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A REVIEW ON: COMPUTER AIDED DRUG DESIGNING

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ABSTRACT :

It is well known that the process of finding and developing a new medicine is extremely difficult and requires a significant investment of time and money. As a result, computer-aided drug design techniques are now routinely employed to improve the effectiveness of the drug development and discovery process. It involves synthesising novel compounds, docking them to target proteins, evaluating molecular interactions, determining the strength of the binding, and determining the characteristics of drugs. The process of Computer Aided Drug Designing (CADD) is economical and does not require any biological experiments. It allows us to learn about the interactions between drugs and receptors. Identification of binding sites, compound selection, docking and stocking, and lead optimisation are all included in structure-based drug design. According to their respective needs, different CADD approaches are deemed promising methodologies; nonetheless, between all of these, ligand- and structure-based drug design approaches are recognised as extremely effective and potent methods in drug discovery and development. It is evident that CADD aids in identifying a drug's appropriate qualities and suitability for pre-clinical testing. An overview of computational approaches a creative method for identifying new leads and support for the drug discovery and development process is provided in this article.

KEYWORD: CADD, structure-based drug design, ligand-based drug design, Target Protein and Binding, molecular docking.

INTRODUCTION:

Computational methods for drug discovery and development are acquiring a great deal of interest in terms of administration, implementation, and exploration. It could be a very complex, costly, and risky process to introduce a replacement medication to the market in terms of labour, money, and time. Drug research and development are often reported to require 0–14 years and around $1 billion in total funding [1]. Therefore, computer power-assisted drug style (CADD) technique is widely applied as a new drug style strategy to reduce time, cost, and risk-borne elements. It has been observed that using CADD techniques can cut medication development and discovery costs by up to five hundredth of the original amount [2]. CADD uses any software-based procedure for creating a standard to connect an activity to a structure [3]. The term "computer power-assisted drug style" (CADD) refers to the increasingly popular approach in the medical specialty field that is being made possible by the development and design of new, potent therapeutic agents with the use of computers in the drug style method. A therapeutic target could be a crucial molecule involved in a particular metabolic pathway linked to a specific disease, illness, or microbiological organism survival. A medication has a specific target and is either an advanced way or a horribly Brobding nagia method. This process began as soon as a chemist identified a drug candidate that exhibits the biological profile, finished the unique chemical entity's optimised chemical synthesis, and determined its activity profile [4,5]. The process of finding and developing a manufactured drug is referred to as an extremely sophisticated one; it requires billions of dollars and at least twelve years to achieve high value. Without this lengthy period of time, the risk of failure is increased to approximately ninetieth, and nearly 70% of funds are lost due to failure due to ineffectiveness or unfavourable side effects through clinical trials. Therefore, CADD is used to address these problems. For the de novo drug style, the three-dimensional organisation of the receptor is utilised to delever evalope a "novel" molecule [6,7]. This approach, which is frequently continuous, involves both lead modification and structure determination with the lead target [8]. With today's rapid rise in the field of pharmaceutical medicine and its discovery as a means of treating various diseases, the intricate method of drug style is particularly important to the creation of pharmaceutical drug advancements.

