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Optimal Function-on-Function Regression with Interaction between Functional Predictors

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Abstract: We consider a functional regression model in the framework of reproducing kernel Hilbert spaces where the interaction effect of two functional predictors, as well as their main effects, over the functional response is of interest. The regression component of our model is expressed by one trivariate coefficient function whose functional ANOVA decomposition yields the main and interaction effects. The trivariate coefficient function is estimated through the optimization of a penalized least squares objective with a roughness penalty on the function estimate. The estimation procedure can be easily implemented via standard numerical tools. Asymptotic results for the proposed model with or without functional measurement errors are established under the reproducing kernel Hilbert space framework. Extensive numerical studies show the advantages of the proposed method over existing ones in terms of prediction and estimation of coefficient functions. An application to the motivating example on histone modifications and gene expressions of a liver cancer cell line further demonstrates the better prediction accuracy of the proposed method against the competitors.

Key words and phrases: Functional ANOVA, Functional interaction, Function-on-Function regression, Measurement errors, Minimax convergence rate, Penalized least squares, Tensor product.

1. Introduction

Functional regression models, such as scalar-on-function, function-on-scalar, and function-on-function regression models, have attracted much attention in the past decades (Ramsay and Silverman, 2005; Ferraty and Vieu, 2006). In this article, we consider a second-order function-on-function regression model. For $1 \leq i \leq n$, the i th response function $Y_i(\cdot)$ is related to two independent functional predictors $X_i(\cdot)$ and $Z_i(\cdot)$ through

$$Y_i(t) = \int_{I_x} \int_{I_z} X_i(r) Z_i(s) \beta(t, r, s) ds dr + \epsilon_i(t), \quad t \in I_y. \quad (1.1)$$

Here $\beta(\cdot, \cdot, \cdot) : I_y \times I_x \times I_z \rightarrow \mathbb{R}$ is an unknown trivariate coefficient function, and $\epsilon_i(\cdot)$, independent of $(X_i(\cdot), Z_i(\cdot))$, is the i.i.d. random error function with zero mean and bounded covariance function. Here we consider both the case without measurement errors when $X_i(\cdot)$ and $Z_i(\cdot)$ are observable and the case with measurement errors. In the latter case, only surrogate processes of $X_i(\cdot)$ and $Z_i(\cdot)$, contaminated by measurement errors, are observable. Without loss of generality, we assume that I_y, I_x , and I_z are the

interval $[0, 1]$ with the notion that their generalization to distinct and general compact intervals is trivial. Through a functional ANOVA decomposition, we shall show later that model (1.1) can be written as the following function-on-function regression model,

$$Y_i(t) = \alpha(t) + \int_{I_x} X_i(r) \beta_x(t, r) dr + \int_{I_z} Z_i(s) \beta_z(t, s) ds + \int_{I_x} \int_{I_z} X_i(r) Z_i(s) \beta_{xz}(t, r, s) ds dr + \epsilon_i(t). \quad (1.2)$$

Here $\alpha(\cdot): I_y \rightarrow \mathbb{R}$ is the intercept function, $\beta_x(\cdot, \cdot)$ is the coefficient function corresponding to the main effect of $X_i(\cdot)$, $\beta_z(\cdot, \cdot)$ is the coefficient function corresponding to the main effect of $Z_i(\cdot)$, and $\beta_{xz}(\cdot, \cdot, \cdot)$ is the coefficient function corresponding to the interaction between $X_i(\cdot)$ and $Z_i(\cdot)$. Certain side conditions on β_x, β_z , and β_{xz} , to be introduced later, are needed to ensure the model identifiability. Our model is motivated from an epigenetics study on how the gene expression level is regularized by the modifications of two histones near the gene for the liver cancer cell line HepG2. The functional response is the normalized gene expression levels of each gene over genome coordinates. The density levels of two histone modifications over genome coordinates are the two functional predictors.

Functional regression models with a scalar response have been studied

extensively. Two main approaches are the functional principal component analysis (FPCA) approach (Yao et al., 2005a,b; Cai et al., 2006; Hall et al., 2007; Yao and Müller, 2010) and the roughness penalty approach (Ramsay and Silverman, 2005; Yuan et al., 2010; Cai and Yuan, 2012; Du and Wang, 2014; Usset et al., 2016). Recently, function-on-function regression models, especially those with a single functional predictor, have received a fair amount of attention. The FPCA approach for the function-on-function regression uses eigenfunctions in the Karhunen-Loève expansions of the response and predictor functions to represent the bivariate coefficient function (Yao et al., 2005a,b; Wu and Müller, 2011; Crambes et al., 2013). For the roughness penalty approach, Sun et al. (2018) extended the work of Cai and Yuan (2012) to model a functional response. The roughness penalty approach for function-on-function regression was also considered in Ramsay and Silverman (2005) and Ivanescu et al. (2015). Other methods include the Nadaraya-Watson approach (Ferraty et al., 2012), the Bayesian mixed model approach (Meyer et al., 2015), and the marginal approach (Lian, 2015). Besides these linear models, various nonlinear function-on-function regression models with a single functional predictor have been developed. For example, Reimherr et al. (2018) provided a function-on-function extension of the scalar-on-function continuously additive model introduced by

Müller et al. (2013). Matsui (2020) and Sun and Wang (2020) extended the functional quadratic regression model in Yao and Müller (2010) to add a quadratic term of $X(s)$ as a second functional predictor.

Function-on-function regression models with multiple functional predictors have been studied by a few papers. Ivanescu et al. (2015) considered an additive linear model with the mix of a multivariate scalar variable and two functional predictors. Scheipl et al. (2015) studied an additive mixed-effect model that includes interactions between scalar variables with a varying coefficient function, smooth effect of scalar variables, and continuously additive model of a functional predictor. However, neither paper considered interactions between two functional predictors or studied the theoretical properties of their estimators. Luo and Qi (2017) introduced a signal compression approach to additive function-on-function regression models. A selected number of leading eigenfunctions in the Karhunen-Loève expansion of the centered regression mean function are used to build up an approximate model, and thus reduce the problem to a principal component analysis type of constrained optimization. However, all these papers have ignored the interaction effects between functional predictors. Such ignorance may result in biased estimation of coefficient functions and incorrect conclusions. On the other hand, the scarcity of functional models incorporating interactions

may attribute to the extra numerical and theoretical complexity induced by the additional dimension in the corresponding coefficient function.

