

## ESTIMATION IN ADDITIVE MODELS WITH HIGHLY OR NONHIGHLY CORRELATED COVARIATES

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Motivated by normalizing DNA microarray data and by predicting the interest rates, we explore nonparametric estimation of additive models with highly correlated covariates. We introduce two novel approaches for estimating the additive components, integration estimation and pooled backfitting estimation. The former is designed for highly correlated covariates, and the latter is useful for nonhighly correlated covariates. Asymptotic normalities of the proposed estimators are established. Simulations are conducted to demonstrate finite sample behaviors of the proposed estimators, and real data examples are given to illustrate the value of the methodology.

**1. Introduction.** The problem of estimating additive components with highly correlated covariates arises from the normalization of DNA microarray. Since the late 1980s, Affymetrix was founded with the revolutionary idea to use semiconductor manufacturing techniques to create GeneChips (an Affymetrix trademark) or generic DNA microarrays. It makes quartz chips for the analysis of DNA microarrays and covers about 82% of the DNA microarray market. A single chip can be used to do thousands of experiments in parallel, so it produces a lot of Affymetrix GeneChip arrays which demand proper normalization for removing systematic biases such as the intensity effects.

Much research has been devoted to eliminating the systematic biases such as the dye, intensity and print-tip block effects. Examples include the rank-invariant selection method of Tseng et al. (2001), the lowess method of Dudoit et al. (2002) and various information aggregation methods of Fan et al. (2005), Fan, Huang and Peng (2005), Huang, Wang and Zhang (2005) and Huang and Zhang (2005), among others.

Fan et al. (2005), Fan, Huang and Peng (2005) propose a semilinear in-slide model (SLIM) to remove intensity effects and identify significant genes for Affymetrix arrays. Suppose that there are  $G$  genes and for each gene there are  $J$

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Received January 2009; revised August 2009.

<sup>1</sup>Supported by NSF Grant DMS-09-06482.

<sup>2</sup>Supported by NSF Grant DMS-09-06784.

<sup>3</sup>Supported by NSF Grants DMS-07-04337 and DMS-07-14554.

*AMS 2000 subject classifications.* Primary 62G10, 60J60; secondary 62G20.

*Key words and phrases.* Additive model, backfitting, local linear smoothing, normalization, varying coefficient.

replications ( $J \geq 2$ ). Let  $A_{gj}$  and  $B_{gj}$  be the log-detection signal of the  $g$ th probe set in the  $j$ th control and treatment arrays, respectively. Then, we compute the log intensities and log-ratios, respectively, as

$$X_{gj} = (A_{gj} + B_{gj})/2, \quad Y_{gj} = B_{gj} - A_{gj}.$$

Fan et al. (2005), Fan, Huang and Peng (2005) use the following model to estimate the treatment effect, the smooth intensity effect:

$$(1.1) \quad Y_{gj} = \alpha_g + m_j(X_{gj}) + \varepsilon_{gj}, \quad g = 1, \dots, G; j = 1, \dots, J,$$

where  $\alpha_g$  is the treatment effect on gene  $g$ ,  $m_j(X_{gj})$  represents the array-dependent intensity effect to be estimated and  $\varepsilon_{gj}$ 's are independent noises with zero means. For identifiability, we assume that  $E[m_j(X_{gj})] = 0$ .

Directly estimating the treatment effects  $\{\alpha_g\}$  is not a good idea due to the existence of unknown intensity effects, as well as the small size  $J$ . In this paper we first treat  $\{\alpha_g\}$  as nuisance parameters and focus on the estimation of  $m_j$ 's. Once a good estimate  $\hat{m}_j$  of  $m_j$  for each  $j$  is obtained,  $\alpha_g$  can be estimated as  $\hat{\alpha}_g = \frac{1}{J} \sum_{j=1}^J (Y_{gj} - \hat{m}_j(X_{gj}))$ . Therefore, it is essential to efficiently estimate treatment effects  $\{\alpha_g\}$ . The setup applies to the c-DNA microarray data [Fan, Huang and Peng (2005), Huang and Zhang (2005)] and Agilent microarray data [Patterson et al. (2006)]. Moreover, it is also applicable to other problems where confounding effects can nonparametrically be removed.

Fan et al. (2005) used a backfitting algorithm to estimate iteratively the intensity effect and the treatment effect. While this method is successful for removing the systematic biases in some certain situations, mathematical properties of the resulting estimators are unknown which requires further study of the estimation. On the other hand, when performing the estimation method, we found that it is unstable and even fails to converge in some situations. A careful study of this problem reveals that it is caused by the high correlation between intensities. An illustrating example is the DNA microarrays data analyzed in Fan et al. (2005). In this example, the log-intensities across different chips are highly correlated, which is evidenced in Figure 1(left), due to the repeatability and accuracy of the measurements. A close look at the almost identical relationship between covariates suggests that  $|X_{g1} - X_{g2}| \rightarrow 0$ . This suggests a simple working model for calibrating the following plausible correlation structure:

$$X_{g1} = X_{g2} + b_G u_{g2},$$

where  $b_G \rightarrow 0$  and  $u_{g2}$  is random noise. Under such a setting, the problem of effectively estimating the confounding effect  $\{m_j(\cdot)\}$  challenges statisticians. The high correlation reduces the accuracy of estimating  $m_j(\cdot)$ , but  $G$  in such an application is also very large, in an order of tens of thousands.

The problem of highly correlated covariates appears often in modeling time series data such as interest rates. Suppose that we would like to use the past 4

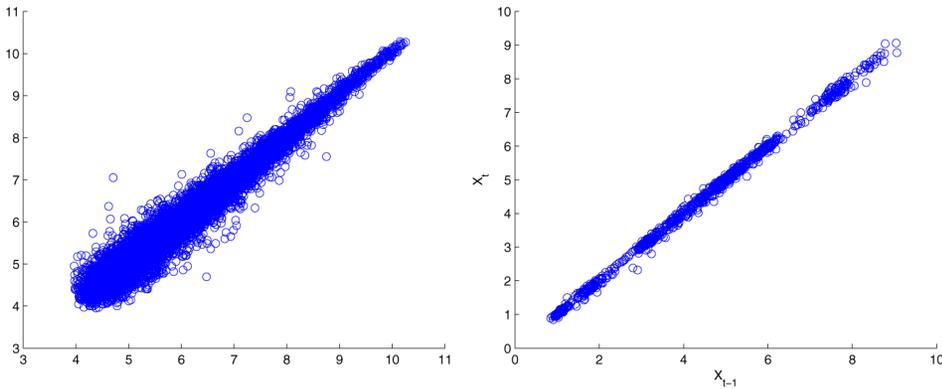


FIG. 1. *Left panel: highly correlated log intensities in Affymetrix array data with  $J = 2$ ; right panel: highly correlated interest rates.  $\{X_t\}$  represents the weekly data of the 6-month treasury bill secondary market rates in the period of June 1, 1988 to June 1, 2008.*

weeks'  $(X_{t-1}, \dots, X_{t-4})$  interest rates to forecast the return of a stock or index  $Y_t$  or the interest rate itself  $Y_t = X_t$  in the next week. A reasonable nonparametric model is the following additive model:

$$Y_t = \mu + m_1(X_{t-1}) + \dots + m_4(X_{t-4}) + \varepsilon_t.$$

Due to the continuity of the interest rate dynamics, the covariates in the above additive model is also highly correlated and can be handled by the idea in this paper. Figure 1(right) shows the scatter plot of  $X_t$  versus  $X_{t-1}$  using the weekly data for the 6-month treasury bill secondary market rates in the period of June 1, 1988 to June 1, 2008.

Existing methods in the literature do not appear enough to address the problem with additive modeling with highly correlated covariates, and a new methodology is needed. In particular, in addition to the aforementioned failure in convergence, the backfitting algorithm usually converges slowly due to the very large number of genes  $G$  which is usually in the order of tens of thousands in a typical microarray application. This motivates us to develop statistical methods fitting the smooth confounding effect model (1.1) with/without highly correlated intensity effects.

The above model received attention in Fan et al. (2005), Fan, Huang and Peng (2005). However, there is no formal study of modeling highly correlated covariates  $X_{gj}$ . For the usual correlation situation, Fan, Huang and Peng (2005) considered the estimator of  $m_j$  using the profile least squares and obtained only an upper bound for the conditional mean squared error of the estimator. However, information across arrays is not used, and the asymptotic distribution of the estimator is unknown which makes the inference about the intensity effects difficult.

In this investigation, we introduce two methods for estimating the nonparametric components  $m_j$ , integration estimation and pooled backfitting estimation. The

former is tailored for modeling highly correlated intensity effects and is a noniterative estimator with fast implementation. It relies on estimating the derivative function in a varying coefficient model, and allows us to handle a very large amount of observations. The latter is an iterative estimate which is designed for modeling nonhighly correlated intensity effects. Asymptotic normalities of the proposed estimators are established. The extent to which the high correlation affects the rates of convergence is explicitly given. Simulation studies are conducted to demonstrate finite sample behaviors of the proposed methods.

The paper is organized as follows. In Section 2 we introduce the integration estimation method along with an alternative of robustness. In Section 3 we develop pooled backfitting estimation of the intensity effects. In Section 4 we conduct simulations. In Section 5 we illustrate the proposed methodology by two real data examples. Finally we conclude the paper with a discussion. Details of assumptions and proofs of theorems are given in Appendices A and B.

**2. Estimation of additive components when covariates are highly correlated.** To use information across arrays, one can take a difference operator to remove the nuisance parameters  $\{\alpha_g\}$  which leads to additive models. Specifically, let  $Y_g^{(k)} = Y_{g1} - Y_{gk}$  and  $\varepsilon_g^{(k)} = \varepsilon_{g1} - \varepsilon_{gk}$ . Then by (1.1), for  $k = 2, \dots, J$ ,

$$(2.1) \quad Y_g^{(k)} = m_1(X_{g1}) - m_k(X_{gk}) + \varepsilon_g^{(k)}, \quad g = 1, \dots, G,$$

which are additive models introduced by Friedman and Stuetzle (1981) and Hastie and Tibshirani (1990) where  $\varepsilon_g^{(k)}$  are the errors with zero means, and for  $j \neq k$ ,  $\text{Cov}(\varepsilon_g^{(j)}, \varepsilon_g^{(k)}) = \sigma^2$  and  $\text{Var}(\varepsilon_g^{(j)}) = 2\sigma^2$ . The additive components can be estimated via the backfitting method. Due to the high correlation between  $X_{g1}$  and  $X_{gk}$ , the estimate based on the backfitting algorithm usually fails in convergence, and the existence of a backfitting estimator is problematic. Moreover, asymptotic properties of the backfitting estimators are unknown in this situation. Thus a new methodology is needed to deal with this problem. To this end, in the following we focus on the cases with highly correlated covariates and introduce the integration estimation and then establish asymptotic normality of the resulting estimators under a working model. The estimators are consistent, regardless of the working model.

