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DEEP LEARNING IN DRUG DISCOVERY

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ABSTRACT

The primary domain in the field of pharmaceutical research and development is the process of discovering drugs, wherein artificial intelligence methods and approaches such as machine learning are implemented. Deep Learning, in particular, represents an emerging category within machine learning that is focused on computing technology to replicate the intellect of humans using Artificial Neural Networks. The drug discovery strategy may entail insufficient effectiveness, imprecise delivery, time investment, and a significant financial outlay that could lead to challenges and problems. The Deep Learning technique has demonstrated its strength when dealing with complicated and massive data that contains all the minute details about the drug discovery process. This approach is used in drug property prediction, protein engineering, drug-target interaction prediction, de novo drug design, expression of genes, as well as data analysis. This also includes generating leads, optimisation, validation, as well as preclinical investigations. Despite all of the benefits that accompany the use of deep learning, the limitations and problems encountered during the process. It is primarily a still-developing sector of technology that could potentially be evolved into an exceptionally advanced and effective way that can be utilised in the process of drug development, which may be extremely beneficial to humanity.

Keywords: Artificial Intelligence, Machine Learning (ML), Deep Learning (DL), Drug Discovery, Neural Networks, and Protein Engineering

INTRODUCTION

AI or Artificial intelligence is widely used in almost every element of our lives. It is a simulation that uses computer-processed techniques to mimic human intelligence. The number of advancements achieved through the usage of AI is multitudinous. AI in terms of machine learning is a broad spectrum that consists of basic cognitive behaviours like learning, reasoning, problem-solving, perception, and language understanding with the help of advanced computational power **[1]**. It is classified into Natural Language Processing (NLP), computational thinking, Machine Learning (ML), and other applications of Deep Learning (DL). Machine learning is fundamental for mastering and predicting long and complex events that deal with human experiences. Deep learning represents an independent subfield in computational neuroscience to eradicate the challenges of any numerical, statistical, or arithmetical approaches. Deep Learning is often called a rebranding of ML algorithms such as Artificial Neural Networks **[2]**. Within the pharmaceutical sector, an interest in deep-learning technology is widely administered for its more reliable prediction and superior results in the technique for the process of discovering drugs. DL is showing comparatively more improved predictivity than the baseline machine learning methods **[4]**. The approach of deep learning is useful when the data sets of the given process to be analyzed are complex and larger in size to which the conventional data analyzing tools, techniques, and software are used. AI deals with systems with human-like behaviour by using trained algorithms with datasets and furtherly DL is an advanced step in machine learning, for example – ANN **[3, 8]**.

DRUG DISCOVERY

The process of evaluating a synthesised chemical or a big biological molecule for additional study as a potential target for the treatment of any disease is known as medicinal drug discovery. Predominantly, the current pharmaceutical development process involves determining a disease that can be treated and creating investigations using in vitro methods, carrying out high-throughput screening (HTS) of component datasets against the target of interest to find and refine hits and developing lead compounds with acceptable intensity and exclusively targeting the biological activity in vitro studies to prove the effectiveness of the hit in a clinical study **[22]**. A quick outline of the drug discovery process includes processes called lead identification. Identification of the target product in transgenic organisms is done using

tests and studies such as phenotypic screening, genome-wide association studies (GWAS), and imaging techniques **[23]**. Following identification, the targeted prospective medications must be confirmed using specialized methods such as antisense and RNAi technologies in genetically engineered animals, as well as proteomics. The next stage is to select the compounds that exhibit the necessary properties as demonstrated by screening assay methods (HTS - High Throughput Screening). The identical assay conditions were used for the confirmatory assessment of the discovered hits **[6]**.

