Adaptive-TMLE for the Average Treatment Effect based on Randomized Controlled Trial Augmented with Real-World Data

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21st Century Cures Act

- A law passed by the US Congress in 2016 [1];
- *Main goal:* Improve the **efficiency of drug and device development** by utilizing evidence from the **real-world** (e.g. observational data, rather than randomized controlled trials), therefore reducing the time to deliver them to patients who are in need;
- ***Framework for FDA's Real-World Evidence Program:*** A framework for evaluating potential use of real-world evidence (RWE) to help support approval of a new indication for a drug already approved or to help support or satisfy drug post-approval study requirements [2];
- Use real-world data (RWD) to augment or replace the control arm of an RCT.

Agenda

- Discuss an application of the highly adaptive lasso (HAL) estimator in data integration/data fusion problems;
- Introduce a super-efficient estimator constructed using the Adaptive-TMLE framework for the average treatment effect of the combined RCT and RWD;
- Demonstrate the ‘atmle’ R software package.

Observed data and statistical model

- $S \in \{0, 1\}$, study indicator ($S = 1$ denotes RCT, $S = 0$ denotes RWD);
- $W \in \mathbb{R}^d$, patient characteristics;
- $A \in \{0, 1\}$, binary treatment;
- $Y \in \mathbb{R}$, outcome;
- Observe n i.i.d $O = (S, W, A, Y) \sim P_0 \in \mathcal{M}$.
- We factorize the density of O as follows

$$p(s, w, a, y) = p_S(s) p_W(w \mid s) g_A(a \mid s, w) q_Y(y \mid s, w, a).$$

- For the statistical model, we only make assumption on $g_A(a \mid s, w)$.

Candidate target parameters

1. Consider the treatment effect only in the RCT, but pool the covariate distribution W. That is, we average over $p_W = p_{W|S=0}p_{S=0} + p_{W|S=1}p_{S=1}$:

$$\Psi(P) = \mathbb{E}_W \mathbb{E}(Y_1 - Y_0 \mid S = 1, W).$$

2. Direct pooling, ignoring whether patients are from RCT or RWD:

$$\tilde{\Psi}(P) = \mathbb{E}(Y_1 - Y_0).$$

Why not use the pooled-ATE parameter $\tilde{\Psi}$?

- The pooled-ATE estimand,

$$\tilde{\Psi}(P_0) = \mathbb{E}[\mathbb{E}(Y \mid A = 1, W) - \mathbb{E}(Y \mid A = 0, W)];$$

- It is quantifying the causal effect while **completely ignoring whether a patient is from the RCT or the RWD**;
- It may be **biased**, i.e.

$$\mathbb{E}_W\mathbb{E}(Y_1 - Y_0 \mid W) \neq \mathbb{E}_W\mathbb{E}(Y \mid W, A = 1) - \mathbb{E}_W\mathbb{E}(Y \mid W, A = 0),$$

due to

$$\mathbb{E}_W\mathbb{E}(Y_1 - Y_0 \mid W, S = 0) \neq \mathbb{E}_W\mathbb{E}(Y \mid S = 0, W, A = 1) - \mathbb{E}_W\mathbb{E}(Y \mid S = 0, W, A = 0).$$

Identification assumptions

$$\Psi(P) = \mathbb{E}_W \mathbb{E}(Y_1 - Y_0 \mid S = 1, W)$$

- Mean exchangeability in the trial (true by design of RCT):

$$\mathbb{E}(Y_a \mid S = 1, W, A = a) = \mathbb{E}(Y_a \mid S = 1, W),\ a \in \mathcal{A}$$

- Positivity of receiving treatment in the trial (true by design of RCT):

$$0 < \mathbb{P}(A = 1 \mid S = 1, W) < 1,\ P_W\text{-a.e.}$$

- Positivity of trial enrollment:

$$\mathbb{P}(S = 1 \mid W) > 0,\ P_W\text{-a.e.}$$

Under the identification assumptions, our target estimand is:

$$\Psi(P_0) = \mathbb{E}[\mathbb{E}(Y \mid S = 1, W, A = 1) - \mathbb{E}(Y \mid S = 1, W, A = 0)].$$

Why do we consider this parameter?

