



Review

Applications of Deep Learning for Drug Discovery Systems with BigData

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Abstract: The adoption of “artificial intelligence (AI) in drug discovery”, where AI is used in the process of pharmaceutical research and development, is progressing. By using the ability to process large amounts of data, which is a characteristic of AI, and achieving advanced data analysis and inference, there are benefits such as shortening development time, reducing costs, and reducing the workload of researchers. There are various problems in drug development, but the following two issues are particularly problematic: (1) the yearly increases in development time and cost of drugs and (2) the difficulty in finding highly accurate target genes. Therefore, screening and simulation using AI are expected. Researchers have high demands for data collection and the utilization of infrastructure for AI analysis. In the field of drug discovery, for example, interest in data use increases with the amount of chemical or biological data available. The application of AI in drug discovery is becoming more active due to improvement in computer processing power and the development and spread of machine-learning frameworks, including deep learning. To evaluate performance, various statistical indices have been introduced. However, the factors affected in performance have not been revealed completely. In this study, we summarized and reviewed the applications of deep learning for drug discovery with BigData.

Keywords: artificial intelligence (AI); BigData; convolutional neural networks; deep learning; recurrent neural network



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1. Introduction

Originally, artificial intelligence (AI) was used in the field of drug discovery for processes such as the pattern matching of molecular structure correlations and the automatic registration of case reports [1–4]. However, due to advances made in recent years, AI can also be used in target search, target selection, lead compound search, and phase optimization. To make medicine, researchers need to know what the keyhole that opens the door that causes the disease looks like, which is the process of target search and selection. To develop a key that fits the keyhole, a compound is developed and optimized. In addition, animal studies and clinical trials are repeated to check whether the door can be unlocked and if there are any problems [5–7]. If the active ingredient is then approved through an application for marketing authorization and testing, it can finally be marketed as a drug. Therefore, the development of a drug usually takes a very long time—more than 10 years on average—and involves enormous costs. However, the probability of success in discovering a drug can be as low as 0.004%, so a tremendous amount of trial and error is required, resulting in increased labor, time, and cost. It is also a daunting task to select drug discovery target proteins from more than one hundred thousand types of in vivo proteins and to try combinations with active compounds. Even when animal studies are successful,

significant side effects often occur in human clinical trials [8]. Due to advances in medical science, research topics have shifted to complex diseases with unknown causes, and the hurdles of drug discovery are becoming higher by the year [9–11]. In addition, tightening pharmaceutical regulations, pressure to raise drug prices, and generic competition lead to an ever-widening innovation gap. Therefore, it is understandable that transforming conventional methods into more efficient drug discovery systems is a great challenge, and AI drug discovery is also attracting increasing attention. However, it is not easy to discover target genes that lead to successful drug development. The failure rate is particularly high in the proof-of-concept (PoC) stage, the proof of superiority assumed at the beginning of drug discovery, and in phase II of small-scale clinical trials [12,13]. The main reasons for this difficulty are the selection of low-accuracy target genes based mainly on animal studies and the start of the drug discovery process with insufficient stratification of patients to be treated. Therefore, efforts are being made in target gene searches to promote new drug discovery targets based on human or other data [14–16]. It is expected that the use of human data such as omics data and clinical information, can reduce failures due to reliance on animal testing [17,18]. Another benefit is the ability to leverage search results from other disease predictors that share drug discovery targets. In the search for lead compounds, efforts have been made toward an AI system performing the screening of a large number of active compounds. In particular, AI is expected to improve development efficiency in the search for lead compounds, such as biopharmaceuticals that have larger molecular sizes and are more complex than low-molecular-weight drugs [19]. Although AI drug discovery is starting to deliver results, it is fair to say that it is still a developing field. For example, aggregated data cannot be used in original form for AI machine learning, and format standardization is insufficient [20–22]. However, as a platform for AI drug discovery that combines genomes and AI, a data-driven drug discovery target search approach is being promoted.

