

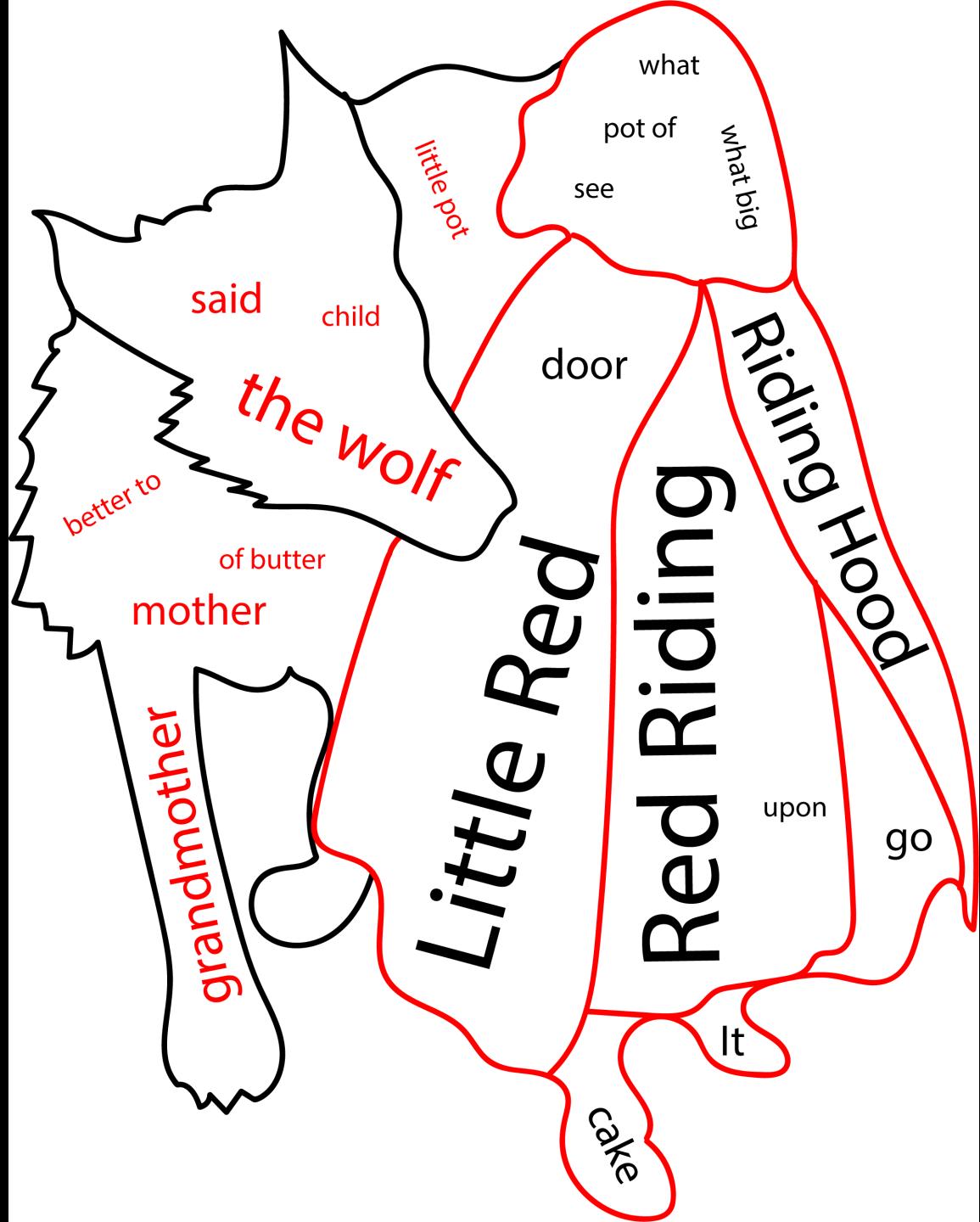


Metaboverse:

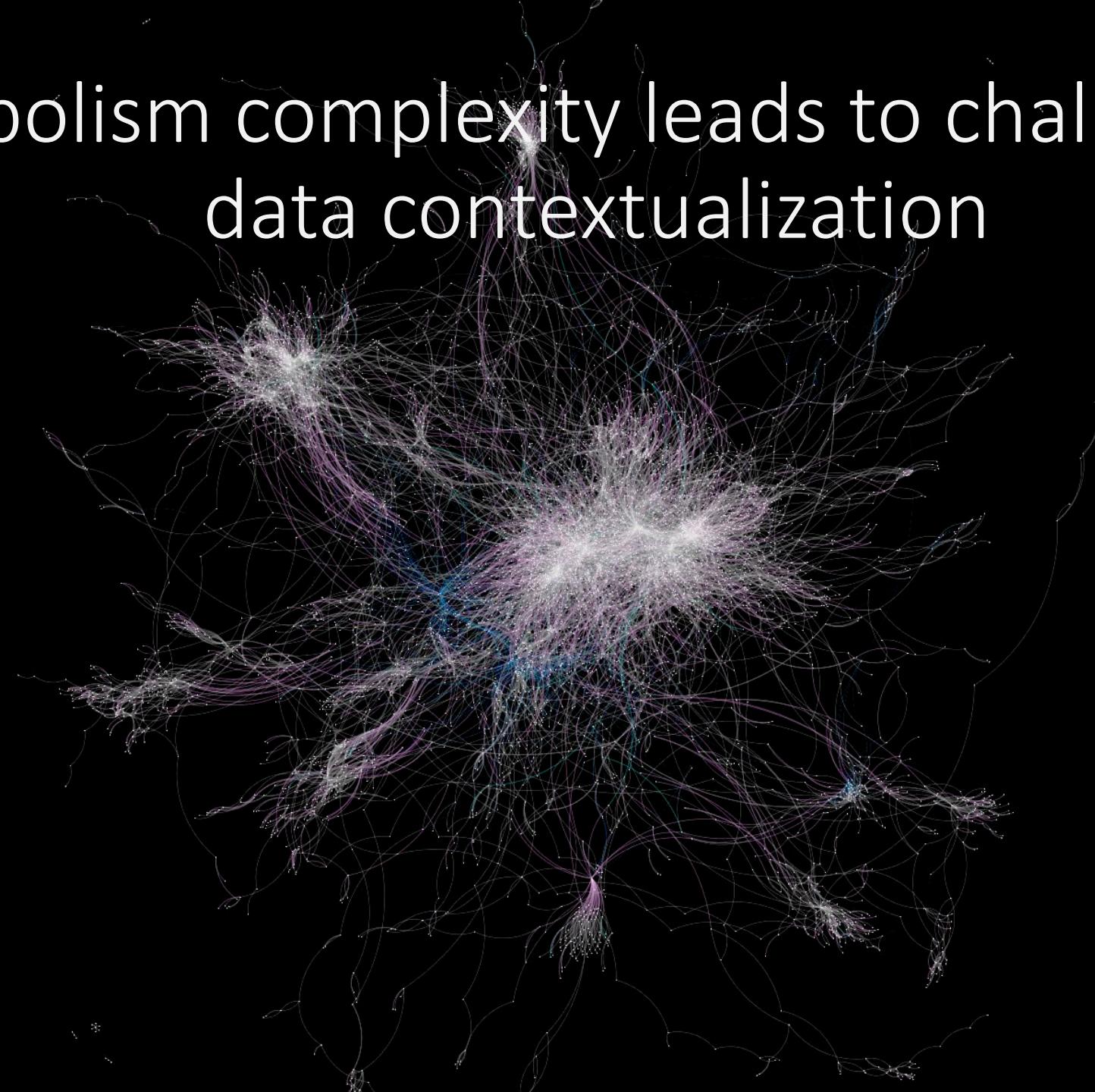
Contextualizing metabolic patterns and
revealing disease-relevant signatures



