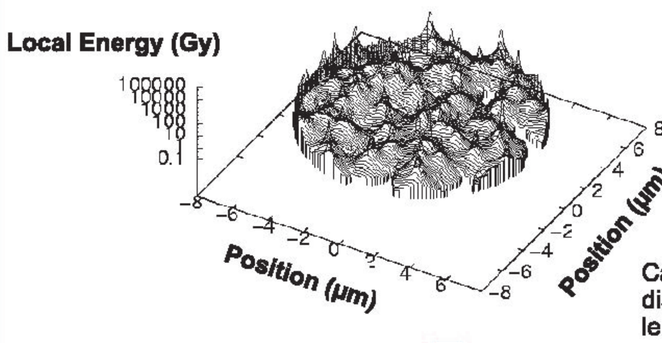
In the Friedland model (Friedland et al. 1999), territorial chromosomes are build from 67 kbp loops (C) which are connected following a constrained random walk.

Ref.: Sachs et al. (1995) Proc. Natl. Acad. Sci. USA 92: 2710-2714. Münkel and Langowski (1998) Phys. Rev. E 57: 5888-5896. Friedland et al. (1999) Radiat. Env. Biophys. 38: 39-47.

The Simulation

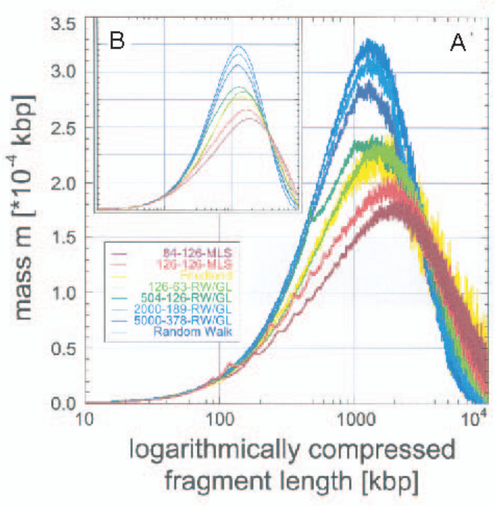


Simulation of distribution of local dose in nucleus (using 2 different track structure models)



Calculation of expected distribution of fragment lengths

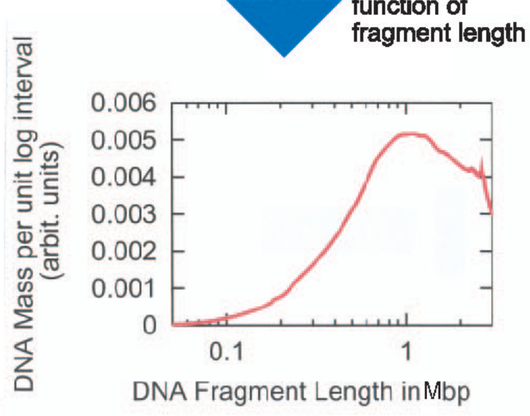
The distribution depends on the chromosome model, the track model and the breakage rate



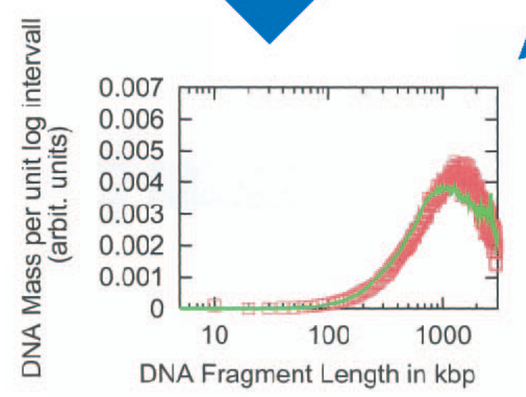
The Experiment

Isolation of genomic DNA and pulsed field gel electro-phoresis

Measurement of DNA mass as function of fragment length



The Comparison



The Result

Least Square Deviation:

Combination	Friedland	RWGL	MLS
Track Model a	356	327	327
Track Model b	402	430	342

Deviation of Variance:

Combination	Friedland	RWGL	MLS
Track Model a	401	431	282
Track Model b	416	371	282

Ranking analysis of the deviation between simulation and experiment. 104 experimental profiles were evaluated with each 6 combinations of models.

The Message

Simulations based on the MLS-model resulted in significantly better agreement with experimental data than simulations based on the other models. We assume that this is because the heterogeneity in chromatin density is highest in the MLS-model.

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Abstract

The structure of chromatin at the level of the 30 nm fibre has been studied in considerable detail, but little is known about how this fibre is arranged within the interphase chromosome territory. Over the years, various polymer models were developed to simulate chromosome structure, for example the random-walk/giant-loop (RWGL) model, the multi-loop subcompartment (MLS) model, and the interconnected-fibre-loop model (Friedland et al., 1999). These models differ mainly in the size and arrangement of the chromatin loops and, correspondingly, in the predicted distribution of chromatin density within the nucleus. It occurred to us that densely ionising radiation can be used to probe the actual distribution of chromatin density in human interphase cells. In contrast to sparsely ionising radiation (e.g. X-rays), which induces DNA double-strand breaks (DSB) that are distributed randomly within the nucleus, irradiation with densely ionising accelerated ions leads to spatial clustering of DSB. This inhomogeneity in DSB localisation, together with an inhomogeneity of DNA density within the nucleus, causes an over-dispersion in the resulting distribution of DNA fragment sizes that can be detected by pulsed-field gel electrophoresis.
Using the above-mentioned chromosome models, we performed computer simulations to predict the DNA fragment size distributions resulting from irradiation with accelerated ions, and compared the predicted distributions with those obtained experimentally. We found that simulations based on the MLS model, in which local variations in chromatin density are higher than in the other models, resulted in the best agreement between calculation and experiment.

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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, auto-fluorescent proteins, CFP, GFP, YFP, DsRed, fusion protein, in vivo labelling.

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