Towards more accurate scoring functions

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One of the challenges for computational chemistry in the pharmaceutical industry is the need for more accurate scoring functions for use in virtual screening [1]. We conducted an assessment of classical fixed charge force fields for determining the hydration free energy of ~300 drug-like molecules, since the hydration free energy is a component of the protein-ligand binding energy for which there is a reasonable amount of experimental data. Our conclusions were that the force fields , in general, give hydration free energies that are not negative enough, especially when effects of polarization [2] are taken into account. In this talk we discuss the calculation of this polarization cost and investigate the use of different protocols for determining improved charges from condensed phase quantum chemistry calculations. The quality of these charges, for use in fixed charge classical force fields, is then evaluated by determining the hydration free energies of the amino acid side chain analogs.

[1] J. Med. Chem. 49, 5912 (2006).

[2] J. Phys. Chem. B 114, 8621, (2010); J. Phys. Chem. B 114, 8631, (2010).