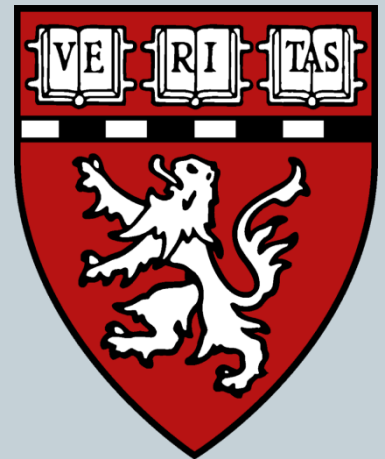


Network Medicine Approaches for the Analysis of Metabolomic Data



JESSICA LASKY-SU
RACHEL KELLY



The Application of Network Medicine to Metabolomics Datasets



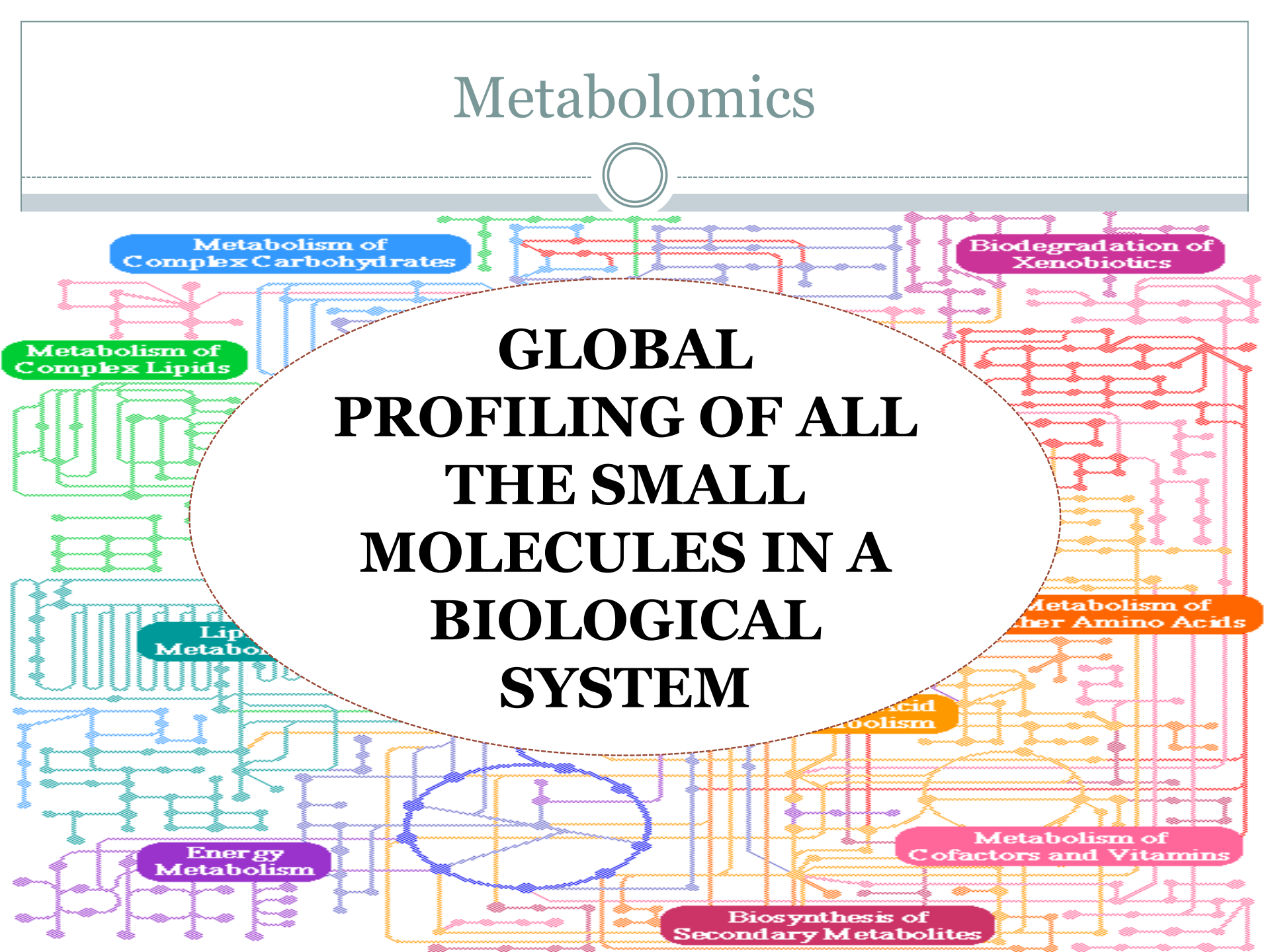
RACHEL KELLY

The Metabolome



THE APPLICATION OF NETWORK MEDICINE TO METABOLOMICS DATASETS

Metabolomics

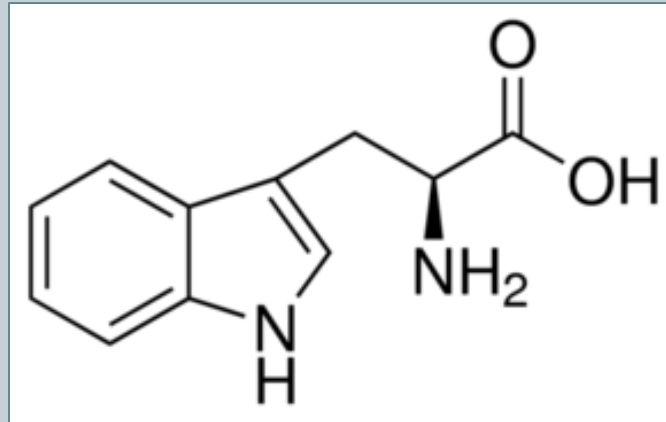
The background of the slide is a complex, colorful network of metabolic pathways. It features numerous nodes (small circles) connected by lines of various colors (red, blue, green, orange, purple). Several specific pathways are highlighted with colored boxes and labels: 'Metabolism of Complex Carbohydrates' (blue box, top left), 'Metabolism of Complex Lipids' (green box, middle left), 'Lipid Metabolism' (teal box, bottom left), 'Energy Metabolism' (purple box, bottom left), 'Biosynthesis of Secondary Metabolites' (dark purple box, bottom center), 'Metabolism of Cofactors and Vitamins' (pink box, bottom right), 'Acid Metabolism' (orange box, middle right), 'Metabolism of Other Amino Acids' (orange box, middle right), and 'Biodegradation of Xenobiotics' (purple box, top right).

GLOBAL PROFILING OF ALL THE SMALL MOLECULES IN A BIOLOGICAL SYSTEM

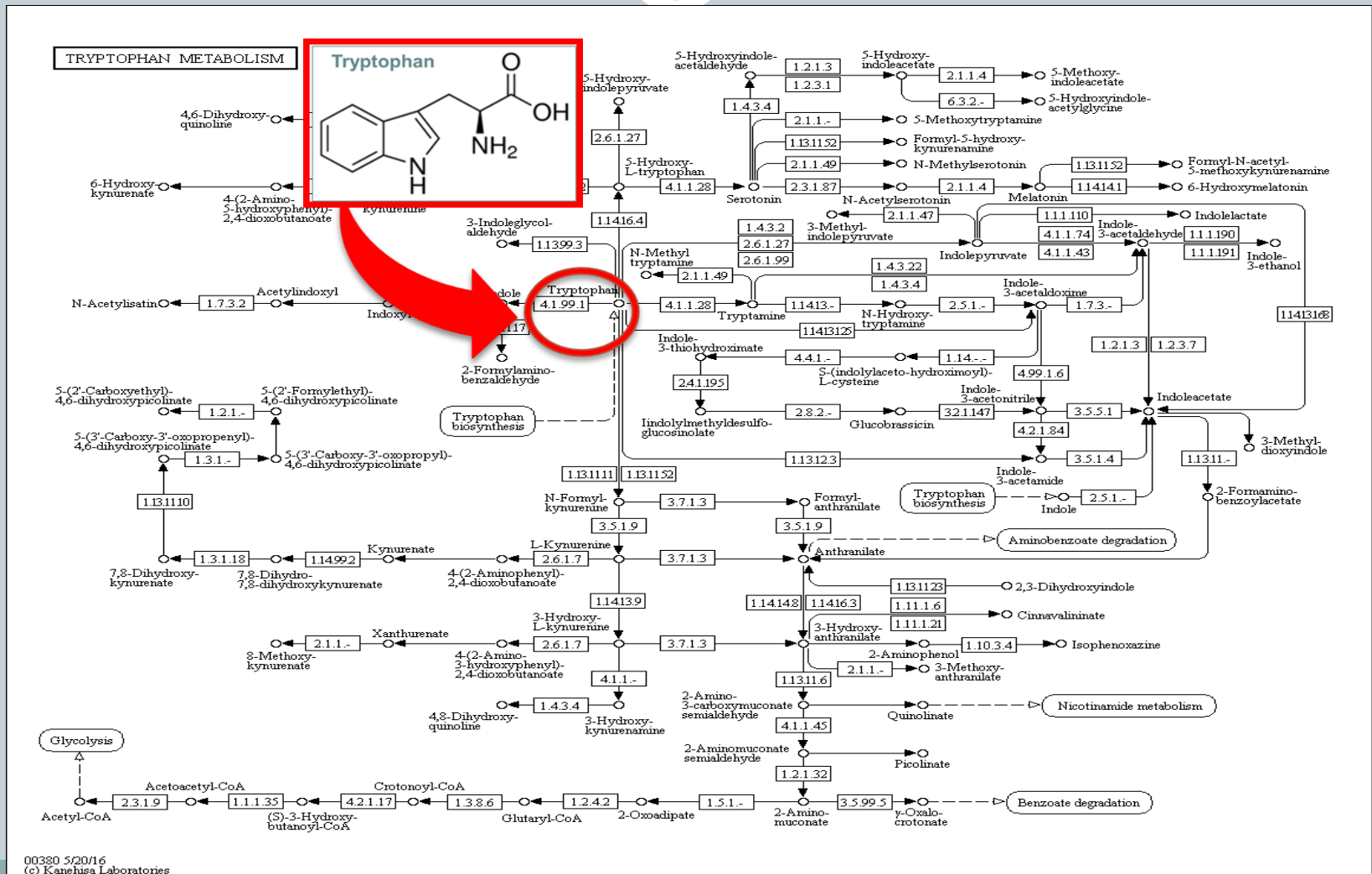
Metabolites do not exist in isolation



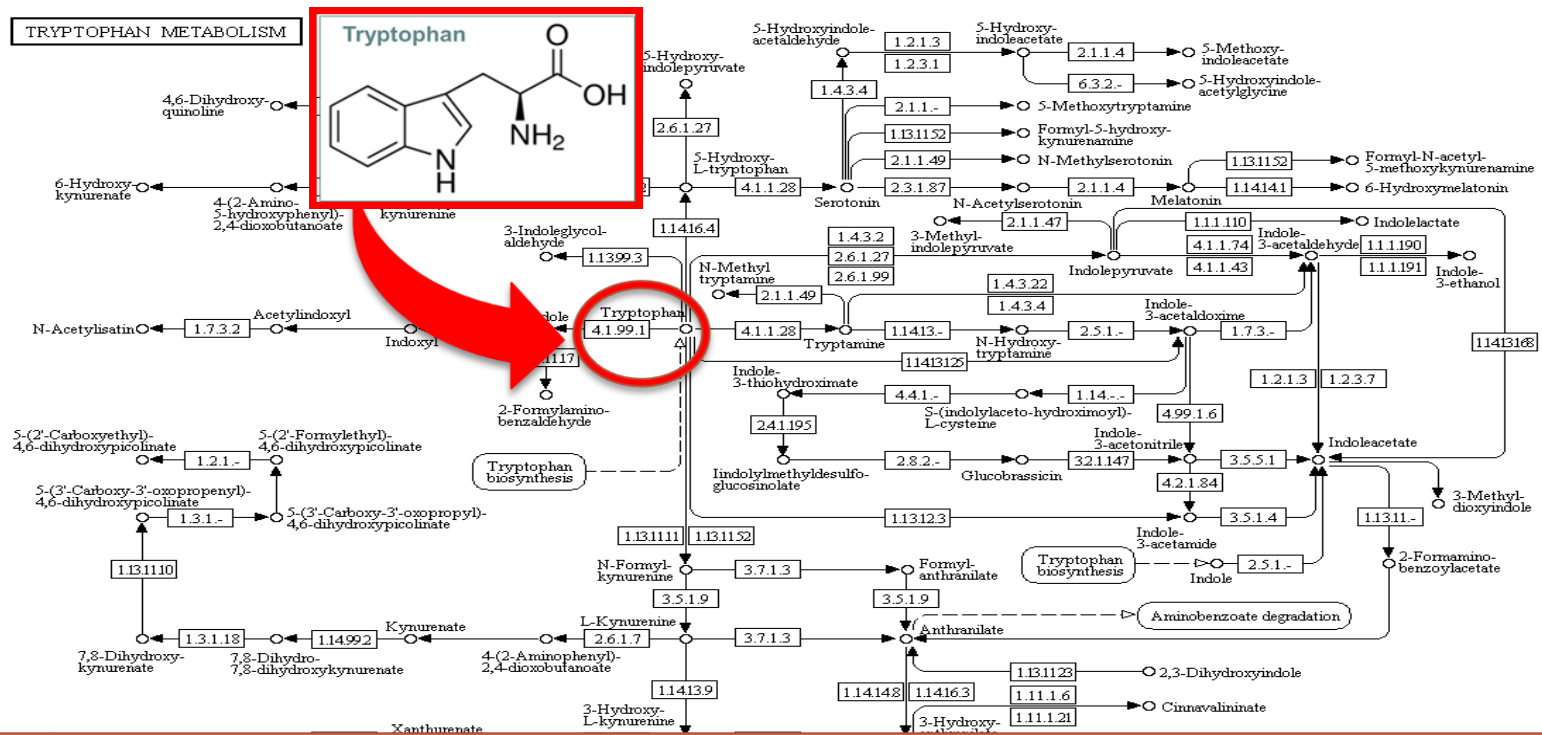
Tryptophan



Metabolites do not exist in isolation



Metabolites do not exist in isolation



METABOLOMIC PATHWAY:
Series of enzyme-catalyzed biochemical reactions that bring multiple metabolites together under the umbrella of a biochemical function

Metabolites do not exist in isolation



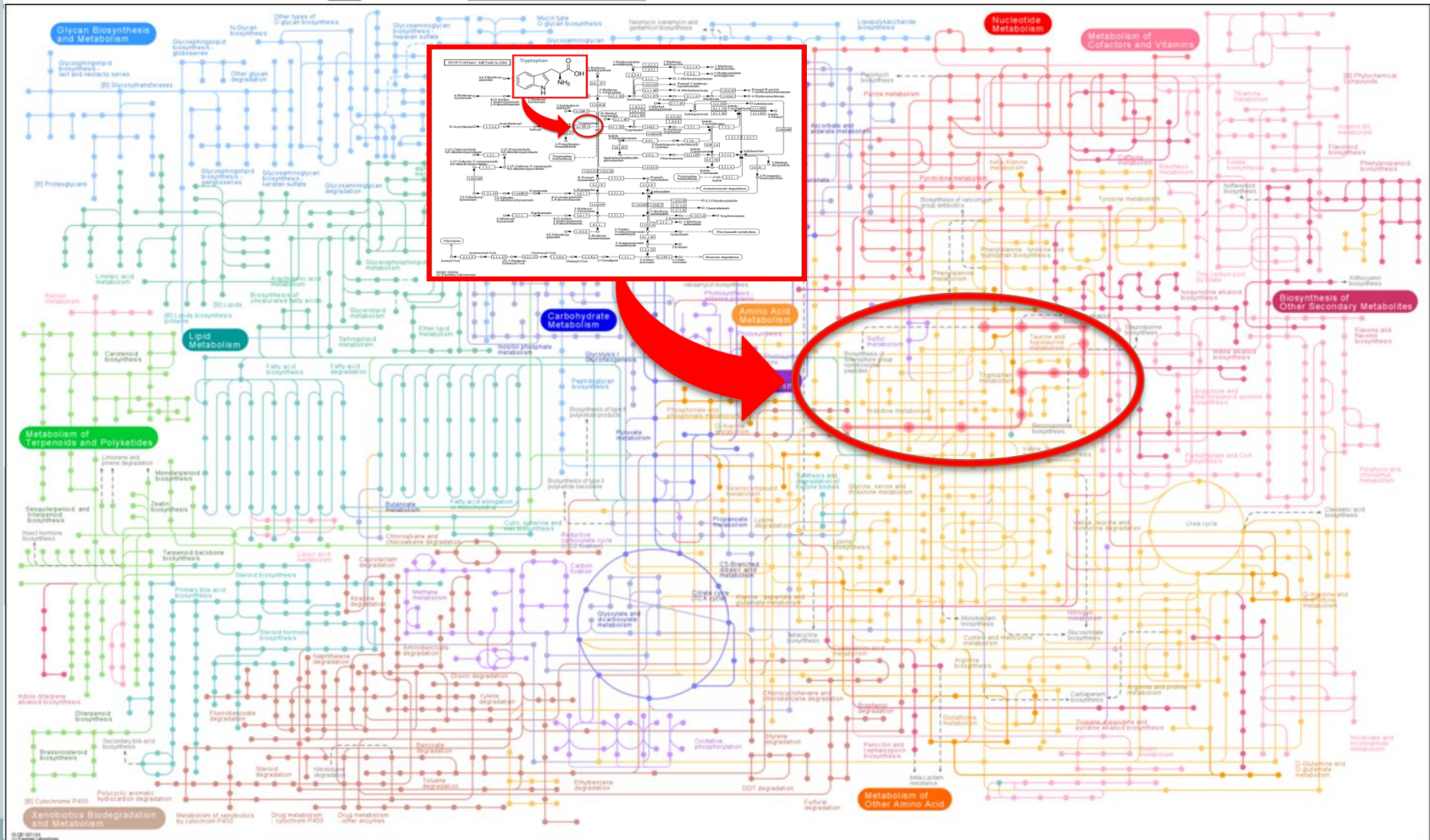
- Cellular metabolism organized around large network of enzyme-catalyzed and spontaneous chemical reactions
- Reactions involve set of diverse metabolites which function together to control materials for cell maintenance and growth, signaling molecules and waste products
- Metabolites need to be analyzed in this context; as components of a much larger network

Metabolites do not exist in isolation

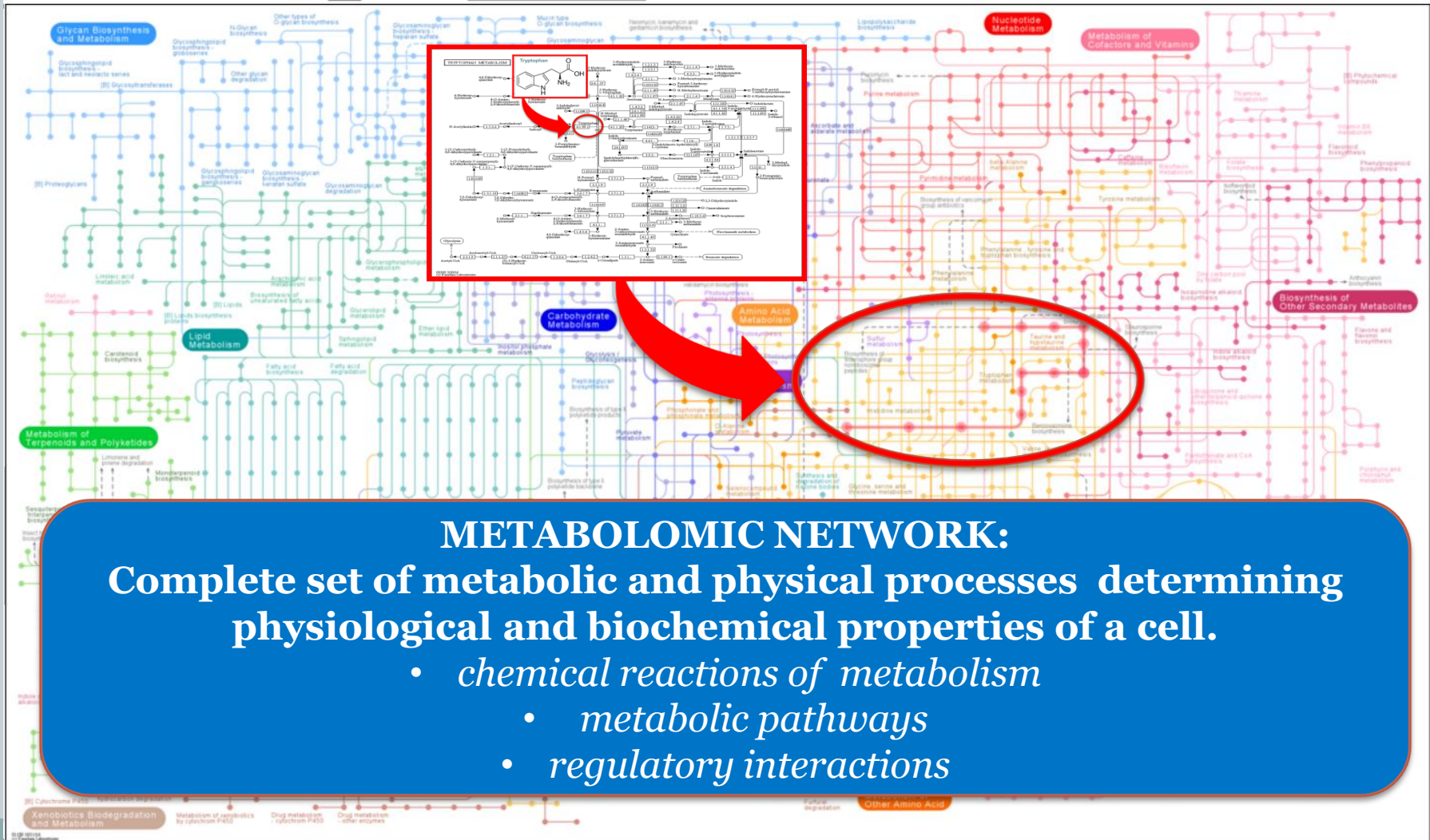


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Metabolic pathways do not exist in isolation



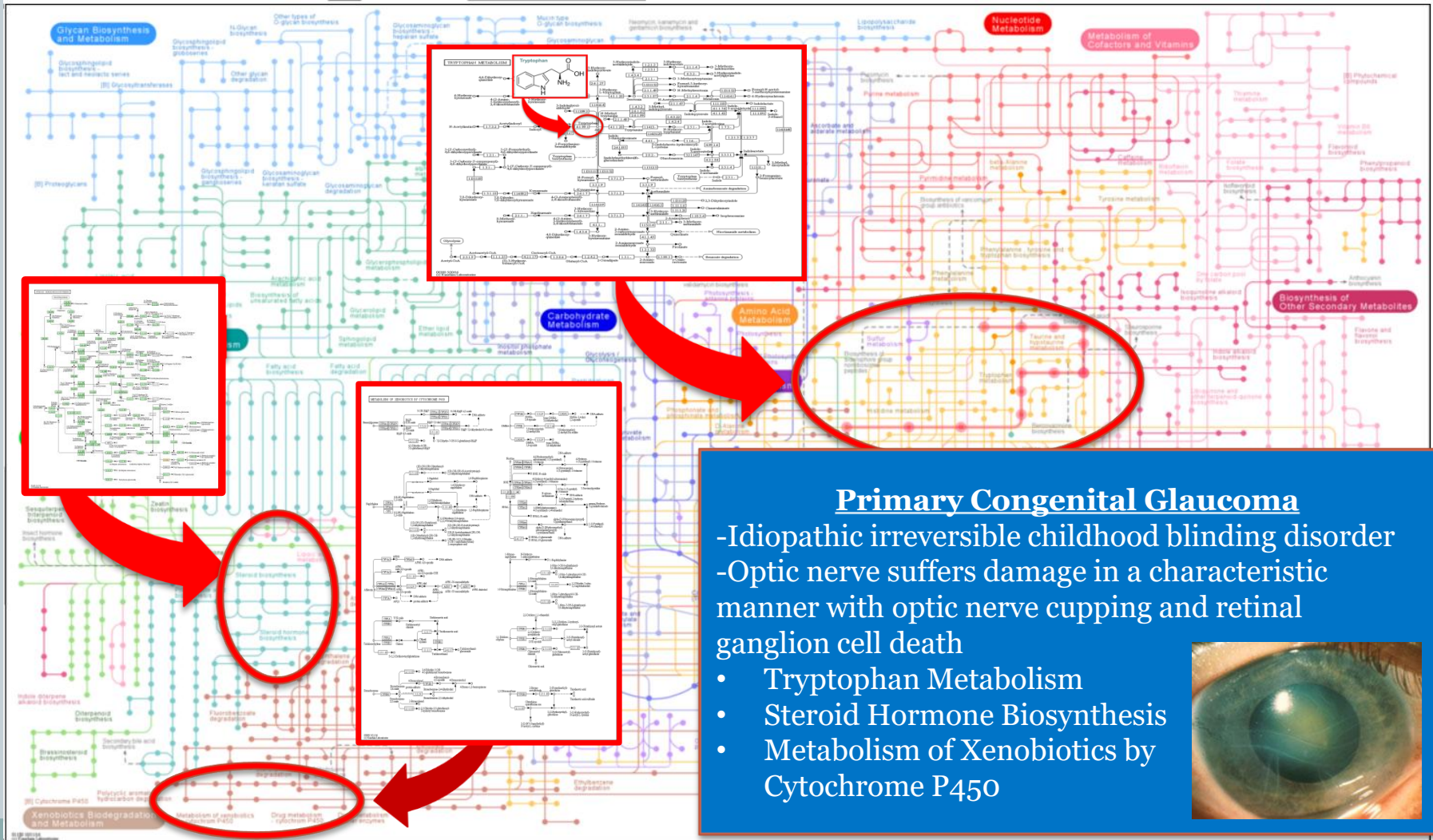
Metabolic pathways do not exist in isolation



