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DeepR2cov: deep representation learning on heterogeneous drug networks to discover anti-inflammatory agents for COVID-19

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Abstract

Recent studies have demonstrated that the excessive inflammatory response is an important factor of death in coronavirus disease 2019 (COVID-19) patients. In this study, we propose a deep representation on heterogeneous drug networks, termed DeepR2cov, to discover potential agents for treating the excessive inflammatory response in COVID-19 patients. This work explores the multi-hub characteristic of a heterogeneous drug network integrating eight unique networks. Inspired by the multi-hub characteristic, we design 3 billion special meta paths to train a deep representation model for learning low-dimensional vectors that integrate long-range structure dependency and complex semantic relation among network nodes. Based on the representation vectors and transcriptomics data, we predict 22 drugs that bind to tumor necrosis factor-α or interleukin-6, whose therapeutic associations with the inflammation storm in COVID-19 patients, and molecular binding model are further validated via data from PubMed publications, ongoing clinical trials and a docking program. In addition, the results on five biomedical applications suggest that DeepR2cov significantly outperforms five existing representation approaches. In summary, DeepR2cov is a powerful network representation approach and holds the potential to accelerate treatment of the inflammatory responses in COVID-19 patients. The source code and data can be downloaded from https://github.com/pengsl-lab/DeepR2cov.git.

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Introduction

The emergence and rapid expansion of the coronavirus disease 2019 (COVID-19) has posed a global health threat. Studies have suggested that the development of severe disease does not seem to be solely related to viral load [1–2] but also that the excessive inflammatory response induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a main cause of death in infected patients [3–4]. The discovery of potential drugs for preventing the excessive inflammatory response in COVID-19 patients is urgently needed [5]. Nevertheless, the new drug development is a complex, lengthy and expensive process that generally takes 0.8–15 billion dollars and 10–15 years [6]. Compared with *de novo* drug development, drug repositioning [7] that is aimed at discovering potential drugs from existing ones can significantly reduce the cost and period of drug development [8] and offers a promising way for the development of treatment of the excessive inflammatory response in COVID-19 patients.

Since the COVID-19 outbreak, numerous studies have suggested that cytokines [e.g. tumor necrosis factor (TNF)-α and interleukin (IL)-6] play key roles in the inflammatory storms of patients with COVID-19 [3–4]. Therefore, there are an increasing number of researchers that used appropriate immunosuppressive agents to treat the excessive inflammation in COVID-19 patients, such as IL-6R antagonists, IL-1 antagonists, TNF inhibitors and Janus kinase inhibitors. Many existing anti-inflammatory drugs have been applied to treat COVID-19 patients and tested in clinical trials. In particular, tocilizumab, an IL-6R antagonist, has been proved to be effective in treating severe ill patients with COVID-19 by small-sample clinical studies from China (clinical trial registration ID: ChiCTR2000029765). However, the side effect associated with tocilizumab (e.g. thrombocytopenia, severe infections and liver damage) should be noted [9]. In addition, the clinical data of these drugs in the treatment of COVID-19 are limited, and the efficacy of these agents in treatment of patients with COVID-19 deserves further exploration. Therefore, in the absence of specific drugs for cytokine storm in COVID-19 patients, it is significant to develop drug repositioning approaches to discover anti-inflammatory agents for patients with COVID-19.

However, the development of promising drug repositioning approaches for the effective treatment of inflammatory response in COVID-19 patients is challenging, because the action mechanisms and biological processes are complex and elusive. Fortunately, with the rapid development of systems biology and network pharmacology, the drug research paradigm has been changed from the linear mode 'one drug, one target, one disease' to the network mode 'multi-drugs, multi-targets, multi diseases' [10]. Intuitively, the integration of multiple type of data contributes to understanding and analysis of molecular action mechanisms [11–13]. Among the advances, network-based methods provide an effective and potential paradigm to accelerate the drug development [14–16]. In most of network-based drug repositioning approaches, network representation technology, which aims to learn a low-dimensional representation vector of vertices, plays a key role. Therefore, many network-based methods integrate the promising network representation technologies to boost the

treatment of COVID-19 patients [17]. Zeng *et al.* [18] reported a network-based deep representation learning methodology to identify drugs for COVID-19. Ge *et al.* [19] proposed a data-driven drug repositioning framework, which applied representation learning and statistical analysis approaches to systematically integrate large-scale available coronavirus-related network data to identify the potential drug candidates against SARS-CoV-2. Zhou *et al.* [20] proposed network-based drug repurposing for novel coronavirus SARS-CoV-2. However, these network-based drugs repurposing for COVID-19 focused on identifying antiviral drugs that are able to suppress the activity and life cycle of SARS-CoV-2 to a certain extent. Unfortunately, the efficacy of existing antiviral agents might be unsatisfactory or insufficient for patients suffering from immune imbalance in COVID-19 patients, and the mechanisms of action of these drugs in this disease are uncertain [21]. On the other hand, most of previous network representation models for drug repurposing are only focused on capture the network structure information and failed to integrate semantic feature among nodes. In other words, these network representation models to discover therapeutics for COVID-19 cannot take into account the heterogeneous types and relations defined in drug networks. Furthermore, it is fairly challenging to consider the long-range dependency and relation among nodes in heterogeneous drug networks.

To address these key issues, we propose a deep representation on heterogeneous drug network, termed DeepR2cov, to discover potential anti-inflammatory agents for COVID-19 patients. We construct a heterogeneous drug network by integrating eight biomedical networks and explore the multi-hub characteristic of this drug network. Specifically, the multi-hub characteristic inspires us to design a meta path-driven deep representation model for automatically learning low-dimensional vectors that can integrate long-range structure dependency and complex semantic relation among network nodes. Using these representation vectors and transcriptomics data, DeepR2cov identifies 22 drugs binding to TNF-α or IL-6. Meanwhile, we future validate the therapeutic associations of the inflammation storm in COVID-19 patients via data from PubMed publications and explore the possible binding modes between drugs and TNF-α/IL-6. In addition, we integrate five biomedical tasks, and the results demonstrate that DeepR2cov significantly outperforms five other network representation approaches. In summary, DeepR2cov is a practically useful tool for accelerating COVID-19 therapeutic development.

Materials and methods

Overview

In this study, we propose DeepR2cov, which is a deep representation on heterogeneous drug network, to discover potential agents for treating the excessive inflammatory response in COVID-19, as shown in Figure 1. First, we construct a heterogeneous drug network integrating the information of drugs, diseases, proteins and side effects. Second, we extract 3 billion meta paths from the heterogeneous drug network, which are used to train a deep bidirectional Transformer encoder for learning low-dimensional representation vectors of network nodes.
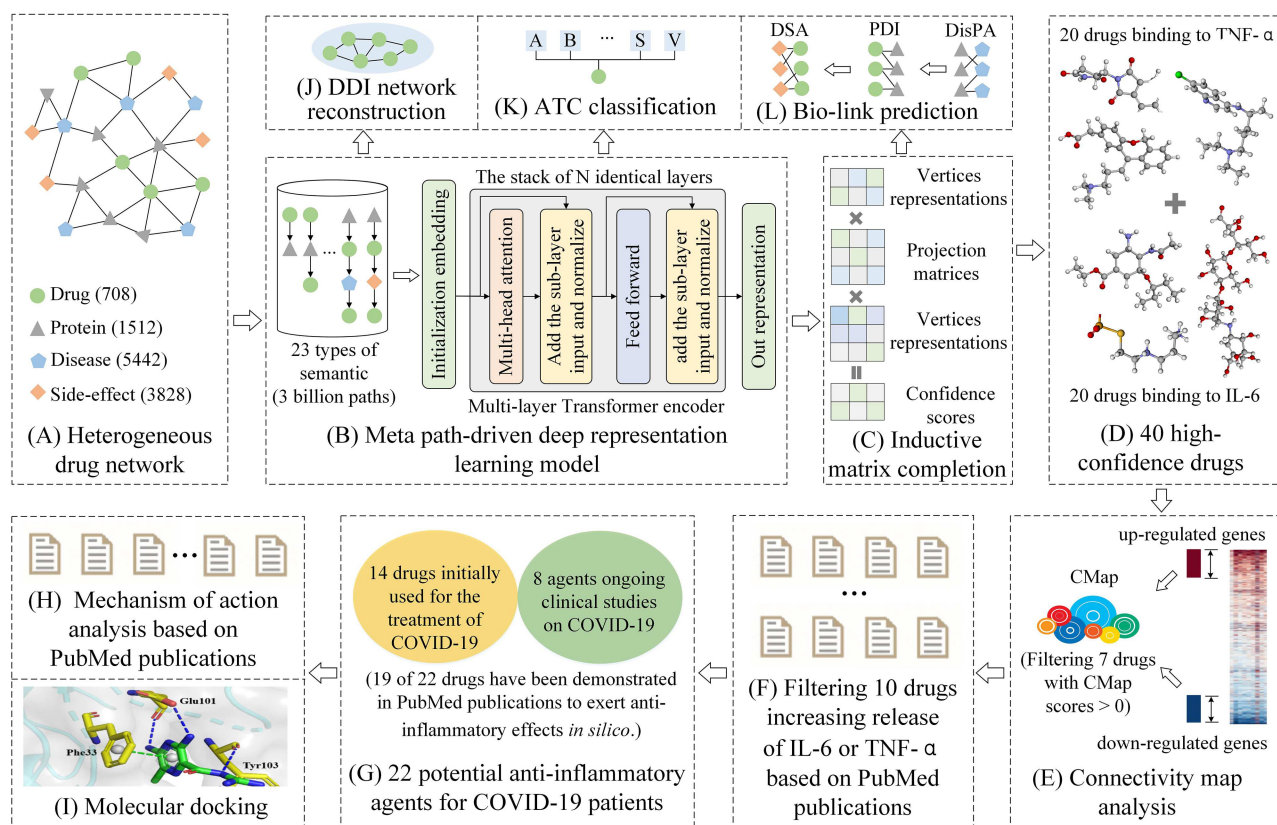
Figure 1. Overall workflow of this study. There is a network pharmacology-based drug discovery platform. (**A**) Constructing a heterogeneous drug network by integrating drugs, diseases, proteins and side effects. (**B**) Extracting 3 billion meta paths from the drug networks, which are used to drive a deep bidirectional Transformer encoder for learning representation vectors of network nodes. (**C**) Using the IMC model to predict the interaction confidence among nodes. (**D**) Selecting 20 high-confidence drugs binding to TNF-α and IL-6, respectively. (**E**) Filtering seven drugs via CMap analysis. (**F**) Filtering 10 drugs increasing release of TNF-α or IL-6 based on PubMed publications. (**G**) Identifying 22 potential anti-inflammatory agents for COVID-19 patients where acarbose is treated as an agent that binds to both TNF-α and IL-6. (**H**) Analyzing mechanisms of action based on PubMed publications. (**I**) Exploring the possible binding modes via docking program. Based on the representation of nodes, (**L**) performing three bio-link predictions including DisPA, PDI and DSA; (**K**) performing ATC classification and (**J**) performing DDI network reconstruction.

