

# A tutorial for metaOmic

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## 1 Introduction

MetaOomics is a GUI for meta-analysis implemented using R shiny. Current version includes MetaQC for quality control, MetaDE for differential expression analysis, MetaPath for pathway enrichment analysis, MetaClust for sparse clustering analysis, MetaPCA for principal component analysis, MetaKTSP for classification analysis, MetaDCN for differential co-expression network analysis, MetaLA for liquid association analysis.

In this tutorial, we will go through installation and usage step by step using a real example.

The metaOomics suit software is publicly available at <https://github.com/metaOmic/metaOomics>. Individual R packages are also available on GitHub and the url will be introduced in each individual package section.

## 2 Preliminaries

### 2.1 Citing MetaOomics

MetaOomics implements many meta-analytic methodology by their authors. Please cite appropriate papers when you use result from MeteOomics suit, by which the authors will receive professional credit for their work.

- MetaOomics suit itself can be cited as:
- MetaQC: Kang, D. D., Sibille, E., Kaminski, N., and Tseng, G. C. (2012). Metaqc: objective quality control and inclusion/exclusion criteria for genomic meta-analysis. *Nucleic acids research*, 40(2):e15–e15.
- MetaDE:
  - Fisher, R. A. (1925). *Statistical methods for research workers*. Genesis Publishing Pvt Ltd.
  - Li, J., Tseng, G. C., et al. (2011). An adaptively weighted statistic for detecting differential gene expression when combining multiple transcriptomic studies. *The Annals of Applied Statistics*, 5(2A):994–1019.

- Choi, J. K., Yu, U., Kim, S., and Yoo, O. J. (2003). Combining multiple microarray studies and modeling interstudy variation. *Bioinformatics*, 19(suppl 1):i84–i90.
  - and many more
- MetaPath:
  - Shen, K. and Tseng, G. C. (2010). Meta-analysis for pathway enrichment analysis when combining multiple genomic studies. *Bioinformatics*, 26(10):1316–1323.
  - Fang, Z., Zeng, X., Lin, C.-W., Ma, T., and Tseng, G. C. (2016). *Comparative Pathway Integrator: a framework of meta-analytic integration of multiple transcriptomic studies for consensual and differential pathway analysis*. PhD thesis, University of Pittsburgh.
- MetaClust: Huo, Z., Ding, Y., Liu, S., Oesterreich, S., and Tseng, G. (2016). Meta-analytic framework for sparse k-means to identify disease subtypes in multiple transcriptomic studies. *Journal of the American Statistical Association*, 111(513):27–42.
- MetaPCA: not published yet.
- MetaKTSP: Kim, S., Lin, C.-W., and Tseng, G. C. (2016). MetaKTSP: A Meta-Analytic Top Scoring Pair Method for Robust Cross-Study Validation of Omics Prediction Analysis. *Bioinformatics*, 32(March):btw115.
- MetaDCN: not published yet.
- MetaLA: not published yet.

## 2.2 Installation

The full instruction of how to install, start are available at <https://github.com/metaOmic/metaOmics>.

### 2.2.1 Requirement

- R >= 3.3.1
- Shiny >= 0.13.2

### 2.2.2 How to start the app

- First, clone the project
- git clone <https://github.com/metaOmic/metaOmics>
- in R (suppose the application directory is metaOmics),
  - > install.packages('shiny')
  - > shiny::runApp('metaOmics', port=9987, launch.browser=T)

### 2.2.3 How to start the documentation

- Install rmarkdown for R
- Inside ‘doc’ directory, start R console, and:
- in R

```
1 rmarkdown::run(shiny_args=list(port=9988, launch.browser=T))
```

- or in command line

```
1 R -e "rmarkdown::run(shiny_args=list(port=9988, launch.browser =T))"
```

If you run into an issue with something like ‘pandoc version 1.12.3 or higher is required and was not found.?’, just install pandoc manually. For example, on Mac, it would be ‘brew install pandoc’. If you have Rstudio, you can also get Rstudio’s pandoc environment. Go to Rstudio console and find the system environment variable for ‘RSTUDIO\_PANDOC’

In R:

```
1 Sys.getenv("RSTUDIO_PANDOC")
```

## 2.3 Question and bug report

Ask Anzhe what is the appropriate way to maintain the package?

## 3 Prepare data

### 3.1 Raw data

Data should be prepared as the example in Figure 1. First column should be feature ID (e.g. gene symbol) and the rest of the columns are samples. The first row is sample ID. Valid data type includes continuous, count.

	A	B	C	D	E	F	G	H	I	J	K
1	ID	GSM445939	GSM445940	GSM445952	GSM445965	GSM445966	GSM445995	GSM446005	GSM446015	GSM446019	GSM446020
2	COX1	14.1741845	14.5190482	13.8179896	14.1805909	14.7791613	14.3450467	14.68766	14.7869009	14.7574207	14.1582959
3	COX2	13.8544454	14.1854915	13.4474018	13.6644626	14.4244321	13.9044761	14.2370772	13.9931093	14.0432901	13.4166744
4	ND4	13.840222	14.4856644	13.5612402	13.8816752	14.5739527	14.1081131	14.5813899	14.2519264	14.2616291	13.8095574
5	RPL41	14.4218804	13.4484882	14.1035968	14.1046225	14.2929066	13.9955247	14.1029454	14.5718506	14.5623457	14.0007759
6	RPS2	14.1384864	13.3737668	13.8091098	13.8294958	13.897014	13.7186942	13.9696975	14.2643786	14.135146	13.7457779
7	RPL23A	13.9851543	13.0577958	13.807726	13.7652435	13.5068014	13.4619198	13.6286114	14.0471201	13.8060203	13.5260356
8	TPT1	14.2015622	13.4487804	13.8933327	13.9124043	14.1997062	14.0453267	14.2141676	14.4791302	14.5081582	13.8800374
9	RPL39	14.1331827	13.1026579	13.6928306	13.8217088	14.1705206	13.8267709	14.069521	14.3923098	14.3014678	13.7313433
10	ND2	11.8044506	14.1266472	13.3268843	13.3365085	14.1230073	13.8853862	14.2394535	13.8835649	13.6857053	13.4025025
11	RPS18	14.1950914	13.2245529	13.8789651	13.9155682	13.9672183	13.8135139	14.1093296	14.3927609	14.3095881	13.8317787
12	RPL37	13.7058004	12.8119102	13.3801223	13.5777508	13.6655865	13.4866264	13.5917687	13.8567646	13.7736878	13.3617574
13	RPL30	13.4054998	12.1211517	13.2228422	13.383714	13.2426155	13.250811	13.4838896	13.7547287	13.5276746	13.101915
14	RPS4X	13.8333138	13.0225864	13.5383624	13.7282801	13.300111	13.3981243	13.7100845	13.9321655	13.7211005	13.5440807
15	RPL32	13.9604926	12.8106502	13.6758375	13.7287171	13.7165548	13.594741	13.9769265	14.0313074	13.9445242	13.3819729
16	TMSB4X	13.3246885	12.1018215	13.1277736	13.3929776	13.9258423	13.5067522	12.9406726	13.7856005	13.8576944	12.8216926
17	RPS17	14.004012	12.8680591	13.7092862	13.7209076	13.472394	13.3000626	13.6710495	14.0922747	13.9272016	13.5751354
18	RPL9	13.7682089	12.7355572	13.4851269	13.6074655	13.3794251	13.3715674	13.6789654	14.0369392	13.7989794	13.3794219
19	RPL11	13.1068926	11.8041819	12.959188	13.2304038	12.6737969	12.8629437	13.2297796	13.531635	13.3865164	12.8034242
20	RPL3	13.1003076	11.2308104	12.6676873	12.856598	11.8035135	12.066841	12.5966984	13.0618903	12.6732755	12.4201737
21	TMSB10	13.4992692	12.4847027	13.3053195	13.9229064	13.4893536	13.403906	13.1984362	13.2277138	13.676856	12.8385526
22	UBC	12.6877469	11.2673769	12.428891	12.6531995	12.8093268	13.0569176	12.772718	13.1046039	12.4465834	12.4462248
23	RPL34	13.6748654	12.6004251	13.435718	13.5799487	13.4795839	13.4485159	13.715027	13.9986572	13.7915361	13.4117338
24	RPS3	13.377261	11.6797357	13.2251255	13.2240022	12.8373728	12.4130461	13.1883117	13.57352	13.3897875	12.9368834
25	GAPDH	11.7615563	10.6091352	12.090135	12.7600258	12.0082746	12.6371621	13.0494016	12.9957249	12.7918573	12.375633
26	UBB	12.9585862	11.8361919	12.7529098	12.6796118	12.394406	11.9336763	12.8433033	13.1560767	12.7851394	12.6930262
27	MPO	11.7578693	10.2667543	11.9584299	12.5560562	10.8735194	11.2210145	10.6698364	12.7304432	12.0959163	11.807057
28	RPL19	13.241946	11.4920457	12.95958	12.9573326	12.4867549	12.8390422	12.8650221	13.2425224	13.0159003	12.5675945
29	RPL6	13.1265705	11.7239338	13.063908	13.2136254	12.6273555	12.8178965	12.9838201	13.3099411	13.1238109	12.7874825
30	EEF2	12.1472604	9.70071474	11.7571483	12.0628499	11.3676495	11.69021	11.7508785	12.2203233	11.7522107	11.5744148

Figure 1: A example data format

### 3.2 Clinical data

Clinical data should be prepared as the example in Figure 2. First column should be sample ID and each row represents a sample. The rest of the columns are clinical information.

	A	B	C	D	E
1		label			
2	GSM445939	inv(16)			
3	GSM445940	inv(16)			
4	GSM445952	inv(16)			
5	GSM445965	inv(16)			
6	GSM445966	inv(16)			
7	GSM445995	inv(16)			
8	GSM446005	inv(16)			
9	GSM446015	inv(16)			
10	GSM446019	inv(16)			
11	GSM446020	inv(16)			
12	GSM446030	inv(16)			
13	GSM446032	inv(16)			
14	GSM446033	inv(16)			
15	GSM446035	inv(16)			
16	GSM446036	inv(16)			
17	GSM446037	inv(16)			
18	GSM446038	inv(16)			
19	GSM446039	inv(16)			
20	GSM446047	inv(16)			
21	GSM446056	inv(16)			
22	GSM446088	inv(16)			
23	GSM446102	inv(16)			
24	GSM446119	inv(16)			
25	GSM446120	inv(16)			
26	GSM446127	inv(16)			
27	GSM446143	inv(16)			
28	GSM446147	inv(16)			
29	GSM445923	t(15;17)			
30	GSM446023	t(15;17)			
31	GSM446027	t(15;17)			

Figure 2: A example clinical data format

## 4 Toolsets

### 4.1 MetaQC

For MetaQC, we used prostate cancer datasets with 8 datasets. ??Decide if we need more description here??

#### 4.1.1 Merging

The datasets from all the 8 studies (uploaded in “Preprocessing” step and named as “p1.csv”, “p2.csv”, etc.) should be merged before implementing MetaQC tool (Figure 3). The genes with low mean or low variance were filtered out (by default, the lowest 30th percentiles). Detailed information can be found in the “preproc” package in the metaOmics software suite (<https://github.com/>

`metaOmic/preproc)`.

The screenshot shows the metaOmic software interface. At the top, there are tabs for 'metaOomics', 'Settings', 'Preprocessing', 'Saved Data', 'Tools/sets', and a green bar indicating the active study is 'prostate' located at 'v/Documents/Pitt'. Below the tabs, the 'Selected Datasets' panel lists files: p1.csv, p2.csv, p3.csv, p4.csv, p5.csv, p6.csv, p8.csv, p7.csv. It includes input fields for 'mean' (0.3) and 'variance' (0.3), a 'Study Name' field set to 'prostate', and a checked checkbox 'Merge from Selected Datasets' which is highlighted with a red box. A 'Danger Zone' button is at the bottom of this panel. To the right, the 'List of saved data' table displays 13 entries with columns: data type, numeric nature, study type, features, and sample size. The table shows various datasets like 'merged', 'study1.csv', 'study2.csv', etc., with details such as sample sizes ranging from 34 to 2688.

	data type	numeric nature	study type	features	sample size
merged	continuous	continuous	multiple	2613	268
study1.csv	microarray	continuous	single	5135	89
study2.csv	microarray	continuous	single	5135	74
study3.csv	microarray	continuous	single	5135	105
p1.csv	microarray	continuous	single	8798	34
p2.csv	microarray	continuous	single	8799	148
p3.csv	microarray	continuous	single	13579	103
p4.csv	microarray	continuous	single	19738	13
p5.csv	microarray	continuous	single	8799	102
p6.csv	microarray	continuous	single	12689	89

Figure 3: Merging data for meta-analysis

#### 4.1.2 MetaQC analysis

After opening the MetaQC page, as shown in Figure 4, there are 2 tabs on the left of the page (“Options” and “Advanced Options”). We generally suggest users not to change any parameter setting in the “Advanced Options” unless users know the underlying methodology well.

