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Chapter

Molecular Docking: Metamorphosis in Drug Discovery

Kishor Danao, Deweshri Nandurkar, Vijayshri Rokde, Ruchi Shivhare and Ujwala Mahajan

Abstract

Molecular docking is recognized a part of computer-aided drug design that is mostly used in medicinal chemistry. It has proven to be an effective, quick, and low-cost technique in both scientific and corporate contexts. It helps in rationalizing the ligands activity towards a target to perform structure-based drug design (SBDD). Docking assists the revealing of novel compound of therapeutic interest, forecasting ligand-protein interaction at a molecular basis and delineating structure activity relationships (SARs). Molecular docking acts as a boon to identify promising agents in emergence of diseases which endangering the human health. In this chapter, we engrossed on the techniques, types, opportunities, challenges and success stories of molecular docking in drug development.

Keywords: molecular docking, drug discovery, ligand-protein interaction, SAR, molecular recognition, drug design

1. Introduction

Medicinal chemistry relates to the design and production of compounds that can be used in medicine for the prevention, treatment or cure of human and animal diseases. Medicinal chemistry includes the study of existing drugs for their biological properties and structure activity relationships (SARs) [1, 2]. The discovery and development of a new drug with desired therapeutic activity is a long, tedious and expensive process. The industry statistics suggest that up to 10,000 compounds are synthesized and tested, up to 100 compounds are assessed for safety and only 10 compounds are tested clinically in humans for every drug that is approved for medical use. Today it takes approximately ten years and requires high cost to bring a new drug in market. In spite of the tremendous costs involved the payoff is also high and improvement made in preventing and controlling human disease. Even when the new drugs come in the market its success is not assured [3, 4]. Many centuries ago, human beings started using chemicals to treat the diseases. Hippocrates recommended the use of metallic salts such as copper and zinc, iron sulphate and cadmium oxide as drugs. In 1500 A.D., Carpensis employed mercuric compounds to treat syphilis. Urea was the first organic compounds to be synthesized in laboratory by Wohler in 1852. Between eighteenth

and nineteenth century, several organic compounds were synthesized which included drugs such as salicylic acid (Kolbe), antipyrine (Knorr), aspirin (Dresser), barbital (Emil Fischer and Mering), prontosil, the first sulpha drug (G. Domagk), chlorpromazine (Charpentier), phenyl magnesium bromide (Victor Grignard), polyethers (Charles J. Pedersen) and others [5]. Except, the therapeutic utility of these agents, nothing more was known about their mechanism of action and it was only believed that they were effective because of their physicochemical parameters like partition coefficient, hydrogen bonding, van der Waal's forces, dipole-dipole interactions and anionic bonds, etc. [6, 7]. Earlier to the chemical era, it was the natural products mostly from plant sources, which were used in therapeutics. Later, progress in knowledge of chemistry helped to isolate and identify the active ingredients in plants. Some of the outstanding achievements of such phytochemical approach include the discoveries such as digitalis glycosides from foxglove plant by William Withering in 1785; the opium alkaloids like morphine and codeine from poppy plant by Serturner in 1806; anti-malarial such as quinine, quinidine, cinchonine from cinchona bark by Pelletier and Dumas in 1823; belladonna alkaloids like atropine and scopolamine by Mein in 1833; rauwolfia alkaloids (reserpine and deserpidine) by Muller et al. in 1952, etc. In addition, many important natural products like antibiotics, steroids and peptide hormones, vitamins, enzymes, prostaglandins and pheromones were discovered in the concurrent period [8, 9]. The synthesis of compounds is followed by screening of its pharmacological actions. The observation of interest and repeatable biological activity in such screening had always opened the pathways for additional chemical research to prepare their analogs so as to obtain significant newer medicinal products. A small change in structure frequently leads a profound change in the pharmacological effect. This logic has prompted to synthesize derivatives of natural compounds and the structural analogues of biologically interesting substances with the "lead" (prototype) compound [10]. Many of the currently used antispasmodics [11–14] (dicyclomine, cyclopentolate, clidinium bromide, mebeverine, metoclopramide, tropicamide), antibiotics [15–20] (penicillins, cloxacillin, amoxacillin, ampicillin, cefadroxil, cefaclor, cefixime, cefepime), sulphonamides [21–25] (sulphacetamide, sulphadiazine, sulphasalazine, sulphamethoxazole), anthelmintics [26–28] (albendazole, mebedazole, pyrantel pamoate, piperazine, diethylcarbamazine citrate, praziquantel, niclosamide), antimycobacterials [29–31] (clofazimine, dapsone, ethambutol, isoniazid, benzothiazole, sulphonamide, rifampin), analgesics [32–35] (aspirin, diclofenac sodium, ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam), anticonvulsants [36–40] (phenytoin, ethosuximide, carbamazepine, sodium valproate, riluzole), antitumours [41–46] (amsacrine, azacitidine, chlorambucil, cyclosporine, fluorouracil), diuretics [47–51] (acetazolamide, chlorothiazide, furosemide, triamterene, spironolactone), antimalarials [52–56] (chloroquine, primaquine, amodiaquine, proguanil, pyrimethamine), antifungals [57–60] (griseofulvin, nystatin, miconazole, tolnaftate, clotrimazole), antihistaminics [61–65] (chlorpheniramine maleate, promethazine, astemizole, cetirizine hydro-chloride, fexofenadine) have been obtained by synthetic or semi-synthetic approach. In recent years, the molecular studies are more directed to discover new targets for better treatment of the disease. In addition, newer screening methods of assays, studying the effect of drug on the cell lines, availability of purified or recombinant enzymes and improved understanding about the nature and properties of receptor systems immensely boosted the drug research. It is well recognized that a medicinal chemist had been a key person in the discovery of a new drug. He synthesizes a new drug, isolates and characterizes natural products and in association of

pharmacologist establishes a rational SAR. Moreover, SAR had proved to be vital and fundamental to drug discovery [66].

1.1 Discovery of drugs of the future

Traditionally, new medications have been discovered by screening a large number of synthetic chemical compounds or natural items for desired effects. Although this method of developing novel pharmacological agents has proven to be successful in the past, it is not optimal for a variety of reasons. The most significant disadvantage of the screening approach is the demand for a proper screening procedure. Another problem with the screening process is that because of its random nature, it is inherently repetitious and time consuming just to find a chemical with the desired activity [67, 68]. Drugs can be created particularly to interact with the target molecule in such a way that the disease is disrupted after the disease process is understood at the molecular level and the target molecule (s) is defined. Because of the large quantity of data that must be gathered in order to produce medications using this method, here is where computer-aided drug design will have the most influence [69, 70].

In discussing various techniques of finding new drugs described in **Figure 1**, it is important to remember that drug discovery is both a cumulative and a reiterative process. Drugs developed mechanistically will likely to be screened and later modified in order to produce the best candidate design [71]. The use of stiff constructs for structure and targets is common in the early stages of using molecular modelling to create medications. In medication design, the flexibility of molecular information, both in single molecules and in molecules interacting with each other, is a crucial and difficult subject.

Since, the discovery of morphine in 1806 lot many important drugs came for remedy of humans, important results in drug discovery during last three centuries is shown in **Table 1**.

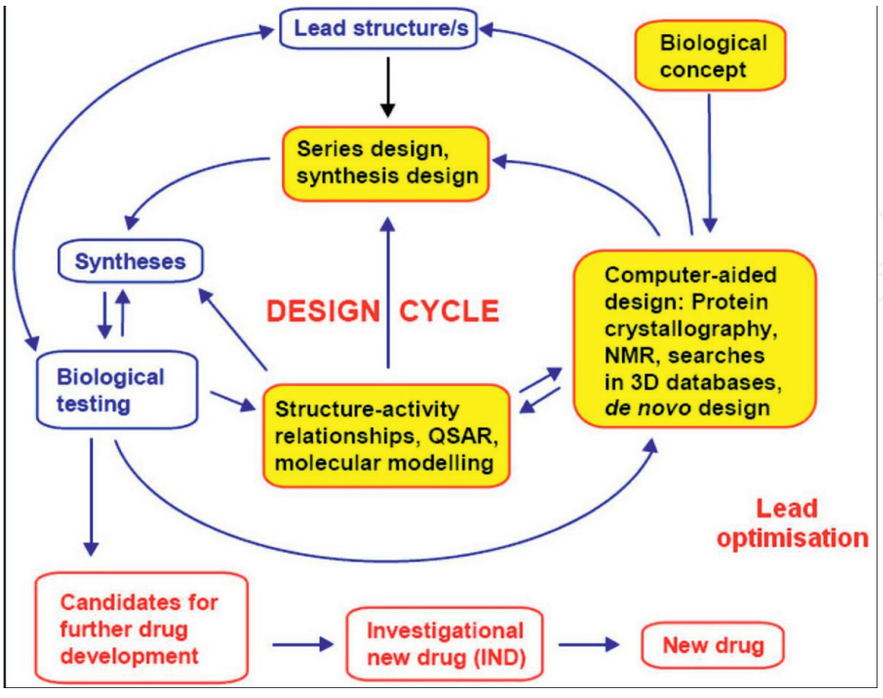


Figure 1.
Lead optimization cycle.

