

Genome scale metabolic modeling & Combining forces for Recon and WikiPathways

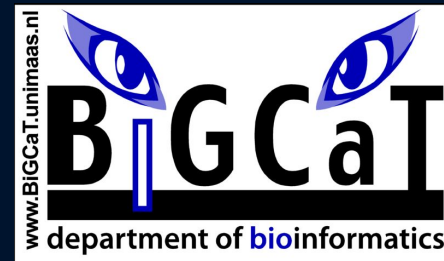
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Modelling intra-cellular metabolism of adipocytes

Omics data integration using genome-scale metabolic models

Chaitra Sarathy

PhD Candidate, MaCSBio

13/06/2019



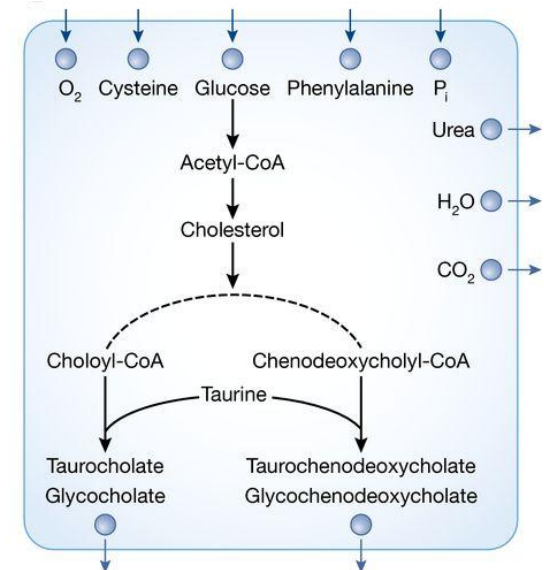
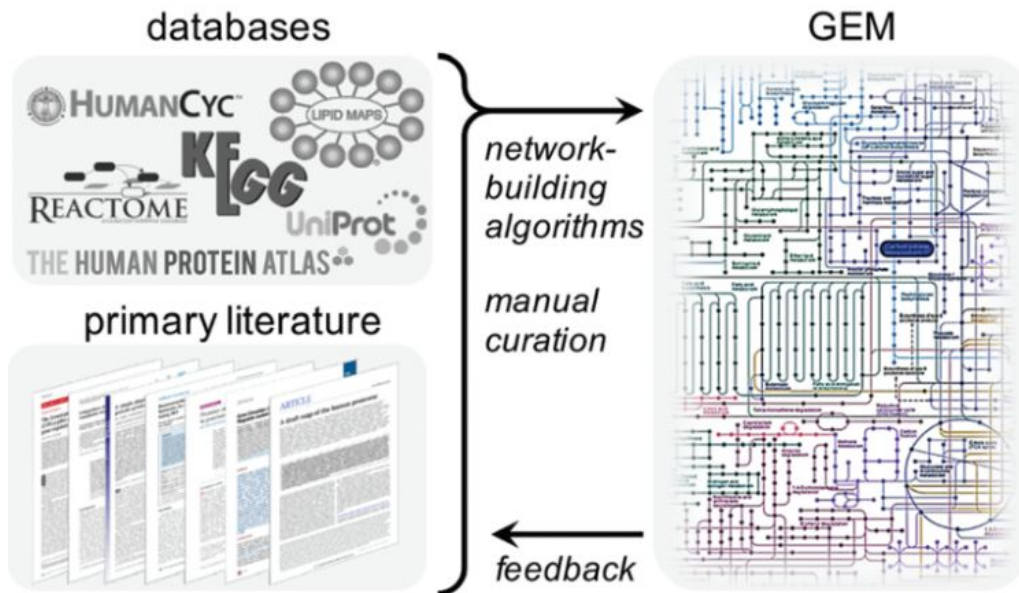
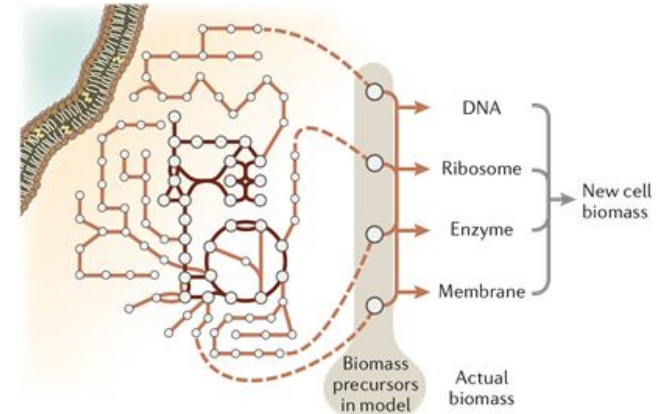
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Genome Scale Metabolic Models

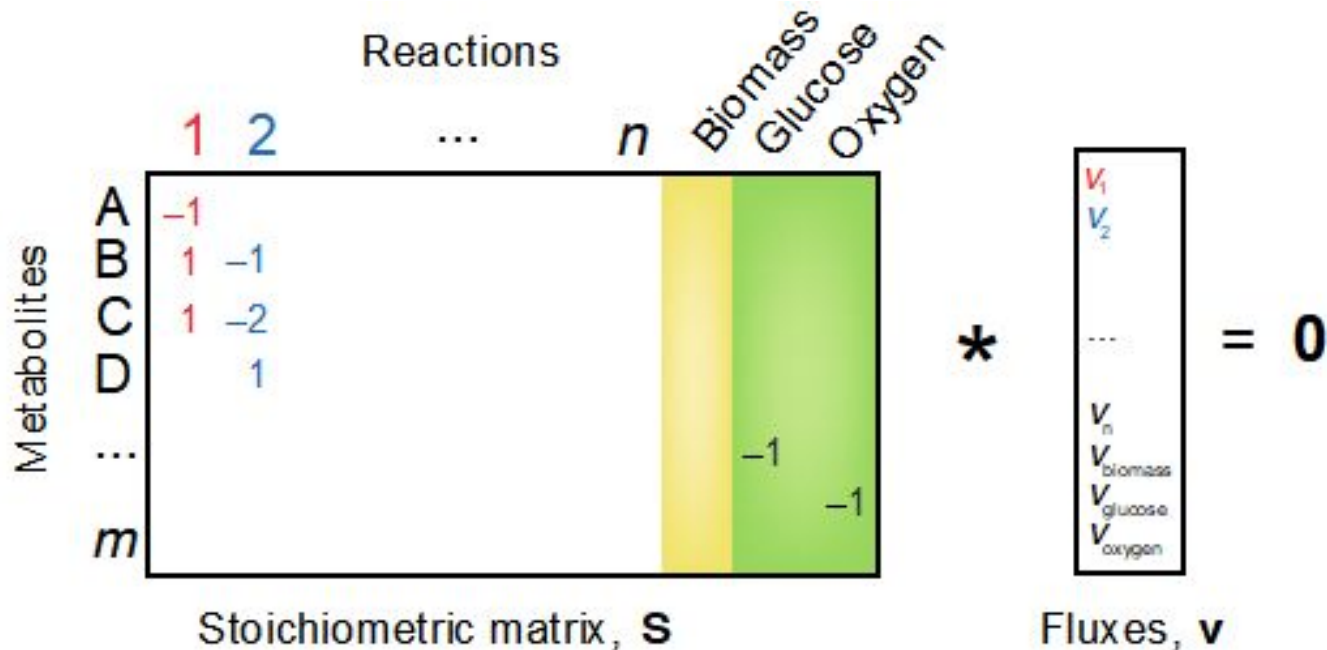
- *in silico* representations of all known metabolic reactions in an organism and the genes that encode each enzyme
- complete description of an organism's metabolic capabilities
- assembled from existing database of genes, proteins, enzymes, metabolites and reactions



Genome Scale Metabolic Models

- Flux Balance Analysis

Stoichiometric Matrix

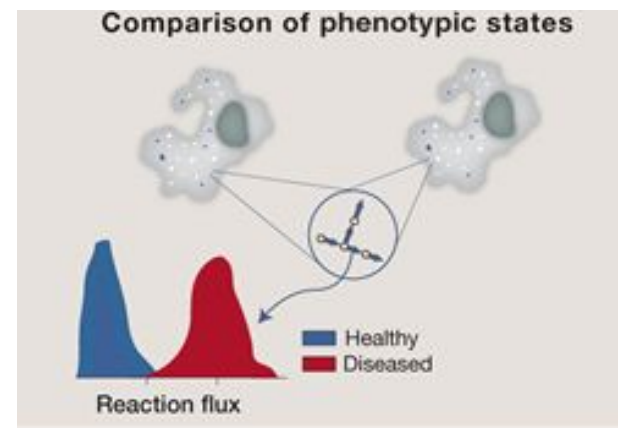
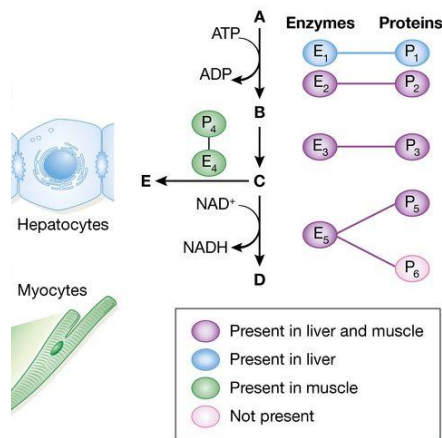
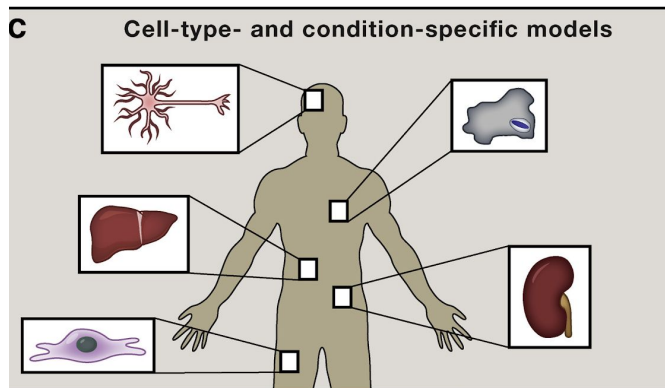
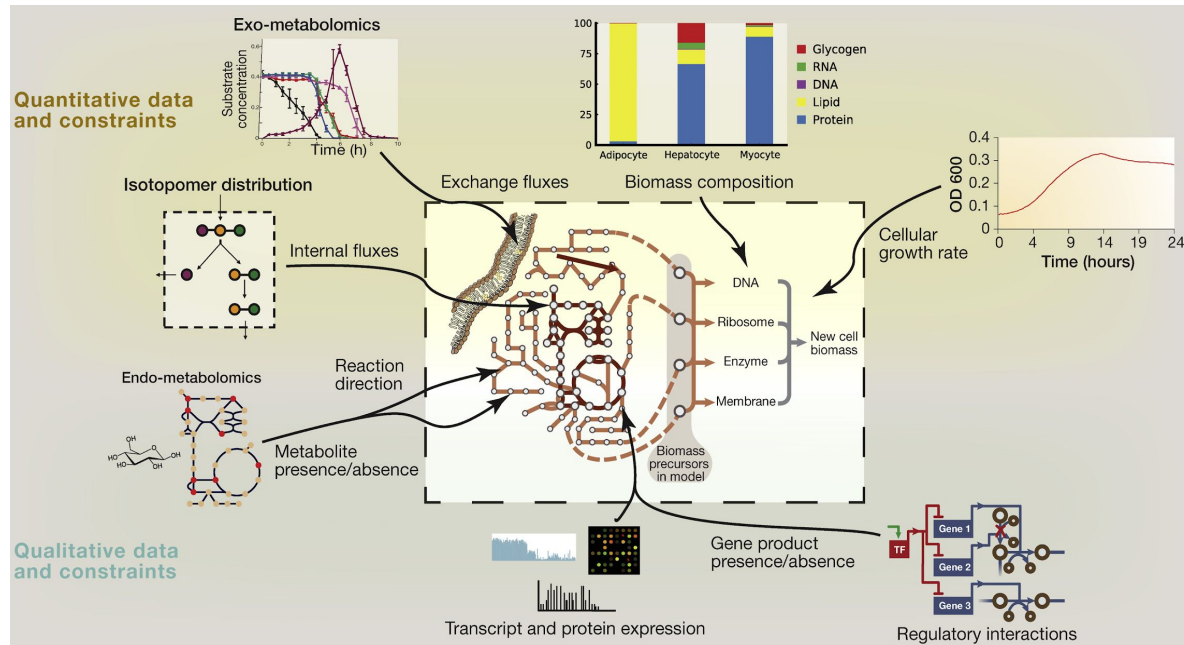


