

Package ‘BE’

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Title Bioequivalence Study Data Analysis

Description Analyze bioequivalence study data with industrial strength. Sample size could be determined for various crossover designs, such as 2x2 design, 2x4 design, 4x4 design, Balaam design, Two-sequence dual design, and William design.

Reference: Chow SC, Liu JP. Design and Analysis of Bioavailability and Bioequivalence Studies. 3rd ed. (2009, ISBN:978-1-58488-668-6).

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LazyLoad yes

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R topics documented:

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| BE-package | <i>Bioequivalence Study Data Analysis</i> |
|------------|---|

Description

Analyze bioequivalence study data with industrial strength. Sample size could be determined for various crossover designs, such as 2x2 design, 2x4 design, 4x4 design, Balaam design, Two-sequence dual design, and William design. Basic assumption is that the variable is distributed as a log-normal distribution. This is SAS PROC GLM style. If you want PROC MIXED style, use nlme::lme.

Details

It performs bioequivalency tests for several variables of a 2x2 study in a data file.

Author(s)

Kyun-Seop Bae <k@acr.kr>

References

1. Chow SC, Liu JP. Design and Analysis of Bioavailability and Bioequivalence Studies. 3rd ed. (2009, ISBN:978-1-58488-668-6)
2. Hauschke D, Steinijans V, Pigeot I. Bioequivalence Studies in Drug Development. (2007, ISBN:978-0-470-09475-4)
3. Diletti E, Hauschke D, Steinijans VW. Sample size determination for bioequivalence assessment by means of confidence intervals. Int J Clinical Pharmacol Ther Tox. 1991;29(1):1-8

Examples

```
# write.csv(NCAResult4BE, "temp.csv", quote=FALSE, row.names=FALSE)
# be2x2("temp.csv", c("AUClast", "Cmax", "Tmax"))
```

| | |
|-------|---|
| be2x2 | <i>Bioequivalence test of a 2x2 study</i> |
|-------|---|

Description

It performs conventional bioequivalence test for 2x2 study. Input is a file. Basic assumption is that the variable is distributed as a log-normal distribution. This is SAS PROC GLM style. If you want PROC MIXED style, use nlme::lme.

Usage

```
be2x2(Data, Columns = c("AUClast", "Cmax", "Tmax"), rtfName="")
```

Arguments

| | |
|---------|--|
| Data | A data.frame or a csv file name. This should have at least the following columns and variable column(s) to be tested. AUC and Cmax should be all positive values. GRP : Group or Sequence, 'RT' or 'TR' PRD : Period, 1 or 2 SUBJ : Subject ID TRT : Treatment or Drug, 'R' or 'T' |
| Columns | Column names of variables to be tested. This is usually c("AUClast", "Cmax", "Tmax") or c("AUClast", "AUCinf", "Cmax", "Tmax") |
| rtfName | Output filename of rich text format(rtf) |

Details

It performs bioequivalency tests for several variables of a 2x2 study in a data file. If you specify output filename in rtfName, the output will be saved in the file.

Value

Returns text output of equivalence test result.

Author(s)

Kyun-Seop Bae <k@acr.kr>

See Also

[test2x2](#), [plot2x2](#)

Examples

```
be2x2(NCAResult4BE, c("AUClast", "Cmax", "Tmax"))
```

| | |
|-------|---|
| ci2cv | <i>Coefficient of variation (CV) from a confidence interval of previous 2x2 study</i> |
|-------|---|

Description

It calculates coefficient of variation (CV) from a confidence interval of previous 2x2 study.

Usage

```
ci2cv(n1, n2, LL, UL, Alpha = 0.1)
```

Arguments

| | |
|-------|---|
| n1 | Subject count of group 1 |
| n2 | Subject count of group 2 |
| LL | Lower limit of the confidence interval of geometric mean ratio (Test/Reference) |
| UL | Upper limit of the confidence interval of geometric mean ratio (Test/Reference) |
| Alpha | Alpha level. This means (1 - alpha/2)*100 % confidence interval is given |

Details

It calculates coefficient of variation (CV) from a confidence interval of 2x2 bioequivalence study.

