Section A-Review Paper
ISSN 2063-5346

Emerging Role of Artificial Intelligence and Machine Learning in Pharmacology: A Review

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ABSTRACT

The subject of pharmacology is only one area where the usage of AI has increased rapidly in recent years in the healthcare industry. From initial medication discovery to practical data mining, AI is currently applied at every stage of the pharmacology research and clinical practice continuum. Therapeutic drug monitoring may be enhanced via the application of supervised machine learning algorithms, while unsupervised clustering of medications or patients can help find promising pharmacological compounds or patient populations. The application of natural language processing in mining electronic health records for real-world data is also on the rise. In this brief study, we will first introduce artificial intelligence and then briefly describe how it is being used in the fields of pharmacology and medicine.

Keywords: Machine learning, Artificial Intelligence, Pharmacology, Clinical Trials, Drug Discovery, Optimization

DOI: 10.48047/ecb/2023.12.Si8.527

Introduction

Machine learning (ML), a subset of AI, has seen explosive growth in healthcare applications during the last several decades. In pharmacology, for example, AI and ML methods are used to analyze a wide variety of data, including the drug's chemical structure, patient demographics, genetic information, and so on. The growing body of research on the use of AI in pharma is more evidence of this trend. Drug development and target identification are two areas where AI has been

used effectively for some time now. Recently, however, AI models have emerged that can characterize patient populations and forecast an individual's treatment response, spanning full drug development to personalized medicine. The use of AI in clinical pharmacology was a hot topic in 2020.[1] Many of these programs have continued success and widespread usage. Many advances, however, have occurred since then. This brief overview will focus on the present use of various AI and ML methods in the discipline of pharmacology.

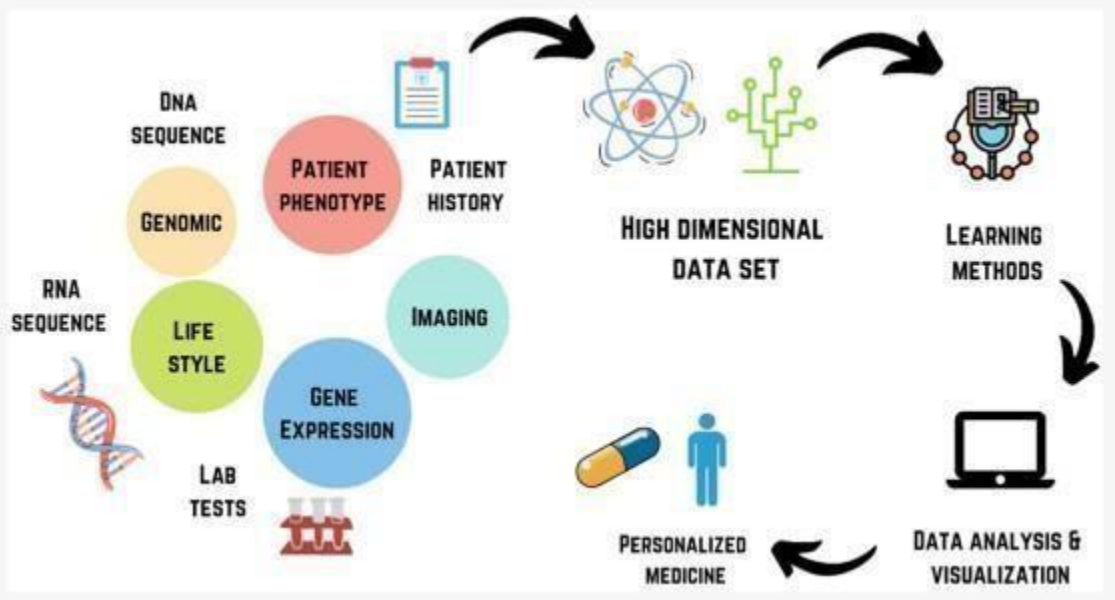

Figure 1. Role of AI in Pharmacological Applications.

Understanding AI

The term "AI" is used to refer to any kind of machine intelligence. This includes anything from learning-based applications to language and reasoning-based processes. When it comes to medical applications of AI, ML is among the most popular options. ML is a subfield of artificial intelligence that, rather than relying on human judgment, places its faith in computers' inherent capacity to draw logical conclusions and anticipate future outcomes. To further categorize ML methods, we may distinguish between supervised learning, which aims to make predictions, and unsupervised learning, which primarily serves to explore and cluster data. Identifying subgroups of patients who have a positive response in a broader cohort is a common use of unsupervised learning. However, supervised learning is often used to create models that can reliably predict one or more clinical outcomes, such as how a given patient would react to a certain medicine.

