On estimation in varying coefficient models for sparse and irregularly sampled functional data

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Abstract

In this paper, we study a smoothness regularization method for a varying coefficient model based on sparse and irregularly sampled functional data which is contaminated with some measurement errors. We estimate the one-dimensional covariance and cross-covariance functions of the underlying stochastic processes based on a reproducing kernel Hilbert space approach. We then obtain least squares estimates of the coefficient functions. Simulation studies demonstrate that the proposed method has good performance. We illustrate our method by an analysis of longitudinal primary biliary liver cirrhosis data.

Keywords: Functional data analysis, regularization, reproducing kernel Hilbert space, sparsity, varying coefficient model.

1 Introduction

Varying coefficient models are introduced by Hastie and Tibshirani (1993). They are an extension of classical linear regression models where the coefficients are smooth functions. They are used for modeling the dynamic impacts of the underlying covariates on the response. Varying coefficient models have been extensively studied in the literature. Various types of varying coefficient models have been studied and developed for longitudinal data, time series, high dimensional data and functional data. See, for example, Hoover et al. (1998), Kauermann and Tutz (1999), Wu and Chiang (2000), Chiang et al. (2001), Huang et al. (2004), Ramsay and Silverman (2005), Şentürk and Müller (2010), Zhu et al. (2012), Verhasselt (2014), Song et al. (2014), Klopp and Pensky (2015) and Lee and Mammen (2016) among others.

In this paper, we consider the following multiple varying coefficient model

$$Y(t) = \beta_0(t) + \sum_{p=1}^{d_1} \beta_p(t) X_p(t) + \sum_{q=1}^{d_2} \alpha_q(t) Z_q + \eta(t), \qquad t \in \mathcal{T}$$
 (1)

where Y(t) is the response process, $X_1(t), \ldots, X_{d_1}(t)$ are the predictor processes, Z_1, \ldots, Z_{d_2} are time-independent predictors, $\eta(t)$ is a noise process with zero mean and independent of the predictors, and $\beta_0(t)$, $\beta_1(t)$, ..., $\beta_{d_1}(t)$ and $\alpha_1(t)$, ..., $\alpha_{d_2}(t)$ are smoothed parameter functions. It is assumed that Y(t) and $X_1(t), \ldots, X_{d_1}(t)$ are square integrable and Z_1, \ldots, Z_{d_2} have finite second moments.

The aim of this article is estimating the parameter functions in the situation that the observations are sparse and irregular longitudinal data and combined with some measurement errors. Following Yao et al. (2005), we model this situation as follows. Let U_{ij} and V_{ij} denote the observations of the random functions X_i and Y_i respectively at the random times T_{ij} , contaminated with measurement errors ε_{pij} and ϵ_{ij} respectively, which are assumed to be independent and identically distributed with means zero and variances $\sigma_{X_p}^2$ and σ_Y^2 respectively, and independent of the random functions. We represent the observed data as

$$U_{pij} = X_{pi}(T_{ij}) + \varepsilon_{pij}, j = 1, ..., M_i; i = 1, ..., n,$$

$$V_{ij} = Y_i(T_{ij}) + \epsilon_{ij}, j = 1, ..., M_i; i = 1, ..., n.$$
(2)

Here M_i is a nonnegative integer-valued random variable that denotes the sampling frequency for *i*th trajectory.

For sparse noisy functional data, Şentürk and Müller (2010) studied model (1) with one functional predictor. They obtained a representation for the coefficient function based on one-dimensional covariance and cross-covariance functions of the predictor and response processes. They used local linear smoother method for their estimation procedures. Şentürk and Nguyen (2011) extended the approach of Şentürk and Müller (2010) to multiple predictors including both functional and non-functional predictors. Mostafaiy et al. (2016) considered one functional predictor. They proposed a reproducing kernel Hilbert space approach to estimate the coefficient function.

By taking expectation from the both sides of (1), we have

$$\beta_0(t) = \mu_Y(t) - \sum_{p=1}^{d_1} \beta_p(t) \mu_{X_p}(t) - \sum_{q=1}^{d_2} \alpha_q(t) \mu_{Z_q}, \qquad t \in \mathcal{T},$$
(3)

where $\mu_Y(t) = E[Y(t)]$, $\mu_{X_p}(t) = E[X_p(t)]$, $p = 1, ..., d_1$ and $\mu_{Z_q} = E[Z_q]$, $q = 1, ..., d_2$. Substituting equation (3) in (1) yields

$$Y(t) - \mu_Y(t) = \sum_{p=1}^{d_1} \beta_p(t) (X_p(t) - \mu_{X_p}(t)) + \sum_{q=1}^{d_2} \alpha_q(t) (Z_q - \mu_{Z_q}) + \eta(t), \qquad t \in \mathcal{T}$$
 (4)

By multiplying both sides of (4) by $X_p(t)$, $p = 1, ..., k_1$ and Z_q , $q = 1, ..., k_2$, and then taking expectations and writing the results in matrix form, we get

$$[\beta_1(t), \dots, \beta_{k_1}(t), \alpha_1(t), \dots, \alpha_{k_2}(t)]' = \Gamma_t^{-1} \gamma_t, \tag{5}$$

where

$$\Gamma_{t} = \begin{bmatrix}
C_{X_{1}X_{1}}(t) & \dots & C_{X_{1}X_{k_{1}}}(t) & C_{X_{1}Z_{1}}(t) & \dots & C_{X_{1}Z_{k_{2}}}(t) \\
\vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\
C_{X_{k_{1}}X_{1}}(t) & \dots & C_{X_{k_{1}}X_{k_{1}}}(t) & C_{X_{k_{1}}Z_{1}}(t) & \dots & C_{X_{k_{1}}Z_{k_{2}}}(t) \\
C_{Z_{1}X_{1}}(t) & \dots & C_{Z_{1}X_{k_{1}}}(t) & C_{Z_{1}Z_{1}} & \dots & C_{Z_{1}Z_{k_{2}}} \\
\vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\
C_{Z_{k_{2}}X_{1}}(t) & \dots & C_{Z_{k_{2}}X_{k_{1}}}(t) & C_{Z_{k_{2}}Z_{1}} & \dots & C_{Z_{k_{2}}Z_{k_{2}}}
\end{bmatrix},$$

and

$$\gamma_t = \begin{bmatrix} C_{YX_1}(t) & \dots & C_{YX_{k_1}}(t) & C_{YZ_1}(t) & \dots & C_{YZ_{k_2}}(t) \end{bmatrix}'$$

