2. Drug Repositioning

Types of Drug Repositioning

Finding a new clinical use for an approved drug

Finding a clinical use for a stalled clinical development stage compound

Finding a new life for retracted drug

Drug Repositioning Saves Money and Time

	Drug discovery	Pre-clinical	Phase 1	Phase 2	Phase 3
Time spent	4-5 years	1-2 years	1-2 years	1-2 years	2-3 years
$ spent	$550M	$125M	$225M	$250M	$250M
Output	5,000 - 10,000 compounds	10-20 candidates	5-10 candidates	2-5 candidates	1-2 candidates

Reposition a stalled phase 2 drug will save $900M and 6-9 years

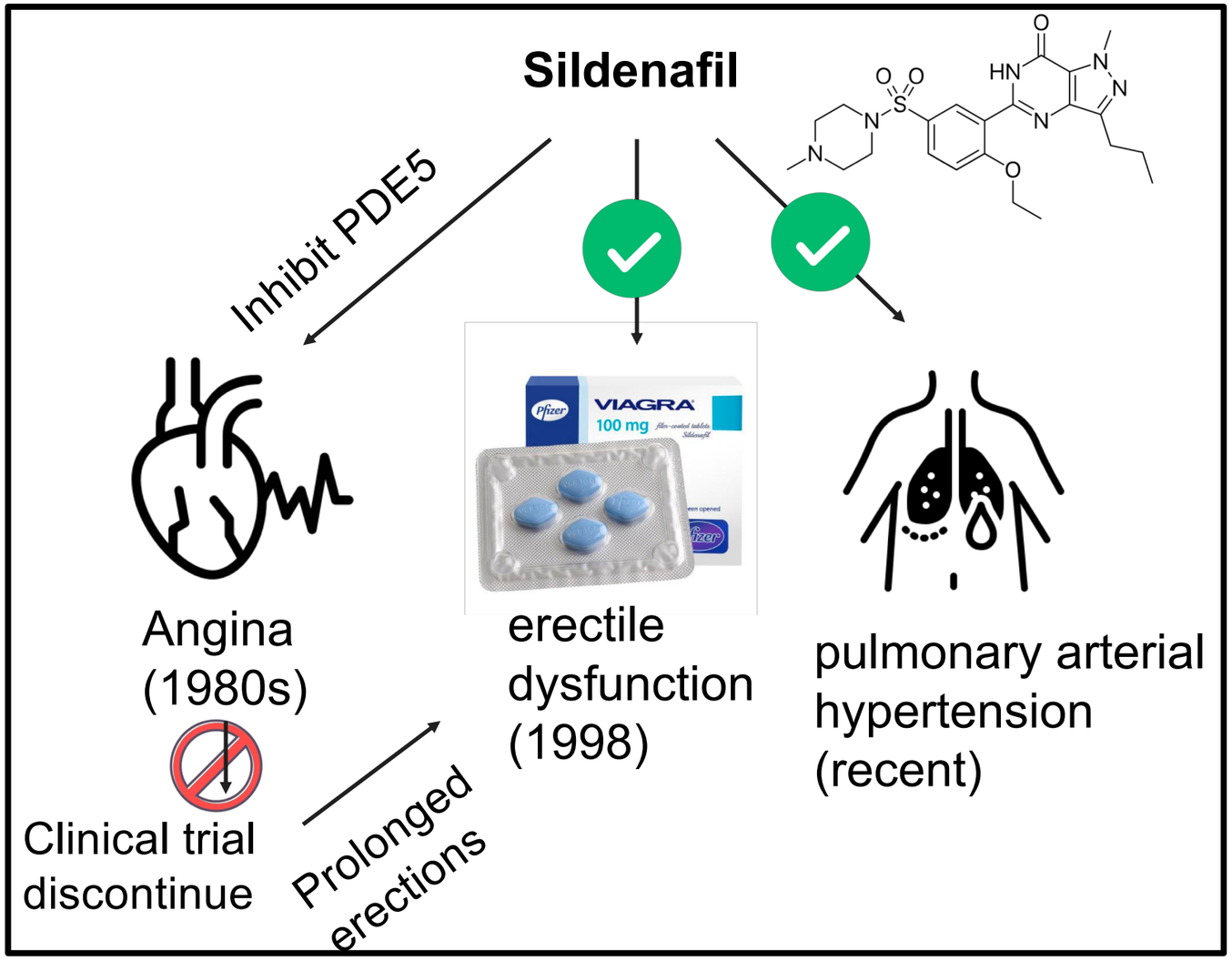
Example of Success in Drug Repositioning

DRUG NAME	ORIGINAL INDICATION	NEW INDICATION	YEAR	PHARMA COMPANY
Amitripyline	Antidepressant	Neuropathic pain	2005	AstraZeneca
Amphotericin B	Antifungal	Leishmaniasis	1997	NeXstar Pharma
Aspirin	Inflammation, Pain	Anti-platelet, heart attack, stroke	Various	Various
Azathioprine	Rheumatoid Arthritis (RA)	IBD, MS, organ transplants	Various	Various
Bimatoprost	Glaucoma	Eyelash growth	2008	Allergan
Bleomycin	Antibiotic	Cancer	1973	Kayaku/BMS
Bromocriptine	Parkinson's Disease	Type II diabetes	2009	Novartis
Buprenorphine	Pain	Drug treatment	2002	Reckitt-Benckiser
Bupropion	Antidepressant	Smoking cessation	1997	GSK
		Weight-loss (combi-therapy)	2014	Orexigen/Takeda
Canakinumab	Rheumatoid Arthritis (RA)	Muckle-Wells Syndrome	2009	Novartis
Clofazime	Tuberculosis	Leprosy	1986	Geigy
Colchicine	Gout	Familial mediterranean fever	2009	URL Pharma
Colesevelam	LDL-lowering	Type II diabetes	2008	Daiichi-Sankyo
Crizotinib	Lymphoma	NSCLC	2011	Pfizer
Cycloserine	Tuberculosis	CNS disorders	Various	Various
Cyclosporine	Organ transplant rejection	Psoriasis, RA	1997	Novartis
Dapoxetine	Antidepressant	Premature ejaculation	2004	J&J
Dimethyl Fumarate	Psoriasis	MS	2013	Biogen IDEC
Donepezil	Alzheimer's Disease	Dementia	2006	Eisai/Pfizer
Doxepin	Antidepressant	Atopic dermatitis	2003	Various
Duloxetine	Depression & GAD	Stress urinary incontinence	2004	Lilly
		Fibromyalgia	2008	Lilly
		Pain	2010	Lilly
Eflornthine	Cancer	Hirsutism	2000	Gillette
		Sleeping sickness	1990	Aventis
Etanercept	Rheumatoid Arthritis (RA)	Plaque psoriasis	2004	Amgen/Pfizer
Everolimus	Organ rejection	Various cancers	Various	Novartis
Finasteride	Hypertension	Benign prostate hyperplasia	1992	Merck
		Male pattern baldness	1997	Merck
Fluoxetine	Antidepressant	PMDD	2002	Lilly
Gabapentin	Seizure	Postherpetic neuralgia	2004	Parke Davis
Galantamine	Chronic fatigue syndrome	Alzheimer's Disease	2001	Various
Gemcitabine	Anti-viral	Various cancers	Various	Lilly
Glycopyrronium	Anti-ulcer	COPD	2005	Sosei/Novartis
Histrelin	Prostate cancer	Precocious puberty	2007	Endo Pharma

Example of Success in Drug Repositioning

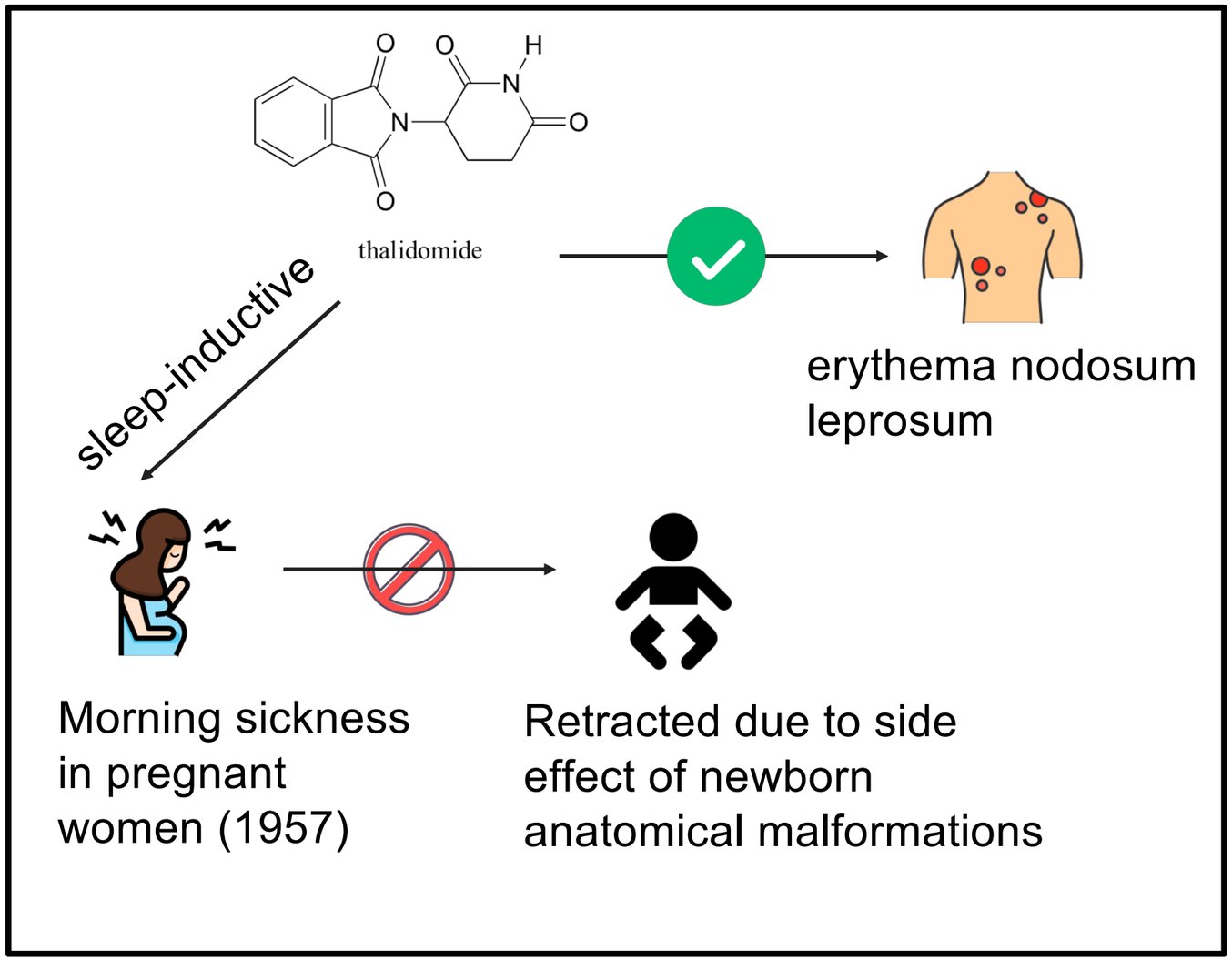
Hydroxychloroquine	Malaria	Lupus, rheumatoid	Various	Various
Ibuprofen	Inflammation, pain	OA, RA, headache, migraine	Various	Various
Imatinib	CML	GIST	2012	Novartis
		ALL	2013	Novartis
Imfliximab	Autoimmune diseases	Crohn's Disease	1998	Janssen
Iproniazid	Tuberculosis	Antidepressant	1958	Various
Lomitapide	Hypercholesterimia	HoFH	2012	Aegerion Pharma
Methotrexate	Cancer	Psoriasis, RA	2001	Barr Labs
Minoxidil	Hypertension	Hair Loss	1988	Upjohn
Milnacipran	Antideprressant	Fibromyalgia	2009	Forest Pharma
Miltefosine	Cancer	Leishamaniasis	2014	Zentaris
Naltrexone	Opiod/alcohol addiction	Weight-loss (combi-therapy)	2014	Orexigen/Takeda
Onabotulinumtocin	Facial spasm	Cervical dystonia	2000	Allergan
		Chronic migraine	2010	Allergan
		Facial cosmetics	2012	Allergan
Paclitael	Various cancers	Stent restenosis prevention	Various	Various
Paroxetine	Antidepressant	Menopausal hot flashes	2013	GSK
Pertuzumab	Various cancers	HER-2 + breast cancer	2013	Genetech
Plerixafor	AIDS/HIV	Lymphoma & multiple myeloma	2008	Genzyme
Pramipexole	Parkinson's Disease	Restless leg syndrome	2006	Boehringer
Pregabalin	Anticonvulsant, neuropathic pain	Fibromyalgia	2007	Pfizer
Propranolol	Hypertension	Migraine, angina, tremors	Various	Various
Retinoic Acid	Acne	Acute myeloid leukaemia	1995	Hoffman La Roche
Raloxifene	Osteoporosis	Breast cancer	2007	Lilly
Rituximab	Various cancers	Rheumatoid Arthritis	2004	IDEC
Ropininole	Parkinson's Disease	Restless leg syndrome	2005	GSK
Sildenafil	Angina	Erectile dysfunction	1998	Pfizer
		PAH	2005	Pfizer
Sunitinib	GIST and RCC	Pancreatic tumors	2010	Pfizer
Thalidomide	Anti-nausea	Leprosy	1998	Celgene
		Multiple myeloma	2006	Celgene
Zidovudine	Cancer	HIV/AIDS	1987	Burroughs

Success Stories: Sildenafil



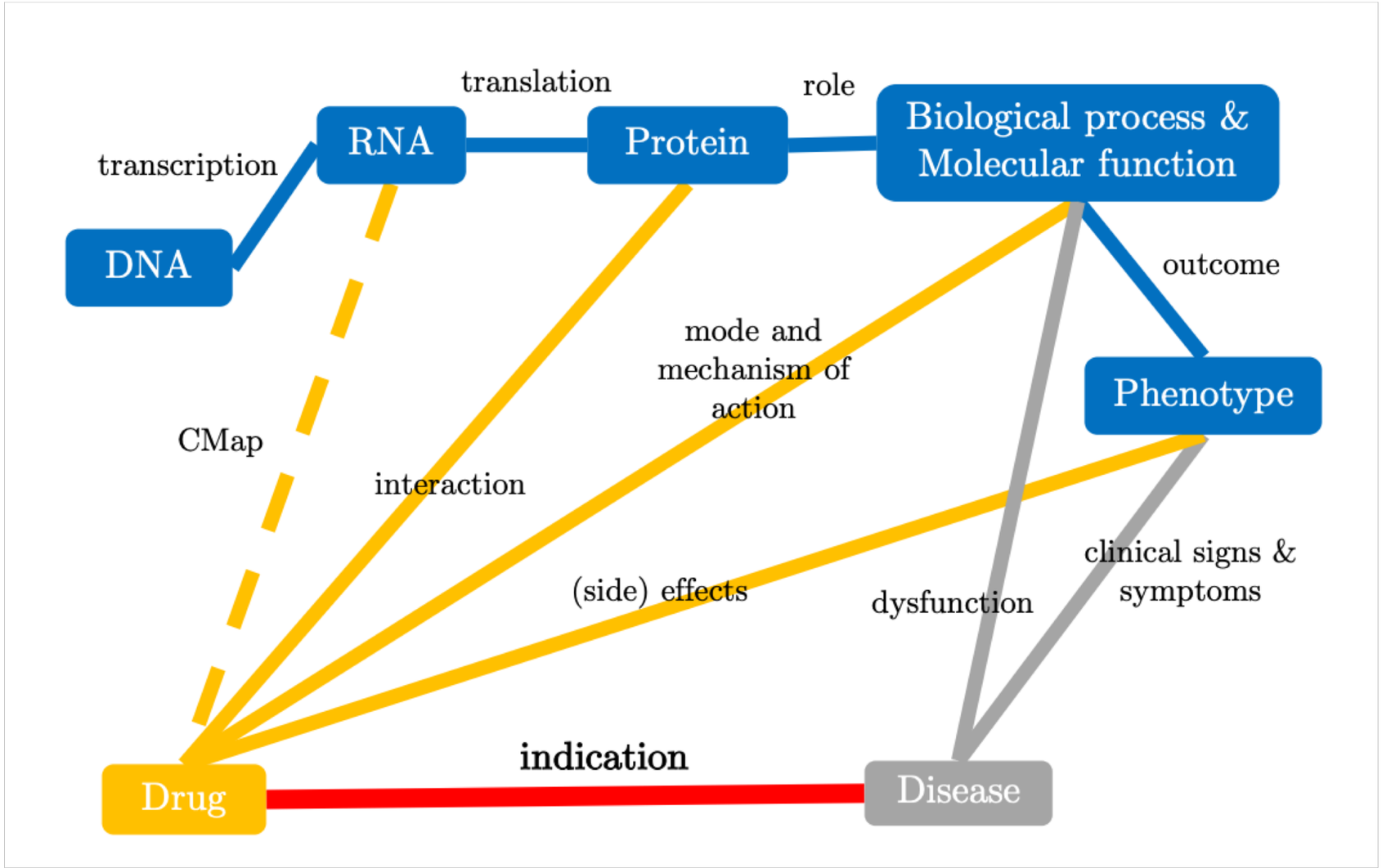
- The repositioning opportunities came from secondary functions of the enzyme targeted.
- Drug repositioning can be logically identified rather than discovered by chance.

