21. Rigid Body Protein-Protein Docking Using Biochemical Data

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Protein-protein interactions are crucial to numerous cellular processes such as signal transduction, regulation of biochemical pathways, immune response, and enzymatic reactions. Therefore, effective computational methods to model macromolecular complex formation are essential for understanding biochemical systems. A rigid body protein-protein docking protocol, that explicitly accounts for biochemical and sequence conservation data, is developed and applied to several unbound structures of proteins that form binary complexes. The tested cases include functionally and structurally diverse complexes such as enzyme-inhibitor, electron transfer, signal transduction and domain-peptide complexes. The main aim of this docking procedure is to efficiently generate encounter complexes, which can be subsequently refined to the structure of the final bound complex using Molecular Dynamics simulations. The docking protocol involves Brownian Dynamics sampling with distance constraints from available biochemical and sequence conservation data. We collect the 500 most energetically favorable complexes and cluster them. The representatives of each cluster are taken for further analysis. The quality of docked complexes is evaluated by calculating backbone root mean square deviation and percentage of native contacts compared to the known experimntal structures of the complexes. We also investigate the value of trimming the side chains of surface accessible residues Arg, Glu and Lys residues to implicitly account for side chain flexibility during rigid body docking. Trimming these side chains appears to be particularly helpful for enzyme-inhibitor complexes which often have narrow grooves and deep pockets at their interfaces. Overall, encounter complexes with acceptable structures are found within the first two clusters with rmsd < 7.0Å and percentage of native contacts > 20%. These structures are suitable conformations for subsequent flexible refinement.