Laboratory automation, including research automation, is gaining attention due to advances in AI technology and data-driven research and development. Alternatively, the development of measurement technology, such as robotic automated experimentation technology, has produced large-scale biological image data that cannot be processed by humans [23–25]. As a result, analyzing and quantifying large amounts of high-resolution biological image data have become important issues in biology. Therefore, “bioinformatics”, which solves these problems using information science methods, has attracted much attention in recent years. Particularly in bioimaging, bioinformatics has been pushing forward and various research has been conducted, such as database development for biological images and the extraction of information from images, including the segmentation of cells and tissues, as well as the visualization of image information [26–28]. Among these, research on the classification and clustering of biological images using machine learning has been the most-studied area. Applied research, such as lesion detection from medical images, has also actively been conducted [29–31]. Since image classification is an important research step in the analysis of biological image data, a method for classifying biological image data with high accuracy and high throughput is desired. In this case, if there are few data, it is possible to classify images visually. However, when there are a lot of data, it is difficult to classify all the images manually. Therefore, it is common to automatically classify image data using a machine-learning method called supervised learning. As methods for learning, multilayer neural networks, such as deep learning, which are currently widely used, are attracting attention due to their amazing prediction performances [32–35]. Deep learning is an AI technology that automatically extracts and learns features based on large amounts of data [36,37]. It essentially consists of a multilayer neural network and an algorithm that mimics human neurons, and it automatically processes and learns input data and passes them to the next layer, which consists of three or more layers; in these layers, it is possible to deepen the characteristics of the data to be learned using multiple layers of this neural network, which result in deep-learning models with extremely high accuracy, sometimes surpassing human recognition accuracy [38–43]. As a deep-learning method, the

structure of a neural network is often used. A neural network has what is called a “hidden layer”, which is about two to three layers in conventional neural networks. However, deep-learning models can have up to 150 hidden layers. For this reason, deep-learning models are also referred to as deep neural networks. Traditionally, feature extraction has been performed manually. However, deep-learning models are trained using large-scale, labeled data and neural network structures, where it is possible to learn features directly from the data, eliminating the need for feature extraction. Convolutional neural networks (CNNs or ConvNets) are used in deep neural networks (Figures 1 and 2) [44–50]. CNNs do not require manual feature extraction and have the advantage of eliminating the need to search for features during image classification. In recent years, deep learning has become an indispensable method for AI development that has been trained with deep learning and has attracted great attention because it has a higher performance than networks trained with other methods. What should be focused on now is thinking about “What kind of data do we collect and for what purpose do we use it”. As for “What can be learned from the data”, we are entering an era where the power of AI can be harnessed. Even in drug discovery research, the amount of data that can be collected and processed is exploding. This is driven by various advantages, such as the proliferation of comprehensive biomolecular measurement devices, including next-generation sequences, or the digitization of medical information [51–55]. In contrast, the pharmaceutical industry faces challenges that complicate the development of new drugs, such as rising research and development costs and the depletion of drug targets that can be developed using conventional approaches. It can be said that the development and introduction of AI systems that search for drug discovery targets are urgently needed as a way out of this situation. Given the rapid decline in data collection and processing costs, the demand for AI, which refers to all attempts to make computers realize the information processing of the human brain, is likely to continue to increase in drug discovery research. Alternatively, machine learning refers to a branch of technology that enables such efforts in AI. One type of machine learning is a method called a neural network, which imitates how information is transmitted from neurons in the brain. In recent years, an extended approach called deep learning has been developed, and it is expanding its range of activities in many fields. For example, one of the reasons why deep learning has become so popular is that a computer figures out “what kind of data should be prepared for computer learning, feature design”, instead of a data analyst. Conversely, deep learning is designed to automatically obtain useful feature values for prediction because it repeats the process of combining input feature values to create new feature values [56–58]. Such features are particularly useful when one is trying to complete a task in a data-driven manner without relying on known information or when large numbers of feature values in the input data make it difficult to determine which feature values are important for prediction.

