Package TCA

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Type Package

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Title Tensor Composition Analysis

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Description Tensor Composition Analysis (TCA) allows the deconvolution of two-dimensional data (features by observations) coming from a mixture of sources into a three-dimensional matrix of signals (features by observations by sources). TCA further allows to test the features in the data for different statistical relations with an outcome of interest while modeling source-specific effects (TCA regression); particularly, it allows to look for statistical relations between source-specific signals and an outcome. For example, TCA can deconvolve bulk tissue-level DNA methylation data (methylation sites by individuals) into a tensor of cell-type-specific methylation levels for each individual (methylation sites by individuals by cell types) and it allows to detect cell-type-specific relations (associations) with an outcome of interest.
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R topics documented:
refactor
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refactor	Sparse principal component analysis using ReFACTor	

Description

Performs unsupervised feature selection followed by principal component analysis (PCA) under a row-sparse model using the ReFACTor algorithm. For example, in the context of bulk tissue-level DNA methylation data coming from a mixture of cell types (i.e. the input is methylation sites by individuals), refactor allows to capture the variation in cell-type composition, which was shown to be a dominant sparse signal in methylation data.

Usage

```
refactor(X, k, sparsity = 500, C = NULL, sd_threshold = NULL,
  num_comp = NULL, rand_svd = FALSE, log_file = "TCA.log",
  debug = FALSE)
```

Arguments

X	An m by n matrix of measurements of m features for n observations. Each column in X is assumed to be a mixture of k different sources. Note that X must include row names and column names and that NA values are currently not supported.
k	A numeric value indicating the dimension of the signal in the data (i.e. the number of sources).
sparsity	A numeric value indicating the sparsity of the signal in the data (the number of signal rows).
С	An n by p design matrix of covariates to be accounted for. Note that C must include row names and column names and that NA values are currently not supported.
sd_threshold	A numeric value indicating a standard deviation threshold to be used for excluding low-variance features in X (i.e. features with standard deviation lower than sd_threshold will be excluded).
num_comp	A numeric value indicating the number of ReFACTor components to return.
rand_svd	A logical value indicating whether to use random svd for estimating the low-rank structure of the data in the first step of the algorithm; random svd can result in a substantial speedup for large data.
log_file	A path to an output log file. Note that if the file log_file already exists then logs will be appended to the end of the file. Set log_file to NULL to prevent output from being saved into a file.
debug	A logical value indicating whether to set the logger to a more detailed debug level; please set debug to TRUE before reporting issues.

Details

ReFACTor is a two-step algorithm for sparse principal component analysis (PCA) under a row-sparse model. The algorithm performs an unsupervised feature selection by ranking the features based on their correlation with their values under a low-rank representation of the data, followed by a calculation of principal components using the top ranking features (ReFACTor components).

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Note that ReFACTor is tuned towards capturing sparse signals of the dominant sources of variation in the data. Therefore, in the presence of other potentially dominant factors in the data (i.e. beyond the variation of interest), these factors should be accounted for by including them as covariates (see argument C).

Value

A list with the estimated components of the ReFACTor model.

scores An n by num_comp matrix of the ReFACTor components (the projection scores).

coeffs A sparsity by num_comp matrix of the coefficients of the ReFACTor compo-

nents (the projection loadings).

ranked_list A vector with the features in the data, ranked by their scores in the feature se-

lection step of the algorithm; the top scoring features (set according to the argument sparsity) are used for calculating the ReFACTor components. Note that features that were excluded according to sd_threshold will not appear in this

ranked_list.

Note

For very large input matrices it is advised to use random svd for speeding up the feature selection step (see argument rand_svd).

References

Rahmani E, Zaitlen N, Baran Y, Eng C, Hu D, Galanter J, Oh S, Burchard EG, Eskin E, Zou J, Halperin E. Sparse PCA corrects for cell type heterogeneity in epigenome-wide association studies. Nature Methods 2016.

Rahmani E, Zaitlen N, Baran Y, Eng C, Hu D, Galanter J, Oh S, Burchard EG, Eskin E, Zou J, Halperin E. Correcting for cell-type heterogeneity in DNA methylation: a comprehensive evaluation. Nature Methods 2017.

