

Package ‘hahmmr’

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Title Haplotype-Aware Hidden Markov Model for RNA

Version 1.0.0

Description Haplotype-aware Hidden Markov Model for RNA (HaHMMR) is a method for detecting copy number variations (CNVs) from bulk RNA-seq data. Additional examples, documentations, and details on the method are available at <https://github.com/kharchenkolab/hahmmr/>.

Depends R (>= 4.1.0)

Imports data.table, dplyr, GenomicRanges, ggplot2, glue, IRanges, methods, patchwork, Rcpp, stringr, tibble, zoo

Suggests ggrastr, testthat

LinkingTo Rcpp, RcppArmadillo, roptim

NeedsCompilation yes

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acen_hg19	<i>centromere regions (hg19)</i>
-----------	----------------------------------

Description

centromere regions (hg19)

Usage

acen_hg19

Format

An object of class `tbl_df` (inherits from `tbl`, `data.frame`) with 22 rows and 3 columns.

acen_hg38	<i>centromere regions (hg38)</i>
-----------	----------------------------------

Description

centromere regions (hg38)

Usage

acen_hg38

Format

An object of class `tbl_df` (inherits from `tbl`, `data.frame`) with 22 rows and 3 columns.

analyze_allele	<i>Analyze allele profile</i>
----------------	-------------------------------

Description

Analyze allele profile

Usage

```
analyze_allele(  
  bulk,  
  t = 1e-05,  
  theta_min = 0.08,  
  gamma = 20,  
  nu = 0.5,  
  r = 0.015,  
  hmm = "S5",  
  fit_theta = FALSE,  
  fit_gamma = FALSE,  
  theta_start = 0.05,  
  verbose = TRUE  
)
```

Arguments

bulk	dataframe Bulk allele profile
t	numeric Transition probability
theta_min	numeric Minimum allele fraction
gamma	numeric Overdispersion parameter

nu	numeric Phase switch rate
r	numeric Alternative allele count bias
hmm	character HMM model to use (S3 or S5)
fit_theta	logical Whether to fit theta_min
fit_gamma	logical Whether to fit gamma
theta_start	numeric Starting value for theta_min
verbose	logical Whether to print progress

Value

dataframe Bulk allele profile with CNV states

Examples

```
bulk_example = analyze_allele(bulk_example, hmm = 'S5')
```

analyze_joint	<i>Analyze allele and expression profile</i>
---------------	--

Description

Analyze allele and expression profile

Usage

```
analyze_joint(
  bulk,
  t = 1e-05,
  gamma = 20,
  theta_min = 0.08,
  logphi_min = 0.25,
  hmm = "S15",
  nu = 1,
  min_genes = 10,
  r = 0.015,
  theta_start = 0.05,
  exclude_neu = TRUE,
  fit_gamma = FALSE,
  fit_theta = FALSE,
  verbose = TRUE
)
```

Arguments

bulk	dataframe Bulk allele and expression profile
t	numeric Transition probability
gamma	numeric Overdispersion parameter
theta_min	numeric Minimum allele fraction
logphi_min	numeric Minimum log2 fold change
hmm	character HMM model to use (S7 or S15)
nu	numeric Phase switch rate
min_genes	integer Minimum number of genes per segment
r	numeric Alternative allele count bias
theta_start	numeric Starting value for theta_min
exclude_neu	logical Whether to exclude neutral segments in retest
fit_gamma	logical Whether to fit gamma
fit_theta	logical Whether to fit theta_min
verbose	logical Whether to print progress

Value

dataframe Bulk allele and expression profile with CNV states

Examples

```
bulk_example = analyze_joint(bulk_example, hmm = 'S15')
```

bulk_example	<i>example pseudobulk dataframe</i>
--------------	-------------------------------------

Description

example pseudobulk dataframe

Usage

```
bulk_example
```

Format

An object of class `tbl_df` (inherits from `tbl`, `data.frame`) with 10321 rows and 58 columns.

chrom_sizes_hg19	<i>chromosome sizes (hg19)</i>
------------------	--------------------------------

Description

chromosome sizes (hg19)

Usage

chrom_sizes_hg19

Format

An object of class `data.table` (inherits from `data.frame`) with 22 rows and 2 columns.

chrom_sizes_hg38	<i>chromosome sizes (hg38)</i>
------------------	--------------------------------

Description

chromosome sizes (hg38)

Usage

chrom_sizes_hg38

Format

An object of class `data.table` (inherits from `data.frame`) with 22 rows and 2 columns.

dbbinom	<i>Beta-binomial distribution density function A distribution is beta-binomial if p, the probability of success, in a binomial distribution has a beta distribution with shape parameters $\alpha > 0$ and $\beta > 0$ For more details, see <code>extraDistr::dbbinom</code></i>
---------	--

