Package 'GSED'

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Type Package

Title Group Sequential Enrichment Design

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Description
Provides function to apply ``Group sequential enrichment design incorporating subgroup selection" (GSED) method proposed by Magnusson and Turnbull (2013) <doi:10.1002/sim.5738>.

License GPL-3

Depends R (>= 3.1.2), memoise (>= 1.0.0), rootSolve (>= 1.6.6), survival (>= 2.37-7), R.utils (>= 2.3.0)

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Contents

GSED-package *Group Sequential Enrichment Design*

Description

Provides function to apply "Group sequential enrichment design incorporating subgroup selection" (GSED) method proposed by Magnusson and Turnbull (2013) <doi:10.1002/sim.5738>.

Details

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Author(s)

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References

Baldur P. Magnusson and Bruce W. Turnbull. Group sequential enrichment design incorporating subgroup selection. Statistics in Medicine, 2013. <doi:10.1002/sim.5738>

boundaries_sim *Lower and upper boundaries for GSED*

Description

`boundaries_sim` is used to estimate lower and upper boundaries for GSED based on simulations of trials.

Usage

```
boundaries_sim(K_stages, N_subsets, f, ratio_Delta_star_d1, ordering,
increasing_theta=FALSE, seed=42, n_trials, alpha_spending,
one_minus_alpha_spending, updateProgress=NULL)
```

Arguments

K_stages	Integer indicating the number of stages in the design.
N_subsets	Integer representing the number of possible subgroups.
f	Vector containing the prevalence rates of each subgroup. Must be of length N_subsets.
ratio_Delta_star_d1	Vector containing the ratio between the (observed Fisher) information increments at each stage >1 with the (observed Fisher) information at stage 1. Must be of length K_stages-1.
ordering	Boolean indicating if the subgroups (theta) are ordered.
increasing_theta	Boolean indicating if greater values of theta parameters represent better treatment effects. The default value is set at FALSE.
seed	Interger representing the seed. The default value is set at 42.
n_trials	Integer indicating the number of trials to simulate.
alpha_spending	Vector containing the values of the alpha-spending function at each time of the analysis (including 0 at time 0 and alpha at time 1). Must be of length K_stages+1.
one_minus_alpha_spending	Vector containing the values of the 1-alpha-spending function at each time of the analysis (including 0 at time 0 and 1-alpha at time 1). Must be of length K_stages+1.
updateProgress	(for Rshiny application)

Value

A list is returned, consisting of two vectors containing the lower and upper boundaries:

l	Vector of lower boundaries at each stage.
u	Vector of upper boundaries at each stage.

Author(s)

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References

Baldur P. Magnusson and Bruce W. Turnbull. Group sequential enrichment design incorporating subgroup selection. Statistics in Medicine, 2013. <doi:10.1002/sim.5738>

Examples

```
#For testing purpose only, larger number of simulations required (see in comments below)
boundaries_sim(K_stages=2, N_subsets=3, f=c(0.6,0.2,0.2), ratio_Delta_star_d1=c(1),
ordering=FALSE, seed=42, n_trials=3, alpha_spending=c(0,0.0125,0.025),
one_minus_alpha_spending=c(0,0.4875,0.975))
```

```
#boundaries_sim(K_stages=2, N_subsets=3, f=c(0.6,0.2,0.2), ratio_Delta_star_d1=c(1),
#ordering=FALSE, seed=42, n_trials=10000000, alpha_spending=c(0,0.0125,0.025),
#one_minus_alpha_spending=c(0,0.4875,0.975))
```

`magnusson_turnbull` *Application of GSED on data*

Description

`magnusson_turnbull` is used apply GSED design, selection or evaluation at each stage, on data.

Usage

```
magnusson_turnbull(stage_cur, keep=NA, N_subsets, Y, I, l, u, ordering,
increasing_theta=FALSE)
```

Arguments

`stage_cur`	Integer representing the current stage. 0 represents selection at stage 1, 1 represents evaluation at stage 1, while k (>1) represents evaluation at stage k.
`keep`	Vector of indices of selected subgroups if selection at stage 1 is already performed. Values must be between 1 and `N_subsets`. By default filled with NA if the function is run for selection step.
`N_subsets`	Integer representing the number of possible subgroups.
`Y`	Efficient score test statistics. For `stage_cur`>0 (evaluation at stage 1 or k (k>1),), value representing the efficient score test statistic for all (pooled) selected subgroup. For `stage_cur`=0 (selection at stage 1), vector representing the efficient score test statistic for each subgroup.
`I`	Observed Fisher information. For `stage_cur`>0 (evaluation at stage 1 or k (k>1),), value representing the observed Fisher information for all (pooled) selected subgroup. For `stage_cur`=0 (selection at stage 1), vector representing the observed Fisher information for each subgroup.
`l`	Vector containing the lower boundaries for stagewise decisions.
`u`	Vector containing the upper boundaries for stagewise decisions.
`ordering`	Boolean indicating if the subgroups (theta) are ordered.
`increasing_theta`	Boolean indicating if greater values of theta parameters represent better treatment effects. The default value is set at FALSE.