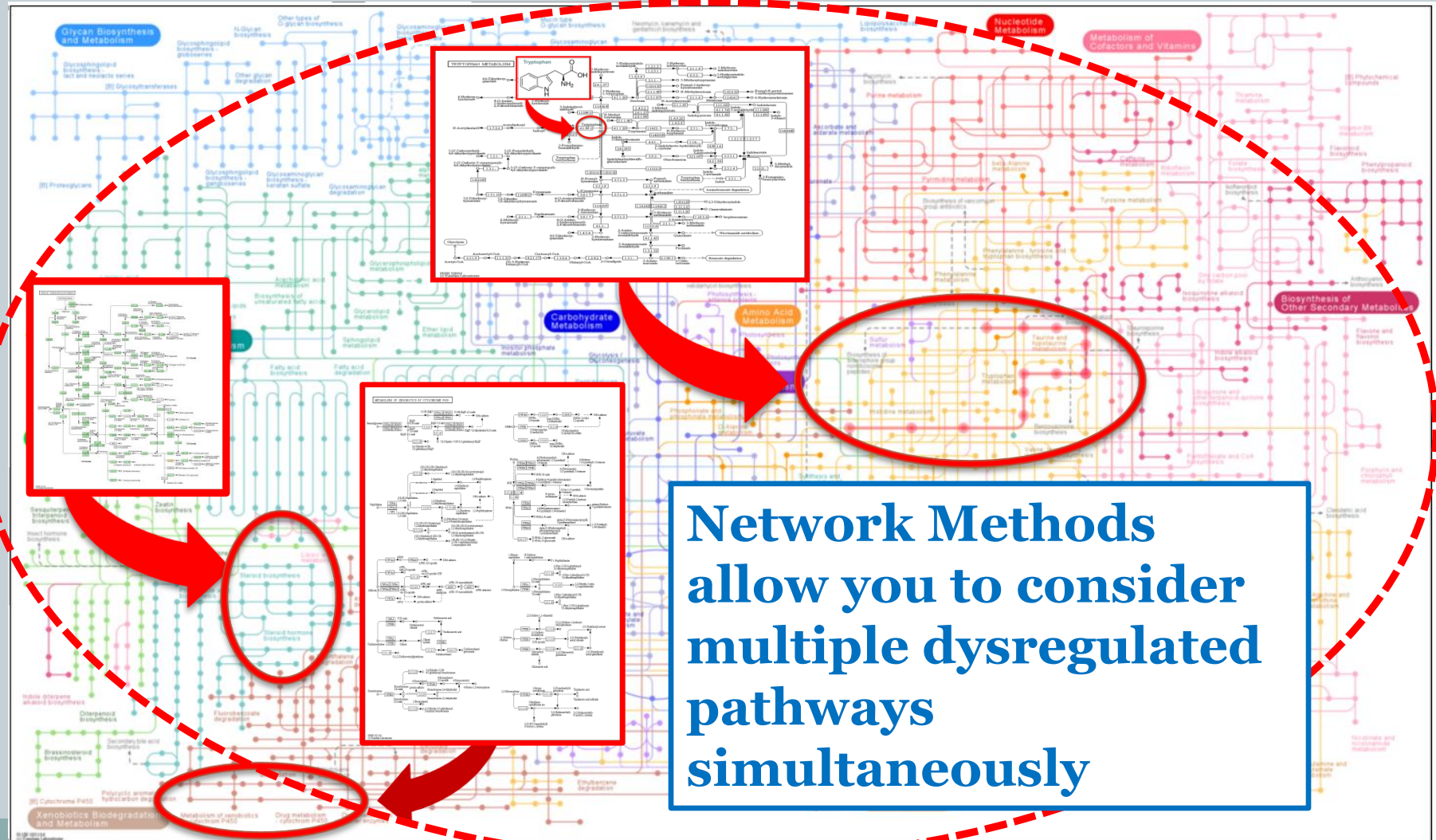
METABOLOMIC NETWORK:
Complete set of metabolic and physical processes determining physiological and biochemical properties of a cell.

- chemical reactions of metabolism
- metabolic pathways
- regulatory interactions

Most Disorders Involve Dysregulation of Multiple Pathways



Most Disorders Involve Dysregulation of Multiple Pathways



Metabolic Networks



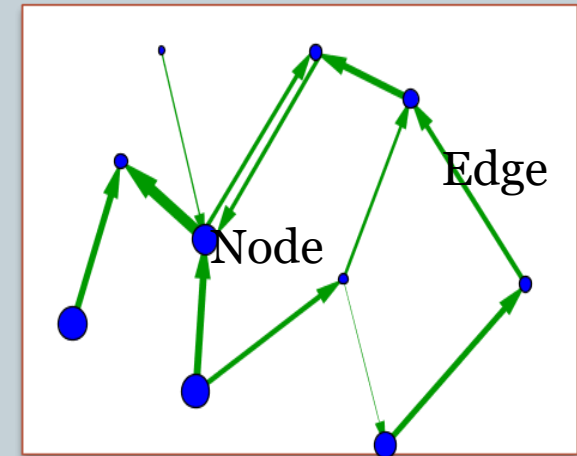
THE APPLICATION OF NETWORK MEDICINE TO METABOLOMICS DATASETS

Networks versus Pathways

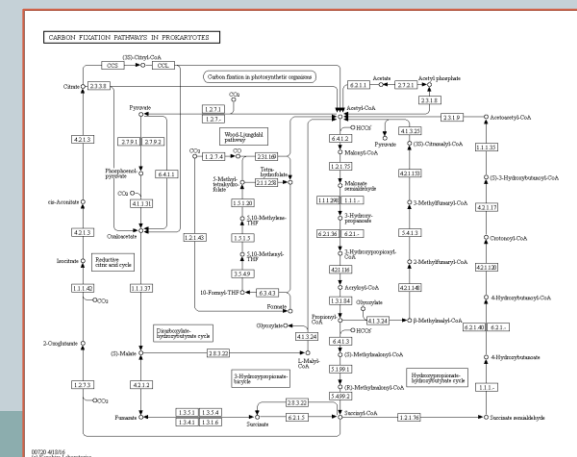


- Networks are data dependent
- Biological pathways are predefined units based on human knowledge

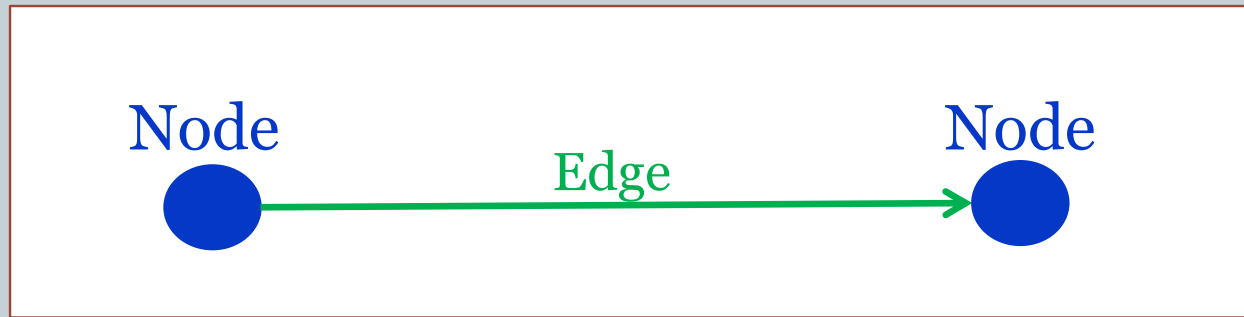
Network



Biological Pathway



Networks versus Pathways



Networks versus Pathways

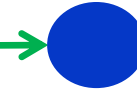


Node

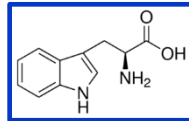


Edge

Node

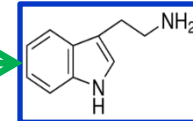


Tryptophan



*tryptophan
decarboxylase*

Tryptamine



Networks versus Pathways

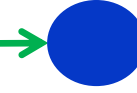


Node

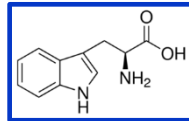


Edge

Node

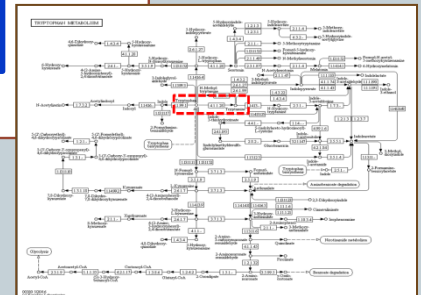
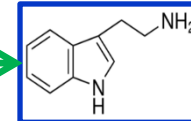


Tryptophan



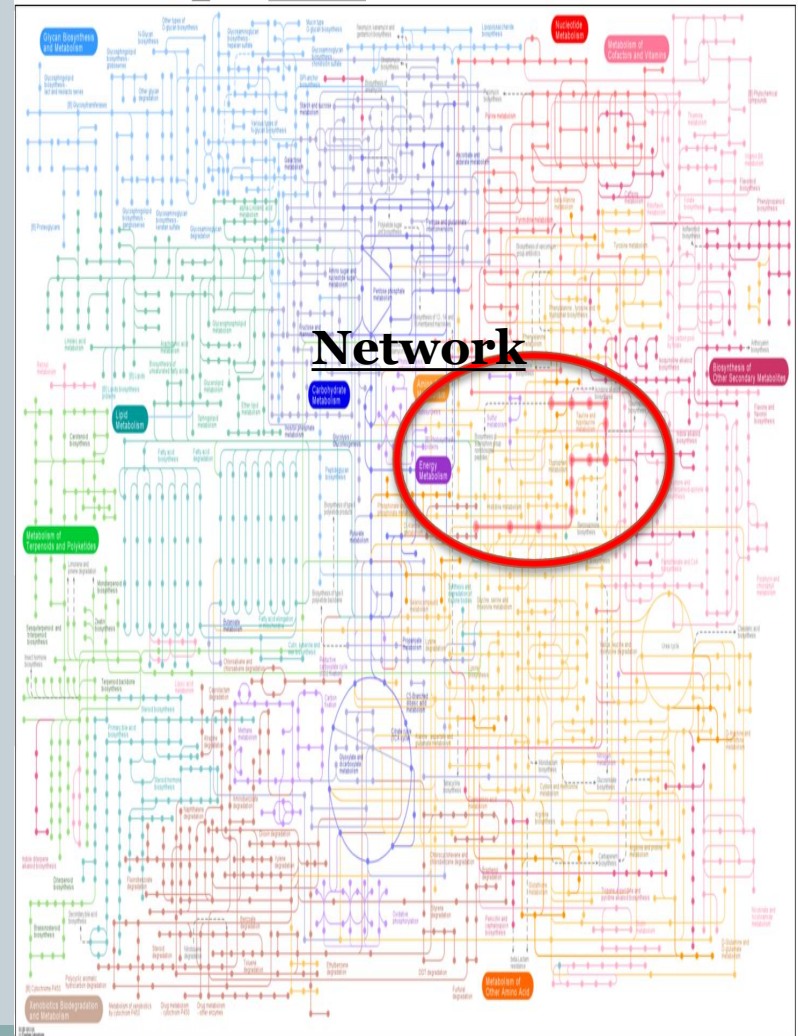
*tryptophan
decarboxylase*

Tryptamine



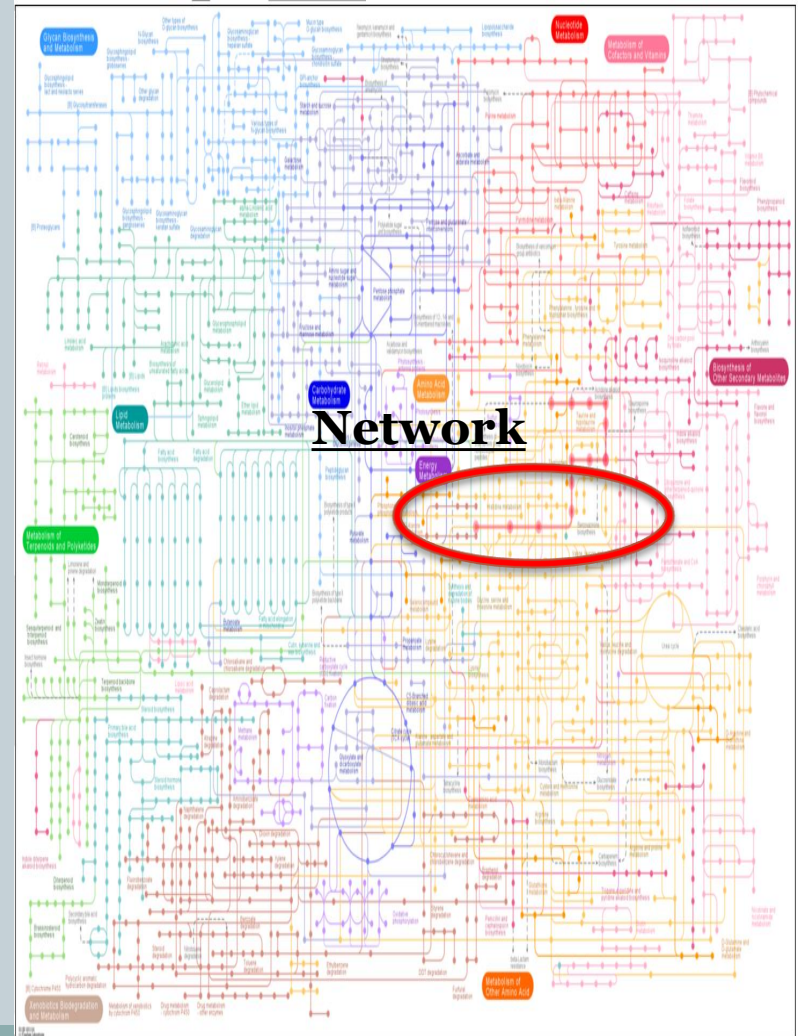
Networks versus Pathways

- A network module can exist within a pathway or between several pathways
- A pathway or several pathways can exist within a network



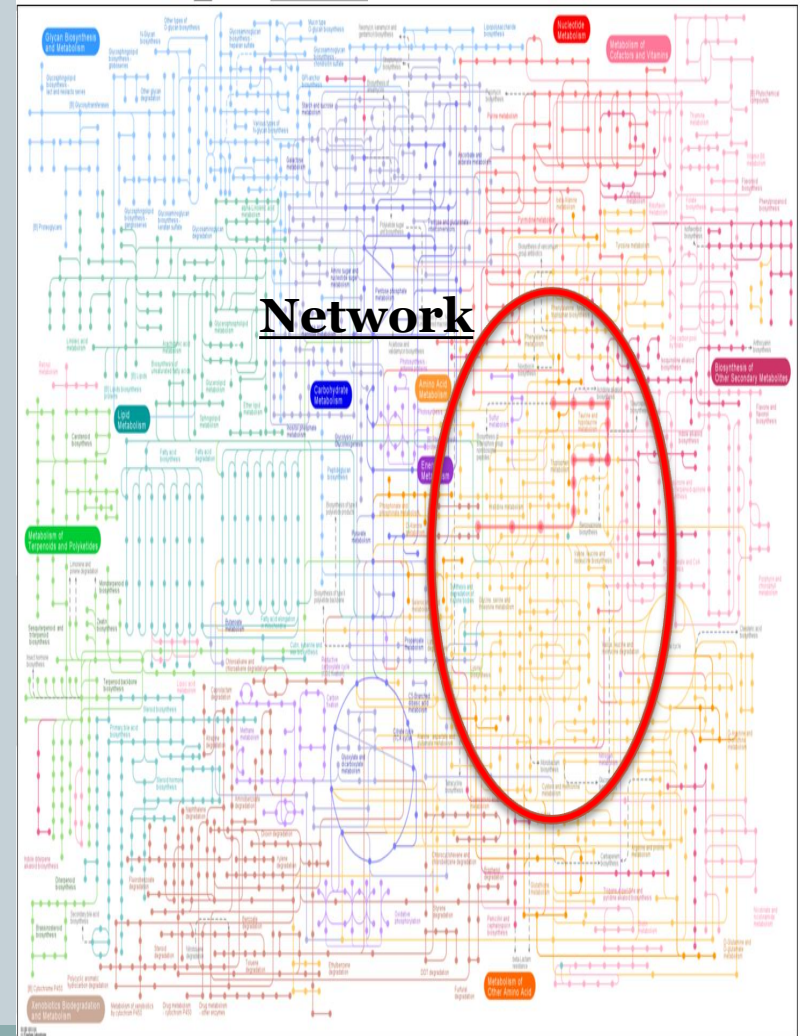
Networks versus Pathways

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Networks versus Pathways

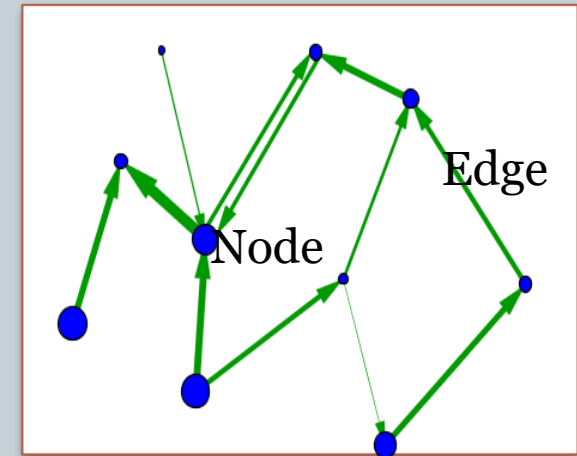
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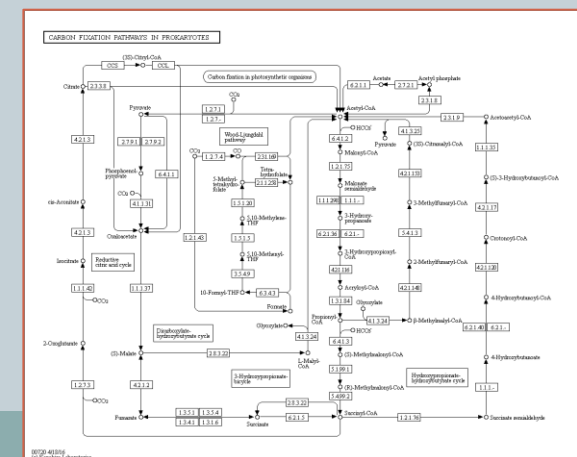
Networks versus Pathways

- The two approaches are complimentary

Network



Biological Pathway



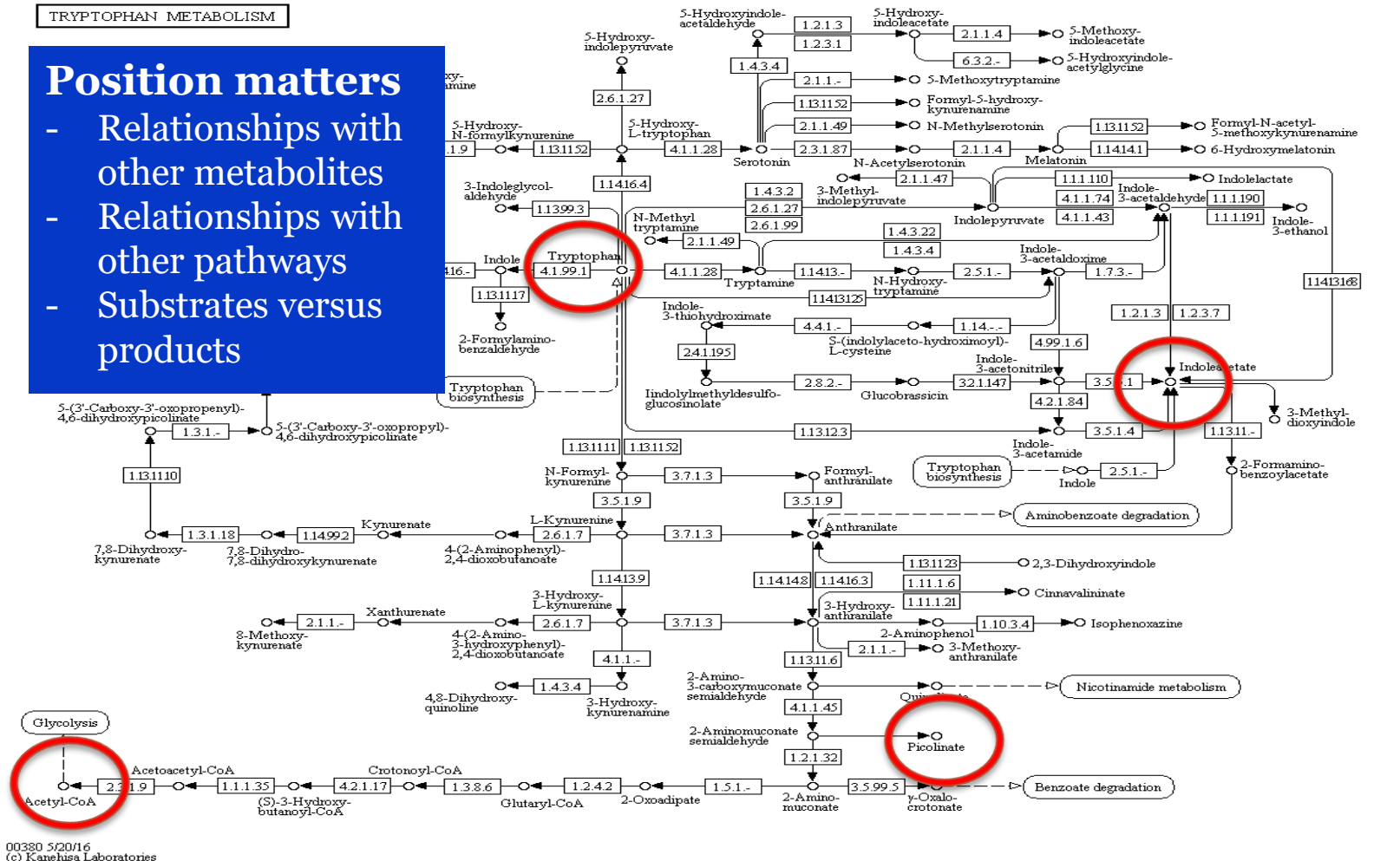


Not All Metabolites are Created Equal

TRYPTOPHAN METABOLISM

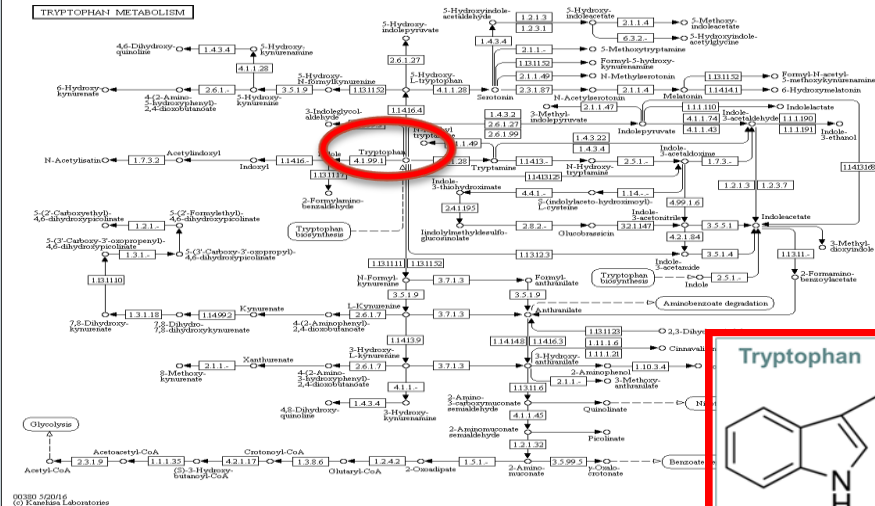
Position matters

- Relationships with other metabolites
- Relationships with other pathways
- Substrates versus products

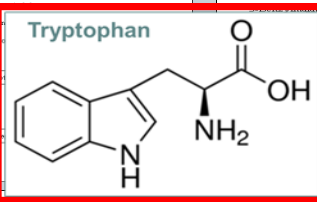
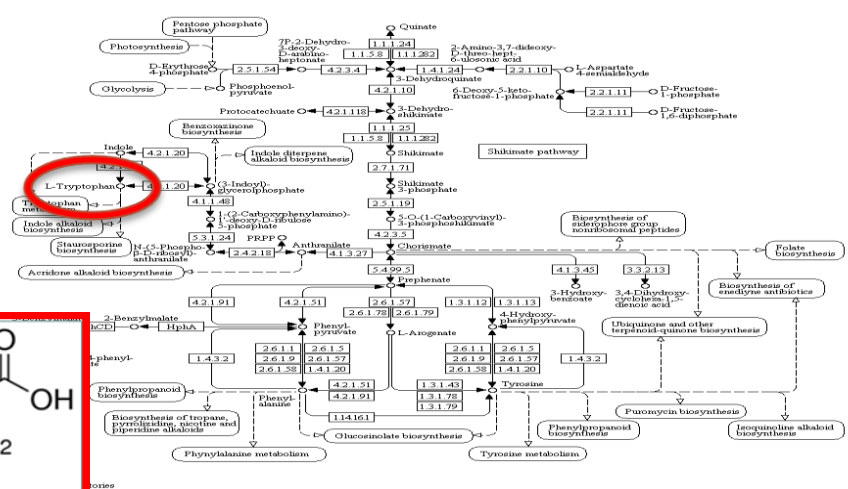