@jordanberg0
@RutterLab

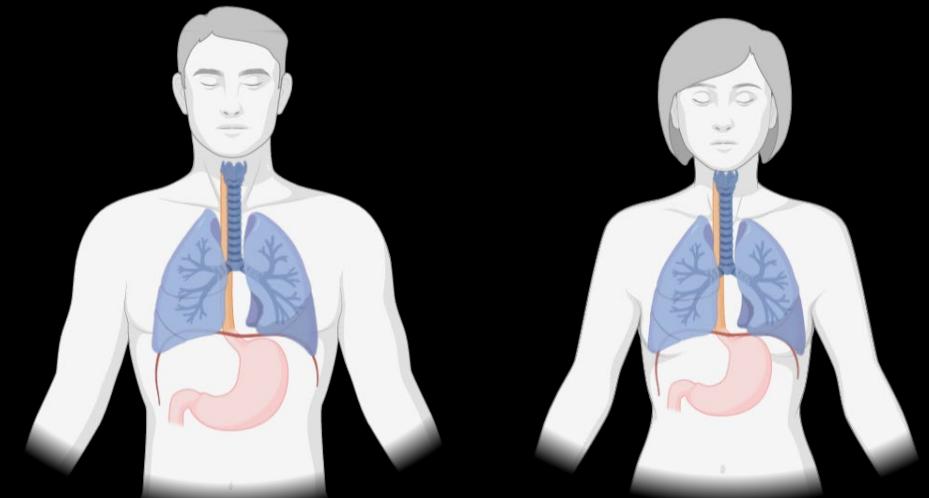


Metabolism complexity leads to challenges in
data contextualization

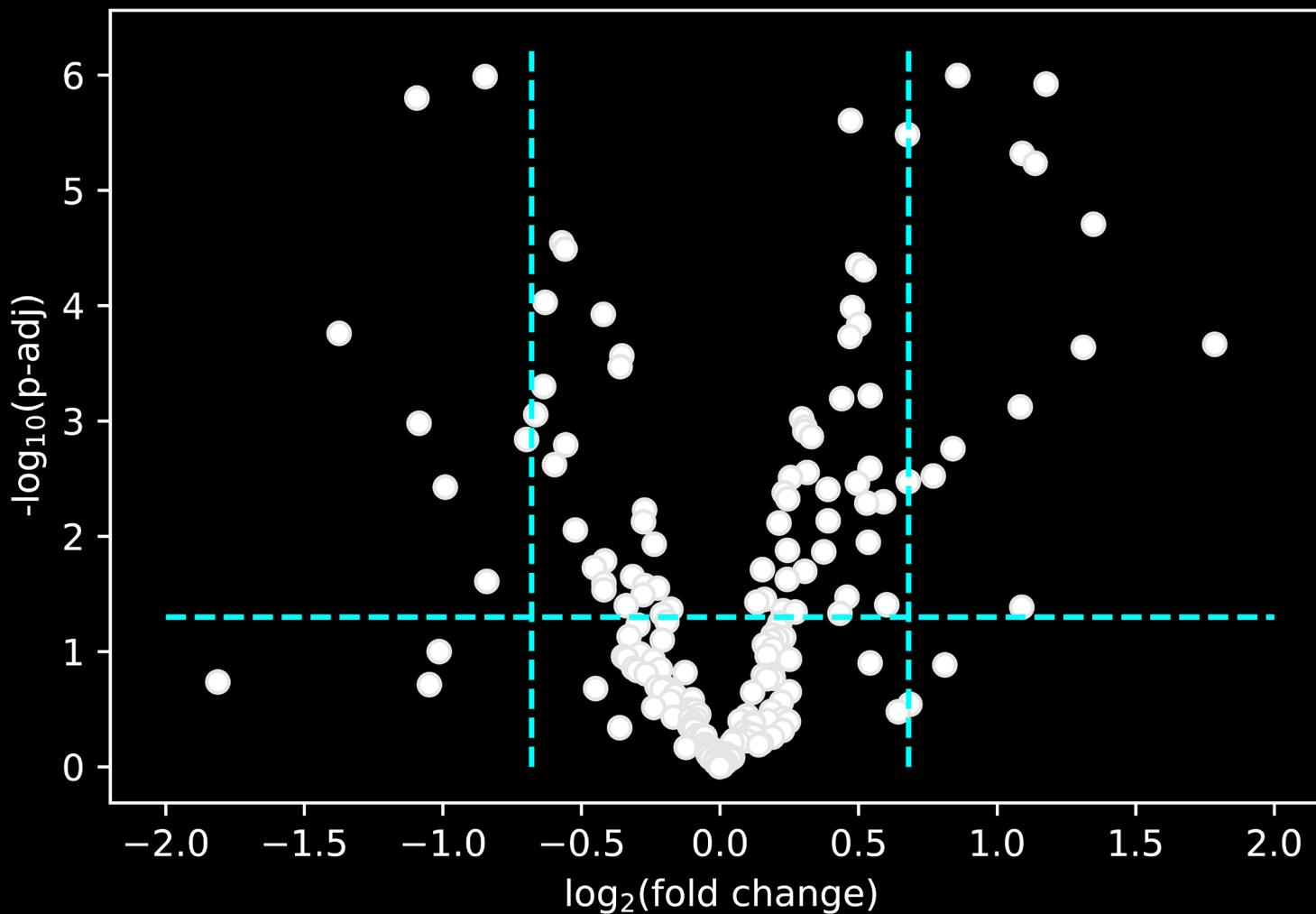


Comparing paired normal and adenocarcinomic lung tissue

- Wikoff et. al., 2015 (data @ Metabolomics Workbench)
- Paired metabolomics of paired samples
 - Non-small cell lung cancer
 - Most frequently diagnosed lung cancer
 - High mortality
- Original study highlighted:
 - Elevated nucleotide metabolism
 - Glucose metabolism perturbation
 - Elevation in cysteine and antioxidant levels
 - Reduced purine salvage
 - Elevated protein glycosylation

