Network Representation Learning-based Drug Mechanism Discovery and Anti-inflammatory Response against COVID-19

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Abstract— Recent studies have been demonstrated that the excessive inflammatory response is an important factor of death in COVID-19 patients. In this study, we proposed a network representation learning-based methodology, termed AIdrug2cov, to discover drug mechanism and anti-inflammatory response for patients with COVID-19. This work explores the multi-hub characteristic of a heterogeneous drug network integrating 8 unique networks. Inspired by the multi-hub characteristic, we design three 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. Using the representation vectors, AIdrug2cov identifies 40 potential targets and 22 high-confidence drugs that bind to tumor necrosis factor(TNF)-α or interleukin(IL)-6 to prevent excessive inflammatory responses in COVID-19 patients. Finally, we analyze mechanisms of action based on PubMed publications and ongoing clinical trials, and explore the possible binding modes between the new predicted drugs and targets via docking program. In addition, the results in 5 pharmacological application suggested that AIdrug2cov significantly outperforms 5 other state-of-the-art network representation approaches, future demonstrating the availability of AIdrug2cov in drug development field. In summary, AIdrug2cov is practically useful for accelerating COVID-19 therapeutic development. The source code and data can be downloaded from https://github.com/pengsl-lab/AIdrug2cov.git.

Index Terms—heterogeneous drug networks, deep representation learning, anti-inflammatory response, COVID-19

1 Introduction

Globally as of 14 January, 2021, there have been over 90,759,370 confirmed cases of COVID-19, including 1,963,169 deaths, reported to World Health Organization (WHO), implying that the novel coronavirus (SARS-CoV-2) has posed a global health threat(https://covid19.who.int/). In addition, it has been well proven that host immune responses are important factors leading to life-threatening acute respiratory distress syndrome (ARDS) in COVID-19 patients [1]. Although numerous of researchers are devoted to elucidating the pathogenic mechanisms of SARS-CoV-2, and to developing effective medications for controlling and preventing COVID-19,Considering that the new drug development is a complex, lengthy and expensive process, one effective method of drug discovery is to apply a drug repositioning [2] strategy to identify the potential drugs among existing ones. Compared to developing a drug *de novo*, discovering potential drugs from existing ones may significantly reduce the cost and period of drug development. Therefore, drug repositioning has received increased attention from pharmaceutical companies, governments agencies and academic researchers in recent year. Nevertheless, the development of promising drug discovery approaches for the effective treatment of COVID-19 is challenging, because of insufficient knowledge regarding drug targets and the

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disease pathology. Therefore, it is important to understand how SARS-CoV-2 give elicits host immune responses, and to apply this knowledge towards the discovery of potential targets and drugs, and elucidation of drug mechanisms of action against COVID-19.

Identification of the proteins involved in COVID-19 is a primary step towards revealing the underlying molecular mechanisms of SARS-CoV-2 infection, and can potentially improve clinical therapies for COVID-19. Unfortunately, limited knowledge regarding the detailed pathogenic mechanism of SARS-CoV-2 has prevented comprehensive identification and evaluation of disease-causing proteins. However, a growing body of research suggests that the clinical manifestations of severe acute respiratory syndrome (SARS) and COVID-19 was highly similar, and they may have similar pathogenesis [3]. In addition, phylogenetic analysis has revealed that the genome of SARS-CoV-2 is similar to that of SARS-CoV, with approximately 79% sequence identity [4]. Above all, they have the similar host-cell receptor usage and cell entry mechanism [5]. Given these apparent similarities between the two viruses and the corresponding diseases, identification of COVID-19-related proteins based on previous SARS studies is an important step towards understanding the nature of COVID-19 and determining a possible cure for the disease.

Since the COVID-19 outbreak, many studies have focused on identifying proteins or drugs related to the entry, fusion, and replication of SARS-CoV-2. For example, scientists have demonstrated that SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) [6], [7] and transmembrane protease serine 2 (TMPRSS2) for entry into host cells [8]. In addition, several antiviral drugs with inhibitory effects against SARS-CoV-2 have been selectively tested in clinical trials [9], [10]. However, recent reports show that the development of severe disease does not seem to be solely related to viral load [11], and that the hyperinflammatory response induced by SARS-CoV-2 is a main cause of severe disease and death in infected patients [12]. Unfortunately, the efficacy of existing antiviral agents, such as favipiravir, arbidol, and darunavir, which are being tested in ongoing clinical studies on COVID-19, might be unsatisfactory or insufficient for patients suffering from immune imbalance, and the mechanisms of action of these drugs in this disease are uncertain [13]. Therefore, aside from the development of an antiviral treatment strategy, proteins that cause excessive inflammation, should be identified, and targeted to discover anti-inflammatory agents, particularly for the patients with severe disease.

Drug repositioning and discovery poses formidable challenges because the pharmacological action mechanisms and biological process are complex and elusive. Fortunately, with the rapid development of the systems biology and network pharmacology fields, the drug research paradigm has changed from the linear mode of "one drug, one target, one disease" to the network mode of "multi-drugs, multi-targets, multi diseases" [14]. Cheng *et al*. have suggested that the integration of multiple perspectives network contributes to understanding and analysis of molecular action mechanisms [14]. Among the advances, network-based methods have already offered promising insights to improve the accuracy of *in silico* drug discovery, and to elucidate action mechanisms for the effective treatment of COVID-19 [15].

In this study, we proposed a network representation learning-based drug mechanism discovery and anti-inflammatory response, termed AIdrug2cov, to identify potential drugs for COVID-19. We construct a heterogeneous drug network by integrating 8 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. In this study, based on the representations and transcriptome data, AIdrug2cov identified 40 potential targets related to COVID-19, and 22 high-confidence drugs binding to TNF-α or IL-6 for preventing excessive inflammatory response in patients with COVID-19. Finally, we analyze mechanisms of action (MOA) 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 [16]. To evaluate and interpret the representation performance of AIdrug2cov, we integrated 3 type of pharmacological tasks: drug-drug interaction network (DDI) reconstruction, Anatomical Therapeutic Chemical (ATC) classification, and bio-link prediction. The results demonstrate that AIdrug2cov significantly outperforms 5 other state-of-the-art network representation approaches. In summary, AIdrug2cov is a practically useful tool for accelerating COVID-19 therapeutic development.

2 Result

2.1 Overview of AIdrug2cov

An overview of the proposed AIdrug2cov, which is a network representation learning-based methodology to discover drug mechanism and anti-inflammatory response for patients with COVID-19, is shown in Fig.1. First, we constructed a comprehensive heterogeneous network to integrate drugs, diseases, proteins, and side-effects. A network representation approach based on semantic paths and deep bidirectional Transformer encoder model was developed to automatically learn a low-dimensional embedding vector by systematically integrating the semantic relation and topological structure of a heterogeneous network. Then, the low-dimensional vector of nodes was fed into an inductive matrix completion (IMC) model [17] to identify the top 45 potential targets related to SARS or COVID-19. Enrichr [18] was used to perform functional enrichment analysis, and we conducted a mechanism of action (MOA) analysis based on the literature search. Note that target identification of COVID-19 is conducted with SARS data, since the clinical manifestation and pathogeneses of these diseases are highly similar [3]. Similarly, AIdrug2cov predicted 40 high-confidence drugs based on the predicted targets TNF-α and IL-6. Next, we performed Connectivity Map (CMap) [19] analysis and literature search to identify 22 agents that bind to TNF-α or IL-6 to prevent cytokine storms and excessive inflammatory responses in patients with COVID-19. Finally, we analyzed multiple mechanisms of action base on literature reports, and explored the possible binding modes between the new predicted drugs and TNF-α and

