

COMPUTER-AIDED DRUG DESIGN

PRINCIPLES, TECHNIQUES,
AND APPLICATIONS

PART 1

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Computer-Aided Drug Design: Principles, Techniques, and Applications

(Part 1)

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FOREWORD

The field of drug discovery has witnessed a paradigm shift in recent decades, evolving from labor-intensive empirical screening toward data-driven, computationally guided innovation. Among the forces driving this transformation, computer-aided drug design (CADD) stands as a cornerstone technology that bridges chemistry, biology, and informatics with unparalleled precision. The integration of computational methods into drug development has not only accelerated the discovery pipeline but also deepened our molecular understanding of disease mechanisms, target interactions, and therapeutic optimization.

This volume, *Computer-Aided Drug Design: Principles and Computational Foundations*, provides a comprehensive and methodical introduction to the concepts and methodologies that form the basis of modern CADD. At a time when computational approaches are becoming indispensable to pharmaceutical sciences, this book offers readers an opportunity to develop a strong conceptual framework in the discipline. The structure of this volume mirrors the foundational progression of the field itself. Beginning with the historical evolution of CADD, the chapters guide readers through classical and well-established methodologies, including quantitative structure–activity relationship (QSAR) analysis, molecular and quantum mechanics, energy minimization, homology modeling, molecular docking, and ADMET prediction. Together, these topics provide the theoretical and practical basis necessary for understanding how computational tools contribute to rational drug discovery.

What distinguishes this volume is its balanced presentation of theory and application. The contributors have successfully combined conceptual clarity with methodological depth, ensuring that readers not only appreciate the scientific principles involved but also understand their relevance within contemporary drug development workflows. The discussions are enriched through practical examples and case-based perspectives that reinforce the importance of these approaches in real-world settings.

The chapters included in this volume have been authored by experts from diverse academic and research backgrounds, reflecting the interdisciplinary nature of computational drug design. Their collective expertise has resulted in a scholarly resource that is equally valuable to students beginning their journey in CADD and to researchers seeking a consolidated reference on fundamental methodologies.

I commend the editors, Ajmer Singh Grewal, Viney Lather, Geeta Deswal, and Kumar Guarve, for their outstanding work and dedication in bringing this comprehensive and insightful edited book to fruition. It is a must-read for researchers, healthcare professionals, and students eager to stay abreast of the latest developments in the pharmaceutical and biomedical sciences.

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PREFACE

Drug discovery has traditionally demanded immense time, resources, and financial investment. Computer-Aided Drug Design (CADD) has revolutionized this process by integrating computational chemistry, molecular modeling, and bioinformatics with experimental pharmacology. These approaches enable efficient identification, optimization, and validation of potential drug candidates while significantly reducing costs and timelines. By simulating molecular interactions, predicting pharmacokinetic properties, and guiding lead optimization, CADD enhances precision and success rates in drug development. Today, it is not merely a supportive tool but a central component of pharmaceutical research, accelerating innovation and enabling the design of safer, more effective, and targeted therapeutic agents.

The motivation behind this book, “**Computer-Aided Drug Design: Principles, Techniques, and Applications**,” lies in providing a comprehensive understanding of both the fundamental principles and the cutting-edge applications of CADD. This volume aims to highlight how advancements in algorithms, computational power, and molecular databases have enabled researchers to probe drug-receptor interactions, predict molecular properties, and design safer, more effective therapeutics. The book is systematically structured to ensure that readers can navigate from foundational knowledge to specialized applications. The opening chapters introduce the history and evolution of CADD, tracing its development from elementary molecular modeling in the 1960s to present-day applications involving high-throughput virtual screening and artificial intelligence. The discussion provides an entry point into essential methods such as molecular docking, Quantitative Structure-Activity Relationship (QSAR) analysis, pharmacophore mapping, and ADMET prediction, supported by case studies and methodological insights.

A major focus of this volume is QSAR, a cornerstone of computational drug design. The chapters provide a detailed account of its origins, theoretical foundations, and evolution into modern 2D, 3D, and advanced 4D approaches. Key aspects such as descriptor selection, statistical modeling, and validation techniques are thoroughly discussed, with emphasis on ensuring predictive reliability. Applications across diverse biological systems illustrate QSAR’s wide utility in drug discovery. Beyond predictive modeling, QSAR is highlighted as an essential tool for mechanistic interpretation, guiding rational drug design and optimization of therapeutic candidates.

Another important section of the book delves into Molecular Mechanics (MM) and Quantum Mechanics (QM), highlighting how computational methods can capture interactions at the atomic level. Through approaches such as QM/MM hybrid techniques, energy minimization algorithms, and molecular dynamics simulations, the chapters illustrate how theoretical frameworks are applied to model complex biomolecular systems and ligand-receptor dynamics. These discussions are complemented by analyses of docking techniques, rigid, flexible, and hybrid methods, which are essential in evaluating binding affinities and guiding lead optimization. Real-world examples of docking against clinically relevant targets such as HIV protease and HMG-CoA reductase reinforce the practical impact of these methodologies.

The prediction and evaluation of ADMET properties are presented as a key stage in reducing attrition rates in drug discovery. This book emphasizes the integration of empirical rules such as Lipinski’s rule of five with modern computational platforms like SwissADME, pkCSM, and ADMETlab. The chapters demonstrate how early pharmacokinetic and toxicity predictions can enhance lead optimization and significantly improve the probability of clinical success. Closely linked to this discussion are chapters on de novo drug design and homology

modeling, which present strategies for designing molecules from scratch and for predicting protein structures when experimental data are lacking.

Further depth is provided through dedicated chapters on pharmacophore mapping, virtual screening, and drug repurposing. These topics showcase how computational tools are applied not only to discover novel molecules but also to re-evaluate existing drugs for new therapeutic indications. The role of artificial intelligence and machine learning in transforming CADD is another highlight of the book. These chapters explore the integration of deep learning, reinforcement learning, and natural language processing in drug discovery workflows, demonstrating how generative models and advanced analytics are driving innovation in molecular design.

The concluding chapters of this volume extend the applications of CADD to advanced and specialized domains. Molecular Dynamics (MD) simulations are emphasized as powerful tools for understanding biomolecular flexibility, conformational dynamics, and thermodynamics that direct drug-target interactions. The book also explores computational strategies targeting epigenetic regulators, highlighting their potential to unlock innovative therapies for cancer, neurodegenerative, and other complex diseases. To enhance practical understanding, tutorials and software-based exercises are incorporated, providing readers with opportunities to apply theoretical knowledge directly in laboratory and academic settings, thereby fostering experiential learning.

This volume represents the collaborative efforts of researchers and academicians from varied domains, including pharmaceutical sciences, computational chemistry, and bioinformatics. Their combined expertise has shaped a text that effectively balances theoretical foundations with practical case studies, making it valuable for both academic and professional audiences. For students and research scholars, it provides a structured introduction to key concepts of CADD, while for researchers and practitioners, it offers comprehensive coverage of advanced methodologies, contemporary tools, and real-world applications in modern drug discovery and development.

