

Package ‘MinimumDistance’

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Type Package

Title A package for de novo CNV detection in case-parent trios

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Description Analysis of de novo copy number variants in trios from high-dimensional genotyping platforms

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Depends R (>= 3.01)

Imports methods, DNACopy, utils, msm, lattice, BiocGenerics, VanillaICE (>= 1.26.1), ff, Biobase (>= 2.23.6), foreach, oligoClasses (>= 1.24.0), IRanges, GenomicRanges, matrixStats

Suggests human610quadv1bCrlmm (>= 1.0.3), SNPchip, RUnit

Enhances snow, doSNOW

Collate AllGenerics.R AllClasses.R methods-AnnotatedDataFrame.R methods-AssayData.R methods-Pedigree.R methods-TrioSet.R methods-TrioSetList.R methods-matrix.R methods-list.R methods-RangedData.R methods-ff_array.R segment2-methods.R mad-methods.R lattice-methods.R functions.R generator-funs.R utils.R zzz.R

LazyLoad yes

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Local Variables

time-stamp-pattern ``8/Date: %3a %3b %2d %02H:%02M:%02S %Z %:y\{\}n"

End

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annotatedDataFrameFrom-methods

Methods for creating AnnotatedDataFrame objects

Description

Methods for creating AnnotatedDataFrame objects in the package **MinimumDistance**.

Methods

signature(object = "array", byrow = "ANY") Creates an AnnotatedDataFrame from an array.
byrow is ignored.

signature(object = "ff_array", byrow = "ANY") Creates an AnnotatedDataFrame from an
ff_array. byrow is ignored.

signature(object = "ff_matrix", byrow = "ANY") Creates an AnnotatedDataFrame from an
ff_matrix. byrow is ignored.

signature(object = "Pedigree", byrow = "logical") Creates an AnnotatedDataFrame from
an object of class Pedigree.

Usage

When object is of class Pedigree, an AnnotatedDataFrame containing phenotypic information on the father, mother, or offspring can be specified by the argument which.

```
annotatedDataFrameFrom(object, byrow, sample.sheet, which=c("offspring", "father", "mother"), row
```

A data.frame containing phenotypic information on the samples can be passed to this method through the argument sample.sheet. The sample.sheet can contain phenotypic information on all the samples. Only the rows relevant to the offspring, for example, will be included when instantiating an AnnotatedDataFrame when which is "offspring". When sample.sheet is missing, an AnnotatedDataFrame with zero rows will be instantiated. When sample.sheet is not missing, row.names must be specified. The row.names are the identifiers for each row in sample.sheet and are matched to sample identifiers stored in object.

calculateMindist *Compute the minimum distance.*

Description

Compute the minimum distance.

Usage

```
calculateMindist(object, ...)
```

Arguments

object	A list of arrays, a TrioSetList object, or an array of the log R ratios.
...	Ignored.

Details

The 'minimum distance' is the minimum signed absolute difference of the parental log R ratios and the offspring log R ratios. Specifically, let |O-F| denote the absolute difference in the log R ratios comparing offspring to father and |O-M| the absolute difference in the log R ratios comparing offspring to mother. The minimum distance at a marker is the signed minimum of |O-M| and |O-F|. After segmentation of the minimum distance, non-zero segments can indicate a de novo difference in the log R ratio of the offspring and either parent. For example, a positive minimum distance suggests that the log R ratio from the offspring is greater than the log R ratio of either parent.

Value

If object is an array, a matrix of the minimum distance is returned. For an object with M markers and T trios, the dimension of the resulting matrix is M x T. If object is a list of arrays or a TrioSetList object, a list of matrices are returned. The dimension of the ith matrix in the list is M_i x T.

Author(s)

R. Scharpf

Examples

```
library(oligoClasses)
data(trioSetListExample)
mdlist <- calculateMindist(lrr(trioSetList))
```

callDenovoSegments *Posterior calling for segmented data.*

Description

This function provides a convenient wrapper for the segmentation and posterior calling steps.

Usage

```
callDenovoSegments(path = "", pedigreeData, ext = "", featureData,
cdfname, chromosome = 1:22, segmentParents, mdThr=0.9, prOutlierBAF=list(initial=1e-3, max=1e-1, maxRO
```

Arguments

path	character string indicating path to BeadStudio files.
pedigreeData	Object of class Pedigree.
ext	character: filename extension
featureData	An object of class AnnotatedDataFrame. Variable labels 'chromosome', 'position', and 'isSnp' are required.
cdfname	Name of the package for annotating the chromosome and physical position. Ignored if featureData is specified.
chromosome	integer indicating which autosomal chromosomes to process
segmentParents	Logical: whether to segment the parental log R ratios using circular binary segmentation
mdThr	numeric: the maximum a posteriori estimate of the trio copy number state is only computed for segments with lmeanl greater than mdThr
prOutlierBAF	Can be helpful to constrain the value for this parameter during the reestimation procedure. Appropriate constraints depend on the platform (Affy or Illumina). See viterbi2Wrapper for details.
verbose	Logical: whether to display verbose output indicating progress.
genome	character: the UCSC genome build used for the probe annotation
...	Additional arguments can be specified for the segment function in the package DNACopy

Details

A wrapper for the segmentation and posterior calling steps. Circular binary segmentation is performed on the minimum distance and the offspring log R ratios. The minimum distance (the signed minimum of the absolute difference of the offspring and parental log₂ R ratios) should have mean zero in regions of inherited CNV and normal diploid genomes. Hence, the segmentation algorithm should smooth over inherited CNV in which the offspring has the same copy number as the parent as well as normal diploid regions. Therefore, the posterior call for a segment that contains both inherited CNV and normal diploid regions will depend on the relative size of these regions. For example, if most of the segment is diploid the posterior call would be '222' (see State Symbols below for details regarding the state symbols). Conversely, if most of the region contains a deletion transmitted from the mother, the state call will be '211'. Of primary interest are regions for which the offspring copy number differs from the parental copy numbers. Note that for such regions, the CNV in the offspring may be Mendelian or non-Mendelian.

