Ensemble Learning Targeted Maximum Likelihood Estimation for Stata Users: 2018 Spanish Stata Conference

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https://maluque.netlify.com

https://github.com/migariane/SUGML

24 October 2018

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Pros: TMLE

- (TMLE) is a general algorithm for the construction of **double-robust**, **semiparametric** MLE, efficient **substitution** estimator (Van der Laan, 2011)
- Better performance than competitors has been largely documented (Porter, et. al.,2011).
- (TMLE) **Respect bounds on Y**, **less sensitive** to **misspecification** and to **near-positivity** violations (Benkeser, 2016).
- (TMLE) **Reduces bias** through **ensemble learning** if misspecification, even dual misspecification.
- For the ATE, **Inference** is based on the **Efficient Influence Curve**. Hence, the **CLT** applies, making inference easier.

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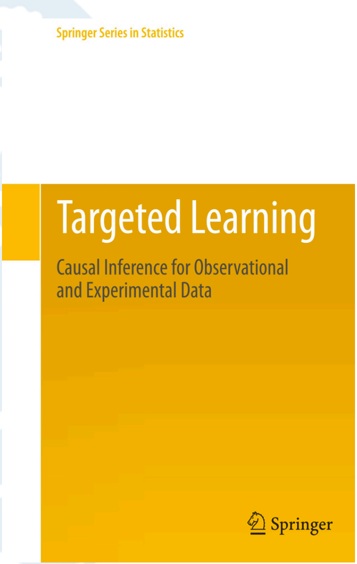
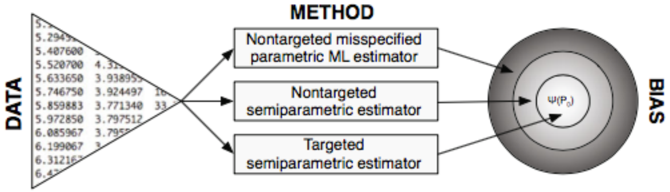
Targeted learning



Source: Mark van der Laan and Sherri Rose. Targeted learning: causal inference for observational and experimental data. Springer Series in Statistics, 2011.

Why Targeted learning?



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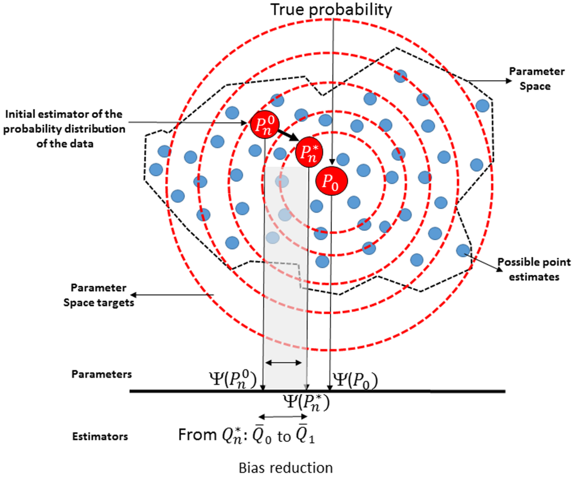
MC simulations: Luque-Fernandez et al, 2017 (in press, American Journal of Epidemiology)

	ATE		BIAS (%)		RMSE		95%CI coverage (%)	
	N=1,000	N=10,000	N=1,000	N=10,000	N=1,000	N=10,000	N=1,000	N=10,000
First scenario* (correctly specified models)								
True ATE	**-0.1813**							
Naïve	-0.2234	-0.2218	23.2	22.3	0.0575	0.0423	77	89
AIPTW	-0.1843	-0.1848	1.6	1.9	0.0534	0.0180	93	94
IPTW-RA	-0.1831	-0.1838	1.0	1.4	0.0500	0.0174	91	95
TMLE	-0.1832	-0.1821	1.0	**0.4**	0.0482	0.0158	**95**	**95**
Second scenario ** (misspecified models)								
True ATE	**-0.1172**							
Naïve	-0.0127	-0.0121	89.2	89.7	0.1470	0.1100	0	0
BFit AIPTW	-0.1155	-0.0920	1.5	**11.7**	0.0928	0.0773	65	65
BFit IPTW-RA	-0.1268	-0.1192	8.2	**1.7**	0.0442	0.0305	52	73
TMLE	-0.1181	-0.1177	**0.8**	**0.4**	0.0281	0.0107	**93**	**95**

