

Flexligdock: A flexible ligand – protein docking tool

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The small molecule docking algorithm Flexligdock is being developed from QFIT into a comprehensive flexible ligand docking tool for lead compound identification in virtual screening. The program can predict experimental ligand binding modes (Fig. 1) through biomolecular-ligand interactions using a probabilistic sampling method in conjunction with a molecular mechanics force field.

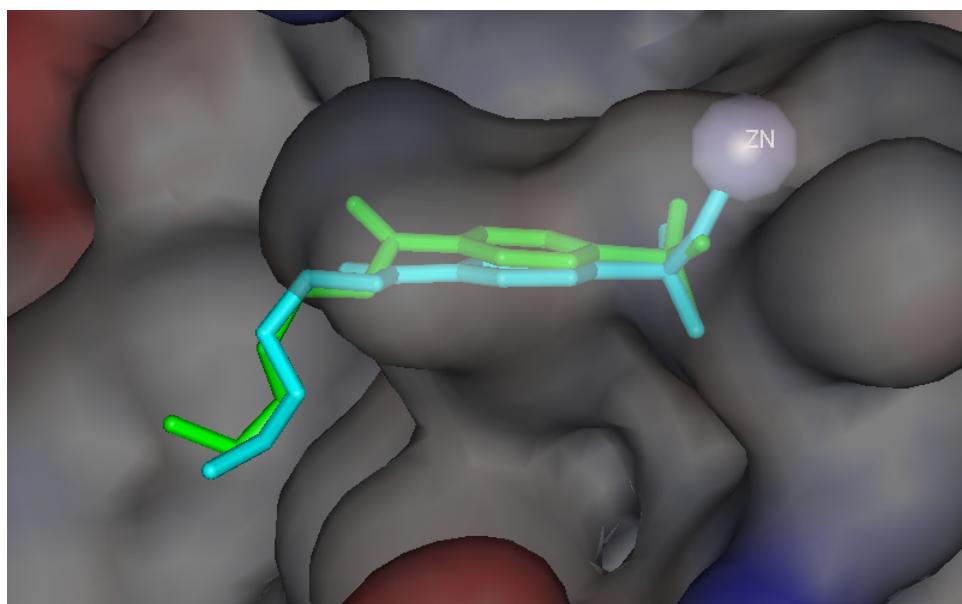
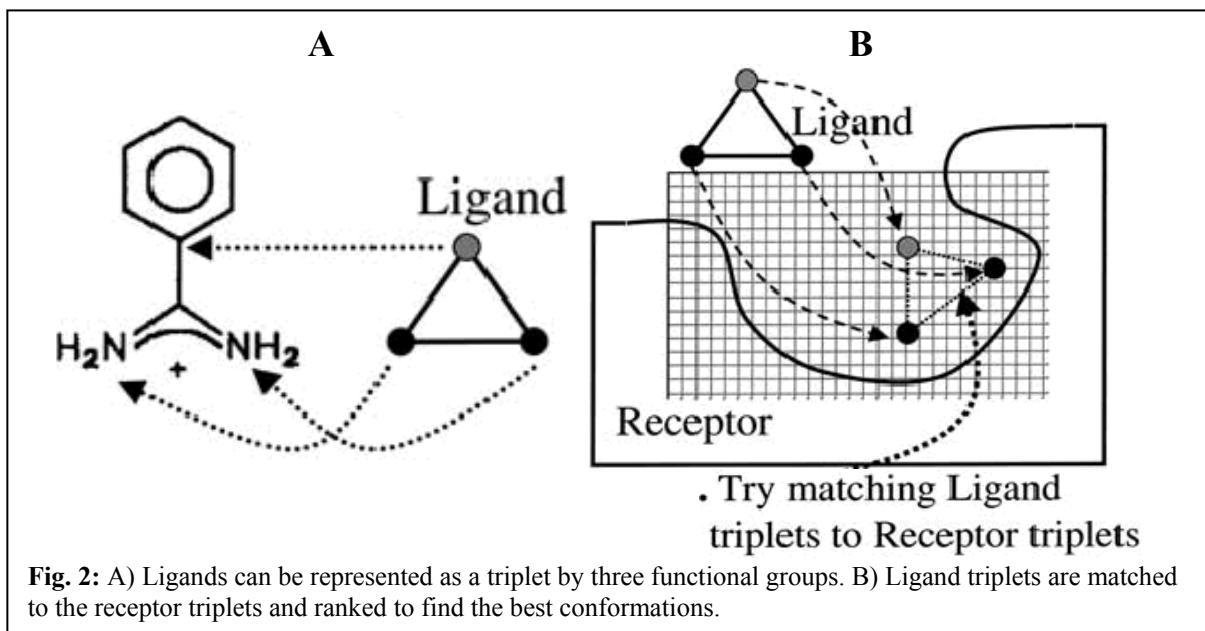


Fig. 1: Ligand conformations of 4-sulphonamide-[1-(4-aminobutane)]benzamide in complex with carbonic anhydrase II. The experimental crystal conformation is shown in light blue and the successfully docked solution is shown in green.

The method fragments a potential ligand along each torsion bond and utilises an interaction point methodology to map the ligand onto an interaction energy grid map of a protein target (Fig. 2). The method proceeds to reassemble/dock the ligand within the protein binding site with an incremental construction method. Predefined torsion angles are used to sample vast areas of chemical space for low energy ligand conformations.

The algorithm has been parameterised on a data set of 46 protein-ligand complexes obtained from a recently released docking data set. The parameterisation data set contained a structurally diverse set of proteins and a variety of ligands that contained 0-23 torsion bonds.

The FlexX validation data set of 200 protein-ligand complexes has been docked with Flexligdock to permit comparison against other existing protein-ligand docking algorithms. The FlexX docking algorithm docks 46% of the data set <2Å RMSD as the top ranked solution, whereas Flexligdock docks 50%. When the entire ranked solution set is considered FlexX docks 70% of the dataset <2Å RMSD, whereas Flexligdock successfully docks 74%. Currently, further improvements to the docking algorithm are being undertaken to increase the accuracy of Flexligdock.



Docking studies on a set of protein kinase structures was undertaken in collaboration with Dr Adam Nelson from the Chemistry department. A set of 20 low energy ligand conformers were obtained from Dr Nelson and docked to PDK1 and GSK-3 β protein structures. The ligands were a set of conformationally diverse macrocyclic bisindolylmaleimides, containing enantiomeric ligands that varied in their size of tether linker.

The results obtained provided supplementary computational evidence that a specific type of enantiomeric conformation of the ligands was more favourable than the other. This had been originally concluded from Dr Nelson's binding affinity data, which was unknown at the time of the docking.

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