I J C R M
International Journal of Contemporary Research In Multidisciplinary

Research Article

Computational Drug Design: Innovations, Applications & Future Perspectives

Sonali Prusty [1], Archanamayee Behera [2*]
[1] PG Department of Chemistry, Rajendra University, Balangir, Odisha, India
[2] Assistant Professor, PG Department of Chemistry, Rajendra University, Balangir, Odisha, India

Corresponding Author: * Archanamayee Behera

DOI: https://doi.org/10.5281/zenodo.20622952

Abstract

Computational Drug Design represents a transformative approach in modern pharmaceutical research, where chemistry, biology, and computer science converge to accelerate the discovery of safer and more effective therapeutic molecules. Instead of relying solely on traditional trial-and-error experimentation, this strategy employs advanced algorithms, molecular modelling, and artificial intelligence to predict how drug candidates interact with biological targets at the atomic level. By simulating molecular behaviour, researchers can identify promising compounds, optimise lead structures, and evaluate pharmacokinetic and toxicity profiles before laboratory synthesis, significantly reducing time, cost, and experimental failure. Techniques such as molecular docking, virtual screening, quantitative structure–activity relationship (QSAR) analysis, molecular dynamics simulations, and ADMET prediction enable precise understanding of drug–target interactions and biological responses. Ultimately, it reshapes drug discovery into a smarter, faster, and more predictive scientific process, paving the way for next-generation therapeutics and improved global healthcare outcomes.

Manuscript Information

- **ISSN No:** 2583-7397
- **Received:** 11-04-2026
- **Accepted:** 05-06-2026
- **Published:** 10-06-2026
- **IJCRM:**5(3); 2026: 732-746

- **Plagiarism Checked:** Yes
- **Peer Review Process:** Yes

How to Cite this Article

Sonali Prusty, Archanamayee Behera. Computational Drug Design: Innovations, Applications & Future Perspectives. Int J Contemp Res Multidiscip. 2026;5(3):732-746.

Access this Article Online

www.multiarticlesjournal.com

KEYWORDS: Computational Drug Design, Molecular Docking, Virtual Screening, QSAR, ADMET Prediction, Molecular Modelling, Drug Discovery, Lead Optimisation, In Silico Studies, Artificial Intelligence.

1. INTRODUCTION

The process of drug discovery is highly complex and requires collaborative efforts from multiple scientific disciplines to develop effective and economically viable drugs. The main objective of drug design is to identify a chemical compound that can bind precisely to a specific active site of a protein target through suitable geometric and chemical interactions. After successful evaluation through animal studies and human clinical trials, the compound is approved and becomes available as a therapeutic drug for patients. Traditional drug design methods mainly relied on random screening of natural or synthetically prepared compounds, which often resulted in lengthy development periods and high costs.[1-3] In contrast, modern approaches such as structure-based drug design, supported by bioinformatics tools and computational techniques, have significantly accelerated and improved the efficiency of the drug discovery process.[4] In recent years, substantial advancements have been achieved across various fields related to drug design and discovery.[5] Computational Drug Design (CDD) is an advanced scientific approach that utilizes computer-based tools, mathematical models, and computational algorithms6 to design, analyze, and optimize drug molecules by predicting their structure, properties, and interactions with biological targets such as proteins, enzymes, or nucleic acids, thereby enabling researchers to identify potential therapeutic compounds efficiently, reduce experimental workload, minimize time and cost involved in traditional drug discovery, and improve the overall success rate of developing safe and effective medicines through rational and target-oriented strategies.[7-8]

2. Computational approach in drug design

Computational methods are increasingly preferred over traditional drug discovery approaches due to their efficiency, accuracy, and cost-effectiveness, as emphasized in many review articles. Computational approaches in drug design utilize computer- based tools and algorithms to identify, analyze, and optimize potential drug molecules efficiently. These methods include molecular modeling, virtual screening, molecular docking, pharmacophore modeling, and quantitative structure–activity relationship (QSAR) analysis. By simulating drug–target interactions at the molecular level, computational techniques help predict binding affinity, selectivity, and stability before experimental testing. Additionally, in silico ADMET prediction evaluates pharmacokinetic and toxicity properties, supporting early identification of safe and effective candidates.9

3. Objective of computational drug design

The primary objective of computational drug design is to develop safe, effective, and selective drug molecules using computer-based tools and theoretical models. It aims to identify suitable biological targets and predict drug–target interactions at the molecular level to enhance therapeutic efficiency. Computational methods help in screening large libraries of compounds, optimizing lead molecules, and improving binding affinity and selectivity while minimizing side effects. Another important objective is to predict pharmacokinetic and toxicity properties through in silico ADMET analysis, reducing experimental failures. Overall, computational drug design seeks to accelerate drug discovery, lower development costs, and increase the success rate of producing clinically effective medicines.[10]

4. Need for computational drug design

Computational drug design is needed to overcome the limitations of traditional drug discovery, which is time-consuming, costly, and often associated with high failure rates. Modern pharmaceutical research requires faster identification of drug candidates and a deeper understanding of molecular interactions, which computational tools provide efficiently.11 These methods enable rapid virtual screening of large compound libraries, prediction of drug–target binding, and early evaluation of pharmacokinetic and toxicity properties through in silico analysis.12 By reducing unnecessary laboratory experiments and minimizing late-stage clinical failures, computational drug design saves resources and improves success rates. Therefore, it is essential for developing safer, more effective drugs in a shorter time frame.[13]

5. Role of target identification and validation

Computational methods play a crucial role in target identification and validation during the early stages of drug discovery. Target identification involves recognizing specific biological molecules, such as proteins, genes, or enzymes, that are associated with a particular disease. Bioinformatics tools and genomic databases help analyze large biological datasets to identify potential therapeutic targets quickly and accurately.14 Computational approaches also assist in understanding disease pathways and molecular mechanisms, enabling selection of the most relevant targets. Target validation is performed using molecular modeling and simulation techniques to confirm that modulation of the target can produce the desired therapeutic effect.[15] These methods predict drug-target interactions, binding sites, and functional responses before experimental studies. As a result, computational tools reduce experimental effort, improve accuracy, and increase the probability of developing effective drug candidates, making them essential in modern drug discovery.[16]

6. Types of computational drug design

A. Structure-based drug design (SBDD)

Structure-Based Drug Design (SBDD) refers to the contemporary and scientific approach in drug development which employs the three-dimensional structure information of the target molecule, usually gained by the methods such as X-ray crystallography and NMR spectroscopy. On the basis of analysis of the structural aspects and active sites of the target molecule, scientists can come up with optimized compounds that demonstrate improved binding ability and specificity. Computational approaches along with molecular modeling methods make it possible to simulate the interaction between ligand and target molecules and modify the chemical structures to increase their efficacy (Fig-2). Being one of the pioneering methods of computer-aided drug design, SBDD has made great contributions towards the discovery of new drugs.[17]

B. Target structure identification

Target structure identification is the process of determining the three-dimensional architecture of a biological target, such as a protein or nucleic acid, involved in disease pathways. X-ray crystallography, NMR spectroscopy, and cryo-electron microscopy techniques are highlighted in various review studies, which enable precise molecular understanding essential for rational drug design and therapeutic optimisation. [18,19]

C. Molecular docking approach

Molecular docking has emerged as a vital computational tool in modern drug discovery. This review provides an overview of various molecular docking methods, their evolution, and applications in pharmaceutical research. Fundamental concepts such as sampling algorithms and scoring functions are discussed, along with comparisons of different docking software and their performance. Flexible receptor docking, particularly involving backbone flexibility, remains a significant challenge for current methods. A newly developed Local Move Monte Carlo (LMMC)–based approach is highlighted as a promising strategy to address these limitations.[20-24]

D. Binding site analysis

Binding site analysis is the process of identifying and characterizing the active or ligand-binding regions of a biological target, typically proteins.19 Review studies emphasize the use of computational tools, structural databases, and physicochemical property evaluation to predict binding pockets, understand molecular interactions, and support structure-based drug design and optimisation.

