Package ‘plrs’

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Description The present package implements a flexible framework for modeling the relationship between DNA copy number and gene expression data using Piecewise Linear Regression Splines (PLRS).
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Description

The present package implements a framework for modeling the relationship between DNA copy number and gene expression data using Piecewise Linear Regression Splines (PLRS). It includes (point and interval) estimation, model selection and testing procedures for such models (possibly under biologically motivated constraints).

Details

The use of the present package can be divided into two approaches:

1. Analysis of a single DNA-mRNA relationship

Main functions are:
   - `plrs`: Fit a single plrs model.
   - `plrs.select`: Model selection based on AIC, AICC, OSAIC or BIC.
   - `plrs.test`: Likelihood ratio test for a given plrs model.
   - `plrs.cb`: Confidence bands for a plrs model.

2. Analysis of multiple DNA-mRNA relationships sequentially

Main function is:
   - `plrs.series`: point and interval estimation, model selection and testing of DNA-mRNA association for a series of arrays.

Note: This function extend the aforementioned univariate analysis genomewise in the same spirit as some functions of the `limma` package do.

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References

criteria

Compute AIC, AICC, BIC and OSAIC for a given plrs model.

Description

Extract AIC, AICC, BIC and OSAIC from an object of class `plrs-class`.

Usage

criteria(obj, crit = "all")

Arguments

- **obj**: object of class `plrs-class`
- **crit**: A character (vector) among "aic", "aicc", "bic", "osaic" or "all".

Value

A list with the following components (if specified):

- **aic**: Akaike's information criterion
- **aicc**: Small sample correction of AIC
- **bic**: Bayesian Information Criterion
- **osaic**: One-Sided AIC. See Hughes and King (2003) for more details.

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References


Examples

```r
# Simulate data
sim <- plrs.sim(n=80, states=4, sigma=0.5)

# Fit
model <- plrs(expr=sim$expr, cghseg=sim$seg, cghcall=sim$cal)

criteria(model)
```
modify.conf

Modify the configuration (of calls) of the plrs model

Description

This function changes the discrete copy number values for a given gene in order to force a minimum number of observations per state.

Usage

modify.conf(cghcall, min.obs = 3, discard = TRUE)

Arguments

- **cghcall**: Vector of called values
- **min.obs**: Minimum number of observations per state
- **discard**: Logical. Whether discrete states with few observations should be discarded from analysis.

Details

Consider that the number of observations of a given state is lower than min.obs, then:

- If discard = FALSE, observations are not discarded and a rearrangement of called values is carried out as follows. The “normal” copy number state is taken as a reference. If the minimum number of observations is not obtained, "losses" will be merged to "normals", "gains" to "normals" and "amplifications" to "gains". Note that this modifies the configuration of the model. Thus, after fitting a model using plrs, original and modified data are stored in the resulting plrs-class object, respectively under slots data and mdata.

- If discard = TRUE, states for which the number of observations is lower than min.obs are discarded (replaced by NAs).

Value

- **val**: Vector of new called values

Note

This function is implemented within function plrs and plrs.series.

Author(s)

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Examples

called <- sample(c(rep(-1,5),rep(0,15),rep(1,2),rep(2,1)))
table(called)
table(modify.conf(called, min.obs=3))
neveCN17  

*Copy number for chromosome 17.*

**Description**

Preprocessed copy number data of Neve et al. (2006) for chromosome 17.

**Usage**

neveCN17

**Format**

An object of class `cghCall`

**Source**

M. Neve et al. in Gray Lab at LBL. Neve2006: expression and CGH data on breast cancer cell lines. R package version 0.1.10.

**References**


**Examples**

```r
data(neveCN17)
dim(neveCN17)
head(fData(neveCN17))
```

neveGE17  

*mRNA expression for chromosome 17.*

**Description**

Normalized gene expression data of Neve et al. (2006) for chromosome 17.

**Usage**

neveGE17

**Format**

An object of class `ExpressionSet`

**Source**

M. Neve et al. in Gray Lab at LBL. Neve2006: expression and CGH data on breast cancer cell lines. R package version 0.1.10.
References


Examples

data(neveGE17)
dim(neveGE17)
head(tData(neveGE17))

plot-methods

Plot functions in package 'plrs'

Description

Methods plot in package 'plrs'

Usage

## S3 method for class 'plrs' plot(x, col.line = "black", col.pts = c("red", "blue","green2", "green4"), col.cb = "yellow", xlim = c(floor(min(x@data$cghseg)),ceiling(max(x@data$cghseg))), ylim = c(floor(min(x@data$expr)),ceiling(max(x@data$expr)))), pch = 16, lwd=4, cex = 1.2, xlab="", ylab="", main = "", add = FALSE, lty = 1, lin = FALSE, ...)

