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A BRIEF REVIEW ON COMPUTATIONAL TECHNIQUES USED IN MODERN DRUG DISCOVERY

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Abstract:
Use of computational techniques has accelerated the discovery process. Traditional drug discovery process was laborious, time consuming and was expensive. The success rate was also very low. In the modern drug discovery process the use of computational techniques has made the drug discovery fast and cost effective with higher success rates. The present review highlights the various computational techniques used in the drug discovery, their advantages and limitations.

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1. INTRODUCTION:

"In silico" refers to work that is "performed on a computer or via computer simulation." The process of finding and developing new drugs is a tedious process. It is thought of as a sequential, linear process that begins with target and lead discovery, moves on to lead optimization, and concludes with pre-clinical in vitro and in vivo investigations to see if these compounds meet a number of predetermined requirements before moving on to clinical development [1]. Drugs are essential for the diagnosis, treatment and prevention of illness. A multitude of novel diseases have been identified. Thus, there is a constant need for perfect medications. The demands of optimal medications necessitate an effective approach to drug development. Drug development is a difficult, costly, time-consuming process that involves many factors to be taken into account. The process of drug development requires a number of multidisciplinary techniques to address these issues; taken as a whole, these approaches would serve as the foundation for rational drug design [2]. As genomics, proteomics, bioinformatics, and technologies like NMR and crystallography advance, the structures of an increasing number of protein targets are coming to light. Therefore, computational techniques that can locate, evaluate, and propose possible therapeutic molecules that can bind to these active spots are required [3]. Since in silico models are created using pre-existing data from laboratory experiments, their dependability depends on the data they are built upon. Toxicologists can employ in silico approaches, an interdisciplinary field of study where models are created by chemo-informatics specialists [4]. Using bioinformatics tools, in silico methods can aid in the identification of pharmacological targets. Additionally, they can be used to rank the molecules based on their binding affinities, dock these molecules with the target, examine the target structures for potential binding or active sites, produce candidate molecules, and assess how similar the molecules are to drugs. Today, computational techniques and computers are used in every facet of drug research, including the foundation of structure-based drug design. The internet, data management software, and high-performance computing are making it easier to access vast amounts of created data and turning complex biological data into useful knowledge for the modern drug discovery process. The likelihood of success is increased in many stages of the discovery process, from the identification of novel targets and the clarification of their activities to the discovery and development of lead compounds with desired properties, by the application of complementary experimental and informatics methodologies [5].

2. APPLICATIONS OF INSILICO TECHNIQUES

The advantage of using these methods is that potential new drugs can be delivered more affordably and promptly. In numerous phases of the discovery process, they raise the probability of success. They make it easier to access vast amounts of created data. They convert the enormous amount of complicated biological data into useful knowledge [6].

3. INSILICO METHODS FOR DRUG DESIGNING

3.1. Types of QSAR Techniques

3.1.1. QSAR: (Quantitative Structural Activity Relationship)

The statistical method known as QSAR aims to connect a molecule's chemical and physical characteristics to its biological functions. The goal of QSAR is to predict the properties of molecules based just on their structure, without requiring in vitro or in vivo experimentation. Both time and resources are saved. Many descriptors are frequently utilized, including molecular weight, the number of rotatable bonds, LogP, and others. In practice, a lot of QSAR techniques are dependent on the data dimensions. 1D QSAR and 6D QSAR are among its ranges. The underlying premise of the so-called quantitative structure-activity relationship (QSAR) approaches is that a certain mathematical algorithm or rule connects the activity, or property, such as the hazardous impact, to the chemical structure [1,7].

Table 1: Types of QSAR techniques based on the data dimensions

DIMENSIONS	METHODS
1D- QSAR	Affinity correlates with pKa, molecular volume etc.
2D- QSAR	Affinity correlates with structure motifs.
3D- QSAR	Affinity correlates with a 3D-structure of the ligand.
4D- QSAR	Ligands are represented as an ensemble of conformers, orientations, protonation states, tautomers and stereoisomers.
5D- QSAR	Like 4D, with additional consideration of different induced-fit models
6D- QSAR	Like 5D, with additional consideration of different solvation scenarios

3.1.2. Hologram quantitative structure activity relationship (HQSAR)

There is no requirement for exact 3D ligand information in Hologram QSAR, a unique QSAR method. Using this method, the molecule splits into a fingerprint that codes for the regularity of occurrence of different kinds of molecular fragments. To put it simply, the size of the fragment to be included in the hologram fingerprint determines the minimum and maximum length of the pieces. A creation of linear and branching fragments, with sizes varying from 4 to 7 atoms, results in molecular holograms 22 [8].

