Package 'dfcomb'

October 5, 2015

Type Package

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

Version 2.1-5

Date 2015-10-05

Author Marie-Karelle Riviere and Jacques-Henri Jourdan

Maintainer Marie-Karelle Riviere <eldamjh@gmail.com>

Description Phase I/II adaptive dose-finding design for combination studies. Several methods are proposed depending on the type of combinations: (1) the combination of two cytotoxic agents, and (2) combination of a molecularly targeted agent with a cytotoxic agent.

License GPL-3

Depends R (>= 3.1.3)

LinkingTo RcppArmadillo (>= 0.4.650), BH (>= 1.55), RcppProgress (>= 0.2.1), Rcpp

NeedsCompilation yes

Repository CRAN

Date/Publication 2015-10-05 22:32:53

R topics documented:

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

Description

This package provides functions to run simulations, and to determine the MTD combination in on-going trials, in the cases of (1) combination of two agents where both toxicity and efficacy are assumed to increase with the dose of each agent (e.q. cytotoxic agents), and (2) combination of two agents where toxicity is increasing with the dose of each agent, but the efficacy of one agent is increasing whereas the efficacy of the other agent can plateaus (e.g. a cytotoxic agent with a molecularly targeted agent).

Details

Package:	dfcomb
Type:	Package
Version:	2.0
Date:	2014-12-08
License:	GPL-3

Author(s)

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

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. Riviere, MK, Yuan, Y, Dubois, F, Zohar, S (2014). A Bayesian dose finding design for clinical trials combining a cytotoxic agent with a molecularly targeted agent. JRSS-C.

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, in_startup=TRUE, 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, n_min)
```

Arguments

ndose_a1	Number of dose levels for agent 1.
ndose_a2	Number of dose levels for agent 2.
target	Toxicity (probability) target (for dose allocation).
target_min	Minimum of the targeted toxicity interval (for dose recommendation).
target_max	Maximum of the targeted toxicity interval (for dose recommendation).
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.
in_startup	A boolean with value FALSE to force the end of the startup phase. If the user uses the diagonal startup phase described in the paper, the function will detect its end automatically. Otherwise, this parameter should be used.
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.
n_min	Minimum number of patients to be included before possible early trial termination.

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).
`startup_in`	Start-up phase is ended or not.
`(cdose1, cdose2)`	NEXT RECOMMENDED COMBINATION.
`cohort`	Cohort size.
`pat_incl`	Number of patients included.
`target`	Toxicity target.
`[target_min, target_max]`	Targeted toxicity interval.
`prior_tox_a1`	Prior toxicity probabilities for agent 1.
`prior_tox_a2`	Prior toxicity probabilities for agent 2.
`n_min`	Minimum number of cohorts to stop the trial.
`c_e`	Escalation threshold.
`c_d`	Deescalation threshold.
`c_stop`	Stopping threshold.
`tite`	Type of outcome for toxicity (time-to-event or binary).
`time_full`	If toxicity is a time-to-event, full follow-up time is also reminded.

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(1,1,1,2,2,2,3,3,3,3,3,3,3,3,4,4,4)
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=0.20,
target_max=0.40, prior_tox_a1=prior_a1, prior_tox_a2=prior_a2, final=FALSE,
pat_incl=18, dose_adm1=dose1, dose_adm2=dose2, tite=FALSE, toxicity=toxicity1,
n_min=6)

next1

next2 =CombIncrease_next(ndose_a1=5, ndose_a2=3, target=0.30, target_min=0.20,
target_max=0.40, prior_tox_a1=prior_a1, prior_tox_a2=prior_a2, final=FALSE,
pat_incl=18, dose_adm1=dose1, dose_adm2=dose2, tite=TRUE, time_full=6,
time_tox=t_tox, time_follow=follow, n_min=6)

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, n_min=6, 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 (for dose allocation).
target_min	Minimum of the targeted toxicity interval (for dose recommendation).
target_max	Maximum of the targeted toxicity interval (for dose recommendation).
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. The default value is set at 0.95.
n_min	Minimum number of patients to be included before possible early trial termination. The default value is set at 6.
seed	Seed of the random number generator. Default value is set at 14061991.

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:

p_tox	True toxicity probabilities.
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.
n_min	Minimum number of cohorts to stop the trial.
nsim	Number of simulations (if function stopped while executed, return the current number of simulations performed with associated other outputs).
cohort	Cohort size.

n_cohort	Number of cohort planned.
pat_tot	Total mean number of patients accrued.
target	Toxicity target.
[target_min, target_max]	Targeted toxicity interval.
prior_tox_a1	Prior toxicity probabilities for agent 1.
prior_tox_a2	Prior toxicity probabilities for agent 2.
c_e	Escalation threshold.
c_d	Deescalation threshold.
c_stop	Stopping threshold.
tite	Type of outcome for toxicity (time-to-event or binary).
time_full	If toxicity is a time-to-event, full follow-up time is also reminded.
poisson_rate	If toxicity is a time-to-event, rate for Poisson process is also reminded.

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_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)
p_tox_sc6 = matrix(c(0.05,0.08,0.10,0.13,0.15,
                     0.09,0.12,0.15,0.30,0.45,
                     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)

# UNCOMMENT THOSE EXAMPLES
#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_a1, prior_tox_a2=prior_a2,
#n_cohort=20, cohort=3, tite=FALSE, nsim=2, c_e=0.85, c_d=0.45, c_stop=0.95,
#n_min=4, seed = 14061991)

#sim1

#sim2 = CombIncrease_sim(ndose_a1=5, ndose_a2=3, p_tox=p_tox_sc6, target=0.30,
#target_min=0.20, target_max=0.40, prior_tox_a1=prior_a1, prior_tox_a2=prior_a2,
```

```
#n_cohort=20, cohort=3, nsim=2)

#sim2

# 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)
```