Value

Returns coefficient of variation (CV) in percent (%).

Author(s)

Kyun-Seop Bae <k@acr.kr>

Examples

```
ci2cv(12, 13, 0.85, 1.11)
```

| | |
|--------|--|
| ci2mse | <i>Mean squared error (MSE) from a confidence interval of previous 2x2 study</i> |
|--------|--|

Description

It calculates mean squared error (MSE) from a confidence interval of previous 2x2 study.

Usage

```
ci2mse(n1, n2, LL, UL, Alpha = 0.1)
```

Arguments

| | |
|-------|--|
| n1 | Subject count of group 1 |
| n2 | Subject count of group 2 |
| LL | Lower limit of the confidence interval of geometric mean ratio (Test/Reference) |
| UL | Upper limit of the confidence interval of geometric mean ratio (Test/Reference) |
| Alpha | Alpha level. This means $(1 - \alpha/2) \times 100$ % confidence interval is given |

Details

It calculates coefficient of variation (CV) from a confidence interval of 2x2 bioequivalence study.

Value

Returns mean squared error (MSE).

Author(s)

Kyun-Seop Bae <k@acr.kr>

Examples

```
ci2mse(12, 13, 0.85, 1.11)
```

cv2mse

*Mean squared error (MSE) from coefficient of variation (CV)***Description**

It calculates mean squared error (MSE) from coefficient of variation (CV).

Usage

```
cv2mse(cv)
```

Arguments

cv Coefficient of variation (%) in the original scale

Details

Coefficient of variation (CV) is percent in original scale and mean squared error (MSE) is log scale.

Value

Returns mean squared error (MSE) in log scale).

Author(s)

Kyun-Seop Bae <k@acr.kr>

Examples

```
cv2mse(25)
```

hodes

*Hodges-Lehmann estimation for a variable of a 2x2 study***Description**

It performs Hodges-Lehmann estimation for 2x2 study. This is usually for Tmax variable.

Usage

```
hodes(bedata, Var)
```

Arguments

| | |
|--------|---|
| bedata | Data table name. This should have at least the following columns and a variable column to be tested. GRP : Group or Sequence, 'RT' or 'TR' PRD : Period, 1 or 2 SUBJ : Subject ID TRT : Treatment or Drug, 'R' or 'T' |
| Var | Variable to be estimated. This should be one of the column names in bedata table. Usually 'Tmax' |

Details

It nonparametrically tests Var variable equivalency from a 2x2 study. This is done for a variable which we cannot assume log-normal distribution.

Value

Wilcoxon Signed-Rank Test

A kind of nonparametric test

Hodges-Lehmann Estimate

90% confidence interval in the original scale and the percent scale

Author(s)

Kyun-Seop Bae <k@acr.kr>

Examples

```
hodges(NCAResult4BE, "Tmax")
```

| | |
|--------|--|
| mse2cv | <i>Coefficient of variation (CV) from mean squared error (MSE)</i> |
|--------|--|

Description

It calculates coefficient of variation (CV) from mean squared error (MSE).

Usage

```
mse2cv(mse)
```

Arguments

mse Mean square error (MSE) in log scale

Details

Coefficient of variation (CV) is percent in the original scale and mean squared error (MSE) is the log scale.

Value

Returns coefficient of variation (CV) in percent (%).

Author(s)

Kyun-Seop Bae <k@acr.kr>

Examples

```
mse2cv(0.06062462)
```

| | |
|--------------|---|
| NCAResult4BE | <i>An Example of Noncompartmental Analysis Result for Bioequivalence Test</i> |
|--------------|---|

Description

Contains a noncompartmental analysis result table from a concentration simulated bioequivalence study.

Usage

```
NCAResult4BE
```

Format

A data frame with 48 observations on the following 10 variables.

