

Package ‘ChromHeatMap’

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Title Heat map plotting by genome coordinate

Description The ChromHeatMap package can be used to plot genome-wide data (e.g. expression, CGH, SNP) along each strand of a given chromosome as a heat map. The generated heat map can be used to interactively identify probes and genes of interest.

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R topics documented:

ALLs.chr22	2
chrdata	3
chrHeatMap	3
ChrMapPlot	5
chrNames	6
ChrStrandData	7
ChrStrandMatrix	8
createChrMatrix	9

cytobands	10
drawMapDendro	11
grabChrMapProbes	12
makeChrStrandData	13
makeChrStrandData-methods	14
makeRangedDataList	15
plotChrMap	16
stains	17
strandName	18
Index	19

ALLs.chr22	<i>Chromosome 22 subset of ALL data for ALL1/AF4 and E2A/PBX1</i>
------------	---

Description

This is a greatly reduced subset of the Chiaretti et al. ALL data set (available in its entirety as the Bioconductor ALL package). The data in this subset consist of microarrays from 15 different individuals with acute lymphoblastic leukemia (ALL). The data are further restricted to chromosome 22 only. This data set is intended for demonstration purposes only.

Usage

ALLs.chr22

Format

- An ExpressionSet with the following covariates:
- ageThe age of the patient in years.
 - mol.bioThe assigned molecular biology of the cancer (mainly for those with B-cell ALL). In this data set this is restricted to ALL1/AF4 and E2A/PBX1.

Source

The ALL Bioconductor data package

References

Sabina Chiaretti, Xiaochun Li, Robert Gentleman, Antonella Vitale, Marco Vignetti, Franco Mandelli, Jerome Ritz, and Robin Foa Gene expression profile of adult T-cell acute lymphocytic leukemia identifies distinct subsets of patients with different response to therapy and survival. Blood, 1 April 2004, Vol. 103, No. 7.

chrdata	<i>The ALLs.chr22 ExpressionSet, reformatted as a ChrStrandData object</i>
---------	--

Description

This is a greatly reduced subset of the Chiaretti et al. ALL data set (available in its entirety as the Bioconductor ALL package). The data in this subset consist of microarrays from 15 different individuals with acute lymphoblastic leukemia (ALL). The data are further restricted to chromosome 22 only. This data set is intended for demonstration purposes only. See the documentation for `makeChrStrandData` for a description of the `ChrStrandData` object format. This format directly associates the `ExpressionSet` data with chromosome location, speeding up retrieval of data during heat map plotting.

Usage

```
chrdata
```

Format

A `ChrStrandData` object

Source

The ALL Bioconductor data package

References

Sabina Chiaretti, Xiaochun Li, Robert Gentleman, Antonella Vitale, Marco Vignetti, Franco Mandelli, Jerome Ritz, and Robin Foa Gene expression profile of adult T-cell acute lymphocytic leukemia identifies distinct subsets of patients with different response to therapy and survival. *Blood*, 1 April 2004, Vol. 103, No. 7.

chrHeatMap	<i>Plot ChrStrandMatrix objects as heat maps along a chromosome</i>
------------	---

Description

Plots a either one or two `ChrStrandMatrix` objects (typically constructed using the `createChrMatrix` function) as heat maps along a specified chromosome, optionally clustering samples and including an idiogram.

Usage

```
chrHeatMap (strand.data, cytopaint.func=NULL, col = "heat.colors",
            start, end, breaks, RowSideColors, title=TRUE,
            margins = c(6, 6), cexCyto = 0.8, srtCyto=90, lmat = NULL, lhei = NULL,
            lwid = NULL, ...)
```

