

A Nonparametric Super-Efficient Estimator of the Average Treatment Effect¹

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Abstract. Doubly robust estimators are a popular means of estimating causal effects. Such estimators combine an estimate of the conditional mean of the outcome given treatment and confounders (the so-called outcome regression) with an estimate of the conditional probability of treatment given confounders (the propensity score) to generate an estimate of the effect of interest. In addition to enjoying the double-robustness property, these estimators have additional benefits. First, flexible regression tools, such as those developed in the field of machine learning, can be utilized to estimate the relevant regressions, while the estimators of the treatment effects retain desirable statistical properties. Furthermore, these estimators are often statistically efficient, achieving the lower bound on the variance of regular, asymptotically linear estimators. However, in spite of their asymptotic optimality, in problems where causal estimands are weakly identifiable, these estimators may behave erratically. We propose new estimation techniques for use in these challenging settings. Our estimators build on two existing frameworks for efficient estimation: targeted minimum loss estimation and one-step estimation. However, rather than using an estimate of the propensity score in their construction, we instead opt for an alternative regression quantity when building our estimators: the conditional probability of treatment given the conditional mean outcome. We discuss the theoretical implications and demonstrate the estimators' performance in simulated and real data.

Key words and phrases: Causal inference, average treatment effect, asymptotic linearity, efficient influence function, collaborative targeted minimum loss estimation, super efficiency.

1. INTRODUCTION

In many areas of research, the scientific question of interest can often be answered by drawing statistical inference about the average effect of a treatment on an outcome. Depending on the setting, this “treatment” might correspond to an actual therapeutic treatment, a harmful exposure, or a policy intervention. We use $Y(1)$ to denote the potential outcome of a typical data unit sampled from the population of interest when the unit receives the treat-

ment of interest, and $Y(0)$ to denote the potential outcome if that unit instead receives control. In this work, we focus on estimation of the average treatment effect (ATE), the average difference between $Y(1)$ and $Y(0)$ in the population of interest.

Often, due to ethical or logistical constraints, units cannot be randomly assigned to receive/not receive the treatment. Thus, to draw valid conclusions about the ATE, we require methodology that adjusts for confounding of the treatment/outcome relationship. Although epidemiological and other applied literatures are still considering the relative merits of various methodologies, the statistical literature has provided direction through consideration of semiparametric efficient methods. The literature provides many examples of such estimators. In some situations, regularized or sieve maximum likelihood estimators can be used (e.g., van der Vaart, 1998); however, this generally requires careful selection of tuning parameters. Existing literature lacks general guidelines for how such parameters can be chosen in practice, which limits the util-

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ity of these strategies. On the other hand, methods that are built around a causal effect parameter’s efficient influence function offer a more straightforward approach to estimation. Foremost amongst these approaches are one-step estimation (Ibragimov and Has’minskii, 1981, Pfanzagl, 1982, Bickel et al., 1998) and targeted minimum loss estimation (TMLE) (van der Laan and Rubin, 2006, van der Laan and Rose, 2011).

The efficient influence function often depends on the observed data distribution through certain key nuisance parameters. In the context of the ATE, these nuisance parameters are the conditional mean of the outcome given treatment and confounders (the so-called outcome regression, OR), the conditional probability of treatment given confounders (the so-called propensity score, PS), and the distribution function of confounders in the population of interest. Once estimators of these key quantities are available, each methodology provides its own recipe for combining the relevant nuisance estimators into an estimate of the causal effect of interest. Assuming nuisance estimators satisfy regularity conditions, the resulting estimators of the ATE, when appropriately centered and scaled, converge in distribution to a mean-zero Gaussian variate with variance equal to the semiparametric efficiency bound for regular estimators. In addition to efficiency, the estimators are doubly-robust, meaning that they are consistent for the causal effect of interest even if one of the OR or PS is inconsistently estimated.

One of the key assumptions underlying any methodology for estimating the ATE using observational data is the strong positivity assumption, which stipulates that the PS must be bounded between zero and one almost everywhere. That is, if we define strata of data units based on their observed confounders, any stratum with positive support must have some probability of receiving and not receiving the treatment. If this condition fails, then the ATE is not identifiable from observed data. Moreover, even if the condition holds theoretically, in practice there may be small estimated propensity scores – so-called *practical* violations of the positivity assumption (Petersen et al., 2012). In such cases, the one-step estimator and TMLE can suffer from erratic, nonrobust behavior.

To combat this behavior, various extensions have been proposed including collaborative TMLE (CTMLE) (van der Laan and Gruber, 2010, Gruber and van der Laan, 2010, Stitelman and van der Laan, 2010, Wang, Rose and van der Laan, 2011, also see Luo, Zhu and Ghosh, 2017 for a related approach based on balancing subspaces). In the CTMLE approach, the OR and PS are estimated *collaboratively*, by selecting an estimate of the PS based on how well it tunes an estimate of the OR. From a theoretical point of view, the goal of the collaborative estimation of the PS is to generate a TMLE that is more robust in finite samples than a typical TMLE (which relies on a

direct, noncollaborative estimate of the PS), but that nevertheless maintains the asymptotic efficiency of a typical TMLE. Many proposed methods for constructing CTMLEs are designed specifically for settings with practical positivity violations, for example by: choosing a truncation level for estimated propensities, selecting variables to be included in the PS, or tuning particular machine learning algorithms (Ju et al., 2019a, 2019b, Ju, Schwab and van der Laan, 2019). These works show that CTMLE can provide greater robustness than TMLE in challenging situations.

In spite of the putative benefits of CTMLE, these estimators are not widely used. There may be several reasons why. First, the approach involves many decision points for the analyst, who must select an increasingly complex sequence of estimators for the PS and implement each of these estimators. Second, the approach often involves extended computation time relative to traditional doubly-robust methods. In particular, cross-validation is needed to validate which PS method should be selected from amongst the user-chosen sequence. Third, from a theoretical perspective, performing robust inference based on existing CTMLE approaches is also challenging, involving either strong assumptions on nuisance estimators (see Appendix 17 of van der Laan and Rose, 2011) or additional iterative computational steps (van der Laan, 2014).

In this work, we seek to overcome these limitations via a new approach to CTMLE. The twist in the present proposal relative to existing CTMLE approaches is that we assume the OR estimator is consistent at a fast rate. Assuming this consistency, we provide an alternative target for a PS estimator that is explicitly adaptive to the OR. In particular, rather than estimating the true PS, we recommend estimating the propensity for receiving treatment as a function of the estimated OR. This low-dimensional regression can be substituted in place of an estimator of the true PS in a standard TMLE or one-step procedure. We show that, when appropriately scaled, the resultant estimator is asymptotically Normal with variance that is generally smaller than that of an efficient estimator. Thus, our proposal provides a new approach to CTMLE that is tailored both for small- and large-sample and performance.

2. BACKGROUND

2.1 Identification of ATE

Suppose we observe n independent copies of $O := (W, A, Y)$, where $W \in \mathcal{W}$ is a vector of putative confounders, $A \in \{0, 1\}$ is a binary treatment, and $Y \in [0, 1]$ is the outcome of interest. Our assumption that $Y \in [0, 1]$ does not sacrifice any generality of our proposed methodology. We denote by P_0 the probability distribution of O and assume that P_0 is an element of a model \mathcal{M} , which we take to be a nonparametric model.

As above, we use $Y(1)$ and $Y(0)$ to denote the counterfactual outcomes under treatment and no treatment, respectively. For $a = 0, 1$, we denote by P_0^a the probability distribution of $Y(a)$. The ATE is defined as $E_{P_0^1}[Y(1)] - E_{P_0^0}[Y(0)]$, the difference in average outcome if the entire population were assigned to receive $A = 1$ versus $A = 0$. The ATE is identifiable from the observed data under the following assumptions: consistency, $Y = Y(a) \mid A = a$; no interference: $Y_i(a)$ does not depend on A_j for $j \neq i$; ignorability: $A \perp (Y(1), Y(0)) \mid W$; and positivity: $\text{pr}_{P_0}\{0 < \text{pr}_{P_0}(A = 1 \mid W) < 1\} = 1$. The first two assumptions are needed in order to have well-defined counterfactual random variables. The ignorability condition is satisfied if there are no unmeasured confounders of A and Y , while the positivity criterion stipulates that every unit has a chance of receiving $A = 1$ and $A = 0$. If these assumptions hold, the average treatment effect is identified by the G-computation formula

$$\begin{aligned} & E_{P_0^1}[Y^{(1)}] - E_{P_0^0}[Y^{(0)}] \\ (1) \quad & = E_{P_0}[E_{P_0}(Y \mid A = 1, W) \\ & \quad - E_{P_0}(Y \mid A = 0, W)]. \end{aligned}$$

2.2 Estimators of the ATE

For simplicity, we hence consider estimation of $\psi_0^1 := E_{P_0}[E_{P_0}(Y \mid A = 1, W)]$, which we refer to as the treatment-specific mean. When discussing the OR, we will write OR^1 to refer to $\bar{Q}_0^1(W) := E_{P_0}(Y \mid A = 1, W)$, the true conditional mean of Y given W amongst units observed to receive the treatment $A = 1$. Symmetric arguments can be made about $\psi_0^0 := E_{P_0}[E_{P_0}(Y \mid A = 0, W)]$. At the end of this subsection, we comment on how these may be combined to estimate the ATE, $\psi_0 := \psi_0^1 - \psi_0^0$.

