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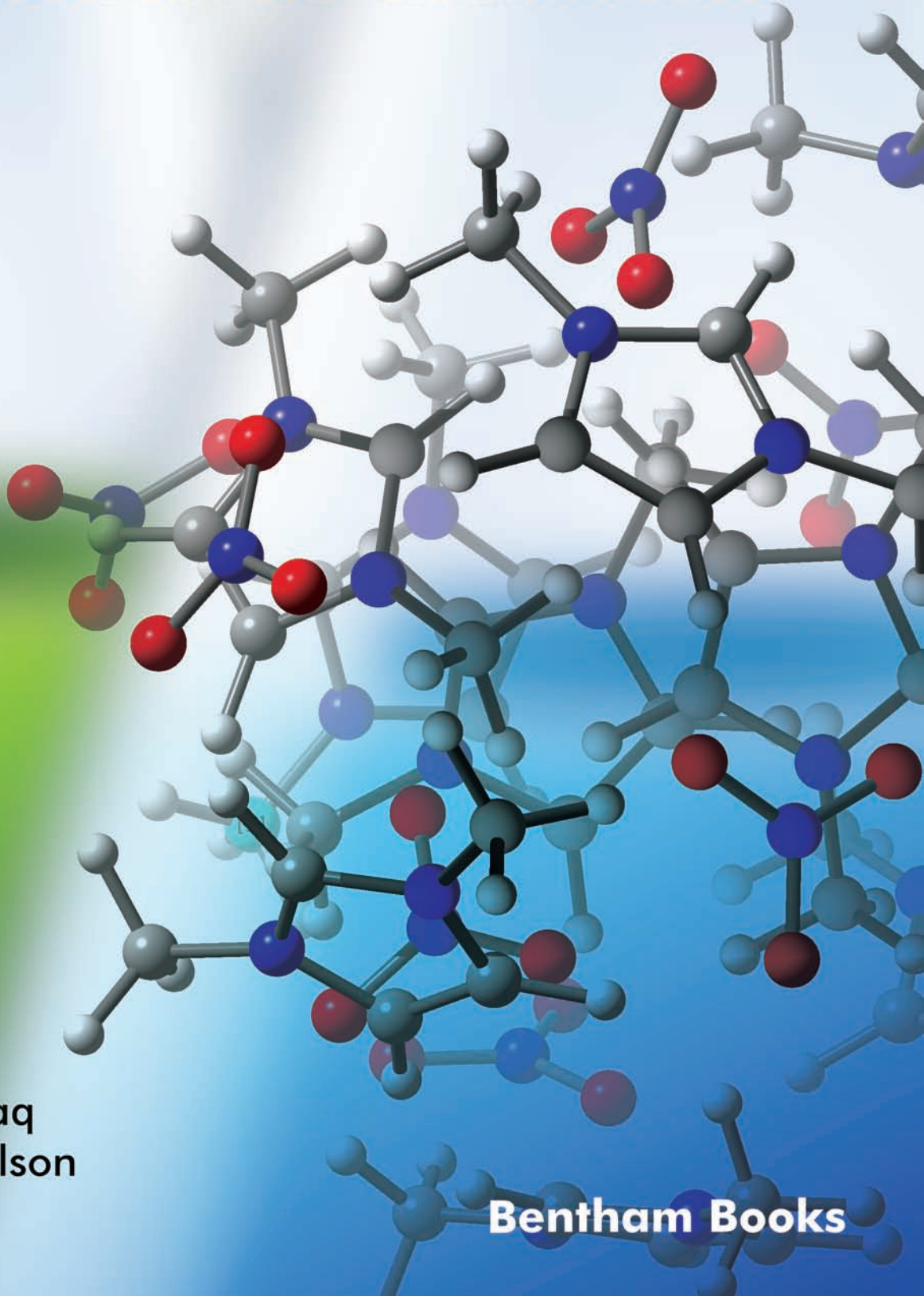

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(Volume 8)

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CONTENTS

PREFACE i

LIST OF CONTRIBUTORS iii

CHAPTER 1 ADVANCEMENTS IN COMPUTER-AIDED DRUG DISCOVERY AND DEVELOPMENT: A COMPREHENSIVE OVERVIEW 1

Harshkumar Brahmbhatt, Rahul Trivedi, Priyanka Soni and *Vishal Soni*

INTRODUCTION 2

FUNDAMENTAL PRINCIPLES OF CADD 2

MOLECULAR MODELING 2

VIRTUAL SCREENING 2

QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP (QSAR) ANALYSIS 3

HIGH-THROUGHPUT SCREENING (HTS) 3

NETWORK PHARMACOLOGY 4

FRAGMENT-BASED DRUG DESIGN (FBDD) 4

***IN SILICO* ADMET PREDICTION** 4

GRAPH-BASED NEURAL NETWORKS (GNNS) 5

THE ROLE OF MACHINE LEARNING AND ARTIFICIAL INTELLIGENCE IN CADD 6

Machine Learning Algorithms in Drug Discovery 6

AI-driven Drug Design 6

APPLICATIONS OF CADD IN DRUG DISCOVERY AND DEVELOPMENT 6

Hit Identification 6

Lead Optimization 7

Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling 7

Clinical Trial Design 7

CHALLENGES AND FUTURE PROSPECTS OF CADD 8

COMPUTER-AIDED DRUG DISCOVERY AND DEVELOPMENT 8

REFERENCES 8

CHAPTER 2 RECENT ADVANCES IN *IN-SILICO* DRUG REPURPOSING: LEVERAGING COMPUTATIONAL TOOLS FOR ENHANCED THERAPEUTIC DISCOVERY 11

Jaimini Patoliya, Khushali Thaker and *Rushikesh Joshi*

INTRODUCTION 12

Definition of Drug Repurposing 12

Strategic Advantage of Drug Repurposing 12

Historical Milestones 13

Distinctive Paths: How Repurposing Differs 14

Pathways of Innovation: De Novo vs. Repurposed Drugs 14

Poly-pharmacology vs. Repurposing 15

Benefits, Barriers, and Boundaries of Drug Repurposing 15

Strategic Advantages 15

Challenges and Limitations Associated with Drug Repurposing 16

In Silico Drug Repurposing 17

Applications of Computational Chemistry in Drug Repurposing 18

TOOLS AND DATABASES FOR *IN SILICO* DRUG REPURPOSING 20

Tools used in *In Silico* Drug Repurposing 26

Data Management and Integration 26

Systems Biology and Network Analysis Tools 27

Cheminformatics and Molecular Modelling 28

ML and AI 29

Visualisation and Analysis 29

In Silico Tools to Mitigate Pathway Interference in Drug Repurposing 30
Databases used in *In Silico* Drug Repurposing 30
VARIOUS EXAMPLES OF DRUG REPURPOSING 33
Drugs in *In Silico* Repurposing Phase 33
Oncology and Cancer Therapy 34
Infectious Diseases 35
Neurological Disorders 37
Cardiovascular Diseases 39
Autoimmune Diseases 39
Drugs in Pre-clinical and Clinical Trials 40
Oncology and Cancer Therapy 47
Infectious Diseases 47
Neurological Disorders 49
Cardiovascular Disease 49
Autoimmune Diseases 50
Success Stories of Repurposed Drugs 51
Oncology and Cancer Therapy 52
Infectious Diseases 53
Neurological Disorders 54
Cardiovascular Disease 55
Autoimmune Diseases 56
ABBREVIATIONS 57
REFERENCES 59

CHAPTER 3 COMPUTATIONAL DESIGN OF THERAPEUTIC PEPTIDES 71
Priyanka Ray Choudhury, Siddharth Yadav, Shivika Jaiswal, Tushita Khanna and *Puniti Mathur*
1. INTRODUCTION 71
2. BRIEF HISTORY OF PEPTIDE BASED DRUG DEVELOPMENT 73
3. APPLICATION OF PEPTIDE-BASED DRUGS 75
3.1. Peptides as Therapeutics 75
3.2. Peptides in Diagnostics 80
3.3. Peptides as Nanomaterials 81
4. METHODS IN COMPUTATIONAL PEPTIDE DESIGN 82
4.1. De Novo Peptide Design 82
4.2. Peptide Design for Inhibition of Protein-protein Interactions (PPI) 85
5. TOOLS AND RESOURCES FOR COMPUTATIONAL PEPTIDE DESIGN 87
5.1. Peptide Specific Databases 87
5.2. Pharmacophore Models in Peptide Design 92
5.3. Peptide-specific Molecular Docking and Lead Optimization Strategies 92
5.3.1. Peptide Specific Docking 92
5.3.2. Hit Identification and Virtual Screening 96
5.3.3. Applications of Molecular Docking in Peptide Drug Design 96
5.3.4. Role of MD Simulations in Understanding Binding Interactions 97
5.4. ML-based Predictive Models in Peptide Drug Design 99
6. CHALLENGES IN PEPTIDE-BASED DRUG DESIGN 106
6.1. Membrane Permeability 106
6.2. Poor Stability 107
6.3. Low Oral Availability 108
CONCLUSION 109
REFERENCES 110

