

Water in Protein Crystals

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Water is the ubiquitous solvent of biomolecules. Even protein crystals can contain up to 80% water by volume [1]. Yet water-protein interactions remain fairly poorly characterized. The probabilistic nature of solvation and the rich geometry and physical chemistry of the protein surface make this environment especially challenging to probe. Interestingly, X-ray diffraction of macromolecules also contains structural information about the solvating water [2,3], and recent computational and methodological advances provide new tools extracting that information.

In this work we compare protein diffraction data for which experimental phasing is available to constrained molecular dynamics (MD) simulation results. By correlating the resulting spatial density maps, we find that MD water models capture the radial extent of water fairly well, but fail to describe its orientation around certain protein atoms. Density correlations are higher for carbons than oxygens and nitrogens, and can even distinguish between different protonation states. We also confirm that water's distribution depends strongly on the protein surface environment, providing an explanation for the weakness of generic solvation models [4-6].

The structural performance of different water models — TIP4P, TIP3P, SPC/E, and SPC — is found to be nearly identical. Markedly improving the agreement between model and experiment would thus require models that are trained differently, or that include other aspects of water solvation. The relative robustness of existing solvent descriptions nonetheless paves the way to treating water's contribution to protein refinement more accurately.

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