For each $w \in \mathcal{W}$, we denote by $\bar{Q}_0^1(w) := E_{P_0}(Y \mid A = 1, W = w)$ the true OR^1 evaluated at $W = w$ and denote by $\bar{Q}_n^1(w)$ an estimate of $\bar{Q}_0^1(w)$ based on O_1, \dots, O_n . We use \bar{Q}^1 to denote the model for the OR^1 implied by \mathcal{M} ; that is, \mathcal{Q}^1 is a collection of all possible OR^1 's allowed by \mathcal{M} . Similarly, for each $w \in \mathcal{W}$, we denote by $\bar{G}_0(w)$ the true PS evaluated at $W = w$, by $\bar{G}_n(w)$ an estimate of $\bar{G}_0(w)$, and by \bar{G} the model for the PS implied by \mathcal{M} . Finally, for each $w \in \mathcal{W}$, we denote by $Q_{0,W}(w) := \text{pr}_{P_0}(W \leq w)$ the distribution function of the vector of confounders. In the remainder, we use the empirical distribution $Q_{n,W}(w) := n^{-1} \sum_{i=1}^n \mathbb{1}(W_i \leq w)$, where $\mathbb{1}$ is the indicator function, as estimate of $Q_{0,W}$. We denote by Q_W the model for $Q_{0,W}$ implied by \mathcal{M} . It is useful to our discussion to regard the parameter of interest as a mapping Ψ^1 from $\mathcal{Q}^1 := \bar{Q}^1 \times Q_W$ to $[0, 1]$. That is, given a $Q^1 := (\bar{Q}^1, Q_W) \in \mathcal{Q}$, $\Psi^1(Q^1) := \int \bar{Q}^1(u) dQ_W(u)$ is the value of the treatment-specific mean implied by the OR^1 \bar{Q} and confounder distribution Q_W . Thus, denoting

by $Q_0^1 := (\bar{Q}_0^1, Q_{0,W})$ the true values of these quantities, we have $\psi_0^1 = \Psi^1(Q_0^1)$.

We remind readers that a regular (see Appendix A in the Supplementary Material (Benkeser, Cai and van der Laan, 2020)) estimator ψ_n^1 of ψ_0^1 is *asymptotically linear* if and only if $\psi_n^1 - \psi_0^1$ behaves approximately as an empirical mean of a mean-zero, finite-variance function of the observed data. This function is referred to as the estimator's *influence function*. Depending on the chosen model, there may be a large class of possible influence functions of regular estimators. The influence function in this class that has the smallest variance is referred to as the *efficient influence function* (EIF). Any estimator with influence function equal to the EIF is said to be *efficient* amongst regular, asymptotically linear estimators. Given $Q^1 \in \mathcal{Q}^1$, $\bar{G} \in \bar{\mathcal{G}}$, and a typical observation o , we define

$$\begin{aligned} & D^1(o \mid \bar{Q}^1, Q_W, \bar{G}) \\ & := \frac{a}{\bar{G}(w)} [y - \bar{Q}^1(w)] + \bar{Q}^1(w) \\ & \quad - \int \bar{Q}^1(u) dQ_W(u). \end{aligned}$$

The efficient influence function of Ψ^1 relative to \mathcal{M} for data generated from P_0 is $D^*(\cdot \mid \bar{Q}_0^1, Q_{0,W}, \bar{G}_0)$.

Several frameworks exist for constructing estimators with a user-specified influence function. By selecting the EIF, these frameworks can be used to generate efficient estimators. We focus on the one-step and targeted minimum loss estimation frameworks. For our discussion, it is useful to introduce the idea of a *plug-in estimator*. We denote by $Q_n^1 := (\bar{Q}_n^1, Q_{n,W})$ an estimate of $Q_0^1 := (\bar{Q}_0^1, Q_{0,W})$. A plug-in estimate of ψ_0^1 is one of the form $\Psi^1(Q_n^1) = \int \bar{Q}_n^1(u) dQ_{n,W}(u) = n^{-1} \sum_{i=1}^n \bar{Q}_n^1(W_i)$. The one-step estimator $\psi_{n,+}^1$ applies an EIF-based correction to the plug-in estimate,

$$\psi_{n,+}^1 := \Psi^1(Q_n^1) + \frac{1}{n} \sum_{i=1}^n D^1(O_i \mid \bar{Q}_n^1, Q_{n,W}, \bar{G}_n).$$

TMLE is a general framework for constructing plug-in estimators that satisfy, possibly several, user-specified equations. The framework is implemented in two steps. First, initial estimators of relevant nuisance parameters (e.g., OR^1 and PS) are generated using a user-chosen technique. Subsequently, the initial estimates are carefully modified such that (i) the modified estimators inherit desirable properties of the initial estimators (e.g., their rate of convergence); and (ii) relevant, user-specified equations are satisfied. For the present problem, a TMLE can be implemented by first generating an initial estimate \bar{Q}_n^1 of the OR^1 and \bar{G}_n of the PS. The regression estimator of OR^1 is subsequently updated to a *targeted* estimator $\bar{Q}_{n,*}^1$, such that the EIF estimating equation, $n^{-1} \sum_{i=1}^n D^1(O_i \mid \bar{Q}_{n,*}^1, Q_{n,W}, \bar{G}_n) = 0$, is satisfied. This can be achieved,

for example, by defining a logistic regression working model for OR^1 with $\text{logit}(\bar{Q}_n^1)$ as an offset, no intercept term, and a single covariate H_n^1 . For each $a \in \{0, 1\}$ and $w \in \mathcal{W}$, we define this covariate as $H_n^1(a, w) := a/\bar{G}_n(w)$. The maximum likelihood estimator (MLE) ϵ_n of the regression coefficient ϵ associated with the covariate H_n^1 is estimated (e.g., via iteratively reweighted least squares). For each $w \in \mathcal{W}$, we define the so-called targeted OR estimator, $\bar{Q}_{n,*}^1(w) = \text{expit}\{\text{logit}[\bar{Q}_n^1(w)] + \epsilon_n H_n^1(1, w)\}$. It is straightforward to show that the score of the coefficient ϵ at $\epsilon = 0$ evaluated at a typical observation o , equals $D^1(o | \bar{Q}_{n,*}^1, Q_{n,W}, \bar{G}_n)$; thus, we may deduce that the EIF estimating equation is satisfied by the updated estimate of OR^1 $\bar{Q}_{n,*}^1$. The TMLE $\psi_{n,*}^1$ of ψ_0^1 is computed as the plug-in estimator based on the modified estimate of OR^1 . That is, we define $Q_{n,*} = (\bar{Q}_{n,*}^1, Q_{n,W})$ and compute the TMLE as $\psi_{n,*}^1 = \Psi^1(Q_{n,*}) = \int \bar{Q}_{n,*}^1(u) dQ_{W,W}(u) = 1/n \sum_{i=1}^n \bar{Q}_{n,*}^1(W_i)$.

