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Topology of Partially Replicated DNA Molecules

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How the topology of DNA changes during replication is still poorly understood. Every DNA molecule in a partial replication state can be modeled as two separated topological domains, the unreplicated and the replicated region, physically connected by replication forks. The balance of energy between these regions has a key role during DNA replication. The topology of a DNA molecule during the replication process is regulated by enzymes called topoisomerases, which are molecular targets for a variety of drugs like antibiotics and anticancer drugs. The processivity of the topoisomerases depends on the conformational and energetic properties of the replicating DNA molecule. These properties of the replication intermediates are not well characterized.

The topological and energetic characterization of circular DNA plasmids depends on the Linking number (Lk), which is an integer that determines the total number of turns of the double helix. Lk is a topological invariant and, according to the Calugareanu-White-Fuller relation, $Lk = Wr + Tw$, where Tw (Twist) determines the degree of torsional deformation of the double helix and Wr (Writhe) is a number that describes the three-dimensional folding of the molecule. The topology of partially replicated plasmids also depends on the pre-catenation number that describes the interlinking number between the two sister chains and equals half of the signed sum of intermolecular nodes. In this work, we performed numerical simulations to qualitatively identify the variation of energy and

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characterize the conformational equilibrium of partial replicated molecules (Replication Intermediates, RIs). To this end, partially replicated circular DNA molecules were considered. We use the wormlike chain model, which has been probed to give a very accurate approximation to experimental observations. The potential energy was calculated as the sum of two elastic potentials: the first one due to the bending of the molecule and the second one representing the twisting effects of the double helix around itself. The model used to simulate a RI was composed of an unreplicated region connected through replication forks to two circular molecules representing the nascent chains of the replicated region. Newly replicated sister DNA molecules can be multiply interlinked with left-handed (LH) precatenanes and unreplicated can be supercoiled region with right-handed (RH) plectonemes. The topology of the RI was modified through fork rotation either by winding or unwinding the plectonemic structure in the unreplicated region or by rotating both nascent curves around each other in the replicated region. To analyze the stability of the equilibrium conformation, the numerical simulation was performed using the Metropolis Monte Carlo method (MMC), starting from several initial topological conformations. At every MMC step we tested the topological invariance property imposed by the molecule linking number. When a local equilibrium conformation was obtained, the algorithm modified the supercoiling of the unreplicated region and performed equivalent rotations of the replication fork, inducing a modification in the precatenation of the nascent chains. As a result, a new local equilibrium conformation was obtained with MMC in order to evaluate its energy.

Our results confirmed that the balance of energy between the unreplicated and replicated regions drives fork swiveling, allowing the interchange and redistribution of supercoiling and precatenation during DNA replication. In addition, the final equilibrium state of energy was asymptotically stable for all the initial topological conformations tested, and it was robust in terms of energy perturbations introduced by the MMC method.

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