

Package ‘mstate’

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Title Data preparation, estimation and prediction in multi-state models

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Depends survival

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Description Functions for data preparation, descriptives, hazard estimation and prediction with Aalen-Johansen or simulation in competing risks and multi-state models

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mstate-package	<i>Data preparation, estimation and prediction in multi-state models</i>
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Description

Functions for data preparation, descriptives, (hazard) estimation and prediction (Aalen-Johansen) in competing risks and multi-state models.

Details

Package: mstate
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An overview of how to use the package, including the most important functions.

Author(s)

Liesbeth de Wreede, Marta Fiocco, Hein Putter. Maintainer: Hein Putter <H.Putter@lumc.nl>

References

Putter H, Fiocco M, Geskus RB (2007). Tutorial in biostatistics: Competing risks and multi-state models. *Statistics in Medicine* 26, 2389–2430.

L. C. de Wreede, M. Fiocco, and H. Putter (2010). The mstate package for estimation and prediction in non- and semi-parametric multi-state and competing risks models. *Computer Methods and Programs in Biomedicine* 99: 261–274.

 bmt

BMT data from Klein and Moeschberger

Description

A data frame of 137 rows (patients) and 22 columns. The included variables are

- group** Disease group; 1 = ALL, 2 = AML Low Risk, 3 = AML High Risk
- t1** Time in days to death or last follow-up
- t2** Disease-free survival time in days (time to relapse, death or last follow-up)
- d1** Death indicator; 1 = dead, 0 = alive
- d2** Relapse indicator; 1 = relapsed, 0 = disease-free
- d3** Disease-free survival indicator; 1 = dead or relapsed, 0 = alive and disease-free)
- ta** Time in days to Acute Graft-versus-Host Disease (AGVHD)
- da** Acute GVHD indicator; 1 = Acute GVHD, 0 = No Acute GVHD
- tc** Time (days) to Chronic Graft-versus-Host Disease (CGVHD)
- dc** Chronic GVHD indicator; 1 = Chronic GVHD, 0 = No Chronic GVHD
- tp** Time (days) to platelet recovery
- dp** Platelet recovery indicator; 1 = platelets returned to normal, 0 = platelets never returned to normal
- z1** Patient age in years
- z2** Donor age in years
- z3** Patient sex; 1 = male, 0 = female
- z4** Donor sex; 1 = male, 0 = female
- z5** Patient CMV status; 1 = CMV positive, 0 = CMV negative
- z6** Donor CMV status; 1 = CMV positive, 0 = CMV negative
- z7** Waiting time to transplant in days
- z8** FAB; 1 = FAB grade 4 or 5 and AML, 0 = Otherwise
- z9** Hospital; 1 = The Ohio State University, 2 = Alferd , 3 = St. Vincent, 4 = Hahnemann
- z10** MTX used as a Graft-versus-Host prophylactic; 1 = yes, 0 = no

Usage

```
data(bmt)
```

Format

A data frame, see [data.frame](#).

References

Klein and Moeschberger (1997). *Survival Analysis Techniques for Censored and Truncated Data*, Springer, New York.

crprep

Function to create weighted data set for competing risks analyses

Description

This function converts a dataset which is in short format (one subject per line, one column indicating type of end point at end of follow-up) into a weighted dataset in counting process style notation. With this data set, competing risks analyses can be performed.

Usage

```
crprep(Tstop, status, data, trans = 1, cens = 0, Tstart=0, id, keep, shorten = TRUE, rm.na = TRUE, origin)
```

Arguments

Tstop	Either 1) a vector containing the time at which the follow-up is ended, or 2) a character string indicating the column name that contains the end times. Missing values are allowed.
status	Either 1) a vector describing status at end of follow-up, or 2) a character string indicating the column name that contains this information. Missing values are allowed. See "Details".
data	Data frame in which to interpret "Tstart", "status", "trans", "cens", "Tstart", "id" and "keep", if appropriate.
trans	Values of "status" that are the event types of interest. Defaults to 1. See "Details".
cens	Value of "status" indicating censoring. Defaults to 0.
Tstart	Either 1) a vector containing the individual times at which the follow-up is started, or 2) a character string indicating the column name that contains the entry times, or 3) One numeric value in case it is the same for every subject. Missing values are allowed. Defaults to 0.
id	Either 1) a vector containing the subject identifiers, or 2) a character string indicating the column name containing these subject identifiers. If not provided, "id" will be assigned with values 1,...,n.
keep	Either 1) a data frame or matrix with n rows or a numeric or factor vector of length n containing covariate(s) that need to be retained in the output dataset, or 2) a character vector containing the column names of these covariates in data. See "Details".
shorten	Logical. If true, number of rows in output is reduced by collapsing rows within a subject in which weights do not change.

rm.na	Logical. If true, rows for which any of "Tstart", "status" or "Tstart" is missing are deleted.
origin	Substract origin time units from all Tstop and Tstart times.
prec.factor	Factor by which to multiply the machine's precision. Censoring and truncation times are shifted by prec.factor*precision if event times and censoring/trunaction times are equal.

Details

The function creates a data set that allows to perform analyses that are based on the subdistribution hazard. For each type of outcome as specified via "trans", individuals with a competing event remain in the risk set with a weight that depends on the censoring and truncation mechanisms in the data. Typically, their weights change over follow-up, and therefore such individuals are split into several rows. Several types of outcome can be specified at once, thus allowing for regression analyses using the "long format" data set (see Putter et al. 2007). A regression on the cause-specific hazard using the created data set can be performed by using "subset=count==0".

If keep is a data.frame or a named matrix, the same names are used for the covariate columns in the output data set. If keep is a matrix without names, then the covariate columns are given the names "V1" until "Vk". If keep is a vector from a (sub)-list, e.g. obj\$name2\$name1, then the column name is based on the most inner part (i.e. "name1"). If keep is a vector of the form obj[, "name1"], then the column is named "name1". For all other specifications, the name is copied as is.

The current function does not allow to create a weighted data set in which the censoring and /or truncation mechanisms depend on covariates. One option is to create a weighted data set for each level of a categorical covariate.

Value

A data frame in long (counting process) format containing the covariates (replicated per subject) and the following columns

patid	subject identifier (1:n if argument "id" was missing)
Tstart	start dates of dataset (counting process notation)
Tstop	stop dates of dataset (counting process notation)
status	status of the subject at the end of his follow-up
weight.cens	weights due to censoring mechanism
weight.trunc	weights due to truncation mechanism (if present)
count	counter per subject and type of end point, 1 to number of rows per subject id and type of end point
failcode	type of end point, thus allowing to perform regression using the "long format" data set

Author(s)

Ronald Geskus <statistics@inter.nl.net>, Kristian van Hemert; some adaptation by Marcel Wolbers

References

Geskus RB (2011). Cause-Specific Cumulative Incidence Estimation and the Fine and Gray Model Under Both Left Truncation and Right Censoring. *Biometrics*, to appear.

Putter H, Fiocco M, Geskus RB (2007). Tutorial in biostatistics: Competing risks and multi-state models. *Statistics in Medicine* **26**, 2389–2430.

