Targeted Learning Methods for Challenges in Liver Diseases

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How can Targeted Learning contribute? Sample Use Cases

- Data-adaptive learning of optimal surrogate endpoints and non-invasive diagnostic biomarkers.
- Data-adaptive learning of optimal individualized treatment regimens
- Efficient and robust analysis of RCT.
- Adaptive trial designs to meet user-specified needs (e.g. increase efficiency, minimize adverse events, learn optimal treatment rule) while preserving validity.
- Address complex data structure of a Natural History Cohort; causal inference from observational data.

Why Targeted Learning?

Traditional approaches in epidemiology and clinical research:

- Fit parametric models for the outcome.
- Report coefficients in the model as effect measures.

- ➢ Reliant on a mis-specified parametric model.
- ➢ Effect interpretation problematic
- ➢ Human subjectivity; prone to overestimate precision.
- ➢ Non-data-adaptive modeling misses opportunities for discovery.

What is Targeted Learning?

An emerging subfield of statistics that integrates:

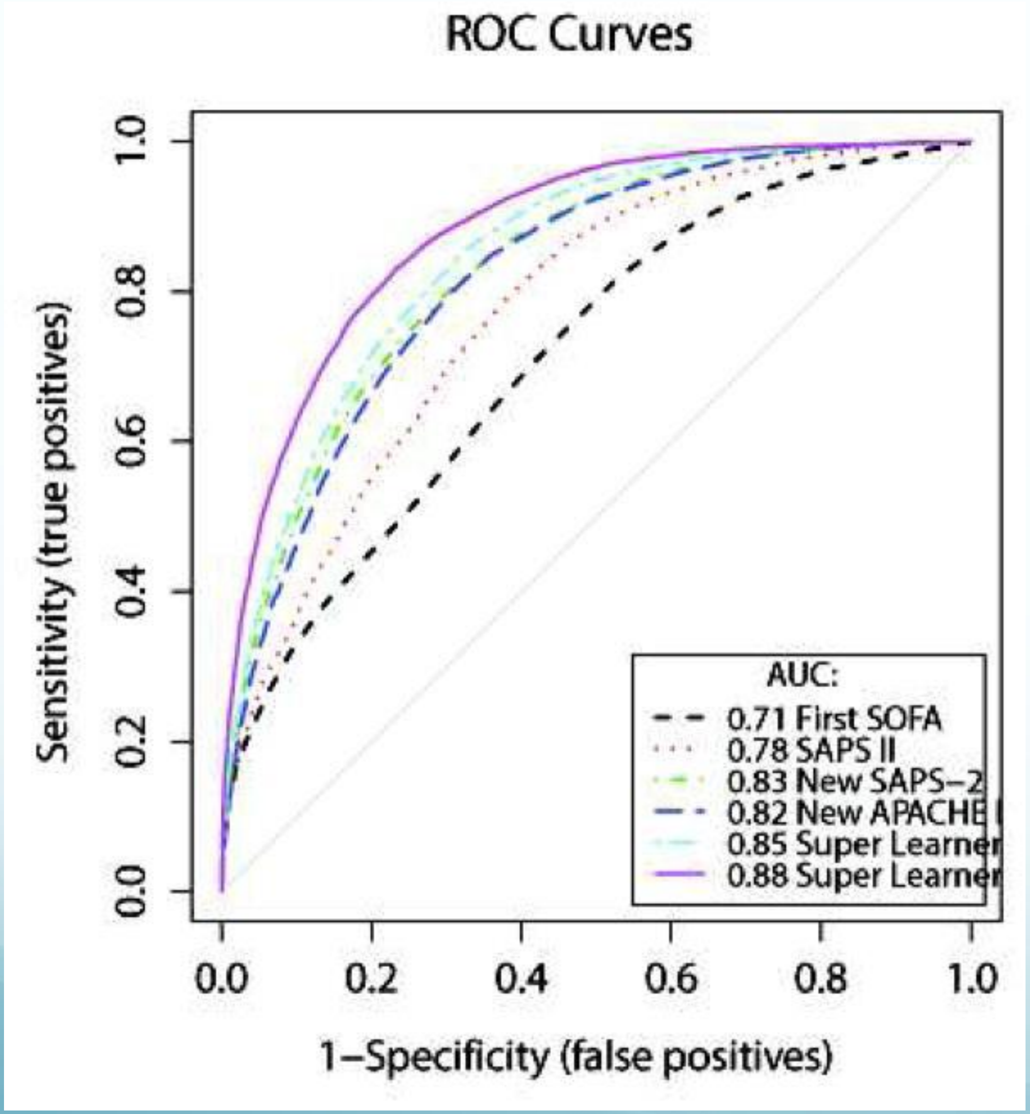
- **Causal Inference** ➔ asking the right questions.
- **Data-Adaptive Estimation**➔ expert knowledge + machine learning prowess. Full potential for prediction and discovery.
- **Robust estimation and Formal Hypothesis Testing** ➔ accurate and actionable information.

