Flexible collaborative estimation of the average causal effect of a treatment using the outcome-highly-adaptive lasso

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Abstract

Many estimators of the average causal effect of an intervention require estimation of the propensity score, the outcome regression, or both. For these estimators, we must carefully consider how to estimate the relevant regressions. It is often beneficial to utilize flexible techniques such as semiparametric regression or machine learning. However, optimal estimation of the regression function does not necessarily lead to optimal estimation of the average causal effect. Therefore, it is important to consider criteria for evaluating regression estimators and selecting hyper-parameters. A recent proposal addressed these issues via the outcome-adaptive lasso, a penalized regression technique for estimating the propensity score. We build on this proposal and offer a method that is simultaneously more flexible and more efficient than the previous proposal. We propose the outcome-highly-adaptive LASSO, a semi-parametric regression estimator designed to down-weight regions of the confounder space that do not contribute variation to the outcome regression. We show that tuning this method using collaborative targeted learning leads to superior finite-sample performance relative to competing estimators.

Keywords: causal inference, instrumental variables, targeted minimum loss-based estimation, adaptive estimation

1 Introduction

Across many fields, researchers are interested in the marginal effects of a treatment on an outcome. Depending on the setting this “treatment” might correspond to a drug, a harmful exposure, or a policy intervention. Often, the treatment may not be randomized due to ethical or logistical reasons, which necessitates statistical methodology to address differences between those observed to take the treatment and those observed not to take the treatment [Rosenbaum and Rubin, 1983]. These differences are often accounted for through regression adjustment, either through estimation of the mean outcome given treatment and confounders (so-called outcome regression), the probability of treatment given confounders (the so-called propensity score), or both. Most commonly, these regressions are estimated using familiar parametric techniques such as linear and logistic regression. However, misspecification of these regression models can lead to extreme bias in estimates of the population-level effect of a treatment [Kang and Schafer, 2007]. This has led to a growing interest in the use of adaptive regression techniques, such as techniques from the machine learning literature, to control for confounding in estimation of treatment effects [van der Laan and Rubin, 2006].
Laan and Rose, 2011, Setoguchi et al., 2008, Lee et al., 2010, Ju et al., 2017a, Karim and Platt, 2017, Wyss et al., 2018, Karim et al., 2018. In particular, the field of targeted learning has emerged as a paradigm for wedding machine learning and formal statistical inference [van der Laan and Rose, 2011, 2018]. While adaptive estimation techniques have been quite successfully applied in many problems, two major questions remain: (i) what variables should be included in the estimation procedures; and (ii) how should hyper-parameter selection be performed?

With regard to (i), recent studies have shown that including instrumental variables – variates that affect the propensity score, but not the outcome regression – in the propensity score can lead to inflation of the variance of the estimator of the average treatment effect [Greenland, 2008, Schisterman et al., 2009, Rotnitzky et al., 2010, van der Laan et al., 2010, Schneeweiss et al., 2009, Myers et al., 2011, Ju et al., 2017b, 2018]. Additionally, some true confounders may cause extreme values in the estimated propensity score, and while it may necessary to include these variables to achieve asymptotically valid estimation of the average treatment effect, in finite samples it may be auspicious to exclude these variables [Gruber and van der Laan, 2010, Petersen et al., 2012].

Combined, these studies lead to the conclusion that naively including all measured variables in the propensity score estimation procedure can not be expected to lead to desirable results. On the other hand, inclusion of variables related only to the outcome may lead to efficiency gains [Brookhart et al., 2006, Zhang et al., 2008, Moore and van der Laan, 2009]. We may conclude that a good variable selection procedure must simultaneously consider what variables to include in estimation of both the outcome regression and propensity score.

Turning to question (ii), we note that typically, hyper-parameters are selected to optimize the nuisance fit with respect to the true nuisance parameter. However, in the present study, nuisance estimation is merely an intermediate step in obtaining an estimator of the average treatment effect. Thus, it may be that the best fit for the sake of estimating the true nuisance parameter might be quite different than the best fit for the sake of estimating the average treatment effect. Indeed, for certain doubly robust estimators it is not even necessary to obtain a consistent estimate of each of the relevant nuisance parameters [van der Laan et al., 2010, Gruber and van der Laan, 2010]. One need only obtain estimates that are collaboratively consistent, in the sense that they combine to appropriately control bias in estimation of the average treatment effect. Therefore, we can conclude that a hyper-parameter optimization routine should also simultaneously consider the estimation of both the outcome regression and the propensity score.

Shortreed and Ertefaie [2017] brilliantly addressed both variable selection and hyper-parameter optimization in a recent proposal. The authors propose a procedure wherein the outcome regression is estimated using a generalized linear model. The coefficients from this fit serve as measures of how strongly each covariate is related to the outcome. The inverse of each coefficient is included in a weighted penalty for estimation of the propensity score via the adaptive lasso [Zou, 2006]. Thus, variables that putatively are related to the outcome are penalized less, and are more likely to receive non-zero coefficients in the propensity score. The authors use this estimated propensity score to construct an inverse probability of treatment weighted estimation procedure. The IPTW estimator uses the PS to balance the covariate distributions between the exposure groups, and so the authors chose to select adaptive lasso hyper-parameter by minimizing a weighted absolute mean difference.

In this work, we build on the proposal of Shortreed and Ertefaie [2017], and improve on their proposal in two ways. First, we show that the outcome-adaptive lasso can be naturally wedded to a more flexible penalized regression technique – the highly adaptive lasso [Benkeser and van der Laan, 2016, van der Laan, 2017]. The highly adaptive lasso can model complex non-linear relationships and covariate interactions, thereby providing a more flexible tool for implementing the outcome-adaptive approach of Shortreed and Ertefaie [2017]. We call the resultant estimator the outcome-
highly-adaptive lasso (OHAL). Secondly, we describe how collaborative targeted minimum loss-based estimation can be used for hyper-parameter selection for OHAL using recent results from Ju et al. [2018]. Doubly-robust estimation approaches are asymptotically efficient, offering theoretical benefits over IPTW. Our numerical studies additionally demonstrate considerable finite-sample gains.

