Package 'dfcomb'

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Title Phase I/II Adaptive Dose-Finding Design for Combination Studies

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Description Phase I/II adaptive dose-finding design for combination studies where toxicity rates are supposed to increase with both agents.

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LinkingTo BH (>= 1.55), Rcpp, RcppProgress (>= 0.2.1)

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dfcomb-package	*Phase I/II Adaptive Dose-Finding Design for Combination Studies*

Description

Phase I/II adaptive dose-finding design for combination studies where toxicity rates are supposed to increase with both agents.

Details

The DESCRIPTION file:

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Type:	Package
Title:	Phase I/II Adaptive Dose-Finding Design for Combination Studies
Version:	3.0-0
Date:	2019-02-25
Author:	Marie-Karelle Riviere and Jacques-Henri Jourdan
Maintainer:	Jacques-Henri Jourdan <jacques-henri.jourdan@normalesup.org>
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Author(s)

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References

Riviere MK, Yuan Y, Dubois F, Zohar S (2014). A Bayesian dose-finding design for drug combination clinical trials based on the logistic model. Pharm Stat, 13, 4:247-57.

CombIncrease_next   *Combination determination with logistic model*

Description

CombIncrease_next is used to determine the next or recommended combination in a phase I combination clinical trial using the design proposed by Riviere et al. entitled "A Bayesian dose-finding design for drug combination clinical trials based on the logistic model".

Usage

```
CombIncrease_next(ndose_a1, ndose_a2, target, target_min, target_max,
  prior_tox_a1, prior_tox_a2, cohort, final, pat_incl, dose_adm1,
  dose_adm2, tite=FALSE, toxicity, time_full=0, time_tox=0,
  time_follow=0, c_e=0.85, c_d=0.45, c_stop=0.95, c_t=0.5, c_over=0.25,
  cmin_overunder=2, cmin_mtd=3, cmin_recom=1, early_stop=1, alloc_rule=1,
  nburn=2000, niter=5000)
```

Arguments

ndose_a1	Number of dose levels for agent 1.
ndose_a2	Number of dose levels for agent 2.
target	Toxicity (probability) target.
target_min	Minimum of the targeted toxicity interval.
target_max	Maximum of the targeted toxicity interval.
prior_tox_a1	A vector of initial guesses of toxicity probabilities associated with the doses of agent 1. Must be of length ndose_a1.
prior_tox_a2	A vector of initial guesses of toxicity probabilities associated with the doses of agent 2. Must be of length ndose_a2.
cohort	Cohort size.
final	A boolean with value TRUE if the trial is finished and the recommended combination for further phases should be given, or FALSE (default value) if the combination determination is performed for the next cohort of patients.
pat_incl	Current number of patients included.
dose_adm1	A vector indicating the dose levels of agents 1 administered to each patient included in the trial. Must be of length pat_incl.
dose_adm2	A vector indicating the dose levels of agents 2 administered to each patient included in the trial. Must be of length pat_incl.
tite	A boolean indicating if the toxicity is considered as a time-to-event outcome (TRUE), or as a binary outcome (default value FALSE).
toxicity	A vector of observed toxicities (DLTs) for each patient included in the trial. Must be of length pat_incl. This argument is used/required only if tite=FALSE.
time_full	Full follow-up time window. This argument is used only if tite=TRUE.