Here $C_{X_{p_1}X_{p_2}}(t) = \text{cov}(X_{p_1}(t), X_{p_2}(t))$, $C_{X_pZ_q}(t) = C_{Z_qX_p}(t) = \text{cov}(X_p(t), Z_q)$, $C_{Z_{q_1}Z_{q_2}} = \text{cov}(Z_{q_1}, Z_{q_2})$, $C_{YX_p}(t) = \text{cov}(Y(t), X_p(t))$ and $C_{YZ_q}(t) = \text{cov}(Y(t), Z_q)$. Based on the representation (5), we introduce an estimate of the parameter functions. To do this, we estimate every elements of Γ_t and γ_t . The scalar parameters of Γ_t can be easily estimated. To estimate the parameter functions of Γ_t and γ_t , we use a reproducing kernel Hilbert space (RKHS) framework. By assuming the sample paths of X_p s, $p = 1, \ldots, k_1$, and Y to be smooth such that they belong to some RKHSs, we show that the one-dimensional covariance and cross-covariance functions come from some RKHSs. Based on these results, we introduce some smoothness regularization methods to estimate these parameter functions. By simulation, we investigate the merits of the proposed method especially by comparing it to some other existing methods.

The paper is organized as follows. In Section 2, we review some basic properties of RKHS. In Section 3, we utilize a regularization method to estimate the one-dimensional covariance and cross-covariance functions and then provide estimates of the coefficient functions. Simulation studies in two cases (one predictor and multiple predictors) are provided in Section 4. In Section 5, we apply the method to longitudinal primary biliary liver cirrhosis data.

2 Reproducing kernel Hilbert spaces

The theory of RKHS plays a pivotal role in this paper. In this section, we present some fundamental concepts and basic facts of RKHS. The readers are referred to Aronszajn

(1950), Berlinet and Thomas-Agnan (2004) and Hsing and Eubank (2015) for more details.

DEFINITION 1. A symmetric, real-valued bivariate function K on $\mathcal{T} \times \mathcal{T}$ is nonnegative definite, denoted by $K \geq 0$, provided that

$$\sum_{i=1}^{N} \sum_{j=1}^{N} \alpha_i \alpha_j K(t_i, t_j) \ge 0,$$

for all $N \in \mathbb{N}$, $\alpha_1, \ldots, \alpha_N \in \mathbb{R}$, and $t_1, \ldots, t_N \in \mathcal{T}$. In other words, $K \geq 0$ provided that for every $N \in \mathbb{N}$ and distinct points, $\{t_1, \ldots, t_N\} \subseteq \mathcal{T}$, the matrix $\mathbf{K} := [K(t_i, t_j)]$ be a nonnegative definite matrix, that is $\mathbf{K} \geq 0$.

LEMMA 1. Let \mathcal{H} is a Hilbert space with inner product $\langle \cdot, \cdot \rangle_{\mathcal{H}}$ and $\phi : \mathcal{T} \longrightarrow \mathcal{H}$ is a function on \mathcal{T} . Then the function $K(s,t) := \langle \phi(s), \phi(t) \rangle_{\mathcal{H}}$ on $\mathcal{T} \times \mathcal{T}$ is nonnegative definite.

DEFINITION 2. For a Hilbert space \mathcal{H} with inner product $\langle \cdot, \cdot \rangle_{\mathcal{H}}$, a bivariate function K(s,t) for $s,t \in \mathcal{T}$ is called a reproducing kernel of \mathcal{H} if the following are satisfied:

- (i) For every $t \in \mathcal{T}$, $K(\cdot, t) \in \mathcal{H}$.
- (ii) For every $t \in \mathcal{T}$ and every $f \in \mathcal{H}$,

$$f(t) = \langle f, K(\cdot, t) \rangle_{\mathcal{H}}.$$
 (6)

Relation (6) is called the reproducing property of K.

DEFINITION 3. A Hilbert space \mathcal{H} of functions on \mathcal{T} is called an RKHS if there exist a reproducing kernel K of \mathcal{H} .

From now on, we denote a reproducing kernel Hilbert space \mathcal{H} with the reproducing kernel K by $\mathcal{H}(K)$ and the corresponding inner product and norm by $\langle \cdot, \cdot \rangle_{\mathcal{H}(K)}$ and $\|\cdot\|_{\mathcal{H}(K)}$, respectively.

By using properties (i) and (ii) in Definition 2, for any $N, N' \in \mathbb{N}$, $\alpha_1, \ldots, \alpha_N, \alpha'_1, \ldots, \alpha'_{N'} \in \mathbb{R}$ and $t_1, \ldots, t_N, t'_1, \ldots, t'_{N'} \in \mathcal{T}$, we have

$$\langle \sum_{i=1}^{N} \alpha_i K(\cdot, t_i), \sum_{j=1}^{N'} \alpha'_j K(\cdot, t'_j) \rangle_{\mathcal{H}(K)} = \sum_{i=1}^{N} \sum_{j=1}^{N'} \alpha_i \alpha'_j K(t_i, t'_j)$$
 (7)

The following proposition states the uniqueness of reproducing kernel K and RKHS $\mathcal{H}(K)$.

