Three-Dimensional Organization of Chromosome Territories in the Human Interphase Cell Nucleus

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The eukaryotic cell is a prime example of a functioning nano machine. The synthesis of proteins, maintenance of structure and duplication of the eukaryotic cell itself are all fine-tuned biochemical processes that depend on the precise structural arrangement of the cellular components. The regulation of genes – their transcription and replication - has been shown to be connected closely to the three-dimensional organization of the genome in the cell nucleus. Despite the successful linear sequencing of the human genome its three-dimensional structure is widely unknown.

With the simulation of chromosomes and cell nuclei in comparison with fluorescence in situ hybridization we show here an approach leading to the detailed determination of the three-dimensional organization of the human genome. The best agreement between simulations and experiment is reached for a Multi-Loop-Subcompartment model, thus the human genome shows a higher degree of determinism than previously thought.

PURPOSE

Random Walk / Giant Loop model
Sachs et al. (1995)

Fig. 2
Ray traced image of the Random-Walk/Giant Loop model. Loop size: 5Mbp, after ~80,000 Monte-Carlo steps. Large loops intertwine freely only allowing to distinguish features like in the MLS model.

SIMULATIONS

Multi-Loop-Subcompartment model
Münkel et al. (1997)

Fig. 3
Ray traced image of the Multi-Loop-Subcompartment model. Loop size: 126kbp, linker size: 126 kbp and ~160,000 Monte-Carlo steps. The resulting behaviour is similar to that of the MLS model.

EXPERIMENTS

Fluorescence in situ hybridization (FISH) in connection with confocal light microscopy is used for the specific marking of small chromosomal DNA regions. Despite the low spatial resolution of FISH, it is possible to interpret the results (Fig. 6) in the 3D distance between genetic markers as a function of their genomic distance with our simulations.

Methods: Human fibroblast cells grown on coverslips to confluent density, in agreement with overlap analysis of confocal image series (data not shown here).

CONCLUSION

The simulation of a whole human cell nucleus with all 46 human chromosomes in connection with the simulation of single chromosomes resulted in the formation of distinct chromosome territories as predicted. In contrast to the RWGL-model the MLS-model leads to a more overlap between chromosome territories as well as chromosome arms, in agreement with overlap analysis of confocal image series (data not shown here).
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Abstract

To study the three-dimensional organization of chromosome territories and the human interphase cell nucleus we developed models which could be compared to experiments. Despite the successful linear sequencing of the human genome its 3D-organization is widely unknown. Using Monte Carlo and Brownian dynamics simulations we managed to model the chromatin fibre as a wormlike-chain polymer. A typical chromosome consists of 20,000 and a nucleus with all 46 chromosomes of 1,200,000 polymer chain segments. The parallel simulations are performed on a SP2512 and a Cray T3E. With fluorescent in situ hybridization and confocal microscopy we determined genomic marker distributions and chromosome arm overlap.

Best agreement between simulations and experiments is reached for a Multi-Loop-Subcompartment model (126 kbp loops connected to rosettes connected by a 126 kbp chromatin linker). A fractal analysis of simulations leads to multi-fractal behaviour in good agreement with porous network research. The formation of chromosome territories was shown as predicted and low overlap of chromosomes and their arms was also reached in contrast to other models.

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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.


**Literature References**

