Package ‘scoper’

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Description Provides a computational framework for identification of B cell clones from Adaptive Immune Receptor Repertoire sequencing (AIRR-Seq) data. Three main functions are included (identicalClones, hierarchicalClones, and spectralClones) that perform clustering among sequences of BCRs/IGs (B cell receptors/immunoglobulins) which share the same V gene, J gene and junction length.
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ExampleDb

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ExampleDb  Example database

Description

A small example database subset from Laserson and Vigneault et al, 2014.

Usage

ExampleDb

Format

A data.frame with the following columns:

• sequence_id: Sequence identifier
• sequence_alignment: IMGT-gapped observed sequence.
• germline_alignment: IMGT-gapped germline sequence.
• germline_alignment_d_mask: IMGT-gapped germline sequence with N, P and D regions
  masked.
• v_call: V region allele assignments.
• v_call_genotyped: TIgGER corrected V region allele assignment.
• d_call: D region allele assignments.
• j_call: J region allele assignments.
• junction: Junction region sequence.
• junction_length: Length of the junction region in nucleotides.
hierarchicalClones  

### References


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**hierarchicalClones**  
*Hierarchical clustering method for clonal partitioning*

**Description**

hierarchicalClones provides a hierarchical agglomerative clustering approach to infer clonal relationships in high-throughput Adaptive Immune Receptor Repertoire sequencing (AIRR-seq) data. This approach clusters B or T cell receptor sequences based on junction region sequence similarity within partitions that share the same V gene, J gene, and junction length, allowing for ambiguous V or J gene annotations.

**Usage**

```r
hierarchicalClones(
  db,
  threshold,
  method = c("nt", "aa"),
  linkage = c("single", "average", "complete"),
  normalize = c("len", "none"),
  junction = "junction",
  v_call = "v_call",
  j_call = "j_call",
  clone = "clone_id",
  fields = NULL,
  cell_id = NULL,
  locus = "locus",
  only_heavy = TRUE,
  split_light = TRUE,
  first = FALSE,
  cdr3 = FALSE,
  mod3 = FALSE,
  max_n = 0,
  nproc = 1,
  verbose = FALSE,
  log = NULL,
  summarize_clones = TRUE
)
```

**Arguments**

- `db`  
  data.frame containing sequence data.
- `threshold`  
  numeric scalar where the tree should be cut (the distance threshold for clonal grouping).
method one of the "nt" for nucleotide based clustering or "aa" for amino acid based clustering.

linkage available linkage are "single", "average", and "complete".

normalize method of normalization. The default is "len", which divides the distance by the length of the sequence group. If "none" then no normalization if performed.

junction character name of the column containing junction sequences. Also used to determine sequence length for grouping.

v_call name of the column containing the V-segment allele calls.

j_call name of the column containing the J-segment allele calls.

clone output column name containing the clonal cluster identifiers.

fields character vector of additional columns to use for grouping. Sequences with disjoint values in the specified fields will be classified as separate clones.

cell_id name of the column containing cell identifiers or barcodes. If specified, grouping will be performed in single-cell mode with the behavior governed by the locus and only_heavy arguments. If set to NULL then the bulk sequencing data is assumed.

locus name of the column containing locus information. Only applicable to single-cell data. Ignored if cell_id=NULL.

only_heavy use only the IGH (BCR) or TRB/TRD (TCR) sequences for grouping. Only applicable to single-cell data. Ignored if cell_id=NULL.

split_light split clones by light chains. Ignored if cell_id=NULL.

first specifies how to handle multiple V(D)J assignments for initial grouping. If TRUE only the first call of the gene assignments is used. If FALSE the union of ambiguous gene assignments is used to group all sequences with any overlapping gene calls.

cdr3 if TRUE removes 3 nucleotides from both ends of "junction" prior to clustering (converts IMGT junction to CDR3 region). If TRUE this will also remove records with a junction length less than 7 nucleotides.

mod3 if TRUE removes records with a junction length that is not divisible by 3 in nucleotide space.

max_n The maximum number of degenerate characters to permit in the junction sequence before excluding the record from clonal assignment. Note, with linkage="single" non-informative positions can create artifactual links between unrelated sequences. Use with caution. Default is set to be zero. Set it as "NULL" for no action.