Examples

```
data <- test_data(100, 200, 3, 0, 0, 0.01)
ref <- refactor(data$X, k = 3, sparsity = 50)</pre>
```

tca

Fitting the TCA model

Description

Fits the TCA model for an input matrix of observations coming from a mixture of k sources, under the assumption that each observation is a mixture of unique source-specific values (in each feature in the data). For example, in the context of bulk tissue-level DNA methylation data coming from a mixture of cell types (i.e. the input is methylation sites by individuals), tca allows to model the methylation of each individual as a mixture of cell-type-specific methylation levels that are unique to the individual.

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Usage

```
tca(X, W, C1 = NULL, C2 = NULL, refit_W = TRUE,
 refit_features = NULL, refit_t = 500, parallel = FALSE,
 num_cores = NULL, max_iters = 10, log_file = "TCA.log",
 debug = FALSE)
```

W (see refit_W).

Arguments

X	An m by n matrix of measurements of m features for n observations. Each column in X is assumed to be a mixture of k different sources. Note that X must include row names and column names and that NA values are currently not supported.
W	An n by k matrix of weights - the weights of k sources for each of the n mixtures (observations). All the weights must be positive and each row, corresponding to the weights of a single observation, must sum up to 1. Note that W must include row names and column names and that NA values are currently not supported. In case where only initial estimates of W are available, tca can be set to re-estimate

An n by p1 design matrix of covariates that may affect the hidden source-specific values (possibly a different effect on each source). Note that C1 must include row names and column names and should not include an intercept term. NA values are currently not supported.

An n by p2 design matrix of covariates that may affect the mixture (i.e. rather than directly the sources of the mixture; for example, variables that capture biases in the collection of the measurements). Note that C2 must include row names and column names and should not include an intercept term. NA values are currently not supported.

A logical value indicating whether to re-estimate the input W under the TCA model. refit_W may be set to TRUE when only an estimate of W is available (rather than the true W).

refit_features A vector with the names of the features in X to consider when re-estimating W (i.e. when refit_W == TRUE). This is useful in cases where just a subset of the features are expected to be informative for estimating W. If refit_features == NULL then the ReFACTor algorithm is used for performing feature selection (see also refit_t).

> The number of features to select using the ReFACTor algorithm when re-estimating W (active only if refit_W == TRUE and refit_features == NULL). Note that refit_t must be lower or equal to m, the number of features in X.

A logical value indicating whether to use parallel computing (possible when using a multi-core machine).

A numeric value indicating the number of cores to use (active only if parallel == TRUE). If num_cores == NULL then all available cores except for one will be used.

A numeric value indicating the maximal number of iterations to use in the optimization of the TCA model (max_iters iterations will be used as long as the optimization does not converge in earlier iterations).

A path to an output log file. Note that if the file log_file already exists then logs will be appended to the end of the file. Set log_file to NULL to prevent output from being saved into a file.

A logical value indicating whether to set the logger to a more detailed debug level; please set debug to TRUE before reporting issues.

C1

C2

refit_W

parallel

refit_t

max_iters

num cores

log_file

debug

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Details

The TCA model assumes that the hidden source-specific values are random variables. Formally, denote by Z_{hj}^i the source-specific value of observation i in feature j source h, the TCA model assumes:

$$Z_{hj}^i \sim N(\mu_{hj}, \sigma_{hj}^2)$$

where μ_{hj} , σ_{hj} represent the mean and standard deviation that are specific to feature j source h. The model further assumes that the observed value of observation i in feature j is a mixture of k different sources:

$$X_{ji} = \sum_{h=1}^{k} W_{ih} Z_{hj}^{i} + \epsilon_{ji}$$

where W_{ih} is the non-negative proportion of source h in the mixture of observation i such that $\sum_{h=1}^{k} W_{ih} = 1$, and $\epsilon_{ji} \sim N(0, \tau^2)$ is an i.i.d. component of variation that models measurement noise. Note that the mixture proportions in W are, in general, unique for each individual, therefore each entry in the data matrix X is coming from a unique distribution (i.e. a different mean and a different variance).

In cases where the true W is unknown, tca can be provided with initial estimates of W and then re-estimate W as part of the optimization procedure (see argument refit_W). These initial estimates should not be random but rather capture the information in W to some extent. When the argument refit_W is used, it is typically the case that only a subset of the features should be used for reestimating W. Therefore, when re-estimating W, tca performs feature selection using the ReFACTor algorithm; alternatively, it can also be provided with a user-specified list of features to be used in the re-estimation (see argument refit_features).

