

Package ‘RISCA’

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Type Package

Title Causal Inference and Prediction in Cohort-Based Analyses

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Description We propose 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 (Le Borgne, 2016, <doi:10.1002/sim.6777>), competing events (Trebern-Launay, 2018, <doi: 10.1007/s10654-017-0322-3>), and multi-state data (Gillaizeau, 2018, <doi: 10.1002/sim.7550>). For multistate data, semi-Markov model with interval censoring (Foucher, 2008, <doi: 10.1177/0962280208093889>) may be considered and we propose the possibility to consider the excess of mortality related to the disease compared to reference lifetime tables (Gillaizeau, 2017, <doi: 10.1177/0962280215586456>). 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 (Le Borgne, 2018, <doi: 10.1177/0962280217702416>). Finally, several functions are available to assess time-dependant ROC curves (Combes-cure, 2017, <doi: 10.1177/0962280212464542>) or survival curves (Combes-cure, 2014, <doi: 10.1002/sim.6111>) from aggregated data.

License GPL (>= 2)

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R topics documented:

auc	3
dataCSL	3
dataDIVAT1	4
dataDIVAT2	5
dataDIVAT3	6
dataDIVAT4	7
dataDIVAT5	8
dataHepatology	10
dataKi67	11
dataKTFS	13
expect.utility1	14
expect.utility2	17
fr.ratetable	19
gc.logistic	20
gc.survival	23
ipw.log.rank	25
ipw.survival	26
lines.roc	28
lrs.multistate	29
markov.3states	31
markov.3states.rsadd	34
markov.4states	38
markov.4states.rsadd	43
mixture.2states	48
plot.roc	51
pred.mixture.2states	52
rein.ratetable	55
roc.binary	56
roc.net	58
roc.summary	61
roc.time	63
semi.markov.3states	65
semi.markov.3states.ic	69
semi.markov.3states.rsadd	74
semi.markov.4states	78
semi.markov.4states.rsadd	82
survival.summary	87
survival.summary.strata	90
usa.ratetable	92

Index

94

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 sensitivities

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](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 (rows) with the 7 following variables (columns):

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 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).
- h1a 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 Expanded 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 (rows) with the 8 following variables (columns).

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

Data were extracted 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 (columns).

`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.

References

Combescurie 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 Combescurie et al. (2016).

Usage

```
data(dataDIVAT5)
```


Format

A data frame with 106 observations (rows) with the 8 following variables (columns).

`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 $\mu\text{mol/l}$).

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

`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

Combes 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))

```

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 (columns).

`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 Fifth 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 (rows) with the 3 following variables (columns).

`time` This numeric vector represents the follow up time in years (until return in dialysis 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. *Kidney International*, 78:1288-94, 2010. <[doi:10.1038/ki.2010.232](https://doi.org/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)

```

expect.utility1	<i>Cut-Off Estimation Of A Prognostic Marker (Only One Observed Group).</i>
-----------------	---

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 observe 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 <code>n.boot=NULL</code> , 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 <code>n.boot</code> is not null, two additional values are returned: <code>CIinf</code> is the lower bound of the 95% confidence interval and <code>CIsup</code> 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 (<code>utility</code>), the proportions of patients with a marker value higher (<code>pA</code>) and lower (<code>pB</code>) than the cut-off value, the numbers of QALYs for patients with a marker value higher (<code>qA</code>) and lower (<code>qB</code>) than the cut-off value, the RMST for patients with a marker value higher (<code>eA</code>) and lower (<code>eB</code>) 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).

<code>delta.qaly</code>	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).
<code>missing</code>	Number of deleted observations due to missing data.