`CombPlateau_next` *Combination determination for the combination of two agents where toxicity is increasing with the dose of both agent and efficacy is increasing and possibly plateaus with the dose of one agent*

Description

`CombPlateau_next` is used to determine the next or recommended combination in a phase I/II clinical trial for combination studies where the toxicity is assumed to increase with the dose of both agents, and the efficacy is asummed to increase with one agent and increase and possibily plateaus with the second agent. This phase I/II adaptive design is performed using the design proposed by Riviere et al. entitled "A Bayesian dose finding design for clinical trials combining a cytotoxic agent with a molecularly targeted agent".

Usage

```
CombPlateau_next(ndose_a1, ndose_a2, tox_max, eff_min, prior_tox_a1,
prior_tox_a2, prior_eff_a1, prior_eff_a2, stage, in_startup, cohort_start=3,
cohort, pat_incl, dose_adm1, dose_adm2, toxicity, time_full, time_prog,
time_follow, cycle=0, c_tox=0.85, c_eff=0.10)
```

Arguments

`ndose_a1`	Number of dose levels for agent 1.
`ndose_a2`	Number of dose levels for agent 2.
`tox_max`	Maximum acceptable toxicity probability.
`eff_min`	Minimum efficacy probability desired.
`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`.
`prior_eff_a1`	A vector of initial guesses of efficacy probabilities associated with the doses of agent 1. Must be of length `ndose_a1`.
`prior_eff_a2`	A vector of initial guesses of efficacy probabilities associated with the doses of agent 2. Must be of length `ndose_a2`.

stage	A integer with value 0 if less than half of the total sample size have been included, 1 if more than half of the total sample size have been included but the trial is still on-going, and 2 if the trial is over and dose recommendation should be done.
in_startup	TRUE if the start-up was not ended, FALSE otherwise.
cohort_start	Cohort size for the start-up phase. Default is set at 3.
cohort	Cohort size for the model-based phase.
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.
toxicity	A vector of observed toxicities (DLTs) for each patient included in the trial. Must be of length pat_incl.
time_full	Full follow-up time window for efficacy evaluation.
time_prog	A vector of times-to-progression for each patient included in the trial. If no progression (stability or efficacy) was observed for a patient, must be filled with +Inf. Must be of length pat_incl.
time_follow	A vector of follow-up times for each patient included in the trial. Must be of length pat_incl.
cycle	Minimum waiting time between two dose cohorts (usually a toxicity cycle). Default value is set at 0.
c_tox	Toxicity threshold for decision rules. The default value is set at 0.85.
c_eff	Efficacy threshold for decision rules. The default value is set at 0.10.

Value

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

n_pat_comb	Number of patients per combination.
n_tox_comb	Number of observed toxicities per combination.
n_eff_comb	Number of observed toxicities per combination.
pi	Estimated toxicity probabilities (if the start-up ended).
ptox_sup	Estimated probabilities that the toxicity probability is superior to tox_max (if the start-up ended).
resp	Estimated efficacy probabilities (if the start-up ended).
qeff_min	Estimated probabilities that the efficacy probability is superior to eff_min (if the start-up ended).
proba_tau	Estimated posterior probabilities for plateau location at each dose of agent 2 (if the start-up ended).