In summary, this book seeks to provide readers with a holistic perspective on the discipline. By encompassing historical context, core methodologies, advanced computational strategies, and applied case studies, the book highlights the central role of CADD in modern drug discovery. It is our hope that this volume will serve not only as a reference text but also as an inspiration for future innovations in computational drug design, ultimately contributing to the development of safer, more targeted, and more effective therapeutics.

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CHAPTER 1

From Molecules to Machines: The Evolution of Computer-Aided Drug Design

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Abstract: Computer-Aided Drug Design (CADD) has transformed pharmaceutical research by converging computational processes with medicinal chemistry to facilitate simplified drug discovery protocols. Through simulated molecular interactions, biologically relevant predictions, and lead compound optimizations, CADD tremendously cuts the time, effort, and materials invested in the conventional drug development pipelines. The chapter presents the basics of CADD in terms of how it has evolved historically from elementary molecular modeling in the 1960s to the current application of sophisticated algorithms, high-throughput virtual screening, and artificial intelligence. It highlights key techniques like molecular docking, quantitative structure-activity relationship, pharmacophore mapping, and ADMET prediction. It also points out the importance of several databases and software packages that facilitate *in silico* drug design. With the ongoing development of computational procedures and data accessibility, CADD continues to be a pillar in contemporary drug discovery, allowing researchers to develop more efficacious and safer therapeutic drugs with greater precision.

Keywords: ADMET, Computational drug design, Computational techniques, Drug discovery, Docking, Molecular modeling, Pharmacophore modeling, QSAR, SBDD, LBDD, Traditional drug development.

INTRODUCTION

Computer-Aided Drug Design (CADD) is an interdisciplinary science that integrates chemistry, biology, pharmacology, and computer science to speed up and maximize the drug discovery and development process. Historically, drug discovery was largely based on trial-and-error laboratory experiments, which were time-consuming, expensive, and frequently inefficient. With the introduction of

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computational systems in the mid-20th century, scientists started modeling and simulating the interactions between molecules, ultimately producing the means to predict how hypothetical drug molecules could bind to biological targets [1]. CADD has evolved from the early molecular modeling methods to several important advances that include the creation of quantitative structure-activity relationship models, molecular docking, pharmacophore modeling, and *in silico* ADMET prediction. The tools enable scientists to virtually screen large collections of compounds, find promising leads, and optimize them according to predicted biological and drug-like properties. CADD is currently a crucial component of drug discovery pipelines in both academia and industry. It supports two main approaches: Ligand-based Drug Design (LBDD), which makes use of data about molecules that are known to bind to a target, and Structure-based Drug Design (SBDD), which makes use of the 3D target structure. The predictive power and efficiency of CADD have also been enhanced by big data, machine learning, and high-performance computing. CADD is now the foundation of modern pharmaceutical research, revolutionizing drug design, optimization, and discovery. CADD enables researchers to forecast, model, and examine the interaction between small molecules and biological targets by utilizing the power of computational resources and algorithms. This method not only accelerates the drug discovery process but also enhances its efficiency and accuracy, thereby saving costs and time for marketing a new drug. Over the decades, CADD has evolved from basic molecular visualization methods to advanced, AI-based platforms that can handle complex issues in drug design [2].

HISTORY AND EVOLUTION OF COMPUTER-AIDED DRUG DESIGN

Early Beginnings of Computational Drug Discovery

Early Foundations: The Genesis of CADD

CADD's origins can be traced back to the development of computational chemistry and molecular modeling in the 1970s. Quantitative Structure-Activity Relationship (QSAR) models were developed as a result of early efforts to clarify chemical structure-biological activity correlations. QSAR models served as the foundation for logical drug design by using statistical methods to correlate pharmacological effects with molecular descriptors. Simultaneously, the advancement of molecular docking techniques made it feasible to predict ligand-receptor interactions, thereby identifying possible therapeutic candidates. However, the size and complexity of these simulations were constrained by the computational power available at the time [3].

The 1990s: Expansion and Integration

Computational power increased dramatically in the 1990s, opening the door to more sophisticated modeling and simulation techniques. Because they provide insights into the dynamic nature of biomolecular systems, Molecular Dynamics (MD) simulations have gained popularity. Researchers were able to more accurately study thermodynamic properties, binding affinities, and conformational changes thanks to the simulations. Additionally, the efficiency of lead identification was increased by combining virtual screening techniques with pharmacophore modeling. Pharmacophore models guided the selection of compounds for additional testing and generalized the essential characteristics of biological activity. Large chemical libraries used in virtual screening made it possible to quickly assess potential drug candidates, improving process efficiency.

The 2000s: High-Throughput and Collaborative Endeavors

High-Throughput Screening (HTS) and cooperative research initiatives brought about a paradigm shift in drug discovery during the year 2000. Large libraries of compounds could be quickly interrogated against biological targets thanks to HTS technologies, creating massive datasets for analysis. CADD tools were pivotal in handling and interpreting this information, identifying leads for further development. The strength of collective wisdom in addressing global health issues was demonstrated by cooperative initiatives such as the Open-Source Drug Discovery (OSDD) movement. By encouraging open-access platforms and pooled resources, these efforts made drug discovery more democratic, enabling researchers from across the globe to drive the process of developing new therapeutics [4].

The 2010s: The Age of Artificial Intelligence

The 2010s have welcomed the integration of Artificial Intelligence (AI) and Machine Learning (ML) in CADD, which has transformed the drug discovery process. AI algorithms, trained on large data sets of chemical and biological data, have enabled the accurate prediction of molecular properties, target interactions, and potential side effects. Most importantly, the development of AlphaFold by DeepMind has been a significant achievement in protein structure prediction. Moreover, AlphaFold, through accurate protein folding predictions, has allowed one to understand complex biological phenomena, thus shortening the drug target discovery process. The development of AlphaFold 3 has increased its possibilities, which now extend to interactions between DNA, RNA, and ligands, thus making it more valuable in drug design. Similarly, other companies, like Insilico Medicine, have introduced AI in drug development, shortening the process. Through the use of Generative Adversarial Networks (GANs) and

CHAPTER 2

Understanding QSAR: Origins, Development, and Current Trends

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Abstract: Algorithms used in Quantitative Structure-Activity Relationship (QSAR) modeling within Computer-Aided Drug Design (CADD) are highly regarded for their ability to extract meaningful insights from large and complex datasets. While these approaches may enhance the interpretation of chemical and biological data, not all of the predictions they provide can be applied immediately in biological screening. QSAR models are often used to analyze biological activity data from different chemical compounds. This helps scientists build new molecules that fit with existing prediction patterns. Conventional QSAR methodologies depend on physicochemical qualities, steric influences, or certain structural characteristics to clarify structure-activity correlations. In contrast, 3D-QSAR methods, particularly Comparative Molecular Field Analysis (CoMFA), acknowledge the spatial arrangement and binding interactions of ligands with target proteins. For a QSAR model to be effective, four fundamental components must be carefully considered: data input, descriptor selection, statistical modeling, and model validation. Among them, validation is an important step that checks whether the model is correct and useful for the purpose for which it was built. Several aspects affecting the robustness of a QSAR model include the validation technique, how the dataset is split up, the choice of descriptors, the statistical method used, and, most crucially, the choice and quality of the dataset itself. This chapter goes into detail about the history of QSAR, the manner in which its techniques have changed over time, how physicochemical properties are taken into account, the validation procedure, and the current status in drug discovery.

