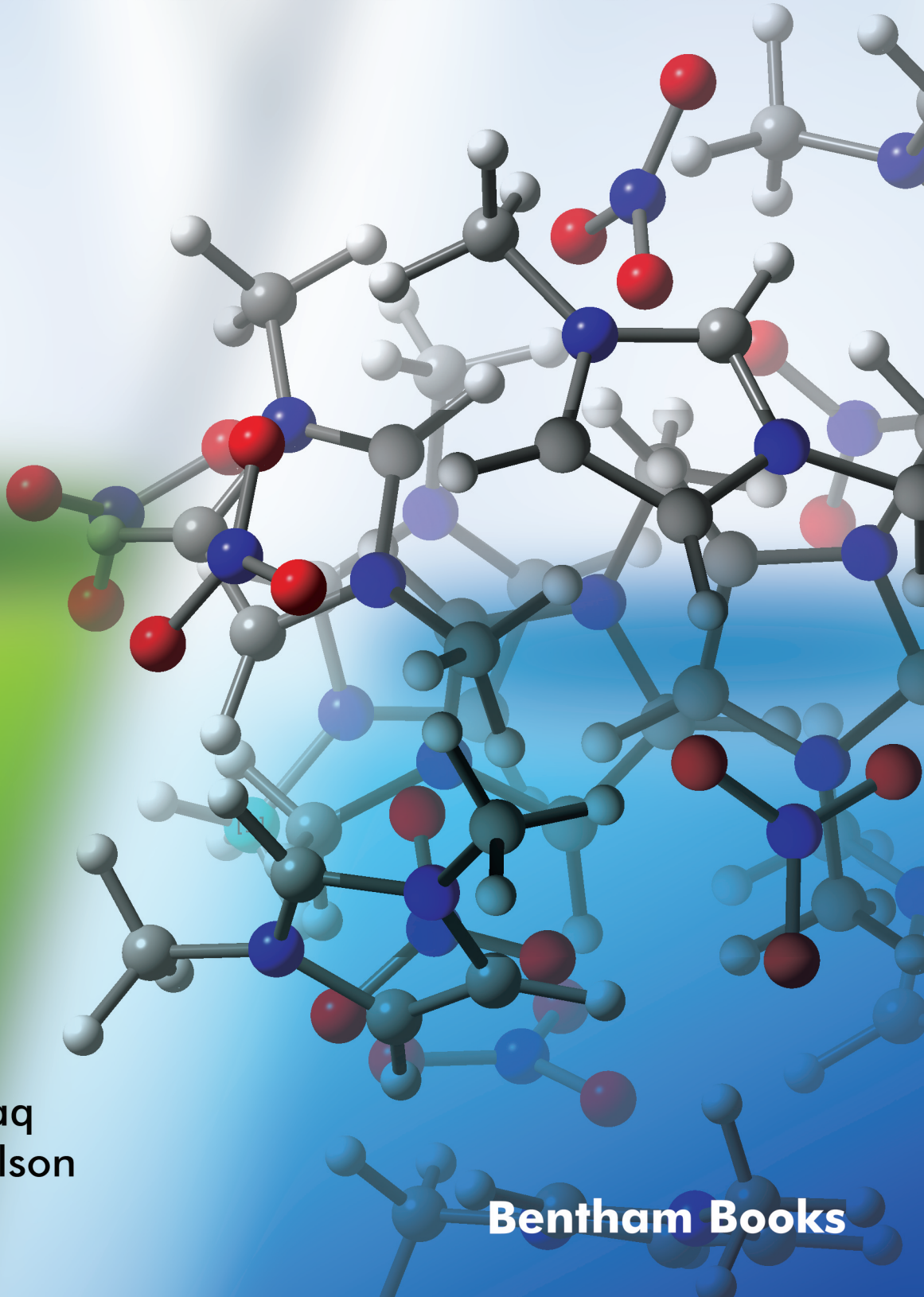
# FRONTIERS IN COMPUTATIONAL CHEMISTRY



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# Frontiers in Computational Chemistry

# (*Volume 6*)

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## Frontiers in Computational Chemistry

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# CONTENTS

# PREFACE

Computational chemistry is a very diverse field that uses computer simulation to assist in solving chemical problems. By using methods of theoretical chemistry, incorporated into computer programs, we can calculate the structures and properties of molecules. In general, computational results normally complement the information obtained by chemical experiments, It is widely used in the design of new drugs and materials. The focus of ***Frontiers in Computational Chemistry*** is to present different techniques used in drug discovery and the drug development process. Topics falling under this umbrella include computer aided molecular design, drug discovery and development, lead generation, lead optimization, database management, and the development of new computational methods or efficient algorithms for the simulation of chemical phenomena including analyses of biological activity. In this volume, we have collected six different perspectives in the application of computational methods towards drug design.

Chapter 1: **Computer-aided molecular design in computational chemistry**

This chapter combines thermodynamics, and numerical optimization to design good or optimal molecular structures with many of them are completely novel. Advances in chemical modeling in the last few decades have greatly benefited CAMD relating chemical structures to properties at several levels of accuracy (molecular mechanics, semi-empirical, ab initio). Though CAMD often uses semi-empirical modeling techniques for their simplicity and efficiency, new approaches incorporating more accurate methods are emerging. In this chapter, the significant advancement, applications of CAMD in the single component product designs, challenges in progression, and the future perspective in designing the chemical compounds by using "computer-aided molecular design" (CAMD) tools is provided.

