[P12] Fragment docking:Pose selection by consensus references binding mode

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Hit finding in fragment-based drug design (FBDD) by computational structure-based approaches is not yet a reliable alternative to experiments, mostly because of our incomplete understanding of molecular interactions [1]. Recently, we analyzed the binding modes of fragments and drug-like ligands bound to 345 diverse targets in the Protein Data Bank (PDB), and found that the two classes of compounds binding to the same cavity have comparable interaction patterns [1], thus suggesting that the binding mode information of fragments can improve the performance of molecular docking of drug-like ligands and vice versa. Here we explore the rescoring performance by using molecular interactions encoded into individual or consensus graphs in pose selection and virtual screening.

Method. 3D-structures were prepared from PDB files using Protoss and additional steps as described in [2]. Docking was performed using PLANTS [3]. Poses were scored using ChemPLP and by similarity to interaction patterns found in reference PDB complexes and encoded in individual graphs (max GRIM rescoring method [4]), or in a consensus 3D-density map which requires the 3D-alignment of all the structures of a protein (the new LID rescoring method).

Pose selection. Our dataset includes 2702 3D-structures and describes 66 proteins, 727 drug-like ligands and 964 fragments. Each target is represented by at least 3 structures with 1 drug-like ligand and 1 fragment. For all the compounds, we perform all possible cross-docking experiments and observe that drug-like ligand binding information improves fragment docking, but the opposite is only true for difficult targets. The combination of drug-like ligands and fragments in the reference set is the most robust option.

Virtual screening. DUD-e dataset [5] contains 6 targets (aces, bace1, cah2, cdk2, esr1 and pgh1) that are presents in our 66 proteins set. Each target is represented by a single structure (one PDB code) prepared with the scPDB process [6]. All available ligands (active and decoys) are docked to their respective protein and rescored. References used during the rescoring process are those presents in our dataset. The use of binding modes discriminates active compounds and decoys pretty good.

Grim vs. LID. Grim and LID show quite similar performance with slight advantage for Grim in pose prediction. However, the binding affinities classification shows equivalent results. But LID can process 100 times more ligands in a given time than Grim.

Bibliography:

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