

Package ‘qrNLMM’

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Type Package

Title Quantile Regression for Nonlinear Mixed-Effects Models

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Imports matrixcalc, mvtnorm, ghyp, quantreg, psych, tcltk, ald

Suggests lqr

Description Quantile regression (QR) for Nonlinear Mixed-Effects Models via the asymmetric Laplace distribution (ALD). It uses the Stochastic Approximation of the EM (SAEM) algorithm for deriving exact maximum likelihood estimates and full inference results for the fixed-effects and variance components. It also provides graphical summaries for assessing the algorithm convergence and fitting results.

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qrNLMM-package

Package for Quantile Regression for Linear Mixed-Effects Model

Description

This package contains a principal function that performs a quantile regression for a Nonlinear Mixed-Effects Model using the Stochastic-Approximation of the EM Algorithm (SAEM) for an unique or a set of quantiles.

Exploiting the nice hierarchical representation of the ALD, our classical approach follows the Stochastic Approximation of the EM(SAEM) algorithm for deriving exact maximum likelihood estimates of the fixed-effects and variance components.

Details

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References

Galarza, C.M., Castro, L.M. Louzada, F. and V. H. Lachos (2016) Quantile Regression for Nonlinear Mixed Effects Models: A Likelihood Based Perspective. Technical Report 8, Universidade Estadual de Campinas. <http://www.ime.unicamp.br/sites/default/files/rp08-2016.pdf>

Yu, K. & Moyeed, R. (2001). Bayesian quantile regression. *Statistics & Probability Letters*, 54(4), 437-447.

Yu, K., & Zhang, J. (2005). A three-parameter asymmetric Laplace distribution and its extension. *Communications in Statistics-Theory and Methods*, 34(9-10), 1867-1879.

See Also

[Soybean](#), [HIV](#), [QRNLMM](#), [lqr](#), [QRLMM](#), [group.plots](#)

Examples

#See examples for the QRNLMM function linked above.

group.plots	<i>Plot function for grouped data</i>
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Description

Functions for plotting a profiles plot for grouped data.

Usage

```
group.plot(x,y,groups,...)
group.lines(x,y,groups,...)
group.points(x,y,groups,...)
```

Arguments

y	the response vector of dimension N where N is the total of observations.
x	vector of longitudinal (repeated measures) covariate of dimension N . For example: Time, location, etc.
groups	factor of dimension N specifying the partitions of the data over which the random effects vary.
...	additional graphical arguments passed to matplot . See par .

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See Also

[Soybean](#), [HIV](#), [QRNLMM](#), [QRLMM](#)

Examples

```
## Not run:
##A full profile plot for Soybean data

data(Soybean)
attach(Soybean)

group.plot(x = Time,y = weight,groups = Plot,type="b",
           main="Soybean profiles",xlab="time (days)",
           ylab="mean leaf weight (gr)")

#Profile plot by genotype

group.plot(x = Time[Variety=="P"],y = weight[Variety=="P"],
           groups = Plot[Variety=="P"],type="l",col="blue",
           main="Soybean profiles by genotype",xlab="time (days)",
           ylab="mean leaf weight (gr)")
```

```
group.lines(x = Time[Variety=="F"],y = weight[Variety=="F"],
           groups = Plot[Variety=="F"],col="black")

## End(Not run)
```

HIV

HIV viral load study

Description

The data set belongs to a clinical trial (ACTG 315) studied in previous researches by Wu (2002) and Lachos et al. (2013). In this study, we analyze the HIV viral load of 46 HIV-1 infected patients under antiretroviral treatment (protease inhibitor and reverse transcriptase inhibitor drugs). The viral load and some other covariates were measured several times days after the start of treatment been 4 and 10 the minimum and maximum number of measures per patient respectively.

Usage

```
data(HIV)
```

Format

This data frame contains the following columns:

patid a numeric vector indicating the patient register number.

ind a numeric vector indicating the number patient on which the measurement was made. It represents the subject number in the study.

day time in days.

cd4 cd4 count in cells/mm^3 .

lgviral viral load in log10 scale.

cd8 cd8 count in cells/mm^3 .

