AG Publishing House

Modern Trends in Medicinal Chemistry: Techniques, Applications, and Innovations (volume-1)

Volume 1
Year: 2025

AG PH Books

Advances in Structure-Based Drug Design: Challenges and Opportunities

Dr. Prashant Mundeja [1*]

[1]*Professor*

Abstract

Drugs for a range of illnesses have been developed with the help of SBDD. Structure-based medication design uses three-dimensional geometric information about macromolecules, including proteins or nucleic acids, to identify suitable ligands. Examine the many studies conducted by researchers on the prospects and difficulties in structure-based medication discovery in this page. This study comes to the conclusion that because of the flexibility of proteins, solvent effects, and important water molecules in target proteins, the existing scoring methods have difficulty properly estimating binding free energy. Improving predictions of protein-ligand interactions still requires addressing these issues. SBDD has a lot of potential to speed up drug development with cutting-edge computational methods, despite these obstacles. Drug-target interaction prediction, ligand binding site identification, and de novo ligand generation provide practical ways to target unknown macromolecular structures. By improving structural refinement, drug association mapping, and protein structure prediction, the use of deep learning into SBDD has created new opportunities. These developments increase the possibility of finding potent medicinal molecules by enabling a more effective search of chemical space.

Keywords: Structure-Based Drug Design (SBDD), Computational techniques, Therapeutic compounds, Drug discovery, Direct drug design, Molecular docking, etc.

1 Introduction

Drug development is still an experimentally rigorous, expensive, and time-consuming process, despite the fact that high-throughput screening (HTS) and whole-cell screens have traditionally been used to

* ISBN No. - 978-93-49028-76-0

identify effects that may be proposed into drug candidates according to a particular target, often an important enzyme [1]. However, in contrast to conventional drug discovery, drug design draws on the existing information for a particular biological target rather than relying just on screening enormous libraries, which is inherently a trial-and-error process [2], [3]. Using the target's three-dimensional structure, structure-based drug design, or SBDD, is a well-known method of drug design that finds or improves compounds that have a high affinity and selectivity for binding to the target [4]. From the early days of structural biology, it was clear that structural information could be used to find potential drugs. However, it took several years before the first successful examples, such as HIV protease inhibitors and carbonic anhydrase inhibitors for glaucoma treatment, were achieved [5].

Therefore, SBDD requires a three-dimensional representation of the target. There are several experimental methods for obtaining the structure, but X-ray crystallography is the most common. The resolution revolution saw a dramatic improvement in the resolution capabilities of single-particle cryo-EM, which piqued interest in "nuclear magnetic resonance (NMR) and, more recently, cryo-electron microscopy (cryo-EM)". Targets with challenging experimental structures are also often subjected to in silico structure prediction. This may be accomplished via homology modelling from a closely related homologous protein when suitable models are available [6].

A. Structure-based drug design

Direct drug design, or structure-based drug design, relies on x-ray crystallography and nuclear magnetic resonance spectroscopy-disclosed three-dimensional structures of biological targets. A homology model of a target protein may be constructed using the experimental data of a similar protein in the event that the target protein's experimental structure is not accessible [7]. A medicinal chemist's intuition combined with interactive visualisations may be used to develop candidate drugs that are expected to attach to the biological target with high affinity and selectivity based on the target's structure. As an alternative, new drug candidates may be proposed using a variety of automated computational processes [8].

There are three major groups into which current structure-based drug design techniques may be broadly classified. The first method uses quick approximation docking tools to search through large datasets of small molecule 3D structures for new ligands that fit the binding pocket of a particular receptor. Virtual screening is the term for this technique [9]. The creation of novel ligands is the subject of a second group. Using this technique, ligand molecules are gradually assembled from tiny fragments to build up inside the binding pocket's limitations. These fragments might be single atoms or pieces of molecules. The capacity to suggest novel structures that aren't included in any database is the primary advantage of this strategy. Optimising existing ligands by assessing suggested analogues within the binding cavity is the third technique [10].