Then, these vectors of nodes are fed into an inductive matrix completion (IMC) model [22] to predict 20 high-confidence drugs binding to TNF-α and IL-6, respectively. Next, DeepR2cov performs Connectivity Map (CMap) [23] analysis based on transcriptome data and experiment verification by PubMed literature to further filter unsatisfactory drugs. Finally, this study predicts 22 agents that bind to TNF-α or IL-6 to prevent cytokine storms in patients with COVID-19. Meanwhile, we analyze the mechanisms of action based on PubMed publications and ongoing clinical trials and explore the possible binding modes between the new predicted drugs and TNF-α/IL-6 via docking program DOCK6.8 [24]. In addition, the representation is applied to five biomedical tasks, that is, drug–drug interaction (DDI) network reconstruction, anatomical therapeutic chemical (ATC) classification and three bio-link predictions, to evaluate and validate the representation performance of DeepR2cov.

Construction of heterogeneous drug networks

In this work, according to NeoDTI [13] and DTINet [25], we assemble four types of nodes (i.e. drug, protein, side effect and disease) and eight types of relationships [i.e. DDI, drug–side effect association (DSA), protein–protein interaction (PPI), protein–drug interaction (PDI), disease–protein association (DisPA), disease–drug association (DisDA), drug–drug structure similarity (DDSS) and protein–protein sequence similarity (PPSS)], which

have been proved by biological or clinical experiments. We ignore other links (i.e. disease–disease association, protein–side effect, disease–side effect, side effect–side effect). To the best of our knowledge, although there are computational methods [26–27] for measuring disease similarity, disease–disease association cannot be verified by biology or clinical experiments. Meanwhile, links (i.e. protein–side effect association, protein–side effect association, disease–side effect association and side effect–side effect association) do not exist in current biomedical question. The DDI and PDI are extracted from DrugBank [28] and ChEMBL [29]. The PPI is extracted from HPRD [30], HuRI [31] and BioGRID [32]. The DisPA and DisDA are collected from CTD [33] and repoDB [34]. We extract DSA from CTD [33] and SIDER [35]. The protein sequence similarity network is obtained by calculating the Smith–Waterman similarities [36] of the amino acid sequence derived from UniProt. Furthermore, the drug similarity network is obtained by calculating the Tanimoto coefficient [37] from the Morgan fingerprint using the RDKit [38]. In the heterogeneous drug network, there are 11 490 nodes and 1887 041 edges; all edges are undirected.

Meta path-driven deep representation learning

The proposed DeepR2cov integrates a deep Transformer encoder model and the masked meta paths to learn the representation of network vertices, as shown in Figure 1B.
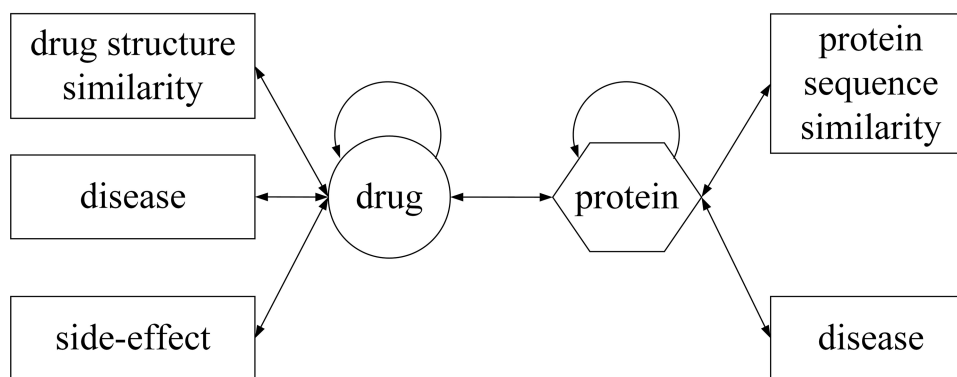
Figure 2. Structure characteristics of heterogeneous drug networks. This work observes that the heterogeneous drug network is a multi-hub network where drugs and proteins are important hubs.

Multi-hub characteristic and meta path of heterogeneous drug networks

A meta path [39] is a composite relation denoting a sequence of adjacent links between any two nodes in heterogeneous networks. The different adjacent links indicate distinct semantic. Meta paths are widely used to capture the rich structure and semantic for nonbiomedical heterogeneous networks. However, not all meta paths have a positive effect on network representation learning; thus, the selection of meta path is still an open question [40–41].

To develop a special representation learning for heterogeneous drug networks, first, DeepR2cov focuses on exploring the structural characteristics of heterogeneous drug networks and observes that the drug network is a multi-hub network as shown in Figure 2, where drugs and proteins are important hubs. Therefore, we specially design 23 types of meta path as shown in Table 1, where the first two nodes in each meta path are drugs and proteins, respectively. Then, we use these meta paths to guide random walks over the heterogeneous drug networks. Based on the above procedure, we extract 3 billion path samples from the heterogeneous drug networks. These paths reflect the interaction mechanisms and topological structures among vertices in heterogeneous drug networks. Note that all the meta paths in this work are reversible, and the lengths of meta paths is no longer than four. Because previous studies have suggested that short meta paths are good enough and that long meta paths may even reduce the quality of semantic meanings [39, 42].

Deep transformers encoder

The network representation model in DeepR2cov is a deep Transformer encoder based on the original framework described in [43], and the implementation is almost identical to the original. The Transformer encoder model is composed of a stack of identical layers, and every layer includes two sublayers as shown in Figure 1B. The first is a multi-head self-attention mechanism, and the second is a simple, position wise fully connected feed-forward network. Meanwhile, a residual connection [44] is employed to connect each of two sublayers, and then layer normalization is performed. The deep Transformer encoder can capture long-range dependency without regarding to their distance limits in input sequence via the attention mechanisms. Therefore, DeepR2cov can learn the complex and long-range structure relation among heterogeneous drug networks.

Masked meta path mechanism

The network representation model designs a masked meta path-based learning strategy to enable deep bidirectional representation inspired by the Cloze task [45]. In the masked meta path mechanism, the input paths are randomly masked by some token, and the objective is to predict the masked nodes based only on its context as shown in Figure 3. DeepR2cov follows the method used in BERT [46] to mask an input meta paths. First, 15% of nodes are randomly selected for masking. For every selected node, it has 80% chance to be replaced by <MASK> token. With 10% and 10% chance, it will be randomly replaced by any other token in the dictionary or kept unchanged correspondingly. The advantage of this procedure is that the randomness can increase the generalization ability of model and can capture bidirectional dependency relation. In addition, because random replacement occurs in only 1.5% of the time for all tokens, it does not seem to harm the model's semantic understanding capability.

