Introduction to iBBiG

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1 iBBiG

Iterative Binary Bi-clustering of Gene sets (iBBiG) is a bi-clustering algorithm optimized for discovery of overlapping biclusters in spare binary matrices of data (Gusenleitner *et al.* in review).

We have optimized this method for the discovery of modules in matrices of discretized *p*-values from gene set enrichment analysis (GSA) of hundreds of datasets. However, it could be applied to any binary (1,0) matrix, such as discretized *p*-values from any sources of binary data. We apply iBBiG to meta-GSA to enable integrated analysis over hundreds of gene expression datasets. By integrating data at the levels of GSA results, we avoid the need to match probes/genes across multiple datasets, making large scale data integration a tractable problem.

iBBiG scales well with the dimensions of meta-datasets and is tolerant to noise characteristic of genomic data. It outperformed other traditional clustering approaches (Hierarchical clustering, k-means) or biclustering methods (bimax, fabia, coalesce) when applied to simulated data.

2 Application to simulated dataset

To demonstrate iBBiG, we will use a simulated binary dataset of 400 rows x 400 columns (as described by Gusenleitner *et al.*), in which a 1 indicates a positive association (or $p < 0.05$) between a gene set (row) and the results of a pairwise test between clinical covariates (column), and a 0 represents a lack of association.

To simulate random noise characteristically observed in genomic data, 10% random background noise (value of 1) was introduced into the matrix.

The matrix was seeded with seven artificial modules or bi-clusters (M1-M7; Figure 1) by assigning associations (value of 1) to its column and row pairs. To replicate the expected properties of real data, seeded modules partially overlapped in columns, in rows and in both rows and columns simultaneously. M1 gene sets overlap with most other modules with the exception of M3. M2 has overlapping pairwise tests with modules M4-7.

Artificial modules also have highly varying sizes and aspect ratios, including "wide" modules driven by a large number of pairwise tests and only a few gene sets and "tall" modules like M1 which consist of 25 pairwise tests and a large number of gene sets ($n = 250$). This latter type of module might represent a complex, well-characterized biological process such as proliferation.

In a real data set the signal strength will vary both between and within modules. Variance between modules was simulated by imposing random noise (1 -> 0 replacement) with different signal strengths on the modules (Figure 1). Within a module, we expect to see a few strong signals (gene sets associated with all pairwise tests) and many weaker signals. Therefore within each module, a noise gradient was also applied so that the first gene sets had the greatest number of associations (Figure 1). This overlaid noise gradient ranged from 10 to 60% and varied between modules (Table 1).

To create this simulated data as described in Gusenleitner, *et al.* use the function `makeArtifical` which creates an object of class *iBBiG*, an extension of *biclust*.

```
> library(iBBiG)
> binMat<-makeArtificial()
```

```
[1] "***** Summary of Design Matrix ******"
   Rows Cols DensityLow DenistyHigh
M1  250   25        0.4         0.9
M2   75  175        0.4         0.8
M3   50   50        0.5         0.8
M4   40   40        0.4         0.9
M5   30   30        0.4         0.8
M6   20   20        0.6         0.9
M7   40   40        0.5         0.6

Cluster sizes in new iBBiG (Biclust) data object
Number of Modules: 7
Rows        250        75        50        40        30        20        40
Columns        25        175        50        40        30        20        40
```