Details

In order to fit the nonlinear data we suggest to use the Nonlinear model proposed by Wu (2002) and also used by Lachos et al. (2013).

Source

Wu, L. (2002). A joint model for nonlinear mixed-effects models with censoring and covariates measured with error, with application to aids studies. *Journal of the American Statistical association*, 97(460), 955-964.

Lachos, V. H., Castro, L. M. & Dey, D. K. (2013). Bayesian inference in nonlinear mixed-effects models using normal independent distributions. *Computational Statistics & Data Analysis*, 64, 237-252.

Examples

```
## Not run:
data(HIV)
attach(HIV)

y      = lgviral           #response
x      = day/100           #time
covar  = cd4/100          #covariate

#Nonlinear model used in Lachos(2013)

#Full Nonlinear expression
exprNL = expression(log(exp(fixed[1]+random[1])*exp(-(fixed[2]+random[2])*x)+
                        exp(fixed[3]+random[3])*exp(-(fixed[4]+random[4]+fixed[5]
                        *covar[1])*x))/log(10))

#Initial values for fixed effects
initial = c(12,31,6,-2,0.6)

#A median regression (by default)
median_reg = QRNLMM(y,x,ind,initial,exprNL,covar)

## End(Not run)
```

QRNLMM

*Quantile Regression for Nonlinear Mixed-Effects Models***Description**

Performs a quantile regression for a NLMEM using the Stochastic-Approximation of the EM Algorithm (SAEM) for an unique or a set of quantiles.

Usage

```
QRNLMM(y,x,groups,initial,exprNL,covar=NA,p=0.5,precision=0.0001,MaxIter=500,
M=20,cp=0.25,beta=NA,sigma=NA,Psi=NA,show.convergence=TRUE,CI=95)
```

Arguments

<code>y</code>	the response vector of dimension N where N is the total of observations.
<code>x</code>	vector of longitudinal (repeated measures) covariate of dimension N . For example: Time, location, etc.
<code>groups</code>	factor of dimension N specifying the partitions of the data over which the random effects vary.
<code>initial</code>	an numeric vector, or list of initial estimates for the fixed effects. It must be provide adequately (see details section) in order to ensure a proper convergence.

exprNL	expression containing the proposed nonlinear function. It can be of class character or expression. It must have a defined structure defined in the details section in order to be correctly read by the derivate R function <code>deriv</code> .
covar	a matrix of dimension $N \times r$ where r represents the number of covariates.
p	unique quantile or a set of quantiles related to the quantile regression.
precision	the convergence maximum error.
MaxIter	the maximum number of iterations of the SAEM algorithm. Default = 500.
M	Number of Monte Carlo simulations used by the SAEM Algorithm. Default = 20. For more accuracy we suggest to use $M=20$.
cp	cut point ($0 \leq cp \leq 1$) which determines the percentage of initial iterations with no memory.
beta	fixed effects vector of initial parameters, if desired.
sigma	dispersion initial parameter for the error term, if desired.
Psi	Variance-covariance random effects matrix of initial parameters, if desired.
show.convergence	if TRUE, it will show a graphical summary for the convergence of the estimates of all parameters for each quantile in order to assess the convergence.
CI	Confidence to be used for the Confidence Interval when a grid of quantiles is provided. Default=95.

Details

This algorithm performs the SAEM algorithm proposed by Delyon et al. (1999), a stochastic version of the usual EM Algorithm deriving exact maximum likelihood estimates of the fixed-effects and variance components. Covariates are allowed, the longitudinal (repeated measures) coded x and a set of covariates $covar$.

Aboutinitialvalues : Estimation for fixed effects parameters involves a Newton-Raphson step. In addition, NL models are highly sensitive to initial values. So, we suggest to set of initial values quite good, this based in the parameter interpretation of the proposed NL function.