The likelihood for the called state and the likelihood for the normal state are named 'lik.state' and 'lik.norm', respectively. The ratio can provide a useful rank whereby large values indicate strong evidence for the called state.

State Symbols:

The MinimumDistance states can be easily remembered as the integer copy number for the father, mother, and offspring, respectively. For example, a region of the genome for which all individuals in the trio are diploid would have state '222'. By contrast, a region for which the father is diploid and the mother and offspring are hemizygous would have the state symbol '211'.

Value

A object of class RangedDataCBS with the predicted trio copy number states. Only states for which the offspring copy number differs from the parental copy numbers are reliable. In particular, the normal state (state '222') may contain both normal and inherited CNV as the minimum distance for both states is near zero.

Author(s)

R. Scharpf

See Also

[state](#) for accessing the state symbols (posterior calls) for the genomic ranges.

[viterbi2Wrapper](#)

Examples

```
library(oligoClasses)
foreach::registerDoSEQ()
path <- system.file("extdata", package="MinimumDistance")
fnames <- list.files(path, pattern=".txt")
ped <- Pedigree(fatherIds=fnames[1], motherIds=fnames[2],
  offspringIds=fnames[3])
map.segs <- callDenovoSegments(path=path,
  ext="",
```

```
pedigreeData=ped,
cdfname="human610quadv1b",
chromosome=1,
segmentParents=FALSE,
genome="hg18")
```

coerceMethods

Methods for coercing objects from one class to another

Description

Methods for coercing objects between classes.

Methods for RangedDataCNV

RangedDataCNV-derived classes will eventually be deprecated in **oligoClasses** and replaced by GRanges. To coerce from a RangedDataCNV object to a GRanges object, use

```
as(object, "GRanges"):
```

The coercion to GRanges retains information on coverage ('numberProbes'), sample identifiers ('sample'), state (when applicable), and segment means (when applicable).

Author(s)

R. Scharpf

concordance

Functions for assessing concordance

Description

Functions for assessing concordance and discordance of copy number variant calls

Usage

```
concAtTop(ranges.query, ranges.subject, list.size, verbose = TRUE, ...)
discAtTop(ranges.query, ranges.subject, verbose=TRUE, ...)
```

Arguments

ranges.query	RangedDataCNV object
ranges.subject	RangedDataCNV object
list.size	size of list in query and subject ranges
verbose	logical
...	Additional arguments passed to findOverlaps.

Details

concAtTop calculates three measures of concordance:

1. the proportion of top ranges that overlap between `ranges.query` and `ranges.subject` objects as a function of list size (we assume that each `RangedDataCNV` object is ordered such that the first range has the highest rank (most evidence of an alteration)).
2. the proportion of top ranges in `ranges.query` that appear anywhere in the `ranges.subject` object. Again, a proportion is calculated as a function of list size until the size of the list is equal to `list.size`.
3. the same as (2), but reversing the role of `ranges.query` and `ranges.subject`.

The function `discAtTop` identifies the ranges in `ranges.query` that do not appear in `ranges.subject`.

Value

`discAtTop` returns an object of the same class as `ranges.query`.

`concAtTop` returns a list of 3 elements, corresponding to the 3 approaches for estimating concordance described in the details.

Author(s)

Rob Scharpf

See Also

[findOverlaps](#)

correspondingCall *Find overlapping ranges*

Description

Finds ranges in a `RangedDataCNV` object that overlap with ranges from another `RangedDataCNV` object.

Usage

```
correspondingCall(ranges.query, ranges.subject, subject.method)
```

Arguments

`ranges.query` A `RangedDataCNV` object.
`ranges.subject` A `RangedDataCNV` object.
`subject.method` A character string. If provided, a column called 'method' will be added to `ranges.subject` that indicates the statistical algorithm used to call the de novo alterations.

Details

Given a set of de novo calls from one statistical algorithm, this function finds the corresponding calls made by a second statistical algorithm. For any given range in `ranges.query`, one or more ranges in `ranges.subject` may overlap.

Value

An object of the same class as `ranges.subject`.

Author(s)

Rob Scharpf

See Also

[findOverlaps](#)

gcSubtract	<i>Generic function for GC correction</i>
------------	---

Description

Generic function for GC correction

Usage

```
gcSubtract(object, ...)
```

Arguments

<code>object</code>	A <code>TrioSet</code> or <code>TrioSetList</code> object.
<code>...</code>	Additional arguments include <code>method</code> and <code>trio.index</code> . <code>Method</code> refers to the type of GC correction ("speed" or "lowess").

Details

For genomes in which the log R ratios look wavy when plotted as a function of physical position, a GC correction step may be helpful. Two options for GC correction are currently implemented. This function is experimental and may change in the future.

Value

An instance of the object (e.g., a `TrioSet` or a `TrioSetList`).

Author(s)

R. Scharpf

References

Need reference for Speed paper and reference.

See Also

[TrioSet](#), [TrioSetList](#)

isDenovo	<i>Indicator for whether a trio copy number state is a de novo copy number alteration.</i>
----------	--

Description

Return an indicator for a de novo copy number alteration.

Usage

```
isDenovo(states)
```

Arguments

`states` a string with 3 characters. Character elements 1-3 indicate the copy number state for the father, mother, and offspring, respectively. See Details.

Details

We consider a copy number alteration occurring in the offspring that is not present in either parent to be de novo, irrespective of whether the copy number alteration is transmitted by a Mendelian mechanism. Each segment is assigned a numeric trio copy number state. The state symbols are numeric. In particular, the state "xyz" indicates that the father has x copies, the mother has y copies, and the offspring has z copies. For example, the state '221' indicates copy number 2 in the mother and father, and a hemizygous deletion in the offspring. See MAP for details. A subset of the possible state combinations, such as '221', are considered de novo.

Value

Logical

Author(s)

Rob Scharpf

See Also

[MAP](#). See [state](#) for the accessor to extract the trio copy number state.

Examples

```
library(oligoClasses)
isDenovo(c(222, 221, 211, 223, 233))
data(map.segs)
table(isDenovo(state(map.segs)))
sts <- unique(state(map.segs))
sts[isDenovo(sts)]
```

mad2

Methods for computing the minimum absolute distance.

