

QUBIC Tutorial

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Gene expression data is very important in experimental molecular biology (Brazma and Vilo 2000), especially for cancer study (Fehrmann et al. 2015). The large-scale microarray data and RNA-seq data provide good opportunity to do the gene co-expression analyses and identify co-expressed gene modules; and the effective and efficient algorithms are needed to implement such analysis. Substantial efforts have been made in this field, such as Cheng and Church (2000), Plaid (Lazzeroni, Owen, and others 2002), Bayesian Biclustering (BCC, Gu and Liu 2008), among them Cheng and Church and Plaid has the R package implementation. It is worth noting that our in-house biclustering algorithm, QUBIC (Li et al. 2009), is reviewed as one of the best programs in terms of their prediction performance on benchmark datasets. Most importantly, it is reviewed as the best one for large-scale real biological data (Eren et al. 2012).

Until now, QUBIC has been cited over 200 times (via Google Scholar) and its web server, QServer, was developed in 2012 to facilitate the users without comprehensive computational background (Zhou et al. 2012). In the past five years, the cost of RNA-sequencing decreased dramatically, and the amount of gene expression data keeps increasing. Upon requests from users and collaborators, we developed this R package of QUBIC to void submitting large data to a webserver.

The unique features of our R package (Zhang et al. 2017) include (1) updated and more stable back-end resource code (re-written by C++), which has better memory control and is more efficient than the one published in 2009. For an input dataset in *Arabidopsis*, with 25,698 genes and 208 samples, we observed more than 40% time saving; and (2) comprehensive functions and examples, including discretize function, heatmap drawing and network analysis.

How to cite

```
citation("QUBIC")
```

Please cite the QUBIC package in your work, whenever you use it:

Yu Zhang, Juan Xie, Jinyu Yang, Anne Fennell, Chi Zhang, Qin Ma; QUBIC: a bioconductor package for qualitative biclustering analysis of gene co-expression data. *Bioinformatics*, 2017; 33 (3): 450-452. doi: 10.1093/bioinformatics/btw635

A BibTeX entry for LaTeX users is

```
@Article{,
  title = {{QUBIC}: a bioconductor package for qualitative biclustering analysis of gene
co-expression data},
  author = {Yu Zhang and Juan Xie and Jinyu Yang and Anne Fennell and Chi Zhang and Qin Ma},
  journal = {Bioinformatics},
  year = {2017},
  volume = {33},
  number = {3},
  pages = {450--452},
  doi = {10.1093/bioinformatics/btw635},
}
```

Other languages

If R is not your thing, there is also a C version of QUBIC.

Help

If you are having trouble with this R package, contact the maintainer, Yu Zhang.

Install and load

Stable version from BioConductor

```
if (!requireNamespace("BiocManager", quietly = TRUE))
  install.packages("BiocManager")
```

```
BiocManager::install("QUBIC")
```

Or development version from GitHub

```
install.packages("devtools")
devtools::install_github("zy26/QUBIC")
```

Load QUBIC

```
library("QUBIC")
```

Functions

There are nine functions provided by QUBIC package.

- `qudiscretize()` creates a discrete matrix for a given gene expression matrix;
- `BCQU()` performs a qualitative biclustering for real matrix;
- `BCQUd()` performs a qualitative biclustering for discretized matrix;
- `quheatmap()` can draw heatmap for single bicluster or overlapped biclusters;
- `qunetwork()` can automatically create co-expression networks based on the identified biclusters by QUBIC;
- `qunet2xml()` can convert the constructed co-expression networks into XGMML format for further network analysis in Cytoscape, BiMax and JNets;
- *query-based biclustering* allows users to input additional biological information to guide the biclustering progress;
- *bicluster expanding* expands existing biclusters under specified consistency level;
- *biclusters comparison* compares biclusters obtained via different algorithms or parameters.

The following examples illustrate how these functions work.