E. Ligand-based drug design (LBDD)

Ligand-based drug design is a significant and widely applied approach in modern drug discovery and optimization. This review outlines the fundamental theoretical principles underlying quantitative structure–activity relationship (QSAR) models, highlighting how molecular properties and structural features are correlated with biological activity to guide rational drug development.[9-12]

F. Pharmacophore modelling

Pharmacophore approaches have emerged as essential tools in drug discovery following significant advancements over the past century. Both ligand-based and structure- based methods enhance pharmacophore (Fig-2) modeling and support virtual screening, de novo drug design, and lead optimization. However, their full potential remains limited, particularly in reducing the high costs of drug development.[25-27]

G. Quantitative structure activity relationship

Quantitative Structure–Activity Relationship (QSAR) (Fig-1) has become a fundamental computational approach in modern drug discovery. It establishes mathematical correlations between chemical structures and biological activities, enabling prediction of compound efficacy. QSAR models support virtual screening, lead optimization, and rational drug design, although challenges remain in model accuracy and data reliability.[9-12]

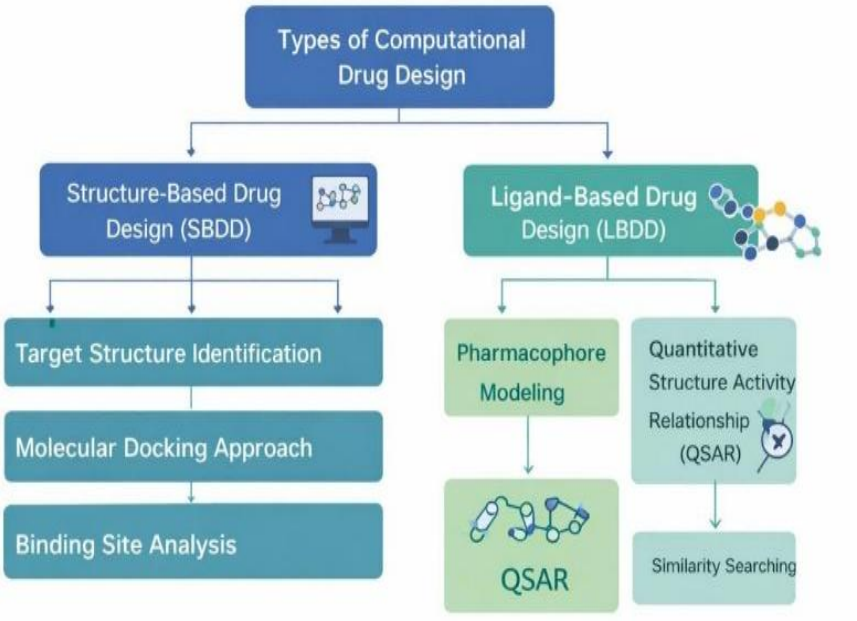

Figure 1: Structural-Based Drug Design (SBDD) workflow diagram

H. Similarity searching

Similarity searching is an important computational technique in drug discovery that identifies compounds with structural or physicochemical resemblance to known active molecules. It operates on the principle that structurally simislar compounds exhibit similar biological activities, thereby supporting virtual screening, lead identification, and efficient exploration of chemical space. [17,28]

7. Important techniques in computational drug design

7.1. Molecular docking

Molecular docking is a computational approach used to predict the binding of molecules, referred to as ligands, to appropriate receptor proteins. It is well explained in figure 2. It is a tool utilized for various computational purposes, including drug discovery. It has become an essential tool in in silico drug development. It is used to study ligand- receptor binding interactions using measures such as docking scores, g-scores, binding free energies, etc. Such a method allows researchers to study small molecules and ensure that they can yield beneficial results before taking them for wet lab experiments.

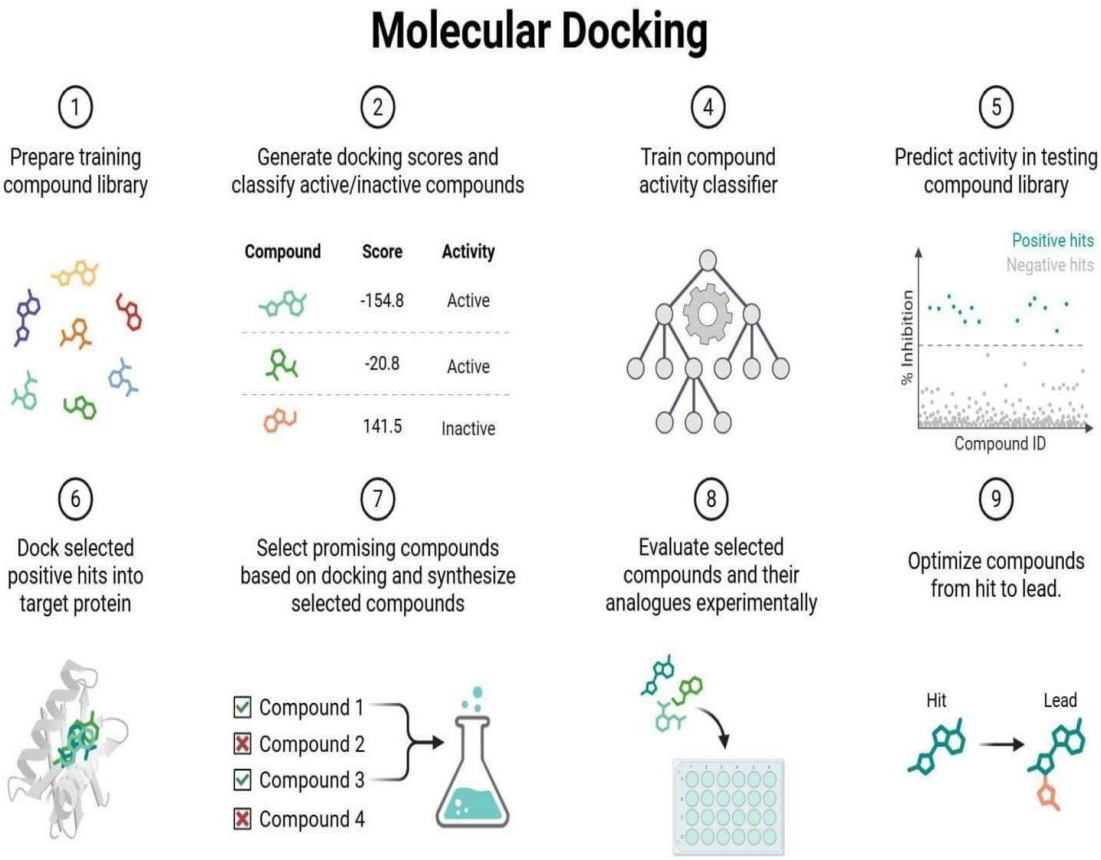

Figure 2: Molecular Docking interaction model (Ligand-receptor binding)

a. Principle of molecular docking

The process of molecular docking normally starts with selecting a biological target and obtaining information about the three-dimensional structural model of that target from existing structural databases. After choosing a target, a specific docking The technique will be utilised to examine the possible interaction between the target and any ligands present.

b. Types of molecular docking

Molecular docking is of three types, such as Flexible ligand docking, Rigid body docking and Flexible docking, which is presented in Fig. 3:

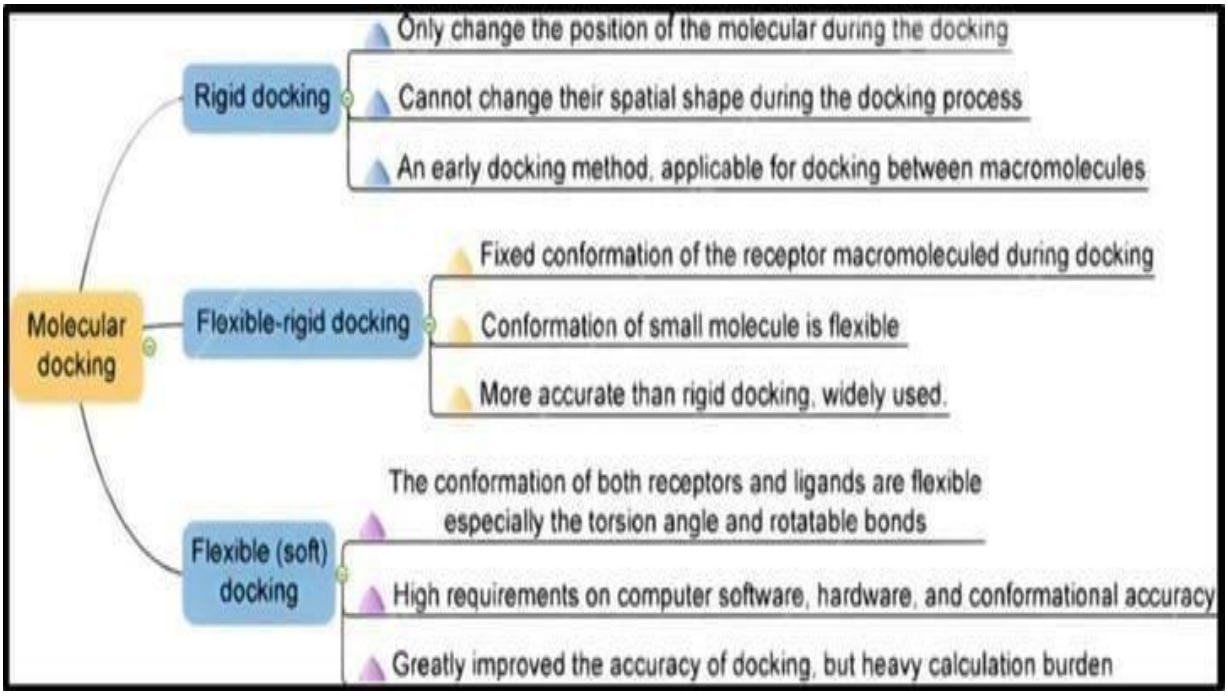

Figure 3: Types of molecular docking

c. Application of molecular docking

Molecular docking has found its use in various sectors. Some of them are mentioned below (Fig. 4):

