

CGHcall

October 5, 2010

CGHcall-package *Calling aberrations for array CGH tumor profiles.*

Description

Calls aberrations for array CGH data using a six state mixture model as well as several biological concepts that are ignored by existing algorithms. Visualization of profiles is also provided.

Details

Package: CGHcall
Type: Package
Version: 2.0.0
Date: 2007-03-14
License: GPL

Author(s)

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References

Mark A. van de Wiel, Kyung In Kim, Sjoerd J. Vosse, Wessel N. van Wieringen, Saskia M. Wilting and Bauke Ylstra. CGHcall: calling aberrations for array CGH tumor profiles. *Bioinformatics*, 23, 892-894.

CGHcall *Calling aberrations for array CGH tumor profiles.*

Description

Calls aberrations for array CGH data using a six state mixture model.

Usage

```
CGHcall(inputSegmented, prior = "auto", nclass = 3, organism = "human", robustsig
```

Arguments

| | |
|-----------------------------|--|
| <code>inputSegmented</code> | An object of class <code>cghSeg</code> |
| <code>prior</code> | Options are <code>all</code> , <code>not all</code> , or <code>auto</code> . See details for more information. |
| <code>nclass</code> | The number of levels to be used for calling. Either 3 (loss, normal, gain) or 4 (including amplifications). |
| <code>organism</code> | Either <code>human</code> or <code>other</code> . This is only used for chromosome arm information when <code>prior</code> is set to <code>all</code> or <code>auto</code> (and <code>samplesize > 20</code>). |
| <code>robustsig</code> | Options are <code>yes</code> or <code>no</code> . <code>yes</code> enforces a lower bound on the standard deviation of the normal segments |
| <code>digits</code> | Number of decimal digits to be saved in the resulting call object. Allows for saving storage space |
| <code>nsegfit</code> | Maximum number of segments used for fitting the mixture model. Posterior probabilities are computed for all segments |
| <code>maxnumseg</code> | Maximum number of segments per profile used for fitting the model |
| <code>minlsforfit</code> | Minimum length of the segment (in Mb) to be used for fitting the model |

Details

Please read the article and the supplementary information for detailed information on the algorithm. The parameter `prior` states how the data is used to determine the prior probabilities. When set to `all`, the probabilities are determined using the entire genome of each sample. When set to `not all` probabilities are determined per chromosome for each sample when `organism` is set to `other` or per chromosome arm when `organism` is `human`. The chromosome arm information is taken from the March 2006 version of the UCSC database. When `prior` is set to `auto`, the way probabilities are determined depends on the sample size. The entire genome is used when the sample size is smaller than 20, otherwise chromosome (arm) information is used. Please note that CGHcall uses information from all input data to determine the aberration probabilities. When for example triploid or tetraploid tumors are observed, we advise to run CGHcall separately on those (groups of) samples. Note that `robustsig = yes` enforces the sd corresponding to the normal segments to be at least half times the pooled gain/loss sd. Use of "nsegfit" significantly lower computing time with respect to previous CGHcall versions without much accuracy loss. Moreover, "maxnumseg" decreases the impact on the results of profiles with inferior segmentation results. Finally, "minlsforfit" decreases the impact of very small aberrations (potentially CNVs rather than CNAs) on the fit of the model. Note that always a result for all segments is produced.

Value

This function return a list with three components:

| | |
|----------------------------|---|
| <code>probabilities</code> | A dataframe with 3 columns of probe information (name, chromosome and position), followed by k columns with aberration probabilities for each sample, where k is the number of levels used for calling (<code>nclass</code>). |
| <code>calls</code> | A dataframe with the calls for each sample. Values are -1 (loss), 0 (normal) or 1 (gain). If 4 levels were used for calling, a value of 2 represents an amplification. |

`segments` A matrix with the segments for each profile. The first column contains the sample number. The second column the level of the current segment and the third and fourth columns the start and end of the segment in probe number respectively.

Author(s)

Sjoerd Vosse & Mark van de Wiel

References

Mark A. van de Wiel, Kyung In Kim, Sjoerd J. Vosse, Wessel N. van Wieringen, Saskia M. Wilting and Bauke Ylstra. CGHcall: calling aberrations for array CGH tumor profiles. *Bioinformatics*, 23, 892-894.