CHAPTER 4 ADVANCING DRUG DISCOVERY THROUGH MOLECULAR DYNAMICS SIMULATIONS: A COMPREHENSIVE APPROACH 129
Amneh Shtaiwi, Imane Yamari, Samir Chtita and *Rohana Adnan*
INTRODUCTION 130
BASIC PRINCIPLES OF MD SIMULATIONS 131
Force Field 131
Newton's Equations of Motion 134
Periodic Boundary Conditions 134
Ensembles and Thermodynamic Control 136
Time and Length Scales 136
Simulation Outputs 136
Simulation Procedure 137
Software for MD Simulation 138
CASE STUDIES 140
Applications of MD Simulations in Cancer Therapy 140
Targeting Mutant p53 Proteins 140
Inhibition of Kinase Proteins 141
Recent Advances in Allosteric Sites and Novel Targets 142
Addressing Drug Resistance Mechanisms 142
Diabetes Case Study: Recent Applications of MD in Therapy 143
Glucagon-like Peptide-1 (GLP-1) Receptor Agonists 143
Inhibition of Dipeptidyl Peptidase-4 (DPP-4) 145
Alzheimer's Disease (AD) 145
Amyloid-beta Aggregation 145
Tau Protein Dynamics 147
Acetylcholinesterase Inhibitors 147
Applications of MD in Infections Therapy 152
Bacterial Infections 152
Viral Infections 153
Leishmaniasis and Malaria Parasite Therapy 155
CONCLUSION AND FUTURE DIRECTIONS 157
REFERENCES 158

CHAPTER 5 ADVANCES IN QUANTUM MECHANICAL METHODS FOR THE COMPUTATION OF PROTEIN-LIGAND BINDING FREE ENERGY 166
Peng Xu, Tosaporn Sattasathuchana, Simon P. Webb, Mark S. Gordon and *Emilie B. Guidez*
1. INTRODUCTION 166
2. APPROACHES TO THE COMPUTATIONAL PREDICTION OF PROTEIN-LIGAND BINDING FREE ENERGIES 168
2.1. Protein-ligand Relative Binding Free Energy (RBFE) Methods (ΔΔGbind) 168
2.2. Protein-ligand Absolute Binding Free Energy (ABFE) methods (ΔGbind) 169
2.2.1. Classical Protein-ligand End-point ABFE Methods 170
2.2.2. Introduction of QM Potentials into Protein-ligand End-point ABFE Methods 172
3. CHALLENGES IN QM-BASED END-POINT PROTEIN-LIGAND ABFE COMPUTATION 173
3.1. Protein-ligand Potential Energy Calculations 173
3.2. Solute Entropy Penalty Contribution 174
3.3. Solvation Models for Accurate Gsolv 175
4. QUANTUM MECHANICS-BASED APPROACHES USED IN THE COMPUTATION OF POTENTIAL ENERGY 175

4.1. QM/MM Methods 176
4.2. ONIOM 177
4.3. Fragmentation Methods 179
4.3.1. The Fragment Molecular Orbital (FMO) Method 179
4.3.2. The Effective Fragment Potential (EFP) Method 182
4.3.3. The Effective Fragment Molecular Orbital (EFMO) Method 186
5. EXPLORATION OF CONFORMATIONAL SPACE AND CONFIGURATIONAL ENTROPY 189
5.1. Conformational Sampling 189
5.2. Computation of Configurational Entropy 192
6. IMPLICIT AND EXPLICIT SOLVATION MODELS 193
7. ENHANCING THE VM2 ALGORITHM WITH QM POTENTIALS (QM-VM2) 195
7.1. The Mining-minima End-point ABFE Method: Basics of the VM2 Algorithm 195
7.2. Description of the QM-VM2 Approach 197
7.3. Protein-ligand Implementation of the QM-VM2 Approach (PLQM-VM2) 198
7.4. Implementation 200
7.5. Performance of PLQM-VM2 on Protein-ligand Binding Affinity Predictions 202
7.6. PLQM-VM2: Towards A Multi-protein Screening Capability 204
SUMMARY AND OUTLOOK 206
REFERENCES 207

CHAPTER 6 CURRENT TRENDS IN COMPUTATIONAL METHODS TO DISCOVER NEW ANTI-INFLAMMATORY AGENTS TARGETING NLRP3 COMPLEX 236
Karla Joane Da Silva Menezes, Fernanda de França Genuíno Ramos Campos, Arthur Gabriel Corrêa De Farias, Wallyson Junio Santos De Araújo, Igor José Dos, Santos Nascimento and *Ricardo Olimpio De Moura*
INTRODUCTION 237
PHYSIOLOGY OF INFLAMMATION 239
Pharmacological Intervention 243
Inflammasomes Function 246
TARGETING NLRP3 INHIBITION 247
Structure and Functions 247
Catalytic Mechanism 247
Drug Design and Discovery 249
PROMISING NLRP3 INHIBITORS IDENTIFIED USING COMPUTATIONAL METHODS 249
Molecular Ling and Molecular Dynamics (MD) Simulations 250
Virtual High Throughput Screening (vHTS) 252
Pharmacophore Models 254
Quantitative Structure-Activity Relationship (QSAR) and Machine Learning Methods 255
CHALLENGES AND OPPORTUNITIES TO DESIGN NEW ANTI-INFLAMMATORY DRUGS TARGETING NLRP3 260
CONCLUSION 261
CONFLICT OF INTEREST 261
ACKNOWLEDGEMENTS 261
REFERENCES 261

CHAPTER 7 COMPUTATIONAL MODELLING OF PHOTOPHYSICAL PROCESSES 269
Rituparna Saha, *Satadal Paul* and *Debosreeta Bose*
INTRODUCTION 270
Overview of Photophysical Processes 271
THEORETICAL BACKGROUND 274

COMPUTATIONAL METHODOLOGY 276
Excited States 283
Basis Function 284
Quantification 285
APPLICATIONS 286
SUMMARY 290
ACKNOWLEDGEMENTS 291
REFERENCES 291
SUBJECT INDEX 300

PREFACE

Computational Chemistry continues to play a transformative role in modern scientific research, integrating diverse computational strategies to address challenges in drug discovery, materials design, and molecular-level understanding of complex biological systems. The *Frontiers in Computational Chemistry* series aims to provide a platform for the dissemination of cutting-edge research and applications of computational techniques in chemistry and biology. This includes advancements in computer-aided drug design, quantum and molecular simulations, peptide modeling, and the development of novel computational algorithms that contribute to the efficient exploration of chemical and biological phenomena.

In this eighth volume, we present seven chapters that collectively highlight the latest progress and methodological innovations across different domains of computational chemistry—from broad overviews of computer-aided drug discovery to specialized approaches using quantum mechanical and molecular dynamics simulations.

Chapter 1, *"Advancements in Computer-Aided Drug Discovery and Development: A Comprehensive Overview,"* provides an integrated understanding of the computational tools and strategies used in modern drug discovery. It emphasizes the pivotal role of artificial intelligence and machine learning in streamlining target identification, virtual screening, and lead optimization.

Chapter 2, *"Recent Advances in In-Silico Drug Repurposing: Leveraging Computational Tools for Enhanced Therapeutic Discovery,"* discusses how computational modeling, network pharmacology, and data-driven approaches are revolutionizing the repurposing of existing drugs for new therapeutic indications, significantly reducing time and cost in the development pipeline.

Chapter 3, *"Computational Design of Therapeutic Peptides,"* explores the growing importance of peptide-based drugs, focusing on computational methods for peptide design, optimization, and molecular simulation. It highlights how computational strategies help overcome challenges of stability, delivery, and bioavailability in peptide therapeutics.

Chapter 4, *"Advancing Drug Discovery through Molecular Dynamics Simulations: A Comprehensive Approach,"* demonstrates how molecular dynamics simulations serve as an essential bridge between static molecular structures and dynamic biological function. The chapter presents applications of MD in understanding conformational flexibility, binding mechanisms, and drug stability.

Chapter 5, *"Advances in Quantum Mechanical Methods for the Computation of Protein-Ligand Binding Free Energy,"* delves into the recent progress in quantum chemical techniques, emphasizing accurate modeling of binding energetics and electronic interactions. The discussion provides valuable insight into hybrid and fragmentation-based approaches that enhance prediction reliability.

Chapter 6, *"Current Trends in Computational Methods to Discover New Anti-inflammatory Agents Targeting NLRP3 Complex,"* focuses on the computational exploration of inflammasome biology and presents novel approaches for identifying NLRP3 inhibitors using structure-based drug design and molecular modeling strategies.

Chapter 7, *"Computational Modelling of Photophysical Processes,"* broadens the scope of this volume by addressing photophysical and photochemical properties of molecules through quantum chemical simulations. This chapter highlights how computational modeling aids in the understanding of excited-state processes relevant to biotechnology, medicine, and energy materials.

We hope that this volume serves as a valuable contribution to the growing body of computational chemistry literature and provides readers with both conceptual clarity and practical insights into current research trends. Together, these chapters reinforce the pivotal role of computational methods in driving innovation across molecular sciences and pharmaceutical research.

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CHAPTER 1

Advancements in Computer-Aided Drug Discovery and Development: A Comprehensive Overview

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Abstract: Computer-aided drug discovery and development (CADD) has emerged as a transformative approach in the pharmaceutical industry, revolutionizing the traditional drug development process. This abstract provides a comprehensive overview of the latest advancements, methodologies, and applications in CADD. The first section outlines the fundamental principles of CADD, emphasizing its integration of computational techniques, algorithms, and databases to expedite the identification of potential drug candidates. Molecular modeling, virtual screening, and quantitative structure-activity relationship (QSAR) analysis are highlighted as primary techniques used to predict ligand-target interactions and optimize drug properties. The second section discusses the role of machine learning (ML) and artificial intelligence (AI) in CADD, showcasing their capability to analyze vast datasets, identify patterns, and predict novel drug-target interactions with unparalleled accuracy. ML algorithms, such as deep learning, have shown promising results in *de novo* drug design, target identification, and toxicity prediction. In the third section, the application of CADD in various stages of drug discovery and development is explored. From hit identification and lead optimization to pharmacokinetic/pharmacodynamic (PK/PD) modeling and clinical trial design, CADD tools streamline decision-making processes, reduce costs, and accelerate the development timeline. Furthermore, this chapter addresses the challenges and future prospects of CADD. Despite its remarkable achievements, CADD still faces limitations, such as the accurate representation of biological systems and the integration of multi-scale modeling approaches. Additionally, ethical considerations regarding data privacy, intellectual property rights, and regulatory compliance remain pivotal in the widespread adoption of CADD methodologies.

