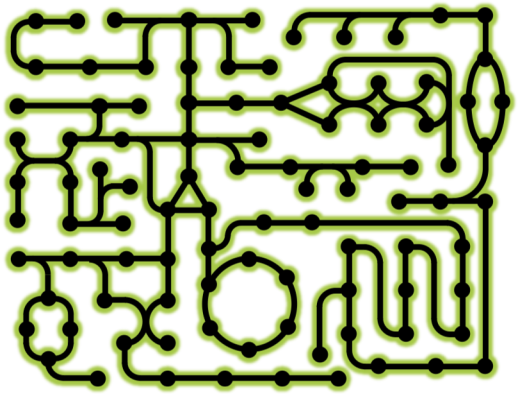

GEMs

Analyzing omics data in the context of metabolism

NBIS Omics Integration and Systems Biology workshop
Fall 2020, Lund University

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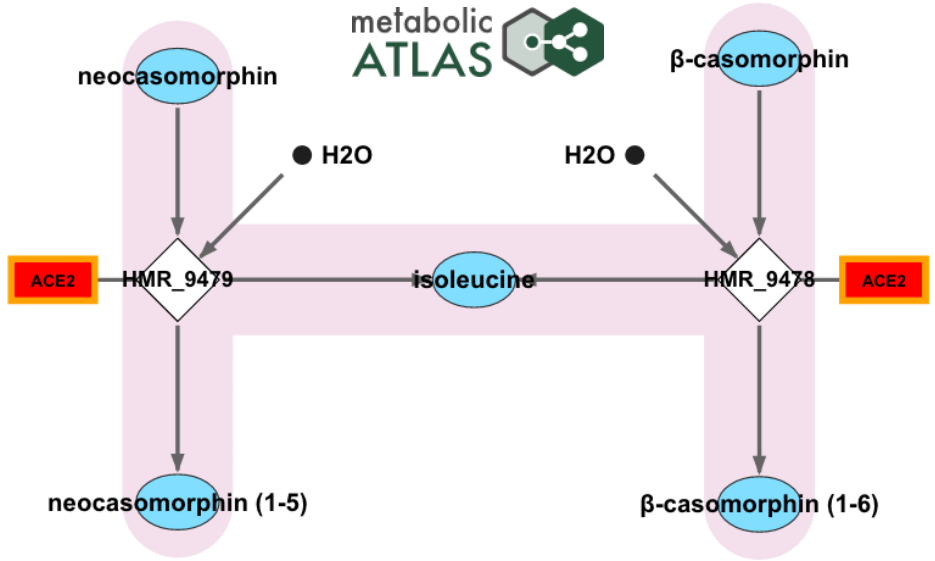
Information paradox

ACE2

Information paradox



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Angiotensin-converting enzyme 2

From Wikipedia, the free encyclopedia

"ACE2" redirects here. For other uses, see Ace 2 (disambiguation).

Angiotensin-converting enzyme 2 (**ACE2**)[5] is an enzyme attached to the cell membrane
kidney, and intestines.[6][7] ACE2 lowers blood pressure by catalyzing the hydrolysis of angi
angiotensin (1–7) (a vasodilator).[8][9][10] ACE2 counters the activity of the related angiotens
amount of angiotensin-II and increasing Ang(1-7),[11] making it a promising drug target for tr

PubMed.gov

1 Cite Share
Circulating ACE2 in Cardiovascular and Kidney Diseases.
Anguiano L, Riera M, Pascual J, Soler MJ.
Curr Med Chem. 2017;24(30):3231-3241. doi: 10.2174/0929867324666170414162841.
PMID: 28413960 Review.
Given that **ACE2** counterbalances the effects of Ang II, it has been proposed as a biomarker in kidney disease patients. Circulating **ACE2** has been studied in human and experimental studies under physiological and pathological conditions and different techniques have b ...

2 Cite Share
Angiotensin-converting enzyme 2 (ACE2) in disease pathogenesis.
Imai Y, Kuba K, Ohto-Nakanishi T, Penninger JM.
Circ J. 2010 Mar;74(3):405-10. doi: 10.1253/circj.cj-10-0045. Epub 2010 Feb 4.
PMID: 20134095 Free article. Review.
Importantly, **ACE2** has been identified as a key SARS-coronavirus receptor and plays a protective role in SARS pathogenesis. Furthermore, the recent explosion of research into the **ACE2** homolog, collectrin, has revealed a new physiological function of **ACE2** as an ...

3 Cite
ACE2 - from the renin-angiotensin system to gut microbiota and malnutrition.
Perlot T, Penninger JM.
Microbes Infect. 2013 Nov;15(13):866-73. doi: 10.1016/j.micinf.2013.08.003. Epub 2013 Aug 17.
PMID: 23962453 Free PMC article. Review.

NCBI

Summary

Official Symbol	ACE2 provided by HGNC
Official Full Name	angiotensin I converting enzyme 2 provided by HGNC
Primary source	HGNC:HGNC:13557
See related	Ensembl:ENSG00000130234 MIM:300335
Gene type	protein coding
RefSeq status	REVIEWED
Organism	Homo sapiens
Lineage	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo
Also known as	ACEH
Summary	The protein encoded by this gene belongs to the angiotensin-converting enzyme family of dipeptidyl carboxydipeptidases and has considerable homology to human angiotensin 1 converting enzyme. This secreted protein catalyzes the cleavage of angiotensin I into angiotensin 1-9, and angiotensin II into the vasodilator angiotensin 1-7. ACE2 is known to be expressed in various human organs, and its organ- and cell-specific expression suggests that it may play a role in the regulation of cardiovascular and renal function, as well as fertility. In addition, the encoded protein is a functional receptor for the spike glycoprotein of the human coronavirus HCoV-NL63 and the human severe acute respiratory syndrome coronaviruses, SARS-CoV and SARS-CoV-2, the causative agent of coronavirus disease-2019 (COVID-19). [provided by RefSeq, Aug 2020]
Annotation information	Note: This gene has been reviewed for its involvement in coronavirus biology, and is involved in SARS-CoV-2 infection.
Expression	Biased expression in small intestine (RPKM 93.7), duodenum (RPKM 69.0) and 5 other tissues See more

NATIONAL BIOINFORMATICS INFRASTRUCTURE SWEDEN

Information paradox

ENOPH1, SLC25A2, GMPPB, SLC1A4, EGFL8, HDC, DNM1L, RHCG, SLC24A4, FABP4, PDSS1, ACSBG1, UGT3A1, TAOK1, CDY1B, PPIE, GCLM, GMPR2, USP9Y, DGKD, ATP2A2, FABP2, ZDHHC7, GLRX2, DPM3, NUP155, GPX1, SLC4A5, POLI, GCH1, APOE, PLPP7, RIPK3, HPSE, PLA2G1B, PYGL, CDK8, MGST1, DGAT2L6, PPP5C, TXNRD3, MACROD2, FABP4, DDR1, USP35, NARS, HERC1, WWP1, PIGF, MACROD1, SUOX, DGKG, PGS1, AURKB, CDY1, TKFC, PIM1, SLC1A4, GLDC, AFMID, FAR1, PHYKPL, ATP2B1, PTPDC1, LCT, ASPG, ACOT1, POLR1C, HEMK1, CDA, UPP2, PARP10, SLC15A1, ASNS, TGFBR2, POLR2F, CARS, CBL, SLC4A9, INPP4A, SUCLG1, MTAP, PKMYT1, CBLL1, MAP2K2, MARS, TECRL, SLC26A3, METTL7B, ME1, AK2, PLA2G12A, DHRS9, EPHA5, GGACT, GGT5, ACYP2, PI4K2A, SLC25A42, USP17L25, TRMT11, DUSP15, PTGR1, PPP3R1, CA1, FN3K, UBE2F, EFL1, TYMS, PPWD1, GCNT4, PFKP, RNF126, PRKCI, TAF9, FDPS, SLC19A3, AGK, BCKDHB, CALM2, HK1, UPRT, SRD5A1, SYVN1, GLA, CTDSPL, CYP2J2, ACOT9, PDE8B, AP000812.4, IDH3B, SULT1B1, MAP3K21, HMGCS1, JMJD7-PLA2G4B, CA3, SLC25A3, ACAT1, NEK9, NEK6, 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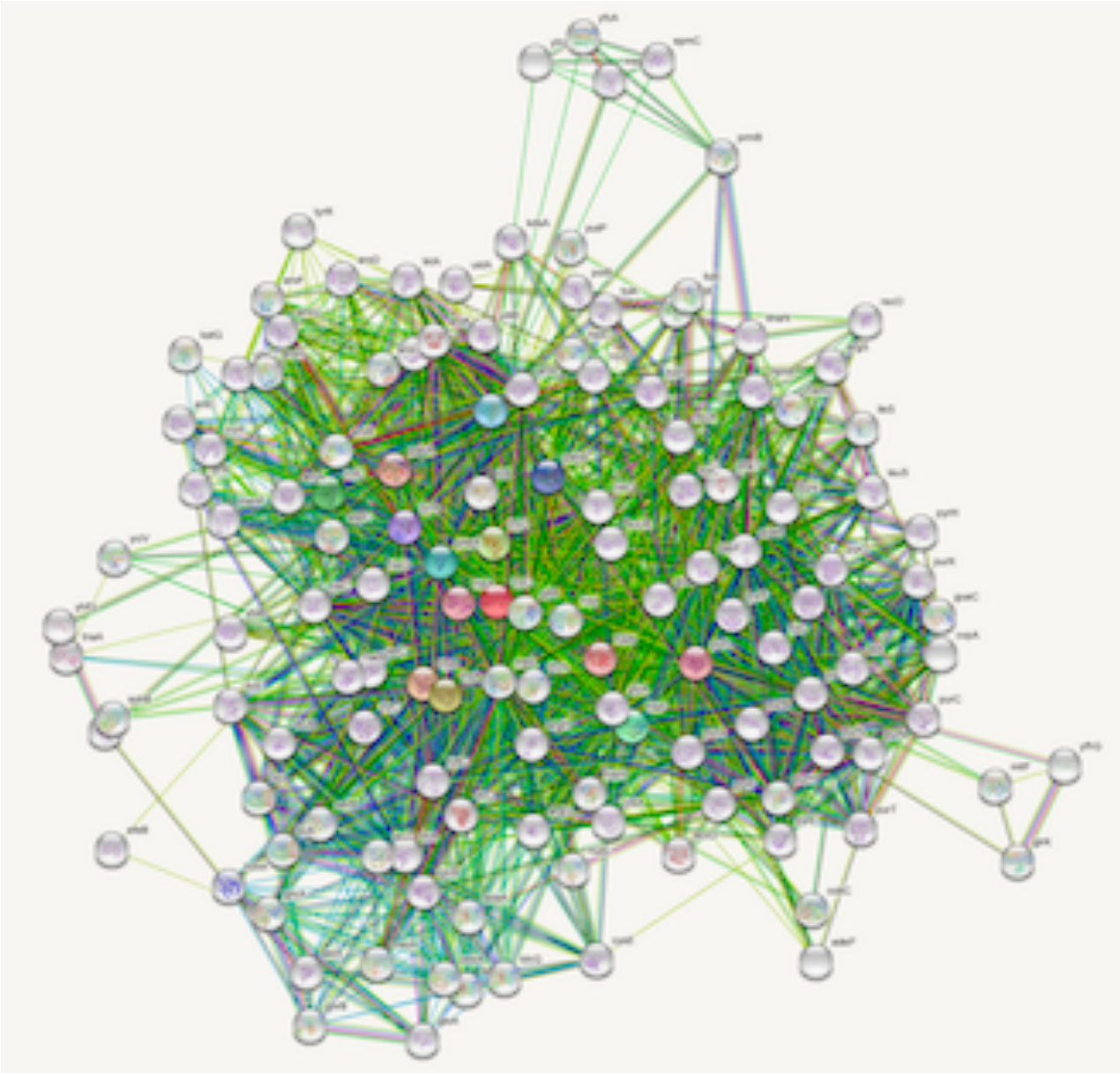
MRM1, SLCO3A1, ALG5, GAD2, EYA2, EEF1A1, BRSK2, SLC27A5, DUSP19, MDH1, NEK9, GMDS, AL160269.1, G6PD, SLC12A3, SLC25A14, MRI1, CHST10, SHPRH, GBA, PLA2G12A, CDK14, TGFBR1, HSPG2, SMYD2, NAA15, CYP4V2, SGPP1, CARNS1, NSUN4, TMEM54, USP21, CLYBL, TPSD1, PLCD4, SLC15A2, NME5, AMY2A, HSD17B11, MYLK2, CNDP2, SPR, SLC7A8, CTDP1, UBE2D1, COASY, PPP2R3A, IMPA1, ETFB, ATP2A2, PRODH, STARD6, INPP5K, POLR1E, PDE1B, GUCY1A2, PYCR2, MAP3K7, SLC29A2, BMP2K, SULT1B1, DCT, TTLL10, DUSP14, ST6GALNAC3, GSTA3, TPMT, RNMT, MDH1, NUP85, SLC29A1, PDE6G, HERC1, ETFB, PTPRZ1, CYP11A1, MET, POR, NAA11, GPAA1, ACAT1, IRAK2, PTPN4, PTPN5, IDH3G, HELZ2, SLC7A9, QTRT2, CBLL2, USP13, FKBP6, USP38, PASK, PTPRB, ST8SIA1, WNK4, NDST3, CYP4F3, ENTPD1, MGAT5, APOC3, LCT, RPEL1, PADI4, PPM1B, NME2, TPSB2, PADI4, PFKM, ZNRD1, SLC2A3, CLOCK, HRASLS2, USP13, STK24, ACSM2A, IL18BP, SULT1E1, SLC1A6, CHST14, AKT2, POLD2, HDLBP, UGDH, NEK4, MDM2, SIRT2, SARDH, GMPPA, PRKG2, USP10