Anti-inflammatory drug discovery for COVID-19

Clinical findings have showed that SARS-CoV-2 infection is associated with the excessive inflammatory response and characterized mainly by elevated plasma concentrations of cytokines, such as IL-6, TNF-α, IL-7, IL-8, IL-9 and IL-10 [3, 47]. In particular, compared with moderate cases, severe patients have markedly higher levels of IL-6 and TNF-α [3, 48]. In addition, recent studies have proposed that IL-6 and TNF-α might be promising therapeutic targets for preventing inflammatory response in COVID-19 patients [4, 49–50]. Therefore, this study focuses on predicting drugs that bind to IL-6 or TNF-α to facilitate the therapies efficacy of COVID-19.

Prediction of drug-TNF-α/ IL-6 confidence scores

In this study, the heterogeneous drug network includes eight types of edge, $r \in R = \{DDI, DSA, PPI, PDI, DisPA, DisDA, DDSS, PPSS\}$. For $r \in \{DDI, DSA, PPI, PDI, DisPA, DisDA\}, Y_{ij}^r = 1$, if node i is linked to node j, and $Y_{ij}^r = 0$ otherwise. For $r \in \{DDSS, PPSS\}$, Y_{ij}^r is equal to the similarity value between node i and j. As shown in Figure 1C, DeepR2cov uses a IMC model [22] to obtain edge-type projection matrices $G_r, H_r \in \mathbb{R}^{d \times k}$ for reconstructing the original edge-type matrix Y^r as much as possible, where d is the dimension of representation vectors and $k \ll d^2$. A similar strategy has been popularly applied to the bio-link prediction

Table 1. The meta path types and statistics where the different types of meta paths indicate distinct semantic

No.	The type of meta path	Count
1	drug–protein	1923
2	drug–protein–drug	153 186
3	drug–protein–protein	8728
4	drug–protein–causes–disease	2209 742
5	drug–protein–protein–drug	12 734
6	drug–protein–protein–disease	11 603 240
7	drug–protein–drug–protein	221 020
8	drug–protein–drug–disease	8243 362
9	drug–protein–drug–side effect	4482 541
10	drug–protein–disease–protein	2020 665 247
11	drug–protein–disease–drug	231 785 524
12	protein–drug–drug	34 260
13	protein–drug–protein	6344
14	protein–drug–disease	636 903
15	protein–drug–side effect	270 234
16	protein–drug–drug–protein	60 096
17	protein–drug–drug–disease	11 188 449
18	protein–drug–drug–side effect	5315 270
19	protein–drug–protein–protein	19 371
20	protein–drug –protein–disease	13 232 097
21	protein–drug–disease–protein	558 541 026
22	protein–drug–disease–drug	115 924 998
23	protein–drug–side effect–drug	38 577 295
Total number	3023 193 590	

[13, 16]. The optimization function is defined as follows:

$$\min_{G_r, H_r} \sum_{r \in \mathbb{R}} \sum_{(i,j) \in V_r} \left\| Y_{ij}^r - F_i G_r H_r^T F_j^T \right\|_2^2 \tag{1}$$

where V_r is a set of node pairs with r type of edge in the heterogeneous drug networks, F_i is the representation of node i.

Based on the representation vectors and edge-type projection matrices, the predicted confidence score of interaction between each drug i and node j that is TNF-α or IL-6 can be obtained by:

$$score\,(i,j) = F_i G_{PDI} H_{PDI}^T F_j^T \tag{2}$$

The top-k candidate drugs are selected according to the confidence scores for TNF-α or IL-6, respectively.

CMap analysis

In this section, we perform the CMap [24] analysis based on transcriptome data to further screen candidate drugs for COVID-19 patients. Due to the clinical manifestation and pathogeneses similarity of COVID-19 and SARS [51], DeepR2cov uses the gene expression profiles from SARS-CoV-infected patients (GEO:GSE1739) [52] to conduct connectivity analysis; the detailed steps are listed as follows.

Step 1: Student's *t*-test is performed to identify genes that are differentially expressed in samples from patients compared with normal samples. For each gene, the statistical significance is assessed by computing *P*-value. The log2(FC) value is calculated as the fold change (FC) between the signal intensity of patients and that of normal human subjects is calculated for each gene. Any genes meeting the criteria of $p < .01$ and an absolute log2(FC)

>1 are considered to be the up- and downregulated genes, according to the protocol described in [53].

Step 2: The CMap score is computed based on the sets of up- and downregulated genes in patients by using a web server (https://clue.io/query).

Step 3: In DeepR2cov, under the hypothesis that if a drug has a gene expression signature that is opposite to a disease signature, that drug could potentially be used as a treatment for that disease [23]. Therefore, drugs with the CMap scores >0 are filtered.

PubMed publication analysis

Based the PubMed publication, we manually filter out drugs that tend to increase the release of TNF-α or IL-6 and that treatment effectiveness to COVID-19 is controversial. In addition, we explore the potential action mechanism of these drugs for the treatment of COVID-19.

Molecular docking

DeepR2cov uses the molecular docking program DOCK6.8 [24] to explore the possible binding modes between the predicted drugs and TNF-α or IL-6. The three-dimensional structures of TNF-α and IL-6 are from the Protein Data Bank (PDB IDs 2AZ5 and 4CNI, respectively). The structures of drugs are from the ZINC database.

Biomedical application of DeepR2cov

To evaluate the representation performance of DeepR2cov, the representation is applied to DDI network reconstruction, ATC classification and three bio-link (i.e. DisPA, PDI and DSA) predictions.
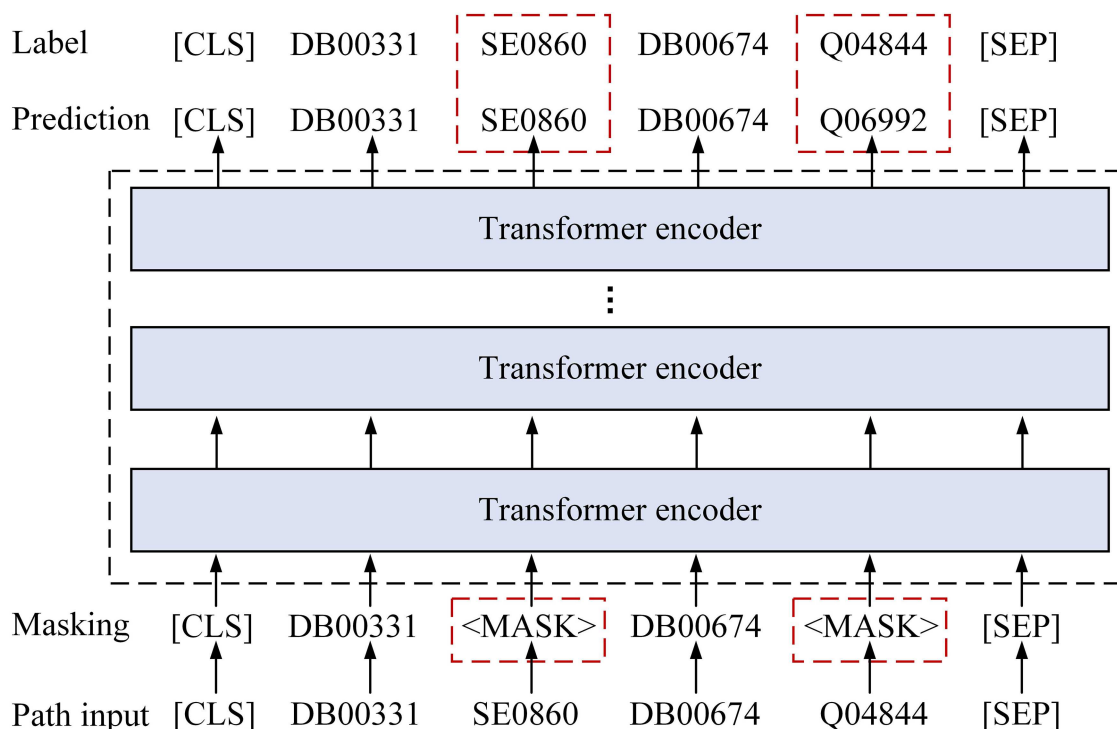
Figure 3. The architecture of the masked meta path learning. In input path, [CLS] and [SEP] represent the beginning and separator token in every input example, other tokens are node ID in the heterogeneous drug networks. The input paths are randomly masked by <MASK> token, and the objective is to predict the masked nodes based only on its context.

DDI network reconstruction

The representation vectors are expected to reconstruct the original networks. Here, we employ the DDI in the heterogeneous drug network as evaluation dataset. The proximity matrix is attained by calculating cosine similarity between representation vectors of all drugs. Then, node pairs are ranked according to their proximity score. Finally, the ratio of real links in the top k pairs of vertices is treated as the reconstruction precision. Generally, a higher reconstruction precision indicates a higher quality representation.

