

Package ‘cpam’

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Title Changepoint Additive Models for Time Series Omics Data

Version 0.1.3

Description Provides a comprehensive framework for time series omics analysis, integrating changepoint detection, smooth and shape-constrained trends, and uncertainty quantification. It supports gene- and transcript-level inferences, p-value aggregation for improved power, and both case-only and case-control designs. It includes an interactive 'shiny' interface. The methods are described in Yates et al. (2024) <[doi:10.1101/2024.12.22.630003](https://doi.org/10.1101/2024.12.22.630003)>.

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<https://github.com/l-a-yates/cpam>

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compute_p_values	<i>Compute p-values for each target ID</i>
------------------	--

Description

Compute p-values for each target ID

Usage

```
compute_p_values(  
  cpo,  
  subset = NULL,  
  p_adj_method = "BH",  
  gam_method = "REML",  
  gam_optimizer = "efs",  
  silent = TRUE  
)
```

Arguments

cpo	a cpam object
subset	a character vector of target_id names
p_adj_method	method for p-value adjustment
gam_method	fitting method for mgcv::gam (default is "REML")
gam_optimizer	optimization method for mgcv::gam (default is "efs")
silent	logical; silences warnings from model fitting (default is TRUE)

Details

This function computes p-values for each `target_id` in the supplied `cpam` object. The p-values are computed from a negative binomial GAM model with a thin-plate spline basis function(s) for time using the `mgcv` package.

The p-values are stored in the new slot `p_table` in the `cpam` object. If `aggregate_to_gene` is set to `TRUE` (default), the target p-values are aggregated to the gene level using the `lancaster` method. The columns `p_val_target` and `p_val_gene` store the raw p-values for target- and gene-level, respectively. The function also computes adjusted p-values using the `p_adj_method`. The default method is "BH" (Benjamini-Hochberg), but any methods supported by the function `p.adjust` can be used. The adjusted p-values are stored in the columns `q_val_target` and `q_val_gene`.

Value

an updated `cpam` object with raw, adjusted, and possibly aggregated p-values stored in the new slot "p_table"

References

Wood, S.N. (2013a) On p-values for smooth components of an extended generalized additive model. *Biometrika* 100:221-228 doi:10.1093/biomet/ass048

Yi L, Pachter L (2018). aggregation: p-Value Aggregation Methods. R package version 1.0.1, <https://CRAN.R-project.org/package=aggregation>.

Examples

```
library(cpam)

# load gene-only example cpam object
load(system.file("extdata", "cpo_example.rda", package = "cpam"))

# run on a small subset of the example data
cpo <- compute_p_values(cpo_example, subset = paste0("g00", 1:9))
cpo$p_table
```

cpam-class

The cpam class

Description

The `cpam` class stores data and analysis results for a time series omics experiment. This object is generated by the `prepare_cpam` function and contains all necessary data and parameters for downstream analysis.

Details

A cpam object is a list with the following components:

exp_design A data frame containing the experimental design information, with columns for 'sample', 'time', and potentially other variables.

count_matrix_raw The original count matrix before filtering.

count_matrix_filtered The count matrix after filtering low-count genes/transcripts.

target_to_keep A vector of transcript/gene IDs that passed the filtering criteria.

data_long A long-format data frame containing all relevant information for each target and sample.

t2g A transcript-to-gene mapping data frame if provided.

regularize Logical; whether empirical Bayes regularization of dispersions was used.

overdispersion.prior Median overdispersion.

model_type String; the type of design used, either "case-only" or "case-control".

condition_var String; the column name in exp_design for the condition variable (for case-control models).

case_value The value of condition_var that indicates the "case" in case-control models.

bootstrap Logical; whether bootstrap samples (inferential replicates) were used.

nboot The number of bootstrap samples used, if applicable.

filter A list containing the filtering function and its arguments used.

gene_level Logical; whether the analysis was performed at the gene level.

aggregate_to_gene Logical; whether p-values should be aggregated from transcript to gene level.

times An ordered vector of unique time points in the experimental design.

num_cores The number of cores used for parallel computation.

fixed_effects The formula for fixed effects in the model.

intercept_cc String; the intercept type for case-control models.

bss A vector of basis function types used for modelling.

