European Review for Medical and Pharmacological Sciences 2020; 24: 11977-11981

# Application of machine intelligence technology in the detection of vaccines and medicines for SARS-CoV-2

M.H. ALSHARIF[1], Y.H. ALSHARIF[2], M.A. ALBREEM[3], A. JAHID[4], A.A.A. SOLYMAN[5], K. YAHYA[6], O.A. ALOMARI[7], M.S. HOSSAIN[8]

[1]Department of Electrical Engineering, College of Electronics and Information Engineering, Sejong University, Gwangjin-gu, Seoul, Korea
[2]Faculty of Medicine, Islamic University of Gaza, Gaza, Palestine
[3]Department of Electronics and Communications Engineering, A'Sharqiyah University, Ibra, Oman
[4]Department of Electrical & Computer Engineering, University of Ottawa, Ottawa, ON, Canada
[5]Department of Electrical and Electronics Engineering, Istanbul Gelisim University, Avcılar, Turkey
[6]Department of Mechatronics Engineering, Istanbul Gelisim University, Istanbul, Turkey
[7]Department of Computer Engineering, Istanbul Gelisim University, Avcılar, Istanbul, Turkey
[8]Department of Electrical, Electronic and Communication Engineering, Military Institute of Science and Technology, Dhaka, Bangladesh

**Abstract. – Researchers have found many similarities between the 2003 severe acute respiratory syndrome (SARS) virus and SARS-CoV-19 through existing data that reveal the SARS's cause. Artificial intelligence (AI) learning models can be created to predict drug structures that can be used to treat COVID-19. Despite the effectively demonstrated repurposed drugs, more repurposed drugs should be recognized. Furthermore, technological advancements have been helpful in the battle against COVID-19. Machine intelligence technology can support this procedure by rapidly determining adequate and effective drugs against COVID-19 and by overcoming any barrier between a large number of repurposed drugs, laboratory/clinical testing, and final drug authorization. This paper reviews the proposed vaccines and medicines for SARS-CoV-2 and the current application of AI in drug repurposing for COVID-19 treatment.**

*Key Words:*
COVID-19, SARS-CoV-2, Coronavirus, Artificial intelligence, Machine learning.

## Introduction

In late December 2019, the Novel Coronavirus disease (COVID-19) caused by SARS-CoV-2 was identified for the first time in Wuhan, Hubei Province, China; SARS-CoV-2 particularly affects the lungs and causes pneumonia[1]. As such, the Chinese government has adopted timely and effective measures, such as wearing masks in public places, frequently washing the hands, maintaining the social distancing policy, quarantining COVID-19-positive cases, and reporting the latest symptom information to regional health centers to prevent and control the spread of COVID-19; however, the scope of the COVID-19 outbreak has developed widely and rapidly[2]. On January 30, 2020, the World Health Organization (WHO) announced that the COVID-19 outbreak has become an international public health emergency and evolved quickly; on March 11, 2020, the WHO declared COVID-19 as a pandemic[3]. Today, COVID-19 is spread in 218 countries, and the number of infected cases and deaths rapidly and significantly increases. Consequently, researchers are inventing new strategies for rapid antiviral treatments.

Host-based antiviral agents target the host cellular machinery essential for viral infections or innate immune responses to interfere with viral pathogenesis[4]. This machinery can be enhanced by applying well-validated drug discovery approaches. Generally, two basic strategies have been used in drug discovery: (i) *conventional drug development* and (ii) *drug repositioning*[5]. The success rate of conventional treatments is very low, and they typically take 10-15 years and entail high investments. They are also expensive.

*Corresponding Author:* Mohammed H. Alsharif, Ph.D; e-mail: malsharif@sejong.ac.kr

By comparison, in drug repositioning, old drugs are reused for exploring new therapeutics; as such, it becomes more efficient, economical, and riskless[6]. However, drug repositioning requires thorough in-depth knowledge of present practices acquired by assessing biological and pharmaceutical learning and interpreting the mechanism-of-action of drugs. Moreover, diagnosing and identifying the unique drug-disease relationship hamper drug repositioning. To address these issues, researchers developed a variety of approaches, including computational approaches (such as artificial intelligence [AI]), experimental biological approaches, and mixed approaches. However, AI and machine learning (ML) are leading-edge technologies for potentially discovering drugs, making treatment plans, designing treatments, and outlining follow-ups of patients with COVID-19 (Figure 1)[7].