$$S \cdot \vec{v} = \vec{0}$$

Flux-balance analysis: Find vector that maximizes e.g. biomass production

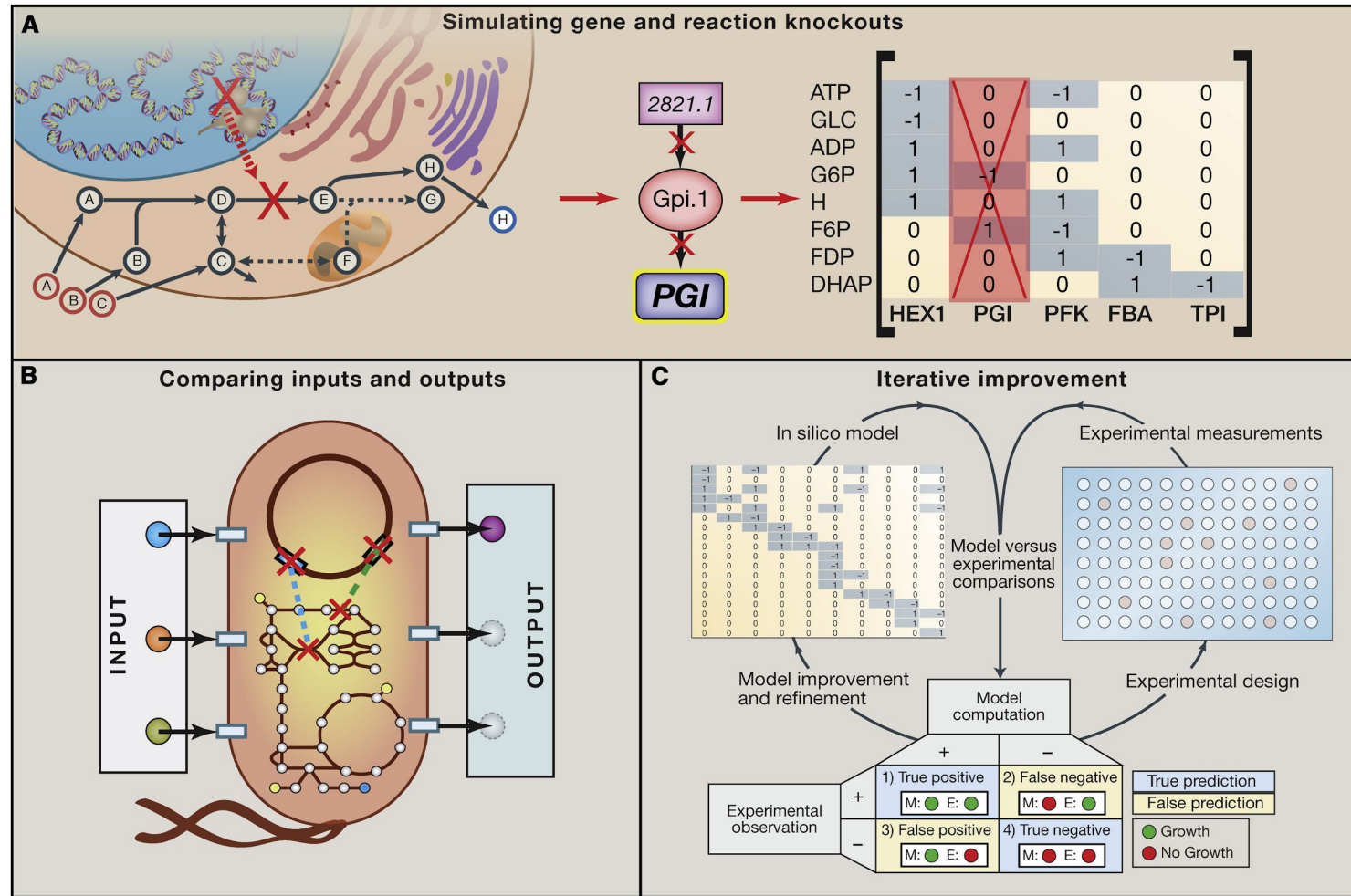
Genome Scale Metabolic Models

- Omics Integration



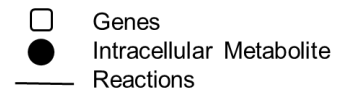
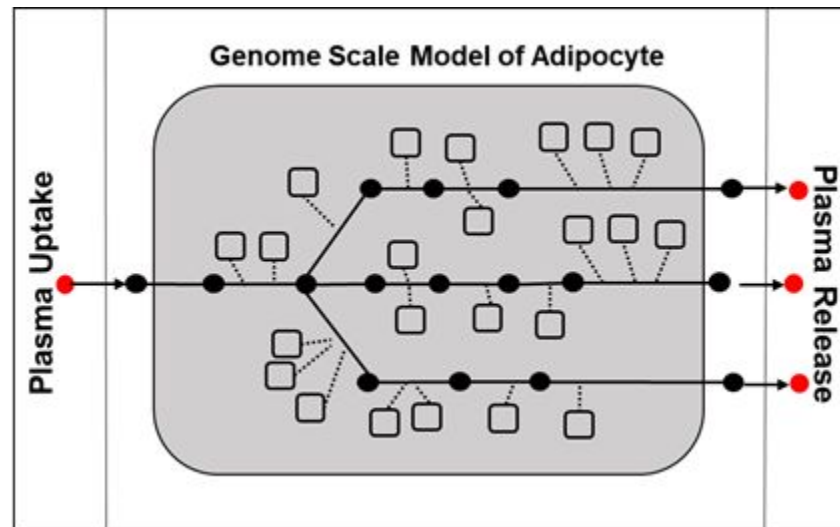
Genome Scale Metabolic Models

- (some) Applications



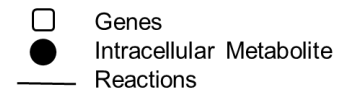
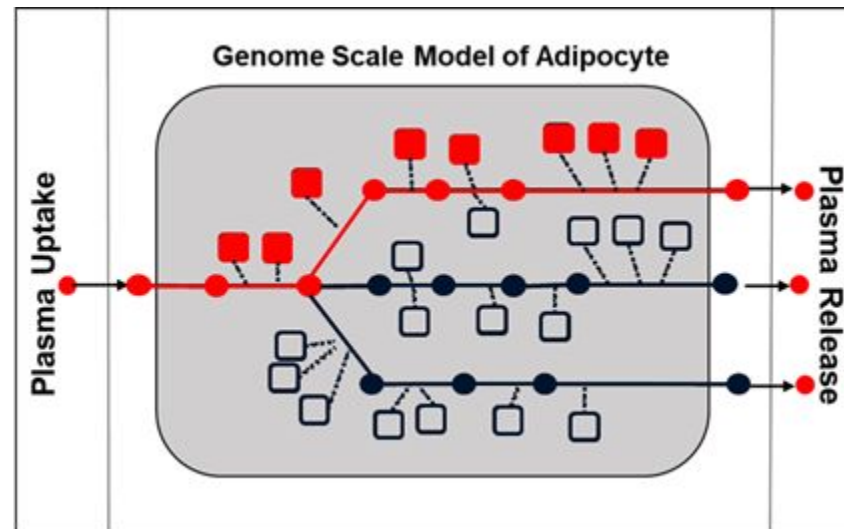
Overall Objective

- Understand role of adipocytes in regulating plasma metabolite levels
- Integrate gene expression from adipose tissue + plasma metabolomics data
- Identify relevant genes, intracellular metabolites and reactions
- Apply GEM-based approaches



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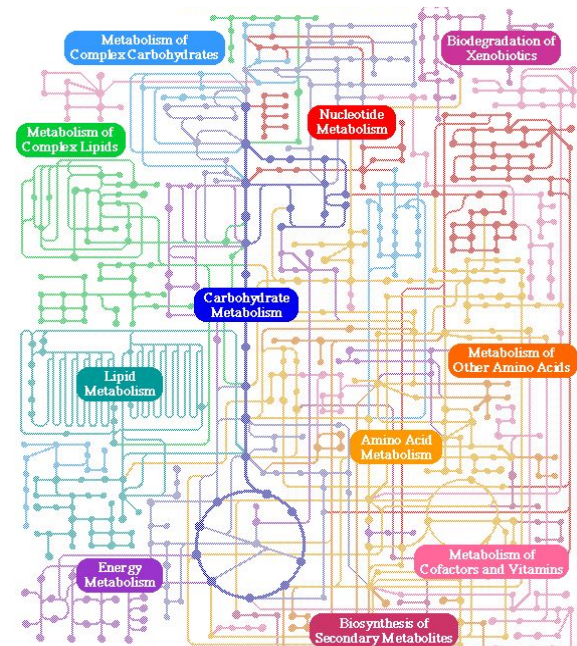
Methods - EFM Analysis

- Elementary Flux Modes (EFMs): non-decomposable, steady-state pathways in metabolic networks
- Network exploration method for identifying possible routes

City Map



Metabolic Map

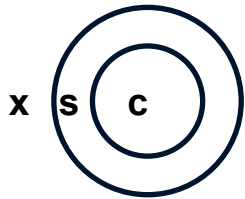


Identify parts of the network important for catabolism of specific plasma metabolites