1. Lead optimisation

Due to its ability to predict an optimised orientation of biomolecules, it can be used to predict different binding modes of the ligand in the binding site of the target molecule. Such information can be further used to develop potent, and efficient analogues.[20]

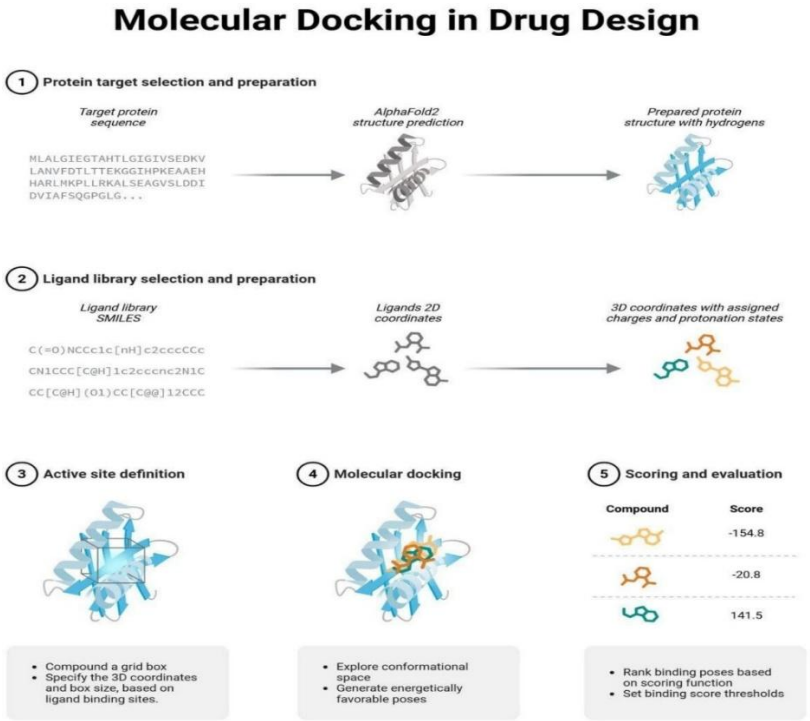

Figure 4: Conformational Ensemble model diagram

2. Hit Identifications

Since molecular makes use of the scoring function and search methods, this can be used to screen huge online databases to retrieve potent biomolecules.[21]

3. Drug-DNA Interactions Studies

A lot of the drugs available in the market utilize nucleic acids and auxiliary processes as their main cellular target. This is seen in the cases of anticancer therapeutic agents. By being able to study the correlation between a drug's molecular structure and its cytotoxicity, rational design and synthesis of new drugs can be done.[22]

4. ADMET prediction

Molecular docking techniques have emerged as important tools that are capable of assessing certain attributes of small molecules, such as Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET). Knowledge gained from such assessments allows scientists to detect any drawbacks in drug candidates even at a very early stage, thereby facilitating better screening and refinement of drug candidates.[23,24]

7.2 . Virtual screening

a. Introduction

Virtual screening is a computer-aided method used a lot in finding new drugs. It looks at heaps of chemicals to find those likely to interact with certain biological targets, which are often proteins like receptors or enzymes. Modulating these targets could produce a good therapeutic effect. This process predicts how well molecules bind and interact with specific spots, helping researchers pick out the best candidates for more tests. Doing this cuts down on the time and costs linked to making drugs the old-fashioned way.

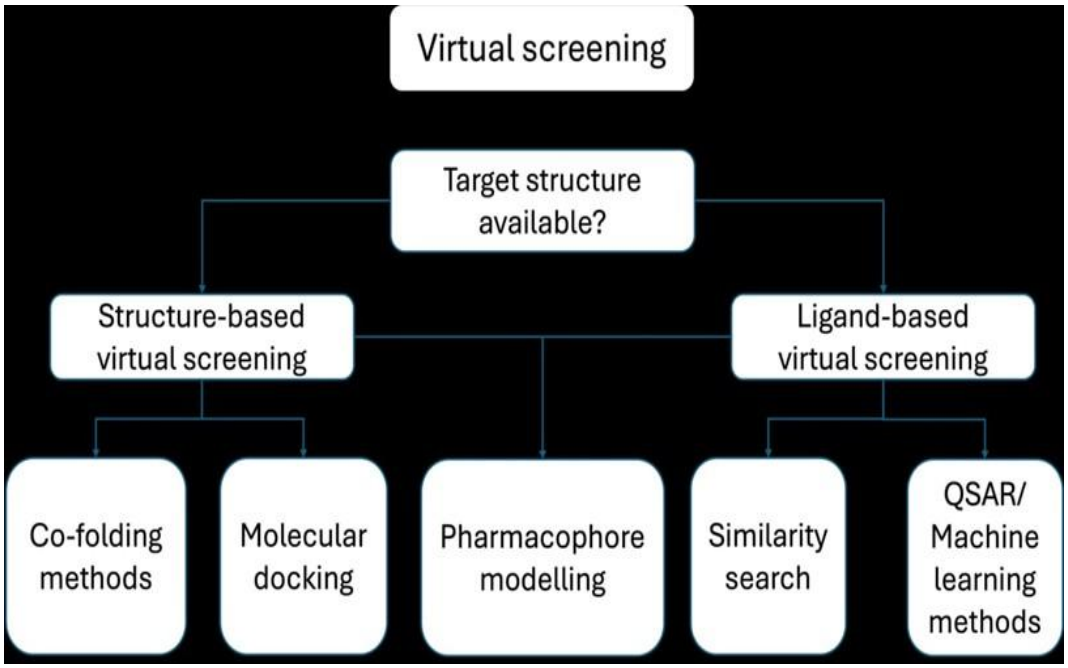

Figure 5: Virtual screening process workflow

b. Methods of virtual screening

Virtual screening methods are mainly split into ligand-based virtual screening (LBVS) and structure-based virtual screening (SBVS). These differ based on the info they use to find potential bioactive compounds, so they are pretty distinct (Fig-5).

(I) Ligand-based method

Ligand-based virtual screening uses known active compounds to find new molecules with similar biological effects. This method's handy when we do not have the three-dimensional structure of the target receptor. Computational techniques look at how compounds match up in terms of their structure, electronic properties, and physical chemical traits – all to spot similarities suggesting they might work in similar ways biologically.

(II). Structure-based method

Structure-based virtual screening uses the 3D structure of the biological target to find potential ligands. This works best when we have detailed info on the receptor, enzyme, or other big molecule targets. There are several comp chem techniques that fit here, like molecular docking, structure-based pharmacophore modeling, and molecular dynamics simulations.

C. APPLICATIONS

1. Virtual screening has been proven as a useful strategy for the early stages of drug discovery research. It helps identify hit compounds that may be used as lead molecules for further medicinal chemistry optimization.
2. One of the key aspects of computer-aided drug design is virtual screening that allows discovering potential drugs. The technology uses mathematical models to analyze chemical compounds stored in huge databases in terms of

possible interaction with the target protein (receptor, enzyme, etc.).

3. Depending on the strategy used in computations, virtual screening is divided into ligand-based and structure-based screening approaches. Ligand-based virtual screening applies knowledge about active compounds to detect new molecules with the same biological activity. 29,30

7.3 Molecular simulation dynamics

A. Introduction

Molecular dynamics simulation (MD) refers to a computational method that has been extensively applied to examine the temporal properties of a system's constituent atoms or molecules. In its application, the fundamental concepts of classical mechanics can be applied to simulate the movement and interactions between particles at the molecular level and, as such, provide detailed analysis regarding structural changes, dynamics, and interactions among particles. The use of MD simulations has proven invaluable in disciplines including but not limited to computational chemistry, biophysics, materials sciences, and drug design.

c. Theoretical background

Molecular Dynamics simulation is fundamentally based on Newton's second law of motion, where the force acting on each atom determines its acceleration (See Figure-6):

The forces between atoms are derived from potential energy functions, commonly referred to as force fields. These include bonded interactions (bond stretching, angle bending, dihedral torsions) and non- bonded interactions (van der Waals and electrostatic forces). By integrating these forces over time, the trajectory of each atom is calculated, producing a dynamic representation of the system.