Keywords: Electronic, Hansch, Lead development, Lipophilicity, Molecular descriptors, Molecular modelling, Physicochemical parameters, QSAR, Statistical validation, Steric, Taft, Y-Randomization.

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INTRODUCTION

Over the last several decades, progress in information and communication technology has fundamentally changed how various types of data are collected, analyzed, stored, and shared. This shift has profoundly influenced scientific inquiry across multiple domains, particularly the development of novel categories of targeted and efficient therapeutics. The PubChem database provides access to results from biological studies along with information on millions of chemical substances. Digital collections are becoming more accessible [1, 2]. To identify new therapeutic candidates, it is essential to efficiently and thoroughly screen chemical databases and virtual libraries against molecules with known actions or properties. Therefore, QSAR modelling serves as a powerful approach for exploring and leveraging the connection between chemical structure and biological activity in the development of novel drug candidates. This computational method for analyzing chemical data is widely recognized. To construct QSAR models, it is necessary to identify chemical descriptor values obtained from molecular structures along with experimentally observed properties or bioactivities of the compounds. The observed relationships may exhibit either linear or nonlinear characteristics. The subsequent phase involves using these models to forecast future outcomes or to design innovative molecules that possess the desired characteristics [3]. The objective of QSAR is to develop models that can forecast the biological activity of analogous molecules. A set of compounds is used for this purpose. In an ideal scenario, these models should be clear and comprehensible for technicians. The relationship between biological activity and the physicochemical or structural characteristics of molecules forms the basis of QSARs, which are fundamentally predictive methodologies. As a result, there are limitations on the application and implementation of QSARs [4]. The three fundamental elements of QSAR include biological data, physicochemical properties, and/or structural properties, along with a statistical methodology. A variety of factors may affect the predictive performance of QSAR models. One example is the application of methods in the modelling process to establish a link between descriptors and biological activity. Another aspect is the optimization of chemical structures. Research in QSAR has employed a diverse array of both linear and nonlinear methodologies, including MLR, PLS, and ANN, among many others [5]. Quantitative SAR analysis began with the establishment of a correlation between the biological activity of the tested compounds and their physicochemical properties, which included the logarithm of the water/n-octanol partition coefficient ($\log P$), the Hammett electronic constant (σ), and the hydrophobic constant (π). The development and application of QSAR models across diverse contexts is practical. The practical application of QSAR involves gathering and analysing the minimal variance in reported responses from various medications tested against specific molecular targets, cell types, tissue types, or

even microbes under controlled conditions [6]. Physicochemical analysis of the observed phenomena can be performed, allowing the prediction of the biological activity of novel samples through a validated QSAR model. This study will advance the design of novel bioactive compounds and enhance our understanding of their molecular mechanisms of action. Employing QSAR models enables the comprehension and prediction of chemical binding affinity towards specific molecular targets, as well as various stages of drug development. This chapter explores various popular QSAR modelling approaches, including data mining and statistical methods, along with diverse techniques for computing descriptive statistics [7].

HISTORY AND DEVELOPMENT OF QSAR

Early Concepts and Pioneering Work in QSAR

Over a hundred years ago, Crum-Brown and Fraser proposed a theory stating that the physiological activity of a drug is determined by its chemical composition and structural characteristics [8]. In 1893, Richet reported that a diverse array of simple organic compounds exhibited an inverse relationship between cytotoxicity and water solubility. At the beginning of the twentieth century, both Meyer and Overton suggested that the partition coefficients of olive oil and water for a group of chemical compounds were directly related to their narcotic (depressant) activity [9, 10]. In 1939, Ferguson introduced a thermodynamic generalisation that elucidated the connection between the depressant effect of volatile chemicals and their relative saturation within the delivery medium. The detailed study conducted by Albert, Bell, and Roblin highlighted the importance of ionising weak acids and bases in bacteriostatic activity [11, 12]. Furthermore, the physical organic community benefited significantly from Hammett's pioneering research in elucidating the influence of substitution on organic reactions, leading to the emergence of the “sigma-rho” culture. Taft developed and commercialised the first steric parameter, E_s , which distinguishes between steric, resonance, and polar effects [13]. The QSAR paradigm originated from the contributions of Hansch and Fujita, who expanded upon the underlying ideas provided by Hammett and Taft.

In 1962, Hansch and Muir conducted an extensive study on the relationships between the structure and activity of plant growth regulators, with particular emphasis on their dependence on hydrophobicity and Hammett constants [14]. A novel hydrophobic scale was established after determining a broad spectrum of partition coefficients (Equation 1) using an octanol/water system. The sigma definition was employed in the characterisation of parameter σ , which denotes the relative hydrophobicity of a substituent [15].

CHAPTER 3

Exploring the Applications of QSAR: Unlocking the Potential of Computational Models in Drug Design and Molecular Prediction

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Abstract: The development of Quantitative Structure-Activity Relationship (QSAR) models for general molecular systems plays a crucial role in rational drug design and molecular prediction across diverse scientific domains. For decades, QSAR has served as a robust and widely accepted computational approach for evaluating the physical, chemical, and biological properties of substances. Employing mathematical equations, it predicts biological activity, often expressed as $\log(1/c)$. Traditional QSAR studies establish correlations between the binding potential of lead compounds and their molecular or atomic properties, such as lipophilicity, polarizability, electronic characteristics, steric factors, and other structural features. This is achieved through the codification of molecular structural information using molecular descriptors, followed by statistical and computational analysis. Such methodologies support the design and virtual screening of novel pharmaceutical candidates. The primary aim of QSAR modelling is to maintain scientific rigour while enhancing the predictive accuracy of the models and facilitating mechanistic interpretations. Moreover, by providing reliable early-stage predictions, QSAR has the potential to significantly reduce the costs associated with drug development, particularly by minimising the reliance on lengthy and expensive animal testing. This chapter concludes with selected case studies demonstrating how QSAR techniques have successfully provided reliable predictions for the biological activity of target molecules. Additionally, it highlights the evolution from traditional QSAR approaches to more advanced methods such as 3D QSAR and 4D QSAR, which are increasingly applied to overcome the limitations of earlier models.

Keywords: Biological activity, CoMFA, CoMSIA, Molecular descriptors, Model validation, Physicochemical property, QSAR, QSAR modelling, 2D QSAR, 3D QSAR, 4D QSAR.

