Functional additive models for optimizing individualized treatment rules

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Abstract

A novel functional additive model is proposed which is uniquely modified and constrained to model nonlinear interactions between a treatment indicator and a potentially large number of functional and/or scalar pretreatment covariates. The primary motivation for this approach is to optimize individualized treatment rules based on data from a randomized clinical trial. We generalize functional additive regression models by incorporating treatment-specific components into additive effect components. A structural constraint is imposed on the treatment-specific components in order to provide a class of additive models with main effects and interaction effects that are orthogonal to each other. If primary interest is in the interaction between treatment and the covariates, as is generally the case when optimizing individualized treatment rules, we can thereby circumvent the need to estimate the main effects of the covariates, obviating the need to specify their form and thus avoiding the issue of model misspecification. The methods are illustrated with data from a depression clinical trial with electroencephalogram functional data as patients’ pretreatment covariates.

Keywords: Individualized treatment rules; Functional additive regression; Sparse additive models; Treatment effect-modifiers

1 Introduction

We propose a flexible functional regression approach to optimizing individualized treatment decision rules (ITRs) where the treatment has to be chosen to optimize the expected treatment outcome. We focus on the situation in which potentially large number of patient characteristics is available as pretreatment functional and/or scalar covariates. Recent advances in biomedical imaging, mass spectrometry, and high-throughput gene expression technology produce massive amounts of data on individual patients, opening up the possibility of tailoring treatments to the biosignatures of individual patients from individual-specific data (McKeague and Qian, 2014). Notably, some randomized clinical trials (e.g., Trivedi et al., 2016) are designed to discover biosignatures that characterize patient heterogeneity in treatment responses from vast amounts of patient pretreatment characteristics. In this paper, we focus on some specific types of high-dimensional pretreatment covariates.

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patient characteristics observed in the form of curves or images, for instance, electroencephalogram (EEG) measurements. Such data can be viewed as functional (e.g., Ramsay and Silverman, 1997) and are becoming increasingly prevalent in modern randomized clinical trials (RCTs) as pretreatment covariates.

Much work has been carried out to develop methods for optimizing ITRs using data from RCTs. Regression-based methodologies are intended to optimize ITRs by estimating treatment-specific response (e.g., Jeng et al., 2018; Lu et al., 2011; Park et al., 2020a,b; Petkova et al., 2020; Qian and Murphy, 2011; Shi et al., 2016; Tian et al., 2014) while attempting to maintain robustness with respect to model misspecification. Machine learning approaches for optimizing ITRs are often framed as a classification problem (e.g., Zhang et al., 2012; Zhao et al., 2019), including outcome weighted learning (e.g., Song et al., 2015; Zhao et al., 2012, 2015) based on support vector machines, tree-based classification (e.g., Laber and Zhao, 2015) and adaptive boosting (Kang et al., 2014), among others. However, to date there has been relatively little research on ITRs that directly utilize pretreatment functional covariates. McKeague and Qian (2014) proposed methods for optimizing ITRs that depend upon a single pretreatment functional covariate. The flexible functional regression approach of Ciarleglio et al. (2016) is also restricted to a single pretreatment functional covariate. Ciarleglio et al. (2015) proposed a method allowing for multiple functional/scalar covariates, and extended to incorporate a simultaneous covariate selection for ITRs in Ciarleglio et al. (2018). However, both of these approaches are limited to a stringent linear model assumption on the treatment-by-covariates interaction effects that limits flexibility in optimizing ITRs and to two treatment conditions.

In this paper, we allow for nonlinear interactions between the treatment and the pretreatment functional covariates on the outcome and also for more than two treatment conditions. We incorporate a simultaneous covariate selection for ITRs through an $L^1$ regularization to deal with a large number of functional and/or scalar covariates. In a review by Morris (2015) on functional regression, two popular approaches to functional additive regression are the functional additive regression of Fan et al. (2015) and the functional generalized additive model of McLean et al. (2014). In this paper, we base our method on the functional additive regression model of Fan et al. (2015) that utilizes one-dimensional data-driven functional indices and the associated additive link functions. In Ciarleglio et al. (2016), nonlinear effects are presented with the functional additive regression of McLean et al. (2014). However, the approach of McLean et al. (2014) requires more parameters for estimation and is based on an $L^2$ penalty rather than on $L^1$ penalties, which is less suitable in the context of many functional covariates and when sparsity is desired. In this paper, we develop a flexible approach to optimizing ITRs that can easily impose structural constraints in modeling nonlinear heterogenous treatment effects with functional and/or scalar pretreatment covariates.

2 Constrained functional additive models

We consider a treatment response $Y \in \mathbb{R}$, a set of $p$ functional-valued pretreatment covariates $X = (X_1, \ldots, X_p)$, and $q$ scalar-valued pretreatment covariates $Z = (Z_1, \ldots, Z_q) \in \mathbb{R}^q$. These pretreatment covariates $(X, Z)$ are considered as potential biomarkers for optimizing ITRs. We will assume that each $X_j$ is a square integrable random function, defined on a compact interval, say, $[0, 1]$, without loss of generality. Suppose there are $L$ available treatment options, with treatment indicator $A \in \{1, \ldots, L\}$ assigned with associated randomization probabilities $(\pi_1, \ldots, \pi_L)$, such that $\sum_{a=1}^{L} \pi_a = 1$, $\pi_a > 0$, independent of $(X, Z)$. 

2
In this context we focus on optimizing ITRs based on \((X, Z)\). For a single decision point, an ITR based on \((X, Z)\), which we denote by \(\mathcal{D}\), maps a patient with pretreatment characteristics \((X, Z)\) to one of the treatment options in \(\{1, \ldots, L\}\). One popular measure of the effectiveness of \(\mathcal{D}\) is the so-called “value” (\(V\)) function (Murphy, 2005), \(V(\mathcal{D}) = E[E[Y|X, Z, A = \mathcal{D}(X, Z)]]\), the aggregate effect of applying a given treatment regime \(\mathcal{D}\) across the population. If we assume, without loss of generality, that a larger value of \(Y\) is better, then the optimal ITR, which we denote as \(\mathcal{D}^{opt}\), can be defined as \(\mathcal{D}\) that maximizes \(V(\mathcal{D})\). Such a rule \(\mathcal{D}^{opt}\) can be shown to satisfy: \(\mathcal{D}^{opt}(X, Z) = \arg \max_{a \in \{1, \ldots, L\}} E[Y|X, Z, A = a]\). In particular, \(\mathcal{D}^{opt}\) does not depend on the “main” effect of the covariates \((X, Z)\) and depends only on the \((X, Z)\)-by-\(A\) interaction effect (Qian and Murphy, 2011) in the mean response function \(E[Y|X, Z, A]\). However, if this mean response model inadequately represents the interaction effect, the associated ITR may perform poorly.

Thus, we will focus on modeling possibly nonlinear \((X, Z)\)-by-\(A\) interaction effects, while allowing for an unspecified main effect of \((X, Z)\). We base the model on the functional additive model (FAM) of Fan et al. (2015) allowing for nonlinear \((X, Z)\)-by-\(A\) interactions:

\[
E[Y|X, Z, A] = \mu(X, Z) + \sum_{j=1}^p g_j((X_j, \beta_j), A) + \sum_{k=1}^q h_k(Z_k, A).
\]

In model (1), the treatment \(a\)-specific (with \(a \in \{1, \ldots, L\}\)) component functions \(\{g_j(\cdot, a), j = 1, \ldots, p\} \cup \{h_k(\cdot, a), k = 1, \ldots, q\}\) are unspecified smooth one-dimensional (1-D) functions. Specifically, each function \(X_j\) appears as a 1-D projection \(\langle X_j, \beta_j \rangle := \int_0^1 X_j(s)\beta_j(s)ds\), via the standard \(L^2\) inner product with a coefficient function \(\beta_j \in \Theta\), where \(\Theta\) is the space of square integrable functions over \([0, 1]\), restricted to a unit \(L^2\) norm for model identifiability (due to the unspecified nature of the associated functions \(g_j(\cdot, a)\)). The form of the function \(\mu\) in (1) is left unspecified. For model (1), we assume an additive noise, \(Y = E[Y|X, Z, A] + \epsilon\), where \(\epsilon \in \mathbb{R}\) is a zero-mean noise with finite variance.

