Data-guided Treatment Recommendation with Feature Scores

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Abstract

Despite the availability of large amounts of genomics data, medical treatment recommendations have not successfully used them. In this paper, we consider the utility of high dimensional genomic-clinical data and nonparametric methods for making cancer treatment recommendations. This builds upon the framework of the individualized treatment rule [Qian and Murphy 2011] but we aim to overcome their method’s limitations, specifically in the instances when the method encounters a large number of covariates and an issue of model misspecification. We tackle this problem using a dimension reduction method, namely Sliced Inverse Regression (SIR, [Li 1991]), with a rich class of models for the treatment response. Notably, SIR defines a feature space for high-dimensional data, offering an advantage similar to those found in the popular neural network models. With the features obtained from SIR, a simple visualization is used to compare different treatment options and present the recommended treatment. Additionally, we derive the consistency and the convergence rate of the proposed recommendation approach through a value function. The effectiveness of the proposed approach is demonstrated through simulation studies and the promising results from a real-data example of the treatment of multiple myeloma.

Keywords: Dimension reduction; Individualized treatment rules; Sliced Inverse Regression; Visualization.
1 Introduction

Conventionally, the approach to recommending disease treatments has been through expert-driven guidance, based on knowledge built over decades. With the availability of large amounts of data, there is a growing interest in using data to help choose different treatment options. For instance, extensive amounts of genomics data have been generated in cancer research, e.g., genetic mutations, mRNA expression, along with clinical data including treatment options and clinical outcomes. These data add valuable information to support and complement expert knowledge for cancer treatments. In this paper, we aim to develop a data-guided tool with simple visualizations that will help doctors and patients evaluate different treatment options and make treatment recommendations.

As a case study, we examine a data set of gene expressions and treatment responses of multi-center clinical trials of bortezomib in treatment of multiple myeloma [Mulligan et al. 2007]. Multiple myeloma is a malignant bone marrow cancer. This disease is highly heterogeneous, meaning that different patients with diverse genomic information show different clinical outcomes [Mitra et al. 2017]. However, the current treatment strategy is limited to the experience of physicians and experts, mainly using patient’s clinical information such as age and cancer stage. With the specific genomic-clinical data set, we aim to make a treatment recommendation between two therapeutic choices, a traditional chemotherapy named dexamethasone and a targeted drug bortezomib.

Our goal is related to research on precision medicine, which has attracted a considerable amount of interests. A recent study on precision oncology for acute myeloid leukemia [Gerstung et al. 2017] analyzed genomic-clinical data to support clinical decision-making. [Zhu and Xie 2015] used a nonparametric method to identify patient subpopulations that would experience stronger treatment effects than the rest of the patient population. These studies, however, were exploratory with no formal framework to define an optimal treatment rule. A valuable formulation has been contributed by [Qian and Murphy 2011]. Formally, we consider a list of random variables \( (X, A, Y) \) from a genomic-clinical dataset, where \( Y \) denotes a treatment response variable (the larger value the better), \( X \in \mathcal{X} \subseteq \mathbb{R}^p \) denotes a set of clinical covariates plus genetic variables, e.g., gene expressions, and \( A \in \mathcal{A} \) denotes the treatment index taking values in a finite discrete space of treatment options, e.g., \( \mathcal{A} = \{-1, 1\} \) corresponding to treatment and control, or \( \mathcal{A} = \{1, \ldots, M\} \) corresponding to \( M \) treatment options. A treatment recommendation rule is a function \( d(X) : \mathcal{X} \rightarrow \mathcal{A} \). It is called an
individualized treatment rule in [Qian and Murphy 2011]. An individualized treatment rule that gives the highest mean response is the optimal one that we hope to find.

There are two types of approaches to construct the optimal treatment rule. One is referred to as direct methods and the other, indirect methods. The direct methods include Outcome Weighted Learning [Zhao et al. 2012], Residual Weighted Learning [Zhou et al. 2017], and other variational forms [Dasgupta and Huang 2020]. The basic idea is to directly optimize a criterion, called the Value function, through the support vector machine (SVM) machine learning method. These approaches, however, are often confined by the limitation of the SVM procedure, e.g., the difficulty with a small separation margin, choices of kernels, etc. The indirect methods consist of two steps. The first step is to estimate a conditional mean of treatment response given clinical variables and the treatment index, \( E(Y|X,A) \). The optimal treatment rule is then defined as the one that maximizes the estimated conditional mean [Rosenwald et al. 2002, van’t Veer and Bernards 2008, Qian and Murphy 2011, Cui et al. 2017, Hager et al. 2018, Bai et al. 2017, Zhao et al. 2019]. There are also methods focusing on dynamic treatment regimes that consider treatment recommendations at multiple times as well as Bayesian approaches of dynamic treatment regimes [Schulte et al. 2014, Zhang et al. 2013, Luckett et al. 2020, Liu et al. 2018, Yang et al. 2018, Laber and Davidian 2017, Xu et al. 2016, Murray et al. 2018]. The indirect methods rely heavily on the correct model specification for the conditional mean \( E(Y|X,A) \) [Qian and Murphy 2011], which is often challenging to achieve. In addition, none of the existing methods are good at handling high-dimensional data.

