

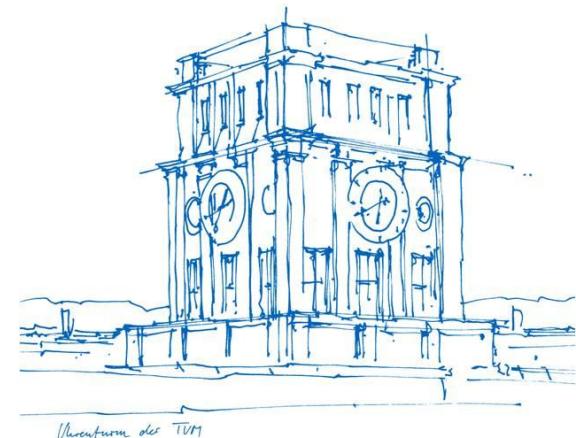


Drugst.One DREAM - Drug Repurposing through Expert Annotation and Modification

Lisa M. Spindler

BC2 2025

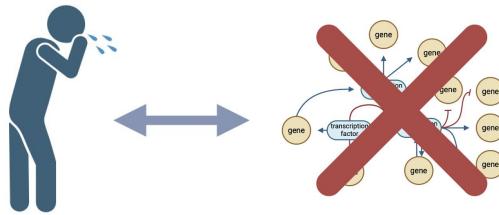
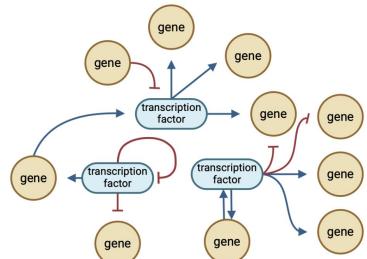
Basel, 08.09.2025





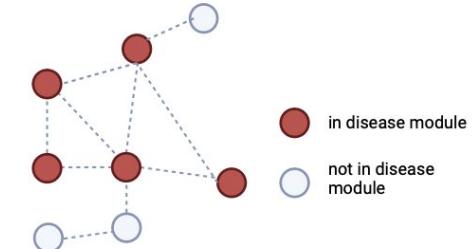
Introduction

Understanding the mechanisms of diseases



Disease understanding is limited by **unknown** biological mechanisms

Often **symptoms** treated rather than causes



Disease modules
(subnetworks of the interactome)
aim to uncover the **underlying mechanisms** within a **PPI** network



Introduction

Disease module refinement



Disease modules as basis for **drug repurposing**: Find new uses for existing drugs



Algorithmic **disease module inference** is only based on seed genes & the **interactome**



Expert refinement ensures **biological relevance** and actionable modules for **drug candidates**



Tools are key for support!
Biological context needed
Tool to easily manipulate networks required

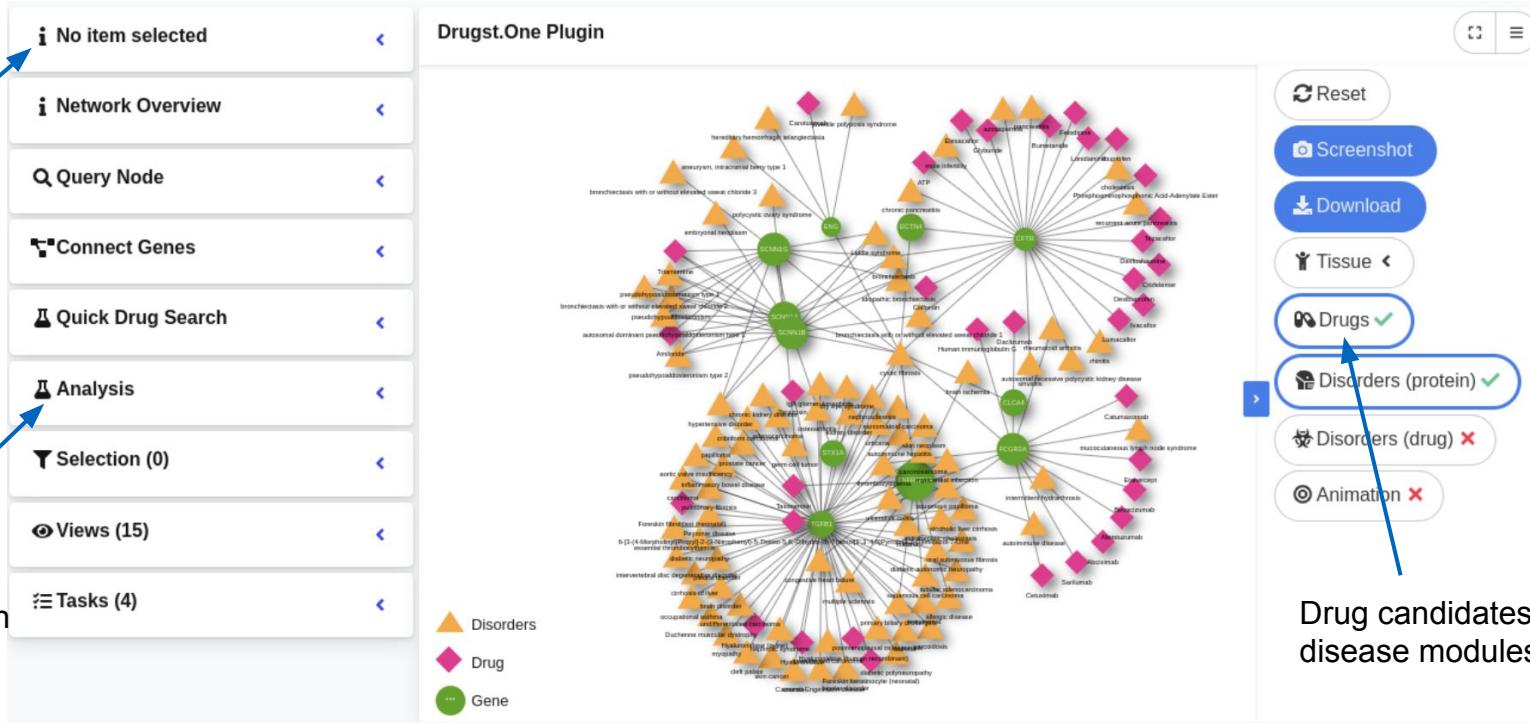


Drugst.One ‘Vanilla’

What is already available?

Additional protein/gene info

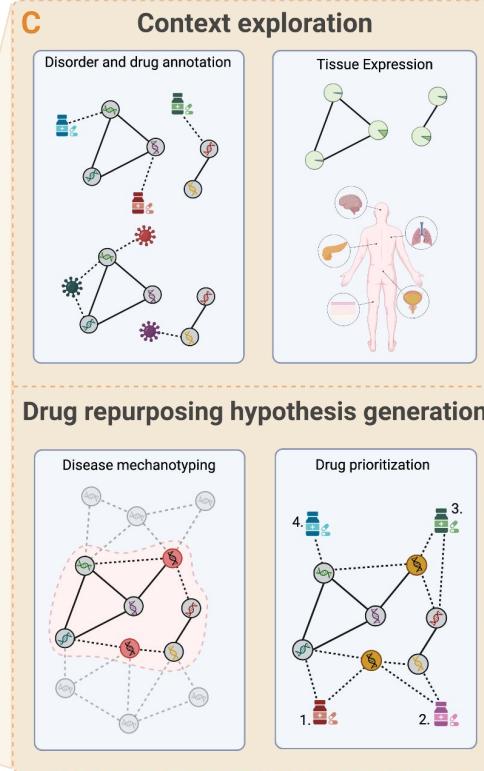
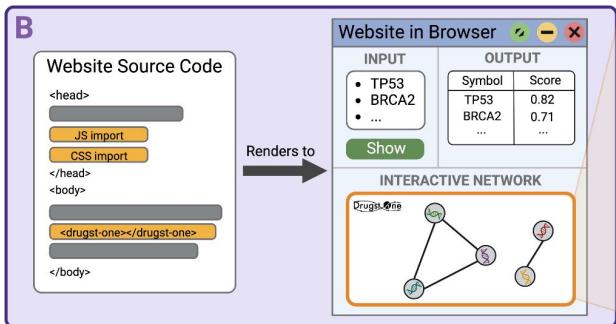
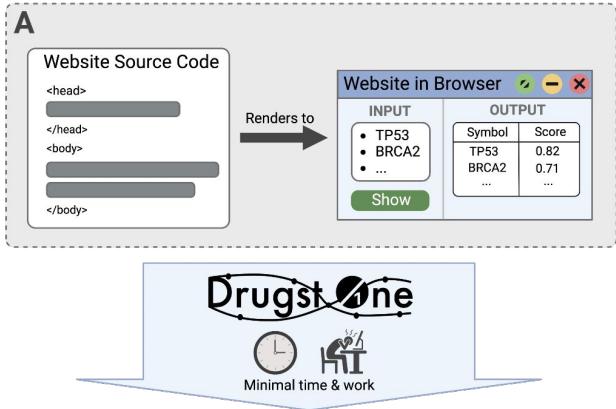
Disease module algorithms and drug prioritization



