

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 110 times (via Google Scholar) and its web server, QServer (Zhou et al. 2012), 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 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.

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

```
source("https://bioconductor.org/biocLite.R")
biocLite("QUBIC")
```

Or development version from GitHub

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

Load QUBIC

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

Functions

There are six 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. 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: 66
##
## Cluster sizes:
##
##          BC 1 BC 2 BC 3 BC 4 BC 5 BC 6 BC 7 BC 8 BC 9 BC 10
## Number of Rows:      10   9   9   9  10   4   3   5   3   2
## Number of Columns:    9   9   8   7   5   4   5   3   5   6
##
##          BC 11 BC 12 BC 13 BC 14 BC 15 BC 16 BC 17 BC 18 BC 19
## Number of Rows:       2   2   2   2   2   2   3   2   3
## Number of Columns:    6   6   6   6   6   6   4   6   4
##
##          BC 20 BC 21 BC 22 BC 23 BC 24 BC 25 BC 26 BC 27 BC 28
## Number of Rows:       3   3   2   2   2   2   2   2   2
## Number of Columns:    4   4   6   6   6   5   5   5   5
##
##          BC 29 BC 30 BC 31 BC 32 BC 33 BC 34 BC 35 BC 36 BC 37
## Number of Rows:       2   2   2   2   2   2   2   2   2
## Number of Columns:    5   5   5   5   5   5   5   5   5
##
##          BC 38 BC 39 BC 40 BC 41 BC 42 BC 43 BC 44 BC 45 BC 46
## Number of Rows:       2   2   2   2   2   2   2   2   2
## Number of Columns:    5   5   5   5   5   5   5   5   5
##
##          BC 47 BC 48 BC 49 BC 50 BC 51 BC 52 BC 53 BC 54 BC 55
## Number of Rows:       2   2   2   2   2   2   2   2   2
## Number of Columns:    5   5   5   5   5   5   5   5   5
##
##          BC 56 BC 57 BC 58 BC 59 BC 60 BC 61 BC 62 BC 63 BC 64
## Number of Rows:       2   2   2   2   2   2   2   2   2
## Number of Columns:    5   5   5   5   5   5   5   5   5
##
##          BC 65 BC 66
## Number of Rows:       2   2
## Number of Columns:    5   5

# Show heatmap
hmcols <- 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 = hmcols, showlabel = TRUE)

## [1] "yto 0"
## [1] "xlo 0"

```

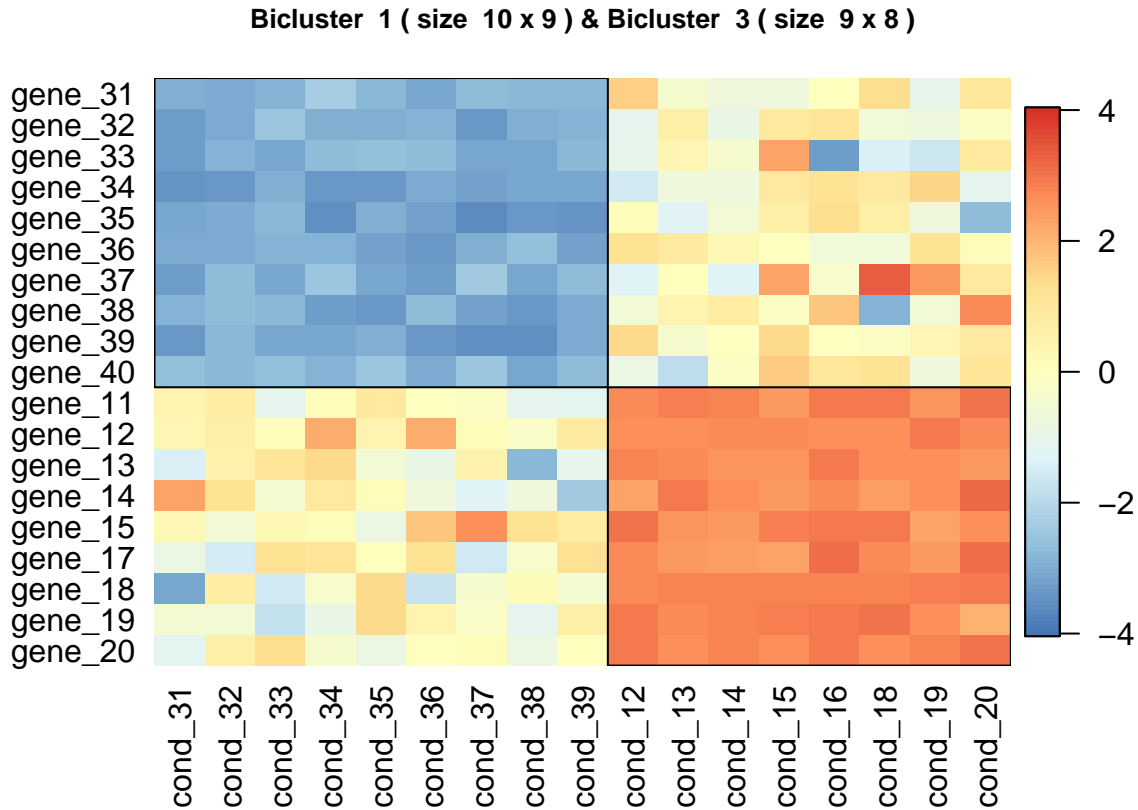


Figure 1: Heatmap for two overlapped biclusters in the simulated matrix

Example of BicatYeast

