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THE ROLE OF ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING IN REVOLUTIONIZING PHARMACEUTICAL DEVELOPMENT

Harini Uppada*[1], Ganapathiraju Sahil Varma[1] and Duvvi Nikhila Reddy[1]

[1]Raghu College of Pharmacy, Dakamarri, Bheemunipatnam (M), Visakhapatnam-531162, Andhra Pradesh, India.

***Corresponding Author: Harini Uppada**
Raghu College of Pharmacy, Dakamarri, Bheemunipatnam (M), Visakhapatnam-531162, Andhra Pradesh, India.

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ABSTRACT
Machine learning (ML) and artificial intelligence (AI) are revolutionizing in pharmaceutical development, research, and quality assurance. These methods such as advanced deep learning techniques excel compared to conventional methods in both precision and accuracy. AI and Ml techniques show high capabilities in identifying potential drug candidates by precisely forecasting protein-ligand interactions. These techniques enable researchers to assess and evaluate vast amount of information finding previously unknown relationships between existing medications, illness targets, and novel remedies. AI and ML have many advantages for example, repurposing existing medications takes existing safety data into consideration which helps in reducing development time and costs. AI can help in the search for successful therapeutics by detecting unanticipated relationships between pharmaceuticals and new targets. This review explores the role of AI and ML in enhancing computer-aided drug design, as well as the challenges and opportunities these technologies present for the pharmaceutical industry.

KEYWORDS: Artificial intelligence, machine learning, drug designing, drug discovery, pharmaceutical industry.

1. INTRODUCTION

Drug discovery is a process through which new medications against diseases are discovered. It involves the use of a wide variety of technologies and knowledge. In general, discovering and developing a drug takes US$2.8 billion and 15 years on average. The low-efficacy and high-cost characteristics of conventional methods have become the barriers of drug discovery. Therefore, developing new methods to deal with such a time-consuming and expensive task is essential. AI and ML have significant potential to solve various challenges in pharmaceutical analysis, they have the potential to aid in the improvements of drug discovery, development, and quality control.

2. METHODS

There are several machine-learning methods used in Quantitative Structure-Activity Relationship (QSAR), Proteochemometric (PCM), and molecular docking studies in binding-affinity prediction. Some of them are explained here.

2.1 Optimal piecewise linear regression

QSAR models developed for predicting compound activity with a better interpretation of selected features.

2.2 Random Forest (RF), Support Vector Machine (SVM), Naive Bayes (NB), and K-Nearest Neighbors (KNN)

Determined an applicability domain for PCM models using MACCS fingerprints for compounds. PCM models trained on various datasets performed better than QSAR; provides estimation of applicability domain as well as estimation of errors of bioactivity predictions. RF helps to develop target-specific models as scoring functions for docking-based target prediction using interaction fingerprints. SVM uses differential geometry-based feature extraction on protein-ligand complexes to develop models for prediction of binding affinity, toxicity, and solvation-free energy.

2.3 Gaussian Process (GP)

Showed that machine-learning scoring functions outperform classical scoring functions on large datasets.

2.4 XG Boost

A new virtual screening method based on interaction energy between protein and ligand in a complex for target prediction.

2.5 Gradient Boosted Trees (GBT)

Models are trained on compounds encoded as vector representations in an unsupervised manner to predict bi-activity. RF and GBT together helps in active learning

strategy using reduced data size and a PCM approach was used to predict compound-protein interactions.[1]

Machine learning has been constantly improving and increasing its ability to solve scientific issues, it has emerged as a major tool in Drug-Target Interaction (DTI) prediction. AI-based target identification uses machine learning algorithms to assess and evaluate big datasets and help in discovering targets that may interact with certain medicine. This method uses a variety of data sources, including but not limited to gene expression profiles, protein-protein interaction networks, and biological pathways, to provide a list of potential targets. ML methods, such as SVMs and neural networks, can then be used to prioritize these targets based on their relevance to the condition under consideration.[2]