Disease module and drug/disease visualization



How does Drugst.One do differently?



- Integration** - Basic Drugst.One version needs 3 lines of code
- Configuration** - Versatile and user friendly:
 - Style and content customizable to fit host page
 - Interactive styling tool generates "copy-pasteable" configurations



Integration of Drugst.One

Add Drugst.One to your website

Step 1: Import

```
<head>
  <script src="https://cdn.drugst.one/latest/drugstone.js"></script>
  <link rel="stylesheet"
    href="https://cdn.drugst.one/latest/styles.css">
</head>
```

Step 2: Integrate & Configure

```
<drugst-one
  groups='{"nodeGroups": {"Protein": {"type": "Protein", "color": "#ff881f", "fontColor": "#ffffff", "groupName": "Protein", "shape": "ellipse"}}, "edgeGroups": {"PPI": {"color": "#111111", "groupName": "PPI"}}}'
  config='{"identifier": "symbol", "title": "Breast cancer example network"}'
  network='{"nodes": [{"id": "BRCA1", "label": "BRCA1", "group": "Protein"}, {"id": "BRCA2", "label": "BRCA2", "group": "Protein"}], "edges": [{"from": "BRCA1", "to": "BRCA2"}]}'>
</drugst-one>
```

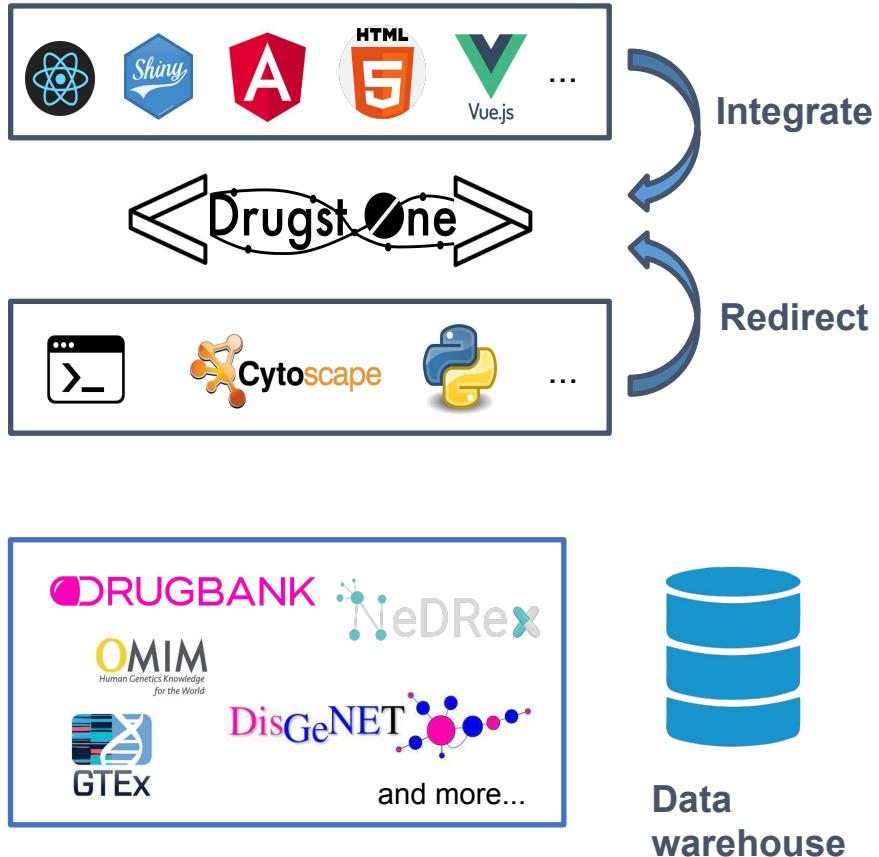
6

Customizing content and style using:

- Groups attribute
- Config attribute
- Network attribute



Drugst.One Initiative

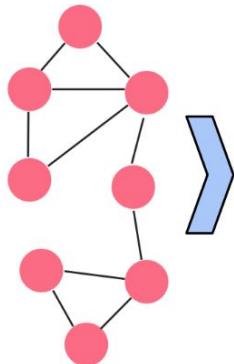




Drugst.One DREAM - Overview

Drug Repurposing through Expert Annotation and Modification

Candidate disease module



Drugst.One DREAM - Drug Repurposing through Expert Annotation and Modification

New Analyses

Community Detection

Pathway Enrichment

Context Visualization

Cellular Components

- Plasma membrane
- Cytoplasm
- Nucleus
- Multiple

Directed PPIs

Modification

Manual Editing

Edit Network

TP53

Add Protein



Property-Based Pruning

SPD

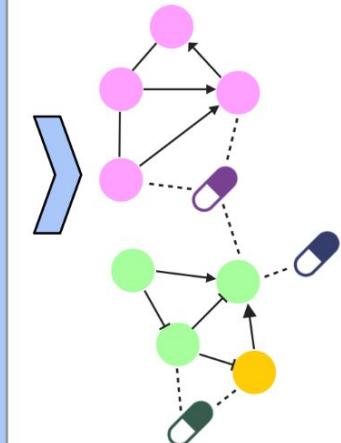
Select Prune Direction:

Greater than/equal

Prune based on range:

0.187

Refined disease module for drug repurposing





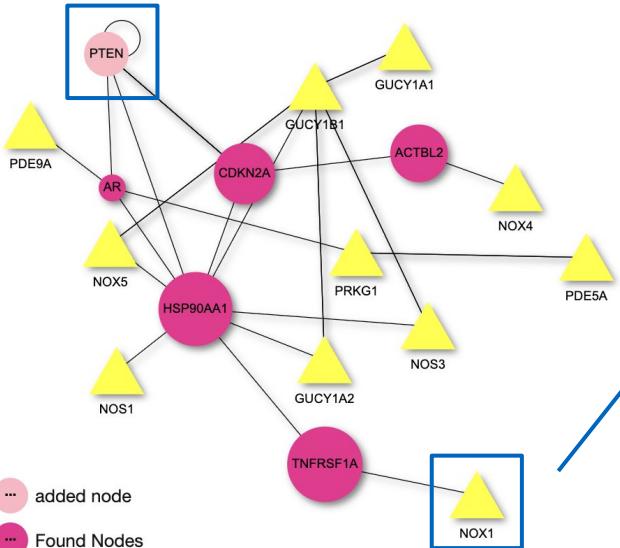
Network Manipulation

Add/delete nodes

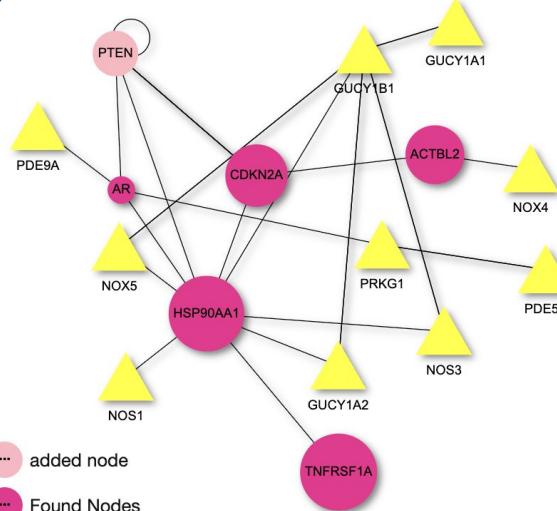
pten
PTEN F6KD01 ENSG00000171862 5728
PTEN P60484 ENSG00000171862 5728

