Genome as a functionally designed mesoscopic soft-matter system

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The genome in a living cell is a micrometer-scale soft matter. Its structure and dynamics play critical roles in gene regulation. Here, an essential issue is to develop coarse-graining technologies to describe genomes from atomic knowledge of molecules. In this study, we report hierarchically coarse-grained models of the human genome. The 3D genome structure has been intensively studied with recent biochemical techniques, such as the Hi-C methods, which revealed the genome-wide pattern of physical proximity between chromatin regions separated along the DNA sequence. The Hi-C data showed that 100 kilo-base (kb) to 1 mega-base (Mb) size domains are building blocks to form 10-100 Mb size compartments, which are organized into the giga-base (Gb) size genome.

We first described chromatin domains using a 1-kb resolution polymer model. The dense distribution of functional complexes in an active type-A domain blocks the movement of a molecular motor, cohesin, along the chromatin chain, which expands the size of the domain. In contrast, the homogeneous movement of cohesin in a functionally inactive type-B domain compactifies the domain. The coarse-grained domain-domain interactions showed a harder repulsion between compactified type-B domains than between loosely packed type-A domains. Such heterogenous repulsions induce heterogeneous movements of chromatin in the genome, which further induce phase separation of type-A and B domains to enhance fluctuations in the cell nucleus, forming A and B compartments in the genome. Thus, our hierarchical coarse-graining methods revealed how the Gb-scale genome structure is dynamically formed through molecular interactions of functional complexes on chromatin.