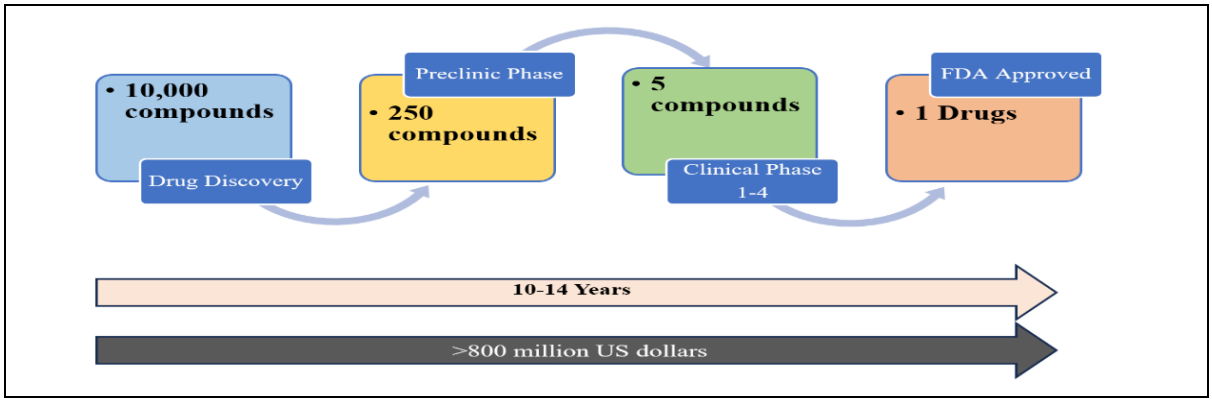

Figure 1:Traditional process of drug discovery and development.

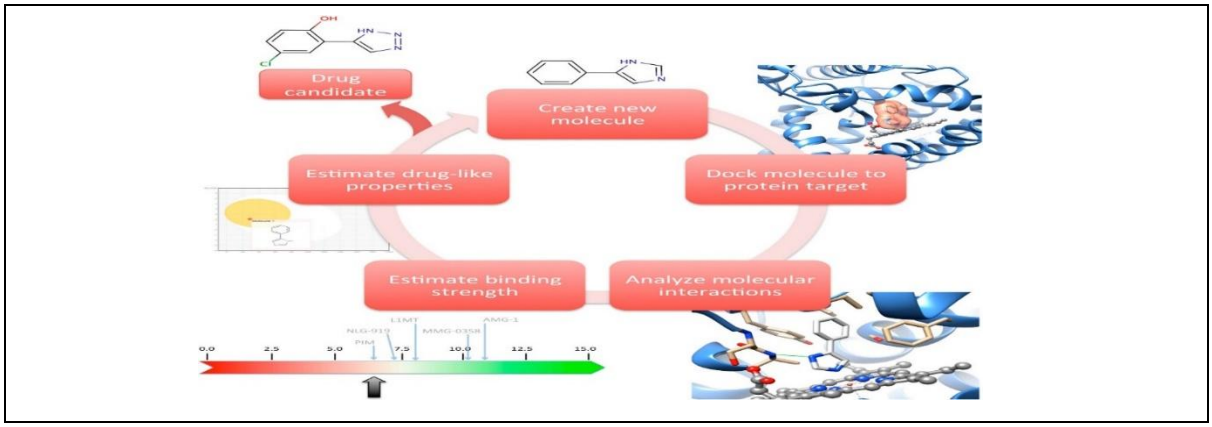

Figure 2:General Principle for Drug design through CADD

A CHRONOLOGY OF CADD:

1900 marked the introduction of the lock-and-key and receptor concepts by P. Ehrlich (1909) and E. Fisher. The principle of Quantitative Structure Activity Relationships (QSAR) was developed in the 1970s, although it had a few limitations. 2-Dimensional, retrospective analysis: the 1980s saw the advent of computer graphics, multidimensional NMR molecular modelling, X-ray crystallography, and CADD molecular biology. In the area of advanced medical research, more contemporary methods including high-throughput screening, combinatorial chemistry, and human genome bioinformatics were introduced in the 1990s [9].

COMPUTER AIDED DRUG DESIGNING PROCESS:

- Target Identification

  It is the pipeline's first essential step in the drug discovery process. Finding the right targets among thousands of potential macromolecules is a laborious task that can be accomplished by pathway analysis, genome analysis, and literature reference [10].

- Target Validation

  Once the target has been identified, a thorough analysis is required to show that changing the target would have the intended therapeutic impact. The goal of the target validation method is to ascertain whether changing the target would have the intended therapeutic outcome [11].

- Lead

  Leads can be identified by using methods such as structure-based design. At this point, strategies to increase the lead's affinity for the target can be found by analysing the structure of the target protein in complex with the lead molecule. Since the leads employed in this instance might not be ideal, it is important to optimise them to improve their affinity for the target sites. They can be optimised by changing their

structural characteristics.

