ANOVAforMRMCLimitsOfAgreement

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Type Package

Title What the Package Does (Title Case)

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Description This package contains the data and function for conducting the simulation study in the manuscript
Wen, S.& Gallas, B. D. (2021). Three_way Mixed Effect ANOVA to Estimate MRMC Limits of Agreement. arXiv preprint arXiv:2107.08891. Submitted to Statistics in Biopharmaceutical Research.

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Imports stats,iMRMC

R topics documented:

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la.anova   *MRMC Analysis of Limits of Agreement using ANOVA*

Description

These two functions calculate two types of Limits of Agreement using ANOVA: Within-Reader Between-Modality(WRBM) and Between-Reader Between-Modality(BRBM). The 95% confidence interval of the mean difference is also provided. The ANOVA method are realized either by applying stats::aov or by matrix multiplication. See more details below about the model structure.

Usage

```
laWRBM.anova(
  df,
  modalitiesToCompare = c("testA", "testB"),
  keyColumns = c("readerID", "caseID", "modalityID", "score"),
  if.aov = TRUE
)

laBRBM.anova(
  df,
  modalitiesToCompare = c("testA", "testB"),
  keyColumns = c("readerID", "caseID", "modalityID", "score"),
  if.aov = TRUE
)
```

Arguments

df
: Data frame of observations, one per row. Columns identify random effects, fixed effects, and the observation. Namely,

  readerID The factor corresponding to the different readers in the study. The readerID is treated as a random effect.

  caseID The factor corresponding to the different cases in the study. The caseID is treated as a random effect.

  modalityID The factor corresponding to the different modalities in the study. The modalityID is treated as a fixed effect.

  score The score given by the reader to the case for the modality indicated.

modalitiesToCompare
: The factors identifying the modalities to compare. It should be at length 2. Default modalitiesToCompare = c("testA", "testB")

keyColumns
: Identify the factors corresponding to the readerID, caseID, modalityID, and score (or alternative random and fixed effects). Default keyColumns = c("readerID","caseID","mo

if.aov
: Boolean value to determine whether using aov function to do ANOVA. Default if.aov = TRUE

Details

Suppose the score from reader j for case k under modality i is X_{ijk}, then the difference score from the same reader for the same cases under two different modalities is $Y_{jk} = X_{1jk} - X_{2jk}$.

- `laWRBM` use two-way random effect ANOVA to analyze the difference scores Y_{jk}. The model is $Y_{jk} = \mu + R_j + C_k + \epsilon_{jk}$, where R_j and C_k are random effects for readers and cases. The variance of mean and individual observation is expressed as the linear combination of the MS given by ANOVA.

- `laBRBM` use three-way mixed effect ANOVA to analyze the scores X_{ijk}. The model is given by $X_{ijk} = \mu + R_j + C_k + m_i + RC_{jk} + mR_{ij} + mC_{ik} + \epsilon_{ijk}$, where R_j and C_k are random effects for readers and cases and m_i is a fixed effect for modality. The variance of mean and individual observation is expressed as the linear combination of the MS given by ANOVA.

Value

A dataframe with one row. Each column is as following:

meanDiff The mean of difference score.

var.MeanDiff The variance of mean difference score

var.1obs The variance of a single WRBM/BRBM difference score

ci95meanDiff.bot Lower bound of 95% CI for the mean difference score. `meanDiff+ 1.96*sqrt(var.MeanDiff)`

ci95meanDiff.top Upper bound of 95% CI for the mean difference score. `meanDiff-1.96*sqrt(var.MeanDiff)`

la.bot Lower bound of WRBM/BRBM Limits of Agreement. `meanDiff+2*sqrt(var.1obs)`

la.top Upper bound of WRBM/BRBM Limits of Agreement. `meanDiff-2*sqrt(var.1obs)`

The two function shows the same 95% CI for the mean difference score, but difference Limits of Agreements.

Examples

```
config <- sim.NormalIG.Hierarchical.config(modalityID = c("testA", "testB"))
# Simulate an MRMC ROC data set
dFrame <- sim.NormalIG.Hierarchical(config)

# Compute Limits of Agreement
laWRBM_result <- laWRBM.anova(dFrame)
print(laWRBM_result)
laBRBM_result <- laBRBM.anova(dFrame)
print(laBRBM_result)
```

---

result.validMRMCVarEstimate.nReader

This is a data frame with the result from the simulation study to validate and characterize the MRMC limits of agreement estimates

---

Description

This is a data frame with the result from the simulation study to validate and characterize the MRMC limits of agreement estimates

Usage

```
result.validMRMCVarEstimate.nReader

result.validMRMCVarEstimate.nCase

result.validMRMCVarEstimate.parameter
```