SUBJ Subject ID
 GRP Group or Sequence character code: 'RT' or 'TR'
 PRD Period numeric value: 1 or 2
 TRT Treatment or Drug code: 'R' or 'T'
 AUClast AUClast positive numeric value
 Cmax Cmax positive numeric value
 Tmax Tmax positive numeric value

Details

This contains a simulated data for 2x2 bioequivalence study data analysis. Noncompartmental analysis results are from the NonCompartment package.

| | |
|---------|--|
| plot2x2 | <i>Plot bioequivalence variable of a 2x2 study</i> |
|---------|--|

Description

It plots two 2x2 plots for a variable.

Usage

```
plot2x2(bedata, Var)
```

Arguments

| | |
|--------|--|
| bedata | Data table name. This should have at least the following columns and a variable column to be plotted. GRP : Group or Sequence, 'RT' or 'TR' PRD : Period, 1 or 2 SUBJ : Subject ID TRT : Treatment or Drug, 'R' or 'T' |
| Var | Variable to be plotted. This should be one of the column names in bedata table. |

Details

It plots Var column values according to GRP, PRD, TRT.

Value

It just draws two 2x2 plots for equivalence exploration.

Author(s)

Kyun-Seop Bae <k@acr.kr>

Examples

```
plot2x2(NCAResult4BE, "AUClast")
plot2x2(NCAResult4BE, "Cmax")
plot2x2(NCAResult4BE, "Tmax")
```

pow2x2ci

Power using a confidence interval of previous 2x2 study

Description

It calculates power for the bioequivalence test on ratio using a confidence interval of previous 2x2 study.

Usage

```
pow2x2ci(n1, n2, LL, UL, Alpha = 0.1)
```

Arguments

| | |
|-------|--|
| n1 | Subject count of group 1 |
| n2 | Subject count of group 2 |
| LL | Lower limit of the confidence interval of geometric mean ratio (Test/Reference) |
| UL | Upper limit of the confidence interval of geometric mean ratio (Test/Reference) |
| Alpha | Alpha level. This means $(1 - \alpha/2) \times 100$ % confidence interval is given |

Details

It calculates power of sample size (n per group) with CV.

Value

Returns power [0, 1)

Author(s)

Kyun-Seop Bae <k@acr.kr>

Examples

```
pow2x2ci(12, 13, 0.85, 1.11)
```

| | |
|-----------|---|
| pow2x2mse | <i>Power using mean squared error (MSE) of previous 2x2 study</i> |
|-----------|---|

Description

It calculates power for the bioequivalence test on ratio using mean squared error (MSE of previous 2x2 study).

Usage

```
pow2x2mse(n1, n2, mse, True.R = 1, Alpha = 0.1, ThetaL = 0.8, ThetaU = 1.25)
```

Arguments

| | |
|--------|--|
| n1 | Subject count of group 1 |
| n2 | Subject count of group 2 |
| mse | Mean squared error |
| True.R | True ratio of test/reference |
| Alpha | Alpha level. This means $(1 - \alpha/2) \times 100$ % confidence interval is given |
| ThetaL | Lower limit of equivalence criteria |
| ThetaU | Upper limit of equivalence criteria |

Details

It calculates power of sample size (n per group) with CV.

Value

Returns power [0, 1)

Author(s)

Kyun-Seop Bae <k@acr.kr>

Examples

```
pow2x2mse(12, 13, 0.0756530)
```

| | |
|-------|--|
| powcv | <i>Power using coefficient of variation (CV)</i> |
|-------|--|

Description

It calculates power for the bioequivalence test on ratio using coefficient of variation (CV).