- IN SILICO ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity)

  Estimate Protein interactions involved in the ADMET process are studied using methods such as data modelling and molecular modelling [12]. The creative process of creating novel drugs based on a biological target's knowledge is known as rational drug design. Most often, a medication is a small organic molecule that either stimulates or inhibits the activity of a biomolecule, like a protein, to provide the patient with a therapeutic benefit. Essentially, drug design is the process of creating tiny compounds that interact with a biomolecular target by being complimentary in form and charge, and so will attach to it. Drug design uses computer modelling approaches often, but not constantly. However, it is crucial to point out that using computers as a tool in the drug design process cannot take the place of having a thorough grasp of the system being studied. Computers are merely supplementary instruments for gaining a deeper understanding of the chemistry and biology involved in the issue. Researchers have spent many years creating medications using computer-aided rational drug design techniques. When these efforts started, easy access to computational resources was not possible.

- MACHINE LEARNING AND DEEP LEARNING TECHNIQUES USED FOR DRUG DISCOVERY

  Researchers have been employing a variety of molecular modelling and molecular docking strategies for a long time. Current developments in machine learning and the process of designing new drugs has been greatly expedited by deep learning techniques. The academic and industrial communities both make extensive use of these methods. Thankfully, there is an abundance of data available in the modern world, even if these machine learning algorithms are typically data-hungry. Currently, a large number of pertinent chemical and biological datasets for deep learning and machine learning models are freely accessible. Drug development uses machine learning models for data mining, data analysis, and molecular property prediction, among other uses. Three categories can be used to categorise machine learning techniques, and each category contains a variety of algorithm types. Figure 3 shows a flowchart with several categories.

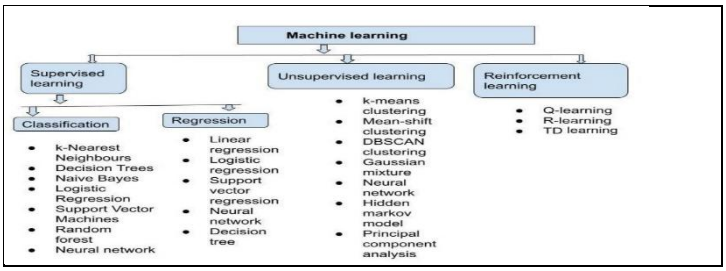

Figure 3:Flowchart of machine learning techniques.

Typically, a dataset is split into training and test sets before being fed into a machine learning model. In supervised learning, models are trained to generate the desired output using a training set. Using training data points, we approximate a function f(x) with the help of this dataset, which has input and output. The correctness of the model is evaluated using a loss function (Lε), and gradient descent is used to adjust the parameters until the error is properly minimised.

$$pn+1 = pn - \nabla L\varepsilon$$

$$\because n = \text{number of steps}, p = \text{parameter vector}$$

Supervised learning spans into two categories: regression and classification.

Test data is categorised using a classification system and assigned to distinct categories. It identifies particular entities in the collection and guesses intelligently as to what labels or definitions such things should have. Among the most popular classification techniques are random forest, k-nearest neighbour, decision trees, support vector machines (SVMs), and linear classifiers. Regression analysis is used to examine the relationship between dependent and independent variables. Predictions are frequently made with it, including those on a company's sales revenue. Polynomial regression, logistic regression, and linear regression are common regression algorithms.

MAJOR TYPES OF APPROACHES IN CADD:

For drug design using CADD, there are primarily two types of approaches:

1. Structure based drug design / direct approach
2. Ligand based drug design / indirect approach

1. STRUCTURE BASED DRUG DESIGN / DIRECT APPROACH:

De novo drug design and virtual screening are both part of the process known as structure-based drug design (SBDD). These techniques are highly effective and provide an alternative strategy for finding and developing drug design courses. The drug chemical compound is computationally screened against the known target structure in virtual screening [13]. In the traditional approach to drug discovery and design, referred to as forward pharmacology or classical drug design, rational drug design is highly effective and expensive. Finding prospective target proteins is the first stage in the rational drug design approach, also known as reverse pharmacology, which is used to screen small molecule libraries. Because they deal with the 3D structure of a target protein about the disease at the molecular level and analysis of binding energetics, ligand protein interaction, and docking process, the methods used in SBDD structure-based virtual screening (SBVS), molecular docking, and molecular dynamics are more specific, efficient, and rapid processes for lead discovery and optimisation **[14].** Several medications are identified by SBDD with the use of various methodologies, such as antibiotic norfloxacin and the MD simulation-discovered thymidylate synthase inhibitor, raltitrexed, and possible inhibitor of HIV protease **[15].** More than 100,000 protein three-dimensional (3D) structures are available in SBDD.

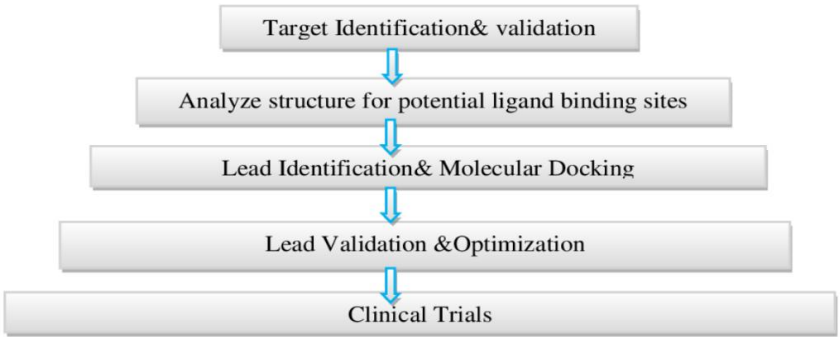

Figure 4:Steps involved in SBDD

Target Protein and Binding Site Identification:

The first stage in the SBDD procedure is to identify the target protein [16]. In order to determine the optimal pharmacophores of the "novel" ligand, the binding site of the target macromolecular supplied precise information regarding protein-ligand interaction, post-docking dynamics, and hydrogen bond formation [17]. binding sites identified by integrated structural biology methods, such as NMR and X-ray crystallography, in the three-dimensional structure of the target macromolecule. After the target protein has been resolved, the binding pocket needs to be located. The cavity in which the ligand binds is minuscule and exhibits the intended therapeutic effect. For the purpose of mapping binding sites, these techniques provide information on the Van der Waals (vdW) forces and energy interaction. Numerous techniques are created by the energy interaction calculations specifically for SBDD binding site mapping, and these techniques pinpoint the unique target protein locations that interact with beneficial functional groups on medications. These are being recognised by the Q-siteFinder protein [18]. The vdW interaction between the protein and methyl probe, a tiny organic chemical, is calculated using the Q-siteFinder method, which is frequently used for binding site prediction. The interaction between the two is graded according to its totality. The target protein's binding cavity is docked when the vdW interaction is discovered [19].

Molecular Docking and Scoring Functions:

A computational method called "molecular docking" is used to examine the molecular interactions between ligands and target receptors. It ranks ligands according to how well they bind to receptors through the use of different scoring algorithms [20]. The target active site-friendly binding poses of ligands depend on two things: (a) an enormous conformational space that accommodates several binding poses; and (b) a clear prediction of the binding affinity of ligands that correspond to each binding pose [21]. Table 1 provides a selection of commonly used molecular docking programmes. Flexible-ligand search docking and flexible protein docking are the two categories into which molecular docking falls. While Monte Carlo (MC) and molecular dynamic (MD) methods are typically used in flexible-protein docking, three algorithms systematic, stochastic, and simulation are most frequently used to account for the ligand flexibility in the case of the flexible-ligand search docking method [22, 23, 24].

