Deep Learning Techniques and COVID-19 Drug Discovery: Fundamentals, State-of-the-Art and Future Directions

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Abstract The world is in a frustrating situation, which is exacerbating due to the time-consuming process of the COVID-19 vaccine design and production. This chapter provides a comprehensive investigation of fundamentals, state-of-the-art and some perspectives to speed up the process of the design, optimization and...
production of the medicine for COVID-19 based on Deep Learning (DL) methods. The proposed platforms are able to be used as predictors to forecast antigens during the infection disregarding their abundance and immunogenicity with no requirement of growing the pathogen in vitro. First, we briefly survey the latest achievements and fundamentals of some DL methodologies, including Deep Boltzmann Machines (DBM), Restricted Boltzmann Machine (RBM), Deep Belief Network (DBN), Hopfield network and Long Short-Term Memory (LSTM). These techniques help us to reach an integrated approach for drug development by non-conventional antigens. We then propose several DL-based platforms to utilize for future applications regarding the latest publications and medical reports. Considering the evolving date on COVID-19 and its ever-changing nature, we believe this survey can give readers some useful ideas and directions to understand the application of Artificial Intelligence (AI) to accelerate the vaccine design not only for COVID-19 but also for many different diseases or viruses.

**Keywords** Artificial intelligence · Artificial neural network · Bioinformatics · COVID-19 · Deep learning · Drug discovery

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1 Introduction

Although the second decade of the third millennium was expected to start with exciting signs of progress in medicine development and some digital technologies to resolve issues associated with major clinical problems and diseases [1]; COVID-19 outbreak and its consequent pandemic and concerns regarding its future bounce back highlighted the need for speed in developing new treatments and designing intervention protocols [2]. However, history has proved that the gravest health challenges can lead to the greatest opportunities for the development of novel treatments, medicines and vaccines. In this particular case where accurate but cheap diagnostic tests are extremely necessary, digital technology, Artificial Intelligence (AI) and Deep Learning (DL) can serve with their potentials in detecting and diagnosing COVID-19 [2, 3]. A novel feature learning method consists of various hidden layers of representation [4]. Recently, a number of researches have proved that Machine Learning (ML) can be considered an appropriate technique to solve complex problems or analyze the big data [5, 6]. Hence, we aim to review some potential methods to direct future research in the case of technology and drug discovery.

In this chapter, we try to introduce reliable techniques regarding the most recent achievements in the area of AI, DL with a concentration on COVID-19 and its different problems. Although we presented some DL methods for diagnosis and treatment to combat COVID-19 in our previous research [3], in this research, we try to develop those platforms that are useful to accelerate the process of drug discovery. Generally, the ideas mentioned in the last research has been developed and extended to drug discovery goals. In Sect. 2, some fundamentals about bioinformatics and drug discovery have been demonstrated to review the ability and potential of these modern approaches to developing drugs and vaccines. In Sect. 3, we explain DL-based drug discovery and state-of-the-art within it. In Sect. 4, the proposed drug discovery strategy is proposed. The proposed algorithm in this section is useful for finding and developing drugs for COVID-19-related diseases. In Sect. 5, some platforms based on the most recent publications for COVID-19 are considered to demonstrate the effectiveness of the algorisms, for instance, prioritizing the vaccine design approaches, prediction of antibody in infants through their mother and prediction of change in patients receiving the drug. These structures are important to give many ideas to apply these methods to combat COVID-19. Section 6 and Sect. 7 present discussion and conclusion, respectively.