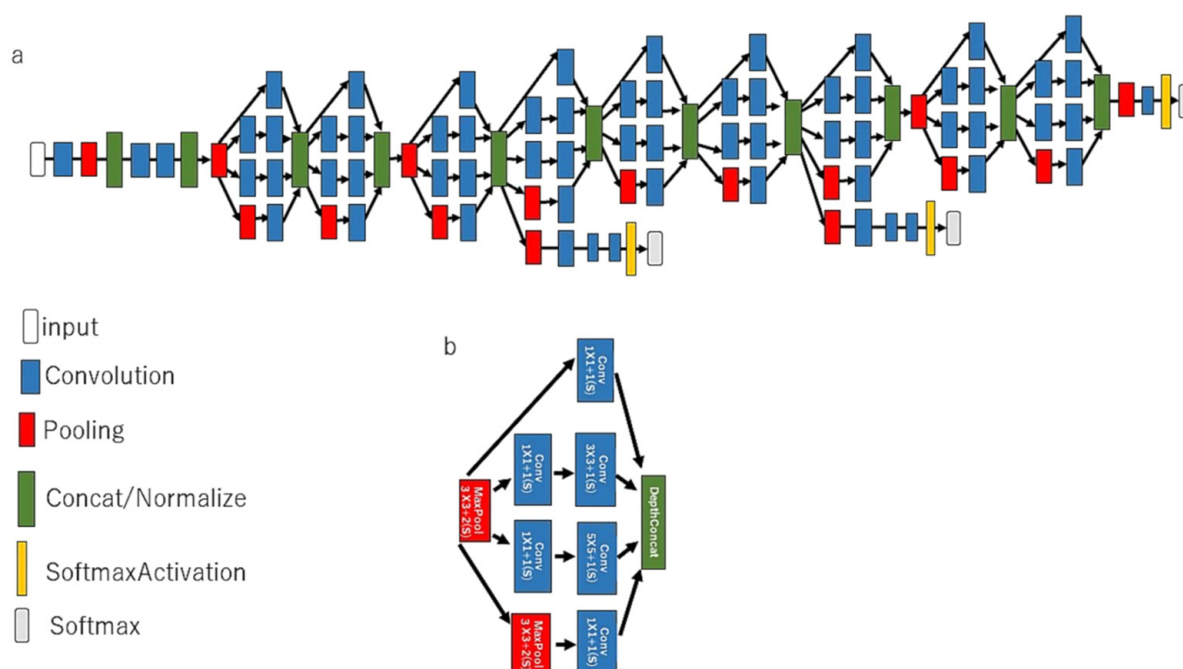


Figure 1. The architecture of a CNN model in GoogLeNet. The pretrained CNN comprises a 22-layer DNN, both (a) implemented with a novel element dubbed an inception module and (b) implemented with batch normalization, image distortion, and RMSprop, including a total of 4 million parameters.

Deep learning has a long history, and the theory itself was proposed in the 1980s [59,60]. One of the reasons why the theory, which has existed for a long time, is attracting attention in modern times is that research on neural networks has made progress, but that is not the only reason. In other words, the reason deep learning is attracting attention today is that it has become easier to prepare the data used for learning. This is because the development of the Internet has made it easier to obtain the data used in deep learning. Another reason is the development of technologies to process unstructured data, such as that of images, voice, and text. In the 1980s, when the theory of deep learning was proposed, it was not yet possible to collect and store large amounts of data. However, in modern times, improved technology has made it possible to collect large amounts of labeled data [61–65]. With this background, it has become possible to realize deep learning, which previously had problems in terms of data. Another reason why deep learning is attracting attention is that the processing power of computers has improved [66–68]. To perform deep learning, a high-performance graphics processing unit (GPU) is essential so that an AI can learn while comparing a large amount of data [69,70]. At the time deep learning was proposed, this advanced technology did not exist. In modern times, the technology has evolved, and it has become possible to improve the accuracy and efficiency of deep learning. In recent years, GPUs have a “parallel configuration” that enables efficient deep learning. In this way, improving the computing power of computers has become an important factor for the development of deep learning in recent years.

On the other hand, GPUs cause high calculation costs compared to those of some conventional processes of machine learning. However, a GPU is the main cause of high performances in CNNs due to the high processing ability of graphical data. CNNs represent an upgrade by improving structural disadvantages. In this review, we summarize the applications of deep learning for drug discovery with BigData.