Description

Compute the median absolute deviation for elements in a list, array, or matrix. For lists, elements of the list can be matrices or arrays or ff-versions of these.

Usage

```
mad2(object, byrow=FALSE, ...)
```

Arguments

object	object can be any of the following: class TrioSetList, TrioSet, or a list of matrices.
byrow	When byrow is TRUE, the MAD is calculated for each marker across all offspring. When byrow is FALSE, the MAD is computed across all autosomal markers for the fathers, mothers, and offspring. The former provides a robust estimate of the marker-level variance across samples, whereas the latter provides an estimate of variance for the samples.
...	Not currently implemented.

Value

A list.

Examples

```
data(trioSetListExample)
foreach::registerDoSEQ()
## computing the MAD of the log R ratios for each individual (across markers)
mads.sample <- mad2(trioSetList, byrow=FALSE)
## compute the MAD of the log R ratio for each marker (across individuals)
## too few samples
##mads.marker <- mad2(trioSetList, byrow=TRUE)
```

MAP

*Estimate the trio copy number for minimum distance segments***Description**

Estimates the trio copy number state for the minimum distance segments as the state that maximizes the posterior probability. The posterior probability for the normal state ('222') is also returned.

Usage

```
MAP(object, ranges, id, TAUP=1e10, tauMAX=1-5e-8, cnStates=c(-2,-0.4, 0, 0, 0.4, 1), pr.nonmendelian=1
```

Arguments

object	A object of class <code>TrioSetList</code> or <code>TrioSet</code> .
ranges	A <code>GRanges</code> object.
id	A vector of trio identifiers (character string) for which to estimate the trio copy number states. If missing, the maximum a posteriori probability (MAP) estimate is computed for all trios in the <code>TrioSetList</code> object.
TAUP	Scalar for the probability that the state of segment t is the same as the state at segment $t-1$. Larger values decrease the probability of transitioning to an different state.
tauMAX	Upper bound for the probability that the state at marker t is the same as the state at marker $t-1$.
cnStates	Initial values for the mean of the copy number states for autosomal chromosomes. Required to be a vector of length 6 with means for homozygous deletion, hemizygous deletion, diploid, diploid region with loss of heterozygosity, single copy gain, two-copy gain.
pr.nonmendelian	Scalar between 0 and 1. The probability that the copy number state of the offspring was not inherited in a Mendelian fashion from the parental copy numbers.
mdThr	Minimum distance segments with $ \text{mean} $ less than <code>mdThr</code> are not called. These segments are assigned the trio-state '222'.
...	Additional arguments are passed to <code>viterbi2Wrapper</code> .

Value

A `GRanges` object. The value label "state" contains the trio copy number state denoted by `xyz`, where `x` is the copy number for the father, `y` is the copy number for the mother, and `z` is the copy number of the offspring.

References

The posterior calling is an extension of the joint HMM described in Wang et al, 2008 *Nucleic Acids Research*.

See Also

[TrioSetList](#), [TrioSet](#) [calculateMindist](#), [viterbi2Wrapper](#)

Examples

```
library(MinimumDistance)
library(oligoClasses)
foreach::registerDoSEQ()
data(trioSetListExample)
data(md.segs)
data(lrr.segs)
mdlist <- calculateMindist(lrr(trioSetList))
mads.md <- mad2(mdlist, byrow=FALSE)
md.segs2 <- narrowRanges(md.segs, lrr.segs, mad.minimumdistance=mads.md, thr=0.9, fD=featureData(trioSetList))
map.segs <- MAP(trioSetList, ranges=md.segs2)
## the trio states
state(map.segs)
```

narrowRanges

Adjust breakpoints from segmentation inward

Description

Narrow the minimum distance ranges by the segmentation of the offspring copy number estimates.

Usage

```
narrowRanges(object, lrr.segs, thr, mad.minimumdistance, verbose = TRUE, fD, genome)
```

Arguments

object	A GRanges object. The segmentation of the minimum distance.
lrr.segs	A GRanges object. The segmentation of the log R ratios.
thr	Numeric. For segments with a segment mean less than thr, the breakpoints are not altered.
mad.minimumdistance	A named numeric vector. The names should be the sampleNames of the TrioSet or TrioSetList object.
verbose	Logical. Whether to display messages that indicate progress.
fD	If object contains genomic ranges for a single chromosome, fD should be an object of class GenomeAnnotatedDataFrame. If object contains genomic intervals from multiple chromosomes, fD should be a list of GenomeAnnotatedDataFrames. To extract a list of GenomeAnnotatedDataFrames, use the method featureData defined for a TrioSetList class. To extract a GenomeAnnotatedDataFrame, apply the featureData method to a TrioSet object. The feature-level annotation contained in this object is used to update the coverage (column 'number-Probes') in the GRanges object after 'narrowing' the ranges.

genome If missing, the UCSC genome build is extracted from the metadata of argument object.

Details

If the start and stop coordinates for a segment $[x, y]$ with mean log R ratio greater than `thr` in absolute value, the x and y coordinates of the interval may be adjusted. If there are no breakpoints from the segmentation of the offspring log R ratio occurring in $[x, y]$, nothing is done. However, if one or more breakpoints occur in the interval $[x, y]$, one or more new segments can be created. For example, suppose a segment from the log R ratio segmentation has breakpoints given by $[a, b]$, where $x < b < y$. Then the following two intervals are created:

1. $[x, b]$
2. $[b, y]$

The motivation is to avoid having a single minimum distance segment spanning differing copy number states in the offspring.

Value

A GRanges object.

Author(s)

Rob Scharpf

Examples

```
library(oligoClasses)
data(trioSetListExample)
data(lrr.segs)
data(md.segs)
md <- calculateMindist(lrr(trioSetList))
md.mads <- mad2(md, byrow=FALSE)
md.segs.narrowed <- narrowRanges(object=md.segs, lrr.segs=lrr.segs, thr=0.9, mad.minimumdistance=md.mads, fd=fea
```

Pedigree

Constructor for Pedigree class

Description

Constructor for Pedigree class

Usage

```
Pedigree(pedigreeInfo, fatherIds=character(), motherIds=character(), offspringIds=character())
```

Arguments

pedigreeInfo	a data.frame with column labels F, M, and O containing sample identifiers for the father (F), mother (M), and offspring (O). Each row of the data.frame corresponds to a single trio.
fatherIds	A vector of sample ids for the father. Ignored if pedigreeInfo is specified.
motherIds	A vector of sample ids for the mother. Ignored if pedigreeInfo is specified.
offspringIds	A vector of sample ids for the mother. Ignored if pedigreeInfo is specified.

