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# A rank-based approach to estimating monotone individualized two treatment regimes

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ABSTRACT

Developing effective individualized treatment rules (ITRs) for diseases is an important goal of clinical research. Much effort has been devoted to estimating individualized treatment effects in the recent literature. However, there have not been systematic studies on the robust inference for individualized treatment effects when there exist potential outliers. We propose a monotone ITR in the framework of a semiparametric generalized regression with two treatments and estimate the treatment effects via a smoothed maximum rank correlation procedure. We provide sufficient conditions under which the proposed estimator has an asymptotically normal distribution whose variance can be consistently estimated based on a resampling procedure. We evaluate the finite-sample properties of our proposed approach via simulation studies. We also illustrate the proposed method by applying it to a data set from an AIDS clinical trials study.

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## 1. Introduction

In clinical studies, treatment effect heterogeneity is often observed. For example, a treatment may be beneficial for all the patients but with different levels of magnitudes, or may only be effective for a subset of patients with certain characteristics. Often, the traditional "one size fits all" approach is not effective, due to significant heterogeneity in response to treatments. Thus, treatments should be tailored to patients according to their own prognostic data. This research area has received much attention in the literature. For instance, Qian and Murphy (2011) proposed a two-step procedure that first estimates a conditional mean for the response and then estimates the rule maximizing this conditional mean. Zhang et al. (2012) proposed inverse propensity score weighted (IPSW) and augmented IPSW (AIPSW) estimators for optimal treatment regimes in a missing data framework. Based on support vector machine techniques, Zhao et al. (2012) considered an outcome-weighted learning approach and Zhou et al. (2017) proposed a residual-weighted learning method, respectively. McKeague and Qian (2014) developed a way of estimating optimal treatment policies based on functional predictors. Zhao et al. (2015a) and Shi et al. (2017) considered dynamic treatment regimes with sequences of decision rules. Laber and Zhao (2015) and Cui et al. (2017) presented tree-based methods for individualized treatment regimes. Zhao et al. (2015b) and Jiang et al. (2017) developed novel methods for estimating an optimal individualized treatment rule for censored data. Song et al. (2017) proposed a semiparametric additive single-index model for estimating

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individualized treatment effects. Fan et al. (2017) proposed a concordance-assisted learning method to estimate optimal individualized treatment regimes, among others.

In this article, we propose a rank-based monotone individualized treatment rule in the framework of a generalized regression model. One main feature of the proposed method is that the optimal treatment regime is derived by a rank-based procedure, which is robust to potential outliers. Second, we use a generalized regression to model the relationships between the response and treatment assignments as well as other covariates, which can explicitly describe the effects of covariates and treatment on response. Third, we establish the $n^{1/2}$-consistency and asymptotic normality of the proposed estimator. A resampling method is developed to estimate the asymptotic variance of the proposed estimator, which can be used to make statistical inference about the optimal treatment rules.

The remainder of the article is organized as follows. In Section 2, we describe some basic notation and concepts, and propose a monotone individualized treatment rule. In Section 3, we propose a smoothed maximum rank correlation estimation procedure. In Section 4, the asymptotic properties of the proposed estimator are established. In Section 5, simulation studies are conducted to evaluate the finite sample performance of our method. In Section 6, an application to an AIDS clinical trials study is presented. Section 7 contains some concluding remarks. The proofs are relegated to the Appendix.

## 2. Monotone individualized treatment rule

Suppose the data of interest are collected from a randomized trial with two-arm treatments denoted by 1 and $-1$. Denote the treatment assignment by $A \in \mathcal{A} = \{1, -1\}$. Let $\mathbf{X} = (X_1, \ldots, X_p)' \in \mathcal{X}$ be a $p$-dimensional vector of prognostic variables or covariates, and let $Y$ be the observed clinical outcome or response. Without loss of generality, we assume that a larger value of response is preferable. The sample includes independently and identically distributed (i.i.d.) observations $\{(\mathbf{X}_i, A_i, Y_i), i = 1, \ldots, n\}$. The ITR, $D(\mathbf{x})$, is a function from the sample space $\mathcal{X}$ to $\mathcal{A}$, which is tailored to each patient according to his or her prognostic data. An optimal ITR $D^*(x)$ is a rule that maximizes the expected response $Y$. In other words, $D^*(\mathbf{x}) = \arg\max_D \{E(Y|\mathbf{X} = \mathbf{x}, A = D(\mathbf{x}))\}$.

The outcome variable $Y$ can be affected by the covariate effects and the interaction (*treatment benefit*) between $A$ and $\mathbf{X}$. Ideally, larger treatment benefit leads to larger response. To evaluate the treatment effect, we adopt a generalized regression model (Han, 1987; Sherman, 1993), which relates the response to covariates and interaction effects,

$$Y = g\{h(\boldsymbol{X}'\boldsymbol{\gamma} + A\tilde{\boldsymbol{X}}'\boldsymbol{\beta}, \epsilon)\}, \tag{2.1}$$

where $g : \mathbb{R} \mapsto \mathbb{R}$ is an unspecified increasing function of its argument, $h : \mathbb{R}^2 \mapsto \mathbb{R}$ is an unspecified and strictly increasing function of each of its arguments; $\tilde{\boldsymbol{X}} = (1, \boldsymbol{X}')' \in \mathbb{R}^{p+1}$, $\boldsymbol{\gamma} = (\gamma_1, \ldots, \gamma_p)'$ is a vector of coefficients for the covariates and $\boldsymbol{\beta} = (\beta_0, \beta_1, \ldots, \beta_p)'$ is a vector of parameters for interaction effects; $\epsilon$ is a random error term. Note that model (2.1) includes many interesting regression models as special cases (Han, 1987). For example, if we take $h(u, v) = u + v$, model (2.1) reduces to a standard linear regression model when $g(w) = w$; a binary choice model when $g(w) = I(w \geq 0)$; a censored regression model when $g(w) = wI(w \geq 0)$.

For given $\boldsymbol{\gamma}$ and $\boldsymbol{\beta}$ in model (2.1), it is clear that $A = \text{sign}(\tilde{\boldsymbol{X}}'\boldsymbol{\beta})$ leads to a larger response because of the monotonicity assumption on $g$ and $h$, where $\text{sign}(x) = 1$ for $x \geq 0$, and $\text{sign}(x) = -1$, otherwise. The primary interest is to estimate the interaction effect $\boldsymbol{\beta}$ in (2.1), from which the optimal treatment regime is given by $D^*(\mathbf{x}) = \text{sign}(\tilde{\mathbf{x}}'\boldsymbol{\beta})$. This is also known as the decision function (Zhao et al., 2012). The generalized regression framework in model (2.1) has some advantages in developing individualized treatment strategy. First, it provides a more flexible semiparametric modeling of the interaction between treatment and covariates, while traditional parametric models potentially suffer from model misspecification. Second, we can easily derive the best treatment strategy with a simple linear decision function, which is interpretable. Third, the proposed rank-based estimator is robust to potential outliers. Moreover, the asymptotic distribution of the proposed estimator is available, which can be used to develop valid inference procedures.

## 3. Estimation procedure

In this section, we present a rank-based approach to estimate the parameters of interest in model (2.1). Given that the response is a stochastically monotone function of the covariate effect and treatment benefit, then the rankings of $Y_i$, and rankings of $\mathbf{X}_i'\boldsymbol{\gamma} + A_i\tilde{\mathbf{X}}_i'\boldsymbol{\beta}$ are expected to be positively correlated. This motivates us to apply the maximum rank correlation (MRC) estimation method (Han, 1987) to the present problem. The MRC objective function is

$$G_n(\boldsymbol{\theta}) = \frac{1}{n(n-1)} \sum_{i \neq j} I(Y_i > Y_j) I(\boldsymbol{X}_i'\boldsymbol{\gamma} + A_i\tilde{\boldsymbol{X}}_i'\boldsymbol{\beta} > \boldsymbol{X}_j'\boldsymbol{\gamma} + A_j\tilde{\boldsymbol{X}}_j'\boldsymbol{\beta}), \tag{3.1}$$

where $\boldsymbol{\theta} = (\boldsymbol{\gamma}', \boldsymbol{\beta}')' \in \mathbb{R}^{2p+1}$, and $I(\cdot)$ is the indicator function. For identifiability, we further require $\|\boldsymbol{\gamma}\| = 1$ and $\|\boldsymbol{\beta}\| = 1$, where $\|\cdot\|$ is the Euclidean norm.

