Package 'IgGeneUsage'

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Type Package

Title Differential gene usage in immune repertoires

Version 1.26.0

Description Detection of biases in the usage of immunoglobulin (Ig) genes is an important task in immune repertoire profiling. IgGeneUsage detects aberrant Ig gene usage between biological conditions using a probabilistic model which is analyzed computationally by Bayes inference. With this IgGeneUsage also avoids some common problems related to the current practice of null-hypothesis significance testing.

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`IgGeneUsage-package` *The R package IgGeneUsage*

Description

IgGeneUsage detects aberrant immunoglobulin (Ig) gene usage between adaptive immune repertoires that belong to different biological conditions using a probabilistic model which is analyzed computationally by Bayes inference.

Details

This package contains functions for:

1. differential Ig gene usage analysis (function DGU)
2. posterior predictive checks (part of results generated by function DGU)
3. leave-one-out cross validation (function LOO)

Author(s)

Authors and maintainers:

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See Also

Useful links:

- https://github.com/snaketron/IgGeneUsage
- Report bugs at https://github.com/snaketron/IgGeneUsage/issues

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`CDR3_Epitopes` *Net charge usage in CDR3 sequences of T-cell receptor repertoires disturbed by Influenza-A and CMV*

Description

Data of CDR3 sequence from human T-cells receptors (TRB-chain) downloaded from VDJdb. CDR3 sequences annotated to epitopes in Influenza-A and CMV were selected from different publications, as long as the publication contains at least 100 CDR3 sequences. Each publication is considered as a repertoire (sample).

To compute the net CDR3 sequence charge, we consider the amino acids K, R and H as +1 charged, while D and E as -1 charged. Thus, we computed the net charge of a CDR3 sequence by adding up the individual residue charges.

Usage

```
data("CDR3_Epitopes")
```

Format

A data frame with 4 columns: "individual_id", "condition", "gene_name" and "gene_usage_count". The format of the data is suitible to be used as input in IgGeneUsage

gene_name = net charge group

Source

https://vdjdb.cdr3.net/

Examples

```
data(CDR3_Epitopes)
head(CDR3_Epitopes)
```

DGU *Differential immunoglobulin (Ig) gene usage in immune repertoires*

Description

IgGeneUsage detects differential gene usage (DGU) in immune repertoires that belong to two biological conditions.

Usage

```
DGU(ud,
    mcmc_warmup,
    mcmc_steps,
    mcmc_chains,
    mcmc_cores,
    hdi_lvl,
    adapt_delta,
    max_treedepth,
    paired = FALSE)
```

Arguments

ud	Data.frame with 4 or 5 columns: • 'individual_id' = character, name of the donor (e.g. Pt1) • 'condition' = character, name of biological conditions (e.g. tumor) • 'gene_name' = character, Ig gene name (e.g. IGHV1-69) • 'gene_usage_count' = number, frequency (=usage) of rearrangements from individual_id x condition x gene_name • [optional] 'replicate' = character or number. Replicate id, if more than one repertoire (biological replicates) is available per individual ud can also be be a SummarizedExperiment object. See examplary data 'data(Ig_SE)' for more information.
mcmc_chains, mcmc_warmup, mcmc_steps, mcmc_cores	Number of MCMC chains (default = 4), number of cores to use (default = 1), length of MCMC chains (default = 1,500), length of adaptive part of MCMC chains (default = 500).
hdi_lvl	Highest density interval (HDI) (default = 0.95).
adapt_delta	MCMC setting (default = 0.95).
max_treedepth	MCMC setting (default = 12).
paired	should a paired samples differential Ig gene analaysis be performed (default = FALSE)?

Details

The main input of IgGeneUsage is a table with Ig gene usage frequencies for a set of repertoires that belong to one of two biological condition. For the DGU analysis between two biological conditions, IgGeneUsage employs a Bayesian hierarchical model for zero-inflated beta-binomial (ZIBB) regression (see vignette 'User Manual: IgGeneUsage').