A symmetric argument can be used to generate one-step and TMLE estimates, respectively $\psi_{n,+}^0$ and $\psi_{n,*}^0$ of ψ_0^0 . In this case, we replace D^1 above by

$$\begin{aligned} D^0(o | \bar{Q}^0, Q_W, \bar{G}) & \\ &:= \frac{1-a}{1-\bar{G}(w)} [y - \bar{Q}^0(w)] + \bar{Q}^0(w) \\ &\quad - \int \bar{Q}^0(u) dQ_W(u), \end{aligned}$$

where \bar{Q}^0 is a regression function in the model \bar{Q}^0 for the conditional mean of Y given W and $A = 0$. We again regard the parameter of interest as a mapping Ψ^0 from $\mathcal{Q}^0 := \bar{Q}^0 \times Q_W$ to $[0, 1]$, where for a given $Q^0 = (\bar{Q}^0, Q_W)$, $\Psi^0(Q^0) = \int \bar{Q}^0(u) dQ_W(w)$. The one-step estimator of ψ_0^0 is

$$\psi_{n,+}^0 := \Psi^0(\bar{Q}_n^0) + \frac{1}{n} \sum_{i=1}^n D^0(O_i | \bar{Q}_n^0, Q_{n,W}, \bar{G}_n),$$

where \bar{Q}_n^0 is a user-selected estimate of \bar{Q}_0^0 . The TMLE proceeds exactly as above but replaces \bar{Q}_n^1 with \bar{Q}_n^0 and replaces H_n^1 by $H_n^0 := (1-a)/\{1-\bar{G}_n(w)\}$. The one-step estimator and TMLE of the ATE can then be computed as $\psi_{n,+}^1 - \psi_{n,+}^0$ and $\psi_{n,*}^1 - \psi_{n,*}^0$, respectively.

We remark that both the one-step and TMLE frameworks can be seen as first generating an initial estimate based on the OR and subsequently applying a correction procedure that involves an estimate of the PS. This view of the estimators is useful to our discussion below.

2.3 Large-Sample Theory

We hence focus discussion on the TMLE of ψ_0^1 , with the understanding that similar arguments apply to the one-step estimator, and to estimators of ψ_0^0 and the ATE. To

study large-sample behavior of the TMLE of ψ_0^1 , we note that under assumptions $\Psi^1(Q_{n,*}^1) - \Psi^1(Q_0^1)$ equals

$$\begin{aligned} (2) \quad & \frac{1}{n} \sum_{i=1}^n D(O_i | \bar{Q}_*^1, Q_{0,W}, \bar{G}) \\ & + R_2(\bar{Q}_n^1, \bar{Q}_0^1, \bar{G}_n, \bar{G}_0, Q_{0,W}) + o_p(n^{-1/2}), \end{aligned}$$

where (\bar{Q}_*^1, \bar{G}) is the in-probability limit of $(\bar{Q}_{n,*}^1, \bar{G}_n)$. A discussion of the involved assumptions and derivation of this equation is included in the supplemental materials. The term R_2 is a second-order remainder that involves a difference between $(\bar{Q}_{n,*}^1, \bar{G}_n)$ and (\bar{Q}_0^1, \bar{G}_0) ,

$$\begin{aligned} (3) \quad & R_2(\bar{Q}_{n,*}^1, \bar{Q}_0^1, \bar{G}_n, \bar{G}_0, Q_{0,W}) \\ & := \int \left[\frac{\bar{G}_n(u) - \bar{G}_0(u)}{\bar{G}_n(u)} \right] \\ & \quad \cdot [\bar{Q}_{n,*}^1(u) - \bar{Q}_0^1(u)] dQ_{0,W}(u). \end{aligned}$$

A key step in establishing asymptotic linearity of a TMLE is showing that R_2 is asymptotically negligible, that is, $R_2(\bar{Q}_{n,*}^1, \bar{Q}_0^1, \bar{G}_n, \bar{G}_0, Q_{0,W}) = o_p(n^{-1/2})$. The typical approach to ensuring the negligibility of R_2 is to generate estimates $\bar{Q}_{n,*}^1$ and \bar{G}_n of \bar{Q}_0^1 and \bar{G}_0 that satisfy that both $\bar{Q}_{n,*}^1 - \bar{Q}_0^1$ and $\bar{G}_n - \bar{G}_0$ are $o_p(n^{-1/4})$ with respect to the $L^2(P_0)$ norm. A crucial difference between our proposed methodology and typical one-step or TMLE estimation is in the strategy for controlling R_2 . We return to this point later.

Assuming that we are able to establish the negligibility of R_2 , then (2) implies that the TMLE is asymptotically linear with influence function equal to $D^1(\cdot | \bar{Q}_*^1, Q_{0,W}, \bar{G})$. If indeed $\bar{Q}_{n,*}^1$ and \bar{G}_n are $L^2(P_0)$ -consistent estimates of \bar{Q}_0^1 and \bar{G}_0 , respectively, then the influence function of the TMLE equals the EIF and thus, by definition, the TMLE is efficient. Moreover, the central limit theorem implies that $n^{1/2}(\psi_n^* - \psi_0)$ converges in distribution to a mean-zero Gaussian variate with variance $\sigma_0^2 := E_{P_0}[D(O | \bar{Q}_0^1, Q_{0,W}, \bar{G}_0)^2]$.

We note an additional interesting feature of efficient estimators of the treatment-specific mean: they are doubly-robust. That is, the estimated treatment-specific mean is consistent for the true treatment-specific mean if either the estimated OR^1 consistently estimates the true OR^1 , the estimated PS consistently estimates the true PS, or both estimators are consistent. The double robustness stems from two features of the present problem. First, the influence function of a locally efficient estimator has mean zero under consistent estimation of either OR^1 or the PS. Second, if at least one of OR^1 and PS consistently estimated, the cross-product structure of (3) implies that the remainder is converging to zero in probability. This latter point is especially important to our subsequent developments. We will see that our method for controlling R_2 ensures asymptotic linearity, but sacrifices the doubly robust behavior of the remainder term.

2.4 Small-Sample Considerations

As with any asymptotic analysis, the results of Section 2.3 provide conditions under which estimators are well-behaved in large samples, but provide no guarantees of small-sample performance. In particular, in settings where the target estimand is weakly identifiable, the TMLE and one-step may be unstable in spite of their asymptotic optimality. For example, when the PS may assume very small values, the variance of the EIF may be large, which can cause erratic behavior of estimators. In the context of TMLE for the treatment-specific mean, this instability may manifest in the estimation of the working model parameter ϵ . The covariate H_n^1 in the parametric working model may have extremely large values, leading to a targeted estimate of OR^1 , $\bar{Q}_{n,*}^1$, whose performance is considerably deteriorated relative to the initial estimate of OR^1 $\bar{Q}_{n,*}^1$.

Often, the analyst has little prior information that would suggest whether or not such issues are present in a given analysis. Thus, we are motivated to consider automated procedures for constructing OR and PS estimators that are adaptive to near positivity violations. One such proposal is CTMLE. A CTMLE can be constructed using a sequence of PS estimators that increase in complexity. For example, in the context of estimating the treatment-specific mean, we may start our sequence with an intercept-only logistic regression model and build a sequence ranging from that simple estimator to a flexible semiparametric estimator such as kernel regression. The sequence of candidate PS estimators is used to generate a sequence of targeted ORs. The best of the targeted ORs is selected via cross-validation and is used to create a plug-in estimator. The principle underlying CTMLE is that the estimator searches for a reduced-dimension alternative to the true PS that is adaptive to how well the estimated OR fits the true OR. If the initial OR estimate provides a good fit, then there may be little benefit (or even detriment) to performing a TMLE correction based on a PS with extremely small values. On the other hand if the initial OR is a poor fit, then we may in fact benefit from such a correction. CTMLE can adapt to each of these situations. Because CTMLE is based on a sequence of increasingly nonparametric PS estimators, the procedure will, with probability tending to 1, select the last consistent estimator of the true PS in the sequence. Thus, in large samples, CTMLE is expected to behave similar to a standard TMLE. In this respect, CTMLE may be generally viewed as a procedure that offers finite-sample improvements over standard TMLE, while maintaining its asymptotic efficiency.

The above discussion of efficiency and finite-sample considerations can be viewed in a more general lens than the context of nonparametric estimation of the ATE. In particular, these issues apply to a more broad set of problems that involve observed data structures that can be represented as a coarsened at random (CAR) version of a

full data structure, while many models and parameters relevant to causal inference are special cases of this setting. The general CAR setting is discussed further in Appendix C.

