# Package 'SurrogateOutcome'

August 28, 2025

Title Estimation of the Proportion of Treatment Effect Explained by

Surrogate Outcome Information

Type Package

version 1.2	
Description Provides functions to estimate the proportion of treatment effect on a commary outcome that is explained by the treatment effect on a censored surrogate come/event. All methods are described in detail in Parast, et al (2020) ``Asse ing the Value of a Censored Surrogate Outcome" <doi:10.1007 1="" s10985-019-0'=""> and Wang et al (2025) ``Model-free Approach to Evaluate a Censored Intercome as a Surrogate for Overall Survival" (Under Review) <doi:10.48550 arx<="" td=""><td>te out- ess- 19473- termediate Out-</td></doi:10.48550></doi:10.1007>	te out- ess- 19473- termediate Out-
License GPL	
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Contents	
censor.weight cumsum2 delta.estimate delta.estimate.RMST delta.q.event.RMST delta.q.event.semi.RMST delta.t.RMST ExampleData helper.si IV.event Kern.FUN new.q pred.smooth.surv R.opt.event R.q.event R.t.estimate	

2 censor.weight

	WEIGHT .																		
	WEIGHT.p	 		 •	•	 •	•	 •		 •	•		•	•	•	•		•	25
Index																			27

 ${\it censor.weight} \qquad \qquad {\it Calculates censoring probability for weighting}$ 

# Description

Helper function; calculates censoring probability needed for inverse probability of censoring weighting

# Usage

```
censor.weight(data.x, data.delta, t, weight = NULL)
```

# Arguments

data.x	numeric vector, the observed event time: $X = min(T, C)$ where T is the time of the primary outcome, C is the censoring time
data.delta	numeric vector of $0/1$ , the censoring indicator: $D = I(T < C)$ where T is the time of the primary outcome, C is the censoring time
t	number, the time of interest
weight	a numeric vector or matrix of weights used for perturbation-resampling, default is null.

### **Details**

Computes the Kaplan Meier estimate of survival for the censoring random variable at the specified time

# Value

Kaplan Meier estimate of survival for censoring at time t

### Author(s)

Layla Parast

# **Examples**

```
data(ExampleData)
censor.weight(data.x = ExampleData$x1, data.delta = ExampleData$delta1, t=5)
```

cumsum2 3

ıction	
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# Description

Helper function; should not be called directly by user.

# Usage

```
cumsum2(mydat)
```

### **Arguments**

mydat mydat

### Value

out matrix

# Author(s)

Layla Parast

delta.estimate	Estimates the treatment effect at time t, defined as the difference in the
	restricted mean survival time

# Description

Estimates the treatment effect at time t, defined as the difference in the restricted mean survival time.

# Usage

```
\label{eq:conf.int} \begin{split} & \texttt{delta.estimate}(\texttt{xone}, \, \texttt{xzero}, \, \texttt{deltaone}, \, \texttt{deltazero}, \, \texttt{t}, \, \texttt{std} = \texttt{FALSE}, \, \texttt{conf.int} = \texttt{FALSE}, \\ & \texttt{weight.perturb} \, = \, \texttt{NULL}) \end{split}
```

# Arguments

xone	numeric vector, observed event times for the primary outcome in the treatment group.
xzero	numeric vector, observed event times for the primary outcome in the control group.
deltaone	numeric vector, event/censoring indicators for the primary outcome in the treatment group.
deltazero	numeric vector, event/censoring indicators for the primary outcome in the control group.
t	time of interest for treatment effect.

4 delta.estimate

TRUE or FALSE; indicates whether standard error estimates should be provided, default is FALSE. Estimates are calculated using perturbation-resampling. Two versions are provided: one that takes the standard deviation of the perturbed estimates (denoted as "sd") and one that takes the median absolute deviation (denoted as "mad").

TRUE or FALSE; indicates whether 95% confidence intervals should be provided. Confidence intervals are calculated using the percentiles of perturbed estimates, default is FALSE. If this is TRUE, standard error estimates are automatically provided.

weight.perturb weights used for perturbation resampling.

#### **Details**

conf.int

Let  $G \in \{1,0\}$  be the randomized treatment indicator and T denote the time of the primary outcome of interest. We use potential outcomes notation such that  $T^{(G)}$  denotes the time of the primary outcome under treatment G, for  $G \in \{1,0\}$ . We define the treatment effect as the difference in restricted mean survival time up to a fixed time t under treatment 1 versus under treatment 0,

$$\Delta(t) = E\{T^{(1)} \wedge t\} - E\{T^{(0)} \wedge t\}$$

where  $\wedge$  indicates the minimum. Due to censoring, data consist of  $n=n_1+n_0$  independent observations  $\{X_{gi},\delta_{gi},i=1,...,n_g,g=1,0\}$ , where  $X_{gi}=T_{gi}\wedge C_{gi}$ ,  $\delta_{gi}=I(T_{gi}< C_{gi})$ ,  $C_{gi}$  denotes the censoring time,  $T_{gi}$  denotes the time of the primary outcome, and  $\{(T_{gi},C_{gi}),i=1,...,n_g\}$  are identically distributed within treatment group. The quantity  $\Delta(t)$  is estimated using inverse probability of censoring weights:

$$\hat{\Delta}(t) = n_1^{-1} \sum_{i=1}^{n_1} \hat{M}_{1i}(t) - n_0^{-1} \sum_{i=1}^{n_0} \hat{M}_{0i}(t)$$

where  $\hat{M}_{gi}(t) = I(X_{gi} > t)t/\hat{W}_g^C(t) + I(X_{gi} < t)X_{gi}\delta_{gi}/\hat{W}_g^C(X_{gi})$  and  $\hat{W}_g^C(t)$  is the Kaplan-Meier estimator of  $P(C_{gi} \ge t)$ .

#### Value

A list is returned:

delta the estimate,  $\hat{\Delta}(t)$ , described above.

rmst.1 the estimated restricted mean survival time in group 1, described above.

rmst.0 the estimated restricted mean survival time in group 0, described above.

delta.sd the standard error estimate of  $\hat{\Delta}(t)$ ; if std = TRUE or conf.int = TRUE.

delta.mad the standard error estimate of  $\hat{\Delta}(t)$  using the median absolute deviation; if std =

TRUE or conf.int = TRUE.

conf.int.delta a vector of size 2; the 95% confidence interval for  $\hat{\Delta}(t)$  based on sample quantiles of the perturbed values; if conf.int = TRUE.

### Author(s)

Layla Parast

delta.estimate.RMST 5

#### References

Parast L, Tian L, and Cai T (2020). Assessing the Value of a Censored Surrogate Outcome. Lifetime Data Analysis, 26(2):245-265.