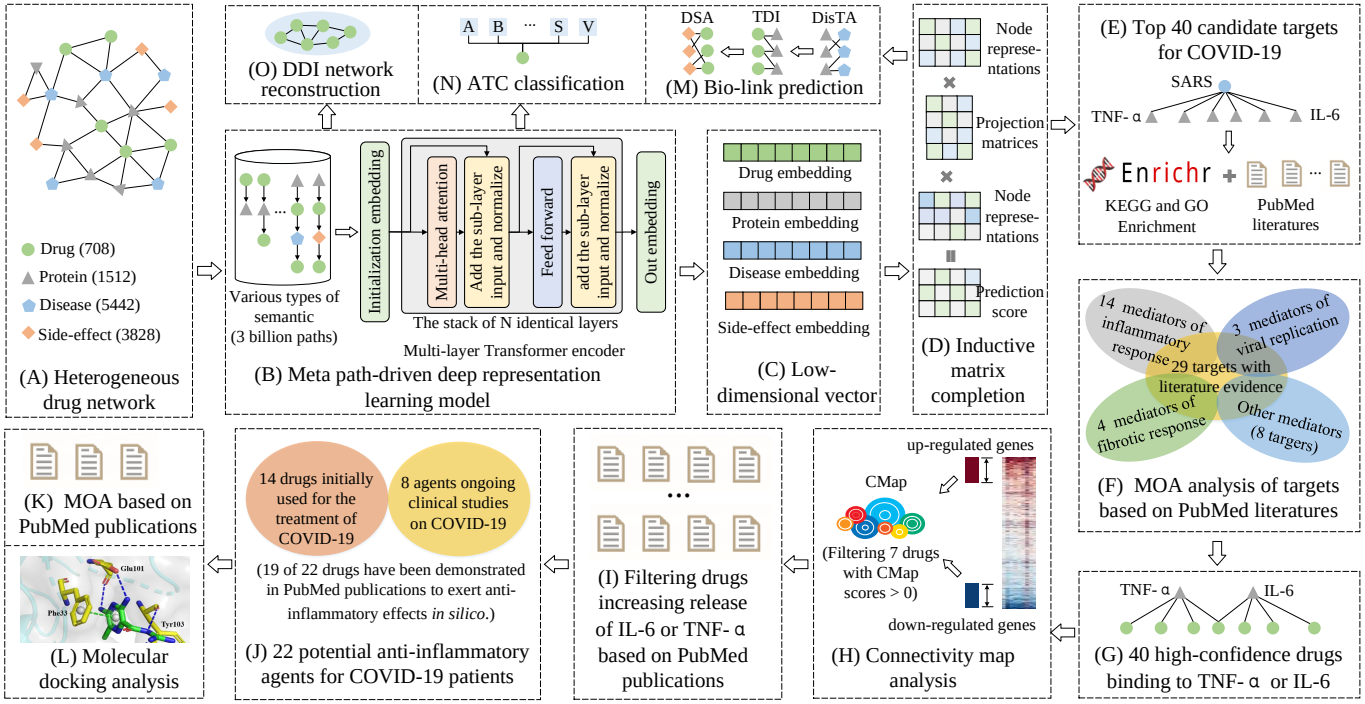


Fig. 1. Overview of AIdrug2cov to identify drug mechanism of action and anti-inflammatory response against COVID-19.

IL-6 with the docking program DOCK6.8 [16]. In addition, this study integrated DDI network reconstruction, ATC classification, and bio-link (i.e., disease→protein→drug→side-effect association) prediction to future evaluate and validate the applicability, and scalability of AIdrug2cov in the drug development process.

2.2 COVID-19 target identification

In this study, the top 40 proteins, which corresponded to roughly 3% of the total number of the protein entity in heterogeneous network, were regarded as potential targets for COVID-19. In this study, Evidence from the literature was used to determine the action mechanism between each target and COVID-19. As shown in Table 1, most of the proteins have been demonstrated to have interaction mechanism or therapeutic associations with SARS or COVID-19. Apparently, the most popular targets seem to be mediators of inflammation, such as TNF [1], [20], IL1B [21], IL-6 [22], [23], CCL2 [21], [24], IFNG [23], [25], [26], and CXCL10 [1], [21]. The targets MAPK3 [27], TP53 [28], and RB1 [29], [30] affect the replication processes of SARS-CoV and SRAS-CoV-2. CASP3 [31], [32] and CYCS [33], [34] induce apoptosis of cells infected with SARS-CoV. AKT1 signaling pathways also play key roles in persistent SARS-CoV infection [35]. Inhibiting EGFR and TGFB1 [36], [37] signaling may prevent an excessive fibrotic response to SARS-CoV and other respiratory viral infections [38]. A GSTM1 null genotype may increase the risk of pulmonary fibrosis of COVID-19 patients [39], and it is worth noting that there has also been one report of a newly emerged fibrosis in a COVID-19 patient [40]. COVID-19 was found to aggravate already compromised NO production in a cohort with NOS3 polymorphism, and management of NOS3/iNOS ratios and NO levels can prevent the development of severe ARDS. In addition, certain crucial proteins are associated with SARS-CoV or SARS-CoV-2, such as, VEGFA [41], RAC1 [37], INS [42], ICAM1 [43], [44], and CDK2 [45], [46].

2.2.1 *Inflammatory response-related targets for COVID-19*

Twelve targets appear to be critical mediators of the inflammatory response in moribund COVID-19 patients, and this response is closely related to the severity of the disease. Similar to the situation in SARS-CoV, the levels of TNF [1], [20], IL1B [21], IL-6 [22], [23], CCL2 [21], [24], IFNG [23], [25], [26] and CXCL10 [1], [21] are significantly elevated and are associated with adverse clinical outcomes in patients with COVID-19. NFKB1 is a key factor in the hyperactivation of monocyte-derived macrophages in COVID-19 [21], which directly affects the inflammatory response. The most important signal transduction pathways activated by viruses leading to the expression of proinflammatory cytokines are mediated by the factors IRF-3 and IRF-7 and JUN [47]. PARP plays a critical role in cytokine release in response to any lung injury causing viral infection, and the course of COVID-19 may be altered by inhibiting this protein [48]. HMOX1 has been shown to display anti-inflammatory properties in models of acute pulmonary inflammation, and is expressed in most cell types in organisms [49], [50]. A large body of evidence from preclinical studies indicates that MAPK14 paly a crucial role in inflammatory cytokine production [32], [51], [52]. MMP2 is a marker that aggravates pulmonary damage in SARS patients, and doxycycline markedly suppresses the levels of proinflammatory cytokines by inhibiting this protein [53], [54], [55]. PPAR is a key regulators of inflammation, and its activation results in reductions in inflammatory cytokine levels.

TABLE 1
Candidate targets and their interaction mechanisms with COVID-19.

NO.	UniProt ID:name	Confidence	Interaction mechanism to COVID-19	References
1	P01375:TNF-α*	0.5962	Cytokine in moribund COVID-19 patients	[1], [20]
2	P35354:PTGS2*	0.5900	A key mediator of inflammation in SARS	[56], [57], [58]
3	P42574:CASP3	0.5811	Critical medium inducing apoptosis of cells infected with SARS-CoV	[31], [32]
4	P10415:BCL2	0.5667	Necessary for survival of persistently SARS-CoV-infected cells	[59]
5	P01584:IL1B*	0.5635	Cytokine in moribund COVID-19 patients	[21]
6	P27361:MAPK3	0.5628	Participant in SARS-CoV replication	[27]
7	P04637:TP53	0.5626	Antagonist of coronavirus replication	[28]
8	P05412:JUN*	0.5368	Induction of proinflammatory cytokines of coronavirus	[47]
9	P28482:MAPK1	0.5367	NA	NA
10	P99999:CYCS	0.5337	Medium inducing apoptosis related to SARS-CoV membrane protein	[33], [34]
11	P37231:PPARG*	0.5288	Key regulators of inflammation	[60]
12	P19838:NFKB1*	0.5282	Hyperactivation of monocytederived macrophages in COVID-19	[21], [61]
13	P09210:GSTA2	0.5204	A factor of pulmonary fibrosis in COVID-19 patients	[39]
14	P05231:IL-6*	0.5170	Cytokine storm in moribund COVID-19 patients	[22], [23]
15	Q03181:PPARD	0.5073	NA	NA
16	P15692:VEGFA	0.5051	A key factor in both ICU and non-ICU COVID-19 patients	[41]
17	P09874:PARP1*	0.5003	An pivotal role on cytokine release in COVID-19	[48]
18	P35228:NOS2	0.4991	Inhibits viral protein and RNA synthesis	[62], [63]
19	P05164:MPO	0.4945	Higher levels of MPO in adult patients with COVID-19	[64]
20	P09601:HMOX1*	0.4920	Anti-inflammatory effects on LPS-induced pulmonary inflammation.	[49], [50]
21	P17302:GJA1	0.4827	NA	NA
22	P01308:INS	0.4824	Obesity-related comorbidities and mechanisms of a severe course of COVID-19	[42]
23	P01137:TGFB1	0.4800	Relation to the fibrosis and fluid homeostasis in the lungs for the severe COVID-19	[36], [37]
24	P00533:EGFR	0.4771	High rate of pulmonary fibrosis	[40], [65]
25	Q16539:MAPK14*	0.4750	Key signaling molecules as therapeutic targets for inflammatory diseases in SARS	[32], [51], [52]
26	P05067:APP	0.4746	NA	NA
27	P45983:MAPK8	0.4742	NA	NA
28	P13500:CCL2*	0.4698	Inflammatory chemokine storms in severe COVID-19 patients	[21], [24]
29	P05362:ICAM1	0.4689	Key hub genes involved in COVID-19	[43], [44]
30	P63000:RAC1	0.4648	A role in SARS-PLpro-induced STAT6 nuclear translocation	[37]
31	P31749:AKT1	0.4608	A key role in persistent SARS-CoV infection	[35]
32	P06400:RB1	0.4607	Initiation of gene expression and viral replication	[29], [30]
33	P08253:MMP2*	0.4601	A marker of inflammation aggravating pulmonary damage in SARS patients	[53], [54], [55]
34	P08684:CYP3A4	0.4579	NA	NA
35	P07101:TH	0.4565	NA	NA
36	O75469:NR1I2	0.4562	NA	NA
37	P09488:GSTM1	0.4560	Aggrandizement the risk of pulmonary fibrosis in COVID-19 patients	[39]
38	P02778:CXCL10*	0.4558	Inflammatory chemokines in COVID-19 patients	[1], [21]
39	P01579:IFNG*	0.4539	A key mediator of inflammation in COVID-19 patients	[23], [25], [26]
40	P24941:CDK2	0.4538	N-protein of SARS-CoV inhibition of CDK2 activity	[45], [46]

Proteins marked with $*$ may be key mediators of inflammation in COVID-19.

