A single-index model with a surface-link for optimizing individualized dose rules

Hyung Park,* Eva Petkova, Thaddeus Tarpey
Division of Biostatistics, Department of Population Health, New York University
and
R. Todd Ogden
Department of Biostatistics, Columbia University

Abstract

This paper focuses on the problem of modeling and estimating interaction effects between covariates and a continuous treatment variable on an outcome, using a simple and intuitive single-index regression approach. The primary motivation is to estimate an optimal individualized dose rule in an observational study. To model possibly nonlinear interaction effects between patients’ covariates and a continuous treatment variable, we employ a two-dimensional penalized spline regression on an index-treatment domain, where the index is defined as a linear projection of the covariates. The method is illustrated using two applications as well as simulation experiments. A unique contribution of this work is in the parsimonious (single-index) parametrization specifically defined for the interaction effect term.

Keywords: Single-index model, individualized dose rules, tensor product P-splines, heterogeneous dose effects

1 Introduction

In precision medicine, a primary goal is to characterize individuals’ heterogeneity in treatment responses so that individual-specific treatment decisions can be made [Murphy, 2003; Robins, 2004]. Most work on developing methods for individualized treatment decisions has focused on a finite number of treatment options. The focus of this paper is to develop individualized treatment decision methodology in the realm of a continuous treatment. Specifically, we consider a semiparametric regression approach for developing optimal individualized dosing rules based on baseline patient characteristics. Often in clinical practice, the maximum dose that a patient can tolerate is the most effective one. However, there are situations where this is not the case. In the example

*This work was supported by National Institute of Health (NIH) grant 5 R01 MH099003.
section below, we present a study of warfarin (an anticoagulant), where too high doses lead to severe bleeding and thus the highest dose is not the optimal dose. In finding the optimal dose, there is an essential non-monotone and nonlinear relationship that needs to be accounted for. A similar case is with insulin for controlling blood glucose levels.

To establish notation, let $X = (X_1, \ldots, X_p)^\top \in \mathcal{X}$ be the set of baseline covariates, $Y \in \mathbb{R}$ be the outcome variable, and $A \in \mathcal{A}$ denote the dose. Without loss of generality, we assume that a larger value of the outcome $Y$ is better. The goal is then to find an optimal individualized dose rule $f : \mathcal{X} \mapsto \mathcal{A}$ such that for a patient with covariate $X$, the dose assignment $A = f(X)$ maximizes the expected response, the so-called value function:

$$V(f) = \mathbb{E}[\mathbb{E}[Y|A = f(X), X]].$$ (1)

In settings in which the treatment can be administered at continuous doses (i.e., when $\mathcal{A}$ is an interval), Chen et al. (2016) proposed to optimize the individualized dosing rule $f$ by maximizing an empirical version of a modified value function (1), optimized under the framework of outcome weighted learning (Zhao et al., 2012). In this paper, we consider a regression-based approach to optimizing $f$ that uses a semiparametric regression model for $\mathbb{E}[Y|A, X]$. While the outcome weighted learning approach of Chen et al. (2016) is highly appealing, regression-based approaches, particularly the proposed semi-parametric models, have the advantage of being simple, easy to implement, and readily interpretable.

It is straightforward to see that, given $X$, the optimal dose $f_{opt}(X)$ (i.e., that which maximizes the value function (1)) is

$$f_{opt}(X) = \arg\max_{a \in \mathcal{A}} m(a, X),$$ (2)

where $m(a, X) = \mathbb{E}[Y|A = a, X]$. If we estimate $m(a, X)$ with $\hat{m}(a, X)$, then the optimal rule $f_{opt}$ in (2) can be approximated as

$$\hat{f}(X) = \arg\max_{a \in \mathcal{A}} \hat{m}(a, X).$$ (3)

Methodologies for optimizing individualized treatment rules $f$ in the literature are developed almost exclusively for the cases in which the treatment variable $A$ is binary or discrete-valued. Regression-based methodologies typically approximate the function $f_{opt}$ in (2) by first estimating the treatment $a$-specific mean response functions $m(a, X)$ to obtain a treatment decision rule, i.e., the left-hand side of (3) (e.g., Qian and Murphy, 2011; Zhang et al., 2012; Gunter et al., 2011; Lu et al., 2013). In particular, Qian and Murphy (2011) show that the optimal individualized treatment rules, in terms of maximizing the expected treatment response (1), depends only on the interaction between treatment $A$ and covariates $X$, and not on the main effects of $X$ present in the mean response functions $m(a, X), a \in \mathcal{A}$. For regression-based methodologies, a successful estimation of the function $f_{opt}$ in (2) boils down to efficiently estimating the $A$-by-$X$ interaction effects on the mean response function. In this paper, we consider a semi-parametric regression model that is useful for estimating such interactions in the case where $A$ is a continuous dose variable.
2 Models

Our goal is to provide an interpretable and flexible approach to modeling and estimating the $A$-by-$X$ interaction effects on $Y$. To achieve this goal, we consider the following additive single-index model:

$$
\mathbb{E}[Y | X, A] = \mu(X) + g(\beta^T X, A)
$$

(4)

where $\mu(X)$ represents an unspecified main effect of $X$, and $g(\beta^T X, A)$ models the $A$-by-$X$ interaction effects. Here, $g(\cdot, \cdot)$ is an unspecified smooth two-dimensional surface link function of the variable $A$ and a single index $\beta^T X$. We shall call model (4) a single-index model with a surface-link (SIMSL). We restrict $\beta \in \Theta := \{ \beta = (\beta_1, \ldots, \beta_p)^T \in \mathbb{R}^p : \|\beta\|_2 = 1, \beta_1 > 0 \}$, as $\beta$ in (4) is only identifiable up to a scale constant without further constraint, due to the unspecified nature of $g$.

Without loss of generality, we assume $\mathbb{E}[Y] = 0$ and $\mathbb{E}[\mu(X)] = 0$, and $\mathbb{E}[g(\beta^T X, A)] = 0$ (where the expectation is with respect to $X$ and $A$), i.e., each of the additive components in model (4) has mean 0, and that $\mu(X)$ and $g(\beta^T X, A)$ have finite variances. That is, let $\mathcal{H}_1$ and $\mathcal{H}_2^{(\beta)}$ (for a fixed $\beta \in \Theta$) denote the Hilbert spaces of measurable functions $\mu(X)$ on $X$ and measurable functions $g(\beta^T X, A)$ on $(\beta^T X, A)$ (which depend on $\beta$), respectively, and we assume $\mu \in \mathcal{H}_1$ and $g \in \mathcal{H}_2^{(\beta)}$.

To eliminate the confounding of the interaction effect with the main effect in (4), we impose an identifiability constraint on the smooth $g \in \mathcal{H}_2^{(\beta)}$:

$$
\mathbb{E} \left[ g(\beta^T X, A) | X \right] = 0, \quad a.s. \quad (X) \quad X \in \mathcal{X}, \quad \beta \in \mathbb{R}^p
$$

(5)

which separates the $X$ main effect term $\mu(X)$ from the $A$-by-$X$ interaction effect term $g(\beta^T X, A)$ in the SIMSL (4) and thus defines the term $g(\beta^T X, A)$ to correspond to a “pure” $A$-by-$X$ interaction.

Under the SIMSL (4), the optimal individualized dose rule, $f_{\text{opt}}$, is specified as: $f_{\text{opt}}(X) = \arg\max_{a \in A} g(\beta^T X, a)$. Therefore, in terms of estimating $f_{\text{opt}}$ in (2), our modeling focus is on estimating $g$ and $\beta$. In this regards, the unspecified function $\mu$ in (4) is a “nuisance” component. For an optimal coefficient vector $\beta$ associated with the term $g(\beta^T X, A)$, the shape of the function $g$ captures a nonlinear interactive structure between $A$ and $\beta^T X$, and the heterogeneous dose effects.