Arguments

strand.data	A ChrStrandMatrix object, or a list of such objects, one per strand to be plotted (or a single matrix for ‘both’ strands), created using the createChrMatrix function.
cytopaint.func	A function closure taking a single argument, ‘boxwidth’, and plotting its enclosed idiogram data at that width. See plotChrMap for the code used to generate this closure.
col	A vector of colors to use for the heat map, or the name of a function generating such a vector.
start	The starting genome coordinate for the plot.
end	The ending genome coordinate for the plot.
breaks	A vector of numeric break points indicating the boundaries between the col colors.
RowSideColors	A vector of colors to use for a color band indicating e.g. sample categories.
title	If TRUE, this causes the function to include default heat map subtitles indicating which chromosome and strand has been plotted. If FALSE or NULL, subtitles will left blank. If this argument is set to a character vector of the same length and order as strand.data its contents will be used as heat map subtitles.
margins	A numeric vector indicating the c(bottom, left) margins of the plot containing X and Y axes labels.
cexCyto	A positive number used to control the font size for the idiogram plot. For plots spanning just a few cytobands it may be worth setting this to a larger number, and srtCyto, below, to zero.
srtCyto	A number indicating the degree to which the idiogram text labels should be rotated. This defaults to 90 degrees, but for more detailed plots a setting of zero here often looks better.
lmat	An optional matrix to be passed to layout.
lhei	An optional vector of layout row heights.
lwid	An optional vector of layout row widths.
...	Additional arguments are passed to the drawMapDendro function.

Details

Typically this function should not be called directly, but rather via the wrapper plotChrMap function. This function uses cytoband data from the UCSC genome annotation database and code adapted from the quantsmooth package to draw an idiogram of the chromosome, or a subset thereof.

Value

This function is executed for its side effects.

Author(s)

Tim F Rayner

References

lodplot and quantsmooth packages

See Also

[plotChrMap](#), [createChrMatrix](#), [drawMapDendro](#)

Examples

```
data('demo')
stranddata <- createChrMatrix( chrdata, chr=22, strand='forward', start=21925000, end=24300000 )
chrHeatMap(stranddata)
```

ChrMapPlot

Class containing a mapping between plot location and probe or gene identifier.

Description

ChrMapPlot objects are generated as an output from the main `plotChrMap` function, which users can then pass to the `grabChrMapProbes` function.

Creating Objects

Objects of this class are created using the `plotChrMap` function:

```
plotChrMap(chrdata, '22')
```

Slots

labels An array of probe or gene identifiers, with names corresponding to chromosome coordinates.

start The leftmost interval number (most usually 1).

end The rightmost interval number.

Methods

Standard generic methods:

`show(ChrMapPlot)` Generates a short description of the ChrMapPlot object.

Author(s)

Tim F Rayner

See Also

[plotChrMap](#), [grabChrMapProbes](#).

Examples

```
data('demo')
plotmap <- plotChrMap(chrdata, '22', cytoband='q11.23')
probes <- grabChrMapProbes(plotmap)
library('hgu95av2.db')
genes <- mget(probes, hgu95av2SYMBOL, ifnotfound=NA)
```

chrNames

Retrieve chromosome names from an object.

Description

This generic function simply returns the names of all the chromosomes represented by a given ChrStrandData or ChrStrandMatrix object. Note that not every sample associated with a ChrStrandData object need have data from every chromosome.

Usage

```
chrNames(object)
```

Arguments

object Object derived from class ChrStrandData or ChrStrandMatrix

Value

chrNames(object) returns a character vector listing the chromosomes.

Author(s)

Tim F Rayner

See Also

[ChrStrandData-class](#)

ChrStrandData	<i>Class to contain data associated with chromosome coordinates across a whole genome.</i>
---------------	--

Description

Container for data from high-throughput assays mapped to chromosome locations.

Creating Objects

The most convenient way to create a ChrStrandData object is to use the `makeChrStrandData` function, which can be used to convert data stored in either an `ExpressionSet` or data frame into a ChrStrandData object:

```
makeChrStrandData(ALL, lib = "hgu95av2.db")
```

Slots

data a 'list', whose components correspond to samples in the same order as appearing in the columns of 'expr'. Each component is also a 'list', named by chromosomes "1"-"22", "X" and "Y". Each named component is again a 'list' with two elements named "posS" and "negS", corresponding to the forward and reverse strands of a chromosome, each of which is a list containing start coordinates ("x"), end coordinates("xe") and the corresponding data values ("y").

lib A string giving the name of the annotation data package to use.

chrs The list of chromosomes represented in the object.

Methods

Class-specific methods.

`annotation(ChrStrandData)` Returns the name of the AnnotationDbi library used to annotate the object.

`chrNames(ChrStrandData)` Returns a list of the chromosomes represented in the object.

`sampleNames(ChrStrandData)` Returns the names of the samples associated with the object.

