Empirical Likelihood Inference in Randomized Controlled Trials with High-Dimensional Covariates

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Abstract

In this paper, we propose a data-adaptive empirical likelihood approach for treatment effect inference, which overcomes the obstacle of the traditional empirical likelihood approaches in the high-dimensional setting by adopting penalized regression and machine learning methods to model the covariate-outcome relationship. In particular, we show that our procedure successfully recovers the true variance of Zhang’s treatment effect estimator (Zhang, 2018) by utilizing a data-splitting technique. Our proposed estimator is proved to be asymptotically normal and semiparametric efficient under mild regularity conditions. Simulation studies indicate that our estimator is more efficient than the estimator proposed by Wager et al. (2016) when random forest is employed to model the covariate-outcome relationship. Moreover, when multiple machine learning models are imposed, our estimator is at least as efficient as any regular estimator with a single machine learning model. We compare our method to existing ones using the ACTG175 data and the GSE118657 data, and confirm the outstanding performance of our approach.

1 Introduction

Randomized controlled trials (RCTs) are recognized as the standard clinical design to eliminate sources of confounding bias. When the outcome of interest is a continuous variable, the difference of mean responses in the treated and controlled groups is an unbiased and consistent estimator for the average treatment effect (ATE), a commonly used estimand to evaluate the effect of a treatment or policy. When the baseline information is involved before receiving the treatment, such as age, sex,

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and other characteristics, adjusting for the pre-treatment covariates helps to improve the efficiency of the ATE estimator.

The key of covariate adjustment is to explore the relationship between the auxiliary covariates and response. Analysis of covariance (ANCOVA) is a classical regression method for covariate adjustment where a linear regression model for \(E[Y|X,D]\) is postulated, i.e.,

\[
E[Y|X,D] = \beta_0 + \beta_d X + \beta_d D. \tag{1}
\]

Here, \(Y\) is the outcome variable, \(X\) is the vector of covariates and \(D\) is the binary treatment indicator variable. The parameter of interest, the unconditional population-level treatment effect, is \(\beta_d\). Consequently, we can make inference about ATE based on the asymptotic normality of the least square estimator \(\hat{\beta}_{d\text{ols}}\) (Imbens and Rubin, 2015). It follows from Leon et al. (2003) and Tsiatis et al. (2008) that \(\hat{\beta}_{d\text{ols}}\) belongs to the class of all regular and asymptotically linear estimators, and more efficient estimators in this class can be obtained by positing two separate working regression models for \(\eta^{(1)}(x) = E[Y|X = x, D = 1]\) and \(\eta^{(0)}(x) = E[Y|X = x, D = 0]\), respectively.

Empirical likelihood (EL) is an alternative way to carry out covariate adjustment. EL is introduced by Owen (Owen, 1988, 1990, 2001) and primarily used to construct confidence intervals for the mean or parameters in the general estimating functions (Qin and Lawless, 1994). It has also been adopted as a tool to efficiently incorporate information of auxiliary covariates in causal inference problems (Huang et al., 2008; Qin and Zhang, 2007). In particular, when multiple parametric regression models are imposed into constraints, the EL estimator has good performance as long as one of multiple models correctly specifies the covariate-outcome relationship without requiring the knowledge of which model is correct. This is known as the multiple robustness property (Han and Wang, 2013). Recently, Zhang (2018) and Tan et al. (2020) extend EL for statistical inference of ATE in RCTs. As shown in their simulation studies, both Zhang and Tan’s EL estimators are considerably more efficient than the estimator of Tsiatis et al. (2008) when the imposed parametric regression model is misspecified.

In practice, the true covariate-outcome model is unknown, which can be much more complicated than a simple linear combination of several variables in equation (1). Furthermore, in the big data era, the number of features may be high-dimensional, where ANCOVA and other traditional methods
are no longer directly applicable. It inspires us to model the highly complex covariate-outcome relationship by modern machine learning (ML) methods, such as Lasso (Tibshirani, 1996), SCAD (Fan and Li, 2001), and random forests (Breiman, 2001). A general semiparametric framework for the statistical inference of treatment effects under which infinite-dimensional nuisance parameters are modelled with ML methods is given by Chernozhukov et al. (2018) and Belloni et al. (2017), where two crucial points are presented:

1. They use Neyman orthogonal scores to remove the bias brought by regularization.
2. They split data to avoid overfitting.

Specifically, the Neyman orthogonal scores technique adjusts for the effect of covariates to reduce sensitivity with respect to the nuisance parameters, and thus promotes the efficiency of treatment effect estimation. It is straightforward to show that the score function developed by Tsiatis et al. (2008) is Neyman orthogonal. With an additional data-splitting procedure, Wager et al. (2016) generalize the results of Tsiatis et al. (2008) to the high-dimensional setting and adopt ML methods to model the covariate-outcome relationship. Under mild regularity conditions, they derive valid inference of ATE due to the data-splitting procedure.

EL and Neyman orthogonal scores play similar roles in RCTs as they both achieve the goal of efficiency improvement of treatment effect estimation by incorporating information of auxiliary covariates. However, the estimator proposed by Wager and his colleagues does not enjoy some unique properties of EL, e.g., multiple robustness. When the single ML algorithm adopted by Wager et al. (2016) does not successfully capture the covariate-outcome relationship, their ATE estimation may incur efficiency loss. We are motivated to propose a Machine Learning and Data-splitting based Empirical Likelihood (MDEL) approach to estimate ATE, where we apply multiple ML algorithms to model the covariate-outcome relationship. Compared with the regression adjustment approach of Wager et al. (2016), our proposed EL approach has the following advantages:

1. When the single ML estimator of nuisance parameters does not perform well, our proposed EL estimator is more efficient, as indicated by our simulation studies.
2. Different estimators of the nuisance parameters can be imposed simultaneously into constraints to enhance the performance of our estimator. Our simulation studies indicate that our EL
estimator with multiple models tends to perform as good as that with the correct model without requiring the knowledge of which model is correct.

Our paper is organized as follows. In section 2 we give a brief introduction to our concerning problems and notations. In addition, we review the semiparametric method proposed by Wager et al. (2016). In section 3, we introduce our proposed empirical likelihood approach. Then we discuss the practical implementation of our EL approach in section 4. In section 5, we compare our proposed EL approach to the existing ones in extensive simulation studies, the ACTG175 data set and the GSE118657 data set.

2 Notation and Review of Semiparametric Inference

Define a binary treatment indicator variable $D \in \{0,1\}$, with value equals to 1 if a unit receives treatment and 0 otherwise. Let $Y$ be the outcome variable, $X$ be the vector of covariates, and $p$ be the dimension of $X$. The estimand of interest is the population-level ATE, defined by $\theta = E[Y|D = 1] - E[Y|D = 0]$. Suppose we observe $n$ independent and identically distributed observations $\{W_i = (Y_i, X_i, D_i), i = 1, \cdots, n\}$ from $W = (Y, X, D)$. The observed outcome of the $i$-th unit, $Y_i$, satisfies $Y_i = D_iY_i(1) + (1 - D_i)Y_i(0)$, where $Y_i(d)$ is the potential outcome of the $i$-th unit under treatment $d \in \{0,1\}$. Since a unit could receive either the treatment or the placebo but not both, we can not simultaneously obtain $Y_i(1)$ and $Y_i(0)$. In this paper, we focus on randomized controlled trials, where $D_i$ is randomly assigned to either 0 or 1 and is independent of all pre-treatment variables and the potential outcomes, i.e.,

$$D_i \perp \{Y_i(1), Y_i(0), X_i\} \quad \text{for} \quad i = 1, \cdots, n.$$ 

Let $n_1 = \sum_{i=1}^{n} D_i$ be the size of the treated group and $n_0 = n - n_1$ be the size of the controlled group. In RCTs, a commonly used consistent estimator of ATE is the difference in the means, defined by

$$\hat{\theta}_{dim} = \bar{Y}^{(1)} - \bar{Y}^{(0)} = \frac{\sum_{i=1}^{n} D_i Y_i}{n_1} - \frac{\sum_{i=1}^{n} (1 - D_i) Y_i}{n_0}.$$ 

However, $\hat{\theta}_{dim}$ ignores information of covariates and thus loses efficiency. Tsiatis et al. (2008) incorporate covariates by modelling the covariate-outcome relationships, $\eta^{(d)}(x) = E[Y|D = d, X = x]$. 

For fixed \( x, d = 0, 1 \), and their estimator of \( \theta \) is

\[
\hat{\theta}_{\text{tdal}} = Y^{(1)} - Y^{(0)} - \sum_{i=1}^{n} \left( D_i - \frac{n_1}{n} \right) \left( n_0^{-1} f_0(X_i, \hat{\alpha}_0) + n_1^{-1} f_1(X_i, \hat{\alpha}_1) \right),
\]

where \( f_d(x, \alpha_d), d = 0, 1 \), are the postulated parametric models for \( \eta^{(0)}(x) \) and \( \eta^{(1)}(x) \), and \( \hat{\alpha}_d, d = 0, 1 \), are estimators of \( \alpha_0 \) and \( \alpha_1 \), respectively. Let \( \delta = P(D = 1) \) be the probability of a unit being assigned to the treatment group in RCTs. Write \( \hat{f}_d(\cdot) = f(\cdot, \hat{\alpha}_d), d = 0, 1 \). The efficient score of \( \theta \) is given by

\[
\varphi(W, \theta, \delta, \eta^{(1)}, \eta^{(0)}) = \frac{D}{\delta} \left( Y - \eta^{(1)}(X) \right) - \frac{1 - D}{1 - \delta} \left( Y - \eta^{(0)}(X) \right) + \eta^{(1)}(X) - \eta^{(0)}(X) - \theta.
\]

Here, \( \eta^{(1)} \) and \( \eta^{(2)} \) are treated as nuisance parameters, and \( \theta \) is the parameter of interest. \( \hat{\theta}_{\text{tdal}} \) can be reformulated as the solution of

\[
\frac{1}{n} \sum_{i=1}^{n} \varphi(W_i, \theta, \delta = \frac{n_1}{n}, \hat{f}_1, \hat{f}_0) = 0.
\]

Let \( I = \{1, \cdots, n\} \) be the sample index set, \( I^{(1)} \) and \( I^{(0)} \) be the index set of the treatment group and placebo group, respectively. We use the notation \( |A| \) as the size of a set \( A \). Suppose we randomly partition \( I^{(d)} \) into \( K \) subsets, denoted by \( (I_{k}^{(d)})_{k=1}^{K} \), for \( d = 0, 1 \). Let \( I_{k} = I_{k}^{(1)} \cup I_{k}^{(0)}, I_{k}^{(d) c} = I^{(d)} \setminus I_{k} \) and \( I_{k}^{c} = I \setminus I_{k} \). Generally, we set \( |I_{k}^{(d)}| = \frac{n}{n} \) and \( |I_{k}^{(d) c}| = \frac{K}{K} \).

