Supplemental materials

Methods

Our model of loop extrusion acting on a polymer fiber consists of (a) a 1D model that governs the dynamics of intra-chromosomal bonds formed by condensins over time and (b) a 3D polymer model of chromosome dynamics subject to the condensins bonds.

The 1D model of loop extrusion

The dynamics of loop extruding condensins on a chromatin fiber is simulated using a 1D lattice simulations as it was described previously for generic loop-extruding factors (1, 2) In the lattice, each position corresponds to one monomer in the 3D polymer simulation. We model a condensin molecule very generally as having two chromatin binding sites or, “heads”, connected by a linker. Each head of a condensin occupies one lattice position at a time, and no two heads can occupy the same lattice position. To simulate the process of loop extrusion, the positions of the two condensin heads stochastically move away from each other over time (simulated with the Gillespie algorithm (3)).

We initialize the simulations by placing condensin molecules at random positions along the polymer chain, with both heads in adjacent positions. To simulate the exchange of condensins between chromatin and solution, condensins stochastically dissociate from the chromatin fiber. Every dissociation event is immediately followed by association of another condensin molecule with the chromatin fiber so that the total number of condensins bound to the chromatin stays constant.

This 1D model has four parameters: the size of the lattice, number of condensins bound to chromatin, speed of extrusion, average residency time of a condensin on the chromatin fiber. We model a 30 Mb chromosome with a lattice of 50000 sites, 600 bp each. The chromosome is bound by 1000 condensins. Without loss of generality, we set the speed of extrusion to be 1 step per unit time and the condensin residency time at 692 units of time, such that the resulting average loop length is equal 167 monomers, or, 100kb, close to previous observations in vivo.

3D simulations of chromosomes

To perform Langevin dynamics polymer simulations we use OpenMM, a high-performance GPU-assisted molecular dynamics API (4, 5). To represent chromatin fibers as polymers, we use a sequence of spherical monomers of 1 unit of length in diameter. Here and below all distances are measured in monomer sizes (~3 nucleosomes, ~10nm), density is measured in particles per cubic unit, and energies are measured in kT. We use the following parameters of the Langevin integrator: particle mass = 1 amu, friction coefficient = 0.01 ps^-1, time step = 1ps, temperature = 300K.

Neighboring monomers are connected by harmonic bonds, with a potential $U = 100(r-1)^2$ (here and below in units of kT). We model polymer stiffness with a three point interaction term, with the potential $U = 5\,(1-\cos(\alpha))$, where alpha is the angle between neighboring bonds.

To allow chain passing, which represents activity of topoisomerase II, we use a soft-core potential for interactions between monomers, similar to (6, 7). All monomers interact via a repulsive potential

$$U = 2.0\left(-1+\left(\frac{r}{\sqrt{6/7}}\right)^{12}\cdot\left(\left(\frac{r}{\sqrt{6/7}}\right)^{2}-1\right)\cdot\frac{823543}{46656}\right)$$

This is a fast and efficient potential designed to be constant at 2.0 kT up to r=0.7-0.8 and then quickly go to zero at r=1.00.

To connect 1D LEF simulations with 3D polymer simulations, we first run 1D LEF dynamics for a total period of 10 condensin residence times, recording the state of the systems each unit of time. We then assign bonds to the monomers in polymer simulations according to the current position of condensins' heads. The two monomers held by the two heads of each condensin are connected by a harmonic bond with the potential $U = 100(r-1)^2$. For each position of condensins' heads from the 1D model, we perform 40000 steps of Langevin dynamics. 3D conformations are recorded every 20000 steps.