Tian, L, Zhao, L, & Wei, LJ (2013). Predicting the restricted mean event time with the subject's baseline covariates in survival analysis. Biostatistics, 15(2), 222-233.

Royston, P, & Parmar, MK (2011). The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. Statistics in Medicine, 30(19), 2409-2421.

### **Examples**

```
data(ExampleData)
names(ExampleData)

delta.estimate(xone = ExampleData$x1, xzero = ExampleData$x0, deltaone = ExampleData$delta1,
deltazero = ExampleData$delta0, t = 5)

delta.estimate(xone = ExampleData$x1, xzero = ExampleData$x0, deltaone = ExampleData$delta1,
deltazero = ExampleData$delta0, t = 5, std = TRUE, conf.int = TRUE)
```

delta.estimate.RMST Helper function

### **Description**

Helper function; used by delta.estimate function

# Usage

```
delta.estimate.RMST(xone, xzero, deltaone, deltazero, t, weight = NULL, delta.only = F)
```

#### **Arguments**

xone	numeric vector, observed event times for the primary outcome in the treatment group.
xzero	numeric vector, observed event times for the primary outcome in the control group.
deltaone	numeric vector, event/censoring indicators for the primary outcome in the treatment group.
deltazero	numeric vector, event/censoring indicators for the primary outcome in the control group.
t	time of interest for treatment effect.
weight	weight; optional
delta.only	TRUE or FALSE; if TRUE then only delta is returned, if FALSE then delta and restricted mean survival time for each treatment group is also returned

6 delta.q.event.RMST

#### Value

A list is returned:

delta the difference in the restricted mean survival between the two treatment groups.

so only if delta.only = F; the restricted mean survival in group 1.
so only if delta.only = F; the restricted mean survival in group 0.

### Author(s)

Layla Parast

delta.q.event.RMST Calculates the residual treatment effect (the difference in restricted

mean survival time at time t) after accounting for the treatment effect

on the surrogate outcome information up to the landmark time

#### **Description**

Calculates the residual treatment effect (the difference in restricted mean survival time at time t) after accounting for the treatment effect on the surrogate outcome information up to the landmark time; uses nonparametric estimation.

#### Usage

delta.q.event.RMST(xone, xzero, deltaone, deltazero, sone, szero, t, weight = NULL, landmark = landmark, deltaslist = TRUE, transform = FALSE, extrapolate=TRUE, number, warn.extrapolate=TRUE)

#### **Arguments**

xone	numeric vector, obse	erved event times	for the primary	outcome in the treatment
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group.

xzero numeric vector, observed event times for the primary outcome in the control

group.

deltaone numeric vector, event/censoring indicators for the primary outcome in the treat-

ment group.

deltazero numeric vector, event/censoring indicators for the primary outcome in the con-

trol group.

sone numeric vector, observed event times for the surrogate outcome in the treatment

group.

szero numeric vector, observed event times for the surrogate outcome in the control

group.

t time of interest for treatment effect.

weight optional weight.

landmark time of interest,  $t_0$ .

deltaslist TRUE or FALSE; if TRUE, each component of the residual treatment effect

is returned along with the residual treatment effect itself, if FALSE, only the

residual treatment effect is returned.

delta.q.event.RMST 7

transform TRUE or FALSE; indicates whether a transformation should be used, default is

FALSE.

extrapolate TRUE or FALSE; indicates whether local constant extrapolation should be used,

default is TRUE.

number of points for RMST calculation, default is 40.

warn.extrapolate

TRUE or FALSE; indicates whether user prefers a warning message when ex-

trapolation is used, default is TRUE.

### **Details**

See documentation for R.q.event for details.

#### Value

#### A list is returned:

delta.q the estimated residual treatment effect

first.term the first term of the residual treatment effect, if deltaslist = TRUE

second term the second term of the residual treatment effect, if deltaslist = TRUE

third.term the third term of the residual treatment effect, if deltaslist = TRUE

### Author(s)

Layla Parast

### References

Parast L, Tian L, and Cai T (2020). Assessing the Value of a Censored Surrogate Outcome. Lifetime Data Analysis, 26(2):245-265.

### **Examples**

```
data(ExampleData)
names(ExampleData)

delta.q.event.RMST(xone = ExampleData$x1, xzero = ExampleData$x0, deltaone = ExampleData$delta1,
deltazero = ExampleData$delta0, sone = ExampleData$s1, szero = ExampleData$s0, t = 5, landmark=2,
```

```
delta.q.event.RMST(xone = ExampleData$x1, xzero = ExampleData$x0, deltaone = ExampleData$delta1,
deltazero = ExampleData$delta0, sone = ExampleData$s1, szero = ExampleData$s0, t = 4, landmark=2,
number = 40)
```

delta.q.event.semi.RMST

Calculates the residual treatment effect (the difference in restricted mean survival time at time t) after accounting for the treatment effect on the surrogate outcome information up to the landmark time

# Description

Calculates the residual treatment effect (the difference in restricted mean survival time at time t) after accounting for the treatment effect on the surrogate outcome information up to the landmark time; uses semi-parametric estimation.

### Usage

```
delta.q.event.semi.RMST(xone, xzero, deltaone, deltazero, sone, szero, t,
weight = NULL, landmark = landmark, deltaslist = TRUE, number)
```

#### **Arguments**

xone	numeric vector, observed event times for the primary outcome in the treatment group.
xzero	numeric vector, observed event times for the primary outcome in the control group.
deltaone	numeric vector, event/censoring indicators for the primary outcome in the treatment group.
deltazero	numeric vector, event/censoring indicators for the primary outcome in the control group.
sone	numeric vector, observed event times for the surrogate outcome in the treatment group.
szero	numeric vector, observed event times for the surrogate outcome in the control group.
t	time of interest for treatment effect.
weight	optional weight.
landmark	landmark time of interest, $t_0$ .
deltaslist	TRUE or FALSE; if TRUE, each component of the residual treatment effect is returned along with the residual treatment effect itself, if FALSE, only the residual treatment effect is returned.
number	number of points for RMST calculation, default is 40.

### **Details**

See documentation for R.q.event for details.

delta.t.RMST 9

#### Value

A list is returned:

delta.q the estimated residual treatment effect

first.term the first term of the residual treatment effect, if deltaslist = TRUE

second.term the second term of the residual treatment effect, if deltaslist = TRUE

third.term the third term of the residual treatment effect, if deltaslist = TRUE

#### Author(s)

Layla Parast

#### References

Parast L, Tian L, and Cai T (2020). Assessing the Value of a Censored Surrogate Outcome. Lifetime Data Analysis, 26(2):245-265.

