Package 'RISCA'

July 21, 2025

Type Package

Title Causal Inference and Prediction in Cohort-Based Analyses

Version 1.0.7

Depends R (>= 4.0.0), splines, survival, relsurv, reticulate, tune

Imports graphics, nlme, MASS, mvtnorm, statmod, parallel, doParallel,
foreach, nnet, kernlab, glmnet, caret, SuperLearner, rpart,
mosaic, cubature

Description Numerous functions for cohort-based analyses, either for prediction or causal inference. For causal inference, it includes Inverse Probability Weighting and G-computation for marginal estimation of an exposure effect when confounders are expected. We deal with binary outcomes, times-to-events, competing events, and multistate data. For multistate data, semi-Markov model with interval censoring may be considered, and we propose the possibility to consider the excess of mortality related to the disease compared to reference lifetime tables. For predictive studies, we propose a set of functions to estimate time-dependent receiver operating characteristic (ROC) curves with the possible consideration of right-censoring times-to-events or the presence of confounders. Finally, several functions are available to assess time-dependent ROC curves or survival curves from aggregated data.

License GPL (>= 2)

LazyLoad yes

NeedsCompilation no

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Repository CRAN

Date/Publication 2025-02-21 09:10:02 UTC

Contents

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auc	*Area Under ROC Curve From Sensitivities And Specificities.*

Description

This function computes the area under ROC curve by using the trapezoidal rule.

Usage

```
auc(sens, spec)
```

Arguments

sens	A numeric vector with the sensitivities
spec	A numeric vector with the specificities

Details

This function computes the area under ROC curve using the trapezoidal rule from two vectors of sensitivities and specificities. The value of the area is directly returned.

Author(s)

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Examples

```
se.temp <- c(0, 0.5, 0.5, 1)
sp.temp <- c(1, 0.5, 0.5, 0)
auc(se.temp, sp.temp)
```

---

dataCSL	*CSL Liver Chirrosis Data.*

Description

Survival status for the liver chirrosis patients of Schlichting et al.

Usage

```
data(dataCSL)
```

Format

This data frame contains the following columns:

id	a numeric vector related to the subject ID.
time	A numeric vector with the time of measurement.
prot	A numeric vector with the prothrombin level at measurement time.
dc	A numeric vector code. 0: censored observation, 1: died at eventT.
eventT	A numeric vector with the time of event (death).
treat	A numeric vector code. 0: active treatment of prednisone, 1: placebo treatment.
sex	A numeric vector code. 0: female, 1: male.
age	A numeric vector with the age of subject at inclusion time subtracted 60.
prot.base	A numeric vector with the prothrombin base level before entering the study
prot.prev	A numeric vector with the level of prothrombin at previous measurement time.
lt	A numeric vector with the starting time for the time-interval.
rt	A numeric vector with the stopping time for the time-interval.

Source

The `timreg` package

References

Schlichting et al. Prognostic factors in cirrhosis identified by Cox's regression model. Hepatology. 1983 Nov-Dec;3(6):889-95. <doi https://doi.org/ 10.1002/ hep.1840030601>

Examples

```
data(dataCSL)
names(dataCSL)
```

---

dataDIVAT1	*A First Sample From The DIVAT Data Bank.*

Description

A data frame with 5943 French kidney transplant recipients from the DIVAT cohort.

Usage

```
data(dataDIVAT1)
```

Format

A data frame with 5943 observations for the 7 following variables:

trajectory A numeric vector with the sequences of observed states. The patient evolution can be described according to a 4-state structure: X=1 represents the healthy state, X=2 represents the acute rejection episode, X=3 the definitive return to dialysis and X=4 the death. These times can be right-censored. A vector of covariates is also collected at the transplantation, i.e. the baseline of the cohort.

time1 A numeric vector with the times (in days) between the transplantation and the first clinical event (acute rejection episode, return to dialysis, or death with a functioning graft), or the times to censoring if `trajectory=1`.

time2 A numeric vector with the time between the transplantation and the second clinical event (return to dialysis or death with a functioning graft), or the the time to censoring if `trajectory=12`.

ageR A numeric vector with the recipient age (in years) at the transplantation.

sexR A character vector with the recipient gender.

year.tx A numeric vector with the calendar year of the transplantation.

z A numeric vector represents the explicative variable under interest, i.e. the delayed graft function (1=yes, 0=no).

Source

URL: www.divat.fr

Examples

```
data(dataDIVAT1)

### a description of transitions
table(dataDIVAT1$trajectory)

### patient-graft survival (first event between the return to dialysis and the patient
### death with a functioning graft)

dataDIVAT1$failure<-1*(dataDIVAT1$trajectory!=1 & dataDIVAT1$trajectory!=12)

dataDIVAT1$time<-NA
dataDIVAT1$time<-ifelse(dataDIVAT1$trajectory %in% c(1,12,13,14),
dataDIVAT1$time1,dataDIVAT1$time1+dataDIVAT1$time2)

plot(survfit(Surv(time/365.24, failure) ~ 1 , data=dataDIVAT1), mark.time=FALSE,
    xlim=c(0,12), ylim=c(0,1), cex=1.5, col=1, lwd=2, lty=1,
    xlab="Times after the transplantation (years)",
    ylab="Patient-graft survival")
```

---

dataDIVAT2 *A Second Sample From the DIVAT Data Bank.*

Description

A data frame with 1912 French kidney transplant recipients from the DIVAT cohort.

Usage

```
data(dataDIVAT2)
```

Format

A data frame with the 4 following variables:

age This numeric vector provides the age of the recipient at the transplantation (in years).

hla This numeric vector provides the indicator of transplantations with at least 4 HLA incompatibilities between the donor and the recipient (1 for high level and 0 otherwise).

retransplant This numeric vector provides the indicator of re-transplantation (1 for more than one transplantation and 0 for first kidney transplantation).

ecd The Expended Criteria Donor (1 for transplantations from ECD and 0 otherwise). ECD are defined by widely accepted criteria, which includes donors older than 60 years of age or 50-59 years of age with two of the following characteristics: history of hypertension, cerebrovascular accident as the cause of death or terminal serum creatinine higher than 1.5 mg/dL.

times This numeric vector is the follow up times of each patient.

failures This numeric vector is the event indicator (0=right censored, 1=event). An event is considered when return in dialysis or patient death with functioning graft is observed.

Source

URL: www.divat.fr

References

Le Borgne F, Giraudeau B, Querard AH, Giral M and Foucher Y. Comparisons of the performances of different statistical tests for time-to-event analysis with confounding factors: practical illustrations in kidney transplantation. Statistics in medicine. 30;35(7):1103-16, 2016. <doi:10.1002/sim.6777>

Examples

```
data(dataDIVAT2)

# Compute the non-adjusted Hazard Ratio related to the ECD versus SCD
cox.ecd<-coxph(Surv(times, failures) ~ ecd, data=dataDIVAT2)
summary(cox.ecd) # Hazard Ratio = 1.97
```

---

dataDIVAT3   *A Third Sample From the DIVAT Data Bank.*

Description

A data frame with 4267 French kidney transplant recipients.

Usage

```
data(dataDIVAT3)
```

Format

A data frame with 4267 observations for the 8 following variables.

ageR This numeric vector represents the age of the recipient (in years)

sexeR This numeric vector represents the gender of the recipient (1=men, 0=female)

year.tx This numeric vector represents the year of the transplantation

ante.diab This numeric vector represents the diabetes statute (1=yes, 0=no)

pra This numeric vector represents the pre-graft immunization using the panel reactive antibody (1=detectable, 0=undetectable)

ageD This numeric vector represents the age of the donor (in years)

death.time This numeric vector represents the follow up time in days (until death or censoring)

death This numeric vector represents the death indicator at the follow-up end (1=death, 0=alive)

Source

URL: www.divat.fr

References

Le Borgne et al. Standardized and weighted time-dependent ROC curves to evaluate the intrinsic prognostic capacities of a marker by taking into account confounding factors. Manuscript submitted. Stat Methods Med Res. 27(11):3397-3410, 2018. <doi: 10.1177/ 0962280217702416.>

Examples

```
data(dataDIVAT3)

### a short summary of the recipient age at the transplantation
summary(dataDIVAT3$ageR)

### Kaplan and Meier estimation of the recipient survival
plot(survfit(Surv(death.time/365.25, death) ~ 1, data = dataDIVAT3),
 xlab="Post transplantation time (in years)", ylab="Patient survival",
 mark.time=FALSE)
```

---

dataDIVAT4 *A Fourth Sample From the DIVAT Data Bank.*

Description

A data frame with 6648 French kidney transplant recipients from the DIVAT cohort. According to this data set, patient and graft survival can be computed for each hospital. This database was used by Combsecure et al. (2014).

Usage

```
data(dataDIVAT4)
```

Format

A data frame with the 3 following variables:

`hospital` This numeric vector represents the hospital in which the kidney transplantation was performed. Six hospitals were included.

`time` For right censored data, this numeric vector represents the follow up time (in days). When the event is observed, this numeric vector represents the exact time-to-event.

`status` This indicator describes the end of the follow-up. The `status` equals 0 for right censored data and 1 if the event is observed.

Details

The data were extracted from the prospective multicentric DIVAT cohort (www.divat.fr). Patients transplanted between 2000 and 2012 in 6 French centers were included. Only adult patients receiving a single kidney transplant and treated by Calcineurin inhibitors and Mycophenolate Mofetil for maintenance therapy after transplantation were considered. In parallel, patients who received multi-organ transplantation were excluded from the study. The time-to-event under interest is the time between the kidney transplantation and the graft failure, i.e. the first event between the return in dialysis or the death of the patient with functional kidney.

Source

URL: www.divat.fr

References

Combescure et al. The multivariate DerSimonian and Laird's methodology applied to meta-analysis of survival curves. 10;33(15):2521-37, 2014. Statistics in Medicine. <doi:10.1002/sim.6111>

Examples

```
data(dataDIVAT4)

divat.surv <- survfit(Surv(time/365.24, status) ~ hospital, data = dataDIVAT4)

plot(divat.surv, lty = 1:6, col=1:6, lwd=2, mark.time=FALSE,
 xlab="Post transplantation time (days)", ylab="Patient and graft survival")
```

---

dataDIVAT5   *The Aggregated Kidney Graft Survival Stratified By The 1-year Serum Creatinine.*

Description

A data frame that presents the aggregated outcomes per center of 5943 French kidney transplant recipients from the DIVAT cohort. It was used by Combescure et al. (2016).

Usage

```
data(dataDIVAT5)
```

Format

A data frame with 106 observations for the 8 following variables:

classe This numeric vector represents the groups of recipients defined using the 1-year serum creatinine. 1 is the first group with the lowest values of 1-year serum creatinine.

n This numeric vector represents the number of recipients at the baseline (date of the transplantation) in each group.

year This numeric vector represents the post transplant time (in years).

surv This numeric vector represents the survival probabilities at each year (obtained using the Kaplan and Meier estimator from the individual data).

n.risk This numeric vector represents the number of subjects at-risk of the event at the corresponding year.

proba This numeric vector represents the proportion of the patients in a center which belong to the corresponding group.

marker.min This numeric vector represents the minimum value of the interval of the 1-year serum creatinine (in $\mu mol/l$).

marker.max This numeric vector represents the maximum value of the interval of the 1-year serum creatinine (in $\mu mol/l$).

centre.num This numeric vector represents the centers.

Details

The immunology and nephrology department of the Nantes University hospital constituted a data bank with the monitoring of medical records for kidney and/or pancreas transplant recipients. Here, we considered a subpopulation of 4195 adult patients and who had received a first kidney graft between January 1996 and Jun 2008. Five centers participated. A total of 511 graft failures were observed (346 returns to dialysis and 165 deaths with a functional kidney). Based on this database, we constructed an aggregated dataset to perform a meta-analysis on 5 published monocentric studies. The medical objective was to evaluate whether 1-year serum creatinine (Cr) is a good predictive marker of graft failure. Cr is a breakdown product and is removed from the body by the kidneys. If kidney function is abnormal, blood Cr levels increase.

Source

URL: www.divat.fr

References

Combescure et al. A literature-based approach to evaluate the predictive capacity of a marker using time-dependent Summary Receiver Operating Characteristics. Stat Methods Med Res, 25(2):674-85, 2016. <doi: 10.1177/ 0962280212464542>

Examples

```
data(dataDIVAT5)

# Kaplan Meier estimations of the graft survival in the first center
plot(dataDIVAT5$year[dataDIVAT5$centre.num==1],
 dataDIVAT5$surv[dataDIVAT5$centre.num==1],
 xlab="Post transplantation time (years)", ylab="Graft survival",
 ylim=c(0.7,1), xlim=c(0, 9), type="n")

# Goup 1
lines(c(0, dataDIVAT5$year[dataDIVAT5$centre.num==1 &
 dataDIVAT5$classe==1]),
 c(1, dataDIVAT5$surv[dataDIVAT5$centre.num==1 &
 dataDIVAT5$classe==1]),
 type="b", col=1, lty=1, lwd=2)

# Goup 2
lines(c(0, dataDIVAT5$year[dataDIVAT5$centre.num==1 &
 dataDIVAT5$classe==2]),
 c(1, dataDIVAT5$surv[dataDIVAT5$centre.num==1 &
 dataDIVAT5$classe==2]),
 type="b", col=2, lty=2, lwd=2)

# legend
legend("bottomleft", c("group #1 (1-year Cr<4.57)",
 "group #2 (1-year Cr>4.57)"), col=c(1, 2),
 lty=c(1, 2), lwd=c(2, 2))
```

---

dataFTR   *Data for First Kidney Transplant Recipients.*

Description

Data were extracted from the DIVAT cohort. It corresponds to the reference sample constituted by first transplant recipients (FTR).

Usage

```
data(dataFTR)
```

Format

A data frame with the 4 following variables:

Tps.Evt This numeric vector provides the post-transplantation time (in days).

Evt This numeric vector provides the indicator of graft failure at the end of the follow-up (1 for failure and 0 for right censoring).

ageR2cl This numeric vector provides the recipient age at transplantation (1 for older than 55 years and 0 otherwise).

sexeR This numeric vector provides the recipient gender (1 for men and 0 for women).

Details

First transplant recipients (FTR) constituted the reference group. Recipients older than 18 years at the date of transplantation between 1996 and 2010 were selected from the French DIVAT (www.divat.fr/en) multicentric prospective cohort. Only recipients with a maintenance therapy with calcineurin inhibitors, mammalian target of rapamycin inhibitors or belatacept, in addition to mycophenolic acid and steroid were included. Simultaneous transplantations were excluded. Two explicative variables are proposed: recipient age at transplantation and recipient gender.

References

K. Trebern-Launay, M. Giral, J. Dantal and Y. Foucher. Comparison of the risk factors effects between two populations: two alternative approaches illustrated by the analysis of first and second kidney transplant recipients. BMC Med Res Methodol. 2013 Aug 6;13:102. <doi: 10.1186/1471-2288-13-102>

Examples

```
data(dataFTR)

# Compute a Cox PH model with both explicative variables
summary(coxph(Surv(Tps.Evt/365.24, Evt) ~ ageR2cl + sexeR, data=dataFTR))
```

---

dataHepatology	*The Data Extracted From The Meta-Analysis By Cabibbo et al. (2010).*

Description

Data were extracted from the studies included in the meta-analysis by Cabibbo et al. which aimed to assess the survival rate in untreated patients with hepatocellular carcinoma.

Usage

```
data(dataHepatology)
```

Format

A data frame with with the 8 following variables:

study This numeric vector represents number of the study.

first.author This vector represents the name of the first author.

year.pub This numeric vector represents the publication year.

time This numeric vector represents the times for which the survival rates are collected in years.

survival This numeric vector represents the survival rates for each value of time

n.risk This numeric vector represents the number of at-risk patients for each value of time

location This factor indicates the location of the study (Asia, North Amercia or Europe)

design This factor indicates if the study is monocentric ou multicentric.

Details

The survival probabilities were extracted from the published survival curves each month during the first six months and then by step of three months. The pictures of the curves were digitalized using the R package ReadImage and the probabilities were extracted using the package digitize proposed by Poisot. The numbers of at-risk patients for each interval of time were derived from the numbers of at-risk patients reported in the studies, and using the methods of Parmar or Williamson to account for censorship. Studies have different length of follow-up. For each study, survival probabilities and the numbers of at-risk patients were collected at all points in time before the end of follow-up.

References

Cabibbo, G., et al., A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. Hepatology, 2010. 51(4): p. 1274-83.

Poisot, T., The digitize Package: Extracting Numerical Data from Scatter-plots. The R Journal, 2011. 3(1): p. 25-26.

Parmar, M.K., V. Torri, and L. Stewart, Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med, 1998. 17(24): p. 2815-34

Examples

```
data(dataHepatology)
times <- dataHepatology$time
survival <- dataHepatology$survival
study  <- dataHepatology$study

plot(times, survival, type="n",
 ylim=c(0,1), xlab="Time",ylab="Survival")

for (i in unique(sort(study)))
{
lines(times[study==i], survival[study==i], type="l", col="grey")
points(max(times[study==i]),
 survival[study==i & times == max( times[study==i])], pch=15)
}
```

---

dataKi67   *The Aggregated Data Published By de Azambuja et al. (2007).*

Description

The aggregated data from the meta-analysis proposed by Azambuja et al. (2007).

Usage

```
data(dataKi67)
```

Format

A data frame with 406 observations (rows) with the 10 following variables (columns).

`classe` This numeric vector represents the groups of patients defined using KI-67. 1 is the first group which is defined by the lowest KI-67 values.

`n` This numeric vector represents the number of recipients at the baseline (date of KI-67 collection) in each group.

`year` This numeric vector represents the survival time (in years).

`surv` This numeric vector represents the survival probabilities at each year (obtained using the Kaplan and Meier estimator from the published papers).

`nrisk` This numeric vector represents the number of subjects at-risk of the event at the corresponding `year`.

`proba` This numeric vector represents the proportion of the patients for a given paper which belong to the corresponding group.

`log.marker.min` This numeric vector represents the logarithm of the minimum value of the KI-67 interval.

`log.marker.max` This numeric vector represents the logarithm of the maximum value of the KI-67 interval.

`study.num` This numeric vector identifies the studies.

`author` This character vector identifies the first author of the paper.

`year.paper` This numeric vector identifies the year of publication.

Details

KI-67 is a marker of the proliferative activity of breast cancer, but its prognostic capacity is still unclear. In their meta-analysis, de Azambuja et al. (2007) concluded that KI-67 positivity conferred a worse survival. This work focused on the 35 evaluable studies of the relationship between KI-67 and the overall survival. 23 studies described survival curves according to the level of KI-67. Survival probabilities were measured every year.

References

de Azambuja et al. Ki-67 as prognostic marker in early breast cancer: a meta-analysis of published studies involving 12 155 patients. British Journal of Cancer. 96:1504-1513, 2007. <doi: 10.1038/ sj.bjc.6603756>

Examples

```
data(dataKi67)

# Kaplan Meier estimations of graft survivals in Wintzer et al. (1991)
plot(dataKi67$year[dataKi67$study.num==1],
 dataKi67$surv[dataKi67$study.num==1],
 xlab="Post transplantation time (years)",
 ylab="Graft survival", ylim=c(0.6,1), xlim=c(0, 4), type="n")

# Goup 1
```

```
lines(c(0, dataKi67$year[dataKi67$study.num==1 & dataKi67$classe==1]),
 c(1, dataKi67$surv[dataKi67$study.num==1 & dataKi67$classe==1]),
 type="b", col=1, lty=1, lwd=2)

# Goup 2
lines(c(0, dataKi67$year[dataKi67$study.num==1 & dataKi67$classe==2]),
 c(1, dataKi67$surv[dataKi67$study.num==1 & dataKi67$classe==2]),
 type="b", col=2, lty=2, lwd=2)

# legend
legend("bottomleft", c("group #1 (log Ki67 < 2.49)",
 "group #2 (log Ki67 > 2.49)"), col=c(1, 2), lty=c(1, 2), lwd=c(2, 2))
```

---

dataKTFS   *A Sixth Sample Of The DIVAT Cohort.*

Description

A data frame with 2169 French kidney transplant recipients for who the Kidney Transplant Failure
Score (KTFS) was collected. The KTFS is a score proposed by Foucher et al. (2010) to stratify the
recipients according to their risk of return in dialysis.

Usage

```
data(dataKTFS)
```

Format

A data frame with 2169 observations for the 3 following variables:

time This numeric vector represents the follow up time in years (until return in dialyis or censoring)

failure This numeric vector represents the graft failure indicator at the follow-up end (1=return,
0=censoring)

score This numeric vector represents the KTFS values.

Source

URL: www.divat.fr

References

Foucher Y. al. A clinical scoring system highly predictive of long-term kidney graft survival. Kid-
ney International, 78:1288-94, 2010. <doi:10.1038/ki.2010.232>

Examples

```
data(dataKTFS)

### a short summary of the recipient age at the transplantation
summary(dataKTFS$score)

### Kaplan and Meier estimation of the recipient survival
plot(survfit(Surv(time, failure) ~ I(score>4.17), data = dataKTFS),
 xlab="Post transplantation time (in years)", ylab="Patient survival",
 mark.time=FALSE, col=c(2,1), lty=c(2,1))

legend("bottomleft", c("Recipients in the high-risk group",
 "Recipients in the low-risk group"), col=1:2, lty=1:2)
```

---

dataOFSEP   *A Simulated Sample From the OFSEP Cohort.*

Description

A data frame with 1300 simulated French patients with multiple sclerosis from the OFSEP cohort. The baseline is 1 year after the initiation of the first-line treatment.

Usage

```
data(dataOFSEP)
```

Format

A data frame with 1300 observations for the 3 following variables:

time This numeric vector represents the follow up time in years (until disease progression or censoring)

event This numeric vector represents the disease progression indicator at the follow-up end (1=progression, 0=censoring)

age This numeric vector represents the patient age (in years) at baseline.

duration This numeric vector represents the disease duration (in days) at baseline.

period This numeric vector represents the calendar period: 1 in-between 2014 and 2018, and 0 otherwise.

gender This numeric vector represents the gender: 1 for women.

relapse This numeric vector represents the diagnosis of at least one relapse since the treatment initiation : 1 if at leat one event, and 0 otherwise.

edss This vector of character string represents the EDSS level : "miss" for missing, "low" for EDSS between 0 to 2, and "high" otherwise.

t1 This vector of character string represents the new gadolinium-enhancing T1 lesion : "missing", "0" or "1+" for at least 1 lesion.

t2 This vector of character string represents the new T2 lesions : "no" or "yes".

rio This numeric vector represents the modified Rio score.

References

Sabathe C et al. SuperLearner for survival prediction from censored data: extension of the R package RISCA. Submited.

Examples

```
data(dataOFSEP)

### Kaplan and Meier estimation of the disease progression free survival
plot(survfit(Surv(time, event) ~ 1, data = dataOFSEP),
     ylab="Disease progression free survival",
     xlab="Time after the first anniversary of the first-line treatment in years")
```

---

dataSTR   *Data for Second Kidney Transplant Recipients.*

Description

Data were extracted from the DIVAT cohort. It corresponds to the relative sample constituted by second transplant recipients (STR).

Usage

```
data(dataSTR)
```

Format

A data frame with the 6 following variables:

Tps.Evt This numeric vector provides the post transplantation time (in days).

Evt This vector provides the indicators of graft failure at the end of the follow-up (1 for failures and 0 for right censoring).

ageR2cl This numeric vector provides the recipient age at transplantation (1 for older than 55 years and 0 otherwise).

sexeR This numeric vector provides the recipient gender (1 for men and 0 for women).

ageD2cl This numeric vector provides the donor age (1 for older than 55 years and 0 otherwise).

Tattente2cl This numeric vector provides the waiting time in dialysis between the two consecutive transplantations (1 for more than 3 years and 0 otherwise).