2 Bioinformatics and Drug Discovery

On the one hand, bioinformatics can be considered a powerful tool to accelerate drug discovery. Considering the current situation, using bioinformatics method is essential to conquering the problem. On the other hand, tools such as binding
simulations, modeling of proteins and computational chemistry, are usually used within the related fields, they should be used cautiously because the conformational space is complex and entropic contributions from the surrounding solvent are strong [7, 8]. Besides, emphasizing the conventional methods to find the drugs are not effective. Because traditional approaches lead to squandering the time and money for Pharmaceutical companies, based on an investigation [9], conventional drug discovery is an expensive process, and it can take approximately 12–16 years. Figure 1 illustrates the long process of drug discovery in a conventional form, including six stages taking several years to reach the approved drugs [9]. Needless to say, to combat COVID-19 or similar viruses which may spread in the future, we need to use a more effective and faster process to decrease the problems associated with such viruses. Fortunately, from the 1960s onward medicinal chemistry has successfully applied different forms of AI to the design compounds and wherever training models have been done through the use of labelled training supervised learning has been applied extensively [10]. In contrast, the present models such as the ones in the industry of drug discovery software are capable of forecasting simple physicochemical features and can use simple mechanisms to predict pharmacokinetic properties of new compounds with relatively high degrees of precision [11]. They are not optimal when it comes to complex biological properties such as drug efficacy and the related side effects [12]. The gravest current challenge of biomedicine is developing new drugs that could be used in fighting against diseases. To overcome this challenge bioinformatics and cheminformatics have started to utilize computational methods in the last three decades to come to a deeper understanding of the molecular mechanisms and find a vantage point to maximize available options for disease treatment [13]. Recognition and characterization of applicable T and B-cell epitopes, which generates the epitopic vaccine to combat SARS-COV-2.

Fig. 1 The process of design and development of drug and vaccine with a conventional approach
could have been possible through the use of immunoinformatics [14]. Advanced computational abilities create the opportunity for conceptual progress of this sort to be accessed while analysis of large data sets of ligands is done at the same time. Therefore, dynamic virtual screening can be utilized as a systematic tool to find new potential drugs [15]. Taking advantage of available large data sets resulting from high throughput experiments with gene expression profiles, AI can play an important role in repurposing drugs [16].

3 DL-Based Drug Discovery: State-of-the-Art

In this section, we take a glance at some most recent accomplishments in Deep Neural Networks (DNN), which can be used in different stages of drug discovery. While conventional approaches in developing vaccines are cumbersome and time-consuming, they are not desirably efficient because there is not only the risk for failure when pathogens are impossible to be cultivated under laboratory conditions, but there are also arrays of antigens with no guarantee to provide immunity against the targeted disease. In contrast, AI-based approaches to vaccine development do not suffer from these weaknesses and provide researchers with the opportunity to identify novel antigen vaccine candidates [17]. Moreover, ML technologies can be introduced to supply chains to establish and consolidate more intelligent supervision [18]. Using various study designs and statistical methods to complete clinical trials in a scientifically effective manner is of great importance when it comes to bringing COVID-19 under control [19]. A useful tool for designing safer medicines with more efficacy seems to be coupling MD simulations with AI approaches as an integral part of a general pharmacological model of drug action [15]. ML methods, including ANN, have a long history of application to predict compound activities and other similar complex variables in both medicine and engineering [20, 21]. There is a collection of layers in ANNs, and they function in a way that one output layer is the next layer input until the list of the outputs is exhausted, and an output layer that could predict a property is reached. A matrix that reflects the weights of connections between the layers represents pairs of connected layers to make ANNs amenable to matrix operations. Recently, ANNs have played a significant role in applications to discover potential drugs, especially the deep versions of these networks [22]. Figure 2 demonstrates a conventional DL method consisting of an input layer, hidden layers, and an output layer. This structure can be used as a simple technique for drug discovery goals as a reliable predictor [23]. DL methods are most importantly employed to address problems in the process of activity prediction [21].

