

Day 2, Lecture 1

Targeted Minimum Loss-based Estimation (TMLE)

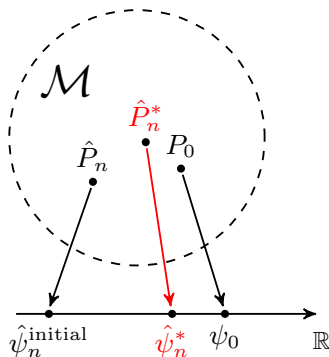
Targeted Minimum Loss-based Estimation (TMLE)

1. Data is a random variable O with a probability P_0
2. P_0 belongs to a statistical model \mathcal{M}
3. Our target is a parameter $\Psi : \mathcal{M} \rightarrow \mathbb{R}$
4. Construct estimator \hat{P}_n for (relevant part of) P_0 and estimate the target parameter by $\hat{\psi}_n = \Psi(\hat{P}_n)$
5. Quantify uncertainty for the estimator $\hat{\psi}_n = \Psi(\hat{P}_n)$

Estimation paradigm

1. P_0 is assumed to belong to a nonparametric model \mathcal{M}
2. Construction of \sqrt{n} -consistent and asymptotically linear estimation of $\psi_0 = \Psi(P_0)$ based the efficient influence function.

Targeted Minimum Loss-based Estimation (TMLE)



Tools from semiparametric efficiency theory and empirical process theory tell us how to construct an **optimal estimator** for a **given target parameter** $\Psi : \mathcal{M} \rightarrow \mathbb{R}$

- ▶ asymptotic linearity/normality
- ▶ asymptotic efficiency

Targeted Minimum Loss-based Estimation (TMLE)

TMLE is a two-step procedure:

Step 1 Construct initial estimator \hat{P}_n for P .

Step 2 Update the estimator $\hat{P}_n \mapsto \hat{P}_n^*$ such that \hat{P}_n^* solves the efficient influence curve equation, i.e.,

$$\mathbb{P}_n \phi^*(\hat{P}_n^*) = \frac{1}{n} \sum_{i=1}^n \phi^*(\hat{P}_n^*)(O_i) \approx 0.$$

Step 1 = "initial estimation step"

Step 2 = "targeting step"

Targeted Minimum Loss-based Estimation (TMLE)

$$\begin{aligned}\Psi(\hat{P}_n) - \Psi(P_0) &= \mathbb{P}_n \phi^*(P_0) + o_P(n^{-1/2}) \\ &\quad + R(\hat{P}_n, P_0) \\ &\quad - \mathbb{P}_n \phi^*(\hat{P}_n)\end{aligned}$$

- ▶ The role of the targeting step (Step 2):
 - ▶ Gaining double robustness in consistency.
 - ▶ Easier to get rid of second-order remainder.
- ▶ The role of the initial estimation step (Step 1):
 - ▶ This should be done well enough to get rid of the second-order remainder.

Targeted Minimum **Loss**-based Estimation (TMLE)

$$f(A, X) = \mathbb{E}_P[Y \mid A, X]$$

A **loss function** $\mathcal{L}(f)(O)$ measuring the distance between an estimator f and the observed outcome Y , e.g., the negative log-likelihood:

$$\mathcal{L}(\hat{f}_n)(Y_i, A_i, X_i) = -(Y_i \log(\hat{f}_n(A_i, X_i)) + (1 - Y_i) \log(1 - \hat{f}_n(A_i, X_i))).$$

- ▶ The estimator \hat{f}_n closest to the true f_0 minimizes the risk:

$$\mathbb{E}_{P_0}[\mathcal{L}(\hat{f}_n)(Y_i, A_i, X_i)].$$

- ▶ Loss-based super learning: Minimizing the cross-validated empirical risk with respect to the loss function \mathcal{L} over the statistical model.