*First scenario : correctly specified models and near-positivity violation

**Second scenario: misspecification, near-positivity violation and adaptive model selection


True probability
Parameter Space
Initial estimator of the probability distribution of the data
P_n^0
P_n^*
P_0
Possible point estimates
Parameter Space targets
Parameters
$\Psi(P_n^0)$
$\Psi(P_0)$
$\Psi(P_n^*)$
Estimators
From Q_n^*: $\bar{Q}_0$ to $\bar{Q}_1$
Bias reduction

TMLE STEPS

Substitution estimation: $\hat{E}(Y \mid A, W)$

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- First compute the outcome regression $\mathbf{E}(\mathbf{Y} \mid \mathbf{A}, \mathbf{W})$ using the **Super-Learner** to then derive the Potential Outcomes and compute $\psi^{(0)} = \mathbf{E}(Y(1) \mid A = 1, W) - \mathbf{E}(Y(0) \mid A = 0, W)$.

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- Compute **HAW** = $\left(\frac{\mathbb{I}(A_i=1)}{P(A_i=1|W_i)} - \frac{\mathbb{I}(A_i=0)}{P(A_i=0|W_i)} \right)$ for each individual, named the **clever covariate H.**

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Fluctuation step ($\hat{\epsilon}_0$, $\hat{\epsilon}_1$)

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$$\Psi^{(1)} : \hat{\Psi} = [\mathbf{E}^*(Y(1) \mid A = 1, W) - \mathbf{E}^*(Y(0) \mid A = 0, W)]$$

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TMLE inference: Influence curve

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$$\textbf{IC} = \left(\frac{(A_i = 1)}{P(A_i = 1 \mid W_i)} - \frac{(A_i = 0)}{P(A_i = 0 \mid W_i)} \right) [Y_i - E_1(Y \mid A_i, W_i)] +$$
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$$\textbf{Standard Error}: \sigma(\psi_0) = \frac{SD(IC_n)}{\sqrt{n}}$$

TMLE inference

- The **Efficient IC**, first introduced by Hampel (1974), is used to apply readily the **CLT** for statistical inference using TMLE.
- The **Efficient IC** is the same as the infinitesimal jackknife and the **nonparametric delta method.** Also named the **"canonical gradient"** of the pathwise derivative of the target parameter ψ or **"approximation by averages"** (Efron, 1982).

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TMLE inference: Influence curve

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$$\textbf{IC} = \left(\frac{(A_i = 1)}{P(A_i = 1 \mid W_i)} - \frac{(A_i = 0)}{P(A_i = 0 \mid W_i)} \right) [Y_i - E_1(Y \mid A_i, W_i)] + [E_1(Y(1) \mid A_i = 1, W_i) - E_1(Y(0) \mid A_i = 0, W_i)] - \psi$$

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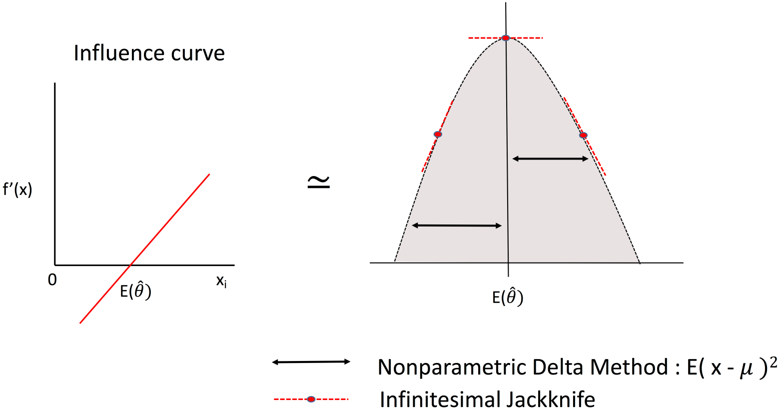
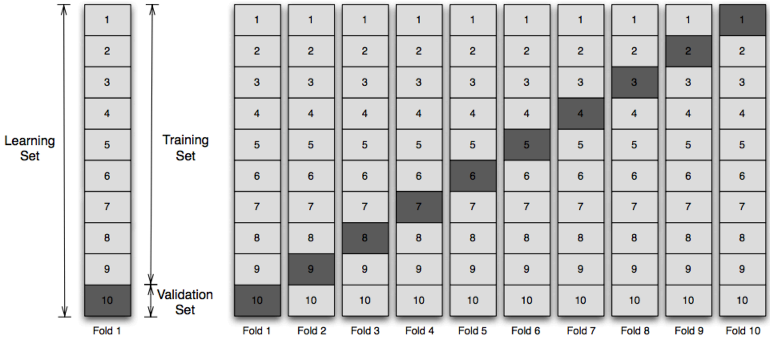
IC: Geometric interpretation