Arguments

x An object of class *plrs-class* or *plrs.select-class*
col.line Color of the fitted line
col.pts Vector of length 4, for colors associated with each state
col.cb Color for the confidence band
xlim The x limits of the plot
ylim The y limits of the plot
pch See *par*
lwd See *par*
cex See *par*
xlab Title of the x-axis
ylab Title of the y-axis
main Main title for the plot
add If the plot should be added to the current device. Default is FALSE
lty See *par*
lin Logical. Whether the simple linear model should also be plotted
... Other arguments, see *par*
Details

plot.plrs plots the observed points, the fitted line and potentially the confidence band.

Methods

signature(x = "plrs") Plot observed points and the fitted line
signature(x = "plrs.select") Plot observed points and the fitted line of the selected model.

Author(s)

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**plrs**

*Fit a (constrained) piecewise linear regression spline*

Description

The function fits a piecewise linear regression spline to explain gene expression by the segmented DNA copy number. The called copy number values are used as a template for model building.

Usage

plrs(expr, cghseg, cghcall=NULL, probloss = NULL, probnorm = NULL, probgain = NULL, probamp = NULL, knots = NULL, continuous = FALSE, constr = TRUE, constr.slopes = 2, constr.intercepts = TRUE, min.obs = 3, discard.obs = TRUE)

Arguments

- **expr**: Vector of gene expression values
- **cghseg**: Vector of segmented copy number values
- **cghcall**: Vector of called copy number values. If not provided, we are reduced to a simple linear model.
- **probloss**: Vector of call probabilities associated with state "loss". Default is NULL.
- **probnorm**: Vector of call probabilities associated with state "normal". Default is NULL.
- **probgain**: Vector of call probabilities associated with state "gain". Default is NULL.
- **probamp**: Vector of call probabilities associated with state "amplification". Default is NULL.
- **knots**: knots or change points. If NULL (default), there are estimated. See details.
- **continuous**: Logical, whether the model is continuous (no jump) or not.
- **constr**: Logical, whether the model is constrained or not. (this has been implemented to turn on and off easily the constraints)
- **constr.slopes**: Type of non-negativity constraints applied on slopes. Either 1 or 2 (default). See details.
- **constr.intercepts**: If TRUE (default) jumps from state to state are also constrained to be non-negative
- **min.obs**: See `modify.conf`
- **discard.obs**: See `modify.conf`
Details

If `cghcall=NULL`, discrete copy number values are omitted, which results in fitting a simple linear model.

If `constr.slopes=1`, all slopes are constrained to be non-negative. If `constr.slopes=2`, the slope associated with state "normal" is constrained to be non-negative and all others are forced to be at least equal to the latter.

Two methods are implemented for the estimation of knots. If call probabilities are provided, a knot is determined so that the sum of (the two adjacent) states membership probabilities is maximized. Otherwise, this is defined as the midpoint of the interval between the two consecutive states.

The constrained least squares problem is solved using function `solve.QP` of package `quadprog`.

Value

An object of class `plrs-class`

Author(s)

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Examples

```r
# Simulate data
sim <- plrs.sim(n=80, states=4, sigma=0.5)

# Fit a model
model <- plrs(expr=sim$expr, cghseg=sim$seg, cghcall=sim$cal)
model

# Methods
coeff(model)
effects(model)
fitted(model)
knots(model)
model.matrix(model)
plot(model)
predict(model, newcghseg=seq(0,5, length.out=100))
residuals(model)
summary(model)
```

---

**plrs-class**

*Class plrs*  

**Description**

An S4 class representing the output of the `plrs` function.
Slots

coefficients: Object of class numeric containing spline coefficients
fitted.values: Object of class numeric containing the fitted values
residuals: Object of class numeric containing the residuals
X: Object of class matrix containing the design matrix
data: Object of class list containing input data
ndata: Object of class list containing (possibly modified) data used to fit the model (See modify.conf).
QP: Object of class list containing input elements used for quadratic programming. If the model is unconstrained this contains a light version of an \texttt{lm} object.
test: Object of class list containing results from testing.
cb: Object of class list containing lower and upper bounds for predicted values.
selected: Object of class logical indicating whether the model results from a selection procedure.
type: Object of class character giving the type of model
call.arg: Object of class list containing the input arguments (for reproducibility)

Methods

\texttt{coef} Returns the coefficients
\texttt{criteria} See \texttt{criteria}
\texttt{effects} Returns matrix of effects
\texttt{fitted} Returns the fitted values
\texttt{knots} Returns the knots
\texttt{model.matrix} Returns the design matrix
\texttt{plot} See \texttt{plot.plrs}
\texttt{predict} See \texttt{predict.plrs}
\texttt{print} Print the object information
\texttt{residuals} Returns the residuals
\texttt{show} Print the object information
\texttt{summary} Print a summary of the object information

Author(s)

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Description
Determine uniform confidence intervals for predicted values of a 'plrs' model.