Success Stories: Thalidomide



- The opportunity came from a disease related off-target.
- A better understanding of the proteins interacting with the molecule could have been helpful to predict the opportunity

Relationship between biomedical concepts in repositioning

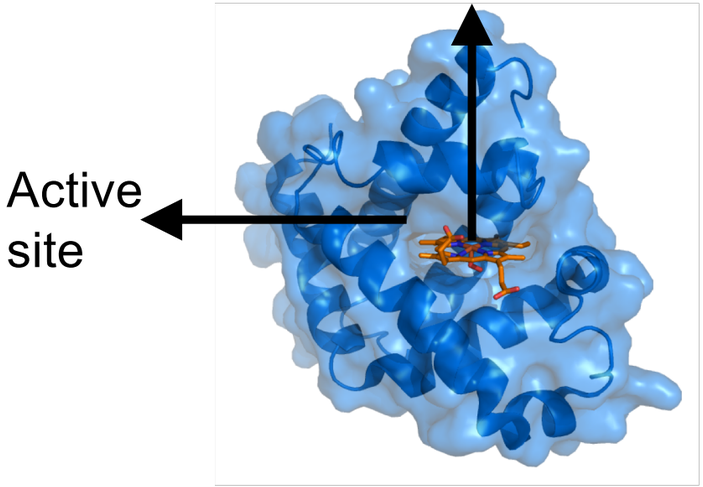


https://www.ebi.ac.uk/sites/ebi.ac.uk/files/shared/documents/phdtheses/Croset_Thesis.pdf

Drug Repositioning via Drug Target Interaction Prediction

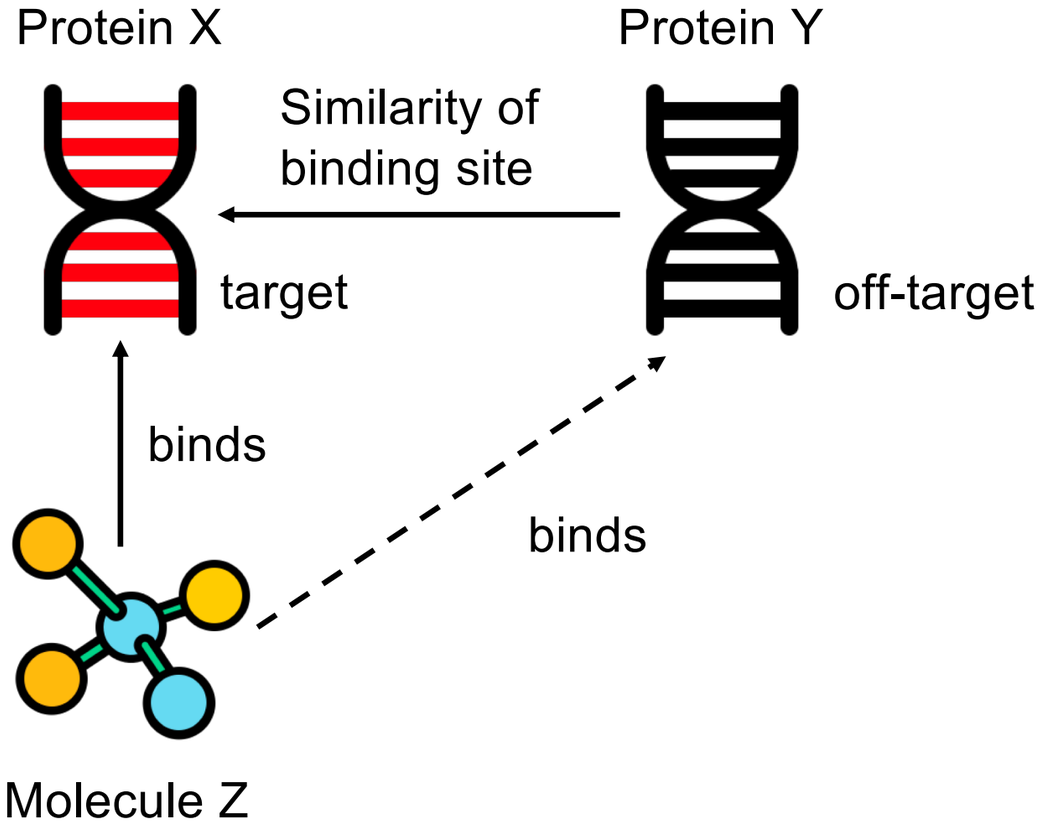
Target: disease modifying proteins

Drug: molecules that interact with target via activating or inhibiting its biological process

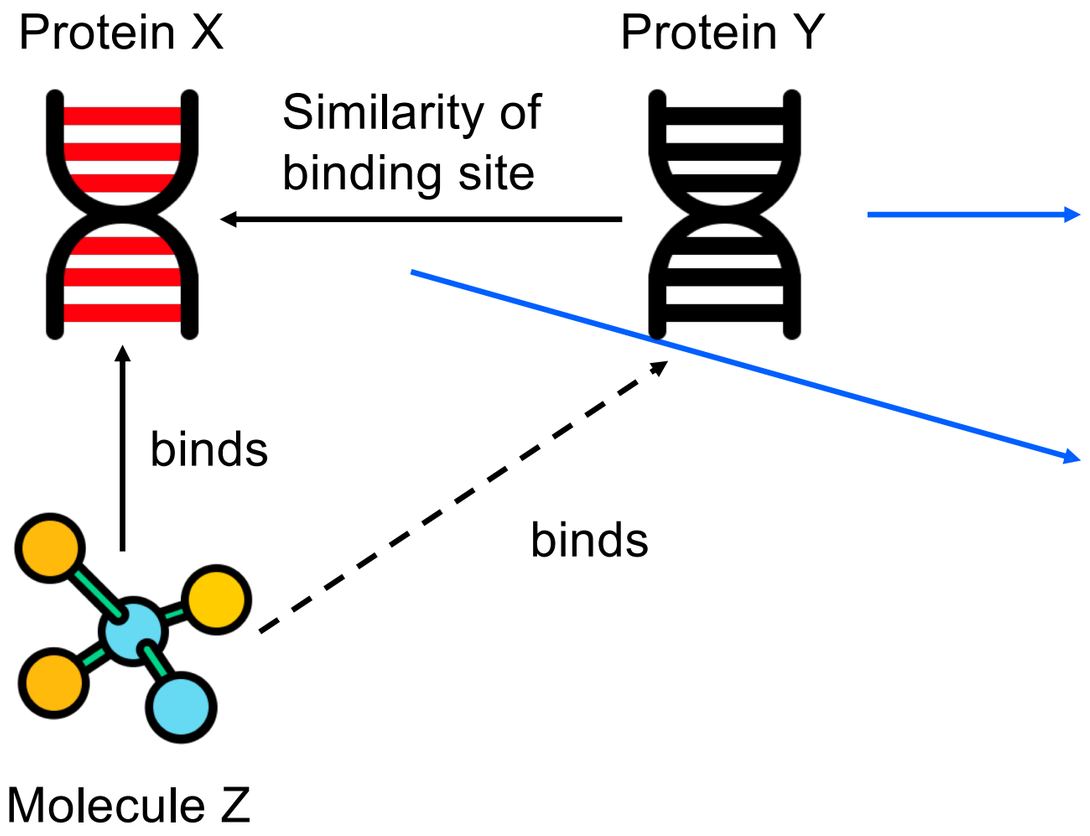


Molecule Docking: screening molecules against the 3D structure of proteins.

Identify potential off-targets



Challenges of Traditional DTI Methods



Docking based? 3D data must be available.

How to predict using 2D Data?

Structural similarity? Sensitive to surrounding substructure

How to recognize contextual difference?

Via biological assays?

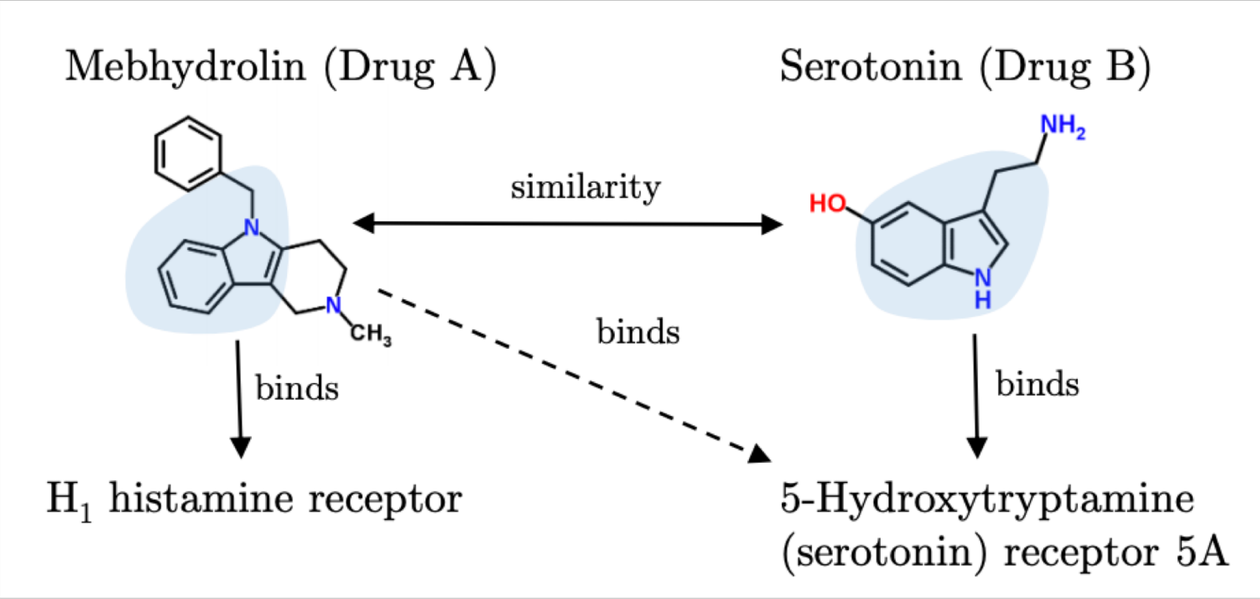
Time and cost consuming

A network integration approach for drug-target interaction prediction and computational drug repositioning from heterogeneous information

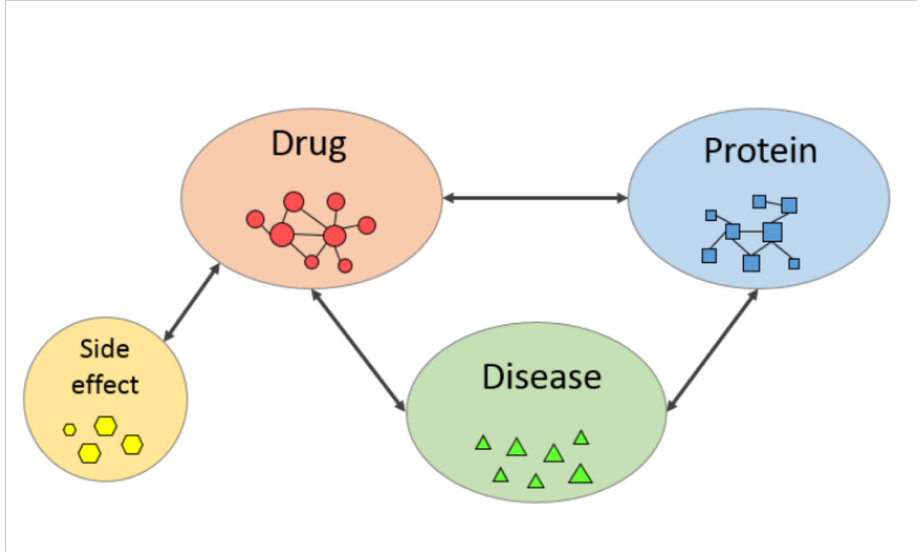
Yunan Luo, Xinbin Zhao, Jingtian Zhou, Jinglin Yang, Yanqing Zhang, Wenhua Kuang, Jian Peng ✉, Ligong Chen ✉ & Jianyang Zeng ✉

Nature Communications **8**, Article number: 573 (2017) | Download Citation ↓

Drug Repositioning via Drug Similarity

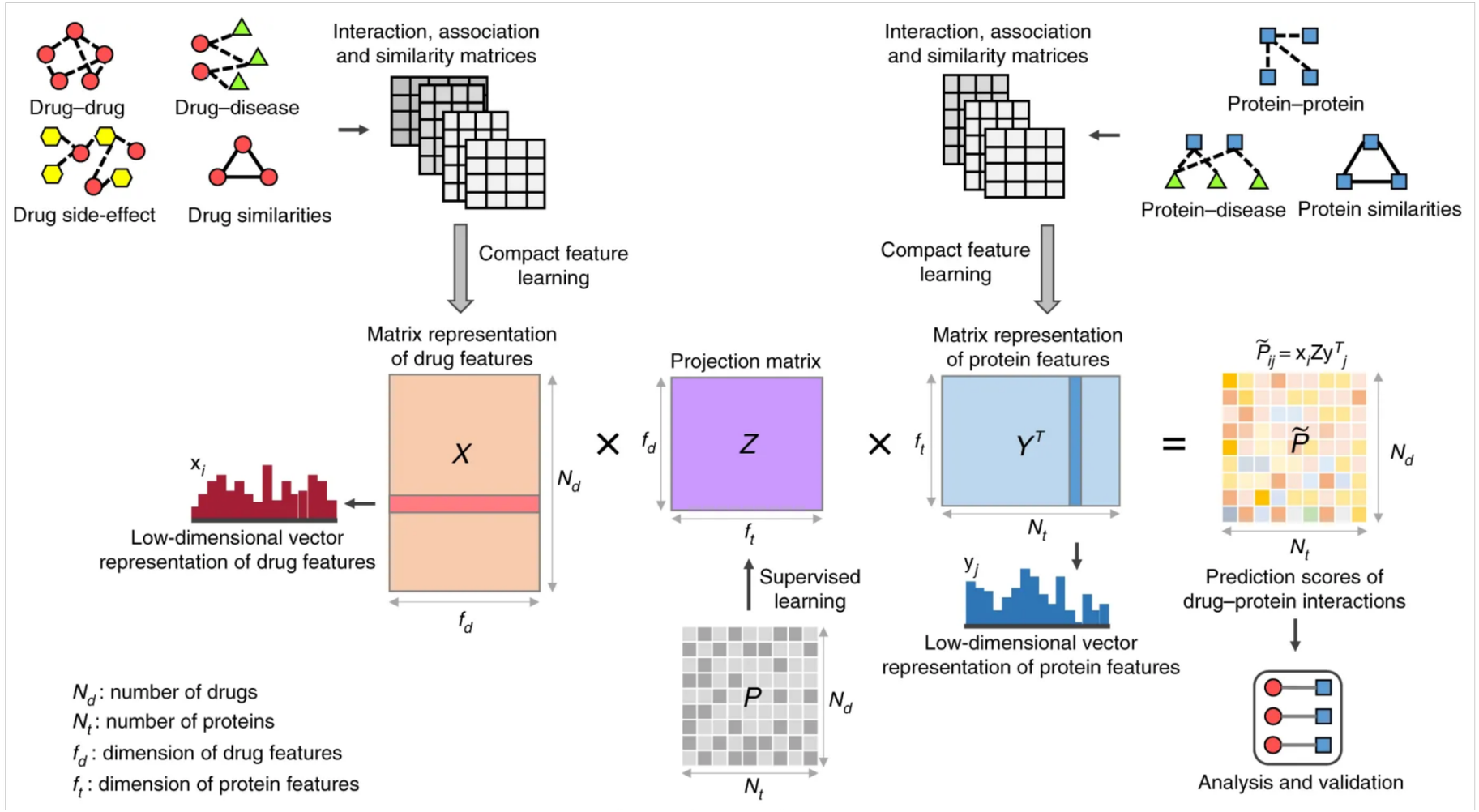


guilt-by-association



heterogeneous network

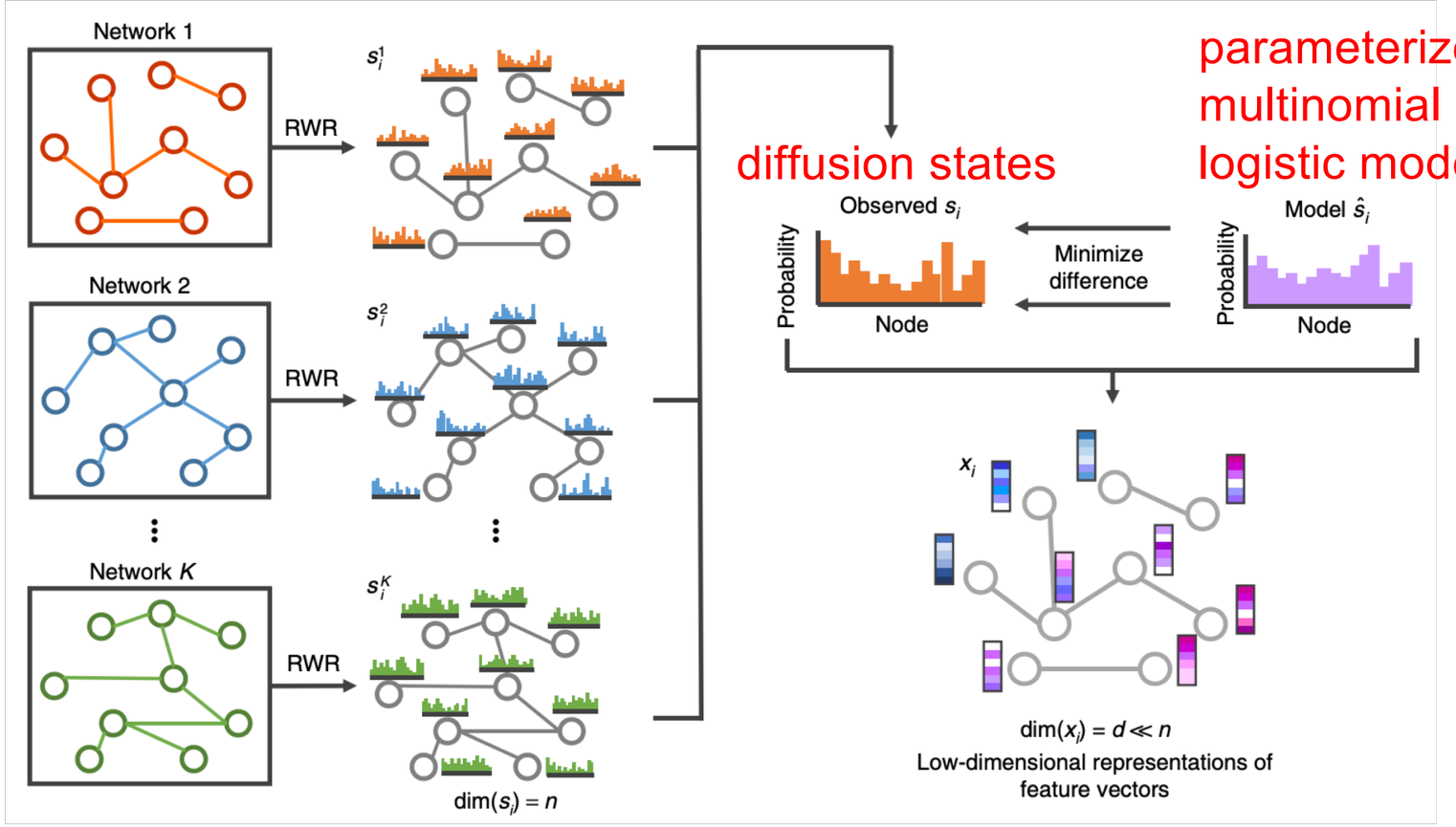
DTINet (Nature Communication 2017)



Y. Luo, J. Zhao, X.and Zhou, J. Yang, W.and Peng J. Zhang, Y.and Kuang, L. Chen, and J. Zeng. 2017. A network integration approach for drug-target interaction prediction and computational drug repositioning from heterogeneous information. Nat. Commun. 8 (2017)

DTINet (Nature Communication 2017)