Chapter 2: **Role of Ensemble Conformational Sampling Using Molecular Docking & Dynamics in Drug Discovery**

Molecular recognition involved in protein interaction with each other or various small molecules with a high specificity and affinity to form a specific complex, constitutes the basis of all processes in living organisms. These interactions can be studied through multiple computational approaches including docking, MD simulation etc. In this chapter, the theoretical background of molecular docking, classical MD simulations, MD-based enhanced sampling methods and hybrid docking-MD based methods are highlighted, demonstrating how protein flexibility has been introduced to optimize and enhance accurate protein-ligand binding predictions. Overall, the evolution of various computational strategies is discussed, from molecular docking to molecular dynamics simulations, to improve the overall drug discovery and development process.

Chapter 3: **Molecular Dynamics Applied to Discover Antiviral Agents**

Molecular Dynamics (MD) remains a valuable tool in optimizing the ligand-protein complexes and understand the ligand binding modes and drug resistance mechanisms in viruses. It is useful for filling in the details about the microscopic events that take place in mere millionths of a second, which experimental methods cannot. Molecular dynamics (MD) simulations utilizes simple approximations based on Newtonian physics to simulate atomic motions. This chapter deals with the concept and applications of MD simulations, as well as their applications in the discovery of drugs against Coronaviruses (SARS-, MERS-CoV, and SARSCoV-2); Influenza (INFV); Chikungunya (CHIKV); Zika (ZIKV); Dengue (DENV);

Ebola (EBOV); and human immunodeficiency virus (HIV). This will contribute a great source of helpful information that could be utilized for designing new compounds against neglected diseases.

Chapter 4: **Pharmacophore modeling approach in drug discovery against the tropical infectious disease malaria**

Despite remarkable improvement in overall global health, Malaria remain a major health problem in the developing world. The crucial role of chemotherapy in curtailing the deleterious health and economic impacts of malaria has invigorated the search for new antimalarial drugs. Among computational approaches pharmacophore modelling is widely employed in identifying the new molecules that trigger the desired biological activity. Due to their simplistic and abstract nature, pharmacophores are both perfectly suited for efficient computer processing and easy to comprehend by life and physical scientists. This chapter aims to provide the pharmacophore concept, pharmacophore modelling methods and its applications in modern computer-aided drug design.

Chapter 5: **Advances in computational network pharmacology for Traditional Chinese Medicine (TCM) research**

Traditional Chinese Medicine (TCM) is well-known for its use of medicinal herb combinations to treat the functional disorders which naturally followed the principal of network pharmacology. In this chapter, systematically the methodologies of network pharmacology in TCM studies are discussed followed by its application on TCM against COVID-19. The forefront study examples are also included to collate and analyze the advantages and limitations of different computational techniques.

Chapter 6: **Progress in Electronic-Structure Based Computational Methods: From Small Molecules to Large Molecular Systems of Biological Significance**

In recent years, understanding of biological systems using electronic structure theory based computational methods with applications to biology and medicine has gained increased interest. Recent computational approaches that account for the effects of electron correlation to a high degree and computational methods that seek to describe large molecular systems with reduced computational cost seek further attention. In this chapter special attention to the computational methods capable of describing phenomena relevant to biological activity and drug discovery and development, as well as the design of new materials relevant to understanding complex biological systems are highlighted.

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# CHAPTER 1

# Computer-Aided Molecular Design in Computational Chemistry

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**Abstract:** In molecular design techniques, thermodynamic properties are predicted through computational tools. Besides, the simple prediction methods explain the space of molecular design while quantum mechanics can accurately predict the properties without any kind of experimental data; however, it is a bit challenging. Therefore, in this chapter, the significant advancement, demurrers in progression, and the future perspective in designing the chemical compounds *via* using "computer-aided molecular design" (CAMD) tools will be elucidated. Since the interest in designing novel and advanced compounds is increasing with time, traditional methods are not efficient now. This is the key factor in the advancement of CAMD tools. The work advancement different classes of methods that predict the properties will be explained in the chapter. Applications of CAMD in the single component product designs, mixture designs, and also in integrated product designs will be evaluated. All the difficulties while operating the designs and also in obtaining the results and future perspectives will be reviewed. COSMO-CAMD successfully designs novel promising solvents in the liquid-liquid extraction of phenol from water; therefore, it will be explained thoroughly. Some would debate that theoretical tools in computational chemistry can now come up with eager understandings of any chemical process. Yet, the goblet of effective and reliable prediction of compound reactivity has remained fugitive. Favorably, recent developments in the electronic structure theory, which is based on both concepts, element, and rank-scanty, along with the appearance of the highly sophisticated computer architecture, prominently increased the time and length scales that can be simulated using molecular dynamics. This opens the door for the newly proposed *ab initio* nanoreactor method. Therefore, *ab initio* methods will be studied completely because we argue that due to this development in molecular designs, the holy grail of computational discovery for complex chemical reactivity is entirely within our reach.

**Keywords:** CAMD, COSMO, DFT, Geometry Optimization, *in silico*, IZA.

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## INTRODUCTION

Chemistry is all about the molecules and also their conversions. So two basic questions that arise in chemistry are:

(i) Which type of molecule should be designed for the required applications?

and

(ii) How can the molecules be designed selectively and efficiently?

It was very challenging due to errors in the synthetic strategies. In the last era, the computer has revolutionized this field by the development of theoretical models that ranges from the electronic structure of the molecule to molecular dynamics as well [1].

Computer-aided molecular design (CAMD) is the process of generating molecules with desired properties that compare with the definite targeting characteristics. The relationship discipline of the CAMD in the development of quantitative structure-activity was explained for the first time by Hansch and Fujita in the 1960s [2]. CAMD is defined as the given arrangements of building blocks and predetermined arrangements of targeted possessions, which conclude the molecule or atomic structure that coordinates these characteristics [3].

