[L10] Feature-based 3D Pharmacophores: The Current and The Future

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Pharmacophore-based molecular modeling, virtual screening, and bio-activity profiling has become one of the most popular in silico techniques for supporting medicinal chemists in their hit finding, hit expansion, hit to lead, and lead optimization programs. (1)

At Inte:Ligand GmbH, we developed the molecular design software LigandScout (2), initially as an integrated 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 into a dynamic one, by generating and 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 of such models, by guiding the user to add or remove pharmacophore features, depending on their frequency and stability during the simulation. (3,4)

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 within the KNIME platform (5).

References:

(1) Langer, T., Mol. Inf. 2010, 29, 470-475.
(2) Wolber, G., Langer, T.; J. Chem. Inf. Model. 2005, 45, 160-169.
(3) Wieder, M., Perricone, U., Boresch, S., Seidel, T., Langer, T. Biochem. Biophys. Res. Comm. 2016, 470, 685-689.
(4) Wieder, M., Perricone, U., Seidel, T., Boresch, S., Langer, T. Monatsh. Chem. 2016, 147, 553-563.
(5) KoNstanz Information MinEr, is available from KNIME.COM AG, Zurich, Switzerland, LigandScout Knime Extensions are available from Inte:Ligand GmbH, Vienna, Austria (www.inteligand.com)