`startup_in`	Start-up phase is ended or not.
`(cdose1, cdose2)`	NEXT RECOMMENDED COMBINATION.
`cohort`	Cohort size.
`pat_incl`	Number of patients included.
`tox_max`	Toxicity upper bound.
`eff_min`	Efficacy lower bound.
`prior_tox_a1`	Prior toxicity probabilities for agent 1.
`prior_tox_a2`	Prior toxicity probabilities for agent 2.
`prior_eff_a1`	Prior efficacy probabilities for agent 1.
`prior_eff_a2`	Prior efficacy probabilities for agent 2.
`c_tox`	Tocixity threshold.
`c_eff`	Efficacy threshold.
`time_full`	Full follow-up time for efficacy is also reminded.

Author(s)

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

References

Riviere, M-K., Yuan, Y., Dubois, F., and Zohar, S. (2015). A Bayesian dose finding design for clinical trials combining a cytotoxic agent with a molecularly targeted agent. Journal of the Royal Statistical Society - Series C.

See Also

`CombPlateau_sim`.

Examples

```
prior_tox_a1 = c(0.2, 0.3, 0.4)
prior_eff_a1 = c(0.3, 0.4, 0.5)
prior_tox_a2 = c(0.12, 0.2, 0.3, 0.4)
prior_eff_a2 = c(0.3, 0.4, 0.5, 0.59)
toxicity = c(0,0,0,0,0,1,0,0,0,0,0,1,0,0,1,0,0,0)
dose1 = c(1,1,1,1,1,1,2,2,2,3,3,3,3,3,3,2,2,2)
dose2 = c(1,1,1,2,2,2,1,1,1,1,1,1,1,1,1,2,2,2)
t_prog = c(1.6,4.2,3.5,5.1,2.4,4.8,2.8,4.4,+Inf,3.9,+Inf,4.6,1.8,+Inf,0.5,5.4,2.8,+Inf)
follow = c(rep(7,15), 4.9, 3.1, 1.3)

next1 = CombPlateau_next(ndose_a1=3, ndose_a2=4, tox_max=0.30, eff_min=0.20,
prior_tox_a1, prior_tox_a2, prior_eff_a1, prior_eff_a2, stage=0, in_startup=FALSE,
cohort=3, pat_incl=18, dose_adm1=dose1, dose_adm2=dose2, toxicity=toxicity,
time_full=7, time_prog=t_prog, time_follow=follow)

next1
```

CombPlateau_sim *Combination design Simulator for the combination of two agents where toxicity is increasing with the dose of both agent and efficacy is increasing and possibly plateaus with the dose of one agent*

Description

CombPlateau_sim is used to generate simulation replicates of phase I/II clinical trial for combination studies where the toxicity is assumed to increase with the dose of both agents, and the efficacy is asummed to increase with one agent and increase and possibily plateaus with the second agent. This phase I/II adaptive design is performed using the design proposed by Riviere et al. entitled "A Bayesian dose finding design for clinical trials combining a cytotoxic agent with a molecularly targeted agent".

Usage

```
CombPlateau_sim(ndose_a1, ndose_a2, p_tox, p_eff, tox_max, eff_min,
prior_tox_a1, prior_tox_a2, prior_eff_a1, prior_eff_a2, n, cohort_start=3,
cohort=3, time_full, poisson_rate, cycle=0, nsim, c_tox=0.85, c_eff=0.10,
seed = 2174892, threads=0)
```

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).
p_eff	A matrix of the true efficacy probabilities associated with the combinations. True efficacy probabilities should be entered with agent 1 in row and agent 2 in column, with increasing (or plateau) efficacy probabilities with both row and column numbers (see examples).
tox_max	Maximum acceptable toxicity probability.
eff_min	Minimum efficacy probability desired.
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.
prior_eff_a1	A vector of initial guesses of efficacy probabilities associated with the doses of agent 1. Must be of length ndose_a1.
prior_eff_a2	A vector of initial guesses of efficacy probabilities associated with the doses of agent 2. Must be of length ndose_a2.
n	Total number of patients to include in the trial.

cohort_start	Cohort size for the start-up phase. Default is set at 3 (recommended).
cohort	Cohort size for the model-based phase. Default is set at 3.
time_full	Full follow-up time window for efficacy evaluation.
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.
cycle	Minimum waiting time between two dose cohorts (usually a toxicity cycle). Default value is set at 0.
nsim	Number of simulations.
c_tox	Tocixity threshold for decision rules. The default value is set at 0.85.
c_eff	Efficacy threshold for decision rules. The default value is set at 0.10.
seed	Seed of the random number generator. Default value is set at 2174892.
threads	Number of threads to use to do the computations. If 0, it uses as many threads as available processors.