Format

A dataframe with the following columns:

nReader Number of Readers

nCase Number of Cases

alpha_R Reader related parameter

sigma_C Case related parameter

WR_var_MCmean Monte Carlo mean of variance estimation for the WRBM difference score

WR_var_MCvar Monte Carlo variance of variance estimation for the WRBM difference score

True_WR_var Theoretical value for WRBM variance derived from the simulation model

WR_var_relative_bias relative bias for WRBM variance

WR_CV coefficient of variation for WRBM variance

BR_var_MCmean Monte Carlo mean of variance estimation for the BRBM difference score

BR_var_MCvar Monte Carlo variance of variance estimation for the BRBM difference score

True_BR_var Theoretical value for BRBM variance derived from the simulation model

BR_var_relative_bias relative bias for BRBM variance

BR_CV coefficient of variation for BRBM variance

An object of class `data.frame` with 11 rows and 14 columns.

An object of class `data.frame` with 25 rows and 14 columns.

Details

There are three parameter sets for this simulation:

result.validMRMCVarEstimate.nReader Different number of readers $J = 3, 4, ..., 10, K = 100, \alpha_R = 10, \sigma_C^2 = 1$

result.validMRMCVarEstimate.nCase Different number of cases $K = 50, 60, ..., 150, J = 5, \alpha_R = 10, \sigma_C^2 = 1$

result.validMRMCVarEstimate.parameter Different reader and case variabilities $(\alpha_R, \sigma_C^2) \in \{3, 4, 6, 11, 21\} \times \{0.1, 0.2, 0.4, \frac{2}{3}, 1\}, J = 5, K = 100$

In all the parameter sets, $\beta_R = \beta_{\tau R} = 1, \alpha_R = \alpha_{\tau R}, \sigma_C^2 = \sigma_{\tau C}^2$. For each parameter setting, we simulate 1000 trials.

result.validSimulation.alphaR

*This is a data frame with the result from the simulation study to verify
the simulation is consistent with the derived theoretical values*

Description

This is a data frame with the result from the simulation study to verify the simulation is consistent
with the derived theoretical values

Usage

```
result.validSimulation.alphaR
```

```
result.validSimulation.sigmaC
```

Format

A dataframe with the following column:

sigma_C Case related parameter

alpha_R Reader related parameter

WR_mean Monte Carlo mean of the WRBM difference score

WR_var Monte Carlo variance of the WRBM difference score

BR_mean Monte Carlo mean of the BRBM difference score

BR_var Monte Carlo variance of the BRBM difference score

True_WR_var Theoretical value for WRBM variance derived from the simulation model

True_BR_var Theoretical value for BRBM variance derived from the simulation model

WR_var_relative_bias relative bias for WRBM variance

BR_var_relative_bias relative bias for BRBM variance

An object of class `data.frame` with 20 rows and 10 columns.

Details

There are two parameter sets for this simulation:

result.validSimulation.alphaR In this study, we fixed the case-related parameter but change the
reader related fixed the case related parameters $\sigma_C^2 = \sigma_{\tau C}^2 = 1$ and allowed the reader related
parameter $\alpha_R(= \alpha_{\tau R})$ to range from 2 to 20.

result.validSimulation.sigmaC In this study, we fixed the reader related parameters $\alpha_R = \alpha_{\tau R} = 10$ and allowed the case related parameter $\sigma_C^2(= \sigma_{\tau C}^2)$ to range from 0.1 to 2, incrementing
by 0.1.

In both parameter sets, $\beta_R = \beta_{\tau R} = 1$, so that the reader variability is only affected by α_R. We
simulated 100,000 trials with each trial having 4 measurements from 2 readers for a single case
under 2 modalities. The Monte Carlo estimates of the variances are the sample variances of the
100,000 independent WRBM and BRBM differences.

```
sim.NormalIG.Hierarchical
```
Simulate an MRMC data set comparing two modalities by a hierarchical model

Description

This procedure simulates an MRMC data set for a MRMC agreement study comparing two modalities.It is a hierarchical model consists of two interaction terms: reader-case interaction and modality-reader-case-replicate interaction. Both the interaction terms are conditional normal distributed, with the case(-related) factor contributing to the conditional mean and the reader(-related) factor contributing to the conditional variance.