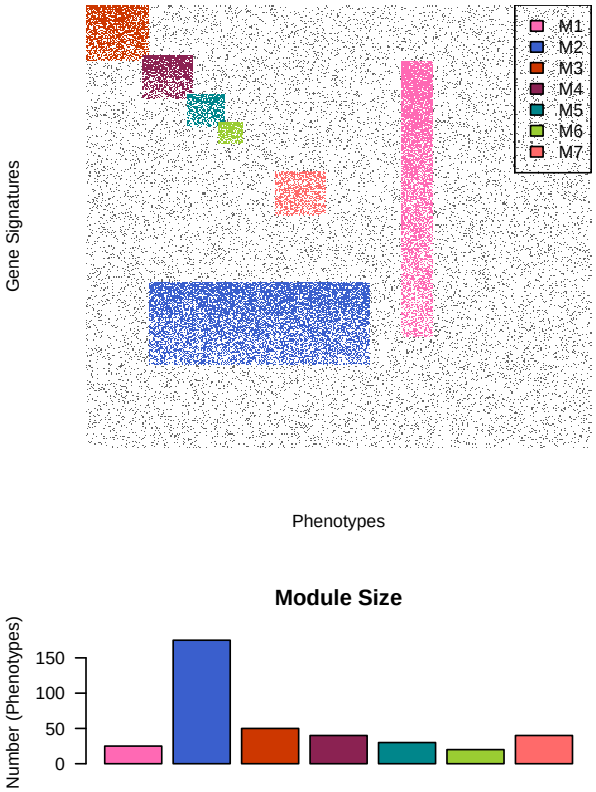
> binMat

```
An object of class iBBiG

Number of Clusters found:  7

First  5  Cluster scores and sizes:
                  [,1] [,2] [,3] [,4] [,5]
Cluster Score       NA   NA   NA   NA   NA
Number of Rows:    250   75   50   40   30
Number of Columns:  25  175   50   40   30
```

> plot(binMat)



The class *BiClust* contains the number of clusters and two logical matrices which indicate whether a row or column are present in the cluster.

```
> str(binMat)

Formal class 'iBBiG' [package "iBBiG"] with 8 slots
  ..@ Seeddata       : num [1:400, 1:400] 1 1 1 1 1 1 0 0 1 1 ...
  .. ..- attr(*, "dimnames")=List of 2
  .. .. ..$ : chr [1:400] "sig_1" "sig_2" "sig_3" "sig_4" ...
  .. .. ..$ : chr [1:400] "cov_1" "cov_2" "cov_3" "cov_4" ...
  ..@ RowScorexNumber: num[0 , 0 ]
  ..@ Clusterscores  : num(0)
  ..@ Parameters     :List of 3
  .. ..$ designMatrix: num [1:7, 1:6] 251 51 1 46 81 106 151 51 251 1 ...
  .. .. ..- attr(*, "dimnames")=List of 2
  .. .. .. ..$ : chr [1:7] "M1" "M2" "M3" "M4" ...
  .. .. .. ..$ : chr [1:6] "startC" "startR" "endC" "endR" ...
  .. ..$ nRow        : num 400
  .. ..$ nCol        : num 400
  ..@ RowxNumber     : logi [1:400, 1:7] FALSE FALSE FALSE FALSE FALSE FALSE ...
  ..@ NumberxCol     : logi [1:7, 1:400] FALSE FALSE TRUE FALSE FALSE FALSE ...
```

```
  ..@ Number          : int 7
  ..@ info            : list()
```

```
> Number(binMat)
```

```
[1] 7
```

```
> RowxNumber(binMat)[1:2,]
```

```
      [,1]  [,2] [,3]  [,4]  [,5]  [,6]  [,7]
[1,] FALSE FALSE TRUE FALSE FALSE FALSE FALSE
[2,] FALSE FALSE TRUE FALSE FALSE FALSE FALSE
```

```
> NumberxCol(binMat)[,1:2]
```

```
      [,1]  [,2]
[1,] FALSE FALSE
[2,] FALSE FALSE
[3,]  TRUE  TRUE
[4,] FALSE FALSE
[5,] FALSE FALSE
[6,] FALSE FALSE
[7,] FALSE FALSE
```