Neural networks are often utilized and are an example of supervised learning. The architecture of a synthetic neural network is designed to be similar to that of a biological one. A neural network has an input layer, an output layer, and hidden layers in between. During training, the weights on the nodes connecting the layers are adjusted to achieve optimal performance.

Neural networks are efficient at processing large volumes of data and excel at recognizing patterns in their training material. Because of this, they are widely used in many different contexts. Each ML model incorporates both a theoretical foundation for solving the issue at hand and an experimental component that is learned by the model during training. Black-box models become increasingly difficult to comprehend as their experimental components get bigger. While the inputs and outputs of the model may be described with reasonable accuracy, the model's underlying logic and weighting of elements remain opaque without further effort on the part of the user.

In addition to ML, NLP is also becoming more commonplace. To "read" and handle the massive volume of (un)structured text, for example, you may utilize NLP, a branch of AI that focuses on processing and understanding natural human language. Data connected to pharmacology, such as clinical outcomes, may be gleaned from databases and electronic health records (EHRs) using natural language processing (NLP).[2,3] The data may be interpreted with the use of advanced NLP techniques, which can also select the most significant things and organize the data for subsequent investigations.

Role of AI in Drug Discovery

There is a lengthy pipeline with numerous selection processes involved in the process of drug development. The method begins with a large pool of potential lead compounds, but rigorous selection is done at each stage of the development pipeline to narrow it down to a single chemical that meets all regulatory requirements. The bigger the number of compounds in a drug's research pipeline, the more it will cost. By analyzing their chemical structure and characteristics, AI may be used to help choose promising compounds for further study.

The use of AI in the pharmaceutical industry has been varied. As a first step, artificial intelligence may be used to determine, given a certain target, what chemical structures are likely to bind to that target. Second, the structure of a prospective pharmacological target may be deduced by comparing it to that of a recognized and effective medication or endogenic factor.

Finally, familiarity with established drug molecules, pharmacokinetics (PKs), and pharmacodynamics allows for the prediction of the in vivo properties of a new chemical. If it can be determined early on in the drug discovery process whether a compound is doomed to fail because it does not bind to the intended target or because it has potentially undesirable absorption, distribution, metabolism, and excretion (ADME) characteristics, then the investment in the development can be halted before costly trials are conducted. These AI-based applications are so commonplace in the pharmaceutical industry that businesses (like Cytoreason) have been created to create and sell models to the industry for the express purpose of studying illness and medication pathways.

The toxicity profile of a new drug is evaluated later in the development process. For this, large databases including in vivo data from clinical investigations are necessary. However, the same methods used in drug development might be utilized, since chemical structure has a significant impact on the incidence of toxicity.

Cardiotoxicity and hepatotoxicity are two major toxicities studied in the course of medication development. Consequently, various organizations have deployed AI techniques to predict whether a compound generates these toxicities in an early stage of the research pipeline, which would significantly minimize the probability of compound failure.[7–9]

Mamoshina et al. have investigated the potential of an AI-based model for predicting cardiotoxicity. They used data from public sources (such as Drugbank and MedDRA) to build a model that can predict cardiotoxicity.

The algorithm accurately classified medications as safe or dangerous with regards to cardiotoxicity (area under the curve [AUC] 79% for validation data and AUC 66% for unexplored data).[10] pharmacological-induced liver damage may be predicted using pharmacological properties similarly, with accuracies as high as 89%.[11]

The use of AI must go beyond only determining which molecule is best and trying to anticipate how it will behave in living organisms. It may also be utilized to discover fresh uses for tried-and-true medications. This medication repositioning is especially helpful for underserved patient groups because doing clinical trials would be impractical, and developing new drugs would be prohibitively expensive.

Drug repositioning may take several forms, but they are all computationally expensive and need vast datasets. First, in a drug-focused strategy, new compounds are compared to existing

medications to find molecules with features comparable to those of the comparator drug, which might then be employed to treat the comparator drug's therapeutic indications. Second, a disease-focused strategy looks to discover medications that work for illnesses that have comparable features by comparing disease characteristics and pathways. The two approaches are often employed together, as when looking for a match between a disease's gene expression profile and a drug's profile.