Metabolites Can Appear in Multiple Pathways

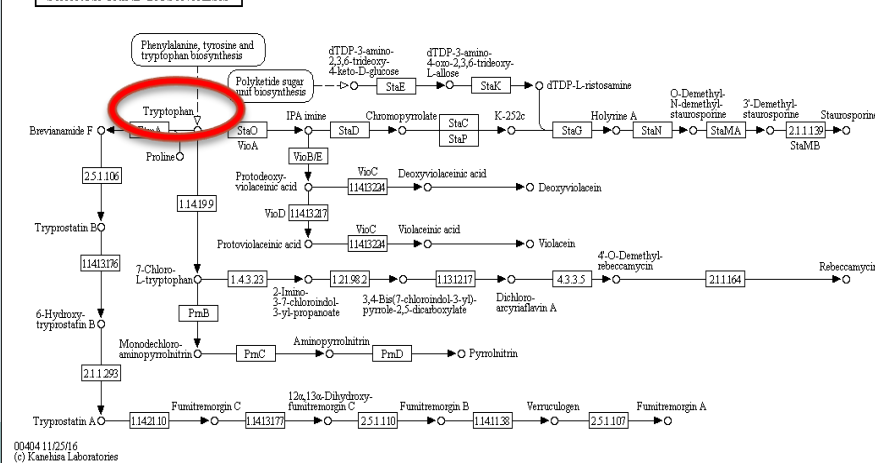
TRYPTOPHAN METABOLISM



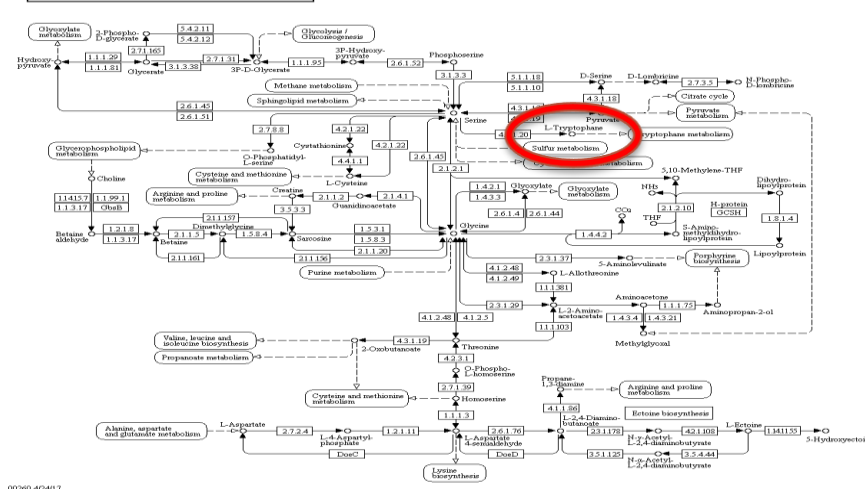
PHENYLALANINE, TYROSINE AND TRYPTOPHAN BIOSYNTHESIS

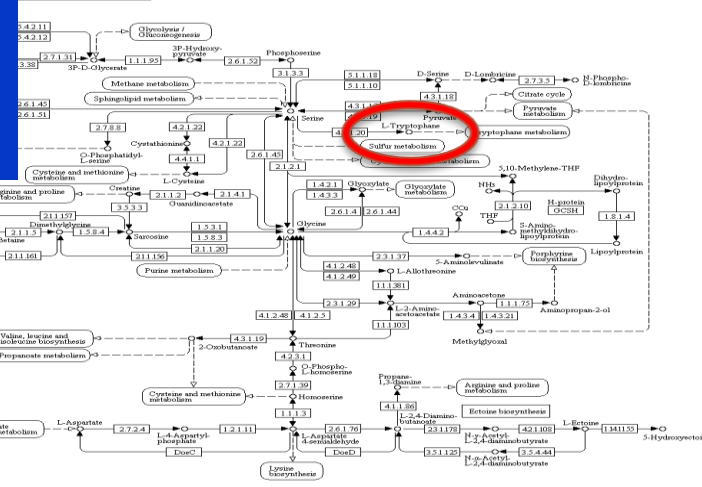


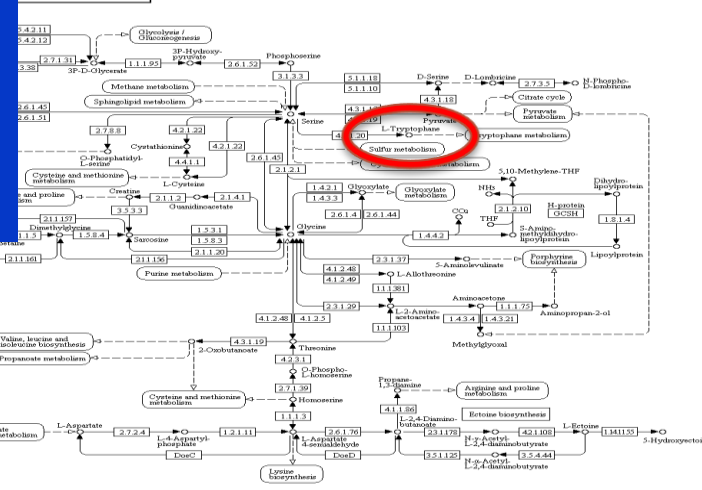
STAUSPORINE BIOSYNTHESIS



GLYCINE, SERINE AND THREONINE METABOLISM







Topology

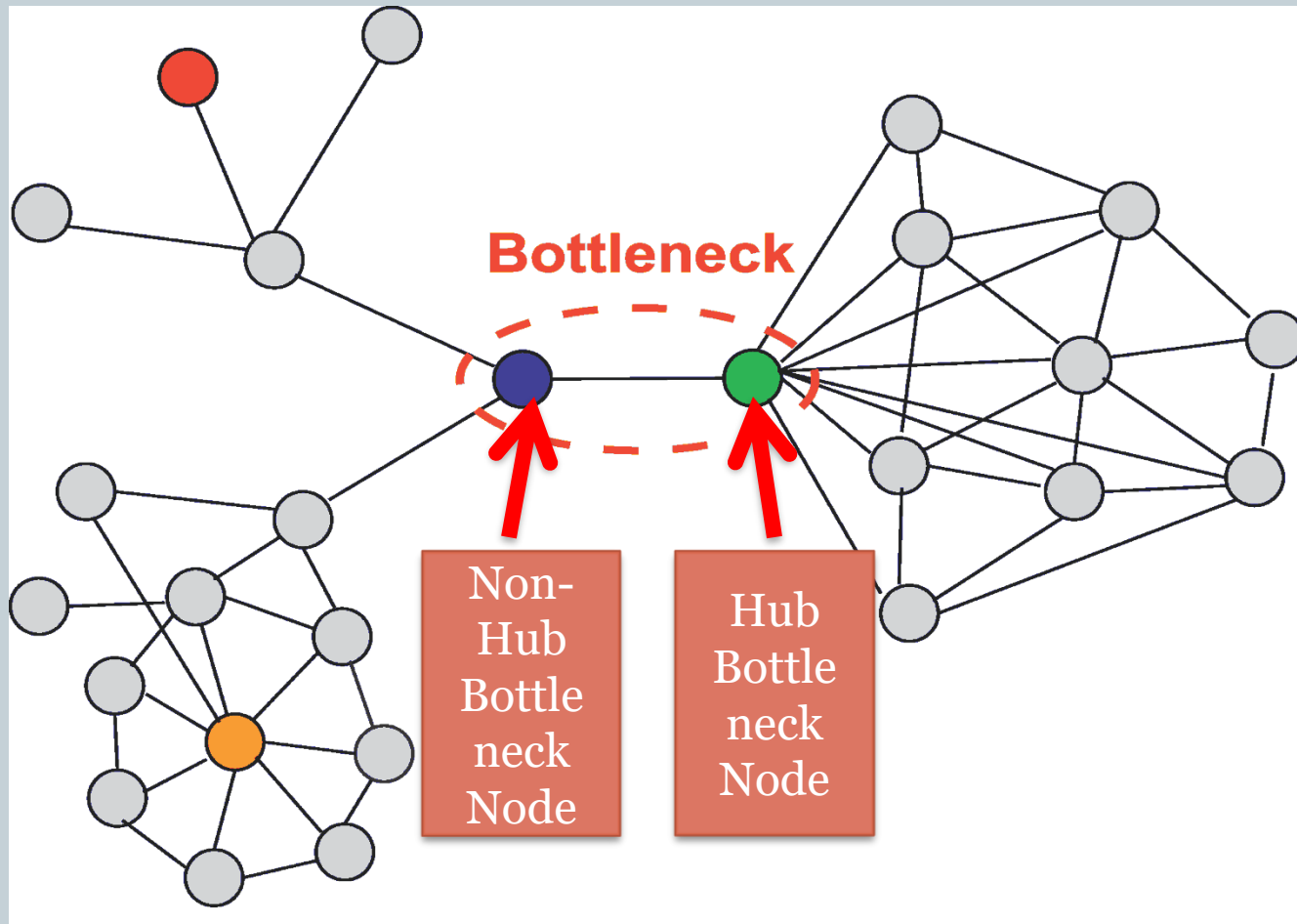


- Importance of a metabolite based on its position within a pathway
- Principals of network methodology can be applied to topology analysis

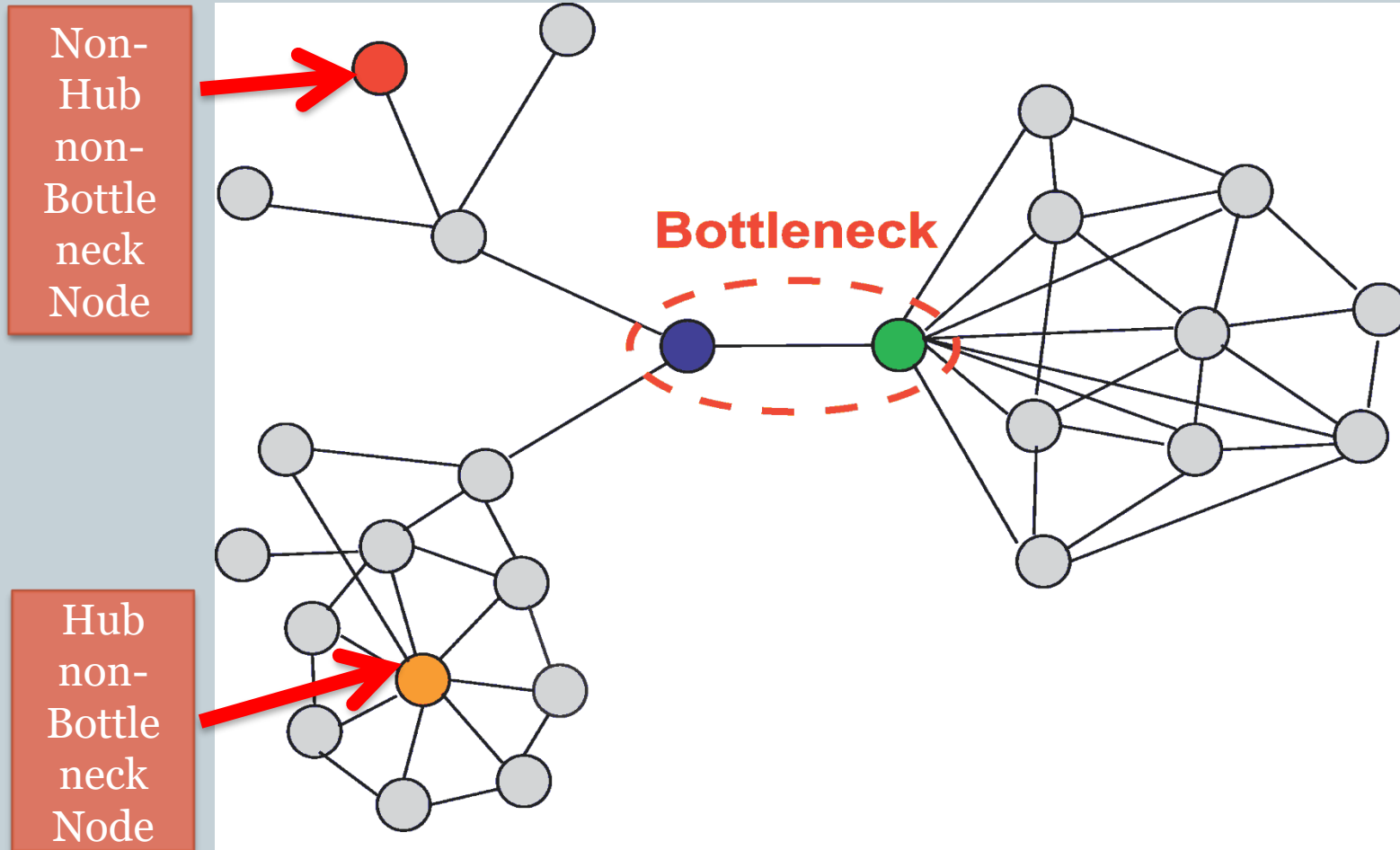
Node Importance

- **Hubs**
 - ▶ Nodes that are highly connected
- **Bottlenecks**
 - ▶ Nodes on many shortest paths between other nodes

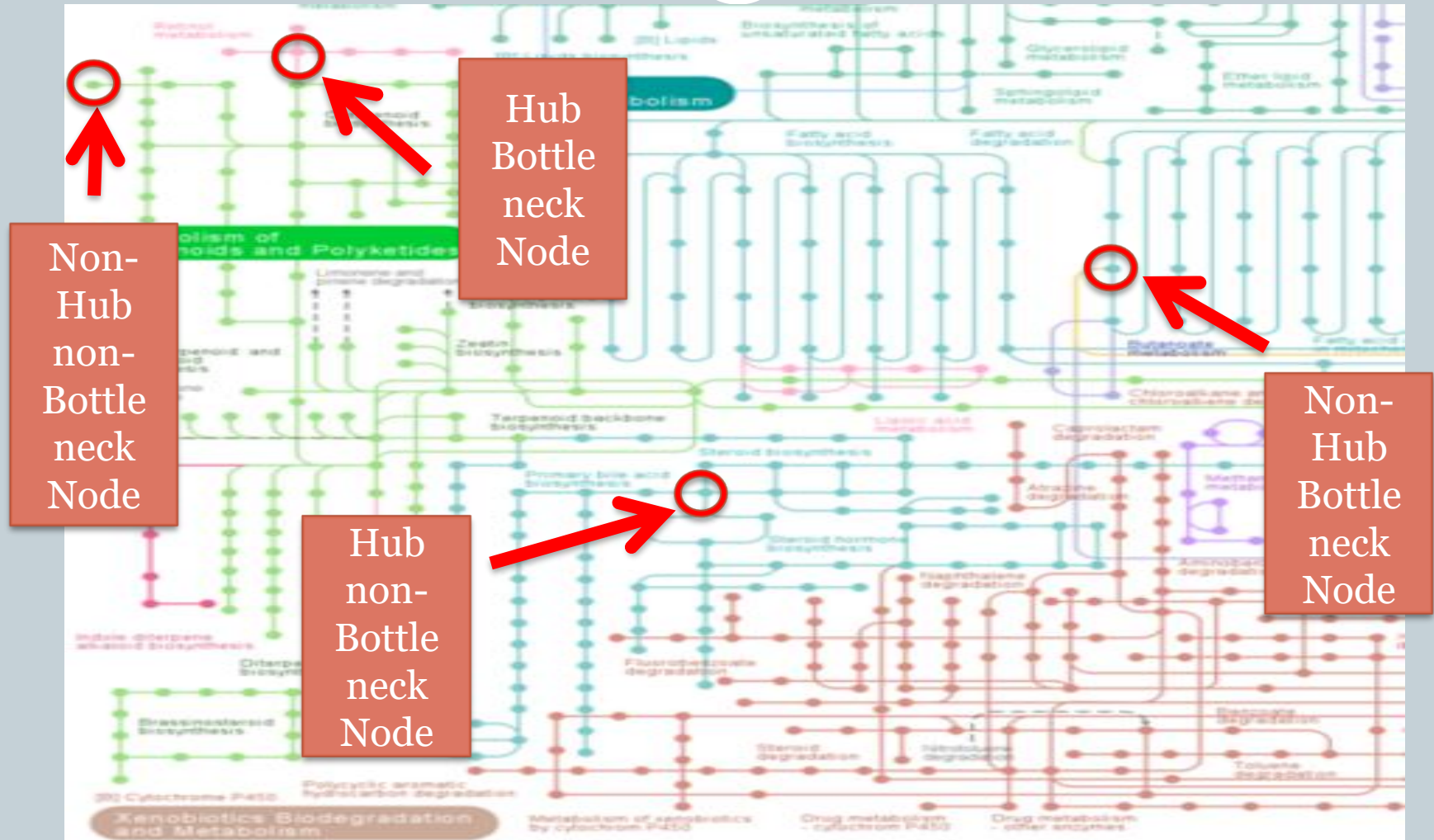
Node Importance



Node Importance



Node Importance



Topology

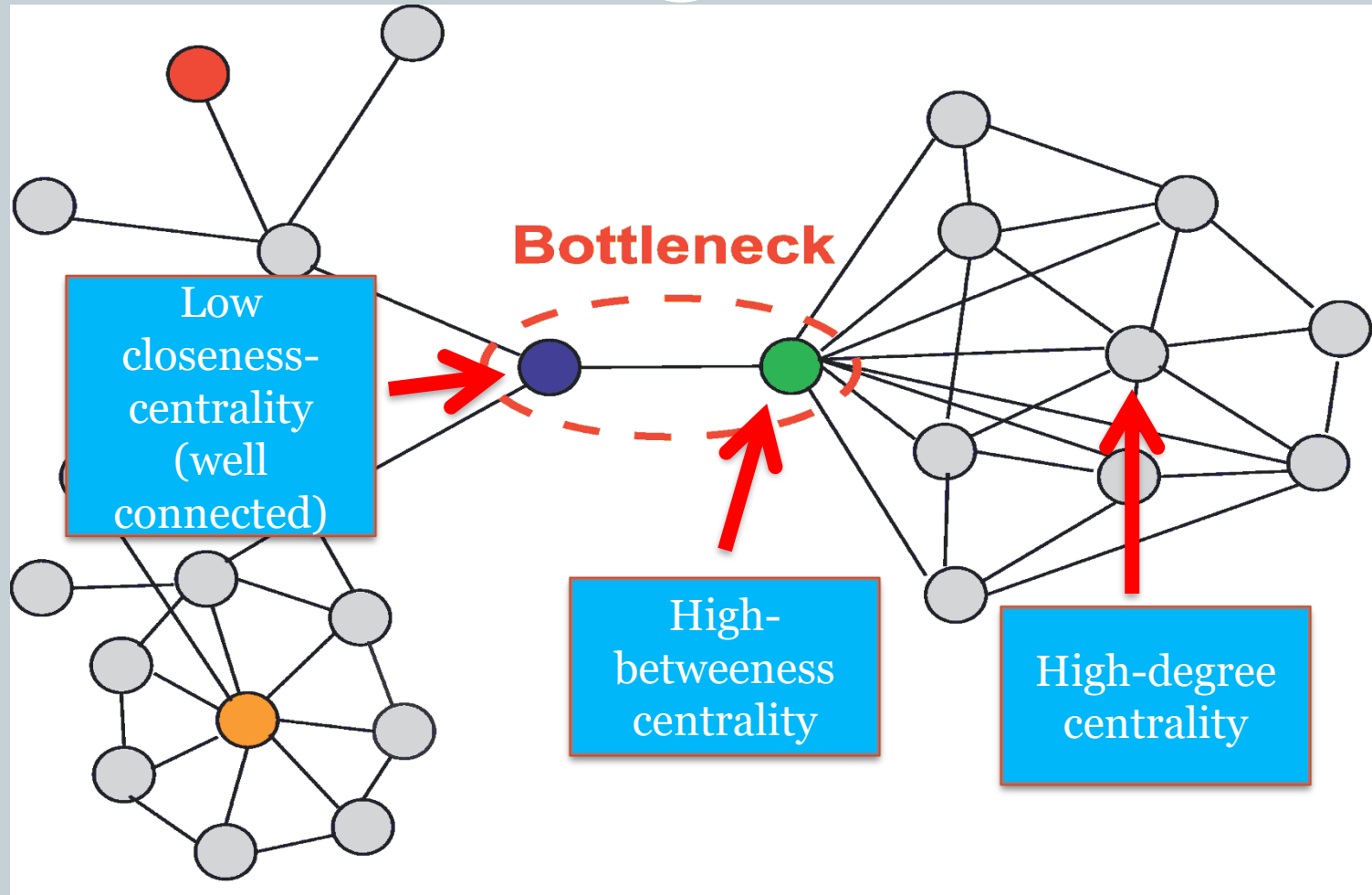


- Importance of a metabolite based on its position within a pathway
- Principals of network methodology can be applied to topology analysis

Graph theory

- **Degree centrality** measures the number of links that connect to a node within a pathway;
- **Closeness centrality** measures the overall distance from a given node to all other nodes in a pathway;
- **Betweenness centrality** measures the number of shortest paths from all nodes to all the others that pass through a given node within a pathway.

Graph Theory



Graph Theory



Glycan Biosynthesis and Metabolism

Glycosphingolipid biosynthesis - lact and neolacto series

[B] Glycosyltransferase

High-degree centrality

[B] Proteoglycans

Glycosphingolipid biosynthesis - ganglioseries

High-betweenness centrality

Low closeness-centrality (well connected)