PROPOSITION 1. If K is a reproducing kernel of $\mathcal{H}(K)$ then K is nonnegative definite and unique. Conversely, if K is a nonnegative definite bivariate function on $\mathcal{T} \times \mathcal{T}$,

there exists a uniquely determined Hilbert space $\mathcal{H}(K)$ of functions on \mathcal{T} , admitting the reproducing kernel K.

In the next proposition, we give a condition which characterizes the function that belong to an RKHS.

PROPOSITION 2. A real-valued function f defined on \mathcal{T} belongs to the reproducing kernel Hilbert space $\mathcal{H}(K)$ if and only if there exists a constant C such that, $C^2K(s,t) - f(s)f(t)$ is a nonnegative definite function on $\mathcal{T} \times \mathcal{T}$, i.e. $C^2K(s,t) - f(s)f(t) \geq 0$.

Let $\mathcal{H}(K_1 \otimes K_2) := \mathcal{H}(K_1) \otimes \mathcal{H}(K_2)$ is the tensor product Hilbert space of $\mathcal{H}(K_1)$ and $\mathcal{H}(K_2)$, where $\mathcal{H}(K_1)$ and $\mathcal{H}(K_2)$ are two RKHSs of functions defined on \mathcal{T} with reproducing kernels K_1 and K_2 respectively. Consider the map $\phi: T \longrightarrow \mathcal{H}(K_1 \otimes K_2)$ defined by $\phi(t)(\cdot, *) = (K_1 \otimes K_2)((\cdot, *), (t, t))$. Then, for $s, t \in \mathcal{T}$,

$$K_1(s,t)K_2(s,t) = \langle K_1(\cdot,s), K_1(\cdot,t) \rangle_{\mathcal{H}(K_1)} \langle K_2(*,s), K_2(*,t) \rangle_{\mathcal{H}(K_2)}$$

$$= \langle (K_1 \otimes K_2)((\cdot,*), (s,s)), (K_1 \otimes K_2)((\cdot,*), (t,t)) \rangle_{\mathcal{H}(K_1 \otimes K_2)}$$

$$= \langle \phi(s), \phi(t) \rangle_{\mathcal{H}(K_1 \otimes K_2)}.$$

Therefore by Lemma 1, the pointwise product of two reproducing kernel K_1 and K_2 is nonnegative definite and so it is a reproducing kernel by Proposition 1. So we can construct the RKHS $\mathcal{H}(K_1K_2)$ uniquely. In particular, if K is reproducing kernel of $\mathcal{H}(K)$ then K^2 is reproducing kernel of $\mathcal{H}(K^2)$.

The following Theorem is fundamental for estimation procedures in the next section.

THEOREM 1. Suppose that X and Y are two stochastic processes such that the sample paths of X and Y, respectively, belong to $\mathcal{H}(K_1)$ and $\mathcal{H}(K_2)$ almost surely and $E\|X\|_{\mathcal{H}(K_1)}^2 < \infty$ and $E\|Y\|_{\mathcal{H}(K_2)}^2 < \infty$. Then

- (i) μ_X and μ_Y belong to $\mathcal{H}(K_1)$ and $\mathcal{H}(K_2)$ respectively.
- (ii) C_{XX} and C_{XY} belong to $\mathcal{H}(K_1^2)$ and $\mathcal{H}(K_1K_2)$ respectively.

The proof is based on the following Lemma.

LEMMA 2. Let \mathbf{A} and \mathbf{B} are two N dimensional matrices and $\mathbf{A} \circ \mathbf{B}$ denotes the Hadamard product of \mathbf{A} and \mathbf{B} .

- (i) If $\mathbf{A} \geq 0$ and $\mathbf{B} \geq 0$ then $\mathbf{A} \circ \mathbf{B} \geq 0$.
- (ii) If $\mathbf{A} \geq \mathbf{B} \geq 0$ then $\mathbf{A} \circ \mathbf{A} \geq \mathbf{B} \circ \mathbf{B}$.

PROOF (i) Let $\mathbf{A} = [a_{ij}]$, $\mathbf{B} = [b_{ij}]$ and $T = \{1, ..., N\}$. Suppose that f_1 and f_2 are two functions on $T \times T$ such that $f_1(i,j) = a_{ij}$ and $f_2(i,j) = b_{ij}$, $(i,j) \in T \times T$. Then f_1 and f_2 are nonnegative definite functions. Because the pointwise product of two nonnegative definite functions is again nonnegative definite, we have $\mathbf{A} \circ \mathbf{B} \geq 0$.

(ii) We have $\mathbf{A} + \mathbf{B} \ge 0$ and $\mathbf{A} - \mathbf{B} \ge 0$. By part (i) of this Lemma, $(\mathbf{A} + \mathbf{B}) \circ (\mathbf{A} - \mathbf{B}) \ge 0$ and so $\mathbf{A} \circ \mathbf{A} - \mathbf{B} \circ \mathbf{B} = (\mathbf{A} + \mathbf{B}) \circ (\mathbf{A} - \mathbf{B}) \ge 0$ or $\mathbf{A} \circ \mathbf{A} \ge \mathbf{B} \circ \mathbf{B}$. \square PROOF of THEOREM 1. By Jensen's inequality, we have

$$\|\mu_X\|_{\mathcal{H}(K_1)}^2 \le E\|X\|_{\mathcal{H}(K_1)}^2 < \infty$$
 and $\|\mu_Y\|_{\mathcal{H}(K_2)}^2 \le E\|Y\|_{\mathcal{H}(K_2)}^2 < \infty$,

which complete proof of (i). To prove (ii), we only show that $C_{XY} \in \mathcal{H}(K_1K_2)$, as $C_{XX} \in \mathcal{H}(K_1^2)$ is an immediate consequence of $C_{XY} \in \mathcal{H}(K_1K_2)$. Let $s, t \in \mathcal{T}$. First notice that

$$C_{XY}(t) = E[X(t)Y(t)] - \mu_X(t)\mu_Y(t)$$

=: $\mu_{XY}(t) - (\mu_X \mu_Y)(t)$.

