

Replica-Exchange Metadynamics Simulations of G-Quadruplex DNA Structures Under Substitution of K⁺ by Na⁺ Ions

Authors : Juan Antonio Mondragon Sanchez, Ruben Santamaria

Abstract : The DNA G-quadruplex is a four-stranded DNA structure conformed by stacked planes of four base paired guanines (G-quartet). The guanine rich DNA sequences are present in many sites of genomic DNA and can potentially lead to the formation of G-quadruplexes, especially at the 3'-terminus of the human telomeric DNA with many TTAGGG repeats. 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 regulate oncogene expression making the G-quadruplex an attractive target for anticancer therapy. Clearly, the G-quadruplex structured in the telomeric DNA is of fundamental importance for rational drug design. In this context, we investigate two G-quadruplex structures, the first follows from the sequence TTAGGG(TTAGGG)3TT (HUT1), and the second from AAAGGG(TTAGGG)3AA (HUT2), both in a K⁺ solution. We determine the free energy surfaces of the HUT1 and HUT2 structures and investigate their conformations using replica-exchange metadynamics simulations. The carbonyl-carbonyl distances belonging to different guanines residues are selected as the main collective variables to determine the free energy surfaces. The surfaces exhibit two main local minima, compatible with experiments on the conformational transformations of HUT1 and HUT2 under substitution of the K⁺ ions by the Na⁺ ions. The conformational transitions are not observed in short MD simulations without the use of the metadynamics approach. The results of this work should be of help to understand the formation and stability of human telomeric G-quadruplex in environments including the presence of K⁺ and Na⁺ ions.

Keywords : g-quadruplex, metadynamics, molecular dynamics, replica-exchange

Conference Title : ICBCBBE 2015 : International Conference on Bioinformatics, Computational Biology and Biomedical Engineering

Conference Location : Paris, France

Conference Dates : September 21-22, 2015