Because the MRC objective function $G_n(\boldsymbol{\theta})$ is a weighted sum of indicator functions, it is difficult to optimize (3.1) when $p$ is relatively large. To deal with this computational problem, we adopt the sigmoid function $s_n(u) = 1/\{1 + \exp(-u/\sigma_n)\}$ to approximate $I(u > 0)$, where $\sigma_n$ is a sequence of strictly positive and decreasing numbers with $\lim_{n\to\infty} \sigma_n = 0$ (see

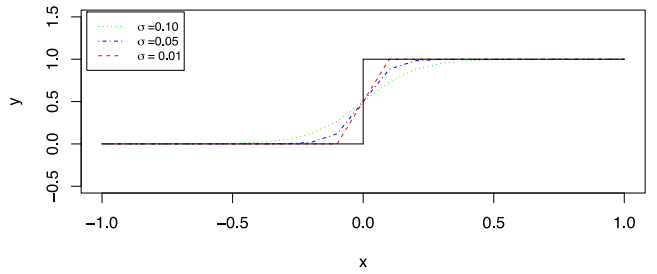


**Fig. 1.** Plots of the sigmoid function $s(x) = 1/\{1 + \exp(-x/\sigma)\}$.

Fig. 1). As suggested by Song et al. (2007), we can use $\sigma_n = cn^{-1/2}$ with some positive $c$ (e.g. $c = 3$). The smoothed version of $G_n(\boldsymbol{\theta})$ is

$$S_n(\boldsymbol{\theta}) = \frac{1}{n(n-1)} \sum_{i \neq j} I(Y_i > Y_j) s_n(\boldsymbol{X}_i'\boldsymbol{\gamma} + A_i\tilde{\boldsymbol{X}}_i'\boldsymbol{\beta} - \boldsymbol{X}_j'\boldsymbol{\gamma} - A_j\tilde{\boldsymbol{X}}_j'\boldsymbol{\beta}). \tag{3.2}$$

Theorem 1 shows that $S_n(\boldsymbol{\theta})$ is a consistent approximation to the maximum rank correlation function $G_n(\boldsymbol{\theta})$. A smoothed maximum rank correlation (SMRC) estimator of $\boldsymbol{\theta}$ is defined as

$$\hat{\boldsymbol{\theta}} = \arg\max_{\boldsymbol{\theta}} S_n(\boldsymbol{\theta}). \tag{3.3}$$

Based on (3.3), an estimated optimal individualized treatment rule is $\hat{D}^*(\mathbf{x}) = \text{sign}(\tilde{\mathbf{x}}'\hat{\boldsymbol{\beta}})$. The optimization of (3.3) can be done by using a standard optimization algorithm, such as the `optim` function in R (Nash et al., 2018; R Core Team, 2019). The criterion function $S(\boldsymbol{\theta})$ depends on the ranks of $Y_i$ rather than their numerical values, which implies that the SMRC estimator $\hat{\boldsymbol{\theta}}$ is more robust than the methods using the numerical values in the presence of outliers in $Y_i$. The robustness property of $\hat{\boldsymbol{\theta}}$ will be studied via simulation in Section 5.

## 4. Asymptotic properties

We now investigate the asymptotic properties of the SMRC estimator $\hat{\boldsymbol{\theta}}$. Denote $\boldsymbol{\theta}_0 = (\boldsymbol{\gamma}_0', \boldsymbol{\beta}_0')'$ as the true parameter. For simplicity of presentation, we first introduce some notation. Let $\mathbf{Z} = (\mathbf{X}, A, Y)$ and $\mathbf{z} = (\mathbf{x}, a, y)$. Define

$$\begin{aligned}\tau_n(\mathbf{z}, \boldsymbol{\theta}) = {} & E[I(y > Y) s_n(\mathbf{x}'\boldsymbol{\gamma} + a\tilde{\mathbf{x}}'\boldsymbol{\beta} - \mathbf{X}'\boldsymbol{\gamma} - A\tilde{\mathbf{X}}'\boldsymbol{\beta})] \\ & + E[I(Y > y) s_n(\mathbf{X}'\boldsymbol{\gamma} + A\tilde{\mathbf{X}}'\boldsymbol{\beta} - \mathbf{x}'\boldsymbol{\gamma} - a\tilde{\mathbf{x}}'\boldsymbol{\beta})],\end{aligned}$$

where the expectation is taken with respect to $\mathbf{Z}$. Let $\triangledown_m \tau_n(\mathbf{z}, \boldsymbol{\theta})$ be the $m$th partial derivative operator with respect to $\boldsymbol{\theta}$. Define

$$|\triangledown_m| \tau_n(\mathbf{z}, \boldsymbol{\theta}) = \sum_{i_1 + \cdots + i_m = m} \left| \frac{\partial^m \tau_n(\mathbf{z}, \boldsymbol{\theta})}{\partial \theta_{i_1} \ldots \partial \theta_{i_m}} \right|.$$

To establish the asymptotic results, we assume the following regularity conditions:

(C.1) The true value $\boldsymbol{\theta}_0$ is an interior point of the parameter space $\Theta$, which is a compact subset of $\mathbb{R}^{2p+1}$.

(C.2) The support of $\mathbf{X}$ is not contained in any linear subspace of $\mathbb{R}^p$. The $d$th component of $\mathbf{X}$ has an everywhere positive Lebesgue density, conditional on the other components. The random error term $\epsilon$ is independent of $\mathbf{X}$ in (2.1).

(C.3) Let $\mathcal{N}$ be a neighborhood of $\boldsymbol{\theta}_0$. For each possible value $\mathbf{z} = (\mathbf{x}, a, y)$ of $\mathbf{Z}$,

(i) the second derivatives of $\tau_n(\mathbf{z}, \boldsymbol{\theta})$ with respect to $\boldsymbol{\theta}$ exist in $\mathcal{N}$.

(ii) there is an integrable function $M(\mathbf{z})$ such that for any $\mathbf{z} \in \mathcal{Z}$, $\boldsymbol{\theta}_1$ and $\boldsymbol{\theta}_2$ in $\Theta$,

$$\|\triangledown_2 \tau_n(\mathbf{z}, \boldsymbol{\theta}_1) - \triangledown_2 \tau_n(\mathbf{z}, \boldsymbol{\theta}_2)\| \leq M(\mathbf{z}) \|\boldsymbol{\theta}_1 - \boldsymbol{\theta}_2\|.$$

(iii) $E\{|\triangledown_1 \tau_n(\mathbf{z}, \boldsymbol{\theta}_0)|^2\} < \infty$; $E\{|\triangledown_2| \tau_n(\mathbf{z}, \boldsymbol{\theta}_0)\} < \infty$.

(iv) the matrix $E\{\triangledown_2 \tau_n(\mathbf{z}, \boldsymbol{\theta}_0)\}$ is negative definite.

(v) both $2\mathbf{V} = \lim_{n\to\infty} E\{\triangledown_2 \tau_n(\cdot, \boldsymbol{\theta}_0)\}$ and $\mathbf{H} = \lim_{n\to\infty} E\{\triangledown_1 \tau_n(\cdot, \boldsymbol{\theta}_0)[\triangledown_1 \tau_n(\cdot, \boldsymbol{\theta}_0)]'\}$ exist, and $\mathbf{V}$ is negative definite.

Conditions (C.1)–(C.3) were also used to establish the large sample properties of the rank-based estimators in Sherman (1993).

**Theorem 1.** *Under conditions (C.1)–(C.3), we have* $\sup_{\boldsymbol{\theta}\in\Theta} |G_n(\boldsymbol{\theta}) - S_n(\boldsymbol{\theta})| \xrightarrow{\mathcal{P}} 0$ *as* $n \to \infty$, *where* $\xrightarrow{\mathcal{P}} 0$ *denotes convergence in probability.*

The above result ensures that the approximation in (3.2) is asymptotically accurate. For the SMRC estimator $\hat{\boldsymbol{\theta}}$, its asymptotic distribution is stated in the following theorem.

**Theorem 2.** *Under conditions (C.1)–(C.3), the* SMRC *estimator* $\hat{\boldsymbol{\theta}}$ *satisfies*

$$n^{1/2}(\hat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0) \xrightarrow{\mathcal{D}} N(\mathbf{0}, \mathbf{V}^{-1}\mathbf{H}\mathbf{V}^{-1}), \tag{4.1}$$

*where* $2\mathbf{V} = \lim_{n\to\infty} E\nabla_2\tau_n(\cdot, \boldsymbol{\theta}_0)$, $\mathbf{H} = \lim_{n\to\infty} E\nabla_1\tau_n(\cdot, \boldsymbol{\theta}_0)[\nabla_1\tau_n(\cdot, \boldsymbol{\theta}_0)]'$, *and* $\xrightarrow{\mathcal{D}}$ *denotes convergence in distribution.*

Since the plug-in estimator of the variance matrix $\mathbf{V}^{-1}\mathbf{H}\mathbf{V}^{-1}$ can be unstable and sensitive to the choice of $\sigma_n$, inspired by the methods of Jin et al. (2001) and Cai et al. (2005), we use a resampling approach to estimating the variance. Specifically, consider a stochastically perturbed version of the SMRC objective function

$$\tilde{S}_n(\boldsymbol{\theta}) = \frac{1}{n(n-1)} \sum_{i\neq j} \xi_i\xi_j I(Y_i > Y_j) s_n(\boldsymbol{X}_i'\boldsymbol{\gamma} + A_i\tilde{\boldsymbol{X}}_i'\boldsymbol{\beta} - \boldsymbol{X}_j'\boldsymbol{\gamma} - A_j\tilde{\boldsymbol{X}}_j'\boldsymbol{\beta}),$$

where $\xi_1, \ldots, \xi_n$ are i.i.d. exponential variables with mean 1. Similar to Fan et al. (2017), let $\tilde{\boldsymbol{\theta}} = \arg\max_{\boldsymbol{\beta}} \tilde{S}_n(\boldsymbol{\theta})$. The variance of $\hat{\boldsymbol{\theta}}$ is approximated by the empirical variance matrix of $\tilde{\boldsymbol{\theta}}$ from repeatedly generating $\{\xi_1, \ldots, \xi_n\}$. The following result justifies the use of the above resampling procedure.

