Bayesian Index Models for Heterogeneous Treatment Effects

A Preprint

Hyung Park, Danni Wu, Eva Petkova, Thaddeus Tarpey
Department of Population Health
New York University, New York, NY 10016
parkh15@nyu.edu

R. Todd Ogden
Department of Biostatistics
Columbia University
New York, NY 10032

Abstract
The general idea of this article is to develop a Bayesian model with a flexible link function connecting an exponential family treatment response to a linear combination of covariates and a treatment indicator and the interaction between the two. Generalized linear models allowing data-driven link functions are often called “single-index models,” and among popular semi-parametric modeling methods. In this article, we will focus on modeling heterogeneous treatment effects, with the goal of developing a treatment benefit index (TBI) incorporating prior information from historical data. This treatment benefit index can be useful for stratifying patients according to their predicted treatment benefit levels and can be especially useful for precision health applications. The proposed method is applied to a COVID-19 treatment study.

Keywords Bayesian single index models · Heterogeneous treatment effects · Precision medicine

1 Introduction
In this paper, we develop a Bayesian estimation of single-index models [Antoniadis et al., 2004, Choi et al., 2011, Poon and B., 2013, Dhara et al., 2020] for heterogeneous treatment effects, to optimize individualized treatment rules (ITRs) [e.g., Qian and Murphy, 2011, Lu et al., 2011, Tian et al., 2014, Shi et al., 2016, Jeng et al., 2018, Zhao et al., 2012, 2015, Song et al., 2015, Laber and Zhao, 2015, Laber and Staicu, 2018]. We consider a treatment variable \( A \) taking a value in \( \{0, 1\} \) with the associated randomization probabilities \( \{\pi_0, \pi_1\} \), in the context of randomized clinical trials (RCTs). The observable potential outcomes are \( (Y(0), Y(1)) \). Depending on \( A \), the observed outcome is \( Y = (1 - A)Y(0) + AY(1) \), with the outcome \( Y \) assumed to be a member of the exponential family. Without loss of generality, we assume that a small value of \( Y \) is desired. On the population level, this means that a small value of \( h(E[Y]) \) is desired, where \( h(\cdot) \) denotes the canonical link of the assumed exponential family distribution. The covariate \( X \in \mathbb{R}^p \) are observed pretreatment measurements and predictors of \( (Y(0), Y(1)) \). Our goal is to utilize the information in \( X \) to develop an ITR optimizing the value of \( h(E[Y]) \) for future patients.

2 Method
2.1 Optimal individualized treatment rules
In this subsection, we define an optimal ITR. The Bayes decision \( a^* : x \mapsto \{0, 1\} \) minimizes, over treatment decision \( a \in \{0, 1\} \), the posterior expected loss for a patient with baseline measures \( X = x \). Let us define the loss function for making treatment decision \( a \) as:

\[
L(a, \theta, x) = h(E[Y(a)]|\theta, x),
\]

where \( \theta \) collectively represents the parameters characterizing the relationship between the potential treatment outcomes \( Y(a) \) and predictors \( X \). In (1), \( E[Y(a)|\theta, x] = (1 - a)E[Y(0)|\theta, x] + aE[Y(1)|\theta, x] \) is the expected outcome under treatment assignment \( a \). Let \( D = \{(Y_i, A_i, X_i), i = 1, \ldots, n\} \) collectively denotes the observed data.
Viewing the loss $L(a, \theta, x)$ in (1) as a function of a for a patient with pretreatment characteristic $x$, the optimal Bayes decision $a^*(x)$ will minimize the posterior expected loss given $x$, i.e.,

$$a^*(x) = \arg\min_{a \in (0, 1)} E_{\theta|x, D}[L(a, \theta, x)],$$

where the expectation is taken with respect to the posterior distribution of $\theta$ (given the observed data $D$). In particular, if we define the loss contrast $\Delta(\theta, x) = L(a = 1, \theta, x) - L(a = 0, \theta, x)$, then the above optimal Bayes decision $a^*(x)$ is equivalently to:

$$a^*(x) = \{E_{\theta|x, D}[\Delta(\theta, x)] < 0\},$$

which we define as the optimal ITR. We will utilize the following standard causal inference assumptions [Rubin (2005); 1) consistency; 2) no unmeasured confoundedness; 3) positivity, we refer to Rubin (2005) for the details. Under those standard assumptions, we can write $\Delta(\theta, x)$ in (2) as: $\Delta(\theta, x) = h(E[Y|A = 1, \theta, x]) - h(E[Y|A = 0, \theta, x])$. Therefore, we can infer the optimal Bayes decision (2) based on posterior inference on the canonical parameter $h(E[Y|A, \theta, X])$ of the exponential family response $Y$. In the following subsection, we will describe how we specify the model for the distributions of $(Y|A, \theta, X)$ and of $\theta$, for the estimation of the optimal ITR (2).