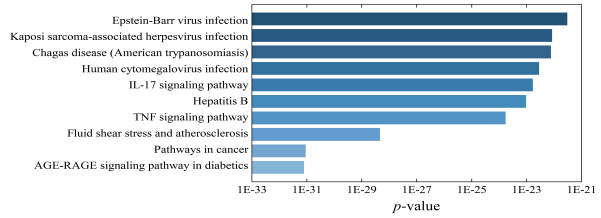
2.2.2 KEGG and GO enrichment analyses of targets

We use Enrichr [18] tool to perform Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) enrichment analyses to comprehensively evaluate the biological relevance and functional pathways of COVID-19 targets predicted by AIdrug2cov. KEGG pathway enrichment analysis revealed the top 10 significant biological pathways (ranked with p-values according to the guidelines in [18]), which included TNF signaling pathway, epstein-Barr virus infection, the IL-17 signaling pathway, and the human cytomegalovirus infection pathway, as shown in Fig.2(A). Similarly, GO biological process enrichment analysis further confirmed that the targets were associated with multiple processes related to host cell lifecycle and viral replication, including cytokine activity, MAP kinase activity, transcription regulatory region DNA binding, protein kinase activity, RNA polymerase II (RNAPII) regulatory region DNA binding, RNAPII transcription factor activity, and sequence-specific transcription regulatory region DNA binding as shown in Fig.2(B).

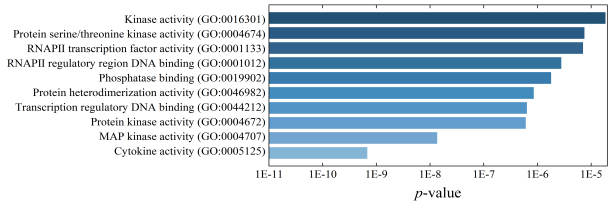
Based on the above results, we concluded that most of the candidate proteins predicted by AIdrug2cov were targeted by SARS-CoV-2 and targetable for COVID-19 treatment. This motivated us to develop a drug repurposing strategy by specifically targeting host proteins for potential treatment of COVID-19.

2.3 Hyperinflammation in patients with COVID-19

Indeed, several recent COVID-19 clinical studies have shown that SARS-CoV-2 induces excessive and aberrant host immune responses that are associated with severe lung



(A) KEGG human pathway analyses



(B) GO enrichment analyses

Fig. 2. KEGG human pathway and GO enrichment analyses for the potential COVID-19 target proteins

pathology, leading to death [1]. Based on previous literature-reported knowledge, we find that the production of cytokines, such as IL-6, and TNF-α, is increased in patients with severe COVID-19. This is similar to the case in patients with SARS-CoV, indicating that SARS-CoV-2 infection is associated with a cytokine storm and severe pulmonary inflammation in moribund patients.

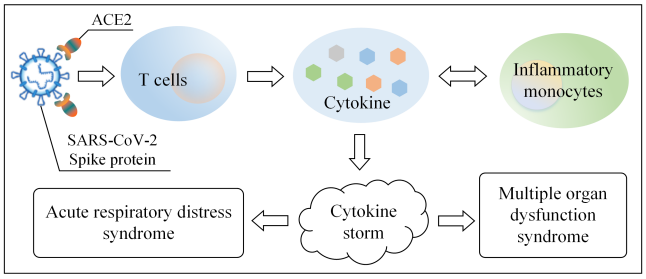


Fig. 3. Possible pathway contributing to excessive inflammatory responses in patientS with COVID-19.

A possible pathway contributing to excessive host inflammatory responses in COVID-19 is shown in Fig.3. First, SARS-CoV-2 is taken up into a host-cell by binding ACE2. Then, T lymphocytes are excessively activated and generate large amounts cytokines such as TNF-α, IL-6, and GM-CSF. The cytokine-rich environment induces inflammatory monocytes with high express of cytokine, and further accelerates the inflammatory response. The aberrantly activated T cells and inflammatory monocytes may enter the pulmonary circulation leading to a cytokine storm, thus causing ARDS or multiple organ dysfunction syndrome.

In addition, recent studies have suggested that drugs targeting IL-6 and TNF-α are effective in blocking inflammatory storms, and are promising treatment agents for severe COVID-19 patients [20], [22]. Therefore, this work focused on drug discovery based on IL-6 and TNF-α to identify potential anti-inflammatory agents with efficacy against COVID-19.

2.4 Anti-inflammatory drug discovery and mechanism of action analysis

In the drug discovery step for the COVID-19, 3% the all drugs in the heterogeneous network were selected as candidate agents binding to TNF-α or IL-6, respectively. Then, seven drugs were filtered via CMap analysis model. Finally, we use subject matter expertise based on literature-reported knowledge to filter out 7 drugs, including arsenic trioxide, hydrochlorothiazide, acetaminophen, isoflurane, halothane, imiquimod and latanoprost, since these drugs tend to increase release of IL-6 or TNF-α. For example, acetaminophen significantly increase the hepatic levels of IL-6, TNF-α, IL-10 and monocyte chemoattractant protein [66], [67]. Isoflurane induced marked upregulation of the proinflammatory cytokines TNF-α, IL1B, IL-6 and IL-8 in hippocampus tissue [68]. The expression levels of IL-6, and TNF-α tend to increase in the birds chronically treated with arsenic trioxide [69]. Halothane potentiates alcohol adduct-induced TNF-α release in heart endothelial cells [70]. Latanoprost stimulated the release of IL-6 from human tendon capsule fibroblasts in a concentration-dependent and time-dependent manner [71]. Hydrochlorothiazide has not had in *in vitro* anti-inflammatory effects at clinical studies. Meanwhile, there was a trend to increase the production of IL1B at the lower concentrations of hydrochlorothiazide [72]. Note that chloroquine (CQ) and hydroxychloroquine (HCQ) have high-confidence scores in this study. However, we still exclude CQ and HCQ from the candidate drugs list, because there is great controversies whether CQ and HCQ is an effective treatment against COVID-19.

Based on the above procedure, we identified 22 high-confidence drugs (10 drugs binding to TNF-α, 13 drugs binding to IL-6) with efficacy against COVID-19 as shown in Table 2; acarbose is treat as agent that binds to both TNF-α and IL-6. We found that 19 drugs that have been previously reported in the literature could reduce the expression and release of TNF-α or IL-6 to exert anti-inflammatory effects *in silico*. Although, most of these drugs are treated as potential therapeutic agents for cytokine storm inhibition, this study suggests their role in inflammatory response prevention in patients with COVID-19 for the first time.

2.4.1 Fourteen anti-inflammatory drugs initially proposed for novel use in COVID-19 patients

To the best of our knowledge, 14 of the drugs predicted by AIdrug2cov were initially proposed as potential therapeutic for COVID-19. The literature evidence suggests that these drugs inhibit cytokine release and the inflammatory response, as listed in column 4 in Table 2. For example, dasatinib, a small molecule Src/Abl tyrosine kinase inhibitor approved for the treatment of chronic myelogenous leukemia, reduces TNF-α and IL-6 secretion in response to TLR stimulation of bone marrow-derived macrophages *in vitro* to modulate the host immune response [78]. Minocycline, a second generation tetracycline antibiotic, exerts its anti-inflammatory effect on microglia by inhibiting the expression and release of TNF-α, and IL1B [80]. IL-6 in lung tissues in methazolamide-treated mice were markedly decreased. Methazolamide treatment has been found to markedly decrease IL-6 levels in mouse lung tissues, and

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

Target ID: name	Drugbank ID: name	Confidence	Mechanism of action to COVID-19	References
P01375:TNF	DB01041:Thalidomide*	0.8719	Decreasing stability of mRNA	[73], [74], [75], [76]
	DB01427:Amrinone	0.7627	Concentration dependent manner	[77]
	DB01254:Dasatinib	0.7034	Unclear	[78]
	DB00284:Acarbose	0.6698	Decreasing the expression of miRNAs	[79]
	DB01017:Minocycline	0.6458	Unclear	[80]
	DB00619:Imatinib*	0.6444	Reducing DNA binding of NF-κB	[81]
	DB00228:Enflurane	0.6282	Unclear	NA
	DB00975:Dipyridamole*	0.6255	Unclear	[82], [83]
	DB01115:Nifedipine	0.6162	Unclear	[84], [85]
	DB00724:Imiquimod	0.6145	Unclear	[86]
	DB00768:Olopatadine	0.6116	Unclear	[87], [88]
P05231:IL-6	DB00198:Oseltamivir*	0.3241	Reducing the mRNA levels	[89], [90]
	DB00284:Acarbose	0.3030	Reducing the mRNA levels	[79]
	DB00302:Tranexamic acid*	0.3004	Concentration dependent manner	[91]
	DB01258:Aliskiren	0.2984	Reducing the mRNA levels	[92], [93]
	DB00819:Acetazolamide	0.2979	Reducing the mRNA levels	[94]
	DB00869:Dorzolamide	0.2976	Unclear	NA
	DB00851:Dacarbazine	0.2917	Unclear	NA
	DB00703:Methazolamide	0.2884	Unclear	[95]
	DB00207:Azithromycin*	0.2850	Unclear	[96], [97], [98]
	DB06228:Rivaroxaban*	0.2745	Reducing the mRNA levels	[99], [100], [101]
	DB00811:Ribavirin*	0.2741	Reducing the mRNA levels	[102], [103], [104], [105]
	DB00594:Amiloride	0.2676	Unclear	[106]
	DB01143:Amifostine	0.2633	Inducing activation of redox sensitive signaling	[107]

a. Drugs marked with $*$ have been used in clinical trials. The others are here proposed for the first time as anti-inflammatory agents for COVID-19 treatment.
b. NA represents that there have been no studies proving that the drug can inhibit the release of TNF or IL-6.

lung inflammatory parameters and pathological changes are attenuated in methazolamide-treated mice compared with control mice [95]. Amiloride inhibits IL-6 release, and is treated as a therapeutic agent in respiratory syncytial virus infections [106]. Thus, these results from literature suggest that the proposed AIdrug2cov is able to predict drug candidates that ameliorate the cytokine storm and inflammatory response in patients with COVID-19.