Using the constrained least squares framework, the right-hand side of (4), subject to constraint (5), can be optimized by solving:

$$
(\mu^*, g^*, \beta^*) = \arg\min_{\mu \in \mathcal{H}_1, g \in \mathcal{H}_2^{(\beta)}, \beta \in \Theta} \mathbb{E} \left[ (Y - \mu(X) - g(\beta^T X, A))^2 \right]
$$

subject to

$$
\mathbb{E} \left[ g(\beta^T X, A) | X \right] = 0.
$$

(6)

Constraint (5) ensures that $\mathbb{E}[\mu(X)g(\beta^T X, A)] = \mathbb{E}[\mu(X)\mathbb{E}[g(\beta^T X, A) | X]] = 0$ (where we apply the iterated expectation rule to condition on $X$), which implies

$$
\mu(X) \perp g(\beta^T X, A).
$$

(7)

The orthogonality (7) implies that the optimization for $\mu^*$ and $(g^*, \beta^*)$ in the optimization (6) can be performed separately, without iterating between the two optimization procedures. That is, first we can solve for the main effect:

$$
\mu^* = \arg\min_{\mu \in \mathcal{H}_1} \mathbb{E} \left[ (Y - \mu(X))^2 \right].
$$

(8)
Then we can solve (for the interaction effect):

$$(g^*, \beta^*) = \arg\min_{g \in H_2^{(\beta)}, \beta \in \Theta} \mathbb{E}[(\tilde{Y} - g(\beta^T X, A))^2]$$

subject to $\mathbb{E} [g(\beta^T X, A) | X] = 0$, \(9\)

where $\tilde{Y} = Y - \hat{\mu}^*(X)$ is the residual from the (main effect) fit (8), in which $\hat{\mu}^*$ denotes some estimate of $\mu^*$ in (8). The residual $\tilde{Y}$ on the right-hand side of (9) can be replaced simply by the original variable $Y$, since taking $\hat{\mu}^* = 0$ does not change the minimizer $(g^*, \beta^*)$ on the left-hand side of (9), due to orthogonality (7) between the two additive terms in model (4).

The optimal individualized dose rule, $f_{opt}$, is then fitted as: $\hat{f}(X) = \arg\max_{a \in A} \hat{g}^*(\hat{\beta}^T X, a)$, where we estimate $(g^*, \beta^*)$ with $(\hat{g}^*, \hat{\beta}^*)$. The interaction effect optimization approach (9) to estimating $f_{opt}$ in (2) is appealing, since, due to orthogonality (7), misspecification of the function $\mu$ in (8), for example, setting $\hat{\mu}^* = 0$ (which is an extreme case), does not affect specification of $g^*$ and $\beta^*$ on the left-hand side of (9).

We focus on solving (9) as our primary focus is on estimating the $A$-by-$X$ interaction effect. For each fixed $\beta$, since the function $g(\beta^T X, A)$ depends on the covariates $X \in \mathcal{X}$ only through the 1-dimensional projection $\beta^T X$, $\mathbb{E} [g(\beta^T X, A)|X] = \mathbb{E} [g(\beta^T X, A)|\beta^T X]$. Then, for each fixed $\beta \in \Theta$, the following constraint on $g \in H_2^{(\beta)}$,

$$\mathbb{E} [g(\beta^T X, A)|\beta^T X] = 0, \quad X \in \mathcal{X}, \quad (10)$$

is a sufficient condition for the original “orthogonality” constraint (5). Thus, the original constraint (5) can be simplified to (10), for each fixed $\beta$. The following iterative procedure will be used to solve (9):

1. For fixed $\beta$, optimize the smooth $g(., .)$ by solving:

$$\arg\min_{g \in H_2^{(\beta)}} \mathbb{E}[(Y - g(\beta^T X, A))^2],$$

subject to the constraint (10).

2. For fixed $g$, optimize the coefficient $\beta \in \Theta$ by minimizing the squared error criterion of (11).

3. Iterate steps (1) and (2) until convergence with $\beta \in \Theta$.

The data version of optimizing $(g, \beta)$ can be derived as an empirical counterpart of the iterative procedure given above. Details on implementing this algorithm are given below.

3 Estimation

3.1 Representation of link surface

Suppose we have observed data $(Y_i, A_i, X_i)$ \((i = 1, \ldots, n)\). For each candidate vector $\beta \in \Theta$, let

$$\eta_i = \eta_i^{(\beta)} = \beta^T X_i \quad (i = 1, \ldots, n),$$

4
where (on the left-hand side), for the notational simplicity, we suppress the dependence of the linear predictor \( \eta^{(\beta)} \in \mathbb{R} \) on the candidate vector \( \beta \).

Eilers and Marx (2003) have used tensor products of \( B \)-splines (de Boor 2001) to represent two-dimensional surfaces, which they termed tensor product \( P \)-splines, with separate difference penalties applied to the coefficients of the \( B \)-splines along the covariate axes. Although alternative nonparametric methods could also be used to estimate the smooth function \( g \in \mathcal{H}_2^{(\beta)} \) given each coefficient vector \( \beta \) in model (4), in this paper we focus on one smoother, the tensor-product \( P \)-splines, for the ease of presentation.

Specifically, for each \( \eta = \beta^\top X \), to represent the 2-dimensional function \( g(\eta, A) \) in (11), we consider the tensor product of the two sets of univariate cubic \( B \)-spline basis functions, say \( \tilde{B} \) and \( \check{B} \), with \( N \) (and \( \check{N} \)) \( B \)-spline knots for the basis functions that are placed along the \( \eta \) (and \( A \)) axis. The number of knots \( N \) (and \( \check{N} \)) is chosen to be large, i.e., to allow the surface much flexibility. Associated with the basis representation defined by the marginal basis function \( B \) (resp., \( \check{B} \)) is an \( N \times N \) (resp., \( \check{N} \times \check{N} \)) roughness penalty matrix, which we denote by \( P \) (and \( \check{P} \)). The penalty matrix \( P \) (and \( \check{P} \)) can be easily constructed, for example, based on a second-order difference matrix (e.g., see Eilers and Marx (2003)).

For each fixed \( \eta_i = \beta^\top X_i \) (\( i = 1, \ldots, n \)), let us write the \( n \times N \) (and \( N \times N \)) \( B \)-spline evaluation matrix \( B \) (and \( \check{B} \)), in which its \( i \)th row is \( B_i = B(\eta_i)^\top \) (and \( \check{B}_i = \check{B}(A_i)^\top \)). For a given knot grid, a flexible surface can be approximated (Marx 2015) at \( n \) points \( (\eta_i, A_i) \) (\( i = 1, \ldots, n \)):

\[
g(\eta_i, A_i) = \sum_{r=1}^N \sum_{s=1}^{\check{N}} B_r(\eta_i) \check{B}_s(A_i) \gamma_{rs} = (B_i \otimes \check{B}_i) \theta \quad (i = 1, \ldots, n),
\]

where the vector \( \theta = (\gamma_{11}, \ldots, \gamma_{1N}; \ldots; \gamma_{N1}, \ldots, \gamma_{NN})^\top \in \mathbb{R}^{NN} \) corresponds to an unknown (vectorized) coefficient vector of the tensor product representation of \( g \), and \( \otimes \) represents the usual Kronecker product. Equation (12) can be compactly written as:

\[
\text{vec}\{g(\eta_i, A_i)\} = g(\eta_{n \times 1}, A_{n \times 1}) = D \theta,
\]

where

\[
D = B \square \check{B} = (B \otimes 1_{\check{N}}^\top) \otimes (1_N^\top \otimes \check{B}),
\]

in which the symbol \( \otimes \) denotes element-wise multiplication of matrices. In Wood (2017), the symbol \( \square \) in (14) is called the row-wise Kronecker product, which results in a \( n \times NN \) tensor product design matrix \( D \) from the two marginal design matrices \( B \) and \( \check{B} \).