add node

Add Protein



delete node



Name: NADPH Oxidase 1
Symbol: NOX1
Uniprot: Q9Y5S8 A6NGA6
Ensembl: ENSG0000007952
Entrez: 27035
Layer: Unknown
Reviewed: False, True
Properties:
degreeInNetwork: 1
degreeInPpi: 37
localClusteringCoefficient: 0
spd: 0.02702702702702703
Group: Default Node Group
Links: IID
 Selected Off



File Upload

Upload .sif, .csv, .graphml or .gt

Upload Network

Upload Network File

Datei auswählen seed_genes_NOX5.sif

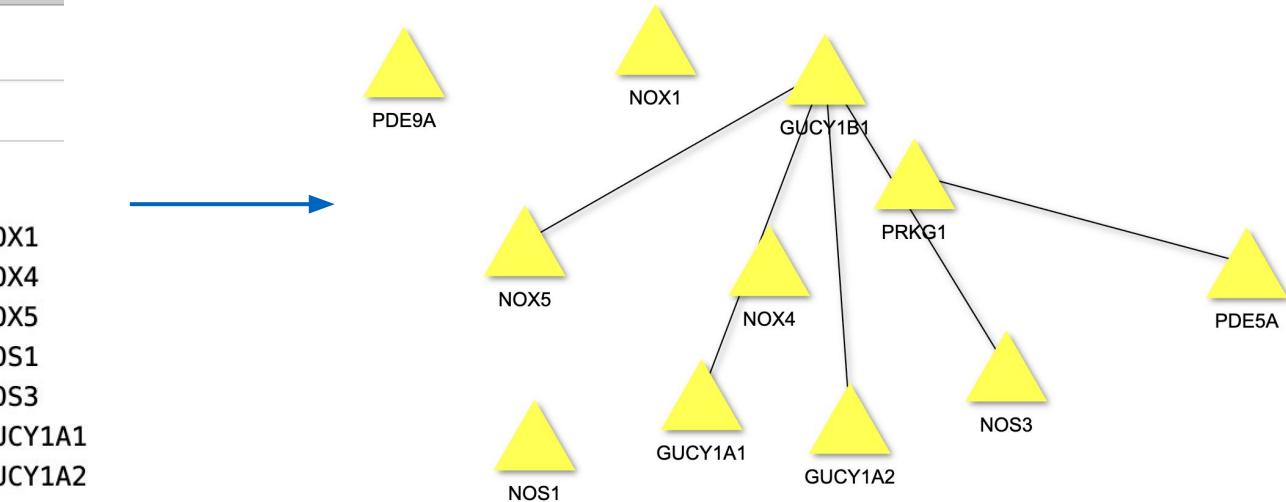
ID-Space

symbol

 Launch

Close

- 1 NOX1
- 2 NOX4
- 3 NOX5
- 4 NOS1
- 5 NOS3
- 6 GUCY1A1
- 7 GUCY1A2
- 8 GUCY1B1
- 9 PDE5A
- 10 PDE9A
- 11 PRKG1

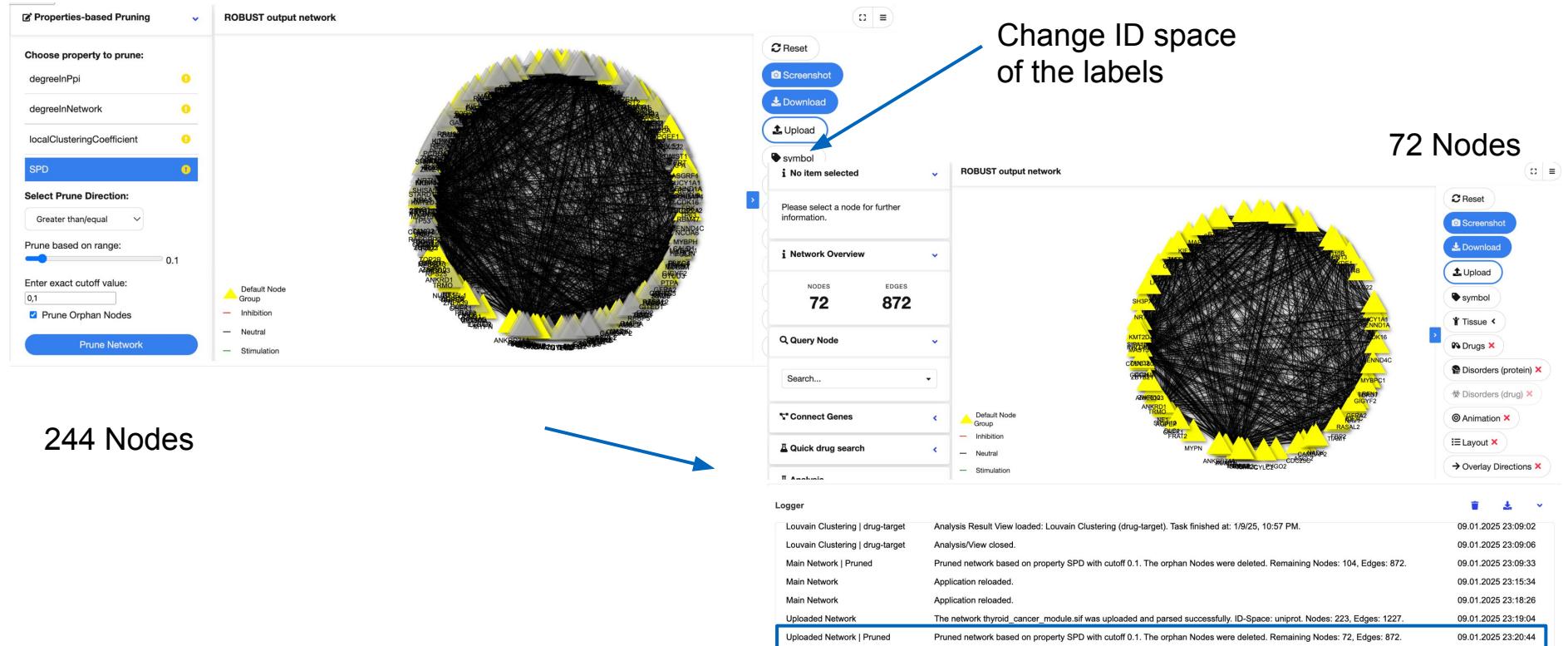


Edges auto filled from the PPI



Pruning

Filter the disease module nodes



Logger for reproducibility



Community Detection

Cluster the disease module into subnetworks

Perform pathway enrichment
on this cluster

Clustering

Louvain Clustering
 Leiden Clustering

About Leiden Clustering

Leiden Clustering is a community detection algorithm that is performed on undirected networks. It is recommended to select all nodes of the graph.

Ignore isolated nodes in Clustering

Ignore isolated nodes

Isolated nodes will not be considered in the clustering algorithm. They would form their own cluster anyways.

