New Insights Into Drug Repurposing for COVID-19 Using Deep Learning

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***Abstract*— The coronavirus disease 2019 (COVID-19) has continued to spread worldwide since late 2019. To expedite the process of providing treatment to those who have contracted the disease and to ensure the accessibility of effective drugs, numerous strategies have been implemented to find potential anti-COVID-19 drugs in a short span of time. Motivated by this critical global challenge, in this review, we detail approaches that have been used for drug repurposing for COVID-19 and suggest improvements to the existing deep learning (DL) approach to identify and repurpose drugs to treat this complex disease. By optimizing hyperparameter settings, deploying suitable activation functions, and designing optimization algorithms, the improved DL approach will be able to perform feature extraction from quality big data, turning the traditional DL approach, referred to as a "black box," which generalizes and learns the transmitted data, into a "glass box" that will have the interpretability of its rationale while maintaining a high level of prediction accuracy. When adopted for drug repurposing for COVID-19, this improved approach will create a new generation of DL approaches that can establish a cause and effect relationship as to why the repurposed drugs are suitable for treating COVID-19. Its ability can also be extended to repurpose drugs for other complex diseases, develop appropriate treatment strategies for new diseases, and provide precision medical treatment to patients, thus paving the way to discover new drugs that can potentially be effective for treating COVID-19.**

***Index Terms*— Coronavirus, coronavirus disease 2019 (COVID-19), deep learning (DL), drug repurposing (DR), interpretable deep learning for anti-COVID-19 drugs prediction, severe acute respiratory syndrome coronavirus 2 (SARS-CoVID-2).**

I. Introduction

THE coronavirus disease 2019 (COVID-19) has had an unprecedented impact globally. According to Reuter, on July 30, 2020, the U.S. economy experienced its steepest decline since the 1947 Great Depression. Due to the lack of effective prevention and treatments, the COVID-19 has caused ongoing and recurrent deadly outbreaks globally.

The coronavirus genome is a positive-sense, nonsegmented, single-stranded RNA, with an astoundingly large size ranging from 27 to 32 kilobases [22]. Four human coronaviruses, namely, HCov-229E, HCovNL63, HCov-OC43, and HKU1, typically affect the upper respiratory tract and cause relatively minor symptoms. In contrast, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERSCoV), and SARS-CoV-2 can infect the lower respiratory tract and cause severe pneumonia resulting in higher fatality risk.

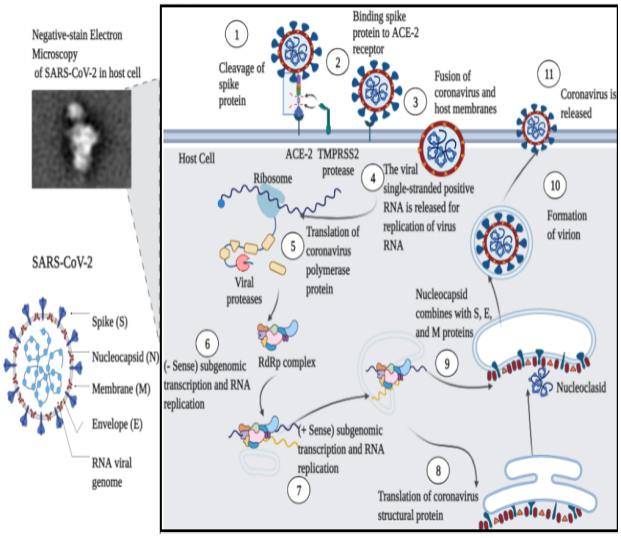

Fig. 1. Schematic of the structure of SARS-CoV-2 and its entry and replication process within the host cell. It has four structural proteins, S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins; the N protein holds the RNA genome, while the S, E, and M proteins together create the viral envelope [53]. 1— coronavirus enters the host cells by cleavage of its spike protein (S glycoprotein). 2—binds to ACE2 receptor with its spike protein. ACE2 receptor is primed by the TMPRSS2 protease. 3—coronavirus then fuses into the host membranes. 4—viral single-stranded positive RNA is released for replication of virus RNA. 5—translation of coronavirus polymerase. 6 and 7—transcriptions and replications of RNA occur. 8—translation of coronavirus structural protein. 9—nucleocapsid then combined with S, E, and M proteins. 10—formation of coronavirus is completed. 11—released to infect other cells.

Through recently improved understanding in molecular mechanisms of COVID-19 infection, it has provided great insight into the repurposing of drugs that target the SARS-CoV-2 proteins or host factors. Generally, the first step in the coronavirus replication cycle involves attachment and entry, which includes binding of the spike protein (S glycoprotein) of the virus to a host cell through the ACE 2 receptor that is primed by TMPRSS2 protease [18], as shown in Fig. 1. High level of angiotensin-converting enzyme 2 (ACE2) protein is found in the lungs and the small intestine, of particular importance are the lungs' AT2 alveolar epithelial cells that are highly prone to viral infection. One of the known regulators of endocytosis is the AP2-associated protein kinase 1 (AAK1).

Manuscript received March 1, 2021; revised August 20, 2021; accepted September 8, 2021. Date of publication September 21, 2021; date of current version October 28, 2021. *(Corresponding author: Yi-Ping Phoebe Chen.)*

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Color versions of one or more figures in this article are available at https://doi.org/10.1109/TNNLS.2021.3111745.

Digital Object Identifier 10.1109/TNNLS.2021.3111745

Disruption of AAK1 might, in turn, interrupt the passage of the virus into cells and also the intracellular assembly of virus particles. Thus, both the lungs and the small intestine provide easily accessible routes for SARS-CoV-2 infection [18], [22]. The ACE2 protein is also present in smooth muscle, pericytes, and endothelial cells of the vasculature, heart, kidneys, and these have led to the multiorgan dysfunction observed in severe COVID-19 patients [18], [22]. In addition, by comparison to SARS-CoV, SARS-COV-2 has 10–20-fold stronger binding affinity to S protein [18] making it a lot more contagious. However, despite the higher contagiousness, SARS-CoV-2 and SARS-CoV share 79% genomic sequence similarity with a highly conserved receptor-binding domain in their spike proteins.

