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Review Article

Artificial Intelligence Tools in Drug Discovery

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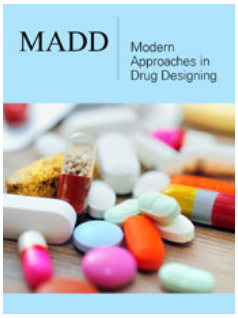
ISSN: 2576-9170



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Submission: September 20, 2024
Published: October 25, 2024

Volume 4 - Issue 3

How to cite this article: Hemachand Tummala* and Mohitha Gade. Artificial Intelligence Tools in Drug Discovery. Mod Appro Drug Des. 4(3). MADD. 000589. 2024.
DOI: 10.31031/MADD.2024.04.000589

Abstract

Artificial Intelligence (AI) is revolutionizing the landscape of drug discovery, offering tools that streamline and accelerate each phase of the process. This mini-review will provide an overview of how the integration of Artificial Intelligence tools in the drug discovery process accelerates the timelines, minimizes failure risks, and lowers overall costs. This manuscript introduces key AI terminology, describes its role in various stages of the drug discovery process, and emphasizes on few popular AI tools used in the discovery process. Additionally, it also discusses the advantages of AI adoption in drug discovery and addresses the challenges faced in its implementation. This review aims to elucidate the current state and prospects of AI-driven drug discovery.

Keywords: Drug Discovery; Artificial Intelligence (AI); Deep Learning (DL); Machine Learning (ML); Artificial neural networks

Introduction

Artificial intelligence is a generic term that encompasses multiple technologies. In simplified terms, AI is a transformative technology within computer science that helps computers perform tasks by mimicking human cognitive functions to solve real-world problems. Recently, AI has become an integral part of the drug discovery process, including peptide identification, drug design, drug efficacy, and effectiveness assessment, prediction of drug toxicity and physiochemical properties, drug repurposing, Quantitative Structure-Activity Relationship (QSAR), and the design of clinical trials [1]. In this manuscript, to give an overview, we first discussed about conventional drug discovery process, followed by describing various AI technologies. Further, the article describes the AI-based tools employed recently to aid in the drug discovery process. Lastly, the advantages and disadvantages of applying AI in the field of drug discovery are discussed.

Conventional Approaches in Drug Discovery

An investigational compound is known as a New Chemical Entity (NCE) until it gets investigated for a particular condition. Once demonstrates some activity, it is then classified as lead compound, which is further optimized to show better activity and/or fewer side effects. Lead compounds can be obtained through various sources, from ancient empirical knowledge to structure or computer-based drug design. The ancient drug discovery process mainly relied on a trial-and-error approach to identify potential medicinal uses of products from plants and animals [2]. Since there was an absence of knowledge about the disease mechanism and molecular targets, although many compounds identified by this process showed efficacy, there were many side effects observed. However, these empirical methods laid the foundation of drug discovery by providing lead compounds. Over decades, with a better understanding of disease processes, lead compounds are emerging by specifically targeting signaling pathways involved in the etiology of the disease.

The modern drug discovery process consists of multiple approaches and stages (Figure 1). It starts with the identification of a lead compound, which could be obtained from the isolation of products from natural sources (such as vincristine and vinblastine from

Catharanthus Roseus), fermentation coupled with the recombinant DNA technology, synthetic chemistry, and combinatorial chemistry, etc. Lead compounds are then generated by creating and screening the large chemical libraries, employing high-throughput screening methodologies or virtual screening techniques, or utilizing fragment-based lead discovery [3]. Recently, lead compounds are increasingly identified through the use of small molecular weight fragments that bind to target proteins. Once these fragments are discovered, they are further developed by adding chemical groups to create more potent lead molecules [4]. These initial leads undergo optimization, where new analogs will be synthesized to further enhance the efficacy, and bioavailability and reduce the side effects of hits. The most promising candidates then enter pre-clinical testing, where their efficacy and safety are evaluated in animal disease models. Compounds that show potential in pre-clinical stages advance to human clinical trials, undergoing extensive testing to further ensure safety and efficacy in humans [5]. Additionally, finding alternative applications of the existing medications through drug repurposing has advantages over conventional drug discovery as it cuts down costs and time duration for the invention of a novel molecule to cure a particular disease. Only after successfully completing these rigorous phases can a drug be considered for market entry. This comprehensive process combines traditional methods with cutting-edge techniques (Figure 1).