Examples

```
# Create simulated data
set.seed(1234)
N <- 200
p <- 0.3
p.t <- 0.6
Z1 <- rnorm(N)
Z2 <- rnorm(N)
tmp <- runif(N)
Data <- data.frame(Tstart=runif(N,0,3)*rbinom(N,1,p.t),
  Tstop=ifelse( tmp>(1-p)^(exp(0.5*Z1+0.5*Z2)),
    -log(1-(1-exp(log(tmp)/exp(0.5*Z1+0.5*Z2)))/p),
    -log(tmp)/exp(-0.5*Z1+0.5*Z2)),
  stat=ifelse(tmp>(1-p)^(exp(0.5*Z1+0.5*Z2)),1,2),
  Z1=Z1, Z2=Z2, tstat=rep(0,N))
Data$type <- Data$stat
Data$tevent <- Data$Tstop
Data$cens <- runif(N,0.5,1)
Data[Data$cens<Data$Tstop,"stat"] <- 0
Data$Tstop <- pmin(Data$Tstop,Data$cens)
Data$tstat <- ifelse(Data$Tstart > Data$Tstop, 1, 0)
Data.weight <- crprep(Data$Tstop, Data$stat, trans=c(1,2))

# calculate cause-specific cumulative incidence, no truncation,
# compare with Cuminc (also from mstate)
ci <- Cuminc(Data$Tstop, Data$stat)
plot(ci$time,ci$CI.1,type="s",lwd=3,col="black",ylim=c(0,0.5),xlab="Time",ylab="Cumulative incidence")
lines(ci$time,ci$CI.2,type="s",lwd=3,col="red")
lines(ci$time,ci$CI.1-qnorm(0.975)*ci$seCI.1,type="s",lty=3)
lines(ci$time,ci$CI.1+qnorm(0.975)*ci$seCI.1,type="s",lty=3)
lines(survfit(Surv(Tstart,Tstop,status==1)~1,data=Data.weight,
  weight=weight.cens,subset=failcode==1),
  fun="event",col="lightblue",lwd=1,mark.time=FALSE)
lines(survfit(Surv(Tstart,Tstop,status==1)~1,data=Data.weight,
  weight=weight.cens,subset=failcode==1),
  fun="event",col="lightblue",mark.time=FALSE,conf.int="only",lty=2)

# Proportional hazards regression on subdistribution and cause-specific hazard,
# with truncation
Data.weight.trunc <- crprep("Tstop", "stat", Tstart="Tstart",
  data=subset(Data,tstat==0), trans=1:2, keep=c("Z1","Z2"))
coxph(Surv(Tstart,Tstop,status==1)~Z1+Z2,data=Data.weight.trunc,
  weight=weight.cens*weight.trunc,subset=failcode==1) #cause 1
```

```

# Both end points, assume effect Z2 same for both
coxph(Surv(Tstart,Tstop,status==1)~strata(failcode)*Z1+Z2,
      data=Data.weight.trunc,weight=weight.cens*weight.trunc)
# Cause-specific hazard
coxph(Surv(Tstart,Tstop,stat==1)~Z1+Z2,data=subset(Data, tstat==0))
coxph(Surv(Tstart,Tstop,status==1)~Z1+Z2,data=Data.weight.trunc,
      subset=failcode==1&count==1)

## Not run:
data(ebmt2)
ebmt2.long <- crprep("time", "status", data=ebmt2, trans=1:6,
                    keep=c("dissub", "match", "tcd", "year", "age"))
# ebmt2.long <- with(ebmt2, crprep(time, cod, trans=levels(cod)[-1], cens="Alive",
#                               keep=c("dissub", "match", "tcd", "year", "age")))
plot(survfit(Surv(time, status>0)~1, data=ebmt2, etype=cod), mark.time=FALSE,
     col=2:7, fun="event",lwd=3)
lines(survfit(Surv(Tstart, Tstop, failcode==status) ~ failcode, data=ebmt2.long,
              weight=weight.cens), lwd=2, lty=2, fun="event", mark.time=FALSE)
## End(Not run)

```

Cuminc

Calculate nonparametric cumulative incidence functions and associated standard errors

Description

This function computes nonparametric cumulative incidence functions and associated standard errors for each value of a group variable.

Usage

```
Cuminc(time, status, data, group, failcodes, na.status=c("remove","extra"),
       variance=TRUE)
```

Arguments

time	Either 1) a numeric vector containing the failure times or 2) a string containing the column name indicating these failure times
status	Either 1) a numeric, factor or character vector containing the failure codes or 2) a string containing the column name indicating these failure codes
data	When appropriate, a data frame containing time, status and/or group variables
group	Optionally, name of column in data indicating a grouping variable; cumulative incidence functions are calculated for each value or level of group. If missing no groups are considered
failcodes	A vector indicating which values of status are considered as different causes of failure; other values of status are considered as censorings. If missing and status is numeric, it is assumed that 0 is censoring and all other values indicate failcodes; if missing and status is character or factor, then it is assumed that each of the levels/values of status is a cause of failure

na.status	One of "remove" (default) or "extra", indicating whether subjects with missing cause of failure should be removed or whether missing cause of failure should be treated as a separate cause of failure
variance	Logical value, indicating whether the standard errors of the cumulative incidences should be output (TRUE, the default) or not

Details

The estimated cumulative incidences are as described in Putter, Fiocco & Geskus (2007); the standard errors are the square roots of the Greenwood variance estimators, see eg. Andersen, Borgan, Gill & Keiding (1993), de Wreede, Fiocco & Putter (2009), and they correspond to the variances in eg. Marubini & Valsecchi (1997). In case of no censoring, the estimated cumulative incidences and variances reduce to simple binomial frequencies and their variances.

Value

A data frame containing the estimated failure-free probabilities and cumulative incidences and their standard errors. The names of the dataframe are time, Surv, seSurv, and cuminc and secuminc followed by the values or levels of the failcodes. If group was specified, a group variable is included with the same name and values/levels as the original grouping variable, and with estimated cumulative incidences (SE) for each value/level of group.

Author(s)

Hein Putter <H.Putter@lumc.nl>

References

- Andersen PK, Borgan O, Gill RD, Keiding N (1993). *Statistical Models Based on Counting Processes*. Springer, New York.
- Marubini E, Valsecchi MG (1995). *Analysing Survival Data from Clinical Trials and Observational Studies*. Wiley, New York.
- Putter H, Fiocco M, Geskus RB (2007). Tutorial in biostatistics: Competing risks and multi-state models. *Statistics in Medicine* **26**, 2389–2430.
- de Wreede L, Fiocco M, Putter H (2009). The mstate package for estimation and prediction in non- and semi-parametric multi-state models. Submitted. www.msbi.nl/multistate.

Examples

```
### These data were used in Putter, Fiocco & Geskus (2007)
data(aidssi)
ci <- Cuminc(time=aidssi$time, status=aidssi$status)
head(ci); tail(ci)
ci <- Cuminc(time="time", status="status", data=aidssi, group="ccr5")
head(ci); tail(ci)

### Some fake data
fake <- data.frame(surv=c(seq(2,10,by=2),seq(1,13,by=3),seq(1,9,by=2),seq(1,13,by=3)),
                  stat=rep(0:3,5),Tstage=c(1:4,rep(1:4,rep(4,4))))
```

```

fake$stat[fake$stat==0 & fake$Tstage==2] <- 3
fake$stat[fake$stat==3 & fake$Tstage==1] <- 2
fake
Cuminc(time="surv", status="stat", data=fake)
# If we remove all entries with status=0,
# we should get binomial sample probabilities and corresponding SEs
fake0 <- fake[fake$stat!=0,]
Cuminc(time="surv", status="stat", data=fake0)
# Use failcodes
Cuminc(time="surv", status="stat", data=fake, failcodes=c(1,3))
# Make grouping variable and status variable a factor
fake$Tstage <- factor(fake$Tstage,labels=c("T1","T2","T3","T4"))
fake$stat <- factor(fake$stat,levels=0:3,
                    labels=c("eventfree","event1","event2","event3"))
Cuminc(time="surv", status="stat", data=fake, group="Tstage")
# (The warnings are a result of the fact that some failure causes
# do not occur for some values/levels of the grouping variable)
# The previous command didn't do what we wanted because we didn't
# tell Cuminc that eventfree is not an event
Cuminc(time="surv", status="stat", data=fake, group="Tstage",
        failcodes=c("event1","event2","event3"))

```

EBMT cause of death data

Data from the European Registry for Blood and Marrow Transplantation (EBMT)

Description

A data frame of 8966 patients transplanted at the EBMT. The included variables are

id Patient identification number

time Time in months from transplantation to death or last follow-up

status Survival status; 0 = censored; 1,...,6 = death due to the following causes: Relapse (1), GvHD (2), Bacterial infections (3), Viral infections (4), Fungal infections (5), Other causes (6)

cod Cause of death as factor with levels "Alive", "Relapse", "GvHD", "Bacterial", "Viral", "Fungal", "Other"

dissub Disease subclassification; factor with levels "AML", "ALL", "CML"

match Donor-recipient gender match; factor with levels "No gender mismatch", "Gender mismatch"

tcd T-cell depletion; factor with levels "No TCD", "TCD", "Unknown"

year Year of transplantation; factor with levels "1985-1989", "1990-1994", "1995-1998"

age Patient age at transplant; factor with levels "<=20", "20-40", ">40"

Usage

`data(ebmt2)`

Format

A data frame, see [data.frame](#).

References

Fiocco M, Putter H, van Houwelingen JC (2005). Reduced rank proportional hazards model for competing risks. *Biostatistics* **6**, 465–478.

