Predicting the protonation state of side chains in proteins with electric fields.

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Amino acids contain ionizable titration groups whose protonation state contributes 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.

Find out more about our work with electric fields here:

[1] Y. Zheng and V. Vaissier Welborn. 2022. Tuning the catalytic activity of synthetic enzyme KE15 with DNA. J. Phys. Chem. B, 126, 3407–3413.

[2] M. M. Lawal and V. Vaissier Welborn. 2022. Structural dynamics support electrostatic interactions in the active site of adenylate kinase. ChemBioChem, e202200097.

[3] J. Nash, T. Barnes and V. Vaissier Welborn. 2020. ELECTRIC: Electric fields Leveraged from multipole Expansion Calculations in Tinker Rapid Interface Code. J. Open Source Softw., 5, 2576.