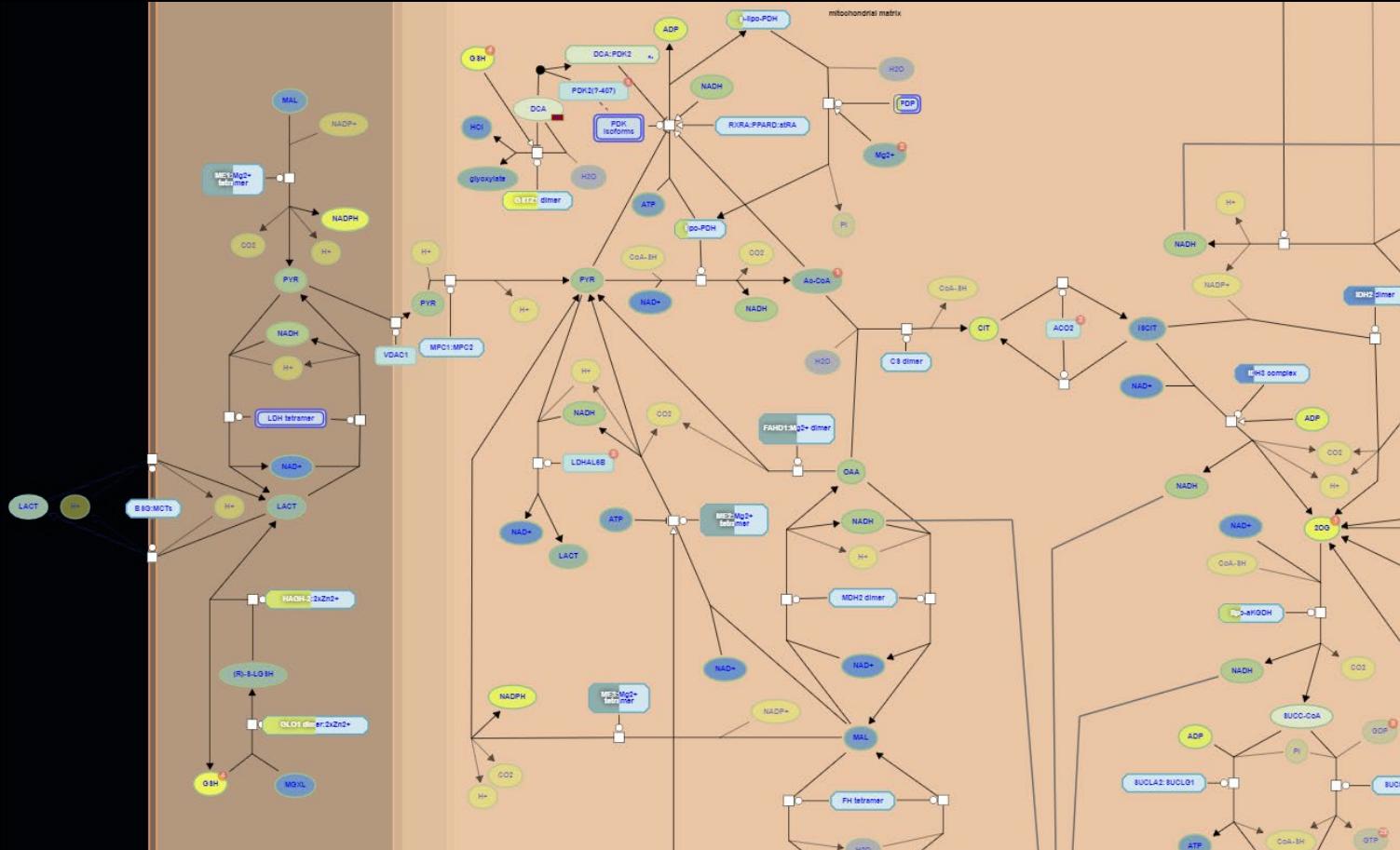


Current conventions limit analysis

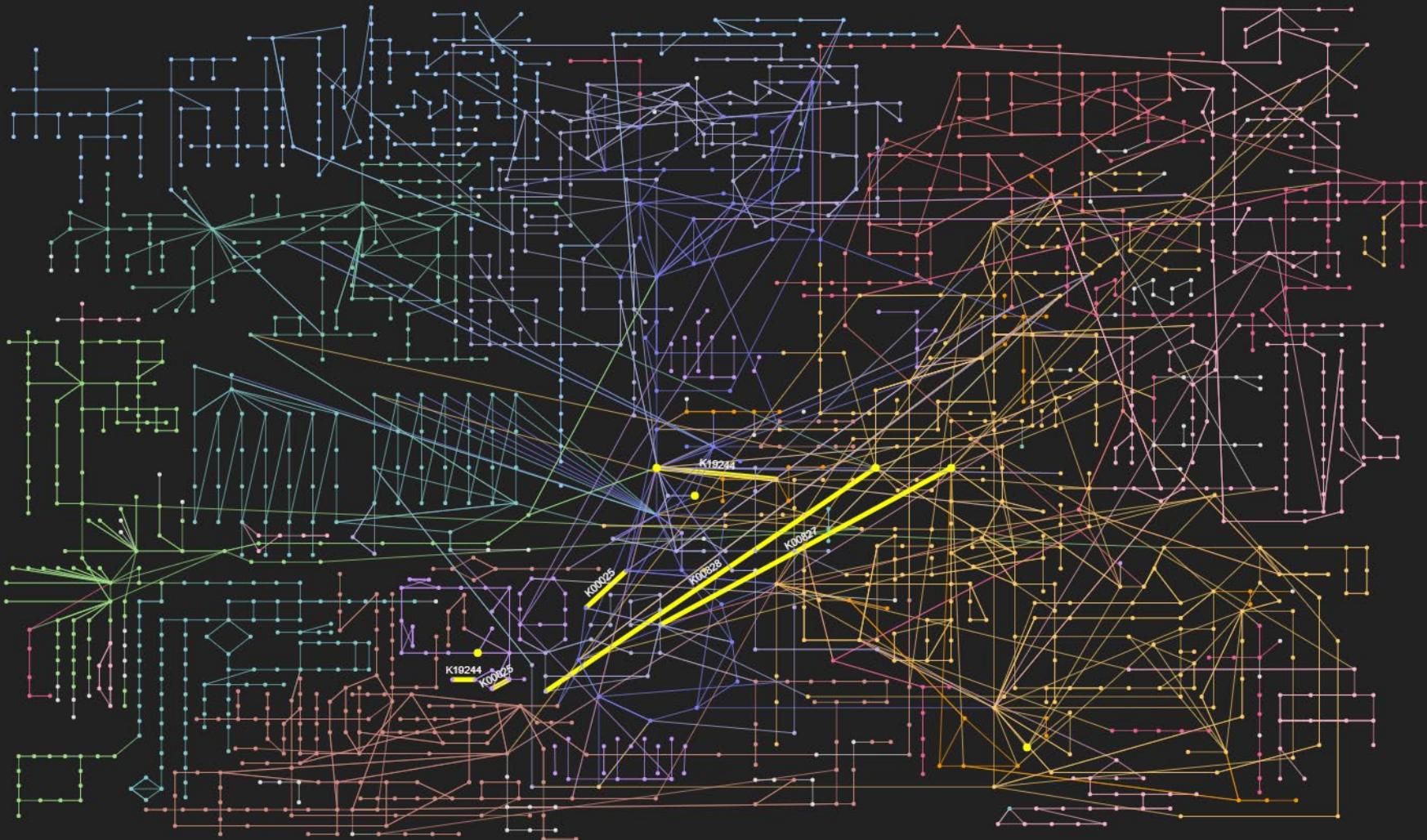


Data: Wikoff et. al., 2015

Current conventions limit analysis

