A step forward in accurate modeling of the electrostatic potential maps of macromolecules

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The quality of image and diffraction data from cryo-electron microscopy and micro-electron diffraction is rapidly increasing. Also, the approaches to model the electrostatic potential maps of macromolecular systems reach beyond the simple point charges or spherical independent atom model (IAM) [1]. We recently applied the multipolar electron scattering factors to calculate the theoretical potential for proteins [2], without using the expensive quantum calculations. We applied the transferable aspherical atom model (TAAM) with the Multipolar Atom Types from Theory and Statistical clustering (MATTs) databank (successor of UBDB2018 [3]). This data bank gathers aspherical atom types, useful for deriving the multipolar electron scattering factors. MATTs is a database universal for proteins, RNA, and other macromolecules as the atom types are transferable between similar chemical environments. Using MATTs it is possible to recreate the electron density distribution of macromolecules via structure factors [4] or to calculate the accurate electrostatic potential maps for small molecules [5]. MATTs is able to reproduce 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 electron diffraction, the scattering amplitudes may become negative when the negatively charged residues are present. We expect that this effect should be more visible at worse resolution. In the current work, we investigate the differences in the theoretically-obtained potential maps of proteins at various resolutions. In Figure 1, the positive contributions to the 2D Fourier density maps from atomic cores are well visible at 1 Å resolution in both IAM and TAAM approaches. At 2 Å resolution, the positive contribution is diminished by the dominating influence of the valence electrons. By subtracting IAM from TAAM, it is possible to capture the difference between the two oxygen atoms of Asp, where one of them is engaged in a hydrogen bond. The electrostatic potential density maps of helices at 3 Å resolution calculated with IAM and TAAM show differences in the vicinity of charged amino acids. This work contributes to better predictions of the visibility of the molecular features in the cryo-electron microscopy density maps at different resolutions and the rationale behind it.

Figure 1. Electrostatic potential density maps of lysozyme. a) 2D Fourier density maps at 1 and 2 Å resolutions for Asp66. The values are given in the absolute scale and the maps take into account the thermal smearing effects. b) 3D Fourier density maps at 3 Å resolution for a helical fragment without thermal smearing.


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