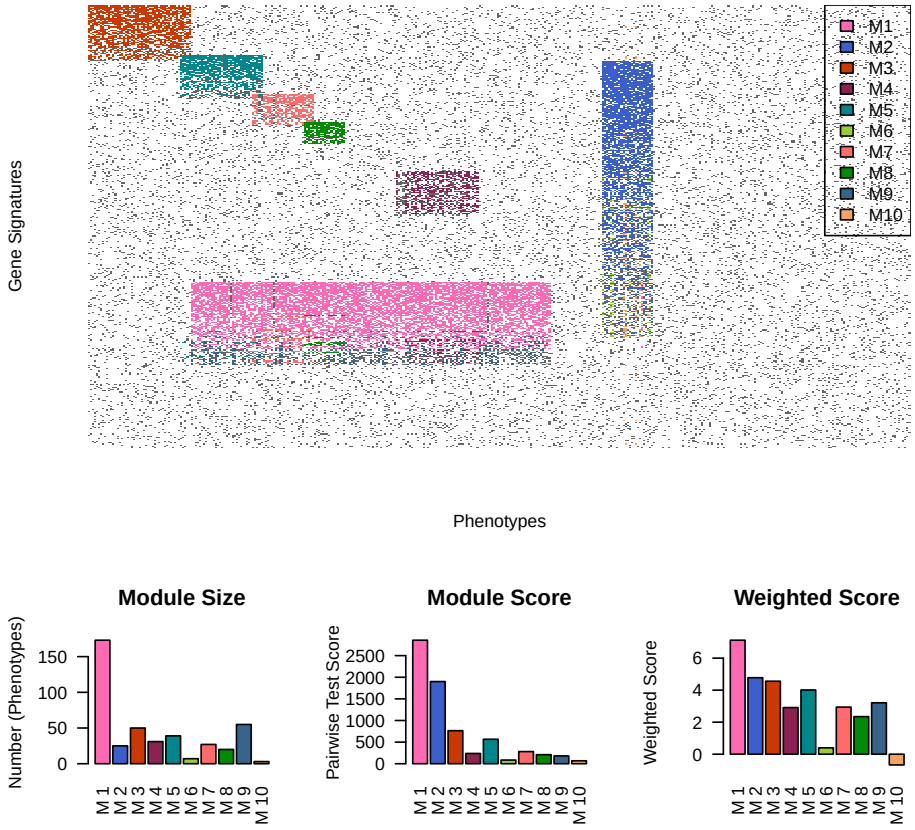
The matrix *RowxNumber* is a logical matrix having a number of rows equal to that of *binMat* and a number of columns equal to the number of detected clusters. *NumberxCol* is reversed; this class has a row count equal to the number of clusters and a column count of the number of columns of *binMat*.

To run iBBiG on this artificial binary matrix, simply call the function `iBBiG`. The function `plot` and `statClust` will provide a visual representation and statistical summary of the results of the cluster analysis.

```
> res<- iBBiG(binMat@Seeddata, nModules=10)
```

```
Module:  1 ... done
Module:  2 ... done
Module:  3 ... done
Module:  4 ... done
Module:  5 ... done
Module:  6 ... done
Module:  7 ... done
Module:  8 ... done
Module:  9 ... done
Module:  10 ... done
```

```
> plot(res)
```



If you wish to compare two `iBBiG` or `Biclust` results, for example a prediction and a gold standard (GS), the function `JIdist` will calculate the Jaccard Index distance between two *Biclust* or *iBBiG* result objects. By default, it calculates the distances between each column. Setting $margin = row$ or $margin = both$ will cause the function to calculate instead the JI distance between the rows, or an average of rows/columns.

