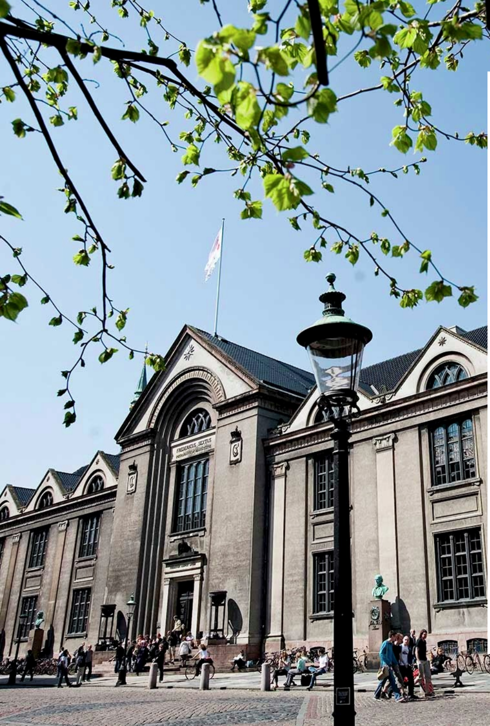

TMLE update step: the fluctuation model

TMLE for breakfast May 23

Mark Bech Knudsen
Section of Biostatistics

UNIVERSITY OF COPENHAGEN

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- R example at the end.

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Challenge: How do we then obtain an efficient estimator of Ψ_0?

Influence functions

If $G_{\bar{A}(k)}(\mathbf{X}) = \prod_{i=0}^{k} G_{A(i)}(\mathbf{X})$, $G_{\bar{C}(k)}(\mathbf{X}) = \prod_{i=1}^{k} G_{C(i)}(\mathbf{X})$, we know that

$$\Psi_0 = \Psi(P_{\mathbf{X}}) = \mathbb{E}_{P_{\mathbf{X}}} \left\{ Y(K) \frac{\mathbb{1}(\bar{A}(K-1) = \bar{a}(K-1), \bar{C}(K) = 1)}{G_{\bar{A}(K-1)}(\mathbf{X}) G_{\bar{C}(K)}(\mathbf{X})} \right\}$$

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$$\hat{\Psi}^{\text{IPTW}} = \frac{1}{n} \sum_{i=1}^{n} Y_i(K) \frac{\mathbb{1}(\bar{A}_i(K-1) = \bar{a}(K-1), \bar{C}_i(K) = 1)}{G_{\bar{A}(K-1)}(\mathbf{X}_i) G_{\bar{C}(K)}(\mathbf{X}_i)}$$

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$$\phi^{\mathsf{IPTW}}(P)(\mathbf{X}) = Y(K) \frac{\mathbb{1}(\bar{A}(K-1) = \bar{a}(K-1), \bar{C}(K) = 1)}{G_{\bar{A}(K-1)}(\mathbf{X})\, G_{\bar{C}(K)}(\mathbf{X})} - \Psi(P)$$

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and see that $\sqrt{n}(\hat{\Psi}^{\mathsf{IPTW}} - \Psi_0) \xrightarrow{\mathcal{D}} \mathcal{N}(0, \mathbb{E}\{\phi^{\mathsf{IPTW}}(P_{\mathbf{X}})(\mathbf{X})^2\})$.

The efficient influence function

There are (potentially) many different estimators $\hat{\Psi}$ of Ψ_0 such that

$$\hat{\Psi} - \Psi_0 = \frac{1}{n}\sum_{i=1}^{n} \phi(P_{\mathbf{X}})(\mathbf{X}_i) + o_P(n^{-\frac{1}{2}})$$

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For details on influence functions see e.g. Kennedy (2016).