B. “Principles of Structure-Based Drug Design (SBDD)’

The foundation of SBDD is the idea of lock-and-key binding, in which a drug molecule attaches itself to a particular location on the target protein in a manner similar to how a key fits into a lock. Depending on the kind of interaction, the drug molecule's binding to the target protein may either inhibit or stimulate

the protein's function [11]. The first step of SBDD is to get the three-dimensional structure of the target protein. Techniques like as X-ray crystallography, cryo-electron microscopy, and nuclear magnetic resonance spectroscopy are all within the realm of possibility. Finding small molecules that can bind to the desired protein as well as alter its function is the next step after determining the protein's structure [12].

One computer method for predicting how tiny compounds would attach to a target protein is called “molecular docking”. The goal of molecular docking is to identify potential ligands for a target protein by searching a database of small molecules for their binding sites. After that, the molecules with the greatest match are chosen for further examination [13]. "Structure-activity relationship (SAR)" study is performed to maximise the specific drugs' interaction to the target protein. In SAR analysis, the compounds' chemical structures are changed, and their ability to interact with the target protein is tested. By comparing the activity of the modified molecules to that of the primary molecule, SAR analysis may help identify the crucial molecular properties required for binding to the desired protein [6].

C. Applications of SBDD

Drugs for a variety of ailments have been successfully developed via SBDD. The creation of protease inhibitors to treat HIV is a prominent example. One enzyme that is essential to the virus's reproduction is HIV protease. Small compounds that could attach to the protease's active site and stop its activity were created using SBDD in order to stop the virus from replicating. Because of this strategy, medications like ritonavir and saquinavir, which are often used to treat HIV, have been developed. Additionally, SBDD has been used in the creation of cancer medications [14]. DNA mutations often seen in cancer cells cause overexpression of certain proteins, which may promote the formation of tumours. In order to delay or halt the development of tumours, SBDD has been utilised to create tiny compounds that can attach to these overexpressed proteins and block their function. "Imatinib, which targets the Bcr-Abl protein in chronic myeloid leukaemia, and vemurafenib", which targets the BRAF protein in melanoma, are two of the cancer drugs developed by SBDD [12].

2 Literature Review

(Batista-Silva et al., 2024) [15] The prognosis for prostate cancer (PCa), one of the most common tumours in males, is dismal due to a lack of appropriate biomarkers or their modulators. In addition to playing a significant part in the initiation and spread of PCa, membrane proteins (MPs) might make appealing therapeutic targets. The successful finding of biomarkers and inhibitors is hampered by experimental difficulties in targeting MPs. Computational techniques may help get beyond this obstacle by screening huge libraries of compounds and providing structural insights, which speeds up lead optimisation and identification. This study aims to investigate new avenues in "computer-aided drug design (CADD)" by identifying the most significant membrane-bound prostate cancer (PCa) indicators using structure-based approaches.

(Giladi et al., 2024) [2] There are still a lot of unanswered questions about the distinct structural and functional characteristics of TSPO ligands in health and illness, even after several classes of ligand

chemotypes have been developed and experimental structures of bacteria and non-human mammals have been clarified. Current computational approaches for simulating the natural structure and ligand-binding activity of this mysterious protein have a number of drawbacks. With this viewpoint, we provide a critical evaluation of the advancements in the use of these techniques, describing their applications, intrinsic drawbacks, and ongoing difficulties. As a means of enhancing our understanding of the TSPO, we suggest unexplored avenues for computational techniques.

(Tang et al., 2024) [8] Growing druglike "make-on-demand" libraries and an ever-increasing number of known and anticipated protein structures need novel computational approaches to structure-based computer-aided drug creation, which is notoriously laborious. By using in silico heuristics, de novo drug design expedites the search in the vast chemical space. Focussing on current developments in structure-based de novo drug design, this study covers everything from deep generative models to evolutionary algorithms, Metropolis Monte Carlo techniques, and traditional fragment-based approaches. As the production of easily accessible drug-like compounds has long been a challenge for de novo drug development, we emphasise the efforts to create synthetic access in each category as well as the benchmarking techniques used to verify the suggested framework.

(Özçelik et al., 2023) [16] Affinity prediction for unknown protein targets, the clarification of "binding mechanisms, and the rationalisation of related chemical kinetic properties" are just a few of the unresolved problems that could be addressed by structure-based drug discovery, even though ligand-based approaches have dominated deep learning efforts in this field. Developments in deep learning techniques and the availability of precise protein tertiary structure predictions support a return to structure-based methods for AI-guided drug development. In this study, the key algorithmic ideas in structure-based deep learning for drug discovery are compiled, and future prospects, uses, and difficulties are anticipated.