Random Number Generator Seed

Enter a seed or leave empty

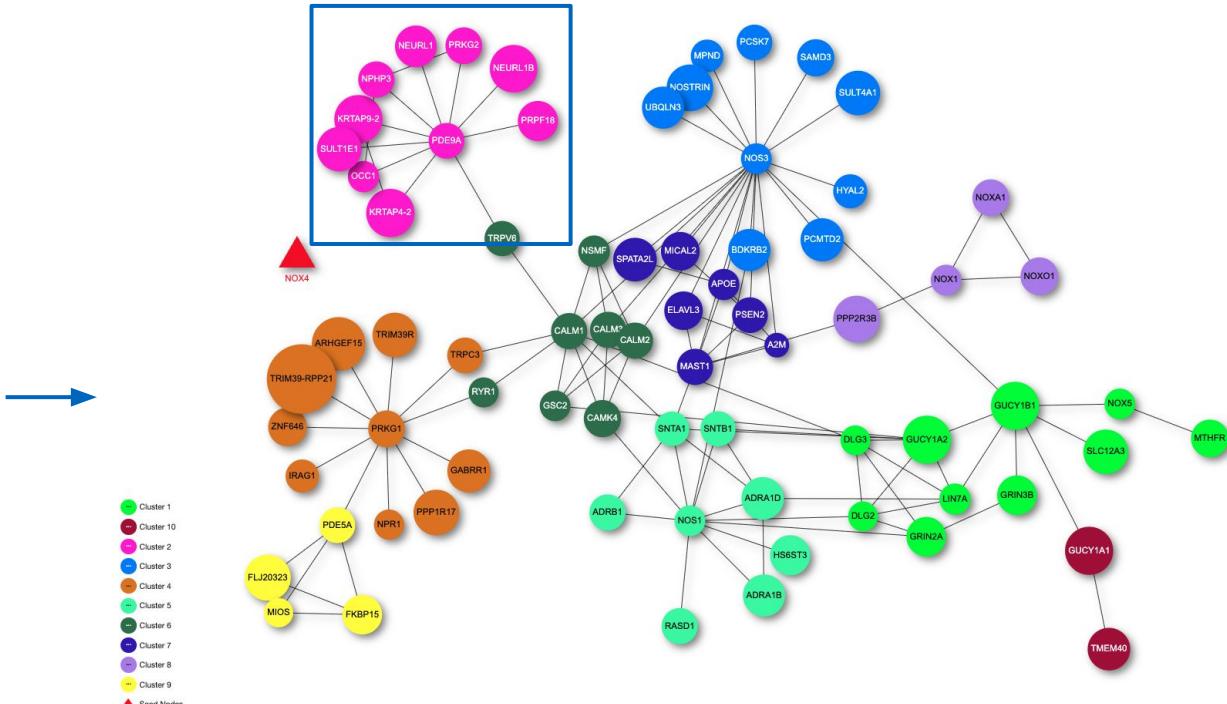
Optional: Provide a seed for the random number generator, or leave empty to auto-generate one.

Max Cluster Size

10

Optional: Provide a maximum cluster size or leave empty for no limit.

Launch Close





Pathway Enrichment - Based on Cluster Table views

Overlapping nodes
Part of the network & the pathway

Visualize pathway

Pathway enrichment								
Geneset Pathway Overlapping Genes Pathway Size Overlap Percentage Adjusted p-value Odds ratio								
▶ reactome	Constitutive Signaling By NOTCH1 HD Domain Mutants	▼	2 15	13.33%	4.2e-4	422.54		
Symbol: NEURL1B	Uniprot: A8MQ27	Entrez: 54492	ENSG:	Protein Name: E3 ubiquitin-protein ligase NEURL1B	Layer: Cytoplasm			
Symbol: NEURL1	Uniprot: O76050	Entrez: 9148	ENSG: ENSG00000107954	Protein Name: E3 ubiquitin-protein ligase NEURL1	Layer: Plasma membrane			
▶ reactome	cGMP Effects	▶	2 15	13.33%	4.2e-4	422.54		
▶ reactome	Nitric Oxide Stimulates Guanylate Cyclase	▶	2 21	9.52%	4.2e-4	292.44		
▶ reactome	NOTCH2 Activation And Transmission Of Signal To Nucleus	▶	2 21	9.52%	4.2e-4	292.44		

{

Link to external pathway website

Proteins

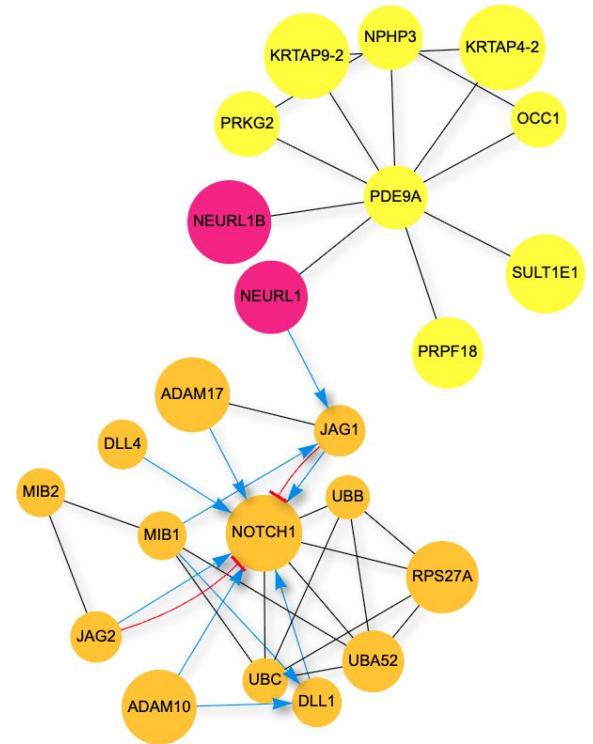
	Symbol ↑↓	Label ↑↓	Name ↑↓	Cluster ↑↓	Cellular Component ↑↓	Enrichment Score ↑↓	Enrichment Rank ↑↓
□	UBC	UBC	polyubiquitin-C		Multiple (Nucleus, Cytoplasm)	0.457	1
□	DLL1	DLL1	delta-like protein 1		Plasma membrane	0.457	1
□	RPS27A	RPS27A	ubiquitin-ribosomal protein eS31 fusion protein		Multiple (Nucleus, Cytoplasm)	0.457	1
□	MIB1	MIB1	E3 ubiquitin-protein ligase MIB1		Cytoplasm	0.457	1
□	NEURL1B	NEURL1B	E3 ubiquitin-protein ligase NEURL1B		Cytoplasm	0.457	1

Pathway enrichment scores
Capture occurrence of nodes in the enriched pathways



Pathway Enrichment

Pathway visualization with context



Pathway in combination with the network

Pathway: Constitutive Signaling By NOTCH1 HD Domain Mutants (Reactome)