Details

Second transplant recipients (STR) constituted the relative group of interest. Recipients older than 18 years at the date of transplantation between 1996 and 2010 were selected from the French DIVAT (www.divat.fr/en) multicentric prospective cohort. Only recipients with a maintenance therapy with calcineurin inhibitors, mammalian target of rapamycin inhibitors or belatacept, in addition to mycophenolic acid and steroid were included. Simultaneous transplantations were excluded. Two explicative variables are common with the reference group: recipient age at transplantation and recipient gender. Two explicative variables are specific to STR: donor age and waiting time in dialysis between the two consecutive transplantations.

References

K. Trebern-Launay, M. Giral, J. Dantal and Y. Foucher. Comparison of the risk factors effects between two populations: two alternative approaches illustrated by the analysis of first and second kidney transplant recipients. BMC Med Res Methodol. 2013 Aug 6;13:102. <doi: 10.1186/1471-2288-13-102>

Examples

```
data(dataSTR)

# Compute a Cox PH model
summary(coxph(Surv(Tps.Evt/365.24, Evt) ~ ageR2cl + Tattente2cl, data=dataSTR))
```

---

expect.utility1	*Cut-Off Estimation Of A Prognostic Marker (Only One Observed Group).*

Description

This function allows the estimation of a cut-off for medical decision making between two treatments A and B from a prognostic marker by maximizing the expected utility in a time-dependent context. Only the observations of one group are available.

Usage

```
expect.utility1(times, failures, variable, pro.time, u.A0, u.A1, u.B0, u.B1,
 n.boot, rmst.change)
```

Arguments

times	A numeric vector with the follow up times for the patients receiving the treatment B.
failures	A numeric vector with the event indicator for the patients receiving the treatment B (0=right censoring, 1=event).
variable	A numeric vector with the observed values of the marker under interest X for the patients receiving the treatment B. This variable is collected at the baseline (times=0). By convention, we assume that patients with X>k will preferentially receive A, k being the optimal cut-off. In contrast, patients with X<k will receive preferentially B.
pro.time	The prognostic time for which the prognostic capacities of the marker and the patient outcomes are considered in the same unit than the one used in the argument times.
u.A0	A value of the utility of a patient receiving the treatment A before the event occurrence. This value should respect the 0-1 scale (from death to perfect health).
u.A1	A value of the utility of a patient receiving the treatment A after the event occurrence. This value should respect the 0-1 scale.

u.B0	A value of the utility of a patient receiving the treatment B before the event occurrence. This value should respect the 0-1 scale.
u.B1	A value of the utility of a patient receiving the treatment B after the event occurrence. This value should respect the 0-1 scale.
n.boot	Number of bootstrap iterations to compute the 95% confidence interval of the optimal cut-off. The default value is NULL: no confidence interval is estimated.
rmst.change	A numeric vector with the expected relative change in the Restricted Mean Survival Time (RMST) by using the treatment A instead of the treatment B among patients with X>k.

Details

The user observes a cohort of patients receiving the treatment B. She(he) assumes that an alternative treatment A would be more convenient for patients with high-values of the marker X. She(he) aims to compute the optimal cut-off value for a future stratified medical decision rule: treatment A for patients with X>k and treatment B for patients with X<k. The user has to enter the observed cohort of patients with the treatment B. Additional to the assumptions related to health-state utilities, the user have to specify in rmst.change, i.e. the expected relative change in terms of RMST between the two treatments. For instance, if the observed life expectancy of a patient with treatment B over the next 8 years (value entered in pro.time) is 6.70 years, and assuming that the treatment A increases this life expectancy during the next 8 years by 1.33 years, the expected relative change in RMST is 0.20 (=1.33/6.7).

Value

estimation	This is a single value if n.boot=NULL, which corresponds to the estimated cut-off that maximizes the time-dependent expected utility of the medical decision. If this value corresponds to the minimum of the marker, all the patients should be treated with A. If this value corresponds to the maximum of the marker, all the patients should conserve the treatment B. When n.boot is not null, two additional values are returned: CIinf is the lower bound of the 95% confidence interval and CIsup is the upper bound of the 95% confidence interval.
max.eu	This value corresponds to the maximum expected utility associated with the estimation.
table	This data frame is composed by 8 columns representing respectively the cut-off values, the time-dependent expected utilities (utility), the proportions of patients with a marker value higher (pA) and lower (pB) than the cut-off value, the numbers of QALYs for patients with a marker value higher (qA) and lower (qB) than the cut-off value, the RMST for patients with a marker value higher (eA) and lower (eB) than the cut-off value.
delta.rmst	This value represents the expected RMST for patients with a marker higher than the estimation (treated with A) minus the observed RMST for patients with a marker higher than the estimation(treated with B).
delta.qaly	This value represents the number of QALYs for patients with a marker higher than the estimation (treated with A) minus the observed number of QALYs for patients with a marker higher than the estimation (treated with B).
missing	Number of deleted observations due to missing data.

Author(s)

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Yohann Foucher <Yohann.Foucher@univ-poitiers.fr>

References

Dantan et al. Optimal threshold estimator of a prognostic marker by maximizing a time-dependent expected utility function for a patient-centered stratified medicine. Statistical Methods in Medical Research, 27(6) :1847-1859. 2016. <doi:10.1177/ 0962280216671161>

Examples

```
data(dataKTFS)

# to respect the CRAN policy (run times < 5s), we reduced the database
# to the first 1500 patients. Removed the first line to use the antire sample.

dataKTFS <- dataKTFS[1:1500,]
dataKTFS$score <- round(dataKTFS$score, 1)

# the expected utility function for a prognostic up to 8 years

EUt.obj <- expect.utility1(dataKTFS$time, dataKTFS$failure, dataKTFS$score,
 pro.time=8, u.A0=0.81*0.95, u.A1=0.53, u.B0=0.81, u.B1=0.53, rmst.change=0.2)

plot(EUt.obj$table$cut.off, EUt.obj$table$utility, type="l",
 xlab="Cut-off values", ylab="Expected utility", col=1, lty=1)

segments(EUt.obj$estimation, 0, EUt.obj$estimation, EUt.obj$max.eu, lty=3)
segments(0, EUt.obj$max.eu, EUt.obj$estimation, EUt.obj$max.eu, lty=3)

text(EUt.obj$estimation-0.2, 6.22,
 paste("Optimal cut-off=", round(EUt.obj$estimation,2)), srt=90, cex=0.8)
 text(min(dataKTFS$score)+1.4, EUt.obj$max.eu-0.006,
 paste("Expected utility=", round(EUt.obj$max.eu, 2)), cex=0.8)

# the optimal cut-off: patients with an higher value should receive the treatment A

EUt.obj$estimation
```

expect.utility2	*Cut-Off Estimation Of A Prognostic Marker (Two Groups Are observed).*

Description

This function allows the estimation of a cut-off of a prognostic marker for medical decision making between two treatments A and B by maximizing the expected utility in a time-dependent context.

Usage

```
expect.utility2(times, failures, variable, treatment, pro.time,
 u.A0, u.A1, u.B0, u.B1,  n.boot)
```

Arguments

times	A numeric vector with the follow up times.
failures	A numeric vector with the event indicator (0=right censoring, 1=event).
variable	A numeric vector with the observed values of the marker/variable under interest X. This variable is collected at the baseline (times=0). By convention, we assume that patients with X>k will preferentially receive A, k being the optimal cut-off. In contrast, patients with X<k will preferentially receive B.
treatment	A character vector with the observed treatment. Only character strings "A" and "B" are allowed.
pro.time	The prognostic time for which the capacities of the marker and the patient outcomes are considered in the same unit than the one used in the argument times.
u.A0	A value of the utility of a patient receiving the treatment A before the event occurrence. This value should respect the 0-1 scale (from death to perfect health).
u.A1	A value of the utility of a patient receiving the treatment A after the event occurrence. This value should respect the 0-1 scale.
u.B0	A value of the utility of a patient receiving the treatment B before the event occurrence. This value should respect the 0-1 scale.
u.B1	A value of the utility of a patient receiving the treatment B after the event occurrence. This value should respect the 0-1 scale.
n.boot	Number of bootstrap iterations to compute the 95% confidence interval of the optimal cut-off. The default value is NULL: no confidence interval is estimated.

Details

The treatments A and B are allocated independently to the value of the marker X. We assume that the treatment A will be more convenient for patients with high value of the marker X. The aim is to compute the optimal cut-off value for a future stratified medical decision rule: treatment A for patients with X>k and treatment B for patients with X<k.

Value

estimation	This is a single value if n.boot=NULL, which corresponds to the estimated cut-off that maximizes the time-dependent expected utility of the medical decision. If this value corresponds to the minimum of the marker, all the patients should be treated with A. If this value corresponds to the maximum of the marker, all the patients should conserve the treatment B. When n.boot is not null, two additional values are returned: CIinf is the lower bound of the 95% confidence interval and CIsup is the upper bound of the 95% confidence interval.
max.eu	This value corresponds to the maximum expected utility associated with the estimation.

table	This data frame is composed by 8 columns representing respectively the cut-off values (`cut.off`), the time-dependent expected utilities (`utility`), the proportions of patients with a marker value higher (pA) and lower (pB) than the cut-off value, the numbers of QALYs for patients with a marker value higher (qA) and lower (qB) than the cut-off value, the RMST for patients with a marker value higher (eA) and lower (eB) than the cut-off value.
delta.rmst	This is a vector with two values. The first value, entitled `high.level`, represents the RMST for patients with a marker higher than the `estimation` and treated with A minus the RMST for patients with a marker higher than the `estimation` and treated with B. The second value, entitled `low.level`, represents the RMST for patients with a marker lower than or equal to the `estimation` and treated by B minus the RMST for patients with a marker lower than or equal to the `estimation` and treated with A.
delta.qaly	This is a vector with two values. The first value, entitled `high.level`, represents the number of QALYs for patients with a marker higher than the `estimation` and treated by A minus the number of QALYs for patients with a marker higher than the `estimation` and treated with B. The second value, entitled `low.level`, represents the number of QALYs for patients with a marker lower than or equal to the `estimation` and treated with B minus the number of QALYs for patients with a marker lower than or equal to the `estimation` and treated with A.
missing	Number of deleted observations due to missing data.

Author(s)

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Yohann Foucher <Yohann.Foucher@univ-poitiers.fr>

References

Dantan et al. Optimal threshold estimator of a prognostic marker by maximizing a time-dependent expected utility function for a patient-centered stratified medicine. Statistical Methods in Medical Research, 27(6) :1847-1859. 2016. <doi:10.1177/ 0962280216671161>

Examples

```
# import and attach the data example

data(dataCSL)
dataCSL <- dataCSL[order(dataCSL$id, dataCSL$time),]
dataCSL$ordre <-0
for (i in unique(dataCSL$id))
 {dataCSL$ordre[dataCSL$id==i] <- 1:sum(dataCSL$id==i)}

dataCSL$ttt[dataCSL$treat==0]<-"A"
dataCSL$ttt[dataCSL$treat==1]<-"B"

dataCSL0 <- dataCSL[dataCSL$ordre==1,]
dataCSL0<-dataCSL0[,c(1,4,5,14,9)]
```

```
# the expected utility function for a prognostic up to 8 years

EUt.obj <- expect.utility2(dataCSL0$eventT, dataCSL0$dc,
 dataCSL0$prot.base, treatment= dataCSL0$ttt,
 pro.time=8, u.A0=0.75*0.95, u.A1=0, u.B0=0.75, u.B1=0)

plot(EUt.obj$table$cut.off, EUt.obj$table$utility, type="l",
 xlab="Cut-off values", ylab="Expected utility",col=1, lty=1)

segments(EUt.obj$estimation, 0, EUt.obj$estimation, EUt.obj$max.eu, lty=3)
segments(0, EUt.obj$max.eu, EUt.obj$estimation, EUt.obj$max.eu, lty=3)

text(EUt.obj$estimation-2, 3.38,
 paste("Optimal cut-off=",round(EUt.obj$estimation,2)), srt=90, cex=0.8)
 text(min(dataCSL0$prot.base)+40, EUt.obj$max.eu-0.005,
 paste("Expected utility=",round(EUt.obj$max.eu,2)), cex=0.8)

# the optimal cut-off: patients with an higher value should receive the treatment A

EUt.obj$estimation
```

---

fr.ratetable   *Expected Mortality Rates of the General French Population*

Description

An object of class ratetable for the expected mortality of the French population. It is an array with three dimensions: age, sex and year.

Usage

```
data(fr.ratetable)
```

Format

The format is "ratetable". The attributes are:

dim	A numeric vector with the length of each dimension.
dimnames	A character vector with the names of each variable of the three dimensions.
dimid	A character vector with the identification of the dimensions: age, year and sex.
factor	A numeric vector of indicators equals to 1 if the corresponding dimension does not vary according to the time. Only the dimension related to sex equals 1.
cutpoints	A list of the thresholds to identify the changes in the mortality rates according to the time-dependent dimensions (NULL for sex).
class	The class of the object: ratetable.

Details

The organization of a ratetable object is described in details by Therneau (1999) and Pohar (2006). The original data and updates can be downloaded from the Human Life-Table Database (HMD, The Human Mortality Database).

Source

URL: www.mortality.org

References

Therneau and Offord. Expected Survival Based on Hazard Rates (Update), Technical Report, Section of Biostatistics, Mayo Clinic 63, 1999.

Pohar and Stare. Relative survival analysis in R. Computer methods and programs in biomedicine, 81: 272-278, 2006.

Examples

```
data(fr.ratetable)

is.ratetable(fr.ratetable)
```

---

gc.logistic	*Marginal Effect for Binary Outcome by G-computation.*

Description

This function allows to estimate the marginal effect of an exposure or a treatment by G-computation for binary outcomes.

Usage

```
gc.logistic(glm.obj, data, group, effect, var.method, iterations, n.cluster, cluster.type)
```

Arguments

glm.obj   A glm object obtained by using the function glm with the argument family = binomial(link=logit) to obtain a multivariate logistic regression. It shall be included the exposition/treatment of interest variable and at least one covariate.

data   A data frame in which to look for the variable related to the outcome, the treatment/exposure and the covariables included in the previous logistic regression glm.obj. The covariates' names have to be identical than the ones included in the logistic model.

group   The name or the variable related to the exposure/treatment variable. This variable shall have only two modalities encoded 0 for the untreated/unexposed patients and 1 for the treated/exposed patients.

effect   The type of the marginal effect to be estimated. Three types are possible (see
                  details): "ATE" (by default), "ATT" and "ATU".

var.method   The method to estimate the variances and the confidence intervals. Two meth-
                  ods are possible: "simulations" (by default) which consists in parametric sim-
                  ulation based on the maximum likelihood estimates of the multivariate logistic
                  regression `glm.obj` and "bootstrap" which consists in bootstrap resampling of
                  the database `data`.

iterations   The number of iterations (simulations or resamples depending on the argument
                  in `var.method`) to estimate of the variances and confidence intervals.

n.cluster   The number of cores to use, i.e., the upper limit for the number of child processes
                  that run simultaneously (1 by default).

cluster.type   A character string with the type of parallelization. The default type is "PSOCK"
                  (it calls makePSOCKcluster, faster on MacOS or Linux platforms). An alterna-
                  tive is "FORK" (it calls makeForkCluster, it does not work on Windows plat-
                  forms).

Details

The ATE corresponds to Average Treatment effect on the Entire population, i.e. the marginal effect
if all the sample is treated versus all the sample is untreated. The ATT corresponds to Average
Treatment effect on the Treated, i.e. the marginal effect if the treated patients (group = 1) would
have been untreated. The ATU corresponds to Average Treatment effect on the Untreated , i.e. the
marginal effect if the untreated patients (group = 0) would have been treated. Simulation method
for variance estimation has a shorter computing time than the boostrap method, but bootstrap is
more accurate.

Value

effect   A character string with the type of the marginal effect.

p0   A table related to the average proportion of events in the unexposed/untreated
                  sample: `estimate` is the estimated value, `ci.lower` and `ci.upper` represent the
                  95% confidence interval.

p1   A table related to the average proportion of events in the exposed/treated sample:
                  `estimate` is the estimated value, `ci.lower` and `ci.upper` represent the 95%
                  confidence interval.

delta   A table related to the difference between the average proportions of events in the
                  exposed/treated sample minus in the unexposed/untreated sample: `estimate` is
                  the estimated value, `std.error` is the corresponding standard error, `ci.lower`
                  and `ci.upper` represent the 95% confidence interval.

logOR   A table related to the logarithm of the average Odds Ratio (OR): `estimate` is
                  the estimated value, `std.error` is the corresponding standard error, `ci.lower`
                  and `ci.upper` represent the 95% confidence interval.

p.value   The p-value of the bilateral test of the null hypothesis p0 = p1, i.e. OR = 1.

Author(s)

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Arthur Chatton <Arthur.Chatton@etu.univ-nantes.fr>

References

Le Borgne et al. G-computation and machine learning for estimating the causal effects of binary exposure statuses on binary outcomes. Scientific Reports. 11(1):1435. 2021. <doi: 10.1038/s41598-021-81110-0>

Examples

```
#data simulation
#treatment = 1 if the patients have been the exposure or treatment of interest and 0 otherwise
treatment <- rbinom(600, 1, prob=0.5)

covariate <- rnorm(600, 0, 1)
covariate[treatment==1] <- rnorm(sum(treatment==1), 0.3, 1)

outcome <- rbinom(600, 1, prob=
exp(-2+0.26*treatment+0.7*covariate)/(1+exp(-2+0.26*treatment+0.7*covariate)))

tab <- data.frame(outcome, treatment, covariate)

#Raw effect of the treatment
glm.raw <- glm(outcome ~ treatment, data=tab, family = binomial(link=logit))
summary(glm.raw)

#Conditional effect of the treatment
glm.multi <- glm(outcome ~ treatment + covariate, data=tab, family = binomial(link=logit))
summary(glm.multi)

#Marginal effects of the treatment (ATE)
gc.ate <- gc.logistic(glm.obj=glm.multi, data=tab, group="treatment", effect="ATE",
 var.method="simulations", iterations=1000, n.cluster=1)

#Sum-up of the 3 ORs
data.frame( raw=exp(glm.raw$coefficients[2]),
conditional=exp(glm.multi$coefficients[2]),
marginal.ate=exp(gc.ate$logOR[,1]) )
```

---

gc.sl.binary	*Marginal Effect for Binary Outcome by Super Learned G-computation.*

Description

This function allows to estimate the marginal effect of an exposure or a treatment by G-computation for binary outcomes, the outcome prediction (Q-model) is obtained by using a super learner.

Usage

```
gc.sl.binary(outcome, group, cov.quanti, cov.quali, keep, data, effect,
 tuneLength, cv, iterations, n.cluster, cluster.type)
```

Arguments

outcome	The name of the variable related to the binary outcome variable. This numeric variable must have only two levels: 0 and 1 (for instance: 0=healthy, 1=diseased).
group	The name of the variable related to the exposure/treatment variable. This numeric variable must have only two levels: 0 for the untreated/unexposed patients and 1 for the treated/exposed patients.
cov.quanti	The name(s) of the variable(s) related to the possible quantitative covariates. These variables must be numeric.
cov.quali	The name(s) of the variable(s) related to the possible qualitative covariates. These variables must be numeric with two levels: 0 and 1. A complete disjunctive form must be used for covariates with more levels.
keep	A logical value indicating whether variable related to the exposure/treatment is kept in the penalized regression (elasticnet or lasso). The default value is TRUE.
data	A data frame in which to look for the variable related to the outcome, the treatment/exposure and the covariables.
effect	The type of the marginal effect to be estimated. Three types are possible (see details): "ATE" (by default), "ATT" and "ATU".
tuneLength	It defines the total number of parameter combinations that will be evaluated in the machine learning techniques. The default value is 10.
cv	The number of splits for cross-validation. The default value is 10.
iterations	The number of bootstrap resamples to estimate of the variances and confidence intervals.
n.cluster	The number of cores to use, i.e., the upper limit for the number of child processes that run simultaneously (1 by default).
cluster.type	A character string with the type of parallelization. The default type is "PSOCK" (it calls makePSOCKcluster, faster on MacOS or Linux platforms). An alternative is "FORK" (it calls makeForkCluster, it does not work on Windows platforms).

Details

The ATE corresponds to Average Treatment effect on the Entire population, i.e. the marginal effect if all the sample is treated versus all the sample is untreated. The ATT corresponds to Average Treatment effect on the Treated, i.e. the marginal effect if the treated patients (group = 1) would have been untreated. The ATU corresponds to Average Treatment effect on the Untreated , i.e. the marginal effect if the untreated patients (group = 0) would have been treated. The Super Learner includes the following machine learning techniques: logistic regression with Lasso penalization, logistic regression with Elasticnet penalization, neural network with one hidden layer, and support vector machine with radial basis, as explained in details by Chatton et al. (2020).

Value

missing	Number of deleted observations due to missing data.
effect	A character string with the type of the marginal effect.
p0	A table related to the average proportion of events in the unexposed/untreated sample: `estimate` is the estimated value, `ci.lower` and `ci.upper` represent the 95% confidence interval.
p1	A table related to the average proportion of events in the exposed/treated sample: `estimate` is the estimated value, `ci.lower` and `ci.upper` represent the 95% confidence interval.
delta	A table related to the difference between the average proportions of events in the exposed/treated sample minus in the unexposed/untreated sample: `estimate` is the estimated value, `std.error` is the corresponding standard error, `ci.lower` and `ci.upper` represent the 95% confidence interval.
logOR	A table related to the logarithm of the average Odds Ratio (OR): `estimate` is the estimated value, `std.error` is the corresponding standard error, `ci.lower` and `ci.upper` represent the 95% confidence interval.
p.value	The p-value of the bilateral test of the null hypothesis p0 = p1, i.e. OR = 1.

Author(s)

Yohann Foucher <Yohann.Foucher@univ-poitiers.fr>

References

Le Borgne et al. G-computation and machine learning for estimating the causal effects of binary exposure statuses on binary outcomes. Scientific Reports. 11(1):1435. 2021. <doi: 10.1038/s41598-021-81110-0>

Examples

```
#data simulation

#treatment = 1 if the patients have been the exposure or treatment of interest and 0 otherwise
#treatment <- rbinom(200, 1, prob=0.5)

#one quantitative covariate

#covariate1 <- rnorm(200, 0, 1)
#covariate1[treatment==1] <- rnorm(sum(treatment==1), 0.3, 1)

#one qualitative covariate

#covariate2 <- rbinom(200, 1, prob=0.5)
#covariate2[treatment==1] <- rbinom(sum(treatment==1), 1, prob=0.4)

#outcome <- rbinom(200, 1, prob = exp(-2+0.26*treatment+0.4*covariate1-

#0.4*covariate2)/(1+exp( -2+0.26*treatment+0.4*covariate1-0.4*covariate2)))
```

```
#tab <- data.frame(outcome, treatment, covariate1, covariate2)

#Raw effect of the treatment

#glm.raw <- glm(outcome ~ treatment, data=tab, family = binomial(link=logit))
#summary(glm.raw)

#Conditional effect of the treatment

#glm.multi <- glm(outcome ~ treatment + covariate1 + covariate2,
# data=tab, family = binomial(link=logit))
#summary(glm.multi)

#Marginal effects of the treatment (ATE) by using logistic regression as the Q-model

#gc.ate1 <- gc.logistic(glm.obj=glm.multi, data=tab, group="treatment", effect="ATE",
# var.method="bootstrap", iterations=1000, n.cluster=1)

#Marginal effects of the treatment (ATE) by using a super learner as the Q-model

#gc.ate2 <- gc.sl.binary(outcome="outcome", group="treatment", cov.quanti="covariate1",
# cov.quali="covariate2", data=tab, effect="ATE", tuneLength=10, cv=3,
# iterations=1000, n.cluster=1)

#Sum-up of the 3 ORs

#data.frame( raw=exp(glm.raw$coefficients[2]),
#conditional=exp(glm.multi$coefficients[2]),
#marginal.ate.logistic=exp(gc.ate1$logOR[,1]),
#marginal.ate.sl=exp(gc.ate2$logOR[,1]) )
```

---

gc.survival	*Marginal Effect for Censored Outcome by G-computation with a Cox Regression for the Outcome Model.*

Description

This function allows to estimate the marginal effect of an exposure or a treatment by G-computation for a censored times-to-event, the Q-model being specified by a Cox model.

