

Targeted Minimum Loss-based Estimation (TMLE) for Causal Inference in Biostatistics

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Overview of topics of course

Background theory

- * Understanding key concepts of semiparametric efficiency theory.
- * Estimation and inference based on the efficient influence function.

The TMLE procedure

- * Targeted loss-based learning incorporating the efficient influence function.
- * Data-adaptive estimation via machine learning.

Causal inference part

- * Model-free (nonparametric) definition of statistical target parameter.
- * Causal interpretation under certain assumptions.

Practical part

- * Explore properties of estimation based on the efficient influence function.
- * Assess model misspecification and estimator performance via simulations in R.

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Please give feedback 😊 (this is the first time, this course runs).

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▷ G-formula, IPW, simulations in R, simple application of TMLE.

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An insight into the background theory. (Anders).

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- ▶ The decomposition and the role of Step 1 & Step 2.

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The targeting step. Solving the efficient influence curve equation.

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Step 2: Super learning. (Thomas).

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Time-dependent treatment decisions. Causal inference in longitudinal data.

▷ Treatment-confounder feedback.

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Longitudinal TMLE. Targeting for time-varying structures.

- ▷ Identification proofs and extension of the time-fixed setting.
- ▷ Software: `ltmle`.

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Day 3: 13 – 15

Evaluation + "buffer".

Day 1, Lecture 1

Introduction: The roadmap of
targeted learning

Overview: The roadmap of targeted learning

Theoretical angle The roadmap of targeted learning

- ▶ data as a random variable having a probability distribution, scientific knowledge represented by a large statistical model, a statistical target parameter representing an answer to the question of interest.

Applied angle The roadmap of targeted learning / causal inference

- ▶ translation from real-world data applications to a mathematical and statistical formulation of the relevant estimation problem.
- ▶ statistical analysis tailored towards answering that question.

Opposed to choosing a model for the data-generating process and using that model to answer all questions.

The roadmap (theoretical)

1. Data is a random variable O with a probability distribution 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 $\hat{\psi}_n = \Psi(\hat{P}_n)$

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$$O_1, \dots, O_n \stackrel{iid}{\sim} P_0$$

O_i is the observation for individual i of the dataset

For example, O consists of

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

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This is the data structure we stick to for now.

The roadmap (theoretical)

2. P_0 belongs to a statistical model \mathcal{M}

What do we know about the probability distribution of the data?

The statistical model \mathcal{M} is the set of all possible probability distributions for our observed data.

Limited statistical knowledge? $\Rightarrow \mathcal{M}$ should be large to reflect that.

The roadmap (theoretical)

Consider a **parametric**¹ **model** for the distribution of $Y \in \{0, 1\}$ given $X \in \mathbb{R}^d$ and $A \in \{0, 1\}$:

¹i.e., distribution can be characterized by a finite number of parameters.

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- ▶ assumption of convenience?

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Another parametric model could be

$$\text{logit } \mathbb{E}[Y \mid A, X] = \gamma_0 + \gamma_A A + \gamma_X^\top X + \gamma_{A,X}^\top A X \quad (\text{M2})$$

- ▶ (M1) and (M2) cannot be true at the same time (except if $\gamma_{A,X} = 0$).

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The roadmap (theoretical)

EXAMPLE:

▶ $O = (X, A, Y) \in [-2, 2] \times \{0, 1\} \times \{0, 1\}$

▶ True model is

$$\text{logit } \mathbb{E}[Y \mid A, X] = \beta_0 + \beta_A A + \beta_X X^2$$

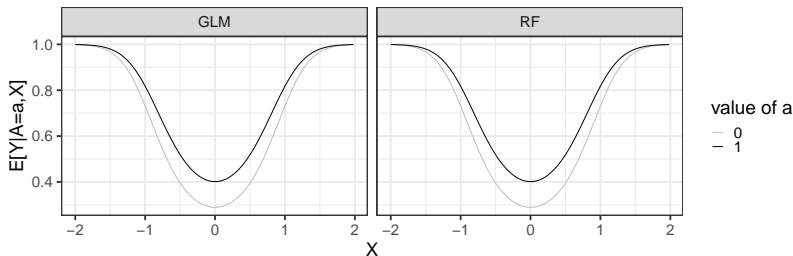
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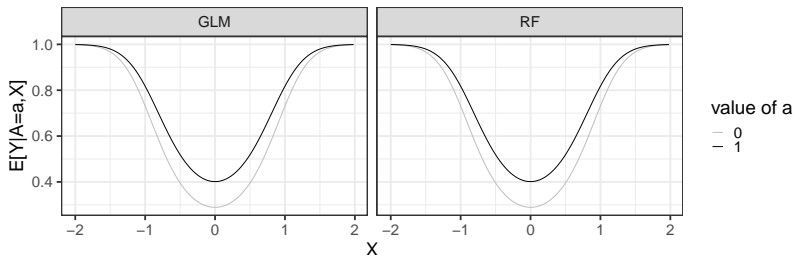
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GLM: $\text{logit } \mathbb{E}[Y \mid A, X] = \alpha_0 + \alpha_A A + \alpha_X X$

