Package: replicateBE (via r-universe)

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Title Average Bioequivalence with Expanding Limits (ABEL)

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Depends R (>= 3.5.0)

Imports readxl (>= 1.0.0), PowerTOST (>= 1.5.3), lmerTest, nlme, pbkrtest, graphics, grDevices

Suggests knitr, rmarkdown, testthat, devtools

Description Performs comparative bioavailability calculations for Average Bioequivalence with Expanding Limits (ABEL). Implemented are 'Method A' / 'Method B' and the detection of outliers. If the design allows, assessment of the empiric Type I Error and iteratively adjusting alpha to control the consumer risk. Average Bioequivalence - optionally with a tighter (narrow therapeutic index drugs) or wider acceptance range (South Africa: Cmax) - is implemented as well.

License GPL (>=3)

LazyData true

VignetteBuilder knitr

URL https://github.com/Helmut01/replicateBE

BugReports https://github.com/Helmut01/replicateBE/issues

Config/pak/sysreqs cmake make libicu-dev

Repository https://helmut01.r-universe.dev

RemoteUrl https://github.com/helmut01/replicatebe

RemoteRef HEAD

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Contents

`ABE` *Comparative BA-calculation for Average Bioequivalence*

Description

This function performs the required calculations for the BE decision via conventional (unscaled) Average Bioequivalence based on ANOVA as recommended in the EMA's guideline.

Usage

```
ABE(alpha = 0.05, path.in, path.out = tempdir(), file, set = "",
    ext, na = ".", sep = ",", dec = ".", logtrans = TRUE,
    print = TRUE, details = FALSE, verbose = FALSE, ask = FALSE,
    data = NULL, theta1, theta2)
```

Arguments

`alpha`	Type I Error (TIE) probability (nominal level of the test). Conventionally set to 0.05, resulting in a $100(1-2\,\alpha)$ confidence interval.
`path.in`	Path to the data file for import.
`path.out`	Path to save the result file if `print = TRUE`. You must have write-permission to the folder. For simplicity your home folder `"~/"` can be used. If missing, R's standard temporary folder will be used.
`file`	Name of the dataset for import (*without* extension). Must be a string (*i.e.*, enclosed in single or double quotation marks). The name is case-sensitive.

`set`	Name of the sheet of an Excel-file (mandatory). Must be a string (*i.e.*, enclosed in single or double quotation marks). The name is case-sensitive.
`ext`	File-extension enclosed in single or double quotation marks. Acceptable are `"csv"` for character delimited variables (CSV) or `"xls"`, `"xlsx"` for Excel-files. The file-extension is not case-sensitive.
`na`	Character string denoting missing values. Acceptable are `"NA"` (not available), `"ND"` (not determined), `"."` (SAS), `"Missing"` (Phoenix WinNonlin), and `""` (EXCEL; empty cell). Missings will be converted to `NA` in the imported data. Defaults to `"."`.
`sep`	Variable separator in the CSV-file. Acceptable are `","` (comma = `ASCII 44`), `";"` (semicolon = `ASCII 59`), and `"\t"` (tabulator = `ASCII 9`). Defaults to `","`.
`dec`	Decimal separator in the CSV-file. Acceptable are `"."` (period = `ASCII 46`) or `","` (comma = `ASCII 44`). Defaults to `"."`.
`logtrans`	If `TRUE` (default) the raw data (provided in column `PK`) will be internally log-transformed and used in the calculations. If `FALSE` the already log-transformed data (provided in the column `logPK`) will be used in the calculations.
`print`	If `TRUE` (default), the function prints its results to a file. If `FALSE`, returns a data frame of results.
`details`	Defaults to `FALSE`. If `TRUE`, the function sends its results in 7-digits precision to a data frame.
`verbose`	Defaults to `FALSE`. If `TRUE` the ANOVA-table is send to the console.
`ask`	Defaults to `FALSE`. If `TRUE` the user will be asked whether an already existing result file should be overwritten.
`data`	Specification of one of the internal reference datasets (`rds01` to `rds30`). If given, the arguments `path.in`, `file`, `set`, and `ext` are ignored. For its use see the examples. If not given, defaults to `NULL` (*i.e.*, import data from a file).
`theta1`	Lower limit of the acceptance range. Defaults to `0.80`. If missing will be set to `1/theta2`.
`theta2`	Upper limit of the acceptance range. Defaults to `1.25`. If missing will be set to `1/theta1`.

Details

The model for the treatment comparison is

```
lm(log(PK) ~ sequence + subject %in% sequence + period + treatment,
data = data)
```

where all effects are fixed.

Tested designs

- 4-period 2-sequence full replicates
  `TRTR | RTRT`
  `TRRT | RTTR`
  `TTRR | RRTT`

- 2-period 4-sequence replicate
  `TR | RT | TT | RR` (Balaam's design)
- 4-period 4-sequence full replicates
  `TRTR | RTRT | TRRT | RTTR`
  `TRRT | RTTR | TTRR | RRTT`
- 3-period 2-sequence full replicates
  `TRT | RTR`
  `TRR | RTT`
- 3-period (partial) replicates
  `TRR | RTR | RRT`
  `TRR | RTR` (extra-reference design)

Data structure

- Columns must have the headers `subject`, `period`, `sequence`, `treatment`, `PK`, and/or `logPK`.
  Any order of columns is acceptable.
  Uppercase and mixed case headers will be internally converted to lowercase headers.
  - `subject` must be integer numbers or (any combination of) alphanumerics `[A-Z, a-z, -, _, #, 0-9]`
  - `period` must be integer numbers.
  - `sequence` must be contained in the tested designs (numbers or *e.g.*, `ABAB` are not acceptable).
  - The Test treatment must be coded `T` and the Reference `R`.

Value

Prints results to a file if argument `print = TRUE` (default).
If argument `print = FALSE`, returns a data frame with the elements:

`Design`	*e.g.*, TRTR|RTRT
`Method`	ABE
`n`	total number of subjects
`nTT`	number of subjects with two treatments of `T` (full replicates only)
`nRR`	number of subjects with two treatments of `R`
`Sub/seq`	number of subjects per sequence
`Miss/seq`	if the design is unbalanced, number of missings per sequence
`Miss/per`	if the design is incomplete, number of missings per period
`alpha`	nominal level of the test
`DF`	degrees of freedom of the treatment comparison
`CVwT(%)`	intra-subject coefficient of variation of the test treatment (full replicates only)
`CVwR(%)`	intra-subject coefficient of variation of the reference treatment
`BE.lo(%)`	lower bioequivalence limit (*e.g.*, `80`)
`BE.hi(%)`	upper bioequivalence limit (*e.g.*, `125`)
`CI.lo(%)`	lower confidence limit of the treatment comparison
`CI.hi(%)`	upper confidence limit of the treatment comparison
`PE(%)`	point estimate of the treatment comparison (aka GMR)
`BE`	assessment whether the $100(1-2\,\alpha)$ CI lies entirely within the acceptance range (`pass|fail`)

Warning

Files may contain a commentary header. If reading from a CSV-file, *each* line of the commentary header *must* start with `"# "` (hashmark space = `ASCII 35 ASCII 32`). If reading from an Excel-file all lines preceding the column headers are treated as a comment.

Clarification

The 'ASCII line chart' in the result file gives the confidence limits with filled black squares and the point estimate as a white rhombus . The BE limits and 100% are given with single vertical lines . The 'resolution' is approximately 0.5% and therefore, not all symbols might be shown. The CI and PE take presedence over the limits.

Disclaimer

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Note

The EMA's model assumes equal [*sic!*] intra-subject variances of test and reference (like in 2×2×2 trials) – even if proven false in one of the full replicate designs (were *both* CV_{wT} and CV_{wR} can be estimated). Hence, amongst biostatisticians it is called the 'crippled model' because the replicative nature of the study is ignored.
Conventional unscaled ABE has to be employed for $C_{\max}$ (if widening of the acceptance range is clinically not justifiable), AUC_{0-t}, AUC_{0-72} (immediate release products) and $C_{\max,\text{ss}}$, $C_{\tau,ss}$, ${}_{\text{partial}}AUC$ (if widening of the acceptance range is clinically not justifiable), and AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{0-\tau}$ (modified release products).

Direct widening of the limits for highly variable $C_{\max}$ to 75.00–133.33% is acceptable in South Africa and Kazakhstan.

Author(s)

Helmut Schütz

References

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See Also

`method.A`	evaluation for ABEL by a fixed effects model (ANOVA)
`method.B`	evaluation for ABEL by a linear mixed effects model

Examples

```
# Importing from a CSV-file, using most of the defaults: variable
# separator comma, decimal separator period, print to file.
# Note: You must adapt the path-variables. The example reads from
# the data provided by the library. Write-permissions must be granted
# for 'path.out' in order to save the result file. Here the deafault
# (R's temporary folder) is used. If you don't know where it is,
# type tempdir() in the console.
path.in <- paste0(find.package("replicateBE"), "/extdata/")
ABE(path.in = path.in, file = "DS", set = "02", ext = "csv")
# Should result in:
#   BE-limits          :  80.00% ... 125.00%
#   Confidence interval:  97.32% ... 107.46%  pass
#   Point estimate     : 102.26%
# Generate the data.frame of results (7-digits precision) and show
# in the console. Use an internal dataset.
x <- ABE(details = TRUE, print = FALSE, data = rds02)
print(x, row.names = FALSE)

# Assuming a NTID and assess BE with narrower limits for one
# of the internal datasets.
ABE(data = rds02, theta1 = 0.90)
# Should result in:
#   BE-limits          :  90.00% ... 111.11%
#   Confidence interval:  97.32% ... 107.46%  pass
#   Point estimate     : 102.26%
```

`method.A` *Comparative BA-calculation for Average Bioequivalence with Expanding Limits by the EMA's 'Method A'*

Description

This function performs the required calculations for the mixed (or aggregate) BE decision via Average Bioequivalence with Expanding Limits (ABEL) based on ANOVA ('Method A') as recommended in *Annex I*.

