

Average treatment effect estimation in observational studies with functional covariates

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Functional data analysis is an important area in modern statistics and has been successfully applied in many fields. Although many scientific studies aim to find causations, a predominant majority of functional data analysis approaches can only reveal correlations. In this paper, average treatment effect estimation is studied for observational data with functional covariates. This paper generalizes various state-of-art propensity score estimation methods for multivariate data to functional data. The resulting average treatment effect estimators via propensity score weighting are numerically evaluated by a simulation study and applied to a real-world dataset to study the causal effect of duloxetine on the pain relief of chronic knee osteoarthritis patients.

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1. INTRODUCTION

Functional data analysis (FDA) has become increasingly important in modern statistics and has been successfully applied in a variety of scientific fields. Apart from books on general introductions to FDA (e.g., Bosq, 2000; Ramsay and Silverman, 2005; Ferraty and Vieu, 2006; Horváth and Kokoszka, 2012; Hsing and Eubank, 2015; Kokoszka and Reimherr, 2017), recent advances of FDA, including innovative methodologies, profound theories, efficient algorithms, and successful applications, have been illustrated by numerous survey papers (e.g., Guo, 2004; Müller, 2008; Delicado et al., 2010; Geenens, 2011; Hörmann and Kokoszka, 2012; Cuevas, 2014; Marron and Alonso, 2014; Shang, 2014; Wang, Chiou and Müller, 2016; Chen et al., 2017; Nagy, 2017; Vieu, 2018; Kokoszka and Reimherr, 2019).

A majority of FDA methods can only reveal correlations primarily via either functional regression models (for reviews see e.g., Morris, 2015; Greven and Scheipl, 2017; Paganoni and Sangalli, 2017; Reiss et al., 2017) or correlation measures (e.g., Leurgans, Moyeed and Silverman, 1993; Dubin

and Müller, 2005; Cupidon et al., 2008; Eubank and Hsing, 2008; Lian, 2014; Shin and Lee, 2015; Zhou, Lin and Wang, 2018). However, FDA methods for causal inference is underdeveloped despite the importance of causation in many scientific studies. Among very few exceptions, almost all of them focus on randomized clinical trials (e.g., Lindquist, 2012; McKeague and Qian, 2014; Ciarleglio et al., 2015, 2018; Zhao et al., 2018; Zhao and Luo, 2019). In classical causal inference for observational studies where multivariate data are of primary interest, the propensity score (Rosenbaum and Rubin, 1983) plays an important role and has been widely applied in epidemiology and political science among others. Despite its popularity, its use in FDA to study causations in observational studies is nearly void.

The main contribution of this paper is to introduce and adapt various state-of-art propensity score methods to observational functional data. We consider the scenario where the treatment is binary and at least one covariate is functional. We generalize the definition of the propensity score to functional data, and study two types of propensity score estimations. The propensity score is estimated by either directly fitting a functional regression model or balancing appropriate functions of the covariates. This paper in particular focuses on propensity score weighting (e.g., Rosenbaum, 1987; Robins, Hernán and Brumback, 2000; Hirano, Imbens and Ridder, 2003), although the propensity score may be used to adjust for confounding through other means, e.g., matching (e.g., Rosenbaum and Rubin, 1985; Rosenbaum, 1989; Abadie and Imbens, 2006) and subclassification (e.g., Rosenbaum and Rubin, 1984; Rosenbaum, 1991; Hansen, 2004). A systematic comparison of two popular propensity-score-weighted average treatment effect estimators is provided in both a simulation study and a real data application.

The rest of the paper proceeds as follows. Section 2 provides the problem setup and generalizes the classical definition of the propensity score to functional data where the treatment is binary and one covariate is functional. Section 3 introduces two types of propensity score estimations via direct modeling and covariate balancing respectively and two widely used average treatment effect estimators via propensity score weighting. The two average treatment effect estimators based on a variety of estimated propensity score weights are comprehensively compared in a simulation study in Section 4. They are also applied in a real data analysis in Section 5 to study the causal effect of duloxetine on the pain

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relief of chronic knee osteoarthritis patients. Discussion in Section 6 concludes the paper.

2. FRAMEWORK

Suppose that Y is a continuous outcome, T is a binary treatment variable which equals either 0 (control) or 1 (treatment), \mathbf{W} is a multivariate covariate, and $X(\cdot)$ is a functional covariate defined on a compact domain \mathcal{T} . Suppose that $E \int_{\mathcal{T}} \{X(t)\}^2 dt < \infty$ and $X(\cdot)$ is smooth, e.g., continuous or twice-differentiable. Without loss of generality $E(\mathbf{W}) = \mathbf{0}$, $\mathcal{T} = [0, 1]$ and $E\{X(t)\} = 0$ for all $t \in [0, 1]$.

Let $Y(1)$ and $Y(0)$ represent the potential values of Y when $T = 1$ and 0 respectively. In practice $Y = TY(1) + (1 - T)Y(0)$ is observable but $Y(1)$ and $Y(0)$ are not both observable. Based on $\{(Y_i, T_i, \mathbf{W}_i, \{X_i(t) : t \in [0, 1]\}) : i = 1, \dots, n\}$, which are independently and identically distributed (i.i.d.) copies of $(Y, T, \mathbf{W}, \{X(t) : t \in [0, 1]\})$, we aim to estimate the average treatment effect $\tau = E\{Y(1) - Y(0)\}$.

