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**Dr. Sushil Kumar Sharma**
Freelance Consultant, ISO 9001, 14001 & GMP. LIG 56, Pkt-1, Sector-A9, Narela, Delhi, India

**Dr. Ekta Sharma**
Assistant Professor & In charge, Dept. of Textiles and Apparel Designing, Ethelind College of Home Science, SHUATS, Allahabad, Uttar Pradesh, India

**Yatendra Sharma**
Young Professional, Ministry of Youth, Affairs and Sports, New Delhi, India

**Correspondence**
**Dr. Sushil Kumar Sharma**
Freelance Consultant, ISO 9001, 14001 & GMP. LIG 56, Pkt-1, Sector-A9, Narela, Delhi, India

# A review: Recent computational approaches in medicinal chemistry: Computer aided drug designing and delivery

**Dr. Sushil Kumar Sharma, Dr. Ekta Sharma and Yatendra Sharma**

**Abstract**
Traditional medicinal chemistry paradigms, relying initially on 'wet' chemistry followed by screening and lead optimizations, are expensive and time consuming. On the other hand, initial in silico screening that guides the synthesis and screening of selected compounds has proven to be a better approach to accelerate drug discovery and reduce the cost of the discovery phase. The Special Focus issue on computational chemistry and computer-aided drug discovery has aimed to assemble contributions covering a wide range of computational approaches with special relevance for medicinal chemistry and drug discovery, including new methodologies and practical applications. In addition, this Special Focus issue has been thought to provide a forum for critical – or even provocative – contributions, given the generally high degree of scientific heterogeneity that characterizes the publication landscape of computational medicinal chemistry. Moreover, prospective applications of computational approaches, established or new, have been most welcome, for example, investigations attempting to identify or design new active compounds. Such prospective applications often provide a good impression of the practical utility and impact computational methods may – or may not – have on experimental programs, which is a critical issue for medicinal chemistry.
The aim of this special issue is to give an overview of and highlight the latest achievements in various computational approaches at a point in time when the field is experiencing tremendous algorithmic advancements in terms of speed and accuracy, with a constant enthusiasm and excitement to meet up the experiments.

**Keywords:** Medicinal Chemistry, Drug designing, Drug delivery

## 1. Introduction
The Special Focus issue on computational chemistry and computer-aided drug discovery has aimed to assemble contributions covering a wide range of computational approaches with special relevance for medicinal chemistry and drug discovery, including new methodologies and practical applications. In addition, this Special Focus issue has been thought to provide a forum for critical or even provocative-contributions, given the generally high degree of scientific heterogeneity that characterizes the publication landscape of computational medicinal chemistry. Computational approaches are an integral part of interdisciplinary drug discovery research. Understanding the science behind computational tools, their opportunities, and limitations is essential to make a true impact on drug discovery at different levels. Herein, current trends in computer-aided drug discovery are reviewed, and selected computational areas are discussed. Approaches are highlighted that aid in the identification and optimization of new drug candidates. Emphasis is put on the presentation and discussion of computational concepts and methods, rather than case studies or application examples. As such, this contribution aims to provide an overview of the current methodological spectrum of computational drug discovery for a broad audience.
Computational approaches commonly used in computer-aided drug design (CADD) have made significant contributions to the different stages of drug discovery. Advances in this filed have been reviewed recently in a number of publications. CADD includes several methodologies that can be classified in two major groups depending on the availability of the three dimensional coordinates of the target, namely structure- based and ligand-based approaches.
The reader is referred to recent reviews of the contributions of specific computational approaches to drug discovery including molecular dynamics, pharmacophore modeling, chemoinformatics

(Duffy *et al.*, 2012), treatment of receptor flexibility to model biomolecular recognition and small molecule and protein-protein docking. Successful contributions of CADD to research projects have been encouraged by the increasing number of software, databases, and online tools available for medicinal chemists, biologists, and the research community in general.