#### **Examples**

```
data(ExampleData)
names(ExampleData)

delta.q.event.semi.RMST(xone = ExampleData$x1, xzero = ExampleData$x0, deltaone =
ExampleData$delta1, deltazero = ExampleData$delta0, sone = ExampleData$s1,
szero = ExampleData$s0, t = 5, landmark=2, number = 40)
delta.q.event.semi.RMST(xone = ExampleData$x1, xzero = ExampleData$x0, deltaone =
ExampleData$delta1, deltazero = ExampleData$delta0, sone = ExampleData$s1,
szero = ExampleData$s0, t = 3, landmark=2, number = 40)
```

delta.t.RMST Calculates the residual treatment effect (the difference in restricted mean survival time at time t) after accounting for the treatment effect

on the primary outcome up to the landmark time

### **Description**

Calculates the residual treatment effect (the difference in restricted mean survival time at time t) after accounting for the treatment effect on the primary outcome up to the landmark time

# Usage

```
delta.t.RMST(xone, xzero, deltaone, deltazero, t, weight = NULL, landmark = landmark)
```

### Arguments

xone numeric vector, observed event times for the primary outcome in the treatment

group.

xzero numeric vector, observed event times for the primary outcome in the control

group.

10 ExampleData

deltaone numeric vector, event/censoring indicators for the primary outcome in the treat-

ment group.

deltazero numeric vector, event/censoring indicators for the primary outcome in the con-

trol group.

t time of interest for treatment effect.

weight optional weight.

landmark time of interest,  $t_0$ .

### **Details**

See documentation for R.t.estimate for details.

#### Value

delta.t the estimated residual treatment effect after accounting for the treatment effect

on the primary outcome up to the landmark time

#### Author(s)

Layla Parast

#### References

Parast L, Tian L, and Cai T (2020). Assessing the Value of a Censored Surrogate Outcome. Lifetime Data Analysis, 26(2):245-265.

### **Examples**

```
data(ExampleData)
names(ExampleData)
delta.t.RMST(xone = ExampleData$x1, xzero = ExampleData$x0, deltaone = ExampleData$delta1,
deltazero = ExampleData$delta0, t = 5, landmark=2)
```

ExampleData

Hypothetical data

### **Description**

Hypothetical data to be used in examples; t=5 and the landmark time = 2.

# Usage

```
data(ExampleData)
```

helper.si 11

#### **Format**

A list with 6 elements representing 1000 observations from a control group and 1000 observations from a treatment group:

- s1 Time of the occurrence of the surrogate outcome for treated observations.
- x1 The observed event or censoring time for treated observations; X = min(T, C) where T is the time of the primary outcome and C is the censoring time.
- delta1 The indicator identifying whether the treated observation was observed to have the event or was censored; D = 1\*(T < C) where T is the time of the primary outcome and C is the censoring time.
- s0 Time of the occurrence of the surrogate outcome for control observations.
- x0 The observed event or censoring time for control observations; X = min(T, C) where T is the time of the primary outcome and C is the censoring time.
- delta0 The indicator identifying whether the control observation was observed to have the event or was censored; D = 1\*(T < C) where T is the time of the primary outcome and C is the censoring time.

#### **Details**

Note that the time of the surrogate outcome is used in all functions only if the surrogate outcome occurs before the minimum of the event time and censoring time.

# **Examples**

```
data(ExampleData)
names(ExampleData)
```

helper.si

Helper function

### **Description**

Helper function; should not be called directly by user.

### Usage

```
helper.si(yy,FUN,Yi,Vi=NULL)
```

### **Arguments**

уу	уу
FUN	FUN
Yi	Yi
Vi	Vi

#### Value

out matrix

### Author(s)

Layla Parast

IV.event

IV.event	Calculates the incremental value of the surrogate outcome information

# Description

Calculates the incremental value of the surrogate outcome information

# Usage

```
IV.event(xone, xzero, deltaone, deltazero, sone, szero, t, landmark, number = 40,
transform = FALSE, extrapolate = TRUE, std = FALSE, conf.int = FALSE,
weight.perturb = NULL, type = "np")
```

# Arguments

Suments	
xone	numeric vector, observed event times for the primary outcome in the treatment group.
xzero	numeric vector, observed event times for the primary outcome in the control group.
deltaone	numeric vector, event/censoring indicators for the primary outcome in the treatment group.
deltazero	numeric vector, event/censoring indicators for the primary outcome in the control group.
sone	numeric vector, observed event times for the surrogate outcome in the treatment group.
szero	numeric vector, observed event times for the surrogate outcome in the control group.
t	time of interest for treatment effect.
landmark	landmark time of interest, $t_0$ .
number	number of points for RMST calculation, default is 40.
transform	TRUE or FALSE; indicates whether a transformation should be used, default is FALSE.
extrapolate	TRUE or FALSE; indicates whether local constant extrapolation should be used, default is FALSE.
std	TRUE or FALSE; indicates whether standard error estimates should be provided, default is FALSE. Estimates are calculated using perturbation-resampling. Two versions are provided: one that takes the standard deviation of the perturbed estimates (denoted as "sd") and one that takes the median absolute deviation (denoted as "mad").
conf.int	TRUE or FALSE; indicates whether 95% confidence intervals should be provided. Confidence intervals are calculated using the percentiles of perturbed estimates, default is FALSE. If this is TRUE, standard error estimates are automatically provided.
weight.perturb	weights used for perturbation resampling.
type	Type of estimate that should be provided; options are "np" for the nonparametric

estimate or "semi" for the semiparametric estimate, default is "np".

IV.event

#### **Details**

The incremental value of the surrogate outcome information only is quantified as  $IV_S(t,t_0)=R_Q(t,t_0)-R_T(t,t_0)$  where the definition and estimation procedures for  $R_Q(t,t_0)$  and  $R_T(t,t_0)$  are described in the documentation for R.q.event and R.t.estimate, respectively. The estimate of the incremental value is  $\hat{IV}_S(t,t_0)=\hat{R}_Q(t,t_0)-\hat{R}_T(t,t_0)$ .

