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Lead optimization: calculating relative binding free energies with FEP+

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The prediction of relative free energies of binding within a congeneric ligand series can be a potential key contribution to the process of ligand optimization. When accurate enough (approx. 1 log unit in the binding constant), free energy predictions can help to reduce the effort spent in compound synthesis and also the total time spent by reducing the number of iterations in the design process.

Traditionally, fast empirical approaches like rigid-receptor docking dominated the field for decades due to their low computational cost, but have proven to be very limited in their predictive power in lead optimization and often required a large amount of experience to interpret since the success of the results can be highly target specific.

Nowadays we are witnessing the beginning of a new era for relative binding free energy predictions due to the emergence of free energy perturbation (FEP) calculations. The general concept is quite old, and the first calculations on small systems were carried out more than twenty years ago. Thanks to a number of scientific and technological advances, we are now finally able to use FEP on a broader scope in real world applications.

The talk will briefly outline the main features of Schrodinger's FEP+ solution, which combines a number of recent advances in the field. FEP+ features high performance MD code that makes use of GPU computing, augmented by enhanced sampling schemes ('replica-exchange solute tempering'), to achieve sufficient sampling to provide converged free energy estimates with modest hardware investment. Error analysis based on cycle-closure correction provides a measure of reliability for the calculations. On the force field side, the accurate all-atom force field OPLS3 is used, including a protocol to conveniently parameterize missing torsional parameters. Together with an automated setup procedure, this enables free energy calculations within real-world industrial projects.

Beyond the technical overview, the presentation will outline a few interesting cases from literature and internal efforts where FEP+ has been used retrospectively and prospectively in order to give an idea about Schrödinger's efforts in extending the domain of applicability of the technique.

HPC content

The presentation describes how computer aided drug design can make use of state of the art general purpose GPUs (GPGPUs) to enhance and speed up the drug discovery process, with a specific focus on Schrodinger's FEP+ tool, which uses extensive, GPGPU accelerated molecular dynamics simulations to predict relative binding free energies of drug candidates in drug discovery.

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