II. Replication of COVID-19

After host cell entry, the viral single-stranded positive RNA gets replicated and translated into the virus polyproteins using the following process: 1) translation of genomic RNA (gRNA); 2) proteolysis of the translated polyprotein with viral 3C-like proteinase; 3) replication of gRNA with the viral replication complex that consists of RNA-dependent RNA polymerase (RdRp), helicase, 30-to-50 exonuclease, endoRNAse, and 20-O-ribose methyltransferase; and 4) assembly of viral components [22]. The typical clinical symptoms of COVID-19 are fever, dry cough, and fatigue 3–7 days after infection, which is similar to symptoms of severe acute respiratory syndrome (SARS) caused by SARS-CoV [22]. Focusing on important viral polyproteins, spike protein plays a crucial role in viral attachment, entry, and fusion into the target host cell. Two other essential proteins constituting the viral replication–transcription complex are helicase and nonstructural protein 12 (nsp12). Nsp12 is an RdRp that binds with nsp7 and nsp8 to make a multisubunit complex essential for viral replication. Helicase (nsp13) assists in viral replication by unwinding the duplex viral RNA. Main protease (Mpro, also called 3CLpro) is another essential protein that works in conjunction with papain-like protease(s) to process the huge polyproteins encoded by the SARS-CoV-2 genome. These proteins are key targets for effective antiviral therapy [4]. Furthermore, despite having only 79% of genomic sequence shared between SARS-CoV and SARS-CoV-2, there is over 95% similarity in their highly conserved proteins involved in targeting host cell, namely RdRp and 3Clpro (also termed Mpro). RdRp is an RdRp required for replicating the viral genome within the host cell, while 3Clpro and Plpro are both viral proteases responsible for breaking down viral polyproteins into functional units within the host cells that are finally assembled into new viruses. The 3Clpro sequences between the two viruses are 96% similar, the Plpro sequence identity is 83%, and their active sites show a high degree of conservation [18]. With so many similarities between the two viruses, this implies that similar approaches can be adopted to prevent the spike protein from binding with the ACE-2 receptor and TMPRSS2-mediated cell entry must be blocked by appropriate vaccine [18]. On the other hand, virus replication and assembly must be inhibited by effective drugs targeting at viral RdRp and main protease (Mpro) [18], [33]. These replication-associated proteins are the primary targets of postentry treatment drugs for suppressing viral replication.

Even though vaccines have been developed and the rollouts of vaccinations have begun in many parts of the world, the slow rolling outs of vaccinations in some countries have allowed the virus to mutate into new variants that put everyone at risk. It was reported that the Delta variant, which is anticipated to be the predominant variant in the months ahead, is more transmissible than the Alpha variant (CNN health, June 21, 2021). Continuous spread of the virus could lead to more numerous and potentially more transmissible and dangerous variants. The only viable alternative to finding effective drugs, without resorting to the time-consuming and expensive traditional de novo drug discovery process, is through repurposing existing approved drugs. So far, several drugs have been repurposed based on two rationales: 1) effectiveness of those drugs in hampering viral entry and replication in the epithelial cells of the airways by coronaviruses or RNA viruses in the past and/or 2) the ability of those drugs to modulate inflammatory reaction [33]. However, only a few have been completed so far with a less-than-expected level of effectiveness. Overall, this current devastating situation has spurred our interest to reexamine the existing deep learning (DL) models used for COVID-19 drug repurposing (DR) and propose a new DL model, which leverages technological advancement to repurpose commercially available drugs, paving a way to discover new drugs that can potentially be effective for treating COVID-19.

III. Drug Repurposing

The need for new antiviral drugs or repurposed drugs in addressing the global challenge of treating COVID-19 is the motivation for us to explore new mechanisms for the development of anti-COVID-19 drugs. The DR approach, which is a process of finding new indications for existing Food and Drug Administration (FDA)-approved drugs, offers a relatively low-cost and high-efficiency approach to the rapid development of efficacious treatments. When applied to viral infectious diseases, DR integrates both screenings of bioactive small-molecule collections and computational methods (*in silico* screenings, mining of database with transcriptomic profiles, and so on) in order to find a molecule, a pathway, or a biological activity that could be recycled to fight a viral pathogen [7]. The DR presents a promising avenue for identifying and expediting safer treatments without incurring the full cost or time required for de novo drug development, as shown in Fig. 2.

In this review, we describe emerging DR strategies deployed to combat the difficult-to-treat COVID-19 through the use of preexisting drugs that act on targets or disease pathways and suggest an innovative as well as promising approach, which can generalize and learn transmitted data to transform the "black box" nature of DL approaches into an interpretable "glass box," hence improving the interpretability of its rationales while maintaining a high level of prediction accuracy. This new approach, when adopted for COVID-19 DR, can establish a cause-and-effect relationship on the suitability of repurposed drugs for the treatment of COVID-19.

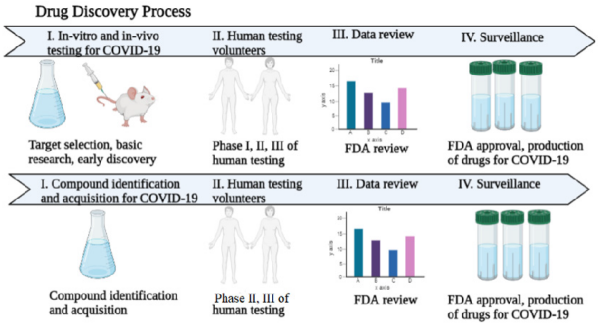


Fig. 2. Comparison of de novo drug discovery and DR journeys. DR begins with compound identification and the acquisition of an existing drug Phase I clinical studies was not required because the results are already available. This is directly followed by phases II and III clinical trials.

A. Clinical DR for COVID-19

Both clinical trials and computational methods have been carried out worldwide for repurposing existing approved drugs for treating COVID-19. We undertook a systematic search using search terms and keywords that are associated with COVID-19, such as "2019 nCoV," "COVID-19", "SARS-2-CoV," "SARS," "DR for COVID-19," "Repurposing drugs for COVID-19 using DL methods," "docking for COVID-19 drugs," "drugs under clinical trials for COVID-19," and "computational or data-driven DR for COVID-19." Knowing that no specific drugs have been designed or repurposed to be very effective for treating COVID-19, we included research studies that have not been undergone peer-reviewed or with no experimental evaluation or are undergoing clinical trial. Eligible studies that are included are those with repurposed drugs that are either already approved by at least one of the following authorities: the U.S. FDA, the European Medicines Agency (EMA), the Japan Pharmaceuticals and Medical Devices Agency (PMDA), or under clinical trials. By considering the above criteria, the works in Table I were selected.

Following the outbreak of the COVID-19 pandemic, broad-spectrum antiviral agents have been introduced into clinical trials. Clinically, it was found that umifenovir had a tendency to reduce viral load and mortality rate but sometimes failed to improve the prognosis and virus clearance [56]. On day 14 after admission, no viral load was detected in the arbidol group, but the viral load was found in 15 (44.1%) patients treated with lopinavir/ritonavir, indicating that arbidol monotherapy may be superior to lopinavir/ritonavir in treating COVID-19 [61]. In addition to monotherapy, the clinical trials extended their exploration to synergetic drug combination. It was reported that when comparing the effect of hydroxychloroquine treatment as a single drug and the effect of hydroxychloroquine and azithromycin combination, there was a significant difference in the treatment results between the two groups at days 3–6 postinclusion [25]. At day 6 postinclusion, 100% of patients treated with hydroxychloroquine and azithromycin combination were virologically cured compared with 57.1% of patients treated with hydroxychloroquine only and 12.5% in the control group ($p < 0.001$). Some of the clinically trialed drugs that were approved for the monotherapeutic treatment of the COVID-19 disease include antimalarial, antiviral, and anti-inflammatory drugs, as shown in Table I.

