Predicting the Sites and Energies of Non-Covalent Intermolecular Interactions Using Local Properties

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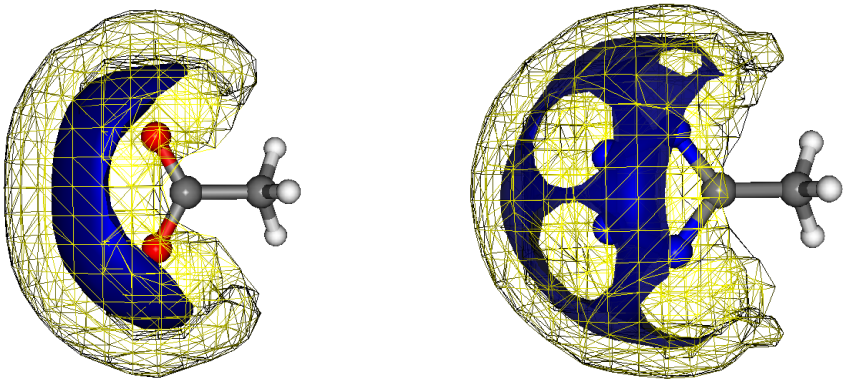
Despite the essential importance of the non-covalent interactions and their key role in many natural processes, they are not treated well by currently available *in silico* techniques. Non-covalent interactions are important on the micro and macro scales and include protein-ligand, protein-protein and protein-DNA binding. [1] Being able to predict such interactions, especially unusual (non-classical) ones, would be of immense value for the molecular modeling field and especially for drug design. We have therefore set out to define a systematic protocol for detecting interaction sites of different types in the vicinity of ligands or receptors and to estimate the strength of the interactions in order to provide a more consistent and complete picture of the intermolecular binding properties of small molecules and biopolymers. Since the points of interaction of molecules lie at or near the molecular surface, surface-based molecular descriptors were used to construct feed-forward artificial neural nets to recognize H-bond donors and acceptor sites on drug-like molecules based on local properties (electron density, molecular electrostatic potential and local ionization energy, electron affinity and polarizability) calculated at grid points around the molecule. Interaction energies for training were obtained from B97-D and ωB97X-D/aug-cc-pVDZ density-functional theory calculations on a series of model central molecules and H-bond acceptor and donor probes constrained to the grid points used for training. The resulting models provide maps of both classical and unusual H- and halogen-bonding sites. Some examples demonstrate the ability of the models to take the electronic and steric nature of the central molecule into consideration and to provide semi-quantitative estimates of interaction energies at low computational cost.



[1] P. Hobza, R. Zahradnik, K. Muller-Dethlefs, *Collect. Czech. Chem. Commun.* **2006,** 71, (4), 443-531.