Targeted Minimum Loss-based Estimation (TMLE)

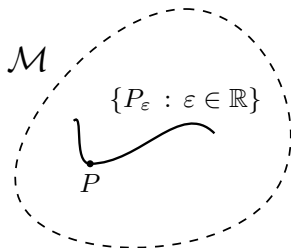
This is all about constructing a good estimator for the conditional expectation f ;

- ▶ does not necessarily yield a good estimator for the particular feature of interest, the target parameter.

This is Step 1.

Targeted Minimum Loss-based Estimation (TMLE)

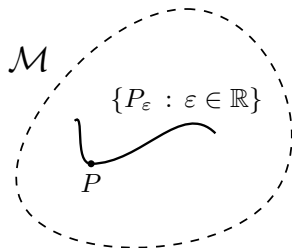
Step 2: We can select a loss function to result in a good estimator for the target.



Loss function $\mathcal{L}(f)(O)$ + clever choice of a parametric submodel $\{P_\varepsilon : \varepsilon \in \mathbb{R}\} \subset \mathcal{M}$.

Targeted Minimum Loss-based Estimation (TMLE)

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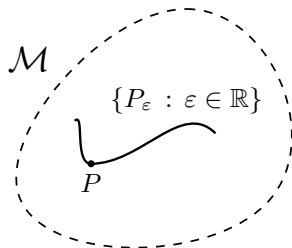


Loss function $\mathcal{L}(f)(O)$ + clever choice of a **parametric submodel** $\{P_\epsilon : \epsilon \in \mathbb{R}\} \subset \mathcal{M}$.

\Rightarrow minimize the loss along the submodel, given the estimator \hat{f}_n from **Step 1**.

Targeted Minimum Loss-based Estimation (TMLE)

Step 2: We can select a loss function to result in a good estimator for the target.



Loss function $\mathcal{L}(f)(O)$ + clever choice of a **parametric submodel** $\{P_\epsilon : \epsilon \in \mathbb{R}\} \subset \mathcal{M}$.

- \Rightarrow minimize the loss along the submodel, given the estimator \hat{f}_n from **Step 1**.
- \Rightarrow update \hat{f}_n along the path defined by P_ϵ : moving by $\hat{\epsilon}_n$ that minimizes the loss.

The targeting step (Step 2)

Construction of the targeting step for a given target parameter $\Psi : \mathcal{M} \rightarrow \mathbb{R}$ with efficient influence function $\phi^*(P)$ requires:

(i) A parametric submodel $\{P_\varepsilon : \varepsilon \in \mathbb{R}\} \subset \mathcal{M}$

(ii) A loss function $(O, P) \mapsto \mathcal{L}(P)(O)$

such that: (1) $P_{\varepsilon=0} = P$, and, (2) $\left. \frac{d}{d\varepsilon} \right|_{\varepsilon=0} \mathcal{L}(P_\varepsilon)(O) = \phi^*(P)(O)$

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- ▶ Initial estimator \hat{P}_n^0
- ▶ Minimizer $\hat{\varepsilon}_{n,0}$ of $\varepsilon \mapsto \mathbb{P}_n \mathcal{L}(\hat{P}_{n,\varepsilon}^0)$
- ▶ Update: $\hat{P}_n^1 := \hat{P}_{\hat{\varepsilon}_{n,0}}^0$

Then: $\mathbb{P}_n \left. \frac{d}{d\varepsilon} \right|_{\varepsilon=\hat{\varepsilon}_{n,0}} \mathcal{L}(\hat{P}_{n,\varepsilon}^0)(O) = 0$

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- ▶ Updated estimator \hat{P}_n^1
- ▶ Minimizer $\hat{\varepsilon}_{n,1}$ of $\varepsilon \mapsto \mathbb{P}_n \mathcal{L}(\hat{P}_{n,\varepsilon}^1)$
- ▶ Update: $\hat{P}_n^2 := \hat{P}_{\hat{\varepsilon}_{n,1}}^1$