nproc number of cores to distribute the function over.

verbose if TRUE prints out a summary of each step cloning process. if FALSE (default) process cloning silently.

log output path and filename to save the verbose log. The input file directory is used if path is not specified. The default is NULL for no action.

summarize_clones if TRUE performs a series of analysis to assess the clonal landscape and returns a ScoperClones object. If FALSE then a modified input db is returned. When grouping by fields, summarize_clones should be FALSE.
identicalClones

Value

If summarize_clones=TRUE (default) a ScoperClones object is returned that includes the clonal assignment summary information and a modified input db in the db slot that contains clonal identifiers in the specified clone column. If summarize_clones=FALSE modified data.frame is returned with clone identifiers in the specified clone column.

Single-cell data

To invoke single-cell mode the cell_id argument must be specified and the locus column must be correct. Otherwise, clustering will be performed with bulk sequencing assumptions, using all input sequences regardless of the values in the locus column.

Values in the locus column must be one of c("IGH", "IGI", "IGK", "IGL") for BCR or c("TRA", "TRB", "TRD", "TRG") for TCR sequences. Otherwise, the operation will exit and return an error message.

Under single-cell mode with paired-chain sequences, there is a choice of whether grouping should be done by (a) using IGH (BCR) or TRB/TRD (TCR) sequences only or (b) using IGH plus IGK/IGL (BCR) or TRB/TRD plus TRA/TRG (TCR) sequences. This is governed by the only_heavy argument. There is also choice as to whether inferred clones should be split by the light/short chain (IGK, IGL, TRA, TRG) following heavy/long chain clustering, which is governed by the split_light argument.

In single-cell mode, clonal clustering will not be performed on data where cells are assigned multiple heavy/long chain sequences (IGH, TRB, TRD). If observed, the operation will exit and return an error message. Cells that lack a heavy/long chain sequence (i.e., cells with light/short chains only) will be assigned a clone_id of NA.

See Also

See plotCloneSummary for plotting summary results. See groupGenes for more details about grouping requirements.

Examples

# Find clonal groups
results <- hierarchicalClones(ExampleDb, threshold=0.15)

# Retrieve modified input data with clonal clustering identifiers
df <- as.data.frame(results)

# Plot clonal summaries
plot(results, binwidth=0.02)
Description

identicalClones provides a simple sequence identity based partitioning approach for inferring clonal relationships in high-throughput Adaptive Immune Receptor Repertoire sequencing (AIRR-seq) data. This approach partitions B or T cell receptor sequences into clonal groups based on junction region sequence identity within partitions that share the same V gene, J gene, and junction length, allowing for ambiguous V or J gene annotations.

Usage

```r
identicalClones(
  db,
  method = c("nt", "aa"),
  junction = "junction",
  v_call = "v_call",
  j_call = "j_call",
  clone = "clone_id",
  fields = NULL,
  cell_id = NULL,
  locus = "locus",
  only_heavy = TRUE,
  split_light = TRUE,
  first = FALSE,
  cdr3 = FALSE,
  mod3 = FALSE,
  max_n = 0,
  nproc = 1,
  verbose = FALSE,
  log = NULL,
  summarize_clones = TRUE
)
```

Arguments

- **db**
  - data.frame containing sequence data.
- **method**
  - one of the "nt" for nucleotide based clustering or "aa" for amino acid based clustering.
- **junction**
  - character name of the column containing junction sequences. Also used to determine sequence length for grouping.
- **v_call**
  - name of the column containing the V-segment allele calls.
- **j_call**
  - name of the column containing the J-segment allele calls.
- **clone**
  - output column name containing the clonal cluster identifiers.
- **fields**
  - character vector of additional columns to use for grouping. Sequences with disjoint values in the specified fields will be classified as separate clones.
- **cell_id**
  - name of the column containing cell identifiers or barcodes. If specified, grouping will be performed in single-cell mode with the behavior governed by the **locus** and **only_heavy** arguments. If set to **NULL** then the bulk sequencing data is assumed.
identicalClones

