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Review Article

IN SILICO DRUG DESIGN-TOOL FOR OVERCOMING THE INNOVATION DEFICIT IN THE DRUG DISCOVERY PROCESS

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ABSTRACT

Increasing costs of drug development and reduced number of new chemical entities have been a growing concern for new drug development in recent years. A number of potential reasons for this outcome have been considered. One of them is a general perception that applied sciences have not kept pace with the advances of basic sciences. Therefore, there is a need for the use of alternative tools to get answers on efficacy and safety faster, with more certainty and at lower cost. One such alternative tool is the *in silico* drug design or the computer aided drug design (CADD). *In silico* drug design can play a significant role in all stages of drug development from the preclinical discovery stage to late stage clinical development. Its use in drug development helps in selecting only a potent lead molecule and may thus prevent the late stage clinical failures; thereby a significant reduction in cost can be achieved. This article gives an insight to all the aspects of *in silico* drug design; its potential, drivers and restraints, current scenario and the future prospects.

Keywords: *In silico* drug design, Computer aided drug design, Virtual screening

INTRODUCTION

Drug discovery and development is a complex, lengthy process and failure of a candidate molecule can occur as a result of combination of reasons such as poor pharmacokinetics, lack of efficacy, Side effect and commercial reasons .Most drugs are discovered by either modifying the structure of known drugs, by screening compound libraries or by developing proteins as therapeutic agents. With the advent of genomics[1], proteomics[2], bioinformatics[3] and technologies like crystallography, NMR, the structures of more and more protein targets are becoming available. So there is a need for computational tools that can identify and analyze active sites and suggest potential drug molecule that can bind to these sites. *In silico* models fill this research lacuna. Studies right from molecular docking, molecular dynamics, quantum mechanics, QSAR to ADMET prediction including dissolution studies are performed *in silico*. Availability of huge database of drugs from drug bank, protein data bank coupled with recent advances in technology further fuel the use of *in silico* models.

In the preceding sections various aspects of *in silico* drug design will be discussed upon beginning with an insight to the conventional drug discovery process and its pitfalls, the need for an alternative tool to reduce the R&D time cycle as well as the cost involved and how *in silico* drug design could play the role of being one such alternative tool. Later the discussion focuses on a list of various globally available *in silico* models emphasizing their possible intervention at various stages of drug design, drivers and restraints in implementing these models, current status of *in silico* drug design and future prospects.

Drug discovery process

The process by which a new drug is brought to market stage is referred to by a number of names most commonly as the development chain or "pipeline" and consists of a number of distinct stages. Broadly it can be grouped under two stages Preclinical and the Clinical. Preclinical involves two-steps process. The first step is to identify and model the biological target within the body (the protein). The second step is to identify a lead compound (molecule) that exhibits drug-like properties with respect to this protein followed by preliminary screening in animals. Subsequently, the drug goes through many phases of clinical development in humans. In the clinical phase, the drug is administered to human volunteers to determine:

- The passage of the drug through the body—from the time it is taken to the time it is excreted
- The effect of the drug on the body
- Its effectiveness on the disease being targeted
- Undesirable side effects of the drug

Cost and the time involved in the drug discovery process

In 2001 Pharmaceutical research and manufacturers of America (PhRMA) estimated the cost at US$802 million over a period of 11 years from the initial research stage to the successful marketing of a new drug[4]. More recent estimates by DiMasi at the Tufts Center for Study of Drug Development (CSDD) that was published in 2003 put the average cost at US$802 million spread over 12 years[5], while the Boston Consulting Group estimates the cost as $880 million over 15 years[6]. At present the cost involved in the drug discovery process ranges from $800 million to $1.8 billion[7]. These estimates are averages and there is significant variation in both time and cost, depending on the nature of the disease being targeted, the type of drug being developed and the nature and scope of the clinical trials required to gain regulatory approval. Table 1 gives an overview of the Drug discovery process and the cost incurred at each stage of drug development.

Table 1: Shows the cost incurred and time involved in the drug discovery process

	Cost US $ Million	Cost %	Time in years
Biology			
Target identification	165	18.8	1.0
Target validation	205	23.3	2.0
Chemistry			
Screening	40	4.5	4.5
Optimization	120	13.6	2.7
Development			
Pre-clinical	90	10.2	1.6
Clinical	260	29.5	7.0
Total	880	100.0	14.7

