

Package ‘tvmediation’

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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.

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Suggests knitr, rmarkdown

License GPL-3

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

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

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

A list containing:

boot.se bootstrapped standard error for the estimated mediation effect

CI.upper percentile bootstrapped CI upper limit for the estimated mediation effect

CI.lower percentile 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>
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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

Alpha_CI	plot for hat.alpha with CIs over t.est
Gamma_CI	plot for hat.gamma with CIs over t.est
Beta_CI	plot for hat.beta with CIs over t.est
Tau_CI	plot for hat.tau with CIs over t.est
MedEff	plot for est.M over t.est
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

plot1_a1 plot for hat.alpha1 with CIs over t.est
 plot2_a2 plot for hat.alpha2 with CIs over t.est
 plot3_g1 plot for hat.gamma1 with CIs over t.est
 plot4_g2 plot for hat.gamma2 with CIs over t.est
 plot5_t1 plot for hat.tau1 with CIs over t.est
 plot6_t2 plot for hat.tau2 with CIs over t.est
 plot7_b plot for hat.beta with CIs over t.est
 MedEff_T1 plot for hat.mediation1 over t.est
 MedEff_T2 plot for hat.mediation2 over t.est
 MedEff_CI_T1 plot for hat.mediation1 with CIs over t.est
 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

plot1_a	plot for alpha_hat with CIs over t.seq
plot2_g	plot for gamma_hat with CIs over t.seq
plot3_b	plot for beta_hat with CIs over t.seq
plot4_t	plot for tau_hat with CIs over t.seq
MedEff	plot for medEffect over t.seq
MedEff_CI	plot for medEffect with CIs over t.seq
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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