

Computational Approaches for Big Data Analytics & Integration

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Outline

- Overview of big omics data
- Approaches in big data analytics
- Approaches in big data integration
- Web-based tools for common omics data analysis & integration

The Promises of Big Omics Data

Comprehensive molecular profiles

- Global systems overview
- Less biased
- Robust to noise?

What we can obtain from this type of data?

- Patterns & trends
 - Group behaviors
 - Collective functions
 - Hypothesis generation
- Mechanisms & knowledge
 - Mechanistic understanding
 - Pathways
 - Networks

Reality: the “Happy” Middle

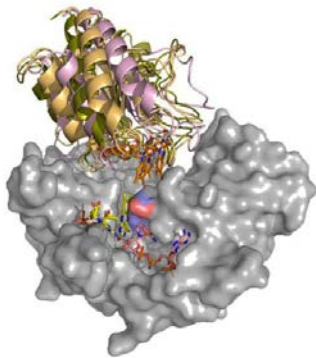
Reductionism

Knowledge of everything

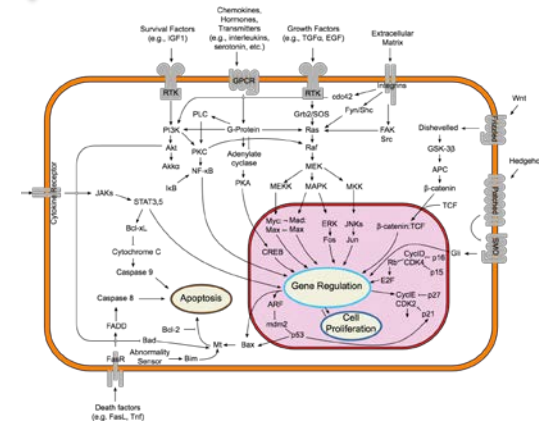
Individual Molecule

Big Data Analytics

Systems Biology



- Optimal simplicity
- Empowering
- Achievable

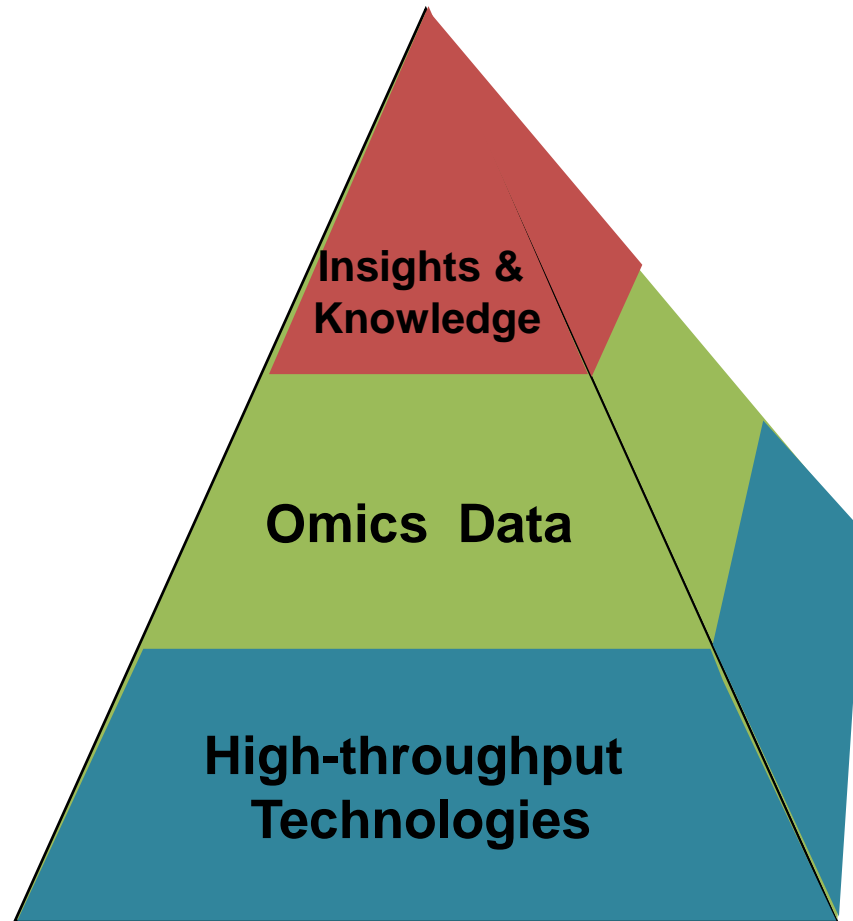


Mechanism

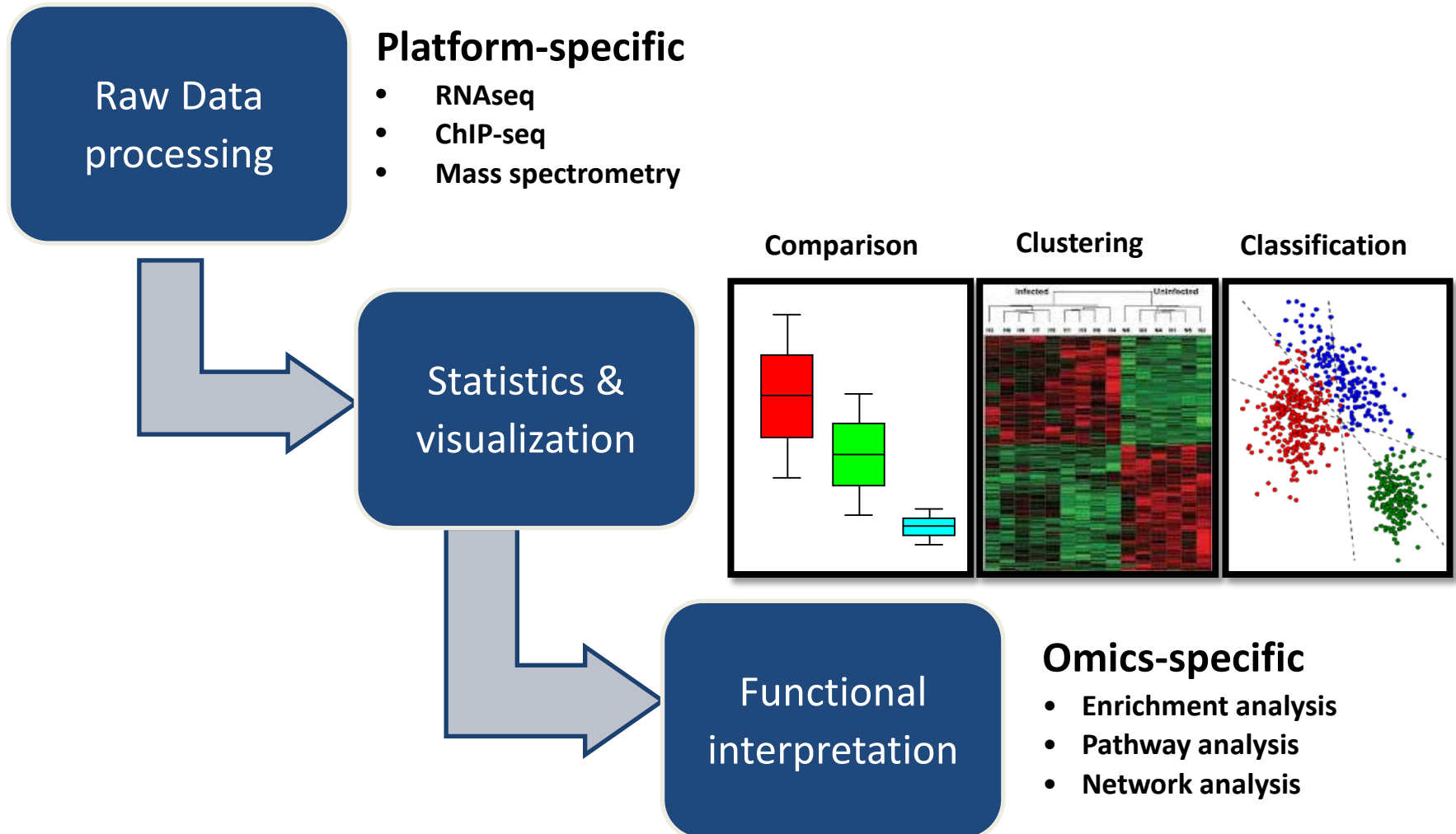
Patterns & Trends

Knowledge

The Big Omics Data



Workflow of Omics Data Analytics



Two distinct big data challenges

- **Size challenge** (raw data)
 - Raw reads, spectra, images
 - Large (100s MB ~ GB)
 - Large storage and computing resources
- **Complexity challenge** (feature table)
 - Feature table (abundance, intensities)
 - Small (100s KB ~ MB)
 - High-dimensional, missing values
 - Data integration usually starts here



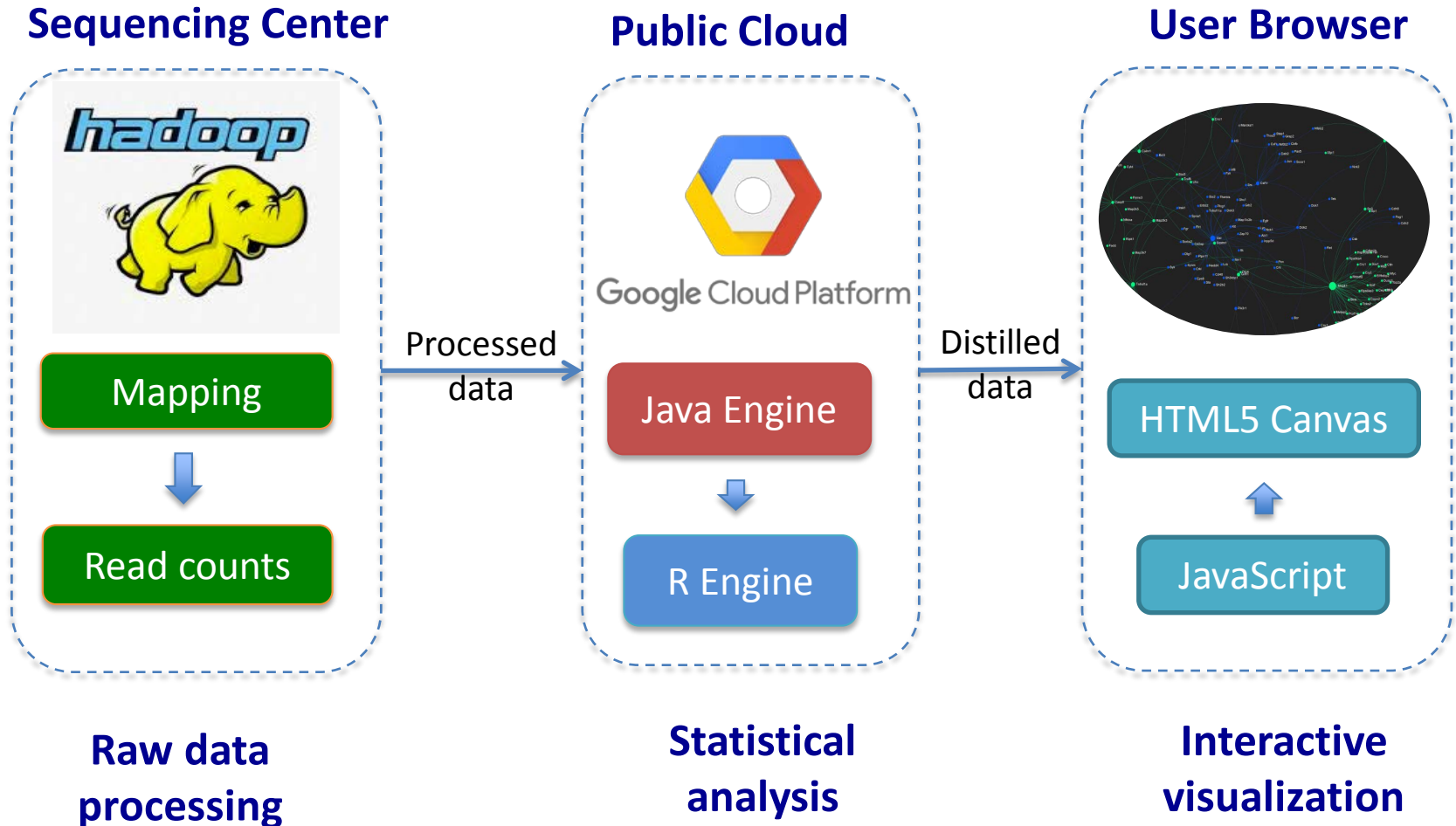
➔ **Divide and conquer**

Dealing with big omics data

- **Bringing analysis to (raw) data**
 - Too big to transfer around
 - Done locally at the same place generating the data (i.e. omics centers)
 - Following standardized operation protocols (SOP)
- **Bringing (processed) data to analysis**
 - Usually done by individual researchers
 - Can be easily uploaded to tools deployed on cloud
 - Highly domain-specific and individualized



