A Parsimonious Personalized Dose Finding Model via Dimension Reduction

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Abstract

Learning an individualized dose rule in personalized medicine is a challenging statistical problem. Existing methods often suffer from the curse of dimensionality, especially when the decision function is estimated nonparametrically. To tackle this problem, we propose a dimension reduction framework that effectively reduces the estimation to a lower-dimensional subspace of the covariates. We exploit that the individualized dose rule can be defined in a subspace spanned by a few linear combinations of the covariates, leading to a more parsimonious model. The proposed framework does not require the inverse probability of the propensity score under observational studies due to a direct maximization of the value function. This distinguishes us from the outcome weighted learning framework, which also solves decision rules directly. Under the same framework, we further propose a pseudo-direct learning approach that focuses more on estimating the dimensionality-reduced subspace of the treatment outcome. Parameters in both approaches can be estimated efficiently using an orthogonality constrained optimization algorithm on the Stiefel manifold. Under mild regularity assumptions, the results on the asymptotic normality of the proposed estimators are established, respectively. We also derive the consistency and convergence rate for the value function under the estimated optimal dose rule. We evaluate the performance of the proposed approaches through extensive simulation studies and a warfarin pharmacogenetic dataset.

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1 Introduction

Personalized medicine is a medical procedure that aims to improve an individual patient’s health outcome by a tailored medical treatment based on the patient’s genetic, prognostic, and clinical information. It has received much attention from the statistical and clinical research communities due to patients’ heterogeneity and the difficulties involved in implementations. There is an extensive literature on developing statistical methodologies for estimating individualized treatment rules, in both single and multiple decision points. Examples include risk level calibration (Cai et al., 2010), penalized models (Lu et al., 2013; Tian et al., 2014), machine learning approaches (Foster et al., 2011; Kang et al., 2014; Laber and Zhao, 2015; Loh et al., 2015), two-step regression-based approaches (Zhao et al., 2009; Qian and Murphy, 2011; Moodie et al., 2014; Zhu and Qu, 2016) and many others. The readers may refer to Kosorok and Laber (2019) for a comprehensive review.

A popular framework for estimating the optimal individualized treatment rule is outcome weighted (Zhao et al., 2012). The advantage of this framework is directly estimating the treatment decision without modeling the relationship between the treatment and outcome. Zhao et al. (2012) developed an approach for binary treatments. It has been extended to other settings such as backward and simultaneous outcome weighted learning (Zhao et al., 2015), the tree-based method of Zhu et al. (2017), residual weighted learning (Zhou et al., 2017), and augmented outcome weighted learning (Liu et al., 2018). For multiclass treatment settings, existing approaches include the offset tree algorithm (Beygelzimer and Langford, 2009), contrast weighting (Tao and Wang, 2017), and others (Zhang et al., 2018; Zhou et al., 2018; Huang et al., 2019). Extensions to dose-finding (Chen et al., 2016) are statistically more challenging due to the cardinality of treatment options.

To obtain more flexible decision rules, many existing methods employ machine learning or nonparametric approaches. Support vector machines (Cortes and Vapnik, 1995) and
random forests (Breiman, 2001) are extensively used in the personalized medicine literature. However, as the complexity of decision rules increases, the sheer number of covariates makes it difficult to estimate the underlying model accurately. Besides linear models, a promising approach is sufficient dimension reduction (Cook, 2009) of the feature space. In a classical setting, sufficient dimension reduction assumes that the response relies only on several linear combinations of the covariates, which greatly reduces the feature space. Furthermore, dimension reduction allows for better interpretability of the fitted model, which is particularly appealing in personalized medicine. Existing works of sufficient dimension reduction include methods proposed by Li (1991); Cook and Weisberg (1991); Xia et al. (2002); Ma and Zhu (2012, 2013a) and many others. We refer readers to Adragni and Cook (2009) and Ma and Zhu (2013b) for more details of this topic.

In this paper, we propose a dimension reduction framework for estimating the optimal individualized dose rule. An immediate advantage is that the nonparametrically optimal dose rule is adaptive to a low-dimensional covariate space. This circumvents the curse of dimensionality and allows for better interpretability. We further propose two approaches: a direct learning approach and a pseudo-direct learning approach. In the direct learning approach, we exploit that the dose rule, instead of the outcome, can be modeled in a linear subspace of the covariates. This leads to a key advantage that we can directly estimate the optimal dose rule without modeling propensity scores in an observational study. On the other hand, the pseudo-direct learning approach is achieved in two-stages. In the first stage, we estimate the low-dimensional subspace of the outcome, while in the second stage, the optimal dose rule can be estimated on the dimensionality-reduced subspace. Interestingly, the pseudo-direct learning approach has a close connection with the partial dimension reduction framework (Feng et al., 2013) when we regard the dose treatment as a conditional variable. The proposed estimators are constructed under a semiparametric framework, where we utilize an orthogonality-constrained optimization algorithm to solve for the parameters.
2 Proposed Method

2.1 Personalized Dose-finding

Consider a dose assignment $A \in \mathcal{A} = [0, 1]$, where $\mathcal{A}$ is a safe dose range. Let $X = (X_1, X_2, ..., X_p)^T \in \mathcal{X}$ denote the prognostic covariates, where $\mathcal{X}$ is the feature space. Let $R$ be the observed clinical outcome. Without loss of generality, we assume that a larger value of $R$ is more desirable. An individualized treatment rule $f$, is a map from $\mathcal{X}$ to a dose assignment space $\mathcal{A}$. To properly define an optimal individualized treatment rule $f_{opt}(X)$, we consider a potential outcomes framework (Rubin, 1974; Robins, 1986). Let $R^*(a)$ be the potential outcome under a given dose level $a$, and we make the following common and well-studied assumptions: (i) strong ignorability (Robins, 1986), $A \perp \perp R^*(a) \mid X$, for all $a \in \mathcal{A}$; (ii) consistency, $R = R^*(A)$; (iii) positivity, $P(A = a \mid X = x) > 0$, almost surely. Under a randomized dose trial, the strong ignorability assumption is trivially satisfied; however in an observational study, it could be unverifiable (Bang and Robins, 2005). Also, the assumption (iii) can be relaxed under our proposed dimension reduction framework and a corresponding discussion will be presented in Remark 2.1. Under the above assumptions, we are able to estimate the optimal treatment rule by using the value function proposed in Qian and Murphy (2011):

$$V_f = E^f(R) = \int R dP^f,$$

where $E^f$ is the expectation with respect to $P^f$ which is defined as the restricted joint distribution of $\{X, R, A = f(X)\}$. Then the optimal individual treatment rule is the maximizer of the value function, that is $f_{opt}(X) = \text{argmax}_f V_f$. When $\mathcal{A}$ is a binary space such that $\mathcal{A} = \{-1, 1\}$, Zhao et al. (2012) estimate $f_{opt}(X)$ by using the value function in (2.1). For dose-finding problems, Chen et al. (2016) extend the binary outcome weighted learning framework to handle continuous treatment options by using a local approximation of the
value function:

$$V_f = \lim_{\phi \to 0^+} E\left( \frac{R\{A \in \{f(X) - \phi, f(X) + \phi\}\}}{2\phi P(A \mid X)} \right) = \lim_{\phi \to 0^+} \tilde{V}_{f,\phi}, \quad (2.2)$$

where $P(A \mid X)$ is the randomization probability of $A$ given $X$. The dose rule can then be solved using the sample version of this approximation.

