

# Targeted Learning in Data Science: Causal Inference for Observational and Experimental Data

Mark van der Laan & Rachael Phillips  
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**Deming Conference on Applied Statistics**  
Short Course 2: 8:00A-5:00P on December 5-6, 2019

## Day 1 Schedule

- **8:00A-9:30A:** Overview of Targeted Learning
- **9:30A-9:50A:** Break
- **9:50A-11:20P:** Causal Inference and Interventions
- **11:20A-12:40P:** Lunch
- **12:40P-2:10P:** Super (Machine) Learning and Targeted Minimum Loss-Based Estimation
- **2:10P-2:30P:** Break
- **2:30P-4:00P:** Super Learning in the `tlverse` software ecosystem
- **4:00P-4:20P:** Break
- **4:20P-5:00P:** Targeted Maximum Likelihood Estimation of the Average Treatment Effect in the `tlverse` software ecosystem

## Day 2 Schedule

- **8:00A-9:30A:** Targeted Minimum Loss-Based Estimation of the Effects of Optimal Dynamic and Shift Interventions.
- **9:30A-9:50A:** Break
- **9:50A-11:20P:** Targeted Minimum Loss-Based Estimation of the Treatment Specific Survival Function for Right-Censored Survival Data
- **11:20A-12:40P:** Lunch
- **12:40P-2:10P:** Targeted Minimum Loss-Based Estimation for Longitudinal Data
- **2:10P-2:30P:** Break
- **2:30P-** : Discussion

## Resources

- The latest version of the presentation slides are available here:  
<https://github.com/tlverse/deming2019-workshop/tree/master/slides>.
- The open source and fully-reproducible electronic vignette for the software tutorials can be found here:  
<https://tlverse.org/deming2019-workshop/>.

# Targeted Machine Learning

## Causal Inference for Real-World Data Science

Mark van der Laan

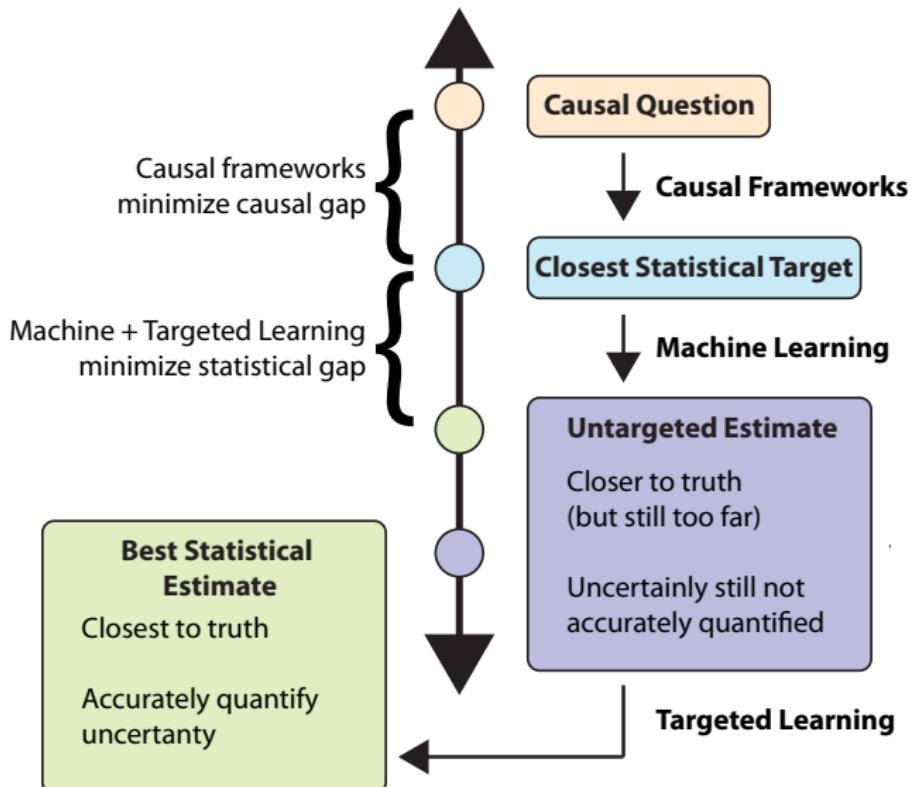
Division of Biostatistics, University of California at Berkeley

**Deming Conference on Applied Statistics**  
December 4-6 2019, Atlantic City NJ

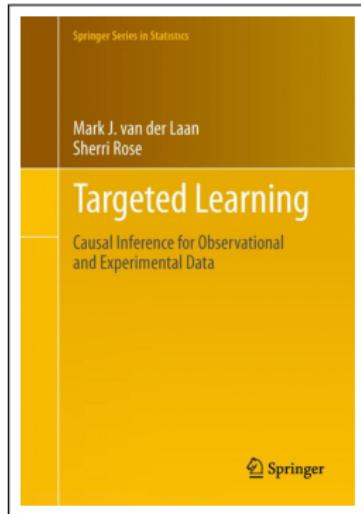
Various slides from Maya Petersen presentation (NIH R01 AI074345)  
and Bill and Melinda Gates Foundation presentation.

# Outline

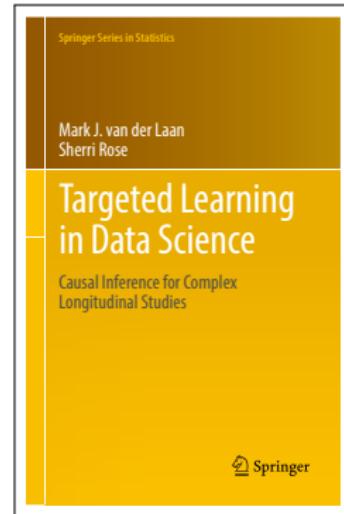
# Targeted Learning fills a much needed gap in machine learning and causal inference



# Targeted Learning is a subfield of statistics



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.

# Outline

# Roadmap for Statistical Learning

- ① Describe observed data
- ② Specify statistical model
- ③ Define statistical query (e.g., using causal roadmap)
- ④ Construct estimator
- ⑤ Obtain inference

# Roadmap for Statistical Learning

STEP 1:  
DESCRIBE  
OBSERVED DATA

STEP 2:  
SPECIFY  
STATISTICAL MODEL

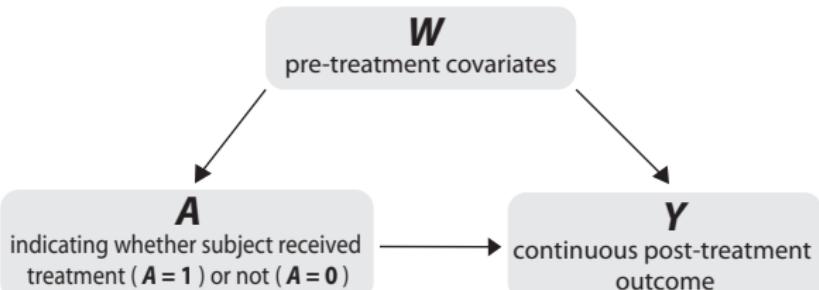
STEP 3:  
DEFINE  
STATISTICAL QUERY

STEP 4:  
CONSTRUCT  
ESTIMATOR

STEP 5:  
OBTAIN INFERENCE

$n = 100$  subjects were sampled independently from each other and from the same population distribution  $P_0$

For each subject, pre-treatment covariates ( $W$ ), treatment ( $A$ ), and outcome ( $Y$ ) vectors were measured



# Roadmap for Statistical Learning

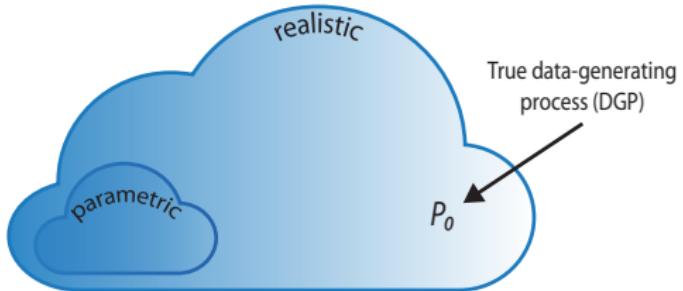
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ESTIMATOR

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## Standard Approach

Parametric statistical model

Does not contain  $P_0$ , the DGP  
(i.e., misspecified model)

## Targeted Learning

Realistic semiparametric or  
nonparametric statistical model

Defined to ensure  $P_0$  is  
contained in model

# Roadmap for Statistical Learning

STEP 1:  
DESCRIBE  
OBSERVED DATA

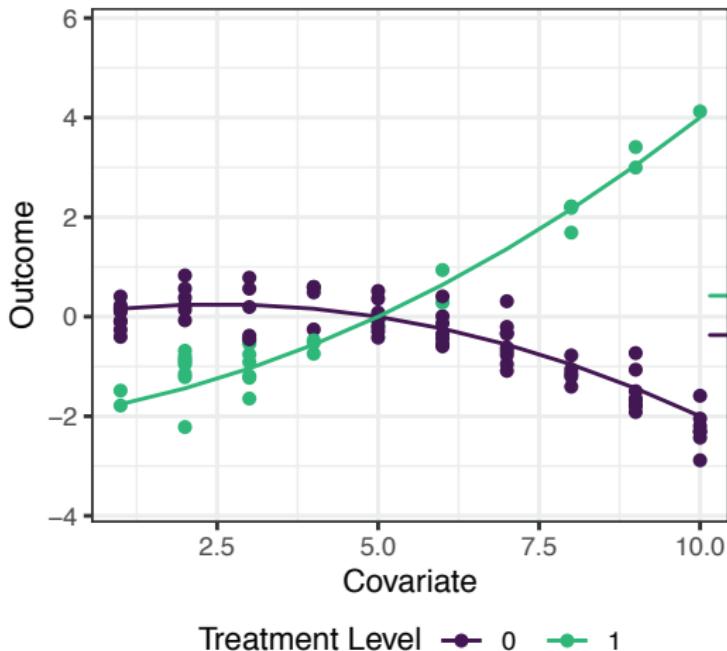
STEP 2:  
SPECIFY  
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Example True DGD



# Roadmap for Statistical Learning

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*What is the average difference in outcomes between treatment groups when adjusting for covariates?*

$$\Psi(P_0) = E_0(E_0[Y|A=1, W] - E_0[Y|A=0, W])$$

$\Psi$  is a function that takes as input  $P_0$  and outputs the answer to the question of interest

The **assumption of positivity** is required to estimate of this quantity from the data. That is, it must be possible to observe both levels of treatment for all strata of  $W$ .

Additional assumptions are required to interpret this estimand as causal

# Causal roadmap for obtaining statistical query answering causal question

Step 3 can be carried out using following causal roadmap:

- Define **potential outcomes**  $Y_0, Y_1$  for each subject, representing (counterfactual) outcome we would have seen if subject would have taken treatment 0 and 1, respectively.
- Link desired full-data  $(W, Y_0, Y_1)$  to observed data  $O = (W, A, \mathbf{Y} = \mathbf{Y}_A)$ .
- Define **causal quantity** of interest:  $E(Y_1 - Y_0)$ , called average treatment effect.
- Establish **identification from DGD**: If treatment is independent of potential outcomes, given  $W$ , and positivity holds, then  $E_0(Y_1 - Y_0)$  equals target estimand  $\Psi(P_0)$ .

# Roadmap for Statistical Learning

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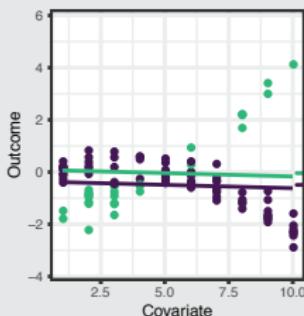
## Standard Approach

Generalized Linear Model (GLM)  
to estimate

$$\mathbf{Y} = \beta_0 + \beta_1 \mathbf{A} + \beta_2 \mathbf{W} + \epsilon$$

Estimated coefficients  
are biased

Cannot detect heterogeneity  
in treatment effect

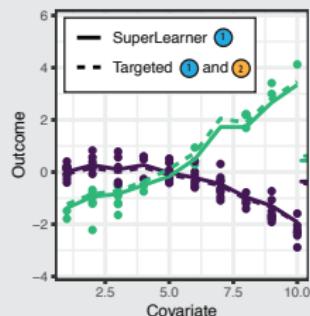


## Targeted Learning

TMLE implements  
a two-step procedure

- 1 initial estimation of  $E_0[Y|A, W]$  with super (machine) learning
- 2 targeting towards optimal bias-variance trade-off for  $\Psi(P_0)$

TMLE estimates are unbiased  
and doubly robust



# Roadmap for Statistical Learning

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## Standard Approach

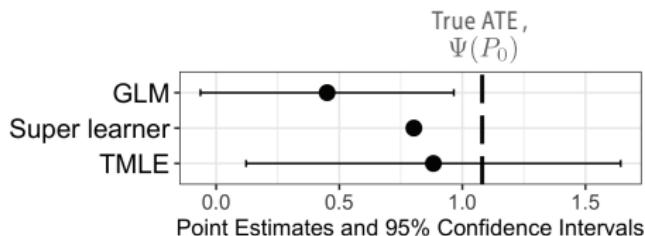
Inference (such as  $p$ -value and confidence interval) assumes parametric model is true

Inference is misleading and erroneous

## Targeted Learning

Targeting (step ②) improves estimate and makes inference possible

Trustworthy inference obtained with efficient influence function



# Roadmap of Statistical Learning Summary

- **Observed data:** Realization of a random variable  $O^n = (O_1, \dots, O_n)$  with a probability distribution (say)  $P_0^n$ , indexed by "sample size"  $n$ .
- **Model stochastic system of observed data realistically:** Statistical model  $\mathcal{M}^n$  is set of possible probability distributions of the data.
- **Define query about stochastic system:** Function  $\Psi$  from model  $\mathcal{M}^n$  to real line, where  $\Psi(P_0^n)$  is the true answer to query about our stochastic system.
- **Estimator:** An a priori-specified algorithm that takes the observed data  $O^n$  and returns an estimate  $\psi_n$  to the *true answer to query*. Benchmarked by a dissimilarity-measure (e.g., MSE) w.r.t true answer to query.
- **Confidence interval for true answer to query:** Establish approximate sampling probability distribution of the estimator (e.g., based on CLT), and corresponding statistical inference.

# Outline

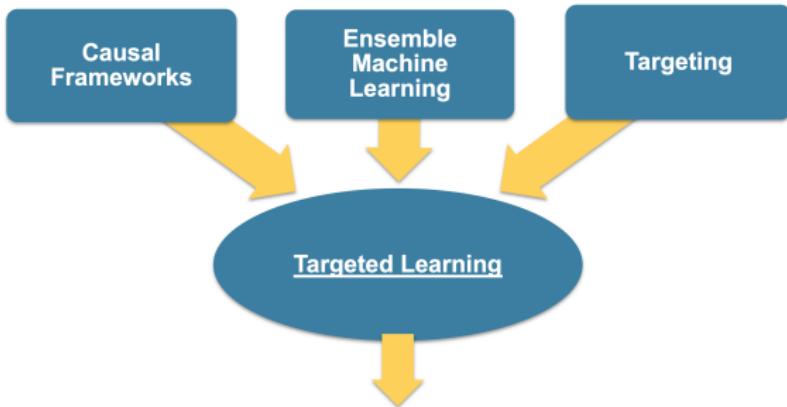
## Example: Nonparametric Estimation of Average Treatment Effect

- Unit (i.i.d.) data  $O \sim P_0$  consists of baseline covariates  $W$ , binary treatment  $A$ , and final binary outcome  $Y$ .
- Statistical model for the data distribution  $P_0$  is nonparametric.
- Statistical target parameter:

$$\Psi(P) = E_P\{P(Y = 1 | A = 1, W) - P(Y = 1 | A = 0, W)\}.$$

- Under causal model, randomization assumption, and positivity assumption,  $\Psi(P) = E(Y_1 - Y_0)$  is the ATE.
- A TMLE will estimate  $P(Y = 1 | A, W)$  with **ensemble machine learning** and a subsequent **Targeting step** using logistic regression with off-set initial fit, and clever covariate  $(2A - 1)/\hat{P}(A|W)$ .

# Targeted Learning



Better (more precise) answers to causal (actionable) questions with  
accurate quantification of uncertainty (signal from noise)

DIA

# Identifying contributing factors for health care spending

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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* 

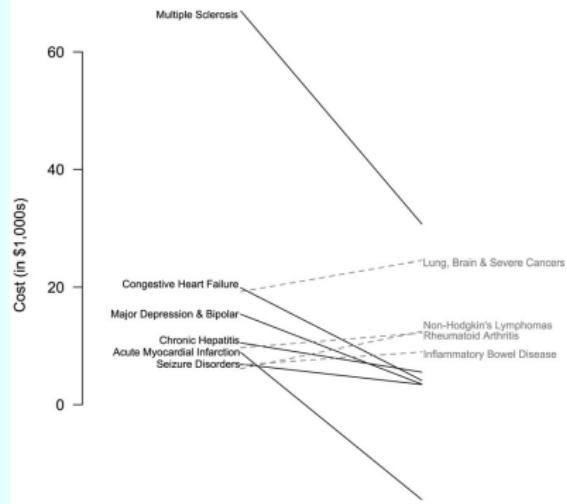
# Identifying contributing factors for health care spending

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DOI: 10.1111/1475-6773.12848  
METHODS ARTICLE

## Robust Machine Learning Variance Importance Analyses of Medication Conditions for Health Care Spending

Sherri Rose 

Figure 4: Top 10 Largest Targeted Learning Effect Estimates



# Average treatment effect in an observational study

International Archives of Occupational and Environmental Health (2019) 92:629–638  
<https://doi.org/10.1007/s00420-018-1397-1>

ORIGINAL ARTICLE



## An educational intervention to improve knowledge about prevention against occupational asthma and allergies using targeted maximum likelihood estimation

Daloha Rodríguez-Molina<sup>1,2</sup> · Swaantje Barth<sup>1</sup> · Ronald Herrera<sup>1</sup> · Constanze Rossmann<sup>3</sup> · Katja Radon<sup>1</sup> · Veronika Karnowski<sup>4</sup>

Received: 15 March 2018 / Accepted: 13 December 2018 / Published online: 14 January 2019  
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**Table 4** Adjusted average treatment effects of the intervention ( $n=116$ ), Bavaria, Germany, 2014

|              | All six correct measures | At least five correct measures | At least four correct measures |
|--------------|--------------------------|--------------------------------|--------------------------------|
| Additive ATE |                          |                                |                                |
| Parameter    | 18.44%                   | 55.53%                         | 29.60%                         |
| 95% CI       | (7.3–29.58%)             | (36.96–74.09%)                 | (12.2–47.0%)                   |
| Additive ATT |                          |                                |                                |
| Parameter    | 16.9%                    | 63.07%                         | 62.78%                         |
| 95% CI       | (5.38–28.51%)            | (46.02–80.13%)                 | (41.64–83.93%)                 |
| Additive ATC |                          |                                |                                |
| Parameter    | 16.8%                    | 32.28%                         | 18.97%                         |
| 95% CI       | (5.02–28.57%)            | (12.84–51.72%)                 | (1.91–36.02%)                  |

