

Challenges and opportunities in systems pharmacology

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Pharmacology - early 1900s

Magic bullet: "one target, one drug"



Paul Ehrlich

First effective treatment of
syphilis

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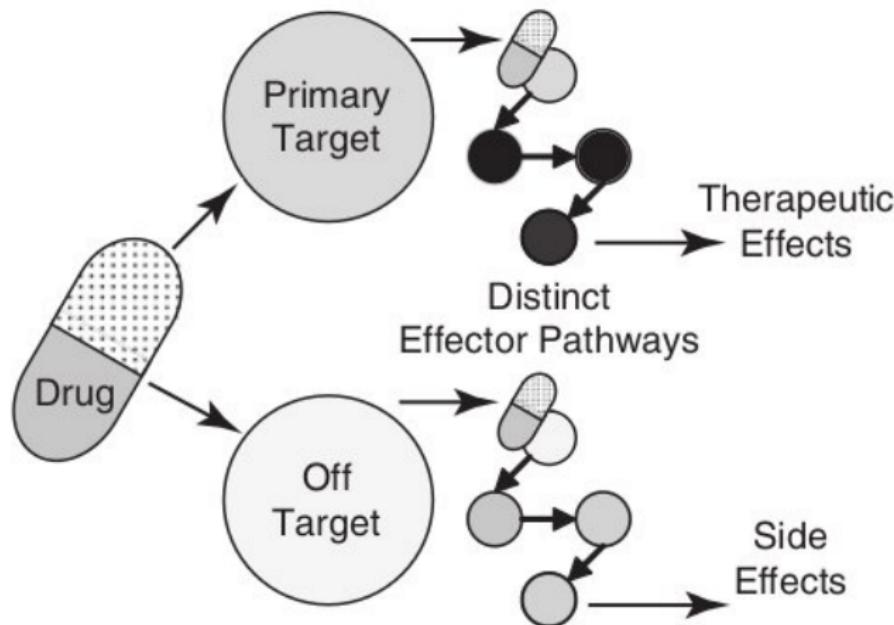
Awarded Nobel Prize jointly with
Élie Metchnikoff
(for their contributions to
immunology)



Images from wikipedia.org

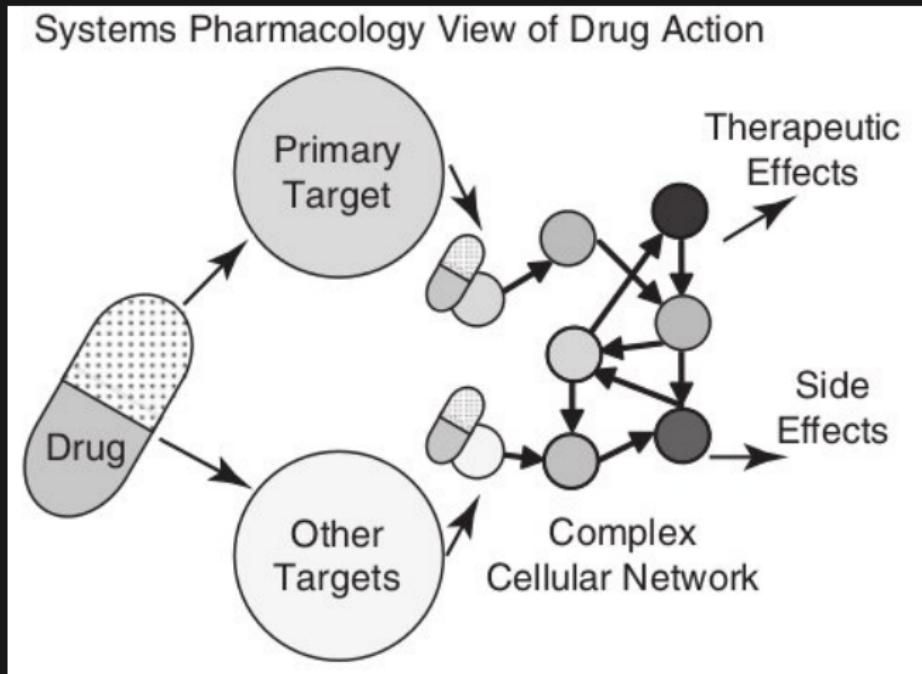
Pharmacology - late 1990s

Classic View of Drug Action



Berger and Iyengar, 2009, Bioinformatics

(Poly)Pharmacology - early 2000s



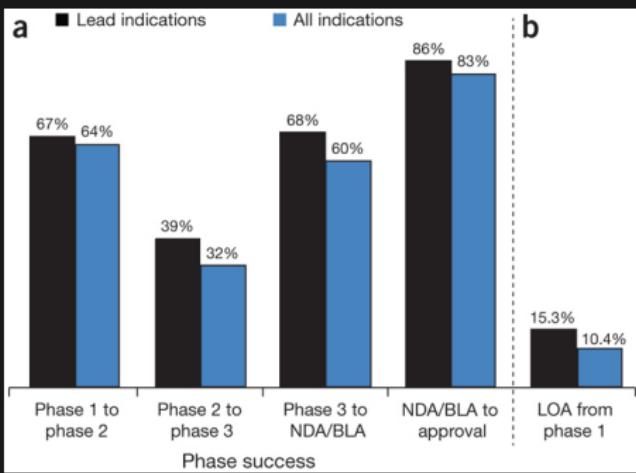
Berger and Iyengar, 2009, Bioinformatics

- difficult to chemically achieve single target specificity
- acting on multiple targets is likely to be more effective

Few drugs make it to the clinic

~10%

Percentage of drugs that get FDA
approval after clinical trials

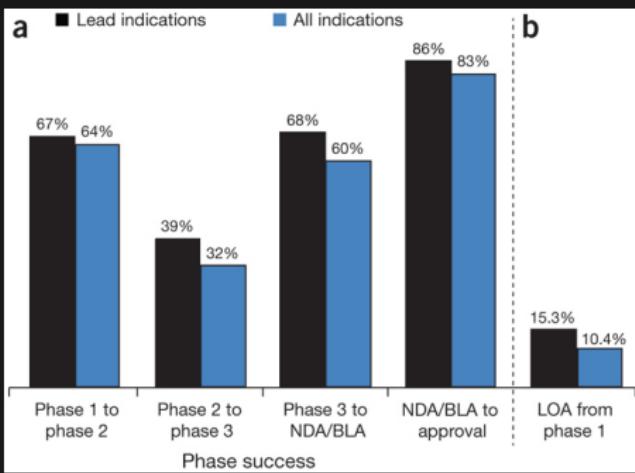


Hay et al., 2014, Nat Biotech

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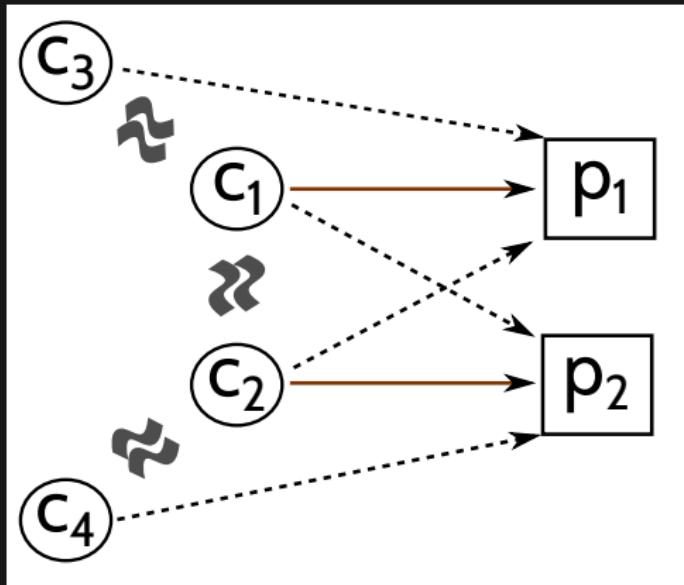


*image from findacure.org.uk

Hay et al., 2014, Nat Biotech

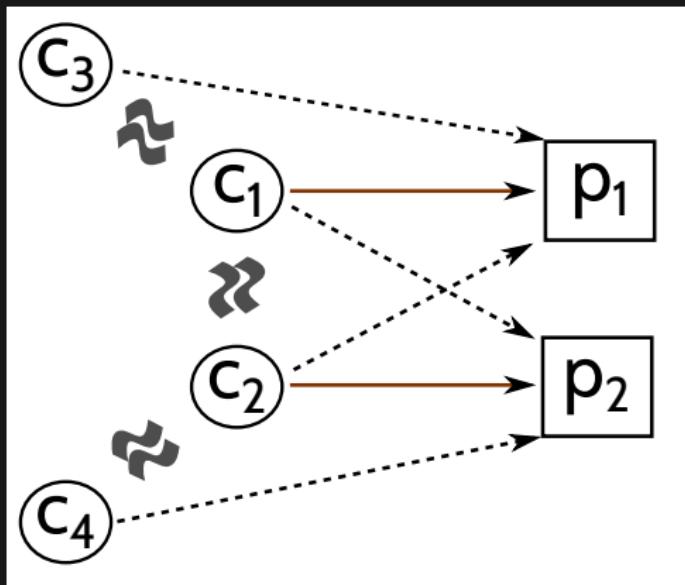
Reuse existing drugs

Similarity-based | Guilt-by-association | Knowledge-based



Reuse existing drugs

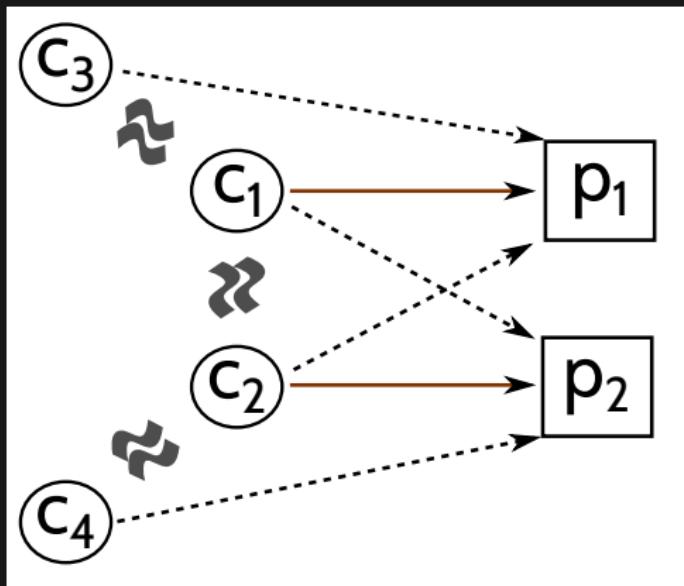
Similarity-based | Guilt-by-association | Knowledge-based



- chemical formula
- target
- side effect
- gene expression

Reuse existing drugs

Similarity-based | Guilt-by-association | Knowledge-based



- chemical formula
- target
- side effect
- gene expression

85-95%
Reported prediction accuracies

Similarity based drug repurposing: Too good to be true?

Vilar and colleagues (2014)

“...bias introduced with the information provided in the construction of the similarity measurement”

Hodos *et al.* (2016)

“...reliance on data existing nearby in pharmacological space”

Reviewer n+1

“...the paper is not quite complete with respect to the number of papers on the topic. In fact, the practical utility of all these studies is still not well demonstrated in concrete case studies.”

Similarity based drug repurposing: Too good to be true?

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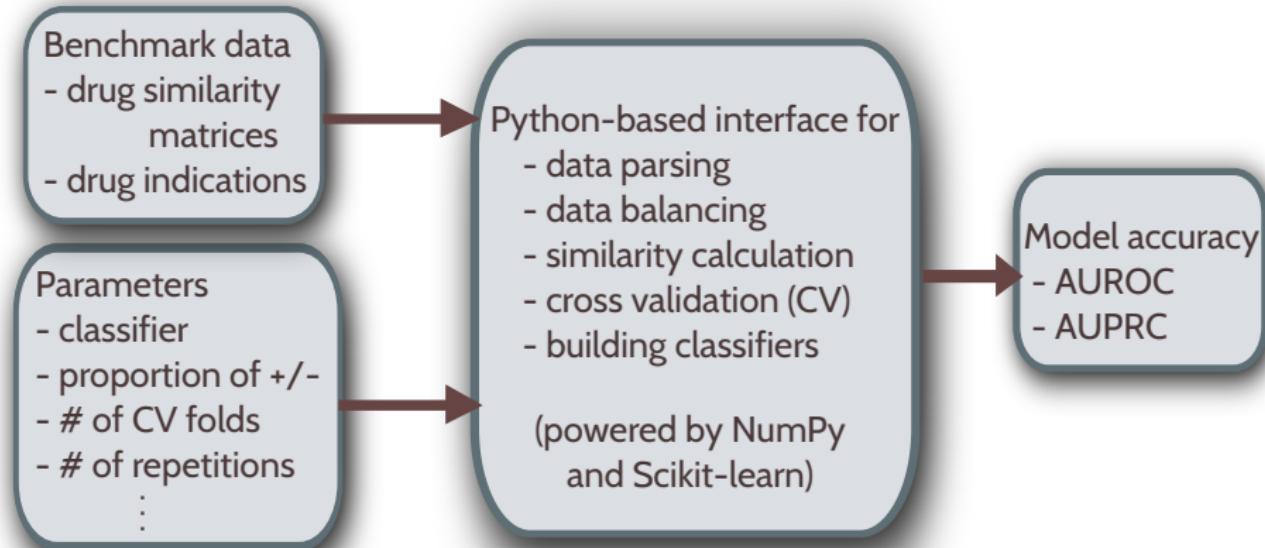
“...reliance on data existing now, contrast various methods and evaluation strategies in pharmacological space”

Reviewer n+1

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Compare & contrast various methods
and evaluation strategies

A Python platform for reproducible similarity-based drug repurposing



[github.org/emreg00/Repurpose](https://github.com/emreg00/Repurpose)

Guney, 2017, Pac. Symp. on Biocomp.