In model (1), to separate the nonparametric \((X, Z)\) “main” effect from the additive \((X, Z)\)-by-\(A\) interaction effect components, and to obtain an identifiable representation, we will constrain the \(p + q\) component functions \(\{g_j, j = 1, \ldots, p\} \cup \{h_k, k = 1, \ldots, q\}\) associated with the \((X, Z)\)-by-\(A\) interaction effect to satisfy the following identifiability conditions:

\[
E[g_j((X_j, \beta_j), A) | X_j] = 0 \quad (\forall \beta_j \in \Theta) \quad (j = 1, \ldots, p) \quad \text{and} \quad E[h_k(Z_k, A) | Z_k] = 0 \quad (k = 1, \ldots, q)
\]

(almost surely), where the expectation is taken with respect to the distribution of \(X_j\) (or \(Z_k\)). Condition (2) implies \(E[\sum_{j=1}^p g_j((X_j, \beta_j), A) + \sum_{k=1}^q h_k(Z_k, A) | X, Z] = 0\) (almost surely), which makes not only representation (1) identifiable, but also the two effect components in model (1) orthogonal to each other. We call model (1) subject to the constraint (2), a constrained functional additive model (CFAM), which is the main model of the paper.

**Notation.** For a fixed \(\beta\), let us denote the \(L^2\) space of component functions, \(g(\cdot, \cdot)\), over the random variables \((X, \beta, A)\) as: \(\mathcal{H}^{(\beta)} = \{g | E[g((X, \beta), A)] = 0, ||g|| < \infty\}\), with \(||g|| = \sqrt{E[g^2((X, \beta), A)]}\), where the expectation is taken with respect to the joint distribution of \((X, \beta, A)\) and the inner product of the space defined as \(\langle g, g' \rangle = E[g((X, \beta), A)g'((X, \beta), A)]\). Similarly, let us denote the \(L^2\) space of component functions, \(h(\cdot, \cdot)\), over \((Z, A)\) as: \(\mathcal{H} = \{h | E[h(Z, A)] = 0, ||h|| < \infty\}\) with \(||h|| = \sqrt{E[h^2(Z, A)]}\), where the expectation is with respect to the distribution of \((Z, A)\), and
similarly defined inner product. We suppress the treatment-specific intercepts in models, by removing the treatment-specific means from $Y$, and assume $E[Y|A=a] = 0$ ($a=1,\ldots,L$), i.e., the main effect of $A$ is 0, without loss of generality.

Under the formulation (1) subject to the constraint (2), the “true” (i.e., optimal) functions, denoted as \{g_j^*, j = 1,\ldots,p\} $\cup$ \{\,$\beta_j^*$, $j = 1,\ldots,p$\} $\cup$ \{h_k^*, $k = 1,\ldots,q$\} that constitute the $(X, Z)$-by-$A$ interaction effect, can be viewed as the solution to the constrained optimization:

$$
\{g_j^*, \beta_j^*, h_k^*\} = \arg\min_{g_j \in \mathcal{H}_j^{[\beta_j^*]}, \beta_j \in \Theta, h_k \in \mathcal{H}_k} E \left\{ Y - \sum_{j=1}^p g_j(\langle X_j, \beta_j \rangle, A) - \sum_{k=1}^q h_k(Z_k, A) \right\}^2,
$$

subject to

$$
E[g_j(\langle X_j, \beta_j \rangle, A)|X_j] = 0 \quad \forall \beta_j \in \Theta \quad (j = 1,\ldots,p) \quad \text{and} \quad E[h_k(Z_k, A)|Z_k] = 0 \quad (k = 1,\ldots,q).
$$

(3)

Specifically, representation (3) does not involve the “main” effect functional $\mu$, due to the orthogonal representation (1) implied by (2). (See Section A.1 of Supporting Information for additional detail.) If $\mu$ in (1) is a complicated functional subject to model misspecification, exploiting the representation on the right-hand side of (3) for \{g_j^*, j = 1,\ldots,p\} $\cup$ \{\,$\beta_j^*$, $j = 1,\ldots,p$\} $\cup$ \{h_k^*, $k = 1,\ldots,q$\} on the left-hand side is particularly appealing, as it provides a means of estimating the interaction terms without having to specify $\mu$, thereby avoiding any issue of possible model misspecification for $\mu$. The function $\mu$ can also be specified similar to (3) and estimated separately (see Section A.6 of Supporting Information), due to orthogonality in model (1). In particular, estimators of \{g_j^*, \beta_j^*, h_k^*\} based on optimization (3) can be improved in terms of efficiency if $Y$ in (3) is replaced by a “residualized” response $Y - \hat{\mu}(X, Z)$, where $\hat{\mu}$ is some estimate of $\mu$ (see also Section A.6 of Supporting Information). However, for simplicity, we will focus on the representation (3) with the “unresidualized” $Y$.

Under model (1), the potential treatment effect-modifying variables among \{X_j, j = 1,\ldots,p\} $\cup$ \{Z_k, $k = 1,\ldots,q$\} appear in the model, only through the interaction effect terms in (1) that specify and characterize the heterogeneous treatment effects. Ravikumar et al. (2009) proposed a sparse additive model (SAM) for relevant covariate selection in a high-dimensional additive regression. As in SAM, to deal with a large $p + q$ and to achieve treatment effect-modifying variable selection, we impose sparsity on the set of component functions \{g_j, j = 1,\ldots,p\} $\cup$ \{h_k, $k = 1,\ldots,q$\} of CFAM (1), under the often reasonable assumption that most covariates are inconsequential as treatment effect-modifiers. This sparsity structure on the set of component functions can be usefully incorporated into the optimization-based representation (3) for \{g_j^*, \beta_j^*, h_k^*\}:

$$
\{g_j^*, \beta_j^*, h_k^*\} = \arg\min_{g_j \in \mathcal{H}_j^{[\beta_j^*]}, \beta_j \in \Theta, h_k \in \mathcal{H}_k} E \left\{ Y - \sum_{j=1}^p g_j(\langle X_j, \beta_j \rangle, A) - \sum_{k=1}^q h_k(Z_k, A) \right\}^2 + \lambda \left\{ \sum_{j=1}^p \|g_j\| + \sum_{k=1}^q \|h_k\| \right\},
$$

subject to

$$
E[g_j(\langle X_j, \beta_j \rangle, A)|X_j] = 0 \quad \forall \beta_j \in \Theta \quad (j = 1,\ldots,p) \quad \text{and} \quad E[h_k(Z_k, A)|Z_k] = 0 \quad (k = 1,\ldots,q),
$$

(4)

for some sparsity-inducing parameter $\lambda \geq 0$. The term $\sum_{j=1}^p \|g_j\| + \sum_{k=1}^q \|h_k\|$ in (4) behaves like an $L^1$ ball across different functional components \{g_j, j = 1,\ldots,p; h_k, k = 1,\ldots,q\} to encourage functional sparsity. For example, a relatively large value of $\lambda$ in (4) will result in many components to be exactly zero, thereby enforcing sparsity on the set of functions \{g_j^*, h_k^*\} on the left-hand side of (4). Specifically, equation (4) can help model selection when dealing with potentially many functional/scalar pretreatment covariates.
3 Estimation

We first consider a population characterization of the algorithm for solving (4) in Section 3.1 and then a sample counterpart of the population algorithm in Section 3.2.

3.1 Population algorithm

For a set of fixed coefficient functions \( \{\beta_j, j = 1, \ldots, p\} \), the minimizing component function \( g_j \in H_j^{(\beta_j)} \) (and \( h_k \in H_k \)) for each \( j \) (and each \( k \)) of the constrained objective function of (4) has a component-wise closed-form expression.

