Collaborative double robustness using the $e$-score

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July 25, 2018

Abstract

Estimation of causal parameters from observational data requires complete confounder adjustment, as well as positivity of the propensity score for each treatment arm. There is often a trade-off between these two assumptions: confounding bias may be reduced through adjustment for a high-dimensional pre-treatment covariate, but positivity is less likely in analyses with more predictors of treatment. Under empirical positivity violations, propensity score weights are highly variable, and doubly robust estimators suffer from high variance and large finite sample bias. To solve this problem, we introduce the $e$-score, which is defined through a dimension reduction for the propensity score. This dimension reduction is based on a recent result known as collaborative double robustness, which roughly states that a propensity score conditioning only on the bias of the outcome regression estimator is sufficient to attain double robustness. We propose methods to construct doubly robust estimators based on the $e$-score, and discuss their properties such as consistency, efficiency, and asymptotic distribution. This allows the construction of asymptotically valid Wald-type confidence intervals and hypothesis tests. We present an illustrative application on estimating the effect of smoking on bone mineral content in adolescent girls as well as a synthetic data simulation illustrating the bias and variance reduction and asymptotic normality achieved by our proposed estimators.

1 Introduction

Estimation of causal effects from observational studies requires two assumptions on the data generating mechanism: the assumption of no unmeasured confounding, and the assumption of positivity of the treatment probabilities. Positivity states that individuals in all strata of the confounders have a positive probability of getting assigned to each treatment arm (Rosenbaum and Rubin, 1983). Theoretical positivity violations, whereby the

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true treatment probabilities are zero for some covariate strata, are problematic because they preclude identification of the causal effect from observational data. Empirical positivity violations, whereby the estimated treatment probabilities are close to zero for some confounder strata, are also problematic because non-parametric regular estimators of the causal effect suffer from large variability and increased finite sample bias. High-dimensional data poses a trade-off between these two assumptions. VanderWeele and Shpitser (2011) show that adjustment for more pre-treatment variables reduces confounding bias, provided that all adjustment variables are causes of either the treatment or the outcome. However, instrumental variables, defined as variables that are cause of the treatment but not of the outcome, are known to inflate the non-parametric efficiency bound (Brookhart et al., 2006; Greenland, 2008; Schisterman et al., 2009; Rotnitzky et al., 2010; Myers et al., 2011), and may lead to positivity violations.

In this article we focus on a class of estimators called doubly robust. Double robustness is a property that ensures consistency of the causal effect estimator under consistency of at least one of two nuisance parameters: the outcome expectation conditional on treatment and covariates (henceforth referred to as outcome regression), or the probability of each treatment arm conditional on covariates (henceforth referred to as the propensity score). Several doubly robust methods for joint selection of the propensity score and outcome regression models have been recently proposed (Belloni et al., 2014; Shortreed and Ertefaie, 2017; Cheng et al., 2017; Ertefaie et al., 2018; Koch et al., 2018). Generally, these methods solve the trade-off between unconfoundedness and positivity by performing variable selection for both models using carefully constructed penalization terms in generalized linear models. Though these parametric models may be useful with a few variables, parametric assumptions in high-dimensional settings are rarely justified by scientific knowledge (Starmans, 2018). This implies that the models are frequently misspecified, yielding inconsistent effect estimators (the consequences of parametric model misspecification in causal inference were demonstrated in an influential simulation study by Kang and Schafer, 2007). Data-adaptive estimation methods offer an opportunity to employ flexible estimators that are more likely to achieve consistency. Methods such as those based on regression trees, regularization, boosting, neural networks, support vector machines, adaptive splines, and stacked ensembles of them, offer flexibility in the specification of interactions, non-linear, and higher-order terms, a flexibility that is not available for parametric models. Because of this, machine learning has gained increasing popularity among causal inference researchers (e.g., van der Laan et al., 2005; van der Laan, 2006; Ridgeway and McCaffrey, 2007; Bembom et al., 2008; Lee et al., 2010; Neugebauer et al., 2016). Indeed, the statistics field of targeted learning (van der Laan and Rubin, 2006; van der Laan and Rose, 2011, 2018), concerned with the development of $n^{1/2}$-consistent, asymptotically normal, and efficient estimators of smooth low-dimensional parameters through the use state-of-the art machine learning, has arisen as an alternative to the widespread use of misspecified parametric models. Though much progress has been made in the field of targeted learning, joint model selection techniques for causal inference using data-adaptive nuisance estimators remains
an open problem. Our manuscript aims to develop methodology to fill this gap in the literature.

Our work is inspired by an important result discovered by van der Laan et al. (2010), called *collaborative double robustness*. Intuitively, this result states a propensity score adjusting for the bias of the outcome regression estimator is sufficient to yield double robustness. Therefore, if the outcome regression is consistent, no propensity score adjustment is necessary, thus avoiding variance inflation and positivity violations. This result was used in a series of papers to develop a number of estimators collectively known as *collaborative targeted minimum loss based estimators* (C-TMLE, van der Laan et al., 2010; Gruber and van der Laan, 2010b; Ju et al., 2017a,b, 2018). These instances of C-TMLE solve the trade-off between unconfoundedness and positivity by introducing joint model selection techniques for the outcome regression and propensity score. They can be described as model selection techniques for the propensity score that optimize a suitably constructed loss function which takes into account the outcome regression bias. For example, the original C-TMLE was developed as a variable selection tool using a greedy search (see page 305 of Gruber and van der Laan, 2011). The refinements of Ju et al. extended C-TMLE to more general model selection frameworks with continuously indexed candidate estimators for the propensity score such as $\ell_1$ regularization (Ju et al., 2017b). In spite of these important developments, all existing C-TMLE methods consist of complex model selection techniques. These model selection approaches have a time complexity that, in the best case scenario, grows linearly with the dimension of the adjustment vector. This time complexity may be computationally prohibitive in certain big data settings. Furthermore, it is not clear how these model selection approaches can be generalized to general data-adaptive estimators, for example tree-based approaches, support vector machines, neural networks, or learning ensembles.

Our main contribution and innovation is to present an alternative collaborative double robustness result, whereby we reduce the dimension of the propensity score through what we define as the $e$-score. This result is inspired by ideas recently proposed by van der Laan (2014); Benkeser et al. (2016); Díaz and van der Laan (2017) in the context of doubly robust asymptotic distributions. The $e$-score and its double robustness property allows us to propose estimation methods that do not involve complex model selection algorithms and are therefore completely scalable as well as generalizable to any initial data-adaptive estimator of the propensity score. Our second main contribution is to study the asymptotic distributions of the proposed collaborative estimator under consistent estimation of both nuisance parameters. This asymptotic result, which is not available for standard C-TMLE, is fundamental to the construction of valid confidence intervals and hypothesis tests.
2 Notation and Inferential Problem

Let $W$ denote a vector of observed baseline variables, let $A$ denote a treatment indicator, and let $Y$ denote the outcome of interest. Throughout, we assume without loss of generality that $Y$ takes values on $[0, 1]$. The word model here refers to a set of probability distributions for the observed data $O = (W, A, Y)$. We assume that the true distribution of $O$, denoted by $P_0$, is an element of the nonparametric model, denoted by $\mathcal{M}$, and defined as the set of all distributions of $O$ dominated by a measure of interest $\nu$. Assume we observe an i.i.d. sample $O_1, \ldots, O_n$, and denote its empirical distribution by $P_n$. For a general distribution $P$ and a function $f$, we use $Pf$ to denote $\int f(o) dP(o)$.