# Value

Α	list	15	returned	٠

	A list is returned.	
	delta	the estimate, $\hat{\Delta}(t)$ , described in delta.estimate documentation.
	delta.q	the estimate, $\hat{\Delta}_Q(t, t_0)$ , described in R.q.event documention.
	R.q	the estimate, $\hat{R}_Q(t,t_0)$ , described in R.q.event documention.
	delta.t	the estimate, $\hat{\Delta}_T(t,t_0)$ , described in R.t.estimate documention.
	R.t	the estimate, $\hat{R}_T(t,t_0)$ , described in R.t.estimate documention.
	IV	the estimated incremental value of the surrogate outcome information, described above. $\\$
	delta.sd	the standard error estimate of $\hat{\Delta}(t)$ ; if std = TRUE or conf.int = TRUE.
	delta.mad	the standard error estimate of $\hat{\Delta}(t)$ using the median absolute deviation; if std = TRUE or conf.int = TRUE.
	delta.q.sd	the standard error estimate of $\hat{\Delta}_Q(t, t_0)$ ; if std = TRUE or conf.int = TRUE.
	delta.q.mad	the standard error estimate of $\hat{\Delta}_Q(t,t_0)$ using the median absolute deviation; if std = TRUE or conf.int = TRUE.
	R.q.sd	the standard error estimate of $\hat{R}_Q(t,t_0)$ ; if std = TRUE or conf.int = TRUE.
	R.q.mad	the standard error estimate of $\hat{R}_Q(t,t_0)$ using the median absolute deviation; if std = TRUE or conf.int = TRUE.
	delta.t.sd	the standard error estimate of $\hat{\Delta}_T(t, t_0)$ ; if std = TRUE or conf.int = TRUE.
	delta.t.mad	the standard error estimate of $\hat{\Delta}_T(t,t_0)$ using the median absolute deviation; if std = TRUE or conf.int = TRUE.
	R.t.sd	the standard error estimate of $\hat{R}_T(t,t_0)$ ; if std = TRUE or conf.int = TRUE.
	R.t.mad	the standard error estimate of $\hat{R}_T(t,t_0)$ using the median absolute deviation; if std = TRUE or conf.int = TRUE.
	IV.sd	the standard error estimate of the incremental value; if $std = TRUE$ or conf.int = TRUE.
	IV.mad	the standard error estimate of the incremental value using the median absolute deviation; if $std = TRUE$ or conf.int = $TRUE$ .
	conf.int.delta	a vector of size 2; the 95% confidence interval for $\hat{\Delta}(t)$ based on sample quantiles of the perturbed values; if conf.int = TRUE.
conf.int.delta.q		
		a vector of size 2; the 95% confidence interval for $\Delta_Q(t,t_0)$ based on sample quantiles of the perturbed values; if conf.int = TRUE.
	conf.int.R.q	a vector of size 2; the 95% confidence interval for $\hat{R}_Q(t,t_0)$ based on sample quantiles of the perturbed values; if conf.int = TRUE.
	conf.int.delta.	t

a vector of size 2; the 95% confidence interval for  $\hat{\Delta}_T(t,t_0)$  based on sample

quantiles of the perturbed values; if conf.int = TRUE.

14 Kern.FUN

conf.int.R.t a vector of size 2; the 95% confidence interval for  $\hat{R}_T(t,t_0)$  based on sample quantiles of the perturbed values; if conf.int = TRUE. conf.int.IV a vector of size 2; the 95% confidence interval for the incremental value based on sample quantiles of the perturbed values; if conf.int = TRUE.

### Author(s)

Layla Parast

#### References

Parast L, Tian L, and Cai T (2020). Assessing the Value of a Censored Surrogate Outcome. Lifetime Data Analysis, 26(2):245-265.

### **Examples**

```
data(ExampleData)
names(ExampleData)

IV.event(xone = ExampleData$x1, xzero = ExampleData$x0, deltaone = ExampleData$delta1,
deltazero = ExampleData$delta0, sone = ExampleData$s1, szero = ExampleData$s0, t = 5,
landmark=2, type = "np")

IV.event(xone = ExampleData$x1, xzero = ExampleData$x0, deltaone = ExampleData$delta1,
deltazero = ExampleData$delta0, sone = ExampleData$s1, szero = ExampleData$s0, t = 5,
landmark=2, type = "np", std = TRUE, conf.int = TRUE)
```

Kern.FUN

Calculates kernel matrix

### **Description**

Helper function; this calculates the kernel matrix

# Usage

```
Kern.FUN(zz, zi, bw, kern0)
```

### **Arguments**

zz zz zi zi

bw bandwidth

kern0 kernel distribution

#### Value

the kernel matrix

### Author(s)

Layla Parast

new.q

|--|

#### **Description**

Helper function; should not be called directly by user. This function differs from the quantile function in that it returns an NA when there are NAs in the supplied vector, rather than causing an error.

### Usage

```
new.q(x, p)
```

### **Arguments**

x vector of numeric valuesp sample quantile that is desired

### Value

returns either NA or the desired sample quantile

#### Author(s)

Layla Parast

pred.smooth.surv	Calculates the conditional probability of survival for control group values
------------------	---

# **Description**

Helper function; calculates the estimated probability of survival for control group surrogate values using treatment group surrogate and outcome information.

### Usage

```
pred.smooth.surv(xone.f, deltaone.f, sone.f, szero.one, myt, bw = NULL,
weight, transform, extrapolate = T)
```

### **Arguments**

bw

xone.f observed event times in the treatment group.
deltaone.f censoring indicators in the treatment group.
sone.f surrogate marker values in the treatment group.
szero.one surrogate marker values in the control group.
myt time of interest.

bandwidth.

16 R.opt.event

weight weight used for perturbation resampling.

transform TRUE or FALSE; indicates whether a transformation should be used, default is

FALSE.

extrapolate TRUE or FALSE; indicates whether local constant extrapolation should be used,

default is TRUE.

#### Value

A list is returned:

Phat.ss conditional probability of survival past t for control group warn.flag warning flag equal to 1 if extrapolation was used; 0 otherwise

### Author(s)

Layla Parast

R.opt.event Calculates the proportion of the treatment effect (the difference in survival at time t) explained by surrogate outcome information observed

up to the landmark time, using the optimal transformation of the sur-

rogate

### **Description**

Calculates the proportion of the treatment effect (the difference in survival at time t) explained by surrogate outcome information observed up to the landmark time, using the optimal transformation of the surrogate; also provides standard error estimate and confidence interval. Details are provided in: Wang X, Cai T, Tian L, Parast L (2025). Model-free Approach to Evaluate a Censored Intermediate Outcome as a Surrogate for Overall Survival. arXiv preprint arXiv:2412.14129.

### Usage

R.opt.event(xone, xzero, deltaone, deltazero, sone, szero, t, landmark, std = FALSE, conf.int = FALSE, gopt = FALSE, ind = FALSE)

### Arguments

xone	numeric vector, observed event times for the primary outcome in the treatment group.
xzero	numeric vector, observed event times for the primary outcome in the control group.
deltaone	numeric vector, event/censoring indicators for the primary outcome in the treatment group.
deltazero	numeric vector, event/censoring indicators for the primary outcome in the control group.
sone	numeric vector, observed event times for the surrogate outcome in the treatment group.
szero	numeric vector, observed event times for the surrogate outcome in the control group.

