Local Structure Similarity
Within Protein Binding Pockets
as a Tool to Infer their Ability
to Bind Specific Functional Groups

Truglio M, Bianchi V, Gherardini P F,
Ausiello G, Helmer-Citterich M
Department of Biology, University of Tor Vergata, Roma

Motivation
We developed a novel knowledge-based procedure to predict ligand functional groups binding preferences in protein binding sites, starting from the hypothesis that structurally and biochemically similar protein motifs are used to bind the same ligand fragment in similar positions. Most of existing approaches are based on global similarity between binding sites taken as a whole, and treat ligands as full-sized compounds or, on the other side, as a set of single atoms. In our method binding pockets are analyzed at a local level of similarity and ligands are managed as modules of functional groups. This method could give a useful contribution to docking algorithms and to lead optimization procedures.

Methods
Given a target protein structure the algorithm searches for structurally and biochemically similar residues patterns against a library of non-redundant binding pockets from the PDB. This search is carried out by Superpose3D (Ausiello, et Al., 2005; Gherardini, et Al., 2010), a local structural comparison method, that identifies structural matches between residues of the target and residues of one or more binding pockets in the library. In a second step, each match triggers the roto-translation of bound functional groups onto the target structure. Each moiety is then positioned in front of the target matching residues, in a protein environment structurally similar to the original one.

Results
The method has been trained on the same pockets used to build the binding pockets library, in order to fine-tune the parameters for each type of functional group. In particular each pocket was separated from its ligand, and launched against the other ones in the library using a leave-one-out approach. Then, we evaluated our predictions compared to the known ligand: this procedure showed that some functional groups, which are well represented in the PDB, are consequently easier to predict in the correct position. Globally, our method correctly placed over one third of the known ligands’ functional groups. To test the method we are using a dataset of structures selected to
test docking methods like FlexX (Rarey et al., 1996), Gold (Jones et al., 1997), and Dock (Kuntz et al., 1982); in a number of cases, our method is able to improve the ranking of docked conformations based solely on energy scores.

Contact email
mauro.truglio@gmail.com