Free Energy Calculations in Fragment Based Drug Design: Applying FEP in Practical Ligand Optimization

Thomas Steinbrecher

Schrödinger

It has long been considered the holy grail of computational drug design to accurately predict binding free energies for novel compounds. This task is of special importance in fragment-based drug design, where multiple rounds of potency improvement starting from initial weak binders are necessary to generate highly active lead structures. Molecular Dynamics based free energy calculations (or FEP for free energy perturbation) are among the most suitable methods to reach this goal, which would significantly impact the modern drug design process. Many of the issues previously encountered with FEP have been mitigated by our introduction of the FEP+ (free energy perturbation plus REST, i.e. replica-exchange with solute tempering) methodology along with the OPLS2.1 force field, together with the computational power offered by GPU computing.

The lack of large scale validation studies on diverse series of ligands are another obstacle for the practical application of FEP, due to the lack of computational resources and the time consuming process of simulation setup and analysis. Recently, we have conducted a validation study of FEP results on more than 10 targets and more than 500 compounds, offering an order of magnitude more data than typical FEP studies and allowing statistically valid conclusion about their efficacy.

Here, we extend this validation study to several fragment hit series, among them the Mcl-1 protein, HSP90 and DNA Ligase A. Relative binding free energies can be calculated with good accuracy, typically with R2 values in the range of 0.5-0.8 and mean unsigned errors (MUE) of less than 1 kcal/mol when comparing to experimental data. This shows that FEP binding energy predictions offer unsurpassed accuracy for fragments and lead precursors as well as for drug-like molecules.