Usage

```
gc.survival(object, data, group, times, failures, max.time, effect,
iterations, n.cluster, cluster.type)
```

Arguments

`object`	A coxph object obtained by using the function coxph with the argument x=TRUE must be specified. It shall be included the exposition/treatment of interest variable and at least one covariate.
`data`	A data frame in which to look for the variables related to the status of the event (observed or censored), the follow-up time, the treatment/exposure and the co-variables included in the previous model `object`. The covariates' names have to be identical than the ones included in `object`.
`group`	The name of the variable related to the exposure/treatment. This variable shall have only two modalities encoded 0 for the untreated/unexposed patients and 1 for the treated/exposed ones.
`times`	The name of the variable related the numeric vector with the follow-up times.
`failures`	The name of the variable related the numeric vector with the event indicators (0=right censored, 1=event).
`max.time`	The maximum time of follow-up to estimate of restricted mean survival time (RMST).
`effect`	The type of marginal effect to be estimated. Three types are possible (see details): "ATE" (by default), "ATT" and "ATU".
`iterations`	The number of bootstrap resamples to estimate of the variances and the confidence intervals.
`n.cluster`	The number of cores to use, i.e., the upper limit for the number of child processes that run simultaneously (1 by default).
`cluster.type`	A character string with the type of parallelization. The default type is "PSOCK" (it calls makePSOCKcluster, faster on MacOS or Linux platforms). An alternative is "FORK" (it calls makeForkCluster, it does not work on Windows platforms).

Details

The ATE corresponds to Average Treatment effect on the Entire population, i.e. the marginal effect if all the sample is treated versus all the sample is untreated. The ATT corresponds to Average Treatment effect on the Treated, i.e. the marginal effect if the treated patients (group = 1) would have been untreated. The ATU corresponds to Average Treatment effect on the Untreated , i.e. the marginal effect if the untreated patients (group = 0) would have been treated. The RMST is the mean survival time of all subjects in the study population followed up to max.time.

Value

`table.surv`	This data frame presents the survival probabilities (`survival`) in each group (`variable`) according to the `times`. The number of individuals at risk (`n.risk`) is also provided.
`effect`	A character string with the type of selected effect.
`max.time`	A scalar related to the maximum time of follow-up.
`RMST0`	A table related to the RMST in the unexposed/untreated sample: `estimate` is the estimated value, `std.error` is the standard error, `ci.lower` and `ci.upper` represent the 95% confidence interval.

RMST1	A table related to the RMST in the exposed/treated sample: `estimate` is the estimated value, `std.error` is the standard error, `ci.lower` and `ci.upper` represent the 95% confidence interval.
delta	A table related to the difference between the RMST in the exposed/treated sample minus in the unexposed/untreated one: `estimate` is the estimated value, `std.error` is the standard error, `ci.lower` and `ci.upper` represent the 95% confidence interval, and `p.value` is the p-value of the bilateral test of the null hypothesis RMST0 = RMST1.
logHR	A table related to the logarithm of the average Hazard Ratio (HR): `estimate` is the estimated value, `std.error` is the standard error, `ci.lower` and `ci.upper` represent the 95% confidence interval, and `p.value` is the p-value of the bilateral test of the null hypothesis HR = 1.

Author(s)

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Arthur Chatton <Arthur.Chatton@etu.univ-nantes.fr>

References

Chatton et al. G-computation and doubly robust standardisation for continuous-time data: A comparison with inverse probability weighting. Stat Methods Med Res. 31(4):706-718. 2022. <doi: 10.1177/09622802211047345>.

Examples

```
data(dataDIVAT2)

#Raw effect of the treatment
cox.raw <- coxph(Surv(times,failures) ~ ecd, data=dataDIVAT2, x=TRUE)
summary(cox.raw)

#Conditional effect of the treatment
cox.cdt <- coxph(Surv(times,failures) ~ ecd + age + retransplant,
 data=dataDIVAT2, x=TRUE)
summary(cox.cdt)

#Marginal effect of the treatment (ATE): use 1000 iterations instead of 10
#We restricted to 10 to respect the CRAN policy in terms of time for computation
gc.ate <- gc.survival(object=cox.cdt, data=dataDIVAT2, group="ecd", times="times",
 failures="failures", max.time=max(dataDIVAT2$times), iterations=10, effect="ATE",
 n.cluster=1)
gc.ate

#Sum-up of the 3 HRs
data.frame( raw=exp(cox.raw$coefficients),
conditional=exp(cox.cdt$coefficients[1]),
marginal.ate=exp(gc.ate$logHR[,1]) )

#Plot the survival curves
```

```
plot(gc.ate, ylab="Confounder-adjusted survival",
 xlab="Time post-transplantation (years)", col=c(1,2))
```

---

ipw.log.rank   *Log-Rank Test for Adjusted Survival Curves.*

Description

The user enters individual survival data and the weights previously calculated (by using logistic regression for instance). The usual log-rank test is adapted to the corresponding adjusted survival curves.

Usage

```
ipw.log.rank(times, failures, variable, weights)
```

Arguments

times	A numeric vector with the follow up times.
failures	A numeric vector with the event indicator (0=right censored, 1=event).
variable	A numeric vector with the binary variable under interest (only two groups).
weights	The weights for correcting the contribution of each individual. By default, the weights are all equaled to 1 and the survival curves correspond to the usual Kaplan-Meier estimator.

Details

For instance, the weights may be equal to 1/p, where p is the estimated probability of the individual to be in its group. The probabilities p are often estimated by a logistic regression in which the dependent binary variable is the group. The possible confounding factors are the explanatory variables of this model.

Value

statistic	The value of the log-rank statistic.
p.value	The p-value associated to the previous log-rank statistic.

Author(s)

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Jun Xie <junxie@purdue.edu>

Florant Le Borgne <fleborgne@idbc.fr>

References

Le Borgne et al. Comparisons of the performances of different statistical tests for time-to-event analysis with confounding factors: practical illustrations in kidney transplantation. Statistics in medicine. 30;35(7):1103-16, 2016. <doi:10.1002/ sim.6777>

Jun Xie and Chaofeng Liu. Adjusted Kaplan-Meier estimator and log-rank test with inverse probability of treatment weighting for survival data. Statistics in medicine, 24(20):3089-3110, 2005. <doi:10.1002/sim.2174>

Examples

```
data(dataDIVAT2)

# adjusted log-rank test
Pr0 <- glm(ecd ~ 1, family = binomial(link="logit"), data=dataDIVAT2)$fitted.values[1]
Pr1 <- glm(ecd ~ age + hla + retransplant, data=dataDIVAT2,
 family=binomial(link = "logit"))$fitted.values
W <- (dataDIVAT2$ecd==1) * (1/Pr1) + (dataDIVAT2$ecd==0) * (1)/(1-Pr1)

ipw.log.rank(dataDIVAT2$times, dataDIVAT2$failures, dataDIVAT2$ecd, W)
```

---

ipw.survival	*Adjusted Survival Curves by Using IPW.*

Description

This function allows to estimate confounder-adjusted survival curves by weighting the individual contributions by the inverse of the probability to be in the group (IPW).

Usage

```
ipw.survival(times, failures, variable, weights)
```

Arguments

times	A numeric vector with the follow up times.
failures	A numeric vector with the event indicators (0=right censored, 1=event).
variable	A numeric vector with the binary variable under interest (only two groups).
weights	The weights for correcting the contribution of each individual. By default, the weights are all equaled to 1 and the survival curves correspond to the usual Kaplan-Meier estimator.

Details

For instance, the weights may be equal to 1/p, where p is the estimated probability of the individual to be in its group. The probabilities p are often estimated by a logistic regression in which the dependent binary variable is the group. The possible confounding factors are the covariates of this model.

Value

table.surv   This data frame presents the survival probabilities (survival) in each group
                  (variable) according to the times. The number of individuals at risk (n.risk)
                  and the number of observed events are also provided (n.event).

Author(s)

Yohann Foucher <Yohann.Foucher@univ-poitiers.fr>

Florent Le Borgne <fleborgne@idbc.fr>

References

Le Borgne et al. Comparisons of the performances of different statistical tests for time-to-event
analysis with confounding factors: practical illustrations in kidney transplantation. Statistics in
medicine. 30;35(7):1103-16, 2016. <doi:10.1002/ sim.6777>

Examples

```
data(dataDIVAT2)

# adjusted Kaplan-Meier estimator by IPW
 Pr0 <- glm(ecd ~ 1, family = binomial(link="logit"), data=dataDIVAT2)$fitted.values[1]
 Pr1 <- glm(ecd ~ age + hla + retransplant, data=dataDIVAT2,
 family=binomial(link = "logit"))$fitted.values
 W <- (dataDIVAT2$ecd==1) * (1/Pr1) + (dataDIVAT2$ecd==0) * (1)/(1-Pr1)
 res.akm <-ipw.survival(times=dataDIVAT2$times, failures=dataDIVAT2$failures,
  variable=dataDIVAT2$ecd, weights=W)

plot(res.akm, ylab="Confounder-adjusted survival",
 xlab="Time post-transplantation (years)", col=c(1,2), grid.lty=1)
```

---

lines.rocrisca   *Add Lines to a ROC Plot*

Description

Used to add an additionnal ROC curve to ROC plot generated with plot.rocrisca.

Usage

```
## S3 method for class 'rocrisca'
lines(x, ...)
```

Arguments

x   An object of class rocrisca, returned by the functions roc.binary, roc.net,
                  roc.summary, and roc.time.

...   Additional arguments affecting the plot line.

Author(s)

Yohann Foucher <Yohann.Foucher@univ-poitiers.fr>

Examples

```
# import and attach the data example

data(dataDIVAT3)

# A subgroup analysis to reduce the time needed for this exemple

dataDIVAT3 <- dataDIVAT3[1:400,]

# The ROC curve to evaluate the crude capacities of the recipient age for the
# prognosis of post kidney transplant mortality (we ignore the censoring process)

roc1 <- roc.binary(status="death", variable="ageR", confounders=~1,
data=dataDIVAT3, precision=seq(0.1,0.9, by=0.1) )

# The standardized and weighted ROC curve to evaluate the capacities
# of the recipient age for the prognosis of post kidney transplant
# mortality by taking into account the donor age and the recipient
# gender (we ignore the censoring process).

# 1. Standardize the marker according to the covariates among the controls
lm1 <- lm(ageR ~ ageD + sexeR, data=dataDIVAT3[dataDIVAT3$death == 0,])
dataDIVAT3$ageR_std <- (dataDIVAT3$ageR - (lm1$coef[1] + lm1$coef[2] *
 dataDIVAT3$ageD + lm1$coef[3] * dataDIVAT3$sexeR)) / sd(lm1$residuals)

# 2. Compute the sensitivity and specificity from the proposed IPW estimators
roc2 <- roc.binary(status="death", variable="ageR_std",
 confounders=~bs(ageD, df=3) + sexeR, data=dataDIVAT3, precision=seq(0.1,0.9, by=0.1))

# The corresponding ROC graph

plot(roc2, type="b", col=2, pch=2, lty=2)

lines(roc1, type="b", col=1, pch=1)

legend("bottomright", lty=1:2, lwd=1, pch=1:2, col=1:2,
 c(paste("Crude estimation, (AUC=", round(roc1$auc, 2), ")", sep=""),
 paste("Adjusted estimation, (AUC=", round(roc2$auc, 2), ")", sep="") ) )
```

---

lrs.multistate	*Likelihood Ratio Statistic to Compare Embedded Multistate Models*

Description

This function computes a Likelihood Ratio Statistic to compare two embedded multistate models.

Usage

```
lrs.multistate(model1, model0)
```

Arguments

model1   A list containing the results after using a function included in the present RISCA
                package.

model0   A list containing the results after using a function included in the present RISCA
                package. The function used to obtained the model0 have to be the same than the
                one used to obtain the model1. The model0 have to be embedded in the model1.

Value

statistic   The value of the statistic.

ddl   The degrees of freedom.

pvalue   The p-value.

Author(s)

Yohann Foucher <Yohann.Foucher@univ-poitiers.fr>

Florence Gillaizeau <Florence.Gillaizeau@univ-nantes.fr>

Examples

```
data(dataDIVAT1)

# A subgroup analysis to reduce the time needed for this example

dataDIVAT1$id<-c(1:nrow(dataDIVAT1))
set.seed(2)
d3<-dataDIVAT1[dataDIVAT1$id %in% sample(dataDIVAT1$id, 250, replace = FALSE),]

# To illustrate the use of a 3-state model, individuals with trajectory 13 and 123 are
# censored at the time of transition into state X=3

d3$trajectory[d3$trajectory==13]<-1
d3$trajectory[d3$trajectory==123]<-12
d3$trajectory[d3$trajectory==14]<-13
d3$trajectory[d3$trajectory==124]<-123

# 3-state parametric semi-Markov model : does 'z' influence both the
# transition 1->3 ? We only reduced the precision and the number of iteration
# to save time in this example, prefere the default values.

m1 <- semi.markov.3states(times1=d3$time1, times2=d3$time2,
  sequences=d3$trajectory, dist=c("E","E","E"),
  ini.dist.12=c(9.93), ini.dist.13=c(11.54), ini.dist.23=c(10.21),
  cov.12=d3$z, init.cov.12=c(-0.13), names.12=c("beta12_z"),
  cov.13=d3$z, init.cov.13=c(1.61),  names.13=c("beta13_z"),
  conf.int=TRUE, silent=FALSE, precision=0.001)
```

```
m1

m0 <- semi.markov.3states(times1=d3$time1, times2=d3$time2,
  sequences=d3$trajectory, dist=c("E","E","E"),
  ini.dist.12=c(9.93), ini.dist.13=c(11.54), ini.dist.23=c(10.21),
  cov.12=d3$z, init.cov.12=c(-0.13), names.12=c("beta12_z"),
  conf.int=TRUE, silent=FALSE, precision=0.001)

m0

lrs.multistate(model1=m1, model0=m0)
```

---

markov.3states   *3-State Time-Inhomogeneous Markov Model*

Description

The 3-state Markov model includes an initial state (X=1), a transient state (X=2) and an absorbing state (X=3). Usually, X=1 corresponds to disease-free or remission, X=2 to relapse, and X=3 to death. In this illness-death model, the possible transitions are: 1->2, 1->3 and 2->3.

Usage

```
markov.3states(times1, times2, sequences, weights=NULL, dist,
cuts.12=NULL, cuts.13=NULL, cuts.23=NULL,
ini.dist.12=NULL, ini.dist.13=NULL, ini.dist.23=NULL,
cov.12=NULL, init.cov.12=NULL, names.12=NULL,
cov.13=NULL, init.cov.13=NULL, names.13=NULL,
cov.23=NULL, init.cov.23=NULL, names.23=NULL,
conf.int=TRUE, silent=TRUE, precision=10^(-6))
```

Arguments

times1	A numeric vector with the observed times (in days) from baseline to the first transition (in X=2 or X=3) or to the right-censoring (in X=1 at the last follow-up).
times2	A numeric vector with the observed times (in days) from baseline to the second transition (in X=3) or to the right censoring (in X=2 at the last follow-up). NA for individuals right-censored in X=1 or individuals who directly transited from X=1 to X=3.
sequences	A numeric vector with the sequences of observed states. Four possible values are allowed: 1 (individual right-censored in X=1), 12 (individual right-censored in X=2), 13 (individual who directly transited from X=1 to X=3), 123 (individual who transited from X=1 to X=3 through X=2).
weights	A numeric vector with the weights for correcting the contribution of each individual. Default is NULL which means that no weighting is applied.

dist	A character vector with three arguments describing respectively the distributions of duration time for transitions 1->2, 1->3 and 2->3. Arguments allowed are "E" for Exponential distribution, "PE" for the piecewise exponential distribution, "W" for Weibull distribution or "WG" for Generalized Weibull distribution. When the user choose "PE", the arguments "cut.XX" have also to be defined.
cuts.12	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.13	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.23	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=3. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
ini.dist.12	A numeric vector of initial values for the distribution from X=1 to X=2. The logarithm of the parameters have to be declared. Default value is 1.
ini.dist.13	A numeric vector of initial values for the distribution from X=1 to X=3. The logarithm of the parameters have to be declared. Default value is 1.
ini.dist.23	A numeric vector of initial values for the distribution from X=2 to X=3. The logarithm of the parameters have to be declared. Default value is 1.
cov.12	A matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=2.
init.cov.12	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.12. Default initial value is 0.
names.12	An optional character vector with name of explicative variables associated to cov.12.
cov.13	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=3.
init.cov.13	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.13. Default initial value is 0.
names.13	An optional character vector with name of explicative variables associated to cov.13.
cov.23	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=2 to X=3.
init.cov.23	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.23. Default initial value is 0.
names.23	An optional character vector with name of explicative variables associated to cov.23.

conf.int   A logical value specifying if the pointwise confidence intervals for parameters
                  and the variance-covariance matrix should be returned. Default is TRUE.

silent   A logical value specifying if the log-likelihood value should be returned at each
                  iteration. Default is TRUE, which corresponds to silent mode (no display).

precision   A numeric positive value indicating the required precision for the log-likelihood
                  maximization between each iteration. Default is 10^{-6}.

Details

Hazard functions available are:

$$
\begin{array}{ll}
\text{Exponential distribution} & \lambda(t) = 1/\sigma \\
\text{Weibull distribution} & \lambda(t) = \nu(\frac{1}{\sigma})^{\nu} t^{\nu-1} \\
\text{Generalized Weibull distribution} & \lambda(t) = \frac{1}{\theta}\left(1 + \left(\frac{t}{\sigma}\right)^{\nu}\right)^{\frac{1}{\theta}-1} \nu\left(\frac{1}{\sigma}\right)^{\nu} t^{\nu-1}
\end{array}
$$

with σ, ν, and $\theta > 0$. The parameter σ varies for each interval when the distribution is piecewise Exponential. We advise to initialize the logarithm of these parameters in ini.dist.12, ini.dist.13 and ini.dist.23.

To estimate the marginal effect of a binary exposure, the weights may be equal to 1/p, where p is the estimated probability that the individual belongs to his or her own observed group of exposure. The probabilities p are often estimated by a logistic regression in which the dependent binary variable is the exposure. The possible confounding factors are the explanatory variables of this logistic model.

Value

object   The character string indicating the estimated model: "markov.3states (3-state
                  time-inhomogeneous markov model)".

dist   A character vector with two arguments describing respectively the distributions
                  of duration time for transitions 1->2, 1->3 and 2->3.

cuts.12   A numeric vector indicating the timepoints in days for the piecewise exponential
                  distribution related to the time from X=1 to X=2.

cuts.13   A numeric vector indicating the timepoints in days for the piecewise exponential
                  distribution related to the time from X=1 to X=3.

cuts.23   A numeric vector indicating the timepoints in days for the piecewise exponential
                  distribution related to the time from X=2 to X=3.

covariates   A numeric vector indicating the numbers of covariates respectively related to
                  the transition 1->2, 1->3 and 2->3.

table   A data frame containing the estimated parameters of the model (Estimate).
                  When the option conf.int=TRUE is specified, this data.frame includes three
                  additional columns: the Standard Errors of parameters (Std.Error), the value
                  of the Wald statistic (t.value), and the related p-value (Pr(>|t|)).

cov.matrix   A data frame corresponding to variance-covariance matrix of the parameters.

LogLik   A numeric value corresponding to the (weighted) log-likelihood of the model.

AIC   A numeric value corresponding to the Akaike Information Criterion of the model.

Author(s)

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Florence Gillaizeau <Florence.Gillaizeau@univ-nantes.fr>

References

Huszti et al. Relative survival multistate Markov model. Stat Med. 10;31(3):269-86, 2012. <DOI: 10.1002/sim.4392>

Gillaizeau et al. Inverse Probability Weighting to control confounding in an illness-death model for interval-censored data. Stat Med. 37(8):1245-1258, 2018. <doi: 10.1002/sim.7550>.

Examples

```
# import the observed data
# X=1 corresponds to initial state with a functioning graft, X=2 to acute rejection episode,
# X=3 to return to dialysis, and X=4 to death with a functioning graft

data(dataDIVAT1)

# A subgroup analysis to reduce the time needed for this example

dataDIVAT1$id<-c(1:nrow(dataDIVAT1))
set.seed(2)
d3<-dataDIVAT1[dataDIVAT1$id %in% sample(dataDIVAT1$id, 300, replace = FALSE),]

# Individuals with trajectory 13 and 123 are
# censored at the time of transition into state X=3

d3$trajectory[d3$trajectory==13]<-1
d3$trajectory[d3$trajectory==123]<-12
d3$trajectory[d3$trajectory==14]<-13
d3$trajectory[d3$trajectory==124]<-123

# 3-state parametric Markov model including one explicative variable
# (z is the delayed graft function) on the transition 1->2. We only reduced
# the precision and the number of iteration to save time in this example,
# prefer the default values.

markov.3states(times1=d3$time1, times2=d3$time2, sequences=d3$trajectory, weights=NULL,
  dist=c("E","E","E"), ini.dist.12=c(9.93),
  ini.dist.13=c(11.54), ini.dist.23=c(10.21),
  cov.12=d3$z, init.cov.12=c(-0.13), names.12=c("beta12_z"),
  conf.int=TRUE,  silent=FALSE, precision=0.001)
```

---

markov.3states.rsadd   *3-state Relative Survival Markov Model with Additive Risks*

Description

The 3-state Markov relative survival model includes an initial state (X=1), a transient state (X=2), and the death (X=3). The possible transitions are: 1->2, 1->3 and 2->3. Assuming additive risks, the observed mortality hazard is the sum of two components: the expected population mortality (X=P) and the excess mortality related to the disease under study (X=E). The expected population mortality hazard (X=P) can be obtained from the death rates provided by life tables of statistical national institutes. These tables indicate the proportion of people dead in a calendar year stratified by birthdate and gender.

Usage

```
markov.3states.rsadd(times1, times2, sequences, weights=NULL, dist,
cuts.12=NULL, cuts.13=NULL, cuts.23=NULL,
ini.dist.12=NULL, ini.dist.13=NULL, ini.dist.23=NULL,
cov.12=NULL, init.cov.12=NULL, names.12=NULL,
cov.13=NULL, init.cov.13=NULL, names.13=NULL,
cov.23=NULL, init.cov.23=NULL, names.23=NULL,
p.age, p.sex, p.year, p.rate.table,
conf.int=TRUE, silent=TRUE, precision=10^(-6))
```

Arguments

times1	A numeric vector with the observed times in days from baseline to the first transition (X=2 or X=3) or to the right-censoring (in X=1 at the last follow-up).
times2	A numeric vector with the observed times in days from baseline to the second transition or to the right censoring (in X=2 at the last follow-up). NA for individuals right-censored in X=1 or individuals who directly transited from X=1 to X=3.
sequences	A numeric vector with the sequences of observed states. Four possible values are allowed: 1 (individual right-censored in X=1), 12 (individual right-censored in X=2), 13 (individual who directly transited from X=1 to X=3), 123 (individual who transited from X=1 to X=3 through X=2).
weights	A numeric vector with the weights for correcting the contribution of each individual. Default is NULL which means that no weighting is applied.
dist	A character vector with three arguments describing respectively the distributions of duration time for transitions 1->2, 1->3 and 2->3. Arguments allowed are "E" for Exponential distribution, "PE" for the piecewise exponential distribution, "W" for Weibull distribution or "WG" for Generalized Weibull distribution. When the user choose "PE", the arguments "cut.XX" have also to be defined.
cuts.12	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.13	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the

	distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.23	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=3. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
ini.dist.12	A numeric vector of initial values for the distribution from X=1 to X=2. The logarithm of the parameters have to be declared. Default value is 1.
ini.dist.13	A numeric vector of initial values for the distribution from X=1 to X=3. The logarithm of the parameters have to be declared. Default value is 1.
ini.dist.23	A numeric vector of initial values for the distribution from X=2 to X=3. The logarithm of the parameters have to be declared. Default value is 1.
cov.12	A matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=2.
init.cov.12	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.12. Default initial value is 0.
names.12	An optional character vector with name of explicative variables associated to cov.12.
cov.13	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=3.
init.cov.13	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.13. Default initial value is 0.
names.13	An optional character vector with name of explicative variables associated to cov.13.
cov.23	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=2 to X=3.
init.cov.23	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.23. Default initial value is 0.
names.23	An optional character vector with name of explicative variables associated to cov.23.
p.age	A numeric vector with the patient ages in days at baseline (X=1).
p.sex	A character vector with the genders: male or female.
p.year	A numeric vector with the entry dates in the study respecting the date format, i.e. in number of days since 01.01.1960.
p.rate.table	A list containing the information related to the expected rates of mortality. This list is organized as a ratetable object.
conf.int	A logical value specifying if the pointwise confidence intervals for parameters and the variance-covariance matrix should be returned. Default is TRUE.
silent	A logical value specifying if the log-likelihood value should be returned at each iteration. Default is TRUE, which corresponds to silent mode (no display).
precision	A numeric positive value indicating the required precision for the log-likelihood maximization between each iteration. Default is 10^{-6}.

