

# Inheritance of chromosome positions throughout mitosis revealed by live cell imaging and computer simulations

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## ABSTRACT

It has long been argued that chromosomes might be localized in a specific topological arrangement of their territories (CTs) inside the cell nucleus, potentially reflecting a global scheme of gene regulation[1, 2]. Studies on the relative positions of CTs by in situ hybridization in fixed cells have provided contradictory results, some showing a defined global organization of the nucleus, others determining a relatively random array of CTs[3-5]. Moreover it is unclear if such an order can be stably maintained from one cell generation to the next. Here, we have developed a noninvasive approach to investigate dynamics of labeled subsets of chromosomes in live mitotic cells. Chromatin was double labeled by co-expressing histone 2B tagged with cyan and yellow fluorescent protein. We then selectively photobleached only YFP in specific subnuclear regions, achieving combinatorial labeling with defined geometrical patterns. Chromosome dynamics were traced by 4-D confocal microscopy and quantitative image reconstruction[6]. We observed a striking order of chromosomal positions throughout mitosis. The labeled pattern in the two daughter nuclei closely resembled the original pattern in the mother nucleus demonstrating that their positions are heritable. Interestingly, the spatial order was partly dismantled in metaphase and reestablished in anaphase. Thus, there exists a mechanism actively restoring the original configuration of CTs.

To investigate this mechanism in detail, we have set up a computer model to simulate chromosome dynamics throughout mitosis. The model takes into account physical parameters such as cytoplasmic viscosity, pulling forces by microtubules, volume exclusion forces of chromosomes and cohesion of sister chromatids. From prophase to metaphase chromosomes move towards the metaphase plate, whereby the order along the plane of the metaphase plate is largely maintained. The active restoration of chromosome positions in the proximal-distal axis is modeled by a chromosome-specific order of sister chromatid separation during meta-anaphase transition. This might involve a

specific timing of cohesin cleavage on each chromosome or by distinct cohesiveness along chromosome arms resulting in specific velocity of chromosome movement towards the spindle poles. Computer simulations suggest that the order along the proximal-distal direction might be specifically perturbed, while the order parallel to the metaphase plate remains intact. We are currently checking this prediction by perturbing pericentromeric chromatin structure through decondensing drugs.

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