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>locus</td>
<td>name of the column containing locus information. Only applicable to single-cell data. Ignored if cell_id=NULL.</td>
</tr>
<tr>
<td>only_heavy</td>
<td>use only the IGH (BCR) or TRB/TRD (TCR) sequences for grouping. Only applicable to single-cell data. Ignored if cell_id=NULL.</td>
</tr>
<tr>
<td>split_light</td>
<td>split clones by light chains. Ignored if cell_id=NULL.</td>
</tr>
<tr>
<td>first</td>
<td>specifies how to handle multiple V(D)J assignments for initial grouping. If TRUE only the first call of the gene assignments is used. If FALSE the union of ambiguous gene assignments is used to group all sequences with any overlapping gene calls.</td>
</tr>
<tr>
<td>cdr3</td>
<td>if TRUE removes 3 nucleotides from both ends of &quot;junction&quot; prior to clustering (converts IMGT junction to CDR3 region). If TRUE this will also remove records with a junction length less than 7 nucleotides.</td>
</tr>
<tr>
<td>mod3</td>
<td>if TRUE removes records with a junction length that is not divisible by 3 in nucleotide space.</td>
</tr>
<tr>
<td>max_n</td>
<td>The maximum number of degenerate characters to permit in the junction sequence before excluding the record from clonal assignment. Default is set to be zero. Set it as &quot;NULL&quot; for no action.</td>
</tr>
<tr>
<td>nproc</td>
<td>number of cores to distribute the function over.</td>
</tr>
<tr>
<td>verbose</td>
<td>if TRUE prints out a summary of each step cloning process. If FALSE (default) process cloning silently.</td>
</tr>
<tr>
<td>log</td>
<td>output path and filename to save the verbose log. The input file directory is used if path is not specified. The default is NULL for no action.</td>
</tr>
<tr>
<td>summarize_clones</td>
<td>if TRUE performs a series of analysis to assess the clonal landscape and returns a ScoperClones object. If FALSE then a modified input db is returned. When grouping by fields, summarize_clones should be FALSE.</td>
</tr>
</tbody>
</table>

**Value**

If summarize_clones=TRUE (default) a ScoperClones object is returned that includes the clonal assignment summary information and a modified input db in the db slot that contains clonal identifiers in the specified clone column. If summarize_clones=FALSE modified data.frame is returned with clone identifiers in the specified clone column.

**Single-cell data**

To invoke single-cell mode the cell_id argument must be specified and the locus column must be correct. Otherwise, clustering will be performed with bulk sequencing assumptions, using all input sequences regardless of the values in the locus column.

Values in the locus column must be one of c("IGH", "IGI", "IGK", "IGL") for BCR or c("TRA", "TRB", "TRD", "TRG") for TCR sequences. Otherwise, the operation will exit and return an error message.

Under single-cell mode with paired-chain sequences, there is a choice of whether grouping should be done by (a) using IGH (BCR) or TRB/TRD (TCR) sequences only or (b) using IGH plus IGK/IGL (BCR) or TRB/TRD plus TRA/TRG (TCR) sequences. This is governed by the only_heavy argument. There is also choice as to whether inferred clones should be split by the light/short
chain (IGK, IGL, TRA, TRG) following heavy/long chain clustering, which is governed by the split_light argument.

In single-cell mode, clonal clustering will not be performed on data where cells are assigned multiple heavy/long chain sequences (IGH, TRB, TRD). If observed, the operation will exit and return an error message. Cells that lack a heavy/long chain sequence (i.e., cells with light/short chains only) will be assigned a clone_id of NA.

See Also

See plotCloneSummary for plotting summary results. See groupGenes for more details about grouping requirements.

Examples

# Find clonal groups
results <- identicalClones(ExampleDb)

# Retrieve modified input data with clonal clustering identifiers
df <- as.data.frame(results)

# Plot clonal summaries
plot(results, binwidth=0.02)

plotCloneSummary  Plot clonal clustering summary

Description

plotCloneSummary plots the results in a ScoperClones object returned by spectralClones, identicalClones or hierarchicalClones. Includes the minimum inter (between) and maximum intra (within) clonal distances and the calculated effective threshold.

