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Variable Selection in Double/debiased Machine Learning for Causal Inference: An Outcome-Adaptive Approach

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ABSTRACT

Access to high-dimensional data has made the use of machine learning in the causal inference more common in recent years. The double/debiased machine learning (DML) estimator for the treatment effect is designed to obtain the valid inference when nuisance functions, in the treatment and the outcome equations, are estimated using machine learning methods. However, when some covariates in the treatment equation are not correlated with the outcome, inclusion of such covariates, called instruments, in the estimation of the propensity score in the treatment equation will result in increasing bias and variance of DML estimator. To solve this issue, we introduce an outcome-adaptive DML estimator which incorporates the outcome-adaptive lasso to exclude the instruments from the propensity score. We evaluate the performance of the proposed method using Monte Carlo simulation. The results indicate that our proposed method outperforms other methods in many cases.

Keywords: Causal inference, Double/debiased Machine Learning, High-dimensional data, Machine Learning, Outcome-Adaptive Lasso.

Abbreviations: ATE, Average treatment effect; IPW, Inverse probability weighted estimator; DR, Doubly robust estimator; DML, Double/debiased machine learning estimator.

INTRODUCTION

In an observational study where the allocation of the treatment of interest is not randomized, the treatment allocation to each subject depends on clinicians or subjects, causing imbalances in the characteristics of the subjects between the groups with and without treatment. Such imbalances often introduce a selection bias to the estimation of the true treatment effect. To remove the selection bias and accurately estimate the true treatment effect, one should consider controlling these unbalanced characteristics by including covariates in a statistical model such as a multivariate regression model. However, in case that the regression model includes a large number of covariates relative to the number of the subjects, the problem of overfitting results in poor performance of regression analysis[1]. In recent years, high-dimensional data is commonly used in observational studies as a result of increasing access to electronic medical records and health claim data. Analysts need to take extra caution in the variable selection, especially if too many candidates of covariates are available in high-dimensional data.

The propensity score approach is useful in the estimation of the treatment effect with high-dimensional data, because the propensity score, defined as the probability of receiving a treatment conditioned on observed covariates, aggregates information from many covariates into a single value[2]. There are several different ways of using the propensity score to remove selection bias in the evaluation of the treatment effect, such as the matching method based on the propensity score[3], stratification according to propensity score intervals[4], and inverse probability weighted (IPW) estimation[4, 5, 6]. The propensity score is often calculated using a multivariate logistic regression model, in which the treatment variable is generated as a function of the covariates representing characteristics of the subjects. As suggested by Schuster et al. (2016)[7] and Chen et al. (2016), overfitting in the propensity score model can lead to inflation of the variance of the treatment effect estimator. So, the overfitting problem remains on how to account for many covariates with high-dimensional data even if one uses the propensity score approach.

In the presence of high-dimensional covariates, the machine learning methods are helpful in reducing the dimension of covariates through regularization [8, 9, 10, 11]. For example, Setoguchi et al. (2008)[12] and Lee et al. (2010)[13] have examined the performance of the

propensity score approaches combined with the machine learning methods in Monte Carlo simulation. They have shown some advantages of using the machine learning methods when the true propensity score model involves non-linearities and interaction terms. At the same time, as pointed out by Chernozhucov et al. (2017, 2018)[14, 15], regularization by the machine learning method may exclude variables relate to both of the outcome and treatment variable which may result in a type of omitted variable bias, which is often referred to as regularization bias. To reduce the regularization bias, Chernozhucov et al. (2018) proposed double/debiased machine learning (DML) estimator which is closely related to the doubly robust (DR) estimator of Robins et al. (1995)[16], Hahn (1998)[17] and Bang and Robins (2005)[18]. The DR estimator controls the effect of covariates by estimating a pair of nuisance functions: (1) the unknown propensity score in the treatment equation, and (2) the unknown conditional mean function in the outcome equation. It is considered robust because the treatment effect can be estimated even if one of the two functions is misspecified. At the same time, the DR estimator is known to be asymptotically more efficient than the IPW estimator[4].

Chernozhukov et al. (2018) pointed out that the DR estimator removes the regularization bias even if the pair of nuisance functions are estimated by machine learning methods because it satisfies Neyman orthogonal property. It is known that using moment condition that satisfies Neyman orthogonal property reduces the sensitivity with respect to nuisance functions in the estimation of the parameter of the interest. At the same time, however, Chernozhukov et al. (2018) suggested that the original DR estimator is subject to a bias from overfitting and the DML removes the bias from overfitting by cross-fitting. In the process of cross-fitting, the dataset is randomly resampled into the auxiliary samples and the main samples. Then, the nuisance functions for the outcome and treatment are estimated using auxiliary samples, whereas the parameter of interest is estimated using main samples. While DML is expected to work well in the presence of many confounders, i.e., covariates that associate with the outcome and the treatment, its performance regarding the variable selection is not yet systematically investigated.