R.opt.event 17

t	time of interest for treatment effect.
landmark	landmark time of interest, $t_0$ .
std	TRUE or FALSE; indicates whether standard error estimates should be provided, default is FALSE. Estimates are calculated using perturbation-resampling.
conf.int	TRUE or FALSE; indicates whether a 95% confidence interval for the PTE should be provided. Confidence intervals are calculated using the percentiles of perturbed estimates, default is FALSE.
gopt	TRUE or FALSE; indicates whether the estimates of the optimal g1(s) and g2 should be provided, default is FALSE.
ind	TRUE or FALSE; indicates whether the estimate of PTE for primary outcome information only up to the landmark time should be provided, default is FALSE.

#### Value

#### A list is returned:

R.opt	the estimate of the PTE of the surrogate outcome
R.opt.ind	the estimate of the PTE for primary outcome information only up to the land-mark time; if ind=TRUE
g1.opt	the estimate of the optimal transformation g1(s); if gopt=TRUE
g2.opt	the estimate of the optimal transformation g2; if gopt=TRUE
R.opt.std	the standard error estimate of the PTE of the surrogate outcome; if std=TRUE
conf.int.R	the confidence interval for the PTE of the surrogate outcome; if cont.int=TRUE
g1.opt.sd	the standard error estimate of the optimal transformation g1(s); if gopt=TRUE and std=TRUE
g2.opt.sd	the standard error estimate of the optimal transformation g2; if gopt=TRUE and std=TRUE

#### Author(s)

Xuan Wang

### References

Wang X, Cai T, Tian L, Parast L (2025). Model-free Approach to Evaluate a Censored Intermediate Outcome as a Surrogate for Overall Survival. arXiv preprint arXiv:2412.14129.

# **Examples**

```
data(ExampleData)
names(ExampleData)

R.opt.event(xone = ExampleData$x1, xzero = ExampleData$x0, deltaone = ExampleData$delta1,
deltazero = ExampleData$delta0, sone = ExampleData$s1, szero = ExampleData$s0, t = 5,
landmark=2)

#with all options as TRUE
R.opt.event(xone = ExampleData$x1, xzero = ExampleData$x0, deltaone = ExampleData$delta1,
deltazero = ExampleData$delta0, sone = ExampleData$s1, szero = ExampleData$s0, t = 5,
landmark=2, std = TRUE, conf.int = TRUE, gopt = TRUE, ind = TRUE)
```

R.q.event

R.q.event	Calculates the proportion of the treatment effect (the difference in restriced mean survival time at time t) explained by surrogate outcome information observed up to the landmark time
	information observed up to the landmark time

# Description

Calculates the proportion of the treatment effect (the difference in restriced mean survival time at time t) explained by surrogate outcome information observed up to the landmark time; also provides standard error estimate and confidence interval.

# Usage

```
R.q.event(xone, xzero, deltaone, deltazero, sone, szero, t, landmark, number = 40,
transform = FALSE, extrapolate = TRUE, std = FALSE, conf.int = FALSE,
weight.perturb = NULL, type = "np")
```

# Arguments

	and the second s
xone	numeric vector, observed event times for the primary outcome in the treatment group.
xzero	numeric vector, observed event times for the primary outcome in the control group.
deltaone	numeric vector, event/censoring indicators for the primary outcome in the treatment group.
deltazero	numeric vector, event/censoring indicators for the primary outcome in the control group.
sone	numeric vector, observed event times for the surrogate outcome in the treatment group.
szero	numeric vector, observed event times for the surrogate outcome in the control group.
t	time of interest for treatment effect.
landmark	landmark time of interest, $t_0$ .
number	number of points for RMST calculation, default is 40.
transform	TRUE or FALSE; indicates whether a transformation should be used, default is FALSE.
extrapolate	TRUE or FALSE; indicates whether local constant extrapolation should be used, default is FALSE.
std	TRUE or FALSE; indicates whether standard error estimates should be provided, default is FALSE. Estimates are calculated using perturbation-resampling. Two versions are provided: one that takes the standard deviation of the perturbed estimates (denoted as "sd") and one that takes the median absolute deviation (denoted as "mad").
conf.int	TRUE or FALSE; indicates whether 95% confidence intervals should be provided. Confidence intervals are calculated using the percentiles of perturbed estimates, default is FALSE. If this is TRUE, standard error estimates are automatically provided.

R.q.event 19

weight.perturb weights used for perturbation resampling.

type Type of estimate that should be provided; options are "np" for the nonparametric estimate or "semi" for the semiparametric estimate, default is "np".

#### **Details**

Let  $G \in \{1,0\}$  be the randomized treatment indicator, T denote the time of the primary outcome of interest, and S denote the time of the surrogate outcome. We use potential outcomes notation such that  $T^{(G)}$  and  $S^{(G)}$  denote the respective times of the primary and surrogate outcomes under treatment G, for  $G \in \{1,0\}$ . In the absence of censoring, we only observe  $(T,S)=(T^{(1)},S^{(1)})$  or  $(T^{(0)},S^{(0)})$  for each individual depending on whether G=1 or G. Due to censoring, data consist of G in G independent observations G independent observations G independent observations G independent G independent observations G independent G independe

We define the treatment effect as the difference in restricted mean survival time up to a fixed time t under treatment 1 versus under treatment 0,

$$\Delta(t) = E\{T^{(1)} \wedge t\} - E\{T^{(0)} \wedge t\}$$

where  $\wedge$  indicates the minimum. To define the proportion of treatment effect explained by the surrogate outcome information, let

$$Q_{t_0}^{(g)} = (Q_{t_01}, Q_{t_02})' = \{S^{(g)} \wedge t_0 I(T^{(g)} > t_0), T^{(g)} I(T^{(g)} \le t_0)\}', g = 1, 0$$

and define the residual treatment effect after accounting for the treatment effect on the surrogate outcome information as:

$$\Delta_Q(t,t_0) = P_{t_0,2}^{(0)} \int_0^{t_0} \phi_1(t|t_0,s) dF_0(s) + P_{t_0,3}^{(0)} \psi_1(t|t_0) - P(T^{(0)} > t_0) \nu_0(t|t_0)$$

where  $P_{t_0,2}^{(0)} = P(T^{(0)} > t_0, S^{(0)} < t_0)$  and  $P_{t_0,3}^{(0)} = P(T^{(0)} > t_0, S^{(0)} > t_0)$ ,  $\psi_1(t \mid t_0) = E(T^{(1)} \wedge t \mid T^{(1)} > t_0, S^{(1)} > t_0)$ ,  $\phi_1(t \mid t_0, s) = E(T^{(1)} \wedge t \mid T^{(1)} > t_0, S^{(1)} = s)$ ,  $\nu_0(t \mid t_0) = E(T^{(0)} \wedge t \mid T^{(0)} > t_0)$ , and  $F_0(\cdot \mid t_0)$  is the cumulative distribution function of  $S^{(0)}$  conditional on  $T^{(0)} > t_0$  and  $S^{(0)} < t_0$ . Then, the proportion of treatment effect on the primary outcome that is explained by surrogate information up to  $t_0$ ,  $Q_{t_0}$ , can be expressed as a contrast between  $\Delta(t)$  and  $\Delta_Q(t,t_0)$ :

$$R_O(t, t_0) = {\Delta(t) - \Delta_O(t, t_0)}/{\Delta(t)} = 1 - {\Delta_O(t, t_0)}/{\Delta(t)}.$$