Keywords: CADD, QSAR, Virtual screening.

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INTRODUCTION

The landscape of drug discovery and development has experienced a profound transformation with the advent of computer-aided drug discovery and development (CADD). Traditionally, the drug discovery process was arduous, expensive, and time-consuming, often taking over a decade and billions of dollars to bring a new drug to market. However, the integration of computational techniques has revolutionized this paradigm, making the process more efficient, cost-effective, and accurate. This chapter provides a comprehensive overview of the latest advancements, methodologies, and applications in CADD, highlighting its pivotal role in modern pharmaceutical research [1, 2].

FUNDAMENTAL PRINCIPLES OF CADD

CADD employs a wide array of computational techniques, algorithms, and databases to expedite and enhance the drug discovery process. At its core, CADD aims to predict ligand-target interactions, optimize drug properties, and streamline the decision-making process in drug development. The fundamental principles of CADD can be categorized into several key methodologies: molecular modeling, virtual screening, and quantitative structure-activity relationship (QSAR) analysis [3].

MOLECULAR MODELING

Molecular modeling involves the use of computational techniques to model or mimic the behavior of molecules. It includes methods such as molecular dynamics (MD) simulations, which explore the physical movements of atoms and molecules over time, and quantum mechanics/molecular mechanics (QM/MM) approaches, which provide detailed insights into molecular interactions at quantum levels. These techniques allow researchers to predict the structural and functional properties of drug candidates, facilitating the identification of promising compounds [4].

VIRTUAL SCREENING

Virtual screening (VS) is a computational process used to search large libraries of compounds to identify those that are most likely to bind to a drug target, usually a protein receptor. There are two main types of virtual screening: ligand-based and structure-based. Ligand-based virtual screening relies on known active compounds to predict the activity of new molecules, while structure-based virtual screening uses the three-dimensional structure of the target protein to identify potential ligands. These methods significantly reduce the number of compounds

that need to be tested experimentally, thereby accelerating the drug discovery process [5, 6].

QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP (QSAR) ANALYSIS

QSAR analysis involves the development of mathematical models to predict the biological activity of compounds based on their chemical structure. By correlating chemical structure with pharmacological activity, QSAR models can predict the efficacy and toxicity of new compounds. This method is invaluable in optimizing drug candidates, ensuring that only the most promising compounds progress through the development pipeline [7].

- **Model Development:** QSAR models can be developed using various statistical and machine learning techniques. Common approaches include linear regression, decision trees, and neural networks. The choice of model often depends on the complexity of the data and the specific application.
- **Descriptors:** To correlate chemical structure with biological activity, QSAR analysis uses molecular descriptors, which are numerical values representing different properties of a compound. These can include topological, electronic, steric, and hydrophobic descriptors.
- **Validation:** A crucial part of developing QSAR models is validation, which ensures that the model can reliably predict the activity of unseen compounds. This is typically done using techniques like cross-validation and external validation with independent test sets.
- **Applications:** QSAR analysis is not limited to predicting efficacy and toxicity. It can also be employed in environmental chemistry to predict the fate and transport of chemicals, in toxicology to assess potential hazards, and in materials science for designing new materials with specific properties.
- **Regulatory Acceptance:** Regulatory agencies, such as the FDA and EPA, increasingly recognize the value of QSAR models in risk assessment and regulatory decision-making. However, these models must be rigorously validated to ensure their reliability in predicting real-world outcomes [8, 9].

HIGH-THROUGHPUT SCREENING (HTS)

High-Throughput Screening (HTS) is a powerful technique used in drug discovery that enables the rapid testing of thousands to millions of compounds for their biological activity against specific targets. The method automates the process of compound testing, allowing researchers to quickly identify potential drug candidates from vast chemical libraries. HTS can be employed to identify compounds that interact with multiple targets, leading to a better understanding of complex diseases [10].

CHAPTER 2

Recent Advances in *In-Silico* Drug Repurposing: Leveraging Computational Tools for Enhanced Therapeutic Discovery

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Abstract: Drug repurposing, or repositioning, is a key strategy in biomedical innovation, leveraging existing approved drugs for new therapeutic uses. This approach significantly cuts development costs and shortens the lengthy traditional drug approval timelines. This approach is especially valuable for rare diseases, addressing unmet needs by overcoming the high costs and challenges of developing new treatments. Drug repurposing optimises drug utility and strategically allocates limited research resources. *In silico* techniques have unlocked extraordinary opportunities in this domain, offering a pathway to identify and validate new therapeutic indications. This can expand treatment options and greatly improve the precision of targeted therapies. The field of drug development has undergone an enormous shift with the introduction of *in silico* techniques. Advanced computational techniques, such as artificial intelligence (AI), machine learning (ML), and chemo-informatics, have driven a paradigm shift in identifying and developing new drug applications. These technologies use vast databases and advanced bioinformatics to uncover elusive drug-target interactions. Tools like Reactome and the Kyoto Encyclopaedia of Genes and Genomes (KEGG) have proven to unravel the complex interactions governing drug efficacy. The focus on a holistic approach, integrating diverse sets of biological, clinical, and epidemiological data, has been instrumental in opening new avenues for repurposing opportunities. Success stories highlight the impact of *in silico* drug repurposing, showcasing its role in meeting unmet medical needs and transforming therapeutic development. While *in silico* drug repurposing prospects are undeniably promising, the field is not without its challenges. The conclusion explores current challenges and potential solutions, highlighting how innovative computational approaches can revolutionise drug development, enhancing efficiency, cost-effectiveness, and speed. The ultimate aim is to advance personalised medicine and improve patient care with unprecedented precision.

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Keywords: Bioinformatics tools, FDA approved drugs, Pharmaceutical repositioning, Precision therapies, Therapeutic innovation.

INTRODUCTION

Definition of Drug Repurposing

Sir James Black, the 1998 Nobel Prize in Physiology and Medicine Laureate, famously stated, "The most fruitful basis for the discovery of a new drug is to start with an old drug." Drug repurposing leverages this principle to accelerate the development of new treatments for various diseases and conditions. By bypassing the traditional drug discovery process, which is often time-consuming and costly, drug repurposing utilises existing knowledge about the safety and pharmacokinetics of approved drugs [1]. Drug repurposing, also known as drug repositioning, is the process of identifying new therapeutic uses for existing drugs that were originally developed for a different indication [2]. The National Center for Advancing Translational Sciences (NCATS) in the USA defines drug repurposing as "studying the drugs that are already approved to treat one disease or condition to see if they are safe and effective for treating other diseases" [3]. This definition excludes substances that have not yet undergone clinical investigation, specifically those held in chemical libraries by academic and industry research groups for screening to identify new biological properties. Drug repositioning excludes any structural modification of the drug. Instead, it utilises the drug's existing biological properties for which it has already been approved, potentially with a different formulation, at a new dose, or *via* a new route of administration. Alternatively, it can exploit the side properties of a drug responsible for its adverse effects to find new therapeutic uses [4].

Repurposing existing drugs offers numerous advantages. The safety, efficacy, and toxicity of such drugs have typically been extensively studied, providing substantial data to support gaining approval from regulatory bodies such as the United States Food and Drug Administration (FDA) or the European Medicines Agency (EMA) for new indications. The availability of this data offers hope to patients with rare cancers for whom the development of new treatments would be prohibitively expensive. Additionally, repurposed drugs generally receive approval more quickly, within 3 to 12 years, and at a reduced cost of 50-60% [5]. This expedited process and cost efficiency make drug repurposing a highly attractive strategy in modern pharmaceutical development.

Strategic Advantage of Drug Repurposing

Drug repurposing is increasingly recognised as a valuable approach within the pharmaceutical industry. Traditionally, pharmaceutical companies begin the R &

D (Research & Development) process by targeting a specific condition and focusing their resources on modifying it appropriately. However, the effects of pharmaceuticals often extend beyond their initial targets due to their ability to influence various biological processes. Pharmaceutical compounds, including small molecules and other active agents, can interact with multiple genes, proteins, and molecular pathways, thereby affecting the genotype and phenotype of humans in both controlled and unforeseen ways. This inherent characteristic of drugs creates opportunities to explore their potential for treating conditions other than those for which they were originally developed.

Approximately 45% of drug development failures are attributed to safety or toxicity issues [6]. Addressing these safety concerns and potentially reducing the average drug development time by 5-7 years makes drug repurposing an attractive strategy. This approach offers significant benefits to both drug developers and patients. For developers, it presents a more cost-effective and less time-consuming path to bringing drugs to market. For patients, it ensures quicker access to treatments with well-documented safety profiles. Pharmaceutical companies possess core expertise in clinical development and are well-positioned to systematically pursue drug repurposing. Leveraging partnerships and collaborations can enhance their chances of identifying successful repurposing candidates. The recent surge in biomedical data, including genomic information and big data from electronic medical records (EMRs), claims data, social media, and sensor data, has created a critical substrate for systematically assessing repurposing candidates. Advances in analytical methods further support this data-driven approach [7]. The accumulation of diverse data types enables a holistic understanding of drugs and diseases, facilitating effective repurposing strategies. This data-driven methodology increases the productivity of drug discovery and aligns with the industry's mission to efficiently bring effective treatments to patients.