```
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
## 0.093   0.004   0.097
```

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

We can draw heatmap for single bicluster.

```
# Draw heatmap for the 2th bicluster identified in BicatYeast data
```

```
library(RColorBrewer)
paleta <- colorRampPalette(rev(brewer.pal(11, "RdYlBu")))(11)
```

Bicluster 2 (size 53 x 5)

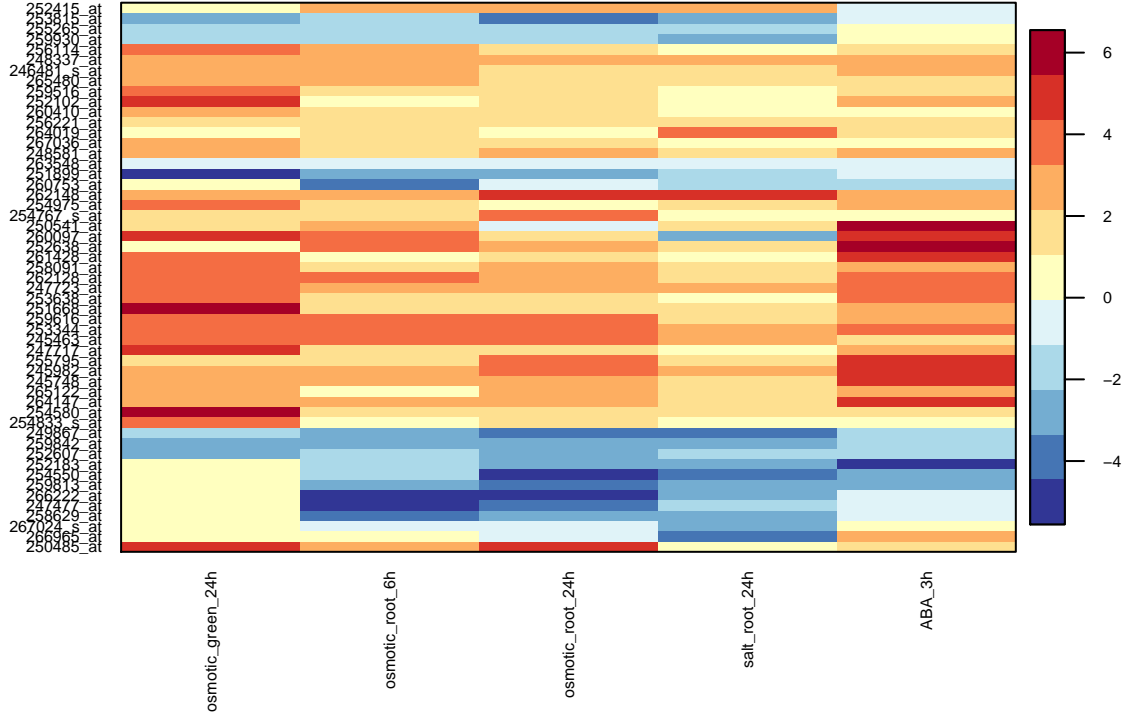


Figure 2: Heatmap for the second bicluster identified in the BicatYeast data. The bicluster consists of 53 genes and 5 conditions

