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The Application and Challenges of Artificial Intelligence in G Protein-Coupled Receptor Drug Virtual Screening

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Abstract:

G protein-coupled receptors play important roles in various diseases and are key targets for drug discovery. Virtual screening has traditionally been used to identify potential drug candidates from large compound libraries but faces challenges in computational resources and time constraints. The integration of artificial intelligence technologies has improved screening precision and reduced costs. This review discusses current developments, challenges, and future directions in leveraging artificial intelligence to advance GPCR drug screening.

Keywords: Artificial Intelligence, Deep Learning, G Protein-Coupled Receptor, Virtual Screening, Drug Discovery

1. Introduction

G protein-coupled receptors (GPCRs) are crucial drug targets implicated in various diseases such as neurological conditions, immune conditions, metabolic disorders, cardiovascular diseases, and cancers. Approximately 34% of FDA-approved drugs act on GPCRs[1], highlighting their therapeutic significance. In drug discovery, virtual screening (VS) is a computational technique used to simulate and screen vast compound libraries to identify potential drug candidates[2]. However, with the exponential growth of compound libraries, traditional virtual screening methods face significant challenges related to computational resources and time constraints[3-5].

Integrating Artificial Intelligence (AI) technologies can greatly enhance the efficiency, accuracy, and cost-effectiveness of GPCR drug virtual screening. Current research indicates that applying deep learning models accelerates data processing and analysis, optimizing the prediction of candidate drugs. This boosts drug development efficiency and reduces research and development costs[6]. Therefore, combining AI with GPCR drug virtual screening stands to revolutionize drug screening methods, offering substantial practical implications and application value.

Despite significant advancements in AI technologies in GPCR drug virtual screening, challenges persist concerning data quality and quantity, as well as the interpretability of models[7-9]. This paper aims to provide a comprehensive review of the development and application of AI in GPCR drug screening, discuss existing limitations and challenges, and offer insights for future improvements in GPCR drug development.

2. The Role of GPCRs in Drug Development

GPCRs, characterized by a seven-transmembrane helical structure, represent the largest family of membrane proteins encoded by the human genome (approximately 800 types). They regulate numerous physiological processes in the human body[10, 11]. Because of their broad physiological regulatory roles, GPCRs constitute the largest category of drug targets. Dysregulation in GPCR signaling can lead to various diseases, including Alzheimer's disease, depression, obesity, diabetes, cardiovascular diseases, and cancers[1, 12-15].

By 2017, the FDA and the European Medicines Agency (EMA) had approved 475-704 drugs acting on various GPCRs[1, 11]. Between 2011 and 2015, the total sales of drugs targeting GPCRs reached 917 billion USD[16]. Therefore, GPCRs hold a pivotal role in drug development. However, due to their complex structure, flexible conformation, and low expression levels, accurately determining their precise structures remains highly challenging, which limits the precise design and development of GPCR-targeted drugs[6, 17-20].

3. The Significance of AI in Drug Screening

3.1 Overview of AI Technology

AI is an interdisciplinary field focused on simulating human cognitive abilities using intelligent machines. It encompasses a wide range of technologies, algorithms, and models, among which machine learning stands out as a crucial area, comprising both supervised and unsupervised learning methods. In particular, deep learning, a subset of machine learning, has rapidly progressed in recent years and is extensively applied in drug design and development. Key algorithms used in these applications include support vector machines, artificial neural networks, convolutional neural networks, random forests, and naive Bayes[21-24].

Current research highlights AI's capacity to integrate adaptive features and learning capabilities into every stage of new drug development, including drug design, chemical synthesis, drug repurposing, polypharmacology, and drug screening[25]. AI is increasingly recognized as a powerful tool in modern drug discovery, promising significant advancements in pharmaceutical research and innovation.

3.2 Limitations of Traditional Virtual Screening

In recent decades, the size of compound libraries has grown exponentially. For example, the number of molecules in databases like ZINC increased from 120 million to 1 billion between 2015 and 2020[3, 4]. Commercial databases now contain tens to hundreds of billions of synthesizable compounds[26, 27]. While these vast libraries offer opportunities to identify potential drug candidates, they also pose substantial challenges related to time and computational resources. Accelerating the screening process for these ultra-large libraries without compromising the hit rate remains a critical issue in drug discovery. The rapid development of AI technologies presents promising solutions to effectively overcome these challenges.