The capability to design molecules with required chemical and biochemical processes is quickly turning into reality. This ability reveals the theoretical introduction in chemistry for the invention of new methods, as well as new computing power control in order to apply for the detailed molecular model analyses [4]. By the group contribution, computer-aided molecular design is the inverse property prediction which has given a lot of attractive properties. For example, it is proposed to discover a mix of basic gatherings and consequently a sub-atomic structure, fulfilling the property determinations. According to the appropriate property measures, the potentially feasible molecules may also be ranked [5].

To design good or optimal molecular structures, the CAMD combining with numerical optimization, thermodynamics, and molecular modeling techniques performs well. By the group, contribution approaches in the computer-aided molecular design the compounds or a mixture of compounds are presented in such a way that the collection of functional groups have a set of the specified range of properties. For the computation of property value, the CAMD can be applied to various types of problems, and in most cases, it produces more than one solution, including the choice of refrigerants, development of drugs, and innovation of

separation processes, as well as finding the design of solvents for the polymers and paint industries.

The CAMD is limited for both, mixtures and pure compounds due to less availability of computing functions, accuracy, and reliability of the models employed to predict the targeted properties [6]. For the efficiency, simplicity, and accuracy of optimal molecular structures of CAMD, the semi-empirical modeling and modern combinatorial optimization are used for CAMD, which ultimately enables the optimization over staggeringly large design spaces which would be inaccessible otherwise [7].

By using the state equation ($E_oS$) and semi-empirical group contribution methods, the CAMD techniques have been used by many authors for the optimization of Organic Rankine Cycle (ORC), which led to the possibility of combining with the operational parameters such as temperature and pressure as well as are used for working fluid design with ORC system design systematically [8].

## METHODS

### Markovian Chemicals "*in silico*" Design (MARCH INSIDE)

At the beginning of the 20$^{th}$ century, Markov's chains were used in different fields such as astronomy, physics, biology, and chemistry. The use of the Markovian process increased tremendously in the fields of epidemiology, and medicine, and artificial intelligence due to methods that are based on the mathematical approach. For analyzing biological sequence data and for the detection of new genes from open reading frames, Markov models are considered useful tools. These models are also used in protein domains and multiple sequence alignment of proteins. It has been used as particle cascades to solve the problems related to many electrons in quantum mechanics by the Monte Carlo method [9].

The molecular structure is represented by many modest descriptors that help the chemist to codify structural information in pharmacological terms [10]. The stochastic nature and simplicity of the Markov chain attracted attention of researchers for their use as meaningful descriptors. Before 2002, the usage of stochastic matrix formalism as a basis of molecular descriptors was not common [11]. For the first time, Markov chain formalism was used by Gonzalez to classify molecular structures towards virtual screening and discovery of fluckicidal drug. It was then extended to the study of protein structure-property relationships.

# CHAPTER 2

# Role of Ensemble Conformational Sampling Using Molecular Docking & Dynamics in Drug Discovery

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**Abstract:** Protein interactions with various other macromolecules is a key biological phenomenon for the molecular recognition process leading to various physiological functions. Throughout decades, researchers have proposed various methods for the investigation of such binding mechanism, starting from static, rigid docking to flexible docking approaches. Rational drug designing approaches were improvised by introducing semi- to full-flexibility in the protein-ligand molecular recognition process, conformational dynamics, and binding kinetics and thermodynamics of conserved waters in the binding site. A better understanding of ligand-binding is quintessential to gain more quantitative and accurate information about molecular recognition for drug and therapeutic interventions. To address these issues, Ensemble docking approaches were introduced, which include protein flexibility through a different set of protein conformations either experimentally or with computational simulations *i.e*., molecular dynamics simulations. MD simulations enable ensemble construction which generates an array of binding site conformations for multiple docking trials of the same protein, though sometimes poorly sampled. To overcome the same, enhanced sampling was introduced. In this chapter, the theoretical background of molecular docking, classical MD simulations, MD-based enhanced sampling methods and hybrid docking-MD based methods are highlighted, demonstrating how protein flexibility has been introduced to optimize and enhance accurate protein-ligand binding predictions. Overall, the evolution of various computational strategies is discussed, from molecular docking to molecular dynamics simulations, to improve the overall drug discovery and development process.

**Keywords:** CADD, Enhanced Sampling, Ensemble Docking, Flexible Docking, Hybrid Docking-MD, Molecular Docking, Molecular Dynamics Simulations, Metadynamics, REMD, Steered Dynamics, Umbrella Sampling.

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# INTRODUCTION

## Drug and Drug Designing

The word “Drug” has an origin from the word “Drogue”, a French word that means Dry Herb/Plant extracts. It strongly recommends that in the early days most primitive drugs were extracted from various plant sources [1]. The drug may be a natural or synthetic substance that shows a physiological effect when introduced to the human body and is used for the prevention, treatment and diagnosis of a specific disease and result in the relief of discomfort. In the context of pharmacology, a drug molecule is a chemical entity that is different from an essential dietary ingredient and develops a biological effect on a living system after administration [2]. Broadly, any substance administered orally, or injected subcutaneously, intramuscularly or intravenously, or applied topically or to a body cavity to treat or prevent a disease or condition is termed as “Drug”. A drug, once it binds to the particular target site may either stimulate or inhibit the function of a biological molecule or macromolecule that outcomes as therapeutic benefits. Drug designing is a magnificent inventive process in the development of novel therapeutics in medicinal chemistry or biological history to produce an important and noteworthy beneficial or therapeutic reaction. Generally, it is also termed rational drug design.