Value

An list is returned, consisting of:

`Rejection`	Interger with value 1 if the decision is to reject the null hypothesis, 0 otherwise.
`Acceptation`	Interger with value 1 if the decision is to accept the null hypothesis, 0 otherwise.
`Keep`	Vector of indices of selected subgroups (between 1 and `N_subsets`).

Author(s)

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References

Baldur P. Magnusson and Bruce W. Turnbull. Group sequential enrichment design incorporating subgroup selection. Statistics in Medicine, 2013. <doi:10.1002/sim.5738>

Examples

```
magnusson_turnbull(stage_cur=0, keep=NA, N_subsets=3, Y=c(-10.71,12.84,19.06),
I=c(480,144,176), l=c(0.7962,2.5204), u=c(2.7625,2.5204), ordering=FALSE)

magnusson_turnbull(stage_cur=2, keep=c(2,3), N_subsets=3, Y=135.57,
I=1120, l=c(0.7962,2.5204), u=c(2.7625,2.5204), ordering=FALSE)
```

---

max_FI *Maximum Fisher information*

Description

max_FI is used to estimate maximum Fisher information based on two power criteria. - The first criterion consider the maxmimum Fisher information such that there is a pre-defined power to declare efficacy in the entire population for a given vector of parameters representing treatment effetcs in each subgroup. - The second criterion consider the maxmimum Fisher information such that there is a pre-defined power to declare efficacy in at least one subgroup for a given vector of parameters representing treatment effetcs in each subgroup.

Usage

```
max_FI(K_stages, N_subsets, f, ratio_Delta_star_d1, l, u, type_outcome, param_theta,
pow, ordering, increasing_theta=FALSE, seed=42, n_trials, rule, updateProgress=NULL)
```

Arguments

K_stages	Integer indicating the number of stages in the design.
N_subsets	Integer representing the number of possible subgroups.
f	Vector containing the prevalence rates of each subgroup. Must be of length N_subsets.
ratio_Delta_star_d1	Vector containing the ratio between the (observed Fisher) information increments at each stage >1 with the (observed Fisher) information at stage 1. Must be of length K_stages-1.
l	Vector containing the lower boundaries for stagewise decisions. Must be of length K_stages.

u	Vector containing the upper boundaries for stagewise decisions. Must be of length K_stages.
type_outcome	A string containing the type of outcome, either "survival", "binary", or "continuous".
param_theta	Vector of parameters representing treatment effects in each subgroup. Must satisfy the properties detailed in Magnusson and Turnbull's article (reparametrization can be needed).
pow	Value representing the desired power.
ordering	Boolean indicating if the subgroups (theta) are ordered.
increasing_theta	Boolean indicating if greater values of theta parameters represent better treatment effects. The default value is set at FALSE.
seed	Interger representing the seed. The default value is set at 42.
n_trials	Integer indicating the number of trials to simulate.
rule	Integer with value either 1 or 2 for power criteria detailed in description section (1 for entire population, 2 for at least one subgroup).
updateProgress	(for Rshiny application)

Value

A value representing the maximum Fisher information is returned.

Author(s)

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References

Baldur P. Magnusson and Bruce W. Turnbull. Group sequential enrichment design incorporating subgroup selection. Statistics in Medicine, 2013. <doi:10.1002/sim.5738>

Examples

```
theta_assumption = list(matrix(c(0.4,0.6,0.4,0.6,0.4,0.6),nrow=2,ncol=3))

#For testing purpose only, larger number of simulations required (see in comments below)
max_FI(K_stages=2, N_subsets=3, f=c(0.6,0.2,0.2), ratio_Delta_star_d1=c(1), l=c(0.7962, 2.5204),
u=c(2.7625, 2.5204), type_outcome="binary", param_theta=theta_assumption, pow=0.9,
ordering=FALSE, increasing_theta=FALSE, seed=140691, n_trials=3, rule=1)

#max_FI(K_stages=2, N_subsets=3, f=c(0.6,0.2,0.2), ratio_Delta_star_d1=c(1), l=c(0.7962, 2.5204),
#u=c(2.7625, 2.5204), type_outcome="binary", param_theta=theta_assumption, pow=0.9,
#ordering=FALSE, increasing_theta=FALSE, seed=140691, n_trials=10000000, rule=1)

#max_FI(K_stages=2, N_subsets=3, f=c(0.6,0.2,0.2), ratio_Delta_star_d1=c(1), l=c(0.7962, 2.5204),
#u=c(2.7625, 2.5204), type_outcome="binary", param_theta=theta_assumption, pow=0.9,
#ordering=FALSE, increasing_theta=FALSE, seed=140691, n_trials=10000000, rule=2)
```

