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Virtual Screening in Drug Discovery, A Topic between Believe and Reality?

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Drug discovery and development is a mission of pharmaceutical companies to take the path from understanding a disease to bring a safe effective new treatment to patients. Drug design (VS) plays a main role of this mission, paving the way for the science of synthetic chemistry that opens a wide gate for the application of other sciences e.g. pharmacology, biochemistry, toxicology, etc. All these parameters need optimization for novel chemotype [1]. Virtual Screening (VS) in drug design is a complementary approach to HTS as it rapidly identifies potential interactions between compounds and target, select most promising compounds for experimental screening and help in the design of target specific libraries. Drug discovery field depends on the use of many data bases that include millions of compounds. Here, calling for computational aid being a must instead of rigorous testing all of these compounds using traditional wet-lab methods [2]. Drug discovery could be accelerated and made less expensive by employing computational methods. Considering that the process of obtaining a drug candidate consists of several steps each of which has different time and technology requirements [3]. So, no one can ignore the time saving and cost effectiveness achieved by using virtual screening technique compared to laboratory experiments [4-7]. Based on the previous facts, open access to the numerous scientific sites and journals is considered a pivotal tool for drug designers as many data bases of growing chemical structures, drug candidates and enzymes will be needed e.g. Zinc [2] and PDB. Further they will need different software programs that handle docking and pharmacophore generation and so on. Evaluation of drug likeness of small molecule is important tool of virtual screening. It will diminish the failure of the drug candidates in the clinical trials. This failure may be not related to the potency against intended drug target, but due to Pharmacokinetic & toxicity issues. So, VS not only provides a drug like molecules but also explores the profile of its absorption, distribution, metabolism, e xcretion and toxicity (ADMET) [8-14].

Three virtual screening or computational methods are used in the modern drug discovery process: Molecular Docking, Quantitative Structure-Activity Relationships (QSAR) and Pharmacopoeia Mapping [15]. The choice of a particular method is often dictated by the level of information e.g. with respect to structural data and economic restraints on computing resources [16]. The main streams of virtual screening are Ligand based virtual screening and structure-based virtual screening. Ligand based virtual screening LBVS is based on "the similarity principle" that states that similar molecules tend to have similar biological properties [17,18]. Structure based virtual screening SBVS relies on docking and scoring to provide potential candidates for further analysis [19] using many docking programs e.g. AutoDock [20], DOCK [21], FlexX [22], FRED [23], GOLD [24] and ICM [25]. Also, the success of a docking is often compromised by the fact that the associated scoring functions often cannot resolve the most likely binding mode [26-28]. This highlights the importance of inspecting multiple conformations for the docked compounds and not only the highest scoring one. The main point here is how much virtual screening is convenient to reality? To answer this question one must consider false positive and negative data. Many researches explored such problems [27] that could be avoided with improving the effect by synergistic combination of pharmacophore and docking approaches e.g. pharmacophore post filtering technique [27,29,30]. Further, the success of a virtual screening campaign can be assessed with several parameters e.g. enrichment factor (EF) [27]. This factor (EF) which is defined as how efficiently known actives can be differentiated from random and pharmaceutically similar 'decoy' compounds and is a common method for evaluation of high throughput docking HTD programs [29].

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