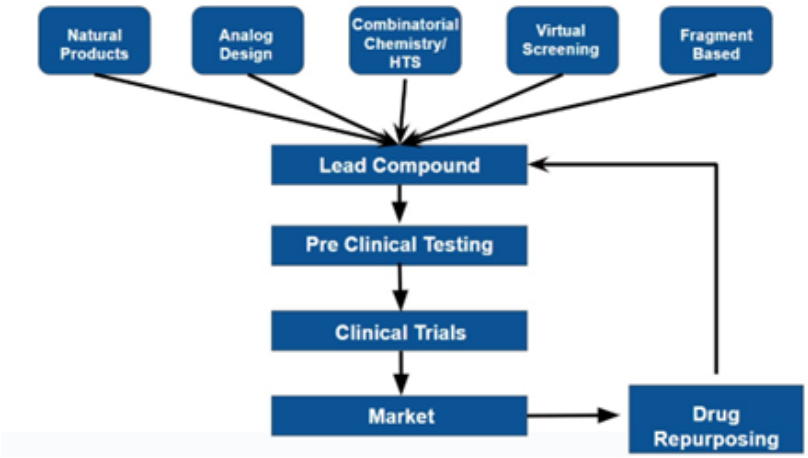

Figure 1: Traditional drug discovery process.

Artificial Intelligence Technologies in Drug Discovery

Artificial Intelligence (AI) is a broad umbrella term used for a variety of technologies designed to mimic human intelligence such as Machine Learning (ML), Deep Learning (DL), and Artificial Neural Networks (ANN). Sometimes the terms for these technologies interchangeably create confusion. Broader definitions of these terms are as below:

A. Artificial Intelligence (AI): AI is a broader term that involves the use of algorithms and data processing to enable machines to simulate human intelligence and cognitive functions and solve complex real-world problems.

B. Machine Learning (ML): A subset of AI that uses algorithms and data analytics to predict the outcomes more accurately.

C. Deep Learning (DL): DL is a further subset of ML that utilizes large data sets and complex algorithms such as image processing and speech recognition for prediction purposes.

D. Artificial Neural Networks (ANN): ANNs are computational models that mimic the functional design of neurons in the brain, which consists of interconnected nodes. Most deep learning algorithms are ANN-based in design; however, ANN can be used for other functions beyond DL.

Artificial intelligence in drug discovery

Recent advancements in GPU technology and deep learning algorithms have led to an explosion of AI applications in the drug discovery process. These sophisticated algorithms can process large datasets, make automatic decisions, and predict crucial pharmaceutical parameters from diverse information sources without performing costly and time-consuming laboratory-based experiments. Therefore, AI is accelerating the drug discovery process at various stages-- drug design, drug screening, polypharmacology, execution of clinical trials, and drug repurposing (Figure 2). In the drug design field, AI can predict the 3D structure of a target protein and its interaction with NCEs. Further, it can also design new drug-like molecules without a starting template, known as de-novo drug design [6]. For example, Protein-Protein Interactions (PPIs) are examined using AI tools like iFitDock, which explores the entire protein surface using small fragment-sized probe molecules to predict interactions with other proteins and small molecules [7]. Further, in the drug screening process, AI can predict various physicochemical properties of the drug, such as log P and solubility, as well as ADME (absorption, distribution, metabolism, and excretion) properties. It can also predict the potential bioactivity and toxicity of the NCEs. Accurately predicting the above critical properties of a drug candidate not only accelerates the drug discovery but also significantly reduces the likelihood of failure in later stages of development. Similarly, deep learning algorithms have been used

in designing molecules with multiple targets or predicting multiple targets of new drug molecules (polypharmacology) [8,9]. In later stages of drug discovery, and clinical testing of the molecules, AI could analyze large data from previous trials and patient records and optimize trial design and execution.