Let $Y_a : a \in \{0, 1\}$ denote the counterfactual outcome that would be observed in a hypothetical world in which $P(A = a) = 1$. The typical observational study is focused on estimation of the counterfactual expectations $E(Y_a)$, or contrasts between them. We focus on estimating $E(Y_1)$; estimators of $E(Y_0)$ may be constructed using symmetric arguments. We use $m(w)$ to denote the outcome regression $E(Y \mid A = 1, W = w)$, $g(w)$ to denote the propensity score $P(A = 1 \mid W = w)$, and use $m_0$ and $g_0$ to denote the true quantities. We introduce the following assumptions which are standard in the causal inference literature.

**A1** (Randomization). $A$ is independent of $Y_1$ conditional on $W$.

**A2** (Strong positivity). $P_0\{g_0(W) > \epsilon\} = 1$ for some $\epsilon > 0$.

Assumption A1 states that treatment assignment is randomized within strata of the covariates, either by nature or by experimentation. We make assumptions A1 and A2 throughout the manuscript. The mean counterfactual outcome $E_0(Y_1)$ is identified from the distribution $P_0$ of the observed data as $\theta_0 = E_0\{m_0(W)\}$ (see e.g., Pearl, 2000). For any distribution $P \in \mathcal{M}$, we define the target parameter mapping as $\theta(P) = E_P\{m(W)\}$, where $m$ is the outcome conditional expectation corresponding to $P$.

2.1 Existing estimators and asymptotic properties

Doubly robust and efficient estimation of $\theta_0$ in the non-parametric model proceeds as follows. Define the estimating function

$$D_{\eta, \theta}(O) = \frac{A}{g(W)}(Y - \mu(W)) + \mu(W) - \theta,$$

(1)

where $\eta = (g, \mu)$. The estimating function $D_{\eta, \theta}(O)$ is a fundamental object for the construction of estimators of $\theta_0$ in the non-parametric model. On one hand, $D_{\eta_0, \theta_0}(O)$ characterizes the efficiency bound in the sense that all regular estimators have a variance that is larger or equal to $\sigma_{\text{eff}}^2 = \text{Var}\{D_{\eta_0, \theta_0}(O)\}$ (Hahn, 1998). On the other hand, for an estimate $\hat{\eta}$ of $\eta_0$, any estimator $\hat{\theta}$ which is a solution of the estimating equation $P_n D_{\hat{\eta}, \theta} = 0$ on $\theta$ is doubly robust, meaning that it is consistent if at least one of $\hat{g}$ and $\hat{m}$ is consistent (see Theorem
Double robustness follows from the fact that $P_0 D_{\eta, \theta_0} = 0$ if either $g_1 = g_0$ or $m_1 = m_0$, where $\eta_1$ denotes the limit of $\hat{\eta}$ as $n \to \infty$.

The estimator obtained by directly solving the estimating equation $P_n D_{\hat{\eta}, \hat{\theta}} = 0$ is also called the augmented inverse probability weighted estimator, and we denote it with $\hat{\theta}_{aipw}$. This estimator is often critiqued because it can lead to estimates outside of the parameter space (Gruber and van der Laan, 2010a). Several estimators have been proposed to remedy this issue (see e.g., Kang and Schafer, 2007; Robins et al., 2007; Tan, 2010). In this paper we focus on the targeted minimum loss based estimation (TMLE) methodology, developed by van der Laan and Rubin (2006). We now briefly review the construction of a TMLE.

The TMLE of $\theta_0$ is defined as $\hat{\theta}_{tmle} = \theta(\hat{P})$, where $\hat{P}$ is an estimator of $P_0$ constructed to satisfy $P_n D_{\hat{\eta}, \hat{\theta}_{tmle}} = 0$. The estimator $\hat{P}$ is constructed by tilting an initial estimate $\hat{P}_0$ towards a solution of the estimating equation, by means of parametric submodel. Specifically, a TMLE may be constructed by fitting the logistic regression model

$$\logit m_\beta(w) = \logit \hat{m}(w) + \frac{1}{\hat{g}(w)} \hat{g}(w),$$

among observations with $A = 1$. Here, $\logit(p) = \log\{p(1-p)^{-1}\}$. In this expression $\beta$ is the parameter of the model, $\logit \hat{m}(w)$ is an offset variable, and the initial estimates $\hat{m}$ and $\hat{g}$ are treated as fixed. The parameter $\beta$ is estimated through the empirical risk minimizer

$$\hat{\beta} = \arg \max_{\beta} \sum_{i=1}^{n} A_i \{ Y_i \log m_\beta(W_i) + (1 - Y_i) \log(1 - m_\beta(W_i)) \}.$$  

The tilted estimator of $m_0(w)$ is defined as $\tilde{m}(w) = m_\hat{\beta}(w) = \expit\{\logit \hat{m}(w) + \hat{\beta}/\hat{g}(w)\}$, where $\expit(x) = \logit^{-1}(x)$. The TMLE of $\theta_0$ is defined as

$$\hat{\theta}_{tmle} = \frac{1}{n} \sum_{i=1}^{n} \tilde{m}(W_i).$$

Because the empirical risk minimizer of model (2) solves the score equation

$$\sum_{i=1}^{n} \frac{A_i}{\hat{g}(W_i)} \{ Y_i - m_\beta(W_i) \} = 0,$$

it follows that $P_n D_{\tilde{\eta}, \hat{\theta}_{tmle}} = 0$ with $\tilde{\eta} = (\hat{g}, \tilde{m})$. The analysis of the asymptotic properties of the TMLE and other estimators that solve the estimating equation $P_n D_{\hat{\eta}, \hat{\theta}} = 0$ may be based on standard $M$-estimation and empirical process theory. For example, Theorems 5.9 of van der Vaart (1998) may be used to prove consistency of $\hat{\theta}_{tmle}$ under C1 below.
C1 (Doubly robust consistency). Let $|| \cdot ||$ denote the $L_2(P_0)$ norm defined as $||f||^2 = \int f^2 dP_0$. Assume there exists $\eta_1 = (g_1, m_1)$ with either $g_1 = g_0$ or $m_1 = m_0$ such that $||\hat{m} - m_1|| = o_P(1)$ and $||\hat{g} - g_1|| = o_P(1)$.