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- ▶ k th updated estimator \hat{P}_n^k
- ▶ Minimizer $\hat{\varepsilon}_{n,k}$ of $\varepsilon \mapsto \mathbb{P}_n \mathcal{L}(\hat{P}_{n,\varepsilon}^k)$
- ▶ Update: $\hat{P}_n^{k+1} := \hat{P}_{\hat{\varepsilon}_{n,k}}^k$

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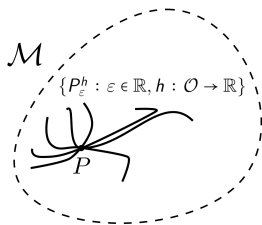
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The targeting step (Step 2) *ASIDE*

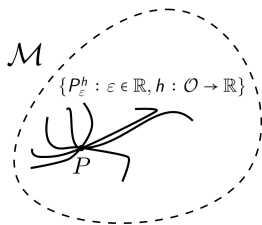
What happens?



Parametric submodels $\{P_\varepsilon : \varepsilon \in \mathbb{R}\} \subset \mathcal{M}$ are also what we use to derive the nonparametric lower bound on the variance.

- ▶ Index the submodel by its score function: $\{P_\varepsilon^h : \varepsilon \in \mathbb{R}, h : \mathcal{O} \rightarrow \mathbb{R}\}$.
- ▶ Easier to estimate Ψ in the smaller model $\{P_\varepsilon^h : \varepsilon \in \mathbb{R}\}$ than in \mathcal{M} .
- ▶ The supremum over Cramér-Rao bounds over all submodels $\{P_\varepsilon^h : \varepsilon \in \mathbb{R}\}$ for estimating $\varepsilon \mapsto \Psi(P_\varepsilon^h)$ at $\varepsilon = 0$ provides **lower bound on the variance for estimating Ψ in \mathcal{M}** .

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The submodel for which the supremum of the Cramér-Rao bounds over all parametric submodels is called the **least favorable submodel**.

- ▶ It is the submodel for which the score is equal to the efficient influence function $\phi^*(P)$.

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The TMLE step uses the **least favorable submodel** as a fluctuation model

- ▶ given a current estimator \hat{P}_n^k the updated estimator is found by fluctuating along the least favorable submodel;
- ▶ the nonparametric efficiency bound is reached when no further fluctuation is needed ($\varepsilon \approx 0$);

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- ▶ the nonparametric efficiency bound is reached when no further fluctuation is needed ($\varepsilon \approx 0$);
- ▶ the estimator **solves the efficient influence curve equation**.

The targeting step (Step 2)

Conditions (asymptotic linearity and efficiency)

(C1) Solve the efficient influence curve equation: $\mathbb{P}_n \phi^*(\hat{P}_n) = o_P(n^{-1/2})$

(C2) Remainder $R(\hat{P}_n, P_0) = o_P(n^{-1/2})$

(C3) Donsker class conditions for $\{\phi^*(P) : P \in \mathcal{M}\}$

Then: $\Psi(\hat{P}_n) \overset{as}{\sim} N(\Psi(P_0), P_0 \phi^*(P_0)^2 / n)$

- ▶ The targeting step ensures that (C1) holds.
- ▶ Assume that (C2) and (C3) hold.

We can use the efficient influence function to compute an estimator for the standard error of the TMLE estimator:

$$\hat{\sigma}_n = \sqrt{\frac{\mathbb{P}_n \{\phi^*(\hat{P}_n)\}^2}{n}}$$

Targeting the average treatment
effect (ATE)

Targeting the average treatment effect (ATE)

EXAMPLE: Average treatment effect (ATE)

Observed data $O = (X, A, Y) \in \mathbb{R}^d \times \{0, 1\} \times \{0, 1\} = \mathcal{O}$

- * $X \in \mathbb{R}^d$ are covariates
- * $A \in \{0, 1\}$ is a binary exposure variable (treatment decision)
- * $Y \in \{0, 1\}$ is a binary outcome variable

$O \sim P_0$ where P_0 assumed to belong to nonparametric model \mathcal{M} .

