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A Comprehensive Review on Machine Learning and Deep Learning Methods in Drug Discovery

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Abstract— Due to its ability to drastically cut the time and money required to develop new medicines, artificial intelligence (AI) based drug discovery has recently attracted a lot of attention. The fields of drug research and development have made use of machine learning (ML) and deep learning (DL) technologies to develop new medication prospects. Machine learning and deep learning-based techniques are emerging at every level of the drug development process as a result of the proliferation of drug-related data. Preclinical testing of a target of interest has proven to be particularly tough for pharmaceutical chemists, who face significant challenges in selecting and developing effective drugs. Machine learning and deep learning algorithms are now extensively used in approaches for generating therapeutic targets and innovative medication development in order to increase the accuracy, efficiency, and quality of created outputs. This review focuses on the application of machine learning and deep learning algorithms in drug development, as well as related approaches. We'll look at the approaches and methods that seem most promising in terms of their potential impact.

Keywords- drug discovery, machine learning, deep learning, algorithms, artificial intelligence

I. INTRODUCTION

The purpose of drug discovery is to find safe and effective therapies for human illnesses. Drug development takes a long time and costs a lot of money, from target identification to step-by-step clinical trials. At each checkpoint, it is crucial to select the best possible pharmaceutical choices for the next phase of treatment. Finding lead compounds from hits and confirming their medical potential requires the "hit-to-lead" method. Clinical trials are plagued by side effects and lack of in vivo efficacy in part because of the polypharmacology theory's [1] assertion that single or multiple medicines frequently interact with several targets. For each sickness model, in-vivo studies would be ideal, but this technique would require a large amount of time and effort, which is not possible. Throughout the 1980s, the hit-to-lead process in modern pharmaceutical R & D has been heavily reliant on computer-aided drug discovery or design tools [2–4]. The pharmaceutical industry's R&D output has been dropping since the mid-1990s, despite the use of this in silico approach.

Recent developments in drug discovery have made it possible for academics and the pharmaceutical industry to apply AI in important and cost-effective ways. Artificial Intelligence (AI) in drug discovery was made possible by the advent of high-performance processors like graphics processing unit computing and the huge volumes of chemical and biological data accumulated over decades [4-6]. Various AI-driven drug development pipelines and frameworks are being created in addition to the implementation of cutting-edge AI technologies in the drug development process [7–9].

AI is widely employed in both the corporate and academic worlds. Machine learning (ML), AI's fundamental component, has been used in a variety of domains, including data collecting and analysis. Applied mathematics and computational theory are essential to algorithm-based techniques like machine learning. DL-aided self-driving cars, improved speech recognition, and smarter search engines are just a few of the possible applications of ML models [10-13].

II. MACHINE LEARNING ALGORITHMS USED IN DRUG DISCOVERY

Machine learning approaches have had a significant impact on drug discovery. Pharmaceutical companies have reaped major benefits from the application of machine learning algorithms in the process of drug discovery. Multiple models for predicting the chemical, biological, and physical properties of molecules have been constructed using machine learning methods [14–22]. It is possible to use machine learning techniques at any stage of the drug discovery process. When it comes to discovering new drug uses, for example, machine learning algorithms have been used to predict drug-protein interactions, identify medicine efficacy, ensure safety biomarkers, and

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optimize molecular bioactivity [23-27]. Examples of machine learning algorithms used in drug development include support vector machine (SVM), Naive Bayesian (NB), Random Forest (RF), etc. [28-30].

