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# Virtual Screening Strategies and Application in Drug Designing

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## Introduction

Remarkable progress, has been made during the past few years, in almost all the areas concerning with drug design and discovery, although it is a complex process, involving the application of many different fields of knowledge. Drug design, discovery and development are thought as an intense, lengthy and interdisciplinary endeavor. Drug design, sometimes referred to as rational drug design or more simply rational design, is the inventive process of finding new medications based on the knowledge of a biological target.

Structure-based drug design is clearly becoming a valuable and integral part of the drug discovery, and is perhaps the most elegant approach for discovering compounds exhibiting high specificity and efficacy. At the present time, a number of recent successful drugs have in part or in whole emerged from a structure-based research approach. Understanding the molecular basis of a drug action and exploring the chemical interactions involved in the complex processes of drug delivery and reaction with a variety of biological molecules are among the most important goals of contemporary drug design.

A major breakthrough in lead identification in the recent years occurred with the availability of fast and cheap computers on one hand and commercially available databases of compounds with more than a million small molecules, on the other. With the exponential rise in the number of viable novel drug targets, computational methods are being increasingly applied to accelerate the drug discovery process. This resulted in Virtual Screening (VS) technologies using *in silico* (computer-aided molecular drug design and chemo-bioinformatics) techniques, such as, high throughput docking, homology searching and pharmacophore searches of 3D databases. VS, has become an integral part of the drug discovery process. The generic definition of VS is significantly wide and may encompass many different methods. It is perhaps the cheapest way to identify a lead and several cases have already proven successful using this technology.

The dominant technique for the identification of new lead compounds in drug discovery is the physical screening of large libraries of chemicals against a biological target. This conventional experimental method like High Throughput Screening (HTS), continues to be the best method for rapid identification of drug leads. HTS identifies lead molecules by performing individual biochemical assays with over millions of compounds. However, the huge cost and time consumed with this technology has lead to the integration of cheaper and effective computational methodology, namely Virtual High Throughput Screening (vHTS), which is an established computational screening method to identify drug candidates from large collection of compound libraries. vHTS is widely applied to screen *in silico* collection of compound libraries to check the binding affinity of the target receptor with the library compounds. This is achieved by using a scoring function which computes the complementarity of the target receptor with the compounds. This computational screening of databases has become increasingly popular in the pharmaceutical research.

Nowadays, the identification of small molecule inhibitors are sought in order to develop molecules useful for the treatment of most diseases. The chemical leads are small potential drug-like molecules, which are capable of modulating the function of the target proteins that are further optimized to act as a therapeutic drug against a targeted disease.

In recent years, as the structures of protein drug targets has increased exponentially, due to advances in genomic and molecular biology techniques, such as crystallography, NMR and bioinformatics, vHTS methods have brought a major drive in the computational approach to use the structure of the protein target as a route to discover novel lead compounds. Nevertheless, the virtual screening of millions of compounds using docking software, for example, is still time consuming even with high-throughput methods. On the contrary, alternative approaches as de novo drug design use search strategies to efficiently explore the chemical space without a full enumeration. vHTS methods include virtual screening, de novo design and fragment based discovery. VS and de novo drug design play an important role within the pharmaceutical industry in lead discovery process. The routes for the VS go back to the structure-based drug design and molecular modeling. Although this technique is essentially based on concepts that have been used for many years by those in molecular modeling, the introduction of more powerful computers has paved the way for the virtual screening of ever growing databases of compounds. Moreover, not only real compounds but also purely theoretical ones can be included in the virtual library and screened *in silico*. This is a very powerful feature that allows purchasing or synthesizing only a reduced set of selected compounds thus reducing the cost and time of the entire study significantly.

VS uses computer based methods as a tool to discover new ligands on the basis of biological structure. This approach refers to computational screening of large libraries of chemicals for compounds that complement targets of known structure which could be tested experimentally. Virtual screening methods are divided into structure-based screening (protein-ligand docking) and ligand-based (e.g. similarity, pharmacophore searches) screening using active compounds as templates (ligand based virtual screening). Ligand-based screening techniques mainly focus on comparing molecular similarity analyses of compounds with known and unknown moiety, regardless of the methods of the used algorithm. Docking is a computational tool of structure based drug design to predict protein ligand interaction geometries and binding affinities.

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VS field recently had important successes: new ligands have been predicted along with their receptor-bound structures- in several cases with hit rates (ligands discovered per molecules tested) significantly greater with high-throughput screening.

De novo design is a complementary strategy for inhibitor discovery. By using the structural features present within the protein only, new inhibitor designs can be built-up sequentially according to the requirements of the targeted binding site. Contrary to virtual screenings used to mine in-house and commercial collections, de novo design can create molecules that do not exist in known compound databases.

Fragment based discovery is based on the premise that most ligands that bind strongly to a protein active site can be considered as a number of smaller fragments or functionalities. Fragments are identified by screening a relatively small library of molecule (400-20,000) by X-ray crystallography, NMR spectroscopy. These structures of the fragment binding to the protein can be used to design new ligands by adding functionality to the fragments or by incorporating features of the fragment onto existing ligands.

VS is cost-effective and reliable technique that can be applied to identify potential leads and avoid undesirable compounds that would otherwise result in expensive and time consuming experimental methods. It should be noted that experience and knowledge about the target are very crucial in identifying true positives in such experiments. Even with its current limitations, virtual screening accesses a large number of possible new ligands, most of which may then be simply purchased and tested. Therefore, VS is a useful and promising tool for modern computer-assisted drug discovery and design.