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

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Outline of estimation part of short-course

- 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

Estimation Roadmap

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, ψ_0^{full}, as a feature of a full data distribution, P_0^{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 $\psi_0^{full} = \Psi(P_0)$.

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 (statistical and possibly causal) interpretation of the result.

Super Learning - Motivation

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

Average Treatment 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).

Prediction/function-estimation requires super-learning, while low dimensional target parameters require super-learning plus TMLE

Traditional Approach

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

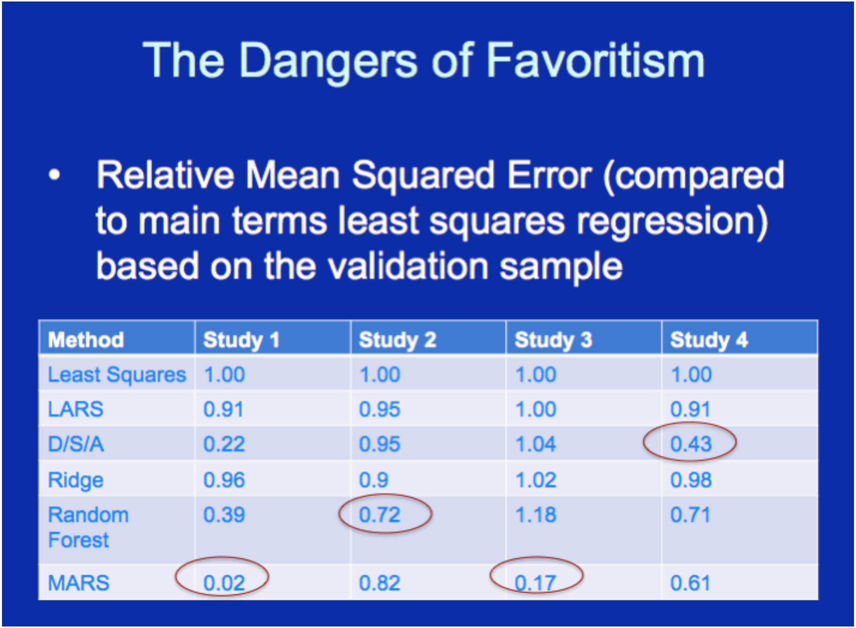
- Potentially thousands of candidate variables to include in the model
- Model complexity can increase exponentially, more unknown parameters than observations
- The true functional for $E_0(Y \mid A, W)$ might be complex, beyond main terms and interaction terms.
- Correct specification is a challenge

The Complications of Human Art in Traditional Practice

- 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/curse of dimensionality

Super Learning - Motivation

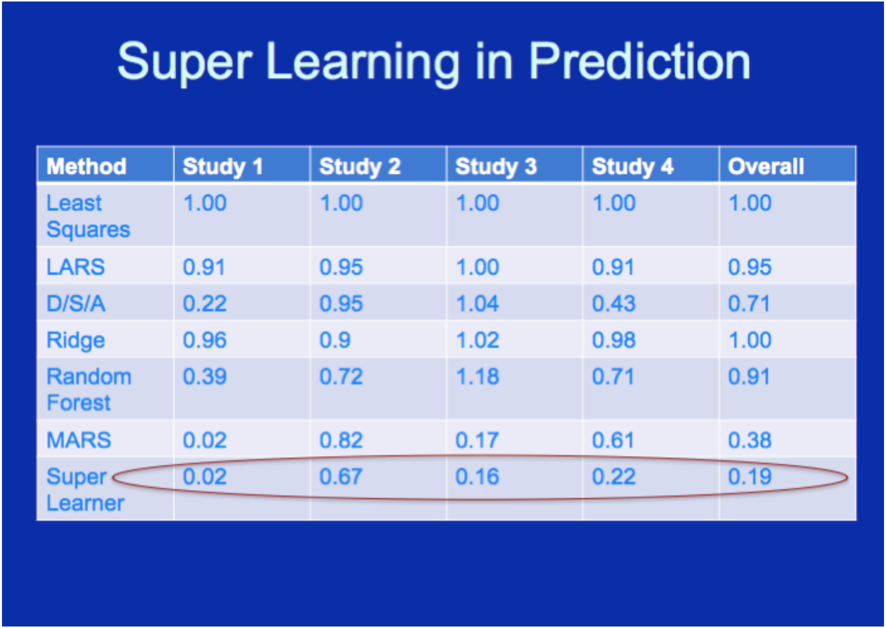
- What we want is an automated algorithm to consistently and optimally estimate $E_0(Y \mid A, W)$ respecting our statistical model.
  - Opportunity to reduce bias due to model misspecification
  - Opportunity to reduce variance by improving the fit for the dependent variable
- Many potential algorithms.
  - 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

Method	Study 1	Study 2	Study 3	Study 4
Least Squares	1.00	1.00	1.00	1.00
LARS	0.91	0.95	1.00	0.91
D/S/A	0.22	0.95	1.04	0.43
Ridge	0.96	0.9	1.02	0.98
Random Forest	0.39	0.72	1.18	0.71
MARS	0.02	0.82	0.17	0.61