Local + Cloud + Browser



Big Data Analytics

Big Data Analytics

Three Keys Factors

1. Data distillation

- Not all data are useful

2. Coupling statistics with visualization

- Support for user exploration

3. Connecting with prior knowledge

- Validation previous findings & identification of novelties

Data distillation

Raw data → processed data → informative data

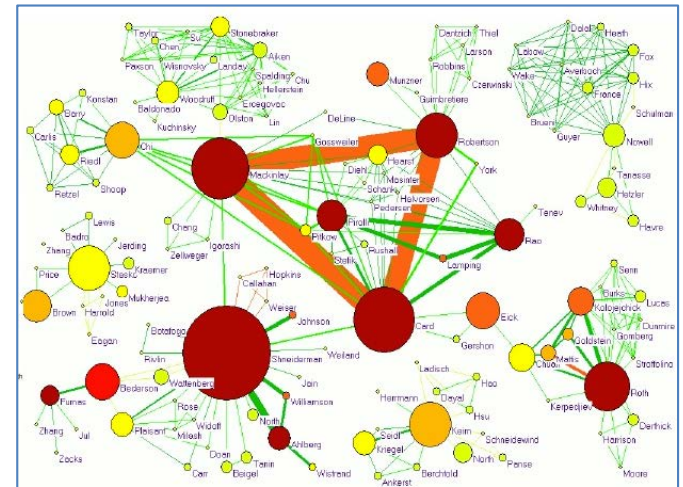
- Only a small portion of molecules will respond to perturbations.
- The majority will still maintain their “normal” states (homeostasis)



Statistics + Visualization

Bringing data closer to domain experts

- Big omics data is complex and heterogeneous
- Statistics often fail to capture the data characteristics
- Disruptive discovery are often driven by the hunches and leaps of faith of the researcher by interacting with the data



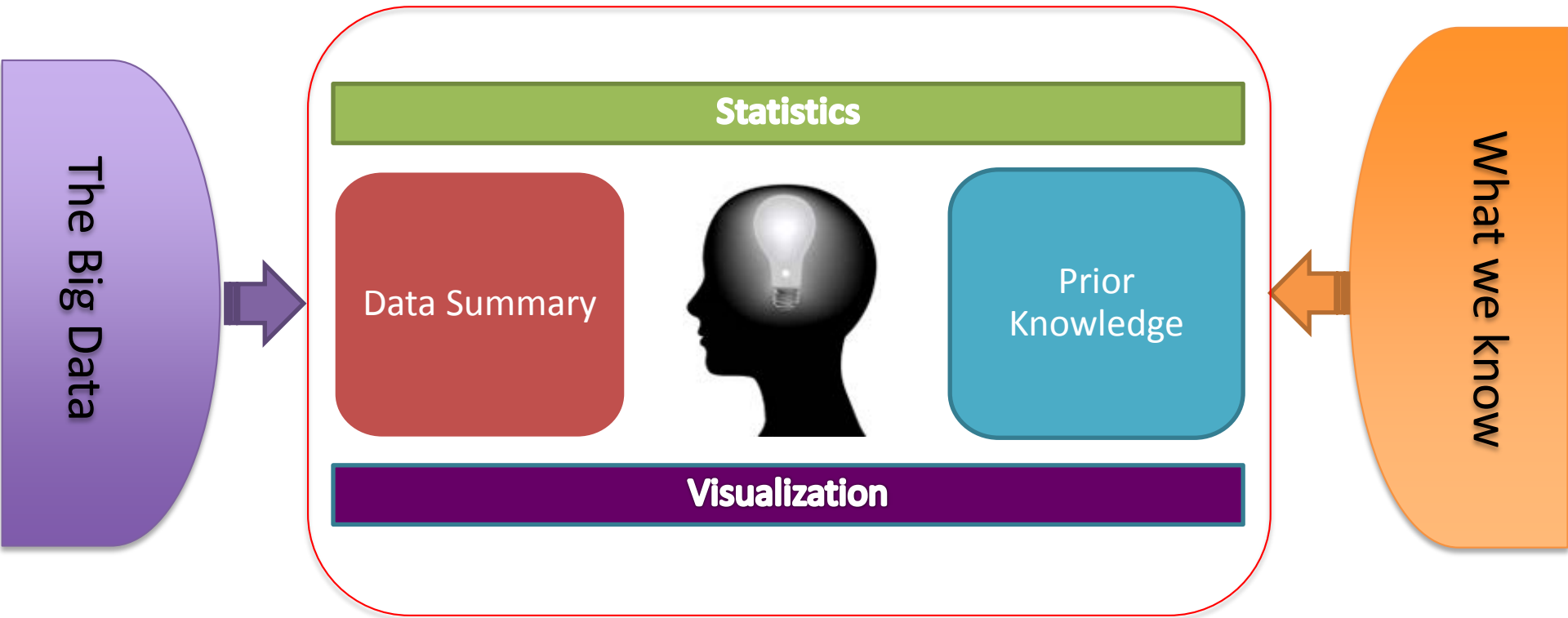
Statistics + Domain Knowledge

Connecting new data with prior knowledge

- Encode knowledge into computable forms
 - Gene sets, pathways, networks
- Evaluating new data within the context of our knowledge
 - Enrichment analysis
 - Pathway analysis
 - Network analysis

