Nonparametric Estimation of Correlation Functions In Longitudinal And Spatial Data, With Application To Colon Carcinogenesis Experiments

Yehua Li[1], Naisyin Wang[2], Meeyoung Hong[3], Nancy D. Turner[3], Joanne R. Lupton[3] and Raymond J. Carroll[2,3]

yehuali@uga.edu, nwang@stat.tamu.edu, meeyoung_hong@yahoo.com,

n-turner@tamu.edu, jlupton@tamu.edu, carroll@stat.tamu.edu

[1]Department of Statistics, University of Georgia, Athens, GA 30602

[2]Department of Statistics, Texas A&M University, TAMU 3143, College Station, TX 77843-3143

[3]Faculty of Nutrition, Texas A&M University, College Station, TX 77843-2253

Abstract

In longitudinal and spatial studies, observations often demonstrate strong correlations that are stationary in time or distance lags, and the times or locations of these data being sampled may not be homogeneous. We propose a nonparametric estimator of the correlation function in such data, using kernel methods. We develop a pointwise asymptotic normal distribution for the proposed estimator, when the number of subjects is fixed and the number of vectors or functions within each subject goes to infinity. Based on the asymptotic theory, we propose a weighted block bootstrapping method for making inferences about the correlation function, where the weights account for the inhomogeneity of the distribution of the times or locations. The method is applied to a data set from a colon carcinogenesis study, in which colonic crypts were sampled from a piece of colon segment from each of the 12 rats in the experiment and the expression level of p27, an important cell cycle protein, was then measured for each cell within the sampled crypts. A simulation study is also provided to illustrate the numerical performance of the proposed method.

KEY WORDS: Asymptotic theory; Bootstrap; Colon carcinogenesis; Correlation functions; Dependent data; Functional data; Gene expression; Kernel regression; Nonparametric regression; Spatial data; Time series.

Short title: Spatial Correlation Functions

1 Introduction

This paper concerns kernel-based nonparametric estimation of covariance and correlation functions. Our methods and theory are applicable to longitudinal and spatial data as well as time series data, where observations within the same subject at different time points or locations have strong correlations, which are stationary in time or distance lags. The structure for the observation at a particular time or location within one subject can be very general, for example a vector or even a function.

Our study arises from a colon carcinogenesis experiment. The biomarker that we are interested in is p27, which is a life cycle protein that affects cell apoptosis, proliferation and differentiation. An important goal of the study is to understand the function of p27 in the early stage of the cancer development process. In the experiment, 12 rats were administered azoxymethane (AOM), which is a colon specific carcinogen. After 24 hours, the rats were terminated and a segment of colon tissue was excised from each rat. About 20 colonic crypts were randomly picked along a linear slice on the colon segment. The physical distances between the crypts were measured. Then, within each crypt, we measured cells at different depths within the crypts, and then the expression level of p27 was measured for each cell within the chosen crypts. In this data set, crypts are naturally functional data (Ramsay and Silverman 1997), that the responses within a crypt are coordinated by cell depths. There is a literature about similar data, for example Morris et al. (2001).

However, in this paper, we will be focused on a very different perspective. In this application, the spatial correlation between crypts is of biological interest, because it helps answer the question: if we observe a crypt with high p27 expression, how likely are the neighboring crypts to have high p27 expression? We will phrase much of our discussion in terms of this example, but as seen later sections, we have a quite general

structure that includes time series as a special case. In that context, the asymptotic theory is as the number of "time series locations", i.e., crypts, increases to infinity.

Although motivated by a very specific problem, nonparametric covariance/correlation estimators are worth being investigated in their own right. They can be used in a statistical analysis as: (a) an exploratory device to help formulate a parametric model; (b) an intermediate tool to do spatial prediction (kriging); (c) a diagnostic for parametric models; (d) a robust tool to test correlation. Understanding the theoretical properties of the nonparametric estimator is important under any of these situation. A limiting distribution theory would be especially valuable for purpose (d).

There is previous work on the subject of nonparametric covariance estimation. Hall et al. (1994) developed an asymptotic convergence rate of a kernel covariance estimator in a time series setting. They required not only an increasing time domain, but increasingly denser observations. Diggle and Verbyla (1998) suggested a kernel weighted local linear regression estimator for estimating the non-stationary variogram in longitudinal data, without developing asymptotic theory. Guan, Sherman and Calvin (2004) used a kernel variogram estimator when assessing isotropy in geostatistics data. They proved asymptotic normality for their kernel variogram estimator in a geostatistics setting, where they required the spatial locations to be sampled from the field according to a two dimensional homogeneous Poisson process.