Examples

```
data(Wilting)
## Convert to cghRaw object
cgh <- make_cghRaw(Wilting)
print(cgh)
## First preprocess the data
raw.data <- preprocess(cgh)
## Simple global median normalization for samples with 75% tumor cells
perc.tumor <- rep(0.75, 3)
normalized.data <- normalize(raw.data, cellularity=perc.tumor)
## Segmentation with slightly relaxed significance level to accept change-points.
## Note that segmentation can take a long time.
## Not run: segmented.data <- segmentData(normalized.data, alpha=0.02)
## Not run: postsegnormalized.data <- postsegnormalize(segmented.data)
## Call aberrations
## Not run: result <- CGHcall(postsegnormalized.data)
```

Wilting

Cervical cancer arrayCGH data

Description

A dataframe containing 4709 rows and 8 columns with arrayCGH data.

Usage

Wilting

Format

A dataframe containing the following 8 columns:

Name The unique identifiers of array elements.

Chromosome Chromosome number of each array element.

Position Chromosomal position in bp of each array element.

AdCA10 Raw log₂ ratios for cervical cancer sample AdCA10.

SCC27 Raw log₂ ratios for cervical cancer sample SCC27.

SCC32 Raw log₂ ratios for cervical cancer sample SCC32.

SCC36 Raw log₂ ratios for cervical cancer sample SCC36.

SCC39 Raw log₂ ratios for cervical cancer sample SCC39.

Source

Wilting, S.M., Snijders, P.J., Meijer, G.A., Ylstra, B., van den IJssel, P.R., Snijders, A.M., Albertson, D.G., Coffa, J., Schouten, J.P., van de Wiel, M.A., Meijer, C.J., & Steenbergen, R.D. (2006). Increased gene copy numbers at chromosome 20q are frequent in both squamous cell carcinomas and adenocarcinomas of the cervix. *Journal of Pathology*, 210, 258-259.

chromosomes

Retrieve feature position data from cgh objects.

Description

These generic functions access the position data stored in the featureData of an object derived from the [cghRaw-class](#), [cghSeg-class](#) or [cghCall-class](#).

Usage

```
chromosomes(object)
bpstart(object)
bpend(object)
```

Arguments

`object` Object derived from class `cghRaw`, `cghSeg`, or `cghCall`

Value

`chromosomes` returns a vector of chromosome numbers; `bpstart` returns a vector of basepair start positions; `bpend` returns a vector of basepair end positions;

Author(s)

Sjoerd Vosse

See Also

[cghRaw-class](#), [cghSeg-class](#), [cghCall-class](#)

`cghCall`*Class to contain and describe called array comparative genomic hybridization data.*

Description

Container for aCGH data and experimental metadata. `cghCall` class is derived from `eSet`, and requires the following matrices of equal dimension

as `assayData` members:

- `copynumber`
- `segmented`
- `calls`
- `probloss`
- `probnorm`
- `probgain`

Furthermore, columns named `Chromosome`, `Start`, and `End` are required as `featureData` members, containing feature position information.

Extends

Directly extends class `eSet`.

Creating Objects

```
new('cghCall', phenoData = [AnnotatedDataFrame], experimentData = [MIAME],
annotation = [character], copynumber = [matrix], segmented = [matrix],
calls = [matrix], probloss = [matrix], probnorm = [matrix], probgain
= [matrix], featureData = [AnnotatedDataFrame], ...)
```

An object of class `cghCall` is generally obtained as output from `CGHcall`.

Slots

Inherited from `eSet`:

assayData: Contains matrices with equal dimensions, and with column number equal to `nrow(phenoData)`.

`assayData` must contain the following matrices

- `copynumber`
- `segmented`
- `calls`
- `probloss`
- `probnorm`
- `probgain`

with rows representing array probes and columns representing samples. Additional matrices of identical size (e.g., representing measurement errors) may also be included in `assayData`.

Class:[AssayData-class](#)

phenoData: See `eSet`

featureData: An [AnnotatedDataFrame](#) with columns
Chromosome, Start, and End containing array element position data.

experimentData: See [eSet](#)

annotation: See [eSet](#)

Methods

Class-specific methods.

`copynumber(cghCall)`, `copynumber(cghCall, matrix)` <- Access and set elements named `copynumber` in the `AssayData`-class slot.

