INSIGHT INTO STRUCTURAL PROPERTIES OF NCP7 PROXIMAL ZINC FINGER: LONG-RANGE ELECTROSTATIC INTERACTIONS EFFECT ON MOLECULAR DYNAMIC SIMULATIONS

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Nucleocapsid protein plays important roles in the viral life-cycle and presents an attractive target for rational drug design. It contains two highly conserved Cys2HisCys zinc fingers that strongly bind Zn(II) through coordination of one Histidine and three Cysteine residues. Long-range interactions are known essential in highly polar biomolecules. In molecular dynamics simulations of nucleic acids and proteins, an accurate treatment of the long-range interactions are crucial for achieving stable nanosecond trajectories. Zinc divalent cation embedded in the Cys2HisCys active sites poses a technical complication in MD simulations. Two general methods have been reported for MD simulations of zinc proteins. The first one, called "bonded model" [1] introduces covalent bonds between the zinc ion and its coordinates to maintain zinc's four-ligand coordination in proteins during MD simulations. This method is not suitable to the present study because it leads to a rigidification of the active site conformation.

In this study, insights structural and dynamical fluctuations in NCp7's N-terminal Cys2HisCys zinc-finger from multi time scale all-atom molecular dynamics Simulations have been investigated, using GROMOS96 force field. The Non-bonded model [2] for metal ion bonds was applied. The impact of log range electrostatic interactions between zinc ion and its liganding atoms on the whole peptide structure has been inspected. For comparison purposes, two simulations were done, one with the twin-range cut-off, and another one using Particle Mesh Ewald (PME). The results were compared with the data generated with conventional non-bonded models and experimental values.

Best structures are those obtained from short MD simulation (< 50ps) as they fit well to native structures of the classical zinc-finger. The Tetrahedral Zinc(II)-coordination sphere was maintained leading to a conservation of the active site hydrophobic core [3] and Short α–helix was observed at 10 and 20ps. The qualities of the structures were evaluated using the PROCHECK [4] software package. For long time scale simulations (>100ps) conformational changes were occurred upon the reorientation of the backbone carbonyl oxygen atoms toward the zinc ion which provide a favorable stabilized electrostatic environment On the subnano-to-nanosecond timescale the Zn(II) binding loops are flexible The entry of water into the peptide core upon unfolding has been mentioned in numerous protein unfolding simulations [5] while the exchange of a zinc-binding Cys(-) for a water molecule has been observed in simulations of other zinc finger proteins [6] Simulation using the PME gave a good agreement with NMR-derived structures. The results indicate that long-range electrostatic interactions are essential for an appropriate study of zinc-containing metalloproteins.

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