The 2019 novel coronavirus (SARS-CoV-2) pandemic has resulted in more than a million deaths, high morbidities, and economic distress worldwide. There is an urgent need to identify medications that would treat and prevent novel diseases like the 2019 coronavirus disease (COVID-19). Drug repurposing is a promising strategy to discover new medical indications of the existing approved drugs due to several advantages in terms of the costs, safety factors, and quick results compared to new drug design and discovery. In this work, we explore computational data-driven methods for drug repurposing and propose a dedicated graph neural network (GNN) based drug repurposing model, called Dr-COVID. Although we analyze the predicted drugs in detail for COVID-19, the model is generic and can be used for any novel diseases. We construct a four-layered heterogeneous graph to model the complex interactions between drugs, diseases, genes, and anatomies. We pose drug repurposing as a link prediction problem. Specifically, we design an encoder based on the scalable inceptive graph neural network (SIGN) to generate embeddings for all the nodes in the four-layered graph and propose a quadratic norm scorer as a decoder to predict treatment for a disease. We provide a detailed analysis of the 150 potential drugs (such as Dexamethasone, Ivermectin) predicted by Dr-COVID for COVID-19 from different pharmacological classes (e.g., corticosteroids, antivirals, antiparasitic). Out of these 150 drugs, 46 drugs are currently in clinical trials. Dr-COVID is evaluated in terms of its prediction performance and its ability to rank the known treatment drugs for diseases as high as possible. For a majority of the diseases, Dr-COVID ranks the actual treatment drug in the top 15.
I. INTRODUCTION

The dreadful pandemic outbreak of the coronavirus disease 2019 (COVID-19) has affected about 56 million people with more than a million deaths worldwide as of November 2020. The June 2020 Global Economic Prospects [1] estimated a 5.2% downfall in the global gross domestic product (GDP) in 2020 that would lead to the worst economic slowdown in history after the Second World War. The disease affects mammals’ respiratory tract and shows symptoms similar to pneumonia, causing mild to severe respiratory tract infections [2]. The pathogen that causes COVID-19 belongs to the Coronaviridae family, which is a family of enveloped positive-strand RNA viruses that affect mammals, birds, and amphibians. The name coronavirus (CoV) is derived because of the crown-shaped spikes that project from their surface. Coronaviruses are majorly grouped into four genera: alphacoronavirus, betacoronavirus, deltacoronavirus, and gammacoronavirus. While deltacoronaviruses and gammacoronaviruses infect birds, alphacoronaviruses and betacoronaviruses infect mammals [3]. Out of the seven known strains of human CoVs (HCoVs), the three betacoronaviruses, namely, middle east respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV), and the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) produce severe symptoms. In the past two decades, the world witnessed highly fatal MERS-CoV and SARS-CoV that led to global epidemics with high mortality. Although the 2003 SARS-CoV outbreak was controlled, it infected 8098 individuals and resulted in 774 deaths. As of November 2019, 2494 cases and 855 deaths were reported due to MERS-CoV, with the majority in Saudi Arabia [3]. In December 2019, similar cases were again reported in Wuhan City, China [4], wherein investigations confirmed it to be the third novel CoV, i.e., SARS-CoV-2, which is also referred to as HCoV-2019, 2019-nCoV, or colloquially simply as coronavirus [5]. SARS-CoV-2 being highly contagious, on 30 January 2020, the World Health Organization (WHO) declared it as a public emergency of international concern warning all the countries with vulnerable health care systems [6].

The current treatment for COVID-19 is completely supportive and symptomatic as there are no specific known medicines. Several research groups around the world are trying to develop a vaccine that would prevent and treat SARS-CoV-2. Looking at the current unpredictable trajectory of how the disease spreads and the life cycle of the virus, there is an urgent need to develop preventive strategies against it. Given this strict timeline, a more realistic solution lies in drug repurposing or drug repositioning, which aims to iden-
identify new medical indications of approved drugs. Drug repurposing offers several advantages. It has a low risk of failure as the drug has already been approved with less unknown harmful adverse effects. It reduces the time frame for drug development as the drugs have passed all the pre-clinical trials and safety norms. Finally, compared to the discovery of a new drug, drug repurposing requires less economic investment and puts fewer lives of volunteers (particularly kids) involved in clinical trials at risk [7]. Some of the examples of repurposed drugs are Sildenafil, which was initially developed as an antihypertensive drug was proved effective in treating erectile dysfunction by Pfizer [7], and Rituximab that was originally used against cancer was proved to be effective against rheumatoid arthritis [7], to name a few. Even for COVID-19, drugs like Remdesivir (a drug for treating Ebola virus disease), Chloroquine/Hydroxychloroquine (antimalarial drugs), Dexamethasone (anti-inflammatory drugs) are being repurposed and are under clinical trials as per the International Clinical Trials Registry Platform (ICTRP), which is a common platform maintained by WHO to track the clinical trial studies across the world.

