

Computational methods for data integration

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Learning Objectives

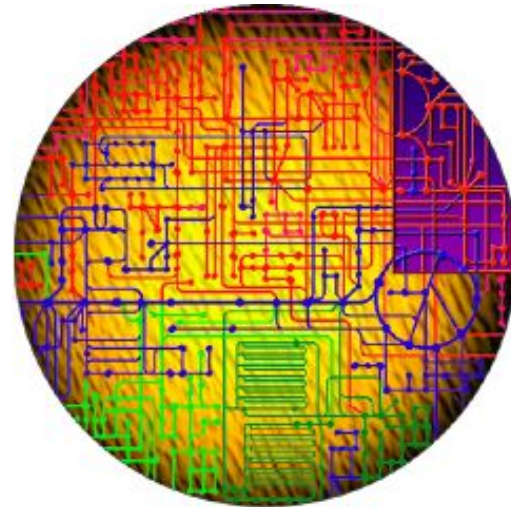
- Understanding of different data integration approaches
- Familiarity with tools for data integration and network visualization

Introduction: A Systems Biology Framework

- The goal of **Systems Biology**:
 - Systems-level understanding of biological systems
 - Analyze not only individual components, but their interactions as well and emergent behavior



Exposures
Internal measurements
Disease states

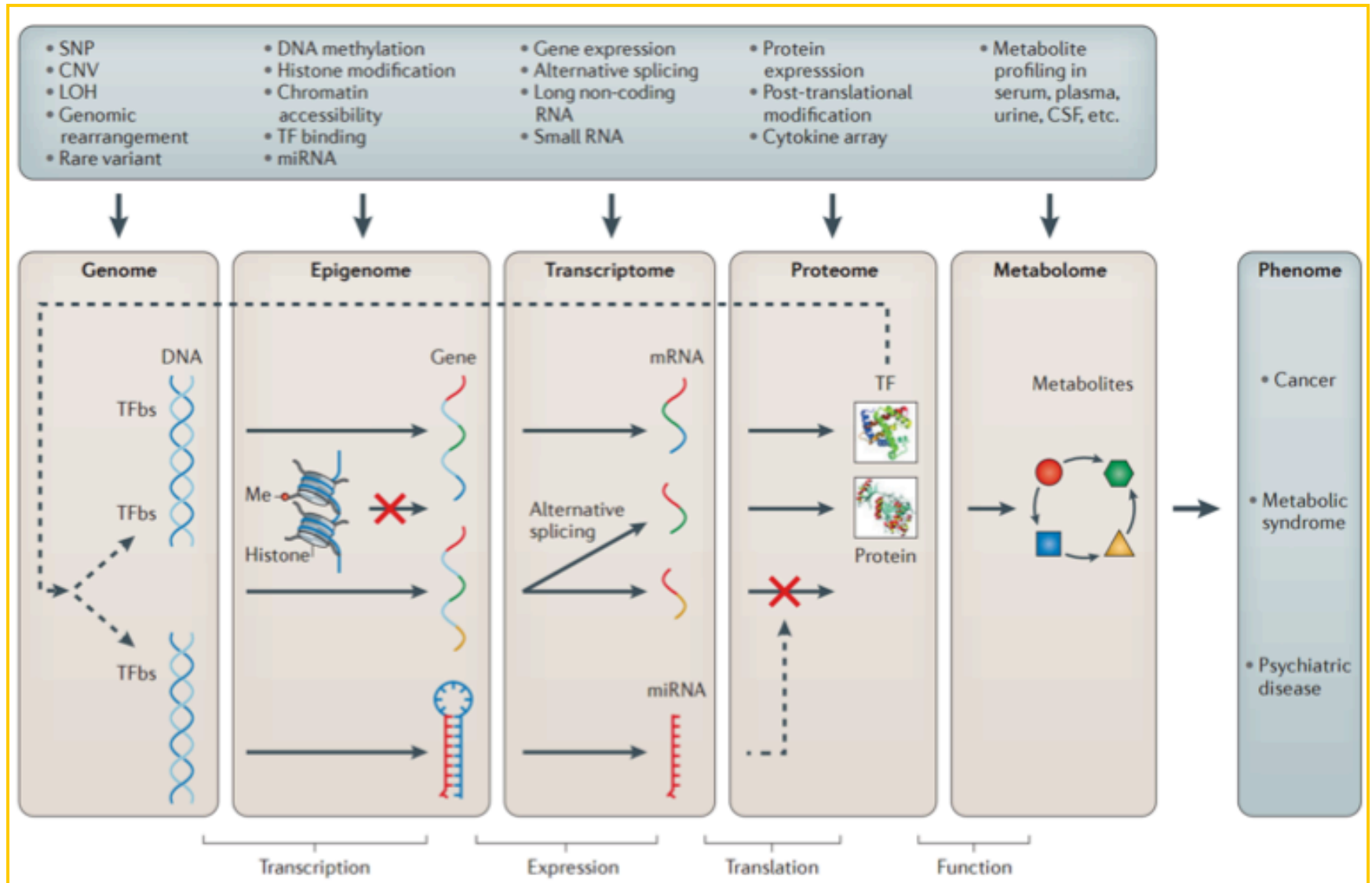


Systems Biology

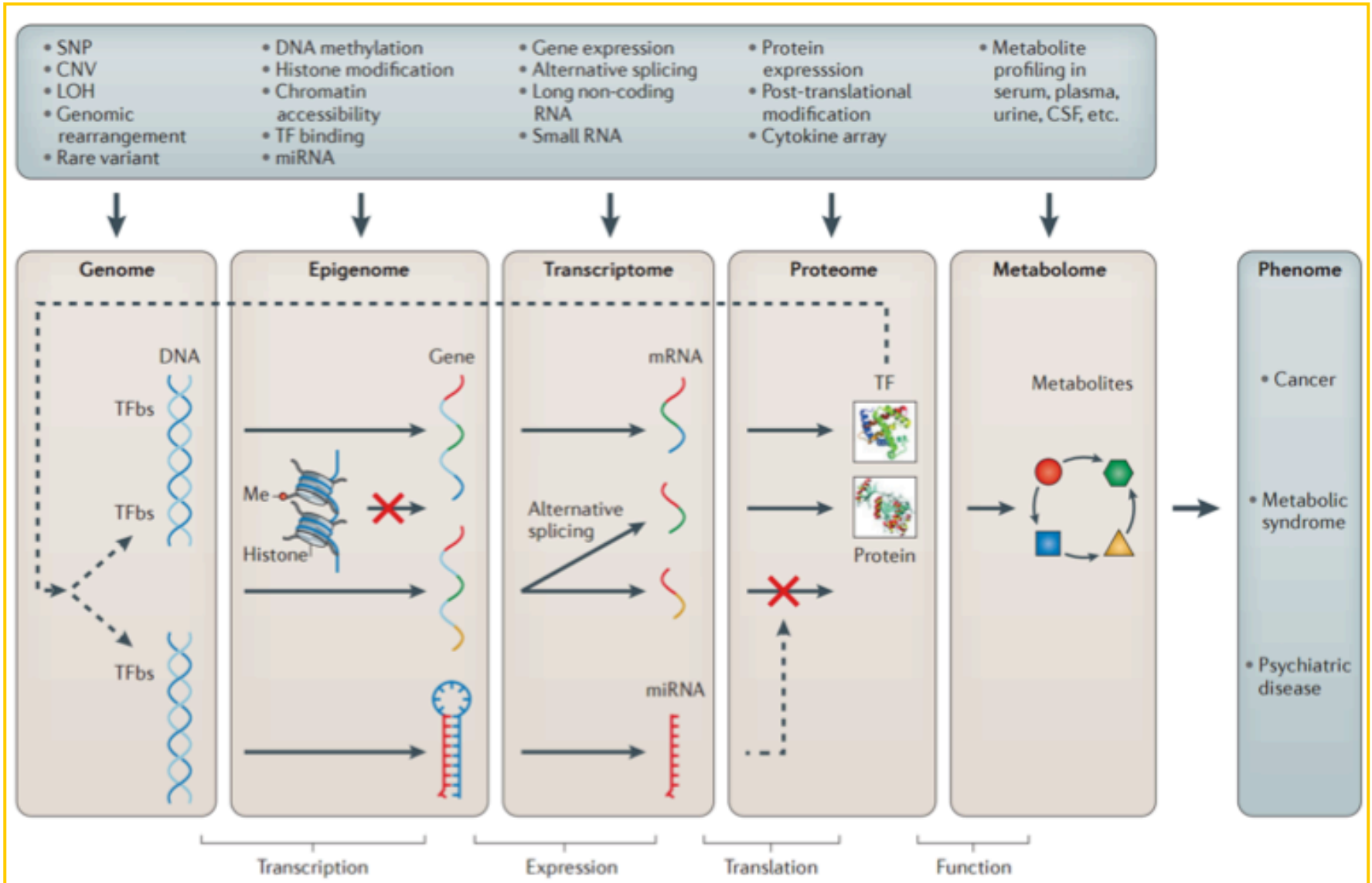
“Integrative approach in which scientists study pathways and networks will touch all areas of biology, including drug discovery”

C. Henry and C. Washington

Dissecting the Biological system via -omics



Dissecting the Biological system via -omics



“Information Overload”: >10,000 variables per -omics experiment

Why data integration?

- Systems level analysis provides:
 - more detailed overview of underlying mechanisms;
 - exploration of interactions between different biomedical entities (genes, proteins, metabolites, etc.)
- Combining multiple types of data compensates for noise or unreliable information in a single data type
- More confidence in results if multiple sources of evidence pointing to the same gene or pathway

Paired integrative –omics analysis

- Discover networks of associations or correlated variables (genes, proteins, metabolites, microbiome, epigenetic alterations, clinical variables, etc.) from paired –omics data measured across same samples
 - Univariate or multivariate regression
 - Example: explaining protein abundance with respect to gene expression
- Determine if different –omics data point to same disease mechanism
- Generate novel hypotheses for further investigation

Main approaches for data integration

- Pathway or knowledge-based integration
 - Datasets are analyzed individually (differentially expressed genes, metabolites, proteins) and integration is performed at the pathway level
 - Examples: MetaboAnalyst, iPEAP, MetScape, MetaCore
- Data-driven integration using meta-dimensional analysis
 - Integration is performed globally such that data from multiple omics layers are combined simultaneously
 - Examples: 3Omics, mixOmics, xMWAS
- Using literature-derived associations for integration
 - Using co-occurrence criteria for establishing relationship
 - Examples: CoPub, ArrowSmith, SEACOIN2.0

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Pathway or knowledge-based integration

Metabolomics data
(n subjects X p metabolites)

	M1	M2	-	Mp
Subject1	199	19	-	100
Subject2	10	40		90
-	-	-		-
SubjectN	50	30	-	20

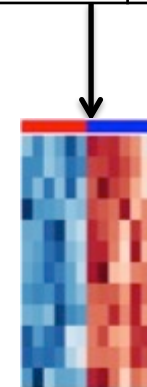


Differentially expressed metabolites

Pathway analysis for metabolites

Transcriptomics data
(n subjects X q genes)

	G1	G2	-	Gq
Subject1	19	19	-	100
Subject2	10	40	-	90
-	-	-	-	-
SubjectN	10	40	-	50



Differentially expressed genes

Pathway analysis for genes

Common pathways or pathway rank aggregation

Pathway or knowledge-based integration

Metabolomics data
(n subjects X p metabolites)

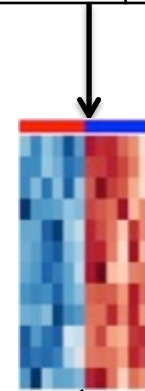
	M1	M2	-	Mp
Subject1	199	19	-	100
Subject2	10	40		90
-	-	-		-
SubjectN	50	30	-	20



Differentially expressed metabolites

Transcriptomics data
(n subjects X q genes)

	G1	G2	-	Gq
Subject1	19	19	-	100
Subject2	10	40	-	90
-	-	-	-	-
SubjectN	10	40	-	50



Differentially expressed genes

Pathway analysis using genes and metabolites (joint)

MetaboAnalyst

(<http://www.metaboanalyst.ca/faces/ModuleView.xhtml>)

The screenshot displays the MetaboAnalyst 4.0 web interface. The browser address bar shows the URL www.metaboanalyst.ca/faces/ModuleView.xhtml. The page title is "MetaboAnalyst -- a comprehensive tool for metabolomics analysis and interpretation".

On the left side, there is a navigation menu with the following links: [Overview](#), [Data Formats](#), [FAQs](#), [Tutorials](#), [Troubleshooting](#), [Resources](#), [Update History](#), [User Stats](#), and [About](#). Below the menu are logos for **GenomeCanada**, **GenomeQuébec**, and **NSERC CRSNG**.

The main content area features a circular menu of analysis modules. A legend in the center explains the color coding for the modules:

- Blue: Targeted or untargeted metabolomics
- Green: Targeted metabolomics only
- Cyan: Untargeted metabolomics
- Blue and white stripes: Multiple metabolomics data
- Green and white stripes: Integrating other omics

The modules in the circular menu are: **Statistical Analysis** (blue), **Enrichment Analysis** (green), **Pathway Analysis** (cyan), **Joint Pathway Analysis** (green and white stripes, highlighted with a red box), **Network Explorer** (green and white stripes), **MS Peaks to Pathways** (cyan), **Other Utilities** (grey), **Spectral Analysis** (grey), **Biomarker Meta-analysis** (blue and white stripes), **Power Analysis** (blue), **Time-series / Two-factor** (blue), and **Biomarker Analysis** (blue).

Below the circular menu, the text reads: "Click a module to proceed, or scroll down for more details:".

At the bottom of the page, the footer text is: "Xia Lab @ McGill (last updated 2018-03-10)".

Upload data and submit

The screenshot shows the MetaboAnalyst 4.0 web interface. The browser address bar displays `www.metaboanalyst.ca/faces/upload/JointUploadView.xhtml`. The page title is "MetaboAnalyst -- a comprehensive tool for metabolomics analysis and interpretation".

On the left sidebar, there is a navigation menu with the following items: "Upload", "Integrative Analysis", "Download", and "Exit".

The main content area contains the following text: "Please upload a gene list and metabolite list to perform joint pathway analysis. Use the **Pathway Analysis** module, if you only have a metabolite list."

There are two main input sections:

- Gene List:** A text area containing a list of genes with their Entrez IDs and log fold changes (logFC). Below the text area is a dropdown menu for "ID Type" set to "Entrez ID".
- Metabolite List:** A text area containing a list of metabolites with their KEGG IDs and log fold changes (logFC). Below the text area is a dropdown menu for "ID Type" set to "KEGG ID".

At the bottom of the form, there is a "Specify organism:" dropdown menu set to "Homo sapiens (human)" and a checked checkbox for "Use our example data". A blue "Submit" button is located at the bottom center.

On the right side, there is a panel titled "R Command History" with a "Keep collapsed" checkbox and a "Save" button.

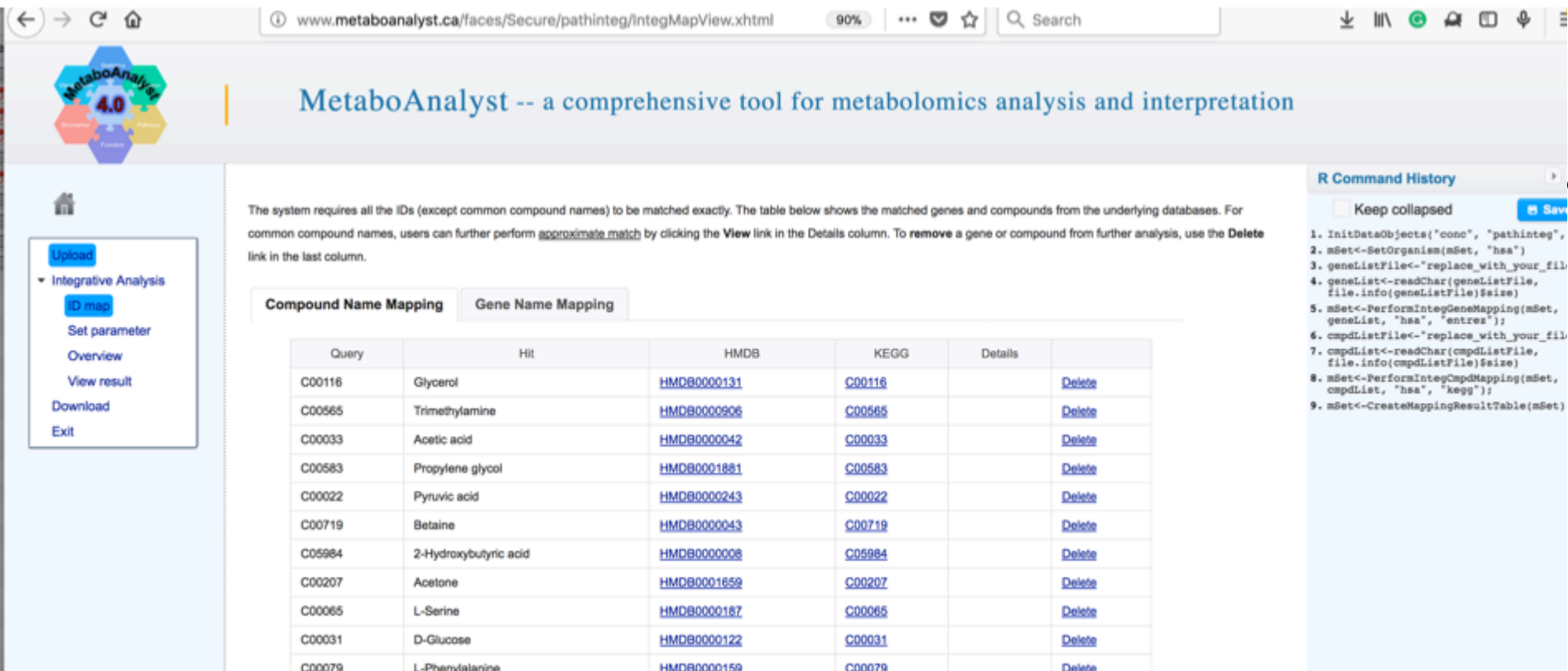
Gene List Data:

#Entrez	logFC
1737	-1.277784317
83440	-1.034136439
3939	-2.231729728
10911	-1.045657875
10690	-0.968308832
10010	-0.861541301
11224	1.187399591
63826	-1.405238611
11031	0.785011172
4190	-1.778774832
10782	-2.140715987
10993	-0.925083829
10455	1.732172706
10963	1.177511121
10282	-1.20754269

Metabolite List Data:

#KEGG	logFC
C00116	1.010972619
C00565	-0.714283001
C00033	0.822193121
C00583	-1.005192252
C00022	-0.623838569
C00719	-0.406052491
C05984	-0.390152174
C00207	-0.932835099
C00065	0.903658797
C00031	0.548035915
C00079	0.416744818
C02632	-0.515041676
C00064	-0.497216411
C00114	1.102078837
C00073	0.516193785

Name Mapping – click Submit



The screenshot shows the MetaboAnalyst 4.0 web interface. The browser address bar displays www.metaboanalyst.ca/faces/Secure/pathinteg/integMapView.xhtml. The page title is "MetaboAnalyst -- a comprehensive tool for metabolomics analysis and interpretation".

