

Package ‘topdownr’

June 16, 2025

Title Investigation of Fragmentation Conditions in Top-Down Proteomics

Version 1.30.0

Description The topdownr package allows automatic and systemic investigation of fragment conditions. It creates Thermo Orbitrap Fusion Lumos method files to test hundreds of fragmentation conditions. Additionally it provides functions to analyse and process the generated MS data and determine the best conditions to maximise overall fragment coverage.

Depends R (>= 3.5), methods, BiocGenerics (>= 0.20.0), ProtGenerics (>= 1.10.0), Biostrings (>= 2.42.1), S4Vectors (>= 0.12.2)

Imports grDevices, stats, tools, utils, Biobase, Matrix (>= 1.4-2), MSnbase (>= 2.33.5), PSMATCH (>= 1.11.4), ggplot2 (>= 2.2.1), mzR (>= 2.27.5)

Suggests topdownrdata (>= 0.2), knitr, rmarkdown, ranger, testthat, BiocStyle, xml2

License GPL (>= 3)

URL <https://github.com/sgibb/topdownr/>

BugReports <https://github.com/sgibb/topdownr/issues/>

LazyData true

VignetteBuilder knitr

Roxygen list(markdown=TRUE)

RoxygenNote 7.3.2

biocViews ImmunoOncology, Infrastructure, Proteomics, MassSpectrometry, Coverage

Encoding UTF-8

git_url <https://git.bioconductor.org/packages/topdownr>

git_branch RELEASE_3_21

git_last_commit c3c074e

git_last_commit_date 2025-04-15

Repository Bioconductor 3.21

Date/Publication 2025-06-15

Author Sebastian Gibb [aut, cre] (ORCID:

<<https://orcid.org/0000-0001-7406-4443>>),

Pavel Shliha [aut] (ORCID: <<https://orcid.org/0000-0003-3092-0724>>),

Ole Nørregaard Jensen [aut] (ORCID:

<<https://orcid.org/0000-0003-1862-8528>>)

Maintainer Sebastian Gibb <mail@sebastiangibb.de>

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topdownr-package	<i>Investigation of Fragmentation Conditions in Top-Down Proteomics</i>
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Description

The topdownr package allows automatic and systemic investigation of fragment conditions. It creates Thermo Orbitrap Fusion Lumos method files to test hundreds of fragmentation conditions. Additionally it provides functions to analyse and process the generated MS data and determine the best conditions to maximise overall fragment coverage.

Details

The usage of the topdownr package is demonstrated in the following vignettes:

- Generate .meth files prior data acquisition for the Thermo Orbitrap Fusion Lumos MS devise: `vignette("data-generation", package="topdownr")`.
- How to analyse top-down fragmentation data: `vignette("analysis", package="topdownr")`

Author(s)

Sebastian Gibb <mail@sebastiangibb.de>, Pavel Shliha <pavels@bmb.sdu.dk>, Ole Nørregaard Jensen <jenseno@bmb.sdu.dk>

References

<https://github.com/sgibb/topdownr/>

See Also

Useful links:

- <https://github.com/sgibb/topdownr/>
- Report bugs at <https://github.com/sgibb/topdownr/issues/>

AbstractTopDownSet-class

The AbstractTopDownSet class

Description

Abstract/VIRTUAL parent class for [TopDownSet](#) and [NCBSet](#) to provide common interface.

Usage

```
## S4 method for signature 'AbstractTopDownSet,ANY,ANY,ANY'
x[i, j, ..., drop = FALSE]

## S4 method for signature 'AbstractTopDownSet,ANY,missing'
x[[i, j, ...]]

## S4 replacement method for signature 'AbstractTopDownSet,ANY,missing'
x[[i, j, ...]] <- value

## S4 method for signature 'AbstractTopDownSet'
x$name

## S4 replacement method for signature 'AbstractTopDownSet'
x$name <- value

## S4 method for signature 'AbstractTopDownSet'
assayData(object)

## S4 method for signature 'AbstractTopDownSet'
colData(object)

## S4 replacement method for signature 'AbstractTopDownSet'
colData(object, ...) <- value

## S4 method for signature 'AbstractTopDownSet,AbstractTopDownSet'
combine(x, y)
```

```

## S4 method for signature 'AbstractTopDownSet'
conditionData(object, ...)

## S4 replacement method for signature 'AbstractTopDownSet'
conditionData(object, ...) <- value

## S4 method for signature 'AbstractTopDownSet'
conditionNames(object)

## S4 method for signature 'AbstractTopDownSet'
dim(x)

## S4 method for signature 'AbstractTopDownSet'
dimnames(x)

## S4 method for signature 'AbstractTopDownSet'
removeEmptyConditions(object)

## S4 method for signature 'AbstractTopDownSet'
rowViews(object, ...)

## S4 method for signature 'AbstractTopDownSet'
show(object)

## S4 method for signature 'AbstractTopDownSet'
summary(object, what = c("rows", "columns"), ...)

## S4 method for signature 'AbstractTopDownSet'
updateConditionNames(
  object,
  sampleColumns = c("Mz", "AgcTarget", "EtdReagentTarget", "EtdActivation",
    "CidActivation", "HcdActivation", "UvpdActivation"),
  verbose = interactive()
)

## S4 method for signature 'AbstractTopDownSet'
updateMedianInjectionTime(
  object,
  by = list(Mz = object$Mz, AgcTarget = object$AgcTarget)
)

```

Arguments

<code>i, j</code>	numeric, logical or character, indices specifying elements to extract or replace.
<code>drop</code>	logical, currently ignored.
<code>value</code>	replacement value.
<code>name</code>	character name of an (non)existing column in <code>colData</code> .

object, x	AbstractTopDownSet
y	AbstractTopDownSet
what	character, specifies whether "rows" or "columns" should be summarized.
sampleColumns	character, column names of the <code>colData()</code> used to define a sample (technical replicate). This is used to add the Sample column (used for easier aggregation, etc.).
verbose	logical, verbose output?
by	list, grouping information.
...	arguments passed to internal/other methods.

