

Package ‘rabhit’

January 29, 2020

Type Package

Title Inference Tool for Antibody Haplotype

Version 0.1.4

Description Infers V-D-J haplotypes and gene deletions from AIRR-seq data, based on IGHJ, IGHD or IGHV as anchor, by adapting a Bayesian framework. It also calculates a Bayes factor, a number that indicates the certainty level of the inference, for each haplotyped gene.

Citation:

Gidoni, et al (2019) <doi:10.1038/s41467-019-08489-3>.

Peres and Gidoni, et al (2019) <doi:10.1093/bioinformatics/btz481>.

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URL <https://yaarilab.bitbucket.io/RAbHIT/>

BugReports <https://bitbucket.org/yaarilab/haplotyper/issues>

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BuildVignettes true

VignetteBuilder knitr

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Author Ayelet Peres [aut, cre],
Moriah Gidoni [aut],
Gur Yaari [aut, cph]

Maintainer Ayelet Peres <peresay@biu.ac.il>

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.onAttach	<i>.onAttach start message</i>
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Description

.onAttach start message

Usage

```
.onAttach(libname, pkgname)
```

Arguments

libname	defunct
pkgname	defunct

Value

invisible()

createFullHaplotype *Anchor gene haplotype inference*

Description

The createFullHaplotype functions infers haplotype based on an anchor gene.

Usage

```
createFullHaplotype(
  clip_db,
  toHap_col = c("V_CALL", "D_CALL"),
  hapBy_col = "J_CALL",
  hapBy = "IGHJ6",
  toHap_GERM,
  relative_freq_priors = TRUE,
  kThreshDel = 3,
  rmPseudo = TRUE,
  deleted_genes = c(),
  nonReliable_Vgenes = c(),
  min_minor_fraction = 0.3,
  chain = c("IGH", "IGK", "IGL")
)
```

Arguments

clip_db	a data.frame in Change-O format. See details.
toHap_col	a vector of column names for which a haplotype should be inferred. Default is V_CALL and D_CALL.
hapBy_col	column name of the anchor gene. Default is J_CALL.
hapBy	a string of the anchor gene name. Default is IGHJ6.
toHap_GERM	a vector of named nucleotide germline sequences matching the allele calls in toHap_col columns in clip_db.
relative_freq_priors	if TRUE, the priors for Bayesian inference are estimated from the relative frequencies in clip_db. Else, priors are set to c(0.5, 0.5). Default is TRUE
kThreshDel	the minimum 1K (log10 of the Bayes factor) to call a deletion. Default is 3.

rmPseudo	if TRUE non-functional and pseudo genes are removed. Default is TRUE.
deleted_genes	double chromosome deletion summary table. A data.frame created by deletionsByBinom.
nonReliable_Vgenes	a list of known non reliable gene assignments. A list created by nonReliableVGenes.
min_minor_fraction	the minimum minor allele fraction to be used as an anchor gene. Default is 0.3
chain	the IG chain: IGH,IGK,IGL. Default is IGH.

Details

Function accepts a data.frame in Change-O format (<https://changeo.readthedocs.io/en/version-0.4.1---airr-standards/standard.html>) containing the following columns:

- 'SUBJECT': The subject name
- 'V_CALL': V allele call(s) (in an IMGT format)
- 'D_CALL': D allele call(s) (in an IMGT format, only for heavy chains)
- 'J_CALL': J allele call(s) (in an IMGT format)

Value

A data.frame, in which each row is the haplotype inference summary of a gene from the column selected in toHap_col.