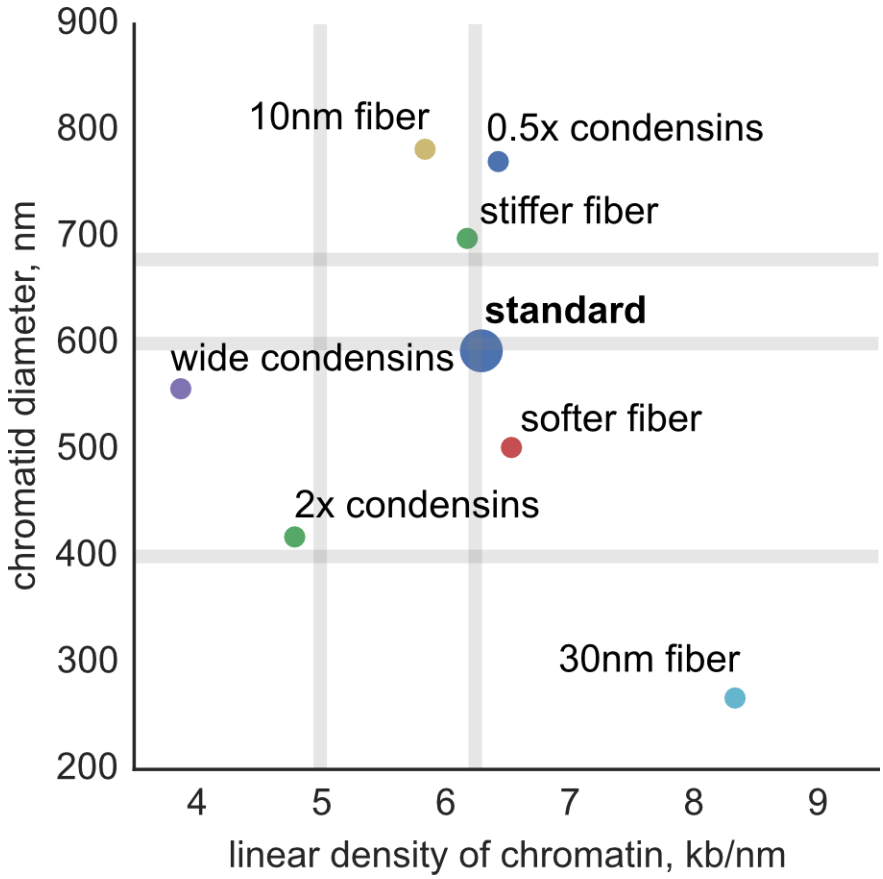
We allow an overlap of the heads of collided condensins at the loop bases (i.e. two heads of collided condensins could occupy the same monomer instead of two adjacent monomers). We implement this by shifting the positions of the downstream heads of all condensins by 1 monomer downstream. This allows us to achieve the maximally possible compaction of the chromosomal core (one loop per one monomer of the axis).

We generate the initial conformation of a single chromosome as following: a polymer chain was spherically compacted to a density of 0.01 particle per unit length^3, then allowed to equilibrate over 4,000,000 steps of Langevin dynamics, with a gradual increase of repulsion energy to equilibrate both the topology and the distribution of density inside the confining sphere. We generate the initial conformations of two sister chromatids by winding of two polymer chains along the conformation of a single chromosome, with one full turn each 100 monomers.

We simulate topo II depletion by adjusting two factors. First, we increase the energy of monomer overlap to 20 kT. Since this measure alone proved to be inefficient to prevent chain passing, we additionally increase the radius of repulsion up to 3 length units. In order to maintain the contour length of the polymer, we keep the length of a monomer bond at 1 and ignore repulsion between pairs of neighboring monomers, up to 3 monomers distance along the chain.

To study how the parameters of simulations affect the geometry of compacted chromosomes, we alter the following parameters: (a) increase 2x and (b) decrease 0.5x the number of condensins, (c) increase 2x and (d) decrease 0.5x the bending energy, (e) disallow overlaps of condensins at loop bases, thus simulating wide condensins; (f) reduce linear DNA density of the chromatin fiber to 400 bp/10nm to model compaction of a 10nm fiber of stacked nucleosomes and (e) increase linear DNA density of the chromatin fiber to 2400 bp/10nm and increased the fiber thickness to 30nm to model compaction of a 30nm fiber.

Supplemental figures.



Supplemental figure 1. The geometrical parameters of compacted chromosomes in simulations with altered parameters. “Stiffer fiber” – simulations with 2x bending energy of the fiber, “softer fiber” – simulations with 0.5x bending energy; “wide condensins” – simulations with reduced overlap between condensins at loop bases; “10nm fiber” - simulations with reduced linear DNA of the fiber; “30nm fiber” – simulations with increased linear DNA density of the fiber and increased fiber thickness, “0.5x condensin” – simulations with 500 condensins, “2x condensins” - simulations with 2000 condensins. The vertical gray lines show the experimental observations on the linear density of DNA along the human prophase chromosome I (6.25 kb/nm) and chromosome XXII (5.0 kb/nm) (8). The horizontal gray lines show the experimental data on the diameter of prophase chromosomes: 400 nm (9), 600 nm (10) and 679 nm (11).

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