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Pharmaceutical Applications of Insilico methods: A Review.

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Review Article

ABSTRACT

Conventionally, drugs were discovered by synthesizing compounds in a time-consuming multi-step processes against a battery of in vivo biological screens and further investigating the promising candidates for their pharmacokinetic properties, metabolism and potential toxicity. Sophisticated insilico approaches has given a tremendous opportunity to pharmaceutical companies to identify new potential drug targets which in turn affect the accomplishment and time of performing clinical trials for discovering new drug targets. The main goal of this review is to summarize the insilico methods in the areas of drug discovery process with emphasis on identifying drug targets, pharmacology and pharmacokinetics.

INTRODUCTION

The term 'insilico' is a modern word usually used to mean experimentation performed by computer and is related to the more commonly known biological terms in vivo and in vitro. The history of the 'insilico' term is poorly defined, with several researchers claiming their role in its origination. However, some of the earliest published examples of the word include the use by Sieburg and Danchin et al. In a more recent book, Danchin (2002) provides a quotation that offers a concise and cogent depiction of the potential of computational tools in chemistry, biology and pharmacology [1].

Insilico methods are a new development in chemical testing that relies on computer simulation or modelling. Results from existing tests are used to model the ways in which a chemical may be hazardous in the body and/or in the environment. In this way the toxicity of a particular chemical used in a particular setting can be predicted and assessed without further tests on animals or living cells.

Insilico methods are widely used (including by regulators in the US) to screen and identify chemicals for priority testing in the laboratory. They are also used in addition to laboratory data to add another line of evidence or argument. For many scientists, the goal is also to replace and improve on animal tests.

In silico models are developed from existing data from laboratory tests, so a model can only be as reliable as the data it is based on. In silico methods are an inter-disciplinary area of work, in which models are developed by experts in chemo-informatics for use by toxicologists [2].

The pharmaceutical industry has a growing and pressing need for accurate and economical methods to identify new lead candidates and to optimize lead compounds during drug development [3]. In silico methods play an important role in this process. Common in silico methods include, but are not limited to, pharmacophore identification followed by searching against three-dimension (3D) structure database [4], virtual screening by docking small molecules into target enzyme for lead discovery, and quantitative structure activity relationship (QSAR) methods for lead optimization and absorption, distribution, metabolism, excretion and toxicity (ADME/Tox) prediction.

In silico methods can help in identifying drug targets via bioinformatics tools. They can also be used to analyze the target structures for possible binding/active sites, generate candidate molecules, check for their drug

likeness, dock these molecules with the target, rank them according to their binding affinities, further optimize the molecules to improve binding characteristics The use of computers and computational methods permeates all aspects of drug discovery today and forms the core of structure-based drug design. High-performance computing, data management software and internet are facilitating the access of huge amount of data generated and transforming the massive complex biological data into workable knowledge in modern day drug discovery process. The use of complementary experimental and informatics techniques increases the chance of success in many stages of the discovery process, from the identification of novel targets and elucidation of their functions to the discovery and development of lead compounds with desired properties [5].

Drug Discovery

Drug discovery and development is an intense, lengthy and an interdisciplinary endeavor. Drug discovery is mostly portrayed as a linear, consecutive process that starts with target and lead discovery, followed by lead optimization and pre-clinical in vitro and in vivo studies to determine if such compounds satisfy a number of pre-set criteria for initiating clinical development. Insilico approach has been of great importance to develop fast and accurate target identification and prediction method for the discovery.

There are five insilico methods in drug discovery. They are Molecular docking, Virtual High through put screening, QSAR (*Quantitative* structure-activity relationship), Pharmacophore mapping, Fragment based screening and which are discussed below.

Molecular docking

Docking is the computational determination of binding affinity between molecules (protein structure and ligand). Given a protein and a ligand find out the binding free energy of the complex formed by docking them. Docking or Computer aided drug designing can be broadly classified as "Receptor based methods" which make use of the structure of the target protein and "Ligand based methods" which is based on the known inhibitors.

Virtual High Throughput Screening

Virtual screening is a computational method where large libraries of compounds are assessed for their potential to bind specific sites on target molecules such as proteins, and well-matched compounds tested. Virtual screening (VS) is a computational technique used in drug discovery research. By using computers, it deals with the quick search of large libraries of chemical structures in order to identify those structures which are most likely to bind to a drug target, typically a protein receptor or enzyme [6].

Walters, *et al.* define virtual screening as "automatically evaluating very large libraries of compounds" using computer program [7]. As this definition suggests, VS has largely been a numbers game focusing on questions like how can we filter down the enormous chemical space of over 1060 conceivable compounds [8] to a manageable number that can be synthesized, purchased, and tested. It is less expensive than High Throughput Screening, Faster than conventional screening, scanning a large number of potential drugs like molecules in very less time.

QSAR (Quantitative structure-activity relationship)

QSAR is statistical approach that attempts to relate physical and chemical properties of molecules to their biological activities. The aim of QSAR is the prediction of molecular properties from their structure without the need to perform the experiment using invitro or invivo. It saves times and resources [5]. Various descriptors like molecular weight, number of rotatable bonds Log P etc. are commonly used. Many QSAR approaches are in practice based on the data dimensions. It ranges from 1D QSAR to 6D QSAR. The methods called quantitative structure-activity relationship (QSAR) are based on the assumption that the activity of a certain chemical compound is related to its structure.

Sometimes it is said that QSAR models represent a way for industry to spend less for toxicological research, or can be used to save animals to be used for experiments. The real challenge is not to identify the best method to protect human beings and environment [9].