Usage

plotCloneSummary(
  data,
  xmin = NULL,
  xmax = NULL,
  breaks = NULL,
  binwidth = NULL,
  title = NULL,
  size = 0.75,
  silent = FALSE,
  ...
**Arguments**

- **data**: `ScoperClones` object output by the `spectralClones`, `identicalClones` or `hierarchicalClones`.
- **xmin**: minimum limit for plotting the x-axis. If `NULL` the limit will be set automatically.
- **xmax**: maximum limit for plotting the x-axis. If `NULL` the limit will be set automatically.
- **breaks**: number of breaks to show on the x-axis. If `NULL` the breaks will be set automatically.
- **binwidth**: binwidth for the histogram. If `NULL` the binwidth will be set automatically.
- **title**: string defining the plot title.
- **size**: numeric value for lines in the plot.
- **silent**: if `TRUE` do not draw the plot and just return the `ggplot2` object; if `FALSE` draw the plot.
- **...**: additional arguments to pass to `ggplot2::theme`.

**Value**

A `ggplot` object defining the plot.

**See Also**

See `ScoperClones` for the input object definition. See `spectralClones`, `identicalClones` and `hierarchicalClones` for generating the input object.

**Examples**

```r
# Find clones
results <- hierarchicalClones(ExampleDb, threshold=0.15)

# Plot clonal summaries
plot(results, binwidth=0.02)
```

**Description**

`scoper` is a member of the Immcantation framework and provides computational approaches for the identification of B cell clones from adaptive immune receptor repertoire sequencing (AIRR-Seq) datasets. It includes methods for assigning clonal identifiers using sequence identity, hierarchical clustering, and spectral clustering.
Clonal clustering

- **identicalClones**: Clonal assignment using sequence identity partitioning.
- **hierarchicalClones**: Hierarchical clustering approach to clonal assignment.
- **spectralClones**: Spectral clustering approach to clonal assignment.

Visualization

- **plotCloneSummary**: Visualize inter- and intra-clone distances.

References


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**ScoperClones-class**  
*S4 class containing clonal assignments and summary data*

**Description**

ScoperClones stores output from **identicalClones**, **hierarchicalClones** and **spectralClones** functions.

**Usage**

```r
## S4 method for signature 'ScoperClones'
print(x)

## S4 method for signature 'ScoperClones'
summary(object)

## S4 method for signature 'ScoperClones,missing'
plot(x, y, ...)

## S4 method for signature 'ScoperClones'
as.data.frame(x)
```

**Arguments**

- `x`  
  ScoperClones object
- `object`  
  ScoperClones object
- `y`  
  Ignored.
- `...`  
  Arguments to pass to `plotCloneSummary`. 
**Slots**

- `db` data.frame of repertoire data including with clonal identifiers in the column specified during processing.
- `vjl_groups` data.frame of clonal summary, including sequence count, V gene, J gene, junction length, and clone counts.
- `inter_intra` data.frame containing minimum inter (between) and maximum intra (within) clonal distances.
- `eff_threshold` effective cut-off separating the inter (between) and intra (within) clonal distances.

**See Also**

- `identicalClones`, `hierarchicalClones` and `spectralClones`
threshold = NULL,
base_sim = 0.95,
iter_max = 1000,
nstart = 1000,
nproc = 1,
verbose = FALSE,
log = NULL,
summarize_clones = TRUE
)

Arguments

db data.frame containing sequence data.
method one of the "novj" or "vj". See Details for description.
germline character name of the column containing the germline or reference sequence.
sequence character name of the column containing input sequences.
junction character name of the column containing junction sequences. Also used to determine sequence length for grouping.
v_call name of the column containing the V-segment allele calls.
jcall name of the column containing the J-segment allele calls.
clone output column name containing the clonal cluster identifiers.
fields character vector of additional columns to use for grouping. Sequences with disjoint values in the specified fields will be classified as separate clones.
cell_id name of the column containing cell identifiers or barcodes. If specified, grouping will be performed in single-cell mode with the behavior governed by the locus and only_heavy arguments. If set to NULL then the bulk sequencing data is assumed.
locus name of the column containing locus information. Only applicable to single-cell data. Ignored if cell_id=NULL.
only_heavy use only the IGH (BCR) or TRB/TRD (TCR) sequences for grouping. Only applicable to single-cell data. Ignored if cell_id=NULL.
split_light split clones by light chains. Ignored if cell_id=NULL.
targeting_model TargetingModel object. Only applicable if method="vj". See Details for description.
len_limit IMGT_V object defining the regions and boundaries of the Ig sequences. If NULL, mutations are counted for entire sequence. Only applicable if method = "vj".
first specifies how to handle multiple V(D)J assignments for initial grouping. If TRUE only the first call of the gene assignments is used. If FALSE the union of ambiguous gene assignments is used to group all sequences with any overlapping gene calls.
cdr3 if TRUE removes 3 nucleotides from both ends of "junction" prior to clustering (converts IMGT junction to CDR3 region). If TRUE this will also remove records with a junction length less than 7 nucleotides.
spectralClones

mod3 if TRUE removes records with a junction length that is not divisible by 3 in nucleotide space.