Value

dgu	DGU statistics for each gene: 1) es = effect size on DGU (mean, median standard error (se), standard deviation (sd), L (low boundary of HDI), H (high boundary of HDI); 2) contrast = direction of the effect; 3) pmax = probability of DGU. This summary is only available if the input data contains at least two conditions
gu	gene usage (GU) summary of each gene in each condition
fit	stanfit object
ppc	two types of posterior predictive checks: 1) repertoire- specific, 2) condition-specific
ud	processed gene usage data used for the model

Author(s)

Simo Kitanovski <simo.kitanovski@uni-due.de>

See Also

LOO, Ig, IGHV_Epitopes, IGHV_HCV, Ig_SE, d_zibb_1, d_zibb_2, d_zibb_3

Examples

```
# input data
data(d_zibb_2)
head(d_zibb_2)

# run differential gene usage (DGU)
M <- DGU(ud = d_zibb_2,
         mcmc_warmup = 350,
         mcmc_steps = 1500,
         mcmc_chains = 2,
         mcmc_cores = 1,
         hdi_lvl = 0.95,
         adapt_delta = 0.8,
         max_treedepth = 10,
         paired = FALSE)

# look at M elements
names(M)

# look at DGU results
head(M$dgu)
```

```
# look at posterior predictive checks (PPC)
head(M$ppc)
```

---

d_zibb_1 *Simulated Ig gene usage data*

Description

A small example dataset that has the following features:

- 1 conditions
- 5 individuals (samples)
- 15 Ig genes

This dataset was simulated from zero-inflated beta-binomial (ZIBB) distribution. Simulation code is available in inst/scripts/d_zibb_1.R

Usage

```
data("d_zibb_1", package = "IgGeneUsage")
```

Format

A data frame with 4 columns:

- "individual_id"
- "condition"
- "gene_name"
- "gene_name_count"

This format is accepted by IgGeneUsage.

Source

Simulation code is provided in inst/scripts/d_zibb_1.R

Examples

```
data("d_zibb_1", package = "IgGeneUsage")
head(d_zibb_1)
```

d_zibb_2 *Simulated Ig gene usage data*

Description

A small example dataset that has the following features:

- 1 conditions
- 5 individuals (samples)
- 3 biological replicates per individual
- 15 Ig genes

This dataset was simulated from zero-inflated beta-binomial (ZIBB) distribution. Simulation code is available in inst/scripts/d_zibb_2.R

Usage

```
data("d_zibb_2", package = "IgGeneUsage")
```

Format

A data frame with columns:

- "individual_id"
- "condition"
- "gene_name"
- "replicate"
- "gene_name_count"

This format is accepted by IgGeneUsage.

Source

Simulation code is provided in inst/scripts/d_zibb_2.R

Examples

```
data("d_zibb_2", package = "IgGeneUsage")
head(d_zibb_2)
```

d_zibb_3 *Simulated Ig gene usage data*

Description

A small example dataset that has the following features:

- 3 conditions
- 5 samples per condition
- 8 Ig genes

This dataset was simulated from zero-inflated beta-binomial (ZIBB) distribution. Simulation code is available in inst/scripts/d_zibb_3.R

Usage

```
data("d_zibb_3", package = "IgGeneUsage")
```

Format

A data frame with columns:

- "individual_id"
- "condition"
- "gene_name"
- "gene_name_count"

This format is accepted by IgGeneUsage.

Source

Simulation code is provided in inst/scripts/d_zibb_3.R

Examples

```
data("d_zibb_3", package = "IgGeneUsage")
head(d_zibb_3)
```

d_zibb_4 *Simulated Ig gene usage data*

Description

A small example dataset that has the following features:

- 2 conditions
- 7 individuals per condition
- 4 replicates per individual
- 8 Ig genes

This dataset was simulated from zero-inflated beta-binomial (ZIBB) distribution. Simulation code is available in inst/scripts/d_zibb_4.R

Usage

```
data("d_zibb_4", package = "IgGeneUsage")
```

Format

A data frame with columns:

- "individual_id"
- "condition"
- "gene_name"
- "replicate"
- "gene_name_count"

This format is accepted by IgGeneUsage.

