Global positioning of interphase chromosomes mediated by local chromatin interactions

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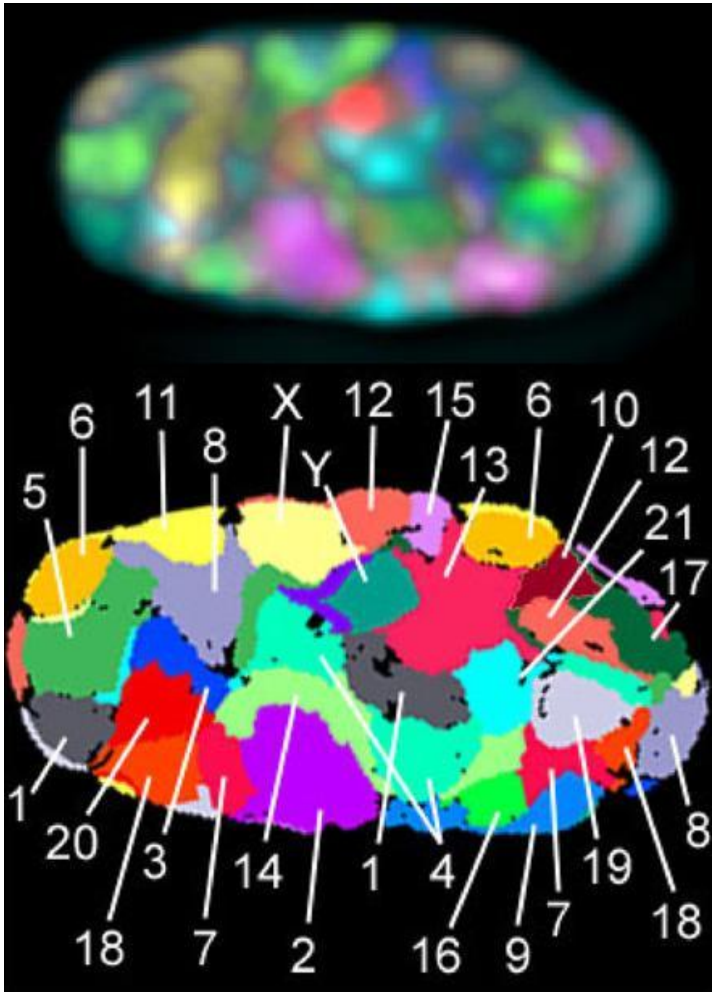
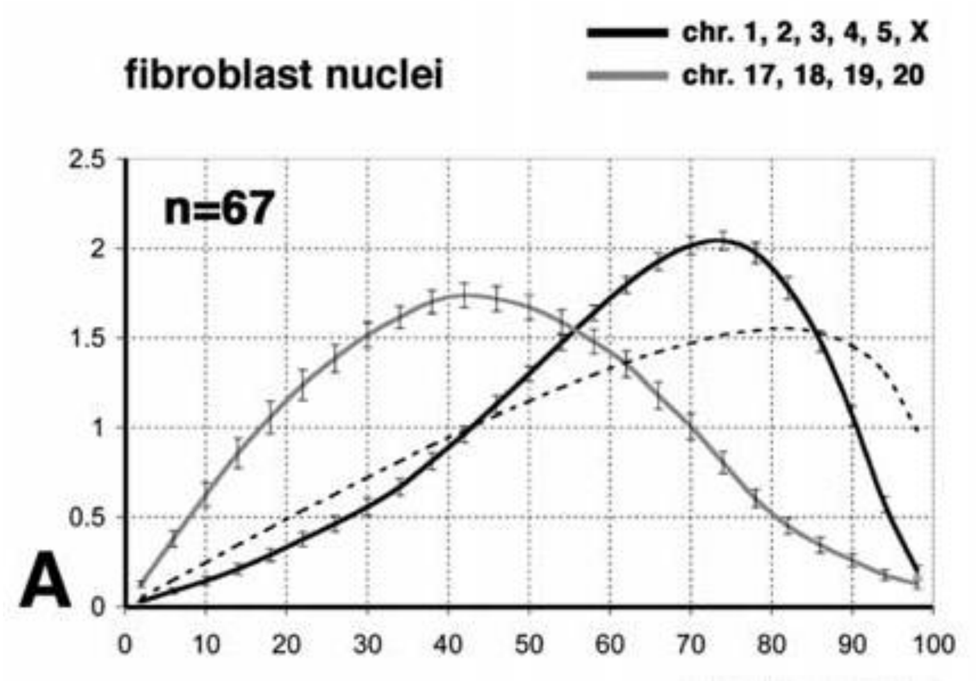
Chromosomes have preferential positions in the nucleus



