

Targeted Learning

Mark van der Laan and Nima Hejazi

The Art of Statistics

TL in Action

TL Roadmap

Describe study

Specify a realistic statistical model

Define estimand

Causal estimand

Statistical estimand

Construct estimator

Obtain inference

Place conclusions in substantive context

Advanced TL

Regularizing TMLE

HAL and HAL-TMLE

Longitudinal TMLE

Variable Importance

Conclusion

Targeted Learning

The bridge from machine learning
to statistical and causal inference

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²Department of Biostatistics, Harvard T.H. Chan School of Public Health

15th November 2024

Harvard Catalyst Workshop

Acknowledgements: Alan Hubbard, Ivana Malenica, Rachael Phillips, Lars van der Laan



A traditional toolbox for statistics

Goal	Type of Data			
	Measurement (from Gaussian Population)	Rank, Score, or Measurement (from Non-Gaussian Population)	Binomial (Two Possible Outcomes)	Survival Time
Describe one group	Mean, SD	Median, interquartile range	Proportion	Kaplan Meier survival curve
Compare one group to a hypothetical value	One-sample ttest	Wilcoxon test	Chi-square or Binomial test **	
Compare two unpaired groups	Unpaired t test	Mann-Whitney test	Fisher's test (chi-square for large samples)	Log-rank test or Mantel-Haenszel*
Compare two paired groups	Paired t test	Wilcoxon test	McNemar's test	Conditional proportional hazards regression*
Compare three or more unmatched groups	One-way ANOVA	Kruskal-Wallis test	Chi-square test	Cox proportional hazard regression**
Compare three or more matched groups	Repeated-measures ANOVA	Friedman test	Cochrane Q**	Conditional proportional hazards regression**
Quantify association between two variables	Pearson correlation	Spearman correlation	Contingency coefficients**	
Predict value from another measured variable	Simple linear regression or Nonlinear regression	Nonparametric regression**	Simple logistic regression*	Cox proportional hazard regression*
Predict value from several measured or binomial variables	Multiple linear regression* or Multiple nonlinear regression**		Multiple logistic regression*	Cox proportional hazard regression*

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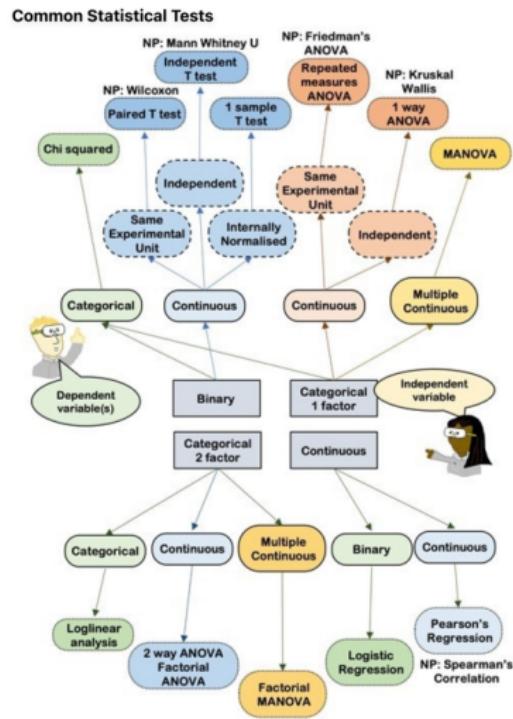
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Table 1.1: A few choices of statistical target parameter as implied by some common regression models.

Outcome Type	Model (or Method)	Statistical Parameter
Continuous $Y \in \mathbb{R}$	linear regression	Difference of means
Continuous and positive $Y \in \mathbb{R}^+$	log-linear regression	Ratio of means
Binary $Y \in \{0, 1\}$	logistic regression	Odds ratio
Count $Y \in \mathbb{Z}^+$	Poisson regression	Ratio of means
Survival time $T = \min(T_F, T_C)$	Cox regression	Hazard ratio

The choices given in Table 1.1 are not exhaustive, and several variations on each of the modeling approaches exist, but, in standard practice, even their off-the-shelf varieties are common. Despite their popularity, how does the flow of logic that led us here hold up to scrutiny? In effect, using Table 1.1 as a guide, we have committed to choosing the target of inference based on the type of the outcome variable Y and an inflexible choice of regression model, the latter of which sharply restricts the set of candidate statistical parameters. This *model-based* or *model-forward* approach limits the answers we are able to seek based not on the scientific question of interest, but instead on the type of data and the limitations of common regression models.

Should the model define the question (parameter)?

Performance of traditional tools

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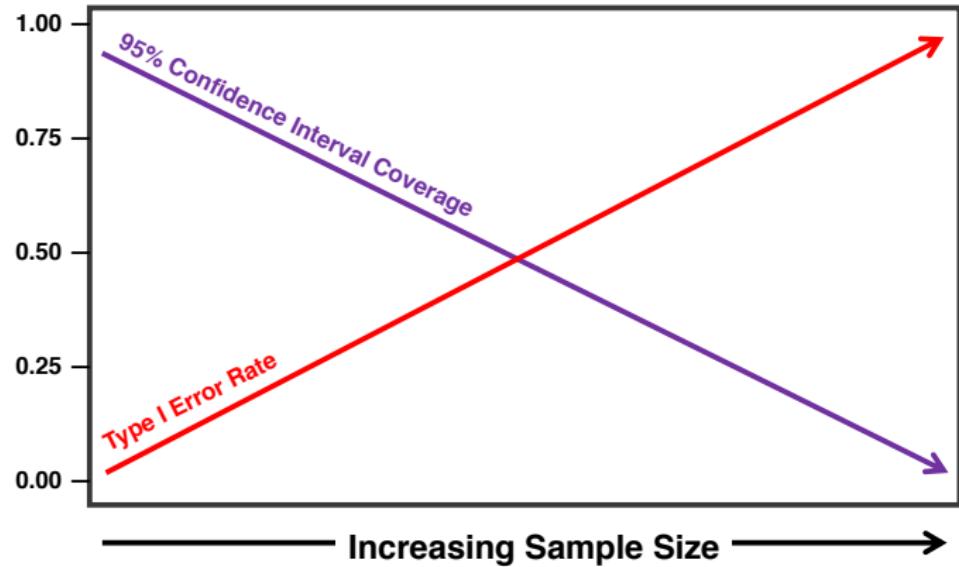
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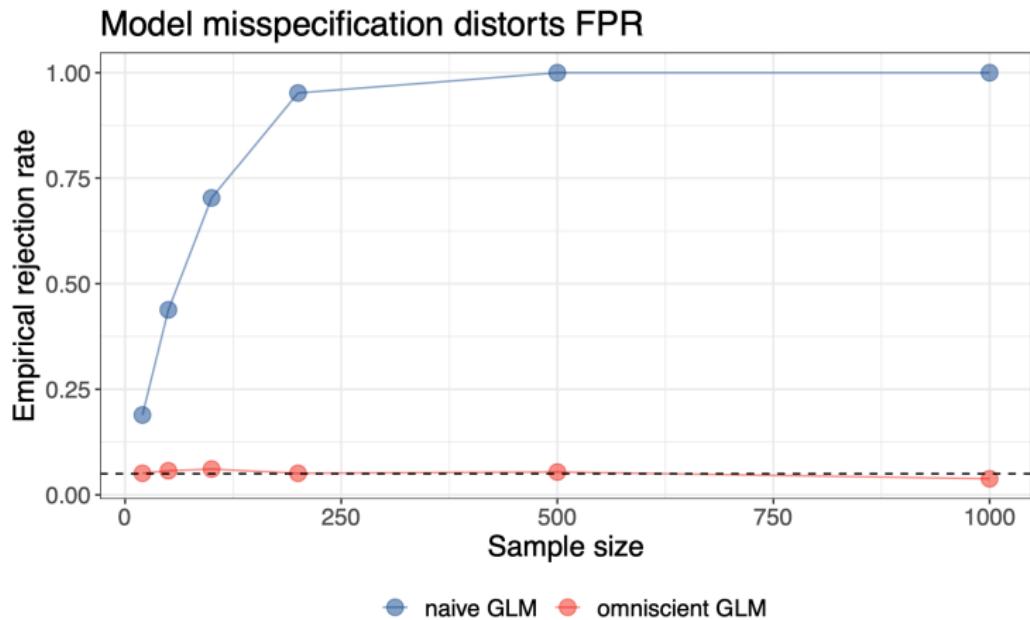
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Truth: No effect of exposure on outcome.

The “art” of statistical inference?

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Why Most Published Research Findings Are False

John P. A. Ioannidis

False-Positive Psychology: Undisclosed Flexibility in Data Collection and Analysis Allows Presenting Anything as Significant

Joseph P. Simmons¹, Leif D. Nelson², and Uri Simonsohn¹

¹The Wharton School, University of Pennsylvania, and ²Haas School of Business, University of California, Berkeley

The Statistical Crisis in Science

Data-dependent analysis—a “garden of forking paths”—explains why many statistically significant comparisons don’t hold up.

Andrew Gelman and Eric Loken



Public health and medicine use real-world data (RWD) for insight and evidence

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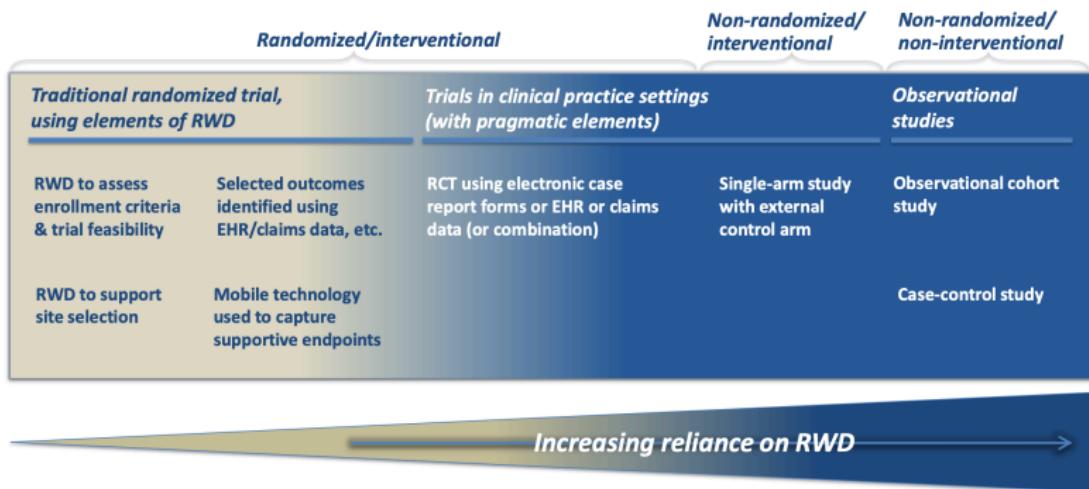
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Courtesy of "FDA Real-World Evidence Program" Webinar by John Concato on 4th August 2021



TL addresses statistical challenges with RWD

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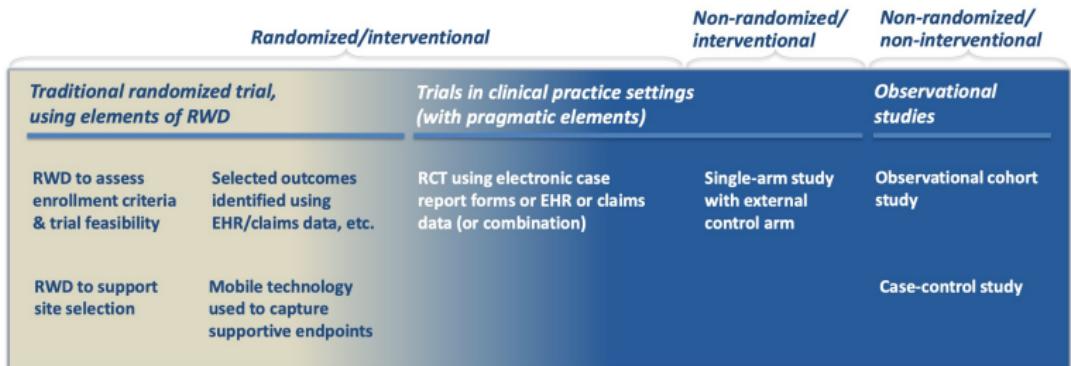
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RWD Challenges

- Selection bias
- Intercurrent events
- Informative missingness
- Treatment by indication
- High dimensional covariates
- Outcome measurement error
- Statistical model misspecification
- Differences between external controls and single trial arm RCT

Targeted Learning path supports regulatory decision making

TL for real-world evidence (RWE) evaluation

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<i>Randomized/interventional</i>	<i>Non-randomized/interventional</i>	<i>Non-randomized/non-interventional</i>
<i>Traditional randomized trial, using elements of RWD</i>	<i>Trials in clinical practice settings (with pragmatic elements)</i>	<i>Observational studies</i>
RWD to assess enrollment criteria & trial feasibility RWD to support site selection	Selected outcomes identified using EHR/claims data, etc. Mobile technology used to capture supportive endpoints	RCT using electronic case report forms or EHR or claims data (or combination) Single-arm study with external control arm Case-control study

RWD Challenges

- ❑ Selection bias
- ❑ Intercurrent events
- ❑ Informative missingness
- ❑ Treatment by indication
- ❑ High dimensional covariates
- ❑ Outcome measurement error
- ❑ Statistical model misspecification
- ❑ Differences between external controls and single trial arm RCT

Targeted Learning path supports regulatory decision making

Targeted Learning

- ✓ Roadmap for causal and statistical inference
- ✓ Realistic statistical model
- ✓ Statistical estimand approximates answer to causal question
- ✓ Flexible estimation and dimension reduction with Super Learner
- ✓ Model-free sensitivity analysis
- ✓ Generate RWE with confidence

TL is a subfield of statistics

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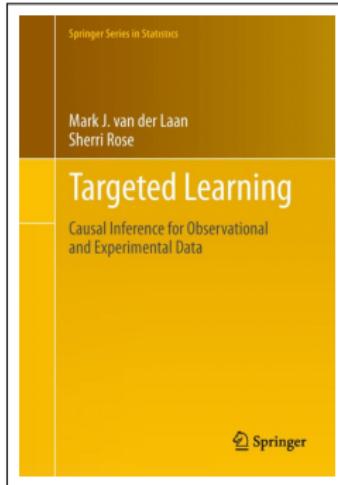
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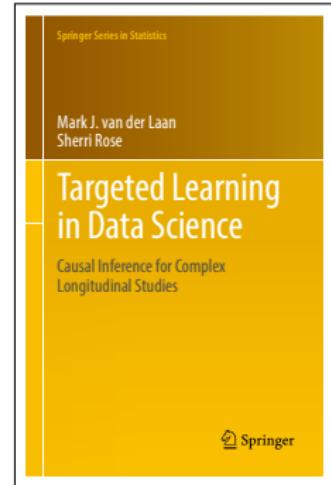
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van der Laan & Rose, *Targeted Learning: Causal Inference for Observational and Experimental Data*. New York: Springer, 2011.



van der Laan & Rose, *Targeted Learning in Data Science: Causal Inference for Complex Longitudinal Studies*. New York: Springer, 2018.