Drug repurposing involves identifying potential drugs and monitoring their in vivo efficacy and potency against the disease. The most critical step in this pipeline is identifying the right candidate drugs, for which experimental and computational approaches are usually considered. To identify potential drugs experimentally, a variety of chromatographic and spectroscopic techniques are available for target-based drug discovery. Phenotype screening is used as an alternative to target-based drug discovery when the identity of the specific drug target and its role in the disease are not known [7]. Recently, computational approaches are receiving attention due to the availability of large biological data. Efficient ways to handle big data has opened up many opportunities in the field of pharmacology. Zitnik, et al. [8] elaborates several data-driven computational tools to integrate large volumes of heterogeneous data and solve problems in pharmacology such as drug-target interaction prediction (identify interactions between a drug and its target genes), drug repurposing, and drug-drug interaction or side effect prediction, to list a few. Hence this field is known as computational pharmacology. Many standard machine learning (ML) and deep learning (DL) techniques have been applied in computational pharmacology. Drug-drug interaction was formulated as a binary classification problem and solved using ML techniques like random forest, support vector machines (SVM), and naive bayes [9], and using DL models like deep multi-layer perceptrons and recurrent neural networks, to name a few. DL techniques often outperform standard ML techniques [10] [11]. However, these methods lack the ability to capture the structural information in the data, specifically the connections between
different biological entities (e.g., interactions between drugs and genes or between drugs and diseases). A
natural and efficient way to represent such structural information is to construct a graph with nodes repre-
senting entities like drugs, genes, diseases, etc., and edges representing the complex interactions between
these entities. Graph neural networks (GNNs) capture the structural information by accounting for the
underlying graph structure while processing the data. Decagon, a GNN-based model designed for pre-
dicting the side effects of a pair of drugs has proved its capability by outperforming the non-graph based
machine learning models in terms of its prediction performance [12]. Similarly, drug repurposing has
been studied using computational methods such as signature matching methods, molecular docking, and
network-based approaches. Recently, network-based and machine learning approaches [13–17], and GNN
based approaches [18] and [19] have been proposed for drug repurposing.

In this work, we propose a GNN architecture for COVID-19 drug repurposing called Dr-COVID, which
is a dedicated model for drug repurposing. We formulate our problem by constructing a four-layered het-
erogeneous graph comprising drugs, genes, diseases, and anatomies. We then build a deep learning model
to predict the links between the drug and disease entities, where a link between a drug-disease entity sug-
gests that the drug treats the disease. Specifically, Dr-COVID is based on the scalable inception graph
neural network (SIGN) architecture [20] for generating the node embeddings of the entities. We propose
a quadratic norm scoring function that rank orders the predicted drugs. All the network information and
node features are derived from the drug repurposing knowledge graph (DRKG) [21]. DRKG is a biological
knowledge graph compiled using several databases, and comprises entities like drugs, diseases, anatomies,
etc., and their connections. We leverage their generic set of low-dimensional embeddings that represent
the graph nodes and edges in the Euclidean space for training. We validate Dr-COVID’s performance on
the known drug-disease pairs. Although we present the results and analysis for COVID-19, Dr-COVID is
generic and is useful for any novel human diseases. From a list of 150 drugs predicted by Dr-COVID for
SARS-CoV-2, 46 drugs are currently in clinical trials. For a majority of diseases with known treatment, the
proposed Dr-COVID model ranks the approved treatment drugs in the top 15, which suggests the efficacy
of the proposed drug repurposing model. As we use the SIGN architecture that does many computations
beforehand, Dr-COVID is computationally efficient as compared to the other GNN-based methods [18, 19].
Specifically, in contrast to [18] we include additional entities such as anatomies as the side information in
our graph. This additional information provides indirect interactions between the disease and gene entities.
The norm scorer we design captures correlations between the drug and disease pairs, and as a consequence, the model predicts many more drugs (e.g., Brexanolone) that are in clinical trials as compared to the existing GNN-based and network-based drug repurposing models.

II. RESULTS AND DISCUSSION

In this section, we present the drugs predicted by Dr-COVID for COVID-19 according to their pharmacological classifications, and elaborate on their roles in treating the disease. We individually predict drugs for the 27 entities that specify the SARS-CoV-2 genome structure as identified by Gordon et al. [22]. This genome structure includes structural proteins, namely, envelope (SARS-CoV2-E), membrane (SARS-CoV2-M), nucleocapsid (SARS-CoV2-N), surface (SARS-CoV2-spike) proteins, 15 non-structural proteins (nsp), and open reading frames (orf) that encode the accessory proteins. We also predict drugs for 6 diseases related to CoV, namely, SARS-CoV, Avian infectious bronchitis virus (IBV), MERS-CoV, CoV-229E, CoV-NL63, and Murine coronavirus (MHV). We choose the top 10 ranked predicted drugs for all these disease targets, combine them, and present them as a single list of 150 drugs (after removing the duplicate entries). We refer to these 33 (i.e., 27 entities related to the SARS-CoV-2 genome structure and 6 CoV diseases) as COVID-19 nodes. Out of these 150 drugs, 46 drugs are in clinical trials in different phases. We provide the predicted scores of all the drugs for all the COVID-19 nodes using Dr-COVID in our github repository. The software to reproduce the results are available at: https://github.com/siddhant-doshi/Dr-COVID