We focus on the indirect method and improve it by developing an approach that contains a class of rich conditional mean models. More specifically, we apply Sliced Inverse Regression, or SIR [Li 1991], to predict the treatment response. SIR is designed to retrieve interesting features of high-dimensional data by low-dimensional projections. The method is able to model the relationship between a treatment response and a set of genomic and clinical variables through an arbitrary unknown function. There is no linear model assumption about the conditional mean of the treatment response. Instead, the model space of the SIR method is often bigger than other indirect methods. We also present the theory to show that the richer model space of SIR leads to improved treatment recommendation.

An important strength of the SIR procedure is that it directly estimates the low-dimensional projection space and represents the high-dimensional data by a few features. This resembles the
feature definition component of the neural network models that are popularly used nowadays. We name the SIR projected data Feature Scores. Specifically, SIR will work well in the instance when there is no strong effect from an individual clinical or genetic variable but the treatment response may depend on an unknown feature, which is a commonly occurring situation in cancer treatment. A simple scatter plot of the treatment response versus Feature Score allows users to visualize and compare different treatment options. Thus, our method offers a tool for doctors and even patients to assess and confirm the available treatment plans. Moreover, we prove that the SIR procedure consistently estimates the optimal treatment rule under moderate assumptions.

In summary, the biggest contribution of this article is to define a small feature space in the framework of individualized treatment rules. The major advantages of the proposed method include 1) dimension reduction with feature detection, 2) rich conditional mean models for consistent estimation of the optimal treatment, 3) visualization of the optimal treatment recommendation, 4) theoretical guarantee with a convergence rate.

The remainder of the article is organized as follows. In Section 2, we introduce the value function, define the Feature Score, and show a visualization of the treatment recommendation. In Section 3, we prove the consistency and derive the convergence rate of the proposed recommendation approach. In Section 4, we show simulations and compare our proposed method with other methods. Section 5 demonstrates the results of applying the proposed method to the case study of treatments for multiple myeloma. Some discussions are given in Section 6. The Supplementary Materials include the information of data and code and technical proofs of the lemma and thereom.

2 Treatment recommendation through Feature Scores

Formally, we have a set of random variables \((X, A, Y)\) in the data set, where \(X \in \mathcal{X} \subset \mathbb{R}^p\) denotes clinical covariates plus a big set of genetic variables, \(A \in \mathcal{A}\) is the treatment index taking values in a finite discrete space \(\mathcal{A}\) of treatment options, \(Y\) is the treatment response variable with larger values indicating better treatment response. A treatment recommendation rule is a function \(d(X)\) with values in the space of \(\mathcal{A}\). Denote the distribution of \((X, A, Y)\) by \(P\), and the conditional mean \(E(Y|X, A)\). Following the framework of individualized treatment rules [Qian and Murphy 2011], we will first show an optimal treatment recommendation rule must maximize \(E(Y|X, A = a)\) over
This result justifies the indirect methods, which focus on the estimation of \(E(Y|X, A = a)\). Next, we will apply SIR [Li 1991] to estimate \(E(Y|X, A = a)\) and then obtain the optimal recommendation rule. The model space for estimation of \(E(Y|X, A = a)\) in the SIR method is very large, which is the biggest advantage of our proposed method.

2.1 Value function and optimal recommendation

By convention, we use upper case letters for random variables and lower case letters for values of the random variables. The likelihood of \((X, A, Y)\) under \(P\) is \(f_0(x)p(a|x)f_1(y|x, a)\), where \(f_0\) is the unknown density of \(X\), \(p(\cdot|x)\) is the randomization probability of \(A\) given \(X = x\), and \(f_1\) is the unknown distribution of \(Y\) conditional on \((X, A)\). Let \(P^d\) denote the distribution of \((X, A, Y)\) when a treatment recommendation rule \(d(X)\) is used to assign treatments, then the likelihood becomes 

\[
f_0(x)1(d(x) = a)f_1(y|x, a). \]

Define the Value of \(d\) as \(V(d) \triangleq E[d]\).

\[
V(d) = \int Y dP^d = \int Y \frac{dP^d}{dP} dP = \int Y \frac{1_{d(X) = A}}{p(X|A)} dP = E \left[ Y \frac{1_{d(X) = A}}{p(A|X)} \right].
\]

An optimal treatment recommendation rule, denoted as \(d_0\), is a rule that has the maximum Value over all possible treatment recommendation rules,

\[
d_0 \in \arg \max_d V(d).
\]

Moreover, denote \(Q_0(X, A) \triangleq E(Y|X, A)\). We also have

\[
V(d) = E \left[ \frac{1(d(X) = A)}{p(X|A)} E[Y|X, A] \right] = E \left[ \sum_{a \in A} 1_{d(X) = a} Q_0(X, a) \right] = E[Q_0(X, d(X))].
\]

Note the Value for the optimal treatment rule \(V(d_0) = E[Q_0(X, d_0(X))] \leq E[\max_{a \in A} Q_0(X, a)]\).

Meanwhile by the definition of \(d_0\), \(V(d_0) \geq V(d)|_{d(X) \in \arg \max_{a \in A} Q_0(X, a)} = E[\max_{a \in A} Q_0(X, a)]\). Thus, the optimal treatment rule satisfies \(d_0(X) \in \arg \max_{a \in A} Q_0(X, a)\). Our goal is to estimate \(d_0\), which will be achieved by first estimating the conditional mean \(Q_0(X, A)\).