3. METHODS

We now propose a particular CTMLE for the treatment-specific mean that is robust to near positivity violations, but avoids the sequential PS estimator selection that is typical of other CTMLE proposals. The distinct aspect of the current proposal relative to previous CTMLE-based proposals is that we rely fully on \bar{Q}_n^1 converging to \bar{Q}_0^1 faster than $n^{-1/4}$ with respect to $L^2(P_0)$ -norm. Because the OR estimator is consistent, any PS estimator will lead to a consistent estimate of the treatment-specific mean, due to the double-robustness of the EIF. However, our procedure asks for a more stringent property on the adaptive PS estimator. We require that the resulting CTMLE be asymptotically linear, and thereby maintain a Normal limiting distribution. The challenge in so-doing is that our selected PS estimator is generally inconsistent for the true PS. Previous work has shown that, even when a nonparametric estimate of the OR is consistent, inconsistent estimation of the PS can have serious implications for the behavior of one-step estimators and TMLEs (van der Laan, 2014, Benkeser et al., 2017). The issue stems from the fact that the second-order remainder is generally not asymptotically negligible. Thus, the key in achieving our goal is to choose an adaptive PS estimator such that the second-order remainder remains asymptotically negligible under reasonable conditions. In Theorem 1, we establish that this goal can be achieved by using an estimate of

$$\bar{G}_0(w | \bar{Q}_0^1) := \text{pr}_{P_0}[A = 1 | \bar{Q}_0^1(W) = \bar{Q}_0^1(w)]$$

rather than an estimate of the true PS. In words, $\bar{G}_0(\cdot | \bar{Q}_0^1)$ describes the probability of receiving treatment as a function of the conditional mean outcome amongst the treated. This adaptive PS estimate is substituted into the usual TMLE (or one-step) procedures for estimation and inference.

Our proposed CTMLE is implemented in the following steps:

1. *estimate OR*: regress Y on W amongst units observed to receive treatment $A = 1$ to obtain \bar{Q}_n^1 ;
2. *predict outcome*: use estimated OR to obtain a prediction $\bar{Q}_n^1(W_i)$ for $i = 1, \dots, n$;
3. *estimate adaptive PS*: regress A on predictions $\bar{Q}_n^1(W_i)$ to obtain adaptive PS estimate $\bar{G}_n(\cdot | \bar{Q}_n^1)$;
4. *predict PS*: use estimated PS to obtain prediction $\bar{G}_n(W_i | \bar{Q}_n^1)$ for $i = 1, \dots, n$;
5. *fit OR working model*: fit logistic regression of outcome Y on covariate $H_n^1(A, W) := A/\bar{G}_n(W | \bar{Q}_n^1)$ with offset $\text{logit}[\bar{Q}_n^1(W)]$; denote by $\epsilon_{n,\#}^1$ the estimated coefficient;

6. *target OR estimate*: use OR working model to obtain a prediction $\bar{Q}_{n,\#}^1(W_i) = \text{expit}\{\text{logit}[\bar{Q}_n^1(W_i)] + \epsilon_{n,\#}^1 H_n^1(1, W_i)\}$ for $i = 1, \dots, n$;

7. *compute plug-in estimate*: the CTMLE is $\psi_{n,\#}^1 := n^{-1} \sum_{i=1}^n \bar{Q}_{n,\#}^1(W_i)$.

A description of the collaborative one-step (COS) estimator is included in Appendix E. Sample R code to compute the estimators is included in Appendix F.

The following theorem establishes the weak convergence of the proposed estimator. We explicitly discuss regularity conditions in Appendix G and strategies for weakening these conditions in Appendix F.

THEOREM 1. *Under the regularity conditions in Appendix G,*

$$\psi_{n,\#}^1 - \psi_0^1 = \frac{1}{n} \sum_{i=1}^n D^1(O_i | \bar{Q}_0^1, Q_{0,W}, \bar{G}_0(\cdot | \bar{Q}_0^1)) + o_p(n^{-1/2}),$$

and $n^{1/2}(\psi_{n,\#}^1 - \psi_0^1)$ converges in distribution to a mean-zero Normal variate with variance $\tau_0^2 := E_{P_0}[D^1(O | \bar{Q}_0^1, Q_{0,W}, \bar{G}_0(\cdot | \bar{Q}_0^1))^2]$.

The asymptotic variance τ_0^2 is generally smaller than that of the standard TMLE σ_0^2 , so that the proposed estimator is super efficient. That is, at any fixed data distribution in \mathcal{M} , this CTMLE will be asymptotically more efficient than the standard TMLE.

3.1 Variance Estimation

We propose to estimate the standard error of $\psi_{n,\#}^1$, based on a cross-validated estimate of the variance of the influence function. Specifically, consider a V -fold cross-validation scheme, wherein data are randomly partitioned into V blocks of approximately equal size. For $v = 1, \dots, V$, denote by $\mathcal{V}_v \subset \{1, \dots, n\}$ the indices of units in each block. For $i = 1, \dots, n$, we denote by $\bar{Q}_{n,v}^1(W_i)$ the predicted outcome for observation i based on an OR estimate fit when observation i was in the hold-out block. That is, to obtain $\bar{Q}_{n,v}^1$, we regress Y_i on W_i in units with $A_i = 1$ and $i \in \{1, \dots, n\} \setminus \mathcal{V}_v$. Then we use this fitted regression to obtain predictions based on W_j , $j \in \mathcal{V}_v$. Similarly, we denote by $\bar{G}_{n,v}(\cdot | \bar{Q}_{n,v}^1)$ the v th estimated adaptive PS, $v = 1, \dots, V$. This quantity is computed by regressing A_i on $\bar{Q}_{n,v}^1(W_i)$ for $i \in \{1, \dots, n\} \setminus \mathcal{V}_v$. This regression is then used to obtain predictions based on $\bar{Q}_{n,v}^1(W_j)$, $j \in \mathcal{V}_v$, which we denote by $\bar{G}_{n,v}(W_j | \bar{Q}_{n,v}^1)$. Finally, let $Q_{n,W,v}$ denote the empirical distribution of W based on $\{O_i : i \in \mathcal{V}_v\}$, $v = 1, \dots, V$.

The cross-validated variance estimator is

$$\tau_n^2 := \frac{1}{V} \sum_{v=1}^V \left[\frac{1}{|\mathcal{V}_v|} \sum_{i \in \mathcal{V}_v} (D_{n,v,i}^1 - \bar{D}_{n,v}^1)^2 \right],$$

where for $v = 1, \dots, V$ and $i = 1, \dots, n$,

$$D_{n,v,i}^1 := D^1(O_i | \bar{Q}_{n,v}^1, Q_{n,W,v}, \bar{G}_{n,v}(\cdot | \bar{Q}_{n,v}^1)),$$

$$\bar{D}_{n,v}^1 := \frac{1}{|\mathcal{V}_v|} \sum_{j \in \mathcal{V}_v} D_{n,v,j}^1.$$

REMARK. For notational simplicity, we have focused on presenting an estimate of the treatment-specific mean. An estimate of ψ_0^0 can similarly be obtained. In steps 1-5, we replace $A = 1$ with $A = 0$, \bar{Q}_n^1 with \bar{Q}_n^0 , H_n^1 with $H_n^0(A, W) := (1 - A)/\{\bar{G}_n(W | \bar{Q}_n^0)\}$, and $\epsilon_{n,\#}^1$ with $\epsilon_{n,\#}^0$. In step 6, we compute $\bar{Q}_{n,\#}^0(W_i) := \text{expit}\{\text{logit}[\bar{Q}_n^0(W_i)] + \epsilon_{n,\#}^0 H_n^0(0, W_i)\}$ for each observed data unit, $i = 1, \dots, n$. In step 7, the final estimate is $\psi_{n,\#}^0 := 1/n \sum_{i=1}^n \bar{Q}_{n,\#}^0(W_i)$. Thus, the final estimate of the ATE is $\psi_{n,\#}^1 - \psi_{n,\#}^0$. The formula for an estimate of the variance of this estimator is provided in Appendix D.

Alternatively, we also propose a CTMLE that directly targets the ATE in Appendix D. The major difference is that the adaptive PS now involves a two-dimensional regression of A on both OR^1 and OR^0 .

4. SIMULATIONS

We evaluated the performance of the proposed collaborative estimators relative to their standard counterparts in two simulation studies. We focus our presentation on comparing CTMLE and TMLE results, while a comparison of the one-step estimators is included in Appendix G. The first simulation evaluated the relative performance of CTMLE vs. TMLE as a function of sample size and strength of positivity violations. In this setting the estimators of the OR and PS are based on correctly-specified parametric models. The results demonstrate the behavior of the proposed estimators as a function both of sample size and strength of positivity violations. The second simulation offers a competitive setting for comparing the various estimators. In this setting, both the OR and PS are highly nonlinear functions of the covariates and involve complex covariate interactions. To consistently estimate these complex functions, we utilize the highly adaptive loss minimum loss estimator (HAL-MLE) (van der Laan, 2017, Benkeser and van der Laan, 2016). This estimator has been shown to the requisite regularity conditions of Theorem 1 under extremely mild assumptions on the true nuisance parameters.

In both simulation settings, we generated and analyzed 1000 Monte Carlo replicate data sets in each setting at each sample size. We evaluated the estimators on their bias, variance, and mean-squared error. To better illustrate differences across sample sizes, we plot bias and variance on a log-scale. We also present visualizations of the estimated sampling distributions of the scaled and centered sampling distributions. Further, we present the coverage

probability of nominal 95% Wald-style confidence intervals based on the Monte Carlo standard deviation of the estimators (i.e., an oracle confidence interval) and based on influence function-based standard error estimates.