To the best of our knowledge, the only existing function-on-function regression model that includes interactions between functional predictors is the signal compression approach (Luo and Qi, 2019), extended from Luo and Qi (2017). The approach is based on the truncated Karhunen-Loève expansion of the centered regression mean function, i.e., the centered version of the double integral term in (1.1). The coefficient functions are estimated as a linear combination of the leading eigenfunctions in the truncated expansion through a constrained optimization procedure. Due to their choice of expanding the regression mean function rather than the functional predictors or response, the selected leading eigenfunctions in the signal compression approach can possibly provide a more effective basis expansion system for the coefficient functions than the FPCA. Furthermore, their approach adds an adaptive roughness penalty to the objective functions to provide a better control over the smoothness of the function estimates than the FPCA. However, such improvements over the FPCA come with a price. Firstly, the computation becomes more complicated. The constrained non-linear optimization procedure requires the tuning of a roughness parameter as well as the specification of a truncation point of the Karhunen-Loève

expansion. Secondly, these improvements also make it difficult to study the asymptotic properties of the resulting estimates. Neither Luo and Qi (2017) nor Luo and Qi (2019) provides a rigorous asymptotic theory. Given the involvement of both a truncation point and a roughness penalty, it is not clear whether such a rigorous theoretical development is even realistic for their approach. Lastly, even with such improvements, our numerical experiments show that its performance is still not as good as the RKHS based method proposed in this paper.

In this paper, we propose a penalized least squares method for the non-additive functional regression model (1.1). Under the RKHS framework, the trivariate coefficient function in (1.1) naturally splits into component coefficient functions through a functional ANOVA decomposition, including both the main effects and the interaction of the functional predictors. The estimators of the coefficient function and the component coefficient functions are obtained through the optimization of a penalized least squares objective. The objective consists of the sum of integrated mean square errors, a roughness penalty, and a smoothing parameter balancing the two parts. The optimization only involves quadratic programming and can be solved by a standard Newton-Raphson procedure. For its theoretical property, we show that the proposed method achieves the minimax convergence rate in

mean prediction for a function-on-function regression model. In the simulation studies, we compare our method with those in Scheipl et al. (2015) and Luo and Qi (2019). In general, our method has the best performance under the non-additive model setting like (1.2) while being competitive under the setting of additive models. In the application to an epigenetic study on human liver cancer cells, our method also shows the best cross-validation prediction performance. In summary, the proposed method has the following advantages: (1) Theoretically, it achieves the optimal rate in the mean prediction for a function-on-function regression model without or with functional measurement errors; (2) Computationally, the penalized least squares optimization is a quadratic programming problem and allows an easy implementation by standard optimization procedures; (3) Numerically, it demonstrates more accurate performance in the coefficient function estimation and the mean prediction, especially in the non-additive model setting; (4) The functional ANOVA decomposition under the RKHS framework provides easy access to main and interaction effects of functional predictors.

The rest of the article is organized as follows. Section 2 introduces the penalized function-on-function regression model incorporating interaction between functional predictors. An easily implementable estimation algo-

rithm is presented in Section 3. The optimal convergence rate in mean prediction is presented in Section 4. Section 5 contains simulations that include comparisons with other methods and a numerical demonstration of the functional ANOVA decomposition. A real data example is presented in Section 6. Discussion in Section 7 concludes the article. The proof of the main theorem and other technical details are collected in the Supplementary Material.

2. Penalized Quadratic Function-on-Function Regression with Functional Interaction

Let $\{(X(r), Z(s), Y(t)) : r \in I_x, s \in I_z, t \in I_y\}$ be random processes defined on domains $I_x, I_z, I_y \subseteq \mathbb{R}$ respectively. The observed data $(X_i(r), Z_i(s), Y_i(t))$, $i = 1, \dots, n$, are independent copies of the three random processes. We consider the quadratic function-on-function regression model in (1.1) and decompose β into the functional ANOVA form

$$\beta = \beta_\emptyset + \beta_t + \beta_r + \beta_s + \beta_{t,r} + \beta_{t,s} + \beta_{r,s} + \beta_{t,r,s}, \quad (2.3)$$

where side conditions are imposed to ensure the estimability. The decomposition (2.3) allows us to rewrite the regression function $\int_{I_x} \int_{I_z} X_i(r) Z_i(s) \beta(t, r, s) ds dr$

in (1.1). The collective term $\int_{I_x} \int_{I_z} X_i(r) Z_i(s) (\beta_\emptyset + \beta_t + \beta_r + \beta_s + \beta_{r,s}) ds dr$ does not depend on r or s and represents the intercept function in model (1.2). The terms $\int_{I_x} \int_{I_z} X_i(r) Z_i(s) \beta_{t,r} ds dr$ and $\int_{I_x} \int_{I_z} X_i(r) Z_i(s) \beta_{t,s} ds dr$ are the respective main effects of $X_i(r)$ and $Z_i(s)$ if we normalize $X_i(r)$ and $Z_i(s)$ to make $\int_{I_x} X_i(r) dr = \int_{I_z} Z_i(s) ds = 1$. The interaction effect in (1.2) now corresponds to $\int_{I_x} \int_{I_z} X_i(r) Z_i(s) \beta_{t,r,s} ds dr$.

Suppose the coefficient function β in (1.1) is an unknown function in a reproducing kernel Hilbert space (RKHS) $\mathcal{H}$ with the reproducing kernel K . We propose to estimate β by minimizing the following penalized least squares

$$\frac{1}{n} \sum_{i=1}^n \int_{I_y} \{Y_i(t) - \int_{I_x} \int_{I_z} \beta(t, r, s) X_i(r) Z_i(s) ds dr\}^2 dt + \lambda J(\beta), \quad (2.4)$$

where the roughness penalty $J(\beta)$ is a squared semi-norm on $\mathcal{H}$ quantifying the roughness of β , and $\lambda > 0$ is the smoothing parameter balancing the trade-off between the goodness-of-fit and the smoothness of β . In this paper we consider a roughness penalty $J(\beta)$ with the exact form and interpretation of its components presented in Supplementary S1. We note that the procedure actually works similarly for other common penalties illustrated in Wahba (1990) and Gu (2013).