Factors that systematically affect the source-specific values Z_{hj}^i can be further considered (see argument C1). In that case, we assume:

$$Z_{hj}^{i} \sim N(\mu_{hj} + c_{i}^{(1)} \gamma_{j}^{h}, \sigma_{hj}^{2})$$

where $c_i^{(1)}$ is a row vector from C1, corresponding to the values of the p_1 factors for observation i, and γ_j^h is a vector of p_1 corresponding effect sizes.

Factors that systematically affect the mixture values X_{ji} , such as variables that capture biases in the collection of the measurements, can also be considered (see argument C2). In that case, we assume:

$$X_{ji} \sim \sum_{h=1}^{k} W_{ih} Z_{hj}^{i} + c_{i}^{(2)} \delta_{j} + \epsilon_{ij}$$

where $c_i^{(2)}$ is a row vector from C2, corresponding to the values of the p_2 factors for observation i, and δ_i is a vector of p_2 corresponding effect sizes.

Value

A list with the estimated parameters of the model. This list can be then used as the input to other functions such as tcareg.

W An n by k matrix of weights. If refit_W == TRUE then this is the re-estimated

W; otherwise this is the input W

mus_hat An m by k matrix of estimates for the mean of each source in each feature.

sigmas_hat An m by k matrix of estimates for the standard deviation of each source in each

feature

tau_hat An estimate of the standard deviation of the i.i.d. component of variation in X.

gammas_hat An m by k*p1 matrix of the estimated effects of the p1 factors in C1 on each of the m features in X, where the first p1 columns are the source-specific effects of the p1 factors on the first source, the following p1 columns are the source-specific

effects on the second source and so on.

deltas_hat An m by p2 matrix of the estimated effects of the p2 factors in C2 on the mixture

values of each of the m features in X.

Note

The function tca may require a long running time when the input matrix X is very large; to alleviate this, it is strongly advised to use the parallel argument, given that a multi-core machine is available.

References

Rahmani E, Schweiger R, Rhead B, Criswell LA, Barcellos LF, Eskin E, Rosset S, Sankararaman S, Halperin E. Cell-type-specific resolution epigenetics without the need for cell sorting or single-cell biology. Nature Communications 2018.

Rahmani E, Zaitlen N, Baran Y, Eng C, Hu D, Galanter J, Oh S, Burchard EG, Eskin E, Zou J, Halperin E. Sparse PCA corrects for cell type heterogeneity in epigenome-wide association studies. Nature Methods 2016.

Examples

```
data <- test_data(100, 20, 3, 1, 1, 0.01)
tca.mdl <- tca(data$X, data$W, data$C1, data$C2, refit_W = FALSE)</pre>
```

tcareg

Fitting a TCA regression model

Description

TCA regression allows to test for several types of statistical relations between source-specific values and an outcome of interest. For example, in the context of bulk tissue-level DNA methylation data coming from a mixture of cell types (i.e. the input is methylation sites by individuals), tcareg allows to test for cell-type-specific effects of methylation on an outcome of interest.

Usage

```
tcareg(X, tca.mdl, y, C3 = NULL, test = "marginal",
  null_model = NULL, alternative_model = NULL, save_results = TRUE,
  output = "TCA", sort_results = TRUE, parallel = FALSE,
  num_cores = NULL, log_file = "TCA.log", features_metadata = NULL,
  debug = FALSE)
```

Arguments

Χ

An m by n matrix of measurements of m features for n observations. Each column in X is assumed to be a mixture of k different sources. Note that X must include row names and column names and that NA values are currently not supported.

tca.mdl

The value returned by applying the function tca to X.

У

An n by 1 matrix of an outcome of interest for each of the n observations in X. Note that y must include row names and column names and that NA values are currently not supported.