By default, RfunctionJIdist returns a *data.frame* with 2 columns, the column n indicating which cluster was the best match (maximum JI) to each cluster of the second iBBiG object (GS). The column JI contains the Jaccard Index distance between the columns of these two clusters. If $best = FALSE$, the function will return the distance matrix instead of the best match.

```
> JIdist(res,binMat)
```

```
      n    JI
GS_1 2 1.000
GS_2 1 0.977
GS_3 3 1.000
GS_4 5 0.975
GS_5 7 0.900
GS_6 8 1.000
GS_7 4 0.775
```

```
> JIdist(res,binMat, margin="col", best=FALSE)
```

```
            GS_1      GS_2       GS_3       GS_4       GS_5
M 1  0.005076142 0.9772727 0.00000000 0.18994413 0.16666667
M 2  1.000000000 0.0000000 0.00000000 0.00000000 0.00000000
M 3  0.000000000 0.0000000 1.00000000 0.05882353 0.00000000
M 4  0.000000000 0.1771429 0.00000000 0.00000000 0.00000000
M 5  0.000000000 0.1888889 0.05952381 0.97500000 0.07812500
M 6  0.280000000 0.0000000 0.00000000 0.00000000 0.00000000
M 7  0.000000000 0.1542857 0.00000000 0.04687500 0.90000000
M 8  0.000000000 0.1142857 0.00000000 0.00000000 0.11111111
M 9  0.000000000 0.3142857 0.00000000 0.15853659 0.08974359
M 10 0.120000000 0.0000000 0.00000000 0.00000000 0.00000000
           GS_6      GS_7
M 1  0.11560694 0.2312139
M 2  0.00000000 0.0000000
M 3  0.00000000 0.0000000
M 4  0.00000000 0.7750000
M 5  0.00000000 0.0000000
M 6  0.00000000 0.0000000
M 7  0.11904762 0.0000000
M 8  1.00000000 0.0000000
M 9  0.07142857 0.1176471
M 10 0.00000000 0.0000000
```

```
> JIdist(res,binMat, margin="col")

     n    JI
GS_1 2 1.000
GS_2 1 0.977
GS_3 3 1.000
GS_4 5 0.975
GS_5 7 0.900
GS_6 8 1.000
GS_7 4 0.775
```

```
> JIdist(res,binMat, margin="row")

     n    JI
GS_1 2 0.756
GS_2 1 0.800
GS_3 3 0.920
GS_4 5 0.786
GS_5 7 0.605
GS_6 8 0.655
GS_7 4 0.640
```

```
> JIdist(res,binMat, margin="both")

     n    JI
GS_1 2 1.756
GS_2 1 1.777
GS_3 3 1.920
GS_4 5 1.761
```

```
GS_5 7 1.505
GS_6 8 1.655
GS_7 4 1.415
```

To view the code of the function JIdist

```
> showMethods(JIdist)
> getMethod(iBBiG:::JIdist, signature(clustObj = "iBBiG", GS = "iBBiG"))
> getMethod("JIdist",  signature(clustObj="iBBiG", GS="iBBiG"))
```

To extract performance statistics between two `iBBiG` results, use `analyzeClust`, which will take a single *iBBiG* result object or a list of objects and compare these to a gold standard (another *iBBiG* or *biclust* object). Again results can be based on matches to the best row, column or both.

```
> analyzeClust(res,binMat)
```

```
[1] "list"
     Run n    JI nRow nCol col-accuracy col-sensitivity
GS_1   1 2 1.000  189   25        1.000           1.000
GS_2   1 1 0.977   60  173        0.990           0.983
GS_3   1 3 1.000   46   50        1.000           1.000
GS_4   1 5 0.975   35   39        0.998           0.975
GS_5   1 7 0.900   39   27        0.992           0.900
GS_6   1 8 1.000   28   20        1.000           1.000
GS_7   1 4 0.775   42   31        0.978           0.775
     col-specificity col-PPV col-NPV row-accuracy
GS_1           1.000   1.000   1.000        0.848
GS_2           0.996   0.994   0.987        0.962
GS_3           1.000   1.000   1.000        0.990
GS_4           1.000   1.000   0.997        0.978
GS_5           1.000   1.000   0.992        0.958
GS_6           1.000   1.000   1.000        0.975
GS_7           1.000   1.000   0.976        0.955
     row-sensitivity row-specificity row-PPV row-NPV
GS_1           0.756           1.000   1.000   0.711
GS_2           0.800           1.000   1.000   0.956
GS_3           0.920           1.000   1.000   0.989
GS_4           0.825           0.994   0.943   0.981
GS_5           0.867           0.965   0.667   0.989
GS_6           0.950           0.976   0.679   0.997
GS_7           0.800           0.972   0.762   0.978
```

```
> analyzeClust(res,binMat, margin="col")
```

```
[1] "list"
     Run n    JI nRow nCol col-accuracy col-sensitivity
GS_1   1 2 1.000  189   25        1.000           1.000
GS_2   1 1 0.977   60  173        0.990           0.983
GS_3   1 3 1.000   46   50        1.000           1.000
GS_4   1 5 0.975   35   39        0.998           0.975
GS_5   1 7 0.900   39   27        0.992           0.900
GS_6   1 8 1.000   28   20        1.000           1.000
GS_7   1 4 0.775   42   31        0.978           0.775
```

```
     col-specificity col-PPV col-NPV row-accuracy
GS_1           1.000   1.000   1.000        0.848
GS_2           0.996   0.994   0.987        0.962
GS_3           1.000   1.000   1.000        0.990
GS_4           1.000   1.000   0.997        0.978
GS_5           1.000   1.000   0.992        0.958
GS_6           1.000   1.000   1.000        0.975
GS_7           1.000   1.000   0.976        0.955
     row-sensitivity row-specificity row-PPV row-NPV
GS_1           0.756           1.000   1.000   0.711
GS_2           0.800           1.000   1.000   0.956
GS_3           0.920           1.000   1.000   0.989
GS_4           0.825           0.994   0.943   0.981
GS_5           0.867           0.965   0.667   0.989
GS_6           0.950           0.976   0.679   0.997
GS_7           0.800           0.972   0.762   0.978
```