We assume that each $X_i(\cdot)$ is fully observed, but the methods below are also applicable for densely measured $X_i(\cdot)$ since its entire trajectory can be accurately recovered by smoothing (e.g., Zhang and Chen, 2007). In this paper we only consider low-dimensional \mathbf{W}_i . The handling of high-dimensional multivariate covariates is beyond the scope of this paper but is a promising topic for future research (e.g., Belloni, Chernozhukov and Hansen, 2014; Farrell, 2015; Belloni et al., 2017; Chernozhukov et al., 2018; Ning, Peng and Imai, 2018).

Similar to its classical counterpart (e.g., Rosenbaum and Rubin, 1983; Robins, Hernán and Brumback, 2000), the propensity score is defined by

$$(1) \quad p(\mathbf{W}_i, X_i) = P(T_i = 1 \mid \mathbf{W}_i, X_i(\cdot)).$$

In this paper we make the following two assumptions:

Assumption 1.

$$T_i \perp (Y_i(0), Y_i(1)) \mid (\mathbf{W}_i, X_i(\cdot)),$$

where “ \perp ” represents independence.

Assumption 2. The propensity score satisfies

$$0 < P(T_i = 1 \mid \mathbf{W}_i = \mathbf{w}, X_i(\cdot) = x(\cdot)) < 1,$$

for all vectors \mathbf{w} and all functions $x(\cdot)$ defined on $[0, 1]$ such that $\int_0^1 \{x(t)\}^2 dt < \infty$.

Assumptions 1 and 2 are straightforward generalizations of the commonly used *strong ignorability* and *positivity* assumptions in classical causal inference respectively. Assumption 1 implies that there is no unmeasured covariate, while Assumption 2 essentially requires that every sample has a positive probability of receiving the treatment or being in the control group.

3. METHODOLOGY

In this section, we introduce various methods for propensity score estimation and two average treatment effect estimators via propensity score weighting.

3.1 Propensity score estimation

We propose two types of propensity score estimations, one via direct modeling and the other via covariate balancing. They will be introduced in Sections 3.1.1 and 3.1.2 respectively.

3.1.1 Direct modeling

To estimate the propensity score $p(\mathbf{W}_i, X_i)$, one may assume a parametric model for $p(\mathbf{W}_i, X_i)$ and fit it with an appropriate estimation procedure.

The simplest model might be the generalized functional partial linear model (GFPLM):

$$(2) \quad \text{logit}\{p(\mathbf{W}_i, X_i)\} = \alpha_0 + \alpha_1^\top \mathbf{W}_i + \int_0^1 \beta(t) X_i(t) dt,$$

where $\text{logit}(x) = \log\{x/(1-x)\}$ and the scalar α_0 , vector α_1 and function $\beta(\cdot)$ are unknown parameters to be estimated. Apparently the GFPLM is an extension of James (2002), Müller and Stadtmüller (2005) and Shin (2009).

Similar to fitting other functional regression models considered in the FDA literature, regularization for the functional coefficient β is needed to fit (2). Popular regularizations include the truncated basis function expansion (e.g., Cardot, Ferraty and Sarda, 1999; Ramsay and Silverman, 2005, Ch. 4), roughness penalization (e.g., Yuan and Cai, 2010) and their combinations (e.g., Cardot, Ferraty and Sarda, 2003; Ramsay and Silverman, 2005, Ch. 5). The most straightforward regularization is perhaps the first one above where the basis functions are obtained by functional principal component analysis (FPCA). Explicitly, the functional covariate may be approximated by $X_i(t) \approx \sum_{k=1}^L A_{ik} \phi_k(t)$ where $\phi_k(\cdot)$, $1 \leq k \leq L < \infty$, are eigenfunctions corresponding to the top L eigenvalues $\lambda_1 \geq \dots \geq \lambda_L > 0$ of the covariance function $\text{Cov}\{X(s), X(t)\}$, and $A_{ik} = \int_0^1 X_i(t) \phi_k(t) dt$, $1 \leq k \leq L$, are corresponding FPC scores. Thus

$$(3) \quad \text{logit}\{p(\mathbf{W}_i, X_i)\} \approx \alpha_0 + \alpha_1^\top \mathbf{W}_i + \sum_{k=1}^L \beta_k A_{ik},$$

where $\beta_k = \int_0^1 \beta(t) \phi_k(t) dt$, $1 \leq k \leq L$. The maximum likelihood method can be used to find the parameter estimates $(\hat{\alpha}_0, \hat{\alpha}_1, \hat{\beta}_1, \dots, \hat{\beta}_L)$ and thus the propensity score estimate $\hat{p}(\mathbf{W}_i, X_i)$.

Remark 1.

1. The terms $\phi_k(\cdot)$, λ_k , A_{ik} , $k \geq 1$ above are all population quantities. In practice one can only obtain their sample versions.