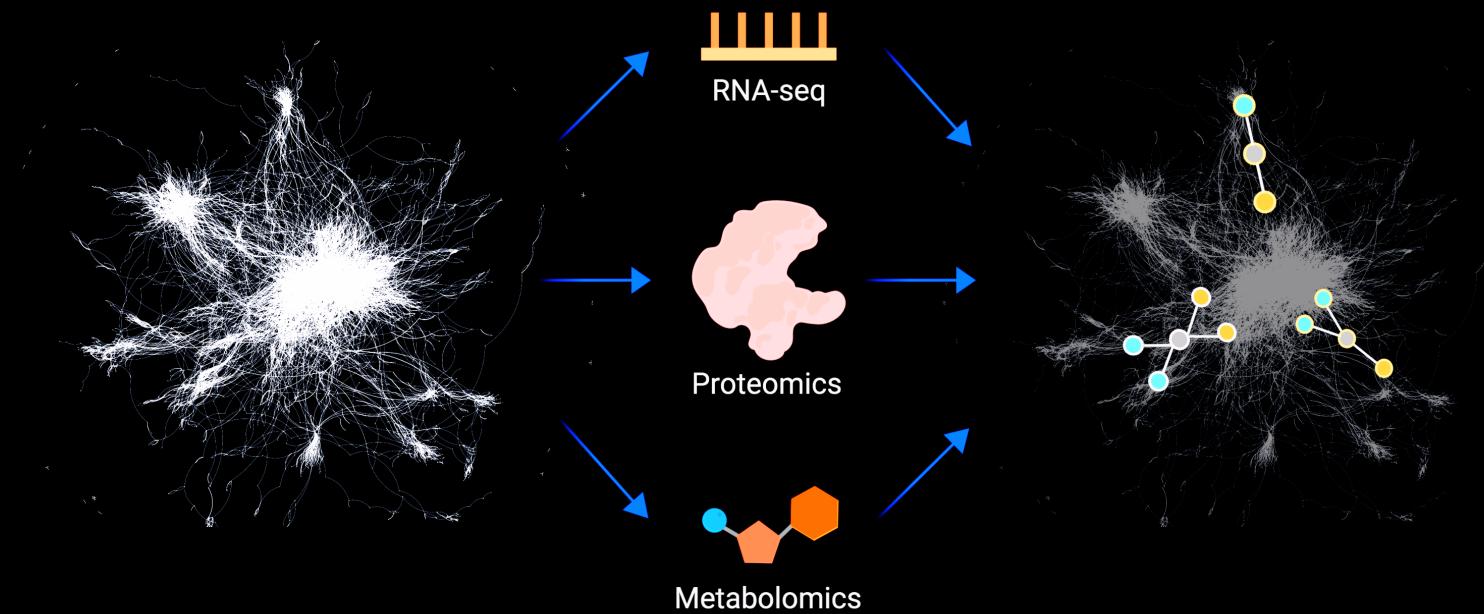


Current conventions limit analysis



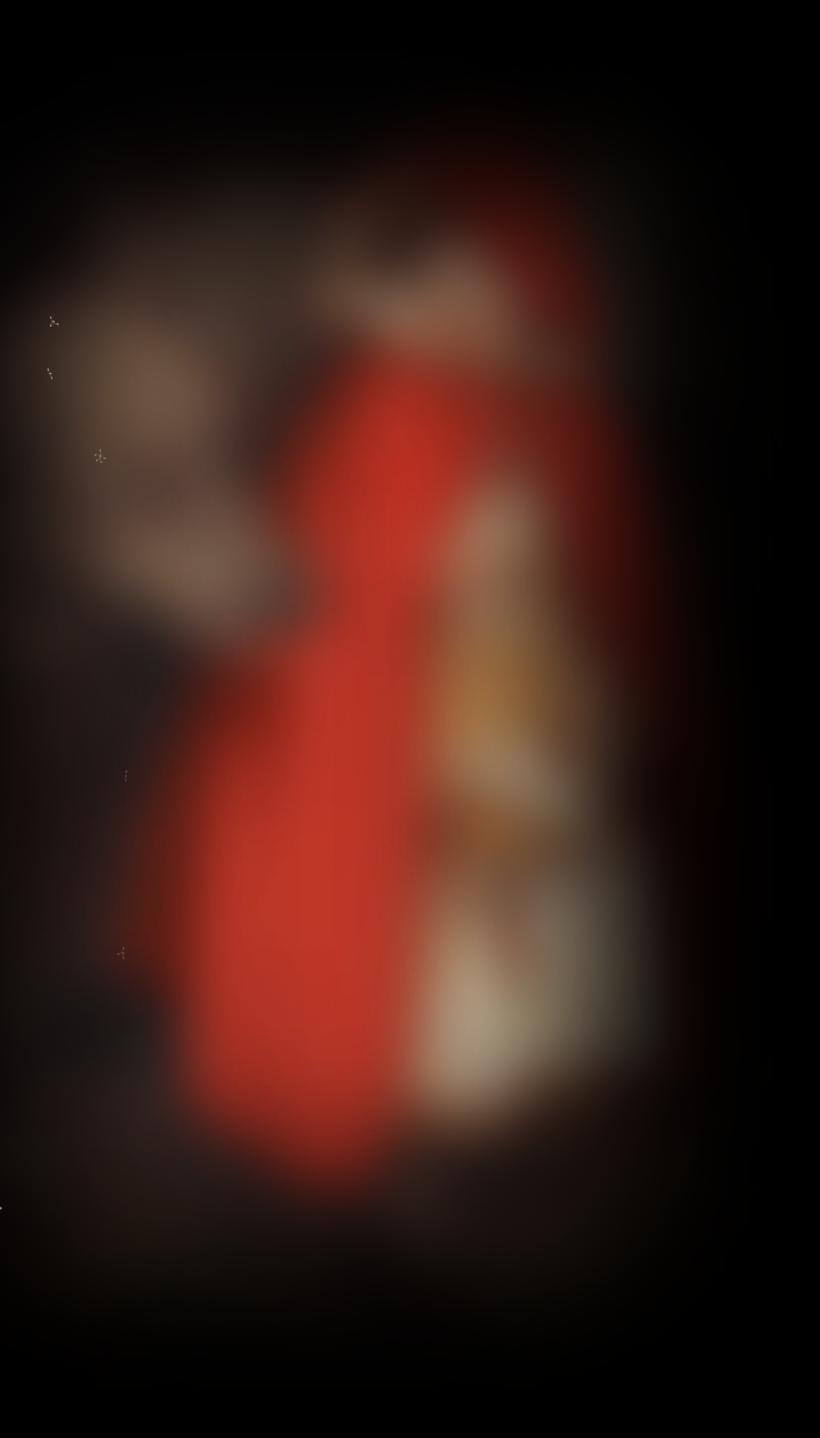
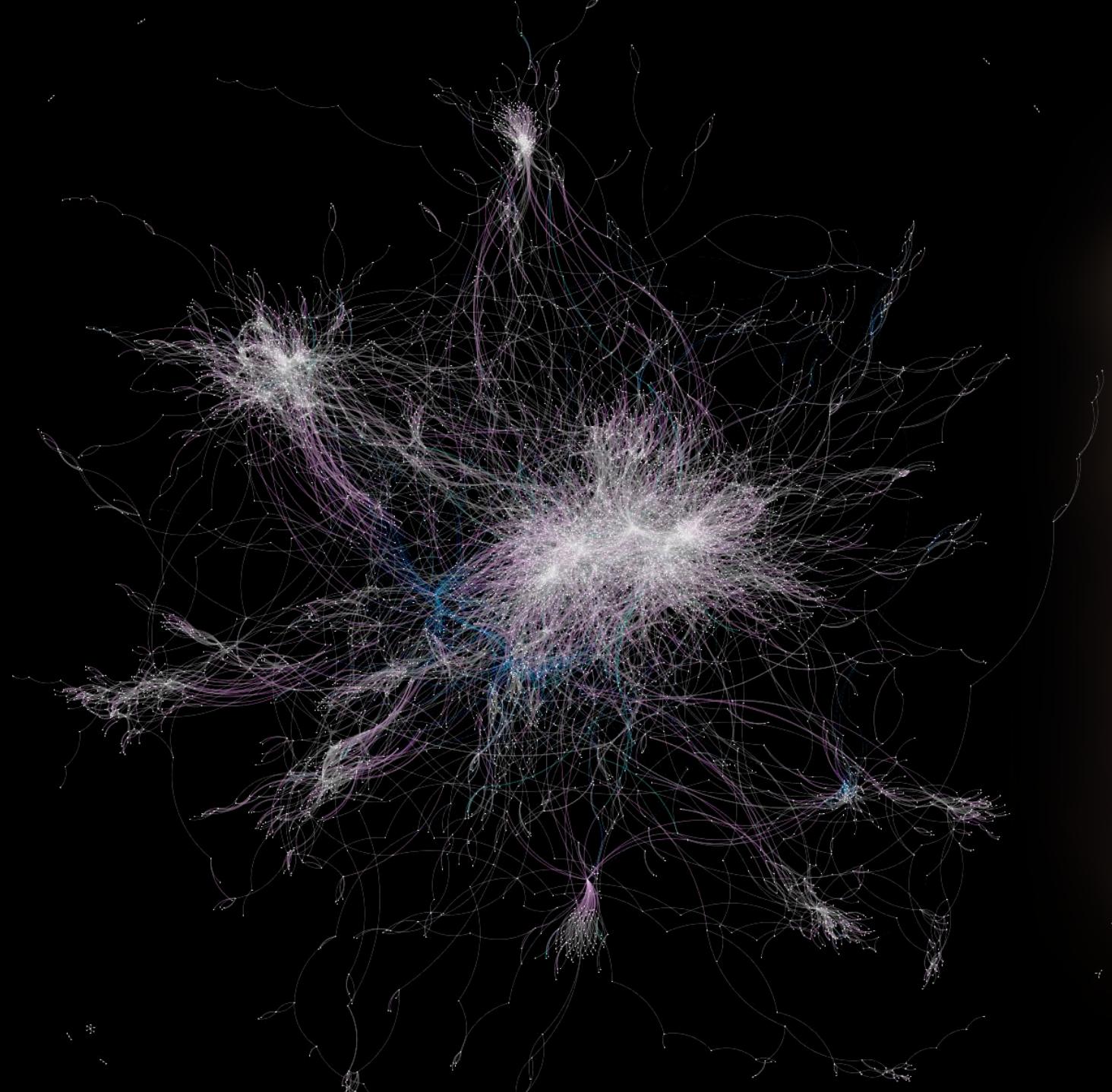
Metaboverse