The remainder of the article is organized as follows. Section 2 reviews identification results of the average treatment effect, and several common strategies for estimating this effect. This section also includes a review of the proposal by Shortreed and Ertefaie [2017]. In Section 3, we review the highly adaptive lasso estimator and introduce the outcome highly adaptive lasso. We also discuss how collaborative targeted minimum loss-based estimation can be used for hyper-parameter optimization. Section 4 contains several numerical evaluations of our proposed estimator. We conclude with a discussion.

2 Background

2.1 Identification of average treatment effect

Suppose we observe \( n \) independent copies of the data unit \( O \sim P_0 \), which consists of \((W,A,Y)\), where \( W \) is a \( p \)-dimensional vector of baseline covariates, \( A \) is a binary treatment assignment, and \( Y \) is an outcome of interest. Without loss of generality, we assume that \( Y \in [0,1] \). Our interest is in evaluating the difference in average outcome if the entire population were assigned to receive \( A = 1 \) versus \( A = 0 \). Specifically, we follow Pearl [2009] and define a non-parametric structural equation model (NPSEM),

\[
\begin{align*}
W &= f_W(U_W) \\
A &= f_A(W,U_A) \\
Y &= f_Y(A,W,U_Y)
\end{align*}
\]

where \( f_W, f_A, f_Y \) are deterministic functions, and \( U_W, U_A, U_Y \) are exogenous variables. This model assume that the data are generated sequentially. First, the pre-treatment variables \( W \) are generated based on the exogenous error \( U_W \) and the function \( f_W \). Next, the treatment \( A \) is generated according to \( f_A \) based on \( W \) and \( U_A \). Finally, the outcome is generated according to \( f_Y \) based on the observed \( A, W \), and \( U_Y \). We can consider intervening in this system to deterministically set \( A \), rather than allowing \( f_A \) to determine its value. This generates \( Y(a) = f_Y(a,W_i,U_{Y,i}) \), \( a \in \{0,1\} \), or so-called counterfactual random variables. For \( a = 0,1 \), we denote by \( P_{a0} \) the distribution of the counterfactual random variable \( Y(a) \). Our parameter of interest is

\[
E_{P_0}[Y^{(1)}] - E_{P_0}[Y^{(0)}],
\]

which we refer to as the average treatment effect (ATE).

The ATE is identifiable under the following assumptions:

- Consistency: \( Y_i = Y_i^{(A_i)} \), \( i = 1,\ldots,n \);
- No interference: \( Y_i^{(A_i)} \) does not depend on \( A_j \) for \( i = 1,\ldots,n \) and \( j \neq i \);
- Ignorability: \( A_i \perp (Y_i^{(1)},Y_i^{(0)})|W_i \), \( i = 1,\ldots,n \);
- Positivity: \( \Pr_{P_0}\{0 < \Pr_{P_0}(A = 1 | W) < 1\} = 1 \).
The first two assumptions are axiomatic in the sense that they are needed so that the counterfactual random variables are well defined. The latter two assumptions are more important to the present discussion. The ignorability condition states that there are no unmeasured confounders of $A$ and $Y$, while the positivity criterion states that every participant has a non-zero probability of receiving $A = 1$ and $A = 0$. If these assumptions hold, the average treatment effect is identified based on the observed data. We write several equivalent identification results to motivate various estimators:

- **G-computation identification**

  $$ E_{P_0}[Y(1)] - E_{P_0}[Y(0)] = E_{P_0}[E_{P_0}(Y \mid A = 1, W) - E_{P_0}(Y \mid A = 0, W)] ; \quad (1) $$

- **Stabilized IPTW identification**

  $$ E_{P_0}[Y(1)] - E_{P_0}[Y(0)] = E_{P_0}\left[\left\{I(A = 1) / pr_{P_0}(A = 1 \mid W) - I(A = 0) / pr_{P_0}(A = 0 \mid W)\right\} Y\right] . \quad (2) $$

2.2 Estimators of the average treatment effect

The identification results (1)-(2) naturally suggest estimators of the ATE. Consider $\bar{Q}_n(a, w)$, an estimate of $Q_0(a, w) = E_{P_0}(Y \mid A = a, W = w)$, and $\bar{G}_n(w) = n^{-1} \sum_{i=1}^{n} I(W_i \leq w)$, the empirical cumulative distribution function of $W$. Equation (1) suggests the estimator

$$ \psi_{n,\text{GCOMP}} = \int \{\bar{Q}_n(1, w) - \bar{Q}_n(0, w)\} d\bar{Q}_n(w) $$

$$ = \frac{1}{n} \sum_{i=1}^{n} \{\bar{Q}_n(1, W_i) - \bar{Q}_n(0, W_i)\} . $$

This estimator is referred to as the G-computation (GCOMP) estimator. On the other hand, (2) suggests an alternative estimator of the ATE. Consider $\bar{G}_n(a, w)$, an estimate of $G_0(a, w) = pr_{P_0}(A = a \mid W = w)$, and $F_n(w, a, y) = n^{-1} \sum_{i=1}^{n} I(W_i \leq w, A_i = a, Y_i \leq y)$, the empirical cumulative distribution function of $O$. Equation (2) suggests the estimator

$$ \psi_{n,\text{SIPTW}} = \int \left\{ \frac{I(a = 1) / G_n(1, w)}{\int I(a = 1) / G_n(1, w) d F_n(w, a, y)} - \frac{I(a = 0) / G_n(0, w)}{\int I(a = 0) / G_n(0, w) d F_n(w, a, y)} \right\} y d F_n(w, a, y) $$

$$ = \sum_{i=1}^{n} \left\{ \frac{I(A_i = 1) / G_n(1, W_i)}{\sum_{i=1}^{n} I(A_i = 1) / G_n(1, W_i)} - \frac{I(A_i = 0) / G_n(0, W_i)}{\sum_{i=1}^{n} I(A_i = 0) / G_n(0, W_i)} \right\} Y_i . \quad (3) $$

This estimator is referred to as the stabilized inverse probability of treatment weighted (SIPTW) estimator.

