

Abstract:

A new approach to predict the 3D structures of proteins by combining the knowledge-based method and Molecular Dynamics Simulation is presented on the chicken villin headpiece subdomain (HP-36). Comparative modeling is employed as the knowledge-based method to predict the core region (Ala9-Asn28) of the protein while the remaining residues are built as extended regions (Met1-Lys8; Leu29-Phe36) which then further refined using Molecular Dynamics Simulation for 120 ns. Since the core region is built based on a high sequence identity to the template (65%) resulting in RMSD of 1.39 Å from the native, it is believed that this well-developed core region can act as a 'nucleation center' for subsequent rapid downhill folding. Results also demonstrate that the formation of the non-native contact which tends to hamper folding rate can be avoided. The best 3D model that exhibits most of the native characteristics is identified using clustering method which then further ranked based on the conformational free energies. It is found that the backbone RMSD of the best model compared to the NMR-MDavg is 1.01 Å and 3.53 Å, for the core region and the complete protein, respectively. In addition to this, the conformational free energy of the best model is lower by 5.85 kcal/mol as compared to the NMR-MDavg. This structure prediction protocol is shown to be effective in predicting the 3D structure of small globular protein with a considerable accuracy in much shorter time compared to the conventional Molecular Dynamics simulation alone.