### 2.2 Model and prior specification

#### 2.2.1 Model

Let $Y = (Y_1, \ldots, Y_n)^\top$ be a vector of the treatment outcomes, with $Y_i$ following an exponential family distribution with density

$$f(Y_i|\eta_i, \phi) = \exp\{\phi^{-1}[Y_i\eta_i - b(\eta_i)] + c(Y_i, \phi)\}$$

$$\eta_i = X_i^\top m + g(X_i^\top \beta, A_i),$$

where the unknown parameters, which we collectively denote as $\theta$, will be estimated in a Bayesian framework. In (3), $b(\cdot)$ and $c(\cdot)$ are known functions specific to the given member of the exponential family, and $\phi > 0$ is an unknown dispersion parameter ($\phi = 1$ specializes to a one-parameter exponential family distribution for the response).

The canonical parameter $\eta \in \mathbb{R}$ in (3) represents the location of the assumed exponential family response $Y$, which is related to the loss function $L(a, \theta, x)$ in (1) through the equations $\eta = h(E[Y|\theta, x, a]) = h(E[Y^{(a)}|\theta, x])$, under the standard causal inference assumptions.

The first term $X^\top m$ in (3) represents the pre-treatment covariates $X$’s “main” effect, and the second term $g(X^\top \beta, A)$ is the $X$-by-$A$ interaction effect, characterized by an unspecified treatment $a$-specific smooth function $g(a, \theta)$ ($a = 0, 1$) which is a function of a linear projection $u = X^\top \beta \in \mathbb{R}$, satisfying $\|\beta\| = 1$. The projection $X^\top \beta$ provides a dimension reduction specifically for the $X$-by-$A$ interaction effect. In (3), we shall impose an identifiability condition

$$E[g(X^\top \beta, A)|X] = 0,$$

which separates the component $g(X^\top \beta, A)$ from the component $X^\top m$ within $\eta$. In (3), the covariates $X$ entering into $X^\top m$ and those into $g(X^\top \beta, A)$ do not need to be the same. The model (3) with the identifiability condition (4) is more suitable to conduct a posterior inference for heterogeneous treatment effects than the model $\eta = X^\top m + g(X^\top \beta)A$, because this particular parametrization (3) is invariant of the choice of coding of $A$. In the latter model, the choice of the treatment coding can meaningfully impact posterior inferences because $X^\top m$ and $g(X^\top \beta)$ alias one another. On the other hand, if we use the model (3) with the condition (4), there is no issue of aliasing of the treatment effects, since $g(X^\top \beta, A)$ is designed to be orthogonal to $X^\top m$, even when $X^\top m$ is misspecified.

For an individual with baseline characteristics $x$, the loss contrast $\Delta(\theta, x)$ in (2) under model (3) is

$$\Delta(\theta, x) = g(x^\top \beta, A = 1) - g(x^\top \beta, A = 0),$$

where only the parameters $g$ and $\beta$ (and not $m$ and $\phi$) in (3) are necessary for estimating the ITR (2), hence we will focus on the estimation of $g$ and $\beta$. Given (3), we can now introduce a “treatment benefit index” (TBI) probability,

$$\text{TBI}(x) := P(\Delta(\theta, x) < 0) \in [0, 1],$$

where the probability is evaluated with respect to the posterior distribution of $\theta$. The optimal Bayes decision $a^*(x)$ in (2) is then $a^*(x) = \{\text{TBI}(x) > 0.5\}$. Since a large (small) value of the TBI will indicate a large (small) value of relative “benefit” from taking the active treatment $A = 1$ compared to $A = 0$, the TBI in (6) constructs a “gradient” of treatment benefit ranging from 0 to 1, comparing $A = 1$ vs $A = 0$, with respect to the covariate value $x$. Furthermore, for each treatment condition $A = a$, we can obtain a prediction of the expected outcome $h^{-1}\{x^\top m + g(x^\top \beta, a)\}$ based on the posterior distribution of the parameters $\theta$, for each $x$. 

2
2.2.2 Representation of the link function $g$

Following Antoniadis et al. [2004], we represent the flexible function $g(\cdot, a)$ of (5) with cubic splines with the $B$-spline basis. Using $B$-splines is appealing because the basis functions are strictly local, as each basis function is only non-zero over the intervals between 5 adjacent knots [Eilers and Marx [1996]]. For each fixed $\beta \in \mathbb{R}^p$, the flexible function $g$ is represented as:

$$g(\beta^\top x_i, a_i) = \tilde{\psi}_\beta(\beta^\top x_i)^\top \tilde{\gamma}_a, \quad (i = 1, \ldots, n)$$

(7)

for some fixed $l$-dimensional basis $\tilde{\psi}(\cdot) \in \mathbb{R}^l$ (e.g., $B$-spline basis on evenly spaced knots on a bounded range of $\{\beta^\top x_i\}_{i=1}^n$) and a set of unknown treatment $a$-specific basis coefficients $\{\tilde{\gamma}_a \in \mathbb{R}^l\}_{a \in (0,1)}$.