Traditional vs disjoint cross validation

Data set	2-fold cross validation		2-fold disjoint cross validation	
	Fold 1	Fold 2	Fold 1	Fold 2
(c ₁ , p ₁ , +)	(c ₃ , p ₁ , -)	(c ₁ , p ₁ , +)	(c ₂ , p ₂ , +)	(c ₁ , p ₁ , +)
(c ₁ , p ₂ , -)	(c ₃ , p ₂ , -)	(c ₂ , p ₁ , -)	(c ₁ , p ₂ , -)	(c ₁ , p ₂ , -)
(c ₂ , p ₁ , -)	(c ₄ , p ₁ , -)	(c ₃ , p ₁ , -)	(c ₃ , p ₂ , -)	(c ₄ , p ₁ , -)
(c ₂ , p ₂ , +)	(c ₄ , p ₂ , -)	(c ₄ , p ₂ , -)	(c ₄ , p ₁ , -)	(c ₃ , p ₂ , -)

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(c ₁ , p ₂ , -)	(c ₃ , p ₂ , -)	(c ₂ , p ₁ , -)	(c ₁ , p ₂ , -)	(c ₁ , p ₂ , -)
(c ₂ , p ₁ , -)	(c ₄ , p ₁ , -)	(c ₃ , p ₁ , -)	(c ₃ , p ₂ , -)	(c ₄ , p ₁ , -)
(c ₂ , p ₂ , +)	(c ₄ , p ₂ , -)	(c ₄ , p ₂ , -)	(c ₄ , p ₁ , -)	(c ₃ , p ₂ , -)

Defining non-overlapping drug groups

D: data set containing drug-disease pairs, *c*: drug, *p*: disease,

l: label (1 if *c* is known to be indicated for *p*, 0 otherwise), *k*: number of cross validation folds,

fold: dictionary containing the fold index of each drug-disease pair

i := random([0, 100])

fold := {}

for each $(c, p, l) \in D$ do

sum := 0

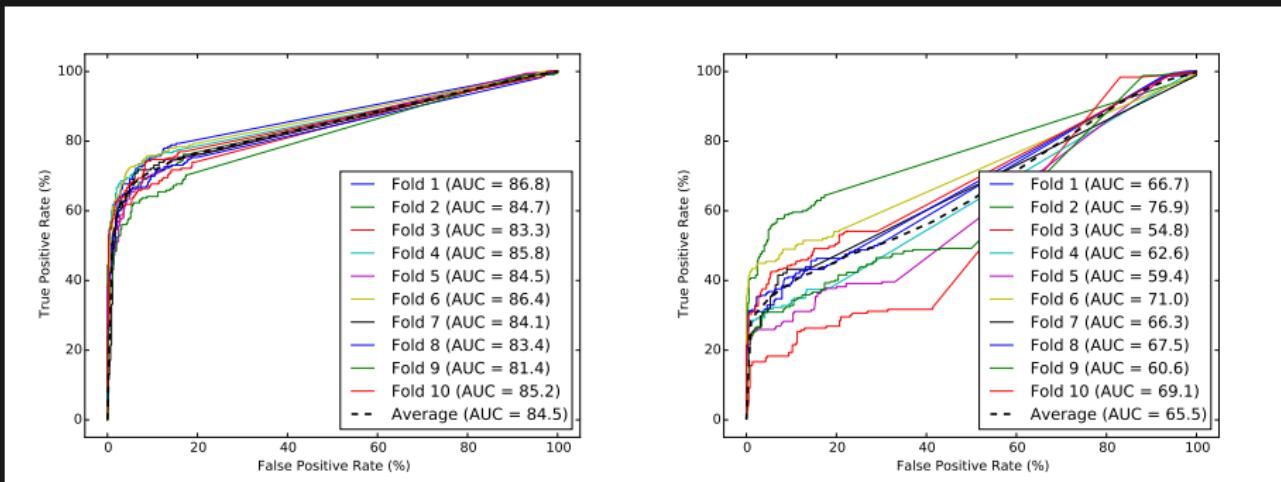
 for each $x \in \text{characters}(c)$ do

sum := *sum* + to_integer(*x*)

fold(*c*, *p*) := modulo(*sum* + *i*, *k*)

return *fold*

Traditional vs disjoint 10-fold cross validation



Disjoint folds	Mean AUC (%)	Mean AUPRC (%)
No	84.1 (\pm 0.3)	83.7 (\pm 0.3)
Yes	65.6 (\pm 0.5)	62.8 (\pm 0.5)

Effect of fold size on disjoint cross validation

Number of folds	Mean AUC (%)	Mean AUPRC (%)
2	80.7 (\pm 0.3)	79.3 (\pm 0.3)
5	73.6 (\pm 0.7)	71.9 (\pm 0.7)
10	65.6 (\pm 0.5)	62.8 (\pm 0.5)
20	59.1 (\pm 0.6)	57.0 (\pm 0.3)

The diversity of the training set has a strong effect on the accuracy

Limitations of similarity-based approaches

- interpretability
- heterogeneity among disease phenotypes and patients



Image from [firebox.com](#)

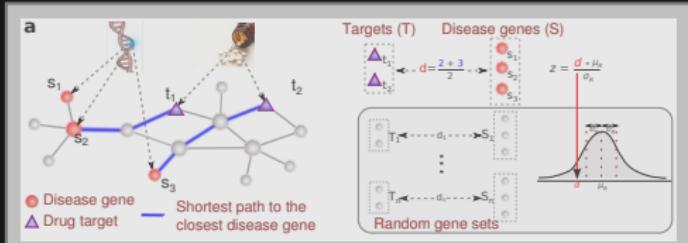
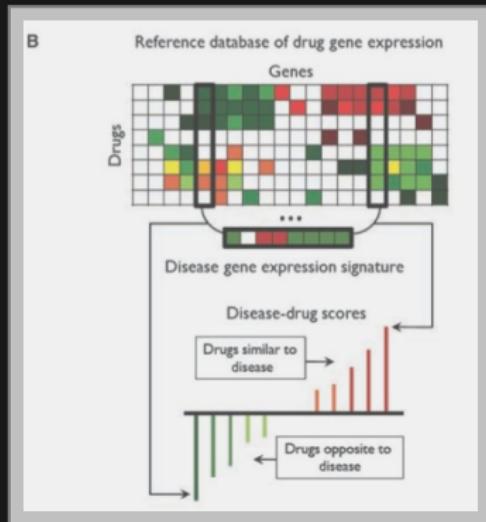
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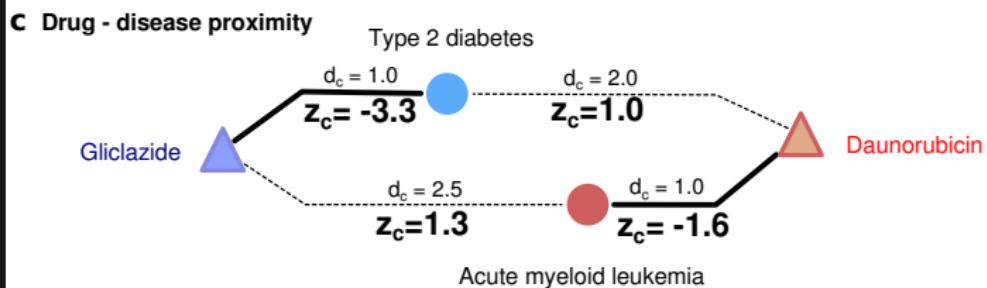
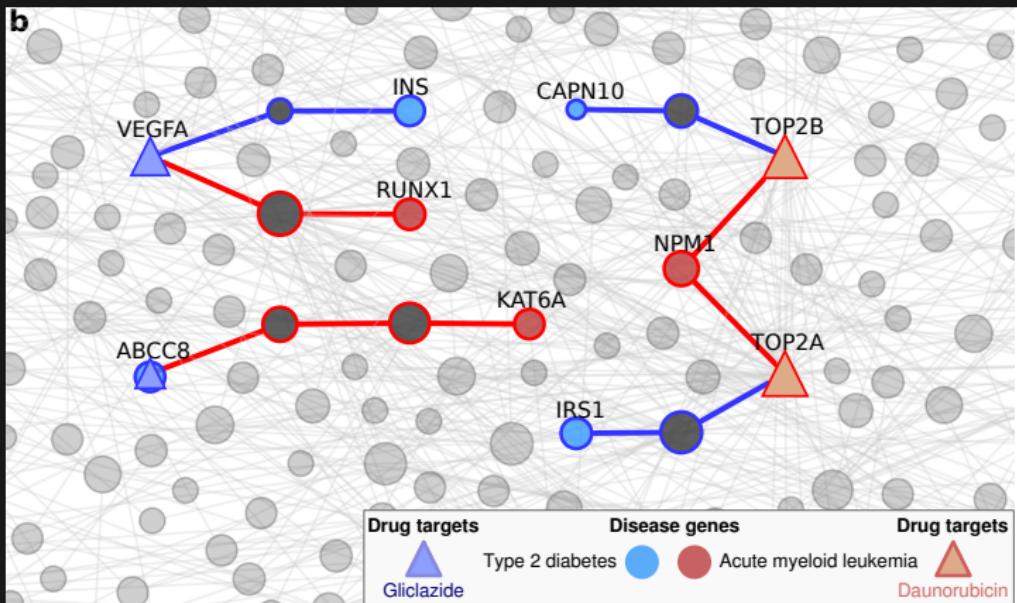
Image from firebox.com