Details

Constructor for object that contains information regarding the case-parent trios

Value

Object of class Pedigree

Note

If pedigreeInfo is missing, the vector of character strings provided to indicate the ids of the father, mother and offspring should be ordered such that the ith element in each vector are the sample identifiers for one trio.

Author(s)

R. Scharpf

See Also

[Pedigree](#)

Examples

```
Pedigree()  
Pedigree(fatherIds=letters[1], motherIds=letters[2],offspringIds=letters[3])  
path <- system.file("extdata", package="MinimumDistance")  
load(file.path(path, "pedigreeInfo.rda"))  
Pedigree(pedigreeInfo)
```

Pedigree-class

Container for storing pedigree information

Description

Container for storing familial information for father, mother, offspring trios.

Objects from the Class

See the examples for instantiating a Pedigree object.

Slots

trios: Object of class "data.frame" ~~
trioIndex: Object of class "data.frame" ~~

Accessors

In the following code descriptions, object is an instance of the Pedigree class:

allNames(object): character vector of unique sample ids. Note that the length of this vector is not necessarily a multiple of 3 if some parents have multiple offspring.

annotatedDataFrameFrom(object, byrow=FALSE, sample.sheet, which=c("offspring", "father", "mother"),
Create an AnnotatedDataFrame for the father, mother or, offspring (depending on value of argument which). Optionally, a data.frame of covariates for the samples can be passed as an argument to sample.sheet. If sample.sheet is not missing, row.names can not be NULL.

dim(object): Returns an integer vector of length 2: the first element is the number of trios; the second element is 3.

fatherNames(object): character vector of father ids (not necessarily unique).

motherNames(object): character vector of mother ids (not necessarily unique).

offspringNames(object): character vector of offspring ids (must be unique).

trios(object): data.frame of sample ids. Each row in the data.frame contains the ids of father, mother, and offspring, respectively.

object[i,]: subset the Pedigree by trio index i.

Author(s)

R. Scharpf

See Also

[Pedigree annotatedDataFrameFrom](#)

Examples

```
showClass("Pedigree")
## an empty container
Pedigree()
```

phenoData

Extract phenotype data for parents in a trio.

Description

Extract phenotype data for parents in a trio.

Usage

```
motherPhenoData(object)  
fatherPhenoData(object)
```

Arguments

object A object of class TrioSet or TrioSetList

Details

Extracts phenotypic data for parents

Value

AnnotatedDataFrame

Author(s)

R. Scharpf

See Also

[TrioSet](#), [TrioSetList](#)

Examples

```
data(trioSetListExample)  
## father phenoData  
fatherPhenoData(trioSetList)  
## mother phenoData  
motherPhenoData(trioSetList)  
## offspring phenoData  
phenoData(trioSetList)
```

RangedDataCBS_Examples

Objects containing segmented data

Description

Example RangedDataCBS objects created from the segmentation of the log R ratios (object `cbs.segs`) and the minimum distance (object `md.segs`).

Usage

```
data(lrr.segs)  
data(md.segs)  
data(map.segs)
```


See Also

See [RangedDataCBS](#) for accessors and methods available for objects of this class. See [MAP](#) for details regarding how the object `map.segs` was instantiated.

Examples

```
data(lrr.segs)
data(md.segs)

###object containing maximum a posterior probabilities
data(map.segs)
```

segment2

Wrapper for segment function in package DNACopy

Description

`segment2` is a wrapper for the `segment` function in `DNACopy`. The first argument can be simple data structures: a list, a matrix, or an array, or more complex: `TrioSetList` and `TrioSet`. If the first argument is a list, each element of the list can be a matrix or an array.

Segmentation of `ff_matrix` and `ff_array` objects is also supported.

Details

When object is a list of arrays, the argument `id` is required. The easiest way to obtain a `data.frame` of the trio sample names is via the method `trios`, as in the example below.

Value

RangedDataCBS object

Arguments

Arguments to `segment2` depend on the class of object. In all forms, additional arguments to the `segment` function in the **DNACopy** package can be passed through the `...` operator.

For `TrioSetList` objects, the arguments are:

```
segment2(object, md=NULL, segmentParents=TRUE, verbose=TRUE, ...): md is a
list of matrices containing the minimum distance. See calculateMindist. segmentParents
must be logical. When TRUE, the parental log R ratios are segmented via circular binary
segmentation. When FALSE, only the offspring log R ratios are segmented.
```

For objects of class `TrioSet`:

```
segment2(object, md=NULL, segmentParents=TRUE, verbose=TRUE, ...): md is a matrix
of the minimum distance where each column corresponds to a trio in the TrioSetList object.
```

For objects of class `list`:

`segment2(object, pos, chrom, id=NULL, featureNames, segmentParents=TRUE, verbose=TRUE, ...)`:
 pos is a list of the genomic positions (integers) for each row of the elements of the object list. Similarly, chrom and featureNames are lists specifying the chromosome (integer) and feature identifiers (character) for each row in the object list elements, respectively. Note: pos, chrom, and featureNames must be lists of the same size.

For objects of class matrix :

`segment2(object, pos, chrom, id=NULL, featureNames, segmentParents=TRUE, verbose=TRUE, ...)`:
 pos is a vector of the genomic positions (integers) for each row in the object matrix. Similarly, chrom and featureNames are vectors specifying the chromosome (integer) and feature identifiers (character) for each row in the object matrix, respectively. Note: pos, chrom, and featureNames must be vectors of the same size.