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INTRODUCTION

Quantitative Structure-Activity Relationships (QSARs) are mathematical models that describe the complex relationship between the chemical structure of a compound and its biological activity. QSAR serves two primary objectives: first, to elucidate the underlying Structure-Activity Relationship (SAR) by identifying chemical features that significantly influence biological activity; and second, to predict the biological properties of untested or unavailable compounds. For these purposes, QSAR models should be as transparent and simple as possible, while retaining strong predictive capabilities, regardless of their complexity. The modelling technique employed in QSAR development often depends on the nature and quality of the input data [1]. Livingstone (1995) [2] differentiated between SAR and QSAR models. While SAR refers to a qualitative link between specific substructures and biological effects, such as the skin-corrosive potential of carboxylic or amino groups, QSAR establishes a quantitative mathematical correlation between structural or physicochemical descriptors and biological activity. QSAR models may be categorised as classification models or regression models [3]. QSAR attempts to establish a quantitative relationship between a compound's structural or physicochemical descriptors and its biological activity. Hansch and Fujita [4] were among the first to apply QSAR in drug discovery, particularly for lead identification and optimisation. Various molecular properties, such as constitutional, thermodynamic, hydrophobic, electronic, topological, conformational, and steric descriptors, as well as Hydrogen Bond Donor (HBD) and Hydrogen Bond Acceptor (HBA) capacities, are used as input variables. In QSAR terminology, structure refers to the descriptors of a molecule, while function pertains to its observed biological activity [5]. QSAR has played an essential role in modern drug discovery and development. It is widely used for evaluating protein-binding affinities, toxicity profiles, rate constants, and more. Its applications extend to both chemical analyses and biological testing. When QSAR models are used to assess physical properties, they are often referred to as Quantitative Structure-Property Relationships (QSPR); for toxicity assessment, the term Quantitative Structure-Toxicity Relationship (QSTR) is used [6]. Understanding how a specific chemical structure elicits a particular biological effect provides valuable insight for rational drug design. Establishing formal correlations between structure and activity forms the basis for creating predictive models. By analysing a series of structurally related compounds, QSAR facilitates the derivation of mathematical relationships between chemical features and biological activity [7, 8]. Simpler, more qualitative interpretations, such as recognising a fragment that contributes to a biological effect, are typically classified as SARs [9]. SAR forms the foundation of CADD. When SARs are translated into mathematical models quantifying relationships between structure, properties, and biological effects, the concept evolves into QSAR. QSAR is

therefore defined as a quantitative relationship between biological activity and the physicochemical properties of compounds [10, 11].

Biological activity = f (physicochemical parameters)

Typically, biological activity is expressed as $\log[1/C]$, where C represents the minimum concentration required to produce a specific biological response. If a weak correlation is observed between the activity and a single descriptor, it suggests that other parameters may significantly influence the compound's pharmacological action and should be incorporated into the QSAR model [12]. Such descriptors may include lipophilicity, shape, and electron distribution, each represented by numerically derived values from experimental data or computational predictions [13]. These numerical descriptors allow for the development of mathematical equations, often using regression analysis, to model the relationship between structural features and biological activity [14]. QSAR studies are commonly performed on sets of structurally similar molecules, but can also be extended to diverse chemical classes. In both cases, it is essential to consider a broad and relevant range of molecular descriptors.

HANSCH ANALYSIS

Fundamentals of Hansch Analysis

Hansch analysis aims to mathematically link therapeutic activity to measurable physicochemical properties of molecules. Hansch proposed that a drug's biological efficacy can be understood through two fundamental phases:

- **Delivery of the drug** to its site of action
- **The binding of the drug** to the biological target

Both steps are influenced by the compound's physicochemical attributes, including hydrophobicity, electronic properties, and steric factors. Hansch formulated a basic mathematical model to describe these relationships:

$$\log 1/C = k_1(\text{partition parameter}) + k_2(\text{electronic parameter}) + k_3(\text{steric parameter}) + k_4 \quad (1)$$

Here, C denotes the minimal concentration necessary to elicit a specific biological response, whereas k_1 , k_2 , k_3 , and k_4 are numerical constants derived by inputting the selected parameter values into an appropriate statistical software package. The parameter values are sourced from the literature (*e.g.*, π , σ , and E_s) or determined experimentally (*e.g.*, C, P, *etc.*). In studies involving several substituent

CHAPTER 4**Advances in Molecular and Quantum Mechanics for Rational Drug Design****Kavita Munjal¹, Arushi², Vinod Kumar Gauttam³, Kiran Bhopate⁴ and Kunal Nepali^{5,*}**¹ *Amity Institute of Pharmacy, Amity University, Noida, Uttar Pradesh, India*² *Maharaja Agrasen Himalayan Garhwal University, Block – Pokhra, Garhwal, Uttarakhand, India*³ *SGT College of Pharmacy, SGT University, Gurugram, Haryana, India*⁴ *IES Institute of Pharmacy, IES University, Bhopal, Madhya Pradesh, India*⁵ *School of Pharmacy, Taipei Medical University, Taipei, Taiwan*

Abstract: Molecular and quantum mechanics are very important to modern drug design because they give very accurate information about how molecules interact with each other at the atomic level. This chapter explains the basic ideas behind these computer-based methods and how they fit into the process of designing drugs with the help of computers. The main goal is to show how these methods help us learn more about how drugs interact with their targets, predict binding affinities, and improve lead compounds. A combination of Molecular Mechanics (MM) and Quantum Mechanics (QM) enables the researchers to model more complicated biological systems in a very detailed manner. This chapter examines the working of the QM/MM hybrid approaches. These methods use quantum mechanics to model chemically active parts of a system and molecular mechanics to model the rest of the system. This method strikes a good balance between speed and accuracy in computing. Other significant new developments in the field discussed in the chapter are improved polarizable force fields and improved solvation models, which result in more accurate simulations. The results indicate how QM/MM methodologies have been successfully applied in drug discovery, particularly in enzyme inhibitor and receptor modulator development. This chapter stresses how important it is to combine molecular and quantum mechanics. It says that this combination is not just a theoretical exercise, but a practical need for improving drug design. This combined approach is necessary for speeding up progress in the field and encouraging new ideas in therapeutic development.

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Keywords: CADD, Force fields, Foundations of binding affinity prediction, Foundations of computational chemistry, Foundations of molecular modeling, Foundations of structure-based drug design, Foundations of therapeutic innovation, Molecular mechanics, Quantum mechanics and QM/MM hybrid, Queen of the Pot, Solvation Foundations of enzyme inhibitors.