(Pliushcheuskaya & Künze, 2023) [10] Computational methods are a vital tool in drug discovery and may expedite lead optimisation and identification, particularly in the early phases of development. This paper covers important facts on ion channels, including their classification, structure, processes, and illness, and focusses on recent advances in computer-aided, structure-based medicine design on ion channels. We highlight research that uses modelling and chemoinformatic techniques in conjunction with structural data to identify and characterise novel compounds that target ion channels. These methods have the potential to significantly improve future ion channel medication development.

(Aplin et al., 2023) [17] prove that structural approaches have now progressed to the stage where they can investigate protein targets' dynamic information. We begin by discussing recent advances in X-ray crystallography techniques, including serial room-temperature crystallography, which allows the analysis of protein-inhibitor complexes with an unparalleled degree of shape-dynamic accuracy. Another high-resolution technique, "cryogenic electron microscopy (cryoEM)", has recently been employed to investigate proteins and protein combinations that are too intricate to crystallise. In conclusion, we introduce small-angle X-ray scattering (SAXS) as a potential high-throughput screening approach for discovering oligomerisation and protein complex inhibitors.

(Bruch et al., 2020) [6] Computer-aided and structure-based drug design methods are generally seen as having been effective in the areas of antiviral and cancer drug discovery, but not so much in the creation of antibacterial drugs. Protein kinase (Pkn) B and PknG, two serine/threonine (Ser/Thr) kinases, have long been thought to be particularly promising targets. One well-known target that has been pharmacologically verified is the DNA gyrase of Mycobacterium TB. These three case studies are the ones studied here. After highlighting some of the difficulties that logical, target-based TB drug discovery efforts continue to encounter, we concluded by talking about the new insights brought about by recent methodological advancements in structural biology and integrative approaches.

(Wang et al., 2018) [18] Computer science's progress serves as an additional incentive that facilitates the effective implementation of computational methods throughout the various phases of drug development and research. These days, researchers may estimate the affinity of ligands to target proteins with a high degree of precision and efficiency by using Structure-Based Drug Design (SBDD) techniques, which also assist forecast the location of small molecules inside a three-dimensional model of the protein structure. Additionally, they decrease the time and expense associated with drug research while speeding up the discovery of powerful drugs. We highlight the recent successes and major challenges of SBDD in drug development, providing an overview of the method's use in this context.

3 Conclusion

Despite significant advancements, structure-based drug design (SBDD) faces several challenges that hinder its full potential in novel ligand discovery. The complexity of target proteins like TSPO, limitations in current computational models, and the oversimplification of experimentally derived protein structures present significant obstacles. Existing scoring functions struggle to accurately estimate binding free energy due to protein flexibility, solvent effects, and key water molecules in target proteins. Addressing these factors remains crucial for improving protein-ligand interaction predictions. Additionally, computational approaches for drug-target interaction prediction require enhanced methodologies and better data integration. Overcoming these barriers will depend on improved data collection, curation, and more accurate homology models, particularly for human proteins where multiple structural templates remain underexplored. Despite these challenges, SBDD holds great promise for accelerating drug discovery through innovative computational techniques. Targeting unknown macromolecular structures may be facilitated by the use of "de novo ligand creation, drug-target interaction prediction, and ligand binding" site identification. The integration of deep learning into SBDD has opened new avenues, enhancing protein structure prediction, drug association mapping, and structural refinement. These developments increase the possibility of finding potent medicinal molecules by enabling a more effective search of chemical space. With continued progress in computational modeling, artificial intelligence, and data-driven methodologies, SBDD is poised to revolutionize drug discovery in the coming years.

References

[1] C. Isert, K. Atz, and G. Schneider, "Structure-based drug design with geometric deep learning," Curr. Opin. Struct. Biol., vol. 79, p. 102548, 2023, doi: 10.1016/j.sbi.2023.102548.

[2] M. Giladi, A. P. Montgomery, M. Kassiou, and J. J. Danon, "Structure-based drug design for TSPO: Challenges and opportunities," Biochimie, vol. 224, pp. 41–50, 2024, doi: 10.1016/j.biochi.2024.05.018.

