Studying conformational transitions of selected proteins using UNRES coarse-grained simulations with Lorentzian restraints

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Identifying the mechanism of conformational transitions of proteins is essential in the understanding of their biological functions. When investigating the conformational transitions, experimental methods provide only fragmentary information about the time evolution of the system such as the distance between donor and acceptor groups or distance distribution, therefore the use of simulation method to interpret the experimental data is necessary. An all-atom structure-based method for the study of the structural transition of proteins by utilizing Lorentzian attractive terms has been developed recently[1]. Two Lorentzian attractive interactions provide a double-well potential with a bounded energy barrier. We implemented this method to coarse-grained UNRES simulations, this enabling us to study larger systems with a smaller at lower computational expense. UNRES is a highly reduced protein model with only two interaction sites per residue[2]. Owing to this reduction, it offers ~1000-fold speed-up compared to all-atom molecular dynamics.

The aim of the study is to test the UNRES implementation of the method of modeling conformational transitions with double-well Lorentzian guiding function. For testing, we selected to fallowing two proteins with two well-defined states: the apo (PDB ID: 1LFH) and the holo (PDB ID: 1LFG) forms of lactoferrin, respectively, and the open (PDB ID: 4AKE) and the closed (PDB ID: 1AKE) forms of adenylate kinase,[3] respectively. The adenylate kinase is a phosphotransferase enzyme found in various organisms. The enzyme plays an essential role in cellular energy homeostasis by catalyzing the interconversion between ADP and ATP. Lactoferrin is an iron-binding protein present in large quantities in colostrum and in breast milk, in external secretions and in polymorphonuclear leukocytes. Lactoferrin's main function is non-immune protection[4]. Martiple conformational transitions between above-mentioned forms were observed in simulations for both proteins. The free energy landscapes were constructed and transition pathways were identified.

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