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Fuzzy virtual ligands for virtual screening

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A new method to bridge the gap between ligand and receptor-based methods in virtual screening (VS) is presented. We introduce a structure-derived virtual ligand (VL) model as an extension to a previously published pseudo-ligand technique [1]: LIQUID [2] fuzzy pharmacophore virtual screening is combined with grid-based protein binding site predictions of PocketPicker [3]. This approach might help reduce bias introduced by manual selection of binding site residues and introduces pocket shape information to the VL. It allows for a combination of several protein structure models into a single "fuzzy" VL representation, which can be used to scan screening compound collections for ligand structures with a similar potential pharmacophore. PocketPicker employs an elaborate grid-based scanning procedure to determine buried cavities and depressions on the protein's surface. Potential binding sites are represented by clusters of grid probes characterizing the shape and accessibility of a cavity. A rule-based system is then applied to project reverse pharmacophore types onto the grid probes of a selected pocket. The pocket pharmacophore types are assigned depending on the properties and geometry of the protein residues surrounding the pocket with regard to their relative position towards the grid probes. LIQUID is used to cluster representative pocket probes by their pharmacophore types describing a fuzzy VL model. The VL is encoded in a correlation vector, which can then be compared to a database of pre-calculated ligand models. A retrospective screening using the fuzzy VL and several protein structures was evaluated by ten fold cross-validation with ROC-AUC and BEDROC metrics, obtaining a significant enrichment of actives. Future work will be devoted to prospective screening using a novel protein target of Helicobacter pylori and compounds from commercial providers.

References

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