See Also

[segment](#)

Examples

```
## Not run: ## examples are checked in the vignette
data(trioSetListExample)
mdlist <- calculateMindist(lrr(trioSetList))
md.segs <- segment2(trioSetList, md=mdlist)
metadata(md.segs)
lrr.segs <- segment2(trioSetList, segmentParents=FALSE)
metadata(lrr.segs)

## End(Not run)
```

`stackRangedDataList` *Stack a list of RangedDataCBS objects.*

Description

Stack a list of RangedDataCBS objects.

Usage

```
stackRangedDataList(...)
```

Arguments

... A list. Each element has class RangedDataCBS.

Value

Object of class RangedDataCBS.

Author(s)

R. Scharpf

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

```
data(map.segs)
stackRangedDataList(list(map.segs, map.segs))
```

TrioSet

*Constructor for TrioSet objects.***Description**

Construct an object of class TrioSet.

Usage

```
TrioSet(pedigreeData = Pedigree(), sample.sheet, row.names = NULL, lrr,
       baf, featureData, cdfname, drop = TRUE, mindist=NULL, genome=c("hg19",
       "hg18"))
```

Arguments

pedigreeData	A Pedigree object.
sample.sheet	A data.frame of sample covariates.
row.names	Row identifiers for sample.sheet that match the names of the trios in the Pedigree object.
lrr	Matrix of log R ratios
baf	Matrix of B allele frequencies
featureData	AnnotatedDataFrame for features.
cdfname	character string for annotation package.
drop	Logical. If FALSE, the row and column dimnames are null.
mindist	A matrix of the minimum distance.
genome	character: the UCSC genome build used for the probe annotation

ValueA object of class [TrioSet](#).

Author(s)

R. Scharpf

See Also[TrioSet](#), [Pedigree](#), [Pedigree](#)**Examples**

```

path <- system.file("extdata", package="MinimumDistance")
load(file.path(path, "logRratio.rda"))
load(file.path(path, "baf.rda"))
load(file.path(path, "pedigreeInfo.rda"))
trioSet <- TrioSet(lrr=logRratio,
  baf=baf,
  pedigree=Pedigree(pedigreeInfo),
  cdfname="human610quadv1bCr1mm",
  genome="hg18")

```

TrioSet-class

*Class "TrioSet"***Description**

A TrioSet is a container for storing high throughput assay data and metadata from genotyping arrays when the study design is case-parent trios. In our application, de novo copy number alterations in affected offspring were of the primary interest. Examination of the joint distribution of the log R ratios and B allele frequencies across members in a trio motivates a container with assay data elements that are 3-dimensional arrays rather than 2-dimensional matrices. The dimension of the arrays is marker x trio x individual. Typically, a TrioSet instance stores the data for a single chromosome and an instance of TrioSetList is a list of TrioSets. While having a single TrioSet for the entire dataset would simplify the classes of objects defined in this package, multiple arrays with thousands of trios and roughly a million markers are impractical on most machines. In addition, storage by chromosome will facilitate parallelization of computation that can be carried out independently on different chromosomes.

Objects from the Class

Objects can be created by calls of the form :

```
new("TrioSet", logRRatio, BAF, phenoArray, mindist, mad, ...).
```

Subsetting

As the TrioSet class is an extension of eSet, the subsetting is similar. One important difference is that the assay data elements are 3 dimensional arrays. While *k* is not a formal argument in the generic for "[", *k* can be passed to the "[" method for TrioSet objects for subsetting the 3rd dimension of the assay data.

`object[i, j, drop]`: `i` selects features, `j` selects trios, and `k` (though not part of the generic) selects for the individual in a trio. Valid values for `k` are 1 (selects father), 2 (selects mother), or 3 (selects offspring).

Accessors

The object in the accessor descriptions that follow is a `TrioSet`:

`allNames(object)`: The individual ids for each subject. See `offspringNames`, `fatherNames`, and `motherNames` to list ids corresponding to membership in the trio.

`baf(object)`: Extract array of B allele frequencies.

`baf(object) <- value`: assign B allele frequencies. `value` is a 3-dimensional array (feature x trio x sample).

`dim(object)`: Returns the dimension of the assay data elements. Each assay data element is a three dimensional array with dimensions for features, trios, and sample, respectively.

`fatherNames(object) <- value`: Assign character string of father sample names.

`fatherNames(object)`: Return character string of father identifiers.

`fatherPhenoData(object)`: Extract `AnnotatedDataFrame` for father pheno data.

`lrr(object) <- value`: assign log R ratios to assayData. `value` is a 3-dimensional array (feature x trio x sample).

`mindist(object)`: Accessor for the minimum distance matrix.

`mindist(object) <- value`: Replacement method for slot `mindist`. Value must be a matrix.

`motherNames(object) <- value`: Assign a character string for the mother identifiers

`motherPhenoData(object)`: Extract `AnnotatedDataFrame` for mother pheno data.

`motherNames(object)` Return a character vector of mother identifiers

`ncol(object)` Number of trios in the `TrioSet` object

`offspringNames(object) <- value`: Assign a character vector of offspring identifiers

`offspringNames(object)`: Retrieve character vector of offspring identifiers. Note that the result will identical to `sampleNames(object)` as the offspring identifiers uniquely identify a trio

`offspringPhenoData(object)`: Extract a `AnnotatedDataFrame` of the sample-level covariates for the offspring. Alternatively, use `phenoData(object)`.

`order(object)`: order `TrioSet` object by chromosome and physical position

`pedigree(object)`: accessor for pedigree slot. Returns an object of class `Pedigree`.

`trios(object)`: Returns the data.frame stored in slot `trios` of the `Pedigree` class object stored in slot `pedigree` of the `TrioSet` object.

Methods for coercing TrioSet objects to another class

`as(object, "TrioSetList")`: coerce an object of class `TrioSet` to an object of class `TrioSetList`

`as(object, "data.frame")`: coerce an object of class `TrioSet` to a `data.frame` with the following column labels: `x` (position), `lrr` (log R ratio), `gt` (genotypes – ignored if genotypes are not included in the `assayData`), `baf` (B allele frequencies), `id`, and `is.snp`. The coercion to a `data.frame` is used primarily for visualization methods using function derived from `xypLOT` in the **lattice** package. This is experimental and subject to change in future versions.

Compute the minimum distance

`calculateMindist(object)`: calculate the minimum distance for an object of class `TrioSet`.

