

Package ‘tvmediation’

July 22, 2025

Type Package

Date 2022-05-13

Version 1.1.0

Title Time Varying Mediation Analysis

Description Provides functions for estimating mediation effects that vary over time as described in Cai X, Coffman DL, Piper ME, Li R. Estimation and inference for the mediation effect in a time-varying mediation model. BMC Med Res Methodol. 2022;22(1):1-12.

RoxygenNote 7.1.2

Depends R (>= 4.0.0)

Imports stats (>= 4.0.2), dplyr (>= 1.0.2), ggplot2 (>= 3.3.2), locpol (>= 0.7-0)

Suggests knitr, rmarkdown

License GPL-3

URL <https://github.com/dcoffman/tvmediation/wiki>

BugReports <https://github.com/dcoffman/tvmediation/issues>

LazyData true

VignetteBuilder knitr

Encoding UTF-8

NeedsCompilation no

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Repository CRAN

Date/Publication 2022-05-25 06:40:02 UTC

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| | |
|-------------------|--|
| bootci_coeff_2trt | <i>Bootstrap function for computing CIs for coefficients for a continuous outcome and two treatment groups</i> |
|-------------------|--|

Description

Part of the set of internal functions for estimating bootstrapped CIs for the coefficients of the mediation model for continuous outcome and two treatment groups.

Usage

```
bootci_coeff_2trt(trt, t.seq, M, Y, t.est, deltat, replicates)
```

Arguments

| | |
|------------|--|
| trt | a vector indicating treatment group |
| t.seq | a vector of time points for each observation |
| M | matrix of mediator values in wide format |
| Y | matrix of outcome values in wide format |
| t.est | time points at which to make the estimation. Default = t.seq |
| deltat | a small constant which controls the time-lag of the effect of the mediator on the outcome. |
| replicates | number of replicates for bootstrapping confidence intervals. Default = 1000 |

Value

CI.upper.alpha CI upper limit for coefficient hat.alpha
 CI.lower.alpha CI lower limit for coefficient hat.alpha
 CI.upper.gamma CI upper limit for coefficient hat.gamma
 CI.lower.gamma CI lower limit for coefficient hat.gamma
 CI.upper.beta CI upper limit for coefficient hat.beta
 CI.lower.beta CI lower limit for coefficient hat.beta
 CI.upper.tau CI upper limit for coefficient hat.tau
 CI.lower.tau CI lower limit for coefficient hat.tau

bootci_coeff_3trt *Bootstrap samples to estimate confidence intervals for coefficients for a continuous outcome and three treatment groups.*

Description

Part of the set of internal functions for estimating bootstrapped confidence intervals for the coefficients of the mediation model for a continuous outcome and three treatment groups.

Usage

```

bootci_coeff_3trt(
  T1,
  T2,
  t.seq,
  mediator,
  outcome,
  t.est,
  original.coeff,
  boot.sample = 1000
)

```

Arguments

T1 a vector indicating assignment to treatment 1
 T2 a vector indicating assignment to treatment 2
 t.seq a vector of time points for each observation
 mediator matrix of mediator values in wide format
 outcome matrix of outcome values in wide format
 t.est time points at which to make the estimation. Default = t.seq
 original.coeff a list of the estimated coefficients.
 boot.sample number of replicates for bootstrapping confidence intervals. Default = 1000.

Value

| | |
|------|---|
| a1w1 | CI lower limit for estimated Treatment 1 effect on mediator |
| aup1 | CI upper limit for estimated Treatment 1 effect on mediator |
| a1w2 | CI lower limit for estimated Treatment 2 effect on mediator |
| aup2 | CI upper limit for estimated Treatment 2 effect on mediator |
| g1w1 | CI lower limit for estimated Treatment 1 direct effect on outcome |
| gup1 | CI upper limit for estimated Treatment 1 direct effect on outcome |
| g1w2 | CI lower limit for estimated Treatment 2 direct effect on outcome |
| gup2 | CI upper limit for estimated Treatment 2 direct effect on outcome |
| t1w1 | CI lower limit for estimated Treatment 1 total effect on outcome |
| tup1 | CI upper limit for estimated Treatment 1 total effect on outcome |
| t1w2 | CI lower limit for estimated Treatment 2 total effect on outcome |
| tup2 | CI upper limit for estimated Treatment 2 total effect on outcome |
| b1w | CI lower limit for estimated effect of mediator on outcome |
| bup | CI upper limit for estimated effect of mediator on outcome |

bootci_coeff_binary *Bootstrap samples to estimate confidence intervals for binary outcome coefficients.*

Description

Internal function for estimating bootstrapped confidence intervals for the coefficients of the mediation model for a binary outcome.