Super Learning in Prediction

Method	Study 1	Study 2	Study 3	Study 4	Overall
Least Squares	1.00	1.00	1.00	1.00	1.00
LARS	0.91	0.95	1.00	0.91	0.95
D/S/A	0.22	0.95	1.04	0.43	0.71
Ridge	0.96	0.9	1.02	0.98	1.00
Random Forest	0.39	0.72	1.18	0.71	0.91
MARS	0.02	0.82	0.17	0.61	0.38
Super Learner	0.02	0.67	0.16	0.22	0.19

Super Learning - Core Concepts

- Loss function Define the target function/parameter Q_0 as a minimizer of the expectation of a loss function: $Q_0 = \arg\min_Q E_{P_0} L(Q, O)$.
- Collection of candidate estimators This could be a discrete set (discrete super-learner) or all weighted combinations of a finite set of estimators (continuous-super-learner).
- Use cross-validated empirical risk to evaluate performance of each candidate estimator
- Select the estimator that minimizes the cross-validated empirical risk

Loss-Based Estimation

- Data structure $O = (W, A, Y) \sim P_0$
  - empirical distribution P_n places probability $1/n$ 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.

Loss-Based Estimation

Examples of loss functions

- L_1 absolute error loss function for the conditional median:

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

- L_2 squared error (or quadratic) loss function for the conditional mean:

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

- Negative log loss function for a conditional probability distribution or density: e.g., if Y is binary,

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

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:

$$\bar{Q}_0 = \arg\min_{\bar{Q}} E_0 L(O, \bar{Q}).$$

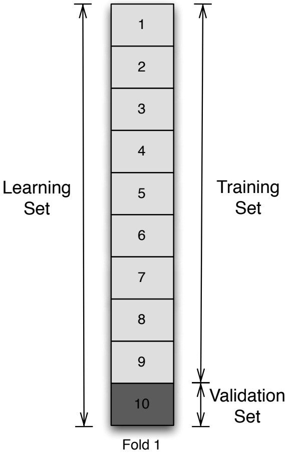
Cross-Validation

Cross-validation to obtain an accurate estimate of risk

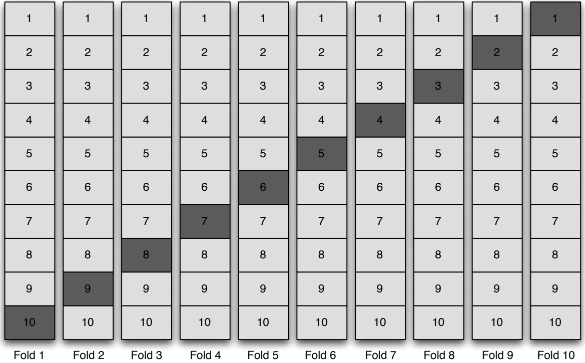
- Partitions the sample of n observations $O_1, \ldots, O_n$ into training and corresponding validation sets.
- Produces an accurate estimate of risk
- Discrete super learner: selects "best" algorithm with smallest risk among a library of algorithms
- We can also use cross-validation to evaluate the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



V-fold Cross-Validation



The validation set rotates V times such that each set is used as the validation set once.

Discrete Super Learner

- 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.

Method	CV-Risk
MLE	0.30
DSA	0.04
Random Forest	0.23

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 α.
    - consider only α-vectors that sum to one, where each weight is non-negative
- Determine which combination minimizes the cross-validated risk

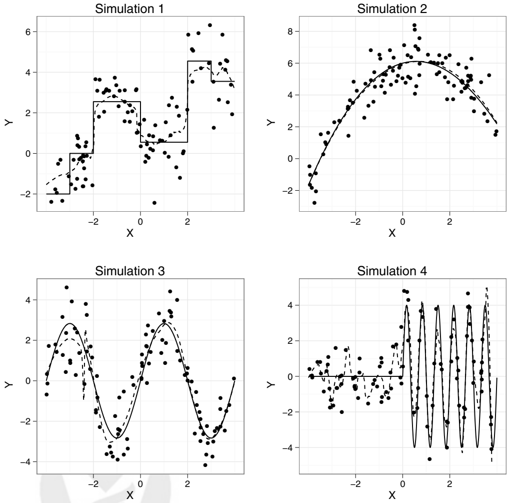
$$P_n(Y = 1 \mid Z) = \text{expit}\left(\alpha_{1,n}Z_1 + \alpha_{2,n}Z_2 + \ldots + \alpha_{K,n}Z_K\right)$$

    - 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',

$$\bar{Q}_n(A, W) = \mathbf{Z}'\alpha_n$$

SL: Finite sample performance

Four simulated datasets ($n = 100$)



—— True functional form

· · · Data points

- - - SL predictions

Fig. 2, Polley and van der Laan, 2010

SL: ICU Mortality Prediction

Cross-validated Area under the Receiver-Operating Curve

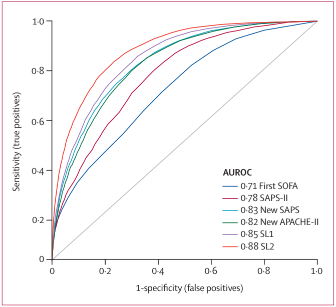


Figure 1: **Receiver-operating characteristics curves**

Pirracchio, et al, *Lancet*, 2014

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

- SL better distinguishes between high and low risk patients

The Bottom Line

- 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