Details

This class just provides a common interface. It is not intended for direct use by the user. Please see [TopDownSet](#) for an example usage of its child class.

Value

This is an *Abstract/VIRTUAL* class to provide a common interface for [TopDownSet](#) and [NCBSet](#). It is not possible to create an AbstractTopDownSet object.

Methods (by generic)

- `x[i]`: Subset operator.
For `i` numeric, logical or character vectors or empty (missing) or NULL are supported. Subsetting is done on the fragment/bond (row) level. character indices could be names (e.g. `c("a1", "b1", "c1", "c2", "c3")`) or types (e.g. `c("c", "x")`) of the fragments for [TopDownSet](#) objects, or names of the bonds (e.g. `c("bond001")`) for [NCBSet](#) objects.
`j` could be a numeric or logical vector and subsetting is done on the condition/run (column) level.
- `x[[i]`: Subset operator.
`i` could be a numeric or logical vector and subsetting is done on the condition/run (column) level.
- ``[[`(x = AbstractTopDownSet, i = ANY, j = missing) <- value`: Setter for a column in the `colData` slot.
The `[[<-` operator is used to add/replace a single column of the `colData` DataFrame.
- `$`: Accessor for columns in the `colData` slot.
The `$` simplifies the accession of a single column of the `colData`. It is identical to the `[[` operator.
- ``$`(AbstractTopDownSet) <- value`: Setter for a column in the `colData` slot.
The `$<-` operator is used to add/replace a single column of the `colData` DataFrame. It is identical to the `[[<-` operator.
- `assayData(AbstractTopDownSet)`: Accessor for the assay slot.
Returns a [Matrix::dgCMatrix](#) that stores the intensity/coverage information of [AbstractTopDownSet](#) object.

- `colData(AbstractTopDownSet)`: Accessor for the `colData` slot.
Returns a [S4Vectors::DataFrame](#) that stores metadata for the conditions/runs (columns) of the [AbstractTopDownSet](#) object.
- `colData(AbstractTopDownSet) <- value`: Setter for the `colData` slot.
Replaces metadata for the conditions/runs (columns) of the [AbstractTopDownSet](#) object.
- `combine(x = AbstractTopDownSet, y = AbstractTopDownSet)`: Combine [AbstractTopDownSet](#) objects.
`combine` allows to combine two or more [AbstractTopDownSet](#) objects. Please note that it uses the default `sampleColumns` to define technical replicates (see [readTopDownFiles\(\)](#)) and the default `by` argument to group ion injection times for the calculation of the median time (see [updateMedianInjectionTime\(\)](#)). Both could be modified after `combine` by calling [updateConditionNames\(\)](#) (with modified `sampleColumns` argument) and [updateMedianInjectionTime\(\)](#) (with modified `by` argument).
- `conditionData(AbstractTopDownSet)`: Accessor for the `colData` slot.
An alias for `colData`.
- `conditionData(AbstractTopDownSet) <- value`: Setter for the `colData` slot.
An alias for `colData<-`.
- `conditionNames(AbstractTopDownSet)`: Accessor for condition names.
Returns a character with names for the conditions/runs (columns).
- `dim(AbstractTopDownSet)`: Accessor for dimensions.
Returns a numeric with number of fragments/bonds (rows) and conditions/runs (columns).
- `dimnames(AbstractTopDownSet)`: Accessor for dimension names.
Returns a list with names for the fragments/bonds (rows) and for the conditions/runs (columns).
- `removeEmptyConditions(AbstractTopDownSet)`: Remove empty conditions/runs.
Removes conditions/runs (columns) without any intensity/coverage information from the [AbstractTopDownSet](#) object. It returns a modified [AbstractTopDownSet](#) object.
- `rowViews(AbstractTopDownSet)`: Accessor for the `rowViews` slot.
Depending on the implementation it returns an [FragmentViews](#) object for [TopDownSet](#) objects or an [Biostrings::XStringViews](#) object for [NCBSet](#) objects.
- `summary(AbstractTopDownSet)`: Summary statistics.
Returns a matrix with some statistics: number of fragments, total/min/first quartile/median/mean/third quartile/maximum of intensity values.
- `updateConditionNames(AbstractTopDownSet)`: Update condition names.
Updates condition names based on `sampleColumns` from `conditionData/colData`. Columns with just identical entries are ignored. This method will create/update the `colData(object)$Sample` column that identifies technical replicates and could be used in other methods.
- `updateMedianInjectionTime(AbstractTopDownSet)`: Update median ion injection times.
Recalculates median ion injection times by a user given grouping variable (default: `Mz`, `Agc-Target`). This is useful if you acquire new data and the ion injection time differs across the runs. Use the `by` argument to provide a `list/data.frame` of grouping variables, e.g. `by=colData(object)[, c("Mz", "AgcTarget", "File")]`.

Slots

rowViews [Biostrings::XStringViews](#), information about fragments/bonds (name, type, sequence, mass, charge), see [Biostrings::XStringViews](#) and [FragmentViews](#) for details.

colData [S4Vectors::DataFrame](#), information about the MS2 experiments and the fragmentation conditions.

assay [Matrix::dgCMatrix](#), intensity/coverage values of the fragments/bonds. The rows correspond to the fragments/bonds and the columns to the condition/run. It just stores values that are different from zero.

files character, files that were imported.

processing character, log messages.

Author(s)

Sebastian Gibb <mail@sebastiangibb.de>

See Also

- [TopDownSet](#) and [NCBSet](#) which both implement/use this interface. These manual pages also provide some example code.
- [FragmentViews](#) (and [Biostrings::XStringViews](#)) for the row view interface.
- [Matrix::dgCMatrix](#) for technical details about the intensity/coverage storage.