The screenshot shows the homepage of the MetaQC tool. At the top, there is a navigation bar with links to 'metaOmics', 'Settings', 'Preprocessing', 'Saved Data', 'Toolsets', and a 'Working Directory' section set to '/Users/matianzhou'. Below the navigation bar is a large form area with a green header labeled 'Options'.

**Perform gene filtering:**

- Yes
- No

cut lowest (xx\*100)th percentile by mean  
0.3

cut lowest (xx\*100)th percentile by variance  
0.3

Use adjusted p-value for selecting DE genes

- Yes
- No

p-value cutoff for selecting DE genes  
0.05

Use adjusted p-value for selecting pathways

- Yes
- No

p-value cutoff for selecting pathways  
0.05

**Advanced Options**

**Run MetaQC Analysis**

Figure 4: Homepage of MetaQC

For the current dataset, we already performed filtering while merging the 8 studies so we do not further filter genes here and chose “No” for gene filtering (Figure 5). Moreover, MetaQC method requires users to choose a cutoff to decide significant DE genes and a cutoff to decide significantly enriched pathways, there are four options available, i.e. p-value cutoff for selecting DE genes, whether to use adjusted p-value or selecting DE genes, p-value cutoff for selecting pathways, whether to use adjusted p-value or selecting pathways. These options can be tuned depending on the overall signal of the datasets. Here, we use the defaults as determined by the prostate data.

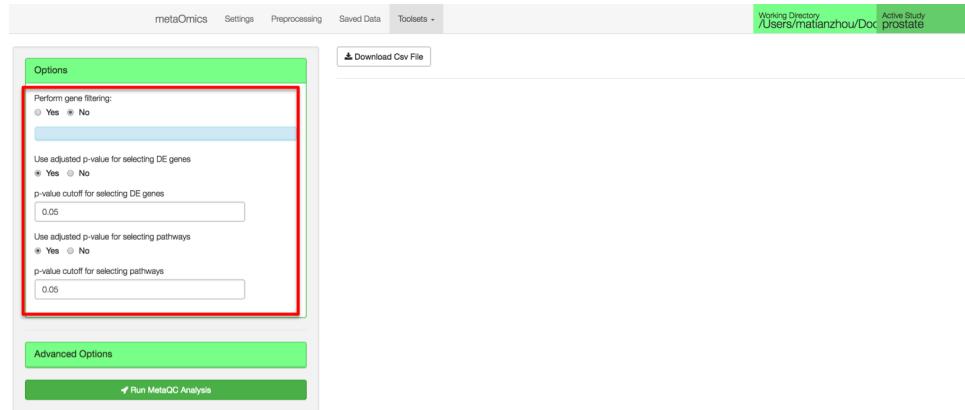


Figure 5: MetaQC Options

\*\* Optionally, we can click on “Advanced Options”, choose “min pathway size” and “max pathway size” to include only pathways of reasonable size. We suggest 100 permutations is sufficient, and generally do not recommend users to change the number of permutations here (Figure 6).

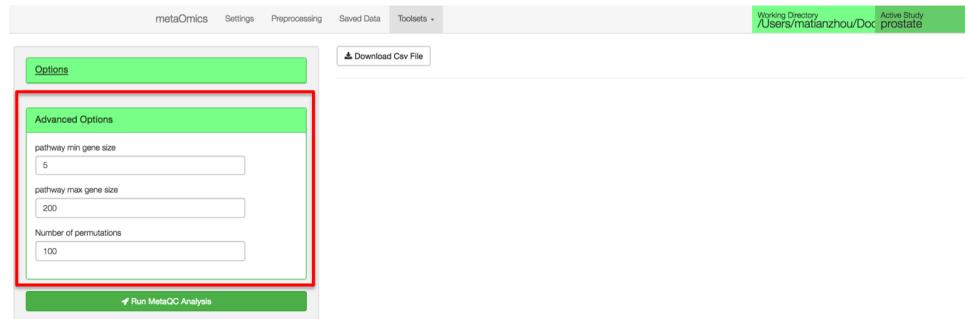


Figure 6: MetaQC Advanced Options

After we click on “Run”, we will see a summary table of MetaQC generated on the right of the page as shown in Figure 7. The table includes seven columns, with the first six columns corresponding to the six quantitative quality control

measures of all studies (a larger value indicates a better quality) and the seventh column is the rank summary statistics of all the six quality measures (a lower rank indicates a better quality). Users can download the full table as a csv file by clicking on “Download Csv File”. In addition to the tabular results, the tool also generated a PCA biplot from the six quality control measures, where the circled number is the study index and arrows indicate different measures (Figure 7). Both tabular summary and biplot are automatically saved to the current working directory.

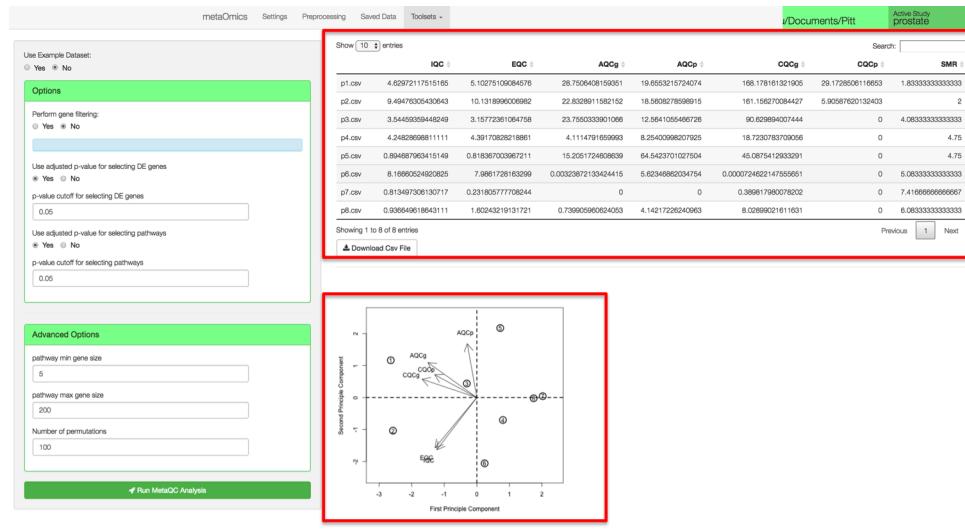


Figure 7: MetaQC results: summary table and PCA biplot

## 4.2 MetaDE

MetaDE package implements 12 major meta-analysis methods for differential expression analysis, and now it allows the analysis of both microarray and RNA-seq data. In this tutorial, we will demonstrate the MetaDE pipeline step by step using two meta-analysis methods: Fisher’s method and Adaptively weighted Fisher’s method (AW-Fisher). Please refer to Fisher (1925) and Li et al. (2011) for details of these two methods. Individual MetaDE package is also available on GitHub at <https://github.com/metaOmic/MetaDE>.

### 4.2.1 Meta analysis

After opening the MetaDE page, as shown in Figure 8, there are 2 drop-down menus (“Meta Method Type” and “Meta Method”) and 4 tabs on the left of the page (“Response Type”, “Setting Individual Study Method”, “Advanced

Options” and “Run”). We generally suggest users not to change any parameter setting in the “Advanced Options” unless users know the underlying methodology well.

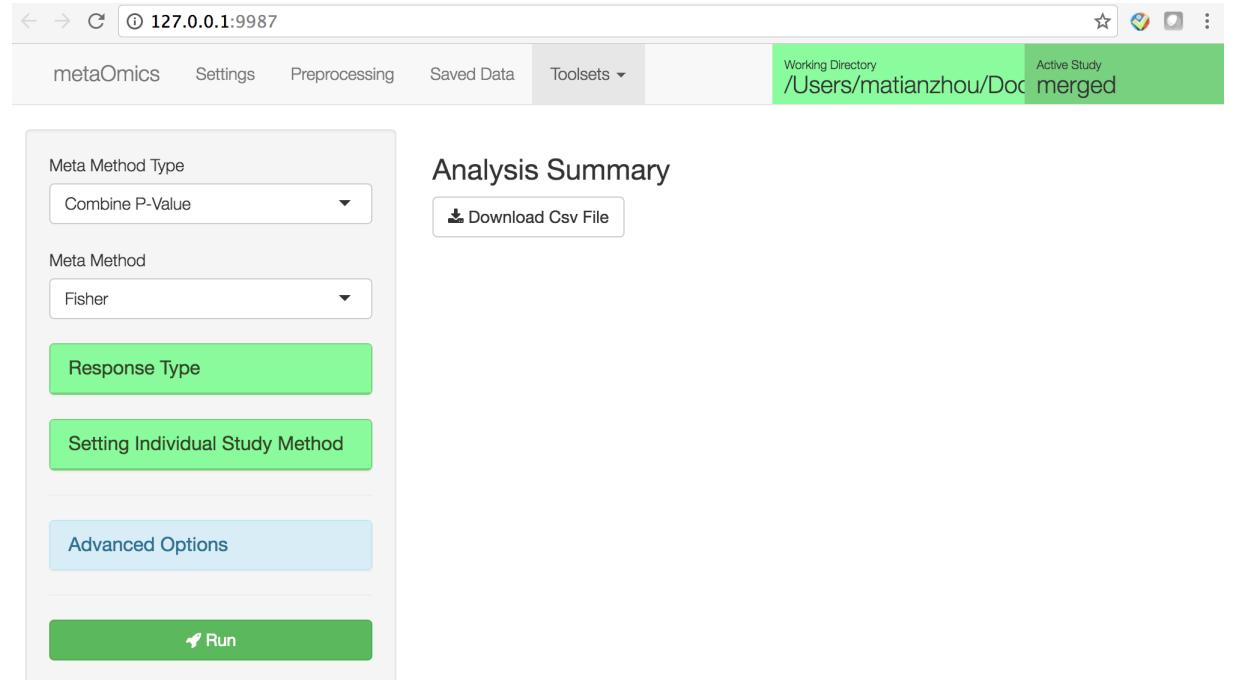


Figure 8: Homepage of MetaDE

For Fisher's method, we will choose “Combine P-value” and “Fisher” (Figure 9); and for AW Fisher's method, we will choose “Combine P-value” and “AW Fisher” (Figure 10).

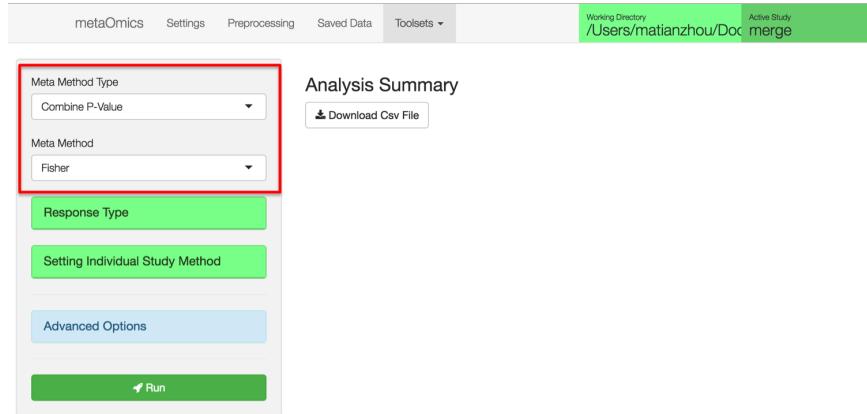


Figure 9: Fisher's method setting

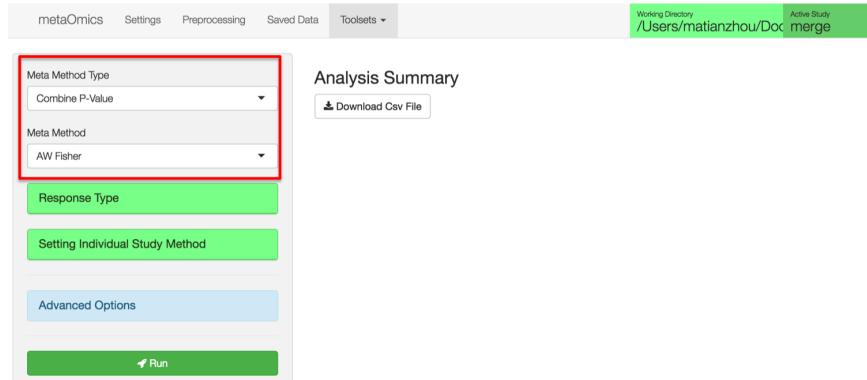


Figure 10: AW Fisher's method setting

Then, in the next step, we click on “Response Type”, for two-class DE analysis, choose “Two Class Comparison”, choose the group label name for the Label Attribute (from the column names of your clinical data). Then for the group label (a factor of at least two levels), choose a name for the “Control Label” and “Experimental Label”, respectively (Figure 23).