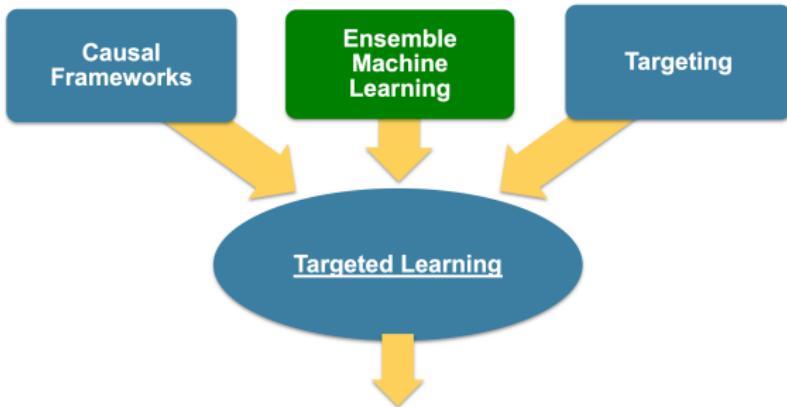
Adjusted for sex, age, education level, smoking status, presence of asthma or rhinoconjunctivitis, riskperception, parental asthma, and knowledge about preventive measures against asthma and allergies before the intervention

The adjusted model using TMLE allowed including both observed data ( $n=47$ ) and missing values ( $n=69$ ) as parameters

ATE average treatment effect, ATT average treatment effect on the treated, CI confidence interval, ATC average treatment effect on the controls, TMLE targeted maximum likelihood estimation

# Outline

# Targeted Learning

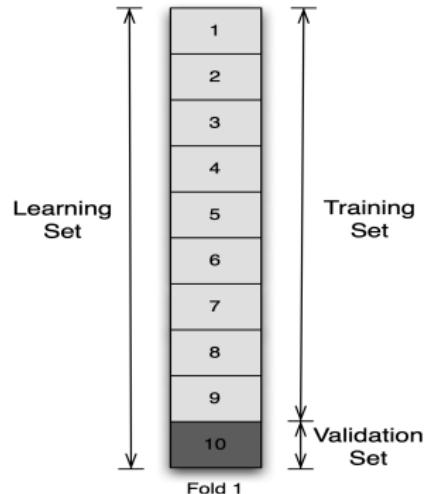


**Better (more precise) answers to causal (actionable) questions with  
accurate quantification of uncertainty (signal from noise)**

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# Super Learning: Ensemble Machine Learning

- “Competition” of algorithms
  - Parametric models
  - Data-adaptive (ex. Random forest, Neural nets)
- Best “team” wins
  - Convex combination of algorithms
- Performance judged on independent data
  - V-fold cross validation (Internal data splits)
- Customizable optimality criterion
  - Standard loss function
  - Minimize false negatives with bounded false positives
  - Respect resource constraints



Van der Laan, Polley, 2007

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# V-fold Cross Validation

|    |    |    |    |    |    |    |    |    |    |
|----|----|----|----|----|----|----|----|----|----|
| 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| 2  | 2  | 2  | 2  | 2  | 2  | 2  | 2  | 2  | 2  |
| 3  | 3  | 3  | 3  | 3  | 3  | 3  | 3  | 3  | 3  |
| 4  | 4  | 4  | 4  | 4  | 4  | 4  | 4  | 4  | 4  |
| 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  |
| 6  | 6  | 6  | 6  | 6  | 6  | 6  | 6  | 6  | 6  |
| 7  | 7  | 7  | 7  | 7  | 7  | 7  | 7  | 7  | 7  |
| 8  | 8  | 8  | 8  | 8  | 8  | 8  | 8  | 8  | 8  |
| 9  | 9  | 9  | 9  | 9  | 9  | 9  | 9  | 9  | 9  |
| 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

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# Improving upon the current standard of predictive analytics in the ICU

## 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

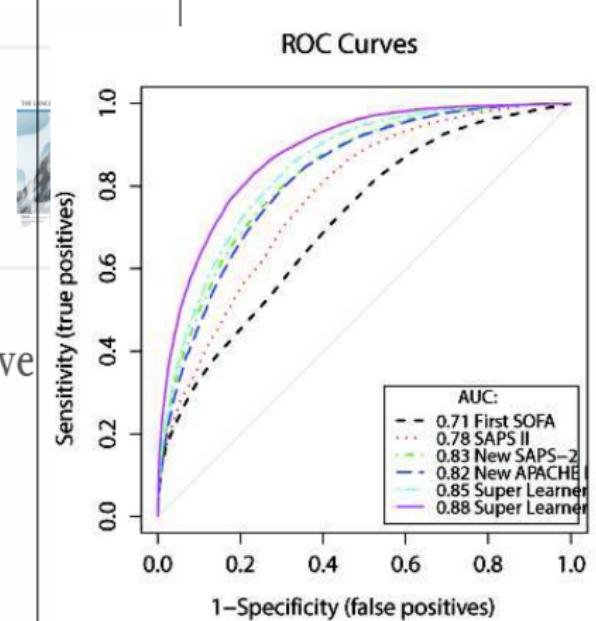
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## Cross-validation is optimal for selection among estimators

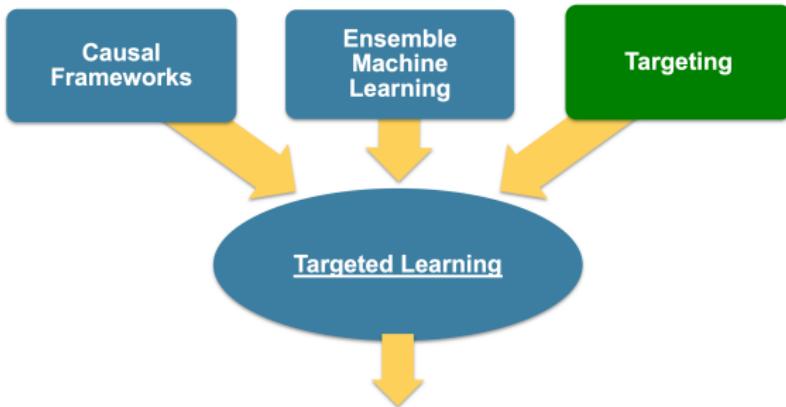
- We established an oracle inequality for the cross-validation selector among a collection of candidate estimators (e.g, van der Laan, Dudoit, 03, van der Vaart et al 06).
- Oracle selector chooses the estimator closest to the true function w.r.t. loss-based dissimilarity.
- It establishes that the loss-based dissimilarity with truth of the cross-validated selected estimator divided by the loss-based dissimilarity of the oracle selected estimator converges to 1, even as the number of candidate estimators converges to infinity as a polynomial in sample size.
- Only condition is that loss-function is uniformly bounded.

## Highly Adaptive Lasso (HAL)

- This is a machine learning algorithm that estimates functionals (e.g outcome regression and propensity score) by approximating them with linear model in **tensor product of spline basis functions** and constraining the  $L_1$ -norm of the coefficients.
- Can be computed with **Lasso**-software implementations.
- Guaranteed to converge to truth at rate  $n^{-1/3}$  (up till  $\log n$ -factors) in sample size  $n$ .
- When used in super-learner library, TMLE (targeted learning) is guaranteed **consistent, (double robust) asymptotically normal and efficient**: one only needs to assume *strong positivity assumption*.

# Outline

# Targeted Learning



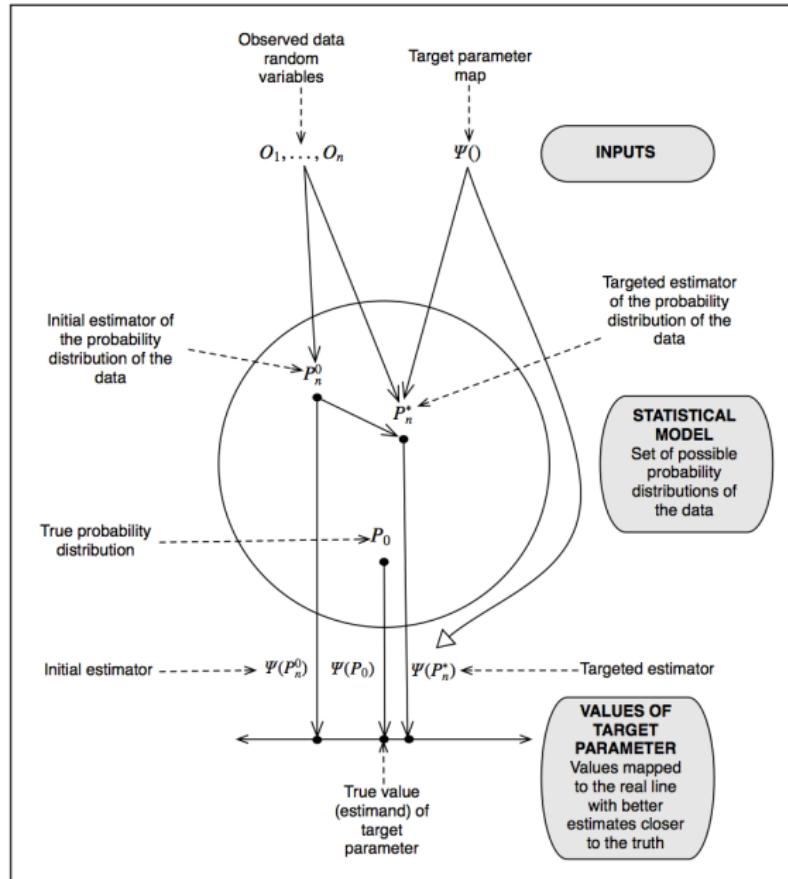
Better (more precise) answers to causal (actionable) questions with  
accurate quantification of uncertainty (signal from noise)

DIA

## Targeted Update of Machine Learning

- Don't try to do a good job for all questions at once.
  - Focus estimation where it matters most for question at hand.
- ➊ Less bias (closer to truth).
  - ➋ Sampling distribution approximately normal, more accurate quantification of uncertainty.

# Targeted Minimum Loss Based Estimation (TMLE)



# Targeted Minimum Loss Based Estimation (TMLE)

- Super learning provides an initial estimator  $\mathbf{P}_n$  of stochastic system  $P_0$ .
- Determine mathematically the fluctuation strategy (least favorable submodel)  $\mathbf{P}_{n,\epsilon}$  of the super-learner fit  $\mathbf{P}_n$  with tuning parameter  $\epsilon$  **so that a small change in  $\epsilon$  corresponds with a maximal small change** in estimated answer  $\Psi(\mathbf{P}_{n,\epsilon})$  to query  $\Psi(P_0)$ : i.e., score equals canonical gradient/**efficient influence curve**  $D^*(\mathbf{P}_n)$ .
- Determine the optimal amount  $\epsilon_n$  of fluctuation based on the data (e.g., maximum likelihood estimation).
- The resulting update  $\mathbf{P}_n^* = \mathbf{P}_{n,\epsilon_n}$  of the initial estimator of stochastic system is the TMLE of  $P_0$  and it implies the TMLE  $\Psi(\mathbf{P}_n^*)$  of the answer to query.
- Thanks to TMLE-update, TMLE solves optimal score equation  $P_n D^*(\mathbf{P}_n^*) \approx 0$ , and is asymptotically normally distributed around true answer to query with minimal asymptotic variance.

## Three general methods for efficient estimation in literature

Three general methods result in asymptotically efficient estimators, given good initial estimator  $\mathbf{P}_n$  of data distribution  $P_0$ , using canonical gradient  $D^*(P)$  of target estimand as ingredient:

- **One-step estimator:**  $\psi_n^1 = \Psi(\mathbf{P}_n) + P_n D^*(\mathbf{P}_n)$ .
- **Estimating equation estimator:** Assume estimating function representation  $D^*(P) = D^*(\psi, \eta(P))$ ; let  $\psi_n$  solution of  $P_n D^*(\psi, \eta(\mathbf{P}_n)) = 0$ .
- **TMLE:**  $\mathbf{P}_{n,\epsilon}$  least favorable submodel through initial  $\mathbf{P}_n$ ;  $\epsilon_n$  MLE;  $P_n^* = \mathbf{P}_{n,\epsilon_n}$ ; TMLE is  $\Psi(P_n^*)$ .
- TMLE is general method that updates initial  $\mathbf{P}_n$  into improved fit  $\mathbf{P}_n^*$  that solves **user supplied set of equations**  $P_n D(\mathbf{P}_n^*) \approx 0$ , allowing for various additional statistical properties beyond asymptotic efficiency.

Each one of the methods has a sample splitting analogue removing Donsker class condition.

## Objective simulation with HAL-TMLE of ATE

We repeatedly sampled random data generating mechanisms and simulated samples of size  $n \in \{100, 500, 1000, 2000\}$  for a total of 25,000 different data generating mechanisms of  $(W, A, Y)$ .

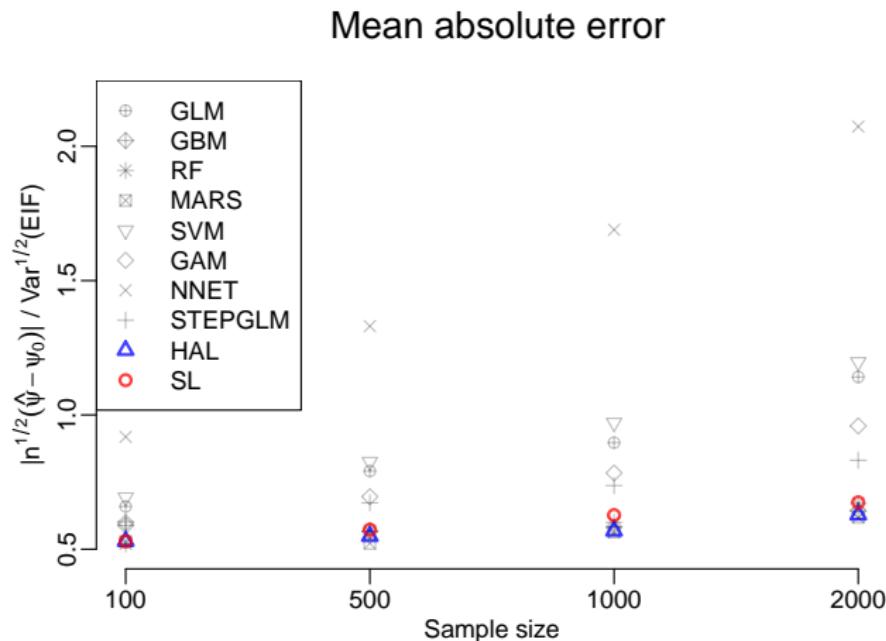
We computed TMLEs of the ATE based on different estimators of  $E_0(Y | A, W)$  and  $P_0(A = 1 | W)$ .

- GLM, Bayes GLM, stepwise GLM (AIC), stepwise GLM (p-value), stepwise GLM with two-way interactions, intercept-only GLM, GAM, GBM\*, random forest\*, linear SVM\*, neural nets\*, regression trees\*, HAL
- Super Learner (based on these algorithms)
- \* = tuning parameters selected via cross-validation

Estimators compared on their absolute error (relative to best achievable SE) and coverage probability of 95% oracle confidence intervals.

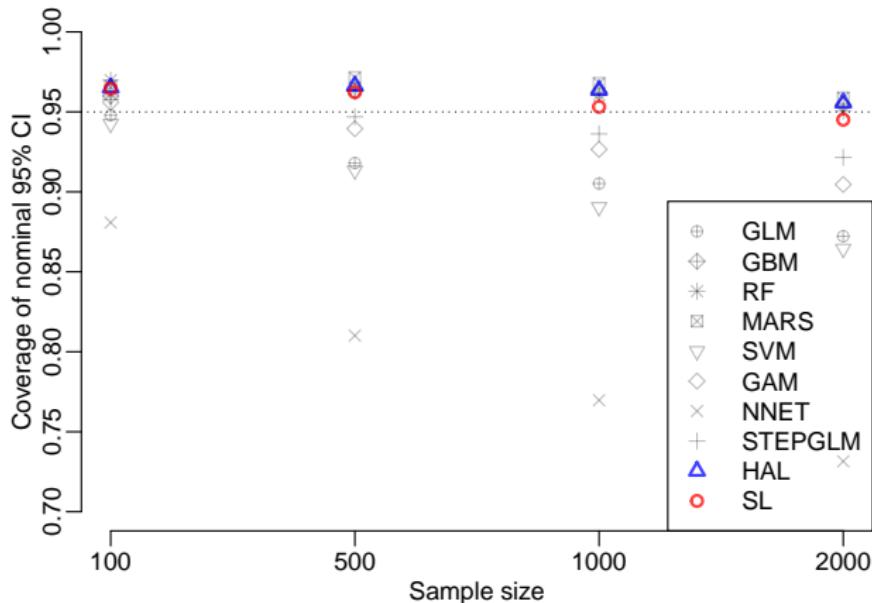
# Results – absolute error by sample size

HAL-TMLE exhibited excellent accuracy relative to competitors.



## Results – coverage by sample size

HAL-TMLE achieves approximate Normality in reasonable sample sizes.

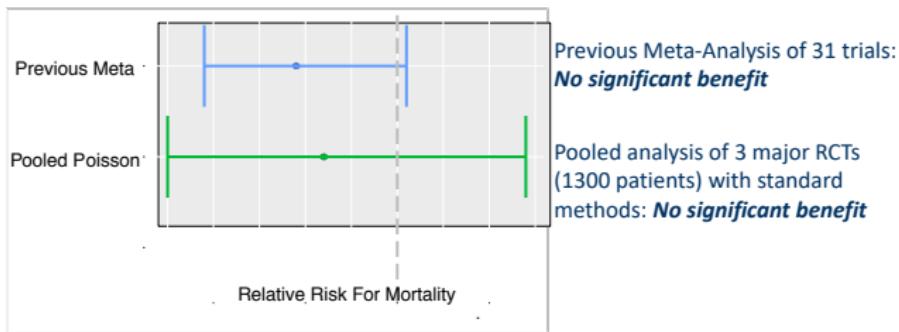


# Outline

## 1

## Better, cheaper trials

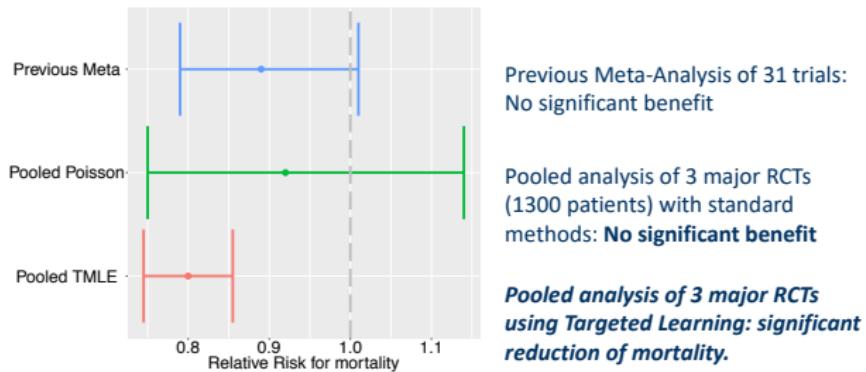
Do corticosteroids reduce mortality for adults with septic shock?



Pirracchio 2016

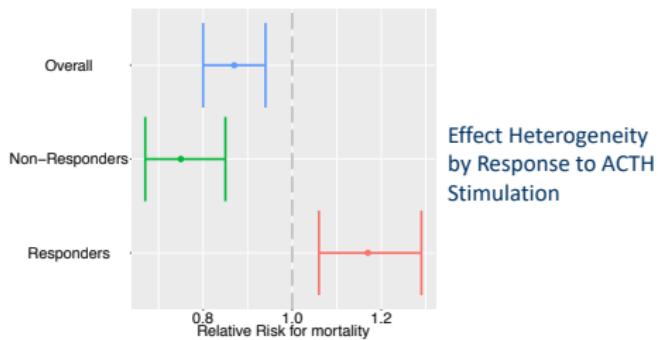
## Better, cheaper trials

Do corticosteroids reduce mortality for adults with septic shock?



