Review Article

Application of Artificial Intelligence in drug discovery, designing, clinical trials and repurposing

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ABSTRACT

Drug development, right from discovery, designing, and repurposing, along with various phases to clinical trials, is a complex and time-consuming process that traditionally relies on the experience of labor forces, along with incessant trial-and-error experimentation. The emergence of various artificial intelligence (AI) tools and techniques is redefining the pharmaceutical industry. The integration of AI-driven methodologies into all stages of the drug development pipeline has enhanced the efficiency and effectiveness of the process. With this review, we aim to provide insights into the application of AI at various stages mentioned, with an emphasis on the latest advancements. The role of AI in speeding up the process of drug development while giving distinct and accurate outcomes is highlighted as well. Finally, we addressed the current challenges in employing AI along with future perspectives in order to enhance AI-augmented drug development, ultimately offering significant benefits to patients and society.

Key words: Artificial intelligence, drug discovery, clinical trial design, neural networks, drug repurposing

Artificial Intelligence (AI) involves the least amount of human intervention possible when utilizing a computer to imitate intelligent behaviour [1]. AI has been implemented in the pharmaceutical industry in recent years. One of the important aspects in medicinal chemistry, drug discovery that involves identifying, formulating, and developing new medications, is an arduous, technique-sensitive, and time-consuming process with long-established protocols that require exorbitant resources with several trial and error experimentations needing a good deal of time [2]. This complex process, further requires an average of 12 years and a cost of $2.6 billion to forge ahead a single molecule from inception till Food and Drug Administration (FDA) approval. In spite of these strenuous endeavours, the process is marked by unfavourable adverse effects of the drugs, high attrition rates, and tenacious challenges in addressing chronic diseases, including cancers and diabetes mellitus [3, 4].

The emergence of AI marks a revolutionary drift in drug development, with the advent of computational tools designed to supplement human capabilities and intelligence rather than replace them [5]. AI leverages suave algorithms for autonomous decision-making, hence revolutionizing the pharmaceutical industry [6]. AI techniques such as machine learning (ML) and deep learning (DL) offer the potential to accelerate the above-mentioned processes by enabling more coherent, efficient, and precise analysis of large amounts of data [7]. AI has also been able to predict the toxicity of drugs; besides its role in drug-target interaction predictions, clinical trial design, and drug repurposing, it is aiding in the reformation of drug development approaches [8, 9].

This narrative review aims to unveil the transformative impact of AI on the whole process of drug discovery till the completion of development and sheds light on the role of AI in drug repurposing as well. The paper also emphasizes the importance of AI in accelerating the development of novel therapeutics while juxtaposing it with traditional methodologies. Furthermore, we also discuss the ongoing challenges with respect to the usage of AI, along with the future of AI in the pharmaceutical industry and the ways it can significantly restructure the global healthcare system.

Revolution of AI

The Dartmouth Workshop conducted in 1956 is considered the foundational event for the advent of AI. It is described as intelligence displayed by man-made machines, dedicated to developing theories, technologies, applications, and methods aimed at replicating, enhancing, and extending human intelligence [10]. Over the past 70 years, AI has evolved from a theoretical notion into a powerful industrial adaptation, revolutionizing industries such as manufacturing, agriculture, finance, and healthcare [11-13].

AI includes various subtypes, some of which are described as follows: machine learning (ML), Natural Language Processing (NLP), Computer Vision (CV), and Fuzzy Logic

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(FL). ML works on algorithms trained for decision-making that learn from the already analyzed data. ML is further classified into supervised learning and unsupervised learning. In supervised learning, pre-catalogued/ labelled data is used as input, whereas in the latter, training data is not catalogued/labelled, and the system must perceive and label the said data. A third sub-category exists, known as semi-supervised learning, a combination of the two previously explained types [14]. Deep learning (DL) is a subgroup of ML based on systems that use artificial neural networks (ANN), which imitate the human brain, and act by interpreting and drawing conclusions from the given data. Whereas, NLP is a branch of AI that recognizes natural language and builds communication between machines and humans. CV is a subtype of AI that allows computers to discern an image and distinguish the individual elements of that particular image by assigning them a meaning. On the other hand, FL uses non-binary values to solve issues that normally require tackling with more values, hence deciphers the problems that classical logic cannot solve [15, 16].

