Package ‘InformativeCensoring’

August 29, 2016

Type Package

Title Multiple Imputation for Informative Censoring

Version 0.3.4

Maintainer Jonathan Bartlett <jonathan.bartlett1@astrazeneca.com>

Author David Ruau [aut],
    Nikolas Burkoff [aut],
    Jonathan Bartlett [aut, cre],
    Dan Jackson [aut],
    Edmund Jones [aut],
    Martin Law [aut],
    Paul Metcalfe [aut]

Description Multiple Imputation for Informative Censoring.
    This package implements two methods. Gamma Imputation
    from Jackson et al. (2014) <DOI:10.1002/sim.6274> and Risk Score Imputation

License GPL (>= 2) | file LICENSE

LazyLoad yes

Depends R (>= 3.1.2), survival (>= 2.36-1)

Imports boot, dplyr (>= 0.4.3), parallel

Suggests knitr, testthat

VignetteBuilder knitr

URL https://github.com/scientific-computing-solutions/InformativeCensoring

RoxygenNote 5.0.1

NeedsCompilation no

Repository CRAN

Date/Publication 2016-08-11 18:40:16
Description

Perform methods of multiple imputation for time to event data

Details


Author(s)

<David.Ruas@astraZeneca.com>
**col.headings**  
* Specify the columns of the data frame required by score imputation method

**Description**

Specify the columns of the data frame required by score imputation method

**Usage**

```r
col.headings(arm, has.event, time, Id, DC0.time, to.impute, 
censor.type = NULL)
```

**Arguments**

- **arm**
  column name which will contain the subject’s treatment group
- **has.event**
  column name which will contain whether the subject has an event (1) or not(0)
- **time**
  column name of censoring/event time
- **Id**
  column name of subject Id
- **DC0.time**
  column name of the time at which the subject would have been censored had they not had an event before data cut off
- **to.impute**
  column name of the logical column as to whether events should be imputed
- **censor.type**
  column name of the column containing the reason for censoring, 0=had event, 1=non-administrative censoring 2=administrative censoring – only subjects with 1 in this column count as having an ‘event’ in the Cox model for censoring (optionally used – if not used then all subjects who are censored are used)

**Value**

A list contain the given arguments

---

**cox.zph**  
* Test Cox proportional hazards assumption

**Description**

See cox.zph function in the survival package

**Usage**

```r
cox.zph(fit, transform = "km", global = TRUE, ...)
```
Arguments

- **fit**: the result of fitting a Cox regression model, using the `coxph` function.
- **transform**: a character string specifying how the survival times should be transformed before the test is performed. Possible values are "km", "rank", "identity" or a function of one argument.
- **global**: should a global chi-square test be done, in addition to the per-variable tests.
- **...**: Additional arguments to `cox.zph`, for example `index` if `fit` is a `GammaStatList` object.

See Also

cox.zph

ExtractSingle

Extract a single risk score/gamma imputed data set/model fit

Description

Extract a single risk score/gamma imputed data set/model fit

Usage

```r
## S3 method for class 'GammaImputedSet'
ExtractSingle(x, index)
```

```r
## S3 method for class 'GammaStatList'
ExtractSingle(x, index)
```

```r
ExtractSingle(x, index)
```

```r
## S3 method for class 'ScoreImputedSet'
ExtractSingle(x, index)
```

```r
## S3 method for class 'ScoreStatList'
ExtractSingle(x, index)
```

Arguments

- **x**: The multiple imputed object
- **index**: Integer, which imputed data set/model fit should be returned

Value

The individual data set/model fit
gammaImpute

Perform gamma-Imputation for a given data set

Description

This function performs the Imputation described in Relaxing the independent censoring assumptions in the Cox proportional hazards model using multiple imputation. (2014) D. Jackson et al. Statist. Med. (33) 4681-4694

Usage

```
gammaImpute(formula, data, m, gamma, gamma.factor, bootstrap.strata = rep(1, nrow(data)), DCO.time, ..., parallel = c("no", "multicore", "snow")[1], ncpus = 1L, cl = NULL)
```