Targeted minimum loss-based estimation (TMLE) provides an alternative estimator of the average treatment effect. This estimator is doubly-robust, in the sense that it is consistent for the true target parameter if either the outcome regression or propensity score is consistently estimated. The estimator is also locally efficient, meaning that if both nuisance parameters are consistently estimated at a sufficiently fast rate, then the TMLE achieves the semiparametric efficiency bound. TMLE begins by generating initial estimates $\bar{Q}_n^1$ and $\bar{G}_n^1$ of $Q_0$ and $G_0$ respectively. Next, we consider a logistic-linear parametric model defined based on the initial estimates,
logit \{ \bar{Q}_{n, \epsilon} \} = \logit(\bar{Q}_{1}^{n}) + \epsilon H, \quad \text{where} \quad H(O_{i}) := \frac{(2A_{i} - 1) - \bar{G}_{n}(A_{i}, W_{i})}{\bar{G}_{n}(A_{i}, W_{i})}.

Note that this defines a logistic regression model with offset given by the initial estimator and single covariate \( H \). A maximum likelihood estimator \( \epsilon_{n} \) of \( \epsilon \) is found (e.g., via iteratively reweighted least-squares) and the TMLE of the ATE is

\[
\psi_{n, \text{TMLE}} := \int \{ \bar{Q}_{n, \epsilon_{n}}(1, w) - \bar{Q}_{n, \epsilon_{n}}(0, w) \}dQ_{n}(w)
\]

\[
= \frac{1}{n} \sum_{i=1}^{n} \{ \bar{Q}_{n, \epsilon_{n}}(1, W_{i}) - \bar{Q}_{n, \epsilon_{n}}(0, W_{i}) \}.
\]

Note that the TMLE estimator is based on the G-computation identification result. The difference between \( \psi_{n, \text{GCOMP}} \) and \( \psi_{n, \text{TMLE}} \) is the latter uses the so-called targeted estimator \( \bar{Q}_{n, \epsilon_{n}} \) of \( Q_{0} \).

The TMLE estimator has been shown to often have improved finite-sample performance relative to other doubly-robust estimators [Porter et al., 2011]. A more general discussion of TMLE may be found in [van der Laan and Rubin, 2006], [van der Laan and Rose, 2011], [van der Laan et al., 2014]. A discussion of the theoretical underpinnings of double-robustness for TML estimators may be found in [Benkeser et al., 2017].

### 2.3 Nuisance parameter estimation

It is clear that for each of the estimators discussed in the previous subsection, we require an estimate of either the outcome regression, the propensity score, or both. By far, the most popular techniques for estimating these regressions in the literature have been generalized linear models. However, researchers have found that even slight misspecification of the nuisance parameters can result in substantial bias of estimated treatment effects [Kang and Schafer, 2007], [Setoguchi et al., 2008]. This has led to increased interest in machine learning approaches for nuisance parameter estimation. [Setoguchi et al., 2008] compared decision trees and neural networks (NNs) with logistic regression in estimation of the propensity score, and found that NNs achieve the smallest bias, but that logistic regression achieves the most robust performance. [Lee et al., 2010] compared logistic regression with tree-based methods, and assessed the performance of estimation and inference for the resulting IPTW estimators. [van der Laan et al., 2007] argued that the best algorithm for nuisance estimation is likely to be different across different settings, and thus recommended cross-validation should be used to select an estimator from amongst many candidate estimators. [Porter et al., 2011] examines this approach in estimation of causal effects.

However, as discussed in the introduction there are more subtle considerations with respect to nuisance parameter estimation. In particular, it is important to decide what variables to include in the nuisance estimation procedures, and, in the case of machine learning approaches, to decide on relevant criterion for hyper-parameter selection. With regard to the first question, the ignorability assumption suggests that we must, at a minimum, include all variables that are related both with the treatment and the outcome. However, there is also potential benefit in including variables related only to the outcome [Zhang et al., 2008], [Moore and van der Laan, 2009], and there is risk in including variables related only to the treatment [Greenland, 2008], [Schisterman et al., 2009], [Rotnitzky et al., 2010], [van der Laan et al., 2010], [Schneeweiss et al., 2009], [Myers et al., 2011]. [Ju et al., 2017b, 2018]. Complicating matters further is the fact that in finite samples it is often beneficial to remove true confounding variables that cause extreme values in the propensity score [Petersen et al., 2012].

With regard to the question of hyper-parameter selection, typically cross-validation is used to select hyper-parameters that lead to the best fit of the nuisance parameter; for example, by optimizing a likelihood or minimizing mean squared-error. However, several authors have noted
that the best fit for the nuisance parameter does not necessarily lead to the best estimate of the ATE [Gruber and van der Laan, 2010]. This is particularly true in the case of the SIPTW-type estimators. The SIPTW estimator controls bias in estimation of the ATE by balancing the covariate distributions between treated and untreated observations. Thus, selecting hyper-parameters that optimize covariate balance rather than fit of the propensity score, may lead to improved performance of SIPTW estimators [dAgostino, 1998; Austin et al., 2007; Pirracchio and Carone, 2016]. On the other hand, GCOMP estimators control bias in estimation of the ATE solely by estimating the conditional ATE given covariates. Thus, for GCOMP estimators it appears that the criterion for hyper-parameter selection should indeed assess the fit of the outcome regression. This idea is the motivation for collaborative TMLE, which we discuss in Section 3.3.

