Determining 3D structures of whole, individual genomes using single-cell Hi-C

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Abstract

Typical DNA sequencing-based chromosome conformation capture (3C) techniques, which are commonly used to investigate spatial genome architecture, involve the sampling of close contacts from a superposition of nuclear states present in a population of cells. While this leads to useful probabilistic data, it is a difficult task to use population data to determine realistic structural models of chromosomes and it can also obscure any cell-to-cell variability present within the sample. Using a Hi-C method adapted to work on intact, individual nuclei it is possible to identify a large number of chromosomal contacts in single cells. This high-fidelity data allows the determination of complex structural models of whole genomes where, within a certain degree of precision, the relative 3D location of almost all sequences is known. These structures are determined by folding a relatively simple model of the chromosomal path with short distance restraints derived from intra- and inter-chromosomal contacts. This represents a new experimental and informatics approach to study whole genome organisation, at single-cell resolution that can answer questions relating to large-scale DNA polymer folding and cell-to-cell variability. Moreover, comparison of structures and chromosomal contacts from different cells shows that large-scale chromosome folding and interactions are highly variable from cell to cell, but nonetheless cells of the same type show the same underlying organisational principles with regards to their nuclear architecture.

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