Methods

Objects of class cpam have print and summary methods available.

See Also

[prepare_cpam](#) for creating a cpam object.

Examples

```
# load gene-only example data
load(system.file("extdata", "exp_design_example.rda", package = "cpam"))
load(system.file("extdata", "count_matrix_example.rda", package = "cpam"))

# Create a cpam object with the example data
cpo <- prepare_cpam(exp_design = exp_design_example,
```

```

count_matrix = count_matrix_example,
gene_level = TRUE)

# Print the object structure
cpo

# Get a summary of the cpam object
summary(cpo)

```

estimate_changepoint *Use model selection to estimate changepoints*

Description

Use model selection to estimate changepoints

Usage

```

estimate_changepoint(
  cpo,
  cps = NULL,
  degs_only = TRUE,
  deg_threshold = 0.05,
  subset = NULL,
  sp = NULL,
  bss = "tp",
  family = c("nb", "gaussian"),
  score = "aic",
  compute_mvn = TRUE
)

```

Arguments

cpo	a cpam object
cps	vector of candidate changepoints. Defaults to the set of observed timepoints
degs_only	logical; should changepoints only be estimated for differentially expressed genes
deg_threshold	logical; the threshold value for DEGs (ignored if degs_only = F)
subset	character vector; names of targets or genes (if cpo\$gene_level = T) for which changepoints will be estimated
sp	numerical >= 0; supply a fixed smoothing parameter. This can decrease the fitting time but it is not recommended as changepoints estimation is sensitive to smoothness.
bss	character vector; names of candidate spline bases (i.e., candidate shape types). Default is thin plate ("tp") splines.

family	character; negative binomial ("nb", default) or Gaussian ("gaussian", not currently supported)
score	character; model selection score, either Generalised Cross Validation ("gcv") or Akaike Information Criterion ("aic")
compute_mvn	Use simulation to compute p-value under multivariate normal model of the model scores

Details

This function estimates changepoints for each target_id. The assumed trajectory type for this modelling stage is initially constant followed by a changepoint into thin-plate smoothing spline.

By default, candidate time points are limited to the discrete observed values in the series, since, despite the use of smoothing constraints, there is generally insufficient information to infer the timing of changepoints beyond the temporal resolution of the data. In any case, the candidate points can be set manually using the cps argument.

To estimate changepoints, a model is fit for each candidate changepoint and generalised cross-validation (GCV, default) or the Akaike Information Criterion (AIC) are used to select among them. Model-selection uncertainty is dealt with by computing the one-standard-error rule, which identifies the least complex model within one standard error of the best scoring model.

Both the minimum and the one-standard-error (default) models are stored in the returned slot "changepoints" so that either can be used. In addition to these, this function also computes the probability (denoted p_mvn) that the null model is the best scoring model, using a simulation based approach based on the multivariate normal model of the pointwise model scores.

Given the computational cost of fitting a separate model for each candidate changepoint, cpam only estimates changepoints for targets associated with 'significant' genes at the chosen threshold deg_threshold.

Value

a cpam object with the estimated changepoint table added to the slot "changepoints"

References

Yates, L. A., S. A. Richards, and B. W. Brook. 2021. Parsimonious model selection using information theory: a modified selection rule. *Ecology* 102(10):e03475. 10.1002/ecy.3475

Examples

```
library(cpam)
library(dplyr)

# load example data
load(system.file("extdata", "exp_design_example.rda", package = "cpam"))
load(system.file("extdata", "count_matrix_example.rda", package = "cpam"))

cpo <- prepare_cpam(exp_design = exp_design_example,
                    count_matrix = count_matrix_example[1:20,],
                    gene_level = TRUE,
```

```

                                num_cores = 1)
cpo <- compute_p_values(cpo)
cpo <- estimate_changepoint(cpo)
cpo$changepoints

```

plot_cluster	<i>Plot clustered targets</i>
--------------	-------------------------------

Description

Plot clustered targets

Usage

```
plot_cluster(cpo, res, changepoints, shapes, alpha = 0.1)
```

Arguments

cpo	a cpam object
res	a tibble, output from results() containing columns target_id, cp, and shape
changepoints	numerical or character; one or more changepoints (these should be the same as the ones used in estimate_changepoint())
shapes	character; one or more shapes (these should be the same as the ones used in select_shape())
alpha	numeric between 0 and 1; controls line transparency in plot (default: 0.1)

Details

Plots the fitted trends for a set of targets whose estimated changepoints and shapes are given by the arguments changepoints and shapes, respectively.