2. The aforementioned FPCA-regularized maximum likelihood method is also applicable to fit a GFPLM if X_i is a multidimensional functional covariate, i.e.,

$$\text{logit}\{p(\mathbf{W}_i, X_i)\} = \alpha_0 + \alpha_1^\top \mathbf{W}_i + \int \beta(\mathbf{u})X_i(\mathbf{u}) \, d\mathbf{u},$$

where \mathbf{u} is a generic and multidimensional index for X_i . With the FPC scores obtained by FPCA, this multidimensional GFPLM can also be approximated by (3) and fitted by the maximum likelihood method.

3. Following the suggestion by Rubin (2007) that the propensity score estimation is conducted without access to outcome data, the number of FPC scores L , a tuning parameter, can be determined by various means when estimating the propensity score, including the fraction of variation explained (e.g., 95% or 99%), cross-validation, the Akaike information criterion (AIC), etc.

In addition to the GFPLM, one may fit other propensity score models, such as the functional generalized additive model (FGAM, e.g., Müller, Wu and Yao, 2013; McLean et al., 2014):

$$(4) \quad \text{logit}\{p(\mathbf{W}_i, X_i)\} = \alpha_0 + \alpha_1^\top \mathbf{W}_i + \int_0^1 \eta(t, X_i(t)) \, dt,$$

where the unknown parameters are α_0 , a scalar, α_1 , a vector, and $\eta(\cdot, \cdot)$, a bivariate function. To fit (4), one may apply the maximum likelihood method after approximating $\eta(\cdot, \cdot)$ by a set of tensor products of B-spline basis functions.

3.1.2 Covariate balancing

In the classical literature on causal inference, it is well known that parametric methods for propensity score estimation may suffer from model misspecification substantially (e.g., Smith and Todd, 2005; Kang and Schafer, 2007). Recently covariate balancing methods, which aim to mimic randomization, have been proposed as important alternatives (e.g., Qin and Zhang, 2007; Hainmueller, 2012; Imai and Ratkovic, 2014; Zubizarreta, 2015; Li, Morgan and Zaslavsky, 2018; Wong and Chan, 2018; Zhao, 2019). To the best of our knowledge, all existing covariate balancing methods so far are developed to handle multivariate covariates and cannot be directly used for functional covariates.

One way of balancing both multivariate covariates \mathbf{W}_i and functional covariate X_i is to generalize the covariate balancing propensity score (CBPS) method (Imai and Ratkovic, 2014) by considering the following functional covariate balancing equation:

$$(5) \quad \frac{1}{n} \sum_{i=1}^n \left\{ \frac{T_i}{p(\mathbf{W}_i, X_i)} - \frac{(1-T_i)}{1-p(\mathbf{W}_i, X_i)} \right\} \mathbf{h}(\mathbf{W}_i, X_i) = \mathbf{0},$$

where a parametric model is assumed for the propensity score $p(\mathbf{W}_i, X_i)$ and $\mathbf{h}(\mathbf{W}_i, X_i)$ is a user-defined vector-valued function to reflect how \mathbf{W}_i and X_i are balanced.

To solve (5), we propose to substitute the functional covariate X_i by a multivariate covariate. For example, by FPCA as in Section 3.1.1, the functional covariate $X_i(\cdot)$ can be approximated by $X_i(t) \approx \sum_{k=1}^L A_{ik} \phi_k(t)$ with a proper integer L such that $\mathbf{A}_i = (A_{i1}, \dots, A_{iL})^\top$ possesses a majority of the information of X_i . Thus \mathbf{A}_i may be used as a substitute of X_i and we may replace $p(\mathbf{W}_i, X_i)$ and $\mathbf{h}(\mathbf{W}_i, X_i)$ in (5) by the substitute propensity score

$$(6) \quad p(\mathbf{C}_i) = P(T_i = 1 \mid \mathbf{C}_i),$$

and another user-defined vector-valued function $\mathbf{h}(\mathbf{C}_i)$ respectively, where $\mathbf{C}_i = (\mathbf{W}_i^\top, \mathbf{A}_i^\top)^\top$. Obviously if $X(\cdot)$ is of finite rank in terms of its spectral decomposition, i.e., FPCA, the substitute propensity score $p(\mathbf{C}_i)$ is equivalent to $p(\mathbf{W}_i, X_i)$ when L is chosen to be the rank of $X(\cdot)$. Then it suffices to solve

$$(7) \quad \frac{1}{n} \sum_{i=1}^n \left\{ \frac{T_i}{p(\mathbf{C}_i)} - \frac{(1-T_i)}{1-p(\mathbf{C}_i)} \right\} \mathbf{h}(\mathbf{C}_i) = \mathbf{0},$$

which is exactly the covariate balancing equation for multivariate covariates (Imai and Ratkovic, 2014).