Usage

```
bootci_coeff_binary(
  treatment,
  t.seq,
  m,
  outcome,
  span = 0.75,
  replicates = 1000
)
```

Arguments

| | |
|------------|--|
| treatment | a vector indicating treatment group |
| t.seq | a vector of unique time points for each observation |
| m | matrix of mediator values in wide format |
| outcome | matrix of outcome values in wide format |
| span | Numeric value of the span to be used for LOESS regression. Default = 0.75. |
| replicates | Number of replicates for bootstrapping confidence intervals. Default = 1000. |

Value

| | |
|------------|------------------------------|
| t.seq | time points of estimation |
| CI.lower.a | CI lower limit for alpha_hat |
| CI.upper.a | CI upper limit for alpha_hat |
| CI.lower.g | CI lower limit for gamma_hat |
| CI.upper.g | CI upper limit for gamma_hat |
| CI.lower.b | CI lower limit for beta_hat |
| CI.upper.b | CI upper limit for beta_hat |
| CI.lower.t | CI lower limit for tau_hat |
| CI.upper.t | CI upper limit for tau_hat |

| | |
|-------------|--|
| bootci_tvmb | <i>Bootstrap samples to estimate confidence intervals for the mediation effect for a binary outcome.</i> |
|-------------|--|

Description

Part of the set of internal functions for estimating bootstrapped confidence intervals for the mediation effect for a binary outcome when user argument CI="boot".

Usage

```
bootci_tvmb(
  treatment,
  t.seq,
  m,
  outcome,
  coeff_data,
  span = 0.75,
  replicates = 1000
)
```

Arguments

| | |
|------------|--|
| treatment | a vector indicating treatment group |
| t.seq | a vector of unique time points for each observation |
| m | matrix of mediator values in wide format |
| outcome | matrix of outcome values in wide format |
| coeff_data | a merged dataset of indirect and direct effects and CIs estimated from bootci_coeff_binary |
| span | Numeric value of the span to be used for LOESS regression. Default = 0.75. |
| replicates | number of replicates for bootstrapping CIs. Default = 1000. |

Value

| | |
|------------|--|
| timeseq | time points of estimation |
| alpha_hat | time-varying treatment effect on the mediator |
| CI.lower.a | CI lower limit for estimated coefficient alpha_hat |
| CI.upper.a | CI upper limit for estimated coefficient alpha_hat |
| gamma_hat | time-varying treatment effect on the outcome (direct effect) |
| CI.lower.g | CI lower limit for estimated coefficient gamma_hat |
| CI.upper.g | CI upper limit for estimated coefficient gamma_hat |
| beta_hat | time-varying effect of the mediator on the outcome |
| CI.lower.b | CI lower limit for estimated coefficient beta_hat |
| CI.upper.b | CI upper limit for estimated coefficient beta_hat |
| tau_hat | time-varying treatment effect on outcome (total effect) |
| CI.lower.t | CI lower limit for estimated coefficient tau_hat |
| CI.upper.t | CI upper limit for estimated coefficient tau_hat |
| medEffect | time varying mediation effect |
| CI.lower | CI lower limit for medEffect |
| CI.upper | CI upper limit for medEffect |

| | |
|-----------------|--|
| bootci_tvm_3trt | <i>Bootstrap samples to estimate confidence intervals for continuous outcome and three treatment groups.</i> |
|-----------------|--|

Description

Internal function for estimating bootstrapped confidence intervals for the mediation effect of continuous outcome and three treatment groups when user argument CI="boot".

Usage

```
bootci_tvm_3trt(boot.sample, orig.data, t.est)
```

Arguments

| | |
|-------------|--|
| boot.sample | number of replicates for bootstrapping confidence intervals. Default = 1000. |
| orig.data | a list of original data T1, T2, mediator, outcome and t.seq. |
| t.est | time points at which to make the estimation. Default = t.seq. |

Value

| | |
|-----------------|--|
| p1w1 | CI lower limit for estimated mediation effect of T1 |
| pup1 | CI upper limit for estimated mediation effect of T1 |
| p1w2 | CI lower limit for estimated mediation effect of T2 |
| pup2 | CI upper limit for estimated mediation effect of T2 |
| orig.se1.all | estimated standard errors for the mediation effect of T1 |
| orig.se2.all | estimated standard errors for the mediation effect of T2 |
| orig.mediation1 | time varying mediation effect for T1 |
| orig.mediation2 | time varying mediation effect for T2 |

| | |
|-------|--|
| coeff | <i>Function to estimate coefficients at time t</i> |
|-------|--|

Description

Part of the set of internal functions called within the `tvmcurve_3trt` function to assist in the estimation of time varying mediation effect.

