Package 'GLAD'

April 23, 2016

1 '
Version 2.34.0
Date 2011-12-19
Title Gain and Loss Analysis of DNA
Depends R (>= 2.10)
SystemRequirements gsl. Note: users should have GSL installed. Windows users: 'consult the README file available in the inst directory of the source distribution for necessary configuration instructions'.
Suggests aws, teltk
Author Philippe Hupe
Maintainer Philippe Hupe <glad@curie.fr></glad@curie.fr>
Description Analysis of array CGH data: detection of breakpoints in genomic profiles and assignment of a status (gain, normal or loss) to each chromosomal regions identified.
License GPL-2
URL http://bioinfo.curie.fr
·
biocViews Microarray, CopyNumberVariation
NeedsCompilation yes
R topics documented:
array
arrayPersp
arrayPlot
as.data.frame.profileCGH
ChrNumeric
ColorBar
cytoband
daglad

2 array

	glad	18
	hclustglad	22
	kernelpen	24
	myPalette	25
	plotProfile	26
	profileCGH	29
	snijders	30
	tkdaglad	31
	veltman	31
Index		33

array

Bladder cancer CGH data

Description

Bladder cancer data from 3 arrays CGH (Comparative Genomic Hybridyzation). Arrays dimension are 4 blocs per column, 4 blocs per row, 21 columns per bloc and 22 rows by blocs.

Usage

```
data(arrayCGH)
```

Format

A data frame composed of the following elements:

Log2Rat Log 2 ratio.

Position BAC position on the genome.

CHROMOSOME Chromosome.

Col Column location on the array.

Row Row location on the array.

Source

Institut Curie, <glad@curie.fr>.

```
data(arrayCGH)
data <- array1 #array1 to array3</pre>
```

arrayCGH 3

arrayCGH	Object of Class arrayCGH

Description

Description of the object arrayCGH.

Value

The object arrayCGH is a list with at least a data.frame named arrayValues and a vector named arrayDesign. The data.frame arrayValues must contain the following fields:

Col Vector of columns coordinates.

Row Vector of rows coordinates.

... Other elements can be added.

The vector arrayDesign is composed of 4 values: c(arrayCol, arrayRow, SpotCol, SpotRow). The array CGH is represented by arrayRow*arrayCol blocs and each bloc is composed of SpotRow*SpotCol spots.

N.B.: Col takes the values in 1:arrayRow*SpotRow and Row takes the values in 1:arrayCol*SpotCol

Note

People interested in tools dealing with array CGH analysis can visit our web-page http://bioinfo.curie.fr.

Author(s)

Philippe Hupé, <glad@curie.fr>.

See Also

glad.

```
data(arrayCGH)
# object of class arrayCGH
array <- list(arrayValues=array2, arrayDesign=c(4,4,21,22))
class(array) <- "arrayCGH"</pre>
```

4 arrayPersp

			_	_		
ar	٦r	ลง	ľ	e	r:	รท

Perspective image of microarray spots statistic

Description

The function arrayPersp creates perspective images of shades of gray or colors that correspond to the values of a statistic for each spot on the array. The statistic can be the intensity log-ratio, a spot quality measure (e.g. spot size or shape), or a test statistic. This function can be used to explore whether there are any spatial effects in the data, for example, print-tip or cover-slip effects.

Usage

Arguments

col

arrayCGH	Object of class arrayCGH.
variable	Variable to be plotted
Statistic	Statistic to be plotted.

Col Vector of columns coordinates.

Row Vector of rows coordinates.

ArrCol Number of columns for the blocs.

ArrRow Number of rows for the blocs.

SpotCol Number of column for each bloc.

SpotRow Number of rows for each bloc.

mediancenter If mediancenter=TRUE, values of Statistic are median-centered.

List of colors such as that generated by Palettes. In addition to these color

palettes functions, a new function myPalette was defined to generate color

palettes from user supplied low, middle, and high color values.

arrayPersp 5

zlim	Numerical vector of length 2 giving the extreme values of z to associate with colors low and high of myPalette. By default zlim is the range of z. Any values of z outside the interval zlim will be truncated to the relevant limit.
bar	If bar=TRUE, a calibration color bar is shown to the right of the image.
	Graphical parameters can be given as arguments to function persp.
	N.B.: Col takes the values in 1:arrayRow*SpotRow and Row takes the values in 1:arrayCol*SpotCol

Value

An image is created on the current graphics device.

Note

People interested in tools dealing with array CGH analysis can visit our web-page http://bioinfo.curie.fr.

Author(s)

```
Philippe Hupé, <glad@curie.fr>.
```

See Also

```
persp, arrayPlot, myPalette.
```

6 arrayPlot

arrayPlot

Spatial image of microarray spots statistic

Description

The function arrayPlot creates spatial images of shades of gray or colors that correspond to the values of a statistic for each spot on the array. The statistic can be the intensity log-ratio, a spot quality measure (e.g. spot size or shape), or a test statistic. This function can be used to explore whether there are any spatial effects in the data, for example, print-tip or cover-slip effects.

Usage

Arguments

arrayCGH	Object of class arrayCGH.
variable	Variable to be plotted
Statistic	Statistic to be plotted.
Col	Vector of columns coordinates.
Row	Vector of rows coordinates.
ArrCol	Number of columns for the blocs.
ArrRow	Number of rows for the blocs.
SpotCol	Number of column for each bloc.
SpotRow	Number of rows for each bloc.
mediancenter	$If \ {\tt mediancenter=TRUE}, \ values \ of \ {\tt Statistic} \ are \ median-centered.$
col	List of colors such as that generated by Palettes. In addition to

List of colors such as that generated by Palettes. In addition to these color palettes functions, a new function myPalette was defined to generate color palettes from user supplied low, middle, and high color values.

arrayPlot 7

contour	If contour=TRUE, contour are plotted, otherwise they are not shown.
nlevels	Numbers of levels added by contour if contour=TRUE.
zlim	Numerical vector of length 2 giving the extreme values of z to associate with colors low and high of myPalette. By default zlim is the range of z. Any values of z outside the interval zlim will be truncated to the relevant limit.
bar	If bar=='horizontal' (resp. 'vertical'), an horizontal (resp. vertical) calibration color bar is shown to the right of the image.
layout	If layout==TRUE plot layout is automatically set when a color bar is asked for
	Graphical parameters can be given as arguments to function image.
	$N.B.: Col\ takes\ the\ values\ in\ 1:arrayRow*SpotRow\ and\ Row\ takes\ the\ values\ in\ 1:arrayCol*SpotCol$

Details

This function is very similar to the maImage written by Sandrine Dudoit (available in marrayPlots package) with added options zlim, mediancenter and layout.