Usage

```
method.A(alpha = 0.05, path.in, path.out = tempdir(), file, set = "",
         ext, na = ".", sep = ",", dec = ".", logtrans = TRUE,
         regulator = "EMA", ola = FALSE, print = TRUE, details = FALSE,
         adjust = FALSE, verbose = FALSE, ask = FALSE,
         plot.bxp = FALSE, fence = 2, data = NULL)
```

Arguments

`alpha`	Type I Error (TIE) probability (nominal level of the test). Conventionally set to 0.05, resulting in a $100(1-2\,\alpha)$ confidence interval.
`path.in`	Path to the data file for import.
`path.out`	Path to save the result file if `print=TRUE`. You must have write-permission to the folder. For simplicity your home folder `"~/"` can be used. If missing, R's standard temporary folder will be used. If a box plot of outliers should be saved (`plot.bxp = TRUE`), this path will be used as well.
`file`	Name of the dataset for import (*without* extension). Must be a string (*i.e.*, enclosed in single or double quotation marks).
`set`	Name of the sheet of an Excel-file (mandatory). Must be a string (*i.e.*, enclosed in single or double quotation marks).
`ext`	File-extension enclosed in single or double quotation marks. Acceptable are `"csv"` for character delimited variables (CSV) or `"xls"`, `"xlsx"` for Excel-files. The file-extension is not case-sensitive.
`na`	Character string denoting missing values. Acceptable are `"NA"` (not available), `"ND"` (not determined), `"."` (SAS), `"Missing"` (Phoenix WinNonlin), and `""` (EXCEL; empty cell). Missings will be converted to `NA` in the imported data. Defaults to `"."`.
`sep`	Variable separator in the CSV-file. Acceptable are `","` (comma = `ASCII 44`), `";"` (semicolon = `ASCII 59`), and `"\t"` (tabulator = `ASCII 9`). Defaults to `","`.
`dec`	Decimal separator in the CSV-file. Acceptable are `"."` (period = `ASCII 46`) or `","` (comma = `ASCII 44`). Defaults to `"."`.
`logtrans`	If `TRUE` (default) the raw data (provided in column `PK`) will be internally log-transformed and used in the calculations. If `FALSE` the already log-transformed data (provided in the column `logPK`) will be used in the calculations.
`regulator`	Set regulatory conditions. If `"EMA"` (default) conventional ABEL will be used. If `"GCC"` direct widening to 75.00–133.33% will be used if `CVwR > 30%`.
`ola`	Defaults to `FALSE`. If `TRUE` an outlier analysis based on the studentized and standardized (aka internally studentized) residuals of the model estimating `CVwR` is performed.

`print`	If `TRUE` (default), the function prints its results to a file. If `FALSE`, returns a data frame of results.
`details`	Defaults to `FALSE`. If `TRUE`, the function sends its results in full precision to a data frame.
`adjust`	Defaults to `FALSE`. If `TRUE`, the empiric Type I Error (*TIE*) is evaluated via simulations (by the function scABEL.ad of library `PowerTOST`). Currently implemented designs are `2x2x4`, `2x2x3`, and `2x3x3`. If the *TIE* exceeds the nominal level of the test `alpha`, α is iteratively adjusted until $TIE = \alpha \pm 10^{-6}$. If `ola = TRUE` and outlier(s) found – which lead to an always lower – recalculated `CVwR`, the assessment is repeated for its value.
`verbose`	Defaults to `FALSE`. If `TRUE` the ANOVA-table is send to the console. If `ola = TRUE` additional information about outliers are shown.
`ask`	Defaults to `FALSE`. If `TRUE` the user will be asked whether an already existing result file (and if outliers are found, the box plot) should be overwritten.
`plot.bxp`	Only observed if `ola = TRUE` and at least one outlier is found. If `FALSE` (default) the box plot will be shown in the graphics device. If `TRUE` the box plot will be saved in PNG format to `path.out`.
`fence`	Only observed if `ola = TRUE`. The limit for outlier detection as a multiplier of the interquartile range. Defaults to 2. Less outliers will be detected with higher values (not recommended).
`data`	Specification of one of the internal reference datasets (`rds01` to `rds30`). If given, the arguments `path.in`, `file`, `set`, and `ext` are ignored. For its use see the examples. If not given, defaults to `NULL` (*i.e.*, import data from a file).

Details

The model for the estimation of `CVwR` is

```
lm(log(PK) ~ sequence + subject %in% sequence + period,
data = data[data$treatment == "R", ])
```

where all effects are fixed.

The model for the treatment comparison is

```
lm(log(PK) ~ sequence + subject %in% sequence + period + treatment,
data = data)
```

where all effects are fixed.

Tested designs

- 4-period 2-sequence full replicates
  `TRTR | RTRT`
  `TRRT | RTTR`
  `TTRR | RRTT`
- 2-period 4-sequence replicate
  `TR | RT | TT | RR` (Balaam's design)

- 4-period 4-sequence full replicates
  `TRTR | RTRT | TRRT | RTTR`
  `TRRT | RTTR | TTRR | RRTT`
- 3-period 2-sequence full replicates
  `TRT | RTR`
  `TRR | RTT`
- 3-period (partial) replicates
  `TRR | RTR | RRT`
  `TRR | RTR` (extra-reference design)

Data structure

- Columns must have the headers `subject`, `period`, `sequence`, `treatment`, `PK`, and/or `logPK`.
  Any order of columns is acceptable.
  Uppercase and mixed case headers will be internally converted to lowercase headers.
  - `subject` must be integers or (any combination of) alphanumerics
    `[A-Z, a-z, -, _, #, 0-9]`
  - `period` must be integer numbers.
  - `sequence` must be contained in the tested designs (numbers or *e.g.*, `ABAB` are not acceptable).
  - The Test treatment must be coded `T` and the Reference `R`.

Value

Prints results to a file if argument `print = TRUE` (default).
If argument `print = FALSE`, returns a data frame with the elements:

`Design`	*e.g.*, TRTR|RTRT
`Method`	A
`n`	total number of subjects
`nTT`	number of subjects with two treatments of `T` (full replicates only)
`nRR`	number of subjects with two treatments of `R`
`Sub/seq`	number of subjects per sequence
`Miss/seq`	if the design is unbalanced, number of missings per sequence
`Miss/per`	if the design is incomplete, number of missings per period
`alpha`	nominal level of the test
`DF`	degrees of freedom of the treatment comparison
`CVwT(%)`	intra-subject coefficient of variation of the test treatment (full replicates only)
`CVwR(%)`	intra-subject coefficient of variation of the reference treatment
`swT`	intra-subject standard deviation of the test treatment (full replicates only)
`swR`	intra-subject standard deviation of the reference treatment
`sw.ratio`	ratio of intra-subject deviations of `T` and `R` (full replicates only)
`sw.ratio.CL`	upper confidence limit of `sw.ratio` (full replicates only)

- If reference-scaling is applicable (*i.e.*, `CVwR(%)` >30%):

`L(%)`	lower expanded limit of the acceptance range (AR)

`U(%)`	upper expanded limit of the acceptance range (AR)

- If reference-scaling is not applicable (*i.e.*, `CVwR(%)` ≤30%):

`BE.lo(%)`	lower limit of the conventional AR (`80`)
`BE.hi(%)`	upper limit of the conventional AR (`125`)

`CL.lo(%)`	lower confidence limit of the treatment comparison
`CL.hi(%)`	upper confidence limit of the treatment comparison
`PE(%)`	point estimate of the treatment comparison (aka GMR)
`CI`	assessment whether the $100(1-2\,\alpha)$ CI lies entirely within the acceptance range (`pass|fail`)
`GMR`	assessment whether the PE lies entirely within the GMR-restriction 80.00–125.00% (`pass|fail`)
`BE`	mixed (aggregate) assessment whether the study demonstrates bioequivalence (`pass|fail`)
`log.half-width`	half-width of the confidence interval in log-scale

If `ola = TRUE` and at least one studentized outlier was detected:

`outlier`	outlying subject(s)
`CVwR.rec(%)`	intra-subject coefficient of variation of `R`; recalculated after exclusion of outlier(s)
`swR.rec`	intra-subject standard deviation of the reference treatment after exclusion of outlier(s)
`sw.ratio.rec`	ratio of intra-subject standard deviations of `T` and `R` after exclusion of outlier(s); full replicates
`sw.ratio.rec.CL`	upper confidence limit of `sw.ratio.rec` (full replicates only)

- If reference-scaling is applicable (*i.e.*, `CVwR(%)` >30):

`L.rec(%)`	recalculated lower expanded limit of the AR
`U.rec(%)`	recalculated upper expanded limit of the AR

- If reference-scaling is not applicable (*i.e.*, `CVwR(%)` ≤30):

`BE.rec.lo(%)`	lower limit of the conventional AR (`80`)
`BE.rec.hi(%)`	upper limit of the conventional AR (`125`)

`CI.rec`	assessment whether the $100(1-2\alpha)$ CI lies entirely within the new acceptance range (`pass|fail`)
`GMR.rec`	assessment whether the PE lies entirely within the GMR-restriction 80.00–125.00% (`pass|fail`)
`BE.rec`	mixed (aggregate) assessment whether the study demonstrates bioequivalence (`pass|fail`)

Warning

Files may contain a commentary header. If reading from a CSV-file, *each* line of the commentary header *must* start with `"# "` (hashmark space = `ASCII 35 ASCII 32`). If reading from an Excel-file all lines preceding the column headers are treated as a comment.

Clarification

The ‘ASCII line chart’ in the result file gives the confidence limits with filled black squares and the point estimate as a white rhombus . If a confidence limit exceeds the maximum possible expansion limit, it is shown as a triangle or . Expanded limits are given as double vertical lines . Unscaled limits, the GMR restriction, and 100% are given with single vertical lines . The ‘resolution’ is approximatelly 0.5% and therefore, not all symbols might be shown. The CI and PE take presedence over the limits and the expanded limits over unscaled ones.

Disclaimer

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Note

The EMA’s model specified as ‘Method B’ in *Annex I* assumes equal [*sic*] intra-subject variances of test and reference (like in $2 \times 2 \times 2$ trials) – even if proven false in one of the full replicate designs (were *both* CV_{wT} and CV_{wR} can be estimated). Hence, amongst biostatisticians it is called the ‘crippled model’ because the replicative nature of the study is ignored.
The half-width of the CI in log-scale allows a comparison of methods (B *vs* A) where a higher value *might* point towards a more conservative decision. In the provided reference datasets – with one exception – the conclusion of BE (based on the mixed CI and GMR criteria) agrees between ‘Method A’ and ‘Method B’. However, for the highly incomplete dataset 14 ‘Method A’ was *liberal* (passing by ANOVA but failing by the mixed effects model).