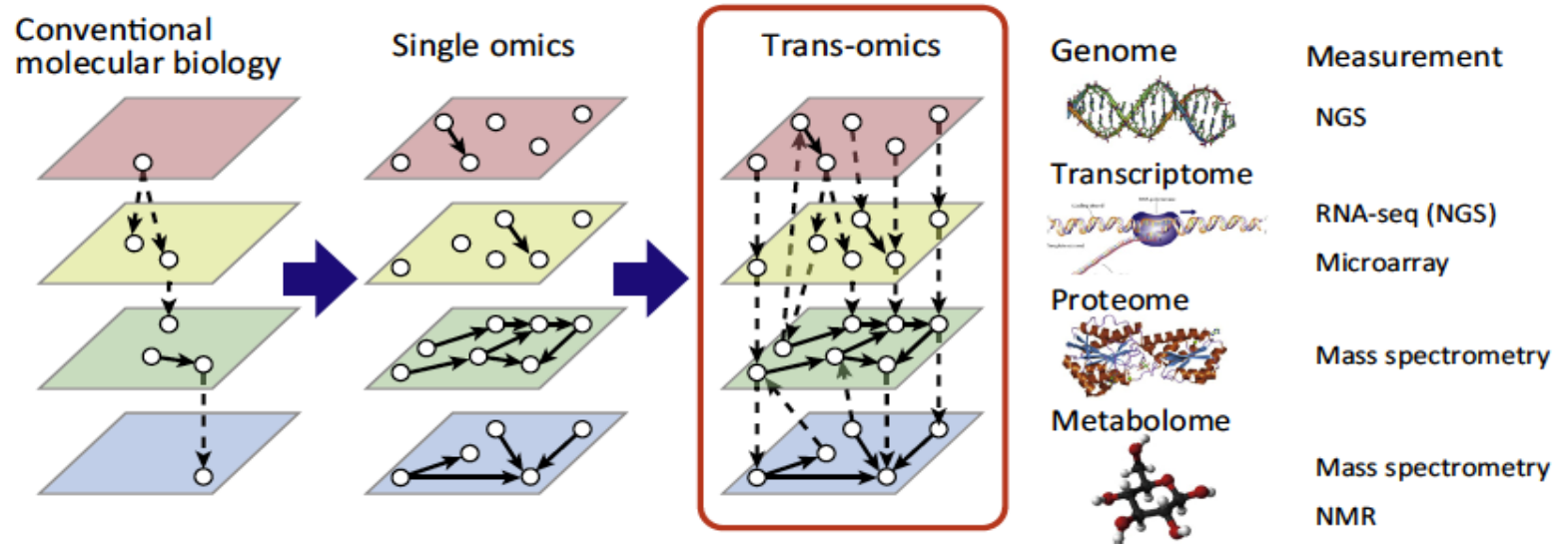


Big data analytics in a nutshell



Omic Data Integration

This is our goal



Trends in Biotechnology, April 2016, Vol. 34, No. 4

Mechanism



Patterns & Trends



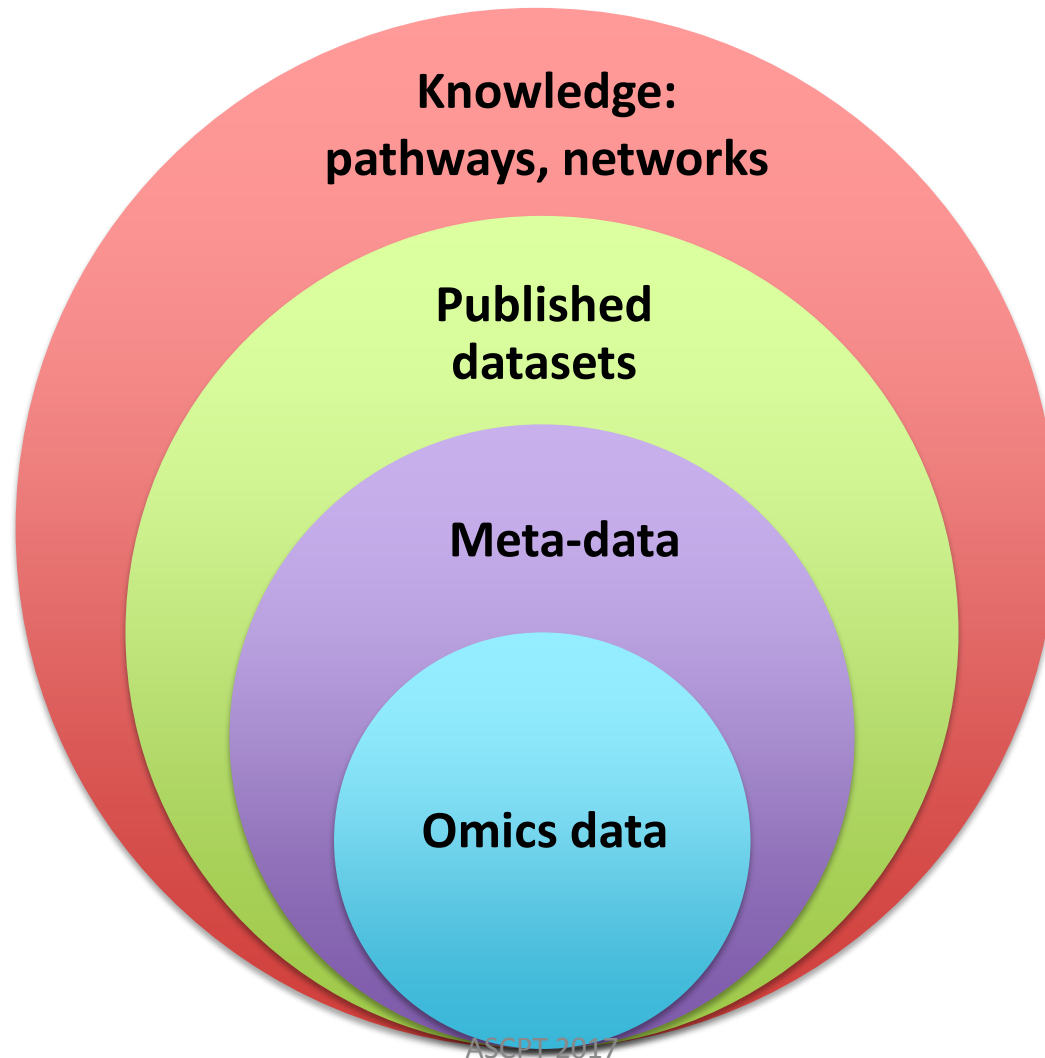
Knowledge



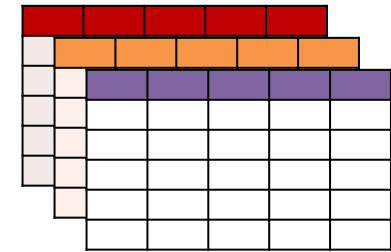
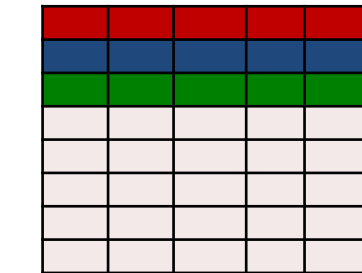
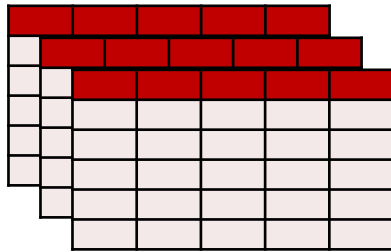
Current Status

- Done for simple organisms under well-controlled experiments
 - E. coli, yeast ...
 - Time series to resolve false patterns
- For human studies, the limiting factor is more technological than computational
 - Longitudinal omics data collections for a large cohorts
 - Data sharing with public for algorithm benchmarking

The 'ecosystem' of big omics data



Data integration - three common scenarios



One disease;
One omics level;
Multiple datasets;

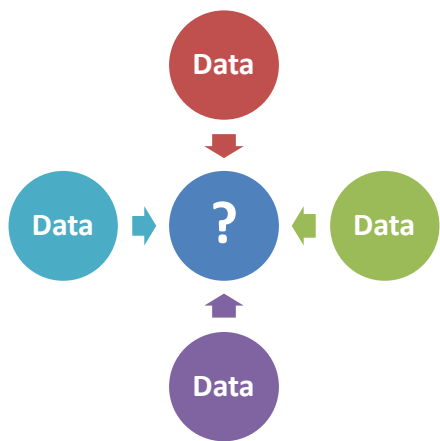
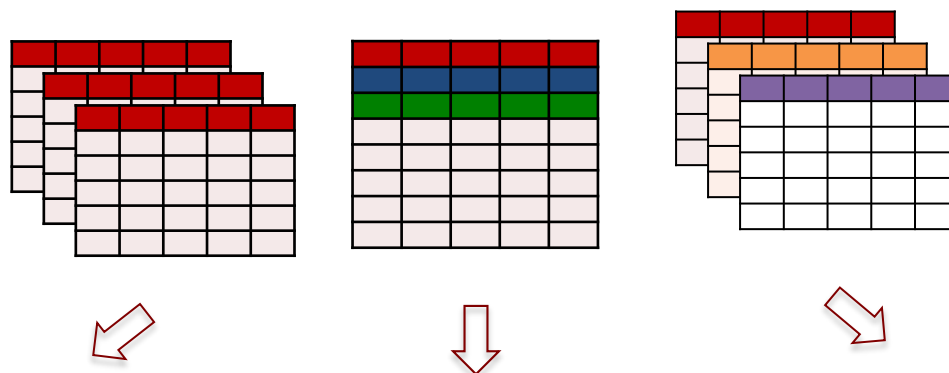
One omics data;
Multiple clinical parameters:

- Diagnosis
- Age, Gender, Ethnicity, Smoking

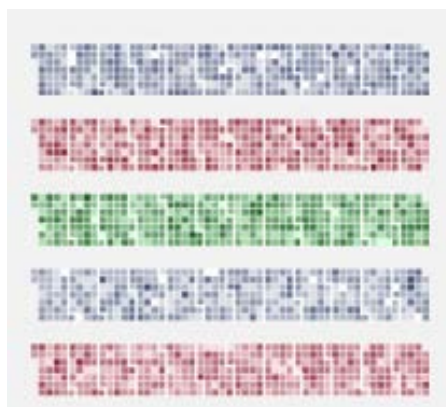
One disease;
Multiple omics level;
Multiple datasets;

Computational Approaches

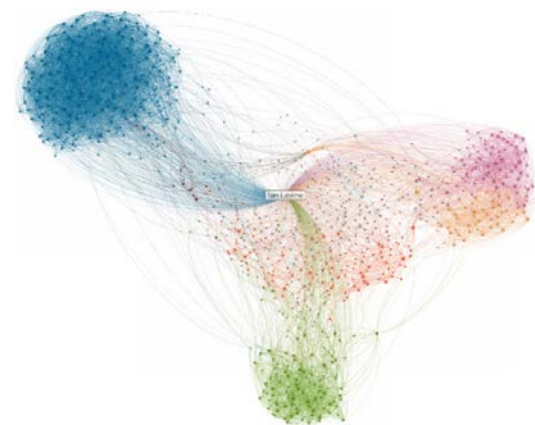
Omics Data



Statistical integration



Visual integration



Network integration

Web-based Tools for Big Omics Data Analysis & Integration

- MetaboAnalyst (since 2009)
 - www.metaboanalyst.ca
 - Metabolomics data analysis & integration
- NetworkAnalyst (since 2012)
 - www.networkanalyst.ca
 - Transcriptomics data analysis & integration
- miRNet (since 2015)
 - www.mirnet.ca
 - miRNA data analysis & integration
- MicrobiomeAnalyst (since 2017)
 - www.microbiomeanalyst.ca
 - Microbiome data analysis & integration

