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Free Energy Computation of A G-Quadruplex-Ligand Structure: A Classical Molecular Dynamics and Metadynamics Simulation Study

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Abstract : The DNA G-quadruplex is a four-stranded DNA structure formed by stacked planes of four base paired guanines (G-quartet). Guanine rich DNA sequences appear in many sites of genomic DNA and can potential form G-quadruplexes, such as those occurring at 3'-terminus of the human telomeric DNA. The formation and stabilization of a G-quadruplex by small ligands at the telomeric region can inhibit the telomerase activity. In turn, the ligands can be used to down regulate oncogene expression making G-quadruplex an attractive target for anticancer therapy. Many G-quadruplex ligands have been proposed with a planar core to facilitate the pi–pi stacking and electrostatic interactions with the G-quartets. However, many drug candidates are impossibilitated to discriminate a G-quadruplex from a double helix DNA structure. In this context, it is important to investigate the site topology for the interaction of a G-quadruplex with a ligand. In this work, we determine the free energy surface of a G-quadruplex-ligand to study the binding modes of the G-quadruplex (TG4T) with the daunomycin (DM) drug. The complex TG4T-DM is studied using classical molecular dynamics in combination with metadynamics simulations. The metadynamics simulations permit an enhanced sampling of the conformational space with a modest computational cost and obtain free energy surfaces in terms of the collective variables (CV). The free energy surfaces of TG4T-DM exhibit other local minima, indicating the presence of additional binding modes of daunomycin that are not observed in short MD simulations without the metadynamics approach. The results are compared with similar calculations on a different structure (the mutated mu-G4T-DM where the 5' thymines on TG4T-DM have been deleted). The results should be of help to design new G-quadruplex drugs, and understand the differences in the recognition topology sites of the duplex and quadruplex DNA structures in their interaction with ligands.

Keywords : g-quadruplex, cancer, molecular dynamics, metadynamics
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