Information paradox



Information paradox

Often it seems that the more information we have, the less we can learn from it.

Using techniques such as clustering and enrichment analysis, we can package the information into bite-sized (human-friendly) pieces.

Gene set analysis (GSA)

- Identifies patterns associated with the genes of interest
- Gene sets are defined based on shared properties, functions, interactions, etc. of the genes

Gene Ontology

Biological Process

Actin crosslink formation
mRNA transport
Carbohydrate transport
Regulation of catabolic process
Erythrocyte development
...

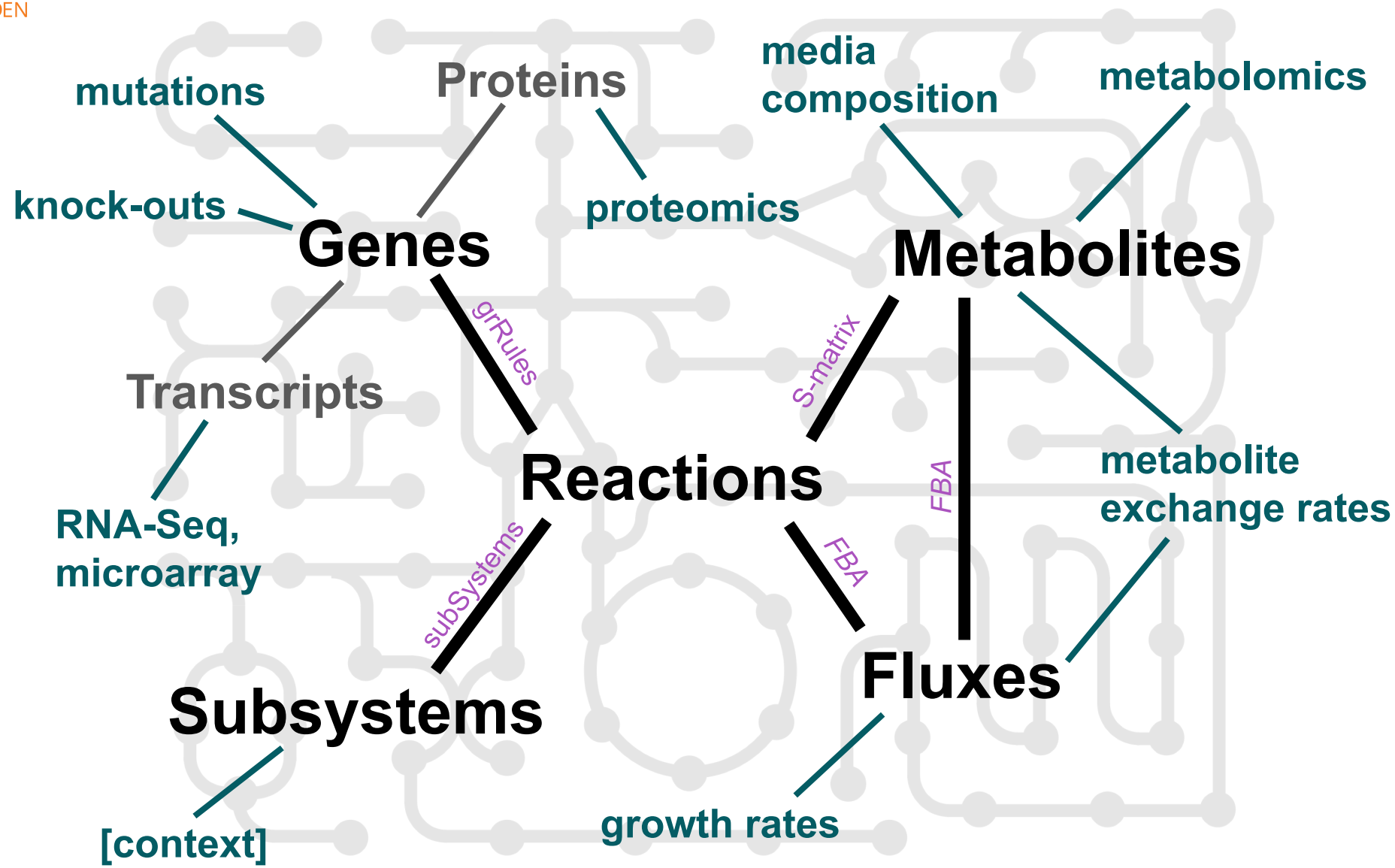
Molecular Function

Glucosidase activity
Alpha actinin binding
Cytokine activity
Oxidized DNA binding
Iron ion binding
...

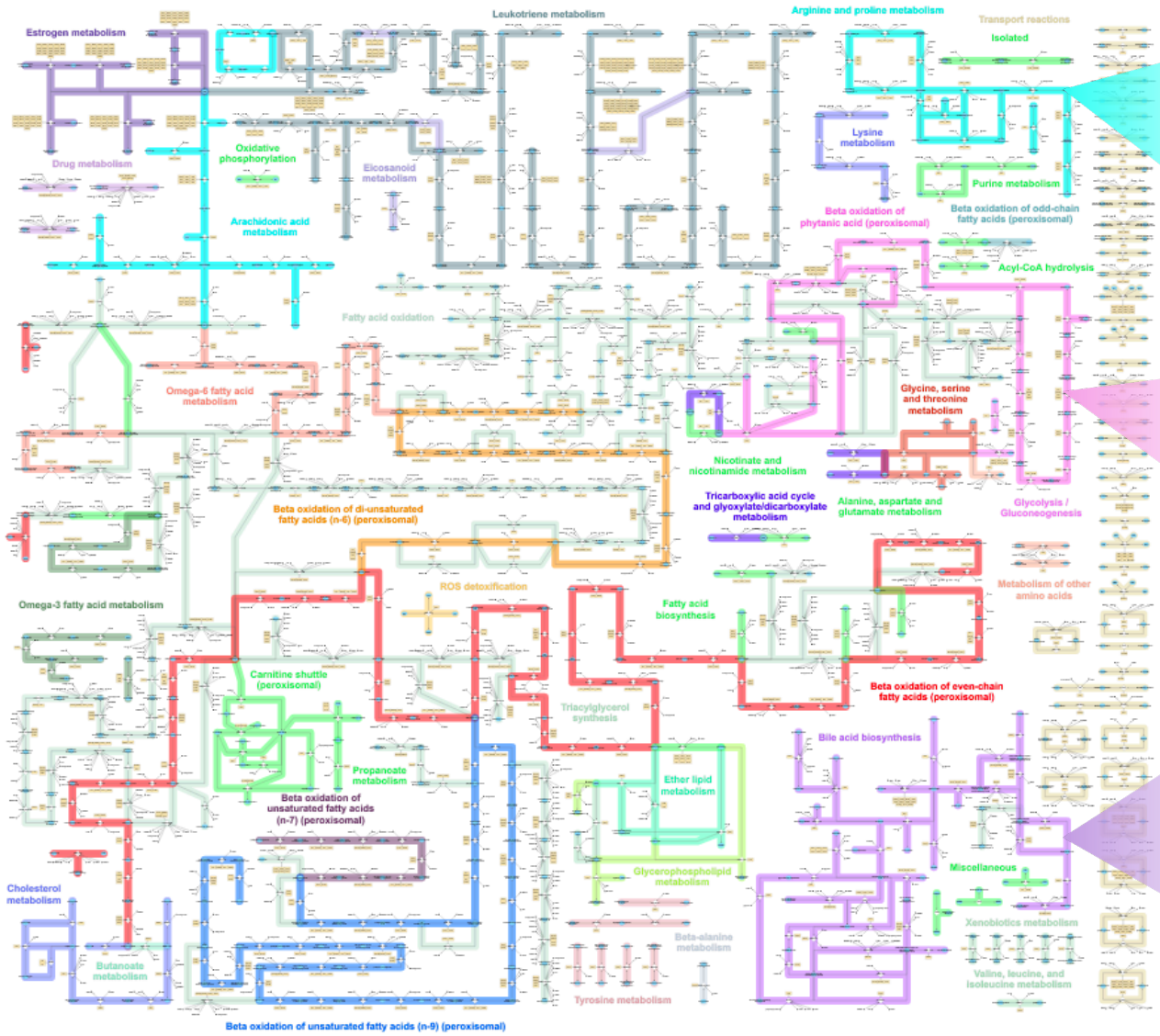
KEGG Pathways

```
▼ 09100 Metabolism
  ▶ 09101 Carbohydrate metabolism
  ▼ 09102 Energy metabolism
    ▶ 00190 Oxidative phosphorylation [PATH:hsa00190]
      00195 Photosynthesis
      00196 Photosynthesis - antenna proteins
      00710 Carbon fixation in photosynthetic organisms
      00720 Carbon fixation pathways in prokaryotes
      00680 Methane metabolism
    ▶ 00910 Nitrogen metabolism [PATH:hsa00910]
    ▶ 00920 Sulfur metabolism [PATH:hsa00920]
  ▶ 09103 Lipid metabolism
  ▶ 09104 Nucleotide metabolism
```

GEM-derived gene sets



Subsystem gene sets



Arginine and proline metabolism

ABHD14A-ACY1 ACY1 AGMAT ALDH18A1 ALDH1B1 ALDH2 ALDH3A2 ALDH4A1
ALDH7A1 ALDH8A1 ALDH9A1 AMD1 AOC1 AOC2 AOC3 ARG1 ARG2 AZIN2
CA5A CA5B CARNS1 CKB CKM CKMT1A CKMT1B CKMT2 CNDP1 CNDP2 DAO
DHPS FAR1 FAR2 GAMT GOT1 GOT2 HOGA1 LEFTY1 MAOA MAOB MTAP [redacted]