Systems level approaches

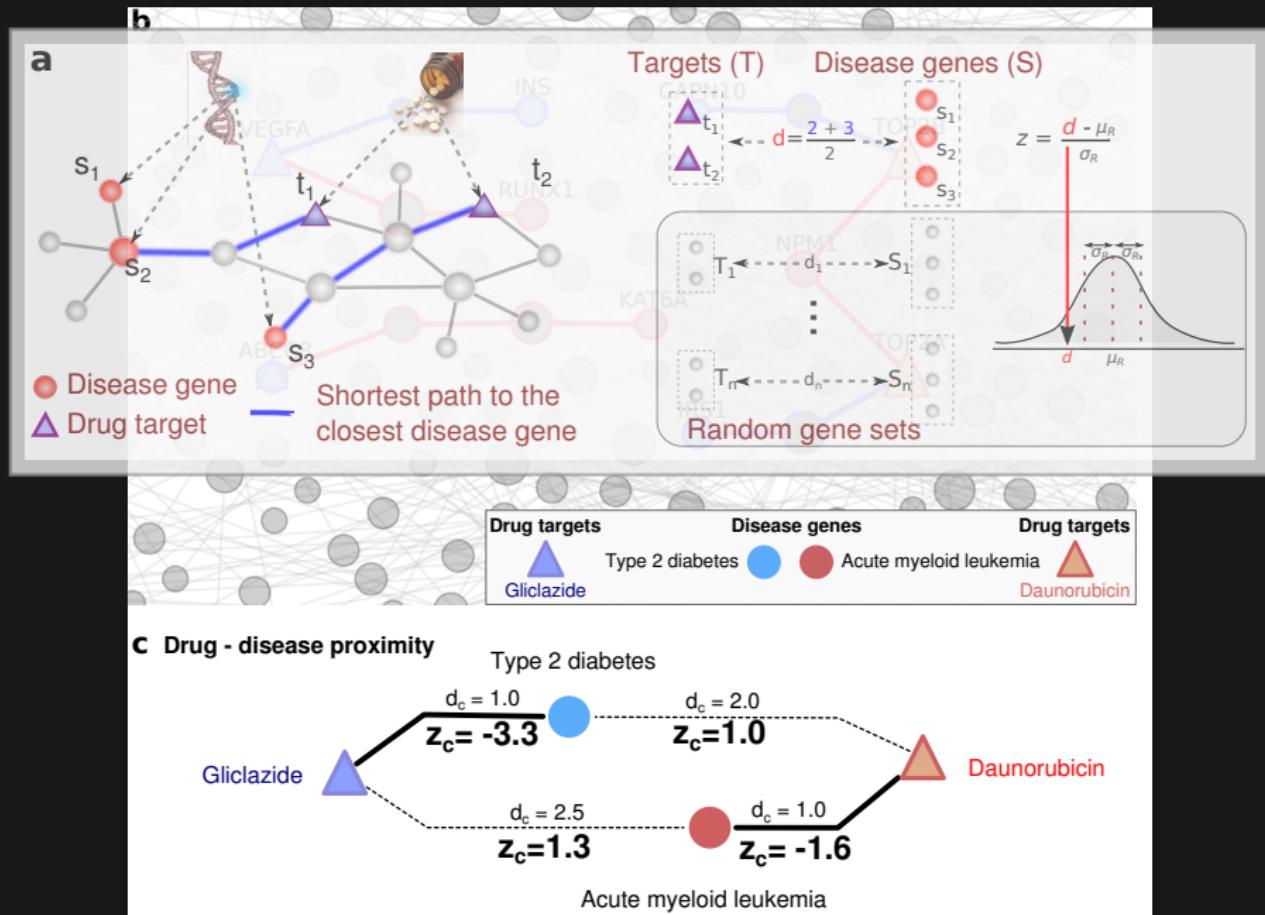


Guney et al., 2016, Nat. Comm.
Guney, 2017, Proc. of CompleNet'17

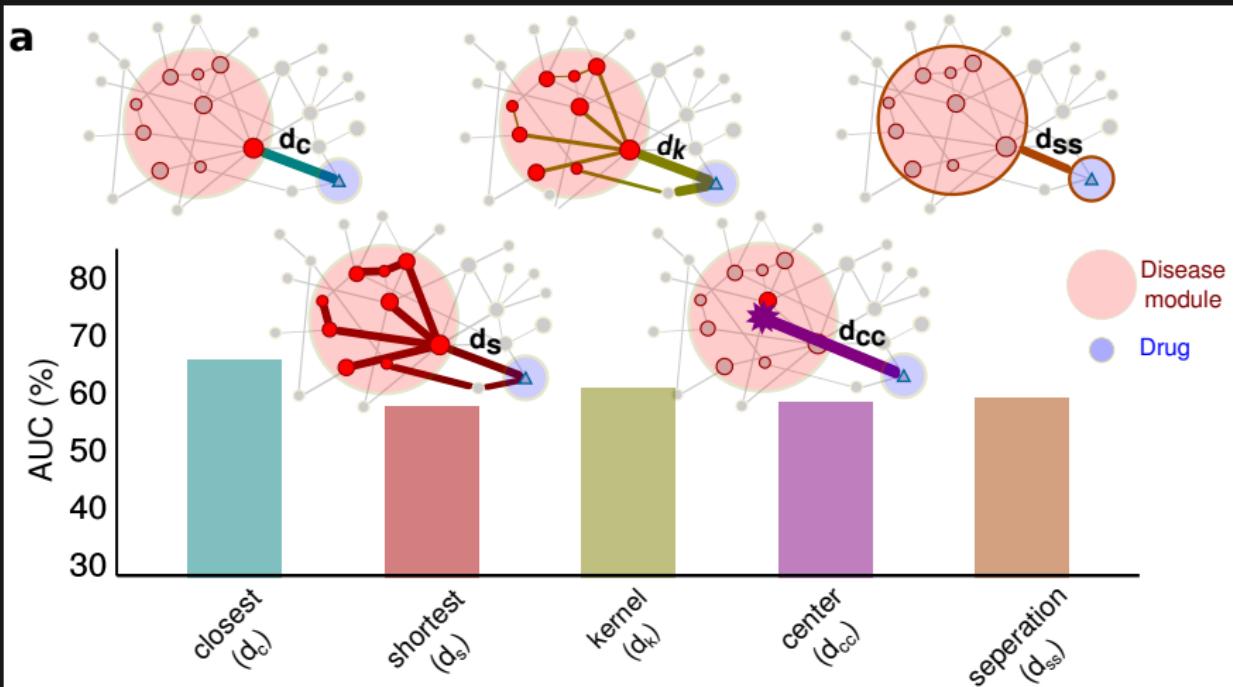
Proximity: A novel interactome-based measure



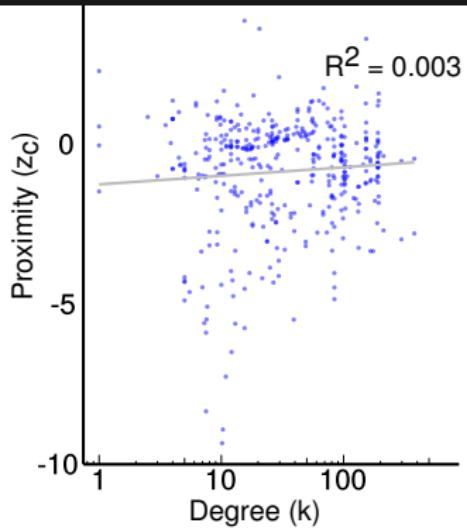
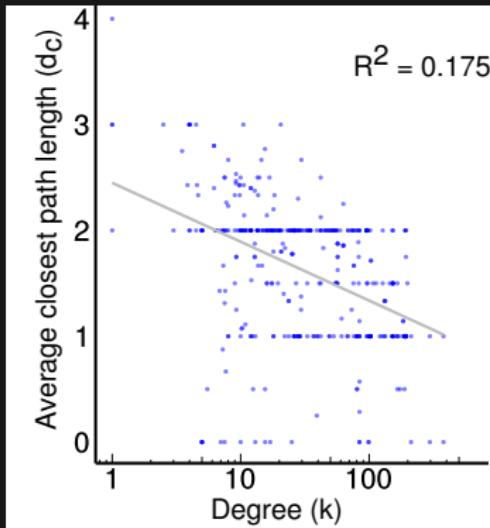
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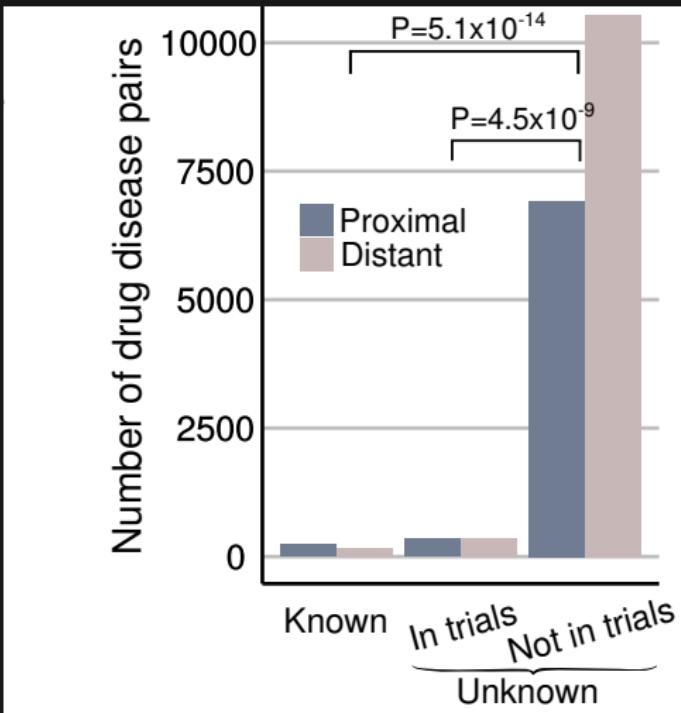
Drugs do not target the disease module as a whole



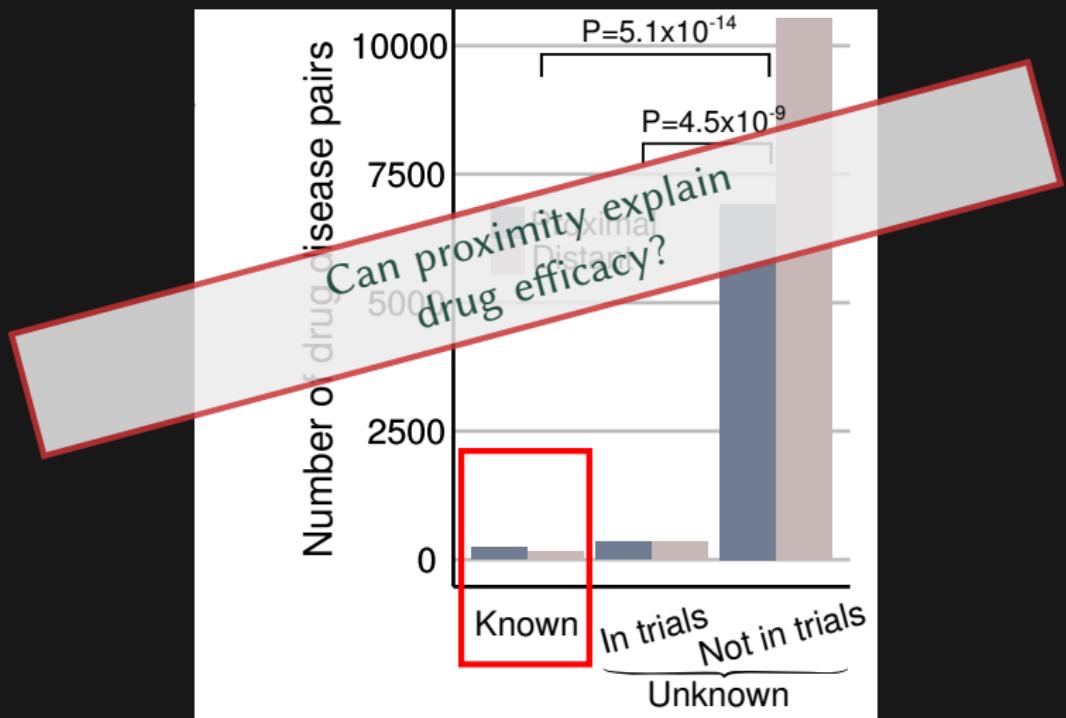
Proximity is not correlated with the degree of the targets



Proximal drug-disease pairs are enriched among known associations



Proximal drug-disease pairs are enriched among known associations



Assessing drug efficacy



About
Updates
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Drugs

$$\text{Relative Efficacy (RE)} = 1 - \frac{\# \text{ of adverse events reporting inefficacy}}{\# \text{ of most common adverse event}}$$

API
Ask
Repo
Drugs
Devices
Foods

Adverse events

Labeling

Enforcement rep

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Adverse drug event reports since 2004

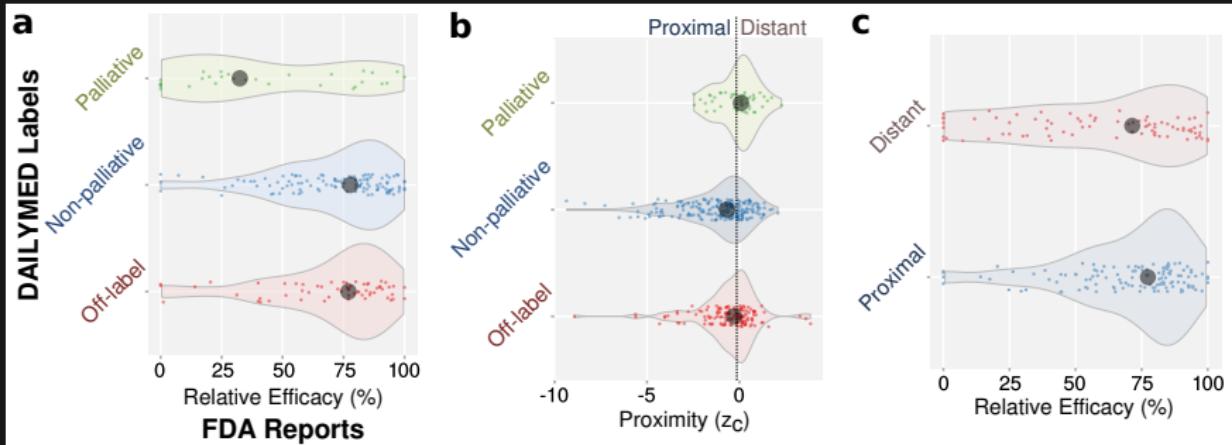
This is the openFDA API endpoint for adverse drug events. An adverse event is submitted to the FDA to report any undesirable experience associated with the use of a drug, including serious drug side effects, product use errors, product quality problems, and therapeutic failures.

Reporting of adverse events by healthcare professionals and consumers is voluntary in the United States. Increases in the total number of adverse events are likely caused by improved reporting, regulatory actions, and other phenomena can also spur reporting.



An adverse event

Proximity is a good proxy for drug's therapeutic effect



Proximal drug-disease pairs are more likely to correspond to effective treatments

$$P = 7.3 \times 10^{-5}$$

$$P = 7.6 \times 10^{-4}$$

(n = 50, 219, 133)

$$P = 4.0 \times 10^{-5}$$

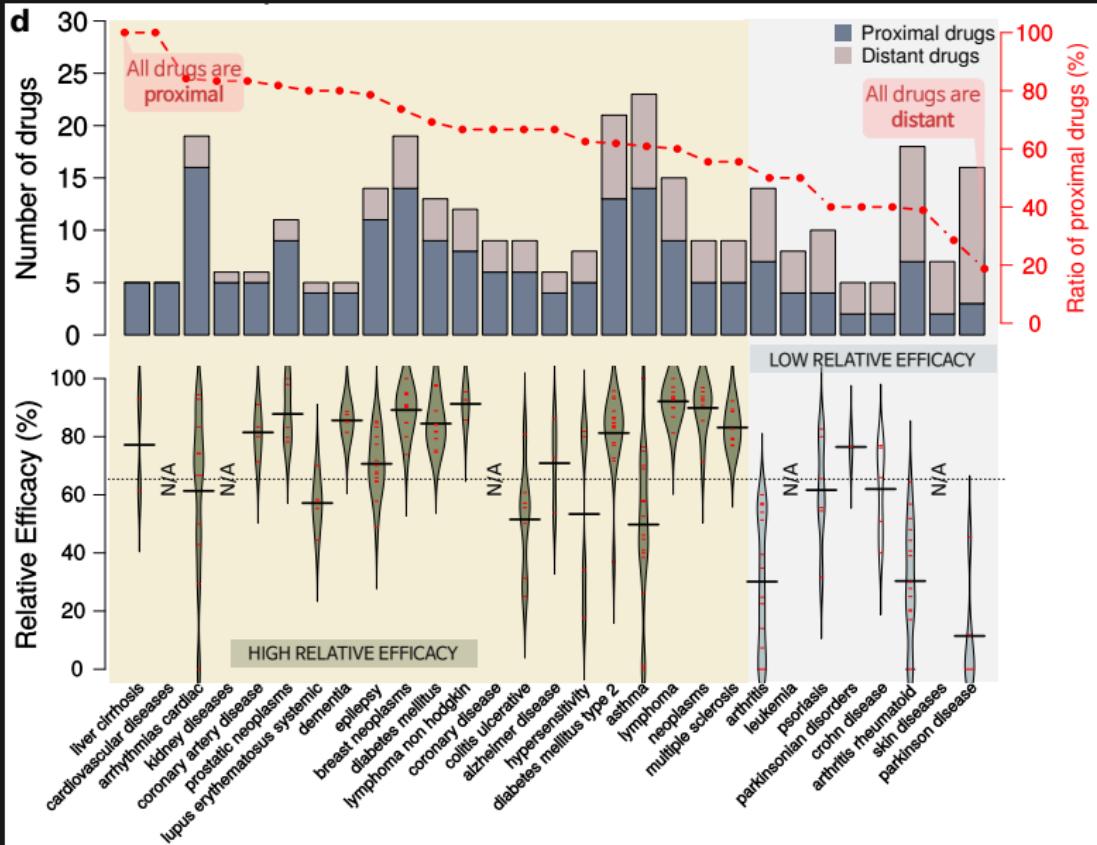
$$P = 0.02$$

(n = 50, 219, 133)

