Package 'AMARETTO'

November 11, 2026

Type Package

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

Version 1.28.0

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,Preprocessin

Suggests testthat, MASS, knitr, BiocStyle

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_23

git_last_commit 4b60a9d

git_last_commit_date 2026-04-28

Repository Bioconductor 3.23

Date/Publication 2026-11-11

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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 expressiosn (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 paralellelization. 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_LarsenBased *AMARETTO_LarsenBased*

Description

AMARETTO_LarsenBased

Usage

```
AMARETTO_LarsenBased(Data, Clusters, RegulatorData, Parameters, NrCores,
  random_seeds, convergence_cutoff)
```

Arguments

Data

Clusters

RegulatorData

Parameters

NrCores

random_seeds

convergence_cutoff

Value

result

AMARETTO_LearnRegulatoryProgramsLarsen *AMARETTO_LearnRegulatoryProgramsLarsen*

Description

AMARETTO_LearnRegulatoryProgramsLarsen

Usage

```
AMARETTO_LearnRegulatoryProgramsLarsen(Data, Clusters, RegulatorData,
  RegulatorSign, Lambda, AutoRegulation, alpha, pmax, random_seeds)
```

Value

result

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)
```

AMARETTO_ReassignGenesToClusters *AMARETTO_ReassignGenesToClusters*

Description

AMARETTO_ReassignGenesToClusters

Usage

```
AMARETTO_ReassignGenesToClusters(Data, RegulatorData, Beta, Clusters,
  AutoRegulation)
```

Value

result

`AMARETTO_Run` *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.*

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)
```

---

aprior *aprior*

Description

Following four find empirical hyper-prior values

Usage

```
aprior(gamma.hat)
```

Value

result

BatchData *BatchData*

Description

A dataset for conducting batch corerction in TCGA samples

Usage

```
BatchData
```

Format

A data frame with 23263 observations and 3 variables:

Source

AMARETTO

Beta.NA *Beta.NA*

Description

Beta.NA

Usage

```
Beta.NA(y, X)
```

Value

result

bprior *bprior*

Description

bprior

Usage

```
bprior(gamma.hat)
```

Value

result

build.design *build.design*

Description

Next two functions make the design matrix (X) from the sample info file

Usage

```
build.design(vec, des = NULL, start = 2)
```

Value

result

cacheResource *cacheResource*

Description

cacheResource

Usage

```
cacheResource(TargetDirectory = TargetDirectory, resource = resource)
```

Value

result

ComBat_NoFiles *ComBat_NoFiles*

Description

ComBat_NoFiles

Usage

```
ComBat_NoFiles(dat, saminfo, type = "txt", write = FALSE,
  covariates = "all", par.prior = TRUE, filter = FALSE, skip = 0,
  prior.plots = FALSE)
```

Value

result

computeGisticURL *computeGisticURL*

Description

computeGisticURL

Usage

```
computeGisticURL(url = NULL, acronym = "CHOL")
```

Value

result

CreateRegulatorData *CreateRegulatorData*

Description

Determine potential regulator genes.

Usage

```
CreateRegulatorData(MA_matrix = MA_matrix, CNV_matrix = NULL,
  MET_matrix = NULL, Driver_list = NULL, PvalueThreshold = 0.001,
  RsquareThreshold = 0.1, method = "union")
```

Value

result

design.mat *design.mat*

Description

design.mat

Usage

```
design.mat(saminfo)
```

Value

result

Driver_Genes *Driver_Genes*

Description

A list of cancer driver genes described in literature.

Usage

```
Driver_Genes
```

Format

List

Source

AMARETTO

filter.absent *filter.absent*

Description

filters data based on presence/absence call

Usage

```
## S3 method for class 'absent'
filter(x, pct)
```

Value

result

FindTranscriptionallyPredictive_CNV *FindTranscriptionallyPredictive_CNV*

Description

Function to identify which genes CNV significantly predict expression of that gene.

Usage

```
FindTranscriptionallyPredictive_CNV(MA_matrix, CNV_matrix,
  PvalueThreshold = 0.001, RsquareThreshold = 0.1)
```

Value

result

geneFiltering *geneFiltering*

Description

Function to filter gene expression matrix

Usage

```
geneFiltering(Type, MAdata, Percentage)
```

Value

result

GeneSetDescription *GeneSetDescription*

Description

GeneSetDescription

Usage

```
GeneSetDescription(filename, MSIGDB)
```

Arguments

filename	The name of the gmt file.
MSIGDB	If True, the gene set description column will be provided from MSIGDB.

Value

result

get_firehoseData *get_firehoseData*

Description

Downloading TCGA dataset via firehose

Usage

```
get_firehoseData(TargetDirectory = "./",
  TCGA_acronym_uppercase = "LUAD", dataType = "stddata",
  dataFileTag = "mRNAseq_Preprocess.Level_3", FFPE = FALSE,
  fileType = "tar.gz",
  gdacURL = "http://gdac.broadinstitute.org/runs/", untarUngzip = TRUE,
  printDisease_abbr = FALSE)
```

Value

result

GmtFromModules *GmtFromModules*

Description

GmtFromModules

Usage

```
GmtFromModules(AMARETTOinit, AMARETTOresults, driverGSEA)
```

Arguments

AMARETTOinit	List output from AMARETTO_Initialize().
AMARETTOresults	List output from AMARETTO_Run().
driverGSEA	if TRUE , module driver genes will also be added to module target genes for GSEA.

