Package ‘adaptIVPT’

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Type Package

Title Adaptive Bioequivalence Design for In-Vitro Permeation Tests

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Description Contains functions carrying out adaptive procedures using mixed scaling approach to establish bioequivalence for in-vitro permeation test (IVPT) data. Currently, the package provides procedures based on parallel replicate design and balanced data, according to the U.S. Food and Drug Administration's ``Draft Guidance on Acyclovir'' <`https://www.accessdata.fda.gov/drugsatfda_docs/psg/Acyclovir_topical%20cream_RLD%2021478_RV12-16.pdf`>. Potvin et al. (2008) <doi:10.1002/pst.294> provides the basis for our adaptive design (see Method B). For a comprehensive overview of the method, refer to Lim et al. (2023) <doi:10.1002/pst.2333>. This package reflects the views of the authors and should not be construed to represent the views or policies of the U.S. Food and Drug Administration.

License GPL (>= 3)

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Suggests knitr, rmarkdown

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`adaptIVPT` *adaptIVPT: Adaptive Bioequivalence Design for In-Vitro Permeation Tests for Pharmacokinetics with Mixed Scaling Approach*

Description

This package helps design and analyze adaptive bioequivalence studies. Main functions are `msabe`, `rss`, `prms`, and `PRsurface`.

`msabe` *Run the mixed scaling approach in bioequivalence (BE) studies*

Description

This function runs hypothesis testing for bioequivalence using the mixed criterion

Usage

```
msabe(Test, Reference, params = list())
```

Arguments

`Test`	An n-by-r matrix of test product data. `n` is the number of donors and `r` is the number of skin section replicates.
`Reference`	An n-by-r matrix of reference product data.
`params`	(Optional) The list of tuning parameters for running the test. • `sigma_W0` - A regulatory constant set by the FDA. Defaults to 0.25. • `m` - Another regulatory constant that determines the bounds within which the estimated GMR should fall for bioequivalence to be established. Defaults to 1.25, representing 80-125% average BE limits, which is the FDA recommendation. • `sig_level` - The significance level (alpha-level).

Value

A list of lists

- `parameters` - A list of true parameter settings.
- `fout` - The test result and related estimators.
- `runtime` - The total elapsed time charged for the execution of the program.

Author(s)

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References

Davit, B. M., Chen, M. L., Conner, D. P., Haidar, S. H., Kim, S., Lee, C. H., Lionberger, R. A., Makhlouf, F. T., Nwakama, P. E., Patel, D. T., Schuirmann, D. J., & Yu, L. X. (2012). Implementation of a reference-scaled average bioequivalence approach for highly variable generic drug products by the US Food and Drug Administration. The AAPS journal, 14(4), 915-924.

Examples

```
n <- 6
r <- 3
Test <- matrix(runif(n*r), nrow = n, ncol = r)
Reference <- matrix(runif(n*r), nrow = n, ncol = r)
out <- msabe(Test, Reference)
```

`prms` *Compute the passing rate for the mixed scaling approach in bioequivalence (BE) studies*

Description

This function runs Monte Carlo simulations to compute the passing rate (PR) of the mixed scaling (MS) approach.

Usage

```
prms(n, r, params = list(), nsim = 1000, ncores = NULL)
```

Arguments

`n`	The number of donors in each simulation.
`r`	The number of replicates from each donor for each simulated dataset.
`params`	(Optional) The list of true parameters to be assumed in data generation. • `sigma_W0` - A regulatory constant set by the FDA. Defaults to 0.25.

- `sigma_WT` - The true standard deviation of the test formulation population.
- `sigma_WR` - The true standard deviation of the reference formulation population.
- `GMR` - The geometric mean ratio of the test and reference values of the pharmacokinetic measures (e.g., Jmax or AUC). If the test-formulation measure is greater than that of the reference formulation, then GMR is typically set to 1.05, which is the initial value of this function. If the reference-formulation measure is bigger, then GMR is typically 0.95. Defaults to 0.95.
- `m` - Another regulatory constant that determines the bounds within which the estimated GMR should fall for bioequivalence to be established. Defaults to 1.25, representing 80-125% average BE limits, which is the FDA recommendation.
- `sig_level` - The significance level (alpha-level). Defaults to 0.05.