**Theorem 3.** *Under conditions (C.1)–(C.3), for the perturbation based estimator* $\tilde{\boldsymbol{\theta}}$, *we have*

$$\sqrt{n}(\tilde{\boldsymbol{\theta}} - \hat{\boldsymbol{\theta}}) \xrightarrow{\mathcal{D}} N(\mathbf{0}, \mathbf{V}^{-1}\mathbf{H}\mathbf{V}^{-1}), \ \text{as } n \to \infty,$$

*where* $\mathbf{V}$ *and* $\mathbf{H}$ *are defined in* (4.1).

## 5. Numerical simulation

In this section, we conduct simulation studies to assess the finite sample performance of the proposed method. We consider the following two models:

Model I: $Y = 1 + (\mathbf{X}'\boldsymbol{\gamma}_0 + A\tilde{\mathbf{X}}'\boldsymbol{\beta}_0)^3 + \epsilon$,

Model II: $Y = 1 + \mathbf{X}'\boldsymbol{\gamma}_0 + A\tilde{\mathbf{X}}'\boldsymbol{\beta}_0 + \epsilon$,

where $\mathbf{X} = (X_1, \ldots, X_p)'$ is generated from a normal distribution $N(\mathbf{0}, \boldsymbol{\Sigma})$ with $\Sigma_{ij} = 0.5^{|i-j|}$ and $p = 8$. The treatment $A$ is generated from $\{-1, 1\}$ with $P(A = 1) = 1/2$, and the random error $\epsilon$ follows $N(0, 1)$. Similar to the settings in Fan et al. (2017), we set $\boldsymbol{\gamma}_0 = (0.5, -0.5, -0.5, 0, 0, -0.5, 0, 0)'$, and $\boldsymbol{\beta}_0 = (0.5, -0.5, 0, 0, 0.5, -0.5, 0, 0, 0)'$ with $\|\boldsymbol{\gamma}_0\| = \|\boldsymbol{\beta}_0\| = 1$. We consider two situations. Case A: the response $Y$ is generated from Models I and II; Case B: $Y$ is generated from Case A, except that three outliers are contained, which follow from a Cauchy distribution with location parameter 0 and scale parameter 500. All the results presented below are based on 200 replications with sample size $n = 300$. All the computations are done in the R (R Core Team, 2019).

To assess the performances of our proposed estimator, we report the estimated bias (BIAS) given by the sample mean of the proposed estimates minus the true value, the sample standard deviation (SSD) of the proposed estimates, the sample mean of the estimated standard errors (ESE), and the empirical coverage probability of the 95% Wald-type confidence interval (CP), where the standard errors of the SMRC estimators are estimated by the resampling method in Section 4 with 200 repetitions. First we try to provide some evaluation of the sensitivity of our proposed method for $\sigma_n = cn^{-1/2}$ with different choices of c. We set $c = 1/3$, 1 and 3, respectively. In Table 1, we only report the results for $\hat{\boldsymbol{\beta}}$ in Model I with Case A (the other cases are similar). From the results, we can see that the choice $c = 1/3$ has the lowest SSD, and $c = 3$ gives much higher SSD values. This indicates that the proposed method is sensitive to $c$. Hence, we need to carefully choose the value of c. Based on the overall performance of the three choices in Table 1, we suggest to use $c = 3$ in the following simulations and real data analysis.

Fan et al. (2017) suggested that the doubly robust concordance-assisted learning (CAL-DR) estimator is more efficient than the IPSW and AIPSW estimators of Zhang et al. (2012). Moreover, the single-index model in Song et al. (2017) is based on the least-squares type estimation, which is sensitive to outliers. Thus, we only compare the proposed SMRC estimator with the CAL-DR estimator of Fan et al. (2017) in the simulations. To assess the performances of the estimators $\hat{\boldsymbol{\gamma}}$ and $\hat{\boldsymbol{\beta}}$, we report the BIAS, SSD, ESE, and CP, respectively. Here the standard errors of the SMRC estimators for $\boldsymbol{\gamma}$ and $\boldsymbol{\beta}$ are estimated by the resampling method in Section 4 with 200 repetitions. To evaluate the accuracy of estimated optimal treatment rule $\hat{D}^*(\tilde{\boldsymbol{X}}) = \text{sign}(\tilde{\boldsymbol{X}}'\hat{\boldsymbol{\beta}})$, we calculate the sample mean and sample standard deviation of the percentage of making correct decisions (PCD), defined as $1 - (2n)^{-1}\sum_{i=1}^{n} |\text{sign}(\tilde{\boldsymbol{X}}'\hat{\boldsymbol{\beta}}) - \text{sign}(\tilde{\boldsymbol{X}}'\boldsymbol{\beta}_0)|$. Let $Y^*(a)$ denote the potential outcome that would result if the subject was given treatment $a \in \mathcal{A}$, then $E[Y^*\{D(\mathbf{X})\}] \triangleq V$ is called the value function of a given treatment regime $D$. This value function is a classical index to assess the treatment regimes (Zhang et al., 2012). Below, we report the sample mean and standard deviation of the value functions for the estimated optimal treatment regime via the simulation-based method in Fan et al. (2017). To be specific, we generate data with $N = 10\,000$ subjects from Models I and II, and

**Table 1**
Evaluation results with different choices of $c$ in the term $\sigma_n = cn^{-1/2}$.

| | Statistic | $\hat{\beta}_0$ | $\hat{\beta}_1$ | $\hat{\beta}_2$ | $\hat{\beta}_3$ | $\hat{\beta}_4$ | $\hat{\beta}_5$ | $\hat{\beta}_6$ | $\hat{\beta}_7$ | $\hat{\beta}_8$ |
|---|---|---|---|---|---|---|---|---|---|---|
| $c = 1/3$ | BIAS | 0.0027 | 0.0043 | 0.0085 | −0.0002 | −0.0022 | 0.0102 | 0.0091 | 0.0011 | 0.0032 |
| | SSD | 0.0336 | 0.0351 | 0.0402 | 0.0479 | 0.0346 | 0.0368 | 0.0408 | 0.0443 | 0.0374 |
| | ESE | 0.0409 | 0.0392 | 0.0462 | 0.0467 | 0.0395 | 0.0386 | 0.0463 | 0.0469 | 0.0448 |
| | CP | 0.975 | 0.995 | 0.970 | 0.950 | 0.975 | 0.970 | 0.970 | 0.970 | 0.985 |
| $c = 1$ | BIAS | −0.0004 | 0.0059 | 0.0022 | 0.0045 | −0.0117 | 0.0058 | 0.0037 | −0.0022 | 0.0064 |
| | SSD | 0.0494 | 0.0460 | 0.0579 | 0.0595 | 0.0475 | 0.0386 | 0.0535 | 0.0568 | 0.0474 |
| | ESE | 0.0529 | 0.0524 | 0.0634 | 0.0635 | 0.0524 | 0.0512 | 0.0634 | 0.0645 | 0.0594 |
| | CP | 0.970 | 0.985 | 0.965 | 0.970 | 0.965 | 1 | 0.985 | 0.990 | 0.975 |
| $c = 3$ | BIAS | −0.0001 | 0.0059 | −0.0055 | 0.0027 | −0.0164 | 0.0188 | −0.0095 | 0.0061 | 0.0020 |
| | SSD | 0.0574 | 0.0606 | 0.0761 | 0.0800 | 0.0551 | 0.0537 | 0.0745 | 0.0742 | 0.0710 |
| | ESE | 0.0626 | 0.0662 | 0.0804 | 0.0809 | 0.0633 | 0.0644 | 0.0807 | 0.0822 | 0.0724 |
| | CP | 0.960 | 0.955 | 0.950 | 0.945 | 0.965 | 0.960 | 0.955 | 0.975 | 0.940 |