Furthermore, AI-based target identification can help in the discovery of new targets that were previously unknown or neglected. We can examine massive datasets from diverse sources, machine learning algorithms can reveal hidden patterns and relationships that older methods may miss. This can lead to the discovery of new biological pathways and targets with potential therapeutic applications. AI-based target identification has the potential to transform the drug discovery process by allowing promising targets to be identified using computational approaches. There are several experimental strategies for discovering pharmacological targets, including affinity pull-downs and genome-wide knockdown screens. However, these approaches involve a large amount of labor, money, and time, and have a high failure rate.[3]

Trypsin is a serine protease enzyme it helps us to break down proteins into smaller peptides, it is employed in mass spectrometry (MS)-based proteomic studies. The digestion of proteins by protease enzyme is a fundamental step in protein identification utilizing MS.[4] A few artificial intelligence (AI) techniques were created to effectively forecast how the protease enzymes would digest.[5] AI techniques use unique algorithms to help in the process of target identification, an example of such algorithm is Deep Digest. Deep Digest is the first program that uses a deep learning method to predict the proteolytic cleavage sites of eight different protease enzymes. The Deep learning model was trained using 19 public large-scale data sets containing eight proteases from four organisms (E. coli, yeast, mouse, and human). The tool's prediction ability was evaluated using the Area under the curve, F1 scores, and Matthew's correlation coefficients (MCCs).[6]

3. APPLICATIONS OF AI

AI has improved High Performance Liquid Chromatography (HPLC) performance compared to conventional methods by increasing throughput, and precision, and safeguarding expensive columns. A smart platform can provide "analytical intelligence" to an instrument by utilizing AI, Internet Of Things (IoT), and machine learning algorithms for advanced monitoring, self-diagnosis, and auto-recovery. Intelligent HPLC equipment may extract insights from all lab instruments, making them a valuable asset rather than just monitoring one. The device automatically detects and resolves important faults, enabling unprecedented HPLC performance. Researchers have access to advanced software that can handle various chromatographic run events, including auto sampling, buffer gradient mixing, pumping, column temperature measurement, fraction collection, and data acquisition. IoT-enabled digital interface may significantly improve workflow, data interpretation, and documentation. Connecting HPLC equipment to the internet can enhance automation and provide remote monitoring of feed-stock levels.

3.1 De novo drug design

Developing new medications is a hard and daunting task, constantly getting tough by continuously changing global health requirements. De novo drug design is a promising technique for accelerating and continuing this process. The use of Generative Artificial Intelligence (AI) algorithms has helped in as majorly shifting our approaches in drug design and optimization, helping to create quick and semi-automatic processes.

De novo molecular design typically uses two methodologies. The first method, "Holistic Generation," involves generating a molecule from scratch. This method is extremely useful for early discovery and extensive exploration of chemical space. The second technique known as "Iterative Generation," involves building molecules step-by-step, making it ideal for refining or adapting them for specific applications.

Table 1: List of de novo design approaches developed over time.[7]

Sr.No	Model	Year	Molecular Representation	Model	Chemical Space	Domain	Applicable Strategies
1.	GALILEO	2023	2D Graph	Iterative addition	Synthon	Hit discovery, hit to lead	Scaffold hopping, scaffold decoration
2.	RJT-RL	2022	2D Graph	Iterative addition	Trained	Hit to lead, lead optimization	Scaffold hopping, scaffold decoration
3.	MolPal	2021	Fingerprints	Active learning	Predefined set	Hit discovery	Chemical space sampling
4.	STONED	2021	SELFIES	Random mutation	Valence rules	Hit discovery, lead optimization	Scaffold decoration

