An exhaustive analysis of analogies in protein binding sites of known structure

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Motivation

The identification of determinants of the interaction specificity in the molecular recognition between proteins and small ligands constitutes some of the most interesting problems still unsolved in structural biology. The unique identification of the ligand by a protein is a complex phenomenon that depends on structural features (shape, flexibility, arrangement of chemical groups) of the protein surface and of the interacting molecule.

Methods

We performed an exhaustive analysis of all known protein - ligand interfaces to identify the structural determinants of molecular recognition and cases in which an arrangement of similar residues is used to recognize analogous chemical group (pharmacophores) in the context of globally diverse ligands. To this aim, we compared in pairs all the interacting interfaces excluding all cases in which the correspondences deal with homologous proteins or similar ligands. The work is divided in the following steps:

- Use of a local structural comparison method, to identify small regions of structural similarity (composed of 3-4 aminoacids) among all protein - ligand interfaces included in the PDB.
- Exclusion from the comparison results of the cases of local similarity between homologous proteins (with the same fold) or interacting with similar ligands (with a high Tanimoto coefficient).
- Analysis of correlation between the type and the position of the identified pharmacophores in the ligands for every interface pairs sharing a region of local similarity.

Results

We tried to identify existing correlations between structural elements that are on the protein surface and their ligands pharmacophores. Some cases of particular interest are discussed as an example of the results obtained by this exhaustive analysis and we will present a statistics of the pharmaphore correspondences on the ligands in function of the distance from the residues with which they interact. The results of the work show that some cases exist in which similar pharmacophores, in the context of diverse ligands, have been recognized by analogous arrangement of the protein residues and that these correspondences concern the part of ligand that effectively is located near the residues in question.

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