EBMT data	<i>Data from the European Registry for Blood and Marrow Transplantation (EBMT)</i>
-----------	--

Description

A data frame of 2279 patients transplanted at the EBMT between 1985 and 1998. These data were used in Fiocco, Putter & van Houwelingen (2008) and van Houwelingen & Putter (2008). The included variables are

id Patient identification number

rec Time in days from transplantation to recovery or last follow-up

rec.s Recovery status; 1 = recovery, 0 = censored

ae Time in days from transplantation to adverse event (AE) or last follow-up

ae.s Adverse event status; 1 = adverse event, 0 = censored

recae Time in days from transplantation to both recovery and AE or last follow-up

plag.s Recovery and AE status; 1 = both recovery and AE, 0 = no recovery or no AE or censored

rel Time in days from transplantation to relapse or last follow-up

rel.s Relapse status; 1 = relapse, 0 = censored

srv Time in days from transplantation to death or last follow-up

srv.s Relapse status; 1 = dead, 0 = censored

year Year of transplantation; factor with levels "1985-1989", "1990-1994", "1995-1998"

agecl Patient age at transplant; factor with levels "<=20", "20-40", ">40"

proph Prophylaxis; factor with levels "no", "yes"

match Donor-recipient gender match; factor with levels "no gender mismatch", "gender mismatch"

Usage

```
data(ebmt4)
```

Format

A data frame, see [data.frame](#).

References

- Fiocco M, Putter H, van Houwelingen HC (2008). Reduced-rank proportional hazards regression and simulation-based prediction for multi-state models. *Statistics in Medicine* **27**, 4340–4358.
- van Houwelingen HC, Putter H (2008). Dynamic predicting by landmarking as an alternative for multi-state modeling: an application to acute lymphoid leukemia data. *Lifetime Data Anal* **14**, 447–463.

EBMT platelet recovery data

Data from the European Registry for Blood and Marrow Transplantation (EBMT)

Description

A data frame of 2204 patients transplanted at the EBMT between 1995 and 1998. These data were used in Section 4 of the tutorial on competing risks and multi-state models (Putter, Fiocco & Geskus, 2007). The included variables are

id Patient identification number

prtime Time in days from transplantation to platelet recovery or last follow-up

prstat Platelet recovery status; 1 = platelet recovery, 0 = censored

rfstime Time in days from transplantation to relapse or death or last follow-up (relapse-free survival time)

rfstat Relapse-free survival status; 1 = relapsed or dead, 0 = censored

dissub Disease subclassification; factor with levels "AML", "ALL", "CML"

age Patient age at transplant; factor with levels "<=20", "20-40", ">40"

drmatch Donor-recipient gender match; factor with levels "No gender mismatch", "Gender mismatch"

tcd T-cell depletion; factor with levels "No TCD", "TCD"

Usage

```
data(ebmt3)
```

Format

A data frame, see [data.frame](#).

References

- Putter H, Fiocco M, Geskus RB (2007). Tutorial in biostatistics: Competing risks and multi-state models. *Statistics in Medicine* **26**, 2389–2430.

EBMT year of relapse data

Data from the European Registry for Blood and Marrow Transplantation (EBMT)

Description

A data frame of 1977 patients transplanted for CML. The included variables are

patid Patient identification number

srv Time in days from transplantation to death or last follow-up

srvstat Survival status; 1 = death; 0 = censored

rel Time in days from transplantation to relapse or last follow-up

relstat Relapse status; 1 = relapsed; 0 = censored

yrel Calendar year of relapse; factor with levels "1993-1996", "1997-1999", "2000-"

age Patient age at transplant (years)

score Gratwohl score; factor with levels "Low risk", "Medium risk", "High risk"

Usage

```
data(ebmt1)
```

Format

A data frame, see [data.frame](#).

References

Fiocco M, Putter H, Iacobelli S, Heim D, de Witte T, Olavarria E, Guglielmi E, Gratwohl A, Brand R, on behalf of the Chronic Leukemia Working party of the European Group for Blood and Marrow Transplantation EBMT (2009). Evaluation of the impact of relapse after allogeneic hematopoietic stem cell transplantation on death rate in patients with chronic myeloid leukemia: the need for a multi-state model. Submitted.

events

Count number of observed transitions

Description

Given a dataset in long format, for instance generated by [msprep](#), and a transition matrix for the multi-state model, this function counts the number of observed transitions in the multi-state model and gives their percentages.

Usage

```
events(msdata)
```

Arguments

msdata An object of class "msdata", such as output by [msprep](#)

Details

Although `msdata` does not need to be the result of a call to [msprep](#), it does need to be an object of class "msdata", which is essentially a data frame in long format, with one row for each transition for which the subject is at risk. The columns `from`, `to`, and `status` need to be present, with appropriate meaning, see [msprep](#). The `msdata` argument needs to have a "trans" attributes, which holds the transition matrix of the multi-state model.

Value

A list containing two tables, the first, called `Frequencies`, with the number of observed transitions in the multi-state model occurring in `msdata`, the second, called `Proportions`, with the corresponding proportions.

Author(s)

Hein Putter <H.Putter@lumc.nl>

Examples

```
tmat <- trans.illdeath(names=c("Tx", "PR", "RelDeath"))
data(ebmt3) # data from Section 4 of Putter, Fiocco & Geskus (2007)
msebmt <- msprep(time=c(NA, "prtime", "rfstime"), status=c(NA, "prstat", "rfsstat"),
  data=ebmt3, id="patid", trans=tmat)
events(msebmt) # see Fig 13 of Putter, Fiocco & Geskus (2007)
```

expand.covs

Expand covariates in dataset in long format

Description

Given a multi-state dataset in long format, and one or more covariates, this function adds transition-specific covariates, expanding the original covariate(s), to the dataset. The original dataset with the transition-specific covariates appended is returned.

Usage

```
expand.covs(data, covs, append=TRUE, longnames=TRUE)
```

Arguments

data	An object of class "msdata", such as output by msprep
covs	A character vector containing the names of the covariates in data to be expanded
append	Logical value indicating whether or not the design matrix for the expanded covariates should be appended to the data (default=TRUE)
longnames	Logical value indicating whether or not the labels are to be used for the names of the expanded covariates that are categorical (default=TRUE); in case of FALSE numbers from 1 up to the number of contrasts are used

Details

For a given basic covariate Z , the transition-specific covariate for transition s is called $Z.s$. The concept of transition-specific covariates in the context of multi-state models was introduced by Andersen, Hansen & Keiding (1991), see also Putter, Fiocco & Geskus (2007). It is only unambiguously defined for numeric covariates or for explicit codings. Then it will take the value 0 for all rows in the long format dataframe for which `trans` does not equal s . For the rows for which `trans` equals s , the original value of Z is copied. In `expand.covs`, when a given covariate is a factor, it will be expanded on the design matrix given by `model.matrix`. Missing values in the basic covariates are allowed and result in missing values in the expanded covariates.

Value

An object of class 'msdata', containing the design matrix for the transition-specific covariates, either on its own (`append=FALSE`) or appended to the data (`append=TRUE`).

Author(s)

Hein Putter <H.Putter@lumc.nl>

References

Andersen PK, Hansen LS, Keiding N (1991). Non- and semi-parametric estimation of transition probabilities from censored observation of a non-homogeneous Markov process. *Scandinavian Journal of Statistics* **18**, 153–167.

Putter H, Fiocco M, Geskus RB (2007). Tutorial in biostatistics: Competing risks and multi-state models. *Statistics in Medicine* **26**, 2389–2430.

Examples

```
# transition matrix for illness-death model
tmat <- trans.illdeath()
# small data set in wide format
tg <- data.frame(illt=c(1,1,6,6,8,9),ills=c(1,0,1,1,0,1),
               dt=c(5,1,9,7,8,12),ds=c(1,1,1,1,1,1),
               x1=c(1,1,1,2,2,2),x2=c(6:1))
tg$x1 <- factor(tg$x1,labels=c("male","female"))
# data in long format using msprep
tglong <- msprep(time=c(NA,"illt","dt"),
                status=c(NA,"ills","ds"),data=tg,
```

```
      keep=c("x1", "x2"), trans=tmat)
# expanded covariates
expand.covs(tglong, c("x1", "x2"), append=FALSE)
expand.covs(tglong, "x1")
expand.covs(tglong, "x1", longnames=FALSE)
```

HIV/AIDS SI data

Data from the Amsterdam Cohort Studies on HIV infection and AIDS

Description

A data frame of 329 homosexual men from the Amsterdam Cohort Studies on HIV infection and AIDS. The included variables are

patid Patient identification number

time Time in years from HIV infection to either SI appearance, AIDS, or last follow-up

status Event indicator; 0 = censored, 1 = AIDS, 2 = SI appearance

cause Failure cause; factor with levels "event-free", "AIDS", "SI"

ccr5 CCR5 genotype; factor with levels "WW" (2 wild-type alleles), "WM" (1 (or possibly two) mutant alleles)

Usage

```
data(aidssi)
```

Format

A data frame, see [data.frame](#).