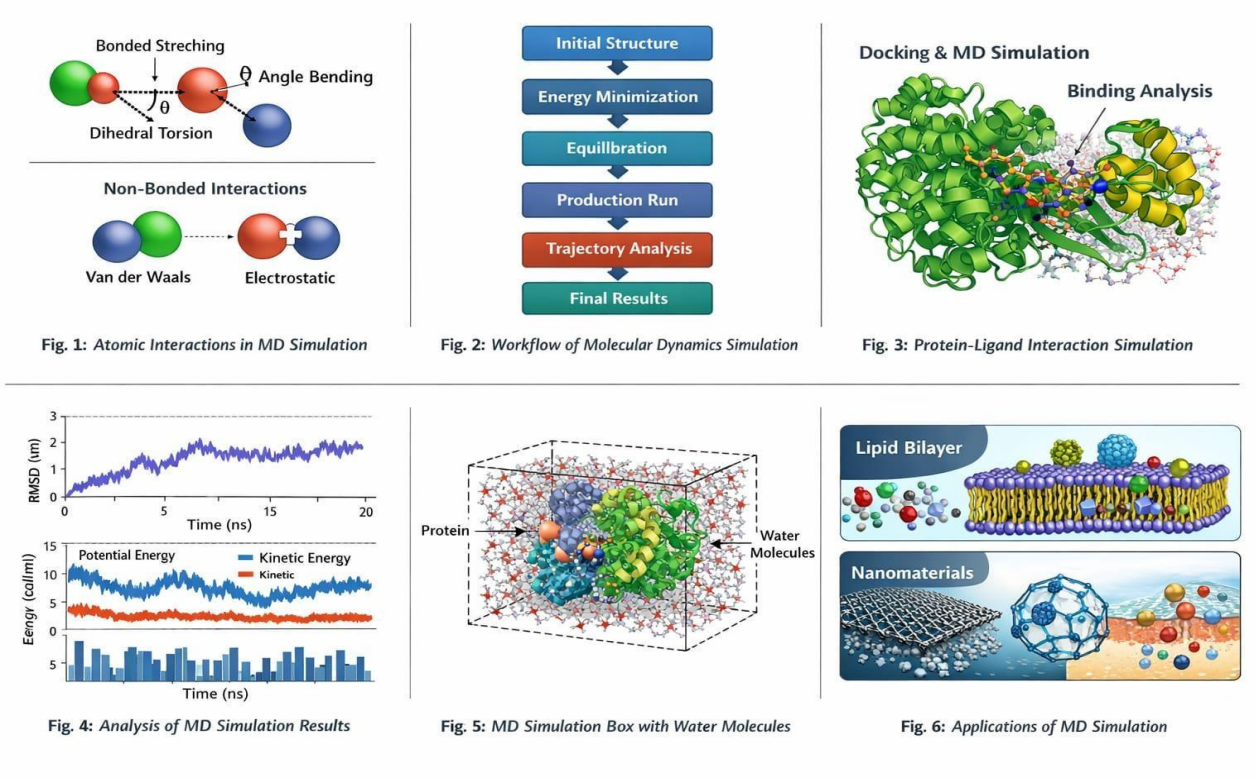

Fig. 1: *Atomic Interactions in MD Simulation* Fig. 2: *Workflow of Molecular Dynamics Simulation* Fig. 3: *Protein-Ligand Interaction Simulation*

Fig. 4: *Analysis of MD Simulation Results* Fig. 5: *MD Simulation Box with Water Molecules* Fig. 6: *Applications of MD Simulation*

Figure 6: Molecular Dynamics simulation representation (atomic motion)

a. Features of molecular dynamics simulations

Molecular Dynamics (MD) simulation possesses several distinctive features that make it a powerful tool in computational science. One of its primary characteristics is its ability to provide atomistic-level resolution, enabling researchers to observe the behaviour of individual atoms and molecules in a system.

b. Properties studied using molecular dynamic simulation

Molecular Dynamics simulations are widely used to calculate and predict a variety of physical, chemical, and biological properties of molecular systems. These properties can be broadly categorized into structural, thermodynamic, dynamic, and transport properties. Structural properties are among the most studied aspects. MD simulations (Fig-7) provide insights into molecular conformations, structural stability, and folding mechanisms of biomolecules. Parameters such as root mean square deviation (RMSD), root mean square fluctuation (RMSF), and radius of gyration are used to evaluate the stability and flexibility of the system over time.

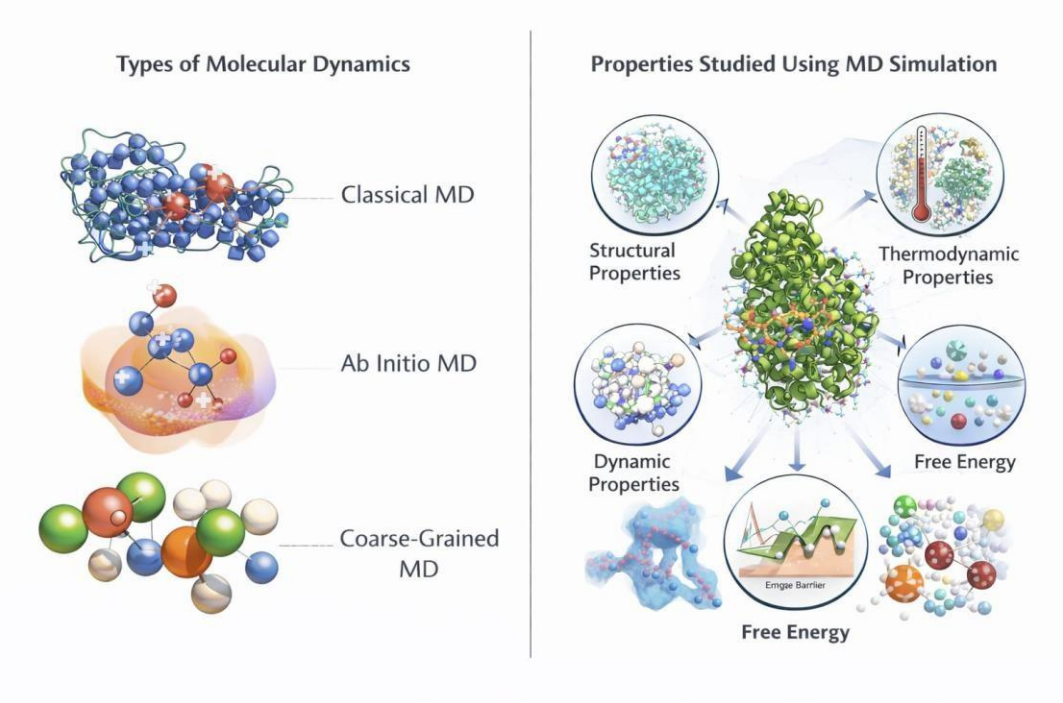

Figure 7: Types and Properties of MD

c. Methods in molecular dynamic simulations

Several methodological approaches have been developed in Molecular Dynamics simulation to address different scientific problems and computational challenges. The most widely used approach is Classical Molecular Dynamics, which is based on Newtonian mechanics. It is computationally efficient and suitable for simulating large biomolecular systems over extended time scales.

d. Applications of molecular dynamic simulations

A. Molecular Dynamics (MD) simulation is widely used in drug discovery, structural biology, and material science
B. In structural biology, MD provides insights into protein folding, enzyme activity, and biomolecular interactions.
C. It is also applied in studying lipid membranes, transport mechanisms, and cellular processes. In material science, MD is used to evaluate thermal, mechanical, and structural properties of polymers and nanomaterials.
D. Additionally, it plays an important role in studying diffusion, phase transitions, and adsorption phenomena, making it a VERSATILE computational tool.

e. Advantages of molecular dynamic simulation

Molecular Dynamics (MD) simulation offers several advantages in computational research. It provides detailed atomic-level insights into molecular systems, enabling visualization of interactions and structural changes. MD allows the study of time-dependent processes such as conformational dynamics and molecular motion. It reduces experimental cost and time by enabling virtual analysis of systems.

f. Limitations of molecular dynamic simulation

Molecular Dynamics simulation has limitations such as high computational cost and restricted simulation time scales. Its accuracy depends on force field quality. Classical MD cannot fully represent quantum effects like bond breaking. Additionally, large data generation and complex analysis require expertise, making interpretation challenging. [31]