A subset of artificial intelligence known as machine learning is not a homogenous category (AI). Supervised algorithms and unsupervised algorithms are the two main categories of machine learning algorithms. In supervised learning, previously labeled samples are used to predict fresh samples' labels. Unsupervised learning may be used to detect patterns in a collection of unlabeled examples. The reduction of a high-dimensional input to a lower-dimensional input is a common goal of unsupervised learning techniques. Even if unsupervised learning is more successful in a low-dimensional space, the pattern that emerges is also more understandable. With semi- and reinforcement-learning approaches, a wide range of data sets may be utilized [31]. The development and expansion of successful machine learning algorithms during the drug discovery process are dependent on the availability of large amounts of data. In precision medicine and drug development, the necessity for high-quality data and well-defined training sets is substantially larger. For the creation of really effective tailored medications, it is necessary to describe all related pan-omic data, such as genomes, transcriptomics, and proteomics. There has been a boom in data development, gathering, and maintenance for drug research as online multi-omic databases and machine learning methods have become more commonly employed over the last two decades. To some extent, attempts at deciphering freshly created data have been effective thanks to analytical advancements. Drug research is currently helped by machine learning methodologies and networked databases via different software/web tools, such as Software. For example, the capacity of new data analytics to mix with known methodologies and current hypotheses to produce new hypotheses has helped with re-positioning, target identification, small molecule discovery, synthesis, and other applications [32–34]. It's possible to get a wide range of information from medical and multi-omics domains. Having data that is inconsistent and derived from a variety of sources is not unusual. Generalized linear models with non-negative reverse inference may be useful when dealing with multidimensional data (NB). There are several different ML techniques and models that are extensively utilized in various fields of research [34-35]. These include regression, clustering, regularization, neural networks, decision trees, and dimensionality reduction.

III. Limitations Of Machine Learning Algorithms

Machine learning is a critical part of the drug discovery process. Through the use of these methods, it is possible to test hundreds of different combinations, which would otherwise be impossible without the aid of modern technology. As previously mentioned, algorithms can be taught through the use of inputted data, but this approach has some drawbacks. There are still no known biological routes or objectives for machine learning despite its extensive history. There may be a lack of extrapolated data for the protein of interest due to a lack of available data. Computational screening of proteins can be done using the Free Energy Perturbation technique [36]. It is used to train algorithms; computer-generated forecasts are utilized instead of actual data collection in some cases. Inaccuracy in the training data may be more than intended. There are still category mistakes in training sets, even if the methods in this paper have a higher error-minimization threshold [36].

IV. Deep Learning Methods Used In Drug Discovery

If you're interested in cutting-edge research and development, deep learning algorithms are an excellent place to start. Deep learning relies on the translation of artificial neural networks (ANNs) from theoretical and predicted applications to workable algorithms, which were first developed in the 1950s, as a fundamental pillar. A multidimensional data representation can be learned through abstraction using DL methods [37]. For example, picture identification and speech recognition have been addressed thanks to deep learning, which is a more advanced kind of machine learning (ML). Drug activity prediction, target discovery, and lead compound discovery have all benefited from the use of DL approaches [38–40]. In NN systems, the DL foundations are widely used to construct systems that can recognize, understand, and produce complicated data.

Three main types of artificial neural networks used in drug discovery are convolutional neural networks (CNNs), deep neural networks (DNNs), and recurrent neural networks (RNNs). The parameters that influence the selection of NNs from the subset's variations are numerous. Data flows from the input layer to the hidden layer(s) and then to the output layer (in DNNs) in a single path. To identify the outputs, trained supervised learning algorithms are typically used. Other machine learning techniques can be utilized to train neural networks in deep learning algorithms. Supervised and reinforcement learning approaches can be used to teach DNNs difficult tasks. Based on existing libraries and training sets, it is possible for a predictive neural network (DNN) like this one to forecast the chemical properties of novel compounds [41,42]. QSAR models are currently being employed in the field to find the link between the chemistry and the activity of these medications. DL-based AI in drug discovery and development is now using QSAR analysis, one of the most advanced versions of DL. Researchers have used 2D chemical structures to discover the physicochemical parameters relevant to the action of the molecule. 3D-QSAR has helped researchers better understand how ligand-target interactions are influenced by the

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structure of the environment [43,44]. Predicting whether newly synthesized lead compounds will act on or miss specified targets has been done using QSAR in the pharmaceutical sector. Algorithmic methods for discovering and developing new products are not without flaws.