B. DL in Drug Discovery

As technology advances along with the availability of a variety of drugs-related and disease-related data, the computational approach, especially DL, has demonstrated its superior performance over other traditional computational methods in drug discovery [40]. DL has an edge over other traditional computational methods, such as molecular docking and conventional similarity-based machine learning methods. This is because molecular docking is a simulation-based method using the 3-D structure features of molecules and proteins that are difficult to obtain [34]. On the other hand, similarity-based methods using traditional machine learning methods are found to have limitations because the feature representations of these methods are limited in the similarity space, and thus, they cannot capture the rich information embedded in the molecule sequence [29], [41]. Moreover, they necessitate the calculation of the similarity matrix, which can limit the maximum number of molecules in the training process. To overcome the limitations of needing to perform featuring engineering and losing rich information when traditional machine learning is deployed, DL-based models, which can automatically find useful features from raw molecules such as simplified molecular-input line-entry system (SMILES) and protein sequences made from amino acid sequences (without the need for feature engineering), have been utilized for DR. The general DL framework that has been used to assist drug discovery and DR so far is shown in Fig. 3.

C. DL-Based DR for COVID-19

Motivated by the successful use of DL in drug discovery, Beck *et al.* [8] used molecule transformer-drug target interaction (MT-DTI) to identify commercially available drugs that could act on viral proteins of SARS-CoV-2. Their results showed that atazanavir, an antiretroviral medication used to treat and prevent the human immunodeficiency virus (HIV), showed an inhibitory potency with Kd of 94.94 nM against the SARS-CoV-2 3C-like proteinase, followed by remdesivir (113.13 nM), efavirenz (199.17 nM), ritonavir (204.05 nM), and dolutegravir (336.91 nM). They also found that lopinavir, ritonavir, and darunavir were not only designed to target viral proteases but were also able to bind to the replication complex components of SARS-CoV-2 with an inhibitory potency of Kd $<$ 1000 nM. In addition, several antiviral agents, such as Kaletra (lopinavir/ritonavir), could also be used for the treatment of SARS-CoV-2, as shown in Table I.

To improve the drug–target interaction DeepDTA model [40], Anwar *et al.* [4] employed bidirectional long short-term memory (BiLSTM) blocks of neural networks instead of using convolutional neural networks (CNNs) as deployed by DeepDTA to learn the 1-D SMILE representation of molecules. A fully connected CNN was engaged to learn the FASTA representation of proteins, as shown in Table II. The model was combined with molecular docking experiments to identify the most promising candidates from a list of FDA

TABLE I

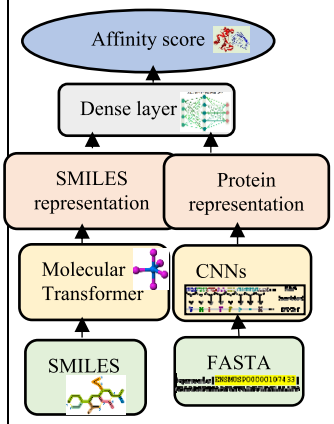
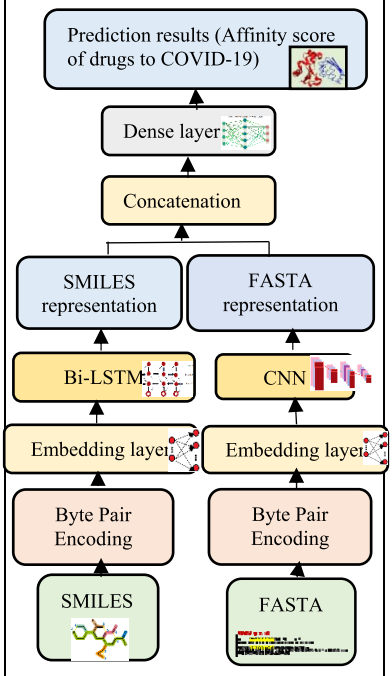
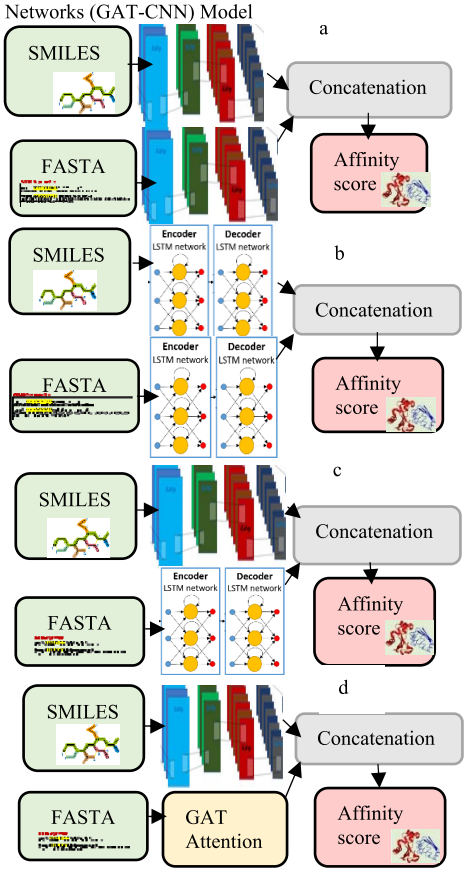
COMPARISON OF REPURPOSED DRUGS OBTAINED USING DIFFERENT METHODS