Author(s)

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Yohann Foucher <Yohann.Foucher@univ-nantes.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*, 0, 1-13, 2016. <doi:10.1177/0962280216671161>

Examples

```
data(dataKTFS)

# to respect the CRAN policy (run times < 5s)

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	<i>Cut-Off Estimation Of A Prognostic Marker (Two Groups Are observed).</i>
-----------------	---

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 <code>times</code> .
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 user has data from in which treatments A and B are allocated independently to the value of the marker X . She(he) assumes that the treatment A will be more convenient for patients with high value of the marker X . She(he) aims to compute the optimal cot-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-nantes.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*, 0, 1-13, 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)
```

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 methods are possible: "simulations" (by default) which consists in parametric simulation 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.

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 bootstrap 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 $p_0 = p_1$, i.e. OR = 1.

Author(s)

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

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

References

Chatton A, Le Borgne F, Gillaizeau F, Leyrat C, Barbin L, Laplaud D, Leger M, Giraudeau B, Foucher Y. G-computation and propensity score-based methods with binary outcome: a comparative study to evaluate their performances for causal inference. Manuscript submitted. 2019.

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)

#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.survival

*Marginal Effect for Censored Outcome by G-computation.***Description**

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

Usage

```
gc.survival(coxph.obj, data, group, times, failures, max.time, effect, iterations)
```

Arguments

coxph.obj	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 covariables included in the previous model coxph.obj. The covariates' names have to be identical than the ones included in coxph.obj.
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.

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, and is simply the area under the survival curve up to max.time obtained by the trapezoidal rule.

Value

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, 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, 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, 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 corresponding 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)

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

References

Chatton A, Le Borgne F, Leyrat C, Foucher Y. G-computation versus inverse probability weighting for time-to-event analyses. Manuscript in progress. 2019.

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(coxph.obj=cox.cdt, data=dataDIVAT2, group="ecd", times="times",
  failures="failures", max.time=max(dataDIVAT2$times), iterations=10, effect="ATE")
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]) )
```

ipw.log.rank	<i>Log-Rank Test for Adjusted Survival Curves.</i>
--------------	--

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 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>

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 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-nantes.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)

# Kaplan-Meier estimator
res.km <- ipw.survival(times=dataDIVAT2$times, failures=dataDIVAT2$failures,
  variable=dataDIVAT2$ecd, weights=NULL)
plot(NULL,xlim=c(0,13),ylim=c(0,1),ylab="Graft and patient survival",
  xlab="Time post-transplantation (years)")
lines(res.km$times[res.km$variable==1], res.km$survival[res.km$variable==1],
  type="s",col=2,lty=2,lwd=2)
lines(res.km$times[res.km$variable==0], res.km$survival[res.km$variable==0],
  type="s",col=1,lty=2,lwd=2)

# 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$ecd, weights=W)
lines(res.akm$times[res.akm$variable==1], res.akm$survival[res.akm$variable==1],
  type="s",col=2,lwd=2)
lines(res.akm$times[res.akm$variable==0], res.akm$survival[res.akm$variable==0],
  type="s",col=1,lwd=2)

nb.risk1<-function(x) {sum(dataDIVAT2$times[dataDIVAT2$ecd==0]>x)}
```

```

nb.risk2<-function(x) {sum(dataDIVAT2$times[dataDIVAT2$ecd==1]>x)}
segments(x0=0, y0=0.1, x1=13, y1=0.1)
text(x=6, y=0.12, "number of at-risk patients", cex=0.8)
tps <- seq(1,12,by=1)
text(x=tps, y=rep(0.07,length(tps)), as.character(sapply(tps, FUN="nb.risk1")),
     cex=0.8, col=1)
text(x=tps, y=rep(0.02,length(tps)), as.character(sapply(tps, FUN="nb.risk2")),
     cex=0.8, col=2)
legend("topright", legend=c("Unadjusted estimator for SCD",
                             "Adjusted estimator for SCD", "Unadjusted estimator for ECD",
                             "Adjusted estimator for ECD"), col=c(1,1,2,2),
       lty=c(2,1,2,1), lwd=2, cex=0.8)

```

lines.roc

Add Lines to a ROC Plot

Description

Used to add an additional ROC curve to ROC plot generated with `plot.roc`.