Creates a combined plot showing fitted expression trends for all targets that share specified change-point times and shape patterns. Each line represents one target's fitted trajectory, with transparency controlled by alpha.

Value

A ggplot object showing overlaid fitted trends, or NULL if no matching targets are found

See Also

[results\(\)](#), [plot_cpam\(\)](#)

Examples

```
library(cpam)

# load gene-only example cpam object
load(system.file("extdata", "cpo_example.rda", package = "cpam"))

# Generate results table
res_example <- results(cpo_example)

# plot all targets with changepoint at timepoint 0 and shape "ilin" (increasing linear)
plot_cluster(cpo_example, res_example, changepoints = 2, shapes = "ilin")
```

plot_cpam

Plot fitted changepoint additive models

Description

Plot fitted changepoint additive models

Usage

```
plot_cpam(
  cpo,
  gene_id = NULL,
  target_id = NULL,
  cp_type = c("cp_1se", "cp_min"),
  shape_type = "shape1",
  bs = "auto",
  cp_fix = -1,
  facet = FALSE,
  sp = NULL,
  show_fit = TRUE,
  show_data = TRUE,
  show_fit_ci = TRUE,
  show_data_ci = TRUE,
  ci_prob = "se",
  remove_null = FALSE,
  null_threshold = 0.05,
  null_threshold_adj = TRUE,
  k_mult = 1.2,
  return_fits_only = FALSE,
  family = "nb",
  common_y_scale = TRUE,
  scaled = FALSE,
  base_size = 12
)
```


Arguments

cpo	A cpam object containing count data, model fits, and optional changepoint/shape estimates
gene_id	character; gene_id (mutually exclusive with target_id)
target_id	character; target_id (mutually exclusive with gene_id)
cp_type	One of "cp_lse" or "cp_min"; rule for selecting changepoint from fitted models. See estimate_changepoint() for details.
shape_type	One of "shape1" or "shape2"; which set of fitted shape patterns to use. See select_shape() for details.
bs	Shape pattern to fit ("null", "lin", "ilin", "dlin", or from cpo\$bss). Use "auto" (default) to use estimated shapes as per shape_type.
cp_fix	Numeric; fixed changepoint time. Set to -1 (default) to use estimated change-points
facet	Logical; for multiple transcripts, plot in separate facets?
sp	numerical; set the smooth parameter. NULL (default) for automatic selection
show_fit	logical; show the fitted trend?
show_data	logical; show (possibly normalized and scaled) data points?
show_fit_ci	logical; show credible interval for the fitted trend?
show_data_ci	logical; show bootstrapped quantile for data points?
ci_prob	"se" for standard error bands (see mgcv::predict.gam()), or numeric for simulation-based intervals. If numerical, sets the probability for the simulation-based estimates of credible interval.
remove_null	logical; only plot differentially expressed transcripts (not applicable for gene-only analyses)
null_threshold	numeric; P value threshold for filtering out NULL transcripts
null_threshold_adj	logical; use adjusted (default) or non-adjusted p-values for filtering targets
k_mult	numerical; multiplier for the number of knots in the spline. Not recommended to change this value.
return_fits_only	logical; return the model fits. Does not plot the function
family	character; negative binomial ("nb", default) or Gaussian ("gaussian")
common_y_scale	logical; for faceted plots of multiple transcripts, should the scale of the y-axis be common or free.
scaled	logical; scaled data by overdispersions (for bootstrapped data only)
base_size	numeric; base font size for the plot

Details

Plots the fitted trend and data points for a given gene or target. If a gene ID is supplied, the function will plot all transcripts for that gene. The function can also be used to return the model fit(s) only, which are `gamObject` objects from the `mgcv` package.