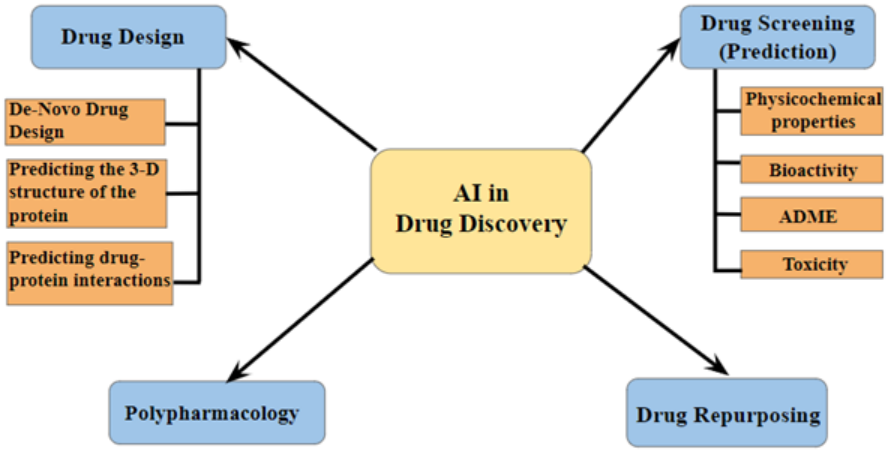

Figure 2: AI applications in drug discovery.

Machine learning in drug discovery

Machine learning is a subset of AI that develops complex algorithms and statistical models that accurately predict drug properties such as chemical, physical, and biological characteristics of NCEs. These ML tools can be incorporated at any stage of the drug discovery process starting from target identification to clinical trials. Machine Learning is broadly classified into supervised and unsupervised learning. The supervised machine learning tools learn from the data set of known examples. In this method, during the learning process, the algorithm is trained with known input and output data sets to identify patterns. By recognizing these patterns, it can then make predictions about new, unseen data. As an application in drug discovery, this could mean predicting the efficacy or side effects of NCEs based on their structural similarities to existing drugs.

In contrast, in an unsupervised learning model, the algorithm is only provided with input data without any corresponding output information. The tool is expected to discover patterns and structures within this data on its own without training [10]. In the end, the high dimensional data is reduced to a lower dimension to identify the patterns that are easy to interpret. This further includes data visualization, extraction of desired features, and clustering of the data. Using unsupervised ML, the scientists could cluster similar compounds based on identifying structural patterns for potential therapeutic applications or toxicities [11]. For example, a new potential antibiotic, Halicin was discovered by unsupervised learning through a clustering process [12].

Deep learning in drug discovery

Deep learning is a subfield of machine learning that utilizes artificial neural networks with multiple layers to analyze complex patterns in large datasets. Since it has capabilities for image interpretation, structure prediction, and computing large sets of data, it has broader and deeper applications in drug discovery [13]. Its integration in various steps of drug discovery assists in predicting target identification, drug interactions, molecular properties, and biological and toxicological responses.

DL models predict Drug-Target Interactions (DTIs) and Drug-Drug Interactions (DDIs), which are essential for identifying therapeutic candidates and preventing adverse effects. It is used in molecular docking as it predicts the pose of ligands based on interactions observed in protein-ligand complexes. For example, TANKBind, a trigonometry-Aware neural network predicts Drug-Protein binding by segmenting the protein into blocks [14]. They also facilitate personalized medicine by analyzing patient data to forecast individual drug responses and potential side effects. In personalized medicine, Deep learning techniques have shown particular progress in early diagnosis, and identifying cancer that assists in treatment decisions [15]. Recently, deep learning techniques have been applied to generate new chemical structures by using a Variational Autoencoder (VAE). Kadurin et al. [16] used VAE as a molecular descriptor generator which is coupled with a generative adversarial network to generate new molecular structures that were predicted to have anti-neoplastic properties [16]. Blaschke et al. [9], have utilized VAE to generate novel molecules which have predicted activity against dopamine type 2 receptor [17].