Examples

```
## Because AbstractTopDownSet is a VIRTUAL class we could not create any
## object of it. Here we demonstrate the usage with an TopDownSet that
## implements the AbstractTopDownSet interface. See `?"TopDownSet-class"` for
## more details an further examples.
```

```
## Example data
data(tds, package="topdownr")
```

```
tds
```

```
head(summary(tds))
```

```
# Accessing slots
rowViews(tds)
colData(tds)
head(assayData(tds))
```

```
# Accessing colData
tds$Mz
tds$FilterString
```

```
# Subsetting
```

```
# First 100 fragments
tds[1:100]
```

```
# All c fragments
tds["c"]

# Just c 152
tds["c152"]

# Condition 1 to 10
tds[, 1:10]
```

```
createExperimentsFragmentOptimisation
```

Create fragment optimisation experiment

Description

This function is used to create a tree-like list of all combinations of a user-given set of MS1 and TMS2 settings for an fragment optimisation experiment. The list could be written to an Orbitrap Fusion Lumos method xml file using [writeMethodXmls\(\)](#).

Usage

```
createExperimentsFragmentOptimisation(
  ms1,
  ...,
  groupBy = c("AgcTarget", "replication"),
  nMs2perMs1 = 10,
  scanDuration = 0,
  replications = 2,
  randomise = TRUE
)
```

Arguments

<code>ms1</code>	<code>data.frame</code> , MS1 settings.
<code>...</code>	further named arguments with <code>data.frames</code> containing the TMS2 settings.
<code>groupBy</code>	character, group experiments by columns in the TMS2 <code>data.frames</code> . The columns have to be present in all <code>data.frames</code> . Each group will be written to its own XML file.
<code>nMs2perMs1</code>	integer, how many TMS2 scans should be run after a MS1 scan?
<code>scanDuration</code>	double, if greater than zero (e.g. <code>scanDuration=0.5</code>) the <code>Start/EndTimeMin</code> are overwritten with a duration of <code>scanDuration</code> . If <code>scanDuration</code> is zero (default) <code>Start/EndTimeMin</code> are not overwritten.
<code>replications</code>	integer, number of replications.
<code>randomise</code>	logical, should the TMS2 scan settings randomised?

Value

list, able to be written via `xml2::as_xml_document()`

See Also

`writeMethodXmIs()`, `expandMs1Conditions()`, `expandTms2Conditions()`

Examples

```
## build experiments within R
ms1 <- expandMs1Conditions(
  FirstMass=400,
  LastMass=1200,
  Microscans=as.integer(10)
)

targetMz <- cbind(mz=c(560.6, 700.5, 933.7), z=rep(1, 3))
common <- list(
  OrbitrapResolution="R120K",
  IsolationWindow=1,
  MaxITTimeInMS=200,
  Microscans=as.integer(40),
  AgcTarget=c(1e5, 5e5, 1e6)
)

cid <- expandTms2Conditions(
  MassList=targetMz,
  common,
  ActivationType="CID",
  CIDCollisionEnergy=seq(7, 35, 7)
)

hcd <- expandTms2Conditions(
  MassList=targetMz,
  common,
  ActivationType="HCD",
  HCDCollisionEnergy=seq(7, 35, 7)
)

etd <- expandTms2Conditions(
  MassList=targetMz,
  common,
  ActivationType="ETD",
  ETDReactionTime=as.double(1:2)
)

etcid <- expandTms2Conditions(
  MassList=targetMz,
  common,
  ActivationType="ETD",
  ETDReactionTime=as.double(1:2),
  ETDSupplementalActivation="ETcid",
  ETDSupplementalActivationEnergy=as.double(1:2)
)

uvpd <- expandTms2Conditions(
```

```

    MassList=targetMz,
    common,
    ActivationType="UVPD"
  )

  exps <- createExperimentsFragmentOptimisation(
    ms1=ms1, cid, hcd, etd, etcid, uvpd,
    groupBy=c("AgcTarget", "replication"), nMs2perMs1=10, scanDuration=0.5,
    replications=2, randomise=TRUE
  )

  ## use different settings for CID
  cid560 <- expandTms2Conditions(
    MassList=cbind(560.6, 1),
    common,
    ActivationType="CID",
    CIDCollisionEnergy=seq(7, 21, 7)
  )
  cid700 <- expandTms2Conditions(
    MassList=cbind(700.5, 1),
    common,
    ActivationType="CID",
    CIDCollisionEnergy=seq(21, 35, 7)
  )

  exps <- createExperimentsFragmentOptimisation(
    ms1=ms1, cid560, cid700,
    groupBy=c("AgcTarget", "replication"), nMs2perMs1=10, scanDuration=0.5,
    replications=2, randomise=TRUE
  )

  ## use a CSV (or excel) file as input
  myCsvContent <- "
  ActivationType, ETDReactionTime, UVPDActivationTime
  UVPD,,1000
  ETD,1000,
  "
  myCsvSettings <- read.csv(text=myCsvContent, stringsAsFactors=FALSE)
  myCsvSettings
  #   ActivationType ETDReactionTime UVPDActivationTime
  # 1             UVPD              NA              1000
  # 2             ETD             1000              NA

  exps <- createExperimentsFragmentOptimisation(
    ms1 = data.frame(FirstMass=500, LastMass=1000),
    ## TMS2
    myCsvSettings,
    ## other arguments
    groupBy="ActivationType"
  )

```

```
createTngFusionMethFiles
```

Windows specific functions.

Description

The functions `runXmlMethodChanger` and `runScanHeadsman` call `XmlMethodChanger.exe` and `ScanHeadsman.exe` with the corresponding arguments. This only work on Windows (maybe on Linux + wine as well but that was never tested).