INTRODUCTION

The success of pharmaceutical companies and the health of society will always be highly dependent on drug discovery since new drugs, which are safer and more effective, are being researched to enhance their use in therapy and their safety. There is a vast number of diseases that the pharmaceutical industry could find and offer a cure to [1]. The contemporary study of drugs began with the development of the field of pharmacology as a science, coinciding with the achievement of chemical sophistication that allowed applying the chemical principles and theories to problems that were not involved in the traditional study of chemistry. By the year 1870, a number of key ideas in chemical theory had already been put in place [2]. Biochemistry had a big effect on drug development in many ways during the 20th century. It was during this time that the idea of targeting enzymes and making drugs that work as inhibitors first came about [3]. Even though drug companies use different research and development (R&D) methods, the failure rate in drug discovery is still too high [4]. A significant factor in this elevated attrition rate is the elimination of active chemical entities owing to adverse absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles [5]. These problems are responsible for almost half of the expensive failures in drug development. It is now widely accepted that ADMET properties should be taken into account as soon as possible during the drug discovery process [6]. The flaws of the current drug-discovery model require new methods that will reduce the time taken to conduct research and development and, at the same time, reduce the costs associated with the processes [7]. *In silico* techniques have the potential to accelerate the process of discovery by simulating significant ADMET characteristics. A chemical compound may be unstable, difficult to prepare in large quantities, excessively expensive to prepare, too toxic, too rapidly excreted by the body, or most probably broken down in the body [8]. Therefore, numerous potential compounds must be discarded in case they have adverse effects on humans. Also, the structure-based drug design has come a long way since it was initially introduced a decade ago. This is due to the large variety of experimental and computational tools, which have assisted scientists in comprehending the structure of proteins that are of importance in medicine better [9]. Fig. (1) below represents the drug discovery and development process.

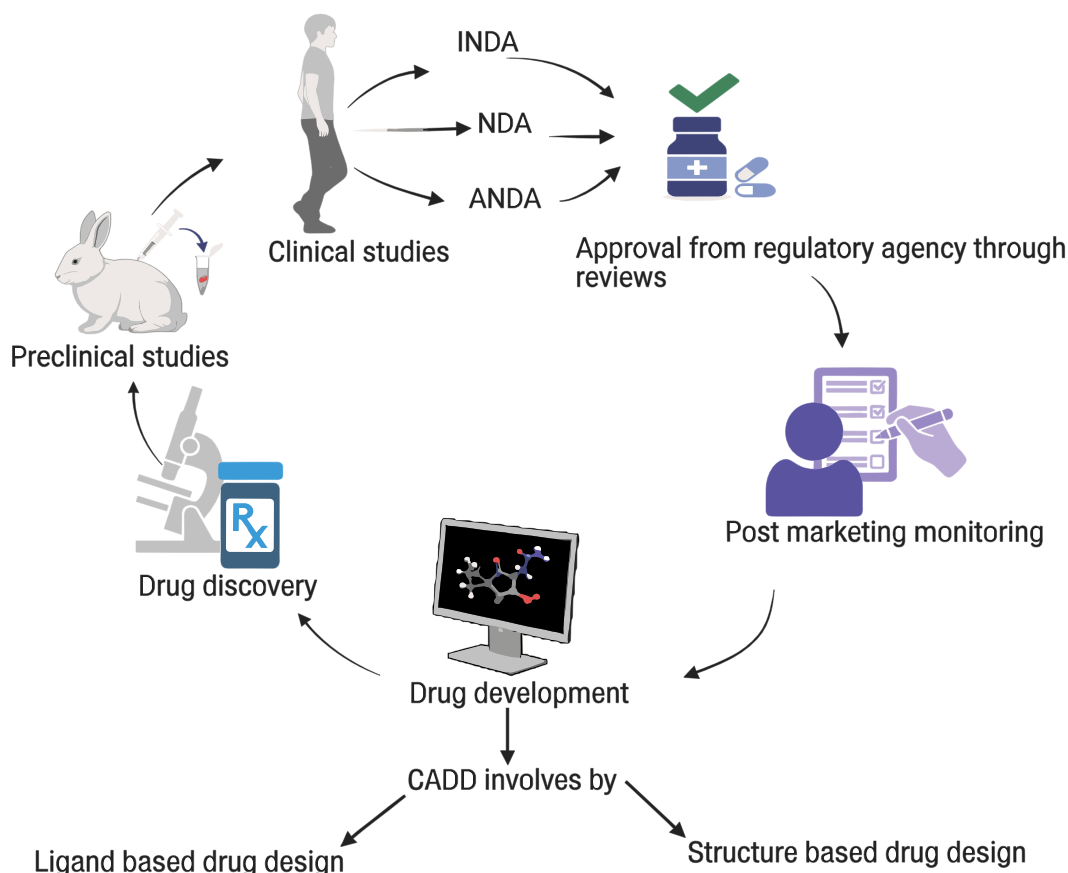


Fig. (1). Drug discovery and development process.

The mechanism of action of a drug is that an enzyme, nucleic acid, or antibody attaches itself to its biological target that is typically a receptor [10]. Receptors bind drugs at the active sites, and homology modeling has helped scientists to make these proteins appear as they appear in nature. Simulated modeled proteins, when simulated, will follow a behavior that is closely related to the behavior of real proteins in nature in their biological habitat [11]. New models run with the aid of computers are being tested on thousands of compounds for various activities [12]. The most popular models of activity screening based on such models include applications on computers that superimpose molecules with flexible alignment to create quantitative structure-activity relationships (QSARs) and/or pharmacophoric patterns, docking of molecules to the receptor or pseudoreceptor, or the design of new pharmaceuticals in a given active site [13]. It

Exploring Molecular Stability: Energy Minimization from Global Minima to Bioactive States

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Abstract: Energy minimization techniques are essential computational tools in molecular modeling, designed to identify stable molecular configurations by locating energy minima on the potential energy surface. In biological systems, the conformation a molecule adopts when bound to its target protein or nucleic acid, known as the bioactive conformation, is critical for its function and activity. It is important to note that it is not always the case that the bioactive conformation is the global minimum conformation. The way the biological target interacts, and even other physiological states, can cause conformational changes that stabilize a higher-energy conformer that is better bound. This chapter gives a comparative analysis of the properties of the global minimum conformations and bioactive conformations, systematically comparing the factors that contribute to the contrasts and the similarities between them. It also talks about computational algorithms, which aid in energy calculations, with a particular focus on the force field-based algorithms that make use of popular force fields of AMBER, CHARMM, OPLS, and GROMOS, and the relevance of appropriate parameterization. More sophisticated computational techniques, such as molecular dynamics, Monte Carlo techniques, and QM/MM, are also studied. The chapter identifies the computational approaches and problems of finding bioactive conformations, indicating that even though energy minimization is a main step, it is typically complemented by more sophisticated methods like molecular dynamics simulations and molecular docking to better represent the dynamics of molecules and their interactions in natural biological systems. It is important to comprehend how an intrinsic molecular stability can interact with an induced fit during binding in order to progress structure-based drug design.

Keywords: Energy minimization methods, Global minimum conformation, Bioactive conformation, Computational algorithms, Force field methods, Structure-based drug design, Virtual screening.