## Computer-Aided Drug Discovery (CADD)

The novel drug discovery process for identifying novel drug/drug-like entities is a costly, multifaceted, and resource-consuming process which includes a wide range of modern tools/techniques and various scientific disciplines. A fair estimate indicates the entire process to take approximately 1.0 billion USD and 10-15 years [3] to complete a traditional drug discovery and development phase, from concept to approval of a novel drug into the market. This resource-intensive process majorly contributes towards the lead synthesis and the testing of the lead compounds/analogues [4]. However, in the early days, with not much information available at the protein structure level, R&D and innovations were pivoted more towards medicinal and combinatorial chemistry as well as high-throughput screening [5]. Now with the advent of high-performance computing, improvised algorithms and availability of 3D protein structure, computer-aided drug discovery (CADD) techniques are in the renaissance period. To circumvent the challenges faced by traditional drug discovery approaches, academia, pharmaceutical companies, and other research organization have employed CADD techniques.

CADD has now become an essential tool for minimizing failures right from the preliminary screening to the final phase of drug discovery and development.

The CADD approaches are further classified into structure-based drug design (SBDD) and ligand-based drug design (LBDD). The structure-based approach relies on the availability of the 3D structure of the target protein for the screening and identification of promising ligand molecules by calculating the interaction energies between the target and compound [6]. In contrast, the latter approach utilizes the information/knowledge of actives and in actives molecules with diverse chemical structures as well as the development of predictive models such as QSAR (Quantitative Structure-Activity Relation) [7]. These models are further utilized for screening and identification of additional newer chemical entities through a large chemical database search, a process called virtual screening.

In the early days of CADD, static docking was much more popular, but with the increasing biological complexity and flexibility of target molecules, a more dynamic approach was needed. To circumvent the problems with static docking, flexible docking methods were employed at ligand and target molecule levels [8]. Researchers also have used Molecular Dynamics (MD) simulations for docking ligands on target molecules which treats the entire protein-ligand complexes in dynamics considering the effect of solvents molecules [9, 10]. The severe limitation of not considering protein flexibility can be overcome by the use of an ensemble of multiple protein structures in the regular docking process. This approach is known as ensemble docking where different conformations of the same target protein, either in complex with some substrate or small molecule or free from any ligand, are taken to generate an ensemble of structures (array of conformations). A typical ensemble docking computation takes protein structural variations into account [11, 12]. More details about flexible & ensemble docking as well as MD simulations are discussed further in the chapter.

Given the ever-increasing novel drug-target molecules and their biological complexity, we will in this chapter discuss the theoretical concepts of molecular docking and its various approach, focussing on sampling methods as well as static and flexible docking methods. We move on to the MD simulations method and conformational space search problem. We focus on those variable & variable-free MD methods employed for enhanced sampling, such as metadynamics, umbrella sampling, steered and replica-exchange MD simulations. This perspective will also touch on the emerging ensemble-based docking approach and discuss its application to address protein flexibility. We close by outlining how hybrid docking-MD approaches are now employed which may help in unraveling more molecules against drug targets. Overall, we present a state-of-the-art review highlighting key applications of the above techniques to CADD from recent years. We envisage a future wherein MD and ensemble approaches are routinely used for *in silico* screening of large small-molecule libraries, thereby accelerating the identification and characterization of a drug candidate.

# CHAPTER 3

# Molecular Dynamics Applied to Discover Antiviral Agents

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**Abstract:** In recent years, the world has faced several outbreaks caused by viral diseases, resulting in deaths and comorbidities, harming the health of the population. Due to the "constant" discovery of new antivirals, vaccines, hygiene habits, and basic sanitation, society had the false impression of being free from these diseases. However, since the 1980s, various outbreaks have occurred, such as HIV (Human immunodeficiency virus) and recently, ZIKV (Zika virus), CHIKV (Chikungunya virus), and EBOV (Ebola virus) have increased the concern about such pathogens, resulting in advances in drug discovery. In addition, the SARS-CoV-2 outbreak responsible for 27,417,497 cases, and 894,241 deaths (to date, September 9$^{th,}$ 2020), showed how scientists should advance to end this disease so damaging to the global health and economy. In this context, researches focused on drug development have been improved in recent years. Thus, it is essential to use computational approaches to accelerate drug discovery in laboratories. Based on this, structure-based drug design (SBDD) techniques constitute the most used computer-aided approaches for discovering and developing new drugs. Among these techniques, molecular dynamics (MD) simulations have been essential steps and their use in virtual screening studies is considered indispensable. The MD considers the macromolecule flexibility using Newtonian principles applied to proteins, enzymes, membranes, nucleic acids, and other systems. Thus, it is possible to analyze protein-ligand interactions, and also the affinity energy that a determined ligand exhibits towards its target. Such information is indispensable for designing and optimizing new active agents. This chapter will be addressed to concepts and applications of MD simulations, as well as their applications in the discovery of drugs against Coronaviruses (SARS-, MERS-CoV, and SARS-CoV-2); Influenza (INFV); Chikungunya (CHIKV); Zika (ZIKV); Dengue (DENV); Ebola (EBOV); and human immunodeficiency virus (HIV), constituting a great source of helpful information that could be utilized for designing new compounds against these diseases.

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**Keywords:** Antiviral Compounds, Molecular Dynamic, Molecular Modeling.

