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AI in Drug Discovery: Present and Future

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ABSTRACT

AI harnesses personalized knowledge and learns from the solutions it generates to address a spectrum of issues, from straightforward to complex. The landscape of drug development stands poised for transformation, propelled by remarkable advances in processing power and AI technology. Presently, the pharmaceutical sector grapples with escalating R&D costs and diminishing efficiency in drug development initiatives. This overview delves into the primary causes behind the high attrition rates in drug approval, explores potential avenues through which AI could enhance the efficacy of the drug research process, and examines collaborations between major players in the pharmaceutical industry and AI-driven drug discovery firms.

INTRODUCTION:

Presently, artificial intelligence (AI) stands as a domain within engineering known for its utilization of innovative ideas and unconventional methods in addressing complex challenges. With ongoing advancements in electronic speed, capacity, and software development, there's a prospect that computers could potentially reach human-like levels of intelligence in the future.[1]

Any software application or system capable of performing tasks deemed intelligent in humans falls under the umbrella of artificial intelligence (AI). AI technologies serve to augment human capabilities by deriving concepts and correlations from data, autonomously learning from patterns within that data. [2]

The field of artificial intelligence within computer science is dedicated to the development of intelligent machines capable of performing tasks traditionally reserved for human intellect. In essence, AI entails the study of cognitive abilities through computational models. John McCarthy coined the term in 1956, defining it as the discipline concerned with creating intelligent machines through science and engineering.[4]

In the realm of medicine, two distinct subtypes of AI emerge: Virtual and Physical. The virtual aspect, epitomized by machine learning or deep learning, employs mathematical algorithms to augment learning through experience. On the other hand, the physical facet encompasses tangible elements such as medical equipment and sophisticated robots, including carebots, which actively participate in patient treatment. For instance, robots are utilized in surgical settings, serving as assistant surgeons or even operating autonomously.[1]

AI holds promise for a range of chemistry-related roles, encompassing molecular design, forecasting the bioactivities of novel drugs, streamlining laboratory processes through automation, and proposing synthetic pathways for intricate molecules, thereby diminishing experimental demands.

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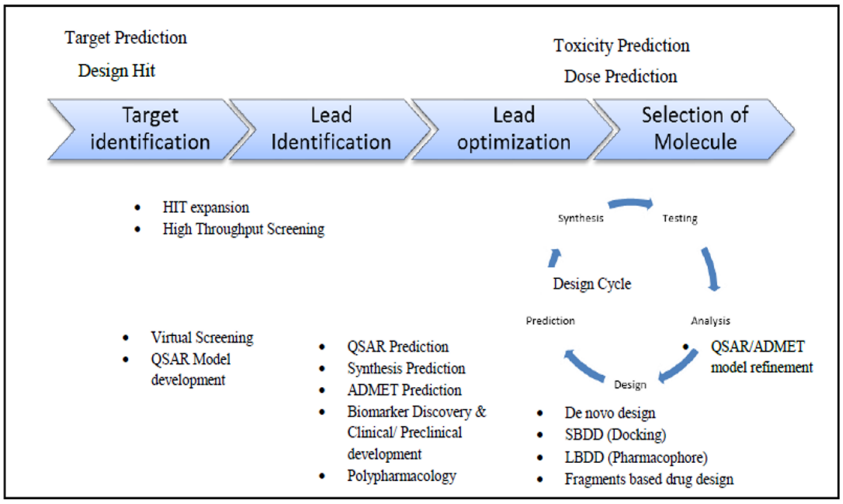
Various stages of early drug discovery stand to gain significantly from the advancement and implementation of AI methodologies. This includes more accurate identification of hits from high throughput screening (HTS) and hit expansion, efficient design of novel drug-like compounds and their synthetic routes, improvement in lead optimization efficiency through the development of more precise ADMET and QSAR models, and reduction in the overall cost and duration of the drug discovery process. (Fig: 1).

In recent decades, drug discovery and development have relied on in-silico QSAR models for predicting drug activity. Algorithms tailored for relatively small datasets, such as multiple linear regression (MLR) and partial least squares (PLS), have been commonly employed for this purpose.



(Fig: 1). Artificial Intelligence and Machine Learning tools are integrated into every stage of the drug discovery process, from lead identification through the discovery of small molecules to the generation of QSAR models and the optimization of lead structures.

