

Genome-Wide Modeling of 3D Chromosome Organization in Yeast S-Phase

From the basic structure of two diverging sister forks to their organization at the nuclear scale, the mechanistic details of how DNA replication influences 3D chromatin organization remain highly debated. To quantitatively address some of these questions, we simulate the entire *Saccharomyces cerevisiae* genome, integrating its 3D Rabl architecture with realistic 1D replication timing patterns. Our model explicitly incorporates chromatin duplication, allowing us to test key hypotheses on replication fork organization. We identify a distinct “fountain” pattern in Hi-C maps, which is characteristic of interacting sister forks and analogous to other extrusion mechanisms. We validate this pattern in new *in vivo* data, where its intensity suggests a coexistence of interacting and non-interacting forks. Our framework also effectively captures large-scale properties throughout yeast S-phase. In particular, we investigate the heterogeneous distribution of replication forks arising from the interplay between the Replication Timing Program and Rabl architecture, as well as its potential role in the detection of larger clusters of forks in the nucleus. Additionally, we examine the spatial and dynamical properties of sister chromatids during and after their synthesis in S-phase.

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