## INTRODUCTION

Human beings are constantly threatened by various diseases, increasing the necessity of discovering new drugs that could be effective to treat them [1, 2]. Drug discovery and development process is a costly, time-consuming, and challenging task. Given that, such challenges are overcome by multidisciplinary methods and computer-aided drug design (CADD) methodologies [2, 3]. Within CADD methods, structure-based drug design (SBDD) and ligand-based drug design (LBDD) are used when the target is known or not, respectively [4, 5]. In fact, SBDD is the preferred approach by researchers mainly due to the availability of free license software and the large availability of crystallized structures of different targets that facilitates the *in silico* screening of new drugs [5 - 7].

In the context of SBDD methods, *hit* identification and *lead* optimization are mainly performed using molecular docking software [8]. However, its major limitation is not considering the ligand and target flexibility. The utilization of molecular dynamics' (MD) simulations is essential in any drug discovery program, generating information on thermodynamics, binding kinetics, and disassociation of ligands [8, 9]. In MD simulations, atoms and molecules can interact in a given time, generating a path resolved by Newton's equations of motion, in which energies are calculated by force field (FF) or molecular mechanics (MM) methods [9, 10]. The algorithm used is capable of determining positions and velocities of each atom, calculation, and force applied to the atom employing interatomic potentials and progression of the speed of atoms in a given time [4]. The protein-ligand interaction information generated in MD simulations is critical in discovering new active molecules [4, 11].

Viral diseases are responsible for severe damage to human health, leading to high mortality rates worldwide [12]. Despite several advances in drug discovery techniques, there are several diseases that still do not have an effective treatment, for example, against Zika virus (ZIKV), Chikungunya virus (CHIKV), and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which are responsible for several outbreaks around the world, requiring new alternatives to fight against them [6, 7]. CADD and even drug repurposing methods have been increasingly highlighted, driven by several significant findings, for example, the discovery of HIV protease inhibitors, such as amprenavir [7, 13 - 15]. Thusly, molecular docking and MD simulations are often used for discovering new antiviral agents [7, 16].

Finally, this chapter will address a brief introduction to MD fundamentals, as well as its applications and relevant studies involving the discovery of new antiviral compounds, focusing on Influenza virus (INFV), Coronaviruses (CoV), ZIKV, Dengue virus (DENV), CHIKV, Ebola virus (EBOV), and HIV.

## VIRAL DISEASES AND THEIR THREAT TO SOCIETY

In modern society, different viral diseases are considered to be one of humanity's biggest woes, responsible for thousands of deaths around the world. However, during the 20$^{th}$ Century, such diseases were not a concern for the general population, mainly due to the evolution of hygiene habits, the discovery of antibiotics, vaccines, and basic sanitation improvements. There was a false impression that society was free of such diseases, leading to the carelessness and growing increase in outbreaks of viral diseases from the 1980s to the present day [7, 17].

The World Health Organization (WHO) classifies an emerging virus that first affects a specific population or that previously affected the population, but it is quickly spreading again at an accelerated rate [18]. Despite notable advances in antiviral therapies, such pathogens remain a challenge in both control and eradication [18, 19]. These infectious diseases are responsible for approximately 20% of global mortality, so that one-third of deaths are due to viral pathogens, mainly related to poor sanitation or even factors related to nutritional status and poor access to health services [20, 21]. In addition, viral factors related to mutations, human factors such as population growth and urbanization, and ecological factors contribute to the emergence of such diseases [22, 23].

In the last decades, the world population has been threatened by seven major viral epidemics (Fig. **1**), leading to severe health and economic damages, among which none comparable to those generated by the pandemic caused by the new Coronavirus (COVID-19) [7, 24, 25]. These viruses have high transmissibility, by oronasal secretions or respiratory aerosols (droplets) released by infected individuals, or even could be transmitted by vectors (arboviruses or arthropod-borne viruses), taking the concern of health agencies and increasing the interest of researchers from all over the world in discovered new therapeutic alternatives against them [26, 27].

Although viral diseases have threatened humanity for many years, some of these diseases have no approved and effective treatments [28]. Also, the repurposing of antiviral drugs, despite being a promising strategy that generates results in less time and at a lower financial cost, In which the emergence of virus resistance mechanisms to available drugs is a significant challenge to be overcome in the

# CHAPTER 4

# Pharmacophore Modeling Approach in Drug Discovery Against the Tropical Infectious Disease Malaria

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**Abstract:** Malaria remains to be a life-threatening disease in the developing world. Recent reports show that the worldwide progress in reducing malaria has slowed. It accounts for causing more than 2.2 million cases and 405,000 deaths in 2018. Therefore, the situation demands the need for the development of new techniques or drugs against malaria. Several antimalarials have shown improvement in the treatment of malaria, but the emergence of drug resistance has intensified the need for the development of novel drugs. Drug discovery is an expensive, laborious, and time-taking process. Alternative to traditional drug design, computer-aided drug design plays a significant role. In this respect, a class of computational techniques known as pharmacophore modeling is considered beneficial for discovering novel lead compounds. Pharmacophore modeling with the virtual screening method has become a popular method for the screening of hit molecules. Pharmacophore modeling techniques are often implemented with molecular docking to improve the outcome of the virtual screening. The current study focuses on the pharmacophore modeling methods used to discover various novel antimalarials. According to the literature, this method is valuable in processes like virtual screening, design of effective hit molecules, and optimization of lead towards clinical trials. The reader will gain insight into the successful applications of the pharmacophore-based virtual screening to discover antimalarials.

**Keywords:** Computer-Aided Drug Design, Electron Transport Chain Enzymes, Fatty Acid Biosynthesis Enzymes, Folate Pathway Enzymes, Malaria, Glycolytic Pathway Enzymes, Isoprenoid Biosynthesis Enzyme, Multicomplex-based Pharmacophore Modeling, *Plasmodium falciparum*, Protease Enzymes.