time_tox	A vector of times-to-toxicity for each patient included in the trial. If no toxicity was observed for a patient, must be filled with +Inf. Must be of length pat_incl. This argument is used/required only if tite=TRUE.
time_follow	A vector of follow-up times for each patient included in the trial. Must be of length pat_incl. This argument is used/required only if tite=TRUE.
c_e	Probability threshold for dose-escalation. The default value is set at 0.85.
c_d	Probability threshold for dose-deescalation. The default value is set at 0.45.
c_stop	Probability threshold for early trial termination. The default value is set at 0.95.
c_t	Probability threshold for early trial termination for finding the MTD (see details). The default value is set at 0.5.
c_over	Probability threshold to control over-dosing (see details).
cmin_overunder	Minimum number of cohorts to be included at the lowest/highest combination before possible early trial termination for over-toxicity or under-toxicity (see details). The default value is set at 2.
cmin_mtd	Minimum number of cohorts to be included at the recommended combination before possible early trial termination for finding the MTD (see details). The default value is set at 3.
cmin_recom	Minimum number of cohorts to be included at the recommended combination at the end of the trial. The default value is set at 1.
alloc_rule	Interger (1, 2, or 3) indicating which allocation rule is used (see details). The default value is set at 1.
early_stop	Interger (1, 2, or 3) indicating which early stopping rule is used (see details). The default value is set at 1.
nburn	Number of burn-in for HMC. The default value is set at 2000.
niter	Number of iterations for HMC. The default value is set at 5000.

Details

Allocation rule:

- alloc_rule=1 (Riviere et al 2014): If P(toxicity probability at combination (i,j) < target) > c_e: among combinations in the neighborhood (-1, +1), (0, +1), (+1, 0), (+1, -1), choose the combination with a higher estimated toxicity probability than the current combination and with the estimated toxicity probability closest to target. If P(toxicity probability at combination (i,j) > target) > 1-c_d: among neighborhood (-1, +1), (-1, 0), (0, -1), (+1, -1), choose the combination with a lower estimated toxicity probability than the current combination and with the estimated toxicity probability closest to target. Otherwise, remain on the same combination.

- alloc_rule=2: Among combinations already tested and combinations in the neighborhood (-1, 0), (-1, +1), (0, +1), (+1, 0), (+1, -1), (0, -1), (-1, -1) of a combination tested, choose the combination with the highest posterior probability to be in the targeted interval [target_min, target_max] while controling overdosing i.e. P(toxicity probability at combination (i,j) > target_max) < c_over.

- alloc_rule=3: Among combinations in the neighborhood (-1, 0), (-1, +1), (0, +1), (+1, 0), (+1, -1), (0, -1), (-1, -1) of the current combination, choose the combination with the highest posterior probability to be in the targeted interval [target_min, target_max] while controling overdosing i.e. P(toxicity probability at combination (i,j) > target_max) < c_over.

Early stopping for over-dosing: If the current combination is the lowest (1, 1) and at least cmin_overunder cohorts have been included at that combination and P(toxicity probability at combination (i,j) > target) >= c_stop then stop the trial and do not recommend any combination.

Early stopping for under-dosing: If the current combination is the highest and at least cmin_overunder cohorts have been included at that combination and P(toxicity probability at combination (i,j) < target) >= c_stop then stop the trial and do not recommend any combination.

Early stopping for identifying the MTD:

- early_stop=1 (Riviere et al 2014): No stopping rule, include patients until maximum sample size is reached.
- early_stop=2: If the next recommended combination has been tested on at least cmin_mtd cohorts and has a posterior probability to be in the targeted interval [target_min, target_max] that is >= c_t and also control overdosing i.e. P(toxicity probability at current combination > target_max) < c_over then stop the trial and recommend this combination.
- early_stop=3: If at least cmin_mtd cohorts have been included at the next recommended combination then stop the trial and recommend this combination.

Stopping at the maximum sample size: If the maximum sample size is reached and no stopping rule is met, then the recommended combination is the one that was tested on at least cmin_recom cohorts and with the highest posterior probability to be in the targeted interval [target_min, target_max].