*2.1. Estimation when covariates are highly correlated.* As illustrated in the previous section, covariates  $X_{gj}$  (for  $j = 1, \dots, J$ ) may be very close and highly correlated, so it is convenient to assume that

$$(2.2) \quad \Delta_{gk} \equiv X_{g1} - X_{gk} \rightarrow 0.$$

Under such a setting, the asymptotic properties of the backfitting estimates are unknown, and the convergence of the backfitting algorithm may also be a problem

since the required condition, that is, the existence of the joint density of covariates, is not always satisfied. See, for example, Opsomer and Ruppert (1997, 1998). Assume  $m_1'$  is continuous; then by Taylor's expansion,

$$(2.3) \quad \begin{aligned} m_1(X_{g1}) &= m_1(X_{gk}) + m_1'(X_{gk})\Delta_{gk} \\ &\quad + \frac{1}{2}m_1''(X_{gk})\Delta_{gk}^2 + o(\Delta_{gk})^2. \end{aligned}$$

Substituting (2.3) into (2.1), we obtain that

$$(2.4) \quad Y_g^{(k)} = m_{k1}(X_{gk}) + m_1'(X_{gk})\Delta_{gk} + \tilde{\varepsilon}_g^{(k)},$$

where  $m_{k1}(X_{gk}) = m_1(X_{gk}) - m_k(X_{gk})$  and  $\tilde{\varepsilon}_g^{(k)} = \frac{1}{2}m_1''(X_{gk})\Delta_{gk}^2 + o(\Delta_{gk})^2 + \varepsilon_g^{(k)}$ . Model (2.4) is actually a varying coefficient model, since the coefficient functions  $m_{k1}(\cdot)$  and  $m_1'(\cdot)$  are unknown functions of  $X_{gk}$ . This allows us to estimate the unknown coefficient functions  $m_1'(\cdot)$  using local smoothing techniques. Given an interior point  $x \in \text{supp}[f_k(\cdot)]$ , using the local linear approximation when  $|X_{gk} - x| \leq h$ , we obtain that

$$(2.5) \quad \begin{aligned} m_{k1}(X_{gk}) + m_1'(X_{gk})\Delta_{gk} \\ \approx \alpha_0 + \alpha_1(X_{gk} - x) + \Delta_{gk}\{\beta_0 + \beta_1(X_{gk} - x)\}. \end{aligned}$$

Then the coefficient function  $m_1'(\cdot)$  can be estimated by minimizing

$$(2.6) \quad \begin{aligned} \sum_{g=1}^G [Y_g^{(k)} - \alpha_0 - \alpha_1(X_{gk} - x) \\ - \Delta_{gk}\{\beta_0 + \beta_1(X_{gk} - x)\}]^2 K_h(X_{gk} - x), \end{aligned}$$

where  $K_h(\cdot) = h^{-1}K(\cdot/h)$  with  $K(\cdot)$  being a kernel function and  $h$  being a bandwidth controlling the amount of data in smoothing. Denote by  $\{\hat{\alpha}(x), \hat{\beta}(x)\}$  with  $\hat{\alpha}(x) = (\hat{\alpha}_0(x), \hat{\alpha}_1(x))$  and  $\hat{\beta}(x) = (\hat{\beta}_0(x), \hat{\beta}_1(x))$  the solution to the above equation. Then  $\hat{\beta}_0(x)$  and  $\hat{\beta}_1(x)$  estimate  $m_1'(x)$  and  $m_1''(x)$ , respectively. If  $\Delta_{gk} = o(1)$ , then  $E[\tilde{\varepsilon}_g^{(k)}|X_{gk} = x] = o(1)$ , and hence the above estimator is consistent. The method is noniterative and can handle the situation where  $G$  is very large. Once the derivative  $m_1'(\cdot)$  is given, the component  $m_1$  in model (2.1) can be derived as follows.

Let  $\mathbf{K} = \text{diag}\{K_h(X_{1k} - x), \dots, K_h(X_{Gk} - x)\}$ ,  $\hat{\theta}(x) = (\hat{\alpha}_0, \hat{\alpha}_1, \hat{\beta}_0, \hat{\beta}_1)^T$ ,

$$Z_g = (1, X_{gk} - x, b_{GU_{gk}}, b_{GU_{gk}}(X_{gk} - x))^T$$

and  $\mathbf{Z} = (Z_1, \dots, Z_G)^T$ . Then  $\hat{\theta}(x)$  admits the following closed form:

$$(2.7) \quad \hat{\theta}(x) = (\mathbf{Z}^T \mathbf{KZ})^{-1} \mathbf{Z}^T \mathbf{KY}_{(k)},$$

where  $\mathbf{Y}_{(k)} = (Y_1^{(k)}, \dots, Y_G^{(k)})^T$ . Let

$$\theta(x) = (m_{1k}(x), m'_{1k}(x), m_1'(x), m_1''(x))^T.$$

Then  $\hat{\theta}(x)$  estimates  $\theta(x)$ , and  $m'_1(x)$  is estimated by  $\hat{m}'_1(x; k) = e_3^T \hat{\theta}(x)$  with  $e_3 = (0, 0, 1, 0)^T$ .

Since averaging can reduce the variance of estimation, we propose to estimate  $m'_1(\cdot)$  by the following average:

$$(2.8) \quad \hat{m}'_1(x) = (J - 1)^{-1} \sum_{k=2}^J \hat{m}'_1(x; k).$$

Note that, for each  $k$ ,  $\hat{m}'_1(x; k)$  is consistent. The estimator  $\hat{m}'_1(\cdot)$  is also consistent. From the estimated derivative function, the original function  $m_1(\cdot)$  can consistently be estimated using integration which we now detail below.

Let  $F_j(\cdot)$  and  $f_j(\cdot)$  be, respectively, the distribution and density functions of  $X_{gj}$ . Due to the identifiability condition  $E[m_1(X_{g1})] = 0$  and  $m_1(x) = m_1(x_0) + \int_{x_0}^x m'_1(t) dt$  (for any  $x_0 \in \text{supp}[F_1(\cdot)]$ ), we obtain that

$$\int \left\{ m_1(x_0) + \int_{x_0}^x m'_1(t) dt \right\} dF_1(x) = 0$$

and hence  $m_1(x_0) = - \int \int_{x_0}^x m'_1(t) dt dF_1(x)$ . Therefore,  $m_1(x)$  can be estimated by

$$(2.9) \quad \hat{m}_1(x) = - \int \int_{x_0}^x \hat{m}'_1(t) dt d\hat{F}_1(x) + \int_{x_0}^x \hat{m}'_1(t) dt,$$

where  $\hat{F}_1$  is the empirical estimator of  $F_1$ . Note that the first term in (2.9) is a constant, making merely the estimated function to satisfy an empirical version of the identifiability condition. Similarly, we can estimate the other components'  $m_j$ 's (for  $j = 2, \dots, J$ ) in model (2.1). Such defined estimators are naturally consistent due to consistency of the estimators of derivative functions.

*2.2. Asymptotic normality.* To provide in-depth analysis on the behavior of the estimators defined in (2.7)–(2.9), we model explicitly the high correlation among covariates. One viable choice is to employ the following working model:

$$(2.10) \quad X_{g1} = X_{gk} + b_G u_{gk},$$

where  $b_G \rightarrow 0$  and  $\{u_{gk}\}_{g=1}^G$  are noises of zero mean and finite variance. Assume that the density function of  $u_{gk}$ ,  $p_k(x)$ , has a compact support and that  $\{u_{gk}\}$  are independent of  $\{X_{gk}\}$  for fixed  $k$ . This specification allows for heteroscedasticity of the errors. Obviously, in model (2.10) the correlation between  $X_{g1}$  and  $X_{gk}$  goes to one as  $b_G \rightarrow 0$ . There are various alternative methods for modelling high correlation between two variables. We focus only on model (2.10) to make an attempt. Note that the working model (2.10) is only used to derive the asymptotic properties. The estimator itself does not depend on such an assumption.

Denote by  $\mu_j(K) = \int t^j K(t) dt$  and  $\nu_j(K) = \int t^j K^2(t) dt$ . Let  $\mathbf{H} = \text{diag}(\mathbf{h}, b_G \mathbf{h})$ ,  $\mathbf{S} = \text{diag}(\mathbf{N}, \mathbf{N})$ ,  $\mathbf{V} = \text{diag}(\mathbf{v}, \mathbf{v})$ ,  $\mathbf{C} = \text{diag}(\mathbf{c}_2, \mathbf{c}_2)$  and  $\mathbf{c}^* = (\mathbf{c}_0^T, \mathbf{c}_0^T E(u_{1k}^3))^T$

where  $\mathbf{h} = \text{diag}(1, h)$ ,  $\mathbf{N} = \text{diag}\{\mu_0(K), \mu_2(K)\}$ ,  $\mathbf{v} = \text{diag}\{v_0(K), v_2(K)\}$  and  $\mathbf{c}_j = (\mu_j(K), \mu_{j+1}(K))^T$ . The following theorems describe the asymptotic properties of the proposed estimators.

**THEOREM 2.1.** *Suppose that the conditions in Appendix A hold. Under the working model (2.10), if  $Gh^5 = O(1)$  and  $Ghb_G^4 = O(1)$ , then*

$$\sqrt{Gh}\{\mathbf{H}[\hat{\theta}(x) - \theta(x)] - \mathbf{b}(x)(1 + o_p(1))\} \xrightarrow{\mathcal{D}} \mathcal{N}(0, \Sigma(x)),$$

where

$$\mathbf{b}(x) = \frac{1}{2}h^2\mathbf{S}^{-1}\mathbf{C}(m''_{1k}(x), b_G m_1^{(3)}(x))^T + \frac{1}{2}b_G^2 m_1''(x)\mathbf{S}^{-1}\mathbf{c}^*$$

and  $\Sigma(x) = 2\sigma^2 f_1^{-1}(x)\mathbf{S}^{-1}\mathbf{V}\mathbf{S}^{-1}$ .

**COROLLARY 2.1.** *Under the conditions in Theorem 2.1,*

$$\sqrt{Ghb_G}\{\hat{m}'_1(x; k) - m'_1(x) - b_1(x)\} \xrightarrow{\mathcal{D}} \mathcal{N}(0, \sigma_1^2(x)),$$

where

$$b_1(x) = \frac{1}{2}h^2\mu_2(K)\mu_0^{-1}(K)m_1^{(3)}(x)(1 + o_p(1)) + \frac{1}{2}b_G m_1''(x)E(u_{1k}^3)(1 + o_p(1))$$

and  $\sigma_1^2(x) = 2\sigma^2 f_1^{-1}(x)v_0(K)\mu_0^{-2}(K)$ .

The above corollary shows that the data from two arrays suffice to obtain a consistent estimate of the derivative function. However, the high correlation reduces the effective sample size from  $G$  to  $Gb_G^2$ , in terms of the rates of convergence.

In order to present asymptotics of the average estimator (2.8), we need the dependence structure of  $\{u_{gk}\}$  across  $k$ . Let  $\rho(\ell, k) = E(u_{g\ell}u_{g,k})$ , which does not depend on  $g$ , and

$$\rho = \left\{ \sum_{k=2}^J \rho(k, k) + \sum_{k_1=2}^J \sum_{k_2=2}^J \rho(k_1, k_2) \right\} / (J - 1)^2.$$

**THEOREM 2.2.** *Under the conditions in Theorem 2.1,*

$$\sqrt{Ghb_G}\{\hat{m}'_1(x) - m'_1(x) - b_1(x)\} \xrightarrow{\mathcal{D}} \mathcal{N}(0, \sigma_2^2(x)),$$

where  $\sigma_2^2(x) = \rho\sigma^2 f_1^{-1}(x)v_0(K)\mu_0^{-2}(K)$ .

The above asymptotics of the estimators is derived under the working model (2.10). However, as previously stated, if condition (2.2) holds, our estimator for  $m'_1(x)$  is consistent whether or not the working model (2.10) holds. This furnishes robustness of our estimator  $\hat{m}'_1(x)$  against mis-specification of the correlation between covariates. If interested in estimating the derivative function, one can directly compute the asymptotic bias and variance of  $\hat{m}'_1(x)$  and obtain the optimal

bandwidth by minimizing the asymptotic mean square error so that a data-driven bandwidth selection rule can be developed as in the one-dimensional nonparametric regression problem. In the following we state the asymptotic normality of the integrated estimator.

**THEOREM 2.3.** *Suppose that the conditions in Appendix A hold. Under the working model (2.10), if  $Gb_G^2h^4 = O(1)$  and  $Gb_G^4 = O(1)$ , then*

$$\sqrt{G}b_G\{\hat{m}_1(x) - m_1(x) - B_1(x)(1 + o_p(1))\} \xrightarrow{D} \mathcal{N}(0, \sigma^2(x)),$$

where  $\sigma^2(x) = \frac{1}{4}\rho\sigma^2 f_1^{-2}(x)$  and

$$B_1(x) = \frac{1}{2}h^2\mu_2(K)\mu_0^{-1}(K)\{m_1''(x) - E[m_1''(X_{11})]\} \\ + \frac{1}{2}b_G E(u_{1k}^3)\{m_1'(x) - E[m_1'(X_{11})]\}.$$

**REMARK 2.1.** If  $h = o(\sqrt{b_G})$ , then the bias term is

$$B_1(x) = \frac{1}{2}b_G E(u_{1k}^3)\{m_1'(x) - E[m_1'(X_{11})]\}(1 + o(1))$$

and hence the asymptotic normality of the estimator does not depend on the smoothing parameter  $h$  nor the kernel  $K$ . It parallels the result of Jiang, Cheng and Wu (2002) for estimating distribution functions and contrasts with the dependence on smoothing parameter of the nonparametric function estimation.

