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Performance evaluation of structure based and ligand based virtual screening methods on ten selected anti-cancer targets

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ABSTRACT

Virtual screening has become an important tool in drug discovery process. Structure based and ligand based approaches are generally used in virtual screening process. To date, several benchmark sets for evaluating the performance of the virtual screening tool are available. In this study, our aim is to compare the performance of both structure based and ligand based virtual screening methods. Ten anti-cancer targets and their corresponding benchmark sets from 'Demanding Evaluation Kits for Objective In silico Screening' (DEKOIS) library were selected. X-ray crystal structures of protein–ligand complexes were selected based on their resolution. Openeye tools such as FRED, vROCS were used and the results were carefully analyzed. At EF1%, vROCS produced better results but at EF5% and EF10%, both FRED and ROCS produced almost similar results. It was noticed that the enrichment factor values were decreased while going from EF1% to EF5% and EF10% in many cases.

Anti-cancer drug discovery is the main focus of many pharmaceutical industries. Several new biomolecular targets are being discovered due to increasing insights in molecular biology and genetics.[1,2] Among the targets identified, kinases are popular anti-cancer targets because they are druggable. According to the recent report,[3] the world market for anti-cancer kinase inhibitors will reach $18.5 billion in 2014. Despite the continuous efforts in the discovery and development of novel drug molecule, cancer is still a highly challenging disease.

Virtual screening and other computational methods play an important role in drug discovery processes.[4–6] Virtual screening methods are inexpensive because they do not use the chemicals and other experimental procedures which are involved in high throughput screening processes in drug discovery. From the collection of large library of compounds, it is possible to select a limited set of compounds. In the literature, there are impressive numbers of successful applications of such methods reported.[7,8]

Numerous software tools have been developed for the purpose of virtual screening. Virtual screening tools are often evaluated for their ability to enrich the fraction of the active ligands from the set of both active and decoys. The benchmark sets usually consist of known actives and for each actives a set of small decoys or inactive. To date, many benchmark sets are made available publically. One of the well-known benchmark set is Directory of Useful Decoys (DUD), a publically available data set of about 100 000 compounds distributed over 40 protein targets. The DUD set has the ligand decoys ratio of 1:36. Decoys are physically similar but topologically different to that of each active ligand.[9]

Maximum Unbiased Validation (MUV) data set[10] is another benchmark set which includes PubChem experimental data. Very recently 'Demanding Evaluation Kits for Objective In silico Screening' (DEKOIS) library[11,12] are made available. In this report, we present a comparative study of performances of both structure-based and ligand-based virtual screening approaches using openeye tools such as FRED and vROCS.

Ten anti-cancer targets were selected form DEKOIS library. Among them, seven targets belong to kinase family. They are RAC-alpha serine/threonine-protein kinase (PKB), Aurora A kinase, B-Raf, PI3-kinase gamma, pim-1, Rho-associated protein kinase-1 and vascular endothelial growth factor rec.2. Two targets belong to histone deacetylases and the other target was p53-binding protein MDM2.

Analysis and the selection of X-ray structures of protein–ligand complexes (Table 1) for the selected targets were done. Receptor grid was generated using the highest resolution structure. For the above mentioned targets, both active ligands and decoys were obtained from the web page.[12] Active ligands and decoys were mixed together[13] and were subjected to conformational analysis[14] using Omega2 program. Crystal structures of highest resolution were selected to generate receptor grids. Multiple conformers of

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