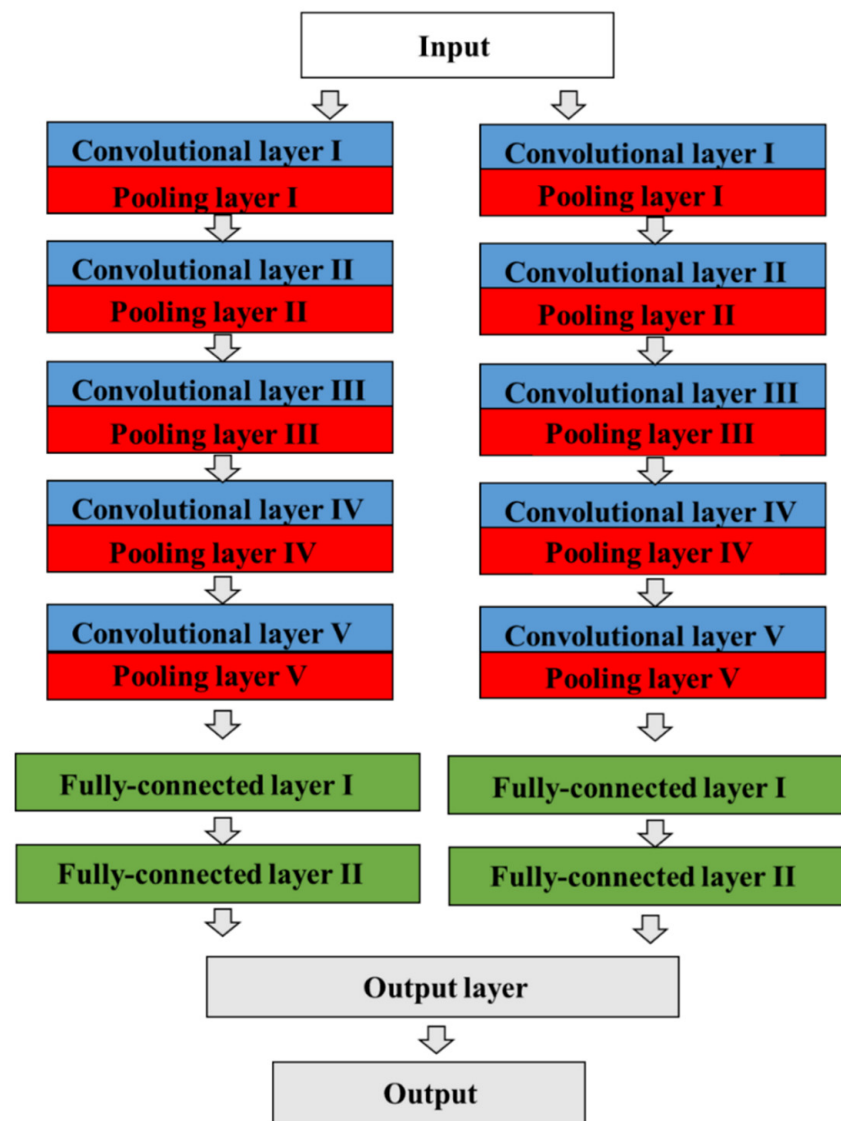


Figure 2. The architecture of a CNN model in AlexNet. The CNN contains a total of eight prelearned layers, which consist of five convolutional and max-pooling layers, three fully connected layers, dropout, data augmentation, rectified linear unit activations, and a stochastic gradient descent with momentum, including a total of 60 million parameters. The two adjacent convolutional and pooling layers are finally combined into a third fully connected layer.

2. Types of Deep-Learning Network Models

2.1. Networks in Deep Learning

Deep learning can be classified into different types depending on the learning method and structure. First, CNNs are mainly used in image recognition [71–73]. Images that contain meaningful information for humans are nothing but numerical data for machines. Therefore, it is not easy for machines to extract the information that humans want to know from images. However, CNNs have high recognition accuracy and learn features directly without requiring humans to extract them. In addition, a generative adversarial network (GAN) consists of two networks, a generator (generative network) and a discriminator (discriminator network), which are characterized by competing with each other to increase accuracy [74–78]. This can be used, for example, to correct blurred photos or to restore old, low-resolution images to high resolution. It can also create images of non-existent people by capturing images of multiple faces [79,80]. It is mainly used in the world of image processing, as it is possible to generate or transform nonexistent data by learning

features from the data. In addition, a recurrent neural network's (RNN's) algorithm is particularly suitable for processing data collected in a timeseries or data that has an ordered meaning [81,82]. By applying various kinds of filters, CNN-based machine-learning models are able to capture high-level representations of the input data, making them popular in computer vision tasks. Examples of CNN applications include image classification (e.g., AlexNet, VGG network, ResNet, and MobileNet) and object detection (e.g., Fast R-CNN, Mask R-CNN, YOLO, and SSD). As shown in Figure 3, the performances of popular CNNs applied to AI vision tasks have gradually improved over the years, surpassing human vision [83]. These models can extract and classify the structural features of images, such as chemical compounds, leading to the discovery of novel drug seeds.