In estimating the unknown propensity score in the treatment equation, the machine learning methods tend to select the variables which have stronger association with the treatment and

exclude the variables which have no association. Brookhart et al. (2006)[19], Bhattacharya et al. (2007)[20], Patric et al. (2011)[21], and Myers et al. (2011)[22] suggested that the inclusion of covariates associated with the treatment variable but not with the outcome variable, i.e., instruments into the propensity score model causes the variance inflation of the estimated treatment effect. Hence, in order to remove the instruments from the propensity score model automatically, Shortreed and Ertefaie (2017)[23] proposed the propensity score estimation using outcome-adaptive lasso which weakly penalizes the coefficients of covariates that are strongly related to the outcome, and selects these covariates in the propensity score model while excluding other covariates such as the instruments. While they focus on the IPW estimator, we are interested in whether the outcome-adaptive approach is also useful in the variable selection when the true effect of the treatment is estimated by the DML estimator.

In this paper, we propose a modification of DML estimator using the outcome-adaptive lasso, so that all true confounders and predictors of outcome are automatically selected and other covariates are excluded in the estimation of the propensity score. We call our proposed estimator by the outcome-adaptive DML estimator. To see if our proposed method works, we conduct simulation experiments to evaluate the performance of our proposed outcome-adaptive DML estimator in various settings. In our simulation, we generate the high-dimensional data where some covariates are (i) confounders, namely, variables correlated with both treatment and outcome, (ii) outcome predictors, namely variables correlated with outcome but not treatment, and (iii) instruments, namely, variables correlated with treatment but not outcome. The performance of our outcome-adaptive DML estimator is compared with that of the IPW estimator using the standard machine learning method considered in Setoguchi et al. (2008) and Lee et al. (2010), the outcome-adaptive IPW estimator considered by Shortreed and Ertefaie (2017), DR estimator and the original DML estimator. Note that two nuisance functions of the DR estimator in our simulation are estimated using the standard machine learning method. Because the effect of variable selection in such a DR estimator is not yet known, we also compare it with the outcome-adaptive DR estimator, which is the outcome-adaptive version of the DR estimator.

METHODS

IPW, DR and DML estimators

We first provide the basic formula for IPW, DR and DML estimators for average treatment effects (ATE). Let $D_i \in \{0, 1\}$ be the binary treatment variable and Y_i be the scalar continuous outcome variable. We follow Chernozhukov et al. (2017, 2018) and consider a model of a vector (Y_i, D_i, X_i) given by

$$Y_i = g(D_i, X_i) + U_i, \tag{1}$$

$$D_i = m(X_i) + V_i, \tag{2}$$

for $i = 1, ..., N$, where $X_i = (X_{1i}, X_{2i}, ..., X_{pi})$ is the p-dimensional vector of the confounders, $g(D, X) = E[Y|D, X]$ is the conditional mean function of the outcome equation, $m(X) = Pr[D = 1|X]$ is the propensity score, and U_i and V_i are error terms that satisfy $E[U|D, X] = 0$ and $E[V|X] = 0$, respectively. In this model, ATE is defined as

$$\theta = E[g(1, X) - g(0, X)] \tag{3}$$

which is the target parameter of interest.

The standard estimators of ATE include the IPW estimator given by

$$\hat{\theta}_{IPW} = \left\{ \sum_{i=1}^{N} \frac{D_i}{\hat{m}(X_i)} \right\}^{-1} \sum_{i=1}^{N} \frac{D_i Y_i}{\hat{m}(X_i)} - \left\{ \sum_{i=1}^{N} \frac{(1 - D_i)}{1 - \hat{m}(X_i)} \right\}^{-1} \sum_{i=1}^{N} \frac{(1 - D_i) Y_i}{1 - \hat{m}(X_i)} \tag{4}$$

and the DR estimator given by

$$\hat{\theta}_{DR} = \frac{1}{N} \sum_{i=1}^{N} \left\{ \hat{g}(1, X_i) - \hat{g}(0, X_i) + \frac{D_i(Y_i - \hat{g}(1, X_i))}{\hat{m}(X_i)} - \frac{(1 - D_i)(Y_i - \hat{g}(0, X_i))}{1 - \hat{m}(X_i)} \right\} \tag{5}$$

where $\hat{g}(D, X)$ and $\hat{m}(X)$ are estimators of $g(D, X)$ and $m(X)$, respectively. Under the unconfoundedness assumption of Rosenbaum and Rubin (1983), both IPW and DR estimators are known to be consistent for θ. Since both $g(D, X)$ and $m(X)$ are unknown and potentially

complex, they can be estimated using the machine learning methods. For example, in simulation experiments, Setoguchi et al. (2008) and Lee et al. (2010) evaluate the effect of using the machine learning method to obtain $\hat{m}(X)$ in the IPW estimator (4). Similarly, the machine learning method can also be employed in the DR estimator (5) to obtain $\hat{g}(D,X)$ and $\hat{m}(X)$. As pointed out by Chernozhukov et al. (2017, 2018), however, naive application of machine learning methods to these estimators leads to bias from overfitting. To overcome this problem, Chernozhukov et al. (2017, 2018) proposed the DML estimator for ATE. The DML estimator is computed using the following steps of cross-fitting. For simplification, we assume that N is a multiple of integer K. Take a K-fold random partition $(I_k)_{k=1}^K$ of $\{1,...,N\}$, such that the size of each fold I_k is fixed at $n = N/K$. For each set I_k, define its complement by $I_k^c = \{1,...,N\} \backslash I_k$. In the first step, for each $k(= 1,...,K)$, estimate the ATE by