Because $X \in \mathcal{H}(K_1)$ almost surely, by Proposition 2, there exists a constant C_1 such that

$$C_1^2 K_1(s,t) - X(s)X(t) \ge 0,$$
 a.s. (8)

Similarly, there exists a constant C_2 such that

$$C_2^2 K_2(s,t) - Y(s)Y(t) \ge 0,$$
 a.s. (9)

Therefore Lemma 2 together with the equations (8) and (9) imply that

$$(C_1C_2)^2(K_1K_2)(s,t) - [X(s)Y(s)][X(t)Y(t)] \ge 0,$$
 a.s.

Now, Proposition 2 implies that XY belongs to $\mathcal{H}(K_1K_2)$ almost surely and therefore by part (i) of this Theorem, $\mu_{XY} \in \mathcal{H}(K_1K_2)$. It remains to show that $\mu_X \mu_Y \in \mathcal{H}(K_1K_2)$. Part (i) of this Theorem and Proposition 2 implies that there exists constants C_3 and C_4 such that

$$C_3^2 K_1(s,t) - \mu_X(s)\mu_X(t) \ge 0$$

and

$$C_4^2 K_2(s,t) - \mu_Y(s)\mu_Y(t) \ge 0.$$

So, by Lemma 2,

$$(C_3C_4)^2(K_1K_2)(s,t) - [\mu_X(s)\mu_Y(s)][\mu_X(t)\mu_Y(t)] \ge 0.$$

Now Proposition 2 implies that $\mu_X \mu_Y \in \mathcal{H}(K_1 K_2)$.

3 Estimation Methods

In this section, we introduce estimates of the parameters involved in (3) and (5). Assume that the sample paths of Y and X_p for $p=1,\ldots,k_1$ respectively belong to $\mathcal{H}(K)$ and $\mathcal{H}(K_p)$ almost surely, where $\mathcal{H}(K)$ and $\mathcal{H}(K_p)$ are some RKHSs. Since Z_q s are time-independent, a natural estimate for μ_{Z_q} is $\hat{\mu}_{Z_q} = \bar{Z}_q = \frac{1}{n} \sum_{i=1}^n Z_{qi}$. Also the mean functions $\mu_Y(t)$ and $\mu_{X_p}(t)$ can be estimated by either of the methods given in Yao et al. (2005), Li and Hsing (2010), Cai and Yuan (2011) and Zhang and Wang (2016). Denote the estimated mean functions of Y and X_p by $\hat{\mu}_Y(t)$ and $\hat{\mu}_{X_p}(t)$ respectively. The covariance $C_{Z_{q_1}Z_{q_2}}$ can be simply estimated by $\hat{C}_{Z_{q_1}Z_{q_2}} = \frac{1}{n} \sum_{i=1}^n (Z_{q_1i} - \bar{Z}_{q_1})(Z_{q_2i} - \bar{Z}_{q_2})$. To estimate the one-dimensional covariance and cross-covariance functions, define the raw covariance terms

$$\begin{split} C_{X_{p_1}X_{p_2},ij}(T_{ij}) &= [U_{p_1ij} - \hat{\mu}_{X_{p_1}}(T_{ij})][U_{p_2ij} - \hat{\mu}_{X_{p_2}}(T_{ij})], \\ C_{YX_p,ij}(T_{ij}) &= [V_{ij} - \hat{\mu}_Y(T_{ij})][U_{pij} - \hat{\mu}_{X_p}(T_{ij})], \\ C_{X_pZ_q,ij}(T_{ij}) &= [U_{pij} - \hat{\mu}_{X_p}(T_{ij})][Z_{qi} - \bar{Z}_q], \\ C_{YZ_q,ij}(T_{ij}) &= [V_{ij} - \hat{\mu}_Y(T_{ij})][Z_{qi} - \bar{Z}_q]. \end{split}$$

By Theorem 1, $C_{X_{p1}X_{p2}} \in \mathcal{H}(K_{p_1}K_{p_2})$, $C_{X_pZ_q} \in \mathcal{H}(K_p)$, $C_{YX_p} \in \mathcal{H}(KK_p)$ and $C_{YZ_q} \in \mathcal{H}(K)$. Based on these results, we estimate the one-dimensional covariance and cross-covariance functions as follows:

• Estimate of $C_{X_{p1}X_{p2}}$. Define

$$\hat{C}_{X_{p_1}X_{p_2}} = \underset{C \in \mathcal{H}(K_{p_1}K_{p_2})}{\arg\min} \left\{ \ell_{X_{p_1}X_{p_2}}(C) + \lambda_{X_{p_1}X_{p_2}} \|C\|_{\mathcal{H}(K_{p_1}K_{p_2})}^2 \right\}, \tag{10}$$

where

$$\ell_{X_{p_1}X_{p_2}}(C) = \frac{1}{n} \sum_{i=1}^{n} \frac{1}{M_i} \sum_{i=1}^{M_i} \left\{ C_{X_{p_1}X_{p_2},ij}(T_{ij}) - C(T_{ij}) \right\}^2,$$

and $\lambda_{{\scriptscriptstyle X_{p_1}X_{p_2}}}$ is a smoothing parameter.