## Not just is there an effect, but for whom?

- In Sepsis re-analysis: Targeted Learning showed **all benefit** occurred in a key subgroup
  - Heterogeneity in patient populations one cause of inconsistent results



# Estimating the causal effect of a community-level intervention in a clustered RCT

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. Ayieko,  
J. Kabami, N. Sang, T. Liegler, G. Charmie, C.S. Camlin, V. Jain, K. Kadede,  
M. Atukunda, T. Ruel, S.B. Shade, E. Ssemmondo, D.M. Byonanebye,  
F. Mwangwa, A. Owaranaganise, W. Oolio, D. Black, K. Snyman, 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

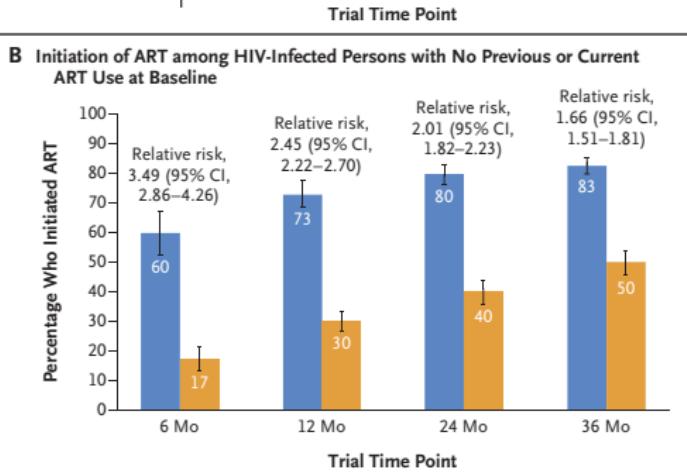
# Estimating the causal effect of a community-level intervention in a clustered RCT

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. A. J. Kabami, N. Sang, T. Liegler, G. Charmie, C.S. Camlin, V. Jain, K. Kad M. Atukunda, T. Ruel, S.B. Shade, E. Ssemmondo, D.M. Byonanyiby F. Mwangwa, A. Owaramanise, W. Oolio, D. Black, K. Snyman, R. Burg M. Getahun, J. Achando, B. Awuonda, H. Nakato, J. Kironde, S. Okir H. Thirumurthy, C. Koss, L. Brown, C. Marquez, J. Schwab, G. Lavoy, A. 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. Peters



# Increasing precision and accuracy by accounting for missing data in estimating impacts of HIV treatment program in clustered RCT

Research

JAMA | Original Investigation

## Association of Implementation of a Universal Testing and Treatment Intervention With HIV Diagnosis, Receipt of Antiretroviral Therapy, and Viral Suppression in East Africa

Maya Petersen, MD, PhD; Laura Balzer, PhD; Dalsone Kwartsima, MBChB, MPH; Norton Sang, MA; Gabriel Chamie, MD, MPH; James Ayieko, MBChB, MPH; Jane Kabami, MPH; Asiphas Owaraganise, MBChB; Teri Liegler, PhD; Florence Mwangwa, MBChB; Kevin Kadede, MA; Vivek Jain, MD, MAS; Albert Plenty, MS; Lillian Brown, MD, PhD; Geoff Lavoy; Joshua Schwab, MS; Douglas Black, BA; Mark van der Laan, PhD; Elizabeth A. Bukusi, MBChB, PhD; Craig R. Cohen, MD, MPH; Tamara D. Clark, MHS; Edwin Charlebois, MPH, PhD; Moses Kamya, MMed; Diane Havlir, MD

# Increasing precision and accuracy by accounting for missing data in estimating impacts of HIV treatment program in clustered RCT

Research

JAMA | Original Investigation

## Association of Implementation and Treatment Intervention of Antiretroviral Therapy

Table 2. Postbaseline HIV Viral Suppression in a Closed Cohort of HIV-Positive Stable Residents of 16 SEARCH Intervention Communities in Rural Uganda and Kenya Who Were Diagnosed At or Before Baseline (n = 7108)\*

| Baseline Diagnosis, Treatment, and Suppression Status    | No. of HIV-Positive Residents (%) <sup>a</sup> | Follow-up Year 1                                                                                      |                                              | Follow-up Year 2                                                                                      |                                              |
|----------------------------------------------------------|------------------------------------------------|-------------------------------------------------------------------------------------------------------|----------------------------------------------|-------------------------------------------------------------------------------------------------------|----------------------------------------------|
|                                                          |                                                | No. of Residents With Viral Suppression/Total No. of Residents With Measured HIV RNA (%) <sup>a</sup> | Adjusted Proportion, % (95% CI) <sup>a</sup> | No. of Residents With Viral Suppression/Total No. of Residents With Measured HIV RNA (%) <sup>a</sup> | Adjusted Proportion, % (95% CI) <sup>a</sup> |
| Overall                                                  | 7108 (100)                                     | 4682/5578 (83.9)                                                                                      | 79.7 (78.7-80.8)                             | 4602/5215 (88.2)                                                                                      | 83.8 (82.8-84.9)                             |
| Newly diagnosed (HIV RNA≥500 copies/mL)                  | 2080 (29.3)                                    | 963/1321 (72.9)                                                                                       | 62.8 (60.4-65.2)                             | 965/1205 (80.1)                                                                                       | 68.8 (66.4-71.2)                             |
| Previously diagnosed with no ART (HIV RNA≥500 copies/mL) | 990 (13.9)                                     | 649/812 (79.9)                                                                                        | 78.1 (75.3-80.8)                             | 685/778 (88.0)                                                                                        | 86.5 (84.2-88.8)                             |
| Previous or current ART                                  | 4038 (56.8)                                    | 3070/3445 (89.1)                                                                                      | 88.8 (87.7-89.9)                             | 2952/3232 (91.3)                                                                                      | 90.5 (89.4-91.6)                             |
| HIV RNA not measured                                     | 1063 (15.0)                                    | 732/846 (86.5)                                                                                        | 86.6 (84.3-88.9)                             | 685/779 (87.9)                                                                                        | 87.2 (84.9-89.5)                             |
| HIV RNA≥500 copies/mL                                    | 426 (6.0)                                      | 175/355 (49.3)                                                                                        | 49.5 (44.2-54.7)                             | 204/325 (62.8)                                                                                        | 62.2 (57.2-67.2)                             |
| HIV RNA<500 copies/mL                                    | 2549 (35.9)                                    | 2163/2244 (96.4)                                                                                      | 96.3 (95.6-97.1)                             | 2063/2128 (96.9)                                                                                      | 96.8 (96.0-97.6)                             |

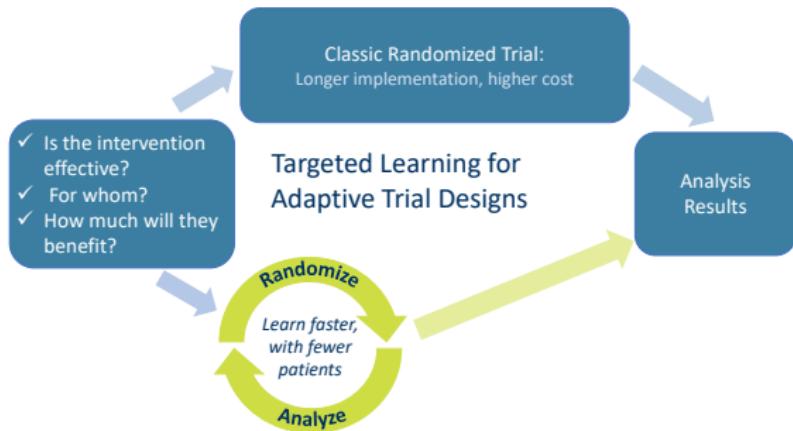
Maya Petersen, MD, PhD; Laura Balzer, PhD; Dalsone Kwasimba, MBChB, MPH; Norton Sang, MA; Gabriel Chamie, MD, MPH; James Ayleko, MBChB, MPH; Jane Kabami, MPH; Asiphas Owaraganise, MBChB; Teri Liegler, PhD; Florence Mwangwa, MBChB; Kevin Kadede, MA; Vivek Jain, MD, MAS; Albert Plenty, MS; Lillian Brown, MD, PhD; Geoff Lavoy; Joshua Schwab, MS; Douglas Black, BA; Mark van der Laan, PhD; Elizabeth A. Bukusi, MBChB, PhD; Craig R. Cohen, MD, MPH; Tamara D. Clark, MHS; Edwin Charlebois, MPH, PhD; Moses Kamya, MMed; Diane Havlir, MD



# Outline

# Robust estimation and inference for sequential designs adapting intervention allocation probabilities based on learning from past

## Optimal intervention allocation: “Learn as you go”



# Outline

# General Longitudinal Data Structure for Complex Observational Studies

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,

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

$A_1(t)$  = Indicator of being treated at time  $t$

$A_2(t)$  = Indicator of being right-censored at time  $t$

$Y(t)$  = Indicator of observing a failure by time  $t$

$L(t)$  Vector of time-dependent measurements

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

# Comparing strategies for diabetes treatment intensification in Comparative Effectiveness Research (CER) study

- Data extracted from diabetes registries of 7 HMO research network sites: Kaiser Permanente, Group Health Cooperative, HealthPartners.
- Enrollment period: Jan 1<sup>st</sup> 2001 to Jun 30<sup>th</sup> 2009
- Enrollment criteria: past A1c < 7% (glucose level) while on 2+ oral agents or basal insulin and  $7\% \leq \text{latest A1c} \leq 8.5\%$  (study entry when glycemia was no longer reined in)

Longitudinal data:

- Follow-up til the earliest of Jun 30<sup>th</sup> 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.

# Comparing strategies for diabetes treatment intensification in Comparative Effectiveness Research (CER) study

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,<sup>a\*†</sup> Julie A. Schmittiel<sup>a</sup> and  
Mark J. van der Laan<sup>b</sup>

# Comparing strategies for diabetes treatment intensification in Comparative Effectiveness Research (CER) study

Statistics  
in Medicine

Research Article

Received 24 May 2013,

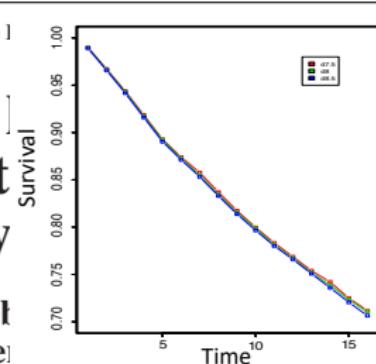
Accepted 5 January 2014

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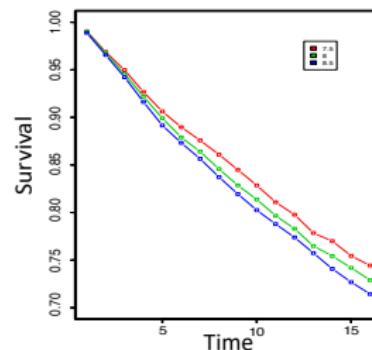
(wileyonlinelibrary.com)

Targeted  
comparat  
time-vary

Romain Neugeb  
Mark J. van de



**Standard methods:** No benefit to more aggressive intensification strategy



**Targeted Learning:** More aggressive intensification protocols result in better outcomes

# Estimating the cumulative, long-term impacts of environmental exposures

ORIGINAL ARTICLE

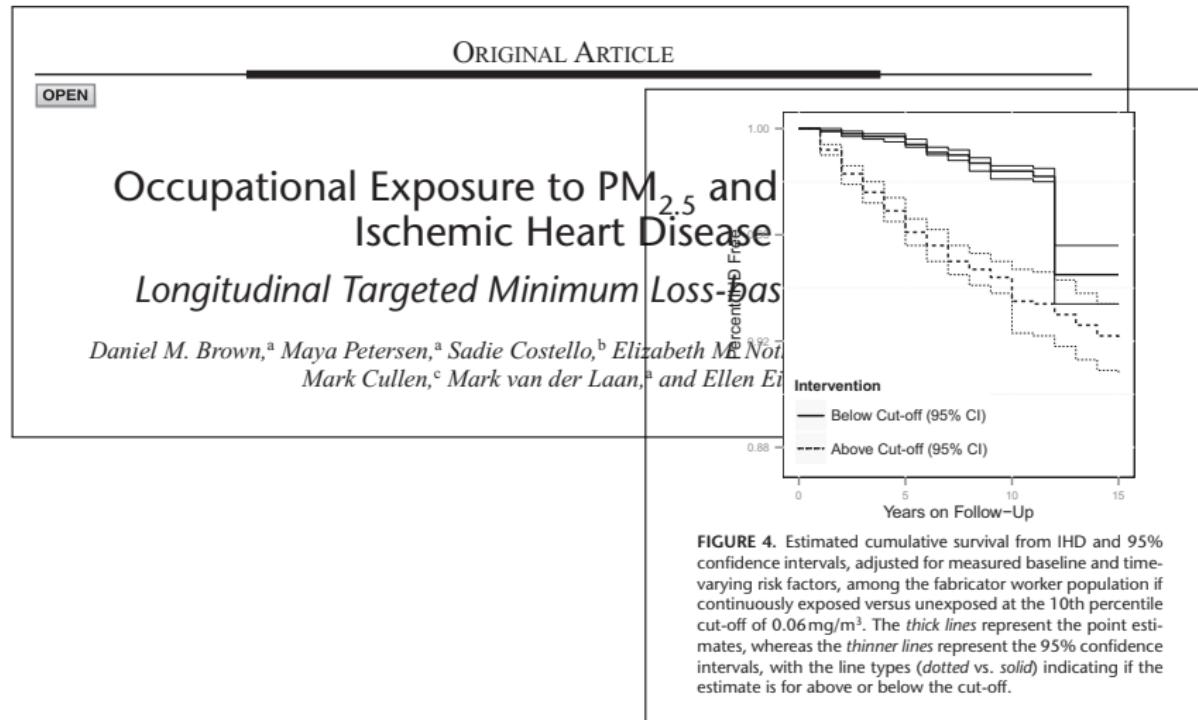
OPEN

## Occupational Exposure to PM<sub>2.5</sub> and Incidence of Ischemic Heart Disease

*Longitudinal Targeted Minimum Loss-based Estimation*

Daniel M. Brown,<sup>a</sup> Maya Petersen,<sup>a</sup> Sadie Costello,<sup>b</sup> Elizabeth M. Noth,<sup>b</sup> Katherine Hammond,<sup>b</sup> Mark Cullen,<sup>c</sup> Mark van der Laan,<sup>a</sup> and Ellen Eisen<sup>b</sup>

# Estimating the cumulative, long-term impacts of environmental exposures



# Estimating the impact of genetic polymorphisms on the efficacy of malaria vaccine on the time to infection

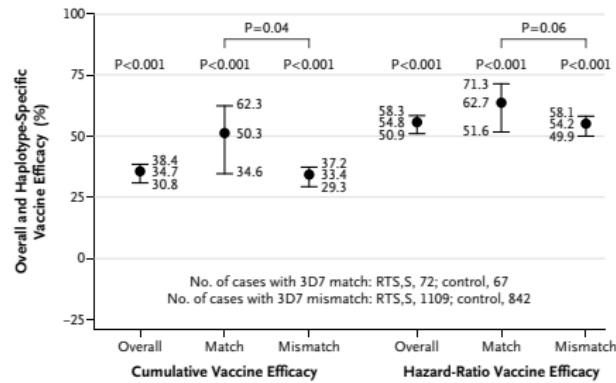
The NEW ENGLAND JOURNAL of MEDICINE

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, M.K. Connolly, U. D'Alessandro, C. Dobaño, S. Gesase, B. Greenwood, J. Grimesby, 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. Molet, E.L. Moss, P. Njuguna, C.F. Ockenhouse, B. Ragama Ogutu, W. Otieno, L. Otieno, K. Otieno, S. Owusu-Agyei, D.J. Park, K. Pellé, 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

### D Cumulative and Hazard-Ratio Vaccine Efficacy



# Outline

## Inference with TMLE

- TMLE is **asymptotically linear with influence curve the canonical gradient**, so that Wald-type confidence intervals are based on estimating variance of its influence curve.
- The simple sample variance of influence curve can underestimate the variance if initial estimator is very adaptive or lack of positivity.
- Robust estimation of this variance by using sample splitting, or TMLE plug-in estimator corrects for this finite sample bias, and can be important (Tran et al, 19).
- One can also use the nonparametric bootstrap if one uses HAL as initial estimator (Cai, vdL, 19), resulting in better finite sample coverage by also picking up higher order behavior.

# Outline

## Advancing the vanilla TMLE: C-TMLE and extra targeting

- The least favorable parametric fluctuation model often depends on nuisance parameter (e.g., propensity score).
- C-TMLE targets estimation of this nuisance parameter based on criterion how well TMLE fits target estimand.
- Important for observational studies (vdL, Gruber, 2010 etc).
- By adding additional parameters to fluctuation model TMLE solves additional score equations that can be chosen to target second order remainder, and thereby improve finite sample performance.
- This has resulted in higher-order TMLE, double robust inference TMLE, etc (vdL, 14, Benkeser et al., Carone et al).

# Outline

# Preparing Statistical Analysis Plan based on TMLE

- Prior data or **outcome blind** data can be used to decide on **target estimand** supported by data.
- Prior data can also be used to set up **realistic simulation** to benchmark *specifications* of TMLE implementation, where benchmarks includes confidence interval coverage and type I error control.
- These **specifications of TMLE** include deciding on library of SL; sample splitting version; C-TMLE for nuisance parameter; adaptive truncation; TMLE-update step (e.g, possible extra targeting).
- Once one commits, it freezes the **a priori-specified estimator** that can be submitted as part of SAP for FDA approval.

# Outline

## tlverse - Targeted Learning software ecosystem in R

- A curated collection of R packages for Targeted Learning
- Shares a consistent underlying philosophy, grammar, and set of data structures
- Open source
- Designed for generality, usability, and extensibility
- Microwave dinners for machine learning

# tlverse outreach to train and support practitioners

- May 2019 - Atlantic Causal Inference Conference (ACIC) Workshop
- June 2019 - tlverse book →
- October 2019 - University of Pittsburgh School of Public Health Workshop
- November 2019 - Bill & Melinda Gates Foundation Workshop
- December 2019 - Deming Conference on Applied Statistics Workshop



- February 2020 - Conference on Statistical Practice (CSP) Workshop
- March 2020 - Alan Turing Institute Workshop

# Outline

## Concluding Remarks

- **Targeted Learning** *optimally estimates* the causal impact of an intervention on an outcome for complex real-world data.
- It integrates **causal inference, machine learning, statistical theory**.
- Targeted Learning learns better answers to causal, actionable questions which result in improved policy, treatments, etc.
- The estimate is accompanied with accurate quantification of uncertainty such as **confidence interval and p-value**.
- We have developed an ongoing targeted learning software environment `tlverse` with growing number of tools and tutorials.

# Structural Causal Model, Causal Quantity, Identification

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**Deming Conference on Applied Statistics**

December 4-6 2019, Atlantic City NJ

# Outline

- 1 The model
- 2 Causal model
- 3 Causal graphs
- 4 Causal target parameter
- 5 Interventions
- 6 Counterfactuals
- 7 Identifiability
- 8 Commit to a statistical model and target parameter
- 9 Positivity assumption
- 10 Target parameter

## Statistical model

We are considering the general case that one observed  $n$  i.i.d. copies of a random variable  $O$  with probability distribution  $P_0$ .

