Targeted Learning for Data Adaptive Causal Inference in Observational and Randomized Studies

Mark van der Laan\textsuperscript{1} and Susan Gruber\textsuperscript{2}

\textsuperscript{1} Department of Biostatistics, University of California, Berkeley School of Public Health

\textsuperscript{2} Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute
Course Outline

- Part 1
  - Targeted Learning Overview
  - Estimation Roadmap
  - Super Learning
- Part 2
  - Targeted Minimum Loss-Based Estimation (TMLE)
- Part 3
  - TMLE for longitudinal data analysis
  - Concluding Remarks
Learning from Data

- Requirements for learning from data
  - A clear question
  - Knowledge about the data generating experiment
  - A straightforward, relevant, interpretable result

- Core concepts in Targeted Learning
  - A (statistical) model represents (statistical) knowledge about the data generating experiment
  - Target parameter defined as a feature of the data generating distribution
  - Efficient, data adaptive estimation + statistical inference
    - Super Learning
    - Targeted minimum loss-based estimation (TMLE)
Traditional Approach to Analyzing Health Care Data

1. Fit several parametric logistic regression models and choose one
2. Report point estimate of coefficient in front of treatment, $p$-value and confidence interval as if this parametric model was pre-specified

- But consider,
  - The parametric model is misspecified
  - The coefficient is interpreted as if the parametric model is correct
  - The model selection procedure is not accounted for in the estimated variance
Targeted Learning

- Targeted Learning provides a paradigm for transforming data into reliable, actionable knowledge
- Define targeted parameter to address a relevant scientific question, not for convenience
- Avoid reliance on human art and unrealistic parametric models: a priori specified estimator.
- Target the fit of data-generating distribution to the target parameter of interest
- Valid statistical inference in terms of a normal limiting distribution
Examples of Targeted Learning Toolbox

- Prediction and classification
- Targeted effect estimation
  - Effects of static or dynamic treatments
  - Direct and indirect effects (mediation analysis)
  - Parameters of marginal structural models
  - Variable importance measures
- Types of data
  - Point treatment
  - Longitudinal/Repeated Measures
  - Censoring/Missingness/Time-dependent confounding
  - Case-Control
  - Randomized clinical trials and observational data
Step 1. Define a statistical model, $\mathcal{M}$, that contains the true probability distribution of the data, $P_0$.

Step 2. Define the target parameter of interest, $\psi_{0}^{\text{full}}$, as a feature of a full data distribution, $P_{0}^{\text{full}}$.

Step 3. Specify a mapping from the full data to observed data, and $\Psi : \mathcal{M} \rightarrow \mathbb{R}^d$ such that under explicitly stated identifying assumptions $\psi_{0}^{\text{full}} = \Psi(P_0)$.

Step 4. Estimation and inference of statistical parameter $\psi_0 = \Psi(P_0)$ using super learning and targeted minimum loss based estimation.

Step 5. Provide a considered interpretation of the result.
Super Learning - Motivation

Both **effect** and **prediction** research questions are inherently **estimation** questions, but they are distinct in their goals.

**Effect:** Interested in estimating the effect of exposure on outcome adjusted for covariates.

**Prediction:** Interested in generating a function to input covariates and predict a value for the outcome.

*Effect parameters where no causal assumptions are made may be referred to as variable importance measures (VIMs).*
Estimation using (misspecified) Parametric Models

- Data \( n \) i.i.d. copies of \( O = (Y, A, W) \)
  - Outcome \( Y \), Treatment \( A \), Covariates \( W \)

- Standard practice for prediction and effect estimation
  - assume a parametric statistical model for \( E_0(Y \mid A, W) \), the conditional mean of \( Y \) given \( A \) and \( W \)
  - use maximum likelihood estimation (MLE) to estimate model parameters

- Parametric regression models
  - varying levels of complexity
  - choice of variables included in model impacts complexity
High Dimensional Data

- Potentially thousands of candidate variables to include in the model
- Model complexity can increase exponentially, more unknown parameters than observations
- The true functional for $E_0(Y \mid A, W)$ might be complex, beyond main terms and interaction terms.
- Correct specification is a challenge
The moment we use **post-hoc arbitrary criteria** and **human judgment** to select the parametric statistical model after looking at the data, the analysis becomes prone to additional bias.