Details

This data was used in the tutorial on competing risks and multi-state models (Putter, Fiocco, Geskus, 2007). For more information refer to the tutorial or to the original papers (Geskus et al., 2000, 2003).

References

Geskus RB (2000). On the inclusion of prevalent cases in HIV/AIDS natural history studies through a marker-based estimate of time since seroconversion. *Statistics in Medicine* **19**, 1753–1769.

Geskus RB, Miedema FA, Goudsmit J, Reiss P, Schuitemaker H, Coutinho RA (2003). Prediction of residual time to AIDS and death based on markers and cofactors. *Journal of AIDS* **32**, 514–521.

Putter H, Fiocco M, Geskus RB (2007). Tutorial in biostatistics: Competing risks and multi-state models. *Statistics in Medicine* **26**, 2389–2430.

Liver cirrhosis data *Abnormal prothrombin levels in liver cirrhosis*

Description

A data frame of 488 liver cirrhosis patients from a randomized clinical trial concerning prednisone treatment in these patients. The dataset is in long format. The included variables are

id Patient identification number

from Starting state

to Receiving state

trans Transition number

Tstart Starting time

Tstop Transition time

status Status variable; 1=transition, 0=censored

treat Treatment; factor with levels "Placebo", "Prednisone"

Usage

```
data(prothr)
```

Format

A data frame, see [data.frame](#).

Details

This data was kindly provided by Per Kragh Andersen. It was introduced in Andersen, Borgan, Gill & Keiding (1993), Example 1.3.12, and used as illustration for computation of transition probabilities in multi-state models, see Sections IV.4 (Example IV.4.4) and VII.2 (Example VII.2.10).

References

Andersen PK, Borgan O, Gill RD, Keiding N (1993). *Statistical Models Based on Counting Processes*. Springer, New York.

`msboot`*Bootstrap function in multi-state models*

Description

A generic nonparametric bootstrapping function for multi-state models.

Usage

```
msboot(theta, data, B=5, id="id", verbose=0, ...)
```

Arguments

<code>theta</code>	A function of data and perhaps other arguments, returning the value of the statistic to be bootstrapped; the output of theta should be a scalar or numeric vector
<code>data</code>	An object of class 'msdata', such as output from msprep
<code>B</code>	The number of bootstrap replications; the default is taken to be quite small (5) since bootstrapping can be time-consuming
<code>id</code>	Character string indicating which column identifies the subjects to be resampled
<code>verbose</code>	The level of output; default 0 = no output, 1 = print the replication
<code>...</code>	Any further arguments to the function theta

Details

The function `msboot` samples randomly with replacement subjects from the original dataset `data`. The individuals are identified with `id`, and bootstrap datasets are produced by concatenating all selected rows.

Value

Matrix of dimension (length of output of theta) x B, with b'th column being the value of theta for the b'th bootstrap dataset

Author(s)

Marta Fiocco, Hein Putter <H.Putter@lumc.nl>

References

Fiocco M, Putter H, van Houwelingen HC (2008). Reduced-rank proportional hazards regression and simulation-based prediction for multi-state models. *Statistics in Medicine* **27**, 4340–4358.

Examples

```
tmat <- trans.illdeath()
data(ebmt1)
covs <- c("score", "yrel")
msebmt <- msprep(time=c(NA, "rel", "srv"), status=c(NA, "relstat", "srvstat"),
  data=ebmt1, id="patid", keep=covs, trans=tmat)
# define a function (this one returns vector of regression coef's)
regcoefvec <- function(data) {
  cx <- coxph(Surv(Tstart, Tstop, status)~score+strata(trans),
    data=data, method="breslow")
  return(coef(cx))
}
regcoefvec(msebmt)
set.seed(1234)
msboot(theta=regcoefvec, data=msebmt, id="patid")
```

msfit

Compute subject-specific transition hazards with (co-)variances

Description

This function computes subject-specific or overall cumulative transition hazards for each of the possible transitions in the multi-state model. If requested, also the variances and covariances of the estimated cumulative transition hazards are calculated.

Usage

```
msfit(object, newdata, variance=TRUE, vartype=c("aalen", "greenwood"), trans)
```

Arguments

object	A coxph object describing the fit of the multi-state model
newdata	A data frame with the same variable names as those that appear in the coxph formula. Its use is somewhat different from survfit . See Details . The argument <code>newdata</code> may be omitted only if the right hand side of the formula in the coxph object is <code>~strata(trans)</code>
variance	A logical value indicating whether the (co-)variances of the subject-specific transition hazards should be computed. Default is TRUE
vartype	A character string specifying the type of variances to be computed (so only needed if <code>variance=TRUE</code>). Possible values are "aalen" or "greenwood"
trans	Transition matrix describing the states and transitions in the multi-state model. See <code>trans</code> in msprep for more detailed information

Details

The data frame needs to have one row for each transition in the multi-state model. An additional column `stratum` (numeric) is needed to describe for each transition to which stratum it belongs. For details refer to de Wreede, Fiocco & Putter (2009). So far, the results have been checked only for the "breslow" method of dealing with ties in [coxph](#).

Value

An object of class "msfit", which is a list containing

Haz	A data frame with time, Haz, trans, containing the estimated subject-specific hazards for each of the transitions in the multi-state model
varHaz	A data frame with time, Haz, trans1, trans2 containing the variances (trans1=trans2) and covariances (trans1<trans2) of the estimated hazards. This element is only returned when variance=TRUE
trans	The transition matrix used

Author(s)

Hein Putter <H.Putter@lumc.nl>

References

Putter H, Fiocco M, Geskus RB (2007). Tutorial in biostatistics: Competing risks and multi-state models. *Statistics in Medicine* **26**, 2389–2430.

Therneau TM, Grambsch PM (2000). *Modeling Survival Data: Extending the Cox Model*. Springer, New York.

L. C. de Wreede, M. Fiocco, and H. Putter (2010). The mstate package for estimation and prediction in non- and semi-parametric multi-state and competing risks models. *Computer Methods and Programs in Biomedicine* **99**: 261–274.

See Also

[plot.msfit](#)

Examples

```
# transition matrix for illness-death model
tmat <- trans.illdeath()
# data in wide format, for transition 1 this is dataset E1 of
# Therneau & Grambsch (2000)
tg <- data.frame(illt=c(1,1,6,6,8,9),ills=c(1,0,1,1,0,1),
                dt=c(5,1,9,7,8,12),ds=c(1,1,1,1,1,1),
                x1=c(1,1,1,0,0,0),x2=c(6:1))
# data in long format using msprep
tglong <- msprep(time=c(NA,"illt","dt"),status=c(NA,"ills","ds"),
                data=tg,keep=c("x1","x2"),trans=tmat)
# events
events(tglong)
table(tglong$status,tglong$to,tglong$from)
# expanded covariates
tglong <- expand.covs(tglong,c("x1","x2"))
# Cox model with different covariate
cx <- coxph(Surv(Tstart,Tstop,status)~x1.1+x2.2+strata(trans),
            data=tglong,method="breslow")
summary(cx)
# new data, to check whether results are the same for transition 1 as
```

```
# those in appendix E.1 of Therneau & Grambsch (2000)
newdata <- data.frame(trans=1:3,x1.1=c(0,0,0),x2.2=c(0,1,0),strata=1:3)
msfit(cx,newdata,trans=tmatrix)
```

msprep	<i>Function to prepare dataset for multi-state modeling in long format from dataset in wide format</i>
--------	--

Description

This function converts a dataset which is in wide format (one subject per line, multiple columns indicating time and status for different states) into a dataset in long format (one line for each transition for which a subject is at risk). Selected covariates are replicated per subjects.

