Day 2, Lecture 2

TMLE: The targeting step

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"

ATE: Statistical estimation problem

 $O_1, \ldots, O_n \stackrel{iid}{\sim} P_0$, O_i is the observation for individual i of the dataset, consists of

- Covariates: $X_i \in \mathcal{X} \subseteq \mathbb{R}^d$
- Exposure/treatment: $A_i \in \{0, 1\}$
- ▶ Outcome: $Y_i \in \{0, 1\}$ or $Y \in \mathbb{R}$

We are interested in:

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

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

A plug-in estimator requires an estimator \hat{f}_n for f:

$$\hat{\psi}_n = \tilde{\Psi}(\hat{f}_n, \mathbb{P}_n) = \frac{1}{n} \sum_{i=1}^n \left(\hat{f}_n(1, X_i) - \hat{f}_n(0, X_i) \right).$$

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

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:

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

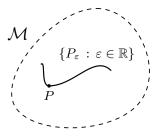
Loss-based super learning: Minimizing the cross-validated empirical risk with respect to the loss function & over the statistical model.

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.

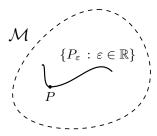
This is Step 1.

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 $\{P_{\varepsilon}: \varepsilon \in \mathbb{R}\} \subset \mathcal{M}$.

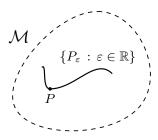
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 \Rightarrow minimize the loss along the submodel, given the estimator \hat{f}_n from Step 1.

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 $\{P_{\varepsilon}: \varepsilon \in \mathbb{R}\} \subset \mathcal{M}$.

- \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 $\hat{\varepsilon}_n$ that minimizes the loss.

- (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) $\frac{d}{d\varepsilon}\Big|_{\varepsilon=0} \mathcal{L}(P_{\varepsilon})(O) = \phi^*(P)(O)$

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

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

Then:
$$\mathbb{P}_n \frac{d}{d\varepsilon}\Big|_{\varepsilon=\hat{\varepsilon}_{n,1}} \mathcal{L}(\hat{P}_{n,\varepsilon}^1)(O) = 0$$

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

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

Construction of the targeting step for a given target parameter

$$\Psi: \mathcal{M} \to \mathbb{R}$$
 with efficient influence function $\phi^*(P)$ requires:

- (i) A parametric submodel $\{P_{\varepsilon}: \varepsilon \in \mathbb{R}\} \subset \mathcal{M}$
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- Minimizer $\hat{\varepsilon}_{n,k}$ of $\varepsilon \mapsto \mathbb{P}_n \mathcal{L}(\hat{P}_{n,\varepsilon}^k)$
- Update: $\hat{P}_n^{k+1} := \hat{P}_{\hat{e}_n}^k$

Then:
$$\mathbb{P}_n \frac{d}{d\varepsilon} \Big|_{\varepsilon = \hat{\varepsilon}_{n,k}} \mathcal{L}(\hat{P}_{n,\varepsilon}^k)(O) = 0$$
, so when $\hat{\varepsilon}_{n,k} \approx 0$: $\mathbb{P}_n \frac{d}{d\varepsilon} \Big|_{\varepsilon = 0} \mathcal{L}(\hat{P}_{n,\varepsilon}^k) = 0$.

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

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

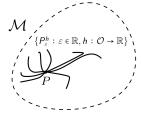
(ii) A loss function $(O, P) \mapsto \mathcal{L}(P)(O)$

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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: $\{P_{\varepsilon}^h : \varepsilon \in \mathbb{R}, h : \mathcal{O} \to \mathbb{R}\}.$
- ▶ 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 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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- 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 ($\varepsilon \approx 0$);
- the estimator solves the efficient influence curve equation.

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

- 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:

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

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.

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

EXAMPLE: Average treatment effect (ATE)

We need:

0. The efficient influence function:

$$\widetilde{\phi}^*(f,\pi)(O) = \left(\frac{A}{\pi(A\mid X)} - \frac{1-A}{\pi(A\mid X)}\right)(Y - f(A,X))$$

+ $f(1,X) - f(0,X) - \tilde{\Psi}(f)$

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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)
$$f_{\varepsilon=0} = f$$
 (2) $\frac{d}{d\varepsilon}\Big|_{\varepsilon=0} \mathscr{L}(f_{\varepsilon})(O) = \tilde{\phi}_{f}^{*}(f,\pi)(O)$

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

(i) Log-likelihood loss function:

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

(ii) Logistic regression model:

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

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

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(1)
$$f_{\varepsilon=0} = f$$
 (2) $\frac{d}{d\varepsilon}\Big|_{\varepsilon=0} \mathscr{L}(f_{\varepsilon})(O) = \tilde{\phi}_f^*(f,\pi)(O)$

