

# Package ‘BE’

June 22, 2018

**Version** 0.1.1

**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).

**Depends** R (>= 3.0.0), rtf

**Author** Kyun-Seop Bae [aut]

**Maintainer** Kyun-Seop Bae <k@acr.kr>

**Copyright** 2018, Kyun-Seop Bae

**License** GPL-3

**NeedsCompilation** no

**LazyLoad** yes

**Repository** CRAN

**URL** <https://cran.r-project.org/package=BE>

## R topics documented:

|                        |    |
|------------------------|----|
| BE-package . . . . .   | 2  |
| be2x2 . . . . .        | 2  |
| ci2cv . . . . .        | 3  |
| ci2mse . . . . .       | 4  |
| cv2mse . . . . .       | 5  |
| hedges . . . . .       | 5  |
| mse2cv . . . . .       | 6  |
| NCAResult4BE . . . . . | 7  |
| plot2x2 . . . . .      | 7  |
| pow2x2ci . . . . .     | 8  |
| pow2x2mse . . . . .    | 9  |
| powcv . . . . .        | 10 |
| powmse . . . . .       | 11 |
| ss2x2ci . . . . .      | 12 |
| sscv . . . . .         | 12 |
| ssmse . . . . .        | 14 |
| test2x2 . . . . .      | 15 |

**Index****16**

BE-package

*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. 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)
print(be2x2("temp.csv", c("AUClast", "Cmax", "Tmax")), na.print="")
```

be2x2

*Bioequivalence test of a 2x2 study***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 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.<br><br>GRP : Group or Sequence, 'RT' or 'TR'<br>PRD : Period, 1 or 2<br>SUBJ : Subject ID<br>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**

```
print(be2x2(NCAResult4BE, c("AUClast", "Cmax", "Tmax")), na.print="")
```

---

|       |   |
|-------|---|
| 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 $(1 - \alpha/2) \times 100$ % 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.<br>GRP : Group or Sequence, 'RT' or 'TR'<br>PRD : Period, 1 or 2<br>SUBJ : Subject ID<br>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

*Coefficient of variation (CV) from mean squared error (MSE)*

---

**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.<br>GRP : Group or Sequence, 'RT' or 'TR'<br>PRD : Period, 1 or 2<br>SUBJ : Subject ID<br>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

*Power using mean squared error (MSE) of previous 2x2 study*

---

### 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.<br><br>Design Number (treatment x sequence x period)<br>1 2x2x2 : RT TR<br>2 2x4x2 (Balaam Design) : TT RR RT TR<br>3 2x2x3 (Two-sequence Dual Design): TRR RTT<br>4 2x2x4 : TRRT RTTR<br>5 2x4x4 : TTRR RRTT TRRT RTTR<br>6 3x6x3 (William Design for 3 treatments) + carry-over effect<br>: RBA ARB BAR ABR BRA RAB<br>7 3x6x3 (William Design for 3 treatments) - carry-over effect<br>: RBA ARB BAR ABR BRA RAB<br>8 4x4x4 (William Design for 4 treatments) + carry-over effect<br>: RCAB ARBC BACR CBRA<br>9 4x4x4 (William Design for 4 treatments) - carry-over effect<br>: 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 | <i>Power using mean squared error (MSE)</i> |
|--------|---|

---

**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.<br><br>Design Number (treatment x sequence x period)<br>1 2x2x2 : RT TR<br>2 2x4x2 (Balaam Design) : TT RR RT TR<br>3 2x2x3 (Two-sequence Dual Design): TRR RTT<br>4 2x2x4 : TRRT RTTR<br>5 2x4x4 : TTRR RRTT TRRT RTTR<br>6 3x6x3 (William Design for 3 treatments) + carry-over effect<br>: RBA ARB BAR ABR BRA RAB<br>7 3x6x3 (William Design for 3 treatments) - carry-over effect<br>: RBA ARB BAR ABR BRA RAB<br>8 4x4x4 (William Design for 4 treatments) + carry-over effect<br>: RCAB ARBC BACR CBRA<br>9 4x4x4 (William Design for 4 treatments) - carry-over effect<br>: 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)
```

---

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.<br><br>Design Number (treatment x sequence x period)<br>1 2x2x2 : RT TR<br>2 2x4x2 (Balaam Design) : TT RR RT TR<br>3 2x2x3 (Two-sequence Dual Design): TRR RTT<br>4 2x2x4 : TRRT RTTR<br>5 2x4x4 : TTRR RRTT TRRT RTTR<br>6 3x6x3 (William Design for 3 treatments) + carry-over effect<br>: RBA ARB BAR ABR BRA RAB<br>7 3x6x3 (William Design for 3 treatments) - carry-over effect<br>: RBA ARB BAR ABR BRA RAB<br>8 4x4x4 (William Design for 4 treatments) + carry-over effect<br>: RCAB ARBC BACR CBRA<br>9 4x4x4 (William Design for 4 treatments) - carry-over effect<br>: 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.<br><br>Design Number (treatment x sequence x period)<br>1 2x2x2 : RT TR<br>2 2x4x2 (Balaam Design) : TT RR RT TR<br>3 2x2x3 (Two-sequence Dual Design): TRR RTT<br>4 2x2x4 : TRRT RTTR<br>5 2x4x4 : TTRR RRTT TRRT RTTR<br>6 3x6x3 (William Design for 3 treatments) + carry-over effect<br>: RBA ARB BAR ABR BRA RAB<br>7 3x6x3 (William Design for 3 treatments) - carry-over effect<br>: RBA ARB BAR ABR BRA RAB<br>8 4x4x4 (William Design for 4 treatments) + carry-over effect<br>: RCAB ARBC BACR CBRA<br>9 4x4x4 (William Design for 4 treatments) - carry-over effect<br>: 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)
```

---

|         |  |
|---------|--|
| test2x2 | <i>Bioequivalence test for a variable of a 2x2 study</i> |
|---------|--|

---

**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.<br><br>GRP : Group or Sequence, 'RT' or 'TR'<br>PRD : Period, 1 or 2<br>SUBJ : Subject ID<br>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**

```
print(test2x2(NCAREsult4BE, "AUClast"), na.print="")
print(test2x2(NCAREsult4BE, "Cmax"), na.print="")
```

# Index

- \*Topic **Plot**
  - plot2x2, [7](#)
- \*Topic **Power**
  - pow2x2ci, [8](#)
  - pow2x2mse, [9](#)
  - powcv, [10](#)
  - powmse, [11](#)
- \*Topic **Report**
  - be2x2, [2](#)
- \*Topic **Sample Size**
  - ss2x2ci, [12](#)
  - sscv, [12](#)
  - ssmse, [14](#)
- \*Topic **Statistical Test**
  - hodges, [5](#)
  - test2x2, [15](#)
- \*Topic **datasets**
  - NCAResult4BE, [7](#)

BE (BE-package), [2](#)  
BE-package, [2](#)  
be2x2, [2](#)

ci2cv, [3](#)  
ci2mse, [4](#)  
cv2mse, [5](#)

hodges, [5](#)

mse2cv, [6](#)

NCAResult4BE, [7](#)

plot2x2, [3](#), [7](#)  
pow2x2ci, [8](#)  
pow2x2mse, [9](#)  
powcv, [10](#)  
powmse, [11](#)

ss2x2ci, [12](#)  
sscv, [12](#)  
ssmse, [14](#)

test2x2, [3](#), [15](#)