Towards Next Generation Pharmacophore Modeling: Concepts and Applications

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Pharmacophore-based compound modeling, virtual screening, and bio-activity profiling as implemented in the advanced molecular design tool LigandScout [1] has become a popular in silico technique for supporting medicinal chemists.

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. The GRAIL (GRids of phArmacophore Interaction fieLds) [2] 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 and to understand relationships among the pharmacophores derived in a hierarchical graph representation. [3]

In the NeuroDeRisk project [4], we utilized all these new developments, together with machine learning methods for adding quantitative pharmacophore feature weighting [5] to predict potential neurotoxic effects of drug candidates.

[1] Wolber G, Langer T, *J Chem Inf Model.* **2005**; 45(1): 160
[2] Schuetz DA, et al., *J Chem Theory Comput.* **2018**; 14: 4958
[3] Garon A et al. Front. Mol. Biosci. **2020**; 7: 599059
[4] NeuroDeRisk IMI2 JU (www.neuroderisk.eu) has received funding under grant agreement No 821528
[5] Kohlbacher SM, et al., *J Cheminform* **2021**; 13, 57