Towards an Efficient and Accurate Computational Framework for Characterizing Protein Hydration, Interactions, and Assembly

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The Protein Data Bank contains structures of over 100,000 proteins at atomistic resolution, and is growing rapidly. Translating this wealth of static structural information into a molecular understanding of dynamic intracellular processes represents a grand challenge, with progress hinging on our ability to understand and predict biomolecular interactions. Water plays a crucial role in mediating these interactions, in particular through non-specific hydrophobic effects. However, characterizing protein hydrophobicity (and consequently interactions) is challenging, as it depends not only on the chemistry of the underlying surface, but also on surface topography, chemical patterning, size/shape of ligand, etc. We have made significant progress towards addressing this challenge through the development of novel molecular simulation techniques that characterize the molecular-level behavior of water near proteins and other complex surfaces. Our results provide a computational framework for mapping the hydrophobicity of these surfaces, with relevance to developing predictive strategies for biomolecular binding, recognition, and aggregation. Our results also shed light on the driving forces and barriers to hydrophobically driven binding and assembly in interfacial environments. Specifically, we show that water near hydrophobic surfaces is situated at the edge of a dewetting transition that can be triggered by small perturbations. This perspective provides unique insights into diverse phenomena ranging from the formation of amyloid fibrils catalyzed by interfaces, and the function of chaperonins, to the vapor-lock gating mechanism of ion channels.