Details

Hazard functions available are:

$$
\begin{array}{rl}
\text{Exponential distribution} & \lambda(t) = 1/\sigma \\
\text{Weibull distribution} & \lambda(t) = \nu(\tfrac{1}{\sigma})^{\nu} t^{\nu-1} \\
\text{Generalized Weibull distribution} & \lambda(t) = \tfrac{1}{\theta} \left(1 + \left(\tfrac{t}{\sigma}\right)^{\nu} \right)^{\tfrac{1}{\theta}-1} \nu \left(\tfrac{1}{\sigma}\right)^{\nu} t^{\nu-1}
\end{array}
$$

with σ, ν, and $\theta > 0$. The parameter σ varies for each interval when the distribution is piecewise Exponential. We advise to initialize the logarithm of these parameters in `ini.dist.12`, `ini.dist.13` and `ini.dist.23`.

To estimate the marginal effect of a binary exposure, the `weights` may be equal to `1/p`, where `p` is the estimated probability that the individual belongs to his or her own observed group of exposure. The probabilities p are often estimated by a logistic regression in which the dependent binary variable is the exposure. The possible confounding factors are the explanatory variables of this logistic model.

Value

`object`	The character string indicating the estimated model: "markov.3states.rsadd (3-state time-inhomogeneous markov model)".
`dist`	A character vector with two arguments describing respectively the distributions of duration time for transitions 1->2, 1->3 and 2->3.
`cuts.12`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2.
`cuts.13`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3.
`cuts.23`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=3.
`covariates`	A numeric vector indicating the numbers of covariates respectively related to the transition 1->2, 1->3 and 2->3.
`table`	A data frame containing the estimated parameters of the model (`Estimate`). When the option `conf.int=TRUE` is specified, this data frame includes three additional columns: the Standard Errors of parameters (`Std.Error`), the value of the Wald statistic (`t.value`), and the related p-value (`Pr(>|t|)`).
`cov.matrix`	A data frame corresponding to variance-covariance matrix of the parameters.
`LogLik`	A numeric value corresponding to the log-likelihood of the estimated model.
`AIC`	A numeric value corresponding to the Akaike Information Criterion of the estimated model.

Author(s)

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Florence Gillaizeau <Florence.Gillaizeau@univ-nantes.fr>

References

Huszti et al. Relative survival multistate Markov model. Stat Med. 10;31(3):269-86, 2012. <DOI: 10.1002/sim.4392>

Gillaizeau et al. A multistate additive relative survival semi-Markov model. Stat Methods Med Res. 26(4):1700-1711, 2017. <doi: 10.1177/ 0962280215586456>.

Gillaizeau et al. Inverse Probability Weighting to control confounding in an illness-death model for interval-censored data. Stat Med. 37(8):1245-1258, 2018. <doi: 10.1002/sim.7550>.

Examples

```
# import the observed data
# (X=1 corresponds to initial state with a functioning graft, X=2 to acute rejection episode,
# X=3 to return to dialysis, X=4 to death with a functioning graft)

data(dataDIVAT1)

# A subgroup analysis to reduce the time needed for this example

dataDIVAT1$id<-c(1:nrow(dataDIVAT1))
set.seed(2)
d3<-dataDIVAT1[dataDIVAT1$id %in% sample(dataDIVAT1$id, 200, replace = FALSE),]

# Individuals with trajectory 13 and 123 are
# censored at the time of transition into state X=3

d3$trajectory[d3$trajectory==13]<-1
d3$trajectory[d3$trajectory==123]<-12
d3$trajectory[d3$trajectory==14]<-13
d3$trajectory[d3$trajectory==124]<-123

# import the expected mortality rates

data(fr.ratetable)

# 3-state Markov model with additive risks including one explicative variable
# (z is the delayed graft function) on all transitions. We only reduced
# the precision and the number of iteration to save time in this example,
# prefer the default values.

markov.3states.rsadd(times1=d3$time1, times2=d3$time2, sequences=d3$trajectory,
  dist=c("E","E","E"), ini.dist.12=c(8.34),
  ini.dist.13=c(10.70), ini.dist.23=c(11.10),
  cov.12=d3$z, init.cov.12=c(0.04), names.12=c("beta12_z"),
  cov.13=d3$z, init.cov.13=c(1.04), names.13=c("beta1E_z"),
  cov.23=d3$z, init.cov.23=c(0.29), names.23=c("beta2E_z"),
  p.age=d3$ageR*365.24, p.sex=d3$sexR,
  p.year=as.numeric(as.Date(paste0(d3$year.tx,"-01-01"), origin = "1960-01-01")),
  p.rate.table=fr.ratetable,  conf.int=TRUE,
  silent=FALSE, precision=0.001)
```

---

markov.4states   *4-State Time-Inhomogeneous Markov Model*

Description

The 4-state Markov model includes an initial state (X=1), a transient state (X=2) and two absorbing states (X=3 and X=4). The possible transitions are: 1->2, 1->3, 1->4, 2->3 and 2->4.

Usage

```
markov.4states(times1, times2, sequences,  weights=NULL, dist,
cuts.12=NULL, cuts.13=NULL, cuts.14=NULL, cuts.23=NULL, cuts.24=NULL,
ini.base.12=NULL, ini.base.13=NULL, ini.base.14=NULL,
ini.base.23=NULL, ini.base.24=NULL,
cov.12=NULL, init.cov.12=NULL, names.12=NULL,
cov.13=NULL, init.cov.13=NULL, names.13=NULL,
cov.14=NULL, init.cov.14=NULL, names.14=NULL,
cov.23=NULL, init.cov.23=NULL, names.23=NULL,
cov.24=NULL, init.cov.24=NULL, names.24=NULL,
conf.int=TRUE, silent=TRUE, precision=10^(-6))
```

Arguments

times1	A numeric vector with the observed times in days from baseline to the first transition (X=2, X=3 or X=4) or to the right-censoring (in X=1 at the last follow-up).
times2	A numeric vector with the observed times in days from baseline to the second transition or to the right censoring (in X=2 at the last follow-up). NA for individuals right-censored in X=1 or individuals who directly transited from X=1 to X=3 or X=4.
sequences	a numeric vector with the sequences of observed states. Six possible values are allowed: 1 (individual right-censored in X=1), 12 (individual right-censored in X=2), 13 (individual who directly transited from X=1 to X=3), 14 (individual who directly transited from X=1 to X=4), 123 (individual who transited from X=1 to X=3 through X=2), 124 (individual who transited from X=1 to X=4 through X=2).
weights	A numeric vector with the weights for correcting the contribution of each individual. When the vector is completed, the IPW estimator is implemented. Default is NULL which means that no weighting is applied.
dist	A character vector with three arguments describing respectively the distributions of duration time for transitions 1->2, 1->3 and 2->3. Arguments allowed are "E" for Exponential distribution, "PE" for the piecewise exponential distribution, "W" for Weibull distribution or "WG" for Generalized Weibull distribution. When the user choose "PE", the arguments "cut.XX" have also to be defined.

cuts.12	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.13	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.14	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=4. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.23	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=3. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.24	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=4. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
ini.base.12	A numeric vector of initial values for the distribution from X=1 to X=2. The logarithm of the parameters have to be declared. Default value is 1.
ini.base.13	A numeric vector of initial values for the distribution from X=1 to X=3. The logarithm of the parameters have to be declared. Default value is 1.
ini.base.14	A numeric vector of initial values for the distribution from X=1 to X=4. The logarithm of the parameters have to be declared. Default value is 1.
ini.base.23	A numeric vector of initial values for the distribution from X=2 to X=3. The logarithm of the parameters have to be declared. Default value is 1.
ini.base.24	A numeric vector of initial values for the distribution from X=2 to X=4. The logarithm of the parameters have to be declared. Default value is 1.
cov.12	A matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=2.
init.cov.12	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.12. Default initial value is 0.
names.12	An optional character vector with name of explicative variables associated to cov.12.
cov.13	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=3.
init.cov.13	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.13. Default initial value is 0.

names.13	An optional character vector with name of explicative variables associated to cov.13.
cov.14	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=4.
init.cov.14	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.14. Default initial value is 0.
names.14	An optional character vector with name of explicative variables associated to cov.14.
cov.23	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=2 to X=3.
init.cov.23	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.23. Default initial value is 0.
names.23	An optional character vector with name of explicative variables associated to cov.23.
cov.24	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=2 to X=4.
init.cov.24	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.24. Default initial value is 0.
names.24	An optional character vector with name of explicative variables associated to cov.24.
conf.int	A logical value specifying if the pointwise confidence intervals for parameters and the variance-covariance matrix should be returned. Default is TRUE.
silent	A logical value specifying if the log-likelihood value should be returned at each iteration. Default is TRUE, which corresponds to silent mode (no display).
precision	A numeric positive value indicating the required precision for the log-likelihood maximization between each iteration. Default is 10^{-6}.

Details

Hazard functions available are:

Exponential distribution	$\lambda(t) = 1/\sigma$
Weibull distribution	$\lambda(t) = \nu(\frac{1}{\sigma})^{\nu} t^{\nu-1}$
Generalized Weibull distribution	$\lambda(t) = \frac{1}{\theta} \left(1 + \left(\frac{t}{\sigma}\right)^{\nu}\right)^{\frac{1}{\theta}-1} \nu \left(\frac{1}{\sigma}\right)^{\nu} t^{\nu-1}$

with σ, ν, and $\theta > 0$. The parameter σ varies for each interval when the distribution is piecewise Exponential. We advise to initialize the logarithm of these parameters in ini.base.12, ini.base.13 and ini.base.23.

To estimate the marginal effect of a binary exposure, the weights may be equal to 1/p, where p is the estimated probability that the individual belongs to his or her own observed group of exposure. The probabilities p are often estimated by a logistic regression in which the dependent binary variable is the exposure. The possible confounding factors are the explanatory variables of this logistic model.

Value

`object`	A character string indicating the estimated model: "markov.4states (4-state time-inhomogeneous markov model)".
`dist`	A character vector with two arguments describing respectively the distributions of duration time for transitions 1->2, 1->3, 1->4, 2->3, and 2->4.
`cuts.12`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2.
`cuts.13`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3.
`cuts.14`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=4.
`cuts.23`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=3.
`cuts.24`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=4.
`covariates`	A numeric vector indicating the numbers of covariates respectively related to the transition 1->2, 1->3, 1->4, 2->3, and 2->4.
`table`	A data frame containing the estimated parameters of the model (Estimate). When the option `conf.int=TRUE` is specified, this data frame includes three additional columns: the Standard Errors of parameters (`Std.Error`), the value of the Wald statistic (`t.value`), and the related p-value (`Pr(>|t|)`).
`cov.matrix`	A data frame corresponding to variance-covariance matrix of the parameters.
`LogLik`	A numeric value corresponding to the log-likelihood of the estimated model.
`AIC`	A numeric value corresponding to the Akaike Information Criterion of the estimated model.

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References

Huszti et al. Relative survival multistate Markov model. Stat Med. 10;31(3):269-86, 2012. <DOI: 10.1002/sim.4392>

Gillaizeau et al. Inverse Probability Weighting to control confounding in an illness-death model for interval-censored data. Stat Med. 37(8):1245-1258, 2018. <doi: 10.1002/sim.7550>.

Examples

```
# import the observed data
# (X=1 corresponds to initial state with a functioning graft, X=2 to acute rejection episode,
# X=3 to return to dialysis, X=4 to death with a functioning graft)

data(dataDIVAT1)
```

```
# A subgroup analysis to reduce the time needed for this example

dataDIVAT1$id<-c(1:nrow(dataDIVAT1))
set.seed(2)
d4<-dataDIVAT1[dataDIVAT1$id %in% sample(dataDIVAT1$id, 200, replace = FALSE),]

# 4-state parametric Markov model including one explicative variable ('z')
# on the trainsition from X=1 to X=2. We only reduced
# the precision and the number of iteration to save time in this example,
# prefer the default values.

markov.4states(times1=d4$time1, times2=d4$time2, sequences=d4$trajectory,
  dist=c("E","E","E","E","E"),
  ini.base.12=c(8.31), ini.base.13=c(10.46), ini.base.14=c(10.83),
  ini.base.23=c(9.01), ini.base.24=c(10.81),
  cov.12=d4$z, init.cov.12=c(-0.02), names.12=c("beta12_z") ,
  conf.int=TRUE, silent=FALSE, precision=0.001)$table
```

---

markov.4states.rsadd   *4-state Relative Survival Markov Model with Additive Risks*

Description

The 4-state Markov relative survival model includes an initial state (X=1), a transient state (X=2), and two absorbing states including death (X=3, and X=4 for death). The possible transitions are: 1->2, 1->3, 1->4, 2->3 and 2->4. Assuming additive risks, the observed mortality hazard (X=4) is the sum of two components: the expected population mortality (X=P) and the excess mortality related to the disease under study (X=E). The expected population mortality hazard (X=P) can be obtained from the death rates provided by life tables of statistical national institutes. These tables indicate the proportion of people dead in a calendar year stratified by birthdate and gender.

Usage

```
markov.4states.rsadd(times1, times2, sequences, weights=NULL, dist,
cuts.12=NULL, cuts.13=NULL, cuts.14=NULL, cuts.23=NULL,
cuts.24=NULL, ini.dist.12=NULL, ini.dist.13=NULL,
ini.dist.14=NULL, ini.dist.23=NULL, ini.dist.24=NULL,
cov.12=NULL, init.cov.12=NULL, names.12=NULL,
cov.13=NULL, init.cov.13=NULL, names.13=NULL,
cov.14=NULL, init.cov.14=NULL, names.14=NULL,
cov.23=NULL, init.cov.23=NULL, names.23=NULL,
cov.24=NULL, init.cov.24=NULL, names.24=NULL,
p.age, p.sex, p.year, p.rate.table,
conf.int=TRUE, silent=TRUE, precision=10^(-6))
```

Arguments

times1	A numeric vector with the observed times in days from baseline to the first transition (X=2, X=3 or X=4) or to the right-censoring (in X=1 at the last follow-up).
times2	A numeric vector with the observed times in days from baseline to the second transition or to the right censoring (in X=2 at the last follow-up). NA for individuals right-censored in X=1 or individuals who directly transited from X=1 to X=3 or X=4.
sequences	A numeric vector with the sequences of observed states. Six possible values are allowed: 1 (individual right-censored in X=1), 12 (individual right-censored in X=2), 13 (individual who directly transited from X=1 to X=3), 14 (individual who directly transited from X=1 to X=4), 123 (individual who transited from X=1 to X=3 through X=2), 124 (individual who transited from X=1 to X=4 through X=2).
weights	a numeric vector with the weights for correcting the contribution of each individual. Default is NULL which means that no weighting is applied.
dist	A character vector with three arguments describing respectively the distributions of duration time for transitions 1->2, 1->3 and 2->3. Arguments allowed are "E" for Exponential distribution, "PE" for the piecewise exponential distribution, "W" for Weibull distribution or "WG" for Generalized Weibull distribution. When the user choose "PE", the arguments "cut.XX" have also to be defined.
cuts.12	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.13	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.14	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=4. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.23	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=3. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.24	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=4. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.

ini.dist.12	A numeric vector of initial values for the distribution from X=1 to X=2. The logarithm of the parameters have to be declared. Default value is 1.
ini.dist.13	A numeric vector of initial values for the distribution from X=1 to X=3. The logarithm of the parameters have to be declared. Default value is 1.
ini.dist.14	A numeric vector of initial values for the distribution from X=1 to X=4. The logarithm of the parameters have to be declared. Default value is 1.
ini.dist.23	A numeric vector of initial values for the distribution from X=2 to X=3. The logarithm of the parameters have to be declared. Default value is 1.
ini.dist.24	A numeric vector of initial values for the distribution from X=2 to X=4. The logarithm of the parameters have to be declared. Default value is 1.
cov.12	A matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=2.
init.cov.12	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.12. Default initial value is 0.
names.12	An optional character vector with name of explicative variables associated to cov.12.
cov.13	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=3.
init.cov.13	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.13. Default initial value is 0.
names.13	An optional character vector with name of explicative variables associated to cov.13.
cov.14	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=4.
init.cov.14	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.14. Default initial value is 0.
names.14	An optional character vector with name of explicative variables associated to cov.14.
cov.23	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=2 to X=3.
init.cov.23	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.23. Default initial value is 0.
names.23	An optional character vector with name of explicative variables associated to cov.23.
cov.24	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=2 to X=4.
init.cov.24	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.24. Default initial value is 0.
names.24	An optional character vector with name of explicative variables associated to cov.24.
p.age	A numeric vector with the patient ages in days at baseline (X=1).
p.sex	A character vector with the genders: male or female.

p.year	A numeric vector with the entry dates in the study respecting the date format, i.e. in number of days since 01.01.1960.
p.rate.table	A list containing the information related to the expected rates of mortality. This list is organized as a `ratetable` object.
conf.int	A logical value specifying if the pointwise confidence intervals for parameters and the variance-covariance matrix should be returned. Default is TRUE.
silent	A logical value specifying if the log-likelihood value should be returned at each iteration. Default is TRUE, which corresponds to silent mode (no display).
precision	A numeric positive value indicating the required precision for the log-likelihood maximization between each iteration. Default is 10^{-6}.

Details

Hazard functions available are:

$$
\begin{array}{ll}
\text{Exponential distribution} & \lambda(t) = 1/\sigma \\
\text{Weibull distribution} & \lambda(t) = \nu(\tfrac{1}{\sigma})^\nu t^{\nu-1} \\
\text{Generalized Weibull distribution} & \lambda(t) = \frac{1}{\theta}\left(1 + \left(\frac{t}{\sigma}\right)^\nu\right)^{\frac{1}{\theta}-1} \nu \left(\frac{1}{\sigma}\right)^\nu t^{\nu-1}
\end{array}
$$

with σ, ν, and $\theta > 0$. The parameter σ varies for each interval when the distribution is piecewise Exponential. We advise to initialize the logarithm of these parameters in `ini.dist.12`, `ini.dist.13` and `ini.dist.23`.

To estimate the marginal effect of a binary exposure, the `weights` may be equal to 1/p, where p is the estimated probability that the individual belongs to his or her own observed group of exposure. The probabilities p are often estimated by a logistic regression in which the dependent binary variable is the exposure. The possible confounding factors are the explanatory variables of this logistic model.

Value

object	A character string indicating the estimated model: "markov.4states.rsadd (4-state relative survival markov model with additive risks)".
dist	A character vector with two arguments describing respectively the distributions of duration time for transitions 1->2, 1->3, 1->4, 2->3, and 2->4.
cuts.12	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2.
cuts.13	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3.
cuts.14	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=4.
cuts.23	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=3.
cuts.24	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=4.

covariates	A numeric vector indicating the numbers of covariates respectively related to the transition 1->2, 1->3, 1->4, 2->3, and 2->4.
table	A data frame containing the estimated parameters of the model (Estimate). When the option conf.int=TRUE is specified, this data.frame includes three additional columns: the Standard Errors of parameters (Std.Error), the value of the Wald statistic (t.value), and the related p-value (Pr(>|t|)).
cov.matrix	A data frame corresponding to variance-covariance matrix of the parameters.
LogLik	A numeric value corresponding to the log-likelihood of the estimated model.
AIC	A numeric value corresponding to the Akaike Information Criterion of the estimated model.

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References

Huszti et al. Relative survival multistate Markov model. Stat Med. 10;31(3):269-86, 2012. <DOI: 10.1002/sim.4392>.

Gillaizeau et al. A multistate additive relative survival semi-Markov model. Stat Methods Med Res. 26(4):1700-1711, 2017. <doi: 10.1177/ 0962280215586456>.

Gillaizeau et al. Inverse Probability Weighting to control confounding in an illness-death model for interval-censored data. Stat Med. 37(8):1245-1258, 2018. <doi: 10.1002/sim.7550>.

Examples

```
# import the observed data
# (X=1 corresponds to initial state with a functioning graft, X=2 to acute rejection episode,
# X=3 to return to dialysis, X=4 to death with a functioning graft)

data(dataDIVAT1)

# A subgroup analysis to reduce the time needed for this example

dataDIVAT1$id<-c(1:nrow(dataDIVAT1))
set.seed(2)
d3<-dataDIVAT1[dataDIVAT1$id %in% sample(dataDIVAT1$id, 200, replace = FALSE),]

# import the expected mortality rates

data(fr.ratetable)

# 4-state parametric additive relative survival Markov model including one
# explicative variable ('z') on the transition 1->2. We only reduced
# the precision and the number of iteration to save time in this example,
# prefer the default values.

markov.4states.rsadd(times1=d3$time1, times2=d3$time2, sequences=d3$trajectory,
```

```
dist=c("E","E","E","E","E"),
ini.dist.12=c(8.34), ini.dist.13=c(10.44), ini.dist.14=c(10.70),
ini.dist.23=c(9.43), ini.dist.24=c(11.11),
cov.12=d3$z, init.cov.12=c(0.04), names.12=c("beta12_z"),
p.age=d3$ageR*365.24, p.sex=d3$sexR,
p.year=as.numeric(as.Date(paste0(d3$year.tx,"-01-01"), origin = "1960-01-01")),
p.rate.table=fr.ratetable, conf.int=TRUE,
silent=FALSE, precision=0.001)
```

---

mixture.2states   *Horizontal Mixture Model for Two Competing Events*

Description

The 2-state mixture model which includes an initial state (X=1) and two absorbing states in compe-
tition (X=2 and X=3). Parameters are estimated by (weighted) Likelihood maximization.