3.1.3. Comparative molecular field analysis (CoMFA)

A novel method for elucidating the structure-activity link is comparative molecular field analysis (CoMFA). It is a well-known 3D QSAR technique, and development on CoMFA got underway in the 1970s. It provides values of CLogP, indicating that the ligands are constrained by the solvent repellent, and it also provides an explanation for the ligands' steric and electrostatic values [9].

3.1.4. Comparative molecular similarity indices analysis (CoMSIA)

It is one of the most recent 3D QSAR techniques. Comparative Molecular Similarity Indices Analysis (CoMSIA) is typically employed in the process of finding new drugs to identify shared uniqueness, which is essential for the appropriate binding of pharmacological receptors. This approach addresses hydrophobic fields, acceptors and donors of hydrogen bonds, as well as steric and electrostatic properties [10].

Table 2: Applications of QSAR

Chemical	Biological	Additional uses
1.Finding the boiling points. 2.Identification of the carbon-to-carbon relationship in alkenes. 3. The Hammett formula. 4. Taft formula. 5. P_{Ka} determination.	1. Identification of the metabolic route. 2. Discovery of drugs. 3. Partition coefficient prediction. 4. Forecast of toxicity.	1. Control of risks. 2. Detection of contaminants with genotoxicity.

3.2. VIRTUAL HIGH THROUGHPUT SCREENING

Using a computational technique called virtual screening, a vast library of chemicals is evaluated for their ability to bind particular locations on target molecules, like proteins, and compounds that are a good fit are tested. It works with the rapid search of huge libraries of chemical structures using computers to find those structures that are most likely to bind to a therapeutic target, usually an enzyme or protein receptor [11]. The process of finding new drugs now includes virtual screening as a crucial component. Virtual screening is described by Walters et al. as "automatically evaluating very large libraries of compounds" through the use of computer programs. The main focus of VS is on problems such as how to reduce the vast chemical space of over 1060 possible compounds to a manageable quantity that can be bought, manufactured and tested. The construction and optimization of targeted combinatorial libraries as well as the enrichment of libraries containing accessible compounds from vendor offerings or internal compound repositories are the main goals of more realistic VS scenarios. It is faster than traditional screening and less expensive than high throughput screening, scanning a large number of possible medicines in a short amount of time [12].

3.3. PHARMACOPHORE MAPPING

It involves obtaining a three-dimensional pharmacophore. A pharmacophore is a collection of characteristics, such as hydrogen bond donors and acceptors, positively and negatively charged groups, hydrophobic areas, and aromatic rings, along with their relative spatial orientation, that are hypothesized to be able to interact with a specific biological target. It is independent of specific chemical connectivity and is dependent on atomic qualities rather than element types. It can map the various combinations of pharmacophoric groups in the molecule and

exhibit conformational flexibility. By superimposing active chemicals, a pharmacophore map can be created to determine their shared characteristics. One can perform de novo design or 3D database searches based on the pharmacophore map. Small molecules frequently push one another out of a binding site on macromolecules due to their drastically differing two-dimensional geometries. Even more frequently, an active molecule becomes inactive when its structure is mono modified. These correlations between structure and bioactivity serve as an indirect means of examining the molecular characteristics and three-dimensional structure of the ligand's macromolecular recognition site [2,13]. Converting such 2D structure-activity data into the 3D specifications needed to bind to the target biomolecule is the aim of pharmacophore mapping. This makes it possible to create new active molecules or search 3D databases for other molecules with these 3D properties. A pharmacophore map identifies the bioactive confirmation of each active molecule and indicates how to superimpose, compare in 3D, the various active compounds. The map shows which kinds of points correspond to which compound conformations. The decisions as to the required points and the bioactive conformations are interdependent. i.e. the choice of one affects the choices available for the other. Features of a pharmacophore include donor and acceptor hydrogen bond atoms as well as donor and acceptor hydrogen bond sites. [1]