The concepts of DLand ANNs were first introduced in the 1980s [24]. Having a lot of hidden layers, Deep Neural Networks (DNNs), as a major interest of information technology companies, was developed as a solution to overcome challenges such as those in speech recognition [25]. ANN were both designed to mimic neuron excitation in the human brain through analogizing the activation of a binary logic
An instance of this case that is used extensively for the prediction of properties is the quantitative structure-activity relationship (QSAR) methodology. In this scenario, for example, log P, solubility and bioactivity for given chemical structures are predicted [27]. If the objective, in QSAR ranking applications, is the identification of compounds with higher activities, the desired ranking goal is to have compounds with greater activities in a higher rank than compounds which have lower activities [27]. Entering an era in which clinical trial failures are minimized to the lowest rate and the process of drug development could be completed in a faster, cheaper and more effective way can be realized if proper methods of AI are employed [28]. As such, extracting knowledge from six categories of data known as proteomics, microarrays, genomics, biological systems, data mining, and text mining is possible through the application of ML techniques [29]. Additionally, advanced feature learning enables DL to achieve high accuracy in identification when the training set contains a huge bulk of data [26]. Due to fast happening and increasing time complexity which is a result of the network architecture complication, more advanced programming skills and hardware technology are needed if DL methods are to be feasible and effective [26]. The output of such AI-based methods comprises designing drug in de novo and selecting the best structure based on experimental tests, both of which are achievable through modelling and quantum chemistry [30]. The idea of employing AI in the process of drug development is now a part of reality and not a dream anymore [31]. AI-related computational algorithms have achieved such levels of advancement that computer-based inference engines are now capable of reaching unprecedentedly deep conclusions [32].

In the process of fighting COVID-19 as a devastating and life-threatening disease, it is important to understand how COVID-19 recognizes the host cell. Moreover, it is impossible to effectively monitor and predict the manner in which the infection spreads during an epidemic if the required
epidemiological data are not available [33]. However, there are other data sources that focus mainly on aggregated case counts in every geographic location [34]. A Deep Boltzmann Machines (DBM) is a structured model that works based on or is adapted to the theory of probability and consists of several layers of variables that are random and mostly latent [35, 36]. DBM have been utilized as effective methods for drug discovery. Figure 3 shows a DBM which has been used in several pieces of research for drug discovery [37]. DBMs are a type of generative models which are able to be used for feature learning techniques. These classifiers are good options to be used as classifiers for COVID-19 vaccine methods. This model is also a good tool for extracting a unified representation that fuses modalities together. It is also very useful in cases such as hyperspectral imagery where human expertise is limited. DBM is also capable of approximating the features of prior knowledge bases samples without having any information available from the labels [38], which makes it a preferable candidate over others in assisting scientists in finding the best way to develop vaccines [39]. Figure 4 demonstrates a Deep Belief Network (DBN), which are used in many complex applications. DBM is an extremely efficient hierarchical generative model for extracting features that are capable of describing highly variant functions and discovering the manifold of the features [40]. The DBN, which was proposed in 2006 was trained to maximize the likelihood of its training data [41]. The DBN is a powerful multilayer generative model in which layers encode statistical dependencies among the units in the layer below them. The advantage of DBN over training methods of traditional deep models such as multilayer perceptron is that DBN can rely on a special unsupervised pre-training procedure to prevent over-fitting to the training set via [4, 40].

Furthermore, Fig. 5 depicts a Hopfield neural network (Hopfield net) structure which is used for predictions problems and drug discovery. Hopfield net is a type of Recurrent ANNs, and it is an appropriate technique for the content type in the

![Fig. 3 The structure of Deep Boltzmann Machine](image-url)
address memories and also it an effective method to solve optimization problems [42]. Although it is an old technique, it has been used in many different types of bioinformatics and biological problems [43, 44]. A type of generative stochastic ANNs called Restricted Boltzmann Machine (RBM) is able to be trained through a probability distribution by inputs. That is why it is an appropriate option to be applied in drug discovery and bioinformatics problems [13, 45]. The structure of an RBM is illustrated in Fig. 6. Sangari and Sethares [46] was the first to develop RBM, a special traditional DBM, that can be formed by hierarchically connecting the neurons of DBM. RBMs have been effectively utilized to model distributions over binary-valued data without any connections between hidden layers [36].
The model serves well when a unified representation that fuses modalities together is to be extracted. The key point is learning a joint density model over the space of multimodal inputs. Table 1 depicts useful information about some powerful techniques based on AI, which can be considered to develop the AI-based platforms for drug discovery. In addition, some most recent publications about COVID-19 and technology have been presented in this table.

Furthermore, Table 2 gives information about the strong publications about AI and drug discovery. Although numerous methods have recently been presented to speed up the drug discovery process, we here try to review those approaches that play a crucial role in drug discovery powered by AI, particularly in the terms applicability, reliability and generalizability. Because not only do such methodologies have to be practical enough to save time, but they also must be flexible to merge with other conventional methods.