Usage

```
msprep(time, status, data, trans, start, id, keep)
```

Arguments

time	Either 1) a matrix or data frame of dimension $n \times S$ (n being the number of individuals and S the number of states in the multi-state model), containing the times at which the states are visited or last follow-up time, or 2) a character vector of length S containing the column names indicating these times. In the latter cases, some elements of time may be NA, see Details
status	Either 1) a matrix or data frame of dimension $n \times S$, containing, for each of the states, event indicators taking the value 1 if the state is visited or 0 if it is not (censored), or 2) a character vector of length S containing the column names indicating these status variables. In the latter cases, some elements of status may be NA, see Details
data	Data frame in wide format in which to interpret time, status, id or keep, if appropriate
trans	Transition matrix describing the states and transitions in the multi-state model. If S is the number of states in the multi-state model, trans should be an $S \times S$ matrix, with (i,j) -element a positive integer if a transition from i to j is possible in the multi-state model, NA otherwise. In particular, all diagonal elements should be NA. The integers indicating the possible transitions in the multi-state model should be sequentially numbered, $1, \dots, K$, with K the number of transitions
start	List with elements state and time, containing starting states and times of the subjects in the data. Default is NULL, in which case all subjects start in state 1 at time 0. If a single state and time are given this state and time is used for all subjects, otherwise the length of state and time should equal the number of subjects in data
id	Either 1) a vector of length n containing the subject identifications, or 2) a character string indicating the column name containing these subject ids. If not provided, "id" will be assigned with values $1, \dots, n$

keep Either 1) a data frame or matrix with n rows or a numeric or factor vector of length n containing covariate(s) that need to be retained in the output dataset, or 2) a character vector containing the column names of these covariates in data

Details

For `msprep`, the transition matrix should correspond to an irreversible acyclic Markov chain. In particular, on the diagonals only NAs are allowed.

The transition matrix, if irreversible and acyclic, will have starting states, i.e. states into which no transitions are possible. For these starting states NAs are allowed in the `time` and `status` arguments, either as columns, when specified as matrix or data frame, or as elements of the character vector when specified as character vector.

The function `msprep` uses a recursive algorithm through calls to the recursive function `msprepEngine`. First, with the current transition matrix, all starting states are detected (defined as states into which there are no transitions). For each of these starting states, all subjects starting from that state are selected and for each subject the next visited state is detected by looking at all transitions from that starting state and determining the smallest transition time with `status=1`. The recursive `msprepEngine` is called again with the starting states deleted from the transition matrix and with subjects deleted that either reached an absorbing state or that were censored. For the remaining subjects the starting states and times are updated in the next call. Datasets returned from the `msprepEngine` calls are appended to the current dataset in long format and finally sorted.

A warning is issued for a subject, if multiple transitions exist with the same smallest transition time (and `status=0`). In such cases the next transition cannot be determined unambiguously, and the state with the smallest number is chosen. In our experience, occasionally the shortest transition time has `status=0`, while a higher transition time has `status=1`. Then this larger transition time and the corresponding transition is selected. No warning is issued for these data inconsistencies.

Value

An object of class "msdata", which is a data frame in long (counting process) format containing the subject id, the covariates (replicated per subject), and

<code>from</code>	the starting state
<code>to</code>	the receiving state
<code>trans</code>	the transition number
<code>Tstart</code>	the starting time of the transition
<code>Tstop</code>	the stopping time of the transition
<code>status</code>	status variable, with 1 indicating an event (transition), 0 a censoring

The "msdata" object has the transition matrix as "trans" attribute.

Author(s)

Hein Putter <H.Putter@lumc.nl> and Marta Fiocco

References

Putter H, Fiocco M, Geskus RB (2007). Tutorial in biostatistics: Competing risks and multi-state models. *Statistics in Medicine* **26**, 2389–2430.

Examples

```
# transition matrix for illness-death model
tmat <- trans.illdeath()
# some data in wide format
tg <- data.frame(stt=rep(0,6),sts=rep(0,6),
  illt=c(1,1,6,6,8,9),ills=c(1,0,1,1,0,1),
  dt=c(5,1,9,7,8,12),ds=c(1,1,1,1,1,1),
  x1=c(1,1,1,2,2,2),x2=c(6:1))
tg$x1 <- factor(tg$x1,labels=c("male","female"))
tg$patid <- factor(2:7,levels=1:8,labels=as.character(1:8))
# define time, status and covariates also as matrices
tt <- matrix(c(rep(NA,6),tg$illt,tg$dt),6,3)
st <- matrix(c(rep(NA,6),tg$ills,tg$ds),6,3)
keepmat <- data.frame(gender=tg$x1,age=tg$x2)
# data in long format using msprep
msprep(time=tt,status=st,trans=tmat,keep=as.matrix(keepmat))
msprep(time=c(NA,"illt","dt"),status=c(NA,"ills","ds"),data=tg,
  id="patid",keep=c("x1","x2"),trans=tmat)
# Patient no 5, 6 now start in state 2 at time t=4 and t=10
msprep(time=tt,status=st,trans=tmat,keep=keepmat,
  start=list(state=c(1,1,1,1,2,2),time=c(0,0,0,0,4,10)))
```

mssample

Sample paths through a multi-state model

Description

Given cumulative transition hazards sample paths through the multi-state model.

Usage

```
mssample(Haz, trans, history=list(state=1,time=0,tstate=NULL),
  beta.state=NULL, clock=c("forward","reset"),
  output=c("state","path","data"),
  tvec, cens=NULL, M=10, do.trace=NULL)
```

Arguments

Haz	Cumulative hazards to be sampled from. These should be given as a data frame with columns time, Haz, trans, for instance as the Haz list element given by msfit .
trans	Transition matrix describing the multi-state model. See trans in msprep for more detailed information
history	A list with elements state, specifying the starting state(s), time, the starting time(s), and tstate, a numeric vector of length the number of states, specifying at what times states have been visited, if appropriate. The default of tstate is NULL; more information can be found under Details.

	The elements <code>state</code> and <code>time</code> may either be scalars or vectors, in which case different sampled paths may start from different states or at different times. By default, all sampled paths start from state 1 at time 0.
<code>beta.state</code>	A matrix of dimension (no states) x (no transitions) specifying estimated effects of times at which earlier states were reached on subsequent transitions. If these are not in the model, the value <code>NULL</code> (default) suffices; more information can be found under <code>Details</code>
<code>clock</code>	Character argument, either <code>"forward"</code> (default) or <code>"reset"</code> , specifying whether the time-scale of the cumulative hazards is in forward time (<code>"forward"</code>) or duration in the present state (<code>"reset"</code>)
<code>output</code>	One of <code>"state"</code> , <code>"path"</code> , or <code>"data"</code> , specifying whether states, paths, or data should be output.
<code>tvec</code>	A numeric vector of time points at which the states or paths should be evaluated. Ignored if <code>output="data"</code>
<code>cens</code>	An independent censoring distribution, given as a data frame with <code>time</code> and <code>Haz</code>
<code>M</code>	The number of sampled trajectories through the multi-state model. The default is 10, since the procedure can become quite time-consuming
<code>do.trace</code>	An integer, specifying that the replication number should be written to the console every <code>do.trace</code> replications. Default is <code>NULL</code> in which case no output is written to the console during the simulation

Details

The procedure is described in detail in Fiocco, Putter & van Houwelingen (2008). The argument `beta.state` and the element `tstate` from the argument `history` are meant to incorporate situations where the time at which some previous states were visited may affect future transition rates. The relation between time of visit of state `s` and transition `k` is assumed to be linear on the log-hazards; the corresponding regression coefficient is to be supplied as the `(s,k)`-element of `beta.state`, which is 0 if no such effect has been included in the model. If no such effects are present, then `beta.state=NULL` (default) suffices. In the `tstate` element of `history`, the `s`-th element is the time at which state `s` was visited. This is only relevant for states which have been visited prior to the beginning of sampling, i.e. before the `time` element of `history`; the elements of `tstate` are internally updated when in the sampling process new states are visited (only if `beta.state` is not `NULL` to avoid unnecessary computations).

Value

`M` simulated paths through the multi-state model given by `trans` and `Haz`. It is either a data frame with columns `time`, `pstate1`, ..., `pstateS` for `S` states when `output="state"`, or with columns `time`, `ppath1`, ..., `ppathP` for the `P` paths specified in `paths(trans)` when `output="path"`. When `output="data"`, the sampled paths are stored in an `"msdata"` object, a data frame in long format such as that obtained by `msprep`. This may be useful for (semi-)parametric bootstrap procedures, in which case `cens` may be used as censoring distribution (assumed to be independent of all transition times and independent of any covariates).

Author(s)

Marta Fiocco, Hein Putter <H.Putter@lumc.nl>

References

Fiocco M, Putter H, van Houwelingen HC (2008). Reduced-rank proportional hazards regression and simulation-based prediction for multi-state models. *Statistics in Medicine* **27**, 4340–4358.

