Package ‘omicwas’

June 2, 2020

Type Package

Title Cell-Type-Specific Association Testing in Bulk Omics Experiments

Version 0.7.0

Description In bulk epigenome/transcriptome experiments, molecular expression
is measured in a tissue, which is a mixture of multiple types of cells.
This package tests association of a disease/phenotype with a molecular marker
for each cell type.
The proportion of cell types in each sample needs to be given as input.
The package is applicable to epigenome-wide association study (EWAS) and
differential gene expression analysis.
Takeuchi and Kato (submitted)
``omicwas: cell-type-specific epigenome-wide and transcriptome association study``.

URL https://github.com/fumi-github/omicwas

BugReports https://github.com/fumi-github/omicwas/issues

Depends R (>= 3.6.0)

biocViews

License GPL-3

Encoding UTF-8

LazyData true

Imports broom, data.table, dplyr, ff, glmnet, magrittr, MASS,
    matrixStats, parallel, PCDimension, rlang, sva, tidyr

RoxygenNote 7.1.0

Suggests testthat, knitr, rmarkdown

VignetteBuilder knitr

NeedsCompilation no

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Repository CRAN

Date/Publication 2020-06-02 09:40:02 UTC
R topics documented:

ctassoc ................................................................. 2
ctcisQTL .............................................................. 5
ctRUV ................................................................. 6
GSE42861small ......................................................... 7
GSE79262small ......................................................... 8
GTExsmall ........................................................... 9
rrs.fit ................................................................. 9

Index

ctassoc ................................. Cell-Type-Specific Association Testing

Description

Cell-Type-Specific Association Testing

Usage

ctassoc(
  X,
  W,
  Y,
  C = NULL,
  test = "full",
  regularize = FALSE,
  num.cores = 1,
  chunk.size = 1000,
  seed = 123
)

Arguments

X Matrix (or vector) of traits; samples x traits.
W Matrix of cell type composition; samples x cell types.
Y Matrix (or vector) of bulk omics measurements; markers x samples.
C Matrix (or vector) of covariates; samples x covariates. X, W, Y, C should be numeric.
test Statistical test to apply; either "full", "marginal", "nls.identity", "nls.log", "nls.logit" or "reducedrankridge".
regularize Whether to apply Tikhonov (ie ridge) regularization to $\beta_{hjk}$. The regularization parameter is chosen automatically according to an unbiased version of (Lawless & Wang, 1976). Effective for nls.* tests.
num.cores Number of CPU cores to use. Full and marginal tests are run in serial, thus num.cores is ignored.
chunk.size  The size of job for a CPU core in one batch. If you have many cores but limited memory, and there is a memory failure, decrease num.cores and/or chunk.size.

seed  Seed for random number generation.

Details

Let the indexes be \( h \) for cell type, \( i \) for sample, \( j \) for marker (CpG site or gene), \( k \) for each trait that has cell-type-specific effect, and \( l \) for each trait that has a uniform effect across cell types. The input data are \( X_{ik}, C_{il}, W_{ih} \) and \( Y_{ji} \), where \( C_{il} \) can be omitted. \( X_{ik} \) and \( C_{il} \) are the values for two types of traits, showing effects that are cell-type-specific or not, respectively. Thus, calling \( X_{ik} \) and \( C_{il} \) as "traits" and "covariates" gives a rough idea, but is not strictly correct. \( W_{ih} \) represents the cell type composition and \( Y_{ji} \) represents the marker level, such as methylation or gene expression. For each tissue sample, the cell type proportion \( W_{ih} \) is the proportion of each cell type in the bulk tissue, which is measured or imputed beforehand. The marker level \( Y_{ji} \) in bulk tissue is measured and provided as input.

The parameters we estimate are the cell-type-specific trait effect \( \beta_{hjk} \), the tissue-uniform trait effect \( \gamma_{jl} \), and the basal marker level \( \alpha_{hj} \) in each cell type.

We first describe the conventional linear regression models. For marker \( j \) in sample \( i \), the maker level specific to cell type \( h \) is

\[
\alpha_{hj} + \sum_k \beta_{hjk} * X_{ik}.
\]

This is a representative value rather than a mean, because we do not model a probability distribution for cell-type-specific expression. The bulk tissue marker level is the average weighted by \( W_{ih} \),

\[
\mu_{ji} = \sum_h W_{ih} [\alpha_{hj} + \sum_k \beta_{hjk} * X_{ik}] + \sum_l \gamma_{jl} C_{il}.
\]

The statistical model is

\[
Y_{ji} = \mu_{ji} + \epsilon_{ji},
\]

\[
\epsilon_{ji} \sim N(0, \sigma_j^2).
\]

The error of the marker level is is normally distributed with variance \( \sigma_j^2 \), independently among samples.