ATC classification

Identification of the ATC class of an uncharacterized compound is a challenging and important task. In this section, we adopt all drugs in the heterogeneous drug network as evaluation dataset of ATC classification prediction. Given known ATC classification of some drugs, the representation vectors of drugs are fed into the Multi-label K-Nearest Neighbor [54] model to predict potential ATC classes of drugs. Generally, high-quality representation vectors should lead to high precision of ATC classification.

Bio-link (DisPA, PDI and DSA) predictions

Link predictions, which refer to predicting the missing edges that may appear in the future, is pervasive in biological network analysis. Therefore, IMC is employed to perform bio-link predictions, that is, DisPA, PDI and DSA. For DisPA prediction, we employ the DisPA in the heterogeneous drug network as evaluation dataset. Given known disease–protein relationships, the representation vectors of all diseases and proteins are fed into IMC model to predict potential associations in disease–protein network. Similarly, we predict PDI and DSA in networks.

Studies suggested that a good network representation model can improve prediction accuracy of link predictions.

Results

Experiment settings and performance evaluation

The parameters of DeepR2cov follow BERT, which is $L = 12, H = 768$ and $A = 12$, where L, H and A are the number of Transformer blocks, the hidden size and the number of self-attention heads, respectively.

To evaluate the representation performance of DeepR2cov, the results on biomedical applications are based on comprehensively compared with those obtained from LINE [55], GraRep [56], struc2vec [57] and NeoDTI [13]. The details of baseline methods and hyperparameter selections can be found in Supplementary Materials Section S1. For DDI network reconstruction, we adopt Precision@k [58] as the evaluation metric. The coverage, one error, ranking loss and average precision, which are defined in [59], are used to evaluate the performance on ATC classification. For bio-link predictions, this work adopts the area under precision recall (AUPR) curve and area under receiver operating characteristic (AUC) curve as the evaluation metric.

Anti-inflammatory drug discovery and mechanism of action analysis

In DeepR2cov, 20 drugs (corresponding to roughly 3% of the total number of drugs), are selected as candidate agents binding to TNF-α and IL-6, respectively. Then, seven drugs with the CMap scores >0 are filtered (as described in Supplementary Materials Section S2). Then, we use knowledge from PubMed publications to filter out drugs that tend to increase release of TNF-α or IL-6

Table 2. Candidate drugs and their interaction mechanisms with COVID-19

Target	Drug name	Mechanism of action to COVID-19	PMID
TNF-α	Thalidomide	Decreasing stability of mRNA	8496685, 8755512, 12105857, 9068814
	Amrinone	Concentration dependent manner	11969359
	Dasatinib	Unclear	19786067
	Acarbose	Decreasing the expression of microRNA	24260283
	Minocycline	Unclear	15904993
	Imatinib	Reducing DNA binding of NF-κB	16174751, 32599278
	Enflurane	NA	NA
	Dipyridamole	Unclear	32318327, 23866809
	Nifedipine	Unclear	11104367, 15018304
	Olopatadine	Unclear	10831003, 15847317
IL-6	Oseltamivir	Unclear	30400276, 10517426
	Acarbose	Reducing the MicroRNA levels	24260283
	Tranexamic acid	Concentration dependent manner	17988379
	Aliskiren	Reducing the mRNA levels	24858618, 30569967
	Acetazolamide	Reducing the mRNA levels	28420165
	Dorzolamide	NA	NA
	Dacarbazine	NA	NA
	Methazolamide	Unclear	27158384
	Azithromycin	Inhibiting of NF-κB activation	24534490, 17012372 15252403
	Rivaroxaban	Reducing the mRNA levels	30867376, 28735510 31984306
	Ribavirin	Reducing the mRNA levels	18007553, 22269828 15607755, 15472864
	Amiloride	Unclear	8770057
	Amifostine	Inducing activation of redox signaling	19010997

NA represents that there has been no study proving that the drug can inhibit the release of TNF-α or IL-6.

(as described in Supplementary Materials Section S3). Finally, we manually filter out drugs (i.e. chloroquine and hydroxychloroquine), because their treatment effectiveness to COVID-19 is controversial (as described in Supplementary Materials Section S4).

Based on above procedure, we identify 22 anti-inflammatory drugs for COVID-19, where acarbose is treated as an agent that binds to both TNF-α and IL-6, as shown in Table 2. We find that 19 of 22 drugs that have been previously reported in PubMed publications could reduce the release of TNF-α or IL-6. Although most of these drugs are treated as therapeutic agents for inflammatory response, this study suggests their role in anti-inflammatory response in COVID-19 patients for the first time.

Fourteen drugs initially used for the anti-inflammatory response in COVID-19 patients

To the best of our knowledge, 14 of the drugs predicted by DeepR2cov are initially proposed as potential therapeutic for inflammatory response in COVID-19 patients. The evidences from PubMed publications suggest that these drugs inhibit the cytokine release and inflammatory response, as listed in column 4 in Table 2. These results suggest that the proposed DeepR2cov is able to predict candidate drugs that ameliorate the cytokine storm and inflammatory response in patients with COVID-19.

Eight agents in current ongoing clinical trials to COVID-19

In DeepR2cov, eight predicted drugs have been determined in clinical studies against COVID-19, as shown in Table 3. Interestingly, seven drugs (i.e. thalidomide, imatinib, oseltamivir, dipyridamole, azithromycin, rivaroxaban and ribavirin) have been used as an immunomodulator to treat the COVID-19

Table 3. Eight drugs in current ongoing clinical trial on COVID-19

Drug name	Clinic trial registration ID	
	Anti-inflammatory	Antiviral
Thalidomide	NCT04273581	NA
Imatinib	NCT04422678	NCT04394416
Oseltamivir	NCT04457609	NCT04516915
Dipyridamole	NCT04424901	NA
Tranexamic acid	NA	NCT04338126
Azithromycin	NCT04341870	NCT04359316
Rivaroxaban	NCT04662684	NA
Ribavirin	NCT04664010	NCT04494399

NA represents that there has been no clinical trial proving that the drug can inhibit inflammatory response or antiviral activity.

patients, which is consistent with the result of DeepR2cov. Meanwhile, clinical studies indicated that four agents (i.e. imatinib, oseltamivir, azithromycin and ribavirin) also play important roles in antiviral process. In addition, we also note that tranexamic acid was not only used to reduce the infectivity and but also virulence of SARS-CoV-2. However, Jimenez *et al*. [60] suggest that tranexamic acid plays a key role in the circulating levels of the proinflammatory cytokine IL-6. Therefore, ongoing clinical studies on COVID-19 should investigate the anti-inflammatory effects of tranexamic acid.

Anti-inflammatory response via multiple pathways

The knowledge from PubMed publications reveals that 19 drugs can inhibit TNF-α and IL-6 release to reduce inflammatory response. As shown in column 3 in Table 2, there are five drugs (i.e. thalidomide, aliskiren, acetazolamide, rivaroxaban

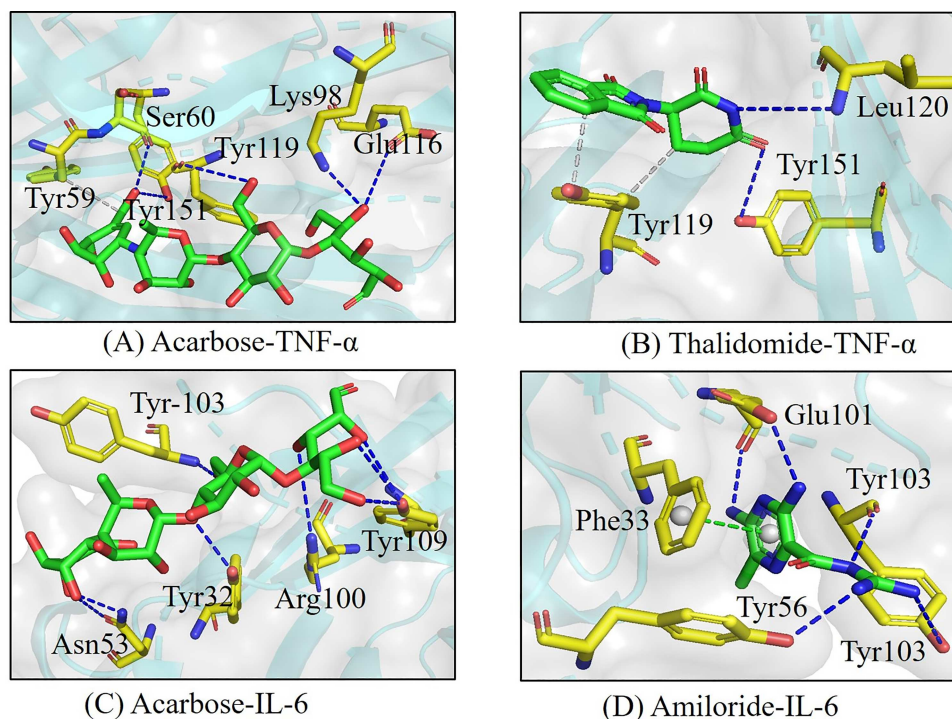**Figure 4**. Four representative molecular docking results for drugs binding to TNF-α or IL-6. The three-dimensional structures of TNF-α and IL-6 are from the PDB (IDs 2AZ5 and 4CNI, respectively). The structures of drugs are from the ZINC database. Here, the blue, green and gray dotted lines represent hydrogen bond, $\pi-\pi$ stacking and hydrophobic interaction between drugs and targets, respectively.