The relationship between artificial intelligence and chemistry is highly interconnected. AI plays a vital role in various aspects of chemistry, particularly in drug discovery and development. This includes tasks such as molecule design, predicting molecular properties, forecasting synthetic routes, and conducting retrosynthesis reactions.[5]

Why AI in drug Discovery?

The adoption of artificial intelligence (AI) among chemists is on the rise for various purposes. Initially, the primary motivation for research into AI applications in chemistry

stemmed from the imperative to accelerate drug development, reduce its substantial expenses, and expedite the time required for new drugs to become available on the market. [6]

For pharmaceutical companies, reducing costs and expediting project timelines are critical objectives. To achieve these goals, AI-based methods are increasingly utilized across various stages of the drug discovery process to enhance efficiency. These methods encompass AI applications in real-time image-based cell sorting and classification, quantum mechanics calculations for compound properties, computer-aided organic synthesis, molecule design, assay development, and predicting the 3D structures of target proteins, among others. Generally, these tasks are laborious and time-consuming, but with AI's assistance, they can be automated and optimized, leading to significant acceleration in the drug discovery R&D process. Below, we explore the different subareas of drug discovery that have benefited from the integration of AI. [2]

Reduce timeline for drug Discovery and Improve research process: Effective innovative technologies have the potential to accelerate the drug discovery process.

Increase the accuracy of predictions on the Efficacy and Safety of drugs: Many drugs fail during clinical trials due to insufficient efficacy and safety concerns. A mere 10% enhancement in prediction accuracy could result in saving billions of dollars otherwise spent on drug development.[3]

Artificial intelligence in drug discovery:

The global prioritization of artificial intelligence (AI) technology has gained increasing significance, particularly following the remarkable successes of Google-owned Alpha Go, Alpha Go Zero, and Alpha Zero in games like Go and chess. The advancement of computers, particularly in the realm of high-performance parallel computing clusters, has led to a substantial increase in computational capabilities. This progress has been further propelled by the emergence of graphics processing unit (GPU) calculations and the exponential growth of chemical informatics data. By December 2018, the ChEMBL database alone contained over a million active compounds, while the availability of chemical data for model training and validation has seen a significant surge with the introduction of databases like PubChem and ChEMBL. Currently, PubChem hosts over 100 million distinct chemicals. [6]

The Defense Advanced Research Projects Agency (DARPA) officially launched the Accelerated Molecular Discovery (AMD) program to introduce innovative AI-based

methodologies to expedite the identification and refinement of high-quality molecules, particularly those with medicinal potential. Furthermore, prominent global pharmaceutical companies such as Merck, Sanofi, Genentech, and Takeda have initiated collaborative efforts with AI firms. These partnerships exemplify the diverse applications of AI in drug development. [2]

Artificial intelligence (AI) and emerging experimental technologies are anticipated to render the search for new therapeutics more affordable, faster, and cost-effective. This review primarily examines the application of AI in drug discovery, particularly focusing on its role in drug design and primary and secondary screening processes. AI aids in predicting the physical and chemical properties of designed molecules, as well as in forecasting synthetic routes and retro synthesis pathways. [2]

It's intriguing to note that among the initial applications of AI techniques in drug development was the focus on generating new synthesis pathways and reverse engineering existing patents. Notably, Exscientia, one of the AI startups, announced that the first immuno-oncology medicine crafted by AI has progressed into clinical trials. [7]

Tools	Details
Deep tox[8]	For prediction of toxicity of molecule
Organic[8]	Tool for the generation of Molecule with desired properties
Deltavina[8]	A Scoring function for drug-ligand binding affinity
Alphafold[10]	A solution for the protein folding problem
DeepChem[10]	Python based AI system to find a suitable candidate in drug discovery
TwoXAR, Atomwise, ReviveMed[9]	To screen compound library for efficacy against a disease to discover new candidate or generating newer drug candidate.
Phenomic.AI, Structura Biotechnology[9]	For understanding disease mechanism.