Usage

```
createTngFusionMethFiles(
  template,
  xml = list.files(pattern = ".*\\.xml$"),
  executable = "XmlMethodChanger.exe",
  verbose = interactive()
)

runXmlMethodChanger(
  template,
  xml = list.files(pattern = ".*\\.xml$"),
  executable = "XmlMethodChanger.exe",
  verbose = interactive()
)

runScanHeadsman(path = ".", executable = "ScanHeadsman.exe")
```

Arguments

<code>template</code>	character, path to template .meth file.
<code>xml</code>	character, vector of path to .xml files.
<code>executable</code>	character, path to the <code>XmlMethodChanger.exe</code> or <code>ScanHeadsman.exe</code> executable.
<code>verbose</code>	logical, if TRUE a progress bar is shown.
<code>path</code>	character, path to the directory containing the .raw files.

Details

`runXmlMethodChanger` applies ‘`XmlMethodChanger.exe`’ on all given XML files generated with `writeMethodXmIs()` to create .meth files from a template.

`runScanHeadsman` calls `ScanHeadsman.exe` on a given directory containing .raw files. `ScanHeadsman.exe` extracts the method and scan header data into .experiments.csv and .txt files, respectively.

Value

Nothing. Used for its side effects.

References

XmlMethodChanger source code: <https://github.com/thermofisherIsms/meth-modifications/>

ScanHeadsman source code: <https://bitbucket.org/caetera/scanheadsman>

See Also

[writeMethodXmIs\(\)](#)

Examples

```
## Not run:
runXmlMethodChanger(templateMeth="TMS2IndependentTemplate240Extended.meth",
                     modificationXml=list.files(pattern="^method.*\\.xml$"),
                     executable="..\\XmlMethodChanger.exe")

## End(Not run)
## Not run:
runScanHeadsman("raw", executable="..\\ScanHeadsman.exe")

## End(Not run)
```

expandMs1Conditions	<i>Expand MS Conditions</i>
---------------------	-----------------------------

Description

Create a data.frame of all possible combinations of the given arguments. It ensures that just arguments are applied that yield a valid MethodModification.xml file.

Usage

```
expandMs1Conditions(..., family = "Calcium", version = "3.2")

expandTms2Conditions(
  ActivationType = c("CID", "HCD", "ETD", "UVPD"),
  ...,
  MassList = NULL,
  family = "Calcium",
  version = "3.2"
)
```

Arguments

...	further named arguments, used to create the combination of conditions.
family	character, currently just Calcium is supported
version	character, currently 3.1, 3.2 (default), 3.3 are supported
ActivationType	character, <i>ActivationType</i> for TMS2, either CID, HCD, ETD, or UVPD.

MassList matrix, 2 columns (mass, z) for targeted mass list, or NULL (default) to not overwrite targeted mass.

Value

data.frame with all possible combinations of conditions/settings.

See Also

[validMs1Settings\(\)](#)
[validTms2Settings\(\)](#), [expand.grid\(\)](#)

Examples

```
expandMs1Conditions(FirstMass=100, LastMass=400)
expandTms2Conditions(
  ActivationType="CID",
  OrbitrapResolution="R120K",
  IsolationWindow=1,
  MaxITTimeInMS=200,
  Microscans=as.integer(40),
  AgcTarget=c(1e5, 5e5, 1e6),
  CIDCollisionEnergy=c(NA, seq(7, 35, 7)),
  MassList=cbind(mz=c(560.6, 700.5, 933.7), z=rep(1, 3))
)
```

FragmentViews-class *The FragmentViews class*

Description

The FragmentViews class is a basic container for storing a set of views (start/end locations) on the same peptides/protein sequence. Additionally it keeps information about mass, type and charge of the fragments.

Usage

```
FragmentViews(
  sequence,
  mass,
  type,
  z = 1L,
  start = NULL,
  end = NULL,
  width = NULL,
  names = NULL,
  metadata = list()
)
```

```
## S4 method for signature 'FragmentViews,FragmentViews'
combine(x, y)

## S4 method for signature 'FragmentViews'
mz(object, ...)

## S4 method for signature 'FragmentViews'
show(object)
```

Arguments

sequence	character/ Biostrings::AAString , complete protein/peptide sequence.
mass	double, mass of the fragments, same length as start/end/width.
type	character, type of the fragments, same length as start/end/width'.
z	integer, charge of the fragments, length one or same length as start/end/width'.
start	integer, start positions of the fragments. At least two of start/end/width' has to be given.
end	integer, end positions of the fragments. At least two of start/end/width' has to be given.
width	integer, width positions of the fragments. At least two of start/end/width' has to be given.
names	character, names of the fragments, same length as start/end/width'.
metadata	list, metadata like modifications.
object, x, y	FragmentViews
...	arguments passed to internal/other methods.

Details

FragmentViews extends [Biostrings::XStringViews](#). In short it combines an [IRanges::IRanges](#) object to store start/end location on a sequence, an [Biostrings::AAString](#) object.

Value

An [FragmentViews](#) object.

Functions

- `FragmentViews()`: Constructor
In general it is not necessary to call the constructor manually. See [readTopDownFiles\(\)](#) instead.

Coercion

`as(object, "data.frame")`: Coerce an [FragmentViews](#) object into a `data.frame`.

Author(s)

Sebastian Gibb <mail@sebastiangibb.de>

See Also

[Biostrings::XStringViews](#)

Examples

```
# Constructor
fv <- FragmentViews("ACE", start=1, width=1:3, names=paste0("b", 1:3),
                    mass=c(72.04439, 232.07504, 361.11763),
                    type="b", z=1)

fv

# Coercion to data.frame
as(fv, "data.frame")
as(fv, "data.frame")
```

NCBSet-class

The NCBSet class

Description

The NCBSet class is a container for a top-down proteomics experiment similar to the [TopDownSet](#) but instead of intensity values it just stores the information if a bond is covered by a N-terminal (encoded as 1), a C-terminal (encoded as 2) and/or bidirectional fragments (encoded as 3).