7.4 Pharmacophore

a. Introduction

Pharmacophore is defined as an abstract concept that captures the important molecular attributes

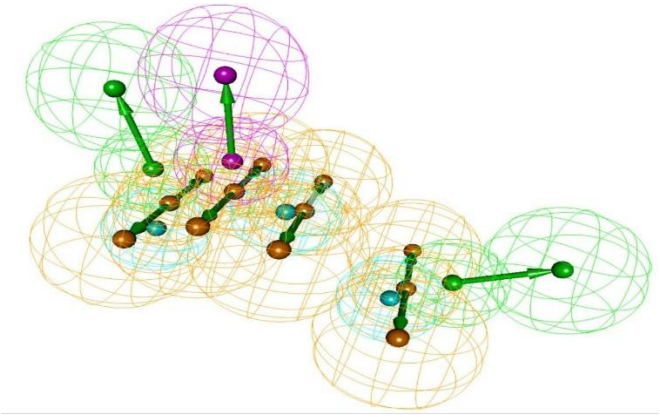

Figure 8: Example of pharmacophore modeling

that allow a ligand to bind and exert its biological effects on a particular target. Such attributes may comprise the proper arrangement of both steric and electronic properties to ensure

effective molecular recognition and elicitation of the desired physiological effect (Fig-8).

b. Features

Pharmacophore is referred to as the three-dimensional organization of functional groups in a molecule, which makes it capable of interacting efficiently with a biological receptor. The key components of a pharmacophore include the hydrophobic region, aromatic system, H-bond donors and acceptors, positive and negative charges. These could be the actual ligand-based functional groups or the sites where interaction can take place in the receptor's active site. Pharmacophore modeling involves mapping the spatial relationship of these important groups to be able to predict other molecules that will exhibit the same biological activities.

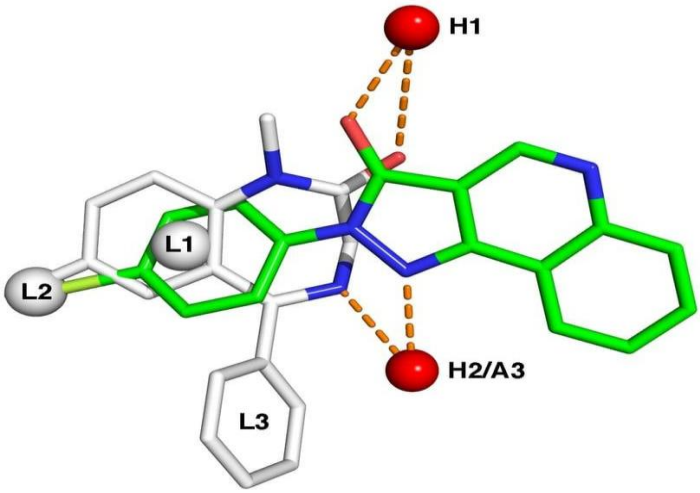

Figure 9: Benzodiazepine binding site pharmacophore model

An example of a pharmacophore model of the benzodiazepine binding site on the GABAA receptor (Fig. 9)

c. APPLICATIONS

A. Virtual Screening

Pharmacophore modelling is used to screen large chemical databases by identifying compounds with essential structural features required for biological activity, helping to rapidly discover potential drug candidates.

B. Lead Optimization

It assists in modifying lead compounds by identifying key functional groups responsible for activity, improving potency, selectivity, and pharmacokinetic properties during the drug development process.

C. Drug Repurposing

Pharmacophore models help identify new therapeutic uses for existing drugs by matching their features with different biological targets, saving time, and reducing the cost of drug discovery.

D. Target Identification

It aids in predicting potential biological targets for unknown compounds by comparing pharmacophoric features, supporting researchers in understanding mechanism of action and guiding experimental validation.

E. Structure-Activity Relationship (SAR) Studies

Pharmacophore modelling helps analyses the relationship between chemical structure and biological activity, allowing researchers to identify essential features influencing drug efficacy and optimize compound design.[32-34]

7.5 QSAR Analysis

a. Introduction

Quantitative Structure-Activity Relationship (QSAR) is a powerful modeling approach frequently used in medicinal chemistry and computer-aided drug designing to find out quantitative relations between the structures of chemical compounds and their biological activities. The main idea behind QSAR is that changes in the molecular structure affect biological effects quantitatively. Types of QSAR analysis

These are basically 5 types (Fig. 10)

1D-QSAR (One-Dimensional QSAR)

This is the simplest type of QSAR, where biological activity is correlated with basic physicochemical properties such as molecular weight, log P (hydrophobicity), and solubility. It does not consider molecular structure in detail and is mainly used for quick, preliminary analysis.

2D-QSAR (Two-Dimensional QSAR)

In this type, structural information like atom connectivity, functional groups, and topological indice are considered. It uses molecular descriptors derived from the 2D structure of compounds. This approach is widely used in medicinal chemistry for drug design and activity prediction.

3D-QSAR (Three-Dimensional QSAR)

3D-QSAR analyses the three-dimensional properties of molecules, such as steric and electrostatic fields. Techniques like CoMFA (Comparative Molecular Field Analysis) and CoMSIA are commonly used. It provides more accurate predictions by considering the spatial arrangement of atoms, making it important in computational drug design.

4D-QSAR (Four-Dimensional QSAR)

This advanced type includes multiple conformations of molecules over time, incorporating flexibility and dynamic behavior. It considers different molecular interactions and conformational changes, improving prediction accuracy compared to 3D-QSAR.

5D-QSAR and 6D-QSAR

These are more complex models that include additional parameters such as different induced-fit models, solvent effects, and receptor flexibility. They provide a more realistic simulation of biological environments but require high computational power.

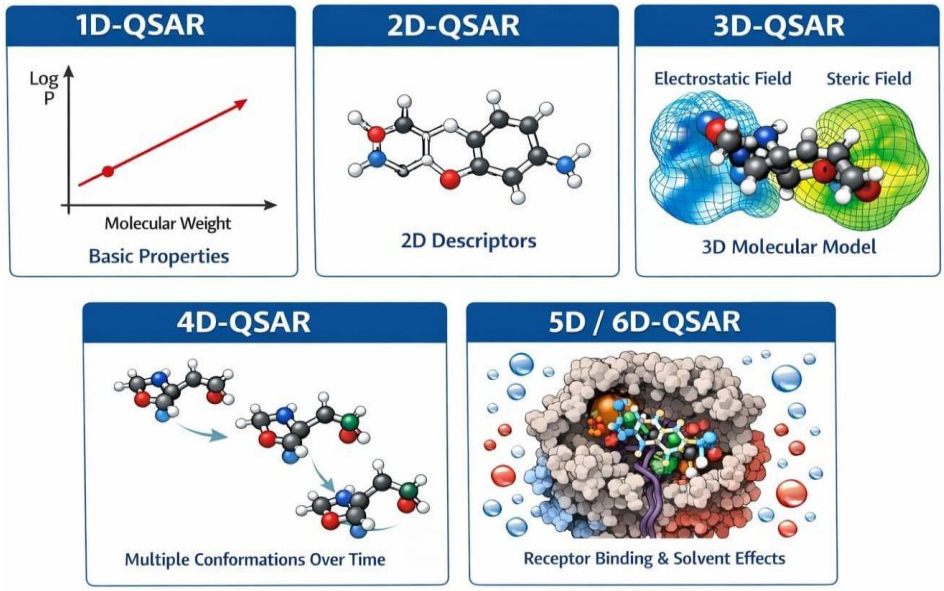

Figure 10: QSAR model workflow

B. Properties

QSAR models are based on various physicochemical and structural properties of molecules. These properties determine how a compound interacts with a biological target:

Hydrophobic Properties

These describe how well a molecule interacts with lipids or water. Parameters like log P (partition coefficient) influence drug absorption and membrane permeability.

Electronic Properties

These include electron distribution, dipole moment, and charge. They affect how a molecule forms bonds or interact with biological receptors.

Steric Properties

Steric factors refer to the size, shape, and spatial arrangement of atoms in a molecule. These properties influence how well a compound fits into a receptor binding site.

Topological Properties

These are derived from the 2D structure of molecules, such as connectivity and branching patterns. They help describe molecular structure without considering 3D geometry.

Thermodynamic Properties

These include energy-related parameters like enthalpy and free energy, which influence molecular stability and binding interactions.

C. APPLICATIONS

Drug Discovery

QSAR plays a crucial role in early drug discovery by predicting the biological activity of compounds before synthesis. It helps researchers identify promising drug candidates quickly, reducing experimental workload, time, and cost in medicinal chemistry (Fig-11).