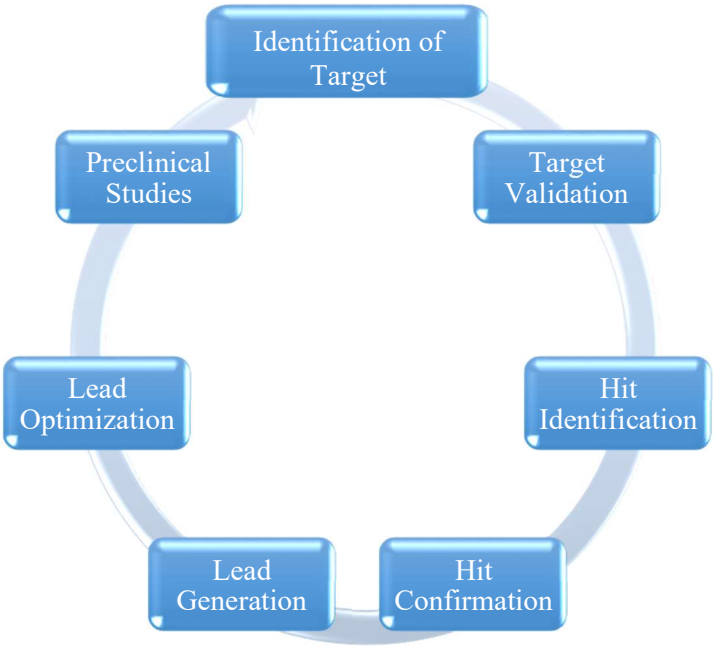

Figure 1: The process of drug discovery

The goal of the lead phase, also known as lead generation, is to develop a QSAR (Quantitative Structure-Activity Relationship), ADME (Absorption, Digestion, Metabolism, Excretion), physicochemical qualities, toxicity, and pharmacokinetic parameters **[26]**. To develop the characteristics of the lead compounds, the detected hits from the manifold series undergo an optimization process. Following that, the preclinical development process begins, in which the regulatory bodies' approved drugs are tested with animals for toxicological and pharmacological studies, as well as stability studies, quality control measures, and formulation development, all of which fall under chemistry, manufacturing, and control (CMC). These investigations must be authorized before the candidate may move forward with the drug into human clinical

trials **[7]**. There will be several phases of clinical research on human participants or volunteers. These methods can be costly and time-consuming since they need a greater number of tests and studies for regulatory authorities to approve them because risks such as shortage of appropriate bioassays, shortcomings of target selectivity, inappropriate pharmacokinetics, or toxicity associated with the generated molecules are involved with the development process **[19]**.

DEEP LEARNING IN THE DISCOVERY OF DRUGS

In the pharmaceutical process of discovering drugs, the volume of biological data is rapidly increasing in the current big data age, owing to the introduction of improved screening technologies **[32]** and massive chemical database systems. Massive amounts of data are easily accessible, and the way they are processed via graphics processing units (GPUs] has resulted in the development of innovative modelling methodologies **[5]**. The new algorithm-based learning called deep learning is a cutting-edge machine learning method. DL may be utilized to get pertinent insights from massive data sets during pharmaceutical discovery and development to enhance the therapeutic prospects of the drug with lesser toxicity and negative effects on patients **[35]**. The deep learning model comprises many layers of neural networks that are interconnected to transfer the data from one representative level to the next level **[3, 19]**.