Description

Beta-binomial distribution density function A distribution is beta-binomial if p , the probability of success, in a binomial distribution has a beta distribution with shape parameters $\alpha > 0$ and $\beta > 0$ For more details, see `extraDistr::dbbinom`

Usage

`dbbinom(x, size, alpha = 1, beta = 1, log = FALSE)`

Arguments

x	vector of quantiles
size	number of trials (zero or more)
alpha	numeric (default=1)
beta	numeric (default=1)
log	boolean (default=FALSE)

Value

numeric Probability density values

Examples

```
dbbinom(1, 1, 1, 1)
```

df_allele_example	<i>example allele count dataframe</i>
-------------------	---------------------------------------

Description

example allele count dataframe

Usage

```
df_allele_example
```

Format

An object of class `data.table` (inherits from `data.frame`) with 9957 rows and 11 columns.

dpoilog	<i>Returns the density for the Poisson lognormal distribution with parameters mu and sig</i>
---------	--

Description

Returns the density for the Poisson lognormal distribution with parameters mu and sig

Usage

```
dpoilog(x, mu, sig, log = FALSE)
```

Arguments

x	vector of integers, the observations
mu	mean of lognormal distribution
sig	standard deviation of lognormal distribution
log	boolean Return the log density if TRUE (default=FALSE)

Value

numeric Probability density values

Examples

```
p = dpoilog(1, 1, 1)
```

fit_lnpois_cpp	<i>Fit MLE of log-normal Poisson model</i>
----------------	--

Description

Fit MLE of log-normal Poisson model

Usage

```
fit_lnpois_cpp(Y_obs, lambda_ref, d)
```

Arguments

Y_obs	Vector of observed counts
lambda_ref	Vector of reference rates
d	integer Total depth

Value

NumericVector MLE estimates of mu and sigma

forward_back_allele	<i>Forward-backward algorithm for allele HMM</i>
---------------------	--

Description

Forward-backward algorithm for allele HMM

Usage

```
forward_back_allele(hmm)
```

Arguments

hmm	HMM object; expect variables x (allele depth), d (total depth), logPi (log transition prob matrix), delta (prior for each state), alpha (alpha for each state), beta (beta for each state), states (states), p_s (phase switch probs)
-----	---

Value

numeric matrix; posterior probabilities

Examples

```
forward_back_allele(pre_likelihood_hmm)
```

gaps_hg19	<i>genome gap regions (hg19)</i>
-----------	----------------------------------

Description

genome gap regions (hg19)

Usage

```
gaps_hg19
```

Format

An object of class `data.table` (inherits from `data.frame`) with 28 rows and 3 columns.

gaps_hg38	<i>genome gap regions (hg38)</i>
-----------	----------------------------------

Description

genome gap regions (hg38)

Usage

gaps_hg38

Format

An object of class `data.table` (inherits from `data.frame`) with 30 rows and 3 columns.

gene_counts_example	<i>example gene expression counts matrix</i>
---------------------	--

Description

example gene expression counts matrix

Usage

gene_counts_example

Format

An object of class `matrix` (inherits from `array`) with 1758 rows and 1 columns.

get_allele_bulk	<i>Aggregate into pseudobulk allele profile</i>
-----------------	---

Description

Aggregate into pseudobulk allele profile

Usage

get_allele_bulk(df_allele, gtf, genetic_map = NULL, nu = 0.5, min_depth = 0)

Arguments

df_allele	dataframe Single-cell allele counts
gtf	dataframe Transcript gtf
genetic_map	dataframe Genetic map
nu	numeric Phase switch rate
min_depth	integer Minimum coverage to filter SNPs

Value

dataframe Pseudobulk allele profile

Examples

```
bulk_example = get_allele_bulk(
  df_allele = df_allele_example,
  gtf = gtf_hg38)
```

get_bulk	<i>Produce combined bulk expression and allele profile</i>
----------	--

Description

Produce combined bulk expression and allele profile

Usage

```
get_bulk(
  count_mat,
  lambdas_ref,
  df_allele,
  gtf,
  genetic_map = NULL,
  min_depth = 0,
  nu = 1,
  verbose = TRUE
)
```

Arguments

count_mat	matrix Gene expression counts
lambdas_ref	matrix Reference expression profiles
df_allele	dataframe Allele counts
gtf	dataframe Transcript gtf
genetic_map	dataframe Genetic map
min_depth	integer Minimum coverage to filter SNPs
nu	numeric Phase switch rate
verbose	logical Whether to print progress