Deep Learning (DL) offers several advantages, including improved predictive accuracy, automated feature engineering, and the ability to handle complex, multi-dimensional datasets that are common in drug discovery. Overall, DL is transforming drug development by enhancing both speed and accuracy. However, to fully realize its potential in the pharmaceutical industry, challenges related to data quality, interpretability, and integration need to be addressed. Future research is expected to focus on building robust datasets and enhancing the explainability of these models [18] (Figure 3).

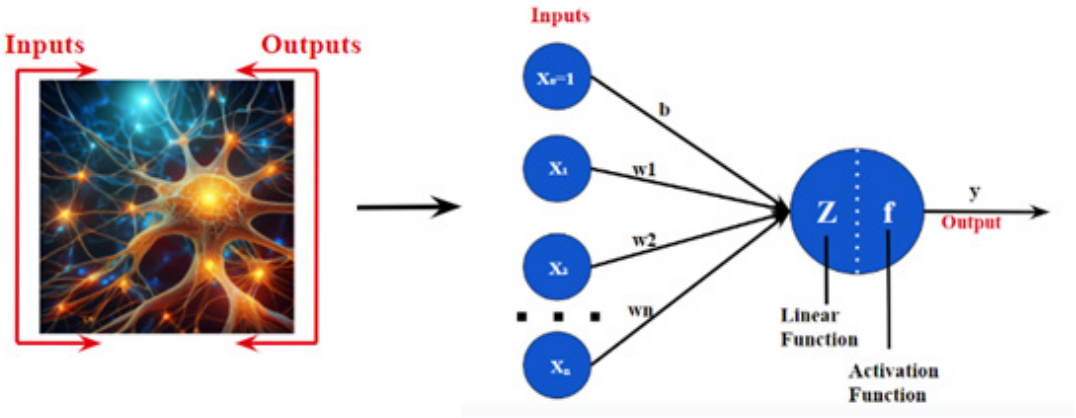

Figure 3: Transformation of neural network in humans to artificial neural network.

Artificial neural networks

Artificial Neural Networks (ANN) consist of interconnected nodes which process information similar to neurons in humans. A typical ANN structure includes ANN's an input layer that receives the initial data, then one or more hidden layers, where the data is transformed or processed through various weighted connections and activation functions, and finally, the output layer that presents the final decisions. ANNs have different array of network types, each specialized in a particular function. The perceptron is the oldest neural network created by Frank Rosenblatt in 1956. The dual function of ANN, capable of both classification and prediction, has made its way into the AI domain [19].

There are different types of artificial networks including:

Feedforward neural network: FNN is the fundamental neural network that has the simplest construction. FNN is composed of an input layer and an output layer. It might have one hidden layer included if the data set provided is more complex. The input layer receives the values, the hidden layer processes the input, then the output layer produces an output. FNN is formed with the help of a training sample set which is a data set of examples used during the learning process which is used to fit the parameters and backpropagation-gradient descendent algorithm, backpropagation and gradient descendent are used to improve the accuracy of the neural networks by improving the output of the neural network [20].

Multilayer Perceptron (MLP): MLP is a subpart of a feed-forward neural network with a few more interconnected layers to process complex data. It is comprised of an input layer, a hidden layer, and an output layer with an additional bias term to set a threshold for neuron activation (Figure 4). They are composed of sigmoid neurons, which use sigmoid function. Sigmoid function gives continuous output which would be a number between 0 and 1. It uses the back proportion algorithm, which is a gradient estimation method to train neural network models. It allows adjustment within the network based on the error between the actual and the expected outputs. This error correction helps MLP to make predictions precisely and enhance its accuracy. In drug discovery, MLP is used for image recognition, natural language processing, and speech recognition [21].

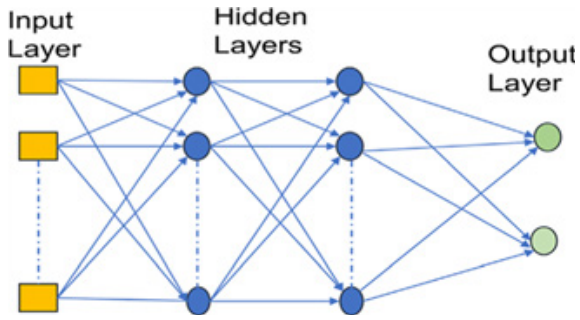

Figure 4: Multilayer perception architecture.