Bias manifests in both the effect estimate and the assessment of uncertainty (i.e., standard errors).

So why not simply use a purely non-parametric model with high dimensional data?

- $p > n!$
- data sparsity
Super Learning - Motivation

- What we want is an automated algorithm to semi-parametrically estimate $E_0(Y \mid A, W)$.
  - Opportunity to reduce bias due to model misspecification
  - Opportunity to reduce variance by improving the fit for the dependent variable
- Many potential algorithms.
  - We cannot bet on a misspecified parametric regression,
  - Many semi-parametric methods that aim to “smooth" the data and estimate this regression function.
  - Yet one particular algorithm is going to do better than the other candidate estimators.
- How to know which one to use?
The Dangers of Favoritism

- Relative Mean Squared Error (compared to main terms least squares regression) based on the validation sample

<table>
<thead>
<tr>
<th>Method</th>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
<th>Study 4</th>
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<td>0.82</td>
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## Super Learning in Prediction

<table>
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Super Learning - Core Concepts

- **Loss Based Estimation**
  - We will use loss functions to define the best estimator of \( E_0(Y \mid A, W) \) from a library of algorithms, and then evaluate it.

- **Cross Validation**
  - Our available data is partitioned to train and validate our estimators.

- **Semi-Parametric Estimation**
  - Allow the data to drive your estimates, but in an honest (cross validated) way.
Data structure \( O = (W, A, Y) \sim P_0 \)
- empirical distribution \( P_n \) places probability \( \frac{1}{n} \) on each observed \( O_i \), \( i = 1, \ldots, n \).

Goal is to estimate conditional mean outcome, \( Q_0 = E_0(Y \mid A, W) \).

Specify a library of learning algorithms.

“Best” algorithm is with respect to a loss function, \( L \).

\[
L : (O, Q) \rightarrow L(O, Q) \in \mathbb{R}
\]

- \( L \) assigns a measure of performance to a candidate function \( Q \) when applied to an observation \( O \).
- \( L \) is a function of the random variable \( O \) and parameter value \( Q \).
Examples of loss functions

- $L_1$ absolute error loss function:

$$L(O, Q) = |Y - Q(A, W)|,$$

- $L_2$ squared error (or quadratic) loss function:

$$L(O, Q) = (Y - Q(A, W))^2,$$

- Negative log loss function:

$$L(O, Q) = -\log(Q(A, W)^Y (1 - Q(A, W))^{1-Y}).$$
Loss-Based Estimation

- Squared error loss: \( L(O, \bar{Q}) = (Y - \bar{Q}(A, W))^2 \)
- Expected squared error loss \( E_0 L(O, \bar{Q}) \) is also known as risk
- Risk evaluates candidate \( \bar{Q} \)
  - Small risk is better
  - Risk is minimized at the optimal choice of \( \bar{Q}_0 \)
- Define our parameter of interest, \( \bar{Q}_0 = E_0(Y \mid A, W) \), as the minimizer of the risk:

\[
\bar{Q}_0 = \arg \min_{\bar{Q}} E_0 L(O, \bar{Q}).
\]
Cross-validation to obtain an accurate estimate of risk

- Partitions the sample of $n$ observations $O_1, \ldots, O_n$ into training and corresponding validation sets.
- Produces an accurate estimate of risk
- Discrete super learner: selects “best” algorithm with smallest risk among a library of algorithms
- We can also use cross-validation to evaluate the overall performance of the super learner itself.
V-fold Cross-Validation

- Observed data $O_1, \ldots, O_n$ is referred to as the learning set.
- Learning set is partitioned into $V$ sets of size $\approx \frac{n}{V}$.
- For each fold, $V - 1$ sets will comprise the training set. The remaining set is the validation set.
- Observations in the training set are used to construct (or train) the candidate estimators.
- Observations in the validation set are used to evaluate risk.
The validation set rotates $V$ times such that each set is used as the validation set once.
Suppose a researcher cannot decide between three different statistical methodologies for estimating $E_0(Y \mid A, W)$.

