Approaches to Next Generation Pharmacophore Modelling

Thierry LANGER

Department of Pharmaceutical Sciences, Pharmaceutical Chemistry Division
University of Vienna, Althanstrasse 14, 1090 Vienna, Austria

Chemical feature based 3D pharmacophore models have been used for several decades supporting medicinal chemists in their early drug discovery programs. (1) In this presentation, an overview on recent approaches in further developing the field of pharmacophore modeling is given.

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 the 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 (3) and to analyze them using both grid-based probability functions (4) as well as hierarchical graphs. (5) 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 and use them to increase prediction power in virtual screening. (6) Machine learning has been utilized to transform qualitative pharmacophore models to quantitative ones. (7)

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, e.g. in order to predict molecular initiating events finally leading to neurotoxic outcomes. We recently have made available this approach as a LigandScout Extension Workflow Node within the NeuroDeRisk KNIME platform. (8,9)

Bibliography:

(1) Langer, T., Pharmacophores in Drug Research, Mol. Inf. 2010, 29, 470.
(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.
(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.
(4) Schütz, D. A., Seidel, T., Garon, A., Martini, R., Körbel, M., Ecker, G.F., Langer, T. GRAIL: GRids of phArmacophore Interaction fieLds, J. Chem. Theory Comput. 2018, 14, 4958.
(5) Garon, A., Wieder, O., Bareis, K., Seidel, T., Ibis, G., Bryant, S. D., Theret, I., Ducrot, P., Langer, T. Hierarchical Graph Representation of Pharmacophore Models. Front Mol Biosici 2020, 7, 599059.
(6) Wieder, M., Garon, A., Perricone, U., Boresch, S., Seidel, T., Almerico, A.M., Langer, T. Common Hits Approach: Combining Pharmacophore Modeling and Molecular Dynamics Simulations. J. Chem. Inf. Model. 2017, 57, 365.
(7) Kohlbacher, S. M., Langer, T., Seidel. T. QPHAR: quantitative pharmacophore activity relationship: method and validation. J Cheminform 2021, 13, 57
(8) KoNstanz Information MinEr, available from KNIME.COM AG, Zurich, Switzerland (https://knime.org), LigandScout Extensions available from Inte:Ligand GmbH, Vienna, Austria (https://www.inteligand.com).
(9) The NeuroDeRisk in silico Toolbox (https://neuroderisk.eu/in-silico-toolbox/)