[3] S. Sahu, J. Boaddh, and V. S. Pawar, "Machine Learning in Diabetes Diagnosis : A Comprehensive Review," pp. 80–85, 2024, doi: 10.69968/ijisem.2024v3i480-85.

[4] S. P. Singh, S. K. Shukla, and R. Yadav, "Artificial intelligence and Machine learning- based approaches for Neurodegenerative Diseases Diagnosis," pp. 31–37, 2023.

[5] J. A. Weller and R. Rohs, "Structure-Based Drug Design with a Deep Hierarchical Generative Model," J. Chem. Inf. Model., vol. 64, no. 16, pp. 6450–6463, 2024, doi: 10.1021/acs.jcim.4c01193.

[6] E. M. Bruch, S. Petrella, and M. Bellinzoni, "Structure-based drug design for tuberculosis: Challenges still ahead," Appl. Sci., vol. 10, no. 12, 2020, doi: 10.3390/app10124248.

[7] D. Cao, P. Zhang, and S. Wang, "Advances in structure-based drug design: The potential for precision therapeutics in psychiatric disorders," Neuron, vol. 112, no. 4, pp. 526–538, 2024, doi: 10.1016/j.neuron.2024.01.004.

[8] Y. Tang, R. Moretti, and J. Meiler, "Recent Advances in Automated Structure-Based De Novo Drug Design," J. Chem. Inf. Model., vol. 64, no. 6, pp. 1794–1805, 2024, doi: 10.1021/acs.jcim.4c00247.

[9] B. L. Staker, G. W. Buchko, and P. J. Myler, "Recent contributions of Structure-Based Drug Design to the development of antibacterial compounds," Physiol. Behav., vol. 176, no. 1, pp. 139–148, 2016, doi: 10.1016/j.mib.2015.09.003.Recent.

[10] P. Pliushcheuskaya and G. Künze, "Recent Advances in Computer-Aided Structure-Based Drug Design on Ion Channels," Int. J. Mol. Sci., vol. 24, no. 11, 2023, doi: 10.3390/ijms24119226.

[11] M. Batool, B. Ahmad, and S. Choi, "A structure-based drug discovery paradigm," Int. J. Mol. Sci., vol. 20, no. 11, 2019, doi: 10.3390/ijms20112783.

[12] A. Peter, "Principle and Applications of Structure Based Drug Design," Drug Des. Open Access, vol. 12, no. 1, pp. 1–1, 2023, doi: 10.35248/2169-0138.23.12.235.

[13] R. R. Ramsay and G. Di Giovanni, "Editorial: Structure-based drug design for diagnosis and treatment of neurological diseases," Front. Pharmacol., vol. 8, no. JAN, pp. 1–2, 2017, doi: 10.3389/fphar.2017.00013.

[14] Y. Li, J. Pei, and L. Lai, “Structure-based: De novo drug design using 3D deep generative models,” Chem. Sci., vol. 12, no. 41, pp. 13664–13675, 2021, doi: 10.1039/d1sc04444c.

[15] J. P. Batista-Silva, D. Gomes, S. F. Sousa, Â. Sousa, and L. A. Passarinha, “Advances in structure-based drug design targeting membrane protein markers in prostate cancer,” Drug Discov. Today, vol. 29, no. 9, p. 104130, 2024, doi: 10.1016/j.drudis.2024.104130.

[16] R. Özçelik, D. van Tilborg, J. Jiménez-Luna, and F. Grisoni, “Structure-Based Drug Discovery with Deep Learning,” 2023.

[17] C. Aplin, S. K. Milano, K. A. Zielinski, L. Pollack, and R. A. Cerione, “Evolving Experimental Techniques for Structure-Based Drug Design,” J. Phys. Chem. B, vol. 126, no. 35, pp. 6599–6607, 2023, doi: 10.1021/acs.jpcb.2c04344.

[18] X. Wang, K. Song, L. Li, and L. Chen, “Structure-Based Drug Design Strategies and Challenges,” Curr. Top. Med. Chem., vol. 18, no. 12, pp. 998–1006, 2018, doi: 10.2174/1568026618666180813152921.