The Necessity of Large System Size in Interpreting Solvent Effects on Hydration and Kinetics in Atomistic Simulations

Dilip Asthagiri [C, S]
Chemical and Biomolecular Engineering, Rice University, Houston, TX, U.S.A.
dna6@rice.edu

Dheeraj Tomar
Xilio Therapeutics, Waltham, MA, U.S.A.

Arjun Valiya Parambathu and Walter Chapman
Chemical and Biomolecular Engineering, Rice University, Houston, TX, U.S.A.

Protein hydration thermodynamics has usually been interpreted on the basis of hydration thermodynamics of small molecule analogues of the protein side-chain or backbone moieties. This group additive approach is central to the extant notion about dominant forces in protein folding and protein solution thermodynamics. In the context of atomistic simulations of proteins, over the last decade a molecular theory and allied algorithmic edifice has been developed that now allows the interrogation of hydration thermodynamics of soluble proteins by treating all protein groups within a single, consistent framework. This approach based on the quasichemical organization of the potential distribution theorem has led to important new insights into the hydrophobic and hydrophilic contributions to bio-macromolecular hydration, including in revealing the surprising finding that hydrophilic contributions determine the temperature signatures that have been attributed to hydrophobic hydration. In this talk, we will present new results that reveal the role of system size in assessing hydration thermodynamics and kinetics, aspects that are of importance in modeling solvent effects within *ab initio* simulations on the one hand and bio-molecular hydration on the other. The free energies to evacuate the first hydration shell around a solute and a cavity defined by the first hydration shell depend on the system size. This observation interpreted within the quasichemical theory shows that both the hydrophilic and the hydrophobic contributions to hydration depend on the system size, decreasing with increasing system size. The net hydration free energy benefits somewhat from the compensation of hydrophilic and hydrophobic contributions; nevertheless a large system appears necessary to describe correctly the balance of these contributions in the hydration of the solute. We illustrate this by discussing the hydration of a hard-sphere (a prototypical hydrophobe), imidazole (a small, polar solute), and a 56 residue protein Gb. We will also present results on the system size dependence of 1H NMR relaxation in water, illustrating one facet of system size dependence on system dynamics.