**REMARK 2.2.** The estimate  $\hat{m}_1(\cdot)$  achieves a maximum convergence rate  $O(G^{-1/4})$  when  $b_G = O(G^{-1/4})$ . The convergence rate can be improved if one uses a higher order polynomial approximation in (2.5).

**2.3. A pooled robust approach.** In model (2.1), we aim at estimating  $m_1(\cdot)$ . It has various versions of implementations. To illustrate the idea, we use aggregated local constant approximation along with the  $L_1$ -loss to illustrate the versatility. For  $|X_{gk} - x| = O(h)$ , we have  $m_{k1}(X_{gk}) \approx m_{k1}(x)$  and  $m_1'(X_{gk}) \approx m_1'(x)$ . Then, by (2.4), we can run the local regression by minimizing

$$(2.11) \quad \sum_{k=2}^J \sum_{g=1}^G |Y_g^{(k)} - \alpha_{k,0} - \beta_0 \Delta_{gk}| K_h(X_{gk} - x)$$

with  $Y_g^{(k)} = Y_{g1} - Y_{gk}$ ,  $\Delta_{gk} = X_{g1} - X_{gk}$  and  $K_h(\cdot) = h^{-1}K(\cdot/h)$ . Notice that we pool data from different replicates in (2.11) to obtain more accurate estimators, and the  $L_1$  norm is used to alleviate the influence of outliers. Denote by  $(\hat{\alpha}_{2,0}, \dots, \hat{\alpha}_{J,0}, \hat{\beta}_0(x))$  the solution to the above minimization problem. Then  $\hat{\beta}_0(x)$  estimates  $m_1'(x)$ . Integrating  $\hat{\beta}_0(x)$  leads to an estimate of  $m_1(x)$ . In our experience, this estimation approach performs similarly to the method in previous sections.

**3. Backfitting estimation of additive components.** In this section, we introduce pooled backfitting estimators of  $m_j$  and study their asymptotic properties under nonhigh correlation situations.

3.1. *Fitting a bivariate additive model using the local linear smoother based on the backfitting algorithm.* There are some methods for fitting the additive model (2.1). For example, the common backfitting estimation of Buja, Hastie and Tibshirani (1989) and Opsomer and Ruppert (1997, 1998), the marginal integration methods of Tjøtheim and Auestad (1994), Linton and Nielsen (1995) and Fan, Härdle and Mammen (1998), the estimating equation method of Mammen, Linton and Nielsen (1999) and the smooth backfitting method in Nielsen and Sperlich (2005), among others. For illustration, we will use the common backfitting algorithm based on the local linear smoother as a building block to estimate the additive components. Other estimation methods can similarly be applied.

To ensure identifiability of the additive component functions  $m_j(\cdot)$ , we impose the constraint  $E[m_j(X_{gj})] = 0$  for  $j = 1, \dots, J$ . Fitting the additive component  $m_j(\cdot)$  in (2.1) requires choosing bandwidths  $\{h_j\}$ . The optimal choice of  $h_j$  can be obtained as in Opsomer and Ruppert (1998). We here follow notation that was introduced by Opsomer and Ruppert (1997). Put  $K_{h_j}(x) = h_j^{-1}K(\frac{x}{h_j})$ ,  $K_s(v) = v^{s-1}K(v)$ ,  $\mathbf{H}_j = \text{diag}(1, h_j)$ ,  $\mathbf{m}_j = \{m_j(X_{1j}), \dots, m_j(X_{Gj})\}^T$ ,  $\mathbf{X}_j = (X_{1j}, \dots, X_{Gj})^T$  and  $\mathbf{Y}_k = (Y_1^{(k)}, \dots, Y_G^{(k)})^T$ . The smoothing matrices for local polynomial regression are

$$\mathbf{S}_j = (\mathbf{s}_{j,X_{1j}}, \dots, \mathbf{s}_{j,X_{Gj}})^T,$$

where  $\mathbf{s}_{j,x_j}^T$  represents the equivalent kernel for the  $j$ th covariate at the point  $x_j$ .

$$(3.1) \quad \mathbf{s}_{j,x_j}^T = \mathbf{e}_1^T (\mathbf{X}_{x_j}^{(j)T} \mathbf{K}_{x_j} \mathbf{X}_{x_j}^{(j)})^{-1} \mathbf{X}_{x_j}^{(j)T} \mathbf{K}_{x_j}.$$

Here  $\mathbf{e}_1^T = (1, 0)$ ,  $\mathbf{K}_{x_j} = \text{diag}\{K_{h_j}(X_{1j} - x_j), \dots, K_{h_j}(X_{Gj} - x_j)\}$  and

$$\mathbf{X}_{x_j}^{(j)} = \begin{bmatrix} 1 & (X_{1j} - x_j) \\ \vdots & \vdots \\ 1 & (X_{Gj} - x_j) \end{bmatrix}.$$

From (2.1),  $\mathbf{m}_j$ 's can be estimated through the solutions to the following set of normal equations [see Buja, Hastie and Tibshirani (1989), Opsomer and Ruppert (1997)]:

$$\begin{bmatrix} \mathbf{I}_G & \mathbf{S}_1^* \\ \mathbf{S}_k^* & \mathbf{I}_G \end{bmatrix} \begin{bmatrix} \hat{\mathbf{m}}_1 \\ -\hat{\mathbf{m}}_k \end{bmatrix} = \begin{bmatrix} \mathbf{S}_1^* \\ \mathbf{S}_k^* \end{bmatrix} \mathbf{Y}^{(k)},$$

where  $\mathbf{S}_j^* = (\mathbf{I}_G - \mathbf{1}\mathbf{1}^T/G)\mathbf{S}_j$  is the centered smoother matrix, and  $\mathbf{1}$  is a  $G \times 1$  vector whose elements are all ones. In practice, the backfitting algorithm [Buja,

Hastie and Tibshirani (1989)] is usually used to solve these equations, and the backfitting estimators converge to the solution,

$$(3.2) \quad \begin{bmatrix} \hat{\mathbf{m}}_1^{(k)} \\ -\hat{\mathbf{m}}_k \end{bmatrix} = \begin{bmatrix} \mathbf{I}_G & \mathbf{S}_1^* \\ \mathbf{S}_k^* & \mathbf{I}_G \end{bmatrix}^{-1} \begin{bmatrix} \mathbf{S}_1^* \\ \mathbf{S}_k^* \end{bmatrix} \mathbf{Y}^{(k)} \quad \text{for } k = 2, \dots, J,$$

where the superscript in  $\hat{\mathbf{m}}_1^{(k)}$  is used to stress the dependence of  $\hat{\mathbf{m}}_1$  on  $k$ .

If  $\|\mathbf{S}_1^* \mathbf{S}_k^*\| < 1$ , then the backfitting estimators exist and are unique where we use  $\|\mathbf{A}\|$  to denote the maximum row sum matrix norm of the square matrix  $\mathbf{A}$ :  $\|\mathbf{A}\| = \max_{1 \leq i \leq G} \sum_{j=1}^G |A_{ij}|$ . A sufficient condition for  $\|\mathbf{S}_1^* \mathbf{S}_k^*\| < 1$  is

$$(3.3) \quad \sup_{x_1, x_k} \left| \frac{f_{1k}(x_1, x_k)}{f_1(x_1)f_k(x_k)} - 1 \right| < 1,$$

where  $f_j(x_j)$  is the density of  $X_j$ , and  $f_{1k}(x_1, x_k)$  is the joint density of  $X_{g1}$  and  $X_{gk}$  [see Opsomer and Ruppert (1997)]. We assume in this section the above condition holds. Note that this condition does not hold for the working model (2.10) since the joint density of  $(X_{g1}, X_{gk})$  is nearly degenerate. Solving (3.2), we get

$$(3.4) \quad \hat{\mathbf{m}}_1^{(k)} = \{\mathbf{I}_G - (\mathbf{I}_G - \mathbf{S}_1^* \mathbf{S}_k^*)^{-1} (\mathbf{I}_G - \mathbf{S}_1^*)\} \mathbf{Y}^{(k)} \equiv \mathbf{W}_{1k} \mathbf{Y}^{(k)}.$$

Since averaging can reduce the variance, we propose to estimate  $\mathbf{m}_1$  by

$$(3.5) \quad \hat{\mathbf{m}}_1 = (J - 1)^{-1} \sum_{k=2}^J \hat{\mathbf{m}}_1^{(k)},$$

which is termed as the pooled backfitting estimator of  $\mathbf{m}_1$ . For other components  $\mathbf{m}_j$ , they can be estimated in a similar way. Thus, in the following, we will focus on the estimation of  $\mathbf{m}_1$ . The integration method in the previous section is simpler and much faster to compute since it uses only one smoothing parameter  $h$  and does not involve any iteration.

To derive the asymptotic properties of  $\hat{\mathbf{m}}_1$ , in the following we introduce some notation in Opsomer and Ruppert (1997). Define

$$D_{x, h_1} = \{t : (x + h_1 t) \in \text{supp}(f_1)\} \cap \text{supp}(K).$$

Then  $x$  is called ‘‘an interior point’’ if any only if  $D_{x, h_1} = \text{supp}(K)$ . Otherwise,  $x$  is a boundary point. Define the kernel  $K_{(1)}(u) = K(u)/\mu_0(K)$ , which is the asymptotic counterpart of the equivalent kernel induced by the local linear fit. Then  $\mu_2(K_{(1)}) = \mu_2(K)\mu_0^{-1}(K)$  and  $\nu_0(K_{(1)}) = \nu_0(K)\mu_0^{-2}(K)$ . Let  $T_{1k}^*$  be a matrix whose  $(i, j)$ th element is

$$[T_{1k}^*]_{ij} = G^{-1} \{f_{1k}(x_1, x_k) f_1^{-1}(x_1) f_k^{-1}(x_k) - 1\}.$$

Let  $\mathbf{t}_g^T$  represent the  $g$ th row of  $(I - T_{1k}^*)^{-1}$ , and  $\mathbf{e}_g$  be the  $g$ th unit vector.

**THEOREM 3.1.** *Suppose that the conditions in Appendix A hold. If  $X_{g1}$  is an interior point, then as  $G \rightarrow \infty$ :*

(i) *the bias of  $\hat{m}_1(X_{g1})$  conditional on  $\mathbf{X} = (\mathbf{X}_1, \mathbf{X}_k)$  is*

$$E\{\hat{m}_1(X_{g1}) - m_1(X_{g1})|\mathbf{X}\} = b_1 - b_2 + O_p\left(\frac{1}{\sqrt{G}}\right) + o_p\left(\sum_{j=1}^J h_j^2\right),$$

where  $b_1 = \frac{1}{2}h_1^2\mu_2(K_{(1)})[m_1''(X_{g1}) + \{(\mathbf{t}_g^T - \mathbf{e}_g^T)\mathbf{m}_1'' - E(m_1''(X_{g1}))\}]$  and

$$b_2 = \frac{1}{2}\mu_2(K_{(1)})\frac{1}{J-1}\sum_{k=2}^J h_k^2\{\mathbf{t}_g^T E(m_k''(X_{gk})|\mathbf{X}_1) - E(m_k''(X_{gk}))\};$$

(ii) *the variance of  $\hat{m}_1(X_{g1})$  conditional on  $\mathbf{X}$  is*

$$\text{Var}\{\hat{m}_1(X_{g1})|\mathbf{X}\} = \frac{J}{J-1}\frac{1}{Gh_1}\sigma^2 f_1^{-1}(X_{g1})v_0(K_{(1)}) + o_p\left(\frac{1}{Gh_1}\right).$$

As in Corollary 4.3 of Opsomer and Ruppert (1997), if the covariates are independent, the conditional bias of  $\hat{m}_1(X_{g1})$  in the interior of  $\text{supp}(f)$  can be approximated by

$$E\{\hat{m}_1(X_{g1}) - m_1(X_{g1})|\mathbf{X}\} = \frac{1}{2}h_1^2\mu_2(K_{(1)})\{m_1''(X_{g1}) - E(m_1''(X_{g1}))\} + O_p(1/\sqrt{G}) + o_p\left(\sum_{j=1}^J h_j^2\right).$$

**3.2. Fitting a  $J$ -variate additive model using local linear smoother based on backfitting.** In the previous section, we used the differences between any two different replicates for genes to eliminate the nuisance parameters. It resulted in two-dimensional additive models, which were easy to implement, but for each additive model, the estimator was asymmetric. In the following we use differences between any replicate and the average of those replicates. This will lead to a  $J$ -dimensional additive model with symmetric estimation.