As we will show below and as implied by the result from Guan et al. (2004), if the observation locations (or times) in the design are random, Hall's assumption, namely that the number of observation on a unit domain goes to infinity, is too restrictive and not necessary. However, in the setting of Guan et al., given the sample size, spatial locations are uniformly distributed within the field, which does not fit our problem, where crypt locations within a rat are, in fact, not even close to uniformly distributed.

3

Our paper differs from the previous work on the kernel covariance estimators in the following ways. First, our approach accommodates more complex data structure at each location or time. Secondly, we allow the spatial locations to be sampled in an inhomogeneous way, and as we will show below that this inhomogeneity will affect the asymptotic results and inference procedures. In doing so, we generalize the setting of Guan et al. (2004), and link it to the setting of Hall et al. (1994). Also, Guan et al. (2004) is mainly concerned with comparing variograms on a few pre-selected distance lags, we, on the other hand, are more interested in the correlation as a function. Thirdly, we propose an inference procedure based upon our theory, thus filling a gap in the previous literature.

The paper is organized as follows. Section 2 introduces our model assumptions and estimators, while asymptotic results are given in Section 3. An analysis of the motivating data is given in Section 4, where we also discuss bandwidth selection and standard error estimation. Section 5 describes simulation studies, and final comments are given in Section 6. All proofs are given in the appendix.

2 Model Assumptions and Estimators

The data considered here have the following structure.

- There are are $r = 1, ..., R$ independent subjects, which in our example are rats.

- The data for each subject have two levels. The first level has an increasing domain, as in time series or spatial statistics, and are the crypts in our example. We label this first level as a "unit", and it is these units that have time series or spatial structure in their locations. Within each subject, there are $i = 1, ..., N_r$ such units.

- The second level of the data consists of observations within each of the primary

units. In our case, these are the cells within the primary units, the colonic crypts. We will label this secondary level as the "sub-units", which are labelled with locations. The locations with the sub-units are on the interval $[0, 1]$. For simplicity, we will assume there are exactly m sub-units (cells) within each unit (crypt), with the jth sub-unit having location (relative cell depth) $x = (j-1)/(m-1)$. However, all theories and methods in our paper will go through if the sub-units take the form of an arbitrary finite set.

- For $m = 1$, define x to be fixed at 0. It is analogous to the time series setting of Hall et al. (1994) or the spatial setting of Guan et al. (2004).

Let $\Theta(s, x)$ be a random field on $\mathcal{T} \times \mathcal{X}$, where s is the unit (crypt) location and and x is the sub-unit(cell) location, so that $\mathcal{T} = [0, \infty)$, $\mathcal{X} = \{(j-1)/(m-1), j = 1, \cdots, m\}$. Assume that $\Theta_r(\cdot, \cdot)$, $r = 1, \cdots, R$, are independent realizations of $\Theta(\cdot, \cdot)$. We use the short-hand notation $\Theta_{ri}(x) = \Theta_r(S_{ri}, x)$, where S_{ri} is the location of the ith unit (crypt) within the rth subject (rat). Our model for the observed data is that

$$Y_{rij} = \Theta_{ri}(x_j) + \epsilon_{rij}, \tag{1}$$

where Y is the response (logarithm of p27 level), ϵ_{rij} are zero-mean uncorrelated measurement errors with variance σ_ϵ^2, $r = 1, \cdots, R$, $i = 1, \cdots, N_r$ and $j = 1, \cdots, m$ are the indices for subjects (rats), units (crypts) and sub-units (cells). Define $\Psi_r(\cdot) = E_r\{\Theta_{ri}(\cdot)\}$ to be the subject-level mean, and the notation "E_r" refers to expectation conditional on the subject. Another way to understand $\Psi_r(\cdot)$ is to decompose the random field $\Theta_r(\cdot, \cdot)$ into the following random effect model, $\Theta_{ri}(x) = \Psi_r(x) + \Lambda_{ri}(x)$, where $\Psi_r(\cdot)$ is the fixed subject effect, and Λ_{ri} is the zero-mean, spatially correlated unit effect.