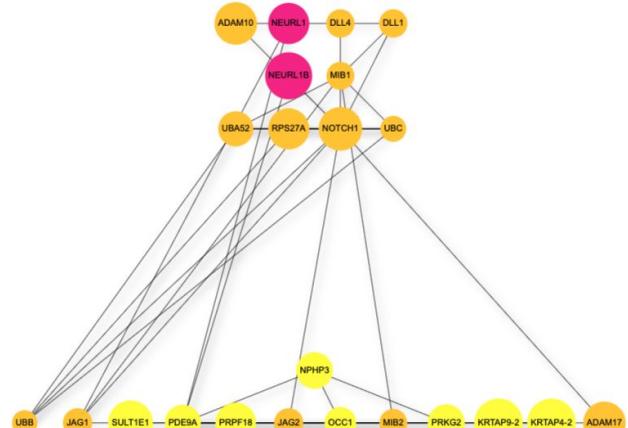
Plasma membrane

Cytoplasm

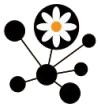
Multiple

Other

Unknown



Cellular component layout



Use Case: NOX5 Module

First neighbors

Settings for the Analysis

Protein-Protein Interaction DB ②

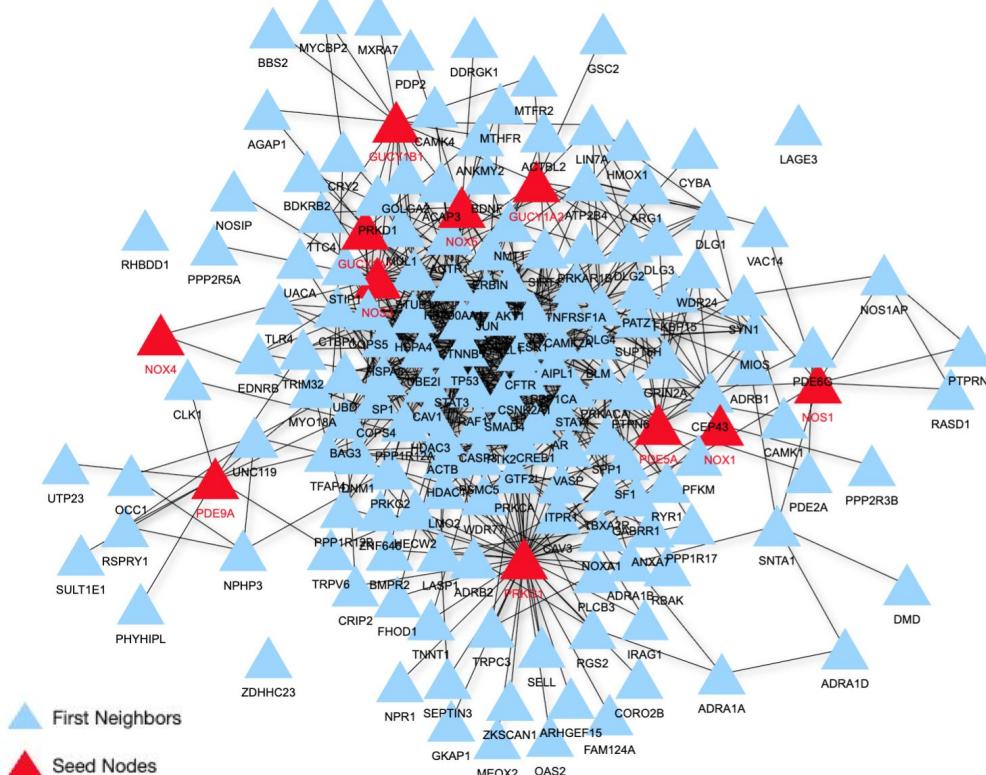
STRING ▾

Only reviewed proteins ② :

Only approved drugs ② :

Seed Genes

NOX genes &
NO-cGMP-related proteins



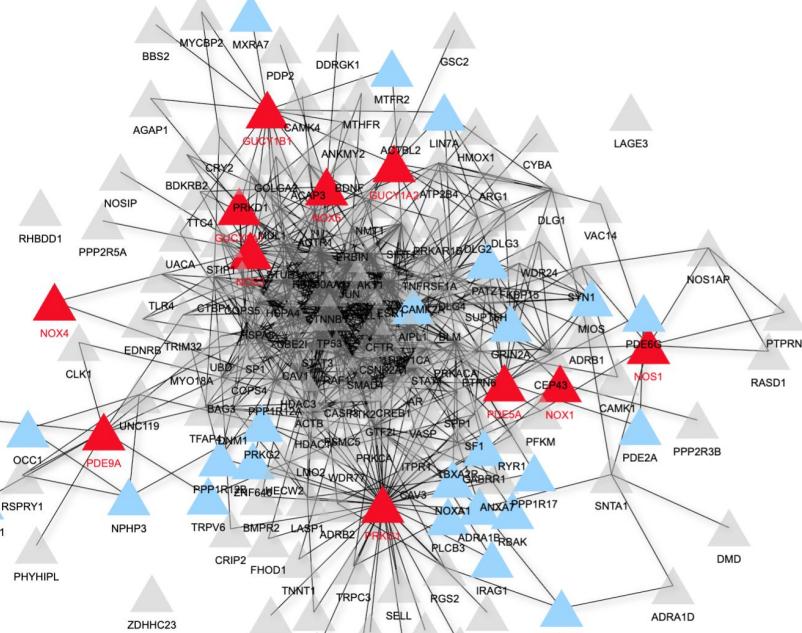
First neighbors



Use Case: NOX5 Module

Pruning based on SPD

$$\text{SPD}(v) = \frac{\deg_{\text{sub}}(v)}{\deg_{\text{full}}(v)}$$



First Neighbors

Seed Nodes

spd

Select Prune Direction:

Greater than/equal

Prune based on range:

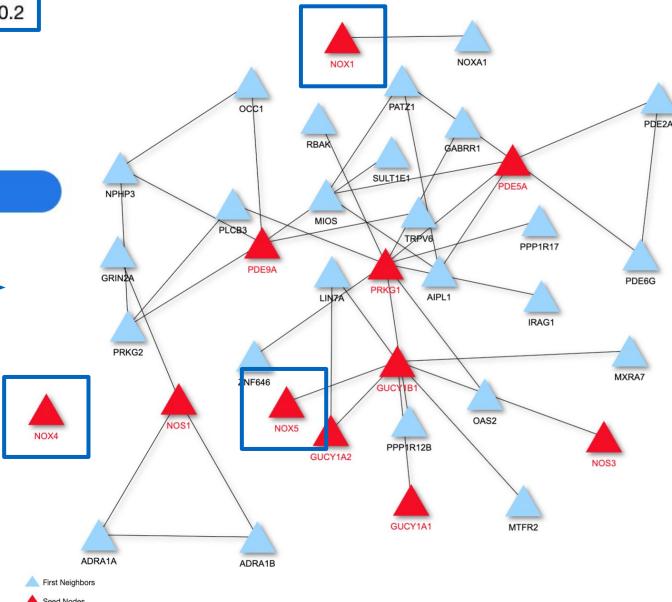
0.2

Enter exact cutoff value:

0.2

Prune Orphan Nodes

Prune Network



First Neighbors

Seed Nodes

Reproduced results



Use Case: NOX5 Module

Cellular component layout & candidate drugs

Plasma membrane

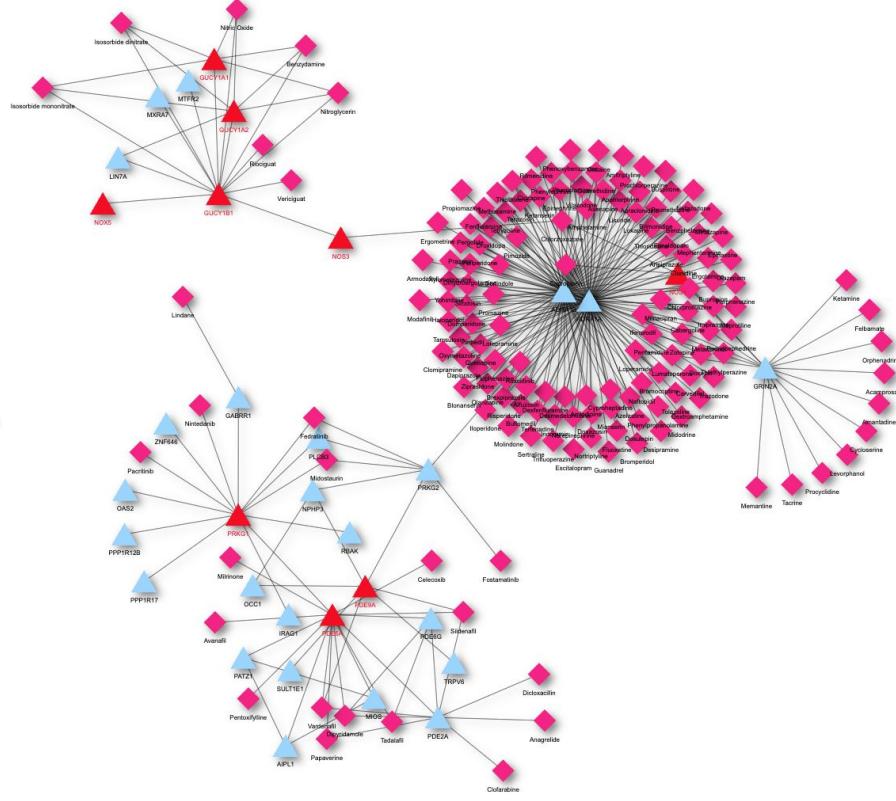
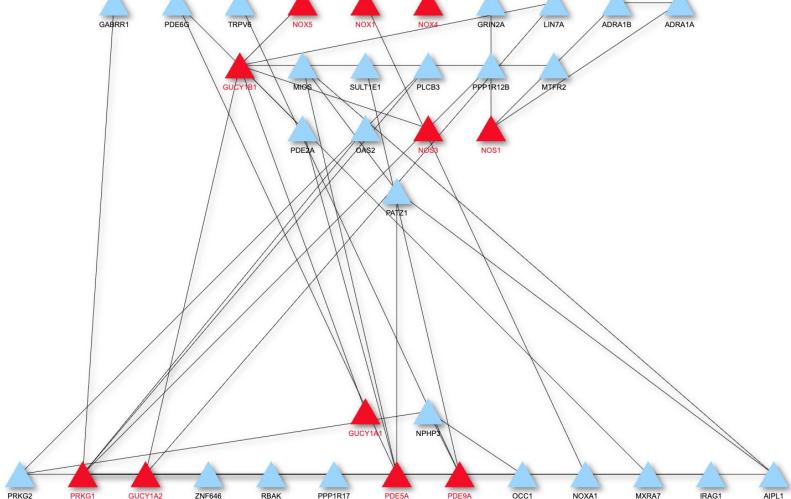
Cytoplasm