$$\hat{\theta}(I_k, I_k^c) = \frac{1}{n} \sum_{i \in I_k} \left\{ \hat{g}(1, X_i; I_k^c) - \hat{g}(0, X_i; I_k^c) + \frac{D_i(Y_i - \hat{g}(1, X_i; I_k^c))}{\hat{m}(X_i; I_k^c)} - \frac{(1 - D_i)(Y_i - \hat{g}(0, X_i; I_k^c))}{1 - \hat{m}(X_i; I_k^c)} \right\}$$

where $\hat{g}(D, X; I_k^c)$ and $\hat{m}(X; I_k^c)$ are $g(D,X)$ and $m(X)$ estimated using (Y_i, D_i, X_i) for $i \in I_k^c$, respectively. In the second step, aggregate $\hat{\theta}(I_k, I_k^c)$ for all $k \in \{1,...,K\}$ and DML estimator is given by

$$\hat{\theta}_{DML} = \frac{1}{K} \sum_{k=1}^{K} \hat{\theta}(I_k, I_k^c). \tag{6}$$

Outcome-adaptive approach for variable selection

Let us now generalize the covariate X in (1) and (2) to incorporate beyond confounders. In particular, we follow Shortreed and Ertefaie (2017) to classify the covariates into four types of variables. The first type of covariates is confounders, that are associated with both treatment and outcome. The second type is outcome predictors, that are associated with outcome but not with treatment. The third type is instruments, that are associated with treatment but not with outcome. The last type is spurious (or irrelevant) variables, that are not associated with treatment nor outcome. We introduce mutually exclusive and exhaustive sets of index to covariates, $\mathcal{C}$, $\mathcal{P}$, $\mathcal{I}$ and $\mathcal{S}$, for confounders, outcome predictors, instruments, and spurious variables, respectively. For expositional simplicity, we also follow Shortreed and Ertefaie (2017)

and impose the linearity of the conditional mean functions. Using this rule of notation, the conditional mean function in (1) and the propensity score in (2) can respectively be written as $g(D,X) = \theta D + \sum_{j=1}^{p} \beta_j X_j$ with $\beta_j = 0$ for $j \in \mathcal{I}$, $\mathcal{S}$ and the propensity score $m(X) = \left\{1 + \exp\left(-\sum_{j=1}^{p} \alpha_j X_j\right)\right\}^{-1}$ with $\alpha_j = 0$ for $j \in \mathcal{P}$, $\mathcal{S}$.

Note that for all of three estimators, namely, IPW estimator (4), DR estimator (5) and DML estimator (6), estimation of $m(X)$ is required. For the IPW estimator (4) with many covariates, for example, natural choice is to employ adaptive lasso for the estimation of $m(X)$. In particular, adaptive lasso estimator of $\alpha = (\alpha_1, \alpha_2, .., \alpha_p)'$ in $m(X) = \left\{1 + \exp\left(-\sum_{j=1}^{p} \alpha_j X_j\right)\right\}^{-1}$ is given by

$$\hat{\alpha}_{AL} = \arg\min_{\alpha} \left[\sum_{i=1}^{N} \left\{ -D_i \left(\sum_{j=1}^{p} \alpha_j X_{ji} \right) + \log\left(1 + \exp\left(\sum_{j=1}^{p} \alpha_j X_{ji} \right) \right) \right\} + \lambda_N \sum_{j=1}^{p} \omega_j |\alpha_j| \right] \tag{7}$$

where λ_N is the regularization parameter, $\omega_j = |\widetilde{\alpha}_j|^{-\gamma}$ with $\gamma > 0$ and $\widetilde{\alpha} = (\widetilde{\alpha}_1, \widetilde{\alpha}_2, ..., \widetilde{\alpha}_p)'$ is the first-step estimator of α using ridge regression. Shortreed and Ertefaie (2017) proposed the outcome-adaptive approach for the variable selection in (2) for computing the IPW estimator. In this approach, adaptive lasso estimator $\hat{\alpha}_{AL}$ is modified so that the penalties for the coefficients of covariates depend on the strength of relations to the outcome. To be specific, their proposed outcome-adaptive lasso estimator $\hat{\alpha}_{OAL}$ replaces $\omega_j = |\widetilde{\alpha}_j|^{-\gamma}$ in (7) by $\omega_j = |\tilde{\beta}_j|^{-\gamma}$, where $\widetilde{\beta} = (\widetilde{\beta}_1, \widetilde{\beta}_2, ..., \widetilde{\beta}_p)'$ is the ridge regression estimator of $\beta = (\beta_1, \beta_2, .., \beta_p)'$ in $g(D,X) = \theta D + \sum_{j=1}^{p} \beta_j X_j$. As shown by Shortreed and Ertefaie (2017), provided $\lambda_N / \sqrt{N} \to 0$ and $\lambda_N N^{(\gamma-1)/2} \to \infty$, an outcome-adaptive lasso estimator is consistent in the sense that $\hat{\alpha}_{OAL} \to_p \alpha^*$, where α^* is a pseudo true value satisfying $\alpha_j^* = 0$ for $j \in \mathcal{I}$, $\mathcal{S}$. As long as the outcome-adaptive lasso correctly selects confounders, the bias from misspecifying the propensity score is typically smaller than the bias and variance that come from selecting instruments. This is an intuitive explanation of why the outcome-adaptive approach works in the presence of instruments. In this paper, we introduce an outcome-adaptive DML estimator where $\hat{m}(X_i; I_k^c)$ in DR estimator (6) is estimated by $\hat{\alpha}_{OAL}$ using a subsample from the set I_k^c. From the argument of Chernozhukov et al. (2017, 2018), an outcome-adaptive DML estimator is asymptotically equivalent to the original DML estimator as long as their assumption 5.1

