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High-performance Computational Modeling of Chromosome Structure

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We present a polymer modeling approach to generate the ensemble of 3D chromosome conformations at different time points of mitosis-interphase transition. Dynamics of structure during mitosis-G1 transition indicates quick and slow stages of chromosome shape alterations. At intermediate and late time scale the changes in chromosome compaction are small. To assess time dependence of contact map establishment during G1 we calculate contact maps at different times after mitotic decondensation. We demonstrate that the patterns of contacts observed soon after mitotic decondensation remain similar during G1. Whole contact map for mouse chromosome 18 at late G1 time correlates with the experimental chromosome conformation capture data. The simulations reproduce the main experimental findings, contact map persistence during G1 as well as specific pattern of long-range interactions in interphase chromosome. Our results suggest that spatial compartmentalization of an interphase chromosome is driven by interactions between different types of megabase sized chromatin domains during the formation of globular chromosome state at the end of mitotis to G1 transition.

Keywords: chromosome conformation capture, chromosome structure, computational modeling, mouse chromosome 18.

Introduction

Whole-genome chromosome conformation capture (Hi-C)-based experiments provide unique information about frequencies of contacts of any genetic loci within and between chromosomes in a cell. In general, the method represents a physico-chemical approach which uses chromatin fragmentation and proximity ligation and gives a snapshot of crosslinked chromosomal contacts in the population of fixed cells in the form of contact maps [5, 8]. To infer 3D chromosome structures from Hi-C data, computational approaches are used [3]. Methods based on polymer physics can predict ensembles of 3D conformations and contact maps, which are sensitive to principles of organization. Studies aimed at polymer modeling of interphase chromosomes for Hi-C analysis use condensation algorithms [1, 4]. The condensation conditions for long polymer chromatin chain due to bridging proteins [4] or attracting potentials [1, 10] are applied, and large scale transition from extended chromatin fiber, as rod or coil, to compact state, associated with interphase chromosome is simulated. These assumptions, however, contradict common knowledge that interphase chromosomes are formed in the course of decondensation of mitotic chromosomes.

To explore complexity of chromosome folding, we have mapped genetic loci contacts and predicted positions of megabase domains in interphase chromosome at different time of mitosis-interphase transition by Monte Carlo simulations. Our results support a mechanism of chromosome folding underlying contact patterns formation via interactions between different types of domains during establishment of globular state at the end of mitotis-G1 (M-G1) transition. This mechanism consistently reproduces a complex chess-like type of contact map and early G1 establishment of long-range contacts, as well as spatial compartmentalization of chromosome.

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1. Chromosome Structure and Dynamics Modeling

Here we link the mitotic decondensation algorithm [2, 6] with several subunit type interactions. Any pair of elements (i, j) interacts through a Lennard-Jones potential. Since the chain is a heteropolymer, different types of elements have their own pairwise interaction potentials. To avoid complexity, subunit diameter d=350 nm was selected for all elements. Interphase structure is formed as a result of decondensation from an ultra-compact rodlike structure representing a mitotic-like chromosome. The Monte Carlo (MC) simulations were performed for times up to 500,000 MC steps at which the macroscopic parameter, chain gyration radius, ceases to change. At different times all macroscopic and microscopic characteristics for individual chromosomes and statistical ensembles (500 structures per each contact map calculation) are obtained.