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INTRODUCTION

The three-dimensional structure of molecules is a crucial aspect of understanding in a variety of scientific fields, but it is especially important in drug development, materials science, and biological sciences. Computational chemistry, as well as pharmaceutical drug design, has a strong dependence on the understanding of molecular stability, conformation, and functionality. One of the major problems in the mentioned fields is determining the most stable molecular form and its biologically active counterpart [1]. Molecular properties and reactions are specific to conformation, *i.e.*, the spatial arrangement of atoms in a molecule. Conformational analysis is based on energy minimization, a computational method of finding a stable molecular structure. Even though energy minimization can help to predict low-energy conformations, the global minimum conformation, which is the lowest point on the Potential Energy Surface (PES), may not always be the physiological relevant or bioactive form of a molecule. The question of understanding the correlation between the thermodynamically stable global minimum state of a molecule and its bioactive state has been a difficult and hotly contested question [2]. The binding interactions, the solvation effect, and the dynamic physiological environment may tend to drive the bioactive conformation to a higher-energy state than the global minimum, and hence the bioactive conformation reflects the higher energy state [2]. The chapter focuses on energy-minimizing methods and complexities in use to get the molecular conformations. The main emphasis is to differentiate between the global minimum and bioactive conformations. The most stable structure in the global minimum is the one that is most stable in theory, whereas the bioactive structure is the real structure that is assumed on binding to a biological target. This difference is essential, since the biological activity of a molecule depends mostly on its ability to adopt certain conformations that are necessary to bind it appropriately, which are not necessarily the lowest-energy structure of the molecule [3]. The main ideas of energy minimization, *e.g.*, molecular mechanics, quantum mechanics, and hybrid QM/MM techniques, are described, and the issues that arise to find global minima, such as force field limitations and the existence of many local minima, are addressed. The next chapter then changes to bioactive conformations with the need to go beyond mere energy minimization and consider solvent effects, protein-ligand interactions and empirical structural data [1]. Real-life examples depict that confirmation is very important in our knowledge of the molecular behavior and therapeutic effect, and, therefore, show the importance of practical applications of the ability to differentiate between global minimum and bioactive states [4].

FUNDAMENTALS OF ENERGY MINIMIZATION

Computational chemistry and molecular modeling are applied to find the most stable conformation of the molecule by minimizing the potential energy of a system. The basis of this process is force fields, mathematical functions that approximate the energy of the molecules depending on their atomic positions. The terms that are usually covered in these functions include bond extension, angle rotation, torsions, van der Waals forces, and electrostatic forces [2]. Energy minimization aims at finding the global minimum on PES, which is the most thermodynamically stable arrangement of the molecules. Nevertheless, the global minimum is not always easy to obtain because of the extremely complicated and multidimensional nature of the PES. Most of the minimization processes only find the closest local minimum, which is not necessarily the global minimum. This limitation notwithstanding, energy minimization is an essential technique in computational chemistry and biophysics, with researchers being able to forecast stable molecular or system structures. Recognition of energy minima on the PES gives an understanding of the stability of molecules and conformational preferences. In this section, the main principles of energy optimization are described [1].

PES and Molecular Configurations

The PES mathematically and graphically provides a system with its energy as a function of atomic coordinates. This is a multidimensional site; the shape of each molecule is a point, and its potential energy is equal to its height. PESs play a vital role in the study of the shape, nature, and response of the molecules. They enable scientists to visualize and predict molecular behavior in the process of reactions [4].

The energy landscape of a molecule is represented by products, intermediates, and reactants. PES regulates the movement, interaction, and reaction of the molecules, and it is therefore important in the study of the behavior of the molecules. The three-dimensional PES landscape displays the energy on the y-axis and the location of the atoms on the x-axis. Peaks are unstable systems (transition states), whereas valleys are stable systems (minima).

Minimal and Transition States

Local minima in a PES (local minimum) are also known to be associated with stable molecular structures or equilibrium geometries, whereas the energy maxima are known as transition states (TS) along a reaction pathway [3]. The transition state is very important as it indicates the point at which the system is most likely to change to products. The transition states are typically first-order

Homology Modeling and Generation of 3D Protein Structures

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Abstract: Homology modelling is a widely used computational method for predicting proteins' three-dimensional (3D) structures based on the knowledge that homologous sequences have parallel structures. This method is highly dynamic in structural biology, bioinformatics, and computer-aided drug designing, especially when new investigational methods such as X-ray crystallography or NMR spectroscopy are unattainable. This method encompasses categorizing a suitable template protein with a known structure, positioning its sequence with the target protein structure, and then generating a 3D model based on the conserved structure of the target protein. Advances in bioinformatics tools and algorithms, like MODELLER and SWISS-MODEL, have reorganized the homology modelling workflow, permitting the rapid and accurate prediction of the target protein structure. The shape of 3D protein structures distributes respected identifications of molecular function, stability, and interactions, which can help with pathway prediction, disease mechanism, enzyme engineering, and drug discovery. Additionally, homology modelling permits the examination of protein-ligand binding sites and their catalytic processes, making it an essential tool in the rational drug design process. Current enhancements, like machine learning and enhanced processing capacity, have proved the rationality and competence of homology modelling. This method, which influences the gap between genomic sequence data and structural understanding, will continue to make considerable contributions to biotechnology, bioinformatics, and clinical research. Its combination with other modelling tools broadens its usefulness in solving complex biological challenges.

Keywords: Bioinformatic and systems biology, Drug design, Homology modeling, Protein structure prediction, Structural biology.

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INTRODUCTION

Proteins have played a vital role in numerous biochemical methods, and their three-dimensional (3D) structures help predict their biological process [1]. Understanding protein structures is crucial in structural biology, bioinformatics, drug discovery, and enzyme engineering [2]. However, experimental methods such as X-ray crystallography and Nuclear Magnetic Resonance (NMR) spectroscopy, which are used for protein structure determination, are time-consuming, luxurious, and challenging for membrane and large proteins [3]. As an alternative, homology modelling (comparative modelling) has emerged as a widely used computational approach to predict protein 3D structures based on sequence similarity with known protein structures [4]. Homology modelling is based on the hypothesis that proteins share significant sequence similarity and are inclined to have conserved 3D structures [5]. This principle permits the prediction of an unknown protein structure (target) using a known structure (template) from homologous proteins accessible in databases like the Protein Data Bank (PDB) [6, 7]. The success of homology modelling chiefly depends on the correctness of sequence alignment and the degree of identity between the target and template sequences [8]. Despite its advantages, encounters such as template limitations, sequence discrepancy, and imprecision in loop modelling persist. However, continuous advancements in machine learning and molecular dynamics simulations improve model accuracy and expand its applicability in complex biological systems [9]. Combining homology modelling with other computational methods, such as molecular docking and molecular dynamics simulations, is additional for improving its efficiency in addressing structural and functional biological questions [10]. With the growing approachability of genomic, transcriptomic, proteomic, and metabolomic data [11], homology modelling remains significant in biotechnology, computational biology, and pharmaceutical research, providing treasured insights into protein function and structure-based drug design [12].

KEY PRINCIPLES OF HOMOLOGY MODELING

Homology modelling, also known as virtual protein modelling, is a computational method mainly used to predict the 3D structure of the respective proteins based on homologous sequences with known structures. The technique is assembled on the principle that proteins with their parallel sequences implement comparable structural folds, making it an essential tool in structural bioinformatics, drug discovery, and functional annotation of the respective protein molecule [13]. Contemporary improvements in investigational performances corresponding to X-ray crystallography, cryo-electron microscopy, and homology modelling were

critical due to their cost-effectiveness and ability in the structural prediction of proteins [14].