2.4 Outcome-adaptive estimation of propensity score for IPTW estimator

Both the issue of variable selection and hyper-parameter selection were addressed by the proposal of Shortreed and Ertefaie [2017]. The proposal can be summarized as follows:

(i) Define a main terms parametric regression model for the outcome regression, \( \bar{Q}_{\alpha, \eta}(a, w) = \alpha_0 + \eta a + w^\top \alpha \) and estimate \((\alpha_0, \eta, \alpha)\) via maximum likelihood. We denote by \( \hat{\alpha}_j \) the coefficient for variable \( W_j \) in the outcome regression, and define \( \hat{\alpha} := (\hat{\alpha}_j : j = 1, \ldots, p) \).

(ii) Define a logistic regression model for the propensity score, \( \logit \{ \bar{G}_{\beta}(1, w) \} = \beta_0 + w^\top \beta \) and estimate \((\beta_0, \beta)\) via the adaptive LASSO [Zou, 2006] with penalty weight for \( \beta_j \) given by \( |\hat{\alpha}_j| - \gamma \). That is, find \( \hat{\beta}_{\gamma}(\lambda) := \arg\min_{\beta_0, \beta} \left( \sum_{i=1}^{n} \left[ -A_i (\beta_0 + W_i^\top \beta) + \log \{ 1 + \exp(W_i^\top \beta) \} \right] + \lambda \sum_{j=1}^{p} |\hat{\alpha}_j| - \gamma |\beta_j| \right) \),

where \( \gamma \) and \( \lambda \) are user-supplied tuning parameters.

(iii) Define the weighted absolute mean difference \( wAMD_n(\lambda) = \sum_{j=1}^{d} |\hat{\alpha}_j| W_{ij} I(A_i = 1) - \sum_{j=1}^{d} |\hat{\alpha}_j| W_{ij} I(A_i = 0) \)

and select hyper-parameter as, \( \lambda_n := \arg\min_{\lambda} wAMD_n(\lambda) \). Shortreed and Ertefaie [2017] suggests \( \gamma = 2 \cdot (3 - \lambda) \) will ensure certain convergence properties for the estimator.

(iv) Create SIPTW estimate \( \bar{G}_{\hat{\beta}_\gamma}(\lambda) \).

The proposal selects variables by fitting a regression model for the outcome in step (1). The coefficients of this model are used as inverse weights in by the adaptive lasso in step (2). This ensures selection of the proper variables to be included in the propensity score estimate. Moreover, in step (iii) the propensity score estimator is then fine-tuned towards performance of the IPTW estimator by minimizing a balance metric for the covariates. While the proposal of Shortreed and Ertefaie [2017] is an important theoretical advance, there may be room to improve on it in several respects. First, the applicability of the method may be limited by the need to correctly specify a parametric regression formula for both the outcome regression and the propensity score. In some settings, it may be of benefit to consider more flexible regression approaches. Additionally, it may be possible to improve on the efficiency of the proposal by utilizing a doubly-robust rather than SIPTW estimators of the ATE.
3 Collaborative TMLE with outcome-adaptive HAL

An alternative approach to variable selection and hyper-parameter selection in estimation of causal effects is collaborative TMLE (CTMLE). Recall that TML estimators are essentially GCOMP estimators and therefore rely on good estimators of the outcome regression to control bias. However, they also make use of the propensity score in the second-stage model fitting procedure, generating a targeted estimate of the outcome regression based on the estimate of the propensity score. It would seem therefore that the best propensity score estimate to use in a TML procedure is one that leads to the best fit of the targeted estimate of the outcome regression. This concept is formalized by collaborative TMLE, where a sequence of targeted outcome regressions and corresponding propensity score estimators is constructed such that both increase in empirical fit. The targeted outcome regression (and corresponding propensity score) with the best cross-validated fit is used to construct the CTMLE estimator.

Depending on how the sequence of propensity score estimators is constructed, this approach can incorporate both variable selection, as well as hyper-parameter selection. For example, [Gruber and van der Laan 2010] proposed a greedy search for variables to include in the propensity score model. More recently, [Ju et al. 2017b] proposed a method wherein CTMLE was used to select the penalty parameter in a lasso regression for the propensity score. As penalized regression shrinks the coefficient of some variables to zero, this method simultaneously achieves variable selection and hyper-parameter selection. In this section, we combine these CTMLE proposals with a more flexible version of the Shortreed and Ertefaie [2017] proposal.

3.1 Highly adaptive lasso

The highly adaptive lasso estimator is a semi-parametric regression estimator that is consistent for the true regression function in a large function class [Benkeser and van der Laan 2016, van der Laan 2017]. In particular, the estimator is consistent assuming only that the true regression function has finite variation norm. The estimator can be written as the solution to a penalized regression problem using a particular set of basis functions. We provide a brief description of the algorithm here and refer readers to the original publications for further details. We generically denote the outcome \( Z \) and \( d \)-dimensional set of predictors \( X \). For each set \( s \subset \{1, \ldots, d\} \), let \( X_i^*(s) \) be the subvector \((X_{ij} : j \in s), i = 1, \ldots, n\). We denote by \( \mathcal{T} \) the set of all such subsets of \( \{1, \ldots, d\} \). For each \( s \in \mathcal{T} \), we define \( n \) basis functions, \( x \rightarrow I(x^*(s) \geq X_{i}^*(s)) \), \( i = 1, \ldots, n \). We define

\[
\mu_{\xi_0, \eta}(x) := \xi_0 + \sum_{s \in \mathcal{T}} \sum_{i=1}^{n} \eta_i(s) I(x^*(s) \geq X_{i}^*(s)).
\]

The coefficient for each basis function is estimated via penalized regression,

\[
(\hat{\xi}_0(\lambda), \hat{\eta}(\lambda)) := \arg\min_{\xi_0, \eta} \sum_{i=1}^{n} (Z_i - \mu_{\xi_0, \eta}(X_i))^2 + \lambda \sum_{s \in \mathcal{T}} \sum_{i=1}^{n} |\eta_i(s)|.
\]

If the outcome is binary (e.g., \( A \)), we could instead minimize negative log-likelihood rather than mean squared-error. The hyper-parameter \( \lambda \) is selected via cross-validation, and we denote by \( \lambda_n \) the value that minimizes cross-validated risk. The highly adaptive lasso estimator is \( \mu_{\hat{\xi}_0(\lambda_n), \hat{\eta}(\lambda_n)} \).