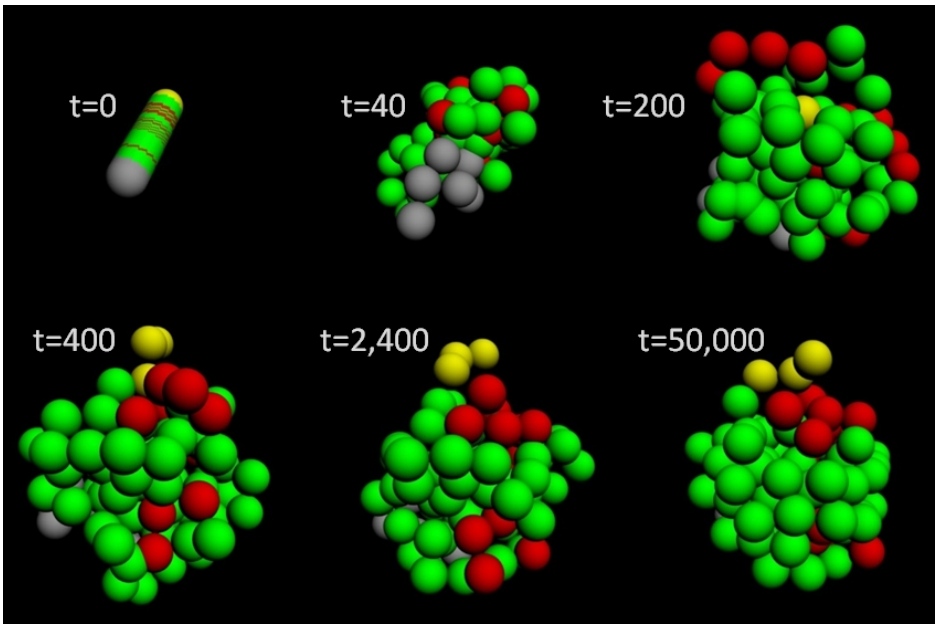
2. Results

Using MC simulations, we observe establishment of interphase chromosome organization in the course of mitosis-G1 transition. At t=0 decondensation begins and the chromosome is extended to the chain of subunits representing megabase-sized domains [5]. Domains interactions shape 3D conformations during mitosis-G1 decondensation and in interphase. The simulated dynamics of mouse chromosome 18 structure is shown in Fig. 1a. Different colors correspond to different subunit type. Dynamics of structure indicates that quick growth of chromosomal size gives way to slow decline. To assess time dependence of contact map establishment during G1 we calculate contact maps at different times after mitotic decondensation: at early (2,400 and 5,000 MC steps), intermediate (10,000 and 50,000 MC steps) and late times (500,000 MC steps) (Fig. 1b–f). We associate these points with different times in G1, from early to late subphases. The boundary of G1 is not determined here, and onset of S phase is not considered in the model.

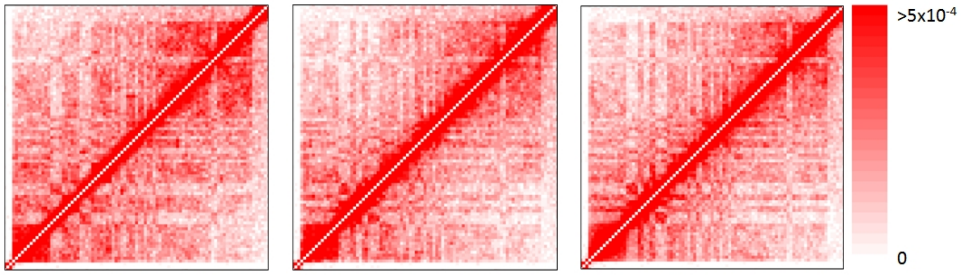
Map calculations for different times, Fig. 1b–f, show that the chess-like contact pattern is blurry at 2,400 MC steps and becomes clearer at 5,000 and 10,000 MC steps. But positions of characteristic dark/light blocks at early time remain unchanged at intermediate and late times. After 50,000 steps the map visually ceases to change. These data reveal that early G1 contact maps (at 2,400 and 5,000 MC steps) are highly correlated with the later time contact maps (Pearson correlation R=0.938 for 2,400 vs 50,000, R=0.923 for 2,400 vs 500,000, R=0.963 for 5,000 vs 50,000, R=0.952 for 5,000 vs 500,000 MC steps). Quality of the contact map in G1 generated by the polymer modeling is demonstrated by its correlation (R=0.897) with the experimental Hi-C map for ch12lx cells [9], Fig. 1g. Thus, main patterns of the experimental map [9] are well reproduced by polymer modeling of interphase chromosome 18, established following mitosis-G1 transition.

3. Discussion

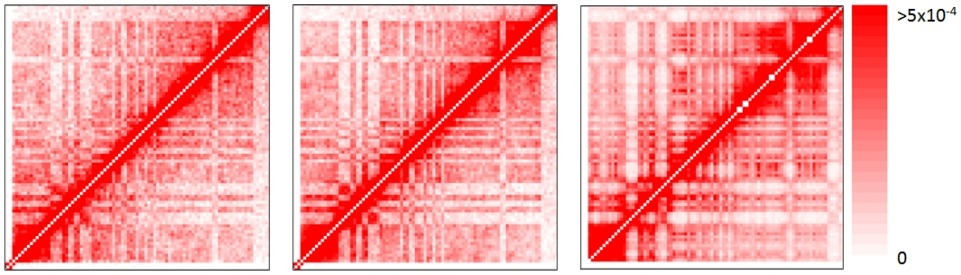
The modeling study of mitosis-G1 transition reveals two-stage dynamics, fast decondensation followed by slow structural rearrangements in G1 accompanied by weak subcondensation. The maps at early vs late times in G1 are highly correlated and look similar. Our polymer approach simulates mitosis-G1 transition as a biologically realistic pathway of establishment of interphase chromosome organization and contact maps during G1 phase of cell cycle. The chess-like contact pattern seen as alternating megabase-sized regions of high vs low intensities on the contact map and spatial compartmentalization ofchromosomal subunits are quantitatively re-



(a) Evolution of the typical conformation in the course of mitosis-G1 transition



(b) 2,400 MC steps (c) 5,000 MC steps (d) 10,000 MC steps



(e) 50,000 MC steps (f) 500,000 MC steps (g) experiment

Figure 1. Structure of mouse chromosome 18 predicted as a result of mitosis-G1 transition algorithm. (a): conformations; (b)–(g): contact maps

produced by mitotic decondensation modeling algorithm. The simulations agree with the main experimental findings, map persistence during G1, as well as specific pattern of long-range contacts in interphase chromosome.

Conclusions

We demonstrated how 3D interphase chromosome structure can be established during M-G1 transition. We identified the physical mechanism of interphase structure formation which incorporates differential interactions between megabase chromatin domains and explains main

features of experimental Hi-C contact maps. The results support the globular model of interphase chromosomes [1].

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