AI includes a subfield called ML, which involves the use of factual strategies with the capacity to learn with or without being modified by an external user. ML is divided into supervised, unsupervised, and reinforcement learning[8]. Another field of ML is deep learning. It uses an AI neural network with multiple hidden layers, as well as input and output layers. With deep learning (DL), machines can be utilized to resolve complex issues in any event by using an informational index that is exceptionally different and unstructured. The deeper the learning calculations learn, the better they perform. DL is developed with the expanding measure of information and the continuous development of computer power. Table I summarizes the recent representative applications of machine intelligence technology in small-molecule drug discovery. This paper reviews the proposed vaccines and medicines for SARS-CoV-2 and the current AI application in drug repurposing for COVID-19 treatment. The remaining parts of this paper are organized as follows. Section 2 discusses the proposed vaccines and medicines of SARS-CoV-2 and the current application of AI in drug repurposing for treating COVID-19. Section 3 briefly summarizes the limitation of machine intelligence technology and future perspectives. Section 4 concludes the work.

## Application of AI in Drug Repurposing for Treating SARS-CoV-2

More than 80 pioneering clinical trials have been conducted to test coronavirus treatments, including potential old drugs and new drugs[23]. In this context, chloroquine and hydroxychloroquine have been utilized to treat viral infections. These drugs have antimalarial activities and show potential for *in vitro* treatments against COVID-19[24]. Similarly, remdesivir, an antiviral drug, is primarily used in Ebola virus-related clinical studies that expose new successful effects against COVID-19 *in vitro*. It is an adenosine analog that integrates into budding viral RNA chains and appears in early termination[25]. Lopinavir and ritonavir are administered to patients with COVID-19. These two antiviral agents mainly affect proteolysis in the coronavirus replication cycle[26]. Ribavirin is an RNA analog and inhibitor of RNA polymerization. This drug has an *in vitro* activity against SARS-CoV-2 in preclinical studies[27]. Furthermore, tocilizumab, an immunosuppressive drug, is applied to treat patients with COVID-19 *in vivo* in China. It is chiefly employed to aid rheumatoid arthritis tested in patients with COVID-19. It also successfully mitigates the clinical symptoms of viral infection, but few patients were investigated[28]. The antiflu drug developed in Japan has yielded significant results in clinical trials on 340 patients[29]. In China, this drug is accepted for influenza treatment and shown

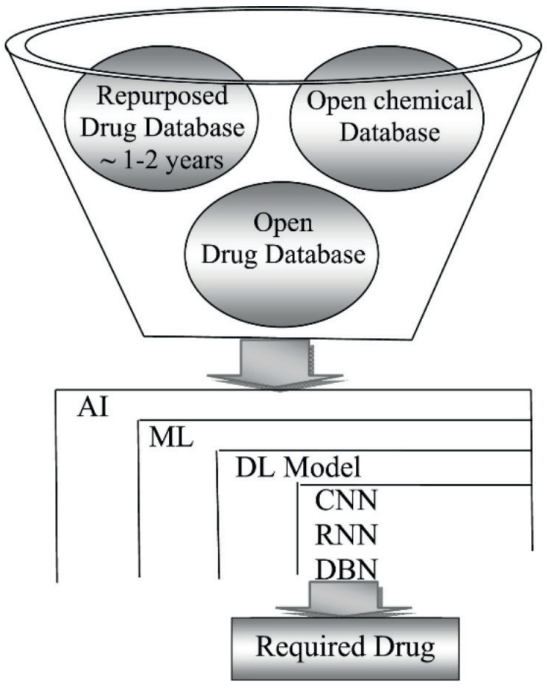


**Figure 1.** Machine intelligence technologies for enabled drug repurposing. Abbreviations: Artificial Intelligence (AI); Machine Learning (ML); Deep Learning (DL); Convolutional Neural Networks (CNN); Recurrent Neural Network (RNN); Deep Belief Network (DBN).