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(1)
$$f_{\varepsilon=0} = f$$
 (2) $\frac{d}{d\varepsilon}\Big|_{\varepsilon=0} \mathscr{L}(f_{\varepsilon})(O) = \tilde{\phi}_f^*(f,\pi)(O)$

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

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

▶ 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:

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

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

Then:
$$\mathbb{P}_n \frac{d}{d\varepsilon} \Big|_{\varepsilon = \hat{\varepsilon}_n} \mathcal{L}(\hat{f}_{n,\varepsilon}) = 0$$
, i.e., $\mathbb{P}_n \tilde{\phi}_f^*(\hat{f}_{n,\hat{\varepsilon}_n}, \hat{\pi}_n) = \mathbb{P}_n \tilde{\phi}_f^*(\hat{f}_n^*, \hat{\pi}_n) = 0$.

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

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:

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

Doing the targeting in practice using the simulated dataset:

```
set.seed(5)
   n < -500
   X \leftarrow runif(n, -2, 2)
   A \leftarrow 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))</pre>
                  XAY
      id
     1 -1.1991422 0 1
  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
```

Initial estimation:

```
#-- treatment distribution;
glm.A <- glm(A~X, data=sim.data, family=binomial)</pre>
pi.1 <- predict(glm.A, type="response")</pre>
#-- outcome distribution (misspecified);
glm.Y <- glm(Y~A+X, data=sim.data, family=binomial)</pre>
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)]</pre>
```

Targeting step:

```
eps = -0.0157708436790858
```

Targeting step:

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:

$$\hat{f}_n^*(1,X) = \hat{f}_{n,\hat{\varepsilon}_n}(1,X) = \operatorname{expit} \bigl(\operatorname{logit}\bigl(\hat{f}_n(1,X)\bigr) + \hat{\varepsilon}_n \hat{H}_n(1,X)\bigr),$$

and likewise with f.AO.tmle.

```
id
                            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
```

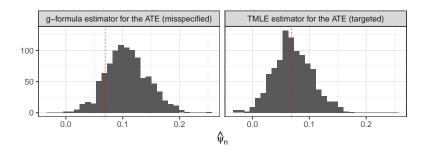
```
id
                            f.A1 f.A0 f.A1.tmle f.A0.tmle
  1:
      1 -1 1991422 0 1 0.7655621 0.6713853 0.7488795 0.6755825
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```

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

```
initial ate est = 0.0975
tmle ate est = 0.0768
```

The targeting step (Step 2)

With 500 repeated simulations:



Practical

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.

[More comments on the following slides].

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:

$$\Psi_{\mathsf{RR}}(P) = \frac{\mathbb{E}_{P}[Y^{1}]}{\mathbb{E}_{P}[Y^{0}]},$$

or,

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

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.

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 $\Psi_a(P) = \mathbb{E}_P[Y^a]$:

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

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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 $\Psi_0(P)$.

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

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

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

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

and,

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

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

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:

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

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.
- \blacktriangleright 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.

Summary of TMLE

$$\begin{split} \tilde{\Psi}(\hat{f}_n^*) - \tilde{\Psi}(f_0) &= \mathbb{P}_n \tilde{\phi}^*(f_0, \pi_0) + o_P(n^{-1/2}) \\ &+ \tilde{R}(\hat{f}_n^*, \hat{\pi}_n, f_0, \pi_0) - \underbrace{\mathbb{P}_n \tilde{\phi}^*(\hat{f}_n^*, \hat{\pi}_n)}_{=0, \text{ by targeting.}} \end{split}$$

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For the ATE, when $\mathbb{P}_n \tilde{\phi}^*(\hat{f}_n^*, \hat{\pi}_n) = 0$, recall that:

$$|\tilde{R}(\hat{f}_{n}^{*},\hat{\pi}_{n},f_{0},\pi_{0})| \leq \sum_{a=0,1} \delta^{-1} \|\pi_{0}(a|\cdot) - \hat{\pi}_{n}(a|\cdot)\|_{\mu_{0}} \|f_{0}(a|\cdot) - \hat{f}_{n}^{*}(a|\cdot)\|_{\mu_{0}}$$

What this tells us:

• Asymptotic linearity when π_0 and f_0 are estimated at rate at least $n^{-1/4}$.

Summary of TMLE

How can we perform estimation of π_0 and f_0 such as to achieve rate at least $n^{-1/4}$?

- Correctly specified parametric models
- Lasso, highly adaptive lasso (HAL), ...
- ► Loss-based super learning
 - oracle property: the super learner achieves the rate of convergence of the best estimator in its library.