All code used to produce these simulations is included in web supplement B (Benkeser, Cai and van der Laan, 2020).

4.1 Simulation 1

For each sample size $n \in \{100, 500, 1000\}$ we generated data as follows. W was an eight-variate vector. We drew the first seven components (W_1, \dots, W_7) of W from a Uniform distribution on $[-1.5, 1.5]^7$. The final component W_8 of W was drawn from a Bernoulli(0.5) distribution. Given $W = w$, the treatment A was drawn from a Bernoulli distribution with success probability $\bar{G}_0(w) = \text{expit}(0.5\gamma - \gamma w_8 + \sum_{j=1}^7 2^{1-j} w_j)$. Given $W = w$ and $A = a$, the outcome Y was drawn from a Normal distribution with unit variance and mean $\bar{Q}_0(a, w) = a - \sum_{j=1}^7 2^{1-j} w_j$. The true ATE in this setting is one. We induced positivity violations by choosing increasingly large values of γ . We evaluated three choices, $\gamma \in \{0, 3, 6\}$, which bounded the PS in $(0.05, 0.95)$, $(0.01, 0.99)$, and $(0.003, 0.997)$, respectively. The standard TMLE and one-step estimators used correctly-specified logistic regres-

sion for the PS and correctly-specified linear regression for the OR. The CTMLE and collaborative one-step used correctly-specified linear regression for the OR and HAL-MLE for the adaptive PS.

In settings with no positivity issues ($\gamma = 0$), we found that CTMLE and TMLE performed approximately equivalently, though CTMLE offered modest benefits at the smallest sample size (Figure 1). As γ increased, propensity scores were pushed towards zero and one, and we saw increased performance of CTMLE relative to TMLE. CTMLE offered significant improvements both in terms of bias and variance, and was more than four times as efficient in the $\gamma = 6, n = 100$ scenario. The sampling distribution of both estimators was well approximated by the reference asymptotic distribution as indicated by nominal coverage of oracle confidence intervals (Figure 2, Panel A). However, while the estimated standard errors of the TMLE estimator performed well in larger samples, the estimated standard errors of CTMLE had poor performance, often underestimating the true variability of the estimator (Figure 2, Panel B).

Results for the collaborative one-step vs. standard one-step estimator were essentially the same as for TMLE (Appendix G).

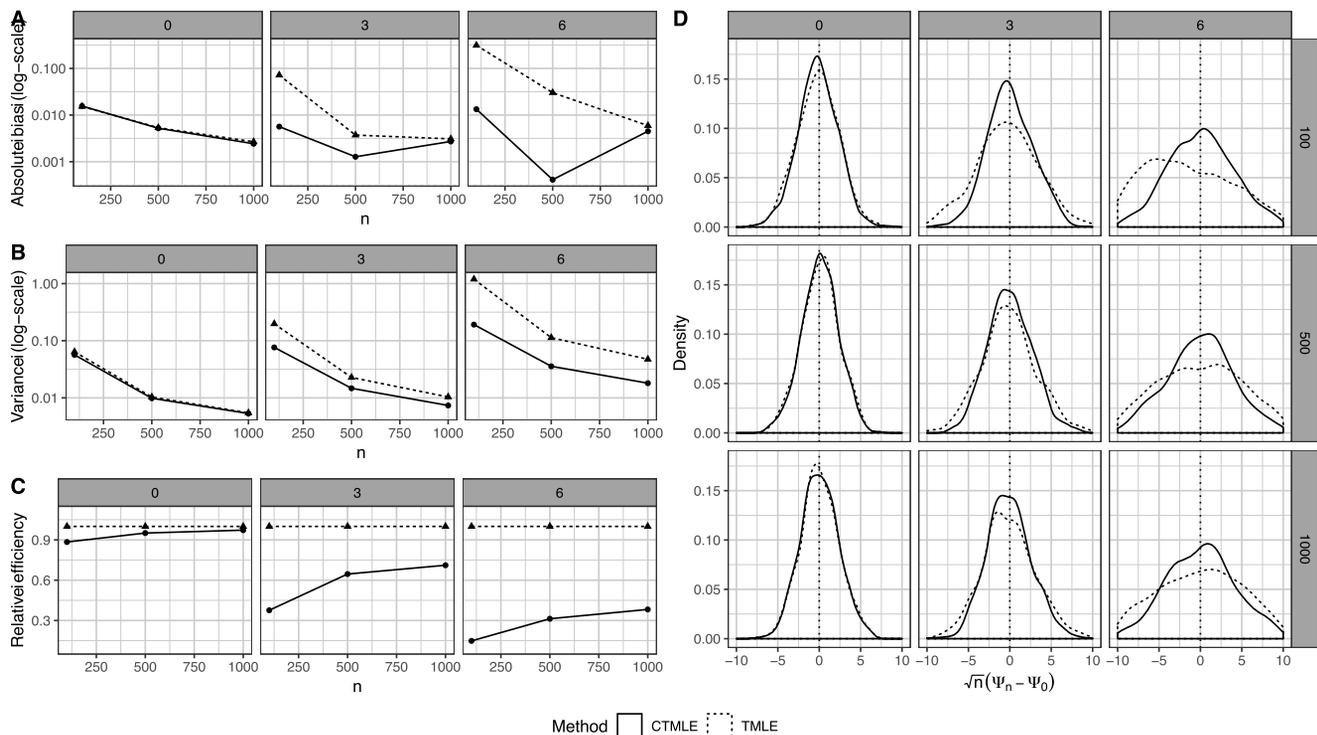


FIG. 1. Results for simulation 1 comparing CTMLE and TMLE. Each panel displays a different performance metric and each sub-panel displays results for $\gamma \in \{0, 3, 6\}$, representing, respectively, settings with no positivity, moderate positivity, and extreme positivity violations. Panel A: Bias (log-scale) of the estimators. Panel B: Variance (log-scale) of the estimators. Panel C: Relative efficiency (defined as ratio of mean squared-error) of CTMLE to TMLE. Numbers below one indicate greater efficiency of CTMLE. Panel D: Kernel density estimates of sampling distributions using a Gaussian kernel and Silverman’s rule of thumb bandwidth (Silverman, 1986).

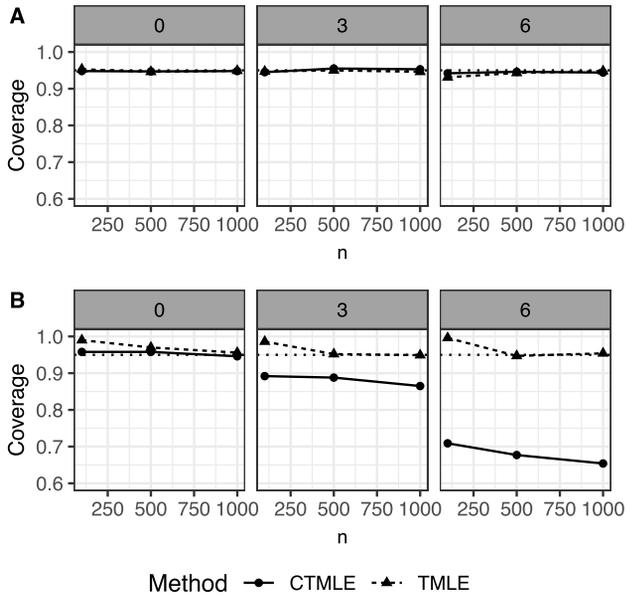


FIG. 2. Results for simulation 1 comparing confidence intervals for CTMLE and TMLE. Each panel displays the coverage as a function of sample size and each sub-panel displays results for $\gamma \in \{0, 3, 6\}$. Panel A: Coverage probability of nominal 95% oracle confidence intervals. Panel B: Coverage probability of nominal 95% confidence intervals based on estimated standard errors.