Methods - EFM Generation

Model compartments

[x] - Blood
[s] - Intrastitial space
[c] - Cytosol



XSC = uptake
CSX = release

Approach used: TreeEFM¹

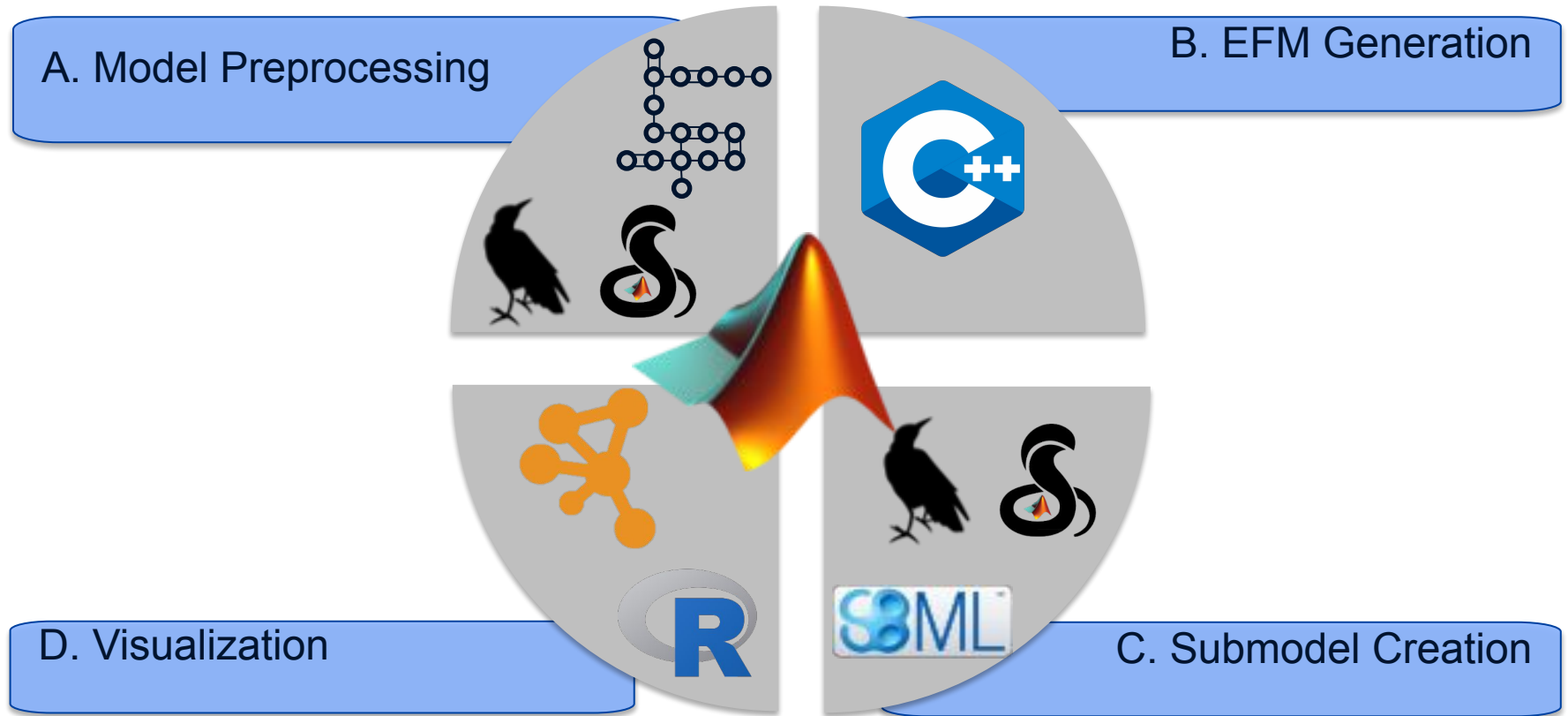
- MILP-based tree search for EFM enumeration
- implemented in C++ (source code unavailable)
- Inputs
 - Stoichiometry (irreversible reactions & cofactors removed)
 - Active reaction – uptake or release

Table 1: Total number of EFMs identified by TreeEFM

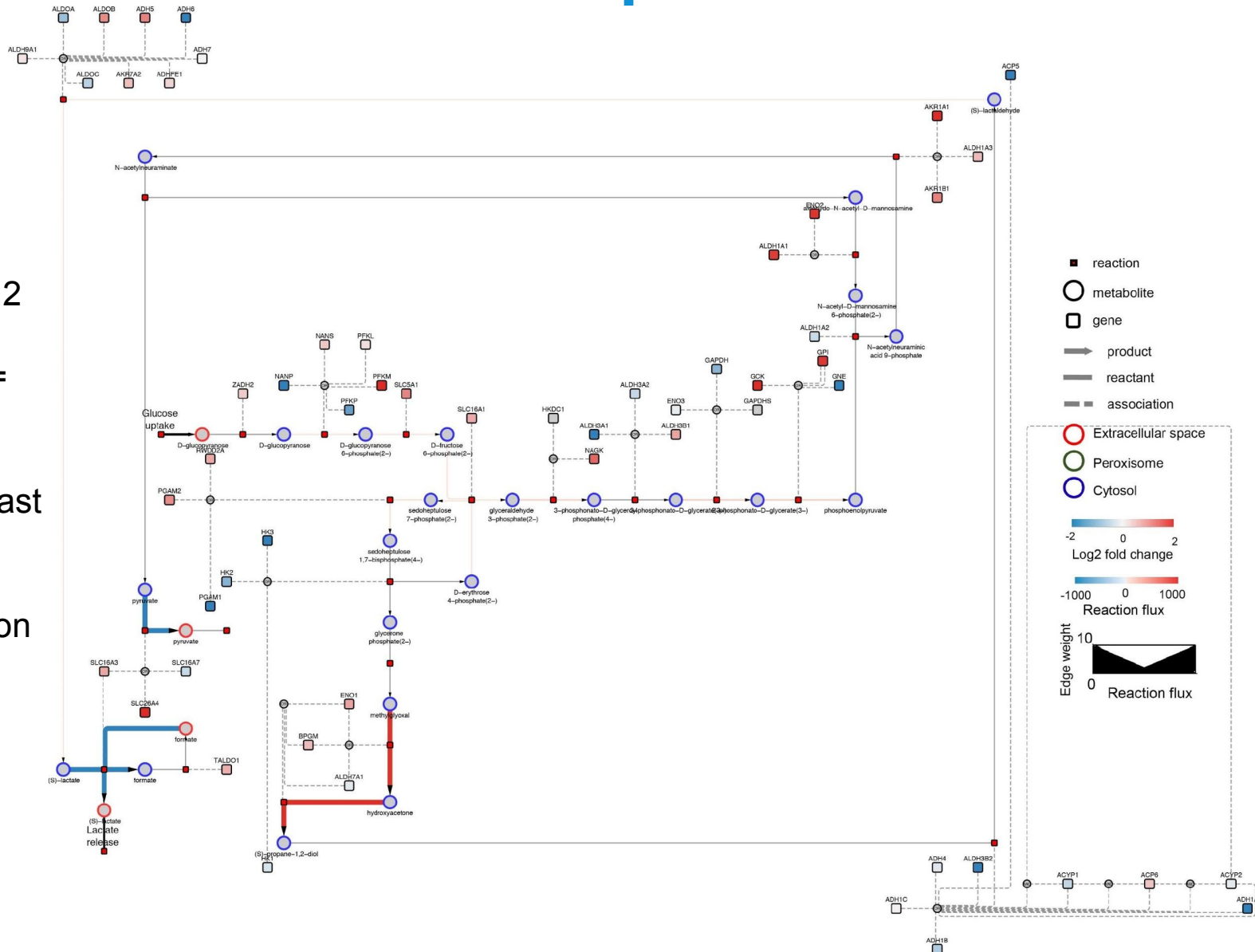
Plasma Metabolites	Uptake (s \rightarrow c)	Uptake EFMs XSC	Release (c \rightarrow s)	Release EFMs CSX
leucine	leucine[s] \Rightarrow leucine[c]	159	leucine[c] \Rightarrow leucine[s]	483

Current work: Identify differential EFMs, Cluster EFMs

EFM Visualization: Workflow



EFM Visualization: Example



Model: Recon 2.2

Active reaction =
glucose uptake

Data: TCGA breast
cancer gene
expression +
simulated reaction
fluxes

EFM Visualization: Challenges

- Identifier mapping
 - Several sources – reactions, metabolites, genes
- Network analysis – less explored
- Combine forces with Wikipathways
 - Add data from these models to Wikipathways
 - Open resources for Metabolic modelling community

Combining forces for Recon and Wikipathways

Denise Slenter

Twitter: @SMaLLCaT4Sci and @BiGCaT_UM

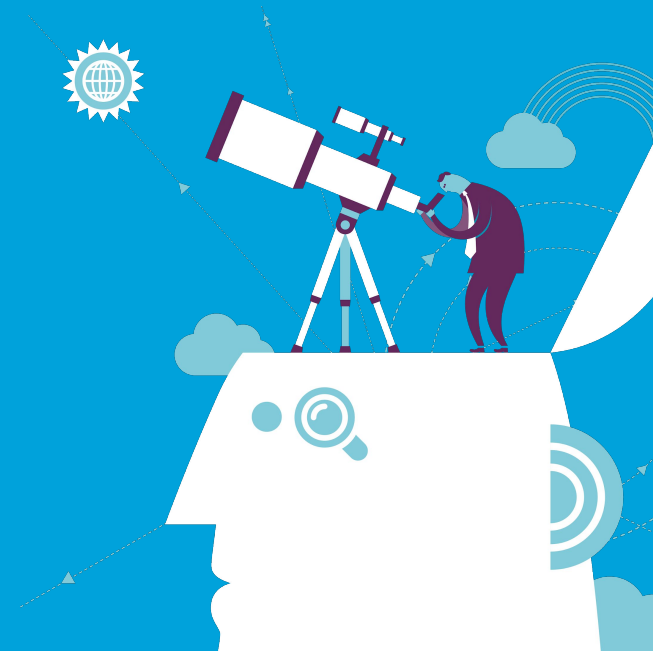
Blog: <http://smallcats4science.blogspot.nl>

ORCID: 0000-0001-8449-1318

2019-06-13 Science Cafe BiGCat



Maastricht University



Current status of WikiPathways* for Humans:

Item	WikiPathways Approved	Reactome
# Pathways	531	475
# GeneProducts	8805	928
# Protein	2553	11319
# Metabolites	2586	1776
#Directed Interactions between two metabolites	3239	4377

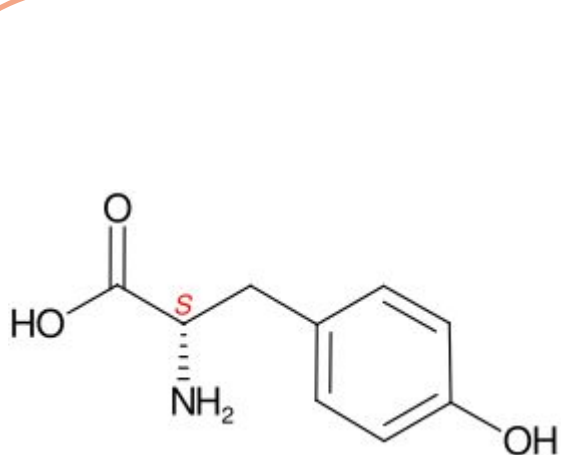
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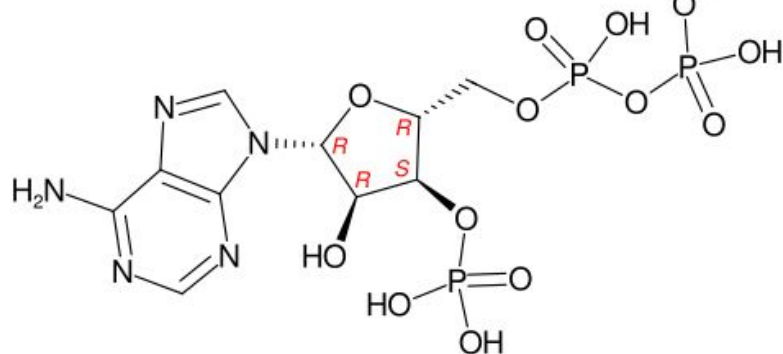
In HMDB: “**40,000** metabolites that have already been identified or are likely to be found in the human body”

<https://en.wikipedia.org/wiki/Metabolome>

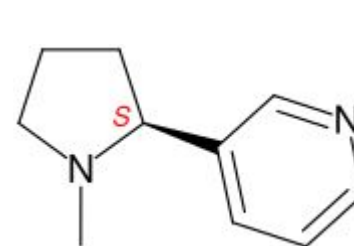
Linking metabolomics data to pathways...