2.4.2 Eight agents in current ongoing clinical trials to COVID-19

In this work, eight predicted drugs have been determined in clinical studies against COVID-19, as shown in Table 3. Interestingly, that seven drugs (i.e., thalidomide, imatinib, oseltamivir, dipyridamole, azithromycin, rivaroxaban, and ribavirin) have been used as an immunomodulator to treat patients with COVID-19 infection, is consistent with the result of AIdrug2cov. 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 only used to reduce the infectivity and virulence of SARS-CoV-2. However, Jimenez *et.al* suggest that tranexamic acid plays a key role in the circulating levels of the proinflammatory cytokines IL-6 [91]. Therefore, ongoing clinical studies on COVID-19 should investigate the anti-inflammatory effects of tranexamic acid.

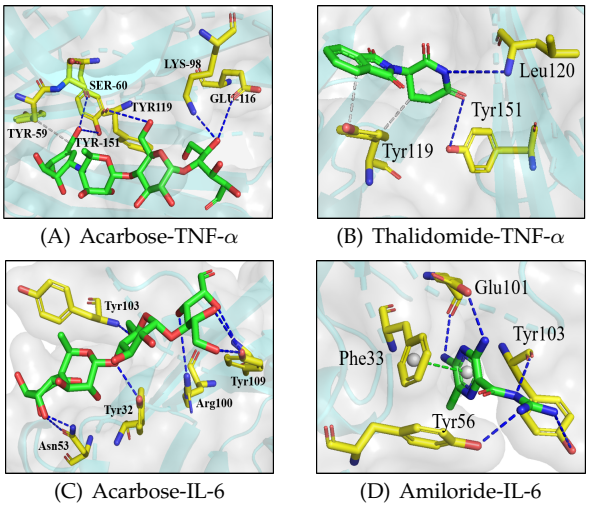
TABLE 3
Eight drugs in Current Ongoing Clinical Trial on COVID-19.

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

2.4.3 Anti-inflammatory actions through multiple pathways

Among these, literature search revealed that 21 drugs are able to inhibit TNF-α, and IL-6 release, and reduce inflammatory responses. Strikingly, 6 drugs, including thalidomide [75], [76], chloroquine [108], [109], aliskiren [92], [93], acetazolamide [94], rivaroxaban [99], [100], [101], and ribavirin [102], exert their inhibitory action on TNF-α, and IL-6 by decreasing mRNA stability or enhancing mRNA degradation. In addition, we found that administration of acarbose to diabetic rats significantly reduces the expression of miRNAs to inhibit the release of TNF-α, and IL-6 in inflammatory pathways [79]. Furthermore, amrinone reduces the release of TNF-α in a concentration dependent manner [77]. Imatinib inhibits TNF-α release by reducing the DNA binding of NFKB [81]. Amifostine is considered a therapeutic agent of lung inflammation that acts by suppressing IL-6 induced activation of redox sensitive signaling [107]. Ribavirin inhibits the expression of TNF-α, IL-6, and IL-10

in blood lymphocytes by reduced their mRNA levels [102], [103]. Notably, a study by Wang *et al.* has suggested that peaks in the levels of inflammatory cytokines (IL-6 and IL-8) levels coincide with or occur after the peaks in SARS-CoV loads, and indicated that viral replication leads to the activation of proinflammatory cytokines, contributing to disease progression [104], [105]. These clinical findings imply that ribavirin is able to reduce the release of IL-6 and IL-8 by inhibiting viral replication to ameliorate lung lesions. The above studies illustrated that these drugs can ameliorate the TNF-α and IL-6 release to reduced inflammatory responses via multiple pathways.



(A) Acarbose-TNF-α (B) Thalidomide-TNF-α

(C) Acarbose-IL-6 (D) Amiloride-IL-6

Fig. 4. Molecular docking results for drugs binding to TNF-α or IL-6. The blue, green, and gray dotted line represent hydrogen bond, π-π stacking, and hydrophobic interaction between drugs and targets, respectively.

2.4.4 *Molecular docking analysis*

In this section, we used the molecular docking program DOCK6.8 [16] to explore the possible modes of binding of new the predicted drugs with TNF-α or IL-6. The three-dimensional (3D) structures of TNF-α and IL-6 used in the docking studies were downloaded from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB IDs 2AZ5 and 4CNI, respectively). The 3D structures of the drugs were obtained from the ZINC database. Here, four representative docking structures are shown in Fig. 4

For the docking model of TNF-α, the molecular docking result in Figure 4(A) shows that acarbose mainly binds to Ser60, Lys98, Glu116, Tyr119, and Tyr151 through five hydrogen bonds, and there is one hydrophobic interaction between acarbose and Tyr59. Figure 4(B) shows that thalidomide binds to TNF-α via two hydrogen bonds with Leu120 and Tyr151, and two hydrophobic interactions. The results indicate that there are the difference in the binding modes of the different drugs, and that acarbose has a stronger ability to bind TNF-α than thalidomide in terms of the hydrogen bond formation. In the docking model for IL-6, seven hydrogen bonds are predicted to form between acarbose and Tyr32, Asn53, Arg100, Tyr103, and Tyr109 of IL-6 as shown in Figure 4(C). The result in Figure 4(D) shows that Tyr56, Phe33, Glu101, and Tyr103 of IL-6 respectively combine with amiloride through five hydrogen bonds, and form an π-π stacking. The results suggest that acarbose has a stronger ability to bind IL-6 than amiloride. In addition, the binding modes between acarbose and TNF-α/IL-6 reveal that acarbose binds with these molecules through different binding sites. The above results suggest that there are the some differences in the binding modes for the different drugs and targets.

2.5 Mechanism of action and the results of clinical trials of CQ and HCQ

In this study, chloroquine (CQ) and hydroxychloroquine (HCQ) had high confidence scores. In particularly, CQ has been added to the list of trial drugs in the Guidelines for the Diagnosis and Treatment of COVID-19 (seventh edition) published by the National Health Commission of the People's Republic of China (http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml). CQ and HCQ are FDA-approved drugs for malaria treatment and are viral mRNA and protein synthesis inhibitors, respectively. However, we still exclude CQ and HCQ from the candidate drugs list, because there is the great controversy whether CQ and HCQ is an effective treatment against COVID-19. Here, based on PubMed publication, we summarize their potential mechanism of action and results of clinical trials in order to promote the understanding of the availability and dangers of CQ and HCQ to patients with COVID-19.

CQ and HCQ share similar chemical structures and mechanisms of action, and demonstrate strong immunomodulatory capacity, preventing inflammation and organ damage as shown in Fig.5. Several *in vitro* studies have shown that CQ inhibits the production of TNF-α and IL-6 via different mechanisms in human monocytes/macrophages. CQ inhibits the release of IL-6 by decreasing the stability of IL-6 mRNA [108]. In contrast, CQ has been shown to inhibit TNF-α synthesis mainly by blocking conversion of cell-associated 26-kDa TNF-α precursor into the soluble 17-kDa mature form, rather than by reducing the stability of TNF-α mRNA [108], [109], [110]. Meanwhile, one anti-inflammatory mechanism of CQ might involve impairment of antigen presentation [111]. CQ increases the intracellular pH and inhibits lysosomal activity in antigen-presenting cells (APCs) including monocytes, macrophages and B cells, thus preventing antigen processing and major histocompatibility complex (MHC) class II-mediated autoantigen presentation to T cells [112]. This process reduces T cell activation, thus reducing the production of cytokines including IL-6 and TNF-α [113]. HCQ is able to decrease the release of cytokines including IL-6 and TNF, via blocking proliferative responses to T-cell mitogens [114], [115]. In addition to a role in immune modulation, HCQ and CQ inhibit receptor binding and membrane fusion, which are required for cell entry by coronaviruses. These drugs can interfere with the glycosylation of ACE2 of SARS-CoV to impede the binding of the virus to receptors on cells [116]. CQ increases the endosomal pH and inhibits protease activity such that the virus/cell fusion process is blocked [117].