`segmented(cghCall)`, `segmented(cghCall, matrix)` <- Access and set elements named `segmented` in the `AssayData`-class slot.

`calls(cghCall)`, `calls(cghCall, matrix)` <- Access and set elements named `calls` in the `AssayData`-class slot.

`probloss(cghCall)`, `probloss(cghCall, matrix)` <- Access and set elements named `probloss` in the `AssayData`-class slot.

`probnorm(cghCall)`, `probnorm(cghCall, matrix)` <- Access and set elements named `probnorm` in the `AssayData`-class slot.

`probgain(cghCall)`, `probgain(cghCall, matrix)` <- Access and set elements named `probgain` in the `AssayData`-class slot.

`chromosomes`, `bpstart`, `bpend` Access the chromosomal positions stored in `featureData`

plot Create a plot containing `log2ratios`, `segments` and call probabilities ordered by chromosomal position. TWO EXTRA OPTIONS PLUS DEFAULTS: `dotres=10`. Every `dotres`-th `log2-ratio` is plotted. `dotres=1` plots all data. However, higher values save a lot of space and allow quicker browsing of the plots. `ylimit=c(-5,5)`: limits of the y-axis

plot.summary Create a plot summarizing the call probabilities of all samples

See [eSet](#) for derived methods.

Author(s)

Sjoerd Vosse

See Also

[eSet-class](#), [cghRaw-class](#), [cghSeg-class](#)

Examples

```
# create an instance of cghCall
new("cghCall")

# create an instance of cghCall through CGHcall
## Not run:
data(Wilting)
rawcgh <- make_cghSeg(Wilting)
normalized <- normalize(rawcgh)
segmented <- segmentData(normalized)
called <- CGHcall(segmented)

# plot the first sample. Default only every 10th log2-ratio is plotted (dotres=10). Ac
```

```

plot(called[,1])
# plot the first chromosome of the first sample
plot(called[chromosomes(called)==1,1])

# get the copynumber values of the third and fourth sample
log2ratios <- copynumber(called[,3:4])

# get the names of the samples
sampleNames(called)

# get the names of the array elements
featureNames(called)

## End(Not run)

```

cghRaw

Class to contain and describe raw or normalized array comparative genomic hybridization data.

Description

Container for aCGH data and experimental metadata. `cghRaw` class is derived from `eSet`, and requires a matrix named `copynumber` as `assayData` member. Furthermore, columns named `Chromosome`, `Start`, and `End` are required as `featureData` members, containing feature position information.

Extends

Directly extends class `eSet`.

Creating Objects

```

new('cghRaw', phenoData = [AnnotatedDataFrame], experimentData = [MIAME],
    annotation = [character], copynumber = [matrix], featureData = [AnnotatedDataFra
    ...])

```

`make_cghRaw` is a function to convert a dataframe or textfile to an object of class `cghRaw`. The input should be either a dataframe or a tabseparated textfile (textfiles must contain a header). The first three columns should contain the name, chromosome and position in bp for each array target respectively. The chromosome and position column must contain numbers only. Following these is a column with log2 ratios for each of your samples. If the input type is a textfile, missing values should be represented as 'NA' or an empty field.

Slots

Inherited from `eSet`:

assayData: Contains matrices with equal dimensions, and with column number equal to `nrow(phenoData)`. `assayData` must contain a matrix `copynumber` with rows representing array probes and columns representing samples. Additional matrices of identical size (e.g., representing measurement errors) may also be included in `assayData`. Class:[AssayData-class](#)

phenoData: See `eSet`

featureData: An `AnnotatedDataFrame` with columns `Chromosome`, `Start`, and `End` containing array element position data.

experimentData: See [eSet](#)

annotation: See [eSet](#)

Methods

Class-specific methods.

`copynumber(cghRaw)`, `copynumber(cghRaw, matrix) <-` Access and set elements named `copynumber` in the `AssayData`-class slot.

`chromosomes`, `bpstart`, `bpend` Access the chromosomal positions stored in `featureData`

plot Create a plot containing `log2ratios` ordered by chromosomal position

See [eSet](#) for derived methods. Annotation functionality is not yet supported.