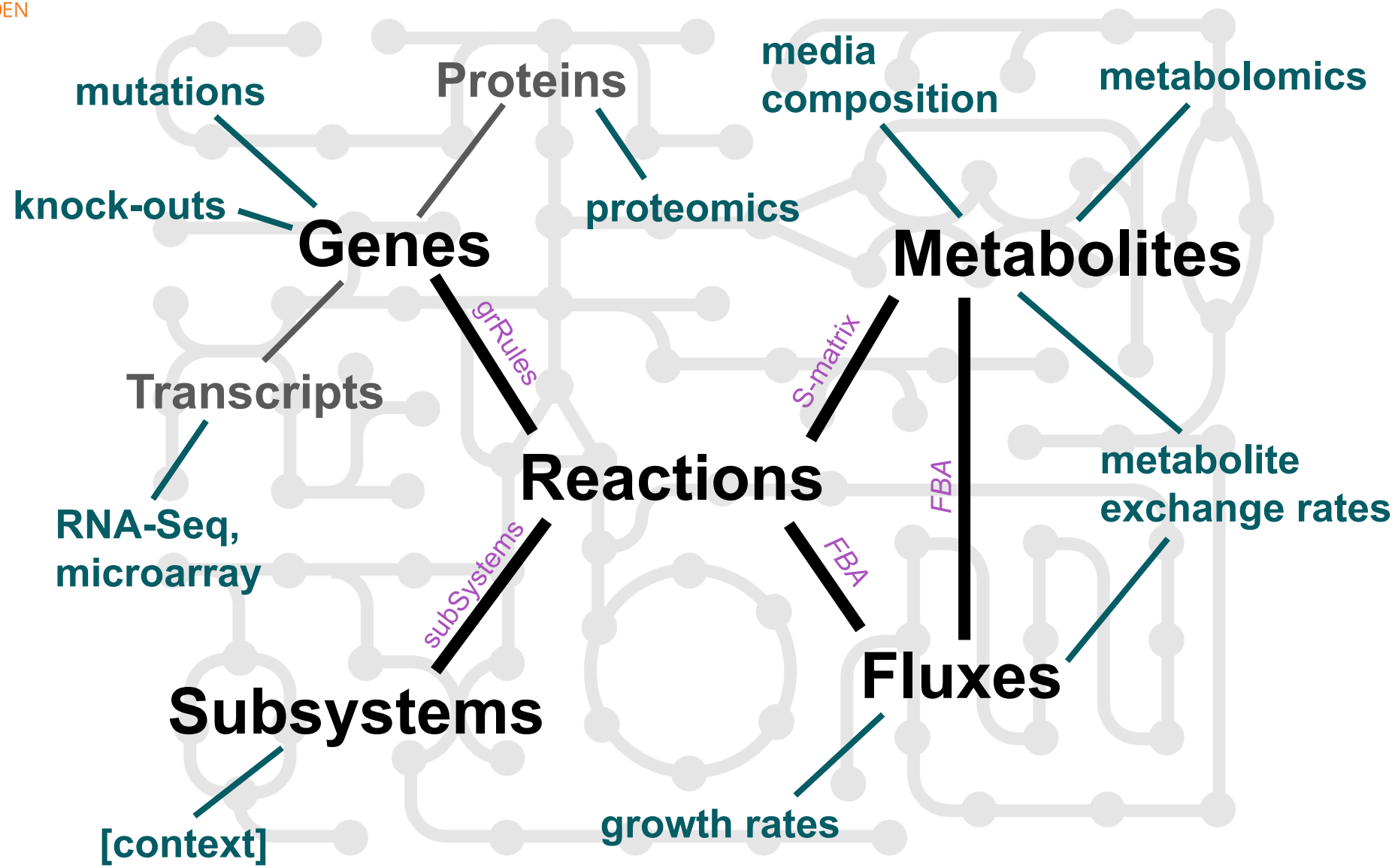
Beta oxidation of phytanic acid

ACAA1 ACOT2 ACOT4 ACOX1 ACOX3 ACSBG1 ACSBG2 ACSL1 ACSL3 ACSL4
ACSL5 ACSL6 AMACR ECI1 ECI2 EHHADH HACL1 HADHA HSD17B4 KRTAP11-1
MEIKIN MYO5B PHYH SLC27A2 ...

[redacted]

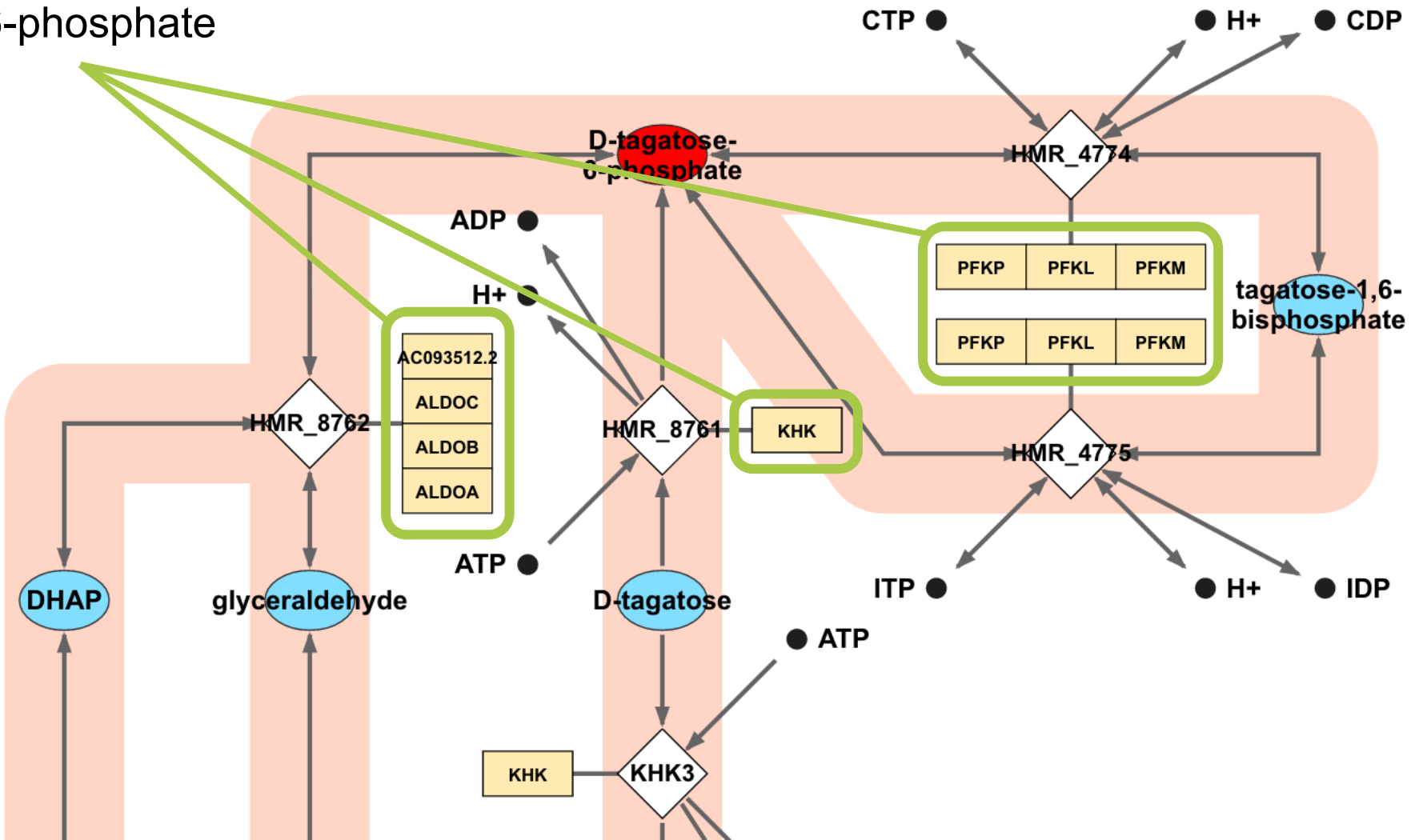
ABCB11 ABCC11 ABCC3 ABCD1 ACAA1 ACAA2 ACOT1 ACOT2 ACOT4 ACOT6
ACOT7 ACOT8 ACOX1 ACOX2 ACOX3 ADH1A ADH1B ADH1C ADH4 ADH5
ADH6 ADH7 ADHFE1 ADO AKR1B10 AKR1B15 AKR1C1 AKR1C2 AKR1C3 AKR1C4
AKR1D1 ALDH1B1 ALDH2 ALDH3A1 ALDH3A2 ALDH7A1 ALDH9A1 AMACR BAAT
BCAP31 [redacted]

GEM-derived gene sets



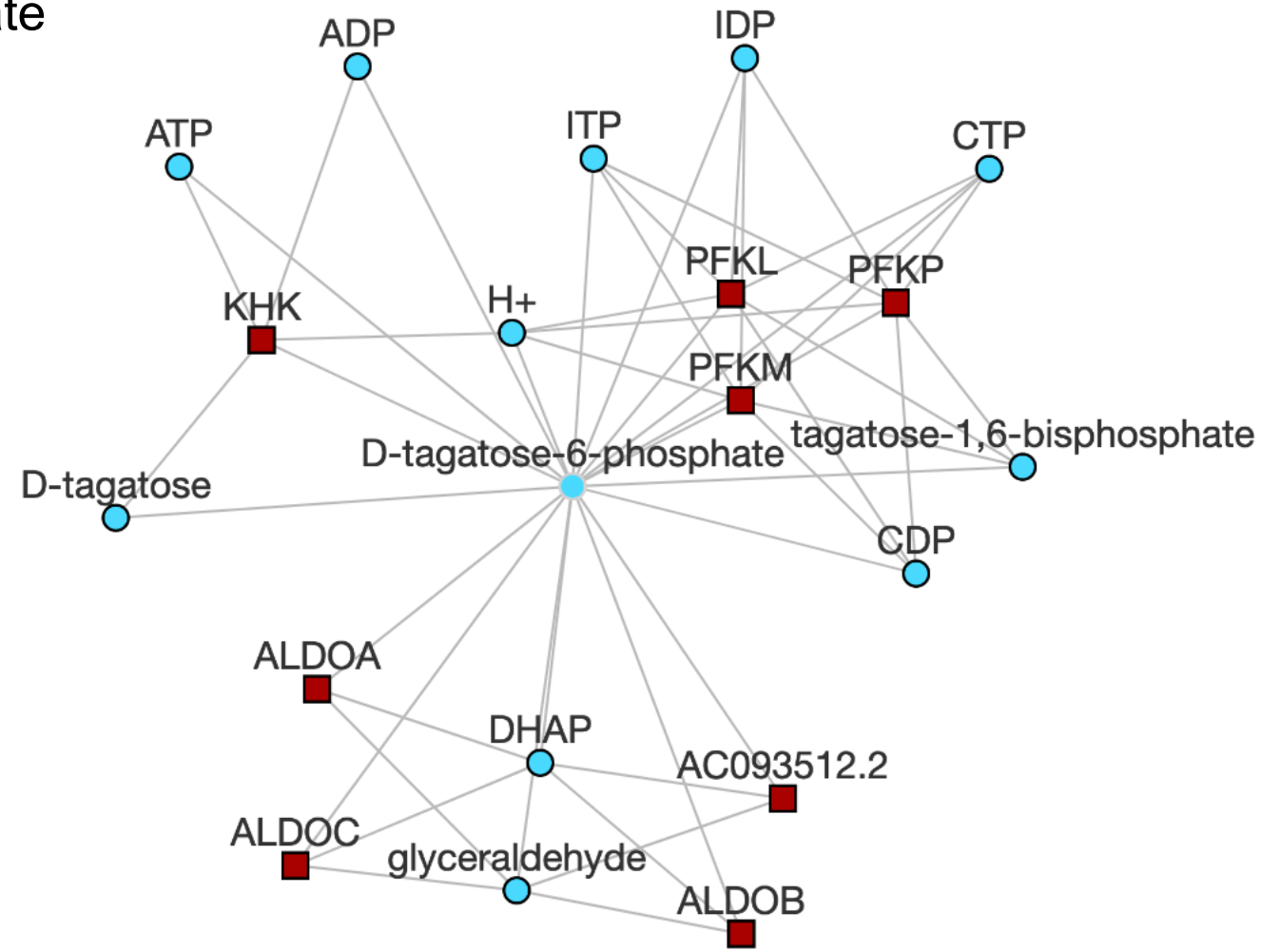
Reporter metabolites

Genes associated with
D-tagatose-6-phosphate



Reporter metabolites

D-tagatose-6-phosphate interaction partners

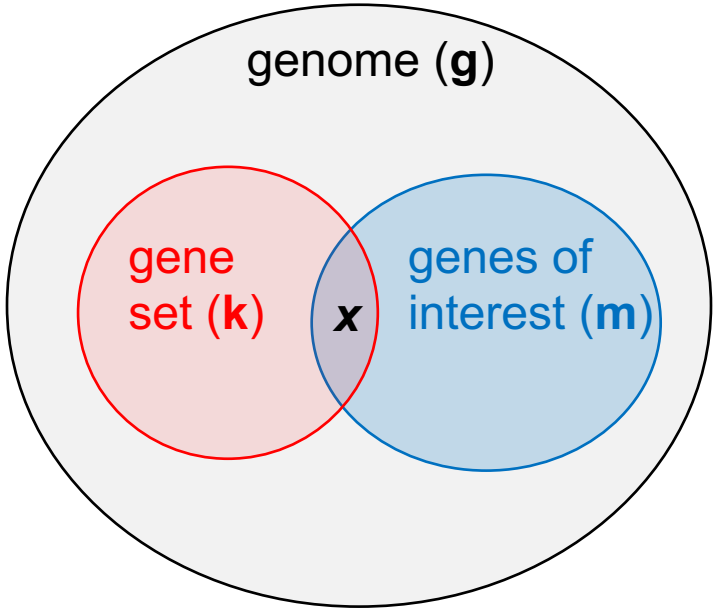


Gene list enrichment

Enrichment or over-representation analysis

Given a list of ***m*** genes of interest out of ***g*** in the genome and a gene-set of ***k*** genes, a statistical enrichment returns the probability that ***x*** out of the ***m*** genes of interest are in the gene-set.