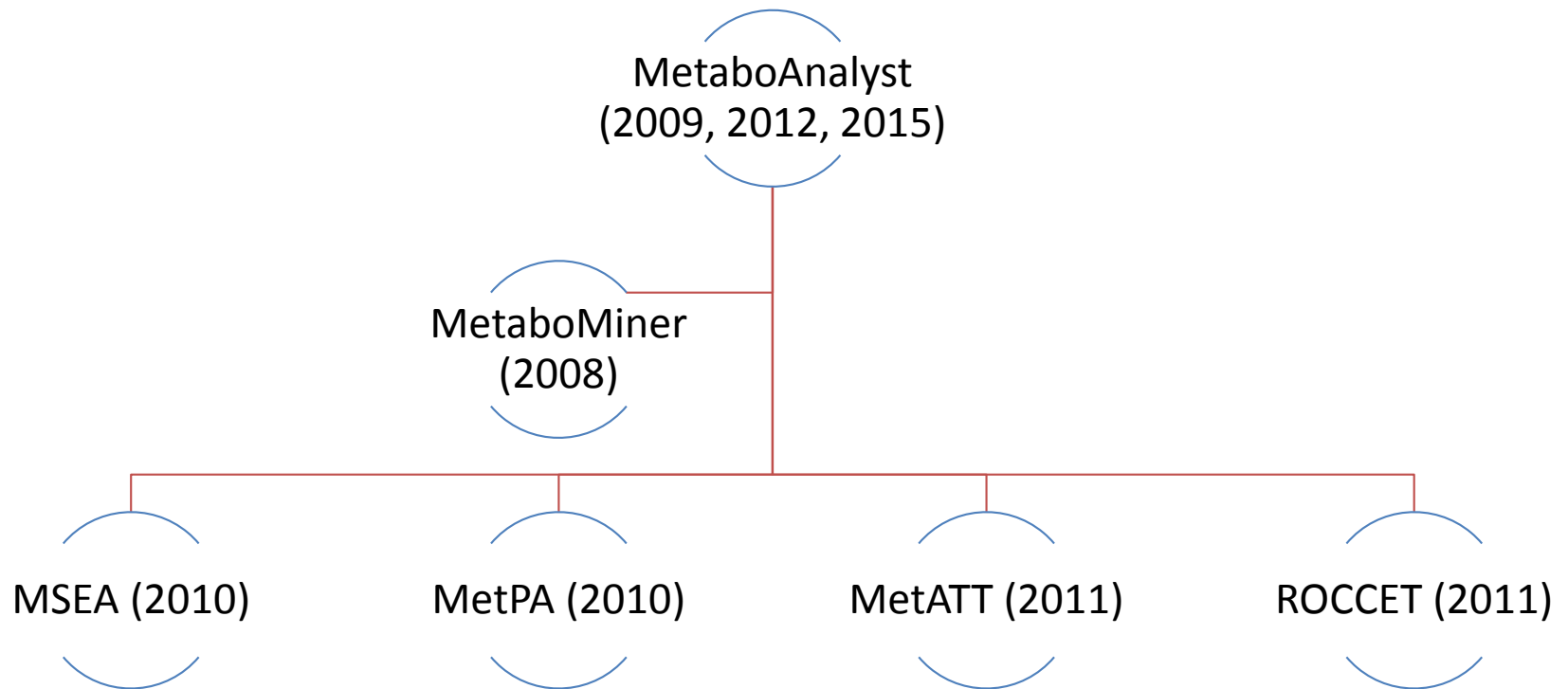
2009 - CURRENT

Metabolomics & MetaboAnalyst

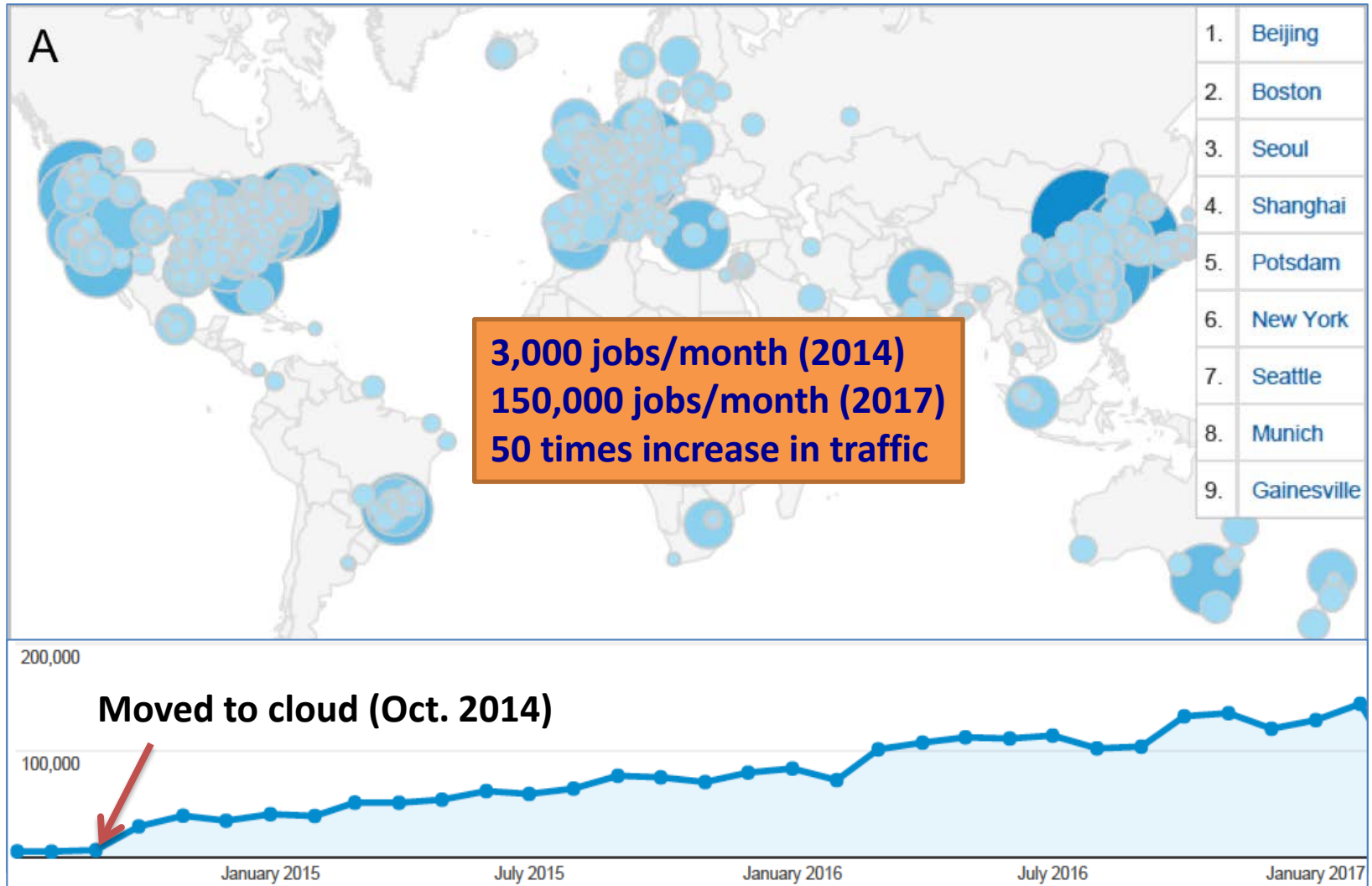
<http://www.metaboanalyst.ca>

- Metabolomics (and integration with genomics)
- Real-time interactive data analysis
- 100,000 users, > 6,000 jobs submitted per day

A Roadmap of MetaboAnalyst



The power of cloud



MetaboAnalyst 3.0

– a comprehensive tool suite for metabolomic data analysis



[Home](#)

[Overview](#)

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News & Updates

- Added support for peak filtering based on QC samples for untargeted metabolomics (03/10/2017); **NEW**
- Added support for "flipping" PCA for cross-study comparison (02/09/2017); **NEW**
- Added support for **network summary** of enrichment analysis result (02/06/2017); **NEW**
- Fixed the bug in feature table display in Biomarker Tester module (01/05/2017); **NEW**
- Updated the pathway result table to show all/matched compounds (11/25/2016);
- Enhanced Normalization and Data Editor for better user experience (11/15/2016);
- Added support for **sparse PLS-DA** (sPLS-DA) analysis (10/28/2016);
- Added support for **quantile normalization** (08/29/2016);
- Improved name mapping functions for common metabolite names (08/18/2016);
- More than **1 million jobs** have been processed since 06/2015 (06/21/2016);

[Read more](#)

Please Cite:

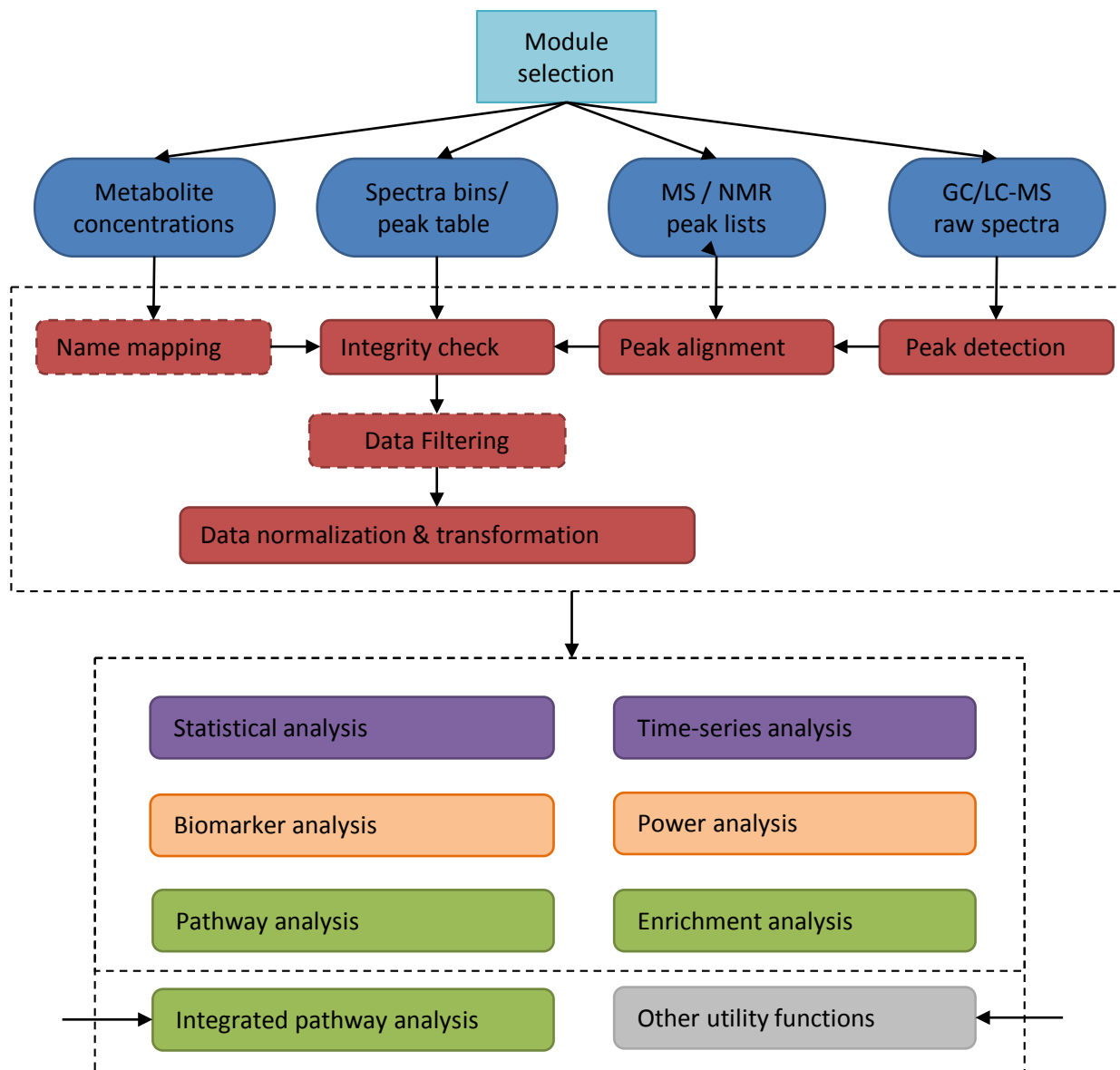
Xia, J. and Wishart, D.S. (2016) [Using MetaboAnalyst 3.0 for Comprehensive Metabolomics Data Analysis](#) Current Protocols in Bioinformatics, 55:14.10.1-14.10.91.

Xia, J., Sinelnikov, I., Han, B., and Wishart, D.S. (2015) [MetaboAnalyst 3.0 - making metabolomics more meaningful](#). Nucl. Acids Res. 43, W251-257.

Xia, J., Mandal, R., Sinelnikov, I., Broadhurst, D., and Wishart, D.S. (2012) [MetaboAnalyst 2.0 - a comprehensive server for metabolomic data analysis](#). Nucl. Acids Res. 40, W127-133.



McGill



Comprehensive Options for Data Analysis

Sample normalization

- None
- Sample-specific normalization (i.e. weight, volume) [Click here to specify](#)
- Normalization by sum
- Normalization by median
- Normalization by a specific reference sample
- Normalization by a pooled sample from group
- Normalization by reference feature
- Quantile normalization

Data transformation

- None
- Log transformation (generalized logarithm transformation or glog)
- Cube root transformation (take cube root of data values)

Data scaling

- None
- Mean centering (mean-centered only)
- Auto scaling (mean-centered and divided by the standard deviation of each variable)
- Pareto scaling (mean-centered and divided by the square root of standard deviation of each variable)
- Range scaling (mean-centered and divided by the range of each variable)

Univariate Analysis

[Fold Change Analysis](#) [T-tests](#) [Volcano plot](#)

One-way Analysis of Variance (ANOVA)

[Correlation Analysis](#) [Pattern Searching](#)

Chemometrics Analysis

[Principal Component Analysis \(PCA\)](#)

[Partial Least Squares - Discriminant Analysis \(PLS-DA\)](#)

[Sparse Partial Least Squares - Discriminant Analysis \(sPLS-DA\)](#)

[Orthogonal Partial Least Squares - Discriminant Analysis \(orthoPLS-DA\)](#)

Feature Identification

[Significance Analysis of Microarray \(and Metabolites\) \(SAM\)](#)

[Empirical Bayesian Analysis of Microarray \(and Metabolites\) \(EBAM\)](#)

Cluster Analysis

Hierarchical Clustering: [Dendrogram](#) [Heatmaps](#)