The main content area contains the following text:

The system requires all the IDs (except common compound names) to be matched exactly. The table below shows the matched genes and compounds from the underlying databases. For common compound names, users can further perform *approximate match* by clicking the **View** link in the Details column. To **remove** a gene or compound from further analysis, use the **Delete** link in the last column.

There are two tabs: "Compound Name Mapping" (selected) and "Gene Name Mapping".

Query	Hit	HMDB	KEGG	Details	
C00116	Glycerol	HMDB0000131	C00116		Delete
C00565	Trimethylamine	HMDB0000906	C00565		Delete
C00033	Acetic acid	HMDB0000042	C00033		Delete
C00583	Propylene glycol	HMDB0001881	C00583		Delete
C00022	Pyruvic acid	HMDB0000243	C00022		Delete
C00719	Betaine	HMDB0000043	C00719		Delete
C05984	2-Hydroxybutyric acid	HMDB0000008	C05984		Delete
C00207	Acetone	HMDB0001659	C00207		Delete
C00065	L-Serine	HMDB0000187	C00065		Delete
C00031	D-Glucose	HMDB0000122	C00031		Delete
C00079	L-Phenylalanine	HMDB0000159	C00079		Delete

On the right side, there is an "R Command History" panel with a "Keep collapsed" checkbox and a "Save" button. The command history contains the following R code:

```
1. InitDataObjects("conc", "pathinteg",
2. mSet<-SetOrganism(mSet, "hsa")
3. geneListFile<- "replace_with_your_fil
4. geneList<-readChar(geneListFile,
file.info(geneListFile)$size)
5. mSet<-PerformIntegGeneMapping(mSet,
geneList, "hsa", "entrez");
6. cmpdListFile<- "replace_with_your_fil
7. cmpdList<-readChar(cmpdListFile,
file.info(cmpdListFile)$size)
8. mSet<-PerformIntegCmpdMapping(mSet,
cmpdList, "hsa", "kegg");
9. mSet<-CreateMappingResultTable(mSet)
```

Set parameters

The screenshot shows the MetaboAnalyst 4.0 web interface. The browser address bar displays `www.metaboanalyst.ca/faces/Secure/pathinteg/IntegAnalView.xhtml`. The page title is "MetaboAnalyst -- a comprehensive tool for metabolomics analysis and interpretation".

In the left sidebar, the "Integrative Analysis" menu is expanded, and the "Set parameter" option is highlighted. Other options include "Upload", "ID map", "Overview", "View result", "Download", and "Exit".

The main content area is divided into three sections:

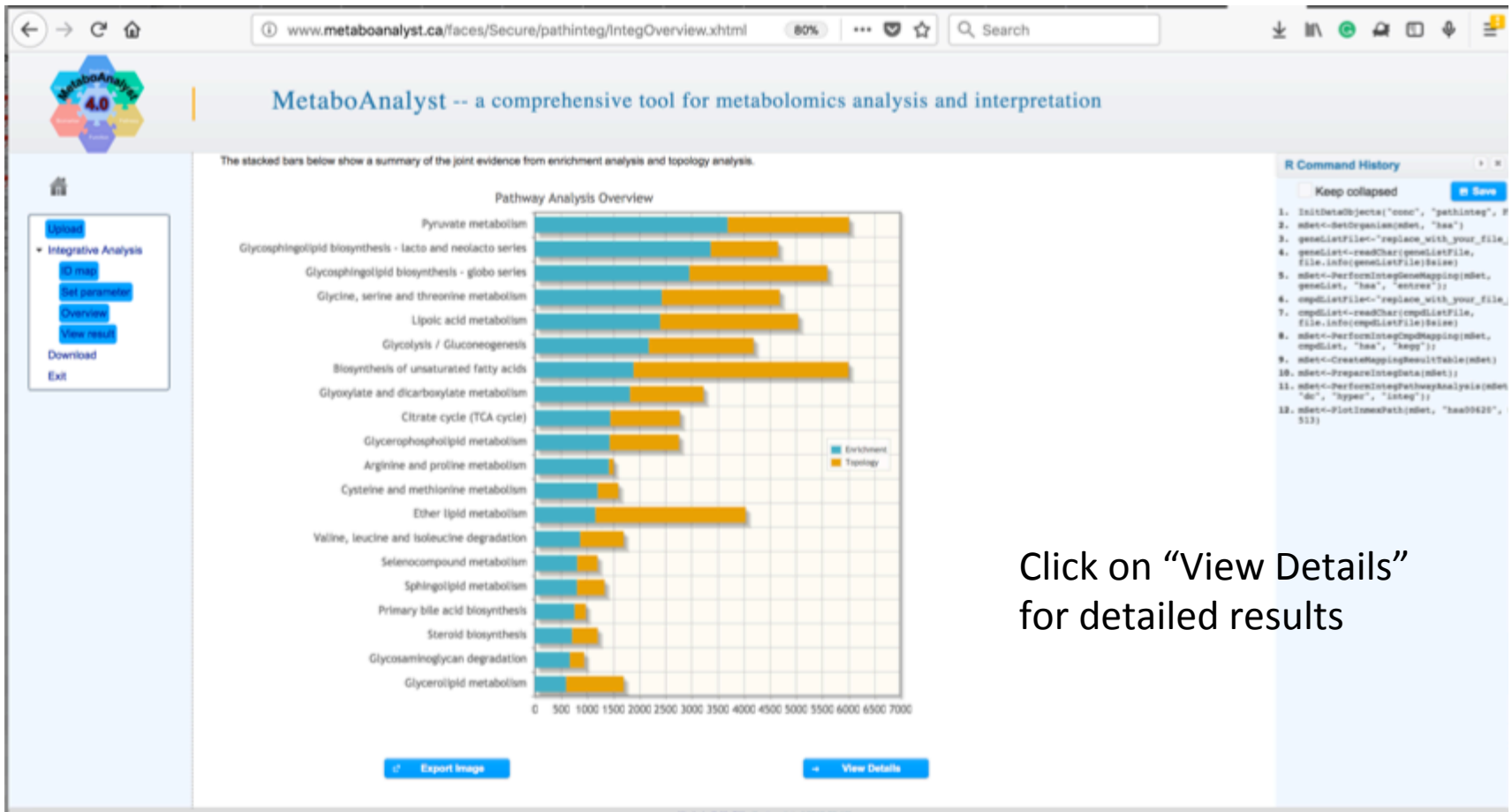
- Enrichment Analysis:** Describes the goal of evaluating gene and metabolite enrichment in a pathway. It offers two radio button options: "Hypergeometric Test" (selected) and "Fisher's Exact Test".
- Topology Analysis:** Describes the goal of evaluating a node's role in a pathway based on its position. It offers three radio button options: "Degree Centrality" (selected), "Betweenness Centrality", and "Closeness Centrality".
- Pathway Databases:** Describes three modes of pathway analysis: "Gene-metabolite pathways" (selected), "Gene-centric pathways", and "Metabolite-centric pathways".

A blue "Submit" button is located at the bottom center of the main content area.

On the right side, the "R Command History" panel is visible, showing a list of 10 R commands used for data processing and analysis.

```
1. InitDataObjects("oone", "pathinteg", 1
2. mdet<-SetOrganism(mdet, "hsa")
3. geneListFile<-replace_with_your_file
4. geneList<-readChar(geneListFile,
file.info(geneListFile)$size)
5. mdet<-PerformIntegGeneMapping(mdet,
geneList, "hsa", "entrez");
6. cmpdListFile<-replace_with_your_file
7. cmpdList<-readChar(cmpdListFile,
file.info(cmpdListFile)$size)
8. mdet<-PerformIntegCmpdMapping(mdet,
cmpdList, "hsa", "kegg");
9. mdet<-CreateMappingResultTable(mdet);
10. mdet<-PrepareIntegData(mdet);
```

Results - Overview



Click on "View Details"
for detailed results

Results - Details

MetaboAnalyst -- a comprehensive tool for metabolomics analysis and interpretation

Pyruvate metabolism (KEGG)

The matched nodes are highlighted in different colors - red (up-regulated), yellow (unknown), green (down-regulated) based on fold change (FC) values. Click on a node to show more details.

Pathway	Total	Expected	Hits	PValue	Topology	View
Pyruvate metabolism	41	1.1233	4	0.023442	0.3913	View
Glycosphingolipid biosynthesis - lacto and neolacto series	28	0.71233	3	0.031941	0.22034	View
Glycosphingolipid biosynthesis - globo series	13	0.35616	2	0.047147	0.44444	View
Cholesterol and bile acid metabolism	57	0.6297	2	0.073705	0.10005	View

```
1. initDataObjects("case", "pathinteg",
2. ndet<-detOrganism(ndet, "hsa")
3. geneListFile<-"replace_with_your_file
4. geneList<-readChar(geneListFile,
file.info(geneListFile)$size)
5. ndet<-PerformIntegGeneMapping(ndet,
geneList, "hsa", "entrez");
6. cpmlistFile<-"replace_with_your_file
7. cpmlist<-readChar(cpmlistFile,
file.info(cpmlistFile)$size)
8. ndet<-PerformIntegCpdMapping(ndet,
cpmlist, "hsa", "kegg");
9. ndet<-CreateMappingResultTable(ndet);
10. ndet<-PrepareIntegData(ndet);
11. ndet<-PerformIntegPathwayAnalysis(ndet,
"de", "hyper", "integ");
12. ndet<-PlotInnxPath(ndet, "hsa04202",
513)
```

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Metabolomics data (n subjects X p metabolites)

	M1	M2	-	Mn
Subject1	199	19	-	100
Subject2	10	40		90
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SubjectN	50	30	-	20

Transcriptomics data (n subjects X q genes)

	G1	G2	-	Gn
Subject1	19	19	-	100
Subject2	10	40	-	90
-	-	-	-	-
SubjectN	10	40	-	50

Association matrix

	G1	G2	-	Gn
M1	0.4	0.9	-	0.3
M2	0.7	0.1	-	0.5
M3	0.1	0.6		0.8

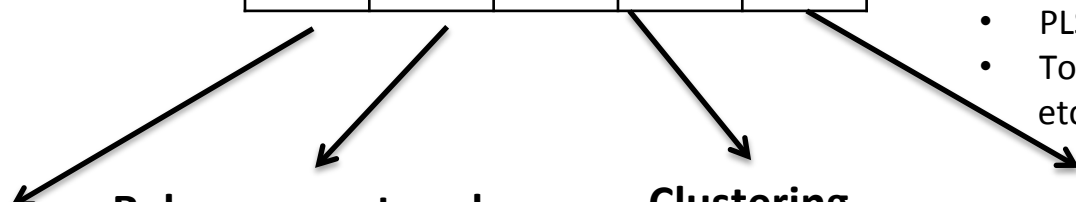
Univariate

- Pearson, Spearman, Partial Correlation
- Tools: 3Omics, MetabNet, etc.

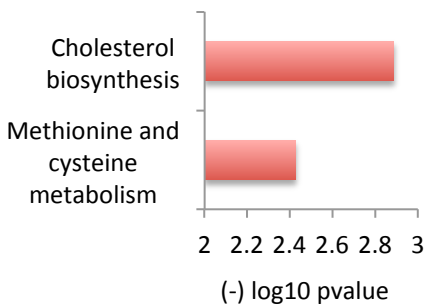
Multivariate

- PLS, CCA, sparse PLS
- Tools: mixOmics (Cao 2009), etc.

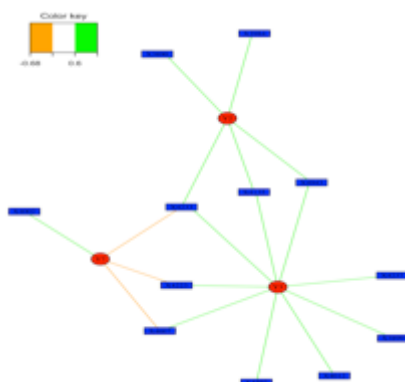
Workflow



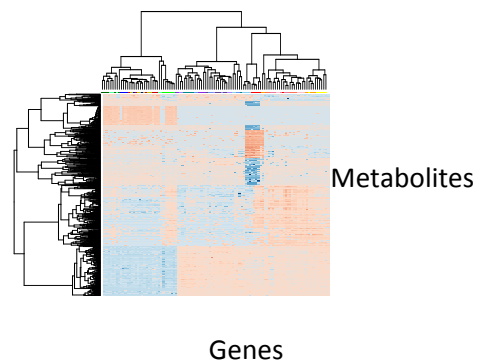
Pathway enrichment



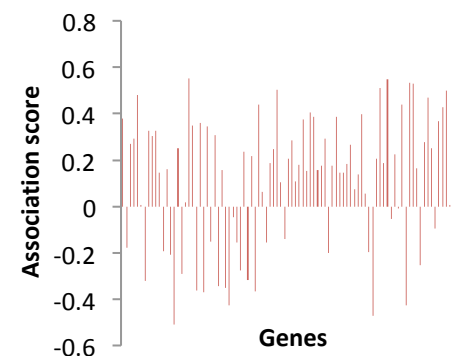
Relevance networks



Clustering

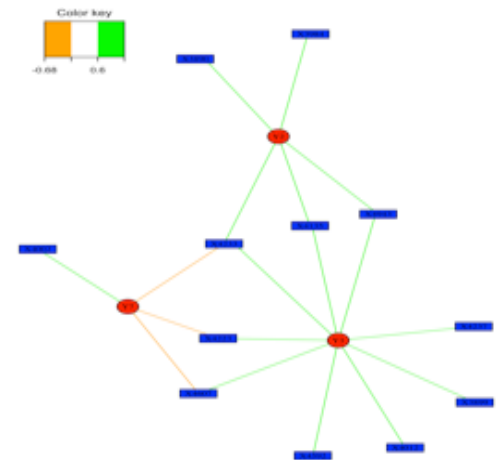


Targeted investigation (e.g.: Arginine x Transcriptome)



Relevance networks

- What is a network (or graph)?
 - A set of nodes (vertices) and edges (links)
 - Edges describe a relationship (e.g. correlation) between the nodes
- What is a relevance network?
 - Networks of highly-correlated biomedical/clinical entities (Butte 2000; PNAS)
 - Metabolomics x Proteomics, Transcriptomics x Proteomics, Metabolomics x Microbiome, Metabolomics x Clinical variables/phenotypes, etc.
 - Generate a bipartite graph network using an association threshold (e.g. 0.5) to visualize positive or negative associations



Circles: microbial species
Rectangles: metabolome features

Methods for generating relevance networks

- Univariate
 - Pairwise Pearson or Spearman correlation between data from different biomedical/clinical technologies (Butte et al. 2000, Uppal et al. 2015)
 - 3Omics (Kuo 2013; a web-based tool for analysis, integration and visualization of human transcriptome, proteome and metabolome data)
 - MetabNet (Uppal 2015; R package for performing pairwise correlation analysis and generating relevance networks)
- Multivariate
 - Multivariate regression techniques such as partial least squares (PLS), sparse partial least squares regression (sPLS), multilevel sparse partial least squares (msPLS) regression, etc.
 - mixOmics (Cao et al. 2009, Liquet et al. 2012; R package for integration and variable selection using multivariate regression)
 - xMWAS (Uppal 2018): R package for data-driven integration and differential network analysis

Univariate methods

3Omics (Kuo et al. BMC Systems Biology 2013)

- A web-based tool for analyzing, integrating and visualizing transcriptomic, proteomic and metabolomic data
- <http://3omics.cmdm.tw/>

3Omics - homepage

3omics.cmdm.tw

3Omics

Project Features

- Overview
- Name-ID Converter
- Help
- Contact Us

Overview

3Omics: A web based systems biology visualization tool for integrating human transcriptomic, proteomic and metabolomic data

3Omics is a one-click web tool for visualizing and rapidly integrating multiple inter- or intra-transcriptomic, proteomic, and metabolomic human data. It covers and connects cascades from transcripts, proteins, and metabolites and provides five commonly used analyses including correlation network, co-expression, phenotype generation, KEGG/HumanCyc pathway enrichment, and GO enrichment.

Please select the desired analysis:

- Transcriptomics-Proteomics-Metabolomics
- Proteomics-Metabolomics
- Transcriptomics only
- Transcriptomics-Proteomics
- Transcriptomics-Metabolomics
- Proteomics only
- Metabolomics only

Please refer to the help page for more details about each integrating method.