New treatments for colorectal cancer (CRC) were discovered using this combinatorial strategy by Al-taie et al. They integrated publicly accessible information on medication expression patterns with clinical data and RNA sequencing data [12].[13] A trained AI model was used to partition the clinical data into several groups. Then, we compared the distinct gene profiles of each subgroup to the medication database to find promising repurposing possibilities.

Twelve of the top 16 medications found using this method are used to treat cancer, and eight of them are approved for the treatment of CRC.[12] There have been parallel applications of AI models to various disease domains. In the case of Alzheimer's disease, for instance, researchers discovered 103 matches, just three of which had any kind of population-based validation study to back them up.[14] Zhang et al. utilized a method to pinpoint drug targets for diabetes, then tracked medications already known to affect those targets. As a result, 58 medicines were detected, of which 9 were deemed useful thanks to their interconnectedness in gene expression patterns.[15]

Recent Clinical Trials

The clinical trial phase of developing a novel medicine follows the expensive preclinical research phase. Patient selection and recruiting are major obstacles in clinical studies. The experiment may have to be terminated if not enough patients can be enrolled. For instance, by analyzing vast volumes of EHR data, AI apps may assist to optimize patient recruitment by selecting the patients who satisfy the eligibility requirements and are most likely to participate. This ensures that patient recruiting expenses are kept to a minimum. Second, AI may aid in patient monitoring as the experiment progresses. Both data mining the EHR and analyzing real-time data from participants' trackers, such as smartwatches and other wearables, may help with this. Finally, EHRs may be mined for useful data, and this data can be processed into clinically meaningful results with the assistance of AI techniques.[16,17]

Numerous AI-based methods exist for the automated analysis of imaging data; these methods have been proven to achieve accuracy rates comparable to those of a radiologist.

Artificial intelligence (AI) may be used to analyze real-world clinical data in a manner analogous to its use in clinical trials. Electronic health records (EHRs) are a gold mine of data on illness progression and treatment response, making them a fantastic resource for postmarket investigations. The volume of information stored in EHRs, however, makes it difficult and time-consuming to perform comprehensive investigations. To make the data in an EHR usable for analysis, NLP-based programs have recently been created. There are, however, difficulties associated with this. Multiple data sources contribute to an EHR, and each one varies in terms of dependability and robustness. For instance, it is not too difficult to get laboratory results since they are objective numbers. However, there are several unknowns in unstructured text, including but not limited to the presence of abbreviations and mistakes.

Data mining in EHRs was assessed by Van Laar et al. by comparing automated extractions with human ones. They looked specifically at the results of treating renal cell cancer. For structured data, they observed excellent levels of accuracy and recall, with an F1 score of 100% for variables like sex and mortality and better than 90% for variables like laboratory measurements. Unstructured data, such as adverse medication events and comorbidities, which are often part of the free text in an EHR, had much poorer accuracy (F1 score 53%-90%) when compared to structured data.[2]

AI may predict a patient's reaction to a medicine using a digital twin, in addition to its usage in traditional clinical trials and data mining. A digital twin is a computerized duplicate of a real-world patient that, once trained, may be used to simulate the effects of various therapeutic interventions on the patient's illness progression.[18]

Role in Drug Optimization

It is helpful and necessary to customize therapy for many available medications. Therapeutic drug monitoring (TDM) is used, for instance, to customize dosing for medications having a narrow therapeutic window. Statistics-based prediction models are often used to extrapolate TDM data for purposes such as determining medication exposure and appropriate treatment methods. Large clinical datasets required to train the models are not widely accessible, which has slowed the development of AI in this area compared to drug discovery.[9,19]

For instance, Labriffe et al. have trained many XGBoost models to replicate everolimus pharmacokinetic (PK) profiles in patients. To create a robust model, XGBoost models use supervised learning to combine several (weak) decision trees. The models were trained using predose, 1-, and 2-hour TDM data of everolimus in both simulated and actual patients. The top-performing model (n = 114, R2 = 0.956, root mean squared error [RMSE] = 10.3%) were trained using 5016 simulated PK profiles and was able to properly predict the everolimus AUC for an external validation set.[20] Methods comparable to this have been developed for additional medications.[21–23] However, these models were built with the assumption that their error margin would be identical to the TDM measurements used to train them. This means that an AI model's accuracy will never exceed that of the result it was trained on.