Multiple

Nucleus

Other

Unknown

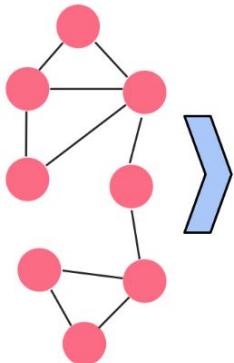




Summary Drugst.One DREAM

Successful implementation for disease module refinement

Candidate disease module



Drugst.~~One~~ DREAM - Drug Repurposing through Expert Annotation and Modification

New Analyses

- Community Detection**: A network graph showing two clusters of green and magenta nodes.
- Pathway Enrichment**: A network graph showing various proteins (e.g., NOS, PDE5A, GSK3B) and their interactions.

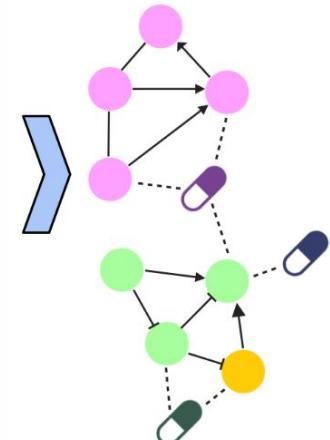
Context Visualization

- Cellular Components**: A network graph showing interactions between proteins across different cellular compartments: Plasma membrane, Cytoplasm, Nucleus, and Multiple.
- Directed PPIs**: A network graph showing directed interactions between specific proteins like AKT1, GSK3B, and GAPDH.

Modification

- Manual Editing**: A section for editing the network, showing a protein node for TP53 with options to "Edit Network", "Add Protein", and a trash can icon.
- Property-Based Pruning**: A section for pruning the network based on properties like SPD, with options to "Select Prune Direction" (Greater than/equal) and "Prune based on range" (0.187).

Refined disease module for drug repurposing





Thanks! Acknowledgments



DaiSyBio

Contact us: Lisa.spindler@tum.de | Markus.List@tum.de



Johannes Kersting



Quirin Manz



Michael Hartung



Andreas Maier



Zeinab M. Mamdouh



Zina Piper



Ana I. Casas



Jan Baumbach



Markus List



DIGEST

In silico validation of disease and gene sets,
clusterings, or subnetworks

Andreas Maier

BC2 2025

Basel, 08.09.2025





DIGEST (Motivation)

The hurdle of drug repurposing research translation

Drug repurposing candidates → |

?

→ Clinical validation

Existing evaluation options:

- Literature confirmation of predicted drug-disease pairs?
- Clinical trials registered for predicted drug-disease combinations?
- Statistical significance evaluation of found disease modules & ranked drugs
- Enrichment based solutions for disease modules

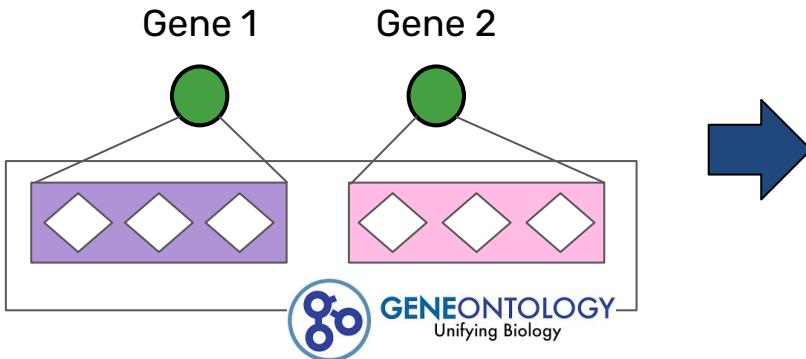
→ Lacking network-medicine & drug repurposing specific in silico validation options



DIGEST

In silico validation of disease and gene sets,
clusterings, or subnetworks

- pairwise similarity (S) based on functional coherence



Jaccard Index

$$S(JI) = \frac{\text{Intersection}(\text{purple}, \text{pink})}{\text{Union}(\text{purple}, \text{pink})}$$

OR

Overlap Coefficient

$$S(OC) = \frac{\text{Intersection}(\text{purple}, \text{pink})}{\text{Min}(\text{purple}, \text{pink})}$$

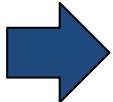
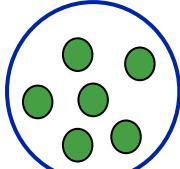


DIGEST

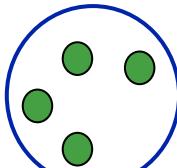
In silico validation of disease and gene sets,
clusterings, or subnetworks

- Functional coherence score (F)