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## INTRODUCTION

Despite the remarkable improvement in implementing strategies to combat drug resistance, the tropical infectious disease malaria remained one of the prime causes of mortality [1, 2]. Malaria is an infectious disease caused by a protozoan parasite. Of the five species of *Plasmodium* parasite, *Plasmodium falciparum* remains the deadliest one. As per the recent data from World Health Organization (WHO), it was estimated that around 228 million cases and 405,000 deaths were reported worldwide. Most of the cases (>90%) arise from African regions, followed by South-East Asian regions (>3%) and Eastern Mediterranean regions (>2%) [3]. Malaria has affected public health and economies; however, countries with high poverty rates were adversely affected [3]. Therefore, owing to the worrying increase in the statistics of the malaria reports, WHO has considered malaria as the top priority tropical disease which requires controlled strategies [3, 4]. There are a number of antimalarial reported so far, but most of them have shown resistance [5 - 9]; for instance, artemisinin combination therapy (ACT) recommended by WHO has shown a reduction in the activity against the *P. falciparum* [10]. Thus, there is an urgent need to search for effective drugs to treat malaria.

The discovery of drugs is counted as one of the costly [11] and laborious processes [12]. It takes years for a successful drug candidate to hit the market [12]. However, in the past, the drug discovery process allied with the identification of drugs was a trial-and-error process [13]. Most of the molecules fail in clinical trials owing to the lack of safety and potency for being an effective drug molecule [13, 14]. Therefore, to overcome the drawbacks of *hit*-and-trial methods, rational strategies were designed to advance drug potency and safety [15, 16]. Hence, computers occupied a ubiquitous position in the timeline of the drug development process [15, 17]. The strategy in which computers are designed to conduct the drug development process is termed computer-aided drug design (CADD) [18]. Over the last few years, CADD has remained beneficial for the pharmaceutical giants [19, 20]. The substantial development in the types of computational techniques has led to the speed up of the drug discovery process while reducing the overall cost and time allied with the drug designing [19 - 21].

While aiming for the discovery of a novel drug candidate, the initial step is the selection of target, tailed by *hit* identification, *hit*-to-lead modification, then optimization of the lead and finally, the clinical trials of the shortlisted candidates [22]. Among the mentioned steps, most of the success depends on the identification of the *hit* molecules, which is mainly performed by employing high-throughput screening (HTS) [23]. It aims for the testing of several molecules with an appropriate activity assay [23]. However, in CADD, alternate to HTS is virtual

screening (VS) which has attained popularity based on the efficiency in the filtering of the potential *hit* candidates from the enormous dataset of the chemical compounds [24 - 26]. Taking this advantage into consideration, extensive efforts have been dedicated to compress the initial phase of the drug discovery process, *i.e*., *hit*-to-lead development and optimization [27]. There are many computational techniques based on the CADD methods that focus on the retrieval of drug like candidates [15]. To start, quantitative structure activity relationship (QSAR) or quantitative structure property relationship (QSPR) methods are counted among the popular methods for the construction of the predictive models to identify the novel inhibitors [28 - 31]. These techniques accurately search the physicochemical properties of the set of compounds associated with the inhibitory activity or toxicity based on certain molecular descriptors (physical or chemical properties of the compounds) [29]. Apart from QSAR/QSPR, molecular docking technique has also been extensively used for the identification of the molecules that bind within the protein cavity [32]. Docking studies gain more interest when the information about the structure of the protein is not available, as it helps in the structural analysis of the protein-ligand interactions [32, 33]. With time, docking has become a popular method in performing the VS of the *hits* where compounds were screened based on the interaction patterns or the proteins (target) were identified by employing inverse docking technique [34, 35]. There is another very popular method of CADD, *i.e*., pharmacophore modeling, and in the present review, the discussion is made with respect to its related methods to perform the VS [36 - 38]. The rationale behind the current review is to provide the advantages of pharmacophore modeling in the identification of the drugs against the tropical infectious disease *P. falciparum* (malaria), and is focused on the medicinal and computational chemists working in the field of antimalarial development. This chapter is focused on the analysis of the pharmacophore modeling approaches applied in the last six years (2015 to 2020) on the druggable enzymes of *Plasmodium falciparum*. Moreover, it highlights the necessity for the validation of the computational outcomes *via* experimental activities.

## PHARMACOPHORE MODELING

Initially, pharmacophore was represented as the chemical groups present in a molecule that are accountable for displaying the biological activity of the molecules. The actual concept of the pharmacophore was developed in the late 1800s by Paul Ehrlich [39] and the terminology was coined by Schueler in the 1960s [40]. Schueler defined pharmacophore as molecular framework of the crucial features present in an inhibitor/molecule [40]. However, in 1997, the International Union of Pure and Applied Chemistry (IUPAC) defined pharmacophore as [41]:

# CHAPTER 5

# Advances in Computational Network Pharmacology for Traditional Chinese Medicine (TCM) Research

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**Abstract:** Traditional Chinese Medicine (TCM) is a complementary and alternative medicine but possesses remarkable clinical efficacy in China and surrounding countries. Hence, systematic analysis and elucidation of the complex chemical basis and action mechanisms of TCM will be highly beneficial. Nowadays, the widespread application of network pharmacology has unveiled the mystery of TCM to some extent by constructing the relationship of "herb-compound-target-disease". Moreover, it can promote the development of drug discovery, medical guidance, and the dissection of the syndrome in TCM. With the integration of computational techniques into network pharmacology, the efficiency of data mining and the accuracy of active compounds identification and target fishing have been improved, and the "herb-compound-targ-t-disease" network has been more systematically and comprehensively explained to reflect the holistic mechanisms of TCM. Therefore, a comprehensive overview of each aspect of the use of computational techniques in TCM network pharmacology is urgent. This chapter systematically dissects the core contents involved in TCM computational network pharmacology and highlights its application on TCM against COVID-19, and severs the cutting-edge study examples to compare and analyze the advantages and limitations of different computational techniques.