max_n the maximum number of degenerate characters to permit in the junction sequence before excluding the record from clonal assignment. Default is set to be zero. Set it as "NULL" for no action.

threshold the supervising cut-off to enforce an upper-limit distance for clonal grouping. A numeric value between (0,1).

base_sim required similarity cut-off for sequences in equal distances from each other.

iter_max the maximum number of iterations allowed for kmean clustering step.

nstart the number of random sets chosen for kmean clustering initialization.

nproc number of cores to distribute the function over.

verbose if TRUE prints out a summary of each step cloning process. if FALSE (default) process cloning silently.

log output path and filename to save the verbose log. The input file directory is used if path is not specified. The default is NULL for no action.

summarize_clones if TRUE performs a series of analysis to assess the clonal landscape and returns a ScoperClones object. If FALSE then a modified input db is returned. When grouping by fields, summarize_clones should be FALSE.

Details

If method="novj", then clonal relationships are inferred using an adaptive threshold that indicates the level of similarity among junction sequences in a local neighborhood.

If method="vj", then clonal relationships are inferred not only on junction region homology, but also taking into account the mutation profiles in the V and J segments. Mutation counts are determined by comparing the input sequences (in the column specified by sequence) to the effective germline sequence (IUPAC representation of sequences in the column specified by germline).

While not mandatory, the influence of SHM hot-cold-spot biases in the clonal inference process will be noted if a SHM targeting model is provided through the targeting_model argument. See TargetingModel for more technical details.

If the threshold argument is specified, then an upper limit for clonal grouping will be imposed to prevent sequences with dissimilarity above the threshold from grouping together. Any sequence with a distance greater than the threshold value from the other sequences, will be assigned to a singleton group.

Value

If summarize_clones=TRUE (default) a ScoperClones object is returned that includes the clonal assignment summary information and a modified input db in the db slot that contains clonal identifiers in the specified clone column. If summarize_clones=FALSE modified data.frame is returned with clone identifiers in the specified clone column.
Single-cell data

To invoke single-cell mode the `cell_id` argument must be specified and the `locus` column must be correct. Otherwise, clustering will be performed with bulk sequencing assumptions, using all input sequences regardless of the values in the `locus` column.

Values in the `locus` column must be one of `c("IGH", "IGI", "IGK", "IGL")` for BCR or `c("TRA", "TRB", "TRD", "TRG")` for TCR sequences. Otherwise, the operation will exit and return an error message.

Under single-cell mode with paired-chain sequences, there is a choice of whether grouping should be done by (a) using IGH (BCR) or TRB/TRD (TCR) sequences only or (b) using IGH plus IGK/IGL (BCR) or TRB/TRD plus TRA/TRG (TCR) sequences. This is governed by the `only_heavy` argument. There is also choice as to whether inferred clones should be split by the light/short chain (IGK, IGL, TRA, TRG) following heavy/long chain clustering, which is governed by the `split_light` argument.

In single-cell mode, clonal clustering will not be performed on data were cells are assigned multiple heavy/long chain sequences (IGH, TRB, TRD). If observed, the operation will exit and return an error message. Cells that lack a heavy/long chain sequence (i.e., cells with light/short chains only) will be assigned a `clone_id` of NA.

See Also

See `plotCloneSummary` for plotting summary results. See `groupGenes` for more details about grouping requirements.

Examples

```r
# Subset example data
db <- subset(ExampleDb, c_call == "IGH")

# Find clonal groups
results <- spectralClones(db, method="novj", germline="germline_alignment_d_mask")

# Retrieve modified input data with clonal clustering identifiers
df <- as.data.frame(results)

# Plot clonal summaries
plot(results, binwidth=0.02)
```
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