Bolzer et al., Plos Biol, 2005

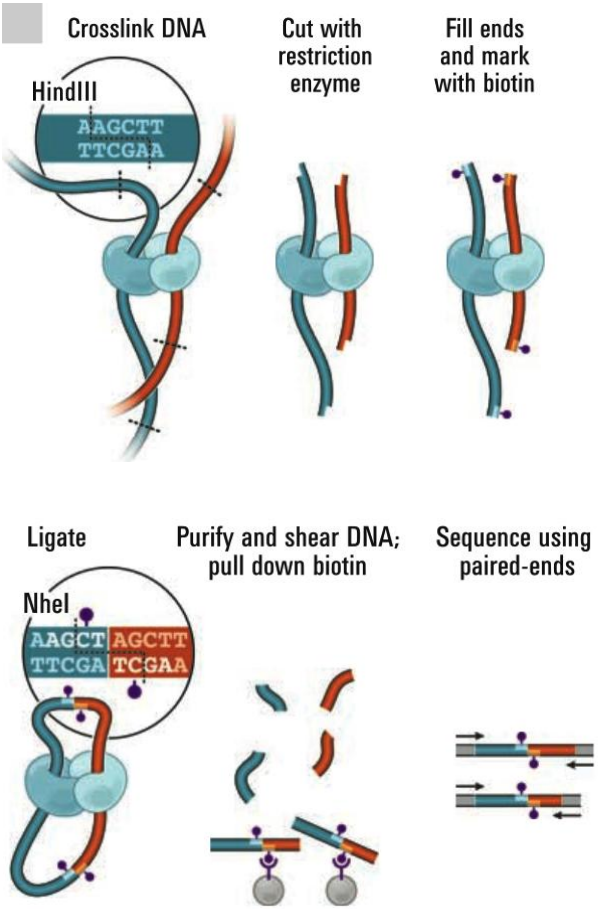


Kreth et al., Biophys J. 2004

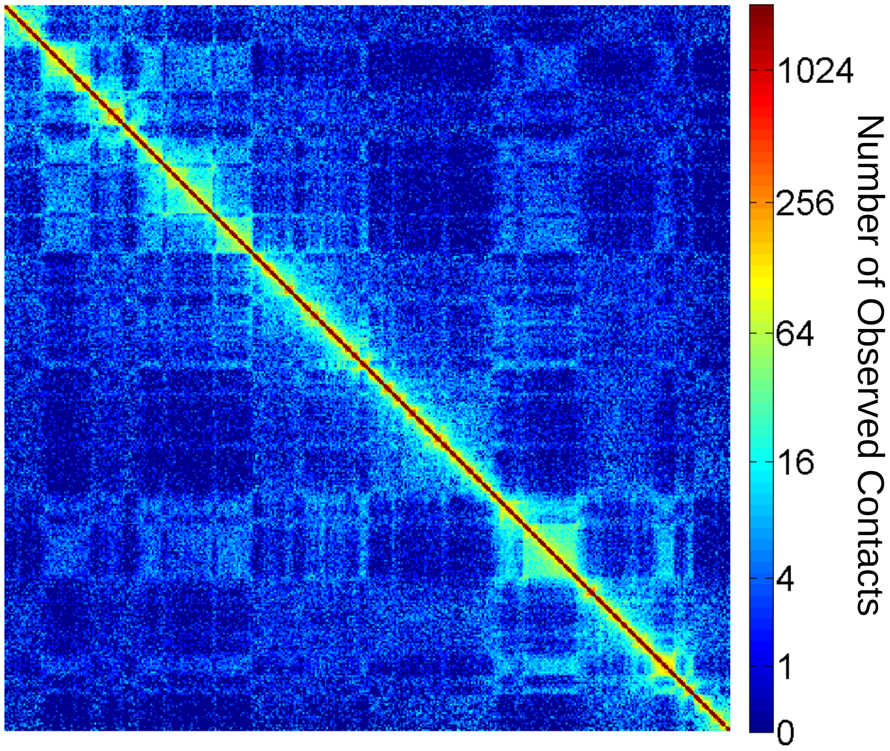
-- gene-rich chromosomes are toward the center of the nucleus
--gene-poor chromosomes are towards the nuclear periphery.

