Package 'adace'

July 22, 2025

Title Estimator of the Adherer Average Causal Effect

Version 1.0.2

Imports reshape2, pracma

Description Estimate the causal treatment effect for subjects that can adhere to one or both of the treatments. Given longitudinal data with missing observations, consistent causal effects are calculated. Unobserved potential outcomes are estimated through direct integration as described in: Qu et al., (2019) <doi:10.1080/19466315.2019.1700157> and Zhang et. al., (2021) <doi:10.1080/19466315.2021.1891965>.

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Encoding UTF-8

RoxygenNote 7.2.3

Depends R (>= 4.0.0)

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Config/testthat/edition 3

NeedsCompilation no

Author Jiaxun Chen [aut],
Rui Jin [aut],
Yongming Qu [aut],
Run Zhuang [aut, cre],
Ying Zhang [aut],
Eli Lilly and Company [cph]

Maintainer Run Zhuang <capecod0321@gmail.com>

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Contents

`est_S_Plus_Plus_MethodA` *Estimate the treatment effects for population S_++ using Method A*

Description

The est_S_Plus_Plus_MethodA function produces estimation of treatment effects for the population that can adhere to both treatments (S_++). This method (Method A) is based on the potential outcome under the hypothetical alternative treatment .

Usage

```
est_S_Plus_Plus_MethodA(X, A, Z, Y, TRT)
```

Arguments

`X`	Matrix of baseline variables. Each row contains the baseline values for each patient.
`A`	Matrix of indicator for adherence. Each row of A contains the adherence information for each patient. Each column contains the adherence indicator after each intermediate time point. A = 1 means adherence and A = 0 means non-adherence. Monotone missing is assumed.
`Z`	List of matrices. Intermediate efficacy and safety outcomes that can affect the probability of adherence. For each matrix, the structure is the same as variable X.
`Y`	Numeric vector of the final outcome (E.g., primary endpoint).
`TRT`	Numeric vector of treatment assignment. TRT = 0 for the control group and TRT = 1 for the experimental treatment group.

Details

The average treatment difference can be denoted as

$$latex$$

The method A exploits the joint distribution of X, Z, and Y by creating a "virtual twin" of the patient from the assigned treatment and estimate the potential outcome of that patient on the alternative treatment for comparison. The variance estimation for the treatment effect is constructed using the sandwich method. Details can be found in the references.

The intermediate post-baseline measurements for each intermediate time point are estimated by regressing Z on X using subjects with experimental treatment or placebo. The covariance matrix is estimated based on the residuals of the regression.

The probability of adherence is estimated by regressing A on X, Z by using all data. The logistic regression is used in this function.

The expected treatment effect is estimated by regression Y on X, Z using subjects with experimental treatment or placebo.

The indicator of adherence prior to the first intermediate time point is not included in this model since this function assumes no intercurrent events prior to the first time point. Thus, the first element of Z should not have missing values.

Each element of Z contains the variables at each intermediate time point, i.e., the first element of Z contains the intermediate variables at time point 1, the second element contains the intermediate variables at time point 2, etc.

Value

A list containing the following components:

`trt_diff`	Estimate of treatment difference for S_++ using Method A
`se`	Estimated standard error
`res1`	Estimated mean for the treatment group
`res0`	Estimated mean for the control group
`se_res1`	Estimated standard error for the treatment group
`se_res0`	Estimated standard error for the control group

References

Qu, Yongming, et al. "A general framework for treatment effect estimators considering patient adherence." Statistics in Biopharmaceutical Research 12.1 (2020): 1-18.

Zhang, Ying, et al. "Statistical inference on the estimators of the adherer average causal effect." Statistics in Biopharmaceutical Research (2021): 1-4.