Value

An object of class "CombIncrease_next" is returned, consisting of determination of the next combination and estimations. Objects generated by CombIncrease_next contain at least the following components:

n_pat_comb	Number of patients per combination.
n_tox_comb	Number of observed toxicities per combination.
pi	Estimated toxicity probabilities (if the start-up ended).
ptox_inf	Estimated probabilities that the toxicity probability is inferior to target (if the start-up ended).
ptox_inf_targ	Estimated probabilities of underdosing, i.e. to be inferior to target_min (if the start-up ended).
ptox_targ	Estimated probabilities to be in the targeted interval [target_min,target_max] (if the start-up ended).
ptox_sup_targ	Estimated probabilities of overdosing, i.e. to be superior to target_max (if the start-up ended).
(cdose1, cdose2)	
	NEXT RECOMMENDED COMBINATION.
inconc	Boolean indicating if trial must stop for under/over dosing.
early_conc	Boolean indicating if trial can be stopped earlier for finding the MTD.

Author(s)

Jacques-Henri Jourdan and Marie-Karelle Riviere-Jourdan `<eldamjh@gmail.com>`

References

Riviere, M-K., Yuan, Y., Dubois, F., and Zohar, S. (2014). A Bayesian dose-finding design for drug combination clinical trials based on the logistic model. Pharmaceutical Statistics.

See Also

CombIncrease_sim.

Examples

```
prior_a1 = c(0.12, 0.2, 0.3, 0.4, 0.5)
prior_a2 = c(0.2, 0.3, 0.4)
toxicity1 = c(0,0,0,0,0,0,0,0,1,0,1,0,0,0,0,0,0,1)
dose1 = c(1,1,1,2,2,2,3,3,3,3,3,3,3,3,3,4,4,4)
dose2 = c(1,1,1,2,2,2,3,3,3,2,2,2,1,1,1,1,1,1)
t_tox = c(rep(+Inf,8),2.9,+Inf,4.6,+Inf,+Inf,+Inf,+Inf,+Inf,+Inf,5.2)
follow = c(rep(6,15), 4.9, 3.1, 1.3)

next1 = CombIncrease_next(ndose_a1=5, ndose_a2=3, target=0.3,
  target_min=0.2, target_max=0.4, prior_tox_a1=prior_a1,
  prior_tox_a2=prior_a2, cohort=3, final=FALSE, pat_incl=18,
  dose_adm1=dose1, dose_adm2=dose2, toxicity=toxicity1, c_over=1,
  cmin_overunder=3, cmin_recom=1, early_stop=1, alloc_rule=1)
next1

next2 = CombIncrease_next(ndose_a1=5, ndose_a2=3, target=0.3,
  target_min=0.2, target_max=0.4, prior_tox_a1=prior_a1, prior_tox_a2=prior_a2,
  cohort=3, final=FALSE, pat_incl=18, dose_adm1=dose1,
  dose_adm2=dose2, tite=TRUE, time_full=6, time_tox=t_tox,
  time_follow=follow, c_over=1, cmin_overunder=3, cmin_recom=1,
  early_stop=1, alloc_rule=1)
next2
```

CombIncrease_sim   *Combination design Simulator using Logistic model*

Description

CombIncrease_sim is used to generate simulation replicates of phase I clinical trial for combination studies where the toxicity and efficacy of both agents is assumed to increase with the dose using the design proposed by Riviere et al. entitled "A Bayesian dose-finding design for drug combination clinical trials based on the logistic model".

Usage

```
CombIncrease_sim(ndose_a1, ndose_a2, p_tox, target, target_min, target_max,
  prior_tox_a1, prior_tox_a2, n_cohort, cohort, tite=FALSE, time_full=0,
  poisson_rate=0, nsim, c_e=0.85, c_d=0.45, c_stop=0.95, c_t=0.5, c_over=0.25,
  cmin_overunder=2, cmin_mtd=3, cmin_recom=1, startup=1, alloc_rule=1,
  early_stop=1, nburn=2000, niter=5000, seed=14061991)
```

