Modelling Halogen Bonding in Protein−Ligand Complexes

Maurizio Sironi[a,b], Federico Dapiaggi[a], Stefano Rendine[c], Alessandra Forni[b], Stefano Pieraccini[a,b]

[a]*Dipartimento di Chimica, Università degli Studi di Milano, Italy.*
[b]*Istituto di Scienze e Tecnologie Molecolari del CNR, Milano, Italy*.
[c] *Syngenta Crop Protection Münchwilen AG, Stein, Switzerland.*

The halogen bond is an important non covalent interaction that is currently receiving increased attention in the study of protein−ligand complexes [1]. A growing number of crystal structures of proteins in complex with halogenated ligands have appeared in the last years [2], where the presence of halogen bonding was confirmed by observing interatomic distances below the sum of the van der Waals radii of the interacting atoms. Due to their high directionality and specificity, halogen bonds can effectively be used in drug design to direct the binding of ligands to the target site. Nonetheless, their correct modeling *in silico* is currently impossible, since existing molecular dynamics force fields do not account for the anisotropy of the charge density around the halogen atoms, and, in particular, for the positive 'σ-hole' which is responsible of their interaction with Lewis bases.-

We have recently proposed a new approach aimed at obtaining an accurate Molecular Mechanics modelling of halogen bonds [3]. The method is based on a modification of the AMBER force field through the introduction of appositely parametrized pseudo-atoms. We show that, unlike the original force field, the modification introduced allows the correct simulation of ligand-protein complexes involving halogen bonds, reproducing both crystallographic data and the results of Quantum Mechanical/Molecular Mechanics calculations. We thus believe our work would be a significant improvement in the modeling of halogen bonds for drug design.

[1] S. Sirimulla, J. B. Bailey, R. Vegesna, M. Narayan, *J. Chem. Inf. Model.* **2013**, *53*, 2781−2791.
[2] Y. Lu, T. Shi, Y. Wang, H. Yang, X. Yan, X. Luo, H. Jiang, W. Zhu, *J. Med. Chem.* **2009**, *52*, 2854-2862.
[3] S. Rendine, S. Pieraccini, A. Forni, M. Sironi, *Phys. Chem. Chem. Phys*. **2011**, *13*, 19508-19516.