

Roadmap of Statistical Targeted Learning

Alessandra Meddis
Section of Biostatistics

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Why Targeted Learning?

The main goal of Targeted Learning is translating real-world problem into a statistical formulation

- Targeted: the analysis is specifically designed to estimate the quantity of interest which is formulated (defined) based on the question to address

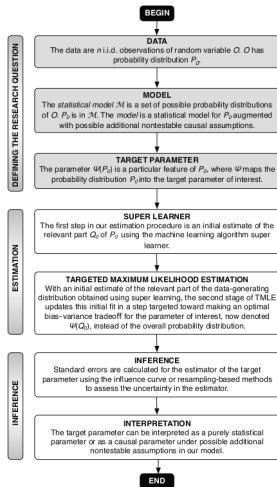
Question (quantity of interest) \rightarrow Statistical model

Instead of

Statistical model \rightarrow Question (interpretation of estimated quantity)

We will define everything into a causal framework (counterfactuals) that helps us understanding whether we would be able to address the scientific question

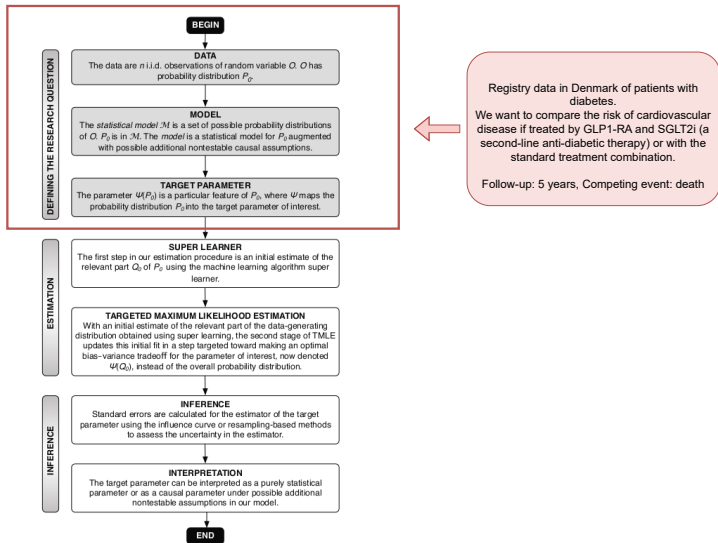
Roadmap of Targeted Learning¹



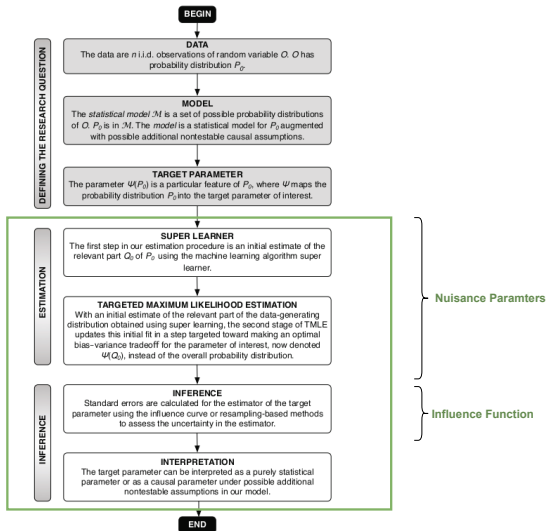
- Scientific question :
 1. Observed data
 2. The Causal model
 3. The Parameter of interest (Target Parameter)
 4. Identifiability
- Statistical part:
 5. Definition of the statistical problem
 6. Estimation

¹Fig 2.6. Van der Laan, Mark J., and Sherri Rose. Targeted learning: causal inference for observational and experimental data. Vol. 4. New York: Springer, 2011

Roadmap of Targeted Learning



Roadmap of Targeted Learning



Statistical model → Question

Standard approach: Cox model → estimate Hazard Ratios

- Relevant interpretation? (instantaneous risk of event)
- Misspecification problems? (semiparametric approach)
- Biased results? (assumption that treatment is changing at random over time)
- Model selection based on data (goodness of fit)

Question → Statistical model

Targeted Learning → estimate the Target Parameter of interest

- Relevant interpretation? Definition of parameter of interest in a causal framework
- Misspecification problems? Model-free definition of the target parameter
- Biased results? Check for identifiability
- Model selection based on data Machine learning methods + cross validation

Observed data

Define which data are available

We discretize the follow-up in k -months length interval.

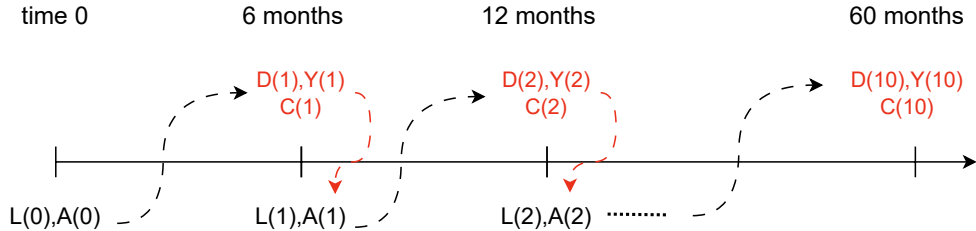
In each time interval $[k, k + 1]$ we observe:

- Covariates: $L(k) \in \mathbb{R}^d$
- Treatment $A(k) \in \{0, 1\}$
- Outcome $Y(k + 1) \in \{0, 1\}$
- Competing event $D(k + 1) \in \{0, 1\}$
- Censoring status $C(k + 1) \in \{0, 1\}$

$$\mathbf{X} = (L(0), A(0), Y(1), D(1), C(1), \dots, Y(K), C(K)) \sim P_{\mathbf{X}}$$

Observed data

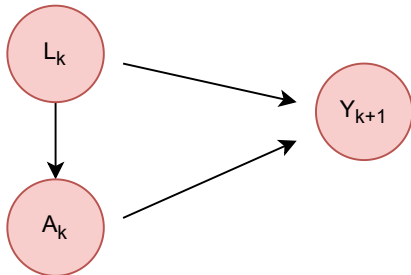
We discretize the follow-up in 6-months length interval.