The functional ANOVA decomposition (2.3) of β is derived from the decomposition of the RKHS $\mathcal{H}$. Based on the tensor sum decomposition, $\mathcal{H}$ can be decomposed as $\mathcal{H} = \mathcal{H}_0 \oplus \mathcal{H}_1$, where $\mathcal{H}_0 = \{\beta \in \mathcal{H} : J(\beta) = 0\}$ with the reproducing kernel K_0 , $\mathcal{H}_1$ is its orthogonal complement with the reproducing kernel K_1 , and $K = K_0 + K_1$. By the tensor product decomposition, one can decompose $\mathcal{H} = \mathcal{H}^y \otimes \mathcal{H}^x \otimes \mathcal{H}^z$, where $\mathcal{H}^y, \mathcal{H}^x, \mathcal{H}^z$ are marginal subspaces of $\mathcal{H}$ for Y, X, Z with reproducing kernels K^y, K^x, K^z respectively, and $K(t_1, r_1, s_1; t_2, r_2, s_2) = K^y(t_1, t_2)K^x(r_1, r_2)K^z(s_1, s_2)$. We then have the following tensor sum decompositions of marginal subspaces $\mathcal{H}^y = \mathcal{H}_0^y \oplus \mathcal{H}_1^y$, $\mathcal{H}^x = \mathcal{H}_0^x \oplus \mathcal{H}_1^x$, and $\mathcal{H}^z = \mathcal{H}_0^z \oplus \mathcal{H}_1^z$ with the reproducing kernels $K^y = K_0^y + K_1^y$, $K^x = K_0^x + K_1^x$, and $K^z = K_0^z + K_1^z$ respectively. Combining the tensor sum and tensor product decomposition, we have

$$\begin{aligned}
 \mathcal{H} &= (\mathcal{H}_0^y \oplus \mathcal{H}_1^y) \otimes (\mathcal{H}_0^x \oplus \mathcal{H}_1^x) \otimes (\mathcal{H}_0^z \oplus \mathcal{H}_1^z) \\
 &= (\mathcal{H}_0^y \otimes \mathcal{H}_0^x \otimes \mathcal{H}_0^z) \oplus (\mathcal{H}_0^y \otimes \mathcal{H}_1^x \otimes \mathcal{H}_0^z) \oplus (\mathcal{H}_0^y \otimes \mathcal{H}_0^x \otimes \mathcal{H}_1^z) \\
 &\quad \oplus (\mathcal{H}_0^y \otimes \mathcal{H}_1^x \otimes \mathcal{H}_1^z) \oplus (\mathcal{H}_1^y \otimes \mathcal{H}_0^x \otimes \mathcal{H}_0^z) \oplus (\mathcal{H}_1^y \otimes \mathcal{H}_1^x \otimes \mathcal{H}_0^z) \\
 &\quad \oplus (\mathcal{H}_1^y \otimes \mathcal{H}_0^x \otimes \mathcal{H}_1^z) \oplus (\mathcal{H}_1^y \otimes \mathcal{H}_1^x \otimes \mathcal{H}_1^z) \\
 &= \mathcal{H}_0 \oplus \mathcal{H}_1,
 \end{aligned} \tag{2.5}$$

where $\mathcal{H}_0 = \mathcal{H}_0^y \otimes \mathcal{H}_0^x \otimes \mathcal{H}_0^z$ and $\mathcal{H}_1$ collects the remaining terms in (2.5). The

corresponding kernels denoted by K_0 and K_1 are defined as $K_0 = K_0^y K_0^x K_0^z$

and

$$K_1 = K_0^y K_1^x K_0^z + K_0^y K_0^x K_1^z + K_0^y K_1^x K_1^z + K_1^y K_0^x K_0^z + K_1^y K_1^x K_0^z + K_1^y K_0^x K_1^z + K_1^y K_1^x K_1^z.$$

With the aid of tensor product and tensor sum decompositions, we now represent the coefficient function β by the basis functions of $\mathcal{H}^y$, $\mathcal{H}^x$, and $\mathcal{H}^z$. Let the basis functions be respectively $\{\psi_j^y, j = 1, \dots, N_y\}$, $\{\psi_j^x, j = 1, \dots, N_x\}$, $\{\psi_j^z, j = 1, \dots, N_z\}$ for $\mathcal{H}_0^y$, $\mathcal{H}_0^x$, $\mathcal{H}_0^z$, and $\phi_i^y(t) = \int_{I_y} K_1^y(t, u) Y_i(u) du$, $\phi_i^x(r) = \int_{I_x} K_1^x(r, u) X_i(u) du$, $\phi_i^z(s) = \int_{I_z} K_1^z(s, u) Z_i(u) du$, $i = 1, \dots, n$ for $\mathcal{H}_1^y$, $\mathcal{H}_1^x$, $\mathcal{H}_1^z$, where $N_y = \dim(\mathcal{H}_0^y)$, $N_x = \dim(\mathcal{H}_0^x)$, and $N_z = \dim(\mathcal{H}_0^z)$. Let $\psi^y = (\psi_1^y, \dots, \psi_{N_y}^y)^T$, $\psi^x = (\psi_1^x, \dots, \psi_{N_x}^x)^T$, $\psi^z = (\psi_1^z, \dots, \psi_{N_z}^z)^T$, $\phi^y = (\phi_1^y, \dots, \phi_n^y)^T$, $\phi^x = (\phi_1^x, \dots, \phi_n^x)^T$, and $\phi^z = (\phi_1^z, \dots, \phi_n^z)^T$. The coefficient function estimate $\hat{\beta}$ is of the form

$$\hat{\beta}(t, r, s) = \{\mathbf{d}_y^T \psi^y(t) + \mathbf{c}_y^T \phi^y(t)\} \{\mathbf{d}_x^T \psi^x(r) + \mathbf{c}_x^T \phi^x(r)\} \{\mathbf{d}_z^T \psi^z(s) + \mathbf{c}_z^T \phi^z(s)\}, \quad (2.6)$$

where $\mathbf{d}_y, \mathbf{c}_y, \mathbf{d}_x, \mathbf{c}_x, \mathbf{d}_z, \mathbf{c}_z$ are coefficient vectors. The major advantage of the representation is that although we only include the quadratic term in the quadratic function-on-function regression model, we can still study the

main effects of X and Z on different subspaces in (2.5). For instance, the main effects of X and Z are estimated on $\mathcal{H}_1^x \otimes \mathcal{H}_0^z \otimes \mathcal{H}_0^y$ and $\mathcal{H}_0^x \otimes \mathcal{H}_1^z \otimes \mathcal{H}_0^y$, respectively.