Two Class Comparison

Label Attribute: label

Control Label: inv(16)

Experimental Label: t(15;17)

**Setting Individual Study Method**

**Advanced Options**

**Run**

Figure 11: Response type setting

Next, we click on “Setting Individual Study Method” and choose “LIMMA” to perform DE analysis in each individual study (Figure 24). Available options include “LIMMA” and “SAM” for continuous data (e.g. microarray), “edgeR”, “DESeq2” and “limmaVoom” for discrete data (e.g. RNA-seq count). Details of the above mentioned DE methods can be found in XXX (reference).

study1.csv

LIMMA (Linear Model for Microarray data)

study2.csv

LIMMA (Linear Model for Microarray data)

study3.csv

LIMMA (Linear Model for Microarray data)

**Advanced Options**

**Run**

Figure 12: Individual study DE analysis method

\*\* Optionally, we can click on “Advanced Options”, choose “Parametric=yes” so parametric methods will be used for inference. We can choose whether to

adjust for any important “Covariates” (e.g. potential confounders) and we set the alternative hypothesis to be “abs”, i.e. two-sided test (Figure 13).

Advanced Options

Use complete options  
 Yes  No

Parametric  
 No  Yes

Covariate:  
 None

Alternative Hypothesis:  
 abs

Figure 13: Advanced Options

After we click on “Run”, we will see a summary table generated on the right of the page as shown in Figure 14. The “Analysis Summary” includes the analysis results of all genes, including individual study statistics/p-value, meta-analysis statistics/p-value/FDR, etc. Users can search the gene name in the “Search” bar, and download the full table as a csv file by clicking on “Download Csv File”.

	ind.stat.study1.csv	ind.stat.study2.csv	ind.stat.study3.csv	ind.p.study1.csv
COX1	0.0126812082556715	-0.0352823378450787	-0.0404256450138021	0.26892893736200
COX2	0.012086567005725	-0.0170330767053708	-0.0479332961282468	0.28994810474082
ND4	0.0115738612113951	-0.014945675881802	-0.0211095447931435	0.32474691664235
RPL41	-0.0160595156310522	-0.0707063583417713	-0.00180747617572272	0.16285867176410
RPS2	0.00377184273132259	-0.06680558060008396	0.000591323212125763	0.73724578494079
RPL23A	-0.0183077872427684	-0.0838415811836129	-0.0106412941765993	0.10654656869934
TPT1	-0.00071750453329344	-0.0539417110424626	0.017762992241745	0.94846427751892
RPL39	-0.010755961519947	-0.0616472700124989	0.00807756500336784	0.33301945214041

Figure 14: Summary table of Meta-analysis results

#### 4.2.2 Visualization

In addition to tabular output, for better visualization, users can also plot heatmap of DE genes at specified FDR cutoff. Users can enter the “FDR Cutoff” (number of genes selected are shown interactively), then click on “Plot DE Genes Hetamap” to draw the heatmap. The “image size” can be adjusted by dragging the scroll bar (Figure 15).

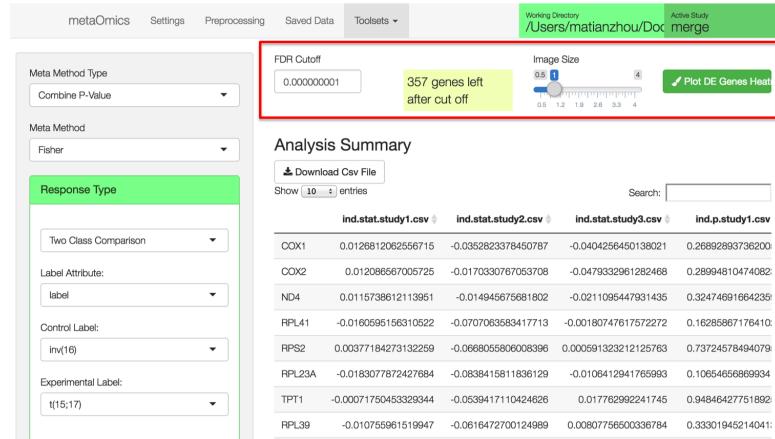


Figure 15: Plot heatmap setting

Shown in Figure 16 and Figure 17 are two heatmaps generated from Fisher and AW Fisher results. Note that one additional column of weight distribution across studies is added in the heatmap of AW-Fisher, and all genes in the heatmap are sorted based on their weight distribution.

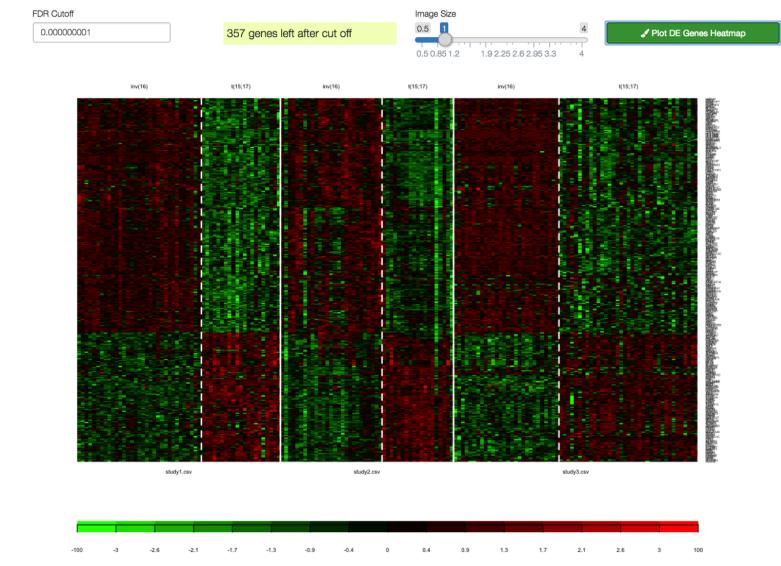


Figure 16: Heatmap based on Fisher results

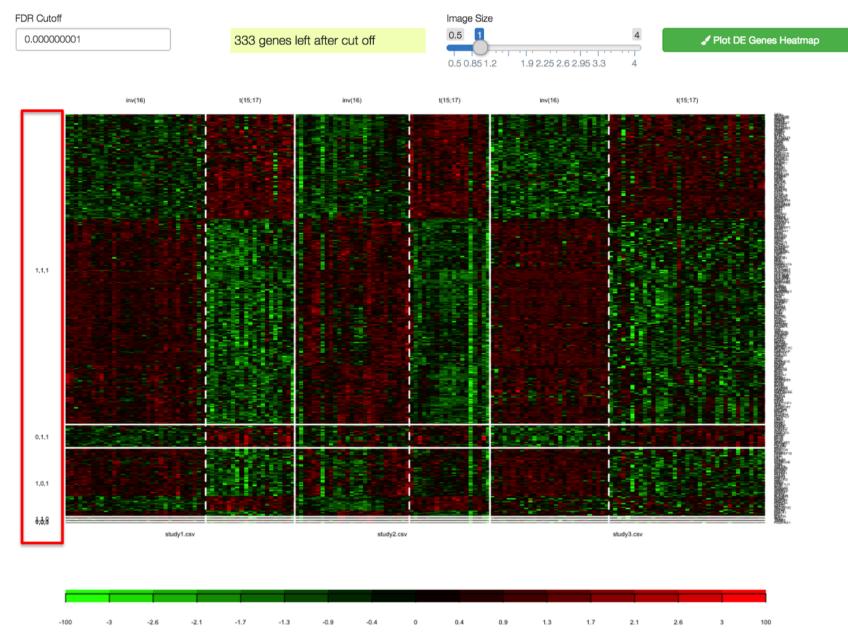


Figure 17: Heatmap based on AW Fisher results

#### 4.2.3 Downstream pathway analysis

Upon getting the meta differential analysis results (users have to perform meta DE analysis first before pathway analysis), we will further perform downstream pathway analysis. As shown in Figure 26, we first need to choose the Pathway databases to be used as shown in the highlighted box. Next we will choose the pathway enrichment method, the default is the Kolmogorov-Smirnov test (KS test, Figure 19). Alternatively, one can choose to use Fisher's exact test, once this method is selected, you need to pick a DE gene set using a hard threshold, either by p-value cutoff or the number of top ranked genes (Figure 28). Lastly, we will specify the minimum/maximum pathway size of pathways we wish to include for functional analysis, then click "Run Pathway Analysis".

	TPT1	RPL39	RPS18	ND2
-0.00071750453329344	-0.010755961519947	-0.0200442322714253	0.010455540876066	
-0.0539417110424626	-0.0616472700124989	-0.0718688592766959	0.00327594223827794	
0.017762992241745	0.00807756500336784	-0.00513492219189818	-0.0410391011942624	
0.94846	0.33301	0.096352	0.35294	

Figure 18: Selection of pathway database

Pathway Dayabases:

- KEGG GO Biological Process
- GO Cellular Component
- GO Molecular Function Reactome
- BioCarta

**Pathway Analysis Options**

Pathway Enrichment Method:

pathway min gene size

pathway max gene size

TPT1	-0.00071750453329344	-0.0539417110424626	0.017762992241745	0.94846	
RPL39	-0.010755961519947	-0.0616472700124989	0.00807756500336784	0.33301	
RPS18	-0.0200442322714253	-0.0718668592766959	-0.00513492219189618	0.096352	
ND2	0.0104555540876066	0.00327594223827794	-0.0410391011942624	0.35294	

Showing 1 to 10 of 2,515 entries    Previous         ...  Next

Figure 19: KS test setting

**Pathway Analysis Options**

Pathway Enrichment Method:

p-value cutoff

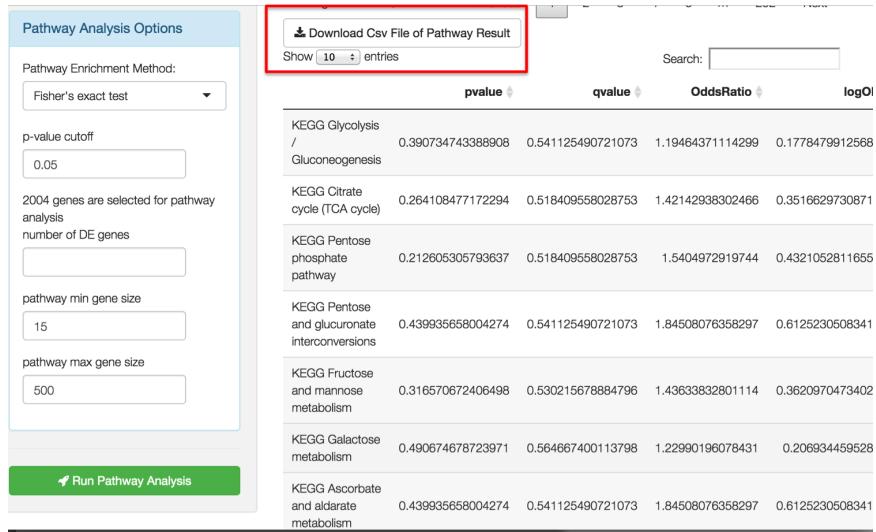
2004 genes are selected for pathway analysis  
 number of DE genes

pathway min gene size

pathway max gene size

Figure 20: Fisher's exact test setting

We will then see a summary table of pathway analysis results generated on the right of the page as shown in Figure 21. Users can search the pathway name in the “Search” bar, and download the full table as a csv file by clicking on “Download Csv File of Pathway Result” as highlighted.