3.4. MOLECULAR DOCKING

The process of computing the binding affinity between molecules (ligand and protein structure) is known as docking. Determine the binding free energy of the complex that forms when a protein and ligand are docked together. The primary goal of molecular docking is to investigate an ideal ligand and the relative orientation of proteins and ligands so as to reduce the system's total free energy. One of the most popular techniques in structure-based drug design (SBDD) is molecular docking. An essential component of logical drug design is docking. The process of playing molecules in the right orientation to interact with a receptor is known as molecular docking. It is a normal process that takes place when two molecules of a cell join forces to create a stable complex [14,15].

3.4.1. Steps Involved

3.4.1.1. Receptor Preparation

Requires a docking tool to be used → Structures and sites to be chosen → Add charges → Frequently requires adding hydrogens → fluids, cofactors, and metals can be added or removed → pre-docking refinement.

3.4.1.2. Preparing the ligand:

Add bond orders → Input structures (extract from PDB or draw the structures using Chem draw or convert from SMILES) → Produce isomers in case chiral centers → Estimate the pka of each potentially charged atom → Create a structure for every combination of charges within a specific pH range → Reduce the number of structures → Typically employing a forcefield from molecular mechanics → Download public sets from pub chem or ZINC (available chemicals) for screening [16**].**

3.4.2. Types of molecular docking

1.Rigid docking.
2.Flexible docking.
3.Manual docking

3.4.3. Applications of Molecular Docking

- It is employed to predict the binding behavior of ligands that are already well-known.
- Determine new and powerful ligands.
- As a predictor of binding affinity.

3.5. MODERN DRUG DISCOVERY PROCESS

Modern drug discovery process involves the following steps:

3.5.1.Target Identification: The first step in target-based drug discovery is figuring out how a possible therapeutic drug target works and how it fits into the target site.. A target is typically a single molecule that is connected to a specific disease, like a gene or protein. A therapeutic target is a critical molecule that is a member of a specific metabolic or signaling pathway associated with a pathology or disease state, or with the survival or infectivity of a microbial pathogen [17].

3.5.2. Target Validation: Once a pharmacological target has been determined, a thorough analysis must be conducted to show that modifying the target will have the intended therapeutic impact. Target validation is the main bottleneck in the drug-discovery process. The target validation step will go much faster if computational techniques are used to speed up this procedure. Determining whether altering a target's function would result in the desired clinical outcome more precisely, the enhancement or eradication of a phenotype is a step in the target-validation process [17].

3.5.3. Hit and Lead Identification: Finding a small chemical "hit" serves as the initial step in the hit-to-lead pathway for many drug research targets.

Modern drug development relies heavily on the identification of small chemical modulators of protein function and the process of turning these into high-content lead series (Robert AG 2006). High-throughput screening (HTS) is typically followed by the "hit-to-lead" phase. A variety of technology-based methods, such as high-throughput biochemical and cellular assays, natural product assays, structure-based design, peptides and peptidomimetics, chemogenomics and virtual HTS and inventions based on literature and patents, can be used to identify hits [17].

3.5.4. Lead Optimization: The difficult, non-linear process of improving a verified hit's therapeutic properties through chemical structure modification is known as lead optimization, and it aims to produce potential medication. Target selectivity and affinity are maximized in lead structures. Nowadays, structure-based absorption, distribution, metabolism, and excretion (ADME) is aided by the use of docking approaches.

3.5.5. Pre-Clinical Studies: The goal of preclinical research and testing methodologies, both with and without the use of animal testing techniques, is to minimize hazards whenever a novel active ingredient is intended for use as a human medication. According to the NIH Clinicaltrials.gov Glossary of Clinical Trial Terms, they should be created to facilitate an early, risk-free, trouble-free, and cost-effective transition from preclinical to clinical trials in the development of pharmaceuticals. Researchers do both in vivo and in vitro experiments [17].