Based on the above findings, compared to exhibiting antiviral ability, HCQ and CQ antagonize the inflammatory

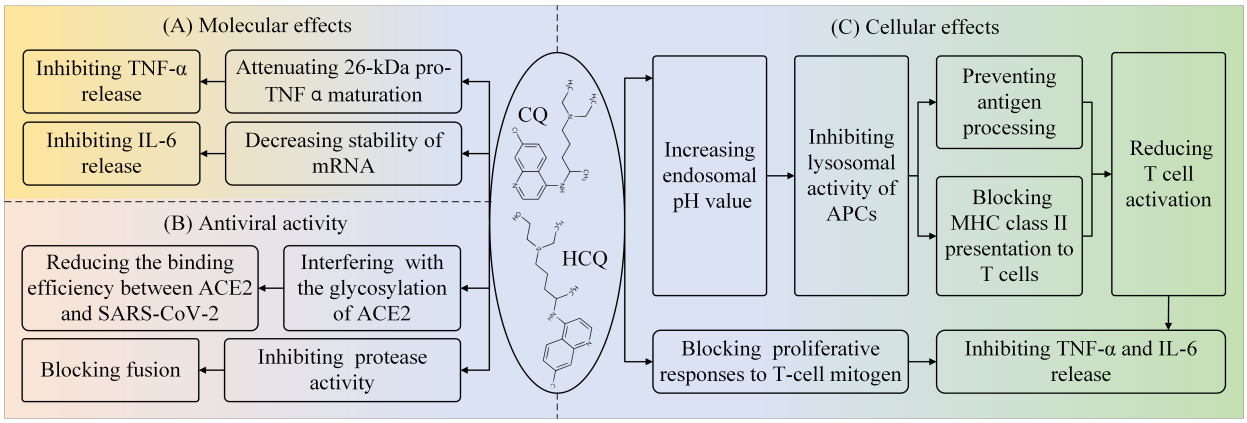


Fig. 5. Possible pathway of CQ and HCQ contributing to excessive inflammatory responses and antiviral effect in patients with COVID-19.

response through more pathways. Interestingly, a clinical study including 550 critically ill COVID-19 patients has demonstrated that low dose HCQ significantly reduces fatality of critically ill COVID-19 patients, and their mechanism of action is likely mediated through its inhibition of inflammatory cytokines on top of its ability in inhibiting viral replication [118]. Meanwhile, we noticed that high concentrations of HCQ or CQ have *in vitro* antiviral effect on several viruses, including SARS-CoV and SARS-CoV-2 [119], [120], which may contribute directly to the therapeutic effects of these drugs in COVID-19 patients. Notably, we also noticed a few negative reports about CQ and HCQ [121], [122]. The negative studies do not support the use of HCQ, either alone or in combination, as an antiviral drug for the treatment of COVID-19 in humans. In addition, WHO announced that the HCQ arm of the Solidarity Trial to find an effective COVID-19 treatment was being stopped, because CQ did not reduce mortality for hospitalised patients with COVID-19 (https://www.who.int/news/item/29-06-2020-covidtimeline). The results of the trial are under review for publication in a medical journal.

2.6 Performance evaluation of AIdrug2cov for pharmacological applications

To evaluate the network representation performance of AIdrug2cov, the pharmacological interpretation results were based on comprehensively compared with those obtained from LINE [123], GraRep [124], struc2vec [125], and NeoDTI [126] models. The first three of these models have shown remarkable performance in the link prediction and node classification for 7 biomedical network datasets [127]. NeoDTI is specially designed to predict drug-target interactions, which also integrate IMC model.

- **LINE:** This model captures local and global network structures by approximating the 1st-order proximity and 2nd order proximity of nodes.
- **GraRep:** This model considers high-order proximity to preserve the network structure, and employs different loss functions to capture local relational information from the different k-step.
- **struc2vec:** This model uses a hierarchy to measure node similarity at different scales, and constructs a multilayer network to encode structural similarities. Then, deepwalk [128] is performed on the multilayer network to learn the low-dimensional vector of each node.
- **NeoDTI:** This model integrates neighborhood information of a heterogeneous network constructed from diverse data sources via a number of information passing and aggregation operations.

2.6.1 Experiment settings and evaluation metrics

The AIdrug2cov model parameters followed those BERT [129] 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. The hyperparameters of the LINE, GraRep, and struc2vec models were selected according to the guidelines in [127], because Yue *et al.* carefully optimized them by grid search. The hyperparameter for the NeoDTI model was set to the default value in [126]. In this study, the embedding dimension(d) was set to 768 for all model.

To evaluate the performance of the embedding methods on DDI network reconstruction, we adopted Precision@k [130] as the evaluation metric. The one error, coverage, ranking loss, and average precision were used to evaluate the overall performance of all representation methods in ATC classification. These metrics are defined in detail in [131], and are frequently used for evaluating the performance of ATC classifiers. The area under precision recall (AUPR) curve and the area under receiver operating characteristic(AUROC) curve were employed to evaluate the performance of all representation methods in bio-link prediction.

2.6.2 DDI network reconstruction

For DDI network reconstruction, the Precision@k was calculated for different k values of 2,000, 4,000, 6,000, 8,000, and 10,000, which corresponded to roughly 20%, 40%, 60%, 80%, 100% of the total number of the DDI edges (10,036), respectively. Fig. 6 illustrates the Precision@k values for the different k values. AIdrug2cov significantly outperformed the baseline methods. In addition, AIdrug2cov showed the best precision while baseline methods, when the was k=6,000, while the baseline methods exhibited the best reconstruction precision when k was 2,000. This finding indicates indicates that AIdrug2cov may reconstruct more edges

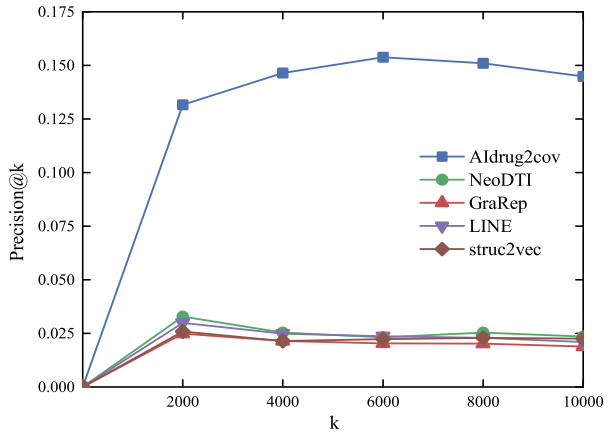


Fig. 6. Precision@k from DDI network reconstruction.

than the baseline methods. This may be attributable to the capability of AIdrug2cov to learn semantic features among nodes through a deep bidirectional Transformer encoder.

2.6.3 ATC classification

For ATC classification, we performed 10-fold cross-validation, in which a subset of 10% of the drug entities were randomly selected as the test set, and the remaining 90% of drugs were treated as the training set. To reduce the data bias of cross-validation, it was repeated 10 times and the average performance was computed.

Table 4 shows the results of ATC classification generated by the AIdrug2cov and baseline methods, and the best results are marked in **boldface**. The results clearly demonstrated that AIdrug2cov was able to achieve better results for ATC classification than the baseline methods. In particular, AIdrug2cov achieved an approximately 50% improvement in terms of one error value. A major reason for this superiority is that AIdrug2cov takes into consideration the various types of semantic information that indicate the anatomical therapeutic chemical of drugs to a certain extent. This result indicates that AIdrug2cov is a powerful network representation method for predicting the ATC classification of given drugs.

TABLE 4
Results of ATC classification generated by AIdrug2cov and baseline methods.

Method	One error	Coverage	Ra-Loss	Avg-pre
AIdrug2cov	**0.4209**	**2.6583**	**0.1642**	**0.6795**
NeoTDI	0.7797	4.2910	0.2904	0.4211
GraRep	0.7628	4.2976	0.2905	0.4237
LINE	0.7685	4.2335	0.2845	0.4307
struc2vec	0.7981	4.3794	0.2966	0.4050

a. Ra-Loss and Avg-pre stand for ranking-loss and average precision, respectively.
b. Among the mentioned evaluation metrics, smaller values show better performance except in the case of average precision.

2.6.4 Bio-link prediction

For bio-link prediction, we performed a 10-fold cross-validation test on all positive pairs and a matching number of randomly sampled negative pairs. Similar to prediction of ATC classification, the ratio between the test and training set was 1:9, and each method was repeated 10 times and the average performance was computed. Table 5 summarizes the overall performance of different methods for the bio-link prediction, that is, disease-target association (DisTA), target-drug interaction (TDI), and drug-side-effect association (DSA).

TABLE 5
Results of bio-link prediction generated by AIdrug2cov and baseline methods.

Method	DisTA		DTI		DSA	
	AUROC	AUPR	AUROC	AUPR	AUROC	AUPR
AIdrug2cov	**0.9613**	**0.9555**	**0.9973**	**0.9968**	**0.9391**	**0.9361**
NeoTDI	0.9209	0.9044	0.8782	0.8806	0.9271	0.9183
GraRep	0.9179	0.8976	0.8050	0.7975	0.8902	0.8786
LINE	0.9020	0.8846	0.8403	0.8352	0.8788	0.8684
struc2vec	0.8336	0.7942	0.7514	0.7426	0.8384	0.8279

In this DisTA, and DSA prediction tasks, AIdrug2cov outperformed the baseline methods. In particular, AIdrug2cov was significantly superior to struc2vec, improving the AUROC and AUPR by over 10%. For DTI prediction, the baseline methods achieved poor results below 0.9 in terms of AUROC and AUPR, while the AIdrug2cov method showed the excellent performance with results close to 1. These findings suggest that AIdrug2cov can still obtain good results when other methods fail to accurately predict the DTI. In addition, we observe that AIdrug2cov greatly outperform other baseline methods, with significant improvement (13% in terms of AUPR and AUROC) over the second best method.