Experimental/clinical findings/ docking					Deep learning	Reference
Symbols	Repurposed drugs	Class	Virus Type	Target		
	Abacavir	Antiviral	SARS-CoV-2	+ssRNA	RdRp, helicase, 3'-to-5'exonuclease, endoRNAse	[8*,30]
	Acyclovir	Antiviral	SARS-CoV-2	+ssRNA	RdRp, helicase, 3'-to-5'exonuclease	[8*]
	Alisporivir	Antiviral	SARS-CoV	+ssRNA*	Cyclophilins inhibition	[52]
	Amiodarone	Antiarrhythmic	SARS-CoV	+ssRNA	Ion channel inhibitor	[48]
	Amodiaquine	Antimalarial	SARS-CoV	+ssRNA	Endosomal membrane	[26]
	Apilimod	Anti-Crohn'	SARS-CoV-2	+ssRNA	PIKfyve kinase inhibitor	[31]
	Umifenovir	Antiviral	SARS-CoV-2	+ssRNA	Spike glycoprotein	[57, 18]
	Asunaprevir	Antiviral	SARS-CoV-2	+ssRNA	3C-like proteinase, RdRp, helicase, 3'-to-5'exonuclease, endoRNAse	[8*]
	Atazanavir	Antiviral	SARS-CoV-2	+ssRNA	3C-like proteinase, RdRp, helicase, 3'-to-5'exonuclease, endoRNAse, 2'-0-ribose methyltransferase	[8*, 20]
	Atazanavir, rotinavir	Antiviral	SARS-COV-2	+ssRNA	Main protease, interleukin 6(IL-6) & TNF-alpha	[20]
	Boceprevir	Antiviral	SARS-CoV-2	+ssRNA	Helicase, endoRNAse, 2'-0-ribosemethyltransferase	[8*, 21, 35]
	Camostat	Anticancer	SARS-CoV	+ssRNA	TMPRSS2	[55]
	Cepharanthine	Anti-inflammatory	SARS-CoV	+ssRNA	Inhibit viral replication, inflammatory responses	[38]
	Chloroquine	Antimalarial	SARS-CoV	+ssRNA	Inhibit viral replication	[18, 26]
	Chlorpromazine	Antipsychotic	SARS-CoV	+ssRNA	Inhibit viral entry and replication	[42]
	Daclatasvir	Antiviral	SARS-CoV-2	+ssRNA	RdRp, helicase, 3'-to-5'exonuclease, endoRNDse	[3, 8*]
	Danoprevir	Antiviral	SARS-CoV-2	+ssRNA	RdRp, helicase, 3'-to-5'exonuclease, endoRNAse	[8*, 13]
	Darunavir	Antiviral	SARS-CoV-2	+ssRNA	RdRp, helicase, 3'-to-5'exonuclease, endoRNAse	[8*, 27]
	Dolutegravir	Antiviral	SARS-CoV-2	+ssRNA	3C-like proteinase, RdRp, helicase, 3'-to-5'exonuclease, endoRNAse, 2'-0-ribose methyltransferase	[8*]
	Efavirenz	Antiviral	SARS-CoV-2		3C-like proteinase, RdRp, helicase, 3'-to-5'exonuclease, endoRNAse, 2'-0-ribose methyltransferase	[8*]
	Elbasvir	Antiviral	SARS-CoV-2	+ssRNA	+ssRNA	[4*, 5]
	Entecavir	Antiviral	SARS-CoV-2	+ssRNA	RdRp, helicase, 3'-to-5'exonuclease	[8*, 30]
	Etravirine	Antiviral	SARS-CoV-2	+ssRNA	RdRp	[8*]
	Favipiravir	Antiviral	SARS-CoV-2	+ssRNA	RdRp	[18, 36*]
	Ganciclovir	Antiviral	SARS-CoV-2	+ssRNA	RdRp, helicase, 3'-to-5'exonuclease	[8*, 30]
	Grazoprevir	Antiviral	SARS-CoV-2	+ssRNA	RdRp, helicase, 3'-to-5'exonuclease, endoRNAse	[5, 8*]
	Hydroxychloroquine	Antimalarial	SARS-CoV	+ssRNA	+ssRNA	[16, 18, 25, 26, 36*]
	Hydroxychloroquine, azithromycin	Antimalarial and antibiotic	SARS-CoV-2	+ssRNA	Inhibition of proinflammatory cytokine production/ spike protein and ACE2 receptor	[25, 26]
	Homoharringtonine	Anticancer	SARS-CoV-2	+ssRNA	Inhibit viral replication	[14]
	Imatinib	Anticancer	SARS-CoV	+ssRNA	Protease inhibitor	[2]
	Indinavir	Antiviral	SARS-CoV-2	+ssRNA	Helicase	[8*, 28]
	Indomethacin	Anti-inflammatory	SARS-CoV-2	+ssRNA	Nsp7 (non-structural viral protein)	[37]
	Ivermectin	Antiprotozoal	SARS-CoV-2	+ssRNA	Inhibit viral replication	[50]
	Lamivudine	Antiviral	SARS-CoV-2	+ssRNA	RdRp	[8*]
	Lomibuvir	Antiviral	SARS-CoV-2	+ssRNA	RdRp, helicase, 3'-to-5'exonuclease, endoRNAse	[8*]
	Lopinavir	Antiviral	SARS-CoV-2	+ssRNA	Helicase, 3'-to-5'exonuclease, endoRNAse	[8*, 18, 36*]
	Mefloquine	Antimalarial	SARS-CoV	+ssRNA	+ssRNA	[26, 36*]
	Nafamostat mesilate	Anticoagulant	SARS-CoV-2	+ssRNA	Spike protein	[18]
	Nelfinavir	Antiviral	SARS-CoV-2	+ssRNA	Helicase, endoRNAse,+ssRNA	[8*, 36*, 39]
	Nevirapine	Antiviral	SARS-CoV-2	+ssRNA	RdRp, helicase	[8*]
	Penciclovir	Antiviral	SARS-CoV-2	+ssRNA	RdRp, helicase, 3'-to-5'exonuclease	[8*, 17]
	Raltegravir	Antiviral	SARS-CoV-2	+ssRNA	RdRp, helicase, 3'-to-5'exonuclease, endoRNAse	[8*]
	Remdesivir	Antiviral	SARS-CoV-2	+ssRNA	3C-like proteinase, RNA, helicase, 3'-to-5'exonuclease, endoRNAse, 2'-0-ribose methyltransferase	[1, 8*, 18, 36*]
	Ribavirin	Antiviral	SARS-CoV-2	+ssRNA	RdRp	[54]
	Rilpivirine	Antiviral	SARS-CoV-2	+ssRNA	RdRp	[8*]
	Ritonavir	Antiviral	SARS-CoV-2	+ssRNA	3C-like proteinase, RNA, helicase, 3'-to-5'exonuclease, endoRNAse	[8*, 18, 36*]
	Lopinavir–Ritonavir	Antiviral	SARS-CoV-2	+ssRNA	Protease inhibitor	[11]
	Saquinavir	Antiviral	SARS-CoV-2	+ssRNA	RdRp	[8*, 9]
	Simeprevir	Antiviral	SARS-CoV-2	+ssRNA	3C-like proteinase, helicase, 3'-to-5'exonuclease, endoRNAse	[8*, 19]
	Teicoplanin	Antibacterial	SARS-CoV	+ssRNA	Inhibit viral replication	[6, 12]
	Telaprevir	Antiviral	SARS-CoV-2	+ssRNA	Helicase, 3'-to-5'exonuclease, endoRNAse	[8*]
	Triflurdine	Antineoplastic	SARS-CoV-2	+ssRNA	RdRp	[8*]

*Studies using deep learning methods
Different findings by deep learning method
Findings by experimental/clinical trials which are not the same as findings by deep learning
Same findings by both DL and other methods
Clinical Drug combination synergy

approved drugs that can be repurposed to treat COVID-19 [4]. Using the combined method, a list of 49 most promising FDA approved drugs with best consensus KIBA scores and AutoDock vina binding affinity values against selected SARS-CoV-2 viral proteins were generated. Other models that were deployed included end-to-end DL models using two CNNs, two LSTM, CNN-LSTM, and graph attention network GAT-CNN [36], as shown in Table II.