Similarly, the roughness penalty matrices associated with the tensor product representation (12) can be constructed from the roughness penalty matrices \( P \) and \( \check{P} \) associated with the univariate (marginal) basis matrices \( B \) and \( \check{B} \), and are given by \( P = P \otimes I_{\check{N}} \) and \( \check{P} = I_N \otimes \check{P} \), for the axis directions \( \eta \) and \( A \), respectively. Here, \( I \) denotes the identity matrix, and both \( P \) and \( \check{P} \) are square matrices with dimension \( NN \).

We now need to impose the constraint \( (10) \) on the 2-dimensional smooth function \( g \) under the tensor product representation (13). For each fixed \( \beta \), the constraint (10) on \( g \) amounts to excluding the main effect of \( \eta = \beta^\top X \) from the function \( g \). We deal with this by a reparametrization of the representation (13) for \( g \).
Consider the following sum-to-zero (over the \( n \) observed values) constraint for the marginal function of \( A \):
\[
1^\top \hat{B} \gamma = 0,
\]

for any arbitrary \( \gamma \in \mathbb{R}^N \), where \( 1 \) is a length \( n \) vector of 1’s. With constraint (15), the linear smoother associated with the basis matrix \( \hat{B} \) cannot reproduce constant functions \( \text{[Hastie and Tibshirani, 1999]} \). That is, the linear constraint (15) removes the span of constant functions from the span of the marginal basis matrix \( \hat{B} \) associated with \( A \). Constraint (15) results in a tensor product basis matrix, \( D = B \otimes \hat{B} \) in (13), that will not include the main effect of \( \eta \) that results from the product of the marginal basis matrix \( B \) with the constant function in the span of the other marginal basis matrix \( \hat{B} \). Therefore, the resultant fit, under representation (13) (subject to (15)) of the smooth function \( g \), excludes the main effect of \( \eta \). See Section 5.6 of Wood (2017) for some more details.

We impose the linear constraint (15) on the matrix \( \hat{B} \), and consequently, the resulting basis matrix \( D \) of representation of \( g \) in (13) becomes independent of the basis associated with the main effect of \( \eta \). Imposition of such a linear constraint (15) on a basis matrix is routine. The key is to find an (orthogonal) basis for the null space of the constraint (15), and then absorb the constraint into the basis construction (14). To be specific, we can create a \( \tilde{N} \times (\tilde{N} - 1) \) matrix, which we denote as \( Z \), such that, given any arbitrary coefficient vector \( \gamma_0 \in \mathbb{R}^{N-1} \), if we set \( \gamma = Z \gamma_0 \), then we have \( 1^\top \hat{B} \gamma = 0 \), and thus automatically satisfy the constraint (15). Such a matrix \( Z \) is constructed using a QR decomposition of \( \hat{B}^\top 1 \). Then we can reparametrize the marginal function of \( A \) by setting its model matrix to \( \hat{B} \leftarrow \tilde{B}Z \) (and its penalty matrix to \( \tilde{P} \leftarrow Z^\top \tilde{P} Z \)). From this point forward, for notational simplicity, we redefine the matrix \( \tilde{B} \) (and \( \tilde{P} \)) to be this reparameterized constrained marginal basis matrix (and the reparameterized constrained penalty matrix).

This sum-to-zero reparametrization of the marginal basis matrix \( \hat{B} \) of \( A \) to satisfy (15) is simple and creates a term \( \text{vec}\{g(\eta_i, A_i)\} \in \mathbb{R}^n \) in (13) that specifies such a pure \( A \)-by-\( X \) interaction (plus the \( A \) main effect) component, that is also orthogonal to the \( X \) main effect. In Wood (2006), this reparameterization approach is used to create an analysis of variance (ANOVA) decomposition of a smooth function of several variables. In this paper we use this same reparameterization to orthogonalize the interaction effect component \( g(\beta^\top X, A) \) from the main effect, and to allow an unspecified/misspecified main effect for \( X \) in the estimation of the SIMSL (4). Provided that the orthogonality constraint (i.e., (15)) issue is addressed, the interaction effect term \( g(\beta^\top X, A) \) of model (4), for each fixed \( \beta \), can be represented using penalized regression splines and estimated based on penalized least squares, which we describe next.

### 3.2 Estimation algorithm

We define the criterion function for estimating \((g, \beta)\) in the SIMSL (4):
\[
Q(\theta, \beta) = \|Y_{n \times 1} - g(X \beta, A_{n \times 1})\|^2 + \lambda \|P\theta\|^2 + \tilde{\lambda} \|\tilde{P}\theta\|^2
\]

subject to the constraint that \( g(\cdot, \cdot) \) satisfies (5). In (16), \( X \) is a \( n \times p \) matrix whose \( i \)th row is \( X_i^\top \). Since both \( \theta \) and \( \beta \) are unknown in (16), estimation of \( \theta \) and \( \beta \) is conducted iteratively. We describe below the estimation procedure.
1. For a fixed estimate of $\beta$ (that defines the linear predictor $\eta$), minimize the following criterion function over $\theta \in \mathbb{R}^{N \times N}$,

$$
\|Y_{n \times 1} - D\theta\|^2 + \lambda\|P\theta\|^2 + \lambda\|ar{P}\theta\|^2,
$$

(17)

where $D$ is given by (14). Given tuning parameters $(\lambda, \bar{\lambda})$, the minimizer $\hat{\theta}$ of (17) is:

$$
\hat{\theta} = \left( D^\top D + \lambda P^\top P + \bar{\lambda} \bar{P}^\top \bar{P} \right)^{-1} D^\top Y_{n \times 1}.
$$

2. For a fixed estimate of the surface $g$ (i.e., given $\theta$), perform a first-order Taylor approximation of $g(X\beta, A_{n \times 1})$ in (16) with respect to $\beta$, around the current estimate, denote as $\bar{\beta} \in \Theta$,

$$
g(X\beta, A_{n \times 1}) \approx g(X\bar{\beta}, A_{n \times 1}) + \text{diag}\{\hat{g}_\partial(X\bar{\beta}, A_{n \times 1})\} X(\beta - \bar{\beta}),
$$

(18)

where $\hat{g}_\partial(u, a)$ denotes the partial first derivative of $g(u, a)$ with respect to the first variable $u$, i.e., $\frac{\partial g(u, a)}{\partial u}$. Utilizing (18), the quadratic loss term in (16) as a function of $\beta$ given $\theta$, can be approximated as:

$$
\left\|Y_{n \times 1} - g(X\bar{\beta}, A_{n \times 1}) - \text{diag}\{\hat{g}_\partial(X\bar{\beta}, A_{n \times 1})\} X(\beta - \bar{\beta})\right\|^2
$$

$$
= \left\|Y_{n \times 1} - g(X\bar{\beta}, A_{n \times 1}) + \text{diag}\{\hat{g}_\partial(X\bar{\beta}, A_{n \times 1})\} X\bar{\beta} - \text{diag}\{\hat{g}_\partial(X\bar{\beta}, A_{n \times 1})\} X\beta\right\|^2
$$

(19)

$$
= \left\|Y_{n \times 1}^* - X^*\beta\right\|^2,
$$

where $Y_{n \times 1}^* = Y_{n \times 1} - g(X\bar{\beta}, A_{n \times 1}) + \text{diag}\{\hat{g}_\partial(X\bar{\beta}, A_{n \times 1})\} X\bar{\beta}$, and $X^* = \text{diag}\{\hat{g}_\partial(X\bar{\beta}, A_{n \times 1})\} X$. The minimizer $\hat{\beta}$ of (19) is:

$$
\hat{\beta} = (X^{*\top} X^*)^{-1} X^{*\top} Y_{n \times 1}^*.
$$

Then we scale $\hat{\beta}$ to unit $L^2$ norm, i.e., $\hat{\beta}/\|\hat{\beta}\|$, and enforce a positive first element to restrict the estimate of $\beta$ to be in $\Theta$.

These two steps can be iterated until convergence to obtain an estimate of $(g^*, \beta^*)$ in (9), which we denote as $(\hat{g}^*, \hat{\beta}^*)$. For Step 1, the tuning parameters $(\lambda, \bar{\lambda})$ can be automatically selected, for example, by the generalized cross-validation (GCV) or the restricted maximum likelihood (REML) methods. In this paper, we use REML for the simulation examples and the applications.