and ribavirin) that exert inhibitory action on TNF-α or IL-6 by decreasing mRNA stability or enhancing mRNA degradation. Administration of acarbose to diabetic rats significantly reduces the expression of microRNA to inhibit the release of TNF-α and IL-6. Amrinone reduces the release of TNF-α in a concentration-dependent manner. Imatinib inhibits TNF-α release by reducing the DNA binding of nuclear factor kappa B. Amifostine is considered as a therapeutic agent of lung inflammation that acts by suppressing IL-6-induced activation of redox-sensitive signaling. Ribavirin inhibits the expression of TNF-α and IL-6 in blood lymphocytes by reducing mRNA levels. Notably, a clinical study implied that ribavirin is able to reduce the release of IL-6 and IL-8 by inhibiting viral replication. The above studies illustrate that these drugs can ameliorate the release of TNF-α and IL-6 to reduce inflammatory responses via multiple pathways.

Molecular docking analysis

In this section, four representative docking results are shown in Figure 4. For the docking model of TNF-α, the docking result in Figure 4A shows that acarbose mainly binds to TNF-α via five hydrogen bonds and one hydrophobic interaction. Figure 4B shows that thalidomide binds to TNF-α via two hydrogen bonds and hydrophobic interactions. In the docking model for IL-6, seven hydrogen bonds are predicted to form interactions between acarbose and IL-6 as shown in Figure 4C. The result in Figure 4D shows that IL-6 combines with amiloride through five hydrogen bonds and form a $\pi-\pi$ stacking, respectively. These results suggest that there are some differences in the binding modes for different drugs and targets.

DeepR2cov-based drug repurposing for Middle East respiratory syndrome (MERS) and SARS

It is interesting and important to discuss more applications of DeepR2cov for other types of viral infections and human diseases. In this section, we use DeepR2cov to predict potential therapeutic agents for patients infected with MERS-CoV or SARS-CoV. Researches have suggested that interferon (IFN)-γ concentrations are markedly increased in MERS-CoV patients compared with healthy controls [61]. Similarly, the expression of IL-1β is upregulated in the blood of patients with SARS [62–63]. These studies also indicated that the excessive of IFN-γ (or IL-1β) are related to the severity disease and death in MERS (or SARS) patients. Therefore, we are working to predicting drugs that can inhibit the release of IFN-γ (or IL-1β) to treat patients with MERS (or SARS).

Based on the same procedure as DeepR2cov, we identify 11 drugs for MERS as shown in Supplementary Table S2. The PubMed publications have reported that eight of these drugs (i.e. imatinib, bupropion, venlafaxine, arsenic trioxide, bortezomib, sunitinib, nifedipine and donepezil) are able to reduce the release of IFN-γ and revealed that these drugs can reduce the release of IFN-γ via multiple pathways of action. For example, venlafaxine and sunitinib exert inhibitory action on IFN-γ by decreasing mRNA expression [64–65]. Arsenic trioxide alters the levels of INF-γ promoter acetylation and the combination of RNA polymerase II to the INF-γ promoter [66]. Bortezomib inhibits the express of IFN-γ by inducing T cell death [67–68].

Similarly, as shown in Supplementary Table S3, we identify 10 therapeutic agents targeting SARS, and the PubMed publications have demonstrated that eight of them can inhibit the express of IL-1β, that is, minocycline, orlistat, oseltamivir, fenofibrate, azithromycin, acetazolamide, gliclazide and tramadol. Based on
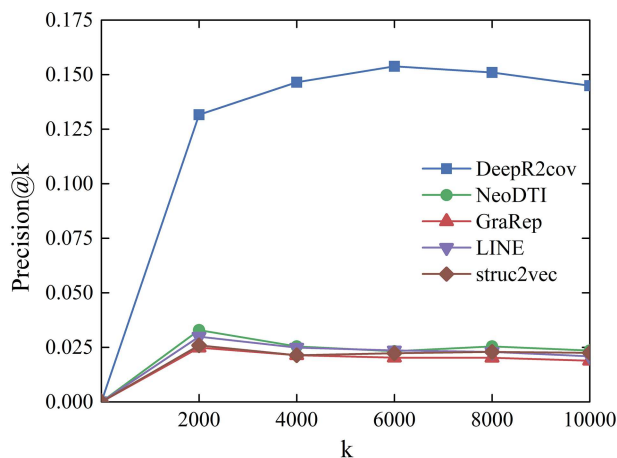
Figure 5. Results of DDI network reconstruction generated by DeepR2cov and baseline methods.

PubMed publications, we also explore the potential mechanism of these drugs for the treatment of MERS. Minocycline suppresses the release of IL-1β by reducing the mRNA expression [69]. Azithromycin significantly inhibits IL-1β secretion by destabilizing mRNA levels and a dose-dependent manner [70–71].

These drugs predicted by DeepR2cov should be taken into consideration in clinical studies on MERS or SARS. These results indicate that the proposed DeepR2cov not only can increase clinical testing accuracy for the emerging disease COVID-19, but also can be applied to develop effective treatment strategies for other types of viral infections and human diseases.

Representation performance on biomedical applications

In this section, we comprehensively analyze the results on biomedical applications to evaluate representation performance of DeepR2cov and baseline approaches.

Results of DDI network reconstruction

As shown in Figure 5, the Precision@k is calculated for different k values, which correspond to roughly 20%, 40%, 60%, 80% and 100% of the total number of the DDI edges (10 036), respectively. DeepR2cov significantly outperforms the baseline methods. Meanwhile, DeepR2cov shows the best precision when the k is 6000, whereas the baseline methods exhibit the best reconstruction precision when k is 2000. This result indicates that DeepR2cov may reconstruct more edges than the baseline methods.

Results of ATC classification

In this section, we perform 10-fold cross-validation, in which a subset of 10% of the drug entities in the heterogeneous drug network is randomly selected as test set, and the remaining 90% of drugs are treated as the training set. To reduce the data bias of cross-validation, DeepR2cov and baseline methods are repeatedly run 10 times and the average performance is computed. Meanwhile, average precision is used in the experiments to ensure a fair comparison, because original papers of baseline methods also compared average precision.

Table 4 shows the results of ATC classification generated by DeepR2cov and baseline methods, and the best results are marked in boldface. The results clearly demonstrate that DeepR2cov is able to achieve better results for ATC classification

than the baseline methods. In particular, DeepR2cov achieves an approximately 50% improvement in terms of one error value compared with baseline approaches. This results indicate that DeepR2cov is a powerful network representation method for predicting ATC classification of given drugs.

Results of three bio-link (DisPA, PDI and DSA) predictions

For bio-link predictions including DisPA, PDI and DSA, we perform a 10-fold cross-validation test on positive pairs and a matching number of randomly sampled negative pairs. Similar to the prediction of ATC classification, each method is repeated 10 times and the average performance is computed. Table 5 summarizes the overall results of the bio-link predictions.

In DisPA and DSA prediction tasks, DeepR2cov outperforms the baseline methods. In particular, DeepR2cov is significantly superior to struc2vec, improving the AUC and AUPR by over 10%. For PDI prediction, the baseline methods achieve poor results below 0.9 in terms of AUC and AUPR, whereas DeepR2cov shows the excellent performance with results close to 1. These findings suggest that DeepR2cov can still obtain good results when other methods fail to accurately predict PDI. In summary, we observe that DeepR2cov greatly outperforms other baseline methods.

