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INSILICO DRUG DISCOVERY: A REVIEW

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ABSTRACT

The purpose of writing this review to compile the present information, current technologies and other contributing factors used to drug discovery of new molecules which can bind to specific target involved in disease causing. Drug discovery process includes identification of lead structure and its analogs and their screening get drug development. In current drug discovery process, identification of accurate drug target is the important task. Use of in silico methods are widely acceptable in drug discovery. The aim of this review article is to focus on some of the in silico methods used in drug discovery and applications of these methods.

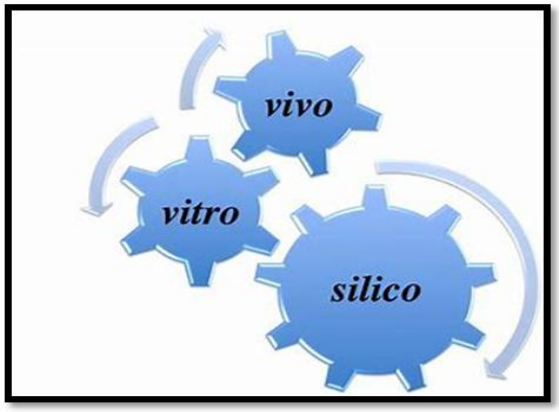
KEYWORDS: *Drug Discovery, Molecular Docking, Pharmacophore, QSAR, Insilico Drug Design, HQSAR.*

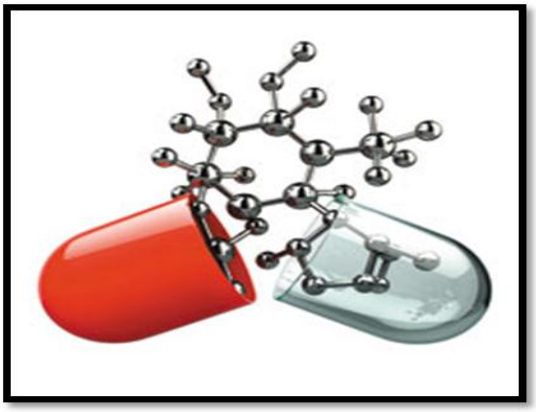
INTRODUCTION

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 altering the structure of known drugs, by screening compound libraries or by developing proteins as therapeutic agents. With the advent of genomics1, proteomics2, bioinformatics3 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.





What is drug discovery?

The drug discovery process includes the identification of the lead structure followed by synthesis of its analogs, there screening to get applicant molecules for drug development. The goal of the drug discovery process is to search for new molecules which can bind to a specific receptors / target known to be involved in causing a disease and change the target's function.

What is in silico drug discovery?

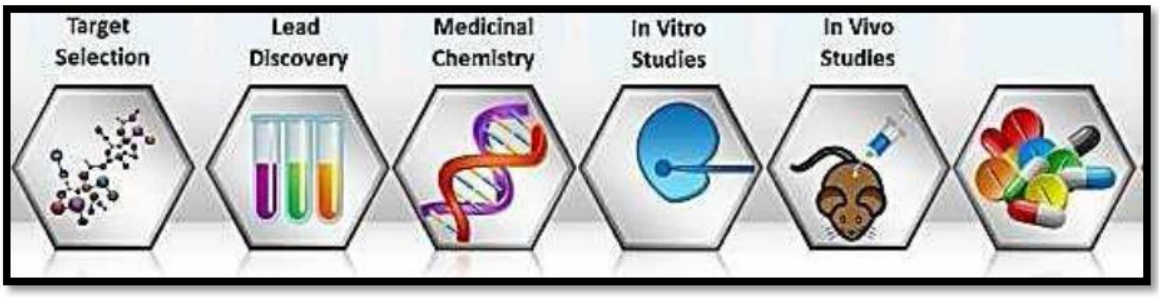
In silico (Pseudo-Latin for "in silicon", alluding to the mass use of silicon for computer chips) is an expression meaning "performed on computer or via computer simulation" in reference to biological experiments. The term in silico was first used by Pedero Miramontes, a mathematician from National Autonomous University of Mexico characterize biological

experiments carried out entirely on a computer. As structures of protein targets available through crystallography, NMR and bioinformatics methods, there is an increasing demand for insilico that can identify and analyze active sites and suggest potential drug molecules that can bind to these sites precisely.

Steps of drug design process

The following sections will describe what we feel are the six major areas of modern drug discovery and design programs. They are-

1. Target Identification
2. Target Validation
3. Lead Identification
4. Lead Optimization
5. Predicting drug-like properties
6. Preclinical Pharmacology and Toxicology.