Usage
plrscb(object, alpha=0.05, newcgh=NULL)

Arguments
- object: An object of class plrs-class.
- alpha: Significance level
- newcgh: Vector of segmented values. Support for building CB.

Details
The input object of class plrs-class has to result from function plrs.test.

The problem of finding (at a given x) a confidence interval for the mean response is expressed as a
semi-definite optimization problem and solved using function csdp of package Rcsdp.

Value
An object of class plrs-class that contains CB information.

Author(s)
Gwenael G.R. Leday <g.g.r.leday@vu.nl>

References

See Also
plrs.test

Examples
# Simulate data
sim <- plrs.sim(n=80, states=4, sigma=0.5)

# Fit a model
model <- plrs(expr=sim$expr, cghseg=sim$seg, cghcall=sim$cal)

# Confidence bands
model <- plrs.test(model)
model <- plrs.cb(model, alpha=0.05)
plot(model)

plrs.select | Model selection

Description
Selection of a model based on an information criterion (AIC, AICC, BIC or OSAIC).

Usage
plrs.select(object, crit = ifelse(object@call.arg$constr,"osaic","aic"))

Arguments
- object: An object of class plrs-class
- crit: Character corresponding to the criterion to use. See criteria.

Value
An object of class plrs.select-class

Author(s)
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plrs.select-class | Class plrs.select

Description
An S4 class representing the output of the plrs.select function.

Slots
- table: Object of class matrix containing the criterion value for all models
- model: Object of class plrs containing the selected model
- crit: Object of class character containing the criterion used for model selection

Methods
- plot See plot.plrs
- print Print the object information
- show Print the object information
- summary Print a summary of the object information

Author(s)
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**plrs.series**  
*Fit plrs models for a series of arrays.*

**Description**

The function fits plrs models for a series of arrays. Model selection and testing procedures may be applied.

**Usage**

```r
plrs.series(expr, cghseg, cghcall=NULL, probloss = NULL, probnorm = NULL, probgain = NULL, probamp = NULL, control.model = list(continuous = FALSE, constr = TRUE, constr.slopes = 2, constr.intercepts = TRUE, min.obs = 3, discard.obs = TRUE), control.select = list(crit = ifelse(control.model$constr, "osaic","aic")), control.test = list(testing = TRUE, cb = FALSE, alpha = 0.05), control.output = list(save.models = FALSE, save.plots = FALSE, plot.lin = FALSE, type = "jpeg"))
```

**Arguments**

- `expr`: Either a matrix of expression profiles or an `ExpressionSet` object.
- `cghseg`: Either a matrix of segmented copy number values or objects of class `cghSeg` or `cghCall`.
- `cghcall`: Matrix of called copy number.
- `probloss`: Matrix of call probabilities associated with state "loss". Default is NULL.
- `probnorm`: Matrix of call probabilities associated with state "normal". Default is NULL.
- `probgain`: Matrix of call probabilities associated with state "gain". Default is NULL.
- `probamp`: Matrix of call probabilities associated with state "amplification". Default is NULL.
- `control.model`: See details.
- `control.select`: See details.
- `control.test`: See details.
- `control.output`: See details.
Details

If DNA and mRNA input data are matrices, rows should correspond to genes and columns to arrays. Alternatively, expression data may be provided as an ExpressionSet object and aCGH data as cghSeg or cghCall objects. A cghCall object contain all data from the calling step, thus arguments probloss, probnorm, probnorm and probamp can be omitted. An object of class cghSeg does not contain such data so only simple linear models will be fitted.

control.model allows the user to specify the type of model that has to be fitted. This must be a list with one or more of the following components: constr, constr.slopes, constr.intercepts, min.obs and discard.obs. See functions plrs and modify.conf for more details.

control.select allows the user to specify whether model selection should be done and how. This must be a list with a component named crit. See function plrs.select for more details. If control.select = NULL then no model selection is done.

control.output allows the user to plot and save each plrs model. This must be a list with components:

- save.models, a logical. This will create within the work directory a new directory named "plrsSeriesObjects" that will contain all objects.
- save.plots, a logical. This will create within the work directory a new directory named "plrsSeriesPlots" that will contains all saved plots.
- plot.lin, a logical. Whether the simple linear model should aslo be plotted.
- type, a character. Format of file. To pass through function savePlot.