Reference-scaling is acceptable for C_{max} (immediate release products) and $C_{\mathrm{max,ss}}$, $C_{\tau,ss}$, and ${}_{\mathrm{partial}}AUC$ (modified release products). However, quoting the BE guideline:
The applicant should justify that the calculated intra-subject variability is a reliable estimate and that it is not the result of outliers.
Quoting the Q&A on the Revised EMA Bioequivalence Guideline:
…a study could be acceptable if the bioequivalence requirements are met both including the outlier subject (using the scaled average bioequivalence approach and the within-subject CV with this subject) and after exclusion of the outlier (using the within-subject CV without this subject).
An outlier test is not an expectation of the medicines agencies but outliers could be shown by a box plot. This would allow the medicines agencies to compare the data between them.

The EMA’s method of reference-scaling for highly variable drugs / drug products is currently recommended in other jurisdictions as well (*e.g.*, the WHO; ASEAN States, Australia, Belarus, Brazil, Chile, Egypt, the Eurasian Economic Union, the East African Community, New Zealand, the Russian Federation).

In a pilot phase the WHO accepted reference-scaling for AUC (4-period full replicate studies are mandatory in order to assess the variability associated with each product). It was an open issue how this assessment should be done. In Population Bioequivalence (PBE) and Individual Bioequivalence (IBE) the $s_{\mathrm{wT}}/s_{\mathrm{wR}}$ ratio was assessed and similar variability was

concluded for a ratio within 0.667–1.500. However, the power of comparing variabilities in a study designed to demonstrate ABE is low. This was one of the reasons why PBE and IBE were not implemented in regulatory practice. An alternative approach is given in the FDA's draft ANDA guidance. Variabilities are considered comparable if the upper confidence limit of $\sigma_{\mathrm{wT}}/\sigma_{\mathrm{wR}}$ is less than or equal to 2.5.
In 2021 the requirement of comparing variabilities was lifted.

Author(s)

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See Also

`method.B`	evaluation by a linear mixed effects model (subjects random)
`ABE`	evaluation for conventional (unscaled) Average Bioequivalence

Examples

```
# Importing from a CSV-file, using most of the defaults: variable
# separator colon, decimal separator period, no outlier-analyis,
# print to file.
# Note: You must adapt the path-variables. The example reads from
# the data provided by the library. Write-permissions must be granted
# for 'path.out' in order to save the result file. Here the default
# (R's temporary folder) is used. If you don't know where it is,
# type tempdir() in the console.

path.in  <- paste0(find.package("replicateBE"), "/extdata/")
method.A(path.in = path.in, file = "DS", set = "01", ext = "csv")
# Should result in:
#   CVwT               :  35.16%
#   swT                :   0.34138
#   CVwR               :  46.96% (reference-scaling applicable)
#   swR                :   0.44645
#   Expanded limits    :  71.23% ... 140.40% [100exp(±0.760·swR)]
#   swT / swR          :   0.7647 (similar variabilities of T and R)
#   sw-ratio (upper CL):   0.9324 (comparable variabilities of T and R)
#   Confidence interval: 107.11% ... 124.89%  pass
#   Point estimate     : 115.66%              pass
#   Mixed (CI & PE)    :                      pass
#
# Internal reference dataset 01 used and results to R's
# temporary folder. Additional outlier-analyis.
method.A(ola = TRUE, data = rds01)
# Should give the same as above. Additionally:
#   Outlier fence      :  2×IQR of studentized residuals.
#   Recalculation due to presence of 2 outliers (subj. 45|52)
#   CVwR (outl. excl.) :  32.16% (reference-scaling applicable)
#   swR (recalculated) :   0.31374
#   Expanded limits    :  78.79% ... 126.93% [100exp(±0.760·swR)]
#   swT / swR (recalc.):   1.0881 (similar variabilities of T and R)
#   sw-ratio (upper CL):   1.3282 (comparable variabilities of T and R)
#   Confidence interval: pass
#   Point estimate     : pass
#   Mixed (CI & PE)    : pass
# Same dataset. Show information about outliers and the ANOVA-table.
method.A(ola = TRUE, print = FALSE, verbose = TRUE, data = rds01)
# Generate the data.frame of results (full precision) and show it
# in the console
x <- method.A(ola = TRUE, details = TRUE, print = FALSE, data = rds01)
print(x, row.names = FALSE)
```

```
#
# Assess the Type I Error and iteratively adjust alpha if necessary.
# Not run: due to timing policy of CRAN for examples

method.A(adjust = TRUE, data = rds01)
# Should give in the result file:
#   Assessment of the empiric Type I Error (TIE); 1,000,000 studies simulated.
#     TIE not > nominal 0.05; consumer risk is controlled.
#
# Same with recalculation based on outliers, iteratively adjust alpha
# if necessary

method.A(ola = TRUE, adjust = TRUE, data = rds01)
# Should give in the result file:
#   Assessment of the empiric Type I Error (TIE) based on original CVwR;
#   1,000,000 studies simulated.
#     TIE not > nominal 0.05; consumer risk is controlled.
#   Assessment of the empiric Type I Error (TIE) based on recalculated CVwR;
#   1,000,000 studies in each of the 8 iterations simulated.
#     TIE for alpha 0.050000         : 0.07018
#     TIE for adjusted alpha 0.033416: 0.05000
#
# Repeat the evaluation with the adjusted alpha.

method.A(alpha = 0.033416, ola = TRUE, adjust = TRUE, data = rds01)
# Should give in the result file:
#   alpha              :   0.033416 (93.3168% CI)
#   Confidence interval: 106.16% ... 126.00%  pass
#   Point estimate     : 115.66%              pass
#   Mixed (CI & PE)    :                      pass
#   Assessment based on recalculated CVwR 32.16%
#   Confidence interval: pass
#   Point estimate     : pass
#   Mixed (CI & PE)    : pass
#   Assessment of the empiric Type I Error (TIE) based on original CVwR;
#   1,000,000 studies simulated.
#     TIE not > nominal 0.05; consumer risk is controlled.
#   Assessment of empiric Type I Error (TIE) based on recalculated CVwR;
#   1,000,000 studies in each of the 8 iterations simulated.
#     TIE for alpha 0.033416         : 0.05000
#     TIE not > nominal 0.05; consumer risk is controlled.
```

`method.B` *Comparative BA-calculation for Average Bioequivalence with Expanding Limits by the EMA's 'Method B'*

Description

This function performs the required calculations for the mixed (or aggregate) BE decision via Average Bioequivalence with Expanding Limits (ABEL) based on a linear mixed effects model with subjects as a random effect ('Method B') as specified in *Annex I.*

Usage

```
method.B(alpha = 0.05, path.in, path.out = tempdir(), file, set = "",
         ext, na = ".", sep = ",", dec = ".", logtrans = TRUE,
         regulator = "EMA", ola = FALSE, print = TRUE, details = FALSE,
         verbose = FALSE, ask = FALSE, plot.bxp = FALSE, fence = 2,
         data = NULL, option = 2)
```

Arguments

`alpha`	Type I Error (TIE) probability (nominal level of the test). Conventionally set to 0.05, resulting in a $100(1-2\,\alpha)$ confidence interval. If `regulator = "HC"` and `alpha = 0.5` only the point estimate will be assessed (for highly variable $C_{\max}$ within 80.0–125.0%).
`path.in`	Path to the data file for import.
`path.out`	Path to save the result file if `print = TRUE`. You must have write-permission to the folder. For simplicity your home folder `"~/"` can be used. If missing, R's standard temporary folder will be used. If a box plot of outliers should be saved (`plot.bxp = TRUE`), this path will be used as well.
`file`	Name of the dataset for import (*without* extension). Must be a string (*i.e.*, enclosed in single or double quotation marks).
`set`	Name of the sheet of an Excel-file (mandatory). Must be a string (*i.e.*, enclosed in single or double quotation marks).
`ext`	File-extension enclosed in single or double quotation marks. Acceptable are `"csv"` for character delimited variables (CSV) or `"xls"`, `"xlsx"` for Excel-files. The file-extension is not case-sensitive.
`na`	Character string denoting missing values. Acceptable are `"NA"` (not available), `"ND"` (not determined), `"."` (SAS), `"Missing"` (Phoenix WinNonlin), and `""` (EXCEL; empty cell). Missings will be converted to `NA` in the imported data. Defaults to `"."`.
`sep`	Variable separator in the CSV-file. Acceptable are `","` (comma = `ASCII 44`), `";"` (semicolon = `ASCII 59`), and `"\t"` (tabulator = `ASCII 9`). Defaults to `","`.
`dec`	Decimal separator in the CSV-file. Acceptable are `"."` (period = `ASCII 46`) or `","` (comma = `ASCII 44`). Defaults to `"."`.
`logtrans`	If `TRUE` (default) the raw data (provided in column `PK`) will be internally log-transformed and used in the calculations. If `FALSE` the already log-transformed data (provided in the column `logPK`) will be used in the calculations.
`regulator`	Set regulatory conditions. If `"EMA"` (default) conventional ABEL will be used. If `"HC"` Health Canada's upper cap of scaling (~57.4%) will be applied. If `"GCC"` direct widening to 75.00–133.33% will be used if `CVwR > 30%`.

`ola`	Defaults to `FALSE`. If `TRUE` an outlier analysis based on the studentized and standardized (aka internally studentized) residuals of the model estimating `CVwR` is performed.
`print`	If `TRUE` (default), the function prints its results to a file. If `FALSE`, returns a data frame of results.
`details`	Defaults to `FALSE`. If `TRUE`, the function sends its results in full precision to a data frame.
`verbose`	Defaults to `FALSE`. If `TRUE` the model-table is send to the console. If `ola = TRUE` additional information about outliers are shown.
`ask`	Defaults to `FALSE`. If `TRUE` the user will be asked whether an already existing result file (and if outliers are found, the box plot) should be overwritten.
`plot.bxp`	Only observed if `ola = TRUE` and at least one outlier is found. If `FALSE` (default) the box plot will be shown in the graphics device. If `TRUE` the box plot will be saved in PNG format to `path.out`.
`fence`	Only observed if `ola = TRUE`. The limit for outlier detection as a multiplier of the interquartile range. Defaults to 2. Less outliers will be detected with higher values (not recommended).
`data`	Specification of one of the internal reference datasets (`rds01` to `rds30`). If given, the arguments `path.in`, `file`, `set`, and `ext` are ignored. For its use see the examples. If not given, defaults to `NULL` (*i.e.*, import data from a file).
`option`	If `2` (default), the model will be evaluated by `lme()` of package `nlme`. The degrees of freedom of the treatment comparison will be equivalent to SAS' `DDFM=CONTAIN` and Phoenix WinNonlin's `Residual`. If `1` or `3`, the model will be evaluated by `lmer()` of package `lmerTest`. With `1` the degrees of freedom of the treatment comparison will be equivalent to SAS' `DDFM=SATTERTHWAITE` and Phoenix WinNonlin's `Satterthwaite`. `3` uses the Kenward-Roger approximation equivalent to Stata's `dfm=Kenward Roger (EIM)`. If `regulator = "HC"`, only `1` or `3` are supported.