This is calculated using Fisher's Exact Test (hypergeometric test):



$$p = \frac{\binom{k}{x}\binom{g-k}{m-x}}{\binom{g}{m}}$$

note: $\binom{n}{k} = \frac{n!}{k!(n-k)!}$

Gene list enrichment

Enrichr

Login | Register

28,099,440 lists analyzed
335,689 terms
168 libraries

Analyze | What's new? | Libraries | Gene search | Term search | About | Help

Input data

Choose an input file to upload. Either in BED format or a list of genes.

Try an example BED file.

Browse... No file selected.

Paste a list of valid Entrez gene symbols on each row in the text-box below. Try a gene set example.

ALDH3B1
EEF1A1
METTL16
UCKL1
UGT1A4
BCAT2
UGT1A9
UCKL1
HYI
PRODH2
ASNS

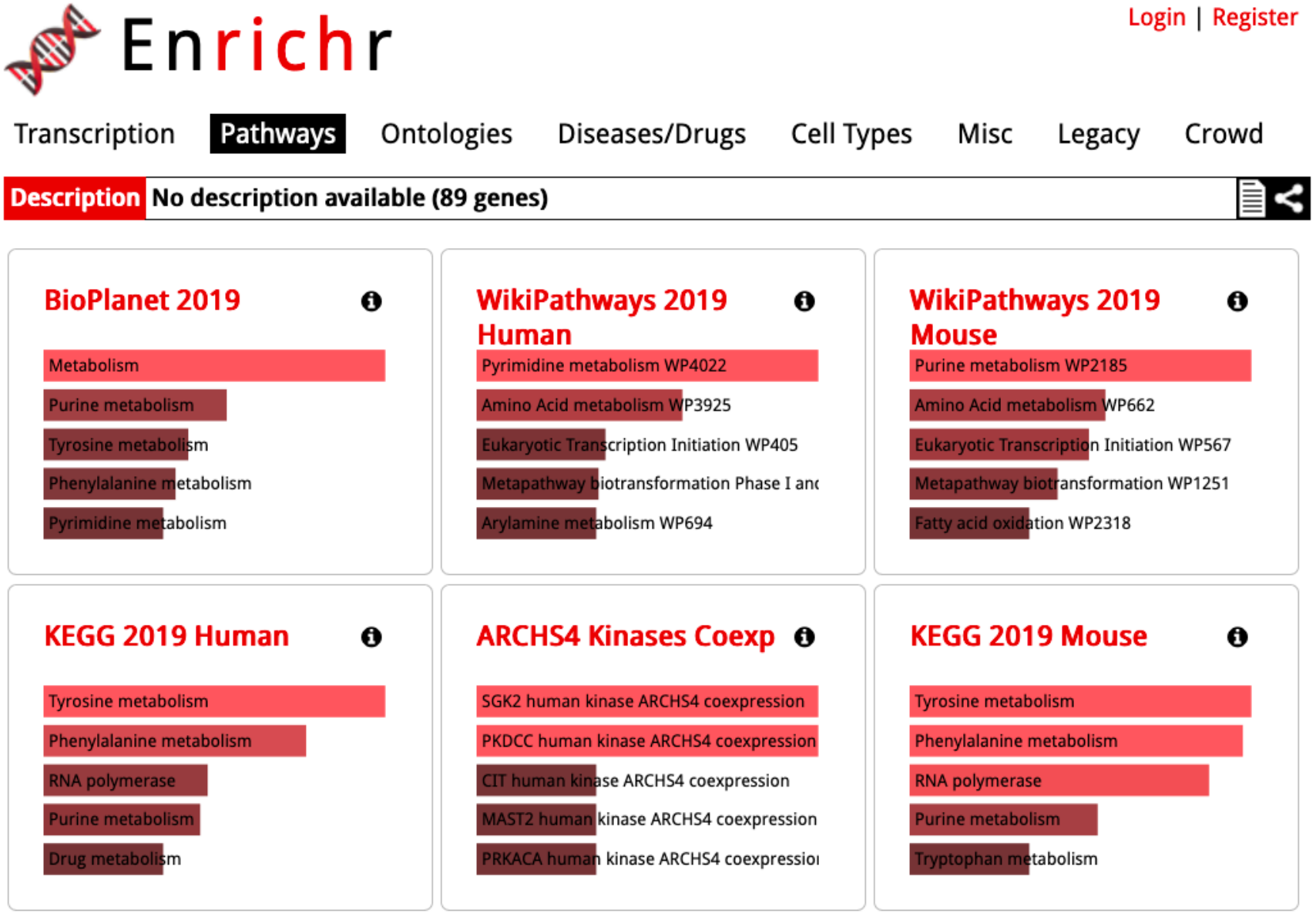
100 gene(s) entered

In order to enable others to search your list please enter a brief description of it.

Contribute your list so it can be searched by others

Submit

Gene list enrichment



Gene list enrichment

Limitations

- Requires arbitrary cutoff to define gene list
- Does not correct for gene-gene correlations
  (false positives)
- No ranking or relative scoring of genes
  (gene at the top of the list is identical to bottom)

Gene set analysis

List of genes

ENOPH1
SLC25A2
GMPPB
SLC1A4
EGFL8
HDC

Includes **only** the genes of interest

Gene-level statistics

0.01	A4GALT
0.89	A4GNT
0.51	AAAS
0.02	AACS
0.33	AADAC
0.08	AADAT
...	...

Includes **ALL** measured/ detected genes

Types of statistics:

- Differential expression p-value
- Differential expression fold-change
- Coefficient or significance of correlation (with phenotype)
- Rank

Gene set analysis

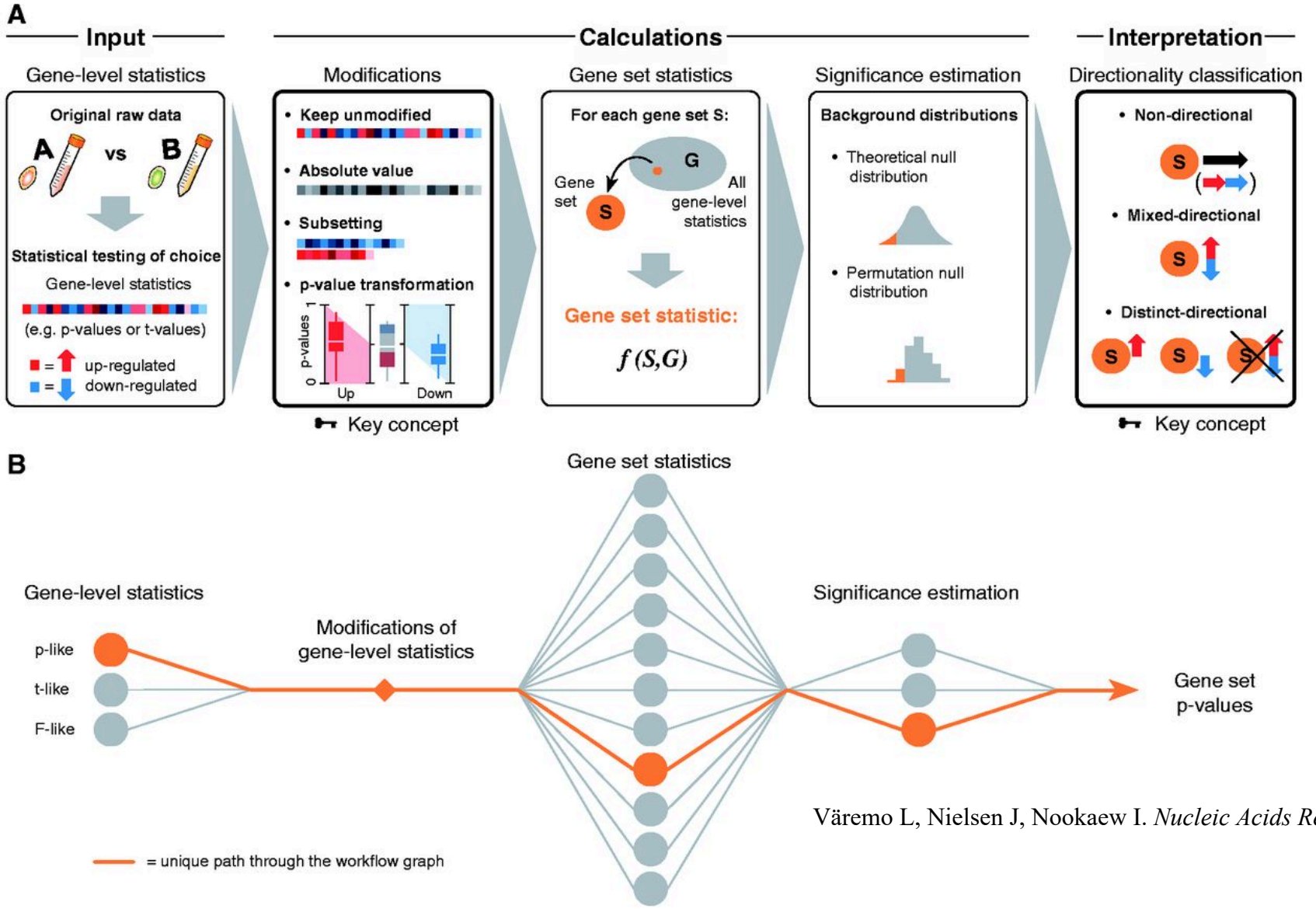
General GSA procedure

1. **Score each gene set** based on the statistics of the genes it contains

2. **Evaluate the significance** of each gene set score based on the score of the null or “background” score distribution

There are ***many*** methods for both steps 1 and 2

GSA Tools: Piano (R)



Väremo L, Nielsen J, Nookaew I. *Nucleic Acids Res*. 2013;41(8):4378-4391.