More specifically, the estimated treatment recommendation rule is defined as

\[
d(X) \in \arg \max_{a \in A} Q(X, a), \quad (1)
\]
where \( Q(X, A) \) is an estimator of the true conditional mean \( Q_0(X, A) \). The following result, modified from [Qian and Murphy 2011], shows that the difference between the largest Value \( V(d_0) \) and \( V(d) \) is controlled by the mean squared error of the estimator \( Q(X, A) \).

We require an assumption similar to the margin condition in classification. Assume both the true conditional mean \( Q_0(X, A) \) and its estimator \( Q(X, A) \) are square integrable. Define \( T(X, A) = Q(X, A) - E[Q(X, A)|X] \) and \( T_0(X, A) = Q_0(X, A) - E[Q_0(X, A)|X] \). They are referred to as the treatment effect terms in [Qian and Murphy 2011]. The following assumption is about the margin of \( T_0 \), i.e., the difference in mean responses between the optimal treatment and the suboptimal treatment.

(A.1) There exist some constants \( C > 0 \) and \( \alpha > 0 \) such that

\[
P \left( \max_{a \in A} T_0(X, a) - \max_{a \in A \setminus \arg\max_a T_0(X, a)} T_0(X, a) \leq \epsilon \right) \leq C \epsilon^\alpha
\]

for any \( \epsilon > 0 \).

**Lemma 1.** Suppose \( p(a|x) \geq S^{-1} \) for a positive constant \( S \) for all \((x, a)\) pairs and assume (A.1). For any treatment rule \( d : \mathcal{X} \rightarrow \mathcal{A} \) and square integrable function \( Q : \mathcal{X} \times \mathcal{A} \rightarrow \mathbb{R} \) such that \( d(X) \in \arg\max_{a \in A} Q(X, a) \), we have

\[
V(d_0) - V(d) \leq C' \left[ E(Q(X, A) - Q_0(X, A))^2 \right]^{(1+\alpha)/(2+\alpha)}
\]

where \( C' = (2^{2+3\alpha} S^{1+\alpha} C)^{1/(2+\alpha)} \).

The proof is in the Supplementary Materials.

### 2.2 A rich conditional mean model

Lemma 1 justifies the use of the indirect methods. When we have a consistent estimator of \( Q_0(X, A) = E(Y|X, A) \), that is, an estimator \( Q(X, A) \) converges to \( Q_0(X, A) \), Lemma 1 shows the Value of the estimated treatment recommendation rule, i.e., \( V(d) \) of \( d(X) \in \arg\max_{a \in A} Q(X, a) \), will also converge to the optimal value \( V(d_0) \). However, this will not happen if the conditional mean is modeled incorrectly. In fact, if the approximation space used in estimating \( Q_0 \) does not contain the truth, then the estimated treatment recommendation rule will not be consistent.
[Qian and Murphy 2011] pointed out this challenge but did not present methods to address it. We attempt to offer a solution via Sliced Inverse Regression (SIR) [Li 1991]. SIR is a novel method for reducing the dimension of \(\mathbf{X}\) without going through any model-fitting process in the first place. It is developed under a very general model, \(Y = g(\beta_1\mathbf{X}, \beta_2\mathbf{X}, ..., \beta_k\mathbf{X}, \epsilon)\), where \(\beta\)'s are unknown row vectors, \(k\) is a small number, \(\epsilon\) is the error term independent of \(\mathbf{X}\), and \(g\) is an arbitrary unknown function. Applying SIR, we make a very general assumption:

(A.2) For each treatment group \(a \in \mathcal{A}\), the conditional mean response depends on a low-dimensional projection of \(\mathbf{X}\). That is, \(E[Y|\mathbf{X}, A = a] = E[Y|\beta_{a,1}\mathbf{X}, \beta_{a,2}\mathbf{X}, ..., \beta_{a,k}\mathbf{X}, A = a]\), with \(k\) as a small number, e.g., \(k = 1\) or \(2\).

In other words, given treatment \(a \in \mathcal{A}\), the conditional mean response is assumed \(E(Y|\mathbf{X}, A = a) = \eta_a(\beta_{a,1}\mathbf{X}, \beta_{a,2}\mathbf{X}, ..., \beta_{a,k}\mathbf{X})\), where \(\eta_a\) is an arbitrary and unknown function. The projection of a set of predictors \(\mathbf{X}\) onto the \(k\) dimensional subspace, \((\beta_{a,1}\mathbf{X}, \beta_{a,2}\mathbf{X}, ..., \beta_{a,k}\mathbf{X})\), captures all we need to know about \(Y\) for the given treatment \(A = a\). The projection space and the arbitrary function \(\eta_a\) are allowed to be different for different treatment groups \(a \in \mathcal{A}\). This assumption offers a rich class of models for the conditional mean \(Q_0(\mathbf{X}, A)\). Specifically, if we denote \(Q\) as the approximation space for \(Q_0\), then \(Q\) contains the linear model, the commonly used generalized linear models, and many more, because the link function \(\eta_a\) can take any functional form. This offers a much richer class of individualized treatment rules than the other existing methods.