Lastly, for model hierarchy, it is common practice to include all lower order effects of variables if there are higher-order interaction terms including that set of variables. Once convergence of the estimate $\hat{\beta}^*$ is reached in the above algorithm and the single-index $\beta^T X$ in the term $g(\beta^T X, A)$ of model (4) is estimated, we recommend fitting one final (unconstrained) smooth function $g$ of $A$ and $\beta^T X$, without enforcing the constraint (15) on $g$. Given the final estimate of $\beta$, the unconstrained final surface-link $g(\cdot, \cdot)$ retains the main effect of $\beta^T X$ and preserves model hierarchy.

4 Extension to a generalized single-index regression for modeling interactions

The proposed approach to optimizing the interaction effect term of model (4) can be extended to a more general setting in which the response $Y$ follows an exponential family distribution given
$X \in \mathcal{X}$ and $A \in \mathcal{A}$. We again assume an additive single-index model \([1]\) for the true mean response function:

$$
\mathbb{E}[Y|X,A] = \mu_0(X) + g_0(\beta_0^\top X, A),
$$

(20)

where the term $\mu_0(X)$ represents an unspecified main effect of $X$, and the term $g_0(\beta_0^\top X, A)$ represents the $A$-by-$X$ interaction effect. (In this section, we use subscript (0) to indicate the “true” value.) In (20), for model identifiability, we set $\beta_0 \in \Theta$ and $\mathbb{E}[g_0(\beta_0^\top X, X)|X] = 0$ separating the $X$ main effect from the $A$-by-$X$ interaction effect. The functions $\mu_0 \in \mathcal{H}_1$ and $g_0 \in \mathcal{H}_2^{(\beta_0)}$ in (20) are assumed to be appropriately defined to give a valid range for the mean of $Y$, given $X$ and $A$ (e.g., for a Bernoulli $Y$, the mean response function $\mathbb{E}[Y|X,A]$ must satisfy $0 \leq \mathbb{E}[Y|X,A] \leq 1$, almost surely).

To approximate the $A$-by-$X$ interaction effect term $g_0(\beta_0^\top X, A)$ in (20) in the presence of the unspecified $X$ main effect term $\mu_0(X)$, we propose to utilize the following working model, without including a term that corresponds to the $X$ main effect component $\mu_0(X)$ in (20):

$$
\mathbb{E}[Y|X,A] \approx h^{-1}(g(\beta^\top X, A)),
$$

(21)

subject to the constraint $\mathbb{E}[g(\beta^\top X, A)|X] = 0$, where $h(\cdot) = \dot{h}(\cdot)$ (in which $\dot{h}(\cdot)$ is the first derivative of $h(\cdot)$) is the canonical link function associated with the assumed exponential family distribution, which is specified by an exponential family density of the form:

$$
\exp \left\{ \left[ Y g(\beta^\top X, A) - b(g(\beta^\top X, A)) \right] / a(\phi) + c(Y, \phi) \right\},
$$

(22)

with $g \in \mathcal{H}_2^{(\beta)}$ and $\beta \in \Theta$. In (22), $\phi$ is an arbitrary “scale” parameter, and the functions $a$, $b$ and $c$ are distribution-specific known functions. We propose to optimize the working model (21) by solving for the constrained maximizer $(g^*, \beta^*)$:

$$
(g^*, \beta^*) = \arg\max_{g \in \mathcal{H}_2^{(\beta)}, \beta \in \Theta} \mathbb{E}[Y g(\beta^\top X, A) - b(g(\beta^\top X, A))]
$$

subject to $\mathbb{E}[g(\beta^\top X, A)|X] = 0$

(23)

where the expectation in the criterion function is with respect to $(Y, A, X)$, in which their relationships are specified by the mean model (20). In (23), $b(u) = u^2/2$ for a Gaussian $Y$ (for which the optimization (22) is a special case of (23)), $b(u) = \log\{1 + \exp(u)\}$ for a Bernoulli $Y$, and $b(u) = \exp(u)$ for a Poisson $Y$. The solution $(g^*, \beta^*)$ of (23) is thus defined as the minimizer of the Kullback-Leibler divergence between the working model (21) and the true model (20).

The constraint $\mathbb{E}[g(\beta^\top X, A)|X] = 0$ in optimization (23) implies:

$$
\mathbb{E}\left[ Y g(\beta^\top X, A) - b(g(\beta^\top X, A)) \right] = \mathbb{E}\left[ \{\mu_0(X) + g_0(\beta_0^\top X, A)\} g(\beta^\top X, A) - b(g(\beta^\top X, A)) \right]
$$

$$
= \mathbb{E}\left[ \mathbb{E}[\mu_0(X)|g(\beta^\top X, A)] \right] + \mathbb{E}\left[ g_0(\beta_0^\top X, A)(g(\beta^\top X, A) - b(g(\beta^\top X, A))) \right]
$$

$$
= \mathbb{E}\left[ g_0(\beta_0^\top X, A)(g(\beta^\top X, A) - b(g(\beta^\top X, A))) \right],
$$

(24)

which is independent of $\mu_0(X)$ in model (20). Therefore, the solution $(g^*, \beta^*)$ for the optimization problem (23) is given independently of the true “main” effect term $\mu_0(X)$ in (20). This independence enables us to focus only on the $A$-by-$X$ interaction effect term of model (20) if our interest
is in the interaction effect term, without having to correctly specify or include the $X$ main effect term in the estimation. From the right-hand side of (24), we can derive how the solution $(g^*, \beta^*)$ of optimization (23) is related to $(g_0, \beta_0)$ of the true mean model (20).

**Proposition 1** The solution $(g^*, \beta^*)$ of the constrained optimization problem (23) satisfies:

$$g_0 = h^{-1} \circ g^* \text{ and } \beta_0 = \beta^*, \quad (25)$$

where $g_0 \in \mathcal{H}_2^{(\beta_0)}$ and $\beta_0 \in \Theta$ are given from the true mean model (20). In (25), the function $h^{-1}$ is the inverse of the canonical link associated with the assumed exponential family distribution and the operator $\circ$ represents the composition of two functions.

The proof of Proposition 1 is in the Supplemental Materials. In (25), $h^{-1}(u) = u$ (the identity function) for a Gaussian $Y$, $h^{-1}(u) = \exp(u)/\{1 + \exp(u)\}$ for a Bernoulli $Y$, and $h^{-1}(u) = \exp(u)$ for a Poisson $Y$.

Given data $(Y_i, A_i, X_i) (i = 1, \ldots, n)$, for each fixed $\beta \in \Theta$, the profile estimator of the function $g$ on the right-hand side of (23) can be obtained by implementing a standard generalized additive model (GAM) fitting procedure (e.g., Hastie and Tibshirani (1999)) that bases on iteratively re-weighted least squares (IRLS), with representation (13) to approximate model (GAM) fitting procedure (e.g., Hastie and Tibshirani (1999)) that bases on iteratively re-weighted least squares (IRLS), with representation (13) to approximate $g$; the only adjustment to be made to the standard GAM fitting procedure is to enforce the constraint $\mathbb{E}[g(\beta^T X, A)|\beta^T X] = 0$ on the smooth $g$. As in Section 3.1, this constraint can be absorbed into the tensor product basis representation (13) in the estimation. Given the finite dimensional representation (13) for $g$, the squared error term in (17) is replaced by an empirical version of the negative of the criterion function in (23). The same iterative procedure alternating between the estimation of $\theta \in \mathbb{R}^{NN}$ and the estimation of $\beta \in \Theta$ can be performed until convergence of $\hat{\beta}$, as in Section 3.2. The resulting estimate of $(g^*, \beta^*)$ in (23) can be used to estimate $(g_0, \beta_0)$ in (20), based on the relationship (25).

In the Supplemental Materials, we provide an example illustrating the approach (23) to modeling interaction effects between $X$ and $A$ on a discrete-valued response $Y$.