• Estimate of $C_{X_pZ_q}$. Define

$$\hat{C}_{X_p Z_q} = \arg\min_{C \in \mathcal{H}(K_p)} \left\{ \ell_{X_p Z_q}(C) + \lambda_{X_p Z_q} \|C\|_{\mathcal{H}(K_p)}^2 \right\}, \tag{11}$$

where

$$\ell_{X_p Z_q}(C) = \frac{1}{n} \sum_{i=1}^n \frac{1}{M_i} \sum_{j=1}^{M_i} \left\{ C_{X_p Z_q, ij}(T_{ij}) - C(T_{ij}) \right\}^2,$$

and $\lambda_{X_pZ_q}$ is a smoothing parameter.

• Estimate of C_{YX_p} . Define

$$\hat{C}_{YX_p} = \underset{C \in \mathcal{H}(KK_p)}{\arg \min} \left\{ \ell_{YX_p}(C) + \lambda_{YX_p} \|C\|_{\mathcal{H}(KK_p)}^2 \right\}, \tag{12}$$

where

$$\ell_{YX_p}(C) = \frac{1}{n} \sum_{i=1}^n \frac{1}{M_i} \sum_{i=1}^{M_i} \left\{ C_{YX_p,ij}(T_{ij}) - C(T_{ij}) \right\}^2,$$

and λ_{YZ_q} is a smoothing parameter.

• Estimate of C_{YZ_q} . Define

$$\hat{C}_{YZ_q} = \arg\min_{C \in \mathcal{H}(K)} \left\{ \ell_{YZ_q}(C) + \lambda_{YZ_q} \|C\|_{\mathcal{H}(K)}^2 \right\}, \tag{13}$$

where

$$\ell_{YZ_q}(C) = \frac{1}{n} \sum_{i=1}^n \frac{1}{M_i} \sum_{j=1}^{M_i} \left\{ C_{YZ_q,ij}(T_{ij}) - C(T_{ij}) \right\}^2,$$

and $\lambda_{{}_{YZ_q}}$ is a smoothing parameter.

Now, we explain how the minimization problem (10) can be solved. The solutions of (11), (12) and (13) are obtained similarly. Following the representer theorem (see Wahba (1990)), we consider $C_{X_{p_1}X_{p_2}}$ as the form

$$C_{X_{p_1}X_{p_2}}(t) = \sum_{i=1}^{n} \sum_{j=1}^{M_i} a_{ij} K_{p_1}(t, T_{ij}) K_{p_2}(t, T_{ij})$$
(14)

for some vector $\mathbf{a} = [a_{11}, \dots, a_{1M_1}, \dots, a_{n1}, \dots, a_{nM_n}]'$. Now by equation (7) we have

$$||C_{X_{p_1}X_{p_2}}||^2_{\mathcal{H}(K_{p_1}K_{p_2})} = \sum_{i=1}^n \sum_{j=1}^{M_i} \sum_{i'=1}^n \sum_{j'=1}^{M_{i'}} a_{ij} a_{i'j'} K_{p_1}(T_{i'j'}, T_{ij}) K_{p_2}(T_{i'j'}, T_{ij})$$

$$= \mathbf{a}' \mathbf{Q} \mathbf{a},$$

where

$$\mathbf{Q} = egin{pmatrix} \mathbf{Q}_{11} & \mathbf{Q}_{12} & \mathbf{Q}_{13} & \cdots & \mathbf{Q}_{1n} \ \mathbf{Q}_{21} & \mathbf{Q}_{22} & \mathbf{Q}_{23} & \cdots & \mathbf{Q}_{2n} \ dots & dots & \ddots & dots & dots \ \mathbf{Q}_{n1} & \mathbf{Q}_{n2} & \mathbf{Q}_{n3} & \cdots & \mathbf{Q}_{nn} \end{pmatrix}$$

and for $i_1, i_2 = 1, \ldots, n$, the (i_1, i_2) partition of \mathbf{Q} , that is $\mathbf{Q}_{i_1 i_2}$, is an $M_{i_1} \times M_{i_2}$ dimensional matrix with entries $K_{p_1}(T_{i_1 j_1}, T_{i_2 j_2})K_{p_2}(T_{i_1 j_1}, T_{i_2 j_2})$. Define

$$\mathbf{g} = [g_{11}, \dots, g_{1M_1}, \dots, g_{n1}, \dots, g_{nM_n}]',$$

where

$$g_{ij} = C_{X_{p_1}X_{p_2},ij}(T_{ij}), \qquad i = 1,\ldots,n, \quad j = 1,\ldots,M_i.$$

Suppose $\|\cdot\|_F^2$ represents the Frobenius norm. Then

$$\ell_2(C_{X_{p_1}X_{p_2}}) + \lambda_2 \|C_{X_{p_1}X_{p_2}}\|_{\mathcal{H}(K_{p_1}K_{p_2})}^2 = \frac{1}{n} \|\mathbf{m} \circ \mathbf{g} - \mathbf{m} \circ (\mathbf{Q}\mathbf{a})\|_F^2 + \lambda_{X_{p_1}X_{p_2}} \mathbf{a}' \mathbf{Q}\mathbf{a}, \quad (15)$$

where $\mathbf{m} = [\frac{1}{\sqrt{M_1}} \mathbf{1}'_{M_1}, \dots, \frac{1}{\sqrt{M_n}} \mathbf{1}'_{M_n}]'$ and $\mathbf{1}_M$ is an M dimensional vector with all one entry. So to solve the minimization problem (10), it suffices to find a vector \mathbf{a} that minimizes the right hand side of (15). It is not hard to show that the minimizer of right hand side of (15) is

$$\mathbf{a} = \left(\mathbf{P} + (\sum_{i=1}^{n} M_i) \lambda_{X_{p_1} X_{p_2}} \mathbf{I}\right)^{-1} (\mathbf{m} \circ \mathbf{m} \circ \mathbf{g}),$$

where $\mathbf{P} = \mathbf{Q} \circ (\mathbf{1'}_{\sum\limits_{i=1}^{n} M_i} \otimes \mathbf{m}) \circ (\mathbf{1'}_{\sum\limits_{i=1}^{n} M_i} \otimes \mathbf{m}).$