The number \(k\) is supposed to be very small, e.g., \(1\) or \(2\), and \(\beta_{a,1}\mathbf{X}\), or \((\beta_{a,1}\mathbf{X}, \beta_{a,2}\mathbf{X})\), provides summary information of a patient for prediction of the treatment response. We name \(\beta_{a,1}\mathbf{X}\), or \((\beta_{a,1}\mathbf{X}, \beta_{a,2}\mathbf{X})\) if \(k = 2\), Feature Score. The use of the Feature Score has the advantage of representing the cancer treatment situation where there would be no strong effect from an individual genetic variable but the treatment response would depend on unknown features. [Li 1991] provided a direct estimator of \(\beta\)'s through the SIR procedure. For each treatment group \(A = a\), suppose we have patient samples of the treatment response and the covariate vector \(\{(y_i, \mathbf{x}_i)\}\). We apply SIR and obtain the first projection direction \(\hat{\beta}_1\). The Feature Score is denoted as \(u_i = \hat{\beta}_1\mathbf{x}_i\), which can be interpreted as a summary feature of a patient and is supposed to capture the majority data information for the prediction of the treatment response \(Y\). More interestingly, this feature definition is analogous to that of the neural network model, and SIR is able to directly estimate...
the features without knowing the link function \( \eta_a \).

### 2.3 Simple visualization with Feature Score

Suppose \( \mathcal{A} = \{1, \ldots, M\} \), so there are \( M \) different treatment groups in a given data set. We conduct SIR for each treatment group and obtain the first projection direction \( \hat{\beta}_{a,1} \), \( a = 1, \ldots, M \). We can project all patients onto a one-dimensional space (line) and calculate their Feature Scores \( u_i = \hat{\beta}_{a,1} x_i \), where the Feature Scores will be different for different treatment groups. We draw a simple scatter plot of \( y_i \) versus \( u_i \) for each treatment group, \( a = 1, \ldots, M \). Even though the Feature Scores of different treatment groups \( u_i = \hat{\beta}_{a,1} x_i \) are not comparable to each other, we can still compare the treatment response via the vertical axis, which has the same scale over different scatter plots (see Figure 1). These plots provide visualization of the treatment options, i.e., \( a = 1, \ldots, M \), where larger vertical values indicate better treatment response.

We also obtain a nonparametric fitting of the function, \( \hat{g}_a(u) \), for example, by local constant estimates, or LOESS (locally weighted smoothing) [Cleveland and Devlin 1988], for each of the treatment groups \( a = 1, \ldots, M \). These nonparametric estimates provide the predicted treatment responses for each treatment option. Given a new patient with data vector \( x \), we first calculate its Feature Score, \( u_a = \hat{\beta}_{a,1} x \), then decide its treatment option to be the one maximizing the predicted treatment responses. More specifically, we will recommend a treatment choice as

\[
\text{argmax}_{a=1,\ldots,M} \hat{g}_a(\hat{\beta}_{a,1} x),
\]

where \( \hat{\beta}_{a,1} \) is from the SIR procedure and \( \hat{g}_a(\cdot) \) is the nonparametric function estimate based on the patient samples \( \{(y_i, u_i)\} \) with \( u_i = \hat{\beta}_{a,1} x_i \). In general, we can have the subspace dimension \( k \geq 1 \) and SIR may project data of different treatment groups onto different subspaces. Nevertheless, we will obtain a nonparametric estimate of the functional relationship, \( \hat{g}_a(\hat{\beta}_{a,1} x, \ldots, \hat{\beta}_{a,k} x) \). The treatment recommendation will be similarly defined as (2).

The visualization through the scatter plot of \( y_i \) versus Feature Score \( u_i \) is a very useful tool. For a patient with Feature Score \( u_a = \hat{\beta}_{a,1} x \), we can locate it on the horizontal axis (or the projected space when the Feature Score is more than one dimensional) and then look at treatment response values based on the vertical axis in the scatter plots, as shown in Figure 2. We can also compare the predicted treatment responses between our proposed treatment plan and the plan based on
current expert guidelines, according to the vertical axis. This will show what improvements in
treatment response may be achieved from the proposed treatment recommendation.

2.4 Data preprocessing and the algorithm

Before implementing the SIR procedure, we should go through a few steps of data preprocessing.
The first step is to confirm that a given genomics data set contains significant information for the
prediction of treatment response. We evaluate the overall dataset information through a global
hypothesis testing method, the Cauchy combination test developed by [Liu and Xie 2019]. The
p-value from the Cauchy combination test serves as evidence to support data-guided treatment
recommendations. If the Cauchy combination test gives a large p-value, we should not consider
the genomic data in forecasting a patient’s prognosis and for recommending treatments.

The second step of data preprocessing is to conduct initial variable selection before implementing
SIR when we analyze a large number of genomic variables. SIR is a dimension reduction method
involving principle component analysis (PCA). In general, some initial reduction in dimensionality
is desirable before applying any PCA-type methods [Johnstone and Lu 2009]. Although more
recent developments of sparse SIR [Lin et al. 2021, Lin et al. 2019] may be directly applied, we
instead consider here two variable selection methods and incorporate selection into the SIR process.
One method is to select variables with the smallest p-values from a simple regression of $Y$ over
$X_j$ and $A$, $j = 1, \ldots, p$, at a false discovery rate (FDR) cutoff, e.g., 5%. Another is to screen for
important variables from nonparametric local regression of $Y$ over $X_j$ and $A$ using LOESS, with
the smallest 5% residual errors. A user can choose to use either variable selection method before
implementing SIR.