SL library consists of (MLE, Deletion/Substitution/Addition (DSA), Random Forest).

Discrete SL chooses the one with the smallest (honest) cross-validated risk.

<table>
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<td>MLE</td>
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<tr>
<td>DSA</td>
<td>0.04</td>
</tr>
<tr>
<td>Random Forest</td>
<td>0.23</td>
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Which algorithm does the discrete super learner pick?
Oracle Properties

- The Oracle selector is the best estimator among the $K$ algorithms in the SL library
  - Chooses the algorithm whose fit on the training samples yields the smallest risk under $P_0$, the true probability distribution of random variable $O$.
  - Unknown, since it depends on both observed data and $P_0$.
- Discrete super learner performs as well as the Oracle selector, up to a second order term.
  - assuming a bounded loss function
  - number of algorithms in the library polynomial in sample size
- That is, ratio of loss-based dissimilarities for oracle selected estimator and cross-validated selected estimator w.r.t. truth converges to 1!
Ensemble Super Learner

- Ensemble super learner improves upon discrete super learning by enlarging set of candidate estimators.
  - Define the SL library as all weighted averages of individual algorithms
    - Each weighted average is a unique candidate algorithm in this augmented library.
    - One of these weighted combinations might perform better than any single algorithm
    - Each individual algorithm remains a candidate
  - Cross-validation guides the selection of the optimal weighted combination
  - Ensemble SL is no more computer intensive than discrete SL
Ensemble Super Learner: How it works

Once the discrete super learner has been completed,

- Propose a family of weighted combinations of library algorithms, indexed by weight vector $\alpha$.
  - consider only $\alpha$-vectors that sum to one, where each weight is non-negative
- Determine which combination minimizes the cross-validated risk
  \[ P_n(Y = 1 \mid Z) = \text{expit} \left( \alpha_{1,n}Z_1 + \alpha_{2,n}Z_2 + \ldots + \alpha_{K,n}Z_K \right) \]
  - Cross-validated predictions ($Z$) for each algorithm are inputs in a working (statistical) model to predict the outcome $Y$.
- SL prediction is a weighted combination of predictions from algorithms fit on the entire dataset. Given $n \times k$ prediction matrix $Z'$,
  \[ \bar{Q}_n(A, W) = Z'\alpha_n \]
SL: Finite sample performance

Four simulated datasets \((n = 100)\)

Simulation 1

Simulation 2

Simulation 3

Simulation 4

Figure 2: Scatterplots of the four simulations. The solid line is the true relationship. The points represent one of the simulated datasets of size \(n = 100\). The dashed line is the super learner fit for the shown dataset.

\[ \text{True functional form} \]
\[ \text{Data points} \]
\[ \text{SL predictions} \]
SL: ICU Mortality Prediction

Cross-validated Area under the Receiver-Operating Curve

- Sepsis-related Organ Failure Assessment (SOFA)
- Simplified Acute Physiology Score (SAPS-II)
- Acute Physiology and Chronic Health Evaluation (APACHE)
- Super Learner, standard categorized variables (SL1)
- Super Learner, non-transformed variables (SL2)

- SL better distinguishes between high and low risk patients
There is no point in painstakingly trying to decide what estimators to enter in the collection; **instead add them all.**

The theory supports this approach and finite sample simulations and data analyses only confirm that **it is very hard to over-fit the super learner by augmenting the collection**, but benefits are obtained.

Indeed, for large data sets, we simply do not have enough algorithms available to build the desired collection that would fully utilize the power of the super learning.
Super Learning Demonstration

- SuperLearner R package (CRAN and GitHub)
- Using the package
- Practical considerations
  - Algorithms for the SL library
  - Loss function
  - Dimension Reduction
  - How to choose $V$