Pharmacogenomics (PGx) is changing similar to those seen in TDM-based therapy optimization. The study of genetic polymorphisms in drug metabolizing enzyme-encoding genes is central to the science of pharmacogenetics (PGx), which seeks to explain PKs. Currently, prediction models that use just a fraction of a person's genetic variations to categorically predict their enzyme activity are used in clinical PGx. Because enzyme activity is a continuous rather than a discrete quantity, it is hard to create even the most fundamental prediction models without the assistance of artificial intelligence.

The CYP2D6 gene, which encodes an enzyme important for the metabolism of 25–30% of routinely prescribed medicines, is an excellent example of a pharmacogenetic with these restrictions. It is still difficult to appropriately categorize people into projected enzyme activity groups due to the complexity of CYP2D6 and the vast number of mutations in this gene. Two methods using artificial intelligence for CYP2D6 activity prediction have recently been described. As a first step, McInnes et al. sought to create a model that could foretell the function of new haplotypes that have not yet been cataloged in the open-access PGx variation database PharmVar. To predict uncurated haplotypes, a network model was first trained using curated alleles from the PharmVar database. The model's 88% accuracy in predicting the activity of the validation set suggests that it may be used to assign activities to alleles that have not been manually curated.[24] As a second step, we built a neural network model to use long-read sequencing data to forecast CYP2D6 enzyme activity. The model was trained on data from full-length CYP2D6 sequencing, namely two alleles containing 77 variants each, and then the data from both alleles were integrated using a combiner model. The ratio of endoxifen metabolism to desmethyl tamoxifen metabolism

was used as an indicator of CYP2D6 function. When it comes to CYP2D6-mediated metabolism, the final model explained 79% of the variation, whereas the traditional category model only explained 54%.[25]

In pharmacogenetics, neural network-based techniques have the benefit of being able to recognize patterns in the input data that would be impossible for humans to do on their own. Historically, pharmacogenetics has used manually selected patterns (haplotypes) to ascribe activity to specific variant combinations. The two examples above demonstrate how the use of AI for pattern recognition and activity assignment may lead to greater precision.

Finally, real-world data extracted from EHRs using NLP might be combined with models to better therapy optimization, as mentioned above. Connecting these models to real-world outcomes as recorded in the EHRs would allow for more accurate predictions of drug metabolism and appropriate dosage based on PKs.

Conclusion

In this brief study, we have shown the widespread use of AI methods throughout the field of pharmacology, including drug development, clinical evidence, and personalized medicine. Artificial intelligence (AI) has emerged as a prominent analytical tool in the pharmaceutical industry in recent years. This brings about several developments and enhancements to the state of pharmacological understanding. However, one has to be cautious while using AI models and aware of the potential hazards. For this reason, the quality of the data utilized to train an AI model is crucial. Data with inherent flaws (such as ethnic, gender, or illness bias, or measurement mistakes) used to train a model would result in a less universal and more difficult-to-apply model. As a result, it is essential to exercise caution before picking the information that will be utilized to train an AI model. The "accuracy-interpretability" trade-off is another obvious barrier to the widespread use of AI in healthcare. More precise AI models are, in general, more challenging to understand. Since no human subjects are engaged at this stage, this is less of an issue in preclinical pharmacology. Transparency and interpretability, however, take on more significance in the therapeutic arena. As a result of this tradeoff, healthcare professionals will have to decide between using a simpler model that is easier to read but less accurate and using a more complex model that is correct but harder to grasp what it accomplishes. However, if one is aware of the benefits and drawbacks of AI methods, the potential uses for these models are almost limitless. We may anticipate the gradual

replacement of present models by AI-based ones in the not-too-distant future. Additionally, in silico clinical trials and AI-based decision support systems that might be considered medical devices will begin to find their way into clinical pharmacology. In light of the impending widespread use of AI in healthcare, the US Food and Drug Administration (FDA) is drafting a guideline for the reliability of computational models employed in medical device and regulatory applications. This will enable us to better optimize pharmacological therapy for each patient and lead to more efficient drug discovery routes.

Conflict of interest

No conflict of interest is declared.

Funding

No agency provided any grants.

Acknowledgment

Nil

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