LAWS: Local Alignment for Water Sites - A Method to Analyze Crystallographic Water in Molecular Dynamics Simulations

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Water is an essential component of biological machinery since it affects proteins' structure and dynamics through the hydrophobic effect, polar interactions, and hydrogen bonding. Protein solvation plays a crucial role in protein's function; hence the accurate modelling of protein solvation is vital for *de novo* drug design and molecular dynamics (MD) simulations. High-resolution x-ray crystallography experiments often obtain positions of crystallographic water sites (CWS) surrounding the protein in the crystal environment. These experiments can be modelled by MD simulations of protein crystals and serve as a strong benchmark for simulation accuracy. Traditional methods for determining positions of CWS in MD simulations rely on global alignment of the protein onto the crystal structure, which introduces substantial errors in the case of flexible dynamics or high deviation. Here we propose a method called local alignment for water sites (LAWS) which is based on multilateration - an algorithm widely used in robotic navigation and GPS tracking. LAWS considers the contacts formed by water and protein atoms in the crystal structure and uses their length to track these water sites in a simulation. It then checks the density of water around these sites and compares it to the bulk water density to decide if the CWS is preserved in MD. Additionally, LAWS provides a framework to quantify how perturbations to the local protein environment affect crystallographic water. We tested our method on a 1-us simulation of a single unit cell of a protein crystal. We demonstrated that almost 80% of CWS are detected within 1.4 angstroms from their experimental positions when using LAWS, and nearly 70% are detected when the global alignment method is used. The results are in agreement with the previous studies. Finally, we showed that the percent of CWS preserved in the simulation depends on the experimental B-factors.