Author(s)

Sjoerd Vosse

See Also

[eSet-class](#), [cghSeg-class](#), [cghCall-class](#)

Examples

```
# create an instance of cghRaw
new("cghRaw")

# create an instance of cghRaw from a dataframe
data(Wilting)
rawcgh <- make_cghRaw(Wilting)

# plot the first sample
plot(rawcgh[,1])
# first three chromosomes
plot(rawcgh[chromosomes(rawcgh)==1,1])

# get the copynumber values of the third and fourth sample
log2ratios <- copynumber(rawcgh[,3:4])

# get the names of the samples
sampleNames(rawcgh)

# get the names of the array elements
featureNames(rawcgh)
```

cghSeg

Class to contain and describe segmented array comparative genomic hybridization data.

Description

Container for aCGH data and experimental metadata. `cghSeg` class is derived from [eSet](#), and requires a matrix named `copynumber` as well as a matrix named `segmented` as `assayData` members of equal dimensions. Furthermore, columns named `Chromosome`, `Start`, and `End` are required as `featureData` members, containing feature position information.

Extends

Directly extends class [eSet](#).

Creating Objects

```
new('cghSeg', phenoData = [AnnotatedDataFrame], experimentData = [MIAME],
  annotation = [character], copynumber = [matrix], segmented = [matrix],
  featureData = [AnnotatedDataFrame], ...)
```

An object of class `cghSeg` is generally obtained as output from [segmentData](#).

Slots

Inherited from `eSet`:

assayData: Contains matrices with equal dimensions, and with column number equal to `nrow(phenoData)`. `assayData` must contain matrices `copynumber` and `segmented` with rows representing array probes and columns representing samples. Additional matrices of identical size (e.g., representing measurement errors) may also be included in `assayData`. Class:[AssayData-class](#)

phenoData: See [eSet](#)

featureData: An [AnnotatedDataFrame](#) with columns `Chromosome`, `Start`, and `End` containing array element position data.

experimentData: See [eSet](#)

annotation: See [eSet](#)

Methods

Class-specific methods.

`copynumber(cghSeg)`, `copynumber(cghSeg, matrix) <-` Access and set elements named `copynumber` in the `AssayData-class` slot.

`segmented(cghSeg)`, `segmented(cghSeg, matrix) <-` Access and set elements named `segmented` in the `AssayData-class` slot.

`chromosomes`, `bpstart`, `bpend` Access the chromosomal positions stored in `featureData`

plot Create a plot containing `log2ratios` and segments ordered by chromosomal position. TWO EXTRA OPTIONS PLUS DEFAULTS:

`dotres=10`. Every `dotres`-th `log2-ratio` is plotted. `dotres=1` plots all data. However, higher values save a lot of space and

allow quicker browsing of the plots. `ylimit=c(-2,5)`: limits of the y-axis

See [eSet](#) for derived methods.

Author(s)

Sjoerd Vosse

See Also

[eSet-class](#), [cghRaw-class](#), [cghCall-class](#)

Examples

```

# create an instance of cghSeg
new("cghSeg")

# create an instance of cghSeg through 'segmentData'
## Not run:
data(Wilting)
rawcgh <- make_cghSeg(Wilting)
normalized <- normalize(rawcgh)
segmented <- segmentData(normalized)

# plot the first sample. Default only every 10th log2-ratio is plotted (dotres=10). Ad
plot(segmented[,1])
# first three chromosomes
plot(segmented[chromosomes(segmented) <= 3, 1])

# get the copynumber values of the third and fourth sample
log2ratios <- copynumber(segmented[,3:4])

# get the names of the samples
sampleNames(segmented)

# get the names of the array elements
featureNames(segmented)

## End(Not run)

```

copynumber

Retrieve copynumber data from cgh objects.

Description

These generic functions access the copynumber values of assay data stored in an object derived from the [cghRaw-class](#), [cghSeg-class](#) or [cghCall-class](#).

Usage

```

copynumber(object)
copynumber(object) <- value
segmented(object)
segmented(object) <- value
calls(object)
calls(object) <- value

```

Arguments

| | |
|--------|---|
| object | Object derived from class <code>cghRaw</code> , <code>cghSeg</code> , or <code>cghCall</code> |
| value | Matrix with rows representing features and columns samples. |

Value

`copynumber` returns a matrix of copynumber values;

Author(s)

Sjoerd Vosse

See Also[cghRaw-class](#), [cghSeg-class](#), [cghCall-class](#)

`make_cghRaw`*Convert a dataframe or textfile to an object of class cghRaw.*

Description

This function converts a dataframe of appropriate format to an object of class `cghRaw`.

