Theoretical electrostatic potential maps of macromolecules calculated with multipolar electron scattering factors

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The maps of electrostatic potential from cryo-electron microscopy and micro-electron diffraction are now being obtained at atomic resolution. This extends the possibility of investigating the electrostatic potential beyond determining the non-hydrogen atom positions, taking into account also the negative regions of the maps. However, accurate tools to calculate this potential for macromolecules, without reaching to the expensive quantum calculations, are lacking. Simple point charges or spherical models do not provide enough accuracy. Here, we apply the multipolar electron scattering factors and investigate the theoretically-obtained potential maps.

The multipolar electron scattering factors are derived from the aspherical atom types from Multipolar Atom Types from Theory and Statistical clustering (MATTS) databank (successor of UBDB2018 [1]). MATTS has been created since electron densities of atom types are transferable between different molecules in similar chemical environment. These atom types can be used to recreate the electron density distribution of macromolecules via structure factors [2] and to calculate the accurate electrostatic potential maps for small molecules [3]. MATTS reproduces the molecular electrostatic potential of molecules within their entire volume better than the simple point charge models used in molecular mechanics or neutral spherical models used in electron crystallography. In this study, we calculate electrostatic potential maps for several chosen macromolecules using aspherical atom databank and compare them with experimental maps from cryo-electron microscopy and micro-electron diffraction at high resolution. Calculations at different resolutions reveal at which spatial frequencies different elements become discernible. We also consider the influence of atomic displacement parameters on the theoretical maps as their physical meaning in cryo-electron microscopy is not as well established as in X-ray crystallography.

This study could potentially pave the way for distinguishing between different ions/water molecules in the active sites of macromolecules in high resolution structures, which is of interest for drug design purposes. It could also facilitate the interpretation of the less-resolved regions of the maps and also advise in simple yet questionable issue of resolution definition in cryo-electron microscopy.

[1] Kumar et al. (2019). Acta Cryst. A75, 398-408

[2] Chodkiewicz et al. (2018). J. Appl. Cryst. 51, 193-199

[3] Gruza et al. (2019), Acta Cryst. A76, 92-109

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