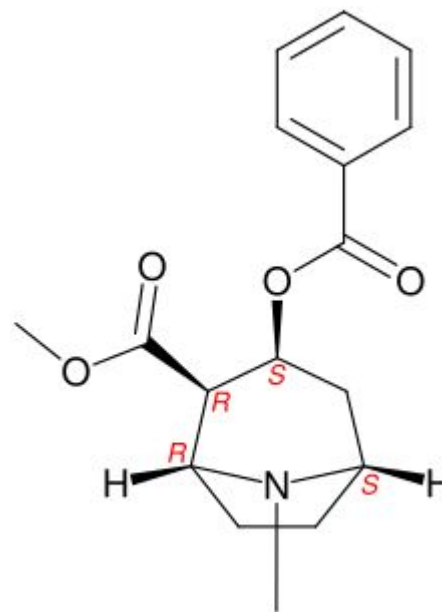
L-tyrosine



Co-A

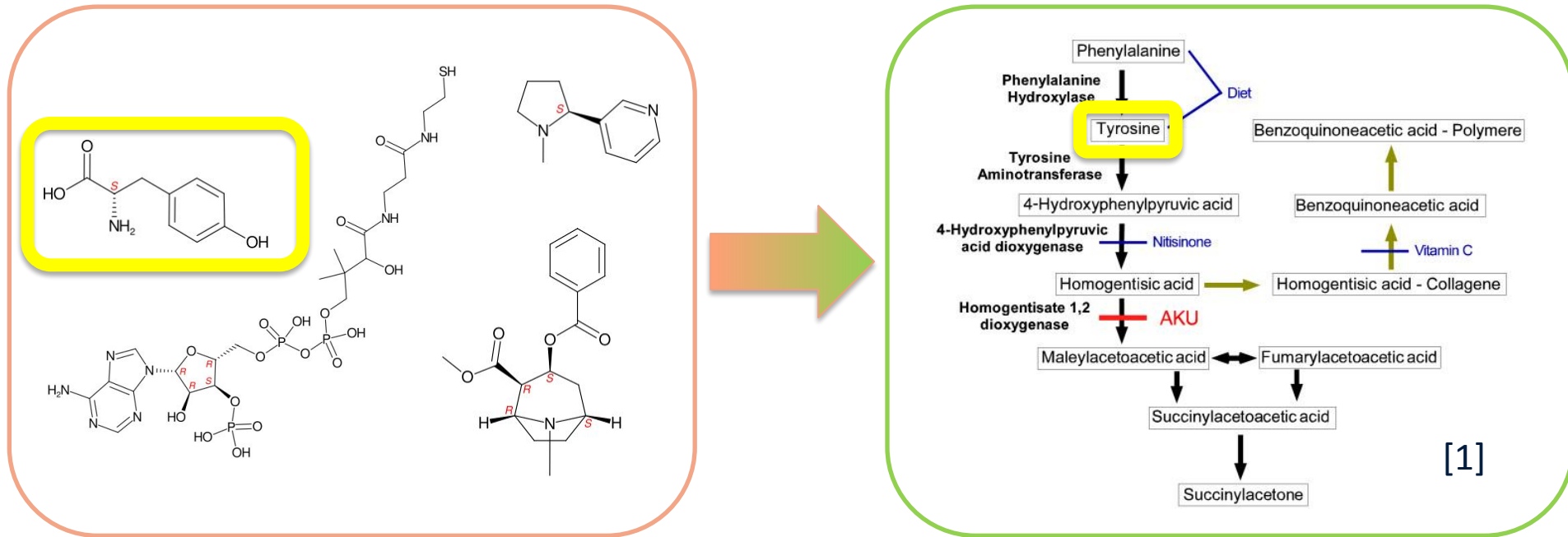


Nicotine



Cocaine

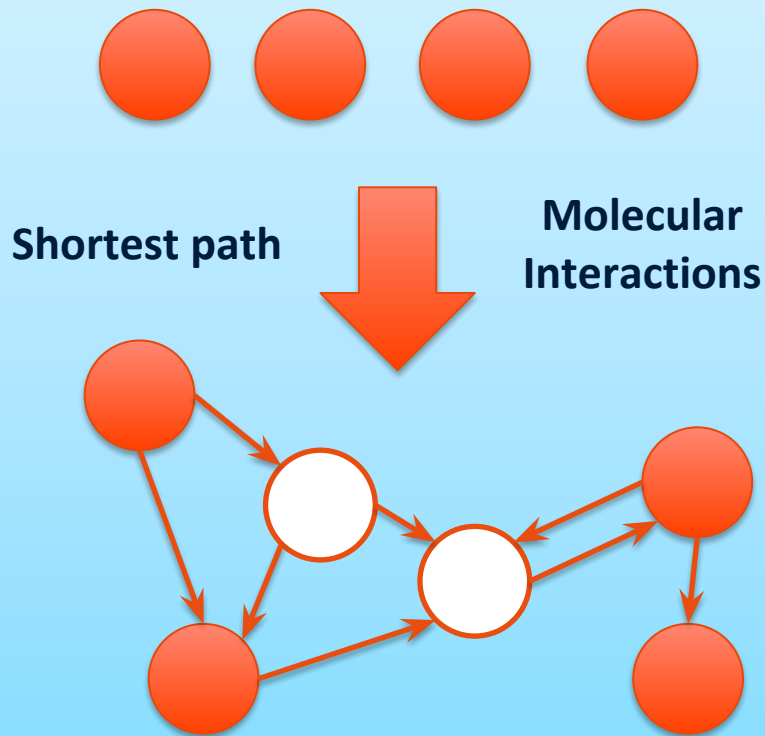
Linking metabolomics data to pathways...



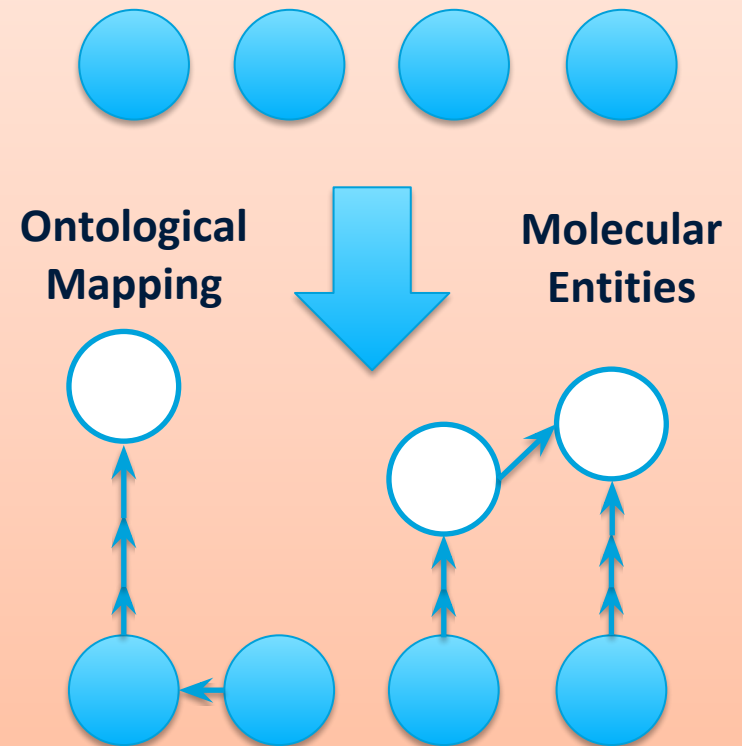
Sparseness of Data

Two approaches:

Network approach [1]

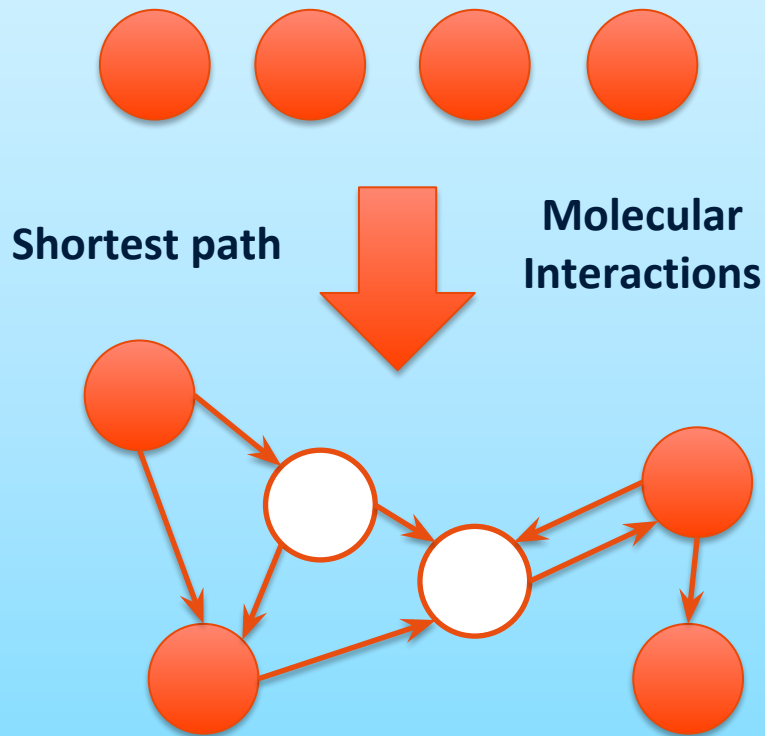


Ontological approach [2]

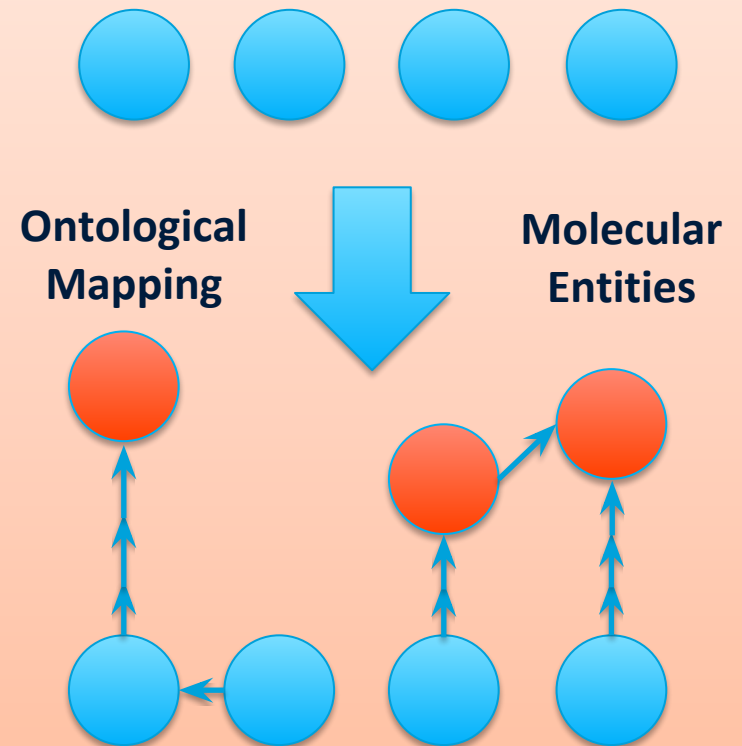


Two approaches:

Network approach [1]



Ontological approach [2]