Training each RBM for modeling samples from the previous RBM’s posterior distribution increases a variational lower bound on the likelihood of the DBM, which can be used as an acceptable approach for initializing the joint model [48]. In 1986 Paul Smolensky invented RBMS prototype, which was called Harmonium [59]. However, its prominence was not achieved until Geoffrey Hinton, and his collaborators equipped them with fast learning algorithms they invented in the mid-2000. Long Short-Term Memory (LSTM) is a type of RNN utilized in the area of DL [60]. This network has feedback connections between its layers, unlike another type of standard feedforward neural networks. LSTM is an efficient ANN to solve many different kinds of problems in drug discovery [52, 53, 61, 62]. The structure of an LSTM is shown in Fig. 7.
| Ref., Author(s) and Year | Publication | Methodology | The purpose of the study | Outcomes |
|--------------------------|-------------|-------------|--------------------------|----------|
| [1] Ting et al. (2020)   | Nature Medicine | AI-based methods | Survey applications for COVID-19 | Describing challenges of AI methods to combat COVID-19 |
| [47] Arpaci et al. (2020) | CMC-Computers Materials & Continua | Evolutionary clustering | Analyzing big data from Twitter | Some useful recommendation to combat COVID-19 |
| [36] Salakhutdinov and Hinton (2009) | Artificial Intelligence and Statistics | DBM | Introducing DBM | Clarification the effectiveness of DBM |
| [37] Taherkhani et al. (2018) | Neurocomputing | DBM | Forecasting | Description of DBM for prediction |
| [39] Hess et al. (2017) | Bioinformatics | Partitioned learning in DBM | Application for SNP data | Description of DBM for SNP data |
| [40] Zhang and Wu (2012) | IEEE Transactions on Audio, Speech, and Language Processing | DBN | Comprehensive research to use DBNs | Showing abilities of DBN to solve complex problems |
| [41] Hinton et al. (2006) | Neural Computation | DBN | Speeding up calculation with DBN | Presenting a fast learning algorithm |
| [42] Maetschke and Ragan (2014) | Bioinformatics | Hopfield networks | Using Hopfield as attractors | Classification of cancer subtypes |
| [43] Conforte et al. (2020) | Frontiers in Genetics | Hopfield networks | Application of Hopfield for medicine | Modelling basins of attraction in breast cancer |
| [44] Al-Maitah (2020) | Neural Computing Applications | Hopfield networks | Using Hopfield for genetic diseases | Some image processing techniques powered by Hopfield |
| [3] Jamshidi et al. (2020) | IEEE Access | DL-based techniques | Diagnosis of COVID-19 by DL | Demonstrating several DL platforms |
| [48] Kim et al. (2020) | Journal of Neuroscience Methods | RBM | Using RBM techniques in medicine. | Analyzing MRI by RBMs |
| [49] Vogelstein et al. (2018) | Nature Methods | Neuro-based computing | Review on big data and calculation | Presenting an open-source platform |

(continued)
Table 1 (continued)

| Ref., Author(s) and Year | Publication | Methodology | The purpose of the study | Outcomes |
|--------------------------|-------------|-------------|--------------------------|----------|
| [50] Beam and Kohane (2018) | Jama | Big data and ML | Review on applications of ML methods | Presenting some fruitful recommendations |
| [51] Arpaci et al. (2020) | Personality and Individual Differences | confirmatory factor analyses | Analysis of phobia associated with COVID-19 | A practical instrument namely, corona phobia scale |