(a) (b) (c) (d) (e)

■ Transcripts ▲ Proteins ● Metabolites — Correlation Literature-derived relationship

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We recommend using the latest version of [Google Chrome](#) or [Mozilla Firefox](#) to get the best experience using 3Omics services.

Features

- Correlation analysis and network visualization
 - Pairwise Pearson correlation analysis
- Database-derived relationships in correlation analysis
 - Uses an internal database based on NCBI Entrez gene, Uniprot proteins, and KEGG metabolites to determine gene-protein-metabolite relationship
- Coexpression analysis
 - Two-way hierarchical clustering analysis
 - Rows: variables (Genes + proteins + metabolites, genes+metabolites, etc.)
 - Columns: samples
- Phenotype analysis
 - Uses OMIM databases to link genes with phenotypes
- Pathway and Gene Ontology Enrichment analysis
 - Using KEGG, HumanCyc, and DAVID

Data upload

Please select the desired analysis.

- a. Transcriptomics-Proteomics-Metabolomics
- b. Transcriptomics-Proteomics

- c. Proteomics-Metabolomics
- d. Transcriptomics-Metabolomics

- e. Transcriptomics only
- f. Proteomics only
- g. Metabolomics only

Please refer to the help page for more details about each integrating method.



[← Back](#)

User may upload three kinds of -omic expression data. All analyses will be performed.

[Use example data](#) [?](#)

Transcriptomics

No file selected. [?](#)

GenBank ID: e.g. [NAT1](#), [ABL1](#)

Proteomics

No file selected. [?](#)

Uniprot Accession: e.g. [P31946](#), [P62258](#)

Metabolomics

No file selected. [?](#)

Data format

(<http://3omics.cmdm.tw/help.php#examples>)

Samples

	timepoint1	timepoint2	timepoint3	timepoint4	timepoint5
akap9	-0.24	-0.6	-0.47	-0.38	-0.31
macf1	-0.3	-0.3	0.48	0.07	-0.36
RNPEP	0.24	0.85	0.15	0.79	0.69
SDHA	0.1	0.37	0.18	0.23	0.33
EEF1B2	-0.04	-0.31	0.06	-0.39	-0.46
EEF1D	0.07	0.29	0.22	0.75	0.47
EIF4A1	0.42	0.65	0.66	0.97	0.78
WARS	1.47	1.72	0.58	1.79	1.69
G3BP2	0.15	0.09	0.1	0.2	-0.22
PAK2	-0.21	-0.14	-0.15	-0.31	-0.4
PPP4C	-0.13	0.05	-0.09	0.21	-0.12
ZNF224	-0.06	0.31	0.17	0.27	0.61
ZNF268	-0.23	0.08	0.01	0.1	-0.1
TRRAP	0.07	-0.12	0.41	0.45	-0.09
RAD23B	-0.07	-0.32	-0.02	-0.02	-0.44
TARDBP	0.23	0.18	0.39	0.63	0.23
CSTF2	0.51	0.65	0.71	1.18	0.89
PSMC2	0.82	0.57	1.15	1.75	0.58
F8	-0.19	-0.02	-0.35	-0.82	-0.81
MYOM1	-0.28	-0.29	-0.54	-1.06	-1.03
ACTR3	0.57	0.48	0.39	0.32	0.72
ITPR2	0.62574	1.771	-0.057392	1.2612	1.7769
NUCB2	-1.1943	-0.96016	-0.71549	-1.1877	-0.70604
CAMK1	0.33342	0.87499	0.059355	0.062122	0.53605
BCL2A1	2.2913	3.8479	-0.12343	1.6604	3.3933
PDCD6IP	0.46362	0.88049	0.20539	0.36177	0.62012

Correlation analysis

[Help](#)

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Parameters Section



How to set up parameters?

Correlation Coefficient Threshold
0.9

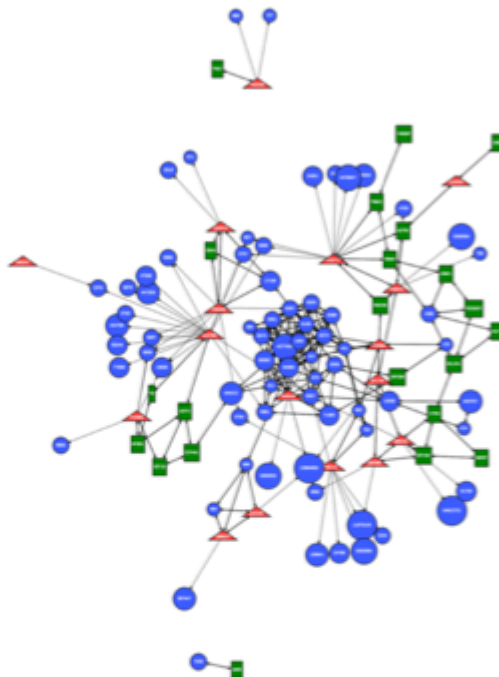
Correlation Network Repulsion
160

Correlation Network Attraction
80

[Refresh](#)

 **MDDL**
 **NATIONAL TAIWAN UNIVERSITY**

Correlation Network of Transcriptomics, Proteomics & Metabolomics



3Omics generates inter-omic correlation network to display the relationship or common patterns in data over time or experimental conditions for all transcripts, proteins and metabolites. Where users may only have two of the three -omics data-sets, 3Omics supplements the missing transcript, protein or metabolite information by searching [iHOP database](#).

Summary of Input molecules

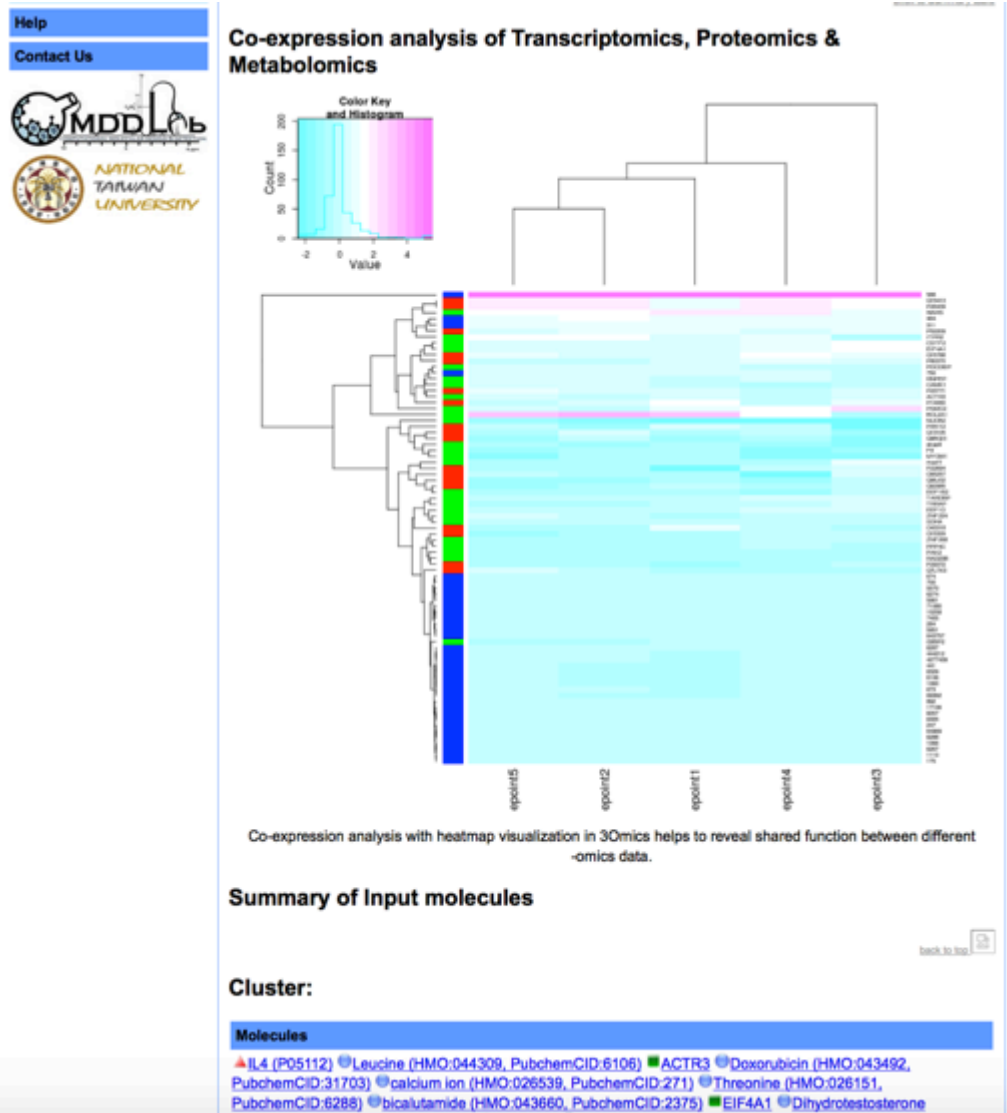
[back to top](#)

Cluster:

Molecules

▲ IL4 (P05112) ● Leucine (HMO:044309, PubchemCID:6106) ■ ACTR3 ● Doxorubicin (HMO:043492, PubchemCID:31703) ● calcium ion (HMO:026539, PubchemCID:271) ● Threonine (HMO:026151, PubchemCID:6288) ● bicalutamide (HMO:043660, PubchemCID:2375) ■ EIF4A1 ● Dihydrotestosterone (HMO:025783, PubchemCID:10635) ■ PDCC6IP ● bortezomib (HMO:048610, PubchemCID:387447) ■ PSMC2

Co-expression analysis



Rows: Variables
Columns: Samples

Phenotype analysis



Project Features
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Correlation Network Coexpression Profile **Phenotype Analysis** Pathway Analysis GO Enrichment Analysis

[Click to Summary table](#)

Phenotype Analysis

A phenotype is defined as any observable characteristic or trait of an organism arising from gene expression, the influence of environmental factors, and the interactions between them. With phenotype-gene association from OMIM, genes and genetic disorders containing information to relate genes in the human genome with specific phenotypes can be identified.

The Transcriptomics data you've input have been used to search through the OMIM database, and the related phenotype and genes can be listed as below:

Please click the link for description and molecular genetic information on OMIM website.

Human-related Phenotype	Related-Gene
[OMIM: 611820] LONG QT SYNDROME 11	akap9
[OMIM: 256000] LEIGH SYNDROME	SDHA
[OMIM: 612069] AMYOTROPHIC LATERAL SCLEROSIS 10, WITH OR WITHOUT FRONTOTEMPORAL DEMENTIA WITH TDP43 INCLUSIONS	TARDBP
[OMIM: 306700] HEMOPHILIA A COAGULATION FACTOR VIII, INCLUDED	F8

Summary of Input molecules

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Cluster:

Molecules



▲ IL4 (P05112) [Leucine \(HMO:044309, PubchemCID:6106\)](#) [ACTR3 \(HMO:043492, PubchemCID:31703\)](#) [calcium Ion \(HMO:026539, PubchemCID:271\)](#) [Threonine \(HMO:026151, PubchemCID:6288\)](#) [bicalutamide \(HMO:043660, PubchemCID:2375\)](#) [EIF4A1 \(HMO:048610, PubchemCID:387447\)](#) [PSMC2 \(HMO:025783, PubchemCID:10635\)](#) [PDCD6IP \(HMO:048610, PubchemCID:387447\)](#) [PSMC2 \(HMO:044577, PubchemCID:284\)](#) [hippuric acid \(HMO:033093, PubchemCID:464\)](#) [Testosterone Propionate \(HMO:043961, PubchemCID:5995\)](#) [Androsterone \(HMO:027989, PubchemCID:5879\)](#) [MYOM1 \(HMO:042148, PubchemCID:857\)](#) [zinc fluoride \(HMO:040479, PubchemCID:24551\)](#) [3d0b \(HMO:049721, PubchemCID:24812721\)](#) [Mifepristone \(HMO:043298, PubchemCID:55245\)](#) [MAP3K7 TAK1 \(O43318\)](#) [Aconitic Acid \(HMO:033434, PubchemCID:444212\)](#) [Indican \(HMO:049137, PubchemCID:10258\)](#) [Estradiol \(HMO:026665, PubchemCID:5757\)](#) [NTH \(HMO:049464, PubchemCID:5289054\)](#) [Inositol \(HMO:036496,](#)

Pathway analysis



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Phenotype Analysis

Pathway Analysis

GO Enrichment Analysis

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Pathway analysis - Normal, non-enrichment

[KEGG section](#) | [HumanCyc section](#)

KEGG Pathway analysis

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KEGG pathway enrichment analysis operates upon metabolomic data to reveal enriched pathways in a KEGG Pathway database by ranking the biological pathways commonly shared by metabolites.

The enriched KEGG metabolic pathways are listed on the bottom of the page. Please click to see mapped pathway images on KEGG Pathway.

(Normal Mode) Show Records: 20

Metabolic Pathways	Hits
(hsa01100) Metabolic pathways - Homo sapiens (human)	19
<ul style="list-style-type: none"> <li style="margin-right: 5px;">* Acetate <li style="margin-right: 5px;">* D-Alanine <li style="margin-right: 5px;">* L-Asparagine <li style="margin-right: 5px;">* Betaine <li style="margin-right: 5px;">* Citrate <li style="margin-right: 5px;">* Ethanolamine <li style="margin-right: 5px;">* Formate <li style="margin-right: 5px;">* 6-Deoxy-L-galactose <li style="margin-right: 5px;">* L-Glutamine <li style="margin-right: 5px;">* Glycine <li style="margin-right: 5px;">* L-Histidine <li style="margin-right: 5px;">* N,N-Dimethylglycine <li style="margin-right: 5px;">* Pyruvate <li style="margin-right: 5px;">* Pyridine-2,3-dicarboxylate <li style="margin-right: 5px;">* L-Serine <li style="margin-right: 5px;">* Succinate <li style="margin-right: 5px;">* L-Tryptophan <li style="margin-right: 5px;">* L-Tyrosine <li style="margin-right: 5px;">* N(p)-Methyl-L-histidine 	
(hsa00970) Aminoacyl-tRNA biosynthesis - Homo sapiens (human)	8
<ul style="list-style-type: none"> <li style="margin-right: 5px;">* L-Asparagine <li style="margin-right: 5px;">* L-Glutamine <li style="margin-right: 5px;">* Glycine <li style="margin-right: 5px;">* L-Histidine <li style="margin-right: 5px;">* L-Serine <li style="margin-right: 5px;">* L-Threonine <li style="margin-right: 5px;">* L-Tryptophan <li style="margin-right: 5px;">* L-Tyrosine 	
(hsa00250) Alanine, aspartate and glutamate metabolism - Homo sapiens (human)	7
<ul style="list-style-type: none"> <li style="margin-right: 5px;">* Acetate <li style="margin-right: 5px;">* L-Asparagine <li style="margin-right: 5px;">* L-Glutamine <li style="margin-right: 5px;">* Glycine <li style="margin-right: 5px;">* Pyruvate <li style="margin-right: 5px;">* Succinate <li style="margin-right: 5px;">* L-Tyrosine 	
(hsa00280) Valine, leucine and isoleucine degradation - Homo sapiens (human)	6
<ul style="list-style-type: none"> <li style="margin-right: 5px;">* Acetate <li style="margin-right: 5px;">* Glycine <li style="margin-right: 5px;">* Pyruvate <li style="margin-right: 5px;">* Succinate <li style="margin-right: 5px;">* L-Tryptophan <li style="margin-right: 5px;">* L-Tyrosine 	
(hsa00270) Cysteine and methionine metabolism - Homo sapiens (human)	6
<ul style="list-style-type: none"> <li style="margin-right: 5px;">* Betaine <li style="margin-right: 5px;">* N,N-Dimethylglycine <li style="margin-right: 5px;">* Pyruvate <li style="margin-right: 5px;">* L-Serine <li style="margin-right: 5px;">* L-Tryptophan <li style="margin-right: 5px;">* L-Tyrosine 	
(hsa00330) Arginine and proline metabolism - Homo sapiens (human)	6
<ul style="list-style-type: none"> <li style="margin-right: 5px;">* Acetate <li style="margin-right: 5px;">* L-Glutamine <li style="margin-right: 5px;">* Glycine <li style="margin-right: 5px;">* Pyruvate <li style="margin-right: 5px;">* Succinate <li style="margin-right: 5px;">* L-Tyrosine 	
(hsa00360) Phenylalanine metabolism - Homo sapiens (human)	5
<ul style="list-style-type: none"> <li style="margin-right: 5px;">* Acetate <li style="margin-right: 5px;">* Glycine <li style="margin-right: 5px;">* L-Histidine <li style="margin-right: 5px;">* L-Tryptophan <li style="margin-right: 5px;">* L-Tyrosine 	
(hsa00340) Histidine metabolism - Homo sapiens (human)	5
<ul style="list-style-type: none"> <li style="margin-right: 5px;">* Acetate <li style="margin-right: 5px;">* L-Histidine <li style="margin-right: 5px;">* L-Tryptophan <li style="margin-right: 5px;">* L-Tyrosine <li style="margin-right: 5px;">* N(p)-Methyl-L-histidine 	
(hsa00260) Glycine, serine and threonine metabolism - Homo sapiens (human)	5
<ul style="list-style-type: none"> <li style="margin-right: 5px;">* Betaine <li style="margin-right: 5px;">* Glycine <li style="margin-right: 5px;">* N,N-Dimethylglycine <li style="margin-right: 5px;">* Pyruvate <li style="margin-right: 5px;">* L-Serine 	
(hsa00520) Amino sugar and nucleotide sugar metabolism - Homo sapiens (human)	4

GO Enrichment Analysis





Project Features

- Overview
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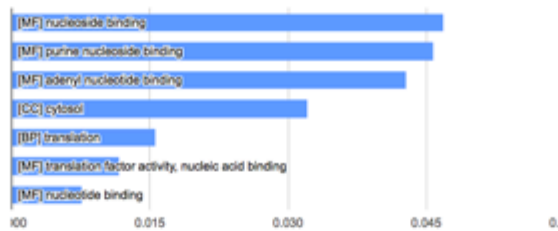
[Click to Summary table](#)

Gene Ontology functional Profiling

The Gene Ontology (GO) provides defined terms for representing the properties of gene product. GO covers three levels of properties: i) cellular component ii) biological process iii) molecular function help users to understand information of gene products from the defined three domains.