- Almost **no additional assumptions** other than the standard RCT assumptions, except for the positivity of trial enrollment, which can typically be made plausible by design (e.g. screening, matching, etc.);
- It offers a way to utilize the **combined RCT data and RWD** for estimation;
- Pushing the sample average treatment effect [5] towards the population average treatment effect, by having **a more realistic and representative sample of the target population**;
- Problem: However, analysis of the efficient influence function of the this target parameter shows that an efficient estimator of this target parameter **does not necessarily offer efficiency gain** over an efficient estimator of the RCT-only target parameter (we will empirically show this in simulations too).

A Cross-Validated Targeted Maximum Likelihood Estimator for Data-Adaptive Experiment Selection Applied to the Augmentation of RCT Control Arms with External Data

A Preprint

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Abstract

Augmenting the control arm of a randomized controlled trial (RCT) with external data may increase power at the risk of introducing bias. Existing data fusion estimators generally rely on stringent assumptions or may have decreased coverage or power in the presence of bias. Framing the problem as one of data-adaptive experiment selection, potential experiments include the RCT only or the RCT combined with different candidate real-world datasets. To select and analyze the experiment with the optimal bias-variance tradeoff, we develop a novel experiment-selector cross-validated targeted maximum likelihood estimator (ES-CVTMLE). The ES-CVTMLE uses two bias estimates: 1) a function of the difference in conditional mean outcome under control between the RCT and combined experiments and 2) an estimate of the average treatment effect on a negative control outcome (NCO). We define the asymptotic distribution of the ES-CVTMLE under varying magnitudes of bias and construct confidence intervals by Monte Carlo simulation. In simulations involving violations of identification assumptions, the ES-CVTMLE had better coverage than test-then-pool approaches and an NCO-based bias adjustment approach and higher power than one implementation of a Bayesian dynamic borrowing approach. We further demonstrate the ability of the ES-CVTMLE to distinguish biased from unbiased external controls through a re-analysis of the effect of liraglutide on glycemic control from the LEADER trial. The ES-CVTMLE has the potential to improve power while providing relatively robust inference for future hybrid RCT-RWD studies.

- Problem: if the **magnitude of the bias is large**, but relatively **simple to learn**, then ES-CVTMLE offers no efficient gain, which is not good):

We want our method...

- To still achieve efficiency gain even when the magnitude of the bias is large, but the bias has a relatively simple form;
- In any case, the estimator should not perform worse than a nonparametrically efficient estimator.
- Can we apply the Adaptive-TMLE [4] estimation framework in this setting?

Decomposition of the target estimand as the difference between pooled-ATE and a bias term [5]

- Target estimand, **RCT-ATE** estimand:

$$\Psi(P_0) = \mathbb{E}[\mathbb{E}(Y \mid S = 1, W, A = 1) - \mathbb{E}(Y \mid S = 1, W, A = 0)]$$

- 1st component, **pooled-ATE** estimand:

$$\tilde{\Psi}(P_0) = \mathbb{E}[\mathbb{E}(Y \mid W, A = 1) - \mathbb{E}(Y \mid W, A = 0)]$$

- 2nd component, **bias** estimand:

$$\Psi^{\#}(P_0) = \tilde{\Psi}(P_0) - \Psi(P_0)$$

$$\Psi(P_0) = \tilde{\Psi}(P_0) - \Psi^{\#}(P_0) \text{ bias correction}$$

So, we need to estimate two components

- 1st component, **pooled-ATE** estimand:

$$\tilde{\Psi}(P_0) = \mathbb{E}[T(W)],$$

where

$$T(W) = \mathbb{E}(Y \mid W, A = 1) - \mathbb{E}(Y \mid W, A = 0);$$

- 2nd component, **bias** estimand:

$$\Psi^{\#}(P_0) = \mathbb{E}[\Pi(0 \mid W, 0)\tau(W, 0) - \Pi(0 \mid W, 1)\tau(W, 1)],$$

where

$$\Pi(s \mid W, A) = \mathbb{P}(S = s \mid W, A),$$

and

$$\tau(W, A) = \mathbb{E}(Y \mid S = 1, W, A) - \mathbb{E}(Y \mid S = 0, W, A)$$

Algorithm 1 Adaptive-TMLE

Initial estimator $\Psi^{\#}_{\mathcal{M}_{w,2,n}}(P_n)$ of $\Psi^{\#}_{\mathcal{M}_{w,2,n}}(P_0)$:

  Obtain nuisance estimate Π_n of $\Pi_0(1 \mid W, A) = P(S = 1 \mid W, A)$;