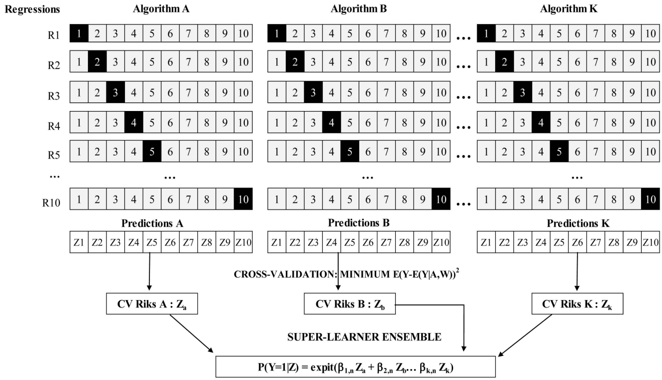
Estimate of the ψ Standard Error using the efficient Influence Curve.
Image credit: Miguel Angel Luque-Fernandez

Targeted learning



Source: Mark van der Laan and Sherri Rose. Targeted learning: causal inference for observational and experimental data. Springer Series in Statistics, 2011.

Super-Learner: Ensemble learning



To apply the **EIC** we need data-adaptive estimation for both, the model of the outcome, and the model of the treatment.
Asymptotically, the final weighted combination of algorithms (Super Learner) performs as well as or better than the best-fitting algorithm (van der Laan, 2007).

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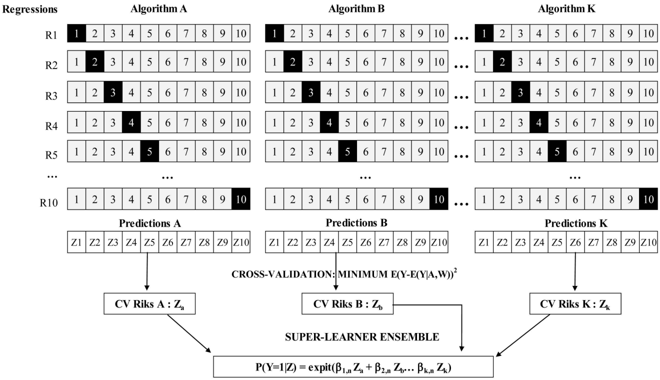

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Ensemble Learning Targeted Maximum Likelihood Estimation

- **eltmle** is a Stata program implementing R-TMLE for the ATE for a binary or continuous outcome and binary treatment.

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Syntax eltmle Stata command

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Stata Implementation: overall structure

eltmle.ado

```
capture program drop eltmle
program define eltmle
      syntax varlist(min=3) [if] [pw] [, tmle tmlebgam tmleglsrf]
      version 13.2
      marksample touse
      local var `varlist' if `touse'
      tokenize `var'
      local yvar = "`1'"
      global flag = cond(`yvar'<=1,1,0)
      qui sum `yvar'
      global b = `r(max)'
      global a = `r(min)'
      qui replace `yvar' = (`yvar' - `r(min)') / (`r(max)' - `r(min)') if `yvar'>1
      local dir `c(pwd)'
      cd "`dir'"
      qui export delimited `var' using "data.csv", nolabel replace
      if "`tmlebgam'" == "" & "`tmleglsrf'" == "" {
         tmle `varlist'
         }
      else if "`tmlebgam'" == "tmlebgam" {
         tmlebgam `varlist'
         }
      else if "`tmleglsrf'" == "tmleglsrf" {
         tmleglsrf `varlist'
         }
end
```