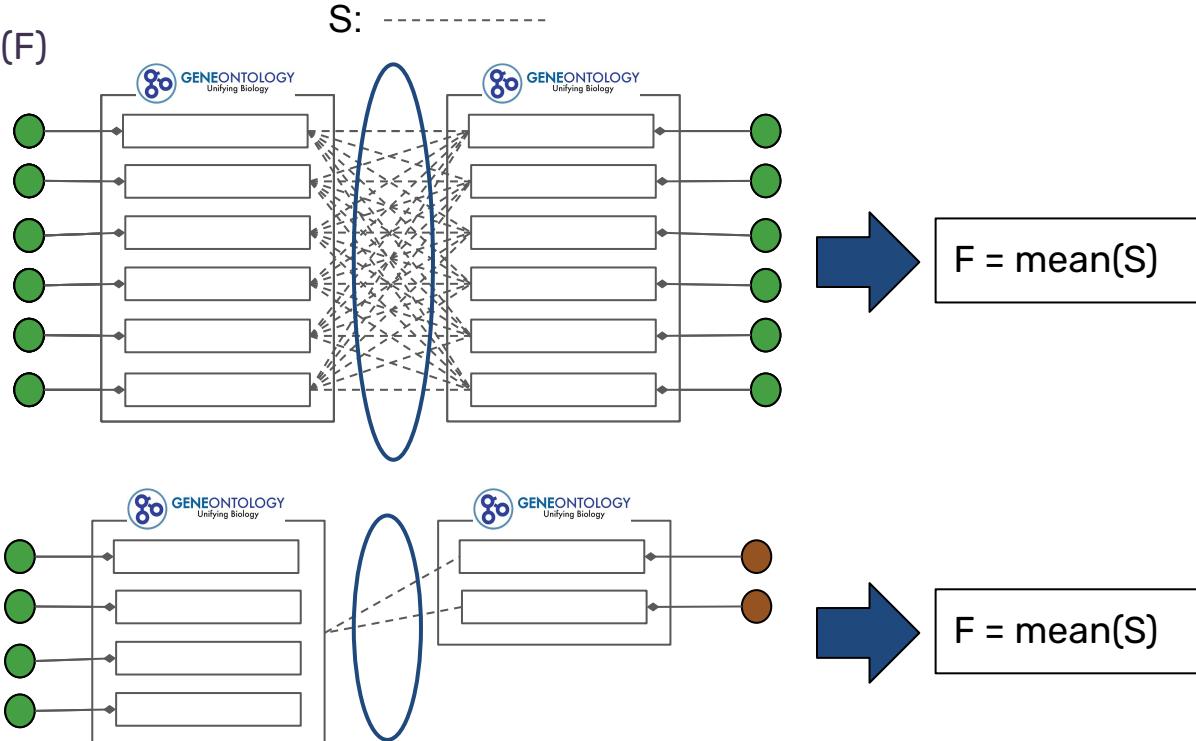
- reference-free



- against reference:



Reference

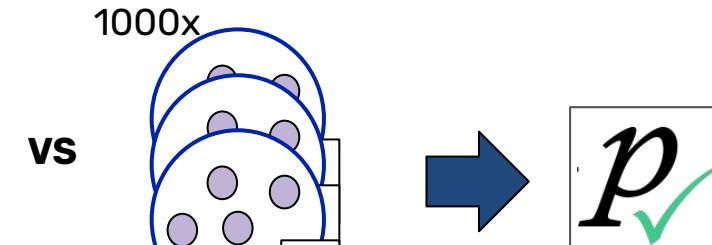




DIGEST

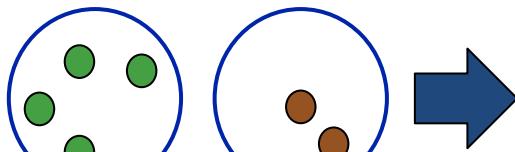
In silico validation of disease and gene sets,
clusterings, or subnetworks

- Computation of empirical P-Value against random background model
 - reference-free

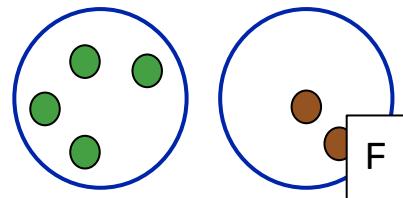


p ✓

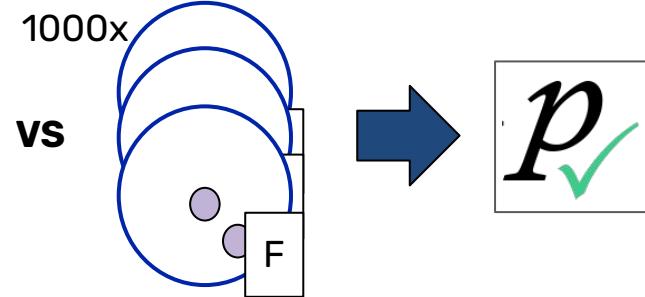
- against reference:



Reference



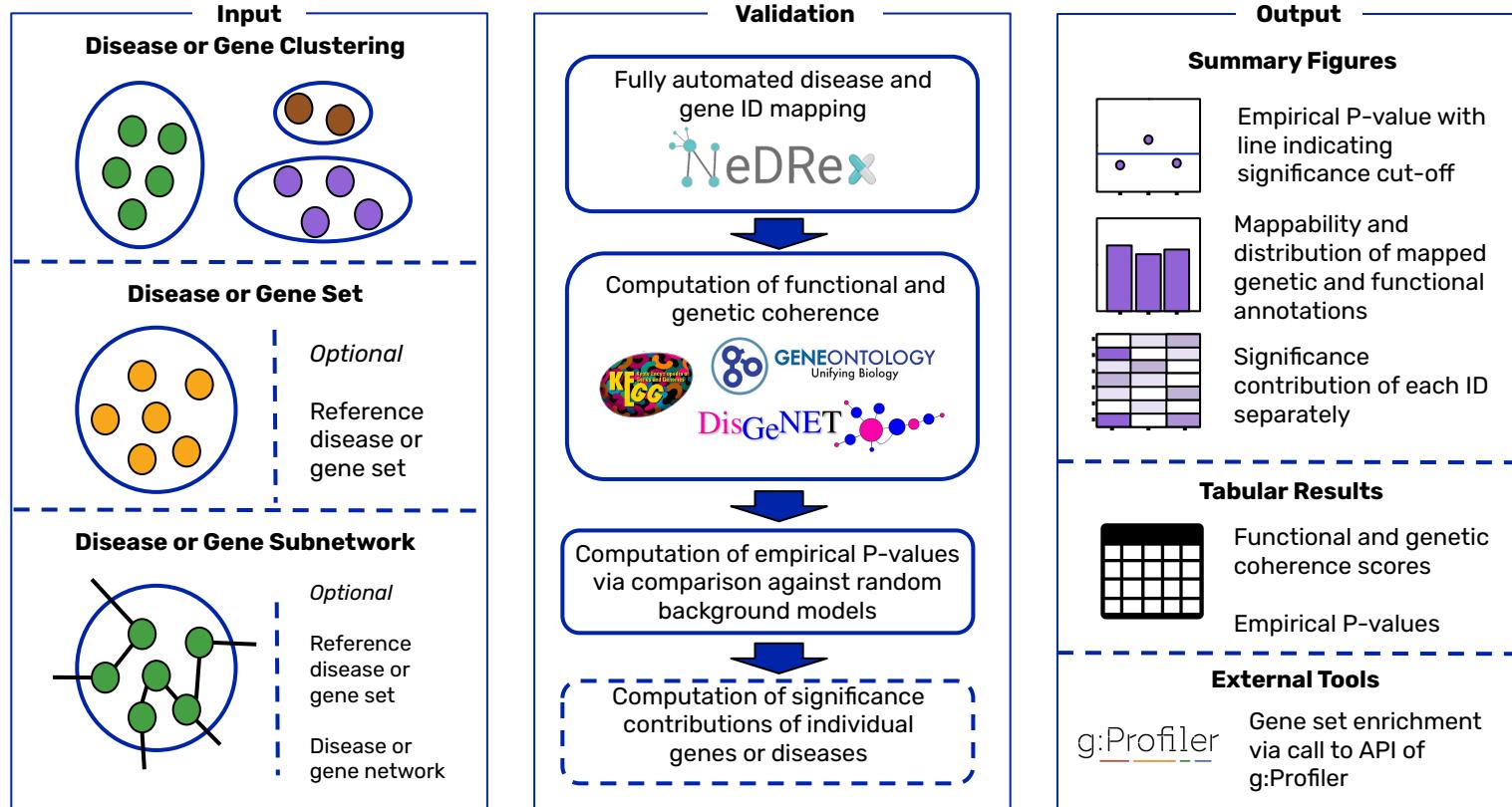
Reference



p ✓



DIGEST - Complete Workflow



Kanehisa, M, et al. (2017). KEGG: new perspectives on genomes, pathways, diseases and drugs, *Nucleic Acids Res.*
Piñero, J, et al. (2019). The DisGeNET knowledge platform for disease genomics: 2019 update, *Nucleic Acids Res.*



Thanks

Researchers

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Prof. Dr. David B. Blumenthal