To determine the number of Feature Scores $k$, which is the dimensions for reduction in the
proposed SIR model, we can use the $\chi^2$ test suggested by [Li 1991]. On the other hand, as SIR is
a PCA-type method, it is common practice to consider one or two Feature Scores, i.e., one or two
principal components, for visualization. The specific algorithm of our treatment recommendation
is provided in the table below.
Algorithm 1 *Treatment recommendation procedure*

1: procedure $s = \text{TreatRcmd}(Y, X, A, x_{\text{new}})$

**Input:** A training data set with observed $(X, A, Y)$, where $Y$ is the treatment response, $X = (X_1, \ldots, X_p)$ is the set of genomic variables and clinical covariates, and $A$ is the treatment index; A new observation with vector value $x_{\text{new}}$ for treatment recommendation.

**Output:** Scatter plots of $Y$ versus Feature Scores; The predicted response under each treatment option for $x_{\text{new}}$ and the optimal treatment option.

▷ **Overall information summary**

2: Calculate p-value from the Cauchy combination test.

3: Alert if the overall p-value is large. Continue only if the p-value is small.

▷ **Subset selection (Optional)**

4: Select a subset of $X_j$’s for the following SIR procedure, using either linear regression or nonparametric local regression of $Y$ over $X_j$ and $A$. A default cutoff is the false discovery rate 5%, or using LOESS with the smallest 5% residual errors.

▷ **Dimension reduction (SIR)**

5: For each treatment group $A = a$, conduct SIR to obtain the low-dimensional projection directions $\hat{\beta}_a$.

6: Make scatter plots of $Y$ versus Feature Score $u_a = \hat{\beta}_a X$ for each treatment group.

▷ **Prediction**

7: For the new data point $x_{\text{new}}$, calculate its Feature Scores $u_a = \hat{\beta}_a x_{\text{new}}$ under each treatment option $A = a$ and predict the response under the corresponding treatment.

8: Obtain the optimal treatment recommendation that gives the largest predicted response.

9: end procedure
3 Consistency and convergence rate

Our treatment recommendation rule is \(d(X) \in \arg\max_{a \in A} Q(X,a)\), where \(Q(X,A)\) is an estimator of \(Q_0(X,A) = E(Y|X,A)\) and is obtained by SIR and the nonparametric procedure LOESS. Recall the Value function defined in Section 2.1. The following theorem shows we can have \(V(d)\) converging to the optimal Value \(V(d_0)\) with a certain rate. Besides the margin condition (A.1), we require additional assumptions from SIR [Li 1991] and for the nonparametric LOESS estimator. We first rewrite the SIR assumption (A.2) by denoting the treatment index as \(i \in A = \{1, \ldots, M\}\) and the projection directions \(\beta\)'s as \(B_i \in \mathbb{R}^{k \times p}, k < p\).

(A.2) There exist some full-rank matrices \(B_i \in \mathbb{R}^{k \times p}, k < p\), such that \(E[Y|X,A = i] = E[Y|B_iX,A = i] = \eta_i(B_iX)\), where \(\eta_i(\cdot)\)'s are \(\rho\)-Lipschitz continuous and have continuous second derivatives. Furthermore, for any row vector \(\xi \in \mathbb{R}^p\), \(E[\xi X|B_iX]\) is a linear function of \(B_iX\). Besides, the dimension of the central inverse curve \(E[X|y,A = i]\) equals to the dimension of the space spanned by the columns of \(B_i\), \(\text{col}(B_i)\), and the variance \(v_i(u) = \text{Var}[Y|B_iX = u, A = i]\) is a continuous function.

(A.3) Denote the kernel function of LOESS by \(K_H(u) = |H|^{-1/2}K(H^{-1/2}u)\), where \(u \in \mathbb{R}^k\) and the bandwidth matrix \(H \in \mathbb{R}^{k \times k}\). Assume the kernel function \(K(\cdot)\) is \(\rho\)-Lipschitz, compactly supported, and satisfies \(\int uu^\top K(u)du = \mu_2(K)I\), where \(I\) is the identity matrix and \(\mu_2(K)\) is a constant depending on \(K\). Moreover, all odd-order moments of \(K\) equal to zero, that is, \(\int u_1^{l_1} \cdots u_d^{l_d} K(u)du = 0\) for all non-negative \(l_1 \cdots l_d\) when their sum is odd. Additionally, the bandwidth matrix \(H\) is symmetric and positive definite with each entry, as well as \(n^{-1}|H|\), tending to 0 as \(n \to \infty\), and the ratio of the largest and the smallest eigenvalue of \(H\) is uniformly bounded for all \(n\).

(A.4) For all \(i \in A\), let \(f_i(\cdot)\) be the conditional density function of \(B_iX\) given \(A = i\). Assume that \(f_i(\cdot)\) is uniformly bounded away from 0 and has a continuous gradient function \(Df_i(\cdot)\).

(A.5) Denote \(n_i = |\{j : A_j = i\}|\) as the number of observations in the treatment group \(A = i\). Assume \(\min_{i \in A} P(A = i) > c\) for some positive constant \(c\) and the support set of \(X\) is bounded.
As represented in (2) in Section 2.3, we write the treatment recommendation rule as \( d(x) \in \arg\max_{i \in A} Q(x, i) \), where \( Q(x, i) = \tilde{g}_i(\widehat{B}_i x) \) with \( \widehat{B}_i \) as the estimated projection directions from SIR and \( \tilde{g}_i(\cdot) \) the LOESS function from the training data \( \{\widehat{B}_i x_j, y_j\}_{j:A_j=i} \).