Usage

```
make_cghRaw(input)
```

Arguments

`input` Either a dataframe or character string containing a filename. See details for the format.

Details

The input should be either a dataframe or a tabseparated textfile (textfiles must contain a header). The first four columns should contain the name, chromosome and the start and end position in bp for each array target respectively. The chromosome and position column must contain numbers only. Following these is a column with log2 ratios for each of your samples. If the input type is a textfile, missing values should be represented as 'NA' or an empty field.

Value

This function returns an object of class [cghRaw-class](#).

Author(s)

Sjoerd Vosse & Mark van de Wiel

Examples

```
data(Wilting)
## Convert to 'cghRaw' object
cgh <- make_cghRaw(Wilting)
```

`normalize`*Normalization and cellularity adjustment for arrayCGH data.*

Description

This function normalizes arrayCGH data using the global mode or median. It can also adjust for the cellularity of your data.

Usage

```
normalize(input, method = "median", cellularity = 1, smoothOutliers = TRUE, ...)
```

Arguments

| | |
|-----------------------------|---|
| <code>input</code> | Object of class <code>cghRaw</code> . |
| <code>method</code> | Normalization method, either 'median', 'mode', or 'none'. |
| <code>cellularity</code> | A vector of cellularities ranging from 0 to 1 to define the contamination of your sample with healthy cells (1 = no contamination). See details for more information. |
| <code>smoothOutliers</code> | Logical. Indicates whether outliers should be smoothed using the <code>smooth.CNA</code> function. |
| <code>...</code> | Arguments for <code>smooth.CNA</code> . |

Details

The cellularity parameter should be a vector of length `n` where `n` is the number of samples in your dataset. The vector is recycled if there are not enough values in it, or truncated if there are too many. For more information on the correction we refer to section 1.6 of the supplementary information for van de Wiel et al. 2006.

Value

This function returns a dataframe in the same format as the input with normalized and/or cellularity adjusted log2 ratios.

Author(s)

Sjoerd Vosse & Mark van de Wiel

Examples

```
data(WiltingData)
## Convert to 'cghRaw' object
cgh <- cghRaw(WiltingData)
## First preprocess the data
raw.data <- preprocess(cgh)
## Simple global median normalization for samples with 75% tumor cells
perc.tumor <- rep(0.75, 3)
normalized.data <- normalize(raw.data, cellularity=perc.tumor)
```

plot.summary *Visualization of aCGH profiles.*

Description

This function creates a summary plot for aCGH profiles.

Usage

```
plot.summary(x, y, ...)
```

Arguments

| | |
|-----|--|
| x | An object of class <code>cghCall</code> . |
| y | This argument is not used and should be missing. |
| ... | Arguments <code>plot</code> . |

Details

We find plotted on the x-axis the array probes sorted by chromosomal position. The vertical bars represent the average probability that the positions they cover are gained (green bars) or lost (red bars). The green bars represent gains, the red bars represent losses. When 4 levels have been used for calling, amplifications are indicated with a blue tickmark at the top of the plot.

Value

This function creates a plot.

Author(s)

Sjoerd Vosse & Mark van de Wiel

References

Mark A. van de Wiel, Kyung In Kim, Sjoerd J. Vosse, Wessel N. van Wieringen, Saskia M. Wilting and Bauke Ylstra. CGHcall: calling aberrations for array CGH tumor profiles. *Bioinformatics*, 23, 892-894.

Examples

```
## Not run:
data(Wilting)
rawcgh <- make_cghSeg(Wilting)
normalized <- normalize(rawcgh)
segmented <- segmentData(normalized)
called <- CGHcall(segmented)
plot.summary(called)

## End(Not run)
```

postsegnormalize *Post-segmentation normalization*

Description

This function normalizes arrayCGH data after segmentation in order to find a better 0-level.

Usage

```
postsegnormalize(segmentData, inter=c(-0.1,0.1))
```

Arguments

`segmentData` Object of class `cghSeg`.
`inter` Interval in which the function should search for the normal level.

Details

This function recursively searches for the interval containing the most segmented data, decreasing the interval length in each recursion.