Let

$$\bar{Y}_g = J^{-1}\sum_{j=1}^J Y_{gj}, \quad \bar{m}(X_g) = J^{-1}\sum_{j=1}^J m_j(X_{gj})$$

and  $\bar{\varepsilon}_g = J^{-1}\sum_{j=1}^J \varepsilon_{gj}$ . Then by (1.1) we have

$$(3.6) \quad \bar{Y}_g = \alpha_g + \bar{m}(X_g) + \bar{\varepsilon}_g.$$

Subtracting (3.6) from (1.1), we obtain that for  $j = 1, \dots, J$ ,

$$(3.7) \quad Y_{gj}^* = -\frac{1}{J}\sum_{k \neq j} m_k(X_{gk}) + \frac{J-1}{J}m_j(X_{gj}) + \varepsilon_{gj}^*,$$

where  $Y_{gj}^* = Y_{gj} - \bar{Y}_g$  and  $\varepsilon_{gj}^* = \varepsilon_{gj} - \bar{\varepsilon}_g$ . It can be seen that  $\text{Var}(\varepsilon_{gj}^*) = (1 - 1/J)\sigma^2$  and  $\text{Cov}(\varepsilon_{gj}^*, \varepsilon_{kj}^*) = 0$  for  $g \neq k$ . For any fixed  $j$ , let

$$m_{j,j}^*(X_{gj}) = (J - 1)J^{-1}m_j(X_{gj})$$

and  $m_{k,j}^*(X_{gk}) = -J^{-1}m_k(X_{gk})$  for  $k \neq j$ . Then (3.7) becomes

$$(3.8) \quad Y_{gj}^* = \sum_{k=1}^J m_{k,j}^*(X_{gk}) + \varepsilon_{gj}^*.$$

This is a  $J$ -variate additive model. Again, we can estimate the additive components using the local linear smoother based on the backfitting algorithm.

Fitting the additive component  $m_j$  in (3.7) requires choosing bandwidths  $\{h_j\}$ . The optimal choice of  $h_j$  can be obtained as in Opsomer and Ruppert (1998) and Opsomer (2000). Put

$$\mathbf{m}_{k,j}^* = \{m_{k,j}^*(X_{1k}), \dots, m_{k,j}^*(X_{Gk})\}^T \quad \text{and} \quad \mathbf{Y}_j^* = (Y_{1j}^*, \dots, Y_{Gj}^*)^T.$$

Then the additive components can be estimated through the solutions to the following set of normal equations:

$$\begin{bmatrix} \mathbf{I}_G & \mathbf{S}_1^* & \cdots & \mathbf{S}_1^* \\ \mathbf{S}_2^* & \mathbf{I}_G & \cdots & \mathbf{S}_2^* \\ \vdots & \vdots & \ddots & \vdots \\ \mathbf{S}_J^* & \mathbf{S}_J^* & \cdots & \mathbf{I}_G \end{bmatrix} \begin{bmatrix} \mathbf{m}_{1,j}^* \\ \mathbf{m}_{2,j}^* \\ \vdots \\ \mathbf{m}_{J,j}^* \end{bmatrix} = \begin{bmatrix} \mathbf{S}_1^* \\ \mathbf{S}_2^* \\ \vdots \\ \mathbf{S}_J^* \end{bmatrix} \mathbf{Y}_j^*,$$

where  $\mathbf{S}_j^* = (\mathbf{I}_G - \mathbf{1}\mathbf{1}^T/G)\mathbf{S}_j$  is the centered smoother matrix, and  $\mathbf{S}_j$  is defined the same as before. The backfitting estimators converge to the solution,

$$(3.9) \quad \begin{bmatrix} \hat{\mathbf{m}}_{1,j}^* \\ \hat{\mathbf{m}}_{2,j}^* \\ \vdots \\ \hat{\mathbf{m}}_{J,j}^* \end{bmatrix} = \begin{bmatrix} \mathbf{I}_G & \mathbf{S}_1^* & \cdots & \mathbf{S}_1^* \\ \mathbf{S}_2^* & \mathbf{I}_G & \cdots & \mathbf{S}_2^* \\ \vdots & \vdots & \ddots & \vdots \\ \mathbf{S}_J^* & \mathbf{S}_J^* & \cdots & \mathbf{I}_G \end{bmatrix}^{-1} \begin{bmatrix} \mathbf{S}_1^* \\ \mathbf{S}_2^* \\ \vdots \\ \mathbf{S}_J^* \end{bmatrix} \mathbf{Y}_j^* \equiv \mathbf{M}^{-1}\mathbf{C}\mathbf{Y}_j^*,$$

provided that the inverse of  $\mathbf{M}$  exists.

As in Opsomer (2000), we define the additive smoother matrix as

$$\mathbf{W}_k = \mathbf{E}_k\mathbf{M}^{-1}\mathbf{C},$$

where  $\mathbf{E}_k$  is a partitioned matrix of dimension  $G \times GJ$  with an  $G \times G$  identity matrix as the  $k$ th “block” and zeros elsewhere. Thus the backfitting estimator for  $\mathbf{m}_{k,j}^*$  is

$$(3.10) \quad \hat{\mathbf{m}}_{k,j}^* = \mathbf{W}_k\mathbf{Y}_j^*.$$

Denote by  $\mathbf{m}_j^* = \sum_{k=1}^J \mathbf{m}_{k,j}^*$  and  $\mathbf{W}_M = \sum_{k=1}^J \mathbf{W}_k$ . The backfitting estimator of  $\mathbf{m}_j^*$  is then  $\hat{\mathbf{m}}_j^* = \mathbf{W}_M\mathbf{Y}_j^*$ . Let  $\mathbf{W}_M^{[-k]}$  be the additive smoother matrix for the data

generated by the  $(J - 1)$ -variate regression model,  $Y'_{gj} = \sum_{k'=1, \neq k}^J m^*_{k',j}(X_{gk'}) + \varepsilon_{gj}^*$ .

If  $\|\mathbf{S}_k^* \mathbf{W}_M^{[-k]}\| < 1$  for some  $k \in \{1, \dots, J\}$ , by Lemma 2.1 of Opsomer (2000), the backfitting estimators exist and are unique, and

$$\begin{aligned} \mathbf{W}_k &= \mathbf{I}_G - (\mathbf{I}_G - \mathbf{S}_k^* \mathbf{W}_M^{[-k]})^{-1} (\mathbf{I}_G - \mathbf{S}_k^*) \\ (3.11) \quad &= (\mathbf{I}_G - \mathbf{S}_k^* \mathbf{W}_M^{[-k]})^{-1} \mathbf{S}_k^* (\mathbf{I}_G - \mathbf{W}_M^{[-k]}). \end{aligned}$$

In this section we make the same assumption that is made in Opsomer (2000), that is, the inequality  $\|\mathbf{S}_k^* \mathbf{W}_M^{[-k]}\| < 1$  holds.

For each  $j$ ,  $\hat{\mathbf{m}}_{k,j}^*$  estimates  $\mathbf{m}_{k,j}^*$ . Define  $\hat{\mathbf{m}}_{k,j}$  equals  $-J\hat{\mathbf{m}}_{k,j}^*$  for  $k \neq j$  and  $J(J - 1)^{-1}\hat{\mathbf{m}}_{k,j}^*$  for  $k = j$ . Then  $\hat{\mathbf{m}}_{k,j}$  estimates  $\mathbf{m}_k$ . Since the variance of  $\hat{\mathbf{m}}_{k,j}$  ( $j \neq k$ ) is much bigger than that of  $\hat{\mathbf{m}}_{k,k}$ , taking the average over  $j$  does not help reduce the variance of  $\hat{\mathbf{m}}_{k,k}$ . We will use  $\hat{\mathbf{m}}_k \equiv \hat{\mathbf{m}}_{k,k}$  as an estimate of  $\mathbf{m}_k$ . The following theorem is a corollary of Theorem 3.1 in Opsomer (2000).

**THEOREM 3.2.** *Suppose that the conditions in Appendix A hold. If  $X_{g1}$  is an interior point, then as  $G \rightarrow \infty$ :*

(i) *The conditional bias of  $\hat{m}_1(X_{g1})$  is*

$$\begin{aligned} &E\{\hat{m}_1(X_{g1}) - m_1(X_{g1})|\mathbf{X}\} \\ &= \mathbf{e}_g^T (\mathbf{I} - \mathbf{S}_1^* \mathbf{W}_M^{[-1]})^{-1} \\ &\quad \times \left\{ \frac{\mu_2(K)}{2} h_1^2 [D^2 \mathbf{m}_1 - E(\mathbf{m}'_1)] - \mathbf{S}_1^* \mathbf{B}_{(-1)} \right\} + o_p(h_1^2), \end{aligned}$$

where  $\mathbf{B}_{(-1)} = (\mathbf{W}_M^{[-1]} - \mathbf{I}_G)\mathbf{m}_{(-1)}$  and  $\mathbf{m}_{(-1)} = \sum_{k=2}^J m_k$ .

(ii) *The conditional variance of  $\hat{m}_1(X_{g1})$  is*

$$\text{Var}\{\hat{m}_1(X_{g1})|\mathbf{X}\} = \frac{J}{J - 1} \frac{1}{Gh_1} \sigma^2 f_1^{-1}(X_{g1}) \nu_0(K_{(1)}) + o_p\left(\frac{1}{Gh_1}\right).$$

As in Corollary 3.2 of Opsomer (2000), if the covariates are mutually independent, the conditional bias of  $\hat{m}_1$  at an interior observation point  $X_{g1}$  is

$$\begin{aligned} &E\{\hat{m}_1(X_{g1}) - m_1(X_{g1})|\mathbf{X}\} \\ &= \frac{\mu_2(K_{(1)})}{2} h_1^2 [m''_1(X_{g1}) - E(m''_1(X_{g1}))] \\ &\quad + O_p(1/\sqrt{G}) + o_p\left(\sum_{j=1}^J h_j^2\right). \end{aligned}$$

This demonstrates that the estimators based on fitting bivariate additive models and a multiple additive model have the same asymptotic bias and variance in the

interior points when the covariates are independent. However, the estimator based on fitting bivariate additive models is easy to implement.

**4. Simulations.** We here conduct simulations to compare the performance of the proposed integration estimation method with the backfitting estimation. To this end, we consider model (1.1) and set  $J = 3$  and  $G = 3000$ . The first variable  $X_{g1}$  is generated from a mixture distribution; that is,  $X_{g1}$  is simulated from the probability distribution  $0.0004 \times (x - 6)^3 I(6 < x < 16)$  with probability 0.6 and from the uniform distribution over  $[6, 16]$  with probability 0.4. The other two variables  $X_{gk}$  ( $k = 2, 3$ ) are generated from model (2.10) with  $b_G = G^{-\gamma}$  and  $u_{gk} \sim_{\text{i.i.d.}} N(0, 1)$  where  $\gamma = 0.05, 0.1$  and  $0.2$  are used to control the correlation between  $X_{gk}$  and  $X_{g1}$ . It is easy to calculate that  $\gamma = 0.05, 0.1$  and  $0.2$  correspond to correlations 0.9919, 0.9962 and 0.9992 between  $X_{g1}$  and  $X_{g2}$ , respectively. The correlations between  $X_{g2}$  and  $X_{g3}$  are very close to the correlations between  $X_{g1}$  and  $X_{g2}$  for different values of  $\gamma$ . The treatment effect  $\alpha_g$  is generated from the double exponential distribution  $\frac{1}{2} \exp(-|x|)$ . The response variable  $Y_{kg}$  is simulated from model (1.1) with  $m_1(x) = \sqrt{5}(\sin(x) - 0.2854)$ ,  $m_2(x) = 0.01(x - 11)^3 - 0.2913$ ,  $m_3(x) = 0.2 \exp(x/5) - 3.0648$  and  $\varepsilon_{kg} \sim_{\text{i.i.d.}} N(0, 1)$ .

