Journal of Global Biosciences
ISSN 2320-1355
Volume 8, Number 4, 2019, pp. 6137-6145
Website: www.mutagens.co.in

Research Paper

DYNAMICS OF BIOINFORMATICS IN THE ARTIFICIAL DESIGNING OF DRUGS

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Abstract

The objective of drug design is to find a chemical compound that can fit to a specific cavity on a protein target both geometrically and chemically. After passing the animal tests and human clinical trials, this compound becomes a drug available to patients. The conventional drug design methods include random screening of chemicals found in nature or synthesized in laboratories. The problems with this method are long design cycle and high cost. Modern approach including structure-based drug design with the help of informatic technologies and computational methods has speeded up the drug discovery process in an efficient manner. Drug discovery and development is a complex, high risk, time consuming and potentially highly rewarding process which requires an interdisciplinary effort to design effective and commercially feasible drugs. Pharmaceutical companies are spending millions of dollar per drug to bring it to the market. The development of a new drug requires a technological expertise, human resources and huge capital investment. It also requires strict adherence to regulations on testing and manufacturing standards before a new drug comes into market and can be used in the general population, in fact, some time it fails to come into market. All these factors just increase the cost for a new chemical entity research and development. Bioinformatics in drug designing process made positive effect on overall process and can accelerate various steps of drug designing, and reduce the cost and over all time. Current note focuses on the role of bioinformatics in drug discovery and development process.

Key words: Dynamics**,** Bioinformatics; Drug designing, Computational technology, Discovery.

INTRODUCTION

The design of a new drug is an incredibly difficult and frustrating task. If it weren't for the potential to earn equally incredible profits, the massive costs and aggravation over failed experiments would dissuade any reasonable person from undertaking such a career. There is no one scientific technique used to design a new pharmaceutical product. It is instead a collaborative process in which every available technique, and a few more invented on the spur of the moment, are utilized in order to achieve the desired results. Drug discovery is the step-by-step process by which new candidate drugs are discovered (Chen and Chen 2008). Traditionally, pharmaceutical companies follow well-established pharmacology and chemistry-based drug discovery approaches, and face various difficulties in finding new drugs (Dhaliwal and Chen 2009). In the highly competitive ''winner takes all'' pharmaceutical industry, the first company to patent a new chemical entity (NCE i.e., new drug candidate) for a specific treatment takes all the spoils, leaving other competitors to mostly wait for patent expirations to partake in the largesse. Nowadays, therefore, Pharmaceutical companies invest heavily in all those approaches that show potential to accelerate any phase of the drug development process (Gane and Dean 2000). The increasing pressure to generate more and more drugs in a short period of time with low risk has resulted in remarkable interest in bioinformatics. In fact, now there is an existence of new, separate field, known as computer-aided drug design (CADD). Computational techniques play a valuable role in the drug design process(Gilbert et.al,2003). Computational Drug Design provides a solid description of those techniques and the roles that they play in the drug design process. This book covers a wide range of computational drug design techniques in an easily understood, nonmathematical format (Grabley and Thiericke 1999). The emphasis is on understanding how each method works, how accurate it is, when to use it, and when not to use it.

Drug design based on bioinformatics tools: The processes of designing a new drug using bioinformatics tools have opened a new area of research (Hecker et.al. 2012). However, computational techniques assist one in searching drug target and designing drug *in silico*, but it is time-consuming and expensive. Bioinformatics tools can provide information about potential targets that include nucleotide and protein sequencing information, homologs, mapping information, gene and protein expression data, function prediction, pathway information, disease associations, variants, structural

information and taxonomic distribution among others. This means that time, effort and money can be saved in characterization of different targets(Iskar et.al, 2012). The field of bioinformatics has become a major part of the drug discovery pipeline, playing a key role for validating drug targets. By integrating data from many inter-related yet heterogeneous resources, bioinformatics can help in our understanding of complex biological processes and help improve drug discovery.

