

ELECTROSTATIC PROPERTIES OF BIOLOGICAL MACROMOLECULES FROM TRANSFERRED EXPERIMENTAL ELECTRON DENSITY OF SMALL MOLECULES

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Abstract: Intermolecular interactions between small molecules can be accurately described and quantified from the analyses of their molecular electron density and electrostatic potential. The ultra-high resolution reached by X-Ray diffraction experiments on small molecule crystals allows modelling subatomic molecular properties (covalent bonds, electron lone pairs...) by using the Hansen and Coppens multipolar model¹ of atomic electron density. The multipolar model cannot be refined for protein crystal diffraction data for several reasons, including low resolution of the data and high thermal displacements parameters. However, it is possible to transfer atomic multipolar parameters and polarizabilities of small molecules from the ELMAM2 database² on macromolecules to gain access to electrostatic properties of proteins on the basis of a continuous electron density distribution. An accurate protein charge density can be reconstructed, while accounting for the local environment thanks to the polarizabilities³, in a very fast way thanks to the MoProViewer software⁴. The electrostatic interaction energy between a ligand and a protein can be very quickly estimated⁵. The expected accuracy is close to that obtained in quantum chemistry for model molecules. We are currently developing the computation of the total interaction energy by evaluating the dispersion and exchange-repulsion contributions based on the transferred densities and polarizabilities. We have already obtained promising results on small organic molecules with a correlation about 97% with quantum chemistry computed-values of the dispersion and exchange energies. Intermolecular interactions can be also analyzed by considering the electrostatic potential topology and the resultant space partition into electrophilic and nucleophilic influence zones⁶. We have developed a tool to explore protein active sites according to these electrophilic and nucleophilic influence zones. The well-known mechanism of the bovine trypsin protease has been analyzed to highlight the benefits of this approach. During this presentation, we will describe our methodological developments based on the transferred electron density and show the perspectives of their applications on biological macromolecules.

- ¹ Hansen, N. K., Coppens, P., Testing aspherical atom refinements on small-molecule data sets, *Acta Crystallographica Section A*, 34, 6, 909-921 (1978).
- ² Domagala, S., Fournier, B., Liebschner, D., Guillot, B., Jelsch, C., An improved experimental databank of transferable multipolar atom models—ELMAM2. Construction details and applications, *Acta Crystallographica Section A*, 68, 3, 337-351 (2012).
- ³ Leduc, T., Aubert, E., Espinosa, E., Jelsch, C., Iordache, C., Guillot, B., Polarization of Electron Density Databases of Transferable Multipolar Atoms, *The Journal of Physical Chemistry A*, 123, 32, 7156-7170 (2019).
- ⁴ Guillot, B., Espinosa, E., Huder, L., Jelsch, C., MoProViewer: a tool to study proteins from a charge density science perspective, *Acta Crystallographica Section A*, 70, A1, C279 (2014).
- ⁵ Vuković, V., Leduc, T., Jelić-Matošević, C., Didierjean, C., Favier, F., Guillot, B., Jelsch, C., A rush to explore protein-ligand electrostatic interaction energy with Charger, *Acta Crystallographica Section D*, D77, 1292-1304 (2021).
- ⁶ Mata, I., Molins, E., Espinosa, E., Zero-flux surfaces of the electrostatic potential: the border of the influence zones of nucleophilic and electrophilic sites in crystalline environment, *The Journal of Physical Chemistry A*, 118, 2, 526-532 (2014).