

## Editorial

### Structure-Based Virtual Screening

Development of a successful drug is the result of a combination of biological activity and drug-like properties. Both features can be estimated by *in silico* methodologies in the initial stages of drug discovery and development. Application of molecular docking simulations to scan a library of small-molecules to identify a potential inhibitor for a protein target is a methodology referred to as structure-based virtual screening (SBVS). This computational methodology has been employed in pharmaceutical research and development for over thirty years [1]. Application of SBVS opened the possibility to test millions of small-molecules compounds against important targets for drug design. This computer simulation process involves using known three-dimensional structure of a protein target to identify potential ligands [2-4]. The main requirements for SBVS are the following: 1) Availability of three-dimensional structure of a validated protein target [5], 2) a virtual library of small molecules to be used in the screening process [6], and 3) an efficient molecular docking algorithm to predict protein-ligand complex. Further steps may be added to include molecular dynamics simulations in order to evaluate protein-ligand interaction using a more robust and accurate methodology [7-9].

Molecular docking is a computer simulation approach able to predict the structure of a receptor-ligand complex, where the receptor is a protein target [10]. It can be defined as a simulation process where a ligand position is determined in a predicted or pre-defined binding site. Molecular docking simulation is capable of reproducing experimental data through docking validation algorithms (redocking), where protein-ligand or protein-protein conformations are obtained *in silico* and compared to structures obtained from X-ray crystallography or nuclear magnetic resonance. It has been shown for a large number of drug targets that the detailed structure of the protein, as obtained from experimental techniques, can be used to design or modify the structure of a small molecule docked to the target structure [2]. Most of the drugs act *via* non-covalent interactions. Therefore, methods to evaluate such interactions are necessary.

The present volume of *Current Drug Targets* brings reviews focused on recent development of structure-based virtual screening methodologies, including reviews on modern computational approaches to molecular docking and evaluation of ligand binding affinity, application of molecular docking to identify new drugs. Special attention is devoted to state-of-art methodologies dedicated to molecular docking simulations. There is also a review focused on *de novo* protein design, also referred to as the inverse protein folding problem, which is the determination of an amino acid sequence, or a set of sequences, that will fold into a given three-dimensional protein template, and its application to four protein systems. This methodology has a broad spectrum of applications, from enhanced design of inhibitors and new sequences with better stability to the design of catalytic sites of enzymes and drug discovery [11].

One key point in the development of docking algorithms is the accuracy of docking simulation. The accuracy may vary depending on what target is being tested and what kind of molecules composes the screening library. Highest speed and highest accuracy are ideal, although opposite features for virtual screening through docking simulations. Methods which are more complex, considering many physicochemical and thermodynamic properties tend to present higher accuracy. However, these methods consume more CPU time. This is exactly the case when we use molecular dynamics simulations to evaluate ligand-binding affinity [7-9]. Likewise, methods which take into account simpler parameters, such as evolutionary algorithms, are able to predict docking conformations in fast speed, however at lower accuracy rate. Recent developments in the application of evolutionary algorithms [12,13] to docking will be reviewed in this volume. We may define evolutionary algorithms as a group of computational approaches based on the concepts of Darwin's theory of evolution that are designed to find optimal solution to problems [14]. Regardless of its definition, evolutionary algorithms are heuristic algorithms. They tend to find the best or one of the best solutions, but they can also be trapped in the local optimal solutions, unable to find the global best result. We can say that in evolutionary algorithms, the evolutionary course is simplified, and consequently it has very little in common with genuine world evolution.

Furthermore, applications of structure-based virtual screening to identify new lead compounds for protein targets are also discussed. Important protein targets such as, cyclin-dependent kinase 2, purine nucleoside phosphorylase, shikimate kinase, human immunodeficiency virus 1, ubiquitin specific protease 7, and influenza A neuraminidase are reviewed here.

Several recent applications of SBVS have identified new drugs, which serve as incentives for the development of new methodologies and also for extending the application to a wide range of protein targets and diseases [14-22]. In conclusion, one of the most defying challenges in the post-genomic era is the understanding of structural features of the protein-drug interaction. Information obtained from structural studies of protein targets [23-30] together with molecular docking simulations will pave the way for discovery and development of a new generation of drugs.

Finally, I would like to express gratitude to the authors for their important contribution to this special issue, which hopefully will be of value to researchers dedicated to structure-based virtual screening projects.

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