3.5.6. Clinical Studies: A clinical trial, which is often referred to as clinical research, is a study conducted on human subjects with specific health questions in mind. The quickest and safest route to discovering therapies that benefit patients and methods to enhance health is through meticulously carried out clinical studies. In the course of the clinical trial, the researchers will: find patients who fit the predefined criteria; provide the treatment or treatments; and gather health-related data from the participants for a certain amount of time. According to the Glossary of Clinical Trial Terms on NIH Clinicaltrials.gov, the U.S. National Institutes of Health (NIH) classifies trials into five different categories: quality of life, diagnostic, treatment, screening, expanded access, and prevention trials [17].

3.5.7.FDA Approval: In the United States, drug sponsors formally request approval from the Food and Drug Administration (FDA) for a novel medicine to be sold and marketed through the novel Drug Application (NDA). The NDA's objectives are to give FDA reviewers just enough information. All of the data from the earlier years of development, together with suggestions for the new medicine's production and labeling, are included in the NDA [17].

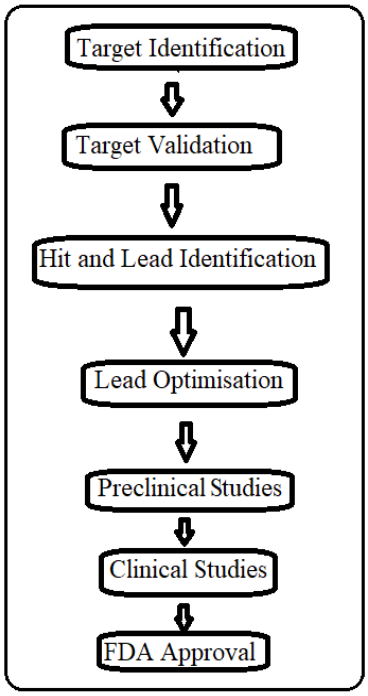

Figure 1: Steps involved in modern drug discovery

4. CHEMINFORMATICS TOOLS IN DRUG DISCOVERY

The field of drug discovery is where cheminformatics is most commonly used. The virtual libraries aid in predicting which substrate would work best for a certain reaction, which leads to the wet lab tests included in the drug-discovery process. Before cheminformatics, a medicine had to be developed for decades before it could be sold. However, because to Cheminformatics, this time has significantly decreased recently. With the aid of high throughput screening, the majority of the improbable candidates for a reaction are eliminated during the virtual screening process, saving a significant amount of time and labor [18].

4.1. SYMYX DRAW

With this free chemical structure sketching software, you may virtually represent chemical compounds in diagram form. It utilizes both standard chemical file formats, such as TGX files and MDL molfiles, in addition to its own file format. Chemical structures and reactions can be drawn manually or with the aid of IUPAC nomenclature. Additionally, it gives the IUPAC names of the chemicals we have identified.

Furthermore, it enables retrieval and search via chemical databases [19].

4.2. CHEM DRAW

Using this structure sketching tool, one may construct 3D chemical reactions and structures including whole rings, chains, functional groups, and bonds. It even enables one to use the tool to determine the qualities of the construction [20].

4.3. CHEM READER

Chemical structure diagrams can be extracted from digital photos using structure recognition software, which then transforms them into computer-readable chemical file formats. Chemical databases can then be searched using this information [21].

4.4. JME MOLECULE EDITOR

This free Java script software lets users create substructure queries that is, queries about the molecular structures and their substructures as well as design and update molecular diagrams. It can transform structures into a wide variety of file formats [22].

4.5. WENDI

Wendi is a search engine for unusual pharmacological information on the web. A kind of web-based integrative data mining technology that uses a variety of information sources to identify relationships between a query chemical and scientific papers, biological characteristics, genes and diseases that are typically confusing [23].

4.6. CHEM MINE TOOL

It is an online tool for small molecule analysis that acts as an interface between data mining and cheminformatics tools for various analytical studies in drug development and chemical genomics [24].

4.7. CML

Chemical markup language, or CML, is an online language that combines textual and non-textual data about chemical structures [25].

4.8. PUBCHEM

It is a database of tiny compounds and the biological activities they exhibit in experiments. It integrates and offers access capabilities for search, retrieval, visualization, and analysis [26].

