Package 'TP.idm'

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Type Package

Title Estimation of Transition Probabilities for the Illness-Death
Model

Version 1.5

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Depends R (>= 3.1.1), graphics, stats

Repository CRAN

Description Estimation of transition probabilities for the illness-death model. Both the Aalen-
Johansen estimator for a Markov model and a novel non-Markovian estimator by de Una-
Alvarez and Meira-Machado (2015) <doi:10.1111/biom.12288>, see also Balboa and de Una-
Alvarez (2018) <doi:10.18637/jss.v083.i10>, are included.

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TP.idm-package   *Estimation of Transition Probabilities for the Illness-Death Model*

Description

Estimation of transition probabilities for the illness-death model. Both the Aalen-Johansen estimator for a Markov model and a novel non-Markovian estimator by de Uña-Álvarez and Meira-Machado (2015) <doi:10.1111/biom.12288>, see also Balboa and de Uña-Álvarez (2018) <doi:10.18637/jss.v083.i10>, are included.

Details

The DESCRIPTION file:

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Version:	1.5
Date:	2018-04-17
Author:	Vanesa Balboa-Barreiro, Jacobo de Una-Alvarez <jacobo@uvigo.es> and Luis Meira-Machado <lmachado@m
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print.TPidm           Print method for a TPidm object
summary.TPidm         Summary method for a TPidm object
test.nm               Graphical tool to check the Markov assumption
```

This package incorporates the function TPidm which can be used to compute a nonparametric transition probability matrix for the illness-death model. For a complete list of functions use library(help=TP.idm).

Author(s)

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References

Andersen P. K., Borgan O., Gill R. D. and Keiding N. (1993). Statistical models based on counting processes. Springer Series in Statistics. New York, NY: Springer.

Datta S. and Satten G. A. (2001). Validity of the Aalen-Johansen estimators of stage occupation probabilities and Nelson-Aalen estimators of integrated transition hazards for non-Markov models. *Statistics and Probability Letters* **55(4)**, 403–411.

de Uña-Álvarez J. and Meira-Machado L. (2015). Nonparametric estimation of transition probabilities in a non-Markov illness-death model: a comparative study. *Biometrics* **71**, 364–375.

Meira-Machado L. F., de Uña-Álvarez J. and Cadarso-Suárez C. (2006). Nonparametric estimation of transition probabilities in a non-Markov illness-death model. *Lifetime Data Annal* **12(3)**, 325–344.

Balboa-Barreiro V., de Uña-Álvarez J. (2018). Estimation of Transition Probabilities for the Illness-Death Model: Package `TP.idm`. *Journal of Statistical Software* **83(10)**, 1–19.

Examples

```
data(colonTP)

# create a TPidm object with s = 0, t = "last" (default),
# CI = TRUE (default) and method = "AJ":
aj0ci <- TPidm(colonTP, s = 0, method = "AJ")
summary(aj0ci) # summarizing the results
plot(aj0ci) # plotting all occupation probabilities
```

---

colonTP   *Chemotherapy for Stage B/C colon cancer*

Description

These are data from one of the first successful trials of adjuvant chemotherapy for colon cancer. Levamisole is a low-toxicity compound previously used to treat worm infestations in animals; 5-FU is a moderately toxic (as these things go) chemotherapy agent. This data frame reproduces the information in the `colon` object of the package `survival`, organized in a slightly different way (only one row is used for each individual).

Usage