### 2.2 Dimensionality-Reduced Personalized Dose Rule

In practice, patients’ prognostic, genetic, and clinical information usually consists of a large number of covariates. This often creates difficulties for estimating the optimal dose rule. For example, support vector regressions used in the outcome weighted learning approaches can be sensitive to the dimension of covariates (Dasgupta et al., 2013). It is then desirable to construct an optimal dose rule in a dimensionality-reduced space. In particular, if there is a $p \times d$ constant matrix $B$ with $d < p$, such that the optimal dose rule can be re-defined as

$$f_{opt}(X) = f_{opt}(B^T X), \quad (2.3)$$

then its estimation can be more efficient. This structure can not only capture the majority of the information carried by the original features but also enjoy better interpretability and can be easier to implement. This falls into the sufficient dimension reduction framework (Li, 1991; Cook, 2009), which is a long-standing and promising technique. With a slight abuse of notation, let $f(B^T X) : \mathbb{R}^d \to \mathcal{A}$ be a dose rule as an analogy of $f(X)$ in the dimensionality-reduced space. We will focus on two goals: estimating the dimension reduction basis matrix $B$ and the optimal rule $f_{opt}$ in the dimensionality-reduced space.
2.3 The Direct Learning Approach

Let us define a new version of the value function as follows:

\[
V_f(B) = E \left[ E\left\{ R \mid X, A = f(B^T X) \right\} \right] \\
= E \left[ E\left\{ R \mid B^T X, A = f(B^T X) \right\} \right]. \tag{2.4}
\]

In this equation, the assigned dose level is a deterministic quantity as a function of \( B^T X \).

Also, \( V_f(B) \) is not necessarily the same as \( V_f \) since \( f(B^T X) \) is more restrictive than \( f(X) \).

However, we can see that the two attain the same maximum under the assumption of the previously defined dimension reduction optimal dose rule (2.3), that is

\[
\max_f V_f = \max_{f,B} V_f(B).
\]

The formulation in (2.4) suggests taking expectation on the restricted distribution \( \{ R, B^T X, A = f(B^T X) \} \) while searching for the best direction \( B \) to directly maximize the value function. This is similar to a regression framework. However, it does not assume that the outcome \( R \) depends only on \( B^T X \). Instead, \( E\{ R \mid B^T X, A = f(B^T X) \} \) can be regarded as a sub-population average who has the same suggested dose level \( f(B^T X) \) with covariate \( B^T X \). The second equality in (2.4) suggests that we do not need to model the regression outcome using the full information of \( X \). This strategy distinguishes us from the outcome weighted learning framework (Zhao et al., 2012), which utilizes the Radon-Nikodym theorem and estimates the value function on the distribution of \( (R, X, A) \). Interestingly, this also allows us to avoid estimating the propensity score in an observational study setting. Another advantage of our proposal is that \( B^T X \) is a low-dimensional vector which circumvents the curse of dimensionality. This leads to the following penalized sample version of the value function through kernel approximations of the conditional expectation.
\[ E\{R \mid B^T X, A = f(B^T X)\} \] for each subject:

\[
V_{n,f}(B) = \frac{1}{n} \sum_{i=1}^{n} \sum_{j=1}^{n} \frac{R_i K_v \left( \{X_j^T B, f(B^T X_j)\}^T - (X_i^T B, A_i) \right)}{\sum_{i=1}^{n} K_v \left( \{X_j^T B, f(B^T X_j)\}^T - (X_i^T B, A_i) \right)} - \lambda_n \|f\|^2. \tag{2.5}
\]

Here, \( K_v(u) = \prod_{k=1}^{d+1} K(u_k/h)/h \) is a \( d + 1 \)-dimensional kernel function with a \( d + 1 \)-dimensional bandwidth vector \( v = (h, \ldots, h)^T \). \( K(u) \) is a univariate kernel and \( d \) is the true structural dimension. Lastly, \( \|f\| \) is some seminorm for \( f \) and \( \lambda_n \) serves as a penalty on the complexity of \( f \). The optimization problem is then defined as

\[
(\hat{B}, \hat{f}_{opt}) = \arg\max_{B \in \mathbb{R}^{p \times d}, f} V_{n,f}(B). \tag{2.6}
\]

Maximizing objective function is still a challenging task because of the two unknowns, \( f \) and \( B \). We consider an update scheme which alternates between \( B \) and \( f \), motivated by a series of semiparametric dimension reduction models (Ma and Zhu, 2012, 2013a; Sun et al., 2019). To be specific, maximizing \( B \) over \( V_{n,f}(B) \) can be viewed as searching for the dimension reduction space, which can be carried out using the computational approach proposed by Sun et al. (2019). On the other hand, when fixing a matrix \( B \), solving \( f \) reduces to a personalized dose-finding problem on the reduced space \( B^T X \). Details of the proposed algorithm is given in Section 3. Furthermore, we shall see from Section 4 that the numerical optimization procedure may affect the asymptotic properties of the estimator. Hence, we will consider two different strategies when optimizing (2.6), one of which involves a sample-splitting procedure, detailed in Section 3.

**Remark 2.1.** Existing propensity score based approaches usually require the positivity assumption such that \( P(A = a \mid X = x) > 0 \). This is not needed for our approach. Instead, we require that \( P(A = a \mid B^T X = z) > 0 \) for all \( B, z \) and \( a \). This is a similar but slightly weaker assumption to ensure that nonparametric estimation can be performed on \( (B^T X, A) \). Such the positivity assumption is natural in nonparametric regressions (Ichimura, 1991; Andrews, 1995).
2.4 The Pseudo-Direct Learning Approach

We may also make a slightly stronger assumption on the outcome to impose a multiple-index model. This connects the proposed framework with a partial dimension reduction model (Feng et al., 2013). In particular, let

\[ E(R \mid X, A) = M(B^T X, A), \]  

(2.7)

where \( M(\cdot) \) is an unknown link function. The implication of \( B \) is slightly different than the direct learning approach. Here, we assume that the outcome \( R \) relies completely on \( B^T X \) and \( A \), whereas in the direct learning approach, \( R \) may still depend on the entire covariates \( X \). However, it is easy to see that the optimal treatment \( f_{\text{opt}} = \arg\max_a M(B^T X, A = a) \) must still be a function of \( B^T X \). If we estimate \( B \) matrix first, the does rule can be estimated in the reduced covariate space \( B^T X \). Therefore, we consider a two-stage approach: In the first stage, we identify the dimensionality-reduced space by estimating \( B \) matrix in (2.7); In the second stage, we apply an existing dose-finding approach to learn the optimal dose rule using \( B^T X \). In the first step, the conditional mean function can be estimated by

\[ \hat{M}(B^T x, a) = \frac{\sum_{i=1}^{n} R_i K_v \{(X_i^T B, A_i)^T - (x^T B, a)^T \}}{\sum_{i=1}^{n} K_v \{(X_i^T B, A_i)^T - (x^T B, a)^T \}}, \]  

(2.8)

where the multidimensional kernel \( K_v(\cdot) \) follows our previous definition in (2.5). The matrix \( B \) can be solved by minimizing the least-squares objective function

\[ \psi(B) = \frac{1}{n} \sum_{i=1}^{n} \{ R_i - \hat{M}(B^T X_i, A_i) \}^2. \]  

(2.9)

Hence, the pseudo-direct learning approach is to solve the minimization problem:

\[ \hat{B} = \arg\min_{B \in \mathbb{R}^{p \times d}} \psi(B). \]  

(2.10)

The implementation of pseudo-direct learning will be discussed in Section 3.3. Note again that there is a connection between our approach and the partial dimension reduction prob-
lem (Feng et al., 2013), which is done by an estimation matrix and eigen-decomposition. Comparisons will be provided in Supplementary Material.

3 Implementation and Algorithms

3.1 Direct Learning Algorithm

We first discuss a general procedure for updating $f$ and $B$. However, our theoretical investigation suggests that, a naive optimization can only guarantee consistency of the estimator. To achieve asymptotic normality of $\hat{B}$, a sample-splitting procedure (Bickel, 1982; Powell et al., 1989) can be incorporated. The sample-splitting procedure will be described in Section 3.2, while in the current section, we focus on a standard procedure. Consider updating $f$ when given $B$ at the $t$-th iteration. We denote $B^{(t)}$ as the current value of the basis matrix $B$, then we turn to solve:

$$\arg\max_f V_n, f(B^{(t)}).$$

(3.1)

This is to find an individualized dose rule in the dimensionality-reduced subspace spanned by $B^{(t)}$. This can be done by considering $f$ from the Reproducing kernel Hilbert Space $\mathcal{H}$:

$$f^{(t)}(\cdot) = \sum_{j=1}^n w_j K(\cdot, B^{(t)^T} X_j),$$

(3.2)

and the penalty term becomes $\|w\|^2$. Hence, plugging (3.2) into the optimization problem (3.1), we solve for the parameter vector $w = (w_1, \ldots, w_n)^T$. This can be done by performing gradient descent. The gradient descent solution may be influenced by its initial value. In practice, we can obtain a warm start $w$ using a kernel ridge regression. Details of this implementation are provided in Supplementary Material.