**Table 2**
Simulation results of the SMRC estimate for $\gamma$.

| Model | Case | Statistic | $\hat{\gamma}_1$ | $\hat{\gamma}_2$ | $\hat{\gamma}_3$ | $\hat{\gamma}_4$ | $\hat{\gamma}_5$ | $\hat{\gamma}_6$ | $\hat{\gamma}_7$ | $\hat{\gamma}_8$ |
|---|---|---|---|---|---|---|---|---|---|---|
| I | A | BIAS | −0.0091 | 0.0192 | −0.0102 | 0.0022 | 0.0022 | 0.0021 | −0.0024 | −0.0036 |
| | | SSD | 0.0585 | 0.0509 | 0.0597 | 0.0765 | 0.0793 | 0.0796 | 0.0809 | 0.0753 |
| | | ESE | 0.0591 | 0.0559 | 0.0666 | 0.0808 | 0.0806 | 0.0753 | 0.0823 | 0.0722 |
| | | CP | 0.935 | 0.970 | 0.960 | 0.955 | 0.945 | 0.935 | 0.955 | 0.925 |
| | B | BIAS | −0.0038 | 0.0237 | −0.0063 | 0.0107 | −0.0189 | 0.0075 | −0.0121 | 0.0036 |
| | | SSD | 0.0542 | 0.0501 | 0.0692 | 0.0779 | 0.0790 | 0.0755 | 0.0844 | 0.0695 |
| | | ESE | 0.0614 | 0.0598 | 0.0687 | 0.0841 | 0.0836 | 0.0786 | 0.0848 | 0.0747 |
| | | CP | 0.975 | 0.980 | 0.960 | 0.960 | 0.950 | 0.945 | 0.935 | 0.950 |
| II | A | BIAS | −0.0279 | 0.0230 | −0.0028 | 0.0084 | −0.0222 | 0.0135 | −0.0026 | −0.0103 |
| | | SSD | 0.0761 | 0.0683 | 0.0743 | 0.1113 | 0.1116 | 0.0868 | 0.0990 | 0.0849 |
| | | ESE | 0.0767 | 0.0704 | 0.0794 | 0.1010 | 0.1018 | 0.0907 | 0.0978 | 0.0874 |
| | | CP | 0.935 | 0.955 | 0.955 | 0.925 | 0.930 | 0.960 | 0.925 | 0.945 |
| | B | BIAS | −0.0137 | 0.0215 | −0.0229 | 0.0166 | −0.0071 | 0.0140 | −0.0100 | 0.0034 |
| | | SSD | 0.0715 | 0.0624 | 0.0835 | 0.1117 | 0.1147 | 0.0883 | 0.1095 | 0.0962 |
| | | ESE | 0.0755 | 0.0703 | 0.0808 | 0.1011 | 0.1003 | 0.0896 | 0.0964 | 0.0873 |
| | | CP | 0.955 | 0.970 | 0.950 | 0.915 | 0.915 | 0.955 | 0.915 | 0.920 |

obtain the estimated value function $\hat{V}$ for $\hat{D}^*(\mathbf{X})$ as

$$\hat{V} = \frac{1}{N}\sum_{i=1}^{N}[1 + \{\mathbf{X}_i'\boldsymbol{\gamma}_0 + \hat{D}^*(\mathbf{X}_i)\cdot\tilde{\mathbf{X}}_i'\boldsymbol{\beta}_0\}^3], \tag{5.1}$$

and

$$\hat{V} = \frac{1}{N}\sum_{i=1}^{N}[1 + \mathbf{X}_i'\boldsymbol{\gamma}_0 + \hat{D}^*(\mathbf{X}_i)\cdot\tilde{\mathbf{X}}_i'\boldsymbol{\beta}_0]. \tag{5.2}$$

Similarly, we can compute the true value function ($V_0$) for the optimal treatment regime as (5.1) and (5.2), respectively.

From the simulation results in Tables 2–4, we can draw the following conclusions. First, our proposed SMRC estimators for $\boldsymbol{\gamma}$ and $\boldsymbol{\beta}$ are nearly unbiased. Second, the estimated standard errors are close to the standard deviation of the SMRC estimators, and the empirical coverage probability of 95% confidence interval is close to the nominal level. Third, the PCD and $\hat{V}$ of the CAL-DR have slightly better performance than our proposed method in Case A. However, the performance of the CAL-DR is very poor in Case B when there exist outliers. One possible explanation for this phenomenon is that the concordance function of CAL-DR method involves the value of $Y$ rather than its ranking. Hence, the CAL-DR estimator is sensitive to outliers in the responses. In summary, the proposed SMRC method is competitive with the CAL-DR method.

**Table 3**
Estimation and classification results for Model I ($V_0 = 2.9312$).

| Case | Method | Statistic | $\hat{\beta}_0$ | $\hat{\beta}_1$ | $\hat{\beta}_2$ | $\hat{\beta}_3$ | $\hat{\beta}_4$ | $\hat{\beta}_5$ | $\hat{\beta}_6$ | $\hat{\beta}_7$ | $\hat{\beta}_8$ | PCD | $\hat{V}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A | SMRC | BIAS | −0.0033 | 0.0106 | −0.0133 | 0.0125 | −0.0153 | 0.0151 | −0.0076 | −0.0001 | −0.0014 | 0.9402[a] | 2.9033[b] |
| | | SSD | 0.0628 | 0.0604 | 0.0741 | 0.0824 | 0.0573 | 0.0642 | 0.0720 | 0.0792 | 0.0690 | 0.0208 | 0.0480 |
| | | ESE | 0.0625 | 0.0657 | 0.0801 | 0.0819 | 0.0636 | 0.0648 | 0.0812 | 0.0823 | 0.0724 | – | – |
| | | CP | 0.925 | 0.965 | 0.980 | 0.935 | 0.975 | 0.950 | 0.985 | 0.950 | 0.955 | – | – |
| | CAL-DR | BIAS | 0.0136 | 0.0033 | 0.0144 | −0.0188 | −0.0162 | 0.0175 | 0.0230 | 0.0049 | 0.0047 | 0.9835[a] | 2.9090[b] |
| | | SSD | 0.0339 | 0.0495 | 0.0540 | 0.0593 | 0.0457 | 0.0463 | 0.0471 | 0.0466 | 0.0542 | 0.0071 | 0.0460 |
| | | ESE | 0.0360 | 0.0409 | 0.0475 | 0.0524 | 0.0430 | 0.0400 | 0.0463 | 0.0455 | 0.0454 | – | – |
| | | CP | 0.945 | 0.925 | 0.930 | 0.945 | 0.960 | 0.915 | 0.965 | 0.960 | 0.910 | – | – |
| B | SMRC | BIAS | −0.0067 | 0.0090 | −0.0096 | 0.0139 | −0.0186 | 0.0154 | −0.0155 | −0.0013 | −0.0001 | 0.9396[a] | 2.8977[b] |
| | | SSD | 0.0646 | 0.0628 | 0.0819 | 0.0799 | 0.0628 | 0.0594 | 0.0849 | 0.0860 | 0.0735 | 0.0226 | 0.0490 |
| | | ESE | 0.0632 | 0.0669 | 0.0821 | 0.0816 | 0.0649 | 0.0649 | 0.0821 | 0.0829 | 0.0731 | – | – |
| | | CP | 0.955 | 0.955 | 0.960 | 0.955 | 0.955 | 0.965 | 0.965 | 0.940 | 0.925 | – | – |
| | CAL-DR | BIAS | −0.1434 | 0.2508 | 0.0037 | −0.0299 | −0.2465 | 0.2272 | 0.0270 | −0.0227 | −0.0198 | 0.6462[a] | 2.0650[b] |
| | | SSD | 0.2188 | 0.2854 | 0.2638 | 0.2713 | 0.3116 | 0.2803 | 0.2507 | 0.2754 | 0.2933 | 0.0276 | 0.7408 |
| | | ESE | 0.1537 | 0.1609 | 0.1521 | 0.1552 | 0.1659 | 0.1679 | 0.1473 | 0.1562 | 0.1568 | – | – |
| | | CP | 0.840 | 0.615 | 0.760 | 0.775 | 0.660 | 0.660 | 0.770 | 0.740 | 0.725 | – | – |

[a]Denotes the estimate of PCD.
[b]Denotes the estimate of $V_0$.

**Table 4**
Estimation and classification results for Model II ($V_0 = 1.6862$).

| Case | Method | Statistic | $\hat{\beta}_0$ | $\hat{\beta}_1$ | $\hat{\beta}_2$ | $\hat{\beta}_3$ | $\hat{\beta}_4$ | $\hat{\beta}_5$ | $\hat{\beta}_6$ | $\hat{\beta}_7$ | $\hat{\beta}_8$ | PCD | $\hat{V}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A | SMRC | BIAS | −0.0061 | 0.0051 | −0.0112 | 0.0230 | −0.0348 | 0.0233 | −0.0144 | 0.0112 | −0.0057 | 0.9256[a] | 1.6655[b] |
| | | SSD | 0.0701 | 0.0816 | 0.0975 | 0.0983 | 0.0671 | 0.0776 | 0.0998 | 0.0961 | 0.0802 | 0.0224 | 0.0120 |
| | | ESE | 0.0675 | 0.0804 | 0.0988 | 0.0991 | 0.0756 | 0.0768 | 0.0984 | 0.0966 | 0.0855 | – | – |
| | | CP | 0.925 | 0.925 | 0.960 | 0.970 | 0.955 | 0.930 | 0.935 | 0.955 | 0.950 | – | – |
| | CAL-DR | BIAS | 0.0167 | 0.0167 | 0.0020 | 0.0035 | −0.0127 | 0.0150 | 0.0010 | −0.0047 | 0.0032 | 0.9352[a] | 1.6761[b] |
| | | SSD | 0.0415 | 0.0477 | 0.0622 | 0.0643 | 0.0514 | 0.0464 | 0.0591 | 0.0584 | 0.0553 | 0.0134 | 0.0123 |
| | | ESE | 0.0405 | 0.0449 | 0.0533 | 0.0535 | 0.0466 | 0.0446 | 0.0536 | 0.0524 | 0.0519 | – | – |
| | | CP | 0.935 | 0.940 | 0.950 | 0.930 | 0.930 | 0.945 | 0.955 | 0.940 | 0.960 | – | – |
| B | SMRC | BIAS | −0.0187 | 0.0108 | −0.0037 | 0.0079 | −0.0226 | 0.0223 | −0.0115 | −0.0021 | 0.0031 | 0.9240[a] | 1.6630[b] |
| | | SSD | 0.0641 | 0.0842 | 0.1060 | 0.1032 | 0.0778 | 0.0774 | 0.1000 | 0.1023 | 0.0865 | 0.0244 | 0.0133 |
| | | ESE | 0.0678 | 0.0816 | 0.0974 | 0.0982 | 0.0754 | 0.0748 | 0.0988 | 0.0939 | 0.0848 | – | – |
| | | CP | 0.955 | 0.945 | 0.925 | 0.925 | 0.930 | 0.955 | 0.940 | 0.915 | 0.935 | – | – |
| | CAL-DR | BIAS | −0.2468 | 0.3155 | 0.0249 | −0.0298 | −0.2595 | 0.3181 | −0.0011 | −0.006 | −0.0469 | 0.6478[a] | 1.2838[b] |
| | | SSD | 0.2572 | 0.2868 | 0.2963 | 0.3115 | 0.3035 | 0.2976 | 0.3066 | 0.2983 | 0.3381 | 0.0274 | 0.2495 |
| | | ESE | 0.1836 | 0.1784 | 0.1674 | 0.1720 | 0.1890 | 0.1884 | 0.1712 | 0.1822 | 0.1755 | – | – |
| | | CP | 0.760 | 0.575 | 0.740 | 0.715 | 0.720 | 0.570 | 0.740 | 0.760 | 0.670 | – | – |