The output contains the following columns:

- SUBJECT: the subject name.
- GENE: the gene name.
- Anchor gene allele 1: the haplotype inference for chromosome one. The column name is the anchor gene with the first allele.
- Anchor gene allele 2: the haplotype inference for chromosome two. The column name is the anchor gene with the second allele.
- ALLELES: allele calls for the gene.
- PRIORS_ROW: priors based on relative allele usage of the anchor gene.
- PRIORS_COL: priors based on relative allele usage of the inferred gene.
- COUNTS1: the appearance count on each chromosome of the first allele from ALLELES, the counts are separated by a comma.
- K1: the Bayesian factor value for the first allele (from ALLELES) inference.
- COUNTS2: the appearance count on each chromosome of the second allele from ALLELES, the counts are separated by a comma.
- K2: the Bayesian factor value for the second allele (from ALLELES) inference.
- COUNTS3: the appearance count on each chromosome of the third allele from ALLELES, the counts are separated by a comma.
- K3: the Bayesian factor value for the third allele (from ALLELES) inference.
- COUNTS4: the appearance count on each chromosome of the fourth allele from ALLELES, the counts are separated by a comma.
- K4: the Bayesian factor value for the fourth allele (from ALLELES) inference.

Examples

```
# Load example data and germlines
data(samples_db, HVGERM, HDGERM)

# Selecting a single individual
clip_db = samples_db[samples_db$SUBJECT=='I5', ]

# Inferring haplotype
haplo_db = createFullHaplotype(clip_db,toHap_col=c('V_CALL', 'D_CALL'),
hapBy_col='J_CALL',hapBy='IGHJ6',toHap_GERM=c(HVGERM,HDGERM))
```

deletionHeatmap	<i>Graphical output of single chromosome deletions</i>
-----------------	--

Description

The deletionHeatmap function generates a graphical output of the single chromosome deletions in multiple samples.

Usage

```
deletionHeatmap(
  hap_table,
  chain = c("IGH", "IGK", "IGL"),
  kThreshDel = 3,
  html_output = FALSE
)
```

Arguments

hap_table	haplotype summary table. See details.
chain	the IG chain: IGH,IGK,IGL. Default is IGH.
kThreshDel	the minimum IK (log10 of the Bayes factor) used in createFullHaplotype to call a deletion. Indicates the color for strong deletion. Default is 3.
html_output	If TRUE, a html5 interactive graph is outputed instead of the normal plot. Default is FALSE

Details

A data.frame created by createFullHaplotype.

Value

A single chromosome deletion visualization.

Examples

```
# Plotting single chromosome deletion from haplotype inference
deletionHeatmap(samplesHaplotype)
```

deletionsByBinom	<i>Double chromosome deletion by relative gene usage</i>
------------------	--

Description

The `deletionsByBinom` function infers double chromosome deletion events by relative gene usage.

Usage

```
deletionsByBinom(
  clip_db,
  chain = c("IGH", "IGK", "IGL"),
  nonReliable_Vgenes = c()
)
```

Arguments

<code>clip_db</code>	a data.frame in Change-O format. See details.
<code>chain</code>	the IG chain: IGH,IGK,IGL. Default is IGH.
<code>nonReliable_Vgenes</code>	a list of known non reliable gene assignments. A list created by <code>nonReliableVGenes</code> .

Details

The function accepts a data.frame in Change-O format (<https://changeo.readthedocs.io/en/version-0.4.1---airr-standards/standard.html>) containing the following columns:

- 'SUBJECT': The subject name
- 'V_CALL': V allele call(s) (in an IMGT format)
- 'D_CALL': D allele call(s) (in an IMGT format, only for heavy chains)
- 'J_CALL': J allele call(s) (in an IMGT format)

Value

A data.frame, in which each row is the double chromosome deletion inference of a gene.

The output contains the following columns:

- SUBJECT: the subject name.
- GENE: the gene call
- FRAC: the relative gene usage of the gene
- CUTOFF: the the cutoff of for the binomial test
- PVAL: the p-value of the binomial test
- DELETION: if a double chromosome deletion event of a gene occurred.

Examples

```
# Load example data and germlines
data(samples_db)

# Selecting a single individual
clip_db = samples_db[samples_db$SUBJECT=='I5', ]
# Infering haplotype
del_binom_df = deletionsByBinom(clip_db)
head(del_binom_df)
```

deletionsByVpooled	<i>Single chromosomal D or J gene deletions inferred by the V pooled method</i>
--------------------	---

Description

The deletionsByVpooled function infers single chromosomal deletion for D and J gene .