We then proceed to solve $B$ by fixing $f$. As pointed out by Sun et al. (2019), the difficulty lies in guaranteeing the column rank of $B$ when all elements of $B$ are of free-changing parameters. Besides, any scale change of an entire column in $B$ gives essentially
the same solution for estimating the optimal rule. Therefore, we consider a fixed \( d \) and estimate \( B \) in a restricted space such that \( B^T B = I_{d \times d} \), which leads to

\[
\hat{B} = \arg\max_{B \in \mathbb{R}^{p \times d}, B^T B = I} V_{n, \hat{f}}(B). 
\]  

This orthogonality constrained space is commonly known as the Stiefel manifold. We use a first-order updating procedure proposed by Wen and Yin (2013), which preserves the solution in the manifold. The procedure works by calculating the gradient matrix \( G \) and the skew-symmetric matrix \( Q \) using

\[
G = \frac{-\partial V_{n, \hat{f}}(B)}{\partial B}\bigg|_{B(t)} \quad \text{and} \quad Q = GB^{(t)}T - B^{(t)}G^T, 
\]  

respectively. Here, the gradient matrix \( G \) can be approximated numerically. Then, we update

\[
B^{(t+1)} = \left(I + \frac{\tau}{2}Q\right)^{-1} \left(I - \frac{\tau}{2}Q\right) B^{(t)}, 
\]  

where \( \tau \) is a small step size chosen to satisfy the Armijo-Wolfe conditions at the current iteration. This updated \( B \) enjoys the property that \( B^{(t+1)}T B^{(t+1)} = B^{(t)}T B^{(t)} = I \), which preserves the orthogonality. Now, this completes the update of \( B \) when fixing \( f \). A summary of the estimating procedure is provided in Algorithm 3.1.

**Direct learning alternating update algorithm.**

1. Initialize: \( D = \{X_i, A_i, R_i\}_{i=1}^n \), \( B^{(0)} \) such that \( B^{(0)}T B^{(0)} = I \), \( \varepsilon \leftarrow 10^{-8} \).
2. For \( t = 1 \) to \( t = \max\text{.iter} \):
   - Fixing \( B^{(t)} \), solve the optimization problem (3.1) by updating \( w \) in (3.2).
   - Fixing \( f^{(t+1)}(\cdot) \), numerically approximate \( G \) and \( Q \) based on equation (3.4).
   - Use a line search algorithm to find a step size \( \tau \) in (3.5).
   - Update \( B^{(t+1)} \leftarrow \left(I + \frac{\tau}{2}Q\right)^{-1} \left(I - \frac{\tau}{2}Q\right) B^{(t)} \).
   - Stop if \( \|G\| \leq \varepsilon \).
3. Return: \( \hat{B} = B^{(t+1)} \) and \( \hat{f}_{\text{opt}} = f^{(t+1)} \).
3.2 Direct Learning with Sample-splitting

In Algorithm 3.1, we utilize the whole sample data when updating $B$ and $f$. Our theoretical analysis shows that $\hat{B}$ based on this algorithm is a consistent estimator, however, it may not achieve asymptotical normality. To address this issue, we incorporate a sample-splitting strategy (Bickel, 1982; Powell et al., 1989). Specifically, we randomly split the whole sample data into two subsets, $D_1 = \{X_i, A_i, R_i\}_{i=1}^n$ and $D_2 = \{X_j, A_j, R_j\}_{i=n_1+1}^n$ using, for example, $n_1 = n/2$. When fixing $f$ and updating $B$, we use $D_1$; when fixing $B$ and updating $f$, we use $D_2$. The detailed algorithm is provided in Supplementary Material.

3.3 Pseudo-Direct Learning Algorithm

The pseudo-direct learning method concerns solving the optimization problem defined in (2.10). Similar to the direct learning approach, we solve this in the Stiefel manifold:

$$\hat{B} = \arg\min_{B \in \mathbb{R}^{p \times d}, B^T B = I} \psi(B). \quad (3.6)$$

where $\psi(B)$ is the $\ell_2$ loss objective function defined in (2.9). The same updating scheme in (3.5) can be used to obtain the solution. We omit the details of the algorithm here since the procedure is largely identical to updating of $B$ when fixing $f$ in the direct learning approach, except that this is a minimization instead of maximization.

Remark 3.1. In both the direct, including direct-split, and pseudo-direct learning algorithms, we use the Gaussian kernel function with a bandwidth $h = \left\{\frac{4}{(d+2)}\right\}^{1/(d+4)n^{-1/(d+4)}} \hat{\sigma}$ on each dimension, where $\hat{\sigma}$ is the estimated standard deviation of the corresponding variable.

Remark 3.2. In all algorithms, we suggest an initial value of $B^{(0)}$ obtained from the partial-SAVE proposed in (Feng et al., 2013), which is computationally fast. Although the method in Feng et al. (2013) is proposed for the partial linear multiple index model, it can still serve as a good warm start based on our numerical experience.
4 Theoretical Properties

In this section, we investigate the theoretical properties of the proposed estimators and algorithms. In Theorem 4.1, we show that \( \hat{B} \) obtained from the pseudo direct learning approach is asymptotically normal. Then, we analyze the consistency of the direct learning estimator in Theorem 4.2. This result also applies to a direct-split algorithm with slight modifications. In Theorem 4.3, we present the asymptotic normality of the estimator obtained from the direct-split algorithm. Lastly, the convergence rate of the value function is established in Theorem 4.4.

To facilitate later arguments, we consider an upper-block diagonal version of the basis matrix \( B \) following the idea in (Ma and Zhu, 2013a). This is mainly for the identifiability concern. To be specific, we can always find a rotation matrix \( U \) such that \( BU = (I_d, B_l^T)^T \) where \( d \) is the true structural dimension, \( I_d \) is a \( d \times d \) identity matrix, and \( B_l \) is a \( (p-d) \times d \) matrix. Hence, the basis matrix \( B \) is identifiable by solving elements in \( B_l \). We further define the concatenation of the columns in any arbitrary \( p \times d \) parameterized matrix \( B \) as \( \text{vecl}(B) = \text{vec}(B_l) = (B_{d+1,1}, ..., B_{p,1}, ..., B_{d+1,d}, ..., B_{p,d})^T \). We also denote \( B_0 \) as the true basis matrix after this parameterization. All proofs in this section are provided in Supplementary Material.

We first provide several regularity assumptions required for showing the asymptotic normality of the pseudo-direct learning estimator. Assumption A1 states some smoothness conditions with respect to the underlying conditional mean function and density function for the convergence of the kernel estimator. Assumption A2 ensures the information matrix of \( B_0 \) is non-singular. Assumption A3 provides bandwidth conditions for the kernel estimator.

**Assumption A1.** Let \( \tilde{X} = (\tilde{X}^T, ..., \tilde{X}^T) \in \mathbb{R}^{(p-d)\times d} \) with \( \tilde{X} = (X_{d+1}, ..., X_p)^T \) and \( Z = B^T X \) for given matrix \( B \). We denote \( (\cdot)^\otimes \) as the Kronecker power of a vector, and \( p(z, a) \) as the probability density function of \( (Z, A) \). For \( k = 1, 2 \) and \( \alpha \in \mathbb{Z}^+ \), we denote \( \alpha \)-th partial derivatives of \( M(z, a) \), \( E\{(\tilde{X} - \tilde{x})^{\otimes k} \mid Z = z\} \) and \( p(z, a) \) with respect to the argument \( z \) as \( \partial_z^\alpha M(z, a) \), \( \partial_z^\alpha E\{(\tilde{X} - \tilde{x})^{\otimes k} \mid Z = z\} \) and \( \partial_z^\alpha p(z, a) \), respectively. These derivatives are Lipschitz continuous over \((z, a)\) with the Lipschitz constant independent of \((z, a)\).
Assumption A2. For \( l = 0, 1 \), let

\[
M^{[1]}(B_0^T x, a) = \partial_{\text{vecl}(B)}[E\{(\tilde{X} - \tilde{x}) \mid B_0^T X = B_0^T x\} \{M(B_0^T x, a)\}^T p(B_0^T x, a)]
\]

and

\[
M^{[1]}(B_0^T x, a) = \sum_{l=0}^{1} \{ -M(B_0^T x, a) \}^T M^{[1]}_{1-l}(B_0^T x, a)/M(B_0^T x, a),
\]

then we assume \( \det(I_{M,B_0}) \neq 0 \), where the information matrix \( I_{M,B_0} = E\{M^{[1]}(B_0^T X, A)^{\otimes 2}\} \).