Year	Drug	Biological action	Year	Drug	Biological action
1806	Morphine	Hypnotic agent	1990	Ondansetron	Antiemetic agent (5-HT3 blocker)
1875	Salicylic acid	Anti-inflammatory agent	1991	Sumatriptan	Anti-migraine agent (5-HT1 blocker)
1884	Cocaine	Stimulant, local anaesthetic agent	1993	Risperidon	Antipsychotic agent (D2/5-HT2 blocker)
1888	Phenacetin	Analgesic and antipyretic agent	1994	Famciclovir	Anti-herpes (DNA polymerase inhibitor)
1899	Acetylsalicylic acid	Analgesic and antipyretic agent	1995	Losartan	Antihypertensive agent (A II antagonist)
1903	Barbiturates	Sedatives	1995	Dorzolamide	Glaucoma (carbonic anhydrase inhibit.)
1909	Arsphenamine	Antisyphilitic agent	1996	Nevirapin	HIV reverse transcriptase inhibitor
1921	Procaine	Local anaesthetic agent	1996	Indinavir, Ritonavir,	HIV protease inhibitors
1922	Insulin	Antidiabetic agent	1997	Saquinavir	HIV protease inhibitor
1928	Estrone	Female sex hormone	1997	Finasteride	Hair loss
1928	Penicillin	Antibiotic agent	1998	Sibutramine	Adipositas (lipase inhibitor)
1935	Sulphachrysoidine	Bacteriostatic agent	1998	Orlistat	Adipositas (lipase inhibitor)
1944	Streptomycin	Antibiotic agent	1999	Sildenafil	Erectile dysfunction
1945	Chloroquine	Antimalarial agent	2000	Celecoxib, Rofecoxib	Anti-arthritis agents (COX-2 inhibitors)
1952	Chlorpromazine	Neuroleptic agent	2001	Amprenavir	HIV protease inhibitor
1956	Tolbutamide	Oral antidiabetic agent	2002	Cyclosporine A	Thrombosis (synthetic LMWH)
1960	Chlordiazepoxide	Tranquillizer	2002	Imantinib	CML (specific ABL-TK inhibitor)
1962	Verapamil	Calcium channel blocker	2005	Telmesetan	Potassium pump inhibitor
1963	Propranolol	Antihypertensive agent (beta-blocker)	2007	Oseltamavir	Antiviral
1964	Furosemide	Diuretic agent	2008	Saxgliptin	Antidiabetic (DPP-4 inhibitor)
1971	L-dopa	Anti-Parkinson agent	2010	Fingolimod	Multiple sclerosis
1975	Nifedipine	Calcium channel blocker	2012	Avanafil	Erective dysfunction
1976	Cimetidine	Anti-ulcers agent (H2 blocker)	2013	Riociguat	Hypertension
1981	Captopril	Antihypertensive agent (ACE inhibitor)	2014	Dapagliflozin	Type II diabetes
1981	Ranitidine	Anti-ulcers agent (H2 blocker)	2015	Ivabradin	Heart failure
1983	Cyclosporine A	Immunosuppressant	2016	Rucaparib	Ovarian cancer

Year	Drug	Biological action	Year	Drug	Biological action
1984	Enalapril	Antihypertensive agent (ACE inhibitor)	2017	Plecanatide	Chronic constipation
1985	Mefloquine	Antimalarial agent	2018	Annovera	Contraceptive
1986	Fluoxetine	Antidepressant (5-HT transporter)	2019	Ubrogepant	Migrain
1987	Artemisinin	Antimalarial agent	2021	Pafolacianine	Cancer
1988	Omeprazole	Anti-ulcer agent (H/K-ATPase inhibitor)	2022	Pafolacianine	Insomnia

Table 1.
Important results in drug discovery.

1.2 Computer-aided drug design

Drug research and discovery is a time-consuming and costly procedure. In order to get a medicine to market, it takes an average of 10–15 years and $500–800 million dollars [72]. This is why, in order to speed up the process, computer-assisted drug design (CADD) technologies have become popular in the pharmaceutical business. CADD, as shown in **Figure 2**, assists scientists in focusing on the most promising compounds in order to reduce the amount of time and money spent on synthetic and biological testing.

In reality, the availability of experimentally defined 3D (three-dimensional) structures of target proteins usually determines which CADD techniques are used. If the structure of a protein is unknown, ligand-based drug design methods such as quantitative structure activity relationship (QSAR) and pharmacophore analysis can be used. If the target structures are known, structure-based techniques such as molecular docking can be utilised to create novel active molecules with improved potency using the target 3D structures. The accuracy of prediction is anticipated to improve as more structures become accessible. In the absence of the receptor 3D information, lead identification and optimization depend on available pharmacologically relevant agents and their bioactivities [73, 74]. The computational approaches include QSAR, pharmacophore modelling and database mining. QSAR can be taken as an example to

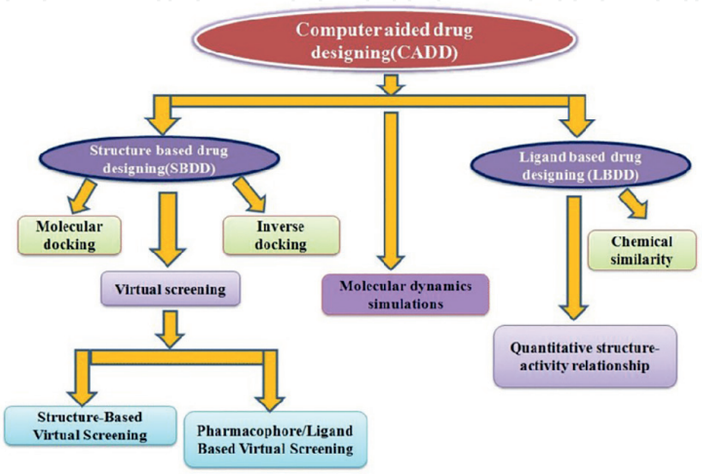


Figure 2.
Computer-aided drug design.

illustrate the workflow. A mathematical relationship between structural features and target properties of a group of compounds is described by QSAR. Over the last few decades, many various 2D (two-dimensional) and 3D QSAR techniques have been developed [75]. Chemical descriptors and mathematical procedures used to build the association between the goal attributes and the descriptors are two key differences between these strategies.

Many graph theoretic indices-based 2D QSAR algorithms have been thoroughly researched. Although the physical significance of these indices is unknown, they do indicate various characteristics of molecular structures. It's been used to predict biological activity in analytical chemistry, toxicology analysis, and other fields. To overcome the shortcomings of 2D QSAR techniques, such as their inability to differentiate stereoisomers, 3D QSAR approaches have been developed. Molecular shape analysis (MSA), distance geometry, and Voronoi procedures are examples of 3D methodologies. The most well-known example of 3D QSAR is comparative molecular field analysis (CoMFA). By elegantly merging the power of molecular graphics and the partial least square (PLS) technique, it has been widely employed in medicinal chemistry and toxicity studies. The linear relationship between a target property and molecular descriptors is frequently assumed in QSAR approaches. However, the rapid development of structural and biological data has put this assumption to the test. To this goal, a number of nonlinear QSAR algorithms have been presented, the majority of which are based on artificial neural network (ANN) or machine learning techniques [76]. Scientists had always concentrated on the development and application of automated algorithms for QSAR studies, including genetic algorithms (GAs)-partial least squares, k-nearest neighbour (k-NN), and support vector machine (SVM). Learning approaches have been widely used in cheminformatics and molecular modelling. For instance, SVM was found to yield better results compared to multiple linear regressions (MLR) and radial basis functions (RBF).

SBDD (structure-based drug design) has played a significant role in drug development and discovery [76]. Understanding receptor–ligand interactions is required for this strategy. The target 3D structure can be used to develop new ligands if it is known. X-ray crystallography, NMR, and homology modelling are all used to obtain structural information. SBDD methods are used to assess complementarities and anticipate potential binding modes and affinities between small compounds and their macromolecular receptors. SBDD's success is extensively proven, and computational approaches differ greatly in methodology, performance, and speed. Some can provide accurate binding modes, while others are better suited to scanning vast datasets quickly [77].

2. Molecular docking study

The production, manipulation, or representation of 3D structures of molecules and their associated physicochemical properties is referred to as molecular docking. It entails a variety of computational strategies for predicting chemical and biological properties based on theoretical chemistry methodologies and experimental data. The subject is sometimes referred to as "molecular graphics," "molecular visualisations," "computational chemistry," or "computational quantum chemistry," depending on the context and rigour. The molecular docking techniques are based on Huckel and Mullikan's conceptions of molecular orbitals and Westheimer et al. classical's mechanical programming.' The foundation of SBDD is 3D molecular structure [78, 79].

