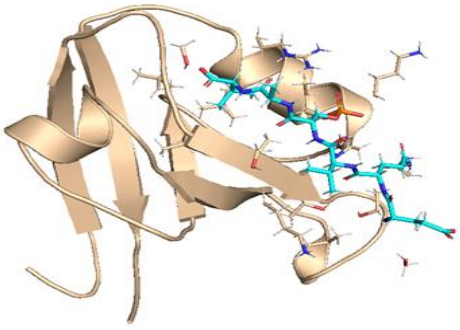
How Phosphorylation Affects Peptide Interaction with Adaptor Domains

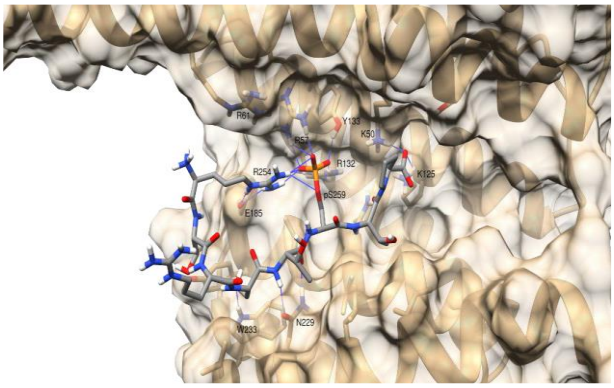
Debarshee Sengupta[1], Jonas Gellner[2], Carter Wilson[3], Volkhard Helms[1]

[1]*Center for Bioinformatics, Saarland University, Germany*

[2]*Department of Theoretical and Computational Biophysics, Max Planck Institute for Multidisciplinary Sciences, Germany*

[3]*Computational Biomolecular Dynamics, Max Planck Institute for Multidisciplinary Sciences, Germany*





Protein-protein interactions (PPIs) are of fundamental relevance to numerous cellular processes and hence the focus of considerable experimental and computational efforts. They are often modulated by posttranslational modifications such as phosphorylation, which can either favor or disfavor the formation of a particular complex. Molecular dynamics (MD) simulations have emerged as a powerful tool to reversibly simulate the association and dissociation of protein complexes, providing insights into binding free energies and kinetic rates that often align well with experimental data. However, recent findings indicate limitations in the AMBER and CHARMM force fields when modeling phosphorylated residues. For example, Rieloff et al.[1] observed that phosphorylated statherin peptides adopted overly compact conformations in simulations using both AMBER and CHARMM36 force fields, diverging from small-angle X-ray scattering data. Similarly, our previous work on phosphorylated versus non-phosphorylated peptides binding to hPTP1E and MAGI1 PDZ domains revealed an overstabilization of phosphorylated peptides by approximately -8 kJ/mol with the CHARMM36m force field and TIP3P water [2]. To address these discrepancies, we are currently evaluating the TIP4P water model for potential improvements in binding free energy predictions and extended our studies to other PDZ domains, including Scribble, Shank and DLG. For complexes lacking crystallographic data, we generated high-confidence structural models of protein:peptide complexes using AlphaFold. These efforts aim to refine the accuracy of MD simulations in capturing the nuanced effects of phosphorylation on PPIs.

[1] Rieloff E, Skepö M (2020) Phosphorylation of a disordered peptide—structural effects and force field inconsistencies. J Chem Theory Comput 16, 1924-1935.
[2] Künzel N, Helms V (2022) How peptides bind to PSD-95/Discs-Large/ZO-1 domains. J Chem Theory Comput 18, 3845–3859.