Standard generic methods:

`show(ChrStrandData)` Generates a short description of the ChrStrandData object.

`summary(ChrStrandData)` Generates a summary of the data available for each chromosome in the ChrStrandData object.

Author(s)

Tim F Rayner

See Also

[makeChrStrandData](#), [ChrStrandMatrix-class](#).

Examples

```
data('demo')
chrdata <- makeChrStrandData(exprs(ALLs.chr22), lib = "hgu95av2.db")
```

ChrStrandMatrix	<i>Class to contain data associated with genome locations for a specific chromosome.</i>
-----------------	--

Description

Container for chromosome-specific subsets of data selected from an genome-wide ChrStrandData object, suitable for use with chrHeatMap.

Creating Objects

Typically, objects of this class are created and used internally by the createChrMatrix and chrHeatMap functions. Objects can be created in a similar fashion by end-users:

```
createChrMatrix(chrdata, chr=22, strand='forward', start=21925000, end=24300000, interval=5000)
```

Note that this function may combine data from multiple probes or genes (taking the mean) into a single chromosomal locus based on the size of the specified interval. If this happens the combined probe/gene identifiers are concatenated in the output object, separated by a semicolon.

Slots

data The data matrix, arranged with samples in columns and genomic locations in rows.

probeID An array of probe or gene identifiers associated with the data. The names attached to this array correspond with chromosome coordinate (specifically, the starting coordinates, i.e. the left-hand edges). These identifiers will ultimately be returned by e.g. the grabChrMapProbes function.

chr The chromosome name or number.

strand The chromosome strand ('forward', 'reverse' or 'both').

start The starting chromosome coordinates for each genomic location.

end The ending chromosome coordinates for each genomic location.

Methods

Class-specific methods.

chrNames(ChrStrandMatrix) Returns the name of the chromosome for the object.

strandName(ChrStrandMatrix) Returns the chromosome strand for the object.

sampleNames(ChrStrandMatrix) Returns the names of the samples associated with the object.

featureNames(ChrStrandMatrix) Returns the probe or gene identifiers associated with the object.

exprs(ChrStrandMatrix) Returns the chromosome-specific data matrix for the object.

Standard generic methods:

show(ChrStrandMatrix) Generates a short description of the ChrStrandMatrix object.

summary(ChrStrandMatrix) Generates a summary of the data available for each sample in the ChrStrandMatrix object.

Author(s)

Tim F Rayner

See Also

[createChrMatrix](#), [ChrStrandData-class](#).

Examples

```
data('demo')
stranddata <- createChrMatrix( chrdata, chr=22, strand='forward', start=21925000, end=24300000 )
```

createChrMatrix	<i>Generate chromosome-based subset matrices from the mapped data structures generated by makeChrStrandData</i>
-----------------	---

Description

Given a data object from makeChrStrandData, generate a matrix containing a subset of the data from a given region of a given chromosome strand, with data binned at appropriate intervals along the chromosome. The minimum width of the binning interval is controlled using the "interval" argument, which can therefore be used to control the output resolution of the data.

Usage

```
createChrMatrix(data, chr, strand = c('forward','reverse','both'), subset = NULL,
  start=1, end, interval=ceiling((end - start)/500))
```

Arguments

data	A ChrStrandData object (e.g. generated by makeChrStrandData).
chr	The name of the chromosome to plot.
strand	The chromosome strand to plot ('both' indicates that both strands should be overlaid in a single heatmap).
subset	An optional numeric vector indicating which samples should be plotted.
start	The starting chromosome coordinate from which to plot.
end	The ending chromosome coordinate.
interval	The (optional) size of the data bins to use along the chromosome, in bases.

Details

Typically this function will not be called directly, but rather via the wrapper `plotChrMap` function.

Note that this function may combine data from multiple probes or genes (taking the mean) into a single chromosomal locus based on the size of the specified interval. If this happens the combined probe/gene identifiers are concatenated in the output object, separated by a semicolon.

Value

A `ChrStrandMatrix` object suitable for use with `chrHeatMap` and `drawMapDendro`.