Value

An image is created on the current graphics device.

Note

People interested in tools dealing with array CGH analysis can visit our web-page http://bioinfo.curie.fr.

Author(s)

```
Philippe Hupé, <glad@curie.fr>.
```

See Also

```
image, contour, arrayPersp, myPalette.
```

```
data(arrayCGH)
pdf(file="arrayCGH.pdf",height=21/cm(1),width=29.7/cm(1))
arrayPlot(array2$Log2Rat, array2$Col, array2$Row, 4,4,21,22, main="Spatial Image of array CGH")
dev.off()

# object of class arrayCGH
array <- list(arrayValues=array2, arrayDesign=c(4,4,21,22))
class(array) <- "arrayCGH"
arrayPlot(array,"Log2Rat", main="Spatial Image of array CGH")</pre>
```

```
as.data.frame.profileCGH profileCGH\ consercion
```

Description

Convert a profileCGH object into a data.frame.

Usage

```
## S3 method for class 'profileCGH'
as.data.frame(x, row.names = NULL, optional = FALSE, ...)
```

Arguments

X	The object to converted into data.frame.
row.names	NULL or a character vector giving the row names for the data frame. Missing values are not allowed.
optional	logical. If 'TRUE', setting row names and converting column names (to syntactic names) is optional. $ \\$

Details

The attributes profileValues and profileValuesNA are binded into a data.frame.

Value

A data.frame object

Note

People interested in tools dealing with array CGH analysis can visit our web-page http://bioinfo.curie.fr.

Author(s)

```
Philippe Hupé, <glad@curie.fr>
```

See Also

```
as.profileCGH
```

as.profileCGH 9

Examples

```
data(snijders)
### Creation of "profileCGH" object
profileCGH <- as.profileCGH(gm13330)</pre>
glad function as described in Hupé et al. (2004)
###
###
res <- glad(profileCGH, mediancenter=FALSE,
             smoothfunc="lawsglad", bandwidth=10, round=2,
             model="Gaussian", lkern="Exponential", qlambda=0.999,
             base=FALSE,
             lambdabreak=8, lambdacluster=8, lambdaclusterGen=40,
             type="tricubic", param=c(d=6),
             alpha=0.001, msize=5,
             method="centroid", nmax=8,
             verbose=FALSE)
res <- as.data.frame(res)</pre>
```

as.profileCGH

Create an object of class profileCGH

Description

Create an object of class profileCGH.

Usage

```
as.profileCGH(object,...)
## S3 method for class 'data.frame'
as.profileCGH(object, infaction=c("value","empty"),
value=20, keepSmoothing=FALSE, ...)
```

Arguments

object A data.frame to be convert into profileCGH.

 $\ \ \, \text{infaction} \qquad \quad \text{If "value" then the LogRatio with infinite values (-Inf, Inf) are replace by + or -} \\$

value according to the sign. If "empty" then NAs are put instead.

10 as.profileCGH

```
value replace Inf by value if infaction is "value".
keepSmoothing if TRUE the smoothing value in object is kept
```

Details

The data.frame to be convert must at least contain the following fields: LogRatio, PosOrder, and Chromosome. If the field Chromosome is of mode character, it is automatically converted into a numeric vector (see ChrNumeric); a field ChromosomeChar contains the character labels. The data.frame to be converted into a profileCGH objet is split into two data.frame: profileValuesNA contains the rows for which there is at least a missing value for either LogRatio, PosOrder or Chromosome; profileValues contains the remaining rows.

Value

```
\begin{tabular}{ll} A list with the following attributes \\ profileValues & A data.frame \\ profileValuesNA & A data.frame \\ \end{tabular}
```

Note

People interested in tools dealing with array CGH analysis can visit our web-page http://bioinfo.curie.fr.

Author(s)

```
Philippe Hupé, <glad@curie.fr>
```

See Also

```
as.data.frame.profileCGH
```

```
data(snijders)
### Creation of "profileCGH" object
profileCGH <- as.profileCGH(gm13330)
attributes(profileCGH)</pre>
```

ChrNumeric 11

ChrNumeric

Convert chromosome into numeric values

Description

Convert chromosome into numeric values.

Usage

```
ChrNumeric(Chromosome)
```

Arguments

Chromosome

A vector with chromosome labels.

Details

For sexual chromosome, labels must contains X or Y which are coded by 23 and 24 respectively.

Note

People interested in tools dealing with array CGH analysis can visit our web-page http://bioinfo.curie.fr.

Author(s)

```
Philippe Hupé, <glad@curie.fr>
```

Examples

```
Chromosome <- c("1","X","Y","chr X", "ChrX", "chrX", "ChrX", "Chr Y")
ChrNumeric(Chromosome)
```

ColorBar

Calibration bar for color images

Description

This function produces a color image (color bar) which can be used for the legend to another color image obtained from the functions image or arrayPlot.