Targeted Learning in R with the `tlverse`

Some applications of TL in the real world

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

HIV Testing and Treatment with the Use of a Community Health Approach in Rural Africa

D.V. Havlir, L.B. Balzer, E.D. Charlebois, T.D. Clark, D. Kwarisiima, J. Aiyelo, J. Kabami, N. Sang, T. Liegler, G. Chamie, C.S. Camlin, V. Jain, K. Kadefeo, M. Atukunda, T. Ruel, S.B. Shade, E. Ssemmondo, D.M. Byonanebye, F. Mwangwa, A. Owaramagise, W. Oollo, D. Black, K. Smyman, R. Burger, M. Getahun, J. Achando, B. Awuonda, H. Nakato, J. Kironde, S. Okiror, H. Thirumurthy, C. Koss, L. Brown, C. Marquez, J. Schwab, G. Lavoy, A. Plenty, E. Mugoma Wafula, P. Omanya, Y.-H. Chen, J.F. Rooney, M. Bacon, M. van der Laan, C.R. Cohen, E. Bukusi, M.R. Kamya, and M. Petersen

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genetic Diversity and Protective Efficacy of the RTS,S/AS01 Malaria Vaccine

D.E. Neafsey, M. Juraska, T. Bedford, D. Benkeser, C. Valim, A. Griggs, M. Lievens, S. Abdulla, S. Adjei, T. Agbenyega, S.T. Agnandji, P. Aide, S. Anderson, D. Ansong, J.J. Aponte, K.P. Asante, P. Bejon, A.J. Birkett, M. Bruls, K.M. Connolly, U. D'Alessandro, C. Dobaño, S. Gesase, B. Greenwood, J. Grimsby, H. Tinto, M.J. Hamel, I. Hoffman, P. Kamthunzi, S. Kariuki, P.G. Kremsner, A. Leach, B. Lell, N.J. Lennon, J. Lusingu, K. Marsh, F. Martinson, J.T. Moiel, E.L. Moss, P. Njuguna, C.F. Ockenhouse, B. Ragama O gutu, W. Otieno, L. Otieno, K. Otieno, S. Owusu-Agyei, D.J. Park, K. Pellié, D. Robbins, C. Russ, E.M. Ryan, J. Sacarlal, B. Sogoloff, H. Sorgho, M. Tanner, T. Theander, I. Valea, S.K. Volkman, Q. Yu, D. Lapierre, B.W. Birren, P.B. Gilbert, and D.F. Wirth

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DOI: 10.1111/1475-6773.12848

METHODS ARTICLE

Robust Machine Learning Variable Importance Analyses of Medical Conditions for Health Care Spending

Sherri Rose 

THE LANCET Respiratory Medicine



Volume 3, Issue 1, January 2015, Pages 42-52

Articles

Mortality prediction in intensive care units with the Super ICU Learner Algorithm (SICULA): a population-based study



Better clinical decisions from observational data

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Statistics
in Medicine

Research Article

Received 24 May 2013,

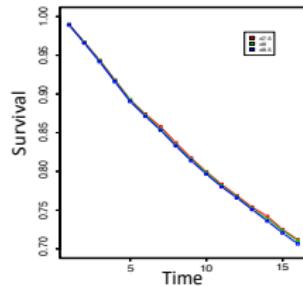
Accepted 5 January 2014

Published online 17 February 2014 in Wiley Online Library

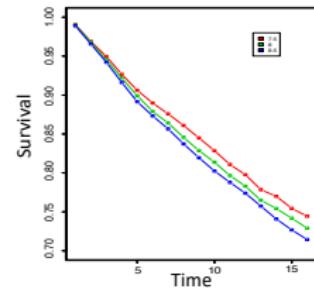
(wileyonlinelibrary.com) DOI: 10.1002/sim.6099

Targeted learning in real-world comparative effectiveness research with time-varying interventions

Romain Neugebauer,^{a*}† Julie A. Schmittield^a and Mark J. van der Laan^b



Standard methods: No benefit to more aggressive intensification strategy



Targeted Learning: More aggressive intensification protocols result in better outcomes

TL for optimal treatment variable importance in meta-analysis of childhood development studies

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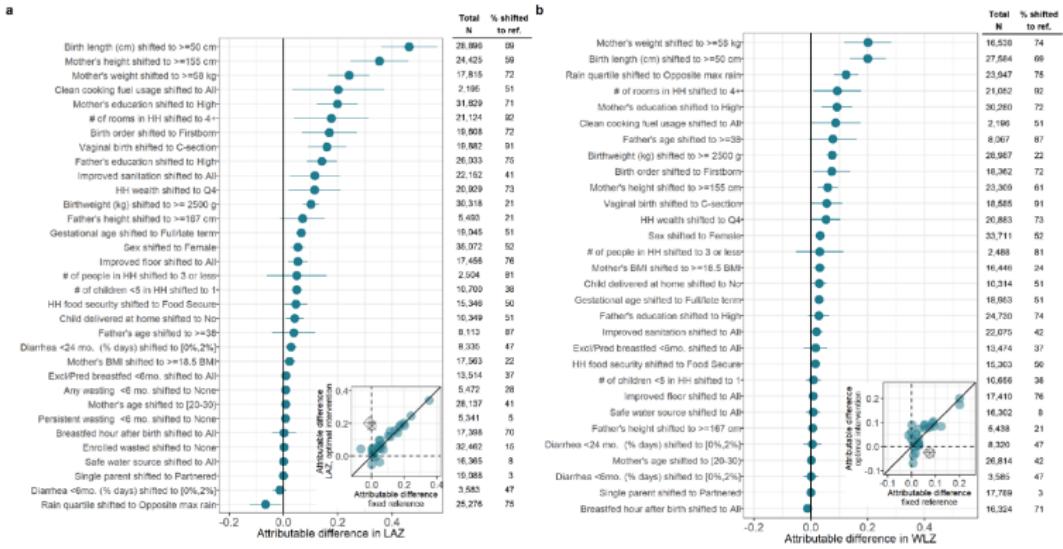


Figure 2 | Rank-ordered attributable differences between child, parental, and household characteristics and population attributable differences in anthropometry Z-scores.



Evaluating counterfactual HIV infection risk after shifting vaccine-induced immune response markers

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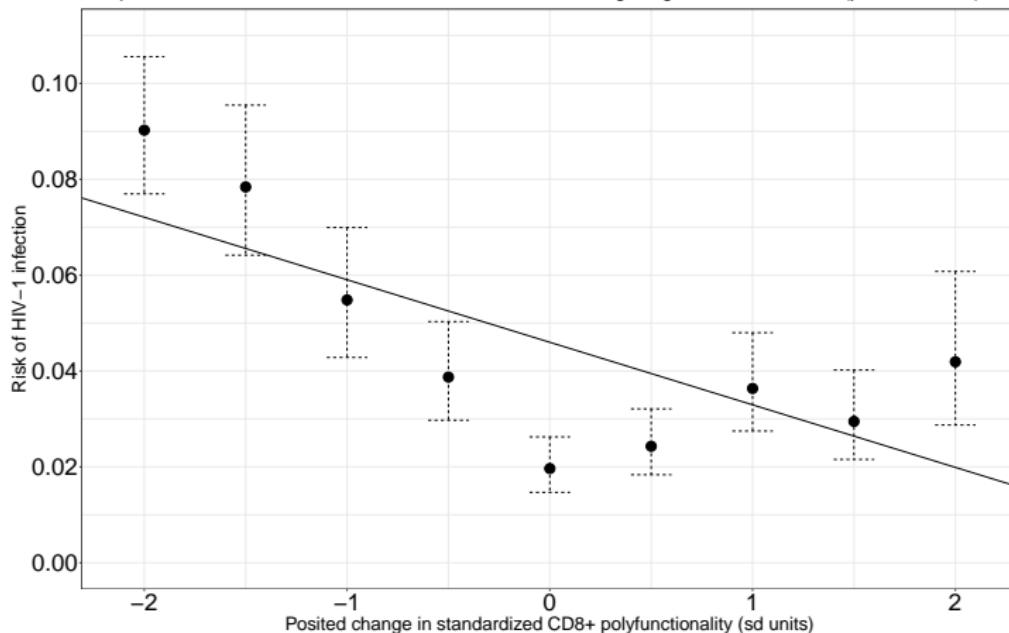
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TML estimates of mean counterfactual HIV-1 infection risk under shifted CD8+ polyfunctionality with pointwise confidence intervals and summarization via working marginal structural model ($\hat{\beta}_{\text{TMLE}} = -0.013$)



Hejazi et al. "Efficient nonparametric inference on the effects of stochastic interventions under two-phase sampling, with applications to vaccine efficacy trials" *Biometrics* (2021). 10.1111/biom.13375

Evaluating COVID-19 vaccine efficacy after shifting immune correlates of protection

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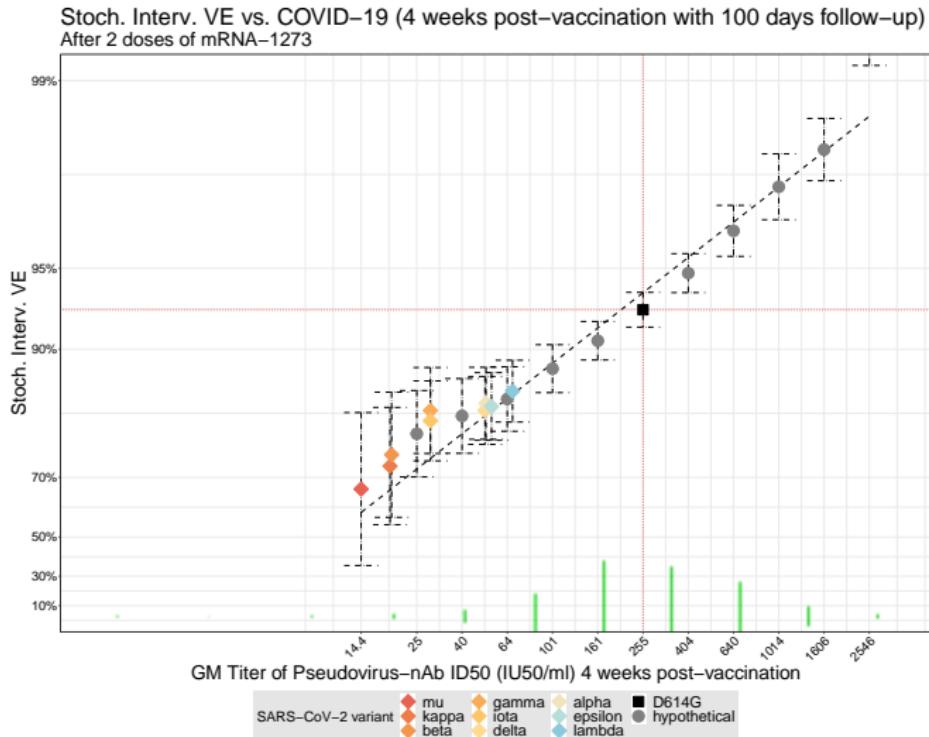
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Hejazi et al. "Stochastic interventional approach to assessing immune correlates of protection: Application to the COVE mRNA-1273 vaccine trial" *IJID* (2023).

Estimating impacts on COVID-19 infection rates by longitudinal policy shift interventions

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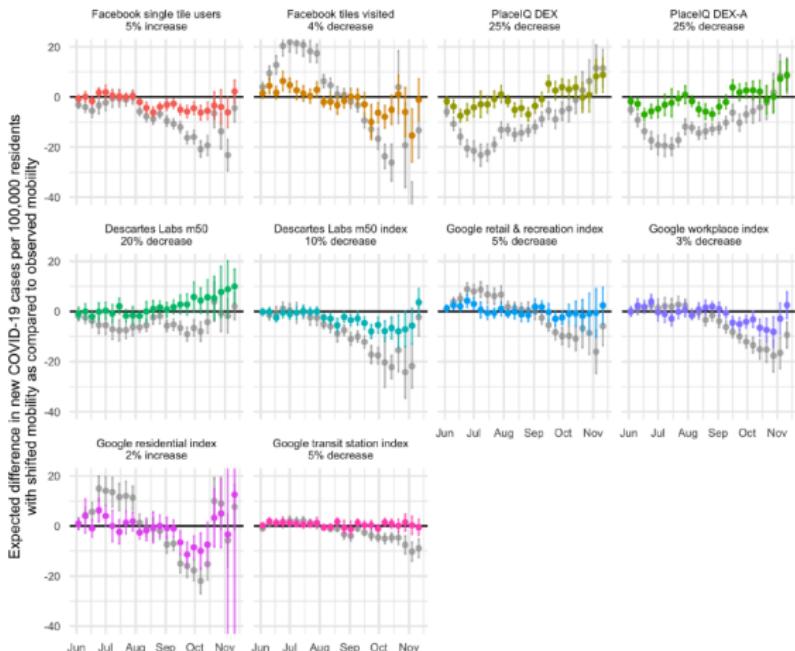
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Nugent and Balzer, "A demonstration of modified treatment policies to evaluate shifts in mobility and COVID-19 case rates in US counties." AJE (2023).



Introduction to the tlverse

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<https://tlverse.org/tlverse-handbook/>

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TL answers statistical questions rooted in causality

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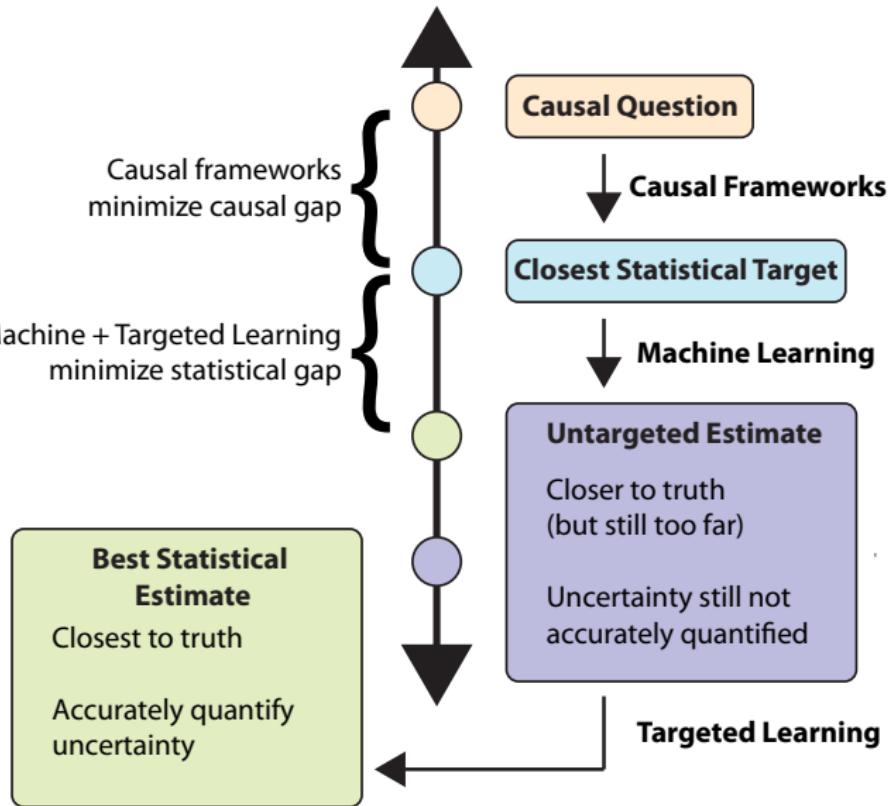
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A roadmap for learning from data

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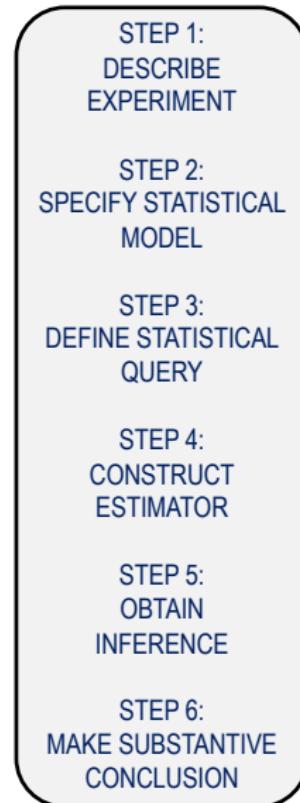
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Step 1: What is the data-generating experiment?