Usage

```
sim.NormalIG.Hierarchical(
  config,
  R = NULL,
  AR = NULL,
  BR = NULL,
  is.within = FALSE
)
```

Arguments

config   [list] of simulation parameters:

- Experiment labels and size
    - modalityID: [vector] label modality A and B.
    - nR: [num] number of readers
    - nC: [num] number of cases
    - C_dist: [chr] distribution of the case. Default `C_dist="normal"`
- Mean and fixed effects:
    - mu: [num] grand mean
    - tau_A: [num] modality A
    - tau_B: [num] modality B
- Reader-case interaction term
    - sigma_C: [num] variance of case factor (if `C_dist="normal"`)
    - a_C: [num] alpha for distribution of case (if `C_dist="beta"`)
    - b_C: [num] beta for distribution of case (if `C_dist="beta"`)
    - alpha_R: [num] shape parameter for reader
    - beta_R: [num] scale parameter for reader
- Modality-reader-case-replicate interaction term for modality A
    - sigma_C.A: [num] variance of case factor (if `C_dist="normal"`)
    - a_C.A: [num] alpha for distribution of case (if `C_dist="beta"`)
    - b_C.A: [num] beta for distribution of case (if `C_dist="beta"`)
    - alpha_R.A: [num] shape parameter for reader
    - beta_R.A: [num] scale parameter for reader

- Modality-reader-case-replicate interaction term for modality B
    - sigma_C.B: [num] variance of case factor (if `C_dist="normal"`)
    - a_C.B: [num] alpha for distribution of case (if `C_dist="beta"`)
    - b_C.B: [num] beta for distribution of case (if `C_dist="beta"`)
    - alpha_R.B: [num] shape parameter for reader
    - beta_R.B: [num] scale parameter for reader
- Scales for the case related terms and interaction terms
    - C_scale: [num] weight for the case factor
    - RC_scale: [num] weight for the reader-case interaction term
    - tauC_scale: [num] weight for the modality-case term
    - tauRCE_scale: [num] weight for the modality-reader-case-replicate interaction term

R	[vector] fix the reader factor across different simulation. Default `R = NULL`
AR	[vector] fix the modality-reader interaction. Default `AR = NULL`
BR	[vector] fix the modality-reader interaction. Default `BR = NULL`
is.within	[bol] whether the data are within-modality (AR==BR). Default `is.within=FALSE`

Details

The model is as the following structure: X.ijkl = mu + m.i + RC.jk + mRCE.ijkl

- mu = grand mean
- m.i = modalities (levels: A and B)
- RC.jk|R.j,C.k ~ N(C.k, R.j) reader-case interaction term
- mRCE.ijkl|mR.ij,mC.ik ~ N(mC.ik, mR.ij) modality-reader-case-replicate term
- C.k and mC.ik are Normal/beta distributed
- R.j and mR.ij are Inverse-Gamma distributed

Value

df [data.frame] with nR x nC x 2 rows including

- readerID: [Factor] w/ nR levels "reader1", "reader2", ...
- caseID: [Factor] w/ nC levels "case1", "case2", ...
- modalityID: [Factor] w/ 1 level config$modalityID
- score: [num] reader score

```
sim.NormalIG.Hierarchical.config
```
                              Create a configuration object for the sim.NormalIG.Hierarchical pro-
                              gram

Description

#' @description This function creates a configuration object for the Hierarchical simulation model
to be used as input for the sim.NormalIG.Hierarchical program.

Usage

```
sim.NormalIG.Hierarchical.config(
  nR = 5,
  nC = 100,
  modalityID = c("testA", "testA*"),
  C_dist = "normal",
  mu = 0,
  tau_A = 0,
  tau_B = 0,
  alpha_R = 10,
  beta_R = 1,
  sigma_C = 1,
  a_C = 0.8,
  b_C = 3,
  sigma_tauC = 1,
  alpha_tauR = 10,
  beta_tauR = 1,
  C_scale = 1,
  RC_scale = 1,
  tauC_scale = 1,
  tauRCE_scale = 1
)
```

Arguments

nR	[num] Number of readers. Default nR = 5
nC	[num] Number of cases. Default nC = 100
modalityID	[vector] List of modalityID. Default modalityID = c("testA","testA*")
C_dist	[chr] Distribution of the case. Default C_dist="normal"
mu	[num] grand mean. Default mu = 0
tau_A	[num] modality A effect. Default tau_A = 0
tau_B	[num] modality B effect. Default tau_B = 0
alpha_R	[num] shape parameter for reader. Default alpha_R = 10
beta_R	[num] scale parameter for reader. Default beta = 1
sigma_C	[num] variance of case factor (if C_dist="normal"). Default sigma_C = 1
a_C	[num] alpha for distribution of case (if C_dist="beta"). Default a_C = 0.8
b_C	[num] beta for distribution of case (if C_dist="beta"). Default b_C = 3

sigma_tauC	[num] variance of modality-case (if C_dist="normal"). Default sigma_tauC = 1
alpha_tauR	[num] shape parameter for modality-reader. Default alpha_tauR = 10
beta_tauR	[num] scale parameter for modality-reader. Default beta_tauR = 1
C_scale	[num] weight for the case factor. Default C_scale = 1
RC_scale	[num] weight for the reader-case interaction term. Default RC_scale = 1
tauC_scale	[num] weight for the modality-case term. Default tauC_scale = 1
tauRCE_scale	[num] weight for the modality-reader-case-replicate interaction term. Default tauRCE_scale = 1

