Package ‘CARM’

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Title  Covariate-Adjusted Adaptive Randomization via Mahalanobis-Distance

Version  1.1.0

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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). "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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**Description**

The CARM package provides function of implement of randomization:

**ARM functions**

please ?ARM and ?ARMM to view function usage

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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 $i$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 $x_1, ..., x_n$.
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:

$$M(n) = np(1 - p)(\bar{x}_1 - \bar{x}_2)^T cov(x)^{-1}(\bar{x}_1 - \bar{x}_2)$$

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**


**Examples**

```r
library(MASS)
#simulate covariates of patients
p <- 6; n <- 30
sigma <- diag(p); mean <- c(rep(0,p))
data <- mvnrnorm(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 data frame corresponds to the covariate profile of a patient.
assignment a vector. If partial patients have been allocated, please input their allocation. If all the patients are not 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 \times K}, where T_{ij} = 1 indicates unit i receives treatment j. Consider p continuous covariates, let \( x_i = (x_{i1}, ..., x_{ip})^T \).

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:

\[
M_{s,t}(n) = 2n/K/K(\hat{x}_1 - \hat{x}_2)^T \text{cov}(x)^{-1}(\hat{x}_1 - \hat{x}_2)
\]
In total, there are $C^2_K$ 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**


**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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