Historical Milestones

Aspirin, marketed by Bayer in 1899 as an analgesic, is considered the oldest example of drug repurposing. In the 1980s, researchers repurposed aspirin as an antiplatelet aggregation drug at low doses [8]. Aspirin is now used to prevent heart attacks and strokes in patients with cardiovascular disease. Aspirin may soon be repositioned for use in oncology. Studies have shown that daily aspirin administration for at least five years can prevent the development of various cancers, particularly colorectal cancer [9]. Aspirin's protective effect against cancer is believed to result from COX-2 inhibition, which blocks the anti-apoptotic effect of COX-2 on malignant cells and promotes their apoptotic death.

CHAPTER 3

Computational Design of Therapeutic Peptides

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Abstract: Peptides have emerged as promising candidates in therapeutics and diagnostics due to their unique properties. They offer advantages over traditional small molecule drugs, including high specificity, reduced off-target effects, biocompatibility, and biodegradability. However, peptide-based therapeutics also present challenges of low stability, delivery, synthesis, membrane permeability, and oral availability. Many strategies such as cyclisation, incorporation of *N*- and *C*- terminal protecting groups, and non-standard amino acid design of appropriate peptide delivery systems have been adopted to mitigate these challenges. Computational techniques enable faster design and development and reduce experimental costs involved in drug discovery and design and therefore, have gained prominence for *in-silico* testing and development of peptides. This chapter explores methods involved in the computational design of therapeutic peptides, with significant attention to peptide-specific molecular docking tools, lead optimization strategies, and Molecular Dynamics (MD) simulations. We also discuss the applicability of peptides in biomedicine and review specialized peptide databases, exemplified by the case study of the PepEngine. A compendium of Machine Learning (ML) tools used in peptide drug design highlights the latest advances in the field. Peptide-based therapeutics are highly promising due to their lower bioaccumulation and toxicity along with high specificity. Many peptide-based drugs, such as insulin, oxytocin, and enfuvirtide, have been widely accepted for therapeutic applications. By mitigating the challenges faced in peptide design and aiding in the development of novel therapeutic peptides, computational approaches have played an instrumental role in the peptide drug development process.

Keywords: Computational drug design, Computational drug development, Computational peptide design, *In-silico* peptide analysis, Peptides, Peptide design, Peptide docking, Peptide databases, Peptide stability, Peptide delivery.

1. INTRODUCTION

Peptides are small fragments of protein; they act as signaling entities in biological systems and can be used in diverse therapeutic applications as well as founda-

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Zaheer Ul-Haq and Angela K. Wilson (Eds.)

tional units for functional biomaterials [1]. Bioactive peptides with specific activities can be designed for use in the pharmaceutical sector and therapeutic biomedical research. Peptides have been used for different therapeutic applications- some notable examples are exendin-4 and pramlintide for diabetes [2, 3], enfuvirtide for the treatment of AIDS [4], bortezomib for the treatment of myeloma [5], and leuprolide for the treatment of prostate cancer [6]. Peptide hormones such as insulin, oxytocin, calcitonin, vasopressin, *etc*. are popular drugs for the treatment of diabetes, psychiatric disorders, osteoporosis, and diabetes insipidus, respectively [7 - 11]. Cell-penetrating peptides have lately been extensively used as carriers for intracellular delivery of cargo such as proteins, nucleic acids, and therapeutic agents. Short peptides have also been reported to form nanospheres, nanotubes and hydrogels for efficient delivery of drugs. In comparison to small molecules, peptides possess increased potency, selectivity, a broader range of targets, potentially lower toxicity, and lower accumulation rates making them favorable for therapeutic applications. There are however certain drawbacks to peptides such as low bioavailability, inability to pass through the cell membrane and blood-brain barrier, lower stability, *etc*. [1, 12 - 14]. Out of a total of 315 new drugs approved by the FDA in the time period 2016-2022, 26 were peptide-based drugs. Additionally, there are approximately 200 peptides in various stages of clinical development and 600 peptides undergoing preclinical studies. The increasing acceptance of "peptides as drugs" is evident from the fact that 5 peptides were approved by the FDA during 2023, which include Trofinetide (Daybue™) that was approved for the treatment of a rare genetic disorder namely, Rett syndrome [15]. This growing interest is reflected in the increasing number of scientific publications and patents related to peptides, with notable reviews on the subject [13, 14]. Currently, there are around 114 FDA-approved peptide-based drugs available for therapeutic and diagnostic use in the market.

There are various strategies employed in the design and development process of peptide-based drugs. The current chapter aims to delve into the computational design of peptides, highlighting their potential in therapeutic and diagnostic applications. The chapter begins with a brief history of peptide design and their common applications followed by the methods and tools involved in their design. We also briefly discuss the challenges involved in their design and highlight the advantages such as high specificity, reduced off-target effects, and biocompatibility, making them valuable tools in targeting complex diseases. The chapter mainly focuses on methods involved in computational peptide design. It covers the development of pharmacophores, virtual screening, peptide-specific molecular docking and lead optimization strategies, MD simulations, development of ML-based predictive models for peptide design, *de novo* peptide design, and design of inhibitors for protein-protein interaction (PPI) complexes. By presenting a comprehensive overview of computational peptide design

methodologies, the chapter aims to demonstrate the power and versatility of computational tools in modern drug discovery, offering potential strategies in the development of therapeutic peptides and elucidating the application of computational techniques in peptide drug development.

2. BRIEF HISTORY OF PEPTIDE BASED DRUG DEVELOPMENT

In the early 1920s, the first medicinal use of insulin for the treatment of Type 1 diabetes marked the beginning of the field of peptide-based therapeutics. Two peptide hormones of the pituitary gland, namely, oxytocin and vasopressin were first extracted and synthesized by Du Vigneaud who was awarded a Nobel Prize in Chemistry for the same in 1955. While oxytocin is responsible for uterine contraction and milk-secretion, vasopressin helps to reabsorb water from the tubules in the nephrons. The synthesis was performed using the conventional solution phase method which is quite challenging, especially for longer peptides [16]. Afterward, with the seminal contribution of Merrifield in 1963 in the form of a new approach to synthesizing peptides, namely "Solid-Phase peptide synthesis", the field of peptide-based drugs received a new impetus [17]. During the period of 1970-1980, also known as the golden age of small molecule pharmaceuticals approximately ~20 new orally available drugs were approved per year. Though the importance of peptides as key biological mediators grew due to their selectivity, low toxicity, and potency, there were still certain limitations to the development of peptide-based therapeutics owing to poor bioavailability, low stability, short circulation time, and most importantly, lack of economically feasible means for large scale manufacturing. This eventually led to stagnation in peptide drug development. Only a few peptides such as human insulin produced using recombinant DNA technology in 1982, synthetic gonadotropin-releasing hormones namely, leuprolide (1985) and goserelin (1989) and synthetic somatostatin- octreotide (1988) were approved as drugs. With the start of the 21st century, increasing number of peptide drug approvals were granted by the FDA. Few examples include enfuvirtide (Fuzeon or T20) a 36 amino acid membrane fusion inhibitor for HIV-1 treatment approved in 2003, Ziconotide (25 mer) which binds to *N*-type calcium channel used for the treatment of chronic pain approved in 2004, *etc*. [18]. As many as six GLP-1 analogs such as exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide and semaglutide were approved between 2003 and 2017 for the treatment of Type 2 diabetes mellitus. The number of peptides entering clinical trials doubled in 2000-2010 compared to the previous decade [16]. Fig. (**1**) depicts the progress in the approval of peptide-based drugs over the years.

CHAPTER 4

Advancing Drug Discovery through Molecular Dynamics Simulations: A Comprehensive Approach

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Abstract: Drug development is a critical endeavor within the pharmaceutical sector. Integrating computational approaches has significantly reduced both the time and costs associated with discovering new drugs. This chapter starts by highlighting the pivotal role of multiscale molecular simulations in determining drug-binding sites on target macromolecules and elucidating the mechanisms underlying drug actions. It then delves into molecular dynamics (MD) simulation methods, focusing on drug design strategies based on structure and ligand considerations. Additionally, the chapter explores the development of advanced analysis tools and the integration of machine learning techniques, which collectively enhance the efficiency of the drug discovery process. Traditional MD analysis methods, such as root mean square deviation (RMSD) of backbone atoms, root mean square fluctuation (RMSF), radius of gyration, and interaction analyses, are extensively used to monitor structural changes and convergence during simulations. Beyond these, newer trajectory mapping methods offer intuitive and conclusive ways to visualize protein simulations by plotting the protein's backbone movements as heat maps. Molecular dynamics simulations utilize physical algorithms to model chemical systems and compute atomic and molecular properties. In drug design and discovery, computational chemistry methods are employed to predict mechanisms such as drug binding to targets and the chemical properties of potential drug candidates. The combined use of traditional and novel analysis methods is anticipated to have wide applications in deriving meaningful insights from protein MD simulations across fields like structural biology, biochemistry, and pharmaceutical research. The chapter concludes with several case studies and success stories demonstrating the application of MD simulations as a powerful computer-aided drug discovery tool in diabetes and Alzheimer's treatments.

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Zaheer Ul-Haq and Angela K. Wilson (Eds.)

Highlighted examples include achievements in anticancer, antibacterial, anti-leishmaniasis, and antiviral drug design, showcasing the impact of *in silico* drug design in developing innovative therapies.

Keywords: Alzheimer's disease , Anticancer, Antimicrobial, Drug discovery, *In silico* drug design, MD simulations.