We are interested in estimating the ATE:

$$\Psi(P) = \mathbb{E}_P[\mathbb{E}_P[Y \mid A = 1, X] - \mathbb{E}_P[Y \mid A = 0, X]].$$

Targeting the average treatment effect (ATE)

EXAMPLE: Average treatment effect (ATE)

For the ATE, as we have seen, we can also write the target parameter $\Psi : \mathcal{M} \rightarrow \mathbb{R}$ as

$$\Psi(P) = \tilde{\Psi}(f, \mu_X) = \int_{\mathbb{R}^d} (f(1, x) - f(0, x)) d\mu_X(x) \quad (*)$$

where

$$f(a, x) = \mathbb{E}[Y \mid A = a, X = x]$$

and μ_X is the marginal distribution of X .

I.e., $\hat{\psi}_n = \tilde{\Psi}(\hat{f}_n, \hat{\mu}_n)$.

Targeting the average treatment effect (ATE)

EXAMPLE: Average treatment effect (ATE)

Step 1 Construct initial estimators $\hat{f}_n, \hat{\pi}_n$ for f, π .

Step 2 Update the estimator $\hat{f}_n \mapsto \hat{f}_n^*$ for f such that \hat{f}_n^* for the fixed $\hat{\pi}_n$ solves the efficient influence curve equation.

For the ATE, Step 2 is simply just an additional logistic regression step.

Targeting the average treatment effect (ATE)

EXAMPLE: Average treatment effect (ATE)

We need:

0. The efficient influence function:

$$\begin{aligned}\tilde{\phi}^*(f, \pi)(O) = & \left(\frac{A}{\pi(A|X)} - \frac{1-A}{\pi(A|X)} \right) (Y - f(A, X)) \\ & + f(1, X) - f(0, X) - \tilde{\Psi}(f)\end{aligned}$$

Targeting the average treatment effect (ATE)

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Further, we need:

- (i) A parametric submodel $\{f_\varepsilon : \varepsilon \in \mathbb{R}\} \subset \mathcal{M}$
- (ii) A loss function $(O, f) \mapsto \mathcal{L}(f)(O)$

such that

$$(1) \quad f_{\varepsilon=0} = f \qquad (2) \quad \left. \frac{d}{d\varepsilon} \right|_{\varepsilon=0} \mathcal{L}(f_\varepsilon)(O) = \tilde{\phi}_f^*(f, \pi)(O)$$

Targeting the average treatment effect (ATE)

(i) Log-likelihood loss function:

$$\text{logit}(p) = \text{expit}^{-1}(p) = \log\left(\frac{p}{1-p}\right)$$

$$\mathcal{L}(f)(O) = -(Y \log(f(A, X)) + (1 - Y) \log(1 - f(A, X)))$$

(ii) Logistic regression model:

$$f_{\varepsilon}(A, X) = \text{expit}(\text{logit}(f(A, X)) + \varepsilon H(A, X))$$

with the so-called "clever covariate": $H(A, X) := \frac{2A - 1}{\pi(A | X)}$.

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To show this, we verify that (i)–(ii) fulfill

$$(1) \quad f_{\varepsilon=0} = f \quad (2) \quad \left. \frac{d}{d\varepsilon} \right|_{\varepsilon=0} \mathcal{L}(f_{\varepsilon})(O) = \tilde{\phi}_f^*(f, \pi)(O)$$

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SMALL EXERCISE: To show this, we verify that (i)–(ii) fulfill

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Targeting the average treatment effect (ATE)

- ▶ Initial estimator \hat{f}_n .
- ▶ Estimate clever covariate by:

$$\hat{H}_n(A, X) = \frac{2A - 1}{\hat{\pi}_n(A | X)}.$$

- ▶ The minimizer $\hat{\varepsilon}_n$ of $\varepsilon \mapsto \mathbb{P}_n \mathcal{L}(\hat{f}_{n,\varepsilon})$ equals the maximum likelihood estimator for ε in the fixed-intercept logistic regression:

$$\text{logit} \mathbb{E}[Y | A, X] = \text{logit}(\hat{f}_n(A, X)) + \varepsilon \hat{H}_n(A, X)$$

- ▶ Update: $\hat{f}_n^* := \hat{f}_{n,\hat{\varepsilon}_n}$.