The screenshot shows the 'Pathway Analysis Options' interface. On the left, there are input fields for 'Pathway Enrichment Method' (set to 'Fisher's exact test'), 'p-value cutoff' (set to '0.05'), and 'number of DE genes' (set to '2004 genes are selected for pathway analysis'). Below these are 'pathway min gene size' (set to '15') and 'pathway max gene size' (set to '500'). A green 'Run Pathway Analysis' button is at the bottom. To the right is a table of pathway results with columns: pvalue, qvalue, OddsRatio, and logOdds. A red box highlights the 'Download Csv File of Pathway Result' button above the table.

	pvalue	qvalue	OddsRatio	logOdds
KEGG Glycolysis / Gluconeogenesis	0.390734743388908	0.541125490721073	1.19464371114299	0.1778479912568
KEGG Citrate cycle (TCA cycle)	0.264108477172294	0.518409558028753	1.42142938302466	0.3516629730871
KEGG Pentose phosphate pathway	0.212605305793637	0.518409558028753	1.5404972919744	0.4321052811655
KEGG Pentose and glucuronate interconversions	0.439935658004274	0.541125490721073	1.84508076358297	0.6125230508341
KEGG Fructose and mannose metabolism	0.316570672406498	0.530215678884796	1.43633832801114	0.3620970473402
KEGG Galactose metabolism	0.490674678723971	0.564667400113798	1.22990196078431	0.206934459528
KEGG Ascorbate and aldarate metabolism	0.439935658004274	0.541125490721073	1.84508076358297	0.6125230508341

Figure 21: Summary of pathway analysis result

## 4.3 MetaPath

### 4.3.1 Run pathway analysis

After opening the MetaPath page, as shown in Figure 22, there are 3 main steps to implement MetaPath. We generally suggest users not to change any parameter setting in “Advanced” and “Advanced Options” unless users know the underlying methodology well.

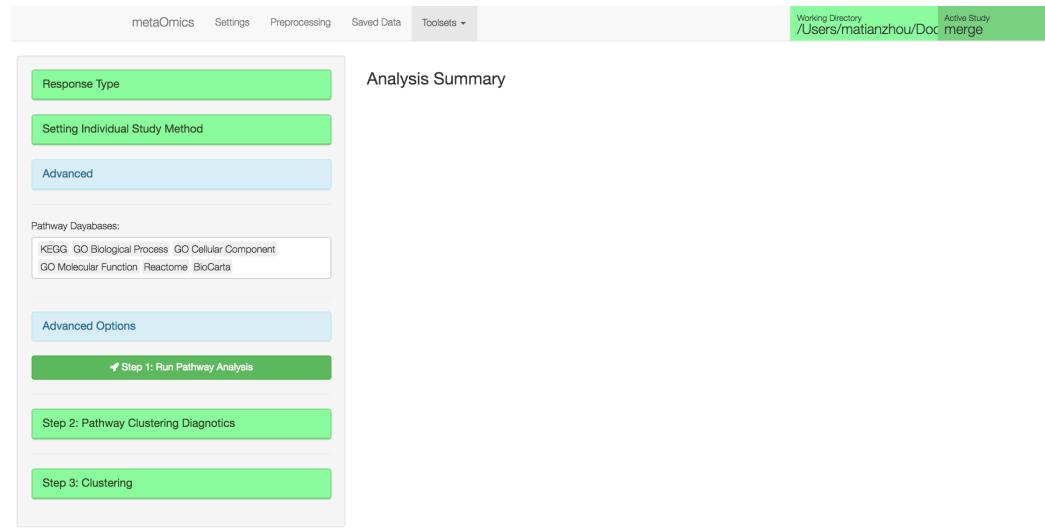


Figure 22: Homepage of MetaPath

To start, we need to perform DE (association) analysis in each individual study before performing pathway analysis for functional annotation. We click on “Response Type”, for two-class DE analysis, choose “Two Class Comparison”, choose the group label name for the Label Attribute (from the column names of your clinical data). Then for the group label (a factor of at least two levels), choose a name for the “Control Label” and “Experimental Label”, respectively (Figure 23).

This screenshot shows the 'Response Type' settings dialog box. A red box highlights the input fields for 'Two Class Comparison', 'Label Attribute', 'Control Label', and 'Experimental Label'. The 'Two Class Comparison' dropdown is set to 'label'. The 'Label Attribute' dropdown is set to 'label'. The 'Control Label' dropdown is set to 'inv(16)'. The 'Experimental Label' dropdown is set to 't(15;17)'. Below this dialog, there are green and blue buttons for 'Setting Individual Study Method' and 'Advanced'.

Figure 23: Response type setting

Then we click on “Setting Individual Study Method” and choose “LIMMA” to perform DE analysis in each individual study (Figure 24). Available options include “LIMMA” and “SAM” for continuous data (e.g. microarray), “edgeR”, “DESeq2” and “limmaVoom” for discrete data (e.g. RNA-seq count). Details of the above mentioned DE methods can be found in XXX (reference).

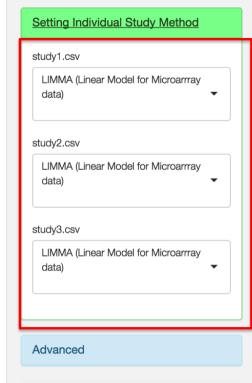


Figure 24: Individual study DE analysis method

Optionally, we can click on “Advanced” and choose whether to adjust for any important “Covariates” (e.g. potential confounders) and we set the alternative hypothesis to be “abs”, i.e. two-sided test (Figure 25).

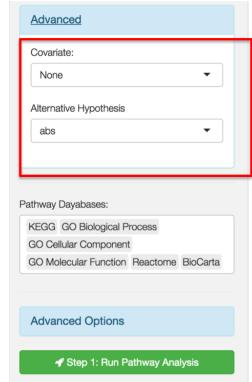


Figure 25: Advanced Options for single study association analysis

Next, we need to specify the parameters for pathway analysis. As shown in Figure 26, we first need to choose the Pathway databases to be used as shown in the highlighted box. Then optionally, we can click on the “Advanced Options” tab and choose the software to be used: CPI or MAPE. For CPI, we

can use the Kolmogorov-Smirnov test (Figure 27). CPI implements AW Fisher's method for meta p-value method in order to see both consensus and differential enrichment patterns. Alternatively, one can choose to use Fisher's exact test, once this method is selected, we need to pick the number of top ranked genes as the DE gene set for pathway analysis (Figure 28). For MAPE, the two tests are also available. There is one additional option of meta p-value method, available options include Fisher's method, maxP, minP, rOP and AW Fisher' method (Figure 29). When rOP is selected, additional option for order statistic of p-value (rth ordered p-value) will be available. Instead of closed-form distributions, users can use permutation of gene labels to get pathway p-value forthe Kolmogorov-Smirnov test (Figure 29). When "Permutation to get p-value" is choosen to be "YES", additional option for number of permutations will be available. However, we generally suggest users not to run permutation because it may take up to hours to compute. Lastly, we will specify the minimum/maximum pathway size of pathways we wish to include for functional analysis, then click "Step 1: Run Pathway Analysis".

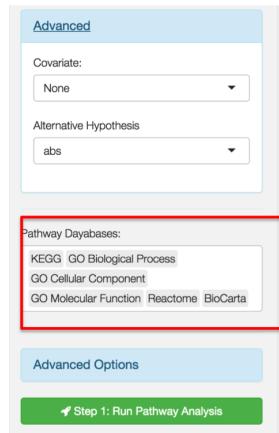


Figure 26: Selection of pathway database

Advanced Options

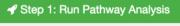
Software: CPI (Comparative Pathway Integrator)

Pathway Enrichment Method: Kolmogorov-Smirnov test

Permutation to get p-value  
 YES  
 No

pathway min gene size: 15

pathway max gene size: 500

 Step 1: Run Pathway Analysis

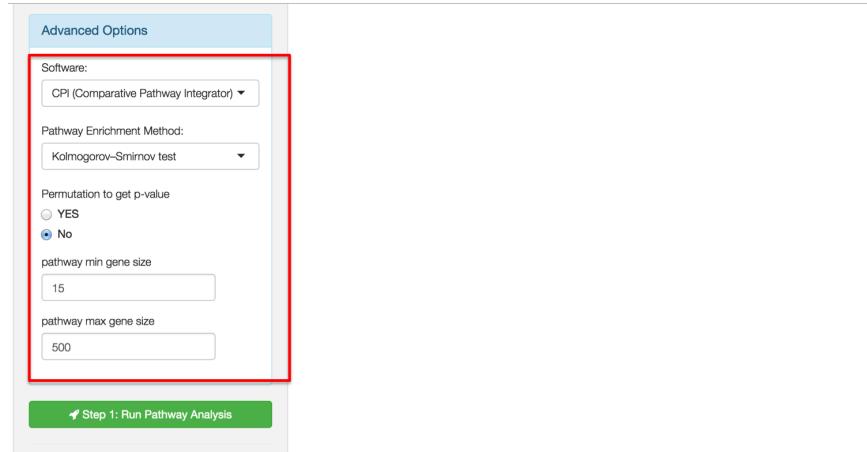


Figure 27: CPI setting

Advanced Options

Software: CPI (Comparative Pathway Integrator)

Pathway Enrichment Method: Fisher's exact test

number of DE genes: 500

pathway min gene size: 15

pathway max gene size: 500

 Step 1: Run Pathway Analysis

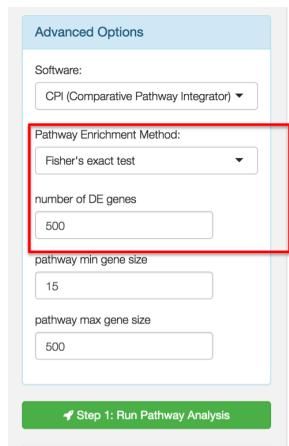


Figure 28: Fisher's Exact Test

Advanced Options

Software: MAPE (Meta Analysis Pathway Enrichment)

meta p-value method: Fisher's method

Pathway Enrichment Method: Kolmogorov-Smirnov test

Permutation to get p-value:  YES  No

pathway min gene size: 15

pathway max gene size: 500

**Step 1: Run Pathway Analysis**

Figure 29: MAPE setting

We will see a summary table generated on the right of the page as shown in Figure 30 (based on the default CPI method). The “Analysis Summary” includes the analysis results of all pathways, including individual study association analysis p-value, meta pathway analysis p-value/FDR, etc. Users can search the gene name in the “Search” bar, and the full table is automatically saved in the working directory specified before.

Analysis Summary

Show: 10 entries Search:

	q_value_meta	p_value_meta	study1.csv	study2.csv	st
KEGG Glycolysis / Gluconeogenesis	0.999891275288248	0.964947989936307	0.768190803653848	0.676076162705849	0.7284606
KEGG Citrate cycle (TCA cycle)	0.891811044872201	0.175518611360224	0.0573525548842899	0.970668185433847	0.8046806
KEGG Pentose phosphate pathway	0.7913969668697601	0.116064687783132	0.150287056538356	0.805413213928083	0.03869676
KEGG Pentose and glucuronate interconversions	0.951646614020744	0.2711446005587264	0.557913386174218	0.0956407642622913	0.4242034
KEGG Fructose and mannose metabolism	0.936196204581523	0.218775012548455	0.41175995909666	0.0741963837197967	0.3142786
KEGG Galactose metabolism	0.802434783787353	0.122637091749799	0.0521931958940879	0.906116662919474	0.1200277
KEGG Ascorbate and aldarate metabolism	0.999891275288248	0.560695412981379	0.741610716462521	0.240307883811889	0.4251336

Figure 30: Summary table of CPI analysis results

### 4.3.2 Pathway clustering

In the next step, we performed clustering diagnostics of pathways at specified FDR cutoff (Figure 31). After clicking on “Pathway Cluster Diagnostics”, we will see two plots generated on the right panel: consensus CDF and Delta area plots (Figure 32), we can use these two plots to determine the optimal number of clusters, to be used in the third clustering step.