Stata Implementation: R code for calling the SL

```
program tmle
// Write R Code dependencies: foreign Surperlearner
set more off
qui: file close _all
qui: file open rcode using SLS.R, write replace
qui: file write rcode ///
        `"set.seed(123)"' _newline ///
        `"list.of.packages <- c("foreign","SuperLearner")"' _newline ///
        `"new.packages <- list.of.packages[!(list.of.packages %in% installed.packages()[,"Package"])]"' _newline ///
        `"if(length(new.packages)) install.packages(new.packages, repos='http://cran.us.r-project.org')"' _newline ///
        `"library(SuperLearner)"' _newline ///
        `"library(foreign)"' _newline ///
        `"data <- read.csv("data.csv", sep=",")"' _newline ///
        `"attach(data)"' _newline ///
        `"SL.library <- c("SL.glm","SL.step","SL.glm.interaction")"' _newline ///
        `"n <- nrow(data)"' _newline ///
        `"nvar <- dim(data)[[2]]"' _newline ///
        `"Y <- data[,1]"' _newline ///
        `"A <- data[,2]"' _newline ///
        `"X <- data[,2:nvar]"' _newline ///
        `"W <- data[,3:nvar]"' _newline ///
        `"X1 <- X0 <- X"' _newline ///
        `"X1[,1] <- 1"' _newline ///
        `"X0[,1] <- 0"' _newline ///
        `"newdata <- rbind(X,X1,X0)"' _newline ///
        `"Q <- try(SuperLearner(Y = data[,1] ,X = X, SL.library=SL.library, family=binomial(), newX=newdata, method="meth
        `"Q <- as.data.frame(Q[[4]])"' _newline ///
        `"QAW <- Q[1:n,]"' _newline ///
        `"Q1W <- Q[((n+1):(2*n)),]"' _newline ///
        `"Q0W <- Q[((2*n+1):(3*n)),]"' _newline ///
        `"g <- suppressWarnings(SuperLearner(Y = data[,2], X = W, SL.library = SL.library, family = binomial(), method =
        `"ps <- g[[4]]"' _newline ///
        `"ps[ps<0.025] <- 0.025"' _newline ///
        `"ps[ps>0.975] <- 0.975"' _newline ///
        `"data <- cbind(data,QAW,Q1W,Q0W,ps,Y,A)"' _newline ///
        `"write.dta(data, "data2.dta")"'
qui: file close rcode
```

Stata Implementation: Batch file executing R

```
qui: file close rcode

// Write bacth file to find R.exe path and R version
set more off
qui: file close _all
qui: file open bat using setup.bat, write replace
qui: file write bat ///
`"@echo off"' _newline ///
`"SET PATHROOT=C:\Program Files\R\"' _newline ///
`"echo Locating path of R..."' _newline ///
`"echo."' _newline ///
`"if not exist "%PATHROOT%" goto:NO_R"' _newline ///
`"for /f "delims=" %%r in (' dir /b "%PATHROOT%R*" ') do ("' _newline ///
        `"echo Found %%r"' _newline ///
        `"echo shell "%PATHROOT%%%r\bin\x64\R.exe" CMD BATCH SLS.R > runr.do"' _newline ///
        `"echo All set!"' _newline ///
        `"goto:DONE"' _newline ///
`")"' _newline ///
`":NO_R"' _newline ///
`"echo R is not installed in your system."' _newline ///
`"echo."' _newline ///
`"echo Download it from https://cran.r-project.org/bin/windows/base/"' _newline ///
`"echo Install it and re-run this script"' _newline ///
`":DONE"' _newline ///
`"echo."' _newline ///
`"pause"'
qui: file close bat

//Run batch
shell setup.bat
//Run R
do runr.do

// Read Revised Data Back to Stata
clear
quietly: use "data2.dta", clear

// Q to logit scale
gen logQAW = log(QAW / (1 - QAW))
gen logQ1W = log(Q1W / (1 - Q1W))
gen logQ0W = log(Q0W / (1 - Q0W))

// Clever covariate HAW
```

Output for continuous outcome

```
. use http://www.stata-press.com/data/r14/cattaneo2.dta
(Excerpt from Cattaneo (2010) Journal of Econometrics 155: 138-154)

. eltmle bweight mbsmoke mage medu prenatal mmarried, tmle
/Users/MALF/Dropbox/CAUSALITY/TARGETED-MACHINE-LEARNING/STATA-ELTMLE/Githu


    Variable |        Obs        Mean    Std. Dev.       Min        Max
-------------+---------------------------------------------------------
        POM1 |      4,642    2833.081    74.84581   2580.186   2958.981
        POM0 |      4,642    3062.785    89.55875   2867.102   3166.985
          PS |      4,642    .1861267     .110755   .0372202   .8494988
________________________________
TMLE: Additive Causal Effect
________________________________
Risk Differences:-229.70; EST VAR:600.9; 95%CI:(-277.75,-181.66);
p-value: 0.0000
________________________________
TMLE: Causal Risk Ratio (CRR)
________________________________
CRR:      0.93; 95%CI:(0.91,0.94)
________________________________
TMLE: Marginal Odds Ratio (MOR)
________________________________
MOR:      0.83; 95%CI:(0.80,0.87)
```