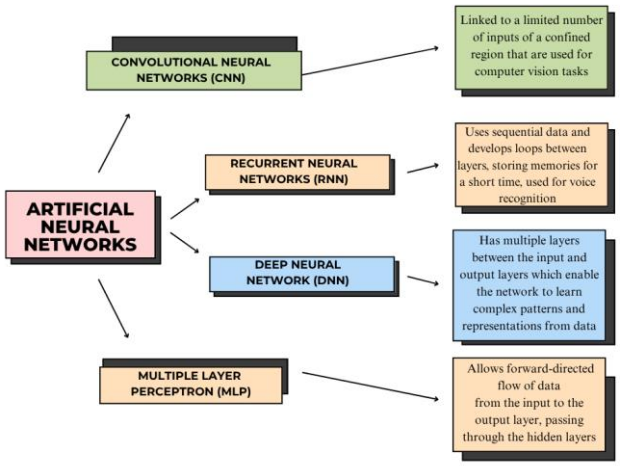

Figure 1: Classification of ANNs [16, 17]

An ML algorithm for any task begins with task definition and ends with model application. Different steps with detailed explanations are described in Table 1.

Table 1: Steps in Machine Learning [16, 17]

S. no	Step	Description
1	**Pre-processing**	Ensures that the algorithm easily interprets the datasets Includes data loading, normalization, aggregation, and standardization of the dataset
2	**Exploratory Data Analysis (EDA)**	Tests several hypotheses and yields a better understanding of dataset variables and their inter-relationships. Check for errors and missing values Helps determine if the statistical techniques that are used for the data analysis are appropriate.
3	**Model Selection**	Creation of a predictive model Algorithms are often grouped according to the ML techniques used such as supervised or unsupervised etc. Few ML algorithms used in medical research are Support Vector Machine (SVM), Multinomial Logistic Regression (MLR), Bayesian networks (BN), and Decision Tree (DT). Few DL algorithms used in medical research are all the sub-types of ANNs, Long short-term memory (LSTM), and mixed networks.
4	**Model Processing and Evaluation**	Datasets are divided into test and train sets, and further cross-validation is done. If the model shows discrepancies, it can be rebuilt using improvement strategies, which is known as 'TUNING' Model evaluation is done with ANNs.

Data, computation, and algorithms, the essential components of AI, serve as the basis of the AI-driven pharmaceutical research [18]. Sources of data in the pharmaceutical industry include public and commercial datasets, and research datasets generated through data mining. The evolution of computational power and the advent of various algorithms have provided critical support for AI pharmaceutical companies in carrying out research using the extremely potent tool, AI [19].

Challenges faced with traditional drug discovery and development methods

Traditional drug discovery, as described before, is a complex, time-consuming, laborious, and costly undertaking. To bring a single drug to the market, it typically takes over a decade and an average cost exceeding $2 billion. Each and every stage, starting from target identification and validation till preclinical testing and clinical trials, requires immense trial-and-error experimentations with huge irreversible expenses along the way [20]. Furthermore, attrition rates of the drug candidates are very high, with almost 90% of them failing owing to insufficient efficacy and/or safety concerns during clinical trials. Additionally, financial losses multiply when toxicity is detected after-market release of the drugs [21].

Hence, evaluation of toxicity and safety is of paramount importance during drug development, which can be achieved by a better understanding of the protein–ligand interactions and predictability of toxicity. The development of computational methods and AI has emerged as a promising approach to tackle the above-mentioned obstacles while developing a drug. The further sections delve into the applications of AI in all the steps of drug development [21].