3. Estimation

Based on the representation of β in (2.6), we transform the penalized least squares (2.4) into a form that can be easily optimized by standard numerical procedures. Plugging (2.6) into (2.4), we have

$$\begin{aligned} \int_{I_x} \int_{I_z} X(r)Z(s)\beta(t, r, s)drds &= \int_{I_x} \int_{I_z} X(r)Z(s)\mathbf{d}^T \psi(t, r, s)drds \\ &+ \int_{I_x} \int_{I_z} X(r)Z(s)\mathbf{c}^T \phi(t, r, s)drds, \end{aligned} \quad (3.7)$$

where $\psi = (\psi_1, \dots, \psi_N)^T = (\psi_1^y \psi_1^x \psi_1^z, \dots, \psi_{N_y}^y \psi_{N_x}^x \psi_{N_z}^z)^T$, $\phi = (\phi_1, \dots, \phi_M)^T = (\phi_1^y \psi_1^x \psi_1^z, \dots, \phi_n^y \phi_n^x \phi_n^z)^T$, and $\mathbf{d}$ and $\mathbf{c}$ are the corresponding coefficient vectors. Different selections of kernel function usually yield different basis function ψ and ϕ . We use the tensor product cubic spline as an example. For the tensor product cubic spline, we have $N_y = N_x = N_z = 2$, and the basis functions $\psi_1^*(r) = 1$, $\psi_2^*(r) = r - 0.5$ with $*$ running through the index set $\{y, x, z\}$. Similarly, the basis functions ϕ are some scaled version of Bernoulli polynomials; see, e.g., Gu (2013). Then the dimension of the

null space $\mathcal{H}_0$ is $N = N_y N_x N_z = 8$, and the number of basis functions in $\mathcal{H}_1$ is $M = (n + N_y)(n + N_x)(n + N_z) - N_y N_x N_z = n^3 + 6n^2 + 12n$.

The integral in (2.4) can be computed by a Gaussian quadrature, see e.g., Abramowitz and Stegun (1970), with weights $(w_1, \dots, w_T)$ and knots $(t_1, \dots, t_T)$: $\int_{I_y} \eta(t) dt = \sum_j w_j \eta(t_j)$. Let W be a diagonal matrix repeating $\text{diag}(w_1, \dots, w_T)$ n times, S be an $nT \times N$ matrix with the $((i-1)T + j, k)$ th entry $\int_{I_x} \int_{I_z} X_i(r) Z_i(s) \psi_k(t_j, r, s) dr ds$, and R be an $nT \times M$ matrix with the $((i-1)T + j, l)$ th entry $\int_{I_x} \int_{I_z} X_i(r) Z_i(s) \phi_l(t_j, r, s) dr ds$, where $i = 1, \dots, n$, $j = 1, \dots, T$, $k = 1, \dots, N$, $l = 1, \dots, M$. Let Σ be an $M \times M$ matrix with the (i, j) th entry $\langle \phi_i(t, r, s), \phi_j(t, r, s) \rangle_{\mathcal{H}_1}$. Then the objective function (2.4) is reduced to

$$\min_{\mathbf{d}, \mathbf{c}} \frac{1}{n} (Y_w - S_w \mathbf{d} - R_w \mathbf{c})^T (Y_w - S_w \mathbf{d} - R_w \mathbf{c}) + \lambda \mathbf{c}^T \Sigma \mathbf{c},$$

where $Y_w = W^{\frac{1}{2}} Y$, $S_w = W^{\frac{1}{2}} S$, $R_w = W^{\frac{1}{2}} R$. We use the generalized cross-validation (GCV) method to select the smoothing parameter λ (Wahba, 1975).

4. Optimal Rate for Mean Prediction

In this section, we show our penalized least squares estimator achieves the minimax rate of convergence for the mean prediction of a quadratic function-on-function regression model. The result is shown for the model with functional measurement errors and also valid for the model without functional measurement errors as a corollary. The complete proof, including all the lemmas, is collected in Supplementary S3.

4.1 Notation and Excess Risk

We start with the definitions of some notations and the excess risk. Recall that the reproducing kernel K of $\mathcal{H}$ can be viewed as the kernel function of a positive definite and compact linear operator L_K defined by

$$L_K(f)(t_1, s_1, r_1) = \int \int \int K(t_1, s_1, r_1; t_2, s_2, r_2) f(t_2, s_2, r_2) dt_2 ds_2 dr_2.$$

It is easy to show that $L_{K^{1/2}}(\mathcal{L}_2) = \mathcal{H}(K)$ and

$$\langle f, g \rangle_{\mathcal{H}} = \langle L_{K^{-1/2}} f, L_{K^{-1/2}} g \rangle_{\mathcal{L}_2} = \langle f, L_{K^{-1}} g \rangle_{\mathcal{L}_2}. \quad (4.8)$$

4.1 Notation and Excess Risk

Since one can move between the $\mathcal{H}$ and $\mathcal{L}_2$ inner products as in (4.8), we will work with $\mathcal{L}_2$ instead of $\mathcal{H}$ for the minimization problem (2.4). Following the functional measurement errors setup in Jadhav and Ma (2020), we assume the observable surrogate processes are U_i and V_i such that $U_i(\cdot) = X_i(\cdot) + \tau_i(\cdot)$ and $V_i(\cdot) = Z_i(\cdot) + v_i(\cdot)$, where $\tau_i(\cdot)$ and $v_i(\cdot)$ are functional measurement error processes independent of X_i , Z_i , and the random error processes ϵ_i . Let β_0 be the true coefficient function and $\hat{\beta}_{n\lambda}$ be the estimator as the minimizer of (2.4) when there exist functional measurement errors. Then there exist $f_0, \hat{f} \in \mathcal{L}_2$ such that $\beta_0 = L_{K^{1/2}} f_0$ and $\hat{\beta}_{n\lambda} = L_{K^{1/2}} \hat{f}_\lambda$. For a given reproducing kernel K and a covariance function C of $U(r)V(s)$, we further define the new kernel function T

$$T((t_1, r_1, s_1), (t_2, r_2, s_2)) = \int \int \int \int \int K^{1/2}((t_1, r_1, s_1), (w, u_1, v_1)) C((u_1, v_1), (u_2, v_2)) \\ K^{1/2}((w, u_2, v_2), (t_2, r_2, s_2)) du_1 dv_1 du_2 dv_2 dw,$$

which, by the spectral theorem, has a decomposition $\sum_{k=1}^{\infty} \rho_k \zeta_k(t_1, s_1, r_1) \zeta_k(t_2, s_2, r_2)$.