Examples

```
# transition matrix for illness-death model
tmat <- trans.illdeath()
# data in wide format, for transition 1 this is dataset E1 of
# Therneau & Grambsch (T&G)
tg <- data.frame(illt=c(1,1,6,6,8,9),ills=c(1,0,1,1,0,1),
                 dt=c(5,1,9,7,8,12),ds=c(1,1,1,1,1,1),
                 x1=c(1,1,1,0,0,0),x2=c(6:1))
# data in long format using msprep
tglong <- msprep(time=c(NA,"illt","dt"),status=c(NA,"ills","ds"),
                 data=tg,keep=c("x1","x2"),trans=tmat)
# expanded covariates
tglong <- expand.covs(tglong,c("x1","x2"))
# Cox model with different covariate
cx <- coxph(Surv(Tstart,Tstop,status)~x1.1+x2.2+strata(trans),
            data=tglong,method="breslow")
# new data, to check whether results are the same for transition 1 as T&G
newdata <- data.frame(trans=1:3,x1.1=c(0,0,0),x2.2=c(0,1,0),strata=1:3)
fit <- msfit(cx,newdata,trans=tmat)
tv <- unique(fit$Haz$time)
# mssample
set.seed(1234)
mssample(Haz=fit$Haz,trans=tmat,tvec=tv,M=100)
set.seed(1234)
paths(tmat)
mssample(Haz=fit$Haz,trans=tmat,tvec=tv,M=100,output="path")
set.seed(1234)
mssample(Haz=fit$Haz,trans=tmat,tvec=tv,M=100,output="data",do.trace=25)
```

paths

Find all possible trajectories through a given multi-state model

Description

For a given multi-state model, specified through a transition matrix, paths recursively finds all the possible trajectories or paths through that multi-state starting from a specified state. DO NOT USE for reversible or cyclic multi-state models.

Usage

```
paths(trans, start=1)
```

Arguments

trans The transition matrix describing the multi-state model, see [msprep](#)
start The starting state for the trajectories

Details

The function is recursive. It starts in `start`, looks at what states can be visited from `start`, and appends the results of the next call to the current value (matrix). If the transition matrix contains loops, the function will find infinitely many paths, so do not use paths for reversible or cyclic multi-state models. A warning is not yet incorporated!

Value

A matrix, each row of which specifies a possible path through the multi-state model.

Author(s)

Hein Putter <H.Putter@lumc.nl>

Examples

```
tmat <- matrix(NA,5,5)
tmat[1,2:3] <- 1:2
tmat[1,5] <- 3
tmat[2,4:5] <- 4:5
tmat[3,4:5] <- 6:7
tmat[4,5] <- 8
paths(tmat)
paths(tmat, start=3)
```

plot.msfit

Plot method for an msfit object

Description

Plot method for an object of class 'msfit'. It plots the estimated cumulative transition intensities in the multi-state model.

Usage

```
## S3 method for class 'msfit'
plot(x,type=c("single","separate"),cols,
     xlab="Time",ylab="Cumulative hazard",ylim,lwd,lty,
     legend,legend.pos,bty="o",...)
```

Arguments

x	Object of class 'msfit', containing estimated cumulative transition intensities for all transitions in a multi-state model
type	One of "single" (default) or "separate"; in case of "single", all estimated cumulative hazards are drawn in a single plot, in case of "separate", separate plots are shown for the estimated transition intensities
cols	A vector specifying colors for the different transitions; default is 1:K (K no of transitions), when type="single", and 1 (black), when type="separate"
xlab	A title for the x-axis; default is "Time"
ylab	A title for the y-axis; default is "Cumulative hazard"
ylim	The y limits of the plot(s); if ylim is specified for type="separate", then all plots use the same ylim for y limits
lwd	The line width, see par ; default is 1
lty	The line type, see par ; default is 1
legend	Character vector of length equal to the number of transitions, to be used in a legend; if missing, numbers will be used; this and the legend arguments following are ignored when type="separate"
legend.pos	The position of the legend, see legend ; default is "topleft"
bty	The box type of the legend, see legend
...	Further arguments to plot

Value

No return value

Author(s)

Hein Putter <H.Putter@lumc.nl>

See Also

[msfit](#)

Examples

```
# transition matrix for illness-death model
tmat <- trans.illdeath()
# data in wide format, for transition 1 this is dataset E1 of
# Therneau & Grambsch (2000)
tg <- data.frame(illt=c(1,1,6,6,8,9),ills=c(1,0,1,1,0,1),
                dt=c(5,1,9,7,8,12),ds=c(1,1,1,1,1,1),
                x1=c(1,1,1,0,0,0),x2=c(6:1))
# data in long format using msprep
tglong <- msprep(time=c(NA,"illt","dt"),status=c(NA,"ills","ds"),
                data=tg,keep=c("x1","x2"),trans=tmat)
# events
```

```

events(tglong)
table(tglong$status, tglong$to, tglong$from)
# expanded covariates
tglong <- expand.covs(tglong, c("x1", "x2"))
# Cox model with different covariate
cx <- coxph(Surv(Tstart, Tstop, status)~x1.1+x2.2+strata(trans),
data=tglong, method="breslow")
summary(cx)
# new data, to check whether results are the same for transition 1 as
# those in appendix E.1 of Therneau & Grambsch (2000)
newdata <- data.frame(trans=1:3, x1.1=c(0,0,0), x2.2=c(0,1,0), strata=1:3)
msf <- msfit(cx, newdata, trans=tmat)
# standard plot
plot(msf)
# specifying line width, color, and legend
plot(msf, lwd=2, col=c("darkgreen", "darkblue", "darkred"), legend=c("1->2", "1->3", "2->3"))
# separate plots
par(mfrow=c(2,2))
plot(msf, type="sep", lwd=2)
par(mfrow=c(1,1))

```

plot.probtrans

Plot method for a probtrans object

Description

Plot method for an object of class 'probtrans'. It plots the transition probabilities as estimated by [probtrans](#).

Usage

```

## S3 method for class 'probtrans'
plot(x, from=1,
      type=c("stacked", "filled", "single", "separate"), ord,
      cols, xlab="Time", ylab="Probability", xlim, ylim, lwd, lty, cex,
      legend, legend.pos, bty="o", ...)

```

Arguments

x	Object of class 'probtrans', containing estimated transition probabilities
from	The starting state from which the probabilities are used to plot
type	One of "stacked" (default), "filled", "single" or "separate"; in case of "stacked", the transition probabilities are stacked and the distance between two adjacent curves indicates the probability, this is also true for "filled", but the space between adjacent curves are filled, in case of "single", the probabilities are shown as different curves in a single plot, in case of "separate", separate plots are shown for the estimated transition probabilities

ord	A vector of length equal to the number of states, specifying the order of plotting in case type="stacked" or "filled"
cols	A vector specifying colors for the different transitions; default is 1:K (K no of transitions), when type="single", and 1 (black), when type="separate"
xlab	A title for the x-axis; default is "Time"
ylab	A title for the y-axis; default is "Probability"
xlim	The x limits of the plot(s), default is range of time
ylim	The y limits of the plot(s); if ylim is specified for type="separate", then all plots use the same ylim for y limits
lwd	The line width, see par ; default is 1
lty	The line type, see par ; default is 1
cex	Character size, used in text; only used when type="stacked" or "filled"
legend	Character vector of length equal to the number of transitions, to be used in a legend; if missing, numbers will be used; this and the legend arguments following are ignored when type="separate"
legend.pos	The position of the legend, see legend ; default is "topleft"
bty	The box type of the legend, see legend
...	Further arguments to plot

Value

No return value

Author(s)

Hein Putter <H.Putter@lumc.nl>

See Also

[probtrans](#)

Examples

```
# transition matrix for illness-death model
tmat <- trans.illdeath()
# data in wide format, for transition 1 this is dataset E1 of
# Therneau & Grambsch (2000)
tg <- data.frame(illt=c(1,1,6,6,8,9),ills=c(1,0,1,1,0,1),
                dt=c(5,1,9,7,8,12),ds=c(1,1,1,1,1,1),
                x1=c(1,1,1,0,0,0),x2=c(6:1))
# data in long format using msprep
tglong <- msprep(time=c(NA,"illt","dt"),status=c(NA,"ills","ds"),
                data=tg,keep=c("x1","x2"),trans=tmat)
# events
events(tglong)
table(tglong$status,tglong$to,tglong$from)
# expanded covariates
```

```

tglong <- expand.covs(tglong,c("x1","x2"))
# Cox model with different covariate
cx <- coxph(Surv(Tstart,Tstop,status)~x1.1+x2.2+strata(trans),
data=tblong,method="breslow")
summary(cx)
# new data, to check whether results are the same for transition 1 as
# those in appendix E.1 of Therneau & Grambsch (2000)
newdata <- data.frame(trans=1:3,x1.1=c(0,0,0),x2.2=c(0,1,0),strata=1:3)
msf <- msfit(cx,newdata,trans=tmat)
# probtrans
pt <- probtrans(msf,prede=0)
# default plot
plot(pt,ord=c(2,3,1),lwd=2,cex=0.75)
# filled plot
plot(pt,type="filled",ord=c(2,3,1),lwd=2,cex=0.75)
# single plot
plot(pt,type="single",lwd=2,col=rep(1,3),lty=1:3,legend.pos=c(8,1))
# separate plots
par(mfrow=c(2,2))
plot(pt,type="sep",lwd=2)
par(mfrow=c(1,1))

```

print.msdata

Print method for a msdata object

Description

Print method for an object of class 'msdata'

Usage

```

## S3 method for class 'msdata'
print(x,trans=FALSE,...)