**Theorem 1.** Assume (A.1)-(A.5). The difference between the optimal Value, \( V(d_0) \), and \( V(d) \) of our treatment recommendation rule converges to 0 in probability as \( n \to \infty \):

\[
V(d_0) - V(d) \leq \left( |H|^{-1} H^{-1/2} \frac{n^2}{\|H\|^2_F} + O_p \left( \frac{|H|^{1/2}}{n} + \|H\|^2_F \right)^{\frac{1+\alpha}{2+\alpha}} \right) + O_p(n^{-\frac{2(1+\alpha)}{(2+\alpha)(1+\alpha)}}),
\]

(3)

where \( \|H\|^1 \) denotes the maximum column absolute sum and \( \|\cdot\|^2_F \) denotes the Frobenius norm.

When the bandwidth matrix \( H = \text{diag}\{h, \cdots, h\} \) with \( h = n^{-\frac{1}{1+\alpha}} \), the upper bound on the right hand side becomes \( O_p(n^{-\frac{2(1+\alpha)}{(2+\alpha)(1+\alpha)}}) \).

The proof is in the Supplementary Materials.

**Remark 1.** Theorem 1 is obtained by combining the estimation errors of the SIR procedure and the LOESS nonparametric regression. The second error term in (3) is the intrinsic estimation error of the LOESS regression and the first error term is the additional estimation error induced by the certainty of the SIR procedure.

**Remark 2.** The conditional mean model assumption and the linearity condition in (A.2) are from SIR. Note that \( B_i \) and \( \eta_i(\cdot) \) are not identifiable (e.g., one can always multiply \( B_i \) to any \( k \times k \) full-rank matrix), but the space spanned by the columns of \( B_i \) is unique.

**Remark 3.** The smoothness assumption of \( \eta_i \) and \( v_i \), the requirements on the kernel choice in (A.3), along with (A.4), ensure the consistency of the nonparametric estimation for each mean regression function \( \eta_i \) via the local linear regression approach. The bandwith matrix \( H \) usually takes simple form as \( \text{diag}\{h, \cdots, h\} \), where \( h > 0 \). Given this simplification the last statement in assumption (A.3) is automatically satisfied.

**Remark 4.** The compactness assumption on the support set of \( X \) in (A.5) greatly facilitates our theoretical analysis, for example, it trivially ensures that \( \|D_f(\cdot)\| \) is bounded. This assumption is reasonable for most medical treatment applications, since the patient measurements, such as gene expression levels, are usually bounded or standardized. We conjecture that our theoretical results will still hold for unbounded \( X \) such as the Gaussian design, while the rigorous convergence analysis for such cases is left for future studies. Assumption (A.5) also ensures that \( n_i \approx n \) in probability.
Remark 5. For the simplicity of representation, our theorem only considers the fixed $p$ and $k$ situation. If $p$ and $k$ increase with respect to $n$, then the corresponding convergence rates can be rigorously studied by utilizing the high dimensional algorithm and theory of SIR developed by, e.g., [Zhu et al. 2006] and [Lin et al. 2018], [Lin et al. 2021], [Lin et al. 2019]. In Section 3 in the Supplementary Materials, we present a convergence result under $p \to \infty$ and $p/n \to 0$.

4 Simulation studies

To assess the proposed method, we perform extensive simulations. We compare our method with several existing approaches, including Outcome Weighted Learning (OWL) [Zhao et al. 2012], Residual Weighted Learning (RWL) [Zhou et al. 2017], and a linear regression method with ordinary least squares estimation of the conditional mean of the treatment response, denoted as OLS.

We generate $p$ covariates $X_1, \ldots, X_p$ from uniform $[-1, 1]$, where a small and a large covariate set are considered with $p = 8$ or 100. We consider two treatment options $A = \{1, -1\}$ of a randomized controlled study. The response $Y$ follows a normal distribution with mean $\mu(x) + t_0(x)a$ and standard deviation 1, where $\mu(x)$ represents the effect of the covariates $x = (x_1, x_2, \ldots, x_p)$ and $t_0(x)a$ represents the treatment effect, which may depend on $x$. We simulate two sample sizes $n = 100$ and $n = 400$, with half of the samples in the treatment group and the other half in the control group. The terms $\mu(x)$ and $t_0(x)a$ are chosen from the following four scenarios:

1. $\mu(x) = 2 + 4x_1 + 4x_2 + 4x_3$, when $a = 1$;
   $\mu(x) = (2 + 4x_1 + 4x_2 + 4x_3)^2$, when $a = -1$;
   $t_0 = 0$.

2. $\mu(x) = 2 + 2x_1 + 2x_2 + 4x_3 + 4x_4$; $t_0(x) = 1.3(x_2 - 2x_1^2 + 0.3)$.

3. $\mu(x) = \frac{10x_1}{0.5 + (x_2 + 1.5)^2}$; $t_0(x) = 1.3(x_2 - 2x_1^2 + 0.3)$.

4. $\mu(x) = \frac{10x_1}{0.5 + (x_2 + 1.5)^2}$; $t_0(x) = 3.8(0.8 - x_1^2 - x_2^2)$.

Scenario 1 is modified from a simulation model of OWL [Zhao et al. 2012]. We define the mean function as a linear function for $a = 1$ and its quadratic function for $a = -1$. Scenario 2 is similar
to the second scenario in RWL [Zhou et al. 2017]. Scenario 3 and 4 have nonlinear functions with $\mu(x)$ modified from a simulation model of SIR [Li 1991].