Despite the fact that this approach has given rise to the successful identification of lead compounds and approved drugs discussed above, it is anticipated that combining computational approaches with experimental-based natural product research will enhance the

Success rate. In this regard, Barlow *et al.* reviewed the integration of in silico studies with Chinese herbal medicine's research. The synergy between other well-established drug discovery approaches such as virtual screening and combinatorial chemistry have been discussed elsewhere.

Drugs are essential for the prevention and treatment of disease. Thus, ideal drugs are in great demand. But the process of Drug design is a tedious, time-consuming and cost intensive process. Thus several approaches are required which collectively would form the basis of Computer Aided or In Silico Drug Designing. Use of computational methods in drug discovery and development process is nowadays gaining popularity, implementation and appreciation. Different terms are being applied to this area, including computer-aided drug design (CADD), computational drug design, computer-aided molecular design (CAMD), computer-aided molecular modeling (CAMM), rational drug design, In Silico drug design, computer-aided rational drug design. All the world's major pharmaceutical and biotechnology companies use computational design tools. At their lowest level the contributions represent the replacement of crude mechanical models by displays of structure which are a much more accurate reflection of molecular reality capable of demonstrating motion and solvent effects. Beyond this, theoretical calculations permit the computation of binding free energies and other relevant molecular properties.

Computer Aided Drug Design (CADD) and Delivery Systems offers an in-depth discussion of the computer-assisted techniques used to discover, design, and optimise new, effective, and safe drugs. The objective of drug design is to find a chemical compound that can fit to a

Specific cavity on a protein target both geometrically and chemically. The use of computers and computational methods permeates all aspects of drug discovery today and forms the core of structure-based drug design. The day is not far away when Computer Aided Drug Designing will be dominant in modern medical services, thus the purpose is to bring forward, the significant advancements, which Computer Aided Drug Designing has made to serve mankind in producing newer drugs with improved effects.

**Drug Discovery in the 20$^{th}$ Century**

The development of small molecule therapeutic agents for the treatment and prevention of diseases has played a critical role in the practice of medicine for many years. In fact, the use of natural extracts for medicinal purposes goes back thousands of years; however, it has only been in the past half century or so that searching for new drugs has found itself in the realm of science. In 1900, one-third of all deaths in the U.S. were from three general causes that are rare today because they are preventable and/or treatable: pneumonia, tuberculosis, and diarrhea. By 1940, the chance of dying from these three causes was 1 in 11; by 2000, the odds were down to 1 in 25. Of the three, only pneumonia remains in the list of top ten causes of death, which is now led by more complex conditions such as cardiovascular disease and cancer. While other factors such as improved sanitation and vaccination certainly played a role in the increase of life expectancy during the twentieth century – from less than 50 years in 1900 to more than 77 years in 2000 – the availability of drugs to control infection, hypertension, hyperlipidemia, and to some extent even cancer, certainly also contributed to the obvious improvement in our collective health and life expectancy during that period. The history of drug discovery in the pharmaceutical industry and academic labs over the past half-century shows a progression of discovery paradigms that began shortly after "miracle drugs" such as the penicillin's became available to the public after World War II. That same decade also saw the rise of synthetic organic chemistry, which had progressed to the point that the large scale preparation of "non-natural" drugs or drug candidates was economically feasible.

**A Brief History of CADD**

In 1900, the concept of receptor and lock-and-key was given by E. Fisher. In 1970s, the concept of Quantitative structure activity relationships (QS- AR) was established, it had Limitations: 2-Dimensional, retrospective analysis; in 1980s there was Beginning of an era of CADD Molecular Biology, X-ray crystallography, multi-dimensional NMR Molecular modeling along with computer graphics. In1990s more modern techniques like Human genome Bioinformatics along with combinatorial chemistry and High-throughput screening were introduced in the world of innovative medical Science.