Figure 31: Pathway clustering diagnostics

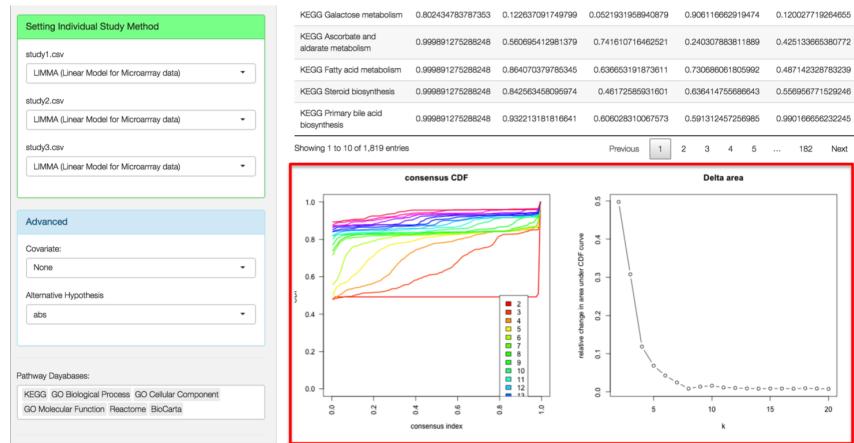


Figure 32: Diagnostic plots

### 4.4 MetaClust

By clicking toolsets and then metaClust, users are directed to metaClust home page as Figure 33.

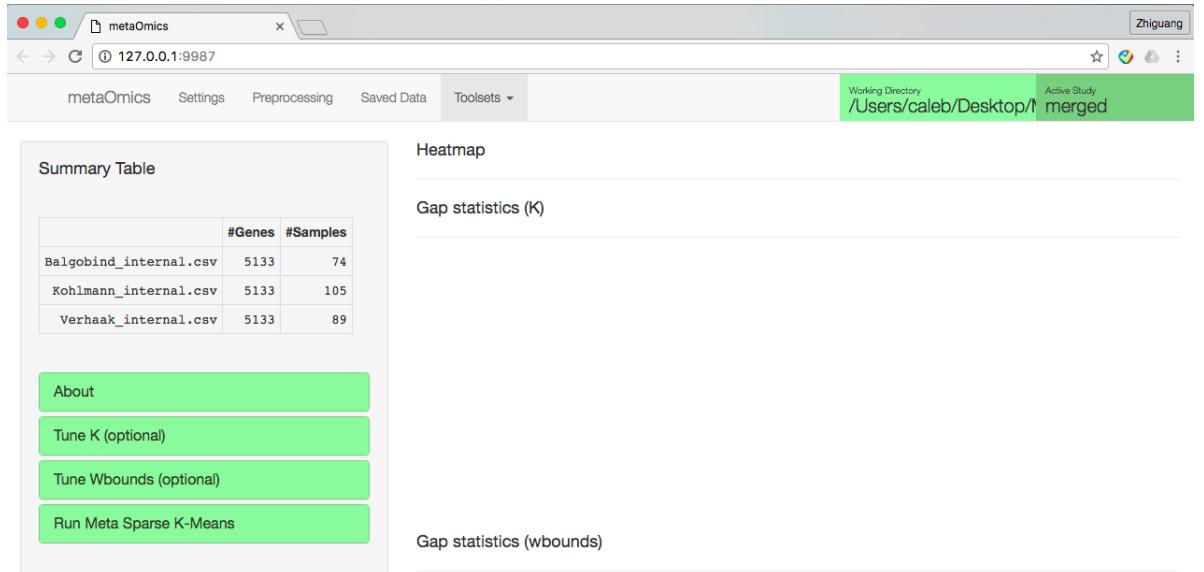


Figure 33: GUI Preprocessing page

On the top left panel users can see data summary Table. Below there are 4 tabs.

#### 4.4.1 About

About tab includes basic introduction of metaClust. Starting with multiple studies, we could run MetaSparseKmeans with pre-specified number of clusters (K) and gene selection tuning parameter (Wbounds). If you are not sure about what are good K and Wbounds, please try Tune K and Tune Wbounds panel.

#### 4.4.2 Tune K

If the users are not sure what is number of clusters, they can start to use the Tune K panel as in Figure 34.

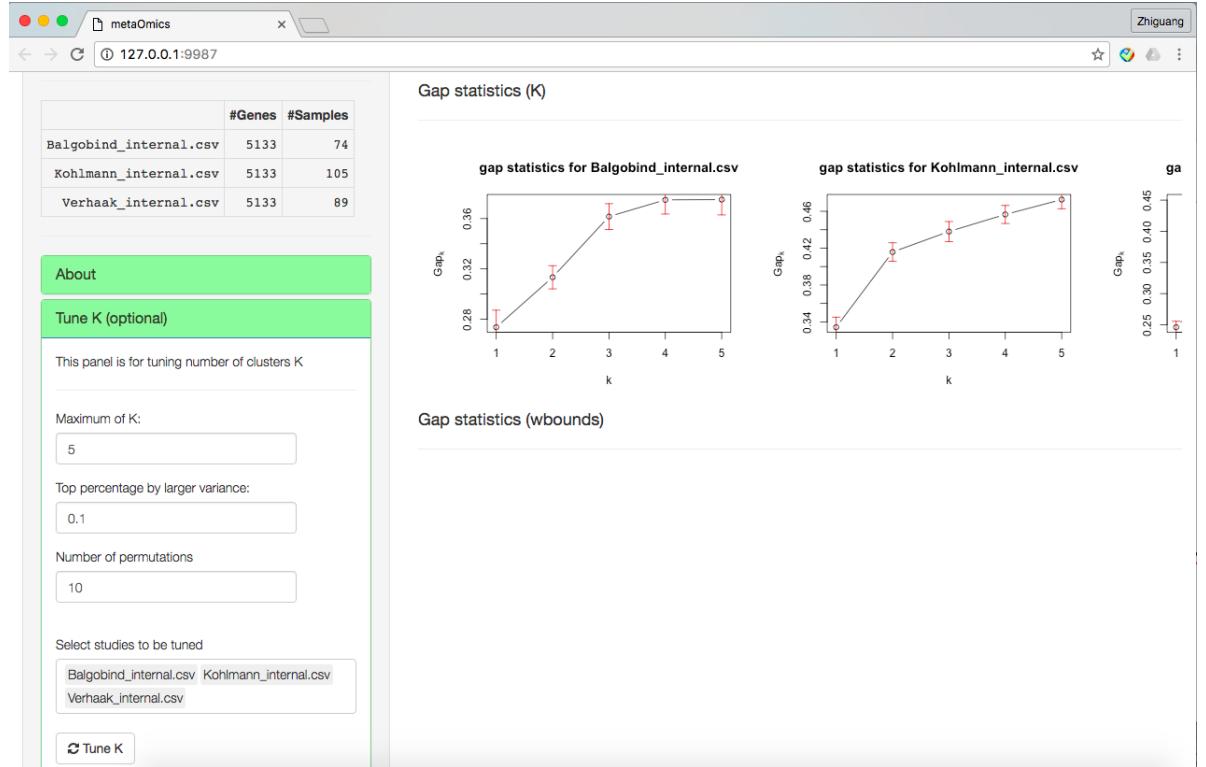


Figure 34: GUI Preprocessing page

Users will use gap statistics to get optimal K for each individual study. Users need to specify maximum number of K, which the algorithm will search number of studies from 1 to K. Top percentage p% by larger variance means that we will use top p% larger variance genes to perform gap statistics. Number of permutation is number of bootstrap samples for gap statistics. After selecting studies to be tuned and clicking button “Tune K”, we will obtain gap statistics plat as in Figure 34. A good K is selected such that the  $\text{Gap}_k$  is maximized or stabilized. From the figure, K=3 is preferred.

#### 4.4.3 Tune Wbounds

Wbounds directly control number of features selected by metaClust. If the users are not sure what is a good Wbound, they can start to use the Tune Wbounds panel as in Figure 35.



Figure 35: GUI Preprocessing page

Again, gap statistics will be used for tuning Wbounds. Users will specify number of clusters for tuning Wbounds, which could be obtained from the previous step. Iterations is the same thing as number of bootstrap samples for gap statistics. Users also need to specify the searching space of Wbounds by minimum of Wbounds, maximum of Wbounds and Step of Wbounds. After all these steps are set, user can click on “Tune Wbounds” button. The results will be shown in Figure 35. Wbound=12 is preferred since the corresponding gap statistics is maximized.

#### 4.4.4 Run Meta Sparse K-Means

Under Run Meta Sparse K-Means panel, user can specify number of clusters, Wbounds and run meta sparse K means, as in Figure 36.

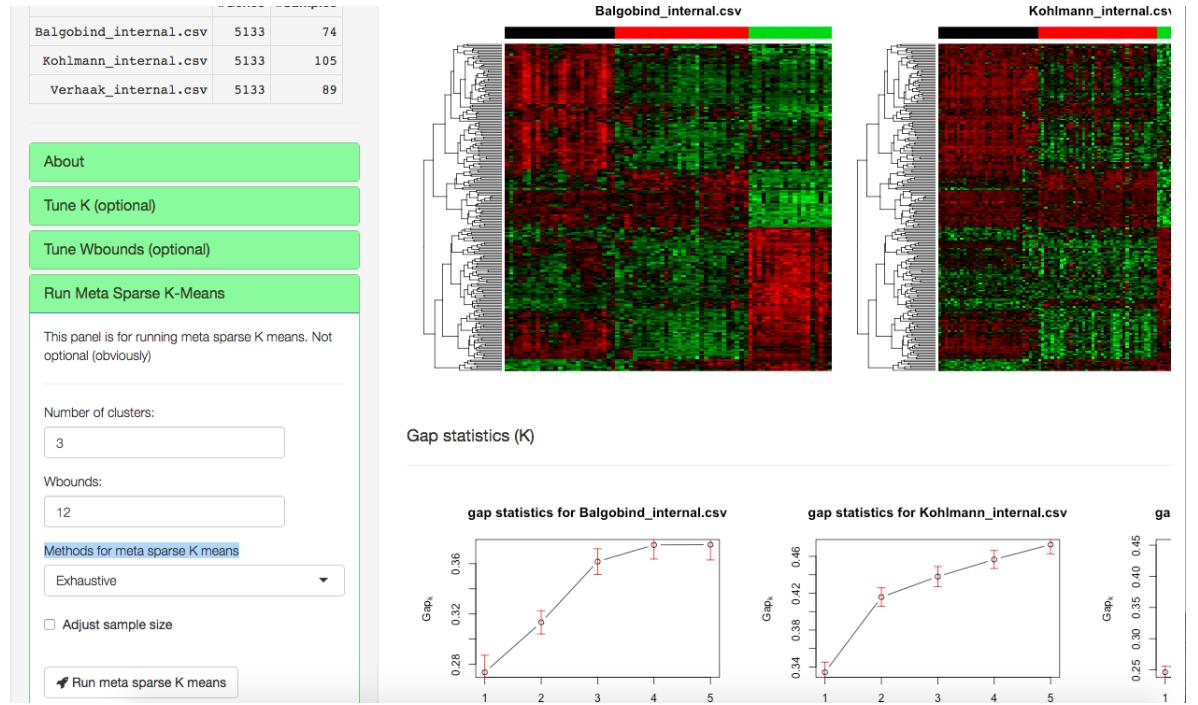


Figure 36: GUI Preprocessing page

There are three clustering matching methods: Exhaustive, linear, MCMC. Exhaustive is suggested if the data is not large. Linear will perform smart search and get solution much faster than Exhaustive, but it may yield less accuracy. MCMC might be very time consuming. Adjust sample size checkbox allows users to adjust sample size effect. After number of clusters and Wbounds are specified, users can click on Run meta sparse K means and obtain results as Figure 36.

#### 4.5 metaPCA

By clicking toolsets and then metaPCA, users are directed to metaPCA home page as Figure 37.