The quantity  $\Delta(t)$  is estimated using inverse probability of censoring weights:

$$\hat{\Delta}(t) = n_1^{-1} \sum_{i=1}^{n_1} \hat{M}_{1i}(t) - n_0^{-1} \sum_{i=1}^{n_0} \hat{M}_{0i}(t)$$

where  $\hat{M}_{gi}(t) = I(X_{gi} > t)t/\hat{W}_g^C(t) + I(X_{gi} < t)X_{gi}\delta_{gi}/\hat{W}_g^C(X_{gi})$  and  $\hat{W}_g^C(t)$  is the Kaplan-Meier estimator of  $P(C_{gi} \geq t)$ . The residual treatment effect  $\Delta_Q(t,t_0)$  can be estimated non-parametrically or seminally. For nonparametric estimation,  $\psi_1(t|t_0)$  is estimated by  $\hat{\psi}_1(t|t_0) = \sum_{i=1}^{n_1} \frac{\hat{W}_1^C(t_0)I(S_{1i}>t_0,X_{1i}>t_0)}{\sum_{i=1}^{n_1}I(S_{1i}>t_0,X_{1i}>t_0)} \hat{M}_{1i}(t)$ , and  $\phi_1(t\mid t_0,s) = E(T^{(1)} \wedge t\mid X^{(1)} > t_0,S^{(1)}=s)$  is estimated using a nonparametric kernel Nelson-Aalen estimator for  $\Lambda_1(t\mid t_0,s)$ , the cumulative hazard function of  $T^{(1)}$  conditional on  $S^{(1)}=s$  and  $T^{(1)}>t_0$ , as

$$\hat{\phi}_1(t \mid t_0, s) = t_0 + \int_{t_0}^t \exp\{-\hat{\Lambda}_1(t \mid t_0, s)\} dt,$$

where

$$\hat{\Lambda}_1(t \mid t_0, s) = \int_{t_0}^t \frac{\sum_{i=1}^{n_1} I(X_{1i} > t_0, S_{1i} < t_0) K_h\{\gamma(S_{1i}) - \gamma(s)\} dN_{1i}(z)}{\sum_{i=1}^{n_1} I(X_{1i} > t_0, S_{1i} < t_0) K_h\{\gamma(S_{1i}) - \gamma(s)\} Y_{1i}(z)},$$

is a consistent estimate of  $\Lambda_1(t \mid t_0, s)$ ,  $Y_{1i}(t) = I(X_{1i} \geq t)$ ,  $N_{1i}(t) = I(X_{1i} \leq t)\delta_i$ ,  $K(\cdot)$  is a smooth symmetric density function,  $K_h(x) = K(x/h)/h$ ,  $\gamma(\cdot)$  is a given monotone transformation function, and  $h = O(n_1^{-\eta})$  is a specified bandwidth with  $\eta \in (1/2, 1/4)$ . Finally, we let

$$\hat{\nu}_0(t|t_0) = \sum_{i=1}^{n_0} \frac{\hat{W}_0^C(t_0)I(X_{0i} > t_0)}{\sum_{i=1}^{n_0} I(X_{0i} > t_0)} \hat{M}_{0i}(t).$$

We then estimate  $\Delta_Q(t,t_0)$  as  $\hat{\Delta}_Q(t,t_0)$  defined as

$$n_0^{-1} \sum_{i=1}^{n_0} \left\{ \frac{I_{t_0,2}(X_{0i}, S_{0i}) \hat{\phi}_1(t \mid t_0, S_{0i}) + I_{t_0,3}(X_{0i}, S_{0i}) \hat{\psi}_1(t \mid t_0) - I_{t_0}(X_{0i}) \hat{\nu}(t \mid t_0)}{\hat{W}_0^C(t_0)} \right\}$$

where  $I_{t_0,2}(x,s) = I(x > t_0, s < t_0)$  and  $I_{t_0,3}(x,s) = I(x > t_0, s > t_0)$  and  $I_{t_0}(x) = I(x > t_0)$  and thus,  $\hat{R}_Q(t,t_0) = 1 - \hat{\Delta}_Q(t,t_0)/\hat{\Delta}(t)$ .

For the semi-parametric estimate,  $\hat{\phi}_1(t|t_0,s)$  is replaced with an estimate obtained using a landmark Cox proportional hazards model

$$P(T^{(1)} > t \mid T^{(1)} > t_0, S^{(1)} < t_0, S^{(1)}) = \exp\{-\Lambda_0(t|t_0)\exp(\beta_0 S^{(1)})\}$$

where  $\Lambda_0(t|t_0)$  is the unspecified baseline cumulative hazard among  $\Omega_{t_0}=\{T^{(1)}>t_0,S^{(1)}< t_0\}$  and  $\beta_0$  is unknown. That is, let  $\tilde{\phi}_1(t|t_0,s)=t_0+\int_{t_0}^t\exp\{-\hat{\Lambda}_0(t|t_0)\exp(\hat{\beta}s)\}dt$ , where  $\hat{\beta}$  is estimated by fitting a Cox model to the subpopulation  $\Omega_{t_0}$  with a single predictor S and  $\hat{\Lambda}_0(\cdot|t_0)$  is the corresponding Breslow estimator. Then the semiparametric estimator for  $\Delta_Q(t,t_0)$  is  $\tilde{\Delta}_Q(t,t_0)$  defined as

$$n_0^{-1} \sum_{i=1}^{n_0} \left\{ \frac{I_{t_0,2}(X_{0i}, S_{0i})\tilde{\phi}_1(t \mid t_0, S_{0i}) + I_{t_0,3}(X_{0i}, S_{0i})\hat{\psi}_1(t \mid t_0) - I_{t_0}(X_{0i})\hat{\nu}(t \mid t_0)}{\hat{W}_0^C(t_0)} \right\}$$

and 
$$\tilde{R}_Q(t,t_0) = 1 - \tilde{\Delta}_Q(t,t_0)/\hat{\Delta}(t)$$
.