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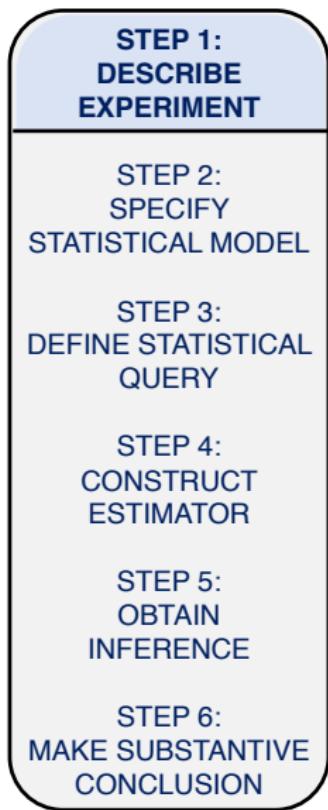
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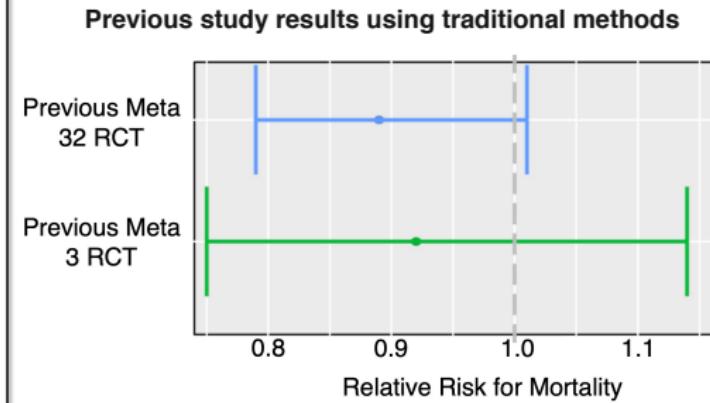
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Three multi-national RCTs assessing impact of corticosteroids on mortality among septic shock patients



Target population of interest

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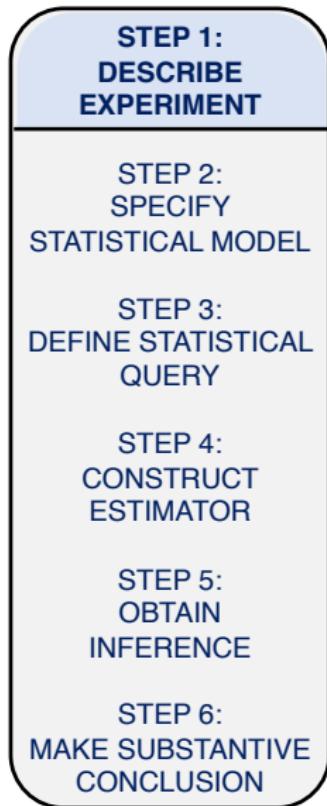
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Three multi-national RCTs assessing impact of corticosteroids on mortality among septic shock patients

Pooled sample of $n = 1,300$ adults in septic shock

Observed data structure

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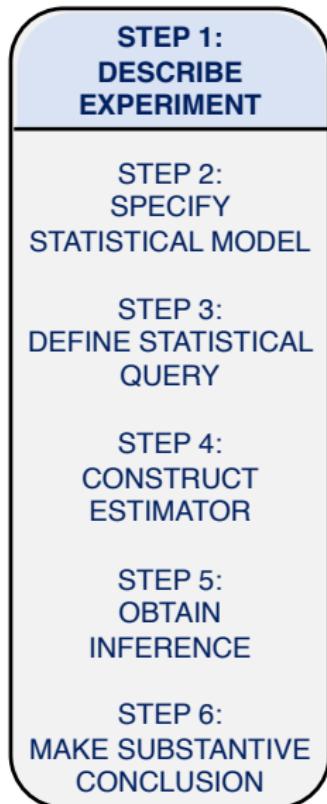
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Three multi-national RCTs assessing impact of corticosteroids on mortality among septic shock patients

Pooled sample of $n = 1,300$ adults in septic shock

BMI	age	sex	steroid treatment	1-month mortality
21	65	F	1	1
22.3	28	F	0	0
19.4	49	F	1	0
24	77	M	1	0

Directed Acyclic Graph (DAG)

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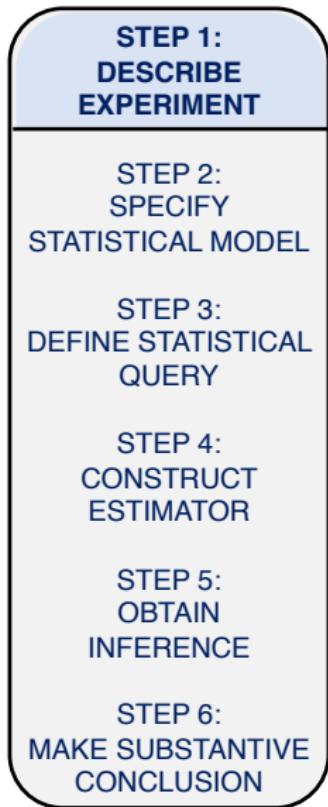
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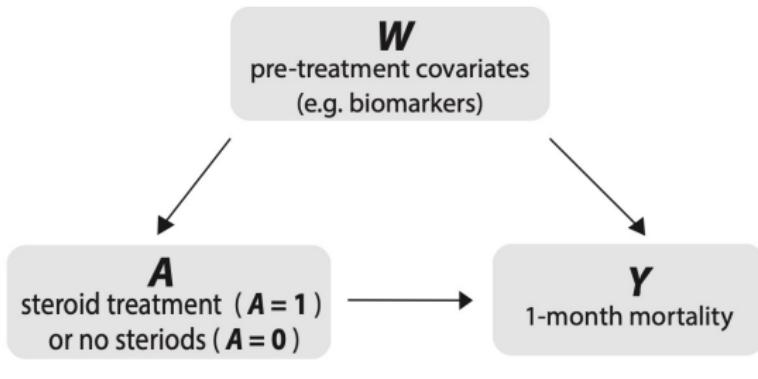
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Three multi-national RCTs assessing impact of corticosteroids on mortality among septic shock patients

Pooled sample of $n = 1,300$ adults in septic shock



Step 2: What is known about stochastic relations of the observed variables?

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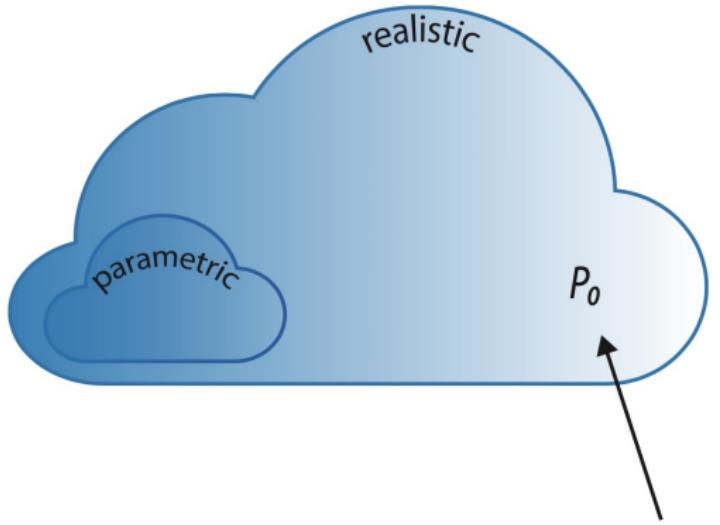
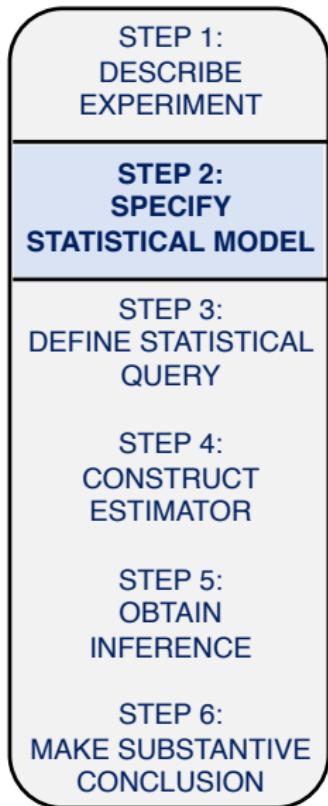
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What happens when the statistical model is misspecified (i.e. does not contain P_0 , the DGP)?

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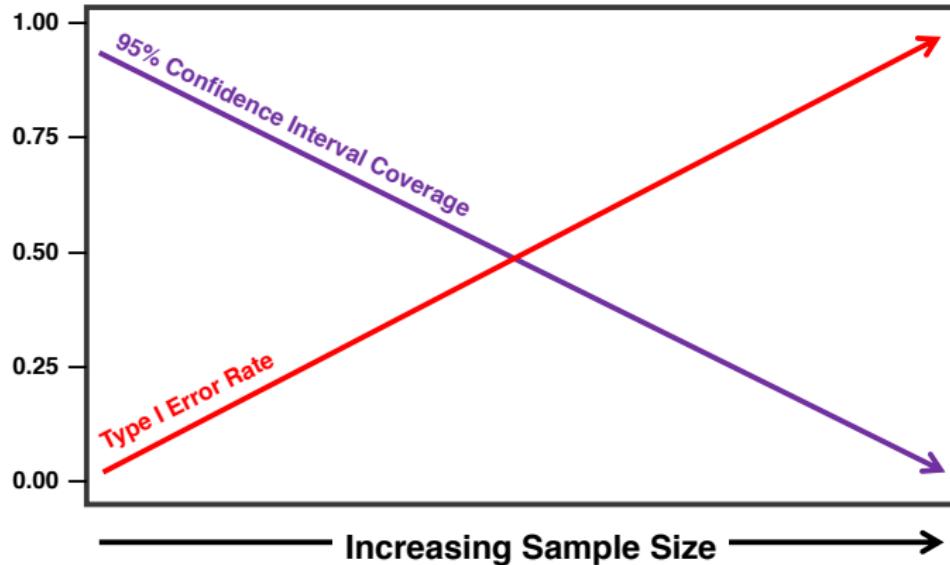
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Step 3a: What is the target causal estimand that we aim to identify from the data?

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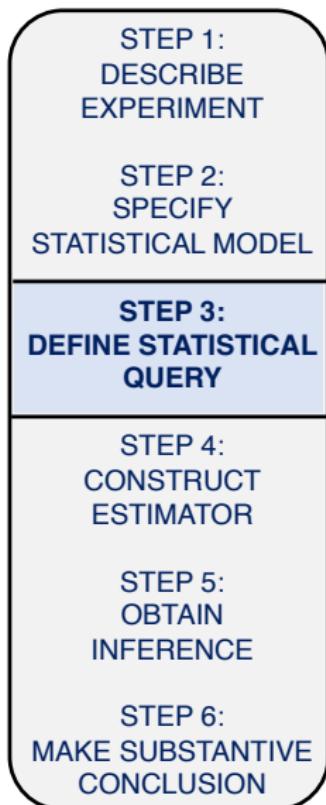
Regularizing TMLE

HAL and HAL-TMLE

Longitudinal TMLE

Variable Importance

Conclusion



What is the causal risk ratio in mortality between treatment groups?

$$\psi_{causal} = \frac{P(Y_1 = 1)}{P(Y_0 = 1)}$$

Proportion of subjects in the population of interest that would have died had they all received steroids

Targeted Learning

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The Art of Statistics

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TL Roadmap

Describe study

Specify a realistic statistical model

Define estimand

Causal estimand

Statistical estimand

Construct estimator

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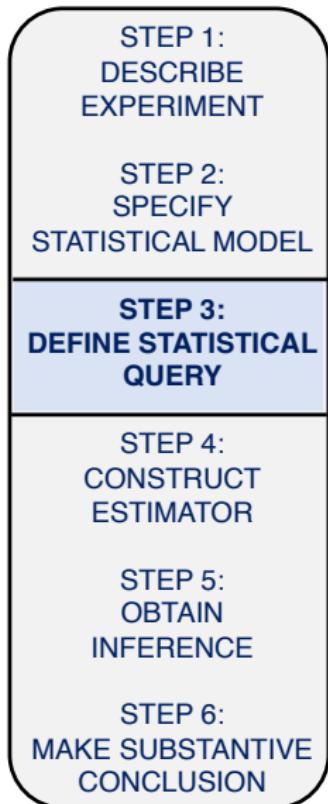
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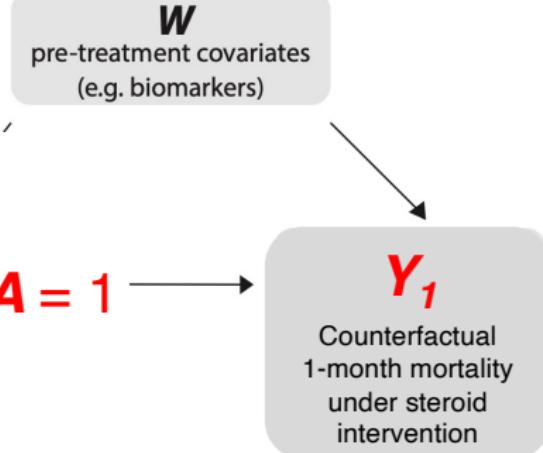
Variable Importance

Conclusion



What is the causal risk ratio in mortality between treatment groups?

$$\psi_{causal} = \frac{P(Y_1 = 1)}{P(Y_0 = 1)}$$



Proportion of subjects in the target population that would have died had they all not received steroids

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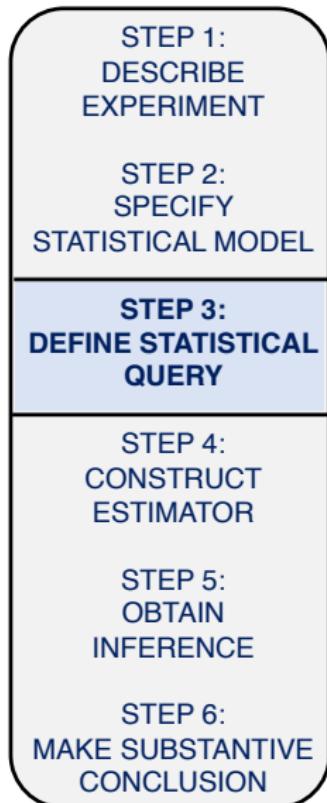
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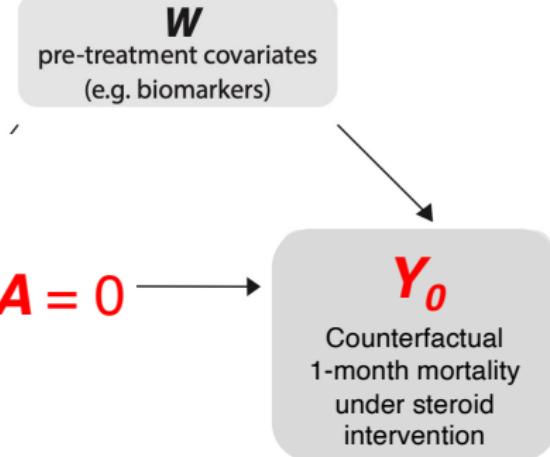
Variable Importance

Conclusion



What is the causal risk ratio in mortality between treatment groups?

$$\psi_{causal} = \frac{P(Y_1 = 1)}{P(Y_0 = 1)}$$



Causal target parameters are functions of the full data under the intervention(s) of interest

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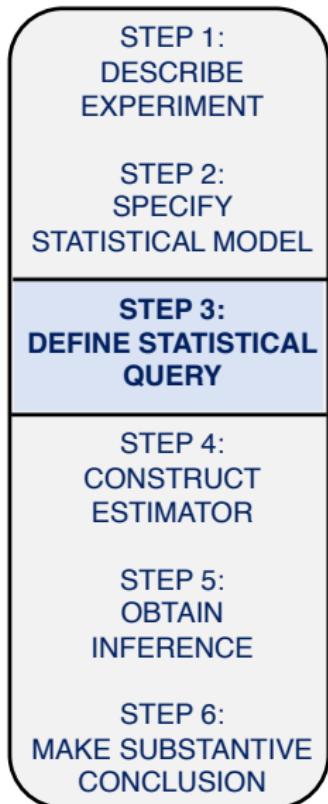
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What is the causal risk ratio in mortality between treatment groups?

$$\psi_{causal} = \frac{P(Y_1 = 1)}{P(Y_0 = 1)}$$

W_1	W_2	W_3	A	Y	Y_1	Y_0
21	65	F	1	1	1	?
22.3	28	F	0	0	?	0
19.4	49	F	1	0	0	?
24	77	M	1	0	0	?