The full model is the linear regression

\[
Y_{ji} = (\sum_h \alpha_{hj} * W_{ih}) + (\sum_{hk} \beta_{hjk} * W_{ih} * X_{ik}) + (\sum_l \gamma_{jl} * C_{il}) + \text{error}.
\]

The marginal model tests the trait association only in one cell type \( h \), under the linear regression,

\[
Y_{ji} = (\sum_{h'} \alpha_{h'j} * W_{ih'}) + (\sum_k \beta_{hjk} * W_{ih} * X_{ik}) + (\sum_l \gamma_{jl} * C_{il}) + \text{error}.
\]

The nonlinear model simultaneously analyze cell type composition in linear scale and differential expression/methylation in log/logit scale. The normalizing function is the natural logarithm \( f = \log \) for gene expression, and \( f = \logit \) for methylation. Conventional linear regression can be formulated by defining \( f \) as the identity function. The three models are named nls.log, nls.logit and
ctassoc. We denote the inverse function of $f$ by $g$; $g = \exp$ for gene expression, and $g = \logistic$ for methylation. The mean normalized marker level of marker $j$ in sample $i$ becomes

$$
\mu_{ji} = f(\sum_h W_{ih} g(\alpha_{hj} + \sum_k \beta_{hjk} \ast X_{ik})) + \sum_l \gamma_{jl} C_{il}.
$$

The statistical model is

$$
f(Y_{ji}) = \mu_{ji} + \epsilon_{ji},$$

$$
\epsilon_{ji} \sim N(0, \sigma^2_j).
$$

The error of the marker level is normally distributed with variance $\sigma^2_j$, independently among samples.

The ridge regression aims to cope with multicollinearity of the interacting terms $W_{ih} \ast X_{ik}$. Ridge regression is fit by minimizing the residual sum of squares (RSS) plus $\lambda \sum h k \beta^2_{hjk}$, where $\lambda > 0$ is the regularization parameter.

**Value**

A list with one element, which is named "coefficients". The element gives the estimate, statistic, p.value in tibble format. In order to transform the estimate for $\alpha_{hj}$ to the original scale, apply `plogis` for `test = nls.logit` and `exp` for `test = nls.log`. The estimate for $\beta_{hjk}$ by `test = nls.log` is the natural logarithm of fold-change, not the log2. If numerical convergence fails, `NA` is returned for that marker.

**References**


**See Also**

ctcisQTL

**Examples**

data(GSE42861small)
X = GSE42861small$X
W = GSE42861small$W
Y = GSE42861small$Y
C = GSE42861small$C
result = ctassoc(X, W, Y, C = C)
result$coefficients
ctcisQTL

Cell-Type-Specific QTL analysis

Description

Cell-Type-Specific QTL analysis

Usage

```r
ctcisQTL(
  X,
  Xpos,
  W,
  Y,
  Ypos,
  C = NULL,
  max.pos.diff = 1e+06,
  outdir = tempdir(),
  outfile = "ctcisQTL.out.txt"
)
```

Arguments

- **X**: Matrix (or vector) of SNP genotypes; SNPs x samples.
- **Xpos**: Vector of the physical position of X
- **W**: Matrix of cell type composition; samples x cell types.
- **Y**: Matrix (or vector) of bulk omics measurements; markers x samples.
- **Ypos**: Vector of the physical position of Y
- **C**: Matrix (or vector) of covariates; samples x covariates. X, Xpos, W, Y, Ypos, C should be numeric.
- **max.pos.diff**: Maximum positional difference to compute cis-QTL. Association analysis is performed between each row of Y and each row of X, only when they are within this limit. Since the limiting is only by position, the function needs to be run separately for each chromosome.
- **outdir**: Output directory.
- **outfile**: Output file.

Details

A function for analyses of QTL, such as eQTL, mQTL, pQTL. The statistical test is almost identical to `ctassoc(test = "nls.identity", regularize = "TRUE")`. Association analysis is performed between each row of Y and each row of X. Usually, the former will be a methylation-expression marker, and the latter will be a SNP. To cope with the large number of combinations, the testing is limited to pairs whose position is within the difference specified by `max.pos.diff`; i.e., limited to cis-QTL. In detail, this function performs linear ridge regression, whereas `ctassoc(test ="
"nls.identity", regularize = "TRUE") actually is nonlinear regression but with \( f = \text{identity} \) as normalizing transformation. In order to speed up computation, first, the parameters \( \alpha_{hk} \) and \( \gamma_{jl} \) are fit by ordinary linear regression assuming \( \beta_{hjk} = 0 \). Next, \( \beta_{hjk} \) are fit and tested by linear ridge regression (see documentation for \text{ctassoc}).

**Value**

The estimate, statistic, p.value are written to the specified file.