Theorem 1. Given \( \lambda \geq 0 \) and a set of fixed single-index coefficient functions \( \{\beta_j, j = 1, \ldots, p\} \), the minimizing component function \( g_j \in H_j^{(\beta_j)} \) of the constrained objective function of (4) satisfies:

\[
g_j(\langle X_j, \beta_j \rangle, A) = \left[ 1 - \frac{\lambda}{\|f_j\|} \right]^+ f_j(\langle X_j, \beta_j \rangle, A) \quad (\text{almost surely}),
\]

where the function \( f_j \in H_j^{(\beta_j)} \):

\[
f_j(\langle X_j, \beta_j \rangle, A) := E[R_j|\langle X_j, \beta_j \rangle, A] - E[R_j|\langle X_j, \beta_j \rangle],
\]

in which

\[
R_j = Y - \sum_{j' \neq j} g_{j'}(\langle X_{j'}, \beta_{j'} \rangle, A) - \sum_{k=1}^{q} h_k(A)(Z_k)
\]

represents the \( j \)th (functional covariate’s) partial residual; similarly, the minimizing component function \( h_k \in H_k \) of the constrained objective function of (4) satisfies:

\[
h_k(Z_k, A) = \left[ 1 - \frac{\lambda}{\|f_k\|} \right]^+ \tilde{f}_k(Z_k, A) \quad (\text{almost surely}),
\]

where the function \( \tilde{f}_k \in H_k \):

\[
\tilde{f}_k(Z_k, A) := E[\tilde{R}_k|Z_k, A] - E[\tilde{R}_k|Z_k],
\]

and

\[
\tilde{R}_k = Y - \sum_{j=1}^{p} g_j(\langle X_j, \beta_j \rangle, A) - \sum_{k' \neq k} h_{k'}(Z_{k'}, A)
\]

represents the \( k \)th (scalar covariate’s) partial residual. (In (5) and (8), \( [u]^+ = \max(0, u) \) represents the positive part of \( u \).)

The proof of Theorem 1 is in Section A.2 of Supporting Information. Given a sparsity tuning parameter \( \lambda \geq 0 \), optimization (4) can be split into two iterative steps (Fan et al., 2014, 2015). First (Step 1), for a set of fixed single-indices \( \langle X_j, \beta_j \rangle \) \( (j = 1, \ldots, p) \), the component functions \( \{g_j, j = 1, \ldots, p\} \cup \{h_k, k = 1, \ldots, q\} \) of the model can be found by a coordinate descent procedure that fixes \( \{g_{j'}; j' \neq j\} \cup \{h_k, k = 1, \ldots, q\} \) and obtains \( g_j \) by equation (5) (and that fixes \( \{g_j, j = 1, \ldots, p\} \cup \{h_{k'}; k' \neq k\} \) and obtains \( h_k \) by equation (8)), and then iterates through all \( j \) and \( k \) until convergence. This step (Step 1) amounts to fitting a SAM (Ravikumar et al., 2009) subject to the
constraint (2). Second (Step 2), for a set of fixed component functions \( \{g_j, j = 1, \ldots, p\} \cup \{h_k, k = 1, \ldots, q\} \), the \( j \)th single-index coefficient function \( \beta_j \in \Theta \) can be optimized by solving, for each \( j \in \{1, \ldots, p\} \) separately:

\[
\begin{aligned}
&\text{minimize}_{\beta_j \in \Theta} \ E \left\{ R_j - g_j(\langle X_j, \beta_j \rangle, A) \right\}^2 \\
&\quad \text{for } j = 1, \ldots, p,
\end{aligned}
\]

(11)

where the \( j \)th partial residual \( R_j \) is defined in (7). These two steps can be iterated until convergence to obtain a population solution \( \{g^*_j, \beta^*_j, h^*_k\} \) on the left-hand side of (4).

To obtain a sample version of the population solution, we can insert sample estimates into the population algorithm, as in standard backfitting in estimating generalized additive models (Hastie and Tibshirani, 1999), which we describe in the next subsection.

### 3.2 Sample version of the population algorithm

To simplify the exposition, we only describe the optimization of \( g_j(\langle X_j, \beta_j \rangle, A) \) \( (j = 1, \ldots, p) \) associated with the functional covariates \( X_j \) \( (j = 1, \ldots, p) \). The components \( h_k(Z_k, A) \) \( (k = 1, \ldots, q) \) associated with the scalar covariates \( Z_k \) \( (k = 1, \ldots, q) \) in (4) are optimized in the same way, except that we do not need to perform Step 2 of the alternating optimization procedure; i.e., when optimizing \( h_k(Z_k, A) \) \( (k = 1, \ldots, q) \), we only perform Step 1.

#### 3.2.1 Step 1

First, we consider a sample version of Step 1 of the population algorithm. Suppose we are given a set of estimates \( \{\hat{\beta}_j, j = 1, \ldots, p\} \) and the data-version of the \( j \)th partial residual \( \hat{R}_j \) in (7):

\[
\hat{R}_{ij} = Y_i - \sum_{j' \neq j} \hat{g}_{j'}(\langle X_{ij'}, \hat{\beta}_{j'} \rangle, A_i) - \sum_{k=1}^{q} \hat{h}_k(Z_{ik}, A_i) \quad (i = 1, \ldots, n),
\]

where \( \hat{g}_{j'} \) represents a current estimate for \( g_{j'} \) and \( \hat{h}_k \) that for \( h_k \). For each \( j \), we update the component function \( g_j \) in (5) in two steps: first, estimate the function \( f_j \) in (6); second, plug the estimate of \( f_j \) into \( 1 - \frac{\lambda}{\|f_j\|}_+ \) in (5), to obtain the soft-thresholded estimate \( \hat{g}_j \).

Although any linear smoothers can be utilized to obtain estimators \( \{\hat{g}_j, j = 1, \ldots, p\} \) (see Section A.3 of Supporting Information), we shall focus on regression spline-type estimators, which are simple and computationally efficient to implement. For each \( j \) and \( \beta_j = \hat{\beta}_j \), we will represent the component function \( g_j \in \mathcal{H}_j(\hat{\beta}_j) \) on the right-hand side of (4) as:

\[
g_j(\langle X_j, \hat{\beta}_j \rangle, a) = \Psi_j(\langle X_j, \hat{\beta}_j \rangle)^\top \theta_{j,a} \quad (a = 1, \ldots, L)
\]

(12)

for some prespecified \( d_j \)-dimensional basis \( \Psi_j(\cdot) \) (e.g., cubic B-spline basis with \( d_j - 4 \) interior knots, evenly placed over the range (scaled to, say, \([0, 1]\)) of the observed values of \( \langle X_j, \hat{\beta}_j \rangle \)) and a set of unknown treatment \( a \)-specific basis coefficients \( \{\theta_{j,a} \in \mathbb{R}^{d_j}\}_{a = 1, \ldots, L} \). Based on representation (12) of \( g_j \in \mathcal{H}_j(\hat{\beta}_j) \) for fixed \( \hat{\beta}_j \), the constraint \( E[g_j(\langle X_j, \beta_j \rangle, A)|X_j] = 0 \) in (4) on \( g_j \), for fixed \( \beta_j = \hat{\beta}_j \), can be simplified to: \( E[\theta_{j,a}A] = \sum_{a=1}^{L} \pi_{a} \theta_{j,a} = 0 \). If we fix \( \beta_j = \hat{\beta}_j \), the constraint in (4) on the function \( g_j \) can then be succinctly written in matrix form:

\[
\pi^{(j)} \theta_j = 0,
\]

(13)
where \( \theta_j := (\theta_{j,1}^\top, \theta_{j,2}^\top, \ldots, \theta_{j,L}^\top)^\top \in \mathbb{R}^{d_j L} \) is the vectorized version of the basis coefficients \( \{\theta_{j,a}\}_{a \in \{1, \ldots, L\}} \), and the \( d_j \times d_j \) matrix \( \pi^{(j)} := (\pi_1 I_{d_j}; \pi_2 I_{d_j}; \ldots; \pi_L I_{d_j}) \) where \( I_{d_j} \) is the \( d_j \times d_j \) identity matrix.

Let the \( n \times d_j \) matrices \( D_{j,a} \) \( (a = 1, \ldots, L) \) denote the evaluation matrices of the basis \( \Psi_j(\cdot) \) on \( \langle X_{ij}, \hat{\beta}_j \rangle \) \( (i = 1, \ldots, n) \) specific to the treatment \( A = a \) \( (a = 1, \ldots, L) \), whose \( i \)th row is the \( 1 \times d_j \) vector \( \Psi_j(\langle X_{ij}, \hat{\beta}_j \rangle) \) if \( A_i = a \), and a row of zeros \( 0^\top \) if \( A_i \neq a \). Then the column-wise concatenation of the design matrices \( \{D_{j,a}\}_{a \in \{1, \ldots, L\}} \), i.e., the \( n \times d_j \) matrix \( D_j = (D_{j,1}; D_{j,2}; \ldots; D_{j,L}) \), defines the model matrix associated with the vectorized basis coefficient \( \theta_j \in \mathbb{R}^{d_j L} \), vectorized across \( \{\theta_{j,a}\}_{a \in \{1, \ldots, L\}} \) in representation (12). We can then represent \( g_j(\langle X_j, \hat{\beta}_j \rangle, A) \) of (12), based on the sample data, by the length-\( n \) vector:

\[
g_j = D_j \theta_j \in \mathbb{R}^n
\]  

subject to the linear constraint (13) on the parameters \( \theta_j \). (Similarly, we can represent \( h_k(Z_k, A) \) by a length-\( n \) vector.)