Usage

```
ColorBar(x, horizontal=TRUE, col=heat.colors(50), scale=1:length(x), k=10, ...)
```

12 ColorBar

Arguments

х	If "numeric", a vector containing the "z" values in the color image, i.e., the values which are represented in the color image. Otherwise, a "character" vector representing colors.
horizontal	If TRUE, the values of x are represented as vertical color strips in the image, else, the values are represented as horizontal color strips.
col	Vector of colors such as that generated by rainbow, heat.colors, topo.colors, terrain.colors, or similar functions. In addition to these color palette functions, a new function myPalette was defined to generate color palettes from user supplied low, middle, and high color values.
scale	A "numeric" vector specifying the "z" values in the color image. This is used when the argument x is a "character" vector representing color information.
k	Object of class "numeric", for the number of labels displayed on the bar.
	Optional graphical parameters, see par.

Author(s)

Sandrine Dudoit, Yee Hwa (Jean) Yang.

See Also

image, arrayPlot myPalette.

```
par(mfrow=c(3,1))
Rcol <- myPalette(low="white", high="red", k=10)
Gcol <- myPalette(low="white", high="green", k=50)
RGcol <- myPalette(low="green", high="red", k=100)
ColorBar(Rcol)
ColorBar(Gcol, scale=c(-5,5))
ColorBar(1:50, col=RGcol)

par(mfrow=c(1,3))
x<-seq(-1, 1, by=0.01)
ColorBar(x, col=Gcol, horizontal=FALSE, k=11)
ColorBar(x, col=Gcol, horizontal=FALSE, k=21)
ColorBar(x, col=Gcol, horizontal=FALSE, k=51)</pre>
```

cytoband 13

cytoband

Cytogenetic banding

Description

Cytogenetic banding

Usage

data(cytoband)

Examples

data(cytoband)
cytoband

daglad

Analysis of array CGH data

Description

This function allows the detection of breakpoints in genomic profiles obtained by array CGH technology and affects a status (gain, normal or lost) to each clone.

Usage

```
## S3 method for class 'profileCGH'
daglad(profileCGH, mediancenter=FALSE,
normalrefcenter=FALSE, genomestep=FALSE,
OnlySmoothing = FALSE, OnlyOptimCall = FALSE,
smoothfunc="lawsglad", lkern="Exponential",
model="Gaussian", qlambda=0.999, bandwidth=10,
sigma=NULL, base=FALSE, round=2,
lambdabreak=8, lambdaclusterGen=40, param=c(d=6),
alpha=0.001, msize=2, method="centroid", nmin=1, nmax=8, region.size=2,
amplicon=1, deletion=-5, deltaN=0.10, forceGL=c(-0.15,0.15),
nbsigma=3, MinBkpWeight=0.35, DelBkpInAmp=TRUE, DelBkpInDel=TRUE,
CheckBkpPos=TRUE, assignGNLOut=TRUE,
breaksFdrQ = 0.0001, haarStartLevel = 1,
haarEndLevel = 5, weights.name = NULL,
verbose=FALSE, ...)
```

Arguments

profileCGH Object of class profileCGH

mediancenter If TRUE, LogRatio are center on their median.

genomestep If TRUE, a smoothing step over the whole genome is performed and a "clustering

throughout the genome" allows to identify a cluster corresponding to the Normal

DNA level. The threshold used in the daglad function (deltaN, forceGL, amplicon, deletion)

and then compared to the median of this cluster.

normalrefcenter

If TRUE, the LogRatio are centered through the median of the cluster identified

during the genomestep.

OnlySmoothing If TRUE, only segmentation is performed without optimization of breakpoints

and calling.

OnlyOptimCall If TRUE, the user can provide data which have been already segmented. In this

case, profileCGH\\$profileValues must contain a field with the name "Smoothing". The daglad function skip the smoothing step but bith the optimization of

breakpoints and calling are performed.

smoothfunc Type of algorithm used to smooth LogRatio by a piecewise constant function.

Choose either lawsglad, haarseg, aws or laws (aws package).

lkern lkern determines the location kernel to be used (see laws in aws package for

details).

model model determines the distribution type of LogRatio (see laws in aws package

for details).

qlambda determines the scale parameter qlambda for the stochastic penalty (see

laws in aws package for details).

base If TRUE, the position of clone is the physical position onto the chromosome,

otherwise the rank position is used.

sigma Value to be passed to either argument sigma2 of aws (see aws package) function

or shape of laws (see aws package). If NULL, sigma is calculated from the data.

bandwidth Set the maximal bandwidth hmax in the aws or laws functions in aws package.

For example, if bandwidth=10 then the hmax value is set to $10*X_N$ where X_N

is the position of the last clone.

round The smoothing results of either aws or laws functions (in aws package) are

rounded or not depending on the round argument. The round value is passed to

the argument digits of the round function.

lambdabreak Penalty term (λ') used during the "Optimization of the number of breakpoints"

step.

lambdaclusterGen

Penalty term $(\lambda*)$ used during the "clustering throughout the genome" step.

param Parameter of kernel used in the penalty term.

alpha Risk alpha used for the "Outlier detection" step.

msize The outliers MAD are calculated on regions with a cardinality greater or equal

to msize.