Author(s)

Tim F Rayner

See Also

[plotChrMap](#), [chrHeatMap](#), [drawMapDendro](#), [ChrStrandMatrix-class](#), [ChrStrandData-class](#)

Examples

```
data('demo')
stranddata <- createChrMatrix( chrdata, chr=22, strand='forward', start=21925000, end=24300000 )
```

cytobands

Cytoband location information

Description

This data set contains cytoband information for a range of species, taken directly from the UCSC genome annotation database. This data set is designed to be easily extendable to cover new species.

Usage

cytobands

Format

A list of data frames, one per species, each with one row per cytoband and the following columns:

- `chr`The chromosome number for the cytoband, prefixed with 'chr'.
- `start`The start coordinate for the cytoband.
- `end`The end coordinate for the cytoband.
- `band`The cytoband number (i.e., the '23.3' in '1q23.3').
- `stain`The cytoband stain (see the `stains` data set).
- `arm`The chromosome arm for the cytoband (i.e., the 'q' in '1q23.3').

The list names (i.e. `names(cytobands)`) should correspond to species names in the `AnnotationDbi` packages used.

Source

The UCSC genome annotation database: <http://hgdownload.cse.ucsc.edu/downloads.html>

drawMapDendro	<i>Draw a heatmap and dendrogram for a strand-specific data matrix generated by createChrMatrix</i>
---------------	---

Description

Given a data matrix, cluster by sample (if desired), and plot the dendrogram and heatmap along chromosome coordinates. This function reuses code from the `gplots` `heatmap.2` function. Note that this function makes assumptions about the current layout of the display device, and so should generally be called only via `plotChrMap`.

Usage

```
drawMapDendro(x, start, end, col = "heat.colors", dendrogram = TRUE, Rowv = TRUE,
              margins = c(6, 6), na.rm=TRUE, hclustfun = hclust, distfun = dist,
              breaks, RowSideColors, cexRow, cexCol,
              xlab, ylab, labRow, labCol, na.color = 'gray', ...)
```

Arguments

<code>x</code>	The strand-specific data matrix to cluster and plot, usually generated using <code>createChrMatrix</code> .
<code>start</code>	The starting genome coordinate for the plot.
<code>end</code>	The ending genome coordinate for the plot.
<code>col</code>	A character vector of colors to use in the heat map, or the name of a function generating such a vector.
<code>dendrogram</code>	A boolean flag indicating whether or not to draw the dendrogram.
<code>Rowv</code>	Determines if and how the sample dendrogram should be reordered. If a dendrogram, then it is used "as-is", i.e., without any reordering. If a vector of integers, then the dendrogram is computed and reordered based on the order of the vector. Set this argument to <code>FALSE</code> or <code>NULL</code> to draw the heatmap without any sample reordering.
<code>margins</code>	A numeric vector indicating the c(bottom, left) margins of the plot containing X and Y axes labels.
<code>na.rm</code>	Whether or not to remove NA from calculations.
<code>hclustfun</code>	Function used to compute the hierarchical clustering when <code>Rowv</code> is not a dendrogram object. Defaults to <code>hclust</code> .
<code>distfun</code>	Function used to compute the distance (dissimilarity) between both rows and columns. Defaults to <code>dist</code> .
<code>breaks</code>	(Optional) Either a numeric vector indicating the splitting points for binning <code>x</code> into colors, or a integer number of break points to be used, in which case the break points will be spaced equally between <code>min(x)</code> and <code>max(x)</code> .

RowSideColors	(Optional) Character vector of length nrow(x) containing the color names for a vertical side bar that may be used to annotate the rows of x.
cexRow, cexCol	(Optional) Positive numbers, used as cex.axis in for the row or column axis labeling. If these arguments are omitted the function will try and calculate a sane axis font size based on the number of rows or columns respectively.
xlab, ylab	X- and Y- axis titles; defaults to none.
labRow, labCol	Character vectors with row and column labels to use; these default to rownames(x) or colnames(x), respectively.
na.color	Color to use for missing value (NA). Defaults to gray.
...	Additional arguments are passed to the image function.

Details

This function makes assumptions about the plot layout, usually set by the enclosing chrHeatMap function. Typically neither of these functions should be called directly, but rather via the wrapper plotChrMap function.

Value

This function is executed for its side effects.