Source

Simulation code is provided in inst/scripts/d_zibb_4.R

Examples

```
data("d_zibb_4", package = "IgGeneUsage")
head(d_zibb_4)
```

d_zibb_5 *Simulated Ig gene usage data*

Description

A small example of paired-sample IRRs with these features:

- 3 conditions
- 6 individuals with one IRRs per condition
- 10 Ig genes

This dataset was simulated from zero-inflated beta-binomial (ZIBB) distribution. Simulation code is available in inst/scripts/d_zibb_5.R

Usage

```
data("d_zibb_5", package = "IgGeneUsage")
```

Format

A data frame with columns:

- "individual_id"
- "condition"
- "gene_name"
- "gene_name_count"

This format is accepted by IgGeneUsage.

Source

Simulation code is provided in inst/scripts/d_zibb_5.R

Examples

```
data("d_zibb_5", package = "IgGeneUsage")
head(d_zibb_5)
```

d_zibb_6 *Simulated Ig gene usage data*

Description

A small example of paired-sample *with replicates* IRRs with these features:

- 3 conditions
- 9 individuals with one IRRs per condition
- 10 Ig genes
- 4 replicates per individual

This dataset was simulated from zero-inflated beta-binomial (ZIBB) distribution. Simulation code is available in inst/scripts/d_zibb_6.R

Usage

```
data("d_zibb_6", package = "IgGeneUsage")
```

Format

A data frame with columns:

- "individual_id"
- "condition"
- "gene_name"
- "replicate"
- "gene_name_count"

This format is accepted by IgGeneUsage.

Source

Simulation code is provided in inst/scripts/d_zibb_6.R

Examples

```
data("d_zibb_6", package = "IgGeneUsage")
head(d_zibb_6)
```

Ig — *IGHV gene family usage in vaccine-challenged B-cell repertoires*

Description

A small example database subset from study evaluating vaccine-induced changes in B-cell populations publicly provided by R-package alakazam (version 0.2.11). It contains IGHV gene family usage, reported in four B-cell populations (samples IgM, IgD, IgG and IgA) across two timepoints (conditions = -1 hour and +7 days).

Usage

```
data("Ig")
```

Format

A data frame with 4 columns: "sample_id", "condition", "gene_name" and "gene_usage_count". The format of the data is suitible to be used as input in IgGeneUsage

Source

R package: alakazam version 0.2.11

References

Laserson U and Vigneault F, et al. High-resolution antibody dynamics of vaccine-induced immune responses. Proc Natl Acad Sci USA. 2014 111:4928-33.

Examples

```
data(Ig)
head(Ig)
```

IGHV_HCV — *IGHV gene usage in HCV+ and healthy individuals*

Description

Publicly available dataset of IGHV segment usage in memory B-cells of 22 HCV+ individuals and 7 healthy donors.

Usage

```
data("IGHV_HCV")
```

Format

A data frame with 4 columns: "individual_id", "condition", "gene_name" and "gene_usage_count". The format of the data is suitible to be used as input in IgGeneUsage

Source

Tucci, Felicia A., et al. "Biased IGH VDJ gene repertoire and clonal expansions in B cells of chronically hepatitis C virus–infected individuals." Blood 131.5 (2018): 546-557.

Examples

```
data(IGHV_HCV)
head(IGHV_HCV)
```

Ig_SE *IGHV gene family usage in vaccine-challenged B-cell repertoires (SummarizedExperiment object)*

Description

A small example database subset from study evaluating vaccine-induced changes in B-cell populations publicly provided by R-package alakazam (version 0.2.11). It contains IGHV gene family usage, reported in four B-cell populations (samples IgM, IgD, IgG and IgA) across two timepoints (conditions = -1 hour and +7 days).

Usage

```
data("Ig_SE")
```

Format

A SummarizedExperiment object with 1) assay data (rows = gene name, columns = repertoires) and 2) column data.frame in which the sample names and the corresponding biological condition labels are noted.