Usage

```
coeff(j, T1, T2, x, y)
```

Arguments

| | |
|----|---|
| j | a number indicating time point of observation |
| T1 | a vector indicating assignment to treatment 1 |
| T2 | a vector indicating assignment to treatment 2 |
| x | matrix of mediator values in wide format |
| y | matrix of outcome outcomes in wide format |

Value

| | |
|-----------------|---|
| coeff.est | estimated coefficients of the mediation model |
| nomissing.index | index of complete cases |

| | |
|------------|---|
| estBootCIs | <i>Bootstrapping samples to estimate mediation effects confidence intervals for continuous outcome and two treatment (exposure) groups.</i> |
|------------|---|

Description

Part of the set of internal functions for estimating bootstrapped confidence intervals for continuous outcome and two treatment groups when user argument CI="boot".

Usage

```
estBootCIs(trt, t.seq, M, Y, t.est, deltat, replicates)
```

Arguments

| | |
|------------|--|
| trt | a vector indicating treatment group |
| t.seq | a vector of time points at each obs |
| M | matrix of mediator values |
| Y | matrix of outcome values |
| t.est | time points at which to make the estimation |
| deltat | a small constant which controls the time-lag of the effect of the mediator on the outcome, half the time between two time points |
| replicates | number of replicates for bootstrapping confidence intervals. |

Value

boot.sebootstrapped standard error for the estimated mediation effect
 CI.upperpercentile bootstrapped CI upper limit for the estimated mediation effect
 CI.lowerpercentile bootstrapped CI lower limit for the estimated mediation effect

| | |
|----------|---|
| estCoeff | <i>Function to estimate coefficients at time t.</i> |
|----------|---|

Description

Part of the set of internal functions called within the tvma function to assist in the estimation of the time varying mediation effect.

Usage

```
estCoeff(newMO.j.est)
```

Arguments

`newM0.j.est` a list containing mean centered mediators and outcomes

Value

`coeff.est` estimated coefficients of the mediation model

LongToWide *Function to transpose the data from long to wide format*

Description

Transposing a dataset with repeated measurements/responses for each subject from longitudinal to wide format.

Usage

```
LongToWide(subject.id, time.sequence, outcome, verbose = FALSE)
```

Arguments

`subject.id` a column of subject identifiers
`time.sequence` a column of time points
`outcome` a column to be transposed
`verbose` TRUE or FALSE (default = FALSE) prints output to screen (OPTIONAL INPUT)

Details

If data is not sorted by `subject.id`, a warning message will appear. The function will then sort the data by `subject.id`. It is recommended that the user sorts the data prior to using this function.

Value

`mat.wide` a matrix in wide format, in which each column is the outcome for each subject and each row is the time sequence

Examples

```
# CREATING A TRANSPOSED MATRIX FOR MEDIATOR `WantToSmokeLst15min`
data(smoker)
mat.wide <- LongToWide(smoker$SubjectID,
                      smoker$timeseq,
                      smoker$WantToSmokeLst15min)
```

| | |
|--------------------|---|
| newMediatorOutcome | <i>Function to compute new Mediator and Outcome using time t and t-1 mean centered on the individual.</i> |
|--------------------|---|

Description

Part of the set of internal functions called within the tvma function to assist in the estimation of time varying mediation effect.

Usage

```
newMediatorOutcome(trt, M, Y)
```

Arguments

| | |
|-----|--|
| trt | numeric binary treatment group indicator for each individual |
| M | (t.seq x N) matrix where N = number of observations. Column 1 is mediator at time t-1. Column 2 is mediator at time t. |
| Y | (Nx1) matrix where N = number of observations. Column 1 is outcome at time t-1. |

Value

| | |
|-------|--|
| newMO | list containing new mediators, outcomes, and index of complete cases |
|-------|--|

| | |
|--------|--|
| smoker | <i>Wisconsin Smokers' Health Study 2</i> |
|--------|--|

Description

The dataset is **simulated** based on the Wisconsin Smokers' Health Study 2.