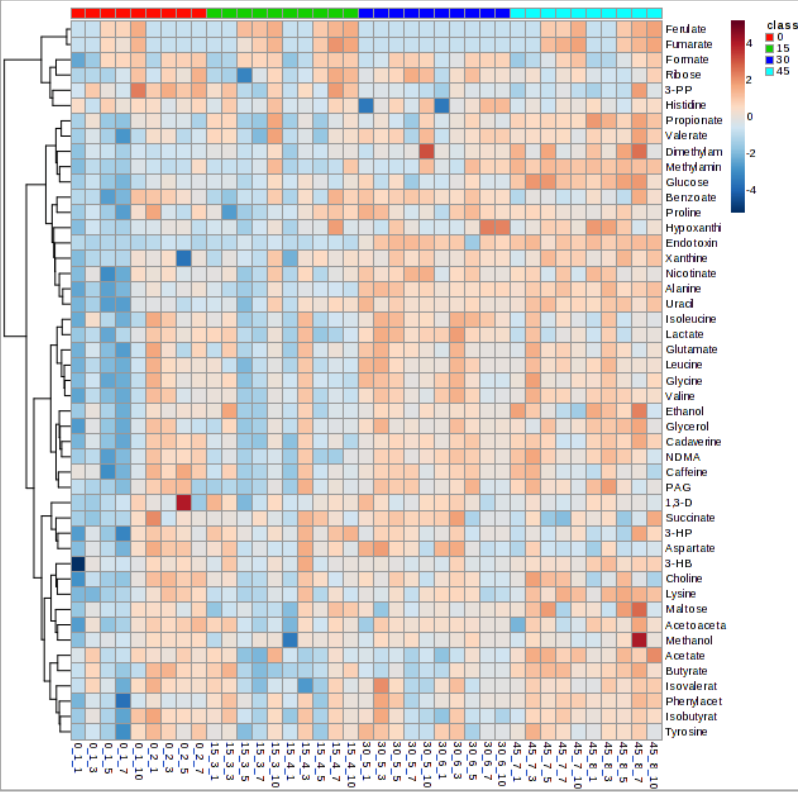
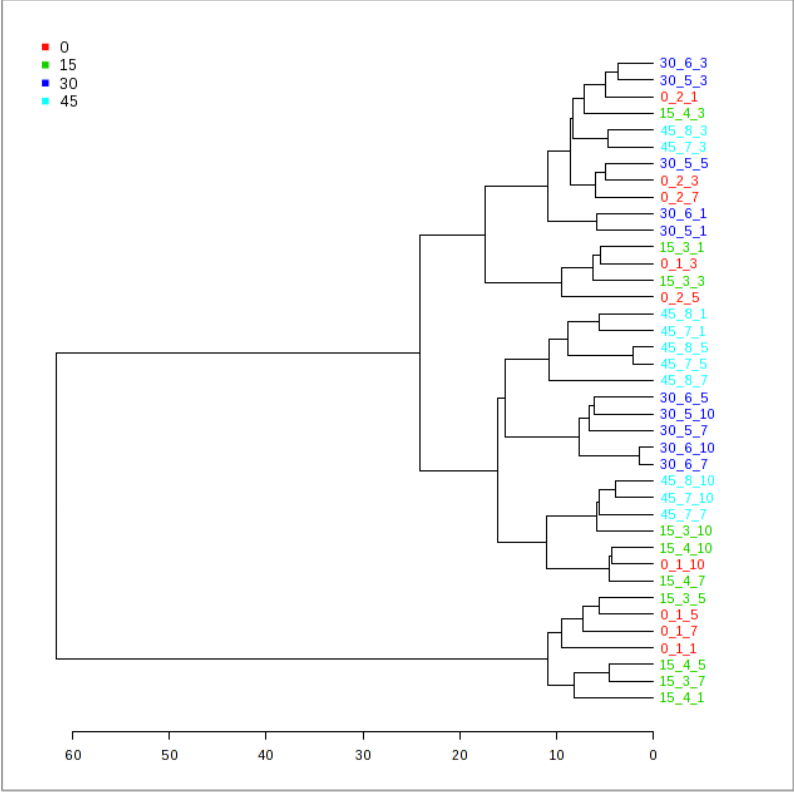
Partitional Clustering: [K-means](#) [Self Organizing Map \(SOM\)](#)

Classification & Feature Selection

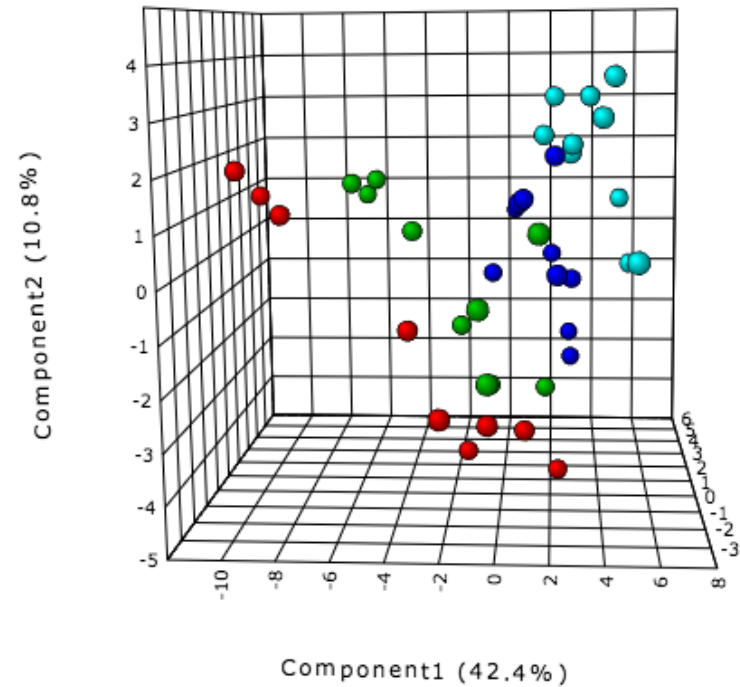
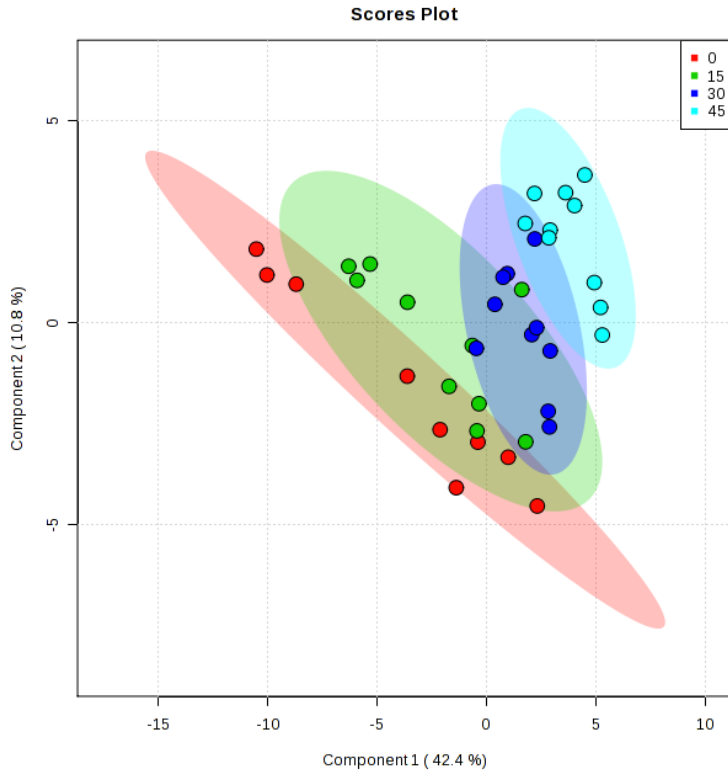
[Random Forest](#)

[Support Vector Machine \(SVM\)](#)

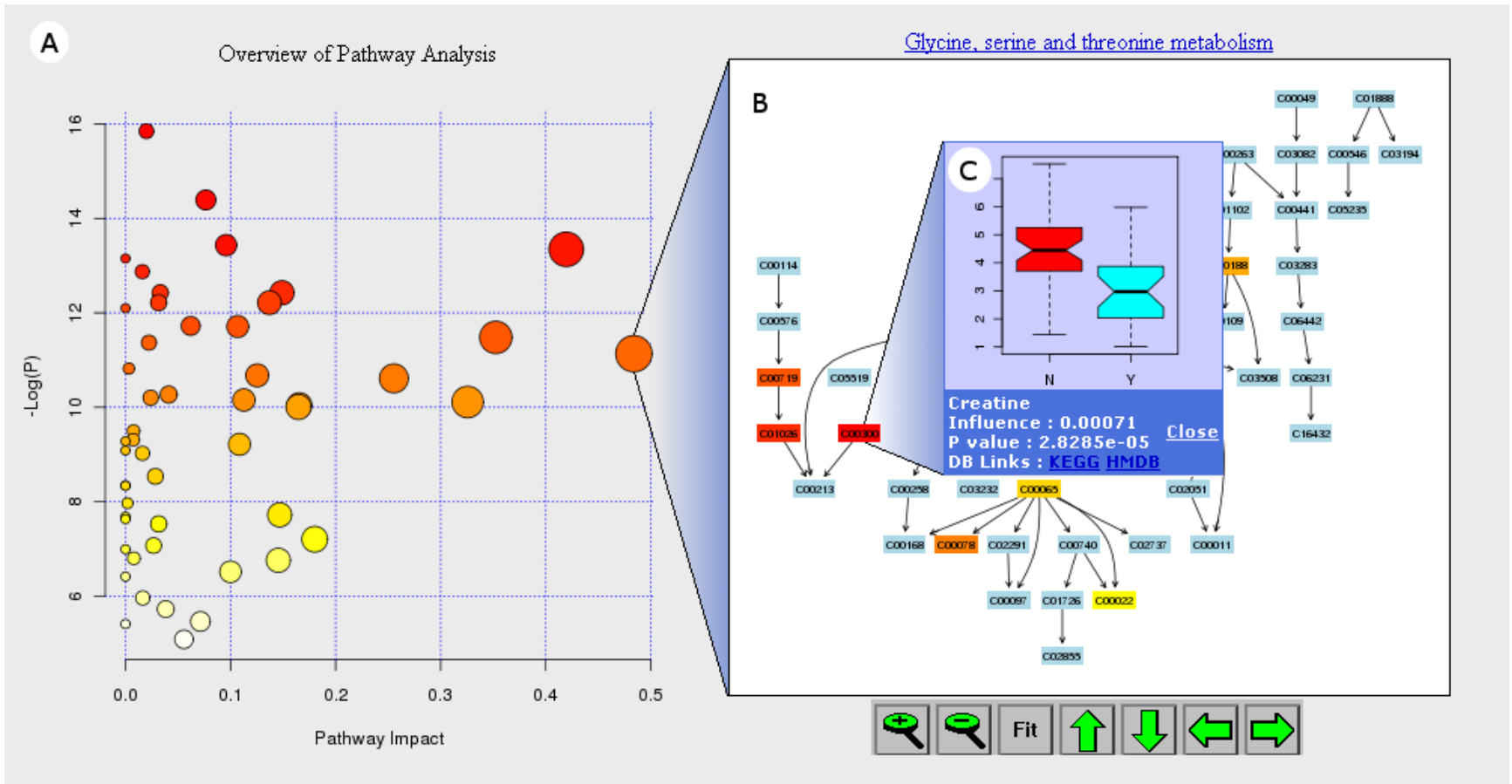
Clustering



Multivariate Statistics

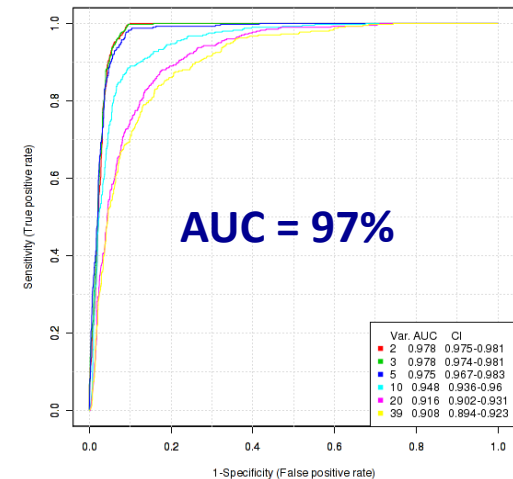
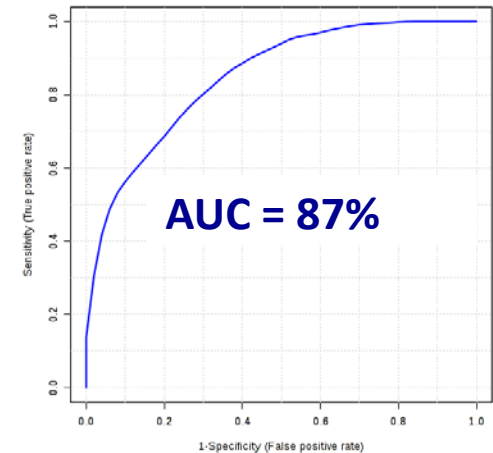