GSA Tools: Piano (R)

Gene-level statistics (DE results)

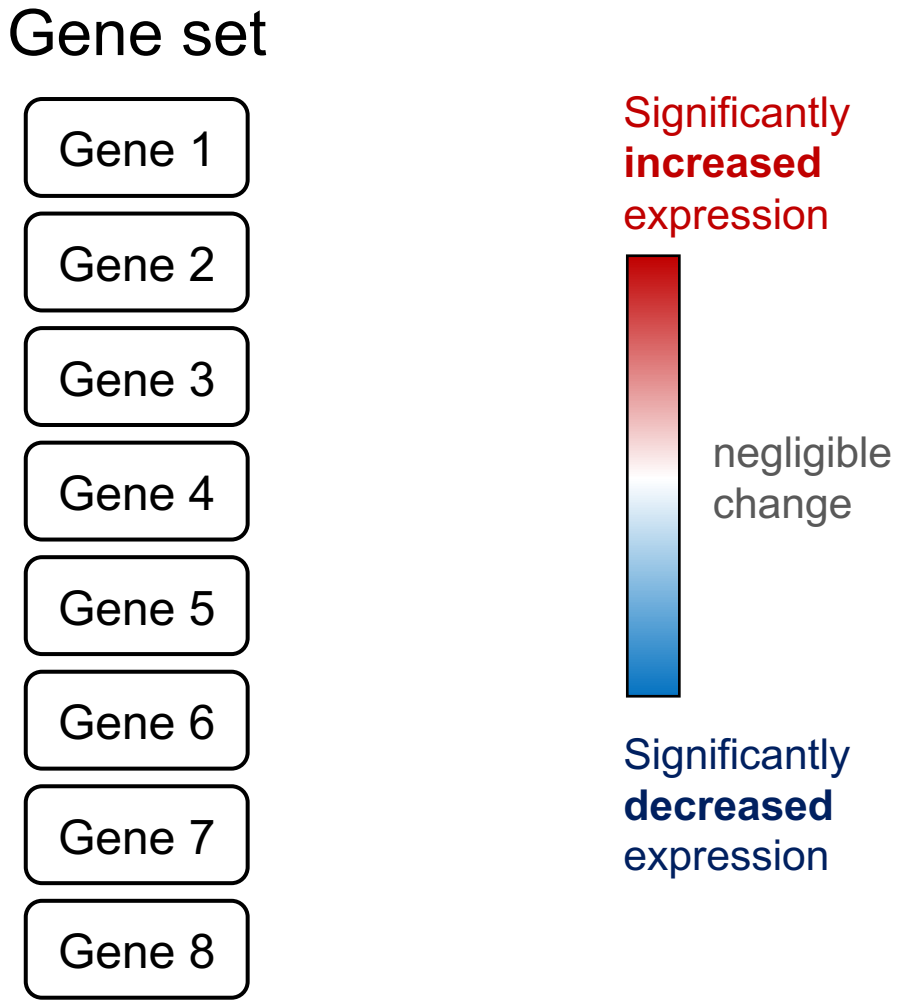
Gene	log2FC	p-value
ENOPH1	-2.4	0.0003
SLC25A2	1.1	0.09
GMPPB	0.3	0.8
SLC1A4	-0.9	0.2
EGFL8	-1.8	0.04
HDC	-6.2	0.0001
A4GALT	3.1	0.0002
...	...	...

GSA Tools: Piano (R)

For each gene set, we can calculate 5 different p-values:

Non-directional:

Test for enrichment of significant (low p-value) genes, ignoring fold-change direction.



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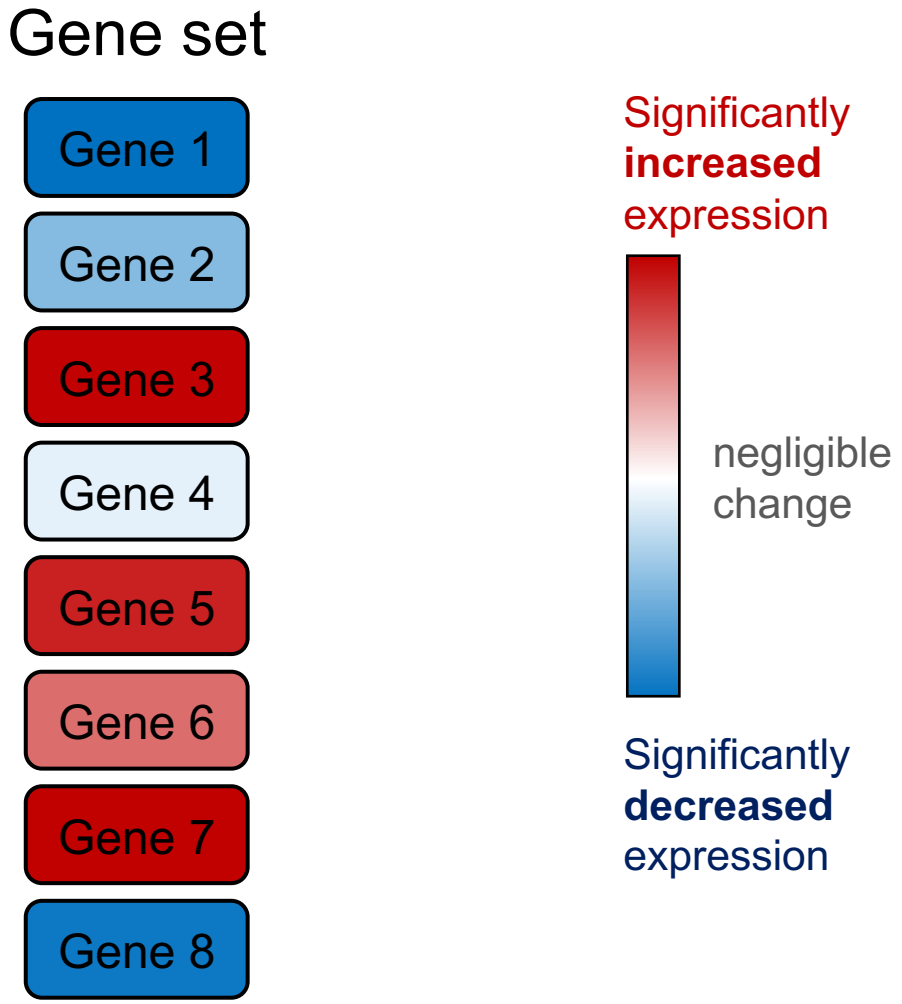


GSA Tools: Piano (R)

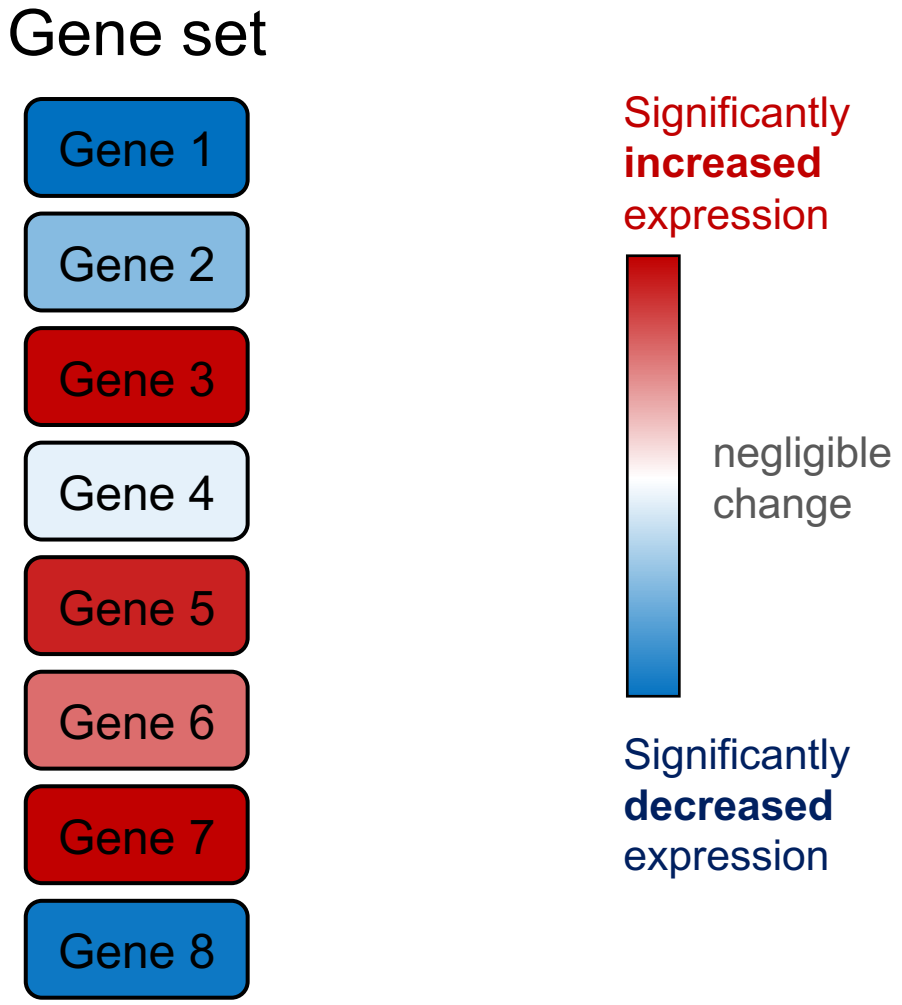
For each gene set, we can calculate 5 different p-values:

Non-directional:

Test for enrichment of significant (low p-value) genes, ignoring fold-change direction.

Mixed-directional (down and up):

Test if a *subset* of the gene set is enriched in significantly increased or decreased genes



GSA Tools: Piano (R)

For each gene set, we can calculate 5 different p-values:

Non-directional:

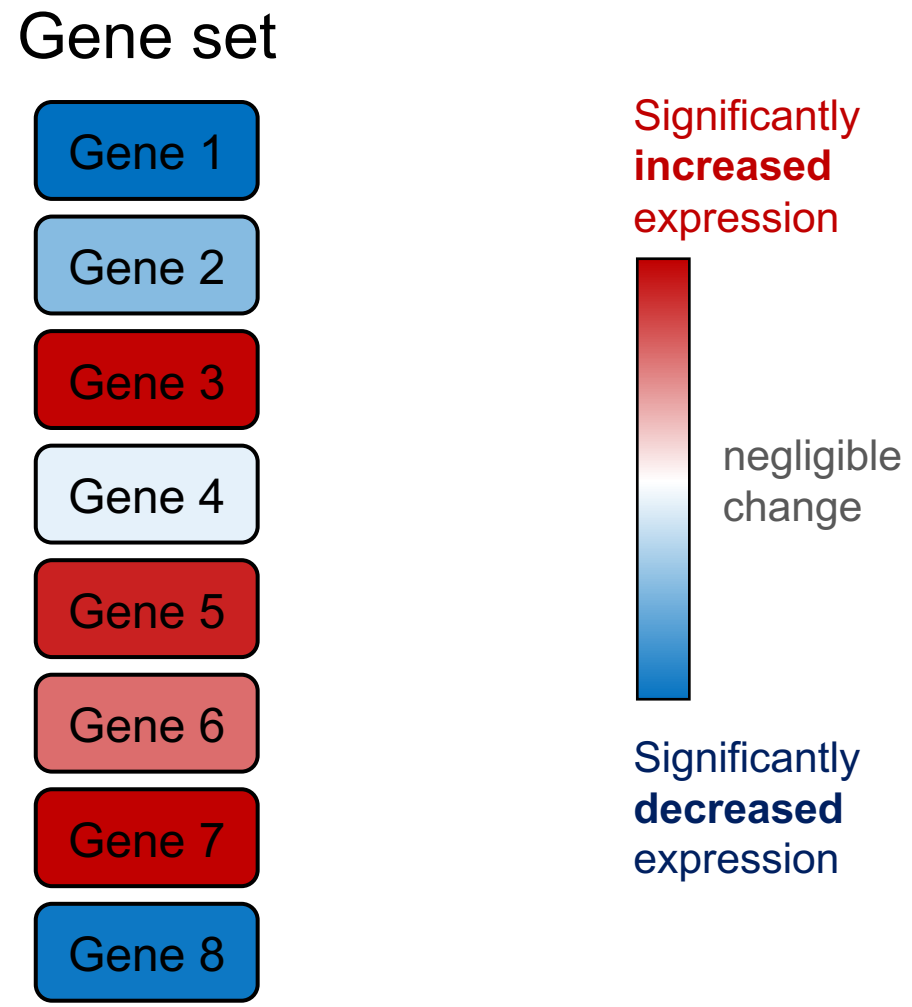
Test for enrichment of significant (low p-value) genes, ignoring fold-change direction.