Arguments

- **formula**: The model formula to be used when fitting the models to calculate the cumulative hazard. A formula for coxph can include strata terms but not cluster or tt and only right-censored Surv objects can be used. Note the function does not allow multiple strata to be written as `strata(w1)+strata(w2)`, use `strata(w1,w2)` instead.
- **data**: A time to event data set for which event times are to be imputed.
- **m**: The number of imputations to be created.
- **gamma**: Either column name containing the value of gamma or a vector of values giving the subject specific size of the step change in the log hazard at censoring. If a subject has NA in this column then no imputation is performed for this subject (i.e. the subject’s censored time remains unchanged after imputation). If a subject has already had an event then the value of gamma is ignored. If gamma.factor is also used then the subject specific gamma are all multiplied by gamma.factor. At least one of gamma and gamma.factor must be included.
- **gamma.factor**: If used, a single numeric value. If no gamma then the step change in log hazard for all subjects at censoring is given by gamma.factor. If gamma is used then for each subject, the step change in log hazard is given by gamma.factor multiplied by the subject specific gamma. At least one of gamma and gamma.factor must be included.
- **bootstrap.strata**: The strata argument for stratified bootstrap sampling, see argument strata for the function boot::boot for further details. If argument is not used then standard sampling with replacement will be used.
- **DCO.time**: Either column name containing the subject’s data cutoff time or a vector of DCO.times for the subjects or a single number to be used as the DCO.time for all subjects (if imputed events are > this DCO.time then subjects are censored at DCO.time in imputed data sets).
- **...**: Additional parameters to be passed into the model fit function.
gammaImpute

parallel The type of parallel operation to be used (if any).

ncpus integer: number of processes to be used in parallel operation: typically one
would chose this to be the number of available CPUs

c1 An optional parallel or snow cluster for use if parallel="snow". If not supplied, a cluster
on the local machine is created for the duration of the call.

Details

See the Gamma Imputation vignette for further details

Value

A GammaImputedSet.object containing the imputed data sets

See Also

GammaImputedSet.object GammaImputedData.object

Examples

## Not run:
data(nwtco)
nwtco <- nwtco[1:500,]

#creating 2 imputed data sets (m=2) for speed, would normally create more
ans <- gammaImpute(formula=Surv(edrel,rel)~histol + instit,
data = nwtco, m=2, gamma.factor=1, DCO.time=6209)

#subject specific gamma (multiplied by gamma.factor to give the jump)
#NA for subjects that are not to be imputed
jumps <- c(rep(NA,10),rep(1,490))
DCO.values <- rep(6209,500)

ans.2 <- gammaImpute(formula=Surv(edrel,rel)~histol + instit + strata(stage),
data = nwtco, m=2, bootstrap.strata=strata(nwtco$stage),
gamma=jumps, gamma.factor=1, DCO.time=DCO.values)

#can also use column names
nwtco$gamma <- jumps
nwtco$DCO.time <- DCO.values
ans.3 <- gammaImpute(formula=Surv(edrel,rel)~histol + instit + strata(stage),
data = nwtco, m=2, bootstrap.strata=strata(nwtco$stage),
gamma="gamma", DCO.time="DCO.time")

## End(Not run)
**GammaImputedData.object**

**Description**

An object which contains

**Slots**

data  A data frame containing the time to event data with 3 new columns impute.time and impute.event, the imputed event/censoring times and event indicators (for subjects whose data is not imputed these columns contain the unchanged event/censoring time and event indicator) and internal_gamma_val which is the value of gamma used for each subject in this data set
default.formula  The default model formula which will be used when fitting the imputed data

**GammaImputedSet.object**

**Description**

An object which contains the set of gamma imputed data frames. Use the ExtractSingle function to extract a single GammaImputedData objects. Use the ImputeStat function to fit models to the entire set of imputed data frames

**Details**

It contains the following:

**Slots**

data  A data frame containing the unimputed time to event data (along with a column internal_gamma_val which is the value of gamma used for each subject in this data set)
m  The number of imputed data sets
gamma.factor  The value of gamma.factor used with the imputation
impute.time  A matrix (1 column per imputed data set) containing the imputed times
impute.event  A matrix (1 column per imputed data set) containing the imputed event indicators
default.formula  The default model formula which will be used when fitting the imputed data

**See Also**

GammaImputedData.object
GammaStat.object

Description
An S3 object which contains the point estimate and test statistic after fitting a model to a GammaImputedData object.

Details
The function print.GammaStat has been implemented. The object contains the following:

Slots
- model: The model used to create the fit
- method: The model used for the fit
- estimate: A point estimate of the test statistic
- var: The estimate for the variance of the test statistic

GammaStatList.object

Description
The object containing the results of fitting models to a GammaImputedSet object.

