

Supplementary Materials for

“Predicting Human Microbe-Drug Associations via Graph Convolution Network with Conditional Random Field”

1. Supplementary Figures

In this paper, we compared our method with some diverse types of state-of-the-art computational methods developed for addressing other biomedical problems, such as microbe-disease prediction (i.e., KATZHMDA, NTSHMDA and WMGHMDA), miRNA-disease prediction (i.e., IMCMDA), miRNA-drug resistance prediction (i.e., GCMDR) and drug-target prediction (i.e., WNN-GIP and GCNMDA). We evaluated the performance for all methods using 2-fold CV, 5-fold CV and 10-fold CV in terms of AUC and AUPR scores. The results for AUC and AUPR have been shown in Table S1 and Table S2, respectively. In addition, for more intuitive comparison, Figure S1 and Figure S2 display corresponding ROC and PR curves, respectively.

Table S1. Performance comparison between baseline methods and our method in terms of AUC. The best results are marked in bold. Underline denotes the second best method.

Method	2-fold CV	5-fold CV	10-fold CV
KATZHMDA	0.7865±0.0254	0.8723±0.0032	<u>0.8929±0.0265</u>
NTSHMDA	0.7766±0.0126	0.8302±0.0089	0.8547±0.0165
WMGHMDA	0.8519±0.0024	0.8654±0.0122	0.8729±0.0130
IMCMDA	0.7285±0.0065	0.7466±0.0102	0.7466±0.0221
GCMDR	0.8432±0.0016	0.8485±0.0062	0.8590±0.0241
BLMNII	<u>0.8583±0.0239</u>	<u>0.9231±0.0170</u>	0.8644±0.0227
WNNGIP	0.8256±0.0516	0.8721±0.0162	0.8711±0.0130
GCNMDA	0.9384±0.0028	0.9423±0.0105	0.9420±0.0078

Table S2. Performance comparison between baseline methods and our method in terms of AUPR. The best results are marked in bold. Underline denotes the second best method.

Method	2-fold CV	5-fold CV	10-fold CV
KATZHMDA	0.6559±0.0034	0.8081±0.0209	0.8403±0.0182
NTSHMDA	0.5674±0.0057	0.6735±0.0092	0.7118±0.0442
WMGHMDA	0.8201±0.0086	0.8381±0.0083	0.8452±0.0117
IMCMDA	0.7618±0.0038	0.7773±0.0113	0.7727±0.0136
GCMDR	<u>0.8423±0.0025</u>	0.8509±0.0040	0.8634±0.0210
BLMNII	0.7805±0.0318	<u>0.9263±0.0152</u>	0.8792±0.0221
WNN-GIP	0.8299±0.0603	0.8922±0.0137	<u>0.8863±0.0232</u>
GCNMDA	0.9316±0.0017	0.9376±0.0114	0.9359±0.0087

