

# Package ‘GNET2’

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**Type** Package

**Title** Constructing gene regulatory networks from expression data through functional module inference

**Version** 1.23.0

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**Description** Cluster genes to functional groups with E-M process. Iteratively perform TF assigning and Gene assigning, until the assignment of genes did not change, or max number of iterations is reached.

**License** Apache License 2.0

**Encoding** UTF-8

**LazyData** true

**LinkingTo** Rcpp

**Depends** R (>= 3.6)

**Imports**

ggplot2,xgboost,Rcpp,reshape2,grid,DiagrammeR,methods,stats,matrixStats,graphics,SummarizedExperiment,dplyr,igraph,grDevices, utils

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**Suggests** knitr, rmarkdown

**VignetteBuilder** knitr

**biocViews** GeneExpression, Regression, Network, NetworkInference, Software

**URL** <https://github.com/chrischen1/GNET2>

**BugReports** <https://github.com/chrischen1/GNET2/issues>

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|              |                               |
|--------------|-------------------------------|
| build_module | <i>Fit a regression tree.</i> |
|--------------|-------------------------------|

---

### Description

Fit a regression tree based on Gaussian Likelihood score. Provided in case the best split is not applicable for R dnorm() function.

### Usage

```
build_module(X, Y, max_depth, cor_cutoff, min_divide_size)
```

### Arguments

|                 |  |
|-----------------|--|
| X               | A n by p matrix as input.  |
| Y               | A n by q matrix as response.   |
| max_depth       | Maximum depth of the tree.   |
| cor_cutoff      | Cutoff for within group Pearson correlation coefficient, if all data belong to a node have average correlation greater or equal to this, the node would not split anymore. |
| min_divide_size | Minimum number of data belong to a node allowed for further split of the node.   |

### Value

A matrix for sample informatrion for each partition level. First column is feature index used by the node and second is the value used to split, the rest of the columns are the split of sample: 0 means less or equal, 1 means greater and -1 means the sample does not belong to this node.

**Examples**

```
build_module(X = matrix(rnorm(5*10),5,10), Y = matrix(rnorm(5*10),5,10),
                 max_depth=3,cor_cutoff=0.9,min_divide_size=3)
```

---

|               |                               |
|---------------|-------------------------------|
| build_moduleR | <i>Build regression tree.</i> |
|---------------|-------------------------------|

---

**Description**

Build regression tree based on Gaussian Likelihood score.

**Usage**

```
build_moduleR(X, Y, max_depth, cor_cutoff, min_divide_size)
```

**Arguments**

|                 |  |
|-----------------|--|
| X               | A n by p matrix as input.  |
| Y               | A n by q matrix as response.   |
| max_depth       | Maximum depth of the tree.   |
| cor_cutoff      | Cutoff for within group Pearson correlation coefficient, if all data belong to a node have average correlation greater or equal to this, the node would not split anymore. |
| min_divide_size | Minimum number of data belong to a node allowed for further split of the node.   |

**Value**

A matrix for sample information for each tree level. First column is feature index used by the node and second is the value used to split, the rest of the columns are the split of sample: 0 means less or equal, 1 means greater and -1 means the sample does not belong to this node.

**Examples**

```
build_moduleR(X = matrix(rnorm(5*10),5,10), Y = matrix(rnorm(5*10),5,10),
                 max_depth=3,cor_cutoff=0.9,min_divide_size=3)
```

---

```
build_moduleR_heuristic
```

*Build regression tree with splits are determined by K-means heuristically.*

---

### Description

Build regression tree based on Gaussian Likelihood score. The splitting of the tree is determined heuristically by k\_means.

### Usage

```
build_moduleR_heuristic(  
  X,  
  Y,  
  max_depth,  
  cor_cutoff,  
  min_divide_size,  
  split_table  
)
```

### Arguments

|                 |  |
|-----------------|--|
| X               | A n by p matrix as input.  |
| Y               | A n by q matrix as response.   |
| max_depth       | Maximum depth of the tree.   |
| cor_cutoff      | Cutoff for within group Pearson correlation coefficient, if all data belong to a node have average correlation greater or equal to this, the node would not split anymore. |
| min_divide_size | Minimum number of data belong to a node allowed for further split of the node.   |
| split_table     | split table generated by K-means with build_split_table()  |

### Value

A matrix for sample information for each tree level. First column is feature index used by the node and second is the value used to split, the rest of the columns are the split of sample: 0 means less or equal, 1 means greater and -1 means the sample does not belong to this node.