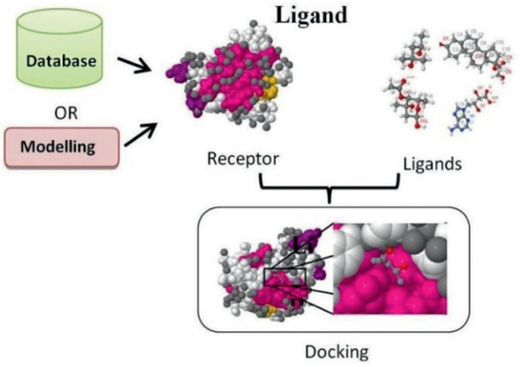


Figure 3.
Molecular docking process.

Separate data for protein structure and medication data are available, but no correlated data is accessible. Docking is the process of fitting two molecules together in complimentary styles in 3D space and designing the molecules rationally, as seen in **Figure 3**. Modeling a drug's interaction with its receptor is a difficult task. Hydrophobic, dispersion or van der Waals, hydrogen bonding, and electrostatic forces all play a role in intermolecular interaction. Hydrophobic interactions appear to be the dominant force for binding, whereas hydrogen bonding and electrostatic interactions appear to influence the specificity of the binding [80, 81].

2.1 Theory of docking

The objectives of molecular docking is to forecasting the ligand-receptor complex by using computer method. Docking is partitioned into two steps that is sampling ligand and scoring function. Sampling algorithms aid to find the energetically most favorable conformations of the ligand in the active site of the protein with their binding mode and further ranked these conformations using a scoring function.

2.1.1 Sampling algorithms

There are a great number of potential binding modes between two molecules due to the six degrees of translational and rotational freedom as well as the conformational degrees of freedom of both the ligand and protein [82]. Unfortunately, computing all of the conceivable conformations would be too expensive. In molecular docking software, various sampling techniques have been developed and are frequently utilized. In terms of shape features and chemical information, matching algorithms (MAs) based on molecular shape map a ligand onto an active site of a protein [83]. Pharmacophores represent the protein and the ligand. Each pharmacophore distance within the protein and ligand is determined for a match; the distance matrix between the pharmacophore and the associated ligand atoms governs new ligand conformations. During the match, chemical parameters such as hydrogen-bond donors and acceptors might be considered. Because MAs are fast, they can be used to enrich active chemicals from vast libraries. DOCK, FLOG, LibDock and SANDOCK programme provides ligand docking MAs [84–86]. The ligand is placed in an active site in a fragmented and incremental manner using incremental construction methods (ICMs). By breaking the ligands rotatable links, it is separated into many fragments, one of which is chosen to dock into the active site first. This anchor is typically the biggest fragment or the piece

that has a functional purpose or interacts with protein. The remaining pieces can be added in stages. The ligand's flexibility is realized by generating different orientations to fit in the active site. DOCK 4.0, FlexX and SLIDE all use the ICM. In supplement to ICM, fragment-based approaches such as multiple copy simultaneous search (MCSS) and Ligue Universitaire D' Improvisation (LUDI) are used to create new ligands and modify existing ligands to improve their binding to the target protein. At the force field of the protein, MCSS creates 1000–5000 copies of a substituent, which are randomly put in the binding site of interest and subjected to simultaneous energy minimization and/or quenched molecular dynamics. Copies solely interact with proteins; interactions between copies are not included. Based on the interaction energies, a collection of energetically favorable binding sites and orientations for the functional group is discovered. Different functional categories are used to map the binding site. The linking of those different functional groups can be used to create new molecules that perfectly match the binding site [87]. The hydrogen bonds and hydrophobic interactions that potentially occur between the ligand and protein are the focus of LUDI. Interaction sites, which are discrete positions in space appropriate for establishing hydrogen bonds or filling a hydrophobic pocket, are the core notion. Using the rules or scanning the database, a set of interaction sites is constructed. After that, the fragment is fitted onto the interaction sites and distance criteria are used to evaluate it. The merging of some or all of the fitted fragments to a single molecule is the final stage. By randomly changing a ligand conformation or a population of ligands, stochastic methods seek the conformational space. Another well-known class of stochastic approaches is genetic algorithm (GA). The GA was inspired by Darwin's theory of evolution. The ligand's degrees of freedom are represented as binary strings called genes. These genes make up the "chromosome," which indicates the ligand's position. In GA, there are two types of genetic operators: mutation and crossover. Crossover swaps genes between two chromosomes, while mutation produces random changes to the genes. A novel ligand structure is created when genetic operators impact genes. New structures will be evaluated using a scoring system, and those that survive will be employed in the upcoming generation. AutoDock, GOLD, DIVALI, and DARWIN all use GAs [88–91].

2.1.2 Scoring functions

The scoring function's goal is to distinguish between proper and inappropriate poses, or binders and inactive substances, in a very short time. Scoring functions, on the other hand, require guessing rather than computing the protein-ligand binding affinity and through these functions, numerous assumptions and simplifications are used. There are three types of scoring functions: force-field-based, empirical, and knowledge-based. Basic force-field-based scoring functions calculate the sum of non-bonded (electrostatics and van der Waals) interactions to determine the binding energy. A Columbic framework is used to determine the electrostatic terms. Due to the difficulty of representing the protein's true environment with point charge calculations, a distance-dependent dielectric function is commonly utilized to regulate the contribution of charge–charge interactions [92–94]. A Lennard-Jones potential function describes the van der Waals terms. The "hardness" of the potential, which regulates how close a contact between protein and ligand atoms can be tolerated, can be varied by using different parameter sets for the Lennard-Jones potential. The processing speed of force-field-based scoring functions is also an issue. To address non-bonded interactions, cut-off distance is used. As a result, the accuracy of long-range effects involved in binding is reduced. Hydrogen bonds, solvations,

and entropy contributions are considered in extensions of force-field-based scoring functions. DOCK, GOLD, and AutoDock are examples of software applications that provide these features [95]. They differ in their treatment of hydrogen bonding, the structure of the energy functions and other aspects. Furthermore, the accuracy of estimating binding energies can be improved by using other techniques also including linear interaction energy and free-energy perturbation methods (FEP) to refine the findings of docking with force-field-based functions. Binding energy is decomposed into multiple energy components in empirical scoring functions, including hydrogen bonds, ionic interactions, hydrophobic effect, and binding entropy. To arrive at a final score, each component is multiplied by a coefficient and then added together. Regression analysis fitted to a test set of ligand-protein complexes with known binding affinities yields coefficients. The energy terms in empirical scoring functions are quite simple to evaluate the affinities. Beyond the training set, however, it is unknown how well they are suited for ligand-protein complexes. Furthermore, various software may treat each term in empirical scoring functions differently, and the amount of terms included may differ as well. Examples of empirical scoring functions include LUDI, piecewise linear potential (PLP), and ChemScore. The interatomic interaction frequencies and/or distances between the ligand and protein are calculated using statistical analysis of ligand-protein complex crystal structures. They are founded on the notion that the more beneficial an encounter is, the more likely it will occur [96, 97]. Pairwise atom-type potentials are created from these frequency distributions. Within a particular cutoff, the score is derived by prioritizing favorable contacts and penalizing repulsive interactions between each atom in the ligand and protein. Knowledge-based functions are appealing because of their computational simplicity, which can be used to screen enormous compound datasets. They can also represent some unusual interactions, such as sulphur-aromatic or cation- that are frequently overlooked in empirical approaches. However, some interactions are underrepresented in the limited training sets of crystal structures, and the bias inherent in the selection of proteins for successful structure determination, so the obtained parameters may not be suitable for widespread use, particularly with implicating metals or halogens. knowledge-based functions such as DrugScore, SMoG, and Bleep that differ mostly in training set size, energy function shape, atom type definition, distance cutoff, and other characteristics [98–100]. Consensus scoring is a new technique for assessing docking conformation that combines numerous different scores. When a ligand or possible binder poses well in a number of different scoring schemes, it may be accepted. In virtual screening, consensus scoring usually enhances enrichment and improves the prediction of bound conformations and poses. However, binding energies predictions may still be wrong. When terms in distinct scoring functions are substantially connected, the utility of consensus scoring decreases. DOCK, ChemScore, PMF, GOLD, and FlexX scoring functions are all combined in CScore [101–103].

2.2 Docking methodologies

2.2.1 Docking of rigid ligand and rigid receptor

The search space is highly constrained when the ligand and receptor are both considered as rigid entities, with only three translational and three rotational degrees of freedom. In this scenario, ligand flexibility might be addressed by allowing for a degree of atom–atom overlap between the protein and the ligand, or by using a precomputed set of ligand conformations. Early versions of DOCK, FLOG, and certain

protein-protein docking systems like FTDOCK used a mechanism that kept the ligand and receptor stiff during the docking process [104, 105].

DOCK is the world's initial automated process for docking a molecule into a receptor site, and it's still evolving. The ligand and receptor are represented as sets of spheres that can be superimposed using a clique detection approach. The ligand-receptor complexes are scored using geometrical and chemical MAs, and steric fit, chemical complementation, and pharmacophore similarity are all taken into account. To account for ligand flexibility, incremental construction approach and exhaustive search have been included to the enhanced versions.

