Package ‘CARM’

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Title Covariate-Adjusted Adaptive Randomization via Mahalanobis-Distance

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Description In randomized controlled trial (RCT), balancing covariate is often one of the most important concern. CARM package provides functions to balance the covariates and generate allocation sequence by covariate-adjusted Adaptive Randomization via Mahalanobis-distance (ARM) for RCT. About what ARM is and how it works please see Y. Qin, Y. Li, W. Ma, H. Yang, and F. Hu (2024). `
tive randomization via Mahalanobis distance'' Statistica Sinica. <doi:10.5705/ss.202020.0440>. In addition, the package is also suitable for the randomization process of multi-arm trials. For details, please see Yang H, Qin Y, Wang F, et al. (2023). ``Balancing covariates in multi-arm trials via adaptive randomization'' Computational Statistics & Data Analysis.<doi:10.1016/j.csda.2022.107642>.

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Contents

`CARM-package` *CARM: Covariate-adjusted Adaptive Randomization via Mahalanobis distance*

Description

The **CARM** package provides functions to implement covariate-adjusted adaptive randomization based on Mahalanobis distance.

Randomization functions

See `ARM()`, `ARMM()`, and `stratum_ARM()` for usage details.

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`ARM` *Adaptive Randomization via Mahalanobis Distance*

Description

Allocates patients to one of two treatments using Adaptive Randomization via Mahalanobis Distance proposed by Yichen Qin,Yang Li, Wei Ma, Haoyu Yang, and Feifang Hu.(2022)

Usage

```
ARM(covariate, assignment, q = 0.75)
```

Arguments

`covariate`	a data frame. A row of the dataframe corresponds to the covariate profile of a patient.
`assignment`	a vector. If partial patients had been allocated , please input their allocation. IF all the patients are not be allocated, please input 'assignment = NA' directly.
`q`	the biased coin probability. q should be larger than 1/2 and less than 1, default = 0.75

Details

Suppose that n patients are to be assigned to two treatment groups. Consider p continuous covariates for each patient. T_i is the assignment of the ith patient. The proposed procedure to assign units to treatment groups, namely adaptive randomization via Mahalanobis distance (ARM), is outlined below.

(1) Arrange all n units randomly into a sequence $x_1, ..., x_n$.

(2) Assign the first two units with $T_1 = 1$ and $T_2 = 2$.

(3) Suppose that $2i$ units have been assigned to treatment groups, for the $2i + 1$-th and $2i + 2$-th units:

(3a) If the $2i + 1$-th unit is assigned to treatment 1 and the $2i + 2$-th unit to treatment 2, then calculate the potential Mahalanobis distance, between the updated treatment groups. with $2i + 2$ units, $M_1(2i + 2)$.

(3b) Similarly, if the $2i + 1$-th unit is assigned to treatment 2 and the $2i + 2$-th unit to treatment 1, then calculate the other potential Mahalanobis distance, $M_2(2i + 2)$.

(4) Assign the $2i + 1$-th unit to treatment groups according to the following probabilities:

if $M_1(2i + 2) < M_2(2i + 2)$, $P(T_{2i+1} = 1) = q$;

if $M_1(2i + 2) > M_2(2i + 2)$, $P(T_{2i+1} = 1) = 1 - q$;

if $M_1(2i + 2) = M_2(2i + 2)$, $P(T_{2i+1} = 1) = 0.5$.

(5) Repeat the last two steps until all units are assigned. If n is odd, assign the last unit to two treatments with equal probabilities.

Mahalanobis distance $M(n)$ between the sample means across different treatment groups is:

$$M(n) = np(1 - p)(\hat{x_1} - \hat{x_2})^T cov(x)^{-1}(\hat{x_1} - \hat{x_2}$$

See the reference for more details.

Value

An object of class "ARM" is a list containing the following components:

`assignment`	Allocation of patients.
`sample_size`	The number of patients in treatment 1 and treatment 2 respectively.
`Mahalanobis_Distance`	Mahalanobis distance between treatment groups 1 and 2.

References

Qin, Y., Li, Y., Ma, W., Yang, H., & Hu, F. (2024). ADAPTIVE RANDOMIZATION VIA MAHALANOBIS DISTANCE. Statistica Sinica, 34, 353-375.