Mixed-directional (down and up):

Test if a *subset* of the gene set is enriched in significantly increased or decreased genes

Distinct-directional (down and up):

Test if the gene set is enriched in significantly increased or decreased genes



GSA Tools: Piano (R)

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Test if a *subset* of the gene set is enriched in significantly increased or decreased genes

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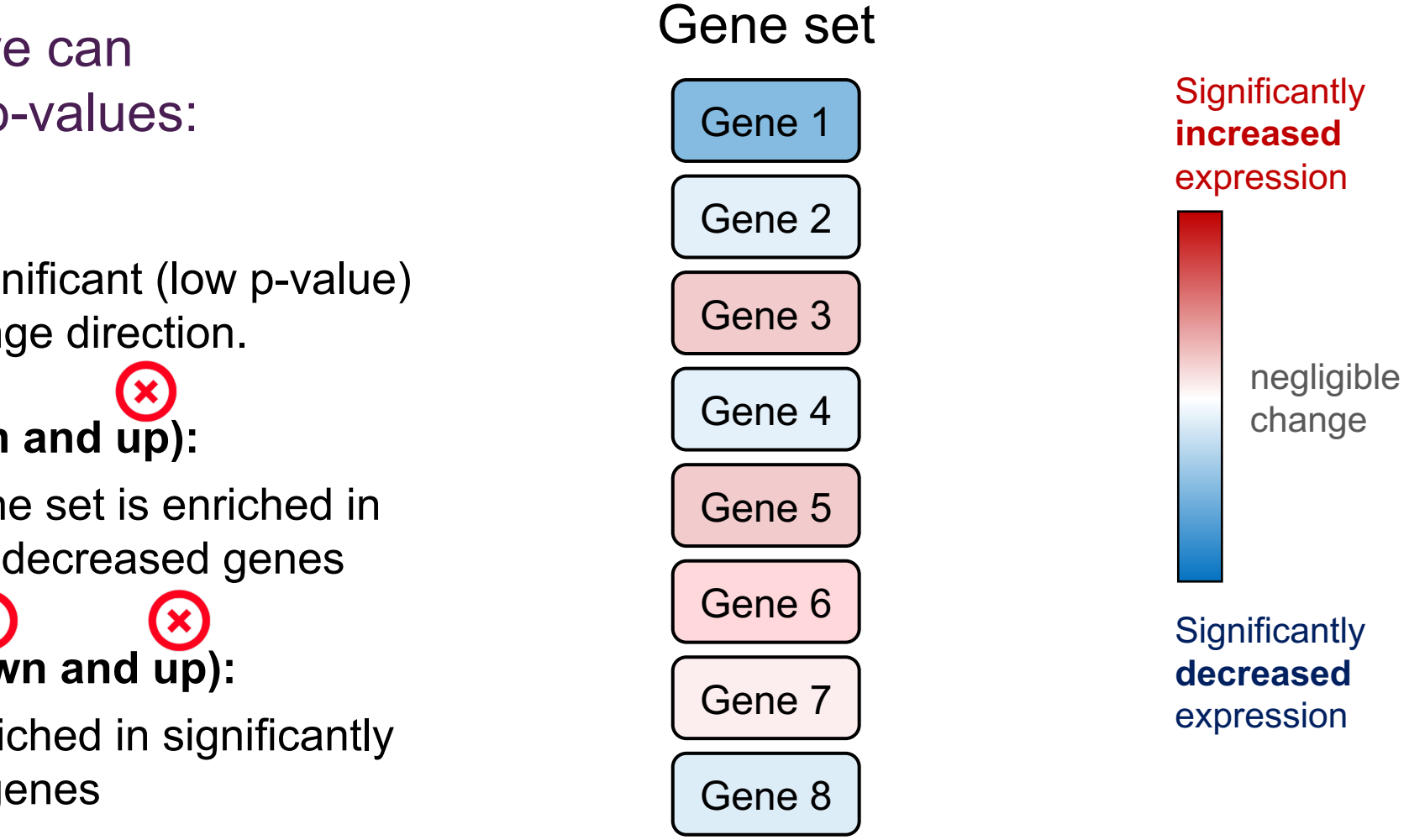

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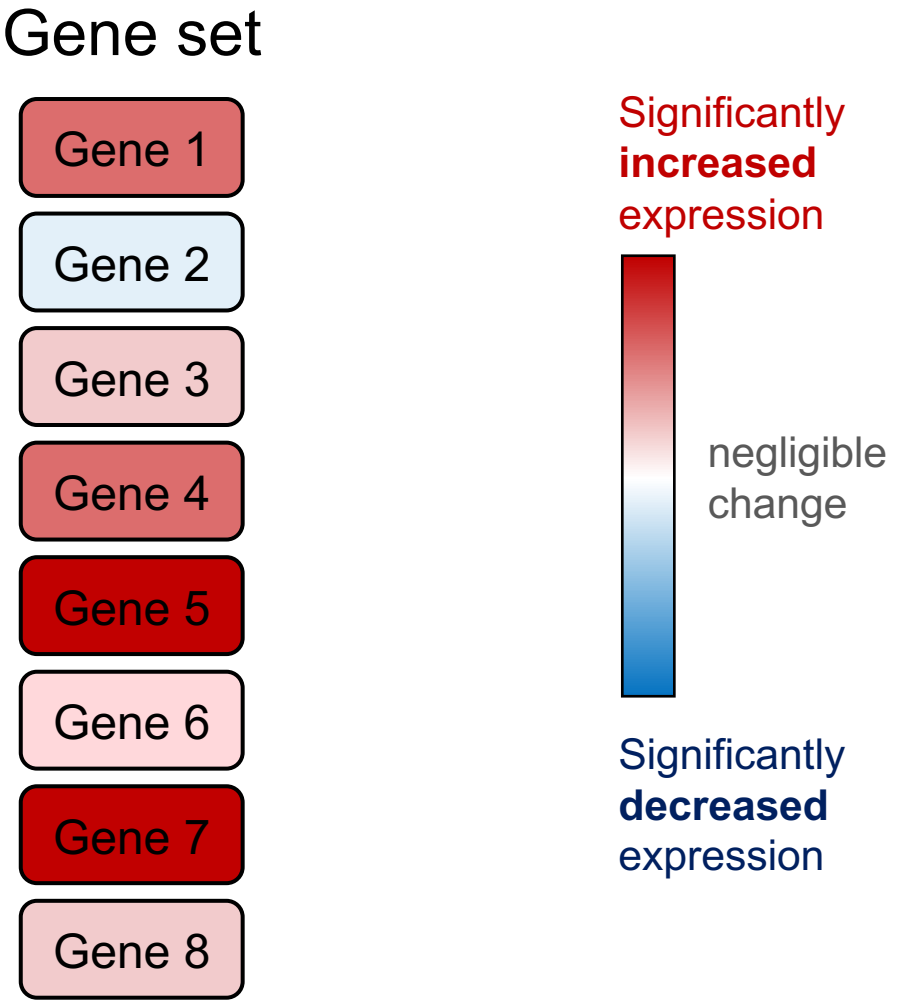
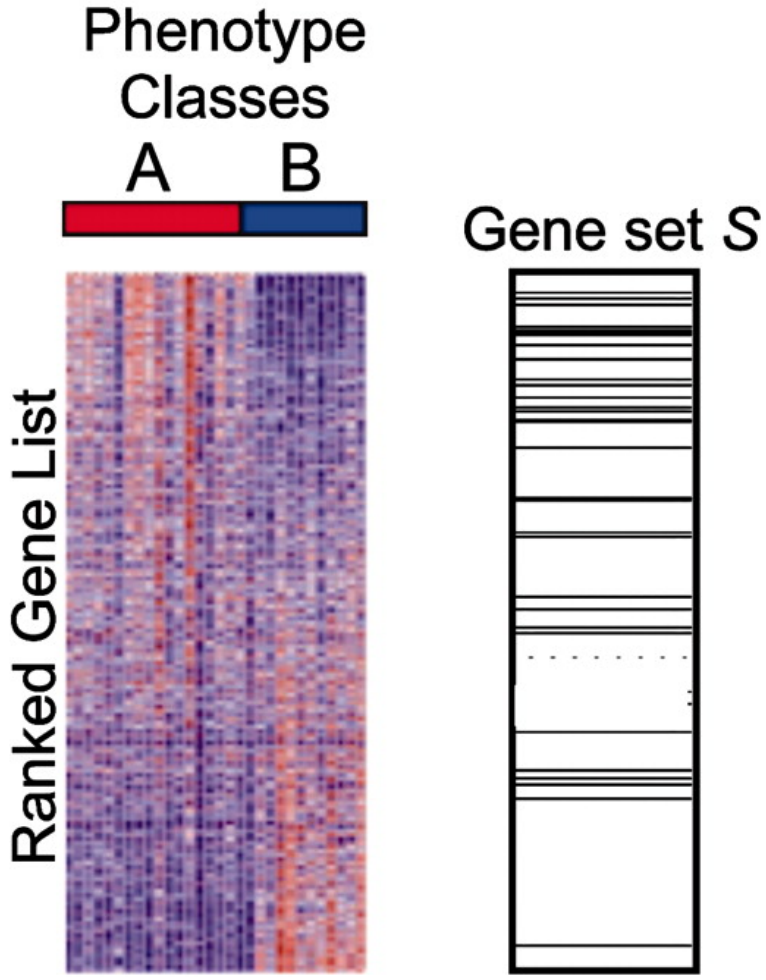
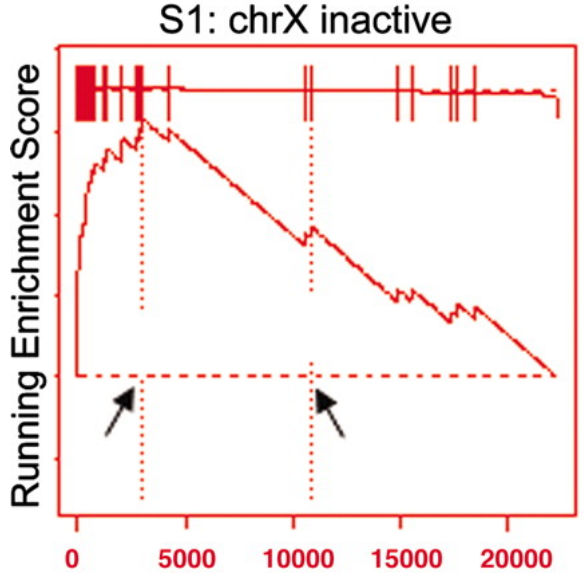
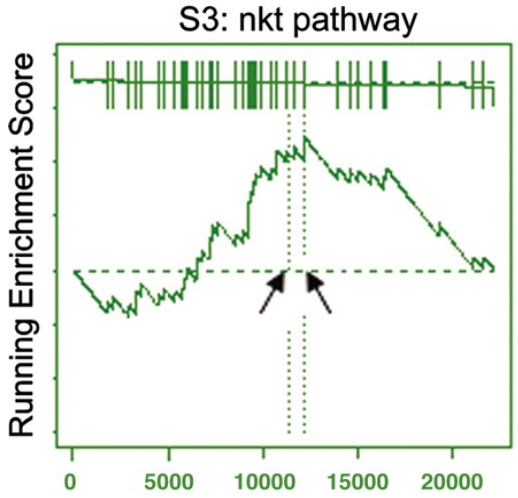


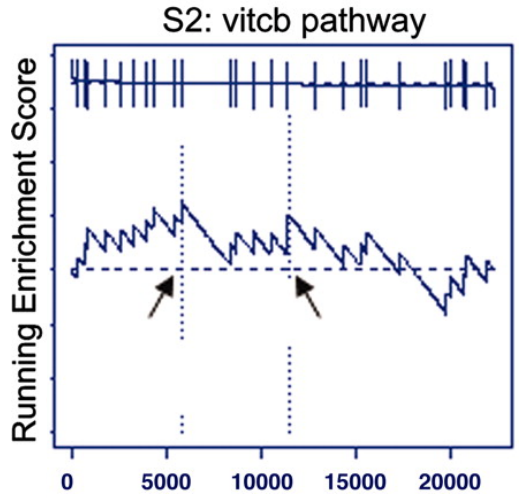
GSA Tools: GSEA (R, python)