Fig 1 gives a heatmap indicating the ranks of these 150 drugs. It is a matrix representation in which the drugs are listed on the vertical axis and COVID-19 nodes on the horizontal axis. All the 150 drugs are grouped based on their first-level anatomical therapeutic chemical (ATC) codes as indicated on the left side. A colored patch in the heatmap indicates the rank of a drug for a disease. The darker the patch, the better is the rank, as indicated by the rank bar on the right side. As can be seen, a major portion of the heatmap is covered with dark patches as we only consider the top 10 ranked drugs. We can infer from the heatmap that cardiovascular drugs (e.g., Captopril, Atenolol) and anti-inflammatory drugs (e.g., Celecoxib, Prednisone) are ranked high for the alphacoronaviruses, and a combination of antiparasitic (e.g., Ivermectin), corticosteroids (e.g., Prednisolone, Dexamethasone), antivirals (e.g., Cidofovir), and antineoplastic drugs (e.g., Methotrexate, Sirolimus) in the case of betacoronaviruses.
FIG. 1. Rank heatmap of the predicted drugs with their corresponding ATC labels.
Fig 2 lists the drugs predicted by Dr-COVID, grouped based on their first level ATC codes such as antiparasitic (P), respiratory system (R), and so on, whereas Fig 1 emphasizes the ranks of these predicted drugs for the COVID-19 nodes. The majority of the corticosteroids we predict belong to the respiratory system (R) class, which has been the primary target for the coronaviruses, as reflected by the symptoms. However, COVID-19 has a multi-organ impact on the human body and is not limited to the respiratory system [23]. Complications due to the cytokine storm with the effects of angiotensin converting enzyme (ACE) have led to cardiac arrest, kidney failure, and liver damage resulting in many deaths. For these reasons, we see drugs from various ATC classes are being considered for clinical trials. Next, we discuss in detail these pharmacological classifications of some of the predicted drugs.

**Anti-inflammatory (AI) agents:** Inflammatory cytokine storms are prominently evident in COVID-19 positive patients and timely anti-inflammation treatment is required [24]. Pneumonia caused by the coronavirus results in a huge amount of inflammatory cell infiltration leading to acute respiratory distress syndrome (ARDS), causing many deaths [25, 26]. A wide range of anti-inflammatory treatments including glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), immunosuppressants, inflammatory cytokines antagonists like tumor necrosis factor (TNF) inhibitors, Janus kinase (JAK) inhibitors, and interleukin-1-receptor antagonist (IL-1RA) are being considered for COVID-19. Our model predicts in the top 10, steroids like Dexamathone, Hydrocortisone, Methylprednisolone; NSAIDs like Ibuprofen, Aspirin (Acetylsalicylic acid); immunosuppressants like Sirolimus and Methotrexate; IL-1RA Anakinra; CoX2 inhibitor Celecoxib. These drugs are currently undergoing clinical trials. Some of the other corticosteroids like Betamethasone, Prednisone, and TNF inhibitor Certolizumab pegol were also ranked high.

**Antiviral and anti-parasitic agents:** Dr-COVID predicts nucleotide analogue antivirals like Acyclovir, Valaclovir, Cidofovir, and Entecavir that have shown positive results in terminating the RNA synthesis catalyzed by polymerases of coronaviruses [27]. Ivermectin and Nitazoxanide are used against many parasite infestations and are also known to have antiviral properties. Mebendazole is another similar anti-parasitic drug that Dr-COVID ranked high. One of the recent reports shows that Ivermectin is an effective inhibitor of the SARS-CoV-2 and many other positive single-stranded RNA viruses. A 5000-fold reduction in the virus titer within 48 hours in cell culture was obtained with a single treatment (5 µM) of Ivermectin [28].

**Statins and ACE inhibitors/ beta-blockers/ calcium channel blockers:** Statins are lipid-lowering drugs that inhibit the cholesterol synthesis enzyme (also known as HMG-CoA reductase), which also has
Drug* - The drug name in red indicates it is undergoing clinical trials and the x gives its current phase.
NA - Phase information not available

FIG. 2. Predicted drugs for COVID, categorized based on their ATC labels.
anti-inflammatory properties. There have been implications of lipid metabolism in the SARS-CoV-2 pathogenesis \cite{29}, due to which there are reports on including statins in the line of treatment for COVID-19. Dr-COVID predicts Atorvastatin, Simvastatin, and Rosuvastatin, where all the three drugs are currently in clinical trials. On the contrary, some studies show that statins tend to increase the cellular expression of ACE inhibitors \cite{30}, to which the SARS-CoV2-spike protein binds at the entry-level in humans \cite{31}. Analyzing this issue, an observational study by Zang et al. \cite{32} reported a reduced mortality rate in the patients treated with statins and no adverse effect was observed by adding an ACE inhibitor drug also to the line of treatment. These ACE inhibitors are cardiovascular drugs causing relaxation of blood vessels that are primarily used to treat high blood pressure and heart failure. Beta-adrenergic and calcium channel blockers are other similar functioning drugs that lower blood pressure, are also currently considered to treat COVID-19. Dr-COVID predicts Captopril (ACE inhibitor), Atenolol (beta-blocker) and Nifedipine (calcium channel blocker), which are currently in clinical trials. Additionally, the list of predicted drugs includes Spironolactone and Hydrochlorothiazide, that help prevent our body from absorbing too much salt and eventually lowering the blood pressure and avoiding cardiac failure.