Value

dataframe Pseudobulk gene expression and allele profile

Examples

```
bulk_example = get_bulk(  
  count_mat = gene_counts_example,  
  lambdas_ref = ref_hca,  
  df_allele = df_allele_example,  
  gtf = gtf_hg38)
```

gtf_hg19	<i>gene model (hg19)</i>
----------	--------------------------

Description

gene model (hg19)

Usage

gtf_hg19

Format

An object of class `data.table` (inherits from `data.frame`) with 26841 rows and 5 columns.

gtf_hg38	<i>gene model (hg38)</i>
----------	--------------------------

Description

gene model (hg38)

Usage

gtf_hg38

Format

An object of class `data.table` (inherits from `data.frame`) with 26807 rows and 5 columns.

gtf_mm10	<i>gene model (mm10)</i>
----------	--------------------------

Description

gene model (mm10)

Usage

```
gtf_mm10
```

Format

An object of class `data.table` (inherits from `data.frame`) with 30336 rows and 5 columns.

likelihood_allele	<i>Only compute total log likelihood from an allele HMM</i>
-------------------	---

Description

Only compute total log likelihood from an allele HMM

Usage

```
likelihood_allele(hmm)
```

Arguments

hmm	HMM object; expect variables x (allele depth), d (total depth), logPi (log transition prob matrix), delta (prior for each state), alpha (alpha for each state), beta (beta for each state), states (states), p_s (phase switch probs)
-----	---

Value

numeric; total log likelihood

Examples

```
likelihood_allele(pre_likelihood_hmm)
```

logSumExp	<i>logSumExp function</i>
Description	
logSumExp function	
Usage	
logSumExp(x)	
Arguments	
x	NumericVector
Value	
double logSumExp of x	
l_bbinom	<i>calculate joint likelihood of allele data</i>

Description

calculate joint likelihood of allele data

Usage

l_bbinom(AD, DP, alpha, beta)

Arguments

- AD numeric vector Variant allele depth
- DP numeric vector Total allele depth
- alpha numeric Alpha parameter of Beta-Binomial distribution
- beta numeric Beta parameter of Beta-Binomial distribution

Value

numeric Joint log likelihood

Examples

l_bbinom(c(1, 2), c(1, 2), 1, 1)

l_inpois	<i>calculate joint likelihood of a PLN model</i>
----------	--

Description

calculate joint likelihood of a PLN model

Usage

```
l_inpois(Y_obs, lambda_ref, d, mu, sig, phi = 1)
```

Arguments

Y_obs	numeric vector Gene expression counts
lambda_ref	numeric vector Reference expression levels
d	numeric Total library size
mu	numeric Global mean expression
sig	numeric Global standard deviation of expression
phi	numeric Fold change of expression

Value

numeric Joint log likelihood

Examples

```
l_inpois(c(1, 2), c(1, 2), 1, 1, 1)
```

plot_bulks	<i>Plot a group of pseudobulk HMM profiles</i>
------------	--

Description

Plot a group of pseudobulk HMM profiles

Usage

```
plot_bulks(bulks, ..., ncol = 1, title = TRUE, title_size = 8)
```

Arguments

bulks	dataframe Pseudobulk profiles annotated with "sample" column
...	additional parameters passed to plot_psbulk()
ncol	integer Number of columns
title	logical Whether to add titles to individual plots
title_size	numeric Size of titles

Value

a ggplot object

Examples

```
p = plot_bulks(bulk_example)
```

plot_psbulk

Plot a pseudobulk HMM profile

Description

Plot a pseudobulk HMM profile

Usage

```
plot_psbulk(
  bulk,
  use_pos = TRUE,
  allele_only = FALSE,
  min_LLR = 5,
  min_depth = 8,
  exp_limit = 2,
  phi_mle = TRUE,
  theta_roll = FALSE,
  dot_size = 0.8,
  dot_alpha = 0.5,
  legend = TRUE,
  exclude_gap = TRUE,
  genome = "hg38",
  text_size = 10,
  raster = FALSE
)
```

Arguments

bulk	dataframe Pseudobulk profile
use_pos	logical Use marker position instead of index as x coordinate
allele_only	logical Only plot alleles
min_LLR	numeric LLR threshold for event filtering
min_depth	numeric Minimum coverage depth for a SNP to be plotted
exp_limit	numeric Expression logFC axis limit
phi_mle	logical Whether to plot estimates of segmental expression fold change
theta_roll	logical Whether to plot rolling estimates of allele imbalance

dot_size	numeric	Size of marker dots
dot_alpha	numeric	Transparency of the marker dots
legend	logical	Whether to show legend
exclude_gap	logical	Whether to mark gap regions and centromeres
genome	character	Genome build, either 'hg38' or 'hg19'
text_size	numeric	Size of text in the plot
raster	logical	Whether to raster images

