NCI-ELMO: towards a more quantitative description of non-covalent interactions in macromolecules

E. K. Wieduwilt[1], R. Laplaza[2], G. Macetti[1], D. Arias-Olivares[2], F. Peccati[2], J. Contreras-García[2], A. Genoni[1]

[1]CNRS & University of Lorraine, Laboratory of Theoretical Physics and Chemistry, UMR CNRS 7019, 1 Boulevard Arago, 57078 Metz, France,
[2]CNRS & Sorbonne University, Laboratory of Theoretical Chemistry, UMR CNRS 7616, 4 Place Jussieu, 75005 Paris, France.
erna-katharina.wieduwilt@univ-lorraine.fr

Non-covalent interactions uniquely define the structure of macromolecules. Therefore, a thorough analysis of the non-covalent interaction network is crucial to gain insights into functions and dynamics of macromolecules.

A strategy that is able to detect non-covalent interactions for a large variety of molecules is the Non-Covalent Interactions (NCI) method [1,2], a technique simultaneously based on the electron densities and the reduced density gradients of the molecules under exam. Unfortunately, accurate molecular electron densities can be obtained through traditional quantum chemistry computations at a feasible computational cost only for small to medium-sized systems, whereas these calculations become impractical for larger molecules. Therefore, until now, for NCI analyses on large systems one had to resort to the promolecular density approximation, where the electron density of the investigated molecule is described as a sum of independent and spherically averaged atomic densities. These promolecular densities lack accuracy, and although they might lead to visually similar results when compared to those obtained from fully quantum mechanical calculations, the underlying electron density is known to be incorrect. Hence, the analysis of the non-covalent interactions is also biased.

To overcome the previous shortcoming, one should exploit techniques that allow to rapidly obtain accurate and reliable electron densities for macromolecules. In this context, one possibility is represented by the recently constructed database of extremely localized molecular orbitals (ELMOs) [3-5]. In fact, ELMOs are orbitals strictly localized on small molecular fragments, i.e. atoms, bonds or functional groups [3]. Due to this strict localization, they are easily transferable from one molecule to another, provided that the subunits on which they are localized have the same chemical environment in the starting and final systems [3,4]. By exploiting this intrinsic transferability, a databank of ELMOs has been constructed [5]. It currently contains orbitals associated with all the fragments for the twenty natural amino acids and allows rapid and reliable reconstructions of wavefunctions and electron densities of very large biomolecules.

The coupling of the NCI technique with the ELMO database gave rise to the new NCI-ELMO method [6] that was successfully applied to analyse a variety of non-covalent interactions in polypeptides and proteins. Test calculations showed that qualitative results obtained with the NCI-ELMO technique are very similar to the ones based on fully quantum chemical calculations, but definitely better than those resulting from the promolecular-NCI approach. In this presentation, the previously mentioned qualitative results [6] will be discussed. Additionally, we will illustrate how the new NCI-ELMO technique has been recently extended to quantify noncovalent interactions. Other than applications to protein-ligand interactions, we will show the results of benchmark calculations on smaller systems (e.g., simple molecular dimers) to highlight the differences between the NCI-ELMO and promolecular-NCI approaches also at a quantitative level.

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