Package ‘dfcomb’

May 24, 2018

Type Package
Title Phase I/II Adaptive Dose-Finding Design for Combination Studies
Version 2.5-0
Date 2018-05-24
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Internationales Servier and Institut national de la sante et de
la recherche medicale.
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 (>= 3.4.0)
LinkingTo RcppArmadillo (>= 0.7.100), BH (>= 1.55), RcppProgress (>=
0.2.1), Rcpp
NeedsCompilation yes
Repository CRAN
Date/Publication 2018-05-24 17:34:52 UTC

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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. 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.

**Details**

The DESCRIPTION file:

```
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Version: 2.5-0
Date: 2018-05-24
Author: Marie-Karelle Riviere and Jacques-Henri Jourdan
Maintainer: Jacques-Henri Jourdan <jacques-henri.jourdan@normalesup.org>
Copyright: src/arms.c and src/arms.h are copyright Wally Gilks. All other files are copyright Institut de Recherches Internationales Servier and Institut national de la sante et de la recherche medicale.
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 (>= 3.4.0)
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```

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- `CombIncrease_sim` - Combination design Simulator using Logistic model
- `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
- `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
- `dfcomb-package` - Phase I/II Adaptive Dose-Finding Design for Combination Studies
Author(s)

Marie-Karelle Riviere and Jacques-Henri Jourdan
Maintainer: Jacques-Henri Jourdan <jacques-henri.jourdan@normalesup.org>

References


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 Toxidity (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.
\textbf{pat_incl} Current number of patients included.
\textbf{dose_adm1} A vector indicating the dose levels of agents 1 administered to each patient included in the trial. Must be of length \textit{pat_incl}.
\textbf{dose_adm2} A vector indicating the dose levels of agents 2 administered to each patient included in the trial. Must be of length \textit{pat_incl}.
\textbf{tite} A boolean indicating if the toxicity is considered as a time-to-event outcome (TRUE), or as a binary outcome (default value FALSE).
\textbf{toxicity} A vector of observed toxicities (DLTs) for each patient included in the trial. Must be of length \textit{pat_incl}. This argument is used/required only if \textit{tite}=FALSE.
\textbf{time_full} Full follow-up time window. This argument is used only if \textit{tite}=TRUE.
\textbf{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 \textit{pat_incl}. This argument is used/required only if \textit{tite}=TRUE.
\textbf{time_follow} A vector of follow-up times for each patient included in the trial. Must be of length \textit{pat_incl}. This argument is used/required only if \textit{tite}=TRUE.
\textbf{c_e} Probability threshold for dose-escalation. The default value is set at 0.85.
\textbf{c_d} Probability threshold for dose-deescalation. The default value is set at 0.45.
\textbf{c_stop} Probability threshold for early trial termination. The default value is set at 0.95.
\textbf{n_min} Minimum number of patients to be included before possible early trial termination.

\textbf{Value}

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

\textbf{n_pat_comb} Number of patients per combination.
\textbf{n_tox_comb} Number of observed toxicities per combination.
\textbf{pi} Estimated toxicity probabilities (if the start-up ended).
\textbf{ptox_inf} Estimated probabilities that the toxicity probability is inferior to \textit{target} (if the start-up ended).
\textbf{ptox_inf_targ} Estimated probabilities of underdosing, i.e. to be inferior to \textit{target_min} (if the start-up ended).
\textbf{ptox_targ} Estimated probabilities to be in the targeted interval \([\textit{target_min}, \textit{target_max}]\) (if the start-up ended).
\textbf{ptox_sup_targ} Estimated probabilities of overdosing, i.e. to be superior to \textit{target_max} (if the start-up ended).
\textbf{startup_in} Start-up phase is ended or not.
\textbf{(cdose1, cdose2)}
\textbf{NEXT RECOMMENDED COMBINATION}.
\textbf{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)
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References

See Also
CombiIncrease_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(0,0,0,0,0,0,1,0,1,0,0,0,0,0,0,1)
dose1 = c(1,1,1,2,2,3,3,3,3,3,3,3,3,4,4,4)
dose2 = c(1,1,2,2,2,2,3,3,3,3,2,2,1,1,1,1)
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 = CombiIncrease_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 =CombiIncrease_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_a1L, ndose_aRL, p_tox, target, target_min, target_maxL, prior_tox_a1L, prior_tox_aRL, n_cohortL, cohortL, titeL, time_fullL, poisson_rateL, nsimL, c_eL, c_dL, c_stopL, n_minL, seedL)

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_a1L.
prior_tox_a2 A vector of initial guesses of toxicity probabilities associated with the doses of agent 2. Must be of length ndose_a2L.
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

CombPlateau_next

See Also

CombIncrease_next.

Examples

```r
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)

sim1 = CombiIncrease_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, title=FALSE, nsim=2, c_e=0.85, c_d=0.45, c_stop=0.95,
                          n_min=4, seed = 14061991)

sim2 = CombiIncrease_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)

# Dummy example, running quickly
useless = CombiIncrease_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 assumed to increase with one agent and increase and possibly 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`: Toxicity 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


See Also

CombPlateau_sim.
CombPlateau_sim  

Examples

```r
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, 1, 0, 0, 0, 0, 1, 0, 0, 0, 0, 0, 0)
dose1 = c(1, 1, 1, 1, 1, 2, 2, 2, 3, 3, 3, 3, 3, 2, 2)
dose2 = c(1, 1, 2, 2, 2, 1, 1, 1, 1, 1, 1, 2, 2, 2)
t_prog = c(1.6, 4.2, 3.5, 1.2, 4.4, 8.2, 8.4, 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)
nnext1 = 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)
```

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 assumed to increase with one agent and increase and possibly 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

```r
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

<table>
<thead>
<tr>
<th>Argument</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ndose_a1</td>
<td>Number of dose levels for agent 1.</td>
</tr>
<tr>
<td>ndose_a2</td>
<td>Number of dose levels for agent 2.</td>
</tr>
<tr>
<td>p_tox</td>
<td>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).</td>
</tr>
</tbody>
</table>
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
Minimum 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
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.

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.
CombPlateau_sim

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 Toxicity 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)
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References

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)

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)

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)

sim1

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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