## 5 Simulation example

In this section, we consider a set of simulation studies with data generated from the four scenarios described in Chen et al. (2016). We generate $p$-dimensional vectors of covariates, $X = (X_1, \ldots, X_p)^\top$, where each entry is generated independently from Uniform$[-1, 1]$. In Scenarios 1 and 2, the treatment $A$ is generated from Uniform$[0, 2]$ independently of $X$, mimicking a randomized trial. In Scenarios 3 and 4, the distribution of $A$ (described below) depends on $X$, mimicking an observational study setting. In each scenario, the outcome $Y$, given $X$ and $A$, is generated from a normal distribution with unit variance, with the following four different mean function scenarios:

1. **Scenario 1**: $\mathbb{E}[Y|X, A] = 8 + 4X_1 - 2X_2 - 2X_3 - 25(f_{opt}(X) - A)^2$, where $f_{opt}(X) = 1 + 0.5X_1 + 0.5X_2$. Here, the optimal individualized dose rule is a linear function of $X$.

2. **Scenario 2**: $\mathbb{E}[Y|X, A] = 8 + 4 \cos(2\pi X_2) - 2X_4 - 8X_5^3 - 15|f_{opt}(X) - A|$, where $f_{opt}(X) = 0.6(-0.5 < X_1 < 0.5) + 1.2(X_1 > 0.5) + 1.2(X_1 < -0.5) + X_4^2 + 0.5\log(|X_7|+1)-0.6$. Here, the optimal individualized dose rule is a nonlinear function of $X$. 


3. Scenario 3 is the same as in Scenario 2, except that the distribution of \( A \) depends on \( X \) as follows:

\[
A \sim \begin{cases} 
\text{TruncN}(-0.5 + 0.5X_1 + 0.5X_2, 0, 2, 0.5), & \text{when } X_3 < 0 \\
\text{TruncN}(0.5 + 1.5X_2, 0, 2, 1), & \text{when } X_3 > 0 
\end{cases}
\]

where \( \text{TruncN}(\mu, a, b, \sigma) \) denotes the truncated normal distribution with mean \( \mu \), lower bound \( a \) and upper bound \( b \), and standard deviation \( \sigma \).  

4. Scenario 4 is the same as in Scenario 2, except that the distribution of \( A \) depends on \( X \) as follows:

\[
A \sim \text{TruncN}(f_{\text{opt}}(X), 0, 2, 0.5).
\]

Following [Chen et al. (2016)], we set \( p = 30 \) in Scenario 1, and \( p = 10 \) for Scenarios 2, 3 and 4. For each simulated dataset, we apply the proposed method of estimating the \( A \)-by-\( X \) interactions using the SIMSL (4) and estimating the optimal dose rule \( f_{\text{opt}} \) by \( \hat{f}(X) = \arg \max_{a \in A} \hat{g}^*(\beta^\top X, a) \).

The main effect estimate \( \hat{\mu}^*(X) \) in (8) is simply taken to be 0. We simulated 200 data sets for each scenario. For comparison, we report results of the estimation approaches considered in Chen et al. (2016), including their Gaussian kernel-based outcome-weighted learning (K-O-learning) and linear kernel-based outcome-weighted learning (L-O-learning). We also report a support vector regression (SVR; Vapnik, 1995; Smola and Scholopf, 2004) with a Gaussian kernel to estimate the nonlinear relationship between \( Y \) and \((A, X)\) (Zhao et al., 2009) that was used for comparison.

Since we are simulating data from known models in which the true relationship \( \mathbb{E}[Y|X, A] \) is known, we can compare the estimated dose rules \( \hat{f} \) derived from each method in terms of the value \( \mathbb{E}[\hat{Y}|X, A] \). Specifically, an independent test set of size \( \hat{n} = 5000 \) was generated and the value of \( \mathbb{V}(\hat{f}) = \hat{n}^{-1} \sum_{i=1}^{\hat{n}} \mathbb{E}[Y_i|X_i, A_i = \hat{f}(X_i)] \) for each simulation run. Given each scenario and a training sample size \( n \), we replicate the simulation experiment 200 times, each time estimating the value. Again, following Chen et al. (2016), we report the averaged estimated values (and standard deviations) for the cases where \( \hat{f} \) is estimated from a training set of size \( n = 50, 100, 200, 400 \) and \( 800 \) for Scenario 1 and 2, and the cases with \( n = 200 \) and \( 800 \) for Scenario 3 and 4. The simulation results are given in Table 1 and 2.

The results in Table 1 and 2 indicate that the proposed regression method for optimizing individualized dose rules outperforms the alternative approaches presented in Chen et al. (2016) in all cases except when the training sample size is very small \( (n = 50) \). In Table 2, K-O-learning(Prp) refers to the propensity score-adjusted K-O-learning of Chen et al. (2016). When the sample size is very small, the outcome-weighted learning approaches outperform the regression-based approaches (SIMSL and SVR), especially for Scenario 1 (with \( p = 30 \)) where the regression approaches exhibit large variances. However, when \( n = 100 \), the performance of the SIMSL approach improves dramatically in terms of both value and small variance. We also note that using \((A, X, X^2)\) instead of \((A, X)\) in Scenario 2 leads to a substantial improvement in performance. If \((X, A)\) is used for fitting the SIMSL in Scenario 2, the estimated values are: \(-7.16(6.34)\), \(-2.04(4.81)\), \(1.90(2.21)\), \(3.68(1.07)\) and \(4.44(0.91)\), for sample sizes \( n = 50, 100, 200, 400 \) and \( 800 \), respectively.
Table 1: Average (and sd) value $\hat{V}(f)$ from 200 replicates from the randomized trial scenarios. In both settings, the oracle $f_{opt}$ attains a value function $V(f_{opt}) = 8$ (boldface denotes the largest in each row).

| n     | SIMSL    | K-O-learning | L-O-learning | SVR       |
|-------|----------|--------------|--------------|-----------|
| 50    | -0.19 (5.05) | 4.78 (0.48)  | **4.83 (1.40)** | -12.21 (7.53) |
| 100   | **7.00 (0.61)** | 5.69 (0.40)  | 5.39 (0.93)  | -2.57 (6.34)  |
| 200   | **7.67 (0.13)** | 6.68 (0.26)  | 6.85 (0.34)  | 3.46 (1.97)   |
| 400   | **7.85 (0.05)** | 7.28 (0.15)  | 7.41 (0.14)  | 6.13 (0.47)   |
| 800   | **7.92 (0.02)** | 7.54 (0.08)  | 7.67 (0.08)  | 7.36 (0.12)   |

Table 2: Average (and sd) value $\hat{V}(f)$ from 200 replicates from observational studies. In both settings, the oracle $f_{opt}$ attains a value function $V(f_{opt}) = 8$ (boldface denotes the largest in each row).

| n     | SIMSL    | K-O-learning | K-O-learning(Prp) | SVR       |
|-------|----------|--------------|-------------------|-----------|
| 200   | **4.01 (1.01)** | 2.68 (0.30)  | 2.74 (0.29)       | 1.99 (0.83) |
| 800   | **5.43 (0.26)** | 4.06 (0.30)  | 4.19 (0.20)       | 4.09 (0.28) |
| 200   | **3.55 (1.08)** | 3.29 (0.28)  | 3.23 (0.28)       | -0.95 (1.57) |
| 800   | **5.24 (0.24)** | 4.91 (0.14)  | 4.73 (0.17)       | 3.04 (0.52) |
6 Application to optimization of the warfarin dose with clinical and pharmacogenetic data

In this section, the utility of the SIMSL approach to personalized dose finding is illustrated from an anticoagulant study. Warfarin is a widely used anticoagulant to treat and prevent blood clots. The therapeutic dosage of warfarin varies widely across patients and its administration must be closely monitored to prevent adverse side effects. Our analysis of the data will broadly follow that of Chen et al. (2016). After removing patients with missing data, the dataset provided by International Warfarin Pharmacogenetics Consortium et al. (2009) (publicly available to download from https://www.pharmgkb.org/downloads/) consists of 1780 subjects, including information on patient covariates \((X)\), final therapeutic dosages \((A)\), and patient outcomes \((\text{INR}, \text{International Normalized Ratio})\). INR is a measure of how rapidly the blood can clot. For patients prescribed warfarin, the target INR is around 2.5. In order to convert the INR to a measurement responding to the warfarin dose level, we construct an outcome \(Y = -|2.5 - \text{INR}|\), and a larger value of \(Y\) is considered desirable.