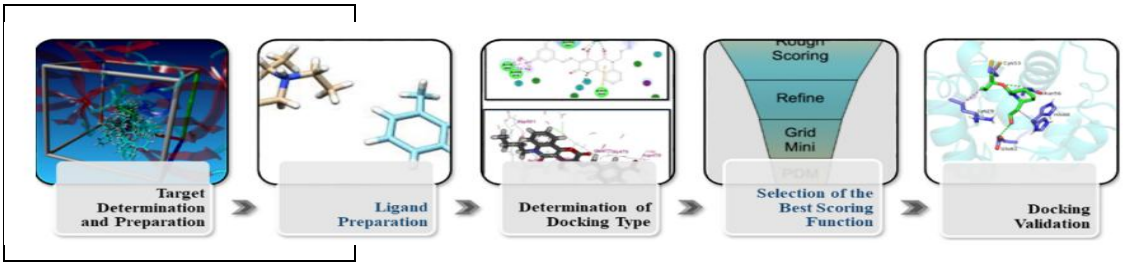

Figure 5:Steps involved in Molecular Docking

Table 1:Programs/ Software for Molecular Docking.

Programs	Availability	Properties
AutoDock [25]	Free	Docking with a rigid body and flexible docking. It is used along with Autodock tools.The grid maps are calculated automatically.
AutoDock Vina [26]	Free	It uses repeating local search global optimization, is faster than AutoDock, and has enhanced binding affinity prediction with a new score algorithm.
Dock [27]	Academic	Flexible docking. It is commonly used for flexible targets and flexible ligands.
LeDock [28]	Academic	Docking is flexible. It is recommended for use in virtual screening since it produces results quickly and with high accuracy.
FlexX [29]	Commercial	Docking with a rigid body and a flexible docking. It has the potential to be used in virtual screening.
Glide [30]	Commercial	Ligands in this docking are flexible. It uses information about the area to decrease the software's search range. It has XP (extra precision), SP (standard precision), and virtual screening modes that are extremely efficient.
GOLD [31]	Commercial	Docking flexibility. The study of its accuracy and reliability appeared to give positive results.
Plants [32]	Academic	It maintains a good balance between usability and efficiency. It helps the calculation of water exchange.
ICM [33]	Commercial	It supports both ligand-protein and protein-protein docking. It includes an ICM-Pro interface that makes docking simple.
MOE [34]	Commercial	It has a good interface and is easy to use. It also includes various techniques used in protein and ligand production.

LIGAND BASED DRUG DESIGN / INDIRECT APPROACH:

An overall method for clarifying connections between the structural and physicochemical characteristics of compounds and ligands and their biological activities is provided by LBDD.

When three-dimensional structural data for a target protein is not available, this method is used. This procedure uses the knowledge currently known about ligands and their biological action to create new, viable therapeutic candidates. Since over 50% of approved medications target membrane proteins for which 3D structures are frequently unavailable, such as GPCR, LBDD is a commonly employed technique in pharmaceutical research. It is predicated on the idea that substances with comparable structural characteristics interact with and inhibit similar target molecules in addition to having similar biological effects. The LBDD technique is predicated on its representation of molecules. Molecular descriptors are numerical numbers that are used to describe a molecule's physical and structural characteristics. The subject of molecular descriptors is remarkably multidisciplinary and encompasses various theories. Molecular descriptors belonging to the 0D-4D class are used to represent active compounds. 0D molecular descriptors are constitutional and count descriptors; 1D descriptors are chemical fingerprints or lists of structural fragments, like SMILES and SLN; 2D descriptors are graph invariants, where atoms are classified as nodes and bonds as edges; 3D descriptors are geometrical, WHIM, and others; and 4D descriptors are those obtained from CoMFA or DRID methods. One important component of the LBDD approach is similarity searching. This method ranks compounds found in a database by using a known active chemical as a query compound to locate comparable compounds. This theory states that molecules with similar structures will have comparable physicochemical and biological properties. To measure the degree of similarity (similarity/dissimilarity), numerical descriptors are used, and a similarity coefficient is defined. For similarity searching, fingerprint-based similarity or 2D similarity measures are frequently employed. LBDD is commonly classified as pharmacophore modelling or Quantitative Structure Activity Relationship (QSAR) [35].