- Multi-omic data integration into 90+ model organisms



Metaboverse requires standard user inputs

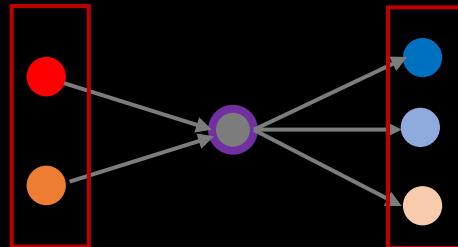
	log2fc	p-adj
ribitol	0.857462879	7.65115E-09
ornithine	-0.84810783	3.22226E-08
UDP GlcNAc	1.176163198	1.94374E-07
glucose	-1.093726866	5.80879E-07
glutamic acid	0.47031405	1.47938E-06
cysteine	0.676315159	2.27775E-06
"5,6-dihydrouracil"	1.09017364	3.7715E-06
tocopherol alpha	1.136906245	4.82214E-06
xanthine	1.347217801	1.86748E-05
citrulline	-0.571123868	2.74974E-05
spermidine	-0.55962869	3.1239E-05
arabitol	0.497203995	4.33157E-05
xylitol	0.519232882	4.77497E-05
histidine	-0.630702184	9.25855E-05
nicotinamide	0.477855672	0.000102797
tagatose	-0.421681013	0.000117947
glyceric acid	0.500730719	0.000144083
lysine	-1.374980178	0.000172834
N-acetyl-D-mannosamine	0.468630833	0.000183534



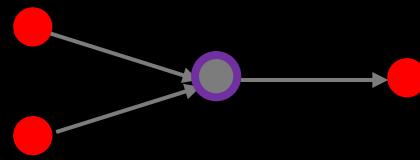
Metaboverse automates searching for regulatory events

