Next Generation Pharmacophore Modeling:
Novel Concepts & Tools for Molecular Design

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Pharmacophore-based compound modeling, virtual screening, and bio-activity profiling are popular in silico techniques for supporting medicinal chemists in their hit finding, hit to lead expansion, and lead optimization efforts. We have developed LigandScout, a widely used molecular design tool [1] as well as CDPKit, an open source toolkit [2] to successfully address one of the most important issues in virtual screening: Enhancing early enrichment while maintaining high computational speed as well as ease of use, as shown by reference studies. [3,4]

As an extension of the static pharmacophore approach, we lately have focused on incorporating dynamic effects of ligand protein binding into our automated interaction determination process. Building on the recently developed GRAIL (GRids of phArmacophore Interaction fieLds) [5] method, which combines the advantages of traditional grid-based approaches for the identification of interaction sites with the power of the pharmacophore concept, a new set of descriptors - GRADE and X-GRADE [6] - have been developed, providing alternative and compute efficient solutions to protein-ligand complex clustering, binding affinity prediction, and 3D-QSAR modeling.

Finally, we address exa-scale pharmacophore based virtual screening by proposing a novel data model of pharmacophore models, which are encoded into vector representations using a graph neural network [7]. This approach enables efficient querying of pre-encoded conformational databases via the order embedding space, thereby bypassing traditional alignment.

References

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