Gene Set Enrichment Analysis





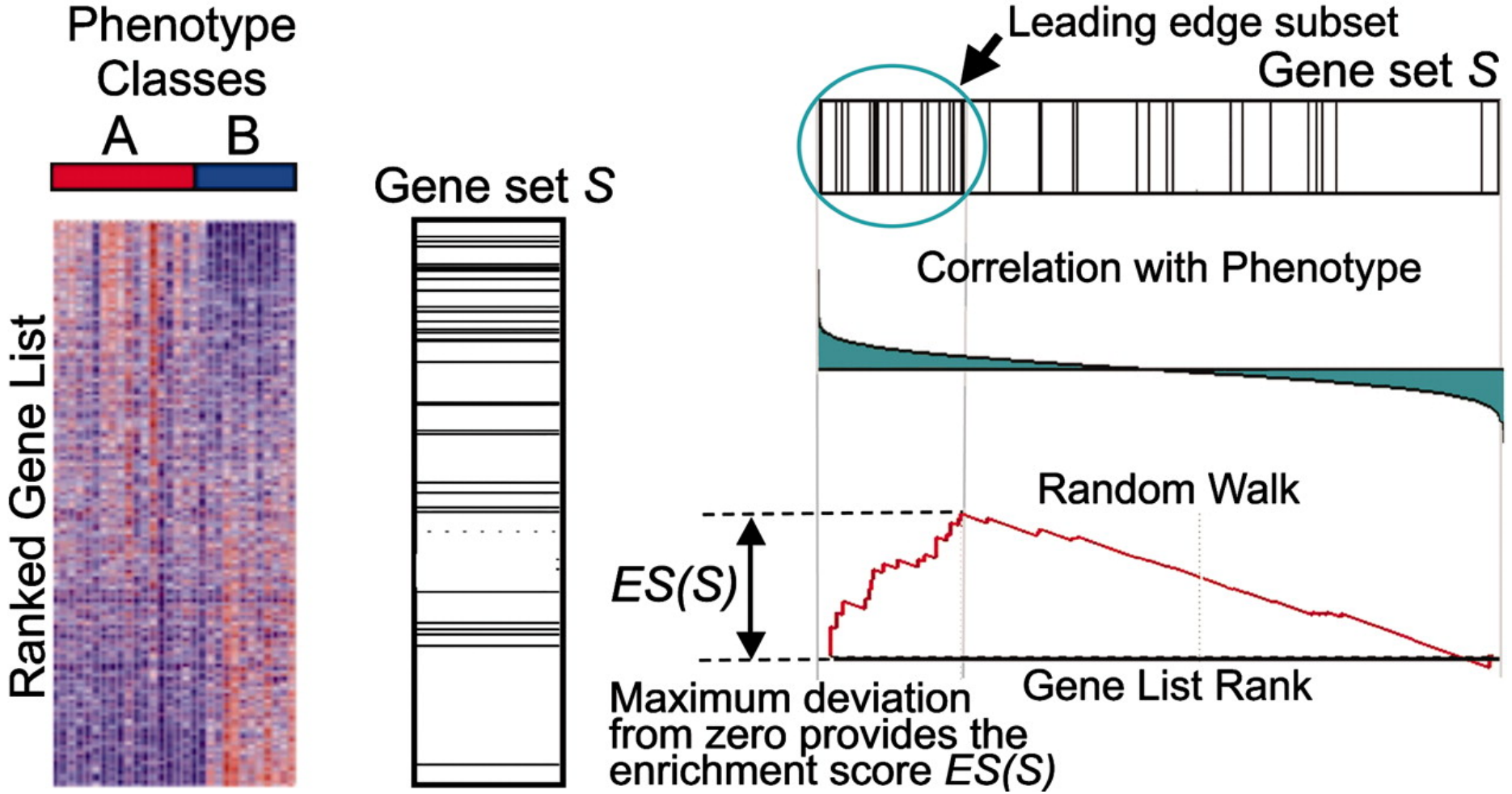




Subramanian, A, et al. *PNAS* 2005, 102 (43) 15545-15550

GSA Tools: GSEA (R, python)

Gene **S**et **E**nrichment **A**nalysis



Subramanian, A, et al. *PNAS* 2005, 102 (43) 15545-15550

Context-specific GEMs

A GEM contains all metabolic reactions that are known to occur within an organism

When working with multicellular organisms (e.g., humans), the **“generic” GEM containing all reactions** is not representative of any real cell or tissue type

We can use omics data to **extract a subset** of the generic GEM that is active in our system of interest

This GEM is called an “**extracted**” or **context-specific** GEM

Context-specific GEMs

There are many methods to generate context-specific GEMs.

For example:

- **iMAT** (Integrative Metabolic Analysis Tool)
- **MBA** (Model Building Algorithm)
- **mCADRE** (metabolic Context-specificity Assessed by Deterministic Reaction Evaluation)
- **tINIT** (Task-driven Integrative Network Inference for Tissues)
- **FASTCORE**

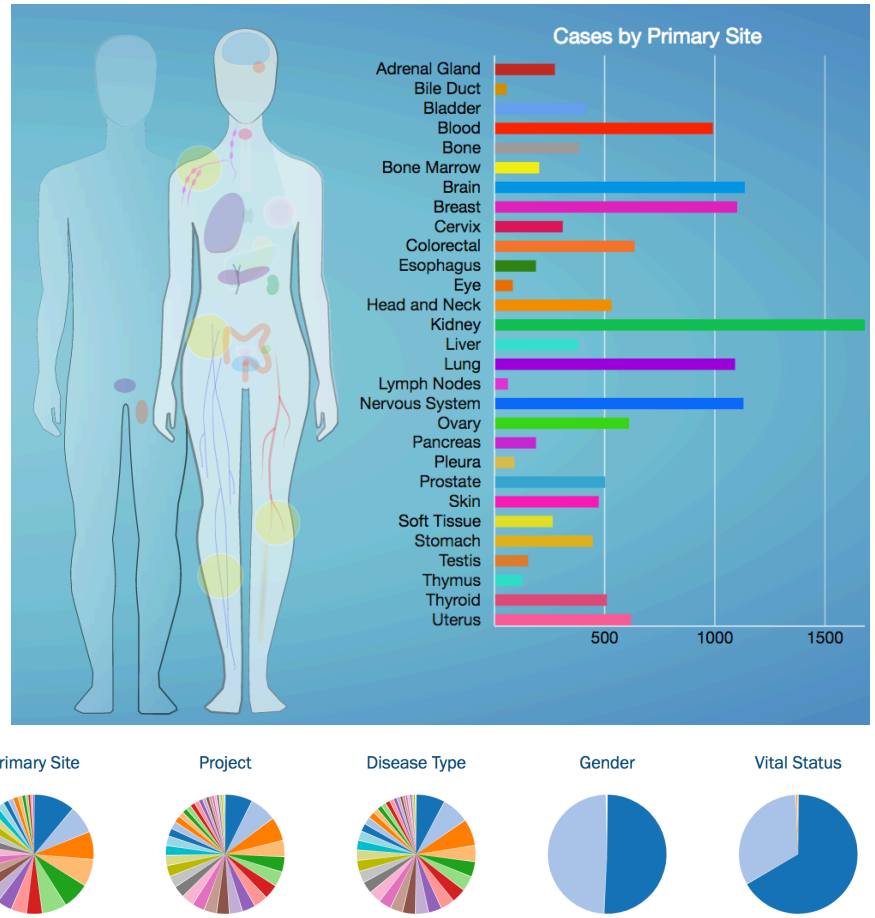
Unfortunately, they were all implemented in MATLAB.

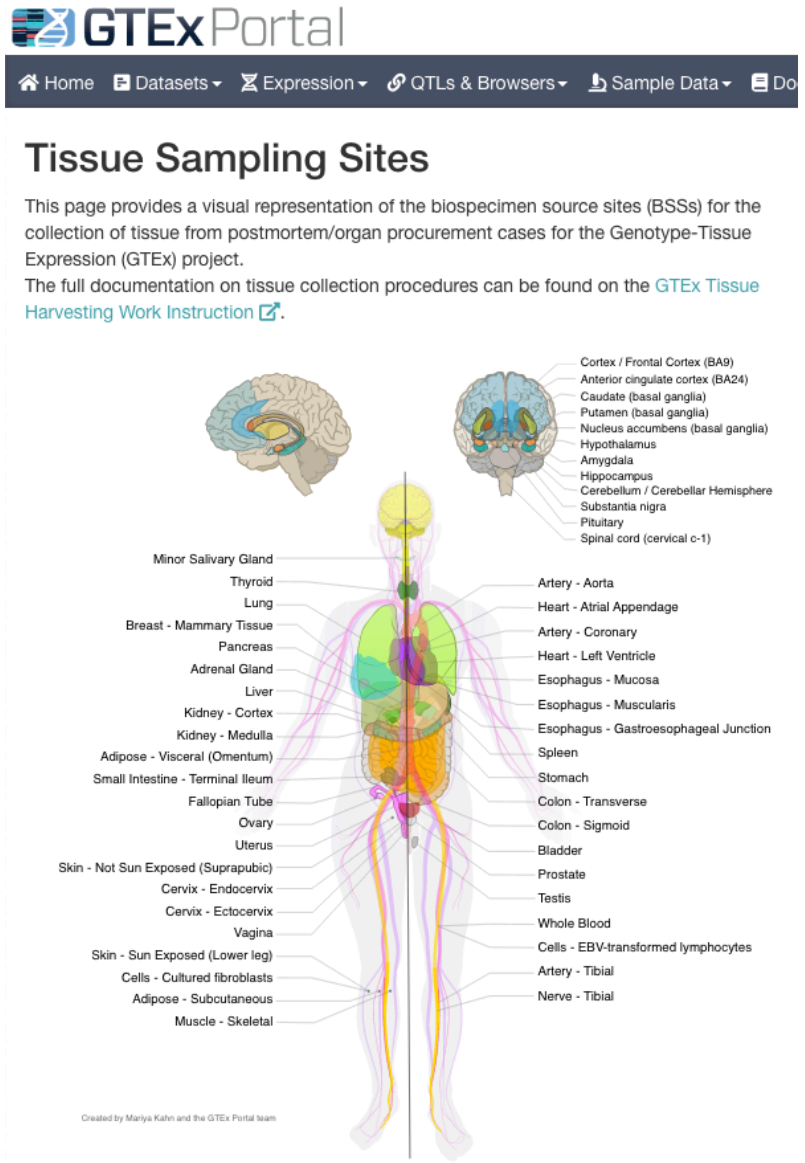
Here are some links to tutorials to using some of the methods:

tINIT: https://sysbiochalmers.github.io/Human-GEM-guide/gem_extraction/
iMAT: https://opencobra.github.io/cobratoolbox/stable/tutorials/tutorialExtractionTranscriptomic.html