Causal identifiability assumptions must hold in order to interpret the estimate causally

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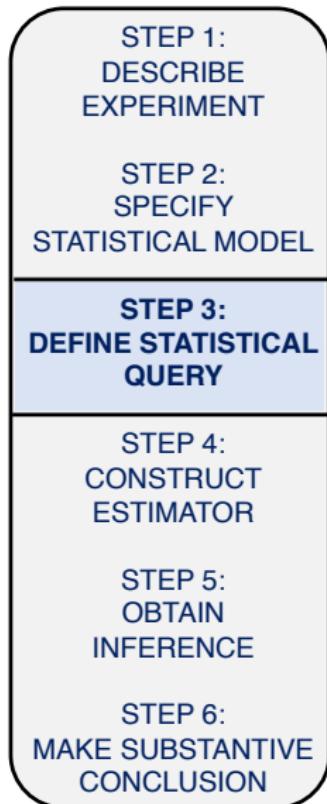
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What is the causal risk ratio in mortality between treatment groups?

$$\psi_{causal} = \frac{P(Y_1 = 1)}{P(Y_0 = 1)}$$

What's needed to *identify* ψ_{causal} from the observed data?

1. No unmeasured confounding / randomization / exchangeability

Some causal identifiability assumptions are also necessary for well-defined statistical estimation

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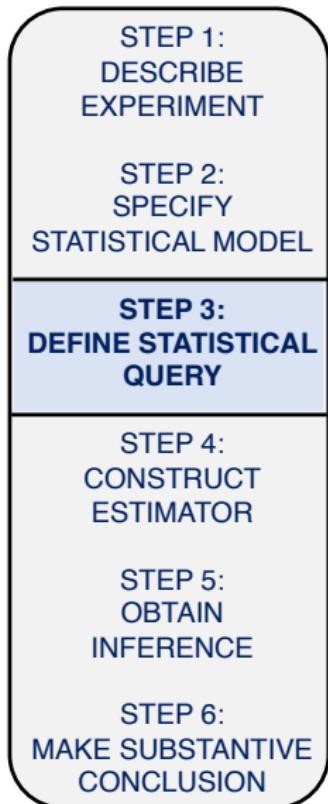
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What is the causal risk ratio in mortality between treatment groups?

$$\psi_{causal} = \frac{P(Y_1 = 1)}{P(Y_0 = 1)}$$

What's needed to ***identify*** ψ_{causal} from the observed data?

1. No unmeasured confounding / randomization / exchangeability
2. Positivity / experimental treatment assignment (ETA) assumption

Identification formula from g-computation

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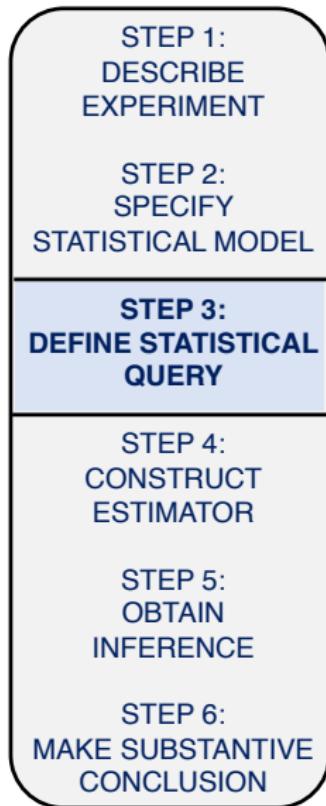
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$$\psi_{causal} = \frac{P(Y_1 = 1)}{P(Y_0 = 1)}$$

$$= \frac{\sum_w P(Y = 1|A = 1, W = w)P(W = w)}{\sum_w P(Y = 1|A = 0, W = w)P(W = w)}$$

$$= \psi_{stat}$$

Step 3b: What is the target statistical estimand that we will learn from the data?

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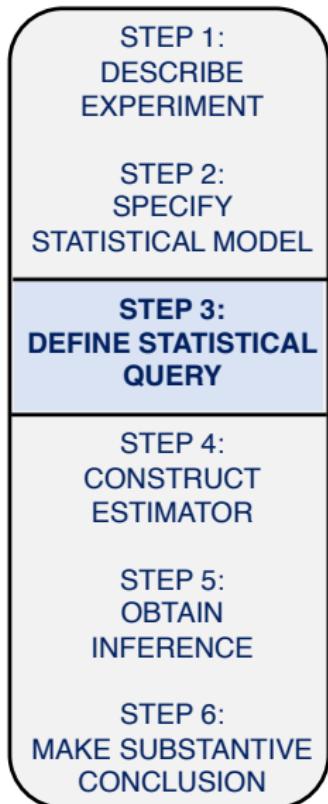
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Conclusion



What is the risk of mortality between treatment groups when adjusting for covariates?

$$\psi_{stat} =$$

$$\frac{\sum_w P(Y = 1|A = 1, W = w)P(W = w)}{\sum_w P(Y = 1|A = 0, W = w)P(W = w)}$$

Step 4: How should we estimate the target estimand?

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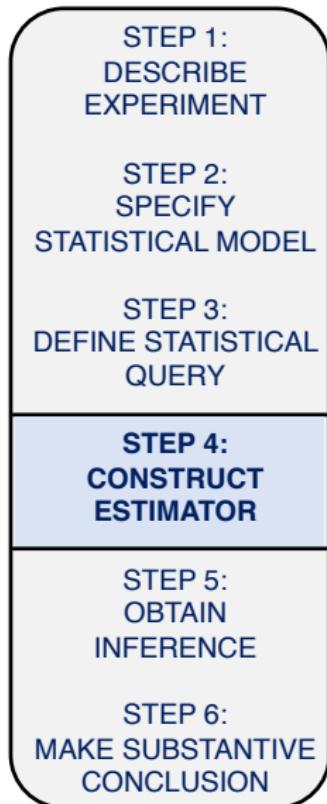
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Statistical properties to consider

- Substitution / plug-in
- Valid inference
- Efficiency
- Ability to optimize finite sample performance

Targeted Maximum Likelihood Estimation (TMLE)

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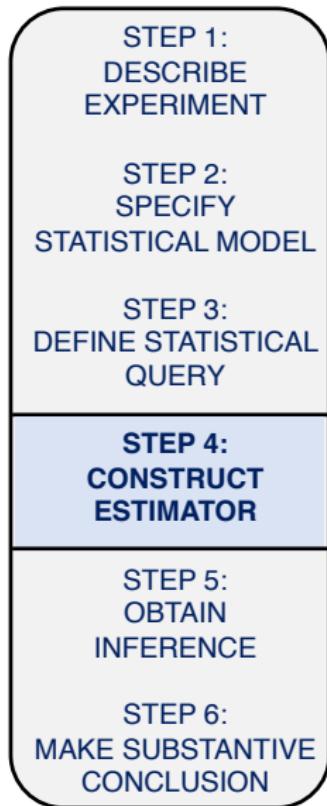
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TMLE

- 1 Initial estimation of $P[Y = 1|A, W]$ with super (machine) learning
- 2 Updating initial estimate to achieve optimal bias-variance trade-off for ψ_{stat}

TMLE estimates are optimal:
plug-in, efficient, unbiased, finite sample robust

Initial estimates via super learner

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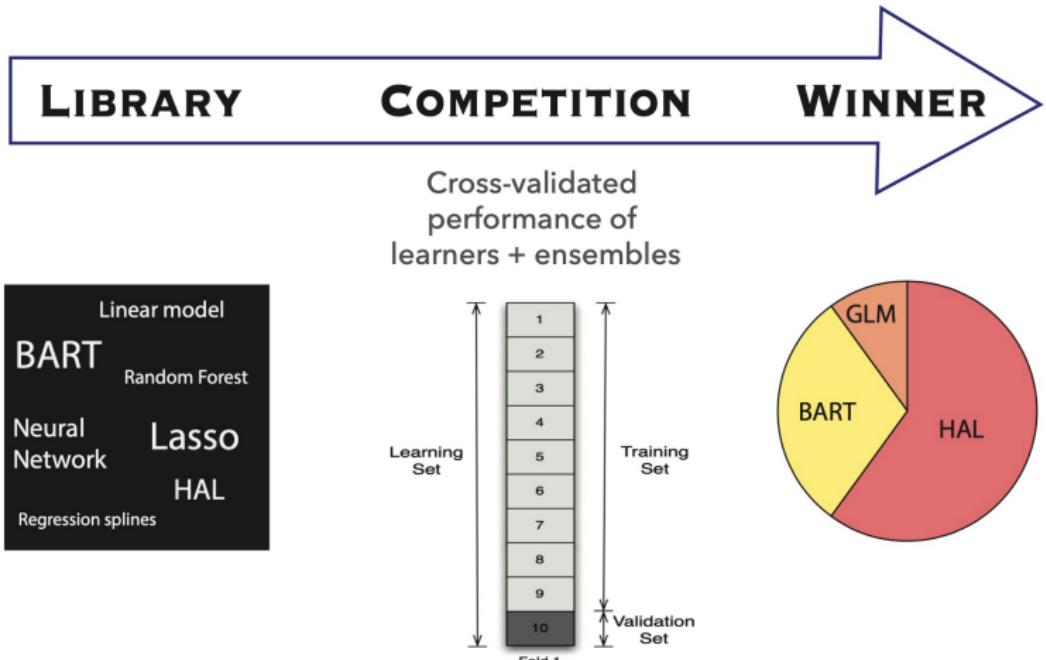
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Variable Importance

Conclusion



Hugely advantageous when coupled with NLP-derived covariates with EHR

Cross-validation to choose a winner

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1	1	1	1	1	1	1	1	1	1	1
2	2	2	2	2	2	2	2	2	2	2
3	3	3	3	3	3	3	3	3	3	3
4	4	4	4	4	4	4	4	4	4	4
5	5	5	5	5	5	5	5	5	5	5
6	6	6	6	6	6	6	6	6	6	6
7	7	7	7	7	7	7	7	7	7	7
8	8	8	8	8	8	8	8	8	8	8
9	9	9	9	9	9	9	9	9	9	9
10	10	10	10	10	10	10	10	10	10	10

Fold 1 Fold 2 Fold 3 Fold 4 Fold 5 Fold 6 Fold 7 Fold 8 Fold 9 Fold 10

Conclusion

Coding exercise: Super learning with sl3

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<https://tlverse.org/tlverse-handbook/sl3.html>

Tip: Include the Highly Adaptive Lasso (HAL) as a candidate in the SL library

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Conclusion

- First estimator to guarantee asymptotically efficient estimation of any pathwise differentiable estimand¹ (e.g., average causal effect or treatment-specific survival), without enforcing local smoothness conditions.
- Mild assumptions, which hold in most practical applications.
- Regularization step can be implemented with standard Lasso software (e.g., `glmnet`).
- Converges to true function at rate $n^{-1/3}(\log n)^{d/2}$.
- Accommodates a variety of function space specifications.

¹An estimand that is a weakly differentiable functional of the density of the data, the case for most causal inference estimands under positivity.



Illustration in Low Dimensions

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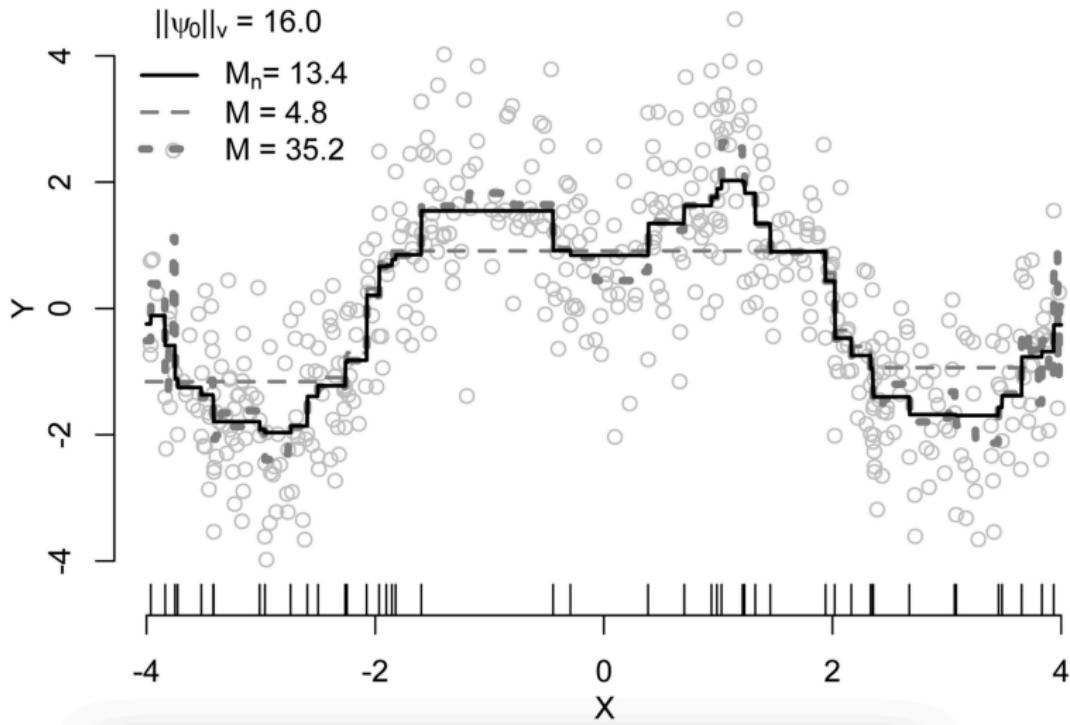
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How should we approximate the sampling distribution of our estimator?