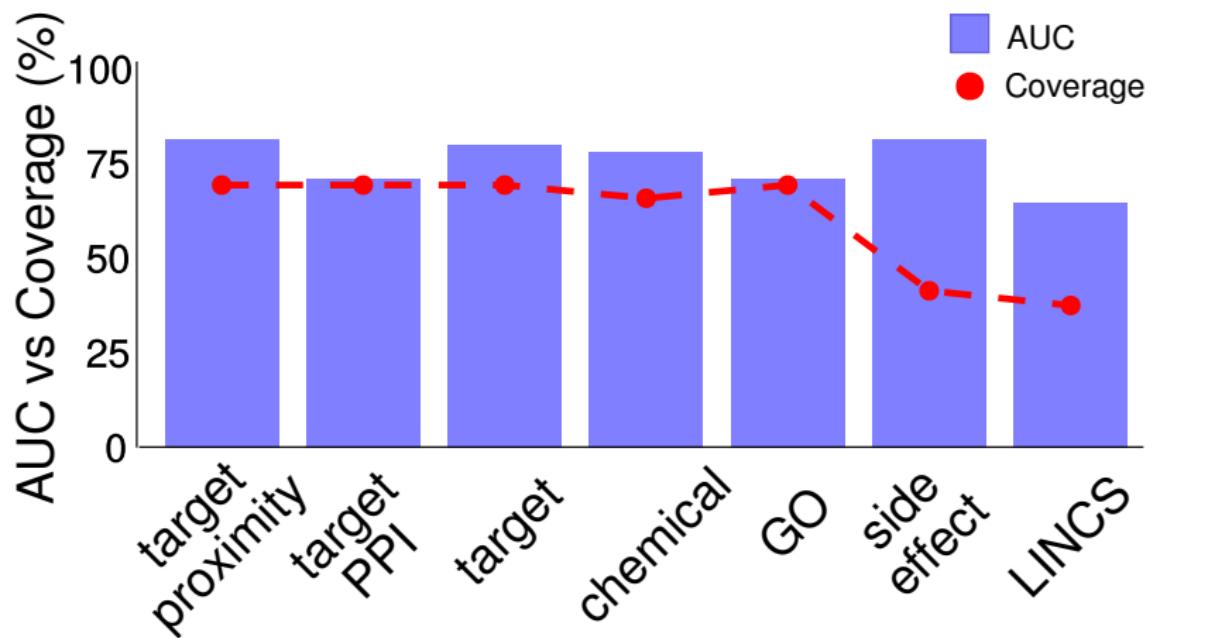
$$P = 0.04$$

(n = 237 vs 165)

Proximity highlights treatment bottlenecks



Proximity in comparison to drug similarity-based approaches



Drug-drug similarity based classification

Drug repurposing using proximity: Glimepiride

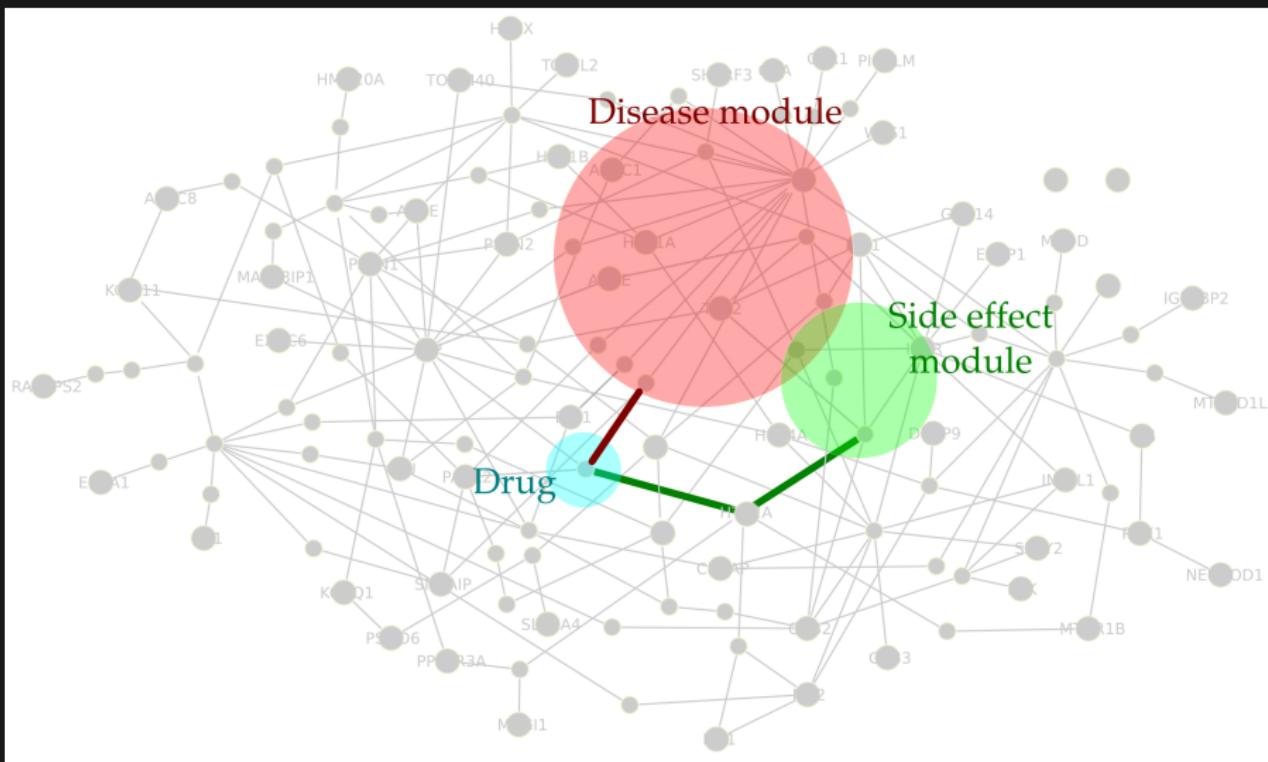
Disease	Proximity (z)
type 2 diabetes	-5.1
cardiac arrhythmias	-3.6
Alzheimer's disease	-1.0
rheumatoid arthritis	-0.7

Glimepiride is approved for use in type 2 diabetes.

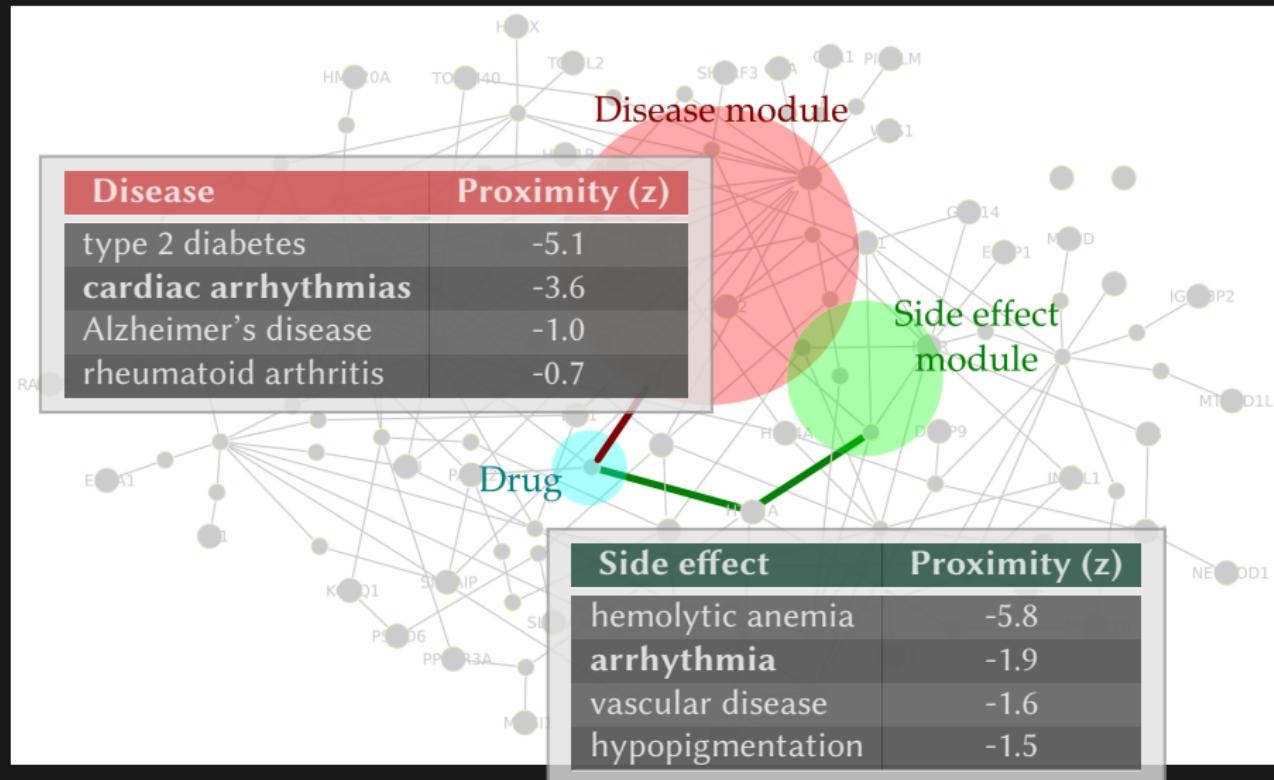
Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. Schramm,

T. K. et al. Eur. Heart J., 32:1900 (2011).

Drug repurposing using proximity: Glimepiride



Drug repurposing using proximity: Glimepiride



Schramm, T. K. et al. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes... Eur. Heart J. 32:1900 (2011).

Proximity highlights the therapeutic link between T2D and AD

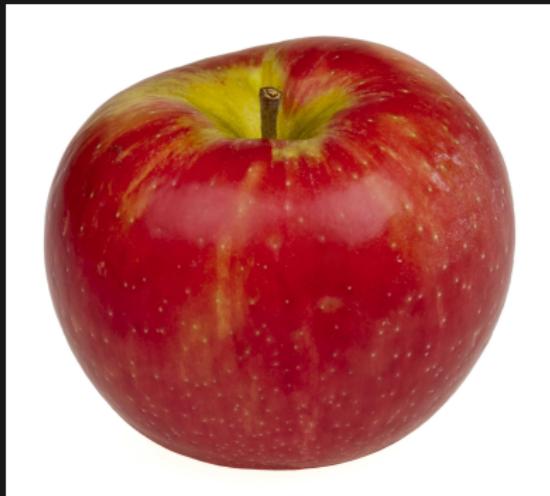
Donepezil

Pathway	n	z
synthesis of phosphatidylcholine	11	-3.3
serotonin receptors	11	-3.3
adenylate cyclase inhibitory pathway	13	-2.2
IL-6 signaling	10	-2.1
the NLRP3 inflammasome	11	-2.1
regulation of insulin secretion by acetylcholine	10	-2.1

Glyburide

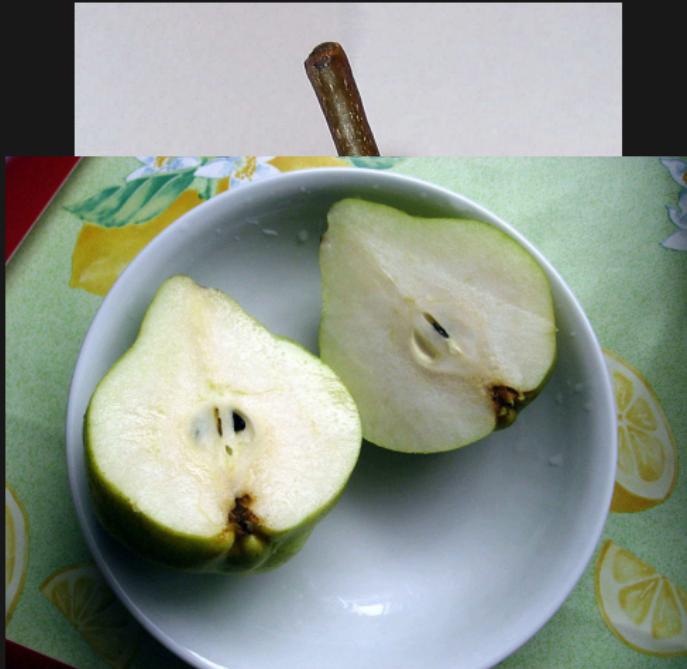
Pathway	n	z
inwardly rectifying K ⁺ channels	30	-9.0
ABC family proteins mediated transport	22	-8.5
Inhibition of voltage gated Ca ⁺² channels via G beta gamma subunits	25	-4.3
GABA _B receptor activation	38	-4.1
regulation of insulin secretion by acetylcholine	10	-3.3
Na ⁺ /Cl ⁻ dependent neurotransmitter transporters	9	-3.3