**Table I.** Summary of recent representative applications of machine intelligence technology in small-molecule drug discovery.

| Reference | Method | Prediction | Features |
|---|---|---|---|
| Lusci et al[9] | DL/RNN | Compound aqueous solubility | Molecular graph |
| Wang et al[10] | DL/DNN | Drug target interactions | Molecular descriptors and protein features |
| Wang and Zeng[11] | DL/DNN | Drug target interactions | Molecular descriptors |
| Shin et al[12] | DL/DNN | permeability | Molecular descriptors |
| Unterthiner et al[13] | DL/DNN | Toxicity | Molecular fingerprints and descriptors |
| Wang et al[14] | DL/RNN | Compound protein interaction | Molecular fingerprints and protein sequence |
| Wallach et al[15] | DL/CNN | Biological activity | Molecular graph (AtomNet) |
| Pereira et al[16] | DL/CNN | Virtual screening | Molecular graph and docking result |
| Goh et al[17] | DL/CNN | Biological activity/toxicity | 2D chemical structure image |
| Bjerrum[18] | DL/RNN | Biological activity | SMILES |
| Lenselink et al[19] | DL/DNN | Biological activity | Molecular descriptors and fingerprints |
| Segler et al[20] | DL/RNN | Generating focused molecular libraries | SMILES |
| Olivecrona et al[21] | DL/RNN | Generating novel molecules | SMILES |
| Yao and Parkhill[22] | DL/CNN | The Kohn-Sham kinetic energy | Fingerprints |

to be efficient against different types of viruses, including SARS-CoV-2. Similarly, ascorbic acid (vitamin C) combined with other antiviral drugs has shown to be supportive in the treatment of patients with COVID-19. In this context, more studies on future drugs against COVID-19 should be performed[30].

Computational biologists are assisting with battling coronavirus by modeling COVID-19 and finding new medications for this disease. Disease dynamic modeling helps elucidating the effect of parameters influencing the spread of the infection and the impact of medications on controlling this spread[31]. Numerous data-driven drug repurposing (drug repositioning) approaches have been proposed by identifying illnesses, conditions, or groups of patients who can be treated with existing medications not known for this disease[32]. In general, when the virus RNA genome first enters a cell, it interacts with the proteins produced by hosts and utilizes host proteins to make viral proteins that can duplicate RNA molecules. These RNA-replicating proteins called "polymerases" are potential treatment targets[33]. Proteins have a 3D structure, which is evaluated in terms of their genetically encoded amino acid sequence, and this structure affects the role of proteins[34]. Two primary ways are applied to manage protein prediction: template modeling, which predicts the structure utilizing similar proteins as a template sequence, and template-free modeling, which predicts the structure of proteins that have unknown related structures. The AlphaFold model depends on an enlarged ResNet architecture and uses amino acid sequences; it also employs features obtained from parallel amino acid sequences through several sequence arrangements to determine the distance and dispersal of angles between amino acid residues[34]. This framework has been applied to predict the structures of six proteins identified with SARS-CoV-2 (i.e., SARS-CoV-2 membrane protein, protein 3a, Nsp2, Nsp4, Nsp6, and papain-like proteinase)[33]. These predictions likely help determine coronavirus capacities and improve treatments against COVID-19. In this context, specialists at the Massachusetts Institute of Technology (MIT) are building an approach to destroy the novel coronavirus that causes COVID-19 by making a "decoy" receptor or a protein that can be taken as a medication. Coronaviruses cause sickness by binding to the body's ACE2 receptors. The MIT specialists are utilizing an AI model trained on data about the ACE2 receptor to simulate the connection between the baits and the virus[35]. Other researchers are focusing on finding novel compounds for SARS-CoV-2 by utilizing an exclusive pipeline to discover inhibitors for the 3C-like protease[36]. In such models, three types of information are applied: the crystal structure of proteins, the co-crystalized ligands, and the homology model of proteins. For each type, various models, including generative auto-encoders and

generative adversarial networks, are utilized[34]. They investigated potential applicants *via* an efficient reinforcement learning approach that consolidates various factors, such as medication dosage, likeness, novelty, and assorted varieties.