Details

The model for the estimation of `CVwR` is

```
lm(log(PK) ~ sequence + subject %in% sequence + period,
data = data[data$treatment == "R", ])
```

where all effects are fixed.

The model for the treatment comparison is with `option = 2` (default)

```
lme(log(PK) ~ sequence +  period + treatment, random = ~1|subject,
data = data)
```

and with `option = 1`, `option = 3`

```
lmer(log(PK) ~ sequence + period + treatment + (1|subject),
data = data)
```

where *sequence*, *period*, and *treatment* are fixed effects and *subject(sequence)* is a random effect.

Tested designs

- 4-period 2-sequence full replicates
  `TRTR | RTRT`
  `TRRT | RTTR`
  `TTRR | RRTT`
- 2-period 4-sequence replicate
  `TR | RT | TT | RR` (Balaam's design)
- 4-period 4-sequence full replicates
  `TRTR | RTRT | TRRT | RTTR`
  `TRRT | RTTR | TTRR | RRTT`
- 3-period 2-sequence full replicates
  `TRT | RTR`
  `TRR | RTT`
- 3-period (partial) replicates
  `TRR | RTR | RRT`
  `TRR | RTR` (extra-reference design)

Data structure

- Columns must have the headers `subject`, `period`, `sequence`, `treatment`, `PK`, and/or `logPK`.
  Any order of columns is acceptable.
  Uppercase and mixed case headers will be internally converted to lowercase headers.
  - `subject` must be integer numbers or (any combination of) alphanumerics `[A-Z, a-z, -, _, #, 0-9]`
  - `period` must be integer numbers.
  - `sequence` must be contained in the tested designs (numbers or *e.g.*, `ABAB` are not acceptable).
  - The Test treatment must be coded `T` and the Reference `R`.

Value

Prints results to a file if argument `print = TRUE` (default).
If argument `print = FALSE`, returns a data.frame with the elements:

`Design`	*e.g.*, TRTR|RTRT
`Method`	B-`option` (`1`, `2`, or `3`)
`n`	total number of subjects
`nTT`	number of subjects with two treatments of `T` (full replicates only)
`nRR`	number of subjects with two treatments of `R`
`Sub/seq`	number of subjects per sequence
`Miss/seq`	if the design is unbalanced, number of missings per sequence
`Miss/per`	if the design is incomplete, number of missings per period
`alpha`	nominal level of the test
`DF`	degrees of freedom of the treatment comparison
`CVwT(%)`	intra-subject coefficient of variation of the test treatment (full replicates only)
`CVwR(%)`	intra-subject coefficient of variation of the reference treatment
`swT`	intra-subject standard deviation of the test treatment (full replicates only)

`swR`	intra-subject standard deviation of the reference treatment
`sw.ratio`	ratio of intra-subject deviations of `T` and `R` (full replicates only)
`sw.ratio.CL`	upper confidence limit of `sw.ratio` (full replicates only)

- If reference-scaling is applicable (*i.e.*, `CVwR(%)` >30):

`L(%)`	lower expanded limit of the acceptance range (AR)
`U(%)`	upper expanded limit of the acceptance range (AR)

- If reference-scaling is not applicable (*i.e.*, ≤30):

`BE.lo(%)`	lower limit of the conventional AR (` 80`)
`BE.hi(%)`	upper limit of the conventional AR (`125`)

`CL.lo(%)`	lower confidence limit of the treatment comparison
`CL.hi(%)`	upper confidence limit of the treatment comparison
`PE(%)`	point estimate of the treatment comparison (aka GMR)
`CI`	assessment whether the $100(1-2\,\alpha)$ CI lies entirely within the acceptance range (`pass|fail`)
`GMR`	assessment whether the PE lies entirely within the GMR-restriction 80.00–125.00% (`pass|fail`)
`BE`	mixed (aggregate) assessment whether the study demonstrates bioequivalence (`pass|fail`)
`log.half-width`	half-width of the confidence interval in log-scale

If `ola = TRUE` and at least one studentized outlier was detected:

`outlier`	outlying subject(s)
`CVwR.rec(%)`	intra-subject coefficient of variation of `R`; recalculated after exclusion of outlier(s)
`swR.rec`	intra-subject standard deviation of the reference treatment after exclusion of outlier(s)
`sw.ratio.rec`	ratio of intra-subjectstandard deviations of `T` and `R` after exclusion of outlier(s); full replicates
`sw.ratio.rec.CL`	upper confidence limit of `sw.ratio.rec` (full replicates only)

- If reference-scaling is applicable (*i.e.*, `CVwR.rec(%)` >30):

`L.rec(%)`	recalculated lower expanded limit of the AR
`U.rec(%)`	recalculated upper expanded limit of the AR

- If reference-scaling is not applicable (*i.e.*, `CVwR.rec(%)` ≤30):

`BE.rec.lo(%)`	lower limit of the conventional AR (` 80`)
`BE.rec.hi(%)`	upper limit of the conventional AR (`125`)

`GMR.rec`	assessment whether the PE lies entirely within the GMR-restriction 80.00–125.00% (`pass|fail`)
`BE.rec`	mixed (aggregate) assessment whether the study demonstrates bioequivalence (`pass|fail`)

Warning

Files may contain a commentary header. If reading from a CSV-file, *each* line of the commentary header *must* start with `"# "` (hashmark space = `ASCII 35 ASCII 32`). If reading from an Excel-file all lines preceding the column headers are treated as a comment.

Clarification

The ‘ASCII line chart’ in the result file gives the confidence limits with filled black squares and the point estimate as a white rhombus . If a confidence limit exceeds the maximum possible expansion limit, it is shown as a triangle or . Expanded limits are given as double vertical lines . Unscaled limits, the GMR restriction, and 100% are given with single vertical lines . The ‘resolution’ is approximatelly 0.5% and therefore, not all symbols might be shown. The CI and PE take presedence over the limits and the expanded limits over unscaled ones.

Disclaimer

Program offered for Use without any Guarantees and Absolutely No Warranty. No Liability is accepted for any Loss and Risk to Public Health Resulting from Use of this R-Code.

Note

The EMA’s model specified as ‘Method B’ in *Annex I* assumes equal [*sic*] intra-subject variances of test and reference (like in $2 \times 2 \times 2$ trials) – even if proven false in one of the full replicate designs (were *both* CV_{wT} and CV_{wR} can be estimated). Hence, amongst biostatisticians it is called the “crippled model” because the replicative nature of the study is ignored.
The method for calculating the degrees of freedom is not specified in the SAS code provided by the EMA in *Annex I.* Hence, the default in `PROC MIXED`, namely `DDFM=CONTAIN` is applied. For incomplete data (*i.e.*, missing periods) Satterthwaite’s approximation of the degrees of freedom (`option = 1`) or Kenward-Roger (`option = 3`) might be better choices – if stated as such in the statistical analysis plan.
The half-width of the confidence interval in log-scale allows a comparison of methods (B *v.s.* A) or options (2 *v.s.* 1). A higher value *might* point towards a more conservative decision. Quoting the Q&A-document:
A simple linear mixed model, which assumes identical within-subject variability (Method B), may be acceptable as long as results obtained with the two methods do not lead to different regulatory decisions. However, in borderline cases [...] additional analysis using Method A might be required.
In the provided reference datasets – with one exception – the conclusion of BE (based on the mixed CI and GMR criteria) agrees between ‘Method A’ and ‘Method B’. However, for the highly incomplete dataset 14 ‘Method A’ was *liberal* (passing by ANOVA but failing by the mixed effects model).

Reference-scaling is acceptable for C_{max} (immediate release products) and $C_{\text{max,ss}}$, $C_{\tau,ss}$, and ${}_{\text{partial}}AUC$ (modified release products). However, quoting the BE guideline:
The applicant should justify that the calculated intra-subject variability is a reliable estimate and that it is not the result of outliers.
Quoting the Q&A on the Revised EMA Bioequivalence Guideline:
...a study could be acceptable if the bioequivalence requirements are met both including the outlier subject (using the scaled average bioequivalence approach and the within-subject CV with this subject) and after exclusion of the outlier (using the within-subject CV without this subject).
An outlier test is not an expectation of the medicines agencies but outliers could be shown

by a box plot. This would allow the medicines agencies to compare the data between them.

The EMA's method of reference-scaling for highly variable drugs / drug products is currently recommended in other jurisdictions as well (*e.g.*, the WHO; ASEAN States, Australia, Belarus, Brazil, Chile, Egypt, the Eurasian Economic Union, the East African Community, New Zealand, the Russian Federation).

Health Canada's variant of ABEL (upper cap of scaling ~57.4% limiting the expansion at 67.7–150.0%) is only approximate because a mixed-effects model would be required.

In a pilot phase the WHO accepted reference-scaling for *AUC* (4-period full replicate studies are mandatory in order to assess the variability associated with each product). It was an open issue how this assessment should be done. In Population Bioequivalence (PBE) and Individual Bioequivalence (IBE) the $s_{\mathrm{wT}}/s_{\mathrm{wR}}$ ratio was assessed and similar variability was concluded for a ratio within 0.667–1.500. However, the power of comparing variabilities in a study designed to demonstrate ABE is low. This was one of the reasons why PBE and IBE were not implemented in regulatory practice. An alternative approach is given in the FDA's draft ANDA guidance. Variabilities are considered comparable if the upper confidence limit of $\sigma_{\mathrm{wT}}/\sigma_{\mathrm{wR}}$ is less than or equal to 2.5.
In 2021 the requirement of comparing variabilities was lifted by the WHO.