4.2 Simulation 2

We based this simulation setting on the oft-cited Kang and Schafer (2007) simulation design. This design is notoriously challenging for causal effect estimators due to extremely nonlinear covariate relationships in the OR and PS and highly complex interactions between covariates. In our simulation, we drew Z_1 from a Uniform(0.5, 2) distribution and drew Z_2, \dots, Z_5 from a Uniform distribution on $[-2, 2]^4$. Given $Z = z$, the treatment A was drawn from a Bernoulli distribution with success probability $\bar{G}_0(z) = \text{expit}(-Z_1 + 0.5Z_2 - Z_3 - 0.1Z_4 + Z_5 + 0.75Z_5^2)$. Given $Z = z$ and $A = a$, the outcome Y was drawn from a Normal distribution with unit variance and mean $\bar{Q}_0(a, z) = 210 + 27.4Z_1 + 13.7Z_2 + 13.7Z_3 + 13.7Z_4$. The true ATE is zero and the true PS is bounded between (0.004, 0.999). A challenge of this simulation setting is that the covariates Z are not available and we must instead base our estimation on $W = W_1, \dots, W_5$, where

$$W_1 = \exp(Z_1/2), \quad W_2 = Z_2/[1 + \exp(Z_1)] + 10,$$

$$W_3 = [(Z_1 Z_3)/25 + 0.6]^3,$$

$$W_4 = (Z_2 + Z_4 + 20)^2, \quad W_5 = Z_5.$$

As such, the true PS and OR, when expressed as functions of W are nonlinear and involve interactions between the various components of Z . To estimate these functions well, we require extremely flexible regression tools. Thus, we use HAL-MLE for the PS and OR used by the TMLE

and one-step estimators. Similarly, we used HAL-MLE for the OR and adaptive PS.

As expected, both the the TMLE and CTMLE struggled in this very challenging simulation study (Figure 3). While CTMLE offered modest benefits in terms of variance, the bias of the two estimators was comparable. Nevertheless, we do see evidence of asymptotic linearity of both estimators in that the sampling distributions of both of the scaled and centered estimators appear to be moving towards an appropriate center at zero. Both estimators had relatively large bias, even in the largest sample size $n = 1000$, as shown by the less-than-nominal coverage of the oracle confidence intervals (Figure 4, Panel A). The cross-validated influence function-based variance estimators overestimated the variability of the TMLE, which resulted in near nominal coverage for those intervals (Panel B). However, as in simulation 1, we found that the proposed variance estimators for the CTMLE significantly underestimated the variability of the estimator, which resulted in poor coverage.

5. DATA ANALYSIS

The broadly neutralizing antibody VRC01 is currently being evaluated for its efficacy to prevent HIV-1 infection (Gilbert et al., 2017). A secondary objective of these to trials is to determine whether and how VRC01 prevention efficacy varies with HIV-1 envelope amino acid (AA) sequence features. Given the number of AAs in the envelope protein, an exhaustive analysis that tests how efficacy depends on every AA residue would have low statistical power. It is therefore of interest to prioritize amino acid positions using existing data ahead of the trial’s analysis (Magaret et al., 2019). Toward that end, we developed an analysis based on the Compile, Analyze and Tally NAb Panels (CATNAP) database (Yoon et al., 2015), which contains measurements of VRC01 neutralization of $n = 611$ HIV-1 pseudoviruses. These data consist of a binary measure of viral sensitivity to VRC01 (defined as a non-right-censored value of the half maximal inhibitory concentration), geographic origin of the virus, and genetic features of the virus, including viral subtype, amino acids present at specific residues, and viral geometry.

We used these data to estimate the importance of each AA residue in a region of the viral genome putatively related to VRC01 antibody binding. Specifically, for each residue r in the VRC01 binding footprint (there are 28 such residues), we set $A_{r,i} = 1$ if the i th virus contained the majority variant at that position, and set $A_{r,i} = 0$ otherwise. The outcome was the binary viral sensitivity measure and we define the importance of residue r as the ATE of A_r on the outcome. The set of potential confounders W included all AA residues outside of the VRC01 binding footprint, geographic origin, subtype, and geometry. In all W contained 677 elements.

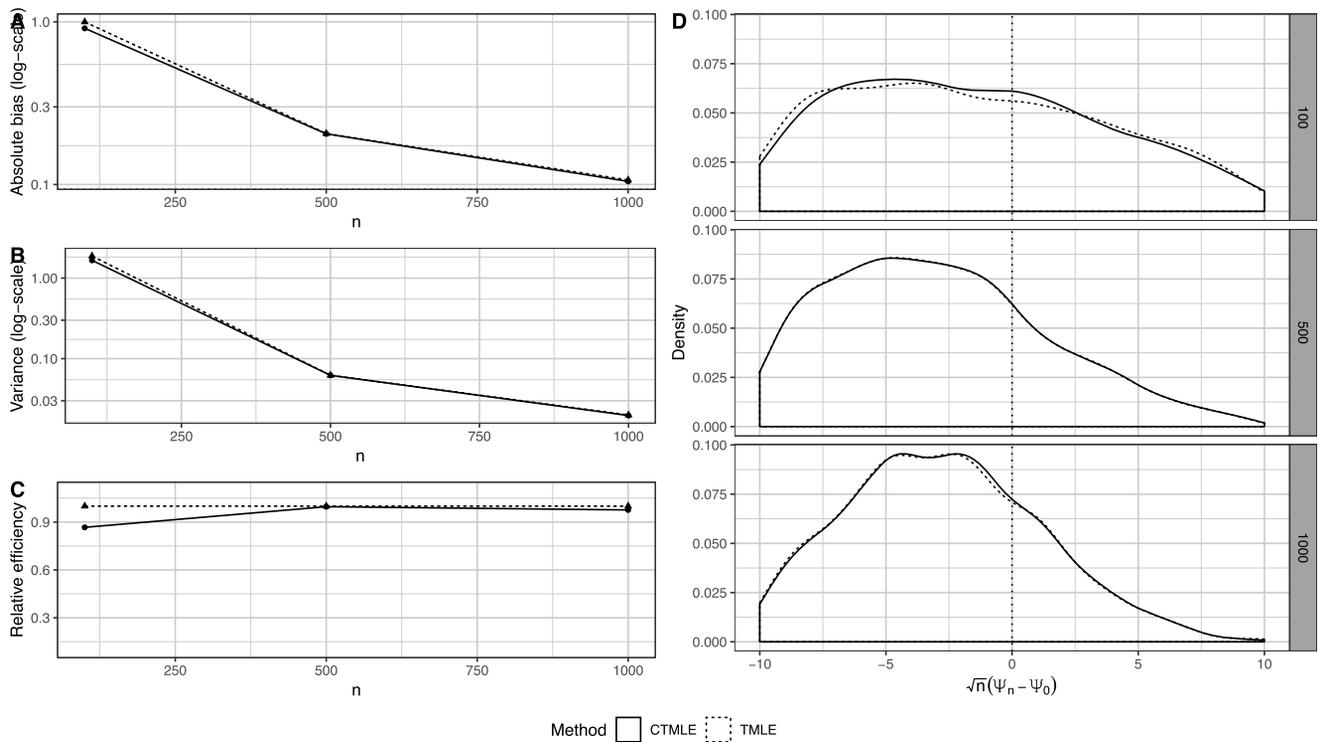


FIG. 3. Results for simulation 2 comparing CTMLE and TMLE. Panel A: Bias (log-scale) of the estimators. Panel B: Variance (log-scale) of the estimators. Panel C: Relative efficiency (defined as ratio of mean squared-error) of CTMLE to TMLE. Numbers below one indicate greater efficiency of CTMLE. Panel D: Kernel density estimates of sampling distributions using a Gaussian kernel and Silverman’s rule of thumb bandwidth (Silverman, 1986).

There are several reasons to expect positivity issues in these data. Foremost is the high dimension of W . Beyond that, there may be fitness restrictions on viruses such that variation in AA outside the VRC01 binding footprint

may functionally restrict variation within these residues. As such, these data may present an opportunity to benefit from our proposed methodology compared to TMLE or one-step. We analyzed these data using our collaborative TMLE and one-step and compared to the results based on a standard implementations of TMLE and one-step, where one uses an estimate of the true propensity score. For the latter, it is common to bound the PS estimates away from zero and one; we used bounds of 0.01 (shown here) and 0.0001 (shown in the supplement). There was little difference in the results. All estimators based the initial estimate of the OR and PS on a LASSO regression with ℓ^1 -penalty selected via 10-fold cross validation.