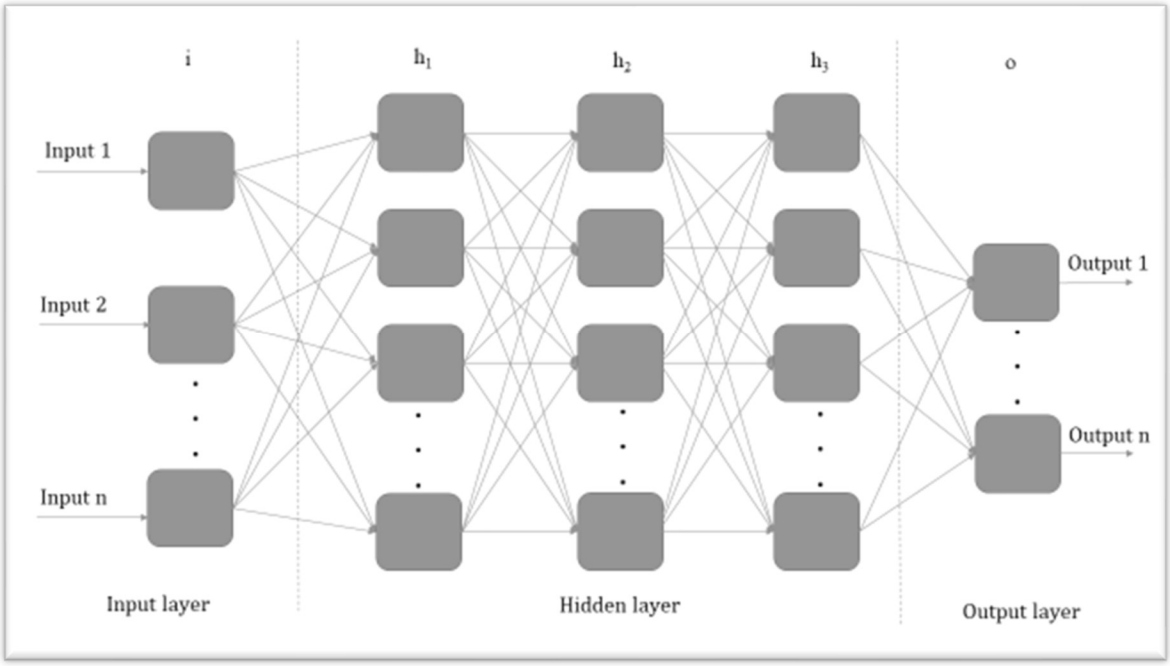

Figure 2: Represents a simple artificial neural network

Conventional Artificial Neural Networks (ANN) approaches implement a layer for input, a layer that is hidden, and an output layer as a way to connect input and output data **(Figure 2) [3]**. In many aspects, DL, or deep neural networks, are comparable to ANN in that they receive input information and replicate how the brain processes information. However, unlike ANN, DL has numerous hidden layers that blend inputs with different weights and send the results further and deeper within the structure of the network before they reach an output layer at the end. Unsupervised learning is possible with deep learning, and it seems to perform well when faced with massive and noisy data **[8]**.

Protein engineering

Protein engineering uses computers to create and simulate proteins. A recent study has explored and uncovered the structures and functions of proteins using deep learning methods. Manifold efforts have already been undertaken to replicate interactions between proteins in conjunction with additional biological variables (such as DNA) to gain an understanding of how proteins function **[17]**. Researchers used a recurrent convolutional neural network to foresee the precise nature of how proteins bound to different DNA loci. They tested their modelling using information from high throughput in vitro studies **[25]**. The best method for determining the preferred binding sites for two proteins and certain DNA sub-regions was demonstrated to be this modelling technique. Additionally, using 3D electron density and electrostatic potential fields as-is for proteins, deep learning techniques may be utilised to predict biological activities **[28, 31]**.

Drug target interaction prediction

Proteins play a crucial role in every living thing and are necessary for every species to operate properly. The 3-Dimensional structure is necessary for proteins to operate properly. The functioning of a protein may be altered by altering its structure, therefore this is a crucial consideration in the search for new drugs. The majority of medications have the purpose of binding to a certain protein. Determining whether or whether the protein is capable of binding to the medication is therefore a key element in drug delivery **[27]**. Forecasting of drug-target interactions is what this is termed. A deep learning-based system for predicting drug-target interactions has been presented by scientists. These deep learning models for predicting drug-target interactions accept data on both proteins and chemicals as input. A chemical may be represented in a variety of ways, as was

already explained, and proteins are able to do the same. They suggested a technique for scoring ligand proteins using convolutional neural networks. Alternative to using text-based depiction, they employed 3D **[9]**.

Gene Expression Data Analysis

Massive volumes of diverse genomics data may now be easily adapted to the needs of deep learning techniques because of the development of next-generation sequencing technology. Deep learning techniques are thus being applied to the creation of precision medicine, the prediction of sequence specifications, and the modelling of genomes for medication repurposing **[15]**. To forecast the therapeutic categories of medicines, scientists examined transcriptional response data. They used a model called the Deep Neural Network (DNN) modelling technique that produced improved categorization precision in comparison to various traditional techniques, including genetic expression data and pathway stimulation rates as further variables. Additionally, they demonstrated how DNN can precisely predict the class of medications with various pharmacokinetic and pharmacodynamic circumstances **[10]**.

de novo drug design

De novo design of drugs refers to the process of developing novel lead compounds with appropriate physiochemical and pharmacological characteristics. The implementation of deep learning, or Deep Learning, has emerged as an important topic in the field of de novo pharmaceutical development, with various DL-based algorithms for molecular synthesis problems established. In broad terms, four paradigms were used to build these techniques: recurrent neural networks, encoder-decoders, reinforcement learning, and generative adversarial networks **[13]**. It is required to design a compound that's able to bind to a specific protein and modify some pathways, but not others, and that can possess particular physical characteristics like solubility range **[36]**.

Pharmacodynamics modelling

For understanding the interactions between medications and their associated targets, pharmacodynamics modelling is essential. Provided the variety of drug compounds and their targets, conceivable interactions between drugs and proteins are equally complicated and have a wide range of possible conformations. Deep learning techniques have recently been utilised to forecast the interactions of various complexes, including homogeneous and drug-protein complexes. Deep Belief Network was recently employed by researchers to forecast drug-target interactions. It shows how deep learning

techniques have a better chance of discovering novel interactions between drugs and targets than QSAR techniques **[30]**.