Example of a random matrix with two different embedded biclusters

```
library(QUBIC)
set.seed(1)
# Create a random matrix
test <- matrix(rnorm(10000), 100, 100)
colnames(test) <- paste("cond", 1:100, sep = "_")
rownames(test) <- paste("gene", 1:100, sep = "_")
```

```
# Discretization
```

```
matrix1 <- test[1:7, 1:4]
matrix1
```

```
##           cond_1      cond_2      cond_3      cond_4
## gene_1 -0.6264538 -0.62036668  0.4094018  0.89367370
## gene_2  0.1836433  0.04211587  1.6888733 -1.04729815
## gene_3 -0.8356286 -0.91092165  1.5865884  1.97133739
## gene_4  1.5952808  0.15802877 -0.3309078 -0.38363211
## gene_5  0.3295078 -0.65458464 -2.2852355  1.65414530
## gene_6 -0.8204684  1.76728727  2.4976616  1.51221269
## gene_7  0.4874291  0.71670748  0.6670662  0.08296573
```

```
matrix2 <- qudiscretize(matrix1)
matrix2
```

```
##           cond_1 cond_2 cond_3 cond_4
## gene_1      -1      0      0      1
## gene_2       0      0      1     -1
## gene_3       0     -1      0      1
## gene_4       1      0      0     -1
## gene_5       0      0     -1      1
## gene_6      -1      0      1      0
## gene_7       0      1      0     -1
```

```
# Fill bicluster blocks
```

```
t1 <- runif(10, 0.8, 1)
t2 <- runif(10, 0.8, 1) * (-1)
t3 <- runif(10, 0.8, 1) * sample(c(-1, 1), 10, replace = TRUE)
test[11:20, 11:20] <- t(rep(t1, 10) * rnorm(100, 3, 0.3))
test[31:40, 31:40] <- t(rep(t2, 10) * rnorm(100, 3, 0.3))
test[51:60, 51:60] <- t(rep(t3, 10) * rnorm(100, 3, 0.3))
```

```
# QUBIC
```

```
res <- biclust::biclust(test, method = BCQU())
summary(res)
```

```
##
## An object of class Biclust
##
## call:
## biclust::biclust(x = test, method = BCQU())
##
## Number of Clusters found:  40
##
## Cluster sizes:
##           BC 1 BC 2 BC 3 BC 4 BC 5 BC 6 BC 7 BC 8 BC 9 BC 10 BC 11 BC 12 BC 13 BC 14
## Number of Rows:    10   10   9   9   3   5   3   3   2   3   3   3   2   2
## Number of Columns:   9   9   8   7   5   3   5   5   6   4   4   4   6   6
##           BC 15 BC 16 BC 17 BC 18 BC 19 BC 20 BC 21 BC 22 BC 23 BC 24 BC 25 BC 26 BC 27
## Number of Rows:     2    2    2    2    2    2    2    2    2    2    2    2    2
## Number of Columns:   6    6    6    6    6    6    6    5    5    5    5    5    5
##           BC 28 BC 29 BC 30 BC 31 BC 32 BC 33 BC 34 BC 35 BC 36 BC 37 BC 38 BC 39 BC 40
## Number of Rows:     2    2    2    2    2    2    2    2    2    2    2    2    2
## Number of Columns:   5    5    5    5    5    5    5    5    5    5    5    5    5
```

```

# Show heatmap
hmcpls <- colorRampPalette(rev(c("#D73027", "#FC8D59", "#FEE090", "#FFFFBF",
  "#E0F3F8", "#91BFDB", "#4575B4")))(100)
# Specify colors

par(mar = c(4, 5, 3, 5) + 0.1)
quheatmap(test, res, number = c(1, 3), col = hmcpls, showlabel = TRUE)

```

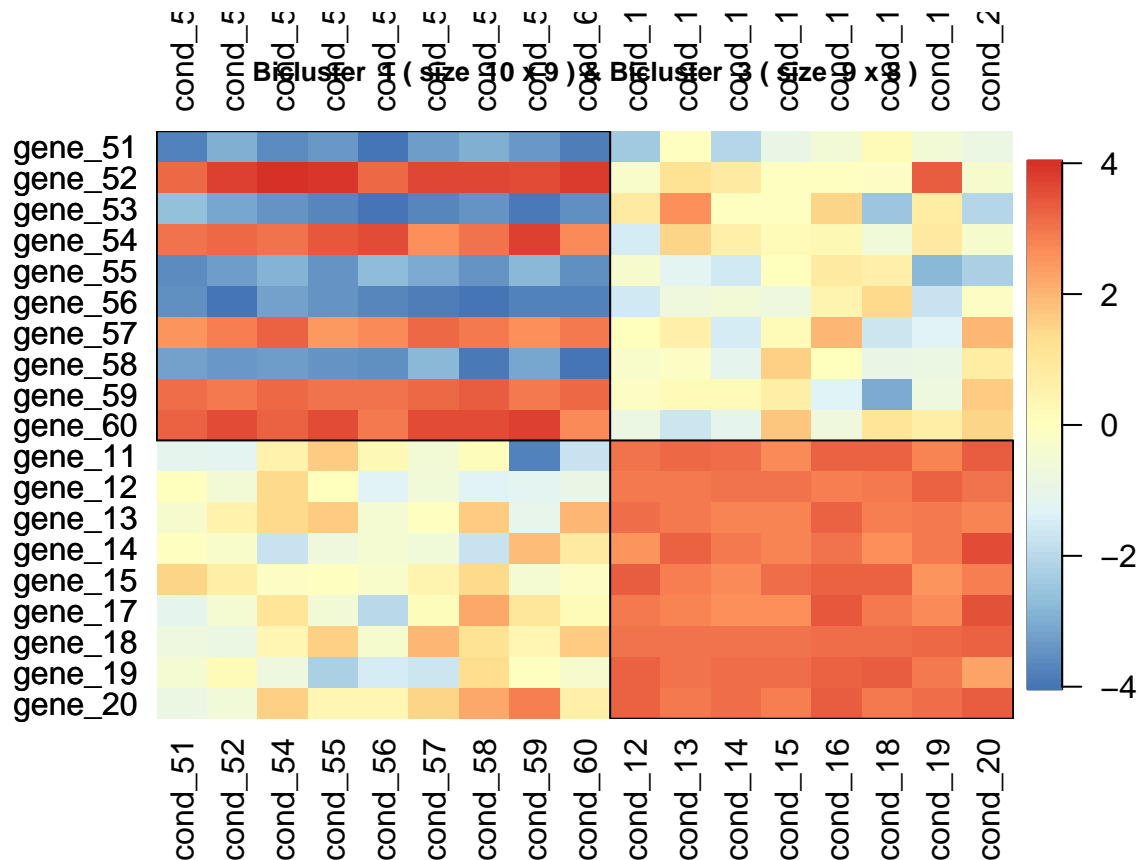


Figure 1: Heatmap for two overlapped biclusters in the simulated matrix

Example of *Saccharomyces cerevisiae*

```

library(QUBIC)
data(BicatYeast)

# Discretization
matrix1 <- BicatYeast[1:7, 1:4]
matrix1