INTRODUCTION

Molecular dynamics (MD) simulations are a computational method used to study the physical movements of molecules and atoms over time. By solving Newton's equations of motion for a system of particles, MD simulations provide detailed, time-resolved information on the dynamical evolution of molecular systems. The technique involves defining a potential energy function (or force field) that represents the interactions between particles and then numerically integrating the equations of motion to simulate trajectories [1].

MD simulations explore various phenomena in chemistry, biology, materials science, and physics, such as protein folding, drug binding, phase transitions, and transport properties. These simulations allow for the prediction of structural, thermodynamic, and kinetic properties of molecular systems at the atomic scale, often serving as a bridge between theoretical models and experimental observations [2].

The accuracy of MD simulations largely depends on the quality of the force field and the time scale over which the simulation is performed. The method is computationally intensive but can be parallelized effectively, making it feasible for large and complex systems with the aid of high-performance computing resources [3].

Integrating molecular dynamics (MD) simulations with experimental techniques like X-ray crystallography, cryo-electron microscopy (cryo-EM), and biophysical assays, alongside computational methods such as quantum mechanical calculations, virtual drug screening, and machine learning, offers powerful insights into drug discovery [4]. However, challenges persist in reconciling discrepancies between experimental data and MD results due to differences in dynamic *versus* static representations of biomolecules. Data format incompatibility and high computational costs further hinder seamless integration, especially when scaling simulations or performing large-scale drug screenings [5]. To improve consistency, multiscale modeling, data fusion techniques, and machine learning can be employed to enhance accuracy and streamline data interpretation. Additionally, standardizing data formats and fostering interdisciplinary collaboration is critical to overcoming computational resource

limitations and optimizing model validation. Addressing these challenges will increase the efficiency and success rate of drug discovery by leveraging the complementary strengths of MD simulations and experimental methodologies [6].

BASIC PRINCIPLES OF MD SIMULATIONS

The basic principles of MD simulations revolve around using classical mechanics to model the behavior of atoms and molecules over time in specific systems to be as actual as possible. Therefore, environments such as the setting of the system, the type of ensemble, velocities of atoms, the numerical algorithm, the boundary condition, and so on must be decided as requirements for the molecular dynamic simulation. Here are the key concepts:

Force Field

The force field, or interatomic/intermolecular potential energy function, is a major component of MD simulations. It describes the interactions between particles, including bonded interactions (stretching bond and bending of angles) and non-bonded interactions (electrostatic interactions and van der Waals forces) (Fig. **1**) [7, 8].

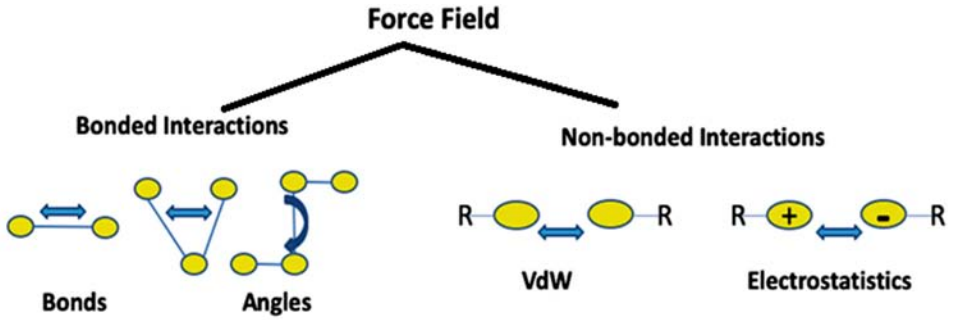

Fig. (1). Components of a force field represent bonded and non-bonded interactions in molecular simulations [7].

The force acting on each particle is derived from the gradient of this potential energy, which elucidates the correlation of the potential energy with the coordinates of atoms. In drug discovery and design, non-reactive or classical force fields are commonly used for host-guest MD simulations, which are commonly used to simulate a wide range of small molecules or drugs with enzymes, proteins, lipids, and polymers [9]. Briefly , Table **1** below discusses the five widely used force fields: Amber [10], Chemistry at Harvard Macromolecular Mechanics (CHARMM) [11, 12], Groningen Molecular Simulation (GROMOS) [13], all-atom optimized potential for liquid simulations (OPLS-AA) [14, 15], and

CHAPTER 5

Advances in Quantum Mechanical Methods for the Computation of Protein-Ligand Binding Free Energy

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Abstract: The computational prediction of protein-ligand binding affinities has become a key step in the successful virtual screening of compounds for drug development and discovery. However, consistently accurate protein-ligand binding affinity calculations are challenging in part due to, 1) the large protein/ligand conformational space that must be sampled/searched, 2) the inconsistent accuracy of classical molecular mechanics potentials, commonly used to compute binding affinities, especially when π-stacking, halogen interaction, or metal centers are present, or when polarization or charge transfer is significant. In this chapter, recent advances in quantum mechanical methods that facilitate their application to protein-ligand binding free energy calculations are discussed, with an emphasis on fragmentation methods and their combination with conformational search algorithms. The accuracy of these new approaches with respect to the prediction of protein-ligand binding free energy is evaluated. New tools to improve workflow and speed up calculations are also discussed.

Keywords: *Ab initio* quantum mechanics, Drug design, Entropy, Fragmentation methods, Mining minima, Protein-ligand binding, QM-VM2, Solvation.

1. INTRODUCTION

The research and development of new drugs is an expensive and time-consuming process. The estimated cost can routinely reach hundreds of millions of dollars [1, 2], and the time spanned between the initial screening stages and launch of the

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Zaheer Ul-Haq and Angela K. Wilson (Eds.)

drug can span over a decade [3]. In order to reduce both the time and monetary costs, fast and accurate screening methods are essential in the early stages of the process. The initial stages of the drug design process are discovery of hit compounds [4], which involves the screening of large libraries of compounds (high throughput screening) to identify those that are active towards the target, followed by lead optimization, where the most promising hit compounds are identified and refined into potential drug candidates by modifying their chemical structure. In the latter stage, highly accurate predictions of the properties and activities of the compounds would significantly speed up the development of drug candidates subject to preclinical studies.

Virtual screening methods, known for their cost-effectiveness and time efficiency, have become an essential part of these early stages of drug discovery [5 - 10]. By computationally ranking compounds, these methods reduce (sometimes significantly) the number of compounds requiring synthesis and subsequent experimental validation *(e.g.*, *in vitro* and *in vivo* biological assays). One of the key variables that needs to be accurately computed during the lead optimization procedure is the protein-ligand binding free energy, as it provides a quantitative measure of how tightly a compound binds to a target site. While rapid advances in computational power and algorithmic innovations have dramatically improved the accessibility of free energy computations, challenges persist. Robust, high-accuracy methods remain resource-intensive, which underscores a pressing need for computational approaches that are efficient as well as accurate. A comprehensive review of all computational approaches used to predict protein-ligand binding free energies is beyond the scope of this chapter given the breadth and complexity of the field, but the reader is referred to various reviews for a survey of these methods [7, 10 - 26].

This chapter will explore the status of protein-ligand binding free energy computations, highlighting the physics and statistical mechanics principles that current methods are built upon, and how their accuracy can be improved by introducing quantum mechanics (QM). Developments for the prediction of absolute binding free energy (ABFE) methods, with a focus on end-point methods, will be presented in Section 2. In Section 3, some of the persistent challenges in the field are discussed, namely, accurate, but tractable, computation of QM-based potential energy *E,* adequate conformational sampling/search, calculation of solute entropy, and accurate description of solvent effects. State-of-the-art quantum mechanics-based methodologies designed to address these challenges, with an emphasis on fragmentation methods, are described in Section 4. Section 5 will showcase developments of solute entropy calculations and conformational search algorithms. Section 6 will briefly highlight some popular MM and QM solvation models, including the treatment of explicit solvent

molecules. In Section 7, the introduction of QM potentials in the VM2 mining minima method [27] will be introduced, providing a significant step toward the routine use of QM-based ABFE calculations for protein-ligand systems.

2. APPROACHES TO THE COMPUTATIONAL PREDICTION OF PROTEIN-LIGAND BINDING FREE ENERGIES

Computational approaches for calculating protein-ligand binding free energy broadly fall into two categories: 1) relative binding free energy (RBFE) methods, which estimate differences in binding free energies between structurally related ligands, and 2) absolute binding free energy (ABFE) methods, which directly quantify the binding free energy of a ligand to its target. These two categories are briefly discussed in Sections 2.1 and 2.2, respectively.

2.1. Protein-ligand Relative Binding Free Energy (RBFE) Methods ($\Delta\Delta G_{bind}$)

RBFE approaches apply alchemical free energy methods that are built on a thermodynamic cycle (Scheme **1**), calculating the difference in binding free energy between ligands ($\Delta\Delta G_{bind}$). Therefore, one can rank a series of ligands according to their relative binding free energy to the target. Commonly used methods (and their variants) include free energy perturbation (FEP) [15, 17, 28 - 31], and thermodynamic integration (TI) [32, 33]. These methods are rigorously based on statistical mechanics, and they enable the calculation of the free energy differences between two states by gradually transforming one state into another. This transformation is achieved by using a coupling parameter, λ, which interpolates between initial and final states. These unphysical intermediate λ-states enhance sampling overlap for convergence but require that a series of molecular dynamics (MD) calculations be performed at each state for binding free energy prediction. While these methods achieve satisfying agreement with experiment in terms of ligand ranking [34] and have found practical use in industry drug development programs [35, 36], they require the ligand series to be structurally similar (common scaffold). They are also computationally expensive, even though they use conventional classical force fields, due to the extensive MD-based sampling required.

