Next Generation Pharmacophore Modeling:

Tools and Applications

Thierry Langer

Department of Pharmaceutical Sciences, University of Vienna, Josef-Holaubek-Platz 2, 1090, Vienna, Austria, thierry.langer@univie.ac.at

Pharmacophore-based compound modeling, virtual screening, and bio-activity profiling is one of the most popular in silico techniques for supporting medicinal chemists. The advanced molecular design tool LigandScout [1] was developed to successfully address one of the most important issues in virtual screening: Enhancing early enrichment while maintaining high computational speed as well as ease of use, as shown by reference studies. [2]

As an extension of the static pharmacophore approach, we lately have focused on incorporating dynamic effects of ligand protein binding into our automated interaction determination process. Our Common Hits Approach (CHA) [3] uses multiple coordinate sets saved during MD simulations. Pharmacophore models with the same pharmacophore features are pooled and virtual screening runs are then performed with every representative pharmacophore model resulting in a consensus hit list. The recently developed GRAIL (GRids of phArmacophore Interaction fieLds) [4] method combines the advantages of traditional grid-based approaches for the identification of interaction sites with the power of the pharmacophore concept: A reduced pharmacophore abstraction of the target system enables the computation of all relevant interaction grid maps in short amounts of time. This allows one to extend the utility of a grid-based method for the analysis of large amounts of coordinate sets obtained by long-time MD simulations. In this way, it is possible to assess conformation dependent characteristics of key interactions over time.

Finally, we address exa-scale pharmacophore based virtual screening by using a novel representation of pharmacophore models, which are encoded into vector representations using a graph neural network. This approach enables efficient querying of pre-encoded conformational databases via the order embedding space, thereby bypassing traditional alignment.

Bibliography

[1] Wolber G, Langer T*, J Chem Inf Model.* **2005**; 45(1): 160
[2] Karaboga AS, et al., *J Chem Inf Model.* **2013**; 53(3):1043
[3] Wieder M, et al., *J Chem Inf Model.* **2017**; 57(2):365
[4] Schuetz DA, et al., *J Chem Theory Comput.* **2018**; 14: 4958