The recursive search makes the post-segmentation normalization robust against local maxima. This function is particularly useful for profiles for which, after segmentation, the 0-level does not coincide with many segments. It is more or less harmless to other profiles. We advise to keep the search interval (`inter`) small, in particular at the positive (gain) side to avoid that the 0-level is set to a common gain level.

Value

This function returns a `cghSeg` object in the same format as the input with post-segmentation-normalized adjusted log2 ratios and segmented values.

Author(s)

Mark van de Wiel

Examples

```
data(Wilting)
## Convert to cghRaw object
cgh <- make_cghRaw(Wilting)
## First preprocess the data
raw.data <- preprocess(cgh)
## Simple global median normalization for samples with 75% tumor cells
perc.tumor <- rep(0.75, 3)
normalized.data <- normalize(raw.data, cellularity=perc.tumor)
## Segmentation with slightly relaxed significance level to accept change-points.
## Note that segmentation can take a long time.
## Not run: segmented.data <- segmentData(normalized.data, alpha=0.02)
## Not run: postsegnormalized.data <- postsegnormalize(segmented.data, inter=c(-0.1,0.1))
```

`preprocess`*Preprocess arrayCGH data*

Description

This function preprocesses your aCGH data so it can be processed by other functions without errors.

Usage

```
preprocess(input, maxmiss = 30, nchrom = 23, ...)
```

Arguments

| | |
|----------------------|---|
| <code>input</code> | Object of class <code>cghRaw</code> . |
| <code>maxmiss</code> | Maximum percentage of missing values per row. |
| <code>nchrom</code> | Number of chromosomes. |
| <code>...</code> | Arguments for <code>impute.knn</code> from the <code>impute</code> package. |

Details

This function performs the following actions on arrayCGH data:

- Filter out data with missing position information.
- Remove data on chromosomes larger than `nchrom`.
- Remove rows with more than `maxmiss` percentage missing values.
- Imputes missing values using the `impute.knn` function from the `impute` package.

Value

This function returns a dataframe in the same format as the input with missing values imputed.

Author(s)

Sjoerd Vosse & Mark van de Wiel

References

Olga Troyanskaya, Michael Cantor, Gavin Sherlock, Pat Brown, Trevor Hastie, Robert Tibshirani, David Botstein, and Russ B. Altman (2001). Missing value estimation methods for DNA microarrays. *Bioinformatics*, 17, 520-525.

Examples

```
data(WiltingRaw)
preprocessed <- preprocess(WiltingRaw, nchrom = 22)
```

| | |
|-----------|---|
| pro Bloss | <i>Retrieve call probabilities from a cghCall object.</i> |
|-----------|---|

Description

These generic functions access the call probabilities from assay data stored in a object derived from the `cghCall-class`.

Usage

```
pro Bloss(object)
pro Bloss(object) <- value
pro bnorm(object)
pro bnorm(object) <- value
pro bgain(object)
pro bgain(object) <- value
pro bamp(object)
pro bamp(object) <- value
```

Arguments

| | |
|--------|---|
| object | Object derived from class <code>cghCall</code> |
| value | Matrix with rows representing features and columns samples. |

Value

`pro Bloss` returns matrix of call probabilities;

Author(s)

Sjoerd Vosse

See Also

`cghCall-class`

| | |
|-------------|--|
| segmentData | <i>Breakpoint detection for arrayCGH data.</i> |
|-------------|--|

Description

A wrapper function to run existing breakpoint detection algorithms on arrayCGH data. Currently only DNACopy is implemented.

Usage

```
segmentData(input, method = "DNACopy", ...)
```

Arguments

| | |
|--------|--|
| input | Object of class <code>cghRaw</code> . |
| method | The method to be used for breakpoint detection. Currently only 'DNAcopy' is supported, which will run the <code>segment</code> function. |
| ... | Arguments for <code>segment</code> . |

Details

See `segment` for details on the algorithm.

Value

This function returns a dataframe in the same format as the input with segmented arrayCGH data.

Author(s)

Sjoerd Vosse & Mark van de Wiel

References

Venkatraman, A.S., Olshen, A.B. (2007). A faster circular binary segmentation algorithm for the analysis of array CGH data. *Bioinformatics*, 23, 657-663.

Examples

```
data(WiltingNorm)
## Not run: segmented.data <- segmentData(WiltingNorm, alpha=0.02)
```

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