```
data("colonTP")
```

Format

A data frame with 929 observations on the following 15 variables.

time1 Disease free survival time (time to recurrence, death, or censoring, whichever occurs first).

event1 Disease free survival indicator (1=dead or relapsed, 0=alive disease free).

Stime Time to death or censoring.

event Death indicator (1=dead, 0=alive).

rx Treatment - Obs(ervation), Lev(amisole), Lev(amisole)+5-FU.

sex 1=male.

age Age in years.

obstruct Obstruction of colon by tumour.

perfor Perforation of colon.

adhere Adherence to nearby organs.

nodes Number of lymph nodes with detectable cancer.

differ Differentiation of tumour (1=well, 2=moderate, 3=poor).

extent Extent of local spread (1=submucosa, 2=muscle, 3=seros, 4=contiguous structures).

surg Time from surgery to registration (0=short, 1=long).

node4 More than 4 positive lymph nodes.

Note

The study is originally described in Laurie et al. (1989). The main report is found in Moertel et al. (1990). This data set is closet to that of the final report in Moertel et al. (1991). A version of the data with less follow-up time was used in the paper by Lin (1994). This data set has been used for illustration purposes in a number of papers, including Meira-Machado et al. (2015) and de Uña-Álvarez and Meira-Machado (2015).

References

de Uña-Álvarez J. and Meira-Machado L. (2015). Nonparametric estimation of transition probabilities in a non-Markov illness-death model: a comparative study. *Biometrics* **71**, 364–375.

Laurie J. A., Moertel C. G., Fleming T. R., Wieand H. S., Leigh J. E., Rubin J., McCormack G. W., Gerstner J. B., Krook J. E. and Malliard J. (1989). Surgical adjuvant therapy of large-bowel carcinoma: An evaluation of levamisole and the combination of levamisole and fluorouracil: The North Central Cancer Treatment Group and the Mayo Clinic. *Journal of Clinical Oncology* **7(10)**, 1447–1456.

Lin D. Y. (1994). Cox regression analysis of multivariate failure time data: the marginal approach. *Statistics in Medicine* **13(21)**, 2233–2247.

Meira-Machado L., de Uña-Álvarez J. and Datta S. (2015). Nonparametric estimation of conditional transition probabilities in a non-Markov illness-death model. Computational Statistics **30**, 377–397.

Moertel C. G., Fleming T. R., MacDonald J. S., Haller D. G., Laurie J. A., Goodman P. J., Ungerleider J. S., Emerson W. A., Tormey D. C., Glick J. H., Veeder M. H. and Maillard J. A. (1990).

Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *New England Journal of Medicine* **322(6)**, 352–358.

Moertel C. G., Fleming T. R., MacDonald J. S., Haller D. G., Laurie J. A., Tangen C. M., Ungerleider J. S., Emerson W. A., Tormey D. C., Glick J. H., Veeder M. H. and Maillard J. A. (1991). Fluorouracil plus Levamisole as an effective adjuvant therapy after resection of stage II colon carcinoma: a final report. *Annals of Internal Medicine* **122(5)**, 321–326.

Examples

```
data(colonTP)
## maybe str(colonTP) ; plot(colonTP) ...
```

---

plot.TPidm   *Plot method for a TPidm object*

Description

Plot method for an object of class 'TPidm'. It draws the estimated occupation probabilities (if s = 0) or transition probabilities (if s > 0) and confidence intervals (only available if CI is TRUE) in a basic scatterplot or in a multipanel layout.

Usage

```
## S3 method for class 'TPidm'
plot(x, chosen.tr = "ALL", col = "black", ...)
```

Arguments

x	An object of class 'TPidm'.
chosen.tr	Character vector of the form 'c("from to", "from to")' specifying which transitions should be plotted. Default, all the transition probabilities are plotted.
col	Character vector specifying colors for each curves. Default col="black".
...	Further arguments to plot.

Examples

```
data(colonTP)

# create a TPidm object with s = 0, t = "last" (default),
# CI = FALSE and method = "NM" (default):
nm0 <- TPidm(colonTP, s = 0, CI=FALSE)

# plot all possible transitions without CI:
plot(nm0)

# or
# create a TPidm object with s = 0, t = "last" (default),
```

```
# CI = TRUE (default) and method = "AJ":
aj0ci <- TPidm(colonTP, s = 0, method = "AJ")

# plot transitions "1 2" and "1 3" with CI:
plot(aj0ci, chosen.tr = c("1 2", "1 3"))

# create a TPidm object with s = 365, t = 1095, cov = "rx",
# CI = FALSE and method = "NM" (default):
nm365cov <- TPidm(colonTP, s = 365, t = 1095, cov = "rx", CI=FALSE)

# plot transitions "1 2" and "1 3" without CI:
plot(nm365cov, chosen.tr = c("1 2", "1 3"), col=c("blue","red","green"))
```

---

print.TPidm   *Print method for a TPidm object*

Description

Print method for an object of class 'TPidm'.

Usage