Role of AI in drug discovery

There exist more than 10^{60} molecules that help in the development of novel drugs [22]. Al has the ability to collect

positional information about molecules within the space to search for bioactive compounds and select appropriate molecules via virtual screening (VS). A few chemical spaces that have open access are ChemBank, PubChem, ChemDB, and DrugBank [17]. Quantitative structure-activity relationship (QSAR)-based computational models are capable of quickly predicting large numbers of physicochemical parameters of the drug candidates. AI-based QSAR models, such as support vector machines (SVMs), linear discriminant analysis (LDA), random forest (RF), and decision trees, are being applied to speed up QSAR analysis [23].

Deep Docking (DD), an open-source protocol for AI-enabled VS, was developed by Gentile and colleagues. It is supposed to be one of the fastest AI-enabled docking platforms being tested on one billion-plus molecular libraries [24]. The input data in DD consists of a particular molecule's Simplified Molecular Input Line Entry System (SMILES) and the target's structure. DD executes molecular docking for a small subset of a large library to deduce the ranking of the unprocessed datasets, followed by ligand-based prediction for the rest of the library. In this way, DD scraps off undockable molecular structures without wasting computational resources [25]. Further, diverse ML techniques, including Naïve Bayesian algorithm (NB), k-nearest neighbor algorithm (kNNs), support vector machine (SVMs), and ANNs, can also be used for VS. Although ANNs and SVMs are commonly considered as the most accurate, NB is excellent in identifying favourable scaffold fragments, while kNN is easy to implement and utilizes multi-task learning (MTL) {MTL training, a sub-field of ML, involves training a model to perform multiple tasks at the same time}. Amalgamating various ML algorithms is preferred as it can enhance performance [26].

DL algorithms are proven to show increased predictability compared to traditional ML models, especially in distribution, metabolism, excretion, and toxicity (ADMET) data sets [27]. The recent rise of Graph Neural Networks (GNNs) has set in motion a new paradigm in ADMET model designing. GNNs offer an informative and compact representation of datasets [28]. The efficacy of GNN algorithms in predicting physiochemical properties of drugs has been validated by frameworks such as Chemi-Net and Molecule-Net, which have superior potential when compared to ML models [29].

Role of Al in drug designing

The most important aspect of drug designing is to predict the structure of the target protein in order to design the drug molecule. AI tools can assist by predicting the 3 dimensional (3D) protein structure, thus helping to predict the effect of a drug molecule on the target prior to its synthesis or production [30]. AlphaFold is an AI tool based on DNNs, used to scrutinize the distance between the adjacent amino acids and the correlating angles of the peptide bonds to predict the 3D target protein structure [17]. The development of AlphaFold is expected to revolutionize personalized medicine and drug discovery. It represents a significant step forward in the use of AI in structural biology. AI platforms such as Self-Organizing Map (SOM) are leveraged to link several compounds to numerous targets along with Bayesian classifiers and similarity ensemble approach (SEA) algorithms, which can be used for integration between the pharmacological profiles of drug molecules and their possible targets [31]. Newer methods based on NLP are implemented, which use the amino acid sequences from sequence databases to learn and predict structural and functional patterns. Evolutionary Scale Modeling-based software ESMfold was developed by Lin et al. in 2022, which utilizes a masked transformer protein language model with a deep understanding of biological properties, trained with over 15 billion parameters [32].

Apart from ML algorithms, DL models, such as Platform for Analytics and Distributed Machine Learning for Enterprises (PADME) and DeepAffinity, have the ability to predict drug-target interactions by integrating drug and target features. PADME helps forecast the strength between drugs and target proteins, leading to accurate predictions of therapeutic efficacy and mechanism of action. DeepAffinity combines RNN and CNN with labeled and unlabeled data, providing a subtle understanding of drug-protein interactions [33, 34].

