From continuum solvation models to hydrophobic descriptors: Application to virtual screening of chemical databases with PharmScreen

Javier Vazquez,†,‡ Alessandro Deplano,† Albert Herrero,† Tiziana Ginex, ‡ Enric Gibert,† Obdulia Rabal,‡ Julen Oyarzabal,§ Enric Herrero,† and F. Javier Luque‡

† Pharmacelera, Plaça Pau Vila, 1, Sector 1, Palau de Mar, Barcelona 08039, Spain

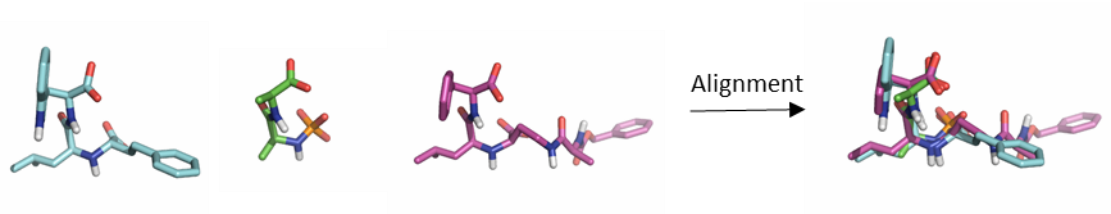
‡ Department of Nutrition, Food Science and Gastronomy, Faculty of Pharmacy and Institute of Biomedicine (IBUB), University of Barcelona, Av. Prat de la Riba 171, Santa Coloma de Gramenet E-08921, Spain

§ Small Molecule Discovery Platform, Molecular Therapeutics Program, Center for Applied Medical Research (CIMA), University of Navarra, Avda. Pio XII 55, Pamplona E-31008, Spain

Determining the degree of similarity between two small molecules is a key step in ligand-based virtual screening of chemical libraries, which is valuable for the cost -effective identification of novel chemical scaffolds. The success of this approach is influenced by several factors, including the quality of the physico-chemical descriptors utilized to account for the molecular determinants of biological activity.

In this communication, we present PharmScreen, which is a novel 3D ligand-based virtual screening algorithm that exploits the partitioning of molecular hydrophobicity into atomic and fragmental contributions within the framework of continuum solvation models. Specifically, we have exploited the quantum mechanical version of the MST continuum method, which was parametrized to describe the solvation of small organic compounds to water and n-octanol[1],[2]. A perturbative approach permits to decompose the solvation free energy into fractional contributions, which can then be combined to obtain 3D distribution of the molecular hydrophobicity/hydrophilicity, leading to concepts such as hydrophobic dipole and hydrophobic similarity[3],[4]. The suitability of these fractional for 3D-QSAR studies has been recently examined[5].

Following this work, we describe here the calibration of these descriptors for molecular alignment and similarity studies, and its implementation within the framework of PharmScreen. Preliminary tests support the suitability of this strategy to find compounds with higher chemical diversity compared to traditional shape/structure-based solutions.



[1] Curutchet, C.; Orozco, M.; Luque, F. J., *J. Comput. Chem.*, **2001**, *11*, 1180.
[2] Soteras, I.; Curutchet, C.; Bidon-Chanal, A.; Orozco, M.; Luque, F. J., *J. Mol. Struct. THEOCHEM*, **2005**, *727*, 29.
[3] Muñoz, J.; Barril, X.; Hernández, B.; Orozco, M.; Luque, F. J., *J. Comput. Chem.*, **2002**, *23*, 554.
[4] Muñoz-Muriedas, J.; Perspicace, S.; Bech, N.; Guccione, S.; Orozco, M.; Luque, F. J., *J. Comput.-Aided Mol. Design*, **2005**, *19*, 401.
[5] Ginex, T.; Muñoz-Muriedas, J.; Herrero, E.; Gibert, E.; Cozzini, P.; Luque, F. J., *J. Comput. Chem.*, **2016**, *37*, 1147.