Three-dimensional Organization of the Human Interphase Nucleus
Experiments compared to Simulations

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Simulated Confocal Section

Fluorescence in situ hybridization (FISH) in connection with confocal laser scanning microscopy followed by image analysis and computing. Such techniques allowed us to simulate chromosome conformation from FISH images (Fig. 2) and small chromosome (Fig. 1B). A comparison between simulated and measured spatial distributions of genomic regions as function of their genomic distances result in a good agreement with the MLS-model only a loop size of around 126 kbp and linker sizes between 60 and 126 kbp (Fig. 3).

Comparison of the RW/GL- and the MLS-model with experimentally

Despite the successful linear sequencing of the genome its three-dimensional structure is widely unknown. It is important for gene regulation and replication. With a comparison between experiments and simulations we show here an interdisciplinary approach leading to the determination of the three-dimensional organization of the human genome.

Simulations of chromosomes and the whole cell nucleus show that only the MLS-model leads to the formation of distinct and clearly defined chromosome territories. The development of GFP-expressing proteins makes it possible to study the chromosome distribution and dynamics resulting from cell cycle, treatment by chemicals or radiation in vivo. The chromosome distribution is similar to those found in the simulation of whole cell nuclei. For this reason it is possible to quantify the in vivo chromosome distribution with fractal analysis and to relate it to differences in morphology. The analysis of fragment distributions based on double irradiation experiments favours an MLS-model (Fig. 7).

Simulations of DNA fragmentation and DNA double strand breakage after carbon-ion irradiation differs in different models. Here again a comparison to experiments shows the simulation of whole cell nuclei. The dynamic behaviour of the chromatin structure and the diffusion of particles in the nucleus are also closely connected to the fractal dimension. The fractal analysis of chromatin distributions in vivo result in significant differences for different morphologies (Fig. 10) and might favour an MLS-model in our experiments towards a 3D-chromosome model.

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With Monte Carlo and Brownian Dynamics methods we simulated various models of human interphase chromosome 15 assuming a DNA molecule with equal probability of bending and associated volume interactions between the segments are considered. Chromosomes are further confined to a spherical potential representing the surrounding chromosomes of the nuclear membrane. Only the MLS-model leads to clearly defined subcompartments. The Fractal Dimension as function of the intensity threshold.

The nucleus is an anisotropic and non-erodable system for which fractal analysis which measures the mass distribution in space is especially suited. The dynamic behaviour of the chromatin structure and the diffusion of particles in the nucleus are also closely connected to the fractal dimension. The fractal analysis of chromatin distributions in vivo result in significant differences for different morphologies (Fig. 10) and might favour an MLS-model in our experiments towards a 3D-chromosome model.
Literature


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