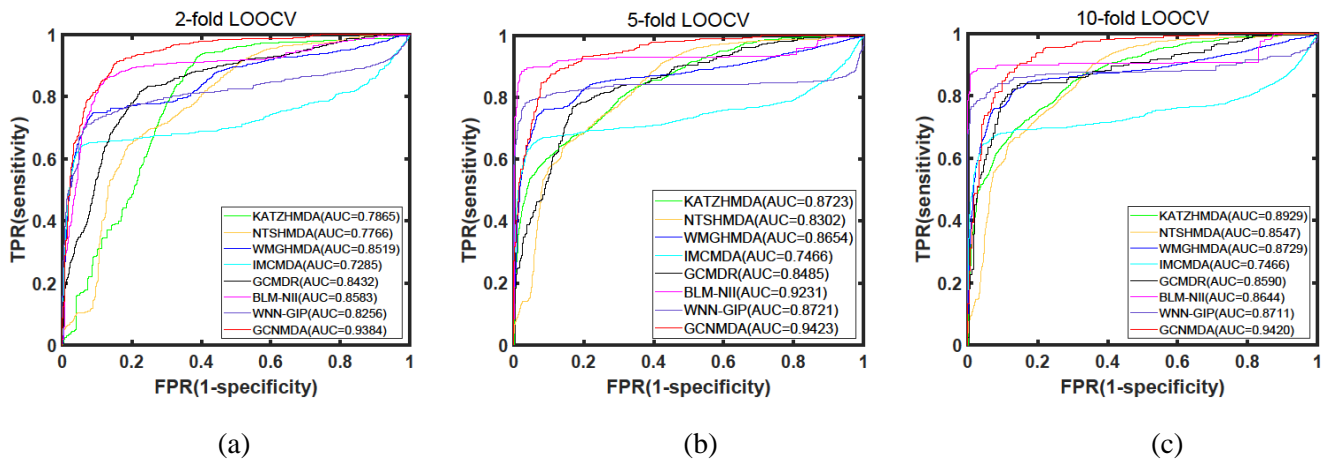


Figure. S1. Comparisons of prediction performance between our method and baseline methods based on MDAD under the frameworks of 2-fold CV, 5-fold CV and 10-fold CV in terms of AUC, respectively. (a) 2-fold CV; (b) 5-fold CV; (c) 10-fold CV.

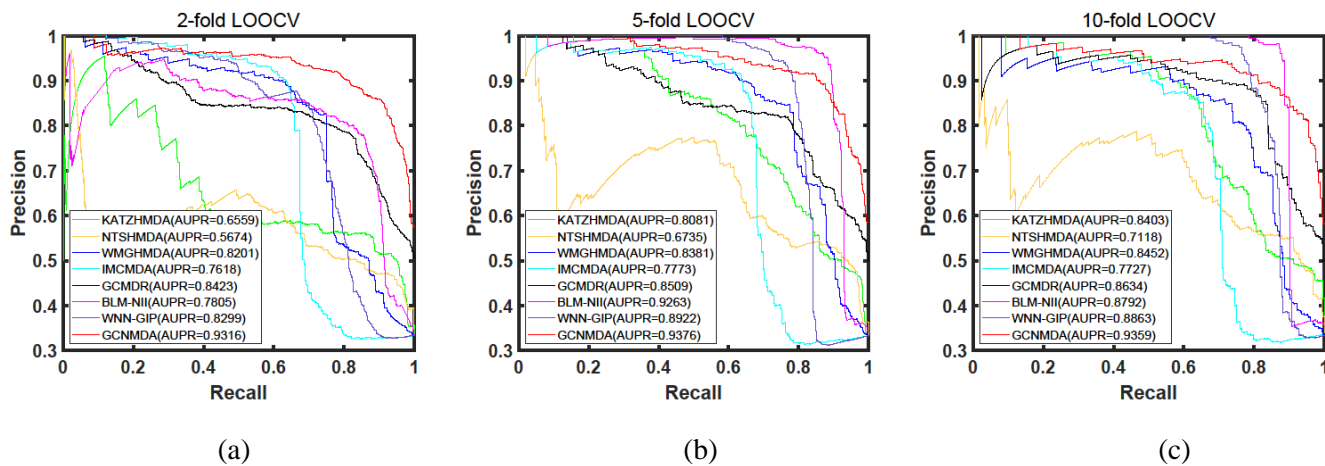


Figure. S2. Comparisons of prediction performance between our method and baseline methods based on MDAD under the frameworks of 2-fold CV, 5-fold CV and 10-fold CV in terms of AUPR, respectively. (a) 2-fold CV; (b) 5-fold CV; (c) 10-fold CV.

2. Supplementary Tables

For further verify the effectiveness of our method, we adopt two popular drugs (i.e., Ciprofloxacin and Moxifloxacin) and two popular microbes (i.e., *Pseudomonas aeruginosa* and *Escherichia coli*.) for case study. We validated the predicted candidate microbes using previous reports. The top 50 predicted candidate microbes have been listed in Table S3 and Table S4 for Ciprofloxacin and Moxifloxacin, respectively. The top 50 predicted candidate drugs have been listed in Table S5 and Table S6 for *Pseudomonas aeruginosa* and *Escherichia coli*., respectively.

Table S3. Prediction results of the top 50 Ciprofloxacin-associated microbes. The first column records top 1-25 associated microbes. The third column records top 26-50 associated microbes.