Given representation (7) for the function $g$ given any $\beta$, the identifiability constraint $E[g(\beta^\top X, A)|X] = 0$ is implied by the linear constraint

$$\pi_0 \tilde{\gamma}_0 + \pi_1 \tilde{\gamma}_1 = \pi \tilde{\gamma} = 0,$$

(8)

where $\pi = [\pi_1 I_l; \pi_2 I_l]$ is the $l \times 2l$ matrix (in which $I_l$ denotes the $l \times l$ identity matrix) and $\tilde{\gamma} = (\tilde{\gamma}_0^\top, \tilde{\gamma}_1^\top)^\top \in \mathbb{R}^{2l}$, an unknown vector. To represent (7) in matrix notation, let the parameter $\gamma$ vector $\{\gamma \in \mathbb{R}^l\}_{a \in (0,1)}$.

Then, we can represent the function $g$ in (7) based on the sample data, by the length-$n$ vector: $g = \tilde{\mathbf{D}}_{\beta} \tilde{\gamma}$.

The linear constraint (8) on $\tilde{\gamma}$ can be conveniently absorbed into the model matrix $\tilde{\mathbf{D}}_{\beta}$ by reparametrization, as we describe next. We can find a $2l \times l$ basis matrix $\mathbf{Z}$, such that if we set $\tilde{\gamma} = \mathbf{Z} \gamma$ for any arbitrary vector $\gamma \in \mathbb{R}^l$, then the vector $\mathbf{Z} \gamma \in \mathbb{R}^{2l}$ automatically satisfies the constraint (8). Such a basis matrix $\mathbf{Z}$ can be constructed by a QR decomposition of the matrix $\pi^\top$. Then representation $g = \tilde{\mathbf{D}}_{\beta} \gamma$ can be reparametrized, in terms of the unconstrained vector $\gamma \in \mathbb{R}^l$, by replacing $\tilde{\mathbf{D}}_{\beta}$ with the reparametrized model matrix $\mathbf{D}_{\beta} = \tilde{\mathbf{D}}_{\beta} \mathbf{Z}$, yielding the representation $g = \mathbf{D}_{\beta} \gamma$.

Once we perform inference on $\gamma$, we can also consider inference on the transformed parameter $\tilde{\gamma} = \mathbf{Z} \gamma$, from which we can make inference on the functions $g(\beta^\top, a) = \tilde{\psi}_\beta(\beta^\top \cdot)^\top \tilde{\gamma}_a (a = 0, 1)$.

2.2.3 Prior specification

How we specify priors for $\beta$, $m$ and $\gamma$ is given in this subsection.

- For the distribution of $\beta$, we will use von Mises-Fisher with concentration parameter $\lambda_{prior} > 0$ and direction parameter $\beta_0 \in \mathbb{R}^p$ with $||\beta_0|| = 1$,

$$P(\beta) \propto \exp(\lambda_{prior} \beta^\top \beta_0),$$

(9)

a probability distribution for $\beta$ on the $(p-1)$-unit-sphere in $\mathbb{R}^p$.

- We will use $m \sim N(m_0, Q)$, for some vector $m_0 \in \mathbb{R}^p$ and $p \times p$ positive definite matrix $Q$.

- Since the domain of the function $g$ in (5) depends on $\beta$, the prior on $g$ will depend on $\beta$. For each fixed $\beta$, we will use data-dependent empirical Bayes prior for $\gamma \in \mathbb{R}^l$

$$\gamma \sim N(\tilde{\gamma}_\beta, (\mathbf{D}_{\beta}^\top \mathbf{W} \mathbf{D}_{\beta})^{-1}),$$

(10)

where the mean $\tilde{\gamma}_\beta$ is

$$\tilde{\gamma}_\beta = (\mathbf{D}_{\beta}^\top \mathbf{W} \mathbf{D}_{\beta} + \rho \mathbf{I})^{-1} \mathbf{D}_{\beta}^\top \mathbf{W} \mathbf{Z}.$$  

(11)

How we specify the tuning parameter $\rho > 0$ and $\mathbf{Z}$ and $\mathbf{W}$ in (11) is given in the next subsection. An advantage of using the prior (10) is that it allows us to analytically integrate $\gamma$ out of the joint posterior $P(\beta, \gamma|m, Y)$, facilitating the Gibbs sampling of $\beta$. For simplicity of the notation in the next subsection, let us write

$$\Sigma_\rho := (\mathbf{D}_{\beta}^\top \mathbf{W} \mathbf{D}_{\beta} + \rho \mathbf{I})^{-1},$$

and $\Sigma_0 = (\mathbf{D}_{\beta}^\top \mathbf{W} \mathbf{D}_{\beta})^{-1}$, which is a special case of $\Sigma_\rho$ at $\rho = 0$. Then the prior in (10) is simply written as

$$\gamma \sim N(\Sigma_\rho \mathbf{D}_{\beta}^\top \mathbf{W} \mathbf{Z}, \Sigma_0).$$

(12)
2.3 Posterior computation

To conduct posterior inference on \((m, \beta, \gamma)\), we will simulate samples from the joint posterior \(P(m, \beta, \gamma|Y)\). Since it is difficult to draw samples directly from this joint posterior, we will use a Metropolis-Within-Gibbs algorithm. The Gibbs algorithm will iterate between the following two steps: Step 1) sample \(m\) from \(P(m|\beta, \gamma, Y)\); and Step 2) sample \((\beta, \gamma)\) from \(P(\beta, \gamma|m, Y)\). In Step 2, since the joint conditional \(P(\beta, \gamma|m, Y)\) does not have a convenient form, we will employ a Metropolis-Hastings step.

