Investigation of pH-dependent effects on proteins by mimicking pH titration experiments with MD simulations

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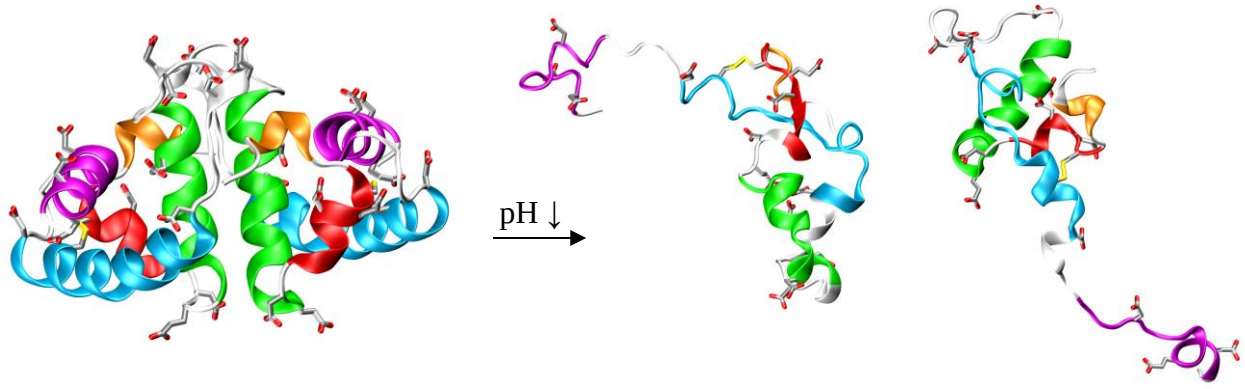
Protein structure and function are highly dependent on the pH of the surrounding environment. However, due to the temporal or spatial resolution of experimental approaches, it is extremely difficult to observe pH-induced conformational changes directly on the atomic level. Molecular dynamics (MD) simulations, which can simulate the atomic motions within biological (macro)molecules were developed to bridge the gap of the resolution. Today, it is also possible to simulate proteins in an environment with constant pH, with so called CpHMD simulations. CpHMD simulations are a huge advantage in comparison to classical MD simulations with constant protonation, because the titrating side chains can switch between different, appropriate protonation states. However, as the name of this CpHMD method suggests, the pH is constant during these simulations. Therefore, we have developed a new application protocol for the CpHMD approach in order to study pH-dependent proteins, in which the change of the pH induces conformational changes. With this pH titrating molecular dynamics (pHtMD) simulation protocol it is possible to decrease or increase the environmental pH over simulation in order to resemble real wet-lab titration experiments. We have validated our pHtMD simulation protocol successfully by investigating small model compounds, Staphylococcus nuclease (SNase) and the bacterial chaperone HdeA as test systems [1].



Here, we present the application of the pHtMD simulation protocol to several different protein systems, which show that pH-dependent processes are widely spread through nature. In each case, our results are comparable to experimental findings. So, we conclude that our protocol provides a versatile and powerful technique for the imitation of pH-dependent effects in proteins.

[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.