Usage

```
data(smoker)
```

Format

A data frame with 40,130 observations on 12 variables.

1. **SubjectID:** Subject ID
2. **treatment:** Treatment group (2 = patch, 3 = varenicline, 4 = combination nicotine replacement therapy)
3. **patch:** Received patch (0 = No, 1 = Yes)
4. **varenicline:** Received varenicline (0 = No, 1 = Yes)

5. **comboNRT**: Received combination nicotine replacement therapy (0 = No, 1 = Yes)
6. **DaysFromTQD**: Number of days from quit date
7. **time.of.day**: Time of day (0 = am, 1 = pm)
8. **timeseq**: Number of days from quit date (.5 indicates pm)
9. **WantToSmokeLst15min**: How did you feel in the last 15 min: wanting to smoke (1 = not at all, 7 = extremely)
10. **NegMoodLst15min**: How did you feel in the last 15 min: Negative mood (1 = not at all, 7 = extremely)
11. **cessFatig**: Cessation fatigue - I am tired of trying to quit smoking (1 = strongly disagree, 7 = strongly agree)
12. **CigCount**: Cigarettes smoked over entire day
13. **smoke_status**: Did you smoke (0 = No, 1 = Yes)

See Also

[tvmb](#), [tvma_3trt](#) [tvma](#), [LongToWide](#)

Examples

```
data(smoker)
```

smoothest

Function to compute local polynomial estimation using rule of thumb for bandwidth selection

Description

Part of the set of internal functions called within the `tvma` function to assist in the estimation of the time varying mediation effect.

Usage

```
smoothest(t.seq, t.coeff, t.est, deltat)
```

Arguments

| | |
|----------------------|--|
| <code>t.seq</code> | a vector of time points at each observation |
| <code>t.coeff</code> | estimated coefficients |
| <code>t.est</code> | time points at which to make the estimation |
| <code>deltat</code> | a small constant which controls the time-lag of the effect of the mediator on the outcome, half the time between two time points |

Value

| | |
|-----------|---|
| bw_alpha | a number computed via Fan and Gijbels' (1996) rule of thumb for bandwidth selector for alpha coefficient. |
| bw_gamma | a number computed via Fan and Gijbels' (1996) rule of thumb for bandwidth selector for gamma coefficient. |
| bw_beta | a number computed via Fan and Gijbels' (1996) rule of thumb for bandwidth selector for beta coefficient. |
| bw_beta | a number computed via Fan and Gijbels' (1996) rule of thumb for bandwidth selector for tau coefficient. |
| hat.alpha | estimated treatment effect on mediator |
| hat.gamma | estimated treatment effect on outcome, adjusted for mediator |
| hat.beta | estimated mediator effect on outcome |
| hat.tau | estimated treatment effect on outcome, not adjusting for mediator |
| est.M | estimated mediation effect, product of hat.alpha and hat.beta |

| | |
|------|---|
| tvma | <i>Time Varying Mediation Function: Continuous Outcome and Two Treatment Groups</i> |
|------|---|

Description

Function to estimate the time-varying mediation effect and bootstrap standard errors for two treatment groups and a continuous outcome.

Usage

```
tvma(
  treatment,
  t.seq,
  mediator,
  outcome,
  t.est = t.seq,
  plot = FALSE,
  CI = "boot",
  replicates = 1000,
  verbose = FALSE
)
```

Arguments

| | |
|-----------|--|
| treatment | a vector indicating treatment group |
| t.seq | a vector of time points for each observation |
| mediator | matrix of mediator values in wide format |

| | |
|------------|---|
| outcome | matrix of outcome values in wide format |
| t.est | a vector of time points at which to estimate. Default = t.seq (OPTIONAL ARGUMENT) |
| plot | TRUE or FALSE for producing plots. Default = "FALSE" (OPTIONAL ARGUMENT) |
| CI | "none" or "boot" method of deriving confidence intervals. Default = "boot" (OPTIONAL ARGUMENT) |
| replicates | number of replicates for bootstrapping confidence intervals. Default = 1000 (OPTIONAL ARGUMENT) |
| verbose | TRUE or FALSE for printing results to screen. Default = "FALSE" (OPTIONAL ARGUMENT) |