Pathway Analysis

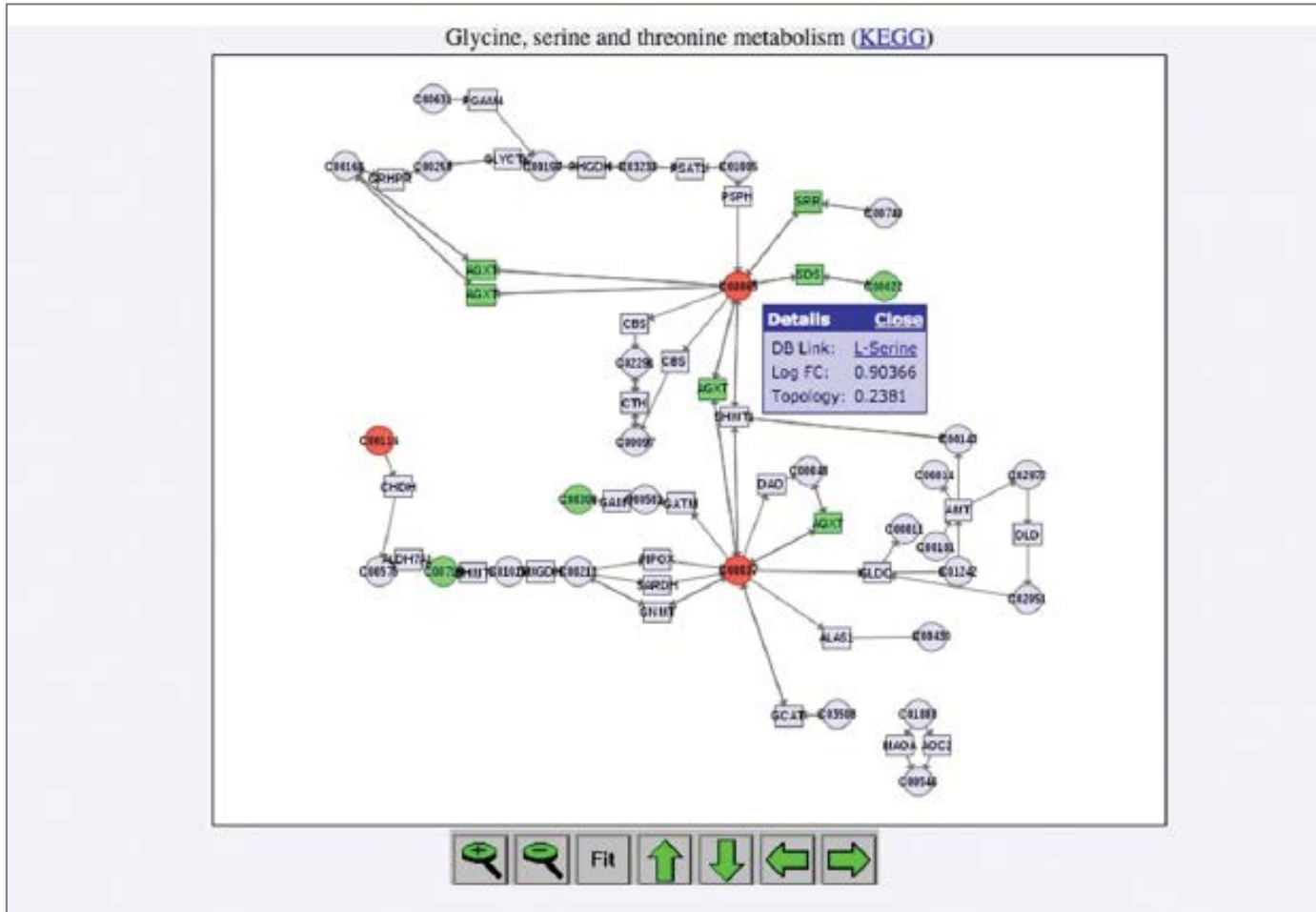


Biomarker Analysis

- Highly relevant for translational studies
- Performance evaluation
 - Receiver operator characteristics (ROC) curve
 - Modern machine learning approaches
 - Cross validation
 - Permutation
 - Predicting new samples



Gene-metabolite joint pathway analysis



Comprehensive report generation

Search Create PDF Comment & Markup Send for Review Secure Sign Forms

Select Object Data Tool 56% Help

2.2 Correlation Analysis

Correlation analysis can be used to identify which features are correlated with a feature of interest. Correlation analysis can also be used to identify if certain features show particular patterns under different conditions. Users first need to define a pattern in the form of a series of bipyelated numbers. For example, in a time-series study with four time points, a pattern of 1-2-3-4 is used to search compounds with increasing the concentration as time changes; while a pattern of 3-2-1-3 can be used to search compounds that decrease at first, then bounce back to the original level.

Figure 3 shows the important features identified by correlation analysis. Table 3 shows the details of these features.

Table 3: Important features identified by Pattern search using correlation analysis

Compound	correlation	t-value	p-value	FDR
1 Mayraze	-0.81202	10923	3.407E-06	0.00000008
2 Sublyraze	-0.90768	12974	9.615E-08	0.00000408
3 5-FF	-0.97235	15635	0.00014063	0.016604
4 Alonate	-0.90453	13359	0.00026611	0.025416
5 5-HB	-0.41943	14024	0.007862	0.041067
6 Isonolazate	-0.39981	13813	0.012090	0.051053
7 Lyraze	-0.34401	12261	0.15439	0.10381
8 Markanal	-0.34297	12277	0.15379	0.10381
9 Perlyraze	-0.32920	12146	0.16028	0.12793
10 Panazate	-0.21986	12050	0.17906	0.13396
11 Hestilazate	-0.2169	12023	0.18474	0.13396
12 Propylazate	-0.21516	11996	0.19012	0.14461
13 Malazate	-0.2093	11859	0.22148	0.17177
14 Alonolazate	-0.17923	11636	0.27007	0.20746
15 Chelazate	-0.11886	11054	0.47111	0.46124
16 Tyraze	-0.10887	10923	0.51847	0.49028
17 PAlZ	-0.079198	10683	0.62041	0.59927
18 5-FF	-0.074919	10620	0.64936	0.62438
19 Perlyraze	-0.051347	10387	0.78623	0.84498
20 Argonazate	-0.031993	10186	0.94874	0.95191
21 Collyraze	0.011541	9783	0.94297	0.94297
22 Nilazate	0.038943	9486.1	0.81391	0.80504
23 1,5-D	0.041198	9443.6	0.75410	0.74434
24 Nicotazate	0.04643	9420	0.75842	0.74824
25 Collyraze	0.057544	9313.9	0.72757	0.74329
26 Collyraze	0.060943	9280.8	0.71392	0.74349
27 Pharyngazate	0.067640	9201.2	0.66986	0.74329
28 Hypoxanthine	0.10011	8602	0.36947	0.47889
29 Ethanol	0.14524	8074.8	0.26271	0.3383
30 NIMA	0.15402	8053	0.24979	0.3383
31 Pyraze	0.18713	7613.0	0.19309	0.2888
32 Glisazate	0.19534	7569.8	0.19309	0.2888
33 Benzazate	0.21978	7216.0	0.13964	0.23396
34 Valazate	0.23938	7151.1	0.14221	0.23396
35 Glycylazate	0.26961	6741.3	0.06960	0.18881
36 Glycylazate	0.28094	7197.3	0.083333	0.21132
37 Nicotazate	0.28432	7081	0.09431	0.21132
38 Methylamine	0.28608	7044.0	0.09431	0.21132
39 Diphosphate	0.30304	6881	0.08855	0.18881
40 Xanthine	0.30544	6861.3	0.08855	0.18881
41 Diethylamine	0.33268	6585.1	0.07198	0.14944
42 Lactone	0.33142	6477.9	0.072044	0.14944
43 Valazate	0.3869	6116.7	0.04744	0.11541
44 Lactate	0.42354	5892.9	0.0271709	0.041097
45 Tricel	0.44172	5413	0.0209808	0.02137
46 Ethoxazine	0.90341	4024.1	0.0011471	0.0009853
47 Alanine	0.62058	3743.8	0.0027006	0.00091008

2.5 Hierarchical Clustering

In (agglomerative) hierarchical cluster analysis, each sample begins as a separate cluster and the algorithm proceeds to combine them until all samples belong to one cluster. Two parameters need to be considered when performing hierarchical clustering. The first one is similarity measure - Euclidean distance, Pearson's correlation, Spearman's rank correlation. The other parameter is clustering algorithms, including average linkage (clustering uses the centroids of the observations), complete linkage (clustering uses the farthest pair of observations between the two groups), single linkage (clustering uses the closest pair of observations) and Ward's linkage (clustering to minimize the sum of squares of any two clusters). Heatmap is often presented as a visual aid in addition to the dendrogram.

Hierarchical clustering is performed with the `hclust` function in `package stat`. Figure 17 shows the clustering result in the form of a dendrogram. Figure 18 shows the clustering result in the form of a heatmap.

2.2 Principal Component Analysis (PCA)

PCA is an unsupervised method aiming to find the directions that best explain the variance in a data set (X) without referring to class labels (Y). The data are summarized into much fewer variables called *scores* which are weighted average of the original variables. The weighting profiles are called *loadings*. The PCA analysis is performed using the `prcomp` package. The calculation is based on singular value decomposition.

The Rscript `clonemetrics.R` is required. Figure 6 is pairwise score plots providing an overview of the various separation patterns among the most significant PCs; Figure 7 is the score plot showing the variances explained by the selected PCs; Figure 8 shows the 2-D score plot between selected PCs; Figure 9 shows the 3-D score plot between selected PCs; Figure 10 shows the loading plot between the selected PCs; Figure 11 shows the biplot between the selected PCs.

Figure 17: Clustering result shown as heatmap (distance measure using pearson, and clustering algorithm using ward).

Figure 6: Pairwise score plots between the selected PCs. The explained variance of each PC is shown in the corresponding diagonal cell.

