

# Package ‘AMARETTO’

April 12, 2022

**Type** Package

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

**Version** 1.10.0

**Date** 2016-06-06

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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

**Encoding** UTF-8

**biocViews**

StatisticalMethod,DifferentialMethylation,GeneRegulation,GeneExpression,MethylationArray,Transcription,Preprocessing

**Suggests** testthat, MASS, knitr

**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

**Roxygen** list(markdown = TRUE)

**RoxygenNote** 6.1.1.9000

**LinkingTo** Rcpp

**VignetteBuilder** knitr

**git\_url** https://git.bioconductor.org/packages/AMARETTO

**git\_branch** RELEASE\_3\_14

**git\_last\_commit** f2da2d8

**git\_last\_commit\_date** 2021-10-26

**Date/Publication** 2022-04-12

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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 method	OneRunStop 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)
```



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AMARETTO_Preprocess	<i>AMARETTO_Preprocess</i>
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---

**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)
```

---

AMARETTO_Run	<i>AMARETTO_Run Function to run AMARETTO, a statistical algorithm to identify cancer drivers by integrating a variety of omics data from cancer and normal tissue.</i>
--------------	--

---

**Description**

AMARETTO\_Run Function to run AMARETTO, a statistical algorithm to identify cancer drivers by integrating a variety of omics data from cancer and normal tissue.

**Usage**

```
AMARETTO_Run(AMARETTOinit)
```

**Arguments**

AMARETTOinit List output from AMARETTO\_Initialize().

**Value**

result

**Examples**

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

---

AMARETTO\_VisualizeModule

*AMARETTO\_VisualizeModule*

---

**Description**

Function to visualize the gene modules

**Usage**

```
AMARETTO_VisualizeModule(AMARETTOinit, AMARETTOresults, ProcessedData,
                          ModuleNr, show_row_names = FALSE, SAMPLE_annotation = NULL,
                          ID = NULL, order_samples = NULL)
```

**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

---

Driver\_Genes

*Driver\_Genes*

---

**Description**

A list of cancer driver genes described in literature.

**Usage**

Driver\_Genes

**Format**

List

**Source**

AMARETTO

---

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

A dataset containing all MSIGDB pathways and their descriptions. .

**Usage**

```
MsigdbMapping
```

**Format**

List

**Source**

AMARETTO

---

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)
```

---

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

---

read_gct	<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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