4.9. PLSR

Partial Least Squares Regression, or PLSR, is a chemometrics tool that evaluates data in the presence of numerous incorrect and even incomplete variables. It relates and operates on two matrices based on some predesigned models [27].

4.10. OPEN BABEL

This software changes structures into various chemical formats by converting them into different chemical formats [28].

4.11. KING DRAW

With KingDraw, users may draw molecules, reactions, organic chemistry objects, and pathways in a free chemical drawing editor. It can also be used by users to forecast compound property. View 3D structures, translate chemical structures to IUPAC names, etc.

4.12. SWISS ADME

With the use of this website, you can forecast the pharmacokinetic characteristics, medicinal chemistry friendliness, druglike nature, ADME parameters, and physical descriptors of one or more small molecules to aid in drug discovery.

4.13. MOLINSPIRATION

A wide range of cheminformatics software tools are available from Molinspiration to support the manipulation and processing of molecules. These tools include the conversion of SMILES and SD files, normalization of molecules, tautomer generation, molecule fragmentation, calculation of various molecular properties required for QSAR, drug design and molecular modeling, high-quality molecule depiction, and molecular database tools that support substructure and similarity searches. Additionally supported by our products are data visualization, bioactivity prediction, and fragment-based virtual screening. Since the molinspiration tools are designed in Java, they are essentially compatible with all computer platforms.

4.14. CHEM SKETCH

Chem Sketch is a molecular modeling software that allows one to create and edit chemical structure images. Additionally, software exists that makes it possible for molecules and three- and two-dimensional molecular models to comprehend the makeup of functional groups and the arrangement of chemical bonds.

4.15. PROTEIN DATA BANK

Large biological molecules like proteins and nucleic acids have three-dimensional structural data stored in a database called the Protein Data Bank (PDB). The information submitted by biologists and biochemists worldwide, usually acquired through NMR spectroscopy, X-ray crystallography, or increasingly, cryo-electron microscopy, is freely available on the Internet through the websites of its member organizations (PDBe, PDBj, RCSB, and BMRB). The

Worldwide Protein Data Bank, or www PDB, is the institution in charge of the PDB.

5. APPLICATIONS OF CHEMINFORMATICS TOOLS

- Store and access the chemical structures throughout various file types.
- Determine whether the substructures match.
- Identify which two structures exactly match (equal).
- Finding shared substructures within a group.
- Break down molecules into smaller pieces.
- Obtain molecules by assembling components or sub molecules.
- Reaction product structures are produced as a result of applying reactions to input reactant structures.
- Make fingerprints on a molecular level. One of the oldest and most important uses of fingerprints is for chemical database indexing.

6. ADVANTAGES OF IN SILCO STUDIES

- Cost effectiveness
- Time efficiency
- Access to impossible to observe system
- Safety
- Predictive Power
- Complimentary to experimental research [29]

7. LIMITATIONS OF IN SILCO STUDIES

- In silico research may not be applicable to a larger population due to restricted analytical examination of the real-world circumstances used in the model.
- Limited to hypothesis testing: Rather than being used for new knowledge discovery or knowing the underlying mechanisms of biomechanical and physicochemical systems, in silico research is generally employed for hypothesis testing and prediction.
- Incorrectness error: The complexity and unpredictability of biomechanical and physicochemical systems are difficult for computer models to accurately capture, which might produce results that are either erroneous or deficient.
- Experimental control: considering that in silico research does not have the same experimental controls as in vitro or in vivo research, it might be challenging to confirm and replicate the outcomes.
- Limited comprehension of the underlying biology: Research conducted in silico depends on our present knowledge of biomechanical and Physicochemical systems, which lack clarity or completeness.
- Loss of real-world context: The complexity and dynamic nature of the real-world environment in which the system functions are not taken into consideration by computer simulations.
- Expensive and time-consuming computation: In silico research can be expensive and time-consuming when computing, especially for big or complex networks. [29].

8. CONCLUSION:

Computer aided drug discovery techniques have turned up to be boon to the scientific community in discovering the new drugs. As these tools are effective in terms of time, cost and man power. Various computational techniques that are used are QSAR prediction tools, Virtual High throughput screening, Molecular docking tools, cheminformatics tools etc. are highly helpful in the drug discovery.

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