```
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)
```

We can draw heatmap for overlapped biclusters.

Draw for the 2th and 3th biclusters identified in BicatYeast 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)
```

```
## [1] "yto 0"
## [1] "xlo 0"
```

We can draw network for single bicluster.

Construct the network for the 2th identified bicluster in BicatYeast

```
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)
```

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))
```

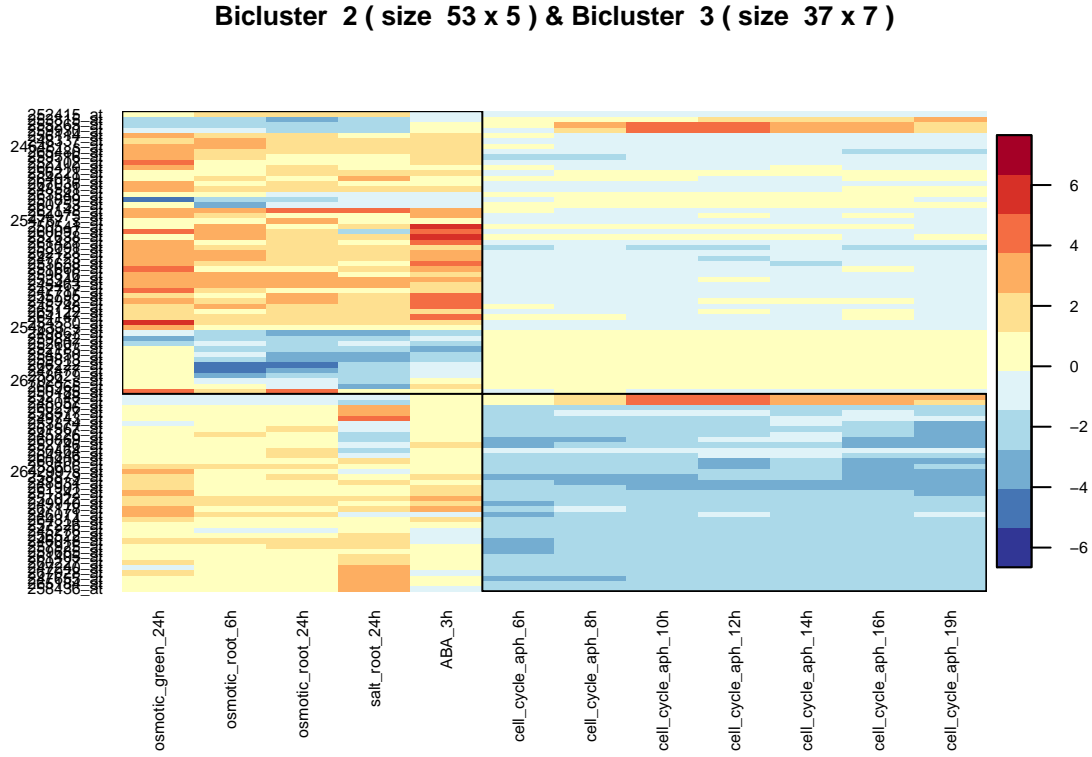


Figure 3: Heatmap for the second and third biclusters identified in the BicatYeast data. Bicluster #2 (topleft) consists of 53 genes and 5 conditions, and bicluster #3 (bottom right) consists of 37 genes and 7 conditions.

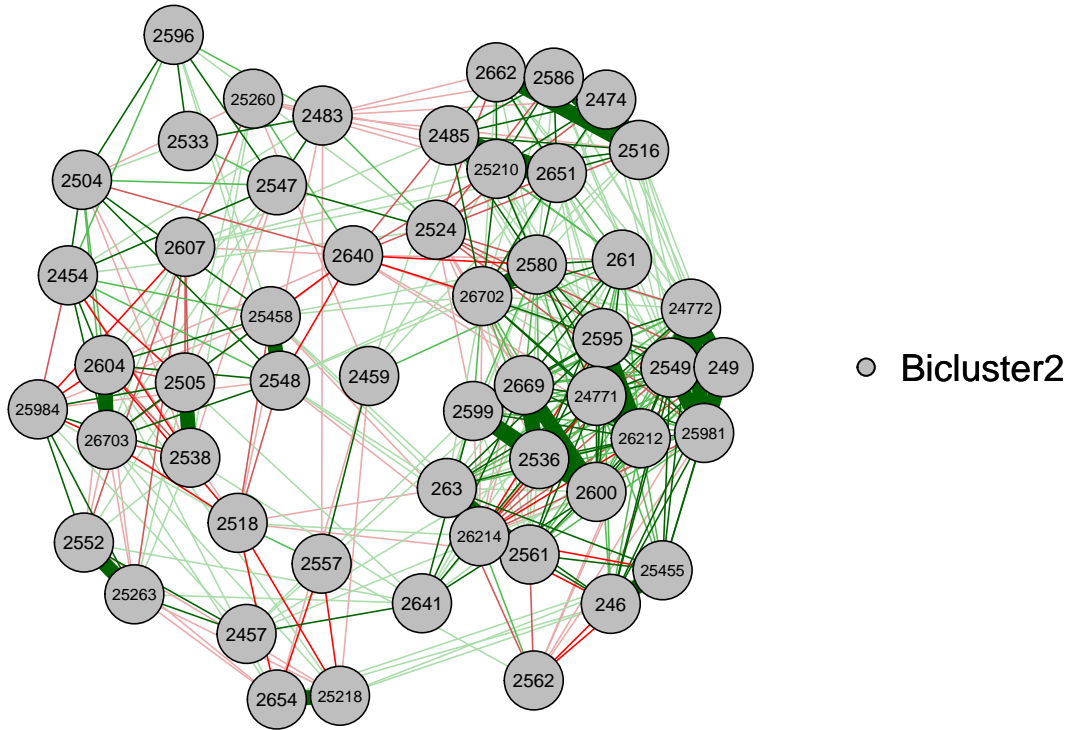


Figure 4: Network for the second bicluster identified in the BicatYeast data.

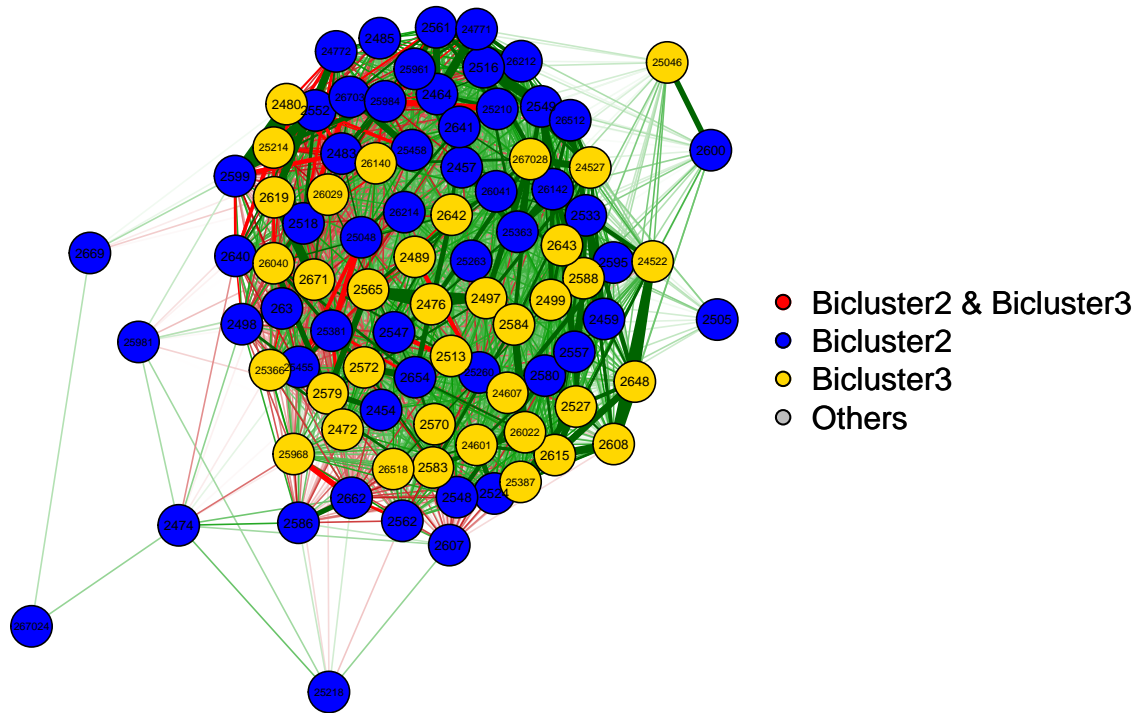


Figure 5: Network for the second and third biclusters identified in the BicatYeast data.