Convolutional neural network: CNN is a type of deep learning algorithm that is mainly designed for image recognition, including image classification, detection, and segmentation. It uses convolutional layers which have filters to extract features from input data at a large scale to recognize patterns within the image. CNN has subsampling layers which reduce the memory requirement and enhance the learning speed. In drug discovery, they are used to analyze one-dimensional data such as a nucleotide or in QSAR and ligand-based bioactivity predictions. An AI tool, Atom Net which predicts new molecules for different targets is constructed with the help of CNN [22].

Deconvolutional neural network: DNN reconstructs high-resolution images from lower-resolution inputs or compressed representations. This is achieved through up-sampling which increases the spatial resolution of the feature maps. DNNs consist of two main parts: an encoder and a decoder. The encoder will extract low- and high-level features from the input and then the decoder will reconstruct a high-resolution output image through up-sampling layers [23].

Recurrent neural network: It is an advanced class of ANN that processes sequential data. In this, the output from the previous step is fed as an input to the current step. RNNs have loops that retain the information of data in each step, facilitating the processing of variable-length input sentences [24]. The hidden state stores the

information of the data in each step. These features enable RNN to capture temporal behavior which is a sequence of entries, each of which contains a particular time and event. It is crucial for analysis of genomic sequences and protein structures. RNN has excelled in its modeling of protein-ligand interactions as it can recognize the sequential relationship between amino acids in proteins and atoms in ligands, which is important for predicting the binding affinity of drug molecules to target the protein of interest.

AI Tools in Drug Discovery

In the rapidly evolving landscape of pharmaceutical research, Artificial Intelligence (AI) tools are being developed and implemented rapidly to revolutionize the drug discovery process. This manuscript focuses on describing a selected group of widely adopted AI tools. By highlighting these commonly used AI tools, we aim to provide insight into how artificial intelligence is being used to overcome traditional methods in drug discovery. It is important to note that this selection represents only a fraction of the AI innovations currently in the pharmaceutical industry, with new tools and approaches emerging regularly to address specific challenges in drug development.

AlphaFold

Built on Deep Neural Networks (DNN) a revolutionary AI tool, which predicts 3D protein structures. AlphaFold precisely predicts the distance between the amino acids and the angle between the peptide bonds. Till now it has predicted 25 out of 43 protein structures precisely. AlphaFold2 is its subsequent version with improved speed and precision in predicting the protein structures (Image 1).

Image 1:

IBM Watson

Image 2:

With the help of natural language processing capabilities, it is designed to derive logical responses from both structured and unstructured data. The natural language processing software used is DeepQA, enabling Watson to comprehend questions and generate accurate answers. DeepQA operates by integrating various modules to produce multiple responses for a particular query, these responses are further evaluated using a multilayer logistic regression to finally produce the most accurate response. It helps oncologists by analyzing the patient data and giving a personalized cancer treatment plan. It also helps in the interpretation of medical images thereby enhancing radiological accuracy (Image 2).

EVEscape

It is an AI tool designed to predict viral mutations and potential outbreaks. It predicts how viruses mutate and evolve to escape the immune system. It also aims to inform vaccine and therapy development. It could successfully predict SARS-CoV-2 variants during the COVID-19 pandemic (Image 3).

Image 3:

Organic

Objective-Reinforced Generative Adversarial Networks for Inverse-Design Chemistry (ORGANIC) is a molecular generation tool that creates molecules with desired properties. It is an important tool used in the early phase of the drug discovery process as it can design novel compounds with specific therapeutic properties. This tool utilizes two machine learning techniques, Generative adversarial Network which generates non-repetitive molecules and Reinforcement learning which ensures that the potent molecules generated meet the desired criteria of interest (Image 4).