[biological process](#) | [cellular component](#) | [molecular function](#)

GO Terms with P-value < 0.05



Biological Process

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A biological process is a process of a living organism. Biological processes are made up of any number of chemical reactions or other events that results in a transformation. Regulation of biological processes occurs where any process is modulated in its frequency, rate or extent. Biological processes are regulated by many means; examples include the control of gene expression, protein modification or interaction with a protein or substrate molecule.

GO Term	No. of Gene-mapped	Coverage	P-value	FDR	Mapped Gene ID
translation	4	17%	0.0156	EEF1D,EEF1B2,EIF4A1,WARS	1936, 1933, 1973, 7453
cell death	4	17%	0.1082	PDCD6IP,BCL2A1,TARDBP,PAK2	10015, 597, 23435, 5062
death	4	17%	0.1104	PDCD6IP,BCL2A1,TARDBP,PAK2	10015, 597, 23435, 5062
apoptosis	3	13%	0.2565	PDCD6IP,BCL2A1,PAK2	10015, 597, 5062

Multivariate methods

Generating relevance network using sPLS or msPLS techniques (Cao 2009, Liquet 2012)

- sparse partial least squares (sPLS) regression or multilevel partial least squares (msPLS) method
- One-step procedure for variable selection as well as integration
- Comparison of different multivariate integration techniques showed that sPLS generates (Cao 2009)
- msPLS – for repeated measures
- Implemented in the R package mixOmics
- Generates association matrix and allows visualization of associations using bipartite relevance networks (Liquet 2012)

sPLS method

- sPLS is a variable selection and dimensionality reduction method that allows integration of heterogeneous omics data from same set of samples
- Robust approximation of Pearson correlation using regression and latent (principal) variates
- Eg: transcriptome (matrix X) and metabolome (matrix Y) data
where,
matrix X is an $n \times p$ matrix that includes n samples and p metabolites
matrix Y is an $n \times q$ matrix that includes n samples and q genes

Objective function

$\max \text{cov}(X_u, Y_v)$

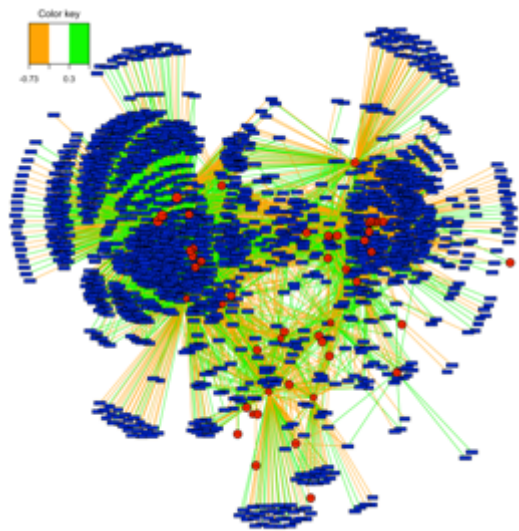
where

$u_1, u_2 \dots u_H$ and $v_1, v_2 \dots v_H$ are the loading vectors

H is the number of PLS-DA dimensions

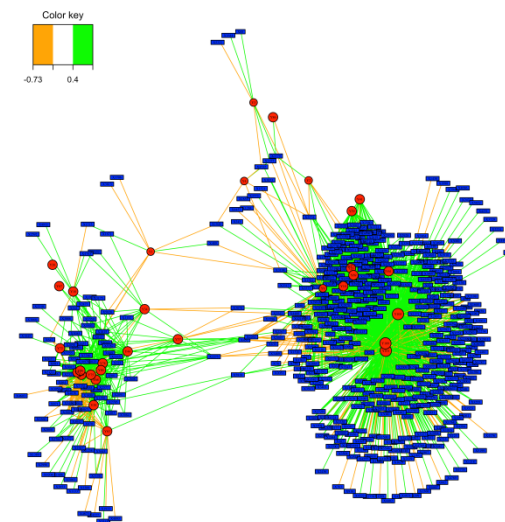
A Lasso based optimization is used to select most relevant variables

Case Study: Application of sPLS technique for integrative –omics. Microbiome-Metabolome Wide Association Study of Lung BAL: Global integration of 5930 m/z features with 153 microbial species using sparse Partial Least Squares regression (Cribbs et al. Microbiome 2016)

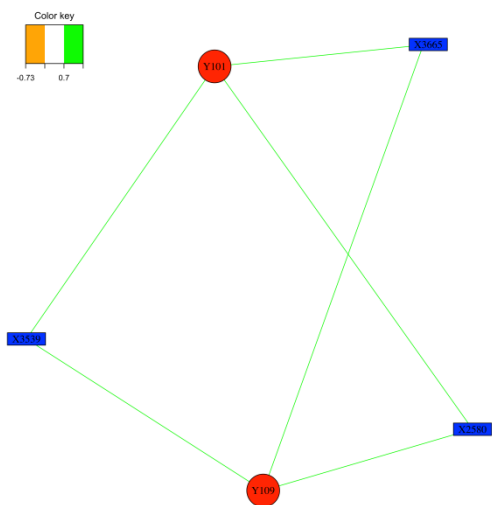


A. Association threshold: 0.3

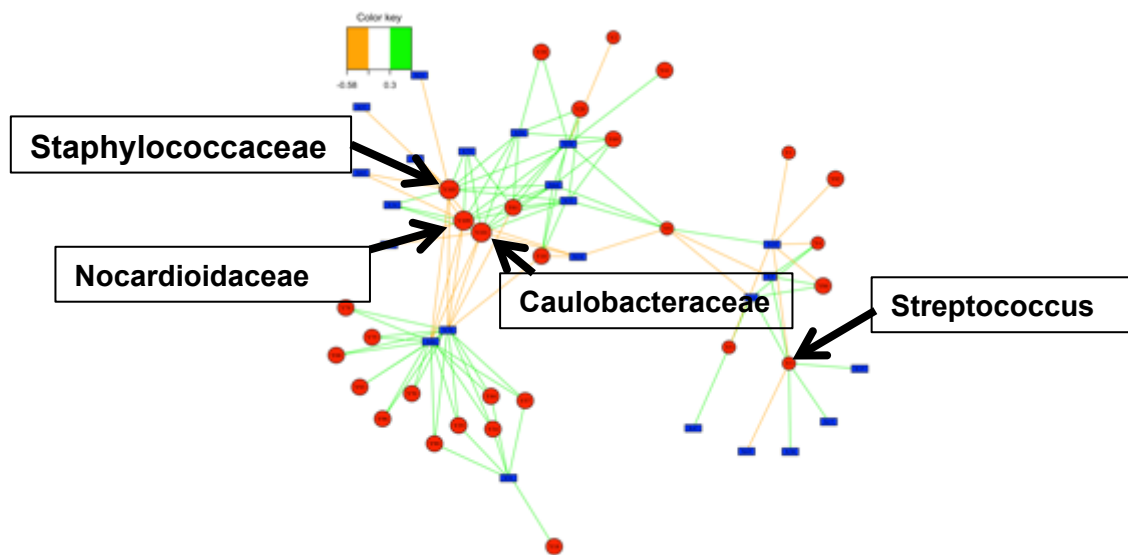
Legend
Circles: microbial species
Rectangles: metabolome features



B. Association threshold: 0.4



C. Association threshold: 0.7



D. Using only subset of metabolic features also associated with HIV status (+ve or -ve)

Integrating more than two datasets

Proteomics data
(n subjects X s proteins)

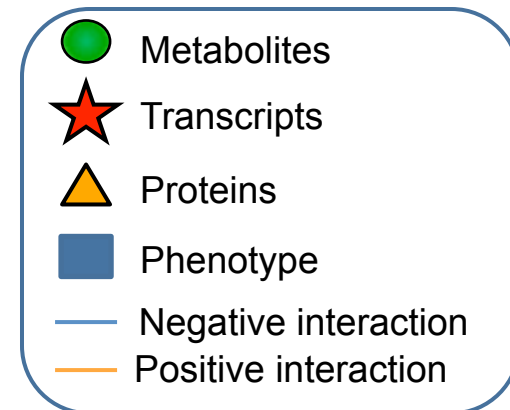
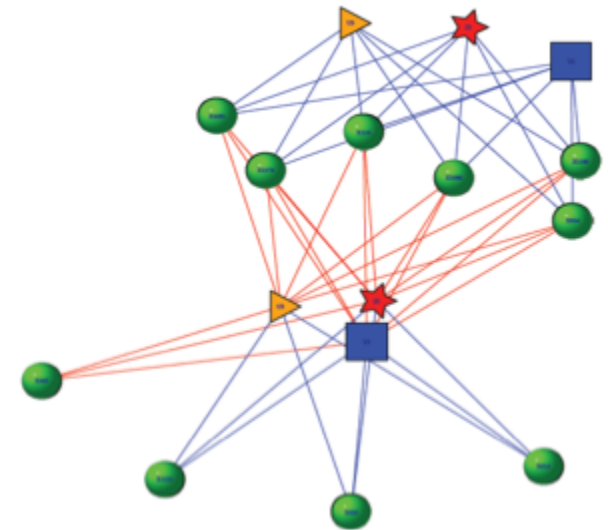
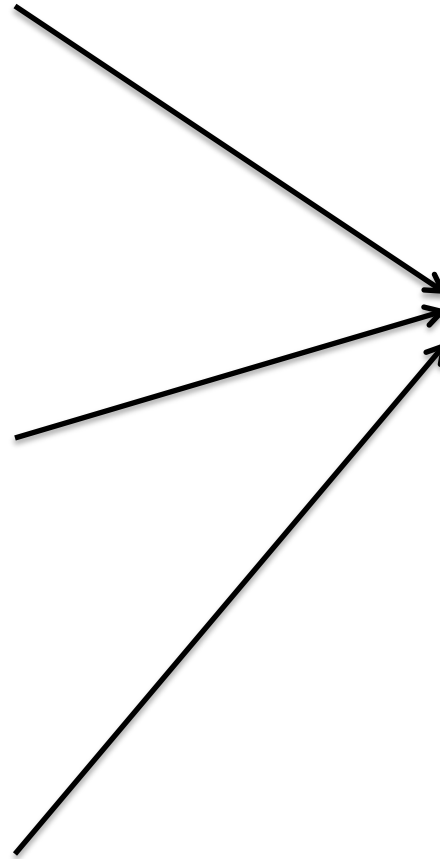
	E1	E2	-	Es
Subject1	199	19	-	100
Subject2	10	40		90
-	-	-		-
SubjectN	50	30	-	20

Metabolomics data
(n subjects X p metabolites)

	M1	M2	-	Mp
Subject1	199	19	-	100
Subject2	10	40		90
-	-	-		-
SubjectN	50	30	-	20

Transcriptomics data
(n subjects X q genes)

	G1	G2	-	Gq
Subject1	19	19	-	100
Subject2	10	40	-	90
-	-	-	-	-
SubjectN	10	40	-	50



xMWAS: R package for data integration and differential network analysis (Uppal 2018, Bioinformatics)

[URL: https://kuppal.shinyapps.io/xmwas/](https://kuppal.shinyapps.io/xmwas/)

A.

Data matrices from multiple assays



Integrative and association analysis

Pairwise integrative and network analysis (e.g. $X \leftrightarrow Y$; $X \leftrightarrow Z$, $Y \leftrightarrow Z$) using (sparse) Partial Least Squares regression



Generate an edge list matrix, L_e , with the list of edges that meet the significance criteria and association score threshold

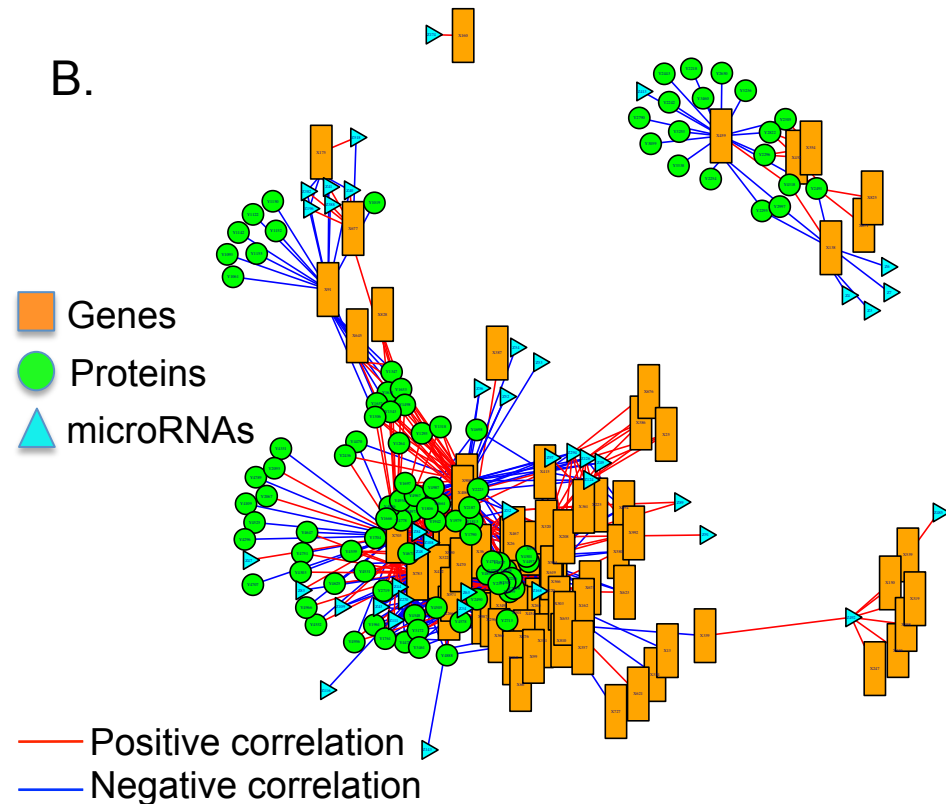


Generate a k-partite graph, G , using the union of edge list matrices

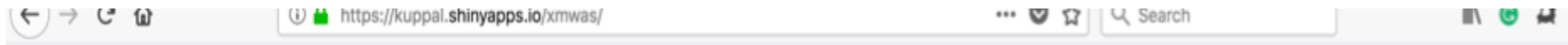


Community detection, differential centrality and rewiring analysis, and network visualization

B.



xMWAS: <https://kuppal.shinyapps.io/xmwas/>



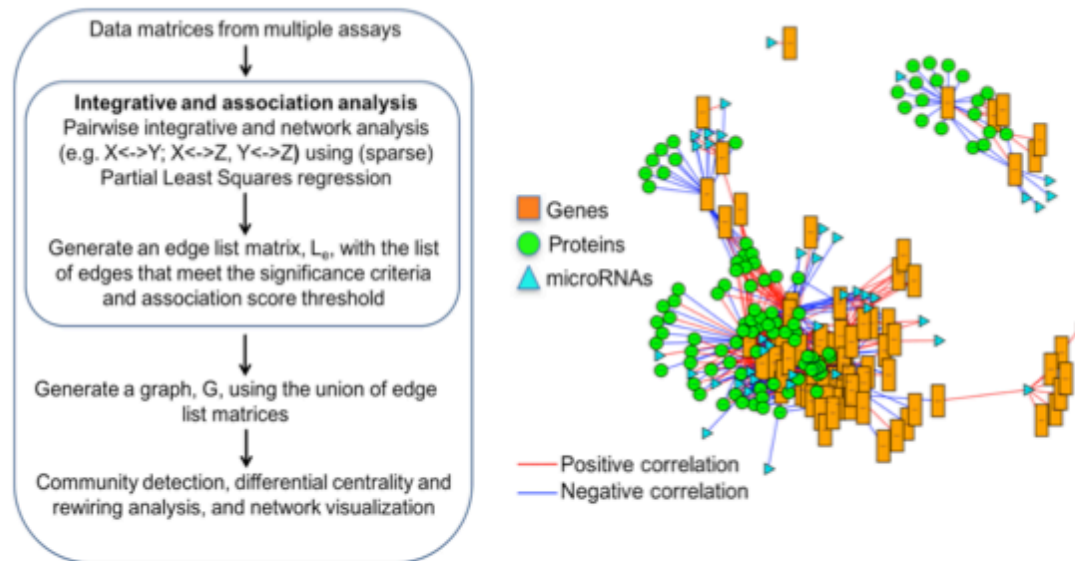
xMWAS - a data-driven integration and network analysis tool (v0.54)

Introduction Analysis Help and Support

xMWAS provides an automated workflow for data integration, network visualization, clustering, and differential network analysis of up to four datasets from biochemical and phenotypic assays, and omics platforms.

For installing xMWAS locally in R run:

```
library(devtools);install_github("kuppal2/xMWAS")
```



Citation: Uppal K, Ma C, Go YM, Jones DP. xMWAS: a data-driven integration and differential network analysis tool. *Bioinformatics*. 2017 Oct 23. PMID: 29069296

Maintained by Chunyu Ma (chunyu.ma@emory.edu) and Karan Uppal (kuppal2@emory.edu) at [Clinical Biomarkers Laboratory](#) , Emory University, Atlanta, GA, USA

Step 1. Upload data files

The screenshot shows the xMWAS web application interface. The browser address bar displays <https://kuppal.shinyapps.io/xmwas/>. The page title is *xMWAS - a data-driven integration and network analysis tool (v0.54)*. The navigation menu includes **Introduction**, **Analysis**, and **Help and Support**. The **Analysis** section is active, showing a sidebar with **Input Files** (containing a **Choose Files (see help and support)** button) and **Parameter Settings** (with a list of steps: 1. Data preparation and filtering, 2. Integration and association analysis, 3. Centrality analysis, 4. Graphical options).