#### Value

A list is returned:

R.q.sd

delta the estimate,  $\hat{\Delta}(t)$ , described in delta.estimate documentation. the estimate,  $\hat{\Delta}_Q(t, t_0)$ , described above. delta.q the estimate,  $\hat{R}_Q(t, t_0)$ , described above. R.q the standard error estimate of  $\hat{\Delta}(t)$ ; if std = TRUE or conf.int = TRUE. delta.sd the standard error estimate of  $\hat{\Delta}(t)$  using the median absolute deviation; if std = delta.mad TRUE or conf.int = TRUE. the standard error estimate of  $\hat{\Delta}_Q(t, t_0)$ ; if std = TRUE or conf.int = TRUE. delta.q.sd the standard error estimate of  $\hat{\Delta}_{Q}(t,t_{0})$  using the median absolute deviation; if delta.q.mad std = TRUE or conf.int = TRUE.

the standard error estimate of  $\hat{R}_Q(t, t_0)$ ; if std = TRUE or conf.int = TRUE.

R.t.estimate 21

R.q.mad	the standard error estimate of $\hat{R}_Q(t,t_0)$ using the median absolute deviation; if std = TRUE or conf.int = TRUE.	
conf.int.delta	a vector of size 2; the 95% confidence interval for $\hat{\Delta}(t)$ based on sample quantiles of the perturbed values; if conf.int = TRUE.	
conf.int.delta.q		
	a vector of size 2; the 95% confidence interval for $\hat{\Delta}_Q(t,t_0)$ based on sample quantiles of the perturbed values; if conf.int = TRUE.	
conf.int.R.q	a vector of size 2; the 95% confidence interval for $\hat{R}_Q(t,t_0)$ based on sample quantiles of the perturbed values; if conf.int = TRUE.	

#### Author(s)

Layla Parast

#### References

Parast L, Tian L, and Cai T (2020). Assessing the Value of a Censored Surrogate Outcome. Lifetime Data Analysis, 26(2):245-265.

Parast, L and Cai, T (2013). Landmark risk prediction of residual life for breast cancer survival. Statistics in Medicine, 32(20), 3459-3471.

### **Examples**

```
data(ExampleData)
names(ExampleData)

R.q.event(xone = ExampleData$x1, xzero = ExampleData$x0, deltaone = ExampleData$delta1,
deltazero = ExampleData$delta0, sone = ExampleData$s1, szero = ExampleData$s0, t = 5,
landmark=2, type = "np")
R.q.event(xone = ExampleData$x1, xzero = ExampleData$x0, deltaone = ExampleData$delta1,
deltazero = ExampleData$delta0, sone = ExampleData$s1, szero = ExampleData$s0, t = 5,
landmark=2, type = "semi")
R.q.event(xone = ExampleData$x1, xzero = ExampleData$x0, deltaone = ExampleData$delta1,
deltazero = ExampleData$delta0, sone = ExampleData$s1, szero = ExampleData$s0, t = 5,
landmark=2, type = "np", std = TRUE, conf.int = TRUE)
```

R.t.estimate

Calculates the proportion of the treatment effect (the difference in restricted mean survival time at time t) explained by primary outcome information observed up to the landmark time

# Description

Calculates the proportion of the treatment effect (the difference in restricted mean survival time at time t) explained by primary outcome information observed up to the landmark time; also provides standard error estimate and confidence interval.

### Usage

#### **Arguments**

xone	numeric vector, observed event times for the primary outcome in the treatment group.
xzero	numeric vector, observed event times for the primary outcome in the control group.
deltaone	numeric vector, event/censoring indicators for the primary outcome in the treatment group.
deltazero	numeric vector, event/censoring indicators for the primary outcome in the control group.
t	time of interest for treatment effect.
landmark	landmark time of interest, $t_0$ .
std	TRUE or FALSE; indicates whether standard error estimates should be provided, default is FALSE. Estimates are calculated using perturbation-resampling. Two versions are provided: one that takes the standard deviation of the perturbed estimates (denoted as "sd") and one that takes the median absolute deviation (denoted as "mad").
conf.int	TRUE or FALSE; indicates whether 95% confidence intervals should be provided. Confidence intervals are calculated using the percentiles of perturbed estimates, default is FALSE. If this is TRUE, standard error estimates are automatically provided.

weight.perturb weights used for perturbation resampling.

#### **Details**

Let  $G \in \{1,0\}$  be the randomized treatment indicator, T denote the time of the primary outcome of interest, and S denote the time of the surrogate outcome. We use potential outcomes notation such that  $T^{(G)}$  and  $S^{(G)}$  denote the respective times of the primary and surrogate outcomes under treatment G, for  $G \in \{1,0\}$ . In the absence of censoring, we only observe  $(T,S)=(T^{(1)},S^{(1)})$  or  $(T^{(0)},S^{(0)})$  for each individual depending on whether G=1 or G. Due to censoring, data consist of G independent observations G independent observations G independent observations G independent G independent G independent observations G independent G independent observations G independent observations of G independent observations of G independent observations G independent observations G independent observations of G in G independent observations of G in

The proportion of treatment effect explained by primary outcome information observed up to the landmark time,  $t_0$ , is defined as  $R_T(t,t_0) = 1 - \Delta_T(t,t_0)/\Delta(t)$  where

$$\Delta_T(t, t_0) = P(T^{(0)} > t_0) E\{T^{(1)} \wedge t - T^{(0)} \wedge t \mid T > t_0\}$$

and  $\Delta(t)$  is the treatment effect on the primary outcome, defined in the documentation for delta.estimate. The quantity  $\Delta_T(t, t_0)$  is estimated using

$$\hat{\Delta}_T(t, t_0) = n_0^{-1} \sum_{i=1}^{n_0} I(X_{0i} > t_0) / \hat{W}_0^C(t_0) \{ \hat{\nu}_1(t|t_0) - \hat{\nu}_0(t|t_0) \}$$

where  $\hat{W}_0^C(t)$  is the Kaplan-Meier estimator of  $P(C_{gi} \ge t)$ ,  $\hat{\nu}_0(t|t_0)$  is defined in the documentation for R.q.event and  $\hat{\nu}_1(t|t_0)$  is obtained by replacing 0 with 1.

