Fast Switching Double Annihilation (FSDAM): an hybrid OpenMP-MPI parallel protocol for accessing absolute binding free energies in drug-receptor systems

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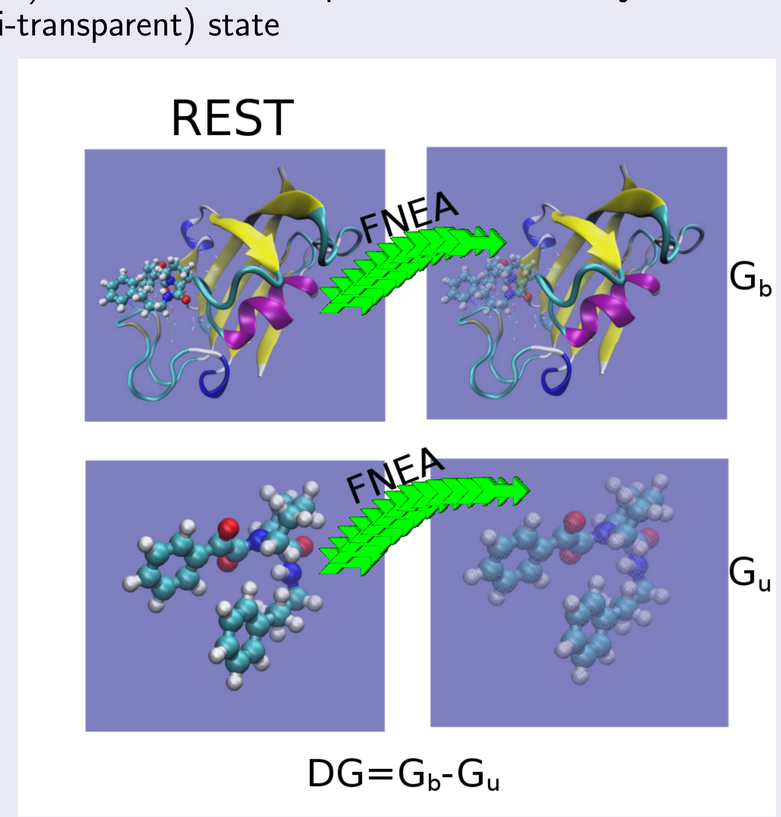
Introduction

The determination of the binding affinity in ligand-receptor systems is placed right at the start of the drug discovery process, in a sequence of increasing capital-intensive steps, from safety tests, lead optimization, preclinical and clinical trials. In silico screening, using advanced molecular dynamics (MD) simulation techniques such as Free Energy Perturbation or Thermodynamic Integration methods, could be in principle a useful tool for designing putative ligands aimed at reducing the economic cost of false positives in the drug development pipeline. Unfortunately, these state-of-the-art computational technologies, being all based on the equilibrium paradigm, require costly simulations that are typically plagued by convergence problems and reproducibility issues. Based on some recent advances in non equilibrium (NE) statistical thermodynamics, in the last three years, we developed on the CRESCO platform a new variant of the alchemical method, relying on an accurate enhanced sampling of the fully coupled states (REST stage) and on the production of many fast (sub-nanosecond) and independent NE ligand annihilation trajectories (FNEA stage). The drug-receptor binding free energies are recovered from the NE annihilation work distribution by using an unbiased unidirectional estimate derived from the Crooks's theorem exploiting the inherent Gaussian nature of the annihilation work. The efficiency, simplicity and inherent parallel nature of the algorithm, is expected to project the methodology as a possible effective tool for a second generation High Throughput Virtual Screening in drug discovery and design.

The FSDAM alchemical algorithm

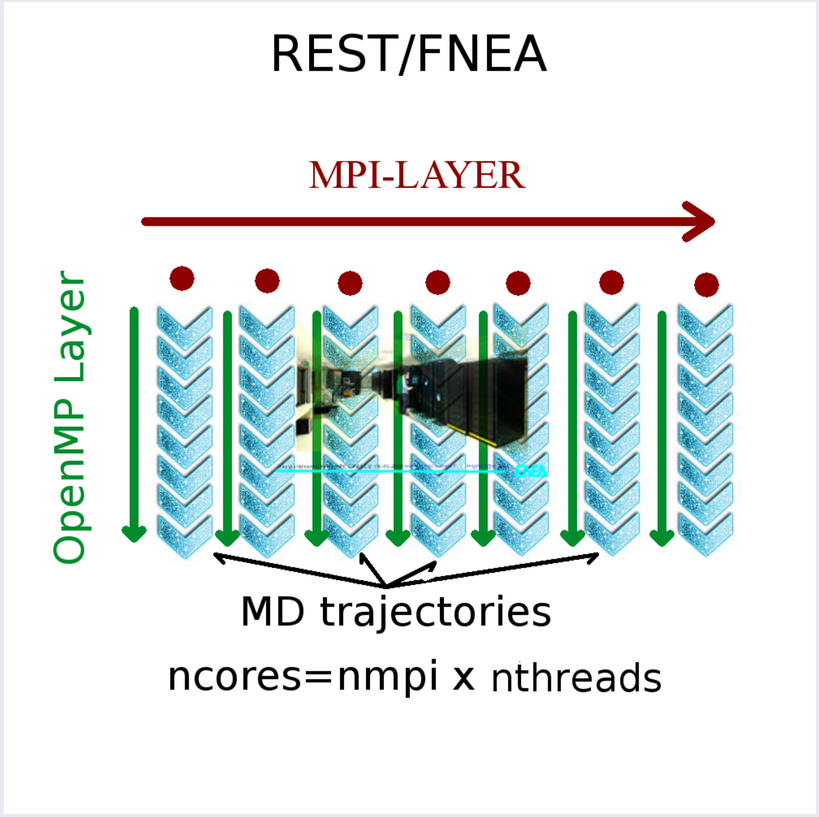
The algorithm is made of two independent sets of simulations for the bound and unbound ligand. In the REST stage, Hamiltonian Replica Exchange simulation is used Fast to efficiently sample the equilibrium states of the fully coupled bound (upper left panel) and unbound ligand (lower left panel). In the transformative FNEA stage, starting from the equilibrium configurations sampled in REST, the ligand is rapidly annihilated in the bound state (upper right panel) and in the unbound state (lower right panel) in a swarm of independent NE MD trajectories, ending up in a decoupled (semi-transparent) state