The efficient influence function for our problem

It is possible to derive the EIF for our problem (van der Laan and Gruber, 2012). It consists of one component for each time point k:

$$\phi^*(P)(\mathbf{X}) = \sum_{k=0}^{K} \phi_k^*(P)(\mathbf{X})$$

$$\phi_K^*(P)(\mathbf{X}) = \frac{\mathbb{1}(\bar{A}(K-1) = \bar{a}(K-1), \bar{C}(K) = 1)}{G_{\bar{A}(K-1)}(\mathbf{X}) G_{\bar{C}(K)}(\mathbf{X})}(Y(K) - \bar{Q}^{\bar{a}}_{L(K)})$$

$$\phi_k^*(P)(\mathbf{X}) = \frac{\mathbb{1}(\bar{A}(k-1) = \bar{a}(k-1), \bar{C}(k) = 1))}{G_{\bar{A}(k-1)}(\mathbf{X}) G_{\bar{C}(k)}(\mathbf{X})}(\bar{Q}^{\bar{a}}_{L(k+1)} - \bar{Q}^{\bar{a}}_{L(k)})$$

$$\phi_0^*(P)(\mathbf{X}) = \bar{Q}^{\bar{a}}_{L(1)} - \bar{Q}^{\bar{a}}_{L(0)} = \bar{Q}^{\bar{a}}_{L(1)} - \Psi(P)$$

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Change estimator: Instead of using $\hat{\Psi}^{\mathsf{SR}}$ or $\hat{\Psi}^{\mathsf{IPTW}}$, we could construct a new estimator based on the EIF:

$$\hat{\Psi}^{\mathsf{EIF}} = \frac{1}{n}\sum_{i=1}^{n}(\phi^*(\hat{P}_{\mathbf{X}})(\mathbf{X_i}) + \Psi_0)$$

where we take the empirical mean of the stochastic part of the EIF, plugging in an estimate $\hat{P}_{\mathbf{X}}$ of $P_{\mathbf{X}}$ (or more precisely, of G_A, G_C, $\bar{Q}^{\bar{a}}$).

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Change estimation of nuisance parameters: Instead of changing the estimator $\hat{\Psi}^{\mathsf{SR}} = \Psi^{\mathsf{SR}}(\hat{\bar{Q}}^{\bar{a}})$, we change the estimator $\hat{\bar{Q}}^{\bar{a}}$ into some $\hat{\bar{Q}}^{\bar{a},*}$ such that $\Psi^{\mathsf{SR}}(\hat{\bar{Q}}^{\bar{a},*})$ becomes efficient $\rightarrow$ the TMLE approach.

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We then make the update $\hat{\bar{Q}}^{\bar{a},*} := \hat{\bar{Q}}^{\bar{a}}(\hat{\epsilon})$

$$\hat{\epsilon} := \operatorname*{argmin}_{\epsilon} \frac{1}{n} \sum_{i=1}^{n} \mathcal{L}(\hat{\bar{Q}}^{\bar{a}}(\epsilon))(\mathbf{X}_i)$$

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Plug $\bar{Q}^{\bar{a}}_{L(k)}(\epsilon_k)$ into loss and minimize sample loss over ϵ_k numerically.

Update as logistic regression with clever covariate

Minimizing the loss over ϵ_k is equivalent to doing logistic regression of $\bar{Q}^{\bar{a}}_{L(k+1)}$ with the IPTW:

$$\frac{\mathbb{1}(\bar{A}(k-1) = \bar{a}(k-1), \bar{C}(k) = 1)}{G_{\bar{A}(k-1)}(\mathbf{X}) G_{\bar{C}(k)}(\mathbf{X})}$$

as a so called clever covariate, and $\operatorname{logit}(\bar{Q}^{\bar{a}}_{L(k)})$ as offset.

This is just a clever way of minimizing the loss over ϵ_k.

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The result is the (L)TMLE of our target parameter.

Targeting step in R: Setup

Same data structure as earlier:

head(d)

	L_0	A_0	C_1	Y_1	L_1	A_1	C_2	Y_2
1 :	1	1	1	0	1	0	1	0
2 :	0	0	1	1	1	0	1	1
3 :	1	0	1	0	1	1	0	0

```
d1 <- copy(d)[, A_0 := 1][, A_1 := 1]
```