Interestingly, GraRep and LINE had improved the link prediction performance compared with struc2vec, whereas their result is lower than NeoDTI of ones. For example, compared with struc2vec, LINE achieved 4.8-11.2% improvement in terms of AUROC value on the 3 bio-link prediction tasks. NeoTDI achieved 5.2% increment with regard to average AUPR in the 3 bio-link prediction tasks, when compared with GraRep. This may be because NeoDTI use a neighborhood information-preserving learning procedure to enforce the extracted feature representations of nodes to match the observed networks. There may be a lack of structural identity in the heterogeneous network, thus leading to the poor performance of struc2vec.

The proposed AIdrug2cov method clearly achieved very promising results in various prediction tasks. Three key factors were responsible. First, AIdrug2cov uses 23 types of meta-paths to integrate the structure and semantic feature among diverse vertices in the heterogeneous network. Second, although AIdrug2cov considers only the first-order proximity of nodes in the construction process of semantic paths, it can capture long-range dependencies without regard to their distance in the input or output sequences by relying entirely on an attention mechanism. Moreover, AIdrug2cov uses masked language models to enable train deep bidirectional representation.

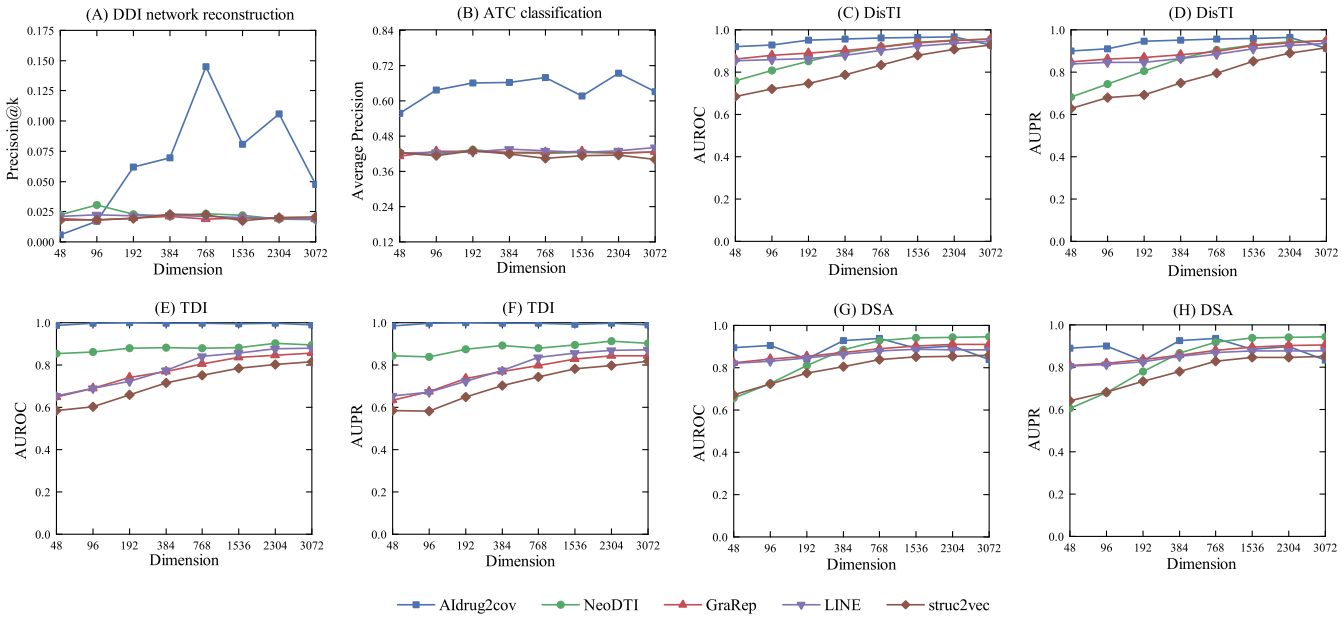


Fig. 7. Results of DDI network reconstruction; ATC classification; DisTI, TDI, and DSeI with different embedding dimensions.

2.6.5 *Effect of dimension*

The embedding dimension (d) is a common hyperparameter among AIdrug2cov, LINE, GraRep, struc2vec, and NeoDTI. In this study, each method was run 8 times with a different embedding dimensions (i.e. d=48, 96, 192, 384, 768, 1,536, 2,304, and 3,072) to evaluate the impact of dimensionality on the prediction performance and time efficiency. Fig.7 illustrates the effects of dimension on DDI network reconstruction (k=10,000), ATC classification, and bio-link prediction. Generally, the prediction performance improved with increasing embedding dimensionality. The same conclusion is described in [127]. 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 increased gradually when the dimension was below 768 but tends to increase sharply (note that the y-axis is log-based) when the dimensionality continued to increase, as shown in Fig. 8. There, we suggest that the dimensionality should be set to approximately 768 to optimize performance and time efficiency.

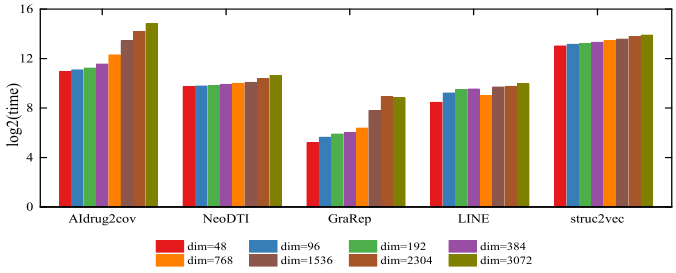


Fig. 8. Influence of dimensionality on the training time of the different embedding methods.

3 Discussion

In this study, we proposed AIdrug2cov, which is a network representation learning-based drug mechanism discovery and anti-inflammatory response to develop an effective therapeutic approach for COVID-19 patients. Based on comprehensive evaluation, AIdrug2cov identified 40 potential targets related to COVID-19 and 22 high-confidence drugs that bind to cytokines to prevent excessive inflammatory responses in patients with COVID-19. In addition, the results of DDI network reconstruction, ATC classification, and bio-link prediction demonstrate that AIdrug2cov significantly outperforms than other state-of-the-art network representation approaches. In summary, AIdrug2cov is a practically useful tool for accelerating COVID-19 therapeutic development.

Previous evidence reported in the literature suggests that the most popular targets predicted by AIdrug2cov are mediators of inflammation; these findings indicate that SARS-CoV-2 infection is associated with a cytokine storm and severe pulmonary inflammation in patients, consistent with the findings of several previous studies [1]. Similar to the case in patients with SARS-CoV infection, the levels of TNF-α [1], [20], IL1B [21], IL-6 [22], [23], CCL2 [21], [24], IFNG [26], and CXCL10 [1], [21] are significantly elevated and are associated with adverse clinical outcomes in patients with COVID-19. Therefore, this work proposed that using TNF and IL-6 target discovers high-confidence drugs for preventing cytokine storm and excessive inflammatory responses in patients with COVID-19. Recent studies have similarly suggested that drugs targeting IL-6 and TNF-α are effective in blocking inflammatory storms, and are promising treatments for severe COVID-19 patients [1], [20], [22], [23]. The data presented in this study and the previous reports in the literature indicate that it is important to identify proteins related to COVID-19, especially those related to inflammatory response, and to apply this knowledge

towards discovering candidate drugs to reduces fatality of patients with COVID-19.

To the best of our knowledge, 14 of the predicted 22 drugs predicted by AIdrug2cov initially proposed as potential anti-inflammatory therapeutic for COVID-19 patients. Eight predicted drugs have been determined in clinical studies against COVID-19. Interestingly, four drug (i.e., imatinib, oseltamivir, azithromycin, and ribavirin) not only as an immunomodulator but also as antiviral agent in clinical trail have been used to treat patients with COVID-19. A possible reasons for the inconsistent result is that these studies use different experimental approaches and drug dosage, thus leading 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 pharmacological tasks, DDI network reconstruction, ATC classification, and 3 bio-link predictions, AIdrug2cov significantly outperformed other state-of-the-art network representation approaches. A major reason for the success of AIdrug2cov is that it takes into consideration types of various semantic information that indicate the anatomical therapeutic chemical of drugs to a certain extent. Recent studies have shown that the semantics of nodes are critical for knowledge discovery in real world biomedical problems [132]. Compared to previous path-based approaches, AIdrug2cov can capture long-range dependencies without regard to their distances in the input or output sequences by relying entirely on an attention mechanism to improve representation performance.

On five biomedical tasks, AIdrug2cov significantly outperforms baseline network representation approaches. These results suggest that AIdrug2cov is a powerful representation technique, and can greatly facilitate the biomedical studies. A major reason for the success of AIdrug2cov is that this work focuses on the exploration of structural characteristics of the heterogeneous drug networks, and observe that the heterogeneous drug networks is multi-hub network where drugs and proteins are important hubs. Therefore, we specially design 23 types of meta path. The multiple types of meta paths integrate the structure and semantic feature among vertices in the heterogeneous drug networks. A mass of studies [133], [134], [135] have suggested that meta paths could contribute to learning meaningful representation for various tasks. However, these meta path-based representation approaches are mainly proposed on non-biomedical networks, and only a few studies are focus on biomedical issues. Meanwhile, compared to previous path-based approaches, AIdrug2cov uses a deep bidirectional Transformer encoder, which can capture long-range dependency without regard to their distance limits in the original network to improve representation performance. In addition, AIdrug2cov uses masked meta path learning strategy to enable train deep bidirectional representation model for capturing context-dependent relation. Nevertheless, most of path-based representation approaches adopts Skip-Gram that is a left-to-right architecture, where every token can only attend to previous tokens [133].