The data-generating distribution  $P_0$  is also known to be an element of a statistical model  $\mathcal{M}$ :  $P_0 \in \mathcal{M}$ .

A **statistical model**  $\mathcal{M}$  is the set of possible probability distributions for  $P_0$ ; it is a collection of probability distributions.

If all we know is that we have  $n$  i.i.d. copies of  $O$ , this can be our statistical model, which we call a nonparametric statistical model

## Statistical model augmented with causal assumptions

A statistical model can be augmented with additional (nontestable causal) assumptions, allowing one to enrich the interpretation of  $\Psi(P_0)$ .

This does not change the statistical model.

We refer to the statistical model augmented with a possibly additional assumptions as the **model**.

- Causal assumptions made by the structural causal model (SCM)

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## Defining the SCM

- We first specify a set of endogenous variables  $X = (X_j : j)$ .
- Endogenous variables are those variables for which the SCM will state that it is a (typically unknown) deterministic function of some of the other endogenous variables and an exogenous error.
- Typically, the endogenous variables  $X$  include the observables  $O$ , but might also include some non-observables that are meaningful and important to the scientific question of interest. Perhaps there was a variable you did not measure, but would have liked to, and it plays a crucial role in defining the scientific question of interest. This variable would then be an unobserved endogenous variable.

## Defining the SCM

- In a very simple example, we might have  $j = 1, \dots, J$ , where  $J = 3$ . Thus,  $X = (X_1, X_2, X_3)$ .
- We can rewrite  $X$  as  $X = (W, A, Y)$  if we say  $X_1 = W$ ,  $X_2 = A$ , and  $X_3 = Y$ .
- Let  $W$  represent the set of baseline covariates for a subject,  $A$  the treatment or exposure, and  $Y$  the outcome.
- All the variables in  $X$  are observed.

## Defining the SCM

- For each endogenous variable  $X_j$  one specifies the parents of  $X_j$  among  $X$ , denoted  $Pa(X_j)$ .
- The specification of the parents might be known by the time ordering in which the  $X_j$  were collected over time: the parents of a variable collected at time  $t$  could be defined as the observed past at time  $t$ .
- We can see the time ordering involved in this process: the baseline covariates occurred before the exposure LTPA, which occurred before the outcome of death:  $W \rightarrow A \rightarrow Y$ .

## Defining the SCM

- We denote a collection of exogenous variables by  $U = (U_{X_j} : j)$ .
- These variables in  $U$  are never observed and are not affected by the endogenous variables in the model, but instead they affect the endogenous variables.
- One assumes that  $X_j$  is some function of  $Pa(X_j)$  and an exogenous  $U_{X_j}$ :

$$X_j = f_{X_j}(Pa(X_j), U_{X_j}), \quad j = 1 \dots, J.$$

- The collection of functions  $f_{X_j}$  indexed by all the endogenous variables is represented by  $f = (f_{X_j} : j)$ .
- Together with the joint distribution of  $U$ , these functions  $f_{X_j}$ , specify the data-generating distribution of  $(U, X)$  as they describe a deterministic system of structural equations (one for each endogenous variable  $X_j$ ) that deterministically maps a realization of  $U$  into a realization of  $X$ .

## Defining the SCM

- In an SCM one also refers to some of the endogenous variables as intervention variables.
- The SCM assumes that intervening on one of the intervention variables by setting their value, thereby making the function for that variable obsolete, does not change the form of the other functions.
- The functions  $f_{X_j}$  are often unspecified, but in some cases it might be reasonable to assume that these functions have to fall in a certain more restrictive class of functions.
- Similarly, there might be some knowledge about the joint distribution of  $U$ .

## Defining the SCM

- The set of possible data-generating distributions of  $(U, X)$  can be obtained by varying the structural equations  $f$  over all allowed forms, and the distribution of the errors  $U$  over all possible error distributions defines the SCM for the full-data  $(U, X)$ , i.e., the SCM is a statistical model for the random variable  $(U, X)$ .
- An example of a fully parametric SCM would be obtained by assuming that all the functions  $f_{X_j}$  are known up to a finite number of parameters and that the error distribution is a multivariate normal distribution with mean zero and unknown covariance matrix. Such parametric structural equation models are not recommended.

## Defining the SCM

The corresponding SCM for the observed data  $O$  also includes specifying the relation between the random variable  $(U, X)$  and the observed data  $O$ , so that the SCM for the full data implies a parameterization of the probability distribution of  $O$  in terms of  $f$  and the distribution  $P_U$  of  $U$ . This SCM for the observed data also implies a statistical model for the probability distribution of  $O$ .

## Defining the SCM: Translation

We have the functions  $f = (f_W, f_A, f_Y)$  and the exogenous variables  $U = (U_W, U_A, U_Y)$ . The values of  $W$ ,  $A$ , and  $Y$  are deterministically assigned by  $U$  corresponding to the functions  $f$ . We specify our structural equation models, based on investigator knowledge, as

$$\begin{aligned} W &= f_W(U_W), \\ A &= f_A(W, U_A), \\ Y &= f_Y(W, A, U_Y), \end{aligned} \tag{1}$$

where no assumptions are made about the true shape of  $f_W$ ,  $f_A$ , and  $f_Y$ . These functions  $f$  are nonparametric as we have not put a priori restrictions on their functional form.

## Defining the SCM: Translation

- We may assume that  $U_A$  is independent of  $U_Y$ , given  $W$ , which corresponds with believing that there are no unmeasured factors that predict both  $A$  and the outcome  $Y$ : this is often called the no unmeasured confounders assumption.
- This SCM represents a semiparametric statistical model for the probability distribution of the errors  $U$  and endogenous variables  $X = (W, A, Y)$ .
- We assume that the observed data structure  $O = (W, A, Y)$  is actually a realization of the endogenous variables  $(W, A, Y)$  generated by this system of structural equations.

This now defines the SCM for the observed data  $O$ .

## Defining the SCM: Translation

We have assumed that the underlying data were generated by the following actions:

- ① Drawing unobservable  $U$  from some probability distribution  $P_U$  ensuring that  $U_A$  is independent of  $U_Y$ , given  $W$ ,
- ② Generating  $W$  as a deterministic function of  $U_W$ ,
- ③ Generating  $A$  as a deterministic function of  $W$  and  $U_A$ ,
- ④ Generating  $Y$  as a deterministic function of  $W$ ,  $A$ , and  $U_Y$ .

## Defining the SCM

- Any probability distribution of  $O$  can be obtained by selecting a particular data-generating distribution of  $(U, X)$  in this SCM.
- Thus, the statistical model for  $P_0$  implied by this SCM is a nonparametric model.
- As a consequence, one cannot determine from observing  $O$  if the assumptions in the SCM contradict the data.
- One states that the SCM represents a set of nontestable causal assumptions we have made about how the data were generated in nature.

# Outline

- 1 The model
- 2 Causal model
- 3 Causal graphs
- 4 Causal target parameter
- 5 Interventions
- 6 Counterfactuals
- 7 Identifiability
- 8 Commit to a statistical model and target parameter
- 9 Positivity assumption
- 10 Target parameter

# Causal Graphs

$U_W[d] U_A[d]$

$W[r] @/_/[rrd] A[dr] U_Y[dl]$   
Y

**Figure:** A possible causal graph for (1).

## Causal Graphs

$U_W[d] @<--> @/ \cdot 5pc / [r] @<--> @/ \cdot 6pc / [drrr] U_A[d] @<--> @/ \cdot 1pc / [$

W [r] @/\_/[rrd] A[dr] U\_Y[dl]  
Y

Figure: A causal graph for (1) with no assumptions on the distribution of  $P_U$

## Causal Graphs

$U_W[d] @<--> @/2.5pc/[drrr] U_A[d]$   $U_W[d] @<--> @/5pc/[r] U_A[d]$

$W[r] @/_/[rrd] A[dr]$   $U_Y[dl] W[r] @/_/[rrd] A[dr]$   $U_Y[dl]$

Y      Y

Figure: Causal graphs for (1) with various assumptions about the distribution of  $P_U$

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## Defining the Causal Target Parameter

We can explicitly define the target parameter of the probability distribution  $P_0$  as some function of  $P_0$ :  $\Psi(P_0)$ .

We are interested in estimating a parameter  $\Psi(P_0)$  of the probability distribution  $P_0 \in \mathcal{M}$ , which is known to be an element of a non-parameteric (or semiparametric) statistical model  $\mathcal{M}$ .

## Defining the Causal Target Parameter

- Formally, we denote the SCM for the full-data  $(U, X)$  by  $\mathcal{M}^F$ , a collection of possible  $P_{U,X}$  as described by the SCM.
- In other words,  $\mathcal{M}^F$ , a model for the full data, is a collection of possible distributions for the underlying data  $(U, X)$ .
- $\Psi^F$  is a mapping applied to a  $P_{U,X}$  giving  $\Psi^F(P_{U,X})$  as the target parameter of  $P_{U,X}$ .

## Defining the Causal Target Parameter

- This mapping needs to be defined for each  $P_{U,X}$  that is a possible distribution of  $(U, X)$ , given our assumptions coded by the posed SCM.
- We state  $\Psi^F : \mathcal{M}^F \rightarrow \mathbb{R}^d$ , where  $\mathbb{R}^d$  indicates that our parameter is a vector of  $d$  real numbers.
- The SCM  $\mathcal{M}^F$  consists of the distributions indexed by the deterministic function  $f = (f_{X_j} : j)$  and distribution  $P_U$  of  $U$ , where  $f$  and this joint distribution  $P_U$  are identifiable from the distribution of the full-data  $(U, X)$ .
- Thus the target parameter can also be represented as a function of  $f$  and the joint distribution of  $U$ .

## Defining the Causal Target Parameter

- Recall our example with data structure  $O = (W, A, Y)$  and SCM given in (1) with no assumptions about the distribution  $P_U$ .
- We can define  $Y_a = f_Y(W, a, U_Y)$  as a random variable corresponding with intervention  $A = a$  in the SCM.
- The marginal probability distribution of  $Y_a$  is thus given by

$$P_{U,X}(Y_a = y) = P_{U,X}(f_Y(W, a, U_Y) = y).$$

- The causal effect of interest for a binary  $A$  (suppose it is the causal risk difference) could then be defined as a parameter of the distribution of  $(U, X)$  given by

$$\Psi^F(P_{U,X}) = E_{U,X} Y_1 - E_{U,X} Y_0.$$

- In other words,  $\Psi^F(P_{U,X})$  is the difference of marginal means of counterfactuals  $Y_1$  and  $Y_0$ .

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## Interventions on the causal model

- We will define our causal target parameter as a parameter of the distribution of the data  $(U, X)$  under an intervention on one or more of the structural equations in  $f$ .
- The intervention defines a random variable that is a function of  $(U, X)$ , so that the target parameter is  $\Psi^F(P_{U,X})$ .
- Intervening on the system defined by our SCM describes the data that would be generated from the system at the different levels of our intervention variable (or variables).

## Interventions

By assumption, intervening and changing the functions  $f_{X_j}$  of the intervention variables does not change the other functions in  $f$ . With the SCM given in (1) we can intervene on  $f_A$  and set  $a = 1$ :

$$\begin{aligned}W &= f_W(U_W), \\a &= 1, \\Y_1 &= f_Y(W, 1, U_Y).\end{aligned}$$

We can also intervene and set  $a = 0$ :

$$\begin{aligned}W &= f_W(U_W), \\a &= 0, \\Y_0 &= f_Y(W, 0, U_Y).\end{aligned}$$

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## Counterfactuals

- We would ideally like to see each individual's outcome at all possible levels of exposure  $A$ . The study is only capable of collecting  $Y$  under one exposure, the exposure the subject experiences.
- $Y_a$  represents the outcome that would have been observed under this system for a particular subject under exposure  $a$ .
- In our example, for each realization  $u$ , which might correspond with an individual randomly drawn from some target population, by intervening on (1), we can generate so-called counterfactual outcomes  $Y_1(u)$  and  $Y_0(u)$ .

## Counterfactuals

- These counterfactual outcomes are implied by our SCM; they are consequences of it.
- That is,  $Y_0(u) = f_Y(W, 0, u_Y)$ , and  $Y_1(u) = f_Y(W, 1, u_Y)$ , where  $W = f_W(u_W)$  is also implied by  $u$ .
- The random counterfactuals  $Y_0 = Y_0(U)$  and  $Y_1 = Y_1(U)$  are random through the probability distribution of  $U$ .
- For example, the expected outcome of  $Y_1$  is the mean of  $Y_1(u)$  with respect to the probability distribution of  $U$ . Our target parameter is a function of the probability distributions of these counterfactuals:  
 $E_0 Y_1 - E_0 Y_0$ .

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## Establishing Identifiability

Are the assumptions we have already made enough to express the causal parameter of interest as a parameter of the probability distribution  $P_0$  of the observed data?

We want to be able to write  $\Psi^F(P_{U,X,0})$  as  $\Psi(P_0)$  for some parameter mapping  $\Psi$ .

Since the true probability distribution of  $(U, X)$  can be any element in the SCM  $\mathcal{M}^F$ , and each such choice  $P_{U,X}$  implies a probability distribution  $P(P_{U,X})$  of  $O$ , this requires that we show that  $\Psi^F(P_{U,X}) = \Psi(P(P_{U,X}))$  for all  $P_{U,X} \in \mathcal{M}^F$ .

## Establishing Identifiability

This step involves establishing possible additional assumptions on the distribution of  $U$ , or sometimes also on the deterministic functions  $f$ , so that we can identify the target parameter from the observed data distribution.

Thus, for each probability distribution of the underlying data  $(U, X)$  satisfying the SCM with these possible additional assumptions on  $P_U$ , we have  $\Psi^F(P_{U,X}) = \Psi(P(P_{U,X}))$  for some  $\Psi$ .

$O$  is implied by the distribution of  $(U, X)$ , such as  $O = X$  or  $O \subset X$ , and  $P = P(P_{X,U})$ , where  $P(P_{U,X})$  is a distribution of  $O$  implied by  $P_{U,X}$ .

## Establishing Identifiability

Let us denote the resulting full-data SCM by  $\mathcal{M}^{F*} \subset \mathcal{M}^F$  to make clear that possible additional assumptions were made that were driven purely by the identifiability problem, not necessarily reflecting reality.

## Establishing Identifiability

Theorems exist that are helpful to establish such a desired identifiability result. For example, if  $O = (W, A, Y)$ , and the distribution of  $U$  is such that,  $A$  is independent of  $Y_1$ , given  $W$ , then the well-known g-formula expresses the distribution of  $Y_1$  in terms of the distribution of  $O$ :

$$P(Y_1 = y) = \int_w P(Y = y \mid A = 1, W = w) dP_W(w).$$

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## Commit to a Statistical Model and Target Parameter

The identifiability result provides us with a purely statistical target parameter  $\Psi(P_0)$  on the distribution  $P_0$  of  $O$ .

The full-data model  $\mathcal{M}^{F^*}$  implies a statistical observed data model  $\mathcal{M} = \{P(P_{X,U}) : P_{X,U} \in \mathcal{M}^{F^*}\}$  for the distribution  $P_0 = P(P_{U,X,0})$  of  $O$ .

This now defines a target parameter  $\Psi : \mathcal{M} \rightarrow \mathbb{R}^d$ .

## Commit to a Statistical Model and Target Parameter

The statistical observed data model for the distribution of  $O$  might be the same for  $\mathcal{M}^F$  and  $\mathcal{M}^{F*}$ .

If not, then one might consider extending the  $\Psi$  to the larger statistical observed data model implied by  $\mathcal{M}^F$ , such as possibly a fully nonparametric model allowing for all probability distributions.

If the more restricted SCM holds, our target parameter would still estimate the target parameter, but one now also allows the data to contradict the more restricted SCM based on additional doubtful assumptions.

## Commit to a Statistical Model and Target Parameter

The causal risk difference in our simple example, in terms of the corresponding statistical parameter  $\Psi(P_0)$ :

$$\begin{aligned}\Psi^F(P_{U,x,0}) &= E_0 Y_1 - E_0 Y_0 \\ &= E_0[E_0(Y | A = 1, W) - E_0(Y | A = 0, W)] \\ &\equiv \Psi(P_0)\end{aligned}$$

where the outer expectation in the definition of  $\Psi(P_0)$  is the mean across the strata for  $W$ .

## Commit to a Statistical Model and Target Parameter

This identifiability result for the additive causal effect as a parameter of the distribution  $P_0$  of  $O$  required making the randomization assumption stating that  $A$  is independent of the counterfactuals  $(Y_0, Y_1)$  within strata of  $W$ .

This assumption might have been included in the original SCM  $\mathcal{M}^F$ , but, if one knows there are unmeasured confounders, then the model  $\mathcal{M}^{F*}$  would be more restrictive by enforcing this “known to be wrong” randomization assumption.

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## Positivity

Another required assumption is that  $P_0(A = 1, W = w) > 0$  and  $P_0(A = 0, W = w) > 0$  are positive for each possible realization  $w$  of  $W$ . Without this assumption, the conditional expectations of  $Y$  in  $\Psi(P_0)$  are not well defined. This positivity assumption is also called the experimental treatment assignment (ETA) assumption.

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## Target Parameter

To be very explicit about how this parameter corresponds with mapping  $P_0$  into a number:

$$\begin{aligned}\Psi(P_0) &= \sum_w \left[ \sum_y y P_0(Y = y \mid A = 1, W = w) \right. \\ &\quad \left. - \sum_y y P_0(Y = y \mid A = 0, W = w) \right] P_0(W = w),\end{aligned}$$

where

$$P_0(Y = y \mid A = a, W = w) = \frac{P_0(W = w, A = a, Y = y)}{\sum_y P_0(W = w, A = a, Y = y)}$$

is the conditional probability distribution of  $Y = y$ , given  $A = a, W = w$ , and

$$P_0(W = w) = \sum_{y,a} P_0(Y = y, A = a, W = w)$$

is the marginal probability distribution of  $W = w$ .

## Interpretation of the Target Parameter

The observed data parameter  $\Psi(P_0)$  can be interpreted in two possibly distinct ways:

- ①  $\Psi(P_0)$  with  $P_0 \in \mathcal{M}$  augmented with the truly reliable additional nonstatistical assumptions that are known to hold (e.g.,  $\mathcal{M}^F$ ). This may involve bounding the deviation of  $\Psi(P_0)$  from the desired target causal effect  $\Psi^F(P_{U,x,0})$  under a realistic causal model  $\mathcal{M}^F$  that is not sufficient for the identifiability of this causal effect.
- ② The truly causal parameter  $\Psi^F(P_{U,x}) = \Psi(P_0)$  under the more restricted SCM  $\mathcal{M}^{F*}$ , thereby now including all causal assumptions that are needed to make the desired causal effect identifiable from the probability distribution  $P_0$  of  $O$ .