Examples

```
library(MASS)
j<- 500
p_z <- 6 ## dimension of Z at each time point
n_t <- 4 ## number of time points
alphas <- list()
gammas <- list()
z_para <- c(-1/p_z, -1/p_z, -1/p_z, -1/p_z, -0.5/p_z,-0.5/p_z, -0.5/p_z,
-0.5/p_z)
Z <- list()
beta = c(0.2, -0.3, -0.01, 0.02, 0.03, 0.04, rep(rep(0.02,p_z), n_t))
beta_T = -0.2
sd_z_x = 0.4
X = mvrnorm(j, mu=c(1,5,6,7,8), Sigma=diag(1,5))
TRT = rbinom(j, size = 1,  prob = 0.5)
Y_constant <- beta[1]+(X%*%beta[2:6])
Y0 <- 0
Y1 <- 0
A <- A1 <- A0 <- matrix(NA, nrow = j, ncol = n_t)
gamma <- c(1,-.1,-0.05,0.05,0.05,.05)
A0[,1] <- rbinom(j, size = 1, prob = 1/(1+exp(-(gamma[1] +
```

```
(X %*% gamma[2:6])))))
A1[,1] <- rbinom(j, size = 1, prob = 1/(1+exp(-(gamma[1] +
(X %*% gamma[2:6])))))
A[,1] <- A1[,1]*TRT + A0[,1]*(1-TRT)
for(i in 2:n_t){
  alphas[[i]] <- matrix(rep(c(2.3, -0.3, -0.01, 0.02, 0.03, 0.04, -0.4),
  p_z),ncol=p_z)
  gammas[[i]] <- c(1, -0.1, 0.2, 0.2, 0.2, 0.2, rep(z_para[i],p_z))
  Z0 <- alphas[[i]][1,]+(X%*%alphas[[i]][2:6,]) + mvrnorm(j, mu = rep(0,p_z)
  , Sigma = diag(sd_z_x,p_z))
  Z1 <- alphas[[i]][1,]+(X%*%alphas[[i]][2:6,])+alphas[[i]][7,] +
    mvrnorm(j, mu = rep(0,p_z), Sigma = diag(sd_z_x,p_z))
  Z[[i]] <- Z1*TRT + Z0*(1-TRT)
  Y0 <- (Y0 + Z0 %*% matrix(beta[ (7 + (i-1)*p_z):
  (6+p_z*i)],ncol = 1) )[,1]
  Y1 <- (Y1 + Z1 %*% matrix(beta[ (7 + (i-1)*p_z):
  (6+p_z*i)],ncol = 1) )[,1]
  A0[,i] <- rbinom(j, size = 1,
                   prob = 1/(1+exp(-(gammas[[i]][1]+
                   (X%*%gammas[[i]][2:6])+Z0%*%matrix(gammas[[i]][7:
                   (7+p_z-1)], ncol=1))[,1])))*A0[,i-1]
  A1[,i] <- rbinom(j, size = 1,
                   prob = 1/(1+exp(-(gammas[[i]][1]+
                   (X%*%gammas[[i]][2:6])+Z1%*%matrix(gammas[[i]][7:
                   (7+p_z-1)], ncol=1))[,1])))*A1[,i-1]

  A[,i] <- A1[,i]*TRT + A0[,i]*(1-TRT)
}
Y0 <- Y0 + rnorm(j, mean = 0, sd = 0.3) + Y_constant
Y1 <- Y1 + + beta_T + rnorm(j, mean = 0, sd = 0.3) + Y_constant
Y <- as.vector( Y1*TRT+Y0*(1-TRT))
for(i in 2:n_t){
  Z[[i]][A[,(i-1)]==0,] <- NA
}
Z[[1]] <- matrix(NA, nrow=nrow(Z1),ncol=ncol(Z1))
Y[A[,n_t] == 0] <- NA
# estimate the treatment difference
fit <- est_S_Plus_Plus_MethodA(X, A, Z, Y, TRT)
fit
# Calculate the true values
true1 <- mean(Y1[A1[,n_t]==1 &A0[,n_t]==1])
true1
true0 <- mean(Y0[A1[,n_t]==1 &A0[,n_t]==1])
true0
true_d  =  true1 - true0
true_d
```

`est_S_Plus_Plus_MethodB` *Estimate the treatment effects for population S_++ using Method B*

Description

The est_S_Plus_Plus_MethodB function produces estimation of treatment effects for the population that can adhere to both treatments (S_++). This method (Method B) is based on the inverse probability weighting (IPW) to estimate the treatment difference in a targeted population.