```

##	cold_green_6h	cold_green_24h	cold_roots_6h	cold_roots_24h
## 249364_at	-0.2759300	-0.5108508	1.74476670	2.12442300
## 253423_at	-0.9405282	3.2669048	-0.37776557	0.06860917
## 250327_at	1.6419950	1.4484175	0.33474782	-0.15095752
## 247474_at	0.6903505	1.6705408	0.04386528	-0.45295456
## 252661_at	1.7493315	0.9260773	2.05519100	2.11200260

```
## 258239_at      0.6110116      -0.6083303      0.60419910      0.43582130
## 248910_at      1.4501406      -0.3107802      0.16640233      0.37186486
```

```
matrix2 <- qudiscretize(matrix1)
matrix2
```

```
##          cold_green_6h cold_green_24h cold_roots_6h cold_roots_24h
## 249364_at           0           -1           0           1
## 253423_at          -1            1           0           0
## 250327_at           1            0           0          -1
## 247474_at           0            1           0          -1
## 252661_at           0           -1           0           1
## 258239_at           1           -1           0           0
## 248910_at           1           -1           0           0
```

```
# QUBIC
x <- BicatYeast
system.time(res <- biclust::biclust(x, method = BCQU()))
```

```
##      user  system elapsed
##      0.06    0.00    0.06
```

```
summary(res)
```

```
##
## An object of class Biclust
##
## call:
## biclust::biclust(x = x, method = BCQU())
##
## Number of Clusters found: 77
##
## Cluster sizes:
##          BC 1 BC 2 BC 3 BC 4 BC 5 BC 6 BC 7 BC 8 BC 9 BC 10 BC 11 BC 12 BC 13 BC 14
## Number of Rows:      72  53  37  80  56  98  47  26  45  35  29  34  42  33
## Number of Columns:    4   5   7   3   4   2   4   7   4   5   6   5   4   5
##          BC 15 BC 16 BC 17 BC 18 BC 19 BC 20 BC 21 BC 22 BC 23 BC 24 BC 25 BC 26 BC 27
## Number of Rows:      41  41  32  53  39  38  74  29  47  23  27  22  33
## Number of Columns:    4   4   5   3   4   4   2   5   3   6   5   6   4
##          BC 28 BC 29 BC 30 BC 31 BC 32 BC 33 BC 34 BC 35 BC 36 BC 37 BC 38 BC 39 BC 40
## Number of Rows:      41  40  19  51  20  16  32  31  23  30  44  44  41
## Number of Columns:    3   3   6   2   5   6   3   3   4   3   2   2   2
##          BC 41 BC 42 BC 43 BC 44 BC 45 BC 46 BC 47 BC 48 BC 49 BC 50 BC 51 BC 52 BC 53
## Number of Rows:      13  39  26  39  19  25  25  25  25  8  36  9  8
## Number of Columns:    6   2   3   2   4   3   3   3   3   9   2   8   9
##          BC 54 BC 55 BC 56 BC 57 BC 58 BC 59 BC 60 BC 61 BC 62 BC 63 BC 64 BC 65 BC 66
## Number of Rows:      12  18  23  16  32  31  20  28  14  11  18  18  17
## Number of Columns:    6   4   3   4   2   2   3   2   4   5   3   3   3
##          BC 67 BC 68 BC 69 BC 70 BC 71 BC 72 BC 73 BC 74 BC 75 BC 76 BC 77
## Number of Rows:      24  24   9  14  14  20  12   9  17   8   3
## Number of Columns:    2   2   5   3   3   2   3   4   2   3   5
```

We can draw heatmap for single bicluster.

```
# Draw heatmap for the second bicluster identified in Saccharomyces cerevisiae data
```

```
library(RColorBrewer)
paleta <- colorRampPalette(rev(brewer.pal(11, "RdYlBu")))(11)
par(mar = c(5, 4, 3, 5) + 0.1, mgp = c(0, 1, 0), cex.lab = 1.1, cex.axis = 0.5,
    cex.main = 1.1)
quheatmap(x, res, number = 2, showlabel = TRUE, col = paleta)
```