The main content area is divided into two columns. The left column contains file selection options:

- Select input file for dataset A** ('.csv' or '.txt', 100MB limit): A **Browse...** button with the text "No file selected".
- Select input file for dataset B** ('.csv' or '.txt', 100MB limit): A **Browse...** button with the text "No file selected".
- Add more datasets:** Two buttons, **+** and **-**.
- Choose a class labels file** ('.csv' or '.txt'): A **Browse...** button with the text "No file selected".

The right column contains text input fields and radio button options:

- Name for dataset A:** A text input field containing "datasetA".
- Name for dataset B:** A text input field containing "datasetB".
- Output folder name:** A text input field containing "Default: xwasresults".
- Are there repeated measurements?** Two radio button options: True - Paired (repeated measures) and False - Unpaired (case-control & multiclass).
- Compare classes?** Two radio button options: True and False.
- Use example data?** Two radio button options: True and False.

<https://kuppal.shinyapps.io/xmwas/>

(See: Help & Support)

Input data format

Metabolomics data
(p metabolites x n subjects)

	Subject1	Subject2	-	Subject N
Metabolite 1	199	19	-	100
Metabolite 2	10	40		90
-	-	-		-
Metabolite p	50	30	-	20

Class labels file

	Class
Subject1	Control
Subject2	Control
-	-
SubjectN	Tumor

Transcriptomics data
(q genes x n subjects)

	Subject1	Subject2	-	Subject N
Gene 1	19	19	-	100
Gene 2	10	40	-	90
-	-	-	-	-
Gene q	10	40	-	50

xMWAS - a data-driven integration and network analysis tool (v0.54)

[Introduction](#)
[Analysis](#)
[Help and Support](#)

User Manual:

Click [here](#) to see the user manual.

Input File Format (no missing values allowed):

Dataset File Format:

mrna_id	CNS.SF_268	CNS.SF_295	CNS.SF_539	CNS.SNB_19	CNS.SNB_75	CNS.U251
5-HT3C2_1_mrna	0.53	-0.42	0	0.5	-0.27	0.43
A1BG-AS1_2_mrna	0.35	0.54	0.8	-0.24	-0.88	-0.1
A2LD1_3_mrna	-0.05	-1.04	0.85	0.12	-0.36	-0.3
A2MP1_4_mrna	-1.09	-1.13	0	-0.43	-0.6	0.42
A4GALT_5_mrna	-0.86	-0.46	-0.57	0.43	1.38	0.4

Each row is a feature and each column is filename

Class Label File Format (multiclass):

FileName	Class
CNS.SF_268	CNS
CNS.SF_295	CNS
CNS.SF_539	CNS
CNS.SNB_19	CNS
CNS.SNB_75	CNS
CNS.U251	CNS
LE.CCRF_CEM	LE
LE.HL_60	LE
LE.K_562	LE
LE.MOLT_4	LE
LE.RPMI_8226	LE
LE.SR	LE

Two columns: the first column is filename; the second column is class. Each row is the information of a file.

Class Label File Format (repeated measure with one factor):

FileName	Subject	Factor1
S1	Subject001	TP1
S2	Subject002	TP1
S3	Subject003	TP1
S4	Subject004	TP1
S5	Subject005	TP1
S6	Subject006	TP1

Step 2. Data preprocessing and filtering

The screenshot shows a web browser window with the URL <https://kuppal.shinyapps.io/xmwas/>. The page title is *xMWAS - a data-driven integration and network analysis tool (v0.54)*. The navigation menu includes 'Introduction', 'Analysis', and 'Help and Support'. The 'Analysis' section is active, and the 'Data preparation and filtering' step is highlighted in blue. The main content area contains several input fields for parameter settings:

- Relative Standard Deviation (RSD) Threshold (rows):** A numeric input field with the value 1.
- Maximum number of datasetA variables to select based on RSD:** A numeric input field with the value 1000.
- Maximum number of datasetB variables to select based on RSD:** A numeric input field with the value 1000.
- Minimum ratio of number of samples with a non-missing value to the total number of samples for a variable (rows):** A numeric input field with the value 0.7.
- How are the missing values represented in the data?:** A text input field with a hyphen (-) entered.

Step 3. Set parameters for integration and association analysis

The screenshot shows the xMWAS web application interface. The browser address bar displays <https://kuppal.shinyapps.io/xmwias/>. The page title is *xMWAS - a data-driven integration and network analysis tool (v0.54)*. The navigation menu includes [Introduction](#), [Analysis](#), and [Help and Support](#). The left sidebar contains the following sections:

- Input Files
 - [Choose Files \(see help and support\)](#)
- Parameter Settings
 - [1. Data preparation and filtering](#)
 - [2. Integration and association analysis](#)**
 - [3. Centrality analysis](#)
 - [4. Graphical options](#)

The main content area is divided into two sections:

Pairwise integrative analysis

Choose a data integration method:

Choose PLS mode:

Number of components to use in PLS model:

Find optimal number of PLS components? True False

Maximum number of datasetA variables to select in sPLS:

Maximum number of datasetB variables to select in sPLS:

Association analysis

Correlation Threshold:

P-value Threshold For Student's T-test:

Step 4. Select method for centrality analysis



xMWAS - a data-driven integration and network analysis tool (v0.54)

Introduction Analysis Help and Support

Input Files

Choose Files (see help and support)

Parameter Settings

1. Data preparation and filtering

2. Integration and association analysis

3. Centrality analysis

4. Graphical options

Method for centrality analysis:

eigenvector

eigenvector

betweenness

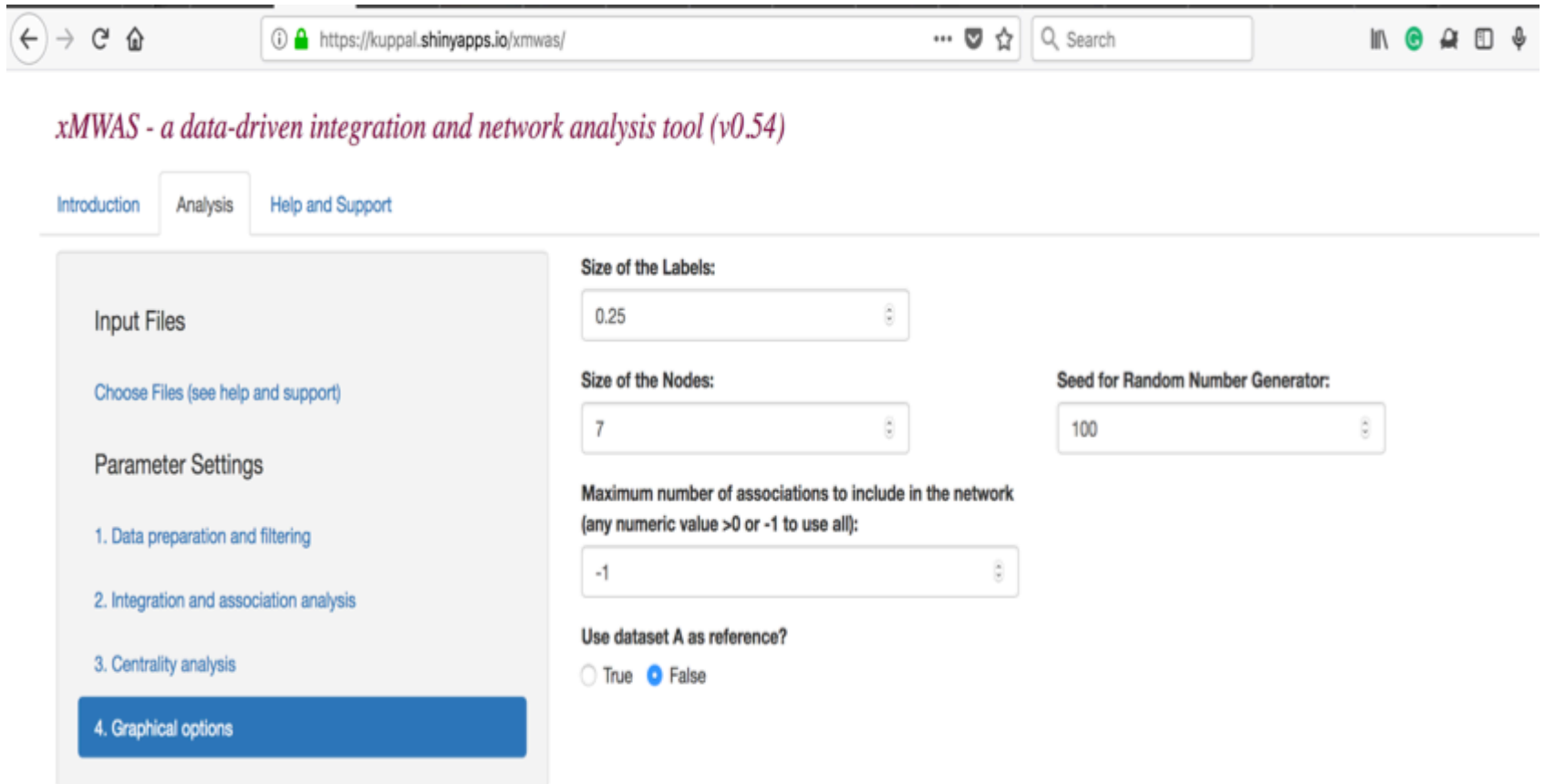
degree.count

degree.weight

closeness

- Eigenvector: based on the number and quality of connections
- Betweenness: based on the extent to which a node lies on the path between other nodes
- Degree.count: based on the number of connections
- Degree.weight: based on the magnitude of edges (association scores)
- Closeness: based on the closeness of a node to all other nodes

Step 5. Set graphical options



The screenshot shows the xMWAS web application interface. The browser address bar displays the URL <https://kuppal.shinyapps.io/xmwas/>. The page title is *xMWAS - a data-driven integration and network analysis tool (v0.54)*. The navigation menu includes [Introduction](#), [Analysis](#), and [Help and Support](#). The left sidebar contains the following sections:

- Input Files
 - [Choose Files \(see help and support\)](#)
- Parameter Settings
 - [1. Data preparation and filtering](#)
 - [2. Integration and association analysis](#)
 - [3. Centrality analysis](#)
 - [4. Graphical options](#)**

The main content area displays the following graphical options:

- Size of the Labels:** A numeric input field with the value 0.25.
- Size of the Nodes:** A numeric input field with the value 7.
- Seed for Random Number Generator:** A numeric input field with the value 100.
- Maximum number of associations to include in the network (any numeric value >0 or -1 to use all):** A numeric input field with the value -1.
- Use dataset A as reference?** Radio buttons for True and False.

Step 6. Click on “Start processing”

The screenshot shows the xMWAS web application interface. The browser address bar displays <https://kuppai.shinyapps.io/xmwas/>. The page title is *xMWAS - a data-driven integration and network analysis tool (v0.54)*. The navigation menu includes [Introduction](#), [Analysis](#), and [Help and Support](#). The main content area is divided into several sections:

- Input Files:** Includes a link to [Choose Files \(see help and support\)](#).
- Parameter Settings:** A list of steps: 1. Data preparation and filtering, 2. Integration and association analysis, 3. Centrality analysis, and 4. Graphical options (highlighted in blue).
- Size of the Labels:** A dropdown menu set to 0.25.
- Size of the Nodes:** A dropdown menu set to 7.
- Seed for Random Number Generator:** A dropdown menu set to 100.
- Maximum number of associations to include in the network (any numeric value >0 or -1 to use all):** A dropdown menu set to -1.
- Use dataset A as reference?** Radio buttons for True and False.

At the bottom of the parameter settings, there are two buttons: **Start processing** (highlighted) and **Download results**. Below this is an **Output** section with a slider labeled "Slide to go to next figure:" ranging from 0 to 5, with the slider currently at 0.

Citation: Uppal K, Ma C, Go YM, Jones DR xMWAS: a data-driven integration and differential network analysis tool. *Bioinformatics*. 2017 Oct 23. PMID: 29060296
Maintained by Chunyu Ma [chunyu.ma@emory.edu] and Karan Uppal [kuppai2@emory.edu] at Clinical Biomarkers Laboratory, Emory University, Atlanta, GA, USA

A notification box in the bottom right corner states: "You're using example data and it is processing now. Your results will be available for download shortly."

Results

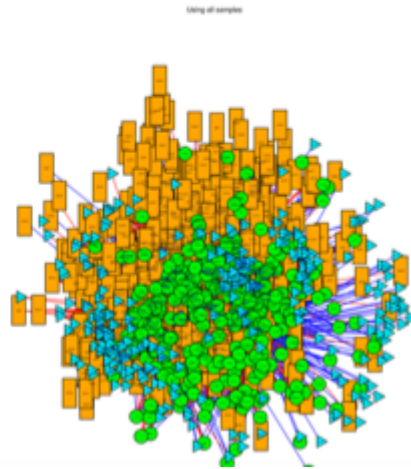
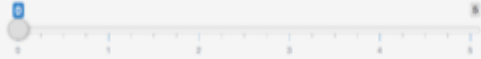
4. Graphical options

Processing complete. Please click on Download to save the results.

Start processing Download results

Output

Slide to go to next figure:



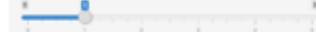
4. Graphical options

Processing complete. Please click on Download to save the results.

Start processing Download results

Output

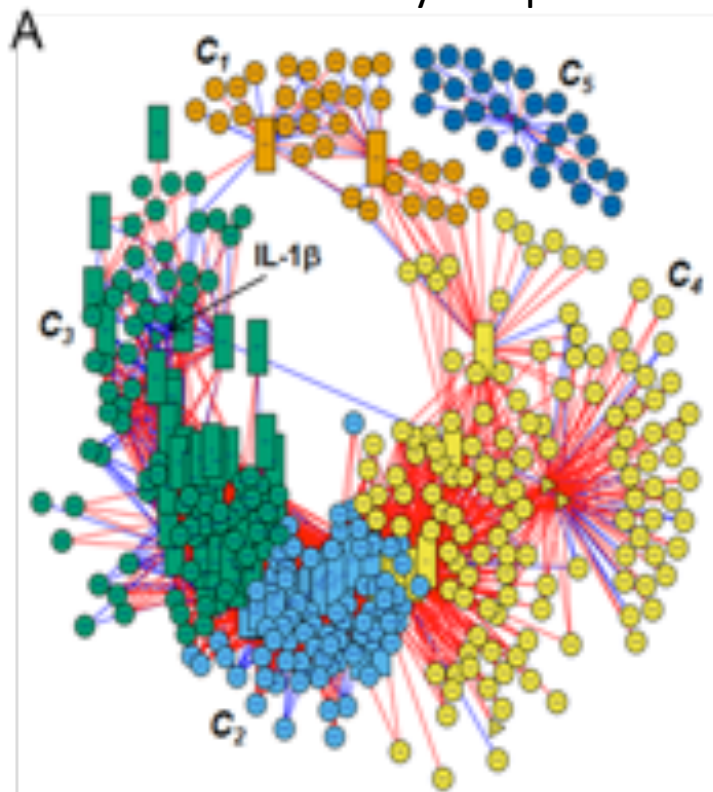
Slide to go to next figure:



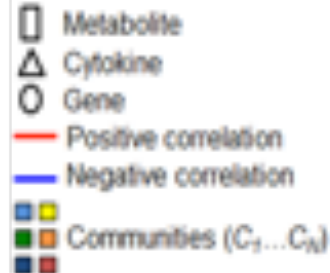
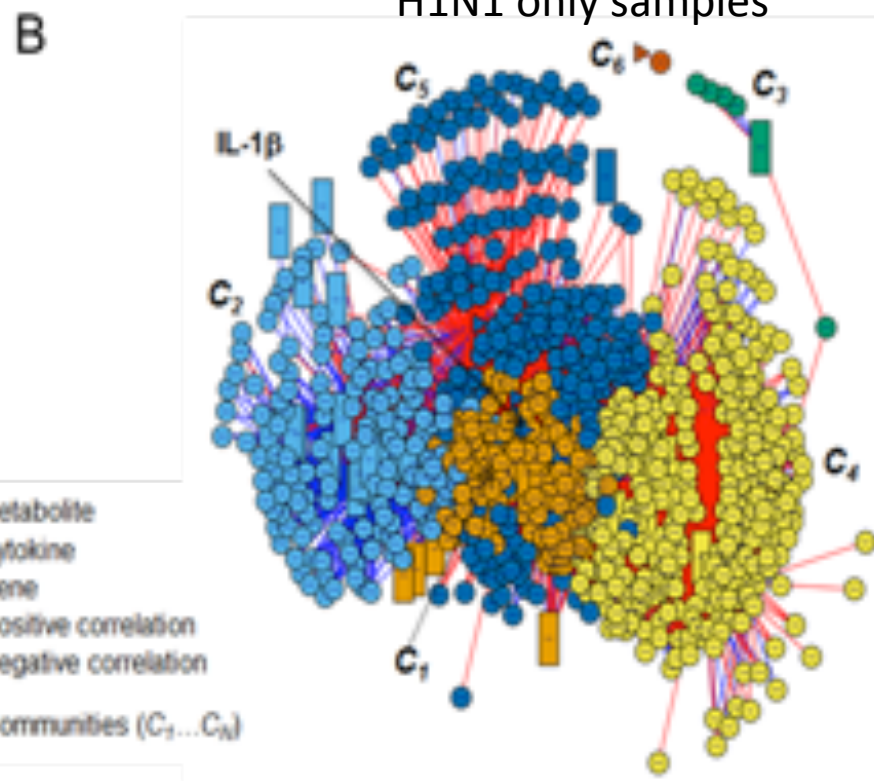
Case Study: Application of xMWAS for integrative –and differential network analysis of more than 2 dataests.