5.	CREM	2020	SMILES	Iterative addition	Matched molecular pairs	Hit to lead, lead optimization	Scaffold hopping, scaffold decoration
6.	DeLinker	2020	3D Graph	Fragment linking latent space	Trained	Scaffold hopping	Fragment based
7.	GENTRL	2019	2D/3D Graph	Exploration	Trained	Hit discovery, lead optimization	Chemical space sampling
8.	JT-VAE	2018	2D Graph	Iterative addition	Trained	Hit discovery, hit to lead	Scaffold decoration, scaffold hopping
9.	COG	2004	2D Graph	Iterative addition	Fragment space	Hit discovery, lead optimization	Scaffold decoration, scaffold hopping
10.	SYNOPSIS	2003	2D Graph	Iterative addition	Synthon	Hit discovery, lead optimization	Scaffold decoration, scaffold hopping

AI works here by encoding chemical structures into a continuous numerical space, which can then be decoded.

These computerized systems have been trained on huge molecular datasets, they'll catch the key traits and helps the investigation of new structures. Learning encodings presents challenges in accurately modeling chemical space and assuring the relevance to drug development, as molecules in the same latent space might have different biological and chemical properties.

These approaches require a training dataset containing molecular structures. Generative algorithms are trained on existing compounds and they are then utilized to produce unique chemical structures.

3.2 Target identification

Target identification is an important phase in the drug discovery process. The conventional approach employs time-consuming and expensive experimental techniques such as high-throughput screening (HTS) and X-ray crystallography. However, the introduction of AI has changed this process, allowing the identification of potential targets through computational methods. AI systems will examine several data sources, such as genetics, proteomics, and clinical data, to find possible treatment targets. AI can also help in building drugs that influence biological processes by identifying disease-related targets and pathways. In comparison, computer approaches have the potential to drastically reduce the work and resources necessary for pharmacological target identification.[3]

3.3 Structure-activity relationship modeling

AI models connect the chemical structure of compounds with their biological activity. Researchers can optimize drug candidates by designing molecules with desired features like high potency, selectivity, and favorable pharmacokinetic profiles. Some of the algorithms are mentioned below:

Recurrent Neural Network (RNN): RNNs are highly effective in generative drug design, they produce novel chemical structures based on training data patterns.[8] Some of the notable innovations include the initial model by Olivecrona et al. and later advancements such as DrugEx which emphasizes multi-objective optimization while considering toxicity.[9]

Transformer-based models, inspired by natural language models such as Bidirectional Encoder Representations from Transformers (BERT), interpret molecules as token sequences. These models often use string-based molecular representations. One noteworthy example is ChemBERTa.[10] Transformers can help optimize drug design by recommending structural alterations.[11]

Gasoline quality prediction was tested using analytical data from gas chromatography (GC) and FT-IR on 45 gasoline samples. The AI system approach included the preprocessing implementation of principal component analysis (PCA) and fuzzy C means (FCM) algorithms. The FT-IR spectra were compressed and denoised using a discrete wavelet analysis method. The preprocessed data were analyzed using a hybrid neural network and support vector machines (SVM) classifier. The authors report an approximately 100% correct classification for six different categories of gasoline using this workflow.[12]

ML in the form of artificial neural networks (ANNs) has been tested for simplifying UV-visible water quality monitoring. Field water samples were obtained, and spectra were analyzed in a laboratory setting between 200 and 800 nm. Optimized CNN and PLS models were examined for water parameters, and the R2 for total organic carbon (TOC) between predicted values and reference values was 0.927 for PLS and 0.953 for CNN. Furthermore, the R2 between predicted and true values for total suspended solids (TSS) concentrations was 0.827 with the PLS model and 0.915 with the CNN model. It was determined that CNN would be chosen over PLS for online water quality monitoring using UV-vis spectroscopy.[13]

