MOLECULAR DOCKING IN DRUG DISCOVERY

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Nowadays, computer modeling methods including virtual screening methodologies are widely used in drug discovery being implemented into the early stages of potential biologically active compounds construction [1]. Molecular docking is one of the most powerful and successful tools for the virtual screening which has been used since the early 1980s. As the structure-based method molecular docking provides the possibility to predict the interaction between the target protein and the ligand, as well as to estimate the energy of their binding, thereby determining the stability of the formed complex.

The main scope of in silico methods application in drug development process is to evaluate a biological effect of a drug candidate based on the binding ability of a ligand towards a specific site of a target protein involved in the development and / or pathogenesis of a disease [2]. Thus, molecular docking, on the one hand, searches for the optimal orientations and conformations of the ligand molecule relative to the receptor protein, and, on the other hand, determines the binding sites of the target protein - the sites of the molecule where docking with the ligand is possible. Moreover, molecular docking possess other predictive functions: it`s also possible to predict the side effects of the investigated drug candidates according to the principle of complementarity of the ligand and the biological target. In polypharmacology molecular docking may be applied for the identification and optimization of pharmaceutical agents which modulate a set of targets simultaneously involved into a certain pathological process or disease. Another major function of molecular docking is ligand-protein binding evaluation and scoring [3]. Different types of scoring functions are implemented into docking software which allows to calculate the approximate energy of the ligand-target complexes, the heat effect and entropy change for the ligand-protein interaction, and to rank the various suitable conformations of the ligand at the binding site to determine the most likely orientation or, if several different ligands are compared, which one has the greatest affinity for the target protein. At this stage, a large number of difficulties arise, since the scoring functions are not always accurate enough due to the occasional errors in the modeling of the complex structure as well as the unsatisfactory accuracy of the free binding energy estimation. During molecular docking many factors must be taken into account: intra- and intermolecular interactions, electrostatic effects, electrodynamic and steric factors, non-valence interactions, the specificity of ligands and targets, the nature of the solvent and many others which greatly complicates an accurate docking procedure. Nevertheless, molecular docking was implemented in a large number of studies which were carried out and aimed at determining the effectiveness of drugs from various pharmacological groups.

Currently a vast number of computer programs were developed for docking and a tremendous amount of researches report the docking results as the background for novel drug candidates design. Most docking algorithms deal satisfactorily with the positioning of the ligand in the binding site of the protein target, which is an important tool in pharmaceutical research. The most widely used software for rigid and flexible molecular docking include

Molecular Operation Environment (MOE) package, Molegro Virtual Docker, AutoDock and AutoDock Vina, FRED as a part of OpenEye Scientific package, GOLD and others.

With the current spread of the novel coronavirus (SARS-CoV-2), the discovery of antiviral drugs is of great importance [4]. AutoDock Vina was reported as a software being used to screen potential drugs by molecular docking with the structural and non-structural protein sites of the coronavirus. The common antiviral drugs ribavirin, remdesivir, chloroquine and luteolin were under this study. In traditional Chinese medicine, honeysuckle is supposed to possess antiviral effect. In the reported research, it was found that luteolin (the main flavonoid of honeysuckle) binds with high affinity to the same regions of the main protease SARS-CoV-2 as the control molecule. Chloroquine has been shown to be clinically effective and can bind to a main protease which may be the assessed as the drugs antiviral mechanism. It has been determined that interaction with a basic protease may play a key role in the fight against viruses.

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