BicARE : Biclustering Analysis and Results Exploration

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1 Overview

This document presents an overview of the *BicARE* package. This package is dedicated to biclustering analysis which allows to discover sets of genes that have the same expression pattern accross a set of samples (for an overview of bicluster analysis see Madeira and Oliveira (2004)).

2 Biclustering analysis

Data set used in this vignette is a subset of the *sample.ExpressionSet*, 26 hgu95av2 arrays normalised by dChip. Only 352 probesets are kept (probesets with a minimal value greater than 1) and expression values are set to log2 scale.

```
> data(sample.bicData)
```

```
[1] "sample.bicData"
```

```
> sample.bicData
```

```
ExpressionSet (storageMode: lockedEnvironment)
assayData: 352 features, 26 samples
  element names: exprs, se.exprs
protocolData: none
phenoData
  sampleNames: A B ... Z (26 total)
  varLabels: sex type score
  varMetadata: labelDescription
featureData: none
experimentData: use 'experimentData(object)'
Annotation: hgu95av2
```

The biclustering algorithm used in *BicARE* is based on the notion of residue which is a measure of coherence of the elements in a bicluster (see Yang et al. (2005) for a definition of the residue). The smaller the residue, the more coherent the bicluster.

Computing the residue of the data matrix :

```
> residue(sample.bicData)

[1] 0.3401921
```

The core of the package is the *FLOC* function which launches a modified version of the FLOC (FLexible Overlapped biClustering) algorithm, see Yang et al. (2005). A predetermined number (parameter k) of biclusters are build such that they are as big as possible with a residue smaller than the threshold (parameter r).

2.1 Random intialisation

In a strictly exploratory approach it is possible to build the biclusters around random seeds (random biclusters that are iteratively improved). The size of the random seeds is controlled by parameters *pGene* and *pSample* such as each gene (sample) has a probability *pGene* (*pSample*) to belong to each bicluster. Other parameters are the number of biclusters build (k), the residue threshold (r), the minimal number of genes (N) per bicluster, the minimal number of conditions (M) per bicluster and the number of iterations (t).

```
> set.seed(1)
> res.biclustering <- FLOC(sample.bicData, k=15, pGene=0.3, pSample=0.6, r=0.01, 10, 8, 200)

> res.biclustering

Call :
FLOC(Data = sample.bicData, k = 15, pGene = 0.3, pSample = 0.6,
    r = 0.01, N = 10, M = 8, t = 200)

Parameters :
 number of biclusters :  15
 residu threshold :  0.01
 gene initial probability :  0.3
 sample initial probability :  0.6
 number of iterations :  200
 date :  Tue Oct 29 19:50:09 2019
Biclusters :
```

```
          residue volume genes conditions     rowvar
 [1,] 0.010981385    216    27          8 0.03232698
 [2,] 0.010601927    152    19          8 0.02681762
 [3,] 0.009838464    120    15          8 0.05982413
 [4,] 0.011122228    184    23          8 0.04301004
 [5,] 0.011192360    144    18          8 0.02923940
 [6,] 0.009947683    136    17          8 0.06057768
 [7,] 0.012914601    232    29          8 0.04375200
 [8,] 0.011085468    200    25          8 0.03728413
 [9,] 0.010992837    152    19          8 0.03444107
[10,] 0.010473421    160    20          8 0.02069323
[11,] 0.013201684    192    24          8 0.04939485
[12,] 0.010653375    120    15          8 0.05523718
[13,] 0.009664497    144    18          8 0.02495003
[14,] 0.011024772    176    22          8 0.03182508
[15,] 0.012577847    168    21          8 0.05608087
```

A data frame (*mat.resvol.bic*) gives the characteristics of the biclusters such as the residue or the size of the biclusters. In the *rowvar* column is displayed the mean of the variance of the genes in the bicluster. It helps to find non-trivial biclusters (e.g. constant bicluster).

2.2 Directed initialisation

It is also possible to build biclusters around previous knowledge. Initialisation can be performed on genes, on samples or on both.

The initialisation is performed by building boolean matrices indicating the membership of the elements to the biclusters.

```
> init.genes <- matrix(data=0, nrow=352, ncol=5)
> init.samples <- matrix(data=0, nrow=26, ncol=5)
> init.genes[1:10,1] <- 1
> init.genes[20:30,2] <- 1
> init.genes[50:60,3] <- 1
> init.samples[1:5,3] <- 1
> init.samples[1:5,4] <- 1
> init.samples[10:15,5] <- 1
```

Here the five first biclusters are initialised. Biclusters 1 and 2 are respectively initialised around genes 1 to 10 and 20 to 30; biclusters 4 and 5 around samples 1 to 5 and 10 to 15; bicluster 3 is initialised around genes 50 to 60 and samples 1 to 5.