Under additional empirical process conditions including strengthening the above convergence by requiring convergence rates at least as fast as $n^{-1/4}$, it may be shown that $\hat{\theta}_{tmle}$ is asymptotically linear (see e.g., van der Laan and Rose, 2011):

$$
\hat{\theta}_{tmle} - \theta_0 = (\mathbb{P}_n - P_0)D_{\eta_0, \theta_0} + o_P(n^{-1/2}).
$$

Together with the above result, the CLT shows that $\hat{\theta}_{tmle}$ is efficient in the sense that its asymptotic variance is equal to the efficiency bound

$$
\sigma_{\text{eff}}^2 = \text{Var}\{D_{\eta_0, \theta_0}(O)\} = E\left\{ \frac{\sigma_0^2(W)}{g_0(W)} \right\} + E\{m_0(W) - \theta_0\}^2,
$$

where $\sigma_0^2(w) = \text{Var}(Y \mid A = 1, W = w)$. Inspection of this bound reveals the consequences of highly variable treatment probabilities. Consider, for example, a randomized trial where $g_0(w)$ is constant in $w$. In this case, the efficiency bound depends solely on characteristics about the variability of the outcome $Y$. In contrast, in observational studies subject to confounding the efficiency bound depends crucially on the correlation between the conditional variance $\sigma_0^2(w)$ and the treatment probabilities $g_0(W)$. Consider, for example, a pathological case in which $g_0(W)$ is highly variable, but it is highly correlated with the conditional variance of the outcome so that the first term of the right hand side in (3) is close to one. In this case, low treatment probabilities do not represent a problem since the effects of low treatment probabilities cancel out with the low variability of the outcome. In this paper we are concerned with problems in which the variance of the weights is large, but the correlation with the conditional variance of the outcome is weak, so that the low treatment probabilities cause dramatic increases in the efficiency bound. The estimator we propose to solve this problem is closely related to the collaborative targeted minimum loss based estimator (C-TMLE) proposed by van der Laan et al. (2010). C-TMLE is built upon a property known as collaborative double robustness, defined as follows.

**Theorem 1** (Collaborative double robustness, Theorem 2 of van der Laan et al. (2010)). Let $s(w)$ denote the asymptotic pointwise bias in estimation of $m_0(w)$. That is, define $s(w) = m_0(w) - m_1(w)$. Let $g_{s,0}(w) = P_0(A = 1 \mid s(W) = s(w))$. Assume $\eta_1 = (g_1, \mu_1)$ is such that either $g_1 = g_{s,0}$, or $m_1 = m_0$. Then $P_0D_{\eta_1, \theta_0} = 0$.

The above theorem implies that the probability $g_0(W)$ does not need to adjust for the full covariate vector $W$. A propensity score $g_{s,0}(W)$ that only adjusts for the residual error $s(W)$ is sufficient to obtain a doubly robust estimating equation. This dimension reduced propensity score has lower or equal variance to the original propensity score, and can therefore generate efficiency gains in estimation of $\theta_0$. Note in particular that if
$m_0(W)$ does not depend on a given covariate $W_1$, then the propensity score does not need to adjust for $W_1$, irrespective of whether $W_1$ is predictive of $A$ or not. This formalizes the advice of Brookhart et al. (2006) and others in the sense that only variables related the outcome should be included in the propensity score model. Available estimators C-TMLE operates under a sparsity assumption that the residual bias $s(W)$ is a function of a subset of the covariates $W$, and proceeds by constructing clever variable selection algorithms to find such subset. In the following section we introduce the $e$-score, which is inspired in the collaborative double robustness result of Theorem 1. Unlike the C-TMLE, the $e$-score reduces the variance of the propensity score without sparsity assumptions, therefore allowing us to construct methods applicable to any data-adaptive estimator of the propensity score such as those based on machine or statistical learning.

3 Collaborative double robustness based on the $e$-score

We start this section by presenting an alternative collaborative double robustness theorem, which provides the foundation for our proposed estimator. Our result is based on the collaborative double robustness principle that, when the outcome regression is consistently estimated at the appropriate rate, then the propensity score may be simply defined as $P_0(A = 1)$. More generally, a propensity score that adjusts for the asymptotic bias of the outcome regression estimator suffices to attain double robustness (Theorem 1).

**Definition 1** ($e$-score). Assume $g_1$ and $m_1$ are as in C1. Let

$$r_0(w) = E_0\{Y - m_1(W) | A = 1, g_1(W) = g_1(w)\}$$

quantify the amount of model misspecification of $m_1$, as a function of the possibly misspecified limit of the propensity score. The $e$-score is defined as

$$e_0(w) = E_0\{g_1(W) | r_0(W) = r_0(w)\}.$$ 

Theorem 2, stated rigorously below, teaches us that an estimator based on the efficient influence function, but constructed using $e_0$ instead of $g_1$, maintains the double robustness property. To introduce this result, define the estimating function

$$D_{\lambda, \theta_0}(O) = \frac{A}{e(W)}\{Y - m(W)\} + m(W) - \theta_0,$$

where we have denoted $\lambda = (e, m)$.

**Theorem 2** (Double robustness based on the $e$-score). Let $(g_1, m_1)$ be such that either $g_1 = g_0$ or $m_1 = m_0$. Let $\lambda_1 = (e_0, m_1)$. Then $P_0 D_{\lambda_1, \theta_0} = 0$.

In the next section we discuss several alternatives to construct a collaborative doubly robust estimator based on Theorem 2. Before we do so, we discuss two important remarks about this result.
Remark 1. If the residual \( Y - m_1(W) \) is a monotone function of \( g_1(W) \), then we have \( e_0(W) = g_1(W) \). In this case our collaborative doubly robustness reduces to standard double robustness estimators. To avoid this monotonicity, we explicitly include \( \hat{g}(W) \) as a covariate when computing the estimator \( \hat{m}(W) \).

Remark 2. There is an important difference between the collaborative double robustness results in Theorem 1 and 2. Double robustness under Theorem 2 requires consistent estimation of the propensity score that conditions on the full vector \( W \), as opposed to the reduced-data propensity score required in Theorem 1.

4 Proposed Estimators

In this section we propose two estimators for \( \theta_0 \) based on the collaborative double robustness result of Theorem 2. Both estimators are constructed under the targeted minimum loss based framework. The first estimator is purely based on obtaining a tilted estimator \( \hat{m} \), which targets a solution to an estimating equation based on \( D_{\lambda, \theta} \). A large sample analysis of this estimator reveals that it is likely not asymptotically linear in many important situations. As a solution to this flaw, we propose a second estimator, in which we target additional estimating equations that yield asymptotic linearity.

To start, we discuss estimators of \( r_0 \) and \( e_0 \). Note that these quantities are one-dimensional regression functions which can be consistently estimated using non-parametric estimators, e.g., kernel smoothing. In particular, for a second-order kernel function \( K_h \) with bandwidth \( h \) we define the estimators as

\[
\hat{r}(w) = \frac{\sum_{i=1}^n M_i K_h \{\hat{g}(W_i) - \hat{g}(w)\} \{Y_i - \hat{m}(W_i)\}}{\sum_{i=1}^n M_i K_h \{\hat{g}(W_i) - \hat{g}(w)\}}.
\]

\[
\hat{e}(w) = \frac{\sum_{i=1}^n M_i K_h \{\hat{r}(W_i) - \hat{r}(w)\} \hat{g}(W_i)}{\sum_{i=1}^n M_i K_h \{\hat{r}(W_i) - \hat{r}(w)\}}.
\]

The optimal bandwidth \( \hat{h}_{\text{opt}} \) is chosen using K-fold cross-validation (the optimality of this selector is discussed in van der Vaart et al., 2006).

Once \( \hat{e}(w) \) is estimated, a variance-reduced TMLE can be computed by applying the TMLE algorithm presented in Section 2.1 with \( \hat{g}(w) \) replaced by \( \hat{e}(w) \). Denote such estimator with \( \hat{\theta}_{\text{e-tmle}} \). The analysis of the asymptotic properties of \( \hat{\theta}_{\text{e-tmle}} \) follows standard arguments in the analysis of \( M \)-estimators, as in Section 2.1. Define the following Donsker condition:

C2 (Donsker). Let \( \xi \) be as in C1. Assume the class of functions \( \{\eta = (g, m) : ||m - m_1|| < \delta, ||g - g_1|| < \delta\} \) is Donsker for some \( \delta > 0 \).