There were 13 covariates \(X = (X_1, \ldots, X_{13})^\top\) in the dataset (both clinical and pharmacogenetic variables): height \((X_1)\), weight \((X_2)\), age \((X_3)\), use of the cytochrome P450 enzyme inducers \((X_4)\); the enzyme inducers considered in this analysis includes phenytoin, carbamazepine, and rifampin), use of amiodarone \((X_5)\), gender \((X_6; 1\) for male, 0 for female), African or black race \((X_7)\), Asian race \((X_8)\), the VKORC1 A/G genotype \((X_9)\), the VKORC1 A/A genotype \((X_{10})\), the CYP2C9 *1/*2 genotype \((X_{11})\), the CYP2C9 *1/*3 genotype \((X_{12})\), and the other CYP2C9 genotypes (except the CYP2C9 *1/*1 genotype which is taken as the baseline genotype) \((X_{13})\). Further details on these covariates are given in International Warfarin Pharmacogenetics Consortium et al. (2009).

The first 3 covariates (height, weight, age) were treated as continuous variables, standardized to mean zero and unit variance; the other 10 covariates are indicator variables. In estimating the optimal individualized dose rule \(f_{\text{opt}}\), modeling the drug (dose level \(A\)) interactions with the patient covariates \(X\) in their effects on \(Y\) is essential. Under the proposed SIMSL approach \((4)\), the \(A\)-by-\(X\) interaction effect term \(g(\beta^\top X, A)\) is the target component of interest, whereas the \(X\) main effect term \(\mu(X)\) is a “nuisance” component, since the optimal dose rule \(f_{\text{opt}}\) does not depend on \(\mu(X)\). To estimate the SIMSL \((4)\), we first approximate the solution \((8)\) of the main effect term \(\hat{\mu}(X)\) of \((4)\), by utilizing an additive working model. This working model consists of a set of linear (parametric) terms for the discrete covariates \(X_4, \ldots, X_{13}\) and a set of cubic \(P\)-spline smooth terms for the continuous covariates \(X_1, X_2\) and \(X_3\), estimated by penalized least squares, with their smoothing parameters estimated by REML. Then, based on the residual \(\hat{Y} = Y - \hat{\mu}^*(X)\), we approximate the solution \((9)\) of the \(A\)-by-\(X\) interaction effect by the procedure described in Section 3.

The estimated \(\beta\) is \((0.18, 0.02, -0.02, 0.52, -0.41, 0.10, -0.23, 0.32, -0.11, 0.05, 0.02, -0.34, -0.48)^\top\). The third panel in Figure 1 displays the estimated interaction surface plot of the 2-dimensional surface-link function \(g(\beta^\top X, A)\) of model \((4)\), showing an interactive relationship on the index-treatment domain. The first two panels in Figure 1 display the plots for the estimated individual smooth function of the dose \(A\) and that of the estimated single-index \(\beta^\top X\), where the individual smooths are obtained from fitting additive models with two univariate cubic \(P\)-spline smooth terms (associated with \(A\) and \(\beta^\top X\), respectively).

Due to the restriction \(\beta \in \Theta\) on the single-index coefficient, building confidence intervals for
\(\beta\) is complicated. In particular, the positivity constraint \((\beta_1 > 0)\) imposed on the estimate of \(\beta_1\) will force the signs of the other single-index coefficient estimates of \(\beta_2, \ldots, \beta_p\) to switch if the sign of \(\beta_1\) is initially estimated to be negative. Especially when \(\beta_1 \approx 0\), the variability of the estimates of \(\beta_2, \ldots, \beta_p\) across (bootstrap) resampled datasets due to their sign switches can be rather dramatic. Therefore, based on a bootstrap approach, instead of estimating the variance of \(\hat{\beta}_j\), we estimate the variance of the more robust measure \(|\hat{\beta}_j|\), which quantifies the magnitude of contribution of each covariate \(X_j\) to the heterogeneous dose responses captured by the model \(g(\beta^\top X, A)\). If we can reasonably assume that the sign of \(\hat{\beta}_j\) correctly estimates that of \(\beta_j\), i.e., if \(\text{sign}(\hat{\beta}_j) = \text{sign}(\beta_j)\), then \(\text{var}(\hat{\beta}_j) = \text{var}(|\hat{\beta}_j|)\). As a heuristic, for this example, we use the approximation, \(\text{var}(\hat{\beta}_j) \approx \text{var}(|\hat{\beta}_j|)\), to build an approximate 95\% normal confidence interval for \(\beta_j\), \((\hat{\beta}_j - 1.96\sqrt{\text{var}(|\hat{\beta}_j|)}, \hat{\beta}_j + 1.96\sqrt{\text{var}(|\hat{\beta}_j|)})\), where \(\text{var}(|\hat{\beta}_j|)\) is estimated from 500 bootstrap resampled datasets.

The approximate 95\% bootstrap confidence intervals for the \(\beta_j\)’s associated with the covariates height \((X_1)\), the use of the cytochrome P450 enzyme inducers \((X_4)\), the use of amiodarone \((X_5)\), the CYP2C9 *1/*3 genotype \((X_{12})\), and the other CYP2C9 genotypes \((X_{13})\) do not include 0. We infer that these covariates are potentially clinically important drug effect modifiers, interacting with warfarin in their effects on INR.

Chen et al. (2016) noted that the analysis results from International Warfarin Pharmacogenetics Consortium et al. (2009), as well as their linear kernel-based outcome-weighted learning results, suggest increasing the dose if patients are taking Cytochrome P450 enzyme \((X_4)\) and decreasing the dose if patients are taking Amiodarone \((X_5)\). Roughly speaking, the interaction surface (the right-most panel) in Figure 1 indicates that for a larger value of \(\beta^\top X\) (e.g., \(\beta^\top X > 0\)), a larger value of \(A\) (e.g., \(A > 60\)) will generally be preferred, whereas for a small value of \(\beta^\top X\), a lower dose level for \(A\) (e.g., \(A < 40\)) will generally be preferred. Considering the sign of the coefficient estimates associated with \(X_4\) \((\hat{\beta}_4 = 0.52)\) and \(X_5\) \((\hat{\beta}_5 = -0.41)\), this is roughly consistent with International Warfarin Pharmacogenetics Consortium et al. (2009) and Chen et al. (2016). However, the non-monotone interaction surface indicates that this dose suggestion should also be exercised with care.

To evaluate the performance of the individualized dose rules estimated from the 6 methods, including the propensity score-adjusted outcome-weighted learning with a linear/Gaussian kernel, denoted as L-O-learning(Prp) and K-O-learning(Prp), respectively) considered in Section 5, we randomly split the dataset at a ratio of 1-to-1 into a training set and a testing set, replicated 100 times, each time estimating \(f_{\text{opt}}\) using the 6 methods based on the training set, and estimating the value \([\overline{1}]\) of each estimated \(f_{\text{opt}}\) based on the testing set. Unlike the simulated data in Section 5, the true relationship between the covariate-specific dose and the response is unknown. Therefore, for each dose rule \(f\), we need to estimate the value \([\overline{1}]\) from the testing data. Given a dose rule \(f\), only a very small proportion (or none) of the observations will satisfy \(A_i = f(X_i)\), and thus only a very small proportion (or none) of the observations in the testing data will contribute information to estimate the value \([\overline{1}]\). However, Cai and Tian (2016) noted that the value \([\overline{1}]\) for each \(f\) can also be written as \(\mathcal{V}(f) = \mathbb{E}[\mathbb{E}[Y|A = f(X), f(X)]]\). Therefore, using a 2-dimensional smoother of \(A\) and \(f(X)\) for \(Y\), one may first obtain a nonparametric estimate of \(\mathbb{E}[Y|A, f(X)]\), denoted as \(\hat{m}(A, f(X))\), and then \(\mathcal{V}(f)\) may be estimated as \(\hat{\mathcal{V}}(f) = n^{-1}\sum_{i=1}^n \hat{m}(f(X_i), f(X_i))\). Specifically, given a dose rule \(f\) estimated from a training set, we can estimate \(\mathbb{E}[Y|A, f(X)]\) based
on \((Y_i, A_i, f(X_i))\) from a test set, using a set of thin plate regression spline bases obtained from a rank-100 eigen-approximation to a thin plate spline, with the smoothness parameter selected by REML, implemented via the R function \(\texttt{mgcv::gam} (\text{Wood}, 2019b)\). A thin plate spline is an isotropic smooth; isotropy is often appropriate for two variables observed on the same scale, which is the case here.