To solve (7), one may assume a logistic model for $p(\mathbf{C}_i)$:

$$(8) \quad \text{logit}\{p(\mathbf{C}_i)\} = \gamma_0 + \gamma_1^\top \mathbf{C}_i,$$

where γ_0 and γ_1 are unknown parameters to be estimated, which is equivalent to the approximate GFPLM in (3). One also needs to specify $\mathbf{h}(\mathbf{C}_i)$ to reflect how \mathbf{C}_i are balanced. For example, one may define $\mathbf{h}(\mathbf{C}_i) = \mathbf{C}_i$ to balance the first moment of \mathbf{C}_i . Alternatively to balance both the first and second moments of \mathbf{C}_i , one may use $\mathbf{h}(\mathbf{C}_i) = (\mathbf{C}_i^\top, (\mathbf{C}_i^2)^\top)^\top$ where \mathbf{C}_i^2 contains the entry-wise square of \mathbf{C}_i . Then we let $\hat{p}(\mathbf{W}_i, X_i) = \hat{p}(\mathbf{C}_i)$ obtained in (7).

3.2 Average treatment effect estimation

To estimate the average treatment effect $\tau = E\{Y(1) - Y(0)\}$, a variety of estimators via propensity score weighting have been proposed, such as the Horvitz-Thompson estimator (Horvitz and Thompson, 1952), the inverse propensity score weighting estimator (Hirano, Imbens and Ridder, 2003), the weighted least squares regression estimator (Robins, Hernán and Brumback, 2000; Freedman and Berk, 2008), and the doubly robust estimator (Robins, Rotnitzky and Zhao, 1994) among others.

In the simulation experiments and real data application below, we will consider two representative average treatment effect estimators, the Horvitz-Thompson (HT) estimator and Hájek estimator, to numerically evaluate and compare the propensity score estimation methods in Section 3.1.

Explicitly, for each propensity score estimate $\hat{p}_i = \hat{p}(\mathbf{W}_i, X_i)$ obtained by either direct modeling or covariate balancing approach, the HT and Hájek estimators are re-

spectively defined by

$$\hat{\tau}_{\text{HT}} = \frac{1}{n} \sum_{i=1}^n \left\{ \frac{T_i Y_i}{\hat{p}_i} - \frac{(1-T_i) Y_i}{1-\hat{p}_i} \right\}, \quad \text{and}$$

$$\hat{\tau}_{\text{Hájek}} = \frac{\sum_{i=1}^n T_i Y_i / \hat{p}_i}{\sum_{i=1}^n T_i / \hat{p}_i} - \frac{\sum_{i=1}^n (1-T_i) Y_i / (1-\hat{p}_i)}{\sum_{i=1}^n (1-T_i) / (1-\hat{p}_i)}.$$

Apparently the Hájek estimator, which normalizes the HT estimator, is a special inverse propensity score weighting estimator.

4. SIMULATION

In this section we present a simulation study to evaluate and compare a few propensity score estimation methods in terms of the performances of their resulting average treatment effect estimations.

We had 1,000 simulation runs where we generated independent subjects with sample size $n = 200$ and 500 respectively. For the i th subject, Z_{i1}, \dots, Z_{i6} were i.i.d. sampled from the standard normal distribution. The multivariate covariate $\mathbf{W}_i = (W_{i1}, W_{i2}, W_{i3})^\top$ was generated by $W_{i1} = Z_{i1} + 2Z_{i2}$, $W_{i2} = Z_{i2}^2 - Z_{i3}^2$, $W_{i3} = \exp(Z_{i3}) - \exp(1/2)$. The functional covariate was generated by $X_i(t) = \sum_{k=1}^6 A_{ik} \phi_k(t)$, $t \in [0, 1]$ where $A_{ik} = 2Z_{ik}/k$, $k = 1, \dots, 6$, and $\phi_{2k-1}(t) = \sqrt{2} \cos(2\pi kt)$, $\phi_{2k}(t) = \sqrt{2} \sin(2\pi kt)$, $k = 1, 2, 3$. Note that $E(\mathbf{W}_i) = \mathbf{0}$ and $E\{X_i(t)\} = 0$, $t \in [0, 1]$.

We generated the treatment T_i using the three propensity score models (PSMs) for $p(\mathbf{W}_i, X_i)$ as follows.

1. PSM 1: The treatment T_i follows a Bernoulli distribution with the probability

$$p(\mathbf{W}_i, X_i) = \frac{\exp\{\alpha^\top \mathbf{W}_i + \int_0^1 \beta_0(t) X_i(t) dt\}}{1 + \exp\{\alpha^\top \mathbf{W}_i + \int_0^1 \beta_0(t) X_i(t) dt\}},$$

where $\alpha = (-1, 0.5, -0.1)^\top$ and $\beta_0(t) = 2\phi_1(t) + 0.5\phi_2(t) + 0.5\phi_3(t) + \phi_4(t)$.

2. PSM 2: The treatment T_i follows a Bernoulli distribution with the probability

$$p(\mathbf{W}_i, X_i) = \frac{\exp\{\alpha^\top \mathbf{W}_i + \int_0^1 \eta_0(t, X_i(t)) dt\}}{1 + \exp\{\alpha^\top \mathbf{W}_i + \int_0^1 \eta_0(t, X_i(t)) dt\}},$$

where $\alpha = (-1, 0.5, -0.1)^\top$ and $\eta_0(t, x) = -0.5 + \exp[-\{(t-0.5)/0.3\}^2 - (x/5)^2]$.