**Classification scheme**

In general, *in silico* approaches with utility for drug discovery can roughly be divided into three major categories. These include the following: first, the design, implementation, and maintenance of computational infrastructures to process, organize, analyze, and store rapidly growing amounts of drug discovery data (e.g. com- pound library, biological screening, pharmacological, clinical, and literature data); second, methods to help identify, characterize, and prioritize biological targets and establish links between target engagement, biology, and disease (these approaches essentially fall into the domain of bioinformatics); and third, methods to help make better compounds and generate drug candidates. While all three categories are equally relevant for drug discovery and development, the following discussion will predominantly focus on the latter one, that is, the core of computer-aided drug discovery and design.

Figure 1 summarizes computational areas that will be highlighted. The definition of subject areas is intentionally broad to provide a general overview. It should be noted that each area covers a variety of computational approaches. For example, "structure-activity relationship (SAR) analysis" includes numerical and graphical approaches as well as ligand- and target structure-based methodologies including, among others, the derivation of mathematical models of SARs or prediction and evaluation of compound binding modes. Similarly, "virtual screening" and "compound design" cover ligand and structure based approaches. "Energy calculations" include molecular mechanics, quantum mechanics, and combined approaches, for example, for conformational analysis, molecular geometry calculations, or affinity

predictions. Furthermore, both "ADME (absorption, distribution, metabolism, excretion) modeling" and the systematic study of "drug-target interactions" involve the application of a variety of machine learning approaches and the derivation of predictive statistical models. A key point is that the current spectrum of computational concepts with relevance for drug discovery is extensive and complex. Providing a general overview inevitably calls for simplification. There are other emerging computational areas that can only partly be covered herein due to size limitations including, for example, the derivation of knowledge from the rapidly growing amounts of increasingly complex and heterogeneous discovery data (which are also becoming available in the public domain). This challenges computational scientists in the pharmaceutical industry to integrate (proprietary) internal and available external data, but provides a significant opportunity to further increase the knowledge base for drug discovery research

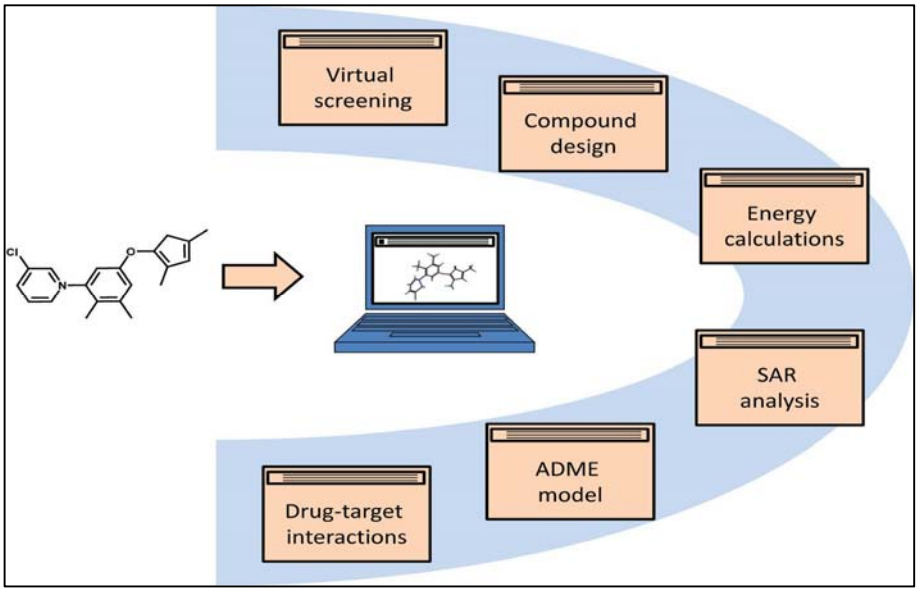


**Fig 1:** Areas of computer-aided drug discovery

Selected computational areas are shown providing focal points of the discussion. Each subject area covers a variety of computational approaches, as discussed in the text.

