Investigation of the replication-transcription conflicts in Trypanosoma brucei through computational dynamical models

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Abstract

In the context of Molecular Cell Biology, DNA replication consists on the process of duplicating the genetic material of a cell. This process can start multiple times during the S-phase of cell cycle, at specific genomic regions named "replication origins". However, the triggering frequency of each origin and the dynamics of its respective replisomes are subject to variations along S-phase. Moreover, the influence of the collisions between these replisomes and the DNA polymerase (DNAP) on the overall duration of the S-phase is unknown. Therefore, our objective in this work is the development of computational dynamic models to test whether replisome/DNAP collisions have relevant impact on the S-phase dynamics in various protozoa species in the kinetoplastida group. We started this investigation with Trypanosoma brucei, the pathogen behind the sleeping sickness. The proposed model consists in a Markov chain whose transition function can be estimated using heterogeneous data (e.g., the distribution of replication origins and the transcription sites of each chromosome) obtained from the literature and also from wet-lab experiments carried out at our lab. This information was organized into a relational database and a model simulator was implemented in Python. Unknown parameters such as the transcription initiation frequency and number of available replication origin sites were evaluated through a comprehensive Monte Carlo sampling on a search space constrained by the biological feasibility of the values obtained in a given simulation. Initial results with T. brucei strain 927 showed that a causal response to replisome/DNAP collisions (e.g., through the ATM/ATR signaling pathways) is not necessary to accomplish DNA replication within the S-phase required time that is reported in the literature. Currently, we are applying this methodology into other protozoa such as T. cruzi, the parasite that causes Chagas disease. Therefore, we expect to elucidate how differences on the replication dynamics of these organisms accounts for differences in the genomic architecture that are observed in kinetoplastids.

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