

Package ‘clonotypeR’

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Type Package

Title High throughput analysis of T cell antigen receptor sequences

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Description High throughput analysis of T cell antigen receptor sequences

The genes encoding T cell receptors are created by somatic recombination, generating an immense combination of V, (D) and J segments. Additional processes during the recombination create extra sequence diversity between the V and J segments. Collectively, this hyper-variable region is called the CDR3 loop.

The purpose of this package is to process and quantitatively analyse millions of V-CDR3-J combination, called clonotypes, from multiple sequence libraries.

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Imports methods

Suggests BiocGenerics, edgeR, knitr, pvclust, RUnit, vegan

VignetteBuilder knitr

biocViews Sequencing

BugReports <http://clonotyper.branchable.com/Bugs/>

NeedsCompilation no

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clonotype_table	<i>Create a table count of clonotypes or other features.</i>
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Description

Using a clonotype data frame loaded with [read_clonotypes](#), `clonotype_table` will create a table counting how many times each clonotypes have been seen in each libraries. By default, the unproductive rearrangements are filtered out.

Usage

```
clonotype_table(libs, feats=c("V","pep","J"), data, filter=(data$unproductive | data$ambiguous), minscore, minqual, sample)
```

Arguments

<code>libs</code>	A character vector containing the name of one or many libraries. Same names must not appear twice. If no library names are provided, all the libraries present in the clonotypes data frame will be used.
<code>feats</code>	What to count. By default, it counts clonotypes, defined as <code>c("V", "pep", "J")</code> . But it can also count single features, such as the V or J segments.
<code>data</code>	Data frame as loaded by read_clonotypes .
<code>filter</code>	Logical vector to filter out clonotypes. By default it relies on the clonotypes data frame to provide a “unproductive” column that indicates clonotypes with a stop codon or a frame shift, and a “ambiguous” column that indicates clonotypes where the DNA sequences has ambiguous (“N”) nucleotides.
<code>minscore</code>	Minimum alignment score. Clonotypes with an alignment score lower than this value are discarded.
<code>minqual</code>	Minimum mapping quality. Clonotypes with a mapping quality lower than this value are discarded.
<code>sample</code>	Indicate the number of clonotypes to randomly sample from the library (no replacement). Default: no subsampling.

Value

`clonotype_table` returns a data frame, where row names are features (clonotypes, segment names, ...), column names are libraries, and values are number of times each feature was found in each library.

Author(s)

Charles Plessy

See Also

[read_clonotypes](#)

Examples

```
# Read the package's example data
clonotypes <- read_clonotypes(system.file('extdata', 'clonotypes.txt.gz', package = "clonotypeR"))

# Inspect the alignment scores
hist(clonotypes$score)

# Count J segments
j <- clonotype_table(levels(clonotypes$lib), "J", data=clonotypes)

# Normalise counts in parts per million
J <- data.frame(prop.table(as.matrix(j),2) * 1000000)
```

common_clonotypes *Reports clonotypes common between libraries.*

Description

When given one group of libraries, lists the clonotypes that have been observed at least in one library of that group. The returned list can be used to subset a data frame produced by [clonotype_table](#).

When given two groups of libraries, lists the clonotypes that have been observed at least in one library of each group. Groups can contain a single library, in which case the returned list is simply the clonotypes found in both libraries.

When given a table of clonotypes, produces a matrix in which each cell reports quantitatively the overlap between each pair of libraries.

Usage

```
common_clonotypes(group1, group2, mode, data)
```

Arguments

group1	A character vector containing clonotype library names.
group2	A character vector containing clonotype library names.
mode	Only when producing a matrix of pairwise comparisons: “count” (default) or “abundance”, see below.
data	A clonotype table where the data is stored.

Value

In “count” mode, each value in a matrix is the number of clonotypes seen in both of the two libraries considered. The matrix is therefore symmetric.

In “abundance” mode, each value indicates, for a given pair of libraries, the cumulative abundance of the common clonotypes (seen in both libraries), calculated for the library indicated by the row. The matrix is therefore not symmetric. For instance, a pair of libraries A and B can have 100 sequences each in total, one clonotype in common, which is found 8 times in A, but 54 times in B.

Author(s)

Charles Plessey

See Also

[clonotype_table](#), [unique_clonotypes](#)

Examples

```
# Load example data
clonotypes.long <- read_clonotypes(system.file('extdata', 'clonotypes.txt.gz', package = "clonotypeR"))
clonotypes <- clonotype_table(levels(clonotypes.long$lib), data=clonotypes.long)
summary(clonotypes)

# List clonotypes found in library A, and B or C.
common_clonotypes(group1="A", group2=c("B","C"), data=clonotypes)

# Count clonotypes found in library A, and B or C.
length(common_clonotypes(group1="A", group2=c("B","C"), data=clonotypes))

# Matrix of numbers of common clonotypes
common_clonotypes(data=clonotypes)

# Matrix of abundance of common clonotypes
common_clonotypes(data=clonotypes, mode="abundance")
```

extdata

Extra data used to calculate ID numbers in Yassai et al.'s nomenclature.