[a]Denotes the estimate of PCD.
[b]Denotes the estimate of $V_0$.

Finally, to further study the robustness of the proposed method against misspecified models, we consider the following two models:

Model III: $Y = 1 + 2(\mathbf{X}'\boldsymbol{\gamma}_0) + 3.5(A\tilde{\mathbf{X}}'\boldsymbol{\beta}_0)^3 + \epsilon$,
Model IV: $Y = 1 + (\mathbf{X}'\boldsymbol{\gamma}_0)^3 + A\tilde{\mathbf{X}}'\boldsymbol{\beta}_0 + \epsilon$,

where the regression parameter's mechanism is the same as Models I and II. Similarly, we generate data with $N = 10\,000$ subjects from Models III and IV. The estimated value functions for $\hat{D}^*(\mathbf{X})$ are

$$\hat{V} = \frac{1}{N}\sum_{i=1}^{N}[1 + 2(\mathbf{X}_i'\boldsymbol{\gamma}_0) + 3.5\{\hat{D}^*(\mathbf{X}_i)\cdot\tilde{\mathbf{X}}_i{}'\boldsymbol{\beta}_0\}^3],$$

**Table 5**
Simulation results of the SMRC estimate for $\gamma$.

| Model | Case | Statistic | $\hat{\gamma}_1$ | $\hat{\gamma}_2$ | $\hat{\gamma}_3$ | $\hat{\gamma}_4$ | $\hat{\gamma}_5$ | $\hat{\gamma}_6$ | $\hat{\gamma}_7$ | $\hat{\gamma}_8$ |
|---|---|---|---|---|---|---|---|---|---|---|
| III | A | BIAS | −0.0321 | 0.0241 | −0.0091 | 0.0607 | −0.0542 | −0.0123 | −0.0175 | −0.0001 |
| | | SSD | 0.0630 | 0.0578 | 0.0604 | 0.0811 | 0.0823 | 0.0780 | 0.0923 | 0.0744 |
| | | ESE | 0.0627 | 0.0565 | 0.0658 | 0.0857 | 0.0856 | 0.0763 | 0.0817 | 0.0717 |
| | | CP | 0.910 | 0.940 | 0.975 | 0.890 | 0.910 | 0.930 | 0.915 | 0.935 |
| | B | BIAS | −0.0380 | 0.0212 | −0.0019 | 0.0441 | −0.0511 | −0.0134 | −0.0087 | −0.0034 |
| | | SSD | 0.0603 | 0.0543 | 0.0642 | 0.0911 | 0.0798 | 0.0746 | 0.0729 | 0.0699 |
| | | ESE | 0.0646 | 0.0575 | 0.0665 | 0.0866 | 0.0868 | 0.0768 | 0.0823 | 0.0732 |
| | | CP | 0.920 | 0.945 | 0.955 | 0.885 | 0.930 | 0.940 | 0.975 | 0.955 |
| IV | A | BIAS | −0.0224 | 0.0182 | −0.0112 | 0.0180 | −0.0212 | 0.0131 | −0.0131 | −0.0002 |
| | | SSD | 0.0706 | 0.0652 | 0.0799 | 0.0987 | 0.0998 | 0.0990 | 0.1007 | 0.0883 |
| | | ESE | 0.0728 | 0.0670 | 0.0774 | 0.0967 | 0.0964 | 0.0869 | 0.0958 | 0.0854 |
| | | CP | 0.955 | 0.940 | 0.940 | 0.965 | 0.940 | 0.905 | 0.920 | 0.945 |
| | B | BIAS | −0.0059 | 0.0154 | −0.0212 | 0.0314 | −0.0276 | 0.0210 | −0.0028 | −0.0107 |
| | | SSD | 0.0720 | 0.0646 | 0.0788 | 0.1005 | 0.1031 | 0.0869 | 0.1008 | 0.0827 |
| | | ESE | 0.0743 | 0.0688 | 0.0796 | 0.0984 | 0.0989 | 0.0890 | 0.0963 | 0.0861 |
| | | CP | 0.975 | 0.965 | 0.965 | 0.920 | 0.925 | 0.955 | 0.945 | 0.950 |

**Table 6**
Estimation and classification results for Model III ($V_0 = 4.2944$).

| Case | Method | Statistic | $\hat{\beta}_0$ | $\hat{\beta}_1$ | $\hat{\beta}_2$ | $\hat{\beta}_3$ | $\hat{\beta}_4$ | $\hat{\beta}_5$ | $\hat{\beta}_6$ | $\hat{\beta}_7$ | $\hat{\beta}_8$ | PCD | $\hat{V}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A | SMRC | BIAS | −0.0342 | 0.0001 | −0.009 | 0.0029 | 0.0101 | −0.0062 | −0.0099 | 0.0001 | −0.0001 | 0.9575[a] | 4.2862[b] |
| | | SSD | 0.0347 | 0.0405 | 0.0517 | 0.0489 | 0.0373 | 0.0350 | 0.0518 | 0.0463 | 0.0407 | 0.0177 | 0.0736 |
| | | ESE | 0.0359 | 0.0419 | 0.0512 | 0.0512 | 0.0363 | 0.0361 | 0.0518 | 0.0481 | 0.0423 | – | – |
| | | CP | 0.850 | 0.940 | 0.945 | 0.965 | 0.930 | 0.945 | 0.930 | 0.960 | 0.960 | – | – |
| | CAL-DR | BIAS | 0.0172 | 0.0104 | 0.0057 | −0.0003 | −0.0077 | 0.0077 | 0.0035 | 0.0035 | 0.0061 | 0.961[a] | 4.2922[b] |
| | | SSD | 0.0220 | 0.0281 | 0.0327 | 0.0344 | 0.0275 | 0.0274 | 0.0314 | 0.0312 | 0.0297 | 0.0112 | 0.0654 |
| | | ESE | 0.0255 | 0.0283 | 0.0334 | 0.0343 | 0.0303 | 0.0275 | 0.0336 | 0.0332 | 0.0313 | – | – |
| | | CP | 0.910 | 0.945 | 0.960 | 0.955 | 0.975 | 0.950 | 0.970 | 0.985 | 0.975 | – | – |
| B | SMRC | BIAS | −0.0328 | −0.0037 | −0.0042 | 0.0076 | 0.0029 | −0.0070 | −0.0090 | 0.0001 | 0.0024 | 0.9576[a] | 4.2884[b] |
| | | SSD | 0.0351 | 0.0441 | 0.0535 | 0.0521 | 0.0354 | 0.0350 | 0.0519 | 0.0496 | 0.0394 | 0.0169 | 0.0645 |
| | | ESE | 0.0369 | 0.0430 | 0.0527 | 0.0530 | 0.0376 | 0.0370 | 0.0518 | 0.0488 | 0.0431 | – | – |
| | | CP | 0.89 | 0.945 | 0.955 | 0.945 | 0.970 | 0.965 | 0.925 | 0.955 | 0.940 | – | – |
| | CAL-DR | BIAS | −0.1065 | 0.1834 | −0.0016 | 0.0094 | −0.1896 | 0.1508 | −0.0208 | −0.0205 | 0.0257 | 0.8486[a] | 3.5931[b] |
| | | SSD | 0.2071 | 0.2304 | 0.2325 | 0.2617 | 0.2651 | 0.2360 | 0.2391 | 0.2688 | 0.2318 | 0.0210 | 0.9392 |
| | | ESE | 0.1351 | 0.1425 | 0.1332 | 0.1402 | 0.1506 | 0.1434 | 0.1375 | 0.1414 | 0.1326 | – | – |
| | | CP | 0.855 | 0.725 | 0.785 | 0.760 | 0.715 | 0.740 | 0.770 | 0.745 | 0.735 | – | – |

[a]Denotes the estimate of PCD.
[b]Denotes the estimate of $V_0$.

and

$$\hat{V} = \frac{1}{N}\sum_{i=1}^{N}[1 + (\mathbf{X}_i'\boldsymbol{\gamma}_0)^3 + \{\hat{D}^*(\mathbf{X}_i)\cdot\tilde{\mathbf{X}}_i'\boldsymbol{\beta}_0\}],$$

respectively. In Table 5, we report the BIAS, SSD, ESE and CP for the estimate of $\boldsymbol{\gamma}$. The results for the treatment rules are presented in Tables 6 and 7. It can be seen that our proposed method is robust to misspecification of models. Hence, our rank-based approach is acceptable to developing personalized treatment rules in practice.

