Enabling Prediction of Protein-Protein Binding Affinities Using FEP+

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Physics-based free energy perturbation (FEP) calculations provide accurate energetics while allowing conformational flexibility by using explicit solvent molecular dynamics (MD) simulations with a state-of-the-art force field. The accuracy and efficiency of these calculations can be improved through enhanced sampling protocols for mutating residue and nearby waters, effective handling of proline and charged amino acids, and automated parameterization of non-canonical amino acids. FEP+[1] and our new constant-pH molecular dynamics (CpHMD) implementation can account for protonation and tautomeric state changes, both upon binding/folding and at different pH values. Our approach was recently demonstrated in a real-world collaboration, where it was able to reduce cost and accelerate the development process significantly.

[1] L. Wang, Y. WU, *J. Chem. Theory Comput.*, **2013**, *9*, 1282-1293.