Abhinav Grover *Editor*

# Drug Design: Principles and Applications

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# Contents

# About the Editor

**Abhinav Grover** is currently working as Assistant Professor and Group Leader, Molecular Modeling and Biotherapeutics Production Laboratory at School of Biotechnology, Jawaharlal Nehru University (JNU), New Delhi, India. He obtained his PhD from the prestigious Indian Institute of Technology Delhi, New Delhi. Prior to joining this position, he received the coveted INSPIRE fellowship from the Department of Science and Technology, Government of India, and worked as Assistant Professor at the University of Delhi. His main area of research includes Drug Design and Development, Bioprocess Technology, Cheminformatics and Computational Biology.

Dr. Grover is a prolific publisher as he has authored more than 80 papers in peer--reviewed international journals of repute and two book chapters in a short span of scientific career. He is recipient of the prestigious NASI Young Scientist Award in 2014, INSA Medal for Young Scientists in 2013, Indo-Swiss Joint Research Fellowship, DST Haryana Yuva Vigyan Ratna Award and many more. Notably he has also won ICAR-Jawaharlal Nehru Award in 2013 for outstanding PhD thesis. He has been supported by a number of research grants from various funding agencies. He is a life member of National Academy of Sciences, India; Indian Science Congress Association; Society of Biological Chemists, India; etc. He is also a member of International Society for Computational Biology. He has delivered invited talks at several national and international conferences and symposia of high repute.

# Applications of Computer-Aided Drug Design

1

Joo Chuan Tong

## 1.1 Introduction

Computer-aided drug design (CADD) plays an instrumental role in the modern discovery of therapeutically important small molecules. It refers to computational methods that can help speed up the lead identification and optimization processes. In its broadest sense, CADD represents tools and resources for the storage, management, analysis, and modeling of compounds [1]. They are deployed in almost every step of the drug discovery pipeline, from the design of small molecule libraries, hits identification, to optimization of the affinity and selectivity of compounds. Digital repositories are useful resources for researchers studying important chemical interaction relationships [2]. Virtual combinatorial libraries can help minimize redundancy or maximize the number of discovered true leads by optimizing a library's diversity or similarity to a target [3]. They allow for both sequential and parallel selections of suitable compounds based on preferred molecular profiles. Many tools are now publicly available, with various methods and algorithms, to help identify protein binding sites and molecular functions [4, 5] as well as design compounds with interesting physicochemical properties for drug interventions [6, 7]. Some early successes of structure-based design include the carbonic anhydrase inhibitor Dorzolamide, and the HIV protease inhibitors Indinavir, Nelfinavir, Ritonavir, and Saquinavir [8]. Collectively, these tools and resources could help improve efficiency in new drug development and reduce costly late stage clinical trial failures. This chapter provides an overview of how various computational methods have been deployed to help expedite the drug design and discovery process.

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## 1.2 Virtual Combinatorial Libraries

Virtual combinatorial libraries offer the potential for improved design by optimizing a library's diversity or similarity to a target [9]. This approach can help identify molecules with desired makeup through systematical exploration of the compound property space. Molecular diversity, coverage, representativeness, physicochemical, and pharmacokinetic properties are concepts that are commonly applied to ensure a good sampling on product space using the minimum number of molecules. In recent years, much emphasis has been placed on designing libraries that allow the consensus selection of suitable molecules by optimizing multiple properties [10]. Such compounds are useful for investigating biological mechanisms and as leads for drug property optimization [11].

The design of a virtual library typically involves reaction encoding, selection of reagents and enumeration [11]. Two approaches are commonly used for enumerating molecular variants: Markush methods and reaction-based techniques. Markush methods enumerate libraries by varying the functional groups to be attached to a common scaffold [12]. While this approach can introduce diversity rapidly into the derived libraries, full (or implicit) enumeration of compounds is computationally expensive by nature. Reaction-based methods, on the other hand, offer a more flexible approach to library enumeration. This approach specifies which parts of the reacting molecules undergo chemical transformations and the type of transformations, allowing for the systematic generation of chemical products through the use of various reagents. However, the derived libraries tend to be smaller, thereby providing less diversity within the available chemical space.

## 1.3 Fold Recognition and Geometric Methods

Fold recognition is a method to model proteins that share the same fold as proteins of known structures, but do not have homologous proteins with known structure. Such method can help identify new binding sites and molecular function [13]. Commonly used methods include sequence comparison and protein threading [4].

