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Chromosome Capture Brings It All Together

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Abstract

A simple, robust model explains higher-order organization of mammalian chromosomes.

The organization and morphogenesis of chromosomes as they prepare to segregate during cell division has fascinated researchers since their first microscopic visualizations. On page XXX of this issue, Naumova *et al.* (1) combine chromosome conformation capture with polymer physics simulations to see inside metaphase chromosomes and elucidate their principles of organization. A new, yet satisfyingly familiar, view emerges.

Electron microscopic visualizations provide compelling evidence that chromosomes are organized as loops (see the figure). Naumova *et al.*'s analysis suggests that chromosome organization is a highly probabilistic process that, without much specification, yields a robust longitudinal assembly of loop bases running along the length of the chromosome. The model reproduces known properties of mitotic chromosomes, including variable positioning of loci and spatial mixing of regions of intermediate (megabase) size. Although average loop size cannot be determined from chromosome capture data, the loop size necessary for the simulations to match experimental results was 80 kilobases, very similar to experimental estimates. The proposed model is highly attractive in its simplicity and robustness. A linear array of chromatin loops forms, at consecutive but apparently random positions, and then is longitudinally compressed. These few rules ensure that chromosomes globally always fold into the same shape, without requiring precise specification of either highly conserved genetic loci or specific length scales.

The model of Naumova *et al.* supports the seminal description of Ulrich Laemmli, formulated nearly 40 years ago (2). Laemmli envisioned a constraining protein network located centrally within the chromosome. This “scaffolding” brings segments together into loops, thereby shaping the chromatin to give rod-like chromosomal bodies rather than spherical balls (3). The underlying organization comprises a linearly folded assembly of scaffold associated regions (SARs), rich in the bases adenine (A) and thymine (T), yielding an “AT queue” (3–5). Topoisomerase II, condensin and AT-hook architectural proteins synergistically collaborate with SARs to give shape (3–5). Compellingly, the AT queue–scaffold model explains classic cytological G/R banding patterns (5). Importantly, in the model of Naumova *et al.*, positioning of loop bases appears random. However, chromosome capture analysis provides a population average description. Different cells may

stochastically choose different SARs from a larger array of possibilities. [The common textbook model of highly ordered scaffold and loops was never Laemmli's view.]

In Naumova *et al.*'s model, the compressed loop array could run along the chromosome in a straight path or a meandering path. Experimental data define a topoisomerase II–condensin core lying radially within the center of the chromosome and running along its entire length (4, 6). However, the substructure of this scaffold may well be complex (with folds or coils) (4, 5). Laemmli postulated that loops emanate outward radially from the scaffold (7). Naumova *et al.*'s model does not specify a radial array but, similarly, envisions loops emanating out from the central axial feature.

Metaphase chromosome organization has also been proposed to comprise a hierarchical folding of larger domains (8) or connectivity spread uniformly through the chromatin (9). Naumova *et al.* exclude these two models.

At prophase of meiosis, chromosomes comprise linear arrays of loops whose bases are decorated with proteins, including topoisomerase II and condensin (10). In yeast, loop-base sequences are locally AT-rich regions (11). In mammals, loop sizes for meiotic prophase chromosomes are the same as for mitotic metaphase chromosomes (~100 kb). The two cases are obviously related. Remarkably, when a mammalian chromosome segment is introduced into yeast, it acquires the same meiotic prophase organization (loop size and spacing) as the endogenous yeast genome (12). Loop organization is thus clearly determined by probabilistic selection of a subset of available sequences. Also, alterations in structural axis components can alter, and increase variability of, loop size (13). Maybe loop size is determined in part by “chromatin fiber” persistence length: loops would form down to the minimum size compatible with fiber stiffness.

In the model of Naumova *et al.*, a linear array of continuous chromatin loops forms and then undergoes longitudinal compression. It will not be surprising if the first stage corresponds to prophase (mitotic and meiotic), while the second stage corresponds to evolution to the metaphase state.

The findings of Naumova *et al.* will reinvigorate discussions of late-stage mitotic chromosome organization and morphogenesis. What is the molecular nature of the final axial compressed loop array? It may comprise a DNA-protein meshwork, as meiotic prophase chromosome axes (10), rather than a continuous protein-protein structure. Primary components of the metaphase scaffold all mediate DNA-DNA linkages. Most strikingly, if new metaphase chromosomes are treated with deoxyribonuclease, they simply disappear, rather than leaving behind a discrete core (9). Also of interest is how mature mitotic chromosomes can be forcibly extended, allowed to retract, and then extended again for multiple successive cycles. Are protein links metastable? Do they act as “slip-rings”? Does an open DNA-protein meshwork allow reversible deformation without disruption of protein-mediated DNA-DNA links? It is also unclear how sister chromatids acquire their side-by-side metaphase relationship. Perhaps loosely connected sister chromatids become longitudinally organized in parallel, and then further compact, with stress on linkages between sisters promoting their further removal (5). However, classically, mitotic and

meiotic prophase chromosomes appear as morphologically single units, hinting at a more complex situation. Finally, by comparing chromosome capture data for interphase and metaphase, Naumova *et al.* show that mitotic chromosomes lose major features observed previously for interphase stages, e.g. cell-type-specific spatial segregation of open domains and closed domains. How epigenetic information for cell-type-specific gene expression is retained during the passage through mitosis is unknown. Are relevant elements locally marked? Or are some cell-type-specific interactions maintained but invisible at the current level of resolution?

These answers to these questions remain for the future, with imaging, conformation capture, polymer modeling, and genetic analysis all destined to play key roles.

Acknowledgments

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Figure 1. Meiotic and mitotic chromosomes

(A) Meiotic homologs of *Chironomus*, each comprising sister linear loop arrays (14). (B, C, D) Mitotic metaphase chromosomes in a human cell line. (B, C) Radially central chromosome “barber pole” appearance due to staining for DNA (blue) and associated proteins (red and green) (4). (D) Radial loops of chromatin fibers (15). (E) A model of the two stages of chromosome assembly from Naumova *et al.* (1).