Aboutthenonlinearexpression : For the NL expression `exprNL` just the variables x , $covar$, $fixed$ and $random$ can be defined. Both x and $covar$ represent the covariates defined above. The fixed effects must be declared as `fixed[1]`, `fixed[2]`, ..., `fixed[d]` representing the first, second and d th fixed effect. Exactly the same for the random effects and covariates where the term `fixed` should be replace for `random` and `covar` respectively.

For instance, if we use the exponential nonlinear function with two parameters, each parameter represented by a fixed and a random effect, this will be defined by

$$y_{ij} = (\beta_1 + b_1) \exp^{-(\beta_2 + b_2)x_{ij}}$$

and the `exprNL` should be a character or and expression defined by

```
exprNL = "(fixed[1]+random[1])*exp(-(fixed[2]+random[2])*x)"
```

or

```
exprNL = expression((fixed[1]+random[1])*exp(-(fixed[2]+random[2])*x)).
```

If we are interested in adding two covariates in order to explain on of the parameters, the covariates covar[1] and covar[2] must be included in the model. For example, for the nonlinear function

$$y_{ij} = (\beta_1 + \beta_3 * covar1_{ij} + b_1) \exp^{-(\beta_2 + \beta_4 * covar2_{ij} + b_2)x_{ij}}$$

the exprNL should be

```
exprNL = "(fixed[1]+fixed[3]*covar[1]+random[1])*exp(-(fixed[2]+fixed[4]*covar[2]+random[2])*x)"
```

or

```
exprNL = expression((fixed[1]+fixed[3]*covar[1]+random[1])*exp(-(fixed[2]+ fixed[4]*covar[2]+random[2])*x))
```

Note that the mathematical function exp was used. For derivating the deriv R function recognizes in the exprNL expression the arithmetic operators +, -, *, / and ^, and the single-variable functions exp, log, sin, cos, tan, sinh, cosh, sqrt, pnorm, dnorm, asin, acos, atan, gamma, lgamma, digamma and trigamma, as well as psigamma for one or two arguments (but derivative only with respect to the first).

General details : When a grid of quantiles is provided, a graphical summary with point estimates and Confidence Intervals for model parameters is shown and also a graphical summary for the convergence of these estimates (for each quantile), if show.convergence=TRUE.

If the convergence graphical summary shows that convergence has not be attained, it's suggested to increase the total number of iterations MaxIter.

About the cut point parameter cp, a number between 0 and 1 ($0 \leq cp \leq 1$) will assure an initial convergence in distribution to a solution neighborhood for the first cp*MaxIter iterations and an almost sure convergence for the rest of the iterations. If you do not know how SAEM algorithm works, these parameters SHOULD NOT be changed.

This program uses progress bars that will close when the algorithm ends. They must not be closed before, if not, the algorithm will stop.

Value

The function returns a list with two objects

conv A two elements list with the matrices teta and se containing the point estimates and standard error estimate for all parameters along all iterations.

The second element of the list is res, a list of 12 elements detailed as

iter	number of iterations.
criteria	attained criteria value.
nlmodel	the proposed nonlinear function.
beta	fixed effects estimates.
weights	random effects weights (b_i).
sigma	scale parameter estimate for the error term.
Psi	Random effects variance-covariance estimate matrix.
SE	Standard Error estimates.
table	Table containing the inference for the fixed effects parameters.

loglik	Log-likelihood value.
AIC	Akaike information criterion.
BIC	Bayesian information criterion.
HQ	Hannan-Quinn information criterion.
time	processing time.

Note

If a grid of quantiles was provided, the result is a list of the same dimension where each element corresponds to each quantile as detailed above.

Author(s)

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References

Galarza, C.M., Castro, LM. Louzada, F. and V. H. Lachos (2016) Quantile Regression for Nonlinear Mixed Effects Models: A Likelihood Based Perspective. Technical Report 8, Universidade Estadual de Campinas. <http://www.ime.unicamp.br/sites/default/files/rp08-2016.pdf>

Delyon, B., Lavielle, M. & Moulines, E. (1999). Convergence of a stochastic approximation version of the EM algorithm. Annals of Statistics, pages 94-128.

