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Ligand protonation states and stereoisomers in virtual screening

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Ligand structure preparation is an essential step during the setup of virtual screening (VS) experiments. In most cases only the crystal structure of a protein-ligand complex is known. Thus, the protonation of the ligand and the binding site is largely unknown and often only limited information about hybridization and connectivity in the ligand structure is provided by the pdb [1]. While manual preparation of the ligand structures is the most accurate method, it is by far too time consuming for bigger datasets. In VS experiments the large number of structures, which are often obtained from different sources, leads to additional problems. A consistent treatment of all active and inactive structures is needed to prevent a preferential treatment of some of the structures, which could lead to artificial enrichments. Additionally, changes in the protonation of the ligand (and the protein), when binding to the active site, have to be considered. The large amount of inactive ligand structures are usually taken from organic molecule data banks like ZINC [2]. In this case, the hydrogen atoms and hybridization are usually known but the data banks often provide only one tautomeric form or stereoisomer for each molecule. Because different protomers/stereoisomers can lead to huge differences in affinity the other stereoisomers of selected ligands should be tested too.

To ensure an equal treatment of all structures for VS experiment we present an automated procedure called structure protonation and recognition system (SPORES) for the setup of VS datasets. It can be used to protonate structures from pdb files and to generate different protonation states, tautomers and stereoisomers. It is based on 3D coordinates only and does not use information about the binding site for ligand preparation or information about active ligands for the setup of the protein binding site. The influence of ligand protonation and stereoisomers on the docking results with PLANTS [3] and Gold [4] was first tested on the well-defined ASTEX clean dataset [5]. Afterward several VS experiments on different target were conducted with PLANTS, in which the influence of ligand protonation states and stereoisomers on the enrichment was tested.

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