```
## S3 method for class 'TPidm'
print(x, ...)
```

Arguments

x   An object of class 'TPidm'.

...   Further arguments to print.

Value

A data.frame is returned with the following variables:

transition   The initial and final states "i j" for each particular transition.

probs   The transition probabilities P_{ij}(s,t).

Note

The print function displays the method used, the user-supplied times s and t, the possible transitions, the estimated transition probabilities and, optionally, confidence limits and variances.

If cov was specified, the print function provides the transition probabilities P_{ij}(s,t) for each level of covariate.

---

summary.TPidm   *Summary method for a TPidm object*

Description

Summary method for an object of class 'TPidm'.

Usage

```
## S3 method for class 'TPidm'
summary(object, ...)
```

Arguments

object   An object of class 'TPidm'.

...   Further arguments to print.

Value

A data.frame is returned with the following variables:

transition   The initial and final states "i j" for each particular transition.

probs   The transition probabilities P_{ij}(s,t).

Note

The summary function prints the method used, the user-supplied times s and t, the possible transitions, the estimated transition probabilities and, optionally, confidence limits and variances.

If cov is specified, the summary function provides the transition probabilities P_{ij}(s,t) for each level of covariate.

Examples

```
data(colonTP)
# create a TPidm object with s = 365, t = 1095, cov = "rx",
# CI = FALSE and method = "NM" (default):
nm365cov <- TPidm(colonTP, s = 365, t = 1095, cov = "rx", CI=FALSE)
summary(nm365cov) # summarizing the results
```

---

test.nm   *Graphical tool to check the Markov assumption*

Description

It constructs a PP-plot which compares the transition probabilities reported by the non-Markovian and Aalen-Johansen estimators. Under the Markov assumption the PP-plot should fit the straight line y=x. When the Markov assumption holds the Aalen-Johansen is preferred since it provides a smaller standard error. If the Markov assumption is violated, the Aalen-Johansen may be inconsistent and therefore the non-Markovian method is recommended.

Usage

```
test.nm(data, s, t = "last")
```

Arguments

data
: A data.frame including at least four columns named `time1`, `event1`, `Stime` and `event`, which correspond to disease free survival time, disease free survival indicator, time to death or censoring, and death indicator, respectively.

s
: The current time for the transition probabilities to be computed.

t
: The future time for the transition probabilities to be computed. Default is "last" which means the largest time among the uncensored entry times for the intermediate state and the final absorbing state.

Details

It constructs a PP-plot which compares the transition probabilities reported by the non-Markovian and Aalen-Johansen estimators. Under the Markov assumption the PP-plot should fit the straight line y=x. When the Markov assumption holds the Aalen-Johansen is preferred since it provides a smaller standard error. If the Markov assumption is violated, the Aalen-Johansen may be inconsistent and therefore the non-Markovian method is recommended. The PP-plot excludes $P_{11}(s,t)$ since both estimators agree in this case. Also, the user-supplied s must be strictly positive, because the Markov assumption is not relevant for the estimation of occupation probabilities (s=0).

Examples

```
data(colonTP)

test.nm(colonTP, s = 0)
# nothig is displayed since the Markov condition is not relevant
# for the case s=0 (occupation probabilities)

test.nm(colonTP, s = 365, t = 1095)
```

TPidm   *Transition probabilities for the illness-death model*

Description

This function computes the transition probability matrix for the illness-death model, by using the Aalen-Johansen technique (suitable for Markov models) or alternatively a non-Markovian estimator. It creates a 'TPidm' object.

Usage