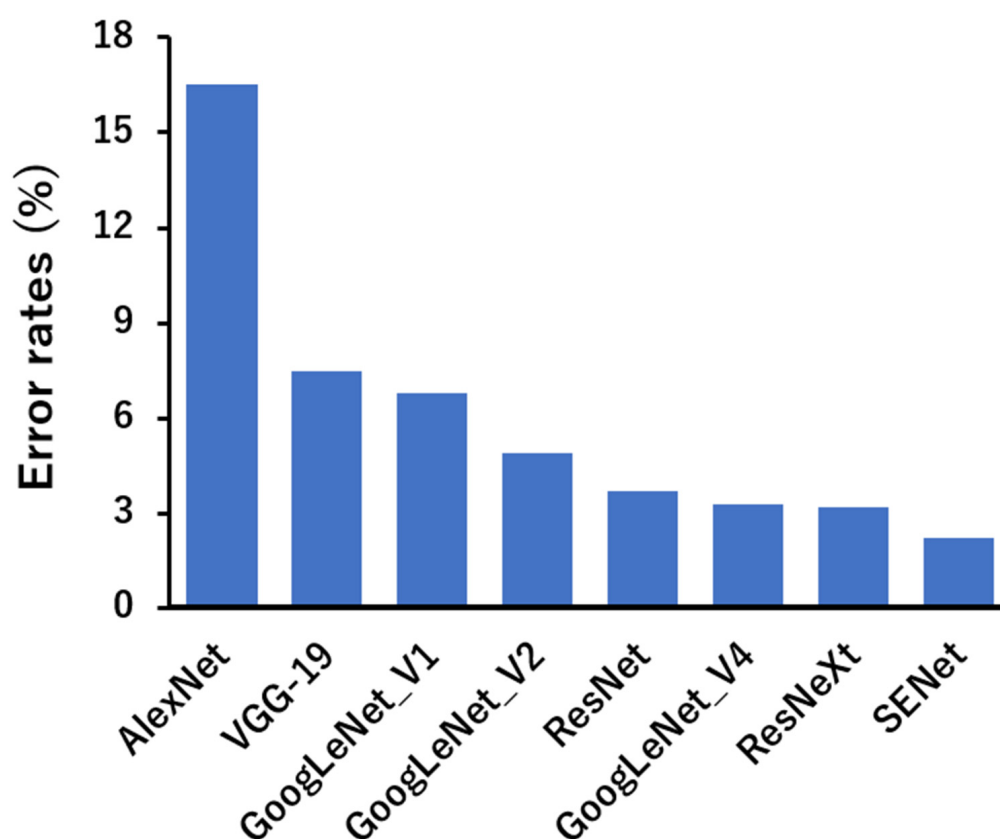


Figure 3. Performances of current popular deep neural networks on ImageNet [83].

2.2. Technological Application in BigData and Deep Learning

The term AI was first used in the summer of 1956 at the Dartmouth Conference by John McCarthy, an American computer scientist [84]. The concept of AI is now widely known and has triggered the entry of many researchers into research, alternating between boom and bust periods [85]. Initially, the first AI boom began in the 1950s and lasted until the 1960s, when “inference” and “exploration” were the main research areas, and it became a boom because it became possible to present solutions to specific problems. However, the problems that people faced in their lives did not choose patterns within specific rules. It became easier to find an optimal answer within set rules, but it was difficult to solve problems that could arise in the real world, and disappointment with AI spread. As a result, the boom ended, and AI research entered a winter period. After that, there were advances in research that used computer processing to reason and solve problems. The second AI boom that followed is said to have occurred in the 1980s, when attention was primarily focused on expert systems, systems in which a computer acts like an expert by taking the “knowledge” of a specialized field into the computer and drawing conclusions. It became possible to solve complex problems by inputting specialized information into

computers and incorporating conditional expressions that provided answers when the conditions were met. The use of expert systems was expected to make it possible to solve practical problems that could not be solved in the first AI boom. In addition, many attempts were made to reproduce intellectual judgments made by humans using manually written rules. However, manual rule writing was limited in terms of expanding scope and maintaining quality, and the scope of its application was not expanded. Although expert systems seemed to be a great approach, they proved to have difficulty with handling all cases accurately. The reason was that the amount of “knowledge” became enormous and contradictory, there was a lack of consistency among the “knowledge”, it was difficult to assess ambiguous cases, and the huge amount of “knowledge” needed to be written and edited by humans. Because of the limitations of such expert systems, expectations for AI again declined. Subsequently, AI research was actively pursued in terms of the memory that stores knowledge in computers. The recent AI boom is referred to as the third AI boom, which was triggered by the spread of the Internet and the advancement of technology, and has continued since the 2000s until today. In 2012, a team using a neural network won an image recognition software competition with a large margin of accuracy [86]. “Machine learning”, in which AI itself acquires knowledge by using a large amount of data known as “BigData”, has been put to practical use. Through a machine-learning approach, it became possible to inductively extract rules from observed data based on case studies, overcoming the limitations of manual rule descriptions.