Because the true relationship between these AA residues and viral sensitivity is unknown, we used two resampling-based simulations to provide a comparison of estimators. First, we examined performance in a “null scenario.” For each of the 28 residues, we randomly permuted the outcome, so that the true ATE equaled 0. We then computed each of the four estimates for 100 permuted data sets and the estimators in terms of bias, variance, MSE, and confidence interval coverage. Second, we specifically examined the variability of the proposed estimators, since this is where we may expect benefits from super efficiency. To that end, we drew bootstrap samples from the observed data and computed each of the four estimates. We repeated this process 100 times for each of

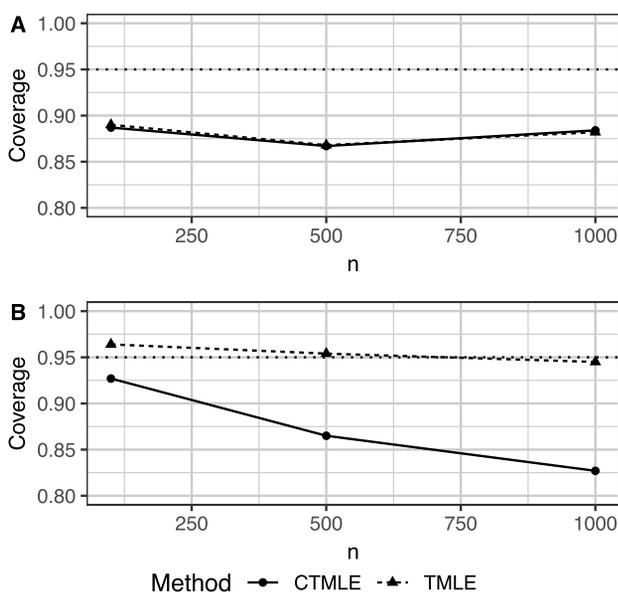


FIG. 4. Results for simulation 1 comparing confidence intervals for CTMLE and TMLE. Panel A: Coverage probability of nominal 95% oracle confidence intervals. Panel B: Coverage probability of nominal 95% confidence intervals based on estimated standard errors.

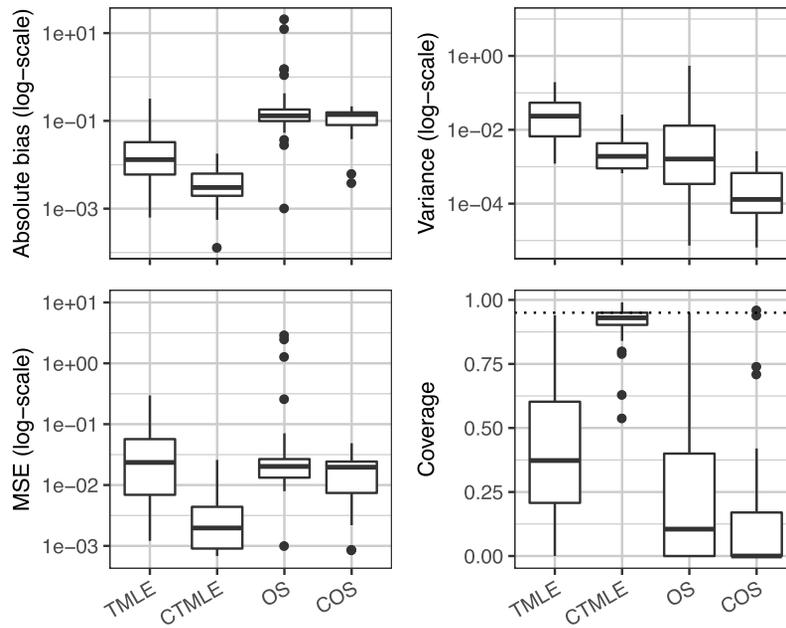


FIG. 5. Results for null scenario comparing CTMLE, TMLE, COS, and OS estimators. Box plots show results for each of 28 AA residues in the VRC01 binding footprint. TMLE and OS estimators used PS estimates bounded between 0.01 and 0.99.

the 28 residues, and studied the variability of each of the four estimators.

In the null simulation, we found that the adaptive propensity score lead to smaller bias and variance of the CTMLE versus the TMLE (Figure 5). The collaborative one-step estimator (COS) avoided some extreme behavior suffered by the one-step estimator (OS), which had large very large bias for several AA residues. The COS also had lower variance than the standard OS. In terms of MSE and coverage, the CTMLE performed best by an order of magnitude.

For the bootstrap simulation, we computed the variance of the estimates across bootstrap samples. The variance of the TMLE and CTMLE was considerably lower than that of both one-step estimators (Figure 6, Panel A). Across

residues, the median variability of the CTMLE was about the same as the TMLE, while the 0.25-quantile of variability was considerably lower. To better understand these results, we plotted the relative efficiency (the ratio of MSE of collaborative variant over regular variant) as a function of the proportion of the sample that had estimated propensity scores between 0.05 and 0.95 (Figure 6, Panel B). When this proportion is close to 0, it indicates near complete separation in the propensity score estimate. On the other hand, when the proportion is close to 1, it indicates a lack of practical positivity violations. We find that in these two extreme scenarios, the collaborative estimators tend to provide little benefit over the standard approaches with relative efficiencies close to 1. However, for scenarios in between, the collaborative estimators tended to be more

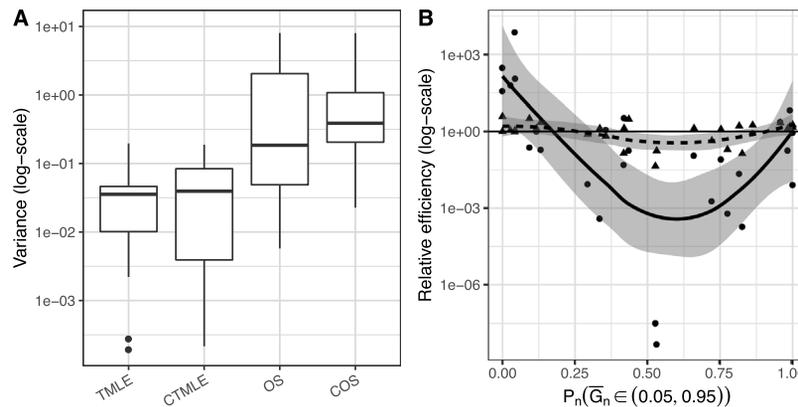


FIG. 6. Results for the bootstrap simulation comparing the efficiency of CTMLE versus TMLE and COS versus OS. Each point is one of the 28 AA residues and a Loess smoother with pointwise 95% confidence bounds has been added over the points. TMLE and OS estimators used PS estimates bounded between 0.01 and 0.99.

efficient. These results support our theory that in settings with moderately strong positivity violations, our proposed estimators will tend to have greater efficiency than locally efficient procedures.

All code used for this analysis is included in web supplement B (Benkeser, Cai and van der Laan, 2020).

6. DISCUSSION

There are important trade-offs to consider when choosing between our estimator and existing, locally efficient approaches. Our approach sacrifices robustness for stability and possibly greater efficiency. It has been recognized in the literature that efficient estimators such as TMLE and one-step can show erratic behavior if the target estimand is weakly identifiable. In these settings, we expect that the proposed CTMLE will exhibit more robust finite-sample performance relative to standard locally efficient approaches. The results of our first simulation support this conclusion. On the other hand, existing locally efficient approaches are doubly robust, while our estimator is not: we cannot compensate for an inconsistent OR estimator by using a consistent PS estimator. Double robustness is often considered an extremely desirable property, especially in cases where low-dimensional parametric regressions are used to estimate nuisance parameters. In contrast, if one utilizes more flexible regression methodologies, concerns of inconsistent estimation may be mitigated to some degree. Indeed, recent developments such as HAL-MLE theoretically ensure that our $n^{-1/4}$ -consistency requirement is satisfied under weak conditions. While some have argued in favor of using flexible regression techniques as a matter of course in locally efficient estimation (e.g., van der Laan and Rose, 2011), these techniques appear to be particularly important for our proposed estimator due to its lack of double robustness. Overall, we conclude that the finite-sample performance of a locally efficient estimator and our proposed super-efficient CTMLE will depend on the particular data generating distribution. Clearly, if one has a-priori knowledge of the propensity score, in particular that it does not suffer from positivity issues, then a standard locally efficient approach may be preferred. If instead, the PS is poorly understood and/or the parameter is weakly identifiable, then the super-efficient CTMLE may be a better option.

Our data analysis highlights the potential pitfalls of naïve application of doubly robust estimators in situations with many instrumental variables. Others have proposed alternative collaborative strategies for estimation of propensity scores using LASSO in these settings (Shortreed and Ertefaie, 2017, Ju et al., 2019b). In future work, we will provide a more general comparison of these methods with our proposed methodology.

