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Fine Tuning Rigid Body Docking Results Using the Dreiding Force Field: A Computational Study of 36 Known Nanobody-Protein Complexes

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Abstract

This paper aims to understand the binding strategies of a nanobody-protein pair by studying known complexes. Rigid body protein-ligand docking programs produce several complexes, called decoys, which are good candidates with high scores of shape complementarity, electrostatic interactions, desolvation, buried surface area, and Lennard-Jones potentials. It is not known which decoy represents the true structure. We studied thirty-seven nanobody-protein complexes from the Single Domain Antibody Database, sd-Ab DB, http://www.sdab-db.ca/. For each structure, a large number of decoys are generated using the Fast Fourier Transform algorithm of the software ZDOCK. The decoys were ranked according to their target protein-nanobody interaction energies, calculated by using the Dreiding Force Field, with rank 1 having the lowest interaction energy. Out of thirty-six PDB structures, twenty-five true structures were predicted as rank 1. Eleven of the remaining structures required Ångstrom size rigid body translations of the nanobody relative to the protein to match the given PDB structure. After the translation the Dreiding interaction (DI) energies of all complexes decreased and became rank 1. In one case, rigid body rotations as well as translations of the nanobody were required for matching the crystal structure. We used a Monte Carlo algorithm that randomly translates and rotates the nanobody of a decoy and calculates the DI energy. Results show that rigid body translations and the DI energy are sufficient for determining the correct binding location and pose of ZDOCK created decoys. A survey of the sd-Ab DB showed that each nanobody makes at least one salt bridge with its partner protein, indicating that salt bridge formation is an essential strategy in nanobody-protein recognition. Based on the analysis of the thirty-six crystal structures and evidence from existing literature, we propose a set of principles that could be used in the design of nanobodies.

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