

HOW INTERFACES AFFECT THE BEHAVIOR OF WATER AND  
WATER-MEDIATED INTERACTIONS: MOLECULAR THEORY  
AND SIMULATIONS

By

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## Abstract

Today, noteworthy advances in science and technology are increasingly occurring through investigations of the nanoscale environment. At these lengthscales, interfaces begin to play an important role vis-à-vis the bulk. In a biological or biotechnological context, the interfaces are almost always aqueous interfaces. *Developing a fundamental understanding of water, and water-mediated interactions at interfaces is the focus of this thesis.* Of the various water-mediated interactions, hydrophobic interactions are possibly the most important in biological systems; they are the primary driver for the folding of proteins, the formation of cell membranes, and various other self-assembly processes.

From a macroscopic perspective, the hydrophobicity of an interface can be quantified by simply measuring the contact angle of a droplet of water. However, such experiments are only thought experiments at the nanoscale; for a fundamental understanding of aqueous interfaces, it is necessary to identify molecular signatures of hydrophobicity. Using extensive molecular simulations of model interfaces, we establish conclusively that density fluctuations, cavity formation probabilities, and solvent pair-correlations provide microscopic measures of hydrophobicity that correlate quantitatively with macroscopic expectations of hydrophobicity. We demonstrate how these results provide a new and robust paradigm to map the hydrophobicity of biomolecules by studying the hydration of a two domain protein. This study also shows the importance of confinement and electrostatic interactions in determining density fluctuations.

Many macromolecules such as proteins, polymers and surfactants are interfacially active, and bind to interfaces. However, the molecular details that drive these processes are not clear. Our studies of how conformationally flexible polymer molecules behave at a range of interfaces establish that water-mediated interactions play the principal if not dominant role in the binding and dynamics of macromolecules at interfaces. Binding free-energies and diffusion coefficients show excellent correlations with surface wettability. Simulations also show that peptides behave almost identically at interface, highlighting the usefulness of a simple polymer model.

Additives such as osmolytes and denaturants can also be used to manipulate water-

mediated interactions. Experiments showed that the protecting osmolyte, trimethylamine-N-oxide can be used to significantly reduce the adsorption of proteins at hydrophobic interfaces. Molecular simulations help understand the molecular basis of these phenomena, and highlight the “osmophobic effect”. Finally, we briefly discuss how one can design model heteropolymers that fold into unique structures in water by tuning the strength of water-mediated interactions. Collectively, this thesis provides significantly new, molecular level insights on processes that occur in the aqueous environment, and especially at interfaces.