Then we have $L_{K^{1/2}CK^{1/2}}(\zeta_k) = \rho_k \zeta_k$ for $k = 1, 2, \dots$, where $L_{K^{1/2}CK^{1/2}}(f) =$

$L_{K^{1/2}}(L_C(L_{K^{1/2}}(f)))$. We are interested in recovering the functional $\eta_\beta(\cdot, \cdot, t) :$

$\mathcal{L}_2 \times \mathcal{L}_2 \rightarrow \mathbb{R}$, where $\eta_\beta(U, V, t) = \int_{I_x} \int_{I_z} U(r)V(s)\beta(t, r, s)drds$. Let $(U_{n+1}, V_{n+1}, Y_{n+1})$

be a new observation that has the same distribution as and is independent

4.2 Asymptotic Results

of $(U_i, V_i, Y_i), i = 1, \dots, n$. The prediction accuracy can be measured by the excess risk

$$\begin{aligned}\mathcal{E}_n^m(\hat{\beta}_{n\lambda}) &= \int_{I_y} \mathbb{E}^* \left\{ \eta_{\hat{\beta}_{n\lambda}}(U_{n+1}, V_{n+1}, t) - \eta_{\beta_0}(U_{n+1}, V_{n+1}, t) \right\}^2 dt \\ &= \langle T^{1/2}(\hat{f} - f_0), T^{1/2}(\hat{f} - f_0) \rangle_{\mathcal{L}_2} = \left\| T^{1/2}(\hat{f} - f_0) \right\|_{\mathcal{L}_2}^2,\end{aligned}$$

where $\mathbb{E}^*$ represents the expectation taken over $(U_{n+1}, V_{n+1}, Y_{n+1})$ only.

4.2 Asymptotic Results

We now show that the proposed method achieves the minimax rate of convergence for the mean prediction in terms of the excess risk $\mathcal{E}_n^m(\cdot)$. We make the following assumptions.

(C1) The reproducing kernel K is symmetric, positive definite, and square integrable.

(C2) Assume that there exists a constant $c > 0$ for any $f \in L_2([0, 1]^3)$ such that

$$\int \mathbb{E} \left\{ \int \int U(s)V(r)f(t, r, s)dsdr \right\}^4 dt \leq c \int \left[\mathbb{E} \left\{ \int \int U(s)V(r)f(t, r, s)dsdr \right\}^2 \right]^2 dt.$$

4.2 Asymptotic Results

(C3) Assume the eigenvalues $\{\rho_k : k \geq 1\}$ of the linear operator $L_{K^{1/2}CK^{1/2}}$

satisfy $\rho_k \asymp k^{-2\omega}$ for some constants $0 < \omega < \infty$.

(C4) For all $i = 1, \dots, n$, there exists a constant $M > 0$ such that $\mathbb{E}(\epsilon_i(t)^2) \leq$

$M < \infty$.

(C5) For all $1 \leq i \leq n$ and $k \geq 1$, we assume that $\langle X_i v_i, L_{K^{1/2}} \zeta_k \rangle_{\mathcal{L}_2}^2 \leq$

ρ_k , $\langle \tau_i Z_i, L_{K^{1/2}} \zeta_k \rangle_{\mathcal{L}_2}^2 \leq \rho_k$, and $\langle \tau_i v_i, L_{K^{1/2}} \zeta_k \rangle_{\mathcal{L}_2}^2 \leq \rho_k$.

Assumption (C1) is to guarantee the spectral decomposition of the kernel via Mercer's theorem. Assumption (C2) is a common assumption in the asymptotic analysis of functional linear models (Cai and Yuan, 2012). It assumes that the fourth moment is bounded by a constant multiplying the square of the second moment. We only make the assumptions for the observed surrogate variables as it is realistic to verify them. The convergence rate in Theorem 1 is determined by the decay rate of the kernel function T , which is assumed in Assumption (C3). The kernel function T is the interaction between the reproducing kernel K and the covariance function C of the two functional predictors. If K and C are perfectly aligned, it is easy to show that the constant r in the rate depends on the decay rates of K and C jointly. In our setting, r is jointly determined by K and C as well as the alignment between K and C in a complicated way. Assumption (C4)

4.2 Asymptotic Results

assumes that the variance of the error terms is bounded. Assumption (C5) ensures that the signal to noise ratios of the functional predictors against the functional measurement errors are sufficiently large for the recovery of the true predictor functions.

Theorem 1. *If Assumptions (C1) to (C5) hold,*

$$\lim_{A \rightarrow \infty} \lim_{n \rightarrow \infty} \sup_{\beta \in \mathcal{H}(K)} \mathbb{P}\{\mathcal{E}_n^m \geq An^{-2\omega/(2\omega+1)}\} = 0,$$

provided that $\lambda \asymp n^{-2\omega/(2\omega+1)}$.

The rate $n^{-2\omega/(2\omega+1)}$ in Theorem 1 matches the minimax lower bound of the convergence rate for the prediction risk under a general function-on-function regression model, as established in Theorem 3 of Sun et al. (2018). Therefore, the rate of the prediction risk for our penalized least squares estimator is the minimax rate.

The model without measurement errors can be considered as a special case with zero measurement errors and its asymptotic result can be proved similarly to Theorem 1 with slightly weaker assumptions. Therefore, we present the result as Corollary 1 with the proof omitted.