Assumption A3. The bandwidth \( h \) satisfy

\[
h n^{1/(2(\alpha-1))} \to 0 \quad \text{and} \quad n^{1/2} h^{d+3} / \log n \to 0
\]

for some \( \alpha \geq [(d+1)/2] + 1 \), where \( \alpha \in \mathbb{Z}^+ \).

Theorem 4.1. Under Assumptions A1-A3 and the model assumption given in (2.7), we have that the estimator of the pseudo-direct learning \( \text{vecl}(\hat{B}) \) is asymptotically normal,

\[
\sqrt{n}\{\text{vecl}(\hat{B}) - \text{vecl}(B_0)\} \to \mathcal{N}(0, E\{\text{vecl}(I_{M,B_0}^{-1} S_{M,B_0})\}^{\otimes 2}),
\]

where \( \text{vecl}(\cdot) \) represents vectorization of the lower block of a matrix, and \( S_{M,B_0} = M^{[1]}(B_0^T X, A)\{R - M(B_0^T X, A)\} \) with \( M^{[1]}(B_0^T X, A) \) and \( I_{M,B_0} \) defined in Assumption A2.

Theoretical results of the direct learning and direct-split learning approaches are significantly different from the pseudo-direct learning approach. It is interesting that standard results of semiparametric theory cannot be directly applied to obtain the asymptotic normality. This is mainly because of the unknown nonparametric function \( f \) involved in the formulation. Some identifiability and smoothness conditions are required to develop the theoretical results. We state them after introducing the following definitions. Let \( \text{vecl}(B) \in \Theta \), where \( \Theta \) is a subset of \( \mathbb{R}^{(p-d)\times d} \). For any \( \delta_1 > 0 \), we define \( \Theta_{\delta_1} = \{\text{vecl}(B) \in \Theta : ||\text{vecl}(B) - \text{vecl}(B_0)|| \leq \delta_1\} \). Further let \( \eta(x, B, f) = E\{R \mid B^T X = B^T x, A = f(B^T x)\} \) and let \( \eta_0(x, B) = E\{R \mid B^T X = B^T x, A = f_{\text{opt}}(B^T x)\} \).

Assumption A4. \( B_0 \) is a unique maximizer of \( E\{\eta_0(X, B)\} \), and \( \text{vecl}(B_0) \) is an interior point in \( \Theta \) which is a compact subset of \( \mathbb{R}^{(p-d)\times d} \).

Assumption A5. Define \( C_{\mathcal{H}}^\alpha(\cdot) \) as a class of functions on a bounded set with uniformly bounded partial derivatives up to order \( \lfloor \alpha \rfloor \). In addition, the highest partial derivatives of
such class of functions possess Lipschitz of order $\alpha - \lfloor \alpha \rfloor$. Assume for any $\text{vecl}(B) \in \Theta_{\delta_1}$, $\eta(x, B, f) \in C^\alpha(\mathcal{X}_d)$, where $\mathcal{X}_d$ is a finite union of bounded and convex subsets of $\mathbb{R}^d$ with nonempty interior.

Assumption A4 is a standard assumption to ensure identifiability. Assumption A5 imposes the smoothness condition for $\eta(x, B, f)$. We now present the consistency result for the direct learning approach implemented through Algorithm 3.1.

**Theorem 4.2.** Let $\text{vecl}(\hat{B})$ be the estimator of the direct learning approach implemented in Algorithm 3.1. Then under Assumption A3-A5, $\text{vecl}(\hat{B})$ is consistent to $\text{vecl}(B_0)$, that is

$$
\|\text{vecl}(\hat{B}) - \text{vecl}(B_0)\| = o_p(1),
$$

where $\| \cdot \|$ is the $L_2$-norm.

Analyzing the asymptotic distribution of the direct learning estimator $\text{vecl}(\hat{B})$ is slightly more involved. We needed to capture the effect of the nonparametric estimation of $\eta_0(x, B)$ which includes two components: the conditional mean function $\eta(x, B, f)$, and the dose rule function $f(B^T x)$ as one of the arguments in $\eta(x, B, f)$. This distinguishes us from the standard semiparametric estimation problems (Newey, 1994; Andrews, 1994; Ichimura and Lee, 2010), which usually only need to capture the effect of the conditional mean function but not the estimation of $f$. On the original non-splitting procedure, the samples used for estimating $f(B^T x)$ is also for the kernel approximation of $\eta(x, B, f)$. Therefore, the covariance between $\hat{f}(B^T x)$ and $\hat{\eta}(x, B, f)$ are non-zero, which will be involved in the reminder term in the asymptotic linear form of $\hat{\eta}(x, B, f)$ and $\partial \hat{\eta}(x, B, f)/\partial \text{vecl}(B)$. Without the fast convergence rate of the reminder terms, the asymptotic normality of $\text{vecl}(\hat{B})$ is hard to be guaranteed (Ichimura and Lee, 2010). To tackle this issue, we consider a cross-fitting strategy, also known as sample splitting (Bickel, 1982; Powell et al., 1989; Chernozhukov et al., 2018; Newey and Robins, 2018). With the sample splitting procedure provided by Algorithm 10.2 in Supplementary Material, the variation of the estimation of $f(B^T x)$ can be evaluated on the samples which are independent from the samples used for the kernel
approximation of $\eta(x, B, f)$. This allows us to control the corresponding remainder term in the linear approximation, thus the asymptotic normality of $\text{vecl}(\hat{B})$ can be established. The following regularity assumptions are needed before we proceed to present the root-$n$ asymptotic normality result in Theorem 4.3. These conditions mainly concern the smoothness of $\eta_0(x, B)$ and its derivative.

**Assumption A6.** As a function of $B$, $\eta_0(x, B)$ is twice continuously differentiable on $\Theta_{\delta_1}$ with bounded derivatives.

**Assumption A7.** For any $\text{vecl}(B) \in \Theta$, $\partial \eta_0(x, B)/\partial \text{vecl}(B)$ is twice continuously differentiable with respect to $x$.

**Theorem 4.3.** Let

$$V_0(X) = E\left\{ \frac{\partial^2 \eta_0(X, B)}{\partial \text{vecl}(B) \partial \text{vecl}(B)^T} \right\}_{\text{vecl}(B)=\text{vecl}(B_0)}$$

and

$$\Gamma_0(X) = \left[ \frac{\partial \eta_0(X, B)}{\partial \text{vecl}(B)} - E\left\{ \frac{\partial \eta_0(X, B)}{\partial \text{vecl}(B)} \right\} \right]_{\text{vecl}(B)=\text{vecl}(B_0)} .$$

Under the assumptions A3-A7, and we assume that $\Omega_0 = E\{\Gamma_0(X)\Gamma_0(X)^T\}$ exists and $V_0$ is a positive definite matrix, then the estimator from the direct-split learning algorithm is asymptotically normal, that is

$$\sqrt{n}\{\text{vecl}(\hat{B}) - \text{vecl}(B_0)\} \to \mathcal{N}(0, \Sigma),$$

where $\Sigma = V_0^{-1}\Omega_0 V_0^{-1}$.

To conclude this section, we present the convergence rate of $V_{\hat{f}_{\text{opt}}} (\hat{B})$ to the optimal value function $V_{f_{\text{opt}}}(B_0)$. A smoothness assumption is needed before we present Theorem 4.4.

**Assumption A8.** For any $\text{vecl}(B) \in \Theta_{\delta_1}$, the conditional expectation $E(R \mid B^T X = B^T x, A = a)$ is Lipschitz continuous over $a$ with the Lipschitz constant independent of $a$.