### Limitations of Machine Intelligence Technology and Future Perspectives

Although DL methods have been successfully applied in many areas, the adaptation of algorithms remains a problem for chemistry-centric modeling in small-molecule drug discovery. This problem is especially observed in recurrent neural networks and convolutional neural networks, which are powerful but have higher restrictions on the format of input data. DL can reach a high identification accuracy if a training set contains a large amount of data. However, with very limited data, DL techniques cannot achieve an unbiased estimate of the generalization[37]. Time complexity rapidly exacerbates because of the complication of the network architecture; as such, stronger hardware facilities and advanced programming skills are required to achieve the feasibility and effectiveness of DL methods. In addition, although DL methods usually have an outstanding performance in practice, tuning the hyperparameters in DL modeling is often tricky. Furthermore, determining the sufficient number of hidden layers and nodes for establishing the best simulation without redundancy for a specific DL modeling is difficult. Unsupervised learning strategies in DL are inspiring but still lacking[38]. In real-world applications, especially drug discovery, most of the data are not labeled, and a high amount of information is included. Therefore, novel unsupervised learning methods should be explored and developed using DL methods. Useful information should also be mined from relevant data.

## Conclusions

The possible choices for fighting COVID-19 should be comprehensively investigated. A repurposed drug database and an open chemical/drug database can be utilized as an input of models. Different algorithms can be applied to the input, and the required drug can be obtained. Modern technology shows potential for systematically integrating data and achieving a new level of AI in drug discovery. Various models of machine intelligence algorithms in real-world clinical practices have been utilized. Potential applicants have also been explored using an efficient reinforcement learning approach that consolidates various factors, such as medication dosage, likeness, novelty, and assorted varieties. Furthermore, novel unsupervised learning methods should be explored and developed with DL methods. Useful information should also be mined from relevant data.

### Conflict of Interests

The Authors declare that they have no conflict of interests.

## References


1) Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382: 727-733.
2) Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA Netw Open 2020; 323: 1239-1242.
3) Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. N Engl J Med 2020; 382: 1199-1207.
4) Li CC, Wang XJ, Wang HR. Repurposing host-based therapeutics to control coronavirus and influenza virus. Drug Discov Today 2019; 24: 726-736.
5) Patil V, Singhal S, Masand N. A systematic review on use of aminoquinolines for the therapeutic management of COVID-19: Efficacy, safety and clinical trials. Life Sci 2020; 254: 117775.
6) Xue H, Li J, Xie H, Wang Y. Review of drug repositioning approaches and resources. Int J Biol Sci 2018; 14: 1232-1244.
7) Mohanty S, Harun Ai Rashid M, Mridul M, Mohanty C, Swayamsiddha S. Application of artificial intelligence in COVID-19 drug repurposing. Diabetes Metab Syndr 2020; 14: 1027-1031.
8) Alsharif HM, Kelechi HA, Yahya K, Chaudhry AS. Machine learning algorithms for smart data analysis in internet of things environment: taxonomies and research trends. Symmetry-Basel 2020; 12: 88.
9) Lusci A, Pollastri G, Baldi P. Deep architectures and deep learning in chemoinformatics: the prediction of aqueous solubility for drug-like molecules. J Chem Inf Model 2013; 53: 1563-1575.