When the dimension of covariates is high, traditional parametric models for \( \eta^{(d)} \) are no longer directly applicable. Modern ML methods, such as Lasso and random forests, are suitable to model the complex nuisance parameters. After data-splitting, Wager et al. (2016) propose to estimate \( \theta \) with \( \hat{\theta}_{\text{wddt}} = \frac{1}{K} \sum_{k=1}^{K} \hat{\theta}_{\text{wddt}}^{(k)} \), where the \( k \)-th sub-estimator, \( \hat{\theta}_{\text{wddt}}^{(k)} \), is the solution of

\[
\frac{1}{|I_{k}|} \sum_{i \in I_{k}} \varphi(W_i, \theta, \delta = \frac{|I_{k}^{(1)}|}{|I_{k}|}, \hat{\eta}_{k}^{(1)}, \hat{\eta}_{k}^{(0)}) = 0.
\]

For fixed \( k \) and \( d \), \( \hat{\eta}_{k}^{(d)} \) is a ML estimator of \( \eta^{(d)} \) obtained via sample \( (W_i)_{i \in I_{k}^{(d) c}} = \{W_i|i \in I_{k}^{(d) c}\} \). It follows immediately that conditional on sample \( (W_i)_{i \in I_{k}^{(d) c}}, \hat{\eta}_{k}^{(d)}(x) \) is a non-random function of
Therefore, the variance of $\hat{\theta}_{\text{tdsl}}$ can be directly estimated by

$$\widehat{\text{Var}}(\hat{\theta}_{\text{tdsl}}) = \sum_{k=1}^{K} \frac{|I_k|^2}{n^2} \text{Var}(\hat{\theta}_{\text{tdsl}}^k),$$

where for a fixed $k$, $\text{Var}(\hat{\theta}_{\text{tdsl}}^k)$ is a moment-based plug-in variance estimator for the conditional variance of $\hat{\theta}_{\text{tdsl}}^k$.

Wager et al. (2016) demonstrate that $\frac{(\hat{\theta}_{\text{tdsl}} - \theta)}{\sqrt{\text{Var}(\hat{\theta}_{\text{tdsl}})}}$ is asymptotically standard normal under certain regularity conditions. Therefore, for statistical inference, the corresponding $1 - \alpha$ confidence interval for $\theta$ is given by

$$\left(\hat{\theta}_{\text{tdsl}} - z_{\frac{\alpha}{2}} \sqrt{\widehat{\text{Var}}(\hat{\theta}_{\text{tdsl}})}, \hat{\theta}_{\text{tdsl}} + z_{\frac{\alpha}{2}} \sqrt{\widehat{\text{Var}}(\hat{\theta}_{\text{tdsl}})}\right),$$

where $z_{\frac{\alpha}{2}}$ is the upper quantile of the standard normal distribution.

### 3 Empirical Likelihood Inference in RCTs

#### 3.1 Traditional EL Approaches in RCTs

Let $f(x) = (f_1(x), f_0(x))^\tau$ be a vector function of $x$ and $\xi = E[f(X)]$. Based on two unbiased estimating functions

$$h_1(D, Y, \theta, \delta) = \frac{DY}{\delta} - \frac{(1 - D)Y}{1 - \delta} - \theta$$

and

$$h_2(D, X, \delta, f, \xi) = \frac{D - \delta}{\delta(1 - \delta)} \{f(X) - \xi\},$$

Zhang (2018) proposes to estimate $\theta$ by maximizing the nonparametric likelihood $L_F = \prod_{i=1}^{n} p_i$ subject to constraints $\sum_{i=1}^{n} p_i = 1, p_i \geq 0$ and $\sum_{i=1}^{n} p_i \left(h_1(D_i, Y_i, \theta, \delta), h_2(D_i, X_i, \delta, f, \xi)\right) = 0$, where

$$\hat{\delta} = \frac{m}{n}, \hat{\xi} = \frac{1}{n} \sum_{i=1}^{n} \hat{f}(X_i), \hat{f} = (\hat{f}_1, \hat{f}_0)^\tau,$$

and $\hat{f}_1$ and $\hat{f}_0$ are estimated working regression models for $\eta^{(1)}$ and $\eta^{(0)}$, respectively. The variance of $\hat{\theta}_{\text{Zhang}}$ is estimated by a sandwich variance estimator.

When the covariates are of low-dimension, where $\hat{f}_d$ is an estimated parametric regression model for $\eta^{(d)}$, $\hat{\theta}_{\text{Zhang}}$ is more efficient than the semiparametric estimator $\hat{\theta}_{\text{tdsl}}$ as suggested by Zhang’s simulation studies. However, when the covariates are of high-dimension and $\hat{f}_d$ is an ML estimator
for model selection, many spurious variables which have high correlations with the response but do not belong to the true feature set will be selected and thus result in serious underestimation of the variance (Fan et al., 2012). We conduct simulations to illustrate this point in Section 3.3.

Tan et al. (2020) extend the two-sample EL approach of Wu and Yan (2012) and propose to estimate $\theta$ based on the property

$$E[f(X) - \xi|D = d] = 0.$$ 

Their estimator is $\hat{\theta}_{\text{Tan}} = \sum_{i \in I^{(1)}} \hat{p}_i Y_i - \sum_{i \in I^{(0)}} \hat{p}_i Y_i$, where $\hat{p}_i, i \in \llbracket d \rrbracket$ are obtained by maximizing the nonparametric likelihood $L_{F} = \prod_{i \in \llbracket d \rrbracket} p_i$ subject to constraints $\sum_{i \in \llbracket d \rrbracket} p_i = 1, p_i \geq 0$ and $\sum_{i \in \llbracket d \rrbracket} p_i \hat{f}_d(X_i) = \frac{1}{n} \sum_{j=1}^{n} \hat{f}_d(X_j)$. Here $\hat{f}_d(x)$ is a guess of $E[Y|X = x, D = d]$. Multiple guesses are allowed in Tan’s method. Estimation for the variance of $\hat{\theta}_{\text{Tan}}$ is given by the bootstrap method.

Tan’s approach is simple and easy to explain. Asymptotic theory and simulation studies of Tan et al. (2020) verify its multiple robustness, which means that the estimator achieves the semiparametric efficiency bound as long as one model of $f_d$ is correctly specified. However, when $\hat{f}_d$ involves ML estimators, their proposed bootstrap re-sampling procedure is no longer applicable as Donsker conditions are inappropriate when the space of $\hat{f}_d$ is highly complicated.

As we can see, both EL approaches in RCTs have desirable properties in the low-dimensional setting but fail to make valid inference in the high-dimensional setting. To maintain multiple robustness and other ideal properties of EL estimators, as well as to overcome the invalid inference problem of traditional EL approaches, we are motivated to extend the approach of Tan et al. (2020), which is very simple to implement, to RCTs with high-dimensional covariates by means of machine learning and data-splitting.

3.2 The Proposed EL Approach

In our proposed approach, the nuisance parameters are allowed to be estimated using multiple ML methods. For $d = 0, 1$, assume we already have an $r$-dimensional vector of estimators of $\eta^{(d)}$, denoted as $\hat{\eta}^{(d)} = (\hat{\eta}_{d,1}^{(d)}, \ldots, \hat{\eta}_{d,r}^{(d)})^\top$, where each component of $\hat{\eta}^{(d)}$ is an ML estimator such as the random forests estimator or Lasso estimator of $\eta^{(d)}$ based on the sub-sample $(W_i)_{i \in \llbracket d \rrbracket}$. Let
\[ \hat{\xi}^{(d)} = \frac{1}{n} \sum_{k=1}^{K} \sum_{i \in \mathcal{I}_k} \hat{g}^{(d)}_k (X_i) \quad \text{and} \quad \hat{\xi}^{(d)} = \frac{1}{|\mathcal{I}|} \sum_{i \in \mathcal{I}} \hat{g}^{(d)}_i (X_i) \quad \text{for} \quad k = 1, \cdots, K \quad \text{and} \quad d = 0, 1. \]

It is easy to check that \( \hat{\xi}^{(d)} = \frac{1}{K} \sum_{k=1}^{K} \hat{\xi}^{(d)}_k \). Due to randomization, we have

\[ E \left[ \hat{\xi}^{(d)}_k (X) \mid D = d, (W_i)_{i \in \mathcal{I}_k^{(d)}} \right] = E \left[ \hat{\xi}^{(d)}_k (X) \mid (W_i)_{i \in \mathcal{I}_k^{(d)}} \right], \]

for \( k = 1, \cdots, K \) and \( d = 0, 1 \), which leads to

\[ \sum_{k=1}^{K} E \left[ \hat{\xi}^{(d)}_k (X) \mid D = d, (W_i)_{i \in \mathcal{I}_k^{(d)}} \right] = \sum_{k=1}^{K} E \left[ \hat{\xi}^{(d)}_k (X) \mid (W_i)_{i \in \mathcal{I}_k^{(d)}} \right] \]

for \( d = 0, 1 \). Consequently, we calculate empirical probability mass, \( \hat{p}_i \), for each data point \( W_i \) by maximizing the nonparametric likelihood \( L = \prod_{i=1}^{n} p_i \) subject to the following constraints:

\[ \sum_{i \in \mathcal{I}^{(d)}} p_i = 1, \quad d = 0, 1, \quad p_i \geq 0, \quad \forall i \in \mathcal{I}, \]

\[ \sum_{k=1}^{K} \sum_{i \in \mathcal{I}_k^{(d)}} p_i \hat{g}^{(d)}_k (X_i) = \frac{1}{K} \sum_{k=1}^{K} \hat{\xi}^{(d)}_k, \quad d = 0, 1. \]