Proteins are said to have a common fold if they share similar major secondary structures in the same arrangement and with the same topological connections. Sequence comparison methods typically begin by searching a protein sequence against a fold library of sequences with known three-dimensional structures, followed by assessing the alignment using substitution matrices, gap penalties, or propensity scales [5, 14, 15]. One good data source for such comparisons is the Structural Classification of Proteins (SCOP) database, which is a rich depository containing detailed structural and evolutionary relations between all proteins with known structures [16]. On the other hand, protein threading works by evaluating the goodness-of-fit of a target sequence on a source structure that is not evolutionarily conserved, followed by substituting the backbone coordinates of the template structure with the target sequence, and assessing the correctness of the model by means of a set of empirical potentials [17–19]. This approach is useful for identifying proteins that are structurally conserved but not evolutionarily related, and for modeling highly conserved molecular complexes.

Geometric algorithms predict active sites by locating cavities or "pockets" on the surface of a protein [20, 21]. Many computational methods have been developed that use geometric characteristics to detect protein pockets. There are several ways to identify pockets using protein geometry only. Computational tools such POCKET [22] and LIGSITE [23] map proteins onto a 3D grid and scan the grid points outside the protein for protein-solvent-protein and surface-solvent-surface events, respectively. SURFNET [24] identifies pockets by fitting spheres into the spaces between atoms. The clustered spheres with greatest volume define the largest pocket. CAST [25] detects pockets by merging neighboring empty tetrahedral that share a common triangle. In PASS [26], cavities in a protein structure are filled with a set of probe spheres, and potential pockets are identified as the probes with the most atom contacts. A benchmark on the performances of LIGSITE, LIGSITE$^{cs}$, LIGSITE$^{csc}$, SURFNET, CAST, and PASS showed that geometric methods can achieve a success rate of 71–77% when tested on a dataset of 48 proteins with unbound structures and 80–87% for 210 proteins with bound structures [27].

## 1.4 Molecular Docking

Molecular docking is commonly used to help understand drug–receptor interaction [6]. Predicting the binding mode of ligands to macromolecular receptors is nontrivial. The method must first identify the correct positioning of a ligand within the receptor binding site [28], and then evaluate how well the ligand can bind to the receptor [13]. A variety of molecular docking software is now available (Table 1.1). Incremental construction algorithms such as FlexX [29], FlexE [30], and DOCK [31] search for optimal binding poses by placing fragments in the receptor binding site and then extend the fragments to fill the space available. Monte Carlo methods such as ICM [32] randomly sample a conformational subspace, and then move to a new random position independent of the previous position, but according to the predefined continuous probability distribution. Ensemble docking methods such as those adopted by ICM [33] and FlexE [34] address the issue of receptor flexibility by using multiple conformations of the protein to dock the ligand [35]. Other methods, such as the use of genetic algorithms [36] for flexible docking of ligands to

**Table 1.1** Some available molecular docking software

| Name | URL |
|---|---|
| Autodock | http://autodock.scripps.edu/ |
| DOCK | http://dock.compbio.ucsf.edu/ |
| FlexX | https://www.biosolveit.de/FlexX/ |
| FlexE | https://www.biosolveit.de/FlexX/ |
| FITTED | http://fitted.ca/ |
| FlipDock | http://flipdock.scripps.edu/ |
| GOLD | http://www.ccdc.cam.ac.uk/solutions/csd-discovery/components/gold/ |
| Glide | https://www.schrodinger.com/glide |
| ICM | http://www.molsoft.com/ |

receptors, have also been described. In 2004, Kellenberger and colleagues [37] performed a comparative evaluation of eight docking tools (DOCK, FlexX, FRED, GLIDE, GOLD, SLIDE, SURFLEX, and QXP) for docking and virtual screening accuracy. Using the crystallographic structures of 100 small-molecular-weight ligands, the team found that molecular docking was capable of recovering 63% of cases at 1 Å r.m.s.d. threshold, with a maximum success rate of 90% at 2 Å r.m.s.d threshold.