Under C1 and C2, a straightforward application of Theorems 5.9 and 5.31 of van der Vaart (1998) (see also example 2.10.10 of van der Vaart and Wellner, 1996) yields

\[
\hat{\theta}_{\text{e-tmle}} - \theta_0 = \beta(\lambda) + (P_n - P_0)D_{\lambda, \theta_0} + o_P(n^{-1/2} + ||\beta(\lambda)||),
\]
where \( \beta(\hat{\lambda}) = P_0 D_{\hat{\lambda}, \theta_0} \). From equation (7) we can see that the only missing element to understand the asymptotic distribution of \( \hat{\theta}_{e\text{-tmle}} \) is the “drift” term \( \beta(\hat{\lambda}) \). If this term, which is equal to

\[
\beta(\hat{\lambda}) = \frac{1}{\hat{e}}(g_0 - \hat{e})(m_0 - \hat{m})dP_0,
\]

(8)
can be shown to be asymptotically linear in the sense that

\[
\beta(\hat{\lambda}) = (P_n - P_0)S + o_P(n^{-1/2}),
\]

(9)
for some function \( S \) of \( O \) that may depend on \( P_0 \), then asymptotic linearity and normality of \( \hat{\theta}_{e\text{-tmle}} \) follows. Unfortunately, \( \beta(\hat{\lambda}) \) is a complex term that cannot be expected to satisfy (9) in general. Recall that \( \hat{\mu} \) and \( \hat{g} \) are constructed using general data-adaptive methods, with the only constraints that the estimators must satisfy conditions C1 and C2. These conditions are satisfied for a large number of estimators for which (9) does not hold. See for example (Bickel et al., 2009) for rate results on \( \ell_1 \) regularization, (Wager and Walther, 2015) for rate results on regression trees, and (Chen and White, 1999) for neural networks. These conditions are also satisfied by the highly adaptive lasso (Benkeser and van der Laan, 2016) under the mild assumption that the true regression function is right-hand continuous with left-hand limits and has variation norm bounded by a constant. Although all of these methods satisfy C1 and C2, they do not generally satisfy (9).

4.1 Achieving asymptotic linearity

We now propose a second estimator, \( \hat{\theta}_{e\text{-tmle-al}} \), which is asymptotically linear. We achieve asymptotic linearity of \( \beta(\hat{\lambda}) \) by using a strategy analogous to that of van der Laan (2014); Benkeser et al. (2016); Díaz and van der Laan (2017). Our estimator \( \hat{\lambda} \) guarantees the asymptotic linearity of \( \beta(\hat{\lambda}) \), under certain conditions, by tilting the initial estimator towards a solution of a score equation carefully constructed to target \( \beta(\hat{\lambda}) \). To develop this construction, we start by requiring specific convergence rates in the double robustness C1:

C3 (Consistency rate of nuisance estimators). Assume \( ||\hat{m} - m_0|| = o_P(n^{-1/4}) \) and \( ||\hat{g} - g_0|| = o_P(n^{-1/4}) \).

Under the above condition, the following lemma provides a representation of the drift term in terms of score functions. This representation is achieved through the following univariate regression:

\[
q_0(w) = E_0 \left\{ A \left( \frac{1}{\hat{e}(W)} - \frac{1}{\hat{g}(W)} \right) \left| \hat{m}(W) = \hat{m}(w) \right. \right\},
\]

where the expectation is taken with respect to the distribution of \((A, W)\), taking \( \hat{e}, \hat{g} \), and \( \hat{m} \) as fixed functions. Like \( r_0 \) and \( e_0 \), we estimate \( q_0 \) consistently through kernel regression.
methods. In particular, for some bandwidth $h \to 0$, let $\hat{q}$ be defined pointwise as

\[ \hat{q}(w) = \frac{\sum_{i=1}^{n} K_h \{ \hat{m}(W_i) - \hat{m}(w) \} [A \{ \hat{e}(W_i)^{-1} - \hat{g}(W_i)^{-1} \}]}{\sum_{i=1}^{n} K_h \{ \hat{m}(W_i) - \hat{m}(w) \}} \]

We have the following result:

**Lemma 1** (Asymptotic representation of the drift term). Let $h_0(w) = q_0(w)/g_0(w)$, and define the score function

\[ S_h(O) = A h(W) \{ Y - \hat{m}(W) \} \]

Under C3 we have $\beta(\hat{\lambda}) = P_0 S_h + oP(n^{-1/2})$.

The proof of the lemma is presented along with all other proofs in the Supplementary Materials. The above lemma sheds light on the characteristics required of an estimator $\hat{\lambda}$ in order to satisfy (9). In particular, the proof of Theorem 3 shows that asymptotic linearity of $\hat{\theta}$ requires that $\hat{\lambda}$ solve the score equation $P_n S_{\hat{h}} = 0$ for $\hat{h}(w) = \hat{q}(w)/\hat{g}(w)$.

We now describe in detail our proposed estimator, which we denote $\hat{\theta}_{e-tmle-al}$, and define through the following iterative algorithm.

**Step 1. Initial estimators.** Obtain initial estimators $\hat{g}$ and $\hat{m}$ of $g_0$ and $m_0$. Construct estimators $\hat{r}$, $\hat{e}$, $\hat{h}$, and $\hat{b}$ using kernel regression estimators as described above.

**Step 2. Solve estimating equations.** Estimate the parameter $\beta = (\beta_1, \beta_2)$ in the logistic tilting model

\[ \logit m_\beta(w) = \logit \hat{m}(w) + \beta_1 \hat{e}(w)^{-1} + \beta_2 \hat{h}(w), \tag{10} \]

Here, logit $\hat{m}(w)$ is an offset variable (i.e., a variable with known parameter equal to one). The parameter $(\beta_1, \beta_2)$ may be estimated through a logistic regression model of $Y$ on the bivariate vector $[\hat{e}(W)^{-1}, \hat{h}(W)]$, with no intercept and with offset logit $\hat{m}(W)$ among observations with $A = 1$. Let $\hat{\beta}$ denote these estimates.

**Step 3. Update estimator and compute e-TMLE.** Define the updated estimator as $\tilde{m} = m_\hat{\beta}$. The proposed TMLE of $\theta_0$ is defined as

\[ \hat{\theta}_{e-tmle-al} = \frac{1}{n} \sum_{i=1}^{n} \tilde{m}(W_i). \]

The large sample distribution of the above TMLE is given in the following theorem:

**Theorem 3** (Asymptotic Linearity of $\hat{\theta}_{e-tmle-al}$). Assume C2 and C3 hold for $\tilde{\eta}$. Define $g_0^*(w) = P(A = 1 \mid m_0(W) = m_0(w))$, and let $p = E_0(A)$. Then

\[ \hat{\theta}_{e-tmle-al} - \theta_0 = (P_n - P_0)IF_0 + oP(n^{-1/2}), \]

10
where

\[ IF_0(O) = \frac{A}{g_0(W)} \left\{ 1 - \frac{g_0^*(W) - g_0(W)}{p} \right\} \{ Y - m_0(W) \} + m_0(W) - \theta_0. \]  

(11)