Usage

```

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

```

Arguments

<code>x</code>	An object of class <code>roc</code> , returned by the functions <code>roc.binary</code> , <code>roc.net</code> , <code>roc.summary</code> , and <code>roc.time</code> .
<code>...</code>	Additional arguments affecting the plot line.

Author(s)

Yohann Foucher <Yohann.Foucher@univ-nantes.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

```

# 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 obtain 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)

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 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

Irs.multistate(model1=m1, model0=m0)

```

markov.3states	<i>3-State Time-Inhomogeneous Markov Model</i>
----------------	--

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 transitioned 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 transitioned from $X=1$ to $X=3$), 123 (individual who transitioned 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 chooses "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:

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 $\sigma, \nu,$ 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

<code>object</code>	The character string indicating the estimated model: "markov.3states (3-state time-inhomogeneous markov model)".
<code>dist</code>	A character vector with two arguments describing respectively the distributions of duration time for transitions 1->2, 1->3 and 2->3.
<code>cuts.12</code>	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2.
<code>cuts.13</code>	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3.
<code>cuts.23</code>	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=3.
<code>covariates</code>	A numeric vector indicating the numbers of covariates respectively related to the transition 1->2, 1->3 and 2->3.
<code>table</code>	A data frame containing the estimated parameters of the model (Estimate). When the option <code>conf.int=TRUE</code> is specified, this data.frame includes three additional columns: the Standard Errors of parameters (<code>Std.Error</code>), the value of the Wald statistic (<code>t.value</code>), and the related p-value (<code>Pr(> t)</code>).
<code>cov.matrix</code>	A data frame corresponding to variance-covariance matrix of the parameters.
<code>LogLik</code>	A numeric value corresponding to the (weighted) log-likelihood of the model.
<code>AIC</code>	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: $1 \rightarrow 2$, $1 \rightarrow 3$ and $2 \rightarrow 3$. 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 transitioned 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 transitioned from X=1 to X=3), 123 (individual who transitioned 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 chooses "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.

<code>ini.dist.23</code>	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.
<code>cov.12</code>	A matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=2.
<code>init.cov.12</code>	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to <code>cov.12</code> . Default initial value is 0.
<code>names.12</code>	An optional character vector with name of explicative variables associated to <code>cov.12</code> .
<code>cov.13</code>	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=1 to X=3.
<code>init.cov.13</code>	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to <code>cov.13</code> . Default initial value is 0.
<code>names.13</code>	An optional character vector with name of explicative variables associated to <code>cov.13</code> .
<code>cov.23</code>	A numeric matrix (or data frame) with the explicative time-fixed variable(s) related to the time from X=2 to X=3.
<code>init.cov.23</code>	A numeric vector of initial values for regression coefficients (logarithm of the cause-specific hazards ratios) associated to <code>cov.23</code> . Default initial value is 0.
<code>names.23</code>	An optional character vector with name of explicative variables associated to <code>cov.23</code> .
<code>p.age</code>	A numeric vector with the patient ages in days at baseline (X=1).
<code>p.sex</code>	A character vector with the genders: male or female.
<code>p.year</code>	A numeric vector with the entry dates in the study respecting the date format, i.e. in number of days since 01.01.1960.
<code>p.rate.table</code>	A list containing the information related to the expected rates of mortality. This list is organized as a <code>ratetable</code> object.
<code>conf.int</code>	A logical value specifying if the pointwise confidence intervals for parameters and the variance-covariance matrix should be returned. Default is TRUE.
<code>silent</code>	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).
<code>precision</code>	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:

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

with $\sigma, \nu,$ 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

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

# 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.date(paste("01", "01", d3$year.tx), order = "mdy"),
  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: $1 \rightarrow 2$, $1 \rightarrow 3$, $1 \rightarrow 4$, $2 \rightarrow 3$ and $2 \rightarrow 4$.