Usage

```
## S4 method for signature 'NCBSet'
bestConditions(
  object,
  n = ncol(object),
  minN = 0L,
  maximise = c("fragments", "bonds"),
  ...
)

## S4 method for signature 'NCBSet'
fragmentationMap(
  object,
  nCombinations = 10,
  cumCoverage = TRUE,
  maximise = c("fragments", "bonds"),
  labels = colnames(object),
  alphaIntensity = TRUE,
  ...
)
```

```
)

## S4 method for signature 'NCBSet'
show(object)

## S4 method for signature 'NCBSet'
summary(object, what = c("conditions", "bonds"), ...)
```

Arguments

<code>object</code>	NCBSet
<code>n</code>	integer, max number of combinations/iterations.
<code>minN</code>	integer, stop if there are less than <code>minN</code> additional fragments
<code>maximise</code>	character, optimisation targeting for the highest number of "fragments" (default) or "bonds".
<code>nCombinations</code>	integer, number of combinations to show (0 to avoid plotting them at all).
<code>cumCoverage</code>	logical, if TRUE (default) cumulative coverage of combinations is shown.
<code>labels</code>	character, overwrite x-axis labels.
<code>alphaIntensity</code>	logical, if TRUE (default) the alpha level of the color is used to show the <code>colData(object)\$AssignedIntensity</code> . If FALSE the alpha is set to 1.
<code>what</code>	character, specifies whether "conditions" (columns; default) or "bonds" (rows) should be summarized.
<code>...</code>	arguments passed to internal/other methods. added.

Value

An [NCBSet](#) object.

Methods (by generic)

- `bestConditions(NCBSet)`: Best combination of conditions.
Finds the best combination of conditions for highest coverage of fragments or bonds. If there are two (or more conditions) that would add the same number of fragments/bonds the one with the highest assigned intensity is used. Use `n` to limit the number of iterations and combinations that should be returned. If `minN` is set at least `minN` fragments have to be added to the combinations. The function returns a 7-column matrix. The first column contains the index (Index) of the condition (column number). The next columns contain the newly added number of fragments or bonds (`FragmentsAddedToCombination`, `BondsAddedToCombination`), the fragments or bonds in the condition (`FragmentsInCondition`, `BondsInCondition`), and the cumulative coverage fragments or bonds (`FragmentCoverage`, `BondCoverage`).
- `fragmentationMap(NCBSet)`: Plot fragmentation map.
Plots a fragmentation map of the Protein. Use `nCombinations` to add another plot with `nCombinations` combined conditions. If `cumCoverage` is TRUE (default) these combinations increase the coverage cumulatively.
- `summary(NCBSet)`: Summary statistics.
Returns a matrix with some statistics: number of fragments, total/min/first quartile/median/mean/third quartile/maximum of intensity values.

Slots

rowViews [Biostrings::XStringViews](#), information about bonds (name, start, end, width, sequence), see [Biostrings::XStringViews](#) for details.

colData [S4Vectors::DataFrame](#), information about the MS2 experiments and the fragmentation conditions.

assay [Matrix::dgCMatrix](#), coverage values of the bonds. The rows correspond to the bonds and the columns to the condition/run. It just stores values that are different from zero. If a bond is covered by an N-terminal fragment its encoded with 1, by an C-terminal fragment with 2 and by both fragment types/bidirectional by 3 respectively.

files character, files that were imported.

processing character, log messages.

Author(s)

Sebastian Gibb <mail@sebastiangibb.de>

See Also

- An NCBSet is generated from an [TopDownSet](#) object.
- [Biostrings::XStringViews](#) for the row view interface.
- [Matrix::dgCMatrix](#) for technical details about the coverage storage.

Examples

```
## Example data
data(tds, package="topdownr")

## Aggregate technical replicates
tds <- aggregate(tds)

## Coercion into an NCBSet object
ncb <- as(tds, "NCBSet")

ncb

head(summary(ncb))

# Accessing slots
rowViews(ncb)
colData(ncb)
head(assayData(ncb))

# Accessing colData
ncb$Mz

# Subsetting

# First 100 bonds
ncb[1:100]
```

```
# Just bond 152
ncb["bond152"]

# Condition 1 to 10
ncb[, 1:10]

# Plot fragmentation map
fragmentationMap(ncb)
```

readTopDownFiles	<i>Read top-down files.</i>
------------------	-----------------------------

Description

It creates an [TopDownSet](#) object and is its only constructor.

Usage

```
readTopDownFiles(
  path,
  pattern = ".*",
  type = c("a", "b", "c", "x", "y", "z"),
  modifications = c("Carbamidomethyl", "Acetyl", "Met-loss"),
  customModifications = data.frame(),
  adducts = data.frame(),
  neutralLoss = PSMATCH::defaultNeutralLoss(),
  sequenceOrder = c("original", "random", "inverse"),
  tolerance = 5e-06,
  redundantIonMatch = c("remove", "closest"),
  redundantFragmentMatch = c("remove", "closest"),
  dropNonInformativeColumns = TRUE,
  sampleColumns = c("Mz", "AgcTarget", "EtdReagentTarget", "EtdActivation",
    "CidActivation", "HcdActivation", "UvpdActivation"),
  conditions = "ScanDescription",
  verbose = interactive()
)
```

Arguments

path	character, path to directory that contains the top-down files.
pattern	character, a filename pattern, the default <code>.*</code> means all files.
type	character, type of fragments, currently <i>a-c</i> and <i>x-z</i> are supported, see PSMATCH::calculateFragments() for details.
modifications	character, unimod names of modifications that should be applied. Currently just <i>Acetyl</i> (Unimod:1 but just protein N-term), <i>Carbamidomethyl</i> (Unimod:4) and <i>Met-loss</i> (Unimod:765) are supported. <i>Met-loss</i> removes M (if followed by

A, C, G, P, S, T, or V; (see also http://www.unimod.org/modifications_view.php?editid1=1, http://www.unimod.org/modifications_view.php?editid1=4, and http://www.unimod.org/modifications_view.php?editid1=10 for details)). Use NULL to disable all modifications.