Value

| | |
|----------------|--|
| hat.alpha | estimated time-varying treatment effect on mediator |
| CI.lower.alpha | CI lower limit for estimated coefficient hat.alpha |
| CI.upper.alpha | CI upper limit for estimated coefficient hat.alpha |
| hat.gamma | estimated time-varying treatment effect on outcome (direct effect) |
| CI.lower.gamma | CI lower limit for estimated coefficient hat.gamma |
| CI.upper.gamma | CI upper limit for estimated coefficient hat.gamma |
| hat.beta | estimated time-varying effect of the mediator on outcome |
| CI.lower.beta | CI lower limit for estimated coefficient hat.beta |
| CI.upper.beta | CI upper limit for estimated coefficient hat.beta |
| hat.tau | estimated time-varying treatment effect on outcome (total effect) |
| CI.lower.tau | CI lower limit for estimated coefficient hat.tau |
| CI.upper.tau | CI upper limit for estimated coefficient hat.tau |
| est.M | time varying mediation effect |
| boot.se.m | estimated standard error for est.M |
| CI.lower | CI lower limit for est.M |
| CI.upper | CI upper limit for est.M |

Plot Returns

1. Alpha_CI plot for hat.alpha with CIs over t.est
2. Gamma_CI plot for hat.gamma with CIs over t.est
3. Beta_CI plot for hat.beta with CIs over t.est
4. Tau_CI plot for hat.tau with CIs over t.est
5. MedEff plot for est.M over t.est
6. MedEff_CI plot for est.M with CIs over t.est

Note

1. **** IMPORTANT **** An alternate way of formatting the data and calling the function is documented in detail in the tutorial for the tvmb() function.

References

1. Fan, J. and Gijbels, I. Local polynomial modelling and its applications: Monographs on statistics and applied probability 66. CRC Press; 1996.
2. Fan J, Zhang W. Statistical Estimation in Varying Coefficient Models. The Annals of Statistics. 1999;27(5):1491-1518.
3. Fan J, Zhang JT. Two-step estimation of functional linear models with applications to longitudinal data. Journal of the Royal Statistical Society: Series B (Statistical Methodology). 2000;62(2):303-322.
4. Cai X, Coffman DL, Piper ME, Li R. Estimation and inference for the mediation effect in a time-varying mediation model. BMC Med Res Methodol. 2022;22(1):1-12.
5. Baker TB, Piper ME, Stein JH, et al. Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial. JAMA. 2016;315(4):371.
6. B. Efron, R. Tibshirani. Bootstrap Methods for Standard Errors, Confidence Intervals, and Other Measures of Statistical Accuracy. Statistical Science. 1986;1(1):54-75.

Examples

```
## Not run: data(smoker)

# REDUCE DATA SET TO ONLY 2 TREATMENT CONDITIONS (EXCLUDING COMBINATION NRT)
smoker.sub <- smoker[smoker$treatment != 4, ]

# GENERATE WIDE FORMATTED MEDIATORS
mediator <- LongToWide(smoker.sub$SubjectID,
                      smoker.sub$timeseq,
                      smoker.sub$NegMoodLst15min)

# GENERATE WIDE FORMATTED OUTCOMES
outcome <- LongToWide(smoker.sub$SubjectID,
                     smoker.sub$timeseq,
                     smoker.sub$cessFatig)

# GENERATE A BINARY TREATMENT VARIABLE
trt <- as.numeric(unique(smoker.sub[,c("SubjectID", "varenicline")][,2]) - 1)

# GENERATE A VECTOR OF UNIQUE TIME POINTS
t.seq <- sort(unique(smoker.sub$timeseq))

# COMPUTE TIME VARYING MEDIATION ANALYSIS USING BOOTSTRAPPED CONFIDENCE INTERVALS
results <- tvma(trt, t.seq, mediator, outcome)

# COMPUTE TIME VARYING MEDIATION ANALYSIS FOR SPECIFIED POINTS IN TIME USING 250 REPLICATES
results <- tvma(trt, t.seq, mediator, outcome,
```

```

t.est = c(0.2, 0.4, 0.6, 0.8),
replicates = 250)
## End(Not run)

```

| | |
|-----------|---|
| tvma_3trt | <i>Time Varying Mediation Function: Continuous Outcome and Three Treatment Groups</i> |
|-----------|---|

Description

Function to estimate the time-varying mediation effect and bootstrap standard errors for three treatment groups and a continuous outcome.

