[P1] Introducing a hybrid virtual screening approach combining docking and binding mode similarity analysis

Andrew Anighoro[1] and Jürgen Bajorath[1]

[1]Department of Life Science Informatics, B-IT, LIMES Program Unit Chemical Biology and Medicinal Chemistry, Rheinische Friedrich-Wilhelms-Universität, Dahlmannstr. 2, D-53113, Bonn, Germany.

Virtual screening (VS) aims at identifying small molecules with a specific biological activity. For this purpose, structure- (SB) and ligand-based (LB) methods are applied. SBVS methods such as molecular docking require the 3D structure of the target as a screening template, whereas LBVS approaches extrapolate from structures of known active compounds. SBVS and LBVS methods and protocols can be combined in various ways. For example, we have recently investigated a hybrid approach that integrates docking and the generation of ligand poses with the assessment of binding mode similarity to known crystallographic ligand(s) [1]. Modeled and experimental binding modes are compared by quantifying ligand 3D similarity and compounds are ranked in the order of decreasing binding mode resemblance, thereby providing an alternative to force field-based scoring and ranking. 3D similarity analysis is facilitated by calculating atomic property density functions taking conformational and positional, differences into account and quantifying their overlap [2]. This approach is further extended by incorporating protein-ligand interaction fingerprints-based Tanimoto similarity as an alternative to whole-molecule 3D similarity [3]. Benchmark calculations have been carried out for a variety of targets including the adenosine A_{2A} receptor, dihydrofolate reductase, glucocorticoid receptor, HIV-1 protease, and vascular endothelial growth factor receptor-2. 3D property density function and interaction fingerprint similarity measures consistently achieved higher recall of active compounds than ranking based on conventional scoring functions. In the case of the adenosine A_{2A} receptor, it was observed that even a co-crystallized agonist could be used as a reference to effectively prioritize antagonists. Results available so far indicate that binding mode similarity measure provide an attractive alternative to conventional scoring and ranking schemes if crystallographic ligands are available as references.

Bibliography:

[1] A. Anighoro; J. Bajorath. J. Chem. Inf. Model. 56 (2016) 580-587.
[2] L. Petalson.; J. Bajorath. Chem. Biol. 14 (2007) 489-497.
[3] A.Anighoro; J.Bajorath. In preparation.