## Example target parameter: Average causal effect

Causal risk difference:

$$\begin{aligned}\Psi(P_0) &= E_0[E_0(Y | A = 1, W) - E_0(Y | A = 0, W)] \\ &= E_0 Y_1 - E_0 Y_0\end{aligned}$$

## Example target parameter: Average Causal Effect Among the Treated

Consider the following modified system of structural equations:

$W = f_W(U_W)$ ,  $A = f_A(W, U_A)$ ,  $A^* = 1$ ,  $Y_1 = f_Y(W, A^*, U_Y)$ . Similarly, we can define this for  $A^* = 0$ . We can now define the causal quantity (i.e.,  $\Psi^F(P_{U,X})$ )

$$E_0(Y_1 - Y_0 \mid A = 1).$$

This is called the effect among the treated. Under RA it is identified by:

$$E_0(Y_1 - Y_0 \mid A = 1) = E_0(E_0(Y \mid A = 1, W) - E_0(Y \mid A = 0, W) \mid A = 1).$$

Let  $\bar{Q}_0(A, W) = E_0(Y \mid A, W)$  and  $g_0(a \mid W) = P_0(A = a \mid W)$ . Then,

$$E(Y_1 - Y_0 \mid A = 1) = \int_w \{\bar{Q}_0(1, w) - \bar{Q}_0(0, w)\} \frac{g_0(1 \mid w)}{P_0(A = 1)} dP_0(w).$$

Only positivity assumption needed is  $P(A = 1 \mid W) > 0$ .

## Example: Average treatment effect among compliers, using an instrument

- Suppose that we observe  $(W, R, A, Y)$ , where  $W$  is covariate vector,  $R$  is randomized treatment (instrument),  $A$  is actual treatment the subject took, and  $Y$  is outcome.
- This corresponds with a structural equation model  $W = f_W(U_W)$ ;  $R = f_R(W, U_R)$ ;  $A = f_A(W, R, U_A)$ ;  $Y = f_Y(W, A, U_Y)$ , assuming that the outcome is only affected by actual treatment.
- $R$  is an instrument since  $U_R$  is independent of  $(U_A, U_Y)$ , given  $W$ , i.e assignment of  $R$  is not affected by unmeasured confounders, while it strongly predicts  $A$  (strength of instrument).

- If we also assume  $P(A = 1 \mid R = 1, W) \geq P(A = 1 \mid R = 0, W)$ , then we have identification of the causal effect among the compliers

$$E(Y_1 - Y_0 \mid A_{R=1} = 1, A_{R=0} = 0)$$

by

$$\frac{E(E(Y \mid R = 1, W) - E(Y \mid R = 0, W))}{E(E(A \mid R = 1, W) - E(A \mid R = 0, W))}.$$

## Examples of Interventions: Optimal, Multiple Time-Point and Stochastic

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**Deming Conference on Applied Statistics**

December 4-6 2019, Atlantic City NJ

# Outline

1 Dynamic interventions

2 Stochastic interventions

3 Multiple time-point interventions

## Dynamic intervention

- $O = (W, A, Y)$ ,  $A$  binary treatment,  $Y$  indicator of bad outcome.
- $W = f_W(U_W)$ ;  $A = f_A(W, U_A)$ ;  $Y = f_Y(W, A, U_Y)$ .
- A dynamic intervention  $W \rightarrow d(W) \in \{0, 1\}$  is a rule that maps characteristics  $W$  of subject into a treatment decision  $A = d(W)$ .
- The counterfactual outcome under intervention  $d$  is given by  $Y_d \equiv f_Y(W, d(W), U_Y)$ .
- $EY_d$  is the mean of  $Y_d$ .

# Optimal Dynamic Intervention

The optimal rule  $W \rightarrow d_0(W)$  is defined by

$$d_0 = \arg \min_d E_0 Y_d.$$

It is given by:

$$d_0(W) = I(B_0(W) > 0),$$

where

$$B_0(W) = E_0(Y | A = 1, W) - E_0(Y | A = 0, W)$$

is the conditional additive treatment effect.

Both the rule  $d_0$  as well as its performance  $E_0 Y_{d_0}$  are quantities of interest in precision medicine.

# Outline

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## Stochastic Intervention

- Let  $G^*$  be a conditional probability distribution of  $A$ , given  $W$ .
- We could modify the structural equation model by replacing the equation  $A = f_A(W, U_A)$  by drawing  $A^* \sim G^*(\cdot | W)$ . One can also define  $A^* = d(W, U^*)$  for a rule  $d$  and random error  $U^*$ .
- This defines a counterfactual  $Y_{G^*} = f_Y(W, A^*, U_Y)$ .
- The mean outcome  $E_0 Y_{G^*}$  is the quantity of interest.

## Identification of mean outcome under stochastic intervention

- Recall  $\bar{Q}_0(A, W) = E_0(Y | A, W)$ ,  $Q_{W,0}$  is probability distribution of  $W$ .
- Under RA, it is identified by

$$E_0 Y_{G^*} = \int_{a,w} \bar{Q}_0(a, w) dG^*(a | w) dQ_{W,0}(w).$$

## Examples of Stochastic Interventions

- $A^* \sim Bernoulli(p)$  for some known  $p$ .
- $A^* \sim Bernoulli(p(W))$  for some known  $p(W)$ .
- $A^* = A + \delta$  for a deterministic rule. This corresponds with first drawing  $A$  from the treatment mechanism, and subsequently evaluating  $A + \delta$ :

$$g^*(a^* | W) = g_0(a^* - \delta | W).$$

- More generally, if  $A^* = d(A, W)$ , then

$$g^*(a^* | W) = g_0(d_W^{-1}(a^*) | W),$$

where  $d_W^{-1}$  is the inverse function of  $a \rightarrow d(a, W)$ .

## Missing and Censoring Indicators can be included in SCM as endogenous variables

- For example, suppose that our observed data structure on one unit is  $(W, A, \Delta, Y^* = \Delta Y) \sim P_0$ .
- We define structural equation model:  $W = f_W(U_W)$ ,  $A = f_A(W, U_A)$ ,  $\Delta = f_\Delta(W, A, U_\Delta)$ ,  $Y = f_Y(W, A, U_Y)$ ,  $Y^* = \Delta Y$ .
- The counterfactual  $Y_1^*$  of interest is now the one corresponding with intervention  $A = 1$  and  $\Delta = 1$ , and similarly  $Y_0^*$ .
- Under RA, the average causal effect  $E_0 Y_1^* - E_0 Y_0^*$  is identified by

$$E_0\{E_0(Y^* | A = 1, \Delta = 1, W) - E_0(Y^* | A = 0, \Delta = 1, W)\}.$$

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## Identification of post-Intervention distribution for multiple time-point interventions: G-Computation Formula

Suppose  $O = (L(0), A(0), L(1), A(1), L(2) = Y) \sim P_0$ , where  
 $A(t) = (A_1(t), \Delta(t))$  with  $A_1(t)$  treatment and  $\Delta(t)$  monitoring indicator.  
We can define an SCM:

$$\begin{aligned}L(0) &= f_{L(0)}(U_{L(0)}) \\A(0) &= f_{A(0)}(L(0), U_{A(0)}) \\L(1) &= f_{L(1)}(L(0), A(0), U_{L(1)}) \\A(1) &= f_{A(1)}(L(0), A(0), L(1), U_{A(1)}) \\Y &= f_Y(L(0), A(0), L(1), A(1), U_Y).\end{aligned}$$

Consider a stochastic intervention  $g_{A(0)}^*, g_{A(1)}^*$  on  $(A(0), A(1))$ . This defines counterfactual  $O_{g^*} = (L(0), A^*(0), L_{g^*}(1), A^*(1), L_{g^*}(2))$ .

## Identification by G-computation formula under Sequential Randomization Assumption

- Assume SRA:  $A(j)$  is independent of  $Y_{g^*}$ , given  $\bar{L}(j)$ ,  $\bar{A}(j-1)$ ,  $j = 0, 1$ .
- Let  $q_{L(j)}$  be the conditional density of  $L(j)$ , given  $\bar{L}(j-1)$ ,  $\bar{A}(j-1)$ .  
The distribution  $P_{g^*}$  of  $L_{g^*}$  is identified by the density  
 $p^{g^*} = q_{L(0)} g_{A(0)}^* q_{L(1)} g_{A(1)}^* q_{L(2)}$ :

$$\begin{aligned} p_{g^*}(o) &= q_{L(0)}(I(0)) g_{A(0)}^*(a(0) | I(0)) \\ &\quad q_{L(1)}(I(1) | I(0), a(0)) g_{A(1)}^*(a(1) | I(0), a(0), I(1)) \\ &\quad q_{L(2)}(I(2) | I(0), a(0), I(1), a(1)). \end{aligned}$$

- The existence of this density relies on conditioning events having positive probability (the positivity assumption):

$$\frac{g_{A(j)}^*(a(j) \mid \bar{L}(j), \bar{A}(j-1))}{g_{0,A(j)}(a(j) \mid \bar{L}(j), \bar{A}(j-1))} < \infty,$$

across all possible histories  $\bar{L}(j), \bar{A}(j-1)$ .

- That is, if the probability that one assigns the value  $a(j)$  to a unit with history  $\bar{L}(j), \bar{A}(j-1)$  equals zero, then we also need that the stochastic intervention assigns this value  $a(j)$  with probability zero.

# Super Learning Theory and Applications

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December 4-6 2019, Atlantic City NJ

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- 1 Super learning and the oracle inequality
- 2 Prediction of survival based on right-censored data
- 3 Super learning of the optimal individualized treatment rule
- 4 Super learning of a conditional density

## Loss-based dissimilarity

Let  $L(\psi)(o)$  be a loss function for  $\psi_0 = \arg \min_{\psi} \int L(\psi)(o) dP_0(o)$ . We can define a loss-based dissimilarity between a candidate  $\psi$  and true parameter value  $\psi_0$ :

$$\begin{aligned}d_0(\psi, \psi_0) &= P_0 L(\psi) - P_0 L(\psi_0) \\&= \int_o L(\psi)(o) dP_0(o) - \int_o L(\psi_0)(o) dP_0(o).\end{aligned}$$

## Cross-validation selector

- Given a library of candidate estimator mappings  $P_n \rightarrow \hat{\Psi}_k(P_n)$ ,  $k = 1, \dots, K_n$ , we will define a cross-validation selector of  $k$ .
- Consider a  $V$ -fold cross-validation scheme that defines  $V$  sample splits in training and validation sample. For each sample split  $v$ , let  $P_{n,v}$  be the empirical probability distribution of the training sample, and let  $Val(v)$  be the set of indices that are in the validation sample.
- Let  $p = 1/V$  the proportion of observations in validation sample.
- The cross-validation selector is defined by

$$k_n = \arg \min_k \frac{1}{V} \sum_{v=1}^V \frac{1}{np} \sum_{i \in Val(v)} L(\hat{\Psi}_k(P_{n,v}))(O_i).$$

## Discrete super learner

The discrete super learner is defined as the estimator

$$\hat{\Psi}(P_n) = \hat{\Psi}_{k_n}(P_n).$$

## Oracle inequality for quadratic loss-based dissimilarities

Suppose that  $\sup_{\psi,o} |L(\psi) - L(\psi_0)|(o) < M_1$  and

$$\sup_{\psi} \frac{P_0 \{L(\psi) - L(\psi_0)\}^2}{P_0 L(\psi) - P_0 L(\psi_0)} < M_2.$$

Let  $p = 1/V$ , and  $C(M_1, M_2, \delta) = O(M_1 + M_2/\delta)$ . Then, for each  $\delta > 0$ , we have

$$\begin{aligned} E_0 \frac{1}{V} \sum_v d_0(\hat{\Psi}_{k_n}(P_{n,v}), \psi_0) &\leq (1 + \delta) E_0 \min_k \frac{1}{V} \sum_v d_0(\hat{\Psi}_k(P_{n,v}), \psi_0) \\ &\quad + C(M_1, M_2, \delta) \frac{\log K_n}{np} \end{aligned}$$

# Asymptotic equivalence of cross-validation selector and oracle selector

Suppose that

$$\frac{\log K_n/n}{E_0 \min_k \frac{1}{V} \sum_v d_0(\hat{\Psi}_k(P_{n,v}), \psi_0)} \rightarrow 0.$$

Then,

$$\frac{E_0 \frac{1}{V} \sum_v d_0(\hat{\Psi}_{K_n}(P_{n,v}), \psi_0)}{E_0 \min_k \frac{1}{V} \sum_v d_0(\hat{\Psi}_k(P_{n,v}), \psi_0)} \rightarrow 1.$$

## Asymptotic equivalence of cross-validation selector and oracle selector

In words, if  $K_n = n^m$  for some finite  $m$ , and the oracle selected estimator converges at a slower rate than  $\log n/n$  (i.e., rate for a correctly specified parametric model), then the ratio of the dissimilarity of the cross-validated selected estimator and the truth and the dissimilarity of the oracle selected estimator and the truth converges to 1.

If, one of the candidate estimators happens to be based on a correctly specified parametric model, then the dissimilarity of the cross-validated selected estimator and the truth converges at rate  $\log n/n$ .

## Oracle inequality for non-quadratic loss-based dissimilarities

Suppose that  $\sup_{\psi,o} | L(\psi) - L(\psi_0) | (o) < M_1$ . Let  $p = 1/V$  and  $C(M_1) = O(M_1)$ . Then,

$$\begin{aligned} E_0 \frac{1}{V} \sum_v d_0(\hat{\Psi}_{k_n}(P_{n,v}), \psi_0) &\leq E_0 \min_k \frac{1}{V} \sum_v d_0(\hat{\Psi}_k(P_{n,v}), \psi_0) \\ &\quad + C(M_1) \frac{(\log K_n)^{0.5}}{(np)^{0.5}}. \end{aligned}$$

# Outline

- 1 Super learning and the oracle inequality
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## Causal effect of treatment on right-censored survival time

Let  $O = (W, A, \Delta = I(T \leq C), \tilde{T} = \min(T, C))$ ,  $T$  is a survival time,  $C$  is a right-censoring time,  $A$  is a binary treatment,  $W$  are baseline covariates. Suppose that  $C$  is independent of  $T$ , given  $A, W$ . Consider the conditional survivor function:

$$S(t_0 | A, W) = P(T > t_0 | A, W).$$

Let

$$\lambda(t | A, W) = P(T = t | A, W, T \geq t)$$

be the conditional hazard of survival at time  $t$ . We have

$$S(t_0 | A, W) = \prod_{s \leq t_0} (1 - \lambda(s | A, W)).$$

If  $T$  is continuous, then this writes as

$$S(t_0 | A, W) = \prod_{s \leq t_0} (1 - d\Lambda(s | A, W)).$$

## Identification of conditional hazard

If  $C$  is independent of  $T$ , given  $A, W$ , then we can identify the conditional hazard as follows:

$$\lambda(t \mid A, W) = P(\tilde{T} = t, \Delta = 1 \mid \tilde{T} \geq t, A, W).$$

Let's denote the right-hand side with  $\tilde{\lambda}(t \mid A, W)$ .

## Treatment specific survival

Define

$$\Psi_a(P) = E_P S(t_0 \mid A = a, W).$$

Under a causal model in which  $T = T_A$ ,  $T_0, T_1$  treatment specific counterfactual survival times, and the assumption that  $A$  is independent of  $T_0, T_1$ , given  $W$ , we have

$$\Psi_a(P) = P(T_a > t_0),$$

the counterfactual survival function at  $t_0$  under intervention  $A = a$ .

## Prediction of survival based on right-censored data

Suppose that we want to estimate  $\psi_0(t_0, A, W) = S_0(t_0 \mid A, W)$  at a given point  $t_0$ , based on the right-censored data structure  $O = (W, A, \Delta, \tilde{T})$ . If there would not be right-censoring, then a valid loss function would be

$$L^F(\psi)(W, A, T) = (I(T > t_0) - \psi(t_0, A, W))^2.$$

## Inverse probability of censoring weighted loss function

Let  $\bar{G}(t | A, W) = P(C \geq t | A, W)$ . We can define the Inverse probability of censoring weighted loss function:

$$L_{G_0}(\psi)(O) = \frac{L^F(\psi)(W, A, \tilde{T})\Delta}{\bar{G}(\tilde{T} | A, W)}.$$

## Improved IPCW-loss

An improved IPCW-loss is given by:

$$L_{G_0}(\psi)(O) = \frac{L^F(\psi)(W, A, \tilde{T})\{I(\tilde{T} \leq t_0, \Delta = 1) + I(\tilde{T} > t_0)\}}{\bar{G}_0(\min(\tilde{T}, t_0) \mid A, W)}.$$

## Cross-validation selector

The cross-validation selector is now defined by:

$$k_n = \arg \min_k \frac{1}{V} \sum_v \sum_{i \in VAL(v)} L_{G_{n,v}}(\hat{\Psi}_k(P_{n,v})(O_i)),$$

where  $G_{n,v}$  is an estimator of  $G_0$  based on the training sample  $P_{n,v}$ .

## Candidate estimators of the conditional survival function: Direct estimators

IPC-weighted logistic regression estimators regressing  $I(T > t_0)$  on  $A, W$  using weights

$$\frac{I(\tilde{T} \leq t_0, \Delta = 1) + I(\tilde{T} > t_0)}{\bar{G}_0(\min(\tilde{T}, t_0) \mid A, W)}.$$

## Candidate estimators of conditional survival function: Hazard based estimators

Consider the case that  $T$  is discrete. For each  $t$ , we can estimate the hazard  $\tilde{\lambda}(t | A, W)$  with logistic regression of the binary outcome  $I(\tilde{T} = t, \Delta = 1)$ , given  $A, W$ , among observations with  $\tilde{T} \geq t$ .

We can also run a pooled logistic regression by creating a row of data for each  $s \leq \tilde{T}$ , defined by  $(W, A, I(\tilde{T} = s, \Delta = 1))$ ,  $s = 1, \dots, \tilde{T}$ , thereby simultaneously fitting the conditional hazard as a function of  $(t, A, W)$ .

## How to handle continuous survival?

- If  $T$  is continuous, we can discretize  $T$  using an interval partition of its range. We can now use the above pooled or  $t$ -specific logistic regression approach to estimate the corresponding discrete conditional hazard.
- By dividing this discrete hazard at time  $t$  by the width  $h(t)$  of the interval that contains  $t$ , we obtain an estimate of the actual continuous conditional hazard.
- The choice of interval partition, width of the interval, can now be a tuning parameter, defining a candidate estimator.
- One could also use Cox-proportional hazard based estimators.

# Outline

- ① Super learning and the oracle inequality
- ② Prediction of survival based on right-censored data
- ③ Super learning of the optimal individualized treatment rule
- ④ Super learning of a conditional density

## Super learning of optimal individualized treatment rule

- $O = (W, A, Y)$ , nonparametric model only assumptions on  $g_0(A | W)$ .
- Target: Optimal treatment rule  $\psi_0(W) = I(B_0(W) > 0)$ , where  $B_0(W) = E_0(Y | A = 1, W) - E_0(Y | A = 0, W)$ .
- Possible loss function for  $\psi_0$  is an IPCW-loss:

$$L_{g_0}(\psi) = \frac{I(A = \psi(W))}{g(A | W)} Y.$$

- Indeed,  $\psi_0$  is the minimizer of  $EL_{g_0}(\psi)$  over all rules  $\psi$ .
- Loss-based dissimilarity:  $d_0(\psi, \psi_0) = E_0 Y_\psi - E_0 Y_{\psi_0}$ .

## Super learning of the optimal individualized treatment rule

- Construct library of candidate estimators of  $\psi_0 = I(B_0 > 0)$ . This can include estimators based on plugging in an estimator of  $B_0$ .
- One could also include a candidate estimator  $I(B_n > 0)$  where  $B_n$  is a super learner of  $B_0$ , e.g. based on loss function

$$L_{g_0}(B) = ((2A - 1)/g(A | W)Y - B(W))^2$$

that directly targets  $B_0 = \arg \min_B P_0 L_{g_0}(B)$ .