Table 2 The approaches powered by AI, ML and DL to accelerate drug discovery; such methods have appropriate potential to find drugs for COVID-19 related disease

| Ref., Author(s) and Year | Publication | Methodology | The purpose of the study | Outcomes |
|--------------------------|-------------|-------------|--------------------------|----------|
| [2] Ton et al. (2020) | Molecular Informatics | Deep Docking (DD) | Finding potential ligands | Forecasting a large number of purchasable molecules quickly |
| [8] Li and Robson (2000) | Drugs and the Pharmaceutical Sciences | Bioinformatics | Survey of computational methods in molecular design | Description of several methods based on bioinformatics for drug discovery |
| [11] Zhu (2020) | Annual Review of Pharmacology and Toxicology | Big data and AI | Review on novel data mining for drug discovery | Demonstrating novel drug development and optimization |
| [13] Rifaioglu et al. (2019) | Briefings in Bioinformatics | DL in silico drug discovery | Review on new machine intelligence methods | Illustrating the original DL-based method for drug discovery |
| [15] Diaz et al. (2019) | Rise of Machines in Medicine | Molecular Dynamics Simulations and ML | Accelerating drug discovery | Classification of ligands and identified functional receptor motifs successfully |
| [16] Zhavoronkov (2018) | Mol. Pharmaceutics | A novel DL method | Improving the productivity in drug discovery | Prediction of HLA class II antigen presentation |
| [17] Chen et al. (2019) | Nature Biotechnology | An integrated DL method | Prediction of antigen | |
| [21] Chen et al. (2018) | Drug Discovery Today | DL methodologies | Survey on the effectiveness of the methods | Future of DL in drug discovery |
| [22] Ghasemi et al. (2018) | Drug Discovery Today | DL in QSAR | A review of DL algorithms | Explaining some drawbacks of the DL methods |
| Ref., Author (s) and Year | Publication | Methodology | The purpose of the study | Outcomes |
|---------------------------|-------------|-------------|--------------------------|----------|
| [24] Gawehn et al. (2016) | Molecular Informatics | RBM and CNN in drug discovery | An overview of DL methods | Analyzing the understudied methods for drug discovery goals |
| [28] Fleming (2018) | Nature | AI and drug discovery | An analysis of the effectiveness | Reflecting the challenges associated with drug discovery |
| [29] Larranaga et al. (2006) | Briefings in Bioinformatics | ML in bioinformatics | Evaluation of The ML methods in biological knowledge | Introducing some practical methods |
| [31] Smalley (2017) | Nature Biotechnology | AI techniques in drug discovery | Overview of different aspects of AI in drug discovery | Some useful analysis |
| [45] Stephenson et al. (2019) | Current Drug Metabolism | ML techniques | Survey on drug discovery | Analysis of ML methods for drug discovery goals |
| [52] Cai et al. (2020) | Journal of Medicinal Chemistry | LSTM | Evaluation of ML in drug discovery | A comprehensive analysis of transfer Learning for Drug Discovery |
| [53] Baskin (2020) | The Expert Opinion on Drug Discovery | LSTM | Review on DL methods in drug discovery | Presenting some useful ideas about DL and drug discovery |
| [54] Yildirim et al. (2016) | Frontiers in Pharmacology | Novel approaches in drug discovery | A review of challenges associated with big data | Analyzing the potential methods to improve drug discovery |
| [55] Walls et al. (2020) | Cell | Infrastructures for the COVID-19 drug discovery | Survey of fundamentals for COVID-19 drug discovery | Fundamental methods for COVID-19 drug discovery |
| [56] Shoichet (2004) | Nature | Technology-based drug discover | An overview of challenges using technology for drug discovery | Presenting some recommendations |
| [57] Zhang et al. (2017) | Drug Discovery Today | DL and ML approaches | A review on progress from ML to DL | Analyzing the pros and cons of both approaches |
| [58] Wang et al. (2018) | Scientific Reports | DL techniques | Possibility of DL-based method for the design of protein | Showing acceptable results |
Discovering a natural or artificial molecule that could battle a protein target implicated in disease is hard and makes Drug discovery a difficult process to complete. Even if millions of molecules are screened the hit rates from screening may be very low. Despite a large number of drugs such as anti-influenza drugs which are present in clinical trials, none could be presented as a practical drug to cure COVID-19 complications. By combining the structural bioinformatics and molecular modeling docking in [63], researchers have predicted the COVID-19 spike binding site to the cell-surface receptor (Glucose Regulated Protein 78 (GRP78)) as the main driving force for host cell recognition. The SARS spike has been used to model spike protein of the COVID-19. The structural alignments and sequence demonstrated that moreover to its cyclic nature, there are four regions, in which similarities to sequence and physicochemical similarities to the cyclic Pep42 do exist. To test the four spike regions that fit tightly in the GRP78 Substrate Binding Domain b (SBD-b), Protein-protein docking was performed [63].