The mean square error (MSE) is employed to evaluate the performance of different estimation methods. The MSE of an estimate  $\hat{m}_j$  of the function  $m_j$  and the MSE of an estimate  $\hat{\alpha} = (\hat{\alpha}_1, \dots, \hat{\alpha}_G)^T$  of the vector  $\alpha = (\alpha_1, \dots, \alpha_G)^T$  are defined, respectively, as follows:

$$\text{MSE}(\hat{m}_j) = \frac{1}{G} \sum_{g=1}^G (\hat{m}_j(X_{gj}) - m_j(X_{gj}))^2,$$

$$\text{MSE}(\hat{\alpha}) = \frac{1}{G} \sum_{g=1}^G (\hat{\alpha}_g - \alpha_g)^2.$$

The integration estimation procedure and the pooled backfitting method are applied to estimate  $m_1(\cdot)$  at 100 equispaced grid points over the interval  $[6, 16]$  using 500 simulated datasets. For the backfitting method, we first tried the Gaussian kernel and the optimal data-driven bandwidth rule in Opsomer and Ruppert (1998) and noticed that the estimated curves for the backfitting estimators were over-smoothed when  $\gamma$  is smaller. Following the reviewers' suggestions, we then used a smaller bandwidth, that is, 0.4 times the optimal bandwidth. For the integration method, its performance is not sensitive to the choice of bandwidth, as long as it is not chosen too large (see Theorem 2.3). Thus we just chose a reasonably small one. The medians of the fitted curves over 500 simulations are summarized in Figure 2. It is seen from Figure 2 that, when  $\gamma$  becomes larger, the correlation between covariates gets higher and the backfitting method performs worse while the integration method becomes better. In fact, when  $\gamma = 0.2$ , our integration procedure gives almost perfect estimates of the true function: very little bias is involved.

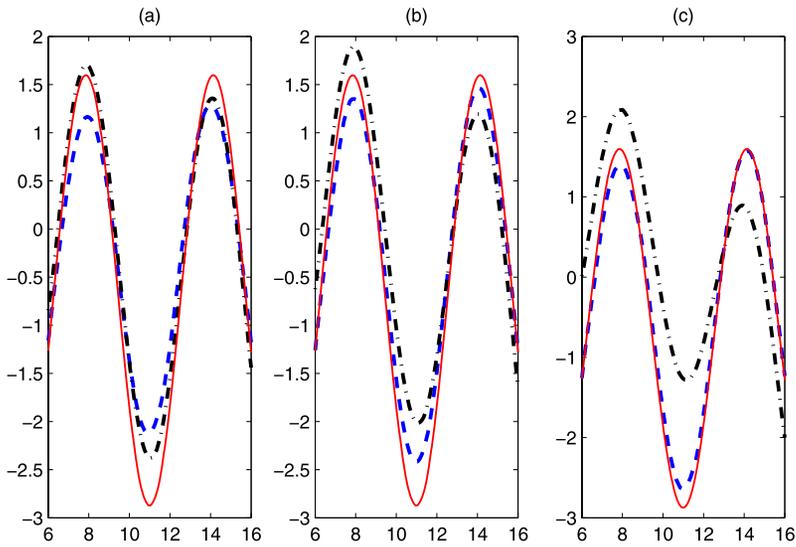


FIG. 2. Estimates of function  $m_1 = \sqrt{5}(\sin(x) - 0.2854)$ . Solid curves (red): the true function. Dashed curves (blue): the integration estimation method. Dash-dotted curves (black): the pooled backfitting method. (a)  $\gamma = 0.05$ ; (b)  $\gamma = 0.1$ ; (c)  $\gamma = 0.2$ .

Similarly, we estimate the functions  $m_2(x)$  and  $m_3(x)$ . The estimated curves are depicted in Figures 3 and 4. It can be seen that due to the high correlation, the pooled backfitting method gives estimates that are highly biased while our inte-

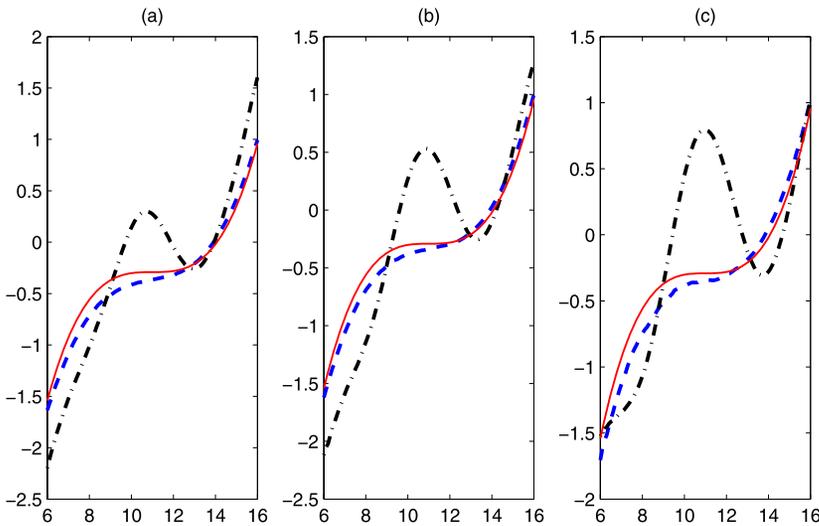


FIG. 3. The same as Figure 2 except that the estimated function is  $m_2(x) = 0.01(x - 11)^3 - 0.2913$ . (a)  $\gamma = 0.05$ ; (b)  $\gamma = 0.1$ ; (c)  $\gamma = 0.2$ .

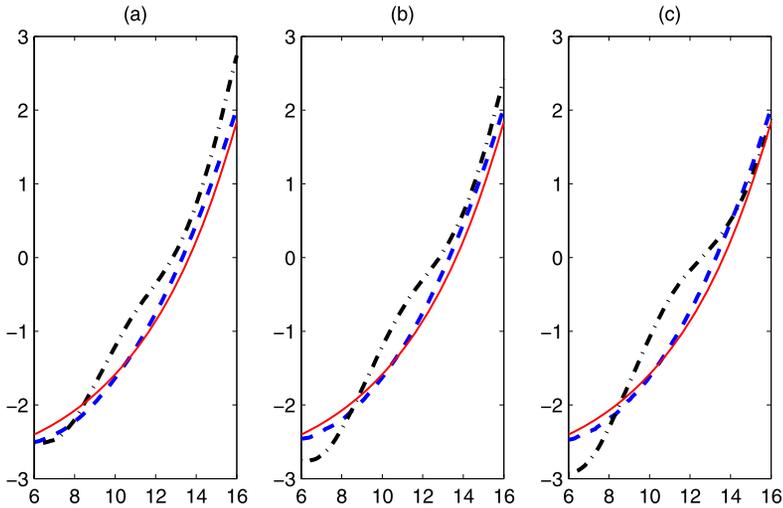


FIG. 4. The same as Figure 2 except that the estimated function is  $m_3(x) = 0.2 \exp(x/5) - 3.0648$ . (a)  $\gamma = 0.05$ ; (b)  $\gamma = 0.1$ ; (c)  $\gamma = 0.2$ .

gration method produces almost perfect fits. The variations of the estimates are accessed by MSE, and the median of these 500 MSEs can be found in Table 1.

Now we estimate  $\alpha_g, g = 1, \dots, G$ . For each of the 500 simulated data sets, let  $\hat{\alpha}_{gj} = Y_{gj} - \hat{m}_j(X_{gj})$ , for  $g = 1, \dots, G$  and  $j = 1, \dots, J$ . Then for each of the simulated data sets we estimate  $\alpha_g$  as

$$\hat{\alpha}_g = \frac{1}{J} \sum_{j=1}^J \hat{\alpha}_{gj}.$$

The performance of  $\hat{\alpha}$  is evaluated by MSE. The median of the 500 MSEs is then calculated. Table 1 reports the medians of MSEs obtained by using the integration and pooled backfitting methods. The integration estimation method dominates the backfitting method in almost all cases.

TABLE 1  
Medians of MSEs for the estimated  $m_j$  and  $\alpha$

	Integration estimation method			Pooled backfitting method		
	$\gamma = 0.05$	$\gamma = 0.1$	$\gamma = 0.2$	$\gamma = 0.05$	$\gamma = 0.1$	$\gamma = 0.2$
$m_1$	0.1471	0.0698	0.1032	0.0774	0.2411	0.8169
$m_2$	0.0121	0.0177	0.0689	0.2310	0.1746	0.2343
$m_3$	0.0202	0.0245	0.0750	0.1007	0.0754	0.1254
$\alpha$	0.3542	0.3565	0.3647	0.3963	0.4125	0.4962

**5. Real data example.**

5.1. *Microarray data analysis.* We apply our new estimation methods to the Neuroblastoma data set collected and analyzed by Fan et al. (2005). Neuroblastoma is the most frequent solid extra cranial neoplasia in children. Various studies have suggested that microphage migration inhibitory factor (MIF) may play an important role in the development of neuroblastoma. To understand the impact of MIF reduction on neuroblastoma cells, the global gene expression of the neuroblastoma cell with MIF-suppressed is compared to those without MIF suppression using Affymetrix GeneChips. Among extracted detection signals, only genes with all detection signals greater than 50 were considered, resulting in 13,980 genes in three control and treatment arrays, respectively. The details of the design and experiments were given by Fan et al. (2005).

For this DNA microarray data set,  $J = 3$  and  $G = 13,980$ . Model (1.1) was used in Fan et al. (2005) to assess the intensity and treatment effects on genes with  $m_j(\cdot)$  representing the intensity effect for the  $j$ th array and  $\alpha_g$  denoting the treatment effect on gene  $g$ . As discussed in Section 1, model (1.1) leads to the additive model

$$(5.1) \quad Y_g^{(k)} = m_1(X_{g1}) - m_k(X_{gk}) + \varepsilon_g^{(k)}, \quad k = 2, 3,$$

where  $Y_g^{(k)} = Y_{g1} - Y_{gk}$ . Now we fit the data using model (5.1) and estimate the components by the integration and pooled backfitting methods. The resulting estimates indicate similar forms of the intensity effects for different slides, as presented in Figure 5. However, the integration and pooled backfitting estimates differ substantially which raises a question about which estimate is more reliable.

In the implementation of the backfitting method, we encounter an almost singular matrix problem when using the Matlab software due to the highly correlated log intensities  $X_{gj}$ , which leads to the extremely low rate of convergence and unreliable results, even though it reports the final estimates. Hence, by intuition and the

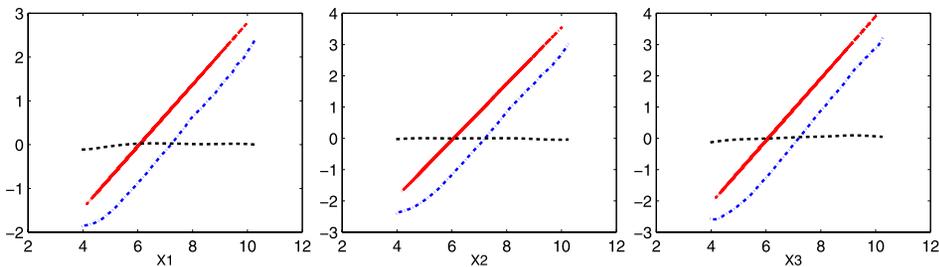


FIG. 5. Fitted regression curves as estimates of the intensity effects for different arrays. Left panel: for the first array, middle panel: for the second array, right panel: for the third array; dashed (black): the backfitting estimate, dashed-dotted (blue): the integration estimate, solid (red): the linear regression.