customModifications	data.frame, with 4 columns, namely: mass, name, location, variable, see details section.
adducts	data.frame, with 3 columns, namely: mass, name, to, see details section.
neutralLoss	list, neutral loss that should be applied, see <code>PSMatch::calculateFragments()</code> and <code>PSMatch::defaultNeutralLoss()</code> for details.
sequenceOrder	character, order of the sequence before fragment calculation and matching is done. "original" doesn't change anything. "inverse" reverse the sequence and "random" arranges the amino acid sequence at random.
tolerance	double, tolerance in <i>ppm</i> that is used to match the theoretical fragments with the observed ones.
redundantIonMatch	character, a m/z could be matched to one, two or more fragments. If it is matched against more than one fragment the match could be "remove"d or the match to the "closest" fragment could be chosen.
redundantFragmentMatch	character, one or more m/z could be matched to the same fragment, these matches could be "remove"d or the match to the "closest" m/z is chosen.
dropNonInformativeColumns	logical, should columns with just one identical value across all runs be removed?
sampleColumns	character, column names of the <code>colData()</code> used to define a sample (technical replicate). This is used to add the Sample column (used for easier aggregation, etc.).
conditions	character/numeric, one of: • "ScanDescription" (default): create condition IDs based on the given "Scan Description" parameter (set automatically by <code>createExperimentsFragmentOptimisation()</code>) • "FilterString": create condition IDs based on mass labels in the <i>FilterString</i> column (included for backward-compatibility, used in <code>writeMethodXmLs()</code> prior version 1.5.2 in Dec 2018). • A single numeric value giving the number of conditions.
verbose	logical, verbose output?

Details

`readTopDownFiles` reads and processes all top-down files, namely:

- .fasta (protein sequence)
- .mzML (spectra)
- .experiments.csv (method/fragmentation conditions)
- .txt (scan header information)

customModifications: additional to the provided unimod modifications available through the modifications argument customModifications allow to apply user-defined modifications to the output of `PSMatch::calculateFragments()`. The customModifications argument takes a `data.frame` with the mass to add, the name of the modification, the location (could be the position of the amino acid or "N-term"/"C-term"), whether the modification is always seen (`variable=FALSE`) or both, the modified and unmodified amino acid are present (`variable=TRUE`), e.g. for Activation (which is available via `modification="Acetyl"`) `data.frame(mass=42.010565, name="Acetyl", location="N-term", variable=FALSE)` or variable one (that could be present or not): `data.frame(mass=365.132, name="Custom", location=10, variable=TRUE)`

If the customModifications `data.frame` contains multiple columns the modifications are applied from row one to the last row one each time.

adducts: *Thermo's Xtract* allows some mistakes in deisotoping, mostly it allows +/- C13-C12 and +/- H+. The adducts argument takes a `data.frame` with the mass to add, the name that should assign to these new fragments and an information to whom the modification should be applied, e.g. for H+ on z, `data.frame(mass=1.008, name="zpH", to="z")`.

Please note: The adducts are added to the output of `PSMatch::calculateFragments()`. That has some limitations, e.g. neutral loss calculation could not be done in `topdownnr-package`. If neutral loss should be applied on adducts you have to create additional rows, e.g.: `data.frame(mass=c(1.008, 1.008), name=c("cpH", "cpH_"), to=c("c", "c_"))`.

Value

A TopDownSet object.

See Also

`PSMatch::calculateFragments()`, `PSMatch::defaultNeutralLoss()`

Examples

```
if (require("topdownnrdata")) {
  # add H+ to z and no neutral loss of water
  tds <- readTopDownFiles(
    topdownnrdata::topDownDataPath("myoglobin"),
    ## Use an artificial pattern to load just the fasta
    ## file and files from m/z == 1211, ETD reagent
    ## target 1e6 and first replicate to keep runtime
    ## of the example short
    pattern=".*fasta.gz$|1211_.*1e6_1",
    adducts=data.frame(mass=1.008, name="zpH", to="z"),
    neutralLoss=PSMatch::defaultNeutralLoss(
      disableWaterLoss=c("Cterm", "D", "E", "S", "T")),
    tolerance=25e-6
  )
}
```

tds	<i>TopDownSet Example Data</i>
-----	--------------------------------

Description

An example data set for topdownr. It is just a subset of the myoglobin dataset available in [topdownrdata::topdownrdata-package](#).

Usage

```
tds
```

Format

A [TopDownSet](#) with 14901 fragments (1949 rows, 351 columns).

Details

It was created as follows:

```
tds <- readTopDownFiles(
  topdownrdata::topDownDataPath("myoglobin"),
  ## Use an artifical pattern to load just the fasta
  ## file and files from m/z == 1211, ETD reagent
  ## target 1e6 and first replicate to keep runtime
  ## of the example short
  pattern=".*fasta.gz$|1211_.*1e6_1",
  adducts=data.frame(mass=1.008, name="zpH", to="z"),
  neutralLoss=PSMatch::defaultNeutralLoss(
    disableWaterLoss=c("Cterm", "D", "E", "S", "T")),
  tolerance=25e-6)
```

Source

Subset taken from the [topdownrdata::topdownrdata-package](#) package.

topdownr-deprecated	<i>Deprecated functions in topdownr</i>
---------------------	---

Description

These functions are provided for compatibility with older versions of ‘MyPkg’ only, and will be defunct at the next release.

Details

The following functions are deprecated and will be made defunct; use the replacement indicated below:

- defaultMs1Settings: [expandMs1Conditions\(\)](#) in combination with [createExperimentsFragmentOptimisation\(\)](#)
- defaultMs2Settings: [expandTms2Conditions\(\)](#) in combination with [createExperimentsFragmentOptimisation\(\)](#)

TopDownSet-class

The TopDownSet class

Description

The TopDownSet class is a container for a whole top-down proteomics experiment.