Value

An object of class plrs.series-class

Author(s)

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Examples

# Simulate data
genes <- 10
array <- 48
rna <- dnaseg <- dnacal <- matrix(NA, genes, array)
idx <- sample(1:4, genes, replace=TRUE, prob=rep(1/4,4))
for(i in 1:genes){
  Sim <- plrs.sim(n=array, states=idx[i], sigma=0.5)
  rna[i,] <- Sim$expr
dnaseg[i,] <- Sim$seg
dnacal[i,] <- Sim$cal
}

# Screening procedure with linear model
series <- plrs.series(expr = rna, cghseg = dnaseg, cghcall = NULL, control.select = NULL)

# Screening procedure with full plrs model
series <- plrs.series(expr = rna, cghseg = dnaseg, cghcall = dnacal, control.select = NULL)
# Model selection
series <- plrs.series(expr = rna, cghseg = dnaseg, cghcall = dnacal)

---

**plrs.series-class**  
*Class plrs.series*

### Description
An S4 class representing the output of the `plrs.series` function.

### Slots
- **coefficients**: Matrix containing coefficients of models
- **effects**: List containing effects
- **test**: Matrix containing results from testing.
- **general**: Matrix providing the distribution of the number genes and arrays regarding the copy number states
- **modelsType**: List providing models' type
- **call.arg**: List providing details on the type of models that have been fitted.

### Methods
- `print`: Print the object information
- `show`: Print the object information
- `summary`: Print a summary of the object information

### Author(s)
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---

**plrs.sim**  
*Simulation of a plrs model*

### Description
Simulation of a piecewise relationship.

The function has been only implemented for convenience of simulations and R examples.

### Usage
```r
plrs.sim(n = 80, states = 4, sigma = 01, x = NULL)
```
### Arguments

- **n**: Number of simulated data points
- **states**: Number of states for the model
- **sigma**: Noise
- **x**: Segmented values.

### Details

To be written...

### Author(s)

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### Examples

```r
# Simulate 1-state model
sim <- plrs.sim(n=80, states=1, sigma=0.5)
model <- plrs(expr=sim$expr, cghseg=sim$seg, cghcall=sim$cal)
plot(model)

# Simulate 2-state model
sim <- plrs.sim(n=80, states=2, sigma=0.5)
model <- plrs(expr=sim$expr, cghseg=sim$seg, cghcall=sim$cal)
plot(model)

# Simulate 3-state model
sim <- plrs.sim(n=90, states=3, sigma=0.5)
model <- plrs(expr=sim$expr, cghseg=sim$seg, cghcall=sim$cal)
plot(model)

# Simulate 4-state model
sim <- plrs.sim(n=80, states=4, sigma=0.5)
model <- plrs(expr=sim$expr, cghseg=sim$seg, cghcall=sim$cal)
plot(model)
```

### plrs.test

**Likelihood ratio test for a plrs model**

### Description

Test whether copy number has an effect on mRNA expression.

### Usage

```r
plrs.test(object, alpha=0.05)
```

### Arguments

- **object**: An object of class `plrs-class`
- **alpha**: Significance level
Details

Two cases present themselves:

1. The model is unconstrained. Thus, the model under the null hypothesis is the intercept and an F-test is performed.

2. The model is constrained and the following hypothesis are tested:
   H0: All constraints are actives (=)
   H1: At least one constraint is strict (>)

Under H0, we always have the intercept model. Indeed, if constr.slopes = 1 (or 2) and constr.intercepts = T, then the only parameter free of inequality constraint is the overall intercept. If constr.intercepts = F, the local intercepts are additionaly constrained to be 0 in order to obtain the intercept model under the null. The likelihood ratio statistic (unknown variance) is asymptotically distributed as a weighted mixture of Beta distribution (cf Gromping (2010)). Calculation of p-values is based on functions ic.weights and pbetabar of package ic.infer. The package mvtnorm is also involved.

In both cases the input model is taken as the model under the alternative.

Value

A list object with the following components:

- stat: Test statistic
- pvalue: Calculated pvalue
- wt.bar: Weights (if the model is constrained)
- df.bar: Degrees of freedom.
- unconstr: Unconstrained model of class plrs-class
- qbetabar: (1-\alpha) quantile of the beta mixture distribution
- alpha: Significance level

Author(s)

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References


Examples

# Simulate data
sim <- plrs.sim(n=80, states=2, sigma=0.5)

# Fit a model
model <- plrs(expr=sim$expr, cghseg=sim$seg, cghcall=sim$cal)

# Testing
model <- plrs.test(model)
model
predict.plrs  

**Predict method for plrs models**

Description

Determine predicted values based on a given plrs model

Usage

```r
## S3 method for class 'plrs'
predict(object, newcghseg, ...)
```

Arguments

- `object`: An object of class `plrs-class`
- `newcghseg`: A vector of new segmented CGH values
- `...`: further arguments

Value

A vector containing the fitted values.

Author(s)

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