Usage

```
deletionsByVpooled(
  clip_db,
  chain = c("IGH", "IGK", "IGL"),
  deletion_col = c("D_CALL", "J_CALL"),
  count_thresh = 50,
  deleted_genes = "",
  min_minor_fraction = 0.3,
  kThreshDel = 3,
  nonReliable_Vgenes = c()
)
```

Arguments

clip_db	a data.frame in Change-O format. See details.
chain	the IG chain: IGH,IGK,IGL. Default is IGH.
deletion_col	a vector of column names for which single chromosome deletions should be inferred. Default is J_CALL and D_CALL.
count_thresh	integer, the minimum number of sequences mapped to a specific V gene to be included in the V pooled inference.
deleted_genes	double chromosome deletion summary table. A data.frame created by deletionsByBinom.
min_minor_fraction	the minimum minor allele fraction to be used as an anchor gene. Default is 0.3
kThreshDel	the minimum IK (log10 of the Bayes factor) to call a deletion. Default is 3.
nonReliable_Vgenes	a list of known non reliable gene assignments. A list created by nonReliableVGenes.

Details

The function accepts a `data.frame` in Change-O format (<https://changeo.readthedocs.io/en/version-0.4.1---airr-standards/standard.html>) containing the following columns:

- 'SUBJECT': The subject name
- 'V_CALL': V allele call(s) (in an IMGT format)
- 'D_CALL': D allele call(s) (in an IMGT format, only for heavy chains)
- 'J_CALL': J allele call(s) (in an IMGT format)

Value

A `data.frame`, in which each row is the single chromosome deletion inference of a gene.

The output contains the following columns:

- SUBJECT: the subject name.
- GENE: the gene call
- DELETION: chromosome deletions inferred. Encoded 1 for deletion and 0 for no deletion.
- K: the Bayesian factor value for the deletion inference.
- COUNTS: the appearance count of the gene on each chromosome, the counts are separated by a comma.

Examples

```
data(samples_db)

# Inferring V pooled deletions
del_db <- deletionsByVpooled(samples_db)
head(del_db)
```

GERM

Human germlines

Description

A list of the germline genes from the human immunoglobulin loci

Usage

GERM

Format

Values correspond to IMGT-gaped nucleotide sequences (with nucleotides capitalized and gaps represented by '.').

hapDendo

Hierarchical clustering of haplotypes graphical output

Description

The hapDendo function generates a graphical output of an hierarchical clustering based on the Jaccard distance between multiple samples' haplotypes.

Usage

```
hapDendo(  
  hap_table,  
  chain = c("IGH", "IGK", "IGL"),  
  gene_sort = c("name", "position"),  
  removeIGH = TRUE,  
  mark_low_ik = TRUE,  
  ik_cutoff = 1  
)
```

Arguments

hap_table	haplotype summary table. See details.
chain	the IG chain: IGH,IGK,IGL. Default is IGH.
gene_sort	if by 'name' the genes in the output are ordered lexicographically, if by 'position' only functional genes are used and are ordered by their chromosomal location. Default is 'position'.
removeIGH	if TRUE, 'IGH'\IGK'\IGL' prefix is removed from gene names. Default is TRUE.
mark_low_ik	if TRUE, a texture is add for low IK values. Default is TRUE.
ik_cutoff	the IK cutoff value to be considered low for texture layer. Default is IK<1.

Details

A data.frame created by createFullHaplotype.

Value

A multiple samples visualization of the distances between haplotypes.

Examples

```
# Plotting haplotype hierarchical clustering based on the Jaccard distance  
hapDendo(samplesHaplotype)
```

 hapHeatmap

Graphical output of alleles division by chromosome

Description

The hapHeatmap function generates a graphical output of the alleles per gene in multiple samples.