The extensive search generates a user-defined number of conformers at random, which is a multiple of the ligand's rotatable bonds. In terms of scoring, DOCK 6.4 now includes AMBER derived forcefield scoring with implicit solvent. Also, the molecular mechanics methodologies such as Poisson–Boltzmann or generalized Born and surface area continuum solvation (MM/PBSA and MM/GBSA) methods are used to determine the chemisorption which estimate the free energy of the binding of small ligands to biological macromolecules [106].

FLOG creates ligand conformations based on distance geometry and calculates the sets of distances using a search technique. For some flexibility, up to 25 specified conformations of the ligand might be employed to dock. Users can identify critical sites that must be associated with ligand atoms using FLOG. If a critical interaction is already known before docking, this method is useful. Van der Waals, electrostatics, hydrogen bonding, and hydrophobic interactions are all taken into account when scoring conformations [107].

2.2.2 Docking of flexible ligand and rigid receptor

As both the ligand and the receptor change conformations to form a minimum energy perfect-fit complex in systems that follow the induced fit paradigm, it is critical to consider the flexibility of both the ligand and receptor. However, when the receptor is also flexible, the cost is very high. As a result, the most typical technique is to consider the ligand as flexible while keeping the receptor stiff during docking, which is likewise a trade-off between accuracy and computational time. Almost all docking applications, such as AutoDock and FlexX, have embraced this concept [108–110]. To mimic ligand flexibility while keeping the receptor stiff, AutoDock 3.0 uses Monte Carlo simulated annealing, evolutionary, genetic, and Lamarckian genetic algorithm (LGA) approaches. The AMBER force field, which includes van der Waals, hydrogen bonding, electrostatic interactions, conformational entropy, and desolvation components, is used to calculate the scoring function. An empirical scaling factor derived from experimental data is used to weight each term. By enabling side-chains to shift, AutoDock 4.0 can model receptor flexibility. In this version of AutoDock, you may also test the interaction of protein-protein docking [111–114]. The latest version of AutoDock Vina for molecular docking and virtual screening was recently published. By redocking the 190 receptor-ligand complexes that had been utilised as a training set for the AutoDock 4, AutoDock Vina demonstrated a two-order exponential increase in speed as well as a considerable improvement in binding mode prediction accuracy [115]. FlexX samples ligand conformations using an incremental building approach. By matching hydrogen bond pairings and metal and aromatic ring interactions between the ligand and protein, the base fragment is docked into the active site. The remaining components are then built up incrementally in line with a set of preset rotatable torsion angles to complete the structure. Electrostatic interactions, directional

hydrogen bonds, rotational entropy, and aromatic and lipophilic interactions are all included in the present edition. The relationships between functional groups are also considered when group types and geometry are assigned [116].

2.2.3 Docking of flexible ligand and flexible receptor

In flexible docking, the docking of the ligand and receptor is difficult task due to protein intrinsic mobility and ligand binding affinity. MD simulations might theoretically model all degrees of freedom in the ligand-receptor combination. However, MD has the previously discussed issue of insufficient sampling. Another stumbling block is the method's high computing cost, which prevents it from being employed in large-scale chemical database screening [117]. Several theoretical models, including conformer selection and conformational induction, have been presented to illustrate the flexible ligand-protein binding process in addition to the historic induced fit. Conformer selection refers to a process in which a ligand selects a favourable conformation from a variety of protein conformations, while conformational induction describes a process in which the ligand induces the protein to adopt a conformation that it would not adopt spontaneously in its unbound state. This conformational change is sometimes compared to a partial refolding of the protein [118]. The most basic is "soft-docking," which lowers the van der Waals repulsion energy term in the scoring function to allow for some atom-to-atom overlap between the receptor and the ligand. This strategy could be lacking in versatility. Nonetheless, it has the advantage of computational efficiency because the receptor coordinates are fixed, and the van der Waals parameters are readily adjusted. To deal with side chain flexibility, AutoDock 4 uses a simultaneous sampling technique. Users can select multiple side chains of the receptor and sample them simultaneously with a ligand using the same methods. During sampling, other parts of the receptor are handled strictly using a grid energy map. Grid energy maps were established to hold receptor energy information and facilitate ligand-receptor interaction energy calculations [119]. Another approach to dealing with protein flexibility is to use an ensemble of protein conformations, which corresponds to conformer selection theory. Instead of docking into a single rigid protein conformation, a ligand is docked into a set of hard protein conformations and the results are merged using the method of choice. This method was first used in DOCK, which constructs an ensemble's average potential energy grid and has since been extended in a variety of programmes. Discrete protein conformations are sampled in a combinatorial approach during the gradual building of a ligand. Based on a comparison of the ligand and each alternative, the highest scoring protein structure is chosen (**Table 2**).

Because there are so many degrees of freedom and little knowledge of the effect of solvent on the binding relationship, modelling the intermolecular interactions in a ligand-protein complex is difficult. The docking of a ligand to a binding site attempts to emulate the natural course of interaction between the ligand and its receptor by taking the shortest path possible. Although there are straightforward ways for docking rigid ligands with rigid receptors and flexible ligands with rigid receptors, docking conformationally flexible ligands and receptors is more difficult. The interaction of macromolecular receptors and tiny drug molecules is a crucial stage in regulatory systems, drug pharmacology, hazardous side effects, and other processes.

The structure of protein-ligand or protein-protein binding sites is exploited in SBDD, however the site is not always known at the outset. Even if the site is identified, researchers may want to look for other potential binding sites that could lead to distinct

biological effects or a new class of drugs. In lead optimization, it's also critical to know how well known binders or docking hits fulfil or violate the receptor's complementarity. One component of molecular modelling is molecular mechanics, which refers to the use of classical/Newtonian mechanics to describe the physical basis of the models. In most molecular models, atoms (the nucleus and electrons combined) are described as point charges with a mass. Spring-like interactions (representing chemical bonds) and Van der Waals forces describe the interactions between nearby atoms. The Lennard-Jones potential is often used to characterise Van der Waals forces. Coulomb's law is used to calculate electrostatic interactions. Atoms are given coordinates in Cartesian space or internal coordinates, and in dynamical simulations, they can also be given velocities. The atomic velocities are proportional to the system's temperature (a macroscopic quantity). A potential function is a mathematical expression that is related to the system's internal energy (U), which is equal to the sum of potential and kinetic energies (a thermodynamic quantity). Energy reduction techniques (e.g., steepest descent and conjugate gradient) are used to reduce potential energy, whereas molecular dynamics methods are used to predict the behaviour of a system with time propagation [120–130].

As previously stated, molecular docking's role in drug design has been divided into two paradigms: one focused on the structure-activity problem, which attempts to rationalise in the absence of detailed 3D structural information about the receptor, and the other focused on understanding the interaction seen in the receptor-ligand complex, which uses the known 3D structure of the therapeutic target to design novel drugs. A binding relationship between a small molecule ligand and an enzyme protein can cause the enzyme to be activated or inhibited. Ligand binding may cause agonism or antagonism if the protein is a receptor. The most common application of docking is in the field of medication design. The most medications are tiny organic compounds and docking may be applied as follows,

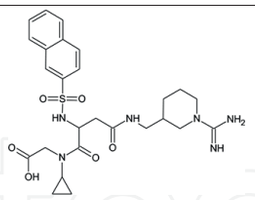
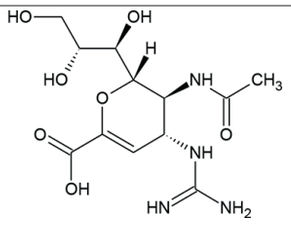
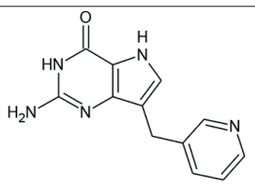
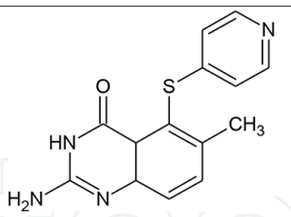
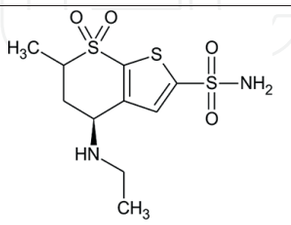
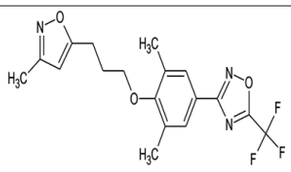
- *Hit identification*: Docking paired with a scoring algorithm can be used to swiftly screen vast databases of prospective medications using hit identification. To find compounds that are likely to bind to a protein target of interest *in silico* (virtual screening).

- *Lead optimization*: Docking can be used to anticipate whether and where a ligand binds to a protein in terms of relative orientation (also referred to as the binding mode or pose). This knowledge could be used to create more potent and selective analogues.

- *Bioremediation*: Protein ligand docking can be used to predict which contaminants enzymes can digest.