CHAPTER 6

Current Trends in Computational Methods to Discover New Anti-inflammatory Agents Targeting NLRP3 Complex

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Abstract: Inflammation is the body's response against an aggressive chemical, physical, or biological agent . Despite being a natural response, if exaggerated , it can damage the organism, making necessary pharmacology interventions. Several drugs can control inflammation , such as COX inhibitors . However , there is a high incidence of side effects. It is well-established that the assembly of NLRP3 triggers an inflammatory response, leading to various diseases and highlighting its significance as a therapeutic target. Discovering new drugs and potential targets is urgent to overcome these limitations . Inflammasomes such as NLRP3 constituting the innate immune responses, leading to the production of pro-inflammatory cytokines, such as IL-1β and TNFα. Thus, targeting NLRP3 can provide a new anti-inflammatory drug that is safe and free of the COX inhibitor's side effects. It is well-established that the assembly of NLRP3 triggers an inflammatory response, leading to various diseases and highlighting its significance as a therapeutic target. Among the methods used in the discovery of new drugs, Computer-Aided Drug Desing (CADD) is widely used due to its numerous advantages, such as less financial investment and time of discovery, being critical, the ability to be used in any drug discovery campaign, including to search new anti-inflammatory drugs targeting NLRP3. Finally, this review aims to present various computational methods, both traditional and current, that facilitate the rational design and discovery of new NLRP3 inflammasome inhibitors. This contributes to developing innovative anti-inflammatory drugs that may be used in future clinical applications.

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Keywords: Anti-inflammatory drugs, CADD, Inflammasomes, Neuronal inflammation, Molecular dynamics, Molecular docking, NLRs, PRRs, PAMPs, QSAR.

INTRODUCTION

The inflammatory response and its vast array of components constitute one of the most complex biological processes encountered in medicine , defined as an adaptive response triggered by harmful events, including infection, tissue injury, stress, and others [1, 2]. In this way, the inflammatory response constitutes a form of defense of the body a ssociated with maladaptive or non-adaptive features that are indissociable from the "healthy" phenomena and present themselves in novel environmental conditions not initially present during the evolution of inflammation [1, 3]. Although inflammation should ideally stay confined to controlled responses, it is often dysregulated, and discerning pathological from physiological inflammatory conditions is a considerable challenge. Inflammation can be limited to an acute event or extend into chronic inflammation, a state responsible for many autoimmune conditions and cardiovascular and metabolic diseases [1, 4].

To recognize potential threats, cells constantly survey their environment using sensors named pattern recognition receptors (PRRs), which are present in complex multimeric protein complexes called inflammasomes. These inflammasomes consist of the apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and a *C*-terminal caspase recruitment domain (CARD). Belonging to these sensor receptor proteins, there is a class of proteins called nucleotide-binding domain leucine-rich repeat-containing receptors (NLRs), and the most extensively studied inflammasome contains the nucleotide-binding domain leucine-rich repeat-containing protein 3 (NLRP3), thus being titled the NLRP3 inflammasome [5 - 7].

When the inflammasome is activated by either of its canonical or non-canonical pathways, all three pieces are assembled through protein-protein interactions, and the activated caspase cleaves pro-interleukins into their active forms, specifically producing IL-1β and IL-18. Pyroptosis, a specific form of programmed cell death in inflammation, may occasionally be triggered by NLRP3, as it is one of many inflammasomes whose caspase-1 module can set off Gasdermin D, which, in turn, opens pores in a cell's lipid bilayer. Nevertheless, Gasdermin D is not reliant on NLRP3 activity and may also trigger this inflammasome through a non-canonical activation pathway caused by lipopolysaccharides from Gram-negative bacteria entering the cell [5, 8 - 10].

The NLRP3 inflammasome is involved in several different pathological processes. During acute or chronic kidney injuries caused by unilateral ureteral

obstruction, NLRP3 may be involved in cell death [11]. In diabetic cardiomyopathy, NLRP3 expression is induced by high glucose levels , and its' caspase-1 activation causes pyroptosis in myocardial cells [12]. In atherosclerosis, NLRP3 exhibits increased expression in the aorta, plaques, and mononuclear cells while being identified as responsible for the increased production of IL-1β, a proatherogenic cytokine [13 - 15]. In rheumatoid arthritis, NLRP3 is highly expressed and activated in affected joint tissues. At the same time, pyroptosis and overproduction of inflammatory cytokines triggered by this inflammasome may be involved in disease occurrence and progression [16].

NLRP3 is also present in aging-related effects due to inflammatory and metabolic alterations that feed into a cycle of redundant signaling between NF-κB-mediated transcription of NLRP3 activated by IL-1-family cytokines since NLRP3 activation heightens the expression of IL-1β and IL-18; this feeds back into NF-κB signaling [17]. Changes in circadian rhythm during aging negatively affect melatonin secretion, occasionally generating several pro-inflammatory effects, which may include NLRP3 inflammasome activation [18]. Disproportionate activation of the NLRP3 inflammasome activation is also involved in tumor pathogenesis. For instance, in breast cancer, IL-1β production provided by NLRP3 activation promoted tumor growth and metastasis. Paradoxically, however, NLRP3 activity simultaneously exhibits anti-tumorigenic effects. In colorectal or colitis-associated cancer, its activity inhibits metastatic growth, while its inhibition results in tumor proliferation and worse disease outcomes [13, 19] .

Concerning gout arthritis, NLRP3 activation is caused by monosodium urate crystals deposited in joints , and increased IL-1β concentrations result in neutrophil infiltration, articular swelling, and pain [20]. NLRP3 dysfunction also plays an essential role in endometriosis, as inflammatory microenvironments promoted by NLRP3 activity in endometrial tissue may contribute to lesions becoming more frequent and severe. Polycystic ovarian syndrome pathogenesis is also affected by NLRP3 due to NF-κB signaling and increased IL-18 expression, potentially aggravating the disease and exacerbating infertility symptoms [21].

In Alzheimer's disease, NLRP3 plays a crucial role as its activation caused by amyloid plaque formation precedes tau pathology, inducing hyperphosphorylation and aggregation of tau proteins in an IL-1β-triggered cascade [22]. Meanwhile, in Parkinson's disease, NLRP3 abnormal activation promoted by the previously mentioned circadian dysfunction may intensify dopaminergic neuron (DA_N) destruction. As aggregated α-synuclein is recognized by NLRP3 as one of the damage-associated molecular patterns, caspase-1 activation may fracture α-synuclein further, which, in turn, activates other inflammasomes, propagating a

CHAPTER 7

Computational Modelling of Photophysical Processes

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Abstract: Information of the electronic structure origin of the photophysical properties is of paramount importance to understand the intricate physical/chemical transformations a molecule undergoes in the process of light absorption. Moreover, experimental analysis of excited states involved in the photophysical phenomenon is often difficult for their transiency, and hence quantum chemical information of the excited state emerges as the only tool for an in-depth understanding of the photoexcitation mechanism. Exploration of the ground (S_0) and excited electronic states of molecules and subsequent estimation of absorption/emission wavelength need rigorous standardization of computational methodology. Hence, the chapter offers a general description of the state-of-the-art methodologies to explore the photophysical properties of the molecules, which are promising candidates for important applications. This bridging would ultimately aid in understanding the complex excited state phenomena occurring in different materials with much clarity fostering their development in varied verticals like medicine, biotechnology, energy, *etc*. Fluorescent active molecules and their subsequent structure-activity correlation would be the prime focus of the present piece thus rendering a suitable explanation of their excited state properties through theoretical modelling and explanation at the level of electronic structure. Application of the standardized methodology on a few chosen molecules of probable industrial importance such as the smallest known Green Fluorescent Protein (GFP), 3-hydroxy-4-pyridine carboxaldehyde (HINA), 2-hydroxy-3-naphthaldehyde semicarbazone (2H3NS), *etc*. would provide ample scope to validate the computational data through comparison with the already available experimental dataset. The theoretical interpretations of photo-responsiveness of future industrially important molecules through standardized computational methodology are likely to be a colossal accrue of the current book chapter.

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Keywords: Computation, Density functional theory, Excited state, Fluorescence, Photophysics.

INTRODUCTION

Absorption of light by photoactive molecules is an important physical phenomenon with paramount applications. The photo-excited state can engage in diverse de-activation processes to return to the ground electronic state (S_0) without altering the chemical identity of the molecules in certain instances giving rise to *photophysical processes* [1]. Vibrational relaxation (VR) occurs when a molecule returns from a higher to a lower vibrational state through non-radiative pathways [2, 3]. In non-radiative VR, excess energy from the excited electron is transferred to vibrational modes as kinetic energy, which is then dissipated as heat through collisions. This process happens rapidly after photon absorption. Radiative deactivation involves the release of excess energy as radiation (visible or UV) when the molecule returns to a lower electronic state [4, 5]. Whether this is classified as fluorescence or phosphorescence depends on the spin multiplicity of the electronic states [6, 7]. Application of the photophysical properties needs *a priori* understanding of the mechanism, which can be partly obtained from the experiment. However, the transiency of the excited states involved in the photophysical process necessitates theoretical investigation of the photoexcitation event and subsequent correlation between theoretical findings and experimental data [8 - 11]. Several research groups are focused on conjoint works of explaining such experimental observations through theoretical computations. In a recent work, Insuasty *et al.* [12] clearly demonstrated intramolecular and twisted intramolecular charge transfer (ICT/TICT) in three unsymmetrical 7-(diethylamino)quinolone chalcones experimentally and corroborated the results deploying density functional theory (DFT). A similar correlation of experimental results with theoretical calculations was also reported by Ganai *et al.*, Khopkar *et al.*, Wazzan *et al.,* and others [13 - 15]. Experimental limitations arise when studying transient species with untraceable geometrical configurations during formation. Additionally, molecules often undergo changes in varying conditions during photophysical transformations that cannot be stepwise monitored experimentally. Thus, theoretical modelling becomes essential for understanding reaction dynamics. Quantum chemical computations, providing potential energy curves/surfaces (PEC/PES), can explain absorption and emission bands [16, 17]. Combining computational simulations with experiments helps visualize the complex mechanisms of photophysical processes. This chapter will mainly emphasize the applicability and significance of computational modelling in understanding the photophysical processes through a discussion of the basic computational methodologies and illustrations.