is satisfied with the original score function $m(X) = \left\{1 + \exp\left(-\sum_{j=1}^{p} \alpha_j X_j\right)\right\}^{-1}$ replaced by $m^*(X) = \left\{1 + \exp\left(-\sum_{j=1}^{p} \alpha_j^* X_j\right)\right\}^{-1}$.

Simulation design

To evaluate the performance of our proposed DML estimator and other estimators for ATE, we conduct Monte Carlo simulation experiments. We fix the number covariates at $p = 200$, the sample size at $N = 500$, and generate $X_i = (X_{1i}, X_{2i}, ..., X_{200i})$ for $i = 1, ..., 500$ from independent multivariate standard normal distribution $N(0, I_{200})$. For each draw, an associated binary treatment variable D_i is given by a Bernoulli distribution with its success probability given by the propensity score $m(X_i) = Pr[D_i = 1|X_i] = \left\{1 + \exp\left(-\sum_{j=1}^{200} \alpha_j X_{ji}\right)\right\}^{-1}$. A continuous outcome variable is then generated from the outcome equation $Y_i = g(D_i, X_i) + U_i$ where $g(D_i, X_i) = \theta D_i + \sum_{j=1}^{200} \beta_j X_{ji}$ and $U_i \sim i.i.d.N(0, 1)$. We follow Shortreed and Ertefaie (2017) and set the target parameter, ATE, at $\theta = 0$ or 2. The role of covariates are controlled by the choice of parameter values in $\alpha = (\alpha_1, \alpha_2, .., \alpha_{200})'$ and $\beta = (\beta_1, \beta_2, .., \beta_{200})'$. Four types of covariates are given as follows: (i) a covariate X_j is a confounder ($j \in \mathcal{C}$) if $\alpha_j \neq 0$ and $\beta_j \neq 0$; (ii) a covariate X_j is an outcome predictor ($j \in \mathcal{P}$) if $\alpha_j = 0$ and $\beta_j \neq 0$; (iii) a covariate X_j is an instrument ($j \in \mathcal{I}$) if $\alpha_j \neq 0$ and $\beta_j = 0$; and (iv) a covariate X_j is a spurious (irrelevant) variable ($j \in \mathcal{S}$) if $\alpha_j = 0$ and $\beta_j = 0$. The relationship between the treatment, outcome, and all four types of covariates is illustrated in Figure 1. To evaluate the effect of strength of instruments and the proportion of confounders, we employ the following sets of parameters in four data generating processes (DGPs).

DGP 1. Benchmark

$$\alpha = (1.0, 1.0,\ \ 0.0, 0.0,\ \ 1.0, 1.0,\ \ 0.0, ..., 0.0)'$$

$$\beta = (\underbrace{0.6, 0.6}_{\mathcal{C}=\{1,2\}},\ \underbrace{0.6, 0.6}_{\mathcal{P}=\{3,4\}},\ \underbrace{0.0, 0.0}_{\mathcal{I}=\{5,6\}},\ \underbrace{0.0, ..., 0.0}_{\mathcal{S}=\{7,...,200\}})'$$

DGP 2. Strong instruments

$$\alpha = (1.0, 1.0,\ \ 0.0, 0.0,\ \ 3.0, 3.0,\ \ 0.0, ..., 0.0)'$$

$$\beta = (\underbrace{0.6, 0.6}_{\mathcal{C}=\{1,2\}},\ \underbrace{0.6, 0.6}_{\mathcal{P}=\{3,4\}},\ \underbrace{0.0, 0.0}_{\mathcal{I}=\{5,6\}},\ \underbrace{0.0, ..., 0.0}_{\mathcal{S}=\{7,...,200\}})'$$

DGP 3. Many confounders

$$\alpha = (1.0, ..., 1.0,\ \ 0.0, 0.0,\ \ 1.0, 1.0,\ \ 0.0, ..., 0.0)'$$

$$\beta = (\underbrace{0.6, ..., 0.6}_{\mathcal{C}=\{1,...,20\}},\ \underbrace{0.6, 0.6}_{\mathcal{P}=\{21,22\}},\ \underbrace{0.0, 0.0}_{\mathcal{I}=\{23,24\}},\ \underbrace{0.0, ..., 0.0}_{\mathcal{S}=\{25,...,200\}})'$$