The linear constraint in (13) on \( \theta_j \) can be conveniently absorbed into the model matrix \( D_j \) in (14) by reparametrization, which we describe next. We can find a \( d_j L \times d_j (L - 1) \) basis matrix \( n^{(j)} \) (that spans the null space of the linear constraint (13)), such that, if we set \( \theta_j = n^{(j)} \tilde{\theta}_j \) for any arbitrary vector \( \tilde{\theta}_j \in \mathbb{R}^{d_j (L - 1)} \), then the vector \( \theta_j \in \mathbb{R}^{d_j L} \) automatically satisfies the constraint (13):

\[
\pi^{(j)} \theta_j = 0.
\]

Such a basis matrix \( n^{(j)} \) can be constructed by a QR decomposition of the matrix \( \pi^{(j)} \). Then representation (14) can be reparametrized, in terms of the unconstrained \( \tilde{\theta}_j \in \mathbb{R}^{d_j (L - 1)} \), by replacing \( D_j \) in (14) with a reparametrized model matrix \( \tilde{D}_j = D_j n^{(j)} \):

\[
g_j = \tilde{D}_j \tilde{\theta}_j.
\]  

Theorem 1, together with Section A.4 of Supporting Information, indicates that (for fixed \( \beta_j = \hat{\beta}_j \)) the coordinate-wise minimizing function \( g_j \) of the right-hand side of (4) can be estimated based on the sample by:

\[
\hat{g}_j = \left[ 1 - \frac{\lambda}{\sqrt{n} \| f_j \|^2} \right]_+ \hat{f}_j
\]  

where

\[
\hat{f}_j = \tilde{D}_j (\tilde{D}_j^\top \tilde{D}_j)^{-1} \tilde{D}_j^\top \hat{R}_j,
\]

in which \( \hat{R}_j = Y - \sum_{j' \neq j} \hat{g}_{j'} - \sum_{k=1}^q \hat{f}_k \) corresponds to the estimated \( j \)th partial residual vector. (Similarly, we can represent the coordinate-wise minimizing function \( h_k \) in (8), based on the observed data by a length-\( n \) vector \( \hat{h}_k \).) If we set each \( \beta_j \) equal to its corresponding estimate \( \hat{\beta}_j \) \( (j = 1, \ldots, p) \), then based on the sample counterpart (16) of the coordinate-wise solution (5), a highly efficient coordinate descent algorithm can be conducted to optimize \( \{g_j, j = 1, \ldots, p\} \cup \{h_k, k = 1, \ldots, q\} \) simultaneously. Let \( s^{(j)}_j := \left[ 1 - \lambda \sqrt{n} / \| f_j \| \right]_+ \) in (16) denote the soft-threshold shrinkage factor associated with the un-shrunk estimate \( \hat{f}_j \) in (17). At convergence of the coordinate descent, we obtain a basis coefficient estimate of \( \tilde{\theta}_j \) associated with representation (15):

\[
\tilde{\theta}_j = s^{(j)}_j (\tilde{D}_j^\top \tilde{D}_j)^{-1} \tilde{D}_j^\top \hat{R}_j,
\]

which in turn implies an estimate of \( \theta_j \) in (14):

\[
\hat{\theta}_j := (\hat{\theta}_{j,1}^\top, \hat{\theta}_{j,2}^\top, \ldots, \hat{\theta}_{j,L}^\top)^\top = n^{(j)} \tilde{\theta}_j.
\]

Specifically, this gives an estimate of the treatment \( a \)-specific function \( g_j(\cdot, a) \) \( (a = 1, \ldots, L) \) in model (1):

\[
\hat{g}_j(\cdot, a) = \Psi_j(\cdot)^\top \hat{\theta}_{j,a} \quad (a = 1, \ldots, L)
\]
We now consider a sample version of $\gamma$ where basis $B$ discretized function points, we approximate $\hat{\langle} B \rangle$ function covariate $X$ a functional linear regression (e.g., Cardot et al., 2003) with scalar response in which each $\hat{g}$ can be approximately achieved based on a first-order Taylor series approximation of the term to (11), we consider estimates $\{\hat{\beta}_j, j = 1, \ldots, p\}$ provided by Step 1. As an empirical approximation to (11), we consider
\[
\min_{\hat{\beta}_j \in \Theta} \sum_{i=1}^{n} \left\{ \hat{R}_{ij} - \hat{g}_j(\langle X_{ij}, \beta_j \rangle, A_i) \right\}^2 \quad (j = 1, \ldots, p),
\]
where $\hat{R}_{ij}$ is the $i$th element of $\hat{R}_{j} \in \mathbb{R}^n$ in (16). For this iterative estimation step, solving (20) can be approximately achieved based on a first-order Taylor series approximation of the term $\hat{g}_j(\langle X_{ij}, \beta_j \rangle, A_i)$ at the current estimate, which we denote as $\hat{\beta}_j^{(c)} \in \Theta$:
\[
\sum_{i=1}^{n} \left\{ \hat{R}_{ij} - \hat{g}_j(\langle X_{ij}, \beta_j \rangle, A_i) \right\}^2 \approx \sum_{i=1}^{n} \left\{ \hat{R}_{ij} - \hat{g}_j(\langle X_{ij}, \hat{\beta}_j^{(c)} \rangle, A_i) - \hat{g}_j(\langle X_{ij}, \hat{\beta}_j^{(c)} \rangle, A_i) \langle X_{ij}, \beta_j - \hat{\beta}_j^{(c)} \rangle \right\}^2
\]
\[
= \sum_{i=1}^{n} \left\{ \hat{R}_{ij}^* - \langle X_{ij}^*, \beta_j \rangle \right\}^2,
\]
where the “modified” residuals $\hat{R}_{ij}^*$ and the “modified” covariates $X_{ij}^*$ are defined as:
\[
\hat{R}_{ij}^* = \hat{R}_{ij} - \hat{g}_j(\langle X_{ij}, \hat{\beta}_j^{(c)} \rangle, A_i) + \hat{g}_j(\langle X_{ij}, \hat{\beta}_j^{(c)} \rangle, A_i) \langle X_{ij}, \hat{\beta}_j^{(c)} \rangle \quad (i = 1, \ldots, n),
\]
\[
X_{ij}^* = \hat{g}_j(\langle X_{ij}, \hat{\beta}_j^{(c)} \rangle, A_i) X_{ij} \quad (i = 1, \ldots, n),
\]
in which each $\hat{g}_j(\cdot, a)$ denotes the first derivative of $\hat{g}_j(\cdot, a)$ in (19) given by Step 1. We can perform a functional linear regression (e.g., Cardot et al., 2003) with scalar response $\hat{R}_{ij}^*$ and (functional) covariate $X_{ij}^*$ to minimize the right-hand side of (21) over $\beta_j \in \Theta$. Specifically, the smooth coefficient function $\hat{\beta}_j$ in (21) is represented by a prespecified and normalized $m_j$-dimensional $B$-spline basis $B_j(s) = (b_{j1}(s), \ldots, b_{jm_j}(s))^\top \in \mathbb{R}^{m_j}$, where $m_j$ depends only on the sample size $n$ (Fan et al., 2015):
\[
\beta_j(s) = \sum_{r=1}^{m_j} b_{jr}(s) \gamma_{jr} \quad s \in [0, 1],
\]
with an unknown basis coefficient vector $\gamma_j = (\gamma_{j1}, \gamma_{j2}, \ldots, \gamma_{jm_j})^\top \in \mathbb{R}^{m_j}$. Suppose the function $X_{ij}$ $(i = 1, \ldots, n)$ is discretized at points $\{s_l : 0 = s_1 < s_2 < \ldots < s_{r_j} = 1\}$. Using the approximation $\langle X_{ij}, \hat{\beta}_j^{(c)} \rangle \approx \sum_{l=1}^{r_j} \Delta_i X_{ij}(s_l) \hat{\beta}_j^{(c)}(s_l)$ where $\Delta_i$ is the distance between two neighboring discretization points, we approximate $\hat{R}_{ij}^*$ and $X_{ij}^*$ in (22). Let $X_j^*$ be the $n \times r_j$ matrix whose $i$th row is the discretized function $X_{ij}(s_l)$ $(l = 1, \ldots, r_j)$, and $B_j$ the $r_j \times m_j$ matrix whose $l$th row is the evaluated basis $B_j(s) \in \mathbb{R}^{m_j}$ at the $l$th point $s = s_l$ $(l = 1, \ldots, r_j)$. Given $\beta_j(s)$ discretized at the points $s = s_l$ $(l = 1, \ldots, r_j)$ in (23), we can represent the right-hand side of (21) as:
\[
\|R_j^* - U_j^* \gamma_j\|^2,
\]
where \( R_j^* := (R_{1j}^*, \ldots, R_{nj}^*)^\top \in \mathbb{R}^n \) and \( U_j^* := \Delta X_j^* B_j \). Minimizing (24) over \( \gamma_j \in \mathbb{R}^d \) for each \( j = 1, \ldots, p \) provides estimates \( \{\hat{\beta}_j, j = 1, \ldots, p\} \) of the coefficient functions; here, the minimizer \( \hat{\gamma}_j \) for (24) is scaled to \( \|\hat{\gamma}_j\| = 1 \), so that the resulting \( \hat{\beta}_j(s) = \sum_{r=1}^{m_j} b_{jr}(s) \hat{\gamma}_{jr} \) \( (s \in [0, 1]) \) satisfies the identifiability constraint \( \hat{\beta}_j \in \Theta \). This completes Step 2 of the alternating optimization procedure.