Usage

```
est_S_Plus_Plus_MethodB(X, A, Z, Y, TRT)
```

Arguments

X	Matrix of baseline variables. Each row contains the baseline values for each patient.
A	Matrix of indicator for adherence. Each row of A contains the adherence information for each patient across multiple time points. Each column contains the adherence indicator after each intermediate time point. A = 1 means adherence and A=0 means non-adherence. Monotone missing is assumed.
Z	List of matrices. Intermediate efficacy and safety outcomes that can affect the probability of adherence. For each matrix, the structure is the same as variable X.
Y	Numeric vector of the final outcome (E.g., primary endpoint).
TRT	Numeric vector of treatment assignment. TRT=0 for the control group and TRT =1 for the experimental treatment group.

Details

The average treatment difference can be denoted as

$$latex$$

The method B exploits the joint distribution of X, Z, and A to estimate the probability that a patient would adhere to the hypothetical alternative treatment, and then use IPW to estimate treatment different for a given population. The variance estimation for the treatment effect is constructed using the sandwich method. Details can be found in the references.

The intermediate post-baseline measurements for each intermediate time point are estimated by regressing Z on X using subjects with experimental treatment or placebo. The covariance matrix is estimated based on the residuals of the regression.

The probability of adherence is estimated by regressing A on X, Z by using all data. The logistic regression is used in this function.

The indicator of adherence prior to the first intermediate time point is not included in this model since this function assumes no intercurrent events prior to the first time point. Thus, the first element of Z should not have missing values.

Each element of Z contains the variables at each intermediate time point, i.e., the first element of Z contains the intermediate variables at time point 1, the second element contains the intermediate variables at time point 2, etc.

Value

A list containing the following components:

trt_diff	Estimate of treatment difference for S_++ using Method B
se	Estimated standard error
res1	Estimated mean for the treatment group
res0	Estimated mean for the control group
se_res1	Estimated standard error for the treatment group
se_res0	Estimated standard error for the control group

References

Qu, Yongming, et al. "A general framework for treatment effect estimators considering patient adherence." Statistics in Biopharmaceutical Research 12.1 (2020): 1-18.

Zhang, Ying, et al. "Statistical inference on the estimators of the adherer average causal effect." Statistics in Biopharmaceutical Research (2021): 1-4.