Description

Data frame derived from Table 1 of Yassai et al., 2009, to construct clonotype names.

Details

V_after_C: sequence of the V segments after their conserved cystein.

J_before_FGxG: sequence of the J segments before their conserved FGxG motif.

codon_ids: data frame derived from Table 1 of Yassai et al., 2009, to construct clonotype names.

The V_after_C and J_before_FGxG tables are, generated from the mouse reference data with the command: `make refresh-data` in the source repository of clonotypeR.

Value

codon_ids:

codon Nucleotide triplet.
aminoacid Single-letter amino acid abbreviation (“O” for stop).
id ID numbers assigned to the codons for each amino acids.

J_before_FGxG:

row name J segment name, for instance “TRAJ61”.
sequence Sequence of the nucleic acids preceding the first codon of the conserved FGxG motif.

V_after_C:

row name V segment name, for instance “TRAV1”.
sequence Sequence of the nucleic acids following the codon of the conserved cysteine.

References

A clonotype nomenclature for T cell receptors. Maryam B. Yassai, Yuri N. Naumov, Elena N. Naumova and Jack Gorski Immunogenetics, 2009, Volume 61, Number 7, Pages 493-502

See Also

[yassai_identifier](#)

Examples

```
V_after_C <- read.table(system.file('extdata', 'V_after_C.txt.gz', package = "clonotypeR"), stringsAsFactors=FALSE)
J_before_FGxG <- read.table(system.file('extdata', 'J_before_FGxG.txt.gz', package = "clonotypeR"), stringsAsFactors=FALSE)
codon_ids <- read.table(system.file('extdata', 'codon_ids.txt.gz', package = "clonotypeR"), header=TRUE, row.names=1)
```

is_unproductive *Determines if clonotype sequences are productive.*

Description

ClonotypeR identifies V and J segments, isolates the DNA sequence between the conserved cysteine and the FGxG motifs, and translates it. This function verifies that this sequence is in frame and has no stop codon.

Usage

```
is_unproductive(data)
```

Arguments

`data` Data frame of clonotype sequences, or character vector describing a single clonotype, where the DNA sequence is available under the name “dna” and its translation available under the name “pep”.

Details

Clonotypes are marked unproductive if the length of their DNA sequence is not a multiple of 3, or if they contain a stop codon, as indicated by an asterisk in the translated sequence.

Value

Returns a logical vector, with one value per row in the original data.

Author(s)

Charles Plessy

See Also

[read_clonotypes](#)

Examples

```
clonotypes <- read_clonotypes(system.file('extdata', 'clonotypes.txt.gz', package = "clonotypeR"))
is_unproductive(clonotypes)
```

`private_clonotypes` *private_clonotypes*

Description

List clonotypes found exclusively in one library.

Usage

```
private_clonotypes(..., data)
```

Arguments

`...` Library names.
`data` A clonotype table.

Value

A vector of clonotype names.

See Also[clonotype_table](#)**Examples**

```
clonotypes <- read_clonotypes(system.file('extdata', 'clonotypes.txt.gz', package = "clonotypeR"))
clonotypes <- clonotype_table(levels(clonotypes$lib), data=clonotypes)
private_clonotypes("C", data=clonotypes)
```

read_clonotypes	<i>Reads a clonotype_table and returns a data frame.</i>
-----------------	--

Description

Reads a clonotype_table in a TAB-separated or OSCT format, and returns a data frame that has eight columns, for library name, V and J segments names, sequence read identifier, DNA, sequence quality, aminoacid sequence of the CDR3 region, mark for unproductive recombinations, and mark for ambiguous sequences.

Usage

```
read_clonotypes(filename, scores=TRUE, ...)
```

Arguments

filename	Path to the tabulation-delimited text file containing the extracted clonotypes.
scores	Set to false to load legacy data that did not contain “score” and “mapq” columns.
...	The rest of the arguments are passed to the read.table() function.

Value

lib	Library name (factor).
V	V segment name (factor).
J	J segment name (factor).
score	Alignment score (numeric).
mapq	Mapping quality (numeric). A sequence with a good alignment score will still have a low mapping quality if there are good alternative alignments to other V segments.
read	Sequence read identifier (character).
dna	DNA sequence of the CDR3 region (character).
qual	Quality values for the DNA sequence (character).
pep	Translation of the DNA sequence (character).
unproductive	Flag indicating stop codons or frame shifts (logical).
ambiguous	Flag indicating that the DNA sequences has ambiguous (“N”) nucleotides (logical).

Author(s)

Charles Plessy

See Also

[clonotype_table](#), [is_unproductive](#), [read.table](#), Order Switchable Column Table (OSCT, <http://sourceforge.net/projects/osctf/>)

Examples

```
clonotypes <- read_clonotypes(system.file('extdata', 'clonotypes.txt.gz', package = "clonotypeR"))
```

unique_clonotypes	<i>Lists unique clonotypes in libraries.</i>
-------------------	--

Description

Finds all the clonotypes expressed in one or more libraries, and returns a vector where they are listed once. This vector can be used to subset a `clonotype_table`.