The annihilation free energies for the bound and unbound ligand, G_b and G_u, are recovered from the distribution of the alchemical annihilation work and the dissociation free energy is given by the difference $\Delta G = G_b - G_u$. The higher is this difference, the higher is the affinity.

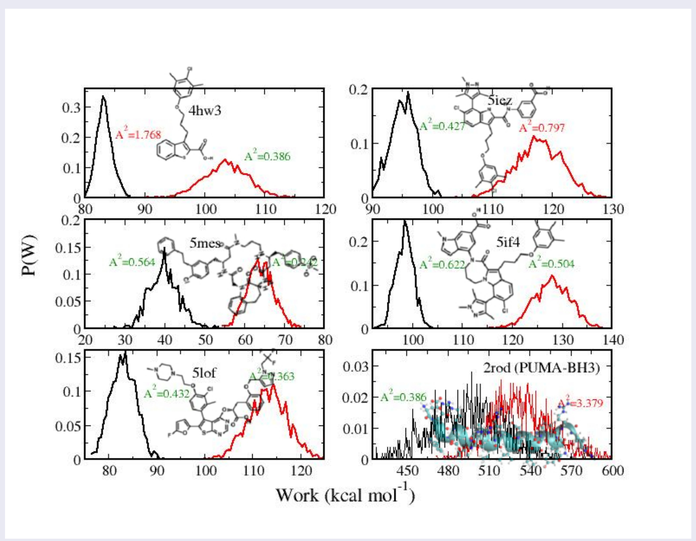
FSDAM on a HPC system

FSDAM is tailored for modern NUMA HPC system. The parallel implementation on CRESCO relies on a hybrid OpenMP/MPI approach. The inter-nodes MPI layer takes care of the weak scaling/low communication Replica Exchange trajectories in REST or of the independent/zero-communication NE trajectories in FNEA. The OpenMP layer is implemented on each of the REST or FNEA MPI-managed trajectories using a force decomposition strong scaling approach in an intra-node shared memory environment.



FSDAM allows to redistribute the available parallel resources among weak scaling instances, related to the production of concurrent REM/NE trajectories, and strong scaling instances, connected to the force computation in the individual trajectories, in a manner that is mostly convenient for the end-user.

Results on the Myeloid Cell Leukemia-1 (Mcl-1) inhibitors



Work distributions obtained in the FNEA stage (bound:red, unbound:black) for five synthetic Mcl-1 inhibitors and for the PUMA BH3 domain. Green A^2 values indicate that the distribution passed the Anderson-Darling normality test

Ligand	$\Delta G_{\rm exp}$	$\Delta G_{\rm calc}$	$\Delta G_b - \Delta G_u$	Est.	$\Delta G_{\rm Vol}$	$\Delta G_{\rm pKa}$
4hw3	8.91	8.1 $\pm$ 0.9	11.0 $\pm$ 0.6	G	-2.9 $\pm$0.3	-
5iez	10.5	11.6 $\pm$ 1.2	14.3 $\pm$ 0.9	G	-2.7 $\pm$0.3	-
5if4	12.8	18.0 $\pm$ 1.1	21.0 $\pm$ 0.7	G	-3.0 $\pm$0.3	-
5lof	13.4	17.1 $\pm$ 1.2	21.9 $\pm$ 1.1	G	-2.7 $\pm$0.3	-2.1$^{(b)}$
5mes	$>$ 11.6	18.1 $\pm$1.2	26.2 $\pm$ 1.2	G	-2.5 $\pm$0.3	-5.6$^{(a)}$
2roc	12.0	43.4 $\pm$ 10.9	45.8$\pm$ 10.5	J	-2.4 $\pm$0.3	-

Table: Experimental ($\Delta G_{\rm exp}$) and Calculated ($\Delta G_{\rm calc}$) standard dissociation free energies for the Mcl-1 ligands. The entries in the "Est." column indicate the estimate used for evaluating the annihilation free energies $\Delta G_{b/u}$ from the corresponding work distributions reported on the left, with "G" and "J" standing for Gaussian and Jarzynski, respectively. $\Delta G_{\rm Vol}$ is the volume contribution and $\Delta G_{\rm pKa}$ is the correction due to the protonation state of the bound ligand. The latter has been computed using pKa=11 for 5mes and pKa=8.5 for 5lof. All reported data are in kcal mol^{-1}.