Prof. Dr. Jan Baumbach

Contact: andi@cosy.bio



<https://digest-validation.net/>

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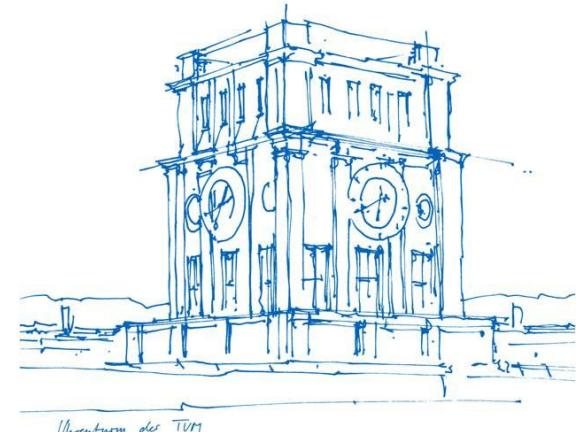
DrugRepoChatter & ChatDRex

The future of Drug Repurposing research

Andreas Maier

BC2 2025

Basel, 08.09.2025



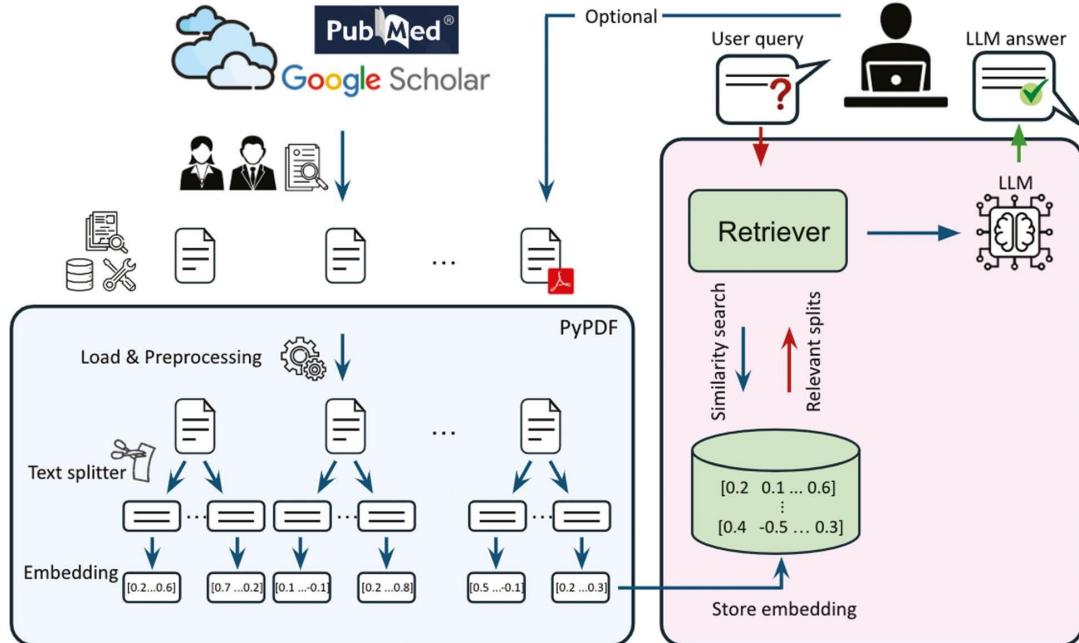


LLM-assisted tools for drug repurposing

A natural language-driven expert on drug repurposing

Project Goals:

- A **chat bot** for drug repurposing related matters
- Built on **expert curated literature**
- **Retrieval Augmented Generation (RAG)** for information-backed answer generation





LLM-assisted tools for drug repurposing

A natural language-driven expert on drug repurposing

Choose a page

- ▷ Login
- ▷ Sign up
- ▷ Q&A**
- ▷ Configure knowledge base
- ▷ About

[logout](#)

DrugRepoChatter



Show texts in original docs

DrugRepoChatter

Questions and Answering with sources

Index loaded successfully



DrugRepoChatter

Hi there, how can I help?

Your question:

Or choose a suggested question:

[Clear Chat](#)



ChatDRex

A Chat-based Drug Repurposing explorer

Suewer, S., Bagemil, K., et al., 2025, in preparation

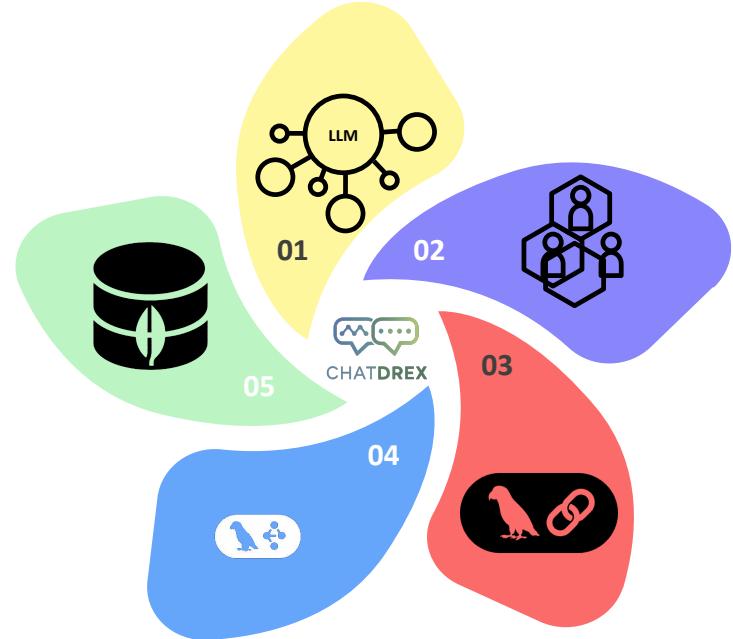


Requirements towards an integrated solution

A Chat-based Drug Repurposing explorer

Relevant functions and resources:

- Disease-gene selection (=> *databases*)
- Disease module and drug repurposing candidate prediction (=> *APIs*)
- In-silico validation (=> *APIs*)
- Result contextualization (=> *literature search*)





The Technologies and Framework

A Chat-based Drug Repurposing explorer

Technologies used:

- Retrieval Augmented Generation
- Model Context Protocol
- Multi-Agent Frameworks
- LangChain & LangGraph



The goal of ChatDRex

A Chat-based Drug Repurposing explorer

B

Which genes are associated with **Huntington's disease?**





Acknowledgments

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Simon Süwer

Sylvie Baier

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Prof. Dr. Harald H. H. W. Schmidt

Prof. Dr. Markus List

Prof. Dr. Jan Baumbach

...and many more



ChatDRex

Tool link in Preprint



Preprint on arxiv.org SOON!



DrugRepoChatter



repo4.eu/the-platform/drugrepochatter/

10.58647/DRUGREPO.24.2.0014

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Contact: andi@cosy.bio



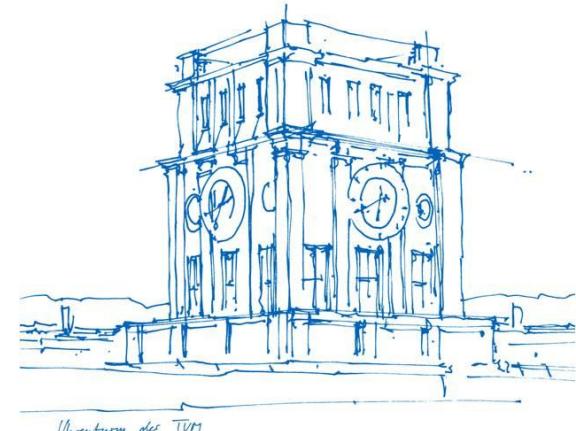
Data Science in Systems Biology
TUM School of Life Sciences
Technical University of Munich

Hands-On Session

Andreas Maier & Lisa M. Spindler

BC2 2025

Basel, 08.09.2025





Follow our Live Demo - NOX5 Use Case

<https://drugst.one/standalone>



Tutorial Overview:

1. Upload .sif with seed genes
(data/DrugstOne_DREAM/seed_genes_NOX5.sif)
2. Settings for analysis
3. First neighbors task
4. Pruning on SPD value
5. Cellular component layout + Overlay directed edges
6. Leiden clustering
7. Pathway enrichment

Try out Drugst.One DREAM