Hydrophobic Similarity: Application to Three-Dimensional Molecular Overlays with PharmScreen

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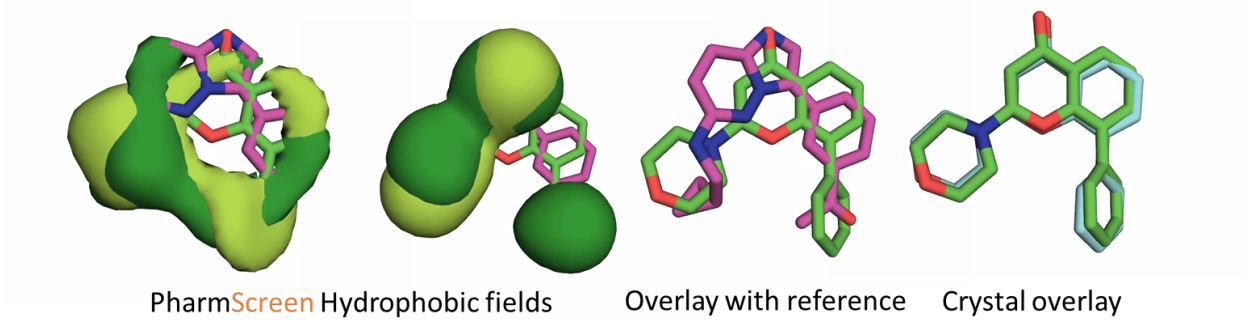
Molecular alignment is a key procedure for measurements of 3D similarity between compounds and pharmacophore elucidation. This process is influenced by several factors, including the quality of the physico-chemical descriptors utilized to account for the molecular determinants of biological activity.

Relying on the hypothesis that the variation in maximal achievable binding affinity for an optimized drug-like molecule is largely due to desolvation[1], we explore here a novel strategy for 3D alignment of small molecules that exploits the partitioning of molecular hydrophobicity into atomic contributions in conjunction with information about the distribution of hydrogen-bond donor /acceptor groups in a given compound.



A brief description of the method, as implemented in the software package PharmScreen, including discussion on the calculation of the fractional hydrophobic contributions within the quantum mechanical version of the MST continuum method[2], and the procedure utilized for searching the optimal superposition between molecules, is presented. The computational procedure is calibrated by using a dataset of 402 molecules pertaining to 14 distinct targets taken from the literature and validated against the AstraZeneca dataset that comprises 121 experimentally derived sets of molecular overlays[3]. The results point out the suitability of the MST based-hydrophobic parameters for generating molecular overlays.

[1] Lemmen, C. Langauer, T. Computational Methods for the Structural Alignment of Molecules. *J. Comput.-Aided Mol. Des*. **2000**, *14*, 215–232.
[2] Curutchet, C. Orozco, M. Luque, F. J. Solvation in Octanol: Parametrization of the Continuum MST Model. *J. Comput. Chem.* **2001**, *22*, 1180–1193
[3] Giangreco, I.; Cosgrove, D. A.; Packer, M. J. An Extensive and Diverse Set of Molecular Overlays for the Validation of Pharmacophore Programs. *J. Chem. Inf. Model.* **2013**, *53*, 852–866.