### Examples

```
X <- matrix(rnorm(5*10),5,10)  
build_moduleR_heuristic(X = X, Y = matrix(rnorm(5*10),5,10),max_depth=3,cor_cutoff=0.9,  
  min_divide_size=3,split_table = build_split_table(X))
```

---

build\_split\_table      *Build split table by K-means heuristicly.*

---

**Description**

Build split table by K-means with 3 cluster centers for each column of X

**Usage**

```
build_split_table(X)
```

**Arguments**

X                      A n by p matrix as input.

**Value**

A n by p matrix with each column consists of 3 clusters: -1 for low, 0 for mid and 1 for high

**Examples**

```
split_table <- build_split_table(matrix(rnorm(5*10),5,10))
```

---

calc\_likelihood\_score      *Calculate Gaussian Likelihood score.*

---

**Description**

Calculate Gaussian Likelihood score.

**Usage**

```
calc_likelihood_score(x, group_labels)
```

**Arguments**

x                      A n by p matrix.  
group\_labels      A vector of length n, indicating the group of rows.

**Value**

The sum of log likelihood score of each group on each column.

**Examples**

```
calc_likelihood_score(x = matrix(rnorm(5*10),5,10), group_labels = c(rep(1,2),rep(2,3)))
```

---

|               |   |
|---------------|---|
| extract_edges | <i>Extract the network from the gnet result</i> |
|---------------|---|

---

**Description**

Extract the network as edge list from the gnet result. For a module, each regulator and downstream gene will form a directed edge.

**Usage**

```
extract_edges(gnet_result)
```

**Arguments**

gnet\_result      Returned results from gnet().

**Value**

A matrix of scores of for the regulator-target interaction.

**Examples**

```
set.seed(1)
init_group_num = 8
init_method = 'kmeans'
exp_data <- matrix(rnorm(50*10),50,10)
reg_names <- paste0('TF',1:5)
rownames(exp_data) <- c(reg_names,paste0('gene',1:(nrow(exp_data)-length(reg_names))))
colnames(exp_data) <- paste0('condition_',1:ncol(exp_data))
se <- SummarizedExperiment::SummarizedExperiment(assays=list(counts=exp_data))
gnet_result <- gnet(se,reg_names,init_method,init_group_num)
edge_list <- extract_edges(gnet_result)
```

---

|                      |   |
|----------------------|---|
| get_correlation_list | <i>Calculate correlation within each group.</i> |
|----------------------|---|

---

**Description**

Calculate Pearson correlation coefficient within each group.

**Usage**

```
get_correlation_list(x, group_labels)
```

**Arguments**

x                      A n by p matrix.  
group\_labels          A vector of length n, indicating the group of rows.

**Value**

An array of Pearson correlation coefficient for each row, rows belong to the same group have same values.

**Examples**

```
get_correlation_list(x = matrix(rnorm(5*10),5,10), group_labels = c(rep(1,2),rep(2,3)))
```

---

gnet

*Run GNET2*


---

**Description**

Build regulation modules by iteratively perform regulator assigning and Gene assigning, until the assignment of genes did not change, or max number of iterations reached.

**Usage**

```
gnet(
  input,
  reg_names,
  init_method = "boosting",
  init_group_num = 4,
  max_depth = 3,
  cor_cutoff = 0.9,
  min_divide_size = 3,
  min_group_size = 2,
  max_iter = 5,
  heuristic = TRUE,
  max_group = 0,
  force_split = 0.5,
  nthread = 4
)
```