**Miscellaneous:** Dr-COVID also predicts some of the pre-discovered vaccines such as Rubella virus vaccine, which is majorly considered for all the healthcare workers, the Yellow fever vaccine \cite{33}, and the Ebola zaire virus vaccine (rVSV-ZEBOV). Further, we also have Mercaptopurine, an antineoplastic agent that has been considered as a selective inhibitor of SARS-CoV \cite{34} in the list of predicted drugs. Antidepressant Brexanolone that is currently considered for patients on ventilator support due to ARDS, vasodilators Nitroglycerine and Alprostadil, nutritional supplements like Riboflavin (Vitamin B2) \cite{35}, Niacin, Cholecalciferol (Vitamin D3), and Iron are some more top-ranked drugs. Interestingly, Ephedra sinica root, a herb generally used to treat asthma and lung congestion, and an ingredient of lung cleansing and detoxifying decoction (LCDD), which is a widely used traditional Chinese medicine \cite{36} is one of the drugs predicted in our list.

In essence, Dr-COVID predicts drugs for COVID-19 from different pharmacological classes like the corticosteroids, antivirals, antiparasitic, NSAIDs, and cardiovascular drugs, as the disease does not target particular anatomy and impacts multiple organs in the human body.
III. DATASET

In this section, we describe the dataset that we use to train and test Dr-COVID for COVID-19 drug repurposing. We also describe how we model the data as a multilayer graph to capture the underlying complex interactions between different biological entities. We derive the required information from DRKG, which is a comprehensive biological knowledge graph relating genes, drugs, diseases, biological processes, side effects, and other eight more entities useful for computational pharmacological tasks like drug repurposing, drug discovery, and drug adverse effect prediction, to list a few. DRKG gathers all this information from six databases, namely, Drugbank [37], Hetionet [38], GNBR [39], STRING [40], IntAct [41], and DGIdb [42]. From DRKG, we consider four entities that are relevant to the drug repurposing task. The four entities are drugs (e.g., Dexamethasone, Sirolimus), diseases (e.g., Scabies, Asthma), anatomies (e.g., Bronchus, Trachea), and genes (e.g., Gene ID: 8446, Gene ID: 5529). All the genes are referred with their respective Entrez IDs throughout the paper. We extract the details about these entities specifically from the Drugbank, Hetionet, and GNBR databases. We form a four-layered heterogeneous graph with these four entities in each layer as illustrated in Fig 3a. The four-layered graph is composed of 8070 drugs, 4166 diseases, 29848 genes, 400 anatomies, and a total of 1,417,624 links, which include all the inter-layer and intra-layer connections. Next, we discuss the interactome that we consider for drug repurposing.

**Interactome**: There are inter-layered connections between the four layers and some have intra-layered connections. The inter-layered connections are of different types. The drug-disease links indicate treatment or palliation, i.e., a drug treats or has a relieving effect on a disease. For example, interaction between Ivermectin-Scabies (as seen in Fig 3b) and Simvastatin-Hyperlipidemia (as seen in Fig 3d) are of type treatment, whereas Atropine-Parkinson’s disease and Diclofenac-Osteoarthritis are of type palliation. The drug-gene and disease-gene links are the direct gene targets of the compound and the disease, respectively. Gene ID: 4306, Gene ID: 387, Gene ID: 1786 are some of the targets of the drug Dexamethasone (see Fig 3b) and Gene ID: 5509, Gene ID: 859 are target genes of the disease Malaria. Some of the genes targeted by the drug (e.g., Dexamethasone, Ivermectin, Simvastatin) as well as by the SARS-CoV-2 virus (referred to as shared genes) are shown in Fig 3 (b,c and d). These common gene targets between a drug and a disease are one of the reasons for the drug to be a potential repurposing candidate against the disease. The disease-anatomy and gene-anatomy connections indicate how the diseases affect the anatomies and
FIG. 3. (a) Four-layered heterogeneous graph illustrating the inter-layer and intra-layer connections. (b), (c) and (d) Subgraph centered around the drugs Dexamethasone, Ivermectin and Simvastatin, respectively.

interactions between the genes and anatomies. For example, Gene ID: 2771 and Gene ID: 3156 belong to the cardiac ventricle anatomy (see Fig 3d); disease Schizophrenia affects multiple anatomies like the central nervous system (CNS) and optic tract.