3. PSM 3: The treatment T_i follows a Bernoulli distribution with the probability

$$p(\mathbf{W}_i, X_i) = \frac{\exp(-Z_{i1} + 0.5Z_{i2} - 0.25Z_{i3} - 0.1Z_{i4})}{1 + \exp(-Z_{i1} + 0.5Z_{i2} - 0.25Z_{i3} - 0.1Z_{i4})}.$$

Obviously PSM 1 is a GFPLM as in (2) and PSM 2 is an FGAM as in (4).

We generated the outcome Y_i based on the following two outcome models (OMs).

1. OM 1: $Y_i = 200 + 10T_i + (1.5T_i - 0.5)(27.4Z_{i1} + 13.7Z_{i2} + 13.7Z_{i3} + 13.7Z_{i4}) + e_i$ where e_i is generated from the standard normal distribution independently of Z_{i1}, \dots, Z_{i6} . The true average treatment effect is $\tau = 10$.
2. OM 2: $Y_i = Z_{i1}Z_{i2}^3Z_{i3}^2Z_{i4} + e_i$ where e_i follows the standard normal distribution which is independent of Z_{i1}, \dots, Z_{i6} . The true average treatment effect is $\tau = 0$.

We compared the performances of five propensity score estimation methods in the simulation study, denoted by GFPLM, FGAM, CBPS1, CBPS2 and KBCB respectively. The first two methods are via direct modeling while the last three are via covariate balancing. By the FPCA approximation and maximum likelihood method as in Section 3.1.1, GFPLM fits (2) to estimate the propensity score. The number of FPC scores L was selected as the smallest integer such that the fraction of variation explained by the top L FPC scores is at least 95%. FGAM obtains the propensity score estimate by fitting (4) directly, where tensor products of seven cubic B-spline basis functions were used to approximate $\eta(\ast, \cdot)$ before the maximum likelihood method was applied. Apparently GFPLM is subject to model misspecification when data are generated from PSM 2, while both GFPLM and FGAM fit incorrect models when data are generated from PSM 3.

Table 1. Bias and RMSE values for the HT and Hájek estimates based on five propensity score estimation methods for PSM 1 and OM 1. The percentages beside a propensity score estimation method, if any, refer to the proportions of simulation runs used to calculate the bias and RMSE values for the HT and Hájek estimates respectively, and “-” denotes 100%. All simulation runs were used for a propensity score estimation method if no such percentages are given

	HT		Hájek	
	Bias	RMSE	Bias	RMSE
n = 200				
GFPLM (99.9%, -)	4.82	100.17	2.28	11.28
FGAM (99.9%, -)	8.44	17.12	9.58	10.47
CBPS1	2.90	45.87	3.00	9.15
CBPS2 (99.8%, -)	1.77	28.58	3.75	7.29
KBCB	1.69	4.43	2.08	4.58
n = 500				
GFPLM	1.78	75.83	1.65	10.07
FGAM	9.02	11.98	9.56	9.86
CBPS1	2.47	39.25	2.27	7.58
CBPS2 (99.8%, -)	1.98	21.26	2.73	5.74
KBCB	0.79	2.56	0.96	2.62

Both CBPS1 and CBPS2 are based on the CBPS method as introduced in Section 3.1.2. The multivariate substitute $\mathbf{A}_i = (A_{i1}, \dots, A_{iL})^\top$ for the functional covariate X_i

was obtained by FPCA which explains at least 95% of the variation of X_i , and (8) was assumed for the substitute propensity score $p(\mathbf{C}_i)$. CBPS1 balanced the first moments of \mathbf{C}_i while CBPS2 balanced both first and second moments of \mathbf{C}_i , and they were performed using the *CBPS* R package. KBCB is another covariate functional balancing method recently proposed by Wong and Chan (2018), which controls the balance of \mathbf{C}_i over a reproducing kernel Hilbert space (RKHS). KBCB was implemented using the *ATE.ncb* R package downloaded from <https://github.com/raymondkw/A TE.ncb> where the RKHS was chosen as the second-order Sobolev space.

With the propensity score estimate obtained by each of the five methods above, we achieved the HT and Hájek estimates for the average treatment effect, i.e., $\hat{\tau}_{HT}$ and $\hat{\tau}_{Hájek}$ as in Section 3.2. Note that KBCB does not give an estimate for the substitute propensity score $p(\mathbf{C}_i)$. Instead it provides estimates for both $T_i/p(\mathbf{C}_i)$ and $(1 - T_i)/\{1 - p(\mathbf{C}_i)\}$, but they suffice to obtain both HT and Hájek estimates.

Table 2. The same as Table 1 except for PSM 2 and OM 1

	HT		Hájek	
	Bias	RMSE	Bias	RMSE
n = 200				
GFPLM (99.9%, -)	1.26	57.49	-0.68	8.20
FGAM (99.8%, -)	-1.05	59.70	-0.93	8.22
CBPS1	-1.22	29.65	-1.44	6.48
CBPS2 (99.9%, -)	-4.19	22.22	-1.81	5.62
KBCB	-1.03	4.11	-0.49	3.95
n = 500				
GFPLM	-2.46	40.28	-0.87	6.00
FGAM	-3.23	43.39	-0.74	5.95
CBPS1	-0.38	22.52	-1.14	4.94
CBPS2	-0.98	15.31	-0.98	3.83
KBCB	-0.35	2.53	-0.17	2.51

The bias and root mean squared error (RMSE) values for the HT and Hájek estimates are given in Tables 1–6. For each average treatment effect estimate based on any propensity score estimation method, we removed the simulation runs of which average treatment effect estimates are ten standard deviations away from the mean, and used the remaining simulated data to calculate bias and RMSE values.