Hi-C measures spatial contacts between chromosomes and obtains a contact map

Hi-C experimental procedure



Contact map for human chromosome 14

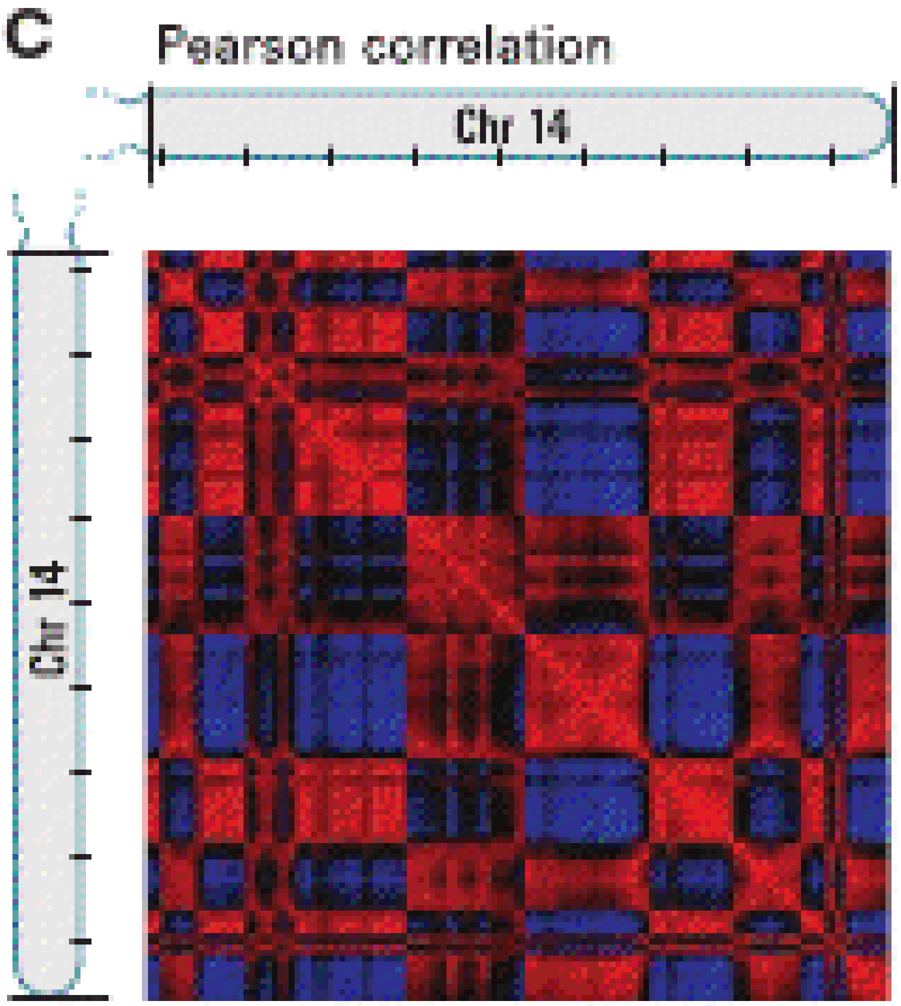


Lieberman-Aiden and van Berkum et al., Science, 2009

Hi-C identifies two genomic compartments

-- gene-rich regions interact more with other gene-rich regions, and less with gene-poor regions

-- gene-poor regions interact more with other gene-poor regions, and less with gene-rich regions