WORKING MODEL OF DEEP LEARNING ALGORITHMS

To recognise completely interconnected neural networks, perceptrons with several layers are typically used. The algorithm is converted into simple two-digit data inputs. This approach enables the inclusion of both nonlinear as well as linear functions **[14]**. The linear equation is a single line that multiplies the inputs it receives with an unchanging factor. Nonlinear function approximations include the Sigmoid Curve, Hyperbolic Tangent, as well as Rectified Linear Unit. This approach is ideal for problems with regression and classification with true-valued data, as well as any type of adaptable model **[11]**. The conventional convolutional neural network (CNN) paradigm represents a sophisticated and high-potential variation ANN that was created to handle increasing difficulty levels, in addition to data preprocessing and compiling. It depends on the arrangement of neurons in an animal's visual brain. CNNs are regarded as the most adaptable technique for analysing information regardless of visuals **[24]**. RNNs were initially developed to aid with sequence identification. As the inputs, these kinds of networks only accept streams of data of varying durations. The understanding of its former state is employed as a parameter by the RNN for generating the greatest current forecast. As an outcome, it may assist network achievers of memory that are brief **[21]**. Long Short-Term Memories are effective in predicting data in time series using memory and have applications in detecting data in time sequences using memory. It consists of two types of RNN designs that help in issue analysis. Input, Output, and Forget are the three different gates **[33]**. Gated RNNs are very useful for predicting temporal patterns utilising memory-based data. Image classification, sentiment analysis, video categorization, and translation into languages are just a few examples of how these algorithms might be employed **[20]**. Some other techniques that are utilized in the working model of Deep Learning are given below.

Boltzmann machines

Given that there currently is no fixed alignment in the aforementioned network architecture, each of the nodes is linked together in a circle-like pattern. In recognition of its distinctiveness, this technique for deep learning is used to produce parameters for the model. Despite all previous deterministic network models, the Boltzmann Machines

model is stochastic. It can keep track of systems, build a binary suggestion platform, and analyse particular datasets **[40]**. The Boltzmann Machine has a two-layer network of neurons design. The initial layer constitutes the visible or input layer, while the subsequent layer is the concealed layer. They are composed of multiple neuron-like elements that perform calculations. These nodes are linked at distinct levels yet not among nodes in the same layer **[41]**.

Deep Autoencoders

This method constitutes one of the most popular algorithms used in deep learning, dynamically activates a function based on the inputs it receives and interprets the result at the final step. As an outcome of the backlog, limited types of information have been generated, and existing data structures are heavily used **[33]**.

Generative Adversarial Networks: GAN

It employs a DL neural network technique that incorporates a generator with one another and a discriminator. The discriminator assists in distinguishing between actual and phoney data, whereas the Generator Network generates spurious data. Both systems fight with each other because the discriminator continuously differentiates between genuine and counterfeit information while the generator continues to make phoney data appear genuine. If an image library is required, the generator network can generate artificial information that mimics authentic photographs **[39]**. A deconvolution technique neural network is subsequently formed. An Image Detector network is subsequently employed to distinguish between fictional and actual pictures. This rivalry will eventually improve the network's overall performance. It may be used to create images and messages, improve the image, and find novel medications **[19]**.

FUTURE OF DEEP LEARNING

ML techniques and current advances in DL provide significant prospects to cut costs, improve efficacy, and conserve time throughout the drug research and development process. Advancements in neural network algorithms, particularly deep learning techniques, as well as improved design technology and simple accessibility to huge data, all point towards the forthcoming new era of Artificial Intelligence **[34]**. Deep learning techniques involved in developing medicines are attracting the fascination of academics to the point that several pharmaceutical corporations are collaborating with AI firms **[3]**. Natural language processing, speech recognition, and, picture identification are examples of AI applications that have outperformed humans when it