`nsim`	(Optional) The number of total simulations to be conducted. Defaults to 1,000.
`ncores`	(Optional) The number of CPU cores to use for parallel processing (OpenMP). If R hasn't been installed with OpenMP configured, this will not take effect. When OpenMP is available, it should not exceed the number of existing cores. If unspecified, it will default to 2 cores or the number of existing cores, whichever is smaller.

Value

A list of lists

- `parameters` - A list of true parameter settings.
- `passing_rate` - The estimated passing rate.
- `runtime` - The total elapsed time charged for the execution of the program.

Author(s)

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References

Davit, B. M., Chen, M. L., Conner, D. P., Haidar, S. H., Kim, S., Lee, C. H., Lionberger, R. A., Makhlouf, F. T., Nwakama, P. E., Patel, D. T., Schuirmann, D. J., & Yu, L. X. (2012). Implementation of a reference-scaled average bioequivalence approach for highly variable generic drug products by the US Food and Drug Administration. The AAPS journal, 14(4), 915-924.

Examples

```
out <- prms(10, 6, nsim = 2)
```

PRsurface *Plot the passing-rate curve and the passing-rate surface in IVPT*

Description

This function plots the power (passing-rate) curve and power (passing-rate) surface of the mixed scaling (MS) approach. A power curve shows the statistical power across different effect sizes. In IVPT studies, the effect size is captured by the difference between the means of log-measurements of the test and reference products (i.e., logGMR). For the passing-rate surface, the corresponding function considers different values of the standard deviation.

Usage

```
PRsurface(
  n,
  r,
  observed_GMR = 0.95,
  observed_sigmaWR = 0.294,
  GMR_grid = seq(0.75, 1.3, length.out = 100),
  sigmaWR_grid = seq(0.2, 1, length.out = 100),
  params = list(),
  nsim = 1000,
  ncores = NULL,
  verbose = FALSE,
  plot = TRUE
)
```

Arguments

`n`	The number of donors in each simulation.
`r`	The number of replicates from each donor for each simulated dataset.
`observed_GMR`	The observed (estimated) GMR of the user's data. Along with the observed sigmaWR, the corresponding passing rate will be displayed in the 3D plot as a vertical line parallel to the z-axis.
`observed_sigmaWR`	The observed (estimated) sigmaWR of the user's data. Along with the observed GMR, the corresponding passing rate will be displayed in the 3D plot as a vertical line parallel to the z-axis.
`GMR_grid`	The grid of GMR values to be used for plotting the 3D surface of passing rates.
`sigmaWR_grid`	The grid of sigmaWR values to be used for plotting the 3D surface of passing rates.
`params`	(Optional) The list of true parameters to be assumed in data generation. • `sigma_W0` - A regulatory constant set by the FDA. Defaults to 0.25. • `sigma_WT` - The true standard deviation of the test formulation population.

- `sigma_WR` - The true standard deviation of the reference formulation population.
- `GMR` - The geometric mean ratio of the test and reference values of the pharmacokinetic measures (e.g., Jmax or AUC). If the test-formulation measure is greater than that of the reference formulation, then GMR is typically set to 1.05, which is the initial value of this function. If the reference-formulation measure is bigger, then GMR is typically 0.95. Defaults to 0.95.
- `m` - Another regulatory constant that determines the bounds within which the estimated GMR should fall for bioequivalence to be established. Defaults to 1.25, representing 80-125% average BE limits, which is the FDA recommendation.
- `sig_level` - The significance level (alpha-level). Defaults to 0.05.

`nsim`	(Optional) The number of total simulations to be conducted. Defaults to 1,000.
`ncores`	(Optional) The number of CPU cores to use for parallel processing (OpenMP). If R hasn't been installed with OpenMP configured, this will not take effect. When OpenMP is available, it should not exceed the number of existing cores. If unspecified, it will default to 2 cores or the number of existing cores, whichever is smaller.
`verbose`	(Optional) A logical value (`TRUE`/`FALSE`) indicating whether to display the progress bar.
`plot`	(Optional) A logical value (`TRUE`/`FALSE`) indicating whether to generate a 3D interactive plot of the surface. If `FALSE`, the function will return the (x, y, z) values as a `list`.