sim_magnusson_turnbull *Simulations of trials with GSED*

Description

sim_magnusson_turnbull is used to simulate clincal trials with GSED for different type of outcome (survival, binary, continuous).

Usage

```
sim_magnusson_turnbull(K_stages, N_subsets, f, l, u, ratio_Delta_star_d1, type_outcome,
param_outcome=NA, n_max=NA, incl_rate=NA, mean_cur_c=NA, HR=NA, nb_required=NA,
nmax_wait=+Inf, ordering, increasing_theta=FALSE, nsim=1000, seed=42,
nsim_tot=NA, num_sc=1, updateProgress=NULL)
```

Arguments

K_stages	Integer indicating the number of stages in the design.
N_subsets	Integer representing the number of possible subgroups.
f	Vector containing the prevalence rates of each subgroup. Must be of length N_subsets.
l	Vector containing the lower boundaries for stagewise decisions. Must be of length K_stages.
u	Vector containing the upper boundaries for stagewise decisions. Must be of length K_stages.
ratio_Delta_star_d1	Vector containing the ratio between the (observed Fisher) information increments at each stage >1 with the (observed Fisher) information at stage 1. Must be of length K_stages-1.
type_outcome	A string containing the type of outcome, either "survival", "binary", or "continuous".
param_outcome	Must be supplied only if type_outcome is equal to "binary" or "continuous". The parameters supplied for the binary outcome must be a list of one element containing a matrix of size 2xN_subsets. The parameters supplied for the continuous outcome must be a list of two elements containing two matrices of size 2xN_subsets. The matrices should contain probabilities of response, or the means and variances respectively, for in row control or treatment, and in column the subgroup number.
n_max	Integer representing the maximum number of patients to enroll in a trial. Must be supplied only if type_outcome is equal to "binary" or "continuous", will be ignored otherwise.
incl_rate	Number representing the inclusion rate. Must be supplied only if type_outcome is equal to "survival", will be ignored otherwise.

mean_cur_c	Number representing the median survival for the control group. Must be supplied only if type_outcome is equal to "survival", will be ignored otherwise.
HR	Vector containing the expected hazard ratios for each subgroup. Must be of length N_subsets. Must be supplied only if type_outcome is equal to "survival", will be ignored otherwise.
nb_required	Integer indicating the maximum number of events required. Must be supplied only if type_outcome is equal to "survival", will be ignored otherwise.
nmax_wait	For type_outcome equal to "survival" only, will be ignored otherwise. If specified, maximum number of patients to include in the trial, the inclusions will be stopped when this number is achieved and trial will pursue until the number of events required is achieved. Must be superior to nb_required. Default value is +Inf.
ordering	Boolean indicating if the subgroups (theta) are ordered.
increasing_theta	Boolean indicating if greater values of theta parameters represent better treatment effects. The default value is set at FALSE.
nsim	Integer indicating the number of trials to simulate. The default value is set at 1000.
seed	Interger representing the seed. The default value is set at 42.
nsim_tot	(for Rshiny application)
num_sc	(for Rshiny application)
updateProgress	(for Rshiny application)

Value

A list is returned composed of:

prob_rejec	Percentage of simulated trials (estimated probability) to reject any subgroup.
prob_accep	Percentage of simulated trials (estimated probability) to accept the null hypothesis, that is there is no treatment effect in any subgroup.
list_keep	A list of the different subgroups that were selected across all simulated trials.
pct_keep	Percentage of selection of each subgroup of list_keep across all simulated trials.
rejec_stage	Vector of percentage of simulated trials (estimated probability) to reject any subgroup at each stage.
accep_stage	Vector of percentage of simulated trials (estimated probability) to accept the null hypothesis (that is there is no treatment effect in any subgroup) at each stage.
mean_pat	Mean number of patients included across all simulated trials.
mean_duration	If type_outcome is equal to "survival", the trial mean duration across all simulated trials is also returned.

