3D-Chemical Feature Based Pharmacophores: Essential Tools for Early Drug Discovery Research

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Pharmacophore modeling and virtual screening are techniques widely used by chemists [1] and modellers involved in pharmaceutical research to rapidly visualize and decipher key interaction features between proteins and ligands [2], find biologically active compounds [3], fish for new targets [4], repurpose existing drugs [5], explore protein-protein interfaces [6], and profile drug targets for side-effects [7]. During the last decade we have developed and expanded the capabilities of LigandScout, our molecular design platform, to further support medicinal chemists and modellers in their hit finding, hit expansion, hit to lead, and lead optimization research using advanced pharmacophore methodology. LigandScout is already well known for its ability to automatically derive 3D-interaction feature models starting from a macromolecular-ligand complex [8, 9]. In addition, we have developed pattern recognition alignment algorithms for creating models based a set of ligands without active-site information and in active sites where no ligands are present. Furthermore, our current research involves developing advanced methods to analyze molecular dynamics simulation trajectories to create pharmacophore ensembles representing the dynamic event of binding. 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 multiple pharmacophore models. In the presentation, an overview of our advanced pharmacophore technology developed over the last decade will be given and the results of several success stories presented. Examples range from proof of concept studies employing natural product compounds that were submitted to in silico activity profiling using the Inte:Ligand Pharmacophore Database [10] to in silico fragment-based discovery of novel enzyme inhibitors.

References

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