DGP 4. Strong instruments and many confounders

$$\alpha = (1.0, ..., 1.0,\ \ 0.0, 0.0,\ \ 3.0, 3.0,\ \ 0.0, ..., 0.0)'$$

$$\beta = (\underbrace{0.6, ..., 0.6}_{\mathcal{C}=\{1,...,20\}},\ \underbrace{0.6, 0.6}_{\mathcal{P}=\{21,22\}},\ \underbrace{0.0, 0.0}_{\mathcal{I}=\{23,24\}},\ \underbrace{0.0, ..., 0.0}_{\mathcal{S}=\{25,...,200\}})'$$

DGP 1 is the benchmark setting identical to the one used by Shortreed and Ertefaie (2017) in their evaluation of the outcome-adaptive IPW estimator. In DGP 2, β_j's for instruments become three times larger than those in DGP 1 to consider the case of stronger correlation between instruments and treatment. In DGP 3, the number of confounders has been increased from 2 to 20, ten times larger than the number in DGP 1. In DGP 4, we consider the combination of stronger instruments in DGP 2 and more confounders in DGP 3.

For each artificially generated data, we compute six estimators for ATE: (i) IPW estimator; (ii) outcome-adaptive IPW estimator; (iii) DR estimator; (iv) outcome-adaptive DR estimator; (v) DML estimator; and (vi) outcome-adaptive DML estimator. For the estimation of the propensity score $m(X_i)$, adaptive lasso is employed for IPW estimator, DR estimator and DML estimator, while outcome-adaptive lasso is employed for outcome-adaptive IPW estimator, outcome-adaptive DR estimator and outcome-adaptive DML estimator. For the choice of the regularization parameter λ_N required for adaptive lasso and outcome-adaptive lasso, we follow the procedure suggested by Shortreed and Ertefaie (2017) and search over the values in

$\{N^{-10}, N^{-5}, N^{-1}, N^{-0.75}, N^{-0.5}, N^{-0.25}, N^{0.25}, N^{0.49}\}$ to minimize the weighted absolute mean difference between the exposure groups defined in their paper. Adaptive lasso is employed for the estimation of the conditional mean function $g(D_i, X_i)$ required to compute DR estimator, outcome-adaptive DR estimator, DML estimator and outcome-adaptive DML estimator. For the cross-fitting used in the DML estimator and outcome-adaptive DML estimator, we use 10-fold random partition ($K = 10$) so that the size of each fold is set at $n = 500/10 = 50$. To incorporate uncertainty induced by sample splitting, we also follow the recommendation by Chernozhukov et al. (2017, 2018) and use the mean value after repeating the cross-fitting 5 times.

We evaluate the performance of six estimators using (i) the absolute bias computed as $R^{-1}\sum_{r=1}^{R}|\widehat{\theta}_r - \theta|$; (ii) standard deviation (SD) computed as $\sqrt{R^{-1}\sum_{r=1}^{R}(\widehat{\theta}_r - \overline{\widehat{\theta}})^2}$ where $\overline{\widehat{\theta}} = R^{-1}\sum_{r=1}^{R}\widehat{\theta}_r$; and (iii) root mean square error (RMSE) computed as $\sqrt{R^{-1}\sum_{r=1}^{R}(\widehat{\theta}_r - \theta)^2}$ where $\widehat{\theta}_r$ represents each of the six estimators using r-th data set in a total of R replications. To evaluate the validity of the variable selection procedure using adaptive lasso and outcome-adaptive lasso, we also compute relative frequencies of selecting each type of covariates in the propensity score estimation in R replications. For example, if X_1 is a confounder, we count how often the coefficient α_1 is estimated to be non-zero in R replications. Since there is more than one variable in each type of covariate, we only report the average of selected frequencies among the same type of covariate. In our experiment, the number of replications is set at $R = 1,000$. All the experiments are conducted using R version 3.6.1 (https://www.r-project.org/).

RESULTS

The results of our Monte Carlo experiments are presented in Figure 2 and Tables 1 and 2. Since similar results are obtained between the cases with $\theta = 0$ and $\theta = 2$, we only report the result of the former case. Figure 2 shows the box plots of 1,000 realizations of six estimators for ATE. Table 1 reports the performance of six estimators in terms of absolute bias, SD and RMSE. It should be noted that mean square error (MSE) can be decomposed into the sum of squared bias and variance. Therefore, by definition, if all three metrics, namely, absolute bias, SD and RMSE are squared, the first two values should sum up to the third value. For this reason, we

can discuss the trade-off between bias and variance using Table 1. Table 2 presents the relative frequencies of selected covariates in propensity score estimation.

DGP 1: The outcome-adaptive approach works well for all three estimators, namely, outcome-adaptive IPW estimator, outcome-adaptive DR estimator and outcome-adaptive DML estimator in reducing the bias and variance. For example, the absolute bias of the IPW estimator is reduced from 0.12 to 0.03, while SD is reduced from 0.23 to 0.12. As a result, all the outcome-adaptive estimators have very small RMSE around 0.11, with both outcome-adaptive DR estimator and outcome-adaptive DML estimator performing slightly better than outcome-adaptive IPW estimator. The top panel of Table 2 clearly shows the source of this improvement comes from the fact that outcome-adaptive lasso selects outcome predictors for 100% of the time, while instruments are selected only for less than 5% of the time. In contrast, when the standard adaptive lasso is used, instruments are selected for almost all the time, which results in larger bias and variance.