Compact feature learning



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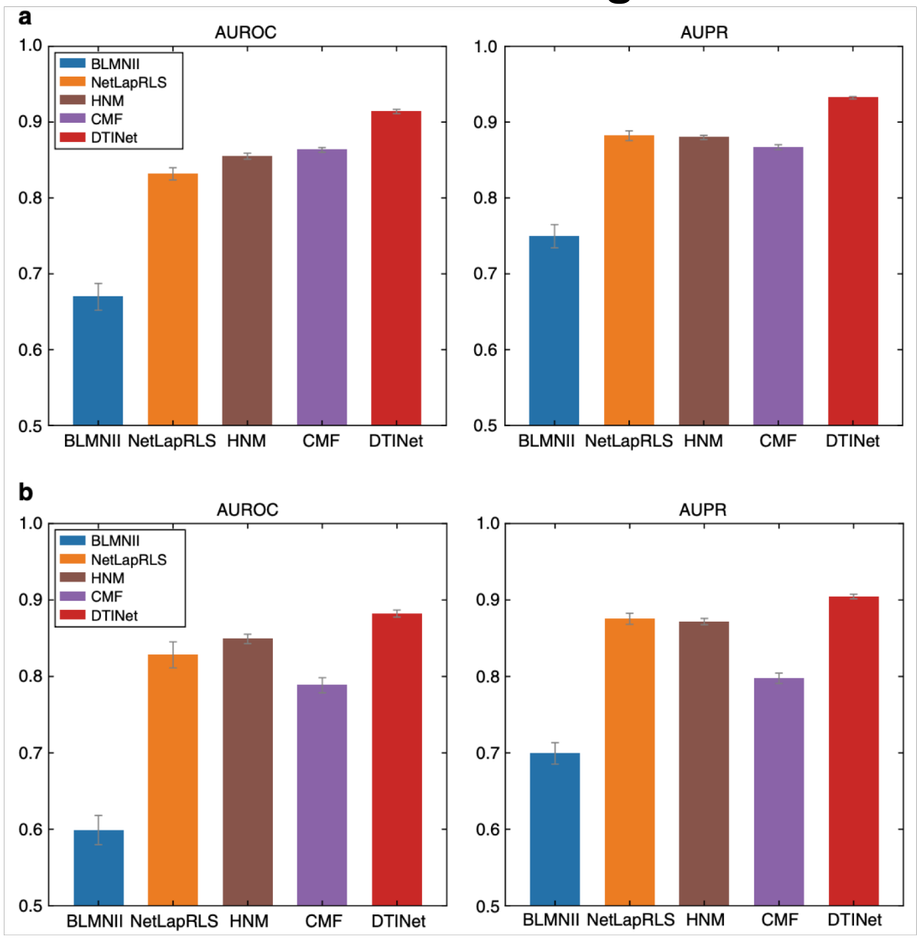
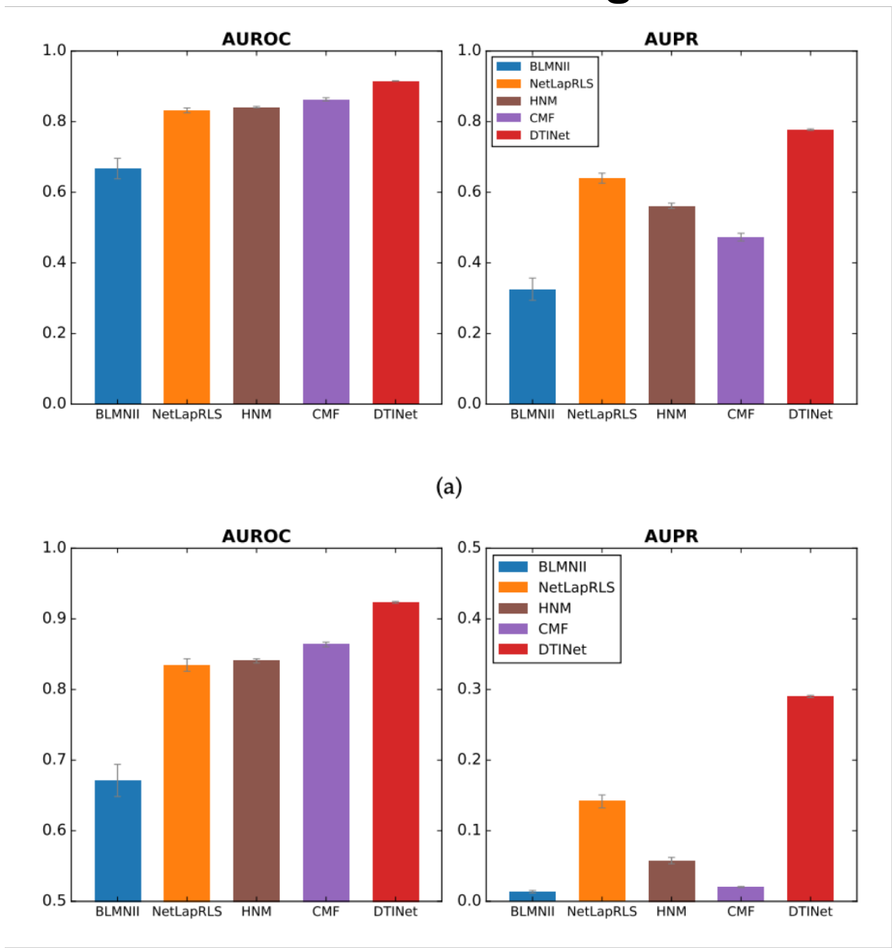
DTINet (Nature Communication 2017)

Classic setting



Skewed setting



Y. Luo, J. Zhao, X.and Zhou, J. Yang, W.and Peng J. Zhang, Y.and Kuang, L. Chen, and J. Zeng. 2017. A network integration approach for drug-target interaction prediction and computational drug repositioning from heterogeneous information. Nat. Commun. 8 (2017)

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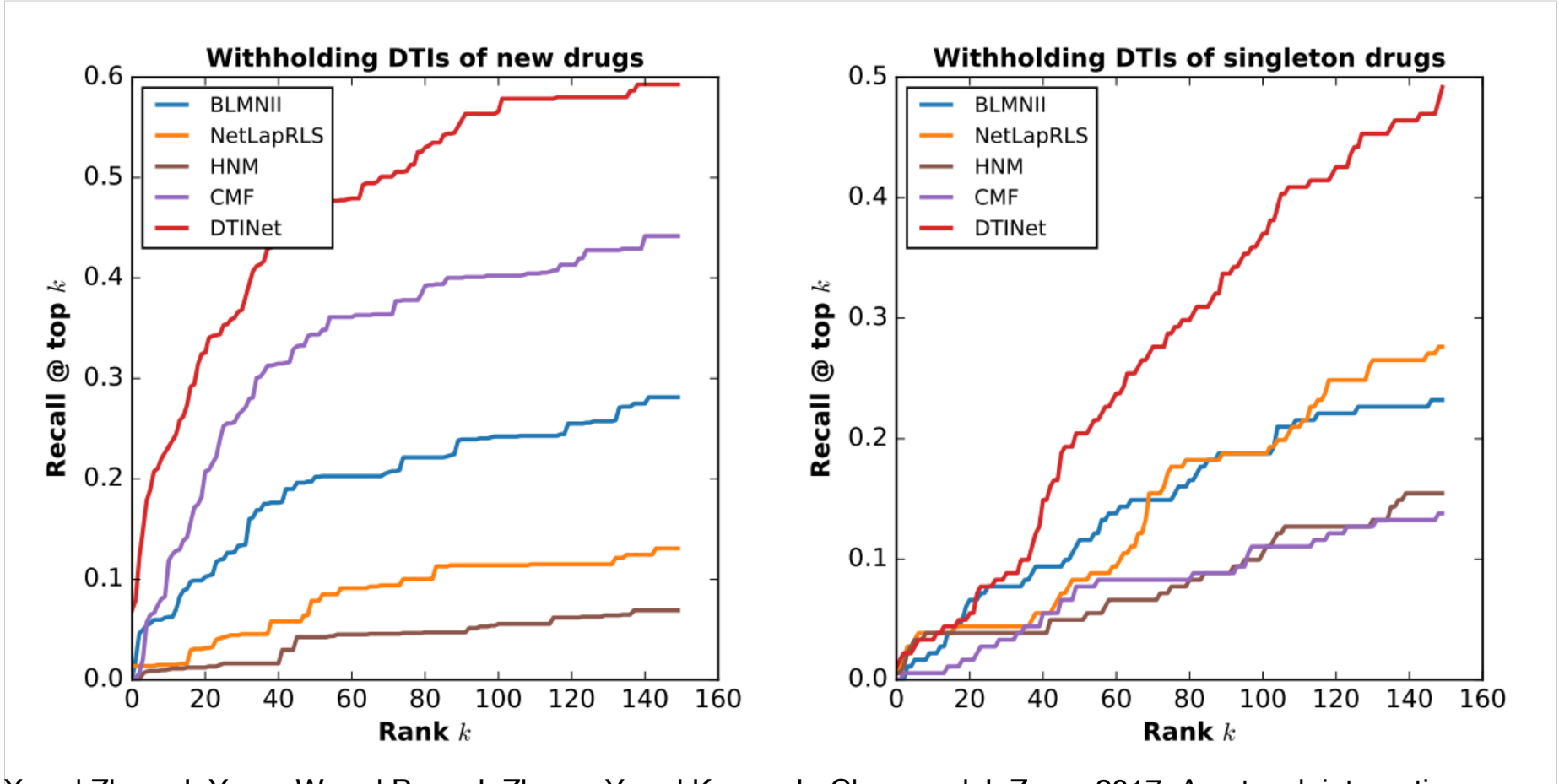

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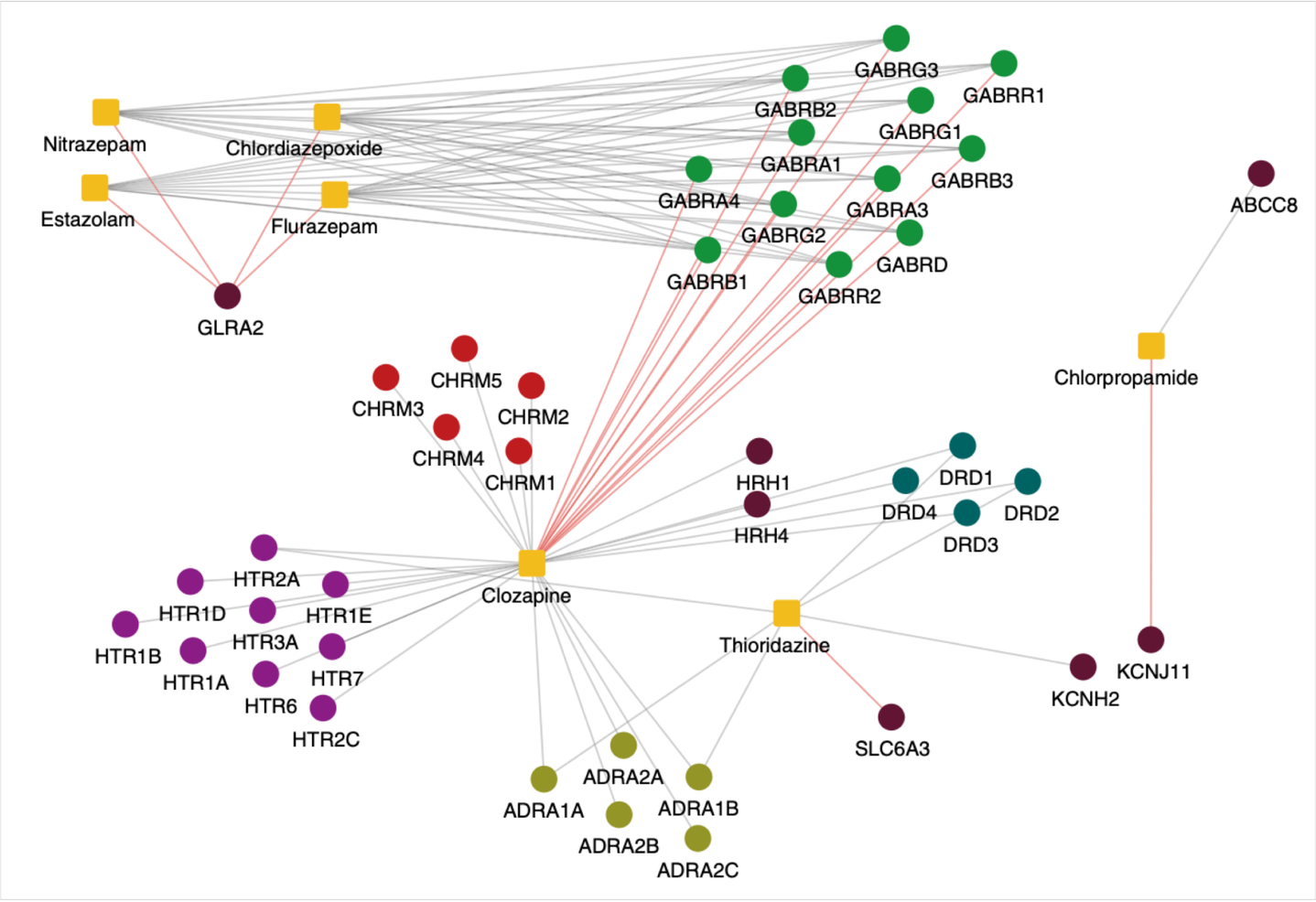

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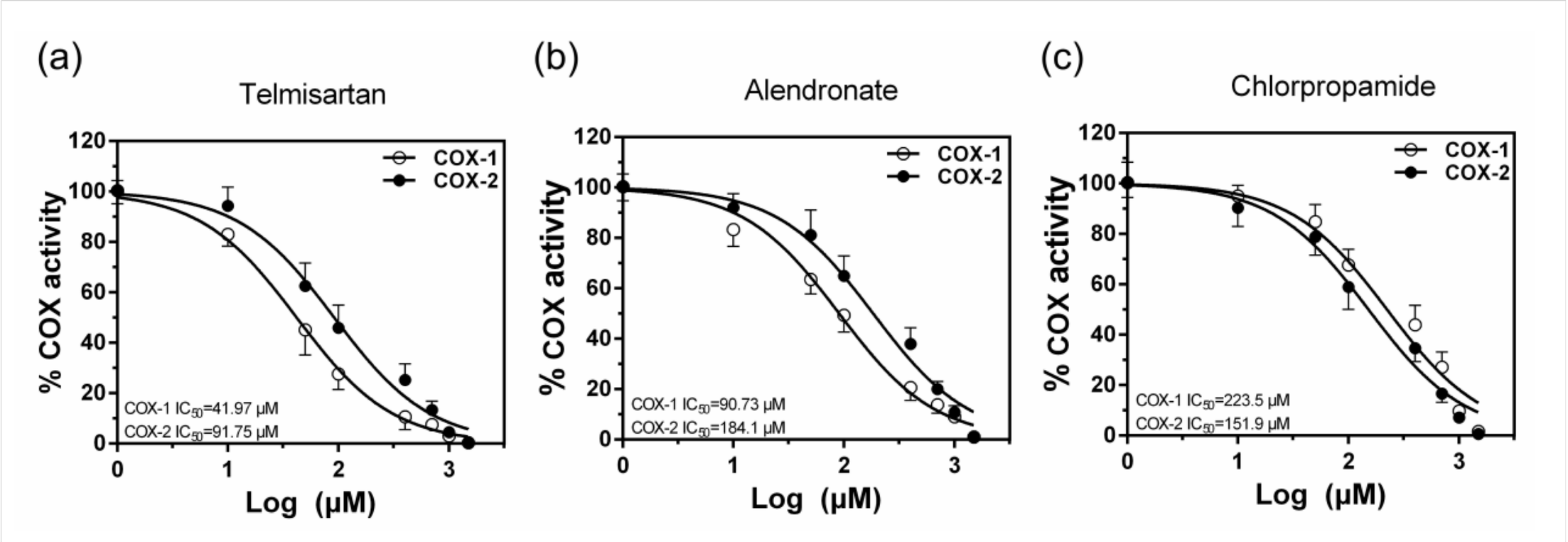
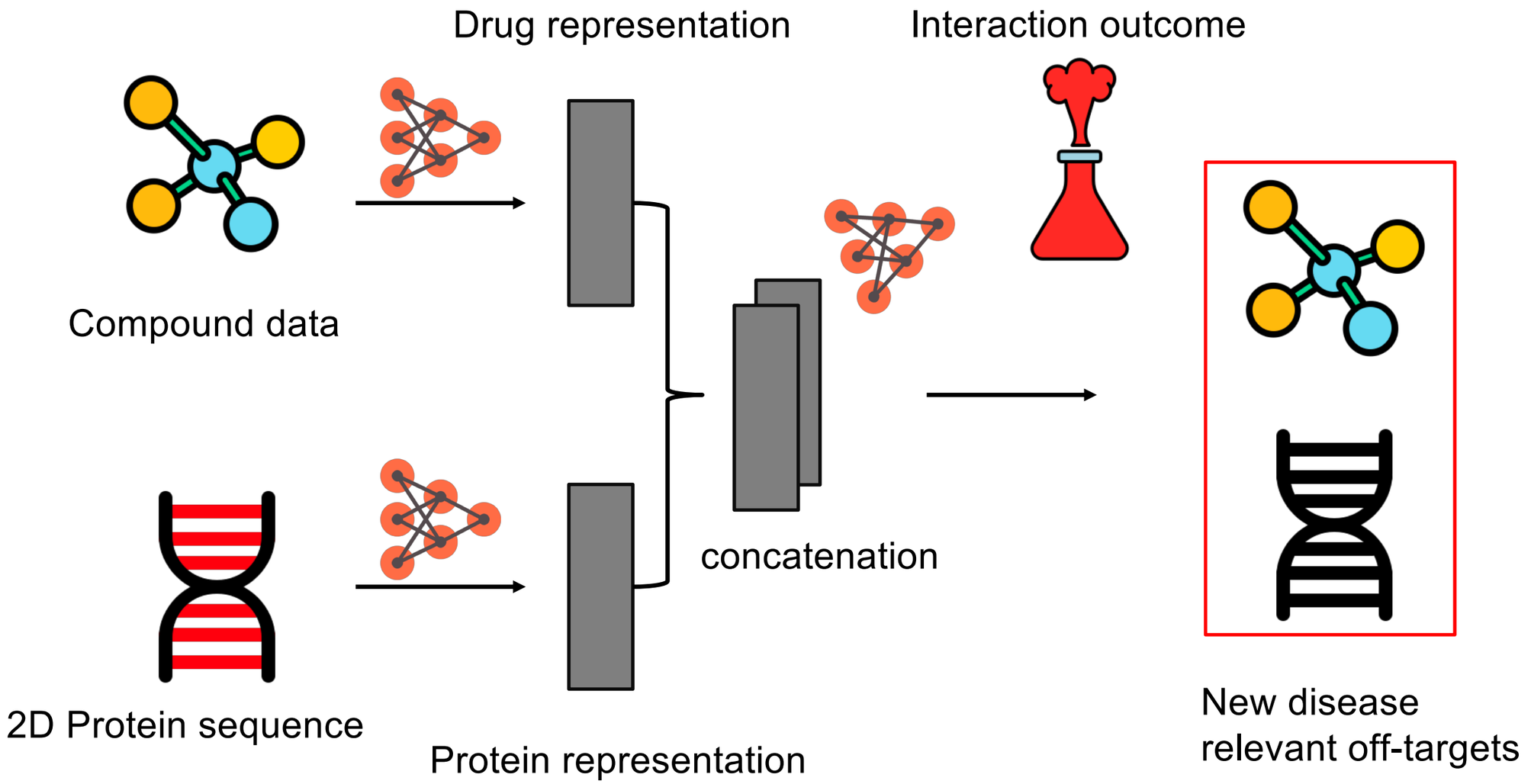


Experimentally validate the novel interactions between three drugs and the cyclooxygenase proteins predicted by DTINet. Identify three potential cyclooxygenase inhibitors in preventing inflammatory diseases.