1) Target Identification

Traditional drug discovery began with a known pathological condition caused by an organism and the development of a therapeutic theory to combat with this condition. A chemical concept would follow to develop compounds for screening. Most of these processes originated with the understandings of some biological pathways and screening for an effect in tissues or cells. This may or may not eventually reveal a "target". Conventional approaches of identifying targets such as protein expression, protein biochemistry, structure function studies, knowledge of biochemical pathways, and genetic studies were instrumental in drug development.

2) Target validation

Selection and validation of novel molecular targets have become of paramount importance in light of the plethora of new potential therapeutic drug targets that are continuously being

discovered. The prospective targets identified in the previous section require confirmation that intervening at this step in a particular pathway will affect an appropriate biological response. The use of reliable animal models and the latest in gene targeting and expression techniques are all, essential to the validation process. Recently, a new approach to validation using specific peptide binders to a potential pathogen target was reported. In this study, peptides were selected by phage display or combinatorial screening based on their binding to prolyl-tRNA synthetase, an essential enzyme in the bacterial life cycle of E. coli.

3) Lead Identification

A lead is defined as a compound (usually a small organic molecule) that demonstrates a desired biological activity on a validated molecular target. To fulfill the criteria of what the industry considers a useful lead, the compound must exceed a specific potency threshold against the target (e.g., < 10 µM inhibition). The compounds used as potential leads could be from numerous sources like from plants, animals, marine, synthetic, semi synthetic etc.

A majority of leads discovered in very recent programs are derived from collection that is now referred to as a "library". These may take the form of natural product libraries, peptides libraries, carbohydrates libraries, and/or small molecule libraries based on a variety of different molecular scaffolds. There are numbers of commercial as well as non-commercial data bases are available, which feed number of new leads for drug discovery.

4) Lead optimization

Once a lead compound is established in the identification process, the medicinal chemist will work closely with molecular pharmacologists to optimize the desirable traits of the lead. This process can be relatively fast since history has taught the medicinal chemistry community how to manipulate molecules to improve activity. Starting with intuitive structural modification to the development of structure-activity relationship (SAR) and quantitative SAR (QSAR) one can gain tremendous information. It is also important to bear in mind that the synthesis of focused chemical libraries using parallel synthesis can facilitate lead optimization. Iterative optimization of lead compounds necessitates a broad knowledge in the general principles of de novo drug design.

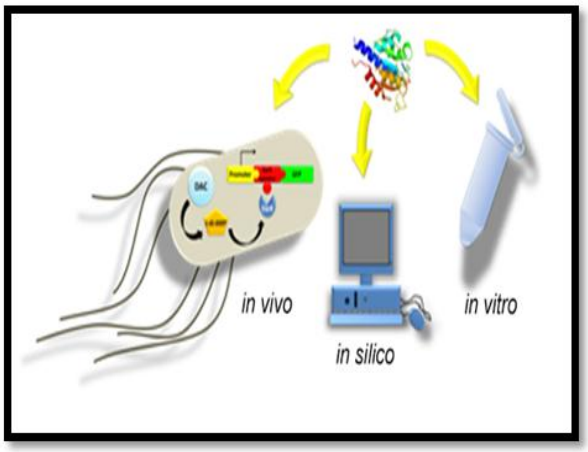
5) Predicting drug-like properties

The phrase "drug-like" is defined as those compounds that have sufficiently acceptable ADME and toxicity properties to survive through the completion of Phase I clinical trials. It

is becoming clear that successful prediction of drug-like properties at the onset of drug discovery will payoff later in drug development. Therefore, there is increasing demand to design computer programs that can accurately predict physicochemical parameters. Such parameters include oral absorption, blood-brain barrier penetration, toxicity, metabolism, aqueous solubility, logP, pKa, half-life, and plasma protein binding.

6) Preclinical Pharmacology and Toxicology

Prior to clinical trials in human, each new chemical entity has to be tested in animals and in many cases, several species. Data concerning toxicity, PK and metabolism is necessary to determine the feasibility and safety of the drug in human. In some cases testing may include xenograft models and a complete toxicology profile should be clearly established at this stage. A careful study of ADME/T characteristics at this phase of design is extremely important since the majority of drug candidates fail clinical trials due to ADME/T deficiencies. Clearly, the benefits of enhancing the ADME/T properties of molecules through computational design in the discovery phase and actual validation of these properties in several species of animals in the preclinical phase are enormous.