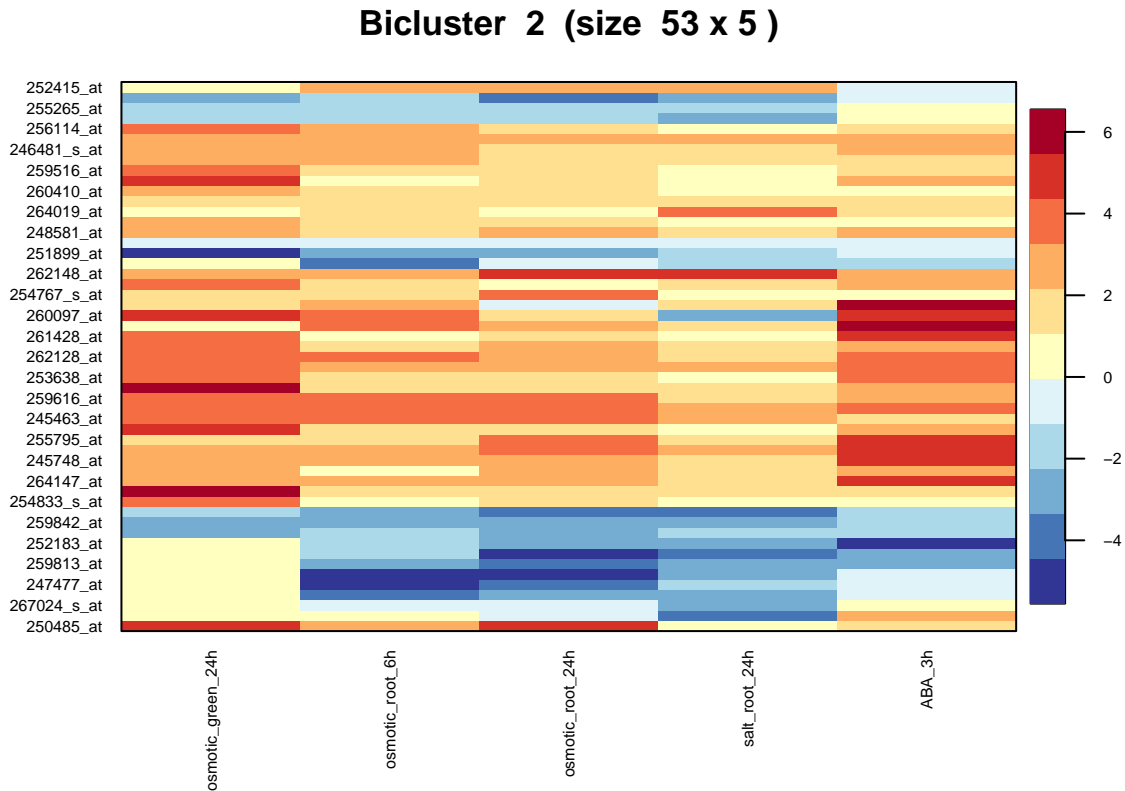


Figure 2: Heatmap for the second bicluster identified in the *Saccharomyces cerevisiae* data. The bicluster consists of 53 genes and 5 conditions

We can draw heatmap for overlapped biclusters.

```
# Draw for the second and third biclusters identified in Saccharomyces cerevisiae data
```

```
par(mar = c(5, 5, 5, 5), cex.lab = 1.1, cex.axis = 0.5, cex.main = 1.1)
paleta <- colorRampPalette(rev(brewer.pal(11, "RdYlBu")))(11)
quheatmap(x, res, number = c(2, 3), showlabel = TRUE, col = paleta)
```

We can draw network for single bicluster.

```
# Construct the network for the second identified bicluster in Saccharomyces cerevisiae
```

```
net <- qunetwork(x, res, number = 2, group = 2, method = "spearman")
if (requireNamespace("qgraph", quietly = TRUE))
  qgraph::qgraph(net[[1]], groups = net[[2]], layout = "spring", minimum = 0.6,
    color = cbind(rainbow(length(net[[2]]) - 1), "gray"), edge.label = FALSE)
```

```
## Warning in qgraph::qgraph(net[[1]], groups = net[[2]], layout = "spring", : The following
## arguments are not documented and likely not arguments of qgraph and thus ignored: edge.label
```

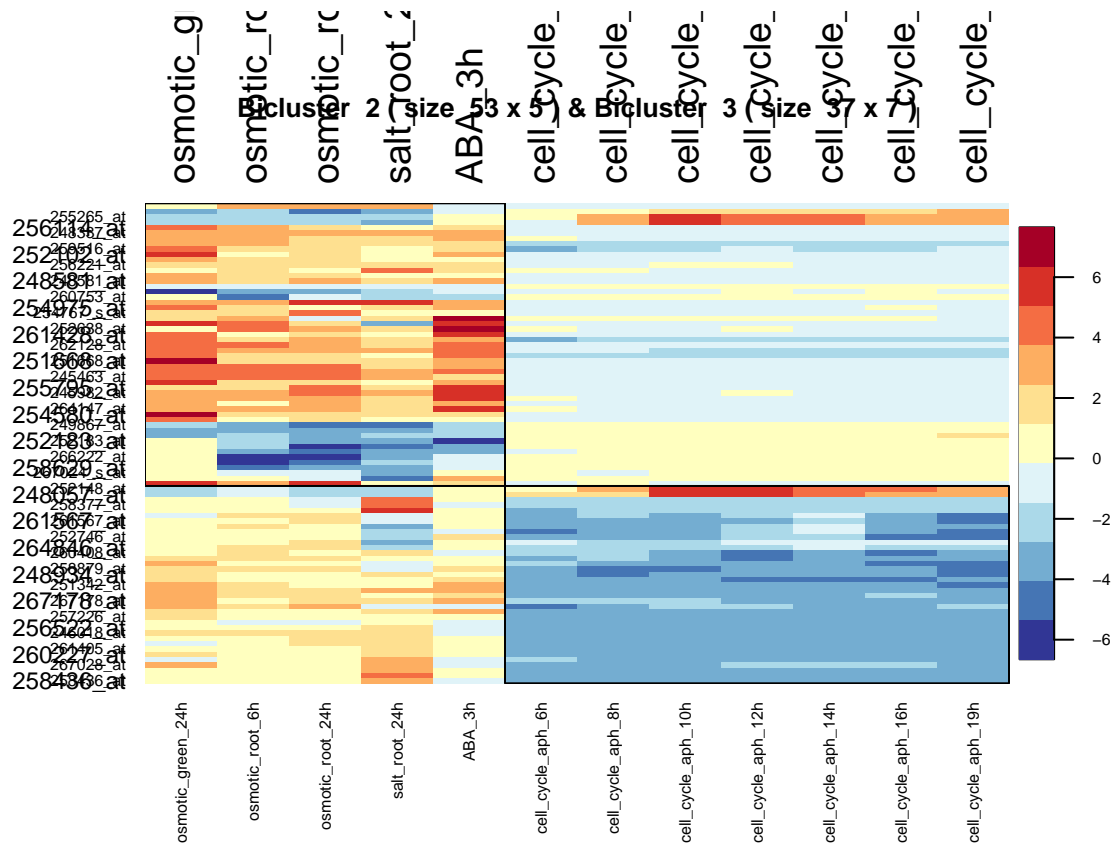


Figure 3: Heatmap for the second and third biclusters identified in the *Saccharomyces cerevisiae* data. Bicluster #2 (topleft) consists of 53 genes and 5 conditions, and bicluster #3 (bottom right) consists of 37 genes and 7 conditions.