Molecular docking not only contributes to the design of potent compounds but also assist various steps in development of new drugs from laboratory to clinic. Few examples of contribution of molecular modeling are design of thimidylate synthetase inhibitors as anticancer agents, HIV protease inhibitors as antiviral agents, neutrophil elastase inhibitors as agents for emphysema, carbonic anhydrase inhibitors as antiglucoma agents and in discovery of novel sweeteners-taste receptor models [131–133]

In addition to the existing large number of docking programs, there are also many molecular mechanics programs applicable to these problems. Of course, there are some programs that are very widely used. Nevertheless it seems that the programs are not that easy to use and require some understanding of the underlying computational principles. Some of the software system are listed below [134–139].

Drug design targets	**Molecules**	**Outcome (brand name of drugs and category)**	**Method employed**	**Research group**
Thrombin inhibition	 Napsagatran	Napsagatran: Direct thrombin inhibitor	Iterative cycles of modelling, synthesis and crystallography to optimise hydrophobic sites.	Hoffman-La Roache, Ltd.
Thrombin inhibition	[D-Phe-Pro-Arg-Pro-(Gly)4-Asn- Gly-Asp-Phe-Glu-Glu-Ile-Pro- Glu-Glu-Tyr-Leu] Bivalirudin	Bivalirudin: Thrombin inhibitor in cardiovascular events	Based on 3D model of thrombin, bifunctional peptide inhibitors were designed.	Biogen, Inc.
Neuramini-dase inhibition	 Desipramine	Desipramine: Treatment of irritable bowel syndrome, depression, vulvodynia, dysautonomia and effective against influenza A and B viruses	Use of primary amine probe from GRID for the neuraminidase binding site.	Monash University/Glaxo Wellcome Lab.
Purine nucleoside phosphorrylase inhibition	 BCX-34 (Peldesine)	BCX-34: In HIV-infected patients and as an anticancer agent.	Modelling, synthesis and crystallography to screen synthetic candidates.	Biocryst pharmaceuticals, Inc.
Thymidylate synthase inhibition	 Thymitaq	Thymitaq, Nolatrexed: Treatment of leukaemia	Modelling, synthesis and crystallography to screen synthetic candidates. GRID program.	Agouron Pharmaceuticals, Inc.
Carbonic anhydrase inhibition	 Dorzolamide	Dorzolamide: Inhibitor of carbonic anhydrase, inhibiting. Commonly used to treat glaucoma.	Multiple crystal structure determination combined with ab initio conformational analysis.	Merck Research Lab.
Human rhinovirus-14 inhibition	 WIN 54954	WIN 54954: Made it past phase I clinical trial as a new broad-spectrum antipicornavirus drug, as a potential treatment of common cold.	Multiple crystal structure analysis and Volume map analysis	Sterling Winthrop Lab.

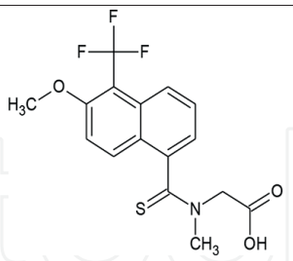
Drug design targets	Molecules	Outcome (brand name of drugs and category)	Method employed	Research group
Aldose reductase inhibition	 Tolrestat	Tolrestat: It was approved for marketed in several countries as antidiabetic agent. It was discontinued by Wyeth in 1997 because of the risk of severe liver toxicity and death.	Extended Huckel molecular orbital calculations, QSAR methodology	Ayerst Laboratories Research, Inc.

Table 2.
The successful application of computer assisted drug design approach to biological targets.

AutoDock: To generate a set of potential conformations, AutoDock use Monte Carlo simulated annealing and the LGA energy minimization is employed as a local search strategy and LGA is used as a global optimizer. The AMBER force field model is used in conjunction with free energy scoring functions and a wide set of protein-ligand complexes with known protein-ligand constants to analyse possible orientations. AutoDock's web pages are more informative than its competitors', and its free academic licence makes it a nice place to start if you're new to molecular docking software.

DOCK: DOCK is one of the most well-known and widely used ligand-protein docking tools. The initial version employed hard ligands; flexibility was later added by building the ligand in the binding pocket incrementally. DOCK, as previously stated, is a fragment-based technique that uses complimentary shape and chemistry methodologies to generate various ligand orientations. Three distinct scoring systems can be used to score these orientations; however, none of them include explicit hydrogen-bonding terms, solvation/desolvation words, or hydrophobicity parameters, limiting their usefulness. DOCK appears to handle polar binding sites well and is beneficial for quick docking, but it isn't the most precise programme available.

FlexX: FlexX is a fragment-based approach that uses hard proteins and flexible ligands. It creates conformers using the MIMUMBA torsion angle database. MIMUMBA is a database of intermolecular interaction patterns that uses interaction geometry to precisely define them. The Boehm function is used for scoring (with slight adjustments for docking). FlexX is used to emphasise the significance of scoring functions. Despite the fact that FlexX and DOCK are both fragment-based approaches, they give very distinct outputs. FlexX behaves in an entirely different way than DOCK, which works well with polar binding sites. It has a slightly lower hit rate than DOCK, but it produces superior Root Mean Square Distance estimates for compounds with accurately predicted binding modes. FlexE, a FlexX extension with flexible receptors, has been demonstrated to yield better outcomes with substantially shorter run times.

Gold: Because of its strong outcomes in independent tests, gold has gained a lot of new users in recent years. It has a good overall hit rate, although it struggles a little when dealing with hydrophobic binding pockets. To offer docking of a flexible ligand and a protein with flexible hydroxyl groups, Gold use a GA. Aside from that, the protein is considered stiff. When the binding pocket contains amino acids that create hydrogen bonds with the ligand, this makes it a favourable choice. Gold employs

a scoring system based on favourable conformations discovered in the Cambridge Structural Database as well as empirical evidence on weak chemical interactions. The current focus of GOLD development is on enhancing the computational algorithm and introducing parallel processing capability.

3. Toxicity prediction and prediction adverse drug reaction

Any chemical's harmful or adverse effects are called as toxicity. Toxicity, such as carcinogenicity or genotoxicity, can be quantitative (e.g., lethal dose to 50% LD_{50} of tested individuals) or qualitative (e.g., toxic or nontoxic). In studies of toxicity the use of acute-exposure (single dose) or multiple-exposure (multiple dose) to determine detrimental effects of chemicals on humans, animals, plants, or the environment (multiple doses). Chemical toxicity is determine through several factors like the mode of exposure (oral, cutaneous or inhalation), dose, exposure frequency (single or multiple), exposure duration, qualities of chemical, biological properties (age, gender) and absorption, distribution, metabolism, excretion (ADME). Generally, animal models have been used for long time for toxicity testing. Nowadays advancements in high throughput screening, *in vitro* toxicity testing are easily achievable. Computational toxicology is one of the best toxicity assessment tool that establish, analyses, models, simulates, visualize or prediction of chemical toxicity. The simulation tools like algorithms, softwares, data, etc., which are projected *in vitro* toxicity experiments in order to avoid the animal models and cost effective toxicity testing which expands toxicity prediction and safety evaluation. Moreover, additional computational tools have the distinct benefits of being able to predict toxicity of substances even before they are created (**Figure 4**) [140].

Softwares (generating molecular descriptors):

- Simulation tools (systems biology and molecular dynamics)
- Modelling methods (toxicity prediction models)
- Statistical tools (generating prediction analysis)

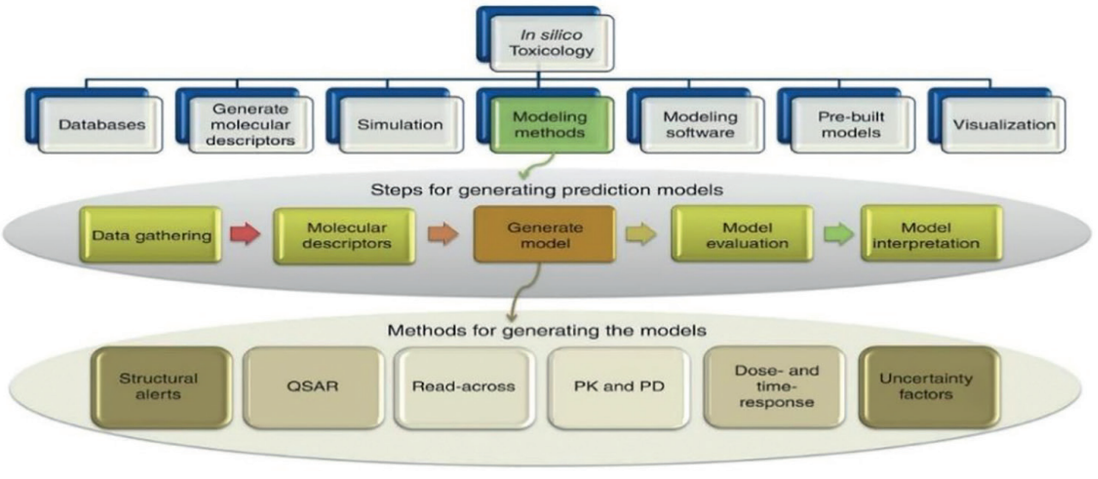


Figure 4.
In silico toxicology tools, steps to generate prediction models, and categories of prediction models [140].