Usage

```
hapHeatmap(
  hap_table,
  chain = c("IGH", "IGK", "IGL"),
  gene_sort = "position",
  removeIGH = TRUE,
  lk_cutoff = 1,
  mark_low_lk = TRUE,
  size_annot = 1.5,
  color_y = NULL,
  order_subject = NULL,
  file = NULL,
  size_text = NULL,
  ylabel_size = 1
)
```

Arguments

hap_table	haplotype summary table. See details.
chain	the IG chain: IGH,IGK,IGL. Default is IGH.
gene_sort	if by 'name' the genes in the output are ordered lexicographically, if by 'position' only functional genes are used and are ordered by their chromosomal location. Default is 'position'.
removeIGH	if TRUE, 'IGH'\IGK'\IGL' prefix is removed from gene names.
lk_cutoff	the IK cutoff value to be considered low for texture layer. Default is IK<1.
mark_low_lk	if TRUE, a texture is add for low IK values. Default is TRUE.
size_annot	size of bottom annotation text. Default is 1.5 .
color_y	named list of the colors for y axis labels.
order_subject	order subject by a vecor.
file	file path for rendering the plot to pdf. If non is supplied than the plot is retured as object. Default is NULL.
size_text	text size for annotations.
ylabel_size	text size for y axis labels.

Details

A data. frame created by createFullHaplotype.

Value

A list with the following:

- 'p': heat-map visualization of the haplotype inference for multiple samples.
- 'width': Optimal width value for rendering plot.
- 'height': Optimal width value for rendering plot.

When a file is supplied the graph is also rendered to pdf.

Examples

```
# Plotting haplotpe heatmap
p <- hapHeatmap(samplesHaplotype)
p$p
```

HDGERM

Human IGHD germlines

Description

A character vector of all 37 human IGHD germline gene segment alleles in IMGT Gene-db release 2018-12-4.

Usage

HDGERM

Format

Values correspond to IMGT nuceltoide sequences.

References

Xochelli *et al.* (2014) Immunoglobulin heavy variable (IGHV) genes and alleles: new entities, new names and implications for research and prognostication in chronic lymphocytic leukaemia. *Immunogenetics*. 67(1):61-6.

HJGERM

Human IGHJ germlines

Description

A character vector of all 13 human IGHJ germline gene segment alleles in IMGT Gene-db release 2018-12-4.

Usage

HJGERM

Format

Values correspond to IMGT nucleotide sequences.

References

Xochelli *et al.* (2014) Immunoglobulin heavy variable (IGHV) genes and alleles: new entities, new names and implications for research and prognostication in chronic lymphocytic leukaemia. *Immunogenetics*. 67(1):61-6.

HVGERM

Human IGHV germlines

Description

A character vector of all 342 human IGHV germline gene segment alleles in IMGT Gene-db release 2018-12-4.

Usage

HVGERM

Format

Values correspond to IMGT-gapped nucleotide sequences (with nucleotides capitalized and gaps represented by '.').

References

Xochelli *et al.* (2014) Immunoglobulin heavy variable (IGHV) genes and alleles: new entities, new names and implications for research and prognostication in chronic lymphocytic leukaemia. *Immunogenetics*. 67(1):61-6.

KJGERM

Human IGKJ germlines

Description

A character vector of all 342 human IGKJ germline gene segment alleles in IMGT Gene-db release 2019-11-18.

Usage

KJGERM

Format

Values correspond to IMGT-gaped nucleotide sequences (with nucleotides capitalized and gaps represented by '.').

KVGERM

Human IGKV germlines

Description

A character vector of all 342 human IGKV germline gene segment alleles in IMGT Gene-db release 2019-11-18.

A character vector of all 342 human IGLV germline gene segment alleles in IMGT Gene-db release 2019-11-18.

Usage

KVGERM

LVGERM

Format

Values correspond to IMGT-gaped nucleotide sequences (with nucleotides capitalized and gaps represented by '.').

LJGERM	<i>Human IGLJ germlines</i>
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Description

A character vector of all 342 human IGLJ germline gene segment alleles in IMGT Gene-db release 2019-11-18.

Usage

LJGERM

Format

Values correspond to IMGT-gaped nucleotide sequences (with nucleotides capitalized and gaps represented by '.').

nonReliableVGenes	<i>Detect non reliable gene assignment</i>
-------------------	--

Description

nonReliableVGenes Takes a data.frame in Change-O format and detect non reliable IGHV genes. A non reliable gene is when the ratio of the multiple assignments with a gene is below the threshold.