Usage

```
## S4 method for signature 'TopDownSet'
aggregate(x, by = x$Sample, ...)

## S4 method for signature 'TopDownSet,TopDownSet'
combine(x, y)

## S4 method for signature 'TopDownSet'
filterCv(object, threshold, by = object$Sample, ...)

## S4 method for signature 'TopDownSet'
filterInjectionTime(
  object,
  maxDeviation = log2(3),
  keepTopN = 2,
  by = object$Sample,
  ...
)

## S4 method for signature 'TopDownSet'
filterIntensity(object, threshold, relative = TRUE, ...)

## S4 method for signature 'TopDownSet'
filterNonReplicatedFragments(object, minN = 2, by = object$Sample, ...)

## S4 method for signature 'TopDownSet'
normalize(object, method = "TIC", ...)

## S4 method for signature 'TopDownSet,missing'
plot(x, y, ..., verbose = interactive())
```

```
## S4 method for signature 'TopDownSet'
show(object)

## S4 method for signature 'TopDownSet'
summary(object, what = c("conditions", "fragments"), ...)
```

Arguments

x, object	TopDownSet
by	list, grouping variable, in general it refers to technical
y	missing, not used.
threshold	double, threshold variable.
maxDeviation	double, maximal allowed deviation in the log2 injection time in ms in comparison to the median ion injection time.
keepTopN	integer, how many technical replicates should be kept?
relative	logical, if relative is TRUE all fragments with intensity below threshold * max(intensity) per fragment are removed, otherwise all fragments below threshold are removed.
minN	numeric, if less than minN of a fragment are found across technical replicates it is removed.
method	character, normalisation method, currently just "TIC" for Total Ion Current normalisation of the scans/conditions (column-wise normalisation) is supported.
verbose	logical, verbose output?
what	character, specifies whether "conditions" (columns; default) or "fragments" (rows) should be summarized.
...	arguments passed to internal/other methods. replicates (that's why the default is the "Sample" column in colData).

Details

See `vignette("analysis", package="topdownr")` for a detailed example how to work with TopDownSet objects.

Value

An [TopDownSet](#) object.

Methods (by generic)

- `aggregate(TopDownSet)`: Aggregate conditions/runs.
Aggregates conditions/runs (columns) in an [TopDownSet](#) object by a user-given value (default is the "Sample" column of colData which has the same value for technical replicates). It combines intensity values and numeric metadata of the grouped conditions/runs (columns) by mean and returns a reduced [TopDownSet](#) object.

- `combine(x = TopDownSet, y = TopDownSet)`: Combine TopDownSet objects.
`combine` allows to combine two or more TopDownSet objects. Please note that it uses the default `sampleColumns` to define technical replicates (see [readTopDownFiles\(\)](#)) and the default by argument to group ion injection times for the calculation of the median time (see [updateMedianInjectionTime\(\)](#)). Both could be modified after combine by calling [updateConditionNames\(\)](#) (with modified `sampleColumns` argument) and [updateMedianInjectionTime\(\)](#) (with modified by argument).
- `filterCv(TopDownSet)`: Filter by CV.
 Filtering is done by coefficient of variation across technical replicates (defined by the `by` argument). All fragments below a given threshold are removed. The threshold is the maximal allowed CV in percent ($sd/mean * 100 < threshold$).
- `filterInjectionTime(TopDownSet)`: Filter by ion injection time.
 Filtering is done by maximal allowed deviation and just the technical keepTopN replicates with the lowest deviation from the median ion injection time are kept.
- `filterIntensity(TopDownSet)`: Filter by intensity.
 Filtering is done by removing all fragments that are below a given (absolute/relative) intensity threshold.
- `filterNonReplicatedFragments(TopDownSet)`: Filter by non-replicated fragments.
 Filtering is done by removing all fragments that don't replicate across technical replicates.
- `normalize(TopDownSet)`: Normalise.
 Applies Total Ion Current normalisation to a [TopDownSet](#) object. The normalisation is done per scans/conditions (column-wise normalisation).
- `plot(x = TopDownSet, y = missing)`: Plotting.
 Plots an [TopDownSet](#) object. The function returns a list of ggplot objects (one item per condition). Use pdf or another non-interactive device to plot the list of ggplot objects (see example section).
- `summary(TopDownSet)`: Summary statistics.
 Returns a matrix with some statistics: number of fragments, total/min/first quartile/median/mean/third quartile/maximum of intensity values.

Slots

`rowViews` [FragmentViews](#), information about fragments (name, type, sequence, mass, charge), see [FragmentViews](#) for details.

`colData` [S4Vectors::DataFrame](#), information about the MS2 experiments and the fragmentation conditions.

`assay` [Matrix::dgCMatrix](#), intensity values of the fragments. The rows correspond to the fragments and the columns to the condition/run. It just stores values that are different from zero.

`files` character, files that were imported.

`tolerance` double, tolerance in *ppm* that were used for matching the experimental m/z values to the theoretical fragments.

`redundantMatching` character, matching strategies for redundant ion/fragment matches. See `redundantIonMatch` and `redundantFragmentMatch` in [readTopDownFiles\(\)](#) for details.

`processing` character, log messages.

Coercion

`'as(object, "MSnSet")`: Coerce an [TopDownSet](#) object into an [MSnbase::MSnSet](#) object.

`'as(object, "NCBSet")`: Coerce an [TopDownSet](#) object into an [NCBSet](#) object.

Author(s)

Sebastian Gibb <mail@sebastiangibb.de>

See Also

- [FragmentViews](#) for the row view interface.
- [Matrix::dgCMatrix](#) for technical details about the intensity storage.
- `?vignette("analysis", package="topdownr")` for a full documented example of an analysis using topdownr.