Posterior summaries

`MAP(object, ranges, mad.marker, mad.sample, returnEmission=FALSE, verbose=TRUE, ...)`:

Compute posterior probabilities for the trio copy number states. The called trio copy number state is the argmax of the posterior probabilities. See examples below for computing the standard deviation of the markers for argument `mad.marker` and the standard deviation of the samples for argument `mad.sample`.

The MAP function returns a `GRanges` or a `GRangesList` object with the genomic intervals annotated by the trio copy number state (see below), the number of markers used to call the region, the segment mean as estimated by circular binary segmentation, the log-likelihood of the diploid state, and the log-likelihood of the MAP estimate.

The trio copy number states are indicated by the integer `xyz`, where `x` is the copy number of the father, `y` is the copy number of the mother, and `z` is the copy number of the offspring.

Visualization

See [xyplotTrio](#)

Miscellaneous

`updateObject(object)`: Currently, this method only checks the class of the `featureData` slot. If the class is `AnnotatedDataFrame`, the `featureData` is updated to the `GenomeAnnotatedDataFrame` class.

Author(s)

R. Scharpf

See Also

[TrioSet](#), [TrioSetList](#), [calculateMindist](#)

Examples

```
library(IRanges)
showClass("TrioSet")
## instantiate a TrioSet with an array of log R ratios (logRR) and B
## allele frequencies
new("TrioSet")
TrioSet()
data(trioSetListExample)
trioSet <- stack(trioSetList)
```

TrioSetList *Constructs and object of class TrioSetList*

Description

Constructs and object of class TrioSetList

Usage

```
TrioSetList(chromosome=integer(), pedigreeData=Pedigree(), sample.sheet,  
row.names=NULL, lrr, baf, featureData, cdfname, ffname="",genome)
```

Arguments

chromosome	Vector of integers indicating which chromosomes are stored in the TrioSetList object.
pedigreeData	A object of class Pedigree.
sample.sheet	A data.frame of sample-level covariates.
row.names	The row.names must match the sample identifiers stored in the argument to pedigreeData. If sample.sheet is missing, row.names is ignored.
lrr	Matrix of log R Ratios
baf	matrix of B allele frequencies
featureData	Object of class AnnotatedDataFrame containing feature annotation. If missing, the argument cdfname must be specified.
cdfname	A character string providing the name of the annotation package.
ffname	Prefix for naming ff files. Ignored if ff package is not loaded.
genome	character string indicating UCSC genome build. Only "hg19" is allowed for annotation packages that support a single build. For annotation packages that support multiple builds, valid builds are "hg18" and "hg19".

Value

An object of class TrioSetList

See Also

[TrioSetList](#), [phenoData](#)

Examples

```
library(oligoClasses)  
TrioSetList()  
TrioSetList(chromosome=1:22)  
  
## A more realistic example
```

```

## Note that a data.frame containing covariates on the samples can be
## passed through the sample.sheet argument
library(human610quadv1bCr1mm)
path <- system.file("extdata", package="MinimumDistance")
load(file.path(path, "pedigreeInfo.rda"))
load(file.path(path, "sample.sheet.rda"))
load(file.path(path, "logRratio.rda"))
load(file.path(path, "baf.rda"))
nms <- paste("NA", substr(sample.sheet$Sample.Name, 6, 10), sep="")
trioSetList <- TrioSetList(lrr=logRratio, ## must provide row.names
  baf=baf,
  pedigree=Pedigree(pedigreeInfo),
  sample.sheet=sample.sheet,
  row.names=nms,
  cdfname="human610quadv1bCr1mm",
  genome="hg18")
motherPhenoData(trioSetList)
fatherPhenoData(trioSetList)
offspringPhenoData(trioSetList)
## log R ratios for the first trioSetList element
str(lrr(trioSetList)[[1]])
## B allele frequencies for the first trioSetList element
str(baf(trioSetList)[[1]])

```

TrioSetList-class *Class "TrioSetList"*

Description

A container storing pedigree information, as well as low-level statistical summaries used for copy number estimation: the log R ratios and B allele frequencies. The list structure is organized by chromosome, where each element of the list is a TrioSet object.

Objects from the Class

Objects from the class can be initialized by:

`new("TrioSetList")`: Instantiate an empty container.

`TrioSetList()`: See [TrioSetList](#).

Slots

assayDataList: list of arrays containing log R ratios and B allele frequencies.

featureDataList: list of containing feature annotation. Each element of the list is a `AnnotatedDataFrame`.

pedigree: Object of class "Pedigree". Contains information on the trio-relationships.

motherPhenoData: Object of class "AnnotatedDataFrame". Contains sample-level covariates for the mother.

fatherPhenoData: Object of class "AnnotatedDataFrame". Contains sample-level covariates for the father.

phenoData: Object of class "AnnotatedDataFrame". Contains sample-level covariates for the offspring.

chromosome: Integer vector indicating which autosomes are contained in the TrioSetList object.

Accessors

In the following accessor descriptions, object is a TrioSetList:

`object$NAME`: Extract phenotype 'NAME' for offspring.

`"[[`": Extract a TrioSet object.

`allnames(object)`: Returns character vector of all the sample names. Note that `sampleNames` of a TrioSetList object is not the same. In particular, `sampleNames(object)` returns only the character vector of offspring ids which uniquely identify a trio. Hence, a separate method, `allNames`, is supplied when all the sample ids in the data set are required. Finally, note that the length of the vector returned by `allNames` is not necessarily a multiple of 3 as mothers and fathers with multiple offspring would be included in multiple trios.

`annotation(object)`: character string indicating the array platform

`baf(object)`: Returns a list of B allele frequencies for each chromosome. Each element in the list is a 3-dimensional array (features x trios x samples).

`dims(object)`: Return dimensions of the low-level statistical summaries (log R ratios and B allele frequencies) for each TrioSet element in the TrioSetList.

`fatherNames(object)`: character vector of father ids.

`fatherPhenoData(object)`: Extract a AnnotatedDataFrame of the sample-level covariates for the father.

`featureData(object)`: Extracts a list of GenomeAnnotatedDataFrames.