**See Also**

\text{ctassoc}

**Examples**

```r
data(GSE79262small)
X = GSE79262small$X
Xpos = GSE79262small$Xpos
W = GSE79262small$W
Y = GSE79262small$Y
Ypos = GSE79262small$Ypos
C = GSE79262small$C
X = X[seq(1, 3601, 100), ] # for brevity
Xpos = Xpos[seq(1, 3601, 100)]
ctcisQTL(X, Xpos, W, Y, Ypos, C = C)
```

---

**ctRU**

Remove Unwanted Variations prior to applying \text{ctassoc}

**Description**

Remove Unwanted Variations prior to applying \text{ctassoc}

**Usage**

\text{ctRU}(X, W, Y, C = \text{NULL}, \text{method} = \text{"PCA"}, nPC = \text{NULL})

**Arguments**

- **X**: Matrix (or vector) of traits; samples x traits.
- **W**: Matrix of proportion of cell types; samples x cell types.
- **Y**: Matrix (or vector) of bulk omics measurements; markers x samples.
- **C**: Matrix (or vector) of covariates; samples x covariates. \( X, W, Y, C \) should be numeric.
- **\text{method}**: "PCA" or "SVA"
- **nPC**: Number of PCs to be regarded as unwanted variation. If \text{NULL}, automatically computed by the Auer-Gervini approach.
Details

First, for each marker, the full linear model of the ctassoc function is fitted, and the residual is computed. For the residuals over all markers, the principal components (PCs) are computed. The top PCs are regarded as the unwanted variations, and subtracted from \( Y \).

Value

\( Y \) adjusted for the unwanted variations.

See Also

cassoc

---

**GSE42861small**  
**Small Subset of GSE42861 Dataset From GEO**

Description

The dataset includes 336 rheumatoid arthritis cases and 322 controls. A subset of 500 CpG sites were randomly selected from the original EWAS dataset.

Usage

data(GSE42861small)

Format

An object of class `list` of length 4.

Source

GEO

See Also

cassoc

Examples

data(GSE42861small)
X = GSE42861small$X
W = GSE42861small$W
Y = GSE42861small$Y
Y = Y[seq(1, 20), ] # for brevity
C = GSE42861small$C
result = ctassoc(X, W, Y, C = C)
result$coefficients
Small Subset of GSE79262 Dataset From GEO

Description

The dataset includes 53 samples. A subset of 737 CpG sites and 3624 SNPs within Chr1:100,000,000-110,000,000 were selected from the original EWAS dataset. DNA methylation was measured in T cells. The estimated proportion of CD4T, CD8T, NK cells are saved in W.

Usage

data(GSE79262small)

Format

An object of class list of length 6.

Source

GEO

See Also

cctisQTL

Examples

data(GSE79262small)
X = GSE79262small$X
Xpos = GSE79262small$Xpos
W = GSE79262small$W
Y = GSE79262small$Y
Ypos = GSE79262small$Ypos
C = GSE79262small$C
X = X[seq(1, 3001, 100), ] # for brevity
Xpos = Xpos[seq(1, 3001, 100)]
Y = Y[seq(1, 501, 100), ]
Ypos = Ypos[seq(1, 501, 100)]
cctisQTL(X, Xpos, W, Y, Ypos, C = C)
GTExsmall

Small Subset of GTEx Dataset

Description

The dataset includes gene expression measured in whole blood for 389 samples. A subset of 500 genes were randomly selected from the original dataset.

Usage

data(GTExsmall)

Format

An object of class list of length 4.

Source

GTEx

See Also

cassoc

Examples

data(GTExsmall)
X = GTExsmall$X
W = GTExsmall$W
Y = GTExsmall$Y + 1
Y = Y[seq(1, 20), ] # for brevity
C = GTExsmall$C
result = ctassoc(X, W, Y, C = C)
result$coefficients

rrs.fit

Fitting reduced-rank ridge regression with given rank and shrinkage penalty

Description

Fitting reduced-rank ridge regression with given rank and shrinkage penalty This is a modification of rrs.fit in rrpack version 0.1-6. In order to handle extremely large q = ncol(Y), generation of a q by q matrix is avoided.
Usage

```r
rrs.fit(Y, X, nrank = min(ncol(Y), ncol(X)), lambda = 1, coefSVD = FALSE)
```

Arguments

- **Y**: a matrix of response (n by q)
- **X**: a matrix of covariate (n by p)
- **nrank**: an integer specifying the desired rank
- **lambda**: tuning parameter for the ridge penalty
- **coefSVD**: logical indicating the need for SVD for the coefficient matrix in the output

Value

S3 `rrr` object, a list consisting of

- **coef**: coefficient of rrs
- **coef.ls**: coefficient of least square
- **fitted**: fitted value of rrs
- **fitted.ls**: fitted value of least square
- **A**: right singular matrix
- **Ad**: singular value vector
- **nrank**: rank of the fitted rrr

References


Examples

```r
Y <- matrix(rnorm(400), 100, 4)
X <- matrix(rnorm(800), 100, 8)
rfit <- rrs.fit(Y, X)
```
Index

*Topic datasets
  GSE42861small, 7
  GSE79262small, 8
  GTExsmall, 9
ctassoc, 2, 6
ctcisQTL, 5
cTRUV, 6
  GSE42861small, 7
  GSE79262small, 8
  GTExsmall, 9
rrs.fit, 9