We first conduct the Cauchy combination test on the entire set of covariates $X_1, ..., X_p$. The Cauchy combination test gives significant results for all simulations. For data sets with a small number of covariates, i.e., $p = 8$, we directly implement the SIR method. On the other hand, for data sets where the dimension is comparable to the sample size, i.e., $p = 100$, we conduct initial variable selection before implementing SIR (See Algorithm 1). A simulated data set typically has 2-7 variables selected, with the exact number varying for different model scenarios and different simulation replicates. We then conduct SIR for each treatment group and obtain the first projection direction $\hat{\beta}_a$, $a = 1$ or $-1$. Feature Scores are calculated for subjects in the corresponding treatment group, either $a = 1$ or $-1$, as $u_i = \hat{\beta}_a x_i$.

Figure 1 shows two scatter plots of $y_i$ versus $u_i$, one for each treatment group. These plots display functional relationships between the response $Y$ and Feature Score and are used to predict responses for a new observation $x$. Figure 2 shows plots of the predicted response versus Feature Scores, where each sample $x_i, i = 1, \ldots, n$, is considered as a new observation (a test data). Each sample has two Feature Scores, $u_{a,i} = \hat{\beta}_a x_i$, $a = 1$ or $-1$, and two predicted treatment responses from the LOESS fits of Figure 1. We use the R package `loess()` with its default bandwidth parameter $h = 0.75$. The vertical axes of these plots use exactly the same scale for treatment response and thus are directly compared. It clearly demonstrates the optimal treatment option, either $a = 1$ or $-1$, for each sample. More specifically, a subject with ID 139, as marked by a small triangle in the plots, has the predicted response value $\hat{Y} = -11.44723$ if it is assigned to treatment $a = 1$, and $\hat{Y} = -2.79185$ if it is assigned to treatment $a = -1$. This subject is then recommended to get treatment $a = -1$ due to the larger predicted response value.

For the simulation studies, we know the true optimal treatment recommendation, which is the treatment option with the larger value of $\mu(x) + t_0(x)a$, for a given subject with covariate values $x$. We are able to evaluate our method and compare it with other existing methods by calculating a misclassification error. More specifically, if the treatment recommendation through an approach gives the same treatment option as the truth, there is no misclassification error. Otherwise, the misclassification error is 1. Four treatment recommendation methods are applied: Outcome Weighted Learning (OWL) [Zhao et al. 2012], Residual Weighted Learning (RWL) [Zhou et al. 2017], linear
regression to predict $Y$ and then to recommend the treatment with a larger predicted value (OLS), and our method denoted as SIR. We use an existing R package to perform OWL and RWL, https://cran.r-project.org/web/packages/DynTxRegime/index.html. We make a treatment recommendation for each sample while considering all other samples as the training data. Figure 3 displays the misclassifications rates. The rate is the percentage of the number of misclassified treatments over the total number of patients (sample size $n$). We repeat the whole simulation procedure 1000 times and plot the mean value and the standard deviation, with two error bars around the mean, in Figure 3.

In general, our approach (SIR) shows better performance with lower misclassification rates. In particular, our approach performs substantially better than RWL and OWL in Scenario 2, 3, 4. The results of SIR and RWL are comparable in Scenario 1. In addition, our approach shows lower misclassification rates than OLS in Scenario 1, 3, 4. The results of SIR and OLS are comparable in Scenario 2. The favorable performance of SIR is due to the general assumption of the treatment response model, i.e., Assumption (A.2), which gives a large approximation space for the true conditional mean function $Q_0$. In other words, the model space of SIR is often bigger than other existing methods with mostly linear models. We improve the treatment recommendation by obtaining a good estimator of $Q_0$.

5 A case study

We have applied our proposed method to the study of bortezomib in treatment of multiple myeloma [Mulligan et al. 2007]. Bortezomib is the first therapeutic proteasome inhibitor tested in humans. It is approved in the U.S. for treating relapsed multiple myeloma. As bortezomib is a therapeutic choice in addition to the standard chemotherapy, there is a need to decide which treatment should be recommended for a given patient. Our goal is to provide a treatment recommendation, either dexamethasone (dex) or bortezomib, based on data information.

To achieve this, we use a genomic-clinical data set from the Gene Expression Omnibus (GEO) database (GSE9782). Data from two platforms of Affymetric microarrays (GPL96 and GPL97) are merged to obtain a large sample size, with a total of 477 patients, 338 of them receiving bortezomib and 139 receiving dex. The merged data contain a smaller number of gene probesets
(or simply genes) than each of the individual platform data. On the other hand, we have verified that significant genes from each data set are included in the merged data. The variables considered in our analysis include:

- a set of clinical prognostic factors, i.e., gender, race, age;
- a treatment index, either bortezomib or dex, denoted as $A$;
- gene expression measurements of 168 genes in the merged data, denoted as $X_j$, $j = 1, \ldots, 168$;
- clinical response denoted as $Y$ with five levels coded as 1-5 corresponding to progressive disease (PD), no change (NC), minimal response (MR), partial response (PR), complete response (CR), respectively.

We first evaluate whether this data set provides significant information for the prediction of treatment response $Y$. The three clinical factors, i.e., gender, race, and age, have no significant effect on $Y$ ($R^2 = 0.004179$) hence are not considered in the following analysis. The Cauchy combination test [Liu and Xie 2019] gives a p-value 0.0004, suggesting that the genomic data set contributes to the treatment response and provides useful information for treatment recommendation.