Author(s)

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See Also

`method.A`	evaluation by a fixed effects model (ANOVA)
`ABE`	evaluation for conventional (unscaled) Average Bioequivalence

Examples

```
# Importing from a CSV-file, using most of the defaults: variable
# separator colon, decimal separator period, no outlier-analyis,
# print to file.
# Note: You must adapt the path-variables. The example reads from
# the data provided by the library. Write-permissions must be granted
# for 'path.out' in order to save the result file. Here the default
# (R's temporary folder) is used. If you don't know where it is,
# type tempdir() in the console.
path.in <- paste0(find.package("replicateBE"), "/extdata/")
method.B(path.in = path.in, file = "DS", set = "01", ext = "csv")
# Should result in:
#   CVwT               :  35.16%
#   swT                :   0.34138
#   CVwR               :  46.96% (reference-scaling applicable)
#   swR                :   0.44645
#   Expanded limits    :  71.23% ... 140.40% [100exp(±0.760·swR)]
#   swT / swR          :   0.7647 (similar variabilities of T and R)
#   sw-ratio (upper CL):   0.9324 (comparable variabilities of T and R)
#   Confidence interval: 107.17% ... 124.97%  pass
#   Point estimate     : 115.73%              pass
#   Mixed (CI & PE)    :                      pass
#
# Internal reference dataset 01 used and results to R's temporary
# folder. Additional outlier-analyis and box plot saved as PNG.
method.B(ola = TRUE, plot.bxp = TRUE, data = rds01)
# Should give the same as above. Additionally:
#   Recalculation due to presence of 2 outliers (subj. 45|52)
#   CVwR (outl. excl.) :  32.16% (reference-scaling applicable)
#   swR  (recalc.)     :   0.31374
#   Expanded limits    :  78.79% ... 126.93% [100exp(±0.760·swR)]
#   swT / swR (recalc.):   1.0881 (similar variabilities of T and R)
```

```
#   sw-ratio (upper CL):   1.3282 (comparable variabilities of T and R)
#   Confidence interval: pass
#   Point estimate     : pass
#   Mixed (CI & PE)    : pass
#
# Same dataset. Show information about outliers and the model-table.
method.B(ola = TRUE, print = FALSE, verbose = TRUE, data = rds01)
# data.frame of results (full precision) shown in the console.
x <- method.B(ola = TRUE, print = FALSE, details = TRUE, data = rds01)
print(x, row.names = FALSE)
# Compare Method B with Method A for all reference datasets.

ds <- substr(grep("rds", unname(unlist(data(package = "replicateBE"))),
                  value = TRUE), start = 1, stop = 5)
for (i in seq_along(ds)) {
  A <- method.A(print=FALSE, details=TRUE, data=eval(parse(text=ds[i])))$BE
  B <- method.B(print=FALSE, details=TRUE, data=eval(parse(text=ds[i])))$BE
  r <- paste0("A ", A, ", B ", B, " - ")
  cat(paste0(ds[i], ":"), r)
  if (A == B) {
    cat("Methods A and B agree.\n")
  } else {
    if (A == "fail" & B == "pass") {
      cat("Method A is conservative.\n")
    } else {
      cat("Method B is conservative.\n")
    }
  }
}
# should give
#   rds01: A pass, B pass - Methods A and B agree.
#   ...
#   rds14: A pass, B fail - Method B is conservative.
#   ...

# Health Canada: Only the PE of Cmax has to lie within 80.0-125.0%
# (i.e., no CI is required). With alpha = 0.5 the CI is practically
# supressed (zero width) and ignored in the assessment.
x    <- method.B(alpha = 0.5, regulator = "HC", option = 1,
                 data = rds03, print = FALSE, details = TRUE)[19:20]
x[1] <- round(x[1], 1) # only one decimal place for HC
print(x, row.names = FALSE)
# Should result in:
# PE(%)  GMR
# 124.5 pass
```

`refdata` *Reference Datasets*

Description

Datasets of replicate designs from the public domain, edited, or obtained by simulations to be evaluated by `method.A()`, `method.B()`, or `ABE()`.

Details

Design	Specification	Dataset	N	CV_{wR} (%)	Evaluation
TRTR|RTRT	full	`rds01`	77	>30	`method.A()`, `method.B()`
TRTR|RTRT	full	`rds06`	77	>30	`method.A()`, `method.B()`
TRTR|RTRT	full	`rds12`	77	>30	`method.A()`, `method.B()`
TRTR|RTRT	full	`rds14`	77	>30	`method.A()`, `method.B()`
TRTR|RTRT	full	`rds18`	77	>30	`method.A()`, `method.B()`
TRTR|RTRT	full	`rds21`	77	>30	`method.A()`, `method.B()`
TRTR|RTRT	full	`rds19`	61	>30	`method.A()`, `method.B()`
TRTR|RTRT	full	`rds20`	61	>30	`method.A()`, `method.B()`
TRTR|RTRT	full	`rds08`	222	>30	`method.A()`, `method.B()`
TRTR|RTRT	full	`rds09`	222	>30	`method.A()`, `method.B()`
TRTR|RTRT	full	`rds13`	222	>30	`method.A()`, `method.B()`
TRTR|RTRT	full	`rds15`	222	>30	`method.A()`, `method.B()`
TRTR|RTRT	full	`rds25`	70	>30	`method.A()`, `method.B()`
TRTR|RTRT	full	`rds29`	12	<30	`method.A()`, `method.B()`, `ABE()`
TRRT|RTTR	full	`rds26`	54	>30	`method.A()`, `method.B()`
TRRT|RTTR	full	`rds05`	26	<30	`method.A()`, `method.B()`, `ABE()`
TRRT|RTTR	full	`rds11`	37	>30	`method.A()`, `method.B()`
TRRT|RTTR	full	`rds16`	38	>30	`method.A()`, `method.B()`
TTRR|RRTT	full	`rds28`	64	<30	`method.A()`, `method.B()`, `ABE()`
TRTR|RTRT|TRRT|RTTR	full	`rds23`	22	>30	`method.A()`, `method.B()`
TRRT|RTTR|TTRR|RRTT	full	`rds24`	39	>30	`method.A()`, `method.B()`
TRT|RTR	full	`rds03`	77	>30	`method.A()`, `method.B()`
TRT|RTR	full	`rds17`	19	>30	`method.A()`, `method.B()`
TRR|RTT	full	`rds10`	18	<30	`method.A()`, `method.B()`, `ABE()`
TR|RT|TT|RR	Balaam's	`rds27`	312	>30	`method.A()`, `method.B()`
TRR|RTR|RRT	partial	`rds02`	24	<30	`method.A()`, `method.B()`, `ABE()`
TRR|RTR|RRT	partial	`rds04`	51	>30	`method.A()`, `method.B()`
TRR|RTR|RRT	partial	`rds07`	360	>30	`method.A()`, `method.B()`
TRR|RTR|RRT	partial	`rds30`	14	<30	`method.A()`, `method.B()`, `ABE()`
TRR|RTR	partial	`rds22`	36	>30	`method.A()`, `method.B()`

In full replicate designs *both* R and T are administered twice (in 3-period designs to ½ of the subjects).
Balaam's design is a mixture of a conventional crossover (½ of the subjects) and a replicate design (¼ of the subjects receive *either* R *or* T twice).
In partial replicate designs *only* R is administered twice.

Author(s)

Helmut Schütz (R-code for simulations by Detlew Labes), Michael Tomashevskiy (simulations in Phoenix NLME)

Source

Dataset	Origin	Description
`rds01`	EMA	Data set in Annex II
`rds06`	`rds01` edited	T and R switched
`rds12`	Phoenix NLME	Simulated with extreme variability
`rds14`	Phoenix NLME	Simulated with high variability and number of dropouts increasing with period
`rds18`	`rds14` edited	Removed T data of subjects 63–78
`rds21`	`rds01` edited	One extreme result of subjects 45 & 52 set to NA
`rds19`	`rds18` edited	Removed data of subjects 63–78
`rds20`	`rds19` edited	Outlier of R (subject 1) introduced: original value ×100
`rds08`	R	Simulated with slight heteroscedasticity
`rds09`	`rds08`	Wide numeric range (data of last 37 subjects multiplied by 1,000,000)
`rds13`	`rds08` edited	Highly incomplete (approx. 50% of period 4 data deleted)
`rds15`	`rds08` edited	Highly incomplete (approx. 50% of period 4 data coded as missing `'NA'`)
`rds25`	R	Simulated with heteroscedasticity
`rds29`	R	Simulated with heteroscedasticity; imbalanced and incomplete
`rds26`	Patterson & Jones 2016	C_{max} data given in Tables 4.30 & 4.31
`rds05`	Shumaker & Metzler	C_{max} data given in the Appendix
`rds11`	Hauschke *et al.*	C_{max} data given in Table 9.6.
`rds16`	FDA, CDER	C_{max} data of Drug 14a
`rds28`	R	Simulated with homoscedasticity
`rds23`	FDA, CDER	C_{max} data of Drug
`rds24`	FDA, CDER	C_{max} data of Drug 1
`rds03`	`rds01` edited	Period 4 removed
`rds17`	`rds03` edited	Highly unbalanced (twelve subjects in RTR and seven in TRT)
`rds10`	Chow & Liu	AUC data given in Table 9.3.3.
`rds27`	R	Simulated with homoscedasticity
`rds02`	EMA	Data set in Annex III
`rds04`	Patterson & Jones 2012	C_{max} data of Table II
`rds07`	R	Simulated with homoscedasticity
`rds30`	R	Simulated with heteroscedasticity; imbalanced and incomplete
`rds22`	R	Simulated with homoscedasticity

References

European Medicines Agency. London, 21 September 2016. *Annex II*, *Annex III*.

Patterson SD, Jones B. *Viewpoint: observations on scaled average bioequivalence.* Pharm Stat. 2012; 11(1): 1–7. doi:10.1002/pst.498

Shumaker RC, Metzler CM. *The Phenytoin Trial is a Case Study of 'Individual' Bioequivalence.* Drug Inf J. 1998; 32(4): 1063–72. doi:10.1177/009286159803200426

Chow SC, Liu JP. *Design and Analysis of Bioavailability and Bioequivalence Studies.* Boca Raton: CRC Press; 3^{rd} edition 2009. p275.

Hauschke D, Steinijans VW, Pigeot I. *Bioequivalence Studies in Drug Development.* Chichester: John Wiley; 2007. p216.

Patterson SD, Jones B. *Bioequivalence and Statistics in Clinical Pharmacology.* Boca Raton: CRC Press; 2nd edition 2016. p105–6.