Research using these AI algorithms have yielded numerous errors and inaccuracies over time. In QSAR studies, it was discovered that NNs have a few drawbacks when compared to other ML techniques. NN redundancy and output blockage result from the existence of unnecessary descriptors. There is a risk that this redundancy will decrease the NN's efficiency and produce results that aren't ideal. The usage of unidentified descriptors is also a problem because they could affect the outcome. In order to acquire a smaller number of higher quality descriptors, these concerns have been addressed by using more specialized feature selection methods; however, NN-based QSAR will continue to face this difficulty These NN-based assays face another challenge in implementing optimal network parameters without sacrificing accuracy [44]. These issues are not going away, despite the fact that workable remedies have been proposed and put in place [45]. Chemical synthesis and identification are prioritized only when significant research into target-molecule interactions has been completed.

As part of the de novo drug design process, descriptive simplified molecular-input line-entry system nomenclature (SMILES) nomenclature is employed widely. RNNs are self-learning neural networks that use generational input processing and the formation of hidden layers. For the creation of new chemical structures, an RNN-type long short-term memory has become the norm. RNNs differ from feed-forward neural networks and DNNs in that they use neurons connected in the same hidden layer to establish a working cycle of processing inputs and outputs, rather than connecting across layers. However, the initial SMILE training sets did not include these RNNs, which have shown promising results in producing unique SMILE structures that are logical, structurally accurate, and viable [46–49]. With the help of generative RNN models, Segler et al. were able to identify possible chemical structures that could be effective against S. aureus and P. falciparum (P. falciparum). Chemical structures with known efficacy against these target organisms were supplied to their models, and they were able to generate a total of 14 percent of the 6051 potential S. aureus molecules. In addition, 28% of the present P. falciparum compounds were produced by the model [50]. Chemical synthesis routes have typically been developed and implemented by chemists alone. However, as artificial intelligence (AI) advances, this position will increasingly entail computer-aided synthesis planning (CASP). Researchers have used Monte Carlo tree search (MCTS) methods to build CASP processes in recent studies. A good method for finding the best conditions and solutions is the MCTS methodology [52,53], which uses a random step search without branching. Three neural networks (NNs) and 12.4 million transformation rules were utilized by researchers Segler and Waller [54] to develop the first real CASP process, which was built using this technology. One of the first NNs, an expansion node, searches the past and predicts if the 12.4 million transformation rules may be used to make the chemical. A better selection of transformations, such as those that are feasible and high-yielding, can be made by the expansion node as a result. With the rollout node, inputs are filtered so that only the most often reported transformation rules are included. This increases transformation success rates. In order to incorporate the new path into the search tree, the update node must be triggered. It was able to solve 80% of retrosy thesis questions in 5 seconds and more than 90% in 60 seconds using this technique. Chemical synthesis and reaction pathways based on artificial intelligence (AI) have been improved in several studies [55–57]. AI-based chemical synthesis and characterization will be able to transfer drug discovery from the bench into in silico by increasing its use across the entire drug discovery process. Discovery and management will be more efficient as a result.

V. Copyright Forms and Reprint Orders

DL models may be divided into categories based on their aim, loss function, learning technique, and structural characteristics. In the early days of DL, there was a research that used only one model; however, these days, there are fewer studies in which only one model is used. It's common to see a combination of two or more of the following models. As far as this area is concerned, we've only discussed the most basic models. In this section, we'll go over the models' benefits and drawbacks from the standpoint of drug discovery.