C3

An n by p3 design matrix of covariates that may affect y. Note that C3 must include row names and column names and should not include an intercept term. NA values are currently not supported.

test

A character vector with the type of test to perform on each of the features in X; one of the following options: 'marginal', 'marginal_conditional',

'joint', 'single_effect', or 'custom'. Setting 'marginal' or 'marginal_conditional' corresponds to testing each feature in X for a statistical relation between y and

 $each \ of \ the \ k \ sources \ separately; for \ any \ particular \ source \ under \ test, \ the \ marginal_conditional$

option further accounts for possible effects of the rest of the k-1 sources ('marginal' will therefore tend to be more powerful in discovering truly related features, but at the same time more prone to falsely tagging the correct related sources if sources are highly correlated). Setting 'joint' or 'single_effect' corresponds to testing each feature for an overall statistical relation with y, while modeling source-specific effects; the latter option further assumes that the source-specific effects are the same within each feature ('single_effect' means only one degree of freedom and will therefore be more powerful when the assumption of a single effect within a feature holds). Finally, 'custom' corresponds to testing each feature in X for a statistical relation with y under a user-specified model (alternative model) with respect to a null model (null model); for example, for

null_model

A vector with a subset of the names of the sources in tca.mdl\$W to be used as a null model (active only if test == 'custom'). Note that the null model must be nested within the alternative model.

testing for relation of the combined (potentially different) effects of features 1 and 2 while accounting for the (potentially different) effects of 3 and 4, set the null model to be sources 3, 4 and the alternative model to be sources 1, 2, 3, 4.

alternative_model

A vector with a subset (or all) of the names of the sources in tca.mdl\$W to be used as an alternative model (active only if test == 'custom').

save_results

A logical value indicating whether to save the returned results in a file. If TRUE and test == 'marginal' or test == 'marginal_conditional' then k files will be saved (one for the results of each source).

output

Prefix for output files (active only if save_results == TRUE).

sort_results

A logical value indicating whether to sort the results by their p-value (i.e. features with lower p-value will appear first in the results).

parallel

A logical value indicating whether to use parallel computing (possible when using a multi-core machine).

num_cores

A numeric value indicating the number of cores to use (active only if parallel == TRUE). If num_cores == NULL then all available cores except for one will be used.

log_file

A path to an output log file. Note that if the file log_file already exists then logs will be appended to the end of the file. Set log_file to NULL to prevent output from being saved into a file.

features_metadata

A path to a csv file containing metadata about the features in X that will be added to the output files (active only if save_results == TRUE). Each row in the metadata file should correspond to one feature (with the row name being the feature identifier, as it appears in the rows of X) and each column should correspond to one metadata descriptor (with an appropriate column name). Features that do not exist in X will be ignored and features in X with missing metadata information will show missing values.

debug

A logical value indicating whether to set the logger to a more detailed debug level; please set debug to TRUE before reporting issues.

Details

TCA models Z_{hj}^i as the source-specific value of observation i in feature j coming from source h (see tca for more details). A TCA regression model tests an outcome Y for a linear statistical relation with the source-specific values of a feature j by assuming:

$$Y_i = \sum_{h=1}^k \beta_{hj} Z_{hj}^i + e_i$$

where $e_i \sim N(0,\phi^2)$. In practice, tcareg fits this model using the conditional distribution Y|X, which, effectively, integrates over the latent Z^i_{hj} parameters. Statistical significance is then calculated using a likelihood ratio test (LRT). Note that the null and alternative models will be set automatically, except when test == 'custom', in which case they will be set according to the user-specified null and alternative hypotheses.

Under the TCA regression model, several statistical tests can be performed by setting the argument test according to one of the following options.

- 1. If test == 'marginal', tcareg will perform the following for each source l. For each feature j, β_{lj} will be estimated and tested for a non-zero effect, while assuming $\beta_{hj}=0$ for all other sources $h \neq l$.
- 2. If test == 'marginal_conditional', tcareg will perform the following for each source l. For each feature j, β_{lj} will be estimated and tested for a non-zero effect, while also estimating the effect sizes β_{hj} for all other sources $h \neq l$.
- 3. If test == 'joint', tcareg will estimate for each feature j the effect sizes of all k sources $\beta_{1j}, \ldots, \beta_{kj}$ and then test the set of k estimates of each feature j for a joint effect.
- 4. If test == 'single_effect', tcareg will estimate for each feature j the effect sizes of all k sources $\beta_{1j}, \ldots, \beta_{kj}$, under the assumption that $\beta_{1j} = \ldots = \beta_{kj}$, and then test the set of k estimates of each feature j for a joint effect.
- 5. If test == 'custom', tcareg will estimate for each feature *j* the effect sizes of a predefined set of sources (defined by a user-specified alternative model) and then test their estimates for a joint effect, while accounting for a nested predefined set of sources (defined by a user-specified null model).

