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Graph-Theoretical Approaches in Drug Discovery at the PDB Scale

Proteins interact with other molecules through their protein binding sites, which are functionally important regions on the protein surface. Each binding site usually binds one or a few specific molecules, the ligands. Detection of binding sites gives insight in protein functionality and is hence essential for drug design. Sequence variants that occur in coding regions of genes may alter protein's amino acids and presumably affect protein function. It was found that disease-causing sequence variants are preferentially located at protein-protein interfaces rather than in noninterface regions of protein surfaces. Binding site sequence variants are of great interest to drug development.

Here we will describe newly developed algorithm and software, based on a novel three-dimensional graph representation of protein molecules and a fast maximum clique algorithm for binding site comparison in drug discovery at the PDB scale.

Summary

We have developed new methodological solutions for prediction and study of protein binding sites at the PDB scale, based on graph theoretical approaches, combined with molecular dynamics simulations. In particular, we have developed computational tools – **ProBiS tools** - which enable drug discovery based on protein structures: ProBiS algorithm, ProBiS, ProBiSCHARMMing, GenProBiS and ProBiS H2O web servers.

- ProBiS algorithm [1] detects and aligns similar binding sites based on graph theoretical approach - on our maximum clique algorithm [2], where proteins are represented as vertices and edges.
- ProBiS web server [3] detects structurally similar protein binding sites and predicts their ligands.
- ProBiSCHARMMing web server [4] predicts and minimizes ligands for any protein and can be used to prepare ligand-receptor complex for molecular dynamics simulation.
- GenProBiS web server [5] implements a novel approach to the discovery of sequence variants that have potentially deleterious effect on protein function and ligand binding through gain or loss of the binding site.
- ProBiS H2O web server [6] uses existing experimental structural data to identify conserved water sites on the interfaces of protein complexes, for example, protein-small molecule interfaces, and elsewhere on the protein structures.

Our newly developed approaches are particularly useful in the context of precision medicine. Our tools enable joining several otherwise disconnected areas of research, for example, graph-theoretical approaches, genome sequence studies, protein structures, and MD simulations [7].

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Primary author: Prof. JANEŽIČ, Dušanka (UP FAMNIT)

Co-author: Dr JANEZ, Konc (UP FAMNIT)

Presenter: Prof. JANEŽIČ, Dušanka (UP FAMNIT)