Usage

```
powcv(n, CV, DesignNo = 1, True.R = 1, Alpha = 0.1, ThetaL = 0.8, ThetaU = 1.25)
```

Arguments

| | |
|----------|--|
| n | Sample size, n per group |
| CV | Coefficient of Variation (%) |
| DesignNo | Crossover design number. Design Number (treatment x sequence x period) 1 2x2x2 : RT TR 2 2x4x2 (Balaam Design) : TT RR RT TR 3 2x2x3 (Two-sequence Dual Design): TRR RTT 4 2x2x4 : TRRT RTTR 5 2x4x4 : TTRR RRTT TRRT RTTR 6 3x6x3 (William Design for 3 treatments) + carry-over effect : RBA ARB BAR ABR BRA RAB 7 3x6x3 (William Design for 3 treatments) - carry-over effect : RBA ARB BAR ABR BRA RAB 8 4x4x4 (William Design for 4 treatments) + carry-over effect : RCAB ARBC BACR CBRA 9 4x4x4 (William Design for 4 treatments) - carry-over effect : RCAB ARBC BACR CBRA |
| True.R | True ratio of test/reference |
| Alpha | Alpha error level |
| ThetaL | Lower limit of equivalence criteria |
| ThetaU | Upper limit of equivalence criteria |

Details

It calculates power of sample size (n per group) with CV.

Value

Returns power [0, 1)

Author(s)

Kyun-Seop Bae <k@acr.kr>

Examples

```
powcv(12, 25)
```

powmse

*Power using mean squared error (MSE)***Description**

It calculates power for the bioequivalence test on ratio using mean squared error (MSE).

Usage

```
powmse(n, mse, DesignNo = 1, True.R = 1, Alpha = 0.1, ThetaL = 0.8, ThetaU = 1.25)
```

Arguments

| | |
|----------|--|
| n | Sample size, n per group |
| mse | Mean squared error |
| DesignNo | Crossover design number. Design Number (treatment x sequence x period) 1 2x2x2 : RT TR 2 2x4x2 (Balaam Design) : TT RR RT TR 3 2x2x3 (Two-sequence Dual Design): TRR RTT 4 2x2x4 : TRRT RTTR 5 2x4x4 : TTRR RRTT TRRT RTTR 6 3x6x3 (William Design for 3 treatments) + carry-over effect : RBA ARB BAR ABR BRA RAB 7 3x6x3 (William Design for 3 treatments) - carry-over effect : RBA ARB BAR ABR BRA RAB 8 4x4x4 (William Design for 4 treatments) + carry-over effect : RCAB ARBC BACR CBRA 9 4x4x4 (William Design for 4 treatments) - carry-over effect : RCAB ARBC BACR CBRA |
| True.R | True ratio of test/reference |
| Alpha | Alpha error level |
| ThetaL | Lower limit of equivalence criteria |
| ThetaU | Upper limit of equivalence criteria |

Details

It calculates power of sample size (n per group) with mse.

Value

Returns power [0, 1))

Author(s)

Kyun-Seop Bae <k@acr.kr>

Examples

```
powmse(12, 0.06)
```

| | |
|-------------|--|
| scaledBound | <i>Widened Bound for Scaled Average Bioequivalence</i> |
|-------------|--|

Description

It calculates widened bound for scaled average bioequivalence.

Usage

```
scaledBound(CV = 40, k = 0.76, digits = 4)
```

Arguments

| | |
|--------|--|
| CV | coefficient of variation in percent |
| k | 0.76 is for EMA and Korea MFDS. US FDA uses 0.893. When CV is 30%, bound becomes (0.8, 1.25). Most regulatory body does not use a more accurate value. |
| digits | Korea MFDS use 4 digits only, while other regulatory bodies use more decimal values. |

Details

CV must be larger than 30%. If CV is larger than 50

Value

widened bound for scaled average bioequivalence

Author(s)

Kyun-Seop Bae <k@acr.kr>

Examples

```
scaledBound(30)
scaledBound(35)
scaledBound(40)
scaledBound(45)
scaledBound(50)
```

ss2x2ci

*Sample size using a confidence interval of previous 2x2 study***Description**

It calculates sample size for the bioequivalence test on ratio using a confidence interval of previous 2x2 study.