method The agglomeration method to be used during the "clustering throughout the genome" steps. Minimum number of clusters (N*max) allowed during the "clustering throughnmin out the genome" clustering step. nmax Maximum number of clusters (N*max) allowed during the "clustering throughout the genome" clustering step. The breakpoints which define regions with a number of probes lower or equal to region.size this value are discared. amplicon Level (and outliers) with a smoothing value (log-ratio value) greater than this threshold are consider as amplicon. Note that first, the data are centered on the normal reference value computed during the "clustering throughout the genome" step. deletion Level (and outliers) with a smoothing value (log-ratio value) lower than this threshold are consider as deletion. Note that first, the data are centered on the normal reference value computed during the "clustering throughout the genome" step. deltaN Region with smoothing values in between the interval [-deltaN,+deltaN] are supposed to be normal. forceGL Level with smoothing value greater (lower) than rangeGL[1] (rangeGL[2]) are considered as gain (lost). Note that first, the data are centered on the normal reference value computed during the "clustering throughout the genome" step. nbsigma For each breakpoints, a weight is calculated which is a function of absolute value of the Gap between the smoothing values of the two consecutive regions. Weight = 1- kernelpen(abs(Gap),param=c(d=nbsigma*Sigma)) where Sigma is the standard deviation of the LogRatio. MinBkpWeight Breakpoints which GNL change == 0 and Weight less than MinBkpWeight are discarded. DelBkpInAmp If TRUE, the breakpoints identified inside amplicon regions are deleted. For amplicon, the log-ratio values are highly variable which lead to identification of false positive breakpoints. DelBkpInDel If TRUE, the breakpoints identified inside deletion regions are deleted. For deletion, the log-ratio values are highly variable which lead to identification of false positive breakpoints. CheckBkpPos If TRUE, the accuracy position of each breakpoints is checked. assignGNLOut If FALSE the status (gain/normal/loss) is not assigned for outliers. breaksFdrQ breaksFdrQ for HaarSeg algorithm. haarStartLevel for HaarSeg algorithm. haarStartLevel haarEndLevel haarEndLevel for HaarSeg algorithm. weights.name The name of the fields which contains the weights used for the haarseg algorithm. By default, the value is set to NULL meaning that all the observations have the same weights. If provided, the field must contain positive values.

If TRUE some information are printed.

verbose

Details

The function daglad implements a slightly modified version of the methodology described in the article: Analysis of array CGH data: from signal ratio to gain and loss of DNA regions (Hupé et al., Bioinformatics, 2004). For smoothing, it is possible to use either the AWS algorithm (Polzehl and Spokoiny, 2002) or the HaarSeg algorithm (Ben-Yaacov and Eldar, Bioinformatics, 2008). The daglad function allows to choose some threshold to help the algorithm to identify the status of the genomic regions. The threshodls are given in the following parameters:

- · deltaN
- forceGL
- · deletion
- amplicon

Value

An object of class "profileCGH" with the following attributes:

profileValues

is a data.frame with the following information:

- SmoothingThe smoothing values correspond to the median of each Level
- **Breakpoints**The last position of a region with identical amount of DNA is flagged by 1 otherwise it is 0. Note that during the "Optimization of the number of breakpoints" step, removed breakpoints are flagged by -1.
- LevelEach position with equal smoothing value are labelled the same way with an integer value starting from one. The label is incremented by one when a new level occurs or when moving to the next chromosome.
- OutliersAwsEach AWS outliers are flagged -1 (if it is in the $\alpha/2$ lower tail of the distribution) or 1 (if it is in the $\alpha/2$ upper tail of the distribution) otherwise it is 0.
- OutliersMadEach MAD outliers are flagged -1 (if it is in the $\alpha/2$ lower tail of the distribution) or 1 (if it is in the $\alpha/2$ upper tail of the distribution) otherwise it is 0.
- OutliersTotOutliersAws + OutliersMad.
- **NormalRef**Clusters which have been used to set the normal reference during the "clustering throughout the genome" step are code by 0. Note that if genomestep=FALSE, all the value are set to 0.
- **ZoneGNL**Status of each clone: Gain is coded by 1, Loss by -1, Amplicon by 2, deletion by -10 and Normal by 0.

BkpInfo

is a data.frame sum up the information for each breakpoint:

- ChromosomeChromosome name.
- SmoothingSmoothing value for the breakpoint.
- Gapabsolute value of the gap between the smoothing values of the two consecutive regions.
- **Sigma**The estimation of the standard-deviation of the chromosome.
- **Weight**1 kernelpen(Gap, type, param=c(d=nbsigma*Sigma))
- **ZoneGNL**Status of the level where is the breakpoint.

- **GNLchange**Takes the value 1 if the ZoneGNL of the two consecutive regions are different.
- LogRatioTest over Reference log-ratio.

NormalRef

If genomestep=TRUE and normalrefcenter=FALSE, then NormalRef is the median of the cluster which has been used to set the normal reference during the "clustering throughout the genome" step. Otherwise NormalRef is 0.

Note

People interested in tools dealing with array CGH analysis can visit our web-page http://bioinfo.curie.fr.

Author(s)

Philippe Hupé, <glad@curie.fr>.

References

Hupé et al. (Bioinformatics, 2004): Analysis of array CGH data: from signal ratio to gain and loss of DNA regions.

Polzehl and Spokoiny (WIAS-Preprint 787, 2002): Local likelihood modelling by adaptive weights smoothing.

Ben-Yaacov and Eldar (Bioinformatics, 2008): A fast and flexible method for the segmentation of aCGH data.

See Also

glad.

MinBkpWeight=0.35, CheckBkpPos=TRUE)

```
### data for cytoband
data(cytoband)

### Genomic profile on the whole genome
plotProfile(res, unit=3, Bkp=TRUE, labels=FALSE, Smoothing="Smoothing",
main="Breakpoints detection: DAGLAD analysis", cytoband = cytoband)

###Genomic profile for chromosome 1
plotProfile(res, unit=3, Bkp=TRUE, labels=TRUE, Chromosome=1,
Smoothing="Smoothing", main="Chromosome 1: DAGLAD analysis", cytoband = cytoband)

### The standard-deviation of LogRatio are:
res$SigmaC

### The list of breakpoints is:
res$BkpInfo
```

glad

Analysis of array CGH data

Description

This function allows the detection of breakpoints in genomic profiles obtained by array CGH technology and affects a status (gain, normal or lost) to each clone.

Usage

Arguments

profileCGH Object of class profileCGH

mediancenter If TRUE, LogRatio are centered on their median.

smoothfunc Type of algorithm used to smooth LogRatio by a piecewise constant function.

Choose either lawsglad, haarseg, aws or laws in aws package.

bandwidth Set the maximal bandwidth hmax in the aws or laws functions in aws package.