### 3.2.3 Initialization and convergence criterion

At the initial iteration, we need some estimates \( \{\hat{\beta}_j, j = 1, \ldots, p\} \) of the single-index coefficient functions to initialize the single-indices \( \{u_j = \langle \hat{\beta}_j, X_j \rangle, j = 1, \ldots, p\} \), in order to perform Step 1 (i.e., the coordinate-descent procedure) of the estimation procedure described in Section 3.2.1. At the initial iteration, we take \( \hat{\beta}_j(s) = 1 \) \( (s \in [0, 1]) \), i.e., we take \( u_j = \int_0^1 X_j(s) ds \) \( (j = 1, \ldots, p) \), which corresponds to the common practice of taking a naïve scalar summary of each functional covariate. The proposed algorithm alternating between Step 1 and Step 2 terminates when the estimates \( \{\hat{\beta}_j, j = 1, \ldots, p\} \) converge. To be specific, the algorithm terminates when \( \max_{j=1,\ldots,p;r=1,\ldots,m_j} \|\hat{\gamma}_{jr} - \hat{\gamma}_{jr}^{(c)}\|/\hat{\gamma}_{jr} \) is less than a prespecified convergence tolerance; here, \( \hat{\gamma}_{jr}^{(c)} \) represents the current estimate for \( \gamma_{jr} \) in (23) at the beginning of Step 1, and \( \hat{\gamma}_{jr} \) is the estimate at the end of Step 2. We summarize the computational procedure in Algorithm 1.

**Algorithm 1** Estimation of constrained functional additive models

1. **Input:** Data \( Y \in \mathbb{R}^n, A \in \mathbb{R}^n, X_j \in \mathbb{R}^n \times \mathbb{R}^{p_j} \) \( (j = 1, \ldots, p) \), and \( \lambda \geq 0 \)
2. **Output:** Estimated functions \( \{\hat{\beta}_j, j = 1, \ldots, p\} \) and \( \{\hat{g}_j, j = 1, \ldots, p\} \)
3. Initialize \( \hat{\beta}_j(s) = 1 \) \( (s \in [0, 1]) \) \( (j = 1, \ldots, p) \).
4. **while** until convergence of \( \{\hat{\beta}_j, j = 1, \ldots, p\} \), **do** iterate between Step 1 and Step 2:
5. (Step 1)
6. Fix \( \{\hat{\beta}_j, j = 1, \ldots, p\} \), and compute \( \bar{D}_j(D_j^\top D_j)^{-1}D_j^\top \) in (17) \( (j = 1, \ldots, p) \).
7. Initialize \( \hat{g}_j = 0 \in \mathbb{R}^{n} \) \( (j = 1, \ldots, p) \).
8. **while** until convergence of \( \{\hat{g}_j, j = 1, \ldots, p\} \), **do** iterate through \( j = 1, \ldots, p \):
9. Compute the partial residual \( \bar{R}_j = Y - \sum_{j' \neq j} \hat{g}_{j'} \).
10. Compute \( \hat{f}_j \) in (17); then compute the thresholded estimate \( \hat{g}_j \) in (16).
11. (Step 2)
12. Fix \( \{\hat{g}_j, j = 1, \ldots, p\} \) in (19), and solve (20) based on (24); update \( \hat{\beta}_j \) \( (j = 1, \ldots, p) \).

In Algorithm 1, if the \( j \)th soft-threshold shrinkage factor \( \hat{s}_j^{(\lambda)} = \left[ 1 - \lambda \sqrt{n}/\|\hat{f}_j\| \right]_+ \) in (16) is 0, then the associated \( X_j \) is absent from the model. Therefore, the corresponding coefficient function \( \hat{\beta}_j \) will not be updated, and this greatly reduces the computational cost when most of the shrinkage factors \( \hat{s}_j^{(\lambda)} \) are zeros. In Algorithm 1, the smoother matrix \( \bar{D}_j(D_j^\top D_j)^{-1}D_j^\top \) in (16) \( (j = 1, \ldots, p) \) needs to be computed only once at the beginning of Step 1 given fixed \( \{\hat{\beta}_j, j = 1, \ldots, p\} \), and therefore the coordinate-descent updates in Step 1 can be performed very efficiently (Fan et al., 2014). The sparsity tuning parameter \( \lambda \geq 0 \) can be chosen to minimize an estimate of the expected squared error of the estimated models over a dense grid of \( \lambda \)'s, estimated, for example, by a 10-fold cross-validation.
4 Simulation study

4.1 ITR estimation performance

In this section, we assess the optimal ITR estimation performance of the proposed method based on simulations. We generate \( n \) independent copies of \( p \) functional-valued covariates \( X_i = (X_{i1}, X_{i2}, \ldots, X_{ip}) (i = 1, \ldots, n) \), where we use a 4-dimensional Fourier basis, \( \Phi(s) = (\sqrt{2}\sin(2\pi s), \sqrt{2}\cos(2\pi s), \sqrt{2}\sin(4\pi s), \sqrt{2}\cos(4\pi s))^\top \in \mathbb{R}^4 (s \in [0,1]) \), and random coefficients \( \bar{x}_{ij} \in \mathbb{R}^4 \), each independently following \( \mathcal{N}(0, I_4) \), to form the functions \( X_{ij}(s) = \Phi(s)^\top \bar{x}_{ij} \) (\( s \in [0,1] \)) \((i = 1, \ldots, n; \ j = 1, \ldots, p)\). Then these covariates are evaluated at 50 equally spaced points \( \{s_l\}_{l=1}^{50} \) between 0 and 1. We also generate \( n \) independent copies of \( q \) scalar covariates \( Z_i = (Z_{i1}, \ldots, Z_{iq})^\top \in \mathbb{R}^q (i = 1, \ldots, n) \), based on the multivariate normal distribution with each component having mean 0 and variance 1, with correlations between the components \( \text{corr}(Z_{ij}, Z_{ik}) = 0.5^{|j-k|} \). We generate the outcomes \( Y_i (i = 1, \ldots, n) \) from:

\[
Y_i = \epsilon_i + \delta \left\{ \sum_{j=1}^{8} \sin(\langle \eta_j, X_{i1} \rangle) + \sum_{k=1}^{8} \sin(Z_{ik}) \right\} + 4(A_i - 1.5) \left[ \sin(\langle \beta_1, X_{i1} \rangle) - \sin(\langle \beta_2, X_{i2} \rangle) + \cos(Z_{i1}) - \cos(Z_{i2}) + \xi (\cos(\langle X_{i1}, X_{i2} \rangle) + \sin(Z_{i1}Z_{i2})) \right],
\]