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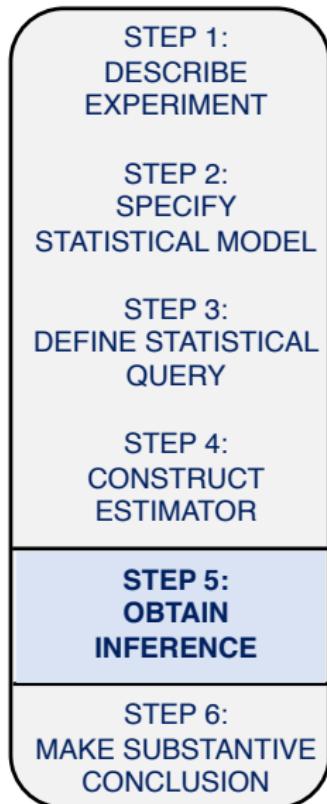
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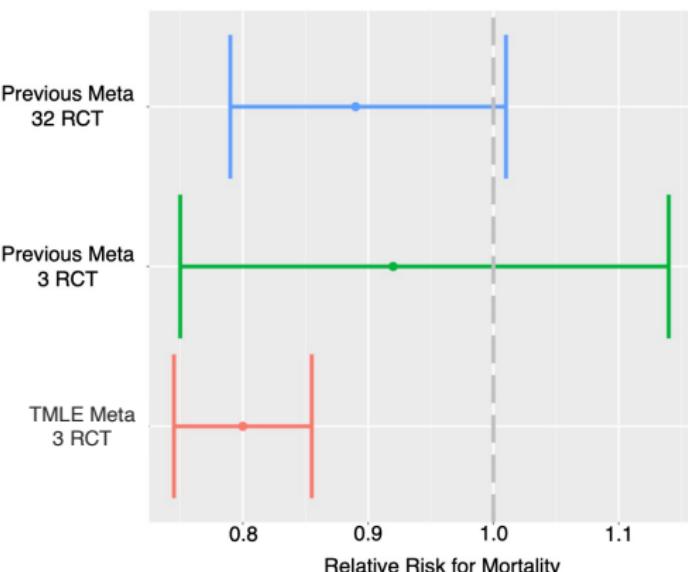
Longitudinal TMLE

Variable Importance

Conclusion



Due to targeting (step ②), the TMLE behaves as the *sample mean* of efficient influence function



Why plug-in estimation?

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Conclusion

- Consider a data unit $O = (W, A, Y)$, where $O \sim P_0 \in \mathcal{M}$ for P_0 the data-generating distribution in a model \mathcal{M} .
- A *plug-in* estimator $\Psi(\hat{P}_n)$ is based on the parameter mapping, where the target parameter is $\Psi(P_0)$ and \hat{P}_n is an estimator of P_0 .
- $\Psi(P_0) = \mathbb{E}_0\{\mathbb{E}_0[Y | A = 1, W] - \mathbb{E}_0[Y | A = 0, W]\}$, the ATE functional, can be approximated by recognizing that:
 - Components of P_0 that impact the plug-in estimator are the conditional mean $\bar{Q}_0(A, W) = \mathbb{E}[Y | A, W]$ and the marginal distribution of W , $Q_{0,W}$.
 - Thus, the plug-in estimator depends on estimates of these: $\bar{Q}_n(A, W) = \hat{\mathbb{E}}[Y | A, W]$ and $Q_{n,W} = P_n(W = w)$.
- By construction, plug-in estimators remain within the bounds of the parameter space.

TMLE Overview

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- TMLE produces an unbiased, efficient substitution estimator of target parameters of a data-generating distribution P_0 .
- A TMLE algorithm is an iterative procedure that updates an initial estimates of relevant components of Q_0 of P_0 , often requiring an estimate of a nuisance parameter g_0 .
 - Initial estimates of (g_n, \bar{Q}_n) of nuisance parameters (g_0, \bar{Q}_0) may be obtained via super learning.
 - These initial estimates are then updated so that the relevant component \bar{Q}_n solves an estimating equation.
- The updating step is a parametric fluctuation that updates \bar{Q}_n to \bar{Q}_n^* based on the nuisance function g_0 .

TMLE Example for the ATE functional

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Conclusion

- Consider again $O = (W, A, Y)$ where $O \sim P_0 \in \mathcal{M}$.
- $\Psi(P_0) = \mathbb{E}\{\mathbb{E}[Y | A = 1, W] - \mathbb{E}[Y | A = 0, W]\}$, the ATE functional, has a plug-in estimator:

$$\Psi(Q_n) = \frac{1}{n} \sum_{i=1}^n \{\bar{Q}_n(1, W) - \bar{Q}_n(0, W)\},$$

where $\bar{Q}_n(a, W) = \hat{\mathbb{E}}[Y | A = a, W]$.

- The TMLE based on this plug-in estimator is

$$\Psi(Q_n^*) = \frac{1}{n} \sum_{i=1}^n \{\bar{Q}_n^*(1, W) - \bar{Q}_n^*(0, W)\},$$

where \bar{Q}_n^* is an update of the initial estimate $\bar{Q}_n(a, W)$

- The update step uses a parametric fluctuation of the form $\text{logit}(\bar{Q}_n^*) = \text{logit}(\bar{Q}_n) + \epsilon H_n(A, W)$, where the form of $H_n(A, W)$ depends on relevant efficiency theory.

TMLE Example for the ATE functional

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- The update step uses a parametric fluctuation of the form $\text{logit}(\bar{Q}_n^*) = \text{logit}(\bar{Q}_n) + \epsilon H_n(A, W)$
- $H_n(A, W) = \{I(A = 1)/g_n(W)\} - \{I(A = 0)/(1 - g_n(W))\}$, a weight in the efficient influence function (EIF) of regular asymptotically linear (RAL) estimators of $\Psi(P_0)$ wrt \mathcal{M} .
- ϵ_n is a maximum likelihood estimator of ϵ , so that the TMLE is $\Psi(P_n^*)$, where $P_n^* = P_n^0(\epsilon_n)$.

TMLE: Targeting by following a path of maximal change in target estimand per unit likelihood

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Asymptotic Linearity of the TMLE

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- The TMLE $\Psi(P_n^*)$ is a RAL estimator, from which it follows that its difference from $\Psi(P_0)$, the truth, can be approximated by an average of i.i.d. RVs, the EIF, of O :

$$\Psi(P_n^*) - \Psi(P_0) \approx \frac{1}{n} \sum_{i=1}^n \text{IC}(P_0)(O_i) ,$$

where $\text{IC}(P_0)(O)$ is the EIF at $P_0 \in \mathcal{M}$.

- Asymptotic linearity of $\Psi(P_n^*)$ implies a normal sampling distribution of the TMLE (by the CLT):

$$\sqrt{n}(\Psi(P_n^*) - \Psi(P_0)) \xrightarrow{d} \mathcal{N}(0, \sigma^2) ,$$

where $\sigma^2 = \mathbb{V}(\text{IC}(P_0)(O))$ is the asymptotic variance of the EIF.

- $\text{IC}(P_0)(O)$ depends on both (g_0, Q_0) , the source of the TMLE update's dependence on g_0 .

Coding exercise: TMLE with tmle3

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<https://tlverse.org/tlverse-handbook/tmle3.html>

Arriving at the substantive conclusion

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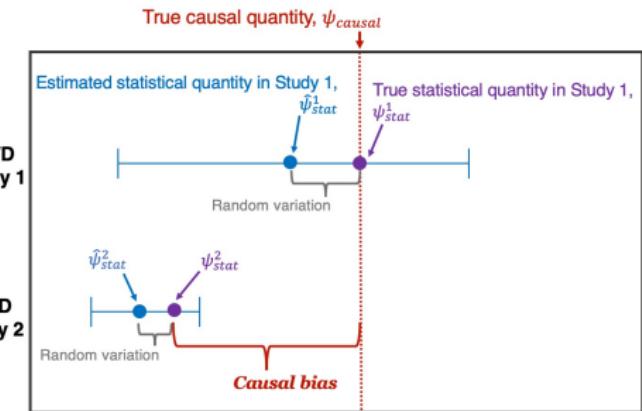
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- STEP 1: DESCRIBE EXPERIMENT
- STEP 2: SPECIFY STATISTICAL MODEL
- STEP 3: DEFINE STATISTICAL QUERY
- STEP 4: CONSTRUCT ESTIMATOR
- STEP 5: OBTAIN INFERENCE
- STEP 6: MAKE SUBSTANTIVE CONCLUSION

Investigate causal bias with sensitivity analysis

Causal bias: Gap between estimate and truth due to violations of any of the causal assumptions (e.g., unmeasured confounding)*



Sensitivity Analysis: Model-free assessment of how reasonable departures from causal assumptions would impact study findings

* Sensitivity analysis can be extended to incorporate statistical bias

TL-based non-parametric sensitivity analysis: RCT with 25% LTFU example

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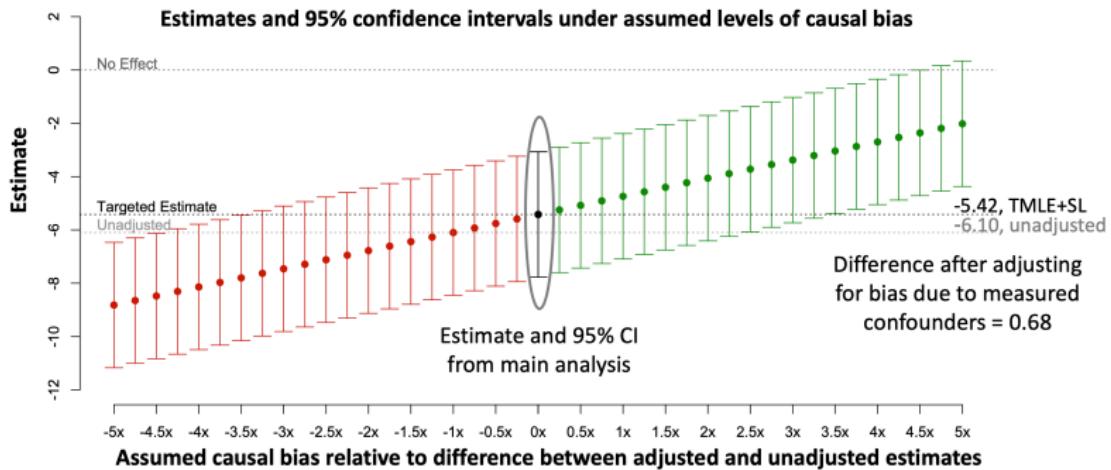
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Courtesy of "Targeted-Learning Based Statistical Analysis Plan" Webinar by Susan Gruber on 28 April 2021



TL-based non-parametric sensitivity analysis: Safety analysis example

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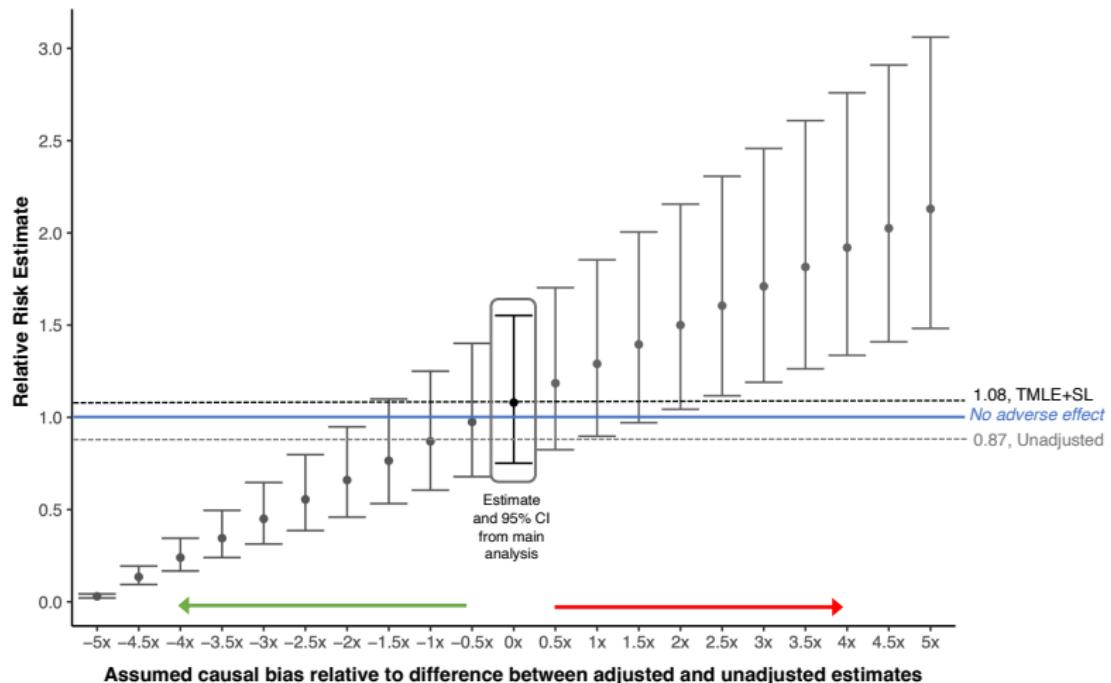
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Relative risk estimates and 95% confidence intervals under assumed levels of causal bias



Possibility to refine question of interest and inform future studies

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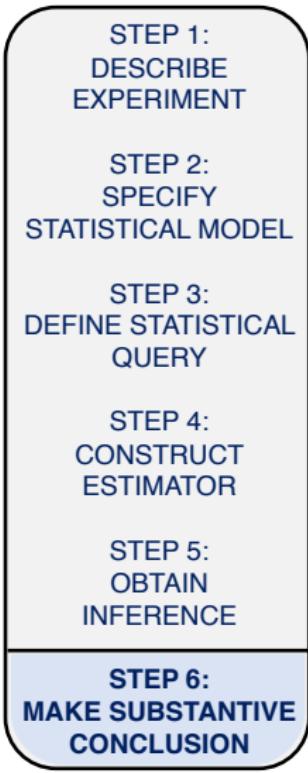
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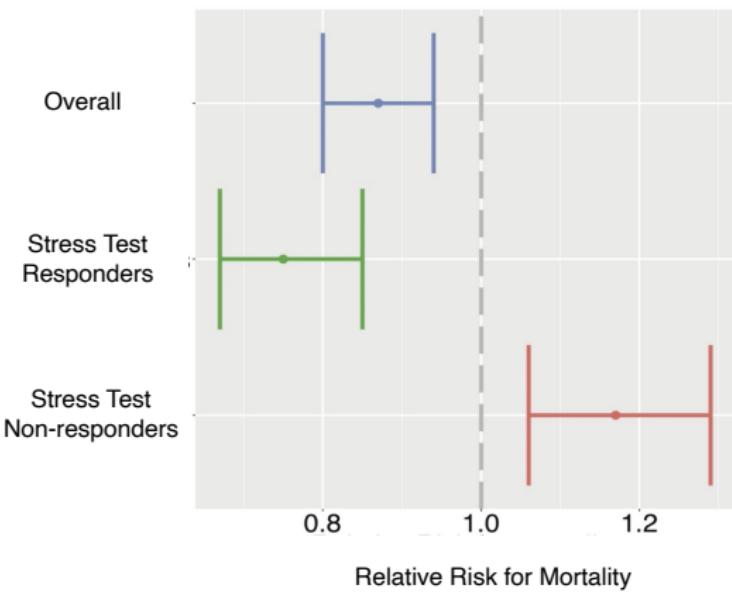
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Variable Importance



What subgroup of patients in septic shock benefit from corticosteroids?