For example, if bandwidth=10 then the hmax value is set to $10*X_N$ where X_N

is the position of the last clone.

round The smoothing results are rounded or not depending on the round argument.

The round value is passed to the argument digits of the round function.

model Determines the distribution type of the LogRatio. Keep always the model as

"Gaussian" (see laws in aws package).

lkern Determines the location kernel to be used (see aws or laws in aws package).

qlambda Determines the scale parameter for the stochastic penalty (see aws or laws in

aws package)

base If TRUE, the position of clone is the physical position on the chromosome, oth-

erwise the rank position is used.

sigma Value to be passed to either argument sigma2 of aws function or shape of laws

(see aws package). If NULL, sigma is calculated from the data.

lambdabreak Penalty term (λ') used during the **Optimization of the number of breakpoints**

step.

lambdacluster Penalty term ($\lambda *$) used during the **MSHR clustering by chromosome** step.

lambdaclusterGen

Penalty term ($\lambda*$) used during the **HCSR clustering throughout the genome**

step.

type Type of kernel function used in the penalty term during the **Optimization of the**

number of breakpoints step, the MSHR clustering by chromosome step and

the HCSR clustering throughout the genome step.

param Parameter of kernel used in the penalty term.

alpha Risk alpha used for the **Outlier detection** step.

msize The outliers MAD are calculated on regions with a cardinality greater or equal

to msize.

method The agglomeration method to be used during the MSHR clustering by chro-

mosome and the HCSR clustering throughout the genome clustering steps.

nmax Maximum number of clusters (N*max) allowed during the the MSHR cluster-

ing by chromosome and the HCSR clustering throughout the genome clus-

tering steps.

assignGNLOut If FALSE the status (gain/normal/loss) is not assigned for outliers.

breaksFdrQ breaksFdrQ for HaarSeg algorithm.
haarStartLevel haarStartLevel for HaarSeg algorithm.

haarEndLevel for HaarSeg algorithm.

verbose If TRUE some information are printed

Details

The function glad implements the methodology which is described in the article: Analysis of array CGH data: from signal ratio to gain and loss of DNA regions (Hupé et al., Bioinformatics, 2004).

The principles of the GLAD algorithm: First, the detection of breakpoints is based on the estimation of a piecewise constant function with the Adaptive Weights Smoothing (AWS) procedure (Polzehl and Spokoiny, 2002). Alternatively, it is possible to use the HaarSeg algorithm (Ben-Yaacov and Eldar, Bioinformatics, 2008). Then, a procedure based on penalyzed maximum likelihood optimizes the number of breakpoints and removes the undesirable breakpoints. Finally, based on the regions previously identified, a two-step unsupervised classification (MSHR clustering by chromosome and the HCSR clustering throughout the genome) with model selection criteria allows a status to be assigned for each region (gain, loss or normal).

Main parameters to be tuned:

qlambda if you want the smoothing to fit some very local effect, choose a smaller qlambda.
bandwidth choose a bandwidth not to small otherwise you will have a lot of little discontinuities.
The higher the parameter is, the higher the number of undesirable breakpoints is.

lambdacluster The higher the parameter is, the higher is the number of the regions within a chromosome which belong lambdaclusterGen More the parameter is high more the regions over the whole genome are supposed to belong to the same

Value

An object of class "profileCGH" with the following attributes:

profileValues:

a data.frame with the following added information:

- Smoothing The smoothing values correspond to the median of each MSHR (i.e. Region).
- **Breakpoints**The last position of a region with identical amount of DNA is flagged by 1 otherwise it is 0. Note that during the "Optimization of the number of breakpoints" step, removed breakpoints are flagged by -1.
- **Region**Each position between two breakpoints are labelled the same way with an integer value starting from one. The label is incremented by one when a new breakpoint is found or when moving to the next chromosome. The variable region is what we call MSHR.
- LevelEach position with equal smoothing value is labelled the same way with an integer value starting from one. The label is incremented by one when a new level is found or when moving to the next chromosome.
- OutliersAwsEach AWS outliers are flagged -1 or 1 otherwise it is 0.
- OutliersMadEach MAD outliers are flagged -1 (if it is in the $\alpha/2$ lower tail of the distribution) or 1 (if it is in the $\alpha/2$ upper tail of the distribution) otherwise it is 0.
- OutliersTotOutliersAws + OutliersMad.
- ZoneChrClusters identified after MSHR (i.e. Region) clustering by chromosome.
- ZoneGenClusters identified after HCSR clustering throughout the genome.
- **ZoneGNL**Status of each clone: Gain is coded by 1, Loss by -1 and Normal by 0.

BkpInfo: the data.frame attribute BkpInfo which gives the list of breakpoints:

- PosOrderThe rank position of each clone on the genome.
- **PosBase**The base position of each clone on the genome.
- ChromosomeChromosome name.

SigmaC: the data.frame attribute SigmaC gives the estimation of the LogRatio standard-

deviation for each chromosome:

- ChromosomeChromosome name.
- ValueThe estimation is based on the Inter Quartile Range.

Note

People interested in tools dealing with array CGH analysis can visit our web-page http://bioinfo.curie.fr.

Author(s)

Philippe Hupé, <glad@curie.fr>.

References

- Hupé et al. (Bioinformatics, 2004) Analysis of array CGH data: from signal ratio to gain and loss of DNA regions.
- Polzehl and Spokoiny (WIAS-Preprint 787, 2002)Local likelihood modelling by adaptive weights smoothing.
- Ben-Yaacov and Eldar (Bioinformatics, 2008)A fast and flexible method for the segmentation of aCGH data.