Examples

```
library(MASS)
j<- 500
p_z <- 6 ## dimension of Z at each time point
n_t <- 4 ## number of time points
alphas <- list()
gammas <- list()
z_para <- c(-1/p_z, -1/p_z, -1/p_z, -1/p_z, -0.5/p_z,-0.5/p_z, -0.5/p_z,
-0.5/p_z)
Z <- list()
beta = c(0.2, -0.3, -0.01, 0.02, 0.03, 0.04, rep(rep(0.02,p_z), n_t))
beta_T = -0.2
sd_z_x = 0.4
X = mvrnorm(j, mu=c(1,5,6,7,8), Sigma=diag(1,5))
TRT = rbinom(j, size = 1,  prob = 0.5)
Y_constant <- beta[1]+(X%*%beta[2:6])
Y0 <- 0
Y1 <- 0
A <- A1 <- A0 <- matrix(NA, nrow = j, ncol = n_t)
gamma <- c(1,-.1,-0.05,0.05,0.05,.05)
A0[,1] <- rbinom(j, size = 1, prob = 1/(1+exp(-(gamma[1] +
(X %*% gamma[2:6])))))
A1[,1] <- rbinom(j, size = 1, prob = 1/(1+exp(-(gamma[1] +
(X %*% gamma[2:6])))))
A[,1] <- A1[,1]*TRT + A0[,1]*(1-TRT)
for(i in 2:n_t){
  alphas[[i]] <- matrix(rep(c(2.3, -0.3, -0.01, 0.02, 0.03, 0.04, -0.4),
  p_z),ncol=p_z)
  gammas[[i]] <- c(1, -0.1, 0.2, 0.2, 0.2, 0.2, rep(z_para[i],p_z))
  Z0 <- alphas[[i]][1,]+(X%*%alphas[[i]][2:6,]) + mvrnorm(j, mu = rep(0,p_z)
  , Sigma = diag(sd_z_x,p_z))
```

```
  Z1 <- alphas[[i]][1,]+(X%*%alphas[[i]][2:6,])+alphas[[i]][7,] +
    mvrnorm(j, mu = rep(0,p_z), Sigma = diag(sd_z_x,p_z))
  Z[[i]] <- Z1*TRT + Z0*(1-TRT)
  Y0 <- (Y0 + Z0 %*% matrix(beta[ (7 + (i-1)*p_z):
  (6+p_z*i)],ncol = 1) )[,1]
  Y1 <- (Y1 + Z1 %*% matrix(beta[ (7 + (i-1)*p_z):
  (6+p_z*i)],ncol = 1) )[,1]
  A0[,i] <- rbinom(j, size = 1,
                   prob = 1/(1+exp(-(gammas[[i]][1]+
                   (X%*%gammas[[i]][2:6])+Z0%*%matrix(gammas[[i]][7:
                   (7+p_z-1)], ncol=1))[,1])))*A0[,i-1]
  A1[,i] <- rbinom(j, size = 1,
                   prob = 1/(1+exp(-(gammas[[i]][1]+
                   (X%*%gammas[[i]][2:6])+Z1%*%matrix(gammas[[i]][7:
                   (7+p_z-1)], ncol=1))[,1])))*A1[,i-1]

  A[,i] <- A1[,i]*TRT + A0[,i]*(1-TRT)
}
Y0 <- Y0 + rnorm(j, mean = 0, sd = 0.3) + Y_constant
Y1 <- Y1 + + beta_T + rnorm(j, mean = 0, sd = 0.3) + Y_constant
Y <- as.vector( Y1*TRT+Y0*(1-TRT))
for(i in 2:n_t){
  Z[[i]][A[,(i-1)]==0,] <- NA
}
Z[[1]] <- matrix(NA, nrow=nrow(Z1),ncol=ncol(Z1))
Y[A[,n_t] == 0] <- NA
# estimate the treatment difference
fit <- est_S_Plus_Plus_MethodB(X, A, Z, Y, TRT)
fit
# Calculate the true values
true1 <- mean(Y1[A1[,n_t]==1 &A0[,n_t]==1])
true1
true0 <- mean(Y0[A1[,n_t]==1 &A0[,n_t]==1])
true0
true_d  =  true1 - true0
true_d
```

`est_S_Star_Plus_MethodA` *Estimate the treatment effects for population S_*+ using Method A*

Description

The est_S_Star_Plus_MethodA function produces estimation of treatment effects for the population that can adhere to the experimental treatment (S_*+). This method (Method A) is based on the potential outcome under the hypothetical alternative treatment .

Usage

```
est_S_Star_Plus_MethodA(X, A, Z, Y, TRT)
```

Arguments

X	Matrix of baseline variables. Each row contains the baseline values for each patient.
A	Matrix of indicator for adherence. Each row of A contains the adherence information for each patient. Each column contains the adherence indicator after each intermediate time point. A = 1 means adherence and A=0 means non-adherence. Monotone missing is assumed.
Z	List of matrices. Intermediate efficacy and safety outcomes that can affect the probability of adherence. For each matrix, the structure is the same as variable X.
Y	Numeric vector of the final outcome (E.g., primary endpoint).
TRT	Numeric vector of treatment assignment. TRT=0 for the control group and TRT =1 for the experimental treatment group.

Value

A list containing the following components:

trt_diff	Estimate of treatment difference for S_++ using Method A
se	Estimated standard error
res1	Estimated mean for the treatment group
res0	Estimated mean for the control group
se_res1	Estimated standard error for the treatment group
se_res0	Estimated standard error for the control group

#' @details The average treatment difference can be denoted as

$$latex$$

The method A exploits the joint distribution of X, Z, and Y by creating a "virtual twin" of the patient from the assigned treatment and estimate the potential outcome of that patient on the alternative treatment for comparison. The variance estimation for the treatment effect is constructed using the sandwich method. Details can be found in the references.