Drug Target Binding Prediction via Neural Embedding

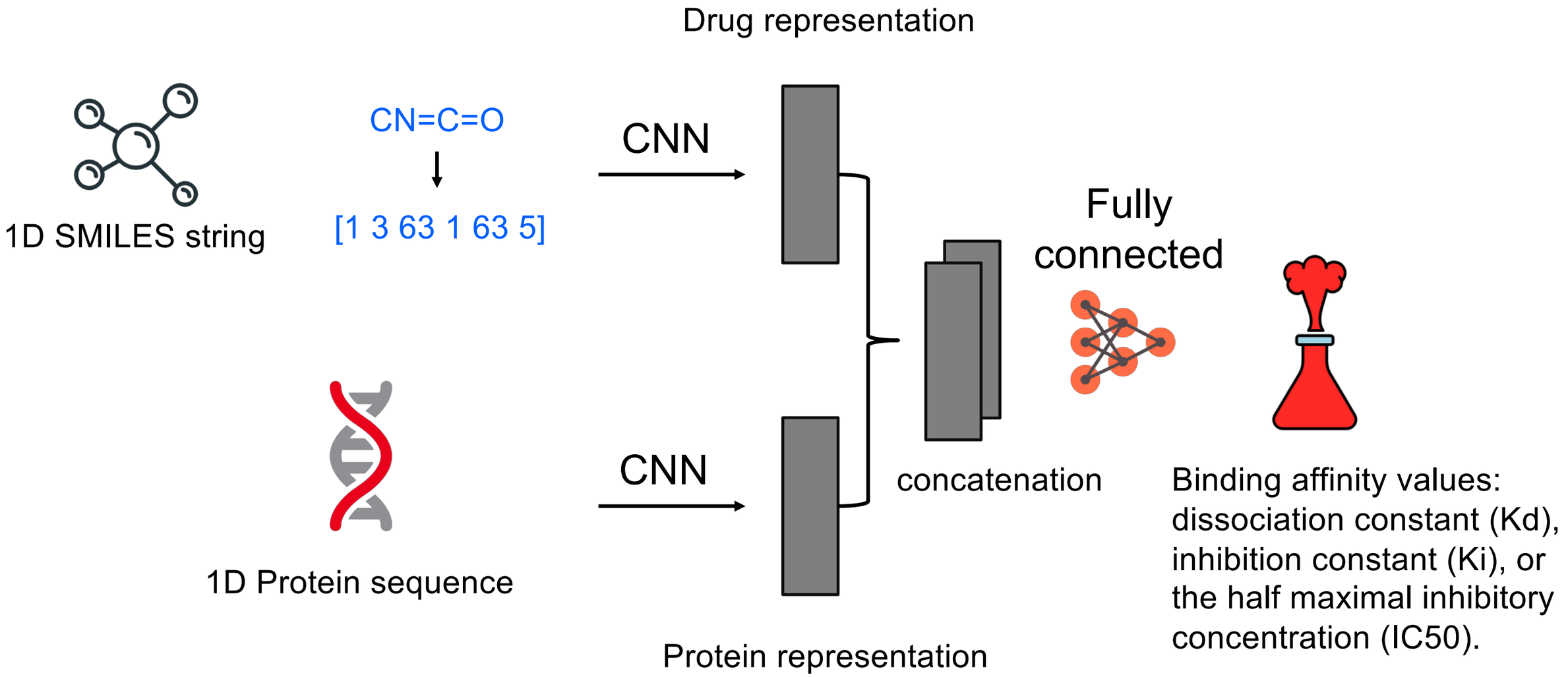


DeepDTA: Deep Drug-Target Binding Affinity Prediction

Hakime Öztürk, Elif Ozkirimli, Arzucan Özgür

Bioinformatics 34(17) · January 2018

DeepDTA (Bioinformatics 2018)



Ozturk et al., DeepDTA: Deep Drug-Target Binding Affinity Prediction, Bioinformatics 2018

DeepDTA (Bioinformatics 2018)

	Proteins	Compounds	Interactions
Davis (K_d)	442	68	30056
KIBA	229	2111	118254

Metrics

1. Concordance Index (CI)
2. mean squared error (MSE)

Baselines

1. KronRLS
2. SimBoost

Davis Kinase binding affinity data set

	Proteins	Compounds	CI (std)	MSE
KronRLS [47]	Smith-Waterman	Pubchem Sim	0.871 (0.0008)	0.379
SimBoost [29]	Smith-Waterman	Pubchem Sim	0.872 (0.002)	0.282
DeepDTA	Smith-Waterman	Pubchem Sim	0.790 (0.009)	0.608
DeepDTA	CNN	Pubchem Sim	0.835 (0.005)	0.419
DeepDTA	Smith-Waterman	CNN	**0.886** (0.008)	0.420
DeepDTA	CNN	CNN	0.878 (0.004)	**0.261**

KIBA large-scale kinase inhibitors bioactivity data

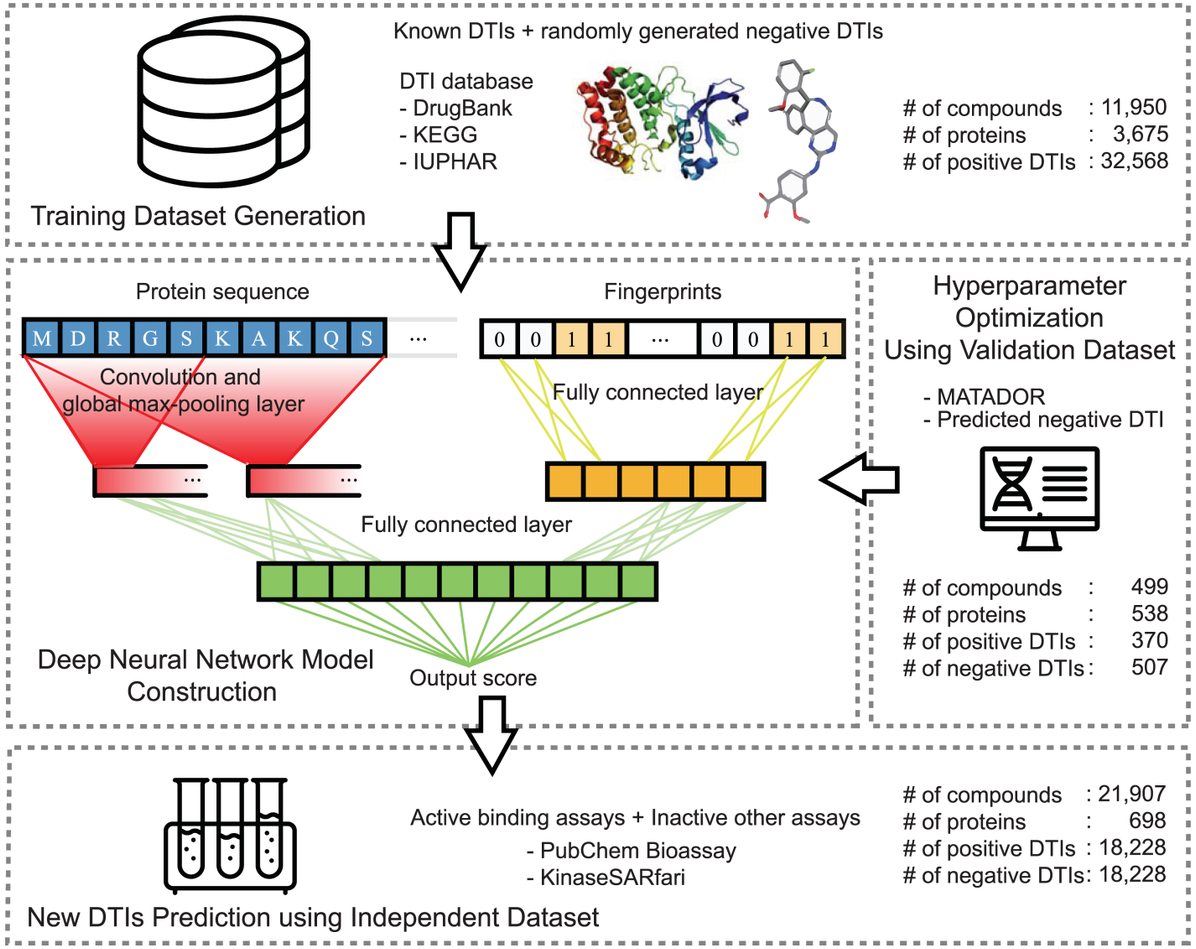
	Proteins	Compounds	CI (std)	MSE
KronRLS [47]	Smith-Waterman	Pubchem Sim	0.782 (0.0009)	0.411
SimBoost [29]	Smith-Waterman	Pubchem Sim	0.836 (0.001)	0.222
DeepDTA	Smith-Waterman	Pubchem Sim	0.710 (0.002)	0.502
DeepDTA	CNN	Pubchem Sim	0.718 (0.004)	0.571
DeepDTA	Smith-Waterman	CNN	0.854 (0.001)	0.204
DeepDTA	CNN	CNN	**0.863** (0.002)	**0.194**

DeepConv-DTI: Prediction of drug-target interactions via deep learning with convolution on protein sequences.

Lee I, Keum J, Nam H

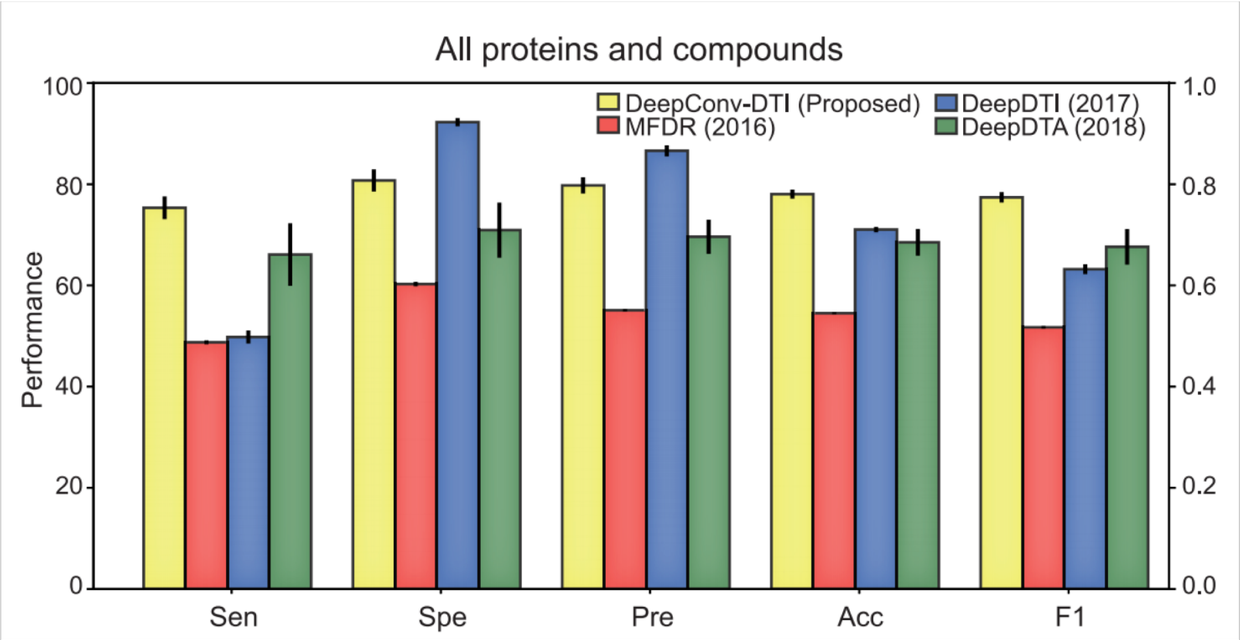
PLOS Computational Biology, 2019

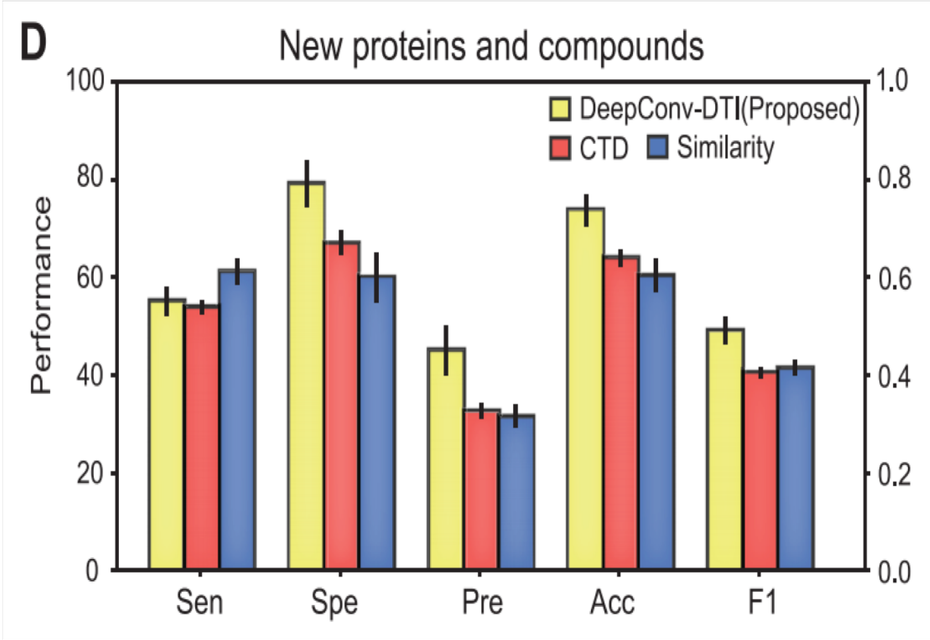
DeepConv-DTI (PLOS Comp Bio 2019)



Lee I, Keum J, Nam H (2019) DeepConv-DTI: Prediction of drug-target interactions via deep learning with convolution on protein sequences. PLOS Computational Biology 15(6): e1007129. https://doi.org/10.1371/journal.pcbi.1007129

DeepConv-DTI (PLOS Comp Bio 2019)





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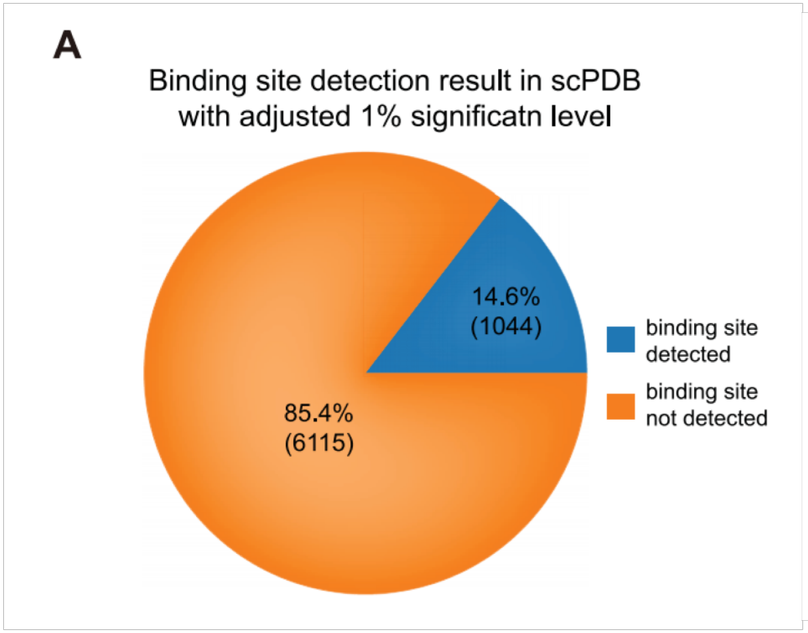
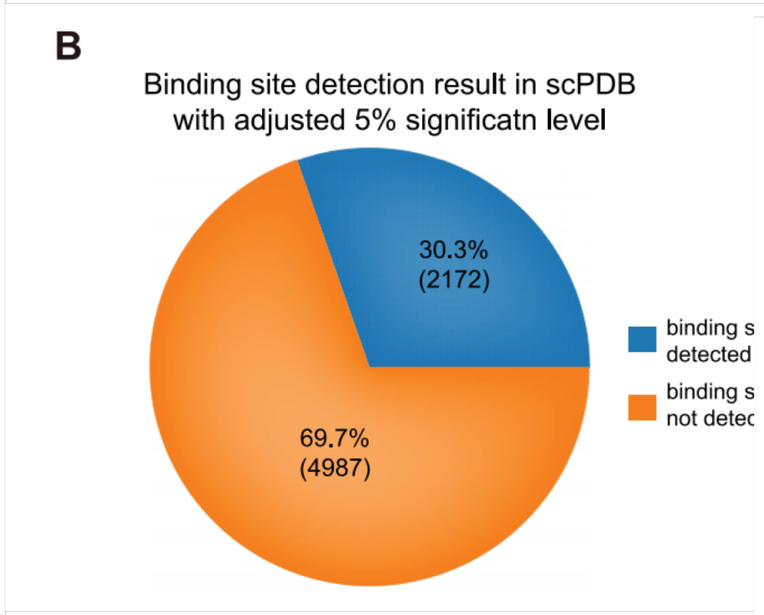
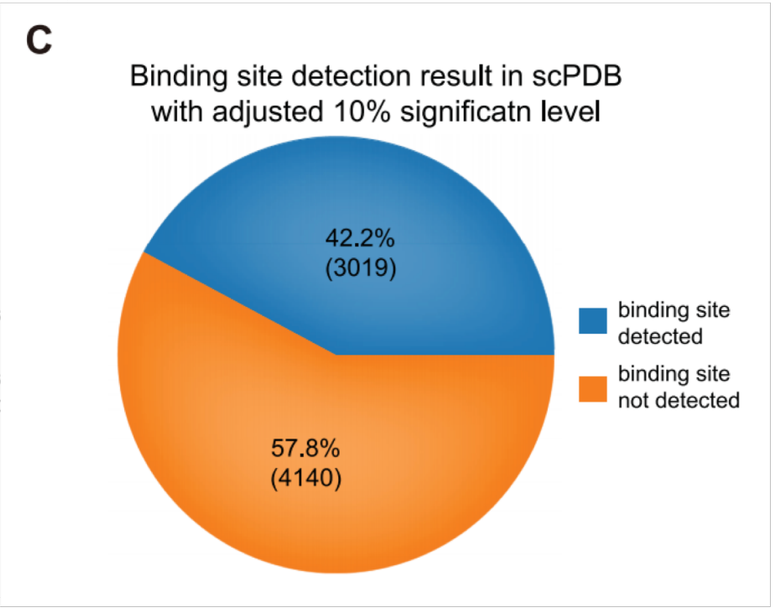
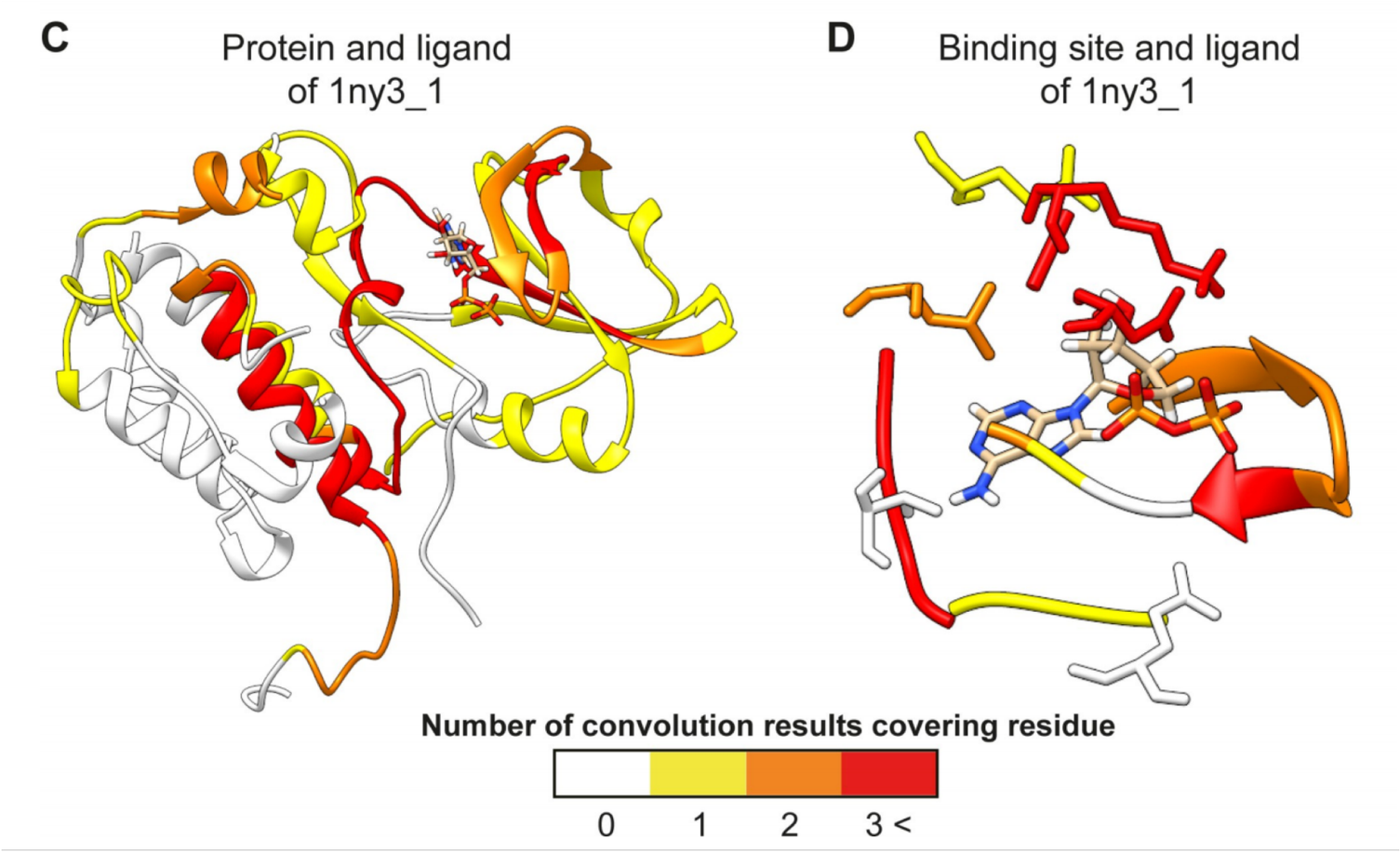
DeepConv-DTI (PLOS Comp Bio 2019)