Value

a ggplot object

Examples

```
library(cpam)

# load gene-only example cpam object
load(system.file("extdata", "cpo_example.rda", package = "cpam"))

# example gene
plot_cpam(cpo_example, gene_id = "g003")

# gene with estimated changepoint at timepoint 3
plot_cpam(cpo_example, gene_id = "g013")

# manually set the changepoint
plot_cpam(cpo_example, gene_id = "g013", cp_fix = 2)
```

```
prepare_cpam
```

```
Prepare a cpam object
```

Description

Prepare a cpam object

Usage

```
prepare_cpam(
  exp_design,
  count_matrix = NULL,
  t2g = NULL,
  import_type = NULL,
  model_type = c("case-only", "case-control"),
  bootstrap = TRUE,
  filter_fun = "ts_filter",
  filter_fun_args = list(min_reads = 5, min_prop = 3/5),
  regularize = TRUE,
  gene_level = FALSE,
  aggregate_to_gene = !gene_level,
  condition_var = "condition",
  case_value = "treatment",
  num_cores = 1,
  normalize = TRUE,
  fixed_effects = NULL,
  intercept_cc = c("1", condition_var)
)
```

Arguments

<code>exp_design</code>	a dataframe or tibble with the experimental design, containing at least a 'time' and a 'sample' column
<code>count_matrix</code>	a matrix of counts. Column names must be in 'sample' column of <code>exp_design</code> ,
<code>t2g</code>	a transcript to gene dataframe or tibble with columns <code>target_id</code> and <code>gene_id</code>
<code>import_type</code>	software used for quantification, one of "kallisto", "salmon" ,.... Ignored if <code>count_matrix</code> is supplied.
<code>model_type</code>	"case-only" (default) or "case-control"
<code>bootstrap</code>	logical; load bootstrap samples, also called inferential replicates, if available, and rescale counts.
<code>filter_fun</code>	filter function to remove lowly expressed genes (default is <code>filter_fun()</code>)
<code>filter_fun_args</code>	arguments for filter function
<code>regularize</code>	logical; use empirical Bayes regularization of dispersions (default is TRUE)
<code>gene_level</code>	logical; aggregate counts to gene level before data preparation and modelling (default is FALSE)
<code>aggregate_to_gene</code>	logical; aggregate p values from transcript- to gene-level
<code>condition_var</code>	string; column name in <code>exp_design</code> for the condition variable (for <code>model_type</code> = "case_control" only)
<code>case_value</code>	value of <code>condition_var</code> that indicates the "case". All other values are deemed to be control
<code>num_cores</code>	integer; number of cores to use for parallel computation
<code>normalize</code>	logical; use model offsets based on sampling depth and gene length
<code>fixed_effects</code>	a model formula of the form <code>~ effect1 + effect2</code>
<code>intercept_cc</code>	string; intercept for case-control model: "1" (default) for common intercept or "condition"

Details

This function prepares a `cpam` object for analysis. The function loads count data from files or a matrix, filters lowly expressed genes, computes normalisation factors, and estimates dispersions. Many of these steps can be customised or turned off.

When bootstrap samples (inferential replicates) are available, it loads and summarises these using means, standard errors, and estimated overdispersions. The latter are a measure of quantification uncertainty and they are used to rescale the counts which accounts for this uncertainty during the modelling steps.

Value

an object of class `cpam-class`. The returned object has methods `print` and `summary` for displaying information. See `cpam-class` for details on the structure of the returned object.

References

Pedro L Baldoni, Yunshun Chen, Soroor Hedyeh-zadeh, Yang Liao, Xueyi Dong, Matthew E Ritchie, Wei Shi, Gordon K Smyth, Dividing out quantification uncertainty allows efficient assessment of differential transcript expression with edgeR, *Nucleic Acids Research*, Volume 52, Issue 3, 9 February 2024, Page e13, <https://doi.org/10.1093/nar/gkad1167>

Yunshun Chen, Lizhong Chen, Aaron T L Lun, Pedro L Baldoni, Gordon K Smyth, edgeR v4: powerful differential analysis of sequencing data with expanded functionality and improved support for small counts and larger datasets, *Nucleic Acids Research*, Volume 53, Issue 2, 27 January 2025, <https://doi.org/10.1093/nar/gkaf018>