Toxicity Prediction

QSAR is widely used to predict the toxic effects of chemicals on humans and the environment. It helps identify harmful compounds early, minimizing risks and reducing reliance on animal testing in computational toxicology studies.

Environmental Risk Assessment

QSAR helps evaluate the environmental impact of chemicals by predicting properties like biodegradability, bioaccumulation, and ecotoxicity. It is useful for regulatory agencies to assess chemical safety without extensive laboratory testing.

Pharmacokinetic Prediction

QSAR models predict ADME properties (Absorption, Distribution, Metabolism, Excretion) of drugs. This helps in understanding how a compound behaves inside the body, improving drug design and reducing late-stage failures.

Enzyme Inhibitor Design

QSAR assists in designing molecules that can inhibit specific enzymes by analysing structure–activity relationships. It helps in developing targeted therapies for diseases by optimizing molecular interactions with enzyme active sites.

Agrochemical Development

QSAR is applied in designing pesticides and herbicides with high efficacy and low toxicity. It helps create environmentally safer agrochemicals by predicting biological activity and environmental behaviour before synthesis.[25,26]

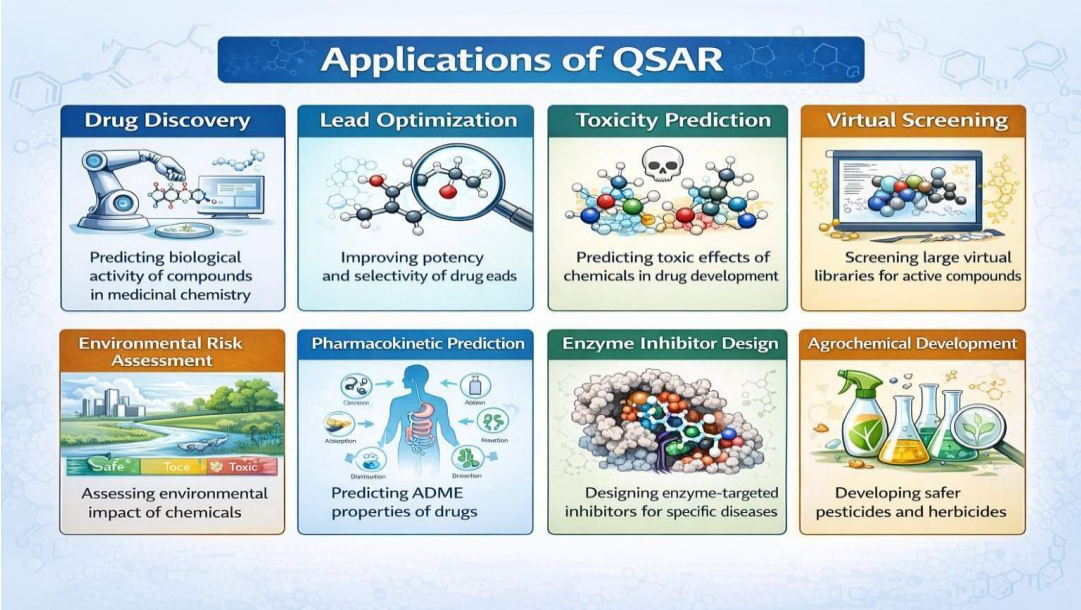

Figure 11: Application of QSAR

D. Advantages and limitations

QSAR offers rapid prediction of biological activity, reduces experimental cost and time, and supports lead optimization in medicinal chemistry. However, it depends on data quality, may lack accuracy for diverse compounds, and has limited applicability domain, making predictions unreliable when extrapolated beyond trained datasets or poorly validated models.[25,26]

7.6 ADMET prediction

As an important part of drug discovery, lead optimisation aims at enhancing the pharmacokinetics and safety features of prospective drug candidates through evaluating their pharmacokinetic properties and toxicities, including their absorptions, distributions, metabolisms, excreting, and toxicities (ADMET properties). Recent breakthroughs in machine learning have allowed researchers to predict multiple ADMET properties simultaneously using a multi-task learning approach (MTL). The need for massive data specific to a particular endpoint has also been reduced due to the advancement. Nevertheless, issues still exist when considering how to better facilitate the sharing of information between related tasks and discovering the influential molecular substructure of ADMET properties (Fig. 12).[10]

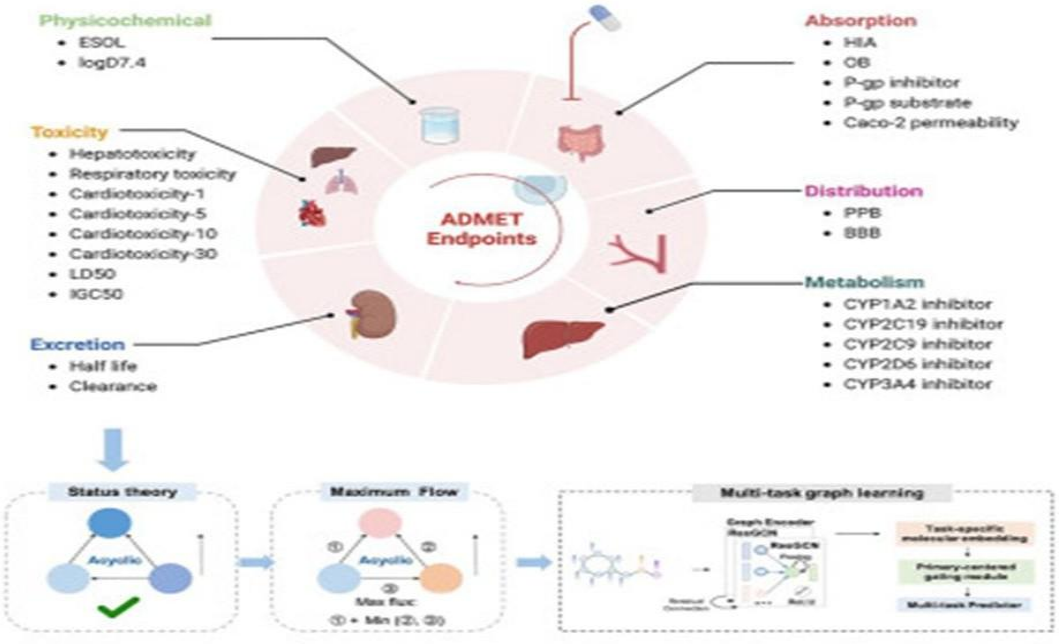

Figure 12: ADMET prediction diagram

a. Property application in drug discovery

- ADMET prediction is applied throughout the drug development pipeline.
- Virtual Screening (Early Stage): Quickly screening thousands of compounds to prioritize only those with favorable ADMET profiles.
- Lead Optimization: Guiding chemists to modify chemical structures to improve properties (e.g., adding a polar group to increase solubility).
- Reducing Late-Stage Failure: Identifying compounds likely to fail due to toxicity before animal studies.
- Drug Repurposing: Finding new applications for existing drugs by analysing their comprehensive ADMET profiles.
- Regulatory Compliance: Assisting in creating a safety data package for regulatory agencies (e.g., FDA). [10,27]

7.7 Density functional theory calculations

Density Functional Theory (DFT) calculation is a quantum mechanical computational method used to study the electronic structure of atoms, molecules, and solids. It is widely applied in quantum chemistry and computational chemistry to calculate molecular properties with good accuracy and reasonable computational cost.[11-13]

a. Properties of DFT

1. **Electron Density-Based Approach**

DFT uses electron density instead of wavefunctions to describe a system, making calculations simpler and computationally efficient in quantum chemistry.

2. **Exchange–Correlation Functionals**

Accuracy of DFT depends on functionals that approximate electron–electron interactions, especially exchange and correlation energies.

3. **Computational Efficiency**

DFT provides a good balance between accuracy and computational cost, making it suitable for large molecular systems.

4. **Ground State Focus**

DFT mainly predicts ground-state properties like total energy, structure, and stability of molecules. Versatility It can be applied to atoms, molecules, and solids across computational chemistry and material science.

b. APPLICATIONS OF DFT

Drug Design (See in Fig-13)

DFT helps in studying molecular interactions, electronic properties, and reactivity of drug molecules, aiding rational drug design.

Material Science

Used to design and analyses materials like semiconductors, nanomaterials, and catalysts by predicting electronic and structural properties.

Reaction Mechanism Study

DFT helps understand reaction pathways, transition states, and activation energies in chemical reactions.

Spectroscopic Analysis

It predicts IR, NMR, and UV spectra, helping in the identification and characterization of compounds.