- Expert system (include pre-built models in web serves or standalone application for predicting toxicity)

- Visualization tools

By and large, modeling approaches comprise five major steps while developing prediction models.

3.1 Why exploration of toxicity prediction is important?

Optimization of molecule is important during initial drug development for good efficacy as well as for pharmacokinetics (PKs) and toxicological properties prediction. Appropriate balance of target potency, selectivity, suitable ADME, and safe preclinical properties all together leads to the choice and clinical development of a potential new drug moiety. In clinical phase I trial the characteristic compound have to undergo years of preclinical testing and acquire only 8% chance of getting to the market. The failure of development of new drug cause by its toxicity. Therefore, executing toxicity analysis to be done in the early phase of the development process which gives significant potential to make value.

The major reasons that impede pharmaceutical companies to conduct earlier screening for toxicity like the big amount of compounds required for *in vivo* studies, the deficiency of *in vitro* assay predictions through high throughput along with inability of *in vitro* and animal models to proper prediction of toxicity in humans. The development of computational tools or *in silico* tools for prediction of toxicity are required to avoid above mentioned hurdles. These tools are structure based or using modeling techniques on human data, which provides approaches for removing the toxic effect in humans before the physical appearance of compound. The importance of computational tools arises from their applicability early in development stage. During the last few years, computational toxicology prediction system tremendously increased their forecasting ability but still unable to achieve the significant achievement because of deficit of big datasets contain toxicological effects like hepatotoxicity, teratogenicity, etc. The development of low throughput data with generations and coordinated efforts and set up on big historical background of experience and trained with small additional efforts may save a big investment and avoid use of animals (**Table 3**) [141].

- QSAR, expert systems, grouping and read-across techniques are used in structure activity modelling.

- Chemoinformatics: generating molecular descriptors for toxicity prediction using computational tools such as quantum chemical methods and molecular dynamics simulations;

- Databases and biological data that contain relationships between chemicals and toxicity endpoints, databases for storing data about chemicals, toxicity, and chemical properties;

- Data mining and analysis: calculating molecular descriptors, generating a prediction model, and evaluating the model;

Studies in laboratory animals have traditionally been used to determine the possible risks of chemicals, with modifications in clinical pathology and histology

***In Silico* methods**	**Description**	**Software/databases**
Quantitative structure-activity relationship models	Use of molecular descriptors to predict chemical toxicity	OECD QSAR
		TopKat
		Derek Nexus
		VEGA
		METEOR
		vLife-QSARpro
Structural alerts and rule-based models	Chemical structures that indicate or associate to toxicity	OECD QSAR
		Toxtree
		OCES
		Derek Nexus
		HazardExpert
		Meteor
		CASE
		PASS
		cat-SAR
Read-across	Predicting unknown toxicity of a chemical using similar chemicals with known toxicity from the same chemical category	OECD QSAR
		Toxmatch
		ToxTree
		AMBIT
		AmbitDiscovery
		AIM
		DSSTox
		ChemIDplus
Dose–response and time–response models	Relation between doses (or time) and the incidence of a defined biological effect.	CEBS
		PubChem
		ToxRefDB
PK and pharmacodynamics (PD) models	PK models calculate concentration at a given time. PD models calculate effect at a given concentration	WinNonlin
		Kinetica
		ADAPT

Table 3.
In silico tools used for predicting toxicity endpoints of chemicals/drugs.

compared to untreated controls defining an adverse effect. In recent decades, there has been a greater degree of agreement in the definition of adversity in experimental animals caused by chemically produced effects, as well as in the assessment of human relevance. More recently, a paradigm change in toxicity testing has been proposed, largely as a result of animal welfare concerns, but also as a result of the development of new technologies. *In vitro* methods, toxicogenomic technologies, and computational tools are already available to provide mechanistic insight into the toxicological mode of action (MOA) of deleterious effects found in laboratory animals. Tox21c

(toxicity testing in the twenty first century) is an idea that intends to forecast *in vivo* toxicity using a bottom-up strategy, starting with an understanding of MOA based on *in vitro* data and eventually predicting detrimental effects in humans [142].

Data sets and metrics used for drug side effect prediction:

- Important data sets for drug side effect prediction
- Metrics for drug side effect prediction
- Literature survey
  - Docking-based approaches
  - Network-based approaches
  - Machine learning-based approaches

Figure 5 depicts the categorization as well as the numerous approaches within each of the categories. The next sections discuss each of these categories and describe some of the most important efforts in the field of drug side effect prediction that have been done in each of these categories.

- *Docking-based approaches:* The preferred orientation of one molecule with another to form a stable compound is referred to as docking. Docking is one of the most used strategies for designing drugs based on structural data. The ability of targets to bind to one another is a critical property that impacts the efficiency of biochemical processes. When a medicine attaches to a certain protein, it can produce side effects. Drug side effect prediction using docking-based techniques

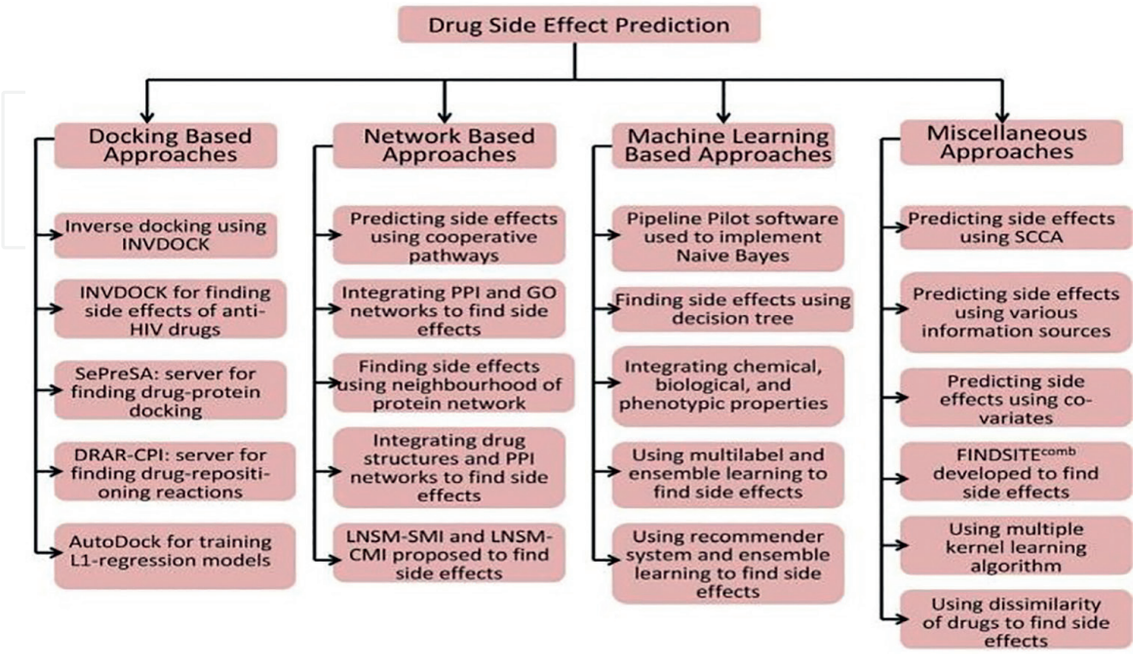


Figure 5.
Classification of drug side effect prediction approaches [143].

identifies possible drug binding sites. Many adverse effects are thought to be caused by an unexpected interaction of a medication molecule with a specific protein [144]. Side effects occur when a medication molecule is overregulated or communicates with a protein in an unexpected way. A molecular docking-based method for finding these target proteins has been presented INVDOCK. Various side effect–protein relationships were discovered during the method's evaluation. Various publications supporting the indicated side effect–protein relationships were discovered by searching the PubMed data collection.

- *Network-based approaches*: Drugs, targets, and side effects are viewed as nodes in a graph by networks. Edges are used to represent nodes. This graph-based visualization is used in network-based approaches to side effect prediction to identify pharmacological side effects. Side effects are induced by a variety of circumstances, including incorrect dose, binding to non-targets, and insufficient metabolization among others. To gain a better understanding of the factors that influence a disease, the actions of pharmaceuticals and their accompanying side effects, chemical substances, and associated targets are seen as a network.

- *Machine learning-based approaches*: Machine learning encompasses a variety of strategies and algorithms for gaining access to data and using it to learn about a certain area. Based on the training data, the various machine learning classifiers divide the observations into different classes. Machine learning-based approaches, on the other hand, use a variety of classifiers to solve the prediction problem. To improve prediction efficiency, the employment of SVM, naive Bayes, RF, and other methods has been recommended. In addition, as compared to other methods, machine learning-based methods take up less computing time. As a result, they can be used in post-market drug screening.