Examples

```
library(cpam)

# load gene-only example data
load(system.file("extdata", "exp_design_example.rda", package = "cpam"))
load(system.file("extdata", "count_matrix_example.rda", package = "cpam"))

cpo <- prepare_cpam(exp_design = exp_design_example,
                    count_matrix = count_matrix_example,
                    gene_level = TRUE)

cpo
```

results

Create a results table from a cpam object

Description

Create a results table from a cpam object

Usage

```
results(
  cpo,
  p_threshold = 0.05,
  p_type = c("p_gam", "p_mvn"),
  min_lfc = 0,
  min_count = 0,
  aggregate_to_gene = cpo$aggregate_to_gene,
  add_lfc = TRUE,
  add_counts = TRUE,
  cp_type = c("cp_1se", "cp_min"),
  shape_type = c("shape1", "shape2"),
  summarise_to_gene = FALSE,
  remove_null_targets = TRUE
)
```

Arguments

<code>cpo</code>	a cpam object
<code>p_threshold</code>	numerical; threshold for adjusted p-values; default is 0.05
<code>p_type</code>	character; choose the type of p-value. Options are "p_gam" (default) or "p_mvn" (see compute_p_values() for details).
<code>min_lfc</code>	numerical; maximum absolute log (base 2) fold change must exceed this minimum value; default is 0
<code>min_count</code>	numerical; maximum of the modelled counts evaluated at the set of observed time points must exceed this minimum value for
<code>aggregate_to_gene</code>	logical; filter by gene-aggregated p-values
<code>add_lfc</code>	logical; add log (base 2) fold changes for each time point
<code>add_counts</code>	logical; add modelled counts for each time point
<code>cp_type</code>	character; model-selection rule used to select the changepoint
<code>shape_type</code>	character; "shape1" to include unconstrained or otherwise "shape2"
<code>summarise_to_gene</code>	logical; return gene-level results only
<code>remove_null_targets</code>	logical; remove targets with null shapes (default is T). If F, targets with null shapes will be included if the aggregated p-value for the corresponding gene passes the specified filtering thresholds.

Details

This function is usually called after [compute_p_values\(\)](#), [estimate_changepoint](#), and [select_shape](#) have been run. The function has several useful filters such as adjusted p-value thresholds, minimum log-fold changes, and minimum counts.

Value

a tibble

Examples

```
library(cpam)

# load gene-only example cpam object
load(system.file("extdata", "cpo_example.rda", package = "cpam"))

results(cpo_example)

# Add filters
results(cpo_example, p_threshold = 0.01, min_lfc = 1)
```

select_shape	<i>Use model selection to select a shape for each target</i>
--------------	--

Description

Use model selection to select a shape for each target

Usage

```
select_shape(
  cpo,
  subset = NULL,
  sp = NULL,
  bss = c("micv", "mdcx", "cv", "cx", "lin", "tp", "null"),
  family = c("nb", "gaussian"),
  score = "gcv",
  cp_type = c("cp_1se", "cp_min")
)
```

Arguments

cpo	a cpam object
subset	character vector; names of targets or genes (if <code>cpo\$gene_level = T</code>) for which changepoints will be estimated
sp	numerical ≥ 0 ; supply a fixed smoothing parameter. If <code>NULL</code> (default), the smoothing parameter is estimated. Note, this fixed value is in any case applied only to shape constrained bases (i.e., not <code>bs = 'tp'</code>).
bss	character vector; names of candidate spline bases (i.e., candidate shape types).
family	character; negative binomial ("nb", default) or Gaussian ("gaussian")
score	character; model selection score, either Generalised Cross Validation ("gcv") or Akaike Information Criterion ("aic")
cp_type	character; if changepoints have been estimated using estimate_changepoint() , which selection rule should be used. See estimate_changepoint() for details.

Details

The function selects the best shape from a list of candidate shapes for each target. It is typically the last step in the analysis, called after p-values have been estimated using [compute_p_values\(\)](#) and changepoints have been estimated using [estimate_changepoint\(\)](#).