Catalysis Research

DFT is widely used to study catalytic processes and design efficient catalysts for industrial and environmental applications.[11-13]

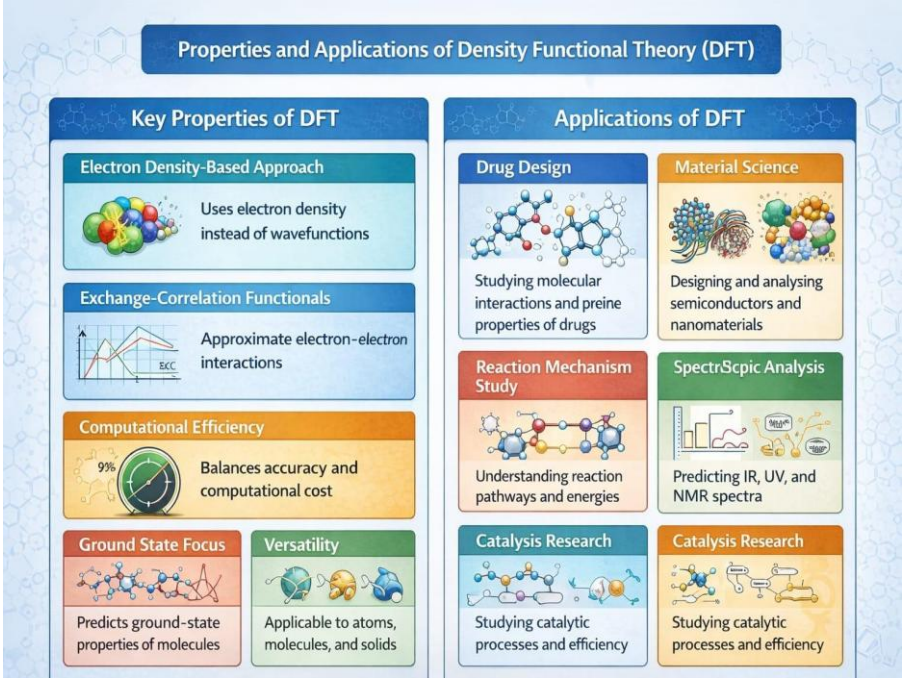

Figure 13: Properties and Application of Density Functional Theory (DFT)

8. Applications of computational drug design

Computational drug design is used to identify potential drug molecules, study their interaction with targets, and improve their effectiveness. It helps in virtual screening, lead optimization, and reducing time and cost in drug development, making the process faster and more efficient in medicinal chemistry.[31]

A. Drug discovery and development

Drug Discovery and Development is a multi-step, interdisciplinary process focused on identifying, designing, and delivering safe and effective therapeutic agents. It begins with target identification and validation, where biological molecules involved in disease are selected. This is followed by lead discovery through experimental screening or computational approaches, and lead optimization to improve potency, selectivity, and pharmacokinetic properties. [32-34]

B. Vaccine design

Vaccine Design is a systematic and scientific process aimed at developing safe and effective vaccines to prevent infectious diseases. It begins with the identification of suitable antigens, typically proteins or molecular components of a pathogen that can trigger an immune response. Advanced computational tools and immunoinformatic approaches are increasingly used to predict antigenic epitopes and enhance vaccine efficiency.[35,36]

C. Cancer drug development

Cancer Drug Development is a complex and targeted process focused on discovering and developing therapies to treat various types of cancer. It begins with identifying molecular targets such as mutated genes or abnormal proteins involved in tumor growth and progression.[19] Researchers then design or screen compounds that can specifically interact with these targets. Promising drug candidates undergo preclinical studies to evaluate their anticancer activity and safety in laboratory and animal models.

D. Antiviral drug design

Antiviral Drug Discovery is a specialized area of research focused on developing drugs to prevent or treat viral infections. The process begins with identifying viral targets such as enzymes or proteins essential for viral replication, including proteases, polymerases, or entry receptors. Researchers then use techniques like high-throughput screening and computational modeling to identify potential antiviral compounds.[32]

E. Enzyme inhibitor design

Enzyme Inhibitor Design is a key strategy in drug discovery that focuses on developing molecules capable of blocking the activity of specific enzymes involved in disease processes. The process begins with identifying a target enzyme and understanding its structure, active site, and mechanism of action.

F. Lead optimization

Lead Optimization is a crucial stage in drug discovery that focuses on improving the properties of lead compounds to develop effective and safe drug candidates. After identifying a promising lead molecule, scientists modify its chemical structure to enhance potency, selectivity, and binding affinity toward the target. At the same time, efforts are made to improve pharmacokinetic properties such as absorption, distribution, metabolism, and excretion (ADME), while minimizing toxicity and side effects.[33-34]

9. Future scope of computational drug design

A. Artificial intelligence in drug design

Artificial intelligence is rapidly emerging as the future of drug design, transforming the way new medicines are discovered and developed. By integrating machine learning, deep learning, and big data analytics, AI can predict molecular behavior, identify novel drug candidates, and optimize compounds with remarkable speed and precision. It enables researchers to explore vast chemical spaces that were once inaccessible, reducing time and cost significantly. Moreover, AI enhances personalized medicine by tailoring treatments based on genetic and clinical data. As technology continues to evolve, artificial intelligence holds the promise of revolutionizing drug discovery, making it more efficient, accurate, and innovative than ever before.[14,35]

B. Machine learning applications

Machine learning is playing a transformative role in drug design, offering powerful tools to analyze complex biological data and predict drug–target interactions with high accuracy. It enables rapid screening of large compound libraries, identification of potential drug candidates, and optimization of molecular properties. By learning from existing datasets, machine learning models improve decision- making and reduce trial-and-error approaches. This leads to faster, more efficient, and cost-effective drug discovery, making it an essential component of the future of pharmaceutical research.[14,15]

Big data in pharmaceutical research is revolutionising pharmaceutical research by enabling the analysis of vast and complex biological, clinical, and chemical datasets. It helps researchers identify patterns, discover new drug targets, and improve decision-making throughout the drug development process. By integrating data from genomics, clinical trials, and patient records, big data supports personalised medicine and enhances treatment outcomes. It also accelerates drug discovery, reduces costs, and increases efficiency, making pharmaceutical research more innovative, data-driven, and impactful in modern healthcare.16

C. Personalised and precision medicine

Personalised and precision medicine represents a transformative shift in modern healthcare, where treatments are no longer designed for the average patient but are carefully tailored to the unique genetic makeup, lifestyle, and environment of everyone. This innovative approach enhances therapeutic effectiveness while minimizing adverse effects, ensuring safer and more targeted interventions.44 As technology continues to evolve, personalized medicine promises a future where healthcare becomes more predictive, preventive, and profoundly effective, improving both quality of life and long-term outcomes (Figure-14).[37,38]

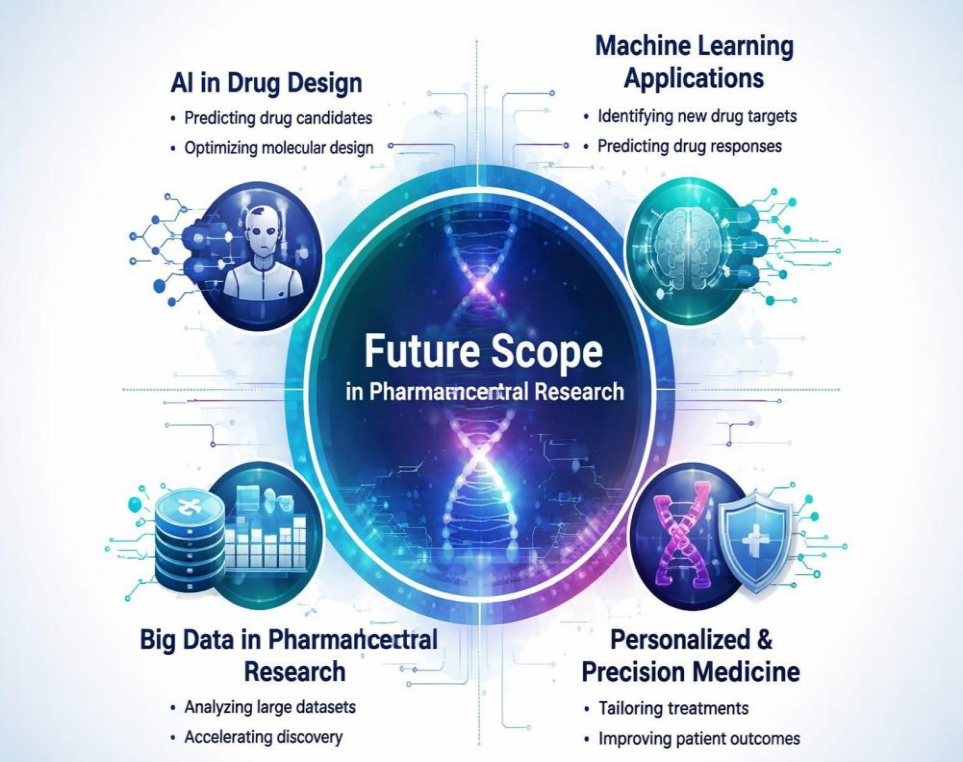

Figure 14: Computational drug design application overview diagram

10. CONCLUSION

Computational drug design stands as a powerful and transformative approach in modern pharmaceutical research, bridging the gap between theoretical science and practical medicine.[1] By integrating advanced computational techniques such as molecular modeling, virtual screening, quantum mechanics, and artificial intelligence, it has revolutionized the way drugs are discovered, designed, and optimized. Despite its remarkable advantages, computational drug design is not without limitations.[39] Challenges such as dependence on accurate data, computational complexity, and the need for experimental validation highlight that it cannot entirely replace traditional methods. Instead, it works best as a complementary tool, guiding and refining laboratory research[35] Ultimately, computational drug design is reshaping the landscape of drug discovery, making it more efficient, innovative, and patient-centric, and paving the way for a new era of smarter and more targeted therapeutic solutions.