Lipid Metabolism

[B] Lipids

[B] Lipids biosynthesis proteins

Biosynthesis of unsaturated fatty acids

Cutin, suberine and wax biosynthesis

Fatty acid biosynthesis

Sphingolipid metabolism

Fatty acid metabolism

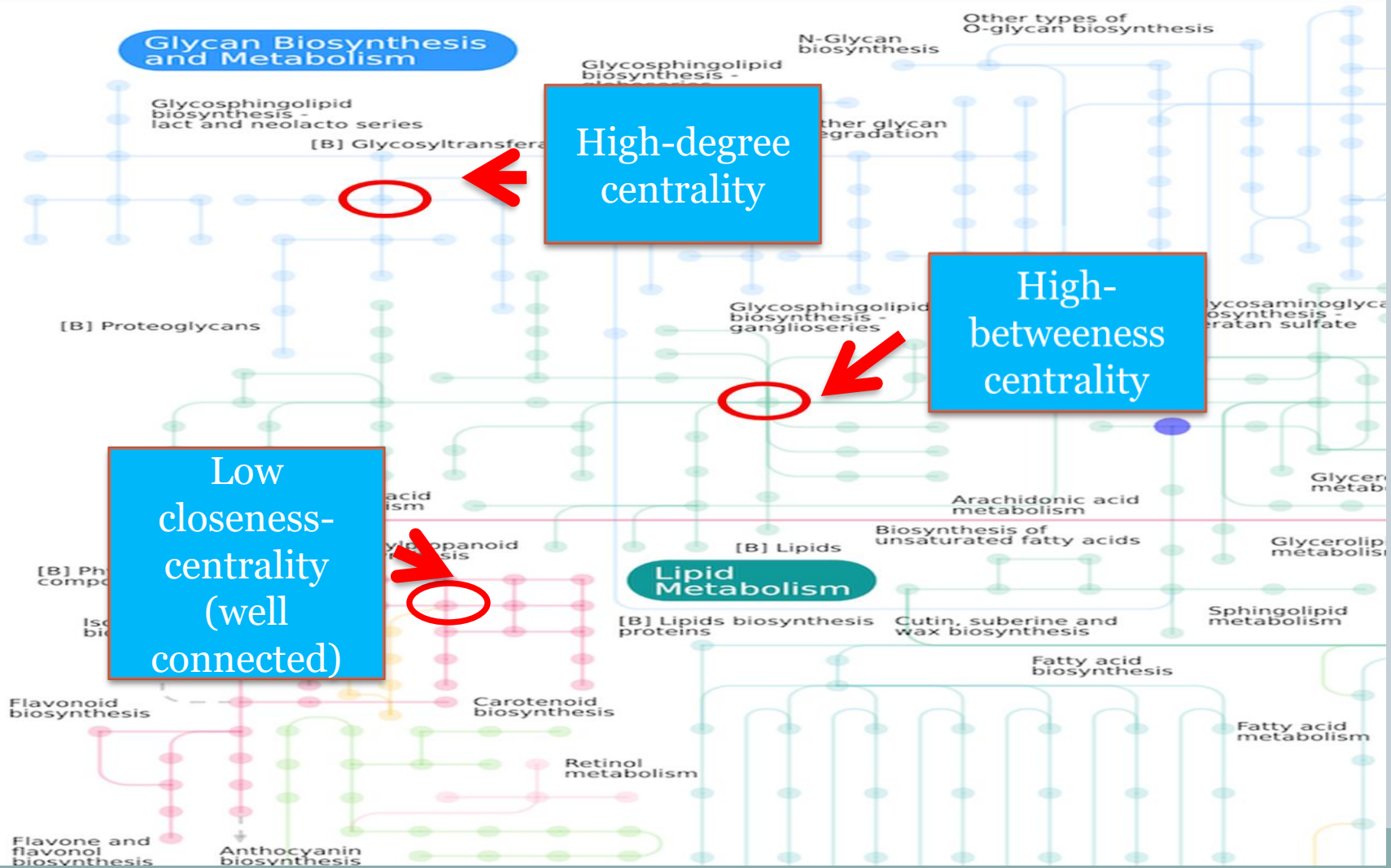
Flavonoid biosynthesis

Carotenoid biosynthesis

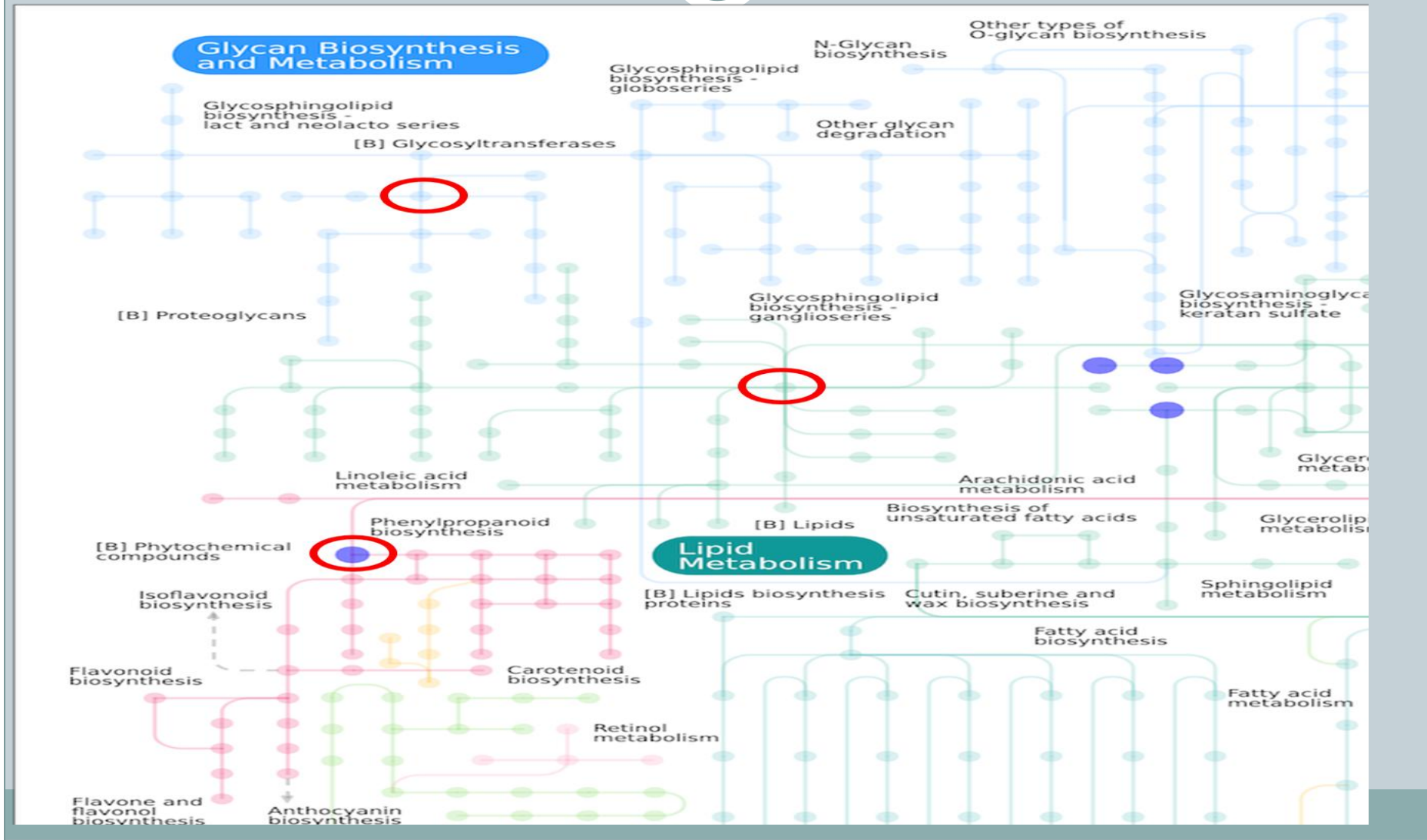
Retinol metabolism

Flavone and flavanol biosynthesis

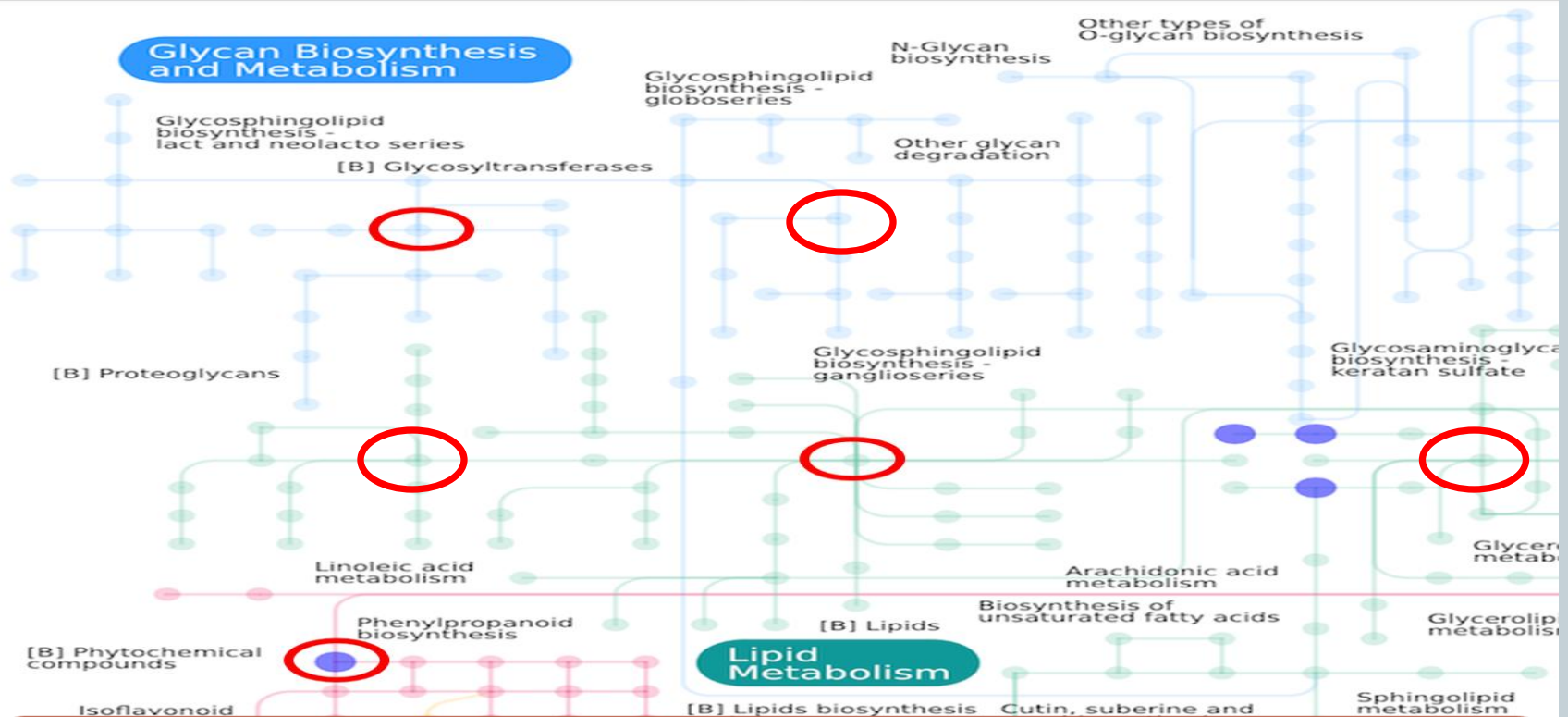
Anthocyanin biosynthesis



Metabolomic networks are Scale-free



Metabolomic networks are Scale-free



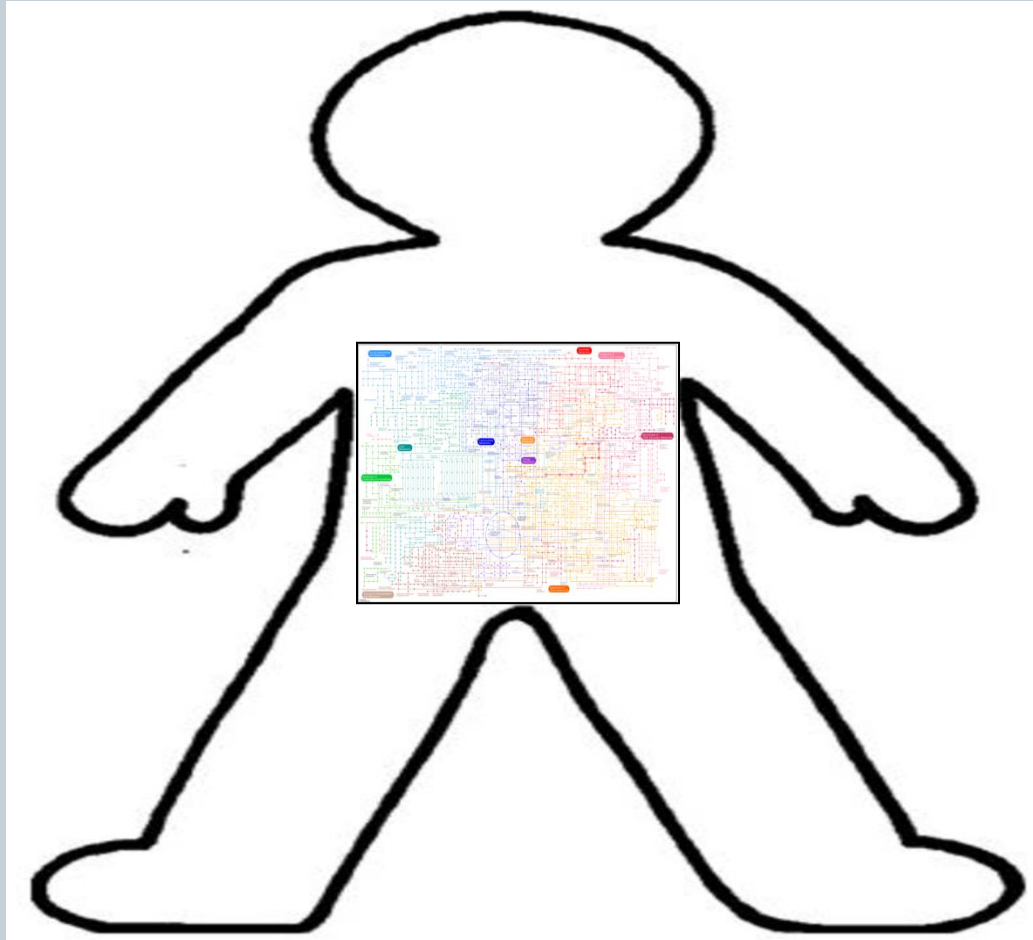
- Small number of very highly connected and central HUB metabolites
 - Majority of metabolites have only a few connections with other metabolites

Integrative omics



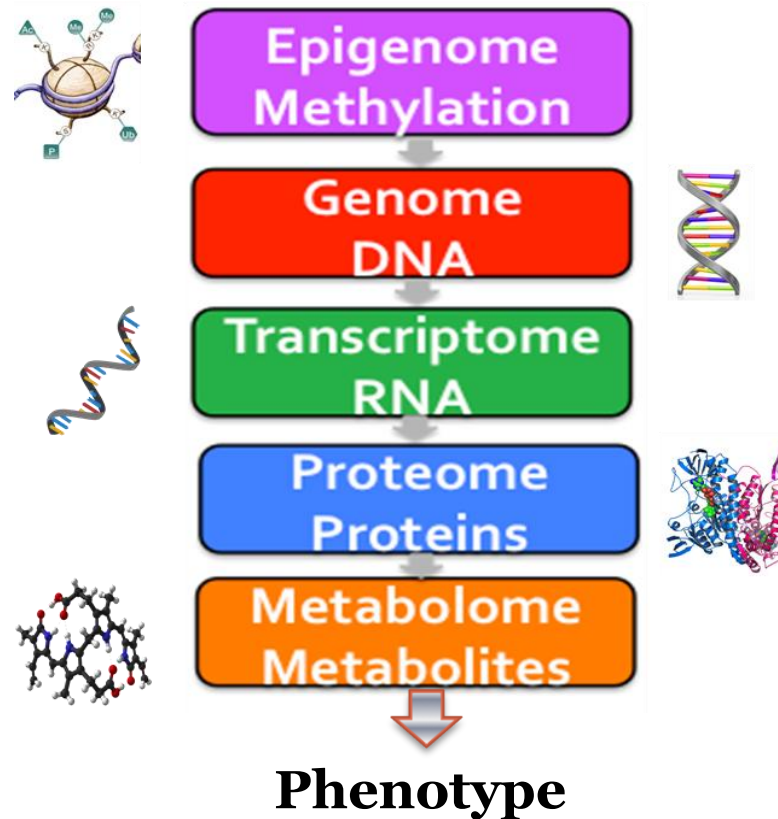
THE APPLICATION OF NETWORK MEDICINE TO METABOLOMICS DATASETS

The Metabolome does not exist in isolation

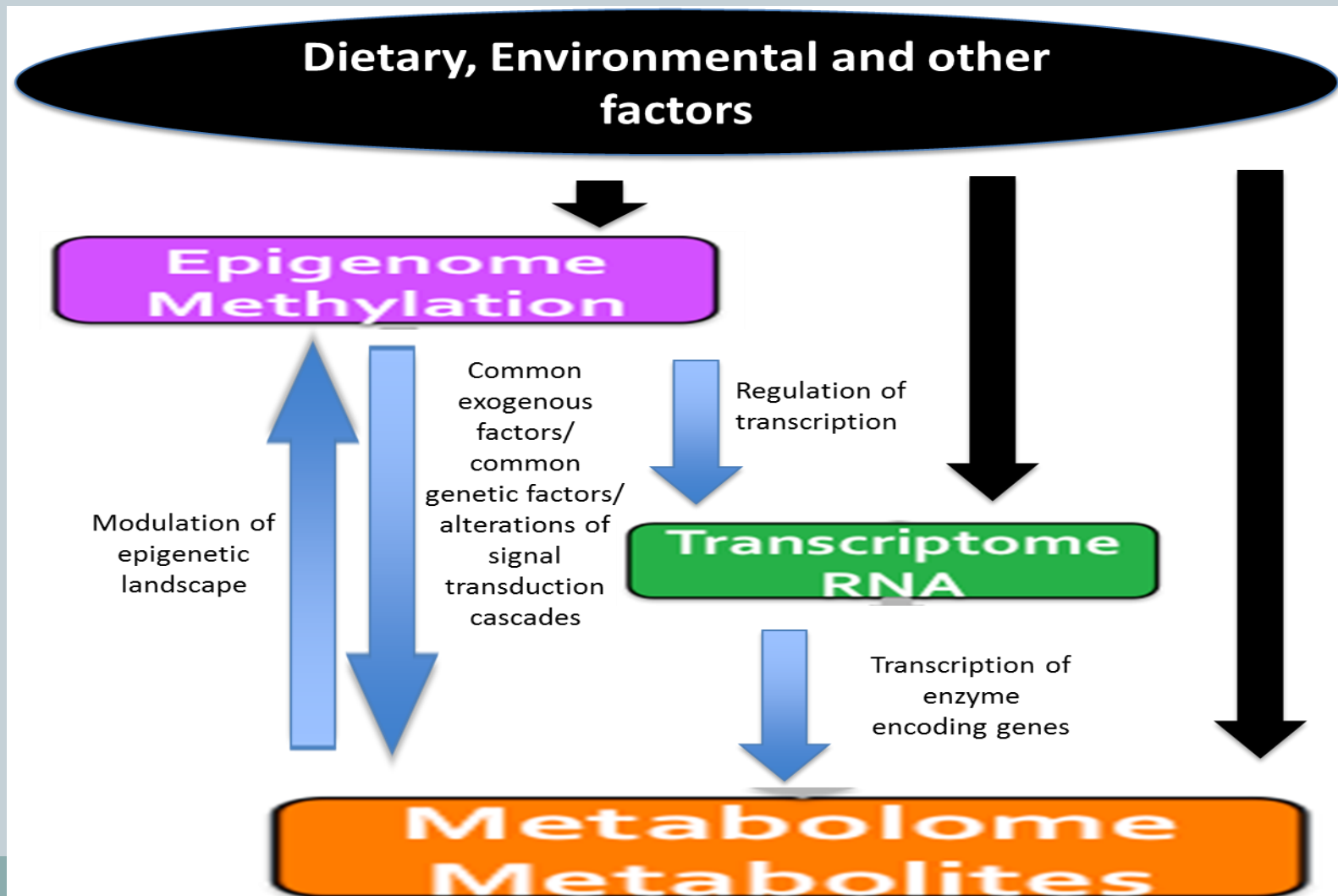


The Metabolome does not exist in isolation

"The Central Dogma"



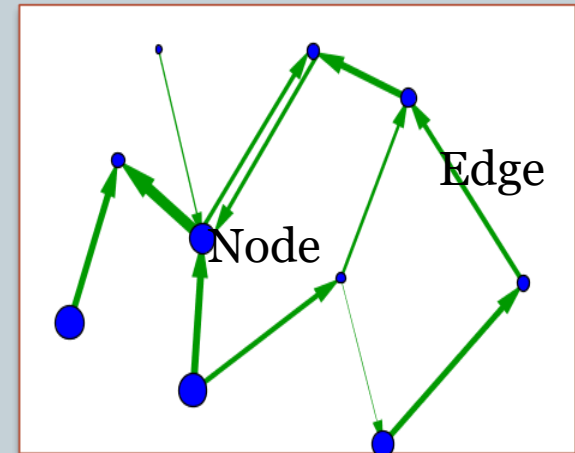
The Metabolome does not exist in isolation



Pathways versus Networks



- Networks can incorporate multiple 'omic' levels including the epigenome, genome transcriptome, proteome, microbiome and metabolome



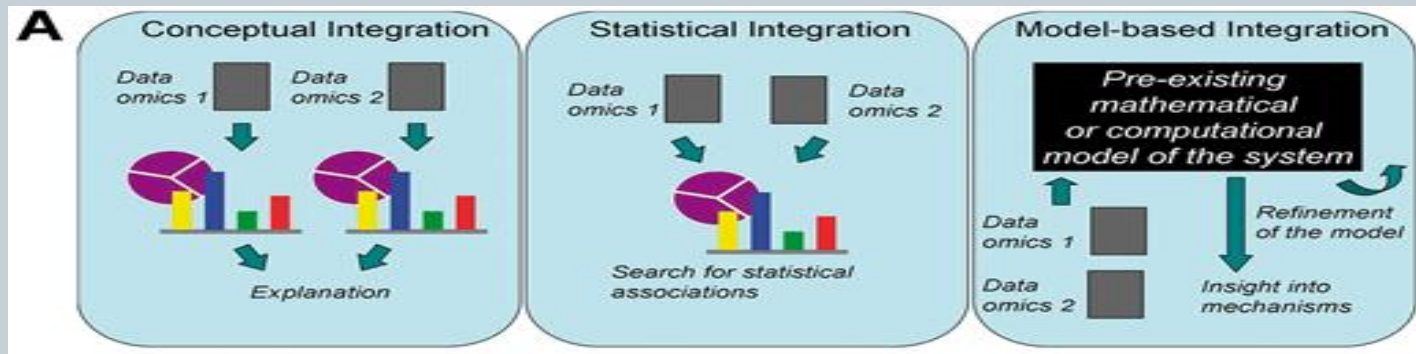
A Word of Caution



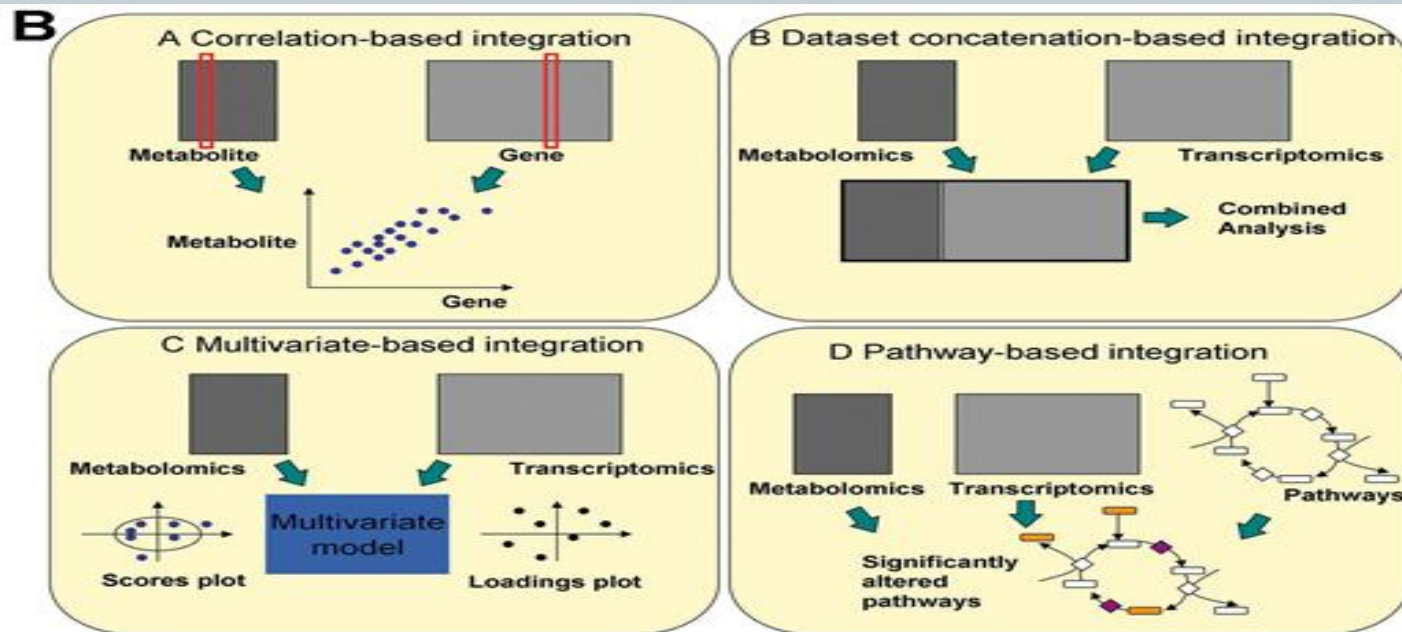
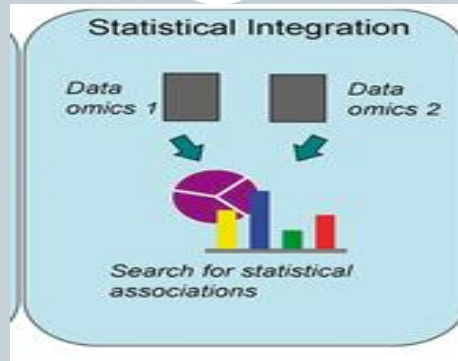
- Not all 'omes' are the same
 - Dimensionality
 - Scale
 - Technique
 - Coverage
 - Normalization and QC procedures
- Must be treated differently and differences accounted for in analyses



Integrative Strategies



Integrative Strategies



Analysing Metabolic Networks



THE APPLICATION OF NETWORK MEDICINE TO METABOLOMICS DATASETS

Defining Aims



**To identify
metabolomic
biomarkers**

**To
understand
underlying
biology**

Defining Aims



**To identify
metabolomic
biomarkers**

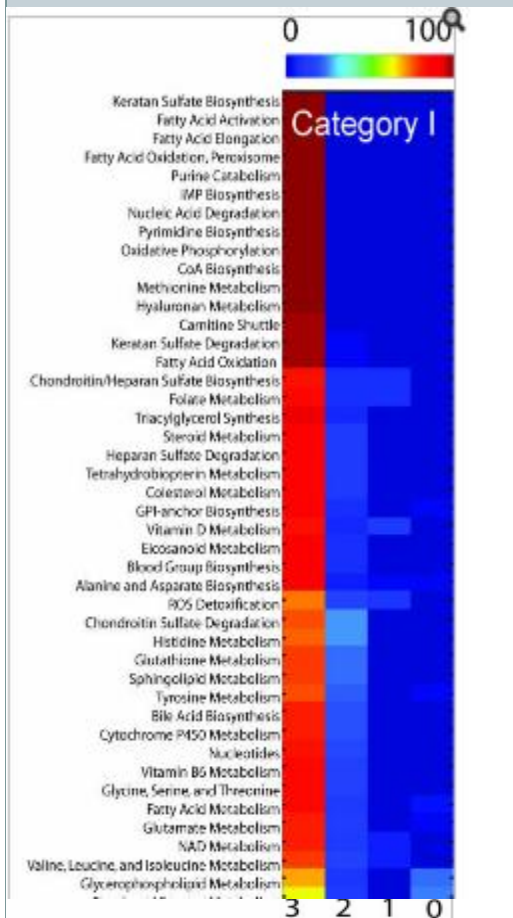
**To
understand
underlying
biology**

Analytical Challenges

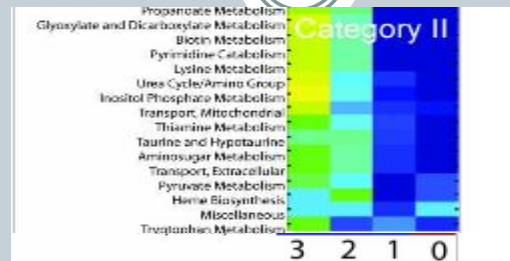


- Temporal Variation
- Unknown Metabolites
- Unmeasured Metabolites
- Poorly Annotated Pathways
- Differences Between Pathway Databases