Again to view the code of the function, you could:

```
> showMethods(analyzeClust)
> getMethod("analyzeClust",  signature(clustObj="iBBiG", GS="iBBiG"))
```

The structure of *iBBiG* differs from *BiClust* in that it contains ClusterScores. ClusterScores are the scores for each module. RowScoreNumber are the scores for each row in the cluster. *Seeddata* is a copy of *binMat*.

```
> str(binMat)
```

```
Formal class 'iBBiG' [package "iBBiG"] with 8 slots
  ..@ Seeddata       : num [1:400, 1:400] 1 1 1 1 1 1 0 0 1 1 ...
  .. ..- attr(*, "dimnames")=List of 2
  .. .. ..$ : chr [1:400] "sig_1" "sig_2" "sig_3" "sig_4" ...
  .. .. ..$ : chr [1:400] "cov_1" "cov_2" "cov_3" "cov_4" ...
  ..@ RowScorexNumber: num[0 , 0 ]
  ..@ Clusterscores  : num(0)
  ..@ Parameters     :List of 3
  .. ..$ designMatrix: num [1:7, 1:6] 251 51 1 46 81 106 151 51 251 1 ...
  .. .. ..- attr(*, "dimnames")=List of 2
  .. .. .. ..$ : chr [1:7] "M1" "M2" "M3" "M4" ...
  .. .. .. ..$ : chr [1:6] "startC" "startR" "endC" "endR" ...
  .. ..$ nRow        : num 400
  .. ..$ nCol        : num 400
  ..@ RowxNumber     : logi [1:400, 1:7] FALSE FALSE FALSE FALSE FALSE FALSE ...
  ..@ NumberxCol     : logi [1:7, 1:400] FALSE FALSE TRUE FALSE FALSE FALSE ...
  ..@ Number         : int 7
  ..@ info           : list()
```

```
> RowScorexNumber(res)[1:2,]
```

```
      M 1 M 2      M 3 M 4 M 5 M 6 M 7 M 8 M 9 M 10
sig_1   0   0 29.12712   0   0   0   0   0   0    0
sig_2   0   0 33.04621   0   0   0   0   0   0    0
```

```
> Clusterscores(res)
```

```
       M 1        M 2        M 3        M 4        M 5
2856.67619 1900.20691  763.99947  237.31744  566.27204
       M 6        M 7        M 8        M 9       M 10
  84.92691  280.49345  209.15203  180.36740   68.03275
```

```
> Seeddata(res)[1:2,1:2]
```

```
      cov_1 cov_2
sig_1     1     1
sig_2     1     0
```

There are also the slots for info and Parameters which can contain additional user-entered information about the analysis. We can subset or reorder the results like so:

```
> res[1:3]
```

```
An object of class iBBiG

Number of Clusters found:  3

First  3  Cluster scores and sizes:
                        M 1      M 2      M 3
Cluster Score      2856.676 1900.207 763.9995
Number of Rows:      60.000  189.000  46.0000
Number of Columns:  173.000   25.000  50.0000
```

```
> res[c(4,2,1)]
```

```
An object of class iBBiG

Number of Clusters found:  3

First  3  Cluster scores and sizes:
                        M 4      M 2      M 1
Cluster Score      237.3174 1900.207 2856.676
Number of Rows:     42.0000  189.000   60.000
Number of Columns:  31.0000   25.000  173.000
```

```
> res[1, drop=FALSE]
```

```
An object of class iBBiG

There was one cluster found with Score 2856.676 and
  60 Rows and  173 columns
```