Usage

```
mixture.2states(times, sequences, weights=NULL, dist, cuts.12=NULL, cuts.13=NULL,
 ini.dist.12=NULL, ini.dist.13=NULL, cov.12=NULL, init.cov.12=NULL,
 names.12=NULL, cov.13=NULL, init.cov.13=NULL, names.13=NULL,
 cov.p=NULL, init.cov.p=NULL, names.p=NULL, init.intercept.p=NULL,
 conf.int=TRUE, silent=TRUE, precision=10^(-6))
```

Arguments

times	A numeric vector with the observed times in days from baseline to the last observation.
sequences	A numeric vector with the sequence of observed states. Three possible values are allowed: 1 (the individual is right-censored in X=1), 12 (the individual transits to X=2) and 13 (the individual transits to X=3).
weights	A numeric vector with the weights for correcting the contribution of each individual. When the vector is completed, the IPW estimator is implemented. Default is NULL which means that no weighting is applied.
dist	A character vector with two arguments describing respectively the distributions of duration time for transitions 1->2 and 1->3. Arguments allowed are "E" for Exponential distribution, "PE" for the piecewise exponential distribution, "W" for Weibull distribution or "WG" for Generalized Weibull distribution. When the user choose "PE", the arguments "cut.XX" have also to be defined.
cuts.12	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.

cuts.13	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
ini.dist.12	A numeric vector of initial values for the distribution from X=1 to X=2. The logarithm of the parameters have to be declared. Default value is 1.
ini.dist.13	A numeric vector of initial values for the distribution from X=1 to X=3. The logarithm of the parameters have to be declared. Default value is 1.
cov.12	A matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=2.
init.cov.12	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.12. Default initial value is 0.
names.12	An optional character vector with name of explicative variables associated to cov.12.
cov.13	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=3.
init.cov.13	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.13. Default initial value is 0.
names.13	An optional character vector with name of explicative variables associated to cov.13.
cov.p	A matrix (or data frame) with the explicative time-fixed variable(s) related to the probability P(X=2), which is regressing according to a logistic function.
init.cov.p	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.p. Default initial value is 0.
names.p	An optional character vector with name of explicative variables associated to cov.p.
init.intercept.p	
	A numeric value to iniate the intercept of the logit of P(X=2). Default value is 0.
conf.int	A logical value specifying if the pointwise confidence intervals for parameters and the variance-covariance matrix should be returned. Default is TRUE.
silent	A logical value specifying if the log-likelihood value should be returned at each iteration. Default is TRUE, which corresponds to silent mode (no display).
precision	A numeric positive value indicating the required precision for the log-likelihood maximization between each iteration. Default is 10^{-6}.

Details

Hazard functions available are:

$$
\begin{array}{ll}
\text{Exponential distribution} & \lambda(t) = 1/\sigma \\
\text{Weibull distribution} & \lambda(t) = \nu(\tfrac{1}{\sigma})^{\nu} t^{\nu-1} \\
\text{Generalized Weibull distribution} & \lambda(t) = \tfrac{1}{\theta}\left(1 + \left(\tfrac{t}{\sigma}\right)^{\nu}\right)^{\frac{1}{\theta}-1} \nu\left(\tfrac{1}{\sigma}\right)^{\nu} t^{\nu-1}
\end{array}
$$

with σ, ν,and $\theta > 0$. The parameter σ varies for each interval when the distribution is piecewise Exponential. We advise to initialize the logarithm of these parameters in `ini.dist.12`, `ini.dist.13` and `ini.dist.23`.

To estimate the marginal effect of a binary exposure, the `weights` may be equal to `1/p`, where `p` is the estimated probability that the individual belongs to his or her own observed group of exposure. The probabilities `p` are often estimated by a logistic regression in which the dependent binary variable is the exposure. The possible confounding factors are the explanatory variables of this logistic model.

Value

`object`	The character string indicating the estimated model: "mixture.2states (mixture model with two competing events)".
`dist`	A character vector with two arguments describing respectively the distributions of duration time for transitions 1->2 and 1->3.
`cuts.12`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2.
`cuts.13`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3.
`covariates`	A numeric vector indicating the numbers of covariates respectively related to the time to the event X=2, the time to the event X=3, the long-term probability P(X=2).
`table`	A data frame containing the estimated parameters of the model (`Estimate`). When the option `conf.int=TRUE` is specified, this data frame includes three additional columns: the Standard Errors of parameters (`Std.Error`), the value of the Wald statistic (`t.value`), and the p-value for the Wald test (`Pr(>|t|)`).
`cov.matrix`	A data frame corresponding to variance-covariance matrix of the parameters.
`LogLik`	A numeric value corresponding to the (weighted) log-likelihood of the model.
`AIC`	A numeric value corresponding to the Akaike Information Criterion of the model.

Author(s)

Yohann Foucher <Yohann.Foucher@univ-poitiers.fr>

References

Trebern-Launay et al. Horizontal mixture model for competing risks: a method used in waitlisted renal transplant candidates. European Journal of Epidemiology. 33(3):275-286, 2018. <doi: 10.1007/s10654-017-0322-3>.

Examples

```
# import the observed data
# X=1 corresponds to initial state with a functioning graft,
# X=2 to acute rejection episode (transient state),
# X=3 to return to dialysis, X=4 to death with a functioning graft
```

```
data(dataDIVAT1)

# A subgroup analysis to reduce the time needed for this example

dataDIVAT1$id<-c(1:nrow(dataDIVAT1))
set.seed(2)
d2<-dataDIVAT1[dataDIVAT1$id %in% sample(dataDIVAT1$id, 300, replace = FALSE),]

# Data-management: two competing events
# the patient death is now X=2
# the return in dialysis is now X=3

d2$time<-NA
d2$time[d2$trajectory==1]<-d2$time1[d2$trajectory==1]

d2$time[d2$trajectory==12]<-d2$time2[d2$trajectory==12]
d2$trajectory[d2$trajectory==12]<-1

d2$time[d2$trajectory==13]<-d2$time1[d2$trajectory==13]

d2$time[d2$trajectory==123]<-d2$time2[d2$trajectory==123]
d2$trajectory[d2$trajectory==123]<-13

d2$time[d2$trajectory==14]<-d2$time1[d2$trajectory==14]

d2$time[d2$trajectory==124]<-d2$time2[d2$trajectory==124]
d2$trajectory[d2$trajectory==124]<-14

d2$trajectory[d2$trajectory==14]<-12

table(d2$trajectory)

# Univariable horizontal mixture model one binary explicative variable
# z is 1 if delayed graft function and 0 otherwise

mm2.test <- mixture.2states(times=d2$time, sequences=d2$trajectory, weights=NULL,
  dist=c("E","W"), cuts.12=NULL, cuts.13=NULL,
  ini.dist.12=c(9.28), ini.dist.13=c(9.92, -0.23),
  cov.12=d2$z, init.cov.12=0.84, names.12="beta_12",
  cov.13=d2$z, init.cov.13=0.76, names.13="beta_13",
  cov.p=NULL, init.cov.p=NULL, names.p=NULL, init.intercept.p=-0.75,
  conf.int=TRUE, silent=FALSE)

mm2.test$table
```

---

plot.rocrisca   *Plot Method for 'rocrisca' Objects*

Description

A plot of ROC curves is produced. In the RISCA package, it concerns the functions `roc.binary`, `roc.net`, `roc.summary`, and `roc.time`.

Usage

```
## S3 method for class 'rocrisca'
plot(x, ..., information=TRUE)
```

Arguments

x	An object of class rocrisca, returned by the functions roc.binary, roc.net, roc.summary, and roc.time.
...	Additional arguments affecting the plot.
information	A logical value indicating whether the non-information line is plotted. The default values is TRUE.

Author(s)

Yohann Foucher <Yohann.Foucher@univ-poitiers.fr>

Examples

```
# import and attach the data example

data(dataDIVAT3)

# A subgroup analysis to reduce the time needed for this exemple

dataDIVAT3 <- dataDIVAT3[1:400,]

# The ROC curve to evaluate the crude capacities of the recipient age for the
# prognosis of post kidney transplant mortality (we ignore the censoring process)

roc1 <- roc.binary(status="death", variable="ageR", confounders=~1,
data=dataDIVAT3, precision=seq(0.1,0.9, by=0.1) )

# The corresponding ROC graph with color and symbols

plot(roc1, type="b", xlab="1-specificity", ylab="sensibility", col=2, pch=2)
```

---

plot.survrisca	*Plot Method for 'survrisca' Objects*

Description

A plot of survival curves is produced. In the RISCA package, it concerns the functions `ipw.survival` and `gc.survival`.

Usage

```
## S3 method for class 'survrisca'
plot(x, ..., col=1, lty=1, lwd=1, type="s", max.time=NULL,
min.y=0, max.y=1, grid.lty=NULL)
```

Arguments

x	An object of class survrisca, returned by the functions ipw.survival gc.survival.
...	Additional arguments affecting the plot.
col	A numeric vector with the color of the survival curves. The default is 1 for black.
lty	A numeric vector with the type of the survival curves. The default is 1.
lwd	A numeric vector with the type of the survival curves. The default is 1.
type	A character string giving the type of plot : "p" for points, "l" for lines, "b" for both points and lines, "c" for empty points joined by lines, "o" for overplotted points and lines. The default is "s" for step function.
max.time	The maximum time of the x-asis. The default is NULL, it corresponds to the maximum follow-up time observed in the database from which the survrisca object was estimated.
min.y	The minimum of the y-axis. The default is 0.
max.y	The maximum of the y-axis. The default is 1.
grid.lty	A character or (integer) numeric with the line type of the grid lines. The default is NULL for no grid.

Author(s)

Yohann Foucher <Yohann.Foucher@univ-poitiers.fr>

Florent Le Borgne <fleborgne@idbc.fr>

Examples

```
data(dataDIVAT2)

res.km <- ipw.survival(times=dataDIVAT2$times, failures=dataDIVAT2$failures,
  variable=dataDIVAT2$ecd, weights=NULL)

plot(res.km, ylab="Graft and patient survival",
 xlab="Time post-transplantation (years)", col=c(1,2), grid.lty=1)
```

---

port   *POsitivity-Regression Tree (PoRT) Algorithm to Identify Positivity Vi-olations.*

Description

This function allows to identify potential posivity violations by using the PoRT algorithm.

Usage

```
port(group, cov.quanti, cov.quali, data, alpha, beta, gamma, pruning,
  minbucket, minsplit, maxdepth)
```

Arguments

group	A character string with the name of the exposure in `data`: 0 for the untreated/unexposed patients and 1 for the treated/exposed patients.
cov.quanti	A character string with the names of the quantitative predictors in `data`.
cov.quali	A character string with the names of the qualitative predictors in `data`.
data	A data frame in which to look for the variables related to the treatment/exposure and the predictors.
alpha	The minimal proportion of the whole sample size to consider a problematic sub-group. The default value is 0.05.
beta	The exposed or unexposed proportion under which one can consider a positivity violation. The default value is 0.05.
gamma	The maximum number of predictors used to define the subgroup. The default value is 2. See 'Details'.
pruning	If `TRUE`, provide only the violations contained between two values for quantitative predictors. The default value is `FALSE`.
minbucket	An `rpart` parameter: minimum number of observations in any leaf. The default value is 6.
minsplit	An `rpart` parameter: minimum number of observations that must exist in a node in order for a split to be attempted. If only one of `minbucket` or `minsplit` is specified, the code either sets `minsplit` to `minbucket*3` or `minbucket` to `minsplit/3`, as appropriate. The default value is 20.
maxdepth	An `rpart` parameter. Set the maximum depth of any node of the final tree, with the root node counted as depth 0. Values greater than 30 rpart will give nonsense results on 32-bit machines. The default value is 30.

Details

In a first step, the PoRT algorithm estimates one tree for each predictor and memorises the leaves corresponding to problematic subgroups according to the hyperparameters `alpha` and `beta` (i.e., the subgroup must at least include `alpha*100` percent of the whole sample, and the exposure prevalence

in the subgroup must be superior to 1-beta or inferior to beta). If gamma=1, the algorithm stops. Otherwise, if at least one problematic subgroup is identified in this first step, the corresponding predictor(s) is(are) not considered in the second step, which estimates one tree for all possible couples of remaining predictors and memorizes the leaves corresponding to problematic subgroups. If gamma=2, the algorithm stops; otherwise, the third step consists of building one tree for all possible trios of remaining covariates not involved in the previously identified subgroups, etc.

Value

The port function returns a characters string summarising all the subgroups identified as violating the positivity assumption, and provides for each of these subgroups the exposure prevalence, the subgroup size and the relative subgroup size (with respect to the sample size).

Author(s)

Arthur Chatton <Arthur.Chatton@univ-nantes.fr>

References

Danelian et al. Identification of positivity violations' using regression trees: The PoRT algorithm. Manuscript submitted. 2022.

Examples

```
data("dataDIVAT2")

# PoRT with default hyperparameters
port(group="ecd", cov.quanti="age", cov.quali=c("hla", "retransplant"),
data=dataDIVAT2)

# Illustration of the 'pruning' argument
port(group="ecd", cov.quanti="age", cov.quali=c("hla", "retransplant"),
    data=dataDIVAT2, beta=0.01)

port(group="ecd", cov.quanti="age", cov.quali=c("hla", "retransplant"),
    data=dataDIVAT2, beta=0.01, pruning=TRUE)
```

---

pred.mixture.2states   *Cumulative Incidence Function Form Horizontal Mixture Model With Two Competing Events*

Description

This function allows to estimate a cumulative incidence function (CIF) from an horizontal mixture model with two competing events, i.e. the results obtained from the function mixture.2states.

Usage

```
pred.mixture.2states(model, failure, times, cov.12=NULL, cov.13=NULL, cov.p=NULL)
```

Arguments

`model`	A list obtained by using the function `mixture.2states`.
`failure`	A numeric value for identifying the event for which the CIF has to be computed. Two possible values are allowed: 2 (for the CIF related to X=2) and 3 (for the CIF related to X=3).
`times`	A numeric vector with positive values related to the times for which the CIF has to be computed.
`cov.12`	A vector, matrix or data frame in which to look for variables related to the time from X=1 to X=2 with which to predict the CIF.
`cov.13`	A vector, matrix or data frame in which to look for variables related to the time from X=1 to X=3 with which to predict the CIF.
`cov.p`	A vector, matrix or data frame in which to look for variables related to the probability P(X=2).

Details

The covariates has to be identical than the ones included in the mixture model declared in the argument `model`. More precisely, the columns of `cov.12`, `cov.13` and `cov.p` must correspond to the same variables.

Value

`times`	A numeric vector with the times for which the CIF has to be computed.
`cif`	A matrix with the predicted CIF for the `times` in columns and the individuals in rows.

Author(s)

Yohann Foucher <Yohann.Foucher@univ-poitiers.fr>

References

Trebern-Launay et al. Horizontal mixture model for competing risks: a method used in wait-listed renal transplant candidates. European Journal of Epidemiology. 33(3):275-286, 2018. <doi: 10.1007/s10654-017-0322-3>.

Examples

```
# import the observed data
# X=1 corresponds to initial state with a functioning graft,
# X=2 to acute rejection episode (transient state),
# X=3 to return to dialysis, X=4 to death with a functioning graft

data(dataDIVAT1)

# A subgroup analysis to reduce the time needed for this example

dataDIVAT1$id<-c(1:nrow(dataDIVAT1))
```

```
set.seed(2)
d2<-dataDIVAT1[dataDIVAT1$id %in% sample(dataDIVAT1$id, 300, replace = FALSE),]

# Data-management: two competing events
# the patient death is now X=2
# the return in dialysis is now X=3

d2$time<-NA
d2$time[d2$trajectory==1]<-d2$time1[d2$trajectory==1]

d2$time[d2$trajectory==12]<-d2$time2[d2$trajectory==12]
d2$trajectory[d2$trajectory==12]<-1

d2$time[d2$trajectory==13]<-d2$time1[d2$trajectory==13]

d2$time[d2$trajectory==123]<-d2$time2[d2$trajectory==123]
d2$trajectory[d2$trajectory==123]<-13

d2$time[d2$trajectory==14]<-d2$time1[d2$trajectory==14]

d2$time[d2$trajectory==124]<-d2$time2[d2$trajectory==124]
d2$trajectory[d2$trajectory==124]<-14

d2$trajectory[d2$trajectory==14]<-12

table(d2$trajectory)

# Univariable horizontal mixture model one binary explicative variable
# z is 1 if delayed graft function and 0 otherwise

mm2.model <- mixture.2states(times=d2$time, sequences=d2$trajectory,
  weights=NULL, dist=c("E","W"), cuts.12=NULL, cuts.13=NULL,
  ini.dist.12=c(9.28), ini.dist.13=c(9.92, -0.23),
  cov.12=d2$z, init.cov.12=0.84, names.12="beta_12",
  cov.13=d2$z, init.cov.13=0.76, names.13="beta_13",
  cov.p=NULL, init.cov.p=NULL, names.p=NULL, init.intercept.p=-0.75,
  conf.int=TRUE, silent=FALSE)

cif2.mm2 <- pred.mixture.2states(mm2.model, failure=2, times=seq(0, 4000, by=30),
 cov.12=c(0,1), cov.13=c(0,1), cov.p=NULL)

plot(cif2.mm2$times/365.25, cif2.mm2$cif[1,], col = 1, type="l", lty = 1,
 ylim=c(0,1), lwd =2, ylab="Cumulative Incidence Function",
 xlab="Times (years)", main="", xlim=c(0, 11), legend=FALSE)

lines(cif2.mm2$times/365.25, cif2.mm2$cif[2,], lwd=2, col=2)
```

---

rmst   *Restricted Mean Survival Times.*

Description

This function allows to estimate the Restricted Mean Survival Times (RMST).

Usage

```
rmst(times, surv.rates, max.time, type)
```

Arguments

times	A numeric vector with the times.
surv.rates	A numeric vector with the survival rates.
max.time	The maximum follow-up time.
type	The type of input survival cirves. Two possible arguments: "s" for a step function or "l" for a continous function.

Details

RMST represents an interesting alternative to the hazard ratio in order to estimate the effect of an exposure. The RMST is the mean survival time in the population followed up to max.time. It corresponds to the area under the survival curve up to max.time.

References

Royston and Parmar. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. BMC Medical Research Methodology 2013;13:152. <doi: 10.1186/ 1471-2288-13-152>.

Examples

```
data(dataDIVAT2)

#Survival according to the donor status (ECD versus SCD)
res <- summary(survfit(Surv(times,failures) ~ ecd, data=dataDIVAT2))

#The mean survival time in ECD recipients followed-up to 10 years
rmst(times = res$time[as.character(res$strata)=="ecd=1"],
 surv.rates = res$surv[as.character(res$strata)=="ecd=1"],
 max.time = 10, type = "s")

#The mean survival time in SCD recipients followed-up to 10 years
rmst(times=res$time[as.character(res$strata)=="ecd=0"],
 surv.rates=res$surv[as.character(res$strata)=="ecd=0"],
 max.time=10, type = "s")
```

---

roc.binary   *ROC Curves For Binary Outcomes.*

Description

This function allows for the estimation of ROC curve by taking into account possible confounding factors. Two methods are implemented: i) the standardized and weighted ROC based on an IPW estimator, and ii) the placement values ROC.

Usage

```
roc.binary(status, variable, confounders,  data, precision, estimator)
```

Arguments

status   A character string with the name of the variable in data which represents the disease status indicator (for instance: 0=healthy, 1=diseased).

variable   A character string with the name of the variable in data which represents the diagnostic/prognostic variable under interest. For the standardized and weighted ROC method, the variable must be previously standardized according to the covariates among the controls as proposed by Le Borgne et al. (2017).

confounders   An object of class "formula". More precisely only the right part with an expression of the form ~ model, where model is the linear predictor of the logistic regressions performed for each cut-off value. The user can use ~1 to obtain the crude estimation.

data   An object of the class data.frame containing the variables previously detailed.

precision   A numeric vector with values between 0 and 1. The values represent the x-axis (1-specificity) of the ROC graph for which the user want to obtain the corresponding sensitivities. 0 and 1 are not allowed.

estimator   Two possible estimators can be used: "ipw" and "pv". IPW is based on the Inverse Probability Weigthing theory as proposed by Le Borgne et al. (2017). This estimator applied on a variable standardized according to the covariates among the controls allows to obtain a standardized and weighted ROC. The IPW estimator is selected by default. The user can also use the placement values (pv) estimator as proposed by Pepe and Cai (Biometrics, 2004).

Details

This function computes confounder-adjusted ROC curve for uncensored data. We adapted the usual estimator by considering the individual probabilities to be diseased, given the possible confounding factors. The standardized and weighted ROC is obtained by both providing a variable under interest standardized according to the possible confounding factors and using "ipw" in the option estimator. The user can also use the estimator first proposed by Pepe and Cai (2004) which is based on placement values.

Value

table	This data frame presents the sensitivities and specificities. J represents the Youden index.
auc	The area under the ROC curve.

Author(s)

Y. Foucher <Yohann.Foucher@univ-poitiers.fr>

References

Blanche et al. (2013) Review and comparison of roc curve estimators for a time-dependent outcome with marker-dependent censoring. Biometrical Journal, 55, 687-704. <doi:10.1002/bimj.201200045>

Pepe and Cai. (2004) The analysis of placement values for evaluating discriminatory measures. Biometrics, 60(2), 528-35. <doi:10.1111/j.0006-341X.2004.00200.x>

Le Borgne et al. Standardized and weighted time-dependent ROC curves to evaluate the intrinsic prognostic capacities of a marker by taking into account confounding factors. Stat Methods Med Res. 27(11):3397-3410, 2018. <doi: 10.1177/ 0962280217702416>.

Examples

```
# import and attach the data example

data(dataDIVAT3)

# A subgroup analysis to reduce the time needed for this exemple

dataDIVAT3 <- dataDIVAT3[1:400,]

# The ROC curve to evaluate the crude capacities of the recipient age for the
# prognosis of post kidney transplant mortality (we ignore the censoring process)

roc1 <- roc.binary(status="death", variable="ageR", confounders=~1,
data=dataDIVAT3, precision=seq(0.1,0.9, by=0.1) )

# The corresponding ROC graph with basic options

plot(roc1, xlab="1-specificity", ylab="sensibility")

# The corresponding ROC graph with color and symbols

plot(roc1, col=2, pch=2, type="b", xlab="1-specificity", ylab="sensibility")

# The standardized and weighted ROC curve to evaluate the capacities
# of the recipient age for the prognosis of post kidney transplant
# mortality by taking into account the donor age and the recipient
# gender (we ignore the censoring process).

# 1. Standardize the marker according to the covariates among the controls
lm1 <- lm(ageR ~ ageD + sexeR, data=dataDIVAT3[dataDIVAT3$death == 0,])
```

```
dataDIVAT3$ageR_std <- (dataDIVAT3$ageR - (lm1$coef[1] + lm1$coef[2] *
 dataDIVAT3$ageD + lm1$coef[3] * dataDIVAT3$sexeR)) / sd(lm1$residuals)

# 2. Compute the sensitivity and specificity from the proposed IPW estimators
roc2 <- roc.binary(status="death", variable="ageR_std",
 confounders=~bs(ageD, df=3) + sexeR, data=dataDIVAT3, precision=seq(0.1,0.9, by=0.1))

# The corresponding ROC graph

plot(roc2, col=2, pch=2, lty=2, type="b", xlab="1-specificity", ylab="sensibility")

lines(roc1, col=1, pch=1, type="b")

legend("bottomright", lty=1:2, lwd=1, pch=1:2, col=1:2,
 c(paste("Crude estimation, (AUC=", round(roc1$auc, 2), ")", sep=""),
 paste("Adjusted estimation, (AUC=", round(roc2$auc, 2), ")", sep="") ) )
```

---

roc.net   *Net Time-Dependent ROC Curves With Right Censored Data.*

Description

This function performs the characteristics of a net time-dependent ROC curve (Lorent, 2013) based
on k-nearest neighbor's (knn) estimator or only based on the Pohar-Perme estimator (Pohar, 2012).

Usage

```
roc.net(times, failures, variable, p.age, p.sex, p.year,
 rate.table, pro.time, cut.off, knn=FALSE, prop=NULL)
```

Arguments

times	A numeric vector with the follow up times.
failures	A numeric vector with the event indicator (0=right censored, 1=event).
variable	A numeric vector with the prognostic variable. This variable is collected at the baseline.
p.age	A numeric vector with the age of the individuals at the baseline (in days).
p.sex	A character vector with the gender the individuals ('male' or 'female').
p.year	A numeric vector with the calendar year at the baseline (number of days from the January 1, 1960).
rate.table	A rate-table object with the expected mortality rates by age, sex, and cohort year. The same units used in p.age, p.sex, p.year
pro.time	The value of prognostic time represents the maximum delay for which the capacity of the variable is evaluated. The same unit than the one used in the argument time.
cut.off	The cut-off values of the variable used to define the possible binary tests.

knn	A logical value indicating whether k-nearest neighbor's estimator should be used.
prop	This is the proportion of the nearest neighbors. The estimation will be based on 2*prop (both right and left proportions) of the total sample size.