Outcome blind simulations to a priori define TMLE: Wyss et al., 2023

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Step 4. Estimation and Inference using TMLE + SL

TMLE software default settings are robust across many situations, but not optimized for your analysis

Recommendation

Compare **coverage, type I error, power** for different specifications using outcome blind simulations, or plasmode simulations based on external data (pilot, Phase 1) sharing key features with your data

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Step 4. Estimation and Inference using TMLE + SL

Case study 1: Evaluating safety and efficacy with **high dimensional RWD**

$$\psi_{RD}^{stat} = E[E(Y | A = 1, W)] - E[E(Y | A = 0, W)]$$

Challenges

- Lack of baseline randomization
- How to model propensity score and outcome regression?
 - Thousands of covariates in linked EHR + claims
 - Traditional parametric model too high dimensional, unknown functional form

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TL in Action

TL Roadmap

Describe study

Specify a realistic statistical model

Define estimand

Causal estimand

Statistical estimand

Construct estimator

Obtain inference

Place conclusions in substantive context

Advanced TL

Regularizing TMLE

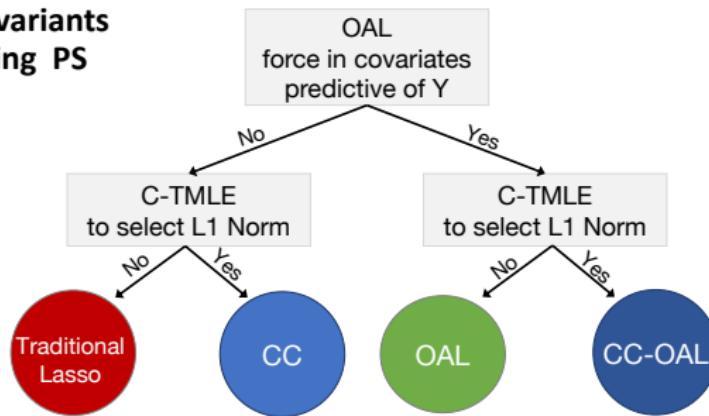
HAL and HAL-TMLE

Longitudinal TMLE

Variable Importance

Step 4. Estimation and Inference using TMLE + SL

Four Lasso variants for estimating PS



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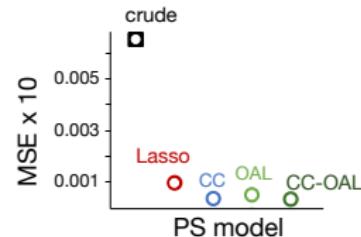
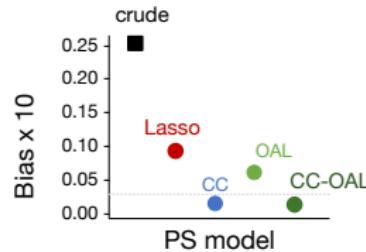
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Step 4. Estimation and Inference using TMLE + SL

Plasmode study results



Collaborative control greatly reduced bias and improved MSE

- Less regularization captured more relevant confounder information in PS

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Step 4. Estimation and Inference using TMLE + SL

Case study 1: Data analysis

- Analyze study data
 - Outcome regression: Lasso with expert-selected covariates forced in
 - PS: **Collaborative control Outcome-adaptive lasso (CC-OAL)**
 - force in covariates selected in the outcome, others as candidates
 - C-TMLE to choose L1 norm
- **Result: $RD = 0.005$ (95% CI: -0.027, 0.038)**
crude $RD = 0.024$ (95% CI: 0.018, 0.030)

Crude estimate indicates NSAIDS increase risk for AKI

Adjustment moves point estimate towards the null

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Conclusion



Zero-order Highly Adaptive Lasso (HAL): A nonparametric MLE

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Key Idea

- Any d -dimensional cadlag function (i.e. right-continuous, left limits) can be represented as an infinite linear combination of spline basis functions.
- The variation norm / complexity of a function is the L_1 -norm of the vector of coefficients.

Zero-order HAL converges to true function at rate $n^{-1/3}(\log n)^{d/2}$ (only assuming finite variation norm)

Formal representation of cadlag function as linear combination of zero order splines

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- A cadlag function $f \in D^{(0)}([0, 1]^d)$ can be represented as

$$f(x) = f(0) + \sum_{s \subset \{1, \dots, d\}} \int_{(0_s, x_s]} df_s(u),$$

where $f_s(x_s) = f(x(j))I(j \in s) : j = 1, \dots, d$ is the section implied by setting coordinates outside s equal to zero, and $x_s = (x(j) : j \in s)$.

- Moreover, we define the sectional variation norm of f as the sum over s of the variation norms of f_s :

$$\|f\|_v^* = \sum_s \|f_s\|_v = |f(0)| + \sum_s \int_{(0_s, 1_s]} |df_s(u)|.$$

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Conclusion

- Now, notice that this writes f as an infinite linear combination of $x \rightarrow I(x_s \geq u)$ of zero order splines with knot-point $u \in (0_s, 1_s]$ and coefficient $df_s(u)$, and that the sectional variation norm is the L_1 -norm in this representation.

Zero-order HAL performance for d=3

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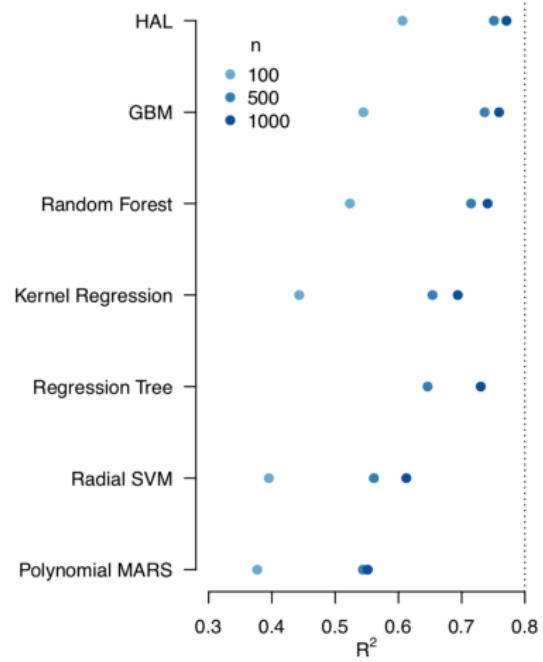
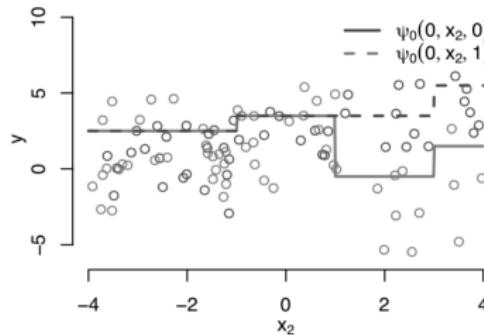
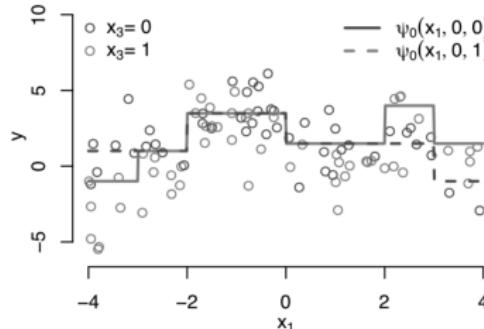
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Conclusion

$$\psi_0(x) = -2x_3 I(x_1 < -3) + 2.5 I(x_1 > -2) - 2 I(x_1 > 0) + 2.5x_3 I(x_1 > 2) \\ -2.5 I(x_1 > 3) + I(x_2 > -1) - 4x_3 I(x_2 > 1) + 2 I(x_2 > 3)$$



HAL Provides Estimators of Large Variety of Nuisance Parameters Needed in Causal Inference

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Conclusion

- Causal Inference requires statistical estimation of nuisance functions.
- In particular, it requires estimation of conditional means; conditional densities or cumulative distribution functions; intensities, conditional hazards. Standard loss functions can be employed for these.
- Moreover, it is often possible to define risk functions that define target functions of interest itself. For example, a variety of risk functions have been proposed for the conditional treatment effect. One can then apply HAL to minimize the empirical risk function.
- In these cases, estimation of the empirical risk function requires itself nuisance parameter estimation, where again HAL could be used.

How to develop a HAL-MLE: parametrize target function in terms of unrestricted function

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Conclusion

- Suppose one is interested in a functional parameter $Q(P)$ such as a conditional density.
- Select a loss function or risk function so that $Q(P) = \arg \min_Q R_P(Q)$, where, for example, $R_P(Q) = PL(Q)$ for some loss $L(Q)$.
- Q might be constrained in some ways. Therefore, find a parametrization $Q = Q_f$ in terms of an unconstrained function f . For example, parametrize a conditional density in terms of conditional hazard and represent the latter as $\exp(f)$.
- Now, model f as a linear combination of zero order splines and compute the MLE

$$\beta_n = \arg \min_{\beta, \|\beta\|_1 < C_n} R_n \left(Q_{\sum_j \beta(j) \phi_j} \right), \text{ where } R_n(Q) \text{ is an estimate of the risk } R_{P_0}(Q) \text{ such as } R_n(Q) = P_n L(Q).$$

- The HAL-MLE of Q_0 is then given by $Q_n = Q_{f_n}$ with



Additive models within the cadlag function space to define subspace specific HALs

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Conclusion

- Instead of selecting the richest set of basis function such as the ones implied by knot-points $\{X_i(s) : i = 1, \dots, n, s \subset \{1, \dots, d\}\}$, one can only model a subset \mathcal{S}_1 of all the additive functions $\tilde{f}_s(x_s) = \int I(x_s \geq u) df_s(u)$ by not including all subsets s in \mathcal{S}_1 .
- If \mathcal{S}_1 represents the collection of all subsets we include, then this defines additive models $f(x_s) = f(0) + \sum_{s \in \mathcal{S}_1} \tilde{f}_s(x_s)$. One can then define a corresponding HAL-MLE f_{n, \mathcal{S}_1} .
- More generally, we define $D^{(0)}(\mathcal{R}^{0,*})$ as the linear span of $\{\phi_j : j \in \mathcal{R}^{0,*}\}$, and by choosing the richest set \mathcal{R}^0 , we have $D^{(0)}(\mathcal{R}^0) = D^{(0)}([0, 1]^d)$.
- We use $D_M^{(0)}(\mathcal{R}^{0,*})$ when bounding L_1 -norm by M .

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- Every choice of subset of basis functions then implies an HAL-MLE.
- One could also first use an initial ML-algorithm, such as MARS, to learn the family of subsets, \mathcal{S}_1 , that appears to be needed, and then compute the resulting HAL-MLE f_{n,\mathcal{S}_1} .
- Of course, the screening algorithm is then part of algorithm, which needs to be respected when using cross-validation to select the L_1 -norm or select tuning parameter of the initial screening.

Rate of convergence of zero order HAL

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Conclusion

- Let $Q_n = Q_{f_n}$ be the HAL-MLE.
- Let $d_0(Q, Q_0) = P_0 L(Q) - P_0 L(Q_0)$ be the loss based dissimilarity.
- We have

$$\begin{aligned} d_0(Q_n, Q_0) &= P_n \{L(Q_n) - L(Q_0)\} \\ &\quad - (P_n - P_0) \{L(Q_n) - L(Q_0)\} \\ &\leq -(P_n - P_0) \{L(Q_n) - L(Q_0)\}. \end{aligned}$$

- Let $\mathcal{F} = \{L(Q_f) - L(Q_0) : f \in D_M^{(0)}([0, 1]^d)\}$.
- The (known) covering number for $D_M^{(0)}([0, 1]^d)$ implies the same covering number for \mathcal{F} .

Using empirical process theory:

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Conclusion

- Let $\mathcal{F}(\delta) = \{f \in \mathcal{F} : P_0 f^2 \leq \delta^2\}$.
- $\sup_{f \in \mathcal{F}(\delta)} |n^{1/2}(P_n - P_0)f|$ can be bounded by the entropy integral $J(\delta, \mathcal{F}(\delta)) = \int_{(0,\delta]} \sqrt{\log N(\epsilon, \mathcal{F}, L^2)} d\epsilon$, which behaves as $\delta^{1/2}$ up till $\log \delta$ -factor.
- Using that $P_0(L(Q) - L(Q_0))^2 \leq Cd_0(Q, Q_0)$, we can then apply an iterative proof bounding

$$d_0(Q_n, Q_0) \leq n^{-1/2} \sup_{f \in \mathcal{F}(\delta^k)} |n^{1/2}(P_n - P_0)f| \quad (1)$$

$$\sim n^{-1/2} J(\delta^k, \mathcal{F}), \quad (2)$$

starting with $\delta^0 = 1$, $\delta^1 = n^{-1/4}$, and so on.

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Conclusion

- The monotone improving (in rate) sequence converges to the fixed point δ^* of equation

$$\delta^2 = n^{-1/2} J(\delta, \mathcal{F}).$$

- This δ^* equals the rate of convergence for $d_0^{1/2}(Q_n, Q_0)$.
- We find $d_0(Q_n, Q_0) = O_P(n^{-2/3}(\log n)^d)$.

Derivation of first order spline representation of cadlag function

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Conclusion

- In the presentation of $f \in D_M^{(0)}([0, 1]^d)$ there appear integrals $\int_{(0(s), x(s)]} df_s(u)$.
- Assume and write $df_s(u) = df_s/dudu$; assume the RN-derivative $f_s^{(1)} = df_s/du \in D_M^{(0)}([0, 1]^d)$, and plug-in the zero order spline representation for

$$f_s^{(1)}(u) = f_s^{(1)}(0) + \sum_{s_1 \subset s} \int_{(0(s_1), u(s_1)]} df_{s_1}^{(1)}(u_1).$$

- Apply Fubini's theorem to the double integrals over (u, u_1) to obtain a representation in terms of tensor products of **first** order splines.

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- As an example, let's do it for a univariate function:

$$\begin{aligned}f(x) &= f(0) + \int_{(0,x]} df(u) \\&= f(0) + \int_{(0,x]} f^{(1)}(u) du \\&= f(0) + \int_{(0,x]} \{f^{(1)}(0) + \int_{(0,u]} df^{(1)}(u_1)\} du \\&= f(0) + xf^{(1)}(0) + \int_{u_1} \int_u I(u \leq x) I(u_1 \leq u) du df^{(1)}(u_1) \\&= f(0) + f^{(1)}(0)x + \int_{u_1} I(x \geq u_1)(x - u_1) df^{(1)}(u_1),\end{aligned}$$

which is a linear combination of first order splines

$\phi_{u_1}^1(x) = I(x \geq u_1)(x - u_1)$, including $\phi_0^1(x) = x$ implied by knot-point $u_1 = 0$.

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Conclusion

- In this manner we obtain the following first order spline representation for a function $f \in D^{(1)}([0, 1]^d)$ (a cadlag function satisfying our first orders smoothness assumption):

$$f(x) = f(0) + \sum_{s \subset \{1, \dots, d\}} \phi_0^1(x(s)) f_s^{(1)}(0) \\ + \sum_{s, s_1 \subset s, |s_1| > 0} \bar{\phi}_{s, s_1}(x) \int \phi_{u(s_1)}^1(x(s_1)) f_{s, s_1}^{(1)}(du).$$

- Here $\bar{\phi}_{s, s_1}(x(s/s_1)) = \prod_{l \in s/s_1} x(l)$ and $f_{s, s_1}^{(1)}$ is the s_1 -section of $f_s^{(1)} = df_s/du$.