Usage

```
ss2x2ci(n1, n2, LL, UL, Alpha = 0.1)
```

Arguments

| | |
|-------|--|
| n1 | Subject count of group 1 |
| n2 | Subject count of group 2 |
| LL | Lower limit of the confidence interval of geometric mean ratio (Test/Reference) |
| UL | Upper limit of the confidence interval of geometric mean ratio (Test/Reference) |
| Alpha | Alpha level. This means $(1 - \alpha/2) \times 100$ % confidence interval is given |

Details

It calculates sample size (n per group) with CV, Alpha, and Beta for bioequivalence test.

Value

Returns sample size (n per group) for bioequivalence test with ratio criteria.

Author(s)

Kyun-Seop Bae <k@acr.kr>

Examples

```
ss2x2ci(12, 13, 0.85, 1.11)
```

sscv

*Sample size using coefficient of variation (CV)***Description**

It calculates sample size for the bioequivalence test on ratio using coefficient of variation (CV).

Usage

```
sscv(CV, DesignNo = 1, True.R = 1, Alpha = 0.1, Beta = 0.2,
      ThetaL = 0.8, ThetaU = 1.25, nMax = 999999)
```

Arguments

| | |
|----------|--|
| CV | Coefficient of Variation (%) |
| DesignNo | Crossover design number. Design Number (treatment x sequence x period) 1 2x2x2 : RT TR 2 2x4x2 (Balaam Design) : TT RR RT TR 3 2x2x3 (Two-sequence Dual Design): TRR RTT 4 2x2x4 : TRRT RTTR 5 2x4x4 : TTRR RRTT TRRT RTTR 6 3x6x3 (William Design for 3 treatments) + carry-over effect : RBA ARB BAR ABR BRA RAB 7 3x6x3 (William Design for 3 treatments) - carry-over effect : RBA ARB BAR ABR BRA RAB 8 4x4x4 (William Design for 4 treatments) + carry-over effect : RCAB ARBC BACR CBRA 9 4x4x4 (William Design for 4 treatments) - carry-over effect : RCAB ARBC BACR CBRA |
| True.R | True ratio of test/reference |
| Alpha | Alpha error level |
| Beta | Beta error level |
| ThetaL | Lower limit of equivalence criteria |
| ThetaU | Upper limit of equivalence criteria |
| nMax | Maximum subject number (sample size) per group |

Details

It calculates sample size (n per group) with CV, Alpha, and Beta for bioequivalence test.

Value

Returns sample size (n per group) for bioequivalence test with ratio criteria.

Author(s)

Kyun-Seop Bae <k@acr.kr>

Examples

```
sscv(25)
```

ssmse

*Sample size using mean squared error (MSE)***Description**

It calculates sample size for the bioequivalence test on ratio using mean squared error (MSE).

Usage

```
ssmse(mse, DesignNo = 1, True.R = 1, Alpha = 0.1, Beta = 0.2,
      ThetaL = 0.8, ThetaU = 1.25, nMax = 999999)
```

Arguments

| | |
|----------|--|
| mse | Mean squared error |
| DesignNo | Crossover design number. Design Number (treatment x sequence x period) 1 2x2x2 : RT TR 2 2x4x2 (Balaam Design) : TT RR RT TR 3 2x2x3 (Two-sequence Dual Design): TRR RTT 4 2x2x4 : TRRT RTTR 5 2x4x4 : TTRR RRTT TRRT RTTR 6 3x6x3 (William Design for 3 treatments) + carry-over effect : RBA ARB BAR ABR BRA RAB 7 3x6x3 (William Design for 3 treatments) - carry-over effect : RBA ARB BAR ABR BRA RAB 8 4x4x4 (William Design for 4 treatments) + carry-over effect : RCAB ARBC BACR CBRA 9 4x4x4 (William Design for 4 treatments) - carry-over effect : RCAB ARBC BACR CBRA |
| True.R | True ratio of test/reference |
| Alpha | Alpha error level |
| Beta | Beta error level |
| ThetaL | Lower limit of equivalence criteria |
| ThetaU | Upper limit of equivalence criteria |
| nMax | Maximum subject number (sample size) per group |

Details

It calculates sample size (n per group) with mse, Alpha, and Beta for bioequivalence test.

