Mimicking titration experiments with MD simulations: A protocol for the investigation of pH-dependent effects on proteins

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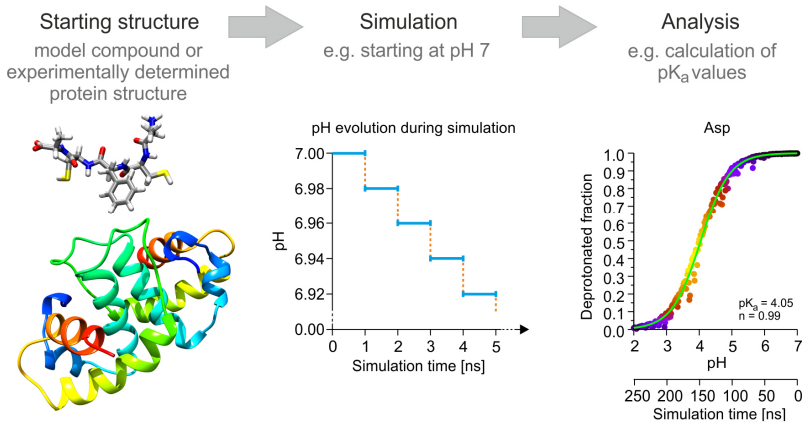
Protein structure and function are highly dependent on the environmental pH. However, the temporal or spatial resolution of experimental approaches hampers direct observation of pH-induced conformational changes at the atomic level. Molecular dynamics (MD) simulation strategies (e.g. constant pH MD) have been developed to bridge this gap. However, one frequent problem is the sampling of unrealistic conformations, which may also lead to poor pK_a predictions. To address this problem, we have developed and benchmarked the pH-titration MD (pHtMD) approach, which is inspired by wet-lab titration experiments. We give several examples how the pHtMD protocol can be applied for pK_a calculation including peptide systems, Staphylococcus nuclease (SNase), and the chaperone HdeA. For HdeA, pHtMD is also capable of monitoring pH-dependent dimer dissociation in accordance with experiments.



We conclude that pHtMD represents a versatile tool for pK_a value calculation and simulation of pH-dependent effects in proteins [1].

[1] E. Socher and H. Sticht, Mimicking titration experiments with MD simulations: A protocol for the investigation of pH-dependent effects on proteins. *Sci. Rep.*, **2016**, *6*, 22523; doi: 10.1038/srep22523.