A study of fragment binding mode. From experimental data analysis to prediction using docking

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With many successes in just twenty years, the fragment approach is now widely used in pharmaceutical research. Fragment-based drug discovery (FBDD) makes extensive use of three-dimensional structures at the atomic scale, which greatly facilitates the design of a drug-like molecule, built step by step in the targeted protein.

The Protein Data Bank provides a wealth of high quality structural information on fragment binding. Our comparative analysis of thousands of protein/fragment and protein/drug-like molecule complexes highlighted the versatility of the binding mode of low molecular weight compounds, and, more unexpectedly, suggested that drug-like molecules and fragments cover the same interactions at the protein site [1-3]. Information on the binding mode is therefore likely to improve the fragment docking. The gain in accuracy of pose prediction was confirmed by our benchmarking of similarity scores using different binding mode representations (interaction fingerprint, graph of pseudo-atoms, or ligand shape) [4]. Considerations on robustness and speed have prompted us to develop a new approach, which combines the entire structural information into a single representation (the LID method) and gives good performance in pose prediction and in virtual screening challenges [5].

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[5] Jacquemard C, Tran-Nguyen VK, Drwal MN, Rognan D, Kellenberger E. (2019) Local Interaction Density (LID), a Fast and Efficient Tool to Prioritize Docking Poses. *Molecules* 24(14) pii: E2610