Numerous methods have been developed for binding free energy estimations. These can be broadly classified into three groups: empirical scoring functions, knowledge-based potentials, and force field methods. Empirical-based potentials perform binding energy estimations by additive approximations of several energy terms such as van der Waals potential, electrostatic potential, hydrophobicity potential, among others [38]. The relationship between these terms and the binding affinity is obtained either by regression or machine-learning algorithms on a training dataset of receptor-ligand crystallographic structures with known binding affinity [39]. Tools that deploy empirical-based scoring functions include FlexX [29], SCORE [40], ICM [33], and VALIDATE [41]. Knowledge-based scoring functions, such as those implemented in Potentials of Mean Force (PMF) [42], DrugScore [43], and ASP [44], estimate binding free energies based on the frequencies of interatomic contacts. This approach is fast but unlike empirical scoring functions, it does not require binding affinity data for training [6]. Force field methods model free energies of binding by summing the strength of van der Waals and electrostatic interactions between all atoms of the two binding partners using established mathematical terms or high-level quantum mechanical calculations. This method had been implemented in AUTODOCK [45], GOLD [46], DOCK [31], and CHARMM [47].

## 1.5 ADME/Tox Assessment

Assessing small molecule compounds for their absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) properties is important for early stage drug discovery. It has been estimated that 40–60% of drug candidates fail due to unsatisfactory ADME/Tox properties [48]. Before a compound can exert a pharmacological effect in tissues, it has to cross the gastrointestinal barrier, the blood–brain barrier, and the microcirculatory barrier to reach the blood stream. From there, the compound is transported to its effector site for distribution into tissues and organs, degraded by specialized enzymes, and finally excreted from the body. Furthermore, some compounds may undergo metabolic activation and cause adverse reactions or toxicity in humans [49]. Accordingly, rapid screening of ADME/Tox properties plays a key role in the initial selection of a drug candidate, and for further optimization of potency and drug-like properties.

Many factors affect the membrane permeability of a compound, including compound size, aqueous solubility, ionizability (p*K*a), and lipophilicity (log *P*). The polar surface area (PSA), defined as the sum of surface contributions of polar atoms in a compound, has been shown to correlate inversely with lipid penetration ability

[50]. Compounds with PSA values of ≤60 Å$^2$ can be completely absorbed by our bodies, while compounds with PSA >140 Å$^2$ are known to be poorly (<10%) absorbed. Poor absorption and permeation are also more common for drugs with molecular weight of <500 g/mol, *C* log *P* < 5, hydrogen bond donors <5, and hydrogen bond acceptors <10 [51]. These criteria constitute the Lipinski's "rule of five" to evaluate and prioritize compounds for properties related to "drugability" [51]. Extensions to this rule were proposed by other researchers, including a more stringent "rule of five" for compounds with molecular weight < 473 g/mol, *C* log *P* < 5, hydrogen bond donors <4, and hydrogen bond acceptors <7 [52]. A "rule of three" for lead-likeness was also defined by Congreve and coworkers [53], for compounds with molecular weight < 300 g/mol, hydrogen bond donors ≤3, and *C* log *P* ≤ 3. While these are useful rules of thumb for evaluating drug-likeness, it should be noted that about 68.7% of compounds in the Available Chemical Directory (ACD) Screening Database (2.4 million compounds) and 55% of compounds in ACD (240 thousand compounds) do not violate the "rule of five" [54]. More complex computational and mathematical models have also been developed to assess ADME/Tox properties. These include methods based on genetic algorithms (GAs), ANNs, SVMs, and statistical models [54]. Collectively, these tools facilitate better understanding of the pharmacokinetics and pharmacodynamics of candidate compounds in the early stages of drug development.

**Conclusion**

A large variety of tools and resources are now available for computer-aided drug design. CADD is now widely accepted as a viable alternative and complement to high-throughput screening. The choice of suitable software is dependent on the availability of data and resources and varies across different targets of interest. Here, we have provided an overview of existing methods and tools for the discovery of new molecular entities. The review is by no means exhaustive, and more comprehensive surveys are available elsewhere [1, 4, 6, 10, 13, 28]. Over the past decade, much progress has been made in CADD. With the continuous developments in the fields of bioinformatics, high-throughput screening, chemical and structural biology, an increasing number of more sophisticated tools and methods can be expected in the future that can help realize the full potential of computer-aided discovery by design.