Computerized drug design: Computational tools have become increasingly important in drug discovery and design processes. Methods from computational chemistry are used routinely to study drug-receptor complexes in atomic detail and to calculate properties of small-molecule drug candidates (Lindpaintner, 2002). Tools from information sciences and statistics are increasingly essential to organize and manage the huge chemical and biological activity databases that all pharmaceutical companies now possess, and to make optimal use of these databases. In addition, the act of generating chemical derivatives is highly amenable to computerized automation. Libraries of derivative compounds are assembled by application of targeted structure-based combinatorial chemistry from the analysis of active sites (Luscombe et.al, 2001). Because of the combinatorial nature of this method, a large number of candidate structures may be possible. A computer can rapidly generate and predict the binding of all potential derivatives, creating a list of best potential candidates. In essence, computer filters all weak binding compounds, allowing the chemist to focus, synthesize, and test only the most promising ligands (Manly et.al, 2000). Thus, using the CADD software to aid in the refinement of lead molecules is the most effective manner in which these tools can be employed. The use of computer modeling to refine structures has become standard practice in modern drug design. So the current role of computer in drug design lies in:

a) Storing and retrieving information-Structures determined experimentally by X-ray cryst allography for biological targets (enzymes) and drug molecules and Molecules and activities to test the affect of small structural changes on biological activity

b) Information about toxicity and its relationship to structure.

c) Visualization of molecules- Similarities/differences between drugs and receptors, Interaction between drugs and receptors and

d) Calculations- Interaction strengths and Motion (dynamics).

Challenges in computerized drug design: Highly intellectual professionals with interdisciplinary knowledge of various facets of science, most importantly, biology, chemistry and computation are required for CADD and this is a major challenge for this field. In scientific computing, accuracy and processing time are always important. Thus, in order to make the calculations in a finite period of time, a plethora of assumptions, significant approximations, and numerous algorithmic shortcuts has to be used (Meyers and Baker, 2001). This, in turn, greatly diminishes the calculated accuracy of any ligand receptor interaction. This remains the most significant challenge in CADD. Another problem is generation of a vast number of undesired chemical structures as there are a nearly infinite number of potential combinations of atoms and most of them are either chemically unstable, synthetically unfeasible or have higher toxicity (Podlogar et.al, 2001). Keeping in mind these shortcomings of CADD, improved generation of softwares with more user-friendly programs, superior and fast computational facilities, and creation of synthetic feasible and stable chemical compounds and with refinement feature has been developed in the last decade.

Identification of Drug Target: One of the major thrusts of current bioinformatics approaches is the prediction and identification of biologically active candidates, and mining and storage of related information (Simoens, 2011). Drugs are usually only developed when the particular drug target for those drugs' actions have been identified and studied. The number of potential targets for drug discovery process is increasing exponentially. Mining and warehousing of the human genome sequence using bioinformatics has helped to define and classify the nucleotide compositions of those genes, which are responsible for the coding of target proteins, in addition to identifying new targets that offer more potential for new drugs (Speck and Cordeiro, 2012). This is an area where the human genome information is expected to play a master role. Drug developers are presented with an unaccustomed luxury of choice as more genes are identified and the drug discovery cycle becomes more data-intensive (Whittaker, 2003). Bioinformatics allows the identification and analysis of more and more biological drug targets; thus expected to greatly increase the breath of potential drugs in the pipelines of pharmaceutical companies.

Validation of Drug Target: Bioinformatics also provides strategies and algorithm to predict new drug targets and to store and manage available drug target information. After the discovery of ‘‘potential’’ drug targets, there is an inappreciable need to establish a strong association between a putative target and disease of interest. The establishment of such a key association provides justification for the drug development process (Yamanishi et.al, 2010). This process, known as target validation, is an area where bioinformatics is playing a significant role. Drug target validation helps to moderate the potential for failure in the clinical testing and approval phases.

Cost Reduction: The current high cost of drug discovery and development is a major cause for concern among pharmaceutical companies. Along with increasing productivity, pharmaceutical companies also aim to reduce the high failure rate in the drug discovery process so that increased number of drugs able to hit the market. The high cost of various phases of clinical trials acts as limiting factors for number of drugs, which can be developed by pharmaceutical companies, and hence selecting the compounds with the best chances for approval is critical. The costs of drug discovery and development generally include total costs from discovery to approval though some studies have included the costs of failed drugs and the costs for commercialization. There is also a cost associated with the elongated process, beginning from discovery all the way to final approval. Advances in bioinformatics accelerate drug discovery process, beginning with drug target identification and validation (viz., Docking), to assay development, and virtual-high-throughput screening (v-HTS)-all with the goal of identifying new potential chemical entities. Bioinformatics provides more efficient target discovery and validation approaches, thus help to ensure that more drug candidates are successful during the approval process and making it more cost-effective.