comes to functionality. As a result, it should come as expected that AI might be employed in the process of finding novel medicines. AI is being employed in the discovery of drug processes such as target identification, ADMET prediction, hit finding, optimization of lead compounds, and clinical trials **[16]**. Deep learning approaches may handle complicated tasks that utilise huge, diverse, and multidimensional sets of information without requiring intervention from humans. These approaches are being demonstrated as being beneficial in a wide range of efficient and commercial contexts, notably drug discovery research **[5]**. The approach of models used in Deep Learning, such as Convolutional Neural Networks (CNN), Recurrent Neural Networks (RNN), as well as Deep Belief Networks (DBN) are used in biomedical research to perform several analytical tasks. A mixture of such methods, which use supervised, unsupervised, and reinforcement learning on various forms of scientific information, is already playing a significant part in the comprehension of basic biological processes and has contributed to the creation of personalised, or categorised, the field of medicine **[12]**. Deep learning system efficiency may frequently be substantially enhanced by just increasing systems up. They typically operate a lot better with significantly more information and much more processing power **[8]**. Model-free reinforcement learning needs a significantly greater number of trials, whereas supervised learning needs an excessive amount of labelled data. Despite significantly less expertise, humans appear to have the ability to generalise well **[14]**. Human beings, who can adjust to these kinds of changes in fewer instances, are more resilient to distributional changes than the present systems. Deep belief networks can be utilised to analyse numerous forms of biological information (going from structural to gene expression) as a general strategy that may be customised as well to minimise overfitting. Given their capacity to gain insight into adaptable and rich data depictions, automatic encoders may be utilised effectively for the extraction of features, decrease in dimensionality, and even as autonomous gene expression information indicators. Because of their ease of learning, Restricted Boltzmann systems were commonly utilised in early structural information investigations **[8]**.

CHALLENGES AND LIMITATIONS OF DEEP LEARNING

Despite the implementation of deep learning algorithms that have demonstrated gains in identifying, categorising, and extracting distinctive characteristics from complex and

noisy data, they also have certain disadvantages compared to classic machine learning approaches **[12]**.

Black box

One of the most significant difficulties for deep learning in biological systems is quality control and understanding. The vast majority of DNNs are "black boxes" which are understood through basic connections and co-occurrences. They offer restricted ways of interpreting the depictions, while some, like CNNs, are highly strong in constructing a substantial degree of depiction **[36]**. While working with pictures, speech, or text-based information, developers may easily evaluate classification performance and evaluate the data quality at the output level. Biology data with high-level dimensions, contrary to which can be challenging to comprehend by humans and need even more quality control and interpretation procedures. As a result, DNNs lack the openness and comprehension of other approaches and have no capacity to find complicated causal and structural links seen in biological processes without human intervention.

Overfitting

A further barrier is a demand for huge training information collections, which might not be accessible easily. When experimentation information is limited, several widely employed machine-learning approaches outperform DNNs. One of the biggest challenges associated with developing DNNs when databases are insufficiently massive includes dealing with the risk of overfitting, which takes place when the percentage of errors for training purposes is minimal but the error rate during testing is significant, resulting in the algorithms used for machine learning become incapable to acquire an appropriate extrapolation based on information encountered within the data set **[38]**.

The Problem faced in Deep Neural Networks type choosing

Given several different varieties of Deep Neural Networks readily accessible, task-appropriate selection seems not consistently easy. While certain tools, for instance, hyperparameter optimisation approaches can help with selection, pipeline design is significantly more involved than any other kind of machine learning methodologies, and novel frameworks are constantly being created **[37]**.

High computational costs of training

At last, while DNNs demand limited computing power to train, the learning approach is often quite computationally costly in terms of time, accessibility and programming abilities using graphics

processing units (GPU) are often necessary. An upcoming technology from Google influenced by Theano, Tensorflow, drastically simplifies deep neural network development and troubleshooting **[29]**.

CONCLUSION

Whilst deep learning is an exciting emerging field in the field of machine intelligence, techniques for deep learning and research remain limited. Primarily there is the accessibility of a vast quantity of excellent quality data will influence deep learning modelling effectiveness and dependability. The huge volumes of biological data the pharmaceutical industry creates are typically not readily accessible to the general population and are instead held as costly private business assets. Furthermore, another disadvantage of models developed with deep learning is a lack of coherent interpretations of connected biological systems. Although they have been proven to have excellent prognosis accuracies, algorithms based on deep learning continue to behave as 'black boxes' which renders it impossible to expose the biological processes that are included in the data utilised for modelling. In the end, deep learning has shown its capacity for usage in the emerging big data era of pharmaceutical research as a novel machine learning approach. Techniques involving deep learning will emerge as a key Computer-Aided Drug Design (CADD) methodology in the coming years as the best information becomes accessible and new methodologies are created. Based on the achievements of current establishing investigations, the researchers have become confident that cutting-edge deep learning systems are going to be advantageous in the upcoming era of big data analysis in the fields of pharmaceutical research, toxicity prediction, protein engineering, and de novo drug design, just to mention a few. Nevertheless, it must be continued to thoroughly comprehend the benefits and drawbacks of deep learning approaches. They should not be used uncritically without additionally using basic linear techniques and investigating chemical similarity techniques. It is believed that the moment has come to rediscover and investigate the implementation of deep learning in pharmaceutical research.

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