TABLE 2  
*The standard deviation of residuals from different estimation for the additive models  
 with different covariates*

Covariates in models	Integration estimation	Pooled backfitting	LSE
$(X_1, X_2)$	0.430	0.451	0.429
$(X_1, X_3)$	0.421	0.462	0.428
$(X_2, X_3)$	0.375	0.455	0.455

previous theory the integration estimation is better. In addition, since both estimation methods lead to roughly linear forms of the intensity effects functions  $m_j(\cdot)$  for  $j = 1, 2, 3$ , the linear model seems plausible. This suggests that we should fit the data using the linear model

$$Y_g^{(k)} = \beta_0 + \beta_1 X_{g1} + \beta_2 X_{gk} + \varepsilon_g^{(k)},$$

as an alternative of model (5.1). For the integration estimation method we do not have the singularity nor convergence problem. Thus we still work with model (5.1).

Figure 5 displays the estimated functions for each array. The pooled backfitting estimates are almost flat and deviate far away from the trends revealed by the least squares estimates (LSEs) for the linear model, but the integration estimates share similar trends as the LSEs. It seems that the estimated intensities from the integration method are increasing and have a similar trend which suggests that the intensity effects for the three slides are similar. Table 2 reports the standard deviation of residuals from the different estimation methods. It favors the integration method.

*5.2. Interest rate data analysis.* In this subsection, we analyze the interest rates data introduced in the Introduction. For simplicity, we consider the model with two additive functions

$$X_t = \mu + m_1(X_{t-1}) + m_2(X_{t-2}) + \varepsilon_t.$$

Note that the above model is exactly model (2.1). Thus backfitting and integration methods can be used to estimate the additive components. Our integration method can be easily extended to the case where there are three or more additive functions. Figure 6 shows the estimated functions  $m_1(x)$  and  $m_2(x)$  by using the integration and pooled backfitting methods. Figure 7 shows the corresponding residuals, which demonstrates that the integration method provides much better fitting than the pooled backfitting method. Failure of the latter method is the result of highly correlated covariates [see also Figure 1(right)] in the fitted model.

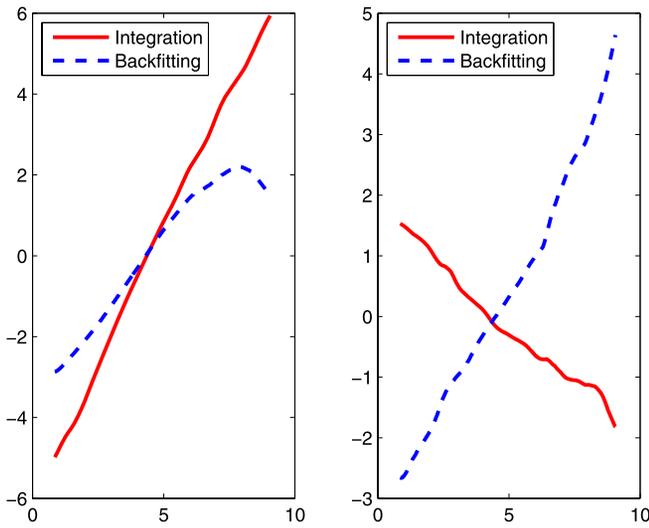


FIG. 6. Left panel: the estimated curve for  $m_1(x)$ ; right panel: the estimated curve for  $m_2(x)$ .

**6. Discussion.** In this article we have proposed several estimation methods for additive models when its covariates are highly correlated and nonhighly correlated. We derived asymptotic normality of the proposed estimators and illustrated their performance in finite samples via simulations. The performance of the proposed methodology was also demonstrated by two real data examples.

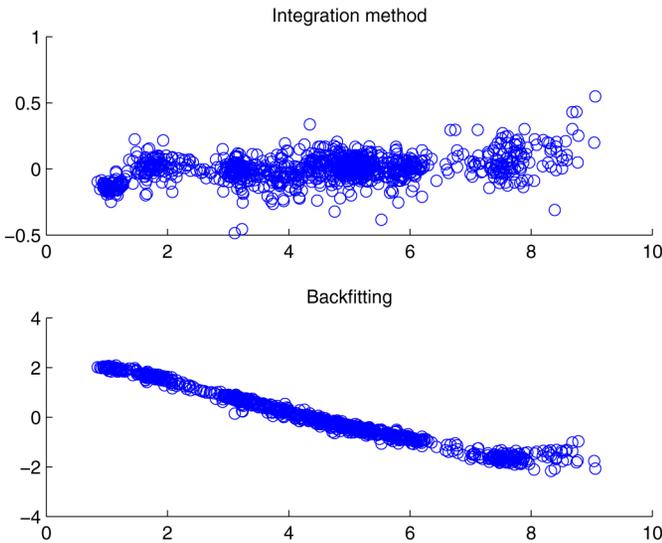


FIG. 7. Top panel: residual plot when the integration method is used; bottom panel: residual plot when the backfitting method is used.

Many problems remain open for the array-dependent model. Examples include:

- (i) Investigation of the asymptotic normality of the backfitting estimators when the covariates are highly correlated.
- (ii) Establishing the asymptotic distribution of the estimators in (2.11).
- (iii) Test if the nonparametric functions  $m_j$  have certain parametric forms. The generalized likelihood ratio tests can be used [see Fan and Jiang (2005, 2007)].

APPENDIX A: CONDITIONS

- (i) The kernel  $K(\cdot)$  is a continuous and symmetric function and has compact support, and its first derivatives had a finite number of sign changes over its support.
- (ii) The densities of  $f_j$ 's are bounded and continuous, have compact support and their first derivatives have a finite number of sign changes over their supports. Also,  $f_j(x_j) > 0$  for all  $x_j \in \text{supp}(f_j)$ .
- (iii) As  $G \rightarrow \infty, h_j \rightarrow 0, h \rightarrow 0, Gh_j / \log G \rightarrow \infty$  and  $Gh / \log G \rightarrow \infty$ .
- (iv) The second derivatives of  $m_j$  exist and are continuous and bounded.

APPENDIX B: PROOFS OF THEOREMS

PROOF OF THEOREM 2.1. Let  $\mathbf{Y}^{(k)} = (Y_1^{(k)}, \dots, Y_G^{(k)})^T$ ,

$$\tilde{\boldsymbol{\varepsilon}}^{(k)} = (\tilde{\varepsilon}_1^{(k)}, \dots, \tilde{\varepsilon}_G^{(k)})^T,$$

$\tilde{m}_g(X_{gk}) = m_{k1}(X_{gk}) + b_{Gu_{gk}} m'_1(X_{gk})$  and  $\tilde{\mathbf{m}} = (\tilde{m}_1(X_{1k}), \dots, \tilde{m}_G(X_{Gk}))^T$ . Then (2.4) becomes

$$\mathbf{Y}^{(k)} = \tilde{\mathbf{m}} + \tilde{\boldsymbol{\varepsilon}}^{(k)}.$$

By (2.7), we have

$$\begin{aligned} \hat{\theta}(x) - \theta(x) &= (\mathbf{Z}^T \mathbf{KZ})^{-1} \mathbf{Z}^T \mathbf{K} \tilde{\boldsymbol{\varepsilon}}^{(k)} + (\mathbf{Z}^T \mathbf{KZ})^{-1} \mathbf{Z}^T \mathbf{K} [\tilde{\mathbf{m}} - \mathbf{Z}\theta(x)] \\ \text{(B.1)} \qquad \qquad &= \mathbf{V}(x) + \mathbf{B}(x). \end{aligned}$$

Note that for  $|X_{gk} - x| \leq h$ ,

$$\begin{aligned} \tilde{m}_g(X_{gk}) &= m_{k1}(x) + m'_{k1}(x)(X_{gk} - x) \\ &\quad + \frac{1}{2} m''_{k1}(x)(X_{gk} - x)^2 + o(X_{gk} - x)^2 \\ &\quad + b_{Gu_{gk}} \{ m'_1(x) + m''_1(x)(X_{gk} - x) \\ &\qquad \qquad \qquad + \frac{1}{2} m_1^{(3)}(x)(X_{gk} - x)^2 \} + o(X_{gk} - x)^2 b_G \\ &= \mathbf{Z}_g^T \theta(x) + \frac{1}{2} m''_{k1}(x)(X_{gk} - x)^2 \\ &\quad + \frac{1}{2} m_1^{(3)}(x) b_{Gu_{gk}} (X_{gk} - x)^2 + o(h^2 + hb_G), \end{aligned}$$

uniformly for  $g = 1, \dots, G$ . Let

$$\mathbf{X} = \begin{bmatrix} (X_{1k} - x)^2 h^{-2} & (X_{1k} - x)^2 h^{-2} u_{1k} \\ \vdots & \vdots \\ (X_{Gk} - x)^2 h^{-2} & (X_{Gk} - x)^2 h^{-2} u_{Gk} \end{bmatrix}.$$

Then

$$(B.2) \quad \tilde{\mathbf{m}}_{1k} - \mathbf{Z}\theta(x) = \frac{h^2}{2} \mathbf{X} \begin{bmatrix} m''_{k1}(x) \\ m_1^{(3)}(x) b_G \end{bmatrix} + o(\mathbf{1})(h^2 + b_G h^2),$$

where  $\mathbf{1}$  is a  $G \times 1$  vector with all elements being 1's, and hence

$$(B.3) \quad \mathbf{B}(x) = (\mathbf{Z}^T \mathbf{K} \mathbf{Z})^{-1} \mathbf{Z}^T \mathbf{K} \left\{ \mathbf{X} \begin{bmatrix} \frac{h^2}{2} m''_{k1}(x) \\ h b_G m_1''(x) \end{bmatrix} + o(\mathbf{1})(h^2 + h^2 b_G) \right\}.$$

Let  $\mathbf{S}_T = \mathbf{Z}^T \mathbf{K} \mathbf{Z}$ . Then  $\mathbf{S}_T = \sum_{g=1}^G K_h(X_{gk} - x) Z_g Z_g^T$ , and the  $(i, j)$ th element of  $\mathbf{S}_T$  is

$$\mathbf{S}_{T,ij} = \begin{cases} \sum_{g=1}^G K_h(X_{gk} - x) (X_{gk} - x)^{i+j-2}, & \text{for } 1 \leq i, j \leq 2; \\ \sum_{g=1}^G K_h(X_{gk} - x) (X_{gk} - x)^{i+j-4} b_G u_{gk}, & \text{for } i = 1, 2; j = 3, 4; \\ \sum_{g=1}^G K_h(X_{gk} - x) (X_{gk} - x)^{i+j-4} b_G u_{gk}, & \text{for } i = 3, 4; j = 1, 2; \\ \sum_{g=1}^G K_h(X_{gk} - x) (X_{gk} - x)^{i+j-6} b_G^2 u_{gk}^2, & \text{for } i, j = 3, 4. \end{cases}$$

Directly computing the mean and variance, we obtain that:

(i) for  $1 \leq i, j \leq 2$ ,

$$\begin{aligned} G^{-1} h^{-(i+j-2)} \mathbf{S}_{T,ij} &= G^{-1} \sum_{g=1}^G K_h(X_{gk} - x) (X_{gk} - x)^{i+j-2} h^{-(i+j-2)} \\ &= f_k(x) \mu_{i+j-2}(K) + O_p(h + 1/\sqrt{Gh}); \end{aligned}$$

(ii) for  $i = 1, 2$  and  $j = 3, 4$ , or  $i = 3, 4$  and  $j = 1, 2$ ,

$$\begin{aligned} G^{-1} h^{-(i+j-4)} b_G^{-1} \mathbf{S}_{T,ij} &= G^{-1} \sum_{g=1}^G K_h(X_{gk} - x) (X_{gk} - x)^{i+j-4} h^{-(i+j-4)} u_{gk} \\ &= O_p(1/\sqrt{Gh}); \end{aligned}$$

(iii) for  $i, j = 3, 4$ ,

$$\begin{aligned} & G^{-1}h^{-(i+j-6)}b_G^{-2}\mathbf{S}_{T,ij} \\ &= G^{-1}\sum_{g=1}^G K_h(X_{gk} - x)(X_{gk} - x)^{i+j-6}h^{-(i+j-6)}u_{gk}^2 \\ &= f_k(x)\mu_{i+j-6}(K) + O_p(h + 1/\sqrt{Gh}). \end{aligned}$$