In silico drug discovery process

Stage 1-It includes Identification of a therapeutic target and structure 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 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 detail in silico ADMET summarizing studies and those molecules that pass these studies are termed as leads.

1. Target Identification and Validation Insilico

Target identification and validation is the first key in the drug discovery channel. However, identification and validation of druggable targets from among thousands of candidate macromolecules is still a challenging task .Numerous technologies for addressing the targets have been developed recently. Genomic and proteomic methods 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 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) tool shave also been developed for target identification. They can be cataloged into sequence-based approach and structure-based Approaches.

2. In silico ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) prediction

Studies indicate that poor pharmacokinetics and toxicity are the most important causes of inflated late-stage failures in drug development and it has become widely valued that these areas should be measured as early as possible in the drug discovery process. Combinatorial chemistry and high-throughput screening have significantly increased the number of compounds for which initial 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 applicable 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.

3. Insilico prediction of drug safety

There is significant interest in computational models to predict drug safety in drug discovery and development. Significant adverse toxicological discoveries for a drug in late-stage clinical trials or post marketing can cause huge financial losses and place patients at risk. The earlier molecules are identified and the drug development process stopped 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 preclinical 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

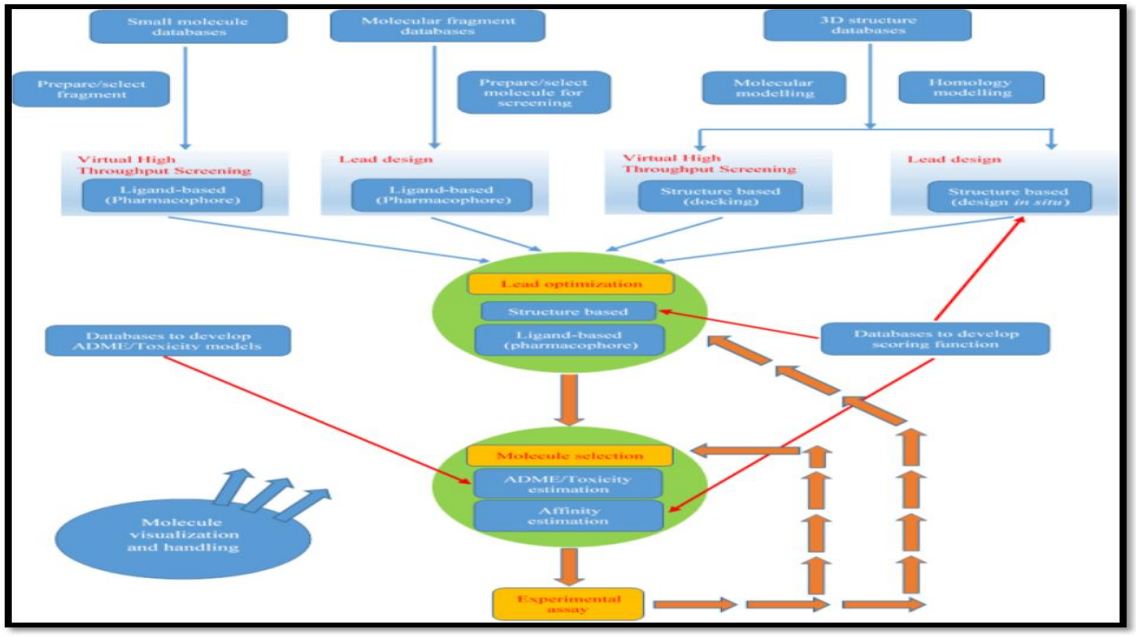
1. Genotoxicity,
2. Liver toxicity,
3. CYP450 inhibition and
4. Cardio toxicity

4. Insilico prediction of drug-drug interactions

Newly, 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. However, 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.

