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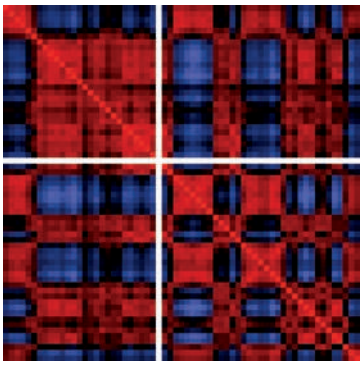
CHROMATIN

Mapping genome-wide chromosome interactions

Understanding chromosome folding is crucial for understanding the relationships between chromatin structure, gene activity and cellular function. Although recent technological developments, such as chromosome conformation capture (3C), have allowed the investigation of long-range interactions associated with specific loci, they do not allow unbiased genome-wide assessment of chromosomal interactions. The development of Hi-C, an adaptation of 3C for unbiased mapping of interactions, allows the three-dimensional architecture of whole genomes to be examined, and therefore promises to provide new insights into chromatin organization.

Lieberman-Aiden *et al.* created a Hi-C library from a karyotypically normal human lymphoblastoid cell line by crosslinking chromatin in the cells, restriction digesting the DNA, adding a biotin tag to the ends of the fragments and then ligating under conditions that favoured ligation between crosslinked fragments that were originally close to each other in the nucleus. The library can be analysed by selecting the biotinylated interacting fragments with streptavidin beads, then massively parallel DNA sequencing the ligated pairs to yield a catalogue of interacting fragments. The authors generated millions of read pairs that could be uniquely aligned to the human genome reference sequence.



A three-dimensional proximity map of chromosome 20. The checked pattern reveals the active and inactive compartments in the genome. Image courtesy of E. Lieberman-Aiden, Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, USA.

The Hi-C data were consistent with known features of genome organization, such as the presence of chromosome territories (the propensity for distant loci that are on the same chromosome to be close to each other in the nucleus) and the tendency of small gene-rich chromosomes to be near each other. They also characterized a higher level of genome organization in which the whole genome can be partitioned into two compartments, with greater interaction occurring within each compartment, rather than across the two compartments. Lieberman-Aiden *et al.* then examined whether the two compartments correlated with any known genetic or epigenetic features and found that one compartment was associated with open, actively transcribed chromatin, whereas the other correlated with closed chromatin.

The authors also found that at the megabase scale, chromatin is packed very densely, which is consistent with a fractal globule conformation. This is the first time that this type of polymer conformation has been observed — it is an unknotted and highly compact structure that provides an efficient solution to packing long chromosomes into the nucleus.

Although the authors focused on interactions that occur at a relatively large scale (megabase regions), Hi-C can also be used to create finer-scale genome-wide interaction maps by increasing the number of sequence reads. This is expected to become increasingly feasible as the cost of sequencing drops, and this method could then also be applied to map precise long-range interactions between specific DNA elements, such as enhancers, silencers and insulators.

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ORIGINAL RESEARCH PAPER
Lieberman-Aiden, E. *et al.* Comprehensive mapping of long-range interactions reveals folding principles of the human genome. *Science* **326**, 289–293 (2009)
FURTHER READING Lanctôt, C., Cheutin, T., Cremer, M., Cavalli, G. & Cremer, T. *et al.* Dynamic genome architecture in the nuclear space: regulation of gene expression in three dimensions. *Nature Rev. Genet.* **8**, 104–115 (2007) | Dekker, J. Gene regulation in the third dimension. *Science* **319**, 1793–1794 (2008)