`length(object)`: The number of chromosomes.

`lrr(object)` Returns list of log R ratios for each chromosome. Each element in the list is a 3-dimensional array (features x trios x samples).

`mad2(object, byrow=TRUE)` Calculates the median absolute deviation (MAD) of the log R ratios in object. When `byrow` is TRUE, the MAD is calculated for each marker across all offspring. When `byrow` is FALSE, the MAD is computed across all autosomal markers for the fathers, mothers, and offspring. The former provides a robust estimate of the marker-level variance across samples, whereas the latter provides an estimate of variance for the samples.

`mindist(object) <- value`: Assigns the minimum distance to each TrioSet element. `value` is a list.

`mindist(object)`: Accessor for the minimum distance in each TrioSet element. Returns a list.

`motherNames(object)`: Character vector of sample identifiers for the mothers.

`motherPhenoData(object)`: Extract a AnnotatedDataFrame of the sample-level covariates for the mother.

`ncol(object)`: the number of trios, or equivalently the number of offspring.

`nrow(object)`: The number of features across all TrioSet elements.

`offspringNames(object)`: Character vector of offspring identifiers. Note that the offspring ids uniquely identify a trio, and the method `sampleNames` will return the same result.

order(object): order TrioSet object by chromosome and physical position

pedigree signature(object = "TrioSetList"): Accessor for pedigree information. See also [Pedigree](#)

offspringPhenoData(object): Extract a AnnotatedDataFrame of the sample-level covariates for the offspring. Alternatively, use phenoData(object).

phenoData(object): Extract a AnnotatedDataFrame of the sample-level covariates for the offspring.

sampleNames(object): Character vector of unique identifiers for father-mother-offspring trio. As the offspring id uniquely identifies a trio, sampleNames returns the same vector of ids as offspringNames

trios(object): Returns a data.frame of the trios. Each row in the data.frame contains the sample identifiers for the father, mother, and offspring. Parents with multiple offspring will appear in multiple rows.

Subsetting

x[i, j]: i selects the list elements. j selects the trio for each list element. The list elements have class [TrioSet](#).

Stacking a TrioSetList object

A TrioSetList object contains a list of elements of class TrioSet. Each list element corresponds to one chromosome. A TrioSet object can be constructed from a TrioSetList by stacking the TrioSet elements:

stack(object): creates a TrioSet object from a TrioSetList object.

Compute the minimum distance

calculateMindist(object): Compute the minimum distance from the list of log R ratio arrays. Returns a list of matrices of the minimum distance; each element in the list is the minimum distance for one chromosome.

Posterior summaries

MAP(object, ranges, mad.marker, mad.sample, returnEmission=FALSE, verbose=TRUE, ...): Compute posterior probabilities for the trio copy number states. The called trio copy number state is the argmax of the posterior probabilities. See examples below for computing the standard deviation of the markers for argument mad.marker and the standard deviation of the samples for argument mad.sample.

The MAP function returns a GRanges or a GRangesList object with the genomic intervals annotated by the trio copy number state (see below), the number of markers used to call the region, the segment mean as estimated by circular binary segmentation, the log-likelihood of the diploid state, and the log-likelihood of the MAP estimate.

The trio copy number states are indicated by the integer xyz, where x is the copy number of the father, y is the copy number of the mother, and z is the copy number of the offspring.

coercion

`as(object, "SummarizedExperiment")` Coerces a TrioSetList object to a SummarizedExperiment.

Miscellaneous

`updateObject(object)`: Currently, this method only checks the class of the elements in the `featureDataList` slot. If the elements are `AnnotatedDataFrame` instead of `GenomeAnnotatedDataFrame`, the `featureDataList` slot is updated.

Author(s)

R. Scharpf

See Also

[TrioSet](#), [Pedigree](#), [gcSubtract](#)

Examples

```
showClass("TrioSetList")
library(Biobase)
TrioSetList()
data(trioSetListExample)
featureData(trioSetList)
```

`trioSetListExample` *An example of a TrioSetList object*

Description

A `TrioSetList` object instantiated from HapMap samples arrayed on a high-throughput Illumina genotyping platform.

Usage

```
data(trioSetListExample)
```

Format

`TrioSetList` object

Details

Each element in the `TrioSetList` is a `TrioSet`.

Source

Two HapMap trios.

Examples

```
data(trioSetListExample)
class(trioSetList[[1]])
```

TrioSetListLD	<i>Constructor for TrioSetList class for large data</i>
---------------	---

Description

Constructor for TrioSetList class for large data

Usage

```
TrioSetListLD(path, fnames, ext="", samplesheet, row.names,
pedigreeData, featureData, annotationPkg, outdir=ldPath(), ffprefix="",
genome=c("hg19", "hg18"))
```

Arguments

path	Path to plain-text files containing log R ratios and B allele frequencies. Files should contain data for a single sample.
fnames	Character string providing the filenames.
ext	Character string indicating whether the fnames has a file extension (e.g., ".txt")
samplesheet	(Optional) data.frame containing phenotypic / experimental covariates on the samples. Note that if samplesheet is provided, row.names must be specified.
row.names	Character vector indicating the sample id for each row in samplesheet. row.names should be unique and, ideally, correspond to fnames,
pedigreeData	An object of class Pedigree.
featureData	A GenomeAnnotatedDataFrame
annotationPkg	Character string indicating the annotation package used to extract information on the features (chromosome, physical position, and whether the feature is polymorphic ('isSnp')).
outdir	Character string indicating the path for storing ff objects. Ignored if the ff package is not loaded.
ffprefix	character string indicating the prefix used to name ff objects. Ignored if the ff package is not loaded.
genome	character string indicating UCSC genome build. Only "hg19" is allowed for annotation packages that support a single build. For annotation packages that support multiple builds, valid builds are "hg18" and "hg19".

Details

If the **ff** package is loaded, the assayData elements will be of class `ff_array`. Otherwise, the assayData elements will be ordinary arrays. For large datasets (or for computers with limited RAM), loading the **ff** may be required.