We employed DL approaches to present a comprehensive strategy for drug discovery of COVID-19. The proposed DL-based method for drug discovery of COVID-19 complications is demonstrated in Fig. 8. As observed in Fig. 8, a drug could be prepared through the introduced DL-based algorithm in 10 layers, commencing from the input data layer to the approved drug layer. The proposed strategy in this study seems to be prominently more efficient than previous ones at least in terms of drug designing for COVID-19; however, it is imperative that the presented methods are investigated along with thorough and close consultant with FDA guidelines. The first layer that contains primary data and pharmaceutical knowledge is the layer of input data, and the data collected from different sources as a Big Data Repository (BDR) is used for building this layer.

BDR’s function is to support the publication and discovery of biomedical data [49]. BDR, as a set of data services, can be used to store and publish biomedical data.
from a host of domains such as neuroimaging, proteomics, and genomics. Using big data facilitates experimentation as well as new knowledge creation and transparency [54]. In health care contexts the sources of data are mainly hospitals and clinics, health insurance companies, pharmaceutical and medical device R&D and physicians with various specialties; however, patient’s behavior and sentiments, and population and public health data could contribute as well. Even data coming from genomic sources and large scale phenotyping efforts may be available to utilize [64]. Virtual screening that includes a supervised DL method responsible for data analysis and identifying the best matching between target identification and the inputs according to virtual screening takes place in the second layer. Virtual screening is employed to search libraries of small molecules during the process of drug discovery to identify structures with a greater possibility of binding to a drug target such as a protein receptor or enzyme [56]. The third layer, classification of the best structure, is a layer in which a Hopfield network classifies the best outputs of the second layer. Recognition and classification of given grain samples are done by a Discrete Hopfield Network, which is a type of Auto-associative NN and is capable of learning and storing the data in the form of weights. Chemical syntheses and prediction of the reactions happen in the third and fourth layer. Being an expensive and
time-consuming drug synthesis as to deal with omnipresent ethical disputes and limited outcomes [65]. In addition to that, a reaction predictor is a DL-based method to reaction prediction operating at the level of elementary reactions. Such design choice is desirable because they reflect the process and the ways that human experts contemplate and understand chemical reactions. Layer sixth and layer seventh are responsible for high throughput screening and lead optimization, respectively. While clinical trials and final analysis are done in order by layer eighth and layer ninth. Finally, the drug will be approved through the layer tenth.

5 Future Directions

The first example to discuss here is related to prioritizing vaccine strategies. Reference [55] presents some significant approaches and candidate antigens to provide effective vaccines against SARS-CoV-2. Since it follows previous studies that focus on prevention and control of seasonal influenza vaccines, the entire virus particle-based preparation of vaccines that consists of attenuated and inactivated virus vaccines is advisable [66]. As [55] demonstrated, we can determine the extent of the effectiveness of the vaccine against SARS-CoV-2 with high precision [67–72]. The DBM illustrated in Fig. 9 can be used to classify the best possible strategy with all of the limitations taken into account. In the process of classification or regression, the main job is predicting the outcome associated with a particular individual while a feature vector that describes the individual is provided. Individuals are grouped together in clustering according to the properties they share. In feature selection, however, the task is the selection of features that play important roles in the prediction of outcome for an individual [40].

Estimating antibody in infants by their mother is another example that we discuss here. Reference [63] illustrates antibodies in infants born to mothers with COVID-19. In the serum of all 6 infants, the antibodies were identified, two of whom had IgM and IgG concentrations more than the normal level (<10 AU/mL).

