Large Scale Free Energy Calculations on Congeneric Ligand Series – Applying FEP in Practical Drug Design

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The holy grail of computational structure based ligand design has long been the accurate prediction of binding free energies for novel compounds. Molecular Dynamics based free energy calculations (FEC) have been proposed as one of the most suitable methods to reach this goal, which would significantly impact the modern drug design process. However, despite many successful studies, FEC have for more than 20 years failed to fulfill this promise. Possible reasons for this include force field deficiencies, insufficient sampling and difficulties in assessing the quality of simulation results. One of the main obstacles in addressing these issues has been the lack of large scale validation studies on diverse series of ligands, due to the lack of computational resources and the time consuming process of simulation setup and analysis. Here, we will present results from FEC conducted on several protein-ligand systems of pharmaceutical interest. Covering more than 10 targets and more than 200 compounds, the results offer more than an order of magnitude more data than typical FEC studies and allow statistically valid conclusion about their efficacy. We show that relative binding free energies can be calculated with good accuracy in most cases, typically with R^2 values in the range of 0.5-0.8 and mean unsigned errors (MUE) of less than 1 kcal/mol on average when comparing to experimental data. We show that FEC consistently outperform other binding energy estimation methods such as Docking and MMGBSA. Statistical error estimates from individual calculations are much smaller than observed deviations from experimental results, but improved error estimates can be obtained from constructing redundant graphs of ligand transformations.