Understanding relationships between diseases



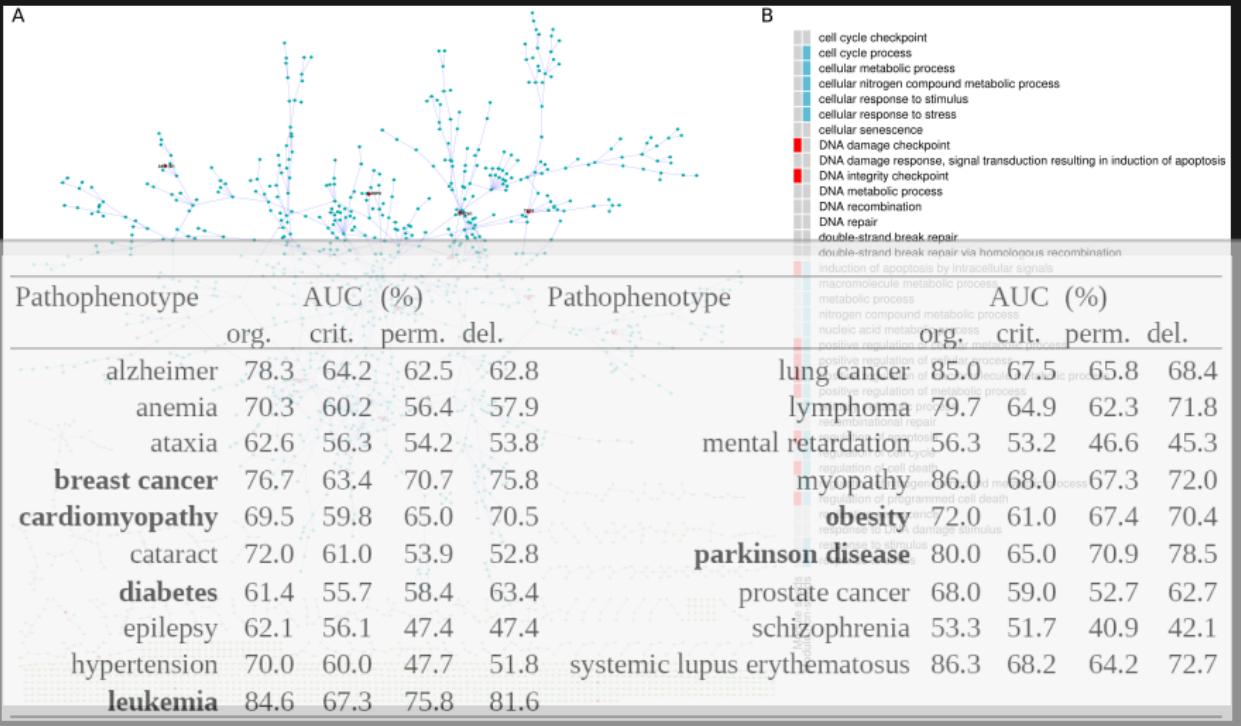
Images from [wikipedia.org](#)

Understanding relationships between diseases



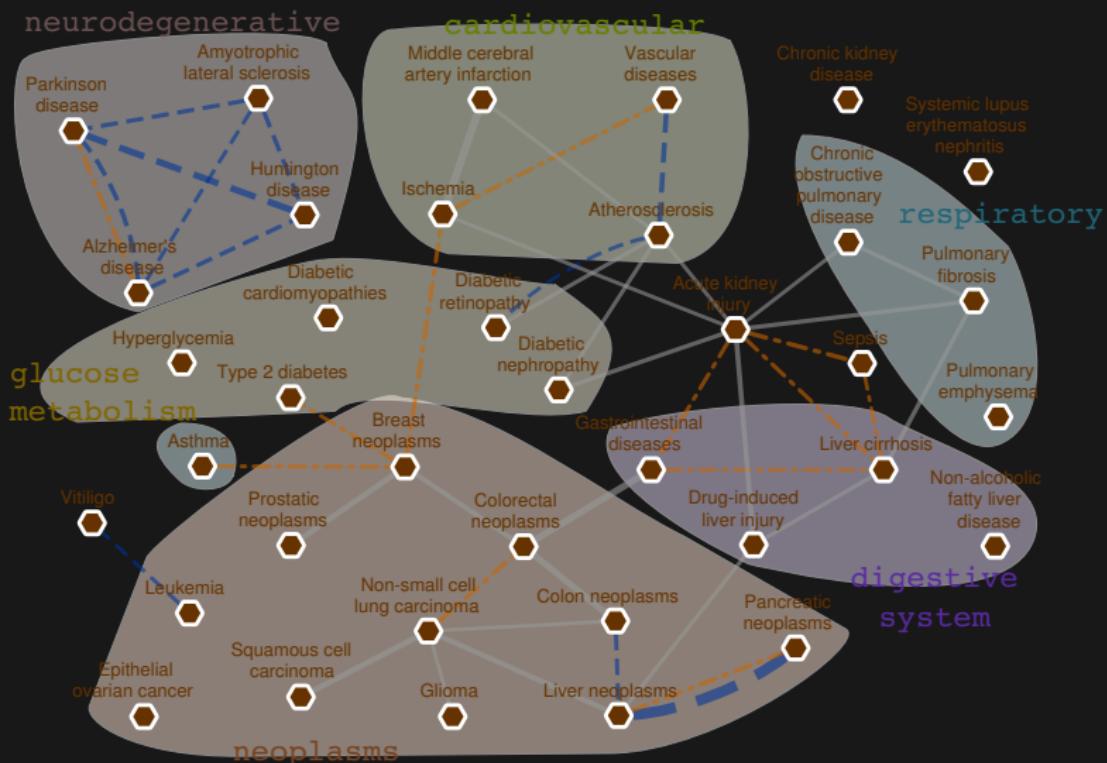
Images from wikipedia.org

Understanding relationships between diseases



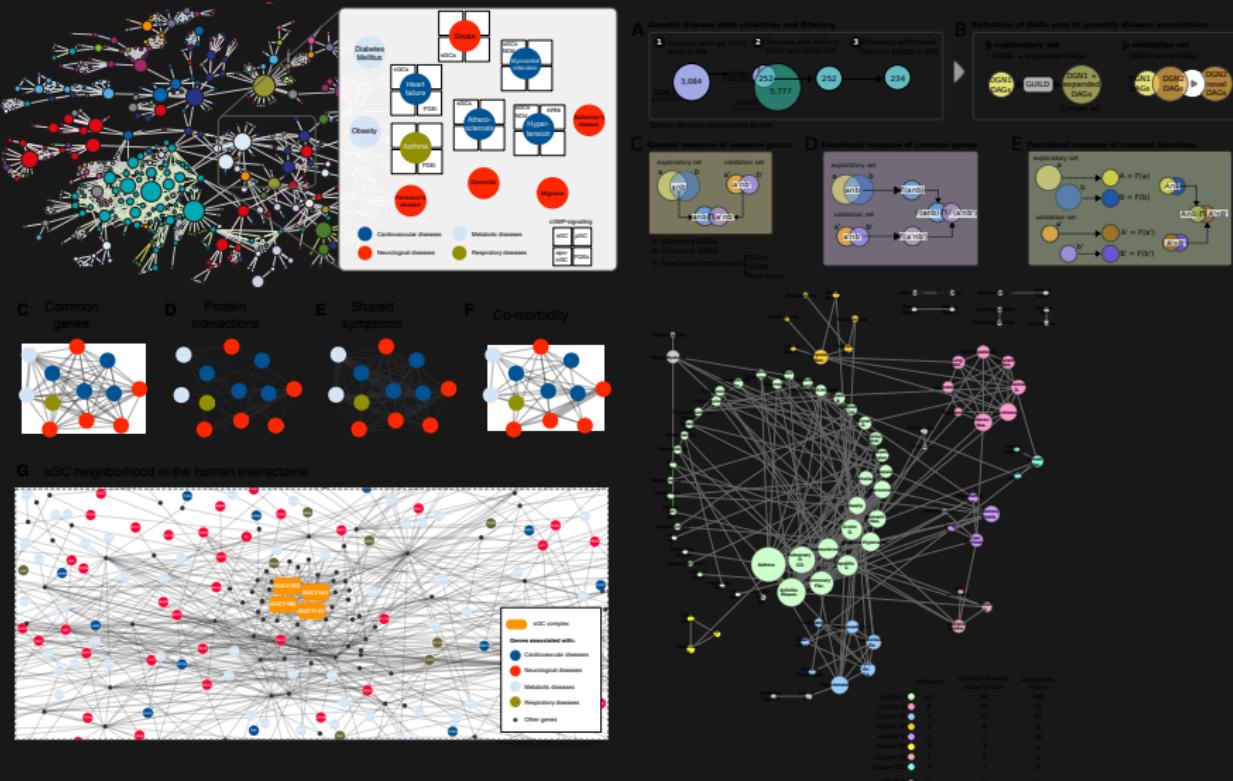
Guney and Oliva, 2014, PLoS ONE

Redefining diseasesome



Disease-disease relationships based on genetic and clinical similarities across diseases

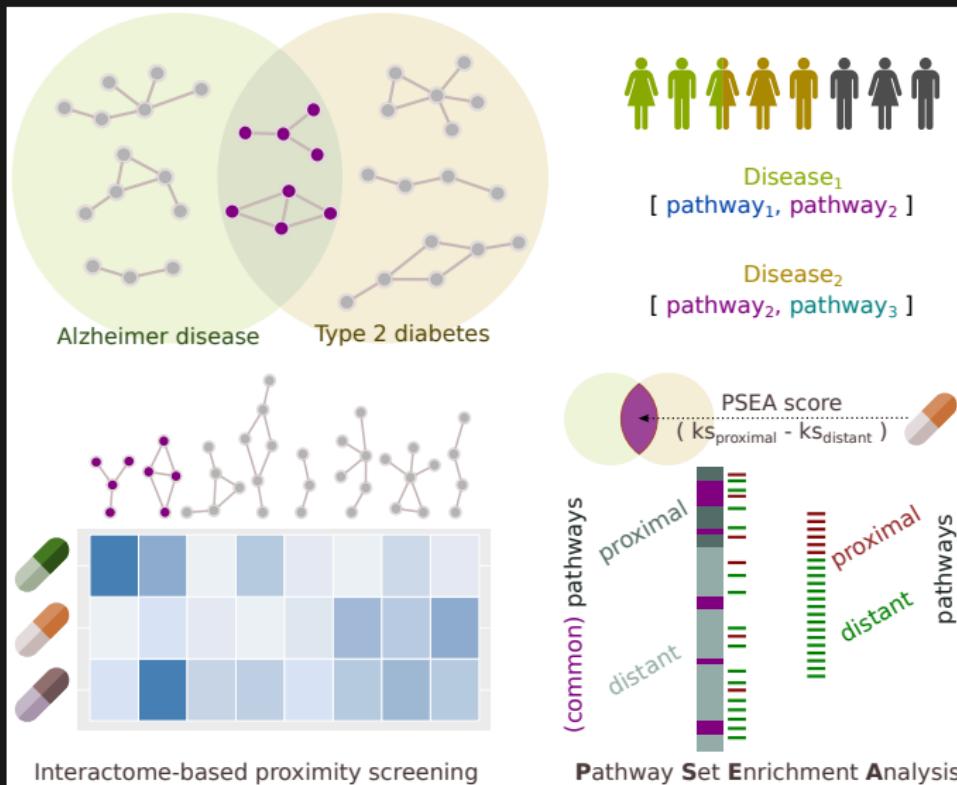
Leveraging diseasesome for novel repurposing opportunities



Langhauser et al., under revision

Rubio-Perez*, Guney* et al., in press

Targeting pathway level commonalities between diseases

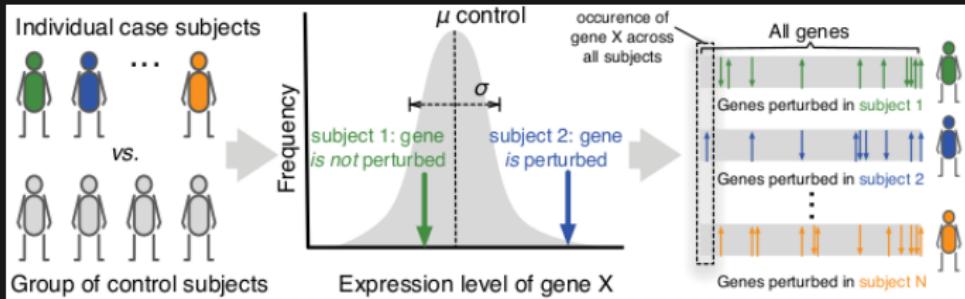


Heterogeneity among patients



Image from [wikipedia.org](#)

Incorporating individualized expression differences



Case	Control
X X X	C C C C
X X X	C C C C

$$z(gene) = \frac{expression_{\text{X}}(gene) - \mu_c(gene)}{\sigma_c(gene)}$$

Menche*, Guney*, et al., 2017, *Npj Sys. Bio. Appl.*

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IRB

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Appendix

Similarity-based classifier

Drug i defined as a binary vector for a given feature

$$X_i^f = [x_1^f, x_2^f, \dots, x_n^f]^T$$

$f:$

- chemical substructures
- targets
- side effects

Similarity between two drugs i and j are defined by the Pearson product-moment correlation

Similarity-based drug-disease score s_{ip}^f is defined as

$$s_{ip}^f = \sum_{j \in \text{NearestNeighbors}(i)} \rho_{ij}^f * I_{jp}$$

where

$$I_{jp} = \begin{cases} 1, & \text{if } j \text{ is indicated for } p \\ 0, & \text{otherwise} \end{cases}$$

Data set

Zhang and coworkers (2013)

- 536 drugs and their targets (DrugBank) & chemical structures (PubChem)
- 2,229 drug-disease associations (NDF-RT) covering 578 diseases
- 40,455 drug-side effect associations (SIDER) covering 1,252 side effects

The data set is publicly available online at

astro.temple.edu/~tua87106/drugreposition.html

Prediction accuracy evaluation

Positive instances: 2,229 known drug-disease associations

Potential negative instances: Remaining possible associations
between 536 drugs and 578 diseases
 $(536 \times 578 - 2,229 = 307,579 \text{ associations})$

Negative instances: Randomly sample twice as many negative
instances as positives