GEM-based comparison of transcriptomes

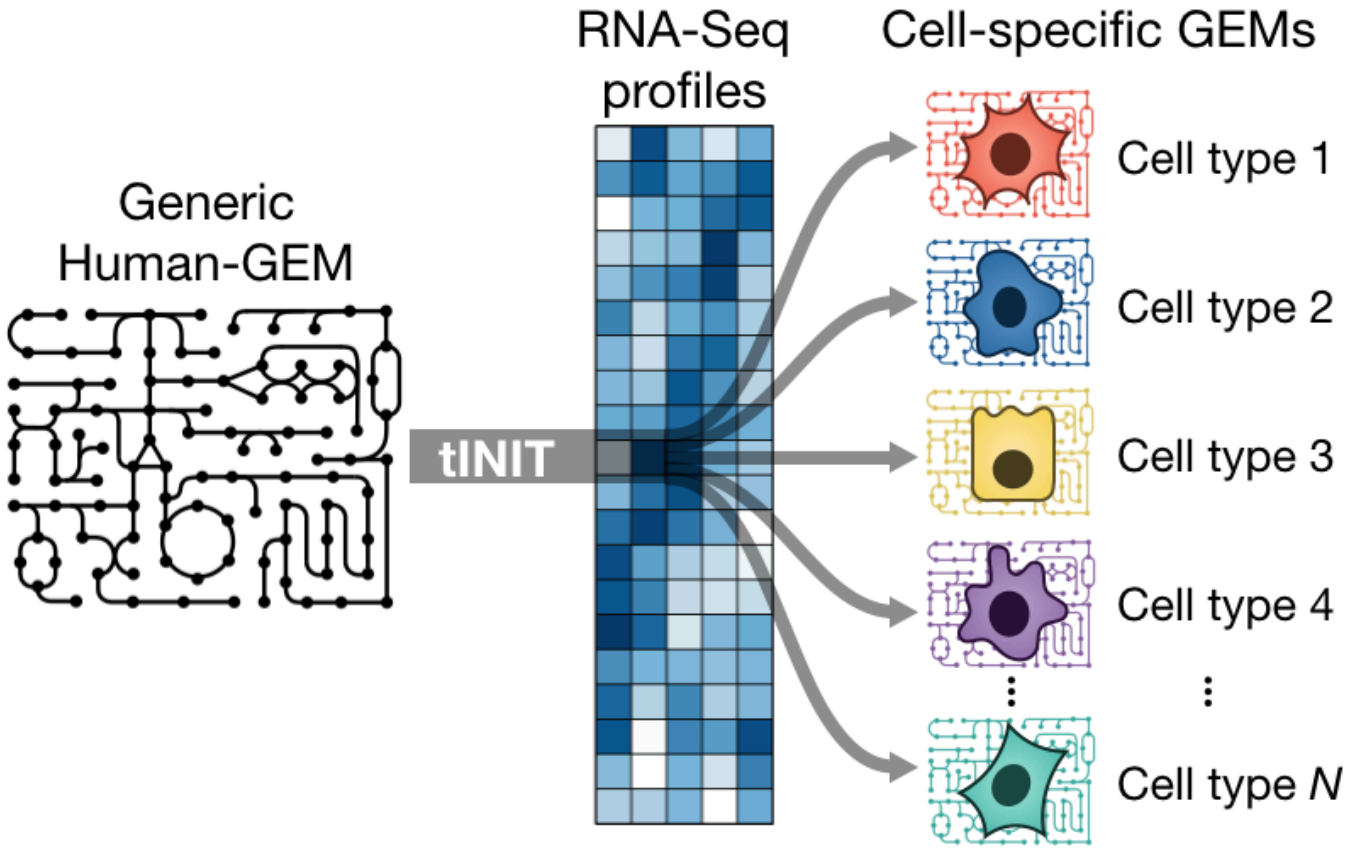
From the study Robinson, et al. An atlas of human metabolism. *Science Signaling* 2020





GEM-based comparison of transcriptomes

Context-specific GEMs were extracted for each of the cancer types and healthy tissue types



GEM-based comparison of transcriptomes

GEM structure (reaction content) can be represented by a binary vector

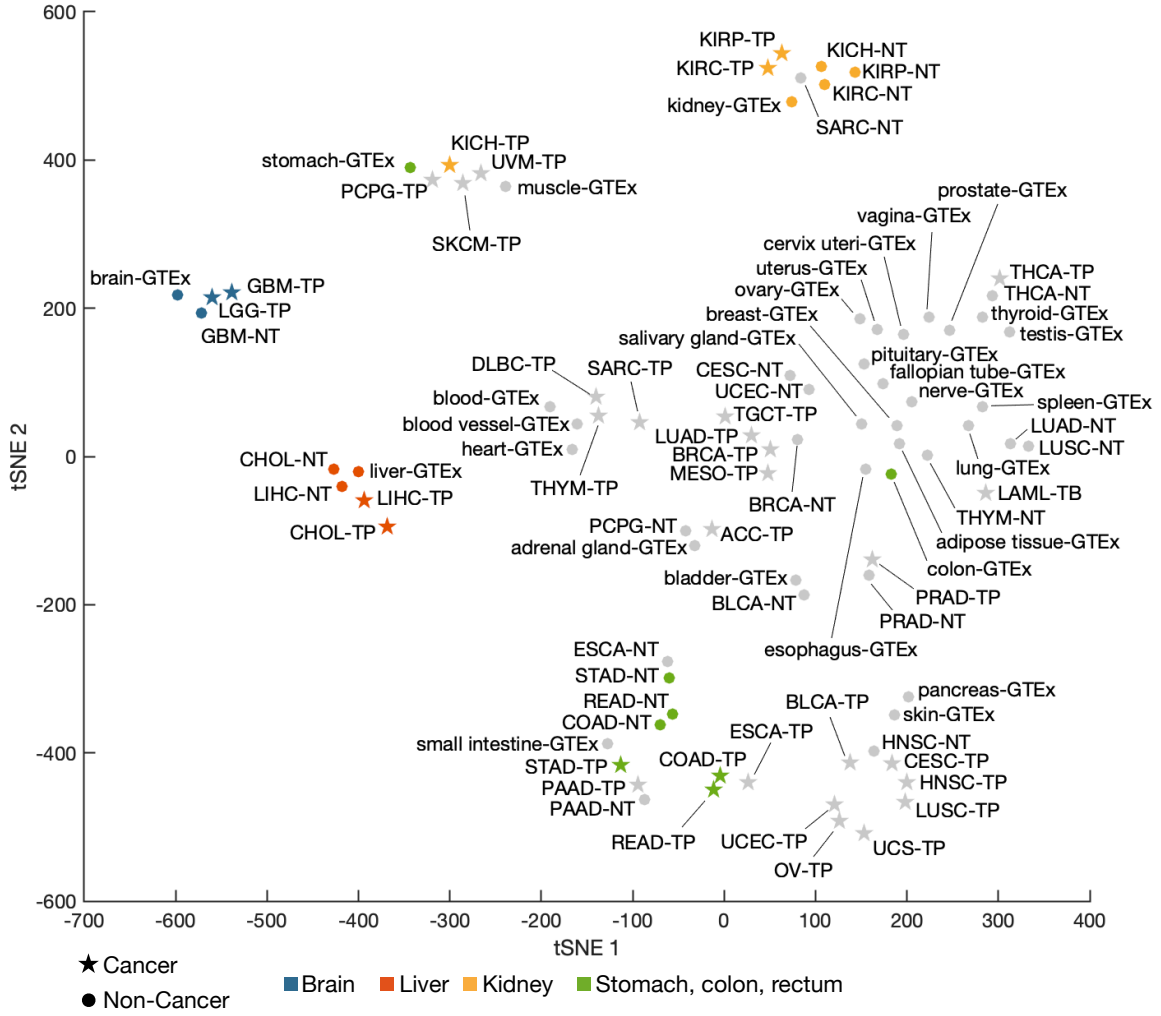
Reaction	Lung Tumor	Lung Paired	Lung Healthy	Brain Tumor	Brain Paired	…
rxn1	1	0	1	1	1	
rxn2	0	1	1	1	1	
rxn3	0	0	0	0	0	
rxn4	0	1	0	1	0	
rxn5	1	1	0	1	1	
rxn6	1	0	0	1	0	
rxn7	0	0	1	1	0	
⋮						⋱

Model **contains** reaction

Model **missing** reaction

GEM-based comparison of transcriptomes

Distance (Hamming) between each GEM reaction content vector can be calculated and projected in a tSNE embedding



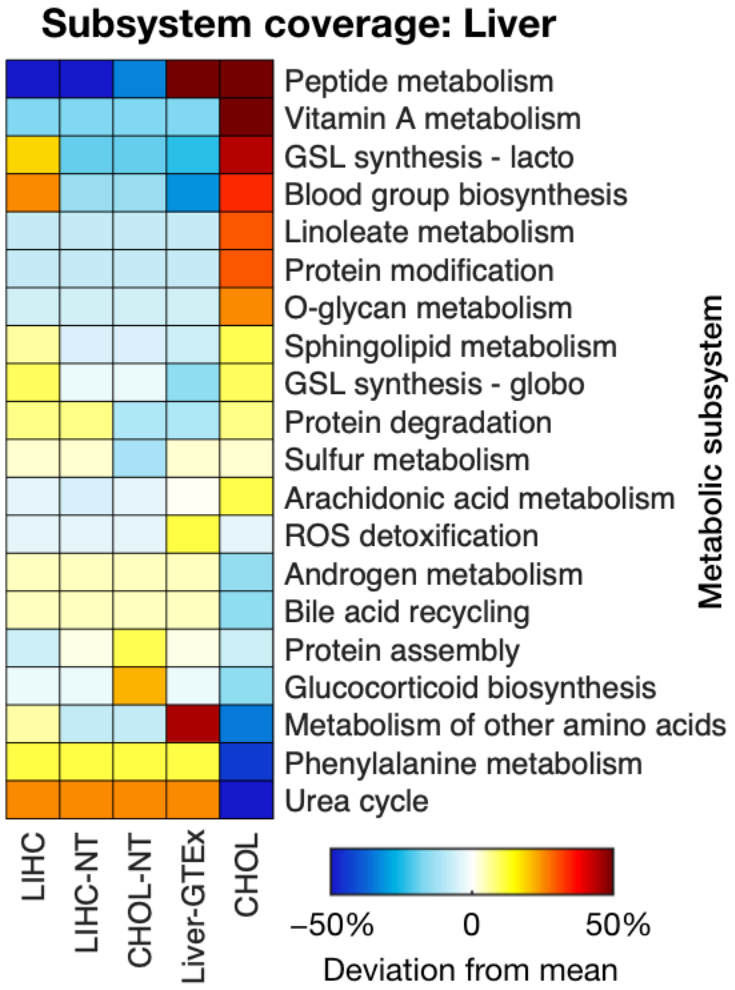
GEM-based comparison of transcriptomes

If reaction subsystem labels are included, we can look at subsystem-specific differences between GEMs

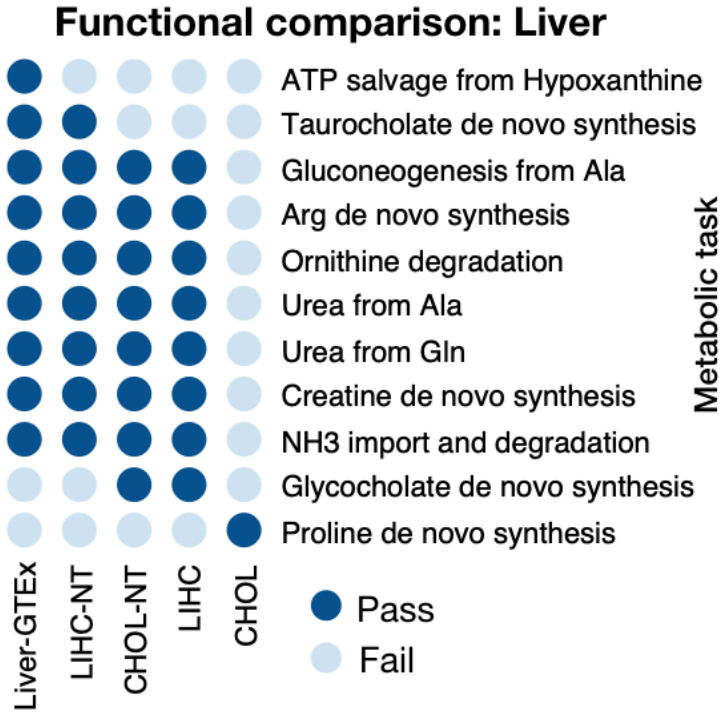
Subsystem	Reaction	Lung Tumor	Lung Paired	Lung Healthy	Brain Tumor	Brain Paired	…
TCA cycle	rxn1	1	0	1	1	1	
TCA cycle	rxn2	0	1	1	1	1	
Glycolysis	rxn3	0	0	0	0	0	
TCA cycle	rxn4	0	1	0	1	0	
Fatty acid oxidation	rxn5	1	1	0	1	1	
Carnitine shuttle	rxn6	1	0	0	1	0	
Glycolysis	rxn7	0	0	1	1	0	
⋮							⋱

GEM-based comparison of transcriptomes

If reaction subsystem labels are included, we can look at subsystem-specific differences between GEMs



Furthermore, FBA can be used to determine what metabolic functions the GEMs can or cannot perform



Exercise: GEM-based GSA

Exercise part 1: (python, short)
Extract metabolite and subsystem gene sets from Human-GEM

Exercise part 2: (R)
Use the GEM-derived gene set collections to evaluate enrichment of differentially expressed genes in different regions of the metabolic network.