R.t.estimate 23

### Value

### A list is returned:

	delta	the estimate, $\hat{\Delta}(t)$ , described in delta.estimate documentation.
	delta.t	the estimate, $\hat{\Delta}_T(t,t_0)$ , described above.
	R.t	the estimate, $\hat{R}_T(t,t_0)$ , described above.
	delta.sd	the standard error estimate of $\hat{\Delta}(t)$ ; if std = TRUE or conf.int = TRUE.
	delta.mad	the standard error estimate of $\hat{\Delta}(t)$ using the median absolute deviation; if std = TRUE or conf.int = TRUE.
	delta.t.sd	the standard error estimate of $\hat{\Delta}_T(t, t_0)$ ; if std = TRUE or conf.int = TRUE.
	delta.t.mad	the standard error estimate of $\hat{\Delta}_T(t,t_0)$ using the median absolute deviation; if std = TRUE or conf.int = TRUE.
	R.t.sd	the standard error estimate of $\hat{R}_T(t,t_0)$ ; if std = TRUE or conf.int = TRUE.
	R.t.mad	the standard error estimate of $\hat{R}_T(t,t_0)$ using the median absolute deviation; if std = TRUE or conf.int = TRUE.
	conf.int.delta	a vector of size 2; the 95% confidence interval for $\hat{\Delta}(t)$ based on sample quantiles of the perturbed values; if conf.int = TRUE.
conf.int.delta.t		
		a vector of size 2; the 95% confidence interval for $\hat{\Delta}_T(t,t_0)$ based on sample quantiles of the perturbed values; if conf.int = TRUE.
	conf.int.R.t	a vector of size 2; the 95% confidence interval for $\hat{R}_T(t,t_0)$ based on sample quantiles of the perturbed values; if conf.int = TRUE.

### Author(s)

Layla Parast

### References

Parast L, Tian L, and Cai T (2020). Assessing the Value of a Censored Surrogate Outcome. Lifetime Data Analysis, 26(2):245-265.

# **Examples**

```
data(ExampleData)
names(ExampleData)

R.t.estimate(xone = ExampleData$x1, xzero = ExampleData$x0, deltaone =ExampleData$delta1,
deltazero = ExampleData$delta0, t = 5, landmark=2)

R.t.estimate(xone = ExampleData$x1, xzero = ExampleData$x0, deltaone = ExampleData$delta1,
deltazero = ExampleData$delta0, t = 5, landmark=2, std = TRUE, conf.int = TRUE)
```

24 VTM

resam	Resampling for standard error estimation

Description

### •

Resamples data to obtain standard error estimates

# Usage

```
resam(vv, t, t.0, tt, data, data1, data2, indexindex)
```

# **Arguments**

VV	random exponential weight
t	number, the time of interest
t.0	landmark time of interest, $t_0$
tt	set of time points between t.0 and t
data	full dataset
data1	a random half from data
-1 - 4 - 2	4

data2 the remaining random half from data indexindex the indices of data contained within data1

### Value

A vector with the first value being the resampled estimate of the PTE, the second value being the resampled estimate of the optimal g2, and the remaining values being the resampled estimate of the optimal g1(s)

# Author(s)

Xuan Wang

VTM	Repeats a row	
-----	---------------	--

# Description

Helper function; this function creates a matrix that repeats vc, dm times where each row is equal to the vc vector.

# Usage

```
VTM(vc, dm)
```

# Arguments

VC	the vector to repeat.
dm	number of rows.

WEIGHT 25

### Value

a matrix that repeats vc, dm times where each row is equal to the vc vector

|--|

# **Description**

Creates a matrix of weights and estimates to be used in estimation of the PTE within R.opt.event

# Usage

```
WEIGHT(xob, deltaob, aob, n, t.0,t)
```

# Arguments

xob	numeric vector, the observed event time: $X = min(T, C)$ where T is the time of the primary outcome, C is the censoring time
deltaob	numeric vector of $0/1$ , the censoring indicator: $D = I(T < C)$ where T is the time of the primary outcome, C is the censoring time
aob	numeric vector of 0/1, indicating treatment group
n	sample size
t.0	landmark time of interest, $t_0$
t	time of interest for treatment effect.

### Value

Returns a matrix of weights and estimates to be used in estimation of the PTE within R.opt.event

### Author(s)

Xuan Wang

WEIGHT.p	Weight function for resampling

# Description

Creates a matrix of weights and estimates to be used in estimation of the standard error of the PTE within resam

# Usage

```
WEIGHT.p(xob, deltaob, aob, n, v, t.0, t)
```

26 WEIGHT.p

### **Arguments**

xob numeric vector, the observed event time: X = min(T, C) where T is the time of

the primary outcome, C is the censoring time

deltaob numeric vector of 0/1, the censoring indicator: D = I(T < C) where T is the time

of the primary outcome, C is the censoring time

aob numeric vector of 0/1, indicating treatment group

n sample size

v random exponential weight t.0 landmark time of interest,  $t_0$ 

t time of interest for treatment effect.

# Value

Returns a matrix of weights and estimates to be used in estimation of the PTE within resam

### Author(s)

Xuan Wang

# **Index**

DMCT	* survival
* RMST	
delta.estimate, 3	censor.weight, 2
delta.q.event.RMST, 6	delta.estimate, 3
delta.q.event.semi.RMST,8	delta.q.event.RMST, 6
delta.t.RMST, 9	delta.q.event.semi.RMST, 8
R.q.event, 18	delta.t.RMST,9
R.t.estimate, 21	IV.event, 12
* arith	pred.smooth.surv, 15
cumsum2, 3	R.q.event, 18
helper.si,11	R.t.estimate, 21
new.q, 15	
* array	censor.weight, 2
VTM, 24	cumsum2, 3
* datasets	delta.estimate, 3
ExampleData, 10	delta.estimate, 5 delta.estimate.RMST, 5
* internal	delta.q.event.RMST, 6
censor.weight, 2	delta.q.event.semi.RMST, 8
cumsum2, 3	delta.t.RMST, 9
delta.estimate.RMST, 5	derta.t.Rh31, 9
helper.si,11	ExampleData, 10
Kern.FUN, 14	
new.q, 15	helper.si,11
pred.smooth.surv, 15	
resam, 24	IV.event, 12
VTM, 24	
WEIGHT, 25	Kern.FUN, 14
WEIGHT.p, 25	
* nonparametric	new.q, 15
censor.weight, 2	pred.smooth.surv, 15
delta.estimate, 3	pred. silloctif. sur v, 13
delta.e.sermate, 5 delta.q.event.RMST, 6	R.opt.event, 16
delta.t.RMST, 9	R.g.event, 18
IV. event, 12	R.t.estimate, 21
Kern. FUN, 14	resam, 24
pred.smooth.surv, 15	,
R.q.event, 18	VTM, 24
R.t.estimate, 21	
* robust	WEIGHT, 25
	WEIGHT.p, 25
Kern.FUN, 14	
pred.smooth.surv, 15 * smooth	
Kern.FUN, 14	
pred.smooth.surv, 15	