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 transitioned 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 transitioned from X=1 to X=3), 14 (individual who directly transitioned from X=1 to X=4), 123 (individual who transitioned from X=1 to X=3 through X=2), 124 (individual who transitioned 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 chooses "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:

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

with $\sigma, \nu,$ 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 <code>conf.int=TRUE</code> is specified, this data frame includes three additional columns: the Standard Errors of parameters (<code>Std.Error</code>), the value of the Wald statistic (<code>t.value</code>), and the related p-value (<code>Pr(> t)</code>).
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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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 transition 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: $1 \rightarrow 2$, $1 \rightarrow 3$, $1 \rightarrow 4$, $2 \rightarrow 3$ and $2 \rightarrow 4$. 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 transitioned 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:

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

with $\sigma, \nu,$ 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

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

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References

Husztai 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.date(paste("01", "01", d3$year.tx), order = "mdy"),
  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 competition (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 initiate 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:

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

with $\sigma, \nu,$ 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 <code>conf.int=TRUE</code> is specified, this data frame includes three additional columns: the Standard Errors of parameters (<code>Std.Error</code>), the value of the Wald statistic (<code>t.value</code>), and the p-value for the Wald test (<code>Pr(> t)</code>).
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

Trebern-Launay K, Kessler M, Bayat-Makoei S, Querard AH, Briancon S, Giral M, Foucher Y. 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.roc

Plot Method for 'roc' 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 'roc'
plot(x, ..., information=TRUE)

```

Arguments

x	An object of class roc, 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-nantes.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

```
# 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", col=2, pch=2)
```

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 <code>mixture.2states</code> .
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 <code>times</code> in columns and the individuals in rows.

Author(s)

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

References

Trebern-Launay K, Kessler M, Bayat-Makoei S, Querard AH, Briancon S, Giral M, Foucher Y. 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.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)

```

rein.ratetable	<i>Expected Mortality Of French Patients With ESKD.</i>
----------------	---

Description

An object of the class rate-table which contains the expected mortality of French patients with End Stage Kidney Disease (ESKD) in dialysis and registered previously on waiting list for renal transplantation. It is an array with two dimensions: the time since the registry on waiting list and the patient profile at this baseline.

Usage

```
data(rein.ratetable)
```

Format

The format is "ratetable". The attributes are:

`dim` A numeric vector with the length of each dimension.

`dimnames` A list of vectors with the names of each variable of both dimensions (see details for modalities of `profile`).

`dimid` A character vector with the identification of the dimensions: `time`, `profile`.

`factor` A vector of indicators=1 if the corresponding dimension do not vary according to the time. The `profile` is associated to 1.

`cutpoints` A list of the thresholds to identify the mortality rates according to the time-varying dimensions (NULL for `profile`).

`class` The class of the object: `ratetable`.

Details

The organization of a rate-table object is described in details by Therneau (1999) and Pohar (2006). We have estimated these data by using the renal epidemiology and information network (REIN). A competing risk model was performed in order to deal with the loss of follow-up to the transplantation. The `profile` represents the concatenation of the significant binary variables associated with the mortality on waiting list. In order to obtain the same variable in her/his database, the user have to concatenate the following values in the same order. These values are collected at the registration date on the waiting list:

- a. 1 if the patient is male and 0 if female.
- b. 1 if the time between the first dialysis and the registration is higher than 1 year and 0 otherwise.
- c. 1 if hemodialysis and 0 if peritoneal dialysis.
- d. 1 if the patient is diabetic and 0 otherwise.
- e. 1 if the patient had history of cardiac failure diabetic and 0 otherwise.
- f. 1 if the patient had history of vascular failure diabetic and 0 otherwise.
- g. 1 if the patient had history of cancer and 0 otherwise.
- h. 1 if the age of the patients is in between 40 and 60 years and 0 otherwise.