Value

ggplot Plot of pseudobulk HMM profile

Examples

```
p = plot_psbulk(bulk_example)
```

pre_likelihood_hmm	<i>HMM object for unit tests</i>
--------------------	----------------------------------

Description

HMM object for unit tests

Usage

```
pre_likelihood_hmm
```

Format

An object of class list of length 10.

ref_hca	<i>reference expression magnitudes from HCA</i>
---------	---

Description

reference expression magnitudes from HCA

Usage

```
ref_hca
```

Format

An object of class matrix (inherits from array) with 24756 rows and 12 columns.

ref_hca_counts	<i>reference expression counts from HCA</i>
----------------	---

Description

reference expression counts from HCA

Usage

ref_hca_counts

Format

An object of class `matrix` (inherits from `array`) with 24857 rows and 12 columns.

run_allele_hmm_s5	<i>Run a 5-state allele-only HMM - two theta levels</i>
-------------------	---

Description

Run a 5-state allele-only HMM - two theta levels

Usage

```
run_allele_hmm_s5(
  pAD,
  DP,
  p_s,
  t = 1e-05,
  theta_min = 0.08,
  gamma = 20,
  prior = NULL,
  ...
)
```

Arguments

pAD	integer vector Paternal allele counts
DP	integer vector Total allele counts
p_s	numeric vector Phase switch probabilities
t	numeric Transition probability between copy number states
theta_min	numeric Minimum haplotype frequency deviation threshold
gamma	numeric Overdispersion in the allele-specific expression
prior	numeric vector Prior probabilities for each state
...	Additional parameters

Value

character vector Decoded states

Examples

```
with(bulk_example, {
  run_allele_hmm_s5(pAD = pAD, DP = DP, R = R, p_s = p_s, theta_min = 0.08, gamma = 30)
})
```

run_joint_hmm_s15	<i>Run 15-state joint HMM on a pseudobulk profile</i>
-------------------	---

Description

Run 15-state joint HMM on a pseudobulk profile

Usage

```
run_joint_hmm_s15(
  pAD,
  DP,
  p_s,
  Y_obs = 0,
  lambda_ref = 0,
  d_total = 0,
  theta_min = 0.08,
  theta_neu = 0,
  bal_cnv = TRUE,
  phi_del = 2^(-0.25),
  phi_amp = 2^(0.25),
  phi_bamp = phi_amp,
  phi_bdel = phi_del,
  mu = 0,
  sig = 1,
  r = 0.015,
  t = 1e-05,
  gamma = 18,
  prior = NULL,
  exp_only = FALSE,
  allele_only = FALSE,
  classify_allele = FALSE,
  debug = FALSE,
  ...
)
```

Arguments

pAD	integer vector Paternal allele counts
DP	integer vector Total allele counts
p_s	numeric vector Phase switch probabilities
Y_obs	numeric vector Observed gene counts
lambda_ref	numeric vector Reference expression rates
d_total	integer Total library size for expression counts
theta_min	numeric Minimum haplotype imbalance threshold
theta_neu	numeric Haplotype imbalance threshold for neutral state
bal_cnv	logical Whether to include balanced CNV states
phi_del	numeric Expected fold change for deletion
phi_amp	numeric Expected fold change for amplification
phi_bamp	numeric Expected fold change for balanced amplification
phi_bdel	numeric Expected fold change for balanced deletion
mu	numeric Global expression bias
sig	numeric Global expression variance
r	numeric Variant mapping bias
t	numeric Transition probability between copy number states
gamma	numeric Overdispersion in the allele-specific expression
prior	numeric vector Prior probabilities for each state
exp_only	logical Whether to only use expression data
allele_only	logical Whether to only use allele data
classify_allele	logical Whether to classify allele states
debug	logical Whether to print debug messages
...	Additional parameters

Value

character vector Decoded states

Examples

```
with(bulk_example, {
  run_joint_hmm_s15(pAD = pAD, DP = DP, p_s = p_s, Y_obs = Y_obs, lambda_ref = lambda_ref,
    d_total = na.omit(unique(d_obs)), mu = mu, sig = sig, t = 1e-5, gamma = 30, theta_min = 0.08)
})
```

segs_example	<i>example CNV segments dataframe</i>
--------------	---------------------------------------

Description

example CNV segments dataframe

Usage

segs_example

Format

An object of class `data.table` (inherits from `data.frame`) with 27 rows and 30 columns.

vcf_meta	<i>example VCF header</i>
----------	---------------------------

Description

example VCF header

Usage

vcf_meta

Format

An object of class `character` of length 65.

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