Figure 2 displays a boxplot describing the distributions for the estimated values \(\ell_i\) of the 6 estimation methods described in Section 5, obtained from the aforementioned 100 random training/testing splits. The boxplots indicate that the proposed SIMSL method and the propensity-score adjusted K-O-learning of Chen et al. (2016) perform at a similar level, while outperforming all other approaches. This illustrates the potential utility of the proposed regression approach to optimizing individualized dose rules. In comparison to the outcome-weighted learning approach of Chen et al. (2016), one advantage of the proposed approach is that it allows visualization of the estimated interactive structure on the dose-index domain as illustrated in the right panel of Figure 3. Additionally, if each of the covariates is standardized to have, say, unit variance, then the relative importance of each covariate in characterizing the heterogeneous dose response can be determined by the magnitude of the estimated coefficients in \(\beta\), rendering a potentially useful interpretation when examining the drug-covariates interactions.

7 Discussion

In this paper, we proposed a variant of a single-index model that utilizes a surface link-function as a function of a linear projection of covariates and a continuous “treatment” variable. This single index model with a surface link can effectively estimate the effect on a response of possibly nonlinear interactions between a set of covariates and the treatment variable defined on a contin-
Figure 2: Boxplots of the estimated values of the individualized dose rules using 6 approaches, obtained from 100 randomly split testing sets. Mean (and sd) of the value estimates: SIMSL (-0.227 (0.03)) SVR: -0.256 (0.02); L-O-learning(Prp): -0.274 (0.01); K-O-learning(Prp): -0.234 (0.03); L-O-learning: -0.274 (0.01); K-O-learning: -0.279 (0.01).

The proposed regression model is useful for developing personalized dose rules in precision medicine, and more generally, in a situation where we are particularly interested in modeling interactions between a set of covariates and a real-valued predictor of interest. The model gives a simple, intuitive and straightforward method of modeling smooth interactions, without the need for a significant change in the established generalized additive regression modeling framework.

In many applications, only a subset of variables may be useful in determining an optimal individualized dose rule. Also, high-dimensional settings can lead to instabilities and issues of overfitting. Forthcoming work will introduce a regularization method that can both avoid overfitting and choose among multiple potential covariates by obtaining a sparse estimate of the single-index coefficient $\beta$. Future extensions of this work could also include an extension of the proposed regression to a multiple-index regression for modeling interactions and the incorporation of a functional covariate.

**SUPPLEMENTAL MATERIALS**

**Supporting Information:** a pdf file containing the proof of Proposition 1 and a data analysis example illustrating an application of the generalized single-index regression approach described in Section 4.

**R-package for SIMSL routine:** R-package `simsl` (Park et al., 2019) available on CRAN containing code to perform the proposed single-index regression method, and the datasets and the simulation examples illustrated in this article.
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A  Proof of Proposition 1

Let $Q(g, \beta) = \mathbb{E}[Yg(\beta^T X, A) - b(g(\beta^T X, A))]$ in (23) of the main manuscript, where the expectation is with respect to $(Y, A, X)$, in which their relationships are specified by the mean model (20) of the main manuscript. We have

$$Q(g, \beta) = \mathbb{E}\left[\{\mu_0(X) + g_0(\beta_0^T X, A)\}g(\beta^T X, A) - b(g(\beta^T X, A))\right]$$

$$= \mathbb{E}\left[E_{A|X}\left[\{\mu_0(X) + g_0(\beta_0^T X, A)\}g(\beta^T X, A) - b(g(\beta^T X, A)) | X\right]\right]$$

$$= \mathbb{E}\left[E_{A|X}\left[\mu_0(X)g(\beta^T X, A) + g_0(\beta_0^T X)g(\beta^T X, A) - b(g(\beta^T X, A)) | X\right]\right]$$

$$= \mathbb{E}\left[g_0(\beta_0^T X, A)g(\beta^T X, A) - b(g(\beta^T X, A))\right]$$

$$= \mathbb{E}\left[g_0(\beta_0^T X, A)|\beta^T X, A\right]g(\beta^T X, A) - b(g(\beta^T X, A))\right],$$

(26)

where the second equality is from an application of the iterated expectation rule to condition on $X$, and the fourth equality is from: $E_{A|X}[\mu_0(X)g(\beta^T X, A)|X] = \mu_0(X)E_{A|X}[g(\beta^T X, A)|X] = 0$, as a result of the constraint in (23) of the main manuscript that we impose on $g$. Notice that $Q(g, \beta)$ in (26) is independent of the “nuisance” term $\mu_0(X)$.

Given each $\beta$ and the corresponding variables $(\beta^T X, A)$, we have

$$\frac{\partial Q(g, \beta)}{\partial g} = \mathbb{E}[g_0(\beta_0^T X, A)|\beta^T X, A] - \dot{b}(g(\beta^T X, A)), \quad (27)$$

and setting the right-hand side of equation (27) to 0 implies that, given each $\beta$ and the corresponding variables $(\beta^T X, A)$, the maximizer $g(\beta^T X, A)$ of the right-hand side of (23) of the main manuscript should satisfy the stationary condition:

$$\dot{b}(g(\beta^T X, A)) = \mathbb{E}[g_0(\beta_0^T X, A)|\beta^T X, A],$$

or equivalently:

$$g(\beta^T X, A) = \dot{b}^{-1}(\mathbb{E}[g_0(\beta_0^T X, A)|\beta^T X, A]). \quad (28)$$

Notice that the maximizer (28) depends only on $g_0(\beta_0^T X, A)$ and not on $\mu_0(X)$. Given each $\beta$ and the corresponding variables $(\beta^T X, A)$, we profile out the term $g(\beta^T X, A)$ in the last line of (26) by its maximizer (28), which results in the following profile objective function, free of the unknown $g$:

$$E\left[E\left[g_0(\beta_0^T X, A)|\beta^T X, A\right] \dot{b}^{-1}(E\left[g_0(\beta_0^T X, A)|\beta^T X, A\right]) - \dot{b}^{-1}(E\left[g_0(\beta_0^T X, A)|\beta^T X, A\right])\right]. \quad (29)$$

For (29), let us reparametrize for the sake of simplicity:

$$\theta(\beta^T X, A) = \dot{b}^{-1}(E\left[g_0(\beta_0^T X, A)|\beta^T X, A\right]). \quad (30)$$

Then, we can re-write (29) as:

$$E\left[E\left[g_0(\beta_0^T X, A)|\beta^T X, A\right] \theta(\beta^T X, A) - \theta(\beta^T X, A)\right] = E\left[E\left[g_0(\beta_0^T X, A)\theta(\beta^T X, A) - \theta(\beta^T X, A)|\beta^T X, A\right]\right]$$

$$= E\left[g_0(\beta_0^T X, A)\theta(\beta^T X, A) - \theta(\beta^T X, A)\right]. \quad (31)$$
The second line of (31) can be viewed as an expression of the negative of the cross-entropy (equivalently, the Kullback-Leibler (KL) divergence) between an exponential family distribution with the canonical parameter $\theta(\beta^T X, A)$ in (30) (i.e., an exponential family distribution with the conditional mean: $\dot{b}(\theta^T X, A) = \mathbb{E}[g_0(\beta_0^T X, A)|\beta^T X, A]$), and some “true” (reference) exponential family distribution with the conditional mean: $g_0(\beta_0^T X, A)$. It is clear that the maximizer, which we denote as $\beta^*$, of the negative of the KL divergence (over $\beta \in \Theta$) occurs at $\beta^* = \beta_0$ (at the true distribution). Thus, the profile maximizer $\beta^* \in \Theta$ of the profile objective function (29) is given by $\beta^* = \beta_0$. Plugging $\beta = \beta_0$ into (28) implies that the maximizer $g^*$ of the objective function $Q(g, \beta_0)$ satisfies: $g^*(\beta_0^T X, A) = \dot{b}_1^{-1}(g_0(\beta_0^T X, A))$, which results in the desired expression of $g^* = h \circ g_0$, since $\dot{b}_1^{-1} = h$ is the canonical link function.