There are also intra-layered connections. The drug-drug and disease-disease connections show the similarity between a pair of drugs and diseases, respectively. The gene-gene links describe the interaction between genes (e.g., epistasis, complementation) and form the whole gene interactome network. This comprehensive gene network serves as a backbone for our model, wherein we predict the unknown links
between drugs and new diseases like COVID-19 as they are connected through genes and anatomies. The anatomy information helps in drug predictions by focusing on the local interactions of genes related to the same anatomy as the genes targeted by the disease. Some examples of the intra-layered connections are Simvastatin-Lovastatin and Gene ID: 23649-Gene ID: 8480 as seen in Fig 3d. While all these interactions reveal the true relations between the entities, we also randomly sample the no-drug-disease links, which give us negative control in the learning process. For example, there is no link between Simvastatin-Scabies, i.e., Simvastatin is not known to treat or suppress the effects of Scabies. Including such negative control in the training process makes our model accurate and reliable.

**HCoV interactome network:** To specialize the drug repurposing model Dr-COVID for COVID-19, as discussed before, we consider the four known HCoVs, namely, SARS-CoV, MERS-CoV, CoV-229E and CoV-NL63, and two non-human CoVs namely MHV, and IBV. We consider interactions of these disease nodes with human genes. There are 129 links between these six disease nodes and the gene nodes [21]. In addition, we consider all the 27 SARS-CoV-2 proteins (including the structured proteins, nsp, and orf) and their 332 links connecting the target human genes as given by Gordon et al. [22]. In other words, there are only disease-gene interactions available for these COVID-19 nodes. With this available information, we train Dr-COVID to predict possible drug connections for these COVID-19 nodes.

**IV. METHODS AND MODELS**

In the last few years, deep learning has gained significant attention from a variety of scientific disciplines due to its extraordinary successes in solving many challenging tasks like data cleansing, mining, and classification, mainly for images, speech, or text datasets. However, in many applications, the structure underlying data is not always Euclidean. Some examples include social networks, transportation networks, brain networks, sensor networks, chemical molecules, protein-protein interactions, meshed surfaces in computer graphics, and the drug repurposing network, as discussed above, to list a few. For these applications, more recently, deep learning for graph-structured data, also known as geometric deep learning (GDL) [43], is receiving steady research attention. GDL aims at building neural network architectures known as graph neural network (GNNs) to learn from graph-structured data. GDL models are used to learn low-dimensional graph representations or node embeddings by taking into account the nodal connectivity information. These
embeddings are then used to solve many graph analysis tasks like node classification, graph classification, and link prediction, to list a few. GNN architectures are developed using concepts from spectral graph theory and generalize the traditional convolution operation in the convolutional neural network (CNN) to the graph setting. In this section, we describe the proposed Dr-COVID architecture for COVID-19 drug repurposing and describe numerical experiments performed to evaluate our model.

Consider an undirected graph $G = (\mathcal{V}, \mathcal{E})$ with a set of vertices $\mathcal{V} = \{v_1, v_2, \cdots, v_N\}$ and edges $e_{ij} \in \mathcal{E}$ denoting a connection between nodes $v_i$ and $v_j$. We represent a graph $G$ using the adjacency matrix $A \in \mathbb{R}^{N \times N}$, where the $(i, j)$th entry of $A$ denoted by $a_{ij}$ is 1 if there exists an edge between nodes $v_i$ and $v_j$, and zero otherwise. To account for the non-uniformity in the degrees of the nodes, we use the normalized adjacency matrix denoted by $\tilde{A} = D^{-\frac{1}{2}}AD^{-\frac{1}{2}}$, where $D \in \mathbb{R}^{N \times N}$ is the diagonal degree matrix. Each node in the graph is associated with its own feature vector (referred to as input feature). Let us denote the input feature of node $i$ by $x_i^{(0)} \in \mathbb{R}^{d}$, which contains key information or attributes of that node (e.g., individual drug side effects). Let $X^{(0)} \in \mathbb{R}^{N \times d}$ be the input feature matrix associated with the $N$ nodes in the graph $G$ obtained by stacking the input features of all the nodes in $G$. The new embeddings for a node is generated by combining information from its neighboring nodes (e.g., diseases or genes) to account for the local interactions. This process of combining information and generating new representations for a node is done by a single GNN block. If we stack $K$ such blocks, we can incorporate information for a node from its $K$-hop neighbors (e.g., in Fig 3c, the drug Ivermectin is a 2-hop neighbor of the anatomy Lung and is connected via Gene ID: 8614). Mathematically, this operation can be represented as

$$X^{(k+1)} = g_k(\tilde{A}X^{(k)}W_k),$$

where $X^{(k)} \in \mathbb{R}^{N \times d_k}$ represents the $k$th layer embedding matrix and $d_k$ is the embedding dimension in the $k$th layer. Here, $\tilde{A} = I + \tilde{A}$, where the identity matrix $I \in \mathbb{R}^{N \times N}$, is added to account for the self-node embeddings, $W_k \in \mathbb{R}^{d_k \times d_{k+1}}$ is the learnable transformation matrix, and $g_k(\cdot)$ is the activation function in the $k$th layer. There exist several GNN variants such as graph convolutional networks (GCN) [44], GraphSAGE [45], graph attention networks (GAT) [46] and scalable inception graph neural network (SIGN) [20], to name a few. GCN is a vanilla flavored GNN based on Eq (1). GAT gives individual attention to the neighboring nodes instead of treating every node equally. To address the issue of scalability, GraphSAGE uses a neighbor sam-


pling method, wherein instead of taking the entire neighborhood, we randomly sample a subset of neighbor nodes. SIGN takes a different approach to solve the scalability issue and introduce a parallel architecture. The proposed Dr-COVID architecture is based on the SIGN approach due to its computational advantages. The predicted list of drugs from other GNNs are available in our repository. Next, we describe the proposed Dr-COVID architecture.