Then: $\mathbb{P}_n \frac{d}{d\varepsilon} \bigg|_{\varepsilon=\hat{\varepsilon}_n} \mathcal{L}(\hat{f}_{n,\varepsilon}) = 0, \quad \text{i.e.,}$

$$\mathbb{P}_n \tilde{\phi}_f^*(\hat{f}_{n,\hat{\varepsilon}_n}, \hat{\pi}_n) = \mathbb{P}_n \tilde{\phi}_f^*(\hat{f}_n^*, \hat{\pi}_n) = 0.$$

Targeting the average treatment effect (ATE)

$$\begin{aligned}\tilde{\phi}^*(f, \pi)(O) &= \underbrace{\left(\frac{A}{\pi(A|X)} - \frac{1-A}{\pi(A|X)} \right) (Y - f(A, X))}_{=\tilde{\phi}_f^*(f, \pi)(O)} \\ &\quad + \underbrace{f(1, X) - f(0, X) - \tilde{\Psi}(f)}_{=\tilde{\phi}_{\mu_X}^*(f)(O)}\end{aligned}$$

Per construction we already have: $\mathbb{P}_n \phi_{\mu}^*(\hat{f}_n^*) = 0$,

since: $\tilde{\Psi}(\hat{f}_n^*) = \frac{1}{n} \sum_{i=1}^n (\hat{f}_n^*(1, X_i) - \hat{f}_n^*(0, X_i)) = \mathbb{P}_n(\hat{f}_n^*(1, \cdot) - \hat{f}_n^*(0, \cdot)).$

The targeting step thus yields:

$$\mathbb{P}_n \tilde{\phi}^*(\hat{f}_n^*, \hat{\pi}_n) = \mathbb{P}_n \tilde{\phi}_f^*(\hat{f}_n^*, \hat{\pi}_n) + \mathbb{P}_n \phi_{\mu}^*(\hat{f}_n^*) = 0.$$

Targeting the average treatment effect (ATE)

Doing the targeting in practice using the simulated dataset:

```
set.seed(5)
n <- 500
X <- runif(n, -2, 2)
A <- rbinom(n, 1, prob=plogis(-0.25 + 1.2*X))
Y <- rbinom(n, 1, prob=plogis(-0.9 + 1.9*X^2 + 0.5*A))
(sim.data <- data.table(id=1:n,X=X,A=A,Y=Y))
```

	id	X	A	Y
1:	1	-1.1991422	0	1
2:	2	0.7408744	1	1
3:	3	1.6675031	1	1
4:	4	-0.8624022	0	1
5:	5	-1.5813995	0	1

496:	496	-0.3978523	1	0
497:	497	-1.5069379	0	1
498:	498	1.8340120	1	1
499:	499	0.6349484	1	0
500:	500	-0.5214807	0	1

Targeting the average treatment effect (ATE)

Initial estimation:

```
#-- treatment distribution;
glm.A <- glm(A~X, data=sim.data, family=binomial)
pi.1 <- predict(glm.A, type="response")

#-- outcome distribution (misspecified);
glm.Y <- glm(Y~A+X, data=sim.data, family=binomial)
sim.data[, f:=predict(glm.Y, type="response")]
sim.data[, f.A1:=predict(glm.Y, type="response",
                        newdata=copy(sim.data)[, A:=1])]
sim.data[, f.A0:=predict(glm.Y, type="response",
                        newdata=copy(sim.data)[, A:=0])]

#-- initial estimate of the ATE;
fit.ate.initial <- sim.data[, mean(f.A1 - f.A0)]
```

Targeting the average treatment effect (ATE)