(25)

where the treatments \( A_i \in \{1, 2\} \) are generated with equal probability, independently of \( (X_{i}, Z_{i}) \) and \( \epsilon_i \sim \mathcal{N}(0, 0.5^2) \). In (25), there are only four “signal” covariates \((X_{i1}, X_{i2}, Z_{i1}, Z_{i2})\) influencing the effect of \( A_i \) on \( Y_i \) (i.e., 4 treatment effect-modifiers). The other \( p + q - 4 \) covariates are “noise” covariates not critical in optimizing ITRs. We set \( p = q = 20 \), therefore we consider a total of 40 pretreatment covariates in this example. In (25), we set the single-index coefficient functions, \( \beta_1 \) and \( \beta_2 \), to be: \( \beta_1(s) = \Phi(s)^\top (0.5, 0.5, 0.5, 0.5) \) and \( \beta_2(s) = \Phi(s)^\top (0.5, -0.5, 0.5, -0.5) \), respectively (see Figure 2). We set the coefficient functions \( \eta_j \) \((j = 1, \ldots, 8)\) associated with the \( X_j \) “main” effect to be: \( \eta_j(s) = \Phi(s)^\top \bar{\eta}_j \), with each \( \bar{\eta}_j \in \mathbb{R}^4 \) \((j = 1, \ldots, 8)\) following \( \mathcal{N}(0, I_4) \) and then rescaled to a unit \( L^2 \) norm \( \| \bar{\eta}_j \| = 1 \). The data model (25) is indexed by a pair \((\delta, \xi)\). The parameter \( \delta \in \{1, 2\} \) controls the the contribution of the \((X_j, Z)\) main effect component, \( \delta \left\{ \sum_{j=1}^{8} \sin(\langle \eta_j, X_{i1} \rangle) + \sum_{k=1}^{8} \sin(Z_{ik}) \right\} \), to the variance of \( Y \), in which \( \delta = 1 \) corresponds to a relatively moderate \((X_j, Z)\) main effect (about 4 times greater than the interaction effect when \( \xi = 0 \)) and \( \delta = 2 \) corresponds to a relatively large \((X_j, Z)\) main effect (about 16 times greater than the interaction effect when \( \xi = 0 \)). In (25), the parameter \( \xi \in \{0, 1\} \) determines whether the \( A \)-by-\((X_j, Z)\) interaction effect component has an additive regression structure \((\xi = 0)\) of the form (1) or whether it deviates from an additive regression structure \((\xi = 1)\). In the case of \( \xi = 0 \), the proposed CFAM (1) is correctly specified, whereas, for the case of \( \xi = 1 \), it is misspecified. For each simulation replication, we consider the following four approaches to estimating \( D^{opt} \):

1. The proposed approach (4), estimated via Algorithm 1, with the dimensions of the cubic \( B \)-spline basis for \( \{g_j, h_k, \beta_j\} \) set at \( d_j = d_k = m_j = 4 + (2n)^{1/5} \) (rounded to the closest integer), following Corollary 3 of Fan et al. (2015). The sparsity tuning parameter \( \lambda > 0 \) is chosen to minimize 10-fold cross-validated prediction error of the fitted models.

2. The functional linear regression approach of Ciarleglio et al. (2018),

\[
\minimize_{\beta_j \in L^2[0,1], \alpha_k \in \mathbb{R}} E \left\{ Y - \sum_{j=1}^{p} \langle \beta_j, X_j(A - 1.5) - \sum_{k=1}^{q} \alpha_k Z_k(A - 1.5) \right\}^2 + \lambda \left\{ \sum_{j=1}^{p} (\| \beta_j \| + \rho_j \gamma_j^\top S_j \gamma_j) + \sum_{k=1}^{q} |\alpha_k| \right\},
\]

10
which tends to result in a sparse set \{\beta_j\} \cup \{\alpha_k\}, performing estimation based on representation (23) for the coefficient functions \beta_j given \(m_j = 10\), with an associated \(m_j \times m_j\) \(P\)-spline penalty matrix \((S_j)\) to ensure appropriate smoothness. The tuning parameters \(\lambda > 0\) and \(\rho = \rho_j > 0\) \((j = 1, \ldots, p)\) are chosen to minimize a 10-fold cross-validated prediction error (Ciarleglio et al., 2018), and the ITR is given by: 
\[
\hat{D}^{\text{opt}}(\mathbf{X}, \mathbf{Z}) = \arg \max_{a \in \{1, \ldots, L\}} \left\{ \sum_{j=1}^{p} (a - 1.5) \langle \beta_j, X_j \rangle + (a - 1.5) \sum_{k=1}^{q} \alpha_k Z_k \right\}. 
\]
Since the component functions \{g_j, h_k\} associated with Ciarleglio et al. (2018) are restricted to be linear (i.e., we restrict them to \(g_j(\langle \beta_j, X_j \rangle, A) = \langle \beta_j, X_j \rangle (A - 1.5)\) and \(h_k(Z_k, A) = \alpha_k Z_k (A - 1.5)\)) corresponding to a special case of CFAM, we call the model of Ciarleglio et al. (2018), a CFAM with linear component functions (CFAM-lin) for the notational simplicity.

3. The outcome weighted learning (OWL; Zhao et al., 2012) method based on a linear kernel (OWL-lin), implemented in the R-package \texttt{DTRlearn}. Since there is no currently available OWL method that deals with functional covariates, we compute a scalar summary of each functional covariate, i.e., \(\bar{X}_j = \int_0^1 X_j(s) ds \in \mathbb{R}\), and use \(\bar{X}_j\) along with the other scalar covariates \(Z_k\) as inputs to the augmented (residualized) OWL procedure. To improve its efficiency, we employ the augmented OWL approach of Liu et al. (2018), which amounts to pre-fitting a linear model for \(\mu\) in (1) via Lasso (Tibshirani, 1996) and residualizing the response \(Y\). The tuning parameter \(\kappa\) in Zhao et al. (2012) is chosen from the grid of \((0.25, 0.5, 1, 2, 4)\) (the default setting of \texttt{DTRlearn}) based on a 10-fold cross-validation.

4. The same approach as in 3 but based on a Gaussian radial basis function kernel (OWL-Gauss) in place of a linear kernel. The inverse bandwidth parameter \(\sigma_r^2\) in Zhao et al. (2012) is chosen from the grid of \((0.01, 0.02, 0.04, \ldots, 0.64, 1.28)\) and \(\kappa\) is chosen from the grid of \((0.25, 0.5, 1, 2, 4)\), based on a 10-fold cross-validation.

Throughout the paper, for CFAM and CFAM-lin, we fit the \((\mathbf{X}, \mathbf{Z})\) “main” effect on \(Y\) based on the (misspecified) linear model with the naive scalar averages of \(X_j\), i.e., \(\bar{X}_j\), along with \(Z_k\), fitted via Lasso with 10-fold cross-validation for the sparsity parameter and utilize the “residualized” response \(Y - \hat{\mu}(\mathbf{X}, \mathbf{Z})\). For each simulation run, we estimate \(\hat{D}^{\text{opt}}\) from each of the above four methods based on a training set (of size \(n \in \{250, 500\}\)), and to evaluate these methods, we compute the value \(V(\hat{D}^{\text{opt}}) = E[E[Y|\mathbf{X}, \mathbf{Z}, A = \hat{D}^{\text{opt}}(\mathbf{X}, \mathbf{Z})]\] given each estimate \(\hat{D}^{\text{opt}}\), using a Monte Carlo approximation based on a separate random sample of size \(10^3\). Since we know the true data generating model in simulation studies, the optimal \(\hat{D}^{\text{opt}}\) can be determined for each simulation run. Given each estimate \(\hat{D}^{\text{opt}}\) of \(D^{\text{opt}}\), we report \(V(\hat{D}^{\text{opt}}) - V(D^{\text{opt}})\), as the performance measure of \(\hat{D}^{\text{opt}}\). A larger (i.e., less negative) value of the measure indicates better performance.
In Figure 1, we present boxplots, obtained from 200 simulation runs, of the normalized values $V(\hat{D}^{opt})$ (normalized by the optimal values $V(D^{opt})$) of the decision rules $\hat{D}^{opt}$ estimated from the four approaches, for each combination of $n \in \{250, 500\}$, $\xi \in \{0, 1\}$ (corresponding to correctly-specified or mis-specified CFAM interaction models, respectively) and $\delta \in \{1, 2\}$ (corresponding to moderate or large main effects, respectively). The results in Figure 1 indicate that the proposed method (CFAM) outperforms all other approaches. In particular, if the sample size is relatively large ($n = 500$), for a correctly-specified CFAM ($\xi = 0$) interaction underlying model, the proposed method gives a close-to-optimal performance in comparison to $D^{opt}$. With nonlinearities present in the underlying model (25), CFAM-lin, which assumes a stringent linear structure on the interaction effect term, is outperformed by CFAM that utilizes the flexible component functions $g_j(\cdot, a)$ and $h_k(\cdot, a)$, while substantially outperforming the OWL-based approaches.

