Package: mbbe (via r-universe)

September 12, 2024

Title Model Based Bio-Equivalence

Version 0.1.0

Description Uses several Nonlinear Mixed effect (NONMEM) models (as NONMEM control files) to perform bootstrap model averaging and Monte Carlo Simulation for Model Based Bio-Equivalence (MBBE). Power is returned as the fraction of the simulations with successful bioequivalence (BE) test, for maximum concentration (Cmax), Area under the curve to the last observed value (AUClast) and Area under the curve extrapolate to infinity (AUCinf). See Hooker, A. (2020) Improved bioequivalence assessment through model-informed and model-based strategies <https://www.fda.gov/media/138035/download>.

URL https://github.com/certara/mbbe

BugReports https://github.com/certara/mbbe/issues

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Encoding UTF-8

Imports dplyr, stringr, xml2, PKNCA, magrittr, nlme, emmeans, future, furrr (>= 0.3.1), processx, tictoc, ggplot2, ps, jsonlite

Roxygen list(markdown = TRUE)

RoxygenNote 7.2.3

Suggests knitr, rmarkdown, testthat

VignetteBuilder knitr

Repository https://certara.r-universe.dev

RemoteUrl https://github.com/certara/mbbe

RemoteRef HEAD

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Contents

`calc_NCA` *Calculate Non-Compartmental Analysis (NCA) Parameters*

Description

This function performs Non-Compartmental Analysis (NCA) to derive key pharmacokinetic parameters such as Cmax, AUCinf, and AUClast for specified time intervals.

Usage

```
calc_NCA(
  run_dir,
  ngroups,
  reference_groups,
  test_groups,
  NCA_end_time,
  samp_size
)
```

Arguments

`run_dir`	Character string specifying the path to the run directory.
`ngroups`	Integer specifying the total number of groups (e.g., 4 for an ABBA design).
`reference_groups`	Numeric vector indicating the group IDs that are designated as reference.
`test_groups`	Numeric vector indicating the group IDs that are designated as test.
`NCA_end_time`	Numeric value specifying the end time for calculations of AUClast and AUCinf.
`samp_size`	Integer indicating the sample size or the total number of samples for the analysis.

Details

The `calc_NCA` function internally calls `getNCA` for each sample in the sequence from 1 to `samp_size`. Note that the function is currently executed in a serial manner and is not parallelized.

Value

The function returns a list containing the derived NCA parameters for each sample.

Examples

```
## Not run:
run_dir <- "c:/Workspace/mbbe"
ngroups <- 4
reference_groups <- c(1,2)
test_groups <- c(3,4)
NCA_end_time <- 7
samp_size <- 6
calc_NCA(run_dir, ngroups, reference_groups, test_groups, NCA_end_time, samp_size)

## End(Not run)
```

`calc_power` *Calculate Bioequivalence Power*

Description

Computes the power for bioequivalence (BE) testing based on EMA standards statistics applied to each Monte Carlo simulation. The power is determined by the proportion of simulations that meet the BE criteria.

Usage

```
calc_power(run_dir, samp_size, alpha, model_averaging_by, NTID)
```

Arguments

`run_dir`	Character string specifying the run directory where simulation outputs are located.
`samp_size`	Integer indicating the number of samples to be used in the analysis.
`alpha`	Numeric value representing the alpha error rate. It must lie between 0 and 1.
`model_averaging_by`	Character string indicating the method for model averaging, either "subject" or "study".
`NTID`	Logical indicating if the drug being tested is a narrow therapeutic index drug.

Details

When the simulation is conducted by study (i.e., a unique model for each study), this results in model averaging at the study level. If `model_averaging_by` is set to "subject", data from different studies are merged. For each study dataset, subjects are randomly selected (without replacement) from across all studies.

The function iterates over each sample, reading the corresponding NCAresults (designated by the sample number). Subsequently, it determines if each sample meets or fails the BE testing criteria.

Value

A list containing the results for:

- `Cmax_result`: Power for the Cmax parameter.
- `AUCinf_result`: Power for the AUCinf parameter.
- `AUClast_result`: Power for the AUClast parameter. All power values range between 0 and 1.

Examples

```
calc_power(
 run_dir = system.file(package = "mbbe", "examples", "calc_power"),
 samp_size = 5,
 alpha = 0.05,
 model_averaging_by = "study",
 NTID = FALSE
)
```

`run_example` *run_example for Model-Based BE Assessment*

Description

This function calls the example models (model1-5.mod), performs the bootstrap, model averaging and the Monte Carlo simulation.