Ai in finding Hit or Lead:

Initially, drug development entails the discovery of new chemical compounds possessing biological activity. This activity often results from the interaction of these compounds with enzymes and specific receptors. A compound demonstrating biological activity against the intended target is termed a "hit". [7]

After identifying the hit molecule, its analogues are examined to ascertain the structure-activity relationship (SAR) of the compounds.[35] Employing AI for lead discovery is more straightforward compared to traditional methods. Collaboration between AI and chemical

space researchers facilitates the identification of potential medication molecules for treating diseases.[36]

The utilization of AI methodologies enhances the potential for computational screening of potential drug candidates by significantly expanding the feature space used to define specific criteria for inclusion or exclusion, encompassing virtual screening, drug repurposing, de novo design for hits, or modification of existing molecules.[11]

In the realm of de novo drug design, the integration of ML techniques and Molecular Dynamics (MD) simulations is enhancing both efficiency and accuracy.[11]

Neural network technology:

Artificial neural networks (ANNs) have been developed based on the networking patterns observed in the human brain (Homo sapiens), serving as widely recognized computer models. ANNs find extensive application in drug design and molecular modeling, simplifying the intricacies associated with statistical models utilized in pharmacokinetic and pharmacodynamic research, QSAR (quantitative structure-activity relationship), and HTVS (high-throughput virtual screening). ANNs are employed in various aspects such as examining comprehensive small molecule databases (HTVS), property prediction (ADME/T), QSAR, pharmacophore analysis, pose validation, formulation, and lead development.[12]

Molecule design facilitated by artificial intelligence:

The utilization of artificial intelligence in molecular design has revolutionized the discipline, enabling groundbreaking discoveries. Molecular characteristic detection proves immensely beneficial in chemistry. By leveraging historical data, scientists establish chemical relationships and construct molecules. Integration of AI algorithms has propelled researchers in compound discovery, leading to notable advancements in AI chemical synthesis. Furthermore, molecular creation unlocks diverse valuable applications, significantly advancing the field of chemistry.[13]

After designing molecules, they can undergo either synthetic production or virtual screening, utilizing software such as docking or AI-based programs, to predict their properties. Only the most promising molecules are retained for further investigation. Alternatively, methods like Bayesian optimization can be employed to systematically search for compounds meeting

specific property criteria, especially when aiming to obtain a small number of precisely designed molecules rather than a large quantity.[14]

Designing from scratch:

De novo design aims to develop algorithms that streamline the process of selecting novel molecules possessing desired property profiles. Through reconstructing organic molecules and gathering specific molecular characteristics from a training set, this technology enables a gradient-based exploration of chemical space, facilitating the discovery of new drugs with targeted qualities. Regrettably, it was found that some undesired compounds, such as those challenging to synthesize, were also generated.[5]

The direction of the de novo design process can vary depending on the data utilized, employing ligand-based approaches, structure-based approaches, or a hybrid of both. Ligand-based methodologies are typically categorized into two main groups: (i) Rule-based approaches involve a predefined set of rules for assembling molecules from reagents or molecular fragments. (ii) Rule-free approaches, on the other hand, do not adhere to strict construction rules but instead focus on generating molecules with desired properties without the constraints of predetermined molecular construction rules.[15]

Utilizing deep learning techniques, which possess powerful generalization and learning capabilities, has been instrumental in automatically generating new chemical entities with predefined features. This application addresses the current challenges encountered in de novo drug discovery.[16]

Prediction of molecular properties using artificial intelligence:

If researchers could accurately predict the attributes of hypothetical molecules, they could focus on synthesizing only the most promising chemicals, thereby avoiding the synthesis and testing of numerous molecules lacking the desired qualities. Traditional methods for predicting molecular characteristics, such as quantitative structure-activity relationships (QSAR) or quantitative structure-property relationships (QSPR), rely on physical principles or empirical correlations that associate the structures of molecules with their properties, often through a predefined set of descriptors. QSAR specifically links a drug's chemical characteristics to its biological function, establishing a connection between the biological activity of pharmaceuticals and the structural and chemical characteristics or descriptors of their smaller sub molecular components**.**[19]

Machine learning techniques are also applicable for predicting chemical properties. These methods can forecast various attributes such as bioactivity, toxicity, solubility, melting temperatures, atomization energies, HOMO/LUMO molecular orbital energies, and numerous others.[17]

Machine Learning Methods for Chemical Property Prediction

Attributes Predicted:

1. Bioactivity
2. Toxicity
3. Solubility
4. Melting Temperatures
5. Atomization Energies
6. HOMO/LUMO Molecular Orbital Energies

Machine Learning Algorithms Used:

1. Regression
2. Classification
3. Neural Networks
4. Support Vector Machines

Deep neural networks have found application in numerous property prediction tasks. Belonging to the category of artificial neural networks, deep neural networks are inspired by the structure and function of the human brain.[18]

The integration of artificial intelligence in organic chemistry synthesis

In chemistry, pathfinding involves identifying the optimal sequence of actions leading to a solution, pinpointing the most favourable approach or pathway.[12]

Quantum mechanical methods enable the calculation of transition states and the subsequent prediction of reaction trajectories.[20]

Assessing the influence of temperature or solvents on reactions poses challenges. Determining the simplicity or complexity of synthesizing a chemical is fundamental in organic synthesis. This aspect holds significant importance in the drug discovery process, particularly due to the generation of numerous new structures through de novo design techniques.[19]

Subsequently, it is the responsibility of the medicinal chemist to select compounds that are more easily synthesized for further investigation. The advancement of techniques for computing values such as synthetic accessibility has empowered chemists to determine the most suitable compounds for synthesis.[13]

Organic chemists have recognized that the complete synthesis of complex molecules, encompassing fully automated multistep synthesis, represents the next evolutionary advancement. This realization stems from the progress made in automated AI-driven reaction techniques over the past decade.[21]

ven reaction techniques over the past decade.[21]

Methods for predicting chemical reactivity through computation often require specialized expertise. Furthermore, bench chemists currently have access to only a limited array of computational tools to aid in organic synthesis planning.[22]

An example of predicting the region selectivity in electrophilic aromatic substitution reactions of heteroaromatic complexes is utilizing the RegioSQM method. RegioSQM has proven to be a dependable tool for guiding organic synthesis.[23]

In a recent breakthrough following over a decade of research, Klucznik et al. introduced the highly efficient Chematica computer program, which can design innovative and effective syntheses for medically significant molecules.[32]

Existing computational models for forecasting solubility in organic solvents remain notably constrained, thereby impeding predictions regarding the implementation of synthesis routes. Fields reliant on human creativity may significantly profit from AI integration, potentially allowing robots to assume routine tasks. [24-25]

Artificial intelligence has also been applied to retrosynthetic analysis. Liu et al. employed a sequence-to-sequence model to forecast retro synthetic reactions. This approach utilizes SMILES strings for RNNs (recursive neural networks) to encode and decode reactants and products, employing an encoder-decoder architecture for their interrelation.[16]

The integration of three deep neural networks with a Monte Carlo tree search for retrosynthetic prediction resulted in outstanding performance. [14-15]

Determining the ease or difficulty of synthesizing a chemical is a fundamental concern in organic synthesis, particularly crucial in the drug discovery process due to the generation of

numerous new structures through de novo design techniques. Subsequently, it falls upon the medicinal chemist to select compounds that are more readily synthesizable for further investigation.[26]

Molecular dynamics simulation:

Advancements in methods and computing capacity have elevated molecular dynamics (MD) simulations to a pivotal tool for examining molecular systems. Through MD simulations, we can delve into intricate processes such as protein folding, construct 4D molecular descriptors, evaluate the thermodynamic and kinetic properties of molecules, and achieve diverse research objectives.[27]

Following AI-based drug discovery:

AI is already playing a role in drug discovery. For instance, AI aids in identifying pharmacological targets, selecting suitable molecules from data libraries, proposing chemical modifications, pinpointing opportunities for repurposing, and more. However, AI must address several challenges in the near future. As emphasized by Mitchell, "New techniques in drug development often face exaggerated expectations, similar to the case of combinatorial chemistry a few years ago, and failing to manage these unrealistic expectations can lead to disappointment in the end. It's better to anticipate incremental improvements and potentially be pleasantly surprised than to promise a revolution that never materializes."[24]

Despite its transformative potential in chemistry, AI faces several obstacles and constraints that must be addressed. One major challenge is the necessity for high-quality data.[33]

The complexity of comprehending intricate models poses another challenge. Chemists may struggle to place trust in predictions generated by deep learning models, particularly due to their complexity and lack of interpretability. Additionally, there are social and ethical considerations. While AI can facilitate the development of new medicines or substances, it also holds the potential for creating hazardous materials like weapons. Therefore, the utilization of AI in chemistry must prioritize ethics and responsibility, with a focus on advancement. AI is expected to propel personalized/precision medicine into the future, potentially becoming standard practice even for the treatment of minor illnesses.

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