Details
A summary.GammaStatList has been implemented which performs Rubin’s multiple imputation rules. The object contains the following:

Slots
- fits: A list of GammaStat objects containing the model fits for the imputed data sets
- statistics: A list with two elements: estimates and vars which contain the coefficient estimates and their variances one column per covariate one row per imputed data set
- m: The number of model fits
Description

S3 generic to fit model(s) to risk score/gamma Imputed objects

Usage

```r
## S3 method for class 'GammaImputedData'
ImputeStat(object, method = c("Cox", "weibull", "exponential")[[1]], formula = NULL, ...)

## S3 method for class 'GammaImputedSet'
ImputeStat(object, method = c("Cox", "weibull", "exponential")[[1]], formula = NULL, ..., parallel = c("no", "multicore", "snow")[[1]], ncpus = 1L, cl = NULL)

ImputeStat(object, method = c("logrank", "Wilcoxon", "Cox", "weibull", "exponential")[[1]], formula, ...)

## S3 method for class 'ScoreImputedSet'
ImputeStat(object, method = c("logrank", "Wilcoxon", "Cox")[[1]], formula = NULL, ..., parallel = c("no", "multicore", "snow")[[1]], ncpus = 1L, cl = NULL)
```

Arguments

- `object`: A ScoreImputedData, ScoreImputedSet, GammaImputedData or GammaImputedSet object to fit the model to.
- `method`: The type of statistical model to fit. There are three methods which can be performed when using Risk Score imputation:
  - "logrank": a logrank test using `survival::survdiff`
  - "Wilcoxon": Peto & Peto modification of the Gehan-Wilcoxon test using `survival::survdiff` with \( \rho = 1 \)
  - "Cox": Fit a cox model using `survival::coxph`

  For gamma imputation the model can be "Cox" (using `survival::coxph`), "weibull" or "exponential" both using `survival::coxph`

- `formula`: The model formula to fit. If no formula argument is used, then `object$default.formula` will be used. For risk score imputation this is \(~ \text{treatment} \cdot \text{group}\) and for gamma imputation this is the formula used when fitting the Cox model.

  For method="Cox", additional covariates can be included by explicitly giving a formula argument. For logrank/Wilcoxon only additional strata terms can be included.
In all cases only the right hand side of the formula is required. The survival object on the left hand side is created automatically. E.g. for a Cox model could use formula=~arm + covar1. The cluster and tt options cannot be used. See the vignettes for further details.

Additional arguments which are passed into the model fit function.

- `parallel`: The type of parallel operation to be used (if any), can be used for GammaImputedSet and ScoreImputedSet.
- `ncpus`: integer: number of processes to be used in parallel operation: typically one would chose this to be the number of available CPUs, can be used for GammaImputedSet and ScoreImputedSet.
- `cl`: An optional parallel or snow cluster for use if parallel="snow". If not supplied, a cluster on the local machine is created for the duration of the call, can be used for GammaImputedSet and ScoreImputedSet.

See Also

- ScoreStat.object
- ScoreImputedData.object

### Description

Create a valid ScoreTD object.

### Usage

```r
MakeTimeDepScore(data, Id, time.start, time.end)
```

### Arguments

- `data`: A data frame of time dependent covariates.
- `Id`: The column name of the subject Id.
- `time.start`: The covariates are valid for the time [time.start,time.end] where time.start is the column name of time.start.
- `time.end`: The covariates are valid for the time [time.start,time.end] where time.end is the column name of time.end.

### Value

A ScoreTD object.
NN.options

Create a list of options which control the nearest neighbour algorithm for risk score imputation

**Description**

Create a list of options which control the nearest neighbour algorithm for risk score imputation

**Usage**

\[
\text{NN.options} (\text{NN} = 5, \text{w.censoring} = 0.2, \text{min.subjects} = 20)
\]

**Arguments**

- **NN**
  - The (maximum) number of subjects to be included in the risk set
- **w.censoring**
  - The weighting on the censoring risk score when calculating distances for the nearest neighbour calculation. A weighting of \((1 - \text{w.censoring})\) is used for the event risk score
- **min.subjects**
  - If using time dependent score imputation include at least this number of subjects when fitting the Cox model (i.e. include some subjects who were censored/had event earlier than the censored observation if necessary)

**Value**

A list of options used within the ScoreImputedData function

---

**ScoreImpute**

Perform risk score multiple imputation method

**Description**

Perform risk score multiple imputation method

**Usage**

\[
\text{ScoreImpute} (\text{data}, \text{event.model}, \text{censor.model} = \text{event.model}, \text{col.control}, \text{NN.control} = \text{NN.options()}, \text{time.dep} = \text{NULL}, \text{m}, \text{bootstrap.strata} = \text{rep(1, nrow(data))}, ..., \text{parallel} = \text{c("no", "multicore", "snow")}[1], \text{ncpus} = 1L, \text{cl} = \text{NULL})
\]
Arguments

