Chromosome positioning from activity-based segregation

N. Ganai, S. Sengupta and G. Menon, Nucleic Acid Research 42, 4145, 4159 (2014)

Recommended with a commentary by Jean-François Joanny ESPCI, Paris.

The nucleus of mammalian cells contains the chromosomes. During Interphase (the phase of the cell cycle where DNA is replicated), the nucleus is not homogeneous and the different chromosomes are not intermingled. The nucleus is rather divided into well-defined chromosome territories with little interpenetration between different chromosomes [2]. New experimental techniques such as HiC (which is based on a random cross-linking of the DNA inside the nucleus to detect DNA contacts) [4] have also shown that the territories themselves are compartmentalized into smaller domains. Moreover, the positions of the chromosomes are not random and gene-rich chromosomes tend to be located in the center of the nucleus whereas gene-poor chromosomes tend to be located at the surface of the nucleus. All these experimental results are unexpected from the polymer physics point of view and have stimulated the development of a new "nuclear" physics.

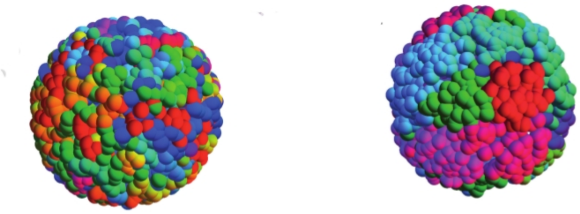

Fig. 1: The surface configuration of monomers, color coded by chromosome calculated in Ref. [1] .The configuration is calculated in the absence of permanent loops for the left figure and in the presence of permanent loops for the right figure

The organization of the nucleus is a challenge for theorists. It has been up to now studied using thermal equilibrium theories for the collapse of the chromosomes and emphasizing the role of topological constraints [3]. The starting point of the paper of Ganai et al. [1] is the fact that the organization of the nucleus must also be related to gene transcription. They take it into account by considering that some regions of the chromosomes contain more expressed genes and are therefore more active in the sense that they interact with active proteins consuming ATP. In practice the authors coarse-grain the DNA of the chromosomes into grains of a size of $1\,\mu\mathrm{m}$ and they distinguish active grains containing more expressed genes and passive grains containing less expressed genes. The dynamics of each grain is described by a classical Langevin equation with a white noise. The amplitude of the noise corresponds to an effective temperature, which is equal to the real temperature T_{eq} for the passive grains and to a higher active temperature T_a that they choose equal to $20T_{eq}$ for the active grains. With this assumption, the nucleus is an active material because energy is permanently transferred locally from the "hot" active grains to the "cold" passive grain. This new type of active material has to my knowledge never been studied in details theoretically. The main result of the paper is that the gradient in activity enhances the compartmentalization of the nucleus.

The gradient of activity is not sufficient however to induce the compartmentalization into territories. It must be combined with a local collapse of the chromosomes, which is induced in the paper by using a random loop model of the polymer where certain loops are frozen in the polymer conformation. Other descriptions of the polymer such as the fractal globule model could presumably be used at this point. The implementation of the numerical work starts with the determination of the active and passive grains of all chromosomes which is done by looking at the gene distribution in a database. The conformation of all the chromosomes is then determined numerically in principle for all chromosomes but in the discussion, the authors focus on the 4 chromosomes 12, 18, 19 and 20. The numerical results show a compartmentalization of the nucleus and little interpenetration between chromosomes. They also show that chromosomes carrying more expressed genes such as chromosome 19 are located preferentially close to the center of the nucleus compared to chromosomes carrying less expressed genes, which are located close to the nucleus surface.

The comparison with the case where all chromosomes are at the same “temperature” (active or passive) shows the relevance of the activity gradient.

The model allows also to change the parameters. Geometrical effects such as an ellipsoidal shape of the nucleus had been claimed to be relevant. It does not seem to play a major role in this model. The preferred location of the chromosomes can be inverted by playing with the interaction between the chromosomes and the nuclear envelope. An “inverted location” where the active chromosomes are located close to the nucleus surface is observed in certain cells such as red blood cells.

The paper of Ganai et al. is a very original paper, which studies in details an interesting conjecture that goes well with the intuition that the structure of the nucleus must have biological relevance. It remains to find precise experiments that could prove or disprove this hypothesis.

References

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