Promote Emerging Drug Development There are some collateral costs that bother the pharmaceutical industry. These costs include commercialization costs, litigation and drug-recall costs, and general costs to society (Zhu et al, 2012). Commercialization costs for new drug to be about $250 million per approved drugs, are high mainly because most ‘‘new’’ drugs approved are essentially functional replicas of drugs that already exist. Most of the copycat drugs are being commercialized to handle the illness for which there are drugs already; thus, there is a need of interface that can attract the

attention of both physicians and patients who already have access to similar medication. Bioinformatics can act as proper interface, and provides new approaches and opportunities to pharmaceutical companies to efficiently discover potential drug targets and develop novel drugs. If drugs are not commercialized in competition with already existing equivalents, their commercialization costs are expected to fall significantly.

Factors affecting drug discovery: There are a number of factors that affect the drug discovery and development process. Important ones are as follows:

Medicinal objective: In general, more precise the medicinal objective, the less likely it is to develop a new drug; for example, it is easy to develop an antacid but much more difficult is to develop specific proton-pump inhibitor. Thus, the medicinal requirements affect the likelihood of success or failure in new drug discovery.

Ability of Medicinal chemist: The attributes of the chemist will influence the outcome of evolving new drugs on the basis of knowledge of chemistry of lead molecule and biology of diseased state.

Screening facilities: A successful and rapid mass screening mainly depends on the capacity to evaluate a large number of compounds and detect potentially clinically useful drugs in a very short span of time. *Drug development facility:* Good facilities with interdisciplinary efforts by chemistry, biology, pharmacy and medical groups are necessary for drug development.

Cost of new drug: The following three factors affect the cost of drug development-

(i) *Number of compounds synthesized*: Of the about 5000-10,000 compounds studied, only one drug reaches the market.

(ii) *Nature of the lead molecule*: Cost of production will be high if the lead molecule is prepared by an expensive route.

(iii) *Standards required for new drugs*: The standards required by cost will be cut by almost a third. The development times are reduced from 10-16 years to only 6-8 years.

Bioinformatics efforts did not make any impeccable changes in the drug discovery and development process. This may be because the practice of bioinformatics is relatively new and has only attained prominence in the years following the partial completion of

the Human Genome Project. Till now, bioinformatics has not made any considerable impact, as projected earlier, on the cost of drugs. The pharmaceutical industry continues to witness rising costs and withdrawals of drugs from the market after they had been approved and commercialized-because of multiple documented cases of adverse drug reactions. It has been observed that several pharmaceutical industries are facing drug discovery and development related challenges. These challenges range from high cost of drug discovery to the lengthy and risky trials and approval process, and some time, withdrawal of previously approved drugs from the market and the innovation gap resulting from the dogged quest for blockbuster drugs. Bioinformatics was widely projected to strengthen the identification of drug targets. The fact that these problems remain mostly unsolved, despite significant bioinformatics investments, is an indication of a larger problem.

CONCLUSION:

The development of new drugs with potential therapeutic applications is one of the most complex and difficult process in the pharmaceutical industry. Millions of dollars and man-hours are devoted to the discovery of new therapeutic agents. As the activity of a drug is the result of a multitude of factors such as bioavailability, toxicity and metabolism, rational drug design has been utopias for centuries. Very recently, impressive technological advances in areas such as structural characterization of bio macromolecules, computer sciences and molecular biology have made rational drug design feasible. CADD is no longer merely a promising technique. It is a practical and realistic way of helping the medicinal chemist. On its own it is unlikely to lead to pharmaceutical novelties but it has become a significant tool, an aid to thought and a guide to synthesis. Still, drugs that are synthesized and tested by the computational techniques, can contribute a clear molecular rationale and above all provide a spur to the imagination. Drug designing is a very complex, expensive and time consuming process. Bioinformatics provide a huge support to overcome the cost and time context in various ways. Bioinformatics provides wide range of drug-related databases and software, which can be used for various purposes, related to drug designing and development process. Bioinformatics is still in their developmental phase and presently facing some hurdles, they show enough potential to help drug development process in near future.

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