Within each subject, we assume that the correlation of the mean unit (crypt)-level functions is stationary over the distances between the units. In addition, the covariance

between unit locations (s_1, s_2) at sub-unit (cell) locations (x_1, x_2) is assumed to have the following form:

$$\mathcal{V}\{x_1, x_2, \Delta\} = E[\{\Theta_r(s_1, x_1) - \Psi_r(x_1)\}\{\Theta_r(s_2, x_2) - \Psi_r(x_2)\}], \qquad (2)$$

where $\Delta = s_1 - s_2$. While we develop general results for model (2), in many cases it is reasonable to assume that the covariance function is separable, i.e.,

$$\mathcal{V}(x_1, x_2, \Delta) = G(x_1, x_2)\rho(\Delta). \qquad (3)$$

When the covariance function is separable, the correlation function at the unit-level, $\rho(\cdot)$, is of interest in itself. In our application, $\rho(\cdot)$ is the correlation between crypts. We provide an estimator of $\rho(\cdot)$ as well as an asymptotic theory for that estimator.

A first estimator for the covariance function has the following form:

$$\widehat{\mathcal{V}}(x_j, x_l, \Delta) = [\sum_r \sum_i \sum_{k \neq i} K_h\{\Delta_r(i,k) - \Delta\}(Y_{rij} - \overline{Y}_{r\cdot j})(Y_{rkl} - \overline{Y}_{r\cdot l})]$$
$$\times[\sum_r \sum_i \sum_{k \neq i} K_h\{\Delta_r(i,k) - \Delta\}]^{-1}, \qquad (4)$$

where $\overline{Y}_{r\cdot j} = N_r^{-1} \sum_{i=1}^{N_r} Y_{rij}$, $\Delta_r(i,k) = S_{ri} - S_{rk}$, $K_h(\cdot) = h^{-1}K(\cdot/h)$ with K being a kernel function satisfying the conditions in Section 3.

It is usually reasonable to assume that $\mathcal{V}(x_1, x_2, \Delta)$ has some symmetry property, that it is an even function in Δ and $\mathcal{V}(x_1, x_2, \Delta) = \mathcal{V}(x_2, x_1, \Delta)$. However, the estimator defined in (4) does not enjoy this property. To see this, we observe that, for $x_j \neq x_l$, although $(Y_{rij} - \overline{Y}_{r\cdot j})(Y_{rkl} - \overline{Y}_{r\cdot l})$ and $(Y_{ril} - \overline{Y}_{r\cdot l})(Y_{rkj} - \overline{Y}_{r\cdot j})$ estimate the same thing, they only contribute to $\widehat{\mathcal{V}}(x_j, x_l, \Delta)$ and $\widehat{\mathcal{V}}(x_j, x_l, -\Delta)$, respectively. We also observe that $\widehat{\mathcal{V}}(x_1, x_2, \Delta) = \widehat{\mathcal{V}}(x_2, x_1, -\Delta)$.

To correct the asymmetry of the covariance estimator, for $\Delta \geq 0$, define

$$\widetilde{\mathcal{V}}(x_j, x_l, \Delta) = [\sum_r \sum_i \sum_{k \neq i} K_h\{|\Delta_r(i,k)| - \Delta\}(Y_{rij} - \overline{Y}_{r\cdot j})(Y_{rkl} - \overline{Y}_{r\cdot l})]$$
$$\times[\sum_r \sum_i \sum_{k \neq i} K_h\{|\Delta_r(i,k)| - \Delta\}]^{-1}, \qquad (5)$$

6

and let $\widetilde{\mathcal{V}}(x_j, x_l, \Delta) = \widetilde{\mathcal{V}}(x_j, x_l, -\Delta)$ for $\Delta < 0$. As shown in the proof of Theorem 2, for a fixed $\Delta \neq 0$, $\widetilde{\mathcal{V}}(x_1, x_2, \Delta)$ is asymptotically equivalent to $\{\widehat{\mathcal{V}}(x_1, x_2, \Delta) + \widehat{\mathcal{V}}(x_1, x_2, -\Delta)\}/2$.

