STUDY OF DRUG-PROTEIN NON-COVALENT INTERACTIONS FROM SMOOTHED ELECTRON DENSITY DISTRIBUTIONS

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The topology of electron density (ED) distributions combined with the non-covalent interaction (NCI) analysis of reduced density gradient distributions (RDG) are extensively used to characterize intermolecular contacts [1]. Here, topological and NCI-based analyses are combined for the multiresolution study of the intermolecular interactions occurring in a drug-protein system (PDB access code: 3UNK). The method involves the search for the critical points (CP) of a promolecular ED [2], and the minima in the corresponding RDG [3]. The stability of the intermolecular interactions is studied by following their corresponding CP trajectory in space at several degrees t of the ED smoothing, and by the evaluation of the local potential energy density (LPDE). The CP networks and their descriptors are seen as a signature of the ligand-protein arrangement, which is proposed to be further used in the characterization of ligand-protein stackings obtained from, e.g., crystal structures, docking calculations, Molecular Dynamics simulations, or pharmacophore designs. The CP-based representation of the intermolecular contacts enriches geometry-based interactions found using a Web server such as PLIP [4].

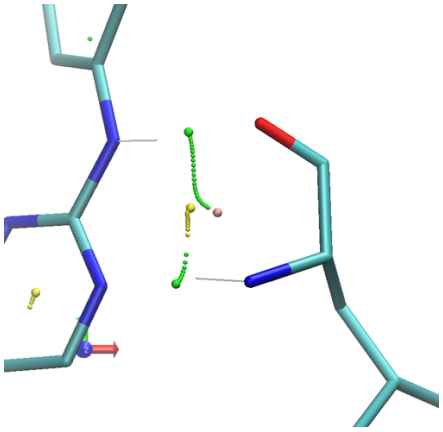

Figure. Trajectories from t = 0.0 to 4.5 bohr^2 of the ED passes (green) and pales (yellow) occurring at the level of the Hbonds between the ligand and Leu83 of CDK2. The NCI minima is displayed at t = 4.5 bohr^2 (pink sphere).

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