Value

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

p_tox	True toxicities.
p_eff	True efficacies.
rec_dose	Percentage of Selection.
n_pat_dose	Number of patients at each combination.
n_tox_dose	Number of toxicities at each combination.
n_eff_dose	Number of toxicities at each combination.
inconc	Percentage of inclusive trials.
nsim	Number of simulations.
cohort_start	Cohort size for the start-up phase.
cohort	Cohort size for the model-based phase.
n	Total number of patients planned in the trial.
pat_tot	Total patients accrued.
tox_max	Toxicity upper bound.
eff_min	Efficacy lower bound.
prior_tox_a1	Prior toxicity probabilities for agent 1.
prior_tox_a2	Prior toxicity probabilities for agent 2.
prior_eff_a1	Prior efficacy probabilities for agent 1.
prior_eff_a2	Prior efficacy probabilities for agent 2.
c_tox	Tocixity threshold.
c_eff	Efficacy threshold.
time_full	Full follow-up time for efficacy is also reminded.
poisson_rate	Rate for Poisson process is also reminded.
duration	Trial mean duration.

Author(s)

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

References

Riviere, M-K., Yuan, Y., Dubois, F., and Zohar, S. (2015). A Bayesian dose finding design for clinical trials combining a cytotoxic agent with a molecularly targeted agent. Journal of the Royal Statistical Society - Series C.

See Also

CombPlateau_next.

Examples

```
p_tox_sc1 = t(matrix(c(0.10,0.15,0.30,0.45,
                       0.15,0.30,0.45,0.50,
                       0.30,0.45,0.55,0.65),nrow=4,ncol=3))
p_eff_sc1 = t(matrix(c(0.25,0.25,0.26,0.27,
                       0.40,0.41,0.41,0.42,
                       0.55,0.55,0.56,0.56),nrow=4,ncol=3))
p_tox_sc4 = t(matrix(c(0.01,0.04,0.08,0.10,
                       0.03,0.05,0.10,0.15,
                       0.07,0.10,0.15,0.30),nrow=4,ncol=3))
p_eff_sc4 = t(matrix(c(0.05,0.20,0.30,0.32,
                       0.10,0.30,0.45,0.46,
                       0.20,0.40,0.60,0.61),nrow=4,ncol=3))
prior_tox_a1 = c(0.2, 0.3, 0.4)
prior_eff_a1 = c(0.3, 0.4, 0.5)
prior_tox_a2 = c(0.12, 0.2, 0.3, 0.4)
prior_eff_a2 = c(0.3, 0.4, 0.5, 0.59)

# UNCOMMENT THOSE EXAMPLES
#sim1 = CombPlateau_sim(ndose_a1=3, ndose_a2=4, p_tox=p_tox_sc1,
#p_eff=p_eff_sc1, tox_max=0.30, eff_min=0.20, prior_tox_a1=prior_tox_a1,
#prior_tox_a2=prior_tox_a2, prior_eff_a1=prior_eff_a1,
#prior_eff_a2=prior_eff_a2, n=75, cohort_start=3, cohort=3, time_full=7,
#poisson_rate=0.28, cycle=0, nsim=2000, c_tox=0.85, c_eff=0.10, seed = 2174892,
#threads=0)

#sim1

#sim2 = CombPlateau_sim(ndose_a1=3, ndose_a2=4, p_tox=p_tox_sc4,
#p_eff=p_eff_sc4, tox_max=0.30, eff_min=0.20, prior_tox_a1=prior_tox_a1,
#prior_tox_a2=prior_tox_a2, prior_eff_a1=prior_eff_a1,
#prior_eff_a2=prior_eff_a2, n=75, cohort=3, time_full=7, poisson_rate=0.28,
#nsim=1000)

#sim2

# Dummy example, running quickly
useless = CombPlateau_sim(ndose_a1=2, ndose_a2=2,
```

```
p_tox=matrix(c(0.05,0.10,0.15,0.25),nrow=2),
p_eff=matrix(c(0.10,0.35,0.30,0.65),nrow=2), tox_max=0.35, eff_min=0.20,
prior_tox_a1=c(0.1,0.3), prior_tox_a2=c(0.1,0.3), prior_eff_a1=c(0.2,0.4),
prior_eff_a2=c(0.2,0.4),
n=15, cohort=3, time_full=7, poisson_rate=1, nsim=1)
```

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