The intermediate post-baseline measurements for each intermediate time point are estimated by regressing Z on X using subjects with experimental treatment or placebo. The covariance matrix is estimated based on the residuals of the regression.

The probability of adherence is estimated by regressing A on X, Z by using all data. The logistic regression is used in this function.

The expected treatment effect is estimated by regression Y on X, Z using subjects with experimental treatment or placebo.

The indicator of adherence prior to the first intermediate time point is not included in this model since this function assumes no intercurrent events prior to the first time point. Thus, the first element of Z should not have missing values.

Each element of Z contains the variables at each intermediate time point, i.e., the first element of Z contains the intermediate variables at time point 1, the second element contains the intermediate variables at time point 2, etc.

References

Qu, Yongming, et al. "A general framework for treatment effect estimators considering patient adherence." Statistics in Biopharmaceutical Research 12.1 (2020): 1-18.

Zhang, Ying, et al. "Statistical inference on the estimators of the adherer average causal effect." Statistics in Biopharmaceutical Research (2021): 1-4.

Examples

```
library(MASS)
j<- 500
p_z <- 6 ## dimension of Z at each time point
n_t <- 4 ## number of time points
alphas <- list()
gammas <- list()
z_para <- c(-1/p_z, -1/p_z, -1/p_z, -1/p_z, -0.5/p_z,-0.5/p_z, -0.5/p_z,
-0.5/p_z)
Z <- list()
beta = c(0.2, -0.3, -0.01, 0.02, 0.03, 0.04, rep(rep(0.02,p_z), n_t))
beta_T = -0.2
sd_z_x = 0.4
X = mvrnorm(j, mu=c(1,5,6,7,8), Sigma=diag(1,5))
TRT = rbinom(j, size = 1,  prob = 0.5)
Y_constant <- beta[1]+(X%*%beta[2:6])
Y0 <- 0
Y1 <- 0
A <- A1 <- A0 <- matrix(NA, nrow = j, ncol = n_t)
gamma <- c(1,-.1,-0.05,0.05,0.05,.05)
A0[,1] <- rbinom(j, size = 1, prob = 1/(1+exp(-(gamma[1] +
(X %*% gamma[2:6])))))
A1[,1] <- rbinom(j, size = 1, prob = 1/(1+exp(-(gamma[1] +
(X %*% gamma[2:6])))))
A[,1] <- A1[,1]*TRT + A0[,1]*(1-TRT)
for(i in 2:n_t){
  alphas[[i]] <- matrix(rep(c(2.3, -0.3, -0.01, 0.02, 0.03, 0.04, -0.4),
  p_z),ncol=p_z)
  gammas[[i]] <- c(1, -0.1, 0.2, 0.2, 0.2, 0.2, rep(z_para[i],p_z))
  Z0 <- alphas[[i]][1,]+(X%*%alphas[[i]][2:6,]) + mvrnorm(j, mu = rep(0,p_z)
  , Sigma = diag(sd_z_x,p_z))
  Z1 <- alphas[[i]][1,]+(X%*%alphas[[i]][2:6,])+alphas[[i]][7,] +
    mvrnorm(j, mu = rep(0,p_z), Sigma = diag(sd_z_x,p_z))
  Z[[i]] <- Z1*TRT + Z0*(1-TRT)
  Y0 <- (Y0 + Z0 %*% matrix(beta[ (7 + (i-1)*p_z):
  (6+p_z*i)],ncol = 1) )[,1]
  Y1 <- (Y1 + Z1 %*% matrix(beta[ (7 + (i-1)*p_z):
  (6+p_z*i)],ncol = 1) )[,1]
  A0[,i] <- rbinom(j, size = 1,
                   prob = 1/(1+exp(-(gammas[[i]][1]+
                   (X%*%gammas[[i]][2:6])+Z0%*%matrix(gammas[[i]][7:
                   (7+p_z-1)], ncol=1))[,1]))*A0[,i-1]
  A1[,i] <- rbinom(j, size = 1,
                   prob = 1/(1+exp(-(gammas[[i]][1]+
```

```
                    (X%*%gammas[[i]][2:6])+Z1%*%matrix(gammas[[i]][7:
                    (7+p_z-1)], ncol=1))[,1])))*A1[,i-1]

  A[,i] <- A1[,i]*TRT + A0[,i]*(1-TRT)
}
Y0 <- Y0 + rnorm(j, mean = 0, sd = 0.3) + Y_constant
Y1 <- Y1 + + beta_T + rnorm(j, mean = 0, sd = 0.3) + Y_constant
Y <- as.vector( Y1*TRT+Y0*(1-TRT))
for(i in 2:n_t){
  Z[[i]][A[,(i-1)]==0,] <- NA
}
Z[[1]] <- matrix(NA, nrow=nrow(Z1),ncol=ncol(Z1))
Y[A[,n_t] == 0] <- NA
# estimate the treatment difference
fit <- est_S_Star_Plus_MethodA(X, A, Z, Y, TRT)
fit
# Calculate the true values
true1 <- mean(Y1[A1[,n_t]==1])
true1
true0 <- mean(Y0[A1[,n_t]==1])
true0
true_d  =  true1 - true0
true_d
```