```
TPidm(data, s, t = "last", cov = NULL, CI = TRUE, level = 0.95,
ci.transformation = "linear", method = "NM")
```

Arguments

data	A data.frame including at least four columns named time1, event1, Stime and event, which correspond to disease free survival time, disease free survival indicator, time to death or censoring, and death indicator, respectively.
s	The current time for the transition probabilities to be computed; s=0 reports the occupation probabilities.
t	The future time for the transition probabilities to be computed. Default is "last" which means the largest time among the uncensored entry times for the intermediate state and the final absorbing state.
cov	A categorical variable for the optional by-group analysis; this variable must be a factor.
CI	If TRUE (default), confidence intervals are computed.
level	Level of confidence intervals. Default is 0.95 (corresponding to 95 %).
ci.transformation	
	Transformation applied to compute confidence intervals. Possible choices are "linear", "log", "log-log" and "cloglog". Default is "linear".
method	The method used to compute the transition probabilities. Possible options are "AJ" (Aalen-Johansen) or "NM" (non-Markovian). Default is "NM".

Details

If s = 0 this function TPidm reports the state occupation probabilities at time t. For s > 0, the transition probabilities are provided. The default method "NM" computes the estimator proposed by de Uña-Álvarez and Meira-Machado (2015), which is consistent regardless the Markov assumption. To fit a Markovian transition probability matrix, use the "AJ" method. Note that the Aalen-Johansen occupation probabilities are consistent even when the process is non-Markov (Datta and Satten, 2001), but this is not true for the Aalen-Johansen transition probabilities (Meira-Machado et al., 2006). If CI is TRUE (default), TPidm calculates the estimated variance and the confidence intervals by using the plug-in variance described in Balboa and de Uña-Álvarez (2018) (method = "NM"), or the standard formulas for Markovian processes (method = "AJ", see Andersen et al., 1993).

Value

An object of class 'TPidm'. It is a list containing the following objects:

s	The user-supplied current time for the transition probabilities.
t	The user-supplied future time for the transition probabilities.
method	The method used to compute the transition probabilities.
times	The uncensored entry times for the intermediate state and the final absorbing state which fall between s and t.
probs	A matrix with transition probability estimates P_{ij}(s,t) for the user-supplied (s, t) and each possible transition from state i (rows) to state j (columns). If CI is TRUE (default), it includes confidence limits and variances.
all.probs	An array with transition probability estimates P_{ij}(s, t_k) for each possible transition, evaluated at all the event times t_k falling between s and t. If CI is TRUE (default), it includes confidence limits and variances.
p.trans	Possible transitions among the states. If s = 0, possible transitions are "1 1", "1 2" and "1 3"; if s > 0 possible transitions are "1 1", "1 2", "1 3", "2 2" and "2 3".
CI	A logical value chosen by the user.
ci.transformation	
	Transformation chosen by the user to compute the confidence intervals.

Note

If time1=Stime and event1=event=1, the function TPidm assumes that a direct transition from the initial state to the final absorbing state has occurred. That is, zero sojourn times are not allowed for the intermediate state (replacing the zeros by a small positive amount is a way to introduce such cases).

If cov is specified, the main function provides estimations of transition probabilities for each level of the covariate.

References

Andersen P. K., Borgan O., Gill R. D. and Keiding N. (1993). Statistical models based on counting processes. Springer Series in Statistics. New York, NY: Springer.

Datta S. and Satten G. A. (2001). Validity of the Aalen-Johansen estimators of the stage occupation probabilities and Nelson-Aalen estimators of integrated transition hazards for non-Markov models. *Statistics and Probability Letters* **55(4)**, 403–411.

de Uña-Álvarez J. and Meira-Machado L. (2015). Nonparametric estimation of transition probabilities in a non-Markov illness-death model: a comparative study. *Biometrics* **71**, 364–375.

Meira-Machado L. F., de Uña-Álvarez J. and Cadarso-Suárez C. (2006). Nonparametric estimation of transition probabilities in a non-Markov illness-death model. *Lifetime Data Anal* **12(3)**, 325–344.

Balboa-Barreiro V., de Uña-Álvarez J. (2018). Estimation of Transition Probabilities for the Illness-Death Model: Package TP.idm. *Journal of Statistical Software* **83(10)**, 1–19.

Examples

```
data(colonTP)

# create a TPidm object with s = 0, t = "last" (default),
# CI = TRUE (default) and method = "AJ":
aj0ci <- TPidm(colonTP, s = 0, method = "AJ")
plot(aj0ci) # plotting all occupation probabilities

#or
# create a TPidm object with s = 365, t = "last" (default),
# CI = FALSE and method = "NM" (default):
nm365 <- TPidm(colonTP, s = 365, CI=FALSE)
summary(nm365) # summarizing the results

# or
# create a TPidm object with cov = "rx":
nm365cov <- TPidm(colonTP, s = 365, t = 1095, cov = "rx", CI=FALSE)
summary(nm365cov) # summarizing the results
```

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