**Computational methods in drug discovery**

Delivering new drug candidates more quickly and at lower cost is the need of the hour. To achieve these objectives, computational approaches in drug discovery process have become quite a necessity. Continued progress in the application of computational power to chemical and biological space has significantly impacted modern drug development India. In today's world, apart from several omics technologies, other modern technologies such as combinatorial chemistry, virtual screening, *in silico* ADMET screening and structure-based drug design (SBDD) have revolutionized the drug discovery process. More importantly, the role of computers and computational techniques in drug discovery and development process has gained popularity and implementation. A simple example is drug-target interaction studies. Since experimental approaches are laborious and costly, prediction of these interactions by *in silico* methods provides valuable information in supporting experimental data. Thus, computational methods are considered complementary to the experimental techniques.

Computer Aided Drug Discovery and Development is being utilized in early stages of DD process that includes hit decades have witnessed the development of therapeutic small molecules solely based on Computer-aided drug discovery/design methods.

Major pharmaceutical and biotechnology companies worldwide are using computational design tools. Structure-based drug design is considered as one of the most innovative and powerful approaches in drug design. Virtual screening has been shown more efficient than commonly used empirical screening. To significantly reduce the time and resource requirements of chemical synthesis and biological testing, *in silico* modeling is employed. Similarly, QSAR and QSPR are commonly used computational methods in predictive toxicology.

Table 1, 2 and 3 lists commonly employed tools and databases in computational drug discovery and development process. Several of them have applications in the early stages of the drug discovery pipeline.

**"Open source" concept"**

The concept of "open source" has hugely impacted the software industry globally. Its roots can be traced back to the beginning of computer software development. A ten point criteria were introduced by Open source initiative to define the term "open source". Of the ten points mentioned, three are considered to be major ones, namely access to source code, free redistribution, and creation of derived works.

**Table 1:** Bioinformatics tools and databases commonly employed in DD process

| Tool name | Brief description of the tool | Steps involved in DD process |
|---|---|---|
| BLAST (Basic Local Alignment Search Tool) [46] | A DNA and protein sequence alignment tool | Target Identification and Validation |
| FASTA (Fast Alignment) Tool [47] | A DNA and protein sequence alignment software package | Target Identification and Validation |
| EMBOSS (European Molecular Biology Open Software Suite) [48] | A free Open Source software analysis package specially developed for the needs of the Molecular biology user community | Target Identification and Validation |
| BioEdit (Biological Editor) [49] | A biological sequence alignment editor with multiple document interface for easy alignment and manipulation of sequences on a desktop computer. | Target Identification and Validation |
| Clustal W [47] | A general purpose multiple sequence alignment program to study evolutionary relationships | Target Identification and Validation |
| RasMol (Raster Molecule) tool [50] | A molecular visualization program tool for DNA/RNA and protein structures. | Structure Based Drug Design, Target Identification and validation |
| PyMOL [51] | Molecular visualization System for DNA/RNA and protein structures. | Structure Based Drug Design, Target Identification and validation |
| Swiss-PDB Viewer [52] | Standalone molecular visualization and modeling tool with advanced features to handle nucleic acid, protein and other organic molecules. | Structure Based Drug Design, Target Identification and validation |
| Discovery Studio [53] | Advanced software focusing on modeling and simulation solutions. | Structure Based Drug Design, Target Identification and validation, Lead selection, Lead optimization, ADME studies |
| Swiss-Modeller [54] | Fully automated protein structure homology modeling server | Structure Based Drug Design, Target Identification and Validation |
| Modeller [55] | Stand alone comparative modeling tool for 3D structures of proteins | Structure Based Drug Design, Target Identification and Validation |
| PHYRE [56] | Automatic Fold recognition server for predicting the structure and function of protein sequence | Structure Based Drug Design, Target Identification and Validation |
| PubMed [57] | Free search engine accessing primarily the MEDLINE database of references and abstracts on life sciences and biomedical topics | Target Identification and Validation |
| DDBJ (DNA Data Bank of Japan) [58] | Collects and distributes nucleotide sequence data | Target Identification and Validation |
| NCBI Genbank [59] | Genetic sequence database | Target Identification and Validation |
| PDB (Protein Data Bank) [60] | An Information Portal to Biological Macromolecular Structures | Structure Based Drug Design, Target Identification and Validation |
| KEGG (Kyoto Encyclopedia of Genes and Genomes) [61] | Database resource for understanding high-level functions and utilities of the biological system | Structure Based Drug Design, Target Identification and Validation |

