Poster Presentation

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Charge density studies of interactions in macromolecules – the case of sunitinib

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Electron density is a key factor in determining properties of molecules. Knowledge of the electron density distribution allows to determine not only the 3D structure of molecules, but also various one-electron properties (electric moments, electrostatic potential, electrostatic interaction energy, etc.). X-ray diffraction is a great tool for obtaining this kind of information. For macromolecules, however, quantitative determination of charge density from experiment is possible on rare occasions only. We will present that with the University at Buffalo pseudoatom database (UBDB) approach [1,2] it is now possible to reconstruct electron density of any macromolecular system for which atomic coordinates are available. The approach is fast and opens an excellent opportunity to investigate macromolecular complexes by means of topological analysis of electron density (and derivatives thereof), electrostatic interaction energy analysis, and many others. The results of our studies on sunitinib (SU) will illustrate the possibilities of the approach. SU is an inhibitor of tyrosine kinases and was approved as a drug in 2006. Comprehensive analysis of the SU malate crystal and SU complexes with a series of protein kinases was carried out. The high resolution single crystal X-ray measurement and UBDB approach served as the basis for the reconstruction of the charge density of SU and the protein complexes. Hirshfeld surface and topological analyses revealed a similar interaction pattern in the SU malate crystal to that in the protein binding pockets. SU forms nine preserved bond paths corresponding to hydrogen bonds and also to the C-H...O and C-H...π contacts common for all analyzed kinases. It interacts typically with similar electrostatic interaction energy with the studied proteins and can adjust its conformation to fit the binding pocket in a way to enhance the electrostatic interactions. Such behavior can be responsible for a broad spectrum of action of SU as kinase inhibitor.

[1] *K. N. Jarzembska, P. M. Dominiak, Acta Crystallogr. A, 2012, 68, 139–147,* ***[2]*** *T. Koritsanszky, A. Volkov, P. Coppens, Acta Crystallogr. A, 2002, 58, 464–472*

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