However, we acknowledge several limitations in our current study. The top-k targets and agents in this study were regarded as candidate entities related to COVID-19 according to a confidence score. The operation is simple and is popularly applied to the recommended systems, but the results neglect statistical significance to a certain extent. How to select associated candidate entities is also an important question for drug repositioning. 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 virus, those predictions with a p-value < 0.05 could be treated as candidates [136].

Owing to the lack of wet-lab validation, the mechanisms of action of the COVID-19 targets and drugs could not be verified in this study. Although previous literatures provide certain evidence proving that the majority of proteins and drugs predicted by AIdrug2cov are able to target COVID-19 through multiple pathways, the previous studies used different experimental platforms and viruses. However, there are some differences in mechanisms of action between different drugs and different types of cells. Therefore, standard assays must be carried out to measure the effects of these targets and drugs on the cytotoxicity, virus yield and infection rate of SARS-CoV-2, and all predicted targets and drugs must be validated in preclinical models experiments and randomized clinical trials before being used in patients.

In conclusion, this study offers a powerful network representation approach for drug mechanism discovery and anti-inflammatory response mechanism analysis that can be used to identify effective therapeutic strategies for patients with COVID-19. Our approach can increase clinical testing accuracy, which is a critical for the rapid development of efficient treatment strategies for the emerging disease COVID-19. Meanwhile, the proposed AIdrug2cov method could also be applied to develop effective treatment strategies for other types of viral infections and human diseases.

4 METHOD

4.1 Construction of a heterogeneous network

A heterogeneous information network is defined as $G = (V, E)$ where V represents the set of vertices, and E is the set of edges. In a heterogeneous network, each vertex v and each edge e are associated with an object type mapping function, $\phi(v) : V \rightarrow A$, and a link type mapping function, $\psi(e) : E \rightarrow R$, respectively. A and R denote the sets of object and link types, where $|A| + |R| > 2$.

In this study, we assembled four types of nodes (i.e., drug, target, side-effect, and disease), and eight types of links(i.e., drug-disease association (DDA), drug-drug interaction (DDI), drug-target interaction (DTI), drug-side-effect association (DSA), protein-protein interaction (PPI), disease-target association (DisTA)), anddrug-drug structure similarity (DDSS) and protein-protein sequence similarity (PPSS)) form the public databases, as shown in Fig.1(A). The drug-drug and drug-target interactions were extracted from DrugBank and ChEMBL. The human protein-protein interactions were extracted from the Human Protein Reference Database (HPRD), the Human Reference Interactome (HuRI) database and the Biological General Repository for Interaction Datasets (BioGRID). The protein-disease

and drug-disease network were collected from the Toxicogenomics Database and repoDB. We also extracted the drug-side-effect associations from the Comparative Toxicogenomics Database (CTD) and the Side Effect Resource (SIDER). In addition, a protein sequence similarity network was obtained by calculating the Smith-Waterman similarities [137] of the amino acid sequence derived from UniProt. Furthermore, the drug similarity network was obtained by calculating the Tanimoto coefficient [138] from the Morgan fingerprint with a radius of 2 using the RDKit [139]. In the heterogeneous network, there were 11,490 nodes and 1,887,041 edges; all edges were nonnegative and undirected.

4.2 Semantic-path and deep bidirectional Transformer encoder-based network representation

We developed a promising heterogeneous network representation approach, AIdrug2cov, by integrating semantic paths and a multi-layer bidirectional Transformer encoder model, as shown in Fig.1(B). In this work, network vertices were regarded as the vocabulary, and a set of semantic paths was treated as a corpus that is fed into a deep bidirectional Transformer encoder model to learn the low-dimensional representation of the network vertices, which existed in a continuous vector space. The proposed network representation was able to capture structural and semantical correlations between diverse vertices in the heterogeneous network, thus encoding latent forms of nodes.

4.2.1 Semantic-path and multi-hub characteristic of network

A meta path [140] is a composite relation denoting a sequence of adjacent links between any two nodes in heterogeneous network. The different adjacent links indicate distinct semantic. For example, meta path(A): drug $\xrightarrow{treats}$ disease $\xrightarrow{treated\ by}$ drug represents that a disease can be treated by two drugs. Meta path(B): drug $\xrightarrow{binds\ to}$ protein $\xrightarrow{causes}$ disease indicates that a drug binds to a protein that causes a disease. Meta paths is widely used to capture the rich structure and semantic for non-biomedical heterogeneous networks. However, not all meta paths have a positive effect on representation learning, and the selection of meta-path is still an open question [141], [142].

To develop a special representation learning for heterogeneous drug networks, first, AIdrug2cov focuses on the exploration of structural characteristics of heterogeneous drug networks, and observes that the drug network is a multi-hub network as shown in Figure 9, where drugs and proteins are important hubs. Therefore, we specially design

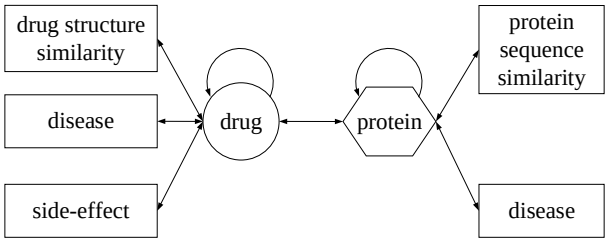


Fig. 9. Structure characteristics of heterogeneous drug networks.

TABLE 6
The semantic path types and statistics

NO.	Semantic path	Count
1	drug $\xrightarrow{binds\ to}$ protein	1,923
2	drug $\xrightarrow{binds\ to}$ protein $\xrightarrow{binds\ to}$ drug	153,186
3	drug $\xrightarrow{binds\ to}$ protein $\xrightarrow{interacts\ with}$ protein	8,728
4	drug $\xrightarrow{binds\ to}$ protein $\xrightarrow{causes}$ disease	2,209,742
5	drug $\xrightarrow{binds\ to}$ protein $\xrightarrow{interacts\ with}$ protein $\xrightarrow{binds\ to}$ drug	12,734
6	drug $\xrightarrow{binds\ to}$ protein $\xrightarrow{interacts\ with}$ protein $\xrightarrow{causes}$ disease	11,603,240
7	drug $\xrightarrow{binds\ to}$ protein $\xrightarrow{binds\ to}$ drug $\xrightarrow{binds\ to}$ protein	221,020
8	drug $\xrightarrow{binds\ to}$ protein $\xrightarrow{binds\ to}$ drug $\xrightarrow{treats}$ disease	8,243,362
9	drug $\xrightarrow{binds\ to}$ protein $\xrightarrow{binds\ to}$ drug $\xrightarrow{causes}$ side-effect	4,482,541
10	drug $\xrightarrow{binds\ to}$ protein $\xrightarrow{causes}$ disease $\xrightarrow{caused\ by}$ protein	2,020,665,247
11	drug $\xrightarrow{binds\ to}$ protein $\xrightarrow{causes}$ disease $\xrightarrow{treated\ by}$ drug	231,785,524
12	protein $\xrightarrow{binds\ to}$ drug $\xrightarrow{interacts\ with}$ drug	34,260
13	protein $\xrightarrow{binds\ to}$ drug $\xrightarrow{binds\ to}$ protein	6,344
14	protein $\xrightarrow{binds\ to}$ drug $\xrightarrow{treat}$ disease	636,903
15	protein $\xrightarrow{binds\ to}$ drug $\xrightarrow{causes}$ side-effect	270,234
16	protein $\xrightarrow{binds\ to}$ drug $\xrightarrow{interacts\ with}$ drug $\xrightarrow{binds\ to}$ protein	60,096
17	protein $\xrightarrow{binds\ to}$ drug $\xrightarrow{interacts\ to}$ drug $\xrightarrow{treats}$ disease	11,188,449
18	protein $\xrightarrow{binds\ to}$ drug $\xrightarrow{interacts\ with}$ drug $\xrightarrow{causes}$ side-effect	5,315,270
19	protein $\xrightarrow{binds\ to}$ drug $\xrightarrow{binds\ to}$ protein $\xrightarrow{interacts\ with}$ protein	19,371
20	protein $\xrightarrow{binds\ to}$ drug $\xrightarrow{binds\ to}$ protein $\xrightarrow{causes}$ disease	13,232,097
21	protein $\xrightarrow{binds\ to}$ drug $\xrightarrow{treats}$ disease $\xrightarrow{caused\ by}$ protein	558,541,026
22	protein $\xrightarrow{binds\ to}$ drug $\xrightarrow{treats}$ disease $\xrightarrow{treated\ by}$ drug	115,924,998
23	protein $\xrightarrow{binds\ to}$ drug $\xrightarrow{causes}$ side-effect $\xrightarrow{caused\ by}$ drug	38,577,295
	Total number	3,023,193,590

23 types of meta path as shown in Table 6, where the first two nodes in each meta path are drugs and proteins, respectively. Note that all the meta paths in this work are reversible, and the meta paths with lengths 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 [134], [140]. Finally, AIdrug2cov constructs three billion meta paths that reflect the interaction mechanisms and topological structures among vertices in heterogeneous drug networks.