In Section A.5 of Supporting Information, we have also considered a similar set of experiments under a “linear” $A$-by-$X$ interaction effect, in which CFAM-lin outperforms CFAM, but by a relatively small amount, whereas if the underlying model deviates from the exact linear structure and $n = 500$, CFAM tends to outperform CFAM-lin. This suggests that, in the absence of prior knowledge about the form of the interaction effect, the more flexible CFAM that accommodates nonlinear treatment effect-modifications can be set as a default approach over CFAM-lin for optimizing ITRs. The estimated values of the OWL methods using linear and Gaussian kernels, respectively, are similar to each other, but both are outperformed by CFAM, even when CFAM is incorrectly specified (i.e., when $\xi = 1$), as the current OWL methods do not directly deal with the functional pretreatment covariates. When the $(X, Z)$ “main” effect dominates the $A$-by-$(X, Z)$ interaction effect (i.e., when $\delta = 2$), although the increased magnitude of this nuisance effect dampens the performance of all approaches to estimating $D^{opt}$, the proposed approach outperforms all other methods.

In Table 1, we additionally illustrate the estimation performance for model parameters $\beta_1$ and $\beta_2$ when $\xi = 0$ (i.e., when CFAM is correctly specified) with varying $\delta \in \{1, 2\}$ and $n \in \{250, 500, 1000\}$, based on the root squared error $RSE(\beta_j) = \int (\hat{\beta}_j(s) - \beta_j(s))^2 ds$ ($j = 1, 2$). In Figure 2, we display typical CFAM estimates $\hat{\beta}_j$ of $\beta_j$ from 10 random samples, for each sample size $n$ (for the case of $\delta = 1$). With sample size increasing, the estimators $\hat{\beta}_j$ get close to the true coefficient functions $\beta_j$. 

Figure 1: Boxplots obtained from 200 Monte Carlo simulations comparing 4 approaches to estimating $D^{opt}$, given each scenario indexed by $\xi \in \{0, 1\}$, $\delta \in \{1, 2\}$ and $n \in \{250, 500\}$. The dotted horizontal line represents the optimal value corresponding to $D^{opt}$. In Figure 1, we present boxplots, obtained from 200 simulation runs, of the normalized values $V(\hat{D}^{opt})$ (normalized by the optimal values $V(D^{opt})$) of the decision rules $\hat{D}^{opt}$ estimated from the four approaches, for each combination of $n \in \{250, 500\}$, $\xi \in \{0, 1\}$ (corresponding to correctly-specified or mis-specified CFAM interaction models, respectively) and $\delta \in \{1, 2\}$ (corresponding to moderate or large main effects, respectively). The results in Figure 1 indicate that the proposed method (CFAM) outperforms all other approaches. In particular, if the sample size is relatively large ($n = 500$), for a correctly-specified CFAM ($\xi = 0$) interaction underlying model, the proposed method gives a close-to-optimal performance in comparison to $D^{opt}$. With nonlinearities present in the underlying model (25), CFAM-lin, which assumes a stringent linear structure on the interaction effect term, is outperformed by CFAM that utilizes the flexible component functions $g_j(\cdot, a)$ and $h_k(\cdot, a)$, while substantially outperforming the OWL-based approaches.

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Figure 1: Boxplots obtained from 200 Monte Carlo simulations comparing 4 approaches to estimating $D^{opt}$, given each scenario indexed by $\xi \in \{0, 1\}$, $\delta \in \{1, 2\}$ and $n \in \{250, 500\}$. The dotted horizontal line represents the optimal value corresponding to $D^{opt}$.
Table 1: The root squared error (RSE) of the estimates \( \hat{\beta}_j \) for \( \beta_j \) \((j = 1, 2)\) for varying sample size \( n \in \{250, 500, 1000\} \), when the “main” effect of \((X, Z)\) is moderate \((\delta = 1)\) and large \((\delta = 2)\), respectively.

<table>
<thead>
<tr>
<th></th>
<th>( \delta = 1 ) (Moderate “main” effect)</th>
<th>( \delta = 2 ) (Large “main” effect)</th>
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<tbody>
<tr>
<td></td>
<td>( n ) 250 500 1000</td>
<td>( n ) 250 500 1000</td>
</tr>
<tr>
<td>\text{RSE}(\hat{\beta}_1)</td>
<td>0.53(0.08) 0.34(0.02) 0.26(0.02)</td>
<td>0.60(0.14) 0.38(0.05) 0.29(0.03)</td>
</tr>
<tr>
<td>\text{RSE}(\hat{\beta}_2)</td>
<td>0.53(0.06) 0.34(0.02) 0.27(0.01)</td>
<td>0.59(0.13) 0.39(0.07) 0.29(0.03)</td>
</tr>
</tbody>
</table>

Figure 2: An illustration of typical 10 CFAM sample estimates \( \hat{\beta}_j(s) \) (black dashed curves) for the parameters \( \beta_j(s) \) (the red solid curves), for \( j = 1 \) and 2 in the top and bottom panels, respectively, with a varying training sample size \( n \in \{125, 250, 500, 1000\} \) for the case of \( \delta = 1 \).

4.2 Treatment effect-modifier variable selection performance

In this subsection, we will report simulation results for the treatment effect-modifier selection among \( \{X_j, j = 1, \ldots, p\} \cup \{Z_k, k = 1, \ldots, q\} \). The complexity of the \((X, Z)\)-by-\( A \) interaction terms of CFAM (1) can be summarized in terms of the size (cardinality) of the index set of \( \{g_j, j = 1, \ldots, p\} \cup \{h_k, k = 1, \ldots, q\} \) that are not identically zero, each of which can be either correctly or incorrectly estimated to be equal to zero. As in Section 4.1, we generate 200 datasets based on (25), with varying \( \xi \in \{0, 1\} \), \( \delta \in \{1, 2\} \) and sample size \( n \in \{50, 100, 200, \ldots, 700, 800\} \) and \( p = q = 20 \), i.e., we consider a total of \( p + q = 40 \) potential treatment effect-modifiers, among which there are only 4 “true” treatment effect-modifiers.
Figure 3: The proportion of the relevant covariates (i.e., the treatment effect-modifiers) correctly selected (the “true positives”; the top gray panels), and the “noise” covariates incorrectly selected (the “false positives”; the bottom white panels), respectively (and ±1 standard deviation), with a varying sample size \( n \in \{50, 100, 200, \ldots, 800\} \), for each combination of \( \xi \in \{0, 1\} \) and \( \delta \in \{1, 2\} \).

Figure 3 summarizes the results of the treatment effect-modifier covariate selection performance with respect to the true/false positive rates (the top/bottom panels, respectively), comparing the proposed CFAM and the CFAM-lin of Ciarleglio et al. (2018). The results are reported as the averages (and ±1 standard deviations) across the 200 simulated datasets, for each simulation scenario. Figure 3 illustrates that the proportion of correct selection out of the 4 true treatment effect-modifiers (i.e., the “true positive” rate; the top gray panels) of CFAM (the red solid curves) tends to 1, as \( n \) increases from \( n = 50 \) to \( n = 800 \), whereas the proportion of incorrect selection (i.e., the “false positive” rate; the bottom white panels) out of the 36 irrelevant “noise” covariates tends to 0; these proportions tend to either 1 or 0 quickly for moderate main effect (\( \delta = 1 \)) scenarios compared to large main effect (\( \delta = 2 \)) scenarios. On the other hand, the proportion of correct selections for CFAM-lin (the blue dotted curves), even with a large \( n \), tends to be only around 0.55, due to the stringent linear model assumption on the from of the \((X, Z)\)-by-\(A\) interaction effect.

5 Application

In this section, we illustrate the utility of CFAM for optimizing ITRs, using data from an RCT (Trivedi et al., 2016) comparing an antidepressant and placebo for treating major depressive disorder. The study collected various scalar and functional patient characteristics at baseline, including electroencephalogram (EEG) data. Study participants were randomized to either placebo (\(A = 1\))
or an antidepressant (sertraline) \((A = 2)\). Subjects were monitored for 8 weeks after initiation of treatment. The primary endpoint of interest was the Hamilton Rating Scale for Depression (HRSD) score at week 8. The outcome \(Y\) was taken to be the improvement in symptoms severity from baseline to week 8 taken as the difference: week 0 HRSD score - week 8 HRSD score (larger values of the outcome \(Y\) are considered desirable).

