2.5. MD Simulations

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2.5. MD Simulations

At atomistic level, MD simulation results helped us to investigate the structural dynamics of receptor CoV-2 protease ($3CL^{pro}$) upon binding with small ligand (proposed drug) molecule. LINUX based platform ''GROMACS 5.1 Package'' (Berendsen et al., 1995) was used for determination of thermodynamics stability of the proposed ligand: protein complex. MD simulations were performed using latest CHARMM36 all atom force field (Soteras et al 2016). Before simulation, separate topologies were prepared for receptor and ligand by different external tools (Gajula et al 2016). For our ligand, before creating the topology first we have optimized the ligand structure by Gaussian 9.0 by Density Functional Theory (DFT) with the basis set 6.31G (d,p) (Becke et al 1997, Frisch et al 2004). With the optimized structure we have generated the ligand topology with the CHARMM General Force Field (CGenFF) program (Vanommeslaeghe et al 2012). In CHARMM all-atom force field, all H atoms of ligand are explicitly represented. For topology we have used the cgenff_charmm2gmx.py (http://mackerell.umaryland.edu/charmm_ff.shtml#gromacs). To perform simulations in aqueous solution, we have used a well known water model: TIP3P. During solvation process, the bare protein and protein: ligand complex were solvated in the cubic box having specific boundary conditions (10 Å buffer distance) with volume as 893,000 $Å^3$. As per procedure $4Na^+$ ions were added for electrically neutralizing the probe system. Before simulation we have done the energy minimization on the system to sort out any bad starting structures and also to minimize solute structure in vacuum before introducing solvent molecules. The Protein ligand complex system was equilibrated under suitable simulation parameters consistent for our selected CHARMM General Force Field for building the energy minimized solvated system. The steepest descent algorithm has been used for energy minimization of the system with varying time (ps) for 500,000 iteration steps. For reducing the steric clashes, the applied algorithm has a cut-off up to 1000 $kJmol^{-1}$ (Kumar et al 2020). The MD simulation has started with the minimization of the system. The minimization has been achieved at two phases each having 500,000 steps. In first part, equilibration was obtained having each step of 2 fs with a boundary condition of constant number of particles (N), volume (V), and temperature (T). We have used 10000-ps *NVT* equilibration. In second phase, the equilibration was achieved under the pressure of 1 atmosphere 298K. Here the boundary condition maintained as constant NPT (particle numbers, pressure, temperature). Such condition is known as isothermal-isobaric ensemble. Energy minimization data and output of MD

simulation data helped us to visualize several thermodynamic parameters like potential energy, kinetic energy, total energy, temperature, density progression, radius of gyration, RMSD, RMSF, SASA, etc. of the bare host protein and ligand: receptor complex. For equilibration step computation, for covalent bond constraints LINCS algorithm was applied. To quantify strength of interaction between ligand and protein it is useful to compute the nonbonded interaction energy between two species rather than calculating free energy of the system. For the nonbonded energy calculation we have used short range Lennard-Jones and Coulomb interaction energies. For these calculation we have maintained a 1.4 nm radius cut-off. For long range electrostatics calculation Particle Mesh Ewald (PME) method was used having 1.6Å of Fourier grid spacing. Berendsen temperature coupling method (V-rescale) has been used for maintaining inside box temperature. NPT equilibration has been achieved by Parrinello-Rahman pressure coupling method. The time parameter has been fixed to 10000 ps with each step of 0.002 fs for the final step of simulation. After final step of each simulation, trajectories were obtained. Obtained trajectories and results were analysed using the graphical tool Origin pro. Least-square fitting method was used to evaluate RMSD for protein backbone. Similarly, RMSF was obtained for protein Cα backbone. The compactness factor of protein was calculated by radius of gyration (R_g). According to rule if the protein or complex structure is stable then the radius of gyration should maintain a stable value. To compute total solvent accessible surface area (SASA) the tool sasa was used. SASA measures the area of receptor exposure to the solvents during the simulation process. Number of hydrogen bonds and distribution of intermolecular hydrogen bond lengths were calculated with maintaining 3.5Å distance cut-off condition throughout the simulation.

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