A. Dr-COVID architecture

The proposed GNN architecture for SARS-CoV-2 drug repurposing has two main components, namely, the encoder and decoder. The encoder based on the SIGN architecture generates the node embeddings of all the nodes in the four-layer graph. The decoder scores a drug-disease pair based on the embeddings. The encoder and decoder networks are trained in an end-to-end manner. Next, we describe these two components of the Dr-COVID architecture, which is illustrated in Fig 4.

Encoder: The Dr-COVID encoder is based on the SIGN architecture [20], which provides low-dimensional node embeddings based on the input features and nodal connectivity information. Recall that the matrix $\mathbf{A}$ is the adjacency matrix of the four-layered graph $\mathcal{G}$ and $\tilde{\mathbf{A}}$ is the normalized adjacency. SIGN uses linear diffusion operators represented using matrices $F_r$, $r = 1, 2, \cdots$, to perform message passing and aggregate local information in the graph. By choosing $F_r = \tilde{\mathbf{A}}^r$ we can incorporate information for node $v$ from its $r$-hop neighbors. Here, $\tilde{\mathbf{A}}^r$ denotes the $r$th matrix power. To start the information exchange between the nodes, we assume that each node has its own $d$ dimensional feature, which we collect in the matrix $\mathbf{X} \in \mathbb{R}^{N \times d}$ to obtain the complete input feature matrix associated with the nodes of $\mathcal{G}$. We can then represent the encoder as

$$Z = \sigma_1 \{ [\mathbf{X} \Theta_0 \| F_1 \mathbf{X} \Theta_1] \cdots \| F_r \mathbf{X} \Theta_r] \} \quad \text{and} \quad Y = \sigma_2 \{ \mathbf{Z} \mathbf{W} \},$$

(2)

where $\mathbf{Y}$ is the final node embedding matrix for the nodes in the graph $\mathcal{G}$, and $\{ \Theta_0, \cdots, \Theta_r, \mathbf{W} \}$ are the learnable parameters. Here, $\|$ represents concatenation and $\sigma_1 \{ \cdot \}$ and $\sigma_2 \{ \cdot \}$ are the nonlinear tanh and leaky rectified linear unit (leaky ReLU) activation functions, respectively. The matrix $F_r \mathbf{X} = \mathbf{D}^{-\frac{1}{2}} \mathbf{A} \mathbf{D}^{-\frac{1}{2}} \mathbf{X}$ captures information about the local interactions over $r$-hop neighbors. Fig 4 shows the encoder architec-
Node embeddings
Individual node information
Information from 1-hop neighbors
Information from 2-hop neighbors
Input features
Concatenate
Drug Diseases Anatomies Genes

Network learnable parameters
𝚯0
𝚯1
𝚯2
Decoder
Pr
indicates the $n$-hop neighborhood of node $v$

FIG. 4. Dr-CoV architecture.
ture. The main benefit of using SIGN over other sequential models (e.g., GCN, GAT, GraphSAGE) is that the matrix product $F_rX$ is independent of the learnable parameters $\Theta_r$. Thus, this matrix product can be pre-computed before training the neural network model. Doing so reduces the computational complexity without compromising the performance.

In our setting, we choose $r = 2$, i.e., the low-dimensional node embeddings have information from 2-hop neighbors. Choosing $r \geq 3$ is not useful for drug repurposing, as we aim to capture the local information of the drug targets such that a drug node embedding should retain information about its target genes and the shared genes in its vicinity. For example, the 1-hop neighbors of Dexamethasone as shown in Fig 3b, are the diseases it treats (e.g., Asthma), and the drugs similar to Dexamethasone (e.g., Methylprednisolone) and its target genes (e.g., Gene ID: 8446, Gene ID: 387). The 2-hop neighbors are the anatomies of the target genes (e.g., Bronchus) of Dexamethasone, and the drugs that have similar effects on the diseases (e.g., Hydrocortisone and Dexamethasone have similar effects on Asthma). It is essential for the embedding related to Dexamethasone to retain this local information for the drug repurposing task, and not much benefit is obtained by propagating more deeper in the network.