Performance evaluations on the external drug repositioning dataset

The above experimental results are based on the heterogeneous drug networks (see Section Construction of heterogeneous drug networks) and maybe lead to overoptimistic results to a certain extent. To further test the validity and generalization ability of DeepR2cov, we employ a different drug repositioning dataset [16] as the external validation set that integrates four types of entities (i.e. drug, protein, side effect and disease) and eight types of relationships (i.e. DDI, DSA, PPI, PDI, DisPA, DisDA, DDSS and PPSS). Based this heterogeneous drug information networks, DeepR2cov automatically learns the representation vectors of entities and then feed the vectors into IMC [22] model to predict potential drug–protein interactions. The performance of DeepR2cov is compared with three state-of-the-art methods (i.e. NeoDTI [13], deepDTnet [16] and DTINet [25]) that are designed for drug repositioning. Based on the guidance in [16], we perform a 5-fold cross-validation test on positive pairs along with a matching number of randomly sampled negative pairs. To make a fair comparison, we adopt the hyperparameters and results from original paper [16] for deepDTnet and DTINet. The results of NeoDTI are attained by performing the source code that is provided by original work NeoDTI [13]. A detailed description of datasets and experiments can be found in Supplementary Materials Section S6. The results of DeepR2cov and baseline methods are listed in Table 6. We observe that DeepR2cov achieves superior performance compared with state-of-the-art methods, improving the AUC and AUPR by at least 2%. These results indicate that DeepR2cov has a high generalization ability and is able to apply to drug repositioning.

Effect of representation dimension

In this section, we evaluate the effect of representation dimension for the performance and time efficiency. The embedding dimension is a hyperparameter for representation learning. Here, each method is run times with different representation dimension to evaluate the impact of dimension on the prediction performance and time efficiency. Figure 6 illustrates the effects

Table 4. Results of ATC classification generated by DeepR2cov and baseline methods

Method	One error[a]	Coverage[a]	Ranking-loss[a]	Average precision[a]
DeepR2cov	**0.421**	**2.658**	**0.164**	**0.680**
NeoTDI	0.779	4.291	0.290	0.421
GraRep	0.763	4.298	0.291	0.424
LINE	0.769	4.234	0.285	0.431
struc2vec	0.798	4.379	0.297	0.405

[a]Among the mentioned evaluation metrics, smaller values show better performance except in the case of average precision.

Table 5. Results of three bio-link (DisPA, PDI and DSA) predictions generated by DeepR2cov and baseline methods

Method	DisPA		PDI		DSA	
	AUC	AUPR	AUC	AUPR	AUC	AUPR
DeepR2cov	**0.961**	**0.956**	**0.997**	**0.997**	**0.939**	**0.936**
NeoTDI	0.921	0.904	0.878	0.881	0.927	0.918
GraRep	0.918	0.898	0.805	0.798	0.890	0.879
LINE	0.902	0.885	0.840	0.835	0.879	0.868
struc2vec	0.834	0.794	0.751	0.743	0.838	0.828

Table 6. Results of DeepR2cov and baseline methods on the external drug repositioning dataset

Methods	AUC	AUPR
DeepR2cov	**0.994**	**0.996**
NeoTDI	0.971	0.970
deepDTnet	0.965	0.969
DTINet	0.963	0.969

of dimension on DDI network reconstruction (k = 10 000), ATC classification and three bio-link predictions. Generally, the prediction performance is improved with increasing representation dimension. The same conclusion is described in [72]. This is intuitive since higher number of dimensions can encode more useful information. However, the performance tends to saturate or decrement when the dimension reaches to a threshold (e.g. 768). In this study, the time cost first increases gradually when the dimension is below 768, but it tends to increase sharply (note that the y-axis is log-based) when the dimensionality continue to increase, as shown in Figure 7. There, we suggest that the dimensionality should be set to approximately 768 to optimize performance and time efficiency.

Discussion

To fight the emerging COVID-19 pandemic, this study proposes a deep representation on heterogeneous drug network to discover anti-inflammatory agents for patients with COVID-19. Based on comprehensive evaluation, DeepR2cov predicts 22 high-confidence drugs binding to cytokines to prevent excessive inflammatory responses in patients with COVID-19. To the best of our knowledge, 14 of these drugs predicted by DeepR2cov are initially proposed as anti-inflammatory therapeutic for COVID-19 patients. Eight drugs have been determined in clinical studies against COVID-19. Interestingly, four drugs (i.e. imatinib, oseltamivir, azithromycin and ribavirin) not only as immunomodulators but also as antiviral agents in clinical trial have been used to treat COVID-19 patients. A possible reason for the inconsistent result is that these studies use different

experimental approaches and drug dosage, thus leading to potential data conflicts or noises. Therefore, standard assays must be carried out to measure the effects of these drugs. In addition, all predicted drugs must be validated in preclinical models experiments and randomized clinical trials before being used in patients.

On five biomedical tasks, DeepR2cov significantly outperforms baseline network representation approaches. These results suggest that DeepR2cov is a powerful representation technique and can greatly facilitate the biomedical studies. A major reason for the success of DeepR2cov is that this work focuses on exploring the structural characteristics of the heterogeneous drug network and observes that the drug networks are multi-hub network. Therefore, we specially design 23 types of meta paths that integrate the structure and semantic feature among vertices in the heterogeneous drug networks. A mass of studies [42, 73–74] have suggested that meta paths could contribute to learning meaningful representation. However, these meta path-based representation approaches are mainly proposed on nonbiomedical networks, and only a few studies are focused on biomedical issues. Meanwhile, compared with previous path-based approaches, DeepR2cov integrates a deep bidirectional Transformer encoder, which can capture long-range dependency without regarding to their distance limits in original network. In addition, DeepR2cov designs the masked meta path learning strategy to enable train deep bidirectional representation model for capturing context-dependent relation. Nevertheless, most of path-based representation approaches adopt Skip-Gram that is a left-to-right architecture, where every token can only attend to previous tokens [73].

However, we acknowledge several limitations in our current study. DeepR2cov uses meta paths to help learning high-quality representation vectors for various tasks. Unfortunately, it only focuses on preserving local structure and semantic information. Therefore, the global information among vertices in heterogeneous drug networks is hard to be fully modeled. In addition, the generation of meta paths in DeepR2cov only consider the multi-hub characteristic of drug networks and ignores the attribute features of vertices in heterogeneous drug networks. However, attribute features of vertices play an important role in network-based drug discovery methods. Therefore, in the future,
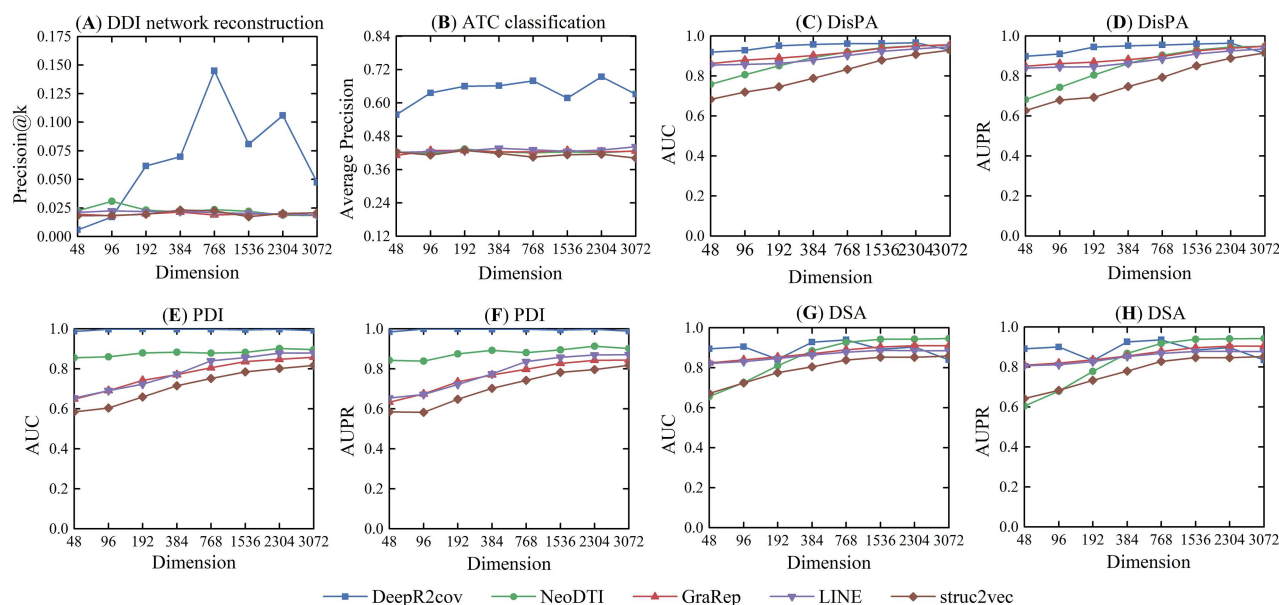
Figure 6. The results generated by DeepR2cov and baseline methods with different dimensions for five biomedical applications. (**A**) and (**B**) are the results of DDI network reconstruction, and ATC classification, respectively. (**C**)–(**H**) are the AUC and AUPR value of three link predictions.
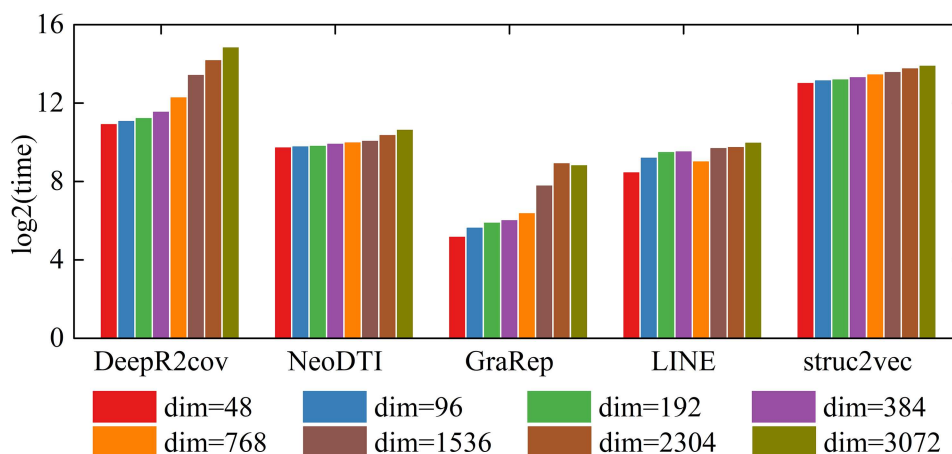