Usage

```

tvma_3trt(
  T1,
  T2,
  t.seq,
  mediator,
  outcome,
  t.est = t.seq,
  plot = FALSE,
  CI = "boot",
  replicates = 1000,
  grpname = "T",
  verbose = FALSE
)

```

Arguments

| | |
|------------|--|
| T1 | a vector indicating assignment to treatment 1 |
| T2 | a vector indicating assignment to treatment 2 |
| t.seq | a vector of time points for each observation |
| mediator | matrix of mediator values in wide format |
| outcome | matrix of outcome values in wide format |
| t.est | a vector of time points at which to make the estimation. Default = t.seq. (OPTIONAL ARGUMENT) |
| plot | TRUE or FALSE for plotting mediation effect. Default = "FALSE". (OPTIONAL ARGUMENT) |
| CI | "none" or "boot" method of deriving confidence intervals. Default = "boot". (OPTIONAL ARGUMENT) |
| replicates | number of replicates for bootstrapping confidence intervals. Default = 1000. (OPTIONAL ARGUMENT) |

| | |
|---------|---|
| grpname | name of the treatment arms (exposure groups) to be displayed in the results. Default = "T". (OPTIONAL ARGUMENT) |
| verbose | TRUE or FALSE for printing results to screen. Default = "FALSE". (OPTIONAL ARGUMENT) |

Value

| | |
|-----------------|--|
| hat.alpha1 | estimated Treatment 1 effect on mediator |
| CI.lower.alpha1 | CI lower limit for estimated coefficient hat.alpha1 |
| CI.upper.alpha1 | CI upper limit for estimated coefficient hat.alpha1 |
| hat.alpha2 | estimated Treatment 2 effect on mediator |
| CI.lower.alpha2 | CI lower limit for estimated coefficient hat.alpha2 |
| CI.upper.alpha2 | CI upper limit for estimated coefficient hat.alpha2 |
| hat.gamma1 | estimated Treatment 1 direct effect on outcome |
| CI.lower.gamma1 | CI lower limit for estimated coefficient hat.gamma1 |
| CI.upper.gamma1 | CI upper limit for estimated coefficient hat.gamma1 |
| hat.gamma2 | estimated Treatment 2 direct effect on outcome |
| CI.lower.gamma2 | CI lower limit for estimated coefficient hat.gamma2 |
| CI.upper.gamma2 | CI upper limit for estimated coefficient hat.gamma2 |
| hat.tau1 | estimated Treatment 1 total effect on outcome |
| CI.lower.tau1 | CI lower limit for estimated coefficient hat.tau1 |
| CI.upper.tau1 | CI upper limit for estimated coefficient hat.tau1 |
| hat.tau2 | estimated Treatment 2 total effect on outcome |
| CI.lower.tau2 | CI lower limit for estimated coefficient hat.tau2 |
| CI.upper.tau2 | CI upper limit for estimated coefficient hat.tau2 |
| hat.beta | estimated mediator effect on outcome |
| CI.lower.beta | CI lower limit for estimated coefficient hat.beta |
| CI.upper.beta | CI upper limit for estimated coefficient hat.beta |
| hat.mediation1 | time varying mediation effect for Treatment 1 on outcome |
| SE_MedEff1 | estimated standard errors of hat.mediation1 |
| CI.upper.T1 | CI upper limit for hat.mediation1 |
| CI.lower.T1 | CI lower limit for hat.mediation1 |
| hat.mediation2 | time varying mediation effect for Treatment 2 on outcome |
| SE_MedEff2 | estimated standard errors of hat.mediation2 |
| CI.upper.T2 | CI upper limit for hat.mediation2 |
| CI.lower.T2 | CI lower limit for hat.mediation2 |

Plot Returns

1. plot1_a1 plot for hat.alpha1 with CIs over t.est
2. plot2_a2 plot for hat.alpha2 with CIs over t.est
3. plot3_g1 plot for hat.gamma1 with CIs over t.est
4. plot4_g2 plot for hat.gamma2 with CIs over t.est
5. plot5_t1 plot for hat.tau1 with CIs over t.est
6. plot6_t2 plot for hat.tau2 with CIs over t.est
7. plot7_b plot for hat.beta with CIs over t.est
8. MedEff_T1 plot for hat.mediation1 over t.est
9. MedEff_T2 plot for hat.mediation2 over t.est
10. MedEff_CI_T1 plot for hat.mediation1 with CIs over t.est
11. MedEff_CI_T2 plot for hat.mediation2 with CIs over t.est