Value

A list

- `GMR` - A list of true parameter settings.
- `passing_rate` - The estimated passing rate.
- `runtime` - The total elapsed time charged for the execution of the program.

Author(s)

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References

Davit, B. M., Chen, M. L., Conner, D. P., Haidar, S. H., Kim, S., Lee, C. H., Lionberger, R. A., Makhlouf, F. T., Nwakama, P. E., Patel, D. T., Schuirmann, D. J., & Yu, L. X. (2012). Implementation of a reference-scaled average bioequivalence approach for highly variable generic drug products by the US Food and Drug Administration. The AAPS journal, 14(4), 915-924.

Examples

```
out <- PRsurface(6, 3, GMR_grid = c(0.90, 1), sigmaWR_grid = c(0.2, 0.5), nsim = 2, plot = FALSE)
```

`rss` *Reestimate the sample size for the adaptive design in bioequivalence (BE) studies using mixed criterion.*

Description

This function reestimates the sample size using mixed criterion required for target power, using binary search. The power (passing rate) function of mixed criterion testing lacks a closed-form expression. Thus, sample size (re-)estimation requires a binary search, after identifying an `n` where the passing rate exceeds the desired level.

Usage

```
rss(n, r, S_WR, params = list(), nsim = 1000, ncores = NULL)
```

Arguments

`n`	The number of donors in each simulation.
`r`	The number of replicates from each donor for each simulated dataset.
`S_WR`	The estimated standard deviation of the reference measurements. The reference-scaled average bioequivalence approach is used if S_WR > 0.249 and the average bioequivalence approach otherwise.
`params`	(Optional) The list of true parameters to be assumed in data generation. • `sigma_W0` - A regulatory constant set by the FDA. Defaults to 0.25. • `GMR` - The geometric mean ratio of the test and reference values of the pharmacokinetic measures (e.g., Jmax or AUC). If the test-formulation measure is greater than that of the reference formulation, then GMR is typically set to 1.05, which is the initial value of this function. If the reference-formulation measure is bigger, then GMR is typically 0.95. Defaults to 0.95. • `m` - Another regulatory constant that determines the bounds within which the estimated GMR should fall for bioequivalence to be established. Defaults to 1.25, representing 80-125% average BE limits, which is the FDA recommendation. • `sig_level` - The significance level (alpha-level). • `nmax` - The upper limit for sample size reestimation. If the sample size exceeds `nmax` inside estimation procedure, the function will return `nmax`. • `target_power` - The threshold for power (or passing rate) for a hypothesis test to be considered powerful. Typically set at 80% and defaults to 0.8.
`nsim`	(Optional) The number of total simulations to be conducted. Defaults to 1,000.
`ncores`	(Optional) The number of CPU cores to use for parallel processing (OpenMP). If R hasn't been installed with OpenMP configured, this will not take effect. When OpenMP is available, it should not exceed the number of existing cores. If unspecified, it will default to 2 cores or the number of existing cores, whichever is smaller.

Value

A list of lists

- `parameters` - A list of true parameter settings.
- `rss` - The reestimated sample size.
- `runtime` - The total elapsed time charged for the execution of the program.

Author(s)

Daeyoung Lim, `<daeyoung.lim@uconn.edu>`

References

Potvin, D., DiLiberti, C. E., Hauck, W. W., Parr, A. F., Schuirmann, D. J., & Smith, R. A. (2008). Sequential design approaches for bioequivalence studies with crossover designs. Pharmaceutical Statistics: The Journal of Applied Statistics in the Pharmaceutical Industry, 7(4), 245-262.

Examples

```
out <- rss(10, 6, S_WR = 0.22, nsim = 2)
```

`summary.msabe` *‘summary‘ method for class "‘msabe‘"*

Description

‘summary‘ method for class "‘msabe‘"

Usage

```
## S3 method for class 'msabe'
summary(object, ...)
```

Arguments

`object`	an output from ‘msabe‘
`...`	additional arguments for print

Value

Does not return anything; print a summary of the output

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