**Decoder:** For drug repurposing, we propose a score function that takes as input the embeddings of the drugs and diseases and outputs a score based on which we decide if a certain drug treats the disease. Fig 4 illustrates the proposed decoder. The columns of the embedding matrix $Y$, contains the embeddings of all the nodes in the four-layer graph, including the embeddings of the disease and drug nodes. Let us denote the embeddings of the $i$th drug as $y_{c_i} \in \mathbb{R}^l$ and the embeddings of the $j$th disease as $y_{d_j} \in \mathbb{R}^l$. The proposed scoring function $f(\cdot)$ to infer whether drug $c_i$ is a promising treatment for disease $d_j$ is defined as

$$s_{ij} = f(y_{c_i}; y_{d_j}) = \sigma \{y_{c_i}^T \Phi y_{d_j}\},$$

where $\sigma \{\cdot\}$ is the nonlinear sigmoid activation function and $\Phi \in \mathbb{R}^{l \times l}$ is a learnable co-efficient matrix. We interpret $s_{ij}$ as the probability that a link exists between drug $c_i$ and disease $d_j$. The term $y_{c_i}^T \Phi y_{d_j}$ can be interpreted as a measure of correlation (induced by $\Phi$) between the disease and drug node embeddings. We use $d = 400$ and $l = 250$ in our implementation. The model is trained in a mini-batch setting in an end-to-end fashion using stochastic gradient descent to minimize the weighted cross entropy loss, where
the loss function for the sample corresponding to the drug-disease pair \((i, j)\) is given by

\[
\ell(s_{ij}, z_{ij}) = wz_{ij} \left( \log \left( \frac{1}{\sigma(s_{ij})} \right) \right) + (1 - z_{ij}) \log \left( \frac{1}{1 - \sigma(s_{ij})} \right),
\]

(4)

where \(z_{ij}\) is the known training label associated with score \(s_{ij}\) for the drug-disease pair. \(z_{ij} = 1\) indicates that drug \(i\) treats disease \(j\) and otherwise when \(z_{ij} = 0\). Here, \(w\) is the weight on the positive samples that we choose to account for the class imbalance. As discussed in the Dataset Section, we include the no-drug-disease links as negative control while training our model. The number of no-drug-disease links is almost thirty times the number of positive samples. To handle this class disparity, we explicitly use a weight \(w > 0\) on the positive samples.

### B. Model evaluation

In this subsection, we evaluate Dr-COVID and discuss the choice of various hyper-parameters. The drug repurposing via link prediction can be viewed as a binary classification problem, wherein a positive class represents the existence of a link between the input drug and disease, and otherwise for a negative class. We have 6113 positive samples (drug-disease links) in our dataset. To account for the negative class samples, we randomly choose 200,000 no-drug-disease links (i.e., there is no link between these drugs and diseases). These links are then divided into the training and testing set with a 90% − 10% split. To use mini-batch stochastic gradient descent, we group the training set in batches of size 512 and train them for 20 epochs. Due to the significant class imbalance, we oversample the drug-disease links while creating batches, thus maintaining the class ratio (ratio of the number of negative samples to the number of positive samples) of 1.5 in each batch. The weight \(w\) on the positives samples (mentioned in Eq (4)), is also chosen to be the class imbalance ratio of each batch, i.e., we fix \(w\) to be 1.5.

We perform experiments on three sequential GNN encoder architectures, namely, GCN [44], GraphSAGE [45], and GAT [46] for the drug repurposing task, which we treat as a link prediction problem, and compare with the proposed Dr-COVID architecture. Specifically, the SIGN encoder in Dr-COVID is replaced with GCN, GraphSAGE, and GAT to evaluate the model performance. Two blocks of these sequential models are stacked to maintain the consistency with \(r = 2\) of the Dr-COVID architecture. We evaluate these models
on the test set, which are known treatments for diseases that are not shown to the model while training. The model is evaluated based on two performance measures. Firstly, we report the ability to classify the links correctly, i.e., to predict the known treatments correctly for diseases in the test set. This is measured through the receiver operating characteristic (ROC) curve of the true positive rate (TPR) versus the false positive rates (FPR). Next, using the list of predicted drugs for the diseases in the test set, we report that model's ability to rank the actual treatment drug as high as possible (the ranking is obtained by ordering the scores in Eq (3)).

ROC curves show the performance of a binary classification model by varying the threshold values used to classify the positive samples, which eventually change the TPR and FPR. Fig 5 shows the ROC curves of different GNN models. The area under ROC (AUROC), which lies in the interval [0,1] indicates the separation ability of a binary classifier, where 1 indicates the best performance, 0.5 means that the model is unable to discriminate between the classes and 0 indicates a completely opposite behavior. We can see from Fig 5 that all the models have very similar AUROC values.