3.3 The Importance of AI Technology in GPCR Drug Screening

The process of drug development is complex and protracted, fraught with high costs and uncertainties. Bringing a new drug from conception to market typically spans over a decade and involves investments exceeding billions of dollars[28, 29]. Advances in technology have enabled the integration of AI algorithms into computer-aided drug design, overcoming traditional constraints of time and resources. AI represents a shift from hypothesis-driven approaches to data-driven methodologies, revolutionizing drug discovery processes[30].

AI technology facilitates the rapid and efficient screening of extensive compound libraries. Through the analysis of extensive chemical and biological datasets, AI pinpoints potential drug targets and accelerates the candidate screening process without compromising analytical rigor. This capability significantly compresses research and development timelines and reduces associated costs. Furthermore, AI algorithms play a pivotal role in forecasting the safety and efficacy profiles of candidate compounds. This predictive capability supports the identification and design of compounds with high affinity and efficacy, thereby lessening dependence on preclinical and clinical trials. Consequently, it streamlines drug development pathways, enhances clinical trial success rates, and ultimately delivers safer and more effective therapeutic solutions[31, 32].

In the realm of GPCR drug discovery, AI offers substantial advantages across various stages. It enhances researchers' abilities to predict GPCR functions and ligand-GPCR binding affinities, design optimal ligands, forecast biological activities, and identify potential agonists. This transformative technology promises to expedite drug development processes, enabling faster transitions from laboratory discoveries to market availability. Ultimately, AI-driven advancements are poised to address diverse therapeutic challenges more effectively, benefiting patients worldwide.

4. Current Development and Application of AI in GPCR Virtual Screening

The progress in cryo-electron microscopy and X-ray crystallography has led to a growing number of high-resolution GPCR structures being resolved[1, 33]. Breakthroughs in artificial intelligence, particularly with deep learning algorithms like AlphaFold, have notably improved the accuracy of protein structure prediction, especially in identifying multiple functional states of GPCRs[34, 35]Hannah K</author><author>Ovchinnikov, Sergey</author><author>Colwell, Lucy</author><author>Kern, Dorothee</author></authors></contributors><titles><title>Prediction of multiple conformational states by combining sequence clustering with AlphaFold2</title><secondary-title>BioRxiv</secondary-title></titles><periodical><full-title>BioRxiv</full-title></periodical><pages>2022.10. 17.512570</pages><dates><year>2022</year></dates><urls></urls></record></Cite></EndNote>. These advancements provide comprehensive information for virtual screening based on GPCR protein structures. The rapid evolution of AI technology, along with improvements in greater access to big data and computational hardware, has significantly

increased the use of AI-driven applications in speeding up GPCR drug discovery. By 2022, AI methods accounted for 3.6% of research in GPCR studies[36].

4.1 Application of AI in GPCR Drug Virtual Screening

Combining AI with structure-based virtual screening has emerged as a prominent area of research. AI models are increasingly utilized for the initial screening of compound libraries, substantially reducing the number of compounds that require molecular docking. This multi-stage virtual screening strategy not only streamlines the process but also mitigates computational expenses. For example, Tang et al. (2023) utilized deep learning models to swiftly screen about 1.4 billion compounds, narrowing the selection down to the top 500,000 for further docking studies, thus avoiding the need to evaluate the whole library[37]. Wang et al. (2021) applied classification models based on neural networks to preliminarily screen extensive compound libraries, reducing over 90% of compounds that require final molecular docking[38]. Machine learning models, trained on molecular docking data, have demonstrated the capability to narrow down the number of docking compounds from billions in virtual libraries to just one percent of the original pool, while simultaneously enriching for high-scoring molecules[39]. A range of virtual screening methods based on machine learning and deep learning have shown superior efficiency and accuracy in scoring compared to traditional docking methods[40, 41]. Furthermore, machine learning models used in ligand-based virtual screening enhance the predictive capability of ligand models, effectively identifying bioactive small molecules. These models are advantageous because they do not need prior knowledge of GPCR precise structures and their interactions with active compounds, making them suitable for GPCRs where structural-based drug design was formerly unfeasible[42]. AutoDock Vina is one of the most commonly used molecular interaction algorithms, the first to improve scoring through a random forest machine learning approach, ranking compounds according to binding affinity (Li et al., 2015) [43]. Zhang et al. (2022) introduced an innovative 2D convolutional neural network approach to identify patterns from protein-ligand interaction matrices, facilitating more effective drug virtual screening and identification of protein-ligand interactions to discern natural protein ligands[44].