5. Virtual screening

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



Methods used in in-silico drug design

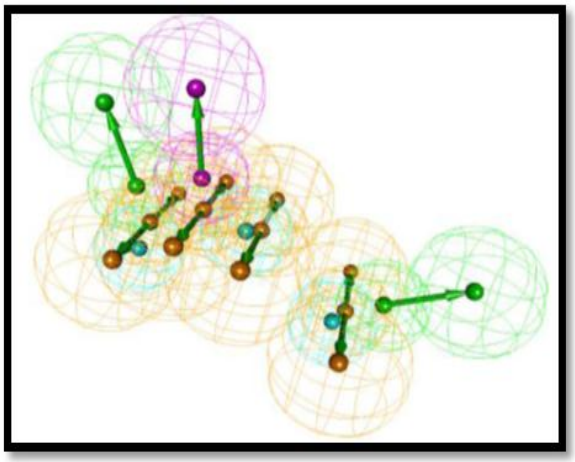
1) Homology modelling

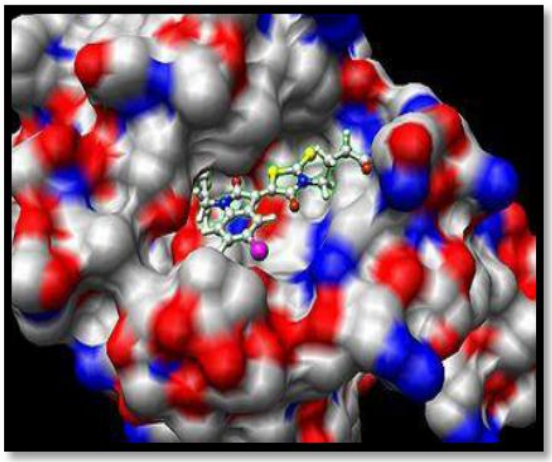
Homology modeling, is also recognized as comparative modelling of protein and it is a method that allows to generate an unknown atomic-resolution model of the "target" protein from its amino acid arrangement and an experimental three dimensional (3D) structure of a related homologous protein (the "template").

Homology modelling includes the recognition of one or more identified protein structures probably to show similarity with the structure of the query sequence, and on the making of an arrangement that maps residues in the query sequence to residues reported that the protein structures are more preserved than protein sequences amongst homologues, but sequences have less than 20% sequence identity and can have very different structures.

1) Molecular docking (Interaction networks)

In the field of molecular modelling docking it is a technique which envisages the favoured orientation of one molecule to a second, when bound to each other to form a stable complex. Molecular docking denotes ligand binding to its receptor or target protein. Molecular docking is used to recognize and optimize drug candidates by examining and modelling molecular interactions between ligand and target macromolecules. Molecular docking are used to generate multiple ligand conformations and orientations and the most appropriate ones are selected.





2) Virtual High-Throughput Screening

Virtual screening is a computational technique where large collections of compounds are evaluated for their probable to bind specific sites on target molecules such as proteins, and

well-matched compounds tested. The research in the drug discovery process comprises virtual screening (VS) which is a computational method used for the rapid investigation of large libraries of chemical structures in order to identify those structures that are most likely to bind to a drug target, usually a protein receptor or enzyme.

3) Quantitative structure activity relationship (QSAR)

Quantitative structure-activity relationships (QSAR) methods are used to show a connection of structural and/or property descriptors of compounds with their biological activities. These descriptors explaining the properties like steric, topologic, electronic, and hydrophobic of several molecules, have been determined through empirical methods.

4) Hologram quantitative structure activity relationship (HQSAR)

In Hologram QSAR, a typical QSAR procedure, there is no need for precise 3D information about the ligands. In this method, the molecule breaks to a molecular fingerprint encoding the frequency of existence of various kinds of molecular fragments. Simply, the minimum and maximum length of the fragments depends on the size of the fragment to be involved in the hologram fingerprint. Molecular holograms are produced by a generation of linear and branched fragments, ranging in size from 4 to 7atoms.

5) Comparative molecular field analysis (COMFA)

Comparative molecular field analysis (CoMFA) is a positive novel technique to explain structure activity relationship. It is a well-known 3D QSAR method and work on CoMFA started in the 70's. It delivers values of ClogP which means the solvent repellent restrictions the ligands and also explains the steric and electrostatic values of the ligands.

6) Comparative molecular similarity indices analysis (COMSIA)

Comparative Molecular Similarity Indices Analysis (CoMSIA) is predicted as one of the new 3DQSAR approaches. It is generally used in the drug discovery process to locate the common characteristics, important for the proper biological receptor binding. This method deals with the steric and electrostatic characteristics, hydrogen bond acceptors, hydrogen bond donor and hydrophobic fields.

7) 3D Pharmacophore mapping

The 3D pharmacophore search is an imperative, dynamic and simple method to quickly recognize lead compounds alongside a preferred target. Conventionally, a pharmacophore is defined as the specific 3D arrangement of functional groups in a molecular framework that are essential to attach to an active site of an enzyme or bind to a macromolecule. It is essentially the first step to define a pharmocophore in order to understand the interaction of a ligand with a receptor. Once a pharmacophore is predictable, the medicinal chemist utilizes the 3D database search tools to retrieve novel compounds that are suitable for the pharmacophore model. The modern drug design process has been used to make it one of the most successful computational tools because the search algorithms have made advancements over the years to capably identify and optimize lead focus combinatorial libraries and help in virtual high-throughput screening.

