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Influence of DNA supercoiling on the kinetics of DSBs rupturing process

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Double-strand breaks (DSB) involve the covalent cut of the DNA backbone over both strands and are widely recognized as the most detrimental lesions associated with the effect of ionizing radiation on cells: Particularly, their misrepair can lead to severe biological consequences, including genomic instability, apoptosis, or carcinogenesis.
DSBs can arise from a variety of processes that range over broad (but intertwined) spatial and temporal scales, making their early-stage characterization challenging to conventional experimental techniques. On the other hand, in silico approaches have proven to achieve valuable insights in this context. Indeed, Monte Carlo track-structure simulations and microdosimetric models have successfully correlated the early effects of cell irradiation with macroscopic biological outcomes (i.e. the cell survival) by providing mean-field descriptions of radiation fields. However, these methods neglect the structural and mechanical dynamics of damaged DNA at the molecular level, which is largely overlooked despite its biological relevance.
In this presentation, we show how coarse-grained molecular dynamics simulations has been employed to characterize the DNA rupturing process in supercoiled DNA minicircles, lesioned by various DSB motifs: Particularly, we systematically explore how topological, structural, and mechanical features influence the rupture kinetics.
Our results reveal that mechanically-strained DNA conformations overall exhibit a higher rupturing probability than their topologically-relaxed counterparts - this effect being significantly enhanced under positive supercoiling regimes - despite highlighting a topological asymmetry in the mechanical response of the DNA to the diverse lesions. Furthermore, the influence of topological and structural features on the DNA rupturing dynamics seemingly decreases over time, as DSBs relieve the topological constraints of circular DNAs and drive the structural relaxation of the excess supercoiling stress.
In conclusion, our findings tally with previous radiobiological observations suggesting that compact DNA conformations reduce its radiosensitivity by minimizing the effective target volume. Moreover, we infer that DNA molecules exhibit minimal rupture enhancement at a biologically-relevant negative superhelical density (σ=−0.06), suggesting that such regime represents a favorable state against exogenous damage. Overall, these results support the idea that negative DNA supercoiling, beyond its roles in gene regulation and genomic organization, may also provide incidental structural protection against radiation-induced damage.

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