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Journal club

CHROMOSOMES: NOW IN 3D!

For decades, microscopy studies have provided us with a picture of eukaryotic chromosomes as highly complex and variable objects that are confined to specific territories, may have preferential chromosome neighbours and have a tendency to localize at the periphery or at the centre of the cell nucleus. Despite this valuable information, it is clear that a much more detailed topography of chromosome architecture must exist.

Lieberman-Aiden *et al.* described a technique termed high-throughput chromosome capture (Hi-C) — a derivative of chromosome conformation capture technology (3C) — that can detect chromatin interactions between loci across the entire genome. Using Hi-C, they and others produced high-resolution maps of chromatin contacts that fine-tuned our view of chromosome architecture. However, as these maps were generated from large ensembles of millions of cells, they only inferred general principles that might govern chromosome folding and did not allow chromosome structures to be derived.

> “Hence, we can now see, for the first time, chromosome structures before our eyes.”

Nagano and co-workers made it possible for us to look even closer at chromosome construction by establishing single-cell Hi-C. This technique refines the regular Hi-C protocol to enable the analysis of individual nuclei, in which chromosome contacts have been captured by formaldehyde cross-linking. Their data showed that individual chromosomes are organized in domains, which is consistent with the data obtained from ensemble maps. Although individual domains are relatively invariant in each cell, interdomain contacts are highly variable among cells, which suggests that chromosomes are extremely dynamic, and thus their data corroborate the results from microscopy studies.

The beauty of single-cell Hi-C, as the maps are derived from a single nucleus, is that each contact can be used to model chromosome architecture, and this can be used to infer the three- dimensional trajectories of chromatin. Hence, we can now see, for the first time, chromosome structures before our eyes.

These are early days and much remains to be done to improve the technology, including the processing of biological samples, as well as the methods for data analysis and modelling. In particular, the genome fraction covered in each single-cell Hi-C experiment should be increased. Furthermore, we need to learn how to apply the procedure to single or rare nuclei that have been isolated from tissues instead of performing Hi-C on large cell populations and isolating single nuclei retrospectively, which is the method Nagano *et al.* used. Nevertheless, we are clearly at the dawn of a new era in chromosome biology.

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ORIGINAL RESEARCH PAPERS Lieberman-Aiden, E. *et al.* Comprehensive mapping of long-range interactions reveals folding principles of the human genome. *Science* **326**, 289–293 (2009) | Nagano, T. *et al.* Single-cell Hi-C reveals cell-to-cell variability in chromosome structure. *Nature* **502**, 59–64 (2013)