8) Microarray analysis

Microarray analysis is a new technique, known as DNA technology which plays a very significant role in the advancement of biotechnology further. These are mostly properly arranged sets of known sequence DNA molecules. Mostly rectangular, which can be consisted of hundreds of thousands sets. Each single feature drives on the array at the accurately demarcated position on the substrate.

The identity of the DNA molecule linked to each feature definitely does not change. Scientists use this information to know the results of their experiments. The microarray study helps scientists to perceive numerous genes in a small sample immediately and also to carry out the analysis of the expression of these genes. That safety is given to facilitate biotechnology and pharmaceutical companies to identify target molecules. Microarray analysis can assist medical companies to participate in the selection of the most suitable candidates in clinical trials of new drugs.

9) Conformational analysis

Conformational analysis deals with deformable molecules and their minimum energy configurations through various calculation methods and interaction networks includes comparing a molecular receptor site of another molecule and calculating the most energetically satisfactory3-D conformation.

10) Molecular dynamic (MD) Simulation

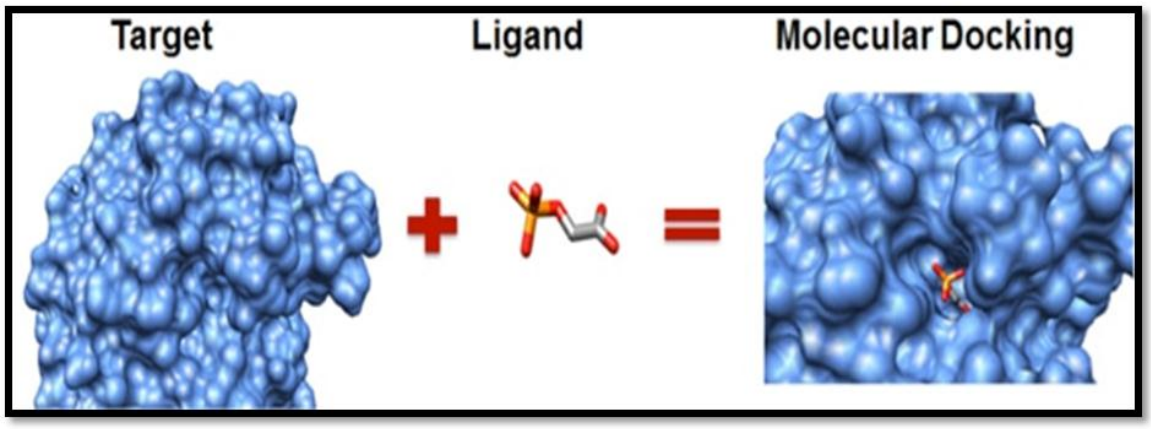
Molecular dynamics is an effective procedure and depends on the molecular motion simulation by solving Newton's equations of motion for each atom and increasing the speed and position of each atom by a small increase of the time duration. MD simulations characterize alternative methods to sample configuration space, based on the above mentioned rule. That is shared with temperatures using "reasonable" (a few hundreds or thousands of degrees), this means that only the local area around the sampled point, and only relatively small barriers are overcome. Generation may be different (local), minimum may be accomplished by selecting configuration appropriate times during the simulation and thus minimize these structures.

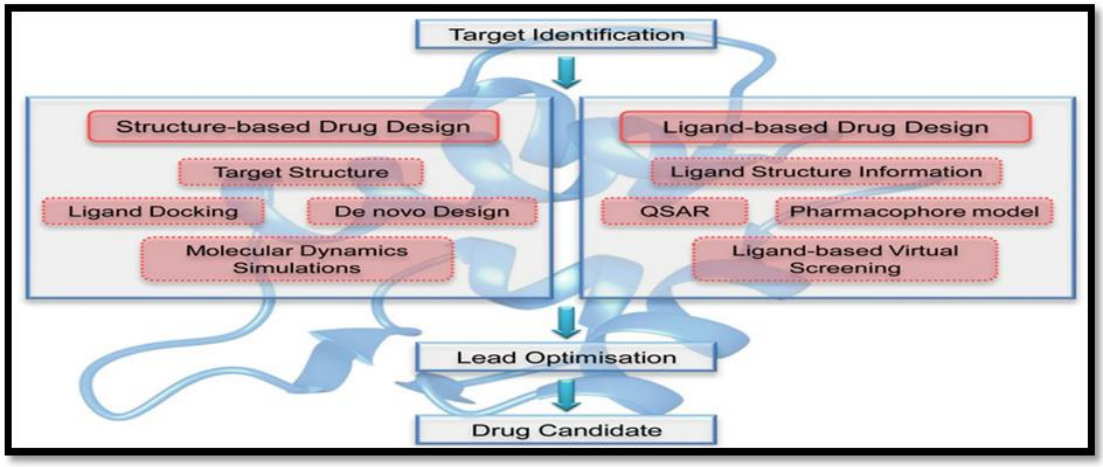
MD methods utilize the inherent dynamics of the system to search deformation modes of low energy and can be used for sampling of the conformational space of a large confined system.