4.2.2 Deep Bidirectional Transformers Encoder

The network embedding model in AIdrug2cov is a deep bidirectional Transformer encoder based on the original implementation described in [143], and the implementation is almost identical to the original. The encoder is composed of a stack of identical layers, and every layer includes two sub-layers as shown in Fig.10. The first is a multi-head self-attention mechanism, and the second is a simple, position wise fully connected feed-forward network. In the encoder model, a residual connection [144] is employed to connect each of two sub-layers, and layer normalization is then performed.

4.2.3 Training regime

The network embedding model uses ”masked language learning” to enable trained deep bidirectional representation

inspired by the Cloze task. In masked language learning, the input corpus is randomly masked by some token, and the objective is to predict the masked word based only on its context. AIdrug2cov follows the method used in BERT [129] to mask an input corpus. First, 15% of tokens were randomly selected for masking. For every selected token, it has 80% time to be replaced by ⟨MASK⟩ token. With 10% and 10% time, 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 the model, and prevent it over-fitting. In addition, because random replacement occurs is only 1.5% (i.e., 15%*10%) of the time for all tokens, it does not seem to harm the model's language understanding capability.

4.3 Identification of potential targets and drugs for the COVID-19

Based on over representations, the inductive matrix completion (IMC) model and CMap were used for target identification and drug repurposing for COVID-19 to facilitate therapeutic efficiency.

4.3.1 Inductive matrix completion-based confidence score prediction

In this work, the heterogeneous drug networks includes 8 type of edge, $r \in R = \{DDA,\ DDI,\ DTI,\ DSA,\ PPI,\ DisTA,\ DDSS,\ PPSS\}$. For $r \in \{DDA,\ DDI,\ DTI,\ DSA,\ PPI,\ DisTA\}$, $P^r_{ij} = 1$ if node i is linked to node j, and $P^r_{ij} = 0$ otherwise. For $r \in \{DDSS,\ PPSS\}$, P^r_{ij} is equal to the similarity value between node i and j. As shown in Figure 1(C), AIdrug2cov uses the IMC model [145] to obtain edge-type projection matrices $G_r, H_r \in R^{d\times k}$ for reconstructing the original edge-type matrix P^r as much as possible, where d is the dimension of representation vectors, and $k \ll d*d$. A similar strategy has been popularly applied to the bio-link prediction [126], [146]. The optimization function is defined as follows:

$$\min_{G_r,H_r} \sum_{r\in R} \sum_{(i,j)\in V_r} \|P^r_{ij} - F_i G_r H_r^{\mathrm{T}} F_j^{\mathrm{T}}\|_2^2 \qquad (1)$$

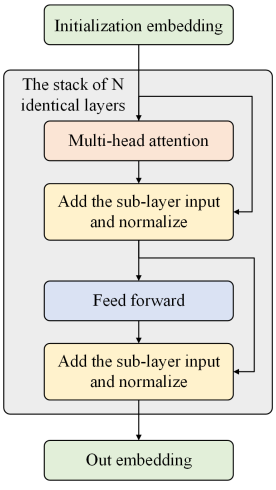


Fig. 10. Learning architecture of the deep bidirectional Transformers encoder model

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

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

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

4.3.2 COVID-19 target identification

In this study, COVID-19 target identification of COVID-19 was conducted with SARS data caused by the virus SARS-CoV since SARS-CoV and SARS-CoV-2 are highly similar and closely related coronaviruses. Phylogenetic analysis has revealed that the genome of SARS-CoV-2 is similar to that of SARS-CoV, with approximately 79% sequence identity [4]. Further sequence alignment has revealed that the similarity of the sequence of the main protease between SARS-CoV-2 and SARS-CoV, which is essential for the life cycle of the virus, is up to 96.1%. In addition, the pathogenic mechanisms of SARS-CoV-2 and SARS-CoV are highly similar [3]. Therefore, predicted targets related to SARS can reasonably be treated as potential targets of COVID-19.

As shown in Fig.1(E), in the process of COVID-19 target identification, the low-dimensional vector of nodes was feed into the IMC model to predict the confidence scores of SARS-protein interactions. Then, the proteins were ranked according to confidence scores, and the top-k proteins were regard as potential targets of COVID-19. Finally, Enrichr [18], a comprehensive gene set enrichment analysis tool, was used to perform functional enrichment analyse, including GO and KEGG enrichment analyses to evaluate the functional pathways and biological relevance of the potential targets of COVID-19.

4.3.3 Anti-inflammatory drug discovery for COVID-19

Studies have shown that SARS-CoV-2 induces excessive and aberrant non-effective host immune responses that are associated with severe lung pathology and lead to death [1]. Similar to SARS-CoV infection, SARS-CoV-2 infection is also associated with a cytokine storm and severe pulmonary inflammation in moribund patients, and is characterized mainly by elevated plasma concentrations of IL-6, TNF-α. In particular, researchers have proposed that IL-6, and TNF-α might be promising therapeutic targets. Therefore, this study predicted drugs related to IL-6 or TNF-α to facilitate the therapies efficacy. Similar to the methods for target identification, IMC model are integrated to predict confidence scores for interaction between drugs and IL-6 or TNF-α and drugs, and the top-k candidate drugs according to confidence scores were selected for IL-6 or TNF-α, respectively. In addition, we performed the CMap [19] analysis to further screen candidate drugs for COVID-19. Due to the lack of gene expression data from the SARS-CoV-2 infected patients, we used the gene expression profiles of peripheral blood mononuclear cells (PBMCs) from ten SARS-CoV infected patients (GEO:GSE1739) [147] to identify potential COVID-19 therapeutic drugs. The detailed connectivity analysis steps are listed as follows.

Step 1: Student's t test was performed to identify genes that were differentially expressed in samples from SARS patients compared with normal samples. For each gene,

the statistical significance was assessed by computing the p value. The $\log_2$(FC) value was calculated as the fold change (FC) between the average signal intensity of 10 SARS patients and that of 4 normal human subjects was calculated for each gene. Any gene meeting the criteria of a p <0.01 and an absolute $\log_2$(FC) > 1 was considered to be the up- and down-regulated genes.

Step 2: The CMap scores were computed based on the sets of up- and down-regulated genes in SARS-CoV infected patients by using a web server (https://clue.io/query).

Step 3: In AIdrug2cov, 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 [148]. Therefore, drugs with the CMap scores < 0 were treated as COVID-19 therapeutic drug candidates.

Finally, we used literature-reported knowledge to filter drugs that tended to increase the release of IL-6 or TNF-α.

4.4 Pharmacological application of AIdrug2cov

To evaluate and interpret the node representation performance of AIdrug2cov, we performed various pharmacological tests, including DDI network reconstruction, ATC classification, and bio-link (i.e., DisTA, TDI, DSA) prediction.

4.4.1 DDI network reconstruction

As network representations, embedding vectors are expected to reconstruct the original networks well [130]. Here, we reconstructed the DDI network edges based on the proximity nodes to evaluate the representation performance of AIdrug2cov. First, the proximity matrix was attained by directly calculating the cosine similarity between embedding vectors. Then, the pairs of nodes were ranked according to their proximity. Finally, the ratio of real links in the top k pairs of vertices was treated as the reconstruction precision. A more reconstruction precision indicated a more higher embedding quality.

4.4.2 ATC classification

In drug development, identification of the ATC class of an uncharacterized compound is a challenging and important task, since such a prediction system could be used to deduce not only a compound's possible active ingredients but also its chemical, therapeutic, pharmacological, and other properties.In addition, node classification, which aims to predict the classes of unlabeled nodes for a partially labeled network, is one of the most important tasks in network analysis. Therefore, the AIdrug2cov low-dimensional embedding vectors were treated as feature of nodes, and fed into the Multi-label K-Nearest Neighbor (ML-KNN) [149] model which is frequently used to predict the ATC classes of drug. Generally, good network embedding should capture the network structure and hence be useful for ATC classification.

4.4.3 Bio-link prediction

Another important task of network embedding is predicting unobserved links in a network, which refers to predicting either missing interactions that may appear in the future. Link prediction is pervasive in biological network analysis, but verifying the existence of links between nodes is time-consuming and cost-expensive [150]. Therefore, a great number of efforts have been devoted to predicting potential interactions based on network embedding approaches, such as deeper [151], and NeoDTI [126].

To further demonstrate the effectiveness of the proposed embedding methods, the IMC model was also employed to predict DisTA, TDI, and DSA, that is, disease $\rightarrow$ protein $\rightarrow$ drug $\rightarrow$ side-effect associations. The IMC model has been widely used for biomedical link prediction, such as drug-target interaction prediction [152], and gene-disease interaction prediction [145]. The previous findings suggest that a good network representation model can significantly improve prediction accuracy, and should be able to capture the inherent structure of a network well enough to predict likely but unobserved links.

AVAILABILITY AND IMPLEMENTATION

The source code and data of AIdrug2cov can be downloaded from https://github.com/pengsl-lab/AIdrug2cov.git.

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