See Also

```
profileCGH, as.profileCGH, plotProfile.
```

22 hclustglad

```
res <- glad(profileCGH, mediancenter=FALSE,
                smoothfunc="lawsglad", bandwidth=10, round=1.5,
                model="Gaussian", lkern="Exponential", qlambda=0.999,
                base=FALSE,
                lambdabreak=8, lambdacluster=8, lambdaclusterGen=40,
                type="tricubic", param=c(d=6),
                alpha=0.001, msize=5,
                method="centroid", nmax=8,
                verbose=FALSE)
### cytoband data to plot chromosomes
data(cytoband)
### Genomic profile on the whole genome
plotProfile(res, unit=3, Bkp=TRUE, labels=FALSE, Smoothing="Smoothing",
main="Breakpoints detection: GLAD analysis", cytoband = cytoband)
###Genomic profile for chromosome 1
plotProfile(res, unit=3, Bkp=TRUE, labels=TRUE, Chromosome=1,
Smoothing="Smoothing", main="Chromosome 1: GLAD analysis", cytoband = cytoband)
### The standard-deviation of LogRatio are:
res$SigmaC
### The list of breakpoints is:
res$BkpInfo
```

hclustglad

Hierarchical Clustering

Description

Hierarchical cluster analysis on a set of dissimilarities and methods for analyzing it.

Usage

```
hclustglad(d, method = "complete", members=NULL)
```

Arguments

d a dissimilarity structure as produced by dist.

method the agglomeration method to be used. This should be (an unambiguous abbre-

viation of) one of "ward", "single", "complete", "average", "mcquitty",

"median" or "centroid".

members NULL or a vector with length size of d.

hclustglad 23

Details

This function performs a hierarchical cluster analysis using a set of dissimilarities for the n objects being clustered. Initially, each object is assigned to its own cluster and then the algorithm proceeds iteratively, at each stage joining the two most similar clusters, continuing until there is just a single cluster. At each stage distances between clusters are recomputed by the Lance-Williams dissimilarity update formula according to the particular clustering method being used.

A number of different clustering methods are provided. *Ward's* minimum variance method aims at finding compact, spherical clusters. The *complete linkage* method finds similar clusters. The *single linkage* method (which is closely related to the minimal spanning tree) adopts a 'friends of friends' clustering strategy. The other methods can be regarded as aiming for clusters with characteristics somewhere between the single and complete link methods.

If members!=NULL, then d is taken to be a dissimilarity matrix between clusters instead of dissimilarities between singletons and members gives the number of observations per cluster. This way the hierarchical cluster algorithm can be "started in the middle of the dendrogram", e.g., in order to reconstruct the part of the tree above a cut (see examples). Dissimilarities between clusters can be efficiently computed (i.e., without hclustglad itself) only for a limited number of distance/linkage combinations, the simplest one being squared Euclidean distance and centroid linkage. In this case the dissimilarities between the clusters are the squared Euclidean distances between cluster means.

In hierarchical cluster displays, a decision is needed at each merge to specify which subtree should go on the left and which on the right. Since, for n observations there are n-1 merges, there are $2^{(n-1)}$ possible orderings for the leaves in a cluster tree, or dendrogram. The algorithm used in hclustglad is to order the subtree so that the tighter cluster is on the left (the last, i.e. most recent, merge of the left subtree is at a lower value than the last merge of the right subtree). Single observations are the tightest clusters possible, and merges involving two observations place them in order by their observation sequence number.

Value

An object of class **hclust** which describes the tree produced by the clustering process. The object is a list with components:

merge	an $n-1$ by 2 matrix. Row i of merge describes the merging of clusters at step i of the clustering. If an element j in the row is negative, then observation $-j$ was merged at this stage. If j is positive then the merge was with the cluster formed at the (earlier) stage j of the algorithm. Thus negative entries in merge indicate agglomerations of singletons, and positive entries indicate agglomerations of non-singletons.
height	a set of $n-1$ non-decreasing real values. The clustering <i>height</i> : that is, the value of the criterion associated with the clustering method for the particular agglomeration.
order	a vector giving the permutation of the original observations suitable for plotting, in the sense that a cluster plot using this ordering and matrix merge will not have crossings of the branches.
labels	labels for each of the objects being clustered.
call	the call which produced the result.
method	the cluster method that has been used.

24 kernelpen

dist.method

the distance that has been used to create d (only returned if the distance object has a "method" attribute).

Author(s)

The hclustglad function is based an Algorithm contributed to STATLIB by F. Murtagh.

References

Everitt, B. (1974). Cluster Analysis. London: Heinemann Educ. Books.

Hartigan, J. A. (1975). Clustering Algorithms. New York: Wiley.

Sneath, P. H. A. and R. R. Sokal (1973). *Numerical Taxonomy*. San Francisco: Freeman.

Anderberg, M. R. (1973). Cluster Analysis for Applications. Academic Press: New York.

Gordon, A. D. (1999). Classification. Second Edition. London: Chapman and Hall / CRC

Murtagh, F. (1985). "Multidimensional Clustering Algorithms", in *COMPSTAT Lectures 4*. Wuerzburg: Physica-Verlag (for algorithmic details of algorithms used).

Examples

```
data(USArrests)
hc <- hclustglad(dist(USArrests), "ave")</pre>
plot(hc)
plot(hc, hang = -1)
## Do the same with centroid clustering and squared Euclidean distance,
## cut the tree into ten clusters and reconstruct the upper part of the
## tree from the cluster centers.
hc <- hclustglad(dist(USArrests)^2, "cen")</pre>
memb <- cutree(hc, k = 10)
cent <- NULL
for(k in 1:10){
  cent <- rbind(cent, colMeans(USArrests[memb == k, , drop = FALSE]))</pre>
hc1 <- hclustglad(dist(cent)^2, method = "cen", members = table(memb))</pre>
opar \leftarrow par(mfrow = c(1, 2))
plot(hc, labels = FALSE, hang = -1, main = "Original Tree")
plot(hc1, labels = FALSE, hang = -1, main = "Re-start from 10 clusters")
par(opar)
```

kernelpen

Kernelpen function

Description

Kernel function used in the penalty term.

myPalette 25

Usage

```
kernelpen(x, type="tricubic", param)
```

Arguments

x Real Value.

type Type of kernelpen to be used

param a named vector.