**Theorem 4.4.** Under Assumptions A3-A8, the estimated value function based on estimators from the direct-split learning algorithm converges to the optimal value function, that
is

\[ V_{\text{opt}}(B_0) - V_{\hat{\text{opt}}}(\hat{B}) = O_p\left(\left(\frac{\log n}{n}\right)^{\frac{\alpha}{2\alpha + d + 1}}\right). \]

**Remark 4.1.** As \( d \ll p \), Theorem 4.4 implies that the convergence rate of \( V_{\hat{\text{opt}}}(\hat{B}) \) is faster than the corresponding value function convergence rate \( O_p\{n^{-1/(4+3p/\alpha)}\} \) in (Chen et al., 2016). When \( d = p \), we can achieve the convergence rate \( O_p\{(\log n/n)^{\alpha/(2\alpha+p+1)}\} \), which is still faster than the rate in Chen et al. (2016).

**Remark 4.2.** For the pseudo direct learning approach, the convergence rate of \( V_{\hat{\text{opt}}}(\hat{B}) \) depends on the existing individualized dose-finding methods used in the second stage. For example, if we use the method of Chen et al. (2016), the corresponding convergence rate should be faster since it enjoys the advantage of the proposed dimension reduction framework, that is \( O_p\{n^{-1/(4+3d/\alpha)}\} \), where \( d \ll p \).

## 5 Simulation Studies

We consider six different simulation settings. In the settings 1-4, data are generated from a randomized trial where the dose assignment \( A \sim \text{Unif}[0,2] \), while in settings 5 and 6, observational data is considered. For each setting, we consider \( p = 10 \) or 20. For all settings, we use \( B = (\beta_1, \beta_2) \) where \( \beta_1 = (1,0.5,0,0,-0.5,0,\ldots,0)^T \) and \( \beta_2 = (0.5,0,0.5,-0.5,1,0,\ldots,0)^T \). The number of 0 elements depends on the size of \( p \). In setting 1, \( X \) is generated independently from \( \text{Unif}[-1,1] \). In settings 2, 3 and 5, \( X \) is generated independently from a standard normal distribution. In setting 4, \( X \sim N(0,\Sigma) \), where \( \Sigma = (0.5^{i-j})_{ij} \). In setting 6, \( X \) are independent normal with mean 2.5 and variance 1.

In setting 5, we let \( A \) follow TruncNormal\((0.25 - 0.25|\beta_1^T X| + (0.75\beta_1^T X + 0.75)^{-1},1,2,0)\), meaning that the propensity score is aligned with one of the dimensions of the treatment decision. Here, TruncNormal\((\mu, \sigma, u, l)\) is a truncated normal distribution with mean \( \mu \), standard deviation \( \sigma \), upper and lower bounds \( u \) and \( l \), respectively. In setting 6, \( A \) follows Beta\((6.5 - X_1 + 2X_4 + X_7, 6.5)\), hence the treatment assignment is not in the dimension
predictors for Lasso, and we implement the random forests approach using “randomForest” (Liaw and Wiener, 2002). Setting 5 of the virtual-twin model (Foster et al., 2011). The code of K-O-learning is provided in the supporting information.

Each experiment is repeated 100 times with a training sample size \( n = 400 \) and testing sample size \( 3000 \). We compare our methods with K-O-learning (Chen et al., 2016), Lasso (Tibshirani, 1996) and random forests (Liaw et al., 2002). Since K-O learning requires positive \( R \) values, and all other methods are invariance under intercept changes, we will force \( R \) to be positive by subtracting its lowest value. Lasso and random forests are regression-based approaches that model the outcome \( R \) first, then select the best dose level by maximizing the predicted outcome for a new subject. \( \{X, A, X^2, X \cdot A, A^2\} \) is used as predictors for Lasso, and \( \{X, A\} \) is used for random forests since the model automatically incorporates interactions. The random forest approach can be viewed as a continuous dose version of the virtual-twin model (Foster et al., 2011). The code of K-O-learning is provided by Chen et al. (2016). For Lasso, we used the R package “glmnet” (Friedman et al., 2010), and we implement the random forests approach using “randomForest” (Liaw and Wiener, 2002) package. Tuning parameters are selected by 10-fold cross-validation except \( \phi \) in
K-O-learning is fixed to be 0.15, similar in Chen et al. (2016).

Settings 5 and 6 are both observational studies. Our direct and direct-split learning approaches do not require to estimate the propensity score. For the pseudo direct learning and K-O-learning approaches, we use a boosting method (Zhu et al., 2015) and Beta regression method (Zeileis et al., 2010) to estimate the propensity score. The propensity score model is misspecified in setting 5 while correctly specified in setting 6 with the Beta regression. We also evaluate pseudo-direct learning and K-O-learning approaches when ignoring the propensity score adjustment. To measure numerical performance of the estimated dose rule, the predicted value function $V_f(B)$ (Zhao et al., 2012), and the squared error of the estimated optimal dose, defined as $E\{(\hat{f}_{opt} - f_{opt})^2\}$, are considered. These results are summarized in Table 1 and Table 2.

We also investigate the accuracy of the estimated column space of the dimension reduction matrix $B$. We mainly compare the proposed methods with Feng et al. (2013), as it is one the few available approach that has the potential to detect iterations between $X$ and $A$. Furthermore, we analyze the robustness of the proposed approaches when $d$ is overspecified. In particular, we consider using $d = 2$ in setting 4. These results are presented and discussed in Supplementary Material.

As the results of Table 1-2, the proposed three approaches achieve significantly better performance compared to existing methods. The performance of direct and direct-split learning is similar. When the outcome function depends on two directions, and the dose rule $f_{opt}$ depends on only one direction, the two direct learning approaches perform similar or better than the pseudo-direct learning. This is mainly because the direct learning approaches only estimate the subspace of $f_{opt}$. Hence, they are more efficient than pseudo-direct learning, which estimates all directions related to the outcome. Among competing methods, the K-O-learning has the best performance, followed by random forests and Lasso. However, K-O-learning is relatively sensitive to the dimension of covariates, suffering more under $p = 20$ compared with $p = 10$. For random forests, another disadvantage is the computational cost. In the settings with $d = 2$, the random forest costs several minutes
### Table 1: Simulation results: mean (sd) predicted value function and mean (sd) squared dose distance

| Method            | Setting 1 |                  |                  | Setting 2 |                  |                  |
|-------------------|-----------|------------------|------------------|-----------|------------------|------------------|
|                   | p = 10    | p = 20           | p = 10           | p = 20    |                  |                  |
|                   | Predicted Value Function | Dose distance | Predicted Value Function | Dose distance | Predicted Value Function | Dose distance |
| Direct            | 6.16 (0.25) | 0.07 (0.02)     | 5.45 (0.44)     | 0.11 (0.02) | 9.41 (0.31)     | 0.13 (0.04)     |
| Direct-Split      | 5.71 (0.33) | 0.09 (0.02)     | 4.89 (0.41)     | 0.14 (0.03) | 9.57 (0.30)     | 0.10 (0.05)     |
| Pseudo-Direct     | 6.52 (0.14) | 0.04 (0.01)     | 6.41 (0.12)     | 0.05 (0.01) | 7.27 (0.18)     | 0.38 (0.02)     |
| K-O-learning      | 4.78 (0.28) | 0.19 (0.02)     | 4.85 (0.25)     | 0.12 (0.05) | 7.12 (0.36)     | 0.40 (0.04)     |
| Random Forests    | 4.10 (0.19) | 0.18 (0.01)     | 3.68 (0.40)     | 0.22 (0.03) | 2.39 (0.17)     | 1.30 (0.04)     |
| Lasso             | 3.05 (3.17) | 0.26 (0.20)     | -5.83 (1.96)    | 0.82 (0.12) |                  |                  |

