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A Polymer Model of the Whole Genome

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Our understanding of the polymeric state of chromosomes has come a long way since chromosome conformation capture (Hi-C) became available (1). We now know that the polymeric state of eukaryotic DNA is radically different from that of ordinary polymers, e.g., by being much less entangled (2). In addition, Hi-C experiments recently led to the discovery of actively extruded loops that play a role in the spatial structuring of interphase chromosomes in topological associating domains (3,4). Other such loops are needed to drive the segregation of the sister chromatids after duplication (5), as originally hypothesized by Nasmyth (6).

However, chromosome conformation capture experiments only provide contact probabilities between different sections of the genome but do not give direct information on their three-dimensional positions. This is why computer simulations of chromosomal polymer models are so important, see e.g., (7). In this issue of *Biophysical Journal*, Zhang and co-workers present such a physical model with the aim of describing the whole human genome (8). To do this, the "monomers" of the polymer model must be fairly coarse grained, 1 Mbp per bead. The above loops are smaller and are therefore not taken into account. The hope is that such a highly coarse-grained model can still predict the overall three-dimensional organization.

With the interactions between three different types of monomers corresponding to three different types of chromatins (A: euchromatin, B: heterochromatin, and C: centromeric regions) trained on the Hi-C data, the model can mimic the Hi-C contact maps with a high degree of accuracy. Various impressive examples are shown in Fig. 2 of (8), with each subplot providing a comparison between the experimental data and the result of the polymer simulations. For instance, Fig. 2 *a* shows the measured and the simulated contact maps of the whole genome, and Fig. 2 *c* shows the corresponding genome-wide averaged contact probabilities as a function of the genomic separation. But is the model more than just an elaborate fit with a large number of fit parameters? To check whether their model is predictive, the authors compare their predictions with FISH and chromosome painting experiments, low-throughput methods that allow one to determine the spatial positions of the chromosomes and their various compartments. The agreement is excellent, see e.g., Fig. 3 *b* of (8) for the radial positioning of the chromosomes. Also, the positioning of the various compartment types (A, B, and C) reproduces the well-known fact that the more active euchromatin (A) is localized at the interior of the nucleus, whereas the heterochromatin (B) resides close to the nuclear envelope, see Fig. 3 *d*.

What makes this model so interesting is that it allows one to study the effects of the various interaction parameters on the genome organization. Ultimately, one could envision studying the differences in the Hi-C maps of healthy and cancer cells or between different cell types and learning what parameters need to be changed to account for these differences. This in turn could lead to a physical understanding of which interactions in the genome are different in the different cases. In this study, the authors use this type of approach to investigate how, for example, the spatial organization is influenced by forcing the inter- and intrachromosomal interactions to be the same, see Fig. 5 *a* of (8).

This is a powerful model that I expect can be further improved upon by looking at exotic special cases. A spectacular example is the inverted genome organization in the nuclei of rod photoreceptor cells of nocturnal mammals (9). This inverted structure—euchromatin is peripheral and heterochromatin is central—is considered beneficial because heterochromatin has a higher refractive index than euchromatin, and its central organization helps light reach photoreceptors by acting as a collective lens. The inversion is caused by changes in the interactions of heterochromatin with the nuclear envelope (10). An interesting application of this model would

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be to extend it to predict this nuclear inversion and then check to which extent this extended model still requires different parameters for intra- versus interchromatin interactions.

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