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Chromatin extrusion explains key features of loop and domain formation in wild-type and engineered genomes ADRIAN SANBORN, SUHAS RAO, Stanford, SU-CHEN HUANG, NEVA DURAND, MIRIAM HUNTLEY, ANDREW JEWETT, IVAN BOCHKOV, DHARMARAJ CHINNAPPAN, ASHOK CUTKOSKY, JIAN LI, KRISTOPHER GEETING, DOUG MCKENNA, ELENA STAMENOVA, Baylor College of Medicine, ANDREAS GNIRKE, ALEXANDRE MELNIKOV, ERIC LANDER, Broad Institute, EREZ AIDEN, Baylor College of Medicine — Our recent kilobase-resolution genome-wide maps of DNA self-contacts demonstrated that mammalian genomes are organized into domains and loops demarcated by the DNA-binding protein CTCF. Here, we combine these maps with new Hi-C, microscopy, and genome-editing experiments to study the physical structure of chromatin fibers, domains, and loops. We find that domains are inconsistent with equilibrium and fractal models. Instead, we use physical simulations to study two models of genome folding. In one, intermonomer attraction during condensation leads to formation of an anisotropic "tension globule." In the other, CTCF and cohesin act together to extrude unknotted loops. Both models are consistent with the observed domains and loops. However, the extrusion model explains a far wider array of observations, such as why the CTCF-binding motifs at pairs of loop anchors lie in the convergent orientation. Finally, we perform 13 genome-editing experiments examining the effect of altering CTCF-binding sites on chromatin folding. The extrusion model predicts *in silico* the experimental maps using only CTCF-binding sites. Thus, we show that it is possible to disrupt, restore, and move loops and domains using targeted mutations as small as a single base pair.

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