3.4 Flaw detection of the formulations

Tablet photos are analyzed using AI algorithms and computer vision techniques, this make that there will be automatic and efficient detection of flaws including cracks, chips, discoloration, and form and size variations. AI models are trained on massive datasets of labeled photos, through this the system learns to reliably categorize and identify many sorts of faults with high precision and recall whenever required. Conventional methods, such as X-ray computed tomography, have been used to investigate the interior structure of tablets, but they are time-consuming and have an impact on the desire for speedy tablet manufacture. Deep learning is used in conjunction with X-ray tomography to detect tablet faults. These researchers produced multiple batches of tablets employing excipients such as microcrystalline cellulose and mannitol. The created batches were assessed using the image augmentation approach. During the same study, three alternative models were utilized, including UNetA, which can be used to distinguish between tablet and bottle characteristics. Module 2 was utilized to identify particular tablets through augmented analysis. The tablet's interior cracks were investigated using UNetB. Such UNet networks are used to check tablet faults with greater accuracy, providing ease of identification of problems with significant reductions in time, financial costs, and workload. This AI-powered detection not only increases the speed and accuracy of problem identification but also decreases the need for manual inspection, reducing human error and subjective judgment. AI systems' real-time monitoring capabilities look to it that the flaws are detected quickly, allowing for early action and averting the distribution of faulty tablets into the market.[14] Incorporating AI into tablet defect detection improves the product quality, promotes efficiency, and ensures the safety and efficacy of pharmaceuticals.[15]

3.5 Recent development in science

Computational pharmaceutics is the modeling of drug delivery systems at many sizes, from molecular interactions to macroscopic behavior. AI algorithms can assess complicated interactions between pharmacological characteristics, formulation components, and physiological parameters to predict drug behavior at all scales. This helps us to get a more comprehensive understanding of drug delivery mechanisms and aids in the design of effective drug delivery systems. This helps in predicting the medication's physicochemical qualities, the in vitro drug release profile, and its stability. The same technology is also used to improve the assessment of in vivo pharmacokinetic parameters and medication distribution, as well as in vivo-in vitro correlation studies.[16] Using the correct collection of AI technologies have helped researchers to discover possible hazards and obstacles connected with medication delivery systems early in the development cycle. This enables proactive alterations and tweaks to reduce hazards and improve drug performance. The application of AI and computer modeling decreases the reliance on time-consuming and costly trial-and-error trials, decreasing the likelihood of unexpected outcomes.[17]

AI is the application of modern technologies and software to acquire human-like abilities. In recent years, such innovation has helped various sectors, including the pharmaceutical business, particularly during the product development phase. Implementing these technologies can save time, money, and resources needed for manufacturing and proper delivery to end users via the supply chain. It also gives a better platform for understanding how process parameters affect product formulation and manufacture.[18] Researchers investigated the use of machine learning approaches to predict solid dispersion stability for six months. They studied the use of machine leaching for solid dispersion dissolution investigations. They employed a random forest algorithm to create a classification model that can discriminate between spring and parachute dissolution profiles. It also helped to maintain supersaturation with 85% accuracy and 86.6% sensitivity. The time-dependent medication release was predicted using the regression model generated by the random forest technique.[19]

AI can also be utilized in the context of systemic drug delivery to predict drug release. Additionally, it is employed to investigate the effects of crucial processing parameters that are integral to tablet manufacturing, with the potential to ensure consistent quality control measures. Certain AI applications have been utilized to identify defects in tablets.[20]

3.6 Physiologically-Based Pharmacokinetic (PBPK) modeling

PBPK modeling software options such as GastroPlus, Simcyp, PK-Sim. PBPK models are commonly used to mimic drug distribution and clearance inside the body. These models are complex, and their construction necessitates substantial data and computational resources. AI-based strategies facilitate the creation of PBPK models by employing machine learning algorithms to determine the most important properties of the mode.[21]

AI-based computational algorithms can optimize the parameters of the PBPK model, potentially reducing the requirement for animal studies and human clinical trials.