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# Advanced Drug Discovery for Alzheimer's Disease: Challenges and Strategies

2

Rizwanul Haque and Aamir Nazir

## 2.1 An Introduction to Alzheimer's Disease

The progressive loss of organization and function of neurons leading to the death of neurons collectively constitutes the Neurodegenerative Diseases (NDs). Age-associated NDs have been a cause of significant health burden because of lack of treatment. NDs pose a great challenge for the elderly population, healthcare providers and caregivers. These diseases result from progressive loss of structure and/or function of neurons. Neuronal death within specific areas of brain predominantly cerebral cortex, hippocampus, and spinal cord results in deficiency of key neurotransmitters further affecting motor functions/movement (known as ataxia), and non-motor functions/mental functioning (known as dementias). Neurons in general don't reproduce or substitute themselves, when they are damaged they cannot be replaced in abundance under normal circumstances though recent studies on neurogenesis provide some hope on neuronal recovery too. NDs are incurable and debilitating conditions that result in progressive degeneration and/or death of nerve cells. A striking number of more than 600 disorders have been reported that affect the nervous system. The most common disorders include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, Spinocerebellar ataxia, Prion disease, and Amyotrophic Lateral Sclerosis (ALS). The cause of each one being believed to be dependent on a number of factors, some most important wherein causes range from particularly genetic or environmental factors [1]. The most common among all NDs is AD with an annual death toll of more than 500,000 people [2]. According to the World Health Organization (WHO) Global Burden of Disease Study in 2012, AD and other dementias are the top fourth cause of death in high income countries after heart disease, stroke, and lung cancer [3]. A 2014 report

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submitted by the US organization reported that more than 5.2 million Americans are currently living with the disease, which includes five million people above the age of 65 years (late-onset AD) and roughly 2 lakh individuals below 65 years of age (early-onset AD) [2], thus making AD the most expensive disease condition in the United States with an estimated $214 billion cost to the American Society. Worldwide, currently more than 25 million people are affected by dementia, most suffering from AD with five million new cases accruing up each year [4]. In Europe, the age-standardized prevalence in people more than 65 years of age is 6.4% for dementia and 4.4% for AD [5]. A new study predicts that the AD in the United States will get doubled by 2050 and the cost of caring will rise to $1.5 trillion per year.

AD has been named after a German physician Alois Alzheimer. On 3rd November 1906, while presenting his findings at the "37th meeting of the Society of Southwest German Psychiatrists" in Tübingen Germany, Alois Alzheimer for the first time described the symptoms of progressive cognitive impairment, focal symptoms, hallucinations, delusions, and psychosocial incompetence changes in a patient called Auguste D, a 51-year-old woman from Frankfurt hospital [6]. The disease was later named by a German psychiatrist Emil Kraepelin as "Alzheimer's Disease." AD is an age-related disorder which affects the population over 65 years of age (elderly population) and is not to be confused with the "normal ageing" phenomenon. Clinically, AD is characterized by progressive and irreversible decline in memory and cognitive functions. In later stages, motor and sensory functions are compromised which leads to drastic personality changes like aggression, apathy, agitation, paranoia, insensitivity to others, lack of initiative, delusional thinking, loss of interest in activities they previously enjoyed, inability to make decisions, and finally the person is socially withdrawn. The cognitive defects are reflected neuropathologically by demise of specific neuronal populations, synaptic loss, and brain atrophy in specific brain areas [7–9] and most importantly by the presence of senile plaques (amyloid plaques) and neurofibrillary tangles (Tau protein) which are formed by improperly processed proteins. These improperly processed proteins tend to form aggregates which are toxic to the neurons and ultimately result in their degeneration [10]. The diagnosis of AD can only be confirmed by autopsy after the death and in living patients it can be done on the basis of some cognitive tests [11]. Patients affected with AD tend to show cognitive decline which includes gradual memory loss, difficulty in performing daily tasks, declining physical coordination, lack of judgment making, personality changes, difficulty in learning, and loss of communication skills [12]. The disease eventually leaves its victims unable to care for themselves and in the final stages; victims are bedridden and normally die due to secondary infections like urinary tract infection, pneumonia, and/or bedsores. The molecular mechanism of the disease progression of AD has been a topic of debate for last several years, and there are two cardinal theories prevailing in the scientific community regarding mechanism of AD. Factors governing neuronal loss can be grouped into genetic, environmental, and endogenous ones. The main culprit is known to be the accumulation of abnormal extracellular protein plaques and neurofibrillary tangles of the microtubules formed by amyloid beta (Aβ) and tau protein, respectively. Aβ is a 40 or 42 amino acid peptide with approximate size of 4 kDa, derived from the precursor protein, namely amyloid