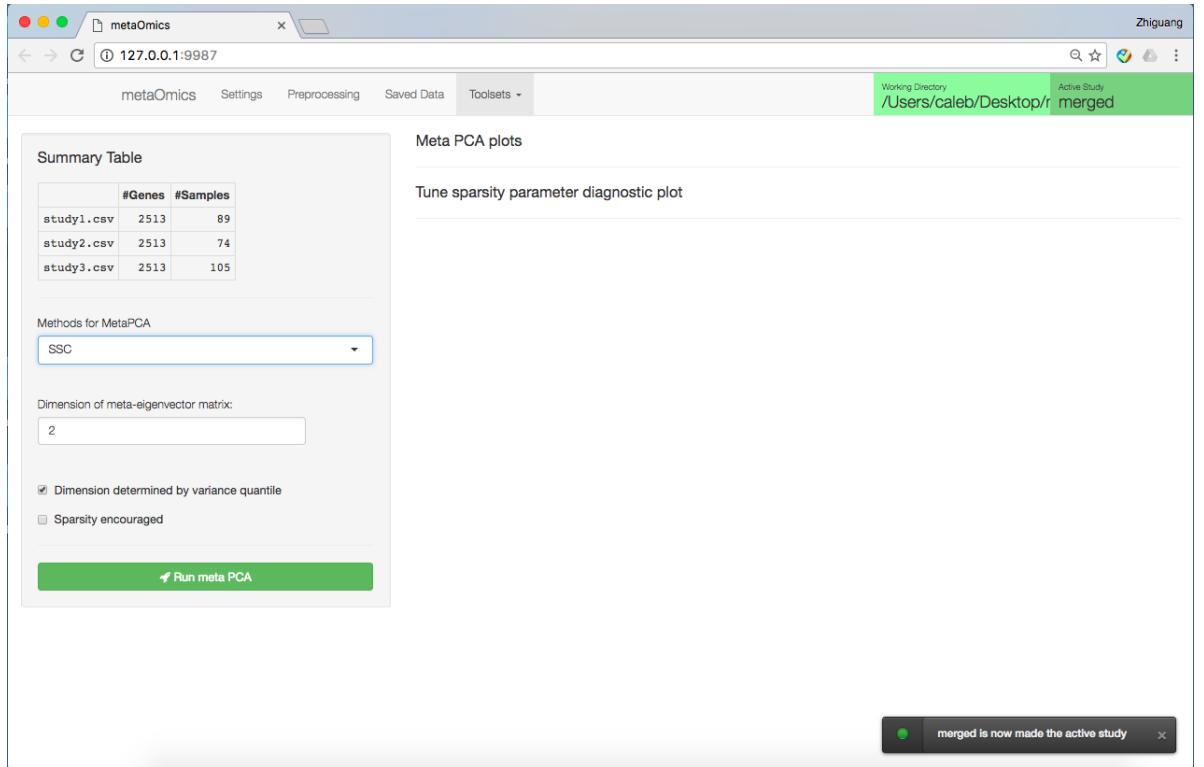


Figure 37: GUI Preprocessing page

On the top left panel users can see data summary Table. Below there are several options.

#### 4.5.1 Methods for MetaPCA

- MetaPCA via sum of variance decomposition (SV)

Let  $X^{(m)}$  be an observed  $p \times n^{(m)}$  data matrix of sample size  $n^{(m)}$  and  $p$  features for study  $m$  ( $1 \leq m \leq M$ ). Denote by  $S^{(m)}$  the maximum likelihood (ML) estimate of the  $p \times p$  covariance matrix  $\Omega^{(m)}$  of  $X^{(m)}$ . MetaPCA via sum of variance decomposition (SV) aims to solve the following eigen-value decomposition problem.

$$T^{SV} = \sum_{m=1}^M w^{(m)} S^{(m)}, \quad (1)$$

where  $w^{(m)}$  is the reciprocal of the largest eigenvalue of  $S^{(m)}$ . The common principal components  $L$  are calculated from the eigen-decomposition of

$T^{SV} : L^T(T^{SV})L = \Lambda$  and  $K$  top common PCs should be retained for down-stream analysis. Selection of the optimal  $K$  will be described later in the section of Parameter selection.

- MetaPCA via sum of squared cosine (SSC) maximization.

the second MetaPCA framework motived by SSC criterion proceeds as below. The top  $j^{(m)}$  eigenvectors are calculated from study  $m$  to form eigenvector matrix  $V^{(m)}$ . We then perform eigen-decomposition on  $T^{SSC} = \sum_{m=1}^M V^{(m)}V^{(m)^T}$  and select the top  $K$  eigenvectors to form the meta-analytic common eigen-space:

$$\left( \sum_{m=1}^M V^{(m)}V^{(m)^T} \right) B^{SSC} = \Lambda^* B^{SSC} \quad (2)$$

where  $V^{(m)}$  is a matrix consisting of  $j^{(m)}$  leading eigenvectors,  $\Lambda^*$  is a diagonal eigenvalue matrix, and  $B^{SSC} = (\beta_1^{SSC}, \dots, \beta_K^{SSC})$  contains the top  $K$  eigenvectors.

#### 4.5.2 Dimension of meta-eigenvector matrix

Dimension of meta-eigenvector matrix option allows user to specify dimension of the output meta-eigenvector matrix.

#### 4.5.3 Dimension determined by variance quantile

Logical value whether dimension size of each study's eigenvector matrix (SSC) is determined by the pre-defined level of variance quantile 80%.

#### 4.5.4 Sparsity encouraged

If the Sparsity encouraged checkbox is selected, we are able to tune the best tuning parameter  $\lambda$  and perform sparse metaPCA. After clicking on search for optimal tuning parameter button, the optimum tuning parameter will be returned to the box “tuning parameter for sparsity”

#### 4.5.5 Run meta PCA

If Sparsity encouraged checkbox is selected, sparse meta PCA will be performed. Otherwise, meta PCA will be performed. The result is shown in the following figures.

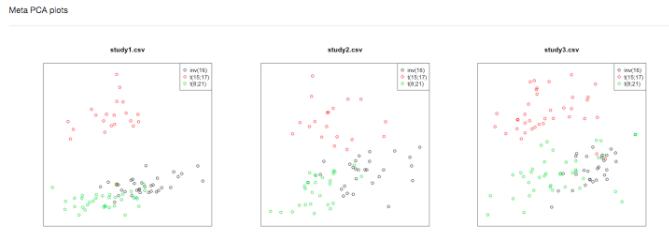


Figure 38: GUI Preprocessing page

## 4.6 MetaKTSP

### 4.6.1 Building prediction model based on meta-analysis

After opening the MetaKTSP page, as shown in Figure 39, there are 1 drop-down menu (“Methods for Meta KTSP”), three number entries (“Max number of top scoring pairs (K)”, “Number of cores for parallel computing” and “Number of top scoring pairs (K)”), three character entries (“Please select TWO labels to cluster”, “Please select studies for training”, and “Please select studies for testing”) , and two tabs (“Train model” and ”Predict”).

The screenshot shows the homepage of the MetaKTSP application. At the top, there is a navigation bar with links for 'metaOmics', 'Settings', 'Preprocessing', 'Saved Data', 'Toolsets', 'Working Directory' (set to '/Users/Masak/Dropbox'), 'Active Study' (set to 'Demo'), and 'Demo'. Below the navigation bar, there are two main sections: 'Summary Table' and 'Gene pair table'.

**Summary Table:**

#Genes	#Samples
2515	89
2515	74
2515	105

**Methods for Meta KTSP:**

Mean score

Max number of top scoring pairs (K): 9

Number of cores for parallel computing: 2

Please select TWO labels to cluster: (empty input field)

Please select studies for training: (empty input field)

Please select ONE study for testing: (empty input field)

**Train model** button (green)

Number of top scoring pairs (K): 9

**Predict** button (green)

**Gene pair table** and **K diagnostic plot** sections are visible but empty.

Figure 39: Homepage of MetaKTSP

First, we need to decide a method to select K top scoring gene pairs from multiple studies (Figure 40). Second, we need to provide the maximum number of top scoring pairs  $K$  (algorithm will search from 1 up to  $K$ ) and the number of cores for parallel computing (Figure 41). Next, we need to select only TWO labels to build the classification model. In other words, if the data exists over two kinds of labels, we need to choose two from them. Our interface will pop up all labels that are available (Figure 42). Then, select the dataset as training data and testing respectively, and click the "Train model" tab to run the MetaKTSP program (Figure 43). It may take a while to run the model.

metaOmics   Settings   Preprocessing   Saved Data   Toolsets ▾

Working Directory  
/Users/Masak/Dropbox

Active Study  
Demo

**Summary Table**

#Genes	#Samples
2515	89
2515	74
2515	105

**Gene pair table**

**K diagnostic plot**

**Methods for Meta KTSP**

Mean score

Max number of top scoring pairs (K)

Number of cores for parallel computing

Please select TWO labels to cluster

Please select studies for training

Please select ONE study for testing

**Train model**

Number of top scoring pairs (K)

**Predict**

Figure 40: Select meta-analysis method.

metaOmics   Settings   Preprocessing   Saved Data   Toolsets ▾

Working Directory  
/Users/Masak/Dropbox

Active Study  
Demo

**Summary Table**

#Genes	#Samples
2515	89
2515	74
2515	105

Methods for Meta KTSP

Mean score

Max number of top scoring pairs (K)  
9

Number of cores for parallel computing  
2

Please select TWO labels to cluster

Please select studies for training

Please select ONE study for testing

Train model

Number of top scoring pairs (K)  
9

Predict

Figure 41: Select maximum number of top scoring pairs and number of cores for parallel computing.

metaOmics   Settings   Preprocessing   Saved Data   Toolsets ▾

Working Directory: /Users/Masak/Dropbox   Active Study: Demo

**Summary Table**

#Genes	#Samples
2515	89
2515	74
2515	105

Methods for Meta KTSP

Mean score

Max number of top scoring pairs (K)  
9

Number of cores for parallel computing  
2

Please select TWO labels to cluster  
 inv(16)    t(8;21)

Please select studies for training

Please select ONE study for testing

 Train model

Number of top scoring pairs (K)  
9

 Predict

**Gene pair table**

K diagnostic plot

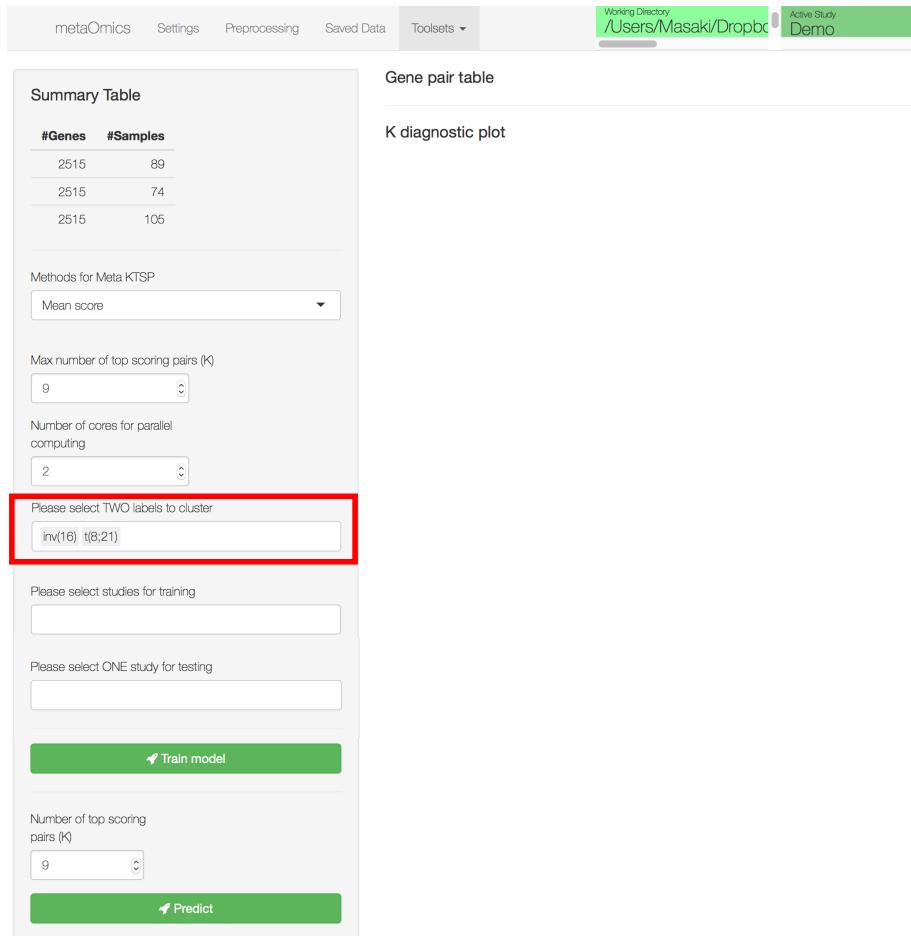


Figure 42: Select only two labels to build the classification model.