Pharmacophore mapping

It is the process of deriving a 3D pharmacophore. A pharmacophore is a set of features together with their relative spatial orientation that are thought to be capable of interaction with a *particular* biological target such as Hydrogen bond donors and acceptors, positively and negatively charged groups, hydrophobic regions and aromatic ring.

A Pharmacophore map can be generated by superposition of active compounds to identify their common features. Based on the pharmacophore map either de novo design or 3D database searching can be carried out. Frequently small molecules with very different 2D structures displace each other from a binding site on macromolecules. The goal of pharmacophore mapping is to transform such 2D structure-activity information into the 3D requirements for binding to the target biomolecule. A pharmacophore features include hydrogen bond acceptor atoms, hydrogen bond donor atoms, hydrogen bond donor site, hydrogen bond acceptor site, and hydrophobic centers.

Pharmacology

Pharmacology over the past 100 years has had a rich tradition of scientists with the ability to form qualitative or semi quantitative relations between molecular structure and activity in cerebro. To test these hypotheses they have consistently used traditional pharmacology tools such as in vivo and in vitro models. Increasingly over the last decade however we have seen that computational (in silico) methods have been developed and applied to pharmacology hypothesis development and testing. These in silico methods include databases, quantitative structure-activity relationships, pharmacophores, homology models and other molecular modeling approaches, machine learning, data mining, network analysis tools and data analysis tools that use a computer.In silico pharmacology (also known as computational therapeutics, computational pharmacology) is a rapidly growing area that globally covers the development of techniques for using software to capture, analyse and integrate biological and medical data from many diverse sources. More specifically, it defines the use of this information in the creation of computational models or simulations that can be used to make predictions, suggest hypotheses, and ultimately provide discoveries or advances in medicine and therapeutics.Computational or in silico methods [1] are helping us to make decisions and simulate virtually every facet of drug discovery and development moving the pharmaceutical industry closer to engineering-based disciplines. Development of in silico pharmacology through the development of methods including databases, quantitative structure–activity relationships, similarity searching, pharmacophores, homology models and other molecular modelling, machine learning, data mining, network analysis tools and data analysis tools that use a computer.

Different methods

Descriptor-based methods.
Knowledge-based approaches
Rule-based methods.
Virtual ligand screening
Ligand-based method
Target-based methods.
Virtual affinity profiling

Drug discovery

In silico methods are widely used in drug discovery to identify potential leads for further experimental evaluation. The methods range from the simple Lipinski's-rule-of-five type of approaches [9] docking, pharmacophore searching on database, to supervised and unsupervised clustering/classification and QSARs. Success is achieved if a few good leads ultimately survive to the drug development stage. A recursive process combining screening assays and in silico modeling has become prevalent throughout much of the pharmaceutical industry. In lead discovery, the process has been called sequential screening [10]. The process starts with assay data for an initial set of compounds from an existing compound library. The resulting data for active compounds, and sometimes for inactive compounds, are then used for initial in silico modeling. The resultant model can be used to identify potential leads in many ways, such as searching a library of existing compounds or assisting in the design of a virtual combinatorial library. The identified potential lead compounds are assayed, and these data are then used to refine the model. In this process, the speed and efficiency of the in silico method is important to enable rapid modeling and provision of new leads for synthesis. Depiction of the sequential screening process is now prevalent in the pharmaceutical industry where in silico modeling and prediction are integral to the process. The output of the process is drug leads that may be further developed. 347 Decision forest for lead discovery outperforms most classification methods in speed and efficiency for model development, refinement and in screening large databases. This is, in part because only 2D descriptors are sufficient to ensure a high quality model. Of course, any type of molecular descriptors, compound properties or even other related biological properties can also be used in decision.

Pharmacokinetics

Computer-based methods are slowly gaining ground in this area and are often used as preliminary criteria for the elimination of compounds likely to present uninteresting pharmacokinetic profiles and unacceptable levels of toxicity from the list of potential drug candidates, hence cutting down the cost of discovery of a drug. The fact that more and more drugs fail to enter the market as a result of poor pharmacokinetic profiles, has necessitated the inclusion of pharmacokinetic considerations at earlier stages of drug discovery programs [11,12]. Computer-based methods have been employed in the prediction of ADMET properties of drug leads at early stages of drug

discovery and such approaches are becoming increasingly popular [13,14]. The rationale behind in silico approaches are the relatively lower cost and the time factor involved, when compared to standard experimental approaches for ADMET profiling [15,16,17]. A molecular descriptor may be defined as a structural or physico-chemical property of a molecule or part of a molecule, for example logarithm of the noctanol/ water partition coefficient (log P), the molar weight (MW) and the total polar surface area (TPSA). A number of relevant molecular properties (descriptors) are often used to help in the assessment of the DMPK properties of potential drug leads. In this paper, an attempt has been made to carry out an in silico assessment of the ADMET profile of this dataset. A number of computed molecular descriptors, currently implemented in a wide range of software, have been used as indicators of the pharmacokinetic properties of a large proportion of currently known drugs.

Different methods

- Data sources and generation of 3D structures
- Initial treatment of chemical structures and calculation of ADMET-related descriptors

Applications: With the help of pharmacokinetic parameter it is very easy to find the following parameters.[19]

Bioavailability prediction
Prediction of blood–brain barrier (BBB) penetration
Prediction of dermal penetration
Prediction of plasma-protein binding
Metabolism prediction

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