DeepConv-DTI (PLOS Comp Bio 2019)



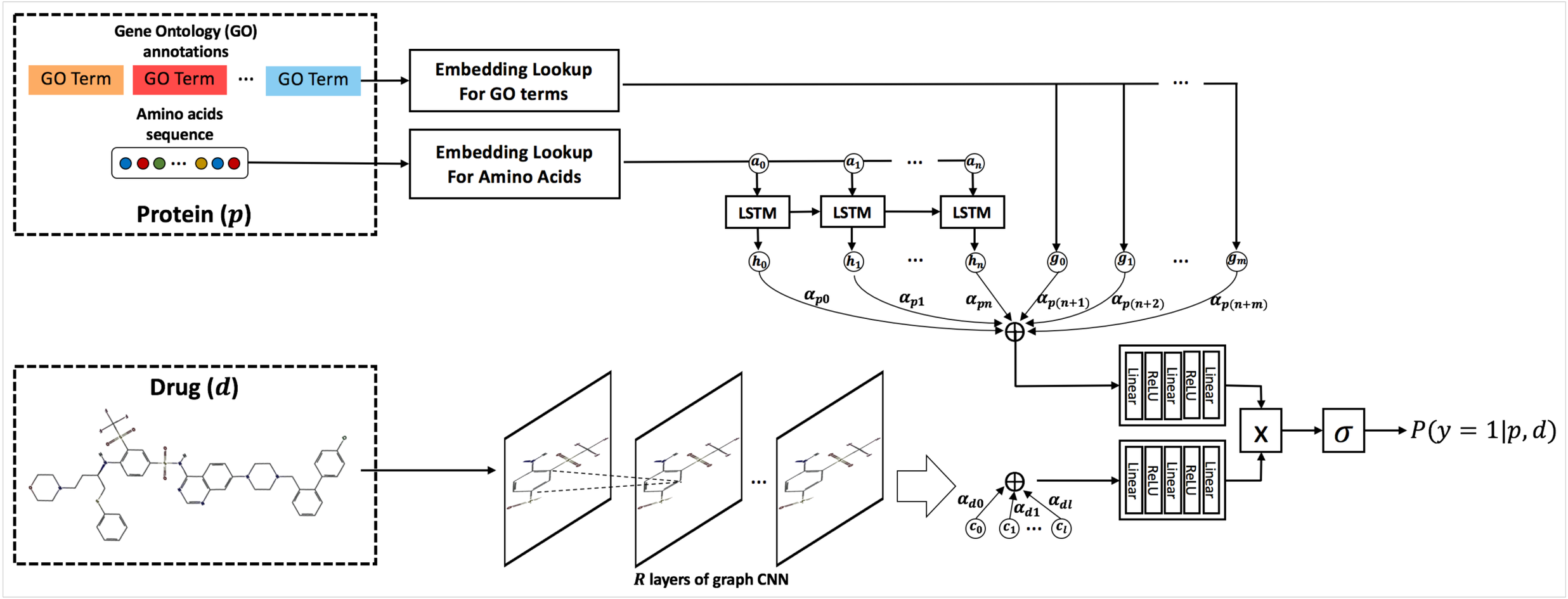
Lee I, Keum J, Nam H (2019) DeepConv-DTI: Prediction of drug-target interactions via deep learning with convolution on protein sequences. PLOS Computational Biology 15(6): e1007129. https://doi.org/10.1371/journal.pcbi.1007129

Interpretable Drug Target Prediction Using Deep Neural Representation

Kyle Gao, Achille Fokoue, Heng Luo, Arun Iyengar, Sanjoy Dey, Ping Zhang

IJCAI’ 18

Interpretable Drug-Target Prediction (IJCAI' 18)

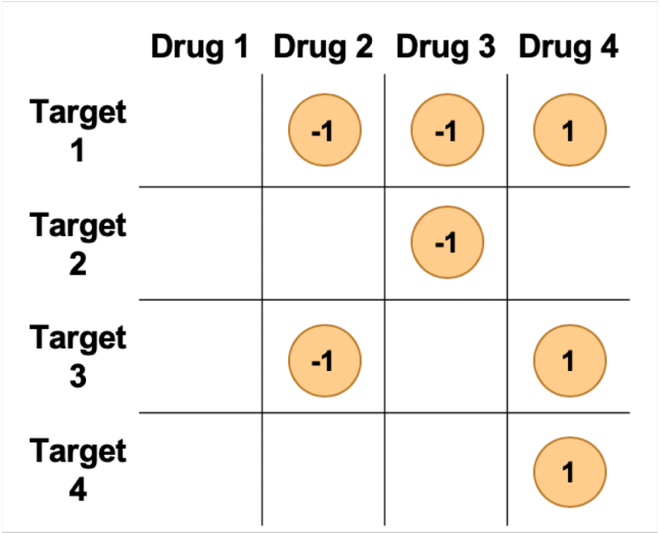


Gao KY, Fokoue A, Luo H, et al. Interpretable drug target prediction using deep neural representation, IJCAI' 18

Interpretable Drug-Target Prediction (IJCAI' 18)

Protein (Gene)
Protein sequences
Gene Ontology labels
Drug (Molecule)
Chemical structures

BindingDB (bindingdb.org)



Labels are based on IC50 value, a primary measure of binding effectiveness, positive if its IC50 is less than 100nm, negative if IC50 greater than 10,000nm

Dataset	Protein	Drug	Positive	Negative
Train	758	43,160	28,240	21,915
Dev	472	5,077	2,831	2,776
Test	466	5,016	2,706	2,802

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Interpretable Drug-Target Prediction (IJCAI' 18)

	Target	Drug
Setting 1	Observed	Observed
Setting 2	Observed	NOT Observed
Setting 3	NOT Observed	Observed
Setting 4	NOT Observed	NOT Observed

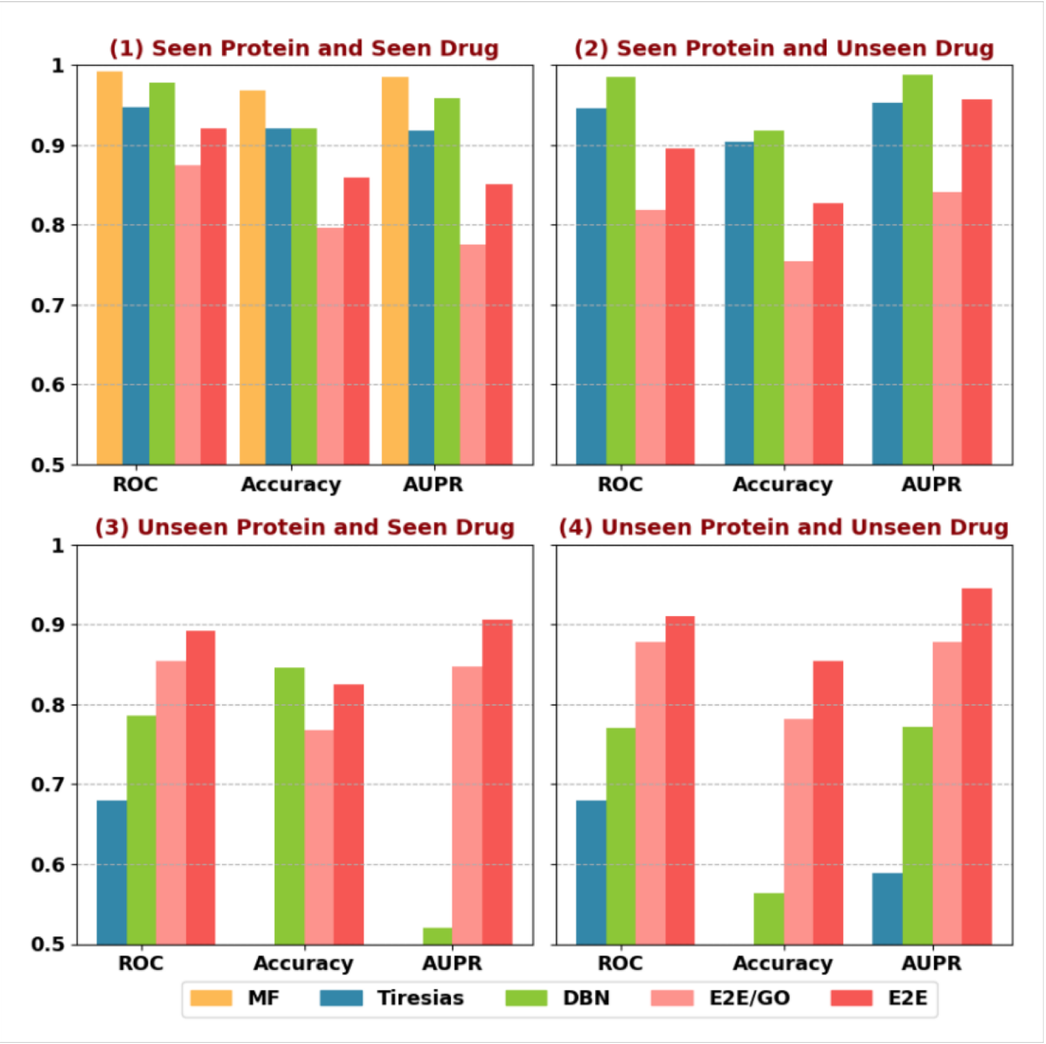
Gao KY, Fokoue A, Luo H, et al. Interpretable drug target prediction using deep neural representation, IJCAI' 18

Interpretable Drug-Target Prediction (IJCAI' 18)

MF (matrix factorization)
A matrix with drugs and targets as rows and columns
Predict missing IC50 values using SVD

Tiresias (similarity-based)
For a DTI pair, build a feature vector from statistics of similarity measures against known DTI pairs
Classification with a logistic regression model

DBN (feature-based DNN classifier)
Represent protein using sequence composition descriptors (a vector of frequencies of {1,2,3}-gram sub-sequence)
Represent drug using ECFP.Transform features and make predictions with a Deep Belief Networks (DBN) model consisting of stacked RBMs



Gao KY, Fokoue A, Luo H, et al. Interpretable drug target prediction using deep neural representation, IJCAI' 18

Summary of Drug Repositioning

Traditional Method

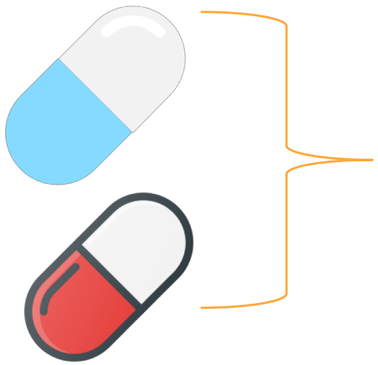
- Molecule docking
- Structural similarity

Neural network based molecular representation

- DL based DTI prediction
- Network integration based similarity

3. Drug drug interaction

Why Need Drug Drug Interaction (DDI) Detection



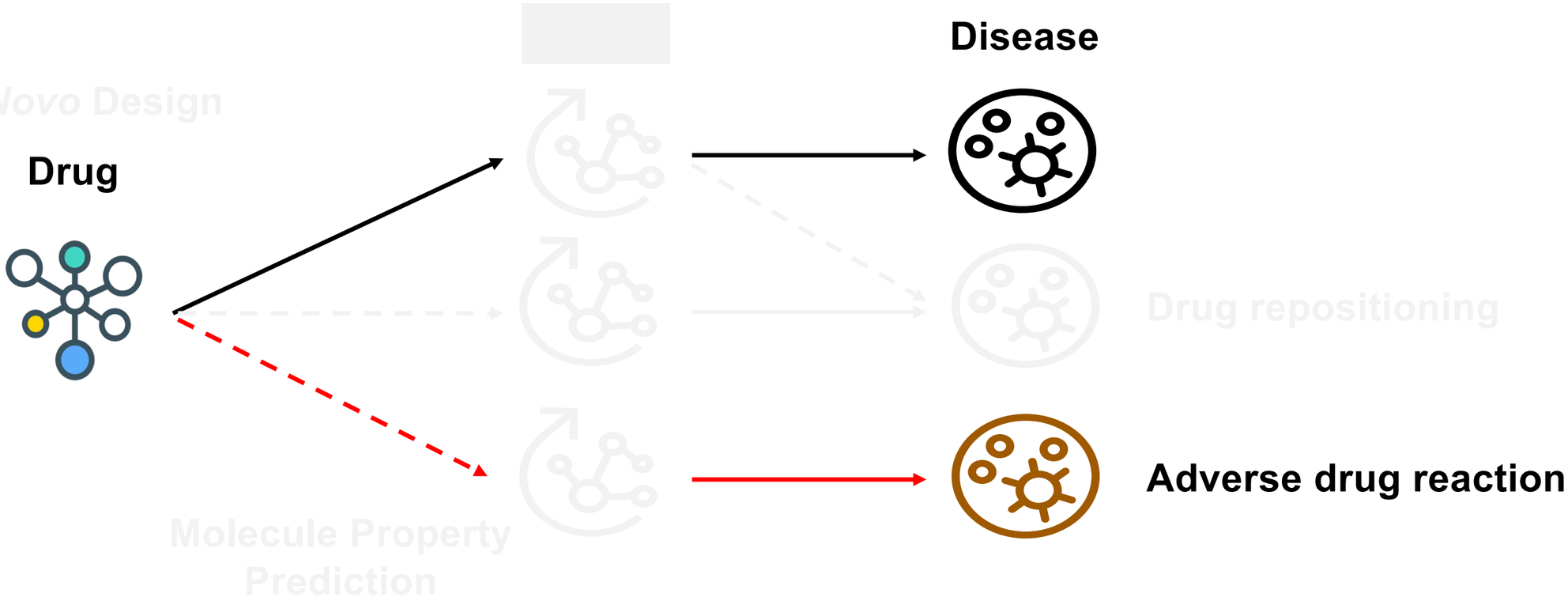
Taking together →  → Post-marketing reporting → FDA

