Research Paper

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In-silico approach to Contemporary Drug Discovery and Development process

Computer Science

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Bhagavati Parekh BCA & PGDCA College, Junagadh

ABSTRACT

Drug research and development (R & D) is a comprehensive, expensive, and time-consuming practice, and it is full of risk throughout the process. It contains a number of stages, each having its own importance and implications on the successful formation of any drug. In the last four decades, computational technologies for drug Research and Development have advanced very quickly, particularly in last few years with the unprecedented development of various disciplines which jointly provide sound and commendable platform for naval drug discovery. There are numerous CADD software, applicable at each stage of Drug Discovert to facilitate and accelerate the process in more efficient manner. Together with the increasing capacity for biological screening and chemical synthesis, more demands for large quantities of early information on Absorption, Distribution, Metabolism and Excretion are rising. The highly increasing need for the medium and high throughput in-vitro screens is the outcome of this changing requirement.

1. Drug Discovery Pipeline:

In the last four decades, computational technologies for drug Research and Development have advanced very quickly, particularly in last few years with the unprecedented development of biology, biomedicine, and bioinformatics applications. In the post genomic era, the dramatic increase in small-molecule and biomacromolecule information has induced the development and application of computational tools to almost every stage of drug Research and Development. This has greatly changed the strategy and pipeline for drug discovery[1]

Drug research and development (R & D) is a comprehensive, expensive, and time-consuming practice, and it is full of risk throughout the process[2]. Numerous new technologies have been developed and applied in drug R & D to shorten the research cycle and to reduce the expenses. Among them, computational approaches have revolutionized the pipeline of discovery and development[1].

1.1. Various stages of the pipeline and applications of *in-silico* techniques on each of them:

The drug discovery process contains a number of stages, each having its own importance and implications on the successful formation of any drug.

Drug discovery involves Different stages, which include: basic exploratory biology on target identification and validation; assay development; lead identification, which usually requires access to high-throughput screening; medicinal chemistry and pharmaceutical lead optimization; and drug candidate selection [3]. Continuous development in the field induces new and faster techniques to gear up the entire set of processes.

1.2 Various computational techniques applied on different stages:

Computational approaches are gaining considerable importance in the process of Drug design and discovery. The available range of software spans almost all stages in discovery and development pipeline, from target identification to lead discovery, from lead optimization to preclinical or clinical trials.

Sr.No.	Software	Functionality
1.	High Throughput Screening (HTS)	It is the method of scientific experimentation, used particularly in the drug discovery process. With the help of specialized software, robotics and sensitive detectors, it allows conducting millions of chemical/genetic/pharmacological tests with the high speed and accuracy.
2.	Virtual screening:	Virtual Screening basically focuses on designing and optimizing targeted combinatorial libraries and enriching libraries of available compounds from in-house compound repositories or vendor offerings.
3.	Molecular modeling:	The behavior of molecules can be modeled or simulated using computers under molecular modeling techniques. Complex calculations in the field of computational chemistry/biology, material science or drug discovery require atomistic level description of the molecular system.
4.	Sequence similarity searching:	This is the method for searching sequence databases by using the alignment to a query sequence. Once the statistical assessment of finding the similarity between the databases and query sequence is done, the homology can be inferred and the information can be transferred to the query sequence.
5.	Drug lead optimization:	This stage of drug discovery concentrates on adding new or more functionality to the compounds, which may thus result in an increase in the values of the physico chemical properties like molecular weight and number of hydrogen bonding groups.

1.3. Computer Aided Drug Design (CADD):

Pharmaceutical and biotech industries have witnessed increasing growth of CADD application software since the late 1980s. In the 1990s, the rapid development of small molecule combinatorial chemistry/parallel synthesis and the high-throughput screening (HTS) technologies spurred renewed interests in the quantitative structure-activity relationship (QSAR) technique.

As the process of drug discovery is quite lengthy and time consuming, various efforts to apply computational power are continuously employed to facilitate various stages of the process in order to streamline the successive steps of drug discovery, design, development and optimization. In biomedical arena, computer-aided or in silico design is adopted to accelerate and facilitate various processes like hit identification, hit-to-lead selection, optimize the absorption, distribution, metabolism, excretion as well as toxicity profiles.

The development of any potential drug begins with the determination of specific receptors (targets), which can be efficiently done using the multidisciplinary solution approach which combines the computational and automatic analytical power of computer and the underlying concepts of pharmaceutical sciences. Starting from this first stage, the computer aided applications extend to all the processes through the final drug outcome. Hence, CADD applications have spanned to almost all the stages of drug discovery pipeline.