**Arguments**

|                |  |
|----------------|--|
| input          | A SummarizedExperiment object, or a p by n matrix of expression data of p genes and n samples, for example log2 RPKM from RNA-Seq.   |
| reg_names      | A list of potential upstream regulators names, for example a list of known transcription factors.  |
| init_method    | Cluster initialization, can be "boosting" or "kmeans", default is using "boosting".  |
| init_group_num | Initial number of function clusters used by the algorithm.   |
| max_depth      | max_depth Maximum depth of the tree.   |
| cor_cutoff     | Cutoff for within group Pearson correlation coefficient, if all data belong to a node have average correlation greater or equal to this, the node would not split anymore. |

|                 |  |
|-----------------|--|
| min_divide_size | Minimum number of data belong to a node allowed for further split of the node.   |
| min_group_size  | Minimum number of genes allowed in a group.  |
| max_iter        | Maximum number of iterations allowed if not converged.   |
| heuristic       | If the splits of the regression tree is determined by k-means heuristically.   |
| max_group       | Max number of group allowed for the first clustering step, default equals init_group_num and is set to 0.                          |
| force_split     | Force split the largest gene group into smaller groups by kmeans. Default is 0.5(Split if it contains more than half target genes) |
| nthread         | Number of threads to run GBDT based clustering   |

**Value**

A list of expression data of genes, expression data of regulators, within group score, table of tree structure and final assigned group of each gene.

**Examples**

```
set.seed(1)
init_group_num = 8
init_method = 'boosting'
exp_data <- matrix(rnorm(50*10),50,10)
reg_names <- paste0('TF',1:5)
rownames(exp_data) <- c(reg_names,paste0('gene',1:(nrow(exp_data)-length(reg_names))))
colnames(exp_data) <- paste0('condition_',1:ncol(exp_data))
se <- SummarizedExperiment::SummarizedExperiment(assays=list(counts=exp_data))
gnet_result <- gnet(se,reg_names,init_method,init_group_num)
```

---

kneepointDetection      *Knee point detection.*

---

**Description**

Detect the knee point of the array.

**Usage**

```
kneepointDetection(vect)
```

**Arguments**

vect                    A list of sorted numbers.

**Value**

The index of the data point which is the knee.



**Examples**

```
kneepointDetection(sort(c(runif(10,1,3),c(runif(10,5,10))),TRUE))
```

---

|                 |                      |
|-----------------|----------------------|
| plot_gene_group | <i>Plot a module</i> |
|-----------------|----------------------|

---

**Description**

Plot the regulators module and heatmap of the expression inferred downstream genes for each sample. It can be interpreted as two parts: the bars at the top shows how samples are splited by the regression tree and the heatmap at the bottom shows how downstream genes are regulated by each subgroup determined by the regulators.

**Usage**

```
plot_gene_group(
  gnet_result,
  group_idx,
  tree_layout = 1,
  max_gene_num = 100,
  plot_leaf_labels = TRUE,
  group_labels = NULL
)
```

**Arguments**

|                  |  |
|------------------|--|
| gnet_result      | Results returned by gnet().  |
| group_idx        | Index of the module.   |
| tree_layout      | zoom ratio for the regulatory tree. Default is 1. Need to be increased for trees with >5 regulators. |
| max_gene_num     | Max size of gene to plot in the heatmap. Only genes with highest n variances will be kept.           |
| plot_leaf_labels | If the plot includes a color bar of leaf labels at the bottom.                                       |
| group_labels     | Labels of experiment conditions,Used for the color bar of experiment conditions. Default is NULL     |

**Value**

None

## Examples

```
set.seed(1)
init_group_num = 5
init_method = 'boosting'
exp_data <- matrix(rnorm(50*10),50,10)
reg_names <- paste0('TF',1:5)
rownames(exp_data) <- c(reg_names,paste0('gene',1:(nrow(exp_data)-length(reg_names))))
colnames(exp_data) <- paste0('condition_',1:ncol(exp_data))
se <- SummarizedExperiment::SummarizedExperiment(assays=list(counts=exp_data))
gnet_result <- gnet(se,reg_names,init_method,init_group_num)
plot_gene_group(gnet_result,group_idx=1)
```

---

plot\_group\_correlation

*Plot the correlation of each group*

---

## Description

Plot the correlation of each group and auto detected knee point. It can be used to determined which clustered are kept for further analysis.

## Usage

```
plot_group_correlation(gnet_result)
```

## Arguments

gnet\_result      Results returned by gnet().

## Value

A list of indices of the data point with correlation higher than the knee point.

