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HAR-ELMO: a new quantum mechanics-based method to refine crystallographic structures of proteins

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Nowadays, due to impressive advances from the technological and experimental points of view, sub-atomic and ultra-high resolution X-ray datasets of macromolecules started appearing and their number will certainly increase in the next few years. This makes the refinement of crystallographic structures of biological systems a more and more crucial and difficult challenge, with the need of developing novel refinement techniques able to fully exploit the information content of the new high-resolution X-ray datasets and, consequently, to get unprecedented structural and electron density details of biological molecules.

In this context, an emerging technique of crystallography that can be promisingly used is the Hirshfeld Atom Refinement (HAR). This is a quantum mechanics-based method that, although using only X-ray diffraction data, allows to determine the hydrogen atoms positions with the same precision and accuracy usually attained through neutron diffraction measurements, even when resolution is as low as 0.8-0.9 Å [1]. This would obviously make HAR the perfect strategy to fully exploit the new high-resolution X-ray datasets of macromolecules. Nevertheless, its straightforward application to large systems is actually prevented by the fact that, at each iteration, it requires a tailor-made quantum mechanical calculation, whose computational cost increases with the size of the systems under exam.

The only possibility to overcome this drawback is to couple HAR with quantum mechanics-based linear scaling techniques and, to this purpose, we have recently decided to include the novel libraries of Extremely Localized Molecular Orbitals (ELMOs) [2,3] into HAR. In fact, ELMOs are orbitals strictly localized on small molecular units (e.g., atoms, bonds or functional groups) and, for this reason, easily transferable from a molecule to another [2,3]. Therefore, following a sort of LEGO approach, databanks of ELMOs have been recently constructed. These libraries currently cover all the possible fragments of the twenty natural amino acids and really allow instantaneous reconstructions of wave functions and electron densities of systems ranging from small polypeptides to very large proteins, thus also giving the possibility of computing a large variety of properties for the investigated molecules.

Here, after briefly illustrating the main capabilities of the new ELMO-libraries and of the associated program for the automatic transfer of ELMOs, we will discuss in detail the coupling of these databanks with HAR and we will show recently obtained results that encourage to further improve the technique, with the final goal of making it a powerful routine-strategy for the refinement of macromolecular crystallographic structures.

References:

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