- Calculate the area under ROC curve (AUC) / Precision-Recall curve (AUPRC)
- Use k-fold cross validation scheme ($k = 2, 5, 10, 20$)
- Report the mean AUC over 10 repetitions of the cross validation procedure

Defining similarity between drugs

Drug i defined as a binary vector for a given feature

$$X_i^f = [x_1^f, x_2^f, \dots, x_n^f]^T \quad f: \begin{aligned} &\bullet \text{ chemical substructures} \\ &\bullet \text{ targets} \\ &\bullet \text{ side effects} \end{aligned}$$

Similarity between two drugs i and j are defined by

$$\rho_{ij}^f = \frac{C_{ij}^f}{\sqrt{C_{ii}^f * C_{jj}^f}}$$

where C_{ij}^f given by

$$C_{ij}^f = \text{cov}(X_i^f, X_j^f) = E[(X_i^f - E(X_i^f))(X_j^f - E(X_j^f))]$$

Similarity-based logistic regression classifier

Probability of observing an association between the drug i and the disease p

$$P(Y_{ip} = 1 | s_{ip}^{\text{chem.}}, s_{ip}^{\text{target}}, s_{ip}^{\text{s.effect}}) = \frac{1}{1 + e^{-(\beta_0 + \beta_1 * s_{ip}^{\text{chem.}} + \beta_2 * s_{ip}^{\text{target}} + \beta_3 * s_{ip}^{\text{s.effect}})}}$$

where the similarity-based drug-disease score s_{ip}^f is defined as

$$s_{ip}^f = \sum_{j \in \text{NearestNeighbors}(i)} \rho_{ij}^f * I_{jp}$$

and

$$I_{jp} = \begin{cases} 1, & \text{if } j \text{ is indicated for } p \\ 0, & \text{otherwise} \end{cases}$$

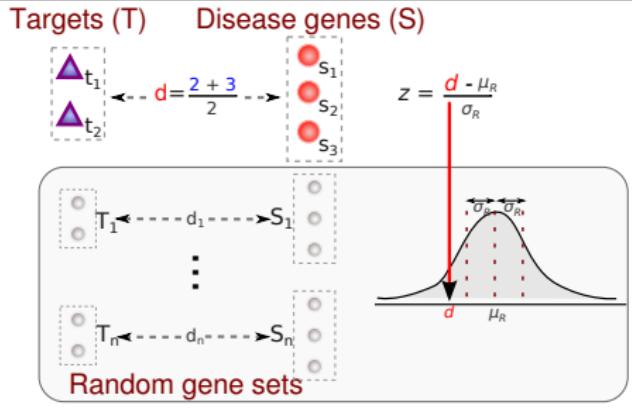
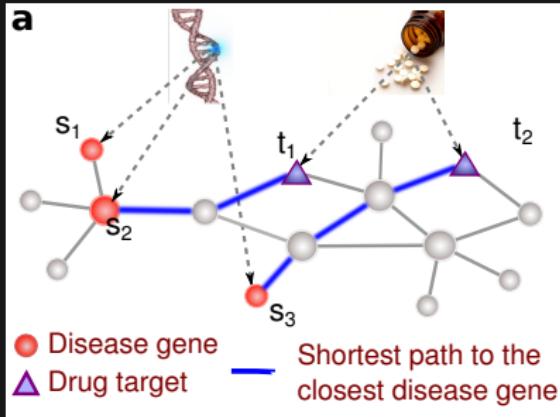
(Subject to L2 regularization, i.e., find β maximizing $\sum_{k=1}^m \log(y_k | x_k, \beta) - \sum_{l=0}^3 \beta_l^2$)

Repurpose in action

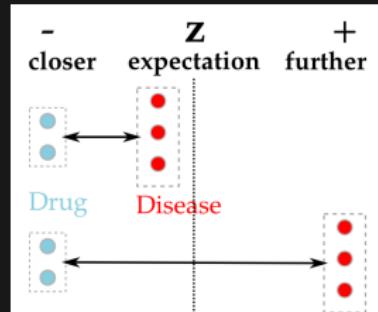
Non-disjoint cross validation Disjoint cross validation

Drug	Chemical score	Target score	Side effect score	Probability	Chemical score	Target score	Side effect score	Probability
<i>Hypercholesterolemia drugs</i>								
fenofibrate	0.76	0.71	1.10	0.82	0.57	0	0.46	0.36
lovastatin	1.93	1.97	2.92	0.99	0	0	0	0.14
<i>Juvenile rheumatoid arthritis drugs</i>								
ibuprofen	0.82	3.50	1.08	1.00	0	0.50	0.43	0.43
sulfasalazine	1.39	1.99	0.43	0.96	0	0.50	0.43	0.43
<i>Acute myeloid leukemia drugs</i>								
daunorubicin	1.77	1.50	0	0.87	0	0	0	0.15
idarubicin	0.78	2.00	0.81	0.97	0	0	0	0.14

Defining proximity

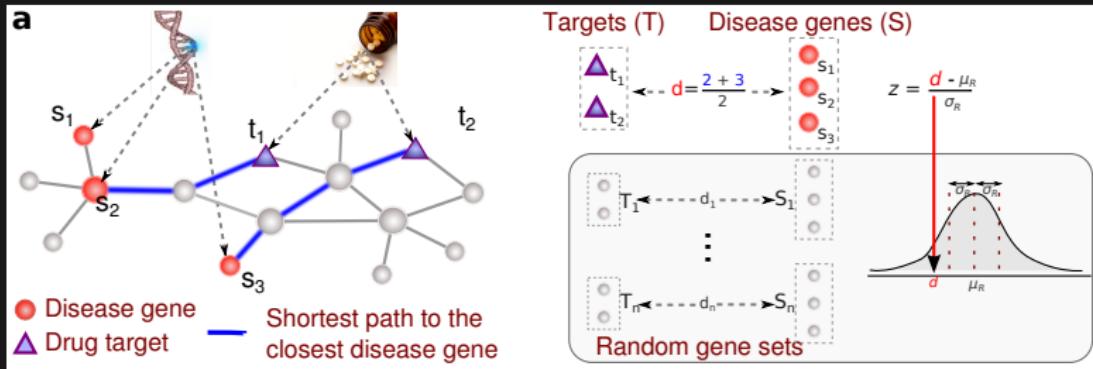


$$z(S, T) = \frac{d(S, T) - \mu_{d(S, T)}}{\sigma_{d(S, T)}}$$



Relative proximity (z): The significance of the observed distance with respect to the random expectation

Evaluating proximity

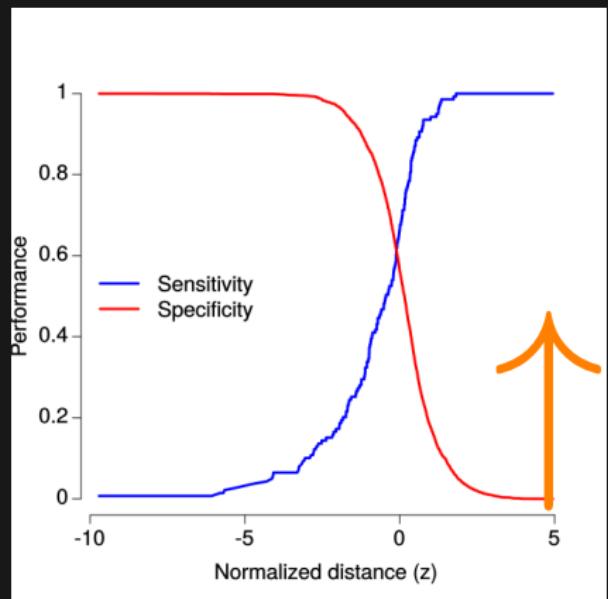


78 diseases x 238 drugs
18,564 possible drug-disease pairs

	Type 2 diabetes	Acute myeloid leukemia
Gliclazide	✓	-
Daunorubicin	-	✓

402 known vs 18,162 unknown drug-disease pairs based on MEDI

Proximity cutoff: Deciding which drugs are proximal to the disease



Proximity ($z \leq -0.15$)	Known	Unknown
Proximal	237	7,276
Distant	165	10,886

Proximity vs therapeutic efficacy

Ketoprofen capsules USP are indicated for **the management of the signs and symptoms of rheumatoid arthritis and osteoarthritis.**

Ketoprofen capsules USP are indicated for **the management of pain.**

<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c2c99853-1268-4998-a44b-2bf0c0b70fd2>

Proximity to rheumatoid arthritis (z) = 1.5
Can proximity explain drug efficacy?

Ropinirole Tablets are indicated for **the treatment of the signs and symptoms of idiopathic Parkinson's disease.**

<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9a25f575-09ab-4d32-b73e-5426f08c00c4>

Proximity to Parkinson's disease (z) = 0.8

Categorizing drugs based on label info

For the phenotype in concern, check the indication information in DailyMed

Off-label use: Not mentioned in the label

Palliative use: Described as symptomatic treatment (manage, alleviate, ...)

Non-Palliative use: None of the above

Defining side effect module using SIDER

SIDER 2 — Side Effect Resource

Glimepiride

Side effects and indications

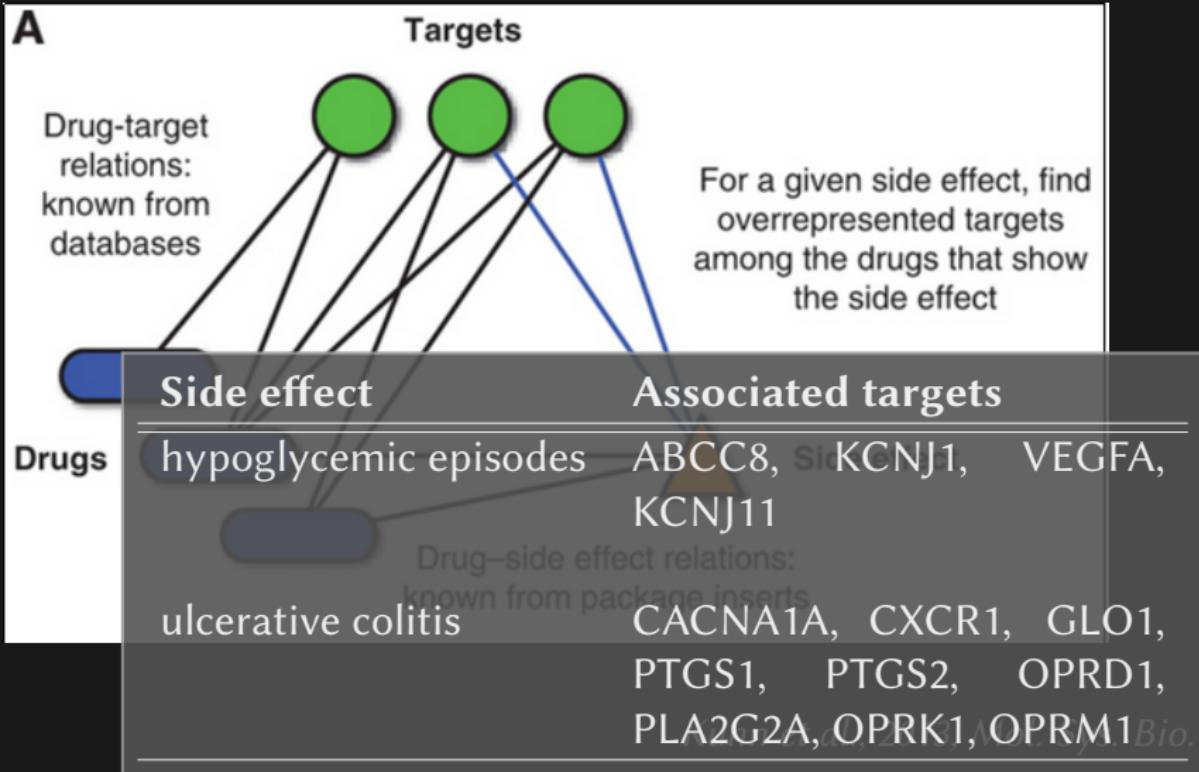
Whenever possible, frequency information about the side effects was extracted from the labels. Aggregated frequency and, if available, placebo is shown. To the right, you can click on shaded boxes to be taken to mentions of the side effects (in some cases, the side effect cannot be highlighted due to conversion problems.) [Information about indications](#) was extracted from the indications and usage sections of the labels.

[Show MedDRA Preferred Terms](#)

Side effect	Data for drug	Placebo Labels (show all 14)
Dizziness <small>def</small>	postmarketing, 0.3% - 1.7%	0.3%
Asthenia <small>def</small>	postmarketing, 1% - 1.6%	1%
Headache <small>def</small>	postmarketing, 1.4% - 1.5%	1.4%
Nausea <small>def</small>	postmarketing, 0% - 1.1%	0%
Abdominal pain <small>def</small>	postmarketing	
Agranulocytosis <small>def</small>	postmarketing	
Anaemia <small>def</small>	postmarketing	
Haemolytic anaemia <small>def</small>	postmarketing	

Kuhn et al., 2010, Mol. Sys. Bio.