3.2 Outcome highly adaptive lasso

Because the highly adaptive lasso is a special case of the usual lasso, it is straightforward to accommodate outcome-adaptive weights in the fitting of the propensity score. An algorithm for
generating nuisance estimators is as follows. First, we compute HAL estimate of the outcome regression, using $Y$ as outcome and $(W, A)$ as features. Note that $(W, A)$ is a vector with $d + 1$-th entry equal to the treatment variable. Following Shortreed and Ertefaie [2017], we first introduce an additive model with no treatment/covariate interactions. To fit such a HAL, one simply removes from $T$ all higher-order subsets of features that include the treatment variable. We can then write

$$\bar{Q}_{\alpha_0, \alpha_A, \alpha}(a, w) = \alpha_0 + \alpha_A a + \sum_{s \in T^*} \sum_{i=1}^{n} \alpha_i(s) I(w^*(s) \geq W_i^*(s)),$$

where $T^* \subset T$ is all subsets of $\{1, \ldots, d + 1\}$ that do not include $d + 1$.

We denote by $\hat{\alpha}_n$ the vector of HAL-estimated coefficients associated for the covariate-related basis functions at the CV-selected hyper-parameter. Next, we fit HAL using the treatment indicator $A$ as outcome, and $W$ as features. However, we can modify the constraint in the minimization (6) to include the outcome-adaptive weights. Specifically, the HAL model for the propensity score is

$$\logit \{ \bar{G}_{\beta_0, \beta}(w) \} := \beta_0 + \sum_{s \in T^*} \sum_{i=1}^{n} \beta_i(s) I(w^*(s) \geq W_i^*(s)).$$

We can write the HAL minimization problem as

$$(\hat{\beta}_0(\lambda), \hat{\beta}(\lambda)) := \arg\min_{\beta_0, \beta} \sum_{i=1}^{n} \log [\bar{G}_{\beta_0, \beta}(1, W_i)^A_i \{1 - \bar{G}_{\beta_0, \beta}(1, W_i)\}^{1-A_i}] + \lambda \sum_{s \in T^*} \sum_{i=1}^{n} |\hat{\alpha}_i(s)|^{-\gamma} |\beta_i(s)|.$$

To accommodate treatment/covariate interactions, we suggest stratifying the estimation of the outcome regression by treatment, thereby generating estimated coefficients $\hat{\alpha}_{n,1}$ and $\hat{\alpha}_{n,0}$ for the outcome regression fit in observations with $A = 1$ and $A = 0$, respectively. The OHAL penalty weight for the propensity score is the average of $\hat{\alpha}_{n,1}$ and $\hat{\alpha}_{n,0}$.

3.3 Tuning via collaborative targeted minimum loss-based estimation

While Shortreed and Ertefaie [2017] selected $\lambda$ by minimizing (4), we use CTMLE to perform this tuning. As discussed above, CTMLE extends the usual TMLE estimator by creating a sequence of TML estimates based on propensity score estimates of increasing complexity. In the present problem, this increase in complexity aligns with selection of smaller values for the tuning parameter $\lambda$ in the OHAL fit of the propensity score. We select the targeted estimate of the outcome regression that minimizes a cross-validated risk criteria, and base our estimate on the selected outcome regression. The CTMLE procedure is implemented as follows. Without loss of generality, we consider that $Y$ is continuous valued on $(0, 1)$.

1. Fit the outcome regression using HAL and select hyper-parameter using cross-validation, e.g., minimizing cross-validated mean squared-error. Denote the coefficients of this fit by $\alpha_{n,cv}$.

Denote the outcome regression fit based on these coefficients by $\bar{Q}_n$.

2. Fix a decreasing sequence $\lambda_1, \ldots, \lambda_N$ of values for the penalty in the propensity score fit.

3. For $j = 1, \ldots, N$, fit OHAL with penalty weights $\alpha_{n,cv}$ and penalty $\lambda_j$. Denote these fits by $G_{n,j}$. For $j = 1, \ldots, N$, define $H_{n,j}(a) := (2a - 1)/G_{n,j}(a, w)$.

4. Let the current initial outcome regression estimate be $\bar{Q}_n^{\text{init}} := \bar{Q}_n$. 8
5. Fit a logistic regression model with outcome \( Y \), offset \( \logit(Q_{n,1}^{\text{init}}) \), and single covariate \( H_{n,1} \). Denote by \( \epsilon_{n,1} \) the estimated coefficient from this fit, and define \( Q_{n,1} := \expit(\logit(Q_{n,1}^{\text{init}}) + \epsilon_{n,1}H_{n,1}) \).

