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Advances in charge density studies of ultra high resolution protein structures

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The number of proteins and nucleic acids structures solved at atomic and subatomic resolution is increasing continuously. Atomic resolution allows observation of chemical group protonation state and subatomic resolution reveals electron density fine details related to the deformation of the electron cloud due to chemical bonding and intermolecular interactions. As in the field of small molecules crystallography, the use of a non spherical model of atomic electron density allows to take into account these features in the refinement. For this purpose the Hansen & Coppens multipolar model [1] has been implemented in the MoPro software [2], along with methods from small molecules charge density studies and biological crystallography fields. Here we will show how these methods, and using multipolar parameter transferability principle [3], allow biological macromolecules charge density analyses and electrostatic properties computation. We will illustrate our results on several high resolution protein and nucleic acid structures, including Human aldose reductase/inhibitors complexes [4].

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Structural studies on collagen binding integrin I domains

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Integrins are cell adhesion receptors that mediate cell-cell or cell-extracellular matrix interactions by bidirectional signaling. The αβ heterodimeric glycoproteins are composed from 19 different α subunits and 8 different β subunits. The collagen binding integrin family consists of four collagen receptors that have a common β1 subunit non-covalently bound either to α1, α2, α10 or α11 subunit. The α subunits include an inserted domain of 200 amino acids, also called the I domain, which is the key ligand-binding domain. The I domain alternates between two conformations, which are important for regulating the affinity of the ligand. The αI domain contains the metal ion-dependent adhesion site (MIDAS), which in the open conformation binds collagen, while in the closed conformation the binding is hindered.
The crystal structure of αAI and α2I, and the complex structure of α2I bound to a collagen-like peptide, have been solved [1,2,3]. We have used mutagenesis to lock the structure of α1I in the open conformation and showed that the mutant binds collagen with several times higher affinity than the wild-type. Our aim is to crystallize the active mutant and determine the structure of the open conformation. We have also modeled the open conformation of αI1 in complex with a collagen-lide peptide and characterized the binding of the ligand [4].

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