DGP 2: For the case of strong instruments, overall results are somewhat similar to the benchmark case of DGP 1 with an exception of IPW estimator. Compared to the case of DGP 1, both bias and variance of IPW estimator are much larger in the case of DGP 2. However, for the outcome-adaptive IPW estimator, both bias and variance in the case of DGP 1 indeed become smaller in the case of DGP 2. As a result, improvement of MSE in DGP 2 from IPW estimator to outcome-adaptive IPW estimator stands out. In this sense, outcome-adaptive IPW estimator of Shortreed and Ertefaie (2017) could become very effective when correlation of instruments and treatment becomes stronger. At the same time, overall performance of outcome-adaptive IPW estimator, outcome-adaptive DR estimator and outcome-adaptive DML estimator suggests that the outcome-adaptive approach works equally well. This is also confirmed by the fact that the proportion of selecting each covariate shown in the second panel of Table 2 is very similar to the values in the top panel of Table 2.

DGP 3: For the case of many confounders, both DML estimator and outcome-adaptive DML estimator outperform other estimators in term of bias reduction. While the outcome-adaptive approach reduces bias from 2.61 to 1.73 for IPW estimator and from 1.61 to 1.33 for DR estimator, the size of reduction seems to be limited. The bias of DML estimator

is smaller than those of outcome-adaptive IPW estimator and outcome-adaptive DR estimator. However, both bias and variance of DML estimator can be further reduced by employing outcome-adaptive DML estimator. Overall, outcome-adaptive DML estimator performs best among all six estimators in terms of bias and MSE. It may be worth noting that the proportion of selecting instruments by outcome-adaptive lasso reported in the third panel of Table 2 is increased to around 9%.

DGP 4: For the case of strong instruments and many confounders, outcome-adaptive DML estimator also performs best among all six estimators. When outcome-adaptive DML estimator is employed, bias is smallest. At the same time, MSE is also the smallest. The bottom panel shows that the proportion of selecting instruments by outcome-adaptive lasso is now above 25% but is still much smaller than the 100% selection probability by adaptive lasso.

DISCUSSION

The DML estimator for treatment effects is designed to incorporate the machine learning methods in estimating unknown nuisance functions when many covariates are available. This paper proposes the outcome-adaptive DML estimator which modifies the DML estimator for the purpose of including outcome predictors and excluding instruments in the process of variable selection in computing propensity scores. The performance of the proposed estimator is examined in a set of Monte Carlo simulation.

With the outcome-adaptive approach, confounders and outcome predictors are likely to be selected, and instruments are likely to be excluded in the propensity score estimation. These results suggest that the outcome-adaptive approach originally applied to IPW estimator by Shortreed and Ertefaie (2017) is also useful in DR estimator and DML estimator. As noted by Brookhart et al. (2006), inclusion of the confounders and the outcome predictors in the propensity score tends to reduce the bias in the ATE estimation. At the same time, as discussed in Brookhart et al. (2006), Bhattacharya et al. (2007), Patric et al. (2011), and Myers et al. (2011) among others, inclusion of instruments in the propensity score tends to increase the variance. As a consequence, bias and variance are reduced by employing the outcome-adaptive DR estimator and outcome-adaptive DML estimator.

It is true that the inclusion of instruments in the propensity score improves the prediction accuracy of the treatment allocation for each patient. However, it is important to realize that improving the accuracy in the treatment allocation does not necessarily improve the accuracy of estimation of the treatment effect, which is the main parameter of interest (see also Westreich et al. (2011)[24]). When the machine learning methods are naively employed in IPW estimator, DR estimator and DML estimator with many covariates, they automatically select variables in the propensity score to maximize the predictability of the treatment. However, when selecting instruments are not desirable, outcome-adaptive lasso seems to be a reasonable choice of a machine learning method.

We also find that, when there is a stronger correlation between the instruments and treatment (DGP 2 and 4), bias and variance of the typical estimators become larger. For the case of strong instruments, adaptive lasso tends to downplay the relative role of confounders and this may be the reason why the standard estimators do not work well. In contrast, since outcome-adaptive lasso selects both confounders and outcome predictors regardless of the strength of instruments, the outcome-adaptive approach remains valid.

Even if there are many confounders, both the original DML estimator and the outcome-adaptive DML estimator outperform other estimators in terms of bias reduction (DGP 3 and DGP 4). The outcome-adaptive DML estimator performs best among all methods even if many confounders are combined with strong instruments. In summary, outcome-adaptive DML estimator provides the smallest MSE for all the data generating processes including the case of many confounders. As a nature of clinical observational study, there are a large number of candidates for confounders available in the clinical database. In such an environment, outcome-adaptive DML estimator is expected to perform well. For the reasons described above, the use of our proposed outcome-adaptive DML estimator is highly recommended.

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APPENDIX

Example: Right Heart Catheterization

As an example of applying outcome-adaptive DML estimator and other estimators, we use SUPPORT (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments) dataset of Murphy and Cluff (1990) [25]. Connors et al. (1996) [26] examined the treatment effect of right heart catheterization (RHC) within the first 24 hours in the intensive care unit (ICU) and provided the causal evidence on increased length of hospital stay, increased total cost for cares, and decreased survival time among 5735 subjects (2184 subjects received the treatment of RHC and 3551 subjects did not receive the treatment).

