Water Models Matter: From Bulk Solvent Properties to Casein Macropeptide Association and Lipid Vesicle Stability

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Water is usually treated as the background medium in biomolecular simulations, but its molecular representation can determine the reliability of the predicted structure, dynamics, and thermodynamics. Here we connect three simulation studies in which water is not a passive solvent, but the common physical variable linking model validation, protein association, and lipid-vesicle stability.

We first evaluated widely used explicit water models by comparing the temperature dependence of density, heat capacity, self-diffusion, shear viscosity, dielectric response, and radial distribution functions. In the biologically relevant range of 280-350 K, four-point models such as TIP4P/2005 and TIP4P-D reproduced experimental trends substantially better than the commonly used TIP3P model. This benchmark provides a reference for choosing solvent models in simulations where temperature, electrostatics, hydration, and molecular mobility are central to the observed behavior.

We then applied this perspective to the casein macropeptide (CMP), an intrinsically disordered peptide obtained from kappa-casein hydrolysis and relevant for whey valorization. Coarse-grained and all-atom simulations, combined with titration models, were used to investigate how pH, salt concentration, glycosylation, and peptide concentration affect CMP charge regulation, conformational properties, self-association, and adsorption on charged surfaces. Because CMP lacks a stable folded structure, its size, compactness, and association pathways are expected to be especially sensitive to the balance between peptide-peptide and peptide-water interactions. Extending these simulations to compare water models is therefore a direct route to assess the robustness of predicted CMP aggregation and purification mechanisms.

Finally, we studied water confined in lipid vesicles composed of ceramides, cholesterol, and fatty acids, motivated by stratum-corneum transport. All-atom molecular dynamics simulations using TIP3P, TIP4P, TIP4P/2005, and TIP4P-D showed that the water model affects vesicle compactness, correlation times, interfacial hydration, internal water layering, interfacial tension, and internal-external pressure differences. In particular, the organization of confined water and its interaction with polar lipid headgroups depended on the chosen model, highlighting the need to validate solvent descriptions before interpreting mechanical stabilization or transport properties.

Together, these results show that water-model selection is a methodological decision with direct biological consequences. A consistent strategy that begins with bulk-water validation and continues through protein and membrane applications can improve the predictive power of molecular simulations of soft and biological matter.

Keywords:
Water models, Computational biophysics, Confined water, Biomolecular hydration

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