Exploring Protein-Ligand Binding Using 3D Pharmacophore Patterns

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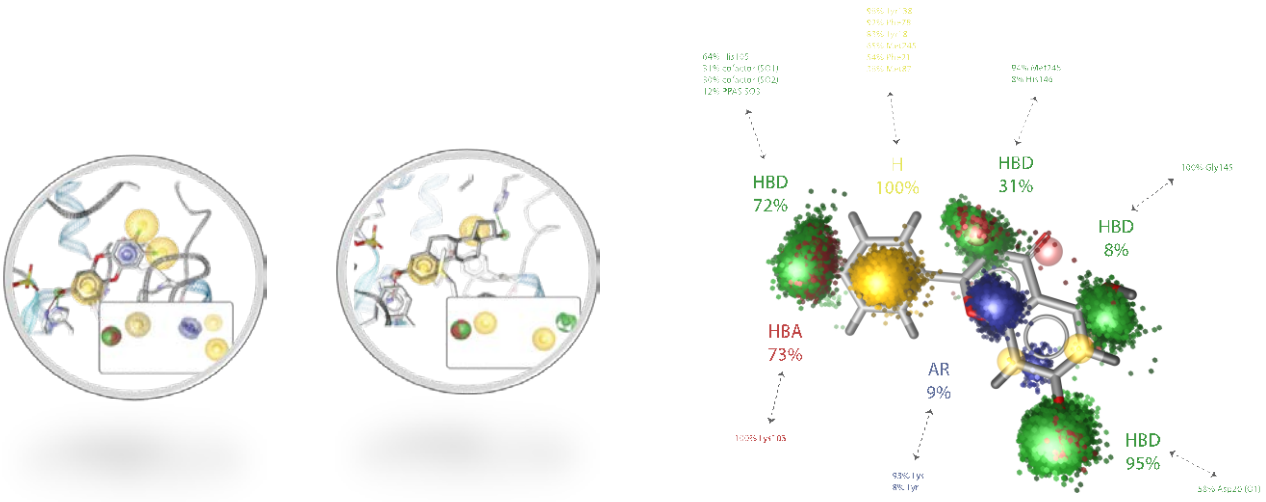

Virtual screening using 3D interaction models has become an established method for in-silico drug discovery – mainly due to the ability of reflecting the way of thinking of medicinal chemists in terms of hit identification, hit expansion and lead optimization [1]. The simplicity and descriptive character of such a 3D interaction model thus enables clear communication and rapid feedback cycles between modeling and synthesis teams. Despite the established usage of the methodology, there are still several pitfalls and challenges for successful modeling – mainly related to the algorithmic challenge of flexibly fitting a molecule to a 3D interaction model in a computationally efficient way. While our static virtual screening algorithm is broadly used, our new *dynophore* concept [2,3] exploits conformational information from molecular dynamics simulations to represent interaction patterns using probability density maps and allows for a considerably more detailed analysis of binding modes and interaction patterns. While static models represent only single conformations (left figure), dynamic models can capture conformational changes in probability density functions (right figure). Both models are efficient virtual screening filters.

In this lecture, several structure- and ligand-based application studies will be presented including the challenges of difficult targets, such as metabolic enzymes [4] and receptors [2,5]. Both application examples and methods will be critically discussed in the context of screening algorithms and overlay algorithms.

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[5] M. S. Murgueitio, S. Ebner, P. Hörtnagl, C. Rakers, R. Bruckner, P. Henneke, G. Wolber, and S. Santos-Sierra., *Biochim. Biophys. Acta*, **2017**, *1861*, 2680-2689.