

Can local chromatin interactions mediate the global positioning of interphase chromosomes?

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At large scales, microscopy studies show that chromosomes adopt preferential locations within the nucleus. Small gene-rich chromosomes localize in the center of the nucleus, while large gene-poor chromosomes reside on the nuclear periphery¹. At smaller scales, Hi-C² demonstrates that the genome is spatially compartmentalized into active loci and inactive compartments; loci from the same compartment are closer in space and from contacts more frequently. However, the determining factors of chromosomal positioning and the link between local interaction preferences of chromatin and global chromosomal positions remain unclear.

Here, we ask whether local chromatin interactions alone can lead to preferential locations of interphase chromosomes in the nucleus. We model human interphase chromosomes as polymers with local interaction preferences extracted from Hi-C data using iterative correction and eigenvector decomposition (ICE₃). We then perform brownian dynamics simulations using the GPU assisted molecular dynamics package, OpenMM⁴, starting our simulations from a mitotic-like chromosomal conformations. To verify the consistency of our model, we check that the pattern of contact enrichment agrees with Hi-C data.

Despite significant co-localization of chromatin compartments, we find no significant differences in radial positions of these compartments or of the relative positions of chromosomes. This contrasts with results of previous models, which suggested that radial chromosome positioning follow directly from distance constraints defined by Hi-C contact frequencies⁵. However, our model has several advantages: first, our model considers only physically-justified short-range chromatin interactions instead of geometrical constraints; second, we model the genome at a fixed 200kb resolution, rather than a highly variable range of resolutions.

We conclude that local chromatin interactions are insufficient to determine preferential chromosome positions in the interphase nucleus. We hypothesize that other mechanisms are responsible for this effect, and may potentially include interactions of inactive chromatin with the nuclear lamina.

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