Arguments

ndose_a1	Number of dose levels for agent 1.
ndose_a2	Number of dose levels for agent 2.
p_tox	A matrix of the true toxicity probabilities associated with the combinations. True toxicity probabilities should be entered with agent 1 in row and agent 2 in column, with increasing toxicity probabilities with both row and column numbers (see examples).
target	Toxicity (probability) target.
target_min	Minimum of the targeted toxicity interval.
target_max	Maximum of the targeted toxicity interval.
prior_tox_a1	A vector of initial guesses of toxicity probabilities associated with the doses of agent 1. Must be of length ndose_a1.
prior_tox_a2	A vector of initial guesses of toxicity probabilities associated with the doses of agent 2. Must be of length ndose_a2.
n_cohort	Total number of cohorts to include in the trial.
cohort	Cohort size.
tite	A boolean indicating if the toxicity is considered as a time-to-event outcome (TRUE), or as a binary outcome (default value FALSE).
time_full	Full follow-up time window. This argument is used only if tite=TRUE.
poisson_rate	A value indicating the rate for the Poisson process used to simulate patient arrival, i.e. expected number of arrivals per observation window. This argument is used only if tite=TRUE.
nsim	Number of simulations.
c_e	Probability threshold for dose-escalation. The default value is set at 0.85.
c_d	Probability threshold for dose-deescalation. The default value is set at 0.45.
c_stop	Probability threshold for early trial termination due to over-toxicity or under-toxicity (see details). The default value is set at 0.95.
c_t	Probability threshold for early trial termination for finding the MTD (see details). The default value is set at 0.5.
c_over	Probability threshold to control over-dosing (see details).
cmin_overunder	Minimum number of cohorts to be included at the lowest/highest combination before possible early trial termination for over-toxicity or under-toxicity (see details). The default value is set at 2.

cmin_mtd	Minimum number of cohorts to be included at the recommended combination before possible early trial termination for finding the MTD (see details). The default value is set at 3.
cmin_recom	Minimum number of cohorts to be included at the recommended combination at the end of the trial. The default value is set at 1.
startup	Interger (0, 1, 2, or 3) indicating which start-up phase is used (see details). The default value is set at 1.
alloc_rule	Interger (1, 2, or 3) indicating which allocation rule is used (see details). The default value is set at 1.
early_stop	Interger (1, 2, or 3) indicating which early stopping rule is used (see details). The default value is set at 1.
nburn	Number of burn-in for HMC. The default value is set at 2000.
niter	Number of iterations for HMC. The default value is set at 5000.
seed	Seed of the random number generator. Default value is set at 14061991.

Details

Start-up phase:

- startup=0: No startup phase.
- startup=1 (Riviere et al 2014): Begin at the lowest combination (1,1) and increase both agent (+1, +1) until the first toxicity is observed or maximum combination is reached.
- startup=2: Begin at the lowest combination (1,1) and increase agent 1 (+1, 0) until a toxicity is observed or maximum dose is reached. Then begin at (1,2) and increase agent 2 (0, +1) until a toxicity is observed or maximum dose is reached.
- startup=3: Begin at the lowest combination (1,1) and increase alternatively each agent (+1, 0) then (0, +1) until the first toxicity is observed or maximum combination is reached.

Allocation rule:

- alloc_rule=1 (Riviere et al 2014): If P(toxicity probability at combination (i,j) < target) > c_e: among combinations in the neighborhood (-1, +1), (0, +1), (+1, 0), (+1, -1), choose the combination with a higher estimated toxicity probability than the current combination and with the estimated toxicity probability closest to target. If P(toxicity probability at combination (i,j) > target) > 1-c_d: among neighborhood (-1, +1), (-1, 0), (0, -1), (+1, -1), choose the combination with a lower estimated toxicity probability than the current combination and with the estimated toxicity probability closest to target. Otherwise, remain on the same combination.
- alloc_rule=2: Among combinations already tested and combinations in the neighborhood (-1, 0), (-1, +1), (0, +1), (+1, 0), (+1, -1), (0, -1), (-1, -1) of a combination tested, choose the combination with the highest posterior probability to be in the targeted interval [target_min, target_max] while controling overdosing i.e. P(toxicity probability at combination (i,j) > target_max) < c_over.
- alloc_rule=3: Among combinations in the neighborhood (-1, 0), (-1, +1), (0, +1), (+1, 0), (+1, -1), (0, -1), (-1, -1) of the current combination, choose the combination with the highest posterior probability to be in the targeted interval [target_min, target_max] while controling overdosing i.e. P(toxicity probability at combination (i,j) > target_max) < c_over.