TABLE II
CHARACTERISTICS OF DEEP LEARNING-BASED DR MODELS FOR COVID-19

Deep Learning Architecture	Molecule Transformer DTI (MT-DTI) [8, 51]	BiLSTM-CNN model [4]	Four end-to-end models [36]
Dataset	Extracted from Drug Target Common (DTC) database and BindingDB database	KIBA dataset comprises assays of kinase proteins family and the associated inhibitors.	Compiled from resources such as MOSES [43] ChEMBL, UniProt, PubChem and NCBI.
Input representation	1-D canonical SMILES and protein sequences	1-D SMILES and protein sequences	1-D SMILES and protein sequences for all his models except for GAT-CNN model which used graph-based representation of a drug molecule
Deep learning model	Multi-layered Molecule Transformer with "self-attention" mechanism. 2 blocks of character-embedded Protein CNNs consisted of one embedding layer, three CNN layers and one max pooling layer. Dense layers to model interactions between a drug and a protein MT-DTI model 	Network consisted of one CNN block and one BiLSTM block 3 layers of CNN was used for learning protein representation. Maximum length is 1000 characters BiLSTM block was used for to learn representation of drugs. Separate representations were concatenated and passed through 3 fully connected layers Bi-LSTM-CNN model 	(a) 2 separate CNN blocks (b) 2 separate LSTM blocks (c) 1 block of CNN and one block of LSTM, connected in parallel (d) Graph Attention Networks-Convolutional Neural Networks (GAT-CNN) Model 
Embedding, pre-training & transfer learning	Adopted character-embedded Masked Language Model (BERT) for re-training MT on publicly available 97 million chemical compounds. Tokenized each drug molecule to a fixed size of 100 characters. Used 128-dimensional vectors for the embedding layers of Protein sequences.	Employed byte pair encoding to encode SMILES of ligands and protein sequences	Used drug autoencoder consisted of a teacher-forcing multi-layered LSTM (TF-LSTM) encoder, LSTM decoder and a sequence to sequence (seq2seq) model to learn low dimensional representation of SMILES strings in unsupervised setting. Used viral protein autoencoder consisted of multi-layered convolution and subsampling layers followed by a fully connected layer to learn low representation of viral protein sequences.

IV. ANTI-COVID-19 DR USING DL: ADVANTAGES AND DISADVANTAGES

Table I gives a snapshot of the existing development in DR and the prediction of repurposed drugs for COVID-19. It provides a platform for analyzing diverse findings and identifying promising drug candidates that can be repurposed to treat COVID-19. Some drugs, which tested effective using traditional methods, were also predicted to be repurposed drugs for COVID-19 by DL. However, some drugs, which tested effective *in vivo* and *in vitro*, were not predicted by DL methods. The differences in these findings can be attributed to advantages and disadvantages of the approaches adopted, as shown in Table III.

A. Requiring No Prior Domain Knowledge

In practice, experimental studies on DR are done using pre-existing drugs that are already known to have inhibitory effects on other similar coronaviruses such as SARS-CoV and/or MERS-CoV, or nucleotide analogs via these criteria such as similarity in size and structure to natural nucleotides, including

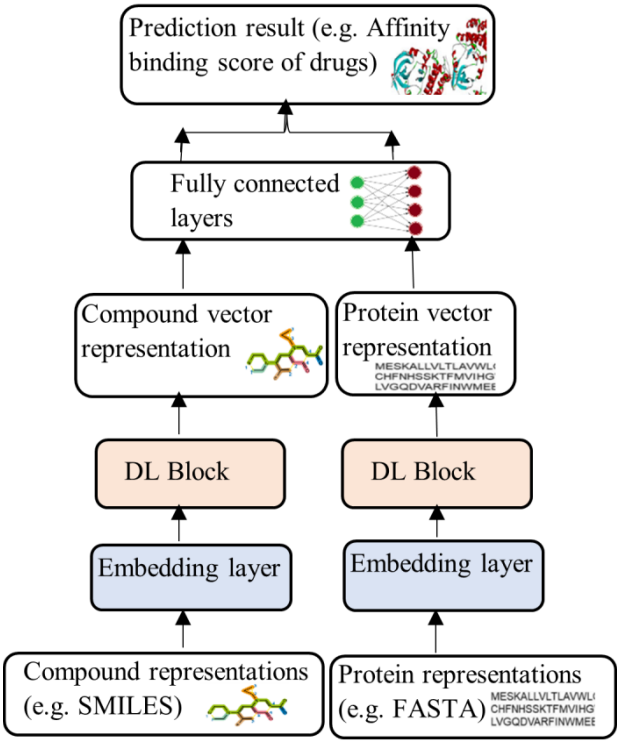


Fig. 3. General deep learning framework used for DR.

the ability to fit within the active sites of the polymerase [30]. On the contrary, DL approaches have the advantage of having the capacity to detect drug–target interactions without having prior domain knowledge. It can successfully identify drugs that target epidermal growth factor receptor that is used in clinics [8]. With the establishment of powerful and easy-to-use DL toolkit such as DeepPurpose, the problem of technical barrier is further addressed. DeepPurpose allows any user, including non-DL technical experts to apply a DL approach in real-life simulation [65]. Because of its unique strength, DL is a powerful tool for identifying and predicting the right drugs to be repurposed for new diseases within a short time frame and in a cost-effective way. However, we cannot deny the fact that having strong domain knowledge can augment the process of designing more precise and accurate predictive models. For DR for COVID-19, if we know more about drug side effects and the complex biological mechanisms underlying the disease such as having good insight on how the virus enters the cell and which tissues are susceptible, in which part of the virus (spike protein) initiates the merging of the viral envelope with the host cell cytomembrane, our expert knowledge in this area can improve the design of DL model and the model would then be able to generalize real-world situations better for repurposing drugs with less side effects.

B. Identification of Multitarget Drugs as a Strength

It is evident from ongoing clinical studies of COVID-19 that treatments with a single drug are unlikely to be sufficient unless the drug can act via the inhibition of multiple pathways. Multitarget drugs have two or more pharmacophores that are structurally overlapping. Table I shows that DL has the ability to identify multitarget drugs. For example, atazanavir was

