Efficient free-energy calculations with a multi-state method

Enveloping distribution sampling (EDS) allows the calculation of free-energy differences between multiple end states from a single simulation [1]. A reference-state Hamiltonian is simulated which envelopes the Hamiltonians of the end states. The challenge when using EDS is the determination of optimal parameters for the reference-state Hamiltonian. Previously, the choice of parameters for an EDS simulation with multiple end states was a non-trivial problem that limited the application of the methodology [2]. To overcome these limitations, we have generalized the replica-exchange EDS (RE-EDS) methodology to arbitrary systems [3,4]. By exchanging configurations between replicas with different parameters for the reference-state Hamiltonian, major parts of the problem to choose optimal parameters are circumvented. Algorithms to estimate the energy offsets and optimize the replica distribution have been developed and to automate the parameter optimization procedure. Our approach was tested successfully for inhibitors for a range of kinases [5,6]. RE-EDS is able to model up to 13 ligands simultaneously with high sampling efficiency, leading to a substantial decrease in computational cost when compared to pairwise methods.

References:

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