The implementation of explicit water molecules in side chain packing algorithms for protein design

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Structure-based computational protein design is an effective tool for the *de novo* generation of protein binding pockets and the optimization of protein-ligand interactions. As for all computational models, there is a trade-off between accuracy and computational feasibility. In contrast to detail-oriented methods like molecular dynamics simulations, side chain packing algorithms, as in our inhouse program MUMBO, are based on highly simplified models of physics and conformational flexibility. Here, the solvent is usually considered implicitly, the backbone of the structure is kept mostly rigid and the conformational flexibility is simulated using rotamer libraries [1]. This enables the *in silico* screening of huge mutant libraries with reasonable computational power to optimize protein-protein interfaces, protein-ligand interactions or to stabilize protein folds.

However, when designing protein binding pockets, these simplifications might be inadequate, because essential interactions like stacking or water- and ion-mediated interactions between the protein and the ligand are not taken into account. Since water-mediated interactions often contribute significantly to the affinity and specificity of ligand binding, we have now implemented this type of interaction in the side chain-packing program MUMBO. Explicit water molecules are added between pairs of rotamers at physically ideal positions (Fig. 1), which leads to a considerable reduction in computational complexity compared to the conventional use of solvated rotamers.

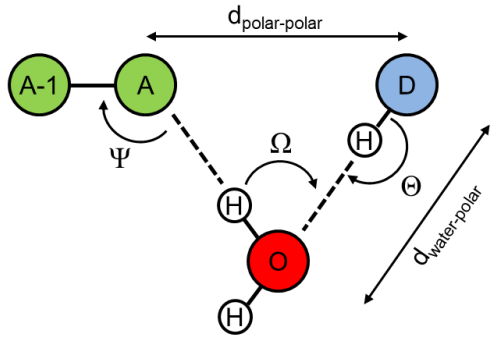

Figure 1. Schematic representation of a water-mediated interaction between an H-bond acceptor and a donor group. The acceptor atom, the acceptor -1 atom (green), the donor atom (blue), the water molecule (red) as well as the for this interaction significant distances and angles are shown.

1. Y. A. Muller & M. T. Stiebritz, MUMBO: A protein-design approach to crystallographic model building and refinement. Acta Crystallographica Section D, **62(6)**, (2006), p. 648 - 658