`est_S_Star_Plus_MethodB` *Estimate the treatment effects for population S_*+ using Method B*

Description

The est_S_Star_Plus_MethodB function produces estimation of treatment effects for the population that can adhere to the experimental treatment (S_*+). This method (Method B) is based on the potential outcome under the hypothetical alternative treatment .

Usage

```
est_S_Star_Plus_MethodB(X, A, Z, Y, TRT)
```

Arguments

X	Matrix of baseline variables. Each row contains the baseline values for each patient across multiple time points.
A	Matrix of indicator for adherence. Each row of A contains the adherence information for each patient. Each column contains the adherence indicator after each intermediate time point. A = 1 means adherence and A=0 means non-adherence. Monotone missing is assumed.

Z	List of matrices. Intermediate efficacy and safety outcomes that can affect the probability of adherence. For each matrix, the structure is the same as variable X.
Y	Numeric vector of the final outcome (E.g., primary endpoint).
TRT	Numeric vector of treatment assignment. TRT=0 for the control group and TRT =1 for the experimental treatment group.

Value

A list containing the following components:

trt_diff	Estimate of treatment difference for S_*+ using Method B
se	Estimated standard error
res1	Estimated mean for the treatment group
res0	Estimated mean for the control group
se_res1	Estimated standard error for the treatment group
se_res0	Estimated standard error for the control group

#' @details The average treatment difference can be denoted as

$$latex$$

The method B exploits the joint distribution of X, Z, and A to estimate the probability that a patient would adhere to the hypothetical alternative treatment, and then use IPW to estimate treatment different for a given population. The variance estimation for the treatment effect is constructed using the sandwich method. Details can be found in the references.

The intermediate post-baseline measurements for each intermediate time point are estimated by regressing Z on X using subjects with experimental treatment or placebo. The covariance matrix is estimated based on the residuals of the regression.

The probability of adherence is estimated by regressing A on X, Z by using all data. The logistic regression is used in this function.

The indicator of adherence prior to the first intermediate time point is not included in this model since this function assumes no intercurrent events prior to the first time point. Thus, the first element of Z should not have missing values.

Each element of Z contains the variables at each intermediate time point, i.e., the first element of Z contains the intermediate variables at time point 1, the second element contains the intermediate variables at time point 2, etc.

References

Qu, Yongming, et al. "A general framework for treatment effect estimators considering patient adherence." Statistics in Biopharmaceutical Research 12.1 (2020): 1-18.

Zhang, Ying, et al. "Statistical inference on the estimators of the adherer average causal effect." Statistics in Biopharmaceutical Research (2021): 1-4.