Early stopping for over-dosing: If the current combination is the lowest (1, 1) and at least `cmin_overunder` cohorts have been included at that combination and P(toxicity probability at combination (i,j) > target) >= `c_stop` then stop the trial and do not recommend any combination.

Early stopping for under-dosing: If the current combination is the highest and at least `cmin_overunder` cohorts have been included at that combination and P(toxicity probability at combination (i,j) < target) >= `c_stop` then stop the trial and do not recommend any combination.

Early stopping for identifying the MTD:

- `early_stop=1` (Riviere et al 2014): No stopping rule, include patients until maximum sample size is reached.

- `early_stop=2`: If the next recommended combination has been tested on at least `cmin_mtd` cohorts and has a posterior probability to be in the targeted interval [`target_min`, `target_max`] that is >= `c_t` and also control overdosing i.e. P(toxicity probability at current combination > `target_max`) < `c_over` then stop the trial and recommend this combination.

- `early_stop=3`: If at least `cmin_mtd` cohorts have been included at the next recommended combination then stop the trial and recommend this combination.

Stopping at the maximum sample size: If the maximum sample size is reached and no stopping rule is met, then the recommended combination is the one that was tested on at least `cmin_recom` cohorts and with the highest posterior probability to be in the targeted interval [`target_min`, `target_max`].

Value

An object of class "CombIncrease_sim" is returned, consisting of the operating characteristics of the design specified. Objects generated by `CombIncrease_sim` contain at least the following components:

`rec_dose`	Percentage of combination selection.
`n_pat_dose`	Mean number of patients at each combination.
`n_tox_dose`	Mean number of toxicities at each combination.
`inconc`	Percentage of inclusive trials.
`early_conc`	Percentage of trials stopping with criterion for finding MTD.
`nsim`	Number of simulations (if function stopped while executed, return the current number of simulations performed with associated other outputs).
`pat_tot`	Total mean number of patients accrued.
`tab_pat`	Vector with the number of patients included for each simulation.

Author(s)

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References

Riviere, M-K., Yuan, Y., Dubois, F., and Zohar, S. (2014). A Bayesian dose-finding design for drug combination clinical trials based on the logistic model. Pharmaceutical Statistics.

See Also

CombIncrease_next.

Examples

```
p_tox_sc1 = matrix(c(0.05,0.10,0.15,0.30,0.45,
                     0.10,0.15,0.30,0.45,0.55,
                     0.15,0.30,0.45,0.50,0.60),nrow=5,ncol=3)
prior_a1 = c(0.12, 0.2, 0.3, 0.4, 0.5)
prior_a2 = c(0.2, 0.3, 0.4)

sim1 = CombIncrease_sim(ndose_a1=5, ndose_a2=3, p_tox=p_tox_sc1, target=0.30,
  target_min=0.20, target_max=0.40, prior_tox_a1=prior_tox_a1,
  prior_tox_a2=prior_tox_a2, n_cohort=20, cohort=3, tite=FALSE, nsim=2000,
  c_over=1, cmin_overunder=3, cmin_recom=1, startup=1, alloc_rule=1,
  early_stop=1, seed=14061991)
sim1


# Dummy example, running quickly
useless = CombIncrease_sim(ndose_a1=3, ndose_a2=2,
  p_tox=matrix(c(0.05,0.15,0.30,0.15,0.30,0.45),nrow=3), target=0.30,
  target_min=0.20, target_max=0.40, prior_tox_a1=c(0.2,0.3,0.4),
  prior_tox_a2=c(0.2,0.3), n_cohort=2, cohort=2, nsim=1)
```

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