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Conclusion

- Notice that finite linear part in this representation of f is just parametric model in x_1, \dots, x_d and its interactions (e.g., for $d = 2$, x_1, x_2, x_1x_2). The remaining infinite linear part is linear combination in tensor products of first order splines with interior knot-points in $(0(s_1), 1(s_1)]$ while having knots at 0 for components x_j with $j \in s \setminus s_1$.
- The L_1 -norm of all coefficients $f_{s,s_1}^{(1)}(du)$ and $f_s^{(1)}(0)$ defines our first order sectional variation norm $\|f\|_{v,1}^*$.
- $D_M^{(1)}([0, 1]^d)$ is defined as all functions $f \in D^{(0)}([0, 1]^d)$ satisfying this first order smoothness with $\|f\|_{v,1}^* \leq M$.

(fine enough) Finite dimensional first order spline working model

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Conclusion

- For each $s \subset \{1, \dots, d\}$, we can select knot-points $\mathcal{R}^1(s) \equiv \{(0(s/s_1), X_i(s_1)) : i = 1, \dots, n, s_1 \subset s\} \subset [0(s), 1(s)]$. The corresponding first order splines are:

$$\{\phi_{u(s)}^1 : u(s) \in \mathcal{R}^1(s)\}.$$

For s_1 the empty set this yields $\{0(s) : s \subset \{1, \dots, d\}\}$, giving the interactions $\phi_{0(s)}^1 = \prod_{j \in s} x_j$.

- The total set of N first order splines is thus;

$$\mathcal{R}_N^1 \equiv \{\phi_{u(s)}^1 : u(s) \in \mathcal{R}^1(s), s \subset \{1, \dots, d\}\}.$$

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Conclusion

- The initial starting model of linear combinations of first order splines is then:

$$D^{(1)}(\mathcal{R}_N^1) = \left\{ \sum_{j \in \mathcal{R}_N^1} \beta(j) \phi_j : \beta \right\}.$$

- This working model $D^{(1)}(\mathcal{R}_N^1) \subset D^{(1)}([0, 1]^d)$ represents a close approximation of $D^{(1)}([0, 1]^d)$ (providing sup-norm approximations going as fast as $n^{-1/2}$).

First order spline HAL

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Conclusion

- We then define

$$\beta_n = \arg \min_{\beta, |\beta|_1 \leq C_n} P_n L(Q_{f_{N,\beta}}),$$

and first order HAL $Q_n = Q_{f_{N,\beta_n}}$.

Rate of convergence for first order HAL

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Conclusion

- One can select J zero order splines $\mathcal{R}^0(J)$ so that $D^{(0)}(\mathcal{R}^0(J))$ yields a $O^+(1/J)$ L^2 -approximation of $D^{(0)}([0, 1]^d)$.
- This explains the dimension free rate of convergence $O^+(n^{-1/3})$ for the zero-order HAL.
- One can select J first order splines, $\mathcal{R}^1(J)$, so that $D^{(1)}(\mathcal{R}^1(J))$ yields a $O^+(1/J^2)$ **supremum norm** approximation of $D^{(1)}([0, 1]^d)$.
- The entropy integral $J(\delta, D_M^{(1)}([0, 1]^d), \|\cdot\|_\infty) = O^+(\delta^{3/4})$ instead of $O^+(\delta^{1/2})$ for $D_M^{(0)}([0, 1]^d)$.
- Our rate of convergence proof yields

$$d_0(Q_n, Q_0) = O_P^+(n^{-4/5}).$$

Higher order spline HAL

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Conclusion

- Analogue as above, we can define $D_M^{(k)}([0, 1]^d) \subset D^{(k-1)}([0, 1]^d)$ as class of k -th order smooth functions with k -th order sectional variation norm bounded by M .
- Analogue we obtain a k -th order spline representation for $f \in D^{(k)}([0, 1]^d)$; a finite dimensional linear working model $D^{(k)}(\mathcal{R}_N^k)$ approximating $D^{(k)}([0, 1]^d)$ and a corresponding k -th order spline HAL-MLE:

$$f_n = \arg \min_{f \in D_{M_n}^{(k)}(\mathcal{R}_N^k)} P_n L(Q_f),$$

and $Q_n = Q_{f_n}$.

- With J well chosen k -th order spline basis functions we can obtain an $O^+(1/J^{k+1})$ sup-norm approximation of $D^{(k)}([0, 1]^d)$.

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- As a consequence, we now have

$$J(\delta, D_M^{(k)}([0, 1]^d), \|\cdot\|_\infty) = O^+(\delta^{(2k+1)/(2k+2)}).$$

- Our rate of convergence proof now yields:

$$d_0(Q_n^k, Q_0) = O_P^+(n^{-2k^*/(2k^*+1)}),$$

with $k^* = k + 1$.

- For example, for $k = 0, 1, 2$, we have the dimension free rates $O_P^+(n^{-1/3})$, $O_P^+(n^{-2/5})$ and $O_P^+(n^{-3/7})$, respectively.

Discrete Super Learner incorporating higher order HAL

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Conclusion

- By varying smoothness degree k and starting sets $\mathcal{R}^k(j)$ of basis functions, one can define many HAL-MLEs over $D_C^{(k)}(\mathcal{R}^k(j))$.
- The discrete super learner using this library of (k, j) -specific HAL-MLEs will perform asymptotically exact as well as the oracle choice among all these HAL estimators, thereby achieves the rate of convergence of HAL for the unknown smoothness k_0 and smallest subspace $D^{(k_0)}(\mathcal{R}_{j_0}(d))$ containing true Q_0 .
- Thus this cross-validated higher order HAL-MLE is minimax **smoothness adaptive** achieving the minimax smoothness adaptive rate of convergence for univariate function estimation, up till $\log n$ -factors.

Asymptotic normality of higher order HAL

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Conclusion

- Let \mathcal{R}_n be a set of J_n k -th order splines providing uniform approximation error $O^+(1/J_n^{k+1})$.
- The non-zero coefficients in the HAL-fit does this for us when we choose a fine enough starting model.
- In addition, HAL will select an adaptive selection that works best for Q_0 .
- Let $D^{(k)}(\mathcal{R}_n)$ be the linear working model. This set yields the $O(1/J_n^{k+1})$ -uniform approximation of Q_0 .
- The HAL-MLE $Q_n = \sum_{j \in \mathcal{R}_n} \beta_n(j) \phi_j$ operates as an MLE of the oracle approximation $Q_{0,n} = \sum_{j \in \mathcal{R}_n} \beta_{0,n}(j) \phi_j$ in this working model.

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- In particular, if we do the relax-HAL (refitting the selected working model without L_1 -penalty), then it is an exact MLE of $Q_{0,n}$.
- One can analyze this parametric MLE Q_n^k w.r.t. $Q_{0,n}$ to establish that $(J_n/n)^{1/2}(Q_n - Q_{0,n})(x) \Rightarrow_d N(0, \sigma_0^2(x))$, while, by our uniform approximation result $\|Q_{0,n} - Q_0\|_\infty \sim O^+(1/J_n^{k+1})$.

Asymptotic normality and uniform rates

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- By selecting $J_n \sim n^{-1/(k+2)}$, the pointwise rate equals $n^{-k^*/(2k^*+1)}$ up till $\log n$ -factors.
- At cost of another $\log n$ -factor this rate is uniform in x .
- Pointwise and uniform confidence intervals follow.
- Beyond inference for Q_0 , these results teach us that we have dimension free **uniform** rates of convergence for $\|Q_n - Q_0\|_\infty = O^+(n^{-k^*/(2k^*+1)})$.

New Results: Asymptotic normality of higher order HAL-MLE itself, van der Laan, 2023

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- Defined higher order smoothness classes $D_C^{(k)}([0, 1]^d)$ with global complexity measure C , $k = 0, \dots$
- We define MLE over this model (k -th order HAL).
- $D_C^{(k)}([0, 1]^d)$ can be represented as linear span of tensor products of $\leq k$ -th order spline basis functions, where L_1 -norm is bounded by C .
- So implementation can be carried out with `glmnet()`.
- With J basis functions, one obtains uniform approximation error $O(1/J^{k^*})$ up till log J -factor, $k^* = k + 1$.
- HAL-MLE $Q_n = \sum_{j \in \mathcal{R}_n} \beta_n(j) \phi_j$ with J_n non-zero coefficients of its oracle MLE $Q_{0,n} = \sum_{j \in \mathcal{R}_n} \beta_{0,n}(j) \phi_j$ satisfies $(J_n/n)^{1/2}(Q_n - Q_{0,n})(x) \Rightarrow_d N(0, \sigma_0^2(x))$, while $\|Q_{0,n} - Q_0\|_\infty \sim O(1/J_n^{k^*})$.
- By selecting $J_n \sim n^{1/(k^*+1)}$, rate equals $n^{-k^*/(2k^*+1)}$ up till log n -factors. HAL will do this for you.



New Results on higher order HAL-MLE

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Conclusion

- So first order HAL converges at rate $n^{-2/5}$ pointwise, ignoring $\log n$ -factors.
- At cost of another $\log n$ -factor this rate is uniform in x .
- Pointwise and simultaneous confidence intervals follow.
- Any of these HAL-estimators result in plug-in estimators of smooth target features that converge at $n^{-1/2}$ and are asymptotically normal, and either efficient and super-efficient (on set of measure zero!).
- Inference can be based on nonparametric bootstrap.

Efficient HAL-TMLE (vdL, Rubin, 2006)

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Conclusion

- Construct initial estimator \mathbf{P}_n ; determine a least favorable path $\{\mathbf{P}_{n,\epsilon} : \epsilon \in (-\delta, \delta)\} \subset \mathcal{M}$ through \mathbf{P}_n with score $D_{\mathbf{P}_n}^*$ at $\epsilon = 0$.
- Compute MLE $\epsilon_n = \arg \max_{\epsilon} P_n L(\mathbf{P}_{n,\epsilon})$, where $L(P)$ is a valid loss function so that $\Psi(\arg \min_P P_0 L(P)) = \Psi(P_0)$.
- Let $\mathbf{P}_n^* = \mathbf{P}_{n,\epsilon_n}$. The TMLE is given by $\Psi(\mathbf{P}_n^*)$.
- By construction,
$$\Psi(\mathbf{P}_n^*) - \Psi(P_0) = (P_n - P_0) D_{\mathbf{P}_n^*}^* + R(\mathbf{P}_n^*, P_0),$$
 with
$$R(P, P_0) \equiv \Psi(P) - \Psi(P_0) - (P - P_0) D_P^*$$
 an exact second order remainder.
- Using the Highly Adaptive Lasso as initial estimator \mathbf{P}_n , we are guaranteed that $\Psi(\mathbf{P}_n^*)$ is asymptotically efficient estimator of $\Psi(P_0)$ (van der Laan, 2017).

HAL-TMLE of Target Estimands is Asymptotically Efficient

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Conclusion

- TMLE is two-stage method for constructing plug-in efficient estimators $\Psi(P_n^*)$ of a pathwise differentiable target estimand $\Psi(P_0)$.
- The HAL-TMLE (using HAL as initial estimator) is efficient in great generality (vdL, 15).
- The only necessary model assumptions are:
 - The true nuisance parameters have finite sectional variation norm
 - The loss functions of the true nuisance parameters are uniformly bounded, so that oracle inequality applies
 - The strong positivity assumption holds

Example: Asymptotic efficiency of (zero-order) HAL-TMLE for treatment-specific mean / ATE

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Conclusion

Consider the HAL-TMLE of $EY_1 = EE(Y | A = 1, W)$ based on $(W, A, Y) \sim P_0$ in a nonparametric statistical model. It is asymptotically efficient if

- ① $\delta < P_0(A = 1 | W)$ for some $\delta > 0$
- ② $W \rightarrow E_0(Y | A = 1, W)$ and $W \rightarrow P_0(A = 1 | W)$ are cadlag
- ③ $W \rightarrow E_0(Y | A = 1, W)$ and $W \rightarrow P_0(A = 1 | W)$ have finite sectional variation norm.

Undersmoothed HAL-MLE is efficient uniformly over large class of target estimands

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- HAL-MLE is efficient for pathwise differentiable target estimands, if L_1 -norm is chosen large enough.
- Due to being an MLE, it solves a large class of score equations, in particular, efficient scores corresponding with target estimands.
- By undersmoothing enough, it uniformly solves a class of score equations that approximates all scores with finite variation norm. As a consequence, it is a globally efficient MLE across most pathwise differentiable features.
- This results can be applied to different assumed subspaces (i.e., additive models of form $D^{(0)}(\mathcal{R}(d))$) or $D^{(0)}([0, 1]^d)$.

Nonparametric Bootstrap of HAL-TMLE or HAL-MLE

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- Fix M at the cross-validation selector M_n or another selector.
- Draw 10,000 samples of size n from empirical measure P_n . For each bootstrap sample $P_n^\#$, recompute the HAL-TMLE(M), say $\mathbf{P}_{n,M}^{\#*}$.
- The HAL on bootstrap sample can be restricted to only include indicator basis functions that were selected by HAL-MLE(M) on original data.
- Use sampling distribution of $\psi_{n,M}^{\#*} = \Psi(\mathbf{P}_{n,M}^{\#*})$, conditional on P_n , to construct 0.95-confidence interval.
- Increase M till plateau in confidence interval for optimal coverage.

Bootstrap works for HAL-TMLE or HAL-MLE

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- Conditional on the data ($P_n : n \geq 1$), the bootstrap sampling distribution of ψ_n^* converges to optimal normal limit distribution $N(0, \sigma_0^2)$.
- The approximation error of bootstrap is driven by performance of nonparametric bootstrap for an empirical process indexed by Donsker class (i.e., cadlag functions with sectional variation norm bounded by M).
- This suggests robust finite sample behavior of the nonparametric bootstrap.

Super-efficient estimation for smooth features of target function

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Conclusion

- The smoothness adaptive HAL (using cross-validation to select k and additive submodel $D^{(k)}(\mathcal{R}_{j_0})$) will asymptotically act like an HAL for an oracle smoothness k_0 and oracle subspace $D^{(k_0)}(\mathcal{R}_{j_0}(d))$.
- As a consequence, by undersmoothing within the oracle subspace it will be plug-in efficient for smooth target features w.r.t. the oracle statistical model on the data distribution that assumes $Q_0 \in D^{(k_0)}(\mathcal{R}_{j_0}(d))$.
- That is, $\Psi(Q_n)$ is asymptotically super-efficient, and is an example of the Adaptive MLE of (Lars van der Laan et al., 2023).

Finite sample robust TMLE

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Conclusion

- The current literature on TMLE has proposed various modifications of TMLE that regularize the TMLE to be better behaved in finite samples when the support is limited (i.e., practical violation of positivity assumption).
- For example, in censored and causal inference literature: adaptive truncation; regularize TMLE step by not fully solving EIC-equation; collaborative TMLE; outcome-adaptive TMLE; super-efficient TMLE (adjusting in PS for outcome regressions $Q_n(1, W)$, $Q_n(0, W)$, beyond a possible baseline model).
- These proposed regularizations have in common that they all concern targeted estimation of the orthogonal nuisance function $g(P_0)$ that is needed in targeting step, while $\Psi(P_0) = \Psi_1(Q_0)$ only depends on certain factors of likelihood.

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- Typically, these variations preserve asymptotic efficiency but adapt the targeting step towards the data to carefully trade-off bias reduction with variance gain.
- Finite sample simulations, theoretical results such as collaborative double robustness etc, have shown that these regularizations are crucial for robust finite sample behavior for poorly supported parameters.
- However, we never developed a truly unifying approach (and super-efficiency theory)!
- Fortunately, Lars did: Lars van der Laan et al. (2023), Adaptive debiased machine learning.

