CHAPTER 6

CONCLUSION

The state of the art of molecular dynamics technique was employed to investigate the structural and dynamics properties of the apo-enzyme human dihydrofolate reductase in aqueous solution at the experimental and physiological temperatures. The molecular dynamics technique has taken the advantage of the empirical functions of the potential energy based on the Amber force fields to generate the structural coordinates of the system corresponding to each simulation time-step. The molecular dynamics simulations were performed for 300 picosecond of the simulation time-length in which the last 250 picosecond were used to assess the structural and dynamics properties of the enzyme.

In conclusion, the solution structures of the enzyme dihydrofolate reductase from Homo sapiens in the absence of substrate and co-factor were simulated to explore its dynamics at two different temperatures, 300K and 310.5K according to the experimental and the physiological temperatures respectively. The results of the study allow us to conclude that the overall structure of the enzyme in aqueous solution at 300K was similar to that of the human body temperature. This study also demonstrates that the solutions structures observed from the simulation and the x-ray structure of the enzyme taken from the literature were rather the same, except for some solvent exposed regions. Apart from the typical movement of hydrophobic amino acid side-chains such as the phenyl groups of tyrosine and phenylalanine, and isopropyl groups of valine or leucine, the flipping of aromatic side-chain of some phenylalanines was observed. The changes of the hydrogen bond involving amide protons effected by the surrounding solvent, which can be observed in the molecular dynamics trajectory of 250 picosecond.

There are much more interesting motions to further investigate the enzyme for instance, the flexibility caused by binding and the opening-closing of active site region, the larger scale motions of folding and unfolding phenomena, etc. The formers can be taken from the simulation of the bound system, the latter needs larger time scale.