We can also draw network for overlapped biclusters.

```
net <- qunetwork(x, res, number = c(2, 3), group = c(2, 3), method = "spearman")
if (requireNamespace("qgraph", quietly = TRUE))
  qgraph::qgraph(net[[1]], groups = net[[2]], layout = "spring", minimum = 0.6,
    legend.cex = 0.5, color = c("red", "blue", "gold", "gray"), edge.label = FALSE)
```

```
## Warning in qgraph::qgraph(net[[1]], groups = net[[2]], layout = "spring", : The following
## arguments are not documented and likely not arguments of qgraph and thus ignored: edge.label
```

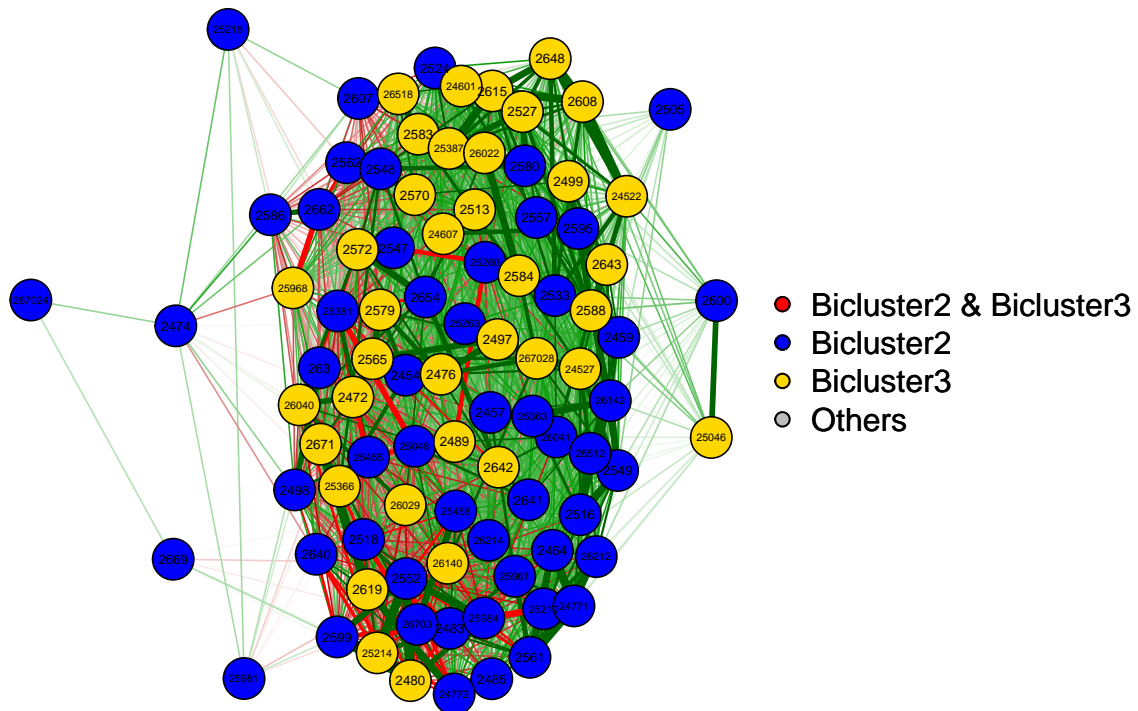


Figure 5: Network for the second and third biclusters identified in the *Saccharomyces cerevisiae* data.

```
# Output overlapping heatmap XML, could be used in other software such
# as Cytoscape, Biomax or JNets
sink('tempnetworkresult.gr')
qunet2xml(net, minimum = 0.6, color = cbind(rainbow(length(net[[2]]) - 1), "gray"))
sink()
# We can use Cytoscape, Biomax or JNets open file named 'tempnetworkresult.gr'
```

Example of *Escherichia coli* data

The *Escherichia coli* data consists of 4,297 genes and 466 conditions.

```
library(QUBIC)
library(QUBICdata)
data("ecoli", package = "QUBICdata")
```

Discretization

```
matrix1 <- ecoli[1:7, 1:4]
matrix1
```

##	dinI_U_N0025	dinP_U_N0025	lexA_U_N0025	lon_U_N0025
## b4634	9.077693	9.225537	9.138900	9.114353
## b3241	7.122300	7.195453	7.051193	7.124200
## b3240	7.184417	7.336610	7.283377	7.188263
## b3243	7.902090	7.963167	7.847747	7.943650
## b3242	6.801900	6.843213	6.795007	6.889897
## b2836	9.114207	9.133303	9.167487	9.189480
## b0885	9.057120	8.918723	8.985483	9.002663

```
matrix2 <- qudiscretize(matrix1)
matrix2
```