The proof of the above theorem is presented in the Supplementary Materials. Together with the central limit theorem, Theorem 3 shows that \( n^{1/2}(\hat{\theta}_{e\text{-tmle-al}} - \theta_0) \to N(0, \sigma_{e\text{-tmle-al}}^2) \), where \( \sigma_{e\text{-tmle-al}}^2 = \text{Var}\{IF_0(O)\} \). The asymptotic distribution of Theorem 3 may be used to construct hypothesis tests and a Wald-type confidence interval as follows. The proof of Lemma 1 in the Supplementary Materials shows that

\[ \hat{\sigma}_{e\text{-tmle-al}}^2 = \frac{1}{n} \sum_{i=1}^n A_i \left\{ 1 - \frac{\hat{q}(W_i)}{\hat{g}(W_i)} \right\} \{ Y_i - \hat{m}(W_i) \} + \hat{m}(W_i) - \hat{\theta}_{e\text{-tmle-al}}^2 \]  

is a consistent estimator of \( \sigma_{e\text{-tmle-al}}^2 \). Intuitively, this is so because under the conditions of Theorem 3, \( \hat{e}(w) \) is a consistent estimator of \( p \), and \( \hat{q}(w) \) is a consistent estimator of \( g_0^*(w)/p - 1 \), so that the term inside square brackets in the above display is a consistent estimator of \( \text{IF}_0(O) \). Thus, the interval \( \hat{\theta}_{e\text{-tmle-al}} \pm z_{\alpha/2} n^{-1/2} \hat{\sigma}_{e\text{-tmle-al}} \) has correct asymptotic coverage \((1 - \alpha)100\%\), whenever \( \hat{q} \) and \( \hat{m} \) converge to their true value at the rate stated in C3.

Remark 3. Inspection of equation (11) reveals the intuition behind the expected efficiency gains. If \( \epsilon < g_0(W) \leq p \), then by construction we have \( g_0(W) \leq g_0^*(W) \leq p \). Thus, large inverse probability weights \( \{ g_0(W) \}^{-1} \) get shrunk by a factor \( 0 \leq 1 - \{ g_0^*(W) - g_0(W) \}/p \leq 1 \). When there are many large weights, this shrinkage has the effect of reducing the variance of the estimator \( \hat{\theta}_{e\text{-tmle-al}} \) in comparison to the efficiency bound \( \sigma_{\text{eff}}^2 \) defined in (3). To illustrate this further, consider an extreme scenario where \( m_0(W) \) is independent of \( A \) such that \( g_0^*(W) = p \). Then \( \sigma_{e\text{-tmle-al}}^2 \) reduces to \( E[p^{-2} \sigma^2(W) g_0(W) + \{ m_0(W) - \theta_0 \}^2] \). If the correlation between \( \sigma^2(W) \) and \( g_0(W) \) is small enough, then it can be expected that \( \sigma_{e\text{-tmle-al}}^2 < \sigma_{\text{eff}}^2 \). The stabilization of large probability weights comes at the price of larger weights for observations \( W \) with large probabilities \( g_0(W) > p \). However, those weights never get magnified by a factor larger than 2. In pathological cases where the correlation between \( \sigma^2(W) \) and \( g_0(W) \) is large, so that \( \sigma^2(W)/g_0(W) \) is nearly constant, then it is possible that \( \sigma_{e\text{-tmle-al}}^2 > \sigma_{\text{eff}}^2 \). Equality of \( \text{IF}_0 \) with the efficient influence function \( D_{\theta_0,\theta_0} \) is obtained trivially when \( g_0^*(w) = g_0(w) \), in which case \( \hat{\theta}_{e\text{-tmle-al}} \) and \( \hat{\theta}_{\text{tmle}} \) are asymptotically equivalent.

5 Simulation Studies

In this section we present a simulation study using synthetic data with the aim of illustrating the properties of the proposed estimators, in comparison with \( \hat{\theta}_{e\text{-tmle}}, \hat{\theta}_{\text{tmle}}, \hat{\theta}_{\text{aipw}}, \) and the G-computation estimator \( \hat{\theta}_{\text{g-comp}} \). For each sample size 200, 800, 1800, 3200, 5000, 7200,
9800, 12800, we generate 1000 datasets as follows. First, a set of variables \( \{Z_1, \ldots, Z_{15}\} \) is generated, where all \( Z_i \)'s are independently distributed \( 2\text{Beta}(1/3, 1/3) - 1 \). Then, a set of covariates \( \{W_1, \ldots, W_{15}\} \) is generated as \( W_j = Z_j \) for odd \( j \) and \( W_j = Z_{j-1}Z_j \) for even \( j \). Then, a variable \( A \) is drawn from a Bernoulli distribution with probabilities \( g_0(W) = \expit\{\delta \sum_{j=1}^{10} W_j\} \), for \( \delta \in \{0, 1\} \). The case \( \delta = 0 \) is a randomized trial and represents a best-case scenario for the variability of the propensity score. Figure 1 shows the high variability of the propensity score for \( \delta = 1 \). The outcome is generated as \( Y = A + \sum_{j=6}^{16} W_j + \mathcal{N}(0, 1) \). We aim to estimate the causal effect of \( A \) on \( Y \), defined as \( E(Y_1 - Y_0) \). The efficiency bounds for this parameter are approximately 6.8 and 16.1 for \( \delta = 0 \) and \( \delta = 1 \), respectively. Note that only \( W_6, \ldots, W_{10} \) are confounders of the causal effect of \( A \) on \( Y \). Note also that the causal effect of \( A \) on \( Y \) is \( \theta_0 = 1 \).

![Figure 1: Probability density function of the propensity score \( g_0(W) \) in the simulation study.](image)

For each generated dataset, we fit four different scenarios of consistent estimation of \( g_0 \) and \( m_0 \): (A) both consistently estimated, (B) only \( m_0 \) consistently estimated, (C) only \( g_0 \) consistently estimated, and (D) both inconsistently estimated. All models consisted of main terms generalized linear regression models with the appropriate link functions (identity for the outcome, logistic for the propensity score). Consistent estimators were constructed using covariates \( W_j \); inconsistent estimators used covariates \( Z_j \). For each of the above scenarios, we computed the four estimators: the \( G \)-computation or regression adjusted estimator, \( \hat{\theta}_{e\text{-tmle}} \), \( \hat{\theta}_{c\text{-tmle}} \), \( \hat{\theta}_{\text{tmle}} \). We compare the performance of the estimators in terms of four metrics:

- Absolute bias: \( |E(\hat{\theta} - \theta_0)| \)
- Absolute bias scaled by \( n^{1/2} \): \( n^{1/2}|E(\hat{\theta} - \theta_0)| \)
- Standard deviation scaled by \( n^{1/2} \): \( n^{1/2}\text{sd}(\hat{\theta}) \)
- Root mean squared error scaled by $n^{1/2}$: $\{nE(\hat{\theta} - \theta_0)^2\}^{1/2}$.
- The quotient $\hat{\sigma}^2 / \text{Var}(\hat{\theta})$. For $\hat{\theta}_\text{c-tmle}$ and $\hat{\theta}_\text{tmle}$, the variance was estimated using the variance of the efficient influence function. For $\hat{\theta}_\text{e-tmle-al}$, the variance was estimated using the doubly robust asymptotic distribution given in Theorem 3. The $G$-computation estimator is not included in this comparison.
- Coverage probability of a Wald-type confidence interval.