Details

If no arguments, this function returns a default simulation configuration for sim.NormalIG.Hierarchical

Value

config [list] Refer to the sim.NormalIG.Hierarchical input variable

---

validateMRMCVarEstimation

Validate and characterize the MRMC limits of agreement estimates

---

Description

This function simulates MRMC study with nReader readers and nCase cases. From the output of laWRBM.anova and laBRBM.anova, we exact the variance estimations for WRBM and BRBM differences. It outputs the Monte Carlo mean of the variance estimation across all the simulation trials. The relative bias of the Monte Carlo mean comparing to the theoretical value of the variance and the coefficient of variation is also calculated.

Usage

```
validateMRMCVarEstimation(
  nR.list,
  nC.list,
  alpha_R.list,
  sigma_C.list,
  nTrials = 1000
)
```

Arguments

nR.list	A r-dimension array for the number of readers in each MRMC study
nC.list	A c-dimension array for the number of cases in each MRMC study
alpha_R.list	A a-dimension array for the reader related parameter
sigma_C.list	A b-dimension array for the case related parameter
nTrials	Number of MRMC simulations. Default is 1000

Details

Let $\hat{V}_{BR}^{12}$ denote the estimation of the variance for the BRBM difference for each simulated MRMC study, then the relative bias is defined as $relativeBias\,(\hat{V}_{BR}^{12}) = (\sum \hat{V}_{BR}^{12}/nTrials - V_{BR}^{12})/V_{BR}^{12}$, and the coefficient of variation is defined as $CV\,(\hat{V}_{BR}^{12}) = sd(\hat{V}_{BR}^{12})/V_{BR}^{12}$, where $sd()$ denote sample standard deviation.

Value

A dataframe with $r * c * a * b$ rows. Each column is as following:

nReader Number of Readers

nCase Number of Cases

alpha_R Reader related parameter

sigma_C Case related parameter

WR_var_MCmean Monte Carlo mean of variance estimation for the WRBM difference score

WR_var_MCvar Monte Carlo variance of variance estimation for the WRBM difference score

True_WR_var Theoretical value for WRBM variance derived from the simulation model

WR_var_relative_bias relative bias for WRBM variance

WR_CV coefficient of variation for WRBM variance

BR_var_MCmean Monte Carlo mean of variance estimation for the BRBM difference score

BR_var_MCvar Monte Carlo variance of variance estimation for the BRBM difference score

True_BR_var Theoretical value for BRBM variance derived from the simulation model

BR_var_relative_bias relative bias for BRBM variance

BR_CV coefficient of variation for BRBM variance

Examples

```
nR.list <- c(5)
nC.list <- c(100)
sigma_C.list <- c(1)
alpha_R.list <- c(10)
#result <- validateMRMCVarEstimation(nR.list, nC.list, alpha_R.list, sigma_C.list)
```

---

validateSimulation   *Verify the simulation is consistent with the derived theoretical values*

Description

This function simulates independent WRBM and BRBM difference scores and outputs the Monte Carlo mean and variance across the trials for each parameter setting. The relative bias of the Monte Carlo variance comparing to the theoretical value of the variance is also calculated.

Usage

```
validateSimulation(alpha_R.list, sigma_C.list, nTrials = 1e+05)
```

Arguments

`alpha_R.list`	A a-dimension array for the reader related parameter
`sigma_C.list`	A b-dimension array for the case related parameter
`nTrials`	Number of independent trials. Default is 100000

Details

Let $\tilde{V}_{BR}^{12}$ denote the Monte Carlo variance of the BRBM difference, then the relative bias is defined as $relativeBias\,(\tilde{V}_{BR}^{12}) = (\tilde{V}_{BR}^{12} - V_{BR}^{12})/V_{BR}^{12}$.

Value

A dataframe with $a * b$ rows. Each column is as following:

sigma_C Case related parameter

alpha_R Reader related parameter

WR_mean Monte Carlo mean of the WRBM difference score

WR_var Monte Carlo variance of the WRBM difference score

BR_mean Monte Carlo mean of the BRBM difference score

BR_var Monte Carlo variance of the BRBM difference score

True_WR_var Theoretical value for WRBM variance derived from the simulation model

True_BR_var Theoretical value for BRBM variance derived from the simulation model

WR_var_relative_bias relative bias for WRBM variance

BR_var_relative_bias relative bias for BRBM variance

Examples

```
sigma_C.list <- c(1)
alpha_R.list <- c(10)
#result <- validateSimulation(alpha_R.list, sigma_C.list)
```

Index