##	dinI_U_N0025	dinP_U_N0025	lexA_U_N0025	lon_U_N0025
## b4634	-1	1	0	0
## b3241	0	1	-1	0
## b3240	-1	1	0	0
## b3243	0	1	-1	0
## b3242	0	0	-1	1
## b2836	-1	0	0	1
## b0885	1	-1	0	0

QUBIC

```
res <- biclust::biclust(ecoli, method = BCQU(), r = 1, q = 0.06, c = 0.95, o = 100,
  f = 0.25, k = max(ncol(ecoli))/%20, 2))
system.time(res <- biclust::biclust(ecoli, method = BCQU(), r = 1, q = 0.06, c = 0.95,
  o = 100, f = 0.25, k = max(ncol(ecoli))/%20, 2))
```

##	user	system	elapsed
##	11.23	0.16	7.92

```
summary(res)
```

```
##
## An object of class Biclust
##
## call:
## biclust::biclust(x = ecoli, method = BCQU(), r = 1, q = 0.06, c = 0.95, o = 100,
##   f = 0.25, k = max(ncol(ecoli))/%20, 2))
##
## Number of Clusters found: 20
##
## Cluster sizes:
##
```

	BC 1	BC 2	BC 3	BC 4	BC 5	BC 6	BC 7	BC 8	BC 9	BC 10	BC 11	BC 12	BC 13	BC 14
## Number of Rows:	437	121	51	108	103	65	41	26	27	20	25	23	17	18
## Number of Columns:	29	45	94	44	38	38	31	33	31	27	19	20	23	21

```
##
```

	BC 15	BC 16	BC 17	BC 18	BC 19	BC 20
## Number of Rows:	14	15	13	11	5	6
## Number of Columns:	26	20	22	25	32	23

```
# Draw heatmap for the 5th bicluster identified in Escherichia coli data
```

```
library(RColorBrewer)
paleta <- colorRampPalette(rev(brewer.pal(11, "RdYlBu")))(11)
par(mar = c(5, 4, 3, 5) + 0.1, mgp = c(0, 1, 0), cex.lab = 1.1, cex.axis = 0.5,
    cex.main = 1.1)
quheatmap(ecoli, res, number = 5, showlabel = TRUE, col = paleta)
```

Bicluster 5 (size 103 x 38)