6. For \( j = 2, \ldots, N \), recursively perform the following steps:
   i) Fit a logistic regression model with outcome \( Y \), offset \( \logit(Q_{n,j}^{\text{init}}) \), and single covariate \( H_{n,j} \). Denote by \( \epsilon_{n,j} \) the estimated coefficient from this fit, and define \( Q_{n,j}^{\text{cand}} := \expit(\logit(Q_{n,j}^{\text{init}}) + \epsilon_{n,j}H_{n,j}) \).
   ii) Evaluate the fit of \( Q_{n,j}^{\text{cand}} \) and \( Q_{n,j}^{-1} \), e.g., by comparing mean squared-error.
   iii) If \( Q_{n,j}^{\text{cand}} \) is a better fit (e.g., has lower mean squared-error), then set \( Q_{n,j} = Q_{n,j}^{\text{cand}} \) and proceed to 6i).
   iv) Otherwise, set the initial outcome regression to \( Q_{n,j}^{\text{init}} := Q_{n,j-1} \) and fit a logistic regression model with outcome \( Y \), offset \( \logit(Q_{n,j}^{\text{init}}) \), and single covariate \( H_{n,j} \). Abusing notation, again denote by \( \epsilon_{n,j} \) the estimated coefficient from this fit, and define \( Q_{n,j} := \expit(\logit(Q_{n,j}^{\text{init}}) + \epsilon_{n,j}H_{n,j}) \). Proceed to 6i).

7. Step 6 generates \( (Q_{n,j}, j = 1, \ldots, N) \), a sequence of \( N \) possible outcome regression estimators. Split the data into \( V \) folds and repeat steps 5 and 6 on each of the training folds. For each \( j \), evaluate the cross-validated fit (e.g., cross-validated mean squared-error) of \( Q_{n,j} \). Denote by \( j_n \) the outcome regression estimator with best cross-validated fit.

8. Construct estimate of the average treatment effect \( \psi_{n,\text{CTMLE}} := n^{-1} \sum_{i=1}^{n} (Q_{n,j_n}(1,W_i) - Q_{n,j_n}(0,W_i)) \).

The implementation of CTMLE algorithm can be found in the \textit{ctmle} R package \cite{Ju+2017} on The Comprehensive R Archive Network.

4 Simulations

4.1 Illustration and comparison to TMLE-HAL and CTMLE-HAL

We begin our numerical studies with a short illustration of how CTMLE-OAL differs from existing HAL-based approaches. We simulated one hundred data sets from the following data generating mechanism. A univariate variable \( W \) was drawn from a Uniform\((-\pi, \pi)\) distribution. The treatment was drawn from a Bernoulli distribution with \( G_0(1,W) = \frac{\sin(2W) + 1.01}{2.1} \). The outcome was drawn from a normal distribution with conditional mean \( Q_0(a,W) = I(W > 0)\sin(2W) \) and variance 0.25. The average treatment effect was zero. In this setting, \( W \) is related to both the treatment probability and the outcome; however, there is no variation in \( Q_0(a,w) \) for \( w > 0, a = 0, 1 \). Thus, we may consider any HAL basis function corresponding with a value of \( W \) greater than zero to be like an instrumental variable. We expected that OHAL would more effectively get rid the propensity score estimator of these basis functions and thereby lead an estimator with lower variance.

We studied three HAL-based estimators of the average treatment effect. The first was TMLE-HAL, which used HAL to estimate both the propensity score and outcome regression, and selected the hyper-parameters by optimizing cross-validated mean squared-error for the outcome regression and deviance for the propensity score \cite{van der Laan+2017}. The second estimator was CTMLE-HAL, which uses HAL to estimate the outcome regression and builds a sequence of candidate HAL fits for the propensity score. CTMLE is used to select the propensity score fit from this sequence.
This is essentially the estimator of Ju et al. [2017b] with the usual lasso replace by HAL. The third estimator was the CTMLE-OHAL, which uses HAL to estimate the outcome regression and builds a sequence of candidate OHAL fits for the propensity score. The estimator again utilizes CTMLE to select an OHAL propensity score fit from this sequence.

| Estimator      | Bias | Standard error | Mean squared-error |
|----------------|------|----------------|--------------------|
| TMLE-HAL       | 1.1  | 8.2            | 8.0                |
| CTMLE-HAL      | 1.9  | 6.6            | 7.9                |
| CTMLE-OHAL     | 1.7  | 6.6            | 7.0                |

Table 1: Comparison of estimators in setting with univariate covariate. Bias has been multiplied by 1e2, standard error and mean squared-error have been multiplied by 1e4.

Using cross-validation to select the HAL hyper-parameter for the outcome regression led to an accurate fit (Figure 1, left). Each estimator is based on this initial estimator of the outcome regression; however, the estimators use different propensity score fits. TMLE-HAL and CTMLE-HAL generate a sequence of potential HAL fits for the propensity score. TMLE-HAL selects the propensity score fit that provides the best fit to the true underlying regression (Figure 1, center, red lines). The resultant estimator had low bias, but larger variance than CTMLE-HAL (Table 1). On the other hand, CTMLE-HAL selects the propensity score that provides the best targeted outcome regression fit, which tended to be an over-smoothed fit of the true propensity score (Figure 1, center, blue lines). The over-smoothing appears fairly uniform over the range of $W$. This propensity score fit resulted in an estimator with larger bias, but lower variance than HAL-TMLE (Table 1); the mean squared-error of the two estimators was about the same. On the other hand, CTMLE-OHAL generates a sequence of potential OHAL fits for the propensity score, and selects from this sequence the propensity score that provides the best targeted outcome regression. This again tended to be an over-smoothed fit to the true propensity score. As we might expect, the over-smoothing was particularly apparent over values of $W > 0$, where the outcome regression does not vary. This propensity score fit resulted in an estimator with significantly improved mean squared-error relative to the other two estimators.