### Table 2: Simulation results for observational studies: mean (sd) predicted value function and mean (sd) squared dose distance

| Method            | Setting 5 |                  |                  | Setting 6 |                  |                  |
|-------------------|-----------|------------------|------------------|-----------|------------------|------------------|
|                   | p = 10    | p = 20           | p = 10           | p = 20    |                  |                  |
|                   | Predicted Value Function | Dose distance | Predicted Value Function | Dose distance | Predicted Value Function | Dose distance |
| Direct            | 9.77 (0.18) | 0.08 (0.03)     | 9.41 (0.31)     | 0.13 (0.04) | 9.57 (0.30)     | 0.10 (0.05)     |
| Direct-Split      | 9.60 (0.40) | 0.11 (0.05)     | 9.23 (0.36)     | 0.15 (0.04) | 7.27 (0.18)     | 0.38 (0.02)     |
| Pseudo-Direct     | 9.64 (0.21) | 0.08 (0.03)     | 9.57 (0.30)     | 0.10 (0.05) | 7.12 (0.36)     | 0.40 (0.04)     |
| K-O-learning      | 9.64 (0.21) | 0.14 (0.02)     | 6.63 (0.08)     | 0.18 (0.01) | 2.39 (0.17)     | 1.30 (0.04)     |
| Pseudo-Direct-Adjust | 6.45 (0.10) | 0.21 (0.02)     | 6.21 (0.16)     | 0.24 (0.02) |                  |                  |
| Lasso             | 5.78 (1.34) | 1.22 (0.27)     | 3.15 (0.26)     | 0.86 (0.06) |                  |                  |

Note: “Pseudo-Direct-Adjust” and “K-O-learning-Adjust” are the methods using the estimated $p(A|X)$.
to estimate the optimal dose level in a single experiment, while the proposed approaches require less than 30 seconds for the same experiment. The Lasso method fails to estimate, as expected, the optimal rule in the non-linear settings. We also observe that the performance of K-O-learning is affected by the propensity score adjustment. In setting 5 where the propensity score model is misspecified, the biased estimation of the propensity score significantly damages the performance. The direct learning, including direct-split learning, outperforms K-O-learning by circumventing the bias from the model misspecification. In setting 6 where the propensity score is correctly specified, K-O-learning-Adjustment has an improved performance comparing to K-O-learning. This implies that the correct specification and accurate estimation of the propensity score play an important role in the K-O-learning approach. However, even if the propensity score is correctly specified, the direct and direct-split learning can still achieve better performance; besides, they also avoid additional computation cost because they exclude the procedure of estimating the propensity score.

6 Data Analysis

Warfarin, commonly known as a “blood thinner”, is one of the most broadly used oral anticoagulant agents to treat blood clots and prevent forming new harmful blood clots to decrease the risk of heart attack or stroke. The appropriate dose level of warfarin significantly affects the treatment effects. Hence, we apply our proposed methods to the dataset provided by International Warfarin Pharmacogenetics Consortium (2009) to estimate the optimal dose level. The International Warfarin Pharmacogenetics Consortium provided one of the most comprehensive and public datasets of clinical and pharmacogenetic covariates. We acquire both the pharmacogenetic and clinical data, including height, weight, age, race, phenytoin, carbamazepine, amiodarone, VKORC1 genotype, and CYP2C9 genotype. To measure the reward, we consider $R = -|2.5 - \text{International Normalized Ratio}|$, where the international normalized ratio is the primary outcome to measure the safety and efficiency of the dose level of warfarin. For patients prescribed warfarin, the target INR is around
2.5. After excluding missing observations, we obtain the data with 2344 patients.

It has been shown in International Warfarin Pharmacogenetics Consortium (2009) that the data were collected from observational studies instead of a randomized dose assignment. Hence, when necessary, such as the pseudo-direct learning and K-O-learning, we adjust for the propensity score \( P(A \mid X) \) using the same approach described in Zhu et al. (2015). Determining the structural dimension is a practically important task. Several approaches are possible. For example, we may treat the number of dimensions as a tuning parameter and select it through cross-validation. Another possible approach is to perform model selection using a BIC type of criterion in (Zhu et al., 2006; Feng et al., 2013) for determining the structure dimension. Besides, we can also follow a modified information criterion method developed in Ma and Zhang (2015). The details are given in Supplementary Material. After applying this method, we found that \( d = 1 \) achieves the best fitting performance for all proposed approaches. Hence, for all subsequent analyses, we set \( d = 1 \).

To make a comparison among the methods, we randomly split the dataset 100 times to obtain the training dataset including 800 patients and testing dataset consisting of the rest 1544 patients. However, in practice, the true dose level is still unknown on the testing set. Hence, there does not exist a direct measure to evaluate the performance. To address this issue, we calculate an expected reward for each subject on the testing dataset. To be specific, suppose the predicted optimal doses are \( a_1, \ldots, a_n \), respectively for subjects on the testing dataset, we then calculate an estimated value function \( \hat{R} \) which is only based on the testing dataset,

\[
\hat{R}_{\text{test}} = \frac{1}{n_{\text{test}}} \sum_{j=1}^{n_{\text{test}}} \sum_{i=1}^{n_{\text{test}}} R_i K_v(X_j - X_i, a_j - A_i) \left/ \sum_{i=1}^{n_{\text{test}}} K_v(X_j - X_i, a_j - A_i) \right.
\]

We report the average values and standard errors of the estimated value function on the testing dataset over repeating 100 experiments in Figure 1. The results suggest that direct and direct-split learning approaches perform best, while the pseudo-direct learning approach slightly outperforms other methods. Most of the observed warfarin dose levels in
the dataset are not far away from the optimal dose level because most observations have an observed INR close to 2.5. Hence, the improvement we observe is minor.

7 Discussion

When the number of covariates is extremely large, most sufficient dimension reduction methods may fail to estimate the subspace spanned by $B$ accurately. Hence, some additional modifications are probably needed (Wang and Zhu, 2013; Wang et al., 2018). It would be interesting to extend the proposed dimension reduction framework to the right-censored outcomes (Zhao et al., 2014; Zhu et al., 2017) and construct a corresponding direct learning approach to estimate the optimal dose rule. To estimate the covariance of the direct-split learning estimator in Theorem 4.3, we may use a sample estimator of $\hat{\Sigma} = \hat{V}_n^{-1}\hat{\Omega}_n\hat{V}_n^{-1}$. However, this requires to compute a second-order partial derivative in the term $\hat{V}_n$. This can lead to unsatisfactory performance when the sample size is small. Alternatively, we can use a bootstrap estimator, and the results of 90% confidence interval are provided in Supplementary Material. We observe a mild under-coverage at around 5%. Since the proposed objective function is non-convex, the result is satisfactory. However, additional work may still be required for further investigation to reduce the under-coverage.
For many complex diseases, a dynamic treatment regime that involves a sequence of
decision rules is often needed. For example, Rich et al. (2014) proposed an adaptive strategy
for the multiple-stage personalized dose-finding; Zhao et al. (2015) estimated the optimal
dynamic treatment regime by converting the estimation problem to a single classification
problem. Estimating the propensity score is again a challenging task. The proposed method
may shed light under such settings.

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9 Supplementary Material

Supplementary material available at Biometrika online includes the details of the warm
start procedure, the direct-split algorithm, the determination of the structure dimension
used in the real data analysis, the additional numerical results, the proofs of Theorems
4.1-4.4 and lemmas.