  Obtain nuisance estimate θ_n of $\theta_0(W, A) = E(Y \mid W, A)$;

  Compute pseudo outcome $Y_{\Psi^{\#},\text{pseudo}} \equiv (Y - \theta_n)/(S - \Pi_n)$ and weight $\mathcal{W}_{\Psi^{\#},\text{pseudo}} \equiv (S - \Pi_n)^2$;

  Fit relaxed-HAL using (W, A) as covariates, $Y_{\Psi^{\#},\text{pseudo}}$ as outcome, and $\mathcal{W}_{\Psi^{\#},\text{pseudo}}$ as weight;

  Get initial estimate $\Psi^{\#}_{\mathcal{M}_{w,2,n}}(P_n) \equiv 1/n \sum_{i=1}^{n} (\Pi_n(0 \mid W_i, 0)\tau_n(W_i, 0) - \Pi_n(0 \mid W_i, 1)\tau_n(W_i, 1))$;

Initial estimator $\tilde{\Psi}_{\mathcal{M}_{w,1,n}}(P_n)$ of $\tilde{\Psi}_{\mathcal{M}_{w,1,n}}(P_0)$:

  Obtain nuisance estimate g_n of $g_0(1 \mid W) = P(A = 1 \mid W)$;

  Obtain nuisance estimate $\tilde{\theta}_n$ of $\tilde{\theta}_0(W) = E(Y \mid W)$;

  Define pseudo outcome $Y_{\tilde{\Psi},\text{pseudo}} \equiv (Y - \theta_n)/(A - g_n)$ and weight $\mathcal{W}_{\tilde{\Psi},\text{pseudo}} \equiv (A - g_n)^2$;

  Fit relaxed-HAL using W as covariates, $Y_{\tilde{\Psi},\text{pseudo}}$ as outcome, and $\mathcal{W}_{\tilde{\Psi},\text{pseudo}}$ as weight;

  Get initial estimate $\tilde{\Psi}_{\mathcal{M}_{w,1,n}}(P_n) \equiv 1/n \sum_{i=1}^{n} (T_n(W_i)) \equiv \tilde{\Psi}_{\mathcal{M}_{w,1,n}}(P_n^*)$;

Additional TMLE targeting for Π-component:

  Compute clever covariate $C(g_n, \beta_n) = I(A = 1)/g_n(1 \mid W)\tau_n(W, 1) - I(A = 0)/g_n(0 \mid W)\tau_n(W, 0)$;

  Use $C(g_n, \beta_n)$ to perform a TMLE targeting and obtain an updated estimate Π_n^* of Π_0;