Microbe	Evidence	Microbe	Evidence
<i>Candida albicans</i>	PMID:31471074	<i>Vibrio anguillarum</i>	PMID:19146525
<i>Streptococcus mutans</i>	PMID:30468214	<i>Proteus mirabilis</i>	PMID:26953206
<i>Staphylococcus epidermis</i>	PMID:10632381	<i>Eikenella corrodens</i>	PMID:16875802
<i>Staphylococcus epidermidis</i>	PMID:28481197	<i>Micrococcus luteus</i>	PMID:26954218
<i>Enterococcus faecalis</i>	PMID:27790716	<i>Bacillus cereus</i>	PMID:26358183
<i>Vibrio harveyi</i>	PMID:27247095	<i>Plasmodium falciparum</i>	PMID:17214980
<i>Salmonella enterica</i>	PMID:26933017	Human immunodeficiency virus	PMID:26195465
Human immunodeficiency virus 1	PMID:9566552	<i>Porphyromonas gingivalis</i>	PMID: 15231772
<i>Actinomyces oris</i>	Unconfirmed	<i>Enterococcus faecium</i>	PMID:28193670
<i>Streptococcus sanguis</i>	PMID: 11347679	<i>Streptococcus gordonii</i>	PMID:22887906
Enteric bacteria and other eubacteria	PMID:27436461	<i>Campylobacter jejuni</i>	PMID:27900889
<i>Listeria monocytogenes</i>	PMID:28355096	<i>Vibrio campbellii</i>	Unconfirmed
<i>Burkholderia cenocepacia</i>	PMID:27799222	<i>Klebsiella planticola</i>	PMID:25465871
<i>Streptococcus pneumoniae</i>	PMID:26100702	Human herpesvirus 1	Unconfirmed
<i>Burkholderia pseudomallei</i>	PMID:24502667	<i>Pichia anomala</i>	Unconfirmed
<i>Burkholderia multivorans</i>	PMID: 19633000	<i>Candida tropicalis</i>	Unconfirmed
<i>Clostridium perfringens</i>	PMID:29978055	<i>Candida glabrata</i>	Unconfirmed
<i>Serratia marcescens</i>	PMID:23751969	<i>Cryptococcus neoformans</i>	Unconfirmed
<i>Streptococcus epidermidis</i>	Unconfirmed	<i>Aeromonas hydrophila</i>	PMID:23084650
<i>Klebsiella pneumoniae</i>	PMID:27257956	<i>Streptococcus pneumoniae</i> serotype 4	PMID: 12543698
<i>Vibrio cholerae</i>	PMID:28270803	Influenza A virus	Unconfirmed
<i>Acinetobacter baumannii</i>	PMID:29998878	<i>Aeromonas sobria</i>	PMID:28484157
<i>Vibrio vulnificus</i>	PMID:28971862	<i>Hafnia alvei</i>	PMID:28537065
<i>Propionibacterium acnes</i>	PMID:27801379	<i>Enterococcus gallinarum</i>	PMID:29030312
<i>Streptococcus sanguinis</i>	PMID:21507381	<i>Mycobacterium avium</i>	PMID:30012773

Table S4. Prediction results of the top 50 Moxifloxacin-associated microbes. The first column records top 1-25 associated microbes. The third column records top 26-50 associated microbes.

Microbe	Evidence	Microbe	Evidence
<i>Pseudomonas aeruginosa</i>	PMID:31691651	<i>Mycobacterium tuberculosis</i>	PMID:31713607
<i>Staphylococcus aureus</i>	PMID:31689174	<i>Vibrio vulnificus</i>	PMID: 12384368
<i>Escherichia coli</i>	PMID:31542319	<i>Propionibacterium acnes</i>	PMID:31538294
<i>Streptococcus mutans</i>	PMID:29160117	<i>Streptococcus sanguinis</i>	Unconfirmed
<i>Staphylococcus epidermis</i>	PMID: 11249827	<i>Vibrio anguillarum</i>	Unconfirmed
<i>Staphylococcus epidermidis</i>	PMID:31516359	<i>Proteus mirabilis</i>	PMID:27351708
<i>Enterococcus faecalis</i>	PMID:31763048	<i>Eikenella corrodens</i>	PMID:14614671
<i>Bacillus subtilis</i>	PMID:30036828	<i>Micrococcus luteus</i>	PMID:24231380
<i>Vibrio harveyi</i>	Unconfirmed	<i>Bacillus cereus</i>	PMID:21834669