Details

This function computes net time-dependent ROC curve with right-censored data using estimator defined by Pohar-Perm et al. (2012) and the k-nearest neighbor's (knn) estimator. The aim is to evaluate the capacity of a variable (measured at the baseline) to predict the excess of mortality of a studied population compared to the general population mortality. Using the knn estimator ensures a monotone and increasing ROC curve, but the computation time may be long. This approach may thus be avoided if the sample size is large because of computing time.

Value

table	This data frame presents the sensitivities and specificities associated with the cut-off values. One can observe NA if the value cannot be computed. J represents the Youden index.
auc	The area under the time-dependent ROC curve for a prognostic up to prognostic time.
missing	Number of deleted observations due to missing data.
warning	This message indicates possible difficulties in the computation of the net ROC curve, for instance if the net survival was not lower or equal1 to 1 for particular cut-off values or times.

Author(s)

Y. Foucher <Yohann.Foucher@univ-poitiers.fr>

References

Lorent et al. Net time-dependent ROC curves: a solution for evaluating the accuracy of a marker to predict disease-related mortality. Statistics in Medicine, 33, 2379-89. 2013. <doi:10.1002/sim.6079>

Examples

```
# import the observed data

data(dataDIVAT3)

# A subgroup analysis to reduce the time needed for this example

dataDIVAT3 <- dataDIVAT3[1:400,]

# import the expected mortality rates

data(fr.ratetable)
```

```
# the values of recipient age used for computing the sensibilities and
# specificities (choose more values in practice)

age.cut <- quantile(dataDIVAT3$ageR, probs=seq(0.1, 0.9, by=0.1))

# recoding of the variables for matching with the ratetable

dataDIVAT3$sex <- "male"
dataDIVAT3$sex[dataDIVAT3$sexeR==0] <- "female"
dataDIVAT3$year <- as.numeric(as.Date(paste0(dataDIVAT3$year.tx, "-01-01")) - as.Date("1960-01-01"))
dataDIVAT3$age <- dataDIVAT3$ageR*365

# the ROC curve (without correction by the knn estimator) to
# reduce the time for computing this example. In practice, the
# correction should by used in case of non-montone results.

roc1 <- roc.net(times=dataDIVAT3$death.time,
 failures=dataDIVAT3$death,  variable=dataDIVAT3$ageR,
 p.age=dataDIVAT3$age, p.sex=dataDIVAT3$sex, p.year=dataDIVAT3$year,
 rate.table=fr.ratetable, pro.time=3000, cut.off=age.cut, knn=FALSE)

# the sensibilities and specificities associated with the cut off values

roc1$table

# the traditional ROC graph

plot(roc1, col=2, pch=2, lty=2, type="b", xlab="1-specificity", ylab="sensibility")

legend("bottomright", paste("Without knn, (AUC=",
 round(roc1$auc, 2), ")", sep=""),lty=1, lwd=2, col=2)
```

---

roc.prognostic.aggregate

Prognostic ROC Curve Based on Survival Probabilities

Description

Prognostic ROC curve is an alternative graphical approach to represent the discriminative capacity of the marker: a receiver operating characteristic (ROC) curve by plotting 1 minus the survival in the high-risk group against 1 minus the survival in the low-risk group. The area under the curve (AUC) corresponds to the probability that a patient in the low-risk group has a longer lifetime than a patient in the high-risk group. The prognostic ROC curve provides complementary information compared to survival curves. The AUC is assessed by using the trapezoidal rules. When survival curves do not reach 0, the prognostic ROC curve is incomplete and the extrapolations of the AUC are performed by assuming pessimist, optimist and non-informative situations. The user enters the survival according to the model she/he chooses. The area under the prognostic ROC curve is assessed by using the trapezoidal rules. The extrapolated areas (when survival curves do not reach 0) are performed by assuming pessimist, optimist and non-informative situation.

Usage

```
roc.prognostic.aggregate(time.lr, surv.lr, time.hr, surv.hr)
```

Arguments

`time.lr`	A numeric vector with the survival times in the low risk group.
`surv.lr`	A numeric vector with the survival probabilities corresponding to `time.lr`
`time.hr`	A numeric vector with the survival times in the high risk group.
`surv.hr`	A numeric vector with the survival probabilities corresponding to `time.hr`.

Details

The maximum prognostic time is the minimum between the maximum of `time.lr` and the maximum of `time.hr`.

Value

`max.time`	This is the maximum prognostic time used for the analysis
`table`	This data frame presents the different time cut-offs associated with the coordinates of the ROC curves.
`auc`	This data frame presents the different estimations of the area under the prognostic ROC curve: the lower bound, the pessimist, the non-informative, the optimist and the upper bound.

Author(s)

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References

Combescure C, Perneger TV, Weber DC, Daures JP and Foucher Y. Prognostic ROC curves: a method for representing the overall discriminative capacity of binary markers with right-censored time-to-event endpoints. Epidemiology 2014 Jan;25(1):103-9. <doi: 10.1097/EDE.0000000000000004>.

Examples

```
# example of two survival curves using exponential distributions
time.hr <- seq(0, 600, by=5)
time.lr <- seq(0, 500, by=2)
surv.hr <- exp(-0.005*time.hr)
surv.lr <- exp(-0.003*time.lr)

# Illustration of both survival curves
plot(time.hr, surv.hr, xlab="Time (in days)",
 ylab="Patient survival", lwd=2, type="l")
lines(time.lr, surv.lr, lty=2, col=2, lwd=2)
legend("topright", c("High-Risk Group", "Low-Risk Group"), lwd=2,
```

```
 col=1:2, lty=1:2)

# Computation of the prognostic ROC curve
proc.result <- roc.prognostic.aggregate(time.lr, surv.lr, time.hr, surv.hr)

# Representation of the prognostic ROC curve
plot(proc.result$table$x, proc.result$table$y, type="l",
 lwd=2, xlim=c(0,1), ylim=c(0,1),
 xlab="1-Survival in the low risk group",
 ylab="1-Survival in the high risk group")
abline(c(0,0), c(1,1), lty=2)

# The pessimist value of the area under the curve
proc.result$auc$pessimist
```

---

roc.prognostic.individual

Prognostic ROC Curve based on Individual Data

Description

The user enters individual survival data. The area under the prognostic ROC curve is assessed by using the trapezoidal rules. The extrapolated areas (when survival curves do not reach 0) are performed by assuming pessimist, optimist and non-informative situation. The confidence intervals are obtained by non-parametric bootstrapping.

Usage

```
roc.prognostic.individual(times, failures, variable, iterations)
```

Arguments

times	A numeric vector with the follow up times.
failures	A numeric vector with the event indicator (0=right censored, 1=event).
variable	A numeric vector with the result of the binary test (only two groups). The variable equals 1 for the high risk group and 0 for the low risk group.
iterations	The number of bootstrap samples to compute the confidence intervals. The default value is 0, which corresponds to no confidence interval computation.

Details

The maximum prognostic time is the minimum between the two last observed times of failure in both groups. Prognostic ROC curve is an alternative graphical approach to represent the discriminative capacity of the marker: a receiver operating characteristic (ROC) curve by plotting 1 minus the survival in the high-risk group against 1 minus the survival in the low-risk group. The area under the curve (AUC) corresponds to the probability that a patient in the low-risk group has a longer lifetime than a patient in the high-risk group. The prognostic ROC curve provides complementary information compared to survival curves. The AUC is assessed by using the trapezoidal rules. When

survival curves do not reach 0, the prognostic ROC curve is incomplete and the extrapolations of the AUC are performed by assuming pessimist, optimist and non-informative situations.

Value

`max.time`	This is the maximum prognostic time used for the analysis
`table`	This data frame presents the different time cut-offs associated with the coordinates of the ROC curves.
`auc`	This data frame presents the different estimations of the area under the prognostic ROC curve: the lower bound, the pessimist, the non-informative, the optimist and the upper bound.
`CI.95`	This data frame presents the 95 percentage confidence intervals of the area under the prognostic ROC curve: the lower bound, the pessimist, the non-informative, the optimist and the upper bound.
`auc.boot`	This data frame presents the different estimations of the area under the prognostic ROC curve for each of the B bootstrap samples: the lower bound, the pessimist, the non-informative, the optimist and the upper bound.

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References

Combescure C, Perneger TV, Weber DC, Daures JP and Foucher Y. Prognostic ROC curves: a method for representing the overall discriminative capacity of binary markers with right-censored time-to-event endpoints. Epidemiology 2014 Jan;25(1):103-9. <doi: 10.1097/EDE.0000000000000004>.

Examples

```
######################################################################
# example of two samples with different exponential distributions #
######################################################################

n1 <- 200
n2 <- 200
grp  <- c(rep(1, n1), rep(0, n2))
time.evt <- c(rexp(n1, rate = 1.2), rexp(n2, rate = 0.5))
time.cen <- rexp(n1+n2, rate = 0.2)
time <- pmin(time.evt, time.cen)
evt  <- 1*(time.evt < time.cen)

# Illustration of both survival curves
surv.temp <- survfit(Surv(time, evt) ~ grp)
plot(surv.temp, lty = 2:3)

# Computation of the prognostic ROC curve
proc.result <- roc.prognostic.individual(time, evt, grp, iterations=50)
```

```
   # Use more than 50 bootstrap samples for real applications

# Representation of the prognostic ROC curve
plot(proc.result$table$x, proc.result$table$y, type="l",
 lwd=2, xlim=c(0,1), ylim=c(0,1),
 xlab="1-Survival in the low risk group",
 ylab="1-Survival in the high risk group")
abline(c(0,0), c(1,1), lty=2)

# The corresponding 95% CI of the pessimist value
proc.result$CI.95$pessimist
```

---

roc.summary   *Summary ROC Curve For Aggregated Data.*

Description

This function computes summary ROC curve (Combescure et al., 2016).

Usage

```
roc.summary(study.num, classe, n, year, surv, nrisk, proba, marker.min,
 marker.max, init.nlme1, precision, pro.time, time.cutoff)
```

Arguments

study.num	A numeric vector (1,2,3,...) with the study identification.
classe	A numeric vector with integers (1,2,3,...) for identifying the groups defined using the studied marker. 1 is the first group with the lowest values of the marker.
n	A numeric vector with the number of subjects at the baseline (date of marker collection).
year	A numeric vector with the survival times.
surv	A numeric vector with the survival probabilities corresponding to the previous times (often obtained graphically using the published survival curves).
nrisk	A numeric vector with the number of subjects at-risk of the event at the corresponding year.
proba	This numeric vector represents the proportion of the patients in a center which belong to the corresponding group.
marker.min	A numeric vector with the minimum values of the marker interval corresponding to the previous class.
marker.max	A numeric vector with the maximum values of the marker interval corresponding to the previous class.
init.nlme1	A numeric vector with the initiate values (mean, sd) of the maker distribution which is assumed to be Gaussian. Default is (0,1).

precision	A numeric vector with the initiate values (mean, sd) of the maker distribution which is assumed to be Gaussian. Default is 10^{-6}.
pro.time	The value of prognostic time is the maximum delay for which the capacity of the variable is evaluated. The same unit than the one used in the argument time.
time.cutoff	The value of internal threasholds for the definition of the piecewise hazard function (3 values for a 4-piece constant function and 4 values for a 5-piece constant function).

Details

This function computes summary ROC curve. The hazard function associated with the time-to-event was defined as a 4-piece or a 5-piece constant function with a specific association with the marker at each interval. The maker distribution is assumed to be Gaussian distributed.

Value

nlme1	An object of class nlme representing the nonlinear mixed-effects model of the marker distribution. The marker is assumed Gaussian distributed. mu and sigma represent the mean and the standard deviation. The inter-study variability is modeled with a random effect on the mean. See nlmeObject for the components of the fit.
nlme2	An object of class nlme representing the nonlinear mixed-effects model of the time distribution. The hazard function is a stepwise function with 5 intervals. exp(beta0.1) and exp(beta0.2) represent the baseline hazard and the hazard ratio in the first interval. exp(beta1.1) and exp(beta1.2) represent the corrections of these parameters for the second interval... The inter-study variability is modeled with a random effect on the baseline parameter beta0.1. See nlmeObject for the components of the fit.
table	This data frame presents the sensitivities (se) and specificities (sp) associated with the cut-off values (cut.off). J represents the Youden index.
auc	The area under the SROC curve for a prognostic up to prognostic time.

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References

Combescure et al. A literature-based approach to evaluate the predictive capacity of a marker using time-dependent Summary Receiver Operating Characteristics. Stat Methods Med Res, 25(2):674-85, 2016. <doi: 10.1177/ 0962280212464542>.

Examples

```
# The example is too long to compute for a submission on the CRAN
# Remove the characters '#'
```

```
### import and attach the data example
# data(dataKi67)

### Compute the SROC curve for a prognostic up to 9 years
# roc9y<-roc.summary(dataKi67$study.num, dataKi67$classe, dataKi67$n,
# dataKi67$year, dataKi67$surv, dataKi67$nrisk, dataKi67$proba,
# dataKi67$log.marker.min, dataKi67$log.marker.max,
# init.nlme1=c(2.55, -0.29), precision=50, pro.time=9,
# time.cutoff=c(2, 4, 8))

### The ROC graph associated to these to SROC curves
# plot(roc9y, col=1, lty=1, lwd=2, type="l", xlab="1-specificity", ylab="sensibility")

### Check of the goodness-of-fit: the observed proportions of
### patients in the $g$th interval of the study $k$ versus the
### fitted proportions (equation 3).

# plot(roc9y$data.marker$proba, roc9y$data.marker$fitted,
# xlab="Observed probabilities", ylab="Fitted probabilities",
# ylim=c(0,1), xlim=c(0,1))
# abline(0,1)

### Check of the goodness-of-fit: the observed bivariate
### probabilities versus the fitted bivariate
### probabilities (equation 4).

# plot(roc9y$data.surv$p.joint, roc9y$data.surv$fitted,
# xlab="Observed probabilities", ylab="Fitted probabilities",
# ylim=c(0,1), xlim=c(0,1))
# abline(0,1)

### Check of the goodness-of-fit: the residuals of the bivariate
### probabilities (equation 4) versus the times.

# plot(roc9y$data.surv$year, roc9y$data.surv$resid,
# xlab="Survival time (years)", ylab="Residuals")
# lines(lowess(roc9y$data.surv$year,
# I(roc9y$data.surv$resid), iter=0))
```

---

roc.time   *Time-Dependent ROC Curves With Right Censored Data.*

Description

This function allows for the estimation of time-dependent ROC curve by taking into account possible confounding factors. This method is implemented by standardizing and weighting based on an IPW estimator.

Usage

```
roc.time(times, failures, variable, confounders, data,
 pro.time, precision)
```

Arguments

times	A character string with the name of the variable in data which represents the follow up times.
failures	A character string with the name of the variable in data which represents the event indicator (0=right censored, 1=event).
variable	A character string with the name of the variable in data which represents the prognostic variable under interest. This variable is collected at the baseline. The variable must be previously standardized according to the covariates among the controls as proposed by Le Borgne et al. (2017).
confounders	An object of class "formula". More precisely only the right part with an expression of the form ~ model, where model is the linear predictor of the logistic regressions performed for each cut-off value. The user can use ~1 to obtain the crude estimation.
data	An object of the class data.frame containing the variables previously detailed.
pro.time	The value of prognostic time represents the maximum delay for which the capacity of the variable is evaluated. The same unit than the one used in the argument times.
precision	The quintiles (between 0 and 1) of the prognostic variable used for computing each point of the time dependent ROC curve. 0 (min) and 1 (max) are not allowed.

Details

This function computes confounder-adjusted time-dependent ROC curve with right-censored data. We adapted the naive IPCW estimator as explained by Blanche, Dartigues and Jacqmin-Gadda (2013) by considering the probability of experiencing the event of interest before the fixed prognostic time, given the possible confounding factors.

Value

table	This data frame presents the sensitivities and specificities associated with the cut-off values. J represents the Youden index.
auc	The area under the time-dependent ROC curve for a prognostic up to pro.time.

Author(s)

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References

Blanche et al. (2013) Review and comparison of roc curve estimators for a time-dependent outcome with marker-dependent censoring. Biometrical Journal, 55, 687-704. <doi:10.1002/ bimj.201200045>

Le Borgne et al. Standardized and weighted time-dependent ROC curves to evaluate the intrinsic prognostic capacities of a marker by taking into account confounding factors. Stat Methods Med Res. 27(11):3397-3410, 2018. <doi: 10.1177/ 0962280217702416>.

Examples

```
# import and attach the data example
data(dataDIVAT3)

# A subgroup analysis to reduce the time needed for this exemple

dataDIVAT3 <- dataDIVAT3[1:400,]

# The standardized and weighted time-dependent ROC curve to evaluate the
# capacities of the recipient age for the prognosis of post kidney
# transplant mortality up to 2000 days by taking into account the
# donor age and the recipient gender.

# 1. Standardize the marker according to the covariates among the controls
lm1 <- lm(ageR ~ ageD + sexeR, data=dataDIVAT3[dataDIVAT3$death.time >= 2500,])
dataDIVAT3$ageR_std <- (dataDIVAT3$ageR - (lm1$coef[1] + lm1$coef[2] * dataDIVAT3$ageD +
 lm1$coef[3] * dataDIVAT3$sexeR)) / sd(lm1$residuals)

# 2. Compute the sensitivity and specificity from the proposed IPW estimators
roc2 <- roc.time(times="death.time", failures="death", variable="ageR_std",
confounders=~bs(ageD, df=3) + sexeR, data=dataDIVAT3, pro.time=2000,
precision=seq(0.1,0.9, by=0.2))

# The corresponding ROC graph
plot(roc2, col=2, pch=2, lty=1, type="b", xlab="1-specificity", ylab="sensibility")


# The corresponding AUC
roc2$auc
```

---

semi.markov.3states   *3-State Semi-Markov Model*

Description

The 3-state SM model includes an initial state (X=1), a transient state (X=2) and an absorbing state (X=3). Usually, X=1 corresponds to disease-free or remission, X=2 to relapse, and X=3 to death. In this illness-death model, the possible transitions are: 1->2, 1->3 and 2->3.

Usage

```
semi.markov.3states(times1, times2, sequences, weights=NULL,
dist, cuts.12=NULL, cuts.13=NULL, cuts.23=NULL,
ini.dist.12=NULL, ini.dist.13=NULL, ini.dist.23=NULL,
cov.12=NULL, init.cov.12=NULL, names.12=NULL,
cov.13=NULL, init.cov.13=NULL, names.13=NULL,
cov.23=NULL, init.cov.23=NULL, names.23=NULL,
conf.int=TRUE, silent=TRUE, precision=10^(-6))
```

Arguments

times1
: A numeric vector with the observed times in days from baseline to the first transition (X=2 or X=3) or to the right-censoring (in X=1 at the last follow-up).

times2
: A numeric vector with the observed times in days from baseline to the second transition or to the right censoring (in X=2 at the last follow-up). NA for individuals right-censored in X=1 or individuals who directly transited from X=1 to X=3.

sequences
: A numeric vector with the sequences of observed states. Four possible values are allowed: 1 (individual right-censored in X=1), 12 (individual right-censored in X=2), 13 (individual who directly transited from X=1 to X=3), 123 (individual who transited from X=1 to X=3 through X=2).

weights
: A numeric vector with the weights for correcting the contribution of each individual. When the vector is completed, the IPW estimator is implemented. Default is NULL which means that no weighting is applied.

dist
: A character vector with three arguments describing respectively the distributions of duration time for transitions 1->2, 1->3 and 2->3. Arguments allowed are "E" for Exponential distribution, "PE" for the piecewise exponential distribution, "W" for Weibull distribution or "WG" for Generalized Weibull distribution. When the user choose "PE", the arguments "cut.XX" have also to be defined.

cuts.12
: A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.

cuts.13
: A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.

cuts.23
: A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=3. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.

ini.dist.12
: A numeric vector of initial values for the distribution from X=1 to X=2. The logarithm of the parameters have to be declared. Default value is 1.

ini.dist.13	A numeric vector of initial values for the distribution from X=1 to X=3. The logarithm of the parameters have to be declared. Default value is 1.
ini.dist.23	A numeric vector of initial values for the distribution from X=2 to X=3. The logarithm of the parameters have to be declared. Default value is 1.
cov.12	A matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=2.
init.cov.12	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.12. Default initial value is 0.
names.12	An optional character vector with name of explicative variables associated to cov.12.
cov.13	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=3.
init.cov.13	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.13. Default initial value is 0.
names.13	An optional character vector with name of explicative variables associated to cov.13.
cov.23	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=2 to X=3.
init.cov.23	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.23. Default initial value is 0.
names.23	An optional character vector with name of explicative variables associated to cov.23.
conf.int	A logical value specifying if the pointwise confidence intervals for parameters and the variance-covariance matrix should be returned. Default is TRUE.
silent	A logical value specifying if the log-likelihood value should be returned at each iteration. Default is TRUE, which corresponds to silent mode (no display).
precision	A numeric positive value indicating the required precision for the log-likelihood maximization between each iteration. Default is 10^{-6}.

Details

Hazard functions available are:

$$
\begin{array}{ll}
\text{Exponential distribution} & \lambda(t) = 1/\sigma \\
\text{Weibull distribution} & \lambda(t) = \nu(\frac{1}{\sigma})^{\nu} t^{\nu-1} \\
\text{Generalized Weibull distribution} & \lambda(t) = \frac{1}{\theta}\left(1 + \left(\frac{t}{\sigma}\right)^{\nu}\right)^{\frac{1}{\theta}-1} \nu\left(\frac{1}{\sigma}\right)^{\nu} t^{\nu-1}
\end{array}
$$

with σ, ν, and $\theta > 0$. The parameter σ varies for each interval when the distribution is piecewise Exponential. We advise to initialize the logarithm of these parameters in ini.dist.12, ini.dist.13 and ini.dist.23.

To estimate the marginal effect of a binary exposure, the weights may be equal to 1/p, where p is the estimated probability that the individual belongs to his or her own observed group of exposure. The probabilities p are often estimated by a logistic regression in which the dependent binary variable is the exposure. The possible confounding factors are the explanatory variables of this logistic model.

Value

`object`	The character string indicating the estimated model: "semi.markov.3states (3-state semi-markov model)".
`dist`	A character vector with two arguments describing respectively the distributions of duration time for transitions 1->2, 1->3 and 2->3.
`cuts.12`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2.
`cuts.13`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3.
`cuts.23`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=3.
`covariates`	A numeric vector indicating the numbers of covariates respectively related to the transition 1->2, 1->3 and 2->3.
`table`	A data frame containing the estimated parameters of the model (Estimate). When the option `conf.int=TRUE` is specified, this data frame includes three additional columns: the Standard Errors of parameters (`Std.Error`), the value of the Wald statistic (`t.value`), and the related p-value for the Wald test (`Pr(>|t|)`).
`cov.matrix`	A data frame corresponding to variance-covariance matrix of the parameters.
`LogLik`	A numeric value corresponding to the (weighted) log-likelihood of the model.
`AIC`	A numeric value corresponding to the Akaike Information Criterion of the model.

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References

Gillaizeau et al. Inverse Probability Weighting to control confounding in an illness-death model for interval-censored data. Stat Med. 37(8):1245-1258, 2018. <doi: 10.1002/sim.7550>.

Gillaizeau et al. A multistate additive relative survival semi-Markov model. Statistical methods in medical research. 26(4):1700-1711, 2017. <doi: 10.1177/ 0962280215586456>.