Author(s)

Tim F Rayner

See Also

[plotChrMap](#), [createChrMatrix](#), [chrHeatMap](#)

Examples

```
data('demo')
stranddata <- createChrMatrix( chrdata, chr=22, strand='forward',
  start=21925000, end=24300000 )
layout(matrix(1:2, ncol=2), widths=c(0.1,1))
drawMapDendro( stranddata, margins=c(0,0) )
```

grabChrMapProbes

Identify the probes or genes plotted using plotChrMap

Description

Allows the user to interactively select regions of the plotChrMap heatmap, identifying all the probes or genes plotted in those regions.

Usage

```
grabChrMapProbes( plotmap )
```

Arguments

plotmap The output of the plotChrMap function.

Details

This function takes the output of the plotChrMap function and uses it to identify the probes or genes responsible for the signals plotted on the plotChrMap heatmap. It asks the user to select two points on either side of the heatmap bands of interest (specifically, boundary for inclusion of a given band is its left-hand edge), and returns a vector of probe/gene identifiers. This can be passed directly to AnnotationDbi::mget to yield gene symbols and other annotation.

Note that the plotting area layout() and par() values are not reset on exit, so that this function can be reused as many times as is desired.

Value

A character vector of probe/gene identifiers. If multiple identifiers have been averaged into a single band these identifiers will be string concatenated, separated by semicolons. The start, end and interval arguments to plotChrMap can be used in such cases to plot the data at a higher resolution, splitting such loci into separate bands.

Author(s)

Tim F Rayner

See Also

[plotChrMap](#)

Examples

```
data('demo')
plotmap <- plotChrMap(chrdata, '22', cytoband='q11.23')
probes <- grabChrMapProbes(plotmap)
library('hgu95av2.db')
genes <- mget(probes, hgu95av2SYMBOL, ifnotfound=NA)
```

makeChrStrandData	<i>Map a data matrix onto chromosome coordinates</i>
-------------------	--

Description

Given an ExpressionSet, or a data matrix with row names corresponding to the probe or gene IDs in an accompanying annotation package, this function returns a data structure that can be used with the plotChrMap function. This code is based on the Makesense method from the geneplotter package, extended to use both the CHRLOC and CHRLOCEND annotation environments from recent AnnotationDbi packages.

In principle, any AnnotationDbi-based package could be used to provide chromosome location data to this function; all that matters is that the probe or gene identifiers used by the annotation package should be from the same source as the data ExpressionSet featureNames or matrix row names.

Usage

```
makeChrStrandData(expr, lib)
```

Arguments

<code>expr</code>	The ExpressionSet or data matrix to remap.
<code>lib</code>	The name of the annotation package to use.

Value

A ChrStrandData object suitable for use with plotChrMap.

Author(s)

Tim F Rayner

References

geneplotter, annotate and AnnotationDbi packages

See Also

[plotChrMap](#), [ChrStrandData-class](#)

Examples

```
data('demo')
chrdata <- makeChrStrandData(exprs(ALLs.chr22), lib = "hgu95av2.db")
```

makeChrStrandData-methods

Map a data matrix onto chromosome coordinates

Description

Given a data matrix with row names corresponding to the probe or gene IDs in an accompanying annotation package, returns a data structure that can be used with the plotChrMap function. Based on the Makesense method from the geneplotter package.

Methods

expr = "ExpressionSet" Given an ExpressionSet object, returns a ChrStrandData object.

expr = "matrix" Given a matrix object (where rownames(expr) yields the probe or gene identifiers used by the annotation package), returns a ChrStrandData object.

makeRangedDataList	<i>Plot expression data as tracks in the UCSC genome browser</i>
--------------------	--

Description

Creates a GRangesList object suitable for uploading to the UCSC genome browser using the rtracklayer package.

Usage

```
makeRangedDataList( data, chr, start = 1, end, genome, subset = NULL,  
                    cytoband, plot=FALSE, session )
```

Arguments

data	A ChrStrandData object, output from the makeChrStrandData function.
chr	Chromosomal id, chromosome to plot 1:22,X,Y.
start	Optional start chromosome position from which to commence plotting.
end	Optional end chromosome position.
genome	The name of the genome from which the data coordinates are taken (e.g. "hg18"). Passed to GenomicData in the rtracklayer package.
subset	Optional numeric vector listing the samples from data to plot.
cytoband	Optional cytological band to plot (e.g. 'q23').
plot	An optional flag indicating whether to automatically plot the resulting GRangesList on the UCSC browser or not.
session	An optional rtracklayer UCSCSession object. Ignored unless plot=TRUE.