Simulations comparing Stata ELTMLE vs R-TMLE

```
. mean psi aipw eltmle
  Mean estimation
  Number of obs    =   1,000
  -------------------------
               |    Mean
  -------------+-----------
          True |    .173
          aipw |    .170
        eltmle |    .170
  -------------------------
        R-TMLE |    .170
  -------------------------
```

SIM and online open-source tutorials

Link to the tutorials

MA Luque-Fernandez et al. Targeted maximum likelihood estimation for a binary treatment: A tutorial. SIM. 2018. https://onlinelibrary.wiley.com/doi/full/10.1002/sim.7628

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```
github install migariane/eltmle
which eltmle
viewsource eltmle.ado
```

One sample simulation: TMLE reduces bias

https://github.com/migariane/SUGML

Next steps for ELTMLE

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Thank you

THANK YOU FOR YOUR TIME

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ibs.GRANADA
INSTITUTO DE INVESTIGACIÓN BIOSANITARIA

GOBIERNO DE ESPAÑA
MINISTERIO DE ECONOMÍA, INDUSTRIA Y COMPETITIVIDAD
Instituto de Salud Carlos III

UNIÓN EUROPEA
Fondo Europeo de Desarrollo Regional
"Una manera de hacer Europa"

registro de cáncer de granada

Background: Potential Outcomes framework

Rubin and Heckman

- This framework was developed first by statisticians (Rubin, 1983) and econometricians (Heckman, 1978) as a new approach for the estimation of **causal effects** from observational data.
- We will keep separate the **causal framework** (a conceptual issue briefly introduce here) and the **"how to estimate causal effects"** (an statistical issue also introduced here)

Causal effects with OBSERVATIONAL data

ASSUMPTIONS for Identification

- Rosebaum & Rubin, 1983: **The Ignorable Treatment Assignment** (A.K.A Ignorability, Unconfoundeness or Conditional Mean Independence).
- **POSITIVITY**.
- **SUTVA**.

Causal effect with OBSERVATIONAL data

IGNORABILITY

$$(Y_i(1), Y_i(0)) \perp A_i \mid W_i$$

POSITIVITY

POSITIVITY: $P(A = a \mid W) > 0$ for all a, W

SUTVA

- We have assumed that there is only on version of the treatment (**consistency**) **Y(1)** if **A = 1** and **Y(0)** if **A = 0**.
- The assignment to the treatment to one unit doesn't affect the outcome of another unit (**no interference**) or **IID** random variables.
- The model used to estimate the assignment probability has to **be correctly specified**.

Causal effect

Potential Outcomes

We only observe:

$$Y_i(1) = Y_i(A = 1) \text{ and } Y_i(0) = Y_i(A = 0)$$

However we would like to know what would have happened if:

Treated $\mathbf{Y_i(1)}$ would have been non-treated $Y_i(A = 0) = Y_i(0)$.

Controls $Y_i(0)$ would have been treated $\mathbf{Y_i(A = 1) = Y_i(1)}$.

Identifiability

- How we can identify the effect of the potential outcomes $\mathbf{Y}^a$ if they are not observed?
- How we can estimate the expected difference between the potential outcomes **E[Y(1) - Y(0)]**, namely the **ATE**.

G-Formula for the **identification** of the ATE with observational data

$$
\begin{aligned}
E(Y^a) &= \sum_y E(Y^a \mid W = w)P(W = w) \\
&= \sum_y E(Y^a \mid A = a, W = w)P(W = w) \text{ by consistency} \\