Figure 7. Influence of dimensionality on the training time of different representation methods.

we will develop more self-supervised learning mechanisms and effective multi-task learning frameworks that integrate the topology, semantic and attribute characteristics of biomedical heterogeneous networks for drug discovery.

In anti-inflammatory drug discovery, the top-*k* agents are regarded as candidate entities related to COVID-19 according to the confidence scores. The operation is simple and popularly applied to the recommended systems. However, the results neglect statistical significance to a certain extent. How to select associated candidate agents is also an important question for drug discovery. The selection strategy of candidates must be improved in order to promote the precision of drug repositioning. For example, the confidence score could be converted to a *z*-score based on permutation tests, and the corresponding *P*-value could be calculated. For each target, those predictions with a *P*-value <.05 could be treated as candidate drugs [19].

Conclusion

In this study, we propose DeepR2cov, which is a deep representation on heterogeneous drug network to discover agents for treating the excessive inflammatory response in COVID-19 patients. This work explores the multi-hub characteristic of heterogeneous drug networks, which inspires us to design a meta path-driven deep representation model. The representation model can capture long-range dependency and complex semantic relation among nodes in heterogeneous drug networks. Based on the representation vectors and transcriptomics data, DeepR2cov identifies 22 potential drugs that bind to TNF-α or IL-6 to prevent excessive inflammatory responses in patients with COVID-19. These drugs predicted by DeepR2cov agreed well with the previous experimental studies in PubMed publications and ongoing clinical trials. In addition, the results of five biomedical applications demonstrate that DeepR2cov significantly outperforms

than other representation approaches. In summary, this study offers a powerful network representation approach and holds the potential to accelerate the treatment of the inflammatory responses in patients with COVID-19. Meanwhile, DeepR2cov could also been applied to develop treatment strategies for other types of human diseases.

Key Points

- We built a heterogeneous drug network by integrating eight unique networks and observe that the drug networks is multi-hub networks, where drugs and proteins are important hubs.
- Inspired by the multi-hub characteristic, we design a meta path-driven deep representation learning model that can integrate long-range structure dependency and complex semantic relation among network nodes.
- We predict 22 drugs, whose therapeutic associations with the inflammation storm in COVID-19 patients, and molecular binding model are further validated via data from PubMed publications, ongoing clinical trials and a docking program.
- The results on five biomedical applications suggest that our proposed approach is a powerful network representation approach and can achieve competitive performance compared with state-of-the-art methods.

Supplementary Data

Supplementary data are available online at https://academic.oup.com/bib.

Data and code availability

The additional data and code related to this paper can be downloaded from https://github.com/pengsl-lab/DeepR2cov.git.

References

1. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunol* 2020;**20**:355–62.
2. Mehta P, McAuley DF, Brown M, *et al*. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;**395**:1033–4.
3. Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;**395**:497–506.
4. Dhall A, Patiyal S, Sharma N, *et al*. Computer-aided prediction and design of IL-6 inducing peptides: IL-6 plays a crucial role in COVID-19. *Brief Bioinform* 2020. doi: 10.1093/bib/bbaa259.
5. Li X, Giorgi EE, Marichannegowda MH, *et al*. Emergence of SARS-CoV-2 through recombination and strong purifying selection. *Sci Adv* 2020;**6**:eabb9153.
6. Dickson M, Gagnon JP. Key factors in the rising cost of new drug discovery and development. *Nat Rev Sci Adv* 2004;**3**:417–29.
7. Pushpakom S, Iorio F, Eyers P, *et al*. Drug repurposing: progress, challenges and recommendations. *Nat Rev Drug Discov* 2019;**18**:41–58.
8. Popova M, Isayev O, Tropsha A. Deep reinforcement learning for de novo drug design. *Sci Adv* 2018;**4**:eaap7885.
9. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'cytokine storm' in COVID-19. *J Infect* 2020;**80**:607–13.
10. Cheng F, Desai RJ, Handy DE, *et al*. Network-based approach to prediction and population-based validation of in silico drug repurposinge. *Nat Commun* 2018;**9**:2691.
11. Badkas A, De Landtsheer S, Sauter T. Topological network measures for drug repositioning. *Brief Bioinform* 2020. doi: 10.1093/bib/bbaa357.
12. Zeng X, Zhu S, Liu X, *et al*. deepDR: a network-based deep learning approach to in silico drug repositioning. *Bioinformatics* 2019;**35**:5191–8.
13. Wan F, Hong L, Xiao A, *et al*. NeoDTI: neural integration of neighbor information from a heterogeneous network for discovering new drug-target interactions. *Bioinformatics* 2019;**35**:104–11.
14. Zong N, Kim H, Ngo V, *et al*. Deep mining heterogeneous networks of biomedical linked data to predict novel drug-target associations. *Bioinformatics* 2017;**33**:2337–44.
15. Zeng X, Zhu S, Hou Y, *et al*. Network-based prediction of drug-target interactions using an arbitrary-order proximity embedded deep forest. *Bioinformatics* 2020;**36**:2805–12.
16. Zeng X, Zhu S, Lu W, *et al*. Target identification among known drugs by deep learning from heterogeneous networks. *Chem Res* 2020;**11**:1775.
17. Dotolo S, Marabotti A, Facchiano A, *et al*. A review on drug repurposing applicable to COVID-19. *Brief Bioinform* 2020. doi: 10.1093/bib/bbaa357.
18. Zeng X, Song X, Ma T, *et al*. Repurpose open data to discover therapeutics for COVID-19 using deep learning. *J Proteome Res* 2020;**19**:4624–36.
19. Ge Y, Tian T, Huang S. Et al., A data-driven drug repositioning framework discovered a potential therapeutic agent targeting COVID-19. *bioRxiv* 2020. doi: 10.1101/ 2020.03.11.986836 preprint: not peer-reviewed. 12 March 2020.
20. Zhou Y, Hou Y, Shen J, *et al*. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS- CoV-2. *Cell Discov* 2020;**6**:14.

21. Chen C, Qi F, Shi K, *et al*. Thalidomide combined with low-dose short- term glucocorticoid in the treatment of critical coronavirus disease. *Clin Transl Med* 2019;**10**:e35.

22. Natarajan N, Dhillon IS. Inductive matrix completion for predicting gene-disease associations. *Bioinformatics* 2014;**30**:i60–8.

23. Lamb J, Crawford ED, Peck D, *et al*. The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease. *Science* 2006;**313**:1929–35.

24. Lang PT, Brozell SR, Mukherjee S, *et al*. DOCK 6: combining techniques to model RNA-small molecule complexes. *RNA (New York, NY)* 2009;**15**:1219–30.

25. Luo Y, Zhao X, Zhou J, *et al*. A network integration approach for drug-target interaction prediction and computational drug repositioning from heterogeneous information. *Nat Commun* 2017;**8**:573.

26. Yu G, Wang LG, Yan GR, *et al*. DOSE: an R/Bioconductor package for disease ontology semantic and enrichment analysis. *Bioinformatics* 2015;**31**:608–9.

27. Cheng L, Zhao H, Wang P, *et al*. Computational methods for identifying similar diseases. *Mol Ther Nucleic Acids* 2019;**18**:590–604.

28. Wishart DS, Feunang YD, Guo AC, *et al*. DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Res* 2018;**46**:D1074–82.

29. Gaulton A, Bellis LJ, Bento AP, *et al*. ChEMBL: a large-scale bioactivity database for drug discovery. *Nucleic Acids Res* 2012;**40**:D1100–7.

30. Keshava Prasad TS, Goel R, Kandasamy K, *et al*. Human protein reference database-2009 update. *Nucleic Acids Res* 2009;**37**:D767–72.