Using the same dataset, we estimate the ATE of RHC on the length of hospital stay, by six estimators: (i) IPW estimator; (ii) outcome-adaptive IPW estimator; (iii) DR estimator; (iv) outcome-adaptive DR estimator; (v) DML estimator; and (vi) outcome-adaptive DML estimator. The outcome variable is the length of hospital stay. Covariates included in this analysis are: age, gender, race, history of education, income, insurance, main disease category, sub disease category, admission diagnosis, ADL, DASI (Duke Activity Status Index), resuscitate status on day1, cancer, Support model estimate of the probability of surviving 2 months, APACHE score, Glasgow Coma Scale, weight, temperature, mean blood pressure, respiratory rate, heart rate, PaO_2/FiO_2, $PaCO_2$, pH, White blood cell count, hematocrit, sodium, pottasium, creatinine, bilirubin, albumin, urine output volume, and comorbidities category. Table 3 provides the point estimates, standard errors, and 95% confidence intervals of ATE from six estimators. When the outcome-adaptive approach is used, estimators of ATE are greater than those based on adaptive lasso. This suggests the possiblity of some negative bias in estimating ATE without using outcome-adaptive lasso. It is also interesting to note that ATE is significantly positive only when outcome-adaptive DML estimator is used.

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TABLES

Table 1. Performance of six estimators for average treatment effects.

	Metrics	IPW	Outcome-adaptive IPW	DR	Outcome-adaptive DR	DML	Outcome-adaptive DML
DGP 1	Bias	0.12	0.03	0.07	0.03	0.15	0.03
	SD	0.23	0.12	0.14	0.10	0.24	0.11
	RMSE	0.25	0.12	0.16	0.11	0.28	0.11
DGP 2	Bias	0.56	0.00	0.09	0.01	0.01	0.02
	SD	0.36	0.09	0.16	0.10	0.25	0.09
	RMSE	0.66	0.09	0.18	0.10	0.25	0.09
DGP 3	Bias	2.61	1.73	1.61	1.33	0.58	0.11
	SD	0.63	0.66	0.37	0.37	1.14	0.93
	RMSE	2.68	1.85	1.66	1.38	1.28	0.94
DGP 4	Bias	3.29	0.46	1.14	0.65	0.58	0.08
	SD	0.80	0.42	0.37	0.27	0.81	0.43
	RMSE	3.39	0.62	1.19	0.70	0.99	0.44

Bias, absolute bias; SD, standard deviation; RMSE, root mean square error; IPW, Inverse probability weighted estimator; DR, Doubly robust estimator; DML, Double/debiased machine learning estimator.

Metrics are computed in 1,000 replications.

Table 2. Proportion of selected covariates in propensity score estimation.

	Methods	Confounders ($\mathcal{C}$)	Outcome predictors ($\mathcal{P}$)	Instruments ($\mathcal{I}$)
DGP 1	Adaptive lasso	99.9%	7%	99.9%
	Outcome-adaptive lasso	100%	100%	4.8%
DGP 2	Adaptive lasso	96.5%	5%	100%
	Outcome-adaptive lasso	100%	100%	5.3%
DGP 3	Adaptive lasso	97.8%	9%	97.8%
	Outcome-adaptive lasso	100%	100%	8.9%
DGP 4	Adaptive lasso	91.2%	6.9%	100%
	Outcome-adaptive lasso	100%	100%	25.9%

Proportion of covariates with non-zero coefficients in 1,000 replications.

Table 3. Average treatment effects of right heart catheterization.

			95% Confidence Interval	
	ATE	Standard Error	Lower	Upper
IPW	1.82	1.27	-0.66	4.3
Outcome-adaptive IPW	2.31	1.23	-0.11	4.72
DR	1.16	1.42	-1.61	3.94
Outcome-adaptive DR	1.97	1.31	-0.61	4.54
DML	2.38	1.24	-0.05	4.8
Outcome-adaptive DML	2.77	1.21	0.4	5.15

ATE, Average treatment effect; IPW, Inverse probability weighted estimator; DR, Doubly robust estimator; DML, Double/debiased machine learning estimator.