Two shape selections are generated. The first selecting among linear, convex and concave shape classes and their monotonic variants (or the shape set given by `bss`), and the second selecting among the first options plus an 'unconstrained' smooth. The inclusion of the 'unconstrained' type provides the flexibility to detect targets beyond simpler trends. For computational reasons, as per the changepoint estimation, shapes are selected only for those genes, or their isoforms, identified as significant at the chosen FDR threshold. This is overridden by providing a subset of target names to the `subset` argument, provided these targets have estimated changepoints.

Value

a cpam object with the selected shapes added to the slot "shapes"

Examples

```
library(cpam)

# load example data
load(system.file("extdata", "exp_design_example.rda", package = "cpam"))
load(system.file("extdata", "count_matrix_example.rda", package = "cpam"))

# Using a small subset of the example data
cpo <- prepare_cpam(exp_design = exp_design_example,
                    count_matrix = count_matrix_example[1:20,],
                    gene_level = TRUE,
                    num_cores = 1)
cpo <- compute_p_values(cpo)
cpo <- estimate_changepoint(cpo)
cpo <- select_shape(cpo)
cpo$shapes
```

ts_filter	<i>Removes lowly expressed genes</i>
-----------	--------------------------------------

Description

Removes lowly expressed genes

Usage

```
ts_filter(data, min_reads = 5, min_prop = 3/5)
```

Arguments

data	A tibble or data.frame containing columns: <ul style="list-style-type: none"> target_id (character): Transcript identifiers time (numeric): Time point of measurement counts (numeric): Read counts
min_reads	minimum reads per transcript per sample
min_prop	minimum proportion of samples that exceed min_read at a given time point (default: 3/5)

Details

Identifies targets that show strong and consistent expression in at least one timepoint. For each time-point, the function calculates the proportion of samples where a targets exceeds min_reads. Targets are retained if they meet the minimum proportion (min_prop) at any timepoint in the experiment.

Value

a character vector of transcript IDs to keep

Examples

```
data <- dplyr::tibble(
  target_id = rep(paste0("t", 1:3), each = 6),
  time = rep(c(0, 4, 8), 6),
  counts = c(6,6,6, 0,0,0, 6,0,6, 0,6,6, 6,6,6, 6,0,0)
)
ts_filter(data)
```

visualise	<i>Launches a Shiny app to visualise the data and fitted models of a cpam object</i>
-----------	--

Description

Launches a Shiny app to visualise the data and fitted models of a cpam object

Usage

```
visualise(
  cpo,
  subset = NULL,
  degs_only = TRUE,
  deg_threshold = 0.05,
  p_type = c("p_gam", "p_mvn"),
  shape_type = c("shape1", "shape2")
)
```

Arguments

cpo	A cpam object containing count data, model fits, and optional changepoint/shape estimates
subset	Character vector; names of targets or genes (if <code>cpo\$gene_level = TRUE</code>) to load into the Shiny app. If <code>NULL</code> , all genes/targets are included based on <code>degs_only</code> .
degs_only	Logical; if <code>TRUE</code> , display only differentially expressed genes/targets with adjusted p-value below <code>deg_threshold</code> . Default is <code>TRUE</code> .
deg_threshold	Numeric; significance threshold for differentially expressed genes/targets. Only used when <code>degs_only = TRUE</code> . Default is 0.05.
p_type	character; choose the type of p-value. Options are "p_gam" (default) or "p_mvn" (see compute_p_values() for details).

`shape_type` character; "shape1" to include unconstrained or otherwise "shape2". Default is "shape1". In some instances, all of the transcripts for a gene may be "null" shaped, but the p-value for the gene may still be significant. This is due to the different methods of determining significance for the changepoints and the gene-level p-values. Here, conservatively, we remove these null-shaped genes from the DEG list.

Value

None (launches Shiny app in browser)

Examples

```
if (interactive()){  
  
  # A simple gene-level example  
  cpo <- cpo_example  
  
  # Launch visualization with all genes  
  visualise(cpo, degs_only = FALSE)  
  
  # Launch with only significant genes  
  visualise(cpo, deg_threshold = 0.05)  
  
  # Launch with specific genes  
  visualise(cpo, subset = c("g001", "g002", "g003"))  
}
```

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