Solving (2) is equivalent to solving two separated minimization problems:

\[
\min_{\hat{p}_i} - \sum_{i \in \mathcal{I}^{(d)}} \log(\hat{p}_i) \\
\text{s.t.} \sum_{i \in \mathcal{I}^{(d)}} p_i = 1, \quad p_i \geq 0, \quad i \in \mathcal{I}^{(d)},
\]

\[
\sum_{k=1}^{K} \sum_{i \in \mathcal{I}_k^{(d)}} p_i \left( \hat{g}^{(d)}_k (X_i) - \hat{\xi}^{(d)}_k \right) = 0.
\]

for \( d = 0, 1 \). Let \( \hat{G} \left( x, \hat{g}^{(d)}_k, \hat{\xi}^{(d)} \right) = \hat{g}^{(d)}_k (x) - \hat{\xi}^{(d)} \). The Lagrange multiplier method shows that the dual problem of (3) is

\[
\max_{\lambda_d} \ell(\lambda_d) : \quad \ell(\lambda_d) = - \sum_{k=1}^{K} \sum_{i \in \mathcal{I}_k^{(d)}} \log \left\{ 1 + \lambda_d \hat{G} \left( X_i, \hat{g}^{(d)}_k, \hat{\xi}^{(d)} \right) \right\} - n_d \log n_d
\]

\[ (4) \]
\[
\hat{p}_i = \left\{ n_d \left( 1 + \lambda_{d} \hat{G} \left( X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)} \right) \right) \right\}^{-1} \text{ for } i \in \mathbb{I}_k^{(d)}, \quad k = 1, \ldots, K,
\]

where \( \lambda_d \) is the solution of (4). Simple calculation reveals that \( \hat{\lambda}_d \) is determined by

\[
\frac{1}{n_d} \sum_{k=1}^{K} \sum_{i \in \mathbb{I}_k^{(d)}} \frac{\hat{G} \left( X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)} \right)}{1 + \lambda_{d} \hat{G} \left( X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)} \right)} = 0.
\]

(5)

Our proposed Machine learning and Data-splitting based Empirical Likelihood (MDEL) estimator for \( \theta \) is

\[
\hat{\theta}_{\text{mdel}} = \hat{\theta}_{\text{mdel}}^{(1)} - \hat{\theta}_{\text{mdel}}^{(0)} = \sum_{i=1}^{n} D_i \hat{p}_i Y_i - \sum_{i=1}^{n} (1 - D_i) \hat{p}_i Y_i.
\]

In the following theorem, we show that our proposed estimator with a single covariate-outcome model is asymptotically normal and semiparametric efficient under certain regularity conditions.

**Theorem 1.** Under regularity conditions (A1)-(A5) in the Appendix, if \( r = 1 \) and

\[
E \left[ \left( \hat{g}_k^{(d)} (X) - \eta^{(d)} (X) \right)^2 \left| \mathbb{W}_i \right. \right]_{i \in \mathbb{I}_k^{(d)c}} \to 0
\]

in probability as \( n \to \infty \) for \( k = 1, \ldots, K \) and \( d = 0, 1 \), \( \hat{\theta}_{\text{mdel}} \) is asymptotically normal with the efficient influence function

\[
\varphi(W, \theta, \delta; \eta^{(1)}, \eta^{(0)}) = \frac{D}{\delta} \left( Y - \eta^{(1)} (X) \right) - \frac{1 - D}{1 - \delta} \left( Y - \eta^{(0)} (X) \right) + \eta^{(1)} (X) - \eta^{(0)} (X) - \theta.
\]

Therefore, \( \hat{\theta}_{\text{mdel}} \) achieves the semiparametric efficiency bound.

Note that the condition, \( E \left[ \left( \hat{g}_k^{(d)} (X) - \eta^{(d)} (X) \right)^2 \left| \mathbb{W}_i \right. \right]_{i \in \mathbb{I}_k^{(d)c}} \to 0 \) in probability as \( n \to \infty \), called “risk consistency” in Wager et al. (2016), is mild for many ML methods when sufficient sparsity is satisfied. When \( r > 1 \), i.e., multiple models are imposed to estimate nuisance parameters, we expect that Theorem 1 still holds when any one of estimators for nuisance parameters satisfies “risk consistency” condition. Moreover, we expect that the convergence rate of the estimator with multiple models is identical to that with the oracle model. However, the asymptotic theory requires further complicated assumptions about the structure of covariates such that the weak law of large
numbers can be applied to dependent terms, and we remain it as future work. Instead, we use simulation studies in Section 5 to show that our proposed estimator attains multiple robustness property and is approximately normally distributed with reasonable coverage rates.

### 3.3 Variance Recovery for Valid Inference

Based on the decomposition of \( \tilde{\theta}_{\text{sel}} \) in the Appendix, we propose to estimate the variance of \( \hat{\theta}_{\text{mdel}} \) with

\[
\hat{\sigma}_{\text{mdel}}^2 = \frac{1}{n} \sum_{d=0,1} \sum_{k=1}^{K} \sum_{i \in I^*(d)} \frac{n_d}{n} \hat{p}_i \left\{ \frac{n}{n_1} D_i (Y_i - \tilde{\theta}_{\text{mdel}}^{(1)}) - \frac{n}{n_1} (D_i - \frac{n_1}{n}) \hat{J}_n^{(1)} \hat{S}_n^{(1)-1} G \left( X_i, \hat{\eta}_k^{(1)}, \hat{\xi}^{(1)} \right) - \right.
\]
\[
\frac{n}{n_0} (1 - D_i) (Y_i - \tilde{\theta}_{\text{mdel}}^{(0)}) + \frac{n}{n_0} (D_i - \frac{n_1}{n}) \hat{J}_n^{(0)} \hat{S}_n^{(0)-1} G \left( X_i, \hat{\eta}_k^{(0)}, \hat{\xi}^{(0)} \right) \left. \right\}^2,
\]

where

\[
\hat{J}_{n}^{(d)} = \sum_{k=1}^{K} \sum_{i \in I^*(d)} \hat{p}_i Y_i \hat{G} \left( X_i, \hat{\eta}_k^{(d)}, \hat{\xi}^{(d)} \right),
\]
\[
\hat{S}_{n}^{(d)} = \sum_{v \in \{0,1\}} \sum_{k=1}^{K} \sum_{i \in I^*(v)} \frac{n_v}{n} \hat{p}_i \hat{G} \left( X_i, \hat{\eta}_k^{(d)}, \hat{\xi}^{(d)} \right) \hat{G} \left( X_i, \hat{\eta}_k^{(d)}, \hat{\xi}^{(d)} \right)^T,
\]

for \( d = 0, 1 \). In the following theorem, we prove that the variance estimator of our EL approach converges to the true variance asymptotically. That is, our variance estimator successfully recovers the true variance.

**Theorem 2.** Under the assumptions and regularity conditions of Theorem 1, we have

\[
\hat{\sigma}_{\text{mdel}}^2 \to \text{Var} \left[ \varphi(W, \theta, \eta^{(1)}, \eta^{(0)}) \right]
\]

in probability as \( n \to \infty \).

**Corollary 3.** Under the assumptions and regularity conditions of Theorem 1, \( (\hat{\sigma}_{\text{mdel}})^{-1} (\tilde{\theta}_{\text{mdel}} - \theta) \) is asymptotically standard normal.
Corollary 3 leads to a $100(1 - \alpha)\%$ Wald confidence interval of $\theta$:

$$CI := \left( \hat{\theta}_{\text{mde}} - z_{\alpha/2} \hat{\sigma}_{\text{mde}}, \quad \hat{\theta}_{\text{mde}} + z_{\alpha/2} \hat{\sigma}_{\text{mde}} \right),$$

where $z_{\alpha/2}$ is the upper quantile of the standard normal distribution.

As we mentioned in Section 3.1, Zhang’s approach with the covariate-outcome relationship estimated by an ML method seriously underestimates the variance. In contrast, our proposed EL approach recovers the true variance. To illustrate this point, we conduct a simulation study following the setting of Wager et al. (2016). The setting is a special case of the simulation studies in Section 5.3 with coefficients equal to $(1, 0, \cdots, 0)$ or a permutation of $(1, \frac{1}{2}, \cdots, \frac{1}{p})$. And for both Zhang’s and our proposed MDEL approach, the covariate-outcome relationship is modelled by Lasso.

![Figure 1: Simulation results based on 500 Monte Carlo replications with $\beta^{(1)} = \beta^{(0)} = (1, 0, \cdots, 0)$, $p = 500$, $\rho = 0$, $\delta = 0.5$ and sample size $n$ ranging from 100 to 500 under a simple setting described in section 5.3. In the left panel, solid lines depict the mean-squared lengths of 95% Wald confidence intervals and dashed-dotted lines depict the mean squared lengths of 99% Wald confidence intervals. In the right panel, solid lines depict coverage proportions of 95% Wald confidence intervals that cover the true $\theta$ and dashed lines depict coverage proportions of 99% Wald confidence intervals that cover the true $\theta$.](attachment:Figure1.png)
In Figure 1, where the true signal is very sparse, the 95% confidence intervals and 99% confidence intervals of our EL approach are shorter than the corresponding confidence intervals based on \( \hat{\theta}_{\text{dim}} \). The coverage probability of the 95% or 99% confidence intervals of Zhang’s EL approach is substantially lower than the true level for \( n = 100, 200 \). In contrast, the coverage probability of our EL approach resembles the nominal level for any sample size.

In Figure 2, where the true signal is geometric, the 95% confidence intervals and 99% confidence intervals of our EL approach are still shorter than the corresponding ones based on \( \hat{\theta}_{\text{dim}} \). The coverage probability of the 95% or 99% confidence intervals of Zhang’s approach is significantly below the nominal level for \( n \) ranging from 100 to 500. In contrast, the coverage probability of our EL approach are very close to the nominal level for any sample size.

In summary, when the true signal is either \((1,0,\cdots,0)\) or a permutation of \((\frac{1}{2}, \frac{1}{2}, \cdots, \frac{1}{p})\), Zhang’s approach is not desirable as his proposed confidence intervals fail to cover \( \theta \) in reasonable proportions whereas our approach recovers true variance and the coverage probabilities are close to the nominal levels.
4 Practical Implementations

In our simulation studies and real data analysis, we utilize three popular ML methods to estimate $\eta^{(d)}$. One is Lasso (Tibshirani, 1996) and the second one is SCAD (Fan and Li, 2001). Lasso and SCAD are both penalized regression methods. Generally, they both lead to sparse solutions and thus work well for variable selection purpose. However, compared with Lasso, large coefficients would not be shrunken by SCAD and some small coefficients cannot survive after punishment. Therefore, SCAD works better for models with strong and sparse signals. The third method we use is random forests (Breiman, 2001), which are increasingly popular in recent years because of its flexibility and outstanding prediction ability for real complex data.