```

Arguments

x	Object of class 'msdata', as prepared for instance by msprep
trans	Boolean specifying whether or not the transition matrix should be printed as well; default is FALSE
...	Further arguments to print

Value

No return value

Author(s)

Hein Putter <H.Putter@lumc.nl>

See Also[probtrans](#)**Examples**

```
# transition matrix for illness-death model
tmat <- trans.illdeath()
# some data in wide format
tg <- data.frame(stt=rep(0,6),sts=rep(0,6),
  illt=c(1,1,6,6,8,9),ills=c(1,0,1,1,0,1),
  dt=c(5,1,9,7,8,12),ds=c(1,1,1,1,1,1),
  x1=c(1,1,1,2,2,2),x2=c(6:1))
tg$x1 <- factor(tg$x1,labels=c("male","female"))
tg$patid <- factor(2:7,levels=1:8,labels=as.character(1:8))
# define time, status and covariates also as matrices
tt <- matrix(c(rep(NA,6),tg$illt,tg$dt),6,3)
st <- matrix(c(rep(NA,6),tg$ills,tg$ds),6,3)
keepmat <- data.frame(gender=tg$x1,age=tg$x2)
# data in long format using msprep
msp <- msprep(time=tt,status=st,trans=tmat,keep=as.matrix(keepmat))
print(msp)
print(msp, trans=TRUE)
```

probtrans

Compute subject-specific or overall transition probabilities with standard errors

Description

This function computes subject-specific or overall transition probabilities in multi-state models. If requested, also standard errors are calculated.

Usage

```
probtrans(object, predt, direction=c("forward","fixedhorizon"),
  method=c("aalen","greenwood"), variance=TRUE, covariance=FALSE)
```

Arguments

object	msfit object containing estimated cumulative hazards for each of the transitions in the multi-state model and, if standard errors are requested, (co)variances of these cumulative hazards for each pair of transitions
predt	A positive number indicating the prediction time. This is either the time at which the prediction is made (if <code>direction="forward"</code>) or the time for which the prediction is to be made (if <code>direction="fixedhorizon"</code>)
direction	One of "forward" (default) or "fixedhorizon", indicating whether prediction is forward or for a fixed horizon

method	A character string specifying the type of variances to be computed (so only needed if either variance or covariance is TRUE). Possible values are "aalen" or "greenwood"
variance	Logical value indicating whether standard errors are to be calculated (default is TRUE)
covariance	Logical value indicating whether covariances of transition probabilities for different states are to be calculated (default is FALSE)

Details

For details refer to de Wreede, Fiocco & Putter (2010).

Value

An object of class "probtrans", which is a list containing S (if covariance=FALSE) or S+1 items (if covariance=TRUE), S being the number of states in the multi-state model. Item [[s]] contains a dataframe with the estimated transition probabilities from state s. If covariance=TRUE, item [[S+1]] contains an array with all the covariances of the estimated transition probabilities. The "probtrans" object has an attribute "trans" containing the transition matrix. Plot and summary methods have been defined for "probtrans" objects.

Author(s)

Liesbeth de Wreede and Hein Putter <H.Putter@lumc.nl>

References

- Andersen PK, Borgan O, Gill RD, Keiding N (1993). *Statistical Models Based on Counting Processes*. Springer, New York.
- Putter H, Fiocco M, Geskus RB (2007). Tutorial in biostatistics: Competing risks and multi-state models. *Statistics in Medicine* **26**, 2389–2430.
- Therneau TM, Grambsch PM (2000). *Modeling Survival Data: Extending the Cox Model*. Springer, New York.
- L. C. de Wreede, M. Fiocco, and H. Putter (2010). The mstate package for estimation and prediction in non- and semi-parametric multi-state and competing risks models. *Computer Methods and Programs in Biomedicine* 99: 261–274.

Examples

```
# transition matrix for illness-death model
tmat <- trans.illdeath()
# data in wide format, for transition 1 this is dataset E1 of
# Therneau & Grambsch (2000)
tg <- data.frame(illt=c(1,1,6,6,8,9),ills=c(1,0,1,1,0,1),
                dt=c(5,1,9,7,8,12),ds=c(1,1,1,1,1,1),
                x1=c(1,1,1,0,0,0),x2=c(6:1))
# data in long format using msprep
tglong <- msprep(time=c(NA,"illt","dt"),status=c(NA,"ills","ds"),
                data=tg,keep=c("x1","x2"),trans=tmat)
```

```

# events
events(tglong)
table(tglong$status, tglong$to, tglong$from)
# expanded covariates
tglong <- expand.covs(tglong, c("x1", "x2"))
# Cox model with different covariate
cx <- coxph(Surv(Tstart, Tstop, status) ~ x1.1 + x2.2 + strata(trans),
            data = tglong, method = "breslow")
summary(cx)
# new data, to check whether results are the same for transition 1 as
# those in appendix E.1 of Therneau & Grambsch (2000)
newdata <- data.frame(trans = 1:3, x1.1 = c(0, 0, 0), x2.2 = c(0, 1, 0), strata = 1:3)
HvH <- msfit(cx, newdata, trans = tmat)
# probtrans
pt <- probtrans(HvH, predt = 0)
# predictions from state 1
pt[[1]]

```

redrank	<i>Reduced rank proportional hazards model for competing risks and multi-state models</i>
---------	---

Description

This function estimates regression coefficients in reduced rank proportional hazards models for competing risks and multi-state models.

Usage

```
redrank(redrank, full = ~1, data, R, strata = NULL, Gamma.start,
        method = "breslow", eps = 1e-5, print.level = 1)
```

Arguments

redrank	Survival formula, starting with either <code>Surv(time, status) ~</code> or with <code>Surv(Tstart, Tstop, status) ~</code> , followed by a formula containing covariates for which a reduced rank estimate is to be found
full	Optional, formula specifying that part which needs to be retained in the model (so not subject to reduced rank)
data	Object of class 'msdata', as prepared for instance by <code>msprep</code> , in which to interpret the <code>redrank</code> and, optionally, the <code>full</code> formulas
R	Numeric, indicating the rank of the solution
strata	Name of covariate to be used inside the <code>strata</code> part of <code>coxph</code>
Gamma.start	A matrix of dimension $K \times R$, with K the number of transitions and R the rank, to be used as starting value
method	The method for handling ties in <code>coxph</code>

eps	Numeric value determining when the iterative algorithm is finished (when for two subsequent iterations the difference in log-likelihood is smaller than eps)
print.level	Determines how much output is written to the screen; 0: no output, 1: iterations, for each iteration solutions of Alpha, Gamma, log-likelihood, 2: also the Cox regression results

Details

For details refer to Fiocco, Putter & van Houwelingen (2005, 2008).

Value

A list with elements

Alpha	the Alpha matrix
Gamma	the Gamma matrix
Beta	the Beta matrix corresponding to covariates
Beta2	the Beta matrix corresponding to fullcovs
cox.itr1	the <code>coxph</code> object resulting from the last call giving Alpha
alphaX	the matrix of prognostic scores given by Alpha, $n \times R$, with n number of subjects
niter	the number of iterations needed to reach convergence
df	the number of regression parameters estimated
loglik	the log-likelihood

Author(s)

Marta Fiocco and Hein Putter <H.Putter@lumc.nl>

References

Fiocco M, Putter H, van Houwelingen JC (2005). Reduced rank proportional hazards model for competing risks. *Biostatistics* **6**, 465–478.

Fiocco M, Putter H, van Houwelingen HC (2008). Reduced-rank proportional hazards regression and simulation-based prediction for multi-state models. *Statistics in Medicine* **27**, 4340–4358.

Putter H, Fiocco M, Geskus RB (2007). Tutorial in biostatistics: Competing risks and multi-state models. *Statistics in Medicine* **26**, 2389–2430.

