

# Package ‘AMARETTO’

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**Type** Package

**Title** Regulatory Network Inference and Driver Gene Evaluation using Integrative Multi-Omics Analysis and Penalized Regression

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**Depends** R (>= 3.6), impute, doParallel, grDevices, dplyr, methods, ComplexHeatmap

**Description** Integrating an increasing number of available multi-omics cancer data remains one of the main challenges to improve our understanding of cancer. One of the main challenges is using multi-omics data for identifying novel cancer driver genes. We have developed an algorithm, called AMARETTO, that integrates copy number, DNA methylation and gene expression data to identify a set of driver genes by analyzing cancer samples and connects them to clusters of co-expressed genes, which we define as modules. We applied AMARETTO in a pancancer setting to identify cancer driver genes and their modules on multiple cancer sites. AMARETTO captures modules enriched in angiogenesis, cell cycle and EMT, and modules that accurately predict survival and molecular subtypes. This allows AMARETTO to identify novel cancer driver genes directing canonical cancer pathways.

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**LazyLoad** yes

**LazyData** true

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**biocViews**

StatisticalMethod,DifferentialMethylation,GeneRegulation,GeneExpression,MethylationArray,Transcription,Preproce

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**NeedsCompilation** no

**Imports** callr (>= 3.0.0.9001), Matrix, Rcpp, BiocFileCache, DT, MultiAssayExperiment, circlize, curatedTCGAData, foreach, glmnet, httr, limma, matrixStats, readr, reshape2, tibble, rmarkdown, graphics, grid, parallel, stats, knitr, ggplot2, gridExtra, utils

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AMARETTO\_CreateModuleData

*AMARETTO\_CreateModuleData*

---

### Description

AMARETTO\_CreateModuleData

### Usage

AMARETTO\_CreateModuleData(AMARETTOinit, AMARETTOresults)

### Arguments

AMARETTOinit List output from AMARETTO\_Initialize().

AMARETTOresults

List output from AMARETTO\_Run()

### Value

result

**Examples**

```
data('ProcessedDataLIHC')
AMARETTOinit <- AMARETTO_Initialize(ProcessedData = ProcessedDataLIHC,
                                   NrModules = 2, VarPercentage = 50)
AMARETTOresults <- AMARETTO_Run(AMARETTOinit)
AMARETTO_MD <- AMARETTO_CreateModuleData(AMARETTOinit, AMARETTOresults)
```

---

AMARETTO\_CreateRegulatorPrograms  
*AMARETTO\_CreateRegulatorPrograms*

---

**Description**

AMARETTO\_CreateRegulatorPrograms

**Usage**

```
AMARETTO_CreateRegulatorPrograms(AMARETTOinit, AMARETTOresults)
```

**Arguments**

AMARETTOinit    List output from AMARETTO\_Initialize().  
AMARETTOresults    List output from AMARETTO\_Run()

**Value**

result

**Examples**

```
data('ProcessedDataLIHC')
AMARETTOinit <- AMARETTO_Initialize(ProcessedData = ProcessedDataLIHC,
                                   NrModules = 2, VarPercentage = 50)
AMARETTOresults <- AMARETTO_Run(AMARETTOinit)
AMARETTO_RP <- AMARETTO_CreateRegulatorPrograms(AMARETTOinit,AMARETTOresults)
```

---

AMARETTO\_Download    *AMARETTO\_Download*

---

**Description**

Downloading TCGA dataset for AMARETTO analysis

**Usage**

```
AMARETTO_Download(CancerSite = "CHOL",
                  TargetDirectory = TargetDirectory)
```

**Arguments**

CancerSite        TCGA cancer code for data download  
 TargetDirectory    Directory path to download data

**Value**

result

**Examples**

```
TargetDirectory <- file.path(getwd(),"Downloads/");dir.create(TargetDirectory)
CancerSite <- 'CHOL'
DataSetDirectories <- AMARETTO_Download(CancerSite,TargetDirectory = TargetDirectory)
```

AMARETTO\_EvaluateTestSet

*AMARETTO\_EvaluateTestSet*

**Description**

Code to evaluate AMARETTO on a new gene expression test set. Uses output from AMARETTO\_Run() and CreateRegulatorData().

**Usage**

```
AMARETTO_EvaluateTestSet(AMARETTOresults = AMARETTOresults,
  MA_Data_TestSet = MA_Data_TestSet,
  RegulatorData_TestSet = RegulatorData_TestSet)
```

**Arguments**

AMARETTOresults                    AMARETTO output from AMARETTO\_Run().  
 MA\_Data\_TestSet                    Gene expression matrix from a test set (that was not used in AMARETTO\_Run()).  
 RegulatorData\_TestSet             Test regulator data from CreateRegulatorData().

