[SC1] Elegant Methods for Drug Discovery Research Using Advanced 3D-Chemical Feature Based Pharmacopohores & LigandScout

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Pharmacophore modeling and virtual screening are techniques widely used by chemists [1] and modelers involved in pharmaceutical research to rapidly visualize and decipher key interactions 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 modelers in their hit finding, hit expansion, hit to lead, and lead optimization research using advanced pharmacophore methodology. LigandScout is already well known for its intuitive interface and ability to automatically derive 3D-interaction feature models starting from a macromolecular-ligand complex [8,9]. However, LigandScout also enables scientists to elegantly and conveniently make sense of modeling results derived from other computational methods in combination with 3D-pharmacophore models. We have developed unique pattern recognition alignment algorithms for creating models based a set of ligands without active-site information and tools for exploring cavities where no ligands are present. Our current research involves developing advanced methods to analyze molecular dynamics simulation trajectories to create pharmacophore ensembles representing the dynamic event of binding. In addition, parallel pharmacophore-based screening has been introduced as an innovative in silico method to predict targets from phenotypic screens as well as off-target effects using the IL PharmDB [10]. 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.

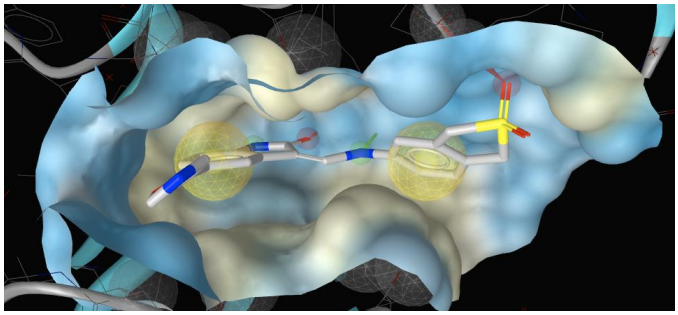

Figure 1: 3D-Chemical feature interaction pharmacophore model automatically derived using LigandScout 4.2 and an x-ray derived structure of cyclin dependent kinase 2 (PDB Code: 1KE7). Interactions displayed include yellow spheres (hydrophobic), red arrows (hydrogen bond acceptors), green arrows (hydrogen-bond donors), and grey spheres (excluded volumes). Such models can be used for rapid virtual screening of compound libraries to find other molecules with similar interaction features in 3D-space and to support lead optimization by aligning them with newly designed molecules.

References

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