**Table 2:** Chemiinformatics tools and databases commonly employed in DD process

| Tool Name | Brief description of the tool | Steps involved in DD process |
|---|---|---|
| ISIS Draw [62] | A chemical structure drawing program available free of cost for academic and personal use | Lead structure determination, Lead optimization, ligand based drug design |
| Chem Draw [63] | A molecule editor to handle chemical molecules and is part of the Chem Office suite of programs. | Lead structure determination, Lead optimization, ligand based drug design |
| ACD Chemsketch [64] | Advanced chemical drawing tool available free of cost for academic use. | Lead structure determination, Lead optimization, ligand based drug design |
| Marvin Sketch [65] | Advanced chemical editor for drawing chemical structures, queries and reactions. | Lead structure determination, Lead optimization, ligand based drug design |
| JME Molecular Editor [66] | A Java applet which allows to draw /edit molecules and reactions and to depict molecules directly within an HTML page. | Lead structure determination, Lead optimization, ligand based drug design |
| ISIS/Base [67] | A database management system for storing, searching, and retrieving chemical structures and associated scientific data | Lead identification, lead optimization, ligand based drug design, virtual screening |
| ACD Chem folder [68] | Advanced software to create and manage databases with thousands of chemical structures and reactions | Lead identification, lead optimization, virtual screening |
| Chem spider [69] | Free chemical structure database | Lead identification, validation and optimization |
| Pub Chem [70] | Database containing structures and physiochemical properties of chemical compounds | Lead identification, validation and optimization |
| CSD (Cambridge Structural Database) [71] | Contains experimentally determined 3D structures of potential ligand molecules | Lead identification, validation and optimization, ligand based drug design |
| Ch EMBL [72] | Chemical database of bioactive molecules with drug-like properties | Lead identification, lead optimization, ligand based drug design |

Following the tremendous success in software development, attempts to successfully employ the open source model to other areas, including biotechnology is underway. Recently, Maurer and Scotchmer reviewed the role of the emerging

open source model in drug discovery. According to Ardal and co researchers, Open source is a desirable model for drug discovery. The concept of open source has been discussed in academic environments for almost a decade. Following its application in tropical diseases, it has also been implemented in Cambia's BiOS and CSIR's (Council for Scientific and Industrial Research) OSDD initiatives. The OSDD model is a unique amalgamation of open source and patenting principles. Recently, it has gained more importance and appreciation in several other research activities.

Recently, World Health Organization's Consultative Expert Working Group has been entrusted with the evaluation of an open source drug discovery (OSDD) concept. To develop new and inexpensive drugs more quickly with wider patient reach, several OSDD has been initiated in several countries.