Targeting step:

```
#-- tmle;  
sim.data[, clever.covariate:=((A==1)/pi.1 - (A==0)/(1-pi.1))]  
eps <- coef(glm(Y ~ offset(qlogis(f))+clever.covariate-1,  
               data=sim.data, family=binomial()))
```

eps = -0.0157708436790858

Targeting the average treatment effect (ATE)

Targeting step:

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eps = -0.0157708436790858

```
#-- tmle update;  
sim.data[, f.A1.tmle:=plogis(qlogis(f.A1) + eps/pi.1)]  
sim.data[, f.A0.tmle:=plogis(qlogis(f.A0) - eps/(1-pi.1))]
```

i.e., `f.A1.tmle` is the estimate of $f(1, X) = \mathbb{E}[Y \mid A = 1, X]$, obtained via the submodel:

$$\hat{f}_n^*(1, X) = \hat{f}_{n, \hat{\epsilon}_n}(1, X) = \text{expit}(\text{logit}(\hat{f}_n(1, X)) + \hat{\epsilon}_n \hat{H}_n(1, X)),$$

and likewise with `f.A0.tmle`.

Targeting the average treatment effect (ATE)

	id		X	A	Y	f.A1	f.A0	f.A1.tmle	f.A0.tmle
1:	1	-1.1991422	0	1	0.7655621	0.6713853	0.7488795	0.6755825	
2:	2	0.7408744	1	1	0.7396070	0.6399080	0.7349584	0.6504368	
3:	3	1.6675031	1	1	0.7265721	0.6244167	0.7228545	0.6481588	
4:	4	-0.8624022	0	1	0.7611886	0.6660214	0.7488197	0.6705960	
5:	5	-1.5813995	0	1	0.7704590	0.6774205	0.7463439	0.6813231	

496:	496	-0.3978523	1	0	0.7550638	0.6585507	0.7464799	0.6639337	
497:	497	-1.5069379	0	1	0.7695108	0.6762494	0.7471142	0.6802008	
498:	498	1.8340120	1	1	0.7241872	0.6216047	0.7205492	0.6495635	
499:	499	0.6349484	1	0	0.7410712	0.6416611	0.7362345	0.6513868	
500:	500	-0.5214807	0	1	0.7567041	0.6605467	0.7472996	0.6656728	

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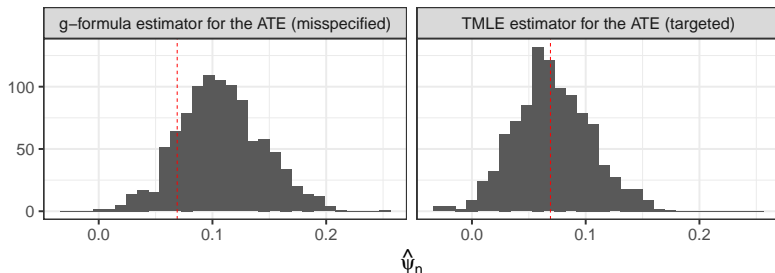
```
fit.ate.tmle <- sim.data[, mean(f.A1.tmle - f.A0.tmle)]
```

```
initial ate est = 0.0975
```

```
tmle ate est    = 0.0768
```


Targeting the average treatment effect (ATE)

With 500 repeated simulations:



Practical 1: Implementing the targeting step

Practical Part 1 Implementing the targeting step.

Practical Part 2 Computing the variances of the ATE, the log RR and the log OR.

Practical Part 3 Large-sample properties (simulation study).

The exercise is described in detail in: **day2-practical1.pdf**.

[More comments on the following slides].

Comments for practical

We focused on the ATE as an example of a causal parameter.

But note that other simple causal parameters can be constructed from $\mathbb{E}_P[Y^1]$ and $\mathbb{E}_P[Y^0]$.