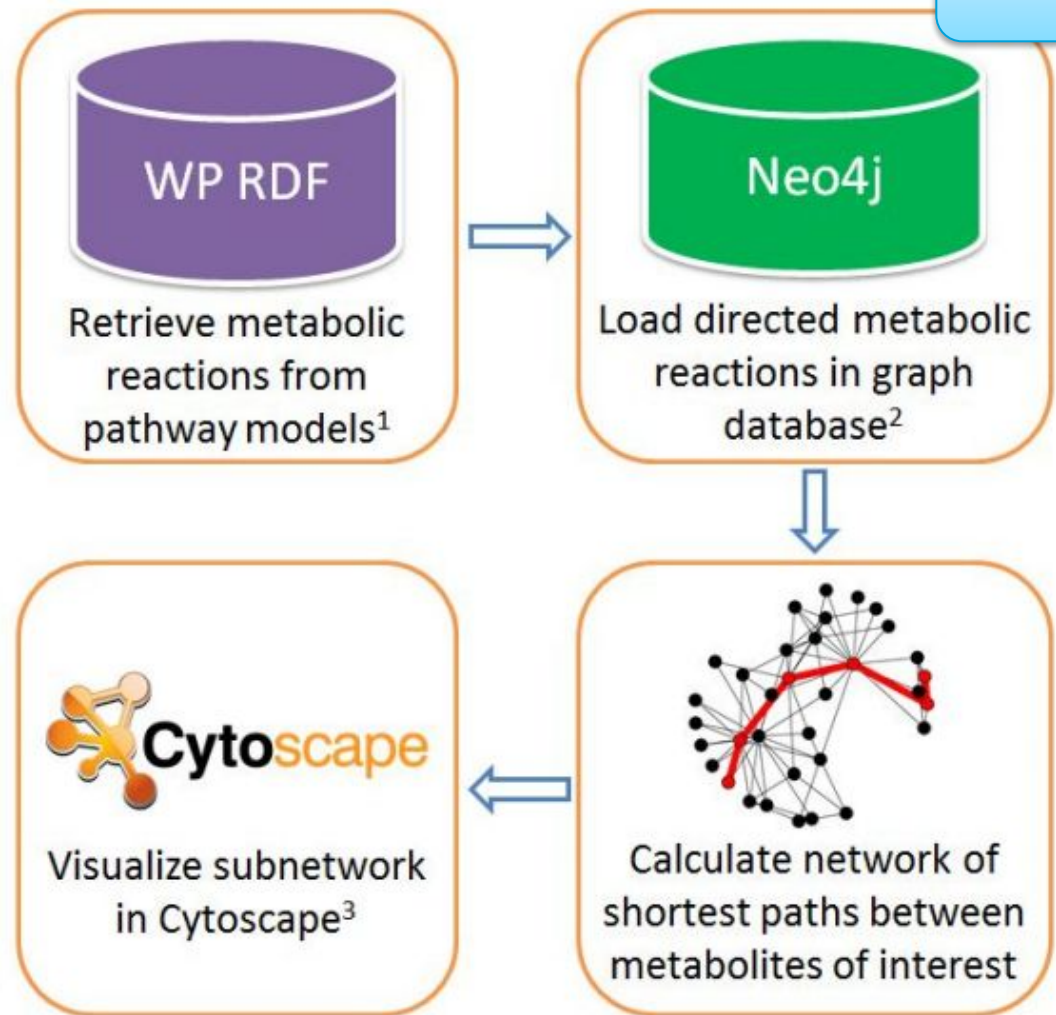
Network approach: AIM



- Directed network of metabolites from pathway knowledge bases
- Calculate sub-network between active metabolites
- Visualise directed paths
- Interpret metabolomics datasets

Workflow

1. Directed metabolic reactions in human pathway models are retrieved from the WikiPathways RDF¹.
2. Those interactions are stored in the graph database Neo4j².
3. Using the Cypher query language the shortest paths between metabolites of interests are calculated.
4. Finally, the resulting subnetwork is visualized in Cytoscape³.



¹ WikiPathways RDF: <http://sparql.wikipathways.org> (released July 10, 2017)
Kutmon *et al.* (2016) doi:10.1093/nar/gkv1024, Waagmeester *et al.* (2016) doi: 10.1371/journal.pcbi.1004989

² Neo4j: <https://neo4j.com/>

³ Cytoscape: <http://cytoscape.org/>
Shannon *et al.* (2003) doi: 10.1101/gr.1239303

FUTURE PERSPECTIVE

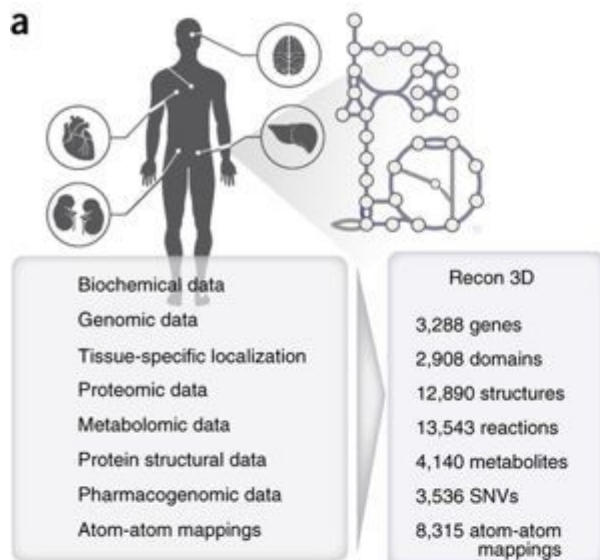
- Add more pathway knowledge bases (now WikiPathways, Reactome and LipidMaps*)
- Create app for direct visualisation with Cytoscape from Neo4j (first tests have been run)
- Allow for integration with other omics data sources, such as proteomics and transcriptomics



Recon vs Wikipathways

- Recon3D – Most recent human reconstruction
- Wikipathways – 2019-05-10 RDF data

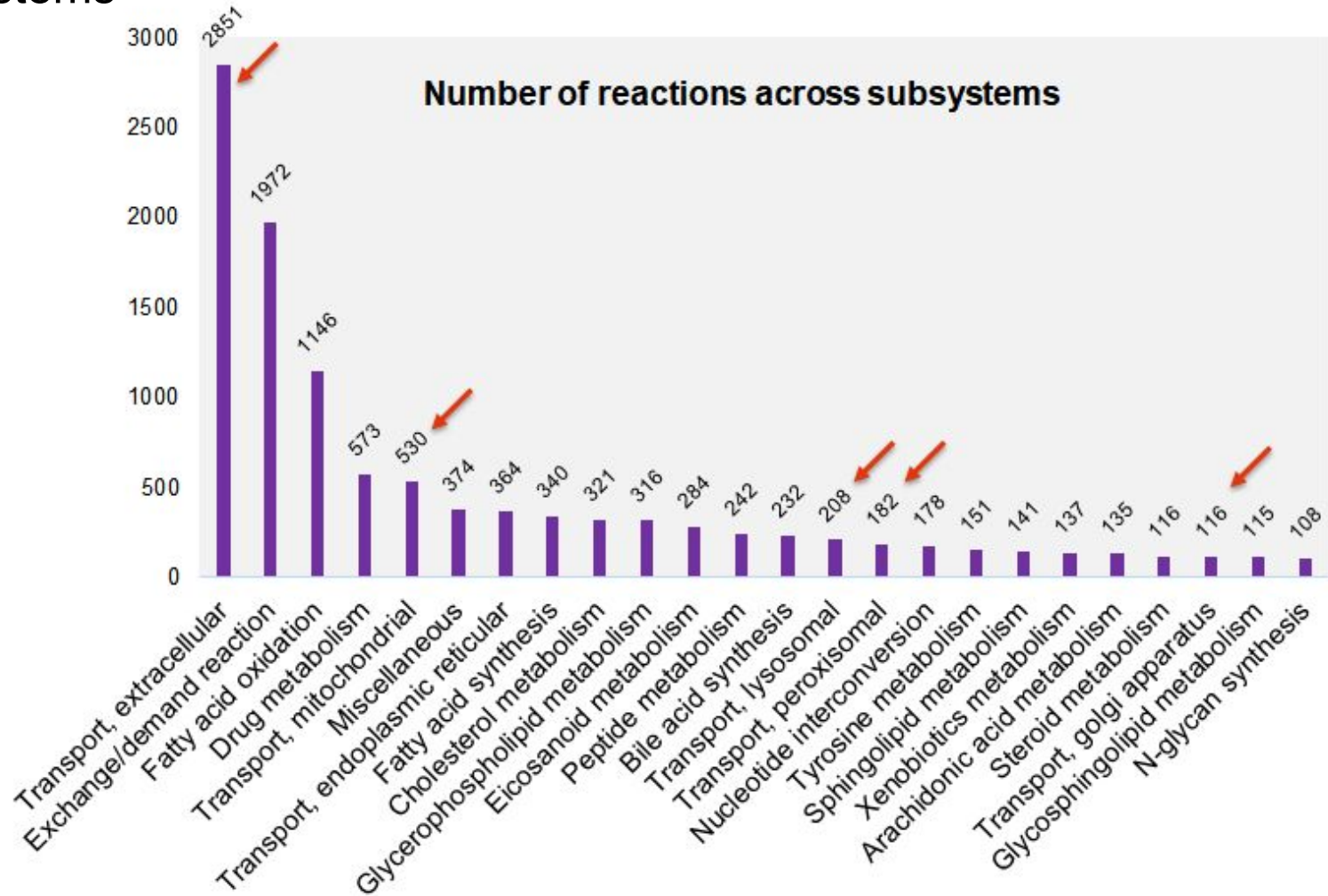
	Genes	Metabolites	Reactions	Pathways
ID format	Entrez	Recon/Wikidata	Metabolic conversions only	Humans only
Recon	3,288	4,140	13,543	111
Wikipathways (Approved + Reactome)	11,869	2,650	7,616	1,006



Recon	metabolite IDs
ReconMap	2024
PdMap	169
ChEBI	1276
PubChemID	1408
KEGG ID	1682
HMDB ID	721