FIGURES

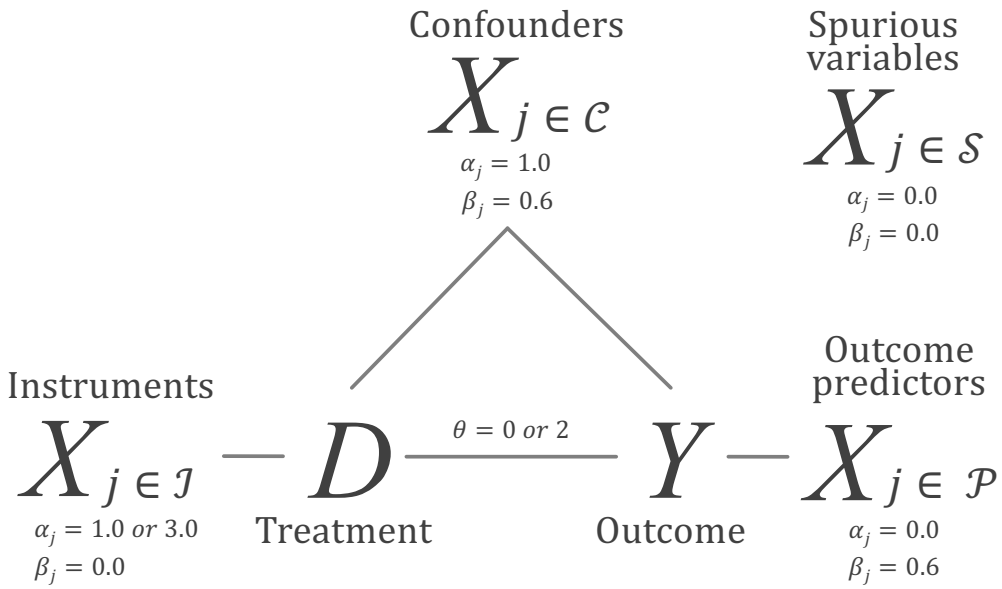

Figure 1. Relationship between treatment, outcome and four types of covariates in simulation design.

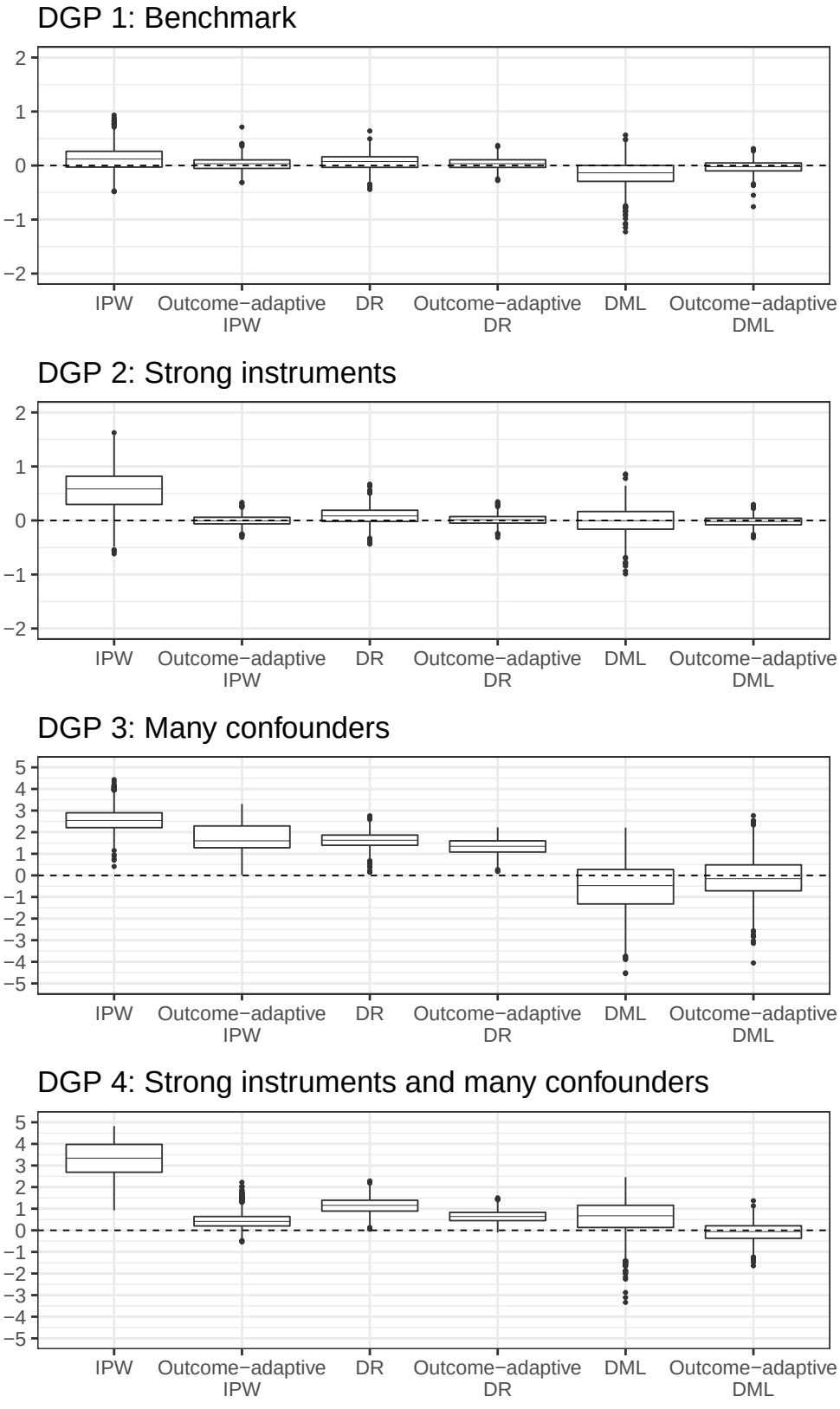

Figure 2. Distribution of six estimators for ATE ($\theta = 0$) in 1,000 replications.

ATE, Average treatment effect; IPW, Inverse probability weighted estimator; DR, Doubly robust estimator; DML, Double/debiased machine learning estimator.