All the above quantities were approximated using Monte-Carlo integrals across the 1000 generated datasets. The results for $\delta = 1$ are presented in Figures 5 and 6. The results for $\delta = 0$, presented in the Supplementary Materials, corroborate that all estimators have nearly identical performance except in small samples.

Figure 2: Simulation Results: bias, variance, and mean squared error for $\delta = 1$. 
Results for scenario A. The TMLE has smaller bias than all competitors in small samples ($n = 200$). The AIPW and TMLE have similar asymptotic performance, with the TMLE having much better small sample performance. This improvement has been demonstrated in several simulation studies (e.g., Porter et al., 2011). The variance of the TMLE is much larger than the variance of its competitors (except AIPW), making its overall performance on mean squared error worse. The $g$-computation estimator and the C-TMLE have similar performance, with the $e$-TMLE having comparable performance. Overall, the asymptotic efficiency gains obtained with the C-TMLE and $e$-TMLE are noticeable, their MSE is similar to that of the $g$-computation estimator, and much smaller than that of the efficient estimator TMLE. In particular, it seems that the $n^{1/2}$-bias of the TMLE does not converge quickly enough, perhaps as a result of the large variability of the inverse probability weights. This problem is solved by the collaborative double robustness
involved in e-TMLE and C-TMLE, which are capable of detecting that the outcome models are correctly specified, and therefore do not adjust for the full covariate vector \( W \) in the propensity score. As predicted by Theorem 3, the confidence interval based on e-TMLE has asymptotically correct coverage. This is also the case for the TMLE. However, the variance for the C-TMLE based on the efficient influence function, which is the default of the R package \texttt{ctmle} used in our simulations is inconsistent and generates important undercoverage of the confidence intervals. This is consistent with the simulation results reported in Ju et al. (2018).

**Results for scenario B.** All estimators have similar performance in terms of bias, with the TMLE having slightly smaller bias at small sample sizes. The MSE of the C-TMLE and e-TMLE is smaller at all sample sizes, but the difference is not as large as it is for scenario (A). The MSE of all estimators is smaller than in scenario (A), this is a consequence of the misspecification of the propensity score model, which reduces the variability of the estimator. The e-TMLE seems to be \( n^{1/2} \)-consistent in this scenario, which is not predicted by our theory. According to our asymptotic analysis in Section 4, \( n^{1/2} \)-consistency of e-TMLE requires that \( \beta(\tilde{\lambda}) = O_P(n^{-1/2}) \), with \( \beta(\tilde{\lambda}) \) defined in (8). If \( \hat{m} \) is the MLE in a correctly specified parametric model for \( m_0 \), as in this simulation, then \( \beta(\tilde{\lambda}) = O_P(n^{-1/2}) \) is expected. However, \( \beta(\tilde{\lambda}) = O_P(n^{-1/2}) \) should not be expected in general, for example for data-adaptive estimators \( \hat{m} \). In this scenario all confidence intervals have coverage probabilities below the nominal level.

**Results for scenario C.** In this scenario all estimators had larger variance, compared to scenarios A and B. This is due to the high variability of the propensity score weights. The \( G \)-computation estimator had smaller bias than the C-TMLE and the e-TMLE, but this is an artifact of our data generating mechanism and preliminary estimator \( \hat{m} \). Although the TMLE has smaller bias at all sample sizes, the C-TMLE and e-TMLE have a better bias-variance trade-off than the plan TMLE. In addition, the only estimator that seems to be \( n^{1/2} \)-consistent is the TMLE. For the e-TMLE, this is a result of (8), which shows that in this case \( \beta(\tilde{\lambda}) \) is not \( O_P(n^{-1/2}) \). In this scenario the confidence intervals for the e-TMLE and C-TMLE have coverage probabilities below the nominal level. The interval based on the TMLE has a coverage probability close to the nominal level. Under consistent estimation of the propensity score, efficient estimation theory predicts that this interval has conservative coverage. This is corroborated in our simulations. The C-TMLE has better asymptotic coverage than the e-TMLE-al in both cases \( \delta = 1 \) and \( \delta = 0 \). We conjecture this is a consequence of the sparsity of our data generating mechanisms, for which the C-TMLE is specially designed.

**Results for scenario D.** All estimators have similar bias that does not disappear at \( n^{1/2} \) rate, as predicted by theory. All confidence intervals in this scenario have poor performance,
and are not shown in Figure 6.

6 Illustrative Application

To illustrate our methods in a real dataset, we revisit the example presented in Kupzyk and Beal (2017); Beal and Kupzyk (2014). The dataset for this study is part of a longitudinal study of adolescent girls originally conducted by Dorn et al. (2008). We reanalyze the data with the objective of assessing whether smoking among adolescent girls negatively affects bone health via depletion in bone mineral content (BMC). The main hypothesis we test is whether smoking causes lower levels of accrual in BMC. Data on 259 adolescent girls was collected each year for three years, and includes information on smoking status, age, race, BMI, SES, age at menarche, Tanner breast stage, birth control, calcium intake, PAQ-C physical activity score, state anxiety T score, and trait anxiety T score. Bone mineral content of the hip, spine, and total body was determined by dual-energy x-ray absorptiometry. The challenge for causal inference is that smoking behavior may be influenced by variety of reasons such as increased depression and physical activity, and those factors may also affect BMC (e.g., depression decreases BMC accrual, earlier onset of puberty have higher BMC accrual levels, etc.) In this article, we will estimate the effect of smoking on the first year of study on BMC measured on the third year of the study. By the third year, 59 girls were lost to follow up, so their outcome is missing. Denote $T \in \{0, 1\}$ an indicator of smoking status, and $M \in \{0, 1\}$ an indicator of not lost to follow-up. We will estimate the average treatment effect by comparing the mean BMC in counterfactual worlds in which $P(T = 1, M = 1) = 1$ and $P(T = 0, M = 1) = 1$, respectively. Denote with $W$ the confounders listed above. The propensity scores that we must estimate are given by $P(T = t, M = 1 \mid W) : t \in \{0, 1\}$. We estimate these probabilities by independently estimating $P(T = t \mid W)$ and $P(M = 1 \mid T = t, W)$, and using the Bayes rule. In order to perform model selection for the propensity score models and the outcome regression, we use 5-fold cross-validation as implemented in the R package SuperLearner (Polley et al., 2017). We compared the risk (negative log-likelihood for binary outcomes, MSE for continuous outcomes) of 9 different candidate prediction methods. The cross-validation results are presented in Table 1. We then computed the estimators for the e-score separately for the two groups. The original propensity score, together with the e-score, are presented in Figure 4. This figure illustrates the reduction in variability of the propensity score achieved with the e-score. For reference, the variance of the inverse propensity score for the treated and untreated groups are 154.7 and 122.9, respectively. The corresponding quantities for the e-score are 0.096 and 0.0005.