Salmonella enterica	PMID:22151215	Plasmodium falciparum	PMID:15125930
Human immunodeficiency virus 1	Unconfirmed	Human immunodeficiency virus	PMID:31388545
Actinomyces oris	PMID: 26538502	Porphyromonas gingivalis	PMID:30048853
Streptococcus sanguis	PMID:10629010	Enterococcus faecium	PMID:23524466
Enteric bacteria and other eubacteria	Unconfirmed	Streptococcus gordonii	PMID:29160117
Listeria monocytogenes	PMID:28739228	Campylobacter jejuni	PMID:16027651
Burkholderia cenocepacia	Unconfirmed	Vibrio campbellii	Unconfirmed
Streptococcus pneumoniae	PMID:31542319	Klebsiella planticola	Unconfirmed
Burkholderia pseudomallei	PMID:15731198	Proteus vulgaris	PMID: 19692210
Burkholderia multivorans	Unconfirmed	Human herpesvirus 1	Unconfirmed
Clostridium perfringens	PMID:29486533	Pichia anomala	Unconfirmed
Serratia marcescens	PMID:17592324	Candida tropicalis	PMID:20455400
Streptococcus epidermidis	Unconfirmed	Candida glabrata	PMID:20455400
Klebsiella pneumoniae	PMID:30058553	Cryptococcus neoformans	Unconfirmed
Vibrio cholerae	PMID:16341343	Aeromonas hydrophila	PMID:12821471
Acinetobacter baumannii	PMID:31261589	Streptococcus pneumoniae serotype	Unconfirmed

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Table S5. Prediction results of the top 50 *Pseudomonas aeruginosa*-associated drugs. The first column records top 1-25 associated drugs. The third column records top 26-50 associated drugs.

Microbe	Evidence	Microbe	Evidence
Biphenyl	PMID: 26519802	Isohydnocarbin	Unknown
L-Phenylalanine-L-Lysine	Unknown	Quercetin Dihydrate	Unknown
Ticarcillin	PMID: 26248364	Sage oil	PMID: 27585258
Ethyl acetate	PMID: 26887538	Silver sulphate	Unknown
2,3-dihydroxybenzoic acid	PMID: 24449781	Phylloseptin-1	Unknown
Ionic silver	PMID: 25001302	Resorcinol	PMID: 28989246
Phloridzin	Unknown	D-Aspartate	PMID: 25656450
3-tetra- decanoyltetronic	Unknown	Oregano oil	PMID: 30344513
Dichloromethane	PMID: 29375509	Quercetin-3-O-glucuronide	Unknown
3-tetradecanoylthiotetronic	PMID: 27999062	3-Hydroxytyrosine	Unknown
(5Z)-2-(1,1-dichloro-7-methyloctyl)-5-{{4-(trifluoromethyl)phenyl}methylidene}-1,3-oxazolidin-4-one	Unknown	(5Z)-2-(1,1-dichloropropyl)-5-{{4-(trifluoromethyl)phenyl}methylidene}-1,3-oxazolidin-4-one	Unknown
(5Z)-2-(1,1-dichlorobut-3-yn-1-yl)-5-{{4-(trifluoromethyl)phenyl}methylidene}-1,3-oxazolidin-4-one	Unknown	PTP-7	Unknown
5- hydroxyethyl-3-tetradecanoyltetramic acid	PMID: 27999062	Silver dihydrogen citrate	Unknown
P10	PMID: 3141560	Pine needle oil	Unknown
CAMA	PMID: 30849936	Na-Propionate	PMID: 10515415
Teichoplanin	Unknown	Tangerine oil	Unknown
cis-Stillbene	Unknown	Diphenyl methane	Unknown
Myricitrin	PMID: 25993634	Clary sage oil	Unknown
Cecropin (1-7)-melittin A (2-9) amide	Unknown	alpha-tocopherol	PMID: 25458794
Myrrh oil	PMID: 22288378	Protamine sulphate	PMID: 7574516
HE4	Unknown	Silybin	PMID: 18758739
Tea tree oil	PMID: 23581401	(2Z)-N-hexyl-2-hydroxy-3-[4-(trifluoromethyl)phenyl]prop-2-enamide	Unknown
Myricetin	PMID: 30213633	Hesperetin	Unknown
trans-Resveratrol	PMID: 29530588	(5Z)-2-(1,1-dichloro-3,3-dimethylbutyl)-5-	Unknown

Methanol	PMID: 28637123	(phenylmethylidene)-1,3-oxazolidin-4-one (10R,11R)-Hydnocarpin D	Unknown
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Table S6. Prediction results of the top 50 *Escherichia coli*.-associated drugs. The first column records top 1-25 associated drugs. The third column records top 26-50 associated drugs.

