MS10-P03 | IMPROVING IDENTIFICATION AND VALIDATION OF WATER MOLECULES IN PROTEIN CRYSTAL STRUCTURES WITH MOLECULAR DYNAMICS SIMULATIONS

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Water molecules in close proximity to the protein surface are fundamental to multiple biological processes, such as protein folding, stability or enzymatic reactions. Furthermore, water molecules mediate protein-ligand interactions and play an important role in the energetics of ligand-binding. Thus, knowledge of the position of water molecules around the protein is crucial for the correct prediction of protein-ligand affinities.

Peak-finding algorithms in crystallographic software packages usually perform well for finding the position of well-ordered water molecules but sometimes fail for water molecules with a less clearly-defined electron density and cannot discern between water molecules and ions or other solvent molecules used in crystallization. These algorithms can be improved by using chemical information, for example from molecular dynamics (MD) simulations.

We performed MD simulations of a sugar-binding protein, galectin-3, in complex with various inhibitors, for which high-resolution crystal structures exist both at cryo-temperature and at room temperature. The simulations were done both in solution and in a crystallographic unit cell. Then, we compared water density maps obtained with grid inhomogeneous solvation theory (GIST) from these MD simulations to X-ray electron density maps and added water molecules if the peaks matched in the two maps. Solution MD simulations gave rather poor agreement to the experimental electron density maps. In contrast, MD simulations in crystallographic unit cells show a better performance in identifying weakly-defined crystal water molecules and are a promising tool in the future development of water molecule identification algorithms.