We then proceeded to compute the estimators studied in Section 5. The C-TMLE was not computed because current methodology and software does not allow for missingness in the outcome. The results are presented in Table 2. The point estimates are somewhat similar for all estimators, and show a statistically significant reduction of around 40–45
### Table 1: Cross-validated risk (negative log-likelihood for binary outcomes, MSE for continuous outcomes) for each estimator.

| Estimator       | Propensity score | Outcome regression |
|-----------------|------------------|--------------------|
|                 | Model for $T$    | Model for $M$      | Exposed  | Controls |
| GLM             | 0.4695           | 0.4868             | 3912.9   | 8676.7   |
| GLM-$\ell_1$    | 0.4332           | 0.4783             | 3893.6   | 8047.9   |
| GLM-$\ell_1 \times 2$ | 0.4413       | 0.4850             | 3909.0   | 7542.8   |
| GLM-$\ell_1 \times 3$ | 0.4388       | 0.4820             | 3940.3   | 8046.9   |
| Bayes GLM       | 0.4568           | 0.4810             | 3911.6   | 8681.6   |
| MARS            | 0.6548           | 0.8024             | 5126.1   | 6852.7   |
| GAM             | 0.4747           | 0.4977             | 3956.7   | 7509.4   |
| Boosted GLM     | 0.4334           | 0.4838             | 4021.7   | 8672.0   |
| Boosted GAM     | 0.4377           | 0.4832             | 3868.9   | 9258.4   |

GLM denotes generalized linear models with canonical link, GLM-$\ell_1$ denotes GLM with $\ell_1$ regularization, GLM-$\ell_1 \times k$ denotes GLM with $k$-way interactions and $\ell_1$ regularization, Bayes GLM is Bayesian GLM with non-informative priors, MARS is multivariate adaptive splines, and GAM is generalized additive model. Tuning parameters were chosen using cross-validation with the caret R package (Kuhn et al., 2017).

Figure 4: Distributions of the estimated propensity and $e$-scores in the smoking–BMC example.

grams of BMC due to smoking. The standard error for the $e$-TMLE is not reported as we do not have methodology to construct a valid estimate. As expected, the AIPW and TMLE have very similar standard errors. The standard error for the $e$-TMLE-AL is substantially different from the other two estimates, yielding efficiency gains of approximately 54% compared to the TMLE. This means that a pre-specified analysis plan using the $e$-TMLE-
AL instead of the TMLE would have required roughly 35% ≈ 1 − (1/1.54) fewer patients (90 out of 259) to achieve the same power.

| Estimator     | Estimate | S.E. | P-value |
|---------------|----------|------|---------|
| AIPW          | -45.7    | 14.81| 0.0020  |
| TMLE          | -45.5    | 14.52| 0.0017  |
| e-TMLE        | -39.6    | —    | —       |
| e-TMLE-AL     | -43.3    | 11.67| 0.0002  |

Table 2: Estimates of the average treatment effect in the smoking–BMC example.

7 Discussion

We have discussed several results for collaborative doubly robust estimation of causal parameters. Our main contribution is the introduction of the e-score, which greatly facilitates the construction of collaborative doubly robust estimators compared to existing methodologies that rely on model selection for the propensity score or sparsity assumptions. Furthermore, we expect the introduction of the e-score will facilitate the generalization of the methods to more complex data structures, such as missing outcomes and longitudinal studies.

A key component of the estimators that we propose is the estimation of certain univariate regression functions using kernel regression. While we propose to estimate the bandwidth of those estimators using the optimal regression bandwidth, this choice may be suboptimal for estimation of causal effects. Choosing the bandwidth in a way that optimizes the MSE of the causal effect estimator will be the subject of future research.

We have proved that one of our estimators, the e-TMLE-AL, is asymptotically linear in the non-parametric model with a variance that may be smaller than the variance of the efficient influence function. Semiparametric efficiency theory (Bickel et al., 1997) dictates that the variance of the efficient influence function is the smallest possible variance attained by any regular estimator. Therefore, it must be that the e-TMLE-AL is an irregular estimator. The implications of this irregularity are still unclear to us. However, we conjecture that it may not have important consequences. Our conjecture is based on the following argument. Consider a non-parametric model $\mathcal{M}$ for the data structure $(I,W,A,Y)$, where $I$ is an instrumental variable (that is, a cause of $A$ but otherwise unrelated to $Y$), and $W$ are true confounders. Consider the efficiency bound $\tau^2$ for estimation of $E(Y_1)$ in such a model. An efficient AIPW or TMLE based on a data reduction given by $(W,A,Y)$ may have smaller variance than the efficiency bound $\tau^2$, and therefore be irregular in $\mathcal{M}$. However, this type of irregularity would hardly seem problematic. Our conjecture that the irregularity of our estimators may not be problematic is based on the observation that our estimators rely on a dimension reduction which has an effect similar to removing instru-
mental variables. However, the practical implications of irregularity in this context remain poorly understood, and rigorous research on this area is necessary.

Lastly, we conjecture that the e-score may have other important uses in addition to the estimators discussed in this manuscript. One particular use is as a tool for outcome model selection. According to our Theorem 2, an e-score with variance zero would mean that the outcome regression, though possibly misspecified, provides a g-computation consistent estimator of the causal parameter of interest. A rigorous development of such methodology will be the subject of future research.

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A  **Theorem 2**

*Proof* For $\lambda_0 = (m_0, e_0)$, we have $E_0 D_{\lambda_0} = 0$, and thus

$$E_0 D_{\lambda_1}(O) = E_0 \{D_{\lambda_1}(O) - D_{\lambda_0}(O)\}$$

$$= \int \frac{m_0(w) - m_1(w)}{e_0(w)} \{a - e_0(w)\} dP_0(a, w)$$

The result for $m_1 = m_0$ is trivially obtained from the above equation. The result for
$g_1 = g_0$ follows from the following argument.

$$E_0 D_{\lambda_1}(O) = \int \frac{m_0(w) - m_1(w)}{e_0(w)} \{a - e_0(w)\} \, dP_0(a, w)$$

$$= \int \frac{m_0(w) - m_1(w)}{e_0(w)} \{g_0(w) - e_0(w)\} \, dP_0(w)$$

$$= \int \frac{a}{g_0(w)} \frac{y - m_1(w)}{e_0(w)} \{g_0(w) - e_0(w)\} \, dP_0(y, a, w, g_0(w))$$

$$= \int \left[ \int \frac{a}{g_0(w)} \frac{y - m_1(w)}{e_0(w)} \{g_0(w) - e_0(w)\} \, dP_0(y, a, w | g_0(w)) \right] dP_0(g_0(w))$$

$$= \int \left[ \int \frac{a}{g_0(w)} \{y - m_1(w)\} \, dP_0(y, a, w | g_0(w)) \right] \frac{g_0(w) - e_0(w)}{e_0(w)} \, dP_0(g_0(w)) \tag{12}$$

$$= \int \frac{r_0(w)}{e_0(w)} \{g_0(w) - e_0(w)\} \, dP_0(g_0(w)) \tag{13}$$

$$= \int \frac{r_0(w)}{e_0(w)} \{g_0(w) - e_0(w)\} \, dP_0(w)$$

$$= \int \frac{r_0(w)}{e_0(w)} \{a - e_0(w)\} \, dP_0(a, w)$$

$$= \int \left[ \int \frac{r_0(w)}{e_0(w)} \{a - e_0(w)\} \, dP_0(a, w, | r_0(w)) \right] dP_0(r_0(w))$$

$$= \int \frac{r_0(w)}{e_0(w)} \{e_0(w) - e_0(w)\} \, dP_0(r_0(w))$$

$$= 0,$$

where (12) follows because $e_0(w)$ is a function of $w$ only through $g_0(w)$, and (13) follows from the definition of $r_0(w)$. \qed

### B Lemma 1

**Proof** Define

$$q_0^0(w) = E_0 \left\{ A \left( \frac{1}{e(W)} - \frac{1}{g(W)} \right) \right\} \left| m_0(W) = m_0(w) \right.$$.

