Comparison of two AMBER force fields regarding structural changes in pH-responsive helical peptides

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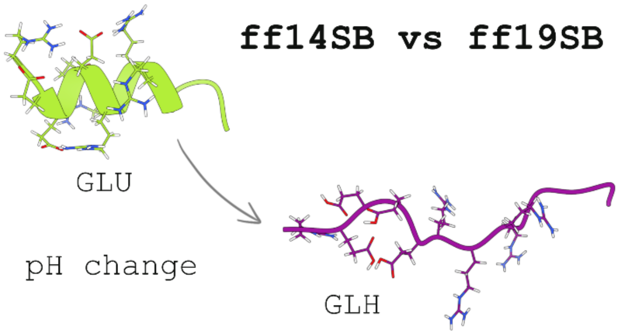

We compared two AMBER biomolecular force fields (ff14SB and ff19SB) in terms of their ability to model structural changes in α-helical peptides in response to pH changes. We were particularly interested in how the two force fields model electrostatic interactions, as these are generally important for the stability of α-helices. We curated a dataset comprising nine peptides, including one non-helical control peptide and six peptides with an experimentally documented pH-dependent structural change. Two of the peptides had an unknown pH response. All systems were simulated at two protonation states, reflecting two different pH values. Both force fields modelled the same unfolding trend for the pH-responsive peptides, which is consistent with existing experimental data. Furthermore, ff14SB and ff19SB model similar side chain interactions for the helical conformation of the peptides. However, we observed differences in backbone and side chain hydrogen bond stability between the two force fields. These differences were particularly evident in peptides with a high alanine content. We propose that this is an effect of the reparameterisation of alanine in the ff19SB force field[1].

To evaluate the potential of molecular dynamics simulations in identifying pH-responsive peptides, we studied two peptides with an unknown pH response. Both force fields modelled pH-dependent unfolding of one peptide, while the other remained helical in its acidic protonation state. These findings were confirmed experimentally by performing circular dichroism spectroscopy at pH 7 and pH 2.

Our work demonstrates that ff14SB and ff19SB can be used to identify pH-responsive peptides and facilitate an understanding of the atomistic reasons behind their structural change. This may be of use when studying pH-sensitive sites in peptides and proteins, or when designing peptide-based pH-sensors. Reporting similarities and differences between the two force fields can contribute to the continuous effort to improve force field and solvent models by the MD community.

[1] C. Tian, K. Kasavajhala, K. A. A. Belfon, L. Raguette, H. Huang, A. N. Migues, J. Bickel, Y. Wang, J. Pincay, Q. Wu, C. Simmerling, “ff19SB: Amino-Acid-Specific Protein Backbone Parameters Trained against Quantum Mechanics Energy Surfaces in Solution” *J. Chem. Theory Comput.* **2020**, *16*, 528–552.