

Abstract: Computational, structure-based, drug design offers insight at an atomic resolution, which is commonly not attainable by experimental means. Detailed calculations on protein-ligand interactions help to rationalize and predict experimental findings. Accurate and efficient calculations of binding free energies is essential in this respect. In addition, knowledge concerning the enthalpic and entropic contributions are highly relevant to determine novel drug design strategies and to understand the underlying principles of ligand binding.

Currently available methods to address ligand affinity either do not include all relevant contributions to the binding free energy, or are too computationally demanding to be applied straightforwardly. In addition, calculations on enthalpy and entropy for drug design purposes are very rare, due to the difficulty in calculating these accurately. This proposal describes the research that leads the way to new, standard applications to be used in drug design processes in academia and industry. Furthermore, we propose to investigate the enthalpic and entropic contributions to ligand binding. We define a ligand-surroundings enthalpy and entropy, which conveys more information than the experimentally accessible enthalpy and entropy of ligand binding.

In support of this research, we will develop new enhanced sampling techniques which not only render the above calculations practically feasible, but which will also find their application in related research questions such as the protein folding problem or the elucidation of protein-protein interactions.

The methods described are highly relevant for the pharmaceutical industry, where currently available computational approaches are insufficient to answer the questions of today's drug discovery programmes.