Source

R package: alakazam version 0.2.11

References

Laserson U and Vigneault F, et al. High-resolution antibody dynamics of vaccine-induced immune responses. Proc Natl Acad Sci USA. 2014 111:4928-33.

Examples

```
# inspect the data
data(Ig_SE)

# repertoire information: must have the two columns: 'condition' and
'individual_id'

SummarizedExperiment::colData(Ig_SE)

# assay counts (gene frequency usage)
SummarizedExperiment::assay(x = Ig_SE)
```

LOO *Leave-one-out analysis for quantitative evaluation of the probability of DGU*

Description

IgGeneUsage detects differential gene usage (DGU) in immune repertoires that belong to two biological conditions.

To quantify the robustness of the estimated probability of DGU (pmax), IgGeneUsage has a built-in procedure for a fully Bayesian leave-one-out (LOO) analysis. In each LOO step we discard the data of one of the repertoires, and use the remaining data to analyze for DGU with IgGeneUsage. In each step we record pmax for all genes. Finally, we evaluate the variability of pmax for a given across the different LOO steps. Low variability in pmax: robust DGU; high variability: unrobust DGU.

For datasets that include many repertoires (e.g. 100) LOO can be computationally costly.

Usage

```
LOO(ud,
    mcmc_warmup,
    mcmc_steps,
    mcmc_chains,
    mcmc_cores,
    hdi_lvl,
    adapt_delta,
    max_treedepth,
    paired = FALSE)
```

Arguments

ud	Data.frame with 4 columns: • 'individual_id' = character, name of the donor (e.g. Pt1) • 'condition' = character, name of biological conditions (e.g. tumor) • 'gene_name' = character, Ig gene name (e.g. IGHV1-69)

- 'gene_usage_count' = number, frequency (=usage) of rearrangements from individual_id x condition x gene_name
- [optional] 'replicate' = character or number. Replicate id, if more than one repertoire (biological replicates) is available per individual

ud can also be be a SummarizedExperiment object. See dataset 'data(Ig_SE)' for more information.

`mcmc_chains`, `mcmc_warmup`, `mcmc_steps`, `mcmc_cores`
: Number of MCMC chains (default = 4), number of cores to use (default = 1), length of MCMC chains (default = 1,500), length of adaptive part of MCMC chains (default = 500).

`hdi_lvl`
: Highest density interval (HDI) (default = 0.95).

`adapt_delta`
: MCMC setting (default = 0.95).

`max_treedepth`
: MCMC setting (default = 12).

`paired`
: should a paired samples differential Ig gene analaysis be performed (default = FALSE)?

Details

IgGeneUsage invokes the function DGU in each LOO step. For more details see help for DGU or vignette 'User Manual: IgGeneUsage'.

Value

`loo`
: DGU statistics for each Ig gene for specific LOO step:

- es = effect size statistics: mean, median, standard error (se), standard deviation (sd), L/H (low/high boundary of HDI)
- contrast = direction of the effect
- pmax = DGU probability
- loo_id (LOO step)
- Neff (effective sample size), Rhat (potential scale reduction factor)

Author(s)

Simo Kitanovski <simo.kitanovski@uni-due.de>

See Also

DGU, Ig, IGHV_Epitopes, IGHV_HCV, Ig_SE, d_zibb_1, d_zibb_2, d_zibb_3

Examples

```
# input data:
data("Ig", package = "IgGeneUsage")
head(Ig)

# run leave-one-out (LOO)
L <- LOO(ud = Ig,
```

```
            mcmc_warmup = 500,
            mcmc_steps = 2000,
            mcmc_chains = 3,
            mcmc_cores = 1,
            hdi_lvl = 0.95,
            adapt_delta = 0.99,
            max_treedepth = 10,
            paired = FALSE)

    # how many LOOs?
    names(L)

    # elements in first LOO, see vignette about how to extract results
    names(L[[1]])
```

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