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

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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 $\Psi : \mathcal{M} \to \mathbb{R}$
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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$O_1, \dots, O_n \overset{iid}{\sim} P_0$

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 probability distributions that we believe are possible 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 $A \in \{0, 1\}$:

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- assumption of convenience?

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Another parametric model could be

$$\operatorname{logit} \mathbb{E}[Y \mid A, X] = \gamma_0 + \gamma_A A + \gamma_X^\top X + \gamma_{A,X}^\top AX \tag{M2}$$

- (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

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

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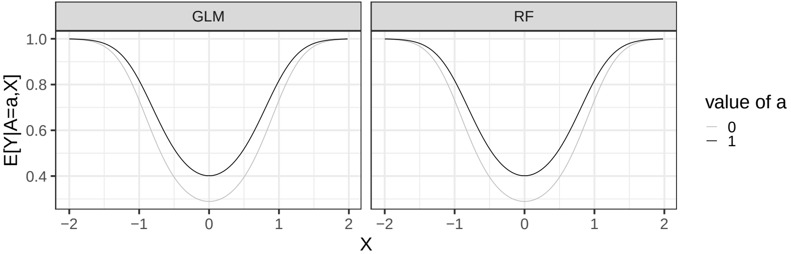

[Truth shown with solid lines]

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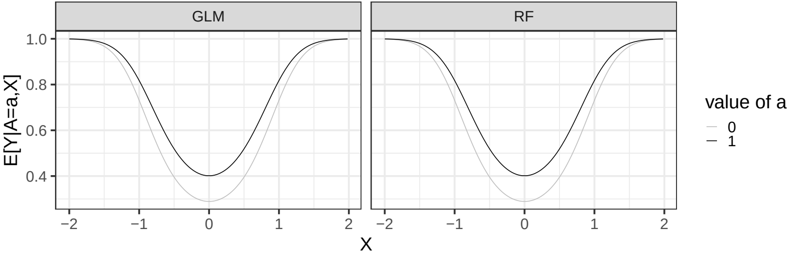

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GLM: $\operatorname{logit} \mathbb{E}[Y \mid A, X] = \alpha_0 + \alpha_A A + \alpha_X X$

RF: Random forest (untuned)

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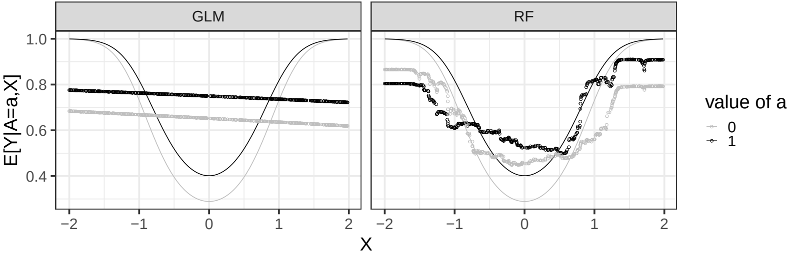

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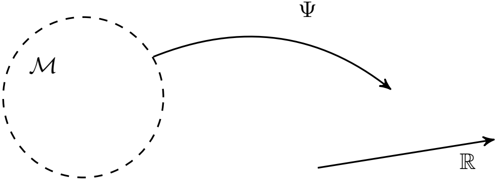
What are we trying to learn from the data?



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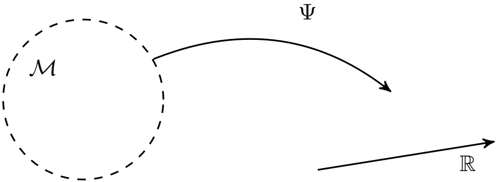

EXAMPLE: Average treatment effect (ATE)

- $O = (X, A, Y) \in \mathbb{R}^d \times \{0, 1\} \times \{0, 1\}$
- 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 $P \in \mathcal{M}$:

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

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

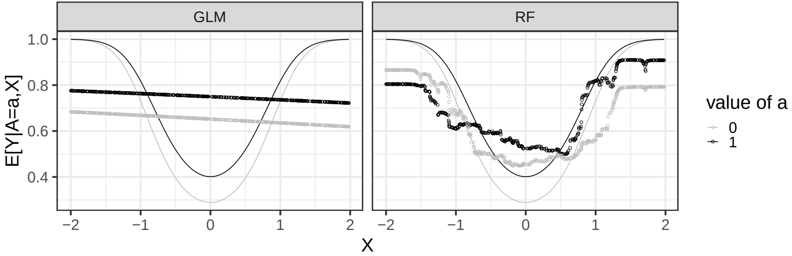
$$\hat{\psi}_n^{\mathrm{ATE}} = \frac{1}{n} \sum_{i=1}^{n} \left\{ \hat{f}_n(1, X_i) - \hat{f}_n(0, X_i) \right\}$$

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



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

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

The roadmap (theoretical)

Contrast this to fitting a logistic regression model

$$\operatorname{logit} \mathbb{E}[\, Y \mid A, X \,] = \beta_0 + \beta_A A + \beta_X^\top X \tag{1}$$

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).

The roadmap (theoretical)

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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+ "targeting" to yield the an estimator with improved properties

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"Initial estimation":

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+ "targeting" to yield the an estimator with improved properties

The roadmap (theoretical)

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.

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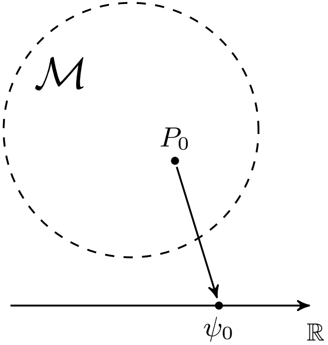

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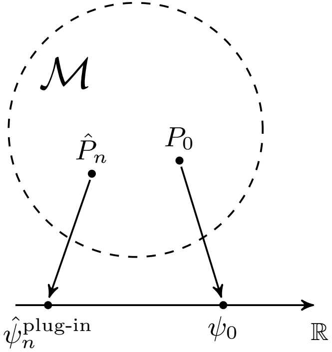

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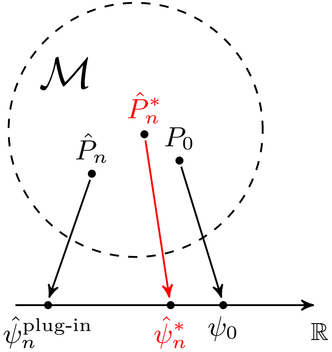

Tools from semiparametric efficiency theory and empirical process theory tell us how to conditions required for 2.

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

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

to provide statistical inference.

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The roadmap (applied)

1. Observed data
2. Causal model
3. Causal question and target causal estimand
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 us[2]

- 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.

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- 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)
4. Identifiability — is data sufficient to estimate the causal effect?

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. . . the rest is purely statistics.

Summary — roadmap of targeted learning

Statistical theory for parametric models

- meant for settings where the model is known a priori
  - the model is rarely known a priori
  - theory does not reflect how data are in fact analyzed (e.g., due to use of model selection strategies)
- the model is chosen for its simplicity and convenience
  - simple summary measures of associations

Targeted learning

- translating scientific question into predefined model-free target parameter
- machine learning based estimators can be constructed and still combined with valid/honest inference (allowing full prespecification of the statistical analysis)