Examples

```
# Based on Fiocco, Putter & van Houwelingen (2005)
data(ebmt2)
# transition matrix for competing risks
tmat <- trans.comprisk(6, names=c("Relapse", "GvHD", "Bacterial", "Viral", "Fungal", "Other"))
# preparing long dataset
ebmt2$stat1 <- as.numeric(ebmt2$status==1)
ebmt2$stat2 <- as.numeric(ebmt2$status==2)
ebmt2$stat3 <- as.numeric(ebmt2$status==3)
```

```

ebmt2$stat4 <- as.numeric(ebmt2$status==4)
ebmt2$stat5 <- as.numeric(ebmt2$status==5)
ebmt2$stat6 <- as.numeric(ebmt2$status==6)
covs <- c("dissub", "match", "tcd", "year", "age")
ebmtlong <- msprep(time=c(NA,rep("time",6)),
                  stat=c(NA,paste("stat",1:6,sep="")),
                  data=ebmt2,keep=covs,trans=tmat)
# Actually run for a subset of the actual data
ebmtlongsub <- ebmtlong[1:1200,] # first 200 patients
# The reduced rank 2 solution
rr2 <- redrank(Surv(Tstart,Tstop,status) ~ dissub+match+tcd+year+age, data=ebmtlongsub, R=2, eps=0.001)
rr2$Alpha; rr2$Gamma; rr2$Beta; rr2$loglik

# This reproduces the results in Fiocco, Putter & van Houwelingen (2005)
# Takes a while to run
## Not run:
# The reduced rank 3 solution
rr3 <- redrank(Surv(Tstart,Tstop,status) ~ dissub+match+tcd+year+age, data=ebmtlong, R=3)
rr3$Alpha; rr3$Gamma; rr3$Beta; rr3$loglik
# The reduced rank 3 solution, with no reduction on age
rr3 <- redrank(Surv(Tstart,Tstop,status) ~ dissub+match+tcd+year, full=~age, data=ebmtlong, R=3)
rr3$Alpha; rr3$Gamma; rr3$Beta; rr3$loglik
# The full rank solution
fullrank <- redrank(Surv(Tstart,Tstop,status) ~ dissub+match+tcd+year+age, data=ebmtlong, R=6)
fullrank$Beta; fullrank$loglik

## End(Not run)

```

summary.msfit

Summary method for an msfit object

Description

Summary method for an object of class 'msfit'. It prints a selection of the estimated cumulative transition intensities, and, if requested, also of the (co)variances.

Usage

```

## S3 method for class 'msfit'
summary(object,complete=FALSE,variance=FALSE,...)

```

Arguments

object	Object of class 'msfit', containing estimated cumulative transition intensities for all transitions in a multi-state model
complete	Whether or not the complete estimated cumulative transition intensities should be printed (TRUE) or not (FALSE); default is FALSE, in which case the estimated cumulative transition hazards will be printed for the first and last 6 time points of each transition (or all when there are at most 12 of these time points)

variance	Whether or not the (co)variances of the estimated cumulative transition intensities should be printed; default is FALSE
...	Further arguments to summary

Value

No return value

Author(s)

Hein Putter <H.Putter@lumc.nl>

See Also

[msfit](#)

Examples

```
# transition matrix for illness-death model
tmat <- trans.illdeath()
# data in wide format, for transition 1 this is dataset E1 of
# Therneau & Grambsch (2000)
tg <- data.frame(illt=c(1,1,6,6,8,9),ills=c(1,0,1,1,0,1),
                dt=c(5,1,9,7,8,12),ds=c(1,1,1,1,1,1),
                x1=c(1,1,1,0,0,0),x2=c(6:1))
# data in long format using msprep
tglong <- msprep(time=c(NA,"illt","dt"),status=c(NA,"ills","ds"),
                data=tg,keep=c("x1","x2"),trans=tmat)
# events
events(tglong)
table(tglong$status,tglong$to,tglong$from)
# expanded covariates
tglong <- expand.covs(tglong,c("x1","x2"))
# Cox model with different covariate
cx <- coxph(Surv(Tstart,Tstop,status)~x1.1+x2.2+strata(trans),
            data=tglong,method="breslow")
summary(cx)
# new data, to check whether results are the same for transition 1 as
# those in appendix E.1 of Therneau & Grambsch (2000)
newdata <- data.frame(trans=1:3,x1.1=c(0,0,0),x2.2=c(0,1,0),strata=1:3)
msf <- msfit(cx,newdata,trans=tmat)
print(msf)
# standard summary
summary(msf)
# including variances and covariances
summary(msf,variance=TRUE)
```

summary.probtrans *Summary method for a probtrans object*

Description

Summary method for an object of class 'probtrans'. It prints a selection of the estimated transition probabilities, and, if requested, also of the variances.

Usage

```
## S3 method for class 'probtrans'
summary(object, from, complete=FALSE, variance=TRUE, ...)
```

Arguments

object	Object of class 'probtrans', containing estimated transition probabilities from and to all states in a multi-state model
from	Specifies from which state the transition probabilities are to be printed. Should be subset of 1:S, with S the number of states in the multi-state model. If missing, transition probabilities are printed from all starting states
complete	Whether or not the complete estimated transition probabilities should be printed (TRUE) or not (FALSE); default is FALSE, in which case the estimated transition probabilities will be printed for the first and last 6 time points of each starting state (or all when there are at most 12 of these time points)
variance	Whether or not the standard errors of the estimated transition probabilities should be printed; default is TRUE
...	Further arguments to summary

Value

No return value

Author(s)

Hein Putter <H.Putter@lumc.nl>

See Also

[probtrans](#)

Examples

```
# transition matrix for illness-death model
tmat <- trans.illdeath()
# data in wide format, for transition 1 this is dataset E1 of
# Therneau & Grambsch (2000)
tg <- data.frame(illt=c(1,1,6,6,8,9), ills=c(1,0,1,1,0,1),
```

```

      dt=c(5,1,9,7,8,12),ds=c(1,1,1,1,1,1),
      x1=c(1,1,1,0,0,0),x2=c(6:1))
# data in long format using msprep
tglong <- msprep(time=c(NA,"illt","dt"),status=c(NA,"ills","ds"),
data=tg,keep=c("x1","x2"),trans=tmat)
# events
events(tglong)
table(tglong$status,tglong$to,tglong$from)
# expanded covariates
tglong <- expand.covs(tglong,c("x1","x2"))
# Cox model with different covariate
cx <- coxph(Surv(Tstart,Tstop,status)~x1.1+x2.2+strata(trans),
data=tglong,method="breslow")
summary(cx)
# new data, to check whether results are the same for transition 1 as
# those in appendix E.1 of Therneau & Grambsch (2000)
newdata <- data.frame(trans=1:3,x1.1=c(0,0,0),x2.2=c(0,1,0),strata=1:3)
msf <- msfit(cx,newdata,trans=tmat)
# probtrans
pt <- probtrans(msf,predt=0)
# default summary
summary(pt)
# summary without standard errors
summary(pt,variance=FALSE)

```

transMat

Define transition matrix for multi-state model

Description

Define transition matrices for multi-state model. Specific functions for defining such transition matrices are pre-defined for common multi-state models like the competing risks model and the illness-death model.

Usage

```

transMat(x, names)
trans.comrisk(K, names)
trans.illdeath(names)

```

Arguments

x	List of possible transitions; $x[[i]]$ consists of a vector of state numbers reachable from state i
K	The number of competing risks
names	A character vector containing the names of either the competing risks or the states in the multi-state model specified by the competing risks or illness-death model. names should have the same length as the list x (for transMat), or either K or $K+1$ (for trans.comrisk), or 3 (for trans.illdeath)

Details

If names is missing, the names "eventfree", "cause1", etcetera are assigned in trans.comprisk, or "healthy", "illness", "death" in trans.illdeath.

Value

A transition matrix describing the states and transitions in the multi-state model.

Author(s)

Steven McKinney <smckinney@bccrc.ca>; Hein Putter <H.Putter@lumc.nl>

Examples

```
transMat(list(c(2, 3), c(), c(1, 2)),
names = c("Disease-free", "Death", "Relapsed"))
tmat <- transMat(x = list( c(2, 3), c(1, 3), c() ),
names = c("Normal", "Low", "Death"))
tmat
transListn <- list("Normal" = c(2, 3), "Low" = c(1, 3), "Death" = c())
transMat(transListn)
trans.comprisk(3)
trans.comprisk(3,c("c1","c2","c3"))
trans.comprisk(3,c("nothing","c1","c2","c3"))
trans.illdeath()
trans.illdeath(c("nothing","ill","death"))
```

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