- ID'd reaction
- Metabolite
- Protein
- Low
- High

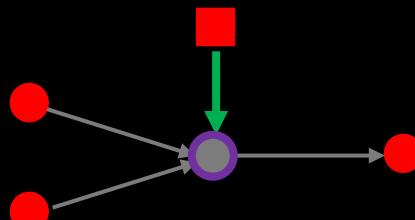
Average



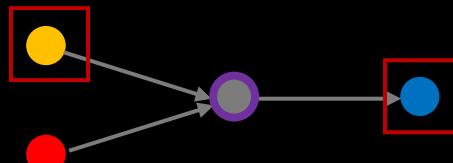
Sustained



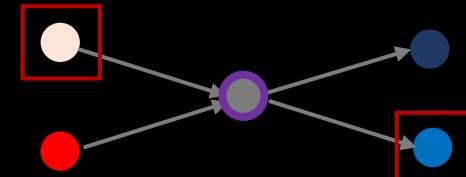
TransReg



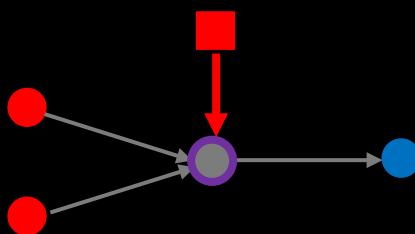
MinMax



MinMin



ModReg



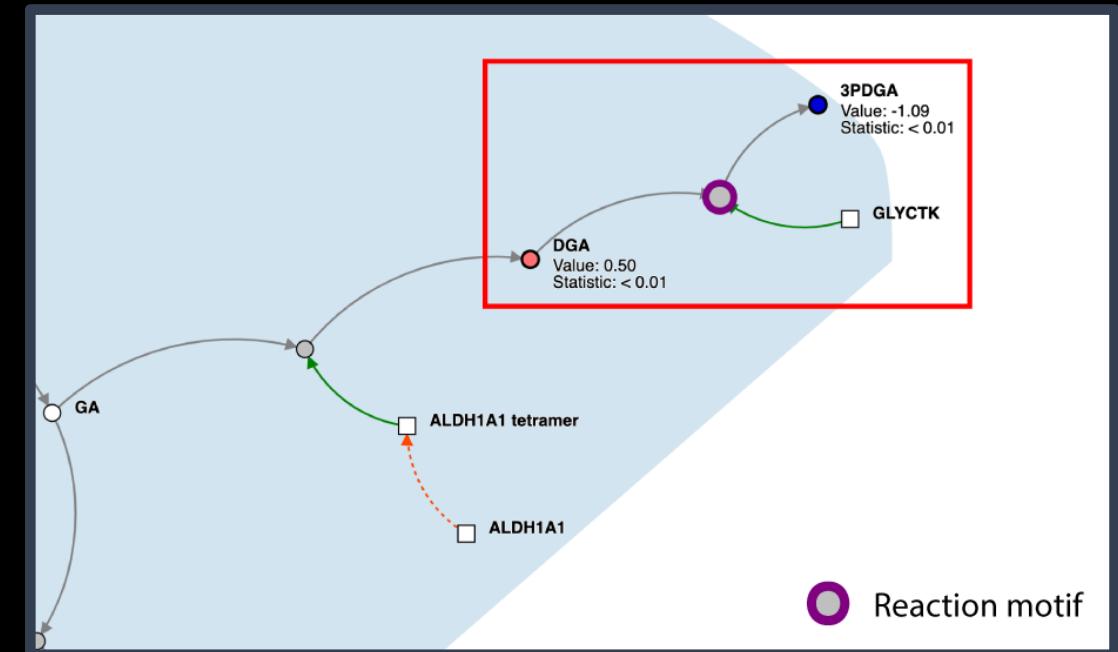
Metaboverse automates searching for regulatory events

- Searches the global reaction network
- Incorporates regulatory information



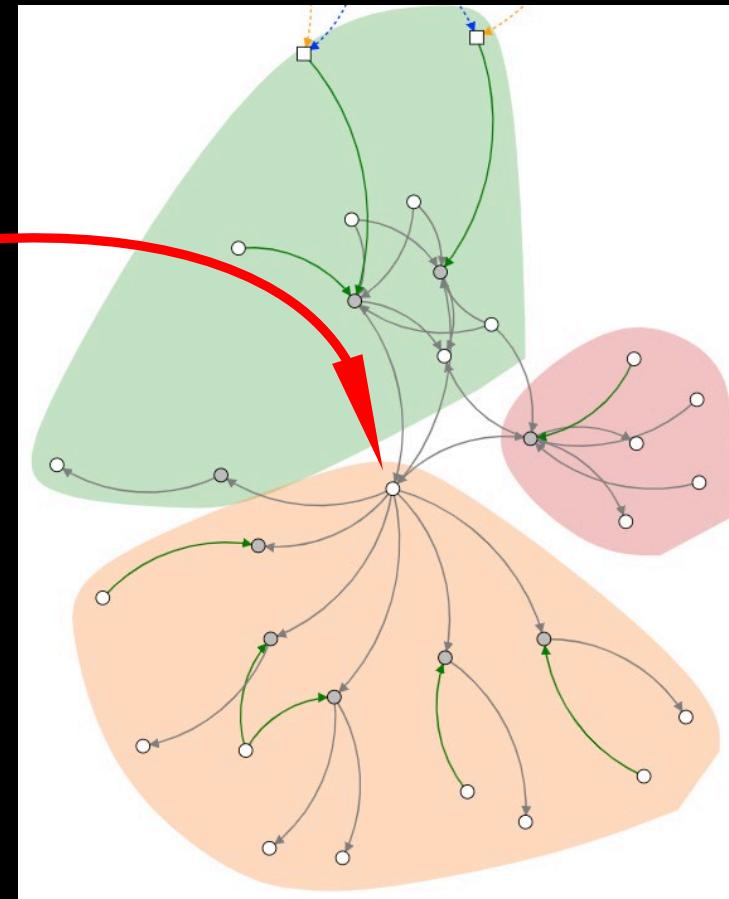
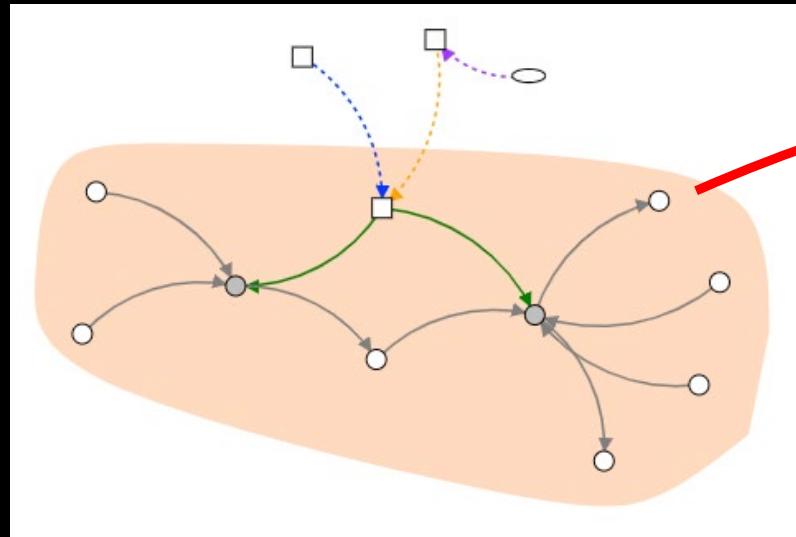
Pattern search analysis reveals putative regulatory mechanisms in disease models

- Glyceric acid up-regulation
- 3-Phosphoglyceric acid down-regulation
- Might indicate glycerate kinase regulation
- Component in serine biosynthesis pathway, key in cancer
- This pattern was missed in the original analysis



Searching global nearest neighbors of points of interest

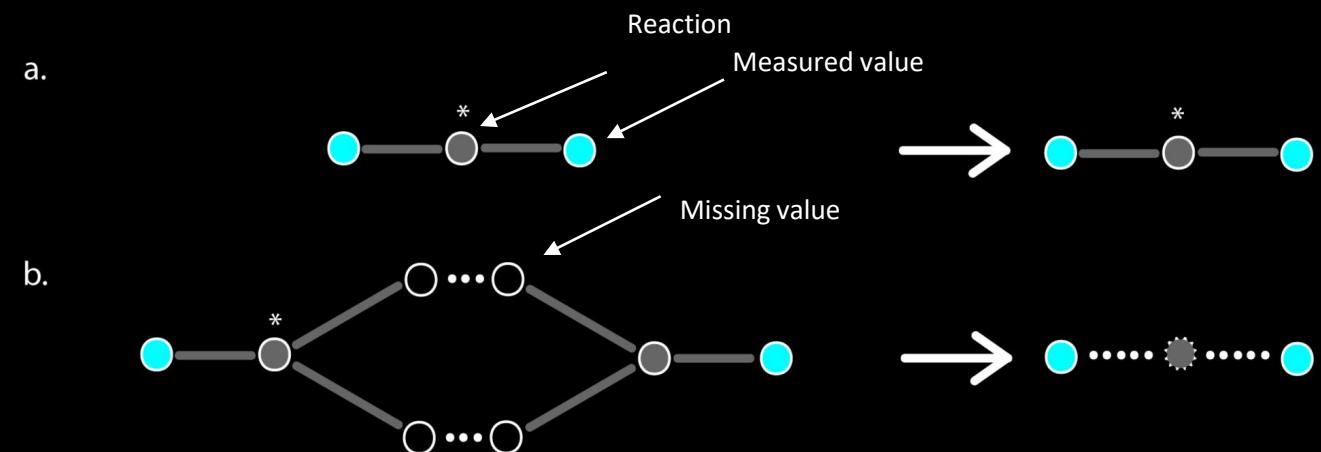
- Explore downstream consequences of a change