## 6. Application to AIDS clinical trials study

We illustrate the application of the proposed method by analyzing the AIDS Clinical Trials Group Protocol 175 study (ACTG175), which consists of 2139 subjects infected with the human immunodeficiency virus (Lu et al., 2011; Fan et al.,

**Table 7**
Estimation and classification results for Model IV ($V_0 = 1.6823$).

| Case | Method | Statistic | $\hat{\beta}_0$ | $\hat{\beta}_1$ | $\hat{\beta}_2$ | $\hat{\beta}_3$ | $\hat{\beta}_4$ | $\hat{\beta}_5$ | $\hat{\beta}_6$ | $\hat{\beta}_7$ | $\hat{\beta}_8$ | PCD | $\hat{V}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A | SMRC | BIAS | 0.0011 | 0.0285 | −0.0368 | 0.0275 | −0.0315 | 0.0324 | −0.0247 | −0.0178 | 0.0133 | 0.9149[a] | 1.6553[b] |
| | | SSD | 0.0772 | 0.0910 | 0.1026 | 0.1097 | 0.0790 | 0.0854 | 0.1189 | 0.1101 | 0.0946 | 0.0245 | 0.0229 |
| | | ESE | 0.0736 | 0.0899 | 0.1064 | 0.1083 | 0.0831 | 0.0821 | 0.1075 | 0.1032 | 0.0925 | – | – |
| | | CP | 0.945 | 0.905 | 0.935 | 0.935 | 0.950 | 0.935 | 0.905 | 0.920 | 0.935 | – | – |
| | CAL-DR | BIAS | 0.0061 | 0.0386 | −0.0001 | 0.0060 | −0.0146 | 0.0258 | −0.0206 | 0.0092 | −0.0026 | 0.9088[a] | 1.6632[b] |
| | | SSD | 0.0544 | 0.0856 | 0.0979 | 0.1044 | 0.0767 | 0.0781 | 0.1129 | 0.0839 | 0.0875 | 0.0151 | 0.0239 |
| | | ESE | 0.0583 | 0.0698 | 0.0788 | 0.0808 | 0.0646 | 0.0638 | 0.0877 | 0.0706 | 0.0708 | – | – |
| | | CP | 0.950 | 0.890 | 0.935 | 0.905 | 0.940 | 0.915 | 0.905 | 0.925 | 0.910 | – | – |
| B | SMRC | BIAS | 0.0043 | 0.0270 | −0.0264 | 0.0385 | −0.0459 | 0.0365 | −0.0297 | −0.0033 | 0.0074 | 0.9126[a] | 1.6588[b] |
| | | SSD | 0.0789 | 0.0887 | 0.1253 | 0.1182 | 0.0873 | 0.0848 | 0.1162 | 0.1206 | 0.1078 | 0.0287 | 0.0221 |
| | | ESE | 0.0745 | 0.0908 | 0.1061 | 0.1082 | 0.0852 | 0.0846 | 0.1092 | 0.1023 | 0.0926 | – | – |
| | | CP | 0.910 | 0.945 | 0.870 | 0.900 | 0.915 | 0.920 | 0.930 | 0.885 | 0.900 | – | – |
| | CAL-DR | BIAS | −0.2048 | 0.2793 | 0.0117 | −0.0181 | −0.3123 | 0.2951 | −0.0016 | −0.0152 | 0.0057 | 0.4605[a] | 1.3134[b] |
| | | SSD | 0.2529 | 0.3068 | 0.3058 | 0.2803 | 0.2921 | 0.3024 | 0.3035 | 0.3056 | 0.3125 | 0.0297 | 0.2258 |
| | | ESE | 0.1801 | 0.1822 | 0.1752 | 0.1760 | 0.2000 | 0.1877 | 0.1774 | 0.1764 | 0.1773 | – | – |
| | | CP | 0.780 | 0.570 | 0.730 | 0.765 | 0.675 | 0.580 | 0.750 | 0.720 | 0.705 | – | – |

[a]Denotes the estimate of PCD.
[b]Denotes the estimate of $V_0$.

2017). In the study, the patients were randomized to four different treatment groups: zidovudine (ZDV) monotherapy, ZDV + didanosine (ddI), ZDV + zalcitabine and ddI monotherapy. We consider the subset of patients receiving the treatment ZDV + ddI or ZDV + zalcitabine, with the goal to find their individualized optimal treatment rules. We use $A = -1$ to denote the treatment ZDV + zalcitabine (524 subjects), and $A = 1$ to denote the treatment ZDV + ddI (522 subjects). Let $Y$ be the CD4 cell count (cells per cubic millimeter) at $20 \pm 5$ weeks post-baseline. We use 12 covariates, including five continuous variables, age (years), weight (kilograms), Karnofsky score (a scale of 0–100), CD4 cell count at baseline and CD8 cell count (cells per cubic millimeter) at baseline, and seven binary variables, haemophilia (0 = no; 1 = yes), homosexual activity (0 = no; 1 = yes), history of intravenous drug use (0 = no; 1 = yes), race (0 = white; 1 = non-white), gender (0 = female; 1 = male), antiretroviral history (0 = naive; 1 = experienced) and symptomatic status (0 = asymptomatic; 1 = symptomatic), where the five continuous covariates are normalized with mean 0 and variance 1 (Fan et al., 2017).

We apply the proposed method to estimate the optimal treatment strategy and conduct statistical inference for the corresponding parameters. The estimates for the coefficients (Est), standard errors (SE), 95% confidence intervals (CI) and P-values are reported in Table 8, respectively. It can be seen that age, haemophilia, homosexual activity, history of intravenous drug use and race are significant covariates at the level of 0.05, where age was also selected as significant covariate by Fan et al. (2017). We refit the proposed estimator with the above three significant covariates, which yields the estimated optimal treatment regime as $\text{sign}(0.6957 + 0.4621 \cdot X_1 - 0.0214 \cdot X_6 - 0.3652 \cdot X_7 - 0.0308 \cdot X_8 - 0.4094 \cdot X_9)$. In other words, if 0.6957 + 0.4621 · age − 0.0214 · haemophilia − 0.3652 · homosexual activity − 0.0308 · history of intravenous drug use − 0.4094 · race $> 0$, the optimal treatment for this patient is ZDV + ddI, otherwise, the optimal treatment rule is ZDV + zalcitabine. According to the estimated optimal decision rule, 759 out of 1046 patients (72.6%) should be assigned to treatment ZDV + ddI.

## 7. Concluding remarks

In this article, we propose a robust approach to estimate optimal individualized treatment rules based on the smoothed maximum rank correlation method under a semiparametric generalized regression model. The asymptotic properties of the proposed estimator are established under reasonable conditions. The performance of our method is evaluated via simulation studies. An application to an AIDS Clinical Trials Group Protocol 175 study is provided.

Note that we use $\sigma_n = cn^{-1/2}$ in the sigmoid function, and the simulation results imply that the choice of $c$ matters. Ideally, $c$ would be treated as a tuning parameter to be estimated somehow, and this issue requires further investigation. Moreover, the proposed method can be generalized to the case of censored survival data. Specifically, let $Y$ denote the survival time in model (2.1), and $C$ denote the censoring time. The observed data consists of $(\tilde{Y}_i, \Delta_i, \mathbf{X}_i)$, where $\tilde{Y}_i = \min(Y_i, C_i)$, and $\Delta_i = I(Y_i \le C_i)$, $i = 1, \ldots, n$. Similar to (3.2), we construct a smoothed rank correlation function

$$S_n^*(\boldsymbol{\theta}) = \frac{1}{n(n-1)} \sum_{i \neq j} \Delta_j I(\tilde{Y}_i > \tilde{Y}_j) s_n(\boldsymbol{X}_i'\boldsymbol{\gamma} + A_i\tilde{\boldsymbol{X}}_i'\boldsymbol{\beta} - \boldsymbol{X}_j'\boldsymbol{\gamma} - A_j\tilde{\boldsymbol{X}}_j'\boldsymbol{\beta}).$$