TABLE III
ADVANTAGES AND DISADVANTAGES OF USING DEEP LEARNING FOR REPURPOSING COVID-19 DRUGS

Advantages	Disadvantages
Enabling inexpensive, rapid and effective detection of drug-target interactions and repurposing [8, 51, 71, 72].	Still requires inputs from relevant experts to ensure its reliability in predicting drug candidates [69, 70, 71].
The potential to aid in designing and discovery of therapies by processing vast datasets and complex pattern recognition capacity involving genomics, proteomics, microarray data and clinical trial data [66, 68, 69, 71, 72].	Due to potential biases in different encoding models and dataset utilized, deep learning models are likely to provide different drug predictions [8, 4, 36].
The ability to identify drugs that target several COVID-19 targets such as variational autoencoders (VAE) which allows the generation of specific molecules with greater diversity, overcoming the limitation of ligand-based designs [58, 69, 71].	Lacks capacity to predict or repurpose synergistic drug combinations as potential treatment for COVID-19, such as those seen in certain clinical studies [25].
Combined with transfer learning technique, it could predict, repurpose, design and discover new COVID-19 therapies using predictive models [69, 71].	Despite strong applicability, it is likely a black box which could provide predictions that are not well understood. Hence, there is a need for more insight into interpretability.
Natural language processing (NLP) can transform unstructured texts into structured data, which can be analyzed appropriately to gain new insights. Various text mining-based tools have been developed: - PISTON, a tool that can predict drug side effects and drug indications, using NLP and topic modeling. - STITCH, text mining-driven database, which contains information on interactions between proteins and chemicals/small molecules [69, 70, 71].	Most approaches adopted for repurposing COVID-19 drugs used SMILES strings and protein sequences as inputs [4,8, 36, 51]. The usage of molecular graphs as molecular topology with nodes and edges representing atoms and chemical bonds are common in most research studies for drug discovery and prediction of drug side effects [71, 73]. Models using SMILES representation of molecular structures as an input for drug-repurposing may have a low rate of valid molecules due to lack of topological information [47].
Ability to predict side effects of new drugs using biological, chemical, and semantic information extracted from structured and unstructured big data [71, 73].	No deep learning approaches have been deployed to design therapies against mutated COVID-19 strains.

predicted by DL to have a potential binding affinity to bind to RdRp, helicase, 3'-to-5' exonuclease, 2'-o-ribose methyltransferase, and endoRNAse. The DL also predicted interactions of grazoprevir with RdRp, helicase, 3'-to-5' exonuclease, and endoRNAse. In view of the strong ability of DL to identify multitarget drugs, we strongly believe that it can provide a new avenue for the therapeutic management of SARS-CoV-2 infection.

C. Reconsidering Reliability of DL in DR

Different studies (Tables I and II) have used different DL models for repurposing COVID-19 drugs. Table I shows that some of the COVID-19 repurposed drugs that have been experimentally tested and could be incorporated into RdRp of SARS-CoV-2 are abacavir, entecavir, and ganciclovir, which are also the drugs predicted by DL for COVID-19. Other repurposed drugs, which are the same, are boceprevir, lopinavir, nelfinavir, and remdesivir. The same results obtained provide a molecular basis for further evaluation of these drugs

in SARS-CoV-2 virus inhibition to test their efficacy for the development of potential COVID-19 therapeutics. It also serves as strong evidence on the reliability of the DL approach for repurposing drugs, as proven computationally in many drug-discovery studies [40], [51], [60]. However, Table I also shows that some differences are observed between the clinical findings and results obtained using DL. These intriguing findings need to be tested experimentally and clinically. The DL frameworks for repurposing drugs in Table II must also be reanalyzed to find potential solutions to overcome this problem. Careful scrutiny of DL algorithm, its architectural framework, as well as data used to train a model are particularly important for verifying correlations made by a DL model. The existing DL model that trained on one set of data is unable to take into consideration many external impacting factors on a patient. For example, the effects of COVID-19 on a patient will change over time, so drugs and method used for treating a patient need to be modified according to the condition of the illness. The models can certainly help to point us in the right direction by identifying repurposed drugs that can safely and effectively treat COVID-19 to avoid having to go through time-consuming and expensive drug development process; however, we still have to run experiments in the laboratory to eventually validate the effectiveness of the repurposed drugs.

D. Room for Drug Combination Synergy

Drug combination therapy has been established clinically for treating COVID-19. For example, when comparing the effect of hydroxychloroquine treatment as a single drug and the effect of hydroxychloroquine and azithromycin in combination, it was found that 100% of patients treated with hydroxychloroquine and azithromycin combination were cured compared with only 57.1% of patients treated with hydroxychloroquine alone [25].

GC376, a preclinical inhibitor against the feline infectious peritonitis (corona) virus (FIPV) that can efficaciously inhibit SARS-CoV-2 by targeting Mpro, was combined clinically with remdesivir, a nucleotide analog inhibitor to fight against viral RdRp [21]. When the two drugs are combined, both GC376 and remdesivir inhibitors bonded to the active side of SARS-CoV-2 protease Mpro and became the main mechanism of inhibition [21]. Clinical findings show that a drug combination may provide critical information for the optimization and design of more potent inhibitors against the SARS-CoV-2 virus. Based on the success of DeepSynergy (which uses combined information about cancer cell lines and drug combinations in its hidden layers to form a combined representation that eventually leads to accurate predictions of drug synergies [45]), we are convinced that with the availability of big data and the advancement of technology, the DL approach can be a valuable tool for selecting and repurposing novel synergistic drug combinations for the treatment of COVID-19 patients.

E. Need for More Insight Into Interpretability

The attention mechanism was adopted to improve the predictive power of DL and to make the model more interpretable [24], [32], [51], [60]. As shown in Tables I and II, DL models built with the attention mechanism give more similar drug predictions for clinical repurposed drugs. It is also shown in Fig. 4 that DL models with the attention mechanism are able to provide biological insights to understand the nature of the predicted interactions in drug discovery [60]. The black regions in Fig. 4 indicate the binding sites for the complex of imatinib and Tyrosineprotein kinase SYK (PDB ID: 1XBB) and the complex of aspirin and Phospholipase A2 (PDB ID: 1TGM) [60]. Even though DL with the attention mechanism has shown great promise in drug discovery by highlighting the features that are important to the prediction, the model is still unable to explain feature interaction and why certain features are more important than others. It is unclear what relationship exists between attention weights and model outputs [65]. When assessing whether attention weights could provide meaningful "explanations" for predictions, it was found that the learned attention weights were frequently uncorrelated with gradient-based measures of feature importance and that the standard attention modules could not provide meaningful explanations to neural network behavior [65].

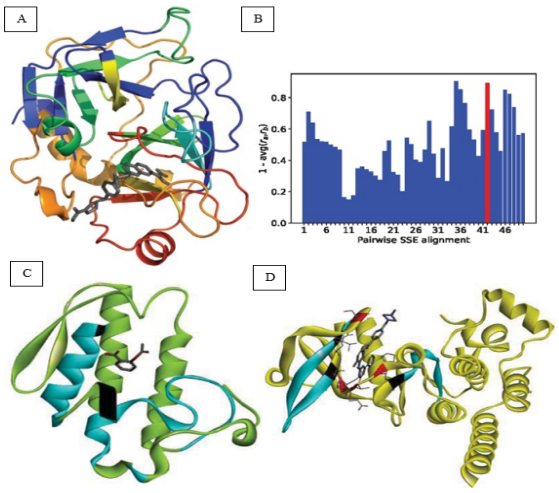


Fig. 4. Warmer color in A indicates features using "attention" mechanism. The highlighted red line in B indicates the binding site of drug and protein sequence. Black regions (C and D) indicate binding sites marked by the attention mechanism [24], [32], [51], [60]. The above shows that model with attention mechanism can give an insight on biological interpretation [23].