See Also

[Soybean](#), [HIV](#), [lqr](#), [QRLMM](#), [group.plots](#)

Examples

```
## Not run:
##Using the Soybean data

data(Soybean)
attach(Soybean)

#####
#A full model (no covariate)

y      = weight      #response
x      = Time        #time

#Expression for the three parameter logistic curve

exprNL = expression(((fixed[1]+random[1])/
                    (1 + exp(((fixed[2]+random[2])- x)/(fixed[3]+random[3])))))

#Initial values for fixed effects
initial = c(max(y),0.6*max(y),0.73*max(y))

#A median regression (by default)
```



```

median_reg = QRNLMM(y,x,Plot,initial,exprNL)

#Assesing the fit

fxd      = median_reg$res$beta
nlmodel  = median_reg$res$nlmodel
seqc     = seq(min(x),max(x),length.out = 500)

group.plot(x = Time,y = weight,groups = Plot,type="l",
           main="Soybean profiles",xlab="time (days)",
           ylab="mean leaf weight (gr)",col="gray")

for(i in 1:48)
{
  lines(seqc,nlmodel(x = seqc,fixed = fxd,random = weights[i,]),lty=2)
}

lines(seqc,nlmodel(x = seqc,fixed = fxd,random = rep(0,3)),
      lwd=3,col="red")

#####
#A model for compairing the two genotypes

y      = weight      #response
x      = Time        #time
covar  = c(Variety)-1 #factor genotype (0=Forrest, 1=Plan Introduction)

#Expression for the three parameter logistic curve with a covariate

exprNL = expression(((fixed[1]+(fixed[4]*covar[1])+random[1])/
                    (1 + exp(((fixed[2]+random[2])- x)/(fixed[3]+random[3])))))

#Initial values for fixed effects
initial = c(max(y),0.6*max(y),0.73*max(y),3)

# A quantile regression for the three quartiles
box_reg = QRNLMM(y,x,Plot,initial,exprNL,covar,p=c(0.25,0.50,0.75))

#Assing the fit for the median (second quartile)

fxd      = box_reg[[2]]$res$beta
nlmodel  = box_reg[[2]]$res$nlmodel
seqc     = seq(min(x),max(x),length.out = 500)

group.plot(x = Time[Variety=="P"],y = weight[Variety=="P"],
           groups = Plot[Variety=="P"],type="l",col="light blue",
           main="Soybean profiles by genotype",xlab="time (days)",
           ylab="mean leaf weight (gr)")

group.lines(x = Time[Variety=="F"],y = weight[Variety=="F"],
            groups = Plot[Variety=="F"],col="gray")

lines(seqc,nlmodel(x = seqc,fixed = fxd,random = rep(0,3),covar=1),

```

```

      lwd=2,col="blue")

lines(seqc,nlmodel(x = seqc,fixed = fxd,random = rep(0,3),covar=0),
      lwd=2,col="black")

#####
#A simple output example

-----
Quantile Regression for Nonlinear Mixed Model
-----

Quantile = 0.5
Subjects = 48 ; Observations = 412

- Nonlinear function

function(x,fixed,random,covar=NA){
  resp = (fixed[1] + random[1])/(1 + exp(((fixed[2] +
      random[2]) - x)/(fixed[3] + random[3])))
  return(resp)}

-----
Estimates
-----
- Fixed effects

      Estimate Std. Error   z value Pr(>|z|)
beta 1 18.80029    0.53098  35.40704    0
beta 2 54.47930    0.29571 184.23015    0
beta 3  8.25797    0.09198  89.78489    0

sigma = 0.31569

Random effects Variance-Covariance Matrix matrix
      b1      b2      b3
b1 24.36687 12.27297 3.24721
b2 12.27297 15.15890 3.09129
b3  3.24721  3.09129 0.67193

-----
Model selection criteria
-----
      Loglik      AIC      BIC      HQ
Value -622.899 1265.798 1306.008 1281.703

-----
Details
-----
Convergence reached? = FALSE
Iterations = 300 / 300
Criteria = 0.00058
MC sample = 20
Cut point = 0.25

```

```
Processing time = 22.83885 mins
```

```
## End(Not run)
```

Soybean

Growth of soybean plants

Description

The Soybean data frame has 412 rows and 5 columns.

