[P30] Generation and virtual screening of protein-based cavity pharmacophores: A prospective study

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Computational drug design strategies to identify novel bioactive molecules are generally classified in ligand-based or structure-based approaches as to whether the structure of ligands or that of the macromolecular target are used as constraints to screen compound libraries. Both types of approaches have advantages and drawbacks. On one side, ligand-based approaches use prior information (2D or 3D structure, pharmacophore, shape) of known ligands to infer novel and chemically different hits supposed to share a key biological activity. However, they do not consider the structure of the target. On the other side, structure-based approaches use only the latter information for docking or de novo ligand building methods at the risk of being unable to properly rank potential hits by decreasing affinity.
We herewith proposed a novel computational approach mixing the advantages of ligand and structure-centric methods. In a first step, a simple pharmacophore query is generated from the sole knowledge of the 3D structure of the protein cavity of interest, thanks to modifications of the cavity detection VolSite algorithm [1]. In a second step, preexisting conformers of the ligands to investigate are aligned to the cavity-based pharmacophore using a smooth Gaussian function aimed at optimizing the volume overlap of pharmacophore and ligand atoms. Ligands are then ranked by different scoring functions based on either the shape overlap score or the simple PLP forcefield [2].
The method, embedded in the in-house developed IChem toolkit [3], was challenged in two scenarios: (1) a posing challenge aimed at recovering the known x-ray structure of 83 diverse protein-ligand complex (Astex Diversity Set) [4], (2) a virtual screening challenge aimed at discriminating true active from chemically similar decoys for 10 targets of pharmaceutical interest (DUD-E set) [5].
In the posing challenge, the in-house developed alignment method was able to recover x-ray structure of protein-bound ligands with much lower rmsd (2.95 Å) than that obtained by standard sphere-based pharmacophore tools (DiscoveryStudio, 4.80 Å; LigandScout, 5.53 Å) and almost similar to the accuracy achieved by docking tools (Surflex-Dock, 2.57 Å). IChem generated cavity-based pharmacophores are therefore simple and accurate enough to accurately pose ligands at a thigh-throughput. In the second virtual screening challenge, none of the alignment methods and scoring functions (shape overlap, PLP energy) tested was able to truly distinguish true active from decoys for 10 different targets (ROC scores < 0.7). Further filters and more sophisticated scoring functions are therefore needed to remove false positive poses from the screening data and fully empower IChem as a novel fast and efficient virtual screening method.

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