Approaches of insilico drug discovery

1) Molecular docking

Docking is the computational determination of binding affinity between molecules (protein structure and ligand). Specified protein and a ligand find out the binding free energy of the complex designed by docking them. Docking or Computer aided drug designing can be generally classified as;





2) Receptor based method

Uses the 3D structure of the target receptor to search for the potential candidate compounds that can modulate the target function. These include molecular docking of each compound in the chemical database into the binding site of the target and predicting the electrostatic fit between them. Receptor based method has been successfully useful in many targets.

3) Ligand based method

In the absence of the structural information of the target, ligand based method make use of the information providing by known inhibitors for the target receptor. Structures similar to the known inhibitors are identified from chemical databases by variety of methods; some of the methods widely used are similarity and substructure searching, pharmacophore matching or 3D shape matching.

For example- 2ZIS-NH8903 OVERLAID ON PHARM-b HYPOTHESIS.
HY- Hydrophobic, RA- Ring Aromatic, HBA-Hydrogen Bond Acceptor, ZB- Zinc Binber.

4) Fragment based screening

Fragment-based lead discovery (also referred to as needles, shapes, binding elements, seed templates or scaffolds) is a new lead discovery approach in which much lower molecular weight (120–250Da) compounds are screened relative to HTS campaigns. Fragment-based hits are characteristically weak inhibitors (10μM–mM), and therefore need to be screened at higher concentration using very sensitive biophysical detection techniques such as protein crystallography and NMR as the primary screening techniques, rather than bioassays.

Compared with HTS hits, these fragments are humbler, less functionalized compounds with correspondingly lower affinity. However, fragment hits characteristically possess high 'ligand efficiency' (binding affinity per heavy atom) and so are highly suitable for optimization into clinical candidates with good drug-like properties. There are now increasing numbers of examples appearing in the literature that demonstrate that fragment-based discovery can identify quality leads for targets where HTS has not succeeded.

Steps involved

1) Receptor preparation

- Dependent on docking program used
- Structure selection
- Site selection
- Add charges
- Frequently have to add hydrogens, some programs more sensitive to positions than other Remove/include waters, cofactors, metals
- Pre-docking refinement
- Remember to consider missing residues or atoms

2) Ligand preparation

- Involvement structures (extract from PDB, draw, convert from SMILES)
- dd bond orders
- Generate isomers if chiral centers
- Calculate charges
- Predict pka's for each potential charged atom
- Create a structure for each charge combination for a given pH range
- Minimize structures
- Generally using a molecular mechanics force field
- For Transmission, can download public sets from ZINC (available compounds) or pubchem.

Commercially available softwares

AutoDock, UCSFDOCK, Glide, GOLD (CCDC), Flex X (BiosolveIT), ICM (Mol soft), Surflex (Tripos).