Image 4:

Addison

ADDISON operates with the help of machine learning to design de novo molecules and virtually screen the novel molecules to predict their pharmacokinetic profiles. It uses AI, machine learning, and CADD to help researchers understand the chemical space and generate new ideas for compound synthesis (Image 5).

Image 5:

AtomNet

AtomNet is A Convolutional Neural Network (CNN) used in structure-based drug discovery for bioactivity prediction. The primary purpose of CNN is image recognition and processing

because of its ability to identify patterns in images. It analyses 3D structure of the proteins to predict protein-ligand binding affinities (Image 6).

Image 6:

DeepTox

DeepTox is designed specifically to predict the potential toxicity of various drugs. With the help of deep learning, it handles complex multilayered data. It predicts the toxic effects of a wide range of chemical compounds within a single neural network by analyzing their molecular structures (Image 7).

Image 7:

Seismic therapeutic – IMPACT

It develops immunology-based therapies for autoimmune diseases by using machine learning. The primary purpose is to develop biologics that can control dysregulated adaptive immunity. Biologics treat autoimmune diseases by targeting pathogenic antibodies. Their major programs include pan-igG protease

for antibody mediated diseases and PD-1 agonists for cell-mediated autoimmunity. It integrates various fields of research like machine learning, structural biology, protein engineering and translational immunology to accelerate the discovery of biologics with improved efficacy (Image 8).

Image 8:

RoseTTAFold

It is an AI system developed for predicting protein structures from amino acid sequences resulting in high-accuracy models. It helps in understanding the three-dimensional shapes of the protein. It employs deep learning approach which aids researchers in understanding protein functions and interactions which is crucial for biological research and drug discovery (Image 9).

Image 9:

Delta vina

It is a machine learning-based protein-ligand scoring software. It is designed to improve the accuracy of scoring in molecular docking simulations. Molecular docking is a computational technique that can predict the binding mode and affinity of a small molecule ligand to a protein target which is used in drug discovery. Accurate scoring functions are necessary for identifying potential drug candidates with high binding affinity and specificity (Image 10).

Image 10:

Machine Learning Tools in Drug Discovery

Support Vector Machine (SVM)

Support vector machine is a supervised machine learning algorithm that separates the compounds based on feature selector by deriving a hyperplane. For the linear data, SVM separates the classes of compounds based on features selected and puts them into chemical feature space, an optimal hyperplane is attained by maximizing the margin between classes in N-dimensional space. In drug discovery, it can distinguish between active and inactive compounds. SVM has a subset binary class prediction that differentiates between active and inactive compounds (Image 11).

Image 11:

Random Forest (RF)

Random Forest is specifically designed for large datasets with several attributes. Based on the relative features, RF removes the outliers and classifies as well as designates datasets. RF has several uncorrelated decision trees in which each tree is responsible for determining one prediction. With the help of multiple decision trees which provide several predictions, RF minimizes individual errors. RFs are mainly used for feature selection, classifiers, or regression in drug discovery. This algorithm is used for predicting the affinity between ligand and the protein by virtual screening molecular descriptors [25].

Naive Bayesian (NB)

NB is a subset of supervised machine learning. It is mainly used in predictive modeling classification. Based on factor correlation, input characteristics, and dimensionality of the data this algorithm classifies the features of the data sets. NB algorithm operates on biomedical data that contains unrelated information and this data is known as noise. When NB is combined with other techniques, it is found to be useful in drug discovery processes, Wei et al, combined NB and support vector machine algorithms to predict compounds that would be active against targets of HIV type-1 and hepatitis C viruses.

K-means clustering

Understanding molecular structures is very important in drug discovery, for this K means clustering plays a crucial role. Based on the centroids, this algorithm forms clusters with the representation of the mean of the data points within each cluster, leads to a group of similar data points, and reveals valuable insights. The main advantage of K means clustering is that it can perfectly handle high dimensional data, identify the hidden complex patterns in large, and also predict the chemical and biological properties. While working with K we will encounter some challenges like sensitivity to initial centroid selection, determining the number of clusters, and dealing with imbalanced datasets. But because of the simplicity, scalability, and adaptability K means is essential in drug discovery. In drug development it is crucial to predict molecular behavior, for this K means helps us in defining the molecular descriptors and numerical representations of a compound's physicochemical properties. K-means also computes similarities between compounds, identifying relationships and potential drug candidates. Additionally, it clusters compound properties and selects protein structures based on similarities, increasing the precision of docking and our knowledge of a drug effect.

