

Publication

Assessing the Predictive Power of Relative Binding Free Energy Calculations for Test Cases Involving Displacement of Binding Site Water Molecules

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)**ID** 4500689**Author(s)** Wahl, Joel; Smiesko, Martin**Author(s) at UniBasel** [Smiesko, Martin](#) ; [Wahl, Joël](#) ;**Year** 2019**Title** Assessing the Predictive Power of Relative Binding Free Energy Calculations for Test Cases Involving Displacement of Binding Site Water Molecules**Journal** Journal of chemical information and modeling**Volume** 59**Number** 2**Pages / Article-Number** 754-765**Mesh terms** Science & TechnologyLife Sciences & BiomedicinePhysical SciencesTechnologyChemistry, MedicinalChemistry, MultidisciplinaryComputer Science, Information SystemsComputer Science, Interdisciplinary ApplicationsPharmacology & PharmacyChemistryComputer Science

Improved sampling methodologies, more accurate force fields, and access to longer simulation time scales have led to an increased application of Relative Binding Free Energy (RBFE) calculations in drug discovery projects. In order to assess the strengths and limitations of such tools, adequate benchmark sets are required that challenge the methodology in certain well-defined aspects. We applied Free Energy Perturbation (FEP) calculations to six congeneric ligand pairs taken from the literature, in which addition of a functional group resulted in the displacement of buried binding site water molecules and compared the calculated relative binding free energies with the experimental ones. We started the perturbations from different initial solvation states and registered large inconsistencies (large hysteresis) between the calculated values. We furthermore applied a Grand Canonical Monte Carlo (GCMC) solvent sampling step prior to the FEP calculation that led to a smaller hysteresis for the simulations. By applying a hydration site analysis to the trajectories of the end-states of the perturbation, we could point out that the low accuracy of the predictions as well as the high dependence of the prediction on the chosen initial state is likely caused by the trapping of binding site water molecules and/or insufficient solvation of buried cavities that are formed upon completion of the perturbation. This work highlights that RBFE calculations can suffer from slow solvent exchange of buried parts of the binding sites with the bulk.

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