Pitfall in current drug discovery process-The productivity gap

- A recent US Government Accountability Office (GAO) report[8] found that Pharma R&D spending grew by 147% between 1993 and 2004 while the overall number of New drug applications (NDAs) submitted to the FDA increased only 38% and, worse still, the number of NDAs submitted for the presumably more innovative New molecular entities (NMEs) increased by only 7% in that time.
- The attrition rate is unacceptably high. Only 1 out of 12 drugs entering clinical trials become a new drug. A particular worry for the pharmaceutical industry is that, despite a variety of approaches being used for R&D, attrition rates remain high during drug development. There are a number of factors attributed to the high attrition rates observed, but the number of active substances with poor pharmacological properties has been cited as a major concern. These are active substances that lack appropriate bioavailability, exhibit poor pharmacokinetics or cause adverse events and will therefore need to be withdrawn from development. It is estimated that these types of failures represent approximately 50% of all failures in drug development. Figure 1 gives the reasons for the failure of the candidate molecule.

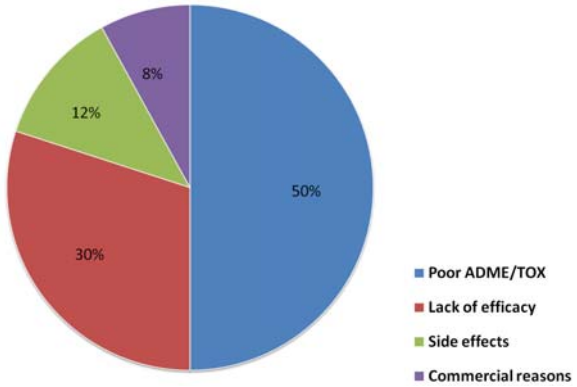

Fig. 1: It shows the potential reasons for failure of a candidate molecule

he sequencing of the human genome in 2000 raised widespread hope for a new era in the prevention and treatment of disease created by the ongoing investment in biomedical research but that new era has not yet arrived. Instead, 2000 marked the start of a slowdown not only in new drug and biologic submissions to the regulatory agencies but also approval of the NME from the regulatory agencies worldwide. The submission of innovative medical device applications has also slowed recently. (Figure 2 gives an insight to R&D spending and the NME approved over the decade).

This means fewer new products can be approved and made available to patients. At a time when basic biomedical knowledge is increasing exponentially, the gap between bench discovery and bedside application appears to be expanding. This declining productivity is partly due to the fact that all the simple disease targets have been addressed and those that are left are much more difficult to address from a traditional chemistry perspective, or their role in disease is not well understood.

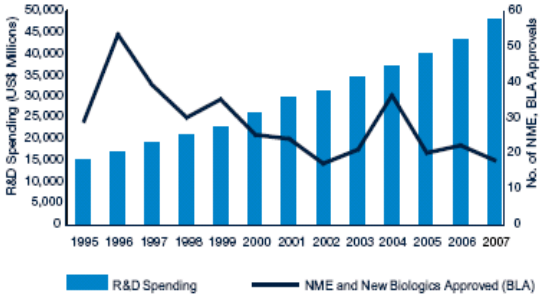

Fig 2: It gives an insight to R&D spending and NME approved over the decade

Need for an alternative tool

From the above facts and figures it is evident that there is an urge for an alternative tool that would not only shorten the R&D time cycle but also reduce the ever increasing cost involved in the drug discovery process. There is a general perception that applied sciences have not kept pace with the advances of basic sciences. According to the FDA report released in 2005, *Innovation and Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*[9] Modeling and simulation could play a key role in overcoming this innovation deficit. It noted that while spending on biomedical research has increased greatly over the last decade, the submission of new molecular entities has remained flat .The report also pointed out that a drug entering phase I trials in 2000 was no more likely to reach the market than one entering phase I trials15years earlier.

Outdated technologies may be one reason for those discouraging numbers, the report states: "Often, developers are forced to rely on the tools of the last century to evaluate this century's advances." But the agency believes there are steps industry can take. "As biomedical knowledge increases and bioinformatics capability likewise grows," the report states, "there is hope that greater predictive power may be obtained from *in silico* (computer modeling) analyses such as predictive modeling." The report, citing data from PricewaterhouseCoopers[10], states that "extensive use of *in silico* technologies could reduce the overall cost of drug development by as much as 50%".

Impact of technology

The process of finding a drug molecule that attaches itself to the target protein in the body has now moved from the lab to the computer[11]. The words *in silico* drug design and computer aided drug design are almost synonymous. In the post genomic era, computer-aided drug design (CADD) has considerably extended its range of applications, spanning almost all stages in the drug discovery pipeline, from target identification to lead discovery, from lead optimization to preclinical or clinical trials[12]. Figure 3 gives an insight to the application of CADD to the various stages of drug development.