U.S. Food and Drug Administration, Center for Drug Evaluation and Research. *Bioequivalence Studies.* Rockville, 1997. bioequivalence study files (archived 2017-07-23)

See Also

4-period full replicates
TRTR.RTRT, TRRT.RTTR, TTRR.RRTT, TRTR.RTRT.TRRT.RTTR, TRRT.RTTR.TTRR.RRTT
2-period replicate (Balaam's design)
TR.RT.TT.RR
3-period full replicates
TRT.RTR, TRR.RTT
3-period partial replicates
TRR.RTR.RRT, TRR.RTR

Examples

```
# show structure of all data sets
ds <- substr(grep("rds", unname(unlist(data(package = "replicateBE"))),
                  value = TRUE), start = 1, stop = 5)
for (i in seq_along(ds)) {
  cat(ds[i], "\n")
  str(eval(parse(text = ds[i])))
}
```

`TR.RT.TT.RR` *Reference Dataset for TR|RT|TT|RR Replicate Designs*

Description

Dataset for Balaam's design obtained by simulations to be evaluated by `method.A()`, `method.B()`.

Usage

`rds27`

Format

- **Reference Dataset 27** (`rds27`)
  312 subjects. Balanced (78 subjects in each of the four sequences) and incomplete (T of subject 111 missing in period 2 of sequence RT). No outliers.
  A data frame with 624 observations on the following 5 variables:

`subject`	a factor with 312 levels: 1, 2, ..., 18
`period`	a factor with 2 levels: 1, 2
`sequence`	a factor with 4 levels: TR, RT, TT, RR

`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling

rds27

Details

Dataset	N	CV_{wR} (%)	Evaluation
`rds27`	312	>30	`method.A()`, `method.B()`

Note

In software sequences and treatments are ranked in lexical order. Hence, executing `str()` or `summary()` will show `sequence` as `"RR"`, `"RT"`, `"TR"`, `"TT"` and `treatment` as `"R"`, `"T"`. In BE – by convention – sequences are ordered with `T` first. The package follows this convention.

Author(s)

Helmut Schütz (R-code for simulations by Detlew Labes)

Source

Dataset	Origin	Description
`rds27`	R	Simulated with $CV_{\text{wT}} = CV_{\text{wR}} = 35\%$, $CV_{\text{bR}} = CV_{\text{bR}} = 75\%$, GMR 0.90.

Examples

```
str(rds27)
row <- c(1:2, 157:158, 313:314, 469:470)
rds27[row, ]
summary(rds27[2:5])
```

`TRR.RTR` *Reference Dataset for TRR|RTR (extra-reference) Designs*

Description

Dataset simulated to be evaluated by `method.A()`, `method.B()`.

Usage

```
rds22
```

Format

- **Reference dataset 22**
  Simulated with $CV_{\text{wT}} = CV_{\text{wR}} = 45\%$, $CV_{\text{bT}} = CV_{\text{bR}} = 100\%$ GMR 0.90. 42 subjects. Balanced (21 subjects in each of the sequences) and complete (no missing data). No outliers.
  A data frame with 126 observations on the following 5 variables:

`subject`	a factor with 42 levels: 1, 2, …, 42
`period`	a factor with 3 levels: 1, 2, 3
`sequence`	a factor with 2 levels: TRR, RTR
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling
`logPK`	a numeric vector of the natural logarithms of `PK`

rds22

Details

Dataset	N	C_{wR} (%)	Evaluation
`rds22`	42	>30	`method.A()`, `method.B()`

Note

In software sequences and treatments are ranked in lexical order. Hence, executing `str()` or `summary()` will show `sequence` as `"RTR", "TRR"` and `treatment` as `"R", "T"`. In BE – by convention – sequences are ordered with `T` first. The package follows this convention.
This partial replicate design is also known as the 'extra-reference design'. Since the Test is not administered in all periods, lacking period effects must be assumed. In the presence of *true* period effects the treatment comparison will be biased. Hence, this design is not recommended.

Author(s)

Helmut Schütz (R-code for simulations by Detlew Labes)

Source

Dataset	Origin	Description
`rds22`	R	Simulated with homoscedasticity.

Examples

```
str(rds22)
rds22[61:66, ]
summary(rds22[2:5])
```

`TRR.RTR.RRT` *Reference Datasets for TRR|RTR|RRT (partial) Replicate Designs*

Description

Datasets from the public domain or simulated to be evaluated by `method.A()`, `method.B()`, or `ABE()`.

Format

- **Reference Dataset 02**
  24 subjects.
  Balanced (eight subjects in each of the three sequences) and complete (no missing data). No outliers.
  A data frame with 72 observations on the following 6 variables:

`subject`	a factor with 24 levels: 1, 2, …, 24
`period`	a factor with 3 levels: 1, 2, 3
`sequence`	a factor with 3 levels: TRR, RTR, RRT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling
`logPK`	a numeric vector of the natural logarithms of `PK`

rds02 In the source evaluated by SAS v9.1 (Proc GLM) for ABEL. Reported results:

`CVwR`	11.2%
`PE`	102.26% (Method A and B)
`90% CI`	97.32% – 107.46% (Method A and B)

- **Reference Dataset 04**
  Data set of Table II given by Patterson & Jones. 51 subjects.
  Balanced (17 subjects in each of the three sequences) and complete. No outliers.
  A data frame with 153 observations on the following 5 variables:

`subject`	a factor with 51 levels: 1, 2, …, 56
`period`	a factor with 3 levels: 1, 2, 3
`sequence`	a factor with 3 levels: TRR, RTR, RRT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses (here C_{max})

rds04 In the source evaluated by SAS (Proc MIXED) with the FDA's mixed effects model (termed 'Method C' by the EMA; not compatible with the guideline). Reported results:

`CVwR`	61%

`PE`	137%
`90% CI`	119% – 159%

- **Reference Dataset 07**
  Simulated with $CV_{\text{wT}} = CV_{\text{wR}} = 35\%$, GMR 0.90. 360 subjects.
  Balanced (120 subjects in each of the three sequences) and complete. No outliers.
  A data frame with 1,080 observations on the following 5 variables:

`subject`	a factor with 360 levels: 1, 2, …, 360
`period`	a factor with 3 levels: 1, 2, 3
`sequence`	a factor with 3 levels: TRR, RTR, RRT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling

rds07

- **Reference Dataset 30**
  Simulated with heteroscedasticity ($CV_{\text{wT}} = 14\%$, $CV_{\text{wR}} = 28\%$, $CV_{\text{bT}} = 28\%$, $CV_{\text{bR}} = 56\%$), GMR = 0.90. 12 subjects. 14 subjects.
  Imbalanced (six subjects in sequence TRR, five in RTR, and three RRT) and incomplete (two missings in sequences TRR and RTR and three in sequence RRT). Missings / period: 0/1, 0/2, 7/3. No outliers.
  A data frame with 35 observations on the following 5 variables:

`subject`	a factor with 14 levels: 1, 2, …, 39
`period`	a factor with 3 levels: 1, 2, 3
`sequence`	a factor with 3 levels: TRR, RTR, RRT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling

rds30

Details

Dataset	N	CV_{wR} (%)	Evaluation
`rds02`	24	<30	`method.A()`, `method.B()`, `ABE()`
`rds04`	51	>30	`method.A()`, `method.B()`
`rds07`	360	>30	`method.A()`, `method.B()`
`rds30`	14	<30	`method.A()`, `method.B()`, `ABE()`

Note

In software sequences and treatments are ranked in lexical order. Hence, executing `str()` or `summary()` will show `sequence` as `"RRT", "RTR", "TRR"` and `treatment` as `"R", "T"`. In BE – by convention – sequences are ordered with `T` first. The package follows this convention.

Author(s)

Helmut Schütz (R-code for simulations by Detlew Labes)

Source

Dataset	Origin	Description
`rds02`	EMA	Annex III.
`rds04`	Patterson & Jones	C_{max} data of Table II.
`rds07`	R	Large simulated data set with homoscedasticity.
`rds30`	R	Simulated with heteroscedasticity; imbalanced and incomplete.

References

European Medicines Agency. London, 21 September 2016. *Annex I*, *Annex III*.

Patterson SD, Jones B. *Viewpoint: observations on scaled average bioequivalence.* Pharm Stat. 2012; 11(1): 1–7. doi:10.1002/pst.498

Examples

```
str(rds02)
row <- c(10:12, 1:3, 16:18)
rds02[row, ]
summary(rds02[2:6])
```

`TRR.RTT` *Reference Dataset for TRR|RTT Replicate Designs*

Description

Dataset from the public domain to be evaluated by `method.A()`, `method.B()`, or `ABE()`.

Usage

```
rds10
```

Format

- **Reference Dataset 10**
  18 subjects.
  Balanced (nine subjects in both sequences) and complete. No outliers.
  A data frame with 54 observations on the following 5 variables:

`subject`	a factor with 18 levels: 1, 2, …, 18
`period`	a factor with 3 levels: 1, 2, 3
`sequence`	a factor with 2 levels: TRR, RTT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses (here AUC)

rds10

Details

Dataset	N	CV_{wR} (%)	Evaluation
`rds10`	36	<30	`method.A()`, `method.B()`, `ABE()`

Note

In software sequences and treatments are ranked in lexical order. Hence, executing `str()` or `summary()` will show `sequence` as `"RTT", "TRR"` and `treatment` as `"R", "T"`. In BE – by convention – sequences are ordered with `T` first. The package follows this convention. In analogy to the EMA's Q&A: Uncertain estimate of `CVwR` since less than twelve subjects in sequence TRR.

Source

Dataset	Origin	Description
`rds10`	Chow & Liu	AUC data given in Table 9.3.3.

References

Chow SC, Liu JP. *Design and Analysis of Bioavailability and Bioequivalence Studies.* Boca Raton: CRC Press; 3^{rd} edition 2009. p275.

Examples

```
str(rds10)
row <- c(1:3, 28:30)
rds10[row, ]
summary(rds10[2:5])
```

`TRRT.RTTR` *Reference Datasets for TRRT/RTTR Replicate Designs*

Description

Datasets from the public domain to be evaluated by `method.A()`, `method.B()`, or `ABE()`.

