Developing a new drug compound is an expensive task that is becoming increasingly more difficult. The current drug-design paradigm faces challenges that can be ameliorated by taking advantage of modern high performance computers and the latest algorithms. There is a demand for new solutions that are sophisticated enough to meet the demands of the drug development market, while also being robust and accurate enough to deal with the challenges presented by new emerging infectious diseases. One of the most prominent and state-of-the-art protocols for the calculation of protein-ligand binding energies is alchemical free energy perturbation (FEP) theory. Within the FEP framework, one determines the binding energy of a molecule to a given receptor by simply measuring the change in the Gibbs free energy caused by the ligand-protein interaction while in solution. The alchemical method is based on a non-physical thermodynamic cycle, where the binding free energy is computed as the sum of multiple steps where the ligand is 'inserted', 'removed' or 'transmuted' while in the pocket (or in solution)

Accurate and rapid predictions of the binding affinity of a compound to a target is one of the ultimate goals of computer aided drug design. Alchemical approaches to free energy estimations follow the path from an initial state of the system to the final state through alchemical changes of the energy function during a molecular dynamics simulation. Herein, we explore the accuracy and efficiency of two such techniques: relative FEP and multi-site lambda dynamics (MSλD). These are applied to a series of inhibitors for the bromodomain-containing protein 4 (BRD4). We demonstrate a procedure for obtaining accurate relative binding free energies using MSλD when dealing with a change in the net charge of the ligand. This resulted in an impressive comparison with experiment, with an average difference of 0.4 ± 0.4 kcal mol^{-1}. In a benchmarking study for the relative FEP calculations, we found that using 20 lambda windows with 0.5 ns of equilibration and 1 ns of data collection for each window gave the optimal compromise between accuracy and speed. Overall, relative FEP and MSλD predicted binding free energies with comparable accuracy, an average of 0.6 kcal mol^{-1} for each method. However, MSλD makes predictions for a larger molecular space over a much shorter timescale than relative FEP, with MSλD requiring a factor of 18 times less simulation time for the entire molecule space.

In the pharmaceutical sector, computer-aided lead discovery and development programmes will increasingly have FEP simulation at the heart of them, with computing hardware becoming more powerful and with the empirical force fields, algorithms and associated protocols leading to more accurate estimates of differences in protein-ligand binding free energies. The calculations are computationally demanding, necessitating the use of high performance computing, and the vastness of chemical space means that one would like to be evaluate many thousands of potential ligands at the FEP level. Searches of chemical spaces at lower levels of theory run the risk of exploring largely irrelevant regions, due to the inherent crudeness of the estimates of binding free energies.