Details

The only kernel available is the "tricubic" kernel which takes the values $(1 - (x/d)^3)^3$. The value of d is given by param=c(d=6) for example.

Note

People interested in tools dealing with array CGH analysis can visit our web-page http://bioinfo.curie.fr.

Author(s)

Philippe Hupé, <glad@curie.fr>

myPalette

Microarray color palette

Description

This function returns a vector of color names corresponding to a range of colors specified in the arguments.

Usage

```
myPalette(low = "white", high = c("green", "red"), mid=NULL, k =50)
```

Arguments

low	Color for the lower end of the color palette, specified using any of the three kinds of R colors, i.e., either a color name (an element of colors), a hexadecimal string of the form "#rrggbb", or an integer i meaning palette()[i].
high	Color for the upper end of the color palette, specified using any of the three kinds of R colors, i.e., either a color name (an element of colors), a hexadecimal string of the form "#rrggbb", or an integer i meaning palette()[i].
mid	Color for the middle portion of the color palette, specified using any of the three kinds of R colors, i.e., either a color name (an element of colors), a hexadecimal string of the form "#rrggbb", or an integer i meaning palette()[i].
k	Number of colors in the palette.

26 plotProfile

Value

A "character" vector of color names. This can be used to create a user-defined color palette for subsequent graphics by palette, in a col= specification in graphics functions, or in par.

Author(s)

```
Sandrine Dudoit, Yee Hwa (Jean) Yang.
```

See Also

```
palette, rgb, colors, col2rgb, image, ColorBar, arrayPlot.
```

Examples

```
par(mfrow=c(1,4))
pal <- myPalette(low="red", high="green")
ColorBar(seq(-2,2, 0.2), col=pal, horizontal=FALSE, k=21)
pal <- myPalette(low="red", high="green", mid="yellow")
ColorBar(seq(-2,2, 0.2), col=pal, horizontal=FALSE, k=21)
pal <- myPalette()
ColorBar(seq(-2,2, 0.2), col=pal, horizontal=FALSE, k=21)
pal <- myPalette(low="purple", high="purple",mid="white")
ColorBar(seq(-2,2, 0.2), col=pal, horizontal=FALSE, k=21)</pre>
```

plotProfile

Plot genomic profile and cytogenetic banding

Description

Plot genomic profile with breakpoints, outliers, smoothing line and cytogenetic banding.

Usage

plotProfile 27

Arguments

profileCGH Object of class profileCGH variable The variable to be plot.

Chromosome A numeric vector with chromosome number to be plotted. Use 23 and 24 for

chromosome X and Y respectively. If NULL, all the genome is plotted.

Smoothing The variable used to plot the smoothing line. If NULL, nothing is plotted.

GNL The variable used to plot the Gain, Normal and Loss color code.

Bkp If TRUE, the breakpoints are represented by a vertical red dashed line.

labels If TRUE, the labels of the cytogenetic banding are written.

plotband If TRUE, the cytogenetic banding are plotted.

unit Give the unit of the PosBase. For example if unit=3, PosBase are in Kb, if

unit=6, PosBase are in Mb, ...

colDAGLAD Color code to plot Deletion, Amplification, Gain, Lost and Normal status.

pchSymbol A vector of two elements to specify the symbol tu be used for plotting point.

pchSymbol[2] is the symbol for outliers.

colCytoBand Color code for cytogenetic banding.

colCentro Color code for centromere.

text A list with the parameters to be passed to the function text.

cytoband cytodand data. For human, cytoband data are avaibale using data(cytoband).

main title of the plot.
ylim range of the y-axis

Details

,, ,,

Value

A plot

Note

People interested in tools dealing with array CGH analysis can visit our web-page http://bioinfo.curie.fr.

Author(s)

Philippe Hupé, <glad@curie.fr>.

See Also

" "

28 plotProfile

```
### Cytogenetic banding information
data(cytoband)
###
data(snijders)
### Creation of "profileCGH" object
profileCGH <- as.profileCGH(gm13330)</pre>
### glad function as described in Hupé et al. (2004)
res <- glad(profileCGH, mediancenter=FALSE,
               smoothfunc="lawsglad", bandwidth=10, round=2,
              model="Gaussian", lkern="Exponential", qlambda=0.999,
              base=FALSE,
              lambdabreak=8, lambdacluster=8, lambdaclusterGen=40,
               type="tricubic", param=c(d=6),
               alpha=0.001, msize=5,
              method="centroid", nmax=8,
              verbose=FALSE)
### cytoband data to plot chromosome
data(cytoband)
### Genomic profile on the whole genome
plotProfile(res, unit=3, Bkp=TRUE, labels=FALSE,
           Smoothing="Smoothing", plotband=FALSE, cytoband = cytoband)
### Genomic profile on the whole genome and cytogenetic banding
plotProfile(res, unit=3, Bkp=TRUE, labels=FALSE, Smoothing="Smoothing",
           cytoband = cytoband)
### Genomic profile for chromosome 1
text <- list(x=c(90000,200000),y=c(0.15,0.3),labels=c("NORMAL","GAIN"), cex=2)
plotProfile(res, unit=3, Bkp=TRUE, labels=TRUE, Chromosome=1,
Smoothing="Smoothing", plotband=FALSE, text=text, cytoband = cytoband)
### Genomic profile for chromosome 1 and cytogenetic banding with labels
text <- list(x=c(90000,200000),y=c(0.15,0.3),labels=c("NORMAL","GAIN"), cex=2)
plotProfile(res, unit=3, Bkp=TRUE, labels=TRUE, Chromosome=1,
Smoothing "Smoothing", text=text, main="Chromosome 1", cytoband = cytoband)
```

profileCGH 29

	.eCGH

Objects of Class profileCGH and profileChr

Description

Description of the objects profileCGH and profileChr. The last object corresponds to data of only one chromosome.