5.1. Multi-Layer Perceptron

Perceptrons with numerous layers are known as Multi-Layer Perceptrons (MLPs). With its many names like "full-connected layer," "linear layer," and so on, the multi-layer perceptron (MLP) is the most common type of neural network. Among MLP's many impressive features are its classification and regression skills. For the most part, it's trained by figuring out which parameters are optimal for minimizing any discrepancies between projected and actual values. Due to the fact that it is a widely used standard model, it is simple to apply and has a proven track record of reliable performance. Because of this, a variety of methods have been developed, and almost all DL frameworks typically include it. Its adaptability allows it to be employed in connection with a wide range of data, including the FP, transcriptome [59], bioassay [60], and molecular properties. DTI prediction was performed using the MLP with four hidden layers, FP for compound, and various information such as

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PseAAC, PsePSSM, NMBroto, and structure features were fused with the target protein information [58].

5.2. Convolutional Neural Network

In order to retrieve local information, convolutional neural networks (CNN) use the same computational filter to calculate several neighboring properties. Stacking CNNs in many layers can be used to recover both global and local information. Single-modal picture recognition often necessitates the use of CNN. The convolution filter is the same no matter how much data is being fed into it. There is a direct correlation between how many calculations are performed and how many parameters are in the DL model. To put it another way, it is a great training tool. It's also not overly sensitive to noise in the data being fed into it. For its ability to handle atomistic geometry, CNN is widely used in conjunction with voxel or image data [65]. Invoking voxel-based techniques, the protein and its receptor can be visualized as, RoseNet [61], AK-score [66], and Deep-Drug3D [64] predict the DTI. RoseNet [61], AK-score [66], and Deep-Drug3D [64] used the protein and ligand as a voxel to predict the DTI, while DEEPScreen [62] employed a 2D image of the molecule. Even though CNN isn't optimized for sequential expression methods like SMILES or amino acids, they are sometimes utilized instead of RNNs [67]. DeepConv-DTI [63] and transformer-CNN [68] used CNNs to create QSAR models based on sequential data.

5.3. Graph Neural Network

As a rule of thumb, the vast majority of data in machine learning is represented as a Euclidean vector. When dealing with data encoded in relational graphs, models like MLP, RNN, and transformer are better suited for use with single-vector or sequential data. A graph neural network (GNN) is a model for learning graph-type data in deep learning [69]. DTI, PPI, and other graph types of data are employed in the identification of new drugs and treatments. The graph convolution network (GCN) and the graph attention network (GAT) are two examples of graph neural networks that use the CNN approach (GNN) [70,71]. There are a number of uses for GNNs, but three stand out the most. Method 1 entails anticipating molecular characteristics with the use of representation learning techniques. The GNN strategy utilized by Yang et al. outperformed current methods in property prediction, according to their findings. The GNN has lately become popular for property prediction [72] due to this trend. The second approach is to gather information about relationships across different domains, such as heterogeneous and bipartite [73,74]. This approach is more general. Patients and diseases, as well as genes and treatments, may be linked using comprehensive metadata [74], making this type of research possible. When it comes to de novo design, the GNN develops or improves molecules [75].

5.4. Recurrent Neural Network

Using a recurrent neural network (RNN), the previous input value affects the next output value when it is supplied sequentially. Natural language processing (NLP) performance improved considerably when RNNs were first invented, and it became one of the most widely used DL models. Additionally, it is feasible to extract the weight of the hidden layer and utilize it as a feature with sequence information for representation learning. There are certain limitations to the naive RNN's structure and performance, though. As the input sequence grows longer, things further away from the currently inserted item have less impact on the vanishing gradient problem [76]. This is especially true for big data sets like proteins and compounds. In addition, as the length of the input sequence grows, so does the training time required because the same technique is repeated. Even though sequential data chunks have complex underlying linkages, their properties are poorly understood.