Fig. 9 The proposed developed strategy for classification of the best strategies to create COVID-19 powered by DBM network

Advantages of:
- Inactivated virus vaccines
- Attenuated virus vaccines
- Viral vector vaccines
- DNA vaccines
- mRNA vaccines

Disadvantages of:
- Inactivated virus vaccines
- Attenuated virus vaccines
- Viral vector vaccines
- DNA vaccines
- mRNA vaccines
Also, their neonatal blood sera samples demonstrated virus-specific antibodies. Five of the infants had elevated IgG concentrations [63]. To estimate antibody and IL-6 levels in infant sera samples based on [63], a Restricted Boltzmann Machine (RBM) is proposed. To learn the proposed network, as illustrated in Fig. 10, it is possible to use values of IgG and IgM antibodies in the mothers’ sera samples.

RBM is a generative stochastic ANN that can learn a probability distribution over the network inputs. In [63], the selected samples, six mothers infected by COVID-19, are limited values for learning the introduced method; therefore, it is advisable that more samples are selected to implement this method. A developed strategy is presented here so that conventional networks could use the DL method. Predictions change after patients receive the drug. Improvement in the patients’ clinical status in [73] followed an administration of convalescent plasma that contains neutralizing antibody. Since the limited sample size and study design prevent the expression of a definitive judgment on the extent of this treatment’s effectiveness, evaluation in clinical trials are required. Hence for [73], an LSTM approach is recommended to predict changes in those patients who receive Convalescent Plasma Transfusion. LSTM is an Artificial Recurrent Neural Network (RNN) architecture that is adopted in the field of DL. Contrary to standard feed-forward neural networks, LSTM has feedback connections and can process single data points as well as the entire sequences of data. The proposed LSTM-powered technique is illustrated in Fig. 11. As is shown in this figure, the clinical characteristics comprise IL-6, pg/mL (normal range, 0–7), length of hospital stay, cycle threshold, PAO2/FIO2 ratio, SOFA score. Moreover, the inputs to achieve such results can be characteristics and antibody titer of Convalescent a plasma donor like donated plasma volume, the interval between symptom onset and discharge, interval between discharge and neutralizing antibody titer RBD-specific IgG ELISA titer, plasma donation and RBD-specific IgM ELISA titer.

A. An integrated Drug and Vaccine Strategy for Future Disease

Figure 12 illustrates the concept of an intelligent approach which can be used as a DL-based method to find the drugs and vaccine. This algorithm can be generalized for finding drugs or vaccines for any disease and virus in the future. In this way,
when a disease is targeted, new compounds with desired and functional activities could be identified by active learning algorithms. Targeting COVID-19 and using novel structural features and network architecture alongside conventional approaches, we applied DL in computational drug and vaccine design in the present study. However, instead of limiting ourselves to a specific drug or method, we extended our study to develop analytical methods and demonstrate several DL networks for the discovery of drugs. Therefore, we aimed at providing an overview of DL approaches to discover drugs. The following section that illustrates DL drug development is followed by three sections present an explanation for the proposed vaccine development strategy, suggest a drug discovery strategy, and present the conclusion in order. DL has been demonstrably efficient and accurate in predicting drug properties and proposing drug candidates, which has been reliable in outlining possible toxicity risks [74]. The spike glycoprotein of SARS-COV-2 was a specific target because of its role in shaping the virus’s characteristic protruding crown [75]. The vaccine component was eventually modelled in the SPARKS-X server [76]. A catalogue of all protein antigens, which can be expressed by pathogen at any time is immediately provided by the genome sequence. In this approach initiated by the genomic sequence, antigens that have the potentials to be the best vaccine candidates are predicted based on computer analysis. However, this approach is naive in the sense that it cannot determine if any of the potential antigen candidates ends in the provision of protective immunity without information regarding the abundance of the antigen or its immunogenicity in the period of infection or when expressed in vitro [77]. DL approaches are apparently more preferable to be used when raw high-dimensional data exist because when compared to conventional ANN, they describe the vanishing effects of gradients [41, 78]. Machine intelligence is now more efficient in drug discovery because of the result of data-driven and power-driven computational studies [57]. As recent research show, DL algorithm is now able to use retinal photographs to detect diabetic retinopathy, and they do this demonstrating equal or even greater sensitivity than ophthalmologists. The diagnosis procedure in this model which is void of human intervention, is learnt from raw pixels of the images and in the absence of ophthalmologists who could annotate pictures with their correct diagnosis [50]. DNNs’ ability to learn features from simple inputs data, such as atom types and coordinates makes them more desirable
for application. Although technical details vary and network architecture and data representations change depending on the type of application, there is just one significant requirement of using deep ANN, and that is the existence and availability of large sets of data [58]. Applying a DNN on the Merck Kaggle challenge dataset through the use of a large number of 2D topological descriptors, Dahl et al.; witnessed that in comparison to the standard Random Forest (RF) method DNN is of slightly better performance in 13 of the total 15 targets [79]. A comprehensive multi-task DNN model that there is Tox21 challenge on a dataset comprising 12,000 compounds for 12 high-throughput toxicity assays was reported in [80]. An interesting attempt that originated a novel theory and attracted a lot of researches and pharmaceutical companies was Hinton et al. [41] research in 2006 in which they introduced the deep belief networks that facilitated the construction of nets that consist many hidden layers.