In addition to technological innovations related to data collection (such as next-generation sequencers) and dramatic improvements in data-processing technology (such as computer specifications), omics analysis, which comprehensively measures tens of thousands of biomolecules (such as transcripts and proteins) in a single experiment, is now essential in the field of life science research [87–91]. Against this backdrop, the economic cost of omics analysis is decreasing, and multi-omics analysis, in which multiple types of omics analyses are performed under certain experimental conditions, is becoming increasingly popular as an attempt to systematically understand life phenomena. The problem at this point is that it is difficult for humans to interpret the data because a large number of elements are measured under specific experimental conditions, and the computational cost is high. To deal with this problem, possible approaches include (1) reducing the feature quantity to only important features or (2) replacing the feature quantity with a smaller amount of feature quantity by replacing the data with a new feature set. For example, a principal components analysis (PCA) plot reduces the high-dimensional (D) data to 2D or 3D, and the data are visualized by plotting the newly obtained feature values on the *x*-axis and the *y*-axis, as well as the *z*-axis (dimensionality reduction) [92–97]. In addition, multilayered autoencoders are also used for dimensionality reduction and are a type of deep learning that compress data that are “recoverably” used for learning [98]. For example, when high-dimensional multi-omics data with tens of thousands of feature values are input, these feature values are added together after they are weighted differently, and then a new feature value is generated through nonlinear transformation using an activation function in a hidden layer (encoder). After this process, the output layer restores the original input data (decoder). In recent years, a model for predicting biological or pathological states of RNA-seq data has been developed by quantifying RNA, miRNAseq, and methylated DNA data using next-generation sequencers. In this analysis pipeline, an autoencoder with three hidden layers is introduced for the dimensionality reduction of omics data. Then, clustering is performed with the new features generated in the intermediate layer, and it can be said that the “omics data are integrated” because new feature values are generated by combining feature values derived from the heterogeneous omics data. However, in the autoencoder, the feature that contributes to the predictions is a black box [99–128]. Even in multi-omics analysis, knowing “which feature value contributed to the prediction” is expected to be useful in drug discovery target search. The development of deep learning, in which the prediction criteria are not black boxes but are interpretable, is also progressing. With the widespread use of high-throughput measurement instruments, such as next-

generation sequencers, the barriers to comprehensive data collection at multiple levels, such as genes, transcripts, proteins, etc., in biological and pathological conditions have already fallen. Conversely, research is still underway on how to integrate heterogeneous but highly interrelated multi-omics data to gain biologically useful insights. Moreover, machine-learning methods, including deep learning, can only perform as expected if the datasets containing multi-omics data are sufficiently large.

The availability of BigData is what makes this approach so effective. In other words, large amounts of data are now collected from various services on the Internet and various sensors in the real world. In addition, improvements in computing power have made it possible to process large amounts of data at high speeds, leading to advances in machine-learning technology [129]. In addition, deep learning has emerged where an AI system learns the elements that define knowledge on its own, which has improved performances in various fields, such as image recognition, voice recognition, and translation. Where will the third AI boom lead? One problem currently being considered is that it is not possible to understand the process by which an AI system makes decisions. The application of machine-learning technology is currently spreading in many fields, along with the use of BigData. Even if the so-called boom comes to an end, there is no doubt that machine-learning technology will continue to spread and permeate society as an effective means of solving various problems.

3. Deep Learning and Technical Problems

3.1. Black Box Problem

Deep learning has become the mainstream of machine learning, and with the expansion of its applications, technical problems from the perspective of real-world problem solving have also emerged, primarily the black box problem: neural network machine-learning in deep learning is a black box [130–144]. The learning results are reflected in the node weights, and the obtained regularities and models are not represented in a form that humans can directly understand. In other words, it is not possible to explain the reasons for the results of the discrimination, classification, prediction, and detection of anomalies. In industrial applications, the data analysts using machine learning and the decision makers using the results of analyses are usually not the same, and data analysts must explain the prediction results and reasons to decision makers. Additionally, in situations such as medical care where people's lives and health are at stake, it is necessary to be able to check the consistency between the results derived from machine learning and medical evidence, as well as to be able to use them according to the correct judgment. Because of these societal demands, transparency and accountability have been discussed as important requirements in AI development guidelines. However, it is difficult to meet these demands and requirements with black box machine learning.

3.2. Gap between Machine Learning and Decisions

There is a gap between machine learning and decision making. Discrimination, classification, prediction, and anomaly detection by machine learning often do not necessarily solve real-world problems. There is a need for solutions that go as far as making decisions based on the results obtained by machine learning. This is true not only for deep learning, but also for general data analysis through machine learning. There are four stages of data analysis: (i) descriptive analysis, (ii) diagnostic analysis, (iii) predictive analysis, and (iv) prescriptive analysis. For these, a solution method is required to be used in decision making.