Advantages of Artificial Intelligence in Drug Discovery

The process of developing a new medicine is time-consuming and a very expensive process. However, Artificial Intelligence is a powerful tool that can revolutionize drug discovery, bringing significant advantages:

Improving accuracy and error reduction

AI has improved the efficacy of target identification and lead compound optimization and it helps in identifying new drug targets and designing novel molecules. AI assists in predicting the efficacy and safety of the potential drugs [26]. Tools like DeepTox which predict the toxicity of different compounds enhance the overall quality of drug development.

Cost savings

One of the major advantages of AI is that it helps in the reduction of the duration of time and costs needed for the development of a formulation. With the help of ML and DL techniques, AI can screen millions of compounds in no time to identify potential drug candidates which would otherwise take years to complete using the traditional drug discovery process [27].

Repurposing existing drugs

Interestingly, AI has opened up new possibilities in drug repurposing and the identification of drug combinations, potentially leading to innovative treatments for complex diseases. It has also shown promise in enhancing clinical trials and improving patient outcomes. These AI tools have the potential to significantly accelerate drug discovery, particularly in response to urgent medical needs such as the COVID-19 pandemic [28].

Personalized medicine

AI can analyze vast amount of diverse patient data, including genomic information, and medical records. ML algorithms can identify patterns and connections in this data, leading to more personalized insights. AI models can forecast disease outcomes and treatment responses based on individual patient data. This allows healthcare professionals to make more accurate decisions about personalized treatment options [29].

Disadvantages in AI for Drug Discovery

Data challenges

The accessibility of high-quality data in health care is limited due to privacy concerns as the patient data may be misused and also the quality of the data may be not consistent and may have errors in them, so the model development will become difficult because of the outdated medical records. AI and ML rely heavily on the data to perform their assigned tasks. If the data is incorrect or biased then it will produce incorrect conclusions which is unwanted [30].

Algorithm challenges

Difficulty in understanding how AI models reach their conclusions, hindering trust and accountability. While working with the AI Algorithms we cannot find the exact reason for the particular solution which questions our accountability also some models may perform on the training data but cannot perform effectively on new patients' data and these algorithms can be biased based on the present data which may lead to the unexpected outcomes.

Computational and resource constraints

The utilization of Al in drug discovery demands a significant amount of computational power and resources. This requirement can increase costs and limit accessibility, especially for limited funding or resource-constrained institutions.

Regulatory and validation challenges

The 'black box' nature of the algorithms makes it difficult to understand and explain their decision-making processes, potentially hindering their adoption in drug discovery. Ethical considerations, including data privacy and the need to mitigate bias in AI algorithms, present challenges that need to be addressed. Overcoming these issues is crucial for the successful use of AI in drug discovery methods [31]. Another significant challenge is the interpretability of AI models, which is critical for gaining regulatory

approval and building trust within the scientific and medical communities. The "black box" nature of some AI algorithms can make it difficult to understand and explain their decision-making processes, potentially hindering their adoption in drug discovery.

Conclusion

Many aspects have influenced the integration of AI and ML into drug discovery particularly in areas like drug design and drug screening. The technological advancements have helped in cutting the time and expense of the research, development, and production and also helped in boosting efficiency. This research paper highlights that AI and Machine Learning can significantly enhance the accuracy of drug discovery and development. They can even replace the clinical trials with stimulations which makes the researchers understand the study of molecules without trials. However, AI and machine learning can develop drug discovery methods yet several challenges remain. Issues like the cleaning of unstructured and heterogeneous datasets and the occasional limitations of computing devices could hinder progress. Overcoming these barriers will be the key to fully leveraging AI and machine learning, paving the way in the pharmaceutical industry.

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