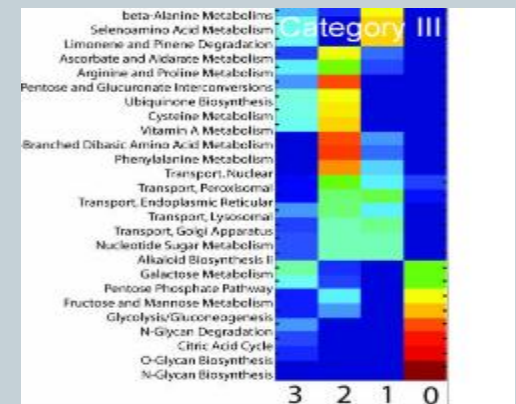
Human Metabolic landscape knowledge: Confidence scores



**extensive primary
literature available**



**~equal proportion of
highly characterized
enzymes/ moderate
biological evidence**



**wide range of
confidence scores
and gene coverage**

Colors represent the percentage of reactions within a pathway that have a confidence score of:

3 - biochemical or genetic evidence

*2 - physiological data or evidence from a nonhuman
mammalian cell*

1 - modeling evidence

0 - unevaluated

Methods



THE APPLICATION OF NETWORK MEDICINE TO METABOLOMICS DATASETS

Network Methods



- **Weighted Gene Co-expression Network Analysis**
 - Module preservation analysis
- Clustering Methodologies
- Bayes Nets
- Structural Equation Modelling
- Metabolomic Reconstruction

Network Methods



- **Weighted Gene Co-expression Network Analysis**
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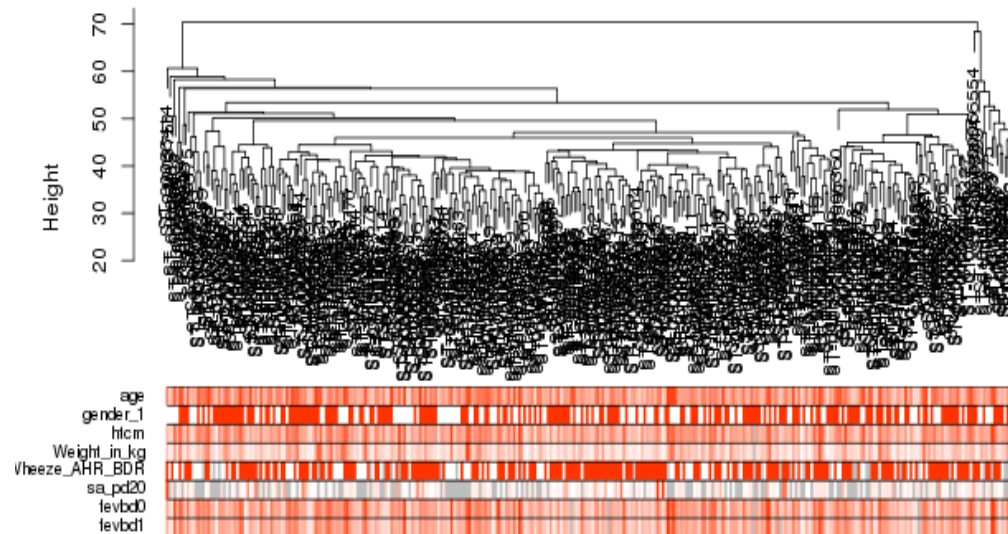
WGCNA



**Metabolomic Profiles of
325 asthmatic children:
8185 metabolomic
features**

**Hierarchical
Clustering**

Sample dendrogram and trait heatmap

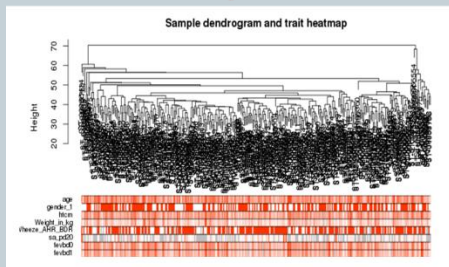




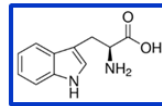
WGCNA



Hierarchical
Clustering

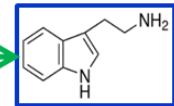


Tryptophan



*Correlation
coefficient*

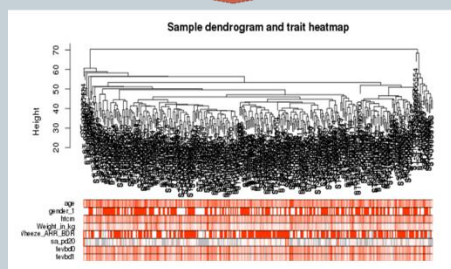
Tryptamine



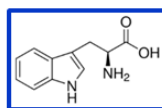
WGCNA



Hierarchical
Clustering

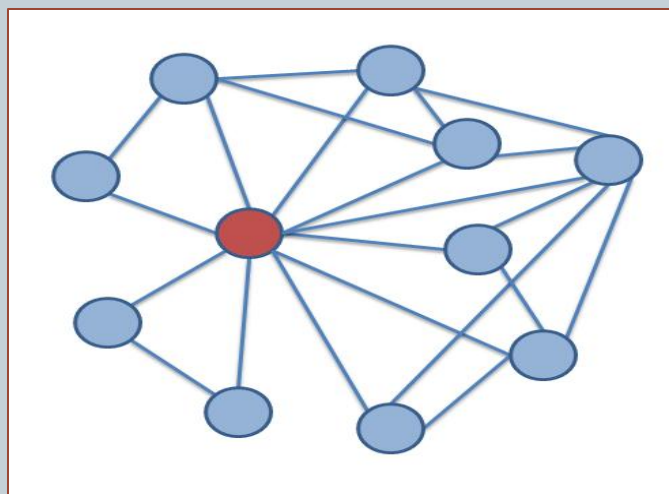
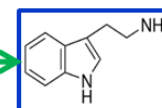


Tryptophan



*Correlation
coefficient*

Tryptamine

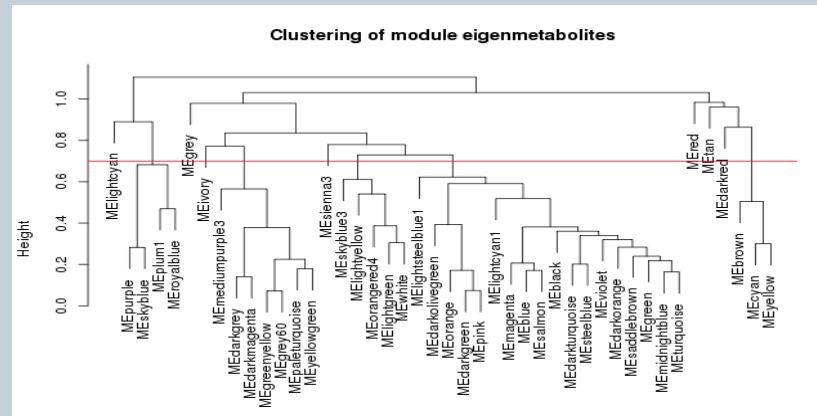
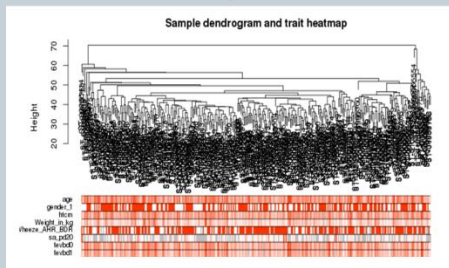


*Correlation
coefficient
for every
edge/
metabolite-
metabolite
pair*

WGCNA



Hierarchical
Clustering



Correlation/
adjacency
matrix

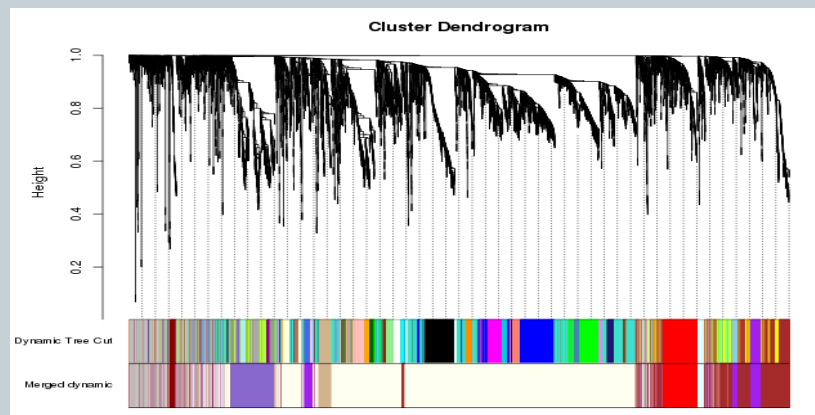
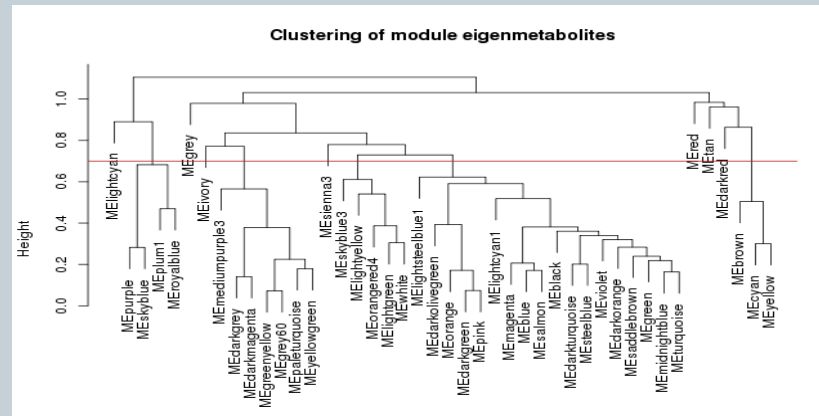
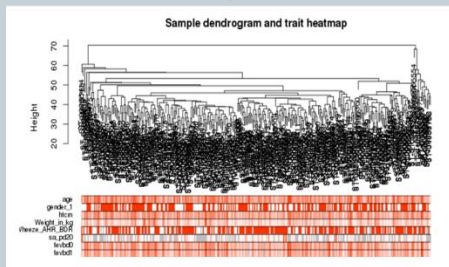
Topological
overlap
measure

Hierarchical
clustering

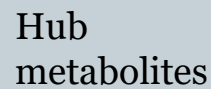
WGCNA



Hierarchical
Clustering



Clusters of
interconnected
metabolites

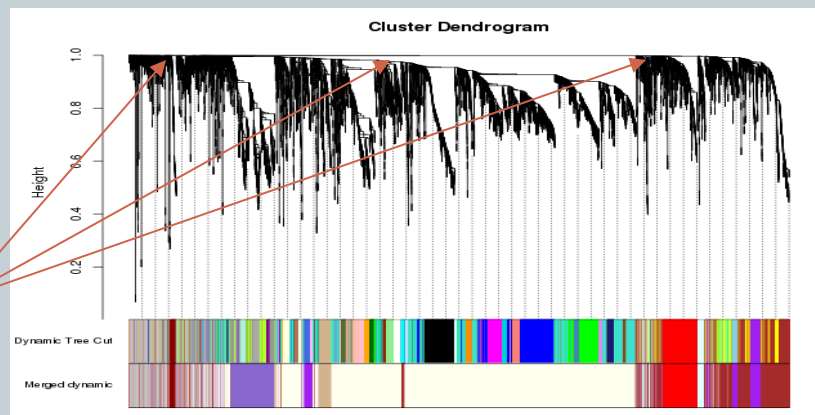
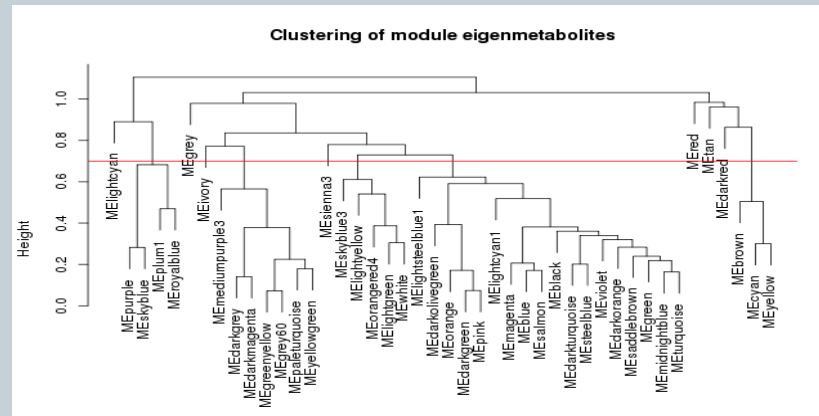
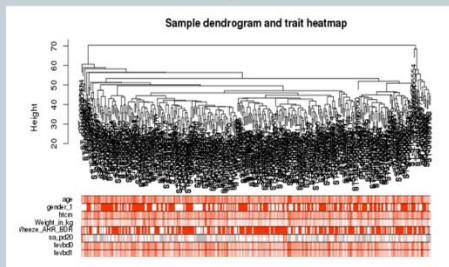


Clusters of interconnected metabolites

WGCNA



Hierarchical
Clustering



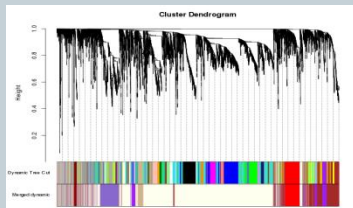
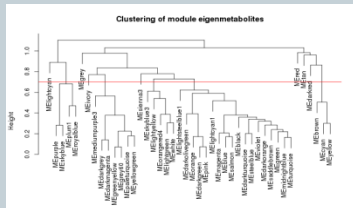
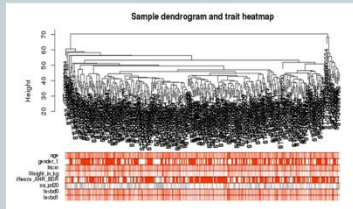
Non-Hub
metabolites

Clusters of
interconnected
metabolites

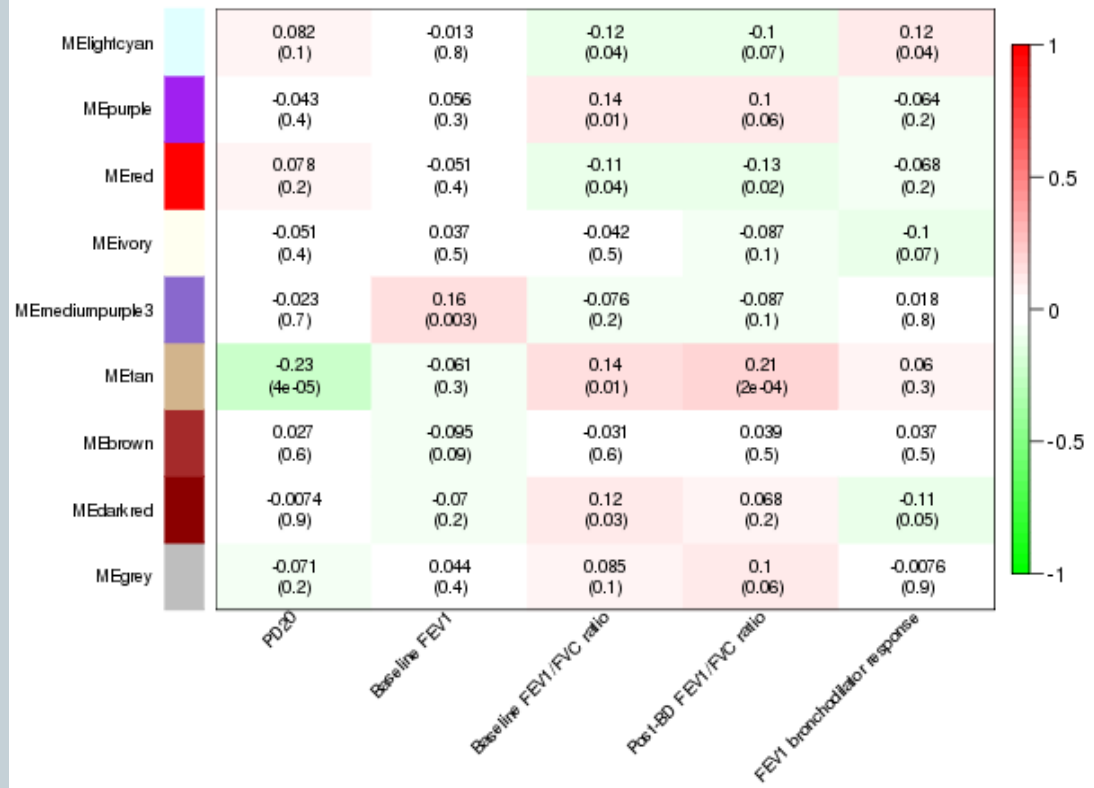
WGCNA



Hierarchical
Clustering



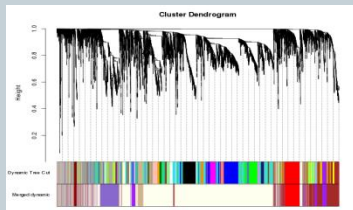
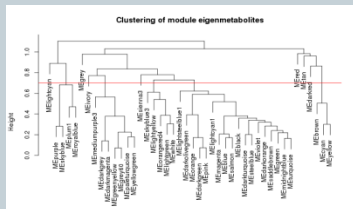
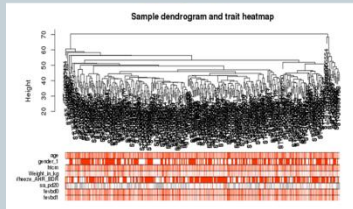
Module-trait relationships



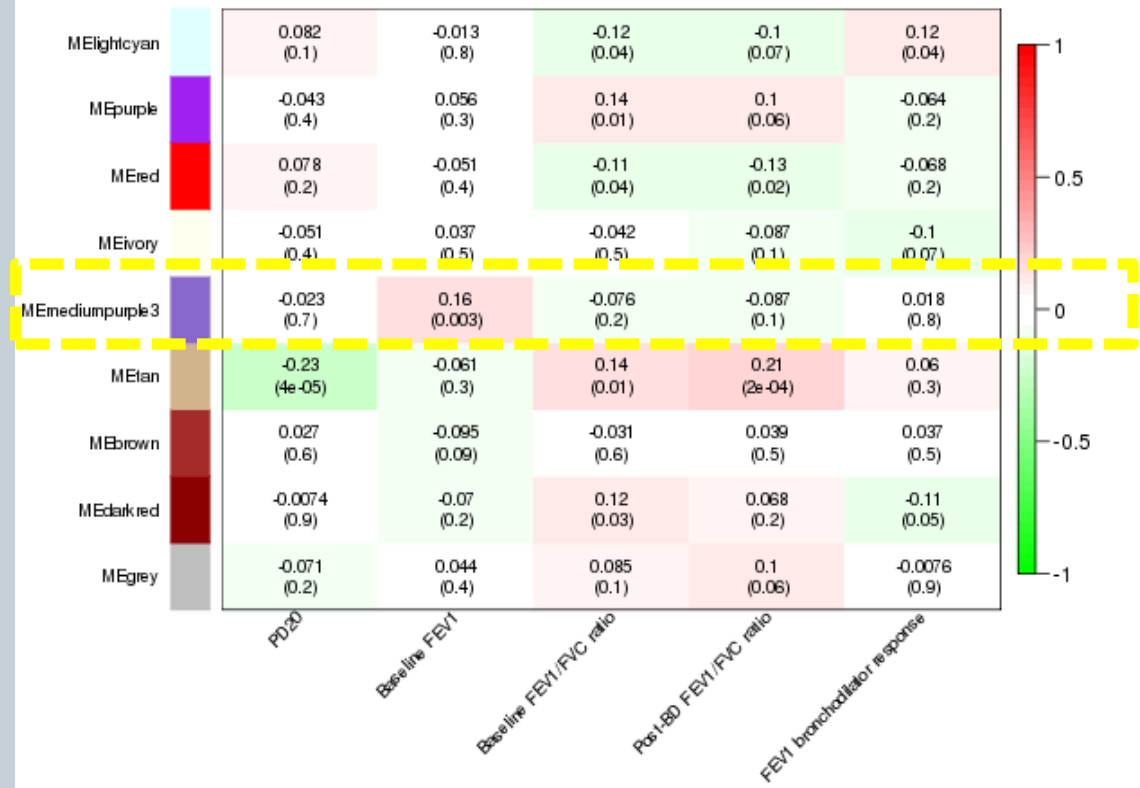
WGCNA



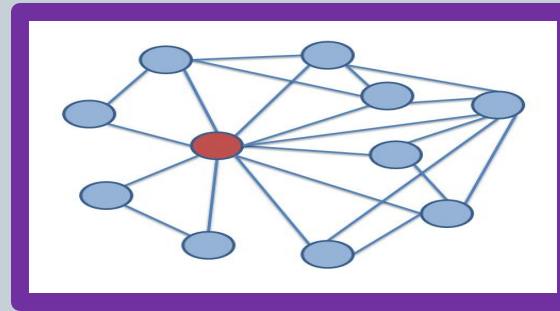
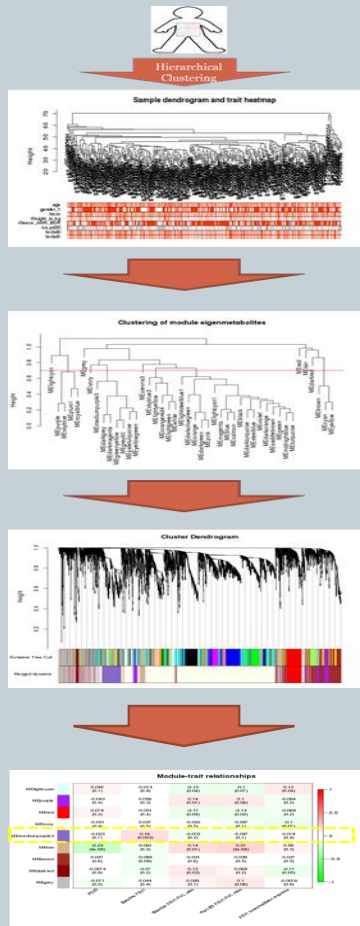
Hierarchical
Clustering



Module-trait relationships



WGCNA

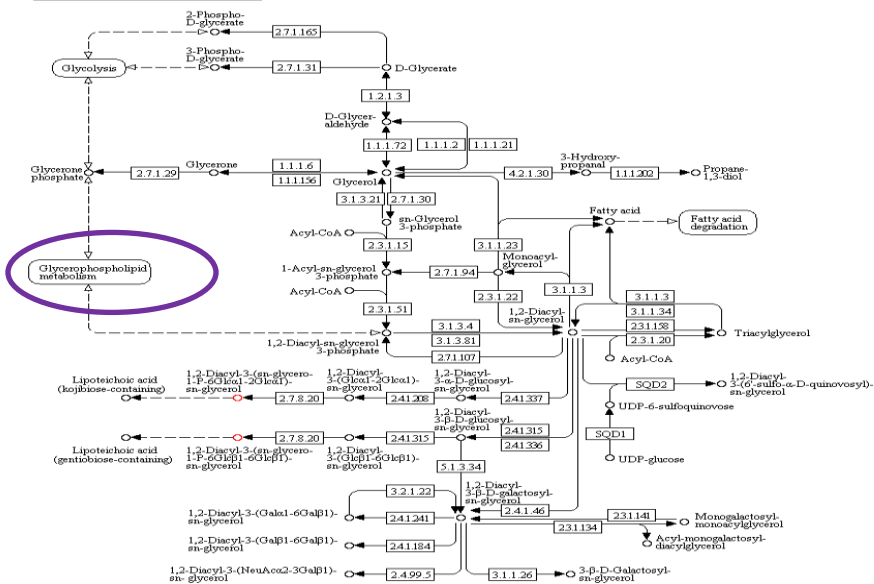


537
metabolite
Features

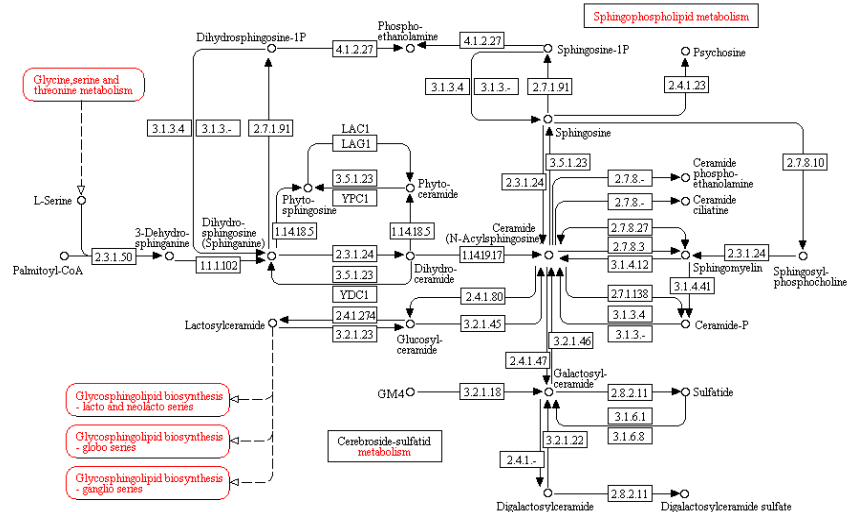
Pathway
enrichment
analysis

GPI-anchor biosynthesis
Sphingolipid metabolism
Glycerolipid metabolism
Glycerophospholipid metabolism

