AcquaAlta: a directional approach to the solvation of ligand-protein complexes

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Author(s) Rossato, G.; Ernst, Beat; Vedani, Angelo; Smiesko, Martin
Author(s) at UniBasel Ernst, Beat ; Rossato, Gianluca ; Vedani, Angelo ; Smiesko, Martin ;
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Water molecules mediating polar interactions in ligand protein complexes can substantially contribute to binding affinity and specificity. To account for such water molecules in computer-aided drug design, we performed an extensive search in the Cambridge Structural Database (CSD) to identify the geometrical criteria defining interactions of water molecules with ligand and protein. In addition, with ab initio calculations the propensity of ligand hydration was evaluated. Based on this information, we developed an algorithm (AcquaAlta) to reproduce water molecules bridging polar interactions between ligand and protein moieties. This approach was validated with 20 crystal structures and yielded a match of 76% between experimental and calculated water positions. When water molecules establishing only weak interactions with the protein were neglected, the match could be improved to 88%. Supported by a pharmacophore-based alignment tool, the solvation algorithm was then applied to the docking of oligopeptides to the periplasmic oligopeptide binding protein A (OppA). Calculated waters based on the crystal poses matched an average of 66% of the experimental waters. With water molecules calculated based on the docked ligands, the average match with the experimental waters dropped to 53%.

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