ASCPT 2017

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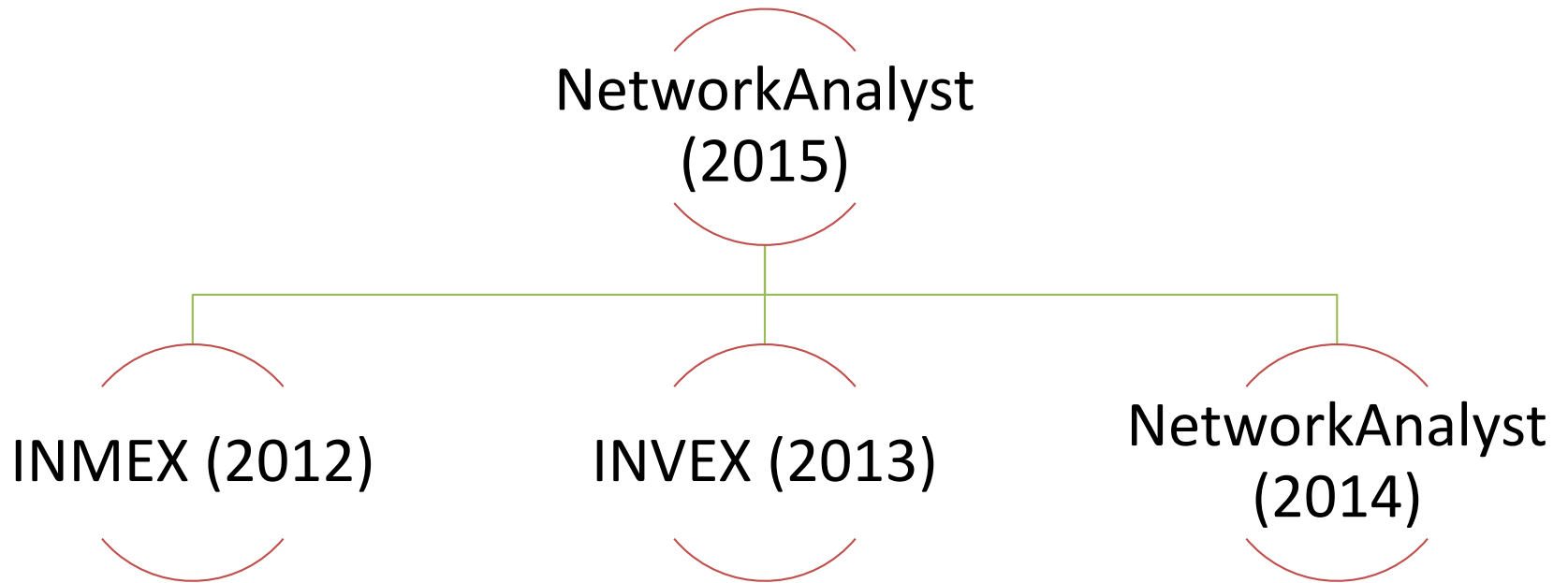
2012 - CURRENT

Transcriptomics & NetworkAnalyst

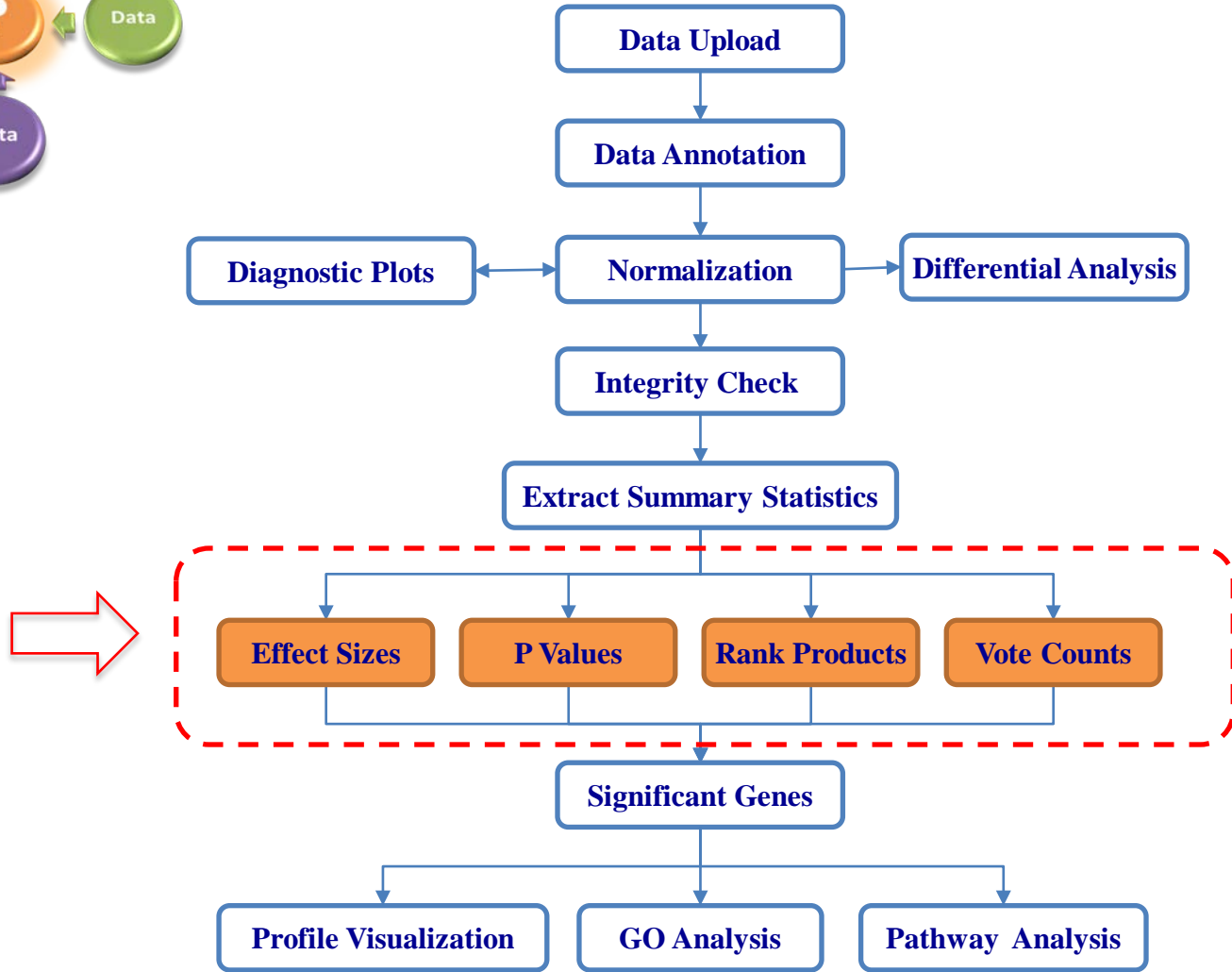
<http://www.networkanalyst.ca>

- Gene expression analysis (microarray & RNAseq)
- Statistical data integration (meta-analysis)
- Visual integration (heatmaps, Venn diagrams, 3D PCA/tSNE)
- Network integration (PPI, KEGG, miRanda)