There were \(n = 180\) subjects. We considered \(p = 19\) pretreatment functional covariates consisting of the current source density (CSD) amplitude spectrum curves over the Alpha frequency range (observed while the participants’ eyes were open), measured from a subset of EEG channels from a total of 72 EEG electrodes which gives a fairly good spatial coverage of the scalp. The locations for these 19 electrodes are indicated in the top panel of Figure 4. The Alpha frequency band (8 to 12 Hz) considered as a potential biomarker of antidepressant response (e.g., Wade and Iosifescu, 2016) was scaled to \([0, 1]\), hence each of the functional covariates \(X = (X_1(s), \ldots, X_{19}(s))\) was defined on the interval \([0, 1]\). We also considered \(q = 5\) baseline scalar covariates consisting of the week 0 HRSD score \((Z_1)\), sex \((Z_2)\), age at evaluation \((Z_3)\), word fluency \((Z_4)\) and Flanker accuracy \((Z_5)\) cognitive test scores, which were identified as predictors of differential treatment response in a previous study (Park et al., 2020c). In this dataset, 49% of the subjects were randomized to the sertraline \((A = 2)\). The average outcomes \(Y\) for the sertraline and placebo groups were 7.41 and 6.29, respectively. The means (and standard deviations) of \(Z_1, Z_3, Z_4\) and \(Z_5\) were 18.59 (4.44), 37.7 (13.57), 38 (11.42) and 0.19 (0.11), respectively, and 67% of the subjects were female.

The proposed CFAM approach (4) selected two functional covariates: “C3” \((X_4)\) and “P3” \((X_5)\) (the selected electrodes are indicated by the red dashed circles in the top panel of Figure 4), and a scalar covariate: “Flanker accuracy test” \((Z_5)\). In the first column of Figure 4, we display CSD curves corresponding to the selected two functional covariates, \(X_4(s)\) and \(X_5(s)\), from the 180 subjects. In the second column of Figure 4, we display the estimated coefficient functions, \(\hat{\beta}_4(s)\) and \(\hat{\beta}_5(s)\) (with 95% confidence bands conditional on the \(j\)th partial residual and the \(j\)th component function \(\hat{g}_j\)), associated with those selected covariates.

The coefficient functions \(\hat{\beta}_j(s)\) summarizing the \(X_j(s)\) lead to data-driven indices \(u_j = \langle \hat{\beta}_j, X_j \rangle \in \mathbb{R}\) that are linked to differential treatment response by two estimated nonzero component functions, \(\hat{g}_j(u_j, A)\) \((j = 4, 5)\) in this example. In Figure 4, the fitted component functions, \(\hat{g}_j(u_j, A)\) associated with the placebo \(A = 1\) (in the third column) and the active drug \(A = 2\) (in the fourth column), are displayed, along with the corresponding partial residuals. Roughly put, in Figure 4, the placebo \((A = 1)\) effect tends to increase with the index \(u_j \ (j = 4, 5)\) whereas the sertraline \((A = 2)\) effect decreases with the index. In the second column of Figure 4, both \(\beta_4\) and \(\beta_5\) put a bulk of their negative weight on lower frequencies (8 to 9 Hz), meaning that patients whose CSD values are small in those frequency regions would have large values of \(\langle \beta_j, X_j \rangle\), over the values which the placebo effects are predicted to be relatively strong, in comparison to the sertraline effects.

To evaluate the performance of ITRs (\(\hat{D}^{opt}\)) estimated from the four different approaches described in Section 4, we randomly split the data into a training set and a testing set (of size \(\tilde{n}\)) using a ratio of 5 : 1, replicated 500 times, each time estimating an ITR \(\hat{D}^{opt}\) based on the training set, and its “value” \(\tilde{V}(\hat{D}^{opt}) = E[Y|X, Z, A = \hat{D}^{opt}(X, Z)]\), by an inverse probability weighted estimator (Murphy, 2005) \(\tilde{V}(\hat{D}^{opt}) = \frac{\sum_{i=1}^{\tilde{n}} Y_i I_{(A_i = \hat{D}^{opt}(X_i, Z_i))}}{\sum_{i=1}^{\tilde{n}} I_{(A_i = \hat{D}^{opt}(X_i, Z_i))}}\), computed based on the testing set (of size \(\tilde{n}\)). For comparison, we also include two naive rules: treating all patients with placebo (“All PBO”) and treating all patients with the active drug (“All DRUG”), each regardless of the individual patient’s characteristics \((X, Z)\). The resulting boxplots obtained from the 500 random splits are illustrated in Figure 6.
Figure 4:  **Top:** The locations for the 19 electrode channels (“A1” and “A2” were not used). Those marked in red circles are the selected electrodes from the proposed approach: “C3” and “P3”.  
**Bottom:** First column: observed current source density (CSD) curves from the selected channels $X_4$ (“C3”) and $X_5$ (“P3”), over the Alpha band (8 to 12 Hz). Second column: the estimated single-index coefficient functions ($\beta_4$ and $\beta_5$) for the selected channels $X_4$ and $X_5$ (and the associated 95% confidence bands, conditioning on the $j$th partial residual and the $j$th component function $\hat{g}_j$). Third and fourth columns: the scatter plots of the ($j$th; $j = 4, 5$, top and bottom, respectively) partial residuals vs. the estimated single-indices $u_4 = \langle X_4, \beta_4 \rangle$ and $u_5 = \langle X_5, \beta_5 \rangle$, respectively, for the placebo $A = 1$ (third column, blue circles) and sertraline $A = 2$ (fourth column, red triangles) treated individuals, with the estimated treatment-specific component functions $g_j(u_j, A)$ ($A = 1, 2$) ($j = 4, 5$) (the dashed curves) overlaid.
Figure 5: The scatter plots of the $k$th partial residual vs. the $k$th scalar covariate, for the selected 5th scalar covariate $Z_5$ “Flanker accuracy test score,” for the placebo $A = 1$ (first column, blue circles) and sertraline $A = 2$ (second column, red triangles) treated individuals, with the estimated treatment-specific component functions $h_5(z_5, A)$ ($A = 1, 2$) (the dashed curves) overlaid.

Figure 6: Boxplots of the estimated values of the treatment rules $\hat{D}_i^{opt}$ estimated from 6 approaches, obtained from 500 randomly split testing sets. Higher values are preferred.
The results in Figure 6 demonstrate that CFAM and CFAM-lin perform at a similar level, showing a clear advantage over the both OWL-lin and OWL-Gauss, suggesting that regression utilizing the functional nature of the EEG measurements, that targets the treatment-by-functional covariates interactions is well-suited in this example. Specifically, in Figure 6, the superiority of CFAM (or CFAM-lin) over the policy of treating everyone with the drug (All DRUG) was of similar magnitude of the superiority of All DRUG over All PBOs. This suggests that accounting for patient characteristics can help treatment decisions. In this example, as can be observed from the third and fourth columns of Figures 4 and 5, the estimated nonlinear treatment effect-modification is rather modest. As a result, the performances of CFAM and CFAM-lin are comparable to each other. However, as demonstrated in Section 4, the more flexible CFAM can be employed as a default approach over CFAM-lin, allowing for potentially essential nonlinearities in treatment effect-modification.

6 Discussion

We have developed a functional additive regression approach specifically focused on extracting possibly nonlinear pertinent interaction effects between treatment and multiple functional/scalar covariates, which is of paramount importance in developing effective ITRs for precision medicine. This is accomplished by imposing appropriate structural constraints, performing treatment effect-modifier selection and extracting one-dimensional functional indices. The estimation approach utilizes an efficient coordinate-descent for the component functions and a functional linear model estimation procedure for the coefficient functions. The proposed functional regression for ITRs extends existing methods by incorporating possibly nonlinear treatment-by-functional covariates interactions. Encouraged by our simulation results and the application, future work will investigate the asymptotic properties of the method related to variable selection and estimation consistency, and a hypothesis testing framework for significant interactions between treatment and functional covariates.

SUPPLEMENTARY MATERIAL

Supplementary Material at the end of the document provides additional technical details referred to in the main paper, including the proof of Theorem 1. Supplementary Material also presents additional simulation examples, including a set of simulation experiments with a “linear” \( A-(X, Z) \) interaction effect scenario.

R-package: R-package famTEMsel (Functional Additive Models for Treatment Effect-Modifier Selection) contains R-codes to perform the methods proposed in the article, and is publicly available on GitHub (syhyunpark/famTEMsel).

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Conflict of interest

None declared.
References