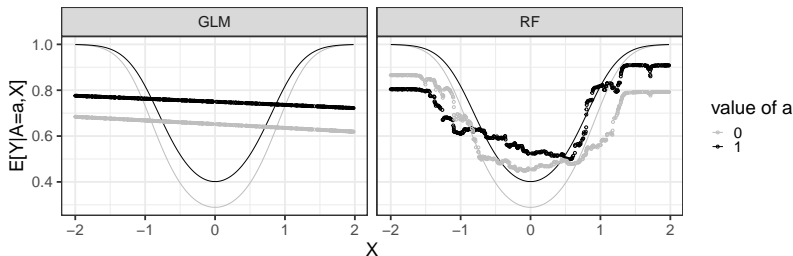
RF: Random forest (untuned)

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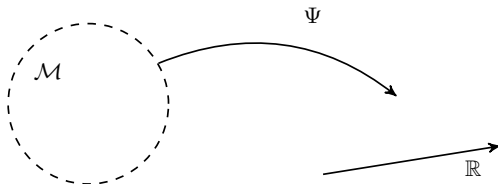
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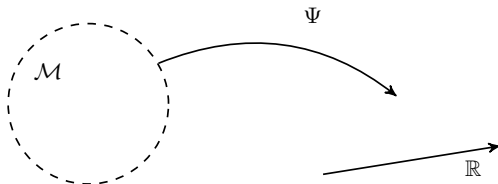
What are we trying to learn from the data?



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What are we trying to learn from the data?



EXAMPLE: Average treatment effect (ATE)

- ▶ $O = (X, A, Y) \in \mathbb{R}^d \times \{0, 1\} \times \{0, 1\}$
- ▶ The ATE is defined for $P \in \mathcal{M}$ as

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

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The ATE can also be written, for $P \in \mathcal{M}$:

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

where $f(a, x) := \mathbb{E}_P[Y \mid A = a, X = x]$ and μ_X is the marginal distribution of X

f, μ_X are called *nuisance parameters*

The roadmap (theoretical)

This suggests a straightforward two-step estimation strategy:

1. estimate the nuisance parameters
2. plug estimates into the expression for the target parameter

A straightforward estimate of the ATE would be

$$\hat{\psi}_n^{\text{ATE}} = \frac{1}{n} \sum_{i=1}^n \{ \hat{f}_n(1, X_i) - \hat{f}_n(0, X_i) \}$$

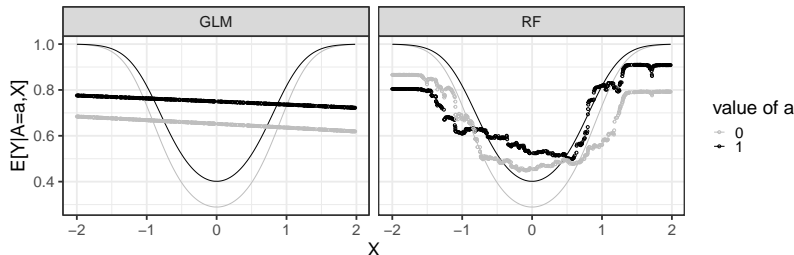
where \hat{f}_n denotes some estimator for $f(a, x) = \mathbb{E}_P[Y \mid A = a, X = x]$

→ logistic regression, random forest, neural network, lasso, ...

The roadmap (theoretical)

In the previous example we had two different estimators for

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



$$\hat{\psi}_n^{\text{ATE, GLM}} = \frac{1}{n} \sum_{i=1}^n \{ \hat{f}_n^{\text{GLM}}(1, X_i) - \hat{f}_n^{\text{GLM}}(0, X_i) \} = 0.0975$$

$$\hat{\psi}_n^{\text{ATE, RF}} = \frac{1}{n} \sum_{i=1}^n \{ \hat{f}_n^{\text{RF}}(1, X_i) - \hat{f}_n^{\text{RF}}(0, X_i) \} = 0.0551$$

The roadmap (theoretical)

Contrast this to fitting a logistic regression model

$$\text{logit } \mathbb{E}[Y \mid A, X] = \beta_0 + \beta_A A + \beta_X^\top X \quad (1)$$

to estimate the conditional odds ratio $\exp(\beta_A)$

- ▶ valid interpretation when model is correct
- ▶ statistical inference when model is correct
- ▶ *conditional* interpretation (crude and adjusted models target different parameters)

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... and: (1) must be a priori specified (the same data cannot be used for testing and for fitting the final model).