- Estimate  $g_0$  if not known.
- Compute cross-validation selector:

$$k_n = \arg \min_k E_{B_n} P_{n, B_n}^1 L_{\hat{g}(P_{n, B_n}^0)}(\hat{\Psi}_k(P_{n, B_n}^0)).$$

- super learner of optimal rule  $\psi_0$ :  $\hat{\Psi}_{k_n}(P_n)$ .

# Outline

- 1 Super learning and the oracle inequality
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## Super learner of a multinomial conditional distribution

Suppose we want to construct a super learner of the conditional probability distribution  $g_0(a | W) = P_0(A = a | W)$ , where  $a \in \mathcal{A}$ . Let's denote the values of  $a$  with  $\{0, 1, \dots, K\}$ . A valid loss function for the conditional density is

$$L(g)(O) = -\log g(A | W).$$

That is,  $g_0 = \arg \min_g P_0 L(g)$ , i.e.,  $g_0$  is the minimizer of the expectation of the log-likelihood loss.

## Candidate estimators

Let  $\hat{g}_k(P_n)$ ,  $k = 1, \dots, K$ , be a collection of candidate estimators of  $g_0$ . The discrete super learner is defined by

$$g_n = \hat{g}_{k_n}(P_n),$$

where

$$k_n = \arg \min_k E_{B_n} P_{n, B_n}^1 L(\hat{g}(P_{n, B_n}^0)) = E_{B_n} \frac{1}{np} \sum_{i: B_n(i)=1} L(\hat{g}(P_{n, B_n}^0))(O_i),$$

and  $B_n \in \{0, 1\}^n$  is a random sample split in training sample  $\{i : B_n(i) = 0\}$  and validation sample  $\{i : B_n(i) = 1\}$ . Here  $p$  is the proportion of observations that are in the validation sample,  $P_{n, B_n}^1$ ,  $P_{n, B_n}^0$  are the empirical probability distributions of the validation and training sample, respectively.

## Weighted combinations

We can also define a parametric family of candidate estimators  $\hat{g}_\alpha(P_n)$ , indexed by a vector  $\alpha$ , such as

$$\hat{g}_\alpha = \sum_{k=1}^K \alpha(k) \hat{g}_k$$

under the constraint that  $\alpha(k) \geq 0$ ,  $k = 1, \dots, K$ , and  $\sum_k \alpha(k) = 1$ . This choice of family is contained in the class of probability distributions.

## Super learner

The super learner for this family of candidate estimators is given by

$$g_n = \hat{g}_{\alpha_n}(P_n),$$

where

$$\alpha_n = \arg \min_{\alpha} E_{B_n} P_{n, B_n}^1 L(\hat{g}_{\alpha}(P_{n, B_n}^0)).$$

One might have to program this optimization over  $\alpha$ , but existing routines are available for doing such constrained maximization problems. This step is often referred to as the meta-learner step.

## Candidate estimators

**Candidate estimators based on multinomial logistic regression:** To start with one can use existing parametric model based MLE and machine learning algorithms in *R* that fit a multinomial regression.

**Candidate estimators based on machine learning for multinomial logistic regression:** Secondly, one can use a machine learning algorithm such as `polyclass()` in *R* that adaptively fits a multinomial logistic regression, which itself has tuning parameters, again generating a class of candidate estimators.

## Incorporating screening

- Note that one can also marry any of these choices with a screening algorithm, thereby creating more candidate estimators of interest.
- The screening can be particularly important when there are many variables.

## Candidate estimators by fitting separate logistic regressions and using post-normalization:

- Code  $A$  in terms of Bernoullis  $B_k = I(A = k)$ ,  $k = 0, \dots, K$ .
- Construct an estimator  $\bar{g}_{nk}$  of  $\bar{g}_{0k}(W) \equiv P_0(B_k = 1 | W)$  using any of the logistic regression algorithms, for all  $k = 0, \dots, K$ .
- This implies an estimator

$$g_n(a | W) = \frac{\bar{g}_{na}(W)}{\sum_{k=0}^K \bar{g}_{nk}(W)}.$$

- In other words, we simply normalize these separate logistic regression estimators so that we obtain a valid conditional distribution.
- This generates an enormous amount of interesting algorithms, since we have available the whole machine learning literature for binary outcome regression.

## Candidate estimators by estimating the conditional "hazard with" pooled logistic regression

Finally, we have used the following strategy in our research for construction of candidate estimators. Note that

$$g_0(a | W) = \lambda_0(a | W)S_0(a | W),$$

where

$$\lambda_0(a | W) = P_0(A = a | A \geq a, W),$$

and  $S_0(a | W) = \prod_{s \leq a} (1 - \lambda_0(s | W))$  is the conditional survivor function  $P_0(A > a | W)$ . So we have now parameterized the conditional distribution of  $A$ , given  $W$ , by a conditional hazard  $\lambda_0(a | W)$ :  $g_0 = g_{\lambda_0}$ .

## Candidate estimators of conditional "hazard"

- We could now focus on constructing candidate estimators of  $\lambda_0(a | W)$ , which implies candidate estimators of  $g_0$ .
- For every observation  $A_i$ , we can create  $A_i + 1$  rows of data  $(W, s, I(A_i = s))$ ,  $s = 0, \dots, A_i$ ,  $i = 1, \dots, n$ . We now run a logistic regression estimator based on the pooled data set, ignoring ID, where we regress the binary outcome  $I(A_i = s)$  on the covariates  $(W, s)$ .

## Pooling across levels or not

- If one assumes a parametric model, then this is nothing else than using the maximum likelihood estimator, demonstrating that ignoring the ID is not inefficient.
- This defines now an estimator of  $\lambda_0(s | W) = P_0(A = s | W, A \geq s)$  as a function of  $(s, W)$ .
- Different choices of logistic regression based estimators will define different estimators.
- The pooling across  $s$  is not very sensible if  $A$  is not an ordered variable. If  $A$  is categorical, we recommend to compute a separate logistic regression estimator of  $\lambda_0(a | W)$  for each  $a$  (i.e., stratify by  $s$  in the above pooled data set).
- For non-categorical  $A$ , one could include both stratified (by level) as well as pooled (across levels) based logistic regression estimators.

# Targeted Maximum Likelihood Estimation

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**Deming Conference on Applied Statistics**

December 4-6 2019, Atlantic City NJ

# Statistical Estimation Problem

**Data:** We observe  $O_1, \dots, O_n \sim_{iid} P_0$ .

**Statistical Model:** We know  $P_0 \in \mathcal{M}$ .

**Target Parameter:** Let  $\Psi : \mathcal{M} \rightarrow \mathbb{R}^d$  denote the target parameter.

**Plug-in estimator:** We want to construct an efficient plug-in estimator  $\Psi(P_n^*)$  of the estimand  $\Psi(P_0)$  that is asymptotically linear, so that we also obtain asymptotic (maximally narrow) confidence intervals.

## Canonical gradient

- Let  $P$  be given.
- Consider class of paths  $\{P_\epsilon : \epsilon\} \subset \mathcal{M}$  through  $P$  at  $\epsilon = 0$  with score  $S$ , and show that for each path

$$\frac{d}{d\epsilon} \Psi(P_\epsilon) \Big|_{\epsilon=0} = E_P D(P) S$$

for some  $D(P) \in L^2(P)$ .

- $O \rightarrow D(P)(O)$  is called a gradient at  $P$ , and the unique gradient that is an element of the tangent space  $T(P)$  (closure of linear span of all scores  $S$ ) is the *canonical gradient* at  $P$ .
- We say  $\Psi$  is pathwise differentiable at  $P$  with canonical gradient  $D^*(P)$ .

## Exact second order expansion for target parameter

- Let

$$R_2(P, P_0) \equiv \Psi(P) - \Psi(P_0) - (P - P_0)D^*(P).$$

- This will behave as a second order difference of  $P$  and  $P_0$ .
- By definition (note  $PD^*(P) = 0$ ), this yields following exact second order expansion of  $\Psi$ :

$$\Psi(P) - \Psi(P_0) = -P_0 D^*(P) + R_2(P, P_0).$$

## Efficient estimator

- An estimator  $\psi_n$  of  $\psi_0 = \Psi(P_0)$  is called asymptotically efficient at  $P_0$  if it is asymptotically linear with influence curve  $D^*(P_0)$ :

$$\psi_n - \psi_0 = \frac{1}{n} \sum_{i=1}^n D^*(P_0)(O_i) + o_P(n^{-1/2}).$$

- Canonical gradient is also called efficient influence curve.
- If this holds, then  $\psi_n$  is also a regular estimator, and it is the asymptotic best estimator among all regular estimators.

## Initial estimator for TMLE

- Let  $\mathbf{P}_n$  be an initial estimator of  $P_0$ .
- If  $\Psi(P) = \Psi(Q(P))$  only depends on  $P$  through a functional parameter  $Q(P)$ , then one only needs  $Q(\mathbf{P}_n)$ , so direct estimators of  $Q(\mathbf{P}_n)$  of  $Q(P_0)$  can (should) be used.

## Loss function

- Let  $L(P)(O)$  be a loss for  $P_0$ , such as  $L(P) = -\log p(O)$ .
- More generally, one can use a loss  $L(Q)(O)$  for relevant part  $Q(P)$  of  $P$ .
- So  $P_0 L(Q_0) = \min_{P \in \mathcal{M}} P_0 L(Q(P))$ .

## Local least favorable submodel (LFM) through initial estimator

- Let  $\{\mathbf{P}_{n,\epsilon} : \epsilon\} \subset \mathcal{M}$  be a finite dimensional submodel so that the linear span of the components of its score at  $\epsilon = 0$  include  $D^*(\mathbf{P}_n)$ .
- Such a submodel is called a local least favorable submodel.
- More generally, let  $\{\mathbf{P}_{n,\epsilon} : \epsilon\} \subset \mathcal{M}$  be a finite dimensional submodel so that the linear span of the components of its generalized score

$$\frac{d}{d\epsilon} L(Q(\mathbf{P}_{n,\epsilon})) \Big|_{\epsilon=0}$$

includes  $D^*(\mathbf{P}_n)$ .

## Uniform least favorable submodel (ULFM) through initial estimator

- Let  $\{\mathbf{P}_{n,\epsilon} : \epsilon\} \subset \mathcal{M}$  be a finite dimensional submodel so that the linear span of the components of its score at *any*  $\epsilon$  include  $D^*(\mathbf{P}_{n,\epsilon})$ .
- Such a submodel is called a *uniform* least favorable submodel.
- Similarly, as above we can generalize this definition to loss function  $L(Q)$  for a parameter  $Q(P)$  chosen so that  $\Psi(P)$  only depends on  $P$  through  $Q(P)$ .

## Update initial estimator with MLE along LFM

- Let

$$\epsilon_n^0 = \arg \min_{\epsilon} P_n L(\mathbf{P}_{n,\epsilon})$$

be the MLE.

- Define the first TMLE-update as  $\mathbf{P}_n^1 = \mathbf{P}_{n,\epsilon_n^0}$ .

## Iterating TMLE-updating till efficient score equation is solved approximately

- Iterate this updating process

$$\epsilon_n^k = \arg \min_{\epsilon} P_n L(\mathbf{P}_{n,\epsilon}^k)$$

and  $\mathbf{P}_n^{k+1} = \mathbf{P}_{n,\epsilon_n^k}$ ,  $k = 1, \dots, \dots, K_n$ .

- One iterates till  $K_n$  satisfies

$$P_n D^*(\mathbf{P}_n^{K_n}) = r(n)$$

for a user-supplied sequence  $r(n) = o(n^{-1/2})$ .

- If one iterates till  $\epsilon_n^K = 0$ , then we have

$$P_n D^*(\mathbf{P}_n^K) = 0.$$

## Universal least favorable submodel

We define a 1-d universal least favorable submodel at  $P$  as a submodel  $\{P_\epsilon : \epsilon\}$  so that for all  $\epsilon$

$$\frac{d}{d\epsilon} \log \frac{dP_\epsilon}{dP} = D^*(P_\epsilon).$$

This acts as a local least favorable submodel at any point  $\epsilon$  on its path.

## One-step TMLE

- If we use a universal LFM, then the above TMLE algorithm converges in one-step, so that  $P_n^* = \mathbf{P}_n^1$ .
- Then,

$$P_n D^*(\mathbf{P}_n^1) = 0.$$

- If the initial estimator  $\mathbf{P}_n$  converges at a rate faster than  $n^{-1/4}$  so that the second order remainder  $R_2(\mathbf{P}_n, P_0) = o_P(n^{-1/2})$ , then under regularity conditions, a first step TMLE using local LFM will satisfy  $P_n D^*(\mathbf{P}_n^1) = o_P(n^{-1/2})$ .

# TMLE

- Let  $P_n^*$  be final update.
- $\psi_n^* = \Psi(P_n^*)$  is the TMLE of  $\psi_0$ .

## TMLE using $n^{-1/4}$ -initial estimator is efficient

- Combining  $P_n D^*(P_n^*) = 0$  with exact second order expansion for  $\Psi(P_n^*) - \Psi(P_0)$  yields

$$\Psi(P_n^*) - \Psi(P_0) = (P_n - P_0)D^*(P_n^*) + R_2(P_n^*, P_0).$$

- Use  $o(n^{-1/4})$ -estimator  $\mathbf{P}_n$  (Highly Adaptive Lasso!) so that  $R_2(P_n^*, P_0) = o_P(n^{-1/2})$ .
- Control overfitting so that  $D^*(P_n^*)$  falls in a Donsker class with probability tending to 1 (e.g, sectional variation norm of  $D^*(P_n^*)$  is bounded with probability tending to 1).
- Then, also  $(P_n - P_0)D^*(P_n^*) = (P_n - P_0)D^*(P_0) + o_P(n^{-1/2})$  so that  $\Psi(P_n^*)$  is asymptotically efficient.

## Inference

- Thus, inference can be based on working model  $\Psi(P_n^*) \sim N(\psi_0, \Sigma_0)$ , where  $\Sigma_0 = P_0 D^*(P_0) D^*(P_0)^\top$ .
- $\Sigma_0$  can be consistently estimated with  $\Sigma_n = P_n D^*(P_n^*) D^*(P_n^*)^\top$ .
- For example,  $\Psi_j(P_n^*) \pm 1.96 \Sigma_n(j,j)^{0.5} / n^{1/2}$  is an asymptotic 0.95-confidence interval for  $\Psi_j(P_0)$ ,  $j = 1, \dots, d$ .

# Targeted Minimum Loss-Based Estimation of the Treatment Specific Survival Function for Right-Censored Survival Data

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**Deming Conference on Applied Statistics**

December 4-6 2019, Atlantic City NJ

# Outline

- 1 Causal model for the counterfactual treatment specific survival curve
- 2 Efficient influence curve
- 3 Super-learner of conditional hazard
- 4 TMLE of treatment specific survival curve
- 5 One-step TMLE of treatment specific survival curve
- 6 Example: HAL-MLE of conditional hazard

## Observed data

- We observe

$$O = (W, A, \tilde{T} = \min(T, C), \Delta = I(T \leq C)) \sim P_0$$

- $W$  baseline covariates.
- $A$  binary treatment.
- $C, T$ , censoring and survival time.

## Causal formulation of observed data

- $T_0, T_1$  potential survival times under control and treatment.
- $C_0, C_1$  potential censoring times under control and treatment.
- $T = T_A, C = C_A, \tilde{T} = \tilde{T}_A, \Delta = \Delta_A$ .
- $O = (W, A, \tilde{T}_A = \min(T_A, C_A), \Delta_A = I(T_A \leq C_A))$ .

## Causal quantity: Treatment specific survival curve

- Let  $W \rightarrow d(W) \in \{0, 1\}$  be a dynamic treatment rule.
- Let  $S_d(t) = P(T_d > t)$ , where  $T_d = T_{d(W)}$  be quantity of interest.

## Coarsening at random assumption on treatment and censoring

- Randomization of treatment: Assume that  $A$  is independent of  $T_d$ , given  $W$ .
- Let  $A_2(t) = I(\tilde{T} \leq t, \Delta = 0)$  is censoring process, jumps at observed censoring time.
- Let  $N(t) = I(\tilde{T} \leq t, \Delta = 1)$  is failure process that jumps at observed failure time.
- $(W, A, \bar{N}(t), \bar{A}_2(t-))$  is available history right before  $A_2(t)$ .
- Non-informative censoring (CAR): Assume that at each time  $t$ ,  $A_2(t)$  is independent of  $T_d$ , given  $(W, A, \bar{N}(t), \bar{A}_2(t-))$ .
- These assumptions are non-testable: put no restrictions on data distribution  $P_0$ .

## Identifiability of treatment specific survival curve

- Under the above CAR assumption we have

$$S_d(t_0) = E_P S(t_0 \mid A = d(W), W).$$

- $S(t_0 \mid A, W) = P(T > t_0 \mid A, W)$  conditional survival curve of  $T$ .
- For any data distribution  $P$ , let  $\Psi(P) = E_P S(t_0 \mid A = d(W), W)$ .

## Longitudinal formulation of observed data

- We can represent the observed data as

$$O = (W, A, \bar{A}_2(\tau), \bar{N}(\tau)),$$

where  $\tau$  is a maximal follow up time.

- This data is time-ordered as:

$$O = (W, A, A_2(0), N(1), A_2(1), N(2), \dots, A_2(\tau - 1), N(\tau)).$$

## Conditional probability distributions of data distribution

- Let  $Q_W$  be probability measure of  $W$ .
- Let  $Q_{N(t)}$  be conditional probability measure of  $N(t)$ , given  $W, A, \bar{N}(t-1), \bar{A}_2(t-1)$ .
- Let  $Q_N = (Q_{N(t)} : t)$ .
- Let  $G_1$  be conditional probability measure of  $A$ , given  $W$ .
- Let  $G_{A_2(t)}$  be conditional probability measure of  $A_2(t)$ , given  $W, A, \bar{A}_2(t-1), \bar{N}(t)$ .
- Let  $G_2 = (G_{A_2(t)} : t)$ .

## Density of data distribution

- The density of a data distribution  $P$  of  $O$  can be factorized as: for  $o = (w, a, \bar{a}_2(\tau), \bar{n}(\tau))$ ,

$$p(o) = q_W(w) \prod_{t=0}^{\tau} q_{N(t)}(n(t) | w, a, \bar{a}_2(t-1), \bar{n}(t-1)) \\ g_1(a | W) \prod_{t=0}^{\tau-1} g_{A_2(t)}(a_2(t) | w, a, \bar{a}_2(t-1), \bar{n}(t)).$$

- $g_1(a | W) = P(A = a | W)$  and  $g_{A_2(t)}$  is conditional probability distribution of  $A_2(t)$ , given  $Pa(A_2(t))$ .
- $q_W(w)$  density of  $W$ , and  $q_{N(t)}$  is conditional probability distribution of  $N(t)$  given  $Pa(N(t))$ .

## Conditional densities become degenerate after failure or censoring event

- Note that if  $N(t) = 1$  or  $A_2(t - 1) = 1$ , then the conditional density  $g_{A_2(t)}$  of  $A_2(t)$  is degenerate at 0 or 1, respectively.
- Note that if  $N(t - 1) = 1$  or  $A_2(t - 1) = 1$ , then the conditional density  $q_{N(t)}$  of  $N(t)$  is degenerate at 1 or 0, respectively.
- Thus, the product over  $t$  for  $q_{N(t)}$  only includes  $t$  with  $n(t - 1) = a_2(t - 1) = 0$ .
- The product over  $t$  for  $g_{A_2(t)}$  only includes  $t$  with  $n(t) = a_2(t - 1) = 0$ .