AI-based models have been used successfully to forecast medication release and absorption parameters. These can also predict the pace and amount of drug release over time by taking into account aspects such as the drug's physicochemical properties, formulation features, and the delivery system's release mechanism. AI-based models can forecast the release kinetics of pharmaceuticals from various drug delivery devices, such as oral tablets, transdermal patches, and inhalers.[22] AI-based models

can estimate drug absorption parameters including bioavailability and absorption rate by taking into account drug solubility, permeability, and formulation properties. These models can examine the drug's physicochemical qualities, such as lipophilicity and molecular weight, and compare them to absorption data to estimate how well the drug is absorbed into the bloodstream. Overall, AI-based models are an effective tool for forecasting medication release and absorption parameters. These models optimize medication formulations, guide drug development decisions, and help the designing of more effective drug delivery systems.[23]

4. LIMITATIONS OF AI

Despite their advantages, AI-based models have numerous drawbacks, including the requirement for big datasets, potential biases, and a lack of interpretation. Therefore, AI-based models should be used with traditional experimental methods to ensure drug safety and efficacy. Some limitations are highlighted below.

AI models use sophisticated algorithms and are commonly referred to as "black boxes" because it is difficult to grasp how the model makes its predictions. This lack of transparency can make it difficult to obtain regulatory approval for AI-based drug development tools because it is difficult to demonstrate that the model is making accurate and reliable predictions.[24] Furthermore, a lack of transparency might lead to a lack of faith in the model's predictions, especially if the model delivers predictions that contradict the expectations of doctors or researchers.[25]

AI models require a large amount of data to make good predictions. However, insufficient data may be available for a specific drug or demographic, resulting in less accurate forecasts or biased results. For example, rare diseases may have inadequate data, making it difficult to construct AI models. Furthermore, the data utilized to train AI models may not be representative of the population of interest, thereby leading to biased conclusions. Certain forms of data, such as longitudinal data or real-world evidence, may not be easily available, limiting the functioning of AI models. These constraints underscore the importance of carefully evaluating the quality and representative data used to construct AI models.

The efficacy and precision of AI models are dependent on the quality of the data used for training. When the data is skewed or incomplete, the forecasts that follow may be biased as well. The homogeneity of patient populations in clinical trials is an important issue in the field of pharmacology. If a given demographic or disease condition is underrepresented in the training data set, the model's ability to make accurate predictions about the drug's efficacy in that population will suffer. Furthermore, in the presence of inadequate or wrong data, the model may make incorrect assumptions, resulting in imprecise forecasts. The use of an artificial intelligence model to guide clinical decision-making can be challenging.[26]

Once an AI model is trained, it can be difficult to add fresh data or update the model, this can be a severe restriction in drug development procedures, as new knowledge and data are frequently updated. For example, as new pharmaceuticals are introduced or clinical trials generate more data, an AI model may need to be updated to represent this new information. However, updating an AI model can be difficult, requiring substantial time and resources to retrain the model with new data. Furthermore, as drug development procedures progress, AI models must keep up with these changes, not keeping up could lead to wrong projections and poor decision-making. Thus, it is critical to carefully analyze AI models' limitations and devise ways to upgrade them whenever new information becomes available. This can involve building models that are easily updated or incorporating the model into a wider framework that can be continuously modified over time.[27]

5. CONCLUSION

AI is revolutionizing medicine delivery, enabling customized, targeted, and adaptable therapeutics. Using AI for data analysis, pattern identification, and optimization can help pharmaceutical researchers and healthcare professionals improve medication development, and effectiveness, reduce adverse effects, and improve patient outcomes. It is advantageous over conventional experimental procedures. Pharmaceutical research and development focuses on discovering and commercializing new drugs, a time-consuming and expensive process. The incorporation of AI technology has the potential to accelerate medication development, improve patient outcomes, and revolutionize the pharmaceutical sector.

The world frequently experiences various epidemic and pandemic outbreaks, bringing enormous human misery and death. AI technology is always growing and will be most effective when the benefits outweigh the constraints. Thus, AI-enabled methodologies will offer numerous new options in many domains of healthcare and pharmaceutical research, potentially changing the game in future studies.

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