Sildenafil

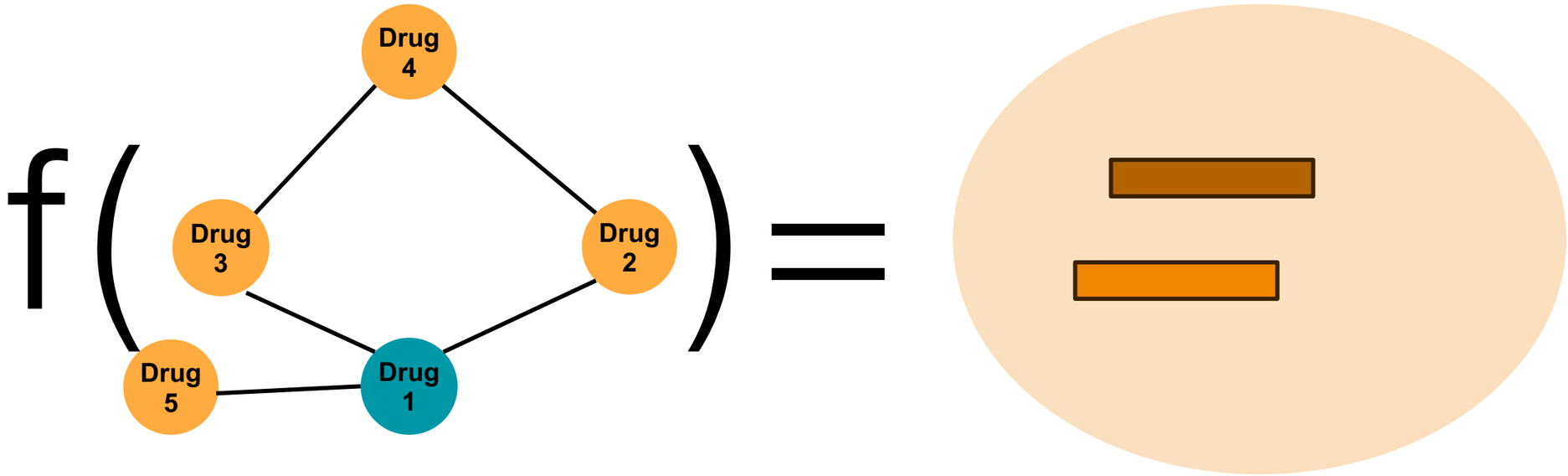
+

Isosorbide mononitrate → Excessive blood pressure drops

Adverse Drug Reaction/
Drug-drug Interaction Prediction



Graph Convolutional Networks (GCN) Basic setting

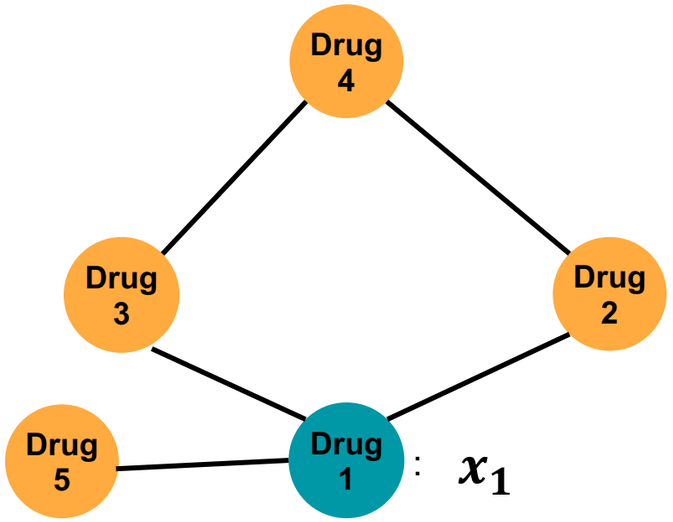


Drug similarity network

Low-dimensional node embeddings

Intuition: Map nodes to d-dimensional embeddings such that similar nodes in the graph are embedded close together

Graph Convolutional Networks (GCN) Basic setting



Graph $g = (\upsilon, \varepsilon, A)$

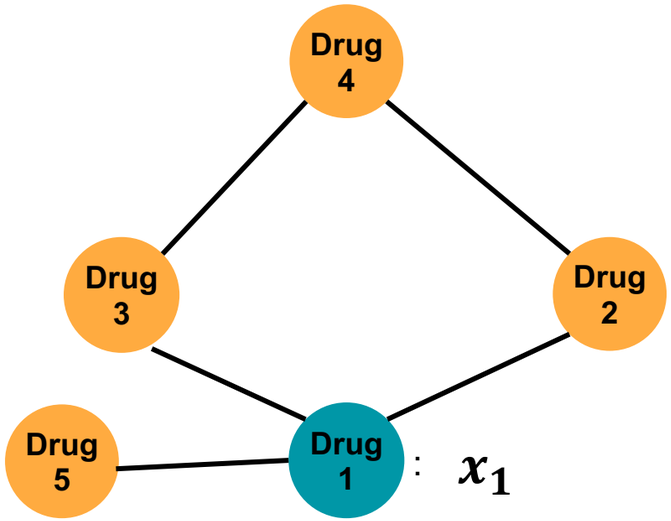
υ: vertex (or node)

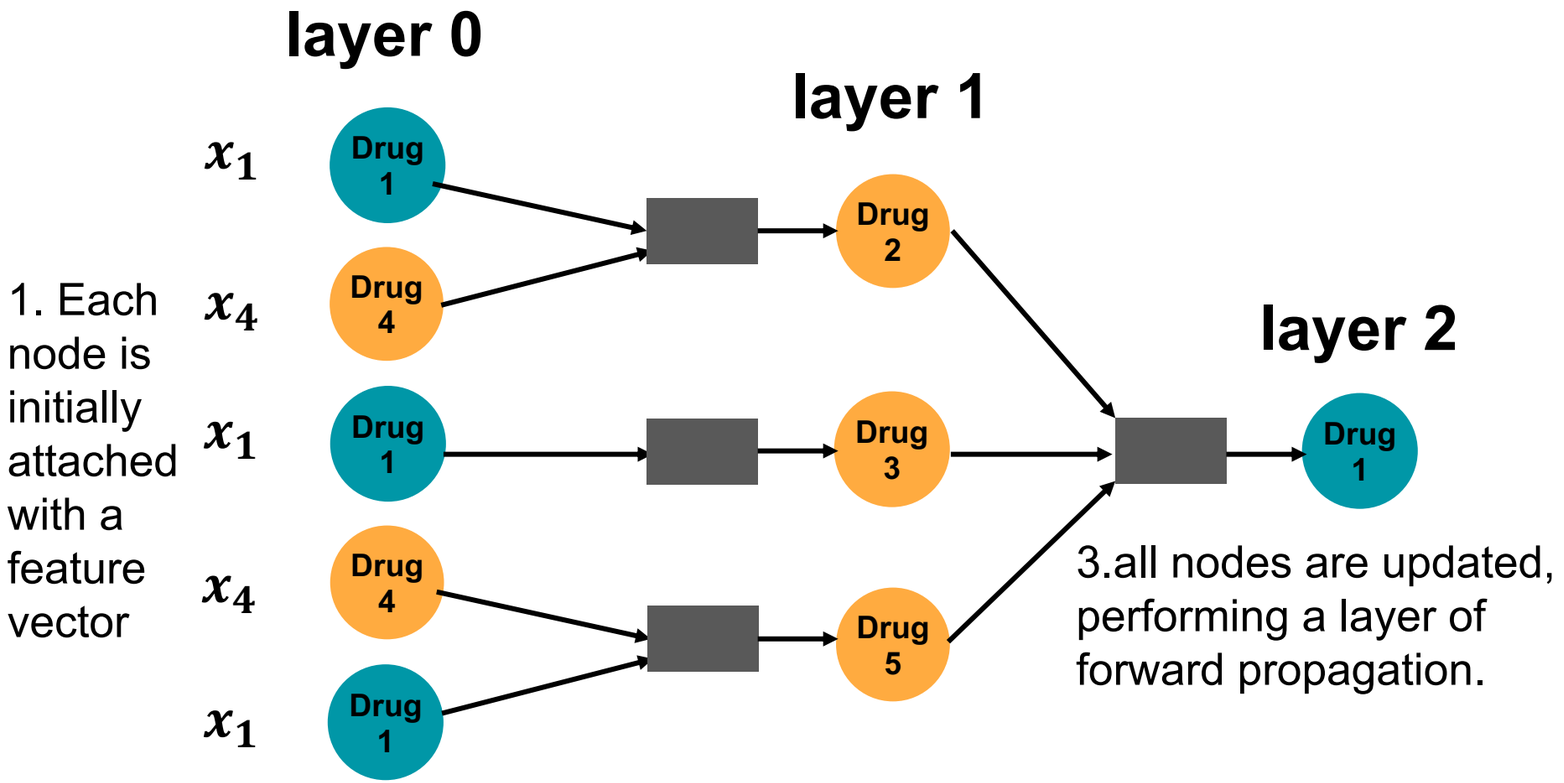
ε: edge (or link)

A: adjacency matrix

A graph signal $\boldsymbol{x}$ is a real-valued vector defined on all vertices

GCN (spatial convolution)





1. Each node is initially attached with a feature vector

2. For each node, the vectors of the neighbors are summed (with weights and transforms) into it.

3.all nodes are updated, performing a layer of forward propagation.

Graph Convolutional Network (Kipf and Welling, 2016)

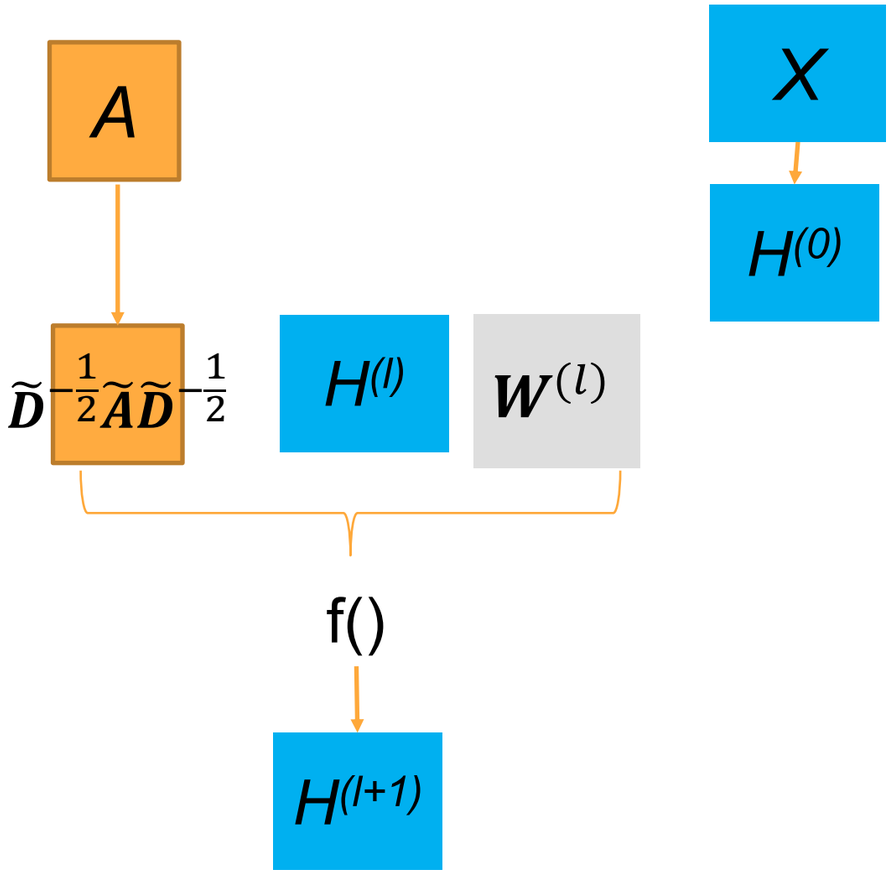
Input : Node features $\boldsymbol{X}$, Adjacency matrix $\boldsymbol{A}$

Output: Node embedding $\boldsymbol{Z}$

Method

$$\boldsymbol{H}^{(l+1)} = f(\widetilde{\boldsymbol{D}}^{-\frac{1}{2}}\widetilde{\boldsymbol{A}}\widetilde{\boldsymbol{D}}^{-\frac{1}{2}}\boldsymbol{H}^{(l)}\boldsymbol{W}^{(l)})$$

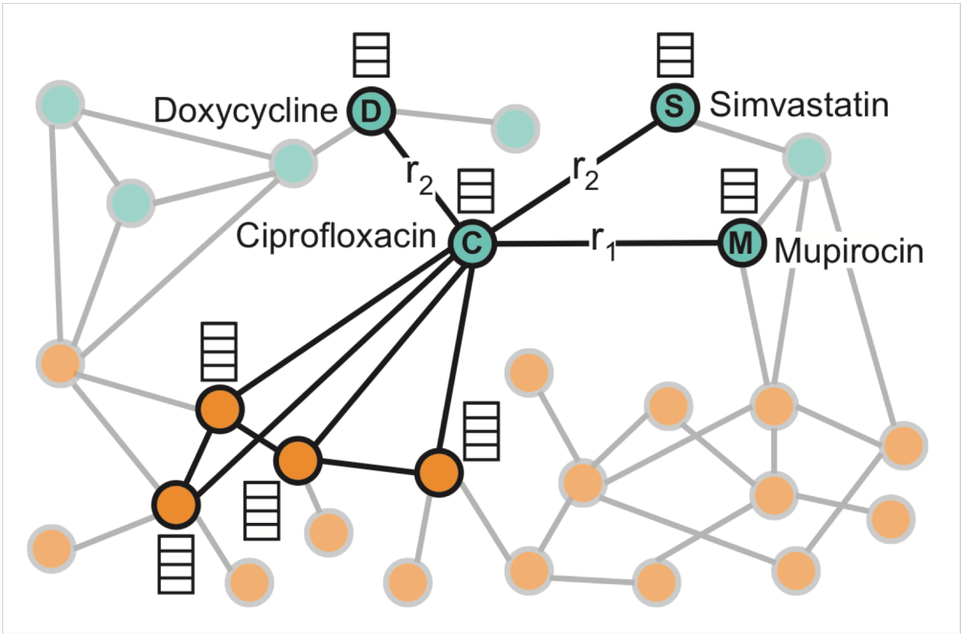
where $\widetilde{\boldsymbol{A}} = \boldsymbol{A} + \boldsymbol{I}_N$, $\boldsymbol{D}$ is a diagonal matrix s.t. $D_{ii} = \sum_j \tilde{A}_{ij}$, $\boldsymbol{W}^{(l)}$ parameters $\boldsymbol{H}^{(l)}$ is node representation of layer l



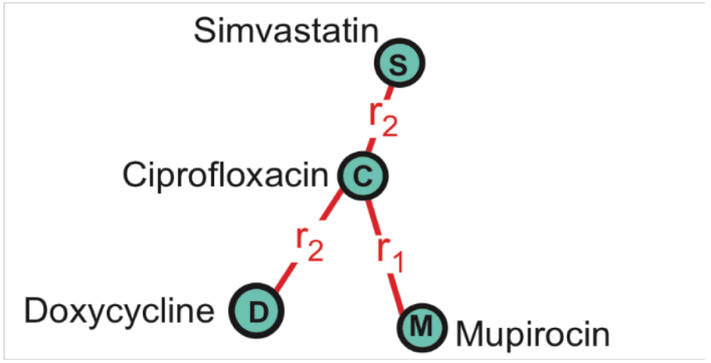
Modeling polypharmacy side effects with graph convolutional networks.

Zitnik M, Agrawal M, Leskovec J. Bioinformatics 2018

DECAGON (Bioinformatics 2018)

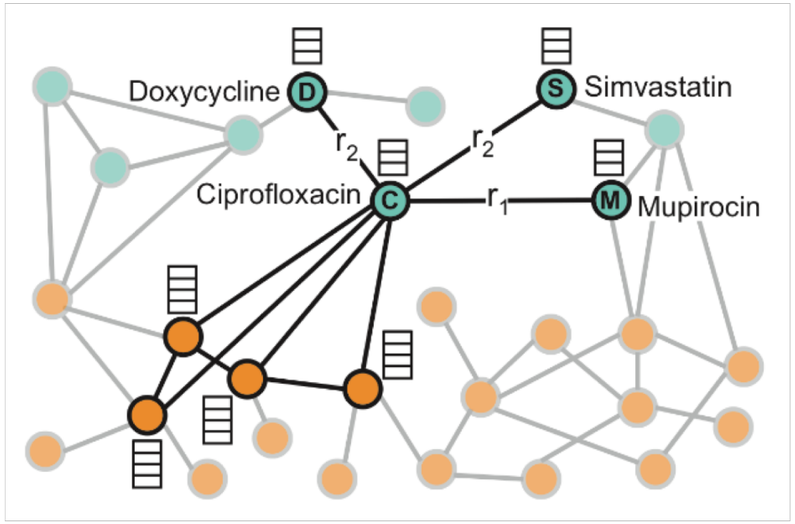


- Predict labeled edges between drugs
  - i.e., predict the likelihood that an edge (c, r_2, s) exists
- Drug combination (c, s) leads to polypharmacy side effect r_2

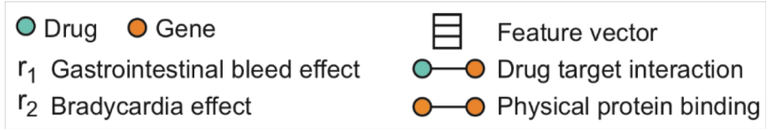


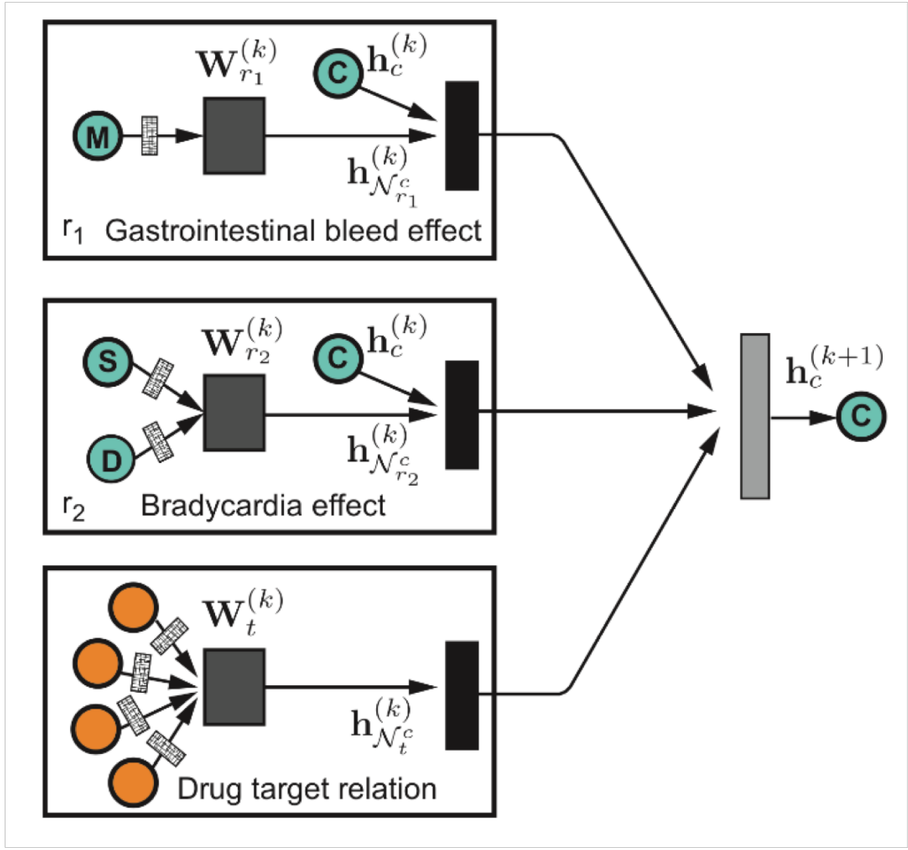
Zitnik M, Agrawal M, Leskovec J. Modeling polypharmacy side effects with graph convolutional networks. Bioinformatics 2018