## Hazard of censoring

- The conditional density  $g_{A_2(t)}(1 \mid W, A, A_2(t-1) = N(t) = 0)$  is a conditional hazard  $\lambda_C(t \mid W, A, N(t) = 0)$ .
- Under CAR, this equals conditional hazard  $\lambda_C(t \mid W, A)$ .
- If censoring  $C$  is continuous, we can replace  $g_{A_2(t)}(1 \mid W, A, \bar{A}_2(t-1), \bar{N}(t))$  by an intensity

$$E(dA_2(t) \mid W, A, \bar{A}_2(t-), \bar{N}(t-)) = I(\tilde{T} \geq t) \lambda_C(t \mid W, A) dt.$$

## Hazard of failure

- The conditional density  $q_{N(t)}(1 \mid W, A, A_2(t-1) = N(t-1) = 0)$  is a conditional hazard  $\lambda(t \mid W, A, A_2(t-1) = 0)$ .
- Under CAR, this equals conditional hazard  $\lambda(t \mid W, A)$ .
- If  $T$  is continuous, we can replace  $q_N(1 \mid W, A, \bar{A}_2(t-1), \bar{N}(t-1))$  by an intensity

$$E(dN(t) \mid W, A, \bar{A}_2(t-), \bar{N}(t-)) = I(\tilde{T} \geq t) \lambda(t \mid W, A) dt.$$

## Observed data density in terms of hazards

- Thus,

$$\begin{aligned} p(o) &= q_W(w) \prod_{t=0}^{\tilde{t}} \lambda(t \mid W, A)^{dn(t)} (1 - \lambda(t \mid W, A))^{1-dn(t)} \\ &\quad \times g_1(a \mid W) \prod_{t=0}^{\tilde{t}} \lambda_C(t \mid w, a)^{da_2(t)} (1 - \lambda_C(t \mid w, a))^{1-da_2(t)}. \end{aligned}$$

## Statistical model

- Recall  $P = P_{Q_W, Q_N, G_1, G_2}$ .
- Parameter space for distribution of  $W$  is nonparametric.
- Parameter space for conditional hazard of  $T$  is nonparametric.
- Parameter space  $\mathcal{G}_1$  for  $G_1$  and parameter space  $\mathcal{G}_2$  for  $G_2$  are possibly restricted.
- The statistical model

$$\mathcal{M} = \{P_{Q_W, Q_N, G_1, G_2} : G_1 \in \mathcal{G}_1, G_2 \in \mathcal{G}_2\}.$$

## Statistical estimation problem

- We observe  $n$  i.i.d. copies of  $O \sim P_0$ .
- We know  $P_0 \in \mathcal{M}$ .
- $\Psi : \mathcal{M} \rightarrow \mathbb{R}$  is statistical target parameter,  
 $\Psi(P) = E_P P(T > t \mid A = d(W), W)$ .
- We want to estimate  $\Psi(P_0)$ .

# Outline

- ① Causal model for the counterfactual treatment specific survival curve
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## Tangent space

- $T_{Q_W} = L_0^2(P_W)$  is all functions of  $W$ .
- $T_{Q_{N(t)}}$  is all functions of  $N(t)$  and  
 $Pa(N(t)) = (W, A, \bar{A}_2(t-1), \bar{N}(t-1))$  with conditional mean zero,  
given  $Pa(N(t))$ .
- $T_{G_1}$  is all function of  $A, W$  with conditional mean zero, given  $W$ .
- $T_{G_{A_2(t)}}$  is all functions of  $A_2(t)$  and  
 $Pa(A_2(t)) = (W, A, \bar{A}_2(t-1), \bar{N}(t))$  with conditional mean zero,  
given  $Pa(A_2(t))$ .

## Tangent space is orthogonal sum of all tangent spaces

- By factorization of  $p(O)$ , the tangent space  $T(P)$  at  $P$  is an orthogonal sum of all these tangent spaces:

$$T(P) = T_{Q_W} \oplus T_{G_1} \oplus \sum_t T_{Q_{N(t)}} \oplus \sum_t T_{G_{A_2(t)}}.$$

Canonical gradient is projection on tangent space for model  $G$  known

- Let  $\mathcal{M}(G) = \{P_{Q_W, Q_N, G_1, G_2} : Q_W, Q_N\}$  be submodel of  $\mathcal{M}$  defined by  $G = (G_1, G_2)$  being known.
- Let  $D$  be a gradient of  $\Psi : \mathcal{M}(G) \rightarrow \mathbb{R}$  at  $P \in \mathcal{M}(G)$ .
- Let  $T_Q(P)$  be the tangent space of  $Q = (Q_W, Q_N)$ .
- Then the canonical gradient equals  $D^* P = \Pi(D \mid T_Q(P))$ .

## Canonical gradient is sum of projections

- So

$$D^*(P) = \Pi(D \mid T_{Q_W}) + \sum_t \Pi(D \mid T_{Q_{N(t)}}).$$

- This equals:

$$D^*(P) = E(D \mid W) + \sum_t \{E(D \mid N(t), Pa(N(t))) - E(D \mid Pa(N(t)))\}.$$

## Initial gradient

- Let

$$D(P) = \frac{I(\tilde{T} > t_0, A = d(W), A_2(t_0) = 0)}{g_1(A | W) \prod_{t \leq t_0} (1 - \lambda_C(t | A, W))} - \Psi(P).$$

- This is influence curve of RAL estimator in model  $\mathcal{M}(G)$  and therefore a gradient.

# Canonical gradient

- Let  $D_0^*(W) = S(t_0 \mid A = d(W), W) - \Psi(P)$ .
- For  $t = 1, \dots, \min(\tau, t_0)$ , define

$$C_t(Q, G) = \frac{I(A = d(W), \bar{A}_2(t-1) = 0)}{g_1(A \mid W) \prod_{s \leq t-1} (1 - \lambda_C(s \mid A, W))} \frac{S(t_0 \mid A, W)}{S(t \mid A, W)}.$$

- and

$$D_t^*(P) = C_t(Q, G)(dN(t) - q_{N(t)}(1 \mid Pa(N(t))).$$

- This can also be written as

$$D_t^*(P) = I(\tilde{T} \geq t) C_t(Q, G)(dN(t) - q_{N(t)}(1 \mid Pa(N(t))).$$

- We have

$$D^*P = \sum_{t=0}^{\min(\tau, t_0)} D_t^*(P).$$

## Clever covariate times residual representation of each score component

- Note that for  $t = 1, \dots, t_0$ , we have

$$D_t^*(P) = C_t(Q_N, G)(W, A, N(t), A_2(t-1))(dN(t) - \lambda(t | A, W)).$$

- We often refer to  $C_t(Q_N, G)$  as the clever covariate (that will target fit of  $\lambda(t | A, W)$  towards  $\Psi(P)$ ).

## Recursive structure in canonical gradient

- Note that for  $t < t_0$ ,

$$\frac{S(t_0 | A, W)}{S(t | A, W)} = \prod_{t+1 \leq s \leq t_0} (1 - \lambda(s | A, W)).$$

- The clever covariate  $C_{t_0}(G)$  does not depend on  $\lambda$ .
- The clever covariate  $C_{t_0-1}(G, Q_{N(t_0)})$  depends  $\lambda(t_0 | \cdot)$ .
- In general, the clever covariate  
 $C_{t_0-k}(G, (Q_{N(s)} : t_0 - k + 1 \leq s \leq t_0))$ .
- This structure allows us to compute a closed form TMLE starting to target the last  $\lambda(t_0 | \cdot)$ , going backwards, each time being able to compute clever covariate from previous targeted fits of  $\lambda$ .

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## Loss function for conditional hazard

- The log-likelihood loss for  $\lambda$  is given by:

$$L(\lambda)(O) = -\log \left\{ \prod_{t \leq \tilde{T}} \lambda(t | A, W)^{dN(t)} (1 - \lambda(t | A, W))^{1-dN(t)} \right\}.$$

- The true failure time hazard

$$\lambda_0 = \arg \min_{\lambda} P_0 L(\lambda).$$

## Estimation of hazard with pooled logistic regression

- $\lambda(t | A, W) = E(dN(t) | A, W, \tilde{T} \geq t)$  is a regression of binary outcome  $dN(t)$  on  $(A, W)$ , given  $\tilde{T} \geq t$ .
- Thus, one can estimate this function with any logistic regression estimator based on pooled data set in which each unit  $i$  has  $\tilde{T}_i$  rows of data with covariates  $(W_i, A_i, t)$  and outcome  $dN(t)$ ,  $t = 1, \dots, \tilde{T}_i$ .
- If  $\tilde{T}$  is continuous, then one could discretize time to create such estimators, or use Cox-proportional hazard regression type estimators.

## Library of candidate estimators of hazard

- Let  $\hat{\lambda}_j : \mathcal{M}_{NP} \rightarrow \sim$  be a candidate estimator,  $j = 1, \dots, J$ .
- This library of  $J$  estimators can include parametric logistic regression, and large variety of machine learning algorithms.

## Cross-validation to evaluate performance of candidate estimators

- Let  $B_n \in \{0, 1\}^n$  be a random split of sample.
- Let  $P_{n, B_n}^1, P_{n, B_n}^0$  be empirical measures for validation sample  $\{O_i : B_n(i) = 1\}$  and training sample  $\{O_i : B_n(i) = 0\}$ , respectively.
- We evaluate performance of  $\hat{\lambda}_j$  with its cross-validated log-likelihood:

$$R(\hat{\lambda}_j, P_n) = E_{B_n} P_{n, B_n}^1 L(\hat{\lambda}_j(P_{n, B_n}^0)).$$

## Super-learner of hazard

- Let

$$J_n = \arg \min_j R(\hat{\lambda}_j, P_n).$$

- The super-learner is defined as

$$\hat{\lambda}_{SL}(P_n) = \hat{\lambda}_{J_n}(P_n).$$

## Oracle inequality

- Let  $\tilde{J}_n(P_0) = \arg \min_j E_{B_n} P_0 L(\hat{\Psi}_j(P_{n,B_n}^0))$  be the oracle selector.
- Let  $d_0(\lambda, \lambda_0) = P_0 L(\lambda) - P_0 L(\lambda_0)$  be the loss-based dissimilarity.
- By the oracle inequality for the cross-validation selector, the super learner is asymptotically equivalent with the oracle selected estimator:

$$\frac{E_0 d_0(\hat{\lambda}_{\tilde{J}_n}(P_{n,B_n}^0), \lambda_0)}{E d_0(\hat{\lambda}_{\tilde{J}_n(P_0)}(P_{n,B_n}^0), P_0)} \rightarrow 1$$

as  $n \rightarrow \infty$ .

- This remains true if the number  $J$  of candidate estimators grows as fast with sample size as  $n^p$  for some finite integer  $p$ .

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## Recap estimation problem

- We want to construct a TMLE of  $\Psi(P_0) = E_{P_0} S_0(t_0 \mid A = d(W), W)$ .
- $S_0(t_0 \mid A, W) = \prod_{t \in [0, t_0]} (1 - \lambda(t \mid A, W))$ .
- Thus,  $\Psi(P) = \Psi(Q_W, \lambda)$ , where  $Q_W$  is probability measure of  $W$ .
- TMLE will be a plug-in estimator  $\Psi(Q_{W,n}, \lambda_n)$ ,  $Q_{W,n}$  empirical measure of  $W_1, \dots, W_n$ .

## Recap loss function for conditional hazard

- The log-likelihood loss for  $\lambda$  is given by:

$$L(\lambda)(O) = -\log \left\{ \prod_{t \leq \tilde{T}} \lambda(t | A, W)^{dN(t)} (1 - \lambda(t | A, W))^{1-dN(t)} \right\}.$$

- The log-likelihood loss for  $\lambda_C$  is given by:

$$L(\lambda_C)(O) = -\log \left\{ \prod_{t \leq \tilde{T}} \lambda(t | A, W)^{dA_2(t)} (1 - \lambda(t | A, W))^{1-dA_2(t)} \right\}.$$

## Loss function for conditional hazard at single time-point $t$

- Loss function for  $\lambda_t = \lambda(t | A, W)$  at fixed  $t$ :

$$L_t(\lambda_t)(O) = -I(t \leq \tilde{T}) \log \left( \lambda(t | A, W)^{dN(t)} (1 - \lambda(t | A, W))^{1-dN(t)} \right).$$

## Recap canonical gradient

- We derived canonical gradient  $D^*(P) = D^*(Q, G)$ ,  $Q = (Q_W, Q_N)$ ,  $Q_N$  is determined by  $\lambda$ .
- $G = (G_1, G_C)$ ,  $G_1$  is determined by  $g_1(a | W)$ ,  $G_C$  is determined by conditional hazard  $\lambda_C(t | A, W)$  of  $C$ .
- $D^*(P) = D_0^*(Q) + \sum_{t=1}^{\tau} D_t^*(Q, G)$ .
- $D_0^*(Q)$  is score of  $Q_W$ .
- $D_t^*(Q, G)$  score of  $\lambda(t | A, W)$ .

## $\lambda$ -component of canonical gradient

- $D_t^*(Q, G) = C_t(Q, G)I(\tilde{T} \geq t)(dN(t) - \lambda(t | A, W)).$
- Clever covariate:

$$C_t(Q, G) = \frac{I(A = d(W), \bar{A}_2(t-1) = 0)}{g_1(A | W) \prod_{s \leq t-1} (1 - \lambda_C(s | A, W))} \frac{S(t_0 | A, W)}{S(t | A, W)}.$$

## Initial estimator

- We estimate  $Q_{0,W}$  with the empirical measure of  $W_1, \dots, W_n$ .
- Let  $\lambda_n$  be an initial estimator of  $\lambda_0$  such as the super-learner presented in previous lecture.
- Let  $\lambda_{Cn}$  be an initial estimator (e.g., super-learner) of the conditional hazard  $\lambda_{0C}(t | A, W)$  of censoring
- Let  $g_{1n}(a | W)$  be estimator of treatment mechanism  $g_{10} = P_0(A = a | W)$ .

## Least favorable submodel for conditional hazard

- Let

$$\text{Logit}\lambda_{n,\epsilon}(t \mid A, W) = \text{Logit}\lambda_n(t \mid A, W) + \epsilon C_t(Q_n, G_n).$$

## Iterative TMLE

- Let  $\epsilon_n^0 = \arg \min_{\epsilon} P_n L(\lambda_{n,\epsilon})$ .
- This is equivalent with running a univariate logistic regression of  $dN(t)$  on  $C_t(Q_n, G_n)(A, W)$  based on pooled data set in which each subject contributes  $\tilde{T}$  rows of data, using as off-set  $\text{Logit}\lambda_n(t | A, W)$ .
- Let  $\lambda_n^1 = \lambda_{n,\epsilon_n^0}$  and  $Q_n^1 = (Q_{W,n}, Q_N(\lambda_n^1))$ .
- Set  $k = 1$ ;

$$\text{Logit}\lambda_{n,\epsilon}^k(t | A, W) = \text{Logit}\lambda_n^k(t | A, W) + \epsilon C_t(Q_n^k, G_n).$$

- $\epsilon_n^k == \arg \min_{\epsilon} P_n L(\lambda_{n,\epsilon}^k); \lambda_n^{k+1} = \lambda_{n,\epsilon_n^k}^k$ .
- Iterate till  $\epsilon_n^k \approx 0$ .

## LFM submodel for recursive TMLE

- For each  $t = 1, \dots, \tau$ , given a current estimator  $\lambda_{n,t}$  of  $\lambda_0(t | A, W)$ ,

$$\text{Logit}\lambda_{n,t,\epsilon}(A, W) = \text{Logit}\lambda_{n,t}(A, W) + \epsilon C_t(Q_n, G_n).$$

- This is a submodel to fluctuate  $\lambda_{n,t}(A, W)$  at fixed  $t$ .
- Its score spans  $D_t^*(Q_n, G_n)$ .

Carry out one-step updates recursively starting at end point  $\tau$

- Let  $\epsilon_n^\tau = \arg \min_\epsilon P_n L_\tau(\lambda_{\tau,n,\epsilon})$ .
- Let  $\lambda_{\tau,n}^* = \lambda_{\tau,n,\epsilon_n^\tau}$ .
- Let  $\lambda_{\tau-1,n,\epsilon}$  be above submodel through  $\lambda_{\tau-1,n}$  with covariate  $C_t(Q_n^*, G_n)$  using latest update  $\lambda_{\tau,n}^*$ .
- Let  $\epsilon_n^{\tau-1} = \arg \min_\epsilon P_n L_{\tau-1}(\lambda_{\tau-1,n,\epsilon})$ .
- Let  $\lambda_{\tau-1,n}^* = \lambda_{\tau-1,n,\epsilon_n^{\tau-1}}$ .

## Closed form recursive TMLE

- Let  $t = \tau - 2$ .
- Let  $\lambda_{t,n,\epsilon}$  be above submodel through  $\lambda_{t,n}$  with covariate  $C_t(Q_n^*, G_n)$  using latest update  $(\lambda_{t+1:\tau,n}^*$ .
- Let  $\epsilon_n^t = \arg \min_\epsilon P_n L_t(\lambda_{t,n,\epsilon})$ .
- Let  $\lambda_{t,n}^* = \lambda_{t,n,\epsilon_n^t}$ .
- Let  $t = t - 1$  and repeat above three steps, iterate, till we end up at  $t = 1$ .
- Then, we have the TMLE  $\lambda_n^* = (\lambda_{t,n}^* : t = 1, \dots, \tau)$ .

## Solves efficient influence curve equation

- The TMLE  $Q_n^* = (Q_{W,n}, Q_N(\lambda_n^*))$  solves

$$0 = P_n D_t^*(Q_n^*, G_n)$$

for each  $t = 0, \dots, \tau$ .

- In particular, it solves  $P_n D^*(Q_n^*, G_n) = 0$ .
- The iterative TMLE will solve approximately  $P_n D^*(Q_n^*, G_n) \approx 0$ .

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## From local least favorable submodel to universal least favorable submodel

- A local least favorable submodel (LLFM) for  $S_d(t)$  around initial estimator of conditional hazard:

$$\text{logit}(\lambda_{n,\varepsilon}(\cdot|A=1, W)) = \text{logit}(\lambda_n(\cdot|A=1, W)) + \varepsilon h_t.$$

- Similarly, we have this local least favorable submodel for a vector  $(S_d(t) : t)$  by adding vector  $(h_t : t)$  extension.
- These imply, as above, universal least favorable submodels for single and multidimensional survival function.

# Simulations for one-step TMLE of survival curve

We investigated the performance of one-step TMLE for treatment specific survival curve in two simulation settings.

## Data structure

- $O = (W, A, T) \sim P_0$
- $A \in \{0, 1\}$
- treatment intervention:  $W \rightarrow d(W) = 1$
- $S_d(t)$  is defined by

$$\Psi(P)(t) = E_P [P(T > t | A = d(W), W)]$$

# Candidate estimators

- ① Kaplan Meier
- ② Iterative TMLE for each single  $t$  separately
- ③ One-step TMLE targeting the whole survival curve  $S_d$

# Results

Figure: Based on one data set

## Monte-carlo results ( $n = 100$ )

**Figure:** Relative efficiency against iterative TMLE, as a function of t

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## Example: HAL-MLE of conditional hazard

- Suppose that  $O = (W, A, \tilde{T} = \min(T, C), \Delta = I(T \leq C))$ , and that we are interested in estimating the conditional hazard  $\lambda(t | A, W)$ .
- Let  $L(\lambda)$  be the log-likelihood loss.
- If  $T$  is continuous, we could parametrize  $\lambda(t | A, W) = \exp(\psi(t, A, W))$ , or, if  $T$  is discrete,  $\text{Logit}\lambda(t | A, W) = \psi(t, A, W)$ .
- We can represent  $\psi = \sum_{s \in \{1, \dots, d\}} \beta_{s,j} \phi_{u_{s,j}}$  as linear combination of indicator basis functions, where  $L^1$ -norm of  $\beta$  represents the sectional variation norm of  $\psi$ .
- Therefore, we can compute the HAL-MLE of  $\lambda$  with either Cox-Lasso or logistic Lasso regression (`glmnet()`).