Format

This data frame contains the following columns:

Plot a factor giving a unique identifier for each plot.

Variety a factor indicating the variety; Forrest (F) or Plant Introduction \#416937 (P).

Year a factor indicating the year the plot was planted.

Time a numeric vector giving the time the sample was taken (days after planting).

weight a numeric vector giving the average leaf weight per plant (g).

Details

These data are described in Davidian and Giltinan (1995, 1.1.3, p.7) as “Data from an experiment to compare growth patterns of two genotypes of soybeans: Plant Introduction \#416937 (P), an experimental strain, and Forrest (F), a commercial variety.” In order to fit the Nonlinear data we suggest to use the three parameter logistic model as in Pinheiro & Bates (1995).

Source

Pinheiro, J. C. and Bates, D. M. (2000), *Mixed-Effects Models in S and S-PLUS*, Springer, New York. (Appendix A.27)

Davidian, M. and Giltinan, D. M. (1995), *Nonlinear Models for Repeated Measurement Data*, Chapman and Hall, London.

Examples

```
## Not run:
data(Soybean)
attach(Soybean)

#####
#A full model (no covariate)

y = weight      #response
x = Time        #time
```

```

#Expression for the three parameter logistic curve

exprNL = expression(((fixed[1]+random[1])/(1 + exp(((fixed[2]+random[2])- x)/(fixed[3]+random[3])))))

#Initial values for fixed effects
initial = c(max(y),0.6*max(y),0.73*max(y))

#A median regression (by default)
median_reg = QRNLMM(y,x,Plot,initial,exprNL)

#Assing the fit

fxd      = median_reg$res$beta
nlmodel = median_reg$res$nlmodel
seqc     = seq(min(x),max(x),length.out = 500)

group.plot(x = Time,y = weight,groups = Plot,type="l",
           main="Soybean profiles",xlab="time (days)",
           ylab="mean leaf weight (gr)",col="gray")

lines(seqc,nlmodel(x = seqc,fixed = fxd,random = rep(0,3)),
      lwd=2,col="blue")

#####
#A model for compairing the two genotypes

y      = weight      #response
x      = Time        #time
covar  = c(Variety)-1 #factor genotype (0=Forrest, 1=Plan Introduction)

#Expression for the three parameter logistic curve with a covariate

exprNL = expression(((fixed[1]+(fixed[4]*covar[1])+random[1])/
                    (1 + exp(((fixed[2]+random[2])- x)/(fixed[3]+random[3])))))

#Initial values for fixed effects
initial = c(max(y),0.6*max(y),0.73*max(y),3)

# A quantile regression for the three quartiles
box_reg = QRNLMM(y,x,Plot,initial,exprNL,covar,p=c(0.25,0.50,0.75))

#Assing the fit for the median (second quartile)

fxd      = box_reg[[2]]$res$beta
nlmodel = box_reg[[2]]$res$nlmodel
seqc     = seq(min(x),max(x),length.out = 500)

group.plot(x = Time[Variety=="P"],y = weight[Variety=="P"],
           groups = Plot[Variety=="P"],type="l",col="light blue",
           main="Soybean profiles by genotype",xlab="time (days)",
           ylab="mean leaf weight (gr)")

group.lines(x = Time[Variety=="F"],y = weight[Variety=="F"],

```

```
      groups = Plot[Variety=="F"],col="gray")  
  
lines(seqc,nlmodel(x = seqc,fixed = fxd,random = rep(0,3),covar=1),  
      lwd=2,col="blue")  
  
lines(seqc,nlmodel(x = seqc,fixed = fxd,random = rep(0,3),covar=0),  
      lwd=2,col="black")  
  
## End(Not run)
```

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