2.3.1 Conditional posteriors

1. Derivation of \((m|\beta, \gamma, Y)\). For fixed \(\beta\) and \(\gamma\), we will approximate the conditional distribution of \((m|\beta, \gamma, Y)\). Specifically, we will quadratically approximate the log likelihood of \(m\), centered at its mode \(\hat{m}\). To find the mode \(\hat{m}\), we will use a Fisher scoring, iteratively updating the center of the quadratic approximation. Given \(\beta\) and \(\gamma\), at the convergence, where \(\hat{\eta}_i = m^\top x_i + \psi(\beta^\top x_i)\gamma\) and \(\hat{\mu}_i = h^{-1}(\hat{\eta}_i)\), and we will have the \(n \times n\) weight matrix \(W = \text{diag}(w_i)\). As a result, for fixed \(\beta\) and \(\gamma\), the negative log likelihood of \(m\) is approximately represented in terms of a weighted least squares (WLS) objective function (up to a constant of proportionality):

\[
\sum_{i=1}^{n} w_i (z_i - m^\top x_i)^2 = (Z - X m)^\top W (Z - X m) = \text{SSE} + (m - (X^\top W X)^{-1} X^\top W Z)^\top X^\top W X (m - (X^\top W X)^{-1} X^\top W Z),
\]

where the term \(\text{SSE} := (Z - X (X^\top W X)^{-1} X^\top W Z)^\top W (Z - X (X^\top W X)^{-1} X^\top W Z)\) does not involve \(m\). Given the prior \(m \sim N(m_0, Q)\) and the second term in the WLS objective (13), the components associated with \(m\) in the negative log posterior are (up to a constant of proportionality):

\[
(m - m_0)^\top Q^{-1} (m - m_0) + (m - (X^\top W X)^{-1} X^\top W Z)^\top X^\top W X (m - (X^\top W X)^{-1} X^\top W Z).
\]

This indicates that the conditional posterior for \(m\) is:

\[
P(m|\beta, \gamma, Y) = N((Q^{-1} + X^\top W X)^{-1}(Q^{-1} m_0 + X^\top W Z), (Q^{-1} + X^\top W X)^{-1}).
\]

2. Derivation of \((\beta, \gamma|m, Y)\). Given that the joint conditional \(P(\beta, \gamma|m, Y) = P(\beta|m, Y)P(\gamma|\beta, m, Y)\), we will first sample \(\beta\) from \(P(\beta|m, Y)\) and then \(\gamma\) from \(P(\gamma|\beta, m, Y)\). Specifically, following [Antoniadis et al. 2004], we will use a Metropolis-Hastings algorithm to sample \(\beta\) from \(p(\beta|m, Y)\). However, this approach employed in [Antoniadis et al. 2004] cannot be directly applied to our settings, since the outcome \(Y_i\) is generally not Gaussian. Thus, we will perform a quadratic approximation of the negative log likelihood of \(\gamma\), at its mode, which we denote as \(\hat{\gamma}\), i.e., approximating the likelihood by a normal density in \(\gamma\) centered at \(\hat{\gamma}\). To find \(\hat{\gamma}\), we will again conduct a Fisher scoring. For each fixed \(\beta\) and \(m\), this quadratic approximation at the convergence of the Fisher scoring is summarized in the form of the WLS objective function (up to a constant of proportionality),

\[
\sum_{i=1}^{n} w_i (z_i - \psi(\beta^\top x_i)^\top \gamma) = (Z - D_\beta \gamma)^\top W (Z - D_\beta \gamma),
\]

as a function of \(\gamma\), in which \(Z = (z_1, \ldots, z_n)^\top \in \mathbb{R}^n\) is the adjusted response vector with \(z_i = h'(\bar{\mu}_i)(y_i - \bar{\mu}_i) + \bar{\eta}_i\) obtained at the convergence, where \(\bar{\eta}_i = m^\top x_i + \psi(\beta^\top x_i)^\top \gamma\) and \(\bar{\mu}_i = h^{-1}(\bar{\eta}_i)\), and \(W = \text{diag}(w_i)\) is the \(n \times n\) weight matrix with \(w_i = 1/\{h'(\bar{\mu}_i)^2 V(\bar{\mu}_i)\}\). Given the quadratic approximation (15), we can write the joint conditional \((\beta, \gamma|m, Y)\):
We will now integrate $\gamma$ out of (16) to obtain an expression for $P(\beta|m, Y)$. Utilizing the empirical Bayes prior $P(\gamma|\beta, m)$ specified in (12), we can write the terms involving $\gamma$ in (16) as:

\[
\alpha \exp \left( -\frac{1}{2} \left\{ (Z - D_\beta \gamma)^\top W (Z - D_\beta \gamma) + (\gamma - \Sigma_\rho D_\beta^\top W Z) \Sigma_0^{-1} (\gamma - \Sigma_\rho D_\beta^\top W Z) \right\} \right)
\]

\[
= \exp \left( -\frac{1}{2} \left\{ (\gamma - \Sigma_\rho D_\beta^\top W Z) \Sigma_0^{-1} (\gamma - \Sigma_\rho D_\beta^\top W Z) + (\gamma - \Sigma_\rho D_\beta^\top W Z) \Sigma_0^{-1} (\gamma - \Sigma_\rho D_\beta^\top W Z) \right\} \right)
\]

\[
= \exp \left( -\frac{1}{2} \left\{ 2\gamma^\top \Sigma_0^{-1} \gamma - 2\gamma^\top (I + \Sigma_0^{-1} \Sigma_\rho) D_\beta^\top W Z + Z^\top W Z \right\},
\]

where

\[
S_1(\beta) = Z^\top W Z + Z^\top W D_\beta \Sigma_\rho \Sigma_0^{-1} \Sigma_\rho D_\beta^\top W Z.
\]

Specifically, using the expression in the third line of (17), we can analytically integrate $\gamma$ out of (16), yielding

\[
P(\beta|m, Y) = \int P(\beta, \gamma|m, Y) d\gamma
\]

\[
\propto \int \exp \left( -\frac{1}{2} \left\{ 2\gamma^\top \Sigma_0^{-1} \gamma - 2\gamma^\top (I + \Sigma_0^{-1} \Sigma_\rho) D_\beta^\top W Z + S_1(\beta) \right\} \right) \frac{1}{\Sigma_0^{1/2}} \exp(\lambda_{prior} D_\beta^\top \beta_0) d\gamma
\]

\[
\propto \mathcal{L}[N(0, \Sigma_0/2)] \left[ - (I + \Sigma_0^{-1} \Sigma_\rho) D_\beta W Z \right] \exp \left( -\frac{1}{2} S_1(\beta) \right) \exp(\lambda_{prior} D_\beta^\top \beta_0)
\]

(18)

where $\mathcal{L}[N(0, \Sigma_0/2)]$ is the Laplace transform of the density function of $N(0, \Sigma_0/2)$, evaluated at the parameter $-(I + \Sigma_0^{-1} \Sigma_\rho) D_\beta W Z$. The familiar closed-form expression of the Laplace transform of Gaussian allows us to write the last line of (18) as:

\[
P(\beta|m, Y) \propto \exp \left( \frac{1}{2} Z^\top W^\top D_\beta^\top \Lambda D_\beta W Z \right) \exp \left( -\frac{1}{2} S_1(\beta) \right) \exp(\lambda_{prior} D_\beta^\top \beta_0),
\]

(19)

where $\Lambda = (I + \Sigma_\rho \Sigma_0^{-1}) \Sigma_0 (I + \Sigma_\rho \Sigma_0^{-1})$. The expression (19) provides a closed form for the approximated $P(\beta|m, Y)$ up to a constant of proportionality, which we will use to conduct a random walk Metropolis Markov chain Monte Carlo (MCMC) algorithm. The MCMC algorithm to sample $(\beta|m, Y)$ is described in the next subsection. Given each $m$ and a sample $\beta$ from $p(\beta|m, Y)$, we can sample $\gamma$ from $P(\gamma|\beta, m, Y)$, specified by the normal density:

\[
P(\gamma|\beta, m, Y) = N\left( \frac{\Sigma_0}{2} (I + \Sigma_0^{-1} \Sigma_\rho) D_\beta^\top W Z, \frac{\Sigma_0}{2} \right).
\]

(20)

### 2.3.2 MCMC algorithm for the posterior sampling

In this subsection, we provide the detailed sampling scheme based on the conditional posterior derived in the previous subsection.

First, we will initialize the model parameters $(m, \beta, \gamma)$ by maximum likelihood estimates, that maximize the likelihood of model (3) with representation (7) for $g$, where the basis coefficient $\gamma$ is determined in the form (11), with the tuning parameter $\rho > 0$ determined based on the GCV. We will then cycle through the following steps.