```
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)
```

```
# 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 E.coli data

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

```
library(QUBIC)

# Load E.coli data
if (requireNamespace("QUBICdata", quietly = TRUE)) {
  data("ecoli", package = "QUBICdata")
} else {
  # Fake ecoli, all result below
  ecoli <- BicatYeast
  warning("All results below are BicatYeast, not ecoli")
}

# 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
## 12.471   0.201  12.683

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
## Number of Rows:    437  121  51  108  103  65  41  26  27  20
## Number of Columns:   29  45  94  44  38  38  31  33  31  27
##      BC 11 BC 12 BC 13 BC 14 BC 15 BC 16 BC 17 BC 18 BC 19
## Number of Rows:     25  23  17  18  14  15  13  11  5
## Number of Columns:   19  20  23  21  26  20  22  25  32
##      BC 20
## Number of Rows:      6
## Number of Columns:   23

```

Bicluster 5 (size 103 x 38)

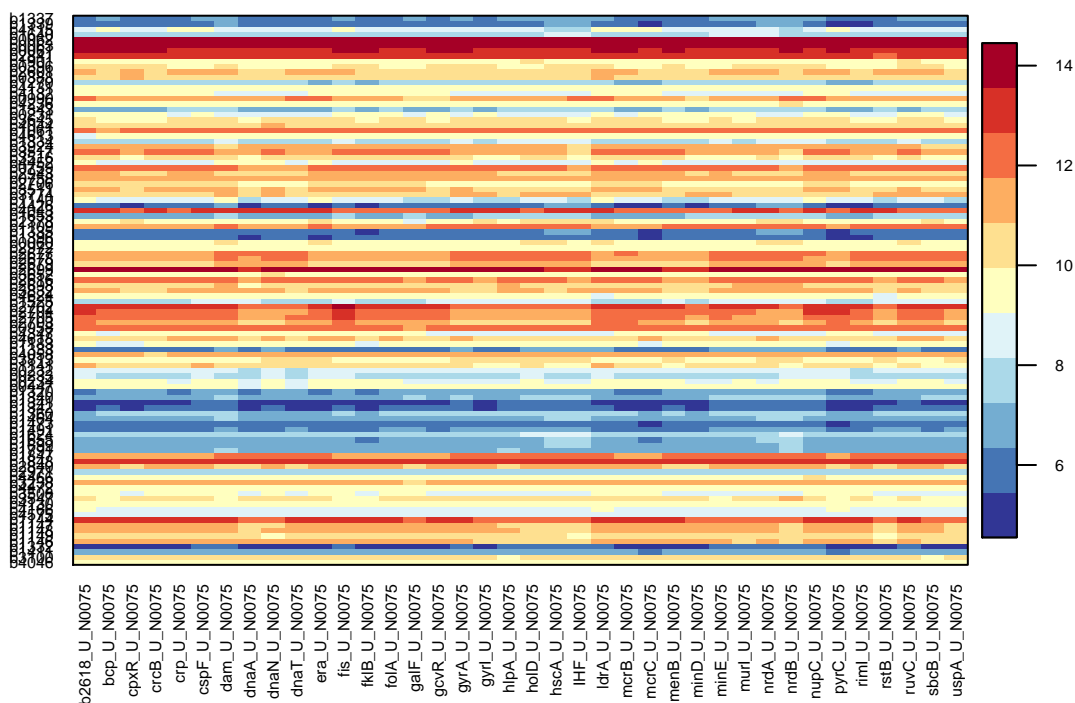


Figure 6: Heatmap for the fifth bicluster identified in the E.coli data. The bicluster consists of 103 genes and 38 conditions