For Lasso, the penalty parameter $\lambda$ is determined by cross-validation criterion using \texttt{cv.glmnet} in R-package \texttt{glmnet} with 10-folds in this paper. For SCAD, the first tuning parameter $a$ is chosen to be default 3.7 and penalty parameter $\lambda$ is determined by cross-validation criterion using \texttt{cv.ncvreg} in R-package \texttt{ncvreg} with 10-folds. For random forests, we build 500 regression trees using \texttt{ranger} in R-package \texttt{ranger}, a fast implementation of random forests for high dimensional data in C++ and R, with parameters set to be default.

To solve the aforementioned optimization problems of our MDEL approach, we carry out a modified Newton-Raphson algorithm with details extensively discussed in Wu (2004).

5 Real Data Analysis and Simulations

5.1 Analysis of ACTG 175 Data Set

In this section, we apply our proposed MDEL method to data from 2139 HIV-infected patients enrolled in AIDS Clinical Trials Group Protocol 175 (ACTG175) (Hammer et al., 1996). It is a double-blinded randomized experiment which was designed to study the treatment of patients receiving 3 different drugs and their combinations. Patients whose CD4 cell counts from 200 to 500 per cubic millimeter were randomly assigned to different antiretroviral regimens: zidovudine (ZDV) monotherapy, ZDV + didanosine (ddI), ZDV + zalcitabine, and ddI monotherapy. We follow the work of Tsiatis et al. (2008), Huang et al. (2008), and Zhang (2018), where two treatment groups are considered: patients who received ZDV monotherapy alone, with $n_0 = 532$ and patients who received
either ZDV + ddI, or ZDV + zalcitabine, or ddI alone, with \( n_1 = 1607 \). Pre-treatment baseline co-
variates are 5 continuous variables: \( cd40 = \text{CD4 count (cells/mm}^3\text{)}, \ cd80 = \text{CD8 count (cells/mm}^3\text{)}, \ age = \text{age (years)}, \ wtkg = \text{weight (kg)}, \ karnof = \text{Karnofsky score (scale of 0-100)}, \) and 7 seven bi-
nary variables: \( \text{hemo = hemophilia, homo = homosexual activity, drug = history of intravenous} \)
drug use, \( \text{race = race (0=white, 1=nonwhite), gender = gender (0=female), str2 = antiretroviral} \)
history (0=naive, 1=experienced), and \( \text{symp = symptomatic status (0=asymptomatic).} \)

In the previous work of Tsiatis et al. (2008), Zhang (2018), and Tan et al. (2020), Forward-
1, a forward step-wise regression model allowing for linear terms of covariates, and Forward-
2, a forward ste-pwise regression model allowing for linear, quadratic and interaction terms of baseline
variables, are adopted. Our proposed MDEL approach enables us to consider a much richer feature
set. Therefore, we take linear and quadratic terms of continuous variables, linear and interaction
terms of binary variables, and interaction terms of above two sets of coordinates as our final feature
set, i.e.,

\[
\mathcal{F}_{\text{ACTG175}} = \left\{ (cd40+cd80+age+wtkg+karnof+1)^2 \times ((\text{hemo+}\text{homo+drug+race+gender} +\text{str2+symp+1})^2 - \text{hemo}^2 - \text{homo}^2 - \text{drug}^2 - \text{race}^2 - \text{gender}^2 - \text{str}^2 - \text{symp}^2) \right\}.
\]

This leads to 608 explanatory variables (excluding the intercept) and we adopt Lasso, SCAD, and
random forests to estimate the variable-outcome relationship using this feature set. Table 1 displays
the estimates, standard errors, and confidence intervals of our proposed approach and some existing
approaches described in Section 2 and 3.

In practice, \( \hat{\theta}_{\text{mde}}(\text{ML}) \) denotes the point estimator of our MDEL approach, where the choices
of ML include LASSO, SCAD, RF, and MULTI. Here, RF indicates the random forests method,
and MULTI means we make use of multiple ML methods (LASSO, SCAD, and RF) in our MDEL
method.
Table 1: Point and interval estimates of $\theta$ for ACTG 175 data.

| Estimator   | Estimate | SE  | Relative Efficiency | 95% Confidence Interval | 99% Confidence Interval |
|-------------|----------|-----|---------------------|-------------------------|-------------------------|
| $\hat{\theta}_{\text{dim}}$ | 46.811   | 6.760| 1.000               | (33.56, 60.06)          | (29.40, 64.22)          |
| $\hat{\theta}_{\text{tdzl}}$ (Forward-1) | 49.896   | 5.139| 1.738               | (39.82, 59.97)          | (36.66, 63.13)          |
| $\hat{\theta}_{\text{tdzl}}$ (Forward-2) | 51.589   | 5.070| 1.797               | (41.65, 61.53)          | (38.53, 64.65)          |
| $\hat{\theta}_{\text{Zhang}}$ (Forward-1) | 49.872   | 5.128| 1.738               | (39.82, 59.92)          | (36.66, 63.08)          |
| $\hat{\theta}_{\text{Zhang}}$ (Forward-2) | 51.395   | 5.028| 1.808               | (41.54, 61.25)          | (38.44, 64.34)          |
| $\hat{\theta}_{\text{wdtt}}$ (LASSO) | 49.785   | 5.233| 1.669               | (39.53, 60.04)          | (36.31, 63.26)          |
| $\hat{\theta}_{\text{wdtt}}$ (SCAD) | 49.991   | 5.210| 1.684               | (39.78, 60.20)          | (36.54, 63.33)          |
| $\hat{\theta}_{\text{wdtt}}$ (RF) | 53.442   | 5.197| 1.692               | (43.15, 63.74)          | (39.91, 66.97)          |
| $\hat{\theta}_{\text{wdtt}}$ (MULTI) | 50.396   | 5.150| 1.723               | (40.30, 60.49)          | (37.13, 63.66)          |

Table 1: Point and interval estimates of $\theta$ for ACTG 175 data. (continued)

| Estimator   | Estimate | SE  | Relative Efficiency | 95% Confidence Interval | 99% Confidence Interval |
|-------------|----------|-----|---------------------|-------------------------|-------------------------|
| $\hat{\theta}_{\text{dim}}$ | 46.811   | 6.760| 1.000               | (33.56, 60.06)          | (29.40, 64.22)          |
| $\hat{\theta}_{\text{tdzl}}$ (Forward-1) | 49.896   | 5.139| 1.738               | (39.82, 59.97)          | (36.66, 63.13)          |
| $\hat{\theta}_{\text{tdzl}}$ (Forward-2) | 51.589   | 5.070| 1.797               | (41.65, 61.53)          | (38.53, 64.65)          |
| $\hat{\theta}_{\text{Zhang}}$ (Forward-1) | 49.872   | 5.128| 1.738               | (39.82, 59.92)          | (36.66, 63.08)          |
| $\hat{\theta}_{\text{Zhang}}$ (Forward-2) | 51.395   | 5.028| 1.808               | (41.54, 61.25)          | (38.44, 64.34)          |
| $\hat{\theta}_{\text{wdtt}}$ (LASSO) | 49.785   | 5.233| 1.669               | (39.53, 60.04)          | (36.31, 63.26)          |
| $\hat{\theta}_{\text{wdtt}}$ (SCAD) | 49.991   | 5.210| 1.684               | (39.78, 60.20)          | (36.54, 63.33)          |
| $\hat{\theta}_{\text{wdtt}}$ (RF) | 53.442   | 5.197| 1.692               | (43.15, 63.74)          | (39.91, 66.97)          |
| $\hat{\theta}_{\text{wdtt}}$ (MULTI) | 50.396   | 5.150| 1.723               | (40.30, 60.49)          | (37.13, 63.66)          |

SE = standard error, Relative Efficiency = $(\text{SE}^2$ of corresponding estimator)/$(\text{SE}^2$ of $\hat{\theta}_{\text{dim}}$).

For inference on $\theta$, both 95% and 99% Wald confidence intervals are provided. The results of Table 1 give us strong evidence to reject the null hypothesis that there is no difference in treatment effect between two groups with different therapies. It is worth to note that, despite a much richer feature set with $p = 608$ variables is considered, our proposed approach does not improve the estimation efficiency. This indicates that, the original explanatory variables are adequate for modeling $\eta(d)(\cdot), d = 0, 1$. However, our data analysis result of ACTG 175 data set is still meaningful because we provide further reliability to use the original set of explanatory variables.