Usage

```
unique_clonotypes(..., data)
```

Arguments

...	One or more character vectors contain clonotype library names
data	The name of the <code>clonotype_table</code> where the data is stored.

Value

Character vector of clonotype names. Their order follows the original row name order of the `clonotype_table`.

Author(s)

Charles Plessy

See Also

[clonotype_table](#), [common_clonotypes](#)

Examples

```
# Load example data
clonotypes.long <- read_clonotypes(system.file('extdata', 'clonotypes.txt.gz', package = "clonotypeR"))
clonotypes <- clonotype_table(levels(clonotypes.long$lib), data=clonotypes.long)
summary(clonotypes)

# List clonotypes found in library A.
unique_clonotypes("A", data=clonotypes)

# List clonotypes found in library A or B.
unique_clonotypes("A","B", data=clonotypes)
```

yassai_identifier *TCR clonotype identifier (Yassai et al.).*

Description

The clonotype nomenclature defined by Yassai et al. in <http://dx.doi.org/10.1007/s00251-009-0383-x>.

Usage

```
yassai_identifier(data, V_after_C, J_before_FGxG, long=FALSE)
```

Arguments

data	A data frame or a character vector containing a clonotype(s) with proper row or element names.
V_after_C	(optional) A data frame indicating the aminoacids following the conserved cystein for each V segment.
J_before_FGxG	(optional) A data frame indicating the aminoacids preceding the conserved FGxG motif for each V segment.
long	(optional) Avoids identifier collisions by displaying the codons, and indicating the position of the V–J junction in ambiguous cases.

Details

By default, `yassai_identifier()` assume mouse sequences and will load the `V_after_C` and `J_before_FGxG` tables distributed in this package. It is possible to provide alternative tables either by passing them directly as argument, or by installing them as `“./inst/extdata/V_after_C.txt.gz”` and `“./inst/extdata/J_before_FGxG.txt.gz”`.

Some clonotypes have a different DNA sequence but the same identifier following the original nomenclature (see below for examples). The ‘long’ mode was created to avoid these collisions. First, it displays all codons, instead of only the non-templated ones and their immediate neighbors. Second, for the clonotypes where all codons are identical to the V or J germline sequence, it indicates the position of the V–J junction in place of the codon IDs.

Value

The name (for instance sIRSSy.1456B19S1B27L11) consists of five segments:

1. CDR3 amino acid identifier (ex. sIRSSy), followed by a dot ;
2. CDR3 nucleotide sequence identifier (ex. 1456) ;
3. variable (V) segment identifier (ex. BV19S1) ;
4. joining (J) segment identifier (ex. BJ2S7) ;
5. CDR3 length identifier (ex. L11).

Author(s)

Charles Plessy

See Also

[codon_ids](#), [J_before_FGxG](#), [V_after_C](#)

Examples

```
clonotypes <- read_clonotypes(system.file('extdata', 'clonotypes.txt.gz', package = "clonotypeR"))
head(yassai_identifier(clonotypes))
```

```
# The following two clonotypes have a the same identifier, and are
# disambiguated by using the long mode
```

```
yassai_identifier(c(V="TRAV14-1", J="TRAJ43", dna="GCAGCTAATAACAACAATGCCCCACGA", pep="AANNNNAPR"))
# [1] "aAn.1A14-1A43L9"
```

```
yassai_identifier(c(V="TRAV14-1", J="TRAJ43", dna="GCAGCAGCTAACAACAATGCCCCACGA", pep="AAANNNAPR"))
# [1] "aAn.1A14-1A43L9"
```

```
yassai_identifier(c(V="TRAV14-1", J="TRAJ43", dna="GCAGCTAATAACAACAATGCCCCACGA", pep="AANNNNAPR"), long=TRUE)
# [1] "aAnnnapr.1A14-1A43L9"
```

```
yassai_identifier(c(V="TRAV14-1", J="TRAJ43", dna="GCAGCAGCTAACAACAATGCCCCACGA", pep="AAANNNAPR"), long=TRUE)
# [1] "aaAnnnapr.1A14-1A43L9"
```

```
# The following two clonotypes would have the same identifier in long mode
# if the position of the V-J junction would not be indicated in place of the
# codon IDs.
```

```
yassai_identifier(c(V="TRAV14N-1", J="TRAJ56", dna="GCAGCTACTGGAGGCAATAATAAGCTGACT", pep="AATGGNNKLT"), long=TRUE)
# [1] "aatggnnklt.1A14N1A56L10"
```

```
yassai_identifier(c(V="TRAV14N-1", J="TRAJ56", dna="GCAGCACTGGAGGCAATAATAAGCTGACT", pep="AATGGNNKLT"), long=TRUE)
# [1] "aatggnnklt.2A14N1A56L10"
```

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