Relationship Between Protein Sequence and Structure

The structure of a protein is mainly determined by its amino acid sequence, a principle acknowledged as Anfinsen's dogma [15], although the major circumstances under which a protein folds into its native structural configuration are constructed based on thermodynamic stability [16]. However, sequence discrepancy often leads to structural variations, making sequence-structure relationships complex [17, 18]. However, due to evolutionary dissimilarities, chaperone-mediated folding, and ecological changes, the sequence-structure association is frequently multifaceted and prejudiced by multiple factors [17, 19]. The Protein structures share >40% sequence identity with a recognized structure repeatedly exhibited with its highly accurate 3D models, while those with lower uniqueness necessitate advanced modelling performances [20]. Multiple Sequence Alignment (MSA) tools, such as Clustal Omega [21] and Multiple Alignment using Fast Fourier Transform (MAFFT) [22, 23], are used to regulate conserved residues essential for structural similarities of the respective proteins [24]. Protein structural databases, like the Protein Data Bank (PDB), serve as a repository for experimentally determined templates, aiding homology modelling [7]. Hydrogen (H) bonding among backbone atoms, which makes secondary structures of α -helices and β -sheets [25]. The complete hydrophobic core packing and disulfide bridge (S-S) formation are formed by tertiary structures, which define the function of the protein [26]. Quaternary structures arise from the gathering of multiple polypeptide chains, as detected in hemoglobin structure [27]. The Molecular Dynamics (MD) simulations and deep learning models like AlphaFold [28] have been used in current bioinformatic studies to show that protein structures can be precisely projected from sequences alone [29, 30].

Evolutionary Conservation of Protein Structures

Protein structural evolution through genetic mutations, mainly insertions, deletions, translocations, and various recombination events; nevertheless, their organizational conformations are unusually preserved across the diversified species [31, 32]. This structural conservation is vital for upholding the various biological processes, as a protein's overall fold and active site geometry are often more crucial than its particular amino acid sequence [33]. Functional limitations executed by natural selection confirm that dangerous motifs, such as catalytic and ligand-binding sites, are conserved, permitting homologous proteins to retain similar biological roles despite sequence divergence [34]. Protein structural folds, like α/β -sheets and TIM barrels, have been constant during growth and

Molecular Docking and Drug-Receptor Interactions

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Abstract: Molecular docking is a computational technique widely used in drug discovery to predict the preferred orientation of ligands when bound to target proteins, allowing the analysis of drug and receptor interactions. These interactions, which include covalent and non-covalent forces, play an important role in determining the pharmacological efficacy, selectivity, and safety of drugs. Classical models such as the lock and key theory and the induced fit theory explain binding specificity and the structural changes that occur when a ligand binds to its target. Rigid docking, flexible docking, and further precise docking methods have been used to evaluate binding affinities, predict binding modes, or aid in lead optimization. The docking methods applied to generate anti-high cholesterol agents, anti-cancer agents, anti-HIV/AIDS agents, and anti-Alzheimer's agents, among others, have relied immensely on target enzymes such as DHFR, HMG-CoA reductase, HIV protease, and cholinesterase. With improved accuracy represented by virtual screening methods using MD simulation, combined with molecular docking methods using quantum or quantum/molecular mechanics calculations, accuracy could be further improved. Additionally, because of the problem of protein flexibility simulation or other issues, it appears that new docking methods to design drugs continually arise.

Keywords: Binding affinity, Computational drug discovery, Drug-receptor interactions, Flexible docking, Molecular docking, Rigid docking, Structure-based drug design, Virtual screening.

INTRODUCTION

Molecular docking is a computational method widely used in drug discovery and design research to predict the preferred orientation of a small molecule or ligand when it binds to a target protein, usually a receptor. This approach provides

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valuable insights into molecular interactions and helps researchers understand how medicines can effectively influence biological pathways. Molecular docking allows for rapid discovery of innovative therapeutic strategies through simulation of the binding process. This renders it relatively easy to identify favourable drug targets and enhance drug structures to predict binding affinities. Drug and receptor interactions also have high significance due to the biological effects that they mediate. The nature and strength of these interactions determine both the safety and the effectiveness of therapeutic agents. Understanding the molecular mechanisms of these interactions is important for drug development capable of selectively engaging certain receptors, thereby limiting side effects and improving therapeutic outcomes. With continuous improvements in algorithms and computing power, molecular docking has become an important and reliable tool in modern medicinal chemistry [1].

FUNDAMENTALS OF DRUG-RECEPTOR INTERACTIONS

Drug and receptor interactions are the chemical processes that occur when a drug binds to a receptor protein. Van der Waals forces, ionic bonds, hydrogen bonds, and covalent bonds can all take part in these interactions. Just as the longer-term or irreversible interaction may consist of higher bonds, such as a chemical bond, short-term drugs will normally generate lower bonds. Large biological molecules known as receptors are essential for chemical interaction on a cellular level. Receptors may reside on the actual cellular membrane or reside within the cytoplasm of the cellular structure. Cell ion conductance, protein phosphorylation, DNA transcription, and enzymatic functions are merely a few functions of cellular biochemistry controlled as a result of receptors [2]. Ligands are substances that bind to receptors, including medications, hormones, and neurotransmitters. Their binding may be reversible or irreversible. A ligand can activate or inactivate a receptor, and this activation can alter the function of a specific cell. Each ligand is capable of binding to multiple receptor subtypes. Very few medications act on only one receptor or subtype; most exhibit a degree of selectivity rather than complete specificity. Selectivity refers to the extent to which a medication acts at one site compared with another, and it is largely determined by the physicochemical interactions between the drug and cellular receptors [3]. A drug's affinity, which is the likelihood that it will be bound to a receptor at a given time, and its intrinsic efficacy, which is the extent to which a ligand activates receptors and produces a cellular effect, both determine its ability to bind to a specific receptor. The chemical composition of the drug determines its affinity and its activity [4]. The residence time of the drug and receptor complex also influences the pharmacologic effect. Dynamic events, such as conformational changes that control the rate at which a drug associates with and dissociates from its target, affect the lifetime of the drug and receptor complex. A prolonged

pharmacologic effect is often the result of an extended residence time. Darunavir and finasteride are examples of medications that have long half-lives. However, when a drug causes prolonged toxicity, an extended residence time can be harmful. For some receptors, the desired pharmacologic effect results from brief drug binding, while prolonged binding may lead to toxicity [5].

The Binding Process: Key Concepts in Drug-Receptor Interactions

All of the known bond types, including ionic, hydrogen, van der Waals, and covalent bonds, can participate in drug and receptor interactions. Short-acting drugs generally form weaker bonds, while irreversible or long-acting drug receptor interactions often involve stronger covalent bonds.