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4. Construct estimator \hat{P}_n for (relevant part of) P_0 and estimate the target parameter by $\hat{\psi}_n = \Psi(\hat{P}_n)$

A priori specified algorithm that maps the data to an estimate in the parameter space for the target parameter

- ▶ a pre-specified logistic regression model
- ▶ a random forest
- ▶ cross-validated selection between a pre-specified library of different models ("super learning")

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"Initial estimation":

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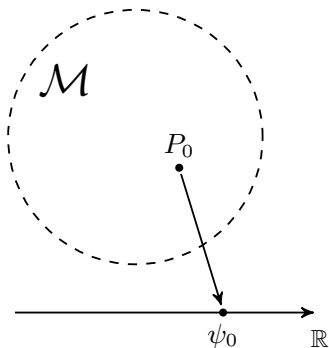
Estimation paradigm

1. Minimal amount of parametric assumptions on P_0 (goal)
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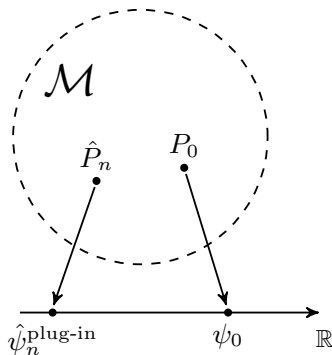
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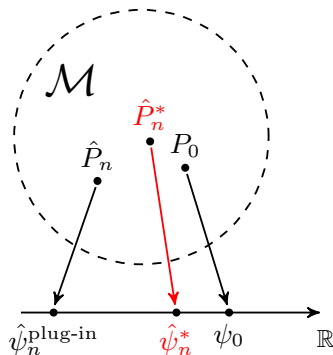
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Tools from semiparametric efficiency theory and empirical process theory tell us how to construct an **optimal estimator**

The roadmap (theoretical)

5. Quantify uncertainty for the estimator $\hat{\psi}_n = \Psi(\hat{P}_n)$

If we repeat the experiment of drawing n observations we would every time end up with a different realization of our estimator.

Across the repetitions, the estimator has a sampling distribution that we wish to quantify.

Under some conditions, we may use the asymptotic distribution

$$\hat{\psi}_n \stackrel{as}{\sim} N(\psi_0, \sigma^2/n)$$

to provide statistical inference.

Overview

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Applied angle The roadmap of targeted learning / causal inference

- ▶ translation from real-world data applications to a mathematical and statistical formulation of the relevant estimation problem.
- ▶ statistical analysis tailored towards answering that question.

Opposed to choosing a model for the data-generating process and using that model to answer all questions.

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4. Identifiability
5. Stating the statistical estimation problem
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... putting things into the right boxes.

... make the statistical analysis about the targeted scientific question (and not the other way around).

... focus on statistical parameters that have a meaningful interpretation.

The roadmap (applied)

A formal causal framework can help us²

- ▷ designing a statistical analysis that come as close as possible to answering scientific/causal questions.
- ▷ understand how far away from a causal conclusion we may be.

²The output of the analysis is not causal just because we use causal inference methods.

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Clearly defining what an EFFECT is and WHAT effect we are interested in

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Clearly defining what an EFFECT is and WHAT effect we are interested in

- ▶ this gets even more relevant when we deal with time-varying settings.

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The roadmap (applied)

At the consultation service at the Section of Biostatistics:

" I need help to choose the right statistical method to analyze my data ... I have a binary outcome and a lot of covariates ... I tried to run a logistic regression ... "

No mentioning of what scientific question is actually of interest.

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No mentioning of what scientific question is actually of interest.

No clear distinction between "the statistical estimation part" and the "scientific question part".

The roadmap (applied)

1. **Observed data** — $O = (X, A, Y)$
2. **Causal model** — what we know/believe/assume about directions of effects
3. **Causal question and target causal estimand** — formulating the scientific question as a contrast between counterfactual outcomes (e.g., in terms of ideal hypothetical experiment)
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... the rest is purely statistics.