10 Addition Results

10.1 Warm start of $w$ in the direct learning algorithm

We use the approach motivated by the empirical location of the maximum procedures
(Müller, 1985). The idea is as follows. For current iterating step $t$, we first take the current
covariates $B^{(t)^T}X$ to solve the following extrema problem for each subject $i = 1, \ldots, n$:

$$
\tilde{A}_i = \arg\max_{a} \hat{R}_i(a, B^{(t)}) ,
$$

(10.1)

where a kernel approximated reward $\hat{R}_i(a, B^{(t)})$ is defined as

$$
\hat{R}_i(a, B^{(t)}) = \frac{\sum_{j=1}^{n} R_j K_v \left\{ \left( X^T j B^{(t)} T A_j \right)^T - \left( X^T i B^{(t)} T a \right)^T \right\} }{\sum_{j=1}^{n} K_v \left\{ (X^T j B^{(t)} T A_j)^T - (X^T i B^{(t)} T a)^T \right\} } .
$$

(10.2)

Note that without the regularity term in (2.5), the new update of $f (B^{(t)^T} X_i) = \tilde{A}_i$ already maximizes the expected reward. By imposing the regularity term, we can solve (3.1) in a class of smooth functions. This can be implemented by a kernel ridge regression approach:

$$
\text{maximize } f \in \mathcal{H} \sum_{i=1}^{n} \{ \tilde{A}_i - f(B^{(t)^T} X_i) \}^2 - \lambda_n \| f \|^2_{\mathcal{H}} = \text{maximize } w \sum_{i=1}^{n} \{ \tilde{A}_i - \sum_{j} w_j K(B^{(t)^T} X_i, B^{(t)^T} X_j) \}^2 - \lambda_n \| w \|^2 ,
$$

(10.3)

where $K(\cdot, \cdot)$ is a $d$-dimensional kernel function, $f$ is from a Reproducing Kernel Hilbert Space $\mathcal{H}$ and $\| \cdot \|_{\mathcal{H}}$ is the corresponding norm. The analytic solution is given by

$$
f^{(t)}(\cdot) = \sum_{j=1}^{n} w_j K(\cdot, B^{(t)^T} X_j) = \tilde{A}^T (K_{n \times n} + \lambda_n I)^{-1} \kappa(\cdot, B^{(t)^T} X) ,
$$

(10.4)

where $K_{n \times n}$ is an $n \times n$ kernel matrix with $K(B^{(t)^T} X_i, B^{(t)^T} X_j)$ as the $(i, j)$’th entry, and $\kappa(\cdot, B^{(t)^T} X)$ is an $n \times 1$ vector with $K(\cdot, B^{(t)^T} X_i)$ as the $i$’th element. Hence, the solution of $w$ is

$$
w = (K_{n \times n} + \lambda_n I)^{-1} \tilde{A} .
$$

(10.5)

The tuning parameter $\lambda_n$ can be chosen adaptively using the generalized cross-validation (Golub et al., 1979).

From a theoretical point of view, $\tilde{A}_i$ should be obtained by maximizing over all possi-
ble values of dose, which may require a one-dimensional gradient descent of the function $\hat{R}_i(\cdot, B^{(t)})$. However, such an approach may not be necessary and is computationally inefficient. Instead, we can simply take a set of grid points on the dose range and optimize on the grid. This is mainly because that our primarily interest is the functional form of $f^{(t)}(\cdot)$ rather than the individual best dose value $\tilde{A}_i$. Following the idea of Müller (1985), we can choose a set of $q = O(n^{1/2})$ grid points such that $\min \{ A_i \} = a_1 < \cdots < a_q = \max \{ A_i \}$, and solve for the maxima $\tilde{A}_i$ on this grid as an approximation of the true maxima in (10.1). This may result in an extra $O(n^{-1/2})$ approximation error, however, it should not affect the theoretical results since the rate of the approximation error is faster than the rate of a kernel ridge regression (Dicker et al., 2017). In practice, we adopt a uniform partitioning which fixes the difference $a_{j+1} - a_j$ as a constant for $j = 1, 2, \ldots, q - 1$. Hence, we obtain $\tilde{A}_i$ as

$$\tilde{A}_i = \arg\max_{a \in \{a_1, \ldots, a_q\}} \hat{R}_i(a, B^{(t)}),$$  \hspace{1cm} (10.6)

then the solution $w$ can be obtained using (10.6) instead of (10.1).

As we mentioned above, another way of solving problem (10.1) is to use a one-dimensional optimization, which may yield a more accurate result for each subject. It should be noted that accuracy for each subject is not a severe issue because the optimal dose rule is jointly modeled by all subjects in (10.4). It can be computationally intensive due to the non-convexity of the objective function, and there is no significant difference in terms of the performance.

### 10.2 Direct-split learning algorithm

The following is a modification of the direct learning algorithm proposed in Algorithm 3.1 provided in the main text. The major modification is to split the data into two separate sets $\mathcal{D}_1$ and $\mathcal{D}_2$, according to the description provided in Section 3.2.
Direct-Split learning algorithm

Initialize: $\mathcal{D} = \{X_i, A_i, R_i\}_{i=1}^n$, $B^{(0)}$ such that $B^{(0)\top}B^{(0)} = I$, $\varepsilon \leftarrow 10^{-8}$.

Splitting: Split $\mathcal{D}$ to $\mathcal{D}_1$ and $\mathcal{D}_2$ randomly.

For $t = 1$ to $t = \text{max.iter}$:

Fixing $B^{(t)}$, calculate $R_i(a, B^{(t)})$ and $\tilde{A}_i$ in equations (10.2) and (10.6) using $\mathcal{D}_1$.

Update $w$ in $f^{(t+1)}(\cdot)$ based on equation (10.4) using $\mathcal{D}_1$.

Fixing $f^{(t+1)}(\cdot)$, numerically approximate $G$ and $Q$ based on equation (3.4) using $\mathcal{D}_2$.

Use a line search algorithm to find the best step size $\tau$ in equation (3.5).

Update $B^{(t+1)} \leftarrow \left( I + \frac{\tau}{2}Q \right)^{-1} \left( I - \frac{\tau}{2}Q \right) B^{(t)}$ using $\mathcal{D}_2$.

Stop if $\|G\| \leq \varepsilon$.

Return: $\hat{B} = B^{(t+1)}$ and $\hat{f}_{\text{opt}} = f^{(t+1)}$.

10.3 Asymptotic variance estimation

In Theorem 4.3, we show that the estimator of direct-split learning vecl($\hat{B}$) is asymptotic normal. We use the bootstrapping method to estimate its asymptotic covariance $\Sigma$. To evaluate performance of the covariance estimation, we calculate the 90\% confidence interval of vecl($\hat{B}$) in the simulation setting 2, where the true parameter for dose rule is $B = (1, 0.5, 0, -0.5, 0, 0, 0, 0, 0, 0)^\top$. As we mention in Section 4, we consider an upper-block diagonal version of the parameter matrix $B$ following the idea in (Ma and Zhu, 2013a). Then the parametrized version of $B$ is vecl($B$) = $\beta = (0.5, 0, 0, -0.5, 0, 0, 0, 0, 0, 0)^\top$. The results are summarized in Figure 2 and Table 3.

Table 3: 90\% bootstrap confidence interval covering times over 100 times simulations

| Elements in $B$ | $B_1$ | $B_2$ | $B_3$ | $B_4$ | $B_5$ | $B_6$ | $B_7$ | $B_8$ | $B_9$ | $B_{10}$ |
|-----------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|----------|
| Parameter value | 1     | 0.5   | 0     | 0     | -0.5  | 0     | 0     | 0     | 0     | 0        |
| Coverage %      | -     | 87    | 82    | 84    | 91    | 90    | 87    | 80    | 79    | 84       |

10.4 Additional simulation results

This section contains additional simulation results of investigating the accuracy of the estimated column space of the dimension reduction matrix $B$. Performance is measured by three criteria: the Frobenius norm distance between the projection matrix $P_B = B(B^\top B)^{-1}B^\top$ and corresponding estimator’s version $\hat{P}_B$; the trace correlation $\text{tr}(P_B\hat{P}_B)/d$, where $d$ is the structural dimension; and the canonical correlation between $B^\top X$ and $\hat{B}^\top X$. For the
Figure 2: 90% bootstrap confidence interval estimation over 100 times simulations under simulation setting 4 with $p = 10$

competing method, we implement partial-SAVE in (Feng et al., 2013). The results are summarized in Table 4. It should be noted that for settings 2 to 6, the direct learning approaches are compared against one true direction of the dose rule, while the pseudo-direct approach and partial-SAVE are compared with two true directions of the outcome.

