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Formation of chromosomal domains in interphase by loop extrusion GEOFFREY FUDENBERG, MIT — While genomes are often considered as one-dimensional sequences, interphase chromosomes are organized in three dimensions with an essential role for regulating gene expression. Recent studies have shown that Topologically Associating Domains (TADs) are fundamental structural and functional building blocks of human interphase chromosomes. Despite observations that architectural proteins, including CTCF, demarcate and maintain the borders of TADs, the mechanisms underlying TAD formation remain unknown. Here we propose that loop extrusion underlies the formation TADs. In this process, cis-acting loop-extruding factors, likely cohesins, form progressively larger loops, but stall at TAD boundaries due to interactions with boundary proteins, including CTCF. This process dynamically forms loops of various sizes within but not between TADs. Using polymer simulations, we find that loop extrusion can produce TADs as determined by our analyses of the highest-resolution experimental data. Moreover, we find that loop extrusion can explain many diverse experimental observations, including: the preferential orientation of CTCF motifs and enrichments of architectural proteins at TAD boundaries; TAD boundary deletion experiments; and experiments with knockdown or depletion of CTCF, cohesin, and cohesin-loading factors. Together, the emerging picture from our work is that TADs are formed by rapidly associating, growing, and dissociating loops, presenting a clear framework for understanding interphase chromosomal organization.

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