Defining side effect module



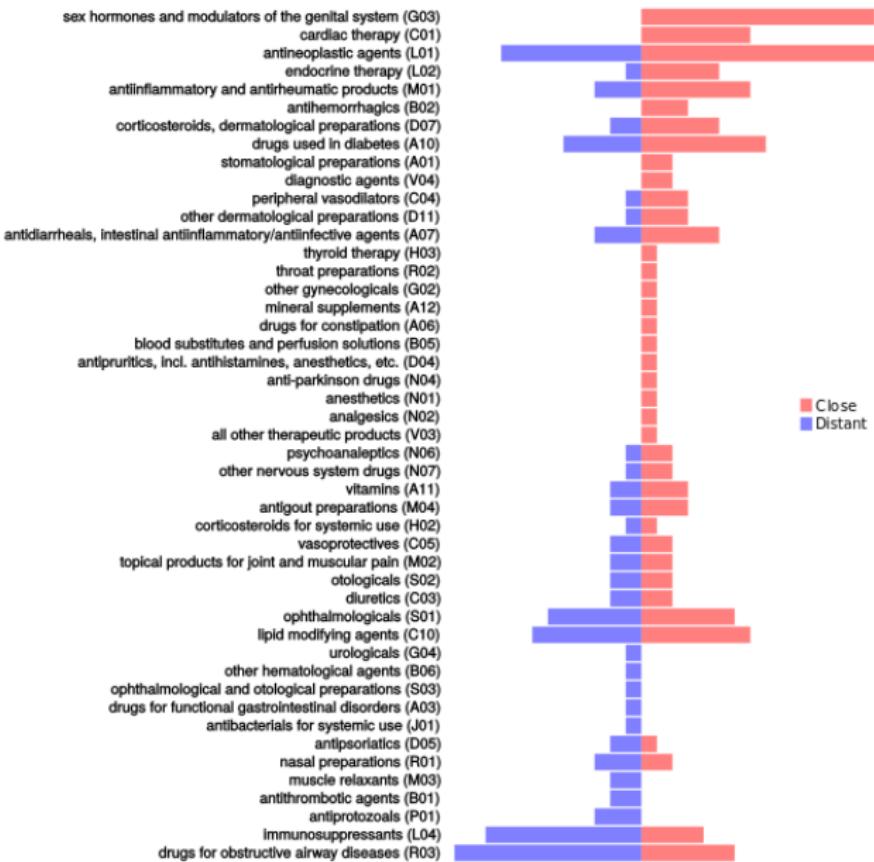
Controlling for data quality

Data set	Number of diseases	Number of drugs	Number of drug-disease pairs	AUC (%)
Original	78	238	402	65.7
<i>Protein interactions</i>				
Binary interactome	50	129	226	58.3
STRING	77	233	396	61.3
<i>Disease-gene associations</i>				
OMIM	35	114	155	71.2
GWAS	44	157	260	60.2
<i>Drug-target associations</i>				
STITCH	73	212	359	64.8
<i>Disease-drug associations</i>				
NDF-RT	61	160	233	66.2
KEGG	16	74	76	71.3

Controlling for data quality

Data set	Number of diseases	Number of drugs	Number of drug-disease pairs	AUC (%)
Diseases				
$n_{gene} \geq 20$	78	238	402	65.7
$n_{gene} \geq 1$	304	462	1192	58.6
$n_{gene} \geq 20$, broad terms filtered	53	205	282	67.2
Drugs				
$n_{target} \geq 3$	49	95	144	64.6
$n_{target \cap gene} = 0$	76	227	384	64.5

ATC classification of proximal and distant drugs



Drug repurposing using proximity

Drug	Description	Phenotype	Proximity (z)
Repurposed uses			
Plerixafor	repurposed to treat non-Hodgkin's lymphoma	non-Hodgkin's lymphoma	-2.4
Ropinirole	repurposed to treat restless legs syndrome	restless legs syndrome	-1.1
Sildenafil	repurposed to treat erectile dysfunction	erectile dysfunction	-1.0
Meta data based observations			
Drospirenone	confer protection against endometrial cancer	endometrial cancer	-1.1
Levonorgestrel	confer protection against endometrial cancer	endometrial cancer	-1.6
Failures due to lack of efficacy			
Tabalumab	showed lack of efficacy for systemic lupus erythematosus	systemic lupus erythematosus	1.8
Preladenant	discontinued trials for parkinson due to lack of improvement compared to placebo	parkinson disease	0.2
Iniparib	failed to achieve improvement while being tested for squamous non-small-cell lung cancer	squamous cell cancer	0.0
Failures due to adverse effects			
Semagacestat	failed trials due to worsening Alzheimer's disease	Alzheimer's disease	-5.6
Terfenadine	withdrawn due to inducing cardiac arrhythmia	cardiac arrhythmia arrhythmia (side effect)	-2.2 -2.6

A2D2: The link between AD and T2D

U.S. News & WORLD REPORT
HEALTH

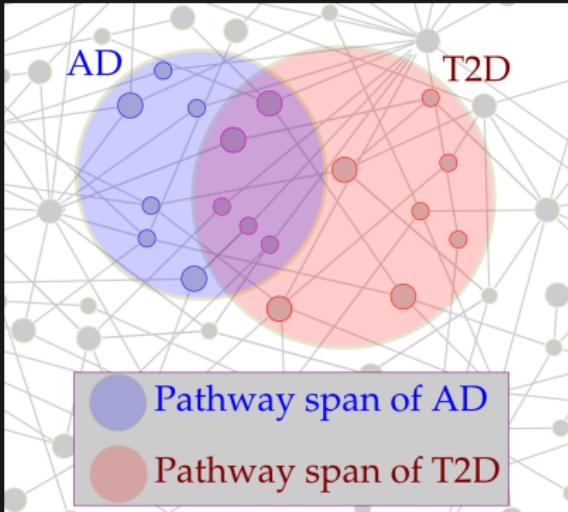
health.usnews.com/health-news/patient-advice/articles/2015/08/28/the-surprising-link-between-type-2-diabetes-and-alzheimers-disease

alzheimer's association®

alzheimer's disease and type 2 diabetes:

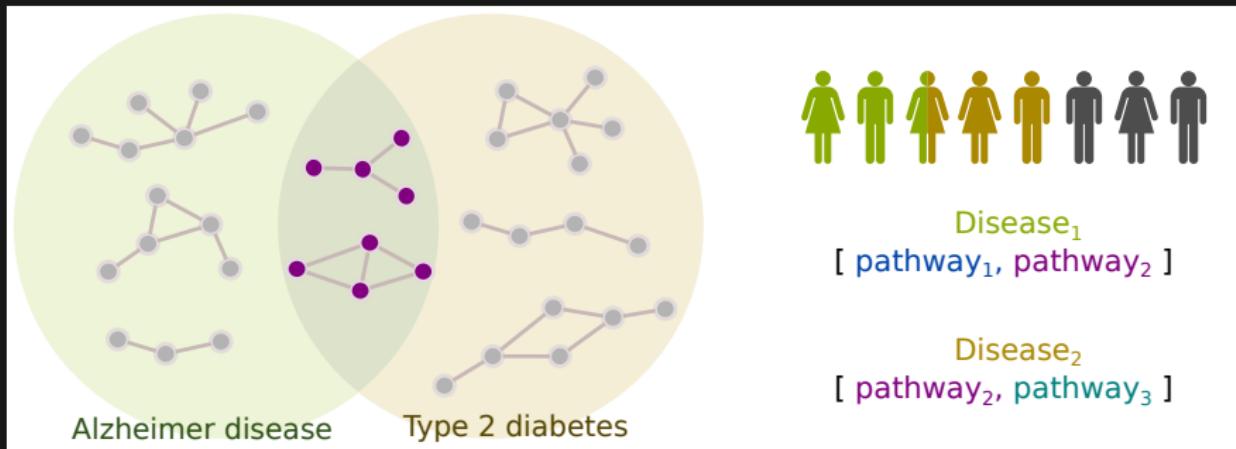
www.alz.org/national/documents/latino_brochure_diabetes.pdf

The pathway based approach



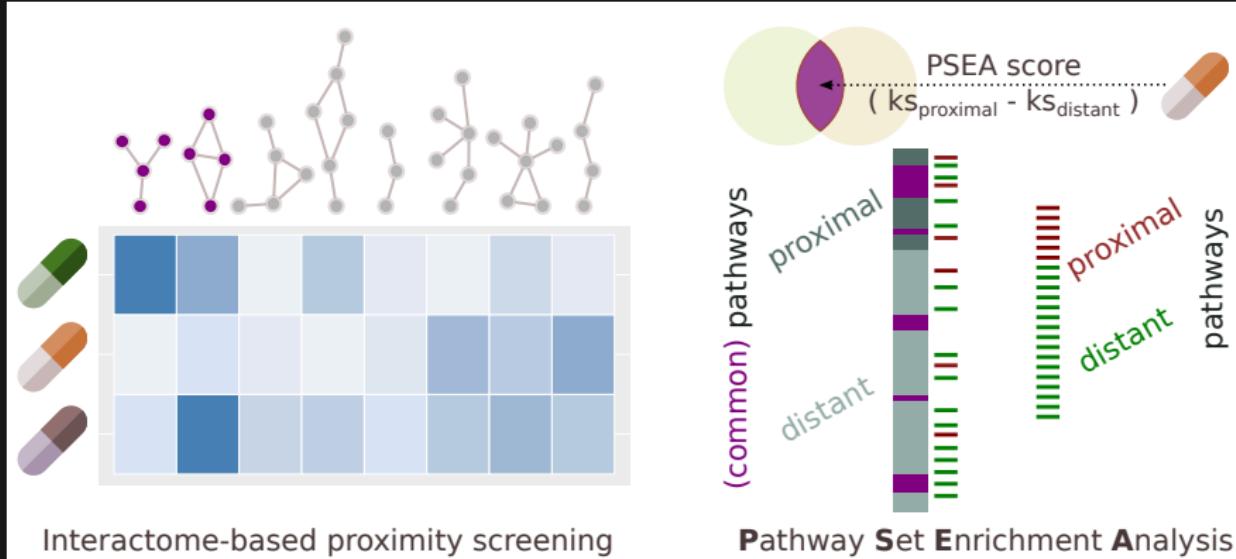
- Only one shared gene between AD and T2D
- Alternative: Pathways involved in the disease
 - Reactome pathways from MSigDB
 - Disease genes from OMIM and GWAS
- Human interactome from *Menche et al., 2015*

Pathway level commonalities between diseases



- Perturbations across various biological pathways give rise to diseases
- Existing methods focus on identifying those pathways via enrichment of perturbed genes
- Often only a handful of genes within a pathway that are involved in the disease (*Menche*, Guney* et al., 2017*)

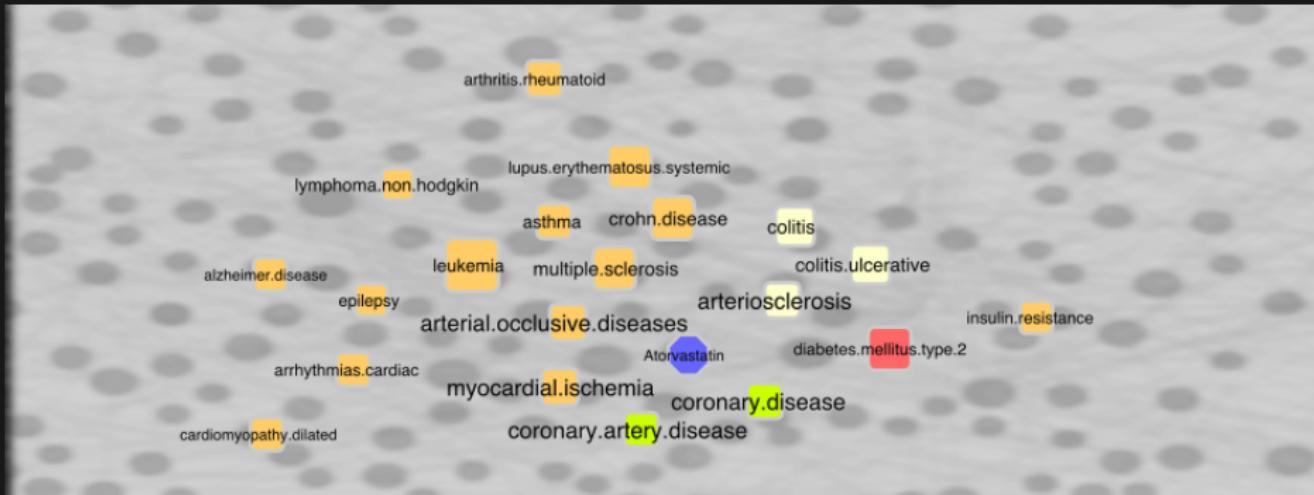
PSEA: Pathway Set Enrichment Analysis



A general framework for calculating the enrichment of pathways ranked with respect to *proximity* or *differential expression*

PSEA identifies **pathway sets** enriched in a disease as opposed to gene sets (GSEA)