1. Sample $m$ from $P(m|\beta, \gamma, Y)$ in (14) given $(\beta, \gamma)$.
2. Sample $\beta$ from $P(\beta|m, Y)$ in (19) given $m$, using the Metropolis algorithm. Specifically, given the current state $\beta^{\text{cur}}$ for $\beta$ of the chain, a new value $\beta^{\text{new}}$ is accepted with the acceptance probability $\min\{1, r\}$, where the Metropolis ratio $r$ is given by:

\[
r = \frac{P(\beta^{\text{new}}|m, Y)}{P(\beta^{\text{cur}}|m, Y)}
\]

using the conditional posterior (19) given $m$. Some more details on this Metropolis procedure.
The proposal distribution for $\beta^{\text{new}}$ was taken to be von Mises-Fisher with concentration parameter $\lambda_{\text{prop}} > 0$ and direction parameter given by the current value $\beta^{\text{cur}}$. In the simulation example in the next section, we used $\lambda_{\text{prop}} = 300$, which gave the acceptance probability of around 0.3 for the proposal, and the sampler appeared to explore the state space for $\beta$ adequately. We used the R package movMF to generate random samples for $\beta$ from von Mises-Fisher distributions.

For the prior distribution of $\beta$ in (4), we can choose $\lambda_{\text{prior}} > 0$ (typically in the range of 100 < $\lambda_{\text{prior}}$ < 700), depending on the degree of confidence in the prior direction $\beta_0$.

$\rho > 0$ in (11) is another unknown that controls the smoothness of the data-driven function $g$, which is crucial to avoid overfitting $g$. This will be selected via an empirical Bayes procedure. Although, technically, an optimal $\rho$ needs to be selected at each MCMC update, in this article, we used the generalized cross-validation (GCV) criterion to select $\rho$ only at the start of the MCMC run with the frequentist’s estimate in place of $\beta$, to reduce the computational demand and since $\rho$ has relatively little effect on the estimation of $\beta$.

3. Sample $\gamma$ from $P(\gamma|\beta, m, Y)$ in (20) given $(\beta, m)$.

To obtain the estimated fit $\hat{y}_{\text{new}}$ given a new $x_{\text{new}}$ and treatment condition $a \in \{0, 1\}$, we take the posterior mean of the expected response $h^{-1}(\eta) = h^{-1}(m^\top x_{\text{new}} + \hat{\psi}_0(\beta^\top x_{\text{new}})\hat{\gamma}_0)$, based on the posterior sampler output. In particular, we make a treatment decision using the posterior distribution of $\hat{\psi}_0(\beta^\top x_{\text{new}})(\hat{\gamma}_1 - \hat{\gamma}_0)$. Specifically, we will use the probability $P(\{\hat{\psi}_0(\beta^\top x_{\text{new}})(\hat{\gamma}_1 - \hat{\gamma}_0) < 0\})$ as the TBI($x_{\text{new}}$), which we will utilize to obtain a decision rule $a^*(x_{\text{new}}) = 1(\text{TBI}(x_{\text{new}}) > 0.5)$, using the probability threshold of 0.5.

3 Application

Here we illustrate an application of the proposed model to real data. Specifically, we apply the proposed model to a COVID-19 convalescent plasma (CCP) study [Troxel et al. 2022], a meta-analysis of pooled individual patient data from 8 randomized clinical trials. The goal of this study was to guide CCP treatment recommendations by providing an estimate of the differential treatment outcome when a patient is treated with CCP vs without CCP [Park et al., 2022]. A larger differential in favor of CCP would indicate a more compelling reason for recommending CCP. In this context, we aim to discover profiles of patients with COVID-19 associated with different benefit from CCP treatment and use these to optimize treatment decisions.

The study included 2369 hospitalized adults, not receiving mechanical ventilation at randomization, enrolled April 2020 to March 2021. We took complete cases for the analysis. A total of 2287 patients were included, with a mean (SD) age of 60.3 (15.2) years and 815 (35.6%) women. One of the primary outcomes of the study was the binary variable indicating mechanical ventilation or death (hence $Y = 1$ indicates a bad outcome) at day 14 post-treatment. The patients were randomized to be treated with either CCP (A = 1) or control (A = 0), i.e., standard of care. Pretreatment patient characteristics were collected at baseline. In our application, the baseline variables that were used to model the covariates “main” effect, i.e., the component associated with the coefficient $m$ in model (3) were age, sex, baseline symptom conditions, age-by-baseline symptom conditions interaction, blood type, the indicators for history of diabetes, pulmonary and cardiovascular disease, and days since the symptoms onset. We also included the RCT-specific intercepts and the patients’ enrollment quarters as part of the covariates “main” effect component.

Since our goal in this analysis is to investigate the differential treatment effect explained by the baseline variables $X$, we will focus on reporting the estimation results of the heterogeneous treatment effect (HTE) term $g(X^\top \beta, A)$ in model (3) and the corresponding treatment effect contrast $\Delta(x, \theta)$ in (5). The patient characteristics $X$ included in the HTE term are given in the first column of Table 1. The posterior mean of the index coefficients $\beta = (\beta_1, \ldots, \beta_7)$, along with the corresponding 95% posterior credible intervals (CrI), are provided in the second column of Table 1. By examining the posterior CrI, the patient’s symptoms severity at baseline, blood type, a history of cardiovascular disease and a history of diabetes appear to be important predictors of HTE.