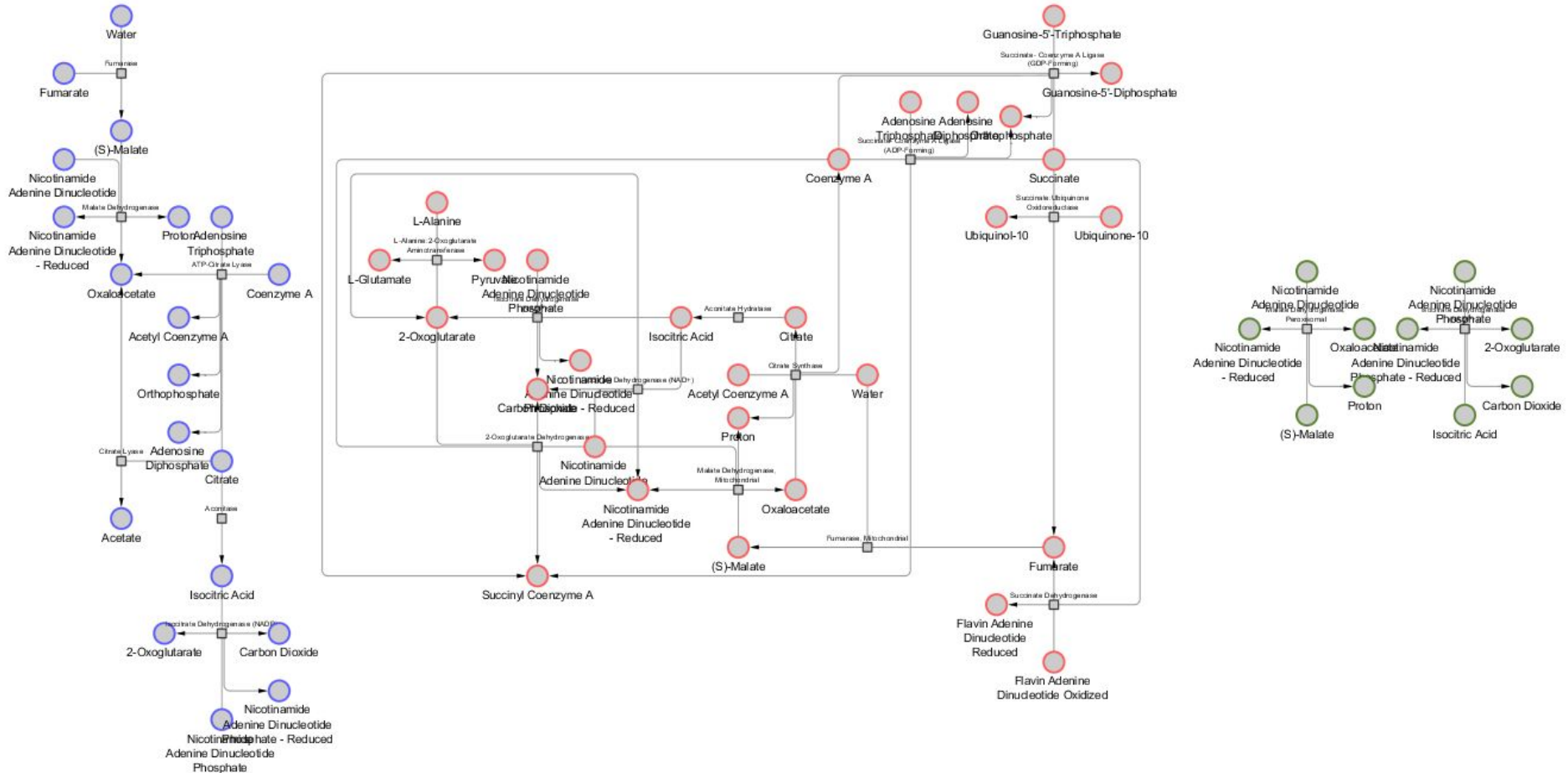
Recon vs Wikipathways

Subsystems



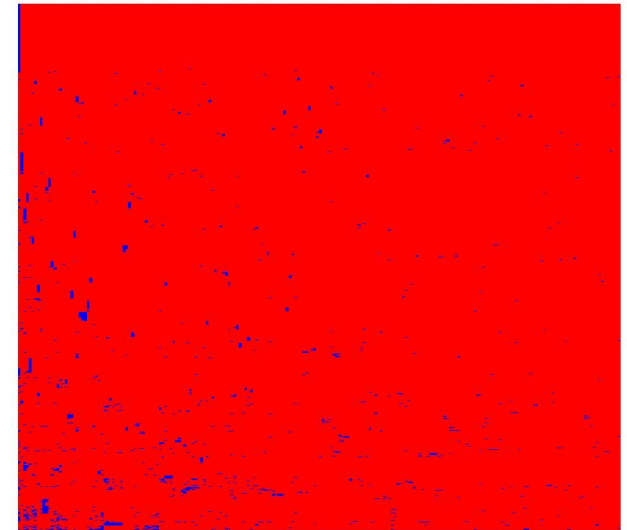
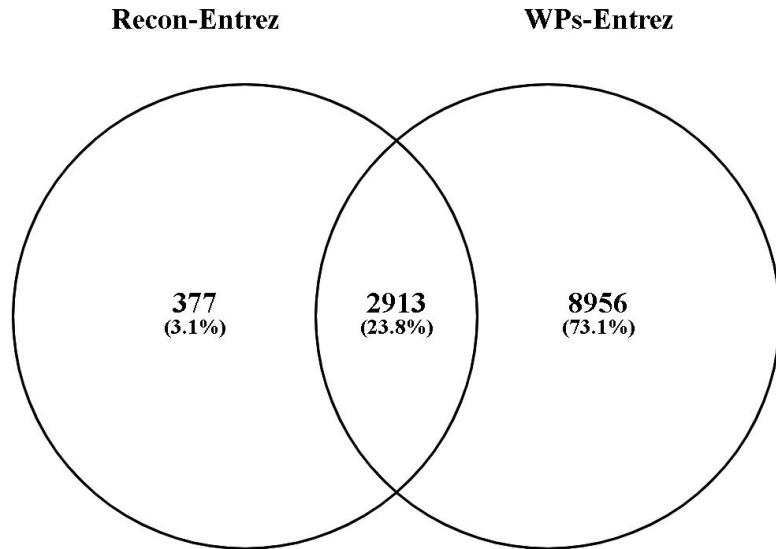
Recon vs Wikipathways

Recon – Subsystem visualized: Citric acid cycle

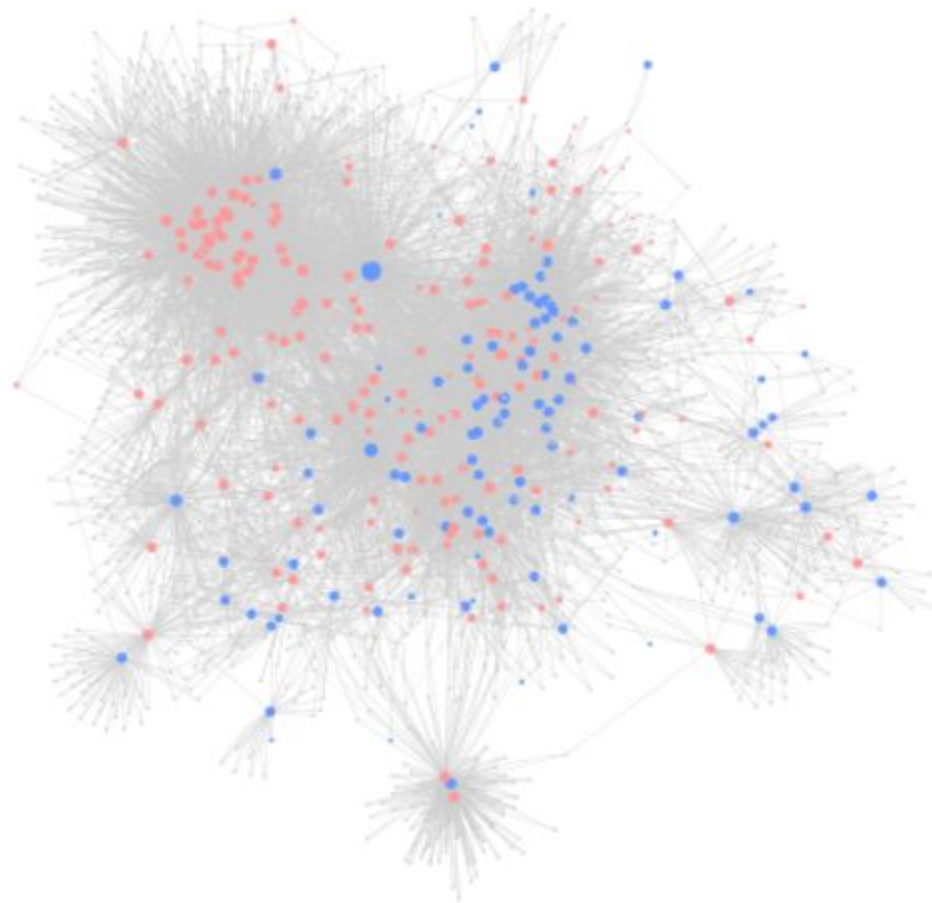


Recon vs Wikipathways

Overlap in genes



Recon vs Wikipathways



Red = Recon

Blue = WPs



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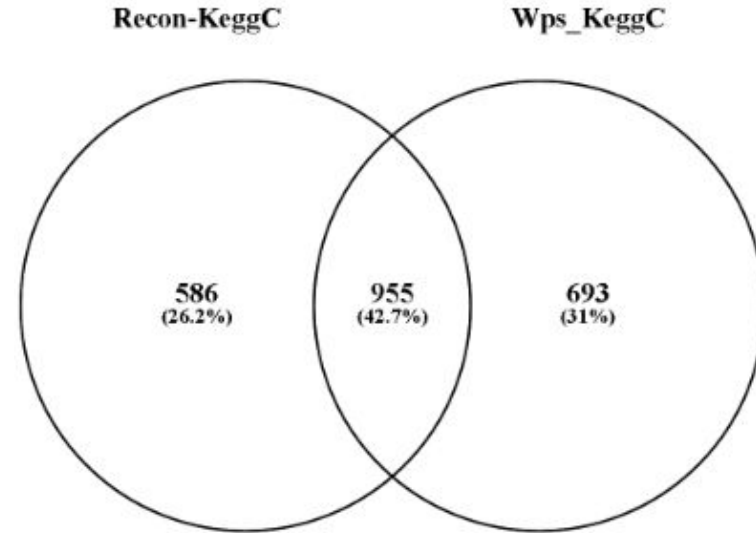
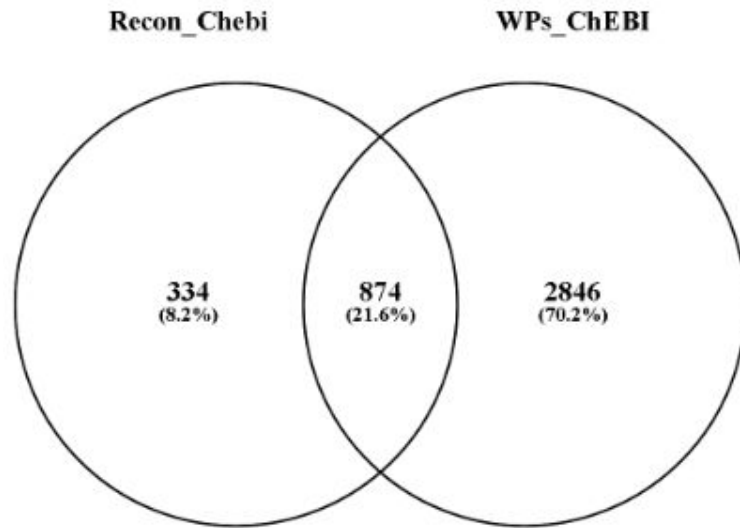
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department of bioinformatics