Limitations of Efficient Estimators such as TMLE

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- Due to lack of nonparametric support, if \mathcal{M} is close to nonparametric, then $D_{P_0}^*(o)$ can have very large values.
- In that case, confidence intervals for standard TMLE will be wide and no significant finding can be obtained.
- However if we would use plug-in HAL $\Psi(\mathbf{P}_n)$ (possibly super-efficient) we might very well still find a significant true result. Somehow, the targeting step can blow up a good initial estimator.
- This is due to an efficient estimator to be regular along all paths through P_0 , including paths that appear to be contradicting the data.

An efficient estimator cannot adapt to structure in the true data distribution

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- For example, suppose $O = (W, A, Y)$ and $\Psi(P) = E_P E_P(Y | A = 1, W)$. A plug-in HAL might end up fitting an additive model for the regression $E(Y | A, W)$ that contains the true regression.
- An efficient estimator of $\Psi(P_0)$ for this additive model would be well supported and have reasonable variance.
- But an efficient estimator for a nonparametric model protects itself against any kind of fluctuation of the data distribution, and as a consequence carries out a bias reduction that (**asymptotically**) holds up uniform in P in a ball around P_0 .
- In other words, it needs to remain asymptotically unbiased under fluctuations adding a 100 way interaction.

Lets reset benchmarks for our estimator

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Conclusion

- **Super-efficient estimator:** Suppose that we require that our estimator of $\Psi(P_0)$ is asymptotically linear at any $P_0 \in \mathcal{M}$, and regular along paths through P_0 that stay in an oracle model $\mathcal{M}_0 \subset \mathcal{M}$, approximated by a data adaptive submodel \mathcal{M}_n satisfying $P_0 \in \mathcal{M}_0$.
- Then, we can construct \mathcal{M}_0 -super-efficient estimators that still provide asymptotically valid confidence interval and are still robust under perturbations of P_0 that stay in the model \mathcal{M}_0 .
- **Regularized efficient estimator:** If our data adaptive model \mathcal{M}_n approximates $\mathcal{M}_0 = \mathcal{M}$, let the estimator behave as an efficient estimator under model \mathcal{M}_n that approximates the a-priori specified model \mathcal{M} as sample size converges to infinity but in a way that carefully balances finite sample bias and variance.

Adaptive TMLE

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- Data adaptively learn a model $\mathcal{M}_n \subset \mathcal{M}$. Make sure that $d(P_0, \mathcal{M}_n) = o_P(n^{-1/4})$ (e.g., use HAL, or cross-validation selection among a large family of submodels).
- Define the projection parameter $\Psi_{\mathcal{M}_n} : \mathcal{M} \rightarrow \mathbb{R}$ defined by $\Psi_{\mathcal{M}_n}(P_0) = \Psi(\Pi_{\mathcal{M}_n} P_0)$, where $P_{0,n} \equiv \Pi_{\mathcal{M}_n}(P_0) = \arg \min_{P \in \mathcal{M}_n} P_0 L(P)$ is the log-likelihood (or loss based) projection of P_0 onto \mathcal{M}_n .
- Construct a TMLE $\Psi_{\mathcal{M}_n}(P_n^*)$ of $\Psi_{\mathcal{M}_n}(P_0)$ based on canonical gradient $D_{\mathcal{M}_n, P}^*$ of this projection parameter. Generally speaking, for log-likelihood loss functions $\Psi_{\mathcal{M}_n}(P_n^*) = \Psi(P_n^*)$ with $P_n^* \in \mathcal{M}_n$.
- Provide confidence intervals for $\Psi_{\mathcal{M}_n}(P_0)$ as usual based on $D_{\mathcal{M}_n, P_0}$.
- Possibly cross-fit, like CV-TMLE.

Why does A-TMLE work: 1) standard TMLE analysis

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- From TMLE analysis we will have that $\Psi_{\mathcal{M}_n}(P_n^*) - \Psi_{\mathcal{M}_n}(P_0)$ behaves as $(P_n - P_0)D_{\mathcal{M}_n, P_0}^*$. Therefore, under an asymptotic stability condition on \mathcal{M}_n so that $D_{\mathcal{M}_n, P_0}^* \rightarrow_p D_{\mathcal{M}_0, P_0}^*$ we have that it behaves as $P_n D_{\mathcal{M}_0, P_0}^*$ and is thus asymptotically normal with mean zero and variance $\sigma_{\mathcal{M}_0}^2(P_0) = P_0 \{D_{\mathcal{M}_0, P_0}^*\}^2$.
- Cross-fitting weakens this need for asymptotic stability. Moreover, one might still have asymptotic normality by standardizing by a variance estimator.
- $D_{\mathcal{M}_0, P_0}^*$ equals the efficient influence curve of $\Psi : \mathcal{M}_0 \rightarrow \mathbb{R}$: i.e. we achieve the efficiency we would achieve with TMLE if we would a priori know that $P_0 \in \mathcal{M}_0$.

Why does A-TMLE work: 2) data adaptive model bias negligible

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- Let $R_{\mathcal{M}_0}(P, P_0) = \Psi_{\mathcal{M}_0}(P) - \Psi_{\mathcal{M}_0}(P_0) + P_0 D_{\mathcal{M}_0, P}^*$.
- We have

$$\begin{aligned}\Psi_{\mathcal{M}_n}(P_0) - \Psi(P_0) = \\ (P_{0,n} - P_0)\{D_{\mathcal{M}_0, P_{0,n}}^* - \Pi_n(D_{\mathcal{M}_0, P_{0,n}}^* \mid T_{\mathcal{M}_n}(P_{0,n}))\} \\ + R_{\mathcal{M}_0}(P_{0,n}, P_0),\end{aligned}$$

where the projection Π_n projects $D_{\mathcal{M}_0, P_{0,n}}^*$ onto tangent space of \mathcal{M}_n at $P_{0,n}$.

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- This is a very nice second order remainder (i.e., $o_P(n^{-1/2})$).
- Therefore, our adaptive TMLE is asymptotically linear estimator of $\Psi(P_0)$ with (super-efficient) influence curve $D_{\mathcal{M}_0, P_0}^*$.
- Since it operates as an efficient estimator of $\Psi_{\mathcal{M}_n}(P_0)$ it will also be regular along any path through P_0 that stays in the limit oracle model \mathcal{M}_0 .

Inverse Probability of Treatment/Censoring Weighted Estimators using HAL (Ertefaie, Hejazi, vdL, 2023)

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- Let $O = \Phi(C, X)$, $P_X \in \mathcal{M}^F$, $G_{C|X}$ satisfying CAR, and let $\Psi^F(P_X)$ be the target.
- One can then construct IPCW-estimators $\psi_{n,IPCW}$ as solutions of $P_n U_{G_n}(D^F(\psi)) = 0$ in ψ with $U_G(D^F)(O)$ an inverse probability weighted full-data estimating function D^F satisfying $E_G(U_G(D^F)(O) | X) = D^F(X)$.
- By using undersmoothed HAL as estimator of the censoring mechanism G , the HAL-IPCW estimator $\psi_{n,IPCW}$ is asymptotically linear with influence curve the IPCW-function $U_G(D^F(\psi))$ minus its projection on the tangent space T_{CAR} .

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Conclusion

- In particular, for nonparametric full-data models, the IPCW-estimator using undersmoothed HAL is asymptotically efficient.
- Similarly, if one uses HAL to estimate G for double robust estimators, then inference and efficiency is preserved under misspecified estimators of the full data distribution P_X .

General Longitudinal Data Structure for Complex Observational Studies

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We observe n i.i.d. copies of a longitudinal data structure

$$O = (L(0), A(0), \dots, L(K), A(K), Y = L(K + 1)),$$

where $A(t)$ denotes a discrete valued **intervention node** whose effect we desire to evaluate, $L(t)$ is an intermediate covariate and outcome realized in between intervention nodes $A(t - 1)$ and $A(t)$, $t = 0, \dots, K$, and Y is a final **outcome** of interest.

Survival outcome example: For example,

$$A(t) = (A_1(t), A_2(t))$$

$$A_1(t) = \text{Indicator of being treated at time } t$$

$$A_2(t) = \text{Indicator of being right-censored at time } t$$

$$Y(t) = \text{Indicator of observing a failure by time } t$$

$$L(t) \quad \text{Vector of time-dependent measurements}$$

$$Y(t) \subset L(t) \text{ and } Y = Y(K + 1).$$

A real-world CER study comparing different rules for treatment intensification for diabetes

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- Data extracted from diabetes registries of 7 HMO research network sites:
 - Kaiser Permanente
 - Group Health Cooperative
 - HealthPartners
- **Enrollment period:** Jan 1st 2001 to Jun 30th 2009

Enrollment criteria:

- $\text{past A1c} < 7\%$ (glucose level) while on 2+ oral agents or basal insulin
- $7\% \leq \text{latest A1c} \leq 8.5\%$ (study entry when glycemia was no longer reined in)

Longitudinal data

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- **Follow-up** til the earliest of Jun 30th 2010, death, health plan disenrollment, or the failure date
- **Failure** defined as onset/progression of albuminuria (a microvascular complication)
- **Treatment** is the indicator being on "treatment intensification" (TI)
- $n \approx 51,000$ with a median follow-up of 2.5 years.
- **Target estimand:** What would survival look like if treatment is intensified when $A1c < x\%$ for various levels $x = 7, 7.5, 8, 8.5?$

Likelihood and Statistical Model

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Conclusion

The probability density/likelihood p_0 of O can be **factorized according to the time-ordering** as

$$\begin{aligned} p_0(O) &= \prod_{t=0}^{K+1} p_0(L(t) \mid Pa(L(t))) \prod_{t=0}^K p_0(A(t) \mid Pa(A(t))) \\ &\equiv \prod_{t=0}^{K+1} q_{0,L(t)}(O) \prod_{t=0}^K g_{0,A(t)}(O) \\ &\equiv q_0 g_0, \end{aligned}$$

where $Pa(L(t)) \equiv (\bar{L}(t-1), \bar{A}(t-1))$ and $Pa(A(t)) \equiv (\bar{L}(t), \bar{A}(t-1))$ denote the parents of $L(t)$ and $A(t)$ in the time-ordered sequence, respectively. The g_0 -factor represents the **intervention mechanism**.

Statistical Model: We make no assumptions on q_0 , but could make assumptions on g_0 .

Statistical Target Parameter: G-computation Formula for Post-dynamic-Intervention Distribution

Targeted Learning

Mark van der Laan and Nima Hejazi

The Art of Statistics

TL in Action

TL Roadmap

Describe study

Specify a realistic statistical model

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- $p_0^{g^*} = q_0(o)g^*(o)$ is the **G-computation formula for the post-intervention distribution** of O under the stochastic intervention $g^* = \prod_{t=0}^K g_{A(t)}^*(O)$.
- Under **sequential randomization assumption** (SRA) and a positivity assumption, the post-intervention distribution p_{g^*} of O equals p_{g^*} , where post-intervention distribution is defined by the structural equation model in which the equations for the intervention nodes $A(t)$ are replaced by drawing from $g_{A(t)}^*$.
- **Causal estimand:** $E_{P_{g^*}} Y$, mean outcome of Y under post-intervention distribution, or survival rate if Y is indicator of survival, under post-intervention P_{g^*} .
- **Target estimand:** $E_{P_{g^*}} Y$, mean outcome of Y under G-computation density.

Better clinical decisions from observational data

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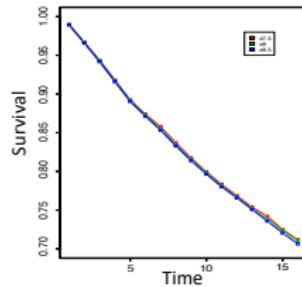
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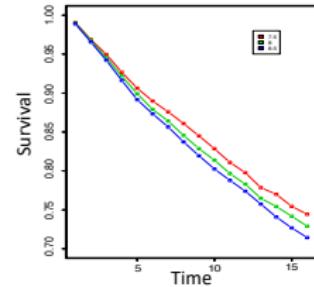
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Targeted learning in real-world comparative effectiveness research with time-varying interventions

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Standard methods: No benefit to more aggressive intensification strategy



Targeted Learning: More aggressive intensification protocols result in better outcomes

Predicting risk for COVID-19 infection, hospitalization or death

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- For any subject in study, define $t = 0$ as January 2022: one might consider other $t = 0$ times individualized by an enrollment criterion).
- $K + 1$ is **number of months of follow up** after $t = 0$ at which we want the outcome Y of interest.
- $L(0)$ represents **baseline history** for this subject, including any past events, medical history etc.
- Define as **intervention nodes** $A(t)$ indicator of being censored by time t (e.g. death by other causes, end of study).
- Define **outcome** Y as the indicator of observing a COVID-19 infection by time $t = K + 1$.
- Define **time-dependent covariates** $L(t)$ as anything observed in month t , before $A(t)$: including COVID-19 Infection/Hospitalization/Death, vaccination, medical treatments etc.

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- Our target is $E(Y_{\bar{a}=0} \mid L(0))$: **conditional risk of COVID-19 infection by time $K + 1$ in counterfactual world without right-censoring.**
- So our goal is to predict risk of COVID-19 event by $K + 1$ -months in world without right-censoring.
- One may look at various **other outcomes** of interest such as hospitalization, death, composite outcomes etc.

Super-learner to Predict COVID-19 Risk from baseline information

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- One can set up a collection of logistic regression machine learning algorithms, including a variety of HAL-model fits.
- One has to select a **measure of performance**, such as AUC, log-likelihood, or MSE.
- To deal with drop-out (right-censoring), we can use **inverse probability of censoring weights** for each candidate algorithm and for evaluating the cross-validated performance of the algorithm.
- The super-learner will output the best performing prediction function, its measure of performance (e.g., AUC) with a confidence interval.

Variable importance analysis using TMLE

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- Let $W = L(0)$.
- One has to **define a measure of importance** for each variable W_j .
- For example, for **binary** W_j , one can use the **ATE** estimand, which measures change in prediction due to $W_j = 0$ versus $W_j = 1$ keeping $W(-j)$ constant.
- For **continuous** W_j one can use the **shift-intervention** estimand, which measures change in prediction due to shifting W_j to $W_j + \delta$, keeping $W(-j)$ constant.
- One can compute TMLE of these W_j -specific variable importance measures, with confidence intervals and p -values.
- One can use **multiple testing adjustments** to control family wise error or false discovery rate.

Concluding Remarks

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- Roadmap for causal inference and Targeted Learning provides systematic principled approach for generating RWE.
- Integrates all advances in machine learning, statistical theory and causal identification.
- SL and TMLE can be tailored towards particular estimation problem in pre-specified manner using outcome blind simulations.
- HAL provides realistic models; theoretical guarantees, dimension free rates, and bridges TMLE to inference for non-pathwise differentiable target functions such as conditional treatment effects, dose response curves etc.
- Bridges such as Deep LTMLE to deep learning community are crucial.

Active TL collaborations and software

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- The Center for Targeted Machine Learning (CTML) at UC Berkeley: <https://ctml.berkeley.edu>
- Government: US Food and Drug Administration (FDA) and National Institute of Allergy and Infectious Diseases (NIAID), California Department of Public Health
- Private sector: Genentech, Gilead, Kaiser Permanente, Accenture, Novo Nordisk
- Software:
 - The `tlverse` software ecosystem: <https://tlverse.org>
 - Additional software: `tmle`, `ltmle`, `SuperLearner`

Thank you!

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Feel free to email us to ask questions, request learning resources, or get involved in TL research and/or CTML.

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