The plug-in estimators of the intercept and coefficient functions are given by

$$[\hat{\beta}_1(t), \dots, \hat{\beta}_{k_1}(t), \hat{\alpha}_1(t), \dots, \hat{\alpha}_{k_2}(t)]' = \hat{\Gamma}_t^{-1} \hat{\gamma}_t$$

and

$$\hat{\beta}_0(t) = \hat{\mu}_Y(t) - \sum_{p=1}^{d_1} \hat{\beta}_p(t) \hat{\mu}_{X_p}(t) - \sum_{q=1}^{d_2} \hat{\alpha}_q(t) \hat{\mu}_{Z_q}.$$

4 Simulation studies

In this section, we evaluate the performance of the proposed method. We provide two simulation examples. In the first simulation, we consider one functional predictor and compare our method, denoted by LSRK, with the methods given in Şentürk and Müller (2010) and Mostafaiy et al. (2016). In the second simulation, we consider two functional and one time-independent predictors and compare our method with the method of Şentürk and Nguyen (2011). The methods of Şentürk and Müller (2010) and Şentürk and Nguyen (2011) are implemented in the MATLAB package PACE which can be downloaded from the website http://www.stat.ucdavis.edu/PACE/. In the all simulation studies, we consider $\mathcal{T} = [0,1]$. To face with sparse and irregular situation, we generated uniformly the number of measurements for each trajectory from $\{4,5,6,7,8\}$ and the random locations T_{ij} s from \mathcal{T} .

As in Şentürk and Nguyen (2011), we measure the estimation accurracy by mean absolute deviation error (MADE) and weighted average squared error (WASE) defined by

$$MADE = \frac{1}{d_1 d_2} \left[\sum_{p=1}^{d_1} \frac{\int_0^1 |\beta_p(t) - \hat{\beta}_p(t)| dt}{\text{range}(\beta_p)} + \sum_{q=1}^{d_2} \frac{\int_0^1 |\alpha_q(t) - \hat{\alpha}_q(t)| dt}{\text{range}(\alpha_q)} \right]$$

and

WASE =
$$\frac{1}{d_1 d_2} \left[\sum_{p=1}^{d_1} \frac{\int_0^1 (\beta_p(t) - \hat{\beta}_p(t))^2 dt}{\text{range}^2(\beta_p)} + \sum_{q=1}^{d_2} \frac{\int_0^1 (\alpha_q(t) - \hat{\alpha}_q(t))^2 dt}{\text{range}^2(\alpha_q)} \right].$$

All integrals numerically computed by Gaussian quadrature method.

We consider various combinations of the sample size $n \in \{100, 150, 200\}$ and the signal-to-noise ratio StN $\in \{4, 8, \infty\}$. For each configuration, we repeat the experiment 500 times.

4.1 Simulation study 1

The random function X_1 was generated as

$$X_1(t) = \mu_{X_1}(t) + \sum_{k=1}^{50} a_k \xi_k \phi_k(t),$$

where

$$\mu_{X_1}(t) = \sum_{k=1}^{50} (-1)^k k^{-3/2} \phi_k(t),$$

$$a_k = 4(-1)^k/k^2,$$

and

$$\phi_k(t) = \sqrt{2}\cos(2k\pi t).$$

The marginal distributions of ξ_1, \ldots, ξ_{50} are N(0,1). Observations from process X(t) were obtained by adding measurement errors $U_{1ij} = X_{1i}(T_{ij}) + \varepsilon_{ij}$, where ε_{ij} s were independently generated from $N(0, \sigma_{X_1}^2)$ with $\sigma_{X_1}^2 = (4.2954/\text{StN})^2$.

In the model (1) with only one predictor X_1 , we consider $\beta_0(t) = 2\sin(2\pi t)$ and $\beta_1(t) = 2e^t$. The sparse and noisy response observations were obtained by $V_{ij} = \beta_0(T_{ij}) + \beta_1(T_{ij})U_{iij} + \epsilon_{ij}$, where the noise terms ϵ_{ij} s randomly drawn from $N(0, \sigma_Y^2)$ with $\sigma_Y^2 = (15.6815/\text{StN})^2$.

Table 1 presents the Monte Carlo values of MADE and WASE for the three competitive methods LSRK (proposed), Şentürk and Müller (2010) and Mostafaiy et al. (2016). Although the method of Mostafaiy et al. (2016) outperforms other two methods but it is slightly better than LSRK. From this Table, we observe that LSRK has significantly better performance than the method of Şentürk and Müller (2010). The performance of LSRK is improved by increasing either the sample size or the signal-to-noise ratio. In Figure 1, we provide the mean integrated squared errors of $\hat{\beta}_0$ and $\hat{\beta}_1$ for the method LSRK. In this Figure, the left panel is for $\hat{\beta}_0$ and the right panel for $\hat{\beta}_1$. We observe that increasing both the sample size n and the signal-to-noise ratio StN lead to accurate estimates. This improvement is more significant when StN is large.

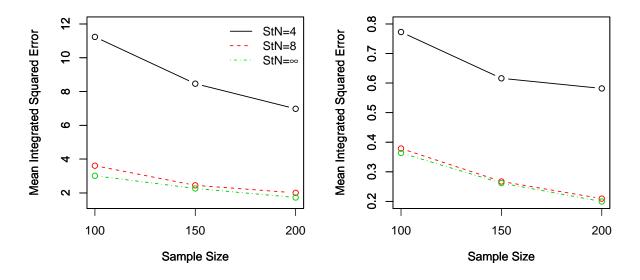


Figure 1: Effect of signal-to-noise ratio and sample size on integrated squared errors of $\hat{\beta}_0$ (left panel) and $\hat{\beta}_1$ (right panel) for the method LSRK.

