CL-FEP: End-state free energy calculations from simulations in explicit solvent

Maximum number of participants: 4

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The accurate evaluation of free energy changes is essential for the study of solvent effects in molecular interactions and properties. However, such evaluation is a computationally demanding task, usually affected by significant convergence challenges. To address this issue, we implemented the Central Limit Free Energy Perturbation approach. Our approach allows evaluating the FEP identity directly from the energy samples from simulations in explicit solvent of the end states of a system transformation without fitted parameters or stratification. The algorithm, which combines the FEP estimator with a Central-Limit-Theorem-based modification of the energy samples, was implemented via a bootstrapping approach that also renders a robust error evaluation for the final estimations. We demonstrated the applicability of CL-FEP in several dissimilar benchmark systems. The mean absolute error of the free energy changes in these systems was between 1.1 and 1.4 kcal/mol, which is in the range of accuracy of the most reliable and computationally demanding free energy approaches applied to these systems. Currently, our approach can be used to accurately predict binding free energies of host-guest systems and biomolecular complexes based on the output of force field molecular dynamics simulations. We implemented the web server CLFEP-GUI (https://clfep.zmb.uni-due.de/) to provide public access to the use of CL-FEP. CLFEP-GUI features the necessary functionalities to compute binding free energies with CL-FEP, given the trajectories. In this module the students will learn the theory and practice of free energy calculations in test systems using the end-state CL-FEP estimator and all-atom simulations in explicit solvent.

Reference: Ruiz-Blanco YB, Sanchez-Garcia E. CL-FEP: An End-State Free Energy Perturbation Approach. J Chem Theory Comput. 2020, 16, 1396-1410. (doi: 10.1021/acs.jctc.9b00725)

Prerequisites: Basic knowledge of MD simulations and free energy concepts.