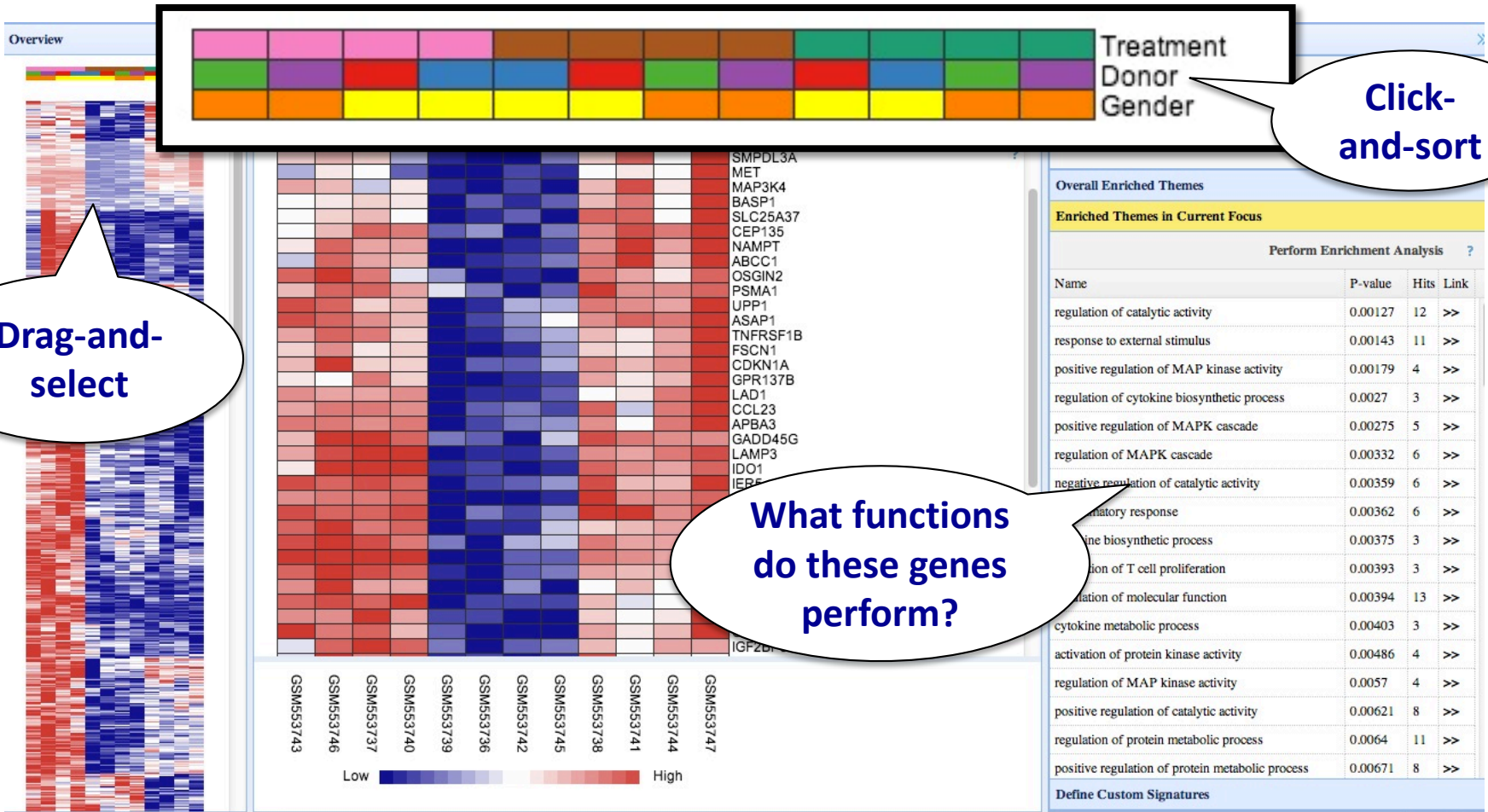
Implementation Roadmap



Statistical Integration

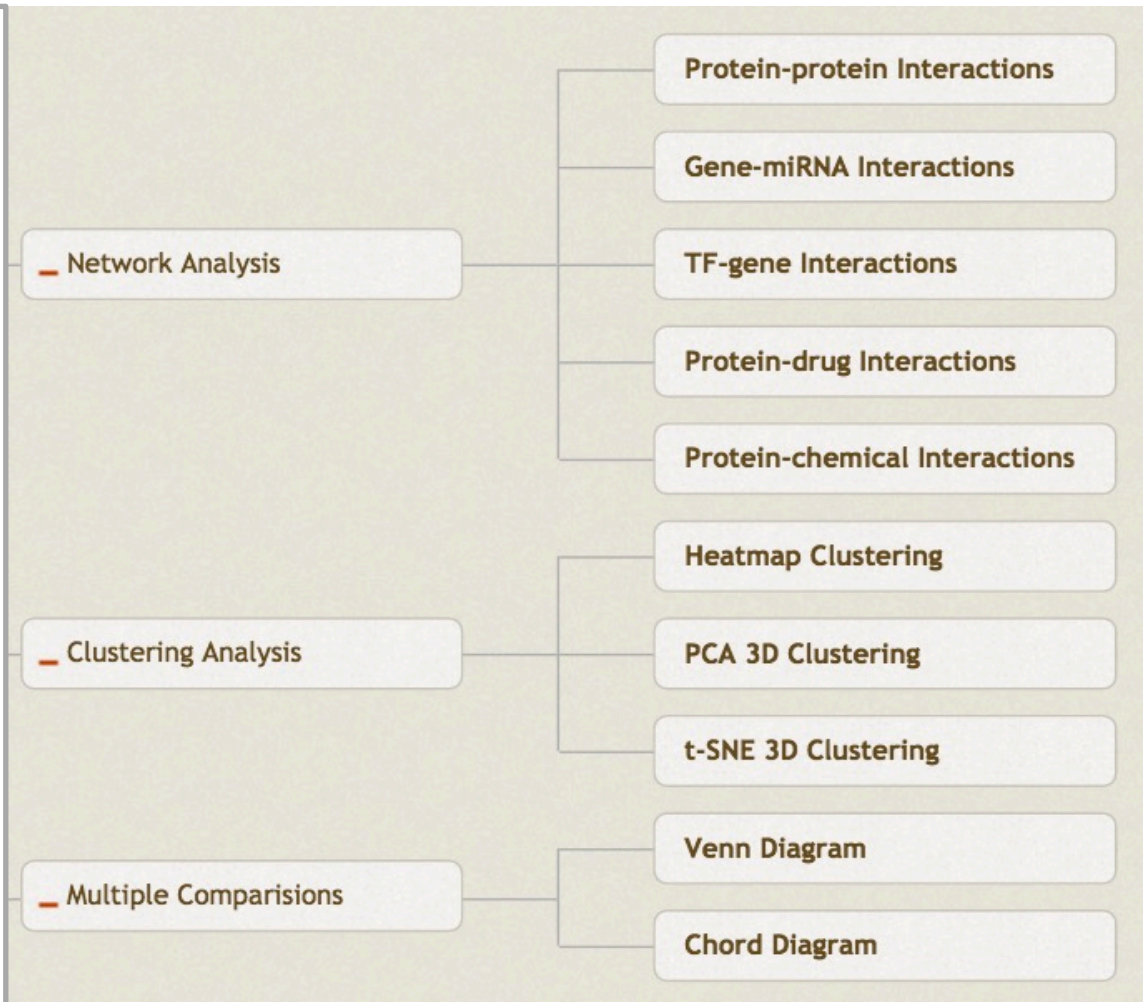


Visual Integration



Integrating with prior knowledge

- Protein-protein interactions
 - STRING
 - InnateDB
- Metabolic pathways
 - KEGG
 - Reactome
- Chemicals
 - DrugBank
 - CTD
- Gene regulations
 - Trans Factor
 - miRNAs



Network Visualization & Exploration

Background: Black View: Default Layout: Default Layout Scope: Single node Download: -- Specify --

Node Explorer

Node ID: Search

ID	Degree	Betweenness	Status
<input type="checkbox"/> mmu-mir-329-3p	107	157	
<input type="checkbox"/> mmu-mir-410-3p	67	705	
<input type="checkbox"/> mmu-mir-495-3p	54	560	
<input type="checkbox"/> mmu-mir-369-3p	48	352	
<input type="checkbox"/> mmu-mir-200b-3p	21	796.71	-
<input type="checkbox"/> mmu-mir-200c-3p	21	796.71	-
<input type="checkbox"/> mmu-mir-429-3p	21	796.71	-
<input type="checkbox"/> mmu-mir-381-3p	17	1106.8	-
<input type="checkbox"/> mmu-mir-431-5p	15	732	-
<input type="checkbox"/> mmu-mir-494-3p	11	499.73	-
<input type="checkbox"/> mmu-mir-5		3	-
<input type="checkbox"/> mmu-mir-3		4	-
<input type="checkbox"/> mmu-mir-4		5	-
<input type="checkbox"/> mmu-mir-199a-3p	8	450.88	-
<input type="checkbox"/> mmu-mir-200a-3p	8	218.21	-
<input type="checkbox"/> Pkib	7	534.57	-
<input type="checkbox"/> mmu-mir-337-3p	6	224.11	-
<input type="checkbox"/> mmu-mir-127-3p	6	7.5	-
<input type="checkbox"/> mmu-mir-136-5p	6	195.15	-
<input type="checkbox"/> Hist1h1d	6	745.64	-
<input type="checkbox"/> Ikzf5	5	155.15	-
<input type="checkbox"/> Foxn3	5	498.66	-

Image Tools

Batch Selection

Node Search

Page 1 of 8

Current Selections

- Pathways in cancer
- Wnt11
- Runx1l1
- Fzd5
- Casp8
- Gsk3b

Functional Analysis

Cluster 1

Cluster 2

Cluster 3

Function Explorer

Query: All genes

Algorithm: Hypergeometric test

Database: KEGG

Name	Hits	Pval	Color
Pathways in cancer	15	0.00608	Red
Signaling pathways regulating i	8	0.0128	
Melanogenesis	7	0.0128	
Proteoglycans in cancer	9	0.0212	
Basal cell carcinoma	5	0.0212	
mTOR signaling pathway	5	0.0241	
Wnt signaling pathway	7	0.0338	
Chagas disease (American tryps	6	0.0338	
Hippo signaling path			
Hedgehog signaling			
Mucin type O-Glyca			
NF-kappa B signalin			
HIF-1 signaling pathway	5	0.135	
Adrenergic signaling in cardion	6	0.135	
Toxoplasmosis	5	0.146	
Carbon metabolism	5	0.149	
Rap1 signaling pathway	7	0.149	
Glycosaminoglycan biosynthesi	2	0.15	
cGMP-PKG signaling pathway	6	0.15	
Apoptosis	4	0.15	

Enriched Functions

View Options Path Finder Batch Highlight

Node Effect

Set size for: Selected Nodes

Decrease -- Submit

Note: you can increase size of any particular node by repeatedly clicking on it

MicroRNA Data (www.mirnet.ca)

The screenshot displays the miRNet website interface. At the top, there is a navigation bar with links for Home, FAQs, Tutorials, Resources, and About. Below the navigation bar, the main content area is divided into several sections:

- News & Updates:** A list of recent updates, including support for chicken, cow, and dynamic network editing, along with updated FAQs and manual batch filter options.
- Click on an input area below to start analysis:** A central diagram showing the flow of data from input methods (Microarray, RNAseq, RT-qPCR) to mRNA, then to miRNA, and finally to various functional categories (Small molecule, Disease, lncRNA, Epigenetic modifier).
- Overview:** A detailed description of miRNet's capabilities, including support for various inputs, comprehensive functional annotation, creation of miRNA-target interaction networks, and high-performance network visual analytics.
- Please Cite:** A section providing the citation for the paper: Fan Y, Siklenka, K., Arora, SK., Ribeiro, P., Kimmins, S., and Xia, J. miRNet - dissecting miRNA-target interactions and functional associations through network-based visual analysis. Nucl. Acids Res. (2016).

Fan, Y et al. (2016) (doi: 10.1093/nar/gkw288)

Microbiome Data (www.microbiomeanalyst.ca)

MicrobiomeAnalyst -- comprehensive statistical, visual and meta-analysis of microbiome data

Home Data Format FAQs Tutorials About

Starting from a 16S rRNA abundance table (OTU table, BIOM file, mothur output)

Marker Data Profiling (MDP)

Starting from a gene list or gene abundance table annotated by KO, EC or COG

Shotgun Data Profiling (SDP)

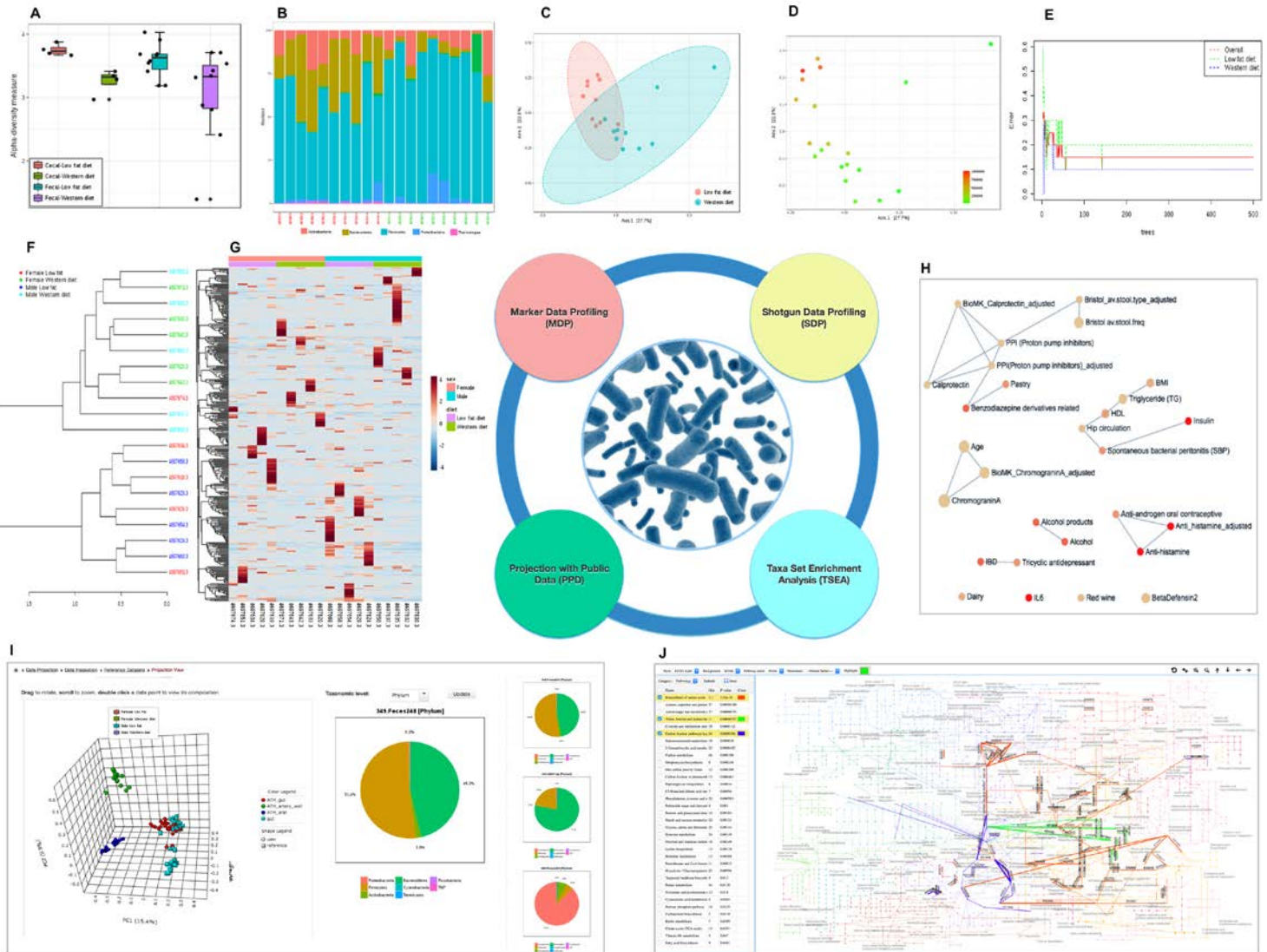
Visually exploring your 16S rRNA data with a public data in a 3D PCoA plot

Projection with Public Data (PPD)

Starting with a list of taxa of interest (strains, species or higher level taxa)

Taxon Set Enrichment Analysis (TSEA)

Microbiome profiling & integration



In the near future



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