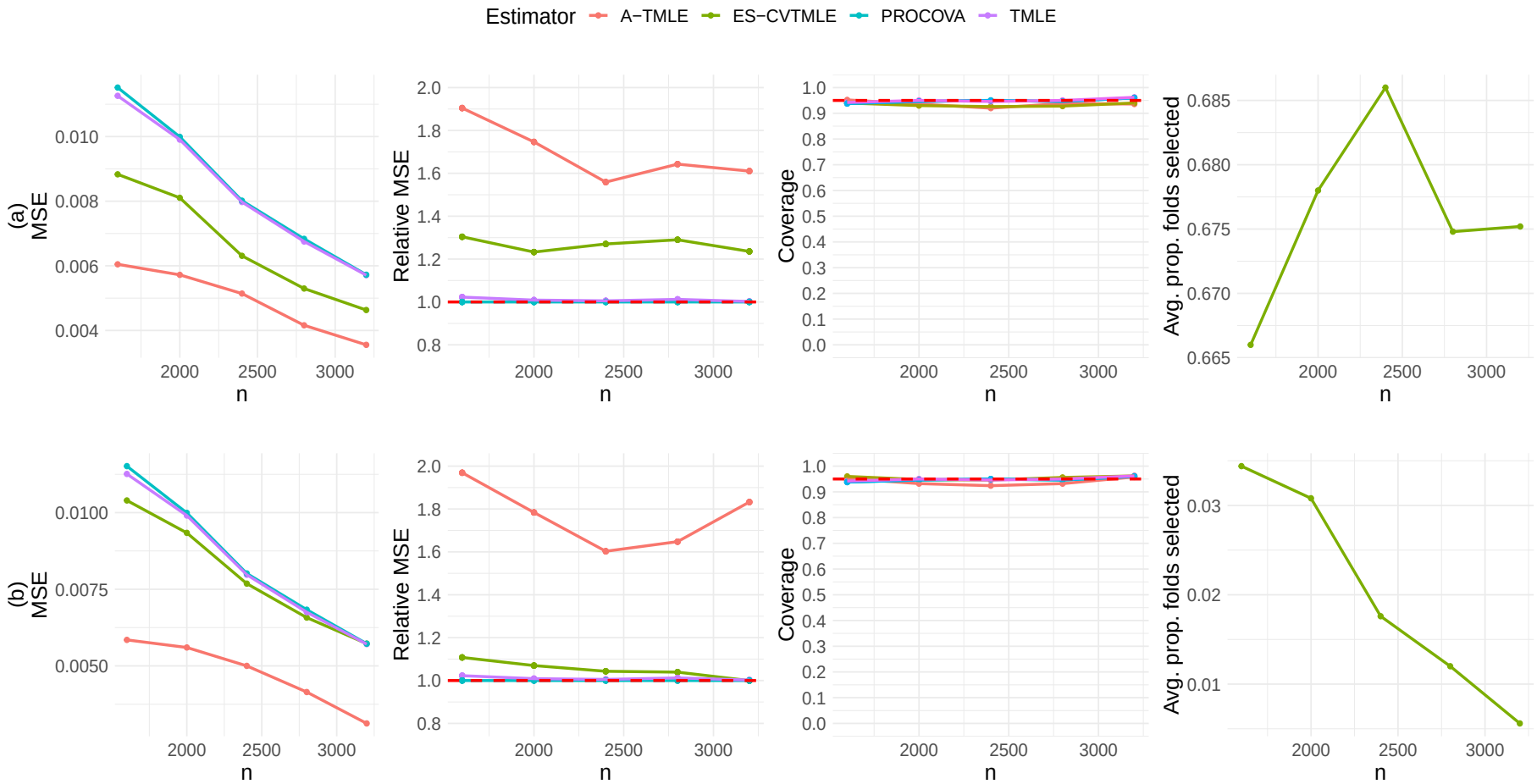
  Get updated estimate $\Psi^{\#}_{\mathcal{M}_{w,2,n}}(P_n^*) \equiv 1/n \sum_{i=1}^{n} (\Pi_n^*(0 \mid W_i, 0)\tau_n(W_i, 0) - \Pi_n^*(0 \mid W_i, 1)\tau_n(W_i, 1))$;

Obtain the final estimate $\Psi_{\mathcal{M}_{w,n}}(P_n^*) = \tilde{\Psi}_{\mathcal{M}_{w,1,n}}(P_n^*) - \Psi^{\#}_{\mathcal{M}_{w,2,n}}(P_n^*)$;

Compute the 95% confidence interval given by $\Psi_{\mathcal{M}_{w,n}}(P_n^*) \pm 1.96\sqrt{P_n(D_{\mathcal{M}_{w,1,n},\tilde{\Psi}} - D_{\mathcal{M}_{w,2,n},\Psi^{\#}})^2/n}$.

Candidate estimators to compare

Estimator	Description
A-TMLE	Our proposed estimator, applying the A-TMLE framework to estimate both the pooled-ATE $\tilde{\Psi}$ and the bias $\Psi^{\#}$.
ES-CVTMLE	An estimator for integrating RCT with RWD within the TMLE framework, data-adaptively chooses between RCT-only or pooled-ATE to optimize bias-variance trade-off. [5] showed its superior efficiency gain over alternatives.
PROCOVA	A prognostic score covariate-adjustment method [6].
TMLE	A standard TMLE for the target parameter.
RCT-only	A standard TMLE for ATE parameter using RCT data alone, serving as the best estimator in the absence of external data.