5.2 Analysis of GSE118657 Data Set

Gene Expression Omnibus dataset (GSE118657) is a Phase II/III randomized controlled trial examining the use of lactoferrin to prevent nosocomial infections in critically ill patients undergoing mechanical ventilation (Lee and Lin, 2019; Muscedere et al., 2018). This data set consists of 61 patients, among which 32 patients were randomized to receive lactoferrin and the remaining ones
were assigned to the placebo group. We are interested in studying the effect of lactoferrin on the length of stay in ICU. For covariate adjustment, we consider four important variables of patients before receiving the treatment-age, sex, SOFA score, and APACHE II score, denoted by $X_b$, and gene expression data of patients, denoted by $X_g$. In the following data analysis, approaches of Zhang (2018) and Tsiatis et al. (2008) are based on modelling $E[Y|X_b, D = d], d = 0, 1$ with Forward-1 or Forward-2 model. To make use of information of the gene expression data, we model $E[Y|X_b, X_g, D = d], d = 0, 1$ by ML methods and subsequently apply the approach of Wager et al. (2016) and our proposed MDEL approach. Since the dimension of $X = (X_b, X_g), p \approx 50000$, is too high, we use sure independent screening (SIS) method (Fan and Lv, 2008) to filter out variables that are relatively weak-correlated with the response, and reduce the dimension of $X$ to a low level, say $d_X = O(n)$, before modelling $E[Y|X, D = 1]$ and $E[Y|X, D = 0]$.  

| Estimator          | Estimate | SE     | Relative Efficiency | 95% Confidence Interval | 99% Confidence Interval |
|--------------------|----------|--------|---------------------|-------------------------|-------------------------|
| $\hat{\theta}_{dim}$ | -8.489   | 13.737 | 1.000               | (-35.41, 18.44)         | (-43.87, 26.90)         |
| $\hat{\theta}_{GAL}(Forward-1)$ | -7.769   | 13.701 | 1.005               | (-34.62, 19.08)         | (-43.06, 27.52)         |
| $\hat{\theta}_{GAL}(Forward-2)$ | -10.993  | 13.965 | 0.968               | (-38.36, 16.38)         | (-46.96, 24.98)         |
| $\hat{\theta}_{Zhang}(Forward-1)$ | -7.933   | 13.204 | 1.082               | (-33.81, 17.95)         | (-41.94, 26.68)         |
| $\hat{\theta}_{Zhang}(Forward-2)$ | -10.083  | 14.143 | 0.908               | (-38.33, 18.17)         | (-47.21, 27.04)         |
| $\hat{\theta}_{wtt}(LASSO)$ | -9.310   | 13.789 | 0.993               | (-36.34, 17.72)         | (-44.83, 26.21)         |
| $\hat{\theta}_{wtt}(SCAD)$ | -10.493  | 14.165 | 0.941               | (-38.26, 17.27)         | (-46.98, 25.99)         |
| $\hat{\theta}_{wtt}(RF)$ | -13.732  | 14.065 | 0.954               | (-41.30, 13.83)         | (-49.96, 22.50)         |
| $\hat{\theta}_{mde}(LASSO)$ | -8.540   | 12.970 | 1.122               | (-33.96, 16.88)         | (-41.95, 24.87)         |
| $\hat{\theta}_{mde}(SCAD)$ | -8.661   | 12.181 | 1.272               | (-32.53, 15.21)         | (-40.04, 22.71)         |
| $\hat{\theta}_{mde}(RF)$ | -8.647   | 13.457 | 1.042               | (-35.02, 17.73)         | (-43.31, 26.02)         |
| $\hat{\theta}_{mde}(MULTI)$ | -7.237   | 10.755 | 1.632               | (-28.32, 13.84)         | (-34.94, 20.46)         |

SE = standard error, Relative Efficiency = (SE$^2$ of corresponding estimator)/(SE$^2$ of $\hat{\theta}_{dim}$).

Results given in Table 2 indicate that there is no improvement about the length of stay in ICU for patients after the use of lactoferrin. Our approach with multiple ML methods, $\hat{\theta}_{mde}(MULTI)$,
is more efficient than other estimators with the shortest confidence intervals.

5.3 Simulation Studies

We consider linear models for $\eta^{(d)}$ with the dimension of covariates $p$ larger than the sample size $n$. The universal settings of our simulations are as follows. The covariates $X_i, i = 1, \cdots, n$ are independent and identically generated from multivariate Gaussian $\mathcal{N}(1_p, \Sigma)$, where $1_p = (1, \cdots, 1)^T$ is a $p$-dimensional vector. The assignment probability is fixed to be $\delta = 0.5$ and $D_i \overset{i.i.d.}{\sim} \text{Bernoulli}(\delta)$. The outcome $Y_i$ of the $i$-th unit under treatment $D_i = d_i$ are generated from $\mathcal{N}(X_i^T \beta^{(d)} + 5I(d_i = 1), 1), i = 1, \cdots, n$. We consider two different size scales $(n, p) = (80, 200)$ and $(n, p) = (200, 1000)$.

Define $0^0 = 1$, signals and the covariance matrix of the covariates, $\Sigma$, are different as follows.

Simulation 1 (Sufficient Sparsity). $\beta_i^{(1)} = 3 \cdot 1(i \leq 3), \beta_j^{(0)} = 2 \cdot 1(j \leq 3)$ and $\Sigma_{ij} = \rho^{i-j}$.

Simulation 2 (Fan et al. (2012)).

$($\beta_i^{(d)}$)_{i=1,2,3,5,7,11,13,17,19,23} = (1.01, -0.06, 0.72, 1.55, 2.32, -0.36, 3.75, -2.04, -0.13, 0.61)^T, d = 0, 1$

and $\Sigma_{ij} = \rho^{|i-j|}$.

Simulation 3 (Dense Geometry (Wager et al., 2016)). $\beta_i^{(1)} = 11^{-10i/p}, \beta_j^{(0)} = 10^{-10j/p}$ and $\Sigma_{ij} = \rho^{|i-j|}$.

Simulation 1 has sparse and strong signals. Simulation 2 has sparse signals with more challenging coefficients. Simulation 3 is identical to the geometric case of Wager et al. (2016). Results of simulations are all based on 5000 Monte Carlo data sets and given in Table 3, 4 and 5. First, we summarize the results in Table 3 and 4 (sparse case):

(a) Compared with the simple approach of difference in means, the EL estimators with any outcome model have significantly smaller SDs and RMSEs.

(b) Among the EL estimators with one outcome model, the estimators using SCAD perform relatively better than other estimators, and estimators using random forests perform worst in sense of RMSE. As expected, the EL estimators with multiple models perform closest to those with SCAD, and better than all other estimators when $\rho = 0.5$ and $(n, p) = (80, 200)$. 

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(c) Using SCAD to model the covariate-outcome relationship, the EL estimators perform similarly to Wager’s estimators in terms of SD and RMSE. However, when Lasso or random forests model are adopted, the EL estimators outperform Wager’s estimators. In Simulation 1, compared with Wager’s estimators with random forests, the EL estimators with random forests have an average of 5% reduction in RMSE for $\rho = 0$ and 7% reduction in RMSE for $\rho = 0.5$. In simulation 2, compared with Wager’s estimators with random forests, the EL estimators with random forests have an average of 4% reduction in RMSE for $\rho = 0$ and 7% reduction in RMSE for $\rho = 0.5$.

(d) The SEs of the EL estimators with one outcome model are very close to their corresponding SDs, and the coverage probabilities of the EL estimators with one model are close to the nominal levels. However, the variances of the EL estimators with multiple models are slightly overestimated, but in a reasonable range.

Results in Table 5 are summarized as follows (dense case):

(a) When $\rho = 0$, compared with the simple approach of difference in means, there is no significant reduction in RMSE for the EL estimators. When $\rho = 0.5$, compared with the difference in means estimators, the EL estimators with any outcome model have significantly smaller SDs and RMSEs.

(b) When $\rho = 0$, there is no significant difference among different estimators. When $\rho = 0.5$, among the EL estimators using one outcome model, the estimators with Lasso perform best and the estimators with random forests perform worst in sense of RMSE. As expected, the EL estimators with multiple ML models perform closest to the ones with Lasso.

(c) When $\rho = 0.5$, under Lasso or SCAD model, the EL estimators perform similarly to Wager’s estimators in terms of RMSE. However, under random forests model, the EL estimators outperform Wager’s estimators. Compared with Wager’s estimators with random forests, the EL estimators with random forests have an average of 11.3% reduction in RMSE when $\rho = 0.5$.

(d) When $\rho = 0$ and $(n, p) = (80, 200)$, the variances of EL estimators are underestimated and the coverage rates of the EL estimators are smaller than the nominal levels, but still in reasonable range.
Table 3: Results of Simulation 1 based on 5000 Monte Carlo replications

| Estimator          | $(n, p) = (80, 200)$ | $(n, p) = (200, 1000)$ | $\rho = 0$ | $\rho = 0.5$ |
|--------------------|----------------------|------------------------|-------------|-------------|
|                    | Bias | SD   | SE   | RMSE | Cov95 | Cov99 | Bias | SD   | SE   | RMSE | Cov95 | Cov99 |
| $\hat{\theta}_{\text{lim}}$ | -0.004 | 1.002 | 1.015 | 1.002 | 0.950 | 0.988 | -0.012 | 1.389 | 1.417 | 1.389 | 0.953 | 0.991 |
| $\hat{\theta}_{\text{edtt}}$ (LASSO) | 0.000 | 0.386 | 0.383 | 0.386 | 0.943 | 0.987 | 0.000 | 0.407 | 0.409 | 0.407 | 0.951 | 0.991 |
| $\hat{\theta}_{\text{edtt}}$ (SCAD) | 0.001 | 0.318 | 0.315 | 0.318 | 0.948 | 0.989 | 0.002 | 0.381 | 0.378 | 0.381 | 0.947 | 0.988 |
| $\hat{\theta}_{\text{edtt}}$ (RF) | -0.005 | 0.959 | 0.970 | 0.959 | 0.947 | 0.988 | -0.010 | 0.820 | 0.841 | 0.820 | 0.955 | 0.990 |
| $\hat{\theta}_{\text{medel}}$ (LASSO) | 0.001 | 0.349 | 0.349 | 0.349 | 0.949 | 0.987 | 0.000 | 0.399 | 0.406 | 0.399 | 0.952 | 0.991 |
| $\hat{\theta}_{\text{medel}}$ (SCAD) | 0.001 | 0.318 | 0.316 | 0.318 | 0.945 | 0.990 | 0.002 | 0.382 | 0.381 | 0.382 | 0.948 | 0.988 |
| $\hat{\theta}_{\text{medel}}$ (RF) | -0.008 | 0.945 | 0.948 | 0.945 | 0.948 | 0.988 | -0.008 | 0.743 | 0.772 | 0.743 | 0.956 | 0.992 |
| $\hat{\theta}_{\text{medel}}$ (MULTI) | 0.003 | 0.321 | 0.341 | 0.321 | 0.959 | 0.992 | 0.002 | 0.374 | 0.397 | 0.374 | 0.957 | 0.993 |

Bias = average bias of 5000 Monte Carlo estimators, SD = sample standard deviation of estimators, SE = average of model-based standard error, RMSE = empirical root mean square error, Cov95 = proportion of 95% Wald confidence intervals covering the true $\theta$, Cov99 = proportion of 99% Wald confidence intervals covering the true $\theta$.