V. Future Perspective

From the perspective of artificial intelligence, interpretable and more reliable DL frameworks must be developed to take advantage of the availability of big data and the advancement of technology. The anticipated new generation of DL models must possess the interpretability attribute, possess the capacity to identify multitarget drugs, promote drug combination synergy, and predict the side effects induced by single drugs as well as drug combinations. The past findings suggest that further improvements are needed to improve the DL methods to support experimental therapeutic options.

A. Utilization of Big Network-Based Data

So far, most DR studies focus on using a drug compound and protein sequence data to predict drug–target binding affinity scores or binding energy. For viral replication, the SARS-CoV-2 must attach to a host cell, ACE2, to gain entry into human cells and release its RNA inside the cell. The virus will either infect and kill the cell or alter the cell's functions or, sometimes, the infected cell loses control over normal cell division and becomes cancerous. Many antiviral drugs work by interfering with the replication of viruses, and if a person has a bacterial infection in addition to a viral infection, an antibiotic is often necessary. To repurpose drugs, the inclusions of virus–drug interactions and virus–protein interactions are important to offer a deep biological perspective in capturing the relationships between drugs–viral protein interactions and drugs–host protein interactions [58], [59]. For example, in addition to information on drug-disease associations, the relationships between drug–drug interactions, drug–viral protein interactions, and drug side effects can be included as input data to the DL model to leverage the capability of DL to capture highly nonlinear, heterogeneous networks that contain diverse information to better learn the representations of drugs and proteins.

B. Using Drug Molecular Structure as Input Data

A sequence-based method that focuses on exploiting omics-scale data of protein sequences and SMILES strings helps to overcome the limited availability of drug structural data. Table II shows that all the aforementioned DL methods, except the GAT-CNN model, adopted the sequence-based method by deploying 1-D drug molecular structure as input data despite the fact that SMILES is too simple to deliver topological information of molecular structures, and when a molecule is projected into the latent space of a DL autoencoder, the molecule may end up being projected to very different areas of the latent space, which can lead to relatively low learning accuracy [10]. To elucidate the correct molecular structure–property relationships from the existing data, it is necessary to use a molecular graph as it can intuitively and concisely express molecules with 2-D topological information to produce highly accurate predictions [10], [23], [46], [47].

C. Adverse Drug Reactions

Medications used to treat COVID-19 may induce neurologic and psychiatric symptoms or other side effects [24]. Cytochrome p450 enzymes are affected by protease inhibitors (lopinavir, ritonavir, and darunavir), which could lead to neurotoxicity by altering plasma concentrations of multiple psychotropic drugs [24]. The lopinavir–ritonavir combination may induce drug–drug interaction as it has been associated with bilateral sensorineural hearing loss after four weeks of treatment and depressive symptoms [24]. With the availability of a massive amount of heterogeneous drug-related data, the same DL model used for DR can be deployed to predict the adverse drug reactions (ADRs) of repurposed drugs and drug–drug interaction caused by a repurposed drug combination used against COVID-19.

D. BERT-Based Model for Smarter Protein Sequence Generation

Beck *et al.* [8] modified the existing BERT [15] to represent molecules by changing the cost function. Modified BERT was used to retrain drug molecules by encoding the relationship among long-distance tokens (atoms) in a sequence. They also modified the protein feature extraction model introduced by Öztürk *et al.* [40] by adding an embedding layer. However, due to the length of a protein sequence that is ten times longer than a molecule sequence on average, the pretraining took about 58 h [51], and hence, we recommend leveraging a knowledge distillation technique during the pretraining phase using DistilBERT to reduce the size of a BERT model by 40% while retaining 97% of its language understanding capabilities and being 60% faster [49]. The smaller, faster, and lighter DistilBERT model is cheaper to pretrain and its capabilities for on-device computations have been demonstrated.

E. Augmented DL Model

Table II shows that MT-DTI was built with a self-attention mechanism to capture the relationship among atoms in a sequence to understand a molecule sequence [8]. The attention mechanism can differentiate atoms in different chemical environments by considering the interaction of each atom with its neighbors [47], [51]. The simultaneous use of both attention and gated skip connections (graph convolutional network (GCN) + attention + gate) results in the smallest mean average error (MAE) compared to the model using only GCN + attention or GCN + gate or vanilla GCN [47]. The augmented DL with attention and gate mechanisms can identify important molecular substructures that are directly related to molecular properties [47], hence presenting a good opportunity to be adopted for the DR initiative.

F. Transforming From "Black Box" to "Glass Box"

The lack of interpretability or the "black box" issue of DL has prevented us from gaining more insight into model behavior. Several approaches have been explored to interpret the predictions produced by deep neural networks. Attention or attention with gated skipped connection augmented DL model can identify features that are important to a model's prediction on a given input [47]. However, these standard attention modules are unable to provide meaningful explanations to neural network behavior [65]. The state-of-the-art language models that use multihead self-attention, such as BERT and its variants, can be used to identify and extract important features that associate with drugs and protein sequences [51]. Deployment of multihead self-attention mechanism in studying chemical molecules can capture relationship among atoms in a sequence to provide a better molecule relationship [51]. Multihead self-attention mechanisms, as shown in the following equation, are introduced to allow us to identify important attributions and give better interpretability:

$$\text{Attention}(Q, K, V) = \text{softmax}\left(\frac{QK^T}{\sqrt{dk}}\right)V$$

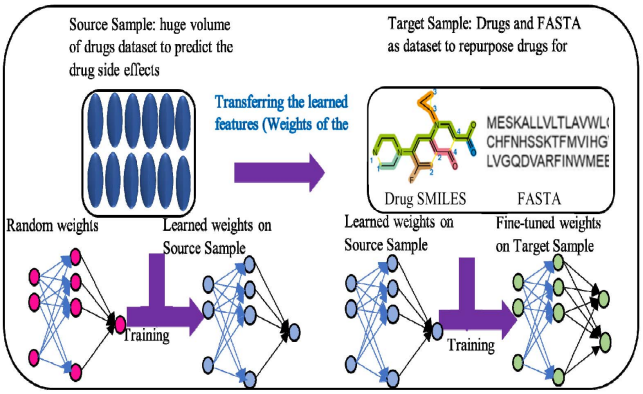


Fig. 5. Illustration shows the concept of transfer learning. (a) Source sample consists of huge volume of drug datasets to predict the drug side effects. Random weights were trained to achieve learned weights on source sample. The learned features from (a) were transferred to (b), for example, the weights of the network were transferred to (b). (b) Target sample that includes drugs SMILES and FASTA. The learned weights on the source sample are then trained to achieve fine-tuned weights on source sample.

where the three values are: V is a value, K is a key, and Q is a query. A scaling factor of $1/\sqrt{d_k}$ is added to ensure that the dot product does not grow too large in magnitude with respect to d_k that is the dimension of the key.