# Targeted Minimum Loss-Based Estimation for Longitudinal Data

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**Deming Conference on Applied Statistics**

December 4-6 2019, Atlantic City NJ

# Outline

- 1 Causal model for longitudinal data with multiple time-point interventions
- 2 Sequential regression representation of target parameter
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## Longitudinal data

- Let

$$O = (L(0), A(0), \dots, L(K), A(K), Y = L(K + 1)) \sim P_0.$$

- $A(t) = (A_1(t), A_2(t))$ ,  $A_1(t)$  discrete valued treatment,  
 $A_2(t) = I(\tilde{T} \leq t, \Delta = 0)$  jumps at right censoring, where  
 $\tilde{T} = \min(T, C)$ .
- $L(t) = (N(t), L_1(t))$ ,  $N(t) = I(\tilde{T} \leq t, \Delta = 1)$ .
- $L_1(t)$  time-dependent covariates.
- $Y = I(\tilde{T} > K + 1)$  indicator of no event by time  $K + 1$ .
- Note that this process is degenerate after failure or censoring.

## Observed data distribution and notation

$$P_0(do) = \prod_{k=1}^{K+1} P_{L(k)}(dl(k) | \bar{l}(k-1), \bar{a}(k-1)) \prod_{k=1}^K P_{A(k)}(a(k) | \bar{a}(k-1), \bar{l}(k)).$$

- Let  $Q_{L(k)}$  denote  $P_{L(k)}$  and  $q_{L(k)}$  be its density,  $k = 0, \dots, K + 1$ .
- Let  $G_{A(k)}$  denote  $P_{A(k)}$ , and  $g_{A(k)}$  be its density (w.r.t. counting measure),  $k = 0, \dots, K$ ,
- Then, density of  $P$ :

$$p(o) = \prod_k q_{L(k)} \prod_k g_{A(k)}.$$

- Let  $Q = (Q_{L(k)} : k)$ ,  $G = (G_{A(k)} : k)$ .

## Statistical model

- Let  $\mathcal{Q}$  be a nonparametric parameter space for  $Q$ .
- Let  $\mathcal{G}$  be a possibly restricted parameter space for  $G$ .
- This allows incorporating assumptions on treatment and censoring mechanism.

$$\mathcal{M} = \{P_{Q,G} : Q \in \mathcal{Q}, G \in \mathcal{G}\}.$$

## Stochastic intervention

- Let  $G^* = (G_{A^*(1)}, \dots, G_{A^*(k)})$  be user supplied choice of conditional distributions.
- $g_{A^*(k)} = g_{A_1^*(k)} g_{A_2^*(k)}$  factorizes in treatment and censoring conditional distribution.
- Let censoring distribution  $G_{A_2^*(k)}$  be degenerate at 0, whatever conditioning event.
- We refer to  $G^*$  as a stochastic intervention if  $g_{A_1^*}$  is non-degenerate, and static or dynamic otherwise.

## G-computation formula for post-intervention distribution

Then,

$$p_{Q,G^*}(do) = \prod_k q_{L(k)}(I(k) | \bar{I}(k-1), \bar{a}(k-1)) \prod_k g_{A^*(k)}(a(k) | \bar{a}(k-1), \bar{I}(k)).$$

- The latter density is called the *G*-computation formula for  $G^*$ -post-intervention distribution.
- Note, it represents a modification of a data distribution  $P_{Q,G}$  obtained by replacing  $G$  by  $G^*$ .

## Statistical target parameter

- Let  $\Psi_{g^*} : \mathcal{M} \rightarrow \mathbb{R}$  be defined by

$$\Psi_{g^*}(P_{Q,G}) = E_{P_{Q,G^*}} Y.$$

- Could be evaluated by Monte-Carlo simulation.

## Causal model

- Define equations  $L(k) = f_{L(k)}(\bar{L}(k-1), \bar{A}(k-1), U_{L(k)})$ ,  
 $k = 1, \dots, K+1$ ,  $A(k) = f_{A(k)}(\bar{A}(k-1), \bar{L}(k), U_{A(k)})$ ,  $k = 1, \dots, K$ .
- Let  $U \sim P_U$  be collecting of exogenous error-variables  $U_{L(k)}$ ,  $U_{A(k)}$ .
- Let  $f$  be collection of functions  $f_{L(k)}$  and  $f_{A(k)}$ .
- Given  $P_U$  and  $f$ , this defines a probability distribution for  $O$ .
- Thus, this defines a parameterization  $P = P_{P_U, f}$ .

## Post-intervention distribution of $P$

- Given  $f$  and  $P_U$  (and thus given  $P$ ).
- Replace evaluation of  $f_{A(k)}$  in this data experiment by drawing from  $G_{A(k)}^*$ .
- This defines a new data distribution.
- We denote the random variable with  $O_{g^*}$  and its distribution with  $P_{g^*}$ .
- $P_{g^*}$  is a post-intervention distribution of  $P$ .

## Intervention specific survival curve under multiple time-point intervention

- Let  $Y_{g^*}$  be final outcome in  $O_{g^*}$ .
- Full-data quantity  $S_{0g^*}(K + 1) = E_0 Y_{g^*}$  treatment specific survival curve under intervention  $g^*$  at time  $K + 1$ .

## Strong sequential randomization assumption

- Assume, under  $P$ ,  $A(t)$  is independent of  $(Y_{a_1 0} : a_1)$ , given  $\bar{L}(t), \bar{A}(t - 1)$ .
- This strong SRA assumption on  $P$  allows identification of any full-data parameter of distribution of  $Y_{g^*}$  from observed data distribution  $P$ .

## Identification

- If strong SRA holds and  $\sup_o |g^*(o)/g(o)| < \infty$  on a support of  $P$ , then

$$p_{g^*} = p_{Q, G^*}.$$

- Thus, then  $S_{g^*}(K + 1) = \Psi_{g^*}(P)$ .
- Note that  $\Psi_{g^*}(P)$  only depends on  $P$  through  $Q(P)$ : we will also use notation  $\Psi_{g^*}(Q)$ .

## Statistical estimation problem

- Given a data set  $O_1, \dots, O_n \sim P_{Q_0, G_0} \in \mathcal{M}$ , we want to construct a TMLE (i.e., efficient plug-in estimator) of  $\Psi_{g^*}(P_0)$ , where  $\Psi_{g^*} : \mathcal{M} \rightarrow \mathbb{R}$  is defined by  $\Psi_{g^*}(P) = E_{P_{Q, G^*}} Y$ .

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Sequentially integration out  $L(k+1)$  and  $A(k)$ , going backwards

- Let  $\bar{Q}_{L(K+1)} = E_P(Y \mid \bar{A}(K), \bar{L}(K))$ .
- Let  $\bar{Q}_{A(K)} = E_{g_{A^*(K)}} \bar{Q}^{g^*}$ .
- Let  $\bar{Q}_{L(K)} = E_{Q_{L(K)}} \bar{Q}_{A(K)}$ .
- Let  $bar{Q}_{A(K-1)} = E_{g_{A^*(K-1)}} \bar{Q}_{L(K)}$ .

## Iterate till all variables are integrated out

- Set  $k = K - 1$ . We just evaluated  $\bar{Q}_{A(k)}$ .
- Let  $\bar{Q}_{L(k)} = E_{Q_{L(k)}} \bar{Q}_{A(k)}$ .
- Let  $\bar{Q}_{A(k-1)} = E_{g_{A^*(k-1)}} \bar{Q}_{L(k)}$ .
- Let  $k = k - 1$  and repeat above 2 steps, and iterate till we obtain  $\bar{Q}_{A(0)}(L(0))$ .

## Sequential regression representation of target parameter

- Let  $\bar{Q}_{L(0)} = E_{Q_{L(0)}} \bar{Q}_{A(0)}$ , marginal expectation over  $L(0)$ .
- Then  $\Psi_{g^*}(P) = \Psi_{g^*}(Q) = \bar{Q}_{L(0)}$ .
- Note that  $\Psi_{g^*}(P)$  depends on  $P$  through  $\bar{Q} = (\bar{Q}_{L(0)}, \bar{Q}_{L(K+1)})$ .
- All the conditional regressions  $\bar{Q}_{A(k)}$  are w.r.t. known stochastic intervention, and do thus not represent parameter of  $P$ .
- If various intervention are considered, then we would use notation  $\bar{Q}_{L(k)}^{g^*}$ ,  $\bar{Q}_{A(k)}^{g^*}$  and  $\bar{Q}^{g^*}$  for the above defined parameters.

## Sequential super-learning

- Note that each  $\bar{Q}_{L(k)}$  is a regression of previous  $\bar{Q}_{A(k)}$  (outcome) on past  $\bar{A}(k-1)$ ,  $\bar{L}(k-1)$ , and similarly, for  $\bar{Q}_{A(k)}$ .
- Therefore, we could estimate any  $\bar{Q}_{L(k)}$  by sequentially fitting a regression (e.g., using super-learning) where the previously fitted regression curve represents the outcome in this regression.
- The evaluations  $\bar{Q}_{A(k)}$  are known and are thus not involving estimation.
- In particular, sequential regression estimation can be used to estimate  $\bar{Q}_{L(0)} = \Psi_{g^*}(P)$ .

## Utilize known degeneracies in data distribution

- The conditional expectation in  $\bar{Q}_{L(k)}$  is known for any history  $\bar{L}(k-1), \bar{A}(k-1)$  for which  $\tilde{T} \leq k-1$ .
- So estimation of  $\bar{Q}_{L(k)}$  focusses on estimation conditional on  $\tilde{T} > k-1$ .
- If other degeneracies are present (e.g.,  $L(k) = L(k-1)$  for history  $\bar{L}(k-1), \bar{A}(k-1)$ ), then these should be respected as well.

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## Recap computation of canonical gradient

- A previous lecture on calculations of canonical gradients shows that

$$D^*(P) = \sum_{k=0}^{K+1} \left\{ E_P(D \mid \bar{L}(k), \bar{A}(k-1)) - E_P(D \mid \bar{L}(k-1), \bar{A}(k-1)) \right\},$$

where  $D = D(P)$  is a gradient of  $\Psi_{g^*}$  at  $P$  in model  $\mathcal{M}(G)$  with  $G$  known

## Initial gradient for model with $G$ known

- Let

$$D(P) = \frac{\prod_{k=1}^K g_{A^*(k)}(O)}{\prod_{k=1}^K g_{A(k)}(O)} Y - \Psi_{g^*}(P).$$

- Note that  $E_P D(P) = 0$ . Thus

$$\psi_n = \frac{1}{n} \sum_{i=1}^n \frac{\prod_{k=1}^K g_{A^*(k)}(O_i)}{\prod_{k=1}^K g_{A(k)}(O_i)} Y_i$$

is RAL (unbiased even) estimator of  $\psi_0$ , and its influence curve equals  $D(P)$ .

- Therefore,  $D(P)$  is a gradient of pathwise derivative of  $\Psi_{g^*}$  at  $P$ .

## Canonical gradient

- Plugging in and some algebra now yields following expression for  $D^*(P)$ .
- We have

$$D^*(P) = \sum_{t=0}^{K+1} D_t^*(P),$$

where  $D_0^*(P) = \bar{Q}_{A(0)} - \bar{Q}_{L(0)}$ , and for  $k = 1, \dots, K + 1$ ,

$$D_k^*(P) = \frac{g_{1:k-1}^*(O)}{g_{1:k-1}(O)} (\bar{Q}_{A(k)} - \bar{Q}_{L(k)}).$$

- Let

$$C_k(g) = \frac{g_{1:k-1}^*(O)}{g_{1:k-1}(O)}.$$

- Here  $g_{1:k} = \prod_{j=1}^k g_{A(j)}$  and similarly we define  $g_{1:k}^* = \prod_{j=1}^k g_{A^*(j)}$ .

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- 2 Sequential regression representation of target parameter
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## Sequential regression based TMLE

- We focus on estimation of the sequential regression  $\bar{Q}_{L(k)}$ .
- The TMLE will target each of these regressions sequentially in same order.
- The final targeted fit of  $\bar{Q}_{L(0)}$  will represent the TMLE of  $\Psi_{g^*}(P_0)$ .

## Submodel

- For  $k = K + 1, \dots, 1$ , let

$$\text{Logit } \bar{Q}_{L(k),\epsilon} = \text{Logit } \bar{Q}_{L(k)} + \epsilon C_k(g),$$

where

$$C_k(g) = \frac{\prod_{j=1}^{k-1} g_{A^*(j)}}{\prod_{j=1}^{k-1} g_{A(j)}} (\bar{L}(k-1), \bar{A}(k-1)).$$

- Let

$$\text{Logit } \bar{Q}_{L(0),\epsilon} = \text{Logit } \bar{Q}_{L(0)} + \epsilon$$

be the submodel through  $\bar{Q}_{L(0)}$ .

## Loss-function

- The loss for  $\bar{Q}_{L(K+1)}$  is

$$L(\bar{Q}_{L(K+1)}) = - \left\{ Y \log \bar{Q}_{L(k)} + (1 - Y) \log(1 - \bar{Q}_{L(k)}) \right\}.$$

- For  $k = K, \dots, 1$ , we define the following loss function for  $\bar{Q}_{L(k)}$ , given that we already computed  $\bar{Q}_{A(k)}$ :

$$L_{\bar{Q}_{A(k)}}(\bar{Q}_{L(k)}) = - \left\{ \bar{Q}_{A(k)} \log \bar{Q}_{L(k)} + (1 - \bar{Q}_{A(k)}) \log(1 - \bar{Q}_{L(k)}) \right\}.$$

- We also define the loss for  $\bar{Q}_{L(0)}$ :

$$L_{\bar{Q}_{A(0)}}(\bar{Q}_{L(0)}) = - \left\{ \bar{Q}_{A(0)} \log \bar{Q}_{L(0)} + (1 - \bar{Q}_{A(0)}) \log(1 - \bar{Q}_{L(0)}) \right\}.$$

- These loss functions can be used in sequence for both sequential (super) learning as well as the sequential targeting.

## Score of submodel generate canonical gradient

- For  $k = K, \dots, 1$ , we have

$$\frac{d}{d\epsilon} L_{\bar{Q}_{A(k)}}(\bar{Q}_{L(k),\epsilon}) \Big|_{\epsilon=0} = C_k(g)(\bar{Q}_{A(k)} - \bar{Q}_{L(k)}),$$

which thus equals  $D_k^*(P)$ . We make the convention that  
 $\bar{Q}_{A(K+1)} = Y$

- In addition, for  $k = 0$ -term

$$\frac{d}{d\epsilon} L_{\bar{Q}_{A(0)}}(\bar{Q}_{L(0),\epsilon}) \Big|_{\epsilon=0} = \bar{Q}_{A(0)} - \bar{Q}_{L(0)},$$

which equals  $D_0^*(P)$ .

- Thus, the linear span of the  $K + 2$  scores of the  $K + 2$  submodels corresponding with  $k = 0, \dots, K + 1$ , includes

$$D^*(P) = -\sum_{k=0}^{K+1} D_k^*(P).$$

## Estimator of treatment and censoring mechanism

- We can use loss-based super-learning to estimate the conditional probability distributions  $g_{A_1(k)}$  and  $g_{A_2(k)}$  of treatment and censoring, respectively.
- One uses the log-likelihood loss.
- One could use a separate estimator for each  $k$ , but one could also treat  $k$  as a covariate and carry out a super-learner of the  $(g_{A_1(k)} : k)$  with its log-likelihood loss applied to pooled data set in which each subject contributes  $\tilde{T}$  rows.

## First step of TMLE

- Obtain estimator  $\bar{Q}_{L(K+1),n}$ .
- Construct submodel  $\bar{Q}_{L(K+1),n,\epsilon}$  and fit  
 $\epsilon_{n,K+1} = \arg \min_{\epsilon} P_n L(\bar{Q}_{L(K+1),n,\epsilon})$ .
- Let  $\bar{Q}_{L(K+1),n}^* = \bar{Q}_{L(K+1),n,\epsilon_{n,K+1}}$ , which is the TMLE of  $\bar{Q}_{L(K+1)}$ .
- Compute  $\bar{Q}_{A(K),n}^*$  by evaluating conditional expectation of  $\bar{Q}_{L(K+1),n}^*$  w.r.t.  $g_{A^*(K)}$ .

## k-th step TMLE

- Let  $k = K$ .
- Obtain estimator  $\bar{Q}_{L(k),n}$ .
- Construct submodel  $\bar{Q}_{L(k),n,\epsilon}$  and fit  
$$\epsilon_{n,k} = \arg \min_{\epsilon} P_n L_{\bar{Q}_{n,A(k)}^*}(\bar{Q}_{L(K+1),n,\epsilon}).$$
- Let  $\bar{Q}_{L(k),n}^* = \bar{Q}_{L(k),n,\epsilon_{n,k}}$ , which is the TMLE of  $\bar{Q}_{L(k)}$ .
- Compute  $\bar{Q}_{A(k-1),n}^*$  by evaluating conditional expectation of  $\bar{Q}_{L(k),n}^*$  w.r.t.  $g_{A^*(k-1)}$ .

# TMLE

- Set  $k = k - 1$ , and iterate the above steps for computing the next TMLE  $\bar{Q}_{L(k),n}^*$  and  $\bar{Q}_{A(k-1),n}^*$ , till  $k = 1$ .
- Estimate  $\bar{Q}_{L(0)}$  with the empirical mean  $\bar{Q}_{L(0),n}^*$  of  $\bar{Q}_{A(0),n}^*(L_i(0))$  over  $L_i(0)$ .
- No need to do a targeting step for the latter (would just set  $\epsilon_{n,k=0} = 0$ ).
- This finalizes the TMLE  $\bar{Q}_n^*$  of  $\bar{Q}_0 = (\bar{Q}_{0,L(k)} : k = 0, \dots, K + 1)$ .
- The TMLE of  $\psi_0$  is thus  $\psi_n^* = \Psi(\bar{Q}_n^*) = \bar{Q}_{L(0),n}^*$ .

## Inference

- We estimate  $D^*(P_0)$  with its plug-in estimator  $D^*(\bar{Q}_n^*, G_n)$ .
- We estimate the variance of  $\psi_n^*$  with  $\sigma_n^2 = P_n D^*(\bar{Q}_n^*, G_n)^2/n$ .
- $\psi_n^* \pm 1.96\sigma_n$  is an asymptotic 0.95-confidence interval.

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`ltmle` package (Petersen et al. (2013), van der Laan, Gruber (2012), Schitzer et al. (2013))

R package: `ltmle`

- Causal effect estimation with multiple intervention nodes
  - Intervention specific mean under longitudinal dynamic interventions
  - Dynamic marginal structural working models
- General longitudinal data structures
  - Repeated measures outcomes, survival
  - Right censoring
  - Inference: different variance estimators.
- Estimators
  - IPTW
  - Non-targeted MLE
  - TMLE (two algorithms for MSM)
- Options include nuisance parameter estimation via `glm` regression formulas or calling `SuperLearner()`