Overall, the proposed methods achieve better performance than partial-SAVE in (Feng et al., 2013). In particular, the pseudo direct learning method achieves the best overall performance except for setting 2. This is probably due to the design of the mean reward function $M(X, B, A)$. When the mean reward function $M(X, B, A)$ has a dimension reduction structure, meaning that $M(X, B, A)$ is a function of $B^T X$, the pseudo direct learning method should be the optimal one since it estimates the whole subspace. On the other hand, the direct learning approaches are under the risk of a greater bias when trying to estimate only one direction.
Table 4: Simulation results: comparison for estimating the dimension reduction space

| Setting | Method       | predictor dimension $p = 10$ | predictor dimension $p = 20$ |
|---------|--------------|-------------------------------|-------------------------------|
|         | Frobenius    | Trace | Canonical | Frobenius   | Trace | Canonical |
| Setting 1 | Direct       | 0.39 (0.13) | 0.95 (0.02) | 0.98 (0.02) | 0.74 (0.21) | 0.85 (0.13) | 0.92 (0.07) |
|         | Direct-Split | 0.63 (0.15) | 0.89 (0.06) | 0.95 (0.04) | 0.98 (0.17) | 0.75 (0.10) | 0.86 (0.06) |
|         | Pseudo-Direct| 0.19 (0.07) | 0.99 (0.02) | 0.99 (0.01) | 0.29 (0.08) | 0.98 (0.02) | 0.99 (0.02) |
|         | partial-SAVE | 0.62 (0.10) | 0.94 (0.03) | 0.99 (0.02) | 0.97 (0.15) | 0.84 (0.08) | 0.87 (0.05) |
| Setting 2 | Direct       | 0.21 (0.08) | 0.97 (0.01) | 0.98 (0.01) | 0.36 (0.09) | 0.93 (0.03) | 0.97 (0.01) |
|         | Direct-Split | 0.27 (0.12) | 0.95 (0.07) | 0.97 (0.05) | 0.40 (0.08) | 0.91 (0.04) | 0.96 (0.02) |
|         | Pseudo-Direct| 0.33 (0.09) | 0.97 (0.02) | 0.98 (0.01) | 0.71 (0.29) | 0.85 (0.13) | 0.89 (0.12) |
|         | partial-SAVE | 0.63 (0.20) | 0.89 (0.08) | 0.94 (0.05) | 1.04 (0.25) | 0.71 (0.13) | 0.81 (0.13) |
| Setting 3 | Direct       | 0.37 (0.19) | 0.90 (0.14) | 0.94 (0.06) | 0.57 (0.21) | 0.81 (0.14) | 0.89 (0.11) |
|         | Direct-Split | 0.45 (0.26) | 0.86 (0.20) | 0.92 (0.16) | 0.61 (0.24) | 0.78 (0.20) | 0.87 (0.16) |
|         | Pseudo-Direct| 0.13 (0.03) | 0.99 (0.01) | 0.99 (0.01) | 0.21 (0.04) | 0.98 (0.01) | 0.99 (0.01) |
|         | partial-SAVE | 0.59 (0.20) | 0.86 (0.07) | 0.89 (0.04) | 0.85 (0.15) | 0.82 (0.07) | 0.90 (0.05) |
| Setting 4 | Direct       | 0.59 (0.10) | 0.95 (0.04) | 0.96 (0.02) | 0.72 (0.10) | 0.75 (0.09) | 0.83 (0.04) |
|         | Direct-Split | 0.71 (0.16) | 0.73 (0.13) | 0.86 (0.08) | 0.87 (0.16) | 0.61 (0.16) | 0.82 (0.09) |
|         | Pseudo-Direct| 0.09 (0.02) | 1.00 (0.00) | 1.00 (0.00) | 0.24 (0.07) | 0.97 (0.02) | 0.99 (0.01) |
|         | partial-SAVE | 0.73 (0.10) | 0.76 (0.07) | 0.87 (0.02) | 0.93 (0.17) | 0.56 (0.17) | 0.79 (0.08) |
| Setting 5 | Direct       | 0.35 (0.13) | 0.93 (0.07) | 0.96 (0.04) | 0.50 (0.15) | 0.87 (0.09) | 0.93 (0.06) |
|         | Direct-Split | 0.38 (0.17) | 0.91 (0.10) | 0.95 (0.06) | 0.53 (0.18) | 0.84 (0.13) | 0.92 (0.10) |
|         | Pseudo-Direct| 0.21 (0.06) | 0.99 (0.01) | 0.99 (0.00) | 0.46 (0.31) | 0.92 (0.13) | 0.95 (0.11) |
|         | partial-SAVE | 0.59 (0.16) | 0.91 (0.06) | 0.95 (0.03) | 0.96 (0.22) | 0.76 (0.12) | 0.86 (0.11) |
| Setting 6 | Direct       | 0.55 (0.23) | 0.82 (0.16) | 0.95 (0.13) | 0.83 (0.25) | 0.62 (0.23) | 0.84 (0.24) |
|         | Direct-Split | 0.55 (0.21) | 0.83 (0.15) | 0.95 (0.12) | 0.82 (0.27) | 0.63 (0.25) | 0.83 (0.25) |
|         | Pseudo-Direct| 0.34 (0.35) | 0.94 (0.13) | 0.97 (0.09) | 0.84 (0.47) | 0.77 (0.20) | 0.84 (0.16) |
|         | partial-SAVE | 0.94 (0.26) | 0.76 (0.13) | 0.86 (0.11) | 1.28 (0.19) | 0.58 (0.12) | 0.77 (0.13) |

10.5 Misspecification of the structure dimension

In this example, we investigate the performance (robustness) of proposed methods under a wrong choice of $d$. Again, we consider setting 4, which is a one-dimensional setting. In the model specification, we force $d = 2$ for all methods, hence an overfitting is likely to occur. The predicted value and dose distance are both slightly worse than the $d = 1$ case presented in the main text. However, the difference is very minor. It should be noted that an under-specification that $d = 0$ is likely to be more harmful to the performance. Hence, the selection of the structure dimension is an importance issue that worth further investigation. The method proposed in the next section, and the discussion section, can be considered in practice.
Table 5: Simulation results: misspecification of structure dimension \((d=2)\) in Setting 4

| Method            | Predicted Value Function | Dose distance | Predicted Value Function | Dose distance |
|-------------------|--------------------------|--------------|--------------------------|--------------|
| Direct            | 7.73 (0.21)              | 0.27 (0.05)  | 7.49 (0.19)              | 0.32 (0.05)  |
| Direct-Split      | 7.51 (0.25)              | 0.35 (0.10)  | 7.29 (0.20)              | 0.39 (0.08)  |
| Pseudo-Direct     | 8.03 (0.17)              | 0.17 (0.02)  | 8.00 (0.19)              | 0.19 (0.03)  |

10.6 Structure dimension determination

In the simulation study, we assume that the true structure dimension \(d_0\) is known. The proposed methods can be modified to estimate \(d_0\). We should note that for the pseudo-direct learning method, since the model in (2.7) can be regarded as a set of nested semiparametric models indexed by \(d\), the determination of true structural dimension \(d_0\) naturally becomes a model selection problem. Therefore, we can follow a similar idea of the BIC-type of criterion (Zhu et al., 2006; Feng et al., 2013) to estimate the true structure dimension. Additionally, we may treat the structure dimension as a tuning parameter and select it through cross-validation. For the direct and direct-split learning approach, a modified information criterion method (Ma and Zhang, 2015) could be applied. Note that we may modify the value function by incorporate an argument \(d\), denoted as \(V_{n,f}(B,d)\). And we further denote the partial derivative of \(V_{n,f}(B,d)\) with respect to vecl\((B)\) as \(V_{n,f}^{(1)}(B,d)\). It is reasonable to consider the framework that

\[
\hat{d} = \arg\min_d \left\| V_{n,f}^{(1)}(\hat{B},d) \right\|^2 + pd\log(n) \]

\[
\hat{\hat{d}} = \arg\min_d \text{IC}(d),
\]

where \(\hat{f}_{\text{opt}}\) and \(\hat{B}\) is the maximizer of \(V_{n,f}(B,d)\) for given \(d\). By some heuristic analysis, as the working structural dimension \(d = d_0\), we would have \(V_{n,f}^{(1)}(\hat{B},d)\) converges to 0 in probability, as \(n \to \infty\); when \(d > d_0\), we have IC\((d) > \text{IC}(d_0)\) with probability approaching to 1; when \(d < d_0\), we have IC\((d) = cn + pd\log(n)\), where \(c\) is some positive constant, and this is also larger than IC\((d_0)\) with probability approaching to 1. Further theoretical analysis maybe required. However, we feel that this is beyond the scope of this paper.
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