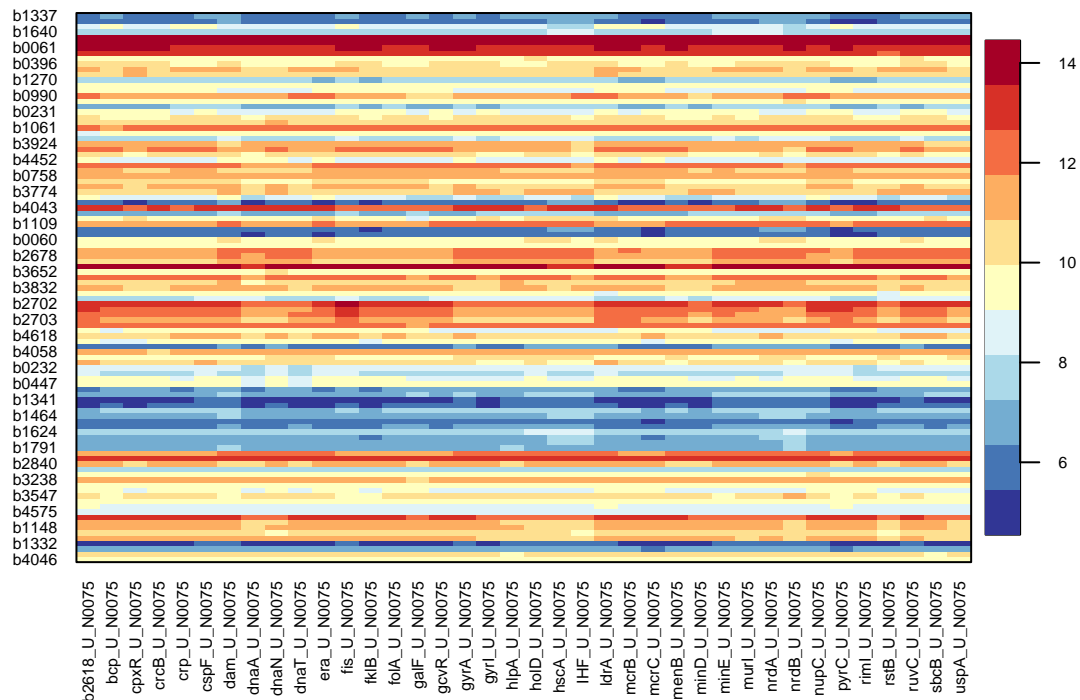


Figure 6: Heatmap for the fifth bicluster identified in the *Escherichia coli* data. The bicluster consists of 103 genes and 38 conditions

```
library(RColorBrewer)
paleta <- colorRampPalette(rev(brewer.pal(11, "RdYlBu")))(11)
par(mar = c(5, 4, 3, 5), cex.lab = 1.1, cex.axis = 0.5, cex.main = 1.1)
quheatmap(ecoli, res, number = c(4, 8), showlabel = TRUE, col = paleta)
```

```
# construct the network for the 5th identified bicluster in Escherichia coli data
net <- qunetwork(ecoli, res, number = 5, group = 5, method = "spearman")
if (requireNamespace("qgraph", quietly = TRUE))
  qgraph::qgraph(net[[1]], groups = net[[2]], layout = "spring", minimum = 0.6,
    color = cbind(rainbow(length(net[[2]]) - 1), "gray"), edge.label = FALSE)
```

```
## Warning in qgraph::qgraph(net[[1]], groups = net[[2]], layout = "spring", : The following
## arguments are not documented and likely not arguments of qgraph and thus ignored: edge.label
```

```
# construct the network for the 4th and 8th identified bicluster in Escherichia coli data
net <- qunetwork(ecoli, res, number = c(4, 8), group = c(4, 8), method = "spearman")
if (requireNamespace("qgraph", quietly = TRUE))
  qgraph::qgraph(net[[1]], groups = net[[2]], legend.cex = 0.5, layout = "spring",
    minimum = 0.6, color = c("red", "blue", "gold", "gray"), edge.label = FALSE)
```

```
## Warning in qgraph::qgraph(net[[1]], groups = net[[2]], legend.cex = 0.5, : The following
## arguments are not documented and likely not arguments of qgraph and thus ignored: edge.label
```

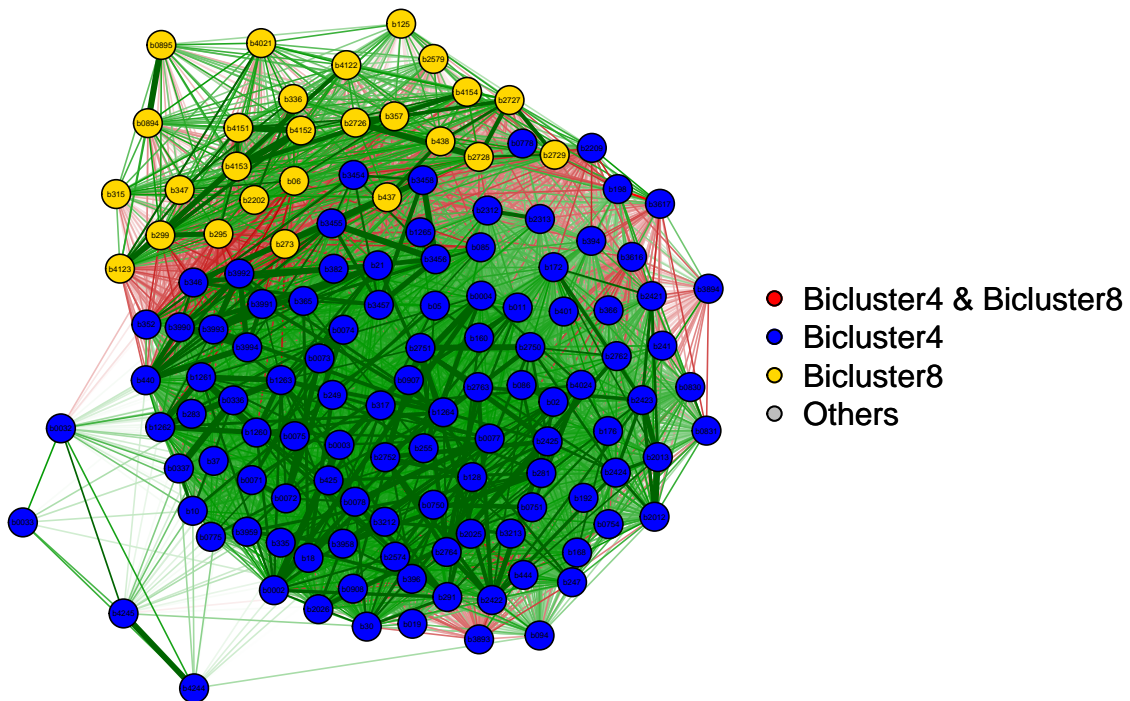


Figure 9: Network for the fourth and eighth biclusters identified in the *Escherichia coli* data.

Query-based biclustering

We can conduct a query-based biclustering by adding the weight parameter. In this example, the instance file “511145.protein.links.v10.txt” (Szklarczyk et al. 2014) was downloaded from string (<http://string-db.org/download/protein.links.v10/511145.protein.links.v10.txt.gz>) and decompressed and saved in working directory.

```
# Here is an example to download and extract the weight
library(igraph)
url <- "http://string-db.org/download/protein.links.v10/511145.protein.links.v10.txt.gz"
tmp <- tempfile()
download.file(url, tmp)
graph = read.graph(gzfile(tmp), format = "ncol")
unlink(tmp)
ecoli.weight <- get.adjacency(graph, attr = "weight")
```

```
library(QUBIC)
library(QUBICdata)
data("ecoli", package = "QUBICdata")
data("ecoli.weight", package = "QUBICdata")
res0 <- biclust(ecoli, method = BCQU(), verbose = FALSE)
res0
```

```
##
## An object of class Biclust
##
## call:
## biclust(x = ecoli, method = BCQU(), verbose = FALSE)
##
## Number of Clusters found: 100
##
## First 5 Cluster sizes:
##           BC 1 BC 2 BC 3 BC 4 BC 5
## Number of Rows: 437 519 178 180 169
## Number of Columns: 29 22 52 50 53
```

```
res4 <- biclust(ecoli, method = BCQU(), weight = ecoli.weight, verbose = FALSE)
res4
```

```
##
## An object of class Biclust
##
## call:
## biclust(x = ecoli, method = BCQU(), weight = ecoli.weight, verbose = FALSE)
##
## Number of Clusters found: 100
##
## First 5 Cluster sizes:
##           BC 1 BC 2 BC 3 BC 4 BC 5
## Number of Rows: 437 519 178 180 169
## Number of Columns: 29 22 52 50 53
```