The screenshot shows the 'metaOmics' software interface with the 'Tools' tab selected. The 'Gene pair table' tab is active. On the left, there's a 'Summary Table' showing the number of genes and samples: 2515 genes across 89, 74, and 105 samples. Below it are sections for 'Methods for Meta KTSP' (Mean score dropdown), 'Max number of top scoring pairs (K)' (set to 9), 'Number of cores for parallel computing' (set to 2), and 'Please select TWO labels to cluster' (inv(16) | t(8;21)). The main area has two input fields: 'Please select studies for training' containing 'study1.csv' and 'study2.csv', and 'Please select ONE study for testing' containing 'study3.csv'. A large green button at the bottom labeled 'Train model' is highlighted with a red box.

Figure 43: Select training dataset and testing dataset and hit the “Train model” tab to run the MetaKTSP program.

After the model training is finished, on the top right it will show up a “Gene pair table” which present the top  $K$  gene pairs statistics (Figure 44). As shown in Figure 45, a diagnostic plot is output to assist users decide which  $K$  to use in the final prediction model. The suggested value is shown in the plot as green line, which is decided by VO method we introduced in the original paper. Users may also decide  $K$  on their own to predict the class label of testing data. After deciding  $K$ , then hit the tab “Predict” (Figure 46). Finally, a confusion matrix is output to show the prediction results (Figure 47).

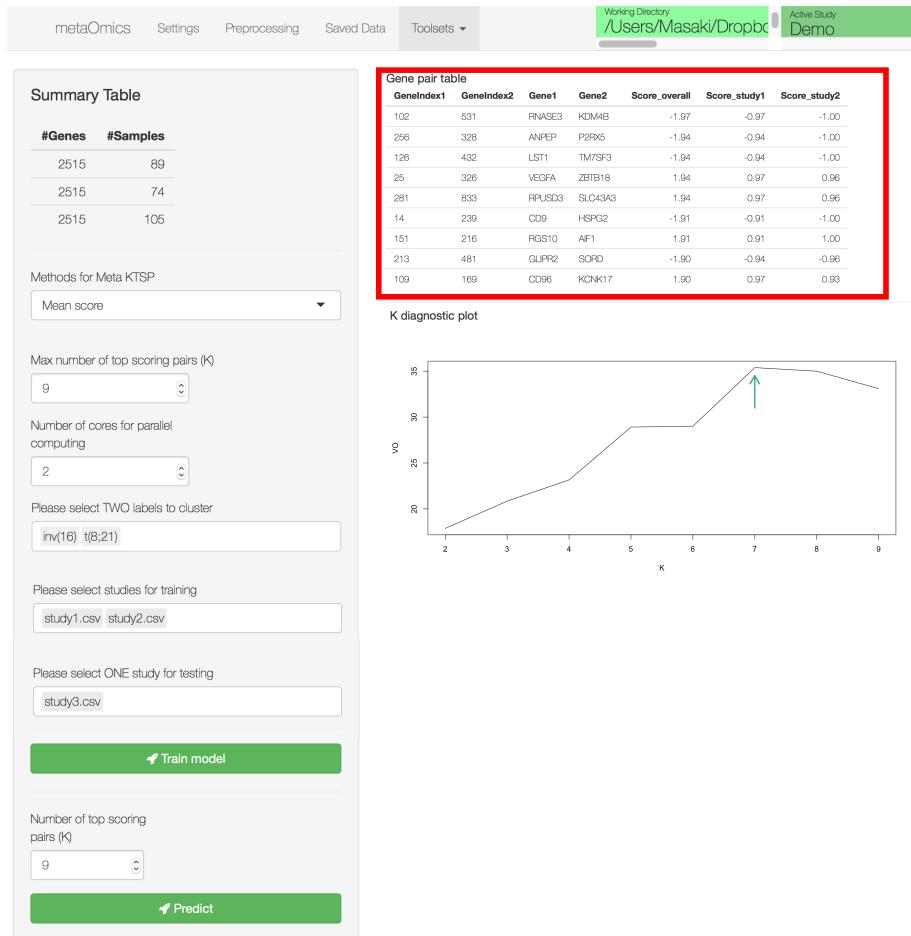


Figure 44: Gene pair table presents the statistics for  $K$  top scoring pairs.

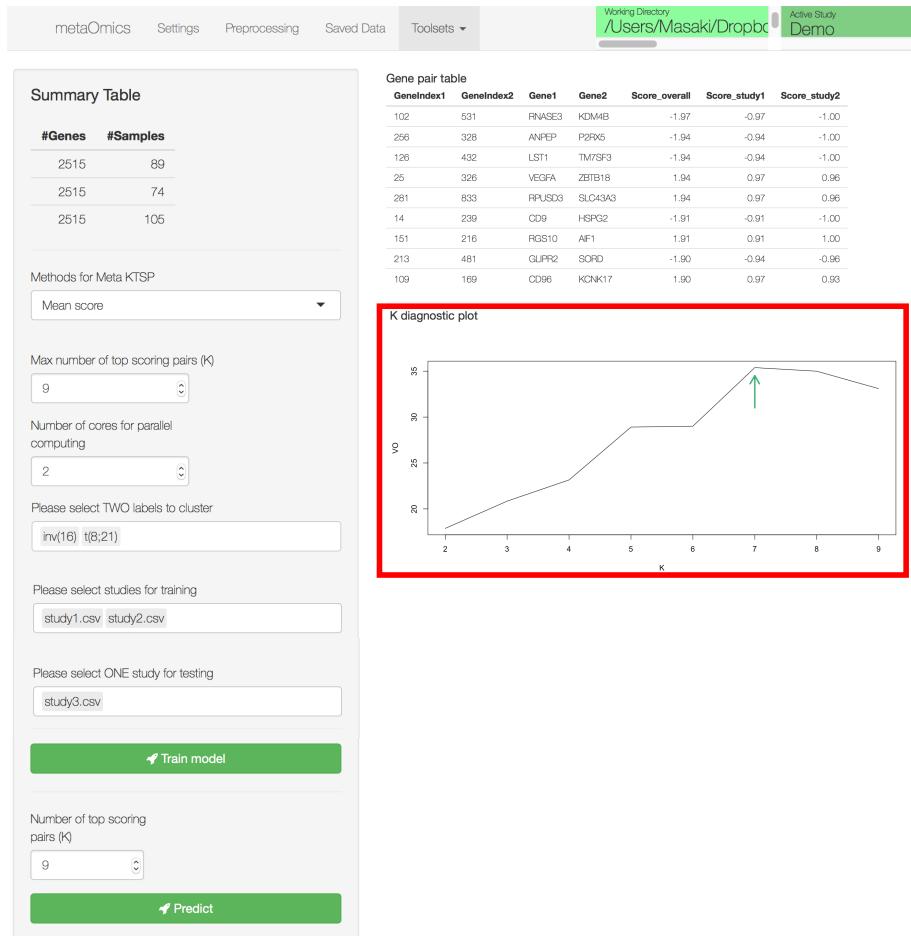


Figure 45: Diagnostic plot for choosing optimal  $K$  from training model. It will be used for predicting the class labels for testing dataset.

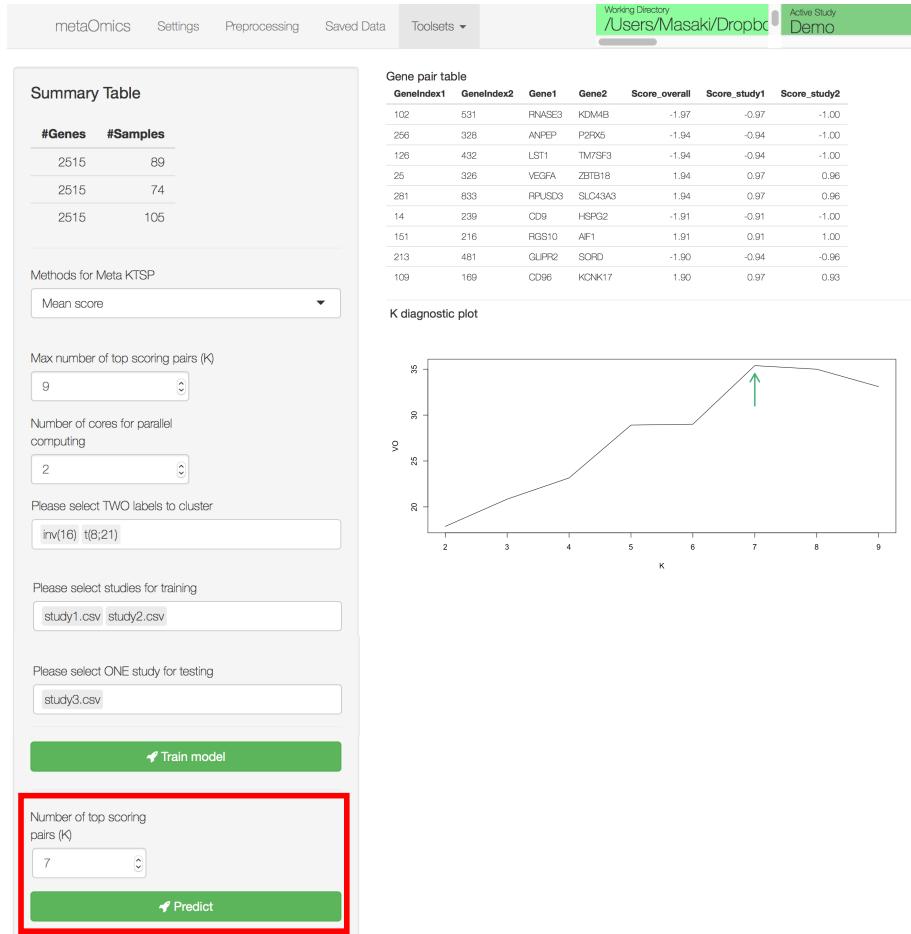


Figure 46: Choose the optimal  $K$  for prediction model. Hit tab “Predict” to perform prediction for testing dataset.

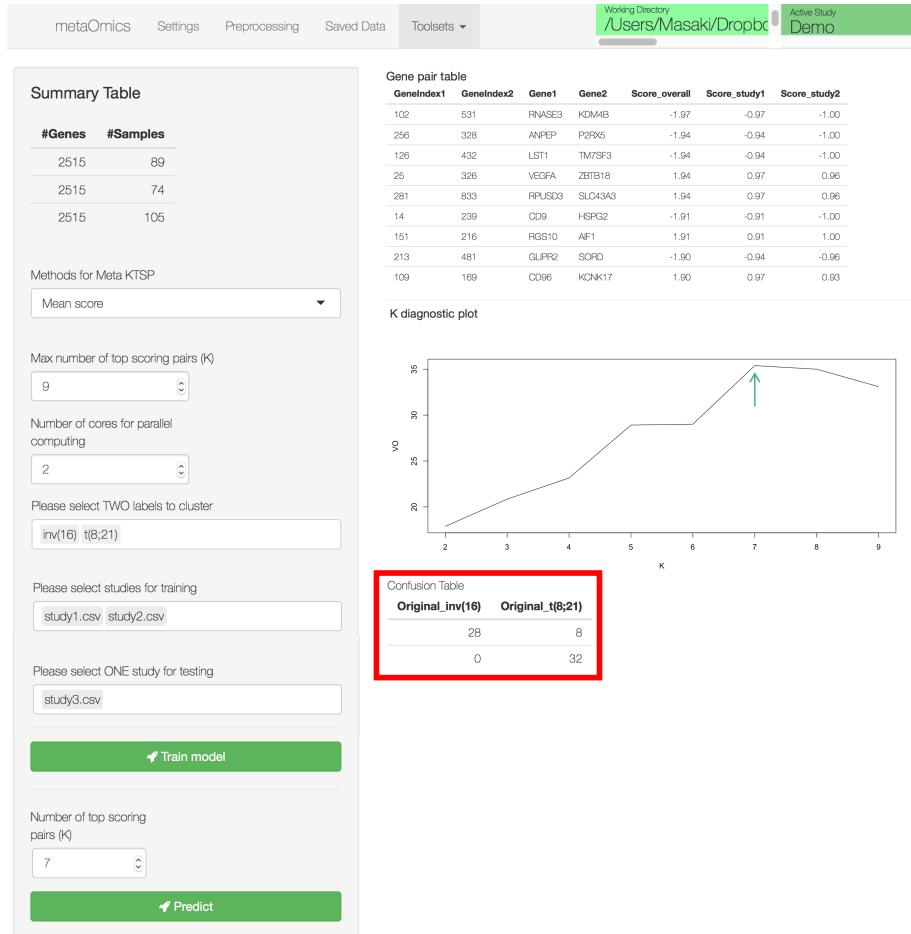


Figure 47: Prediction result based on testing data using 7 top scoring pairs derived from MetaKTSP model. The column of the confusion matrix is the given class label and the row is the prediction result.