(C2') Assume that there exists a constant $c > 0$ for any $f \in L_2([0, 1]^3)$ such

that

$$\int \mathbb{E} \left\{ \int \int X(s)Z(r)f(t, r, s)dsdr \right\}^4 dt \leq c \int \left[\mathbb{E} \left\{ \int \int X(s)Z(r)f(t, r, s)dsdr \right\}^2 \right]^2 dt.$$

Corollary 1. *Let $\mathcal{E}_n$ be the excess risk for the model without functional measurement errors. If Assumptions (C1), (C2'), (C3), and C(4) hold,*

$$\lim_{A \rightarrow \infty} \lim_{n \rightarrow \infty} \sup_{\beta \in \mathcal{H}(K)} \mathbb{P}\{\mathcal{E}_n \geq An^{-2\omega/(2\omega+1)}\} = 0,$$

provided that $\lambda \asymp n^{-2\omega/(2\omega+1)}$.

5. Numerical Experiments

In this section, we study the numerical performance of the proposed approach through simulations. We first compare the proposed method with two other existing methods and then demonstrate how the functional ANOVA works between models (1.1) and (1.2).

We simulated data according to model (1.1) under three different scenarios with different coefficient functions as specified below.

Scenario 1: $\beta(t, r, s) = (r - 0.5)^2 \exp(t) - t\{(s - 0.5)^2 - 0.3s\}$

Scenario 2: $\beta(t, r, s) = \sin(t) \cos(\pi r^3) + \cos(t) \sin(2\pi s)$

5.1 Comparisons with Other Methods

Scenario 3: $\beta(t, r, s) = \exp(-t)\{s^2 + r^2 \cos(\pi s)\}$

When t is fixed, the coefficient function β is additive in r and s in Scenarios 1 and 2, but contains an interaction term between r and s in Scenario 3.

For each scenario, the functional predictors X_i and Z_i were generated from

$$X_i(r) = \sum_{k=1}^{50} (-1)^{k+1} k^{-1} W_{ik} \vartheta_1(r, k), \text{ and } Z_i(s) = \sum_{k=1}^{50} (-1)^{k+1} k^{-1} W_{ik} \vartheta_2(s, k),$$

where the constants W_{ik} were generated from the uniform distribution

$$U(-\sqrt{3}, \sqrt{3}), \vartheta_1(r, k) = 1 \text{ if } k = 1 \text{ and } \vartheta_1(r, k) = \sqrt{2} \cos\{(k-1)\pi r\}$$

otherwise, and $\vartheta_2(s, k) = s^2$ if $k = 1$ and $\vartheta_2(s, k) = \frac{1 - \cos((k-1)\pi s)}{\{(k-1)\pi\}^2}$ otherwise.

We generated $n = 50$ samples, each with 20 time points on the interval $[0, 1]$. The random errors $\epsilon(t)$ were from a normal distribution with zero mean and a constant variance σ^2 . The signal-to-noise ratios (SNR),

$\sum_i \int \mathbb{E}\{\eta_i^2(t)\} dt / \sum_i \int \mathbb{E}\{\epsilon_i^2(t)\} dt$, were set to 1, 5, and 10 in each scenario,

where $\eta_i(t) = \int_0^1 \int_0^1 X_i(r) Z_i(s) \beta(t, r, s) dr ds$.

5.1 Comparisons with Other Methods

We compare our method, *QFFR*, with two function-on-function regression

models for multiple functional predictors, the additive function-on-function

regression method of Scheipl et al. (2015), denoted by *pffr*, and the signal

compression function-on-function regression method of Luo and Qi (2019),

denoted by *FRegSig*. For *pffr* and *FRegSig*, we used their respective R

5.1 Comparisons with Other Methods

	SNR	$QFFR$	$pffr$	$FRegSig$
Scenario 1	1	2.529(1.480)	1.096 (1.023)	4.736(14.83)
	5	1.288(0.510)	0.357 (0.287)	0.815(1.468)
	10	0.747(0.419)	0.157 (0.163)	0.327(0.758)
Scenario 2	1	0.208 (0.148)	5.565(16.44)	1.641(1.951)
	5	0.469 (0.291)	375.7(190.7)	3.414(30.87)
	10	0.225 (0.361)	382.7(398.0)	1.652(1.741)
Scenario 3	1	0.613 (1.026)	5.066(7.862)	2.149(43.98)
	5	0.0398 (0.0669)	0.376(1.063)	0.603(0.819)
	10	0.0198 (0.0316)	0.286(0.462)	0.831(1.253)

Table 1: The averages (standard deviations) of MISEs ($\times 10^{-3}$) under three scenarios. The best result is in boldface.

packages in all the simulations in this section and the real data analysis in the next section.

The prediction accuracy was quantified by the mean integrated squared error $MISE = \frac{1}{\check{n}} \sum_{i=1}^{\check{n}} \int_0^1 \{\eta_i(t) - \hat{\eta}_i(t)\}^2 dt$, where $\check{n}$ was the sample size of testing data, and $\hat{\eta}_i(t) = \int_0^1 \int_0^1 X_i(r) Z_i(s) \hat{\beta}(t, r, s) dr ds$. We repeated the simulation 100 times for testing data of size $\check{n} = 50$. The prediction performances of $QFFR$, $pffr$, and $FRegSig$ in terms of MISE are summarized in Table 1. We also showed the true coefficient functions and their estimates from the three methods when t is fixed at 0.48 in Figure 1. As expected, the MISEs in Table 1 decreased as the SNR increased for each method in each scenario except for the $pffr$ in Scenario 2. Specifically, in Scenario 1 where the true model was additive, $pffr$ had the best performance with the smallest

5.1 Comparisons with Other Methods

MISEs in all the scenarios. This is not surprising since $pffr$ is designed for the additive model, while the interaction terms in $QFFR$ could lead to a slight overfitting problem. Also note that the difference between the MISEs of the two methods is small. Visual inspection in Figure 1 confirms that $QFFR$ indeed did a decent job in estimation and was comparable to $pffr$, but the $FRegSig$ estimate was a little off. For Scenario 2, the true model was also additive but $pffr$ clearly had difficulty in this scenario. The $pffr$ estimate shown in Figure 1 for Scenario 2 was completely off the target, which was also revealed in Table 1. The sinusoidal functions might be challenging for $pffr$. On the other hand, the proposed $QFFR$ method had the best performance both numerically and visually. In Scenario 3, the true model was non-additive. So $pffr$ was expected not to perform well since it assumed an additive structure. Despite this, $pffr$ still had a better performance than $FRegSig$ when the SNRs were high. On the other hand, $QFFR$ was clearly the best both numerically and visually in this non-additive scenario.