Examples

```
library(MASS)
j<- 500
p_z <- 6 ## dimension of Z at each time point
n_t <- 4 ## number of time points
alphas <- list()
gammas <- list()
z_para <- c(-1/p_z, -1/p_z, -1/p_z, -1/p_z, -0.5/p_z,-0.5/p_z, -0.5/p_z,
-0.5/p_z)
Z <- list()
beta = c(0.2, -0.3, -0.01, 0.02, 0.03, 0.04, rep(rep(0.02,p_z), n_t))
beta_T = -0.2
sd_z_x = 0.4
X = mvrnorm(j, mu=c(1,5,6,7,8), Sigma=diag(1,5))
TRT = rbinom(j, size = 1,  prob = 0.5)
Y_constant <- beta[1]+(X%*%beta[2:6])
Y0 <- 0
Y1 <- 0
A <- A1 <- A0 <- matrix(NA, nrow = j, ncol = n_t)
gamma <- c(1,-.1,-0.05,0.05,0.05,.05)
A0[,1] <- rbinom(j, size = 1, prob = 1/(1+exp(-(gamma[1] +
(X %*% gamma[2:6])))))
A1[,1] <- rbinom(j, size = 1, prob = 1/(1+exp(-(gamma[1] +
(X %*% gamma[2:6])))))
A[,1] <- A1[,1]*TRT + A0[,1]*(1-TRT)
for(i in 2:n_t){
  alphas[[i]] <- matrix(rep(c(2.3, -0.3, -0.01, 0.02, 0.03, 0.04, -0.4),
  p_z),ncol=p_z)
  gammas[[i]] <- c(1, -0.1, 0.2, 0.2, 0.2, 0.2, rep(z_para[i],p_z))
  Z0 <- alphas[[i]][1,]+(X%*%alphas[[i]][2:6,]) + mvrnorm(j, mu = rep(0,p_z)
  , Sigma = diag(sd_z_x,p_z))
  Z1 <- alphas[[i]][1,]+(X%*%alphas[[i]][2:6,])+alphas[[i]][7,] +
    mvrnorm(j, mu = rep(0,p_z), Sigma = diag(sd_z_x,p_z))
  Z[[i]] <- Z1*TRT + Z0*(1-TRT)
  Y0 <- (Y0 + Z0 %*% matrix(beta[ (7 + (i-1)*p_z):
  (6+p_z*i)],ncol = 1) )[,1]
  Y1 <- (Y1 + Z1 %*% matrix(beta[ (7 + (i-1)*p_z):
  (6+p_z*i)],ncol = 1) )[,1]
  A0[,i] <- rbinom(j, size = 1,
                   prob = 1/(1+exp(-(gammas[[i]][1]+
                   (X%*%gammas[[i]][2:6])+Z0%*%matrix(gammas[[i]][7:
                   (7+p_z-1)], ncol=1))[,1])))*A0[,i-1]
  A1[,i] <- rbinom(j, size = 1,
                   prob = 1/(1+exp(-(gammas[[i]][1]+
                   (X%*%gammas[[i]][2:6])+Z1%*%matrix(gammas[[i]][7:
                   (7+p_z-1)], ncol=1))[,1])))*A1[,i-1]

  A[,i] <- A1[,i]*TRT + A0[,i]*(1-TRT)
}
Y0 <- Y0 + rnorm(j, mean = 0, sd = 0.3) + Y_constant
Y1 <- Y1 + + beta_T + rnorm(j, mean = 0, sd = 0.3) + Y_constant
Y <- as.vector( Y1*TRT+Y0*(1-TRT))
```

```
for(i in 2:n_t){
  Z[[i]][A[,(i-1)]==0,] <- NA
}
Z[[1]] <- matrix(NA, nrow=nrow(Z1),ncol=ncol(Z1))
Y[A[,n_t] == 0] <- NA
# estimate the treatment difference
fit <- est_S_Star_Plus_MethodA(X, A, Z, Y, TRT)
fit
# Calculate the true values
true1 <- mean(Y1[A1[,n_t]==1])
true1
true0 <- mean(Y0[A1[,n_t]==1])
true0
true_d  =  true1 - true0
true_d
```

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