High throughput re-scoring of docking hit-list using MD Simulation and MM/PBSA method through open source packages

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Virtual screening through docking is one of the important computational tools for the identification of the lead molecules. Major drawback of docking methods concerns the application of scoring functions that largely fail to estimate ligand binding energies in reasonable agreement with experiments and docking techniques still lack reliable simulation of the flexibility of both ligands and receptor. Also the presences of water molecules which may play an important role in the complex formation are ignored during docking process. In the recent years, MM/PBSA combined with the molecular dynamics (MD) simulations has emerged as a fast and approximate method for the calculation of binding free energy [1-2]. This approach is employed in the re-scoring of the docked complex to remove false positives obtained from the docking methods [3]. GROMACS is one of the most widely open source MD simulation package but it does not include the implementation of the MM/PBSA method. Also, protein – ligand simulations could be performed through this package using AMBER force field, one of the most widely used force field for proteins. In this work, we implemented MM/PBSA methods through GROMACS and APBS where former was used for the MD simulations and later was used for Poisson-Boltzmann calculation. Variants of PB solvation and SA parameters have been used to compare the results for achieving high correlation between predicted and experimental results. Large data-sets are needed to be validated to show high throughput capability of this implementation and also, there are lot of scope for the optimization of the entire protocol and the method. Therefore, the whole method is implemented using a perl script written in-house and validated on the HIV Protease I with inhibitors that have a broad K_i range. After optimization, good correlation was obtained between calculated relative binding energy and the experimental $logK_i$ values. This optimized method is used to re-score the docked complexes of DHDP (DiHydroDiPicolinate) reductase, a key enzyme of Diaminopimelate pathway of *M. tuberculosis*. Docked complexes of some other known *M. tuberculosis* target are also re-scored which clearly discriminate between active and in-active compounds from docking hit-list. Re-scoring of top ranking inhibitors from docking experiments by MM/PBSA can be used as a filter to more accurately select molecules for experimental validation.

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