**Value**

result

**Examples**

```
data('ProcessedDataLIHC')
AMARETTOinit <- AMARETTO_Initialize(ProcessedData = ProcessedDataLIHC,
  NrModules = 2, VarPercentage = 50)

AMARETTOresults <- AMARETTO_Run(AMARETTOinit)
AMARETTOtestReport <- AMARETTO_EvaluateTestSet(AMARETTOresults = AMARETTOresults,
  MA_Data_TestSet = AMARETTOinit$MA_matrix_Var,
  RegulatorData_TestSet = AMARETTOinit$RegulatorData)
```

---

 AMARETTO\_ExportResults

*AMARETTO\_ExportResults*


---

### Description

Retrieve a download of all the data linked with the run (including heatmaps)

### Usage

```
AMARETTO_ExportResults(AMARETTOinit, AMARETTOresults, data_address,
  Heatmaps = TRUE, CNV_matrix = NULL, MET_matrix = NULL)
```

### Arguments

AMARETTOinit	AMARETTO initialize output
AMARETTOresults	AMARETTO results output
data_address	Directory to save data folder
Heatmaps	Output heatmaps as pdf
CNV_matrix	CNV_matrix
MET_matrix	MET_matrix

### Value

result

### Examples

```
data('ProcessedDataLIHC')
TargetDirectory <- file.path(getwd(),"Downloads/");dir.create(TargetDirectory)
AMARETTOinit <- AMARETTO_Initialize(ProcessedData = ProcessedDataLIHC,
  NrModules = 2, VarPercentage = 50)

AMARETTOresults <- AMARETTO_Run(AMARETTOinit)
AMARETTO_ExportResults(AMARETTOinit,AMARETTOresults,TargetDirectory,Heatmaps = FALSE)
```

---

 AMARETTO\_HTMLreport    *AMARETTO\_HTMLreport*


---

### Description

Retrieve an interactive html report, including gene set enrichment analysis if asked for.

### Usage

```
AMARETTO_HTMLreport(AMARETTOinit, AMARETTOresults, ProcessedData,
  show_row_names = FALSE, SAMPLE_annotation = NULL, ID = NULL,
  hyper_geo_test_bool = FALSE, hyper_geo_reference = NULL,
  output_address = "./", MSIGDB = TRUE, driverGSEA = TRUE,
  phenotype_association_table = NULL)
```

**Arguments**

AMARETTOinit AMARETTO initialize output  
 AMARETTOresults AMARETTO results output  
 ProcessedData List of processed input data  
 show\_row\_names if True, sample names will appear in the heatmap  
 SAMPLE\_annotation SAMPLE annotation will be added to heatmap  
 ID ID column of the SAMPLE annotation data frame  
 hyper\_geo\_test\_bool Boolean if a hyper geometric test needs to be performed. If TRUE provide a GMT file in the hyper\_geo\_reference parameter.  
 hyper\_geo\_reference GMT file with gene sets to compare with.  
 output\_address Output directory for the html files.  
 MSIGDB TRUE if gene sets were retrieved from MSIGDB. Links will be created in the report.  
 driverGSEA if TRUE, module drivers will also be included in the hypergeometric test.  
 phenotype\_association\_table a Data Frame, containing all modules phenotype association data. Optional.

**Value**

result

**Examples**

```

## Not run:
data('ProcessedDataLIHC')
AMARETTOinit <- AMARETTO_Initialize(ProcessedData = ProcessedDataLIHC,
                                   NrModules = 2, VarPercentage = 50)

AMARETTOresults <- AMARETTO_Run(AMARETTOinit)

AMARETTO_HTMLreport(AMARETTOinit= AMARETTOinit,AMARETTOresults= AMARETTOresults,
                    ProcessedData = ProcessedDataLIHC,
                    hyper_geo_test_bool=FALSE,
                    output_address='./')

## End(Not run)

```

---

AMARETTO\_Initialize    *AMARETTO\_Initialize (version: reorder and filter MA\_Matrix)*

---

**Description**

Code used to initialize the seed clusters for an AMARETTO run. Requires processed gene expressions (rna-seq or microarray), CNV (usually from a GISTIC run), and methylation (from MethylMix, provided in this package) data. Uses the function CreateRegulatorData() and results are fed into the function AMARETTO\_Run().

**Usage**

```
AMARETTO_Initialize(ProcessedData = ProcessedData, Driver_list = NULL,
  NrModules, VarPercentage, PvalueThreshold = 0.001,
  RsquareThreshold = 0.1, pmax = 10, NrCores = 1, OneRunStop = 0,
  method = "union", random_seeds = NULL, convergence_cutoff = 0.01)
```