Machine learning algorithms, including neural networks, support vector machines, and Bayesian frameworks contribute significantly to managing large bioactivity datasets, enabling more precise and expedient screening based on predicted activities against specific targets for subsequent experimental validation[45-47].

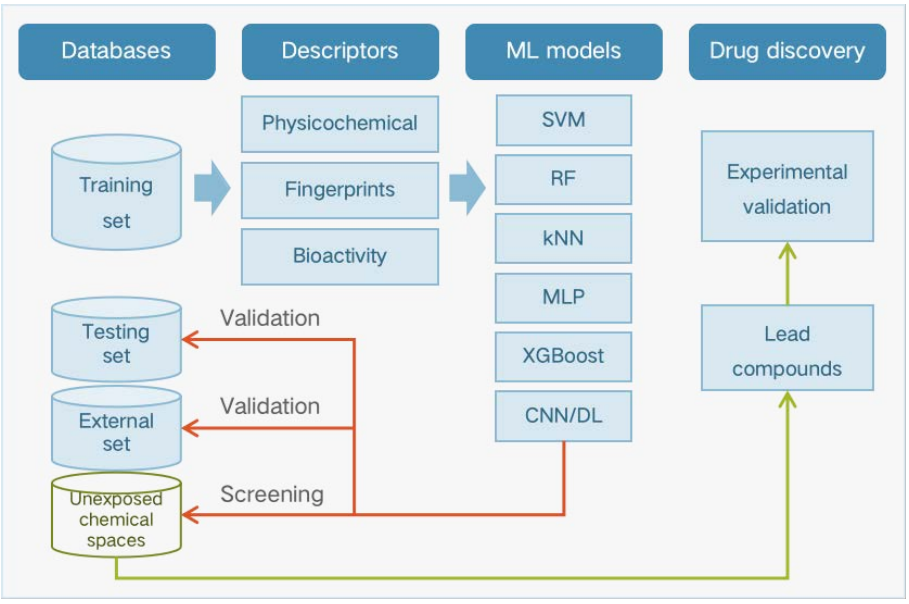

Figure 1 Workflow of AI-driven structure and ligand-based virtual screening protocols[48].

4.2 Clinical Trial Progress of GPCR Drugs Based on AI Technology

The first wave of drugs developed using AI has brought new hope to diseases with limited treatment options. In January 2020, Exscientia, a pharmaceutical company based in the UK, revealed that its compound DSP-1181, a powerful and long-lasting serotonin 5-HT_{1A} receptor agonist designed for the treatment of obsessive-compulsive disorder, had advanced to Phase I clinical trials. DSP-1181, developed using an AI platform, was reported as the

first of its kind to enter clinical trials. The process, from initial screening to the completion of preclinical studies, took less than 12 months, which is notably faster than the industry average[49]. Despite disappointing Phase I trial results, this marks a significant milestone in AI-driven drug discovery.

In June 2022, Exscientia reported preliminary Phase I trial results for EXS-21546, a highly selective A_{2A} receptor antagonist created in collaboration with Evotec AG in Hamburg, Germany. The results included the drug's potency, high receptor selectivity, and safety profile regarding the central nervous system. Subsequently, this small molecule progressed to Phase 1b/2 clinical trials targeting patients with tumors characterized by elevated adenosine signaling[50, 51]. These advancements not only demonstrate the feasibility of AI in GPCR drug screening and development but also highlight its potential to accelerate therapeutic innovation.

5. Challenges of AI in GPCR Drug Virtual Screening

Despite the promising prospects AI presents in the field of drug discovery, it encounters many obstacles like inadequate data and lack of interpretability. Further exploration of these issues will help us better understand how AI can be practically applied in drug screening and will provide direction for its future development.

