Enabling medium- to high-throughput free energy calculations with the AMBER suite

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During the last decades great effort has been undertaken to develop methodologies for the computational prediction of binding affinities of potential drug molecules. In particular, three methods show promise for correctly ranking ligands by their binding affinities: molecular mechanics / Poisson-Boltzmann surface area (MM-PBSA), molecular mechanics / generalized Born surface area (MM-GBSA), and thermodynamic integration (TI) [1, 2]. Until recently, however, the analysis of large ligand data sets was hampered by the computational burden of these methods. Consequently, no setup and analyses procedures are available at present in the AMBER suite of programs [3] that allow medium- to high-throughput analyses with these methods. Instead, performing the calculations requires many manual interventions.

To enable an easy, fast, and consistent determination of binding free energies for series of related ligands binding to one target with AMBER, we developed the workflow programs WAMM (Workflow Analysis for MM-PBSA & MM-GBSA) and TIW (Thermodynamic Integration Workflow) for automated setup and analysis of MM-PBSA, MM-GBSA, and TI calculations. Based on a command file, in which the system specific parameters are defined, the programs carry out all steps required for preparation of the calculations, thus integrating tasks that had to be performed separately so far with different modules of the AMBER suite. We paid particular attention to the adaptability of WAMM and TIW to different cluster architectures and batch systems by using a template-based setup procedure, in which the required input and batch files are generated according to single template files provided by the user.

The workflow programs were successfully tested on Factor Xa inhibitors [4] with modeled complex geometries. 19 out of 25 ligands were correctly ranked in an all-pairwise manner in more than 50% of the cases. With respect to efficiency, the setup allows to compute binding free energies for tens of ligands within a week on a state-of-the-art compute cluster.

With increasing compute power and improved simulation technology in the next years, we expect that computed binding free energies for large ligand data sets will be more frequently applied for guiding lead optimization efforts. The workflow tools presented here will considerably facilitate these computations.

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