**Table 8**
Estimated optimal treatment regimes for the ACTG175 data.

| | Est | SE | CI | P-value |
|---|---|---|---|---|
| $\hat{\beta}_0$ | 0.5258 | 0.1093 | [0.3114, 0.7402] | $< 10^{-5}$ |
| $\hat{\beta}_1$ | 0.1519 | 0.0612 | [0.0319, 0.2719] | 0.0130 |
| $\hat{\beta}_2$ | −0.0635 | 0.0670 | [−0.1950, 0.0679] | 0.3433 |
| $\hat{\beta}_3$ | −0.0017 | 0.0456 | [−0.0912, 0.0876] | 0.9685 |
| $\hat{\beta}_4$ | 0.1331 | 0.0895 | [−0.0423, 0.3086] | 0.1370 |
| $\hat{\beta}_5$ | −0.0794 | 0.0523 | [−0.1820, 0.0230] | 0.1287 |
| $\hat{\beta}_6$ | −0.4021 | 0.1424 | [−0.6814, −0.1229] | 0.0047 |
| $\hat{\beta}_7$ | −0.4561 | 0.0885 | [−0.6297, −0.2825] | $< 10^{-5}$ |
| $\hat{\beta}_8$ | −0.3302 | 0.1451 | [−0.6147, −0.0456] | 0.0229 |
| $\hat{\beta}_9$ | −0.3624 | 0.1043 | [−0.5669, −0.1579] | 0.0005 |
| $\hat{\beta}_{10}$ | 0.2413 | 0.1283 | [−0.0101, 0.4928] | 0.0600 |
| $\hat{\beta}_{11}$ | −0.0605 | 0.1098 | [−0.2757, 0.1547] | 0.5817 |
| $\hat{\beta}_{12}$ | 0.0131 | 0.1269 | [−0.2356, 0.2619] | 0.9174 |
| $\hat{\gamma}_1$ | −0.0455 | 0.0328 | [−0.1100, 0.0189] | 0.1662 |
| $\hat{\gamma}_2$ | 0.0160 | 0.0408 | [−0.0641, 0.0961] | 0.6949 |
| $\hat{\gamma}_3$ | 0.0555 | 0.0271 | [0.0023, 0.1087] | 0.0405 |
| $\hat{\gamma}_4$ | 0.8068 | 0.0384 | [0.7314, 0.8822] | $< 10^{-5}$ |
| $\hat{\gamma}_5$ | −0.1090 | 0.0277 | [−0.1635, −0.0546] | $8 \times 10^{-5}$ |
| $\hat{\gamma}_6$ | −0.1322 | 0.1037 | [−0.3356, 0.0711] | 0.2025 |
| $\hat{\gamma}_7$ | −0.0581 | 0.0690 | [−0.1934, 0.0770] | 0.39931 |
| $\hat{\gamma}_8$ | 0.2099 | 0.0795 | [0.0539, 0.3659] | 0.0083 |
| $\hat{\gamma}_9$ | −0.2698 | 0.0650 | [−0.3973, −0.1423] | $3 \times 10^{-5}$ |
| $\hat{\gamma}_{10}$ | −0.0277 | 0.0934 | [−0.2109, 0.1555] | 0.7668 |
| $\hat{\gamma}_{11}$ | −0.4367 | 0.0650 | [−0.5641, −0.3092] | $< 10^{-5}$ |
| $\hat{\gamma}_{12}$ | −0.0493 | 0.0659 | [−0.1785, 0.0799] | 0.4546 |

The resulting SMRC estimator $\hat{\boldsymbol{\theta}}^*$, as the maximizer of $S_n^*(\boldsymbol{\theta})$, is consistent and asymptotically normal, which can be derived by the proof techniques in the Appendix. As pointed out by one reviewer, the topics on optimal treatment rules with three or more treatments are of great practical importance (Lou et al., 2018; Qi et al., 2018). It is still unclear how to extend our rank-based method to the setting with multiple treatments, which requires further research efforts.

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## Appendix

**Proof of Theorem 1.** For convenience, denote $u_{ij} = \boldsymbol{\gamma}'(\boldsymbol{X}_i - \boldsymbol{X}_j) + \boldsymbol{\beta}'(A_i\tilde{\boldsymbol{X}}_i - A_j\tilde{\boldsymbol{X}}_j)$. From the definition of $G_n(\cdot)$ and $S_n(\cdot)$, we can derive that

$$|G_n(\boldsymbol{\theta}) - S_n(\boldsymbol{\theta})| \le \frac{1}{n(n-1)} \sum_{i \neq j} |I(u_{ij} > 0) - s_n(u_{ij})|.$$

For any $v > 0$,

$$|G_n(\boldsymbol{\theta}) - S_n(\boldsymbol{\theta})| \le T_{n1} + T_{n2}, \tag{A.1}$$

where

$$T_{n1} = \frac{1}{n(n-1)} \sum_{i \neq j} |I(u_{ij} > 0) - s_n(u_{ij})| \cdot I(|u_{ij}| \ge v),$$

$$T_{n2} = \frac{1}{n(n-1)} \sum_{i \neq j} |I(u_{ij} > 0) - s_n(u_{ij})| \cdot I(|u_{ij}| < v).$$

Since $|I(u_{ij} > 0) - s_n(u_{ij})| \leq \exp(-|u_{ij}|/\sigma_n) < \exp(-|v|/\sigma_n)$ on the set $\{|u_{ij}| \geq v\}$, then $\sigma_n \to 0$ implies that $s_n(w) \to I(u_{ij} > 0)$ uniformly. Thus, $T_{n1}$ converges to 0 uniformly over $\Theta$ as $n \to \infty$.

Because $s_n(\cdot)$ is bounded by 1, the second term $T_{2n} \leq \frac{1}{n(n-1)} \sum_{i \neq j} I(|u_{ij}| < v)$. By the uniform convergence theorem of U-processes (Nolan and Pollard, 1987), the right-hand side converges almost surely to $P(|u_{ij}| < v)$. Under condition (C.2), we can prove in a similar way as Lemma 4 of Horowitz (1992) that $\lim_{v \to 0} P(|u_{ij}| < v) = 0$, and $T_{n2}$ converges to 0. Therefore, the right-hand side of (A.1) converges to 0 uniformly over $\boldsymbol{\theta} \in \Theta$. This completes the proof. □

**Proof of Theorem 2.** For each $\boldsymbol{\theta} \in \Theta$, write $\Gamma_n(\boldsymbol{\theta}) = S_n(\boldsymbol{\theta}) - S_n(\boldsymbol{\theta}_0)$, then $\hat{\boldsymbol{\theta}}$ maximizes $\Gamma_n(\boldsymbol{\theta})$ over $\Theta$. For each $(\mathbf{z}_1, \mathbf{z}_2) \in \mathcal{Z} \otimes \mathcal{Z}$ and $\boldsymbol{\theta} \in \Theta$, define

$$\begin{aligned} f_n(\mathbf{z}_1, \mathbf{z}_2, \boldsymbol{\theta}) = I(y_1 > y_2)[&s_n(\mathbf{x}_1'\boldsymbol{\gamma} - \mathbf{x}_2'\boldsymbol{\gamma} + a_1\tilde{\mathbf{x}}_1'\boldsymbol{\beta} - a_2\tilde{\mathbf{x}}_2'\boldsymbol{\beta}) \\ &- s_n(\mathbf{x}_1'\boldsymbol{\gamma}_0 - \mathbf{x}_2'\boldsymbol{\gamma}_0 + a_1\tilde{\mathbf{x}}_1'\boldsymbol{\beta}_0 - a_2\tilde{\mathbf{x}}_2'\boldsymbol{\beta}_0)]. \end{aligned}$$

Because $\Gamma_n(\cdot)$ is a U-statistics of order 2, we have the Hoeffding decomposition:

$$\Gamma_n(\boldsymbol{\theta}) = E\Gamma_n(\boldsymbol{\theta}) + \mathbb{P}_n g(\cdot, \boldsymbol{\theta}) + \mathbb{U}_n h(\cdot, \cdot, \boldsymbol{\theta}),$$

where

$$\begin{aligned} g(\mathbf{Z}, \boldsymbol{\theta}) &= Ef(\mathbf{Z}, \cdot, \boldsymbol{\theta}) + Ef(\cdot, \mathbf{Z}, \boldsymbol{\theta}) - 2E\Gamma_n(\boldsymbol{\theta}), \\ h(\mathbf{Z}_1, \mathbf{Z}_2, \boldsymbol{\theta}) &= f(\mathbf{Z}_1, \mathbf{Z}_2, \boldsymbol{\theta}) - Ef(\mathbf{Z}_1, \cdot, \boldsymbol{\theta}) - Ef(\cdot, \mathbf{Z}_2, \boldsymbol{\theta}) + E\Gamma_n(\boldsymbol{\theta}), \end{aligned}$$

$\mathbb{P}_n$ is the empirical measure that places mass $1/n$ on each observation $\mathbf{Z}_i = (\mathbf{X}_i, A_i, Y_i)$ $(i = 1, \ldots, n)$, and $\mathbb{U}_n$ is the U-process operator given as $\mathbb{U}_n h(\cdot, \cdot, \boldsymbol{\theta}) = 1/[n(n-1)] \sum_{i \neq j} h(\mathbf{Z}_i, \mathbf{Z}_j, \boldsymbol{\theta})$.