Given the sample size and the number of genes are comparable, we deem initial variable selection is necessary before running the SIR procedure. We select a subset of 8 most significant genes at a false discovery rate cutoff (0.002). They are the genes of ribosomal proteins and translation initiation factors. Interestingly, these genes match with the literature that patients with perturbation of certain ribosomal proteins and translation initiation factors showed responses to the bortezomib treatment [Mulligan et al. 2007, Sulima and Keersmaecker 2017, Hofman et al. 2017].

We then apply our SIR method of treatment recommendation using this set of 8 genes and compare the performance with OLS and RWL. For the SIR method, Feature Score is calculated as a one-dimensional projection of the gene predictors for each treatment group.

More specifically, we randomly split the data into five equal-sized parts. Four parts (training data) are used to fit a model, either OLS, SIR, or RWL, and the remaining one part (test data) is used to evaluate the corresponding treatment recommendation methods. Different from the simulation examples, we do not know the true optimal treatment recommendation for this case study hence cannot calculate the misclassification errors. Instead, we calculate an unbiased estimator of
the Value function as in [Qian and Murphy 2011]. We repeat the process 1000 times and report the
mean and standard deviation of the estimated Value functions in Table 1. The observed treatment
index $A$ in the data also corresponds to a treatment recommendation rule. Its estimated Value
function serves as a baseline for the performance comparison.

Table 1 shows that SIR improves the baseline Value function from 2.54 to 2.82 and is slightly
better than the OLS and RWL methods, although the difference from OLS and RWL is minimal.
Plots of $Y$ versus Feature Score (plots not shown here) actually display a certain degree of linear
trend and the predicted $Y$ curves from OLS and SIR are not very different from each other.
This explains the similar result of different methods in Table 1. On the other hand, RWL is
computational expensive, costing about 300 more times than SIR and OLS.

Figure 4 is a plot of the predicted treatment response versus Feature Score in a random test data
set. Note that Feature Score is different for the two treatment groups but we can still directly com-
pare the predicted treatment response on the vertical axes. A specific data point, patient ID 471,
is marked for visualization of the treatment recommendation. This patient has a lower predicted
treatment response value under bortezomib than under dex. Therefore, the optimal treatment
recommendation is the standard chemotherapy dex for this patient. This recommendation is based
on the gene expression data through the Feature Score generated by SIR. To conclude, our data-
guided method is able to provide the multiple myeloma patients with a treatment recommendation
between bortezomib and dexamethasone with better performance than not used. The data-guided
method attempts to connect information from the gene expression with treatment responses and
may reveal relationships between genes and the corresponding phenotype.

6 Discussion

A major advantage of the proposed method lies in its low-dimensional representation of data,
i.e., the Feature Score definition, and the automatic detection of these features through the SIR
approach. In comparison to the lasso-type approaches such as seen in [Qian and Murphy 2011],
SIR works better than variable selection methods when the effects from individual predictors are
minimal. The features from the SIR approach resemble the feature definition of the popular neural
network models, with a wide potential of applications. Additionally, the SIR procedure is much
simpler than learning a neural network model.

SIR is a novel method for reducing the dimension of $\mathbf{X}$ without going through any model-fitting process in the first place. It is developed under a very general model assumption that the treatment response $Y$ depends on the covariates $\mathbf{X}$ through a low-dimensional projection space. This general assumption corresponds to a large approximation space for the true conditional mean function $Q_0$, hence resulting in a consistent estimation of the optimal recommendation rule. In other words, Assumption (A.2) is the most critical assumption for the theoretical guarantee, whereas the other assumptions are standard.

The proposed method does not, however, consider dynamic treatment regimes that involve treatment recommendations being made at multiple times. Since there are far more datasets with only one-time treatment information as compared to multiple-time treatment information, the proposed method would have broader applications than the methods of dynamic treatment regimes. Besides treatment recommendation, the proposed method can also be applied to other precision medicine research, such as risk prediction, treatment effect estimation, and even causal inference. Those will be the topics of our future work.

7 Supplementary Materials

The reader is referred to the online Supplementary Materials for the information of data and code and technical proofs.

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Table 1: Comparison of the empirical value function in a random testing dataset using different methods, OLS, SIR, and RWL. Mean (std) values of the empirical value function through 1000 resampling are reported.

| Observed | OLS     | SIR     | RWL     |
|----------|---------|---------|---------|
| 2.542(0.127) | 2.818(0.157) | 2.825(0.158) | 2.804(0.166) |

Figure 1: Scatter plot of $Y$ versus Feature Score $u_a = \hat{\beta}_a x$ under each treatment (Scenario 3).
Figure 2: Predicted response value versus Feature Score $u_a = \hat{\beta}_a x$ under each treatment (Scenario 3). A specific data point, ID 139, is marked for visualization of the optimal treatment.
Figure 3: Comparison of different treatment recommendation methods in terms of the mean (center) and the standard deviation (error bars) of misclassification rates from 1000 simulations: A. FDR is used to screen all $p = 100$ variables in the first step; B. LOESS is used to screen all $p = 100$ variables in the first step; C. No screening but $p = 8$. 
Figure 4: Scatter plot of treatment response versus Feature Score for each treatment group in a test data set of the real data example. A specific data point, patient ID 471, is marked for visualization of the optimal treatment.