Decagon (Bioinformatics 2018)



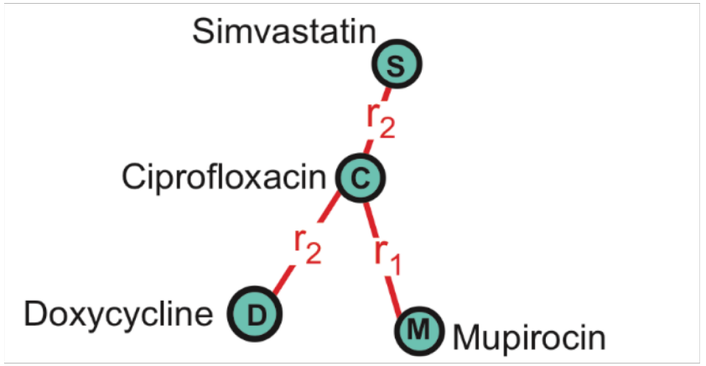
- Input: graph, additional node features
- Output: node embeddings



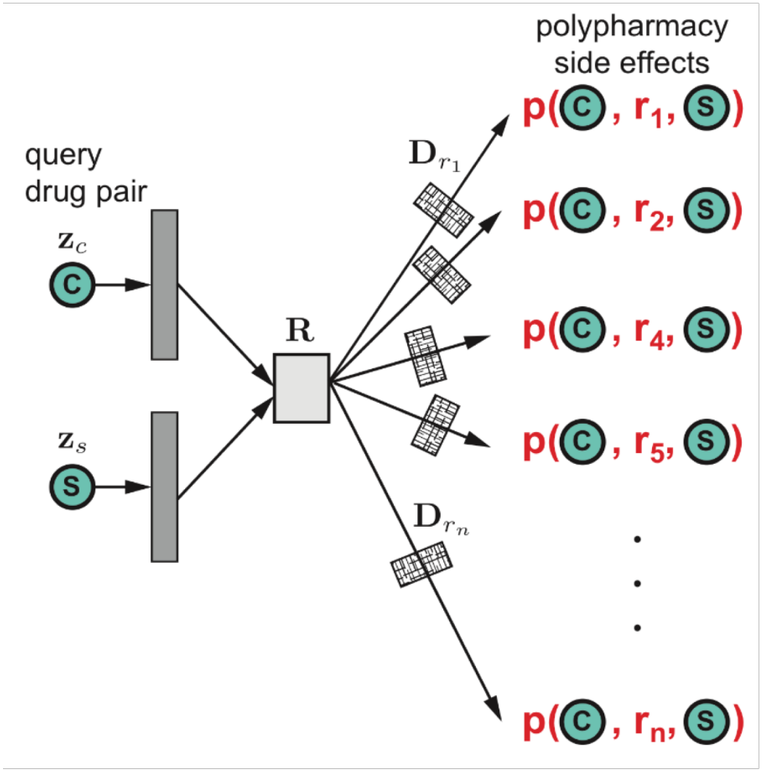


Zitnik M, Agrawal M, Leskovec J. Modeling polypharmacy side effects with graph convolutional networks. Bioinformatics 2018

Decagon (Bioinformatics 2018)



- Input: Query drug pairs and their embeddings
- Output: predicted edges



Zitnik M, Agrawal M, Leskovec J. Modeling polypharmacy side effects with graph convolutional networks. Bioinformatics 2018

Decagon (Bioinformatics 2018)

Data:
Molecular: protein-protein interactions and drug target relationships
Patient data: Side effects of individual drugs, polypharmacy side effects of drug combinations

Setup:
Construct a heterogeneous graph of all the data
Train: Fit a model to predict known associations of drug pairs and polypharmacy side effects
Test: Given a query drug pair, predict candidate polypharmacy side effects

	AUROC	AUPRC	AP@50
Decagon (3-layer)	**0.834**	**0.776**	**0.731**
Decagon (2-layer)	0.809	0.762	0.713
RESCAL	0.693	0.613	0.476
Node2vec	0.725	0.708	0.643
Drug features	0.736	0.722	0.679

Zitnik M, Agrawal M, Leskovec J. Modeling polypharmacy side effects with graph convolutional networks. Bioinformatics 2018

Enhancing drug–drug interaction extraction from texts by molecular structure information

Asada M, Miwa M, Sasaki Y.

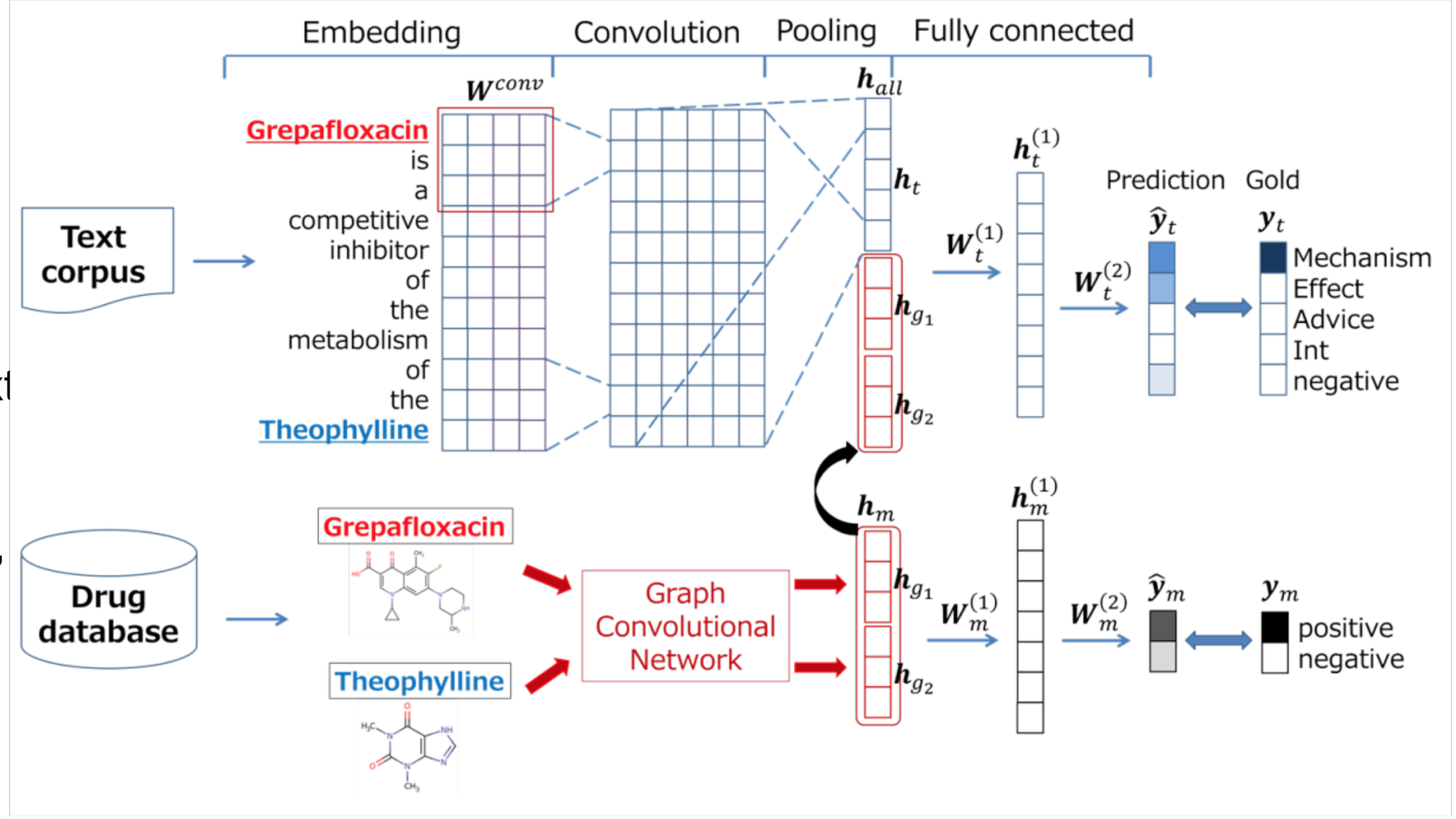
ACL 2018

Enhancing DDI from Texts by Molecular Structure Information (ACL 2018)

Task: Extract DDI label from biomedical text.

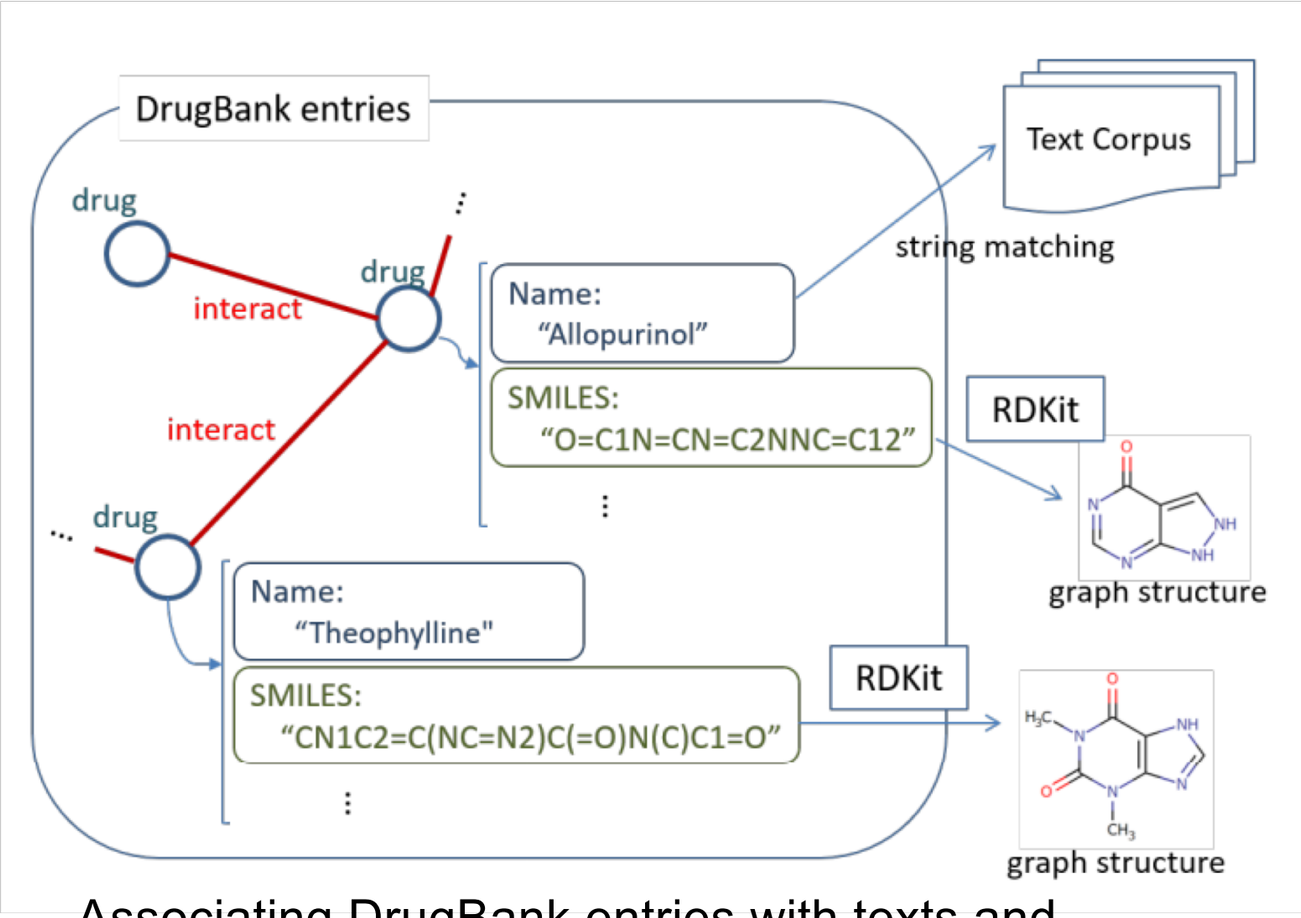
Method:
Basically leverage Molecular graph into text Classification problem.

For text, CNN encoding,
For drug molecules, GCN encoding.



Asada M, Miwa M, Sasaki Y. Enhancing drug–drug interaction extraction from texts by molecular structure information. ACL 2018

Enhancing DDI from Texts by Molecular Structure Information (ACL 2018)



Associating DrugBank entries with texts and molecular graph structures

Methods	P	R	F (%)
Liu et al. (2016)	75.29	60.37	67.01
Zheng et al. (2017)	75.9	68.7	71.5
Lim et al. (2018)	74.4	69.3	71.7
Text-only	71.97	68.44	70.16
+ NFP	72.62	71.81	72.21
+ GGNN	73.31	71.81	72.55

Table 1: Evaluation on DDI extraction from texts

DDI Type	*Mech.*	*Effect*	*Adv.*	*Int* (%)
Text-only	69.52	69.27	79.81	48.18
+ NFP	72.70	72.44	79.56	46.98
+ GGNN	73.83	71.03	81.62	45.83

Table 2: Performance on individual DDI types in F-scores

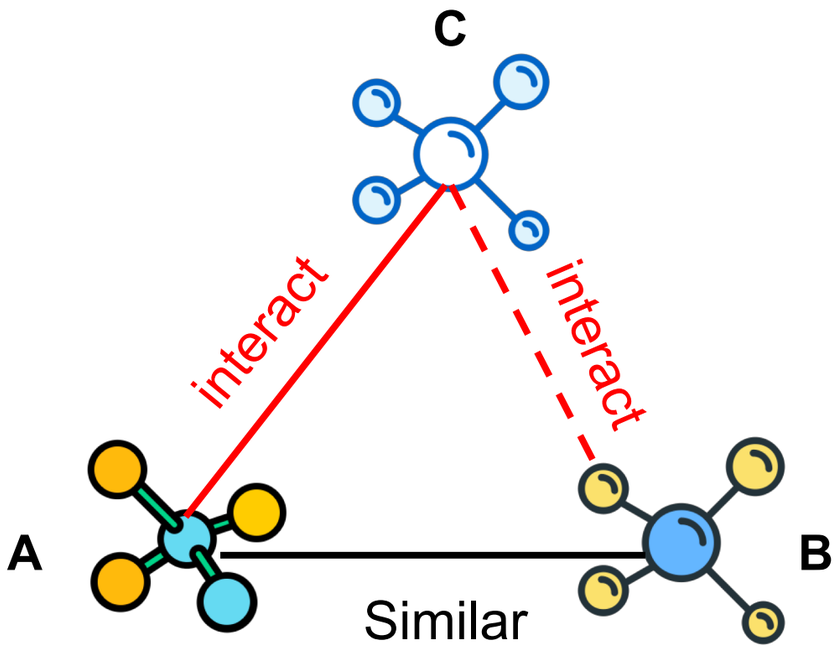
Asada M, Miwa M, Sasaki Y. Enhancing drug–drug interaction extraction from texts by molecular structure information. ACL 2018

Drug Similarity Integration Through Attentive Multi-view Graph Auto-Encoders

Tengfei Ma, Cao Xiao, Jiayu Zhou, Fei Wang

IJCAI 2018

Multi-View GAE for DDI Prediction (IJCAI 18)



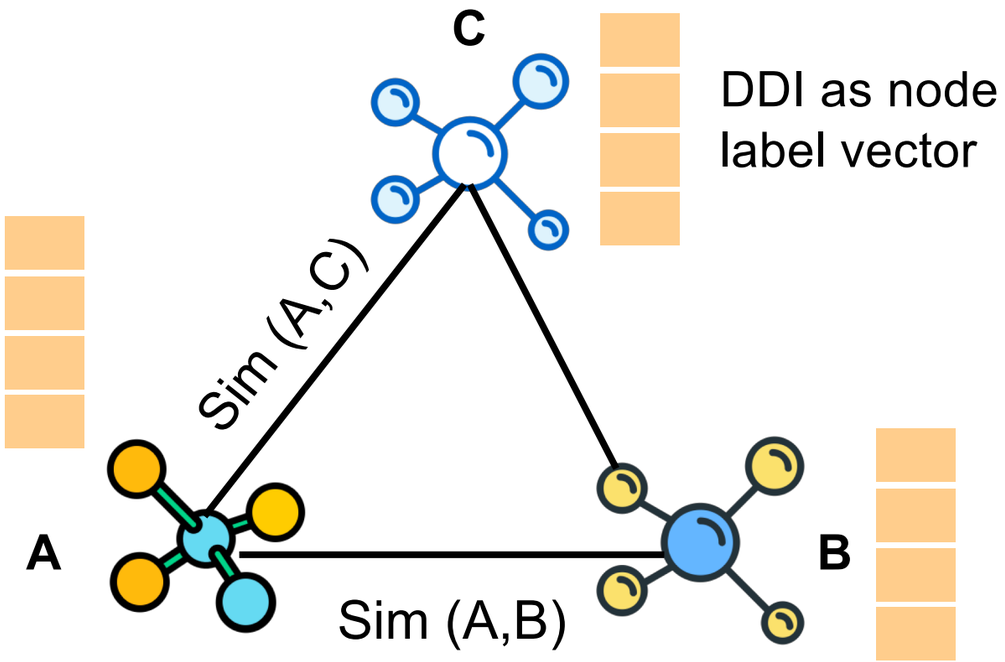
Guilt-by-association

Goal: Learn better drug similarity based on Multiview drug features

Drug Features (database)

Label Side Effect (SIDER)
Off-Label Side Effect (OFFSIDES)
Molecular substructure
Drug Indication (MedDRA)
……

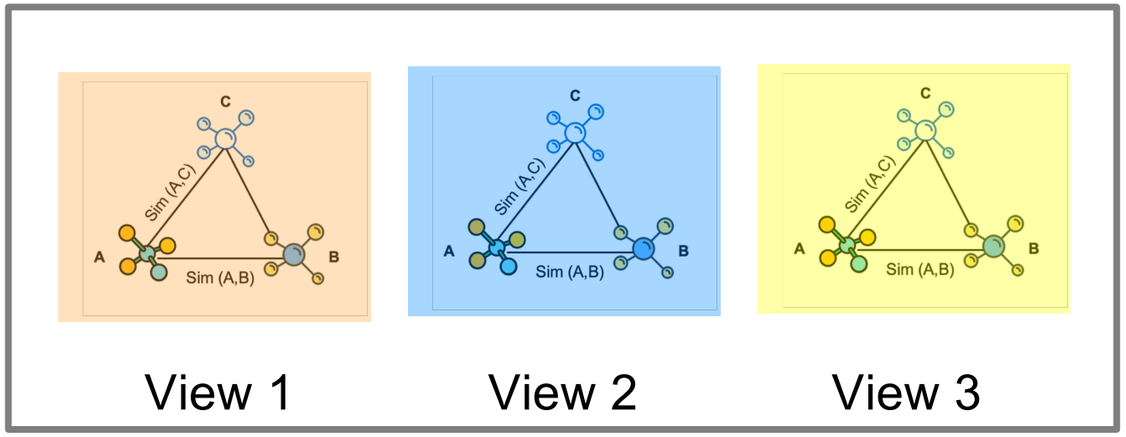
Multi-View GAE for DDI Prediction (IJCAI 18)



DDI as node label vector

- Drug as graph nodes
- DDI labels as node labels

- Drug features as node attributes
- Fuse across multiple views for improved drug similarity



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Multi-View GAE for DDI Prediction (IJCAI 18)

- **State-of-the-art**
  - Nearest neighbor methods (Zhang *et al*, 2015, Zhang *et al*, 2017)
  - Random walk based methods (Wang *et al*, 2010)
  - Unsupervised iterative methods (Angione *et al*, 2014, Xu *et al*, 2016)
  - Multiple kernel learning (Zhuang *et al*, 2011, McFee *et al*, 2011)

- **Challenges**
  - the underlying relations of biomedical events are often **nonlinear** and **complex** over all types of features
  - features have **different importance** toward different target outcomes

Drug Similarity Integration Through Attentive Multi-view Graph Auto-Encoders, Tengfei Ma, Cao Xiao, Jiayu Zhou, Fei Wang, IJCAI 2018

GCN (Kipf and Welling, 2016)

- Objective: graph node embedding for arbitrary graphs, distance similarity of local graph structures
- Input
  - Node features $\boldsymbol{x}$
  - Adjacency matrix $\boldsymbol{A}$ that represents graph structure
- Output: Node embedding $\boldsymbol{Z}$
- Method

$$\boldsymbol{H}^{(l+1)} = f(\widetilde{\boldsymbol{D}}^{-\frac{1}{2}}\widetilde{\boldsymbol{A}}\widetilde{\boldsymbol{D}}^{-\frac{1}{2}}\boldsymbol{H}^{(l)}\boldsymbol{W}^{(l)})$$

where $\widetilde{\boldsymbol{A}} = \boldsymbol{A} + \boldsymbol{I}_N$, $\boldsymbol{D}$ is a diagonal matrix such that $D_{ii} = \sum_j \tilde{A}_{ij}$, $\boldsymbol{W}^{(l)}$ is layer-specific parameter matrix, $\boldsymbol{H}^{(l)}$ is node representation of lth layer.