5.1 Data Quality and Quantity

AI technology heavily depends on extensive, high-quality data to build precise models. While data related to GPCRs has increased, it remains comparatively scarce in contrast to other research fields. GPCRs constitute a diverse family of receptors with notable functional and structural diversity[52]. To train robust AI models requires well-balanced datasets covering various GPCR subtypes and ligand categories. Addressing this challenge involves strategies like collaborative data sharing, multi-source data collection, data annotation, standardized experimental protocols, and quality control measures[36]. Moreover, AI-driven techniques for data augmentation can be employed to generate synthetic datasets. The combined implementation of these strategies will contribute to developing more powerful, accurate, and generalizable AI models in GPCR drug discovery.

5.2 Model Interpretability

A major challenge lies in the interpretability of AI models and their predictive outputs. Given the intricate structural and functional properties of GPCRs, understanding the molecular mechanisms behind ligand-receptor interactions is essential for rational drug design. AI models, especially those based on deep learning, frequently face criticism for their opaque, black-box nature and limited transparency in interpretation[8, 53]. Previous deep learning approaches have shown contradictory results in determining optimal solutions, raising doubts about their predictive accuracy in practical applications[54]. Some researchers argue that only interpretable models are trustworthy[55, 56]. Addressing this challenge involves efforts to develop AI models capable of providing interpretable results. Introducing attention mechanisms into AI models allows researchers to identify and focus on particular regions or features within ligands or GPCRs that are most relevant to the model's predictions[57]. Moreover, feature importance analysis can enhance interpretability[58]. Researchers can determine the most significant descriptors or features by evaluating the impact of each input feature on the model's predictions. Recent advancements in enhancing the interpretability of deep learning models are promising[59-61], and we anticipate that machine learning approaches equipped with explanatory mechanisms will be more widely employed in the process of GPCR drug discovery.

5.3 Model Interpretability

5.3.1 Biological System Complexity

The human body is an intricate system where genes, proteins, and numerous physiological processes interact in complex ways. To predict interactions and potential outcomes between drugs and GPCR targets with accuracy, AI algorithms must tackle these complexities. A deep understanding of biological system complexity is essential for the successful application of AI in advancing GPCR drug development.

5.3.2 Validation and Reproducibility

In AI-driven drug development, validating models and ensuring result reproducibility are crucial. Rigorous validation processes are vital for confirming the reliability and generalizability of AI-generated predictions.

5.3.3 Resource and Infrastructure Investments

Integrating AI technology into drug development often necessitates substantial investments in technology, infrastructure, and skilled personnel. These investments are essential to support the computational power, data management systems, and expertise required to effectively utilize AI in GPCR drug screening and development.

6. Conclusion and Future Perspectives

The use of AI in virtual screening for GPCR-targeted drugs has demonstrated significant progress and tremendous potential. Through the extensive utilization of machine learning/deep learning models and other AI technol-

ogies, researchers have greatly improved the accuracy and efficiency of GPCR drug virtual screening, overcoming limitations in computational resources and time inherent in traditional drug screening methods. AI has accelerated the drug discovery process and optimized the prediction of candidate drugs, thereby improving research and development efficiency while reducing costs.

However, the future application of AI in GPCR drug screening still faces many challenges. First, it is essential to establish high-quality, diverse datasets of GPCRs and ligands. Enhancing data quality and quantity through collaborative data sharing, multi-source data collection, and standardized experimental protocols will improve the accuracy and generalizability of AI models. Secondly, model interpretability remains a critical research direction. It is vital to develop AI models that produce transparent and interpretable results for researchers to understand and trust AI predictions. Additionally, experimental validation poses a significant challenge in AI-powered GPCR drug screening. To ensure the reliability and applicability of AI-generated predictions, establishing robust validation frameworks is essential. These systems will effectively assess and enhance the performance and prediction accuracy of AI models, thereby increasing their credibility in practical applications. By continually overcoming these challenges, the prospects of AI in GPCR drug virtual screening will broaden, leading to breakthroughs in drug development.

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