Another important direction for future research will be into methods that are adaptive to situations with and without positivity violations. For example, one such strategy is as follows. First, obtain an estimate of the OR. Next, obtain an initial estimate of the propensity score, but subject to the constraint that it is bounded between $(\delta, 1 - \delta)$, for a user-selected δ . Then augment the initial PS estimate to additionally adjust for the estimate of the OR (e.g., fit a univariate logistic regression with logit of the initial PS estimate treated as offset and basis functions of estimated OR as covariates). Target this augmented PS estimate to ensure asymptotic linearity of the remainder, as in Benkeser et al., 2017. Under typical regularity conditions this estimator is locally efficient if the target parameter is *not* weakly identifiable (i.e., the true PS is bounded in $(\delta, 1 - \delta)$). Moreover, we conjecture that this estimator will be asymptotically linear if *either* the initial PS estimator is consistent at a fast rate (even when the OR is inconsistent) *or* the initial OR estimator is consistent at a fast rate, but the initial PS estimator is inconsistent. Thus, the estimator retains some of the desirable properties of doubly robust estimators, while adapting to weak identifiability. We leave the implementation and theoretical study of this estimator to future work.

In future work, we will additionally generalize our asymptotic linearity results to the more general CAR setting described in Appendix B. Such extensions would allow us to tackle other challenging problems in causal inference, such as estimation of the counterfactual mean of a treatment administered at several timepoints subject to time-varying confounding.

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SUPPLEMENTARY MATERIAL

Supplement A to “A Nonparametric Super-Efficient Estimator of the Average Treatment Effect” (DOI: 10.1214/19-ST735SUPPA; .pdf). Proofs and additional results for simulation studies and data analysis.

Supplement B to “A Nonparametric Super-Efficient Estimator of the Average Treatment Effect” (DOI: 10.1214/19-ST735SUPPB; .zip). Code and data used for simulation study and data analysis.

REFERENCES

- BENKESER, D., CAI, W. and VAN DER LAAN, M. J. (2020). Supplement to “A Nonparametric Super-Efficient Estimator of the Average Treatment Effect.” <https://doi.org/10.1214/19-STS735SUPPA>, <https://doi.org/10.1214/19-STS735SUPPB>.
- BENKESER, D. and VAN DER LAAN, M. J. (2016). The highly adaptive lasso estimator. In *Proceedings of the International Conference on Data Science and Advanced Analytics 2016* 689–696. <https://doi.org/10.1109/DSAA.2016.93>.
- BENKESER, D., CARONE, M., VAN DER LAAN, M. J. and GILBERT, P. B. (2017). Doubly robust nonparametric inference on the average treatment effect. *Biometrika* **104** 863–880. MR3737309 <https://doi.org/10.1093/biomet/asx053>
- BICKEL, P. J., KLAASSEN, C. A. J., RITOV, Y. and WELLNER, J. A. (1998). *Efficient and Adaptive Estimation for Semiparametric Models*. Springer, New York. Reprint of the 1993 original. MR1623559
- GILBERT, P. B., JURASKA, M., DECAMP, A. C. et al. (2017). Basis and statistical design of the passive HIV-1 antibody mediated prevention (AMP) test-of-concept efficacy trials. *Stat. Commun. Infect. Dis.* **9** 20160001. MR3743441 <https://doi.org/10.1515/scid-2016-0001>
- GRUBER, S. and VAN DER LAAN, M. J. (2010). An application of collaborative targeted maximum likelihood estimation in causal inference and genomics. *Int. J. Biostat.* **6** Art. 18, 31. MR2653847 <https://doi.org/10.2202/1557-4679.1182>
- IBRAGIMOV, I. A. and HAS’MINSKIĬ, R. Z. (1981). *Statistical Estimation: Asymptotic Theory. Applications of Mathematics* **16**. Springer, New York–Berlin. Translated from the Russian by Samuel Kotz. MR0620321
- JU, C., SCHWAB, J. and VAN DER LAAN, M. J. (2019). On adaptive propensity score truncation in causal inference. *Stat. Methods Med. Res.* **28** 1741–1760. MR3961963 <https://doi.org/10.1177/0962280218774817>
- JU, C., GRUBER, S., LENDLE, S. D., CHAMBAZ, A., FRANKLIN, J. M., WYSS, R., SCHNEEWEISS, S. and VAN DER LAAN, M. J. (2019a). Scalable collaborative targeted learning for high-dimensional data. *Stat. Methods Med. Res.* **28** 532–554. MR3903757 <https://doi.org/10.1177/0962280217729845>
- JU, C., WYSS, R., FRANKLIN, J. M., SCHNEEWEISS, S., HÄGGSTRÖM, J. and VAN DER LAAN, M. J. (2019b). Collaborative-controlled LASSO for constructing propensity score-based estimators in high-dimensional data. *Stat. Methods Med. Res.* **28** 1044–1063. MR3934634 <https://doi.org/10.1177/0962280217744588>
- KANG, J. D. Y. and SCHAFER, J. L. (2007). Demystifying double robustness: A comparison of alternative strategies for estimating a population mean from incomplete data. *Statist. Sci.* **22** 523–539. MR2420458 <https://doi.org/10.1214/07-STS227>
- LUO, W., ZHU, Y. and GHOSH, D. (2017). On estimating regression-based causal effects using sufficient dimension reduction. *Biometrika* **104** 51–65. MR3626479 <https://doi.org/10.1093/biomet/asw068>
- MAGARET, C. A., BENKESER, D. C., WILLIAMSON, B. D., BORATE, B. R., CARPP, L. N., GEORGIEV, I. S., SETLIFF, I., DINGENS, A. S., SIMON, N. et al. (2019). Prediction of VRC01 neutralization sensitivity by HIV-1 gp160 sequence features. *PLoS Comput. Biol.* **15** e1006952.
- PETERSEN, M. L., PORTER, K. E., GRUBER, S., WANG, Y. and VAN DER LAAN, M. J. (2012). Diagnosing and responding to violations in the positivity assumption. *Stat. Methods Med. Res.* **21** 31–54. MR2867537 <https://doi.org/10.1177/0962280210386207>
- PFANZAGL, J. (1982). *Contributions to a General Asymptotic Statistical Theory. Lecture Notes in Statistics* **13**. Springer, New York–Berlin. With the assistance of W. Wefelmeyer. MR0675954
- SHORTREED, S. M. and ERTEFAIE, A. (2017). Outcome-adaptive lasso: Variable selection for causal inference. *Biometrics* **73** 1111–1122. MR3744525 <https://doi.org/10.1111/biom.12679>
- SILVERMAN, B. W. (1986). *Density Estimation*. CRC Press, London, UK.
- STITELMAN, O. M. and VAN DER LAAN, M. J. (2010). Collaborative targeted maximum likelihood for time to event data. *Int. J. Biostat.* **6** Art. 21, 46. MR2659056 <https://doi.org/10.2202/1557-4679.1249>
- VAN DER LAAN, M. J. (2014). Targeted estimation of nuisance parameters to obtain valid statistical inference. *Int. J. Biostat.* **10** 29–57. MR3208072 <https://doi.org/10.1515/ijb-2012-0038>
- VAN DER LAAN, M. (2017). A generally efficient targeted minimum loss based estimator based on the highly adaptive Lasso. *Int. J. Biostat.* **13** 20150097, 35. MR3724476 <https://doi.org/10.1515/ijb-2015-0097>
- VAN DER LAAN, M. J. and GRUBER, S. (2010). Collaborative double robust targeted maximum likelihood estimation. *Int. J. Biostat.* **6** Art. 17, 70. MR2653848 <https://doi.org/10.2202/1557-4679.1181>
- VAN DER LAAN, M. J. and ROSE, S. (2011). *Targeted Learning: Causal Inference for Observational and Experimental Data. Springer Series in Statistics*. Springer, New York. MR2867111 <https://doi.org/10.1007/978-1-4419-9782-1>
- VAN DER LAAN, M. J. and RUBIN, D. (2006). Targeted maximum likelihood learning. *Int. J. Biostat.* **2** Art. 11, 40. MR2306500 <https://doi.org/10.2202/1557-4679.1043>
- VAN DER VAART, A. W. (1998). *Asymptotic Statistics. Cambridge Series in Statistical and Probabilistic Mathematics* **3**. Cambridge Univ. Press, Cambridge. MR1652247 <https://doi.org/10.1017/CBO9780511802256>
- WANG, H., ROSE, S. and VAN DER LAAN, M. J. (2011). Finding quantitative trait loci genes with collaborative targeted maximum likelihood learning. *Statist. Probab. Lett.* **81** 792–796. MR2793745 <https://doi.org/10.1016/j.spl.2010.11.001>
- YOON, H., MACKE, J., WEST JR, A. P., FOLEY, B., BJORKMAN, P. J., KORBER, B. and YUSIM, K. (2015). CATNAP: A tool to compile, analyze and tally neutralizing antibody panels. *Nucleic Acids Res.* **43** W213–W219.