		LSRK		Şentürk and Müller (2010)		Mostafaiy et al. (2016)	
n	StN	MADE	WASE	MADE	WASE	MADE	WASE
100	4	0.4366	0.4083	0.7273	1.8194	0.3109	0.2576
	8	0.2477	0.1736	0.6053	1.3622	0.1197	0.0446
	∞	0.2238	0.1434	0.6213	1.3932	0.0895	0.0302
150	4	0.3806	0.3270	0.7143	4.3996	0.2666	0.1867
	8	0.2036	0.1109	0.6470	2.0066	0.1083	0.0371
	∞	0.1905	0.1015	0.6235	1.1665	0.0886	0.0293
200	4	0.3527	0.2739	0.7028	1.5030	0.2388	0.1487
	8	0.1817	0.0857	0.6670	1.5393	0.1055	0.0354
	∞	0.1669	0.0766	0.6400	1.3321	0.0855	0.0259

Table 1: Mean absolute deviation error (MADE) and weighted average squared error (WASE) for various combinations of sample size (n) and signal-to-noise ratio (StN). The compared three methods are: LSRK (proposed), Şentürk and Müller (2010), and Mostafaiy et al. (2016).

4.2 Simulation study 2

The first functional predictor is same as previous subsection. For the second functional predictor, we took

$$X_2(t) = \mu_{X_2}(t) + \sum_{k=1}^{50} b_k \zeta_k \psi_k(t),$$

where

$$\mu_{X_2}(t) = \sin(2\pi t) - te^{-t},$$

$$\psi_k(t) = \begin{cases} \sqrt{2}\sin(2k\pi t) & \text{for } k \le 49\\ 1 & \text{for } k = 50 \end{cases}$$

and

$$b_k = \begin{cases} \sqrt{3}/2^k & \text{for } k \le 49\\ \sqrt{3} & \text{for } k = 50 \,. \end{cases}$$

Also $\zeta_1, \ldots, \zeta_{50}$ are marginally distributed as N(0,1). Sparse and noisy observations U_{2ij} s from random function X_2 were obtained based on model (2), where ε_{2ij} s were independent

distributed as $N(0, \sigma_{X_2}^2)$ with $\sigma_{X_2}^2 = (1.2733/\text{StN})^2$. The marginal distribution of the time-independent covariate Z is N(1,1). To have correlation between the predictors, let $\Sigma = [\Sigma_{kl}]$ be the covariance matrix of the random vector $[Z, \xi_1, \ldots, \xi_{50}, \zeta_1, \ldots, \zeta_{50}]'$, where

$$\Sigma_{kl} = \begin{cases} 1 & \text{for } k = l \\ 0.4^{l-1} & \text{for } k = 1, \ 2 \le l \le 51 \\ (-0.3)^{l-51} & \text{for } k = 1, \ l \ge 52 \\ 0.8^{l-50} & \text{for } k = l - 50, \ l \ge 52 \\ 0 & \text{otherwise} \,. \end{cases}$$

The response observations V_{ij} s were obtained from

$$V_{ij} = \beta_0(T_{ij}) + \beta_1(T_{ij})U_{1ij} + \beta_2(T_{ij})U_{2ij} + \alpha_1(T_{ij})Z_i + \epsilon_{ij},$$

where random errors ϵ_{ij} s were independently generated from $N(0, \sigma_Y^2)$ with $\sigma_Y^2 = (15.8525/\text{StN})^2$. Also $\beta_0(t)$ and $\beta_1(t)$ are same as simulation study 1, and $\beta_2(t) = 5te^{-t}$ and $\alpha_1(t) = 2t$.

We compare LSRK with the method of Sentürk and Nguyen (2011). Table 2 summarizes the Monte Carlo values of MADE and WASE for two methods. In all combinations of n and StN, LSRK has the smallest values of MADE and WASE. Moreover, LSRK appears to be more stable. As expected, increasing either sample size n and signal-to-noise ration StN decreases estimation errors. Figure 2 displays mean integrated squared errors of the estimated coefficient functions, the top left panel for $\hat{\beta}_0$, the top right panel for $\hat{\alpha}_1$, the bottom left panel for $\hat{\beta}_1$ and the bottom right panel for $\hat{\beta}_2$. This Figure reveals that there is a general tendency for the mean integrated squared errors to decrease as either sample size or signal-to-noise ratio increases.

5 Application

Primary biliary cirrhosis (PBC) is an autoimmune liver disease. It caused by damage to the bile (a fluid produced in the liver to aid in the digestion of fat) ducts in the liver. When the bile ducts are damaged, bile builds up and causes liver scarring, cirrhosis, and eventually liver failure. The dataset that we use in this paper was collected by the Mayo Clinic between 1974 and 1984. The dataset is given in Appendix D of Fleming and Harrington (1991) and also included in the R package survival which is available at https://cran.r-project.org/package=survival. The patients were scheduled to have their blood characteristics measured at six months, one year and annually after

		LSRK		Şentürk and Nguyen (2011)		
n	StN	MADE	WASE	MADE	WASE	
	4	0.5556	0.7703	1.6690	8378.6490	
100	8	0.3228	0.4987	0.9533	280.0505	
	∞	0.2918	0.3709	0.8757	412.0377	
150	4	0.4808	0.4899	1.3142	1177.7210	
	8	0.2587	0.3119	0.8899	98.4621	
	∞	0.2220	0.2771	0.9590	279.5293	
200	4	0.4255	0.3679	1.1581	312.3150	
	8	0.2197	0.2809	0.9329	636.4345	
	∞	0.1922	0.2254	0.9388	675.6874	

Table 2: Mean absolute deviation error (MADE) and weighted average squared error (WASE) for various combinations of sample size (n) and signal-to-noise ratio (StN). The compared two methods are: LSRK (proposed), and Sentürk and Nguyen (2011).

diagnosis. Because of missing appointments, death or liver transplantation during the study and other factors, the actual times of the measurements are random, irregular and sparse.