Draw heatmap for the 5th bicluster identified in E.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)
```

```
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)
```

```
## [1] "yto 0"
## [1] "xlo 1"
```

construct the network for the 5th identified bicluster in E.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)
```

construct the network for the 4th and 8th identified bicluster in E.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",
```

Heatmap visualization showing gene expression data across 100 samples. The color scale ranges from 2 (dark blue) to 16 (dark red). The samples are grouped into three main clusters: a large cluster of 60 samples on the left, a cluster of 20 samples in the middle, and a cluster of 20 samples on the right. The genes are listed on the y-axis, with labels rotated 90 degrees. The heatmap shows a clear pattern of gene expression across the samples, with some genes showing high expression (red) in specific clusters and others showing low expression (blue).

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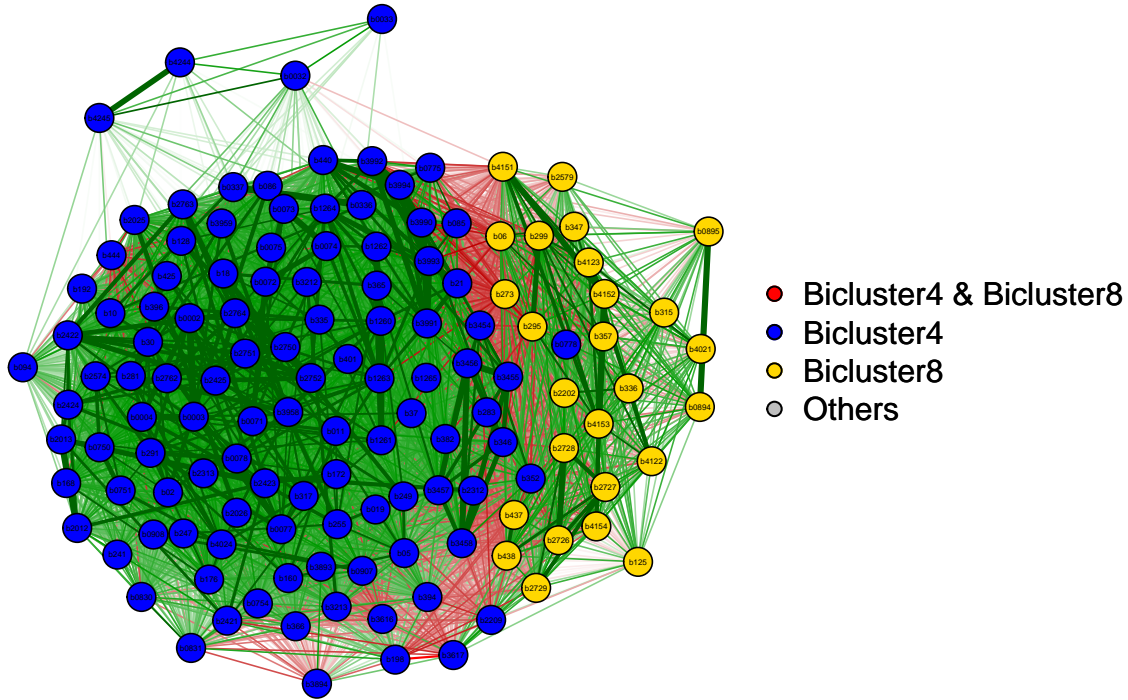


Figure 9: Network for the fourth and eighth biclusters identified in the E.coli data.

```
minimum = 0.6, color = c("red", "blue", "gold", "gray"), edge.label = FALSE)
```

References

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- 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). Nature Publishing Group: 115–25.
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