Examples

```
# import the observed data
# (X=1 corresponds to initial state with a functioning graft, X=2 to acute rejection episode,
# X=3 to return to dialysis, X=4 to death with a functioning graft)

data(dataDIVAT1)

# A subgroup analysis to reduce the time needed for this example

dataDIVAT1$id<-c(1:nrow(dataDIVAT1))
set.seed(2)
d3<-dataDIVAT1[dataDIVAT1$id %in% sample(dataDIVAT1$id, 250, replace = FALSE),]
```

```
# To illustrate the use of a 3-state model, individuals with trajectory 13 and 123 are
# censored at the time of transition into state X=3

d3$trajectory[d3$trajectory==13]<-1
d3$trajectory[d3$trajectory==123]<-12
d3$trajectory[d3$trajectory==14]<-13
d3$trajectory[d3$trajectory==124]<-123

# 3-state parametric semi-Markov model including one explicative variable
# on the transition 1->2 (z is 1 if delayed graft function and 0 otherwise).
# We only reduced the precision and the number of iteration to save time in this example,
# prefer the default values.

semi.markov.3states(times1=d3$time1, times2=d3$time2, sequences=d3$trajectory,
 dist=c("E","E","E"), ini.dist.12=c(9.93), ini.dist.13=c(11.54), ini.dist.23=c(10.21),
  cov.12=d3$z, init.cov.12=c(-0.13), names.12=c("beta12_z"),
  conf.int=TRUE, silent=FALSE, precision=0.001)$table
```

---

semi.markov.3states.ic

3-State Semi-Markov Model With Interval-Censored Data

Description

The 3-state SM model includes an initial state (X=1), a transient state (X=2) and an absorbing state (X=3). Usually, X=1 corresponds to disease-free or remission, X=2 to relapse, and X=3 to death. In this illness-death model, the possible transitions are: 1->2, 1->3 and 2->3. The time from X=1 to X=2 is interval-censored. Parameters are estimated by (weighted) Likelihood maximization.

Usage

```
semi.markov.3states.ic(times0, times1, times2, sequences, weights=NULL,
dist, cuts.12=NULL, cuts.13=NULL, cuts.23=NULL,
ini.dist.12=NULL, ini.dist.13=NULL, ini.dist.23=NULL,
cov.12=NULL, init.cov.12=NULL, names.12=NULL,
cov.13=NULL, init.cov.13=NULL, names.13=NULL,
cov.23=NULL, init.cov.23=NULL, names.23=NULL,
conf.int=TRUE, silent=TRUE, precision=10^(-6),
legendre=30, homogeneous=TRUE)
```

Arguments

times0	A numeric vector with the observed times in days from baseline to the last observation time in X=1.
times1	A numeric vector with the observed times in days from baseline to the first observation time in X=2. NA for individuals right-censored in X=1 or individuals who are directly in X=3 after X=1 (without any observation in X=2).

times2	A numeric vector with the observed times in days from baseline to the last follow-up.
sequences	A numeric vector with the sequences of observed states. Four possible values are allowed: 1 (individual right-censored in X=1), 12 (individual right-censored in X=2), 13 (individual who directly observed in X=3 after X=3, without any observation of X=2), 123 (individual who transited from X=1 to X=3 through X=2).
weights	A numeric vector with the weights for correcting the contribution of each individual. When the vector is completed, the IPW estimator is implemented. Default is NULL which means that no weighting is applied.
dist	A character vector with three arguments describing respectively the distributions of duration time for transitions 1->2, 1->3 and 2->3. Arguments allowed are "E" for Exponential distribution, "PE" for the piecewise exponential distribution, "W" for Weibull distribution or "WG" for Generalized Weibull distribution. When the user choose "PE", the arguments "cut.XX" have also to be defined.
cuts.12	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.13	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.23	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=3. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
ini.dist.12	A numeric vector of initial values for the distribution from X=1 to X=2. The logarithm of the parameters have to be declared. Default value is 1.
ini.dist.13	A numeric vector of initial values for the distribution from X=1 to X=3. The logarithm of the parameters have to be declared. Default value is 1.
ini.dist.23	A numeric vector of initial values for the distribution from X=2 to X=3. The logarithm of the parameters have to be declared. Default value is 1.
cov.12	A matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=2.
init.cov.12	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.12. Default initial value is 0.
names.12	An optional character vector with name of explicative variables associated to cov.12.
cov.13	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=3.

init.cov.13	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.13. Default initial value is 0.
names.13	An optional character vector with name of explicative variables associated to cov.13.
cov.23	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=2 to X=3.
init.cov.23	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.23. Default initial value is 0.
names.23	An optional character vector with name of explicative variables associated to cov.23.
conf.int	A logical value specifying if the pointwise confidence intervals for parameters and the variance-covariance matrix should be returned. Default is TRUE.
silent	A logical value specifying if the log-likelihood value should be returned at each iteration. Default is TRUE, which corresponds to silent mode (no display).
precision	A numeric positive value indicating the required precision for the log-likelihood maximization between each iteration. Default is 10^{-6}.
legendre	A numeric value indicating the number of knots and weights for Gaussian quadrature used in convolution products. Default is 30.
homogeneous	A logical value specifying if the time spent in the state X=1 is considered as non-associated with the distribution of the time from the entry in the state X=2 to the transition in the state X=3. Default is TRUE, assuming no association.

Details

Hazard functions available are:

$$
\begin{array}{rl}
\text{Exponential distribution} & \lambda(t) = 1/\sigma \\
\text{Weibull distribution} & \lambda(t) = \nu(\tfrac{1}{\sigma})^\nu t^{\nu-1} \\
\text{Generalized Weibull distribution} & \lambda(t) = \tfrac{1}{\theta}\left(1+\left(\tfrac{t}{\sigma}\right)^\nu\right)^{\frac{1}{\theta}-1} \nu\left(\tfrac{1}{\sigma}\right)^\nu t^{\nu-1}
\end{array}
$$

with σ, ν, and $\theta > 0$. The parameter σ varies for each interval when the distribution is piecewise Exponential. We advise to initialize the logarithm of these parameters in ini.dist.12, ini.dist.13 and ini.dist.23.

To estimate the marginal effect of a binary exposure, the weights may be equal to 1/p, where p is the estimated probability that the individual belongs to his or her own observed group of exposure. The probabilities p are often estimated by a logistic regression in which the dependent binary variable is the exposure. The possible confounding factors are the explanatory variables of this logistic model.

Two kinds of model can be estimated: homogeneous and non-homogeneous semi-Markov model. In the first one, the hazard functions only depend on the times spent in the corresponding state. Note that for the transitions from the state X=1, the time spent in the state corresponds to the chronological time from the baseline of the study, as for Markov models. In the second one, the hazard function of the transition from the state X=2 to X=3 depends on two time scales: the time spent in the state 2 which is the random variable of interest, and the time spend in the state X=1 as a covariate.

Value

`object`	The character string indicating the model: "semi.markov.3states.ic (3-state semi-markov model with interval-censored data)".
`dist`	A character vector with two arguments describing respectively the distributions of duration time for transitions 1->2, 1->3 and 2->3.
`cuts.12`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2.
`cuts.13`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3.
`cuts.23`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=3.
`covariates`	A numeric vector indicating the numbers of covariates respectively related to the transition 1->2, 1->3 and 2->3.
`table`	A data frame containing the estimated parameters of the model (Estimate). When the option `conf.int=TRUE` is specified, this data frame includes three additional columns: the Standard Errors of parameters (`Std.Error`), the value of the Wald statistic (`t.value`), and the related p-value for the Wald test (`Pr(>|t|)`).
`cov.matrix`	A data frame corresponding to variance-covariance matrix of the parameters.
`LogLik`	A numeric value corresponding to the (weighted) log-likelihood of the model.
`AIC`	A numeric value corresponding to the Akaike Information Criterion of the model.

Author(s)

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Florence Gillaizeau <Florence.Gillaizeau@univ-nantes.fr>

References

Gillaizeau et al. Inverse Probability Weighting to control confounding in an illness-death model for interval-censored data. Stat Med. 37(8):1245-1258, 2018. <doi: 10.1002/sim.7550>.

Examples

```
# The example is too long to compute for a submission on the CRAN
# Remove the characters '#'

# import the observed data (read the application in Gillaizeau et al. for more details)
# X=1 corresponds to initial state with a functioning graft, X=2 to acute rejection episode,
# X=3 to return to dialysis, X=4 to death with a functioning graft

# data(dataDIVAT1)

# A subgroup analysis to reduce the time needed for this example

# dataDIVAT1$id<-c(1:nrow(dataDIVAT1))
# set.seed(2)
# d3<-dataDIVAT1[dataDIVAT1$id %in% sample(dataDIVAT1$id, 100, replace = FALSE),]
```

```
# To illustrate the use of a 3-state model, the return in dialysis are right-censored

# d3$trajectory[d3$trajectory==13]<-1
# d3$trajectory[d3$trajectory==123]<-12
# d3$trajectory[d3$trajectory==14]<-13
# d3$trajectory[d3$trajectory==124]<-123
# table(d3$trajectory)

# X=2 is supposed to be interval-censored between 'times0' and 'times1' because
# health examinations take place each year after inclusion

# d3$times0<-NA
# d3$times1<-NA
# d3$time2_<-NA

# i<-d3$trajectory==1
# d3$times0[i]<-trunc(d3$time1[i]/365.24)*365.24+1
# d3$times1[i]<-NA
# d3$times2[i]<- d3$time1[i]+1

# i<-d3$trajectory==12
# d3$times0[i]<-trunc(d3$time1[i]/365.24)*365.24+1
# d3$times1[i]<-(trunc(d3$time1[d3$trajectory==12]/365.24)+1)*365.24
# d3$times2[i]<-pmax(d3$time2[i], (trunc(d3$time1[i]/365.24)+2)*365.24)

# i<-d3$trajectory==13
# d3$times0[i]<-trunc(d3$time1[i]/365.24)*365.24+1
# d3$times1[i]<-NA
# d3$times2[i]<-d3$time1[i]

# i<-d3$trajectory==123
# d3$times0[i]<-trunc(d3$time1[i]/365.24)*365.24+1
# d3$times1[i]<-(trunc(d3$time1[i]/365.24)+1)*365.24
# d3$times2[i]<- pmax(d3$time2[i], (trunc(d3$time1[i]/365.24)+2)*365.24)

# 3-state homogeneous semi-Markov model with interval-censored data
# including one binary explicative variable (z is 1 if delayed graft function and
# 0 otherwise).
# Estimation of the marginal effect of z on the transition from X=1 to X=2
# by adjusting for 2 possible confounding factors (age and gender)
# We only reduced the precision and the number of iteration to save time in this example,
# prefer the default values.

# propensity.score <- glm(z ~ ageR + sexR, family=binomial(link="logit"),data=d3)
# d3$fit<-propensity.score$fitted.values

# p1<-mean(d3$z)
# d3$w <- p1/d3$fit
# d3$w[d3$z==0]<-(1-p1)/(1-d3$fit[d3$z==0])

# semi.markov.3states.ic(times0=d3$times0, times1=d3$times1,
# times2=d3$times2, sequences=d3$trajectory,
```

```
# weights=d3$w, dist=c("E","E","E"), cuts.12=NULL, cuts.13=NULL, cuts.23=NULL,
# ini.dist.12=c(8.23), ini.dist.13=c(10.92), ini.dist.23=c(10.67),
# cov.12=d3$z, init.cov.12=c(0.02), names.12=c("beta12_z"),
# conf.int=TRUE, silent=FALSE, precision=0.001, legendre=20)$table
```

---

semi.markov.3states.rsadd

3-State Relative Survival Semi-Markov Model With Additive Risks

---

Description

The 3-state SMRS model includes an initial state (X=1), a transient state (X=2), and the death (X=3). The possible transitions are: 1->2, 1->3 and 2->3. Assuming additive risks, the observed mortality hazard is the sum of two components: the expected population mortality (X=P) and the excess mortality related to the disease under study (X=E). The expected population mortality hazard (X=P) can be obtained from the death rates provided by life tables of statistical national institutes. These tables indicate the proportion of people dead in a calendar year stratified by birthdate and gender.

Usage

```
semi.markov.3states.rsadd(times1, times2, sequences, weights=NULL, dist,
cuts.12=NULL, cuts.13=NULL, cuts.23=NULL,
ini.dist.12=NULL, ini.dist.13=NULL, ini.dist.23=NULL,
cov.12=NULL, init.cov.12=NULL, names.12=NULL,
cov.13=NULL, init.cov.13=NULL, names.13=NULL,
cov.23=NULL, init.cov.23=NULL, names.23=NULL,
p.age, p.sex, p.year, p.rate.table,
conf.int=TRUE, silent=TRUE, precision=10^(-6))
```

Arguments

times1	A numeric vector with the observed times in days from baseline to the first transition (X=2 or X=3) or to the right-censoring (in X=1 at the last follow-up).
times2	A numeric vector with the observed times in days from baseline to the second transition or to the right censoring (in X=2 at the last follow-up). NA for individuals right-censored in X=1 or individuals who directly transited from X=1 to X=3.
sequences	A numeric vector with the sequences of observed states. Four possible values are allowed: 1 (individual right-censored in X=1), 12 (individual right-censored in X=2), 13 (individual who directly transited from X=1 to X=3), 123 (individual who transited from X=1 to X=3 through X=2).
weights	A numeric vector with the weights for correcting the contribution of each individual. Default is NULL which means that no weighting is applied.

dist	A character vector with three arguments describing respectively the distributions of duration time for transitions 1->2, 1->3 and 2->3. Arguments allowed are "E" for Exponential distribution, "PE" for the piecewise exponential distribution, "W" for Weibull distribution or "WG" for Generalized Weibull distribution. When the user choose "PE", the arguments "cut.XX" have also to be defined.
cuts.12	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.13	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.23	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=3. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
ini.dist.12	A numeric vector of initial values for the distribution from X=1 to X=2. The logarithm of the parameters have to be declared. Default value is 1.
ini.dist.13	A numeric vector of initial values for the distribution from X=1 to X=3. The logarithm of the parameters have to be declared. Default value is 1.
ini.dist.23	A numeric vector of initial values for the distribution from X=2 to X=3. The logarithm of the parameters have to be declared. Default value is 1.
cov.12	A matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=2.
init.cov.12	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.12. Default initial value is 0.
names.12	An optional character vector with name of explicative variables associated to cov.12.
cov.13	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=3.
init.cov.13	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.13. Default initial value is 0.
names.13	An optional character vector with name of explicative variables associated to cov.13.
cov.23	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=2 to X=3.
init.cov.23	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.23. Default initial value is 0.
names.23	An optional character vector with name of explicative variables associated to cov.23.

p.age	A numeric vector with the patient ages in days at baseline (X=1).
p.sex	A character vector with the genders: `male` or `female`.
p.year	A numeric vector with the entry dates in the study respecting the date format, i.e. in number of days since 01.01.1960.
p.rate.table	A list contaning the information related to the expected rates of mortality. This list is organized as a `ratetable` object.
conf.int	A logical value specifying if the pointwise confidence intervals for parameters and the variance-covariance matrix should be returned. Default is `TRUE`.
silent	A logical value specifying if the log-likelihood value should be returned at each iteration. Default is `TRUE`, which corresponds to silent mode (no display).
precision	A numeric positive value indicating the required precision for the log-likelihood maximization between each iteration. Default is 10^{-6}.

Details

Hazard functions available are:

$$
\begin{array}{ll}
\text{Exponential distribution} & \lambda(t) = 1/\sigma \\
\text{Weibull distribution} & \lambda(t) = \nu (\frac{1}{\sigma})^\nu t^{\nu-1} \\
\text{Generalized Weibull distribution} & \lambda(t) = \frac{1}{\theta} \left(1 + \left(\frac{t}{\sigma}\right)^\nu\right)^{\frac{1}{\theta}-1} \nu \left(\frac{1}{\sigma}\right)^\nu t^{\nu-1}
\end{array}
$$

with σ, ν, and $\theta > 0$. The parameter σ varies for each interval when the distribution is piecewise Exponential. We advise to initialize the logarithm of these parameters in `ini.dist.12`, `ini.dist.13` and `ini.dist.23`.

To estimate the marginal effect of a binary exposure, the `weights` may be equal to `1/p`, where `p` is the estimated probability that the individual belongs to his or her own observed group of exposure. The probabilities `p` are often estimated by a logistic regression in which the dependent binary variable is the exposure. The possible confounding factors are the explanatory variables of this logistic model.

Value

object	The character string indicating the estimated model: "semi.markov.3states.rsadd (3-state relative survival semi-Markov model with additive risks)".
dist	A character vector with two arguments describing respectively the distributions of duration time for transitions 1->2, 1->3 and 2->3.
cuts.12	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2.
cuts.13	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3.
cuts.23	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=3.
covariates	A numeric vector indicating the numbers of covariates respectively related to the transition 1->2, 1->3 and 2->3.

table   A data frame containing the estimated parameters of the model (Estimate).
                When the option conf.int=TRUE is specified, this data frame includes three
                additional columns: the Standard Errors of parameters (Std.Error), the value
                of the Wald statistic (t.value), and the related p-value (Pr(>|t|)).

cov.matrix   A data frame corresponding to variance-covariance matrix of the parameters.

LogLik   A numeric value corresponding to the log-likelihood of the estimated model.

AIC   A numeric value corresponding to the Akaike Information Criterion of the esti-
                mated model.

Author(s)

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References

Gillaizeau et al. Inverse Probability Weighting to control confounding in an illness-death model for
interval-censored data. Stat Med. 37(8):1245-1258, 2018. <doi: 10.1002/sim.7550>.

Gillaizeau et al. A multistate additive relative survival semi-Markov model. Statistical methods in
medical research. 26(4):1700-1711, 2017. <doi: 10.1177/ 0962280215586456>.

Examples

```
# import the observed data
# (X=1 corresponds to initial state with a functioning graft, X=2 to acute rejection episode,
# X=3 to return to dialysis, X=4 to death with a functioning graft)

data(dataDIVAT1)

# A subgroup analysis to reduce the time needed for this example

dataDIVAT1$id<-c(1:nrow(dataDIVAT1))
set.seed(2)
d3<-dataDIVAT1[dataDIVAT1$id %in% sample(dataDIVAT1$id, 150, replace = FALSE),]

# To use a 3-state model, individuals with trajectory 13 and 123 are censored at the time
# of transition into state X=3

d3$trajectory[d3$trajectory==13]<-1
d3$trajectory[d3$trajectory==123]<-12
d3$trajectory[d3$trajectory==14]<-13
d3$trajectory[d3$trajectory==124]<-123

# import the expected mortality rates

data(fr.ratetable)

# 3-state parametric additive relative survival semi-Markov model including one
# explicative variable (z is the delayed graft function) on all transitions. We only reduced
# the precision and the number of iteration to save time in this example,
```

```
# prefer the default values.

# Note: a semi-Markovian process with sojourn times exponentially distributed
# is a time-homogeneous Markov process

semi.markov.3states.rsadd(times1=d3$time1, times2=d3$time2, sequences=d3$trajectory,
  dist=c("E","E","E"),
  ini.dist.12=c(10.70), ini.dist.13=c(11.10), ini.dist.23=c(0.04),
  cov.12=d3$z, init.cov.12=c(0.04), names.12=c("beta12_z"),
  cov.13=d3$z, init.cov.13=c(1.04), names.13=c("beta1E_z"),
  cov.23=d3$z, init.cov.23=c(0.29), names.23=c("beta2E_z"),
  p.age=d3$ageR*365.24,  p.sex=d3$sexR,
  p.year=as.numeric(as.Date(paste0(d3$year.tx,"-01-01"), origin = "1960-01-01")),
  p.rate.table=fr.ratetable,
  conf.int=TRUE, silent=FALSE, precision=0.005)
```

---

semi.markov.4states   *4-State Semi-Markov Model*

Description

The 4-state SM model includes an initial state (X=1), a transient state (X=2) and two absorbing states (X=3 and X=4). Usually, X=1 corresponds to disease-free or remission and X=4 to death. The possible transitions are: 1->2, 1->3, 1->4, 2->3 and 2->4.

Usage

```
semi.markov.4states(times1, times2, sequences, weights=NULL, dist,
cuts.12=NULL, cuts.13=NULL, cuts.14=NULL, cuts.23=NULL, cuts.24=NULL,
ini.base.12=NULL, ini.base.13=NULL, ini.base.14=NULL,
ini.base.23=NULL, ini.base.24=NULL,
cov.12=NULL, init.cov.12=NULL, names.12=NULL,
cov.13=NULL, init.cov.13=NULL, names.13=NULL,
cov.14=NULL, init.cov.14=NULL, names.14=NULL,
cov.23=NULL, init.cov.23=NULL, names.23=NULL,
cov.24=NULL, init.cov.24=NULL, names.24=NULL,
conf.int=TRUE, silent=TRUE, precision=10^(-6))
```

Arguments

times1   A numeric vector with the observed times in days from baseline to the first transition (X=2, X=3 or X=4) or to the right-censoring (in X=1 at the last follow-up).

times2   A numeric vector with the observed times in days from baseline to the second transition or to the right censoring (in X=2 at the last follow-up). NA for individuals right-censored in X=1 or individuals who directly transited from X=1 to X=3 or X=4.

sequences	a numeric vector with the sequences of observed states. Six possible values are allowed: 1 (individual right-censored in X=1), 12 (individual right-censored in X=2), 13 (individual who directly transited from X=1 to X=3), 14 (individual who directly transited from X=1 to X=4), 123 (individual who transited from X=1 to X=3 through X=2), 124 (individual who transited from X=1 to X=4 through X=2).
weights	A numeric vector with the weights for correcting the contribution of each individual. When the vector is completed, the IPW estimator is implemented. Default is NULL which means that no weighting is applied.
dist	A character vector with three arguments describing respectively the distributions of duration time for transitions 1->2, 1->3 and 2->3. Arguments allowed are "E" for Exponential distribution, "PE" for the piecewise exponential distribution, "W" for Weibull distribution or "WG" for Generalized Weibull distribution. When the user choose "PE", the arguments "cut.XX" have also to be defined.
cuts.12	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.13	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.14	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=4. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.23	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=3. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.24	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=4. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
ini.base.12	A numeric vector of initial values for the distribution from X=1 to X=2. The logarithm of the parameters have to be declared. Default value is 1.
ini.base.13	A numeric vector of initial values for the distribution from X=1 to X=3. The logarithm of the parameters have to be declared. Default value is 1.
ini.base.14	A numeric vector of initial values for the distribution from X=1 to X=4. The logarithm of the parameters have to be declared. Default value is 1.

`ini.base.23`	A numeric vector of initial values for the distribution from X=2 to X=3. The logarithm of the parameters have to be declared. Default value is 1.
`ini.base.24`	A numeric vector of initial values for the distribution from X=2 to X=4. The logarithm of the parameters have to be declared. Default value is 1.
`cov.12`	A matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=2.
`init.cov.12`	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to `cov.12`. Default initial value is 0.
`names.12`	An optional character vector with name of explicative variables associated to `cov.12`.
`cov.13`	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=3.
`init.cov.13`	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to `cov.13`. Default initial value is 0.
`names.13`	An optional character vector with name of explicative variables associated to `cov.13`.
`cov.14`	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=4.
`init.cov.14`	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to `cov.14`. Default initial value is 0.
`names.14`	An optional character vector with name of explicative variables associated to `cov.14`.
`cov.23`	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=2 to X=3.
`init.cov.23`	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to `cov.23`. Default initial value is 0.
`names.23`	An optional character vector with name of explicative variables associated to `cov.23`.
`cov.24`	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=2 to X=4.
`init.cov.24`	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to `cov.24`. Default initial value is 0.
`names.24`	An optional character vector with name of explicative variables associated to `cov.24`.
`conf.int`	A logical value specifying if the pointwise confidence intervals for parameters and the variance-covariance matrix should be returned. Default is `TRUE`.
`silent`	A logical value specifying if the log-likelihood value should be returned at each iteration. Default is `TRUE`, which corresponds to silent mode (no display).
`precision`	A numeric positive value indicating the required precision for the log-likelihood maximization between each iteration. Default is 10^{-6}.

Details

Hazard functions available are:

$$
\begin{array}{rl}
\text{Exponential distribution} & \lambda(t) = 1/\sigma \\
\text{Weibull distribution} & \lambda(t) = \nu(\frac{1}{\sigma})^\nu t^{\nu-1} \\
\text{Generalized Weibull distribution} & \lambda(t) = \frac{1}{\theta}\left(1 + \left(\frac{t}{\sigma}\right)^\nu\right)^{\frac{1}{\theta}-1} \nu \left(\frac{1}{\sigma}\right)^\nu t^{\nu-1}
\end{array}
$$

with σ, ν, and $\theta > 0$. The parameter σ varies for each interval when the distribution is piecewise Exponential. We advise to initialize the logarithm of these parameters in `ini.base.12`, `ini.base.13` and `ini.base.23`.

