Next-Generation Pharmacophore Modeling: Bridging 3D Molecular Interaction Analysis and Generative AI

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For decades, 3D pharmacophore modeling has been a cornerstone of structure-based drug discovery, providing interpretable and computationally efficient frameworks for virtual screening and lead optimization. This talk charts its evolution into the AI era, surveying current methods and future directions in next-generation pharmacophore modeling. We first introduce FragmentScout [1], as one of the recent algorithmic and workflow advances in the novel high performance platform LigandScout XT [2], showing how feature-based models now accommodate dynamic structural data, complex target profiling, and seamless integration with modern machine learning. We then present two tools that merge pharmacophoric concepts with deep learning: GRIPHIN [3], a hybrid neural framework that combines voxelized pharmacophore interaction fields of the protein binding site (via GRAIL) with graph-based ligand representations to deliver competitive affinity prediction and actionable, attribution-driven interaction insights; and PharmacoMatch [4], a novel contrastive learning framework that reformulates pharmacophore screening as an approximate neural subgraph matching problem: By leveraging a graph neural network (GNN) encoder trained in a self-supervised manner, PharmacoMatch maps 3D pharmacophores into an order embedding space. This allows for the ultra-fast querying of massive conformational databases through efficient vector comparisons, entirely bypassing computationally expensive rigid-body alignment algorithms. Together, these advances unite classical pharmacophore interpretability with powerful generative and hybrid models to enable practical, scalable applications in drug design.

Bibliography :

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