Value

A TrioSetList object

Author(s)

R. Scharpf

See Also

[TrioSetList](#)

Examples

```
if(require("ff")){
  library(ff)
  library(oligoClasses)
  ldPath(tempdir())
  path <- system.file("extdata", package="MinimumDistance")
  fnames <- list.files(path, pattern="[FMO].txt")
  trioSetListff <- TrioSetListLD(path=path,
    fnames=fnames,
    pedigreeData=Pedigree(data.frame(F="F.txt",
    M="M.txt", O="O.txt")),
    annotationPkg="human610quadv1bCr1mm",
    outdir=ldPath(),
    genome="hg19")
}
```

xypanelTrio

Panel function for a lattice-style plot of log R ratios, BAFs, and the minimum distance for a trio.

Description

Panel function for plotting log R ratios, BAFs, and the minimum distance for a trio. This function is not called directly by the user, but passes as the argument to panel in the function xyplotTrio.

Usage

```
xypanelTrio(x, y, memberId, baf, is.snp, range, lrr.segments,
  md.segments, baf.color="blue", col.hom = "grey20", fill.hom =
  "lightblue", col.het = "grey20", fill.het = "salmon", col.np = "grey20",
  fill.np = "grey60", state.show = TRUE, state.cex = 1, state.col =
  "blue", segment.col="grey50", ped, nchar_sampleid,..., subscripts)
```

Arguments

<code>x</code>	Physical position. Remark: plotted as $x/1e6$ for Mb units.
<code>y</code>	log R ratios or minimum distance
<code>memberId</code>	father, mother or offspring.
<code>baf</code>	B allele frequencies
<code>is.snp</code>	Logical for whether the marker is at a SNP
<code>range</code>	A <code>RangedDataCNV</code> -derived object with physical position for the range, a <code>'chrom'</code> , and an <code>'id'</code> columns. Should be only one genomic interval.
<code>lrr.segments</code>	Optional. A <code>RangedDataCBS</code> containing the results from a (CBS) segmentation of the log R ratios
<code>md.segments</code>	Optional. A <code>RangedDataCBS</code> containing the results from a (CBS) segmentation of the minimum distance.
<code>baf.color</code>	Color for plotting BAFs.
<code>col.hom</code>	Color for homozygous genotypes
<code>fill.hom</code>	Fill color for homozygous genotypes
<code>col.het</code>	Color for heterozygous genotypes
<code>fill.het</code>	Fill color for heterozygous genotypes
<code>col.np</code>	Color for nonpolymorphic markers (genotypes irrelevant)
<code>fill.np</code>	Fill color for nonpolymorphic markers (genotypes irrelevant)
<code>state.show</code>	Whether to display the inferred state from the <code>rd</code> object.
<code>state.cex</code>	The size of the displayed state. Ignored if <code>show.state</code> is <code>FALSE</code> .
<code>state.col</code>	Color of the text used for displaying the state.
<code>segment.col</code>	Line color for overplotting the segment means (e.g., from CBS) in the <code>lrr.segments</code> and <code>md.segments</code> objects.
<code>ped</code>	Object of class <code>Pedigree</code>
<code>nchar_sampleid</code>	Integer indicating the number of characters of the sample identifier printed in the panel strip.
<code>...</code>	Additional arguments to <code>lpoints</code> and <code>panel.xyplot</code>
<code>subscripts</code>	See <code>xyplot</code>

Value

This function is used to plot data in the panels of a lattice graphic and is not called directly by the user.

Author(s)

R Scharpf

See Also

[xyplot](#), [xyplotTrio](#), [lpoints](#), [panel.xyplot](#)

xyplotTrio	<i>Function for plotting log R ratios, BAFs, and the minimum distance for a trio using lattice.</i>
------------	---

Description

Function for plotting log R ratios, BAFs, and the minimum distance for a trio using lattice.

Usage

```
xyplotTrio(rd, object, frame = 2e+05, lrr.segments, md.segments,
           nchar_sampleid=15L, ...)
```

Arguments

rd	A genomic interval represented as a RangedDataCNV-derived object such as the RangedDataHMM class
object	An object of class TrioSetList.
frame	The distance (in basepairs) to plot upstream and downstream of the genomic interval in rd.
lrr.segments	Optional. A RangedDataCBS object containing the results of a segmentation of the log R ratios (e.g, by circular binary segmentation).
md.segments	Optional. A RangedDataCBS object containing the results of a segmentation of the minimum distance (e.g, by circular binary segmentation).
nchar_sampleid	Integer specifying the number of characters of the sample identifier to display in the panel. The default is 15 characters.
...	Additional arguments are passed to xypanelTrio and low-level lattice functions including panel.xyplot and lpoints.

Value

A trellis object

Author(s)

R Scharpf

See Also

[RangedDataHMM](#), [RangedDataCBS](#), [xyplot](#), [xypanelTrio](#)

Examples

```

library(oligoClasses)
library(MinimumDistance)
data(trioSetListExample)
data(map.segs)
data(lrr.segs)
data(md.segs)
## select a range with a possible de novo copy number alteration in the offspring
rd <- map.segs[which(isDenovo(state(map.segs)))[1], ]
trioSet <- trioSetList[[match(as.character(chromosome(rd)), paste("chr",chromosome(trioSetList),sep=""))]][, ma
mindist(trioSet) <- calculateMindist(lrr(trioSet))
figs <- xyplotTrio(rd=rd,
  object=trioSet,
  frame=200e3,
  ylab="log R ratio and BAFs",
  xlab="physical position (Mb)",
  panel=xypanelTrio,
  scales=list(x="same",
  y=list(alternating=1,
  at=c(-1, 0, log2(3/2), log2(4/2)),
  labels=expression(-1, 0, log[2](3/2), log[2](4/2))),
  lrr.segments=lrr.segs,
  md.segments=md.segs,
  layout=c(1, 4),
  col.hom="grey50",
  col.het="grey50",
  col.np="grey20",
  state.cex=0.8,
  cex=0.3,
  ylim=c(-3, 1.5),
  par.strip.text=list(lines=0.8, cex=0.6),
  key=list(text=list(c(expression(log[2]("R ratios")), expression("B allele frequencies")),
  col=c("black", "blue")), columns=2))
print(figs)

```


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