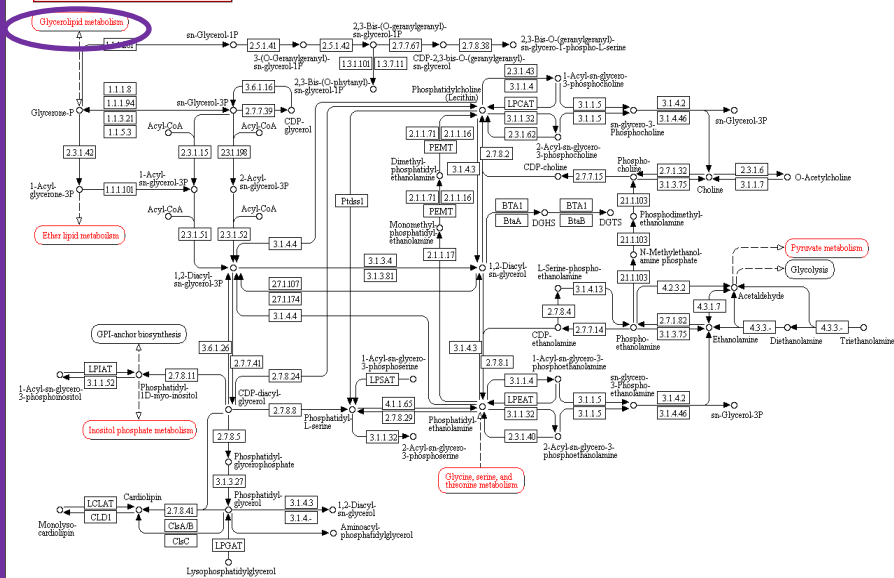
GLYCEROLIPID METABOLISM



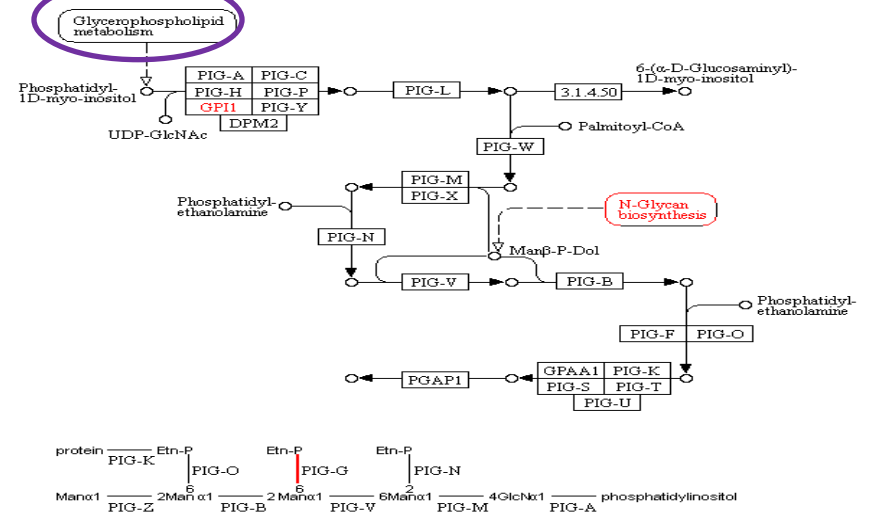
SPHINGOLIPID METABOLISM



GLYCEROPHOSPHOLIPID METABOLISM



GLYCOSYLPHOSPHATIDYLINOSITOL (GPI) - ANCHOR BIOSYNTHESIS



Network Methods



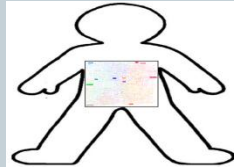
- **Weighted Gene Co-expression Network Analysis**
 - Module preservation analysis
- Clustering Methodologies
- Bayes Nets
- Structural Equation Modelling
- Metabolomic Reconstruction

WGCNA Preservation Analysis



- Determining how the properties of a network module change across conditions/systems/groups
- Network analysis is conducted independently in the two datasets
- Identify consensus modules preserved across networks in the two datasets
- Identify modules that differ across networks in the two datasets

WGCNA Preservation Analysis



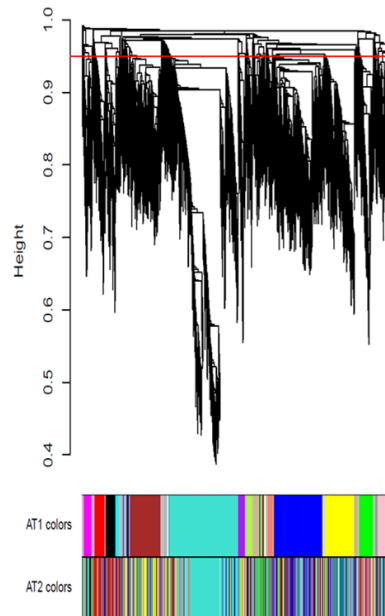
**Metabolomic Profiles of
two different lung cell
types in control donors**



AT1 cells

28 modules

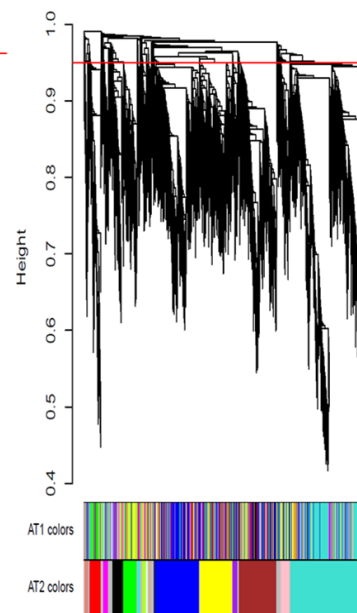
module	n genes
black	300
blue	1537
brown	967
cyan	106
darkgreen	41
darkgrey	37
darkorange	30
darkred	41
darkturquoise	38
green	428
greenyellow	173
grey	1133
grey60	64
lightcyan	66
lightgreen	63
lightyellow	48
magenta	254
midnightblue	75
orange	35
pink	258
purple	212
red	321
royalblue	46
salmon	138
tan	148
turquoise	2146
white	30
yellow	933



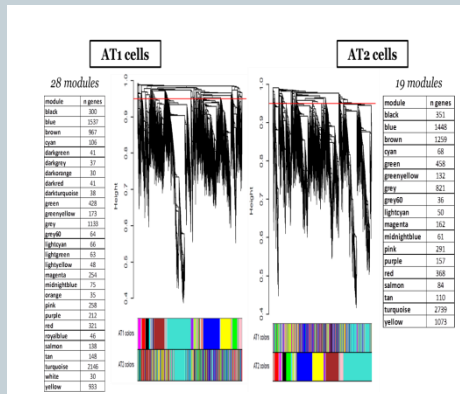
AT2 cells

19 modules

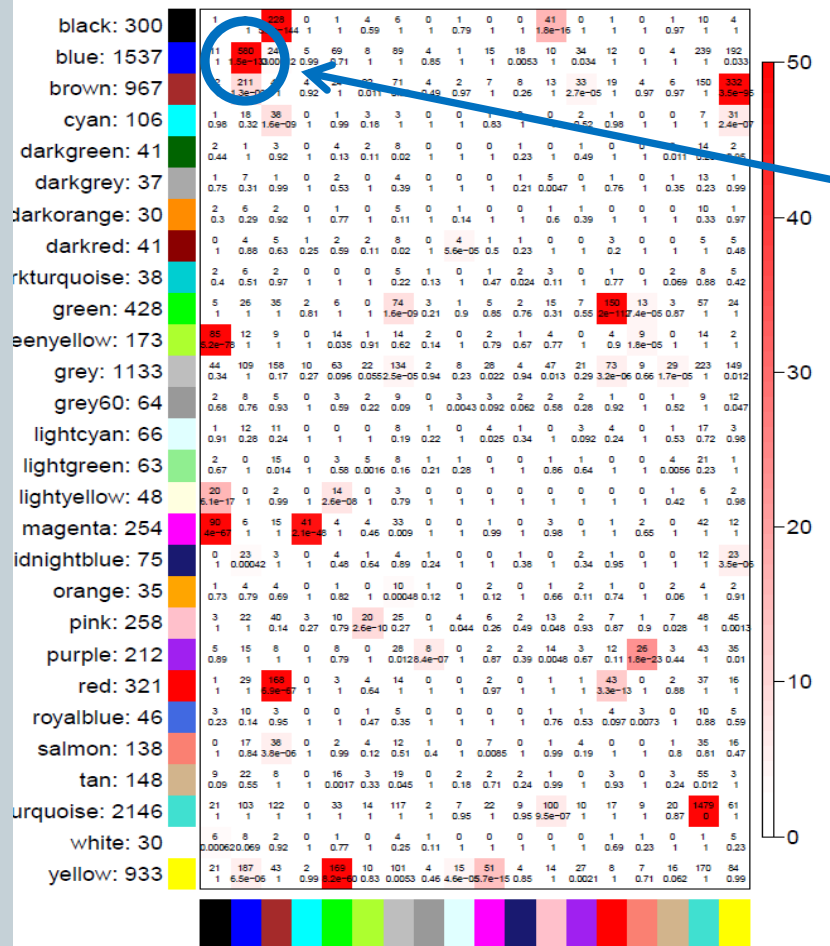
module	n genes
black	351
blue	1448
brown	1259
cyan	68
green	458
greenyellow	132
grey	821
grey60	36
lightcyan	50
magenta	162
midnightblue	61
pink	291
purple	157
red	368
salmon	84
tan	110
turquoise	2739
yellow	1073



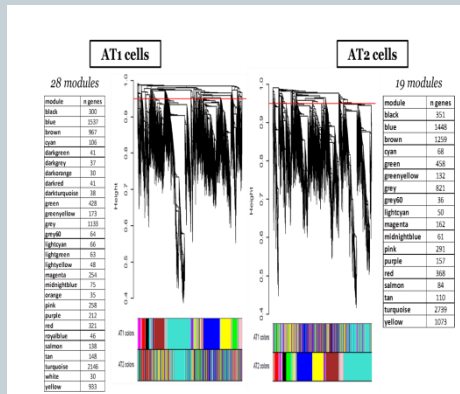
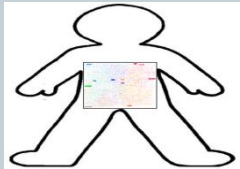
WGCNA Preservation Analysis



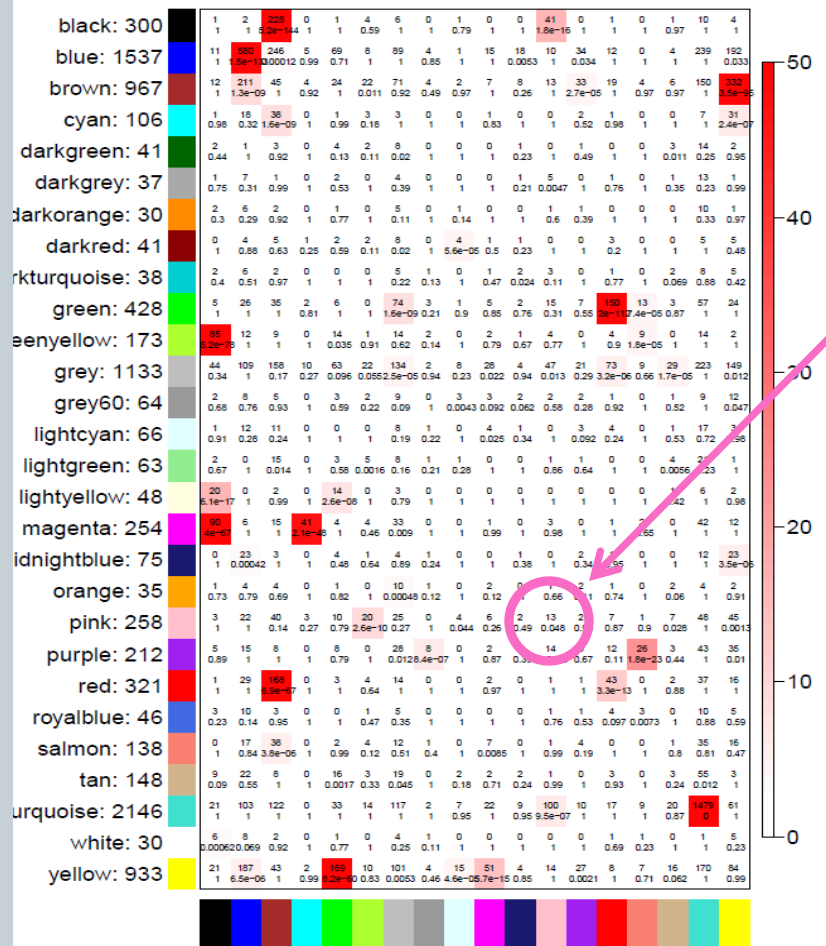
C. AT1 modules (rows) vs. AT2 modules (columns)



WGCNA Preservation Analysis



C. AT1 modules (rows) vs. AT2 modules (columns)



WGCNA



For further details see:

<https://labs.genetics.ucla.edu/horvath/CoexpressionNetwork/Rpackages/WGCNA/>

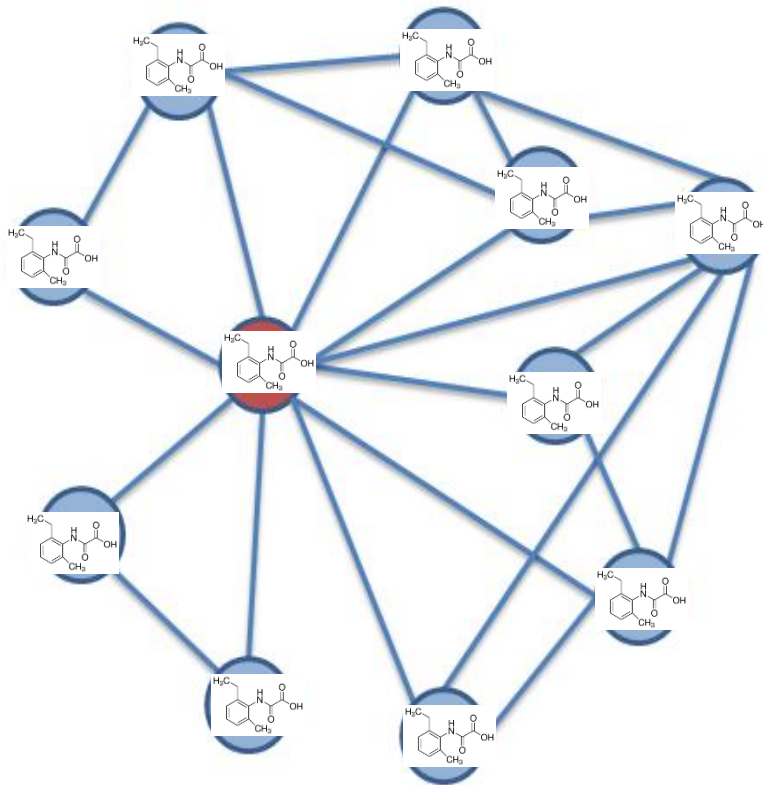
[Langfelder P](#), [Horvath S](#) WGCNA:
an R package for weighted correlation network analysis. [BMC](#)
[Bioinformatics](#). 2008;9:559

Network Methods



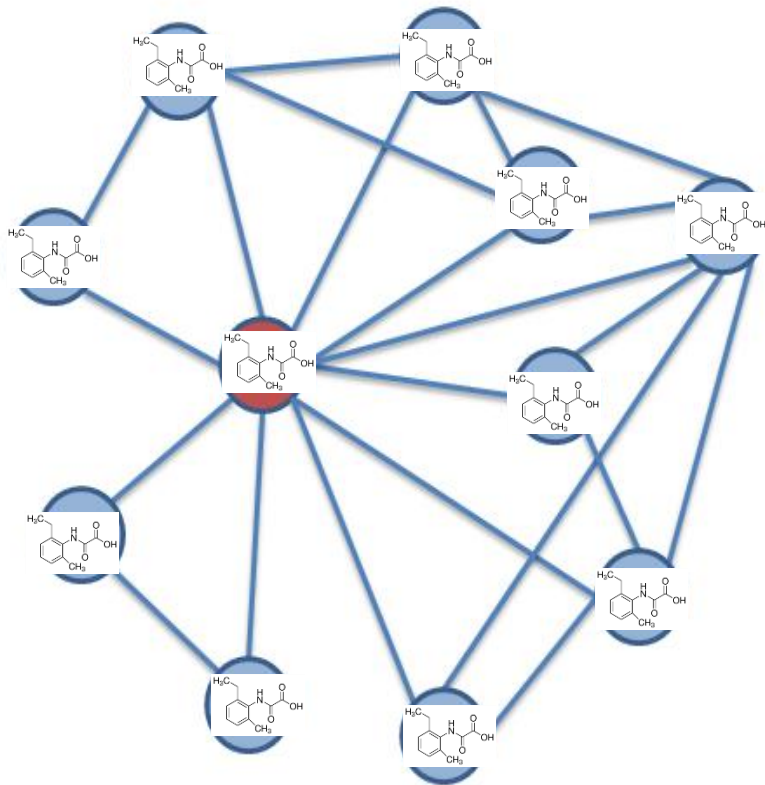
- **Weighted Gene Co-expression Network Analysis**
 - Module preservation analysis
- **Clustering Methodologies**
- **Bayes Nets**
- **Structural Equation Modelling**
- **Metabolomic Reconstruction**

Clustering Methodologies

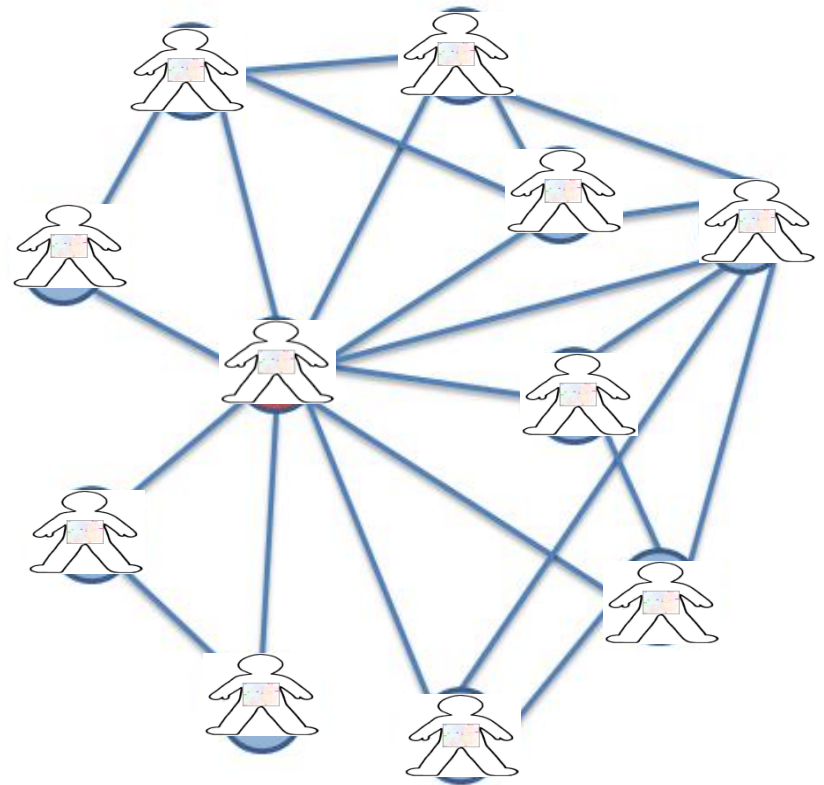


Clustering metabolites

Clustering Methodologies

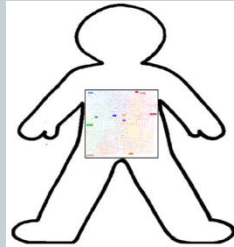


Clustering metabolites



Clustering people

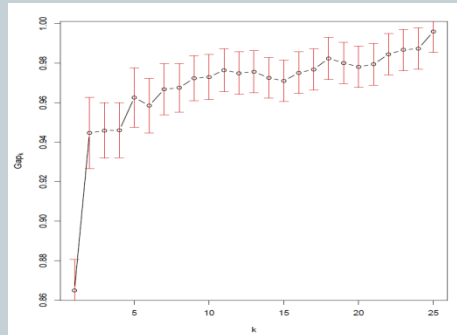
Clustering Methodologies



**Metabolomic Profiles of
245 children from the
Vitamin D Antenatal
Asthma Reduction Trial:
713 metabolites**

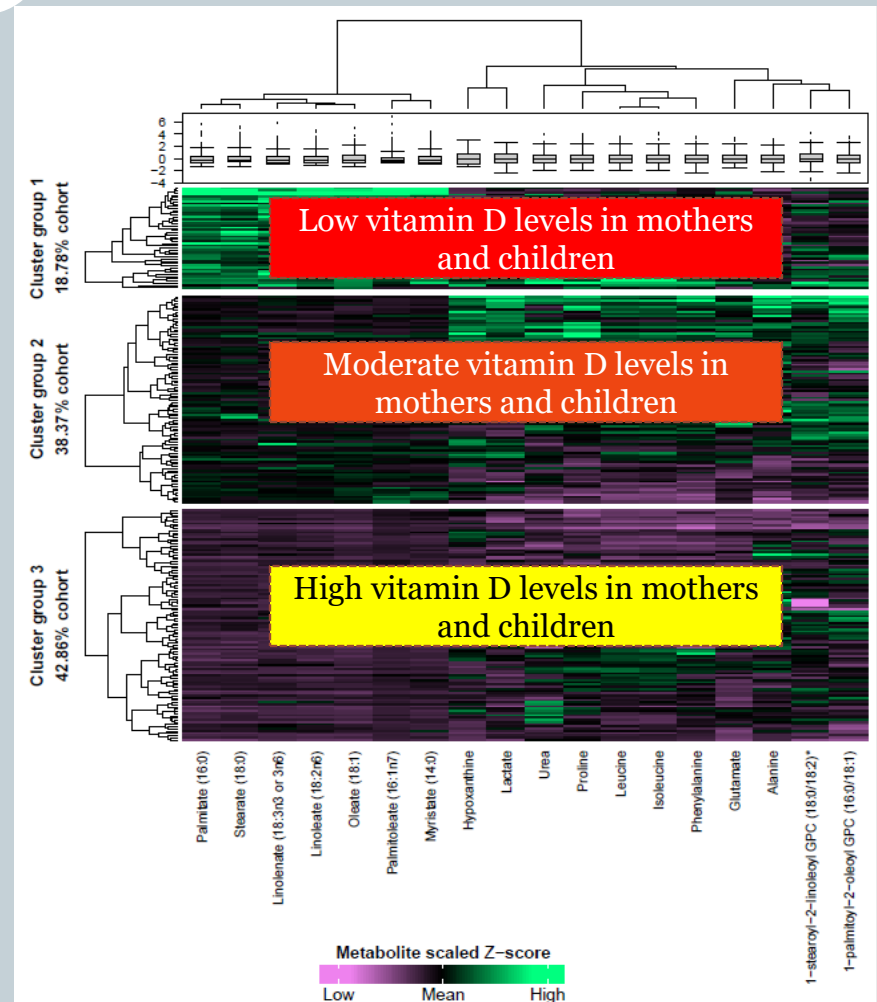


**Unsupervised clustering using the
Gap statistic**



Clustering Methodologies

- Children segregated into three clusters based on metabolomic profile
- Clusters mirrored vitamin D status in the children and their mothers
- Cluster formation driven by inflammatory metabolites

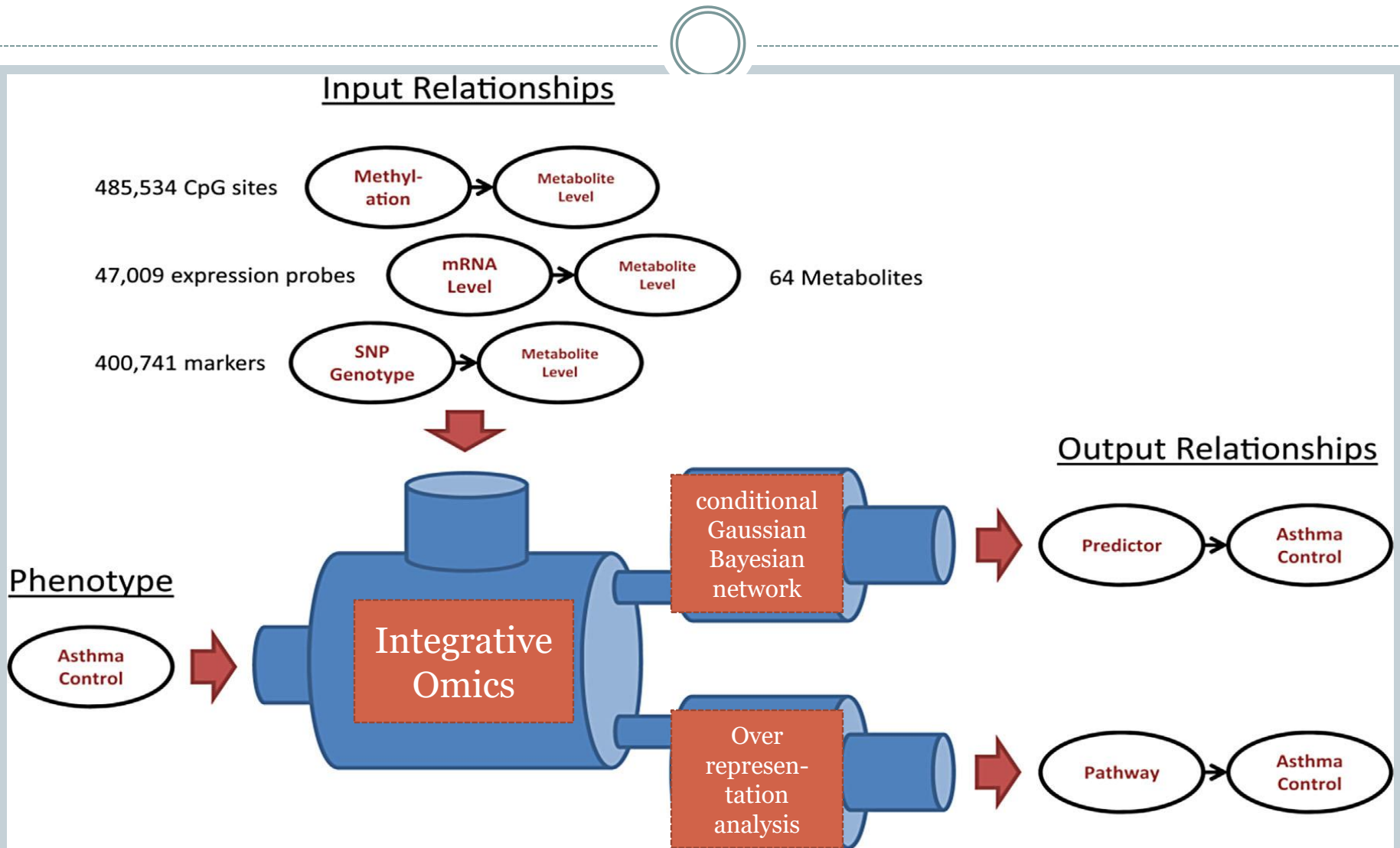


Network Methods



- **Weighted Gene Co-expression Network Analysis**
 - Module preservation analysis
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- Metabolomic Reconstruction