The six tables show that for any propensity score estimation methods but KBCB, a larger sample size generally improves the average treatment effect estimation accuracy measured by RMSE, but it unnecessarily improves the bias. With respect to RMSE, the three covariate balancing methods are generally better than the two directly modeling methods, although FGAM occasionally outperforms the two CBPS methods (see Tables 1 and 3). Between the two direct modeling methods, FGAM almost always performs better than GFPLM in terms of RMSE even when the latter correctly specifies PSM 1, but the former is often worse in terms

of bias. The results for the two CBPS methods indicate that balancing additional covariate moments can typically improve average treatment effect estimation. Among all five propensity score estimation methods, KBCB performs overall the best in terms of both bias and RMSE with the only exceptions for PSM 1 and OM 2 (see Table 4) and for PSM 2 and OM 2 with $n = 200$ (see Table 5).

Table 3. The same as Table 1 except for PSM 3 and OM 1

	HT		Hájek	
	Bias	RMSE	Bias	RMSE
n = 200				
GFPLM (99.9%, -)	0.15	22.19	-0.15	5.66
FGAM (99.9%, -)	-4.22	9.16	-4.37	5.96
CBPS1	-1.83	13.02	-1.14	4.63
CBPS2 (99.8%, -)	-1.69	14.80	-1.11	4.83
KBCB	-0.37	3.92	-0.27	3.90
n=500				
GFPLM	-0.04	12.51	-0.09	3.45
FGAM	-4.03	5.84	-4.37	5.05
CBPS1	-0.63	9.12	-0.70	3.06
CBPS2	-1.27	8.40	-0.81	2.91
KBCB	-0.07	2.46	-0.05	2.46

Table 4. The same as Table 1 except for PSM 1 and OM 2. All bias and RMSE values are given in the unit of 10^{-1}

10^{-1}	HT		Hájek	
	Bias	RMSE	Bias	RMSE
n = 200				
GFPLM (99.9%, 99.8%)	0.05	18.26	0.27	12.48
FGAM (99.9%, 99.9%)	3.28	11.83	3.29	11.75
CBPS1 (99.9%, 99.9%)	0.59	9.74	0.65	10.71
CBPS2 (99.8%, -)	0.99	7.92	1.04	8.26
KBCB	0.95	8.70	0.95	8.71
n = 500				
GFPLM (99.8%, 99.9%)	-0.07	11.59	-0.04	10.76
FGAM (99.8%, 99.8%)	4.01	10.40	4.02	10.43
CBPS1 (99.9%, 99.9%)	0.11	8.49	0.22	8.63
CBPS2 (99.8%, 99.9%)	0.51	6.74	0.64	6.58
KBCB	1.04	6.71	1.04	6.71

In terms of computational stability, all propensity score estimation methods perform satisfactorily, but KBCB is the most robust method since it never produces outlying average treatment effect estimates. CBPS1 is slightly less likely to produce extreme average treatment effect estimates than CBPS2. This is somewhat unsurprising since the latter additionally balances the second moments of covariates. Compare to the HT estimates, the Hájek estimates generally have fewer outlying values and smaller RMSE values for all propensity score estimation methods but KBCB. This observation demonstrates the benefit of inverse propensity score weighting.

Table 5. The same as Table 4 except for PSM 2 and OM 2

10^{-1}	HT		Hájek	
	Bias	RMSE	Bias	RMSE
n = 200				
GFPLM (99.8%, 99.8%)	-0.54	10.24	-0.52	9.29
FGAM (99.7%, 99.9%)	-0.21	10.17	-0.24	9.91
CBPS1	-0.50	8.43	-0.51	8.87
CBPS2 (99.9%, -)	-0.35	5.95	-0.34	6.70
KBCB	-0.66	7.13	-0.66	7.14
n = 500				
GFPLM (99.8%, 99.9%)	-0.53	8.46	-0.54	8.25
FGAM (99.8%, 99.9%)	-0.54	9.70	-0.55	8.96
CBPS1	-0.62	6.86	-0.67	7.17
CBPS2 (99.9%, 99.9%)	-0.55	6.24	-0.60	6.35
KBCB	-0.60	5.12	-0.60	5.12

Table 6. The same as Table 4 except for PSM 3 and OM 2

10^{-1}	HT		Hájek	
	Bias	RMSE	Bias	RMSE
n = 200				
GFPLM (99.9%, 99.9%)	-0.43	10.91	-0.39	10.49
FGAM (99.8%, 99.8%)	-0.29	10.19	-0.30	10.31
CBPS1	-0.35	8.43	-0.37	8.75
CBPS2 (99.9%, 99.9%)	-0.37	10.43	-0.31	8.94
KBCB	-0.12	7.10	-0.12	7.11
n = 500				
GFPLM	-0.92	7.44	-0.90	7.35
FGAM	-1.12	7.91	-1.13	7.92
CBPS1	-0.70	6.29	-0.72	6.42
CBPS2 (99.9%, 99.9%)	-0.59	5.89	-0.60	6.04
KBCB	-0.30	4.88	-0.30	4.88