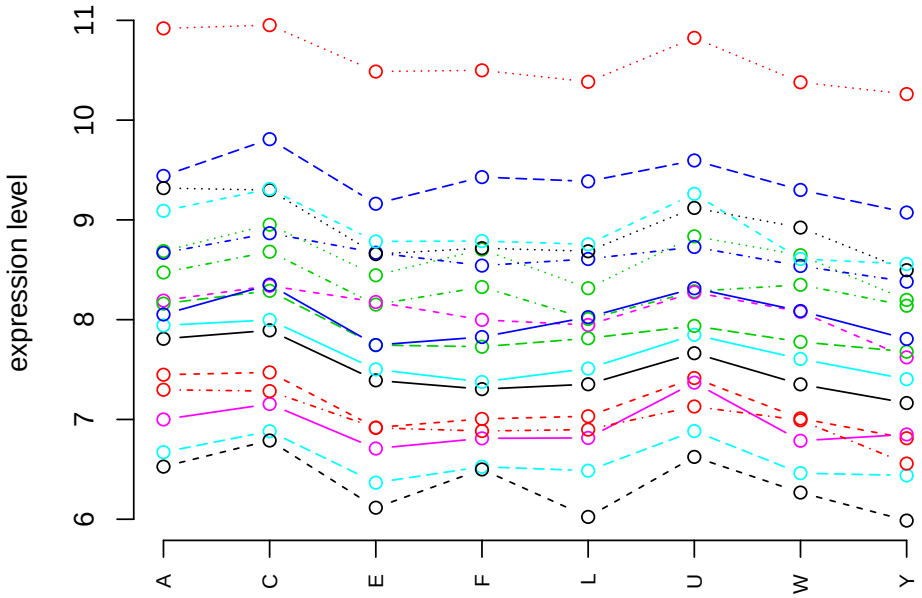
If the number of biclusters initialised is different from the parameter k, the real number of biclusters searched is the greater of the two.

The two initialisation matrices are given as arguments *blocGene* and *blocSample* to the *FLOC* function.

2.3 Bicluster extraction

The *bicluster* function extracts a bicluster from a *biclustering* object. The bicluster is returned as a matrix with the genes on rows and the conditions on columns. The *graph* option determines if a graphic should be plotted.

```
> bic <- bicluster(res.biclustering, 6, graph=FALSE)
> plot(bic)
```



3 Additionnal analyses

Additionnal analyses can be performed on the biclustering results. These analyses allows a functionnal view of the biclusters by testing the over-representation of gene sets or a characterisation of the samples (e.g. clinical covariates).

3.1 Genesets enrichment

A functionnal view of the biclusters can be obtained by testing the over-representation of a priori defined gene sets. This over-representation is evaluated by an hypergometric test. The gene sets are in the *GeneSetCollection* format.

```
> gsc <- GeneSetCollection(res.biclustering$ExpressionSet[1:50], setType=GOCollection())
> res.bic2 <- testSet(res.biclustering, gsc)
```

The *testSet* function returns an updated *biclustering* object with a new attribute *geneSet*. It is a list containing the *GeneSetCollection* used, the p-values (from an hypergeometric test) and the adjusted p-values.

3.2 Sample covariates enrichment

Three covariates for the samples are provided in the example data set. Function *testAnnot* only uses categorical covariates (here *sex* and *type*). For each bicluster, the function evaluates, with a χ^2 test of adequation, the enrichment of each level of the covariates.

```
> pData(sample.bicData)
```

```
     sex    type score
A Female Control  0.75
B   Male    Case  0.40
C   Male Control  0.73
D   Male    Case  0.42
E Female    Case  0.93
F   Male Control  0.22
G   Male    Case  0.96
H   Male    Case  0.79
I Female    Case  0.37
J   Male Control  0.63
K   Male    Case  0.26
L Female Control  0.36
M   Male    Case  0.41
N   Male    Case  0.80
O Female    Case  0.10
P Female Control  0.41
Q Female    Case  0.16
R   Male Control  0.72
S   Male    Case  0.17
T Female    Case  0.74
U   Male Control  0.35
V Female Control  0.77
W   Male Control  0.27
X   Male Control  0.98
Y Female    Case  0.94
Z Female    Case  0.32
```

```
> res.bic2 <- testAnnot(res.biclustering, annot=pData(sample.bicData), covariates=c("sex", "typ
```

As *testSet* does, the *testAnnot* function returns an updated *biclustering* object with a new attribute *covar*. It is a list containing the covariates used, the p-values and adjusted p-values, the numbers of each level in each bicluster and the residuals of the tests.

4 Building html report

Dealing with biclustering results is a tedious task because of the amount of data to explore. A user-friendly report can be created with the function *makeReport*. It allows an easy navigation through the results by different approaches :

- by bicluster
- by gene sets in order to examine the biclusters enriched in gene sets of interest

- by sample covariates in order to examine the biclusters enriched in samples with characteristics of interest

Each bicluster is presented by the lists of the genes and samples and by a plot of the expression profiles.

```
> dirPath <- getwd()
> dirName <- "test"
> makeReport(dirPath=dirPath, dirName=dirName, resBic=res.bic2, browse=FALSE)
```

The html report is created in the directory *dirName* in the current working directory. The *browse* option determines if the web browser is opened on the *home.html* file. Before running *makeReport* it is advised to check if the results directory can be created.

References

Madeira, S. and Oliveira, A. (2004). Biclustering algorithms for biological data analysis : a survey. *IEEE Transactions on Computational Biology and Bioinformatics*, 1(1):24–45.

Yang, J., Wang, H., Wang, W., and Yu, P. (2005). An improved biclustering method for analyzing gene expression. *International Journal on Artificial Tools*, 14(5):771–789.