Format

- **Reference Dataset 05**
  26 subjects.
  Balanced (13 subjects in both sequences) and complete. No outliers.
  A data frame with 104 observations on the following 5 variables:

`subject`	a factor with 26 levels: 1, 2, …, 26
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 2 levels: TRRT, RTTR
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses (here $C_{\max}$)

  rds05 In the source evaluated by SAS (Prox MIXED) with the FDA's mixed effects model (termed 'Method C' by the EMA; not compatible with the guideline). Reported results:

`CVwR`	5.47%
`CVwT`	6.75%
`PE`	107.90%
`90% CI`	103.66% – 112.2%

- **Reference Dataset 11**
  37 subjects.
  Unbalanced (18 subjects in sequence TRRT and 19 subjects in RTTR) and complete. No outliers.
  A data frame with 148 observations on the following 5 variables

`subject`	a factor with 37 levels: 1, 2, …, 37
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 2 levels: TRRT, RTTR
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses (here $C_{\max}$)

  rds11 In the source evaluated by SAS (Proc MIXED) with the FDA's mixed effects model (termed 'Method C' by the EMA; not compatible with the guideline). Reported results:

`PE`	90.0%

`90% CI` 79.6% – 101.7%

- **Reference Dataset 16**
  38 subjects.
  Unbalanced (18 subjects in sequence TRRT and 20 in RTTR) and complete. No outliers.
  A data frame with 152 observations on the following 5 variables:

`subject`	a factor with 38 levels: 1, 2, …, 38
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 2 levels: TRRT, RTTR
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses (here $C_{\max}$)

  rds16

Details

Dataset	N	CV_{wR} (%)	Evaluation
`rds05`	26	<30	`method.A()`, `method.B()`, `ABE()`
`rds11`	37	>30	`method.A()`, `method.B()`
`rds16`	38	>30	`method.A()`, `method.B()`

Note

In software sequences and treatments are ranked in lexical order. Hence, executing `str()` or `summary()` will show `sequence` as `"RTTR", "TRRT"` and `treatment` as `"R", "T"`. In BE – by convention – sequences are ordered with `T` first. The package follows this convention.

Source

Dataset	Origin	Description
`rds05`	Shumaker & Metzler	$C_{\max}$ data given in the Appendix.
`rds11`	Hauschke *et al.*	$C_{\max}$ data given in Table 9.6.
`rds16`	FDA, CDER	$C_{\max}$ data of Drug 14a.

References

Shumaker RC, Metzler CM. *The Phenytoin Trial is a Case Study of 'Individual' Bioequivalence.* Drug Inf J. 1998; 32(4): 1063–72. doi:10.1177/009286159803200426

Hauschke D, Steinijans VW, Pigeot I. *Bioequivalence Studies in Drug Development.* Chichester: John Wiley; 2007. p216.

U.S. Food and Drug Administration, Center for Drug Evaluation and Research. *Bioequivalence Studies.* Rockville, 1997. bioequivalence study files (archived 2017-07-23)

Examples

```
str(rds05)
summary(rds05[2:5])
head(rds11, 8)
```

`TRRT.RTTR.TTRR.RRTT` *Reference Dataset for TRRT|RTTR|TTRR|RRTT Designs*

Description

Dataset from the public domain to be evaluated by `method.A()` and/or `method.B()`.

Format

- **Reference Dataset 24**
  40 subjects (one completely missing).
  Unbalanced (nine subjects in sequence TRRT and ten in each of the other three) and complete. Two outliers (subject 3 in sequence RTTR and subject 30 in sequence TTRR).
  A data frame with 160 observations on the following 5 variables:

`subject`	a factor with 40 levels: 1, 2, ..., 932
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 4 levels: TRRT, RTTR, TTRR, RRTT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling (here $C_{\max}$)

rds24

Details

Dataset	N	CV_{wR} (%)	Evaluation
`rds24`	39	>30	`method.A()`, `method.B()`

Note

In software sequences and treatments are ranked in lexical order. Hence, executing `str()` or `summary()` will show `sequence` as `"RRTT", "RTTR", "TRRT", "TTRR"` and `treatment` as `"R", "T"`. In BE – by convention – sequences are ordered with `T` first. The package follows this convention.

Source

Dataset	Origin	Description
`rds24`	FDA, CDER	$C_{\max}$ data of Drug 1.

References

U.S. Food and Drug Administration, Center for Drug Evaluation and Research. *Bioequivalence Studies.* Rockville, 1997. bioequivalence study files (archived 2017-07-23)

Examples

```
str(rds24)
row <- c(13:16, 9:12, 1:4, 5:8)
rds24[row, ]
summary(rds24[2:5])
```

`TRT.RTR` *Reference Datasets for TRT|RTR Replicate Designs*

Description

Datasets from the public domain and edited to be evaluated by `method.A()` and/or `method.B()`.

Format

- **Reference dataset 03**
  Based on `rds01`. Removed all data of period 4. 77 subjects.
  Unbalanced (39 subjects in sequence TRT and 38 in RTR) and incomplete (six missings in sequence TRT and two in RTR). Missings / period: 0/1, 1/2, 7/3. Two outliers (subjects 45 and 52) in sequence RTR.
  A data frame with 223 observations on the following 6 variables:

`subject`	a factor with 77 levels: 1, 2, …, 78
`period`	a factor with 3 levels: 1, 2, 3
`sequence`	a factor with 2 levels: TRT, RTR
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling

  rds03

- **Reference dataset 17**
  Based on `rds03`. 19 subjects.
  Unbalanced (seven subjects in sequence TRT and twelve in RTR) and incomplete (one missing in sequence TRT). Missings / period: 0/1, 0/2, 1/3. One outlier (subject 18) in sequence RTR.
  A data frame with 56 observations on the following 6 variables:

`subject`	a factor with 19 levels: 1, 2, …, 22
`period`	a factor with 3 levels: 1, 2, 3
`sequence`	a factor with 2 levels: TRT, RTR
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling

rds17

Details

Dataset	N	CV_{wR} (%)	Evaluation
`rds03`	77	>30	`method.A()`, `method.B()`
`rds17`	19	>30	`method.A()`, `method.B()`

Note

In software sequences and treatments are ranked in lexical order. Hence, executing `str()` or `summary()` will show `sequence` as `"RTR", "TRT"` and `treatment` as `"R", "T"`. In BE – by convention – sequences are ordered with `T` first. The package follows this convention.

Author(s)

Helmut Schütz

Source

Dataset	Origin	Description
`rds03`	`rds01` edited	Period 4 removed.
`rds17`	`rds03` edited	Highly unbalanced (seven subjects in TRT and twelve in RTR).

Examples

```
head(rds03, 6)
summary(rds03[2:5])
```

`TRTR.RTRT` *Reference Datasets for TRTR|RTRT Designs*

Description

Datasets from the public domain, edited, or obtained by simulations to be evaluated by `method.A()` and/or `method.B()`.

Format

- **Reference dataset 01**
  77 subjects.
  Unbalanced (39 subjects in sequence TRTR and 38 in RTRT) and incomplete (seven missings in sequence TRTR and three in sequence RTRT). Missings / period: 0/1, 1/2, 7/3, 2/4. Two outliers (subjects 45 and 52) in sequence RTRT.
  A data frame with 298 observations on the following 6 variables:

`subject`	a factor with 77 levels: 1, 2, …, 78
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 2 levels: TRTR, RTRT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling
`logPK`	a numeric vector of the natural logarithms of `PK`

rds01 In the source evaluated by SAS (Proc GLM) v9.1 for ABEL. Reported results:

`CVwR`	47.0%
`PE`	115.66% (Method A)
	115.73% (Method B)
`90% CI`	107.11% – 124.89% (Method A)
	107.17% – 124.97% (Method B)

- **Reference dataset 06**
  Based on `rds01`. 77 subjects. Responses of T and R switched.
  Unbalanced (39 subjects in sequence TRTR and 38 in RTRT) and incomplete (seven missings in sequence TRTR and three in sequence RTRT). Missings / period: 0/1, 1/2, 7/3, 2/4. No outliers.
  A data frame with 298 observations on the following 6 variables:

`subject`	a factor with 77 levels: 1, 2, …, 78
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 2 levels: TRTR, RTRT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling

rds06

- **Reference dataset 08**
  Simulated with slight heteroscedasticity (CV_{wT} = 70%, CV_{wR} = 80%), CV_{bT} = CV_{bR} = 150%, GMR = 0.85. 222 subjects.
  Balanced (222 subjects in both sequences) and complete. No outliers.
  The extreme sample size results from high variability, an assumed true GMR 0.85, and target power 90%.
  A data frame with 888 observations on the following 5 variables:

`subject`	a factor with 222 levels: 1, 2, …, 222
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 2 levels: TRTR, RTRT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling

rds08

- **Reference dataset 09**
  Based on `rds08`. Wide numeric range (data of last 37 subjects multiplied by 1,000,000). 222 subjects.
  Balanced (222 subjects in both sequences) and complete. No outliers.
  A data frame with 888 observations on the following 5 variables:

`subject`	a factor with 222 levels: 1, 2, …, 222
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 2 levels: TRTR, RTRT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling

rds09

- **Reference dataset 12**
  Simulated with extreme intra- and intersubject variability, GMR = 1.6487. 77 subjects.
  Unbalanced (39 subjects in sequence TRTR and 38 in RTRT) and incomplete (seven missings in sequence TRTR and three in sequence RTRT). Missings / period: 0/1, 1/2, 7/3, 2/4. No outliers.
  A data frame with 298 observations on the following 6 variables:

`subject`	a factor with 77 levels: 1, 2, …, 78
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 2 levels: TRTR, RTRT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling

rds12

- **Reference dataset 13**
  Based on `rds08`. Highly incomplete (approx. 50% of period 4 data deleted). 222 subjects.
  Balanced (111 subjects in both sequences) and incomplete (56 missings in both sequences). Missings / period: 0/0, 0/0, 0/0, 112/4. No outliers.
  A data frame with 776 observations on the following 5 variables:

`subject`	a factor with 222 levels: 1, 2, …, 222
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 2 levels: TRTR, RTRT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling

rds13

- **Reference dataset 14**
  Simulated with high variability, GMR = 1. Dropouts as a hazard function growing with period. 77 subjects.
  Unbalanced (39 subjects in sequence TRTR and 38 in RTRT) and incomplete (18 missings in sequence TRTR and 17 in sequence RTRT). Missings / period: 0/1, 4/2, 12/3, 19/4. No outliers.
  A data frame with 273 observations on the following 6 variables:

`subject`	a factor with 77 levels: 1, 2, …, 78
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 2 levels: TRTR, RTRT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling

rds14

- **Reference dataset 15**
  Based on `ref08`. Highly incomplete (approx. 50% of period 4 data coded as missing `'NA'`). 222 subjects.
  Balanced (111 subjects in both sequences) and incomplete (56 missings in both sequences). Missings / period: 0/1, 0/2, 0/3, 112/4. No outliers.
  A data frame with 888 observations (112 `NA`) on the following 5 variables