- i. 1 if the age of the patients is higher than 60 years and 0 otherwise.
- j. 1 if the calendar year at registration is strictly higher than 2007 and 0

Source

URL: www.agence-biomedecine.fr/Le-programme-REIN

References

Pohar and Stare Relative survival analysis in R. Computer methods and programs in biomedicine, 81, 272-278, 2006. <doi:10.1016/j.cmpb.2006.01.004>

Examples

```
data(rein.ratetable)

is.ratetable(rein.ratetable)
```

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 \sim 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 Weighing 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.
auc	The area under the ROC curve.

Author(s)

Y. Foucher <Yohann.Foucher@univ-nantes.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. Manuscript submitted. *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)

# The corresponding ROC graph with color and symbols

plot(roc1, col=2, pch=2, type="b")

# 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")

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.
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 equal 1 for particular cut-off values or times.

Author(s)

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

References

Pohar M., Stare J., Esteve J. (2012) On Estimation in Relative Survival. *Biometrics*, 68, 113-120. <doi:10.1111/j.1541-0420.2011.01640.x>

Lorent M., Giral M., Foucher Y. (2013) 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. <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 <- mdy.date(month=01, day=01, year=dataDIVAT3$year.tx,
  nineteen = TRUE, fillday = FALSE, fillmonth = FALSE)
dataDIVAT3$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 be used in case of non-monotone 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(c(1,1-roc1$table$sp,0), c(1,roc1$table$se,0), ylim=c(0,1), xlim=c(0,1),
```

```

ylab="sensitivity", xlab="1-specificity", type="l", lty=1, col=2, lwd=2)

abline(c(0,0), c(1,1), lty=2)

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

```

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 thresholds 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 marker 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. μ and σ 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. $\exp(\beta_{0.1})$ and $\exp(\beta_{0.2})$ represent the baseline hazard and the hazard ratio in the first interval. $\exp(\beta_{1.1})$ and $\exp(\beta_{1.2})$ represent the corrections of these parameters for the second interval... The inter-study variability is modeled with a random effect on the baseline parameter $\beta_{0.1}$. 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).
auc	The area under the SROC curve for a prognostic up to prognostic time.

Author(s)

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

Christophe Combescure <christophe.combescure@hcuge.ch>

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$urv, dataKi67$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, 6, 8))
```

```

### Compute the SROC curve for a prognostic up to 3 years
#roc3y<-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.nlmef=c(2.55, -0.29), precision=50, pro.time=3,
# time.cutoff=c(2, 4, 6, 8))

### The ROC graph associated to these to SROC curves
#plot(c(1,1-roc9y$table$sp,0), c(1,roc9y$table$se,0),
# xlab="1-specificity", ylab="sensitivity", type="l",
# col=1, lty=1, lwd=2)

#lines(c(1,1-roc3y$table$sp,0), c(1,roc3y$table$se,0), type="l",
# col=2, lty=2, lwd=2)

#legend("bottomright", c(paste("Prognostic up to 9 years (AUC=",
# round(roc9y$auc,2), ")"), sep=""), paste(
# "Prognostic up to 3 years (AUC=", round(roc3y$auc,2), ")"),
# sep=""), col=c(1, 2), lty=c(1, 2), lwd=c(2, 2))

### 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))

```

Description

This function allows for the estimation of time-dependent 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.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 <code>~ model</code> , where <code>model</code> is the linear predictor of the logistic regressions performed for each cut-off value. The user can use <code>~1</code> to obtain the crude estimation.
data	An object of the class <code>data.frame</code> 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 <code>times</code> .
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.
auc	The area under the time-dependent ROC curve for a prognostic up to <code>pro.time</code> .