In addition, when the separable structure (3) is assumed, define the estimator for the within-unit covariance as

$$\widehat{G}(x_1, x_2) = \widetilde{\mathcal{V}}(x_1, x_2, 0), \tag{6}$$

and the estimator for the correlation function as

$$\widehat{\rho}(\Delta) = \{\sum_{x_1 \in \mathcal{X}} \sum_{x_2 \leq x_1} \widetilde{\mathcal{V}}(x_1, x_2, \Delta)\}/\{\sum_{x_1 \in \mathcal{X}} \sum_{x_2 \leq x_1} \widehat{G}(x_1, x_2)\}. \tag{7}$$

3   Asymptotic Results

The following are our model assumptions. Each subject (rat) is of length L, where in our example L is the length of the segment of tissue from each rat. The units (crypts) are located on the interval $[0, L]$, and in our asymptotics we let $L \to \infty$, so that we have an increasing domain. Suppose that the positions of the units (crypts) within the rth subject (rat) are $S_{r1}, \cdots, S_{rN_r}$, where the S_{ri}'s are points from an inhomogeneous Poisson process on $[0, L]$. Then $\Delta_{r,ik} = S_{ri} - S_{rk}$. The definition of an inhomogeneous Poisson process is adopted from Cressie (1993). We assume the inhomogeneous Poisson process has a local intensity $\nu g^*(s)$, where ν is a positive constant and $g^*(s) = g(s/L)$ for a continuous density function $g(\cdot)$ on $[0, 1]$.

A special case of our setting is that $g(\cdot)$ is a uniform density function and the units (crypts) are sampled according to a homogeneous Poisson process. This is the setting investigated in Guan et al. (2004). Our setting resembles that of Hall et al. (1994) in the sense that we also model the unit locations as random variables with the same distribution: in our setting, the number of units within a subject (rat) is $N_r \sim$

Poisson(νL); given N_r, $S_{r1}/L, \cdots, S_{r,N_r}/L$ are independent and identically distributed with density $g(\cdot)$. By properties of Poisson processes, $N_r/L = O(\nu)$ almost surely, as $L \to \infty$, that is, the number of units (crypts) on a unit length tends to a constant. It is worth noting that Hall et al. (1994) required this ratio to go to infinity. We require less samples on the domain than do Hall et al. (1994).

In what follows, we provide a list of definitions and conditions.

1. We assume that $g(\cdot)$ is continuous and $c_1 \geq g(t) \geq c_2 > 0$ for all $t \in [0, 1]$. Suppose t_i, $i = 1, 2, 3, 4$, are independent random variables with density $g(\cdot)$, define f_1, f_2, f_3 to be the density for $t_1 - t_2$, $(t_1 - t_2, t_3 - t_2)$, $(t_1 - t_2, t_3 - t_4, t_2 - t_4)$, respectively. Since $g(\cdot)$ is bounded, one can easily derive that $f_1(0)$, $f_2(0, 0)$ and $f_3(0, 0, 0)$ are positive. We also assume that f_1 and f_2 are Lipschitz continuous in the neighborhood of $\mathbf{0}$, i.e. $|f_i(\boldsymbol{u}) - f_i(\mathbf{0})| \leq \lambda_i \|\boldsymbol{u}\|$, for $\forall \boldsymbol{u}$ and some fixed constants $\lambda_i > 0$, $i = 1, 2$.

2. Assume $\mathcal{V}(x_1, x_2, \Delta)$ has two bounded continuous partial derivatives in Δ, and that $\sup_{x_1, x_2} \int |\mathcal{V}(x_1, x_2, \Delta)| d\Delta < \infty$.

3. Let

$$
\begin{aligned}
\mathcal{M}&(x_1, x_2, x_3, x_4, u, v, w) \\
&= E_r\Big[\{\Theta_{ri_1}(x_1) - \Psi_r(x_1)\}\{\Theta_{ri_2}(x_2) - \Psi_r(x_2)\}\{\Theta_{ri_3}(x_3) - \Psi_r(x_3)\} \\
&\quad \{\Theta_{ri_4}(x_4) - \Psi_r(x_4)\}|\Delta_r(i_1, i_2) = u, \Delta_r(i_3, i_4) = v, \\
&\quad \Delta_r(i_2, i_4) = w\Big] - \mathcal{V}(x_1, x_2, u)\mathcal{V}(x_3, x_4, v).
\end{aligned}
$$

We assume $\mathcal{M}$ has bounded partial derivatives in u, v and w, and

$$
\sup_{x_1, x_2, x_3, x_4, u, v} \int |\mathcal{M}(x_1, x_2, x_3, x_4, u, v, w)| dw < \infty. \tag{8}
$$