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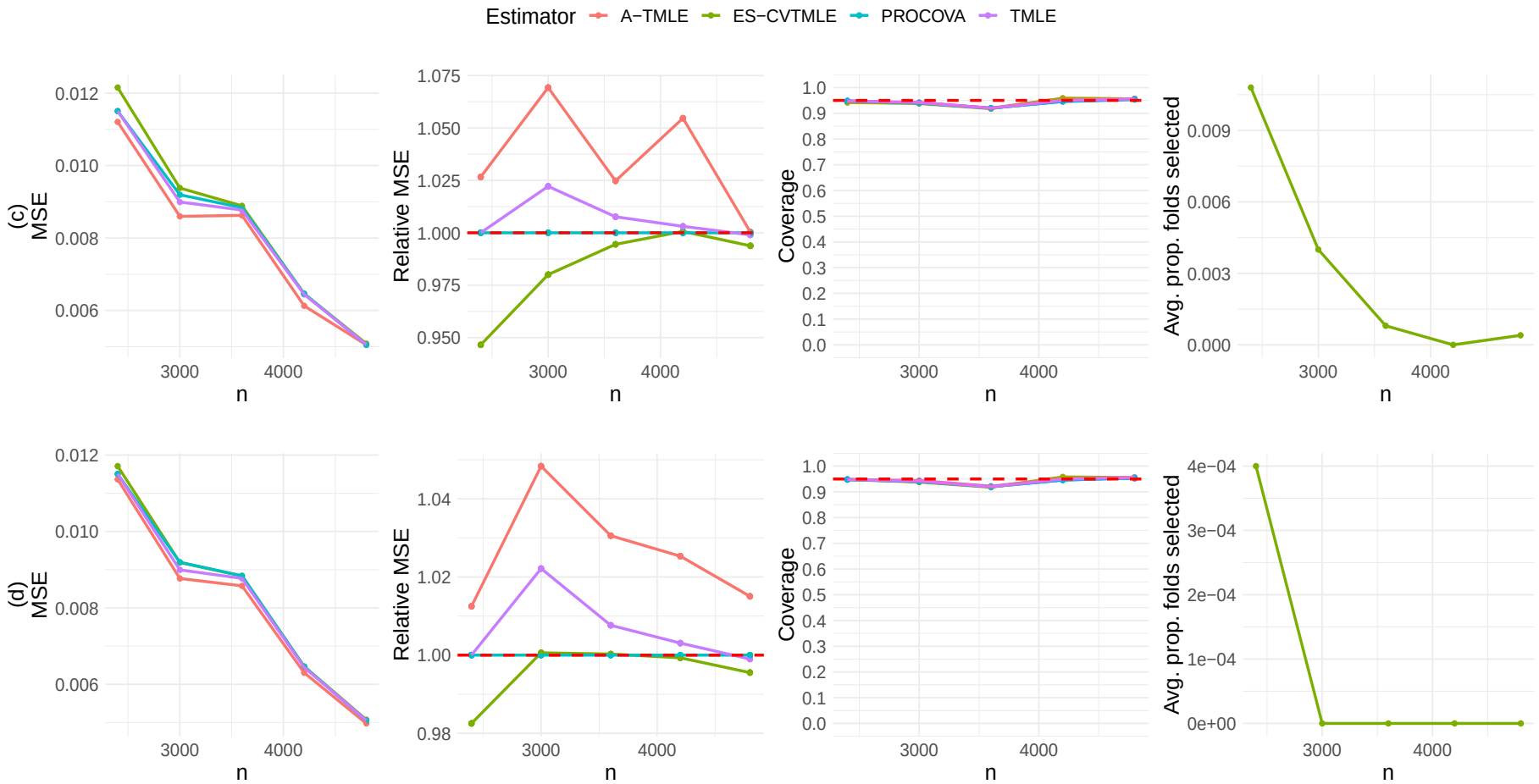

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95% CI width comparisons

Table 1: A-TMLE's 95% CI width as a percentage of other methods'.

Method	Scenario (a)	Scenario (b)	Scenario (c)	Scenario (d)
ES-CVTMLE	66.1%	60.4%	98.3%	98.2%
Regular TMLE	59.1%	61.2%	99.1%	99.1%
PROCOVA	59.0%	61.1%	99.0%	99.0%
RCT-only	59.0%	61.1%	99.0%	99.0%

`atmle` : Adaptive-TMLE for RCT + RWD

License GPL v3

> Adaptive Targeted Minimum Loss-Based Estimation. This package uses adaptive targeted minimum loss-based estimation to estimate the average treatment effect from combined randomized trial and real-world data.