4.2 Kang and Schafer’s simulation

We studied the performance of our estimator on the simulation of Kang and Schafer [2007], which has been studied extensively in the literature (e.g., Porter et al. [2011]). Data for this simulation are generated as follows. An unmeasured pre-treatment variable $Z := (Z_1, \ldots, Z_4)$ is drawn from a mean-zero multivariate normal distribution with the identity covariance matrix. The treatment indicator is drawn from a Bernoulli distribution with

$$\logit\{\Pr(P_0(A = 1 \mid Z)\} = -Z_1 + 0.5Z_2 - 0.25Z_3 - 0.1Z_4.$$  

Potential outcomes are generated as

$$Y^{(1)} = Y^{(0)} = 210 + 27.4Z_1 + 13.7Z_2 + 13.7Z_3 + 13.7Z_4 + \epsilon,$$

where $\epsilon$ is drawn from a mean-zero normal distribution with unit variance. The true average treatment effect is zero. While treatment and outcome are drawn based on $Z$, only a transformation of $Z$ is available to the analyst. Specifically, we observe $W = (W_1, \ldots, W_4)$, where

$$W_1(Z) = \exp(Z_1/2)$$
$$W_2(Z) = Z_2/\{1 + \exp(Z_1)\} + 10$$
$$W_3(Z) = (Z_1Z_3/25 + 0.6)^3$$
$$W_4(Z) = (Z_2 + Z_4 + 20)^2.$$  

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We also studied performance of the estimators when an instrumental variable is included in the Kang and Schafer simulation. The treatment probability in this simulation was

\[
\text{pr}_0(A = 1|W, Z) = \expit\left\{ (\frac{-Z_1 + 0.5Z_2 - 0.25Z_3 - 0.1Z_4}{2} + W_5) \right\} ,
\]

where \(W_5\) was generated from a mean-zero normal distribution with unit variance. Including \(W_5\) in estimation of the propensity score should improve the fitting relative to the true propensity score; however, it will not help with estimation of the average treatment effect.

In each setting, we considered six estimators: GCOMP using linear regression to estimate the outcome regression, SIPTW using logistic regression to estimate the propensity score, SIPTW using linear regression to estimate the outcome regression and OAL to estimate the propensity score (the Shortreed and Ertefaie [2017] estimator), TMLE using HAL for the outcome regression and the propensity score, CTMLE using HAL for the outcome regression and propensity score, and CTMLE using HAL for the outcome regression and OHAL for the propensity score. The sequence of possible values of \(\lambda\) for the outcome regression was of length fifty with values between \(\exp(-30)\) to \(\exp(-2)\) that were equally spaced on the log-scale. For the propensity score, the sequence of possible values of \(\lambda\) was the default sequence used by the \texttt{glmnet} function in R [Friedman et al., 2010]. We set \(\gamma = 1\) for both OAL and OHAL. Note that GCOMP in this case is equivalent with the ordinary least squares estimate of the treatment coefficient in the linear model. We compared the various estimators on their Monte Carlo bias, standard error, and mean squared-error based on 1000 simulated data sets.

Inconsistent estimation of the outcome regression resulted in high bias, but low standard error for the GCOMP estimator in the original Kang and Schafer simulation (Table 2). In contrast, inconsistent estimation of the propensity score by SIPTW and SIPTW-OAL resulted in low bias, but high standard error. Thus, neither estimator performed well by mean squared-error. On the other hand, the flexible nuisance modeling afforded by the TMLE-HAL, CTMLE-HAL, and CTMLE-OHAL approaches led to a more balanced trade-off of bias and variance. Indeed, we find all three estimators have mean squared-error decreasing with \(n\). However, comparing these
three estimators, we find that utilizing OHAL rather than HAL for the propensity score estimation resulted in lower bias and thus lower mean squared-error for CTMLE-OHAL relative to TMLE-HAL and CTMLE-HAL. The gains are appreciable, with considerably lower mean squared-error at each sample size.

Results for the modified Kang and Schafer simulation were largely similar. The GCOMP estimator was biased by the inconsistent estimate of the outcome regression. The SIPTW estimator was highly variable, while the SIPTW-OAL estimator had lower variance owing to its ability to correctly shrink the coefficient for \( W_5 \) in the propensity score estimation. Nevertheless, we found that TMLE-HAL and the two CTMLEs outperformed other estimators owing to their ability to flexibly estimate the nuisance parameters. The improvements of CTMLE-OHAL relative to TMLE-HAL and CTMLE-HAL are even more striking in this setting with CTMLE-OHAL achieving mean squared-error less than half that of the other HAL-based estimators.

### 5 Shortreed simulations

A limitation of HAL is that the computational complexity increases exponentially with \( d \). Thus, it may be infeasible to apply HAL (and by extension, OHAL) to high-dimensional data. Nevertheless, there may yet be benefits to utilizing CTMLE with the OAL relative to the SIPTW...
estimator proposed in Shortreed and Ertefaie [2017]. To study this point, we re-examined one of the simulations in Shortreed and Ertefaie [2017]. We generated $d = 500$ pre-treatment variables by sampling from a mean-zero multivariate normal distribution, with identity covariance matrix. The treatment is drawn from a Bernoulli distribution, with logit $\{ \Pr(A = 1 \mid W) \} = \alpha^\top W$. The outcome is generated as $Y = \eta \cdot A \beta^\top W + \epsilon$, where $\epsilon$ is drawn from a mean-zero normal distribution with unit variance. We set $\beta_j = 0.6$ for $j = 1, \ldots, 4$ and $\beta_j = 0$ otherwise. We set $\eta = 0$, so the ATE is 0. We considered four cases for $\alpha$,

Case 1: $\alpha = (0.4, 0.4, 0, 0, 1, 1, 0, \ldots, 0)$,  
Case 2: $\alpha = (1, 1, 0, 0, 1, 1, 0, \ldots, 0)$,  
Case 3: $\alpha = (0.4, 0.4, 0, 0, 1, 1, d^{-1}, \ldots, d^{-1})$,  
Case 4: $\alpha = (1, 1, 0, 0, 1, 1, d^{-1}, \ldots, d^{-1})$.