Overview of Photophysical Processes

A radiative transition occurs between two states that have identical spin multiplicity better termed 'fluorescence'. The emission is characterized by a rate constant, k_f, and singlet state lifetime, τ_f^0 (~10^{-7} — 10^{-10} s) [18]. Alternatively, phosphorescence is the transition from the first excited triplet state to the lowest vibrational level of the ground state. The lifetime of an excited triplet state is generally longer τ_f^0 (~10^{-5} — 10 s) than that in fluorescence especially due to the spin forbidden character of transition [7]. However, the process of delayed fluorescence may result from reverse inter-system crossing (rISC) after the triplet population, which shows thermal dependence. This process is generally known as thermally activated delayed fluorescence (TADF) [8 - 11].

The natural radiative lifetime, τ_N, is explained as the reciprocal of the radiative transition probability. The rate constant for fluorescence emission, k_f, in the absence of any deactivating perturbations, is inversely related to the natural radiative lifetime, τ_N, of the molecule, and it is given by Eq. (**1**).

$$k_f = \frac{1}{\tau_N} = \frac{1}{\tau_f^0} \quad \textbf{(1)}$$

Similarly, in the case of phosphorescence, the intrinsic lifetime of triplet state (T_1) τ_P^0, is the reciprocal of the rate constant for phosphorescence emission, k_p. In the radiative processes, usually, the emission takes place from the lowest excited state to the ground state of a specific multiplicity (S_0), which is known as *Kasha's rule* [6, 7, 11]. However, violation of this rule has been observed in fluorescent compounds like azulene, thiocarbonyl, dicarbonyl compounds like benzil, anthril, naphthil, *etc.*, and hydroxy flavones, *etc.* A similar violation of Kasha's rule is also observed in the $T_n \rightarrow S_0$ (n>1) transition in the phosphorescence of fluoranthene and ferrocene [18, 19].

The non-radiative transition between the electronic states is a form of electronic relaxation in which the energy is transferred to molecules that collide with the excited molecule and release some of this energy through translational, rotational, or vibrational motion. A radiation-less *internal conversion* (IC) refers to the transition between states that have identical spin multiplicity and the nonradiative transfer from the singlet to the triplet electronic states or vice-versa is called *intersystem crossing* (ISC) [20]. Internal conversion occurs most readily at the intersection point of the two molecular potential energy curves, where the nuclear geometries of the two states are identical [21]. Internal conversion or vibrational relaxation involving $S_n \rightsquigarrow S_{n-1}$ transition within singlet states S_n and S_{n-1} usually occurs rapidly ($k_{IC} \approx 10^{12}$ s^{-1}) when n>1. The $S_n \rightsquigarrow S_{n-1}$ (n>1) transition is more

SUBJECT INDEX

A

ACE inhibitory activities 97
Acetylcholine degradation 149
Acetylcholinesterase inhibitors 147
Acetylsalicylic acid 243, 244
AChE 54, 148
  inhibition 54
  inhibitors 148
Acids 36, 244
  acetic 244
  enolic 244
  propionic 244
  sialic 36
Action, anti-inflammatory 243
Activation 98, 144, 238, 240, 241, 242, 243, 247, 248, 251
  immune system 240
  inflammasome 247
  transcriptional 247
Activity 2, 3, 6, 32, 37, 47, 48, 50, 51, 53, 56, 89, 251, 252, 253, 258, 260
  antimicrobial 89
  antitumor 47
  autoimmune 56
  inflammatory 51
Aggregation, tau protein 147
Alzheimer's disease 37, 43, 57, 130, 145, 146, 147, 148, 150, 157, 238
  combat 147
  medication 146
  pathology 146
  therapies 148
AMBER software 251
Analysis 17, 21, 25, 108, 198
  cheminformatics 21
  computational 17, 25, 108
  thermodynamic 198
Androgen receptor (AR) 35, 39, 57
Anemia in chronic kidney disease 78
Anti-inflammatory activity 14, 252
Antimicrobial 89
  drug discovery and functional analysis 89
  peptide databases 89
  phytopeptides 89
ATPase activity 247
Autoimmune diseases 39, 40, 45, 50, 54, 56, 77

B

Bioinformatics tools streamline 19
Biological 4, 21, 27, 29, 260, 289
  activity prediction 260
  molecules, fluorescent 289
  networks 4, 21, 27, 29
Boundaries of drug repurposing 15
Bowel disease 40, 45, 51, 56
  inflammatory 40, 56
  treating inflammatory 51
Bowel disorders 77
Breast cancer 35, 52, 53, 238
  metastatic 53

C

CADD 6, 7
  techniques 6
  tools 6, 7
Cancer(s) 13, 34, 35, 41, 42, 45, 47, 52, 53, 54, 56, 75, 77, 80, 81, 82, 140, 141, 142
  brain 35
  gemcitabine-resistant bladder 52
  pancreatic 52
  skin 47
  therapy 34, 35, 41, 47, 52, 75, 81, 82, 141, 142
  treatment 35, 47, 52, 53, 56
Carcinoma, renal cell 7, 47
Cardiovascular 13, 39, 44, 49, 50, 55, 75, 77
  death 44, 55
  disease management 55
  diseases 13, 39, 44, 49, 50, 55, 75, 77

Central nervous system (CNS) 39, 49, 244, 245
Charge transfer (CT) 166, 170, 173, 178, 181, 183, 185, 187, 188, 273
  effects 185
  processes 273
Chemical 19, 99, 175
  bonding interactions 175
  crosslinking mass spectrometry 99
  informatics techniques 19
Cheminformatics and pharmacophore modeling tools 30
Chemotherapy 47, 52
Chronic 7, 41, 44, 50, 52, 53, 57, 78, 142, 143
  kidney disease (CKD) 50, 78
  lymphocytic leukaemia (CLL) 53
  metabolic disorder 143
  myeloid leukemia (CML) 7, 41, 52, 57, 142
  stable angina 44
Chymotrypsin 107
Circadian dysfunction 238
Clinical data analysis tools 29, 31, 32
Commercial cloud computing (CCC) 291
Computational 2, 8, 16, 18, 21, 23, 71, 73, 74, 83, 84, 86, 109, 251
  techniques 2, 8, 18, 21, 71, 73, 251
  tools 16, 23, 73, 74, 83, 84, 86, 109
Computer 182, 206
  aided combinatorial chemistry methods 182
  hardware/software 206
Convolutional neural network (CNN) 86, 102, 103, 104, 105, 259
Coulomb and polarization 187
  components 187
  effects 187
Coulombic forces 133
Coulomb's law 133
COX inhibitors 236
Cytokines, proinflammatory 247

D

DAMPD database 89
Density-functional tight-binding (DFTB) 178, 180, 188
Diabetes 73, 75, 90, 143, 144
  mellitus 73
  therapy 75, 90, 143, 144
Diabetic cardiomyopathy 238
Disorders 6, 37, 43, 49, 54, 55, 72
  neurodegenerative 49
  neurological 6, 37, 43, 49, 54, 55
  psychiatric 72
Disruption, sensing 153
Distance fluctuation (DF) 259
Distributed multipole analysis (DMA) 183
Drugs 12, 13, 14, 15, 16, 17, 18, 19, 21, 28, 31, 32, 33, 34, 36, 37, 38, 40, 41, 48, 52, 71, 153, 157, 239, 244, 246
  anti-influenza 48
  anti-malarial 36
  antihypertensive 14
  antimalarial 157
  antiplatelet aggregation 13
  antiviral 153
  innovative anti-inflammatory 239, 246
  traditional small molecule 71
Duschinsky 275, 276, 277, 285
  rotation 276, 277, 285
  transformation 275
Dysfunctions, thyroid 81

E

Effects 13, 34, 35, 41, 49, 52, 149, 238, 244, 258
  aging-related 238
  anti-angiogenic 41
  anti-apoptotic 13
  anti-inflammatory 244
  anti-tumor 34
  anti-tumorigenic 238
  immunomodulatory 52
  inhibited gout-associated NLRP3 258
  inhibitory 35
  neuroprotective 49, 149
  pro-inflammatory 238
  renal 244
Efficacy, radiotherapy 52
Electron 97, 133, 180, 276, 277, 281, 282
  correlation, mutual 277
  density 97, 133, 180, 276, 281, 282
Electronic 25, 26, 29, 274, 275, 276, 285, 288
  health records (EHRs) 25, 26, 29
  transitions 274, 275, 276, 285, 288
Electrostatics and charge transfer 181
Emission tomography 81
Energy, thermodynamic 282
Enzymes 107, 242

angiotensin-converting 107
inflammatory 242

F

Failure, therapeutic 142
FDA-approved 72, 76
peptide-based drugs 72
peptide drugs 76
peptides 76
Fluorescence 271, 272, 287
emission 271, 287
spectroscopy 272
Follicular lymphoma (FL) 53
Förster resonance energy transfer 272
Free energy 168, 191, 200, 203
end-point method, established 191
perturbation (FEP) 168, 203
processing 200
Function, mitochondrial 50