REFERENCES

1. Kitchen, D.B.; Decornez, H.; Furr, J.R.; Bajorath, J. "Docking and Scoring in Virtual Screening for Drug Discovery." *Nat. Rev. Drug Discov.* 2004, *3*, 935–949.
2. Schneider, G. "Virtual Screening: An Endless Staircase?" *Nat. Rev. Drug Discov.* 2010, *9*, 273–276.
3. Walters, W.P.; Stahl, M.T.; Murcko, M.A. "Virtual Screening—An Overview." *J. Med. Chem.* 1998, *41*, 2249–2260.
4. Paul, S.M.; Mytelka, D.S.; Dunwiddie, C.T.; et al. "How to Improve R&D Productivity." *Nat. Rev. Drug Discov.* 2010, *9*, 203–214.
5. Hughes, J.P.; Rees, S.; Kalindjian, S.B.; Philpott, K.L. "Principles of Early Drug Discovery." *Br. J. Pharmacol.* 2011, *162*, 1239–1249.
6. Drews, J. "Drug Discovery: A Historical Perspective." *Science* 2000, *287*, 1960–1964.
7. DiMasi, J.A.; Hansen, R.W.; Grabowski, H.G. "Cost of Drug Development." *J. Health Econ.* 2003, *22*, 151–185.
8. Lionta, E.; Spyrou, G.; Vassilatis, D.K.; Cournia, Z. "Structure-Based Virtual Screening." *J. Med. Chem.* 2014, *57*, 615–628.
9. Di, L.; Kerns, E.H. "Drug-Like Properties." *Curr. Opin. Chem. Biol.* 2003, *7*, 402–408.
10. Gleeson, M.P.; Hersey, A.; Overington, J. "ADMET Relationships." *Nat. Rev. Drug Discov.* 2011, *10*, 197–208.
11. Hohenberg, P.; Kohn, W. "Density Functional Theory." *Phys. Rev.* 1964, *136*, B864–B871.
12. Kohn, W.; Sham, L.J. "DFT Equations." *Phys. Rev.* 1965, *140*, A1133–A1138.
13. Parr, R.G.; Yang, W. *DFT Theory.* Oxford University Press: Oxford, 1989, pp 1–333.
14. Hospital, A.; Goñi, J.R.; Orozco, M.; Gelpí, J.L. "Molecular Dynamics Simulations: Advances and Applications." *Adv. Appl. Bioinform.* 2015, *67*, 1–20.
15. Yang, S.Y. "Pharmacophore Modeling and Applications in Drug Discovery: Challenges and Recent Advances." *Drug Discov. Today* 2010, *15*, 444–450.
16. Roy, K. *A Primer on QSAR/QSPR Modeling: Fundamental Concepts.* Springer: 2015, ISBN: 978-3-319-17281-1.
17. (a) Shoichet, B.K. "Virtual Screening of Chemical Libraries." *Nature* 2004, *432*, 862–865. (b) Karplus, M.; McCammon, J.A. "Molecular Dynamics Simulations."

Nat. Struct. Biol. 2002, *9*, 646–652.
18. Varma, M.V.; Obach, R.S.; Rotter, C.; Miller, H.R.; Chang, G.; El-Kattan, A.; Troutman, M.D. "Physicochemical Space for Optimum Oral Bioavailability: Contribution of Human Intestinal Absorption and First-Pass Elimination." *J. Med. Chem.* 2010, *53*, 1098–1108.
19. Jones, R.O. "Density Functional Theory: Its Origins, Rise to Prominence, and Future." *Rev. Mod. Phys.* 2015, *87*, 897–923.
20. Trott, O.; Olson, A.J. "AutoDock Vina." *J. Comput. Chem.* 2010, *31*, 455–461.
21. Meng, X.Y.; Zhang, H.X.; Mezei, M.; Cui, M. "Molecular Docking Review." *Curr. Comput. Aided Drug Des.* 2011, *7*, 146–157.
22. Ferreira, L.G.; dos Santos, R.N.; Oliva, G.; Andricopulo, A.D. "Docking and Scoring Review." *Molecules* 2015, *20*, 13384–13421.
23. Pagadala, N.S.; Syed, K.; Tuszynski, J. "Software for Molecular Docking." *Biophys. Rev.* 2017, *9*, 91–102.
24. Gorgulla, C.; Boeszoermenyi, A.; Wang, Z.F.; et al. "VirtualFlow." *Nat. Methods* 2020, *17*, 686–688.
25. Cherkasov, A.; Muratov, E.N.; Fourches, D.; et al. "QSAR Modeling." *J. Med. Chem.* 2014, *57*, 4977–5010.
26. Gramatica, P. "QSAR Validation." *QSAR Comb. Sci.* 2007, *26*, 694–701.
27. (a) Tropsha, A. "QSAR Best Practices." *Mol. Inform.* 2010, *29*, 476–488. (b) van de Waterbeemd, H.; Gifford, E. "ADMET Prediction." *Nat. Rev. Drug Discov.* 2003, *2*, 192–204.
28. Dror, R.O.; Dirks, R.M.; Grossman, J.P.; Xu, H.; Shaw, D.E. "Biomolecular Simulation." *Annu. Rev. Biophys.* 2012, *41*, 429–452.
29. Lavecchia, A.; Di Giovanni, C. "Virtual Screening Strategies." *Curr. Med. Chem.* 2013, *20*, 2839–2860.
30. Ripphausen, P.; Nisius, B.; Bajorath, J. "State of the Art in Virtual Screening." *Drug Discov. Today* 2011, *16*, 372–376.
31. (a) Vamathevan, J.; Clark, D.; Czodrowski, P.; et al. "Machine Learning in Drug Discovery." *Nat. Rev. Drug Discov.* 2019, *18*, 463–477. (b) Stephens, Z.D.; Lee, S.Y.; Faghri, F.; et al. "Big Data Challenges." *PLoS Biol.* 2015, *13*, e1002195.
32. Ashley, E.A. "Precision Medicine." *JAMA* 2016, *316*, 2119–2120.
33. Collins, F.S.; Varmus, H. "Precision Medicine Initiative." *N. Engl. J. Med.* 2015, *372*, 793–795. Bajorath, J. *J. Med. Chem.* 2002, *45*, 469–482.
34. Anderson, A.C. *Chem. Biol.* 2003, *10*, 787–797.
35. Shaw, D.E. "Atomic-Level Characterization of the Structural Dynamics of Proteins." *Science* 2010, *330*, 341–346.
36. Yang, S.Y. "Pharmacophore Modeling and Applications in Drug Discovery: Challenges and Recent Advances." *Drug Discov. Today* 2010, *15*, 444–450.
37. Todeschini, R.; Consonni, V. *Molecular Descriptors for Chemoinformatics.* Wiley: 2009, pp 1257.
38. Ekins, S.J. *Computational Toxicology: Risk Assessment for Pharmaceutical and Environmental Chemicals.* Wiley: 2007.
39. Sliwoski, G.; Kothiwale, S.; Meiler, J.; Lowe, E.W. "Computational Methods in Drug Discovery." *Pharmacol. Rev.* 2014, *66*, 334–395.

About the Corresponding Author

Archanamayee Behera is an Assistant Professor in the PG Department of Chemistry at Rajendra University, Balangir, Odisha, India. Her research interests span computational chemistry and drug discovery. She is dedicated to advancing chemical sciences through teaching and research at the postgraduate level.