10) Wang C, Liu J, Luo F, Tan Y, Deng Z, Hu QN. Pairwise input neural network for target-ligand interaction prediction. Proc in IEEE International Conference on Bioinformatics and Biomedicine (BIBM) 2014: 67-70.
11) Wang Y, Zeng J. Predicting drug-target interactions using restricted Boltzmann machines. Bioinform 2013; 29: i126-i134.
12) Shin M, Jang D, Nam H, Lee D. Predicting the absorption potential of chemical compounds through a deep learning approach. IEEE/ACM Trans Comput Biol Bioinform 2016; 15: 432-440.
13) Mayr A, Klambauer G, Unterthiner T, Hochreiter S. DeepTox: toxicity prediction using deep learning. Front Environ Sci 2016; 3: 80.
14) Wan F, Zeng J. Deep learning with feature embedding for compound-protein interaction prediction. BioRxiv 2016; DOI: https://doi.org/10.1101/086033.
15) Wallach I, Dzamba M, Heifets A. AtomNet: a deep convolutional neural network for bioactivity prediction in structure-based drug discovery. Available online: arXiv preprint arXiv:1510.02855 2015.
16) Pereira JC, Caffarena ER, Dos Santos CN. Boosting docking-based virtual screening with deep learning. J Chem Inf Model 2016; 56: 2495-2506.
17) Goh BG, Siegel C, Vishnu A, Hodas N, Baker N. How much chemistry does a deep neural network need to know to make accurate predictions? Proc in IEEE Winter Conference on Applications of Computer Vision (WACV), 2018: 1340-1349.
18) Bjerrum JE. SMILES enumeration as data augmentation for neural network modeling of molecules. Available online: arXiv preprint arXiv:1703.07076 2017.
19) Lenselink EB, Ten Dijke N, Bongers B, Papadatos G, van Vlijmen HWT, Kowalczyk W, IJzerman AP, van Westen GJP. Beyond the hype: deep neural networks outperform established methods using a ChEMBL bioactivity benchmark set. J Cheminform 2017; 9: 45.
20) Segler M, Kogej T, Tyrchan C, Waller M. Generating focused molecule libraries for drug discovery with recurrent neural networks. ACS Cent Sci 2018; 4: 120-131.
21) Olivecrona M, Blaschke T, Engkvist O, Chen H. Molecular de-novo design through deep reinforcement learning. J Cheminform 2017; 9: 48.
22) Yao K, Parkhill J. Kinetic energy of hydrocarbons as a function of electron density and convolutional neural networks. J Chem Theory Comput 2016; 12: 1139-1147.
23) Sanders J, Monogue M, Jodlowski T, Cutrell J. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA 2020; 323: 1824-1836.
24) Rolain J, Colson P, Raoult D. Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century. Int J Antimicrob Agents 2007; 30: 297-308.
25) Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, Tissot Dupont H, Honoré S, Colson P, Chabrière E, La Scola B, Rolain JM, Brouqui P, Raoult D. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020; 56: 105949.
26) Shah S, Das S, Jain A, Misra PD, Negi SV. A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in coronavirus disease-19 (COVID-19). Int J Rheum Dis 2020; 23: 613-619.
27) Wang L, Wang Y, Ye D, Liu Q. A review of the 2019 Novel Coronavirus (COVID-19) based on current evidence. Int J Antimicrob Agents 2020; 55: 105948.
28) Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020; 323: 1775-1776.
29) Chan JF, Chan KH, Kao RY, To KK, Zheng BJ, Li CP, Li PT, Dai J, Mok FK, Chen H, Hayden FG, Yuen KY. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. J Infect 2013; 67: 606-616.
30) Chan JF, Yao Y, Yeung ML, Deng W, Bao L, Jia L, Li F, Xiao C, Gao H, Yu P, Cai JP, Chu H, Zhou J, Chen H, Qin C, Yuen KY. Treatment with lopinavir/ritonavir or interferon-β1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. J Infect Dis 2015; 212: 1904-1913.
31) Ferguson N, Laydon D, Gilani G, Baguelin M. Report 9: Impact of non-pharmaceutical interventions (NPIs) to reduce COVID19 mortality and healthcare demand. Imperial College COVID-19 Response Team 2020; DOI: https://doi.org/10.25561/77482.
32) Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, Rawling M, Savory E, Stebbing J. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet 2020; 395: e30-e31.
33) Joynt GM, Wu WK. Understanding COVID-19: what does viral RNA load really mean?. Lancet Infect Dis 2020; 20: 635-636.
34) Kumar A, Gupta P, Srivastava A. A review of modern technologies for tackling COVID-19 pandemic. Diabetes Metab Syndr 2020; 14: 569-573.
35) Busse L, Chow J, McCurdy M, Khanna A. COVID-19 and the RAAS–a potential role for angiotensin II?. ed: BioMed Central, 2020.
36) Zhavoronkov A, Zagribelnyy B, Zhebrak A, Vanhaelen Q. Potential non-covalent SARS-CoV-2 3C-like protease inhibitors designed using generative deep learning approaches and reviewed by human medicinal chemist in virtual reality. ChemRxiv 2020; DOI: 10.26434/chemrxiv.12301457.v1
37) Winkler D, Le T. Performance of deep and shallow neural networks, the universal approximation theorem, activity cliffs, and QSAR. Mol Inform 2017; 36: 1600118.
38) Jing Y, Bian Y, Hu Z, Xie X. Deep learning for drug design: an artificial intelligence paradigm for drug discovery in the big data era. AAPS J 2018; 20: 58.