Author(s)

Y. Foucher <Yohann.Foucher@univ-nantes.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>

Le Borgne F. 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

```
# 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(1-roc2$table$sp, roc2$table$se, ylim=c(0,1), xlim=c(0,1), ylab="sensitivity",
  xlab="1-specificity", type="l", lty=1, col=1, lwd=2)
abline(c(0,0), c(1,1), lty=2)
# 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: $1 \rightarrow 2$, $1 \rightarrow 3$ and $2 \rightarrow 3$.

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 transitioned 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 transitioned from X=1 to X=3), 123 (individual who transitioned 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 chooses "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:

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

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 <code>conf.int=TRUE</code> is specified, this data frame includes three additional columns: the Standard Errors of parameters (<code>Std.Error</code>), the value of the Wald statistic (<code>t.value</code>), and the related p-value for the Wald test (<code>Pr(> t)</code>).
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>.

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:

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

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.

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 <code>conf.int=TRUE</code> is specified, this data frame includes three additional columns: the Standard Errors of parameters (<code>Std.Error</code>), the value of the Wald statistic (<code>t.value</code>), and the related p-value for the Wald test (<code>Pr(> t)</code>).
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>.

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: $1 \rightarrow 2$, $1 \rightarrow 3$ and $2 \rightarrow 3$. 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 transitioned 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 transitioned from $X=1$ to $X=3$), 123 (individual who transitioned 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:

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

with $\sigma, \nu,$ 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 <code>conf.int=TRUE</code> is specified, this data frame includes three additional columns: the Standard Errors of parameters (Std.Error), the value of the Wald statistic (<code>t.value</code>), and the related p-value (<code>Pr(> t)</code>).
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$id<-c(1:nrow(dataDIVAT1))
set.seed(2)
d3<-dataDIVAT1[dataDIVAT1$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.date(paste("01","01",d3$year.tx),order = "mdy"),
  p.rate.table=fr.ratetable,
  conf.int=TRUE, silent=FALSE, precision=0.001)

```

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 transitioned 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 $\sigma, \nu,$ 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

<code>object</code>	A character string indicating the estimated model: "semi.markov.4states (4-state semi-Markov model)".
<code>dist</code>	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.
<code>cuts.12</code>	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=2.
<code>cuts.13</code>	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=3.
<code>cuts.14</code>	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=1 to X=4.
<code>cuts.23</code>	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=3.
<code>cuts.24</code>	A numeric vector indicating the timepoints in days for the piecewise exponential distribution related to the time from X=2 to X=4.
<code>covariates</code>	A numeric vector indicating the numbers of covariates respectively related to the transition 1->2, 1->3, 1->4, 2->3, and 2->4.
<code>table</code>	A data frame containing the estimated parameters of the model (Estimate). When the option <code>conf.int=TRUE</code> is specified, this data frame includes three additional columns: the Standard Errors of parameters (Std.Error), the value of the Wald statistic (<code>t.value</code>), and the related p-value for the Wald test (<code>Pr(> t)</code>).
<code>cov.matrix</code>	A data frame corresponding to variance-covariance matrix of the parameters.
<code>LogLik</code>	A numeric value corresponding to the (weighted) log-likelihood of the model.
<code>AIC</code>	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$id<-c(1:nrow(dataDIVAT1))
set.seed(2)
d4<-dataDIVAT1[dataDIVAT1$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: $1 \rightarrow 2$, $1 \rightarrow 3$, $1 \rightarrow 4$, $2 \rightarrow 3$ and $2 \rightarrow 4$. 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 transitioned 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 transitioned from X=1 to X=3), 14 (individual who directly transitioned from X=1 to X=4), 123 (individual who transitioned from X=1 to X=3 through X=2), 124 (individual who transitioned 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 chooses "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:

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 $\sigma, \nu,$ 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 <code>conf.int=TRUE</code> is specified, this data frame includes three additional columns: the Standard Errors of parameters (<code>Std.Error</code>), the value of the Wald statistic (<code>t.value</code>), and the related p-value for the Wald test (<code>Pr(> t)</code>).
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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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.date(paste("01", "01", d4$year.tx), order = "mdy"),
  p.rate.table=fr.ratetable, conf.int=TRUE,
  silent=FALSE, precision=0.001)

```

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 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. 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

<code>verif.data</code>	A data frame in which the first column (<code>study</code>) correspond to the number of the study and the second column (<code>check</code>) 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).
<code>summary.fixed</code>	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 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. The last element of the list is the summary survival when all strata are pooled.
<code>summary.random</code>	A list object containing the summarized survival probabilities in each stratum assuming random effects. The results are presented similarly as <code>summary.fixed</code> .
<code>median.fixed</code>	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.
<code>mean.fixed</code>	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.
<code>heterogeneity</code>	A numerical vector containing the value of the Q statistic for the heterogeneity, the H index and the I-squared index (in percentage).
<code>p.value</code>	The p-value of the test for the null hypothesis that the between-strata heterogeneity 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
```