Therefore,

$$(B.4) \quad G^{-1}\mathbf{H}^{-1}\mathbf{S}_T\mathbf{H}^{-1} = f_k(x)\mathbf{S} + O_p(\mathbf{11}^T)\left(h + \frac{1}{\sqrt{Gh}}\right).$$

By simple algebra and (B.2), we have

$$\begin{aligned} & G^{-1}\mathbf{H}^{-1}\mathbf{Z}^T\mathbf{K}[\tilde{\mathbf{m}}_{1k} - \mathbf{Z}\theta(x)] \\ &= G^{-1}\mathbf{H}^{-1}\mathbf{Z}^T\mathbf{K} \\ &\quad \times \left\{ \mathbf{X} \begin{bmatrix} \frac{h^2}{2}m''_{k1}(x) \\ \frac{h^2}{2}m_1^{(3)}(x)b_G \end{bmatrix} + o(\mathbf{1})(h^2 + b_Gh) \right\} \\ &= \mathbf{A} \begin{bmatrix} \frac{h^2}{2}m''_{k1}(x) \\ hb_Gm'_1(x) \end{bmatrix} + o(h^2 + b_Gh), \end{aligned}$$

uniformly for components where  $\mathbf{A} = (A_{ij})$  is a  $4 \times 2$  matrix with

$$A_{ij} = \begin{cases} G^{-1}\sum_{g=1}^G K_h(X_{gk} - x)h^{-(i+j)}(X_{gk} - x)^{i+j}, & \text{for } i = 1, 2 \text{ and } j = 1; \\ G^{-1}\sum_{g=1}^G K_h(X_{gk} - x)h^{-i}(X_{gk} - x)^i u_{gk}, & \text{for } i = 1, 2 \text{ and } j = 2; \\ G^{-1}\sum_{g=1}^G K_h(X_{gk} - x)h^{-2}(X_{gk} - x)^2 u_{gk}, & \text{for } i = 3, j = 1; \\ G^{-1}\sum_{g=1}^G K_h(X_{gk} - x)h^{-1}(X_{gk} - x)u_{gk}^2, & \text{for } i = 3, j = 2; \\ G^{-1}\sum_{g=1}^G K_h(X_{gk} - x)h^{-3}(X_{gk} - x)^3 u_{gk}, & \text{for } i = 4, j = 1; \\ G^{-1}\sum_{g=1}^G K_h(X_{gk} - x)h^{-3}(X_{gk} - x)^3 u_{gk}^2, & \text{for } i = 4, j = 2. \end{cases}$$

Directly computing the mean and variance of  $A_{ij}$ , we obtain that  $\mathbf{A} = f_k(x)\mathbf{C} + o(h^2 + b_G h)$ , uniformly for components. Then

$$\begin{aligned} &G^{-1}\mathbf{H}^{-1}\mathbf{Z}^T\mathbf{K}[\tilde{\mathbf{m}}_{1k} - \mathbf{Z}\theta(x)] \\ &= f_k(x) \begin{bmatrix} \mu_2 & 0 \\ \mu_3 & 0 \\ 0 & \mu_2 \\ 0 & \mu_3 \end{bmatrix} \begin{bmatrix} \frac{h^2}{2}m''_{k1}(x) \\ \frac{h^2}{2}b_G m_1^{(3)}(x) \end{bmatrix} + o(h^2 + b_G h) \\ &= \frac{h^2}{2}f_k(x)\mathbf{C}(m''_{k1}(x), m_1^{(3)}(x)b_G)^T + o(h^2 + b_G h), \end{aligned}$$

uniformly for components. Thus

$$\begin{aligned} \mathbf{HB}(x) &= \mathbf{HS}_T^{-1}\mathbf{Z}^T\mathbf{K}[\tilde{\mathbf{m}}_{1k} - \mathbf{Z}\theta(x)] \\ &= (\mathbf{H}^{-1}\mathbf{S}_T\mathbf{H}^{-1})^{-1}\mathbf{H}^{-1}\mathbf{Z}^T\mathbf{K}[\tilde{\mathbf{m}}_{1k} - \mathbf{Z}\theta(x)] \\ &= \frac{h^2}{2}\mathbf{S}^{-1}\mathbf{C}(m''_{k1}(x), m_1^{(3)}(x)b_G)^T(1 + o_p(1)). \end{aligned}$$

This combined with (B.1) yields that

$$(B.5) \quad \mathbf{H}(\hat{\theta}(x) - \theta(x)) - \frac{h^2}{2}\mathbf{S}^{-1}\mathbf{C}(m''_{k1}(x), b_G m_1^{(3)}(x))^T(1 + o_p(1)) = \mathbf{HV}(x).$$

By the definition of  $\mathbf{V}(x)$  we have

$$\mathbf{HV}(x) = \mathbf{HS}_T^{-1}\mathbf{Z}^T\mathbf{K}\tilde{\boldsymbol{\varepsilon}}^{(k)} = (\mathbf{H}^{-1}\mathbf{S}_T\mathbf{H}^{-1})^{-1}\mathbf{H}^{-1}\mathbf{Z}^T\mathbf{K}\tilde{\boldsymbol{\varepsilon}}^{(k)}.$$

Plugging (B.4) into the right-hand side above, we establish that

$$\begin{aligned} \mathbf{HV}(x) &= G^{-1}(f_k(x)\mathbf{S})^{-1} \begin{bmatrix} 1 & \cdots & 1 \\ \frac{X_{1k} - x}{h} & \cdots & \frac{X_{Gk} - x}{h} \\ u_{1k} & \cdots & u_{Gk} \\ \frac{X_{1k} - x}{h}u_{1k} & \cdots & \frac{X_{Gk} - x}{h}u_{Gk} \end{bmatrix} \mathbf{K} \begin{bmatrix} \tilde{\varepsilon}_1^{(k)} \\ \vdots \\ \tilde{\varepsilon}_G^{(k)} \end{bmatrix} \\ &= f_k^{-1}(x)\mathbf{S}^{-1}J_G(x), \end{aligned}$$

where

$$J_G(x) = \begin{bmatrix} G^{-1} \sum_{g=1}^G K_h(X_{gk} - x)\tilde{\varepsilon}_g^{(k)} \\ G^{-1} \sum_{g=1}^G K_h(X_{gk} - x)\left(\frac{X_{gk} - x}{h}\right)\tilde{\varepsilon}_g^{(k)} \\ G^{-1} \sum_{g=1}^G K_h(X_{gk} - x)u_{gk}\tilde{\varepsilon}_g^{(k)} \\ G^{-1} \sum_{g=1}^G K_h(X_{gk} - x)\left(\frac{X_{gk} - x}{h}\right)u_{gk}\tilde{\varepsilon}_g^{(k)} \end{bmatrix}.$$

Under the working model (2.10), we obtain from (2.4) that

$$(B.6) \quad \tilde{\varepsilon}_g^{(k)} = \frac{1}{2}m_1''(X_{gk})b_G^2u_{gk}^2(1 + o_p(1)) + \varepsilon_g^{(k)}.$$

Using an argument similar to that for Lemma 7.3 of Jiang and Mack (2001), we can show that

$$\begin{aligned} & \sqrt{Gh}[\mathbf{H}\mathbf{V}(x) - \frac{1}{2}b_G^2m_1''(x)\mathbf{S}^{-1}\mathbf{c}^*(1 + o_p(1)) + O_p(b_G^2/\sqrt{Gh})] \\ & \xrightarrow{D} N(0, 2f_k^{-1}(x)\sigma^2\mathbf{S}^{-1}\mathbf{V}\mathbf{S}^{-1}), \end{aligned}$$

which together with (B.5) and  $f_1(x) = f_k(x)(1 + o(1))$  leads to the result of the theorem.  $\square$

**PROOF OF COROLLARY 2.1.** Let  $e_3 = (0, 0, 1, 0)^T$ . Then

$$\begin{aligned} & \hat{m}'_1(x; k) - m'_1(x) \\ & = e_3^T(\hat{\theta}(x) - \theta(x)) \\ & = e_3^T \frac{h^2}{2} \mathbf{H}^{-1} \mathbf{S}^{-1} \mathbf{C}(m''_{k1}(x), b_G m_1^{(3)}(x))^T (1 + o_p(1)) \\ & \quad + e_3^T f_k^{-1}(x) \mathbf{H}^{-1} \mathbf{S}^{-1} J_G(x). \end{aligned}$$

It is easy to verify that  $e_3^T \mathbf{H}^{-1} \mathbf{S}^{-1} = (0, 0, b_G^{-1} \mu_0^{-1}(K), 0)$ . Then

$$(B.7) \quad \begin{aligned} & \hat{m}'_1(x; k) - m'_1(x) \\ & = \frac{h^2}{2} \mu_2(K) \mu_0^{-1}(K) m_1^{(3)}(x) (1 + o_p(1)) \\ & \quad + f_k^{-1}(x) \mu_0^{-1}(K) b_G^{-1} G^{-1} \sum_{g=1}^G K_h(X_{gk} - x) u_{gk} \tilde{\varepsilon}_g^{(k)}. \end{aligned}$$

This combined with the asymptotic normality of  $J_G(x)$  completes the proof of the corollary.  $\square$

**PROOF OF THEOREM 2.2.** By (B.7),

$$\begin{aligned} & \hat{m}'_1(x) - m'_1(x) \\ & = \frac{h^2}{2} \mu_2(K) \mu_0^{-1}(K) m_1^{(3)}(x) (1 + o_p(1)) \\ & \quad + \frac{1}{J-1} \sum_{k=2}^J f_k^{-1}(x) \mu_0^{-1}(K) b_G^{-1} G^{-1} \sum_{g=1}^G K_h(X_{gk} - x) u_{gk} \tilde{\varepsilon}_g^{(k)}. \end{aligned}$$

Then using (B.6), we obtain that

$$\begin{aligned}
 & \hat{m}'_1(x) - m'_1(x) \\
 &= \frac{h^2}{2} \mu_2(K) \mu_0^{-1}(K) m_1^{(3)}(x) (1 + o_p(1)) \\
 \text{(B.8)} \quad &+ \frac{1}{2} b_G m''_1(x) E(u_{1k}^3) (1 + o_p(1)) \\
 &+ \frac{1}{J-1} \sum_{k=2}^J f_k^{-1}(x) \mu_0^{-1}(K) b_G^{-1} G^{-1} \sum_{g=1}^G K_h(X_{gk} - x) u_{gk} \varepsilon_g^{(k)}.
 \end{aligned}$$

Let  $B_G(x) = \frac{1}{J-1} \sum_{k=2}^J f_k^{-1}(x) \mu_0^{-1}(K) b_G^{-1} G^{-1} \sum_{g=1}^G K_h(X_{gk} - x) u_{gk} \varepsilon_g^{(k)}$ . Then  $E[B_G(x)] = 0$ . Note that  $E(u_{gk_1} u_{gk_2}) = \rho(k_1, k_2)$  and  $E\{\varepsilon_g^{(k_1)} \varepsilon_g^{(k_2)}\} = \sigma^2$  for  $k_1 \neq k_2$  and  $2\sigma^2$  for  $k_1 = k_2$ . It follows that

$$\begin{aligned}
 & E[\sqrt{G} h b_G B_G(x)]^2 \\
 &= \frac{1}{(J-1)^2} \sum_{k_1, k_2=2}^J f_{k_1}^{-1}(x) f_{k_2}^{-1}(x) \mu_0^{-2}(K) \\
 &\quad \times E\{h K_h(X_{gk_1} - x) K_h(X_{gk_2} - x) \\
 &\quad \times E(\varepsilon_g^{(k_1)} \varepsilon_g^{(k_2)}) E(u_{gk_1} u_{gk_2})\} \\
 &= \frac{2}{(J-1)^2} \sum_{k=2}^J f_k^{-2}(x) \mu_0^{-2}(K) E\{h K_h^2(X_{gk} - x)\} \sigma^2 \rho(k, k) \\
 &\quad + \frac{1}{(J-1)^2} \sum_{k_1 \neq k_2} f_{k_1}^{-1}(x) f_{k_2}^{-1}(x) \mu_0^{-2}(K) \\
 &\quad \times E\{h K_h(X_{gk_1} - x) K_h(X_{gk_2} - x)\} \sigma^2 \rho(k_1, k_2).
 \end{aligned}$$

