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Protein-Protein Docking Guided by Biochemical Data

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Short Abstract: We present a protein-protein docking protocol comprised of rigid-body docking with Brownian Dynamics and flexible refinement with Molecular Dynamics. Docking is done subject to biochemical constraints. The protocol is applied to a structurally and functionally diverse set of test cases.

Long Abstract:
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. We describe a protocol for computational modeling of protein-protein association and prediction of the structures of complexes. We aim to create a modular procedure with well defined steps which allow this protocol to be used as a protein docking pipeline and as a tool for detailed investigation of association processes of particular macromolecular complexes. Overall, the method can be divided into Rigid Body docking and Flexible Refinement stages. In Rigid Body docking, we employ Brownian Dynamics based sampling as implemented in a SDA program. An efficient and simple force field is used comprising of electrostatic and shape exclusion terms. Ways to implicitly account for protein flexibility are included at this stage. In addition, we incorporate available biochemical data relevant to complex formation as docking constraints. We cluster the docked solutions based on their structural similarity and score them using cluster population, electrostatic energy and residue propensities. The representatives of these clusters are subjected to flexible refinement stage. For flexible refinement we use Molecular Dynamics with the NPSA implicit solvent model and enhanced sampling techniques. We tested the protein-protein docking protocol on a number of structurally and functionally different proteins including enzyme-inhibitor, electron-transfer, signal transduction, antibody-antigen and domain peptide complexes. In most cases, already after Rigid-Body docking, we identify structures of complexes with rmsd < 7Å and the number of native contacts > 20%. The results of subsequent Flexible Refinement with MD largely depend on the quality of the protein-protein complex produced by Rigid Body docking. The number of native contacts during the Flexible Refinement increases by several to 60%.