usa.ratetable	<i>Expected Mortality Rates Of The General United States Population.</i>
---------------	--

Description

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

Usage

```
data(usa.ratetable)
```

Format

The format is "ratetable". The attributes are:

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

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* 2016; 81: 272-278. <DOI: 10.1016/j.cmpb.2006.01.004>

Examples

```
data(usa.ratetable)
```

```
is.ratetable(usa.ratetable)
```

Index

- *Topic **Competing events**
 - mixture.2states, 48
 - pred.mixture.2states, 52
 - *Topic **Dataset**
 - dataCSL, 3
 - dataDIVAT1, 4
 - dataDIVAT2, 5
 - dataDIVAT3, 6
 - dataDIVAT4, 7
 - dataDIVAT5, 8
 - dataHepatology, 10
 - dataKi67, 11
 - dataKTFS, 13
 - *Topic **G-computation**
 - gc.logistic, 20
 - gc.survival, 23
 - *Topic **Inverse Probability Weighting**
 - ipw.log.rank, 25
 - ipw.survival, 26
 - *Topic **Markov**
 - lrs.multistate, 29
 - markov.3states, 31
 - markov.3states.rsadd, 34
 - markov.4states, 38
 - markov.4states.rsadd, 43
 - *Topic **Pooled statistic**
 - survival.summary, 87
 - survival.summary.strata, 90
 - *Topic **ROC**
 - auc, 3
 - lines.roc, 28
 - plot.roc, 51
 - roc.binary, 56
 - roc.net, 58
 - roc.summary, 61
 - roc.time, 63
 - *Topic **Ratetable**
 - fr.ratetable, 19
 - rein.ratetable, 55
 - usa.ratetable, 92
 - *Topic **Semi-Markov**
 - lrs.multistate, 29
 - semi.markov.3states, 65
 - semi.markov.3states.ic, 69
 - semi.markov.3states.rsadd, 74
 - semi.markov.4states, 78
 - semi.markov.4states.rsadd, 82
 - *Topic **Utility**
 - expect.utility1, 14
 - expect.utility2, 17
- auc, 3
- dataCSL, 3
- dataDIVAT1, 4
- dataDIVAT2, 5
- dataDIVAT3, 6
- dataDIVAT4, 7
- dataDIVAT5, 8
- dataHepatology, 10
- dataKi67, 11
- dataKTFS, 13
- expect.utility1, 14
- expect.utility2, 17
- fr.ratetable, 19
- gc.logistic, 20
- gc.survival, 23
- ipw.log.rank, 25
- ipw.survival, 26
- lines.roc, 28
- lrs.multistate, 29
- markov.3states, 31
- markov.3states.rsadd, 34
- markov.4states, 38

markov.4states.rsadd, [43](#)
mixture.2states, [48](#)

plot.roc, [51](#)
pred.mixture.2states, [52](#)

rein.ratetable, [55](#)
roc.binary, [56](#)
roc.net, [58](#)
roc.summary, [61](#)
roc.time, [63](#)

semi.markov.3states, [65](#)
semi.markov.3states.ic, [69](#)
semi.markov.3states.rsadd, [74](#)
semi.markov.4states, [78](#)
semi.markov.4states.rsadd, [82](#)
survival.summary, [87](#)
survival.summary.strata, [90](#)

usa.ratetable, [92](#)