Details

This function is used to create GRangesList objects from ChrStrandData objects (see the makeChrStrandData function). If the plot argument is set to TRUE, the data is also uploaded to a UCSC browser session using default settings. See the rtracklayer package for more information on RangedData and UCSCSession objects.

Value

A GRangesList object containing the data for the specified genome region. See the rtracklayer package for more information on this object class.

Author(s)

Tim F Rayner

References

rtracklayer package

See Also

[makeChrStrandData](#), [GRangesList](#) [plotChrMap](#),

Examples

```
data('demo')
r <- makeRangedDataList( data=chrdata, chr=22, cytoband='q11.23', genome='hg18' )
```

plotChrMap	<i>Plot data as an annotated heat map along a chromosome</i>
------------	--

Description

Given a ChrStrandData object (produced by the makeChrStrandData function), this function plots a heat map of its data values along a specified chromosome, optionally clustering samples and including an idiogram.

Usage

```
plotChrMap( data, chr, start = 1, end, subset = NULL,
            cytoband, interval = ceiling((end-start)/500),
            strands = c('forward', 'reverse'), ... )
```

Arguments

data	A ChrStrandData object, output from the makeChrStrandData function.
chr	Chromosomal id, chromosome to plot 1:22,X,Y.
start	Optional start chromosome position from which to commence plotting.
end	Optional end chromosome position.
subset	Optional numeric vector listing the samples from data to plot.
cytoband	Optional cytological band to plot (e.g. 'q23').
interval	An optional interval size controlling the plot detail level.
strands	The chromosome strands to plot (a one- or two-element character vector, values 'forward', 'reverse', or 'both').
...	Additional arguments are passed to the chrHeatMap function.

Details

This function is used to plot ChrStrandData objects (the output of the makeChrStrandData function) as heatmaps arranged along genome coordinates. The default heat map will plot the entire forward strand for the chosen chromosome at the top of the figure, with an idiogram and the reverse strand below it. To plot both strands overlaid, use the strands='both' argument. Probe or gene signals are averaged over a window size controlled by interval, such that the default length of each heat map segment is 1/500 the total heat map width. This can be varied as required to control

the resolution of the plot. This function uses both the start and end chromosomal locations for each gene to plot heatmap positions, and as such will not work with older AnnotationDbi packages.

See the related functions from this package for further plotting arguments which may be passed to this function. In particular, see the `drawMapDendro` documentation for arguments used to control sample clustering and plot axis font sizes, and `chrHeatMap` for arguments relating to the idiogram plot. Note that the plotting area `layout()` and `par()` values are not reset on exit, so that `grabChrMapProbes` can be subsequently used on the output.

Idiogram plotting is currently only supported for data mapping to human, mouse and rat genomes. In principle this is extendable to any organism for which the UCSC genome browser includes cytoband information. Please contact the maintainer of this package for help in such cases.

Value

A `ChrMapPlot` object containing a list of probe/gene identifiers mapped to their corresponding display locations, for use with `grabChrMapProbes`.

Author(s)

Tim F Rayner

References

annotate package

See Also

[drawMapDendro](#), [chrHeatMap](#), [makeChrStrandData](#), [grabChrMapProbes](#)

Examples

```
data('demo')
plotChrMap(chrdata, '22', cytoband='q11', labRow=ALLs.chr22$mol.biol,
cexCol=0.8, cexCyto=1.2, srtCyto=0)
```

stains

Cytoband display information

Description

This is a data set describing the display parameters used to plot cytoband data.

Usage

```
stains
```

Format

A data frame with one row per cytoband type, and the following columns:

- **type**The cytoband type. This must correspond to the "stain" column in the cytoband data frame (see the cytobands documentation).
- **bandcol**The shade of gray used to colour the cytobands. A number between 0 (black) and 1 (white). Passed as the "col" argument to `rect`.
- **textcol**The shade of gray used for the cytoband text labels. A number between 0 (black) and 1 (white). Passed as the "col" argument to `text`.
- **banddens**The shading density to use for the band colour. Passed as the "density" argument to `rect`.
- **bandbord**The shade of gray used for the plotted cytoband borders. A number between 0 (black) and 1 (white). Passed as the "border" argument to `rect`.