Computer-aided drug design uses computational chemistry as a base line concept to study, discern and enhance drugs and related biologically active molecules with the most elementary goal to predict whether a given molecule will bind to a target and if so how strongly. To predict the conformation of the small molecule and to model conformational changes in the biological target, the basic theories of molecular mechanics or molecular dynamics are most often used. Semi-empirical, *ab initio* quantum chemistry methods, or density functional theory are often used to provide optimized parameters for the molecular mechanics calculations and also provide an estimate of the electronic properties (electrostatic potential, polarizability, etc.) of the drug candidate that will influence binding affinity.

Semi-quantitative prediction of the binding affinity might also be provided using the molecular mechanics methods. Also, knowledge-based scoring function may be used to provide binding affinity estimates. These methods use linear regression, machine learning, neural nets or other statistical techniques to derive predictive binding affinity equations by fitting experimental affinities to computationally derived interaction energies between the small molecule and the target[4][5].

1.2 Contemporary drug discovery and development:

1.2.1 The shift in drug discovery paradigm:

The process of drug discovery and development has undergone tremendous changes over past couple of decades. It isn't an old history, when the process of drug discovery was carried out in the sequential steps, wasting too much a time on the repetitive processes during lead selection and structure optimization.

Nevertheless, this paradigm has shifted today in several ways. The drug or compound is tested for its pharmacokinetic, metabolism or toxicity much earlier, even before the decision is taken to evaluate the compound in the clinic as shown below:

Today, the rate at which the biological screening data are obtained has increased enormously. The new High Throughput Screening (HTS) has blown the drug discovery and development regime to the new and greater extent. In response to these developments, a new discipline of chemistry – the Combinational Chemistry has emerged to feed this new thirst of research activities. The new and rapidly developing era of Combinational Chemistry, Chemoinformatics and other related disciplines form the interactive pool of knowledge; where from naval inputs to the research and discovery process are derived. Together with the increasing capacity for biological screening and chemical synthesis, more demands for large quantities of early information on Absorption, Distribution, Metabolism and Excretion are rising. The highly increasing need for the medium and high throughput in-vitro screens is the outcome of this changing requirement. In addition, there is an increasing need of good tools for predicting these properties to serve two main purposes:

Predicting the ADME as well as physicochemical properties at the design stage of compounds and compound libraries to reduce the risk of attrition at the later stage. Today, the 40% of the attritions rate of CDs is directly related to the poor PK profiles.

Optimizing the screening and testing processes by making available only potential and relevant candidates. These reliable screening factors are highly desirable to avoid the risk of late attrition.

1.3 Why to perform dissolution/solubility studies at early stage of drug discovery?

The oral absorption of a drug is the tandem process of the dissolution and the intestinal membrane permeation of a drug in the gastrointestinal (GI) tract. Therefore, low solubility, a low dissolution rate and low permeability, can all result in incomplete and variable oral absorption. The salt/solid form selection and the formulation studies start at the final stage of drug discovery, or in the early development stage. Since the discovery-development transition is practically irreversible, it is necessary to map out a successful strategy to achieve an acceptable dissolution profile during the discovery stage. Therefore, a comprehensive assessment of solubility and dissolution is required in drug discovery whether or not it can be improved in the later stages[6]

1.4 *in silico* approach to prediction of aqueous solubility:

Recent analytical studies have shown that in spite of increased investment in preclinical pharmaceutical research, the overall number of new drugs registered by regulatory agencies remained approximately unchanged over the last decade. It is estimated that the total preapproval cost of production of a new drug is in the range from US $800 million[2] to more than $1,7 billion dollars.

The first step in the drug absorption process is the disintegration of the tablet or capsule, followed by the dissolution of the active drug. Obviously, low solubility is detrimental to good and complete oral absorption, and so the early measurement of this property is of great importance in drug discovery[7] Reflecting this need, rapid, robust methods have been developed to efficiently measure the solubility of large numbers of compounds.

With advent of computational biology and combinatorial chemistry, numerous solubility prediction methods and models based on these methods have been developed. However, most of these models were developed based on statistical analysis. Such models are found to be less accurate and non-reliable in predicting diverse values. The variations lying in different chemicals belonging to diverse chemical spaces have greatly reduced the efficiency of models. However, the Empirical Methods for building predictive models of the relationships between molecular structure and useful properties are becoming increasingly important.

Conclusion:

In-silico methods help predicting various physiochemical properties of drugs at the early stage of its development process. The oral absorption of a drug is the tandem process of the dissolu-

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tion and the intestinal membrane permeation of a drug in the gastrointestinal (GI) tract. Therefore, low solubility, a low dissolution rate and low permeability, can all result in incomplete and variable oral absorption. The need of an hour is to develop naval computational software which can facilitate the prediction of important properties including solubility and absorption at the early stage of drug discovery and development.

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