Table 4: Results of Simulation 2 based on 5000 Monte Carlo replications

| Estimator          | $(n, p) = (80, 200)$ | $(n, p) = (200, 1000)$ | $\rho = 0$ | $\rho = 0.5$ |
|--------------------|----------------------|------------------------|-------------|-------------|
|                    | Bias | SD   | SE   | RMSE | Cov95 | Cov99 | Bias | SD   | SE   | RMSE | Cov95 | Cov99 |
| $\hat{\theta}_{\text{lim}}$ | -0.003 | 0.773 | 0.763 | 0.773 | 0.945 | 0.988 | -0.002 | 0.796 | 0.785 | 0.796 | 0.949 | 0.988 |
| $\hat{\theta}_{\text{edtt}}$ (LASSO) | 0.001 | 0.226 | 0.222 | 0.226 | 0.945 | 0.991 | 0.001 | 0.212 | 0.209 | 0.212 | 0.945 | 0.990 |
| $\hat{\theta}_{\text{edtt}}$ (SCAD) | 0.002 | 0.164 | 0.163 | 0.164 | 0.950 | 0.990 | 0.003 | 0.166 | 0.164 | 0.166 | 0.948 | 0.989 |
| $\hat{\theta}_{\text{edtt}}$ (RF) | -0.003 | 0.746 | 0.736 | 0.746 | 0.946 | 0.988 | -0.002 | 0.758 | 0.748 | 0.758 | 0.949 | 0.987 |
| $\hat{\theta}_{\text{medel}}$ (LASSO) | 0.001 | 0.199 | 0.198 | 0.199 | 0.949 | 0.992 | 0.002 | 0.185 | 0.185 | 0.185 | 0.951 | 0.991 |
| $\hat{\theta}_{\text{medel}}$ (SCAD) | 0.002 | 0.164 | 0.164 | 0.164 | 0.952 | 0.990 | 0.003 | 0.167 | 0.165 | 0.167 | 0.948 | 0.990 |
| $\hat{\theta}_{\text{medel}}$ (RF) | -0.003 | 0.695 | 0.696 | 0.695 | 0.949 | 0.989 | -0.006 | 0.671 | 0.677 | 0.671 | 0.949 | 0.991 |
| $\hat{\theta}_{\text{medel}}$ (MULTI) | 0.002 | 0.165 | 0.175 | 0.165 | 0.965 | 0.995 | 0.003 | 0.168 | 0.177 | 0.168 | 0.962 | 0.993 |

Bias = average bias of 5000 Monte Carlo estimators, SD = sample standard deviation of estimators, SE = average of model-based standard error, RMSE = empirical root mean square error, Cov95 = proportion of 95% Wald confidence intervals covering the true $\theta$, Cov99 = proportion of 99% Wald confidence intervals covering the true $\theta$. 
Table 5: Results of Simulation 3 based on 5000 Monte Carlo replications

| Estimator       | \( \rho = 0 \) | \( \rho = 0.5 \) |
|-----------------|----------------|-----------------|
|                 | \( (n, p) = (80, 200) \) | \( (n, p) = (200, 1000) \) |
|                 | \( (n, p) = (80, 200) \) | \( (n, p) = (200, 1000) \) |
| \( \hat{\theta}_{\text{dim}} \) | 0.003 0.489 0.490 0.489 0.949 0.990 | 0.002 0.732 0.737 0.732 0.949 0.990 |
| \( \hat{\theta}_{\text{wdtt}}(\text{LASSO}) \) | 0.002 0.453 0.451 0.453 0.946 0.987 | 0.000 0.435 0.432 0.435 0.945 0.985 |
| \( \hat{\theta}_{\text{wdtt}}(\text{SCAD}) \) | 0.004 0.458 0.460 0.458 0.946 0.988 | 0.002 0.497 0.497 0.497 0.945 0.984 |
| \( \hat{\theta}_{\text{wdtt}}(\text{RF}) \) | 0.002 0.478 0.478 0.478 0.947 0.991 | 0.000 0.667 0.671 0.667 0.948 0.990 |
| \( \hat{\theta}_{\text{mdel}}(\text{LASSO}) \) | 0.003 0.464 0.452 0.464 0.943 0.987 | 0.000 0.425 0.422 0.425 0.945 0.988 |
| \( \hat{\theta}_{\text{mdel}}(\text{SCAD}) \) | 0.003 0.469 0.459 0.469 0.940 0.987 | 0.003 0.510 0.507 0.510 0.946 0.984 |
| \( \hat{\theta}_{\text{mdel}}(\text{RF}) \) | 0.003 0.489 0.478 0.489 0.940 0.987 | -0.002 0.583 0.599 0.582 0.952 0.992 |
| \( \hat{\theta}_{\text{mdel}}(\text{MULTI}) \) | 0.005 0.470 0.446 0.470 0.932 0.983 | 0.001 0.433 0.425 0.433 0.943 0.986 |

Bias = average bias of 5000 Monte Carlo estimators, SD = sample standard deviation of estimators, SE = average of model-based standard error, RMSE = empirical root mean square error, Cov95 = proportion of 95% Wald confidence intervals covering the true \( \theta \), Cov99 = proportion of 99% Wald confidence intervals covering the true \( \theta \).

Figure 3: Boxplot of 5000 Monte Carlo biases based on Simulation 1 (in the left panel) and Simulation 3 (in the right panel).
6 Conclusions and Further Discussions

In this paper, we propose a machine learning and data-splitting based EL approach to make statistical inference on the average treatment effect in randomized controlled trials. Our approach not only maintains the advantages of the traditional EL approaches, but also overcomes the shortage that the traditional EL approaches usually make invalid inference in high-dimensional settings. Compared with the regression adjustment approach proposed by Wager et al. (2016), our proposed approach has two attractive characteristics, which are illustrated by our simulation studies: (i). Compared with semiparametric estimators, our proposed estimators perform better when we use random forests to estimate the nuisance parameters; (ii). Our MDEL estimators with multiple ML models are likely to perform as good as that with the oracle model, known as multiple robustness.

For future work, we plan to (i) study the asymptotic theory of the proposed EL estimator with multiple models; (ii) generalize our proposed approach to high-dimensional observational studies by modelling propensity scores and imposing additional constraints about the propensity scores.

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Appendix: Decomposition of $\hat{\theta}_{mdei}$ and Proofs of Theorems

Additional Notations
For $d = 0, 1$, let $\hat{\xi}^{(d)} = \frac{1}{K} \sum_{k=1}^{K} E \left[ \hat{g}_{k}^{(d)}(X) \bigg| (W_{i})_{i \in I_{k}^{(d)}} \right]$, $\hat{G} \left( x, \hat{g}_{k}^{(d)}, \hat{\xi}^{(d)} \right) = \hat{g}_{k}^{(d)}(x) - \hat{\xi}^{(d)}$, 

$$
\tilde{j}_{n}^{(d)} = \frac{1}{n} \sum_{k=1}^{K} \sum_{i \in I_{k}^{(d)}} \frac{(Y_{i} - \theta_{d}) \hat{G} \left( X_{i}, \hat{g}_{k}^{(d)}, \hat{\xi}^{(d)} \right)}{(2d - 1)\delta + 1 - d},
$$

and

$$
\tilde{s}_{n}^{(d)} = \frac{1}{n} \sum_{k=1}^{K} \sum_{i \in I_{k}^{(d)}} \hat{G} \left( X_{i}, \hat{g}_{k}^{(d)}, \hat{\xi}^{(d)} \right) \otimes \left( \frac{2d - 1 + \delta}{2d - 1 + \delta + 1} \right),
$$

where, for any vector or matrix $H$, $H \otimes 2 = HH^{\tau}$. For simplicity, we use $[x]_{i}$ to denote the $i$-th element of a vector $x$.

Regularity Conditions

(A1) $\frac{n_{1}}{n} \to c_{1} > 0$ and $\frac{n_{0}}{n} \to c_{2} > 0$, as $n \to \infty$.

(A2) \[
\lim_{n \to \infty} P \left( \min \text{ eigen} \left\{ \frac{1}{n_{d}} \sum_{k=1}^{K} \sum_{i \in I_{k}^{(d)}} \hat{G} \left( X_{i}, \hat{g}_{k}^{(d)}, \hat{\xi}^{(d)} \right) \otimes ^{2} \right\} \right) > 0 \right) = 1
\]

and

\[
\lim_{n \to \infty} P \left( \max \text{ eigen} \left\{ \frac{1}{n_{d}} \sum_{k=1}^{K} \sum_{i \in I_{k}^{(d)}} \hat{G} \left( X_{i}, \hat{g}_{k}^{(d)}, \hat{\xi}^{(d)} \right) \otimes ^{2} \right\} \right) < \infty \right) = 1
\]

for $d = 0, 1$ where eigen{$H$} denotes the eigenvalues of a matrix $H$.

(A3) $E \left[ \hat{g}_{k}^{(d)}(X) \bigg| (W_{i})_{i \in I_{k}^{(d)}} \right] < \infty$ with probability tending to 1 as $n$ goes to infinity for $j = 1, \cdots, r$ and $k = 1, \cdots, K$.

(A4) $\tilde{s}_{n}^{(d)}$, $d = 0, 1$ are invertible for a given $n$.

(A5) $E[Y^{2} | D = d] < \infty$. for $d = 0, 1$.

(A1) is a basic “positivity” condition in causal inference problems. (A2), (A3) and (A4) are necessary for the validity of the EL approach with multiple models and obtaining the decomposition.
form of the EL estimator with multiple models. (A5) is necessary for the weak convergence property of our estimators.

**Lemmas**

**Lemma 1** (Chernozhukov et al. (2018); Conditional Convergence implies Unconditional). Let \( \{X_m\} \) and \( \{Y_m\} \) be random vectors. (a) If for \( \varepsilon_m \to 0 \), \( \mathbb{P}(||X_m|| > \varepsilon_m|Y_m) \to 0 \) as \( m \to \infty \), then \( \mathbb{P}(||X_m|| > \varepsilon_m) \to 0 \) as \( m \to \infty \). (b) Let \( \{A_m\} \) be a sequence of positive constants. If \( ||X_m|| = O_p(A_m) \) conditional on \( Y_m \), then \( ||X_m|| = O_p(A_m) \) holds unconditionally.

**Lemma 2.** Under conditions (A1)-(A4), we have \( \hat{\lambda}_d = O_p(\frac{1}{\sqrt{n}}) \) for \( d \in \{0, 1\} \).