In the first panel of Figure 1 we display the individualized treatment effect, $\Delta(x, \theta)$, as a function of the single-index $x^\top \beta$. Specifically, we display the posterior mean of $x^\top \beta$ and the values $x_i^\top \beta$ ($i = 1, \ldots, n$) ($n = 2287$) on the horizontal axis, where these “observed” values are represented by the small blue ticks on the horizontal axis. The uncertainty in the estimation of the single-index coefficient $\beta$ (as well as that of $m$) is also accounted for in the credible bands in Figure 1. For the interpretability, we exponentiate the HTE estimate $\Delta(x, \theta) = g(x^\top \beta, A = 1) - g(x^\top \beta, A = 0)$, so that the vertical axis in the panel represents the odds ratio (CCP vs. control) for a bad outcome (mechanical ventilation or death). An odds ratio of less than 1 indicates a superior CCP efficacy over the control treatment. As most of the observed values $x_i^\top \beta$ of the single-index fall below the line representing the odds ratio of 1,
most of the patients are expected to benefit from CCP treatment, except those with the $x_i^T \beta$ values greater than 0.45, where their corresponding expected individualized odds ratios are greater than 1 (about 28% of the observed patients). The $U$-shaped nonlinear relationship between the odds ratio and the single-index of the model suggests that the use of the flexible link function $g$ in (5) is more adequate than using a more restricted linear model for this HTE modeling.

Table 1: Pretreatment patient characteristics $X$ and the corresponding estimated index coefficients $\beta$ (and 95% CrI)

| Pretreatment characteristic $x_j$ | Index coefficient $\beta_j$ [95% CrI] |
|-----------------------------------|--------------------------------------|
| Oxygen by mask or nasal prongs* (1/0) | 0.68 [0.50, 0.80] |
| Oxygen by high flow* (1/0) | 0.47 [0.16, 0.61] |
| Age (dichotomized, $\geq 67$) (1/0) | -0.13 [-0.46, 0.04] |
| Blood type (A or AB vs. O or B) (1/0) | -0.31 [-0.49, -0.16] |
| Cardiovascular disease (1/0) | -0.24 [-0.65, -0.06] |
| Diabetes (1/0) | -0.26 [-0.52, -0.08] |
| Pulmonary disease (1/0) | 0.05 [-0.16, 0.22] |

* The reference level: hospitalized but no oxygen therapy required.

Although the first panel of Figure 1 displays a useful information about the relationship between the individualized treatment effect $\exp(\Delta(x))$ (i.e., the individualized odds ratio) and the posterior mean of the single-index $x^T \beta$, this relationship is non-monotonic, which makes it difficult to construct a “gradient” of the treatment benefit from $A = 1$ vs $A = 0$, as a function of the patient characteristics $x$. Thus, in the second panel of Figure 1, we display the individualized odds ratio $\exp(\Delta(x))$, as a function of the TBI defined in (6), i.e., $P(\exp(\Delta(x)) \leq 1)$, where the probability is evaluated with respect to the posterior distribution of the parameters in $\Delta$. The TBI provides a gradient of benefit that ranges from 0 to 1, with a higher value of the TBI indicating a greater benefit from the CCP treatment, compared to control. The observed values for the quantities on the horizontal axes are represented by the small blue ticks.

The second panel of Figure 1 displays a monotonically decreasing trend of the expected odds ratio (an increasing CCP benefit), as the TBI score increases from 0 to 1. Some portions of the expected odds ratio and the corresponding 95% CrI exceed 1 for very small TBI values, suggesting the possibility of harm from CCP as the TBI approaches 0, whereas the TBI values close to 1 indicate a substantial benefit from the CCP treatment over the control treatment. We can use the TBI score to stratify patients according to their predicted treatment benefit levels.
4 Discussion

The idea in the Bayesian estimation approach of [Antoniadis et al. 2004] was to treat the link function $g$ as another unknown and approximate it by a linear combination of $B$-spline basis functions. In this article, to model heterogeneous treatment effect using a flexible link function, in (12), we specify the prior for the $B$-spline coefficient $\gamma$, conditional on $\beta$, as normal with the same dispersion matrix as the WLS estimator (i.e., a Zellner’s g-prior) defined based on the adjusted responses and the weights associated with the first step of IWLS, for each sampler. The approximation under the IWLS framework and the specific prior choice (12) allows us to analytically integrate $\gamma$ out of the approximated posterior (16), which simplifies the sampling procedure for $\beta$. Although the sampling was done using approximated conditional posteriors, this approach appeared to work reasonably well.

References

A. Antoniadis, G. Gregoire, and I. McKeague. Bayesian estimation in single-index models. *Statistica Sinica*, 14: 1147–1164, 2004.

T. Choi, J. Shi, and B. Wang. A gaussian process regression approach to a single-index model. *Journal of Nonparametric Statistics*, 23:21–36, 2011.