To estimate the marginal effect of a binary exposure, the `weights` may be equal to `1/p`, where `p` is the estimated probability that the individual belongs to his or her own observed group of exposure. The probabilities p are often estimated by a logistic regression in which the dependent binary variable is the exposure. The possible confounding factors are the explanatory variables of this logistic model.

Value

`object`	A character string indicating the estimated model: "semi.markov.4states (4-state semi-Markov model)".
`dist`	A character vector with two arguments describing respectively the distributions of duration time for transitions 1->2, 1->3, 1->4, 2->3, and 2->4.
`cuts.12`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2.
`cuts.13`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3.
`cuts.14`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=4.
`cuts.23`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=3.
`cuts.24`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=4.
`covariates`	A numeric vector indicating the numbers of covariates respectively related to the transition 1->2, 1->3, 1->4, 2->3, and 2->4.
`table`	A data frame containing the estimated parameters of the model (`Estimate`). When the option `conf.int=TRUE` is specified, this data frame includes three additional columns: the Standard Errors of parameters (`Std.Error`), the value of the Wald statistic (`t.value`), and the related p-value for the Wald test (`Pr(>|t|)`).
`cov.matrix`	A data frame corresponding to variance-covariance matrix of the parameters.
`LogLik`	A numeric value corresponding to the (weighted) log-likelihood of the model.
`AIC`	A numeric value corresponding to the Akaike Information Criterion of the model.

Author(s)

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References

Gillaizeau et al. Inverse Probability Weighting to control confounding in an illness-death model for interval-censored data. Stat Med. 37(8):1245-1258, 2018. <doi: 10.1002/sim.7550>.

Gillaizeau et al. A multistate additive relative survival semi-Markov model. Statistical methods in medical research. 26(4):1700-1711, 2017. <doi: 10.1177/ 0962280215586456>.

Examples

```
# import the observed data
# (X=1 corresponds to initial state with a functioning graft, X=2 to acute rejection episode,
# X=3 to return to dialysis, X=4 to death with a functioning graft)

data(dataDIVAT1)

# A subgroup analysis to reduce the time needed for this example

dataDIVAT1$id<-c(1:nrow(dataDIVAT1))
set.seed(2)
d4<-dataDIVAT1[dataDIVAT1$id %in% sample(dataDIVAT1$id, 200, replace = FALSE),]

# 4-state parametric semi-Markov model including one explicative variable
# (z is the delayed graft function) on the transition from X=1 to X=2

# Note: a semi-Markovian process with sojourn times exponentially distributed
# is a time-homogeneous Markov process

# We only reduced the precision and the number of iteration to save time in this example,
# prefer the default values.

semi.markov.4states(times1=d4$time1, times2=d4$time2, sequences=d4$trajectory,
  dist=c("E","E","E","E","E"),
  ini.base.12=c(8.31), ini.base.13=c(10.46), ini.base.14=c(10.83),
  ini.base.23=c(9.01), ini.base.24=c(10.81),
  cov.12=d4$z, init.cov.12=c(-0.02), names.12=c("beta12_z"),
  conf.int=TRUE,  silent=FALSE,  precision=0.001)$table
```

---

semi.markov.4states.rsadd

4-State Relative Survival Semi-Markov Model With Additive Risks

---

Description

The 4-state SMRS model includes an initial state (X=1), a transient state (X=2) and two absorbing states (X=3 X=4 for death). The possible transitions are: 1->2, 1->3, 1->4, 2->3 and 2->4. Assuming additive risks, the observed mortality hazard is the sum of two components: the expected population mortality (X=P) and the excess mortality related to the disease under study (X=E). The expected population mortality hazard (X=P) can be obtained from the death rates provided by life tables of statistical national institutes. These tables indicate the proportion of people dead in a calendar year stratified by birthdate and gender.

Usage

```
semi.markov.4states.rsadd(times1, times2, sequences, weights=NULL, dist,
cuts.12=NULL, cuts.13=NULL, cuts.14=NULL, cuts.23=NULL, cuts.24=NULL,
ini.dist.12=NULL, ini.dist.13=NULL, ini.dist.14=NULL,
ini.dist.23=NULL, ini.dist.24=NULL,
cov.12=NULL, init.cov.12=NULL, names.12=NULL,
cov.13=NULL, init.cov.13=NULL, names.13=NULL,
cov.14=NULL, init.cov.14=NULL, names.14=NULL,
cov.23=NULL, init.cov.23=NULL, names.23=NULL,
cov.24=NULL, init.cov.24=NULL, names.24=NULL,
p.age, p.sex, p.year, p.rate.table,
conf.int=TRUE, silent=TRUE, precision=10^(-6))
```

Arguments

times1	A numeric vector with the observed times in days from baseline to the first transition (X=2, X=3 or X=4) or to the right-censoring (in X=1 at the last follow-up).
times2	A numeric vector with the observed times in days from baseline to the second transition or to the right censoring (in X=2 at the last follow-up). NA for individuals right-censored in X=1 or individuals who directly transited from X=1 to X=3 or X=4.
sequences	a numeric vector with the sequences of observed states. Six possible values are allowed: 1 (individual right-censored in X=1), 12 (individual right-censored in X=2), 13 (individual who directly transited from X=1 to X=3), 14 (individual who directly transited from X=1 to X=4), 123 (individual who transited from X=1 to X=3 through X=2), 124 (individual who transited from X=1 to X=4 through X=2).
weights	A numeric vector with the weights for correcting the contribution of each individual. When the vector is completed, the IPW estimator is implemented. Default is NULL which means that no weighting is applied.
dist	A character vector with three arguments describing respectively the distributions of duration time for transitions 1->2, 1->3 and 2->3. Arguments allowed are "E" for Exponential distribution, "PE" for the piecewise exponential distribution, "W" for Weibull distribution or "WG" for Generalized Weibull distribution. When the user choose "PE", the arguments "cut.XX" have also to be defined.

cuts.12	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.13	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.14	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=4. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.23	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=3. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
cuts.24	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=4. Only internal timepoints are allowed: timepoints cannot be 0 or Inf. Default is NULL which means that the distribution is not piecewise. Piecewise model is only allowed for exponential distribution.
ini.dist.12	A numeric vector of initial values for the distribution from X=1 to X=2. The logarithm of the parameters have to be declared. Default value is 1.
ini.dist.13	A numeric vector of initial values for the distribution from X=1 to X=3. The logarithm of the parameters have to be declared. Default value is 1.
ini.dist.14	A numeric vector of initial values for the distribution from X=1 to X=4. The logarithm of the parameters have to be declared. Default value is 1.
ini.dist.23	A numeric vector of initial values for the distribution from X=2 to X=3. The logarithm of the parameters have to be declared. Default value is 1.
ini.dist.24	A numeric vector of initial values for the distribution from X=2 to X=4. The logarithm of the parameters have to be declared. Default value is 1.
cov.12	A matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=2.
init.cov.12	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.12. Default initial value is 0.
names.12	An optional character vector with name of explicative variables associated to cov.12.
cov.13	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=3.
init.cov.13	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to cov.13. Default initial value is 0.

names.13	An optional character vector with name of explicative variables associated to `cov.13`.
cov.14	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=4.
init.cov.14	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to `cov.14`. Default initial value is 0.
names.14	An optional character vector with name of explicative variables associated to `cov.14`.
cov.23	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=2 to X=3.
init.cov.23	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to `cov.23`. Default initial value is 0.
names.23	An optional character vector with name of explicative variables associated to `cov.23`.
cov.24	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=2 to X=4.
init.cov.24	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to `cov.24`. Default initial value is 0.
names.24	An optional character vector with name of explicative variables associated to `cov.24`.
p.age	A numeric vector with the patient ages in days at baseline (X=1).
p.sex	A character vector with the genders: `male` or `female`.
p.year	A numeric vector with the entry dates in the study respecting the date format, i.e. in number of days since 01.01.1960.
p.rate.table	A list contaning the information related to the expected rates of mortality. This list is organized as a `ratetable` object.
conf.int	A logical value specifying if the pointwise confidence intervals for parameters and the variance-covariance matrix should be returned. Default is `TRUE`.
silent	A logical value specifying if the log-likelihood value should be returned at each iteration. Default is `TRUE`, which corresponds to silent mode (no display).
precision	A numeric positive value indicating the required precision for the log-likelihood maximization between each iteration. Default is 10^{-6}.

Details

Hazard functions available are:

$$
\begin{array}{ll}
\text{Exponential distribution} & \lambda(t) = 1/\sigma \\
\text{Weibull distribution} & \lambda(t) = \nu(\frac{1}{\sigma})^{\nu} t^{\nu-1} \\
\text{Generalized Weibull distribution} & \lambda(t) = \frac{1}{\theta}\left(1 + \left(\frac{t}{\sigma}\right)^{\nu}\right)^{\frac{1}{\theta}-1} \nu \left(\frac{1}{\sigma}\right)^{\nu} t^{\nu-1}
\end{array}
$$

with σ, ν, and $\theta > 0$. The parameter σ varies for each interval when the distribution is piecewise Exponential. We advise to initialize the logarithm of these parameters in `ini.dist.12`, `ini.dist.13` and `ini.dist.23`.

To estimate the marginal effect of a binary exposure, the `weights` may be equal to `1/p`, where p is the estimated probability that the individual belongs to his or her own observed group of exposure. The probabilities p are often estimated by a logistic regression in which the dependent binary variable is the exposure. The possible confounding factors are the explanatory variables of this logistic model.

Value

`object`	A character string indicating the estimated model: "semi.markov.4states.rsadd (4-state relative survival semi-Markov model with additive risks)".
`dist`	A character vector with two arguments describing respectively the distributions of duration time for transitions 1->2, 1->3, 1->4, 2->3, and 2->4.
`cuts.12`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2.
`cuts.13`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3.
`cuts.14`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=4.
`cuts.23`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=3.
`cuts.24`	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=4.
`covariates`	A numeric vector indicating the numbers of covariates respectively related to the transition 1->2, 1->3, 1->4, 2->3, and 2->4.
`table`	A data frame containing the estimated parameters of the model (Estimate). When the option `conf.int=TRUE` is specified, this data frame includes three additional columns: the Standard Errors of parameters (`Std.Error`), the value of the Wald statistic (`t.value`), and the related p-value for the Wald test (`Pr(>|t|)`).
`cov.matrix`	A data frame corresponding to variance-covariance matrix of the parameters.
`LogLik`	A numeric value corresponding to the log-likelihood of the estimated model.
`AIC`	A numeric value corresponding to the Akaike Information Criterion of the estimated model.

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References

Gillaizeau et al. Inverse Probability Weighting to control confounding in an illness-death model for interval-censored data. Stat Med. 37(8):1245-1258, 2018. <doi: 10.1002/sim.7550>.

Gillaizeau et al. A multistate additive relative survival semi-Markov model. Statistical methods in medical research. 26(4):1700-1711, 2017. <doi: 10.1177/ 0962280215586456>.

Examples

```
# import the observed data
# (X=1 corresponds to initial state with a functioning graft, X=2 to acute rejection episode,
# X=3 to return to dialysis, X=4 to death with a functioning graft)

data(dataDIVAT1)

# A subgroup analysis to reduce the time needed for this example

dataDIVAT1$id<-c(1:nrow(dataDIVAT1))
set.seed(2)
d4<-dataDIVAT1[dataDIVAT1$id %in% sample(dataDIVAT1$id, 300, replace = FALSE),]

# import the expected mortality rates

data(fr.ratetable)

# 4-state parametric additive relative survival semi-Markov model including one
# explicative variable (z is the delayed graft function) on the transition from X=1 to X=2

# Note: a semi-Markovian process with sojourn times exponentially distributed
# is a time-homogeneous Markov process

# We only reduced the precision and the number of iteration to save time in this example,
# prefer the default values.

semi.markov.4states.rsadd(times1=d4$time1, times2=d4$time2, sequences=d4$trajectory,
  dist=c("E","E","E","E","E"),
  ini.dist.12=c(8.34),  ini.dist.13=c(10.44),  ini.dist.14=c(10.70),
  ini.dist.23=c(9.43),  ini.dist.24=c(11.11),
  cov.12=d4$z, init.cov.12=c(0.04), names.12=c("beta12_z"),
  p.age=d4$ageR*365.24,  p.sex=d4$sexR,
  p.year=as.numeric(as.Date(paste0(d4$year.tx,"-01-01"), origin = "1960-01-01")),
  p.rate.table=fr.ratetable, conf.int=TRUE,
  silent=FALSE, precision=0.001)
```

---

survival.mr	*Multiplicative-Regression Model to Compare the Risk Factors Between Two Reference and Relative Populations*

Description

Compute a multiplicative-regression model to compare the risk factors between a reference and a relative population.

Usage

```
survival.mr(times, failures, cov.relative, data,
cox.reference, cov.reference, ini, iterations)
```

Arguments

times	The column name in `data`, in which the time of follow-up of each individual is collected.
failures	The column name in `data`, in which the indicator of event at the end of follow-up is collected (1 if the event is observed and 0 if right censoring).
cov.relative	The column(s) name(s) in `data` in order to declare the explicative variable included in the multiplicative relative model.
data	A data frame with the variables (columns) of the individuals (raw) of the relative sample.
cox.reference	The results of the Cox model performed in the reference sample, i.e an object obtained by the `coxph` function.
cov.reference	The column(s) name(s) in `data` in order to declare the explicative variable corresponding to those included in the Cox model `cox.reference`. Please, note that the order of these variables is important and have to be similar with the order in `cox.reference`.
ini	A vector with the same length than `cov.relative` with the initial values for the parameters to be optimized.
iterations	The number of iterations of the bootstrap resampling.

Details

We proposed here an adaptation of a multiplicative-regression model for relative survival to study the heterogeneity of risk factors between two groups of patients. Estimation of parameters is based on partial likelihood maximization and Monte-Carlo simulations associated with bootstrap re-sampling yields to obtain the corresponding standard deviations. The expected hazard ratios are obtained by using a PH Cox model.

Value

matrix.coef	A matrix containing the parameters estimations at each of the B iterations.
estim.coef	A numerical vector containing the mean of the previous estimation
lower95.coef	A numerical vector containing the lower bounds of the 95% confidence intervals.
upper95.coef	A numerical vector containing the upper bounds of the 95% confidence intervals.

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K. Trebern-Launay <katygre@yahoo.fr>

References

K. Trebern-Launay et al. Comparison of the risk factors effects between two populations: two alternative approaches illustrated by the analysis of first and second kidney transplant recipients. BMC Med Res Methodol. 2013 Aug 6;13:102. <doi: 10.1186/1471-2288-13-102>.

Examples

```
# import and attach both samples
data(dataFTR)
data(dataSTR)

# We reduce the dimension to save time for this example (CRAN policies)
# Compute the Cox model in the First Kidney Transplantations (FTR)
cox.FTR<-coxph(Surv(Tps.Evt, Evt)~ ageR2cl + sexeR, data=dataFTR[1:100,])
summary(cox.FTR)

# Compute the multiplicative relative model
# for Second Kidney Transplantations  (STR)
# Choose iterations>>5 for real applications
mrs.STR <- survival.mr(times="Tps.Evt", failures="Evt",
 cov.relative=c("ageR2cl", "Tattente2cl"), data=dataSTR[1:100,],
 cox.reference=cox.FTR, cov.reference=c("ageR2cl", "sexeR"),
 ini=c(0,0), iterations=5)


# The parameters estimations (mean of the values)
mrs.STR$estim.coef

# The 95 percent. confidence intervals
cbind(mrs.STR$lower95.coef, mrs.STR$upper95.coef)
```

---

survival.summary   *Summary Survival Curve From Aggregated Data*

Description

Estimation of the summary survival curve from the survival rates and the numbers of at-risk individuals extracted from studies of a meta-analysis.

Usage

```
survival.summary(study, time, n.risk, surv.rate, confidence)
```

Arguments

study	A numeric vector with the numbering of the studies included in the meta-analysis. The numbering of a study is repeated for each survival probabilities extracted from this study.
time	A numeric vector with the time at which the survival probabilities are collected.
n.risk	A numeric vector with the number of at-risk patients in the study for each value of thr `time`.
surv.rate	A numeric vector with the survival rates collected per study for each value of `time`.
confidence	A text argument indicating the method to calculate the 95% confidence interval of the summary survival probabilities: "Greenwood" or "MonteCarlo".

Details

The survival probabilities have to be extracted at the same set of points in time for all studies. Missing data are not allowed. The studies included in the meta-analysis can have different length of follow-up. For a study ending after the time t, all survival probabilities until t have to be entered in data. The data are sorted by study and by time. The conditional survival probabilities are arc-sine transformed and thus pooled assuming fixed effects or random effects. A correction of 0.25 is applied to the arc-sine transformation. For random effects, the multivariate methodology of DerSimonian and Laird is applied and the between-study covariances are accounted. The summary survival probabilities are obtained by the product of the pooled conditional survival probabilities. The mean and median survival times are derived from the summary survival curve assuming a linear interpolation of the survival between the points.

Value

`verif.data`	A data frame in which the first column (`study`) correspond to the number of the study and the second column (`check`) equals 1 if the time of collection for this study respects the other times for the other studies and 0 otherwise. Remember that the times of survival rates have to be identical between studies. The end of each study can be different. If at least one study did not respect this format, the other arguments values are non-attributed (NA).
`summary.fixed`	A matrix containing the summarized survival probabilities assuming fixed effects. The first column contains the time at which the summary survivals are computed. The second column contains the estimations of the summary survival probabilities. The third and fourth columns contain the lower and the upper bound of the 95% confidence interval, computed by either the Greenwood or the Monte Carlo approach as specified by the user.
`median.fixed`	A numerical vector containing the estimated median survival time computed from the summary survival curve assuming fixed effects and the lower and upper bounds of the 95% confidence interval computed by a Monte Carlo approach.
`mean.fixed`	A numerical vector containing the estimated mean survival time computed from the summary survival curve assuming fixed effects and the lower and upper bounds of the 95% confidence interval computed by a Monte Carlo approach.
`heterogeneity`	A numerical vector containing the value of the Q statistic for the heterogeneity, the H index and the I-squared index (in percentage).
`summary.random`	A matrix containing the summarized survival probabilities assuming random effects. The first column contains the time at which the summary survivals are computed. The second column contains the estimations of the summary survival probabilities. The third and fourth columns contain the lower and the upper bound of the 95% confidence interval around the summary survival probabilities, computed by either the Greenwood or the Monte Carlo approach as specified by the user.
`median.random`	A numerical vector containing the estimated median survival time computed from the summary survival curve assuming random effects and the lower and upper bounds of the 95% confidence interval computed by a Monte Carlo approach.

mean.random   A numerical vector containing the estimated mean survival time computed from
                     the summary survival curve assuming random effects and the lower and upper
                     bounds of the 95% confidence interval computed by a Monte Carlo approach.

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References

Combescure et al. The multivariate DerSimonian and Laird's methodology applied to meta-analysis
of survival curves. 10;33(15):2521-37, 2014. Statistics in Medicine. <doi:10.1002/sim.6111>.

Examples

```
# import and attach the data example
data(dataHepatology)
attach(dataHepatology)

# computation of the summary survivals

results<-survival.summary(study, time, n.risk, survival, confidence="Greenwood")
results

# plot the estimated summary survival curve against the extracted ones

RandomEffectSummary<- results$summary.random

plot(time, survival, type="n", col="grey", ylim=c(0,1),xlab="Time",
 ylab="Survival")

for (i in unique(sort(study)))
{
lines(time[study==i], survival[study==i], type="l", col="grey")
points(max(time[study==i]),
 survival[study==i & time==max(time[study==i])], pch=15)
}

lines(RandomEffectSummary[,1], RandomEffectSummary[,2], type="l",
 col="red", lwd=3)
points(RandomEffectSummary[,1], RandomEffectSummary[,3], type="l",
 col="red", lty=3, lwd=3)
points(RandomEffectSummary[,1], RandomEffectSummary[,4], type="l",
 col="red", lty=3, lwd=3)
```

---

survival.summary.strata
Summary Survival Curve And Comparison Between Strata.

Description

Estimation of the summary survival curve from the survival rates and the numbers of at-risk individuals extracted from studies of a meta-analysis and comparisons between strata of studies.

Usage

```
survival.summary.strata(study, time, n.risk, surv.rate, confidence, strata)
```

Arguments

study	A numeric vector with the numbering of the studies included in the meta-analysis. The numbering of a study is repeated for each survival probabilities extracted from this study.
time	A numeric vector with the time at which the survival probabilities are collected.
n.risk	A numeric vector with the number of at-risk patients in the study for each value of thr `time`.
surv.rate	A numeric vector with the survival rates collected per study for each value of `time`.
confidence	A text argument indicating the method to calculate the 95% confidence interval of the summary survival probabilities: "Greenwood" or "MonteCarlo".
strata	A factor designing the strata. Each stratum has to contain at least two studies.

Details

The survival probabilities have to be extracted at the same set of points in time for all studies. Missing data are not allowed. The studies included in the meta-analysis can have different length of follow-up. For a study ending after the time t, all survival probabilities until t have to be entered in data. The data are sorted by study and by time. The conditional survival probabilities are arcsine transformed and thus pooled assuming fixed effects or random effects. A correction of 0.25 is applied to the arc-sine transformation. For random effects, the multivariate methodology of DerSimonian and Laird is applied and the between-study covariances are accounted. The summary survival probabilities are obtained by the product of the pooled conditional survival probabilities. The mean and median survival times are derived from the summary survival curve assuming a linear interpolation of the survival between the points. The summary survival curve is assessed in each stratum. The duration of follow-up is the greatest duration for which each stratum contains at least two studies reporting the survival at this duration. The between-strata is assessed and tested.

Value

verif.data   A data frame in which the first column (`study`) correspond to the number of the
                 study and the second column (`check`) equals 1 if the time of collection for this
                 study respects the other times for the other studies and 0 otherwise. Remember
                 that the times of survival rates have to be identical between studies. The end of
                 each study can be different. If at least one study did not respect this format, the
                 other arguments values are non-attributed (NA).

summary.fixed   A list list of matrix. Each matrix contains the summarized survival probabilities
                 assuming fixed effects. Each matrix provides the results for one stratum. The
                 first column contains the time at which the summary survivals are computed.
                 The second column contains the estimations of the summary survival probabili-
                 ties. The third and fourth columns contain the lower and the upper bound of the
                 95% confidence interval, computed by either the Greenwood or the Monte Carlo
                 approach as specified by the user. The last element of the list is the summary
                 survival when all strata are pooled.

summary.random A list object containing the summarized survival probabilities in each stratum as-
                 suming random effects. The results are presented similarly as `summary.fixed`.

median.fixed   A numerical vector containing the estimated median survival time computed
                 from the summary survival curve assuming fixed effects and the lower and upper
                 bounds of the 95% confidence interval computed by a Monte Carlo approach.

mean.fixed   A numerical vector containing the estimated mean survival time computed from
                 the summary survival curve assuming fixed effects and the lower and upper
                 bounds of the 95% confidence interval computed by a Monte Carlo approach.

heterogeneity   A numerical vector containing the value of the Q statistic for the heterogeneity,
                 the H index and the I-squared index (in percentage).

p.value   The p-value of the test for the null hypothesis that the between-strata hetero-
                 geneity is null.

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References

Combescure et al. The multivariate DerSimonian and Laird's methodology applied to meta-analysis
of survival curves. 10;33(15):2521-37, 2014. Statistics in Medicine. <doi:10.1002/sim.6111>.

Examples

```
# import and attach the data example
data(dataHepatology)

attach(dataHepatology)

# computation of the summary survivals
```

```
results<-survival.summary.strata(study = study, time = time, n.risk = n.risk,
 surv.rate = survival, confidence="Greenwood", strata = location)

results
```

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