### B Application to estimation of a pollutant-season interaction on mortality from air-pollution data

In this section, we consider a data analysis example illustrating an application of the generalized single-index regression method (described in Section 4 of the main manuscript) that models interactions between a set of predictors ($X$) and a variable ($A$) in their effects on a non-normal response (counts) variable.

Several time series studies of air pollution and health have provided compelling evidence of a positive association between short-term variation in ambient levels of particulate matter and daily mortality counts (see, e.g., Pope et al., 1995; Dockery and Pope, 1996; Bell et al., 2004). Peng and Dominici (2008) noted that the short-term effects of particulate matter on mortality might exhibit seasonal (time) variation. In particular, the characteristics of the particulate matter mixture can vary seasonally throughout the year. Patterns of human activity also change from season to season, and as a result, an air pollution concentration in one season may lead to a different effect in a different season. Other potential time-varying confounding and modifying factors (such as temperature and influenza epidemics) can also impact effects of air pollution on mortality differently in different seasons (Peng and Dominici, 2008). Therefore, the relationships between mortality and air pollution levels can vary considerably across seasons. In this section, we illustrate the utility of the SIMSL approach to estimating the interactions between seasonal variation and particulate matter on their effects on mortality.

The data are from Peng and Welty (2004) and publicly available from the R (R Core Team, 2019) package gamair (Wood, 2019a). The response of interest is the daily number of deaths in Chicago over 14 years. The outcomes $Y_t$ represent a time series of daily mortality counts (indicating the number of deaths that occurred on day $t$), with the conditional mean, $m_t$, that depends on particulate matter levels and season. As typical for modeling time series of counts, we assume a Poisson distribution for the counts $Y_t$. To model seasonal variation, we introduce the “day of a year” variable that ranges from 0 to 364, defined as $A_t := t \mod 365$, in which $A_t = 0$ corresponds to the first calendar day of a year.

To study the pollutant-season interaction effects, we consider the following SIMSL (see model
Figure 3: Estimated individual (i.e., marginal) effect functions, $g_1$ (left panel) and $g_2$ (center panel), obtained by fitting the GAM: 
\[ \log(\mathbb{E}[Y|\beta^T X, A]) = g_1(A) + g_2(\beta^T X), \]
conditioning on the estimated single-index $\beta^T X$ of the generalized SIMSL (21) of the main manuscript. The third panel: Estimated link surface, $g(\cdot, \cdot)$ of the generalized SIMSL (21) of the main manuscript, for the pollutant ($\beta^T X$) and season ($A$) interaction; the red and green surfaces are at plus or minus one standard error from the estimate (the black surface in the middle).

(20) of the main manuscript, for the identifiability condition imposed on $g_0$:

\[ m_t = \mathbb{E}[Y_t|X_t, X_{t-1}, \ldots, X_{t-K}, A_t] = \mu_0(X_t, X_{t-1}, \ldots, X_{t-K}) + g_0 \left( \sum_{j=0}^{K} \beta_j X_{t-j}, A_t \right) \quad (t = 1, \ldots, n) \]  

(32)

where the single-index $\beta^T X$ is defined in terms of distributed lag model:

\[ \sum_{j=0}^{K} \beta_j X_{t-j} \quad (t = 1, \ldots, n) \]

where $X_t \in \mathbb{R}$ is the time series of daily (day $t$) particulate matter levels, and $K$ is the maximum lag. Hence, the model includes multiple lags of pollution, rather than the pollution level only on the day $t$ itself. This $K$-lagged model is reasonable, as any effects would likely take some time to manifest themselves via the aggravation of existing medical conditions [Wood 2017]. This accumulated particulate matter over $K$ days enters into the function $g_0(\cdot, \cdot)$ in model (32). The coefficients $\beta_j \in \mathbb{R}$ associated with this weighted sum need to be estimated from data, and we are particularly interested in summarizing the variability in the lagged particulate matter levels $(X_t, X_{t-1}, \ldots, X_{t-K})$ that is related to the seasonal variation $A_t$ in their effects on the outcome $Y_t$, rather than the “nuisance” variability unrelated to $A_t$. The function $\mu_0$ on the right-hand side of (32) represents the pollutant “main” effect unrelated to $A_t$. Our focus is on estimating the interaction effect term term of model (32) to study the pollutant-season interactions on mortality.

We estimate the pollutant-season interactions based on the working model (21) of the main manuscript, with the logarithmic link $h(\cdot) = \log(\cdot)$:

\[ \log(m_t) \approx g(\beta^T X_t, A_t) \quad (t = 1, \ldots, n) \]  

(33)
subject to the constraint $E[g(\beta^T X, A) | X] = 0$, in which $X := (X_t, X_{t-1}, \ldots, X_{t-K})^T$ and $\beta := (\beta_0, \ldots, \beta_K)^T$, where we omit the subscript $t$ in writing $X$ and $A$, for notational simplicity. In this illustration, we take $K = 4$. We model the seasonal effect to vary smoothly over the course of a year, but we constrain the effect to be periodic across years. We accomplish this by utilizing a set of cyclic cubic spline basis functions $\hat{B}$ (whose left and right ends match, up to a second derivative) to define the model matrix $\hat{B}$ associated with the variable $A$ (which is again subject to the linear constraint (15) of the main manuscript, for the “orthogonality” condition), and use this cyclic basis matrix $\hat{B}$ to construct the tensor product basis matrix $D$ in (14) of the main manuscript for representing $g$.

The single-index coefficient $\beta$ in model (33) is estimated as $(0.80, 0.54, 0.14, 0.17, 0.13)^T$. The approximate 95% bootstrap confidence intervals (based on 500 bootstrap replications; see Section 6 of the main manuscript for description of the approximate bootstrap confidence interval construction procedure) associated with the lag 0 and the lag 1 (i.e., the first two elements of $\beta$) particulate matter concentration levels do not include 0, indicating that (not surprisingly) the particulate matter level on the day itself and one day prior are determined to be important for modeling the pollutant-season interaction.

The estimated surface-link $g(\beta^T X, A)$ plot displayed in the right-most panel in Figure 3 indicates that for a small value of $\beta^T X$, the mortality is largely explained by the U-shaped individual effect of the season (i.e., the variable $A$) (see the left-most panel in Figure 3), which exhibits the usual pattern of a low mortality rate during the summer and a high mortality rate during the winter. Moreover, the middle panel in Figure 3 indicates that mortality, not surprisingly, increases monotonically with the accumulated particulate matter ($\beta^T X$). However, the estimated surface-link on the right-most panel in Figure 3 visualizes the pollutant-season interactions on mortality, which indicates that the effect the accumulated particulate matter ($\beta^T X$) has a larger effect in the spring (e.g., around $A = 100$) and smaller effects in the other seasons (e.g., around $A = 300$), showing an interesting pollutant-season interaction pattern. In particular, for a large value of $\beta^T X$ (say, $\beta^T X > 2$) the contribution of the accumulated particulate matter ($\beta^T X$) on mortality in the spring time (around $A = 100$) can be quite substantial.