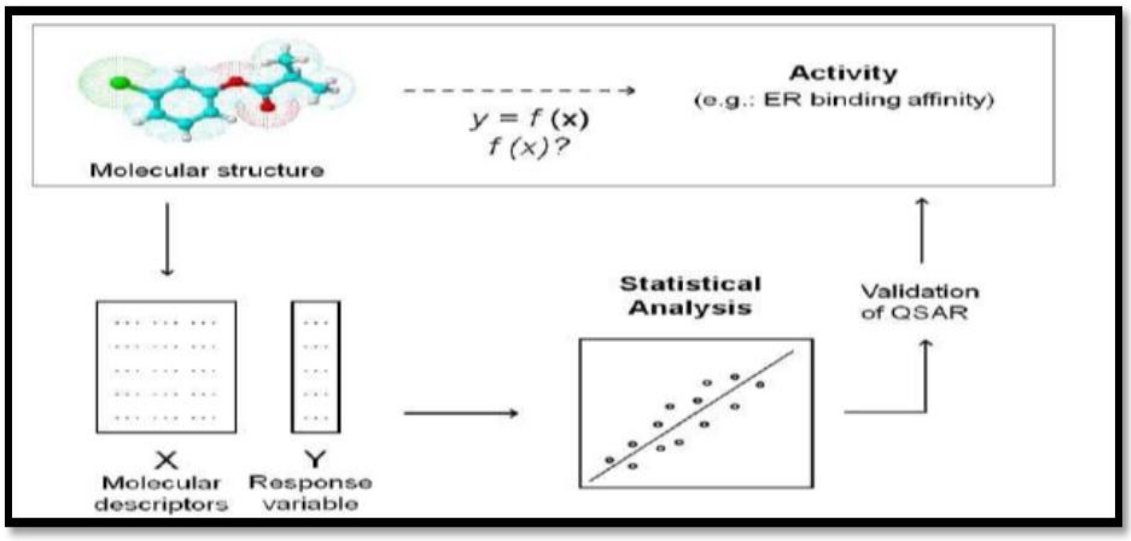
Virtual high throughput screening

Virtual screening is a computational method where large libraries of compounds are evaluated for their potential to bind specific sites on target molecules such as proteins, and well-matched compounds tested. 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, characteristically a protein receptor or enzyme .Virtual screening has become an essential part of the drug discovery process.

Walters, et al. define virtual screening as "automatically evaluating very large libraries of compounds" using computer program. VS focuses on questions like how can we filter down the enormous chemical space of over 1060 conceivable compounds to a manageable number that can be synthesized, purchased, and tested.

QSAR (Quantitative structure-activity relationship)

QSAR is statistical approach that challenges 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 in vitro or in vivo. It saves times and resources. Several descriptors like molecular weight, number of rotatable bonds, LogP 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, or the property, for instance the toxic effect, is related to the chemical structure through a certain mathematical algorithm, or rule.



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 rings. It depends on atomic properties rather than element types, it does not depend on specific chemical connectivity. It has conformational flexibility and planning the different combinations of pharmacophoric groups in the molecule.

Advantages of in-silico drug design

1. **Cost saving:** Many pharmaceutical companies uses computational methods and bioinformatics tools to reduce their cost burden. Virtual screening, lead optimization and prediction of bioavailability and bioactivity can help to guide the research and development programmed.

2. **Time-to-Market:** The prediction power of CADD (Computer Aided Drug Design) can help drug research programs choose only the most appropriate drug candidates. By focusing drug research on specific lead candidates and avoiding potential "dead end" compounds, pharmaceutical companies can get drug to market more quickly.

3. **Insight:** One of the non-quantitative benefits of CADD and the use of bioinformatics tools is the deep insight that researchers acquire about drug receptor interactions. When we show researchers new molecular models of their assumed drug compounds, their protein targets and how the two bind together; they frequently come up with new ideas on how to change the drug compounds for improved fit. This is an imperceptible benefits that can help design research programmers.

Limitations

1. "Sequence implies the Structure and Structure implies the Function"
2. Selected protein structures from databases such as PDB, FSSP, SCOP or CATH after removing proteins with high sequence similarity act as structural templates for the alignment.
3. These computational models often represent only fractions of the full length of desired protein.