Two part methodology: Super Learning + Targeted Minimum Loss Estimation

Part 1: Super Learning

- Combines a library of learning algorithms (including machine learning) to build a better predictor.
- Uses Cross-validation to find best combination.
- ➔ Does at least as well as the best member in library.
- ➔ Incorporates expert knowledge in the library; let data pick the best combination.
- ➔ Allows data-adaptive modeling of data-generating process. No unrealistic or rigid modeling assumptions.

Super Learning in Action



Mortality prediction in ICU using the Super ICU Learning Algorithm: a population-based study.

Pirracchio, et.al.
Lancet Resp. Med. 2015 Jan; 3(1): 42-52

- Improved performance over all existing methods for predicting mortality of patients in ICU.

Part 2: Targeted Minimum Loss Estimation

- Updates initial estimators from Super Learner.
- Tailor bias-variance trade-off towards the target parameter of interest.
- Incorporates outcome model and exposure model.
- Robust estimates against model-misspecification ➔ **increased accuracy**.
- Efficient estimator ➔ **increased precision, learns more with less**.
- Framework for Formal Hypothesis Testing ➔ **actionable information for decision making**

Sample Uses Cases of Targeted Learning

- Data-adaptive learning of optimal surrogate endpoints and non-invasive diagnostic biomarkers.
- Data-adaptive learning of optimal individualized treatment regimens
- Efficient and robust analysis of RCT.
- Innovative adaptive trial designs to meet user-specified needs (e.g. increase efficiency, minimize adverse events) while preserving validity.
- Address complex data structure of a Natural History Cohort; causal inference from observational data.

Data-adaptive learning of surrogate markers

- From RCT or observational data
- Learn most predictive non-invasive diagnostic biomarkers of underlying disease status.
- Learn surrogate endpoint that best capture the intervention effect on endpoint of interest.
- Incorporates subject-matter expertise with machine learning prowess.
- Avoid unrealistic assumptions on unknown outcome-surrogate interactions ➔ maximize potentials for discovery
- Optimality-measure independent of model-specification ➔ robust interpretation

Data-adaptive learning of optimal individualized treatment strategies

- From RCT or from observational data
- Learn the best treatment/management strategy to prescribe regimen based on individual profile. → precision medicine
- Formal hypothesis testing for effect of optimal strategy.
- Parallel application to learning optimal subgroup to receive treatment
- Incorporates subject-matter expertise with machine learning prowess.
- Avoids unrealistic parametric assumptions on the exposure-outcome relation.

Design and Analysis of RCT

- Increased efficiency and addresses heterogeneity by adjusting for covariates.
- Robust effect estimates even under mis-specified outcome models.
- Adaptive designs to meet user-specified goals (eg. Maximize efficiency, minimize adverse events), while preserving validity.
- Adaptive designs tailored to learn optimal treatment rule, or optimal surrogate markers.

Analysis of the Natural History Cohort

- Complex longitudinal data structure.
- Have rigorous methods to deal with ‘messy’ data: informative missing data, time-varying confounding, etc.
- Have formal framework for drawing causal inference from observational data.
- Increased accuracy and precision through doubly robust and efficient estimators.
- Potentials for regulatory considerations of previously ‘untestable’ clinical questions.

Thank you

- More on the methodology: Targeted Learning Book, van der Laan and Rose, Springer 2011.

- The Center for Targeted Learning in Big Data:

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