Mapping the favourable character of intermolecular contacts by electrostatic fingerprints

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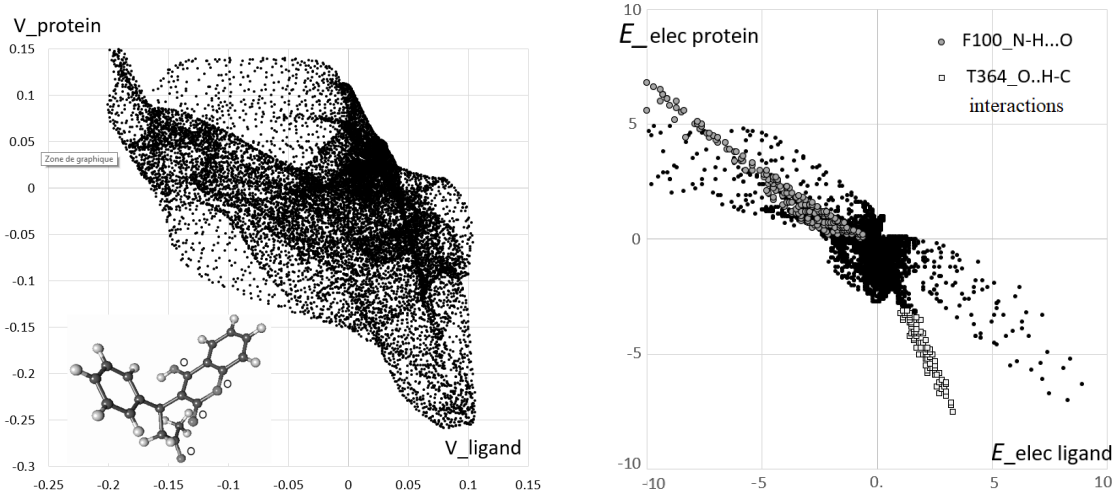
Structure-based methods including docking and scoring of ligands poses aim to select the best potential hits for in vitro assays by ranking them according to predicted binding affinities. Virtual screening is based on docking programs providing several poses of the ligand within a binding site and a score attributed to each pose. Accurate prediction of the correct binding pose remains a major scientific challenge for current scoring functions in order to retrieve the true ligands.
The newly developed descriptor [1] concerns a computer-based method for evaluating the stability of a complex formed by two molecular entities. It provides a score and at the same time a fingerprint of the intermolecular interactions. The descriptor can be applied, for example to protein / ligand complexes, either experimental (native) or produced by docking software. The function is projected on the intermolecular Hirshfeld interface and is homogenous to an electrostatic energy density. This electrostatic complementarity descriptor can act as filter to detect most false ligand poses among diverse poses proposed by molecular docking programs. The crystal structure of the cytochrome P450 2C9 / warfarin complex is analyzed in Fig. 1 [2]. A good electrostatic complementarity is typically manifested by a correlation coefficient between surfaces interior and exterior properties close to -1 and by a fingerprint plot with points located close to the diagonal line y = -x. The lines of points correspond to strong interactions.

Figure 1. Left: scatterplot of electrostatic potential generated by the ligand warfarin and the protein CYP 2C9 on the Hirshfeld interface. Right: scatterplot of electrostatic energy density. The charge density was transferred from ELMAM2 database [3] of multipolar atoms. Electrostatic and Hirshfeld surface calculations were done with VMoPro and MoProViewer [4] software.



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