Predicting the protonation state of protein residues with polarizable molecular dynamics

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Amino acids contain ionizable titration groups whose protonation state contribute to protein structure and function. For example, cysteine residues can act as catalytic bases in thiolate form or structure stabilizer in thiol form, through the formation of disulfide bonds. Therefore, the ability to predict the protonation state of these residues under physiological conditions is key to elucidate the molecular mechanisms responsible for protein function.

However, the protein interior is often subject to local pH variations that differ from the surrounding aqueous environment, modulating the protonation states of key residues in ways we do not fully understand. In this talk, I will present an approach to access the protonation state of protein residues from electric field calculations performed with polarizable molecular dynamics, which circumvent the need for the more tedious constant-pH MD or quantum-based simulations usually undertaken to estimate individual pKa values. I will demonstrate the applicability of the method by predicting the protonation state of cysteine in various aqueous and protein environments, comparing with experimental data when available.