Examples

```
library(MASS)
#simulate covariates of patients
p <- 6; n <- 30
sigma <- diag(p); mean <- c(rep(0,p))
data <- mvrnorm(n, mean, sigma)
covariate <- as.data.frame(data)
#IF all the patients are not be allocated
ARM(covariate = covariate, assignment = NA, q=0.75)
#IF you had allocated partial patients
ARM(covariate = covariate,assignment = c(1,2),q=0.75)
```

`ARMM` *Adaptive Randomization via Mahalanobis distance for Multi-arm design*

Description

Randomize patients into treatment groups for multi-arm trials using ARMM proposed by Haoyu Yang, Yichen Qin, Yang Li, Fan Wang, and Feifang Hu.(2022)

Usage

```
ARMM(covariate, assignment, K, q = 0.75, method)
```

Arguments

`covariate`	a data frame. A row of the dataframe corresponds to the covariate profile of a patient.
`assignment`	a vector. If partial patients had been allocated , please input their allocation. IF all the patients are not be allocated, please input 'assignment = NA' directly.
`K`	an integer; number of arms of the trial.
`q`	the biased coin probability. q should be larger than 1/2 and less than 1, default = 0.75
`method`	Methods for calculating Mahalanobis distance, input one of these texts: 'mean', 'max' or 'median'.

Details

Suppose n units (participants) are to be assigned to K treatment groups. For each unit $i, i = 1, ..., n$ and treatment $j, j = 1, ..., K$, define the assignment matrix $[T_{ij}]^{n*K}$, where $T_{ij} = 1$ indicates unit i receives treatment j. Consider p continuous covariates, let $x_i = (x_{i1}, ..., x_{in})^T$.

The proposed method, namely the adaptive randomization via Mahalanobis distance for multi-arm design (ARMM), is outlined below. The implement of ARMM is similar to ARM.

First assume that n units are in a sequence and then assign the first K units to K treatment groups randomly as the initialization. Then, the following units are assigned in blocks of K sequentially and adaptively until all the units are assigned. For K units are assigned to K groups, there are in total $K!$ possible allocations. Calculate $K!$ potential overall covariate imbalance measurement according to pairwise Mahalanobis distance under the $K!$ possible allocations. Choose the allocation which corresponds to the smallest Mahalanobis distance with a probability of q across all potential allocations. Repeat the process until all units are assigned.

For any pair of treatments s and t among the K treatment groups, calculate the Mahalanobis distance by:

$$M_{s,t}(n) = 2n/K/K(\hat{x}_1 - \hat{x}_2)^T cov(x)^{-1}(\hat{x}_1 - \hat{x}_2)$$

In total, there are C_K^2 pairs of Mahalanobis distances among K treatment groups.Finally, calculate the mean, the median or the maximum to represent the total imbalance.

See the reference for more details.

Value

An object of class "ARMM" is a list containing the following components:

`assignment`	Allocation of patients.
`sample_size`	The number of patients from treatment 1 to treatment K respectively.
`Mahalanobis_Distance`	Mahalanobis distance among treatment groups .

References

Yang H, Qin Y, Wang F, et al. Balancing covariates in multi-arm trials via adaptive randomization. Computational Statistics & Data Analysis, 2023, 179: 107642. https://doi.org/10.1016/j.csda.2022.107642

Examples

```
library(MASS)
#simulate covariates of patients
p <- 6; n <- 30
sigma <- diag(p); mean <- c(rep(0,p))
data <- mvrnorm(n, mean, sigma)
covariate <- as.data.frame(data)
#IF all the patients are not be allocated
ARMM(covariate = covariate, assignment = NA, K = 3, q = 0.75, method = 'mean')
#IF you had allocated partial patients
ARMM(covariate = covariate, assignment = c(1,2), K=4, q=0.75, method = 'max')
```

`covariate` *Example dataset: covariate*

Description

Covariate table for implement of CARM randomization.

Usage

```
covariate
```

Format

A data frame with N rows and P columns:

center the hospital of trial implement

male 1 = male, 0 = female

age age

X_6MWD1 Baseline 6-minute walk distance, 6MWD

SF12_PCS1 Baseline SF-12 Physical Health Component Scores (PCS-12)

Source

Telerehabilitation program for COVID-19 survivors (TERECO) - Randomized controlled trial. Published Jul 11, 2021 on Dryad. https://doi.org/10.5061/dryad.59zw3r27n

Examples

```
data(covariate)
str(covariate)
```

`stratum_ARM` *Stratified Adaptive Randomization via Mahalanobis Distance*

Description

Update Strata for ARM

Usage

```
stratum_ARM(
  covariate,
  assignment,
  cont_var = c("C1"),
  cat_var = c("N1", "N2"),
  levels_list = list(C1 = 0:1),
  q = 0.75
)
```

Arguments

`covariate`	a data frame. A row of the dataframe corresponds to the covariate profile of a patient.
`assignment`	a vector. If partial patients had been allocated , please input their allocation. IF all the patients are not be allocated, please input 'assignment = NA' directly.
`cont_var`	name of continuous covariates
`cat_var`	name of categorical covariates
`levels_list`	levels of each categorical covariate
`q`	the biased coin probability. q should be larger than 1/2 and less than 1, default = 0.75

Value

An object of class "ARM" is a list containing the following components:

`assignment`	Allocation of patients.
`sample_size`	The number of patients in treatment 1 and treatment 2 respectively.
`Mahalanobis_Distance`	Mahalanobis distance between treatment groups 1 and 2.

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