Usage

```
nonReliableVGenes(clip_db, thresh = 0.9, appearance = 0.01)
```

Arguments

clip_db	a data.frame in Change-O format. See details.
thresh	the threshold to consider non reliable gene. Default is 0.9
appearance	the minimum fraction of gene appearance to be considered for reliability check. Default is 0.01.

Details

The function accepts a data.frame in Change-O format (<https://changeo.readthedocs.io/en/version-0.4.1---airr-standards/standard.html>) containing the following columns:

- 'SUBJECT': subject names
- 'V_CALL': V allele call(s) (in an IMGT format)

Value

a nested list of non reliable genes for all subject.

Examples

```
# Example IGHV call data frame
clip_db <- data.frame(SUBJECT=rep('S1',6),
  V_CALL=c('IGHV1-69*01','IGHV1-69*01','IGHV1-69*01,IGHV1-69*02',
  'IGHV4-59*01,IGHV4-61*01','IGHV4-59*01,IGHV4-31*02','IGHV4-59*01'))
# Detect non reliable genes
nonReliableVGenes(clip_db)
```

plotDeletionsByBinom *Graphical output of double chromosome deletions*

Description

The plotDeletionsByBinom function generates a graphical output of the double chromosome deletions in multiple samples.

Usage

```
plotDeletionsByBinom(
  GENE.usage.df,
  genes.low.cer = c("IGHV3-43", "IGHV3-20"),
  genes.dup = c("IGHD4-11", "IGHD5-18")
)
```

Arguments

GENE.usage.df	double chromosome deletion summary table. See details.
genes.low.cer	a vector of IGH genes known to be with low certantiny in the binomial test. Default is IGHV3-43 and IGHV3-20
genes.dup	a vector of IGH genes known to have a duplicated gene. Default is IGHD4-11 that his duplicate is IGHD4-4 and IGHD5-18 that his duplicate is IGHD5-5

Details

A data.frame created by binom_test_deletion.

Value

A double chromosome deletion visualization.

Examples

```
# Load example data and germlines
data(samples_db)

# Inferring haplotype
deletions_db = deletionsByBinom(samples_db);
plotDeletionsByBinom(deletions_db)
```

plotDeletionsByVpooled

Graphical output for single chromosome D or J gene deletions according to V pooled method

Description

The plotDeletionsByVpooled function generates a graphical output for single chromosome D or J gene deletions (for heavy chain only).

Usage

```
plotDeletionsByVpooled(
  del.df,
  chain = c("IGH", "IGK", "IGL"),
  K_ranges = c(3, 7)
)
```

Arguments

del.df	a data.frame created by deletionsByVpooled
chain	the IG chain: IGH,IGK,IGL. Default is IGH..
K_ranges	vector of one or two integers for log(K) certainty level thresholds

Details

A data.frame created by deletionsByVpooled.

Value

A single chromosome deletion visualization.

Examples

```
# Load example data and germlines
data(samples_db)
del_db <- deletionsByVpooled(samples_db)
plotDeletionsByVpooled(del_db)
```

plotHaplotype *Graphical output of an inferred haplotype*

Description

The plotHaplotype functions visualizes an inferred haplotype.

Usage

```
plotHaplotype(
  hap_table,
  html_output = FALSE,
  gene_sort = c("name", "position"),
  text_size = 14,
  removeIGH = TRUE,
  plotYaxis = TRUE,
  chain = c("IGH", "IGK", "IGL"),
  dir
)
```

Arguments

hap_table	haplotype summary table. See details.
html_output	if TRUE, a html5 interactive graph is outputed. Default is FALSE.
gene_sort	if by 'name' the genes in the output are ordered lexicographically, if by 'position' only functional genes are used and are ordered by their chromosomal location. Default is 'position'.
text_size	the size of graph labels. Default is 14 (pts).
removeIGH	if TRUE, 'IGH'\IGK'\IGL' prefix is removed from gene names.
plotYaxis	if TRUE, Y axis labels (gene names) are plotted on the middle and right plots. Default is TRUE.
chain	the Ig chain: IGH,IGK,IGL. Default is IGH.
dir	The output folder for saving the haplotype map for multiple individuals.