Integrative Bayes Nets 'Pipeline'



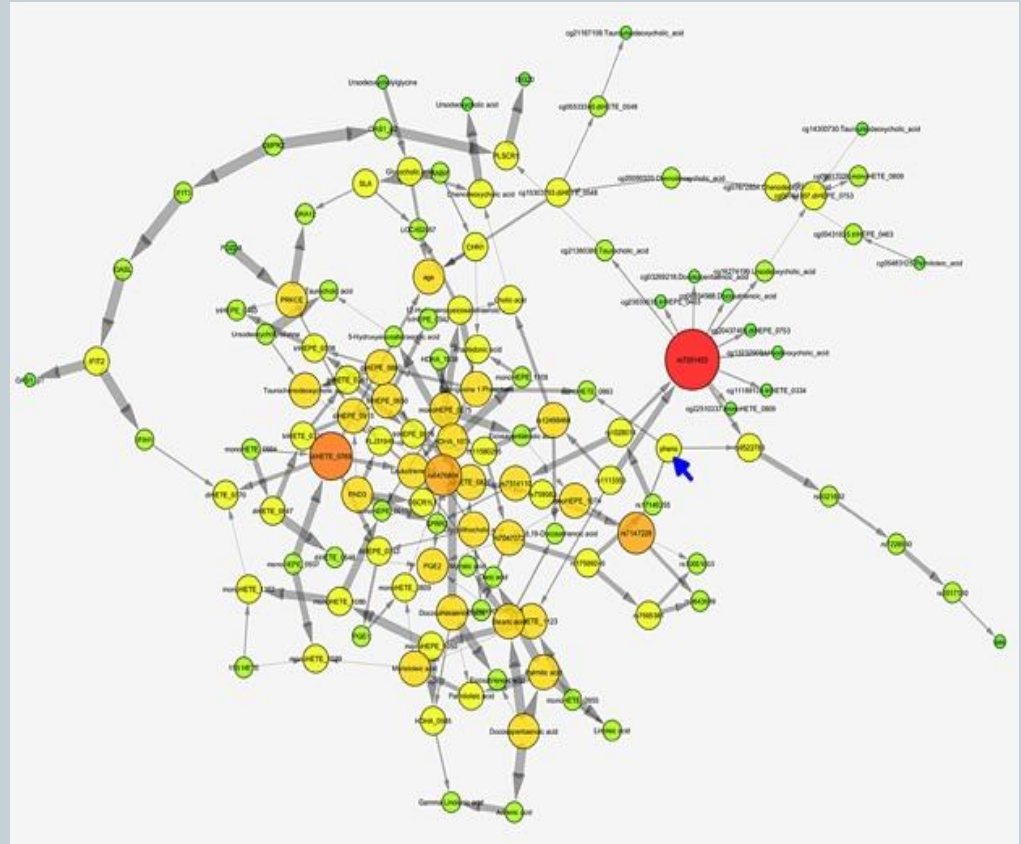
Conditional Gaussian Bayesian network



- Machine learning technique
- Generates network model using the Bayesian conditional independence between metabolites, SNPs, CpG sites and mRNA probes
- Starts with empty network then adds edges sequentially based on posterior likelihood
- Builds a network that maximizes the cross-validated Area Under the Curve to predict asthma control
- *For details see:* <http://www.cgbayesnets.com/>

Integrated Bayesian Network

- Integrated Bayesian network predicts uncontrolled asthma: AUC 95%
- Sphingosine-1-phosphate (S1P) identified as a crucial network hub
- Implicates altered metabolic pathways, related to sphingolipid metabolism
- Provides insight into the pathophysiology of asthma control.



Network Methods



- **Weighted Gene Co-expression Network Analysis**
 - Module preservation analysis
- Clustering Methodologies
- Bayes Nets
- **Structural Equation Modelling**
- Metabolomic Reconstruction

Structural Equation Modelling



- Combination of factor analysis and multiple regression analysis
- Allows exploration of relationships between multiple independent, and multiple dependent variables
- Allows inclusion of both directly observable variables and latent constructs of unobservable relationships
- Results can be used to construct causal pathways

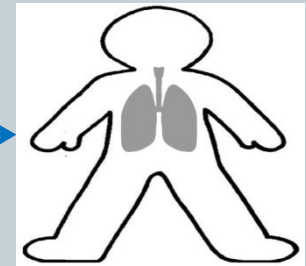
Structural Equation Modelling



Metabolomic Profiles of
245 children from the
Vitamin D Antenatal
Asthma Reduction Trial:
713 metabolites



Maternal
Intervention

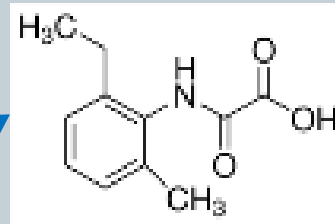


Offspring
asthma risk

Structural Equation Modelling



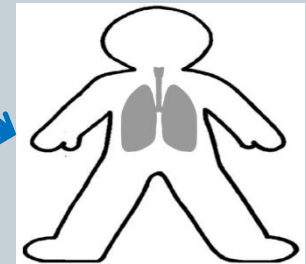
Metabolomic Profiles of
245 children from the
Vitamin D Antenatal
Asthma Reduction Trial:
713 metabolites



Metabolite



Maternal
Intervention

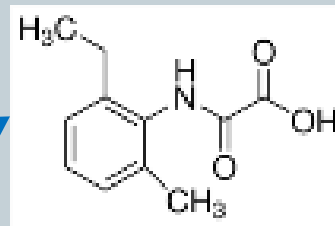


Offspring
asthma risk

Structural Equation Modelling



Metabolomic Profiles of
245 children from the
Vitamin D Antenatal
Asthma Reduction Trial:
713 metabolites

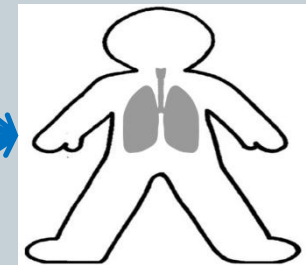
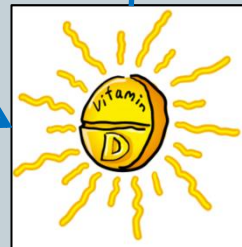


Metabolite



Maternal
Intervention

Vit D levels

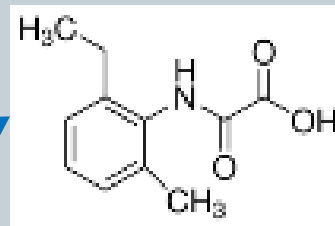


Offspring
asthma risk

Structural Equation Modelling



Metabolomic Profiles of
245 children from the
Vitamin D Antenatal
Asthma Reduction Trial:
713 metabolites

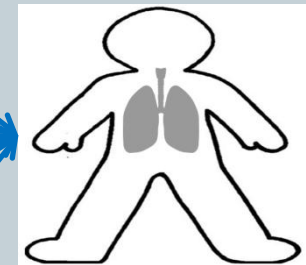
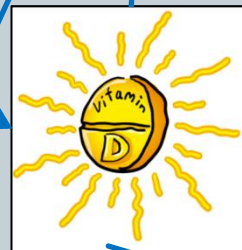


Metabolite



Maternal
Intervention

Vit D levels



Offspring
asthma risk

Genotype

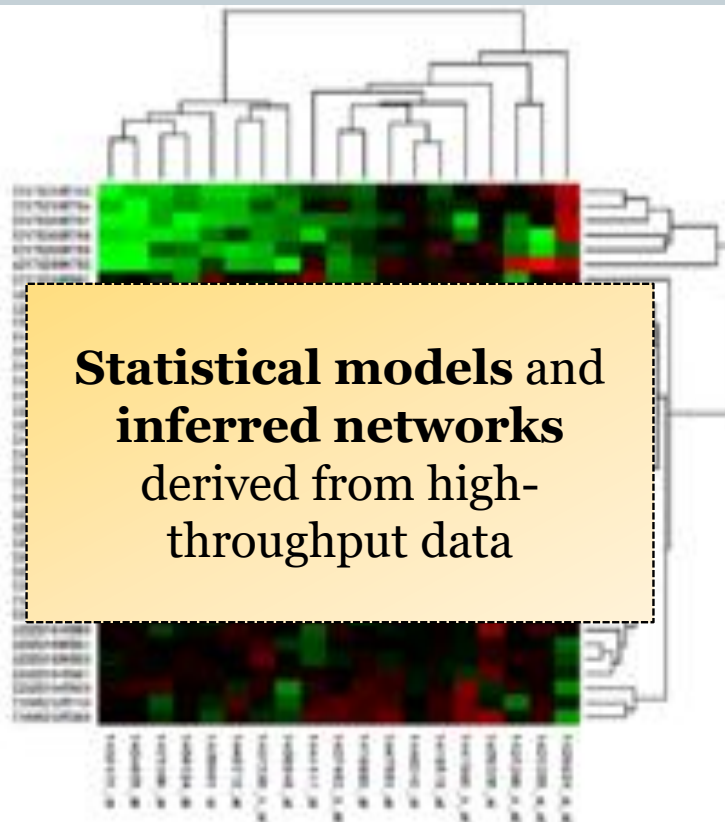


Network Methods

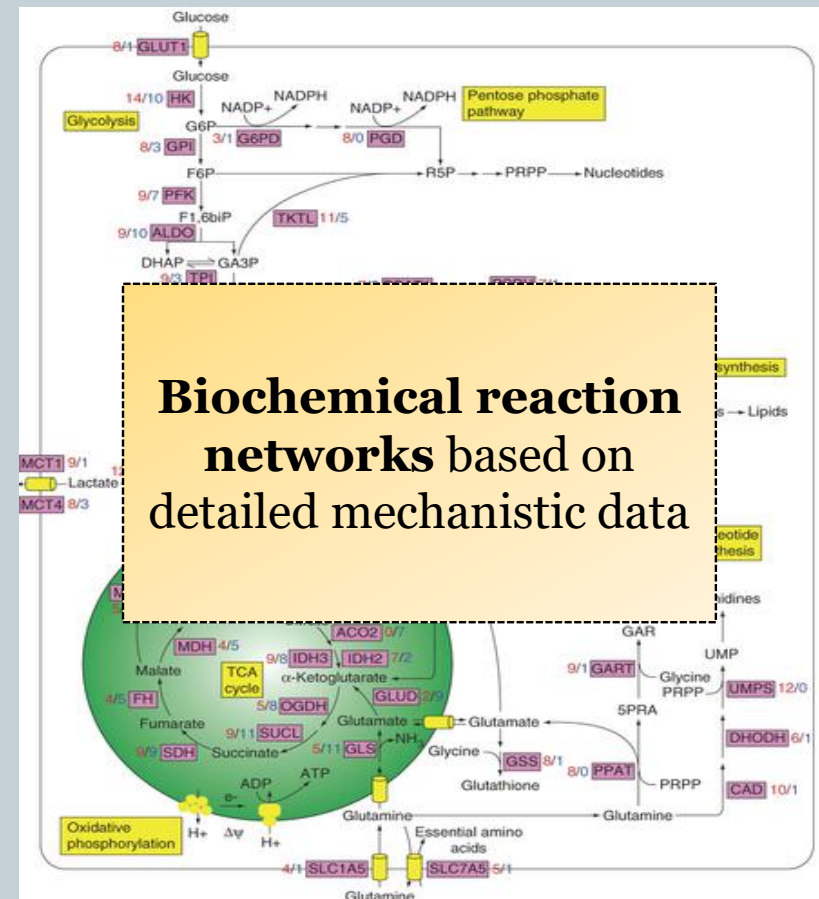


- **Weighted Gene Co-expression Network Analysis**
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- Structural Equation Modelling
- **Metabolomic Network Reconstruction**

Statistical versus Biological Networks

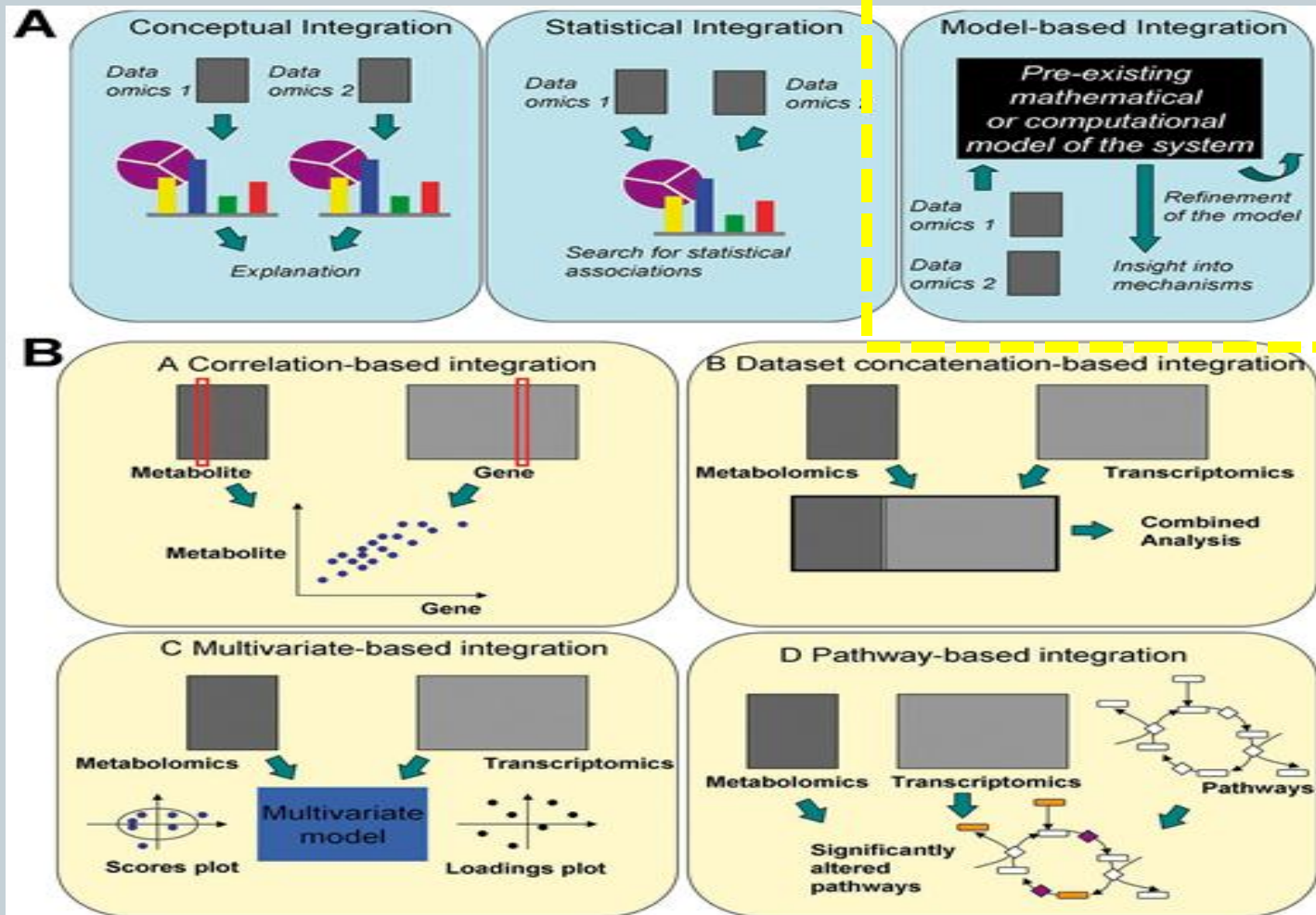


Statistical models and inferred networks derived from high-throughput data

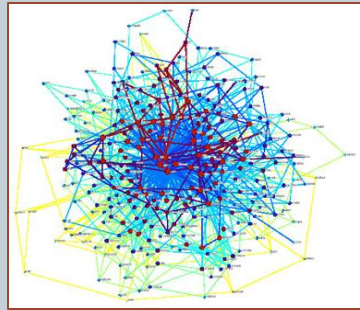


Biochemical reaction networks based on detailed mechanistic data

Integrative Strategies



Metabolic Network Reconstruction



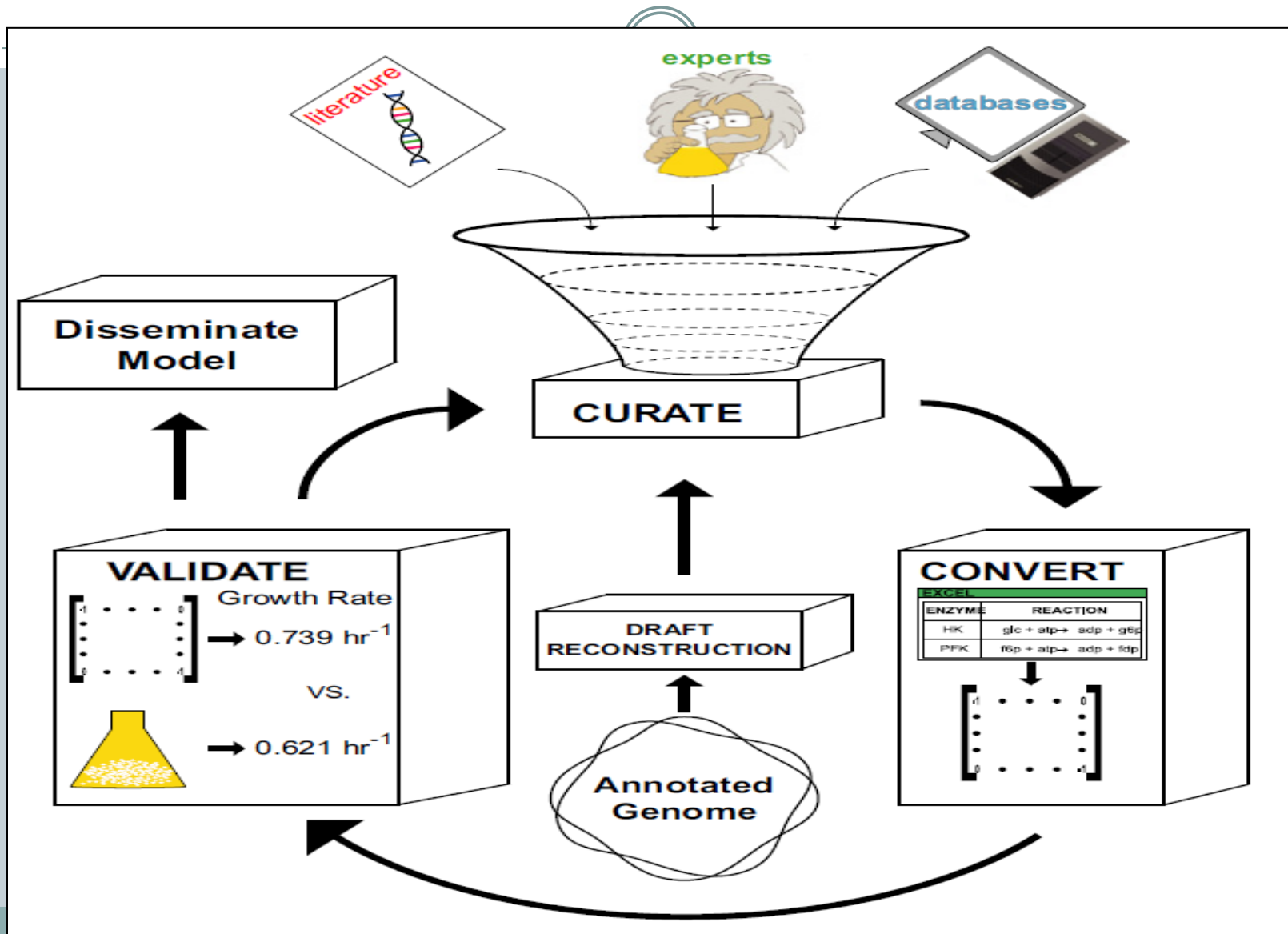
- Breaks down metabolic pathways into respective reactions and enzymes, and analyzes them within perspective of entire network
- Utilizes biochemical studies and existing literature
- Provides in-depth insight into molecular mechanisms of a cell
- Correlates the genome to enzymatic activity
- Converts metabolic network into a mathematical model that can be utilized in systems biology
- Metabolic reconstructions of >30 organisms published to date

Uses of Metabolic Network Reconstruction: Omics Data Analysis

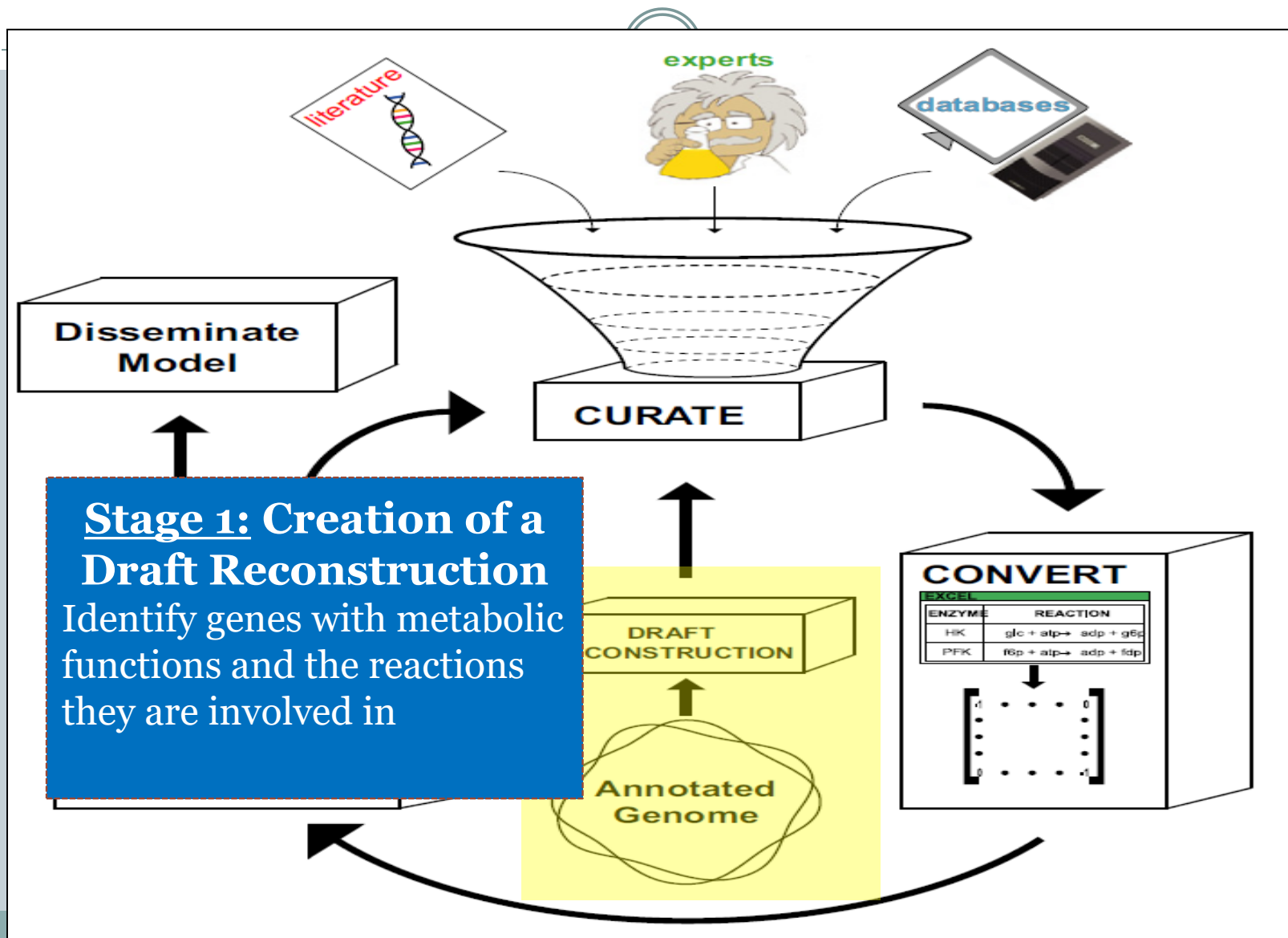


- Context-based approach for High-throughput data analysis
- Increasing predictive power for metabolic behavior
- Overlaying omics data onto networks to visualize the effects of perturbations
- Construction of tissue-specific models of metabolism