I. Quantitative Structure-Activity Relationships (QSAR):

An integral component of the drug optimisation process is the QSAR approach. The QSAR method is used to quantify the relationship between a set of chemicals' chemical structure and biological process [36,37]. The created QSAR model serves as a roadmap for determining which compounds to alter and for optimising the active ingredient to increase pertinent biological activity.

The methods some are used in QSAR

1. Determine the target biological activity's value through experimentation, and then choose the best ligand.
2. Find molecular descriptors based on the physical-chemical characteristics of molecules.
3. The link between biological activity and molecular description is found.
4. QSAR model for statistical stability was tested at the last stage.

The QSAR method's workflow:

First, determine or pick the group of molecules or compounds whose intended biological activity has been empirically determined. After the molecules are chosen, they are studied utilising quantum mechanical or molecular mechanism techniques in the silico-model [38–40]. Molecular descriptors are created to characterise the chemical properties of compounds once the active ligand has been identified. Choose appropriate molecular descriptors based on the physical-chemical characteristics of molecules. Every molecule has a unique molecular "Fingerprint" that is produced using molecular descriptors. Molecular descriptors are produced using knowledge-based molecular mechanical or quantum chemical methods. Using molecular descriptors, a mathematical relationship explaining the variety of molecular biological activity was developed. The last stage involves putting the constructed models through both internal and external validation processes to assess their statistical resilience and predictive ability.

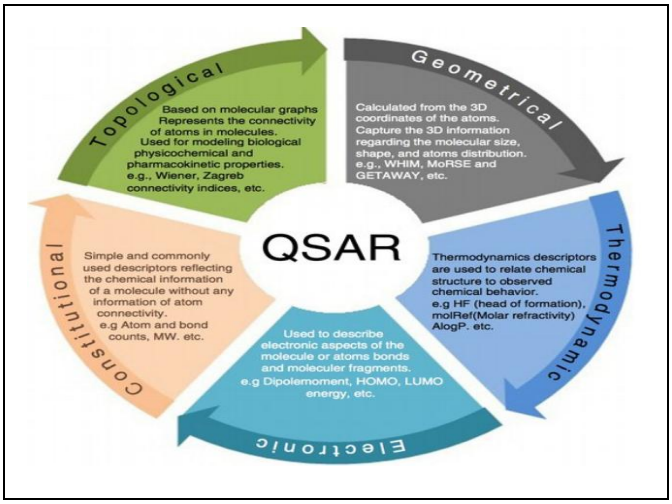

Figure 6:QSAR based drug design

Pharmacophore Modeling:

The spatial arrangement of chemical characteristics of ligands necessary for interaction with the target receptor is explained by a pharmacophore model [41]. Hydrogen bond donors, hydrogen bond acceptors, aromatic ring systems, hydrophobic regions, positively and negatively charged ionizable groups are a few of the chemical elements that are employed in pharmacophore modelling. Pharmacophore-based virtual screening can identify ligands with diverse scaffolds that share a similar spatial arrangement of important interacting functional moieties. The pharmacophore model can be extended to include the bioactive conformation of the molecules inside the target binding site. In QSAR investigations, the pharmacophore model is frequently employed during the molecular alignment phase [42]. A few often-used programmes that enable the pharmacophore model to be constructed automatically include GALAHAD, PharmMapper, PHASE, LigandScout, and Catalyst. Spatial restrictions in areas where inactive molecules are present are also incorporated into a good pharmacophore model, and the model is frequently further optimised to reduce its restrictiveness. Every pharmacophoric characteristic that isn't reliably found in active compounds is either eliminated or turned into an optional element in the finished model. To reduce the possibility of false negative and false positive outcomes, the pharmacophore model that is developed needs to have the highest possible sensitivity and specificity. It also needs to be validated using an external, independent test set [43]. A sequence-derived 3D pharmacophore model is very helpful if neither of the known active chemicals or the 3D structure of a receptor are known. Pharma3D, for instance, uses homology models and 3D crystal structures to determine the common sequence motif that is crucial for receptor ligand biomolecular interactions in protein families [44, 45].