Apart from target protein prediction, the prediction of drug–target binding affinity (DTBA) is critical for evaluating the efficacy of drug molecules. AI tools such as ChemMapper and SEA, along with ML and DL techniques such as SimBoost, DeepDTA, and PADME, have been employed to accurately predict DTBA [34]. These AI approaches have provided an upgrade to the traditional methods by deploying computational models for predicting interactions between drugs and protein targets. In recent times, DL methods have been used in de novo drug designing [35]. In 2018, Popova et al. developed a Reinforcement Learning (RL) algorithm for de novo drug synthesis, which involves employing generative and predictive DNNs to develop new drug molecules. The generative models are used to produce more unique molecules, whereas the predictive models foretell the properties of the developed compound [36]. The involvement of AI in the de novo drug design is beneficial to the pharmaceutical sector as it provides optimization of the already-learned data while suggesting possible synthesis routes for drug molecules, leading to prompt lead design and development [37, 38].

Role of Al in clinical trials

Clinical trials are necessary to prove the safety and efficacy of a drug for a particular disease condition and require anywhere from 6–7 years with substantial financial investments [17]. Clinical trial failure rates, especially in oncology and other diseases, can reach as high as 95% which further contributes to financial strain. Applying AI in various steps of clinical trials helps to improve patient stratification, intensify recruitment efficiency, and in the long run increase the likelihood of trial success [18]. In silico clinical trials (ISCT) are anticipated to

significantly reduce the costs of clinical trials while enhancing overall success rates [39]. ISCT integrates physiological and pathological data to generate patient-specific predictions that provide decisions regarding diagnosis, dose selection, prognosis, and the identification of suitable patient groups [40]. A newer concept, Virtual Physiological Human (VPH), configures virtual patient groups to test the safety and efficacy of new drugs and medical devices. VPH acts as an adjuvant to the traditional clinical trials by reducing the number of patients needed for the trials and enhancing the statistical power of the results [41]. Additionally, AI contributes to clinical trial success by linking patient genetic data and electronic health records, along with cumulating clinical trial databases to predict drug toxicity, and assisting with patient trial matching and recruitment, plus monitoring patient adherence during trials [18, 42].

One of the major causes of failure of clinical trials is toxicity. In light of this, PrOCTOR, a toxicity prediction model, was designed by Gayvert, et al. that helps to distinguish between FDA-approved drugs and drugs that failed during clinical trials due to toxicity. This enables the design of therapeutic agents with less toxicity [43]. TargeTox is another toxicity prediction model that produces and unites pharmacological and functional properties in an ML classifier to predict drug toxicity [44]. In order to increase patient adherence in clinical trials, AI-powered facial recognition algorithms are implemented, in which patients need to record a video of themselves swallowing the pills.

The AI system then confirms that the correct person has taken the prescribed medication [45]. In a trial of patients with schizophrenia, adherence increased from 50% to 90% within a span of six months, exhibiting the success of AI-driven monitoring approaches [46]. A systematic review in 2024 deduced that AI-derived drugs can have a success rate of 80–90% in Phase I trials, around 40% in Phase II trials, which have shown to have substantially higher success rates than traditionally derived drugs [47]. In the forthcoming years, as more clinical results for AI-discovered drug molecules become available, it will be exhilarating to see how AI technologies will impact the pharmaceutical industry at the drug trial level.

Table 2: AI tools/techniques employed in drug discovery [1, 17]

S. no	Tool/Technique name	Description
1	Machine learning	Predicts drug-target interactions, helps analyse biological activity, and optimizes lead molecular compounds
2	Deep learning	Helps in de novo drug designing, virtual screening, and predicting drug properties
3	Reinforcement learning	Applied to optimize drug combinations and dosages by taking multiple variables into consideration and maximizing desired outcomes
4	Neural graph fingerprints	Helps in various aspects of drug discovery, such as lead optimization, virtual screening, and drug properties' prediction
5	DeepChem	Uses a Python-based AI system to find a suitable candidate in drug discovery
6	AlphaFold	Predicts 3D structures of target proteins
7	PotentialNet	Uses neural networks to predict binding affinity of ligands
8	DeepTox	Software that predicts the toxicity of around 12,000 drugs

