

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 (2022). "Covariate-adjusted adaptive 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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CARM-package	CARM: Covariate-adjusted Adaptive Randomization via Mahalanobis-distance
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Description

The CARM package provides function of implement of randomization:

ARM functions

please ?ARM and ?ARMM to view function usage

ARM	Adaptive Randomization via Mahalanobis Distance
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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 i th 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 $x_1, \dots, x_n$.
 - (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., Y. Li, W. Ma, H. Yang, and F. Hu (2022). Adaptive randomization via mahalanobis distance. Statistica Sinica.DOI:<10.5705/ss.202020.0440>.

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 $i, i = 1, \dots, n$ and treatment $j, j = 1, \dots, K$, define the assignment matrix $[T_{ij}]^{n \times K}$, where $T_{ij} = 1$ indicates unit i receives treatment j . Consider p continuous covariates, let $x_i = (x_{i1}, \dots, x_{in})^T$.

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')
```

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