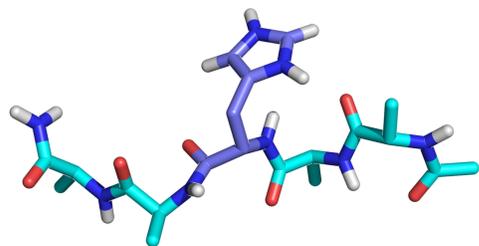


Improving pK_a calculations of membrane inserting amino acids using replica exchange CpHMD simulations

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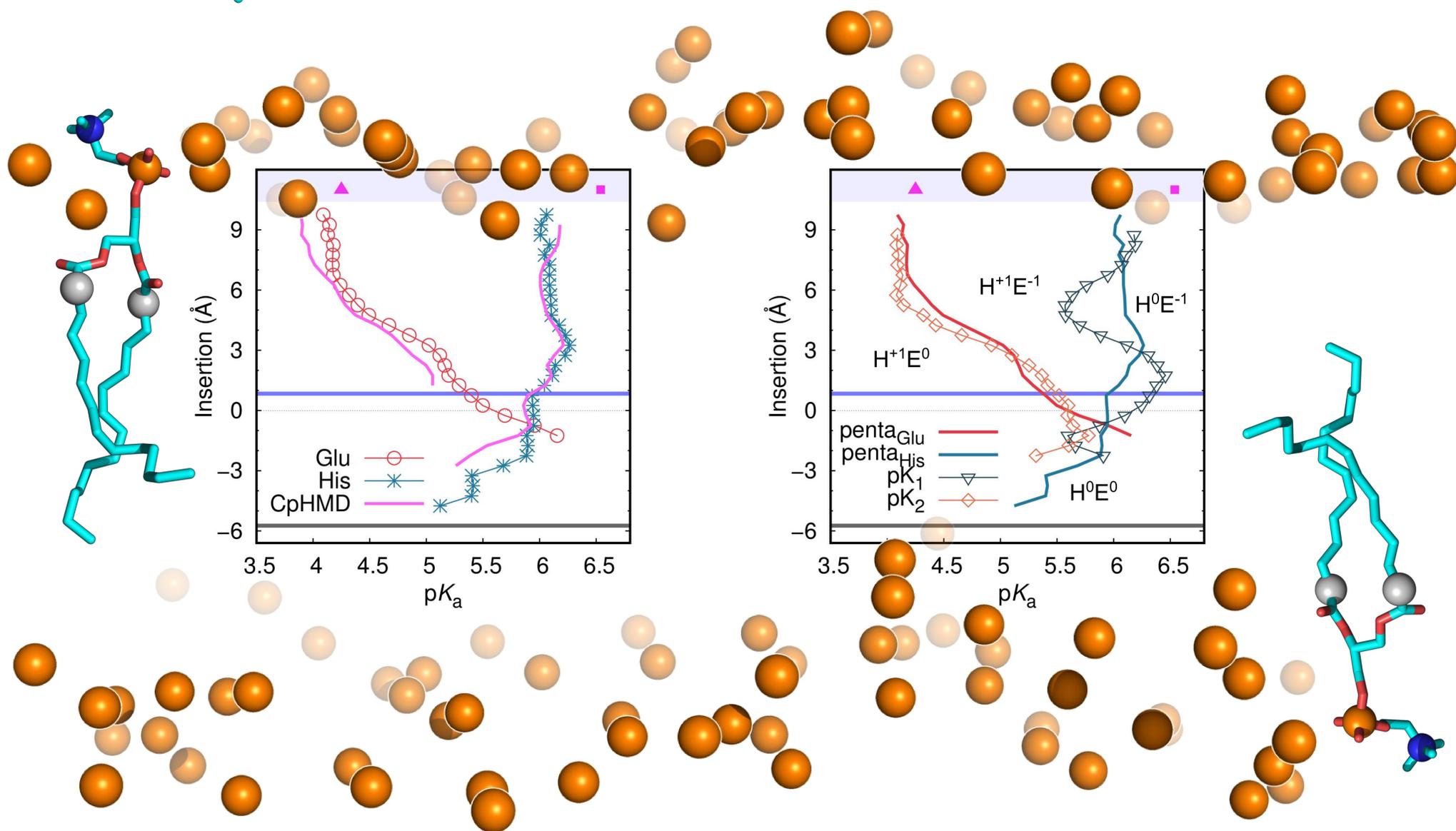
A A X A A
X = {H, E}



To investigate the pK_a values of titrable amino acids at the water/membrane interface, we have used CpHMD¹. Most residues retained their neutral state upon insertion/desolvation in the timescale of our simulations, resulting in poor sampling in inserted regions.

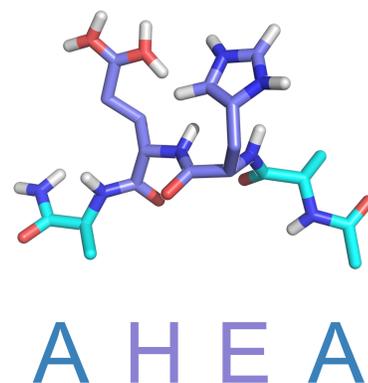
In this work we applied a pH-based replica exchange (pHRE)² in an attempt to circumvent the sampling issues we observed in the alanine based pentapeptides (AAXAA).

pHRE results outperformed previous CpHMD ones, providing more sampling in less simulation time, which suggests pHRE should become the primary method to study pH dependent phenomena.



The AXXX tetrapeptides were designed to study the effect of closely interacting titrable amino acids. Our results suggest that upon membrane insertion both residues prefer to adopt a neutral state rather than mutually stabilize their ionizable forms, through a salt bridge configuration.

To more accurately describe the membrane influence on the pK_a profiles of titrable amino acids, we have used the pHRE methodology, a newly developed method to calculate insertion, and more rigorous criteria to define the acceptable protonation sampling.



[1] V. H. Teixeira, D. Vila Viçosa, P. B. P. S. Reis, and M. Machuqueiro, "pK_a Values of Titrable Amino Acids at the Water/Membrane Interface," *Journal of Chemical Theory and Computation*, vol. 12, pp. 930–934, mar 2016.

[2] D. Vila-Viçosa, A. M. Baptista, C. Oostenbrink, and M. Machuqueiro, "A pH replica exchange scheme in the stochastic titration constant-pH MD method," In preparation.

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