Details

A data.frame in a haplotype format created by createFullHaplotype function.

Value

A haplotype map visualization. If more than one subject is visualized, a pdf is created. If `html_output` is TRUE, a folder named `html_output` is created with individual graphs.

Examples

```
# Selecting a single individual from the haplotype samples data
haplo_db = samplesHaplotype[samplesHaplotype$SUBJECT=='I5', ]

# plot haplotype
plotHaplotype(haplo_db)
```

rabit

The RABHIT package

Description

The `rabit` package provides a robust novel method for determining antibody heavy and light chain haplotypes by adapting a Bayesian framework. The key functions in `rabit`, broken down by topic, are described below.

Haplotype and deletions inference

`rabit` provides tools to infer haplotypes based on given anchor genes, deletion detection based on relative gene usage, pooling `v` genes, and a single anchor gene.

- [createFullHaplotype](#): Haplotypes inference and single chromosome deletions based on an anchor gene.
- [deletionsByVpooled](#): Single chromosomal deletion detection by pooling `V` genes.
- [deletionsByBinom](#): Double chromosomal deletion detection by relative gene usage.
- [nonReliableVGenes](#): Non reliable gene assignment detection.

Haplotype and deletions visualization

Functions for visualization of the inferred haplotypes and deletions

- [plotHaplotype](#): Haplotype inference map.
- [deletionHeatmap](#): Single chromosome deletions heatmap.
- [hapHeatmap](#): Chromosome comparison of multiple samples.
- [hapDendo](#): Hierarchical clustering of multiple haplotypes based on Jaccard distance.
- [plotDeletionsByVpooled](#): `V` pooled based single chromosome deletions heatmap.
- [plotDeletionsByBinom](#): Double chromosome deletions heatmap.

References

1. Gidoni, M., Snir, O., Peres, A., Polak, P., Lindeman, I., Mikocziova, I., . . . Yaari, G. (2019). Mosaic deletion patterns of the human antibody heavy chain gene locus shown by Bayesian haplotyping. *Nature Communications*, 10(1). doi:10.1038/s41467-019-08489-3

samplesHaplotype

Example haplotype inference results

Description

A data.frame of example haplotype inference results from [createFullHaplotype](#) after double chromosome deletion inference via [deletionsByBinom](#) and non reliable V genes detection via [nonReliableVGenes](#). Source data is a collection of IGH human naive b-cell repertoire data from five individuals (see references). Overall, the data set includes 6 samples. A single individual has two samples (Individual I5), one is short read sequences from BIOMED-2 protocol primers for framework 2 region (The sample is annotated I5_FR2).

Usage

samplesHaplotype

Format

A data.frame, in which each row is the haplotype inference summary of a gene of an individual, from the column selected to preform the haplotype inference on.

References

Gidoni, Moriah, *et al.* Mosaic deletion patterns of the human antibody heavy chain gene locus shown by Bayesian haplotyping. *Nature Communications*. 10.1 (2019): 628.

See Also

See [createFullHaplotype](#) for detailed column descriptions.

samples_db

Example IGH human naive b-cell repertoire

Description

A data.frame of example IGH human naive b-cell repertoire data from five individuals (see references). Overall, the data set includes 6 samples. A single individual has two samples (Individual I5), one is short read sequences from BIOMED-2 protocol primers for framework 2 region (The sample is annotated I5_FR2).

Usage

samples_db

Format

A data.frame in Change-O format (<https://changeo.readthedocs.io/en/version-0.4.1---airr-standards/standard.html>) containing the following columns:

- 'SUBJECT': subject names
- 'V_CALL': V allele call(s) (in an IMGT format)
- 'D_CALL': D allele call(s) (in an IMGT format, only for heavy chains)
- 'J_CALL': J allele call(s) (in an IMGT format)

References

Gidoni, Moriah, *et al.* Mosaic deletion patterns of the human antibody heavy chain gene locus shown by Bayesian haplotyping. *Nature Communications*. 10.1 (2019): 628.

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