Details

LogRatio, Chromosome and PosOrder are compulsory.

Value

Objects profileCGH and profileChr are composed of a list with the first element profileValues which is a data.frame with the following columns names:

LogRatio Test over Reference log-ratio.

PosOrder The rank position of each clone on the genome.

PosBase The base position of each clone on the genome.

Chromosome name.

Clone The name of the corresponding clone.

... Other elements can be added.

Note

People interested in tools dealing with array CGH analysis can visit our web-page http://bioinfo.curie.fr.

Author(s)

Philippe Hupé, <glad@curie.fr>.

See Also

```
glad, as.profileCGH.
```

30 snijders

Examples

```
data(snijders)
gm13330$Clone <- gm13330$BAC
profileCGH <- as.profileCGH(gm13330)
class(profileCGH) <- "profileCGH"

profileChr <- as.profileCGH(gm13330[which(gm13330$Chromosome==1),])
class(profileChr) <- "profileChr"</pre>
```

snijders

Public CGH data of Snijders

Description

The data consist of 15 human cell strains with known karyotype (12 fibroblast cell strains, 2 chorionic villus cell strains, 1 lymploblast cell strain) from the NIGMS Human Genetics Cell Repository (http://locus.umdnj.edu/nigms). Each cell strain has been hybridized onto a CGH-array of 2276 BAC's spotted in triplicate.

Usage

```
data(snijders)
```

Source

http://www.nature.com/ng/journal/v29/n3/suppinfo/ng754_S1.html

References

A M Snijders, N Nowak, R Segraves, S Blackwood, N Brown, J Conroy, G Hamilton, A K Hindle, B Huey, K Kimura, S Law, K Myambo, J Palmer, B Ylstra, J P Yue, J W Gray, A N Jain, D Pinkel & D G Albertson, Assembly of microarrays for genome-wide measurement of DNA copy number, *Nature Genetics* 29, pp 263 - 264 (2001) Brief Communications.

```
data(snijders)
array <- gm13330</pre>
```

tkdaglad 31

tkdaglad

Graphical interface for GLAD package

Description

A graphical interface to analyse array CGH data.

Arguments

list

A character vector with the array to be analysed

Note

People interested in tools dealing with array CGH analysis can visit our web-page http://bioinfo.curie.fr.

Author(s)

```
Philippe Hupé, <glad@curie.fr>.
```

See Also

```
glad, daglad, plotProfile.
```

Examples

```
data(snijders)
array1 <- as.profileCGH(gm13330)
array2 <- as.profileCGH(gm04435)

## tkdaglad(c("array1","array2"))
## tkglad(c("array1","array2"))</pre>
```

veltman

Public CGH data of Veltman

Description

The data consist of 2 bladder cancer tumors obtained by Veltman et al (2003).

Usage

```
data(veltman)
```

32 veltman

Source

http://cancerres.aacrjournals.org/cgi/content/full/63/11/2872

References

Joris A. Veltman, Jane Fridlyand, Sunanda Pejavar, Adam B. Olshen, James E. Korkola, Sandy DeVries, Peter Carroll, Wen-Lin Kuo, Daniel Pinkel, Donna Albertson, Carlos Cordon-Cardo, Ajay N. Jain and Frederic M. Waldman. Array-based Comparative Genomic Hybridization for Genome-Wide Screening of DNA Copy Number in Bladder Tumors. *Cancer Research* 63, 2872-2880, 2003.

Examples

data(veltman)

Index

*Topic classes arrayCGH, 3	ChrNumeric, <i>10</i> , 11 ColorBar, 11, <i>26</i>
profileCGH, 29	cytoband, 13
*Topic cluster	,
hclustglad, 22	daglad, 13, <i>31</i>
*Topic color	
myPalette, 25	glad, 3, 17, 18, 29, 31
*Topic datasets	gm00143 (snijders), 30
array, 2	gm01524 (snijders), 30
cytoband, 13	gm01535(snijders), 30
snijders, 30	gm01750 (snijders), 30
veltman, 31	gm02948 (snijders), 30
*Topic hplot	gm03134 (snijders), 30
arrayPersp, 4	gm03563 (snijders), 30
arrayPlot, 6	gm03576 (snijders), 30
ColorBar, 11	gm04435 (snijders), 30
plotProfile, 26	gm05296 (snijders), 30
*Topic manip	gm07081 (snijders), 30
as.data.frame.profileCGH, 8	gm07408 (snijders), 30
as.profileCGH,9	gm10315 (snijders), 30
ChrNumeric, 11	gm13031 (snijders), 30
*Topic math	gm13330 (snijders), 30
kernelpen, 24	
*Topic models	hclustglad, 22
daglad, 13	
glad, 18	image, <i>11</i> , <i>12</i> , <i>26</i>
*Topic multivariate	
hclustglad, 22	kernelpen, 24
*Topic utilities	myPalette, 4-7, 12, 25
tkdaglad, 31	myr dictic, 4 7, 12, 23
G ,	P20 (veltman), 31
array, 2	P9 (veltman), 31
array1 (array), 2	par, 12, 26
array2 (array), 2	plotProfile, 21, 26, 31
array3 (array), 2	profileCGH, <i>14</i> , <i>19</i> , <i>21</i> , <i>27</i> , 29
arrayCGH, 3, 4, 6	profileChr (profileCGH), 29
arrayPersp, 4, 7	p. 5. 2. 2. 5
arrayPlot, 5, 6, 11, 12, 26	snijders, 30
as.data.frame.profileCGH, 8, 10	
as.profileCGH, 8, 9, 21, 29	text, 27

34 INDEX

```
tkdaglad, 31
tkglad (tkdaglad), 31
veltman, 31
```