Author(s)

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References

Baldur P. Magnusson and Bruce W. Turnbull. Group sequential enrichment design incorporating subgroup selection. Statistics in Medicine, 2013. <doi:10.1002/sim.5738>

Examples

```
#For testing purpose only, larger number of simulations required (see in comments below)
sim_magnusson_turnbull(K_stages=2, N_subsets=3, f=c(0.6,0.2,0.2), l=c(0.7962, 2.5204),
u=c(2.7625, 2.5204), ratio_Delta_star_d1=c(1), type_outcome="binary", param_outcome=
list(matrix(c(0.4,0.4,0.4,0.6,0.6,0.6),nrow=2,ncol=3,byrow=TRUE)), n_max=1496,
ordering=FALSE, nsim=2, seed=42)

#sim_magnusson_turnbull(K_stages=2, N_subsets=3, f=c(0.6,0.2,0.2), l=c(0.7962, 2.5204),
#u=c(2.7625, 2.5204), ratio_Delta_star_d1=c(1), type_outcome="binary", param_outcome=
#list(matrix(c(0.4,0.4,0.4,0.6,0.6,0.6),nrow=2,ncol=3,byrow=TRUE)), n_max=1496,
#ordering=FALSE, nsim=1000, seed=42)

#sim_magnusson_turnbull(K_stages=2, N_subsets=3, f=c(0.6,0.2,0.2), l=c(0.7962, 2.5204),
#u=c(2.7625, 2.5204), ratio_Delta_star_d1=c(1), type_outcome="binary", param_outcome=
#list(matrix(c(0.5,0.5,0.5,0.5,0.5,0.5),nrow=2,ncol=3,byrow=TRUE)), n_max=1496,
#ordering=FALSE, nsim=1000, seed=42)

#sim_magnusson_turnbull(K_stages=2, N_subsets=4, f=c(0.25,0.25,0.25,0.25), l=c(0.98,2.35),
#u=c(2.59,2.35), ratio_Delta_star_d1=c(1), type_outcome="survival", incl_rate=1/28,
#mean_cur_c=7/log(2), HR=c(0.8,0.8,0.8,0.8), nb_required=1030, ordering=TRUE,
#increasing_theta=FALSE, nsim=1000, seed=42)
```

---

stage_1_evaluation *Stage 1-evaluation step of GSED*

Description

`stage_1_evaluation` is used to evaluate the efficacy of the subgroup selected at the end of the first stage of GSED.

Usage

```
stage_1_evaluation(keep, Z_1j, f, u)
```

Arguments

`keep`	Vector containing the indices of the subgroups selected at stage 1.
`Z_1j`	Vector containing the Z-statistics (standard normal under H0) for each subgroup. Must be of length `N_subsets`.
`f`	Vector containing the prevalence rates of each subgroup.
`u`	Vector containing the upper boundaries for stagewise decisions.

Value

A list is returned, consisting of:

stage	Integer containing the current step. Value is 1 by default, or -1 if the trial stops earlier for efficacy after this evaluation step.
S	Vector containing the indices of the subgroups selected at stage 1 (=keep).

Author(s)

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References

Baldur P. Magnusson and Bruce W. Turnbull. Group sequential enrichment design incorporating subgroup selection. Statistics in Medicine, 2013. <doi:10.1002/sim.5738>

Examples

```
stage_1_evaluation(keep=c(2,3), Z_1j=c(-0.49,1.07,1.44), f=c(0.6,0.2,0.2), u=c(2.7625,2.5204))
```

---

stage_1_selection *Stage 1-selection step of GSED*

Description

stage_1_selection is used to determine the subgroup selected at the end of the first stage of GSED.

Usage

```
stage_1_selection(N_subsets, Z_1j, l, ordering, increasing_theta=FALSE)
```

Arguments

N_subsets	Integer representing the number of possible subgroups.
Z_1j	Vector containing the Z-statistics (standard normal under H0) for each subgroup. Must be of length N_subsets.
l	Vector containing the lower boundaries for stagewise decisions.
ordering	Boolean indicating if the subgroups (theta) are ordered.
increasing_theta	Boolean indicating if greater values of theta parameters represent better treatment effects. The default value is set at FALSE.

Value

A vector containing the indices of the subgroups selected is returned.

Author(s)

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References

Baldur P. Magnusson and Bruce W. Turnbull. Group sequential enrichment design incorporating subgroup selection. Statistics in Medicine, 2013. <doi:10.1002/sim.5738>

Examples

```
stage_1_selection(N_subsets=3, Z_1j=c(-0.49,1.07,1.44), l=c(0.7962,2.5204), ordering=FALSE)
```

---

test_BC *For internal use*

Description

For internal use

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