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Editorial Open Access

Success, Limitation and Future of Computer Aided Drug Designing

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Editorial

Application of computer in drug discovery has marked a revolutionary change in process of drug designing. Initially, drug designing process was time-taking, laborious and costly, and has high risk of failure. But, now the drug discovery process has become reliable, accurate and cost effective due to availability of large amount of genomic and proteomic information, application of tools for modeling, ligand designing, pharmacophore mapping, protein-ligand simulation, molecular descritpors and toxicity prediction. With the advent of high computational systems and use of high performance approaches and algorithms, now it become easy to solve biological problem in a short time with a higher accuracy. Computer aided drug designing is an alternative to high throughput screening provide the structure of drug target is known. X-ray crystallography and NMR verified protein 3-D structures are increases very rapidly which provides the basis for structure based drug designing. These proteins can be used as a drug target to design potential ligand/inhibitor that can best fit in binding site of protein. Structure of the target in the presence of a ligand provide important insight into the geometric fit of ligand into the binding site, low-energy conformation, ideal molecular electrostatic potentials, the presence of charged and/or neutral hydrogen bonds between functional groups, and hydrophobic interactions between lipophilic surfaces [1]. With the advent of new technologies a large number of natural leads are also being discovered day by day. A computational method helps in in silico design and evaluation of a large number of chemical compounds to identify potential lead candidates that can be synthesized and tested. Further, process of lead optimization not only increasing the dimension of search space for potential inhibitor, but also reduces the risk of toxicity as most of the leads are natural. Novel compound can be assembled in silico by de novo generation, but they need to be synthesized practically in the laboratory. Combinatorial chemistry and high-throughput screening methods has speed up the process of drug discovery by synthesizing and screening thousands of thousands of new compounds. No doubt, these methods generate a large number of new candidate drugs and are a milestone in drug discovery. However, all these candidate drugs are not successful in clinical trial because of high molecular weight, lipophilicity, toxicity, low absorption, distribution, metabolism excretion (ADME) and nonspecific binding.

Success of computer aided drug designing depends on the accuracy of modeled structure, accuracy of tools used for predicting binding site, performance of docking algorithms, correctness in mapping the pharmacophore, accuracy of energy minimization and simulation algorithms, reliability of ADME and toxicity prediction tools as well as on synthetic feasibility of designed inhibitor or drug. Selection of drug target also decides the success and failure of drug discovery. Drug target should be unique: no other pathway should be able to supplement the function of target, as well as it should be able to be inhibited by a small molecule. Proteomics provides detailed information about structure, function, expression level and sub cellular location of proteins and also helps us in understanding the mechanism of disease as well in finding the new drug target. There are many stories related to success of rational drug designing. Captopril, Dorzolamide, Saquinavir, Zanamivir, Oseltamivir, Aliskiren, Boceprevir, Nolatrexed, and Rupintrivir are the examples of structure based drug designing. Free availability of a large number of drugs like compounds in drug databases also supports and encourages the drug designing process. Biological system is highly flexible and governed by so many significant parameters. Due to certain limitations, it is not possible to copy and simulate the entire real biological system on computer system. But efforts are being made to add as many as parameters possible. Proteins and ligand molecules are highly flexible in solution due to conformation changes. Therefore, designing an inhibitor or drug molecule keeping in mind a single, rigid structure may lead to wrong result. Docking tools provide enough flexibility to the ligand, and no or limited flexibility to the residues present near binding site of protein. On the other hand, considering the complete molecular flexibility increases the space and time complexity of computation [2]. The effect of water molecules and other solvent should be properly incorporated into docking algorithm. A biggest remaining challenge in the drug discovery is to consider target flexibility. Toxicity prediction model helps in assessing the toxicity of drug candidate to liver, kidney, heart, lung and other organs. In order to generate a pharmacological effect, a candidate drug must reach to target by passing various physiological barriers, such as the gastrointestinal barrier, the blood–brain barrier and the microcirculatory barrier. Lack of reliable experimental data and parameters related to ADME and toxicity limits the accuracy of prediction models. It is also interesting to note that only 40% of drug candidates in clinical trial get approval for large scale synthesis and marketing. There is also a risk that a potential, safe and biologically active drug candidate has not been considered by predictive computational model. Accuracy of these predictive models can be further improved by adding more reliable data and significant parameter related to toxicity. There is a need to design a high quality database for drug designing that should contain information about mechanism of a specific disease, genomic and proteomic data, potential drug targets, natural leads, physicochemical properties, Pharmacophore, QSAR and ADMET models, previous efforts made in drug discovery, success/failure, clinical trial data, efficacy and side-effects. Drug designing is an art, but the application of computer will play a major role in the attempts to make it more rational and successful in the future. Extensive use of computational approaches with higher accuracy could reduce the overall cost and failure of drug designing.

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