5.5. Attention-Based Model

Self-attention is a mechanism for incorporating machine translation into natural language processing that was first proposed by the transformer model. The relationship between the elements in a sequence can be calculated, and the results can be used to extract features for each one. One would call it "self-attention." Focusing on past data allows you to fully utilize the correlation with distant tokens rather than using a single hidden state in which all time step values are assumed. Bidirectional encoder representations from trans-formers (BERT) were developed in 2018 by Devlin et al. [83] and have been extensively employed in medication development since.

DTI's classic RNN-based QSAR modeling seamlessly incorporated the transformer model. CNN was applied to a transformer with SMILES as input by Karpov and colleagues [68] to predict the pharmacological effects of drugs for the prediction of drug-target binding affinity by embedding protein sequences in CNN and molecule structures in BERT, Shin and colleagues [66] suggested a molecular transformer DTI model (MT-DTI). GCN and BERT were used in the model by Lennox and colleagues [84] to represent both protein and chemical structures. According to Lennox et al., their model outperformed the MT DTI in terms of the prediction of binding affinity.

5.6. Generative Adversarial Network

DL's most widely used generative model is the generative adversarial network (GAN), which was initially published in 2014 [85]. De novo drug design is the only use for the GAN, not DTI. Discriminators and generators work in tandem to produce bogus results that the generator can't tell apart from real ones, and the two modules are taught against each other. A

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powerful tool for making visuals, the GAN has a difficult time constructing big molecules. Additionally, the training difficulty is higher than for other models, and it incorporates issues such as mode collapse. It is widely accepted that the GAN, when coupled with reinforcement learning (RL), is an excellent model for creating novel compounds. Drug discovery has a range of GAN architectural applications [86], but we'll focus on only two extremely simple ones here. Objective reinforced generative adversarial networks (ORGAN) [81] and molecular GAN (MolGAN) [81] have been successful models. In order to make use of SMILES data, ORGAN leverages the sequenceGAN (seqGAN) framework [87] and incorporates RL. Drug-likeness and synthesizability were both better than the RNN naïve, but solubility was lacking. The ORGAN and its RNN are outperformed by the MolGAN, which employs the GCN based on molecular graph representation.

5.7. Autoencoder

AE is an unsupervised learning framework that compresses and decompresses data. In this system, data is compressed and then decoded back into its original form. This symmetric approach automatically identifies the most distinctive feature that separates the data. Compression of abstract points into a latent space can be used as additional features in other models by using the encoder. A decoder is used to generate new data, while the encoder is discarded after training and used for data encoding, dimension reduction, or visualization. In conjunction with other DL models, dimension reduction can be performed without the need for data labels [88].

The AE creates a patchwork pattern in the latent space, but the pattern itself is meaningless. A variational autoencoder uses a Gaussian-shaped stochastic fence to restrict the latent space (VAE). By raising the latent space density, the data become more continuous and smoother. Gómez-Bombarelli et al. used the SMILES [89] to build a chemical latent space that allowed them to explore continuously from one compound to the next. DTI uses AE because of its great data compression, while de novo drug design uses VAE because of its lower compression performance and the latent space properties noted above.

DL model combines GAN and VAE structures to compress and produce features in Adversarial AE (AAE) [90]. Despite its ability to condense compound properties, the VAE is unable to generate accurate findings. However, the GAN is biassed by a single mode and has weak diversity ratings, despite the fact that it may produce real compounds and credible discoveries for the detection and development of novel co pounds, Insilico Medicine published the AAE [91,92] in 2016 [92] and the druGAN [93] in 2017. By condensing the data to the latent space, the AAE approach can produce novel molecules with good outcomes. Modifying the input compound's lipophilicity (logP) and synthetic accessibility by providing a condition control feature to AAE resulted in unique compounds [94].

VI. Conclusion

Computer power and chemical & biological data have made a huge influence on drug discovery efforts due to artificial intelligence. Deep learning and machine learning research have surged in recent years. For individuals who are new to machine learning and deep learning-based drug discovery, this paper serves as a useful starting point. Machine learning and deep learning methods for drug discovery are examined in this research.

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