Like:

$$\psi_{\text{RR}}(P) = \frac{\mathbb{E}_P[Y^1]}{\mathbb{E}_P[Y^0]},$$

or,

$$\psi_{\text{OR}}(P) = \frac{\mathbb{E}_P[Y^1]/(1 - \mathbb{E}_P[Y^1])}{\mathbb{E}_P[Y^0]/(1 - \mathbb{E}_P[Y^0])},$$

Comments for practical

For the targeting step, we can choose to target $\psi_1(P) = \mathbb{E}_P[Y^1]$ and $\psi_0(P) = \mathbb{E}_P[Y^0]$ separately.

Comments for practical

For the targeting step, we can choose to target $\Psi_1(P) = \mathbb{E}_P[Y^1]$ and $\Psi_0(P) = \mathbb{E}_P[Y^0]$ separately.

The efficient influence function for the treatment-specific mean $\Psi_a(P) = \mathbb{E}_P[Y^a]$:

$$\tilde{\phi}_a^*(f, \pi)(O) = \underbrace{\frac{1\{A=a\}}{\pi(a|X)}}_{\text{clever covar.}} (Y - f(A, X)) + f(a, X) - \Psi_a(P)$$

Comments for practical

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If we target $\Psi_1(P)$ and $\Psi_0(P)$ separately, we obtain two sets of updated estimators $\hat{f}_n \mapsto \hat{f}_{n,1}^*$ and $\hat{f}_n \mapsto \hat{f}_{n,0}^*$

- ▶ one to construct a targeted estimator $\hat{\psi}_{1,n}^*$ for $\Psi_1(P)$;
- ▶ and the other to construct a targeted estimator $\hat{\psi}_{0,n}^*$ for $\Psi_0(P)$.

Comments for practical

We can then compute an estimate for the ATE as

$$\hat{\psi}_n^* = \hat{\psi}_{n,1}^* - \hat{\psi}_{n,0}^*,$$

and we can estimate the variance of this estimator by

$$\mathbb{P}_n\{\tilde{\phi}_1^*(\hat{f}_{n,1}^*, \hat{\pi}_n) - \tilde{\phi}_0^*(\hat{f}_{n,0}^*, \hat{\pi}_n)\}^2;$$

since efficient influence function for the ATE is

$$\tilde{\phi}^*(f, \pi) = \tilde{\phi}_1^*(f, \pi) - \tilde{\phi}_0^*(f, \pi).$$

Comments for practical

Similarly we can construct estimators for the RR and the OR by simple plug-in:

$$\hat{\psi}_{\text{RR},n}^* = \frac{\hat{\psi}_{1,n}^*}{\hat{\psi}_{0,n}^*},$$

and,

$$\hat{\psi}_{\text{OR},n}^* = \frac{\hat{\psi}_{1,n}^*/(1 - \hat{\psi}_{1,n}^*)}{\hat{\psi}_{0,n}^*/(1 - \hat{\psi}_{0,n}^*)}.$$

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We can use the **delta method** to derive the efficient influence functions of $\Psi_{\text{RR}}(P)$ and $\Psi_{\text{OR}}(P)$.

Comments for practical

Let $\phi^*(P)$ be the efficient influence function for a parameter $\Psi(P)$. Say that interest is in $h(\Psi(P))$ for a function h .

The delta method yields that:

If the first derivative $h'(\psi) = \frac{d}{d\psi} h(\psi)$ of h exists and is non-zero, then the efficient influence function of $h(\Psi(P))$ is:

$$\phi_h^*(P) = h'(\Psi(P))\phi^*(P).$$

Comments for practical

So, once we have TMLE (targeted) estimators for $\Psi_1(P) = \mathbb{E}[Y^1]$ and $\Psi_0(P) = \mathbb{E}[Y^0]$:

- ▶ We can construct estimators for the ATE, the RR and the OR.
- ▶ We can compute the variance of the ATE estimator, the log RR estimator and the log OR estimator.

Practical

Practical Part 1 Implementing the targeting step.

Practical Part 2 Computing the variances of the ATE, the log RR and the log OR.

Practical Part 3 Large-sample properties (simulation study).

The exercise is described in detail in: **day2-practical1.pdf**.