## Examples

```
set.seed(1)
gnet_result <- list('group_score'=c(runif(10,1,3),c(runif(10,5,3))))
group_keep <- plot_group_correlation(gnet_result)
```

---

|           |                                  |
|-----------|----------------------------------|
| plot_tree | <i>Plot the regression tree.</i> |
|-----------|----------------------------------|

---

**Description**

Plot the regression tree given the index of a module.

**Usage**

```
plot_tree(gnet_result, group_idx)
```

**Arguments**

|             |                             |
|-------------|-----------------------------|
| gnet_result | Results returned by gnet(). |
| group_idx   | Index of the module.        |

**Value**

None

**Examples**

```
set.seed(1)
init_group_num = 5
init_method = 'boosting'
exp_data <- matrix(rnorm(50*10),50,10)
reg_names <- paste0('TF',1:5)
rownames(exp_data) <- c(reg_names,paste0('gene',1:(nrow(exp_data)-length(reg_names))))
colnames(exp_data) <- paste0('condition_',1:ncol(exp_data))
se <- SummarizedExperiment::SummarizedExperiment(assays=list(counts=exp_data))
gnet_result <- gnet(se,reg_names,init_method,init_group_num)
plot_tree(gnet_result,group_idx=1)
```

---

|           |                               |
|-----------|-------------------------------|
| save_gnet | <i>Save the GNET2 results</i> |
|-----------|-------------------------------|

---

**Description**

Save the edge list, group index of each gene and plot the top groups

**Usage**

```
save_gnet(gnet_result, save_path = ".", num_module = 10, max_gene_num = 100)
```

**Arguments**

|                           |   |
|---------------------------|---|
| <code>gnet_result</code>  | Results returned by <code>gnet()</code> .         |
| <code>save_path</code>    | path to save files                                |
| <code>num_module</code>   | The number of modules with highest score to plot. |
| <code>max_gene_num</code> | The max number of genes to show in the heatmap.   |

**Value**

None

**Examples**

```
set.seed(1)
init_group_num = 5
init_method = 'boosting'
exp_data <- matrix(rnorm(50*10),50,10)
reg_names <- paste0('TF',1:5)
rownames(exp_data) <- c(reg_names,paste0('gene',1:(nrow(exp_data)-length(reg_names))))
colnames(exp_data) <- paste0('condition_',1:ncol(exp_data))
se <- SummarizedExperiment::SummarizedExperiment(assays=list(counts=exp_data))
gnet_result <- gnet(se,reg_names,init_method,init_group_num)
save_gnet(gnet_result)
```

---

|                               |   |
|-------------------------------|---|
| <code>similarity_score</code> | <i>Compute the similarity from a predefined condition group</i> |
|-------------------------------|---|

---

**Description**

Compute the similarity between a predefined condition grouping and the sample cluster of each module, which is defined as the Adjusted Rand index between the two vectors, or the inverse of K-L divergence between the upper triangle matrix of the pairwise distance of predefined ranked condition grouping and the pairwise distance of sample cluster of each module.

**Usage**

```
similarity_score(gnet_result, group, ranked = FALSE)
```

**Arguments**

|                          |   |
|--------------------------|---|
| <code>gnet_result</code> | Returned results from <code>gnet()</code> .   |
| <code>group</code>       | predefined condition grouping   |
| <code>ranked</code>      | the grouping information is categorical(treatment/control) or ordinal(dosage, time points)? |

**Value**

A list of similarity scores between a predefined condition grouping and the sample cluster of each module, and the p values for the similarity scores based on permutation.

**Examples**

```
set.seed(1)
init_group_num = 8
init_method = 'kmeans'
exp_data <- matrix(rnorm(50*10),50,10)
reg_names <- paste0('TF',1:5)
rownames(exp_data) <- c(reg_names,paste0('gene',1:(nrow(exp_data)-length(reg_names))))
colnames(exp_data) <- paste0('condition_',1:ncol(exp_data))
se <- SummarizedExperiment::SummarizedExperiment(assays=list(counts=exp_data))
gnet_result <- gnet(se,reg_names,init_method,init_group_num)
s <- similarity_score(gnet_result,rep(1:5,each = 2))
```

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