G

Gene expression 26, 32, 287
Generative adversarial network (GANs) 24, 29, 83, 85
Genetic data and molecular docking techniques 40
Genome-wide association studies (GWAS) 40
Genomics 5, 17, 18, 20, 26, 32, 34
aggregating 26
Glutamate neurotransmission 43, 49
Green fluorescent protein (GFP) 269, 287, 288
Groningen molecular simulation (GROMOS) 131

H

Heart failure 44, 50, 55
symptomatic 55
High-throughput screening (HTS) 3, 5, 96, 239
methods, traditional 96
virtual 239
HIV 47, 48, 74, 178, 182, 199, 202, 203, 204, 205
1 protease 182, 199, 202, 203, 204, 205
protease 205
protease enzyme 48
protease inhibitors 47, 48, 74
protease-ligand 178
reverse transcriptase 48
Hypoxia-inducible factors (HIFs) 40

I

Immune system 39, 47, 51, 56, 243
Immunosuppressive peptides 91
Infections 36, 42, 53, 75, 152, 153, 155, 156, 237, 247, 260
bacterial 53, 152, 153
microbial 75
parasitic 155, 156
respiratory 53
skin 53
Infections therapy 152
parasitic 152
Infectious diseases 6, 35, 42, 47, 53, 152, 246
Inflammation 39, 40, 44, 50, 54, 236, 237, 239, 240, 243, 245, 246, 255
chronic 237
microglia-induced 255
Inflammatory 40, 51, 56, 238, 242
bowel disease (IBD) 40, 51, 56
cytokines 238, 242
microenvironments 238
Ingenuity pathway analysis (IPA) 22
Inhibition of kinase proteins 141
Inhibitors, hydroxylase 40
Inter-fragment interaction energy (IFIE) 181
Intermolecular 132, 133, 142, 183, 185, 282, 286, 289
energy transfer (IET) 286
hydrogen bonds 142
perturbation theory 183, 185
proton transfer 289
Ischemic heart disease 50

J

JAK-STAT pathway 51, 243
Japanese encephalitis virus (JEV) 36

K

Kinetic energy, exact electronic 282

L

Leukaemia 7, 41, 52, 53, 142
  acute lymphoblastic 52
  chronic lymphocytic 53
  chronic myeloid 7, 41, 142
Ligand-based 2, 92, 239
  drug design (LBDD) 92, 239
  virtual screening 2
Lipinski's rule 103, 258

M

Machine learning 3, 24, 129, 255, 258, 259
  approaches 258, 259
  library in Python 24
  methods 255
  techniques 3, 129
Malaria parasite therapy 155
MAPK pathway 243
Migration inhibitory factor (MIF) 49
Mitogen-activated protein kinase (MAPK) 240
MRI-detected brain lesions 51
MTT assay 35
Multi-constraint molecular generation (MCMG) 259
Multi-reference configuration interaction (MRCI) 280
Mutations 21, 137, 140, 141, 142, 152, 156
  drug-resistant 156
Myocardial infarction 44, 50

N

Natural language processing (NLP) 27, 104
Network analysis tools 22, 27, 30, 32
Networks 4, 21, 22, 24, 27, 143, 256
  allosteric signaling 143
  metabolic 27
Neural networks 3, 24, 102, 104, 105, 259
  deep 104, 105
Neuroendocrine tumors 80
Neurological peptide databases 90
Neuronal 145, 147
  dysfunction 145
  membranes 147
Neutron spectroscopy 134
Nicotinamide adenine dinucleotide 50
Nidoviral RNA endoribonuclease 48
NLRP3 250, 251, 254, 255, 257, 258, 259, 260, 261
  inhibition 254, 255, 258
  inhibitory 257
  inhibitory activity 255, 260
  monomer's mechanisms 259
  pathway 250
  protein 251, 261
NLRP3 inflammasome 238, 239, 247, 249, 252, 259
  activation 238, 247
  formation 249
  in synovial fluid cells 252
  inhibition 239, 259
NMR spectroscopy 4
Non-Hodgkin's lymphoma (NHL) 41, 45, 47, 51, 52, 53, 56
Normal-mode analysis (NMA) 191, 192

O

Obsessive-compulsive disorder (OCD) 43, 54
Occupation restricted multiple active spaces (ORMAS) 179
Orphan diseases 16, 17
Osteoarthritis 47
Osteoporosis 72, 79
Osteosarcoma 80

P

Pair interaction energy (PIE) 181
Parkinson's disease (PD) 42, 53, 238, 256
Pathogenesis, ovarian syndrome 238
Pathways, serotonergic 37
Peptide(s) 72, 73, 75, 83, 85, 89, 90, 92, 93, 96, 97, 99, 100, 101, 103, 107
  antidiabetic 90
  antihypertensive 99
  anti-microbial 89, 100
  anti-tubercular 90, 103
  antiviral 75, 83, 90, 100
  docking tools 93
  drug design 96, 99
  glycosylation 107
  hormones 72, 73
  inhibition 97
  inhibitors 85, 92
  tumor homing 101
Peptide-based 71, 73, 88, 93, 109

molecules 93
therapeutics 71, 73, 88, 109
Peptide design 89, 90
for chronic diseases 89
for diabetes therapy 90
PET imaging peptide agents 80
Phosphorescence spectroscopy 274
PIE decomposition analysis 181
Plotnikov's theory 285
Principal component analysis (PCA) 102, 142, 151, 193
Pro-inflammatory 240, 243
cytokines 240, 243
interleukins 240
Proatherogenic cytokine 238
Properties 3, 4, 5, 6, 7, 21, 23, 28, 32, 36, 38, 49, 52, 54, 55, 81, 89, 90, 101, 104, 136, 139, 179
anti-angiogenic 52
anti-inflammatory 49
antiangiogenic 52
antiparasitic 36
cardioprotective 55
electrochemical 81
immunosuppressive 54
physicochemical 89, 90, 101, 104
physiochemical 104
Protein(s) 22, 27, 35, 72, 85, 86, 93, 94, 132, 138, 139, 140, 141, 142, 143, 170, 174, 195, 199, 204, 237, 242, 246, 248, 256, 259
caspases 246
disease-related 85
heat-shock 248
inflammatory 242
-protein interaction (PPIs) 22, 27, 72, 85, 237, 256, 259
transmembrane 143
Protein-ligand 172, 195
end-point ABFE methods 172
PLQM-VM2 method 195
Protein-ligand binding 166, 167, 169, 173, 175, 178, 189, 190, 193, 194, 195, 199, 201, 202, 204, 206
simulations 178
Pulmonary arterial hypertension (PAH) 39
Python workflow 200, 201

Q

Quantitative structure-activity relationship (QSAR) 1, 2, 3, 92, 237, 239, 255, 257, 260
Quasi-sequence order (QSO) 102, 104

R

Radiative transition probability 271
RBFE methods 169
Reactive oxygen species (ROS) 242, 248
Recurrent neural network (RNN) 102, 259
Relative binding free energy (RBFE) 168
Resistance 15, 24, 141, 142, 143, 152, 153, 154, 156, 157
antibiotic 152
antimicrobial 153, 157
antiviral 154
mutations 142
Respiratory syncytial virus (RSV) 42, 53, 58
Rheumatoid arthritis (RA) 40, 42, 45, 47, 50, 51, 54, 56, 58, 238, 245
Rigid rotor harmonic oscillator's (RRHO) 171, 192, 198
RNA synthesis 35, 36, 47, 48
terminating 48
viral 36
viruses 47
Runge-Gross theorem 283

S

SARS-CoV-2 36, 37, 43, 58, 81, 83
infection 81
spike protein 36
virus 83
Selective serotonin reuptake inhibitor (SSRI) 37, 43, 58
Signaling pathways 240
Simulating 23, 139
cell biology processes 23
protein dynamics 139
Simulation 23, 28
and modeling tools 23, 28
software for predicting drug absorption 23
Single-point energy (SPE) 201
Solvation model density (SMD) 194
Spin-orbit coupling (SOC) 272, 275, 276, 284
Steroid anti-inflammatories (SAIs) 245, 246

Stress, oxidative 39, 49, 50
Structure-based drug design (SBDD) 4, 182, 239
Support vector classifier (SVC) 102
Symmetry adapted perturbation theory (SAPT) 184
Systemic lupus erythematosus (SLE) 45, 51, 56

T

Tableau data visualization software 24
Tamm-Dancoff approximation (TDA) 283
Tau 147
  protein dynamics 147
  proteins stabilize microtubules 147
Theory, molecular orbital 282
Therapies 82, 91
  immunosuppressive 91
  photothermal 82
Thermally activated delayed fluorescence (TADF) 271
Tick-borne encephalitis virus (TBEV) 36, 58
Toll-like receptors (TLRs) 240, 241, 246, 247
Total interaction energies (TIE) 184
Transitional motion 135
Treatment 38, 52, 53, 54, 55, 72, 73, 75, 76, 82, 148, 149, 152, 153, 191, 280, 281
  glioblastoma 82
  noninvasive topical 91
Triple-negative breast cancer (TNBC) 35, 58
Two-photon absorption (TPA) 273, 274

V

Vibrational 172, 189, 192, 270, 271
  entropy 172, 189, 192
  relaxation (VR) 270, 271

X

X-ray crystallography 4, 91, 97, 130
Xanthine oxidase 50

Y

Yellow fever virus (YFV) 36

Z

Zika virus 36

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