5. DATA APPLICATION

We applied three propensity score weighting methods introduced above to a pain relief dataset (Tétreault et al., 2016), which was downloaded from OpenNeuro (<https://openneuro.org/datasets/ds000208/versions/1.0.0>). The dataset consists of 56 chronic knee osteoarthritis pain patients in two separate clinical trials. The first trial was single-blind where all 17 subjects took placebo pills, while the second trial was double-blind where 39 subjects were randomized to take either duloxetine (30/60mg QD) or placebo. With the observational data obtained by combining the two trials, we aimed to estimate the average treatment effect of duloxetine compared to placebos on chronic knee osteoarthritis pain relief. The pain relief was measured by the visual analog scale (VAS) score, and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, and we studied the average duloxetine effect on both measures separately.

A subject is considered to receive the treatment if he/she took duloxetine; those who took placebo pills are regarded to be in the control group. The multivariate covariates \mathbf{W}_i

are age and gender. Each subject also underwent pretreatment brain scans, via both anatomical magnetic resonance imaging (MRI) and resting state functional MRI (rsfMRI). Using the FMRIB Software Library v6.0 (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki>), we preprocessed the rsfMRI scans of each subject, registered them to template MNI152 through his/her anatomical MRI scan, and then downsampled each registered rsfMRI scan to the spatial resolution of voxel size 4mm^3 . Finally, inspired by Tétreault et al. (2016), we obtained a connectivity network/matrix for each subject which contains the Pearson correlation of the brain signals from every pair of voxels, and we treated this network as a functional covariate X_i . Since each voxel is indexed by a three-dimensional spatial coordinate, the functional covariate is six-dimensional.

Table 7. The HT and Hájek estimates for the average treatment effect of duloxetine on pain relief measured by the VAS score. Bootstrap standard errors (SE) and 95% bootstrap percentile confidence intervals were obtained by 1,000 bootstrap samples

	$\hat{\tau}$	SE	[2.5%, 97.5%]
HT			
GFPLM	-5.99	11.62	[-22.77, 6.49]
CBPS	-5.26	4.12	[-12.21, 3.17]
KBCB	0.39	3.43	[-6.29, 7.21]
Hájek			
GFPLM	-0.52	4.27	[-9.04, 7.58]
CBPS	-0.23	3.64	[-6.87, 7.18]
KBCB	0.28	3.37	[-6.14, 7.17]

Table 8. The same as Table 7 except for the WOMAC score

	$\hat{\tau}$	SE	[2.5%, 97.5%]
HT			
GFPLM	-8.41	11.23	[-26.25, 5.35]
CBPS	-7.63	4.79	[-16.22, 2.08]
KBCB	1.16	4.18	[-7.54, 8.45]
Hájek			
GFPLM	-3.18	4.72	[-11.66, 6.50]
CBPS	-2.85	4.31	[-10.56, 6.52]
KBCB	1.05	4.17	[-7.76, 8.50]

We considered three methods for propensity score estimation, GFPLM, CBPS and KBCB. GFPLM refers to the direct modeling method where the propensity score is estimated by fitting the model in Remark 1.2. The top L FPC scores of X_i , denoted by $\mathbf{A}_i = (A_{i1}, \dots, A_{iL})^\top$, were used in the approximate model (3) for GFPLM. They were also used as the multivariate substitute of X_i to define the substitute propensity score as in (6) to perform CBPS and KBCB. To apply CBPS, (8) was assumed for the substitute propensity score, and only the first moments of $\mathbf{C}_i = (\mathbf{W}_i^\top, \mathbf{A}_i^\top)^\top$ were balanced due to a small sample size. We used $L = 4$ in all

three methods, which was selected as the smallest integer such that the corresponding AIC value no longer decreases when the top FPC scores are sequentially added to (3).

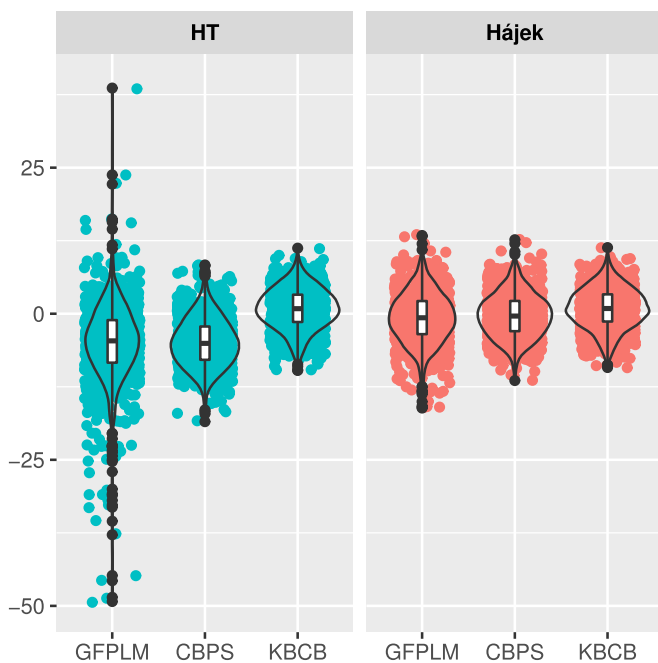


Figure 1. Violin plots for the 1,000 bootstrap HT and Hájek estimates for the average treatment effect of duloxetine on the VAS score.