- `data`: The data set for which imputation is required.
- `event.model`: The right hand side of the formula to be used for fitting the Cox model for calculating the time to event score e.g. \(~Z1+Z2+Z3\).
- `censor.model`: The right hand side of the formula to be used for fitting the Cox model for calculating the time to censoring score if not included then `event.model` will be used.
- `col.control`: A list of the columns names of `data` which are used by the imputation algorithm. See example below and for further details of these columns and their purpose see `col.headings`.
- `nn.control`: Parameters which control the nearest neighbour algorithm. See `NN.options`.
- `time.dep`: A ScoreTD object, to be included if the time dependent score imputation method is to be used, otherwise it should be `NULL`.
- `m`: The number of data sets to impute.
- `bootstrap.strata`: When performing the bootstrap procedure for fitting the models, how should the data be stratified (see strata argument to `boot::boot`). If argument is not used then standard sampling with replacement is used to generate the bootstrap data.
- `...`: Additional arguments passed into the Cox model. Note the subset and na.action arguments should not be used (na.fail will be used when fitting the Cox model).
- `parallel`: The type of parallel operation to be used (if any).
- `ncpus`: Integer: number of processes to be used in parallel operation: typically one would chose this to be the number of available CPUs.
- `cl`: An optional parallel or snow cluster for use if `parallel="snow"`. If not supplied, a cluster on the local machine is created for the duration of the call.

Details

Note that coxph may fail to converge and the following output Warning in fitter(X, Y, strats, offset, init, control, weights = weights, : Ran out of iterations and did not converge.

It is possible to use ridge regression by including a ridge term in the model formula (e.g. \(~Z1+\text{ridge}(Z2, \text{theta}=1)\)). See `ridge` for further details.

Value

A ScoreImputedSet object

See Also

`ScoreImputedSet.object`
Examples

data(ScoreInd)

col.control <- col.headings(has.event="event", time="time",
Id="Id", arm="arm",
DCO.time="DCO.time",
to.impute="to.impute")

## Not run:
ans <- ScoreImpute(data=ScoreInd, event.model=~Z1+Z2+Z3+Z4+Z5,
col.control=col.control, m=5,
bootstrap.strata=ScoreInd$arm,
NN.control=NN.options(NN=5, w.censoring = 0.2))

## End(Not run)

ScoreImputedData.object

ScoreImputedData object

Description

An object which contains

Slots

data A data frame containing the time to event data with 2 new columns impute.time and impute.event, the imputed event/censoring times and event indicators (for subjects whose data is not imputed these columns contain the unchanged event/censoring time and event indicator )

col.control The list of column names the risk score imputation method requires see col.headings for further details. If censor.type was not used then col.control$censor.type="using_has.event_col"

default.formula The default model formula which will be used when fitting the imputed data using a Cox model

ScoreImputedSet.object

ScoreImputedSet object

Description

An object which contains the set of score imputed data frames. Use the ExtractSingle function to extract a single ScoreImputedData object. Use the ScoreStat function to fit models to the entire set of imputed data frames
Details

It contains the following:

Slots

data  A data frame containing the unimputed time to event data
col.control  The list of column names the score imputation method requires see col.headings for further details
m  The number of imputed data sets
impute.time  A matrix (1 column per imputed data set) containing the imputed times
impute.event  A matrix (1 column per imputed data set) containing the imputed event indicators
default.formula  The default model formula which will be used when fitting the imputed data using a Cox model

See Also

ScoreImputedData.object

ScoreInd

Simulated time to event data with 5 time independent covariates

Description

This dataset is inspired by the simulation described in Hsu and Taylor, Statistics in Medicine (2009) 28:462-475 with an additional DCO.time column

Format

A data.frame containing a row per subject with eleven columns:

Fields

Id  subject identifier
arm  factor for treatment group control=0, active=1
Z1  binary time independent covariate
Z2  continuous time independent covariate
Z3  binary time independent covariate
Z4  continuous time independent covariate
Z5  binary time independent covariate
event  event indicator (1 yes, 0 no)
time  subject censoring/event time (in years)
to.impute  logical, should an event time be imputed for this subject? (this is ignored if subject has event time)
DCO.time  The time the subject would have been censored if they had not had an event or been censored before the data cut off date
**ScoreStat.object**  

**ScoreStat object**

---

**Description**

An S3 object which contains the point estimate and test statistic after fitting a model to a ScoreImputedData object.