References

1. Fan, J. and Gijbels, I. Local polynomial modelling and its applications: Monographs on statistics and applied probability 66. CRC Press; 1996.
2. Fan J, Zhang W. Statistical Estimation in Varying Coefficient Models. The Annals of Statistics. 1999;27(5):1491-1518.
3. Fan J, Zhang JT. Two-step estimation of functional linear models with applications to longitudinal data. Journal of the Royal Statistical Society: Series B (Statistical Methodology). 2000;62(2):303-322.
4. Cai X, Coffman DL, Piper ME, Li R. Estimation and inference for the mediation effect in a time-varying mediation model. BMC Med Res Methodol. 2022;22(1):1-12.
5. Baker TB, Piper ME, Stein JH, et al. Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial. JAMA. 2016;315(4):371.
6. B. Efron, R. Tibshirani. Bootstrap Methods for Standard Errors, Confidence Intervals, and Other Measures of Statistical Accuracy. Statistical Science. 1986;1(1):54-75.

Examples

```
## Not run: data(smoker)

# GENERATE WIDE FORMATTED MEDIATORS
mediator <- LongToWide(smoker$SubjectID,
                      smoker$timeseq,
                      smoker$NegMoodLst15min)

# GENERATE WIDE FORMATTED OUTCOMES
outcome <- LongToWide(smoker$SubjectID,
                     smoker$timeseq,
                     smoker$cessFatig)

# GENERATE TWO BINARY TREATMENT VARIABLES
```

```

NRT1 <- as.numeric(unique(smoker[,c("SubjectID","varenicline")][,2])-1)
NRT2 <- as.numeric(unique(smoker[,c("SubjectID","comboNRT")][,2])-1)

# GENERATE A VECTOR OF UNIQUE TIME POINTS
t.seq <- sort(unique(smoker$timeseq))

# COMPUTE TIME VARYING MEDIATION ANALYSIS USING BOOTSTRAPPED CONFIDENCE INTERVALS
results <- tvma_3trt(NRT1, NRT2, t.seq, mediator, outcome)

# COMPUTE TIME VARYING MEDIATION ANALYSIS FOR SPECIFIED POINTS IN TIME USING 250 REPLICATES
results <- tvma_3trt(NRT1, NRT2, t.seq, mediator, outcome,
                    t.est = c(0.2, 0.4, 0.6, 0.8),
                    replicates = 250)

## End(Not run)

```

tvmb

Time Varying Mediation Function: Binary Outcome and Two Treatment Groups

Description

Function to estimate the time-varying mediation effect and bootstrap standard errors, involving two treatment groups and binary outcome.

Usage

```

tvmb(
  treatment,
  t.seq,
  mediator,
  outcome,
  span = 0.75,
  plot = FALSE,
  CI = "boot",
  replicates = 1000,
  verbose = FALSE
)

```

Arguments

| | |
|-----------|--|
| treatment | a vector indicating treatment group |
| t.seq | a vector of unique time points for each observation |
| mediator | matrix of mediator values in wide format |
| outcome | matrix of outcome values in wide format |
| span | Numeric value of the span to be used for LOESS regression. Default = 0.75. |

| | |
|------------|--|
| plot | TRUE or FALSE for producing plots. Default = "FALSE". (OPTIONAL ARGUMENT) |
| CI | "none" or "boot" method of deriving confidence intervals. Default = "boot". (OPTIONAL ARGUMENT) |
| replicates | Number of replicates for bootstrapping confidence intervals. Default = 1000. (OPTIONAL ARGUMENT) |
| verbose | TRUE or FALSE for printing results to screen. Default = "FALSE". (OPTIONAL ARGUMENT) |

Value

| | |
|------------|---|
| timeseq | time points of estimation |
| alpha_hat | estimated treatment effect on mediator |
| CI.lower.a | CI lower limit for estimated coefficient alpha_hat |
| CI.upper.a | CI upper limit for estimated coefficient alpha_hat |
| gamma_hat | estimated treatment effect on outcome (direct effect) |
| CI.lower.g | CI lower limit for estimated coefficient gamma_hat |
| CI.upper.g | CI upper limit for estimated coefficient gamma_hat |
| beta_hat | estimated mediator effect on outcome |
| CI.lower.b | CI lower limit for estimated coefficient beta_hat |
| CI.upper.b | CI upper limit for estimated coefficient beta_hat |
| tau_hat | estimated treatment effect on outcome (total effect) |
| CI.lower.t | CI lower limit for estimated coefficient tau_hat |
| CI.upper.t | CI upper limit for estimated coefficient tau_hat |
| medEffect | time varying mediation effect |
| CI.lower | CI lower limit for medEffect |
| CI.upper | CI upper limit for medEffect |