Targeting step in R: Treatment and censoring propensity models

First estimate all treatment and censoring propensities:

```
G_A0 <- glm(A_0 ~ L_0, family = binomial(), data = d)
G_A0_hat <- predict(G_A0, newdata = d1, type = "response")

G_A1 <- glm(A_1 ~ L_0 + A_0 + L_1, family = binomial(),
            data = d[C_1 == 1 & Y_1 == 0])
G_A1_hat <- predict(G_A1, newdata = d1, type = "response")

G_C1 <- glm(C_1 ~ L_0 + A_0, family = binomial(), data = d)
G_C1_hat <- predict(G_C1, newdata = d1, type = "response")

G_C2 <- glm(C_2 ~ L_0 + A_0 + L_1 + A_1, family = binomial(),
            data = d[C_1 == 1 & Y_1 == 0])
G_C2_hat <- predict(G_C2, newdata = d1, type = "response")

d[, G_A0_hat := G_A0_hat][, G_A1_hat := G_A1_hat][
    , G_C1_hat := G_C1_hat][, G_C2_hat := G_C2_hat]
```

Targeting step in R: Time 2

Fit outcome regression as before:

```
Q2 <- glm(Y_2 ~ L_0 + A_0 + L_1 + A_1,
          family = binomial(),
          data = d[Y_1 == 0 & C_1 == 1 & C_2 == 1])
Q2_hat <- predict(Q2, newdata = d1, type = "response")
d[, Q2_hat := Y_1 + (1 - Y_1) * Q2_hat]
```

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          family = binomial(),
          data = d[Y_1 == 0 & C_1 == 1 & C_2 == 1])
Q2_hat <- predict(Q2, newdata = d1, type = "response")
d[, Q2_hat := Y_1 + (1 - Y_1) * Q2_hat]
```

Do the targeting step:

```
Q2star <- glm(Y_2 ~ I((A_0 == 1 & A_1 == 1) /
              (G_A0_hat * G_A1_hat * G_C1_hat * G_C2_hat)),
              family = binomial(), offset = qlogis(Q2_hat),
              data = d[Y_1 == 0 & C_1 == 1 & C_2 == 1])
Q2star_hat <- predict(Q2star, newdata = d1,
                      type = "response")
d[, Q2star_hat := Y_1 + (1 - Y_1) * Q2star_hat]
```

Targeting step in R: Time 1

We use targeted estimate from previous step as outcome:

```
Q1 <- glm(Q2star_hat ~ L_0 + A_0, family = quasibinomial(),
          data = d[C_1 == 1])
Q1_hat <- predict(Q1, newdata = d1, type = "response")
d[, Q1_hat := Q1_hat]
```

Targeting step in R: Time 1

We use targeted estimate from previous step as outcome:

```
Q1 <- glm(Q2star_hat ~ L_0 + A_0, family = quasibinomial(),
          data = d[C_1 == 1])
Q1_hat <- predict(Q1, newdata = d1, type = "response")
d[, Q1_hat := Q1_hat]
```

And then do another targeting step:

```
Q1star <- glm(Q2star_hat ~
                  I((A_0 == 1) / (G_A0_hat * G_C1_hat)),
              family = quasibinomial(),
              offset = qlogis(Q1_hat),
              data = d[C_1 == 1])
Q1star_hat <- predict(Q1star, newdata = d1,
                      type = "response")
```

Targeting step in R: Results

Again take sample mean for the final estimate:

```
mean(Q1star_hat)
[1] 0.04852176

fit <- ltmle::ltmle(
  d, # have to use original data without intermediate calcs
  Anodes = c("A_0", "A_1"),
  Cnodes = c("C_1", "C_2"),
  Lnodes = c("L_0", "L_1"),
  Ynodes = c("Y_1", "Y_2"),
  survivalOutcome = TRUE,
  abar = c(1, 1),
  gcomp = FALSE
)
[1] 0.04849969
```

Discrepancy (hopefully) due to implementation details, e.g. bounding of weights in ltmle.

References

- Kennedy, Edward H. (2016). *Semiparametric theory and empirical processes in causal inference*. arXiv: 1510.04740 [math.ST].
- Petersen, Maya, Joshua Schwab, Susan Gruber, Nello Blaser, Michael Schomaker, and Mark van der Laan (2014). "Targeted Maximum Likelihood Estimation for Dynamic and Static Longitudinal Marginal Structural Working Models". In: *Journal of Causal Inference* 2.2, pp. 147–185. ISSN: 2193-3677. DOI: 10.1515/jci-2013-0007.
- van der Laan, Mark J. and Susan Gruber (2012). "Targeted Minimum Loss Based Estimation of Causal Effects of Multiple Time Point Interventions". In: *The International Journal of Biostatistics* 8.1. DOI: doi:10.1515/1557-4679.1370.