**Details**

The functions `print.ScoreStat` and `as.vector.ScoreStat` have been included

The object contains the following:

The test statistic should be normally distributed and hence for the logrank test \( Z = (O_2 - E_2)/\sqrt{V_2} \), i.e. the square root of the standard Chi squared statistic (with the appropriate sign)

**Slots**

- `model` The model used to create the fit
- `method` The method used for the fit
- `estimate` A point estimate of the test statistic
- `var` The estimate for the variance of the test statistic
- `statistic` The test statistic given by `estimate/sqrt(var)`

---

**ScoreStatList.object**  

**ScoreStatList**

---

**Description**

The object containing the results of fitting models to a ScoreImputedSet object.

**Details**

A `summary.ScoreStatList` has been implemented.

The object contains the following

**Slots**

- `fits` A list of ScoreStat objects containing the model fits for the imputed data sets
- `statistics` A ScoreStatSet object containing the statistics
- `n` The number of model fits

**See Also**

`ScoreStatSet.object` `ScoreStat.object`
ScoreStatSet is an S3 generic to create a `ScoreStatSet` object.

**Description**

S3 generic to create a `ScoreStatSet` object

**Usage**

```r
ScoreStatSet(x)
```

**Arguments**

- `x` The object to convert into a `ScoreStatSet` object

**Value**

A `ScoreStatSet` object

**See Also**

- `ScoreStatSet.object`

---

`ScoreStatSet.object` is an object which contains the test statistic and estimators for a set of model fits to imputed data using risk score imputation.

**Description**

The object is a Mx3 matrix, one row per imputed data set and columns: estimate (the point estimates), var (their variances) and Z (the test statistic). M must be > 4

**Details**

- Note the Z should be ~ standard normal (so we do not use the chi_squared test statistic see `ScoreStat.object` for further details)
- The summary.ScoreStatSet function will apply the MI averaging procedures and estimates of the test statistic and p-value

**See Also**

- `summary.ScoreStatSet`
Description

This data frame holds time dependent covariates for use with risk score imputation.

Details

The data frame contains the following columns: 'Id' for subject ID, 'time.start' and 'time.end' the range of time for which the covariate values are valid - i.e. [time.start, time.end]. Additional columns are the time dependent covariates.

All data for a single subject should be stored in consecutive rows, sorted by time and the starting time of a row should match the ending time of the previous row.

See Also

MakeTimeDepScore

Description

This data set contains time dependent covariates for the ScoreInd time to event data.

Format

A data.frame containing 1 row per subject-visit.

Fields

<table>
<thead>
<tr>
<th>Field</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Id</td>
<td>The Subject Id</td>
</tr>
<tr>
<td>start</td>
<td>The covariate given in each row are for a given subject from time 'start'...</td>
</tr>
<tr>
<td>end</td>
<td>... until time end</td>
</tr>
<tr>
<td>w1</td>
<td>The value of a (binary) time dependent variable for the subject with the given 'Id' between times 'start' and 'end'</td>
</tr>
<tr>
<td>w2</td>
<td>The value of a (continuous) time dependent variable for the subject with the given 'Id' between times 'start' and 'end'</td>
</tr>
</tbody>
</table>
summary.ScoreStatSet  

Summary object of ScoreStatSet object

Description

This object contains the multiple imputed averages/p-values of a set of estimates from risk score imputed data sets.

Details

A print.summary.ScoreStatSet function has been implemented

This object contains three lists meth1 and meth2 and methRubin meth1 averages the point estimates to produce an F test statistic, meth2 averages the test statistics and produces a t test statistic and methRubin follows Rubin’s standard rules and is used for calculating confidence intervals

See the vignette for further details.

meth1, meth2 and methRubin are lists with the following elements: estimate: average estimator for meth1, NOTE: for meth2 this is the average test statistic, var: estimate of variance of "estimate" field, test.stat: test statistic, distribution: distribution of statistical test (i.e. F or t), p.value: p-value of test
Index

col.headings, 3, 12–14
cox.zph, 3, 4

ExtractSingle, 4
gammaImpute, 5
GammaImputedData.object, 6, 7, 7
GammaImputedSet.object, 6, 7
GammaStat.object, 8
GammaStatList.object, 8

ImputeStat, 9
InformativeCensoring
  (InformativeCensoring-package), 2
InformativeCensoring-package, 2

MakeTimeDepScore, 10, 17

NN.options, 11, 12

ridge, 12

ScoreImpute, 11
ScoreImputedData.object, 10, 13, 14
ScoreImputedSet.object, 12, 13
ScoreInd, 14, 17
ScoreStat.object, 10, 15, 15, 16
ScoreStatList.object, 15
ScoreStatSet, 16
ScoreStatSet.object, 15, 16, 16
ScoreTD.object, 17
ScoreTimeDep, 17
summary.ScoreStatSet, 16, 18