3.3. Amounts of Data and Computational Power

The amounts of data and computational power required for learning have increased. Deep learning uses DNNs with hundreds of layers and a large number of parameters related to structure [145–161]. Therefore, it is prone to overfitting, which is a condition where the learning data are overfitted, generalization is not possible, and high accuracy cannot be achieved with unknown data. To suppress overfitting and achieve high accuracy, a large amount of training data is required, but in practice, it is not always easy to collect a large amount of training data [162–178]. Moreover, it takes a long time to input a large amount of training data into a large-scale DNN and execute the learning process. In addition, network structures tend to become multilayered and complex, so the time required for learning keeps increasing.

3.4. Theoretical Explanation

There is difficulty in developing analytical processes. There is no theoretical explanation for why deep learning achieves such high accuracy. The structural design of a DNN and the method of learning to achieve high accuracy depend on the accumulation of expertise and empirical rules, and it is still difficult to fully exploit deep learning. In addition, when applying machine-learning technology, which is not limited to deep learning, data analysts usually hypothesize and test by repeated trial and error to select methods and models and determine feature values and parameters, as well as the learning method.

4. Approaches to Technical Problems in Deep Learning

4.1. Interpretability of Learning Results

The previous section addressed four technical issues facing deep learning today. Some approaches to technical challenges that have presented to solve them are introduced, with one approach being ensuring the interpretability of learning results [179–199]. In response to the black box problem, the US Defense Advanced Research Projects Agency (DARPA) announced an investment program for explainable AI in 2016. The plan states that machine-learning technology represents a trade-off between accuracy and interpretability and that research and development are required to achieve both. This study presents two approaches to achieving both accuracy and interpretability. The first approach is to give interpretability to highly accurate black box methods, such as deep learning. For example, this approach attempts to investigate what input patterns a trained neural network responds to and to infer from the results what it focuses on. Another approach is to develop white box thinking, with interpretability such as decision trees and linear regression to achieve high accuracy. Heterogeneous mixture learning and factorized asymptotic Bayesian inference [200,201], have shown that this approach can achieve both high accuracy and good interpretability, which is high when the target data can be expressed in a simple format, such as a linear sum of feature quantities or explanatory variables. However, when target data with complex behavior are expressed in a simple format, approximation becomes rough and accuracy deteriorates. Therefore, by dividing the target data into several parts and applying a simple format to each part, one can achieve both high accuracy and good interpretability. Heterogeneous mixture learning uses this strategy to automatically calculate an optimal data division method and apply it to each division of data. In addition, with deep learning, there is no theoretical explanation as to why high accuracy is achieved in the first place. Deep learning is known to be a non-convex optimization learning method, and the theory of convex optimization learning, which has been theoretically elucidated, cannot be applied. Efforts to fundamentally and theoretically clarify the black box problem are also important.

4.2. Interpretability of Learning Results

Realization of solutions from machine learning to decision making is needed. For the problem of the gap between machine learning and decision making, solution methods have been researched and developed that take the path from machine learning to decision-making. There are mainly three types of approaches. (II-a) Deep reinforcement learning is a machine-learning algorithm that deals with a type of problem where a learner performs a certain state and receives a certain reward [202–213]. By repeatedly selecting actions and receiving rewards, it learns decision-making strategies for selecting actions that yield more rewards in the future. In reinforcement learning, it is necessary to find a value function that expresses how good it is to choose a certain action in a certain state, and learning this value function and policy through deep learning is deep reinforcement learning. This approach is suitable for problems where a large number of examples can be easily collected or where simulation can generate a large number of examples. (II-b) The second approach is predictive decision-making optimization based on machine learning. Deep reinforcement learning is suitable for problems where a large number of examples can be collected or created, i.e., problems where it is easy to repeatedly try decision making. In contrast, decision-making problems such as those addressed in classical operation research (OR) suffer great damage when decision making fails, and it is difficult to repeatedly try decision making. In a classical OR problem, it is assumed that the data are static, but machine learning has made it possible to generate a large number of predictions dynamically, with uncertain information that can be wrong. A new development is born when considering this as an OR problem based on a large amount of output from machine learning. A concrete approach to this is a machine learning–OR pipeline framework called predictive decision-making optimization, which is based on generating a large number of predictors through heterogeneous mixture learning.