Integrative network analysis of cytokine, metabolome and transcriptome datasets from a study of H1N1 virus infection of mice (Chandler et al. 2016)

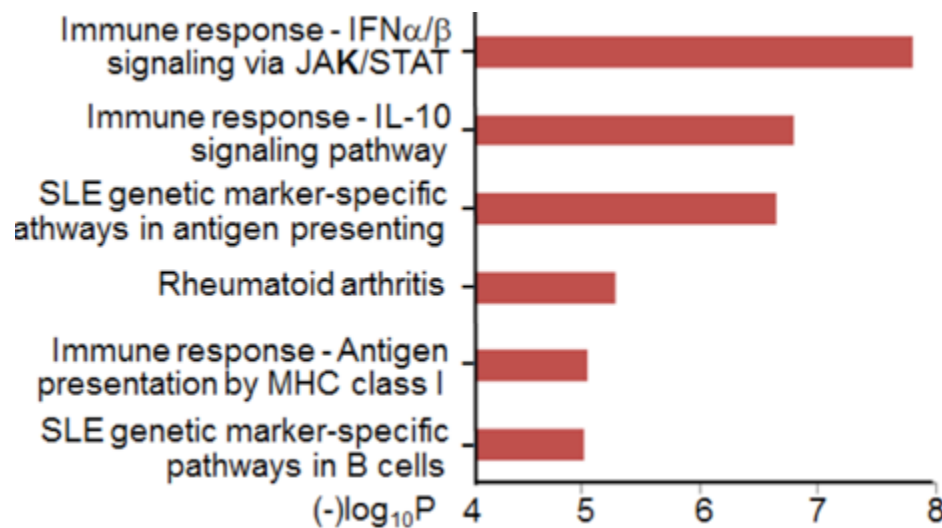
Control only samples



H1N1 only samples



C



Main approaches for data integration

- Pathway or knowledge-based integration
 - Datasets are analyzed individually (differentially expressed genes, metabolites, proteins) and integration is performed at the pathway level
 - Examples: MetaboAnalyst, iPEAP, MetScape, MetaCore
- Data-driven integration using meta-dimensional analysis
 - Integration is performed globally such that data from multiple omics layers are combined simultaneously
 - Examples: 3Omics, mixOmics, xMWAS
- **Using literature-derived associations for integration**
 - **Using co-occurrence criteria for establishing relationship**
 - **Examples: HiPub, CoPub, ArrowSmith**

Text mining tools for literature-based relation discovery biomedical text

NCBI Resources How To

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed "breast cancer" Search

Create RSS Create alert Advanced

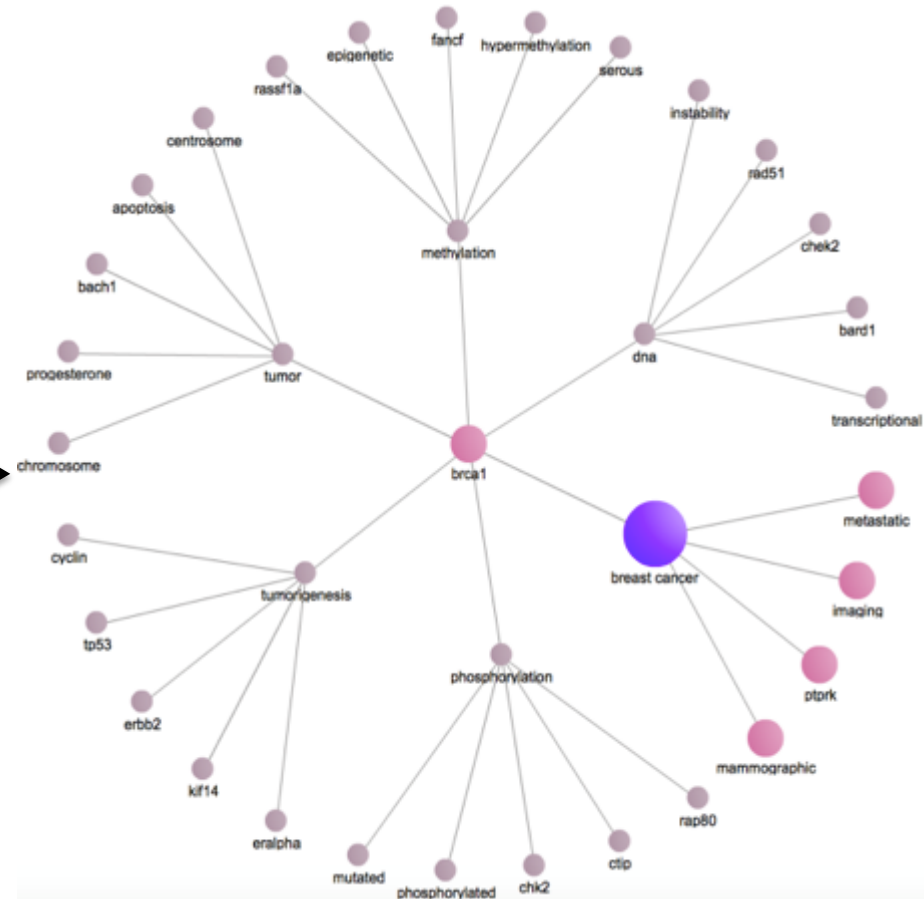
Article types Summary 20 per page Sort by Most Recent Send to

Results: 1 to 20 of 191685 << First < Prev Page 1 of 9585 Next > Last >>

Targeting ceramide metabolic pathway induces apoptosis in human breast cancer cell lines.

1. Vethakanraj HS, Babu TA, Sudarsanan GB, Duraisamy PK, Kumar SA. *Biochem Biophys Res Commun.* 2015 Jul 15. pii: S0006-291X(15)30278-3. doi: 10.1016/j.bbrc.2015.07.047. [Epub ahead of print]
PMID: 26188095
[Similar articles](#)

Text availability
Abstract
Free full text
Full text
PubMed
CrossMark



Association mining based on co-occurrence

HiPub (Lee 2016): <http://hipub.korea.ac.kr/>

The screenshot shows a web browser displaying a PubMed article page. The address bar shows the URL <https://www.ncbi.nlm.nih.gov/pubmed/24009732>. The page header includes the NCBI logo, "Resources", "How To", and a "Sign in to NCBI" link. The main content area features the article title: "The conformational control inhibitor of tyrosine kinases DCC-2036 is effective for imatinib-resistant cells expressing T674I FIP1L1-PDGFR α ." Below the title is the author information: "Shen Y¹, Shi X, Pan J." and a link to "Author information". The abstract text describes the study's findings on the effectiveness of DCC-2036 against imatinib-resistant cells. The right sidebar contains sections for "Full text links" (with PLOS and PMC logos), "Save items" (with an "Add to Favorites" button), "Similar articles" (listing related research), and "Cited by 5 PubMed Central articles". At the bottom, there is a section for "Images from this publication" showing several thumbnail images. A "HiPub" logo is visible in the bottom right corner of the browser window.

Format: Abstract -

PLoS One. 2013 Aug 29;8(8):e73059. doi: 10.1371/journal.pone.0073059. eCollection 2013.

The conformational control inhibitor of tyrosine kinases DCC-2036 is effective for imatinib-resistant cells expressing T674I FIP1L1-PDGFR α .

Shen Y¹, Shi X, Pan J.

[Author information](#)

Abstract

The cells expressing the T674I point mutant of FIP1-like-1-platelet-derived growth factor receptor alpha (FIP1L1-PDGFR α) in hyper eosinophils syndrome (HES) are resistant to imatinib and some second-generation tyrosine kinase inhibitors (TKIs). There is a desperate need to develop therapy to combat this acquired drug resistance. DCC-2036 has been synthesized as a third-generation TKI to combat especially the Bcr-Abl T315I mutant in chronic myeloid leukemia. This study evaluated the effect of DCC-2036 on FIP1L1-PDGFR α -positive cells, including the wild type (WT) and the T674I mutant. The in vitro effects of DCC-2036 on the PDGFR α signal pathways, proliferation, cell cycling and apoptosis of FIP1L1-PDGFR α -positive cells were investigated, and a nude mouse xenograft model was employed to assess the in vivo antitumor activity. We found that DCC-2036 decreased the phosphorylated levels of PDGFR α and its downstream targets without apparent effects on total protein levels. DCC-2036 inhibited proliferation, and induced apoptosis with MEK-dependent up-regulation of the pro-apoptotic protein Bim in FIP1L1-PDGFR α -positive cells. DCC-2036 also exhibited in vivo antineoplastic activity against cells with T674I FIP1L1-PDGFR α . In summary, FIP1L1-PDGFR α -positive cells are sensitive to DCC-2036 regardless of their sensitivity to imatinib. DCC-2036 may be a potential compound to treat imatinib-resistant HES.

PMID: 24009732 PMID: PMC3756952 DOI: 10.1371/journal.pone.0073059

[Indexed for MEDLINE] [Free PMC Article](#)

[f](#) [t](#) [i](#)

Images from this publication. See all images (7) Free text

[HiPub](#)

HiPub (Lee 2016):

The screenshot displays the HiPub Biomedical Entity Network interface. The browser address bar shows the URL <https://www.ncbi.nlm.nih.gov/pubmed/24009732>. The interface includes a navigation bar with options: "Biomedical Entity Network", "Add Similar Articles", "Search External DB", and "Enrichment Analysis".

On the left, a sidebar menu contains sections for "EXPORT", "LAYOUT", "EXPAND", "GENE", and "DISEASE". The "GENE" section is expanded, listing entities with "abstract" checkboxes:

- PDGFRA (platelet-derived growth factor receptor alpha)
- PDGFRA
- FIP1L1
- bcr abl (Bcr-Abl)
- MAP2K7 (MEK)
- Blim

The "DISEASE" section is also expanded, listing:

- HES
- chronic myeloid leukemias (chronic myeloid leukemia)

The main area features a network graph with nodes and edges. A legend at the top identifies the nodes and edges:

- Gene: Purple star icon
- Disease: Orange star icon
- Chemical: Green star icon
- Co-occurrence: Light blue line
- Known interaction: Grey line
- In Abstract (normal): Solid grey circle
- Not In Abstract (blurred): Blurred grey circle

The network graph shows connections between genes (Blim, FIP1L1, MAP2K7, PDGFRA, PDGFRA) and diseases (HES, chronic myeloid leukemias). A button at the bottom right reads "Show in BERE X (All visible nodes)".

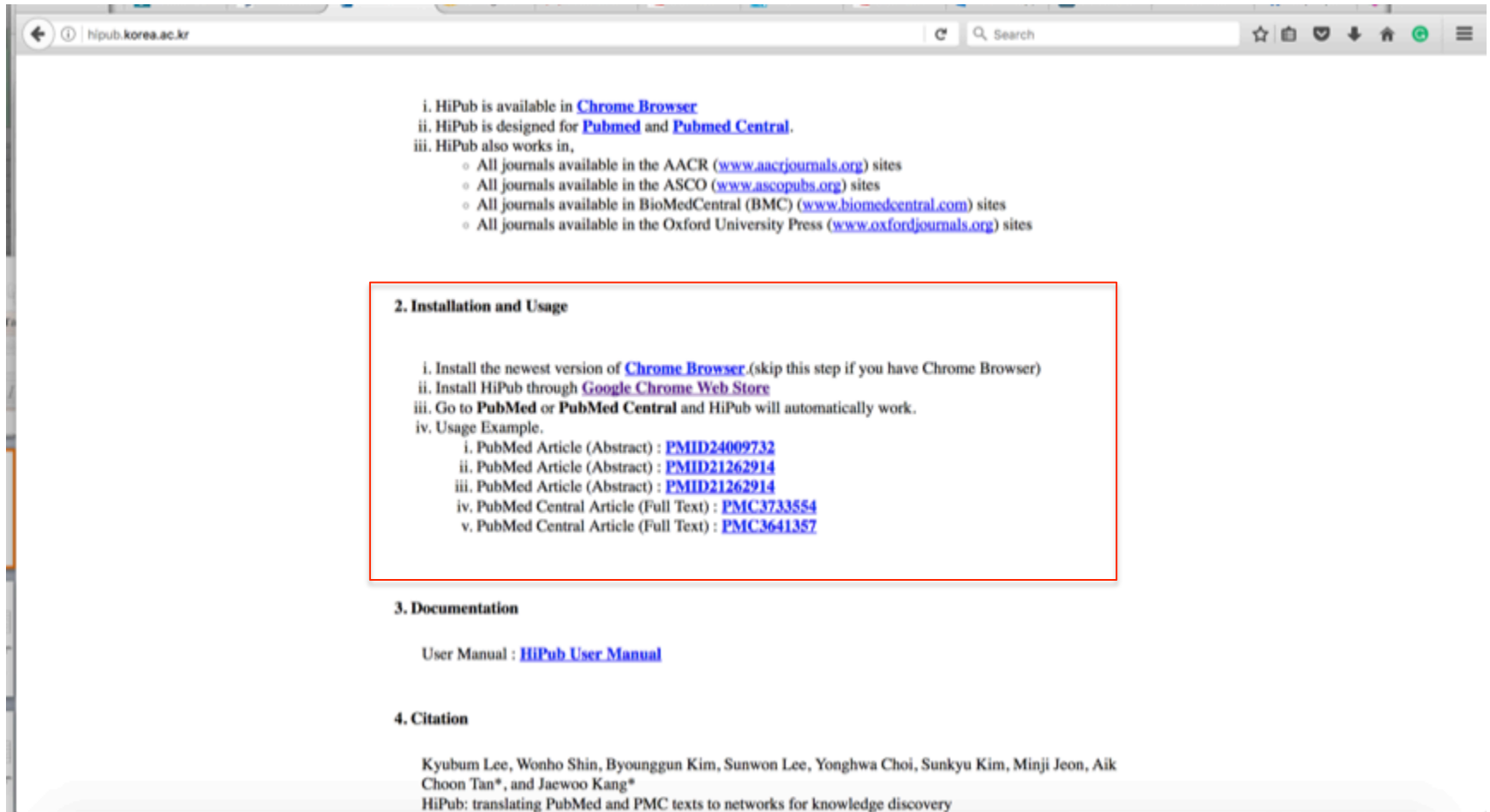
Summary

- Various tools and techniques are available for integrating and visualization multi –omics data
- Integrative –omics drives systems biology and could play a critical role in personalized medicine

Hands-on exercises

1. HiPub

Go to: <http://hipub.korea.ac.kr/>



The screenshot shows a web browser window with the address bar displaying "hipub.korea.ac.kr". The main content area contains several sections of text and a list of instructions. A red rectangular box highlights the "2. Installation and Usage" section. Below this box are sections for "3. Documentation" and "4. Citation".

i. HiPub is available in [Chrome Browser](#)
ii. HiPub is designed for [Pubmed](#) and [Pubmed Central](#).
iii. HiPub also works in,

- o All journals available in the AACR (www.aacrjournals.org) sites
- o All journals available in the ASCO (www.ascopubs.org) sites
- o All journals available in BioMedCentral (BMC) (www.biomedcentral.com) sites
- o All journals available in the Oxford University Press (www.oxfordjournals.org) sites

2. Installation and Usage

i. Install the newest version of [Chrome Browser](#).(skip this step if you have Chrome Browser)
ii. Install HiPub through [Google Chrome Web Store](#)
iii. Go to **PubMed** or **PubMed Central** and HiPub will automatically work.
iv. Usage Example,

- i. PubMed Article (Abstract) : [PMID24009732](#)
- ii. PubMed Article (Abstract) : [PMID21262914](#)
- iii. PubMed Article (Abstract) : [PMID21262914](#)
- iv. PubMed Central Article (Full Text) : [PMC3733554](#)
- v. PubMed Central Article (Full Text) : [PMC3641357](#)

3. Documentation

User Manual : [HiPub User Manual](#)

4. Citation

Kyubum Lee, Wonho Shin, Byounggun Kim, Sunwon Lee, Yonghwa Choi, Sunkyu Kim, Minji Jeon, Aik Choon Tan*, and Jaewoo Kang*
HiPub: translating PubMed and PMC texts to networks for knowledge discovery

Steps for installing HiPub

- Install Chrome browser:
<https://www.google.com/chrome/browser/desktop/>
- Install the HiPub plugin:
<https://chrome.google.com/webstore/detail/hipub/jlbmiklemigmbmcodhjgdpooldjcjam>
- Test installation:
<https://www.ncbi.nlm.nih.gov/pubmed/24009732>
 - You should see an annotated title and abstract when you go to the PubMed page above as shown on the next slide

Format: Abstract

Send to

PLoS One, 2013 Aug 29;8(8):e73059. doi: 10.1371/journal.pone.0073059. eCollection 2013.

The conformational control inhibitor of tyrosine kinases DCC-2036 is effective for imatinib-resistant cells expressing T674I FIP1L1-PDGFR α .