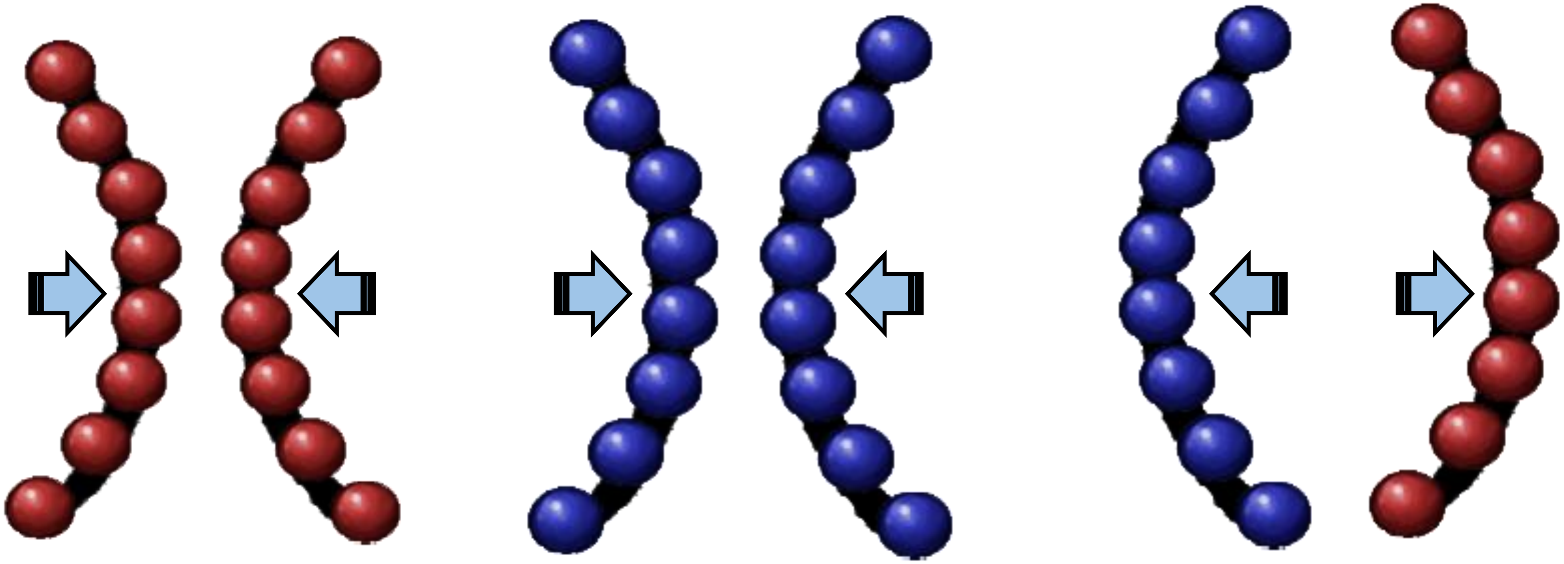


Lieberman-Aiden and van Berkum et al., Science, 2009

Can preferential interaction between chromosomal loci determine the global positioning of whole chromosomes?

-- Like domains attract while different domains repel.

-- Red represents gene-rich loci while blue represents gene-poor loci



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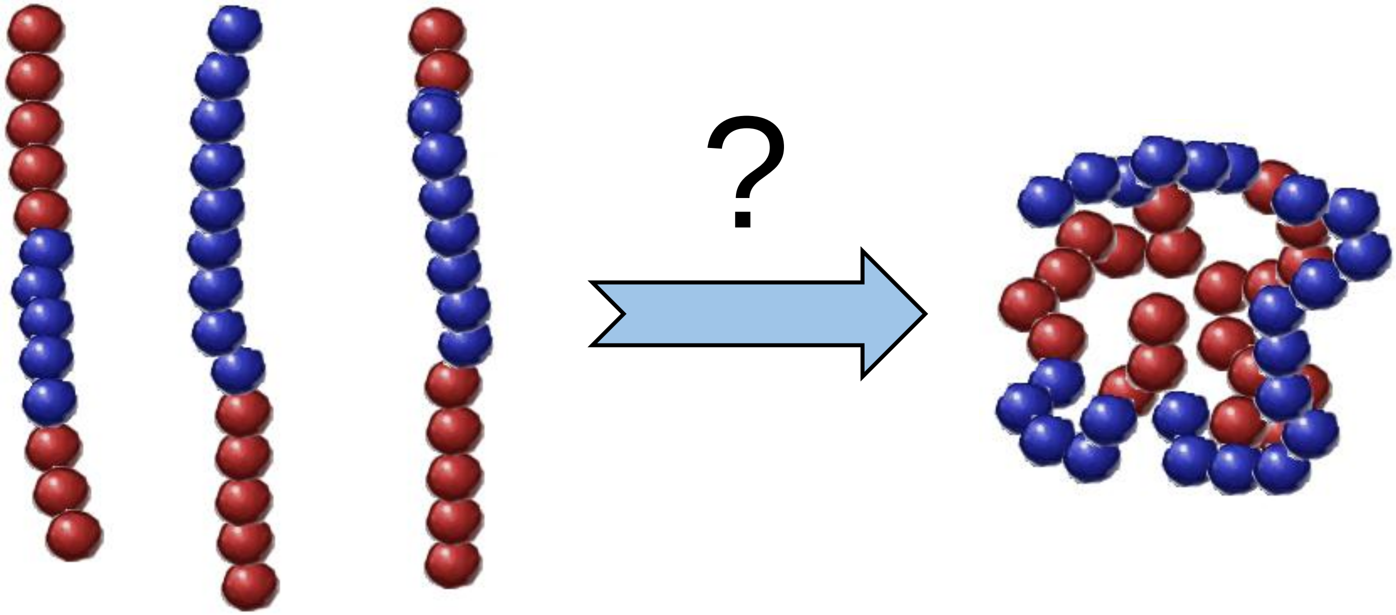