- *Miscellaneous approaches*: Miscellaneous approaches also provide valuable interaction prediction strategies. The SCCA-based method is also efficient in terms of computing time. Diverse scoring systems are used to quantify the chance of medicinal compounds interacting with their protein targets in various techniques to predict pharmacological side effects. The scoring approaches are effective in terms of computational complexity.

4. Polypharmacology and drug repositioning

Polypharmacology, a new paradigm in drug discovery that focuses on multi-target medicines (MTDs), has applications in drug repurposing, the process of finding new uses for already-approved pharmaceuticals, off-target toxicology prediction, and rational MTD design. In this situation, computational approaches have shown great promise in predicting polypharmacology and assisting with pharmaceutical repurposing [145].

The goal of polypharmacology is to identify a small ligands with off-target activities. Polypharmacology and chemogenomics have a high level of interaction. Chemogenomics is the study of the relationship between targets and their ligands in terms of structure and activity. The information about a target's ligands and its distance from other targets in biological space can be used to aid in the evaluation of new compounds for one or more novel targets. Both approaches can be employed in

the early stages of development to screen out compounds and reduce the probability of failure due to significant adverse effects. When used on known medications, polypharmacological approaches can lead to a compound's repurposing for a new indication. Drug repurposing is suitable for marketed medications or development candidates that have failed in clinical trials due to lack of efficacy but have a strong safety profile and PK features [146]. Because prior clinical trial studies provide valuable data on drug PKs/PDs and toxicity profiles, repurposing previously approved pharmaceuticals saves time and money in drug development when compared to generating novel drugs from scratch. Sildenafil (Viagra®), a medicine that was originally created to treat hypertension but is now marketed to treat penile erection dysfunction, is a well-known example of drug repositioning [147].

Most pharmaceutical corporations and specialized service providers are increasing their medication repurposing activities in response to the present productivity problem and the need to minimize attrition rates in drug development. Because large pharmaceutical corporations, in particular, have a large pool of unsuccessful drug candidates, dedicated divisions have been formed and collaboration agreements have been negotiated. As a result of the endeavour, there has been a rise in the development and application of *in silico* approaches in this field. Due to computational constraints, *in silico* approaches for polypharmacology analysis and medication repurposing have primarily relied on 2D representations of small compounds. First, 3D approaches have already been outlined, but further research will allow for the discovery of target-target correlations that are not conceivable in the 2D world. This, together with recent breakthroughs in 3D tool computational throughput, suggests that these methods will be able to be used on the same scale as 2D tools in the near future [148]. Because of its potential applications and recent successes, polypharmacology has inspired a lot of interest in drug discovery [149]. Polypharmacology is exemplified by kinase inhibitors. Imatinib, for example, was developed to target the BCR-ABL protein and was licenced by the Food and Drug Administration to treat chronic myelogenous leukaemia [150].

High-throughput virtual screening (HTVS) is a simple tool for detecting hits in a single-target drug discovery project, but it is insufficient when several targets are investigated at the same time. In order to address polypharmacology, a multi-target approach must be developed. In order to identify the "magic shotgun" that can target numerous receptors at the same time, inverse docking techniques must be used. This enables the bioactivity and secondary effects of a potential new drug to be predicted, as well as the repositioning of existing treatments. Polypharmacology of known drugs and novel compounds is predicted *in silico* using structure-based and ligand-based approaches, as well as the rational design of MTDs.

In silico approaches have advanced as a valuable strategy in early drug development, and as additional target structures, structural bioactivity data, and therefore enhanced chemoinformatic tools become accessible, their influence will certainly grow. Because medications with a certain polypharmacologic profile will allow for better treatment of certain diseases, one of the most important computational challenges ahead is the application and development of algorithms for identifying suitable molecules (**Figure 6**).

Polypharmacology can be predicted using computational methods. Statistical data analysis and bioinformatics, ligand-based, and structure-based approaches can be used singly or in combination to take use of each approach's unique characteristics and strengths. The figure's lower half depicts three separate proteins (A–C) interacting with the same ligand, emphasising that the ligand's final pharmacological effect is the product of synergistic effects emerging from interactions with all targets.

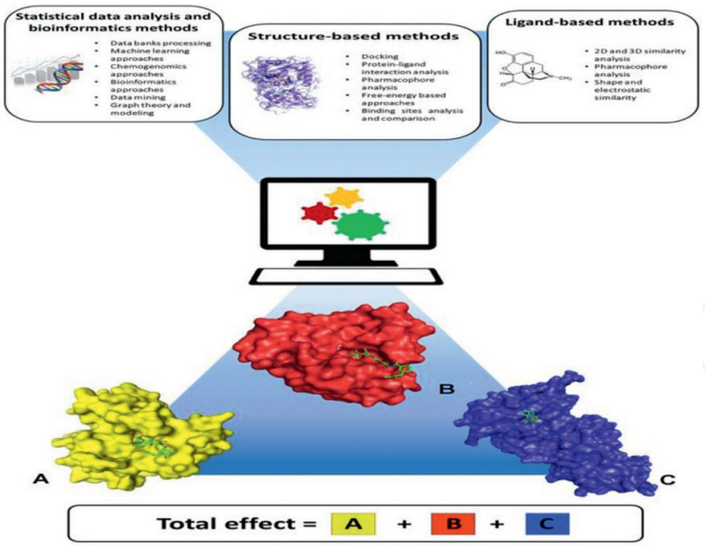


Figure 6.
Polypharmacology can be predicted using computational methods [148].

Structure-based approaches, ligand-based methods, and systems biology methods are the three categories of methodologies that can be used to anticipate unknown targets for small compounds.

- *Structure-based methods*: Inverse docking, binding site similarities, inverse pharmacophore modelling, molecular dynamics simulations, and fragment-based multi-target drug design are examples of structure-based techniques. Currently, the Protein Data Bank (PDB) has substantially includes 3D protein structures that refined by protein crystallography, nuclear magnetic resonance spectroscopy, and electron microscopy. Due to the availability of such structural data, inverse docking algorithms have been developed, with the primary goal of docking a small molecule into binding sites of many targets for hit identification. INVDOCK, TarFisDock, and idTarget are some of the modified scoring functions that have been developed specifically for target ranking in recent years. Binding site similarity-based search, in addition to inverse docking, is commonly employed for target prediction. It's based on the idea that structurally comparable proteins have similar chemical functions, thus they'll probably bind to structurally similar substances. Combining the GRID Molecular Interaction Fields with pharmacophoric characteristics, the Fingerprints for Ligands and Proteins (FLAP) algorithm was recently developed. Drug repurposing and hit identification can both benefit from binding site similarity technologies. It can also be employed in the lead optimization process by comparing binding locations. Advanced pharmacophore approaches have recently been developed to connect structure-based pharmacophore models of targets with small molecule pharmacophoric features to small molecule pharmacophoric features. Fragments are smaller, simpler chemical entities than drug/lead-like compounds, and they have a higher promiscuous nature. Fragment-based techniques boost the likelihood of obtaining hits and aid in the discovery of novel compounds because a small number of pieces can cover a large chemical search area. As a result, they can be utilised for hit detection, lead generation, and lead optimization.

- *Ligand-based methods*: The characteristics and activities of compounds are used to anticipate unknown targets utilising ligand-based techniques. This is based on the notion that structurally similar molecules attach to similar targets. The similarity ensemble approach (SEA) is a similarity-based method for determining the likelihood of a molecule binding to a target based on topological similarities between the ligands. Recently smooth surface triangulator (SMART) algorithm, pair-wise kernel method (PKM), Gaussian interaction profile, Laplacian regularized least squares (LapRLS), kernel regression, kernelized Bayesian matrix factorization with twin kernels (KBMF2K), and bipartite local method have been developed.
- *Systems biology methods*: With the development of high-throughput techniques yielding massive amounts of data in domains like genomics and proteomics, understanding diseases, especially complex ones, has never been more detailed. The term "Network Pharmacology" was coined to propose that combining chemogenomics data with network biology might aid in the development of new ways to target disease-causing networks rather than specific genes or targets. The database, which contains over millions of drug-induced gene expression patterns, can be utilised to find new polypharmacology medicines.

The concept that comparable drugs bind to similar targets still underpins the majority of polypharmacology research. The development of precise and robust scoring algorithms that can rank targets rather than tiny molecules is a big challenge. Novel approaches to rational design of multi-targeting small molecules are now being investigated. Apart from traditional structure- and ligand-based approaches, there has been an upsurge in interest in system biology and bioinformatics-based methodologies, as well as community-wide activities. These approaches have been demonstrated to not only anticipate new small molecule targets, but also to aid in the understanding of disease dynamics and the molecular interaction pathways that lie beneath. Polypharmacology, which can predict both on-target and off-target therapeutic effects, could help in illness targeting. As a result, the rational polypharmacological drug design (PDD) holds a lot of promise and possibility for drug discovery in the future. However, in order to reach such ambitious aims and, eventually, translate information into successful patient therapy, we must overcome a number of flaws and roadblocks [151].