**Proof.** For fixed \( d \), from \( \frac{1}{n_d} \sum_{k=1}^{K} \sum_{i \in I^d_k} \frac{\hat{G}(X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)})}{1 + \hat{\lambda}_d \hat{G}(X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)})} = 0 \) we have

\[
0 = \frac{1}{n_d} \sum_{k=1}^{K} \sum_{i \in I^d_k} \hat{G}(X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)}) \left[ 1 - \frac{1}{1 + \hat{\lambda}_d \hat{G}(X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)})} \right] \\
= \frac{1}{n_d} \sum_{k=1}^{K} \sum_{i \in I^d_k} \hat{G}(X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)}) - \frac{1}{n_d} \sum_{k=1}^{K} \sum_{i \in I^d_k} \hat{G}(X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)}) \frac{\hat{\lambda}_d}{1 + \hat{\lambda}_d \hat{G}(X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)})}.
\]

Therefore,

\[
\frac{1}{n_d} \sum_{k=1}^{K} \sum_{i \in I^d_k} \hat{G}(X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)}) = \frac{1}{n_d} \sum_{k=1}^{K} \sum_{i \in I^d_k} \frac{\hat{G}(X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)})}{1 + \hat{\lambda}_d \hat{G}(X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)})} \hat{\lambda}_d. \tag{7}
\]

For fixed \( k \), conditional on \( (W_i)_{i \in I^d_k} \), Central Limit Theorem indicates

\[
\frac{1}{|I^d_k|} \sum_{i \in I^d_k} \left( \hat{g}_k^{(d)}(X_i) - \hat{\xi}_k^{(d)} \right) - \mathbb{E} \left[ \hat{g}_k^{(d)}(X) - \hat{\xi}_k^{(d)} \middle| (W_i)_{i \in I^d_k} \right] = O_p(\frac{1}{\sqrt{n}}).
\]

Then, lemma 1 gives \( \frac{1}{|I^d_k|} \sum_{i \in I^d_k} \left( \hat{g}_k^{(d)}(X_i) - \hat{\xi}_k^{(d)} \right) = O_p(\frac{1}{\sqrt{n}}) \) unconditionally. Therefore, the left term of (7) is

\[
\frac{1}{n_d} \sum_{k=1}^{K} \sum_{i \in I^d_k} \hat{G}(X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)}) = \frac{1}{K} \sum_{k=1}^{K} \frac{1}{|I^d_k|} \sum_{i \in I^d_k} \left( \hat{g}_k^{(d)}(X_i) - \hat{\xi}_k^{(d)} \right) = O_p(\frac{1}{\sqrt{n}}).
\]
Turn to the right term of (7), and let $\nu_d = \frac{\hat{\lambda}_d}{||\lambda_d||}$, where $|| \cdot ||$ is the Euclidean norm. We have

$$1 + \hat{\lambda}_d^T \hat{G} \left( X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)} \right) \leq 1 + ||\hat{\lambda}_d|| \nu_d^T \hat{G} \left( X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)} \right) \leq 1 + 2||\hat{\lambda}_d|| \sqrt{r} \max_{k \in \{1, \ldots, K\}} \max_{j=1, \ldots, r} \max_{i \in I_k} \left| \hat{r}_k^{(d)}(X_i) \right|.$$  

Condition (A3), lemma 11.2 in Owen (2001), and lemma 1 indicate $\max_{k \in \{1, \ldots, K\}} \max_{j=1, \ldots, r} \max_{i \in I_k} \left| \hat{r}_k^{(d)}(X_i) \right| = o_p(n^{1/2})$. Multiply $\nu_d^T$ on both sides of (7), we have

$$\frac{1}{n_d} \sum_{k=1}^{K} \sum_{i \in I_k^{(d)}} \nu_d^T \hat{G} \left( X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)} \right)^{\otimes 2} \nu_d \leq \frac{1}{n_d} \sum_{k=1}^{K} \sum_{i \in I_k^{(d)}} \hat{G} \left( X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)} \right) \left( 1 + 2||\hat{\lambda}_d|| \sqrt{r} \max_{k \in \{1, \ldots, K\}} \max_{j=1, \ldots, r} \max_{i \in I_k} \left| \hat{r}_k^{(d)}(X_i) \right| \right)$$

Under condition (A2), we have $\frac{1}{n_d} \sum_{k=1}^{K} \sum_{i \in I_k^{(d)}} \nu_d^T \hat{G} \left( X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)} \right)^{\otimes 2} \nu_d \sim 1$. It follows from all above results that

$$||\hat{\lambda}_d|| \leq O_p\left( \frac{1}{\sqrt{n}} \right)(1 + 2||\hat{\lambda}_d||o_p(n^{1/2})). \quad (8)$$

Equation (8) indicates $||\hat{\lambda}_d|| = O_p\left( \frac{1}{\sqrt{n}} \right)$. This completes the proof. \hfill \Box

**Lemma 3.** For $i \in I_k$, $\hat{G} \left( X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)} \right) = \hat{G} \left( X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)} \right) + O_p\left( \frac{1}{\sqrt{n}} \right)$, $d \in \{0, 1\}$.

**Proof.** Note $\hat{G} \left( X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)} \right) - \hat{G} \left( X_i, \hat{g}_k^{(d)}, \hat{\xi}^{(d)} \right) = \frac{1}{K} \sum_{k=1}^{K} \frac{1}{||x||} \sum_{i \in I_k} \left( \hat{g}_k^{(d)}(X_i) - E \left[ \hat{g}_k^{(d)}(X_i) \right| (W_j)_{j \in I_k^{(d)}} \right)$, then the proof is completed by Central Limit Theorem and lemma 1. \hfill \Box
Decomposition of $\hat{\theta}_{\text{mdl}}$

First, we consider the case $d = 1$ and the case $d = 0$ will be similar. Taylor expansion, Lemma 2, and Lemma 3 lead to

$$
0 = \sqrt{n} \frac{1}{n_1} \sum_{k=1}^{K} \sum_{i \in I_k} \frac{1}{1 + \lambda_i^2} \hat{G} \left( X_i, \hat{g}_k^{(1)}(1), \hat{\xi}(1) \right)
= \frac{1}{\sqrt{n}} \sum_{k=1}^{K} \sum_{i \in I_k} \frac{D_i}{\delta} \hat{G} \left( X_i, \hat{g}_k^{(1)}(1), \hat{\xi}(1) \right) - \sqrt{n} \frac{1}{K} \sum_{k=1}^{K} \frac{1}{|I_k|} \sum_{i \in I_k} \frac{D_i}{\delta} \hat{G} \left( X_i, \hat{g}_k^{(1)}(1), \hat{\xi}(1) \right)^{\otimes 2} \lambda_1 + o_p(1)
$$

Therefore, we have

$$
\sqrt{n} \lambda_1 = \delta^{(1)}_n^{-1} \frac{1}{\sqrt{n}} \sum_{k=1}^{K} \sum_{i \in I_k} \frac{D_i}{\delta} \hat{G} \left( X_i, \hat{g}_k^{(1)}(1), \hat{\xi}(1) \right) + o_p(1).
$$

By Taylor expansion, Lemma 2, Lemma 3, and (10), we have

$$
\sqrt{n} \left( \hat{\theta}^{(1)}_{\text{mdl}} - \theta_1 \right) = \sqrt{n} \sum_{k=1}^{K} \sum_{i \in I_k} D_i \hat{p}_i \left( Y_i - \theta_1 \right)
= \frac{1}{\sqrt{n}} \sum_{k=1}^{K} \sum_{i \in I_k} \frac{D_i}{\delta} \frac{Y_i - \theta_1}{1 + \lambda_i^2} \hat{G} \left( X_i, \hat{g}_k^{(1)}(1), \hat{\xi}(1) \right) + o_p(1)
= \frac{1}{\sqrt{n}} \sum_{k=1}^{K} \sum_{i \in I_k} \frac{D_i}{\delta} (Y_i - \theta_1) - \frac{1}{\sqrt{n}} \sum_{k=1}^{K} \sum_{i \in I_k} \frac{D_i}{\delta} (Y_i - \theta_1) \hat{G} \left( X_i, \hat{g}_k^{(1)}(1), \hat{\xi}(1) \right) \lambda_1 + o_p(1)
= \frac{1}{\sqrt{n}} \sum_{k=1}^{K} \sum_{i \in I_k} \frac{D_i}{\delta} (Y_i - \theta_1) - \frac{1}{\sqrt{n}} \sum_{k=1}^{K} \sum_{i \in I_k} \frac{D_i}{\delta} (Y_i - \theta_1) \hat{G} \left( X_i, \hat{g}_k^{(1)}(1), \hat{\xi}(1) \right) \lambda_1 + o_p(1)
= \frac{1}{\sqrt{n}} \sum_{k=1}^{K} \sum_{i \in I_k} \left[ \frac{D_i}{\delta} (Y_i - \theta_1) - \frac{D_i}{\delta} \hat{J}_n^{(1)} \hat{S}_n^{(1)}^{-1} \hat{G} \left( X_i, \hat{g}_k^{(1)}(1), \hat{\xi}(1) \right) \right] + o_p(1)
$$

It is easy to give the form of $\sqrt{n} \left( \hat{\theta}^{(0)}_{\text{mdl}} - \theta_0 \right)$ in a similar way:

$$
\sqrt{n} \left( \hat{\theta}^{(0)}_{\text{mdl}} - \theta_0 \right) = \frac{1}{\sqrt{n}} \sum_{k=1}^{K} \sum_{i \in I_k} \left[ \frac{1 - D_i}{1 - \delta} (Y_i - \theta_0) - \frac{D_i}{1 - \delta} \hat{J}_n^{(0)} \hat{S}_n^{(0)}^{-1} \hat{G} \left( X_i, \hat{g}_k^{(0)}(1), \hat{\xi}(0) \right) \right] + o_p(1).
$$
Above all, we have
\[
\sqrt{n} (\hat{\theta}_{\text{model}} - \theta) = \frac{1}{\sqrt{n}} \sum_{k=1}^{K} \sum_{i \in I_k} \left[ \frac{D_i}{\delta} (Y_i - \theta_1) - \frac{D_i - \delta}{\delta} \tilde{G}_{n}^{(1)} S_n^{(1)-1} G \left( X_i, \tilde{g}_{k}^{(1)} , \tilde{\xi}^{(1)} \right) \right] - \frac{1 - D_i}{1 - \delta} (Y_i - \theta_0) + \frac{D_i - \delta}{1 - \delta} \tilde{G}_{n}^{(0)} S_n^{(0)-1} G \left( X_i, \tilde{g}_{k}^{(0)} , \tilde{\xi}^{(0)} \right) + o_p(1).
\]