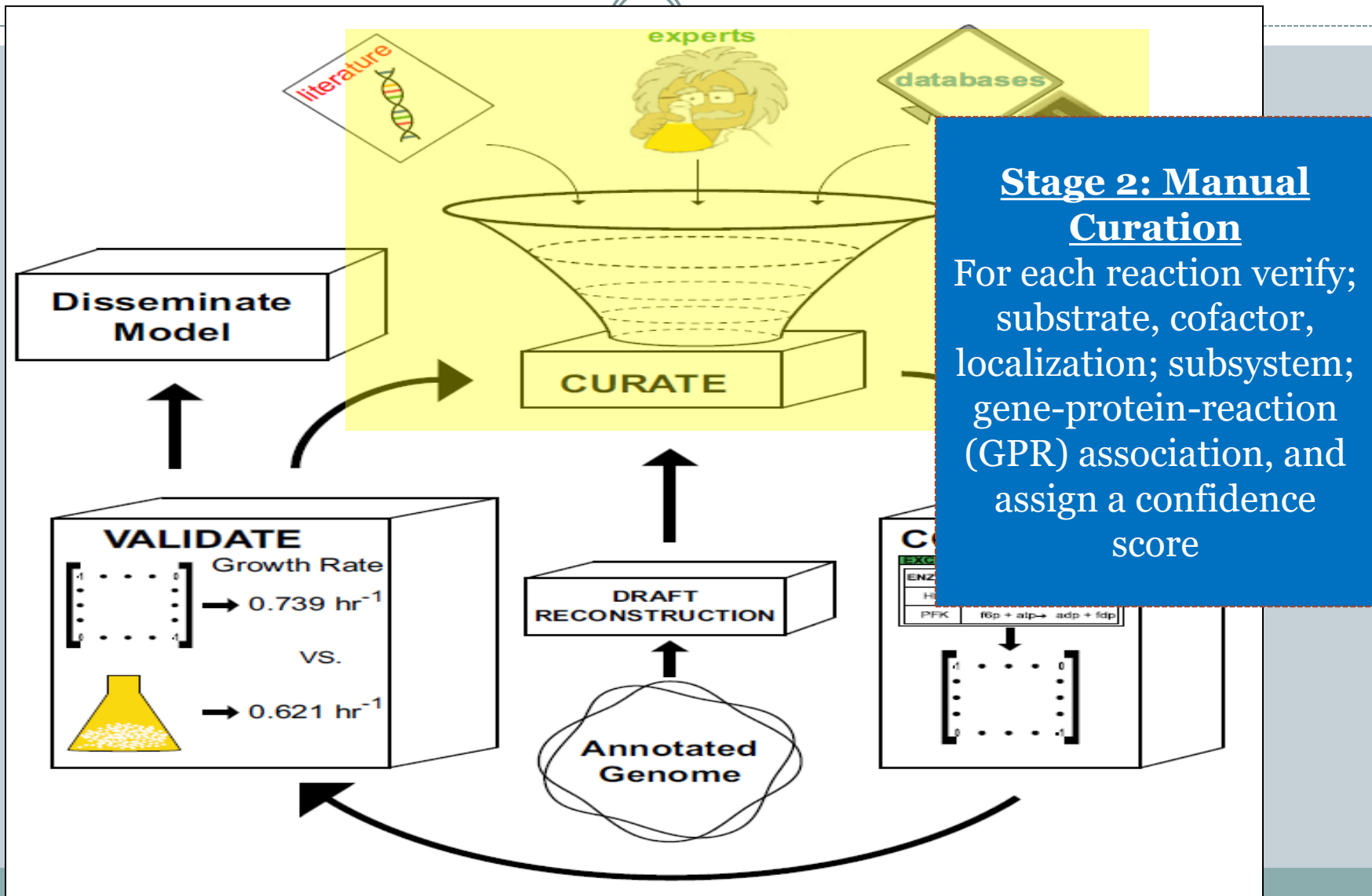
THE RECONSTRUCTION PROCESS



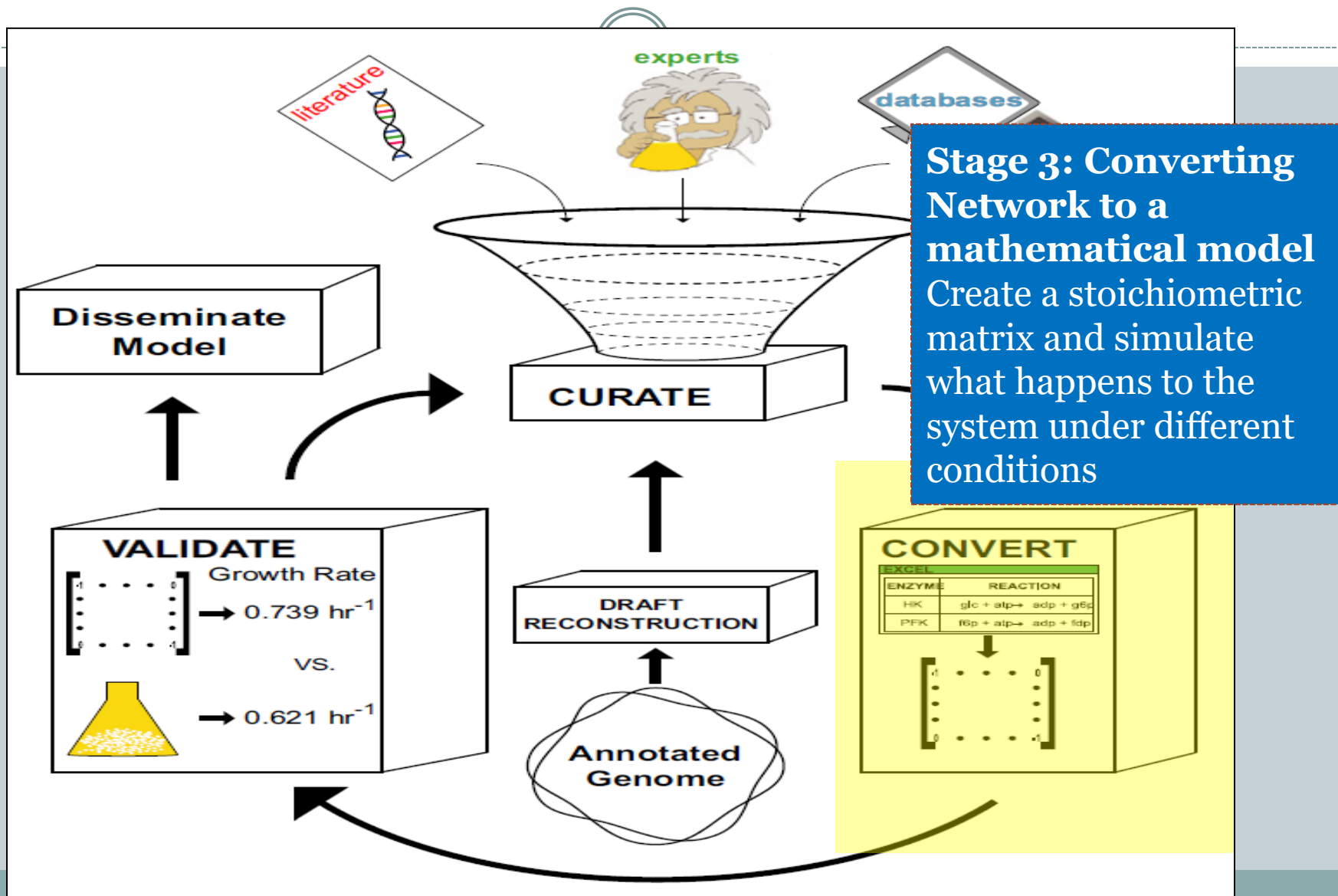
THE RECONSTRUCTION PROCESS



THE RECONSTRUCTION PROCESS



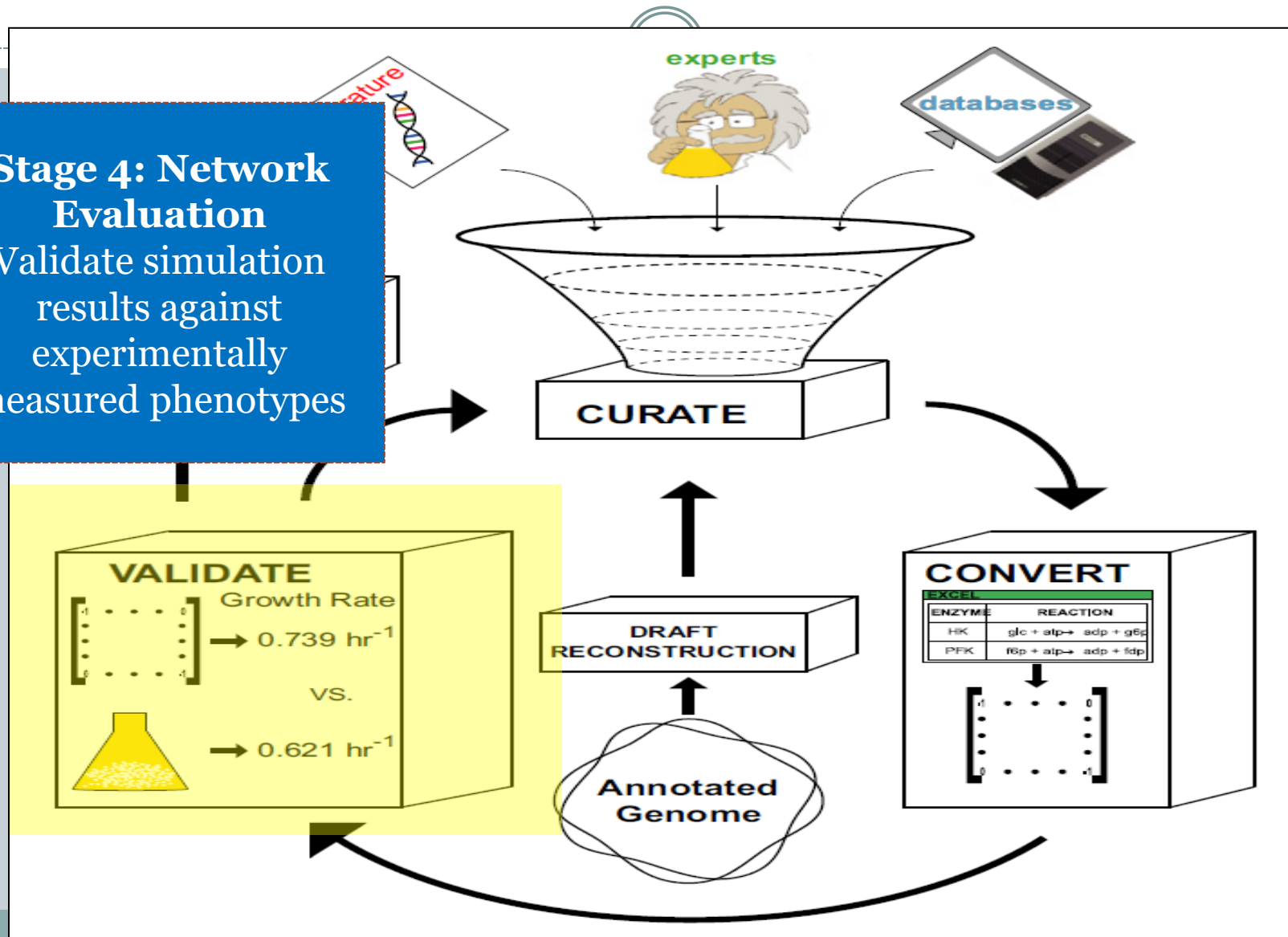
THE RECONSTRUCTION PROCESS



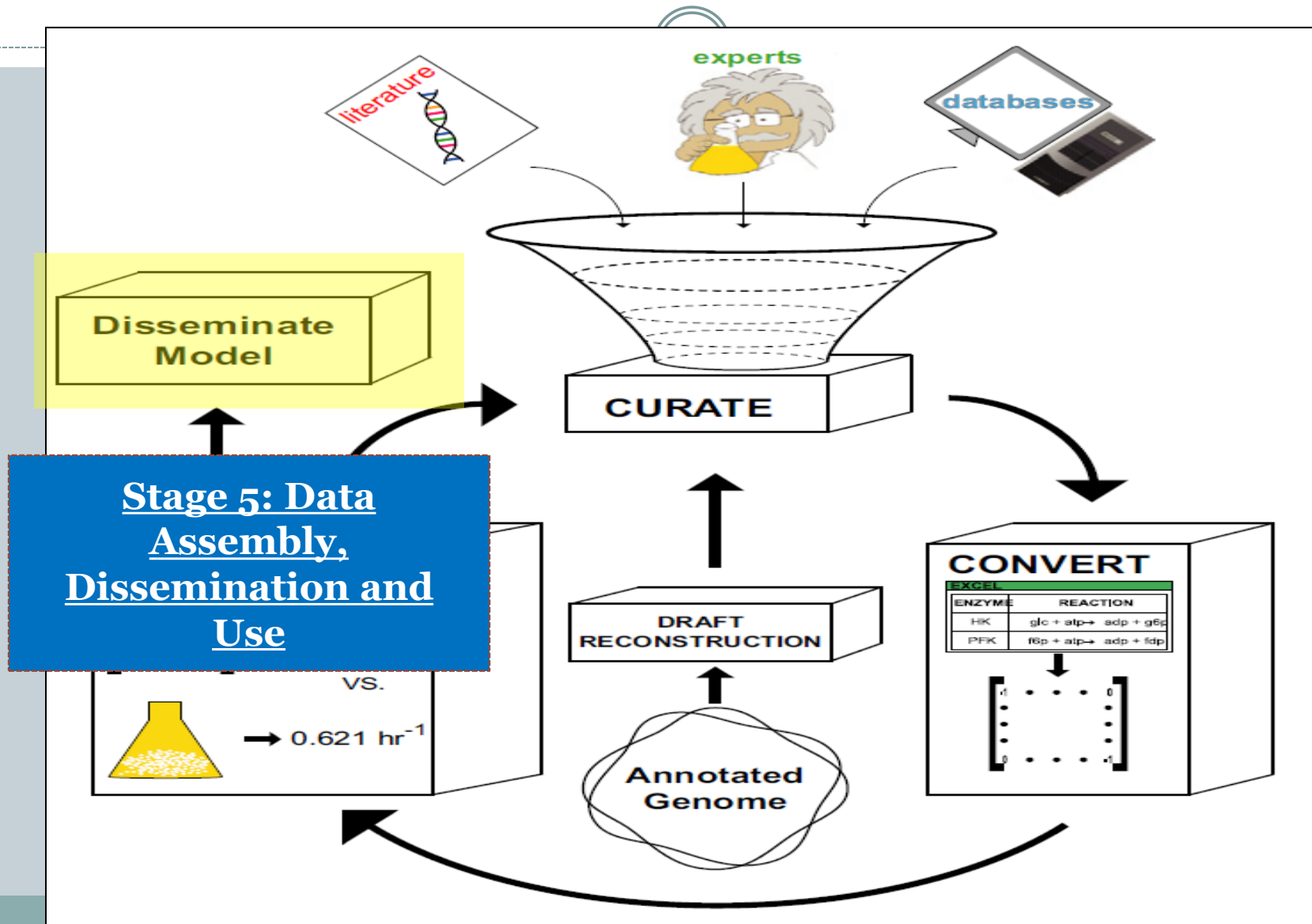
THE RECONSTRUCTION PROCESS

Stage 4: Network Evaluation

Validate simulation results against experimentally measured phenotypes



THE RECONSTRUCTION PROCESS



Metabolomic Reconstruction

A community-driven global reconstruction of human metabolism

Ines Thiele, Neil Swainston, Ronan M T Fleming, Andreas Hoppe, Swagatika Sahoo, Maike K Aurich, Hulda Haraldsdottir, Monica L Mo, Ottar Rolfsson, Miranda D Stobbe, Stefan G Thorleifsson, Rasmus Agren, Christian Bölling, Sergio Bordel, Arvind K Chavali, Paul Dobson, Warwick B Dunn, Lukas Endler, David Hala, Michael Hucka, Duncan Hull, Daniel Jameson, Neema Jamshidi, Jon J Jonsson, Nick Juty *et al.*

[Affiliations](#) | [Contributions](#) | [Corresponding author](#)

Nature Biotechnology 31, 419–425 (2013) | doi:10.1038/nbt.2488

Received 07 September 2012 | Accepted 19 December 2012 | Published online 03 March 2013

Nature Protocols 5, 93 – 121 (2010)

Published online: 7 January 2010 | doi:10.1038/nprot.2009.203

Subject Categories: [Biochemistry and protein analysis](#) | [Computational organisms](#)

A protocol for generating a high-quality genome-scale metabolic reconstruction

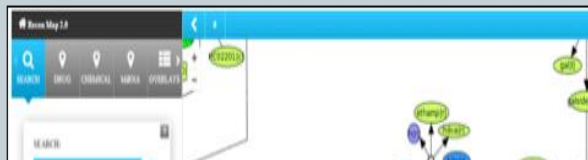
Ines Thiele^{1,2} & Bernhard Ø Palsson¹

UC San Diego News Center

March 04, 2013 | By Catherine Hockmuth

International Consortium Builds ‘Google Map’ of Human Metabolism

<https://vmh.uni.lu/>

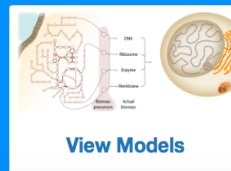


BiGG Models

Search the database by model, reaction, metabolite, or gene

Search

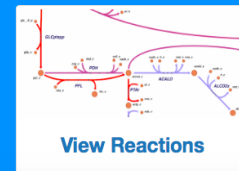
Latest update Version 1.3: Introducing the iCHO model



[View Models](#)

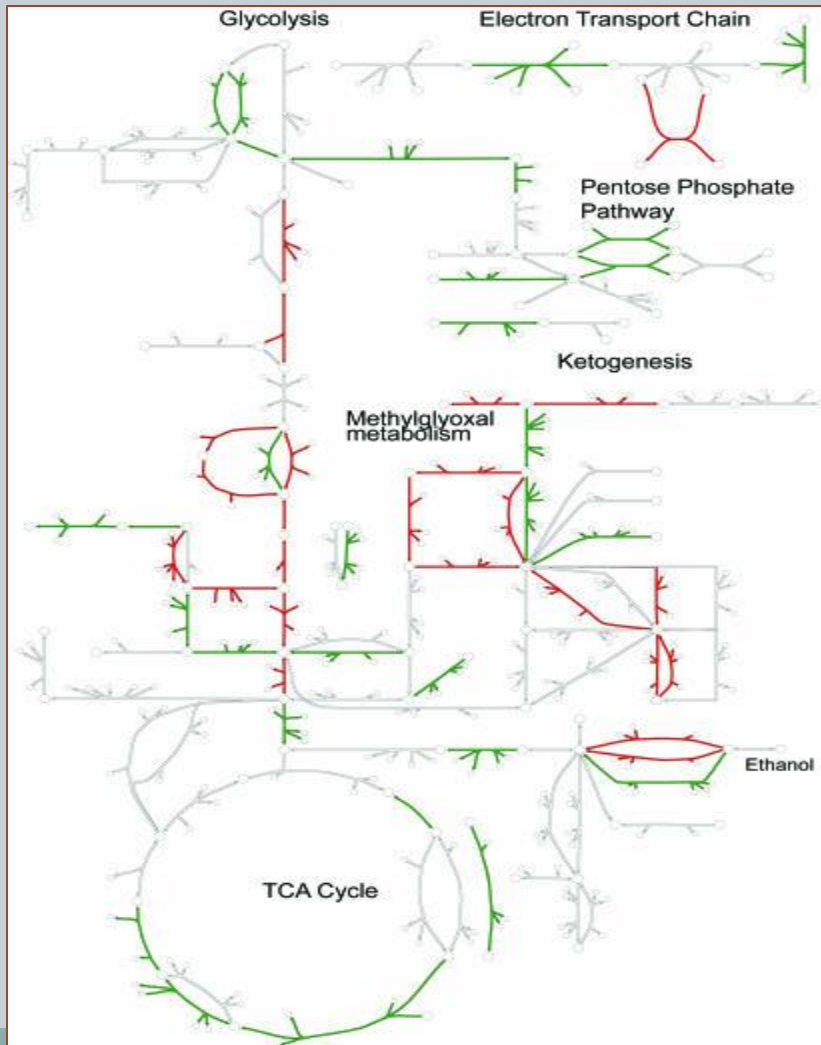


[View Metabolites](#)



[View Reactions](#)

Integrated analysis of gene expression and metabolomic data



- Gastric bypass patients before surgery and 1 year afterward
- Expression measurements visualized on human metabolic maps
- Reactions color-coded based on gene expression changes
 - Green: down-regulated
 - Red: up-regulated
 - White: no data available
- Observed general trend of up-regulated anaerobic metabolism and down-regulated oxidative phosphorylation after surgery
- Genes in glycolysis, pentose phosphate pathway, and oxidative phosphorylation showing consistent overall patterns of expression change

Duarte et al. **Global reconstruction of the human metabolic network based on genomic and bibliomic data** [Proc Natl Acad Sci U S A. 2007 Feb 6; 104\(6\): 1777–1782.](#)

A Word of Caution



- Most tools optimized in humans
 - Limited options for other organisms
- No agreed standards in the field
- Better and standardized pathway annotation is needed
- Complex and time consuming

Online Tools



THE APPLICATION OF NETWORK MEDICINE TO METABOLOMICS DATASETS

Additional tools for omic data analysis and integration



Pathway Enrichment Analyses

- IMPALA** Integrated pathway-level analysis: gene or protein expression and metabolomics data
- iPEAP** Integrated pathway-level analysis: transcriptomics, proteomics, metabolomics, and GWAS data
Java-based desktop software (<http://www.tongji.edu.cn/~qiliu/ipeap.html>)
- MetaboAnalyst** Integrated pathway-level analysis: gene expression and metabolomics data
web-based application (<http://www.metaboanalyst.ca>)

Biological network analyses

- MetaMapR** Calculate biochemical reaction, structural similarity, mass spectral similarity, and correlation-based networks
R package (<http://dgrapov.github.io/MetaMapR>)
- MetScape** Gene, enzyme, and metabolite networks analysis with emphasis on metabolic pathways
Cytoscape plugin (<http://metscape.ncibi.org>)
- Grinn** Integrated neo4j graph-database supporting reconstruction metabolite-protein-gene-pathway
R package (<https://github.com/kwanjeeraw/grinn>)

Empirical correlation analysis

- WGCNA** Integrated analysis of correlation and network topology
R package (<http://labs.genetics.ucla.edu/horvath/CoexpressionNetwork/Rpackages/WGCNA>)
- MixOmic** Variety of multivariate analysis and visualization methods
R package (<http://mixomics.qfab.org>)
- DiffCorr** Compare changes in correlation patterns between two experimental conditions
R package (<http://cran.r-project.org/web/packages/DiffCorr/index.html>)
- qpgraph** Estimation of partial correlation and q-order partial correlation
R package (<http://www.bioconductor.org/packages/release/bioc/html/qpgraph.html>)
- huge** Fast computation for high-dimensional data using lasso estimate of the inverse covariance matrix
R package (<https://cran.r-project.org/web/packages/huge/index.html>)

Metabolite mapping



[Pathwhiz
\(smpdb.ca/pathwhiz\)](http://smpdb.ca/pathwhiz)



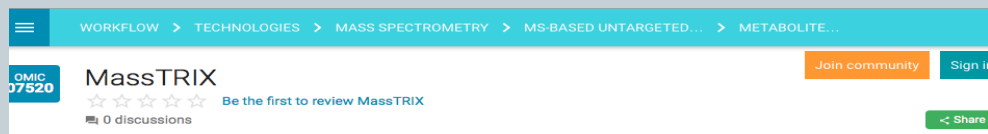
[MetaMapp
\(imdevsoftware.wordpress.com/tag/metamapp/\)](http://imdevsoftware.wordpress.com/tag/metamapp/)



[PaintOMICS
\(www.paintomics.org/cgi-bin/main2.cgi\)](http://www.paintomics.org/cgi-bin/main2.cgi)



[Pathos
\(motif.gla.ac.uk/Pathos/\)](http://motif.gla.ac.uk/Pathos/)



[MassTRIX
\(omictools.com/masstrix-tool\)](http://omictools.com/masstrix-tool)



[STITCH \(http://stitch.embl.de/\)](http://stitch.embl.de/)

Commercial tools including Ingenuity Systems Inc. also available

Summary



THE APPLICATION OF NETWORK MEDICINE TO METABOLOMICS DATASETS

Network Medicine in Metabolomics



- Metabolites should be contextualized within reactions and pathways and networks and a multiomic system
- The role and position of a metabolite within this system is crucial
- Statistical integration is the most common way to explore metabolites and their networks
- Multiple network methods available
- Constrained by limitations; metabolomic network reconstruction is the gold standard but is rare
- Network methods are likely to form an increasing proportion of the literature

Thank you!



CONTACTS:

JESSICA LASKY-SU:
JESSICA.SU@CHANNING.HARVARD.EDU

RACHEL KELLY:
HPRKE@CHANNING.HARVARD.EDU