Lock-and-Key Model

According to the model of enzyme and substrate interaction, the geometric shapes of the substrate and the enzyme fit together exactly. “This model shows just how specialized enzymes are. It is not until after being bonded with their respective substrates that these enzymes are capable of catalyzing biochemical reactions.” The concept reiterates the complex molecular interaction that ensues between substrates and the enzyme [6]. Examples of the lock-and-key model include:

- Lactate dehydrogenase is a specific enzyme that has an active site that is unique to pyruvate and lactate substrates. Pyruvate and lactate conversion during anaerobic respiration is facilitated by the complex.
- A specific carbonic anhydrase enzyme with an active site that allows the carbon dioxide and water substrates to reach. The complex makes it easier for carbon dioxide to be hydrated into bicarbonate.
- The binding of lysozyme to a peptidoglycan in the bacterial cell wall is a crucial immunological function [7].

Induced Fit Hypothesis

The Lock and Key model of enzymatic function was developed further by Daniel Koshland’s Induced Fit model of 1958. This model highlights the ability of enzymes to adapt to substrate/enzyme interactions. This theory proposes that when an enzyme performs binding, it causes a change in its active sites to adapt to the binding of the substrate, thereby establishing that enzymes are not rigid bodies. The binding of the substrate to the active site of the enzyme results in a change that helps in binding, hence forming the enzyme-substrate complex, which drives the chemical reaction. After the reaction is complete, the product is released, and the enzyme returns to its original state. This model explains the specificity of enzyme and substrate interactions while also highlighting enzyme

CHAPTER 8

Prediction and Analysis of ADMET Properties in Drug Design

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Abstract: A successful drug discovery requires a complete understanding of its pharmacokinetics, safety, and efficacy. The characterization of Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties is the most critical aspect fundamental to early-stage drug discovery and development. For a newly designed molecule to become a viable drug, it must not only exhibit the desired biological activity and safety but also possess a satisfactory pharmacokinetic profile, including acceptable toxicity parameters. Thus, it is essential to predict ADMET characteristics of any molecule using *in silico* tools to increase its success rate. For instance, Lipinski's Rule of Five, an *in silico* tool based on molecular modeling or empirical methods, anticipates drug solubility, its absorption through biological membranes, and other pharmacokinetic parameters. This chapter highlights the significance of various *in silico* drug design and discovery software like SwissADME, pkCSM, and ADMETlab, as well as methods including molecular docking, QSAR, and machine learning-based prediction techniques, along with their existing issues and new developments. Some case studies demonstrating their successful application and lessons learned from difficulties related to inadequate ADMET features have also been discussed. This study will help the researchers to use predictive ADMET analysis to speed up drug development.

Keywords: ADMET, ADMETlab, Drug design, Machine learning, Molecular docking, Pharmacokinetics, pkCSM, Prediction, QSAR, SwissADME.

INTRODUCTION

The advancement of molecules with poor pharmacokinetic profiles into successful drugs is a complex and costly process [1]. Such unfavorable pharmacokinetic properties have increased the demand for new methodologies capable of accurately predicting a drug's ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties [2 - 7]. Successful drug development, therefore, requires both effective ADMET prediction and strong therapeutic efficacy. In

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recent years, newly developed *in silico* models based on pharmacokinetic profiling have gained significant importance in drug discovery, as these can predict ADMET characteristics with great accuracy, which can further determine drug availability at the targeted site of action [8, 9]. The origin of ADMET prediction tools dates back to 1863, when efforts were primarily focused on understanding the relationship between drug solubility and toxicity. With the evolution of new computational methods for predicting ADMET, drug development has evolved dramatically. Earlier drug discovery was supported by *in vitro* and *in vivo* trials [10]. But nowadays, early ADMET prediction by *in silico* makes it possible to produce effective medications faster and with better dosage schedules. Because they aid in evaluating a compound's effectiveness following administration, ADMET data are thought to be essential for the development of innovative therapeutic candidates [11 - 13]. Decisions regarding the advancement, refinement, or discontinuation of a developed compound are similarly influenced by these characteristics [14]. Since the development of effective and economical drugs is still challenging for researchers, optimizing physicochemical and ADMET-related features to reduce side effects and enhance therapeutic performance has become crucial [15]. During the drug design process, factors such as molecular size, dose frequency, bioavailability, clearance, volume of distribution, and blood-brain barrier (BBB) penetration must also be carefully taken into account [16].

ADMET PARAMETERS

These pharmacokinetic and pharmacodynamic parameters, including absorption, distribution, metabolism, and excretion, aid in assessing the therapeutic potential of any compound.

Absorption

Intestinal absorption is a critical determinant of the pharmacological profile of orally administered compounds. Generally, higher absorption rates correlate with increased systemic bioavailability and, consequently, greater therapeutic efficacy. Various physicochemical properties, *viz.*, solubility, membrane penetrability, transporter interactions, and substrate specificity for drug-metabolizing enzymes, are crucial in predicting absorption [17, 18]. The various factors influencing drug absorption includes physiochemical, pharmaceutical, and patient-linked [19, 20].

Physicochemical Factors: These include drug solubility, dissolution rate, stability, effective surface area, particle size, polymorphism, lipophilicity, pH, and pKa, which have a major impact on drug absorption and bioavailability.

Pharmaceutical Factors: These include formulation-related variables like dosage form and its stability, type and composition of pharmaceutical excipients, storage conditions, disintegration, and dissolution time.

Patient-linked Factors: These include patient-related factors, including administration route, patient's age, intestinal transit time, gastric emptying, illness status, food-drug interactions, *etc.*

Membrane Permeability and Transport Mechanisms

Membrane permeability is the membrane's ability to allow constituents to pass through it. Based on this property, membranes can be classified into three types: impermeable membranes (not permitting any substance to pass through); semi-permeable membranes (allowing only the solvent to pass through); and selectively permeable membranes (permitting the passage of specific substances) [21].

Membrane transport describes the mechanisms that regulate the movement of solutes, including nutrients, oxygen, water, and other essential substances, across biological membranes (comprised of lipid bilayers embedded with proteins). These processes mainly include active and passive transport. Active transport is an energy-coupled or energy-dependent process (requiring ATP) that utilizes both chemical and mechanical mechanisms for the movement of particles from regions of lower concentration to higher concentration, whereas passive transport depends on size, charge, and concentration gradient of solutes, and facilitates the diffusion of tiny, uncharged molecules across the membrane until equilibrium is accomplished [21].

Distribution

After absorption, the drugs are distributed across several tissues, experiencing reversible movement across distinctive compartments within the body. This distribution depends on several physiological, physicochemical, and pharmacokinetic characteristics [1]. For instance, plasma protein binding, a substantial pharmacokinetic parameter, influences drug distribution and excretion as well as its pharmacological activity and possible toxicological effects, thereby playing a critical role in drug transport throughout the human body.

Plasma Protein Binding (PPB)

After a drug passes through the bloodstream, it binds reversibly to plasma proteins (albumin and alpha-1-acid glycoprotein) to varying extents, and it is already known that only the unbound fraction in systemic circulation is able to pass through tissue membranes and bind with receptors to produce pharmacodynamic

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