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The cells expressing the T674I point mutant of FIP1-like-1-platelet-derived growth factor receptor alpha (FIP1L1-PDGFR α) in hypereosinophilic syndrome (HES) are resistant to imatinib and some second-generation tyrosine kinase inhibitors (TKIs). There is a desperate need to develop therapy to combat this acquired drug resistance. DCC-2036 has been synthesized as a third-generation TKI to combat especially the Bcr-Abl T315I mutant in chronic myeloid leukemia. This study evaluated the effect of DCC-2036 on FIP1L1-PDGFR α -positive cells, including the wild type (WT) and the T674I mutant. The in vitro effects of DCC-2036 on the PDGFR α signal pathways, proliferation, cell cycling and apoptosis of FIP1L1-PDGFR α -positive cells were investigated, and a nude mouse xenograft model was employed to assess the in vivo antitumor activity. We found that DCC-2036 decreased the phosphorylated levels of PDGFR α and its downstream targets without apparent effects on total protein levels. DCC-2036 inhibited proliferation, and induced apoptosis with MEK-dependent up-regulation of the pro-apoptotic protein Bim in FIP1L1-PDGFR α -positive cells. DCC-2036 also exhibited in vivo antineoplastic activity against cells with T674I FIP1L1-PDGFR α . In summary, FIP1L1-PDGFR α -positive cells are sensitive to DCC-2036 regardless of their sensitivity to imatinib. DCC-2036 may be a potential compound to treat imatinib-resistant HES.

PMID: 24009732 PMCID: PMC3756952 DOI: 10.1371/journal.pone.0073059

[Indexed for MEDLINE] [Free PMC Article](#)

Full text links



Save items

Add to Favorites

Similar articles

Antitumor activity of S116836, a novel tyrosine kinase inhibitor, against imatinib-resistant chronic myeloid leukemia cells [Oncotarget. 2014]

Cyclin-dependent kinase 7/9 inhibitor SNS-032 abrogates FIP1-like-1 ple [Clin Cancer Res. 2012]

Ponatinib efficiently kills imatinib-resistant chronic eosinophilic leukemia cells [Mol Cancer. 2014]

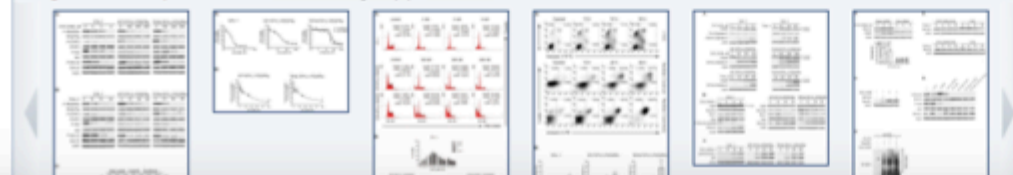
Review FIP1L1-PDGFR α positive chronic eosinophilic [Zhonghua Xue Ye Xue Za Zhi. 2013]

Review The FIP1L1-PDGFR α fusion tyrosine kinase in hypereosinophilic [Blood. 2004]

See reviews...

See all...

Images from this publication. See all images (7) [Free text](#)



Cited by 5 PubMed Central articles

Verteporfin induces apoptosis and eliminates cancer stem-like cells in [Am J Cancer Res. 2016]

Review The Role of New Tyrosine Kinase Inhibitors in Chronic Myeloid Leu [C]

Review Platelet-derived growth factor

2. xMWAS: Web version

- URL: <https://kuppal.shinyapps.io/xmwas/>
- Input files:
https://github.com/kuppal2/xMWAS/upload/master/example_manual_tutorial
 - exh1n1_transcriptome.txt
 - exh1n1_metabolome.txt
 - exh1n1_cytokine.txt
 - exh1n1_classlabels.txt

xMWAS - a data-driven integration and network analysis tool (v0.54)

Input Files

[Choose Files \(see help and support\)](#)

Parameter Settings

1. Data preparation and filtering
2. Integration and association analysis
3. Centrality analysis
4. Graphical options

Select input file for dataset A (.csv' or '.txt', 100MB limit)

Browse... exh1n1_metabolome.txt

Select input file for dataset B (.csv' or '.txt', 100MB limit)

Browse... exh1n1_transcriptome.txt

Select input file for dataset C (.csv' or '.txt', 100MB limit)

Browse... exh1n1_cytokine.txt

Add more datasets: + -

Name for dataset A:

metabolome

Name for dataset B:

transcriptome

Name for dataset C:

cytokine

Choose a class labels file (.csv' or '.txt):

Browse... exh1n1_classlabels.txt

Output folder name:

Default: xwasresults

Are there repeated measurements?

- True - Paired (repeated measures)
- False - Unpaired (case-control & multiclass)

Compare classes?

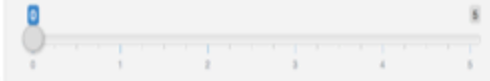
- True
- False

Use example data?

- True
- False

Output

Slide to go to next figure:



xMWAS - a data-driven integration and network analysis tool (v0.54)

[Introduction](#) [Analysis](#) [Help and Support](#)

Input Files

[Choose Files \(see help and support\)](#)

Parameter Settings

1. Data preparation and filtering

2. Integration and association analysis

3. Centrality analysis

4. Graphical options

Relative Standard Deviation (RSD) Threshold

(rows):

1

Maximum number of datasetA variables to select based on RSD:

1000

Maximum number of datasetB variables to select based on RSD:

1000

Maximum number of datasetC variables to select based on RSD:

1000

Minimum ratio of number of samples with a non-missing value to the total number of samples for a variable (rows):

0.7

How are the missing values represented in the data?:

0

xMWAS - a data-driven integration and network analysis tool (v0.54)

Input Files

[Choose Files \(see help and support\)](#)

Parameter Settings

1. Data preparation and filtering
- 2. Integration and association analysis**
3. Centrality analysis
4. Graphical options

Pairwise integrative analysis

Choose a data integration method:

Choose PLS mode:

Number of components to use in PLS model:

Find optimal number of PLS components? True False

Maximum number of datasetA variables to select in sPLS:

Maximum number of datasetB variables to select in sPLS:

Maximum number of datasetC variables to select in sPLS:

Association analysis

Correlation Threshold:

P-value Threshold For Student's T-test:

Start processing Download results

Output



xMWAS - a data-driven integration and network analysis tool (v0.54)

[Introduction](#) [Analysis](#) [Help and Support](#)

Input Files

[Choose Files](#) (see help and support)

Parameter Settings

1. Data preparation and filtering
2. Integration and association analysis
3. Centrality analysis
4. Graphical options

Start processing

Output

Slide to go to next figure:



Size of the Labels:

0.25

Size of the Nodes:

7

Seed for Random Number Generator:

100

Maximum number of associations to include in the network
(any numeric value >0 or -1 to use all):

-1

Use dataset A as reference?

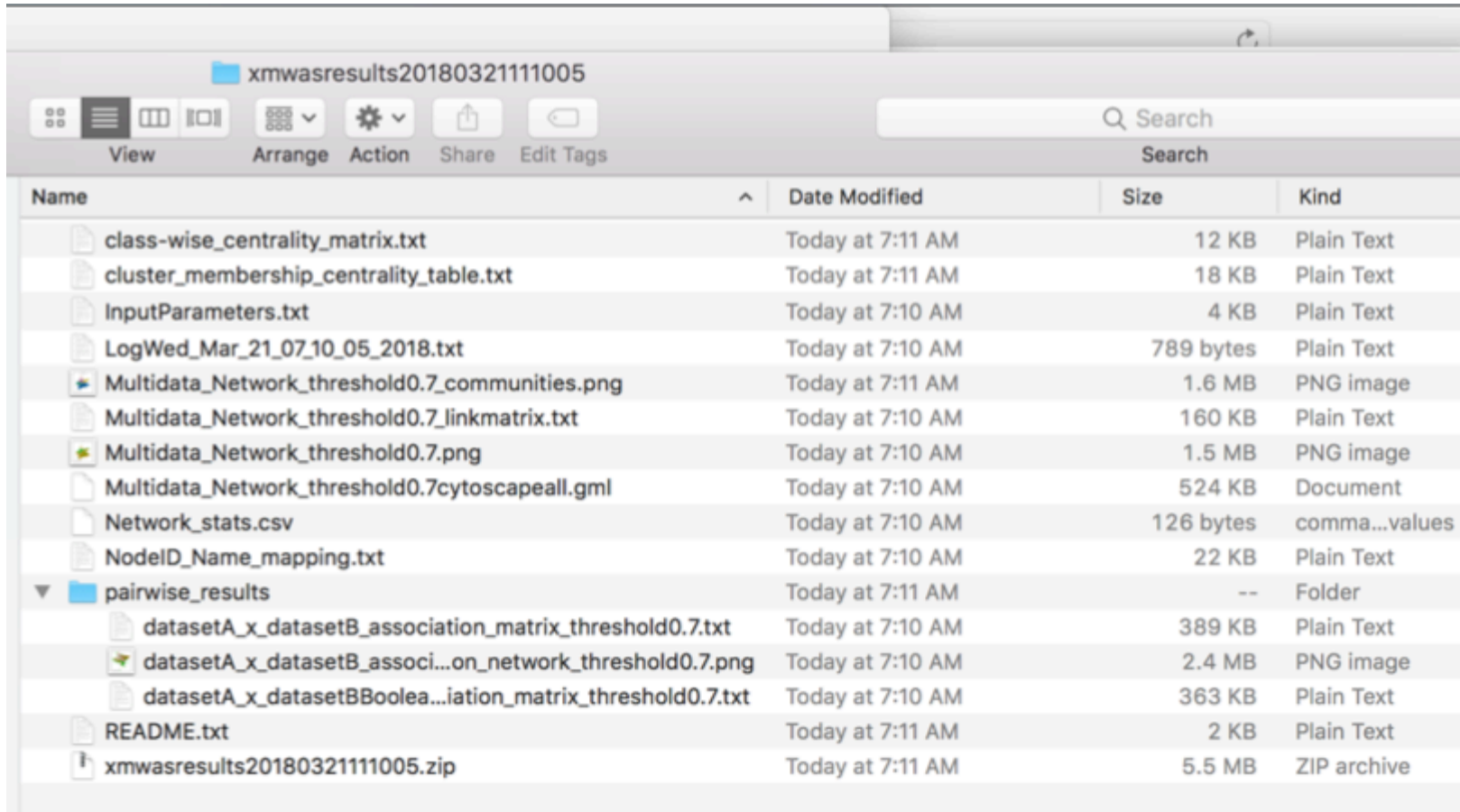
True False

Starting processing now. Your results will be available for download shortly. The processing time depends on the number of variables. Please use the data filtering options to reduce the run time. ✕

Results



Download results



The screenshot shows a file manager window with the following details:

- Folder name: xmwasresults20180321111005
- Search bar: Search
- Toolbar: View, Arrange, Action, Share, Edit Tags
- Table columns: Name, Date Modified, Size, Kind

Name	Date Modified	Size	Kind
class-wise_centrality_matrix.txt	Today at 7:11 AM	12 KB	Plain Text
cluster_membership_centrality_table.txt	Today at 7:11 AM	18 KB	Plain Text
InputParameters.txt	Today at 7:10 AM	4 KB	Plain Text
LogWed_Mar_21_07_10_05_2018.txt	Today at 7:10 AM	789 bytes	Plain Text
Multidata_Network_threshold0.7_communities.png	Today at 7:11 AM	1.6 MB	PNG image
Multidata_Network_threshold0.7_linkmatrix.txt	Today at 7:10 AM	160 KB	Plain Text
Multidata_Network_threshold0.7.png	Today at 7:10 AM	1.5 MB	PNG image
Multidata_Network_threshold0.7_cytoscapeall.gml	Today at 7:10 AM	524 KB	Document
Network_stats.csv	Today at 7:10 AM	126 bytes	comma...values
NodeID_Name_mapping.txt	Today at 7:10 AM	22 KB	Plain Text
pairwise_results	Today at 7:11 AM	--	Folder
datasetA_x_datasetB_association_matrix_threshold0.7.txt	Today at 7:10 AM	389 KB	Plain Text
datasetA_x_datasetB_associ...on_network_threshold0.7.png	Today at 7:10 AM	2.4 MB	PNG image
datasetA_x_datasetBBoolea...iation_matrix_threshold0.7.txt	Today at 7:10 AM	363 KB	Plain Text
README.txt	Today at 7:11 AM	2 KB	Plain Text
xmwasresults20180321111005.zip	Today at 7:11 AM	5.5 MB	ZIP archive

3. xMWAS R package installation instructions for Windows

- Install R: <https://cran.cnr.berkeley.edu/>
- Install R dependencies
 - R command for installation:

```
source("https://bioconductor.org/biocLite.R");  
biocLite(c("GO.db","graph","RBGL","impute","preprocessCore"),dependencies=TRUE);  
install.packages(c("devtools","WGCNA","mixOmics","snow","igraph","plyr","plsgenomics")  
,dependencies=TRUE,type="binary",repos="http://cran.r-project.org")
```
- Install R package xMWAS
 - R command for installation:

```
library(devtools); install_github("kuppal2/xMWAS")
```
- Test installation:
 - R command for loading the package:

```
library(xMWAS)
```

xMWAS R package installation instructions for Mac OS X

- Install Xquartz: <https://www.xquartz.org/>
- Install R: <https://cran.cnr.berkeley.edu/>
- Install R dependencies
 - R command for installation:

```
source("https://bioconductor.org/biocLite.R");  
biocLite(c("GO.db","graph","RBGL","impute","preprocessCore"),dependencies=TRUE);  
install.packages(c("devtools","WGCNA","mixOmics","snow","igraph","plyr","plsgenomics")  
,dependencies=TRUE,type="source", repos="http://cran.r-project.org")
```
- Install R package xMWAS
 - R command for installation:

```
library(devtools); install_github("kuppal2/xMWAS")
```
- Test installation:
 - R command for loading the package:

```
library(xMWAS)
```

R script for xMWAS using the example dataset

(URL: https://github.com/kuppal2/xMWAS/blob/master/example_manual_tutorial/example_xmwas_runscript_v0.5.R)

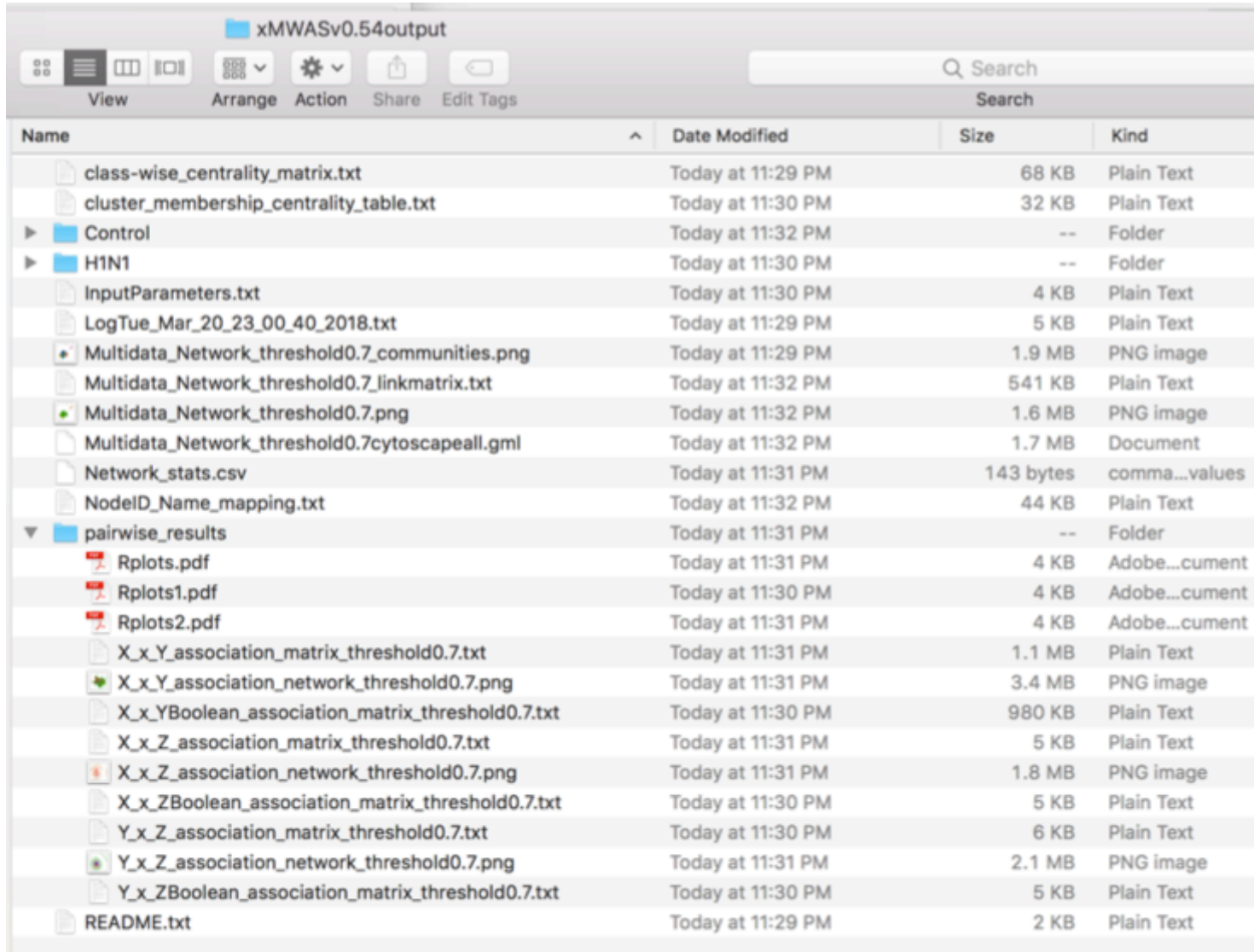
```
#load package
library(xMWAS)

#example dataset that includes metabolome, transcriptome, and cytokine data from the H1N1 mice study (Chandler 2016)
data(exh1n1)
data(classlabels_casecontrol) #example classlabels file for case vs control design
data(classlabels_repeatmeasures) #example classlabels file for repeat measures design
xMat<-exh1n1$metabolome
yMat<-exh1n1$transcriptome
zMat<-exh1n1$cytokine
classlabels<-exh1n1$classlabels

output<-"/home/kuppal2/xMWASv0.54output/"

#call the run_xmwas() function:
xmwas_res<-run_xmwas(Xome_data=xMat,Yome_data=yMat,Zome_data=zMat,Wome_data=NA,outloc=output,
classlabels=classlabels,class_fname=NA,xmwasmethod="splS",plsmode="canonical",max_xvar=1000,max_yvar=1000,
max_zvar=1000,max_wvar=1000,rsd.filt.thresh=1,corthresh=0.7,keepX=100,keepY=100,keepZ=100,keepW=100,
pairedanalysis=FALSE,optselect=TRUE,rawPthresh=0.05,numcomps=10,net_edge_colors=c("blue","red"),
net_node_colors=c("orange","green","cyan","pink"),Xname="X",Yname="Y",Zname="Z",Wname="W",
net_node_shape=c("rectangle","circle","triangle","star"),all.missing.thresh=0.7,missing.val=0,
seednum=100,label.cex=0.2,vertex.size=6,graphclustering=TRUE,interactive=FALSE,max_connections=100000,
centrality_method="eigenvector",use.X.reference=FALSE,removeRda=TRUE,compare.classes=TRUE,class.comparison.allvar=TRUE)
suppressWarnings(try(sink(file=NULL),silent=TRUE))
```

