# [L15] Adventures in Computer-Assisted Molecular Design

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In the presentation, an overview on methods developed over the last decades which should support decision making in hit finding, hit to lead expansion, as well as lead optimization is given. Starting from pharmacophore-based compound modeling, virtual screening, and bio-activity profiling have become popular in silico methods for supporting medicinal chemists in their drug discovery programs. (1)

At Inte:Ligand GmbH, we developed the program LigandScout (2) as an integrated software solution containing rapid and efficient tools for automatic interpretation of ligand-protein interactions and subsequent transformation of this information into 3D chemical feature-based pharmacophore models. In addition, pattern recognition-based algorithms were developed for ligand-based pharmacophore modeling in the absence of a target 3D structure, as well as for establishing a novel and accurate virtual technique.

Since recently, we study the possibility to transfer pharmacophore concept from a static approach to a dynamic one, by analyzing molecular dynamics simulation trajectories, in order to develop pharmacophore ensembles representing the dynamic event of binding. First results obtained from frequency information are indicating that MD simulations can add significantly to the refinement such models, by guiding the user to add or remove pharmacophore features, depending on their stability during the simulation. (3)

Finally, as an extension of this approach, parallel pharmacophore-based screening has been introduced as an innovative in silico method to predict the potential biological activities of compounds by screening them with a multitude of pharmacophore models. We have made available recently this approach as a LigandScout Extension Workflow Node within the KNIME platform. (4)

Bibliography:

[1]. Langer, T., Pharmacophores in Drug Research, Mol. Inf. 2010, 29, 470-475.
[2]. Wolber, G., Langer, T.; LigandScout: 3D Pharmacophores Derived from Protein-Bound Ligands and their Use as Virtual Screening Filters, J. Chem. Inf. Model. 2005, 45, 160-169.
[3]. Wieder, M., Perricone, U., Boresch, S., Seidel, T., Langer, T.: Evaluating the stability of pharmacophore features using molecular dynamics simulations, Biochem. Biophys. Res. Comm. 2016, 470, 685-689.
[4]. KoNstanz Information MinEr, available from KNIME.COM AG, Zurich, Switzerland (http://knime.org), LigandScout Extensions available from Inte:Ligand GmbG, Vienna, Austria (http://www.inteligand.com).