Plot Returns

1. plot1_a plot for alpha_hat with CIs over t.seq
2. plot2_g plot for gamma_hat with CIs over t.seq
3. plot3_b plot for beta_hat with CIs over t.seq
4. plot4_t plot for tau_hat with CIs over t.seq
5. MedEff plot for medEffect over t.seq
6. MedEff_CI plot for medEffect with CIs over t.seq
7. bootstrap plot for estimated medEffect from bootstrapped samples over t.seq

Note

1. Currently supports 2 treatment groups
2. **** IMPORTANT **** An alternate way of formatting the data and calling the function is documented in detail in the tutorial for the tvmb() function.

References

1. Fan, J. and Gijbels, I. Local polynomial modelling and its applications: Monographs on statistics and applied probability 66. CRC Press; 1996.
2. Fan J, Zhang W. Statistical Estimation in Varying Coefficient Models. The Annals of Statistics. 1999;27(5):1491-1518.
3. Fan J, Zhang JT. Two-step estimation of functional linear models with applications to longitudinal data. Journal of the Royal Statistical Society: Series B (Statistical Methodology). 2000;62(2):303-322.
4. Baker TB, Piper ME, Stein JH, et al. Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial. JAMA. 2016;315(4):371.
5. B. Efron, R. Tibshirani. Bootstrap Methods for Standard Errors, Confidence Intervals, and Other Measures of Statistical Accuracy. Statistical Science. 1986;1(1):54-75.

Examples

```
## Not run: data(smoker)

# REDUCE DATA SET TO ONLY 2 TREATMENT CONDITIONS (EXCLUDE COMBINATION NRT)
smoker.sub <- smoker[smoker$treatment != 4, ]

# GENERATE WIDE FORMATTED MEDIATORS
mediator <- LongToWide(smoker.sub$SubjectID,
                      smoker.sub$timeseq,
                      smoker.sub$NegMoodLst15min)

# GENERATE WIDE FORMATTED OUTCOMES
outcome <- LongToWide(smoker.sub$SubjectID,
                     smoker.sub$timeseq,
                     smoker.sub$smoke_status)

# GENERATE A BINARY TREATMENT VARIABLE
trt <- as.numeric(unique(smoker.sub[, c("SubjectID", "varenicline")])[, 2])-1

# GENERATE A VECTOR OF UNIQUE TIME POINTS
t.seq <- sort(unique(smoker.sub$timeseq))

# COMPUTE TIME VARYING MEDIATION ANALYSIS USING BOOTSTRAPPED CONFIDENCE INTERVALS
results <- tvmb(trt, t.seq, mediator, outcome)
## End(Not run)
```

tvmcurve_3trt

Main function for time varying mediation function for continuous outcome and three treatment arms (i.e., exposure groups).

Description

Part of the set of internal functions to estimate the time-varying mediation effect and bootstrap standard errors for three treatment groups and continuous outcome.

Usage

```
tvmcurve_3trt(T1, T2, t.seq, x, y, t.est)
```

Arguments

| | |
|-------|--|
| T1 | a vector indicating assignment to treatment 1 |
| T2 | a vector indicating assignment to treatment 2 |
| t.seq | a vector of time points for each observation |
| x | matrix of mediator values in wide format |
| y | matrix of outcome values in wide format |
| t.est | time points at which to make the estimation. Default = t.seq |

Value

| | |
|----------------|--|
| hat.alpha1 | estimated Treatment 1 effect on mediator |
| hat.alpha2 | estimated Treatment 2 effect on mediator |
| hat.gamma1 | estimated Treatment 1 direct effect on outcome |
| hat.gamma2 | estimated Treatment 2 direct effect on outcome |
| hat.tau1 | estimated Treatment 1 total effect on outcome |
| hat.tau2 | estimated Treatment 2 total effect on outcome |
| hat.beta | estimated mediator effect on outcome |
| hat.mediation1 | time varying mediation effect for Treatment 1 on outcome |
| hat.mediation2 | time varying mediation effect for Treatment 2 on outcome |

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