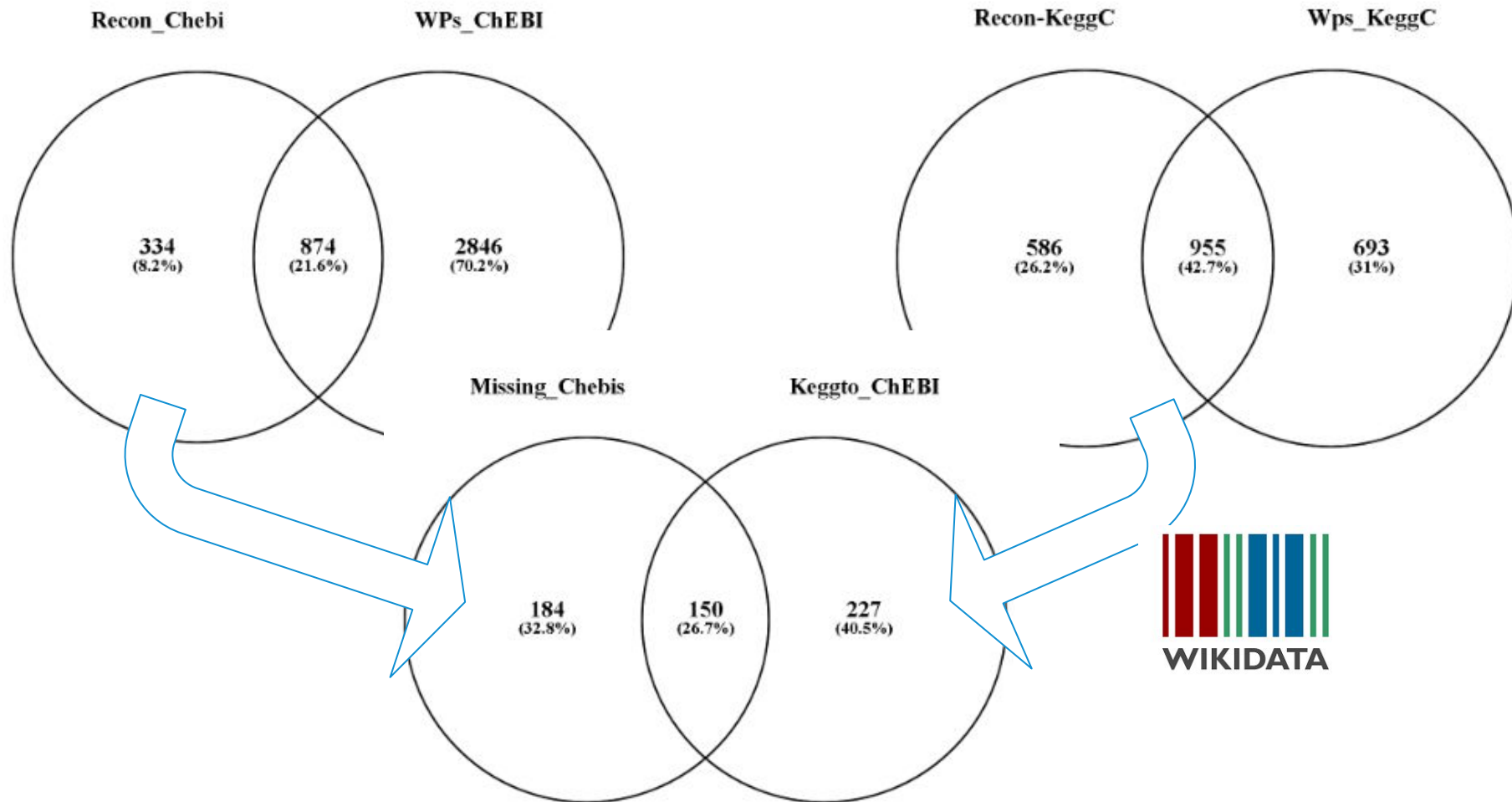
Recon vs Wikipathways

Overlap in metabolites

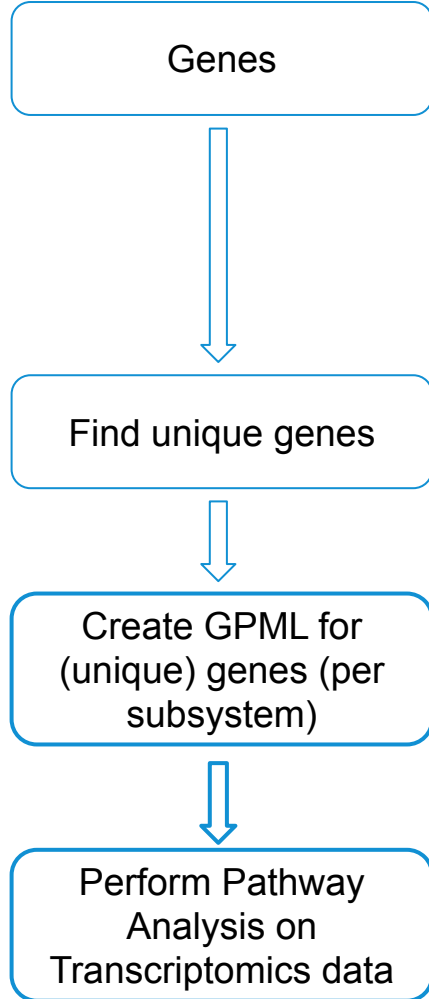


Recon vs Wikipathways

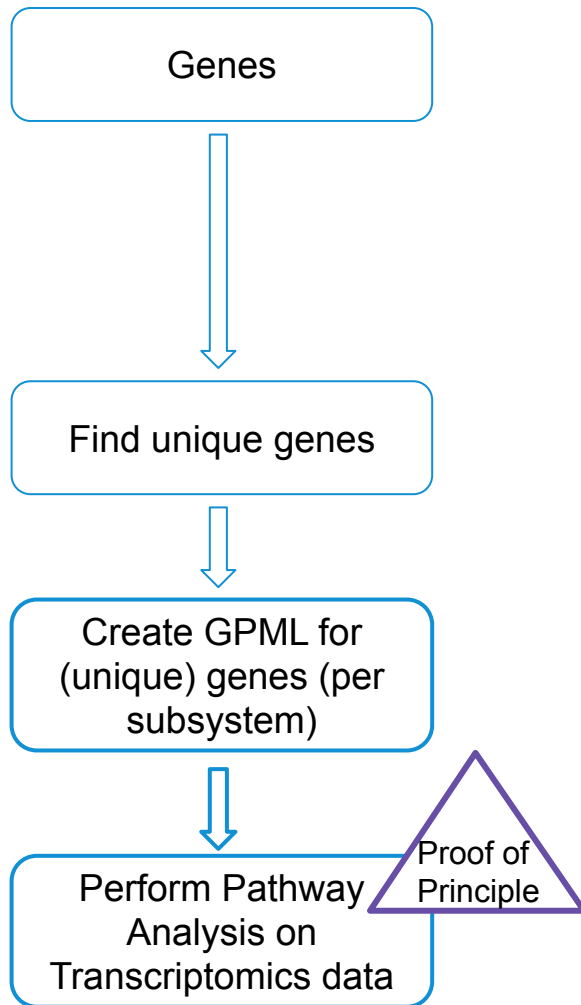
Overlap in metabolites



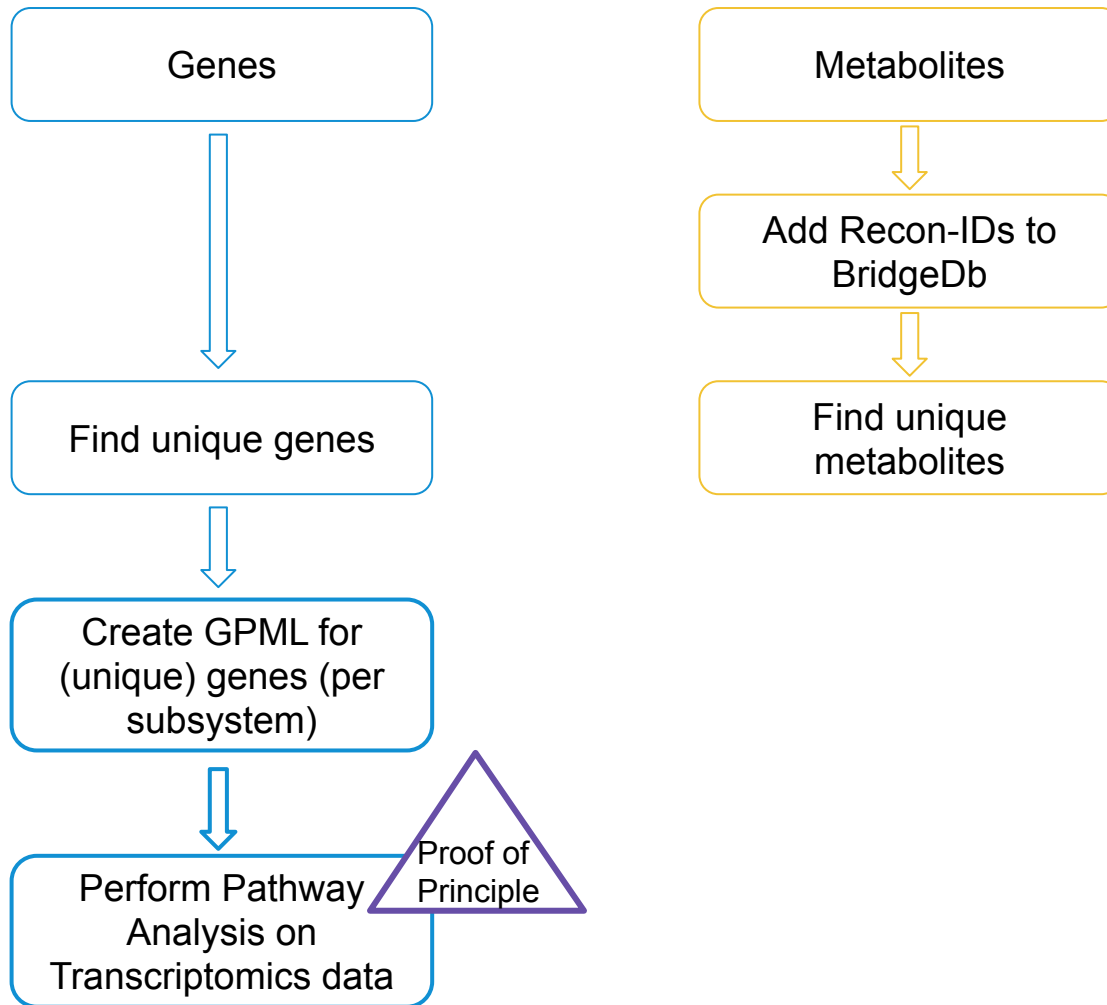
Proposed workflow for integration:



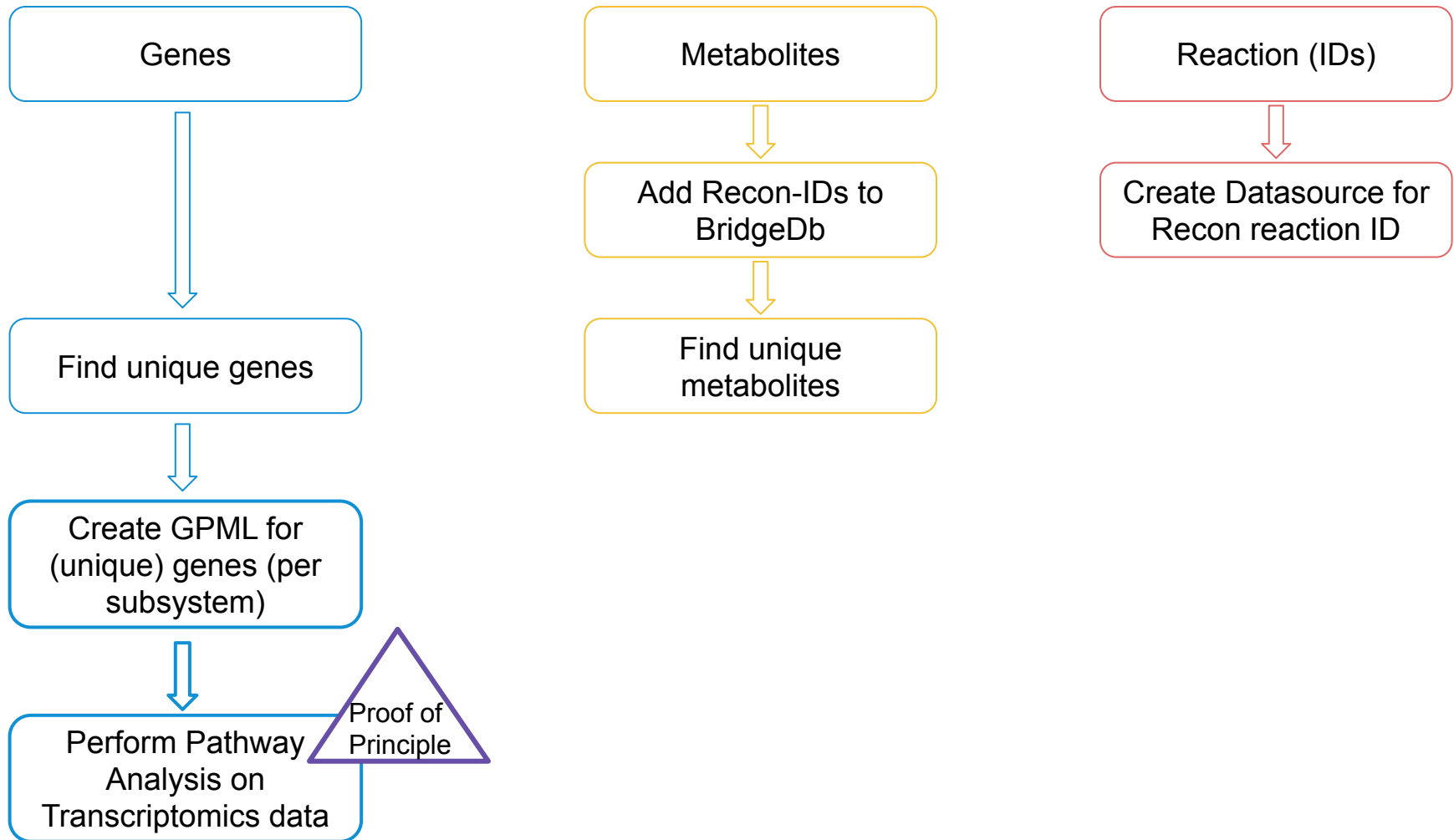
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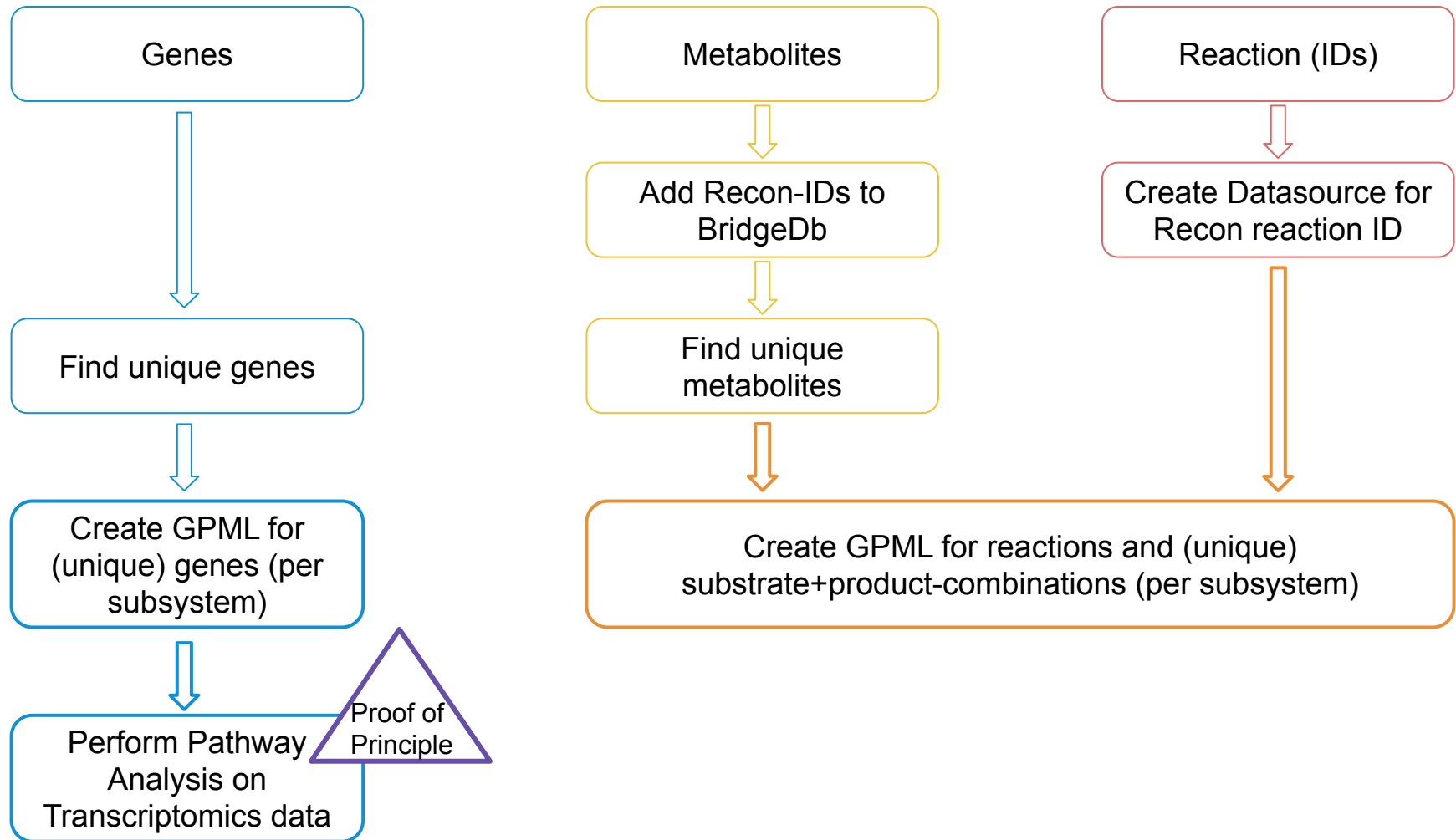
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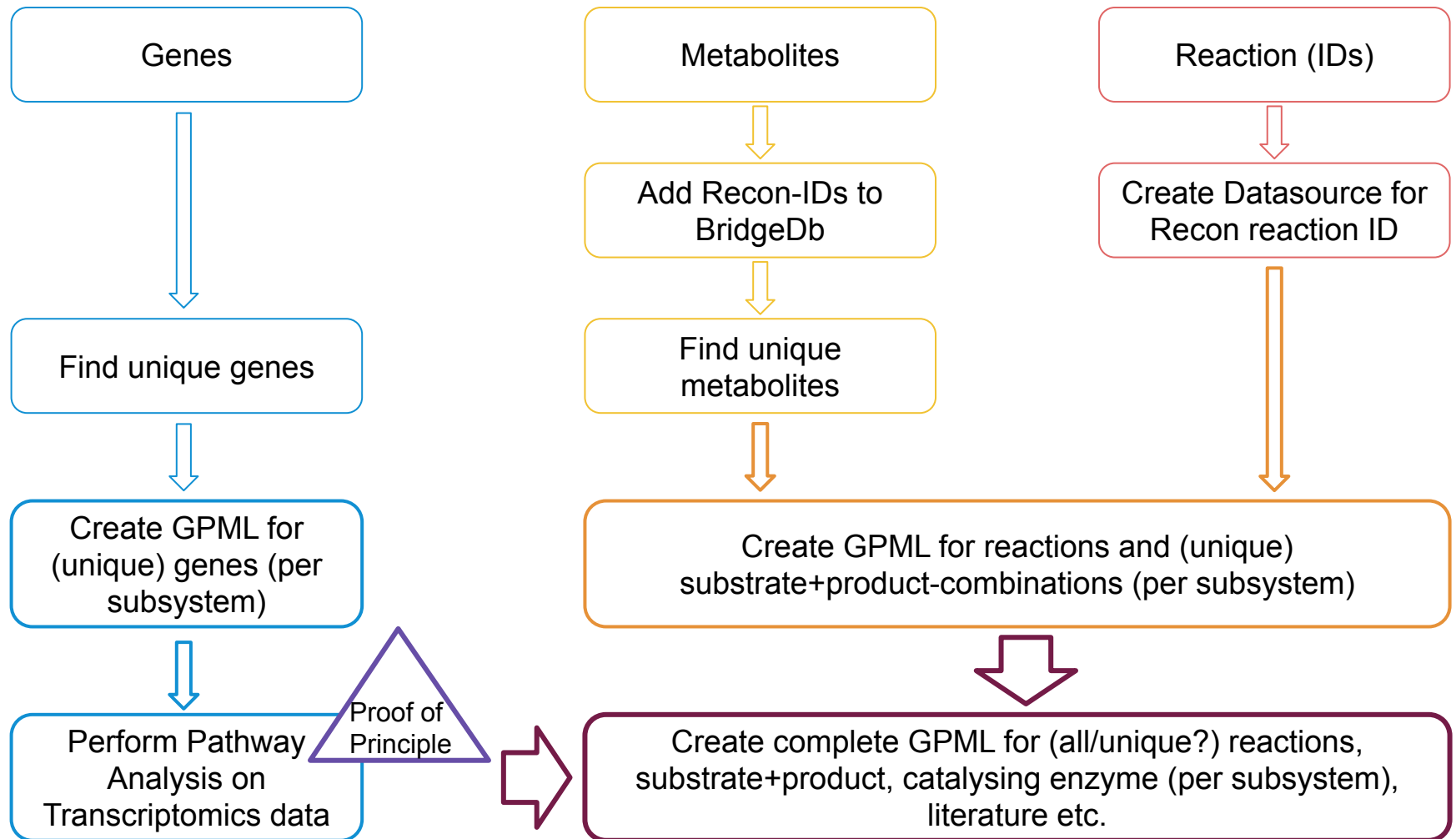
Proposed workflow for integration:



Proposed workflow for integration:



Proposed workflow for integration:



Challenges

Besides the ones already mentioned:

- Layout of subsystems (coordinates for DataNode boxes).
- Add location (cellular and tissue level) → Not possible in PathVisio (yet).
- Map Recon metabolite IDs to more than InchiKey (for example, to Wikidata).
- Mappings from Rhea to Recon-Reaction IDs currently not possible; therefore fluxomics is difficult.
- Do we need GPMLs in WPs? Or do we (only) want info in RDF?

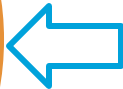
Acknowledgements, questions, discussion



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Ryan Miller
Georg Summer
Chris T Evelo
Egon L Willighagen

Acknowledgements, questions, discussion



Recon vs Wikipathways (Extra)

Subsystems

Transport, extracellular	2851
Exchange/demand reaction	1972
Fatty acid oxidation	1146
Drug metabolism	573
Transport, mitochondrial	530
Miscellaneous	374
Transport, endoplasmic reticular	364
Fatty acid synthesis	340
Cholesterol metabolism	321
Glycerophospholipid metabolism	316
Eicosanoid metabolism	284
Peptide metabolism	242
Bile acid synthesis	232
Transport, lysosomal	208
Transport, peroxisomal	182
Nucleotide interconversion	178
Tyrosine metabolism	151
Sphingolipid metabolism	141
Xenobiotics metabolism	137

Arachidonic acid metabolism	135
Steroid metabolism	116
Transport, golgi apparatus	116
Glycosphingolipid metabolism	115
N-glycan synthesis	108
Vitamin A metabolism	107
Transport, nuclear	92
Inositol phosphate metabolism	90
Androgen and estrogen synthesis and metabolism	85
Tryptophan metabolism	77
Keratan sulfate degradation	76
Urea cycle	69
Folate metabolism	62
Phosphatidylinositol phosphate metabolism	60
Keratan sulfate synthesis	59
Methionine and cysteine metabolism	55
Valine, leucine, and isoleucine metabolism	52
Arginine and proline metabolism	51
Phenylalanine metabolism	50
R group synthesis	50
Glycine, serine, alanine, and threonine metabolism	49