Proof of Theorem 1

Proof. Conditional on \((W_i)_{i \in \mathbb{I}^{(d)c}}\), Holder inequality gives
\[
E \left[ \left| \tilde{g}^{(d)}_k (X) - \eta^{(d)}(X) \right| \left| (W_i)_{i \in \mathbb{I}^{(d)c}} \right| \right] \leq \sqrt{E \left[ \left( \tilde{g}^{(d)}_k (X) - \eta^{(d)}(X) \right)^2 \right]} \left| (W_i)_{i \in \mathbb{I}^{(d)c}} \right|.
\]

Therefore, we have \(E \left[ \left| \tilde{g}^{(d)}_k (X) - \eta^{(d)}(X) \right| \left| (W_i)_{i \in \mathbb{I}^{(d)c}} \right| \right] \to 0\) in probability as \(n \to \infty\) for \(k = 1, \cdots, K\). Let \(G(X_i, \eta^{(d)}(X), \theta_d) = \eta^{(d)}(X_i) - \theta_d\). For simplicity, write \(\tilde{s}_k^{(d)}(X_i) = \tilde{g}^{(d)}_k (X_i) - \eta^{(d)}(X_i)\). Then, we immediately have \(\tilde{G} \left( X_i, \tilde{g}^{(d)}_k , \tilde{\xi}^{(d)} \right) - G(X_i, \eta^{(d)}, \theta_d) = \tilde{s}_k^{(d)}(X_i) + o_p(1)\) by lemma 1. Following (9), it is easy to verify
\[
0 = \frac{1}{\sqrt{n}} \sum_{i \in I} \frac{D_i - \delta}{\delta} G(X_i, \eta^{(1)}(X), \theta_1) - \frac{1}{\sqrt{n}} \sum_{i \in I} \frac{D_i}{\delta} G(X_i, \eta^{(1)}(X), \theta_1)^2 \tilde{\lambda}_1 + o_p(1)
\]
\[
+ \frac{1}{\sqrt{n}} \sum_{k=1}^{K} \sum_{i \in I_k} \frac{D_i - \delta}{\delta} s_k^{(1)}(X_i) + \frac{1}{\sqrt{n}} \sum_{k=1}^{K} \sum_{i \in I_k} s_k^{(1)}(X_i)^2 \tilde{\lambda}_1 - \frac{2}{\sqrt{n}} \sum_{k=1}^{K} \sum_{i \in I_k} \frac{D_i}{\delta} s_k^{(1)}(X_i) G(X_i, \eta^{(1)}, \theta_1) \tilde{\lambda}_1.
\]

Now we bound \(A = \frac{1}{\sqrt{n}} \sum_{k=1}^{K} \sum_{i \in I_k} \frac{D_i - \delta}{\delta} s_k^{(1)}(X_i), B = \frac{1}{\sqrt{n}} \sum_{k=1}^{K} \sum_{i \in I_k} s_k^{(1)}(X_i)^2 \tilde{\lambda}_1\) and
\[
C = \frac{1}{\sqrt{n}} \sum_{k=1}^{K} \sum_{i \in I_k} \frac{D_i}{\delta} s_k^{(1)}(X_i) G(X_i, \eta^{(1)}, \theta_1) \tilde{\lambda}_1, \text{ respectively. Conditional on } (W_i)_{i \in \mathbb{I}^{(d)c}}, \text{ the mean of }
\]
\[
\frac{1}{\sqrt{|\mathbb{I}^{(d)c}|}} \sum_{i \in \mathbb{I}^{(d)c}} \frac{D_i - \delta}{\delta} s_k^{(1)}(X_i) \text{ is zero and the variance is given by}
\]
\[
E[(D - \delta)^2] \cdot E \left[ s_k^{(1)}(X)^2 \right] \left| (W_i)_{i \in \mathbb{I}^{(d)c}} \right|,
\]
which converges to zero in probability as \(n \to \infty\). Then \(A = o_p(1)\) by Chebyshev’s inequality and lemma 1. \(B\) vanishes in probability because \(\sqrt{n} \tilde{\lambda}_1 = O_p(1)\). For \(C\), Cauchy-Schwarz inequality
gives
\[ C \leq \sqrt{n} \lambda_1 \frac{1}{K} \sum_{k=1}^{K} \left( \frac{1}{|I_k|} \sum_{i \in I_k} \zeta^{(1)}_k (X_i)^2 \right) \cdot \sqrt{\frac{1}{|I_k|} \sum_{i \in I_k} \left( \frac{D_i}{\delta} G(X_i, \eta^{(1)}, \theta_1) \right)^2}. \]

Conditional on \((W_i)_{i \in [d]^c}\), the right term of above inequality converges to 0 in probability as \( n \to \infty \); therefore \( C = o_p(1) \) by lemma 1. Above all, we have

\[ \sqrt{n} \lambda_1 = \mathbb{E} \left[ G(X_i, \eta^{(1)}, \theta_1)^2 \right]^{-1} \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \frac{D_i - \delta}{\delta} G(X_i, \eta^{(1)}, \theta_1) + o_p(1). \]

Similarly, it is easy to check that

\[ \sqrt{n} \lambda_0 = \mathbb{E} \left[ G(X_i, \eta^{(0)}, \theta_0)^2 \right]^{-1} \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \frac{D_i - \delta}{1 - \delta} G(X_i, \eta^{(0)}, \theta_0) + o_p(1). \]

Using above results, Taylor expansion indicates that

\[ \sqrt{n} \left( \tilde{\theta}^{(1)}_{\text{mde}l} - \theta_1 \right) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \frac{D_i}{\delta} (Y_i - \theta_1) - \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \frac{D_i}{\delta} (Y_i - \theta_1) G(X_i, \eta^{(1)}, \theta_1) \lambda_1 + o_p(1) \]
\[ = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \left\{ \frac{D_i}{\delta} (Y_i - \theta_1) \right\} \]
\[ - \frac{D_i - \delta}{\delta} \mathbb{E} \left[ \frac{D}{\delta} (Y - \theta_1) G(X, \eta^{(1)}, \theta_1) \right] \mathbb{E} \left[ G(X, \eta^{(1)}, \theta_1)^2 \right]^{-1} G(X, \eta^{(1)}, \theta_1) \}
\[ + o_p(1). \]

Following from

\[ \mathbb{E} \left[ \frac{D}{\delta} (Y - \theta_1) G(X, \eta^{(1)}, \theta_1)(X) \right] = \frac{\mathbb{P}(D = 1)}{\delta} \mathbb{E} \left[ (Y - \theta_1) G(X, \eta^{(1)}, \theta_1) | D = 1 \right] \]
\[ = \mathbb{E} \left[ (Y - \theta_1) | X, D = 1 \right] G(X, \eta^{(1)}, \theta_1) = \mathbb{E} \left[ G(X, \eta^{(1)}, \theta_1)^2 \right], \]

we have

\[ \sqrt{n} \left( \tilde{\theta}^{(1)}_{\text{mde}l} - \theta_1 \right) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \left\{ \frac{D_i}{\delta} (Y_i - \theta_1) - \frac{D_i - \delta}{\delta} (\eta^{(1)}(X_i) - \theta_1) \right\} + o_p(1) \]
\[ = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \left\{ \frac{D_i}{\delta} (Y_i - \eta^{(1)}(X_i)) + (\eta^{(1)}(X_i) - \theta_1) \right\} + o_p(1). \]
Similarly, when \( d = 0 \), it is easy to obtain

\[
\sqrt{n} \left( \hat{\theta}_{\text{mdel}}^{(0)} - \theta_0 \right) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \left\{ \frac{1 - D_i}{1 - \delta} \left( Y_i - \eta^{(0)}(X_i) \right) + \left( \eta^{(0)}(X_i) - \theta_0 \right) \right\} + o_p(1).
\]

Therefore, we have

\[
\sqrt{n} \left( \hat{\theta}_{\text{mdel}} - \theta \right) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \left\{ \frac{D_i}{\delta} \left( Y_i - \eta^{(1)}(X_i) \right) - \frac{1 - D_i}{1 - \delta} \left( Y_i - \eta^{(0)}(X_i) \right) \right. \\
\left. + \eta^{(1)}(X_i) - \eta^{(0)}(X_i) - \theta \right\} + o_p(1).
\]

This completes the proof. \( \square \)

**Proof of Theorem 2**

*Proof.* Following the proof of Theorem 1, it is easy to verify that

\[ \hat{J}_n^{(d)} = \frac{1}{n_d} \sum_{k=1}^{K} \sum_{i \in I_k^{(d)}} Y_i \hat{G} \left( X_i, \eta^{(1)}(X_i), \theta_k \right) + o_p(1) \quad \text{and} \quad \hat{S}_n^{(d)} = \frac{1}{n} \sum_{k=1}^{K} \sum_{i \in I_k} \hat{G} \left( X_i, \eta^{(1)}(X_i), \theta_k \right)^2 + o_p(1). \]

Then, some algebra gives

\[
\hat{\sigma}_{\text{mdel}}^2 = \frac{1}{n} \sum_{d=0,1} \sum_{k=1}^{K} \sum_{i \in I_k^{(d)}} \frac{n_d \hat{p}_i \left( \frac{n_d}{n_1} D_i (Y_i - \eta^{(1)}(X_i) + \theta_k - \hat{\theta}_{\text{mdel}}^{(1)}) + \eta^{(1)}(X_i) - \theta_k \right)^2 + o_p(1)}{n_0 (1 - D_i)(Y_i - \eta^{(0)}(X_i) + \theta_0 - \hat{\theta}_{\text{mdel}}^{(0)}) + \eta^{(0)}(X_i) - \theta_0^2} + o_p(1)
\]

\[
= \frac{1}{n} \sum_{i=1}^{n} \left\{ \frac{D_i}{\delta} \left( Y_i - \eta^{(1)}(X_i) \right) - \frac{1 - D_i}{1 - \delta} \left( Y_i - \eta^{(0)}(X_i) \right) + \eta^{(1)}(X_i) - \eta^{(0)}(X_i) - \theta \right\}^2 + o_p(1).
\]

(13)

This completes the proof. \( \square \)