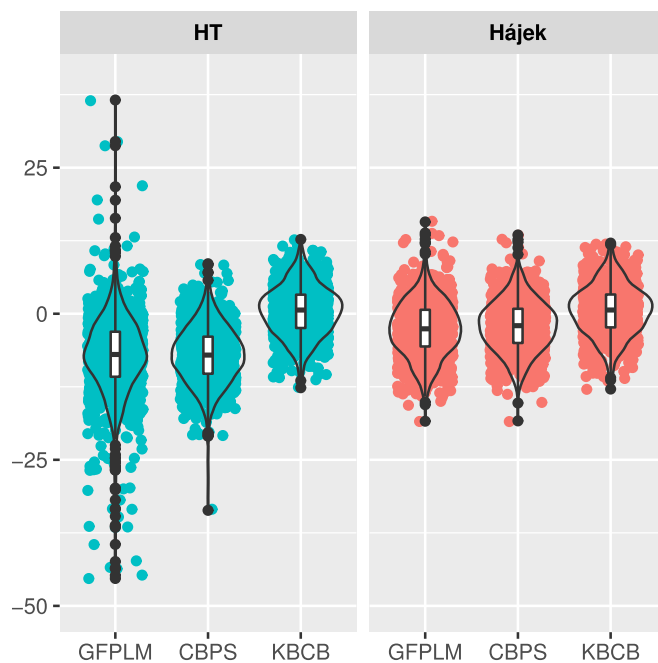


Figure 2. The same as Figure 1 except for the WOMAC score.

For each propensity score estimation and each pain relief measure, i.e., VAS or WOMAC score, we obtained its corresponding HT and Hájek estimates for the average treatment effect of duloxetine. We used 1,000 bootstrap samples to provide uncertainty measures, including standard errors and confidence intervals.

Tables 7 and 8 provide the HT and Hájek estimates, bootstrap standard errors and 95% bootstrap percentile confidence intervals for the average treatment effect of duloxetine on VAS and WOMAC scores respectively. They indicate no significant treatment effect of duloxetine over placebo pills on pain relief. This is consistent with Tétreault et al. (2016), although their conclusion was made from a double-blind clinical trial, i.e., the second trial, while we based our finding on an observational dataset. Explicitly, the 95% confidence intervals for the average treatment effect of duloxetine on VAS and WOMAC scores obtained from the double-blind trial are $[-8.402, 6.760]$ and $[-9.717, 8.832]$ respectively. Both confidence intervals are based on t statistics assuming normality of each treatment or control group and equal variances of the two groups, which are validated by the Shapiro-Wilk tests and F-tests respectively.

The 1,000 bootstrap HT and Hájek average treatment effect estimates are illustrated in Figures 1 and 2 for VAS and WOMAC scores respectively. Both figures show that the HT estimates based on GFPLM for propensity score estimation have a much larger variation than the two covariate balancing methods, but inverse propensity score weighting can substantially reduce their differences as revealed by the Hájek estimates. The median of the Hájek estimates is shifted towards zero compared to that of the HT estimates when the propensity score is estimated by either GFPLM or CBPS. The two average treatment effect estimates essentially show no difference for KBCB.

6. DISCUSSION

To the best of our knowledge, this paper has made the first attempt to study average treatment effect estimation via propensity score weighting for functional data in observational studies. The paper introduces both direct modeling and covariate balancing methods for propensity score estimation and systematically evaluates their performances via a simulation experiment and a real data application. The results confirm the benefits of both inverse propensity score weighting and covariate balancing methods as advocated for multivariate data.

The methods introduced in this paper for average treatment effect estimation only focus on the scenario where the outcome is a continuous scalar variable and there is only one functional covariate. However, with straightforward modifications, they may be generalized to handle multiple functional covariates and continuous functional outcomes.

The covariate balancing methods introduced above rely on a satisfactory multivariate substitute for the functional covariate, which requires the functional covariate to be ei-

ther fully observed or densely measured (e.g., Dauxois, Pousse and Romain, 1982; Hall and Hosseini-Nasab, 2006; Hall, Müller and Wang, 2006). A future research topic is to develop covariate balancing methods for sparsely measured functional covariates (e.g., James, Hastie and Sugar, 2000; Yao, Müller and Wang, 2005) or a unified approach for all types of functional covariates (e.g., Li and Hsing, 2010; Zhang and Wang, 2016; Liebl, 2019). Another interesting direction is to study non-truncation regularization methods, e.g., the roughness penalization, to solve covariate balancing equations with functional covariates.

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