

# Package ‘CARM’

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**Title** Covariate-Adjusted Adaptive Randomization via  
Mahalanobis-Distance

**Version** 2.0.0

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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 (2024). "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 | <i>CARM: Covariate-adjusted Adaptive Randomization via Mahalanobis distance</i> |
|--------------|---------------------------------------------------------------------------------|

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## 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 | <i>Adaptive Randomization via Mahalanobis Distance</i> |
|-----|--------------------------------------------------------|

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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., 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)
```

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|      |                                                                             |
|------|-----------------------------------------------------------------------------|
| ARMM | <i>Adaptive Randomization via Mahalanobis distance for Multi-arm design</i> |
|------|-----------------------------------------------------------------------------|

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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:

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

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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|           |                                   |
|-----------|-----------------------------------|
| covariate | <i>Example dataset: covariate</i> |
|-----------|-----------------------------------|

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### 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)
```

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|             |                                                                   |
|-------------|-------------------------------------------------------------------|
| stratum_ARM | <i>Stratified Adaptive Randomization via Mahalanobis Distance</i> |
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### 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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