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# The large-scale hierarchical features of chromatin spatial organization

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## Abstract

Chromosomes have a complex spatial organization within the cell nucleus. They are folded into an array of megabase-sized regions, known as TADs, marked by locally enriched chromatin interactions. TADs have internal sub-structures, but their higher-order organization remains elusive. In this work, we investigate interactions between TADs and find that, far from being isolated structures, they form a functional hierarchy of domains-within-domains (metaTADs), which extends across genomic scales up to entire chromosomes. We map chromatin contacts with Hi-C along a differentiation time-course from proliferating mESCs, through neuronal precursor cells, and terminally differentiated neurons. We find that TAD-TAD interactions generate a tree-like, hierarchical structure irrespective of cell type, reflecting a general organizational principle of mammalian genomes. Hierarchical topologies have the potential to produce complex, yet highly efficient folding, by combining structural stability with local adaptability. We explore the mechanisms of hierarchical folding using polymer modelling, and demonstrate that it can promote efficient chromatin packaging without loss of contact specificity. We find that the structures of metaTAD trees correlate with genetic, epigenetic and expression features. The structural rearrangements in metaTAD trees observed during differentiation correlate with changes in transcriptional state, highlighting a functional role of the hierarchical organization far beyond simple packing efficiency.

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