where, as in $q_0$, the expectation is taken with respect to the distribution of $(A, W)$, taking
Arguing as in equation (7) of the main document we get

\[ \beta(\hat{\lambda}) = \int \frac{1}{\hat{e}(w)} \{ g_0(w) - \hat{e}(w) \} \{ m_0(w) - \hat{m}(w) \} \, dP_0(w) \]
\[ = \int g_0(w) \left\{ \frac{1}{\hat{e}(w)} - \frac{1}{\hat{g}(w)} \right\} \{ m_0(w) - \hat{m}(w) \} \, dP_0(w) \]
\[ + \int \frac{1}{\hat{g}(w)} \{ g_0(w) - \hat{g}(w) \} \{ m_0(w) - \hat{m}(w) \} \, dP_0(w) \]
\[ = \int g_0(w) \left\{ \frac{1}{\hat{e}(w)} - \frac{1}{\hat{g}(w)} \right\} \{ m_0(w) - \hat{m}(w) \} \, dP_0(w) + o_P(n^{-1/2}) \quad (14) \]
\[ = \int a \left\{ \frac{1}{\hat{e}(w)} - \frac{1}{\hat{g}(w)} \right\} \{ m_0(w) - \hat{m}(w) \} \, dP_0(a, w) + o_P(n^{-1/2}) \]
\[ = \int q_0^0(w)m_0(w) \, dP_0(w) - \int q_0(w)\hat{m}(w) \, dP_0(w) + o_P(n^{-1/2}) \quad (15) \]
\[ = \int q_0(w)\{ m_0(w) - \hat{m}(w) \} \, dP_0(w) - \int \{ q_0(w) - q_0^0(w) \} m_0(w) \, dP_0(w) + o_P(n^{-1/2}) \]
\[ = \int q_0(w)\{ m_0(w) - \hat{m}(w) \} \, dP_0(w) + o_P(n^{-1/2}) \quad (16) \]
\[ = \int a \frac{q_0(w)}{g_0(w)} \{ m_0(w) - \hat{m}(w) \} \, dP_0(a, w) + o_P(n^{-1/2}) \]
\[ = \int a \frac{q_0(w)}{g_0(w)} \{ y - \hat{m}(w) \} \, dP_0(y, a, w) + o_P(n^{-1/2}), \]

where (14) follows from Condition C3 in the main document of the manuscript, (15) follows from the definitions of \( q_0(w) \) and \( q_0^0(w) \), and (16) follows from applying the law of iterated expectation to show that

\[ \int \{ q_0(w) - q_0^0(w) \} m_0(w) \, dP_0(w) = 0. \]

\[ \square \]

**C  Theorem 3**

Arguing as in equation (7) of the main document we get

\[ \theta_{\text{tmle-al}} - \theta_0 = \beta(\hat{\lambda}) + (P_n - P_0)D_{\lambda_0, \theta_0} + o_P\left( n^{-1/2} + |\beta(\hat{\lambda})| \right) \]

Lemma 2 below gives the asymptotic expression for \( \beta(\hat{\eta}) \). Substituting this expression we get

\[ \hat{\theta}_{\text{tmle}} - \theta_0 = (P_n - P_0)(D_{\lambda_0, \theta_0} - S(O)) + o_P\left( n^{-1/2} + O_P(n^{-1/2}) \right), \]

25
where
\[ S(O) = A \frac{g_0^*(w) - E(A)}{g_0(W)} \{ Y - m_0(W) \}. \]

This, together with the central limit theorem concludes the proof.

**Lemma 2 (Asymptotic Linearity of \( \beta(\tilde{\lambda}) \)).** For any function \( b(W) \), denote \( S_{b,m}(O) = Ab(W)\{Y - m(W)\} \). Assume C2 and C3. Then
\[ \beta(\tilde{\lambda}) = -(\mathbb{P}_n - P_0)S_{b_0,m_0}(O) + o_P(n^{-1/2}), \]

where
\[ b_0(w) = \frac{g_0^*(w) - E(A)}{E(A)g_0(W)}. \]

**Proof** From Lemma 1, we have
\[ \beta(\tilde{\lambda}) = P_0 S_{h_0,\hat{m}}(O) + o_P(n^{-1/2}) \]

By construction we have \( \mathbb{P}_n S_{\hat{h},\hat{m}} = 0 \), thus
\[ \beta(\tilde{\lambda}) = -(\mathbb{P}_n - P_0)S_{h_0,\hat{m}} - P_0(S_{h_0,m_0} - S_{h_0,\hat{m}}). \quad (17) \]

We have
\[
\begin{align*}
P_0(S_{h_0,m_0} - S_{h_0,\hat{m}}) &= \int a(h_0 - \hat{h})(y - \hat{m})dP_0 \\
&= \int a \left( \frac{q_0}{g_0} - \frac{q_0}{\hat{g}} + \frac{q_0}{\hat{g}} - \frac{\hat{g}}{g} \right) (y - \hat{m})dP_0 \\
&= -\int \frac{g_0}{\hat{g}}(g_0 - \hat{g})(m_0 - \hat{m})dP_0 + \int \frac{g_0}{\hat{g}}(q_0 - \hat{q})(m_0 - \hat{m})dP_0
\end{align*}
\]

Using the Cauchy-Schwartz inequality, we obtain
\[ P_0(S_{h_0,m_0} - S_{h_0,\hat{m}}) = O_P(||m_0 - \hat{m}|| + ||q_0 - \hat{q}|| + ||g_0 - \hat{g}||). \quad (18) \]

Since \( \hat{q} \) is a kernel regression with optimal bandwidth, \( ||q_0 - \hat{q}|| = O_P(n^{-2/5}) \). Condition C3 then ensures the term (18) is \( o_P(n^{-1/2}) \). Under Condition C1, we have \( \hat{c}(W) \rightarrow E(A) \), and therefore
\[ \hat{q}(w) \rightarrow E_0 \left\{ A \left( \frac{1}{E(A)} - \frac{1}{g_0(W)} \right) \bigg| m_0(W) = m_0(w) \right\} \]

The law of total expectation shows that the right hand side of the above expression is equal to \( g_0^*(w)/E(A) - 1 \). This shows that \( \hat{h} \rightarrow b_0 \). Application of Theorem 19.24 of van der Vaart (1998) to (17) shows that:
\[ \beta(\tilde{\lambda}) = -(\mathbb{P}_n - P_0)S_{b_0,m_0}(O) + o_P(n^{-1/2}), \]

completing the proof of the lemma.
D Simulation Results

Figure 5: Simulation Results: bias, variance, and mean squared error for $\delta = 0$. 

| Scenario A | Scenario B | Scenario C | Scenario D |
|------------|------------|------------|------------|
| $|\text{Bias}|$ | $n^{1/2}|\text{Bias}|$ | $n^{1/2}\text{sd}(\hat{\theta})$ | $(n\text{MSE})^{1/2}$ |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

- Scenario A
- Scenario B
- Scenario C
- Scenario D

Legend:
- $\diamondsuit$ AIPW
- $\triangle$ TMLE
- $\ast$ e-TMLE
- $\ast$ e-TMLE-al

Figure 5: Simulation Results: bias, variance, and mean squared error for $\delta = 0$. 
Figure 6: Simulation Results: variance estimation and coverage probabilities for $\delta = 0$. 