Microbe	Evidence	Microbe	Evidence
Indol AHL	PMID: 22101045	Seg6D	Unknown
7-bromoindole	PMID: 27921270	Zinc Dichloride	PMID: 16955743
(2S,3R,4S,5S,6R)-6-(Acetoxymethyl)-3-(3-oxohexanamido)tetrahydro-2H-pyran-2,4,5-triyl triacetate	PMID: 28049617	D, L- K6L9	Unknown
LF11-322	PMID: 21515687	2-(5-Bromo-2-(2-chloroacetamido)phenyl)-2-oxo-N-(prop-2-yn-1-yl)acetamide	Unknown
N-((2R,3R,4S,5S,6R)-2,4,5-Trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-3-yl)hexanamide	PMID: 28049617	Gallium cation	Unknown
Cobalt Ion	PMID: 16158232	Silver Ion	PMID: 28458540
ZnO nanoparticles	PMID: 27614583	3beta-Hydroxyolean-12-en-28-al 3-p-coumarate	Unknown
Indirubin	PMID: 24500796	Furanone	PMID: 24118802
4-tertiary butyl benzyl decyl beta-maltoside	Unknown	3-fluoroaniline	Turan <i>et al.</i> (2012)
14,15,29,30-Tetrahydro-5H,20H-dibenzo[h,s]bis([1,2,3]triazolo)[5,1-c:5',1'-n][1,4,7,12,15,18]hexaazacyclodocosine-6,12,13,21,27,28(7H,22H)-hexaone	Unknown	D-galactose cluster	PMID: 15382922
14,15,29,30-Tetrahydro-5H,20H-dibenzo[h,s]bis([1,2,3]triazolo)[5,1-c:5',1'-n][1,4,7,12,15,18]hexaazacyclodocosine-6,12,13,21,27,28(7H,22H)-hexaone	Unknown	14-Glycinyll andrographolide hydrochloride	PMID: 19152987
2-((3,4-dichlorophenyl)sulfonyl)-4-(1H-tetrazol-1-yl)pyrimidine	Unknown	7-fluoroindole	PMID: 22251040
Tellurite	PMID: 25447814	7-methylindole	Unknown
7-chloroindole	PMID: 27921270	14-dehydroxy-11,12-didehydroandrographolide- 3,19-bis(succinic acid) potassium sodium salt	Unknown
2-oxindole	PMID: 25664629	4-tertiary butyl benzyl dodecyl beta-maltoside	Unknown
7-Bicyclic brominated furanones	Unknown	Norpinguisone	Jorge <i>et al.</i> 2013
N-(5-Methyl-1,2-oxazol-3-yl)butanamide	Unknown	Delphinidin	PMID: 29765781
Tricaine	PMID: 20019794	5-Chloro-1-(2-chloroacetyl)indoline-2,3-dione	PMID: 28654117
N-Decanoyl cyclopentylamide	PMID: 17369333	Decyl beta-maltoside	Unknown
O-LF11-215	Unknown	para-ethylaniline	Unknown
Pelargonidin	PMID: 29554804	6-MO-LF11-215	Unknown
Benzocaine	PMID: 22556388	2-(2-(2-Azidoacetamido)-5-fluorophenyl)-2-oxo-N-(prop-2-yn-1-yl)acetamide	PMID: 28654117
(2S,3R,4S,5S,6R)-6-(Acetoxymethyl)-3-(3-oxooctanamido)tetrahydro-2H-pyran-2,4,5-triyl triacetate	PMID: 28049617	N-((2R,3R,4S,5S,6R)-2,4,5-Trihydroxy-6-	PMID: 28049617

		(hydroxymethyl)tetrahydro-2H-pyran-3-yl)butyramide	
2-(4-Bromophenyl)-N-((2R,3R,4S,5S,6R)-2,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-3-yl)acetamide	PMID: 28049617	4-methanesulfonylaniline	Unknown
para-ethoxyaniline	Unknown	8-fluoroquinoline	PMID: 22251040

Reference

- Turan, N. *et al.* (2012) Synthesis, Characterization of Poly(E)-3-amino-4-((3-bromophenyl)diazenyl)1H-pyrazol-5-ol: Investigation of Antibacterial Activity, Fluorescence, and Optical Properties. *Fibers and Polymers*, 13, 415-424.
- Jorge, C.S. *et al.* (2013) Bioprospecting, a tool to conserve Chilean bryophytes. *Gayana Bot*, 70, 16-25.