Role of AI in drug repurposing

The process of bringing new drugs to the market has significant hurdles in terms of time, labour, and cost. But finding new indications for an already existing drug can considerably reduce these costs by repurposing or repositioning it for other diseases [48]. Drug repurposing allows the drug in question to enter phase II and III clinical trials instantly, with notably lower development costs, as pharmacokinetic, pharmacodynamic, and toxicity profiles of the drug are already established [48].

Reker, et al have developed a method called self-organizing map-based prediction of drug equivalence relationships (SPiDER). The model predicts molecular targets of known drugs, including key-target and off-target proteins [49]. Benevolent AI, an AI-enabled drug discovery company, utilizes AI tools to unwrap novel connections within vast, unstructured datasets with respect to drugs, and their clinical trial information, enabling drug repurposing and facilitating the discovery of valuable new indications of the same. Benevolent AI, in collaboration with Johnson & Johnson, has been redeveloping histamine H3 receptor inverse agonist, Bavisant, which was originally intended for attention deficit hyperactivity disorder (ADHD), and has been repositioned for the treatment of extreme daytime sleepiness in Parkinson's disease [50, 51]. The synergy between AI and drug repurposing is therefore of paramount importance for addressing the unmet medical needs.

Challenges and obstacles to using AI

Despite the significant potential of AI in transforming the landscape of the pharmaceutical industry, several challenges are prevalent and need to be addressed. A few of the challenges include resource sustainability, the quality and suitability of data used to train models, and potential for bias, all of which could result in unequal access to medical treatment of certain groups of people, undermining the principles of equality and justice [25]. An example explaining the likelihood of bias is during drug target prediction, when the training dataset contains an excess amount of target data related to a 'X' disease while having insufficient data for the disease 'Y', the model may

predict targets for the 'X' more accurately, while predictions for 'Y' may be biased, thereby affecting the accuracy, specificity, and efficacy of a new drug development [18].

The use of AI also raises concerns about job losses due to the emergence of automated technologies. Additionally, the use of AI in the pharmaceutical industry sparks debate about data privacy and security breaches. As AI systems depend on large amounts of data in order to function, the probability of sensitive personal information being accessed or misused increases. It is imperative that the collection and use of personal data be done in a way that respects the privacy of individuals and is in accordance with the relevant regulations [52].

Future perspectives

As AI technology continues to evolve, its role in drug discovery and other aspects is expected to expand as well. A major breakthrough was sought recently when the pharmaceutical industry's first AI-driven drug discovery, developed by Insilico Medicine, was approved by the FDA for clinical trials, which is in Phase II trials at the moment. The drug in question is Rentosertib, also known as ISM001-055, developed for the treatment of idiopathic pulmonary fibrosis (IPF) using their in-house generative AI platform called Pharma.AI [52]. This development substantially paves the way for further expansion. Latest tools, such as quantum computing, could supplement AI's computational abilities, enabling rapid and more precise predictions [20].

It is very much possible that the future of AI-assisted drug discovery would pivot on developing a virtual human, allowing for accurate predictions of all interactions between drug molecules and exploring all therapeutic capabilities and adverse side effects [2]. Association between AI organizations, pharmaceutical companies, and policymakers will be vital for creating an ecosystem in which AI-powered drug discovery and development becomes the customary standard [20].

CONCLUSION

Artificial Intelligence has a crucial role in the various stages of drug development, ranging from drug discovery, design, formulation, clinical trials, repositioning, and up to the final market introduction. Various tools assist in all the stages, enhancing efficiency and outcomes, while needing less time and man-power. Forging ahead, there is a need to strengthen data management, elucidate superior AI models, ensuring vigorous ethical and legal considerations, with the aim of sustainable and robust development of AI in the pharmaceutical industry.

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