**Keywords:** Algorithms, COVID-19, Molecular modeling, Network pharmacology, Traditional Chinese medicine.

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## INTRODUCTION

Traditional Chinese medicine (TCM), as complementary and alternative medicine, has been developed and practiced in China and surrounding countries [1]. After thousands of years of training and testing, as well as improvement and perfection, a unique and complete theoretical system of TCM has finally been formed [2]. Distinct from western medicine, TCM, characterized by holistic, personalized, rich experience-based and multicomponent therapy, provides a bright prospect for the systematic control of complex diseases. With the development of human society and the change of surroundings, human diseases have gradually transformed from infectious diseases to chronic non-communicable diseases (*e.g.*, cardiovascular diseases, diabetes mellitus, and tumors, *etc*.). TCM is prominent in the treatment of these chronic diseases caused by intrinsic and extrinsic factors simultaneously [3]. In clinical practice, TCM is mostly used in the form of formulae, which often follows the principle of "sovereign-minister-assistant-envoy (Jun-Chen-Zuo-Shi in Chinese)" to achieve the comprehensive and synergistic therapeutic effect by the combination of various natural products (*e.g.*, plants, animals and minerals, *etc*.). For this reason, TCM formulae contain hundreds of chemical ingredients, which makes it challenging to understand the mechanisms of action and bioactive ingredients. Due to the complexity of TCM and the limitations of experimental applications, only a few TCMs' specific mechanisms of action have been fully elucidated, such as the molecular mechanisms of Realgar-Indigo naturalis formula on promyelocytic leukemia [4]. Undoubtedly, it is difficult for traditional reductionist methods to reveal the complicated interplays between the multiple compounds and multiple targets of TCM, which is becoming the major obstacle to the modernization of TCM [5].

With the gradual rise of interdisciplinary disciplines such as system biology, bioinformatics, artificial intelligence, and big data science, the research of TCM has been transformed from a single and isolated mode to a multi-angle and systematic research mode [6]. One of the breakthrough advances is to dissect the mechanisms of action from the perspective of the biomolecular network. Utilizing the "network" to regain the "whole" generates an unprecedented opportunity for the systematic research of TCM. Accordingly, network pharmacology is evolving as a systematic paradigm as well as a new frontier to guide the research and development of TCM. The concept of network pharmacology was first proposed by Andrew L. Hopkins in 2007 [7]. It combines network biology with polypharmacology based on the poor efficacy of highly selective single-target drugs. Through network pharmacology, we can directly identify drugs and disease targets from a large amount of data and understand the mechanisms and pathways between them. Network pharmacology studies emphasize the paradigm shift from

"one target, one drug" to "network target, multi-component therapeutics," highlighting holistic thinking also shared by TCM [2, 3]. In the last decade, network pharmacology studies have bloomed to decipher the potential bioactive compounds and underlying mechanisms of TCM [8]. The conventional TCM network pharmacology generally starts by following a database-based strategy to identify the active compounds present in TCM formulae and their plausible corresponding targets and finally investigate the signaling pathways and sub-networks regulated by the formulae and evaluate their effects on disease-associated gene sets or networks [9, 10]. However, due to the definitive limitations of database-based strategy, the poor involvement of computational techniques and the lack of experimental verification, TCM network pharmacology research has stagnated and encountered bottlenecks, as well as much repetitive work of limited value, has emerged [11, 12].

Nowadays, the rapid development of computational methodologies and high-performance computational resources is being witnessed. Computer algorithms play a vital role in meeting the data-driven research in the various aspects of TCM network pharmacology. Specifically, machine-learning (ML) algorithms for predicting ADMET (absorption, distribution, metabolism, excretion, and toxicity) parameters and targets facilitate filtering active TCM compounds and identifying putative targets [13, 14]; network propagation-like algorithms can recognize proteins influenced by TCMs [15]; and algorithms for finding hub nodes in networks boost the identification of core compounds and targets of TCMs [1, 16, 17].

This chapter is structured into two main sections. In the first section, the cutting-edge computational network pharmacology studies on active compounds mining, compound-target interactions prediction, gene ontology (GO) enrichment and pathway analysis methods, and network topology analysis were reviewed and summarized. Further, the application of network pharmacology in the mechanistic investigation of TCM against COVID-19 was highlighted in the second section.

## COMPUTATIONAL NETWORK PHARMACOLOGY ON TCM

### Active Compounds Mining

The unclear bioactive compounds of TCM are one of the key issues restricting the research and development of TCM, so a comprehensive method for the identification of bioactive compounds is urgently required. However, it is very time-consuming and labor-intensive to obtain the chemical composition of TCM based on traditional chemical methods (chemical separation, analysis, and identification). Owing to many natural product databases are published as open-

# CHAPTER 6

# Progress in Electronic-Structure Based Computational Methods: From Small Molecules to Large Molecular Systems of Biological Significance

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**Abstract:** A review of *ab initio* computational chemistry methods that can be used for accurate studies of molecules and molecular design and simulation of chemical phenomena with applications that are relevant in exploring biological activity is presented. The review includes a discussion of recent computational approaches that account for the effects of electron correlation to a high degree and computational methods that seek to describe large molecular systems with reduced computational cost yet achieving good quality results. Comparison with available experimental data demonstrates the effectiveness of these computational methods in estimating accuracy, reliability, and scalability of the computational approaches discussed in this review. In recent years, the understanding of biological systems using electronic structure theory-based computational methods with applications to biology and medicine has gained increased interest. We draw special attention to the computational methods capable of describing phenomena relevant to biological activity and drug discovery and development, as well as the design of new materials relevant to understanding complex biological systems. As an application of these electronic structure methods, we include the case study of perboranation in aza-derivatives of aromatic five and six-membered rings.