W. Y. Poon and Wang H. B. Bayesian analysis of generalized partially linear single-index models. *Computational Statistics and Data Analysis*, 68:251–261, 2013.

Kumaresh Dhara, Stuart Lipsitz, Debdeep Pati, and Debajyoti Sinha. A new bayesian single index model with or without covariates missing at random. *Bayesian Analysis*, 15(3):759–780, 2020.

M. Qian and S. A. Murphy. Performance guarantees for individualized treatment rules. *The Annals of Statistics*, 39(2): 1180–1210, 2011.

W. Lu, H. Zhang, and D. Zeng. Variable selection for optimal treatment decision. *Statistical Methods in Medical Research*, 22:493–504, 2011.

L. Tian, A. Alizadeh, A. Gentles, and R. Tibshirani. A simple method for estimating interactions between a treatment and a large number of covariates. *Journal of the American Statistical Association*, 109(508):1517–1532, 2014.

C. Shi, R. Song, and W. Lu. Robust learning for optimal treatment decision with np-dimensionality. *Electronic Journal of Statistics*, 10:2894–2921, 2016.

X. Jeng, W. Lu, and H. Peng. High-dimensional inference for personalized treatment decision. *Electronic Journal of Statistics*, 12:2074–2089, 2018.

Y. Zhao, D. Zeng, A. J. Rush, and M. R. Kosorok. Estimating individualized treatment rules using outcome weighted learning. *Journal of the American Statistical Association*, 107:1106–1118, 2012.

Y. Zhao, D. Zheng, E. B. Laber, and M. R. Kosorok. New statistical learning methods for estimating optimal dynamic treatment regimes. *Journal of the American Statistical Association*, 110:583–598, 2015.

R. Song, M. Kosorok, D. Zeng, Y. Zhao, E. B. Laber, and M. Yuan. On sparse representation for optimal individualized treatment selection with penalized outcome weighted learning. *Stat*, 4:59–68, 2015.

E. B. Laber and Y. Zhao. Tree-based methods for individualized treatment regimes. *Biometrika*, 102:501–514, 2015.

E. B. Laber and A. Staicu. Functional feature construction for individualized treatment regimes. *Journal of the American Statistical Association*, 113:1219–1227, 2018.

D. B. Rubin. Causal inference using potential outcomes: Design, modeling, decisions. *Journal of the American Statistical Association*, 100(469):322–331, 2005.

Paul Eilers and Brian Marx. Flexible smoothing with B-splines and penalties. *Statistical Science*, 11(2):89–121, 1996.

Andrea B. Troxel, Eva Petkova, Keith Goldfeld, Mengling Liu, Thaddeus Tarpey, Yinxiang Wu, Danni Wu, Anup Agarwal, Cristina Avendaño-Solá, Emma Bainbridge, Katherine J. Bar, Timothy Devos, Rafael F. Duarte, Arvind Gharbhawan, Priscilla Y. Hsue, Gunjan Kumar, Annie F. Luetskemeyer, Geert Meyfroidt, André M. Nicola, Aparna Mukherjee, Mila B. Ortigoza, Liise-anne Pirofski, Bart J. A. Rijnders, Casper Rokx, Arantxa Sancho-Lopez, Pamela Shaw, Pablo Tebas, Hyun Ah Yoon, Corita Grudzen, Judith Hochman, and Elliott M. Antman. Association of Convalescent Plasma Treatment With Clinical Status in Patients Hospitalized With COVID-19: A Meta-analysis. *JAMA Network Open*, 5(1):e2147331–e2147331, 2022. ISSN 2574-3805. doi:10.1001/jamanetworkopen.2021.47331. URL https://doi.org/10.1001/jamanetworkopen.2021.47331
Hyung Park, Thaddeus Tarpey, Mengling Liu, Keith Goldfeld, Yinxiang Wu, Danni Wu, Yi Li, Jinchun Zhang, Dipayan Ganguly, Yogiraj Ray, Shekhar Ranjan Paul, Prasun Bhattacharya, Artur Belov, Yin Huang, Carlos Villa, Richard Forshee, Nicole C. Verdun, Hyun ah Yoon, Anup Agarwal, Ventura Alejandro Simonovich, Paula Scibona, Leandro Burgos Pratx, Waldo Bellos, Cristina Avendaño-Solá, Katharine J Bar, Rafael F. Duarte, Priscilla Y. Hsue, Anne F. Luetkemeyer, Geert Meyfroidt, André M. Nicola, Aparna Mukherjee, Mila B. Ortigosa, Liise-anne Pirofski, Bart J. A. Rijnders, Andrea Troxel, Elliott M. Antman, and Eva Petkova. Development and Validation of a Treatment Benefit Index to Identify Hospitalized Patients With COVID-19 Who May Benefit From Convalescent Plasma. *JAMA Network Open*, 5(1):e2147375–e2147375, 2022. ISSN 2574-3805. doi:10.1001/jamanetworkopen.2021.47375 [URL https://doi.org/10.1001/jamanetworkopen.2021.47375]