4.3. Acceleration and Efficiency of Deep Learning

For deep learning, which requires large amounts of data and computational power, efforts are being made to accelerate processing and improve computational efficiency, both in terms of hardware and algorithms. In terms of hardware, the development of a GPU that can perform high-speed deep learning is underway. A processor suitable for deep learning called a tensor processing unit (TPU) was developed, which could provide 10 times more computational power, especially in inference processing, per power consumption compared to GPU [214]. This new hardware achieves high-speed learning by performing floating-point calculations in single precision or half precision instead of double precision, as in the past. In contrast, as an algorithmic improvement, deep residual networks (ResNets) should be mentioned, whose features allow efficient learning, even with deep hierarchies, due to a network structure with detours [215,216]. It has attracted attention due to its overwhelming victory at ILSVRC2015, which used a ResNet with 152 layers, which was about eight times deeper than any network before. Moreover, it is not necessarily easy to collect a large amount of training data sufficient to improve accuracy. To solve this problem, various strategies have been considered: (1) active learning, in which only a part of the data is efficiently labeled to improve the accuracy; (2) semi-supervised learning, in which some labeled data are used as clues for learning unlabeled data; and (3) transfer learning and domain adaptation, in which large amounts of data and learning results from similar data are used for learning, considering the imbalance in the number of samples per class, data generation by physics simulation, etc.

4.4. Establishment of Machine-Learning System Development Methodology

Attempts to directly improve the difficulty developing analytical procedures include automating the development of analytical procedures through the development and extension of machine-learning technology. Finally, given data and a specific purpose, there is a need to automatically determine an optimal analysis method or procedure to obtain results. Although there are still limitations in terms of purpose, method, scale, etc., several trials have just begun. In terms of neural network structure design, a technique to automatically generate an intermediate layer using the as-if-silent (Ais) method has been reported. In addition, predictive analysis automation technology that automatically selects feature values from relational databases and analysis methods, i.e., prediction models, and combines them according to a purpose has been reported. Alternatively, more and more machine-learning technologies have been integrated into various systems, which may undoubtedly lead to a paradigm shift in system development methods. In the past, the paradigm of system development shifted from wired logic, i.e., hardware logic circuits assembled from physical connections, to software-defined systems that define the behavior of a system by writing program code. However, systems based on machine-learning technology define the behavior of a system inductively by learning a large amount of data, which is also referred to as BigData-defined system development. It is necessary to establish and maintain new methodologies, such as system requirement definition, operation, and quality assurance concepts, and boundary optimization with software-defined, operational optimization as a “learning factory”, including data collection and input efficiency. By the application of these approaches, efforts toward drug discovery have proposed some novel systems using deep learning (Table 1) [217–251].

Table 1. Deep learning based drug discovery programs.

No.	Program Name	Target
1	CAT-CPI	Compound image features for predicting compound-protein interactions
2	REDDA	Heterogeneous graph neural network for drug-disease association
3	GeneralizedDTA	Drug-target binding affinity
4	DTI-BERT	Interactions in Cellular Networking Based on BERT
5	D3AI-CoV	Developing highly effective drugs against COVID-19
6	ICAN	Protein interactions
7	gr Predictor	Hydration Structures around Proteins
8	AMPlify	Antibiotic resistance
9	QPoweredCompound2DeNovoDrugPropMax	Interaction for Compound
10	DeepCarc	Carcinogenicity Prediction
11	DeepFlu	Symptomatic influenza A infection based on pre-exposure gene expression.
12	SyntaLinker	Fragment-based drug design
13	DeepR2cov	Agents for treating the excessive inflammatory response
14	DeepSARM	Structure-activity relationship (SAR) matrix (SARM) methodology
15	MutagenPred-GCNNs	Mutagenicity of compounds and structure alerts in compounds
16	OCTAD	Compounds targeting precise groups of patients with cancer using gene expression features
17	DRIM	Integrative multi-omics and time-series data analysis framework
18	MDeePred	Multiple types of protein features such as sequence, structural, evolutionary and physicochemical properties
19	Deep Docking	Docking billions of molecular structures

5. Conclusions

In order for society to enjoy the benefits of extracting knowledge from data, it is necessary not only to develop AI technologies, but also to organize many processes, such as data collection, cleaning, analysis, interpretation, and evaluation. There are still some issues regarding AI application in practical and medical fields. For example, the generality of performances in various datasets has not been applied completely. The need for the development of AI technologies is high in many fields, and it is already being vigorously pursued, but these efforts are not enough to bring AI into drug discovery research. The introduction of AI cannot achieve a breakthrough in the area of drug discovery target search unless legal and cultural issues are resolved. AI technology may be suitable for the screening of seeds for new drugs. Therefore, to enable better use of data, which is expected to increase in the future, it is desirable to invest in infrastructure development as early as possible, not only from scientific and technological perspectives, but also from a humanities perspective.

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