31. Figeys D. Mapping the human protein interactome. *Cell Res* 2008;**18**:716–24.

32. Oughtred R, Stark C, Breitkreutz BJ, *et al*. The BioGRID interaction database: 2019 update. *Nucleic Acids Res* 2019;**47**:D529–41.

33. Davis AP, Grondin CJ, Johnson RJ, *et al*. The comparative toxicogenomics database: update 2017. *Nucleic Acids Res* 2017;**45**:D972–8.

34. Brown AS, Patel CJ. A standard database for drug repositioning. *Sci Data* 2017;**4**:170029.

35. Kuhn M, Campillos M, Letunic I, *et al*. A side effect resource to capture phenotypic effects of drugs. *Mol Syst Biol* 2010;**6**:343.

36. Smith TF, Waterman MS. Identification of common molecular subsequences. *J Mol Biol* 1981;**147**:195–7.

37. Hattori M, Okuno Y, Goto S, *et al*. Development of a chemical structure comparison method for integrated analysis of chemical and genomic information in the metabolic pathways. *J Am Chem Soc* 2003;**125**:11853–65.

38. Rogers D, Hahn M. Extended-connectivity fingerprints. *J Chem Inf Model* 2010;**50**:742–54.

39. Sun Y, Han J, Yan X, *et al*. Pathsim: meta path-based top-k similarity search in heterogeneous information networks. *Proc VLDB Endowt* 2011;**4**:992–1003.

40. Sun Y, Norick B, Han J, *et al*. Pathselclus: integrating meta-path selection with user-guided object clustering in heterogeneous information networks. *ACM Trans Knowl Discov Data* 2012;**7**:1–23.

41. Shi C, Lu Y, Hu L, *et al*. Rhine: relation structure-aware heterogeneous information network embedding. *IEEE Trans Knowl Data Eng* 2020;**1**. doi: 10.1109/TKDE.2020.2982898.

42. Fu G, Ding Y, Seal A, *et al*. Predicting drug target interactions using meta-path-based semantic network analysis. *BMC Bioinform* 2016;**17**:160.

43. Vaswani A, Shazeer N, Parmar N, *et al*. Attention is all you need. In: *Proceedings of the 31st International Conference on Neural Information Processing Systems*, Curran Associates Inc., 57 Morehouse Lane, Red Hook, NY, United States. Long Beach, CA. 2017;6000–10.

44. He K, Zhang X, Ren S, *et al*. Deep residual learning for image recognition. *Proc IEEE Conf Comput Vis Pattern Recogn* 2016;770–8.

45. Taylor WL. Cloze procedure: a new tool for measuring readability. *Journalism Q* 1953;**30**:415–33.

46. Devlin, J., Chang, M., Lee, K., *et al*. BERT: pre-training of deep bidirectional transformers for language understanding. In: *Proceedings of the 2019 Conference of the North American Chapter of the Association for Computational Linguistics: Human Language Technologies*, Association for Computational Linguistics. Minneapolis, Minnesota, USA. 2019;4171–86.

47. Qin C, Zhou L, Hu Z, *et al*. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis* 2020;**71**:762–8.

48. Chen G, Wu D, Guo W, *et al*. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020;**130**:2620–9.

49. Feldmann M, Maini RN, Woody JN, *et al*. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. *Lancet* 2020;**395**:1407–9.

50. Chen X, Zhao B, Qu Y, *et al*. Detectable serum severe acute respiratory syndrome coronavirus 2 viral load (RNAemia) is closely correlated with drastically elevated interleukin 6 level in critically ill patients with coronavirus disease 2019. *Clin Infect Dis* 2020;**71**:1937–42.

51. Xu J, Zhao S, Teng T, *et al*. Systematic comparison of two animal-to-human transmitted human coronaviruses: SARS-CoV-2 and SARS-CoV. *Viruses* 2020;**12**:244.

52. Reghunathan R, Jayapal M, Hsu LY, *et al*. Expression profile of immune response genes in patients with severe acute respiratory syndrome. *BMC Immunol* 2005;**6**:2.

53. Josset L, Menachery VD, Gralinski LE, *et al*. Cell host response to infection with novel human coronavirus EMC predicts potential antivirals and important differences with SARS coronavirus. *MBio* 2013;**4**:e00165–13.

54. Nanni L, Brahnam S. Multi-label classifier based on histogram of gradients for predicting the anatomical therapeutic chemical class/classes of a given compound. *Bioinformatics* 2017;**33**:2837–41.

55. Tang J, Qu M, Wang M, *et al*. Line: large-scale information network embedding. In: *Proceedings of the 24th International Conference on World Wide Web*, International World Wide Web Conferences Steering Committee, Republic and Canton of Geneva, Switzerland. Florence Italy. 2015; 1067–77.

56. Cao S., Lu W. and Xu Q. Grarep: learning graph representations with global structural information. In: *Proceedings of the 24th ACM International on Conference on Information and Knowledge*, Association for Computing Machinery, New York, NY, United States. Melbourne Australia. 2015; 891–900.

57. Ribeiro LFR, Saverese P and Figueiredo DR. struc2vec: learning node representations from structural identity. In: *Proceedings of the 23rd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*, Association for Computing Machinery, New York, NY, United States. Halifax NS Canada. 2017;385–94.

58. Ou M, Cui P, Pei J, *et al*. Asymmetric transitivity preserving graph embedding. In: *Proceedings of the 22nd ACM SIGKDD*

International Conference on Knowledge Discovery and Data Mining, Association for Computing Machinery, New York, NY, United States. San Francisco California USA. 2016;1105–14.

59. Kashef S, Nezamabadi-Pour H, Nikpour B. Multilabel feature selection: a comprehensive review and guiding experiments. *Wiley Interdiscip Rev Data Min Knowl Discov* 2018;**8**: e1240.

60. Jimenez JJ, Iribarren JL, Lorente L, *et al*. Tranexamic acid attenuates inflammatory response in cardiopulmonary bypass surgery through blockade of fibrinolysis: a case control study followed by a randomized double-blind controlled trial. *Crit Care* 2007;**11**:R117.

61. Mahallawi WH, Khabour OF, Zhang Q, *et al*. MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. *Cytokine* 2018;**104**:8–13.

62. Perlman S, Dandekar AA. Immunopathogenesis of coronavirus infections: implications for SARS. *Nat Rev Immunol* 2005;**5**:917–27.

63. Peiris JS, Guan Y, Yuen KY. Severe acute respiratory syndrome. *Nat Med* 2004;**10**:S88–97.

64. Vollmar P, Nessler S, Kalluri SR, *et al*. The antidepressant venlafaxine ameliorates murine experimental autoimmune encephalomyelitis by suppression of proinflammatory cytokines. *Int J Neuropsychopharmacol* 2009;**12**: 525–36.

65. Chen L, Xu P, Xiao Q, *et al*. Sunitinib malate inhibits intestinal tumor development in male ApcMin/+ mice by down-regulating inflammation-related factors with suppressing β-cateinin/c-Myc pathway and re-balancing Bcl-6 and Caspase-3. *Int Immunopharmacol* 2021;**90**: 107128.

66. Hu H, Chen E, Li Y, *et al*. Effects of arsenic trioxide on INF-gamma gene expression in MRL/lpr mice and human lupus. *Biol Trace Elem Res* 2018;**184**:391–7.

67. Yanaba K, Asano Y, Tada Y, *et al*. Proteasome inhibitor bortezomib ameliorates intestinal injury in mice. *PLoS One* 2012;**7**:e34587.

68. Yanaba K, Yoshizaki A, Muroi E, *et al*. The proteasome inhibitor bortezomib inhibits T cell-dependent inflammatory responses. *J Leukoc Biol* 2010;**88**:117–22.

69. Azarabadi M, Heidari F, Khaki AA, *et al*. Minocycline attenuates testicular damages in a rat model of ischaemia/reperfusion (I/R) injury. *Andrologia* 2020;**52**:e13704.

70. Gualdoni GA, Lingscheid T, Schmetterer KG, *et al*. Azithromycin inhibits IL-1 secretion and non-canonical inflammasome activation. *Sci Rep* 2015;**5**:12016.

71. Lendermon EA, Coon TA, Bednash JS, *et al*. Azithromycin decreases NALP3 mRNA stability in monocytes to limit inflammasome-dependent inflammation. *Respir Res* 2017;**18**:131.

72. Yue X, Wang Z, Huang J, *et al*. Graph embedding on biomedical networks: methods, applications and evaluations. *Bioinformatics* 2020;**36**:1241–51.

73. Dong Y, Chawla NV and Swami A Metapath2vec: scalable representation learning for heterogeneous networks. In: *Proceedings of the 23rd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*, Association for Computing Machinery, New York, NY, United States. Halifax NS Canada. 2017;135–44.

74. Shi C, Hu B, Zhao WX, *et al*. Heterogeneous information network embedding for recommendation. *IEEE Trans Knowl Data Eng* 2019;**31**:357–70.