Using  $f_k(x) = f_1(x)(1 + o(1))$  and

$$\begin{aligned}
 E\{h K_h(X_{gk_1} - x) K_h(X_{gk_2} - x)\} &= E\{h K_h^2(X_{g1} - x)\} (1 + o(1)) \\
 &= f_1(x) v_0(K) (1 + o(1)),
 \end{aligned}$$

we arrive at

$$E[\sqrt{G} h b_G B_G(x)]^2 = \rho \sigma^2 f_1^{-1}(x) \mu_0^{-2}(K) v_0(K) (1 + o(1)),$$

where  $\rho = \frac{1}{(J-1)^2} [\sum_{k=2}^J \rho(k, k) + \sum_{k_1=2}^J \sum_{k_2=2}^J \rho(k_1, k_2)]$ . Therefore,  $\sqrt{G} h b_G \times B_G(x)$  is asymptotically normal with mean zero and variance  $\sigma_2^2(x)$ . This together with (B.8) completes the proof of the theorem.  $\square$

PROOF OF THEOREM 2.3. Observing that

$$\begin{aligned} \hat{m}_1(x) &= -G^{-1} \sum_{g=1}^G \int_{x_0}^{X_{g1}} \hat{m}'_1(t) dt + \int_{x_0}^x \hat{m}'_1(t) dt \\ &= -G^{-1} \sum_{g=1}^G \int_{x_0}^{X_{g1}} [\hat{m}'_1(t) - m'_1(t)] dt + \int_{x_0}^x [\hat{m}'_1(t) - m'_1(t)] dt \\ &\quad + m_1(x) - G^{-1} \sum_{g=1}^G m_1(X_{g1}) \end{aligned}$$

and  $G^{-1} \sum_{g=1}^G m_1(X_{g1}) = O_p(G^{-1/2})$ , we obtain that

$$\begin{aligned} \hat{m}_1(x) - m_1(x) &= -G^{-1} \sum_{g=1}^G \int_{x_0}^{X_{g1}} [\hat{m}'_1(t) - m'_1(t)] dt \\ &\quad + \int_{x_0}^x [\hat{m}'_1(t) - m'_1(t)] dt + O_p(G^{-1/2}) \\ &= G^{-1} \sum_{g=1}^G \int_{X_{g1}}^x [\hat{m}'_1(t) - m'_1(t)] dt + O_p(G^{-1/2}). \end{aligned}$$

Let  $J_{k,G} = G^{-1} \sum_{g=1}^G u_{gk} \varepsilon_g^{(k)} \int_{X_{g1}}^x K_h(X_{gk} - t) dt$ . Then by (B.8) and simple algebra,

$$\begin{aligned} \hat{m}_1(x) - m_1(x) &= \frac{h^2}{2} \mu_2(K) \mu_0^{-1}(K) [m''_1(x) - Em''_1(X_{11})] (1 + o_p(1)) \\ &\quad + \frac{1}{2} b_G E(u_{1k}^3) [m'_1(x) - Em'_1(X_{11})] (1 + o_p(1)) \\ &\quad + O_p(G^{-1/2}) + \mu_0^{-1}(K) b_G^{-1} (J - 1)^{-1} \sum_{k=2}^J f_k^{-1}(x) J_{k,G}. \end{aligned}$$

Let

$$\begin{aligned} C_G(x) &= \frac{1}{J-1} \sum_{k=2}^J f_k^{-1}(x) \mu_0^{-1}(K) b_G^{-1} G^{-1} \\ &\quad \times \sum_{g=1}^G u_{gk} \varepsilon_g^{(k)} \int_{X_{g1}}^x K_h(X_{gk} - t) dt. \end{aligned}$$

Then

$$\begin{aligned}
 & E[\sqrt{G}b_G C_G(x)]^2 \\
 &= \frac{2}{(J-1)^2} \sum_{k=2}^J f_k^{-2}(x) \mu_0^{-2}(K) E \left\{ \int_{X_{g1}}^x K_h(X_{gk} - t) dt \right\}^2 \sigma^2 \rho(k, k) \\
 &+ \frac{1}{(J-1)^2} \sum_{k_1 \neq k_2} f_{k_1}^{-1}(x) f_{k_2}^{-1}(x) \mu_0^{-2}(K) \\
 &\quad \times E \left\{ \int_{X_{g1}}^x K_h(X_{gk_1} - t) dt \right. \\
 &\quad \left. \times \int_{X_{g1}}^x K_h(X_{gk_2} - t) dt \right\} \sigma^2 \rho(k_1, k_2).
 \end{aligned}$$

Since

$$\begin{aligned}
 & E \left\{ \int_{X_{g1}}^x K_h(X_{gk_1} - t) dt \int_{X_{g1}}^x K_h(X_{gk_2} - t) dt \right\} \\
 &= E \left\{ \int_{X_{g1}}^x K_h(X_{g1} - t) dt \right\}^2 (1 + o(1)) \\
 &= \int_{-\infty}^{\infty} f_1(u) du \left\{ \int_u^x K_h(u - t) dt \right\}^2 \\
 &= \frac{1}{4} \mu_0^2(K) (1 + o(1)), \\
 & E[\sqrt{G}b_G C_G(x)]^2 = \frac{1}{4} f_1^{-2}(x) \sigma^2 \rho + o(1).
 \end{aligned}$$

Therefore,  $\sqrt{G}b_G C_G(x)$  is asymptotically normal with mean zero and variance  $\sigma^2(x)$ .  $\square$

PROOF OF THEOREM 3.1. As in Opsomer and Ruppert (1997), we let

$$\mathbf{Q}_{m_1}(x_1) = \begin{bmatrix} (X_{11} - x_1)^2 \\ \vdots \\ (X_{G1} - x_1)^2 \end{bmatrix} \frac{\partial m_1(x_1)}{\partial x_1^2}, \quad \mathbf{Q}_1 = \begin{bmatrix} \mathbf{s}_{1, X_{11}}^T \mathbf{Q}_{m_1}(\mathbf{X}_{11}) \\ \vdots \\ \mathbf{s}_{1, X_{G1}}^T \mathbf{Q}_{m_1}(\mathbf{X}_{G1}) \end{bmatrix},$$

and similarly for  $\mathbf{Q}_{m_k}(x_k)$  and  $\mathbf{Q}_k$ . Let  $h_j^2 = h_j^2 \mathbf{1}$ . Then by the proof of Theorem 4.1 of Opsomer and Ruppert (1997),

$$(\mathbf{I}_G - \mathbf{S}_1^* \mathbf{S}_k^*)^{-1} (\mathbf{I}_G - \mathbf{S}_1^*) \mathbf{m}_k = \mathbf{m}_k + \frac{1}{2} (\mathbf{I}_G - \mathbf{S}_1^* \mathbf{S}_k^*)^{-1} \mathbf{S}_1^* \mathbf{Q}_k + o_p(\mathbf{h}_k^2)$$

and

$$(\mathbf{I}_G - \mathbf{S}_1^* \mathbf{S}_k^*)^{-1} (\mathbf{I}_G - \mathbf{S}_1^*) \mathbf{m}_1 = \bar{\mathbf{m}}_1 - \frac{1}{2} (\mathbf{I}_G - \mathbf{S}_1^* \mathbf{S}_k^*)^{-1} \mathbf{Q}_1^* + o_p(\mathbf{h}_1^2),$$

where  $\mathbf{Q}_1^* = (\mathbf{I}_G - \mathbf{1}\mathbf{1}^T/G)\mathbf{Q}_1$ . Thus,

$$(B.9) \quad E(\hat{\mathbf{m}}_1 - \mathbf{m}_1 | \mathbf{X}) = \frac{1}{2}(\mathbf{I}_G - \mathbf{S}_k^* \mathbf{S}_1^*)^{-1}(\mathbf{Q}_1^* - \mathbf{S}_1^* \mathbf{Q}_k) + o_p(\mathbf{h}_1^2 + \mathbf{h}_k^2).$$

By (3.4),  $\hat{\mathbf{m}}_1^{(j)} = \mathbf{W}_{1j} \mathbf{m} + \mathbf{W}_{1j} \varepsilon_g^{(j)}$ . Note that  $\text{Var}(\varepsilon_g^{(j)} | \mathbf{X}) = 2\sigma^2 I_G$  and for  $j \neq k$ ,  $\text{Cov}(\varepsilon_g^{(j)}, \varepsilon_g^{(k)} | \mathbf{X}) = \sigma^2 \mathbf{I}_G$ . It follows that

$$(B.10) \quad \begin{aligned} & \text{Cov}\{\hat{m}_1^{(j)}(X_{g1}), \hat{m}_1^{(k)}(X_{g1}) | \mathbf{X}\} \\ &= \sigma^2 \{1 - \mathbf{e}_g^T (\mathbf{I} - \mathbf{S}_1^* \mathbf{S}_j^*)^{-1} (\mathbf{I} - \mathbf{S}_1^*) \mathbf{e}_g - \mathbf{e}_g^T (\mathbf{I} - \mathbf{S}_1^* \mathbf{S}_k^*)^{-1} (\mathbf{I} - \mathbf{S}_1^*) \mathbf{e}_g \\ & \quad + \mathbf{e}_g^T (\mathbf{I} - \mathbf{S}_1^* \mathbf{S}_j^*)^{-1} (\mathbf{I} - \mathbf{S}_1^*) (\mathbf{I} - \mathbf{S}_1^*)^T (\mathbf{I} - \mathbf{S}_1^* \mathbf{S}_k^*)^{-T} \mathbf{e}_g\} \end{aligned}$$

and

$$(B.11) \quad \begin{aligned} & \text{Var}\{\hat{m}_1^{(j)}(X_{g1}) | \mathbf{X}\} \\ &= 2\sigma^2 \{1 - 2\mathbf{e}_g^T (\mathbf{I} - \mathbf{S}_1^* \mathbf{S}_j^*)^{-1} (\mathbf{I} - \mathbf{S}_1^*) \mathbf{e}_g \\ & \quad + \mathbf{e}_g^T (\mathbf{I} - \mathbf{S}_1^* \mathbf{S}_j^*)^{-1} (\mathbf{I} - \mathbf{S}_1^*) (\mathbf{I} - \mathbf{S}_1^*)^T (\mathbf{I} - \mathbf{S}_1^* \mathbf{S}_j^*)^{-T} \mathbf{e}_g\}. \end{aligned}$$

Using the same argument as that for (10) in Opsomer and Ruppert (1997), we obtain that for  $j, k = 2, \dots, J$  ( $j \neq k$ ),

$$\text{Cov}(\hat{m}_1^{(j)}(X_{g1}), \hat{m}_1^{(k)}(X_{g1}) | \mathbf{X}) = \frac{1}{Gh_1} \sigma^2 f_1^{-1}(X_{g1}) \nu_0(K) + o_p\left(\frac{1}{Gh_1}\right)$$

and

$$\text{Var}(\hat{m}_1^{(j)}(X_{g1}) | \mathbf{X}) = \frac{2}{Gh_1} \sigma^2 f_1^{-1}(X_{g1}) \nu_0(K) + o_p\left(\frac{1}{Gh_1}\right).$$

Therefore, by (3.5),

$$\begin{aligned} \text{Var}(\hat{m}_1(X_{g1}) | \mathbf{X}) &= (J - 1)^{-2} \sum_{j,k=2}^J \text{Cov}(\hat{m}_1^{(j)}(X_{g1}), \hat{m}_1^{(k)}(X_{g1}) | \mathbf{X}) \\ &= \frac{J}{J - 1} \frac{1}{Gh_1} \sigma^2 f_1^{-1}(X_{g1}) \nu_0(K) + o_p\left(\frac{1}{Gh_1}\right). \end{aligned}$$

The conditional bias of  $\hat{m}_1$  is obviously the sum of biases for each  $\hat{m}_1^{(k)}$  ( $k = 2, \dots, J$ ). This completes the proof of the theorem.  $\square$

**PROOF OF THEOREM 3.2.** The result can be proved along the line of Theorem 3.1 in Opsomer (2000).  $\square$

**Acknowledgments.** The authors thanks the Associate Editor and the referees for constructive comments that substantially improved an earlier version of this paper.

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