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**Keywords:** Configuration Interaction, Density Functional Theory, Dimethylmercury, Electron Correlation, Electronic Structure, Ellipticine/DNA Complex, Enzymes, Excited Electronic States, Green Fluoroprotein Chromophore, Ground Electronic States, Molecular Dynamics, Molecular Interaction Energies, Molecular Mechanics, Molecular Toxicity, Multiscale Models of Complex Chemical Systems, Novel Heteroborane Compounds, Perboranated Azines, Perboranated Azoles, pH, Polyenes, Potential Energy Surfaces, Proteins, Quantum Chemistry, Quantum Mechanics, Reaction Coordinate, Renormalization Group Approach, Seniority Number, Symmetry-Adapted Perturbation Theory, Toxicology, β-carotene.

## INTRODUCTION

Accurate and reliable theoretical description of complex chemical systems of biological importance is of great significance and has been a subject of numerous efforts by method developers. In particular, these efforts have manifested in a production of a number of Quantum Chemical Computational Packages that have been widely used by scientific researchers focusing on a variety of problems of chemical and biological significance, from evaluating the biological activity of molecular species to attempts in predicting potent and effective drugs to address various health issues. Recent breakthroughs [1, 2], in our understanding of the structure, functionality, and chemical reactivity of complex bio-chemical systems like DNA, RNA, proteins, carbohydrates, lipids, see, *e.g* [3]. or extensive molecular structures like fullerenes, nanotubes and graphene-sheets [4 - 9] necessitate the development of high-quality quantum chemical models that are capable of providing the underlying description of complex systems at the microscopical (quantum) level of theory. While the ability to determine structural parameters of equilibrium geometries is important, the most challenging task is the elucidation of functionality of the complex biomolecules, like DNA repair, metabolism, the mechanism of image formation upon photon absorption *via* isomerization reaction from cis-to-trans structure involving the light-detecting - protein rhodopsin [10], the $FeO_2$ bonding mechanism in oxy-myoglobin [11], the process of synthesis of biomolecule NO in humans using nitric oxide synthase isoforms [12], nitrogen fixation, *i.e*., synthesis of $NH_3$ from $N_2$ [13], the mechanism for intein C-terminal cleavage [14], and many other phenomena of biological interest. Notably, the theoretical modeling of a wide variety of enzymatic reactions has been a subject of intense research over many years [15 - 18]. Among many breakthrough studies, for example, one can mention recent findings by Schulz *et al.* [18] in the computational investigation of the diiron core intermediate structures that are involved in the catalytic cycle of methane oxygenase, the enzyme that facilitates the conversion of methane to

methanol. These researchers were able to identify the most likely geometry of $MMOH_Q$ intermediate to be an open-core configuration with mono-oxo-bridged iron ions.

Another important avenue in biochemical research using quantum chemical computational methods concerns the molecular processes and molecular species that control concentrations of toxic chemicals, like elucidating the effect of the hydronium ion concentration (acidity level of the solution) on the stability of highly toxic compound dimethylmercury (DMeHg) [19]. The *ab initio* computational results [19] indicate that DMeHg is unstable under acidic conditions (low pH levels), decomposing readily into methane ($CH_4$) and $CH_3$-H--$OH_2^+$ ion. The recent experimental investigations confirm [20] that DMeHg is indeed unstable under acidic conditions (low pH levels), producing methane as one of the decomposition products as predicted. This result is also consistent with the earlier experimental observation [21] that alkaline conditions are necessary for the formation of DMeHg. Thus, the predictive power of quantum chemical computations elucidating the decomposition pathways of bio-toxic compound DMeHg is very encouraging. Another example that illustrates the effectiveness of *ab initio* methods can be seen in the analysis of toxicity originating from thiophene-containing drugs [22], as well as toxicity studies of toxic nitroaromatic compounds by examining reduction potential and hydrophobicity [23].

Since the early days of quantum mechanics, starting in about 1926 [24, 25], numerous theoretical models to approximate accurate properties of molecular systems and extended-solid materials have been developed [26 - 30]. Ideally, the most desirable quantum-theoretical models to be used to describe essential features of various physical, chemical, and bio-chemical phenomena correctly are being developed with two main considerations in mind, namely, to provide as high accuracy as possible with the lowest computational cost possible [26 - 30]. Needless to say this is a highly challenging task [31, 32]. Most of the advances in theoretical quantum method development have been dedicated to finding approximate solutions to the (non-relativistic) Schrodinger equation [24]. However, the relativistic quantum effects are very important in cases when, for example, high (near-spectroscopic) accuracy is desired [33 - 36] or when molecular systems involve heavy nuclei [29, 30]. In the quest of achieving the optimum balance between high accuracy and the lowest computational cost possible, the efforts in quantum chemistry method development ordinarily start with the mean-field level of theory, *e.g*., Hartree-Fock [28 - 30], and then include electron-electron correlation in a systematic way following various frameworks. While the wave-function-based approaches [26] *via* the use of molecular orbitals generated from the Hartree-Fock procedure offers a systematic (hierarchical) improvement by including electron-electron correlation *via* Configuration

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