We also evaluate Dr-COVID in terms of ranks of the actual treatment drug in the predicted list for a disease from the testing set, where the rank is computed by rank ordering the scores as before. In addition, we compute the network proximity scores \(13\) and rank order the drugs based on these scores to compare...
with other GNN encoder models. These network proximity scores are a measure of the shortest distance between drugs and diseases. They are computed as

\[ P_{ij} = \frac{1}{|C| + |T|} \left( \sum_{p \in C} \min_{q \in T} d(p, q) + \sum_{q \in T} \min_{p \in C} d(p, q) \right), \tag{5} \]

where \( P_{ij} \) is a proximity score of drug \( c_i \) and disease \( d_j \). Here, \( C \) is the set of target genes of \( c_i \), \( T \) is the set of target genes of \( d_j \), and \( d(p, q) \) is the shortest distance between a gene \( p \in C \) and a gene \( q \in T \) in the gene interactome. We convert these into Z-scores using the permutation test as

\[ Z_{ij} = \frac{P_{ij} - \mu}{\omega}, \tag{6} \]

where \( \mu \) is the mean proximity score of \( c_i \) and \( d_j \), which we compute by randomly selecting subsets of genes with the same degree distribution as that of \( C \) and \( T \) from the gene interactome, and \( \omega \) is the standard deviation of the scores generated in the permutation test. Table I gives the rankings, which clearly show that the Dr-COVID results in better ranks on the unseen diseases than the other GNN variants. Also, compared to the network proximity measure, which is solely based on the gene interactome, Dr-COVID performs better. We choose these drug-disease pairs for evaluation as these links are not shown during the training. It is evident that the diseases on which we evaluate are not confined to single anatomy (e.g., rectal neoplasms are associated to the rectum anatomy, whereas pulmonary fibrosis is a lung disease), nor do they require a similar family of drugs for their treatment (e.g., Fluorouracil is an antineoplastic drug, and Prednisone is an anti-inflammatory corticosteroid). Thus, showcasing our model’s unbiased nature. For a majority of the diseases in the test set Dr-COVID ranks the treatment drug in top 10 (as seen in Table I).

In the case of Leukemia (blood cancer), other antineoplastic drugs like Hydroxyurea and Methotrexate are ranked high (in top 10) and its known treatment drug Azacitidine is ranked 17. We give more importance to the ranking parameter as any drug predictor requires classifying and ranking the correct drugs as high as possible. Considering this AUROC-ranking trade-off we can see that Dr-COVID with SIGN encoder performs the best.

**COVID-19 analysis**: We perform a similar analysis and identify potential candidate drugs for SARS-CoV-2. For all the COVID-19 nodes in our dataset comprising 27 proteins (structured, nsp and orf), SARS-
TABLE I. **Ranking Table.** The Table gives the ranking performance of Dr-COVID compared with other GNN variants and the network proximity measures. There are no associated genes with some of the disease in our database, which makes it impossible to compute the Z scores. These are indicated as “Not computable”. The best results are highlighted in bold font.

| Disease                  | Treatment drug | Dr-CoV (SIGN) | SAGE | GCN | GAT | Network proximity |
|--------------------------|----------------|---------------|------|-----|-----|-------------------|
| *Encephalitis*           | Acyclovir      | **10**        | 35   | 35  | 295 | 5462              |
| *Rectal neoplasms*       | Fluorouracil   | 9             | 421  | 16  | 231 | 2831              |
| *Pulmonary fibrosis*     | Prednisone     | 5             | 3    | 10  | 9   | 2072              |
| *Atrioventricular block*| Atropine       | 6             | 79   | 8   | 14  | 4453              |
| *Pellagra*               | Niacin         | 2             | 56   | 497 | 484 | Not computable    |
| *Colic*                  | Hyoscyanine    | 1             | 1    | 501 | 205 | Not computable    |
| *Leukemia*               | Azacitidine    | **17**        | 120  | 31  | 332 | 377               |

CoV, IBV, MERS-CoV, CoV-229E, CoV-NL63, and MHV, we individually predict the drugs for all these 33 entities. Each protein in SARS-CoV-2 targets a different set of genes in humans, so we give individual predictions. We then pick the top 10 drugs from all the predicted drugs and list 150 candidate repurposed drugs for COVID-19. Out of these 150 drugs, 46 are currently in clinical trials. Our predictions have a mixture of antivirals, antineoplastic, corticosteroids, monoclonal antibodies (mAb), non-steroidal anti-inflammatory drugs (NSAIDs), ACE inhibitors, and statin family of drugs, and some of the vaccines discovered previously for other diseases. Refer to the Results Section for a detailed discussion on the analysis of the predicted drugs for COVID-19.

V. **CONCLUSIONS**

In this work, we presented a generalized drug repurposing model, called Dr-COVID for novel human diseases. We constructed a biological network of drugs, diseases, genes, and anatomies and formulated the drug repurposing task as a link prediction problem. We proposed a graph neural network model, which was then trained to predict drugs for new diseases. Dr-COVID predicted 150 potential drugs for COVID-19, of which 46 drugs are currently in clinical trials. The considered GNN model is computationally efficient and better ranks known treatment drugs for diseases than the other GNN variants and non-deep methods like the network proximity approaches. This work can be extended along several directions. Considering the
availability of substantial biological data, the inclusion of information like individual side effects of drugs, the molecular structure of the drugs, etc., may further improve the predictions. Considering the comorbidities of a patient would help us analyze the biological process and gene interactions in the body specific to an individual and accordingly prescribe the line of treatment. Predicting a synergistic combination of drugs for a disease would be another area of interest where graph neural networks can be beneficial.

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DATA AND CODE AVAILABILITY

All the implementation and the data required to reproduce the results in the paper are available at https://github.com/siddhant-doshi/Dr-COVID.

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