Value

result

HyperGTestGeneEnrichment

Hyper Geometric Geneset Enrichement Test

Description

Calculates the p-values for unranked gene set enrichment based on two gmt files as input and the hyper geometric test.

Usage

```
HyperGTestGeneEnrichment(gmtfile, testgmtfile, NrCores,
  ref.numb.genes = 45956)
```

Arguments

gmtfile	The gmt file with reference gene set.
testgmtfile	The gmt file with gene sets to test. In our case, the gmt file of the modules.
NrCores	Number of cores used for parallelization.
ref.numb.genes	The total number of genes teste, standard equal to 45 956 (MSIGDB standard).

Value

result

`int.eprior` *int.eprior*

Description

Monte Carlo integration function to find the nonparametric adjustments

Usage

```
int.eprior(sdat, g.hat, d.hat)
```

Value

result

`it.sol` *it.sol*

Description

Pass in entire data set, the design matrix for the entire data, the batch means, the batch variances, priors (m, t2, a, b), columns of the data matrix for the batch. Uses the EM to find the parametric batch adjustments

Usage

```
it.sol(sdat, g.hat, d.hat, g.bar, t2, a, b, conv = 1e-04)
```

Value

result

`L` *L*

Description

likelihood function

Usage

```
L(x, g.hat, d.hat)
```

Value

result

Lambda_Sequence *Lambda_Sequence*

Description

Lambda_Sequence

Usage

```
Lambda_Sequence(sx, sy)
```

Value

result

list.batch *list.batch*

Description

Makes a list with elements pointing to which array belongs to which batch

Usage

```
list.batch(saminfo)
```

Value

result

MsigdbMapping *MsigdbMapping*

Description

A dataset containing all MSIGDB pathways and their descriptions. .

Usage

```
MsigdbMapping
```

Format

List

Source

AMARETTO

plot_run_history *Title plot_run_history*

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)
```

postmean *postmean*

Description

postmean

Usage

```
postmean(g.hat, g.bar, n, d.star, t2)
```

Value

result

postvar *postvar*

Description

postvar

Usage

```
postvar(sum2, n, a, b)
```

Value

result

Preprocess_MAdata *Preprocess_MAdata*

Description

Preprocess_MAdata

Usage

```
Preprocess_MAdata(CancerSite = CancerSite, MAEO_ge = MAEO_ge,
  BatchData = BatchData)
```

Value

result

printf *printf*

Description

Wrapper function for C-style formatted output.

Usage

```
printf(...)
```

Value

result

ProcessedDataLIHC *ProcessedDataLIHC*

Description

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

Usage

```
ProcessedDataLIHC
```

Format

List

Source

AMARETTO

readGMT *readGMT*

Description

readGMT

Usage

```
readGMT(filename)
```

Arguments

filename

Value

result

read_gct *read_gct*

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="")
```

Save_CancerSite *Save_CancerSite*

Description

Save_CancerSite

Usage

```
Save_CancerSite(CancerSite, TargetDirectory, DataSetDirectories,
  ProcessedData)
```

Value

result

TCGA_BatchCorrection_MolecularData
TCGA_BatchCorrection_MolecularData

Description

TCGA_BatchCorrection_MolecularData

Usage

```
TCGA_BatchCorrection_MolecularData(GEN_Data = GEN_Data,
  BatchData = BatchData, MinInBatch = MinInBatch)
```

Value

result

TCGA_GENERIC_BatchCorrection
TCGA_GENERIC_BatchCorrection

Description

TCGA_GENERIC_BatchCorrection

Usage

```
TCGA_GENERIC_BatchCorrection(GEN_Data = GEN_Data,
  BatchData = BatchData)
```

Value

result

TCGA_GENERIC_CheckBatchEffect
TCGA_GENERIC_CheckBatchEffect

Description

TCGA_GENERIC_CheckBatchEffect

Usage

```
TCGA_GENERIC_CheckBatchEffect(GEN_Data, BatchData)
```

Value

result

TCGA_GENERIC_CleanUpSampleNames
TCGA_GENERIC_CleanUpSampleNames

Description

TCGA_GENERIC_CleanUpSampleNames

Usage

```
TCGA_GENERIC_CleanUpSampleNames(GEN_Data = GEN_Data, IDlength = 12)
```

Value

result

TCGA_GENERIC_GetSampleGroups
TCGA_GENERIC_GetSampleGroups

Description

TCGA_GENERIC_GetSampleGroups

Usage

```
TCGA_GENERIC_GetSampleGroups(SampleNames)
```

Value

result

TCGA_GENERIC_MergeData *TCGA_GENERIC_MergeData*

Description

TCGA_GENERIC_MergeData

Usage

```
TCGA_GENERIC_MergeData(NewIDListUnique, DataMatrix, MergeMethod)
```

Value

result

TCGA_Load_GISTICdata *TCGA_Load_GISTICdata*

Description

TCGA_Load_GISTICdata

Usage

```
TCGA_Load_GISTICdata(GisticDirectory)
```

Value

result

TCGA_Load_MolecularData *TCGA_Load_MolecularData*

Description

TCGA_Load_MolecularData

Usage

```
TCGA_Load_MolecularData(MAEO_ge)
```

Value

result

trim.dat *trim.dat*

Description

Trims the data of extra columns, note your array names cannot be named 'X' or start with 'X.'

Usage

```
trim.dat(dat)
```

Value

result

write_gct *write_gct*

Description

write_gct

Usage

```
write_gct(data_in, file_address)
```

Value

result

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