First, we prove that as $\boldsymbol{\theta} \to \boldsymbol{\theta}_0$,

$$\Gamma_n(\boldsymbol{\theta}) = \frac{1}{2}(\boldsymbol{\theta} - \boldsymbol{\theta}_0)'\mathbf{V}(\boldsymbol{\theta} - \boldsymbol{\theta}_0) + o(\|\boldsymbol{\theta} - \boldsymbol{\theta}_0\|^2) + o_p(1). \tag{A.2}$$

By the Taylor expansion of $\tau_n(\mathbf{Z}, \boldsymbol{\theta})$ about $\boldsymbol{\theta}$,

$$\tau_n(\mathbf{Z}, \boldsymbol{\theta}) = \tau_n(\mathbf{Z}, \boldsymbol{\theta}_0) + (\boldsymbol{\theta} - \boldsymbol{\theta}_0)'\nabla_1(\mathbf{Z}, \boldsymbol{\theta}_0) + \frac{1}{2}(\boldsymbol{\theta} - \boldsymbol{\theta}_0)'\nabla_2(\mathbf{Z}, \boldsymbol{\theta}^*)(\boldsymbol{\theta} - \boldsymbol{\theta}_0), \tag{A.3}$$

where $\boldsymbol{\theta}^*$ is between $\boldsymbol{\theta}$ and $\boldsymbol{\theta}_0$. By conditions (C.1)–(C.3), for each $\boldsymbol{\theta}$ in $\Theta$ and $\mathbf{Z} \in \mathcal{Z}$,

$$\|(\boldsymbol{\theta} - \boldsymbol{\theta}_0)'[\nabla_2\tau_n(\mathbf{Z}, \boldsymbol{\theta}) - \nabla_2\tau_n(\mathbf{Z}, \boldsymbol{\theta}_0)](\boldsymbol{\theta} - \boldsymbol{\theta}_0)\| \leq M(\mathbf{Z})\|\boldsymbol{\theta} - \boldsymbol{\theta}_0\|^3. \tag{A.4}$$

Taking expectations in (A.3), together with (A.4) and the integrability of $M(\cdot)$,

$$2\Gamma_n(\boldsymbol{\theta}) = (\boldsymbol{\theta} - \boldsymbol{\theta}_0)'E\nabla_1\tau_n(\cdot, \boldsymbol{\theta}) + (\boldsymbol{\theta} - \boldsymbol{\theta}_0)'\mathbf{V}(\boldsymbol{\theta} - \boldsymbol{\theta}_0) + o(\|\boldsymbol{\theta} - \boldsymbol{\theta}_0\|^2) + o_p(1). \tag{A.5}$$

It follows that $\Gamma_n(\boldsymbol{\theta})$ is maximized at $\boldsymbol{\theta}_0$, and the coefficients of linear term in (A.5) must be zeros. Hence it can be concluded that $E\nabla_1\tau_n(\cdot, \boldsymbol{\theta}) = 0$, and (A.2) holds.

Next, we need to show that

$$\mathbb{P}_n g(\cdot, \boldsymbol{\theta}) = \frac{1}{\sqrt{n}}(\boldsymbol{\theta} - \boldsymbol{\theta}_0)'\mathbf{W}_n + o(\|\boldsymbol{\theta} - \boldsymbol{\theta}_0\|^2), \tag{A.6}$$

where $\mathbf{W}_n \xrightarrow{\mathcal{D}} N(\mathbf{0}, \mathbf{H})$ as $n \to \infty$. Using $g(\mathbf{Z}, \boldsymbol{\theta}) = \tau_n(Z, \boldsymbol{\theta}) - \tau_n(Z, \boldsymbol{\theta}_0) - 2E\Gamma_n(\boldsymbol{\theta})$, together with (A.2)–(A.4), we have

$$\mathbb{P}_n g(\cdot, \boldsymbol{\theta}) = \frac{1}{\sqrt{n}}(\boldsymbol{\theta} - \boldsymbol{\theta}_0)'\mathbf{W}_n + \frac{1}{2}(\boldsymbol{\theta} - \boldsymbol{\theta}_0)'\mathbf{B}_n(\boldsymbol{\theta} - \boldsymbol{\theta}_0) + o(\|\boldsymbol{\theta} - \boldsymbol{\theta}_0\|^2) + T_n(\boldsymbol{\theta}) \tag{A.7}$$

uniformly over $o_p(1)$ neighborhoods of $\boldsymbol{\theta}_0$, where

$$\begin{aligned} \mathbf{W}_n &= \sqrt{n}\mathbb{P}_n\nabla_1\tau_n(\cdot, \boldsymbol{\theta}_0) = \frac{1}{\sqrt{n}}\sum_{i=1}^{n} \nabla_1\tau_n(z_i, \boldsymbol{\theta}_0), \\ \mathbf{B}_n &= \mathbb{P}_n\nabla_2\tau_n(\cdot, \boldsymbol{\theta}_0) - 2\mathbf{V}, \end{aligned}$$

and $|T_n(\boldsymbol{\theta})| \leq \|\boldsymbol{\theta} - \boldsymbol{\theta}_0\|^3\mathbb{P}_n M(\cdot)$. By $E\nabla_1\tau_n(\cdot, \boldsymbol{\theta}) = 0$ and the Slutsky's theorem, $\mathbf{W}_n$ converges in distribution to $N(0, \mathbf{H})$. The law of large numbers implies that $\mathbf{B}_n \xrightarrow{p} 0$ as $n \to \infty$. Moreover, by the integrability of $M(\cdot)$, we have $T_n(\boldsymbol{\theta}) = o_p(\|\boldsymbol{\theta} - \boldsymbol{\theta}_0\|^2)$.

Finally, by Theorem 4 of Sherman (1993), we can prove

$$\mathbb{U}_n h(\cdot, \cdot, \boldsymbol{\theta}) = o_p(n^{-1}) \tag{A.8}$$

uniformly over $o_p(1)$ neighborhoods of $\boldsymbol{\theta}_0$. Thus, (A.2), (A.6) and (A.8) indicate that

$$\Gamma_n(\boldsymbol{\theta}) = \frac{1}{2}(\boldsymbol{\theta}-\boldsymbol{\theta}_0)'\mathbf{V}(\boldsymbol{\theta}-\boldsymbol{\theta}_0) + \frac{1}{\sqrt{n}}(\boldsymbol{\theta}-\boldsymbol{\theta}_0)'\mathbf{W}_n + o(\|\boldsymbol{\theta}-\boldsymbol{\theta}_0\|^2) + o_p(n^{-1}) + o_p(1). \tag{A.9}$$

Since $\mathbf{V}$ is a negative definite matrix, it follows from Theorem 2 of Sherman (1993) that

$$\sqrt{n}(\hat{\boldsymbol{\theta}}-\boldsymbol{\theta}_0) = -\mathbf{V}^{-1}\frac{1}{\sqrt{n}}\sum_{i=1}^{n}\triangledown_1\tau_n(z_i,\boldsymbol{\theta}_0) + o_P(1). \tag{A.10}$$

Hence the central limit theorem and the Slutsky's theorem show that

$$\sqrt{n}(\hat{\boldsymbol{\theta}}-\boldsymbol{\theta}_0) \xrightarrow{\mathcal{D}} N(0, \mathbf{V}^{-1}\mathbf{H}\mathbf{V}^{-1}) \quad \text{as} \quad n \to \infty.$$

This ends the proof. □

**Proof of Theorem 3.** Note that

$$\tilde{S}_n(\boldsymbol{\theta}) = \frac{1}{n(n-1)}\sum_{i\neq j}\xi_i\xi_j I(Y_i > Y_j)s_n(\boldsymbol{X}_i'\boldsymbol{\gamma} + A_i\tilde{\boldsymbol{X}}_i'\boldsymbol{\beta} - \boldsymbol{X}_j'\boldsymbol{\gamma} - A_j\tilde{\boldsymbol{X}}_j'\boldsymbol{\beta}).$$

Due to $\xi_i\xi_j$ are independent of the term $I(Y_i > Y_j)s_n(\boldsymbol{X}_i'\boldsymbol{\gamma} + A_i\tilde{\boldsymbol{X}}_i'\boldsymbol{\beta} - \boldsymbol{X}_j'\boldsymbol{\gamma} - A_j\tilde{\boldsymbol{X}}_j'\boldsymbol{\beta})$, following similar arguments as in the proofs of (A.10), we have

$$\sqrt{n}(\tilde{\boldsymbol{\theta}}-\boldsymbol{\theta}_0) = -\mathbf{V}^{-1}\frac{1}{\sqrt{n}}\sum_{i=1}^{n}\xi_i\triangledown_1\tau_n(z_i,\boldsymbol{\theta}_0) + o_P(1). \tag{A.11}$$

In view of (A.10) and (A.11), some straightforward calculations show that

$$\sqrt{n}(\tilde{\boldsymbol{\theta}}-\hat{\boldsymbol{\theta}}) = -\mathbf{V}^{-1}\frac{1}{\sqrt{n}}\sum_{i=1}^{n}(\xi_i-1)\triangledown_1\tau_n(z_i,\boldsymbol{\theta}_0) + o_P(1).$$

Because $\xi_i$ are i.i.d. random variables with $E(\xi_i) = 1$ and $Var(\xi_i) = 1$, it follows from the central limit theorem and the Slutsky's theorem that

$$\sqrt{n}(\tilde{\boldsymbol{\theta}}-\hat{\boldsymbol{\theta}}) \xrightarrow{\mathcal{D}} N(\mathbf{0}, \mathbf{V}^{-1}\mathbf{H}\mathbf{V}^{-1}).$$

This ends the proof. □

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