Value

A list with the results of applying the TCA regression model to each of the features in the data. If test == 'marginal' or test == 'marginal_conditional' then a list of k such lists of results are returned, one for the results of each source.

An estimate of the standard deviation of the i.i.d. component of variation in the TCA regression model.

beta	A matrix of effect size estimates for the source-specific effects, such that each row corresponds to the estimated effect sizes of one feature. The number of columns corresponds to the number of estimated effects (e.g., if test is set to marginal then beta will include a single column, if test is set to joint then beta will include k columns and so on).
intercept	An m by 1 matrix of estimates for the intercept of each feature.
alpha	An m by p3 matrix of effect size estimates for the p3 covariates in C3, such that each row corresponds to the estimated effect sizes of one feature.
null_ll	An m by 1 matrix of the log-likelihood of the model under the null hypothesis.
alternative_ll	An $\mathfrak m$ by 1 matrix of the log-likelihood of the model under the alternative hypothesis.
stats	An m by 1 matrix of the LRT statistic for each feature in the data.
df	The degrees of freedom for deriving p-values using LRT.
pvals	An m by 1 matrix of the p-value for each feature in the data.
qvals	An m by 1 matrix of the q-value (FDR-adjusted p-values) for each feature in the data.

Note

The function tcareg may require a long running time when the input matrix X is very large; to alleviate this, it is strongly advised to use the parallel argument, given that a multi-core machine is available.

References

Rahmani E, Schweiger R, Rhead B, Criswell LA, Barcellos LF, Eskin E, Rosset S, Sankararaman S, Halperin E. Cell-type-specific resolution epigenetics without the need for cell sorting or single-cell biology. Nature Communications 2018.

Examples

```
n <- 50
m <- 10
k <- 3
p1 <- 1
p2 <- 1
data <- test_data(n, m, k, p1, p2, 0.01)
tca.mdl <- tca(data$X, data$W, data$C1, data$C2, refit_W = FALSE)
y <- matrix(rexp(n, rate=.1), ncol=1)
# joint test:
res1 <- tcareg(data$X, tca.mdl, y, test = "joint", save_results = FALSE)
# custom test, testing for a joint effect of sources 1,2 while accounting for source 3
res2 <- tcareg(data$X, tca.mdl, y, test = "custom", null_model = c("3"),
alternative_model = c("1","2","3"), save_results = FALSE)</pre>
```

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tcasub	Subsetting features from a TCA model	

Description

Extracts from a fitted TCA model (i.e. a value returned by the function tca) a subset of the features.

Usage

```
tcasub(tca.mdl, features, log_file = "TCA.log", debug = FALSE)
```

Arguments

tca.mdl	The value returned by applying the function tca to some data matrixX.
features	A vector with the identifiers of the features to extract (as they appear in the rows of X).
log_file	A path to an output log file. Note that if the file log_file already exists then logs will be appended to the end of the file. Set log_file to NULL to prevent output from being saved into a file.
debug	A logical value indicating whether to set the logger to a more detailed debug level; please set debug to TRUE before reporting issues.

Details

This function allows to extract a subset of the features from a fitted TCA model (i.e. from a value returned by the function tca). This allows, for example, to extract and then perform post-hoc tests on only a small set of candidate features (e.g., using the function tcareg), without the need to run tca again for fitting the model to the candidate features.

Value

A list with the estimated parameters of the model for the given set of features.

W	Equals to tca.mdl\$W
mus_hat	A q by k matrix which is a subset of the matrix tca.mdl\$mus_hat, where q is the number of features in the argument features.
sigmas_hat	A q by k matrix which is a subset of the matrix tca.mdl\$sigmas_hat, where q is the number of features in the argument features.
tau_hat	Equals to tca.mdl\$tau_hat
gammas_hat	A q by $k*p1$ matrix which is a subset of the matrix tca.mdl\$gammas_hat, where q is the number of features in the argument features.
deltas_hat	A q by p2 matrix which is a subset of the matrix tca.mdl\$deltas_hat, where q is the number of features in the argument features.