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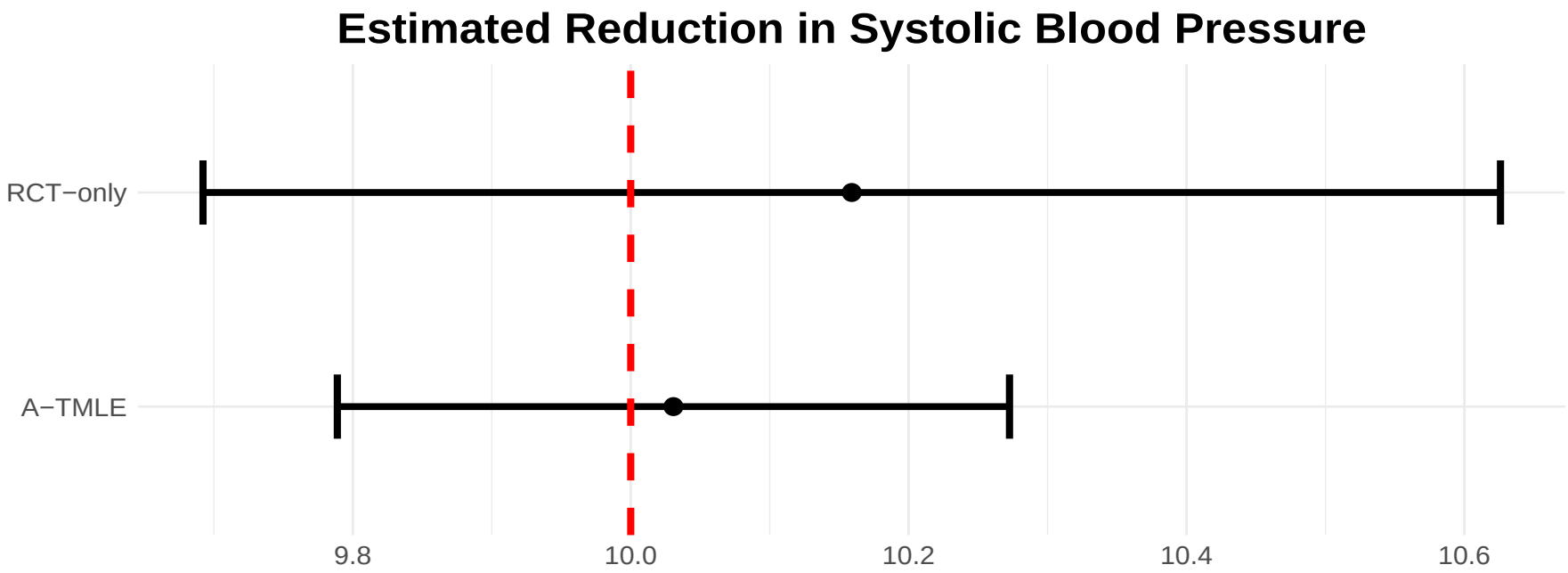
https://github.com/tq21/atmle

```
> atmle_res <- atmle(data = data,
+                    S_node = 1,
+                    W_node = c(2, 3, 4),
+                    A_node = 5,
+                    Y_node = 6,
+                    controls_only = FALSE,
+                    theta_method = "glm",
+                    Pi_method = "glm",
+                    theta_tilde_method = "glm",
+                    g_method = "glm",
+                    bias_working_model = "HAL",
+                    pooled_working_model = "HAL",
+                    g_rct = 0.67,
+                    family = "gaussian")
learning θ(W,A)=E(Y|W,A)...Done!
learning Π(S=1|W,A)=P(S=1|W,A)...Done!
learning g(A=1|W)=P(A=1|W)...Done!
learning τ(W,A)=E(Y|S=1,W,A)-E(Y|S=0,W,A)...Done!
targeting Π(S=1|W,A)=P(S=1|W,A)...Done!
learning θ̃(W)=E(Y|W)...Done!
learning T(W)=E(Y|W,A=1)-E(Y|W,A=0)...Done!

Pooled ATE: 1.6 (1.45, 1.76)
Bias-corrected ATE: 1.46 (1.29, 1.63)
```

Vignette


Estimated Reduction in Systolic Blood Pressure
RCT−only
A−TMLE
9.8
10.0
10.2
10.4
10.6

Summary

- We introduced an application of the highly adaptive lasso (HAL) estimator for more efficient estimation of ATE using RCT + RWD;
- A-TMLE utilizes real-world data to improve the efficiency of randomized trial results without biasing the estimates of intervention effects. This approach could allow for smaller, faster trials, decreasing the time until patients can receive effective interventions;
- Unlike existing data fusion methods, our estimator still achieves efficiency gain even when the magnitude of the bias is large but the bias has a relatively simple form. As the simple parametric form becomes nonparametric, the estimand becomes the estimand that ignores the outcome data in the external study, corresponding with a nonparametric efficient estimator.

Bibliography I

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