Bicluster-expanding

we can expand existing biclustering results to recruit more genes according to certain consistency level:

```
res5 <- biclust(x = ecoli, method = BCQU(), seedbicluster = res, f = 0.25, verbose = FALSE)
summary(res5)
```

```
##
## An object of class Biclust
##
## call:
## biclust(x = ecoli, method = BCQU(), seedbicluster = res, f = 0.25, verbose = FALSE)
##
## Number of Clusters found: 20
##
## Cluster sizes:
##           BC 1 BC 2 BC 3 BC 4 BC 5 BC 6 BC 7 BC 8 BC 9 BC 10 BC 11 BC 12 BC 13 BC 14
## Number of Rows: 593 151 51 110 117 68 84 27 43 20 36 30 17 19
## Number of Columns: 29 45 94 44 38 38 31 33 31 27 19 20 23 21
##           BC 15 BC 16 BC 17 BC 18 BC 19 BC 20
```

```
## Number of Rows:      14      16      16      11      5      6
## Number of Columns:   26      20      22      25      32      23
```

Biclusters comparison

We can compare the biclustering results obtained from different algorithms, or from a same algorithm with different combinations of parameter.

```
test <- ecoli[1:50,]
res6 <- biclust(test, method = BCQU(), verbose = FALSE)
res7 <- biclust(test, method = BCCC())
res8 <- biclust(test, method = BCBimax())
showinfo(test, c(res6, res7, res8))
```

```
## 1: Call and Parameter
## 2: number of detected biclusters
## 3: nrow of the first bicluster
## 4: ncol of the first bicluster
## 5: area of the first bicluster
## 6: ratio (nrow / ncol) of the first bicluster
## 7: ratio (nrow / ncol) of the matrix
## 8: max nrow and corresponding bicluster
## 9: max ncol and corresponding bicluster
## 10: max area and corresponding bicluster
## 11: union of rows, (# and %)
## 12: union of columns, (# and %)
## 13: overlap of first two biclusters (row, col, area)
##
##
## 1      2      3      4      5      6      7      8      9      10     11     12     13
## biclust(x = test, method = BCQU(), verbose = FALSE) 59    11    25    275 0.44      0.1072961    11 1
##              42 12    275 1    49 98    283 60.72961      1 0 0
## biclust(x = test, method = BCCC())      1    50   466 23300    0.1072961    0.1072961    50 1    466 1
##              23300 1 50 100    1 100
## biclust(x = test, method = BCBimax())      1    50   466 23300    0.1072961    0.1072961    50 1
##              466 1    23300 1 50 100   466 100
```

References

- Brazma, Alvis, and Jaak Vilo. 2000. “Gene Expression Data Analysis.” *FEBS Letters* 480 (1): 17–24.
- Cheng, Yizong, and George M Church. 2000. “Biclustering of Expression Data.” In *Proceedings of the Eighth International Conference on Intelligent Systems for Molecular Biology*, edited by Philip Bourne, Michael Gribskov, Russ Altman, Nancy Jensen, Debra Hope, Thomas Lengauer, Julie Mitchell, et al., 8:93–103. AAAI Press, Menlo Park, CA.
- Eren, Kemal, Mehmet Deveci, Onur Küçüktunç, and Ümit V. Çatalyürek. 2012. “A Comparative Analysis of Biclustering Algorithms for Gene Expression Data.” *Briefings in Bioinformatics*. <https://doi.org/10.1093/bib/bbs032>.
- Fehrmann, Rudolf SN, Juha M Karjalainen, Małgorzata Krajewska, Harm-Jan Westra, David Maloney, Anton Simeonov, Tune H Pers, et al. 2015. “Gene Expression Analysis Identifies Global Gene Dosage Sensitivity in Cancer.” *Nature Genetics* 47 (2): 115–25.
- Gu, Jiajun, and Jun S Liu. 2008. “Bayesian Biclustering of Gene Expression Data.” *BMC Genomics* 9 (Suppl 1): S4.

- Lazzeroni, Laura, Art Owen, and others. 2002. “Plaid Models for Gene Expression Data.” *Statistica Sinica* 12 (1): 61–86.
- Li, Guojun, Qin Ma, Haibao Tang, Andrew H Paterson, and Ying Xu. 2009. “QUBIC: A Qualitative Biclustering Algorithm for Analyses of Gene Expression Data.” *Nucleic Acids Research* 37 (15): e101.
- Szklarczyk, Damian, Andrea Franceschini, Stefan Wyder, Kristoffer Forslund, Davide Heller, Jaime Huerta-Cepas, Milan Simonovic, et al. 2014. “STRING V10: Protein–Protein Interaction Networks, Integrated over the Tree of Life.” *Nucleic Acids Research* 43: D447–D452. <https://doi.org/10.1093/nar/gku1003>.
- Zhang, Yu, Juan Xie, Jinyu Yang, Anne Fennell, Chi Zhang, and Qin Ma. 2017. “QUBIC: A Bioconductor Package for Qualitative Biclustering Analysis of Gene Co- Expression Data.” *Bioinformatics* 33 (3): 450–52. <https://doi.org/10.1093/bioinformatics/btw635>.
- Zhou, Fengfeng, Qin Ma, Guojun Li, and Ying Xu. 2012. “QServer: A Biclustering Server for Prediction and Assessment of Co-Expressed Gene Clusters.” *PLoS ONE* 7 (3): e32660. <https://doi.org/10.1371/journal.pone.0032660>.