Usage

```
run_example(run_dir, nmfe_path, Include_R_Code = FALSE, plan = "multisession")
```

Arguments

`run_dir`	Character string specifying the directory containing the parent folder where the models are to be run.
`nmfe_path`	Character string indicating the path to the nmfe batch file (e.g., nmfe?.bat).
`Include_R_Code`	Logical, whether the include the code in R_Penalty_Code in model averaging algorithm, Default is FALSE
`plan`	for future execution, one of "sequential", "multisession","multicore", Default is multisession

Details

The function executes the mbbe::run_mbbe_json() function. A user supplied installation of NONMEM is required run_dir is the parent folder where the models are to be run, nmfe_path is the path the nmfe??.bat where ?? is the version of NONMEM available plan is "sequential", "multisession","multicore", defining the plan for parallel execution (sequential is non-parallel execution) The function uses the included file mbbeargs.json as the options file for the run, and runs 5 supplied models for model averaging. Monte Carlo Simulation is then done, with the number of samples set in the mbbearg.json file, to 10 (probaby more would be appropriate for and actual power analysis) The model selection for the model averaging also includes a penalty calculate by the script RPenaltyCode.r for missing Cmax, AUCinf and AUClast Run time on 32 cores is ~3 minutes without the R code execution an 10 minutes with and the output should include:

Value

A list containing:

- `Cmax_power`: Power for Cmax
- `AUClast_power`: Power for AUClast
- `AUCinf_power`: Power for AUCinf
- `run_dir`: Directory where the function was executed
- `Num_identifiable`: Number of identifiable parameters
- `BICS`: Bayesian Information Criterion Scores

Examples

```
## Not run:
run_dir <- tempdir()
mbbe::run_example(run_dir = run_dir,
  nmfe_path = "c:/nm74g64/util/nmfe74.bat",
  plan = "multisession")

## End(Not run)
```

`run_mbbe` *Execute MBBE Analysis*

Description

This function runs the MBBE analysis. It's typically called by `run_mbbe_json` which provides the necessary options via a JSON file.

Usage

```
run_mbbe(
  crash_value,
  ngroups,
  reference_groups,
  test_groups,
  num_parallel,
  samp_size,
  run_dir,
  model_source,
  nmfe_path,
  delta_parms,
  use_check_identifiable,
  NCA_end_time,
  rndseed,
  simulation_data_path,
  plan = c("multisession", "sequential", "multicore"),
  alpha_error = 0.05,
  NTID = FALSE,
  model_averaging_by = "study",
  user_R_code = FALSE,
  R_code_path = "",
  save_plots = FALSE,
  ...
)
```

Arguments

crash_value	Numeric. Value to be returned for BIC in models that crash during either bootstrap or simulation.
ngroups	Integer. Number of groups in the simulated data (e.g., an ABBA design has 4 groups).
reference_groups	Numeric vector. Indices of the groups representing the reference formulation (e.g., c(2,3) for an ABBA design).
test_groups	Numeric vector. Indices of the groups representing the test formulation (e.g., c(1,4) for an ABBA design).
num_parallel	Integer. Number of NONMEM processes (both bootstrap and simulation) to run concurrently.
samp_size	Integer. Size of the bootstrap and simulation samples.
run_dir	Character string. Directory for NONMEM execution.
model_source	Character string. Paths to the NONMEM control files for model averaging.
nmfe_path	Character string. Path to the nmfe executable.
delta_parms	Numeric. Parameter difference threshold defining identifiability.

`use_check_identifiable`
: Logical. Should identifiability be checked based on the criterion defined by Aoki?

`NCA_end_time`
: Numeric. The NCA calculation will start at 0 and end at this value.

`rndseed`
: Integer. Random seed for reproducibility.

`simulation_data_path`
: Character string. Path to the simulation dataset.

`plan`
: Character string (default: "multisession"). Parallel execution plan. Can be "multisession", "sequential", or "multicore".

`alpha_error`
: Numeric (default: 0.05). Alpha error rate for statistical tests.

`NTID`
: Logical (default: FALSE). Is the drug a narrow therapeutic index drug?

`model_averaging_by`
: Character string (default: "study"). Method of model averaging, either "study" or "subject".

`user_R_code`
: Logical (default: FALSE). Should custom R code be used for model penalty?

`R_code_path`
: Character string. If `user_R_code` is TRUE, this parameter defines the path to the custom R script.

`save_plots`
: Logical (default: `FALSE`). Set to `TRUE` to save plot output.

`...`
: Additional args

Details

This function is primarily intended to be called by `run_mbbe_json`, which provides input parameters through a JSON configuration.

Value

A list containing:

- `Cmax_power`: Power for Cmax
- `AUClast_power`: Power for AUClast
- `AUCinf_power`: Power for AUCinf
- `run_dir`: Directory where the function was executed
- `Num_identifiable`: Number of identifiable parameters
- `BICS`: Bayesian Information Criterion Scores

run_mbbe_json *run_mbbe_json*

Description

Runs MBBE from a json file of options e.g., calls run_mbbe

Usage

```
run_mbbe_json(Args.json)
```

Arguments

Args.json	path to JSON file with arguments

Value

A list containing:

- Cmax_power: Power for Cmax
- AUClast_power: Power for AUClast
- AUCinf_power: Power for AUCinf
- run_dir: Directory where the function was executed
- Num_identifiable: Number of identifiable parameters
- BICS: Bayesian Information Criterion Scores

Examples

```
## Not run:
run_mbbe_json("Args.json")

## End(Not run)
```

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