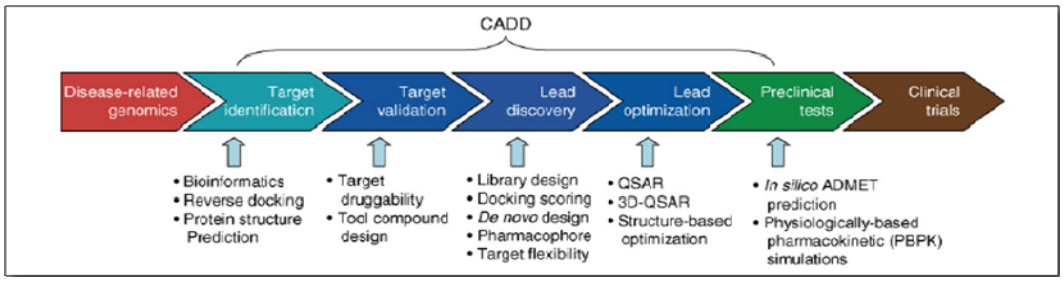

Fig. 3: It shows the Applications of CADD to the various stages of drug development.

***In silico* drug discovery process comprises of 3 stages[13]**

Stage 1-It involves Identification of a therapeutic target and building a heterogeneous small molecule library to be tested against it. This is followed by the development of a virtual screening protocol initialized by either docking of small molecules from the library or building these structures in the active site by employing *De novo* design methods.

Stage 2- These selected hits are checked for specificity by docking at binding sites of other known drug targets.

Stage 3-These selected hits are subjected to detailed in silico ADMET profiling studies and those molecules that pass these studies are termed as leads

Target identification and validation *in silico*

Target identification and validation is the first key stage in the drug discovery pipeline. However, identification and validation of druggable targets from among thousands of candidate macromolecules is still a challenging task[14] .Numerous technologies for addressing the targets have been developed recently. Genomic and proteomic approaches are the major tools for target identification. For example, a proteomic approach for identification of binding proteins for a given small molecule involves comparison of the protein expression profiles for a given cell or tissue in the presence or absence of the given molecule. This method has not been proved very successful in target discovery because it is laborious and time-consuming. Therefore, complementary to the experimental methods, a series of computational (*in silico)* tools have also been developed for target identification. They can be cataloged into sequence-based approach and structure-based approaches.

Sequence-based approach contributes to the processes of target identification by providing functional information about target candidates and positioning information to biological networks. For those diseases caused by external pathogens such as bacteria and viruses, unique targets might be found in the pathogens by comparing functional genomics from humans with the corresponding genomics from pathogens. For example, Dutta e.t al.[15] used a subtractive genomic method to analyze the completed genome of Helicobacter pylori (H. pylori) and identified a set of genes that are likely to be essential to the pathogen but are absent in humans.

***In silico* ADMET (absorption, distribution, metabolism, excretion, toxicity) prediction[16]**

Studies indicate that poor pharmacokinetics and toxicity are the most important causes of costly late-stage failures in drug development and it has become widely appreciated that these areas should be considered as early as possible in the drug discovery process. Combinatorial chemistry and high-throughput screening have significantly increased the number of compounds for which early data on absorption, distribution, metabolism, excretion (ADME) and toxicity (T) are needed. With use of *in silico* tools it is possible to model the most relevant pharmacokinetic, Metabolic and toxicity endpoints, thereby accelerating the drug discovery process. *In silico* approach helps in selecting only a potent lead molecule which can be further carried through the drug discovery and development cycle. There are Programs like DD plus and Gastro plus which gives the pharmacokinetic profile of the drug once the structure of drug is given.

***In silico* prediction of drug safety[17]**

There is considerable interest in computational models to predict drug safety in drug discovery and development. Significant adverse toxicological findings for a drug in late-stage clinical trials or post-marketing can cause enormous financial losses and place patients at risk. The earlier such molecules are identified and the drug development process halted the better. In addition, insights into the toxicological potential of a scaffold or series of structures early on in the drug discovery process could help medicinal chemists to prioritize particular scaffolds or hits. Finally, computational toxicity models could be used to help understand pre-clinical toxicity data and select appropriate experimental end-points for further studies during clinical candidate selection and early clinical studies. There are tools to predict toxicities like

(1) Genotoxicity,
(2) Liver toxicity,
(3) CYP450 inhibition and
(4) Cardiotoxicity.

***In silico* prediction of drug-drug interactions [18]**

Recently, metabolic drug–drug interactions (M-DDI) have raised some high-profile problems in drug development resulting in restricted use, withdrawal or non approval by regulatory agencies. The use of in vitro technologies to evaluate the potential for M-DDI has become routine in the drug development process. Nevertheless, in the absence of an integrated approach, their interpretation and value remains the subject of debate, and the vital distinction between a useful ''simulation'' and a precise ''prediction'' is not often appreciated. Various *in silico* software are now available for the simulation of M-DDI.One such software is SIMCYP.