Handling sparse datasets

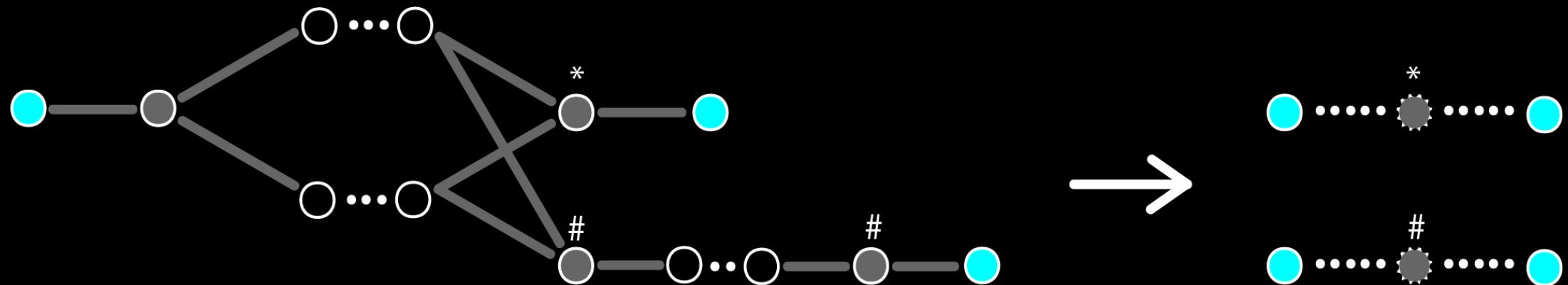
- Missing data a challenge in metabolomics
- Missing data may result in interesting regulatory patterns across a couple reactions being missed
- During curation, up to 3 reactions can be collapsed

* = Reaction being considered for collapse



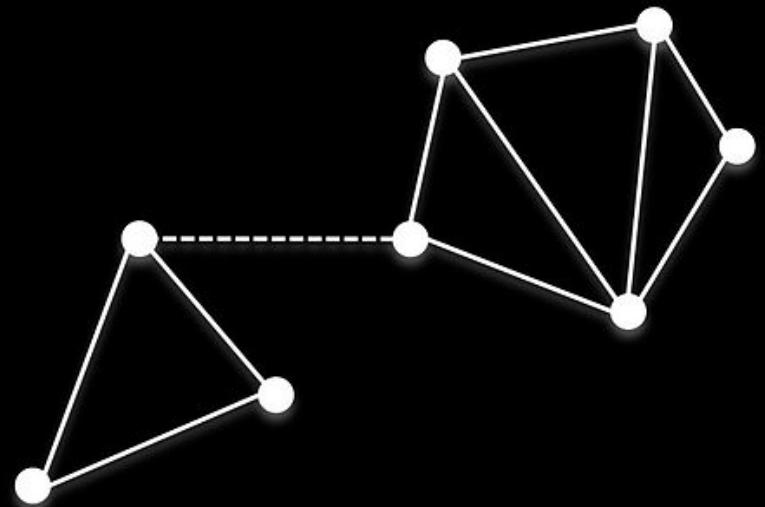
Exhaustive collapsing

- Collapse every possible sub-pathway with terminal measurements



Metabolic Perturbation Networks

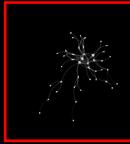
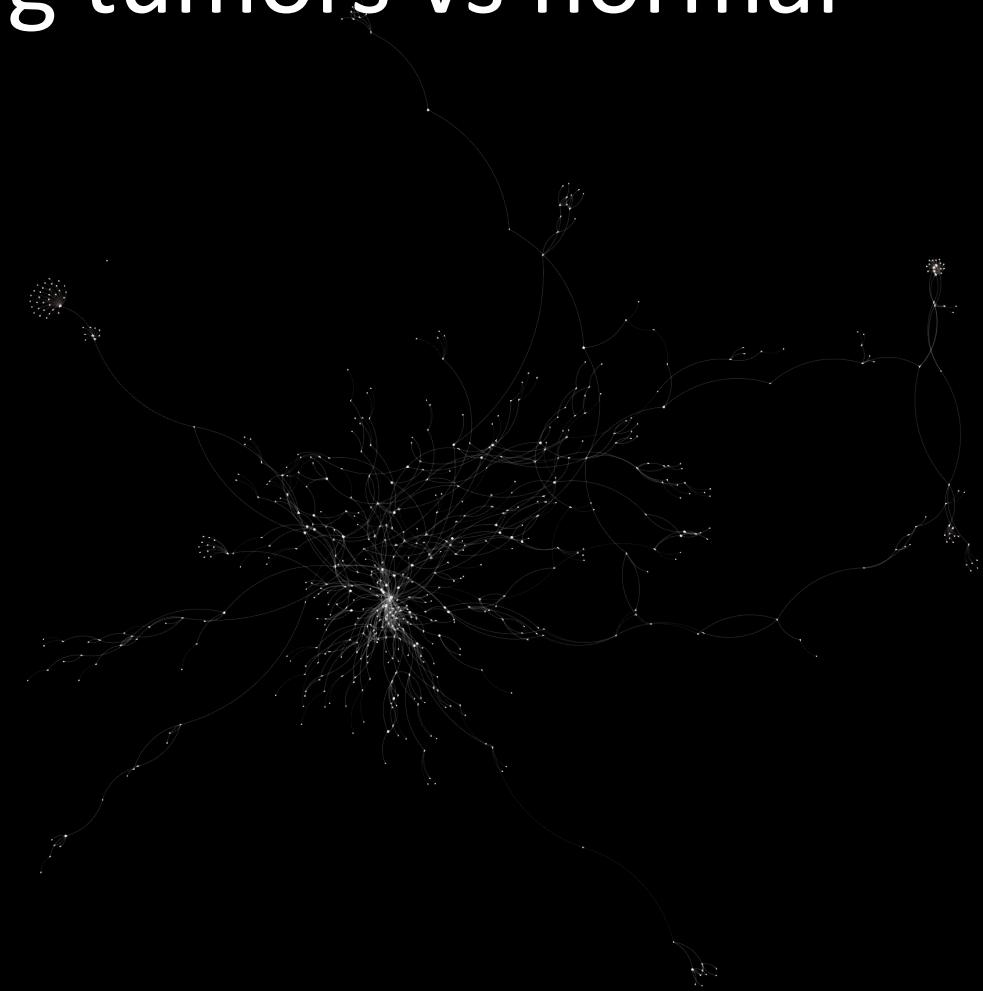
- Connectivity = resilience as a network
- Remove the dashed line and the graph becomes disconnected