No competing event and No censoring from now on
Discussion for Tomorrow

Causal model

What do we know/assume about the data generation mechanism?
Causal relations among variables?²



²DAG for time interval $(k, k + 1]$

Factorization of Data

$P_X \in \mathcal{P}$ where \mathcal{P} is the set of possible probability distributions that could describe the process by which our observed data have been generated.

We can factorize the joint distribution of the data:

$$P_X(dx) = \prod_{k=1}^K P_{Y(k)|\mathcal{F}_{Y(k)}} P_{A(k-1)|\mathcal{F}_{A(k-1)}} P_{L(k-1)|\mathcal{F}_{L(k-1)}}$$

where \mathcal{F} denotes the history/filtration to a given variable, for example $\mathcal{F}_{A(2)} = (L(0), A(0), Y(1), L(1), A(1))$

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Causal framework:

Causal Inference is related to counterfactuals (potential outcomes).

We introduce counterfactuals for one intervention with two levels (0,1 / treated, non-treated) without the longitudinal aspect

Each individual has two potential outcomes:

$Y^{a=0}$: Outcome if allocated to treatment $a = 0$

$Y^{a=1}$: Outcome if allocated to treatment $a = 1$

Subjects receive at most one of the treatment, so at least one will not be observed
→ counterfactual.

We have interpretation for: outcome if individuals had received the intervention of interest.

Parameter of interest

What do we want to learn from the data?

Define the causal question formulating the scientific problem into counterfactuals from an hypothetical experiment

Define the target parameter: $\Psi : \tilde{\mathcal{P}} \rightarrow R$, where $\tilde{P} \in \tilde{\mathcal{P}}$ is the probability distribution for the hypothetical population of counterfactuals

$$(L(0), Y^1(1), Y^0(1), L^1(1), L^0(1), \dots, Y^1(10), Y^0(10)) \sim \tilde{P}$$

Parameter of interest

In our example

- Scientific problem: Evaluate whether exposure to the dual second-line treatment with d GLP1-RA and SGLT2i ($A=1$) increase the risk of cardiovascular disease after 5 years in diabetic patients
- Hypothetical experiment: as a function of counterfactuals
 1. Assigning $A=1$ continuously to the whole population and observing the outcome after 5 years $Y^1(10)$
 2. Assigning $A=0$ continuously to the whole population and observing the outcome after 5 years $Y^0(10)$

→ Target Parameter: 5-years Risk difference under the two treatment assignments

$$\psi(\tilde{P}) = ATE = \tilde{P}(Y^1(10) = 1) - \tilde{P}(Y^0(10) = 1)$$

Identifiability

Can we estimate the target parameter from the observed data?

We cannot observe both counterfactual outcomes for each individual because we can assign either exposure or no exposure to one individual.

→ We cannot directly estimate counterfactual outcomes but we need some assumptions under which the target parameter is identifiable and so it may be estimated from the observed data:

Define with a^* the treatment intervention

- Exchangeability: $Y^{a^*(k)} \perp A(k)_{|\mathcal{F}_{A(k)}} \forall k$
- Consistency: $Y^{a^*(k)} = Y$ if $A(k) = a^*(k) \forall k$
- Positivity: $0 < P_{A(k)|\mathcal{F}_{A(k)}}(A(k) = a^*(k)) < 1 \forall k$

Identifiability

Can we estimate the target parameter from the observed data?

- Exchangeability: $Y^{a^*(k)} \perp A(k)_{|\mathcal{F}_{A(k)}} \forall k$
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When these assumptions are verified we can write the parameter as a function of the observed data

$$\tilde{P}(Y^1(10) = 1) = P(Y(10) = 1 | \bar{A}(10) = 1)$$

where $\bar{A}(10) = a$ is equal to assign $A(k) = a \forall k$

Definition of the statistical problem

Nuisance Parameters: what do we need as support for the estimation of the target parameter?

Under some calculations $\tilde{P}(Y(10) = 1)$ can be rewritten as a sequence of nested expectation/integrals of the Q and the G functions at different times.

$$\tilde{P}(Y^1(10) = 1) = \int \dots \int Q_{Y(10)}(1|a(k-1), l(k-1)) \times \\ \prod_{k=1}^9 Q_{Y(k)}(dy(k)|1, l(k)) G_{A(k)}^*(da(k)|l(k), a(k-1)) Q_{L(k)}(dl(k)|1, l(k-1))$$

with $G_{A(k)}^*$ denotes the counterfactual distribution for $A(k) = a^*(k)$

Statistical Estimation

For the ATE the nuisance parameters are:

- Propensity score model (G-function)
- Outcome model (Q-function)

How can we estimate the nuisance parameters?

- glm (logistic regression)
- Machine learning method
- Superlearner

Statistical estimation

Uncertainty of $\hat{\Psi}$: How do we construct Confidence Interval?

$$\hat{\Psi} - \Psi = \frac{1}{n} \sum_{i=1}^n IC(X_i, \nu) + o_p(n^{-1/2})$$

where $IC(X_i, \nu)$ is the influence function that depends on the observed data and the nuisance parameters ν

Sum up

Targeted Learning : from the research question to the estimation of the parameter of interest (Target Parameter)