## 4.7 MetaDCN

By clicking toolsets and then metaDCN, users are directed to metaDCN home page as Figure 48.

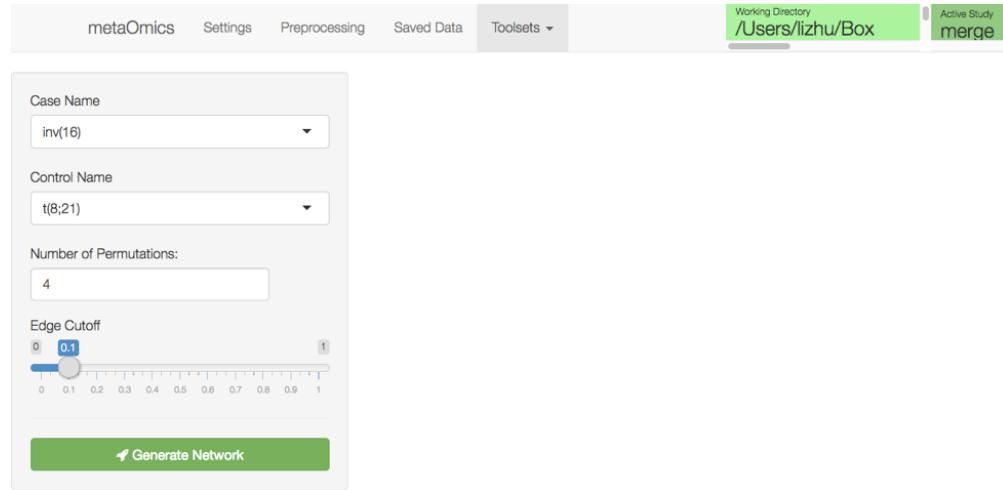


Figure 48: MetaDCN homepage

MetaDCN includes three steps to get differentially co-expressed networks: generate network, search for basic modules, and assemble supermodules. The left screen is the control panel of step 1. The control panel for next step will show up after the previous step is done.

#### 4.7.1 Generate Network

The first step of MetaDCN is to generate network. In this step, the network for permuted data will also be generated. Users need to select case and control names, the number of permutations, and edge cut-off which determines the proportion of edges to be kept in the network. After clicking **Generate Network** button, screen will show message indicating the algorithm is running to generate network.

After the generate network step is done, no output will show up in the screen. Instead, a message box indicating several Rdata files are saved in the Meta DCN folder, including:

- **AdjacencyMatrices.Rdata** is a list of adjacency matrices for case and control subjects in each study. The order is study1 case, study2 case, ..., studyS case, study1 control, study2 control, ..., studyS control.
- **CorrelationMatrices.Rdata** is a list of correlation matrices for case and control subjects in each study.
- **AdjacencyMatricesPermutationP.Rdata** is a list of adjacency matrices for permuted datasets in permutation P.

#### 4.7.2 Search for basic modules

After the generate network step is done, the control panel will be as Figure 49. The next step is to search for basic modules. Users need to specify the number of repeats used for each initial seed modules (Number to repeat), the maximum Monte Carlo steps for simulated annealing algorithm (MC Steps), and the maximum pairwise Jaccard index allowed for basic modules (Jaccard Cutoff). After clicking **Search for basic modules** button, screen will show message indicating the algorithm is running to search for basic modules.

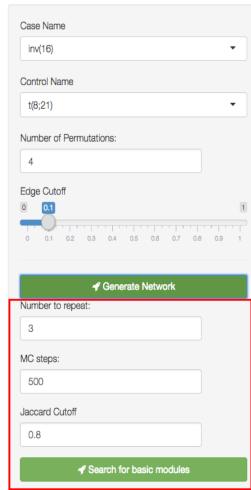


Figure 49: MetaDCN control panel for search for basic modules

Search for basic modules will take minutes, especially if a large number of genes are used. After this step is done, the screen will show a table of basic modules higher correlated in case and a table of basic modules higher correlated in control as Figure 50. Meanwhile, several files will be saved in the Meta DCN folder:

- basic\_modules\_summary\_forward\_weight\_w1.csv is a summary table of basic modules that are higher correlated in case, detected using w1.
- basic\_modules\_summary\_backward\_weight\_w1.csv is a summary table of basic modules that are higher correlated in control, detected using w1.
- threshold\_forward.csv is a table of number of basic modules higher correlated in case, detected under different w1 values and FDR cut-offs.
- threshold\_backward.csv is a table of number of basic modules higher correlated in control, detected under different w1 values and FDR cut-offs.

- permutation\_energy\_forward\_P.Rdata is a list of energies for basic modules that higher correlated in case, detected from permutation P.
- permutation\_energy\_backward\_P.Rdata is a list of energies for basic modules that higher correlated in control, detected from permutation P.

Basic modules higher correlated in case:

Module.Index Component.Number Repeat.Index Gene.Set			
1 H1	2	1	PSAP/CTSS/CECR1/LGALS3/AP1S2/TLR2/HEXB/SMM24/CTSB/OGFRL1/MYO1F/CPXM1/SERPINA1/MNDA/TNF
2 H2	2	2	SERPINA1/AP1S2/CECR1/SMM24/PSAP/TRBV27/RGS10/CPXM1/TLR2/CAPN2/OGFRL1/MS4A6A
3 H3	2	3	CTSB/TLR2/RGS10/HEXB/SERPINA1/CECR1/LGALS3/AP1S2/SMM24/S100A9/CPXM1/MAP2K1/CAPN2
4 H4	6	1	NFIL3/IER3/CD83/CPXM1/EZR/RIPK2/SLC2A3
5 H5	6	2	NFIL3/IER3/LCP1/CDKN1A/TCEAL4/TGFB1
6 H6	6	3	NFIL3/LYN/IER3/LCP1/UCP2/MARCKSL1/RAB11FIP1

Showing 1 to 6 of 6 entries

Previous 1 Next

Basic modules higher correlated in control:

Module.Index Component.Number Repeat.Index Gene.Set			
1 L1	2	1	GCA/FABP5/PRR11/PCNA/C1QBP/MAFF/FAM107B/PRDX3/TNFSF13B/PRTN3/PRKACB/CBF/CAT/RAB10/AN1
2 L2	2	2	ICAM3/TGFB1/TYROBP/PLP2/BIN2/HCST/MYO1F/TIMP1/LAPTM5/S100A9
3 L3	2	3	PCNA/FAM107B/GCA/PRTN3/C1QBP/KIAA0101/EZR/RAB10/CAT/PRDX3/TNFSF13B/ANP32E/DYNLL1
4 L4	6	1	SLC2A3/JUP/LYN/PPP1R15A/EZR/PCNA/RAB10/FLNA/PIM3/KLF6
5 L5	6	2	STAM/JUP/LYN/PIM3/PDLIM1/HLA-DPA1/ITM2A/TPSAB1/CST
6 L6	6	3	SLC2A3/STAM/JUP/LYN/PPP1R15A/PCNA/FLNA/PLP2/HLA-DPA1

Showing 1 to 6 of 6 entries

Previous 1 Next

Figure 50: MetaDCN output from search for basic modules step

#### 4.7.3 Assemble supermodules

After search for basic modules step is done, the control panel will be Figure 51. The last step is to assemble supermodules. Users can decide the FDR cut-off to select basic modules for supermodule assembly. After clicking **Assemble supermodules** button, screen will show message indicating the algorithm is running to assemble supermodules.

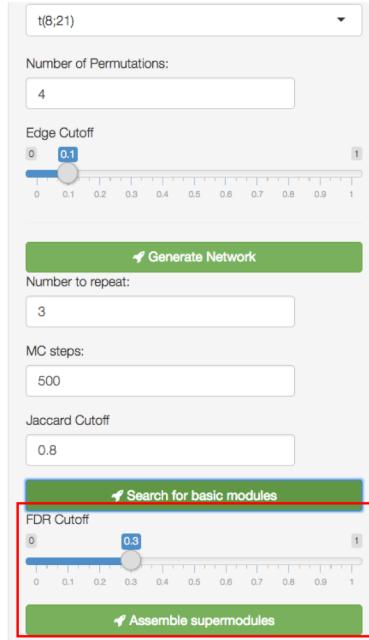


Figure 51: MetaDCN control panel for assemble supermodules step

After supermodule assembly is done, screen will show a table of supermodules (Figure 52). Users can also select basic modules to plot (Figure 53). Meanwhile several files will be saved in the folder MetaDCN:

- module\_assembly\_summary\_weight\_w1.csv is summary table of supermodules using w1 weight.
- CytoscapeFiles folder contains the input files for Cytoscape to visualize supermodules.

MetaDCN pathway-guided supermodules				
pathway_name	pathway_size	p_value	q_value	size
KEGG_LYSOSOME	121	9.73e-05	0.01	20
REACTOME_MHC_CLASS_I_ANTIGEN_PRESENTATION	91	0.00697	0.093	20
REACTOME_PLATELET_ACTIVATION_SIGNALING_AND_AGGREGATION	208	0.00495	0.093	25
REACTOME_RESPONSE_TO_ELEVATED_PLATELET_CYTOSOLIC_CA2_	89	0.00281	0.093	22
BIOCARTA_MCALPAIN_PATHWAY	25	0.00283	0.093	30
GO_CYTOSKELETAL_PROTEIN_BINDING	159	0.00185	0.093	13
REACTOME_COSTIMULATION_BY_THE_CD28_FAMILY	63	0.00431	0.093	14
GO_ACTIN_FILAMENT_BINDING	25	0.00369	0.093	13
BIOCARTA_CTRP_PATHWAY	12	0.00725	0.093	18
GO_ACTIN_CYTOSKELETON_ORGANIZATION_AND_BIogenesis	105	0.00697	0.093	20

Showing 1 to 10 of 103 entries      Previous 1 2 3 4 5 ... 11 Next

Figure 52: MetaDCN supermodules table

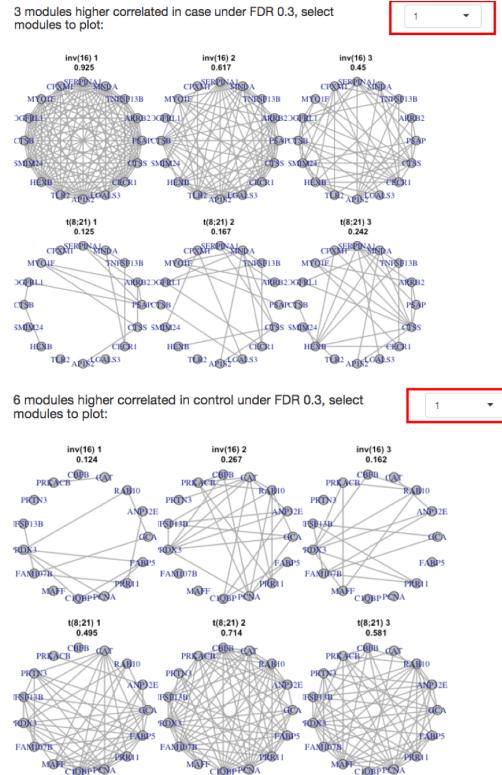


Figure 53: MetaDCN select basic modules to plot

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