REPLISAGE: A STOCHASTIC MULTI-SCALE FRAMEWORK FOR CHROMATIN FOLDING AND REPLICATION MODELED AS A PHASE TRANSITION SYSTEM

Sevastianos Korsak,* Krzysztof H. Banecki, and Dariusz Plewczynski
Laboratory of Bioinformatics and Computational Genomics,
Faculty of Mathematics and Information Science, Warsaw University of Technology, Warsaw, Poland and
Laboratory of Functional and Structural Genomics, Centre of New Technologies, University of Warsaw, Warsaw, Poland

Karolina Buka
Laboratory of Functional and Structural Genomics, Centre of New Technologies, University of Warsaw, Warsaw, Poland

Piotr J. Górski
Group of Physics in Economy and Social Sciences, Faculty of Physics, Warsaw University of Technology, Warsaw, Poland

RepliSage is a stochastic, multi-scale modeling framework for simulating chromatin folding and DNA replication dynamics across the cell cycle. It integrates population-level replication timing data and 3C-based chromatin interaction maps (e.g., ChIA-PET or HiChIP) to reconstruct ensembles of 3D genome conformations across G1, S, and G2/M phases. The model consists of three coupled components: (i) Monte Carlo simulation of replication fork propagation based on origin firing probabilities; (ii) a loop extrusion model incorporating replication forks as dynamic barriers and epigenetic mark evolution; and (iii) Langevin dynamics with OpenMM to produce 3D structures based on a biophysically informed energy functional. A key feature is the treatment of the cell cycle as a hysteresis-like phase transition system, where order parameters (e.g., number of loop extruding proteins, folding or replication energy parameters) may change during the simulation. This allows RepliSage to explore how structural metrics (e.g., radius of gyration, convex volume) change with parameter shifts, revealing folding transitions in chromatin architecture. Validation against orthogonal datasets—including single-cell Hi-C/HiChIP loop patterns and compartmentalization profiles—demonstrates robust performance across replication states and stress conditions.

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* s.korsak@datascience.edu.pl