Value

Returns sample size (n per group) for bioequivalence test with ratio criteria.

Author(s)

Kyun-Seop Bae <k@acr.kr>

Examples

```
ssmse(0.06)
```

SSSCV

Sample Size for Scaled Average BE using coefficient of variation (CV)

Description

It calculates sample size for the scaled average bioequivalence test on ratio using coefficient of variation (CV).

Usage

```
ssscv(CV, DesignNo = 1, True.R = 1, Alpha = 0.1, Beta = 0.2, Region = "EU", nMax = 999999)
```

Arguments

| | |
|----------|--|
| CV | Coefficient of Variation (%) |
| DesignNo | Crossover design number. Design Number (treatment x sequence x period) 1 2x2x2 : RT TR 2 2x4x2 (Balaam Design) : TT RR RT TR 3 2x2x3 (Two-sequence Dual Design): TRR RTT 4 2x2x4 : TRRT RTTR 5 2x4x4 : TTRR RRTT TRRT RTTR 6 3x6x3 (William Design for 3 treatments) + carry-over effect : RBA ARB BAR ABR BRA RAB 7 3x6x3 (William Design for 3 treatments) - carry-over effect : RBA ARB BAR ABR BRA RAB 8 4x4x4 (William Design for 4 treatments) + carry-over effect : RCAB ARBC BACR CBRA 9 4x4x4 (William Design for 4 treatments) - carry-over effect : RCAB ARBC BACR CBRA |
| True.R | True ratio of test/reference |
| Alpha | Alpha error level |
| Beta | Beta error level |
| Region | US or FDA for US FDA, KR or MFDS for Korea MFDS, EU or EMA for other regions or countries |
| nMax | Maximum subject number (sample size) per group |

Details

It calculates sample size (n per group) with CV, Alpha, and Beta for scaled average bioequivalence test. US FDA uses this widened bound for both AUClast and Cmax, while EU EMA and Korea MFDA use this for Cmax only.

Value

Returns sample size (n per group) for scaled average bioequivalence test with ratio criteria.

Author(s)

Kyun-Seop Bae <k@acr.kr>

Examples

```
ssscv(42.2, DesignNo=4, True.R=0.9) # 14 per group, EU EMA. This applies only for Cmax
ssscv(42.2, DesignNo=4, True.R=0.9, Region="US") # 9 per group, US FDA
ssscv(42.2, DesignNo=4, True.R=0.9, Region="KR") # 14 per group, Korea MFDS. Only for Cmax
```

test2x2

Bioequivalence test for a variable of a 2x2 study

Description

It performs conventional bioequivalence test for 2x2 study. Basic assumption is that the variable is distributed as a log-normal distribution. This is SAS PROC GLM style. If you want PROC MIXED style use nlme::lme.

Usage

```
test2x2(bedata, Var)
```

Arguments

| | |
|--------|--|
| bedata | Data table name. This should have at least the following columns and a variable column to be tested. Var column values should be all positive values. GRP : Group or Sequence, 'RT' or 'TR' PRD : Period, 1 or 2 SUBJ : Subject ID TRT : Treatment or Drug, 'R' or 'T' |
| Var | Variable to be tested. This should be one of the column names in bedata table. Usually 'AUClast' or 'Cmax' |

Details

It tests Var variable equivalency from a 2x2 study. Current regulatory requirement is that the 90% confidence interval of geometric mean ratio (Test/Reference) should be within [0.8, 1.25].

Value

| | |
|--|---|
| Analysis of Variance (log scale) | Analysis of Variance in log scale |
| Between and Within Subject Variability | Variance in log scale and coefficient of variance in original scale |
| Least Square Means | Geometric means |
| 90% Confidence Interval | 90% confidence interval of geometric mean ratio (T/R) |
| Sample Size | Sample size for the replication of this study |

Author(s)

Kyun-Seop Bae <k@acr.kr>

Examples

```
test2x2(NCAREsult4BE, "AUClast")  
test2x2(NCAREsult4BE, "Cmax")
```

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