6 Discussion

Despite the full-paced attempts of companies whose aim is to develop a vaccine against coronavirus, the most optimistic news for the public considers a period of 1–1.5 years until such an aim is achieved. It is hard to come into terms with such a long interval when a look is taken at the numbers of ever-increasing patients and death tolls caused by COVID-19; however, new technologies developed in recent
years, as well as the converging international efforts to find a way out of the pandemic, provide us with a firm ground of optimism regarding an ultimate solution to get away from COVID-19. Exacerbating the frustrating situation put the whole world in danger leading to recession and the risk of putting lives at risk. While attaining ideal solutions might not be a possibility in the short-run, we cannot afford losing sight of the present possibilities available to us in battling against COVID-19 [81]. All attempts to develop a vaccine for the disease are currently passing through primary clinical trials to ensure that they do not cause further risks for the receivers, while, in the meantime, more and more patients have to face the risk of hospitalization and even death. Therefore, the use of DL-based methods to find effective drugs and vaccines for COVID-19 could have a great impact on the fight against the disease spread. The present study aligns with this aim and suggests such models enhance approaches that could realize the objectives of the study. The comprehensive approach illustrated in Fig. 9 provides us with a powerful tool to improve conventional and recent intelligent techniques. The suggested algorithm in this study (Fig. 12) adds more value to such straightforward techniques in the sense that it decreases the amount of time needed in conventional and AI-based models to ensure safety and precision. One important feature of these techniques is that predicting vaccines or drugs’ caused reaction in the body is quite possible prior to its application to animals and humans. Another significant feature is to analyze the results of trails by DBN. Various descriptors successfully used in this network to ensure the cost-effectiveness of ligand-based virtual screening in chemical data bases demonstrated that similarity searching was performed as expected. Vaccines cannot be made available to the public until they have obtained official approval for the competent authorities. Besides, there is always the probability of diseases disappearing by themselves or fresh medicine or drugs being released to the market for disease treatment. In either case, manufacturers could be at risk of losing their resources which in such case they have to suffer the loss of precious resources that could be employed and used elsewhere and for another disease. The suggested models in this study make it possible to review a large number of drug discovery methods and merge them with the effective DL-based techniques that demonstrate a well-matched AI approach to not only save resources of the pharmaceutical industry but also create a synergistic approach that could contribute to better quality and fine tune the distribution system performance.

7 Conclusion

Amidst the outbreak of COVID-19 and in the absence of a definite medical treatment and working vaccine to fight and possibly stop the fast-moving pandemic, we need to rely on the massive and rapid shift in behavior to bring the disease under control. Utilizing novel intelligent approaches based on Deep Learning (DL) and Artificial Intelligence (AI) can help us through speeding the process of design and optimization any potential drugs and vaccines. This chapter proposed a survey of
fundamentals and state-of-the-art to use DL-based methods for drug discovery goals. The proposed methods included Deep Boltzmann Machines (DBM), Hopfield network, Restricted Boltzmann Machine (RBM), Long Short-Term Memory (LSTM), and Deep Belief Network (DBN). Particular emphasis was placed on proposing some DL-based platforms for applications of DL in different aspects of drug discovery and describing a comprehensive approach consisting of several AI-based layers to find the best results in the shortest possible time.

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