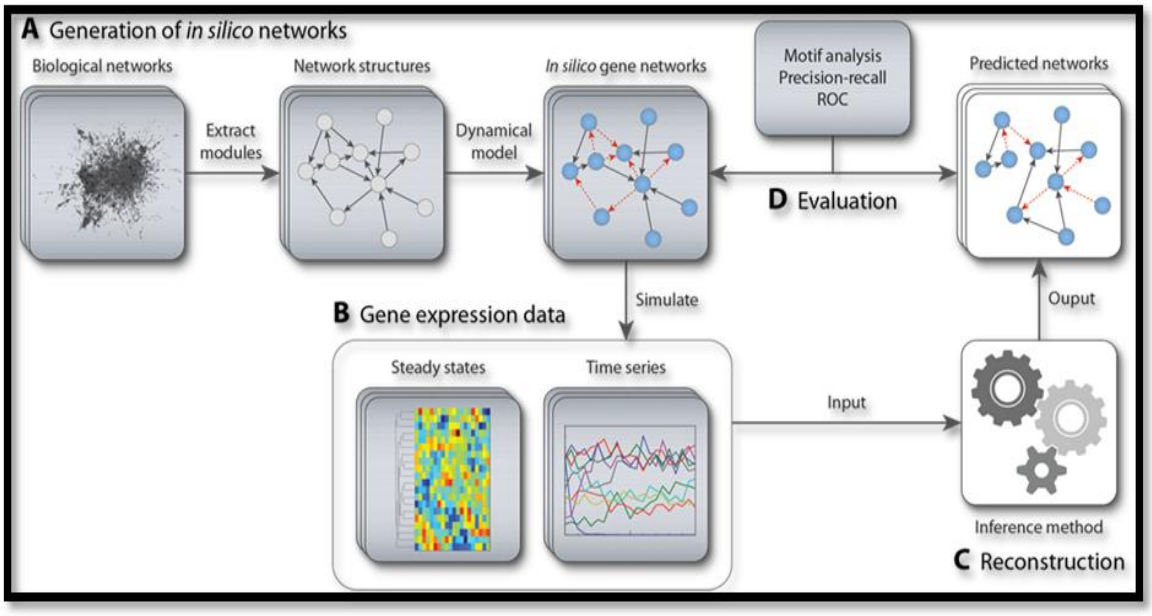
4. Oftenly, a drug's market price is high, this is not because of the manufacturing cost of the sole drug but the price of failed drugs is also added to it. In such scenarios, in silico studies can be of great help as they can reduce the production cost and thereby the marketed price. They represent 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. The challenge is to take advantage of all the contributions that each approach, in vivo, in vitro, and Insilco offer.

Applications

1) In silico gene-expression analysis

Because only ~3% of the 3×109 bases of the human genome sequence actually encode proteins and *in silico* gene identification is still a difficult task , public and private expressed sequence tag (EST) databases represent an significant source for target discovery. Such databases contain short order information from expressed genes, which permits their identification and which is taken as symptomatic of the encoded proteins.

The value of such databases has endlessly increased by adding sequences from different human tissues and states of development and disease: the public EST databases alone contain more than 1.6 million human sequences. One significant use of these databases in target discovery is to infer relative gene expression levels, simply by counting how often a given EST sequence appears in a given cell or tissue.



2) Prediction of gene function

Elucidation of gene function *in silico* is another significant field for bioinformatics in target discovery. Characteristically, a new DNA sequence [which could come from the above gene-expression analysis (e.g. a gene up regulated in a diseased tissue)] is first subjected to resemblance searches [e.g. using basic local alignment search tool (blast)] in sequence databases such as the public GenBank (nucleic acid level) and SWISS–PROT (protein level), and often its function can be derived from similarities and homologies to sequences of known function. In about 30–35% of cases, where no clear functional prediction is possible, several recently developed computational methods in comparative genomics can help to deduce specific functions. Usually a target is much more attractive if its function can be demonstrated. Function can indicate a biochemical and/or pathophysiological pathway that the target is involved in, thus shedding further light on its relevance for the disease under study.

3) In silico library design and virtual screening

In silico (or virtual) compound library design operates to diminish the number of compounds to be tested, and two elementary applications can be distinguished: diversity and structure-based design. Variety of design aims to select a smaller sub-library from a larger compound library in such a way that the full range of chemical diversity is best represented.

When no structural info about the target and/or target ligands is available, diversity design is the method of choice. The different computational methods for compound selection are mostly based on compound similarity clustering, grid-like partitioning of chemical space or the application of genetic algorithms. The results of such *in silico* diversity selections (*in silico* screening) are smaller sub-libraries of controllable size with a high degree of chemical diversity that are then subjected to HTS *in vitro*.

4) Prediction of drug-likeness

When lead molecules have been recognized, they have to be enhanced in terms of potency, selectivity, pharmacokinetics (absorption, distribution, metabolism and excretion (ADME)] and toxicology before they can become candidates for drug development. Because the high overall erosion rate in drug discovery is caused mostly by the non-'drug-likeness' of the compounds identified, the early analysis in this respect is becoming common practice. *In silico* approaches to predict pharmacokinetic parameters (ADME).

By reviewing the physicochemical properties of >2000 drugs from the WDI (World Drug Index, Derwent Information, London), which can be assumed to have entered Phase II human clinical trials (and therefore must possess drug-like properties), the so-called 'rule-of-five' was derived to predict oral bioavailability (intestinal absorption) of a compound that can be considered as the major goal of drug development. If the hydrogen bond donors are <5, hydrogen acceptors <10, relative molecular weight <500 and lipophilicity (logP) <5, the compound will probably be orally bioavailable.

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, Newjersy, 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 to prove yourself. 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 justifying 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-silico methods have been of great importance in target identification and in prediction of novel drugs. 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

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