Besides attention mechanisms, in drug discovery, the attribution method is used to extract chemical substructures from a large toxicity dataset for classifying them into toxic and nontoxic chemical compounds [62]. It was found that the fully connected neural network consisting of four rectified linear unit (RELU) layers with 2048 hidden units each was able to cluster positive attributions to form substructures and differentiate indicative parts from irrelevant parts of the input [62]. Despite having the ability to identify the most relevant components of a compound, the attribution method is regarded as "local" interpretability method that is able to quantify the effect of one nucleotide, but it is unable to read the effect that all substructures have on model predictions [63]. In short, the attribution method can offer only the first-order approximation to a complex nonlinear function, but it fails to capture higher order effects caused by drug–protein interaction or interactions between atoms and bond features [64]. In order to understand a model's behavior, a DL model must be able to learn, explain not only feature attributions but also generate intuitive interactions that can explain interactions, and can be applied to any neural network architecture, paving the way to transform the "black box" into a "glass box" for DR.

VI. Proposed DL Frameworks for COVID-19 DR

Many research studies have been conducted to explore the possibility of increasing interpretability of DL. Transfer learning technique was used to help fast track the development of AI model and reduce the model training computational costs [67]. It is a technique where a model is trained on a large dataset and the knowledge learned is then transferred to perform similar tasks on another smaller dataset, as shown in Fig. 5. It is widely used to combat with the limitation of sample size for adapting generalizability [66].

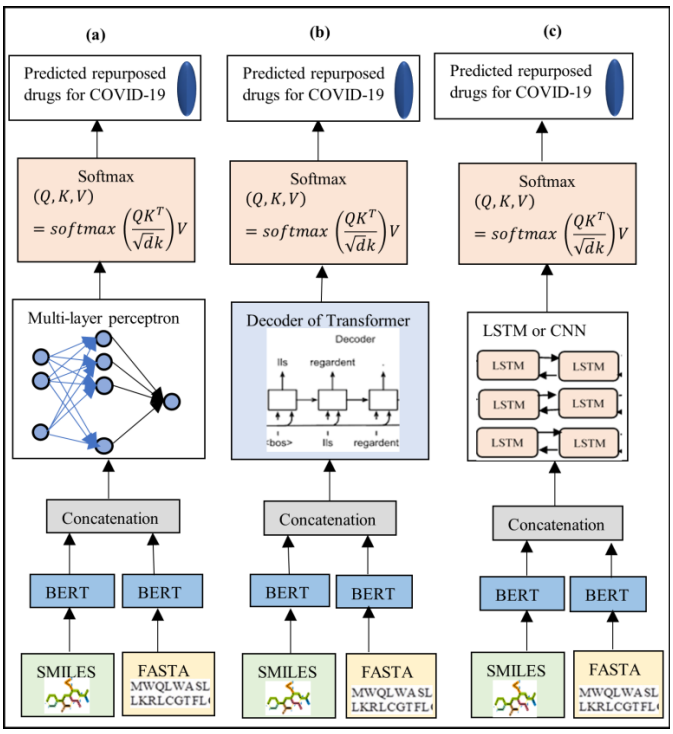


Fig. 6. Illustration of four proposed encoder–decoder frameworks for predicting repurposed drug candidates for COVID-19. The two inputs are represented by molecular structures and protein sequences. After training the task-specific datasets using pretrained BERT-based models, the outputs from the pretrained encoders are concatenated and directed to a decoder. (a) Two inputs, drug molecules (SMILES) and protein molecules (FASTA), which are processed by BERT. The outputs are then concatenated before processed using multilayer perceptron with an activated softmax to predict repurposed drug candidates for COVID-19. (b) Two inputs, drug molecules (SMILES) and protein molecules (FASTA). The two inputs are processed by BERT and the outputs are concatenated before processed by transformer with activated softmax to predict repurposed drugs. (c) Two inputs, drug molecules (SMILES) and protein molecules (FASTA). The two inputs are processed by BERT and the outputs are then concatenated before processed using either LSTM or CNN with activated softmax to predict repurposed drug candidates for COVID-19.

For repurposing drugs for COVID-19, BERT or its variants can be pretrained on large drug molecule and protein sequence datasets. The weights and architect of the pretrained models can then be transferred and applied in the smaller dataset of the COVID-19 DR case study. The output layer of the pretrained model can be removed, and the entire model can be retrained on the smaller dataset by initializing all the weights randomly. It can then be used to extract features from the smaller dataset for predicting repurposed drugs.

Pretrained BERT-based models with SMILES and protein sequences can learn and process billions of chemical properties and protein features, and these models can be used to transfer the learning to downstream tasks for identifying binding sites and molecular structures [51]. We suggest to pretrain the networks to significantly reduce learning time and resources for achieving desirable performance. Our proposed frameworks for repurposing COVID-19 drugs model after the transformer model that consists of encoder–decoder architecture. The SMILES strings are fed as input to one pretrained encoder, while protein sequences are fed as input to another pretrained encoder, as shown in Fig. 6. The fine-tuned

networks will extract meaningful representations that are then concatenated and fed as an input to the decoder. The decoder uses these representations to predict COVID-19 repurposed drugs. For this type of model, the encoders are pretrained BERT-based models, but the decoder is randomly initialized. Since the BERT-based models are pretrained with SMILES strings and protein sequences independently, they may overfit; on the other hand, because the decoder is not pretrained, it may underfit and will cause a discrepancy during fine-tuning. To overcome this problem, three Adam optimizers must be used with one optimizer for each encoder and the other for the decoder. Similarly, different learning rates have to be set for the encoders and decoder. A lower learning rate has to be set for the pretrained encoders to smooth decay for the encoder. A variety of decoders, such as multiperceptron layers or transformer decoder or LSTM or CNN, can be used where the second-order derivatives can then be applied to allow the model to identify and understand the reasons behind the binding activities. The proposed frameworks can carry out regression work to repurpose drugs for treating COVID-19. They can also identify features that contribute to binding activities, interpret feature interaction at binding sites, as well as quantify pairwise feature interactions to unveil the "black box" characteristics of DL.

VII. Conclusion

Although significant progress has been made in the field of repurposing drugs against COVID-19 using the DL approach, challenges still exist in terms of giving accurate predictions for effective repurposed drugs. We suggest that DL DR against COVID-19 could benefit from using big network-based data, adopting a 2-D graph molecular structure as input data and pretraining the input data using the BERT-based network before feeding the data into an augmented DL network to explore the relationships between drug–target–disease heterogeneous networks for prediction. Because the existing DP models are only able to identify the input features that are relevant to the prediction but are unable to give a higher order explanation on the relation between these features, the development of more advanced DL models is a rewarding topic for future research to identify combined drugs, which can act together to fight against a complex disease such as COVID-19. Interpretable DL constitutes another promising direction on integrating explanations into the new generation DL to improve its performance or reduce its flaws, to give more accurate predictions on repurposing single and combined drugs against viral infections such as COVID-19.

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