To assess the effect of error distributions, we performed the same simulations using heavy-tailed error distributions. In particular, errors from t -distributions with different SNRs were considered. The results, collected in Supplementary Material, show similar patterns to the findings with normally distributed errors.

5.1 Comparisons with Other Methods

Figure 1: Perspective plots of the true coefficient functions $\beta(t, r, s)$ (left panels) and their estimates by $QFFR$, $pffr$, and $FRegSig$ at $t = 0.48$ for the three scenarios.

We also conducted a simulation study to illustrate the finite sample properties of the proposed estimator. The signal-to-noise ratio was set as 5 in Scenarios 1 to 3, and the sample size varied from 20 to 1000. The results ($\log(\text{MISE})$) of the proposed method $QFFR$ as well as $pffr$ and $FRegSig$ were shown in Figure 2. The proposed method converged as the sample size increased. We observed similar patterns for the method $FRegSig$ in different scenarios. The method $pffr$ had the best performance in Scenario

5.1 Comparisons with Other Methods

Figure 2: MISEs of the three methods in (a) Scenario 1, (b) Scenario 2, and (c) Scenario 3

1, but failed to converge in Scenario 2 and 3.

In summary, $QFFR$ is a competitive method in the scenarios of additive models and the best method in the non-additive scenario. While $FRegSig$ delivers satisfactory performance in all the scenarios, it is surely much less accurate than $QFFR$. Since all the three methods employ roughness penalties on the function estimates, a possible reason for $FRegSig$'s lower accuracy might be that its principal component type of optimization is numerically more challenging than the penalized least squares used in the other two methods.

5.2 Functional Measurement Errors

5.2 Functional Measurement Errors

In this section, we showed the estimation results when the covariate functions contained normal distributed errors under the same experiment setting. In particular, we first generated $X_i(r)$ and $Z_i(s)$ as before. Then we added the measurement errors and applied the methods for comparison to $U_i(r) = X_i(r) + \tau_i(r)$ and $V_i(s) = Z_i(s) + v_i(s)$, where $\tau_i(r_j) \sim N(0, \tau^2)$ and $v_i(s_k) \sim N(0, v^2)$ for $i = 1, \dots, n$, $j = 1, \dots, J$, $k = 1, \dots, K$. The response function Y_i was generated using (1.1). In the simulation, we set the SNR of the response to 10 and the SNR of the covariates

$$\text{SNR}_{XZ} = \frac{\sum_i \int \mathbb{E}\{X_i^2(r)\} dr}{\sum_i \tau_i^2} = \frac{\sum_i \int \mathbb{E}\{Z_i^2(s)\} ds}{\sum_i v_i^2}$$

to 2, 5, and 10.

In Table 2, we presented the MISEs of the three methods, i.e., $QFFR$, $pffr$, and $FRegSig$, with their standard deviations under the three scenarios. The distribution of MISEs in Table 2 is similar to that in Table 1. It was expected that the MISEs decreased as the SNR_{XZ} increased. The proposed method $QFFR$ had the best performance in Scenarios 2 and 3. Comparing the results in scenarios with and without measurement errors, we observed that the MISEs increased significantly under scenarios with measurement

5.3 Functional ANOVA Demonstration

	SNR_{XZ}	$QFFR$	$pffr$	$FRegSig$
Scenario 1	2	9.123(2.001)	4.551 (1.221)	10.757(6.830)
	5	1.488(0.475)	1.205 (0.332)	3.075(2.500)
	10	0.998(0.502)	0.875 (0.267)	1.588(0.917)
Scenario 2	2	3.822 (0.971)	7.355(3.487)	9.956(6.751)
	5	1.074 (0.291)	4.357(1.335)	2.462(1.490)
	10	0.569 (0.401)	97.35(78.00)	1.998(0.812)
Scenario 3	2	4.332 (2.083)	4.353(2.105)	8.414(3.025)
	5	0.475 (0.241)	3.257(2.809)	2.782(0.723)
	10	0.180 (0.099)	4.201(0.462)	1.055(0.801)

Table 2: The averages (standard deviations) of MISEs ($\times 10^{-3}$) under three scenarios with measurement errors. The best result is in boldface.

errors. However, when the SNR_{XZ} was large enough, e.g., $\text{SNR}_{XZ} = 10$, the prediction performance was close to that when there were no measurement errors.

5.3 Functional ANOVA Demonstration

We now numerically demonstrate that model (1.1) can be transformed to model (1.2) via the functional ANOVA. To show the transformation, we used the non-additive model from Scenario 3 when there are no measurement errors and set the SNR to 2. Following the functional ANOVA decomposition in (2.3), we estimated the main and interaction coefficient functions in the corresponding function spaces in (2.5). For instance, the main effect coefficient function for the functional predictor $X(t)$ was estimated in the

function subspace $\mathcal{H}_1^y \otimes \mathcal{H}_1^x \otimes \mathcal{H}_0^z$ by using the kernel $K_1^y K_1^x K_0^z$. The details about the kernels and inner products are listed in in Supplementary S2. Then fitting model (1.2) is equivalent to estimating the coefficient vectors corresponding to the basis functions in the subspaces. The three-component coefficient functions for the main and interaction effects in model (1.2) of $\beta(t, r, s) = \exp(-t)\{s^2 + r^2 \cos(\pi s)\}$ are shown in the first row of Figure 3, and the fitted ones are shown in the second row. To graphically present results, we set $t = 0.48$ for the three-dimensional function $\beta_{t,r,s}$. Clearly, the proposed method can successfully recover all the true component coefficient functions via the functional ANOVA.

6. Application: Epigenetic Study for Liver Cancer Cells

In this section, we studied how two types of histone modifications, H3K4me2 and H3K9me3, impacted the gene expression in human liver cancer cell line (HepG2) (Consortium et al., 2012). We calculated the values of fold change over control for histone modifications levels on the promoter region, that is, 1000 bp upstream or downstream of where a gene's transcription begins. To study the liver cancer tumorigenesis, we selected 2,475 liver cancer related genes (Lee et al., 2011). There were 2,142 genes left after filtering out the genes with low histone modifications and gene expression levels.