This dataset contains some general information for example age in days and sex, and some multiple laboratory results for example serum bilirubin in mg/dl, albumin in gm/dl and prothrombin time in seconds. Bilirubin is a yellow substance that is formed during the normal breakdown of red blood cells. After circulating in the blood, the liver excretes bilirubin into bile ducts. The normal adult serum bilirubin level is less than 1 mg/dl. The accumulation of bilirubin leads to jaundice. Albumin is a protein made by the liver. It is the main protein in the blood that causes fluid to remain within the bloodstream. A diseased liver produces insufficient albumin. The normal albumin range is 3.5 to 5.5 g/dl. Prothrombin time is the time it takes for blood to clot. Liver disease can cause slow blood clotting. The average time range for prothrombin time is about 10 to 14 seconds.

The objective of this analysis is to explore the association between prothrombin time (Y) as a response and age (Z_1) , serum bilirubin (X_1) and albumin (X_2) as predictors. Among 276 female patients, we include 137 patients having D-penicillamine and their measurements before 2500 days. The median number of observations per patients is 5.

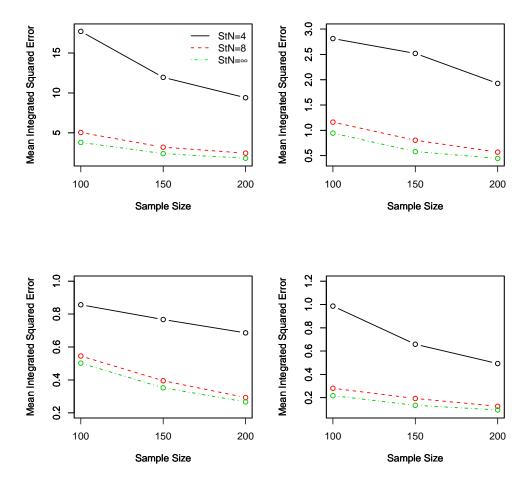


Figure 2: Effect of signal-to-noise ratio and sample size on integrated squared errors of $\hat{\beta}_0$ (top left panel), $\hat{\alpha}_1$ (top right panel), $\hat{\beta}_1$ (bottom left panel) and $\hat{\beta}_2$ (bottom right panel) for the method LSRK.

Individual trajectories and data along with the smoothed estimated mean functions of prothrombin time, bilirubin and albumin are given in Figure 3. The mean prothrombin time slightly increases by passing time but it is normal. The mean amount of bilirubin is above the normal level and it has an increasing trend. By passing the time, the mean amount of albumin made by the liver decreases.

Figure 4 plots the estimated varying coefficient functions β_0 , α_1 , β_1 and β_2 using LSRK. From the Figure we observe that before 2000 days the association between age and prothrombin time is negligible but after 2000 days age has a negative effect on prothrombin time. There exists a negative association between albumin and prothrombin time, especially after 2000 days. The effect of bilirubin on prothrombin time before 2000 days is minor and fluctuates between positive and negative while after 2000 days the

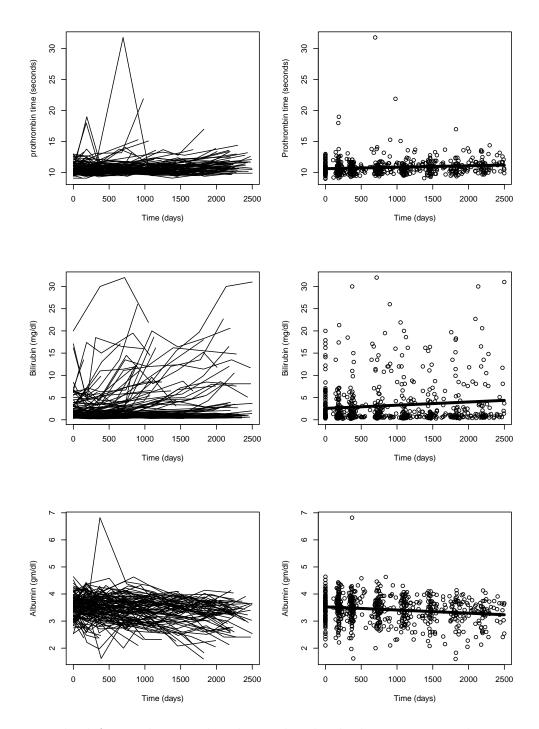


Figure 3: The left panels give the observed individual trajectories, the top panel for prothrombin time, the middle panel for bilirubin, and the lower panel for albumin. The observed data along with the estimated mean functions (solid line) are shown in the right panels, the top panel for prothrombin time, the middle panel for bilirubin, and the lower panel for albumin.

association tends to be negative.

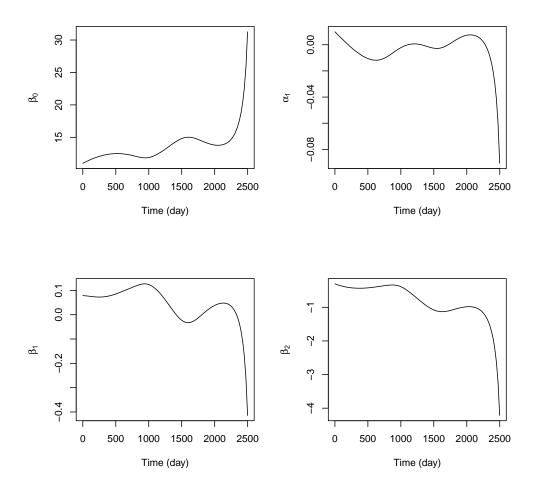


Figure 4: The estimated varying coefficient functions β_0 , α_1 , β_1 and β_2 .

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