3 Using biclust functions

An object from *iBBiG* extends the class *biclust* and can therefore use methods available to a *biclust* object. For example, there are several plot functions in *BiClust*

```
> class(res)
> par(mfrow=c(2,1))
> drawHeatmap2(res@Seeddata, res, number=4)
```

```
> biclustmember(res,res@Seeddata)
> biclustbarchart(res@Seeddata, Bicres=res)
> plotclust(res, res@Seeddata)
```

Statistical measures of biclustering performance including the Chia and Karuturi Function, Coherence measures and F Statistics are available within the *biclust* R packages.

There are function to process data, binarize or discretize data. For example, given gene expression data we can binarize or discretize the data matrix as follows and this can be input into iBBiG

```
> data(BicatYeast)
> BicatYeast[1:5,1:5]
> binarize(BicatYeast[1:5,1:5], threshold=0.2)
> discretize(BicatYeast[1:5,1:5])
```

The sub-matrices of each cluster can be extracted from the original matrix, using the function `bicluster`

```
> Modules<-bicluster(res@Seeddata, res, 1:3)
> str(Modules)
```

```
List of 3
 $ Bicluster1: num [1:60, 1:173] 0 1 1 1 1 1 0 0 1 1 ...
  ..- attr(*, "dimnames")=List of 2
  .. ..$ : chr [1:60] "sig_251" "sig_252" "sig_253" "sig_254" ...
  .. ..$ : chr [1:173] "cov_51" "cov_52" "cov_53" "cov_54" ...
 $ Bicluster2: num [1:189, 1:25] 1 1 1 1 1 1 1 1 1 1 ...
  ..- attr(*, "dimnames")=List of 2
  .. ..$ : chr [1:189] "sig_51" "sig_52" "sig_53" "sig_54" ...
  .. ..$ : chr [1:25] "cov_251" "cov_252" "cov_253" "cov_254" ...
 $ Bicluster3: num [1:46, 1:50] 1 1 1 1 1 1 0 0 1 1 ...
  ..- attr(*, "dimnames")=List of 2
  .. ..$ : chr [1:46] "sig_1" "sig_2" "sig_3" "sig_4" ...
  .. ..$ : chr [1:50] "cov_1" "cov_2" "cov_3" "cov_4" ...
```

```
> Modules[[1]][1:3,1:4]
```

```
        cov_51 cov_52 cov_53 cov_54
sig_251      0      0      1      0
sig_252      1      1      0      1
sig_253      1      0      1      1
```

To write results to a file use the following:

```
> writeBiclusterResults("Modules.txt", res, bicName="Output from iBBiG with default pa
>
```

4 Session Info

- R version 2.15.1 (2012-06-22), `x86_64-unknown-linux-gnu`
- Locale: `LC_CTYPE=en_US.UTF-8`, `LC_NUMERIC=C`, `LC_TIME=en_US.UTF-8`, `LC_COLLATE=C`, `LC_MONETARY=en_US.UTF-8`, `LC_MESSAGES=en_US.UTF-8`, `LC_PAPER=C`, `LC_NAME=C`, `LC_ADDRESS=C`, `LC_TELEPHONE=C`, `LC_MEASUREMENT=en_US.UTF-8`, `LC_IDENTIFICATION=C`

- Base packages: base, datasets, grDevices, graphics, grid, methods, stats, utils
- Other packages: MASS 7.3-21, biclust 1.0.1, colorspace 1.1-1, iBBiG 1.2.0, lattice 0.20-10
- Loaded via a namespace (and not attached): ade4 1.5-1, stats4 2.15.1, tools 2.15.1, xtable 1.7-0

References