The field of computational polypharmacology has progressed to the point where concrete hypotheses may be formulated using prediction results to guide wet-lab research. The field of computational polypharmacology has advanced to the point where concrete hypotheses may be established and used to guide wet lab research utilizing prediction results. Furthermore, the majority of contemporary approaches are implemented as web servers or standalone applications. As community efforts become more essential, it will be necessary to create portable programming libraries that community developers can use to alter existing toolkits or create new ones. More cell-free, cell-based, and animal models are needed in experimental assays to examine the impact of drugs on various targets or functions at the same time.

5. Opportunities and challenges

There are six components to the CADD challenges. Chemical and biological space are the two major categories. The term "chemical space" refers to the large number

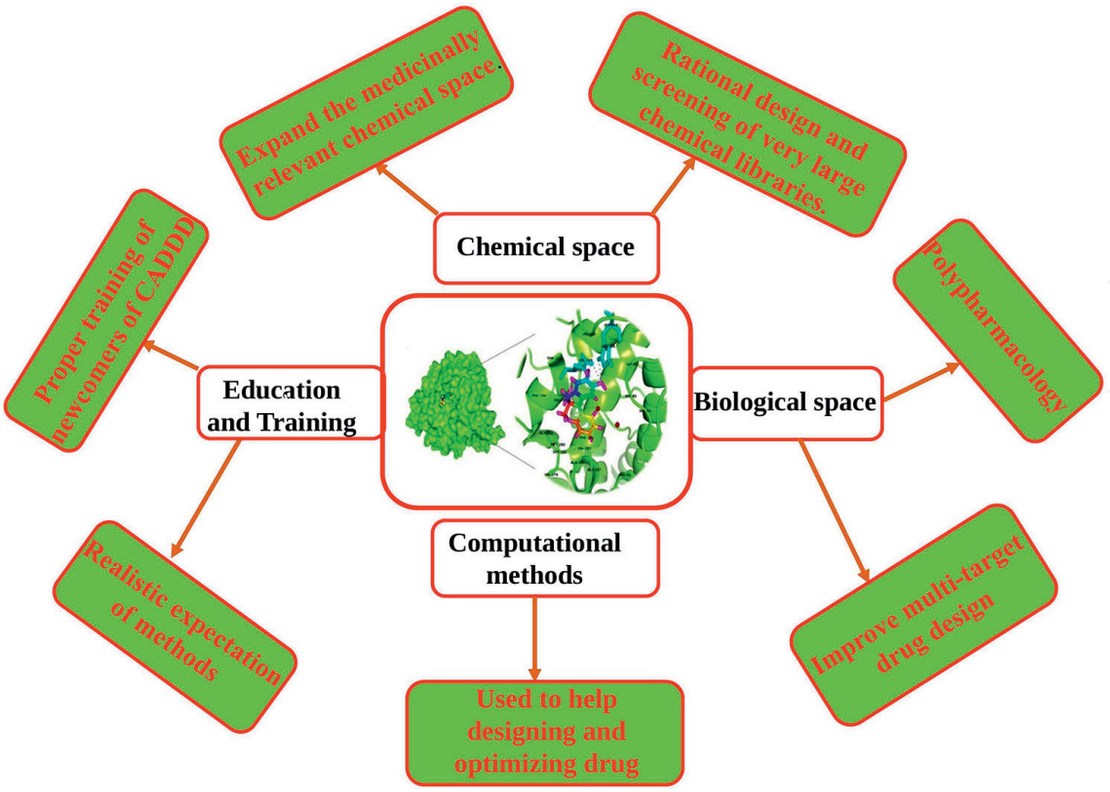


Figure 7.
In silico methods showing outstanding challenges during drug discovery and design.

of possibilities for discovering hit substances. Third is methodologies challenges, in which for designing and optimizing drug candidate's computational methods could be used. Last one is the proper training of newcomers like investigators of CADD for multidisciplinary work (**Figure 7**) [152–155].

The topic of drug repurposing is gaining impetus toward novel therapeutic molecule development, aided by an ever-increasing number of innovative computational techniques and enormous sequencing databases. Antibiotic resistance among key clinical pathogens is a grim prospect, as per infection-related death rate continues to rise despite a slowing rate of new antibiotic discovery.

6. Applications and limitations

CADD is useful in the treatment of neurodegenerative disorders particularly targeting Amyloid-β in case of Alzheimer's disease. For nearly two decades, in pharmaceutical research docking calculations have been used. Virtual screening using protein templates differs from virtual screening approaches based on molecular similarity and ligands beneficial for de novo identification of active complex. Three important factors in CADD pays close attention include: (1) As per target structure, screening a large number of molecules, which can then be assessed using both experimental and computational techniques; (2) as per affinity, criteria on toxicity and PK study, guiding the optimization of lead compounds and (3) based on the structure, supporting in the design of novel compounds to recover functions of drug. For modelling of drug the CADD approach is extremely helpful. Computed chemistry and bioinformatics, as well as combinatorial chemistry, are used to handle the many issues connected

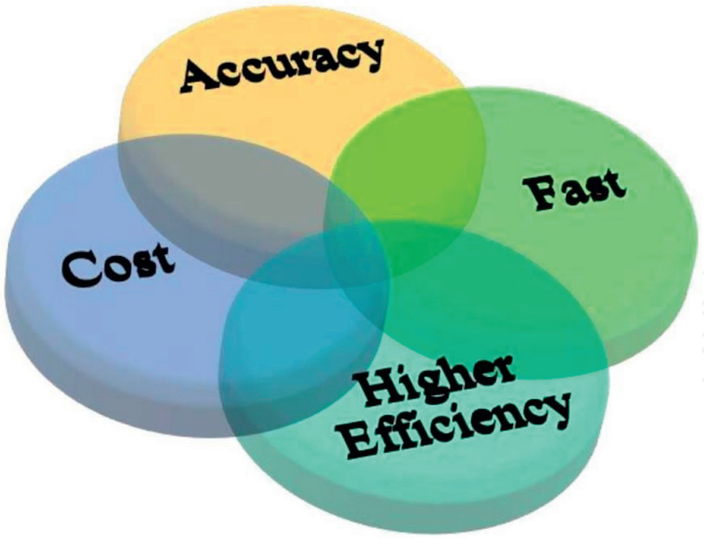


Figure 8.
Advantages of CADD.

with the drug discovery pipeline in less time and expense. As per **Figure 8**, general advantages of CADD are found to be cost effective, with higher efficiency, speed and accuracy in results [156–159].

FDA approved drugs like human immunodeficiency virus (HIV)-1-inhibiting drugs identified by SBDD available on the market. Other example is thymidylate synthase inhibitor, raltitrexed, by protein modelling, inhibitor of HIV protease, amprenavir is discovered. Computer assisted techniques are hypothetical and results must be confirmed in real-world systems, and pharmacological activities discovered through CADD in lead compounds have failed. Most of the methods of CADD methods like QSAR, molecular dynamics, molecular docking, etc. have their specific

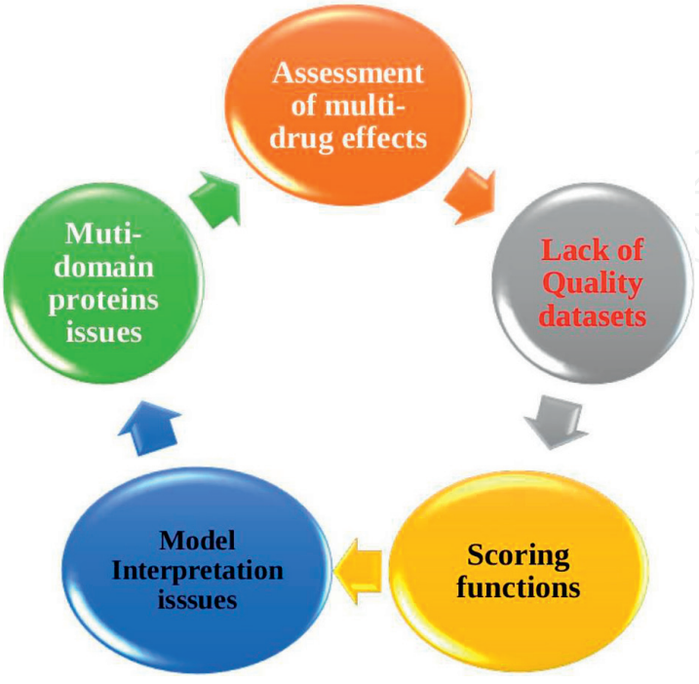


Figure 9.
Limitations of CADD.

restrictions. Limitations are found to be multi-domain protein issues that means protein flexibility which is the most problematic challenge, assessment of multi-drug effects, in some cases lack of quality datasets observed (**Figure 9**).

One failure example of SBDD is RPX00023 which was reported as an antidepressant activity as an agonist of the 5-HT1A receptor. However, it was found to be an inhibitors of 5-HT1A receptor [160–164].

Conflict of interest

We confirm that there is no conflict of interest.

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