Virtual screening[19]

Virtual screening involves the docking of selected lead molecules against the biological target. This is followed by a scoring pattern. There is a number of software available for this. Some are commercially available and some are free to use.

Commonly used software for drug design or intermediate steps thereof

While Table 2 gives a list of commonly used drug design software for the intermediate steps Table 3 gives a comprehensive list of drug discovery software packages available commercially.

Table 2: List of commonly used *in silico* software for the intermediate steps in the drug discovery process

Programs	Company
TOPKAT, Tsar, LigandGel, ZDOCKPro, DS MedChem Explorer, AEI,	Accelrys
ACD/LogD Suite and ACD/Log Sol Suite, ACD/LogD Batch and ACD/Log Sol Batch, ACD/Structure Design Suite, ACD/PhysChem batch	ACD/Labs
ADMET Modeler, ADMET Predictor, Class Pharmer 4.0, GastroPlus, DDDPlus	Simulations Plus, Inc.
ToxML, LeadScope Toxicity Database, LeadScope Known Drugs Databases, LeadScope Enterprise, LeadScope Personal	LeadScope
Algorithm Builder, QSAR Builder, ADME Boxes v. 3.0, Tox Boxes v. 1.0, ADME/Tox WEB, DMSO Solubility, ADME Batches, Absolv	Pharma Algorithms

Table 3: List of drug discovery software packages available commercially

Sl. No.	Software name	Company/institution	Provided utilities and URL
1	Insight II, Discovery studio, Cerius	Accelrys	Molecular modeling and de novo drug design. http://www.accelrys.com/products
2	Sybyl	Tripos	Computational informatics software for drug discovery. http://www.tripos.com
3	Phase, Glide, Liasion	Schrodinger	Pharmacophore modeling, Ligand-receptor docking. http://www. Schrodinger.com
4	Bio-suite	Tata consultancy services	Genomics, Protein modeling, structural analysis, simulation and drug design. http://www. Atc.tcs.com/biosuite
5	Sanjeevini	Indian institute of technology, Delhi	Active site directed drug design http://www.scfbioitd.in/research/drugdesign.htm

Drivers in implementing *in silico* models

- Improvement in drug attrition rates drive increased adoption of *in silico* technologies
- Costly failures of late drug development spurs the use of *in silico* models for early ADME/Tox screening
- Improved computational power drives the development of *in silico* ADME/Tox screening products
- Improved and reliable models increases adoption by pharmaceutical companies
- Increased rate of target identification drives the adoption of *in silico* models that ultimately seek to screen targets at the same rate as they are discovered.
- Collaborations/partnerships between *in silico* product vendors and pharmaceutical companies has resulted in the ability to develop "global" off-the-shelf products as well as "local" customized products

Restraints in implementing *in silico* models

- Lack of accurate/reliable experimental data restricts the development of improved in silico ADME/Tox models
- Predictive value of many *in silico* ADME/Tox technologies remains unproven
- The risk that a potentially safe and viable drug candidate may fail by utilizing *in silico* models and subsequently not put forward for in vitro/in vivo analysis
- No complete list of successful projects regularly updated in which modeling & simulation had an important effect
- Lack of test standardization and Proof of concept remains a major constraint

Future prospects

In silico modeling will play a role in the future of pharmaceutical discovery and development, but the extent of that role remains to be seen. "At this point [it won't] fizzle out," says Mallalieu, senior principal scientist in discovery pharmacology at the Nutley, New jersy, USA."But I wish it spread faster than it has, and I think the reason that it hasn't is that it hasn't caught on. It's a vicious cycle. You have to prove yourself to grow, but you need a certain critical mass in order toproveyourself."

Lalonde (Principal scientist at Pfizer) is optimistic. "The ones that can successfully implement this(*in silico* approaches) will probably be swallowing up other companies that are not so successful, because they will keep doing it the old-fashioned way and driving up the cost to astronomical levels, costs that will be very hard to justify in the marketplace. All successful companies will have to do this routinely because it's just too expensive to do it by trial and error, the way it's often been done in the past."

CONCLUSION

In the selection of new drug candidates, many efforts are focused on the early elimination of compounds that might cause several side effects or interact with other drugs. *In silico* techniques help in this regard and they are going to become a central issue in any rigid drug discovery process. In silico technology alone cannot guarantee the identification of new safe and effective lead compound but more realistically future success depend on the proper integration of new promising technologies with the experience and strategies of classical medicinal chemistry.

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