Package 'SurrogateSeq'

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Type Package

Title Group Sequential Testing of a Treatment Effect Using a Surrogate Marker

Version 1.0

Description
Provides functions to implement group sequential procedures that allow for early stopping to declare efficacy using a surrogate marker and the possibility of futility stopping. More details are available in: Parast, L. and Bartroff, J (2024) <doi:10.1093/biomtc/ujae108>. A tutorial for this package can be found at <https://laylaparast.com/home/SurrogateSeq.html>.

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Imports stats, MASS, ggplot2

NeedsCompilation no

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Contents

`delta.e.estimate` *Tests for a treatment effect on the primary outcome using surrogate marker information*

Description

Nonparametric test for a treatment effect on the primary outcome using surrogate marker information. This test borrows information from a prior study (Study A) about the relationship between the surrogate and the primary outcome to test for a treatment effect in the current study (Study B).

Usage

```
delta.e.estimate(sone = NULL, szero = NULL, szerop, yzerop, extrapolate = TRUE,
mat = NULL, n1 = NULL, n0 = NULL)
```

Arguments

`sone`	surrogate marker in the treated group in Study B
`szero`	surrogate marker in the control group in Study B
`szerop`	surrogate marker in the control group in Study A
`yzerop`	primary outcome in the control group in Study A
`extrapolate`	TRUE or FALSE; extrapolate for values outside of the support in Study A
`mat`	for Study B, the user can either provide sone and szero or can provide a vector, mat, where the first n1 values are the surrogate marker in the treated group in the Study B, and the remaining values are the surrogate marker in the control group in Study B
`n1`	sample size of treated group in Study B; only needed if mat is provided instead of sone and szero
`n0`	sample size of control group in Study B; only needed if mat is provided instead of sone and szero

Value

`delta.e`	estimated treatment effect using surrogate marker information
`sd.closed`	estimated standard error of treatment effect estimate
`delta.e.z`	test statistic
`delta.e.p`	p-value of test statistic

Author(s)

Layla Parast

References

Parast, Cai, and Tian (2023). Using a Surrogate with Heterogeneous Utility to Test for a Treatment Effect. Statistics in Medicine, 42(1): 68-88.

Parast and Bartroff (2024). Group sequential testing of a treatment effect using a surrogate marker. Biometrics, 80(4), ujae108.

Examples

```
data(example.data)
delta.e.estimate(sone = example.data$s1, szero = example.data$s0, szerop = example.data$s0.p,
yzerop = example.data$y0.p)

data(StudyA.aids)
data(StudyB.aids)
s1.studyb = StudyB.aids$s1
s0.studyb = StudyB.aids$s0
s0.studya = StudyA.aids$s0

#24 weeks

delta.e.vec = delta.e.estimate(sone=s1.studyb$CD4_24weeks[!is.na(s1.studyb$CD4_24weeks)],
szero=s0.studyb$CD4_24weeks[!is.na(s0.studyb$CD4_24weeks)], szerop = s0.studya$CD4_24weeks,
yzerop = StudyA.aids$y0, extrapolate = TRUE)
delta.e.vec
```

`example.data` *Example data*

Description

Example data

Usage

```
data("example.data")
```

Format

A list with 9 elements:

`w0.p` the baseline covariate in the control group in the prior study (Study A)

`s0.p` the surrogate marker in the control group in the prior study (Study A

`y0.p` the primary outcome in the control group in the prior study (Study A

`w1` a baseline covariate in the treatment group in the current study (Study B)

`w0` a baseline covariate in the control group in the current study (Study B)

`s1` the surrogate marker in the treatment group in the current study (Study B)

`s0` the surrogate marker in the control group in the current study (Study B)

`y1` the primary outcome in the treatment group in the current study (Study B)

`y0` the primary outcome in the control group in the current study (Study B)

Examples

```
data(example.data)
names(example.data)
```

`gs.boundaries` *Computes group sequential boundaries*

Description

Computes group sequential (and naive) boundaries for the nonparametric test for a treatment effect on the primary outcome using surrogate marker information. The boundaries and test statistic borrow information from a prior study (Study A) about the relationship between the surrogate and the primary outcome to test for a treatment effect in the current study (Study B).

Usage

```
gs.boundaries(szerop, sonep, yzerop, nzero, none, n.stg, B.norm = 1e+06,
alpha = 0.05, pp = 0.4, inf.fraction = (1:n.stg)/n.stg, plot=FALSE)
```

Arguments

`szerop`	surrogate marker in the control group in Study A
`sonep`	surrogate marker in the treated group in Study A
`yzerop`	primary outcome in the control group in Study A
`nzero`	sample size of control group in Study B
`none`	sample size of treated group in Study B
`n.stg`	maximum number of analyses
`B.norm`	number of multivariate normal vectors to use in simulation for boundaries; default is 1e+06
`alpha`	desired rejection probability of the test; default is 0.05
`pp`	power parameter for Wang-Tsiatis boundaries; default is 0.4
`inf.fraction`	information fraction vector of the same length as n.stg which reflects the fraction of information at each analysis, should be positive, non-decreasing, and the last entry should be 1; default is (1:n.stg)/n.stg, user may want to specify a different vector for unequal time points
`plot`	TRUE or FALSE if a plot of the boundaries is desired; default is FALSE

Value

Returns a list of boundaries:

`Naive`	Naive boundaries
`Bonf`	Bonferroni boundaries
`Pocock`	Pocock boundaries
`OBrien_Fleming`	O'Brien-Fleming boundaries
`Wang_Tsiatis`	Wang-Tsiatis boundaries

Author(s)

Layla Parast and Jay Bartroff

References

Parast and Bartroff (2024). Group sequential testing of a treatment effect using a surrogate marker. Biometrics, 80(4), ujae108.