Figure 3: The functional ANOVA of coefficient functions. The first row shows the decomposition of true function, and those in the second row are fitted coefficient functions.

We removed the genes when the maximum expression value or maximum histone density level was zero. The tight clustering method was applied to the gene expression, H3K4me2, and H3K9me3 levels, respectively (Tseng and Wong, 2005). A tight cluster that contained 59 genes with similar expression patterns was selected. The selected gene names can be found in Supplementary S5. The resulting data are displayed in Figure 4.

We applied *pffr*, *FRegSig*, and the proposed method *QFFR* to the data. Since we were interested in studying how histone modifications regulated gene activities on the promoter region, we used the gene expression levels

Figure 4: Histone modifications and gene expression levels for liver cancer cell line data. The x -axes represent genome coordinates normalized into $[0, 1]$. The y -axes denote normalized density levels of histone modifications (left two panels) and reads per kilobase of transcript, per million mapped reads (RPKM) for gene expression (rightmost panel).

	1st Qu.	Median	Mean (SD)	3rd Qu.
$QFFR$	0.462	0.503	0.487 (0.077)	0.522
$pffr$	0.417	0.515	0.577 (0.227)	0.742
$FRegSig$	0.405	0.565	0.559 (0.382)	0.761

Table 3: The leave-one-out cross-validation scores for $QFFR$, $pffr$, and $FRegSig$ in the liver cancer cell line data. The best result on each metric is in boldface.

as the functional response and the density levels of two histone modifications as the functional predictors. Our proposed method $QFFR$ performed better than the other two methods in terms of the prediction accuracy measured by the leave-one-out cross-validation score, as shown in Table 3. The cross-validation score is defined by $\frac{\sum_{i=1}^n \int \{Y_i(t) - \hat{Y}^{-i}(t)\}^2 dt}{\sum_{i=1}^n \int \{Y_i(t)\}^2 dt}$, where $\hat{Y}^{-i}(t)$ is the predicted value from the model fitted after deleting the i th gene in training data.

Figure 5: Fitted coefficient functions by (a) $QFFR$, (b) $pffr$, and (c) $FRegSig$.

In Figure 5, we showed the coefficient functions estimated by $QFFR$, $pffr$, and $FRegSig$. Each slice represents the estimated coefficient function at a fixed region of genes. It demonstrates how H3K9me3 and H3K4me2 regulate (positively or negatively) gene activities over the promoter region. The coefficient function fitted by $pffr$ displayed a clear pattern of additive effects by H3K4me2 and H3K9me3, i.e., the predicted gene expression level was a simple addition of the separate effects from the two types of histone modifications; see panel (b) of Figure 5. Both $FRegSig$ and $QFFR$ recovered the interaction effect of similar patterns between H3K4me2 and H3K9me3 successfully. However, the interaction effect from our model was more significant than the one in $FRegSig$. For example, according to $FRegSig$, the two histone modifications had only negative effects on gene activities at slices from 0 to 0.2 along the axis of gene; see panel (c) of Figure 5. On the

other hand, the $QFFR$ coefficient estimate revealed more dynamic changes in these slices; see panel (a) of Figure 5. Based on the results in Table 3, $QFFR$ may have estimated the interaction effect more accurately than $FRegSig$.

In Figure 6, we provided the functional ANOVA decomposition of the coefficient function $\hat{\beta}$ estimated by $QFFR$. In panels (a) and (b), we showed the main effects of two types of histone modifications, i.e., H3K4me2 and H3K9me3, respectively. The histone modifications have varied modification effects on gene expression over the promoter regions. The regulation effects were increasing from the starting to the end points of the promoter region, see Panel (a). The regulation patterns for H3K9me3 were clearly different from the patterns for H3K4me2, see Panel (b). When they were working jointly, H3K9me3 regulation effect was more active at the end point of the promoter region for H3K4me2 compared with its effect at the starting point of the promoter region for H3K4me2, see Panel (c).

7. Discussion

In this paper, we propose a penalized least squares method to estimate the coefficient function in a quadratic function-on-function regression model including the interaction between functional predictors. Through the func-

Figure 6: Functional ANOVA decomposition of the coefficient function estimated by *QFFR*. (a) The main effect of H3K4me2, (b) The main effect of H3K9me3, and (c) The interaction effect between H3K4me2 and H3K9me3 at the midpoint of the promoter region of genes.

tional ANOVA decomposition under a RKHS framework, the trivariate coefficient function can naturally split into the main and interaction effects of functional predictors, whose separate estimates are readily available from the trivariate coefficient function estimate. Theoretically, we prove that the estimator for the model with or without functional measurement errors achieves the optimal convergence rate in mean prediction. The simulation studies demonstrate the proposed method has numerical advantages over existent ones. The application to liver cancer cell line data shows how two histone modifications at the promoter region jointly regulated gene activities.

The proposed *QFFR* method also allows easy extensions in several

aspects. For example, separate penalties on different components of the trivariate coefficient function can be enforced by introducing multiple smoothing parameters in the roughness penalty; see, e.g., Section 2.4 in Gu (2013). Also, the model here only contains two functional predictors, but it can be easily extended to models with more than two functional predictors although the computation will become more complicated if three-way or higher order interactions are included. Furthermore, the method can be extended to model a categorical response function such as binary or count response functions.

The number of sampling points per curve is an interesting topic in functional regression models (Cai and Yuan, 2011; Zhang and Wang, 2016). In this paper, we focus on the case when curves are densely sampled such that the asymptotic property of the estimator is the same as the case when the curves are completely known. However, when the curves are sparsely sampled with sampling points randomly dispersed across the curve domain, a common approach is to use the principal component analysis through conditional expectation (PACE) method in Yao et al. (2005a) to perform presmoothing of the curves first; see, e.g., Sun et al. (2018).

Supplementary

In the Supplementary Material, we introduce an example of roughness penalty in S1 and the corresponding reproducing kernels in S2. S3 provides the proof of Theorem 1. The simulation results with random errors from heavy-tailed distributions are shown in S4. In S5, we list the gene names in the real data example. The link to the R codes of the proposed method can be found in S6.

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