**Table 3:** Miscellaneous computational tools widely employed in DD process

| Tool Name | Brief description of tool | Steps involved in DD process |
|---|---|---|
| Open Babel [73] | Open source Chemical toolbox used primarily for converting chemical file formats | Lead optimization, virtual screening |
| Auto Dock [74] | Molecular modeling simulation software | Molecular docking, virtual screening, molecular simulation |
| Argus Lab [75] | Molecular modeling, graphics and drug design program | Molecular docking, molecular simulation, ligand based drug design |
| Vega ZZ [76] | Molecular modeling suite | Molecular modeling, molecular docking, simulation and ligand based drug design |
| HEX [77] | Protein docking and molecular superposition program | Molecular docking, simulation, ligand based drug design |

**Finding new active compounds**

For the identification of new hits, high-throughput screening is the primary approach in pharmaceutical research. For many years, biological screening has been augmented by computational com- pound database searching, so-called virtual screening, starting from known active compounds as templates (ligand-based virtual screening) and/or three-dimensional structures of target proteins (structure-based virtual screening). For ligand-based virtual screening, the molecular similarity relationship between known active and database compounds must be computationally explored; for structure-based virtual screening, test compounds are computation- ally screened on known ligand binding (active) sites of targets using docking calculations. State-of-the-art ligand docking involves a conformational search of ligands within the structural constraints of active sites to model putative binding modes, followed by ranking of docked compounds according to their likelihood of activity. Ranking is based on computational scoring functions that approximate interaction energies. Figure 2 shows the X-ray structure of an exemplary enzyme-inhibitor complex and the putative binding mode of another inhibitor predicted by docking. Although virtual screening methods have a long history in computer-aided drug discovery, their accuracy is limited, mostly due to energy- or similarity-based scoring problems that has been known for many years, but is still not solved scientifically. In ligand-based virtual screening, calculated molecular similarity relationships (using different molecular representations and similarity functions) cannot be confidently correlated with observed activity relationships, representing a challenge for the identification of specifically active compounds. Furthermore, while the conformational search problem in docking is essentially solved, it is difficult to accurately rank compounds on the basis of force fields and energy functions and distinguish true positives (active compounds) from false positives. Despite these limitations, virtual screening studies have successfully identified many new hits for therapeutically relevant targets (including difficult screening targets).

OSDD is application of collaboration and open access concepts of open source computing in the drug discovery process. This influential model has potential for developing new medicines/diagnostics for neglected diseases [79]. In OSDD, all experimental results, wet lab as well as *in silico*, are published along with raw data to enable other experts of the domain to critically review it [82]. Case studies of Cambia and India's OSDD by Masum and coworkers [80] clearly pinpoint the high potential of OSDD in the developing world. They also believe that the open source model in drug discovery will enable huge gains.

**Future perspective & conclusion**

After three decades of development, CADD has become a valuable component of drug discovery and development. To describe its typical use, at the beginning of a drug-discovery project, chemoinformatics tools are employed to choose compounds from available sources

to be assayed. Some marginally active or better compounds may be found, and then chemical similarity searching techniques are used to find more compounds that should be assayed. If some compounds that are more active are discovered, computationally more expensive techniques are applied, such as docking and pharmacophore modeling, to identify more potent compounds or optimize more ADME/T favorable compounds. Techniques of CADD also provide other options for understanding chemical systems, which yield information that is not easy to obtain in laboratory analysis, and, furthermore, is typically (much) less costly than by experiment. After ups and downs of the perception of CADD in the field of drug development, and perhaps some over-hyping of its promises, especially in the initial phases of new trends in development, one can probably say that the discipline of computational medicinal chemistry has begun to mature and become a realistically assessed and routinely used component of modern drug discovery. The breadth of techniques and tools described in this article imply that, to become a successful computational medicinal chemist, it will be highly beneficial to master different kinds of CADD programs and utilize all computational resources that are valuable for drug design. In addition, having skills in one or more programming languages, such as Python, will help smooth routine drug-design work in a contemporary CADD setup. While it would be desirable, one cannot bank on the fact that a quantum leap in precision of docking or pharmacophore search will occur in the next few years. Nevertheless, SBVS and LBVS are very likely to become routine in drug-discovery projects if they have not already done so. The use of more accurate methods, such as MD and QM, will continue to grow. Currently, sophisticated CADD

tools are typically applied by modeling experts, but are increasingly spreading to the desktops of medicinal chemists as well.

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