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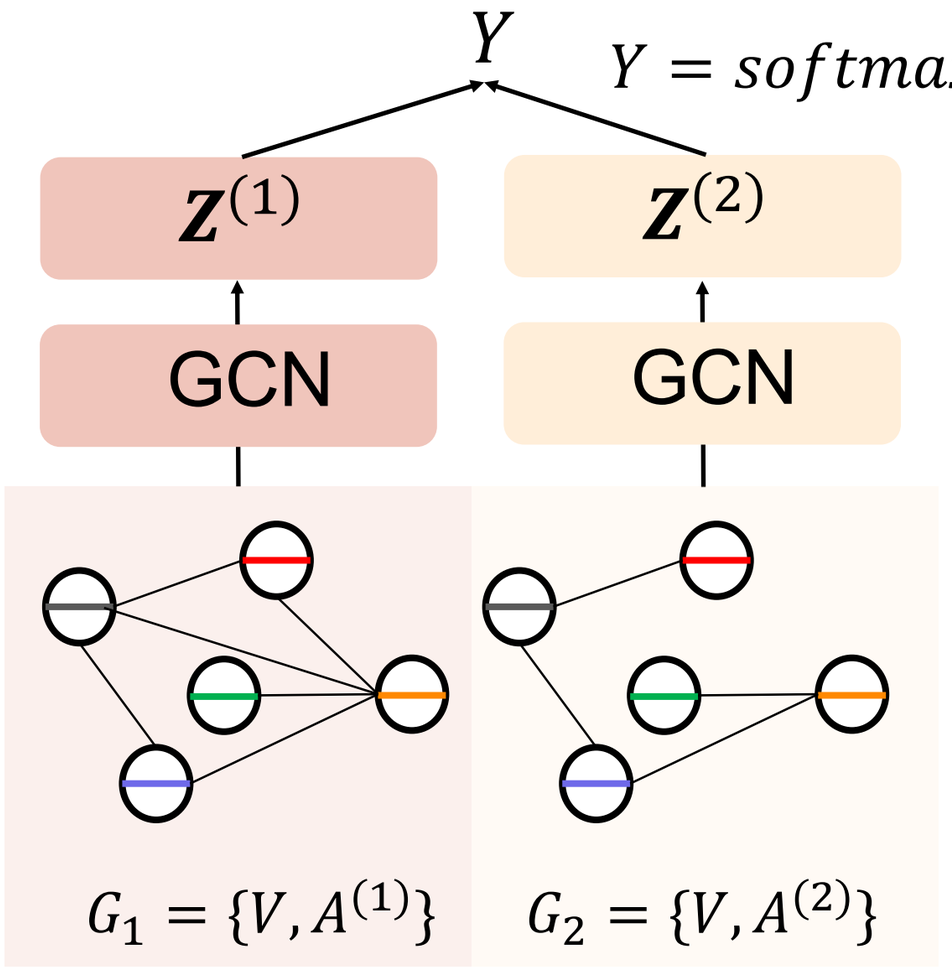
Multi-View GAE for DDI Prediction (IJCAI 18)



For view $u \in \{1,\ldots,T\}$, we encode the nodes as

$$\boldsymbol{Z}^{(u)} = f\left(\boldsymbol{X}^{(u)}, \boldsymbol{A}^{(u)}; \boldsymbol{W}_1^{(u)}\right)$$
$$= softmax(\widehat{\boldsymbol{A}}^{u} ReLU(\widehat{\boldsymbol{A}}^{u} \boldsymbol{X}^{(u)} \boldsymbol{W}_0^{(u)}) \boldsymbol{W}_1^{(u)})$$

where $\widehat{\boldsymbol{A}}^{u} = \widetilde{\boldsymbol{D}}^{(u)-\frac{1}{2}} \widetilde{\boldsymbol{A}}^{(u)} \widetilde{\boldsymbol{D}}^{(u)-\frac{1}{2}}$, and $\boldsymbol{W}_0^{(u)}$ and $\boldsymbol{W}_1^{(u)}$ are weight matrices.

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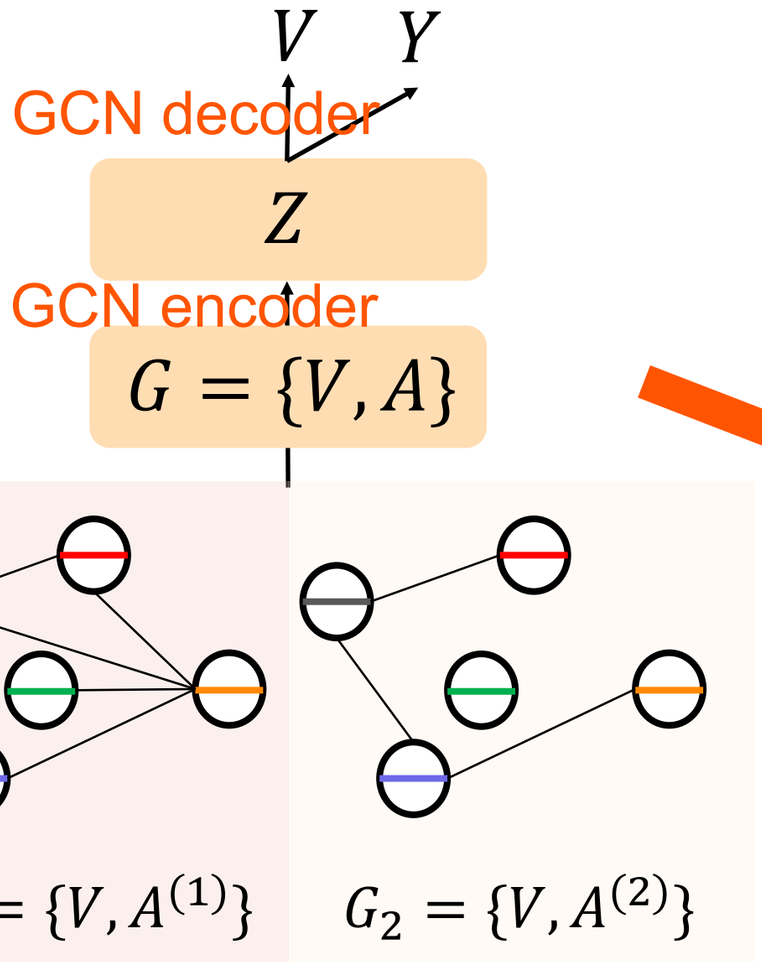


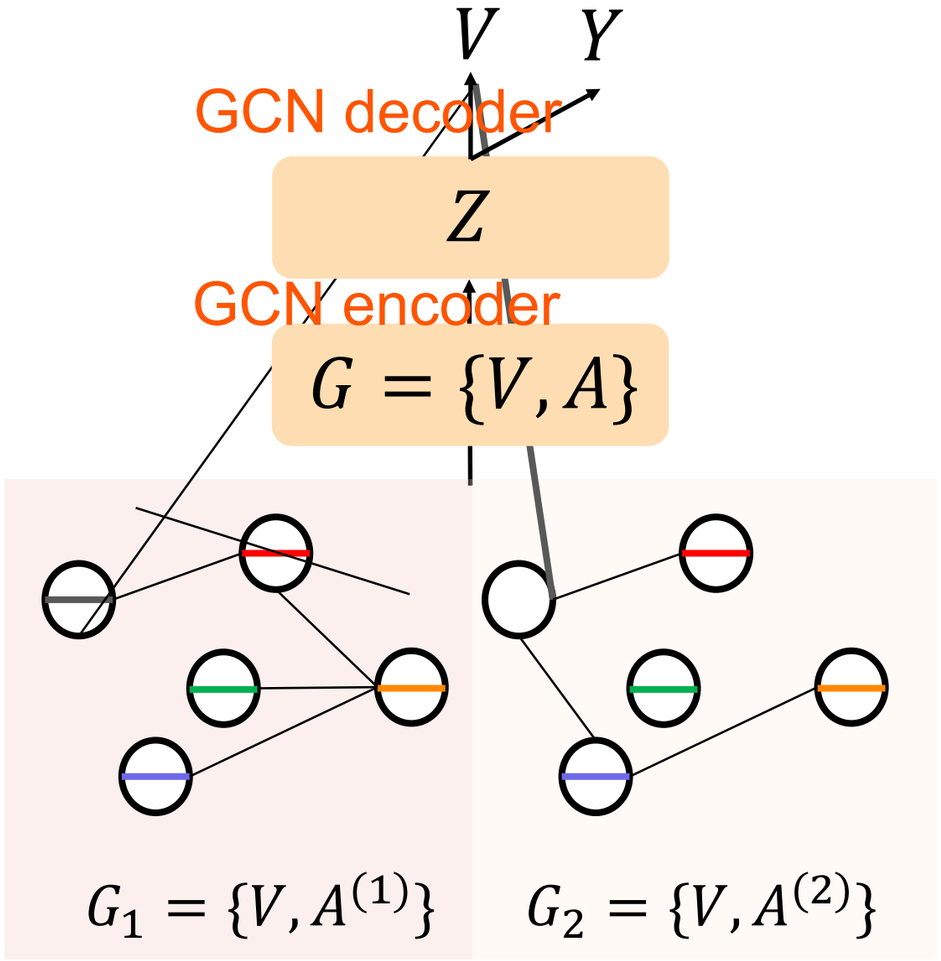
When we do not have labels, we reconstruct $\boldsymbol{V}$ from $\boldsymbol{Z}$ to minimize autoencoder loss, $\mathrm{L}_{ed} = \sum|\boldsymbol{X} - \boldsymbol{X}'|^2$.

$$A = \sum_u diag(g^u) * A^u$$

$$g'^u = W^u A^u + b^u \quad \text{Normalize} \rightarrow \quad g^u$$

attention weights decided by data and target

Multi-View GAE for DDI Prediction (IJCAI 18)



SemiGAE (for partial labels)

Objective: $\min L = L_{train} + L_{ed}$

Training loss for labeled data

$$L_{train} = \sum_{y \in Y_{train}} \sum_{y' \in h(Z_{train})} -y \ln y'$$

Auto-encoder loss for all data

$$L_{ed} = \sum |X - X'|^2$$

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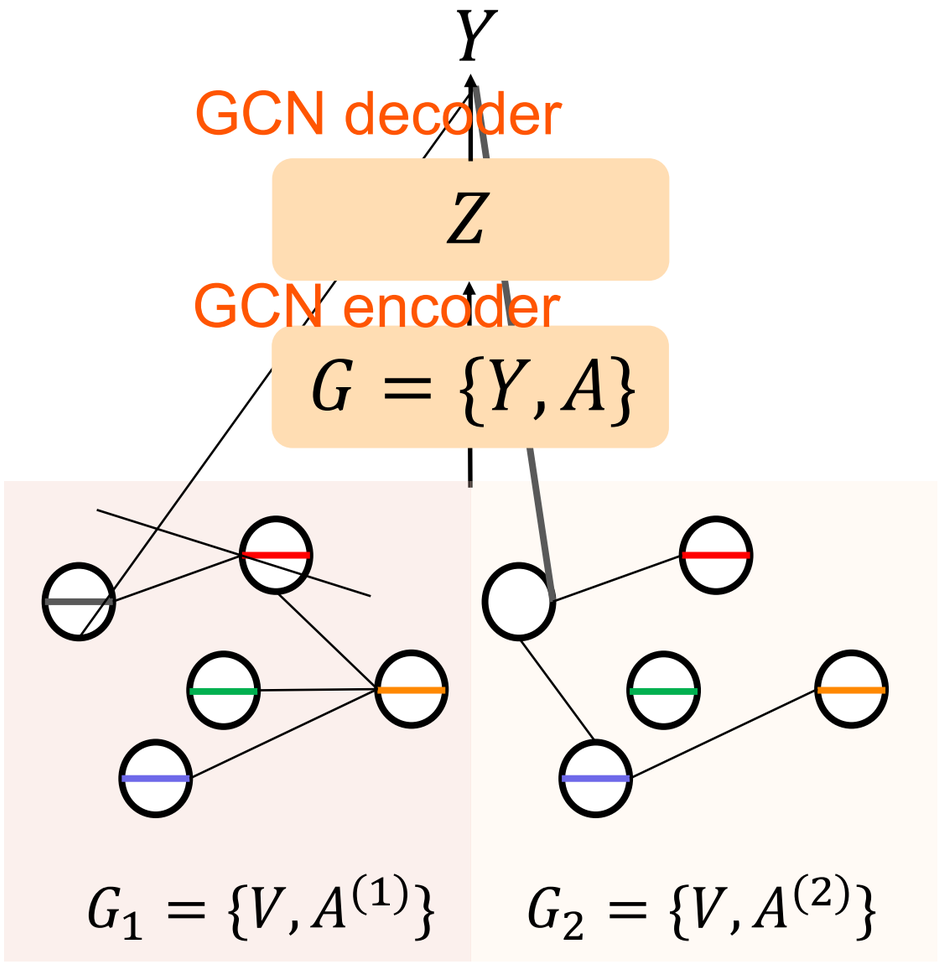

TransGAE (for lack of node features)

For the case when we do not have node feature

$$\min L = |Y'_{train} - Y_{train}|^2 + |Y'_{test} - Y_{test}|^2 + \mu|Y_{test}|^2$$

where we also treat DDI label as input variable

$$\{Y'_{train}, Y'_{test}\} = f'(f(\{Y_{train}, Y_{test}\}, \hat{A}), \hat{A})$$

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Experiments

Data (Binary)	Dimension
drugs (pairs)	645 (63473)
DDI	1318
label ADR	4192
off-label ADR	10093
Substructure	645 x 1024

Data (Multi)	Dimension
drugs (pairs)	222 (63473)
DDI	1301
indication	1702
CPI	611
TTD	207
Substructure	645 x 582

Baselines

- Nearest neighbor [Vilar et al. 2012]
- Label Propagation [Zhang et al. 2015]
- Multiple Kernel Learning [Strazar and Curk 2016]
- Basic Multi-view GraphCNN

Evaluation

- Same strategy as [Zhang et al. 2015]
- Selecting a fixed percentage of drugs randomly and all DDIs associated with these drugs are used for testing
- For the remaining training data, 90%/10% split for training/validation
- Evaluation metrics: ROC-AUC, PR-AUC

Multi-View GAE for DDI Prediction (IJCAI 18)

Table 2: Predicting Specific DDI Types (Multiple Outcomes) on Dataset 2.

	Methods	Test Split (25%)		Test Split (50%)	
		ROC-AUC	PR-AUC	ROC-AUC	PR-AUC
Using Single View					
Baselines	NN	0.627 ± 0.043	0.594 ± 0.078	0.594 ± 0.033	0.554 ± 0.061
	LP	0.773 ± 0.025	$\mathbf{0.670 \pm 0.052}$	0.747 ± 0.028	$\mathbf{0.650 \pm 0.053}$
	GraphCNN	0.738 ± 0.047	0.594 ± 0.080	0.698 ± 0.090	0.583 ± 0.102
Proposed	SemiGAE	$\mathbf{0.798 \pm 0.029}$	0.661 ± 0.059	$\mathbf{0.784 \pm 0.028}$	0.649 ± 0.059
	TransGAE	0.790 ± 0.028	0.661 ± 0.068	0.770 ± 0.031	0.633 ± 0.080
Using Multiple Views					
Baselines	LP	0.774 ± 0.025	0.672 ± 0.052	0.748 ± 0.028	0.653 ± 0.055
	GraphCNN	0.601 ± 0.067	0.526 ± 0.120	0.578 ± 0.067	0.526 ± 0.108
	MKL	0.766 ± 0.030	0.650 ± 0.061	0.724 ± 0.026	0.586 ± 0.066
Proposed	AttSemiGAE	$\mathbf{0.802 \pm 0.029}$	$\mathbf{0.678 \pm 0.060}$	$\mathbf{0.786 \pm 0.030}$	$\mathbf{0.662 \pm 0.064}$
	AttTransGAE	0.782 ± 0.026	0.670 ± 0.058	0.764 ± 0.025	0.652 ± 0.061

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		Attention Weights			
DDI Type	AUC	Chem.	indi.	TTDS	CPI
Chest Pain	0.772	0.151	0.303	0.144	0.402
Insomnia	0.755	0.380	0.261	0.078	0.291
indication	0.774	0.117	0.301	0.283	0.299

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Multi-View GAE for DDI Prediction (IJCAI 18)

Method

- A deep learning framework: Graph Auto-encoders
  - Extending GCN to Graph Auto-encoders
- Proposed a new method for similarity integration
  - Attention based similarity matrix integration

Application

- A graph neural networks for DDI prediction
  - SemiGAE: reconstruct node features and predict node labels
  - TransGAE: using test labels as variables and reconstruct all node labels

Drug Similarity Integration Through Attentive Multi-view Graph Auto-Encoders, Tengfei Ma, Cao Xiao, Jiayu Zhou, Fei Wang, IJCAI 2018