Source

Developed based on the design of the idiogram Bioconductor package

strandName	<i>Retrieve strand information from a ChrStrandMatrix object.</i>
------------	---

Description

This generic function simply returns the chromosome strand which name of all the chromosomes represented by a given ChrStrandData object. Note that not every sample associated with the object need have data from every chromosome.

Usage

```
strandName(object)
```

Arguments

object Object derived from class ChrStrandMatrix

Value

`strandName(object)` returns the name of the strand from which the object data is taken.

Author(s)

Tim F Rayner

See Also

[ChrStrandMatrix-class](#)

Index

- * **array**
 - createChrMatrix, [9](#)
 - makeChrStrandData, [13](#)
 - * **classes**
 - ChrMapPlot, [5](#)
 - ChrStrandData, [7](#)
 - ChrStrandMatrix, [8](#)
 - * **datasets**
 - ALLs.chr22, [2](#)
 - chrdata, [3](#)
 - cytobands, [10](#)
 - stains, [17](#)
 - * **hplot**
 - chrHeatMap, [3](#)
 - drawMapDendro, [11](#)
 - grabChrMapProbes, [12](#)
 - plotChrMap, [16](#)
 - * **manip**
 - chrNames, [6](#)
 - strandName, [18](#)
 - * **methods**
 - makeChrStrandData-methods, [14](#)
- ALLs.chr22, [2](#)
- annotation, ChrStrandData-method
(ChrStrandData), [7](#)
- chrdata, [3](#)
- chrHeatMap, [3](#), [10](#), [12](#), [17](#)
- ChrMapPlot, [5](#)
- ChrMapPlot-class (ChrMapPlot), [5](#)
- chrNames, [6](#)
- chrNames, ChrStrandData-method
(ChrStrandData), [7](#)
- chrNames, ChrStrandMatrix-method
(ChrStrandMatrix), [8](#)
- ChrStrandData, [7](#)
- ChrStrandData-class (ChrStrandData), [7](#)
- ChrStrandMatrix, [8](#)
- ChrStrandMatrix-class
(ChrStrandMatrix), [8](#)
- class:ChrMapPlot (ChrMapPlot), [5](#)
- class:ChrStrandData (ChrStrandData), [7](#)
- class:ChrStrandMatrix
(ChrStrandMatrix), [8](#)
- createChrMatrix, [5](#), [9](#), [9](#), [12](#)
- cytobands, [10](#)
- drawMapDendro, [5](#), [10](#), [11](#), [17](#)
- exprs, ChrStrandMatrix-method
(ChrStrandMatrix), [8](#)
- featureNames, ChrStrandMatrix-method
(ChrStrandMatrix), [8](#)
- grabChrMapProbes, [6](#), [12](#), [17](#)
- GRangesList, [16](#)
- makeChrStrandData, [8](#), [13](#), [16](#), [17](#)
- makeChrStrandData, ExpressionSet-method
(makeChrStrandData-methods), [14](#)
- makeChrStrandData, matrix-method
(makeChrStrandData-methods), [14](#)
- makeChrStrandData-methods, [14](#)
- makeRangedDataList, [15](#)
- plotChrMap, [5](#), [6](#), [10](#), [12–14](#), [16](#), [16](#)
- sampleNames, ChrStrandData-method
(ChrStrandData), [7](#)
- sampleNames, ChrStrandMatrix-method
(ChrStrandMatrix), [8](#)
- show, ChrMapPlot-method (ChrMapPlot), [5](#)
- show, ChrStrandData-method
(ChrStrandData), [7](#)
- show, ChrStrandMatrix-method
(ChrStrandMatrix), [8](#)
- stains, [17](#)
- strandName, [18](#)

strandName,ChrStrandMatrix-method
 (ChrStrandMatrix), [8](#)
summary,ChrMapPlot-method (ChrMapPlot),
 [5](#)
summary,ChrStrandData-method
 (ChrStrandData), [7](#)
summary,ChrStrandMatrix-method
 (ChrStrandMatrix), [8](#)