Table 2: A list of pharmacophore modelling tools.

Tools	Description	Reference
Catalyst	The catalyst programme uses an algorithm to find three-dimensional arrangements of chemical characteristics shared by a group of ligands. Each arrangement is assigned a score based on how common it is to the input set as well as how rare it is thought to be.	[46]
LigandScout	The pharmacophore model utilised for high throughput virtual screening is based on protein-ligand interactions, such as hydrogen bond interactions, charge transfers, and lipophilic areas, which are detected and classified by LigandScout, a fully automated tool for pharmacophore generation.	[47]
DISCO	As an adjunct to 3D QSAR, DISCO is an automated pharmacophore approach that searches the data for all plausible pharmacophore hypotheses.	[48]
PharmaGist	PharmaGist is a publicly accessible online service that creates ligand-based pharmacophore models from a set of drug-like compounds (up to a maximum of 32) with a binding affinity for the target protein.	[49]
PharmMapper	Using the pharmacophore mapping method, PharmMapper server is a freely accessible web server that is frequently used to identify putative target receptors for a particular small drug.	[50]

BENEFITS OF CADD :

For drug development initiatives, bioinformatics technologies and CADD techniques provide a number of advantages [51].

- Cost Savings:
  According to the Tufts Report, each drug that is successfully introduced to the market comes at a cost of $800 million in drug discovery and development. Nowadays, a lot of biopharmaceutical businesses use bioinformatics tools and computational techniques to lower this expense burden. Experimental research can be guided by virtual screening, lead optimisation, and bioavailability and bioactivity predictions. Based on the outcomes of CADD simulations, only the most promising experimental lines of inquiry can be pursued and experimental dead ends can be avoided early.
- Time-to-Market:
  Programmes for drug development can select only the most promising drug candidates with the aid of CADD's predictive power. Biopharmaceutical companies can accelerate the time to market by zeroing in on certain lead candidates and avoiding potentially "dead-end" substances in their medication research.
- Insight:
  The profound understanding that researchers gain regarding drug-receptor interactions is one of the intangible advantages of CADD and the application of bioinformatics techniques.

Drug compound molecular models can provide light on complex, atomic-scale binding features that are hard to picture in any other manner. Researchers frequently come up with novel suggestions on how to alter drug compounds for better match when we show them fresh molecular models of their potential drug compounds, their protein targets, and how the two bind together. This is an intangible advantage that might support the planning of research initiatives.

When combined, bioinformatics and CADD are a potent tool for drug discovery and development. Finding qualified, experienced individuals to oversee all of the bioinformatics tools at our disposal will be a significant difficulty for us moving forward; this will be the subject of a later essay.

- More Computer-aided Drug Design Developed Will Speed up Drug Development

Researchers in Germany have documented a step towards the long-awaited day when scientists would virtually exclusively use computers to identify and develop medications for conditions like cancer, AIDS, arthritis, and other illnesses rather than depending on the antiquated trial-and-error approach. Michael C. Hutter [52] and colleagues observe in the article that computer-aided drug design is already a valuable research tool. The process entails analysing the chemical structures of possible medications using computers in order to identify the most promising ones. Computer programmes currently in use examine a variety of chemical properties to assist in differentiating between substances that resemble drugs and those that do not. These programmes typically aren't able to test for every trait at once, which runs the danger of missing potentially useful chemicals that resemble drugs.
Researchers present a more progressive and effective system in the new study. Their new programme runs a brief screen to look for signs of drug use, and then it runs a second, more thorough check to look for more signs of drug use. They used their novel classification scheme on a set of around 5,000 compounds that had undergone prior drug-like activity screening. The researchers report that the new approach was more effective at detecting molecules that resembled pharmaceuticals, "thereby up to 92 percent of the nondrugs can be sorted out without losing considerably more drugs in the succeeding steps."

WHAT IS THE NEXT STAGE IN CADD METHODS?