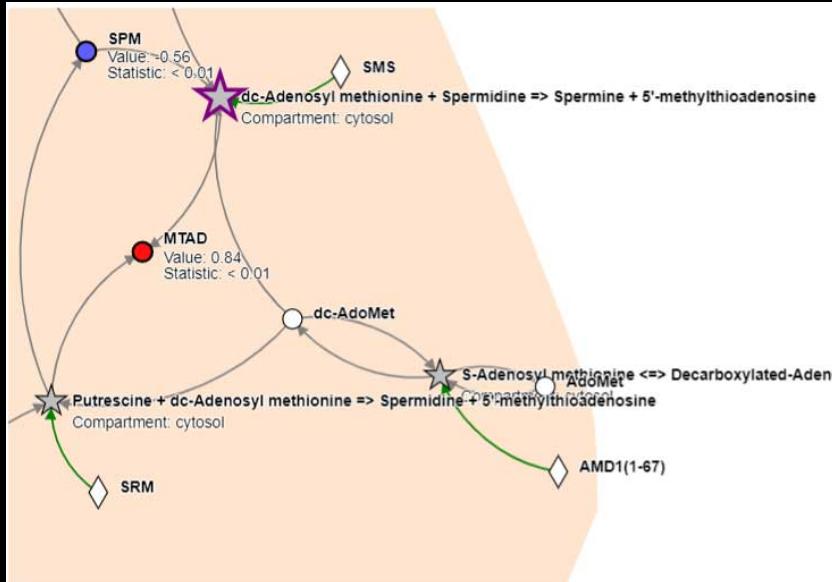
Perturbation networks in lung tumors vs normal

Many connected reactions center around carbon metabolism

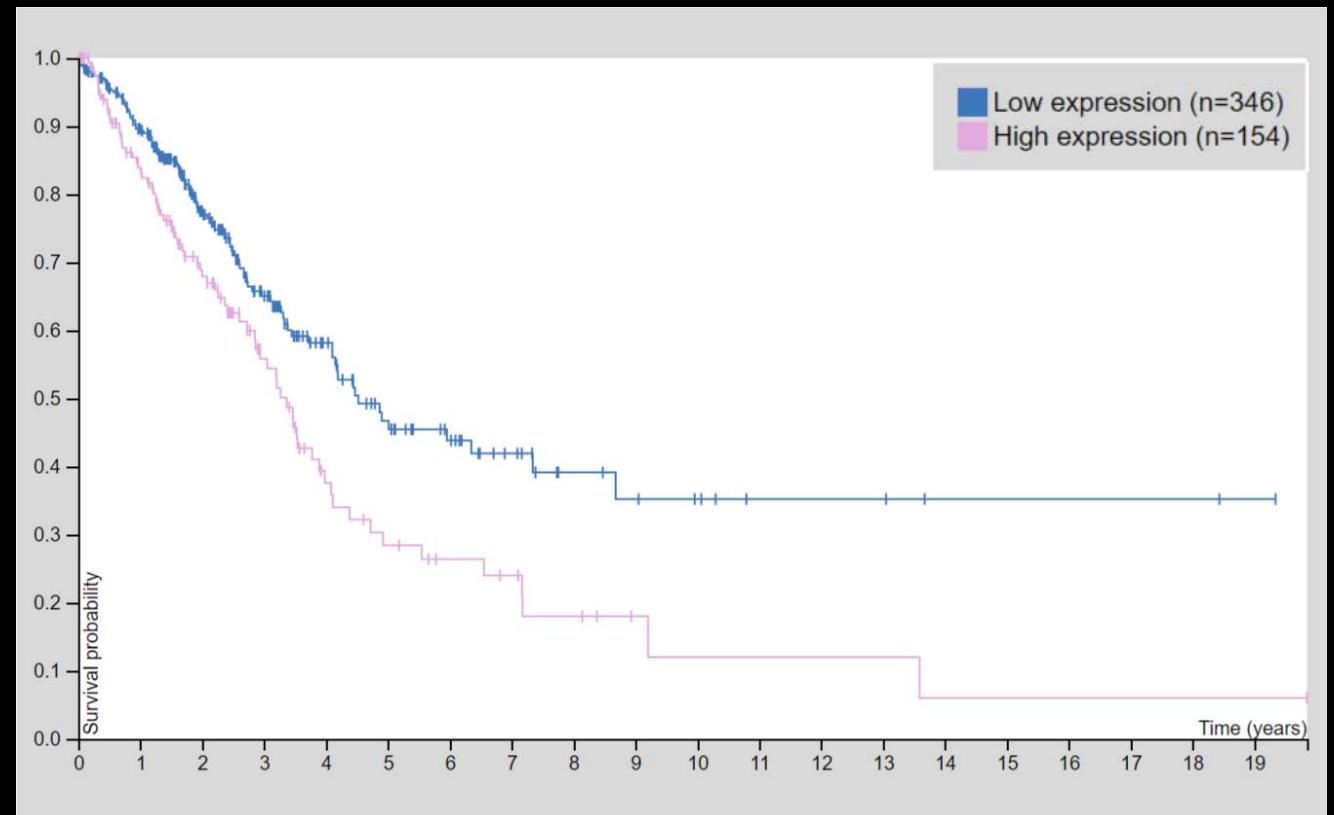
- *How could understanding proximal metabolic disruptions inform our understanding of a system?*
- *Are disconnected perturbed reactions with less redundancy better therapeutic targets?*
- *However, there are caveats associated with the sparsity problem.*



Spermine Synthase activity predicted by Metaboverse



- Metaboverse identifies SMS-related reaction pattern in LUAD data
- SMS gene expression appears to be prognostic marker for LUAD survival



Metaboverse

- Automates complex pattern recognition
 - Identified known and unknown features from study
- Comprehensively searches entire reaction network
- Integrates multiple dimensions from data
 - Magnitude shift
 - Statistical significance
- Search all downstream or upstream reactions of a given metabolite
- Integrate locational information (cellular compartments)
- Handles data sparsity
- Allows for identification of sub-pathway utilization
- Explore extent and consequences of connected perturbations
- Inform druggability, etc.



Acknowledgements

Metaverse:

- Youjia Zhou
- Yeyun Ouyang
- Cameron Waller
- Sara Nowinski
- Tyler Van Ry
- Ian George
- James Cox
- ***Bei Wang***
- ***Jared Rutter***

The Rutter Lab

- Alex Bott
 - Ahmad Cluntun
 - Kevin Hicks
 - Jeff Morgan
 - And all others
-
- Tom O'Connell



@jordanberg0
@RutterLab



1T32DK11096601



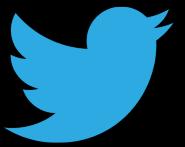
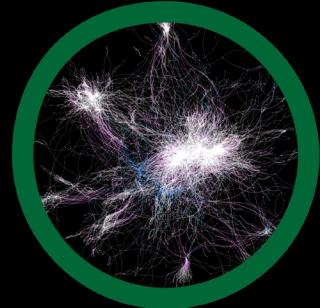
1F99CA253744



R35GM131854



NSF DBI-1661375
NSF IIS-1513616



@jordanberg0
@RutterLab

github.com/Metaboverse

Software

GPL-3.0

Presentation

CC-BY 4.0

Pre-print

CC-BY 4.0