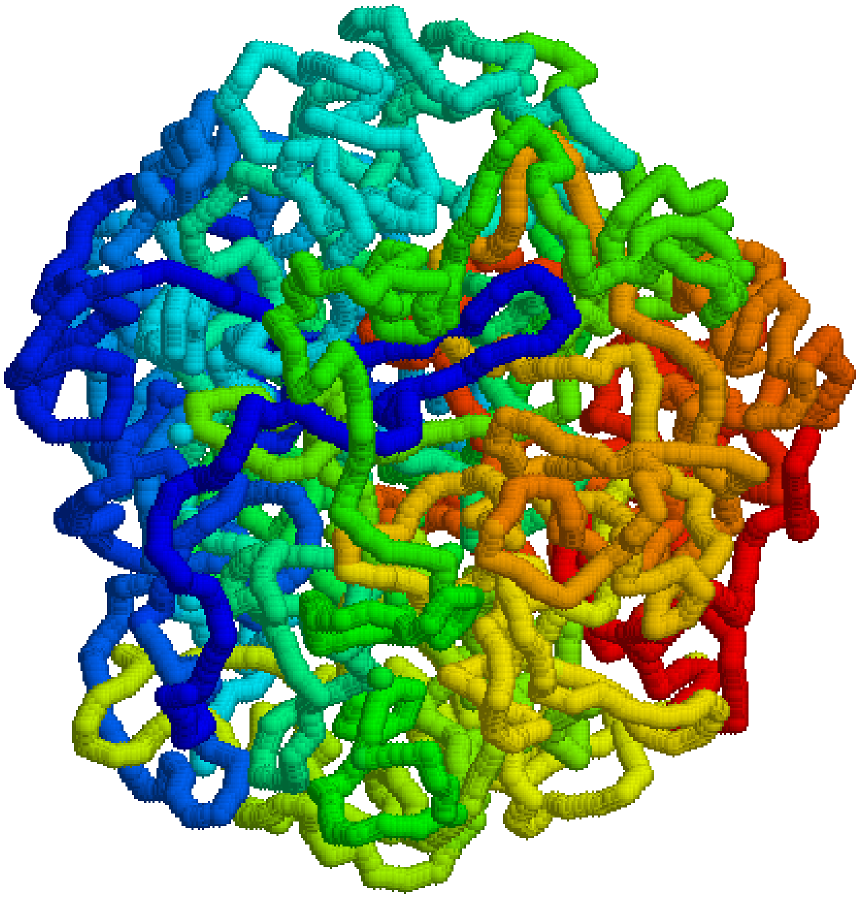
Polymer simulation initialized with post-mitotic-like chromosome conformations

Human Mitotic Chromosomes

NHGRI

Simulating the chromosomes within the nucleus

We let the chromosomes decondense within the spherical nucleus allowing for intermolecular forces and domain interactions.



Observations

-- Spiral starting conformations quickly decondense after the start of the simulation

-- Non-overlapping initial conformations are crucial for obtaining meaningful simulations

-- Nucleus must be sufficiently large for a given number of monomers

-- Randomization is key to avoid starting conformation bias in simulations

Future Directions

-- Explore different functional forms of the potential energy

-- Calibrate simulated contact probabilities between polymers with experimental Hi-C data on chromosomal contacts.

-- Measure radial distribution of simulated chromosomes.

-- Investigate other factors that may contribute to chromosomal positioning

-- Contrast with previous constraint based models of chromosomal positioning.

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