Drug response heterogeneity



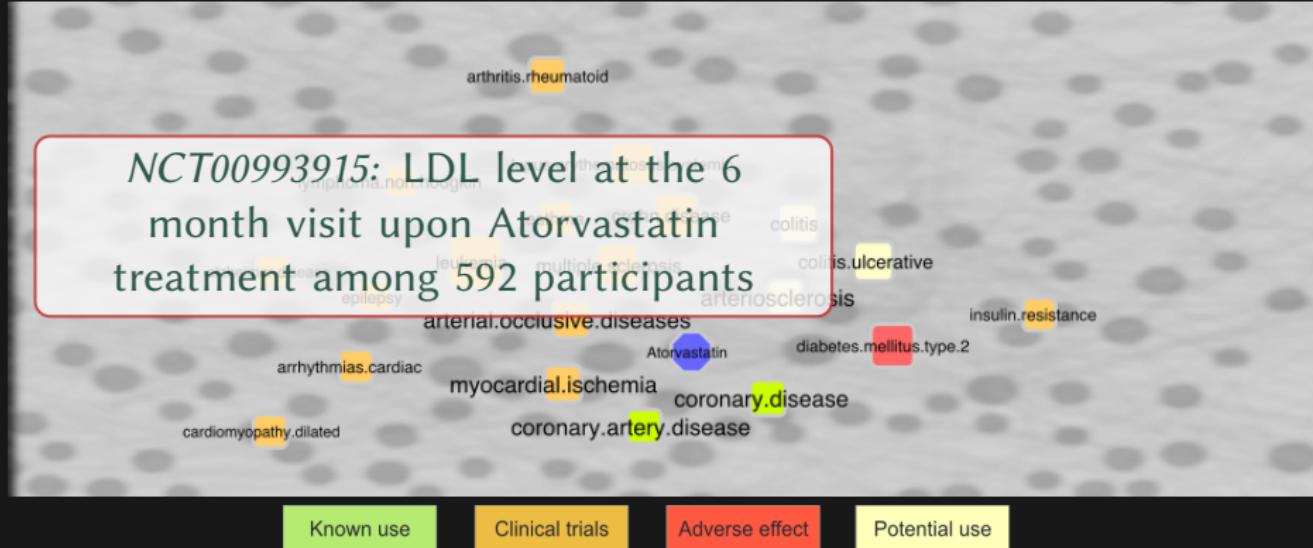
Known use

Clinical trials

Adverse effect

Potential use

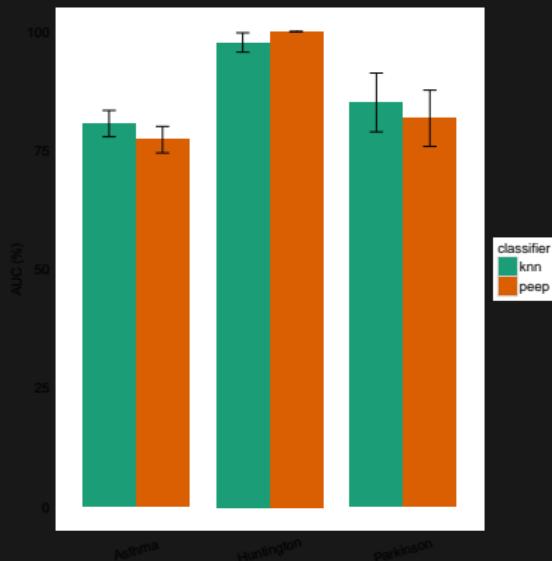
Drug response heterogeneity



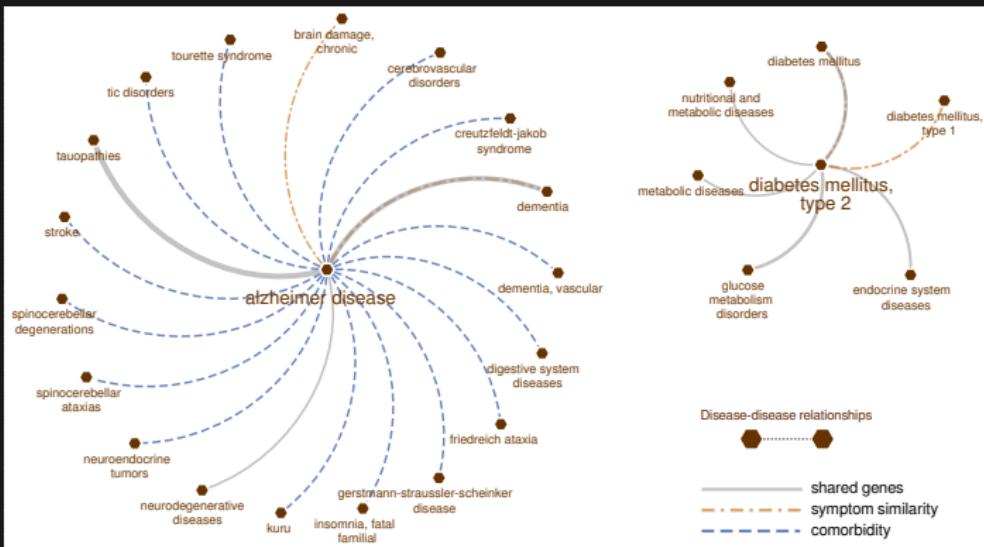
Before treatment: The average LDL level 179 mg/dL

After treatment: 52% of the participants had LDL \leq 100 mg/dL

Incorporating individualized expression differences



Leveraging diseasesome



Genetic and functional characterization
of disease-disease relationships

AD: 6 → 11 drugs

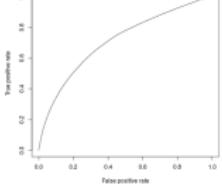
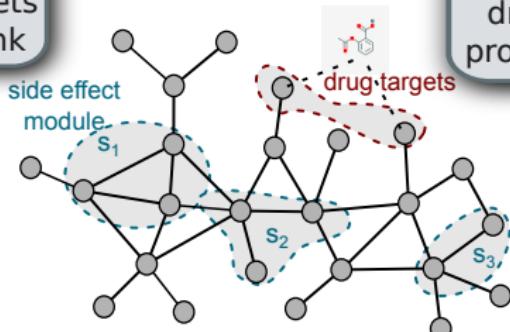
T2D: 21 → 23 drugs

- Common genes
- Shared symptoms
- Comorbidity

ProXide: Proximity based side effect detection

(i) Fetch drugs and their targets from DrugBank

(ii) Calculate drug-side effect proximity score (z)



(vi) Validate ranking using known drug side effects

(iii) Rank side effects based on proximity

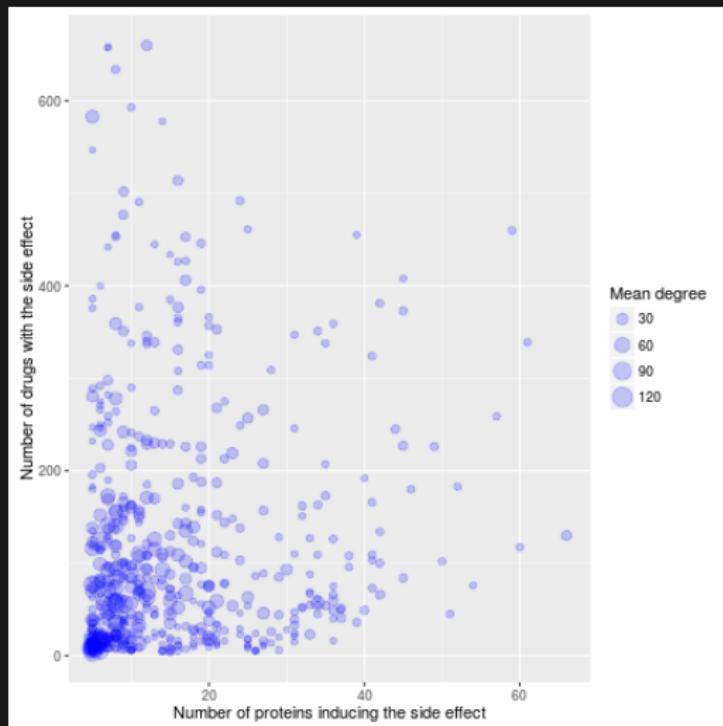
drug

S₂
S₁
⋮
S₃

ProXide data set

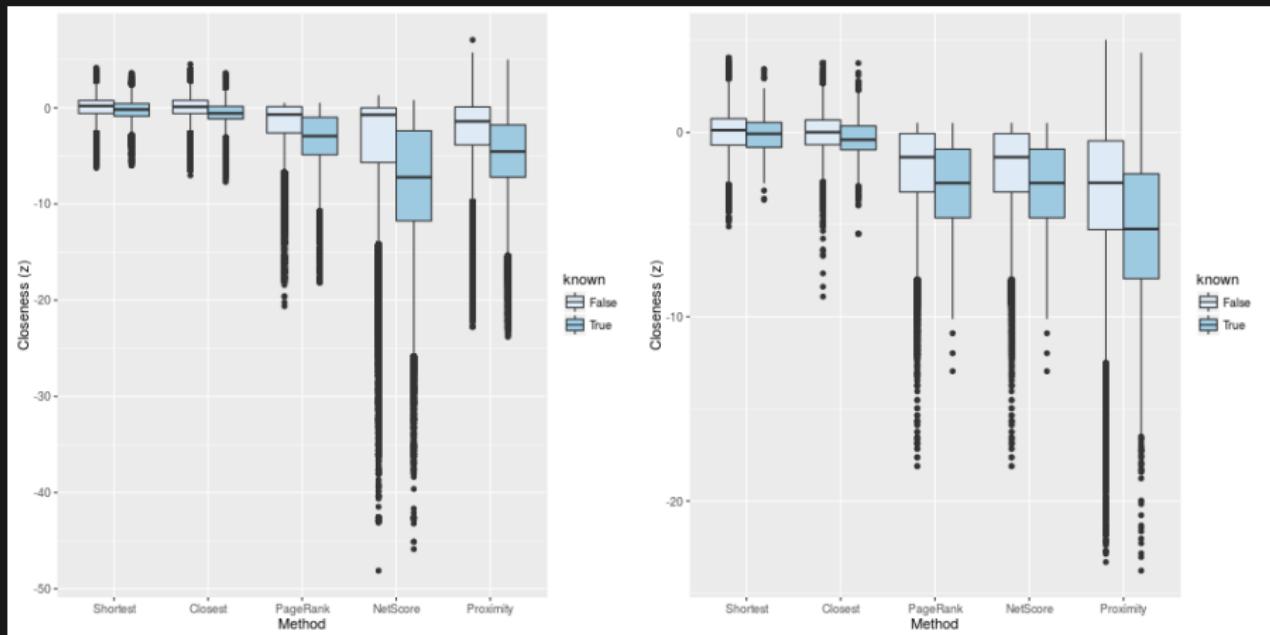
	SIDER	OFFSIDES
Number of drugs	817	269
Number of side effects	537	118
Number of known drug-side effect associations	64,885	2,060
Percentage of known associations	14.8%	6.5%

Side effect modules



Neither the number nor degrees of the proteins in the modules are not a good descriptor of observed side effects

Network-based closeness of side effects



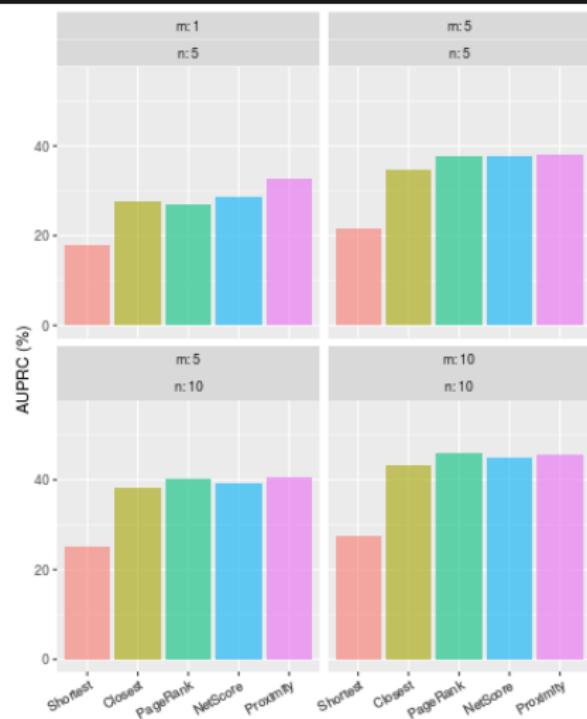
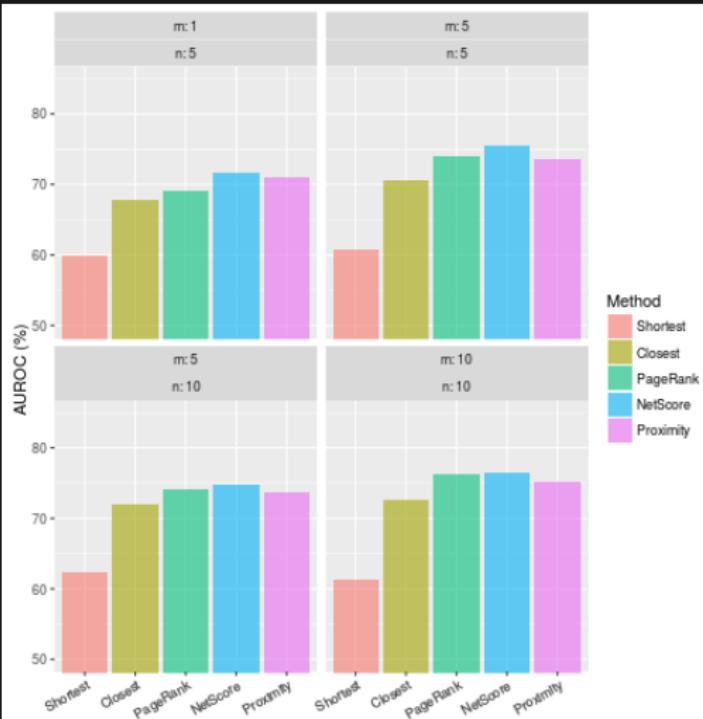
Prediction accuracy of network-based side effect detection

	AUROC (%)		AUPRC (%)		Correct at top (%)	
	SIDER	OFFSIDES	SIDER	OFFSIDES	SIDER	OFFSIDES
Shortest	59.8	53.9	17.8	7.1	15.9	8.2
Closest	67.9	57.7	27.6	8.5	79.6	28.6
PageRank	69.0	59.6	27.0	8.6	55.8	13.0
NetScore	71.7	61.9	28.8	9.6	52.1	14.5
Proximity	71.1	63.6	32.8	11.4	56.7	11.5

†Area under ROC curve (AUROC)

‡Area under Precision-Recall curve (AUPRC)

Robustness of network-based drug side effect detection



Top 10 side effects predicted for tamoxifen using ProXide

Rank	Side effect	in SIDER	ProXide score (z)
1	muscular weakness	0	-12.9
2	musculoskeletal discomfort	1	-12.3
3	alopecia	1	-12.1
4	neuropathy peripheral	0	-12.1
5	drug interaction	1	-11.7
6	hepatitis	1	-11.7
7	diarrhoea	1	-11.7
8	myalgia	1	-11.6
9	injury	1	-11.5
10	discomfort	1	-11.3