&= \sum_y E(Y = y \mid A = a, W = w)P(W = w) \text{ by ignorability}
\end{aligned}
$$

The **ATE**=

$$\sum_{\mathbf{w}} \left[\sum_{\mathbf{y}} \mathbf{P}(\mathbf{Y} = \mathbf{y} \mid \mathbf{A} = \mathbf{1}, \mathbf{W} = \mathbf{w}) - \sum_{\mathbf{y}} \mathbf{P}(\mathbf{Y} = \mathbf{y} \mid \mathbf{A} = \mathbf{0}, \mathbf{W} = \mathbf{w}) \right] \mathbf{P}(\mathbf{W} = \mathbf{w})$$

$$P(W = w) = \sum_{y,a} P(W = w, A = a, Y = y)$$

G-Formula, (Robins, 1986)

G-Formula for the identification of the ATE with observational data

The **ATE**=

$$\sum_{\mathbf{w}} \left[\sum_{\mathbf{y}} \mathbf{P}(\mathbf{Y} = \mathbf{y} \mid \mathbf{A} = \mathbf{1}, \mathbf{W} = \mathbf{w}) - \sum_{\mathbf{y}} \mathbf{P}(\mathbf{Y} = \mathbf{y} \mid \mathbf{A} = \mathbf{0}, \mathbf{W} = \mathbf{w}) \right] \mathbf{P}(\mathbf{W} = \mathbf{w})$$

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G-Formula

- The sums is generic notation. In reality, likely involves sums and integrals (we are just integrating out the W's).
- The **g-formula** is a **generalization of standardization** and allow to estimate unbiased treatment effect estimates.

RA

Regression-adjustment

$$\widehat{ATE}_{RA} = N^{-1} \sum_{i=1}^{N} [E(Y_i \mid A = 1, W_i) - E(Y_i \mid A = 0, W_i)]$$

$$m_A(w_i) = E(Y_i \mid A_i = A, W_i)$$

$$\widehat{ATE}_{RA} = N^{-1} \sum_{i=1}^{N} [\hat{m}_1(w_i) - \hat{m}_0(w_i)]$$

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IPTW

IPTW (Inverse probability treatment weighting)

Survey theory (Horvitz-Thompson)

$$\hat{P}_i = E(A_i \mid W_i) \text{ ; So , } \frac{\mathbf{1}}{\hat{\mathbf{p}}_\mathbf{i}} \text{ , if A = 1 and , } \frac{\mathbf{1}}{(\mathbf{1} - \hat{\mathbf{p}}_\mathbf{i})} \text{ , if A = 0}$$

over the total number of individuals

$$\widehat{ATE}_{IPTW} = N^{-1} \sum_{i=1}^{N} \frac{A_i Y_i}{\hat{p}_i} - N^{-1} \sum_{i=1}^{N} \frac{(1 - A_i) Y_i}{(1 - \hat{p}_i)}$$

AIPTW

AIPTW (Augmented Inverse probability treatment weighting)

Solving Estimating Equations

$$\widehat{ATE}_{AIPTW} =$$

$$N^{-1}\sum_{i=1}^{N}[(Y(1) \mid A_i = 1, W_i) - (Y(0) \mid A_i = 0, W_i)] +$$

$$N^{-1}\sum_{i=1}^{N}\left(\frac{(A_i = 1)}{P(A_i = 1 \mid W_i)} - \frac{(A_i = 0)}{P(A_i = 0 \mid W_i)}\right)[Y_i - E(Y \mid A_i, W_i)]$$

TMLE inference: INFLUENCE CURVE

M-ESTIMATORS: Semi-parametric and Empirical processes theory

An estimator is **asymptotically linear** with **influence function** φ **(IC)** if the estimator can be **approximate by an empirical average** in the sense that

$$(\hat{\theta} - \theta_0) = \frac{1}{n}\sum_{i=1}^{n}(IC) + Op(1/\sqrt{n})$$

(Bickel, 1997).

TMLE inference: Bickel (1993); Tsiatis (2007); Van der Laan (2011); Kennedy (2016)

- The **IC** estimation is a more general approach than M-estimation.
- The **Efficient IC** has mean zero $E(IC_{\hat{\psi}}(y_i, \psi_0)) = 0$ and **finite variance.**
- By the Weak Law of the Large Numbers, the **Op** converges to zero in a rate $1/\sqrt{n}$ as n $\rightarrow\infty$ (Bickel, 1993).
- The **Efficient IC** requires **asymptotically linear** estimators.

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Thank you

THANK YOU FOR YOUR TIME

"Una manera de hacer Europa"