**Arguments**

ProcessedData	List of Expression, CNV and MethylMix data matrices, with genes in rows and samples in columns.
Driver_list	Custom list of driver genes to be considered in analysis
NrModules	How many gene co-expression modules should AMARETTO search for? Usually around 100 is acceptable, given the large number of possible driver-passenger gene combinations.
VarPercentage	Minimum percentage by variance for filtering of genes; for example, 75% would indicate that the CreateRegulatorData() function only analyses genes that have a variance above the 75th percentile across all samples.
PvalueThreshold	Threshold used to find relevant driver genes with CNV alterations: maximal p-value.
RsquareThreshold	Threshold used to find relevant driver genes with CNV alterations: minimal R-square value between CNV and gene expression data.
pmax	'pmax' variable for glmnet function from glmnet package; the maximum number of variables aver to be nonzero. Should not be changed by user unless she/he fully understands the AMARETTO algorithm and how its parameters choices affect model output.
NrCores	A numeric variable indicating the number of computer/server cores to use for parallelization. Default is 1, i.e. no parallelization. Please check your computer or server's computing capacities before increasing this number. Parallelization is done via the RParallel package. Mac vs. Windows environments may behave differently when using parallelization.
OneRunStop	OneRunStop
method	Perform union or intersection of the driver genes evaluated from the input data matrices and custom driver gene list provided.
random_seeds	A numeric vector of length 2, containing two seed numbers for randomization : 1st for kmeans and 2nd for glmnet
convergence_cutoff	A numeric value (E.g. 0.01) representing the fraction of the total number of genes, in which, The algorithm is considered reaching convergence and will stop, if Nr of Gene-replacements in an iteration falls below this threshold * total number of genes.

**Value**

result

**Examples**

```
data('ProcessedDataLIHC')
data('Driver_Genes')
AMARETTOinit <- AMARETTO_Initialize(ProcessedData = ProcessedDataLIHC,
                                   NrModules = 2, VarPercentage = 50)

## Not run:
AMARETTOinit <- AMARETTO_Initialize(ProcessedData = ProcessedDataLIHC,
                                   Driver_list = Driver_Genes[['MSigDB']],
                                   NrModules = 2, VarPercentage = 50)

## End(Not run)
```

---

AMARETTO\_Preprocess    *AMARETTO\_Preprocess*

---

**Description**

Wrapper code that analyzes process TCGA GISTIC (CNV) and gene expression (rna-seq or microarray) data via one call

**Usage**

```
AMARETTO_Preprocess(DataSetDirectories = DataSetDirectories,
                    BatchData = BatchData)
```

**Arguments**

```
DataSetDirectories
    DataSetDirectories
BatchData          BatchData
```

**Value**

result

**Examples**

```
## Not run:
TargetDirectory <- "Downloads" # path to data download directory
CancerSite <- 'CHOL'
DataSetDirectories <- AMARETTO_Download(CancerSite,TargetDirectory)
ProcessedData <- AMARETTO_Preprocess(DataSetDirectories,BatchData)

## End(Not run)
```





**Arguments**

AMARETTOinit List output from AMARETTO\_Initialize().  
AMARETTOresults List output from AMARETTO\_Run().  
ProcessedData List of processed input data  
ModuleNr Module number to visualize  
show\_row\_names If TRUE, row names will be shown on the plot.  
SAMPLE\_annotation Matrix or Dataframe with sample annotation  
ID Column used as sample name  
order\_samples Order samples in heatmap by mean or by clustering

**Value**

result

**Examples**

```
data('ProcessedDataLIHC')
AMARETTOinit <- AMARETTO_Initialize(ProcessedData = ProcessedDataLIHC,
                                   NrModules = 2, VarPercentage = 50)

AMARETTOresults <- AMARETTO_Run(AMARETTOinit)

AMARETTO_VisualizeModule(AMARETTOinit = AMARETTOinit, AMARETTOresults = AMARETTOresults,
                        ProcessedData = ProcessedDataLIHC, ModuleNr = 1)
```

---

BatchData

*BatchData*

---

**Description**

A dataset for conducting batch corection in TCGA samples

**Usage**

BatchData

**Format**

A data frame with 23263 observations and 3 variables:

**Source**

AMARETTO

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Driver_Genes	<i>Driver_Genes</i>
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---

**Description**

A list of cancer driver genes described in literature.

**Usage**

Driver\_Genes

**Format**

List

**Source**

AMARETTO

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MsigdbMapping	<i>MsigdbMapping</i>
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**Description**

A dataset containing all MSIGDB pathways and their descriptions. .

**Usage**

MsigdbMapping

**Format**

List

**Source**

AMARETTO

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plot_run_history	<i>Title plot_run_history</i>
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---

**Description**

Title plot\_run\_history

**Usage**

```
plot_run_history(AMARETTOinit, AMARETTOresults)
```

**Arguments**

```
AMARETTOinit  AMARETTO initialize output
AMARETTOresults
               AMARETTO results output
```

**Value**

plot

**Examples**

```
data('ProcessedDataLIHC')
AMARETTOinit <- AMARETTO_Initialize(ProcessedData = ProcessedDataLIHC,
                                   NrModules = 2, VarPercentage = 50)

AMARETTOresults <- AMARETTO_Run(AMARETTOinit)

plot_run_history(AMARETTOinit,AMARETTOresults)
```

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ProcessedDataLIHC	<i>ProcessedDataLIHC</i>
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---

**Description**

A list of dataframes of processed toy example dataset from TCGA-LIHC.

**Usage**

```
ProcessedDataLIHC
```

**Format**

List

**Source**

AMARETTO

---

<i>read_gct</i>	<i>read_gct</i>
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---

**Description**

Function to turn a .gct data files into a matrix format

**Usage**

```
read_gct(file_address)
```

**Arguments**

`file_address` Address of the input gct file.

**Value**

result

**Examples**

```
data_matrix<-read_gct(file_address="")
```

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