Over time, there have been several modifications in the formulation and discovery of new medications. The empiricism of drug design and identification has given way to rational design with the advent of software development and informatics advancements [53]. Furthermore, as shown by the numerous publications and ongoing discoveries in this sector, bioinformatics advancements and high-quality software stimulate the development of new CADD-based methodologies [54]. Still, where will the development of CADD ultimately lead us?

As time went on, several obstacles were removed, and the protocols improved in effectiveness. Flexibility is still the most important feature to be surpassed in CADD-based virtual screening, even after much advancement [55,56]. The technique that has been investigated the most and produced the best results is the combination of molecular docking with dynamics. Nonetheless, efforts must be made to produce force fields that are more realistic, and developments in informatics engineering enable molecular dynamics with little computer resources, which is now a standard procedure in any lab that designs drugs [57,58]. Our goal is to create software that seamlessly integrates these two approaches, making it simple to use and quickly applicable in any drug screening initiative. Will a "new" approach to drug design be based on virtual screening using molecular dynamics in this way? The Ge et al. paper emphasises that increasing the Graphics Processing Unit (GPU) is closely related to high-performance computing through molecular dynamics simulations, and this computer feature might be a substitute to enhance new virtual screening investigations [59].

Thus, the next generation of CADD techniques and virtual screening might be the field's frequent advancement.
The novel product is invalidated when evaluated in an in vivo model or in clinical trials due to incorrect pharmacokinetic properties and toxicity, which are actually attributable to the drug design process's inadequacies [60]. Therefore, drug discovery campaigns may benefit greatly from computational techniques that can be used to predict these features [61]. Moreover, a medication that knocks down a gene can be created in systems biology [62]. Finding important variables in a multifactorial setting that initiates a disease is crucial because it enables the study of drug additive effects and epistatic interactions [63]. Could the next step involve utilising computational techniques to examine these pharmacological properties? System biology is crucial to pharmaceutical companies, according to Kohl et al., primarily for determining a drug's multitarget profile and mapping the additive effects of a therapeutic combination [64]. Thus, the use of computational approaches in this approach can be significant.

Molecular docking, dynamics, and other conventional techniques are examples of CADD-based classical methods that must overcome various obstacles. As a result, techniques based on artificial intelligence (AI), like machine learning (ML) and deep learning (DL) algorithms, may represent the next evolution of CADD since the real method necessitates a number of steps, including biological assays, lead optimisation, and target validation. By using data from past entries, machine learning can address problems. The machine mimics "human reasoning" when solving issues. Artificial intelligence (AI) algorithms are finding application in drug screening, finding novel compounds and targets, repurposing drugs, directing molecular manufacturing, biological assessment, and other areas. In a shorter amount of time, this method has been used to find promising medications in databases including millions of molecules [65,66]. In this sense, would the upcoming generation of CADD methodologies and drug design incorporate AI, ML, and DL? In this regard, we'll wait for our colleagues' advancements in software development and algorithms to make this method indispensable in research labs.

APPLICATION OF CADD [67]:

1. CADD can help prevent some of the blind spots from earlier studies and make intuitive design more accessible, guiding the development of new medications with purpose.
2. By removing the molecules with undesired features using in silico filters, it provides the most promising medication candidate.
3. It minimises the need for artificial and biological testing.
4. It is quick, automatic, economical, and saves time.
5. It is familiar with the pattern of drug receptor interactions.
6. The techniques decrease the probability of final phase failures.
7. By searching through large compound libraries in silico, it provides compounds with higher hit rates than traditional high throughput screening.

CONCLUSION:

In the field of drug discovery and development, computer-aided drug design is a useful technology that allows us to quickly and affordably identify the most promising therapeutic candidate. It consistently gives promise for advancements in the field of drug research. Computer-aided medication design has produced several noteworthy research findings in recent years, and it will likely play a significant role in the near future. With the advancements made so far, computer-aided drug design appears to have a bright future that will help find many more therapeutics in the future. The computational approach to drug design is becoming more popular these days because everyone wants to make more money in less time and is interested in saving money and time, especially in the case of industries.
In addition, the newly created molecules could serve as a probe for additional study, guaranteeing CADD a prosperous future in the years to come.

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