Examples

```
data(example.data)
data(StudyA.aids)
data(StudyB.aids)
s0.studya = StudyA.aids$s0
s1.studya = StudyA.aids$s1


bound = gs.boundaries(szerop = s0.studya, sonep = s1.studya, yzerop=StudyA.aids$y0,
nzero = nrow(StudyB.aids$s0),none = nrow(StudyB.aids$s1), n.stg=4, B.norm=1e6,
alpha=0.05)

bound
```

---

gs.boundaries.fut *Computes group sequential boundaries with futility stopping*

Description

Computes group sequential (and naive) boundaries for the nonparametric test for a treatment effect on the primary outcome using surrogate marker information. The boundaries and test statistic borrow information from a prior study (Study A) about the relationship between the surrogate and the primary outcome to test for a treatment effect in the current study (Study B). The group sequential boundaries allow for futility stopping (bounds given).

Usage

```
gs.boundaries.fut(szerop, sonep, yzerop, nzero, none, n.stg, B.norm = 1e+06,
alpha = 0.05, pp = 0.4, inf.fraction = (1:n.stg)/n.stg, j.star=1,
alpha0=(j.star/n.stg)*alpha,
plot = FALSE)
```

Arguments

szerop	surrogate marker in the control group in Study A
sonep	surrogate marker in the treated group in Study A
yzerop	primary outcome in the control group in Study A
nzero	sample size of control group in Study B
none	sample size of treated group in Study B
n.stg	maximum number of analyses
B.norm	number of multivariate normal vectors to use in simulation for boundaries; default is 1e+06
alpha	desired rejection probability of the test; default is 0.05
pp	power parameter for Wang-Tsiatis boundaries; default is 0.4
inf.fraction	information fraction vector of the same length as n.stg which reflects the fraction of information at each analysis, should be positive, non-decreasing, and the last entry should be 1; default is (1:n.stg)/n.stg, user may want to specify a different vector for unequal time points
j.star	earliest stage at which futility stopping is allowed. Should be <= n.stg-1 (there is already "futility stopping" at the n.stg-th stage anyway). Default is 1.
alpha0	the part of alpha that c1 is chosen to spend in first j.star stages; default is (j.star/n.stg)*alpha
plot	TRUE or FALSE if a plot of the boundaries is desired; default is FALSE

Value

Returns a list of boundaries:

Naive	Naive boundaries
Bonf	Bonferroni boundaries
Pocock.futility	Pocock futility boundaries
Pocock.nullrejection	Pocock null rejection boundaries
OBrien_Fleming.futility	O'Brien-Fleming futility boundaries
OBrien_Fleming.nullrejection	O'Brien-Fleming null rejection boundaries
Wang_Tsiatis.futility	Wang-Tsiatis futility boundaries
Wang_Tsiatis.nullrejection	Wang-Tsiatis null rejection boundaries

Author(s)

Layla Parast and Jay Bartroff

References

Parast and Bartroff (2024). Group sequential testing of a treatment effect using a surrogate marker. Biometrics, 80(4), ujae108.

Examples

```
data(example.data)
data(StudyA.aids)
data(StudyB.aids)
s0.studya = StudyA.aids$s0
s1.studya = StudyA.aids$s1


bound = gs.boundaries.fut(szerop = s0.studya, sonep = s1.studya, yzerop=StudyA.aids$y0,
nzero = nrow(StudyB.aids$s0),none = nrow(StudyB.aids$s1), n.stg=4, B.norm=1e6,
alpha=0.05)

bound
```

StudyA.aids *ACTG 320 clinical trial data*

Description

Primary outcome and surrogate marker measurements over time from the ACTG 320 clinical trial data

Usage

```
data("StudyA.aids")
```

Format

A list with 4 elements:

- `y1` the primary outcome in the treatment group in Study A; the primary outcome is defined as -1 times (log of RNA at 40 weeks - log of RNA at baseline) because a DECREASE in RNA is better
- `y0` the primary outcome in the control group in Study A
- `s1` a dataframe of the surrogate markers at different time points in the treatment group in Study A; the surrogate marker is change in CD4 cell count from baseline to 4 weeks (CD4_4weeks), 8 weeks (CD4_8weeks), 24 weeks (CD4_24weeks), and 40 weeks (CD4_40weeks). Note that higher values indicate increasing CD4 cell count which is "better".
- `s0` a dataframe of the surrogate markers at different time points in the control group in Study A

Examples

```
data(StudyA.aids)
```

`StudyB.aids` *ACTG 193A clinical trial data*

Description

Surrogate marker measurements over time from the ACTG 193A clinical trial data. Note that the time points do not exactly match up to ACTG 320. In the paper, we use Study A surrogate data at 24 weeks to construct the conditional mean function applied to Study B at 16 weeks. Also note that some subjects are missing values of the surrogate at one or more time points. The naive estimate of the treatment effect using the surrogates uses all non-missing data available at each time point.

Usage

```
data("StudyB.aids")
```

Format

A list with 2 elements:

`s1` a dataframe of the surrogate markers at different time points in the treatment group in Study B; the surrogate marker is change in CD4 cell count from baseline to 8 weeks (CD4_8weeks), 16 weeks (CD4_16weeks), 24 weeks (CD4_24weeks), and 40 weeks (CD4_40weeks). Note that higher values indicate increasing CD4 cell count which is "better".

`s0` a dataframe of the surrogate markers at different time points in the control group in Study B

Examples

```
data(StudyB.aids)
```

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