`subject`	a factor with 222 levels: 1, 2, …, 222
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 2 levels: TRTR, RTRT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling

rds15

- **Reference dataset 18**
  Data set based on `rds14`. Removed T data of subjects 63–78. 77 subjects.
  Unbalanced (39 subjects in sequence TRTR and 38 in RTRT) and incomplete (32 missings in sequence TRTR and 31 in sequence RTRT). Missings / period: 8/1, 12/2, 18/3, 25/4. No outliers.
  A data frame with 245 observations on the following 6 variables:

`subject`	a factor with 77 levels: 1, 2, …, 78
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 2 levels: TRTR, RTRT

`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling

rds18

- **Reference dataset 19**
  Data set based on `rds18`. Removed data of subjects 63–78. 61 subjects.
  Unbalanced (31 subjects in sequence TRTR and 30 in RTRT) and incomplete (14 missings in both sequences). Missings / period: 0/1, 4/2, 9/3, 15/4. Two outliers (subjects 18 and 51 in sequence RTRT).
  A data frame with 216 observations on the following 6 variables:

`subject`	a factor with 61 levels: 1, 2, …, 62
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 2 levels: TRTR, RTRT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling

rds19

- **Reference dataset 20**
  Data set based on `rds19`. Extreme outlier of R (subject 1) introduced: original value ×100). 61 subjects.
  Unbalanced (31 subjects in sequence TRTR and 30 in RTRT) and incomplete (14 missings in both sequences). Missings / period: 0/1, 4/2, 9/3, 15/4. Two outliers (subjects 1 and 51 in sequence RTRT).
  A data frame with 216 observations on the following 6 variables:

`subject`	a factor with 61 levels: 1, 2, …, 62
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 2 levels: TRTR, RTRT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling

rds20

- **Reference dataset 21**
  Based on `rds01`. 77 subjects. One extreme result of subjects 45 & 52 set to NA.
  Unbalanced (39 subjects in sequence TRTR and 38 in RTRT) and incomplete (seven missings in sequence TRTR and five in sequence RTRT). Missings / period: 1/1, 1/2, 8/3, 2/4. No outliers.
  A data frame with 298 observations (2 NA) on the following 6 variables:

`subject`	a factor with 61 levels: 1, 2, …, 62
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 2 levels: TRTR, RTRT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling

rds21

- **Reference dataset 25**
  Simulated with heteroscedasticity ($CV_{\text{wT}} = 50\%$, $CV_{\text{wR}} = 80\%$), $CV_{\text{bT}} = CV_{\text{bR}} = 130\%$, GMR = 0.85. 70 subjects.
  Balanced (70 subjects in both sequences) and complete. No outliers.
  A data frame with 280 observations on the following 5 variables:

`subject`	a factor with 70 levels: 1, 2, …, 70
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 2 levels: TRTR, RTRT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling

  rds25

- **Reference dataset 26**
  54 subjects.
  Balanced (27 subjects in both sequences) and incomplete (two missings in both sequences). Missings / period: 0/1, 0/2, 2/3, 2/4. One outlier (subject 49) in sequence RTRT.
  A data frame with 216 observations on the following 5 variables:

`subject`	a factor with 54 levels: 1, 2, …, 57
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 2 levels: TRTR, RTRT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling (here $C_{\max}$)

  rds26 In the source evaluated by SAS (Proc GLM) for ABEL. Reported results (Method A):

`CVwR`	60.25%
`PE`	151.3%
`90% CI`	133.5% – 171.4%

- **Reference dataset 29**
  Simulated with heteroscedasticity ($CV_{\text{wT}} = 14\%$, $CV_{\text{wR}} = 28\%$, $CV_{\text{bT}} = 28\%$, $CV_{\text{bR}} = 56\%$), GMR = 0.90. 12 subjects.
  Imbalanced (five subjects in sequence TRTR and seven in sequence RTRT) and incomplete (three missings in sequence TRTR and four in sequence RTRT). Missings / period: 0/1, 1/2, 2/3, 4/4. One outlier (subject 11) in sequence RTRT.
  A data frame with 41 observations on the following 5 variables:

`subject`	a factor with 12 levels: 1, 2, …, 20
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 2 levels: TRTR, RTRT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling

  rds29

Details

Dataset	N	CV_{wR} (%)	Evaluation
`rds01`	77	>30	`method.A()`, `method.B()`
`rds06`	77	>30	`method.A()`, `method.B()`
`rds08`	222	>30	`method.A()`, `method.B()`
`rds09`	222	>30	`method.A()`, `method.B()`
`rds12`	77	>30	`method.A()`, `method.B()`
`rds13`	222	>30	`method.A()`, `method.B()`
`rds14`	77	>30	`method.A()`, `method.B()`
`rds15`	222	>30	`method.A()`, `method.B()`
`rds18`	77	>30	`method.A()`, `method.B()`
`rds19`	61	>30	`method.A()`, `method.B()`
`rds20`	61	>30	`method.A()`, `method.B()`
`rds21`	77	>30	`method.A()`, `method.B()`
`rds25`	70	>30	`method.A()`, `method.B()`
`rds26`	54	>30	`method.A()`, `method.B()`
`rds29`	12	<30	`method.A()`, `method.B()`, `ABE()`

Note

In software sequences and treatments are ranked in lexical order. Hence, executing `str()` or `summary()` will show `sequence` as `"RTRT", "TRTR"` and `treatment` as `"R", "T"`. In BE – by convention – sequences are ordered with `T` first. The package follows this convention.

Author(s)

Helmut Schütz (R-code for simulations by Detlew Labes), Michael Tomashevskiy (simulations in Phoenix NLME)

Source

Dataset	Origin	Description
`rds01`	EMA	Annex II.
`rds06`	`rds01` edited	T and R switched.
`rds08`	R	Large simulated data set with slight heteroscedasticity.
`rds09`	`rds08`	Wide numeric range (data of last 37 subjects multiplied by 1,000,000).
`rds12`	Phoenix NLME	Simulated with extreme intra- and intersubject variability.
`rds13`	`rds08` edited	Highly incomplete (approx. 50% of period 4 data deleted).
`rds14`	Phoenix NLME	Simulated with high intra-/intersubject variability and number of dropouts increasing with period.
`rds15`	`rds08` edited	Highly incomplete (approx. 50% of period 4 data coded as missing `'NA'`).
`rds18`	`rds14` edited	Removed T data of subjects 63–78.
`rds19`	`rds18` edited	Removed data of subjects 63–78.
`rds20`	`rds19` edited	Outlier of R (subject 1) introduced: original value ×100.
`rds21`	`rds01` edited	One extreme result of subjects 45 & 52 set to NA.

`rds25`	R	Simulated with heteroscedasticity.
`rds26`	Patterson & Jones	$C_{\max}$ data given in Tables 4.40 and 4.31.
`rds29`	R	Simulated with heteroscedasticity; imbalanced and incomplete.

References

European Medicines Agency. London, 21 September 2016. *Annex I*, *Annex II*.

Patterson SD, Jones B. *Bioequivalence and Statistics in Clinical Pharmacology.* Boca Raton: CRC Press; 2^{nd} edition 2016. p105–6.

Examples

```
str(rds01)
summary(rds01[2:6])
```

`TRTR.RTRT.TRRT.RTTR` *Reference Dataset for TRTR|RTRT|TRRT|RTTR Designs*

Description

Dataset from the public domain to be evaluated by `method.A()` and/or `method.B()`.

Format

- **Reference Dataset 23**
  22 subjects.
  Unbalanced (four subjects in sequence RTRT and six in each of the other three) and complete. Two outliers (subjects 8 and 17) in sequence TRTR.
  A data frame with 88 observations on the following 5 variables:

`subject`	a factor with 22 levels: 1, 2, ..., 27
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 4 levels: TRTR, RTRT, TRRT, RTTR
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling (here $C_{\max}$)

rds23

Details

Dataset	N	CV_{wR} (%)	Evaluation
`rds23`	22	>30	`method.A()`, `method.B()`

Note

In software sequences and treatments are ranked in lexical order. Hence, executing `str()` or `summary()` will show `sequence` as `"RTRT"`, `"RTTR"`, `"TRRT"`, `"TRTR"` and `treatment` as `"R"`, `"T"`. In BE – by convention – sequences are ordered with `T` first. The package follows this convention.

Source

Data~set	Origin	Description
`rds23`	FDA, CDER	$C_{\max}$ data of Drug 7.

References

U.S. Food and Drug Administration, Center for Drug Evaluation and Research. *Bioequivalence Studies.* Rockville, 1997. bioequivalence study files (archived 2017-07-23)

Examples

```
str(rds23)
row <- c(25:28, 5:8, 9:12, 1:4)
rds23[row, ]
summary(rds23[2:5])
```

`TTRR.RRTT` *Reference Datasets for TTRR/RRTT Designs*

Description

Dataset obtained by simulations to be evaluated by `method.A()` and/or `method.B()`.

Format

- **Reference Dataset 28**
  64 subjects. Balanced (64 subjects in both sequences) and complete. No outliers.
  A data frame with 256 observations on the following 5 variables:

`subject`	a factor with 64 levels: 1, 2, …, 64
`period`	a factor with 4 levels: 1, 2, 3, 4
`sequence`	a factor with 2 levels: TTRR, RRTT
`treatment`	a factor with 2 levels: T, R
`PK`	a numeric vector of pharmacokinetic responses acceptable for reference-scaling

rds28

Details

Dataset	N	CV_{wR} (%)	Evaluation
`rds28`	64	<30	`method.A()`, `method.B()`

Note

In software sequences and treatments are ranked in lexical order. Hence, executing `str()` or `summary()` will show `sequence` as `"RRTT", "TTRR"` and `treatment` as `"R", "T"`. In BE – by convention – sequences are ordered with `T` first. The package follows this convention.

Author(s)

Helmut Schütz (R-code for simulations by Detlew Labes)

Source

Dataset	Origin	Description
`rds28`	R	Simulated with $CV_{\text{wT}} = CV_{\text{wR}} = 35\%$, $CV_{\text{bR}} = CV_{\text{bR}} = 75\%$, GMR 0.90.

Examples

```
str(rds28)
summary(rds28[1:5])
```

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