UCLA College | Physical Sciences Chemistry & Biochemistry

SPECIAL PHYSICAL CHEMISTRY SEMINAR

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Thursday, Jan 13, 2022
12:00 PM
via Zoom

"CL-FEP: An Accurate End-State Free Energy Perturbation Approach"

Abstract: The accurate evaluation of free energy changes is essential for the study of chemical and biological systems. However, such evaluation is a computationally demanding task, commonly affected by convergence challenges. To address this issue, we implemented the Central Limit Free Energy Perturbation approach (CL-FEP) (1). CL-FEP, which is freely accessible at the CLFEP-GUI web server, allows evaluating the FEP identity directly from the energy samples of the end states of a system transformation without fitted parameters or stratification. The CL-FEP approach delivers excellent accuracy estimating the binding free energy of molecular and biomolecular complexes. The deviation between CL-FEP estimations and experimental values in dissimilar benchmark systems was below 1 kcal/mol. For large test sets, the mean absolute error of the free energy changes calculated with CL-FEP is 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.

We also employed CL-FEP to evaluate the interaction of Alpha-1 antitrypsin with the TMPRSS2 protease which results in the inhibition of SARS-CoV-2 infection (2). CL-FEP also found applications in the study of the antimicrobial activity of supramolecular ligands (3). Our work demonstrates that CL-FEP provides an attractive alternative to current end-state estimators of free energy changes. Delivering accurate free energy estimations at a reduced computational cost makes these calculations accessible even to large protein-protein complexes. Finally, since multiscale approaches are also in the focus of our research, we applied a rational prioritization strategy combining free energy and QM/MM calculations to address the problem of antibiotic resistance (4).

(1) JCTC 2020, 16, 1396.
(2) Nature Communications 2021, 12, 1726.
(3) Cell Chemical Biology 2021, 28, 1310.
(4) PNAS 2021, 118, e2113632118.

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