In each case, $W_5$ and $W_6$ are instrumental variables that are strongly related to the treatment. In case 1, these variables are more strongly related to the treatment probability than the true confounders $W_1$ and $W_2$. In case 2, the strength of the confounder relationship with the treatment is the same magnitude as that of the instrumental variables. Case 1 and 2 were studied in Shortreed and Ertefaie [2017]. We considered two additional cases, where we added many weak instrumental variables to the settings in cases 1 and 2. Thus, we expect cases 3 and 4 to be more challenging than cases 1 and 2, respectively. We considered a grid $\lambda \in \{n^2 : x = \{0.49, 0.1, 0.05\} \cup \{-2, -4, \ldots, -40\}\}$ and chose $\gamma$ to satisfy $\lambda n^{\gamma/2-1} = n^2$ as suggested in Shortreed and Ertefaie [2017].

In each setting, we considered five estimators: GCOMP using linear regression to estimate the outcome regression, SIPTW using LASSO to estimate the propensity score, where the hyper-parameter is selected by minimizing cross-validated deviance, SIPTW using linear regression to estimate the outcome regression and OAL to estimate the propensity score (the Shortreed and Ertefaie [2017] estimator), CTMLE that used linear regression for the outcome regression, and LASSO for the propensity score where the LASSO hyper-parameter was selected to minimize deviance, CTMLE that used linear regression for the outcome, and OAL for the propensity score with hyper-parameter selected via CTMLE. We compared the various estimators on their Monte Carlo bias, standard error, and mean squared-error based on 1,000 simulated data sets of size $n = 1,000$.

| Estimator       | Case | Bias 1 2 3 4 | Standard error 1 2 3 4 | Mean squared-error 1 2 3 4 |
|-----------------|------|------------|------------------------|--------------------------|
| GCOMP           | 0.1  | 0.1 0.7 0.5 | 7.4 8.0 7.3 7.7        | 0.5 0.6 0.5 0.6          |
| SIPTW-L         | 19.1 | 26.7 19.5 26.4 | 9.4 11.7 9.8 10.7    | 4.5 8.4 4.7 8.1          |
| SIPTW-OAL       | 1.7  | 4.1 1.6 2.8 | 8.3 10.1 8.5 10.3    | 0.7 1.2 0.7 1.1          |
| CTMLE-L         | 0.1  | 0.2 0.6 0.1 | 7.8 9.8 7.9 9.1      | 0.6 0.9 0.6 0.8          |
| CTMLE-OAL       | 0.2  | 0.0 0.6 0.6 | 7.7 8.1 7.5 7.9      | 0.6 0.6 0.5 0.6          |

Table 4: Results for the modified Shortreed simulation. All numbers are reported as the true value multiplied by 1e2. Abbreviations: see Table 2. CTMLE-L = collaborative targeted minimum loss-based estimator with linear regression for outcome regression and LASSO for propensity score with hyper-parameter selected my minimizing cross-validated deviance; CTMLE-OAL = collaborative targeted minimum loss-based estimator with linear regression for outcome and outcome-adaptive LASSO for propensity score with hyper-parameter selected via CTMLE.

We note that the GCOMP estimator is an efficient estimator in the correctly-specified linear regression model. Thus, it performed well by all three of our criterion (Table 4), and may be considered the benchmark estimator in this simulation. The SIPTW-L estimator that used lasso
for the propensity score had large bias, and correspondingly large MSE, while the SIPTW-OAL estimator improved the bias relative to SIPTW-L. However, this estimator had larger variance and mean-squared error than the GCOMP and CTMLE estimators. Comparing the two CTMLE estimators, we found that their bias of both estimators was comparable to GCOMP, while the standard error of the CTMLE-OAL tended to be lower than that of CTMLE-L. Thus, the mean squared-error of the CTMLE-OAL was lower than that of CTMLE-L, and was comparable to GCOMP.

This simulation demonstrates the potential for improvements over the SIPTW-OAL estimator by utilizing efficient and doubly-robust estimators. Such estimators appear to more efficiently utilize the correctly specified the outcome regression when constructing estimators of the average treatment effect.

6 Discussion

OHAL provides a tool for flexibly estimating the propensity score that simultaneously accounts for variable selection. The results of the Kang and Schafer [2007] simulation study demonstrated the benefits of flexible nuisance estimation in settings where complex non-linearities and interactions are present. It is interesting that we found that CTMLE-OHAL had superior performance relative even to asymptotically efficient estimators, even in settings without true instrumental variables. A possible explanation is that we can consider the HAL basis functions to each be their own separate instrumental variable. Basis functions that receive zero coefficient in the HAL fit of the outcome regression are not predictive of the outcome, and thus might be considered an instrument. We thus can expect that removing these basis functions from the propensity score will improve the variance of the resultant treatment effect estimator. Furthermore, our proposed method promises greater efficiency relative to the SIPTW-based proposal of Shortreed and Ertefaie [2017] by virtue of utilizing doubly-robust estimation. This was demonstrated by the third simulation study. Moreover, because Shortreed and Ertefaie [2017] requires an estimate of the outcome regression, our proposal adds little computational burden.

In future work it will be important to investigate the performance of CTMLE-OHAL as a means of estimating different causal parameters, such as the causal effect of a treatment administered over several time points. In addition, we are interested in further investigating how to adaptively tune the regularization for HAL outcome regression. The outcome regression in OHAL plays a particularly important role as it contributes to the estimation of the average treatment effect both through its role as an estimator of the true outcome regression, as well as through its role in the propensity score estimation. Thus, errors in tuning the outcome regression may easily propagate down to the estimate of the average treatment effect. We have begun experimentation with recursive tuning procedures, but so far have found no change in the estimators’ performance. Another important consideration is selection of the hyper-parameter $\gamma$ in OHAL. In the Kang and Schafer [2007] study, we simply set $\gamma = 1$ for all sample sizes to reduce the computational burden of the LASSO fitting for OHAL. Thus, we expect that with more careful tuning of $\gamma$, the performance of CTMLE-OHAL may improve even more.

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