Examples

```
data <- test_data(50, 20, 3, 0, 0, 0.01)
tca.mdl <- tca(data$X, data$W, refit_W = FALSE)
tca.mdl.subset <- tcasub(tca.mdl, rownames(data$X)[1:10])</pre>
```

tensor 11

tensor	Extracting hidden 3D signals from 2D input
--------	--

Description

Estimates 3-dimensional signals (features by observations by sources) from input of mixtures (features by observations), under the assumption of the TCA model that each observation is a mixture of unique source-specific values (in each feature in the data). For example, in the context of bulk tissue-level DNA methylation data coming from a mixture of cell types (i.e. the input is methylation sites by individuals), tensor allows to estimate a tensor of cell-type-specific levels for each individual in each methylation site (i.e. a tensor of methylation sites by individuals by cell types).

Usage

```
tensor(X, tca.mdl, parallel = FALSE, num_cores = NULL,
  log_file = "TCA.log", debug = FALSE)
```

Arguments

X	An m by n matrix of measurements of m features for n observations. Each column in X is assumed to be a mixture of k different sources. Note that X must include row names and column names and that NA values are currently not supported.
tca.mdl	The value returned by applying the function tca to X.
parallel	A logical value indicating whether to use parallel computing (possible when using a multi-core machine).
num_cores	A numeric value indicating the number of cores to use (active only if parallel == TRUE). If num_cores == NULL then all available cores except for one will be used.
log_file	A path to an output log file. Note that if the file log_file already exists then logs will be appended to the end of the file. Set log_file to NULL to prevent output from being saved into a file.
debug	A logical value indicating whether to set the logger to a more detailed debug level; please set debug to TRUE before reporting issues.

Details

See tca for notations and details about the TCA model. Given estimates of the parameters of the model (given by tca), tensor uses the conditional distribution $Z_{hj}^i|X_{ji}$ for estimating the k source-specific levels of each observation i in each feature j.

Value

A list with the estimated source-specific values. The first element in the list is an m by n matrix (features by observations) corresponding to the estimated values coming from the first source, the second element in the list is another m by n matrix (features by observations) corresponding to the estimated values coming from the second source and so on.

References

Rahmani E, Schweiger R, Rhead B, Criswell LA, Barcellos LF, Eskin E, Rosset S, Sankararaman S, Halperin E. Cell-type-specific resolution epigenetics without the need for cell sorting or single-cell biology. Nature Communications 2018.

12 test_data

Examples

```
data <- test_data(50, 20, 3, 2, 2, 0.01)
tca.mdl <- tca(data$X, data$W, data$C1, data$C2, refit_W = FALSE)
Z_hat <- tensor(data$X, tca.mdl)</pre>
```

test_data

Generate test data

Description

Generates simple test data following the TCA model.

Usage

```
test_data(n, m, k, p1, p2, tau, log_file = "TCA.log")
```

Arguments

The number of observations to simulate.
The number of features to simulate.
The number of sources to simulate.
The number of covariates that affect the source-specific values to simulate.
The number of covariates that affect the mixture values to simulate.
The variance of the i.i.d. component of variation to add on top of the simulated mixture values.
A path to an output log file. Note that if the file log_file already exists then logs will be appended to the end of the file. Set log_file to NULL to prevent output from being saved into a file.

Details

See tca for details about the TCA model.

Value

A list with the simulated data and parameters.

X	An m by n matrix of simulated data with m features for n observations.
Z	A list with the simulated source-specific values, where the first element in the list is an m by n matrix (features by observations) corresponding to the values coming from the first source, the second element in the list is another m by n matrix (features by observations) corresponding to the values coming from the second source and so on.
W	An n by k matrix of simulated weights - the weights of the k sources for each of the n mixtures (observations).
mus	An m by k matrix of the mean of each of the m features for each of the k sources.
sigmas	An m by k matrix of the standard variation of each of the m features for each of the k sources.

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C1 An n by p1 design matrix of simulated covariates that affect the hidden source-

specific values.

C2 An n by p2 design matrix of simulated covariates that affect the mixture.

gammas An m by k*p1 matrix of the effects of the p1 factors in C1 on each of the m

features in X, where the first p1 columns are the source-specific effects of the p1 factors on the first source, the following p1 columns are the source-specific

effects on the second source and so on.

deltas An m by p2 matrix of the effects of the p2 factors in C2 on the mixture values of

each of the m features in X.

Examples

data <- test_data(100, 50, 3, 2, 2, 0.01)

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