Examples

```
## Example data
data(tds, package="topdownr")

tds

head(summary(tds))

# Accessing slots
rowViews(tds)
colData(tds)
head(assayData(tds))

# Accessing colData
tds$Mz
tds$FilterString

# Subsetting

# First 100 fragments
tds[1:100]

# All c fragments
tds["c"]

# Just c 152
tds["c152"]

# Condition 1 to 10
tds[, 1:10]

# Filtering
# Filter all intensities that don't have at least 10 % of the highest
# intensity per fragment.
```

```

tds <- filterIntensity(tds, threshold=0.1)

# Filter all conditions with a CV above 30 % (across technical replicates)
tds <- filterCv(tds, threshold=30)

# Filter all conditions with a large deviation in injection time
tds <- filterInjectionTime(tds, maxDeviation=log2(3), keepTopN=2)

# Filter all conditions where fragments don't replicate
tds <- filterNonReplicatedFragments(tds)

# Normalise by TIC
tds <- normalize(tds)

# Aggregate technical replicates
tds <- aggregate(tds)

head(summary(tds))

# Coercion
as(tds, "NCBSet")

if (require("MSnbase")) {
  as(tds, "MSnSet")
}
## Not run:
# plot a single condition
# pseudo-code (replace topdownset with your object)
plot(topdownset[,1])

# plot the whole object
pdf("topdown-spectra.pdf", paper="a4r", width=12)
# pseudo-code (replace topdownset with your object)
plot(topdownset)
dev.off()

## End(Not run)

```

validMs1Settings

List valid MS settings.

Description

These functions list settings for MS1 or TMS2 that are supported by *Thermo's XmlMethodChanger*.

Usage

```

validMs1Settings(family = "Calcium", version = "3.2")

validTms2Settings(

```

```

    type = c("All", "TMS2", "ETD", "CID", "HCD", "UVPD"),
    family = "Calcium",
    version = "3.2"
  )

```

Arguments

family	character, currently just Calcium is supported
version	character, currently 3.1, 3.2 (default), 3.3 are supported
type	character, type of activation.

Value

matrix with three columns:

- name: element name
- class: expected R class of the value
- type: MS/ActivationType, e.g. MS1/TMS2/ETD/...

Examples

```

validMs1Settings()
validTms2Settings()
validTms2Settings("TMS2")
validTms2Settings("ETD")
validTms2Settings(c("TMS2", "ETD"))

```

writeMethodXmIs	<i>Create Orbitrap Fusion Lumos method.xml files.</i>
-----------------	---

Description

This function is used to create Orbitrap Fusion Lumos method files from a tree-like list experiment generated by e.g. [createExperimentsFragmentOptimisation\(\)](#).

Usage

```
writeMethodXmIs(exps, pattern = "method-%s.xml", verbose = interactive())
```

Arguments

exps	list, generated by e.g. createExperimentsFragmentOptimisation()
pattern	character, file name pattern for the method.xml files.
verbose	logical, verbose output?

Details

- `exps`: a named tree-like list object generated by e.g. `createExperimentsFragmentOptimisation()`. Its names are used as filename.
- `pattern`: The file name pattern used to name different method files. It must contain a "%s" that is replaced by the conditions defined in `groupBy`.

DEFUNCT options:

- `ms1Settings`: A list of MS1 settings. This has to be a named list. Valid MS1 settings are: `c("FirstMass", "LastMass", "Microscans", "MaxITTimeInMS", "AgcTarget")`
- `ms2Settings`: A list of MS2 settings. This has to be a named list. Valid MS2 settings are: `c("ActivationType", "IsolationWindow", "EnableMultiplexIons", "EnableMSXIds", "MaxNoOfMultiplexIons", "OrbitrapResolution", "AgcTarget", "MinAgcTarget", "MaxITTimeInMS", "Microscans", "ETDReactionTime", "ETDReagentTarget", "MaximumETDReagentInjectionTime", "UseInternalCalibratedETD", "ETDSupplementalActivationEnergy", "ETDSupplementalActivation")`
- `groupBy`: The `groupBy` parameter is used to split methods into different files. Valid entries are all settings that could be used in `ms2Settings` and "replication".
- `massLabeling`: The Orbitrap Fusion devices seems not to respect the start and end times of the runs given in the method.xml files. That's why it is nearly impossible to identify the run with its conditions based on the timings. If `massLabeling` is TRUE (default) the mass values given in `mz` are rounded to the first decimal place and the second to fourth decimal place is used as numeric identifier.

Author(s)

Sebastian Gibb <mail@sebastiangibb.de>, Pavel V. Shliaha <pavels@bmb.sdu.dk>

See Also

[createExperimentsFragmentOptimisation\(\)](#)

Examples

```
ms1 <- expandMs1Conditions(FirstMass=400, LastMass=1200, Microscans=as.integer(10))

targetMz <- cbind(mz=c(560.6, 700.5, 933.7), z=rep(1, 3))
common <- list(
  OrbitrapResolution="R120K",
  IsolationWindow=1,
  MaxITTimeInMS=200,
  Microscans=as.integer(40),
  AgcTarget=c(1e5, 5e5, 1e6)
)
cid <- expandTms2Conditions(
  MassList=targetMz,
  common,
  ActivationType="CID",
  CIDCollisionEnergy=seq(7, 35, 7)
)
hcd <- expandTms2Conditions(
```

```
      MassList=targetMz,
      common,
      ActivationType="HCD",
      HCDCollisionEnergy=seq(7, 35, 7)
    )
    etd <- expandTms2Conditions(
      MassList=targetMz,
      common,
      ActivationType="ETD",
      ETDReagentTarget=c(1e6, 5e6, 1e7),
      ETDReactionTime=c(2.5, 5, 10, 15, 30, 50),
      ETDSupplementalActivation=c("None", "ETciD", "ETHcd"),
      ETDSupplementalActivationEnergy=seq(7, 35, 7)
    )
    exps <- createExperimentsFragmentOptimisation(ms1=ms1, cid, hcd, etd,
      groupBy=c("AgcTarget", "replication"), nMs2perMs1=10, scanDuration=0.5,
      replications=2, randomise=TRUE
    )
    writeMethodXmIs(exps=exps)
```

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