xMWAS output



Name	Date Modified	Size	Kind
class-wise_centrality_matrix.txt	Today at 11:29 PM	68 KB	Plain Text
cluster_membership_centrality_table.txt	Today at 11:30 PM	32 KB	Plain Text
Control	Today at 11:32 PM	--	Folder
H1N1	Today at 11:30 PM	--	Folder
InputParameters.txt	Today at 11:30 PM	4 KB	Plain Text
LogTue_Mar_20_23_00_40_2018.txt	Today at 11:29 PM	5 KB	Plain Text
Multidata_Network_threshold0.7_communities.png	Today at 11:29 PM	1.9 MB	PNG image
Multidata_Network_threshold0.7_linkmatrix.txt	Today at 11:32 PM	541 KB	Plain Text
Multidata_Network_threshold0.7.png	Today at 11:32 PM	1.6 MB	PNG image
Multidata_Network_threshold0.7_cytoscapeall.gml	Today at 11:32 PM	1.7 MB	Document
Network_stats.csv	Today at 11:31 PM	143 bytes	comma...values
NodeID_Name_mapping.txt	Today at 11:32 PM	44 KB	Plain Text
pairwise_results	Today at 11:31 PM	--	Folder
Rplots.pdf	Today at 11:31 PM	4 KB	Adobe...cument
Rplots1.pdf	Today at 11:30 PM	4 KB	Adobe...cument
Rplots2.pdf	Today at 11:31 PM	4 KB	Adobe...cument
X_x_Y_association_matrix_threshold0.7.txt	Today at 11:31 PM	1.1 MB	Plain Text
X_x_Y_association_network_threshold0.7.png	Today at 11:31 PM	3.4 MB	PNG image
X_x_YBoolean_association_matrix_threshold0.7.txt	Today at 11:30 PM	980 KB	Plain Text
X_x_Z_association_matrix_threshold0.7.txt	Today at 11:31 PM	5 KB	Plain Text
X_x_Z_association_network_threshold0.7.png	Today at 11:31 PM	1.8 MB	PNG image
X_x_ZBoolean_association_matrix_threshold0.7.txt	Today at 11:30 PM	5 KB	Plain Text
Y_x_Z_association_matrix_threshold0.7.txt	Today at 11:30 PM	6 KB	Plain Text
Y_x_Z_association_network_threshold0.7.png	Today at 11:31 PM	2.1 MB	PNG image
Y_x_ZBoolean_association_matrix_threshold0.7.txt	Today at 11:30 PM	5 KB	Plain Text
README.txt	Today at 11:29 PM	2 KB	Plain Text

Input Parameters

```
InputParameters.txt
[1] "#####xMWAS v0.54 Parameters#####"
[1] "xmwasmethod: spls"
[1] "plsmode: canonical"
[1] "max_xvar: 1000"
[1] "max_yvar: 1000"
[1] "max_zvar: 1000"
[1] "max_wvar: 5000"
[1] "rsd.filt.thresh: 1"
[1] "all.missing.thresh: 0.7"
[1] "missing.val: 0"
[1] "corthresh: 0.7"
[1] "keepX: 100"
[1] "keepY: 100"
[1] "keepZ: 100"
[1] "keepW: 100"
[1] "pairedanalysis: FALSE"
[1] "optselect: TRUE"
[1] "rawPthresh: 0.05"
[1] "numcomps: 10"
[1] "seednum: 100"
[1] "graphclustering: TRUE"
[1] "max_connections: 1e+05"
[1] "centrality_method: eigenvector"
[1] "use.X.reference: FALSE"
[1] "compare.classes: TRUE"
[1] "class.comparison.allvar: TRUE"
[1] "#####"
[1] "#####Loaded packages in the current session#####"
R version 3.4.0 (2017-04-21)
Platform: x86_64-pc-linux-gnu (64-bit)
Running under: Ubuntu 14.04.5 LTS

Matrix products: default
BLAS: /usr/lib/libblas/libblas.so.3.0
LAPACK: /usr/lib/lapack/liblapack.so.3.0

locale:
 [1] LC_CTYPE=en_US.UTF-8      LC_NUMERIC=C
 [3] LC_TIME=en_US.UTF-8      LC_COLLATE=en_US.UTF-8
 [5] LC_MONETARY=en_US.UTF-8  LC_MESSAGES=en_US.UTF-8
 [7] LC_PAPER=en_US.UTF-8     LC_NAME=C
 [9] LC_ADDRESS=C             LC_TELEPHONE=C
[11] LC_MEASUREMENT=en_US.UTF-8 LC_IDENTIFICATION=C
```


Description of output: Readme.txt

README.txt

"Description of files"

"1: X labels correspond to xome_fname data, Y labels correspond to yome_fname data, Z labels correspond to zome_fname data, W labels correspond to wome_fname data"

"2: Pairwise integrative analysis results are under pairwise_results. The files corresponding to each pairwise comparison (X<->Y, X<->Z, Y<-Z,..) are: XYassociation_matrix_corthresh0.9.txt (correlation matrix with mapping between node labels and original variable names), XYassociation_networkthresholdX.pdf that includes the pairwise network plots, XYBoolean association_matrix_corthreshX.txt (same as correlation matrix but correlations meeting the threshold are represented 1, and 0 otherwise)"

"3: Multiome_Network_corthreshx.pdf: includes multiome network plot using all significantly associated variables."

"4: Multiome_Network_corthreshx_communities.pdf: includes multiome network plot with the communities identified using the multilevel community detection algorithm. Members of each community are assigned colors based on community/module/cluster membership (1: orange; 2: light blue; 3: dark green, and so on)."

"5: MultiOme_Network_corthreshx_cytoscape.gml: GML file for all significantly associated variables that can be uploaded to Cytoscape"

"6: The cluster_membership_centrality_mapped.txt file includes community detection results using the multilevel community detection algorithm and the centrality measures."

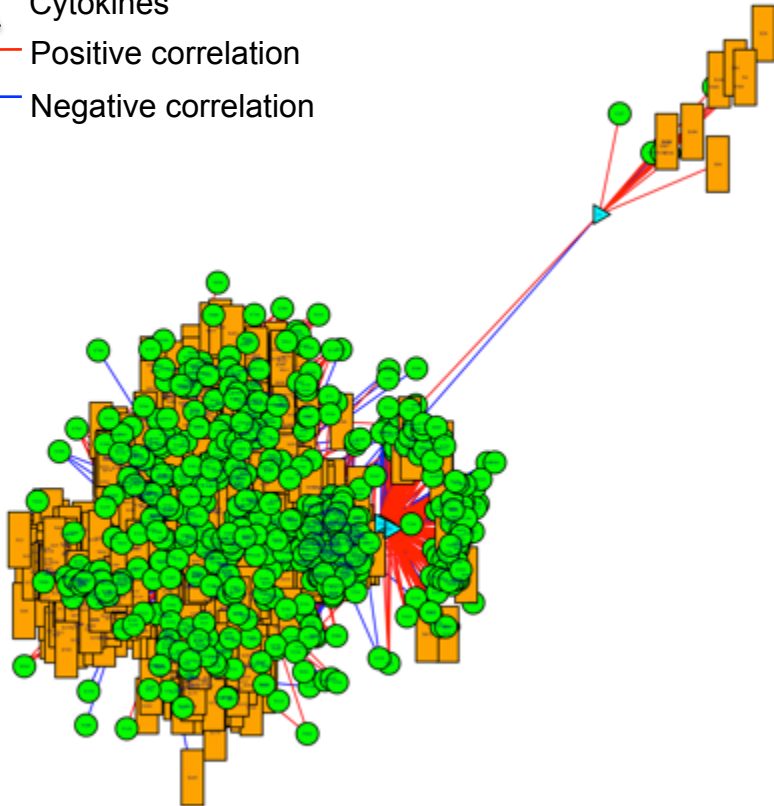
"7: The matrix_centrality.txt file includes the centrality measures across different conditions for nodes that meet the association criteria and include in the association networks."

"8: If the classlabels are provided, network analysis is performed for samples from each class. The results are written in individual subfolders."

Network graphs

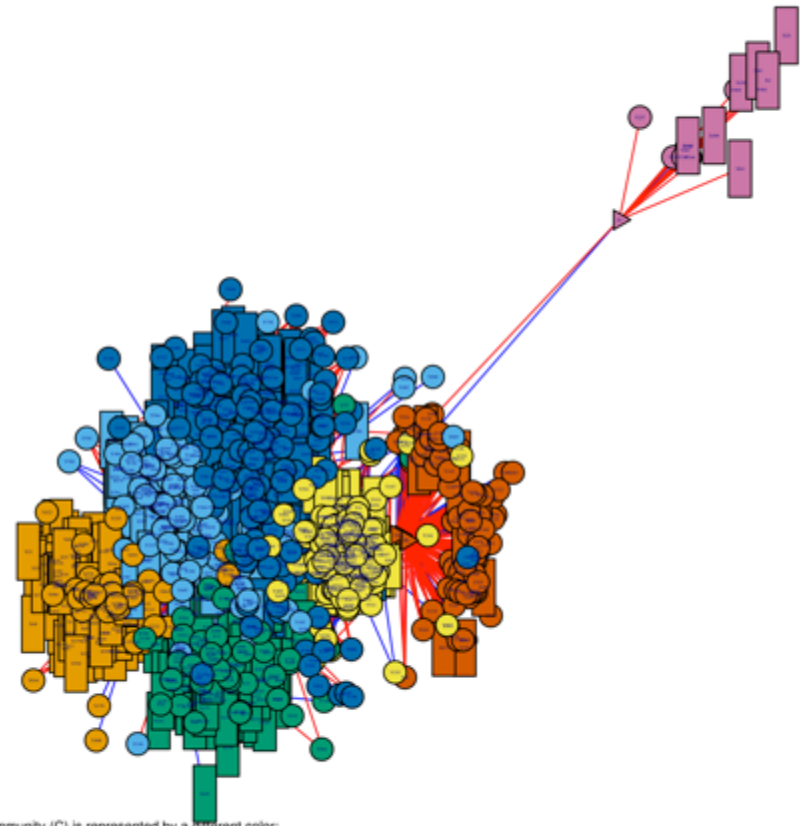
A. Colored by data type

- Metabolites
 - Genes
 - Cytokines
 - Positive correlation
 - Negative correlation
- Using all samples



B. Colored by community membership

- (Edges) Red: +ve correlation; Blue: -ve correlation
(Nodes) Rectangle: X; Circle: Y; Triangle: Z
Using all samples



- Each community (C) is represented by a different color:
C1; C2; C3; C4; C5; C6; C7;

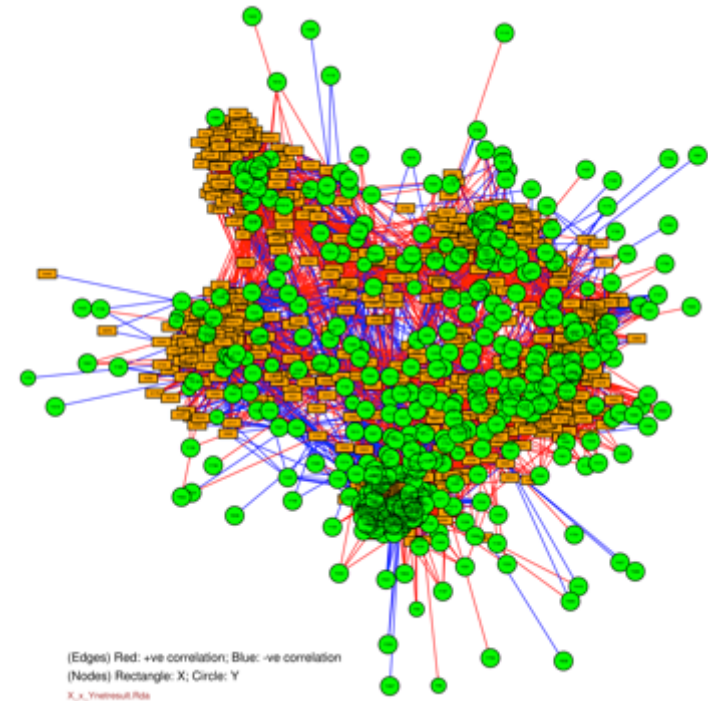
(Edges) Red: +ve correlation; Blue: -ve correlation
(Nodes) Rectangle: X; Circle: Y; Triangle: Z

Pairwise results – $X \leftrightarrow Y$, $X \leftrightarrow Z$, $Y \leftrightarrow Z$

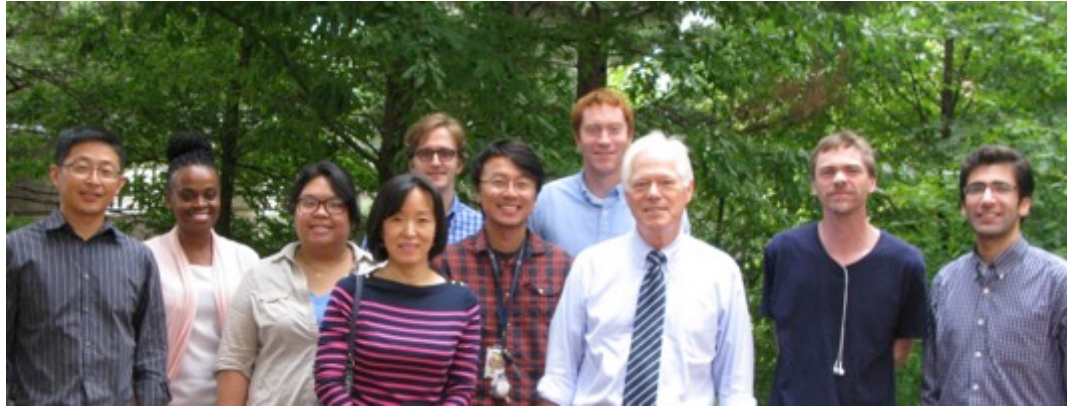
xMWASv0.54output

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Name	Date Modified	Size	Kind
class_wise_centrality_matrix.txt	Today at 11:29 PM	68 KB	Plain Text
cluster_membership_centrality_table.txt	Today at 11:30 PM	32 KB	Plain Text
Control	Today at 11:32 PM	--	Folder
H1N1	Today at 11:30 PM	--	Folder
InputParameters.txt	Today at 11:30 PM	4 KB	Plain Text
LogTue_Mar_20_23_00_40_2018.txt	Today at 11:29 PM	5 KB	Plain Text
Multidata_Network_threshold0.7_communities.png	Today at 11:29 PM	1.9 MB	PNG image
Multidata_Network_threshold0.7_linkmatrix.txt	Today at 11:32 PM	541 KB	Plain Text
Multidata_Network_threshold0.7.png	Today at 11:32 PM	1.6 MB	PNG image
Multidata_Network_threshold0.7_cytoscapeall.gml	Today at 11:32 PM	1.7 MB	Document
Network_stats.csv	Today at 11:31 PM	143 bytes	comma...values
NodeID_Name_mapping.txt	Today at 11:32 PM	44 KB	Plain Text
pairwise_results	Today at 11:31 PM	--	Folder
Rplots.pdf	Today at 11:31 PM	4 KB	Adobe...cument
Rplots1.pdf	Today at 11:30 PM	4 KB	Adobe...cument
Rplots2.pdf	Today at 11:31 PM	4 KB	Adobe...cument
X_x_Y_association_matrix_threshold0.7.txt	Today at 11:31 PM	1.1 MB	Plain Text
X_x_Y_association_network_threshold0.7.png	Today at 11:31 PM	3.4 MB	PNG image
X_x_Y_Boolean_association_matrix_threshold0.7.txt	Today at 11:30 PM	980 KB	Plain Text
X_x_Z_association_matrix_threshold0.7.txt	Today at 11:31 PM	5 KB	Plain Text
X_x_Z_association_network_threshold0.7.png	Today at 11:31 PM	1.8 MB	PNG image
X_x_Z_Boolean_association_matrix_threshold0.7.txt	Today at 11:30 PM	5 KB	Plain Text
Y_x_Z_association_matrix_threshold0.7.txt	Today at 11:30 PM	6 KB	Plain Text
Y_x_Z_association_network_threshold0.7.png	Today at 11:31 PM	2.1 MB	PNG image
Y_x_Z_Boolean_association_matrix_threshold0.7.txt	Today at 11:30 PM	5 KB	Plain Text
README.txt	Today at 11:29 PM	2 KB	Plain Text



Clinical Biomarkers Laboratory



Dean Jones, Young-Mi Go, Shuzaho Li, Karan Uppal, Douglas Walker, Josh Chandler, Sophia Banton, Ken Liu, Vilinh Tran, Michael Orr, Bill Liang (not shown)

Lab website: <http://clinicalmetabolomics.org/>

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Questions?