4. Denote $b_r(x_1, x_2, \Delta) = L^{-1} \sum_i \sum_{k \neq i} K_h\{\Delta - \Delta_r(i,k)\}\{Y_r(S_{ri}, x_1) - \Psi_r(x_1)\} \times \{Y_r(S_{rk}, x_2) - \Psi_r(x_2)\}$. We assume that, for any fixed Δ, for some $\eta > 0$,

$$\sup_{L, x_1, x_2} E(|\text{var}^{-1/2}\{b_r(x_1, x_2, \Delta)\}[b_r(x_1, x_2, \Delta) - E\{b_r(x_1, x_2, \Delta)\}]|^{2+\eta}) \leq C_\eta < \infty. \quad (9)$$

5. Let $\mathcal{F}(T)$ be the σ-algebra generated by $\{\Theta(s, x), s \in T, x \in \mathcal{X}\}$, for any Borel set $T \subset \mathcal{T}$. Assume that the random field satisfies the following mixing condition

$$\begin{aligned}
\alpha(\tau) &= \sup_t[|P(A_1 \cap A_2) - P(A_1)P(A_2)| : A_1 \in \mathcal{F}\{[0,t]\}, A_2 \in \mathcal{F}\{[t+\tau, \infty)\}] \\
&= O(\tau^{-\delta}) \text{ for some } \delta > 0. \quad (10)
\end{aligned}$$

6. The kernel function K is a symmetric, continuous probability density function, supported on $[-1, 1]$. Define $\sigma_K^2 = \int u^2 K(u) du$ and $R_K = \int K^2(v) dv$.

7. Assume that m and R are fixed numbers, $L \to \infty$, $h \to 0$, $Lh \to \infty$, and $Lh^5 = O(1)$.

In assumption 1, we are imposing some regularity conditions on g and f_i. In fact, when g is differentiable f_i are piecewise differentiable, but usually not differentiable at $\mathbf{0}$. However, the Lipschitz conditions on f_1 and f_2 are easily satisfied when, for example, g is Lipschitz continuous on $[0, 1]$.

Since we are estimating the covariance function, which is the second moment function, we need a regularity condition on the 4th moment function as in (8). Condition (9) may seem strong at the first sight, but it is simply a condition that bounds the tail probability of our statistics. For example, if we have an assumption analogous to (8) for the 8th moment of $\Theta_r(s, x)$, one can use arguments as in Lemma 3 to show that $E([b_r(x_1, x_2, \Delta) - E\{b_r(x_1, x_2, \Delta)\}]^4) = O(L^{-3}h^{-3})$, therefore condition (9) is satisfied for $\eta = 2$. In general, when the distribution of Θ is neither too skewed nor has a much

9

heavier tail than that of Gaussian, equation (9) will be satisfied. Assumption 6 and 7 are standard in the literature of kernel estimators.

Denote $\mathcal{V}^{(0,0,2)}(x_1, x_2, \Delta) = \partial^2 \mathcal{V}(x_1, x_2, \Delta)/\partial \Delta^2$. Let $\mathcal{V}(\Delta)$, $\widehat{\mathcal{V}}(\Delta)$ and $\widetilde{\mathcal{V}}(\Delta)$ denote the vectors collecting $\mathcal{V}(x_1, x_2, \Delta)$, $\widehat{\mathcal{V}}(x_1, x_2, \Delta)$ and $\widetilde{\mathcal{V}}(x_1, x_2, \Delta)$ respectively, for all distinct pairs of (x_1, x_2). The following are our main theoretical results: all proofs are provided in the appendix. Note that Theorem 1 refers to $\widehat{\mathcal{V}}(\cdot)$ in (4), while Theorem 2 refers to $\widetilde{\mathcal{V}}(\cdot)$ in (5).

<u>THEOREM</u> 1 Under assumptions 1-7, for $\Delta \neq \Delta'$, we have

$$(RLh)^{1/2} \left[\begin{array}{c} \widehat{\mathcal{V}}(\Delta) - \mathcal{V}(\Delta) - \text{bias}\{\widehat{\mathcal{V}}(\Delta)\} \\ \widehat{\mathcal{V}}(\Delta') - \mathcal{V}(\Delta') - \text{bias}\{\widehat{\mathcal{V}}(\Delta')\} \end{array} \right]$$

$$\Rightarrow \text{Normal} \left[0, \{\nu^2 f_1(0)\}^{-1} \left(\begin{array}{cc} \Sigma(\Delta) & C(\Delta, \Delta') \\ C^T(\Delta, \Delta') & \Sigma(\Delta') \end{array} \right) \right],$$

where the asymptotic bias $\text{bias}\{\widehat{\mathcal{V}}(\Delta)\}$ is a vector having entries $\text{bias}\{\widehat{\mathcal{V}}(x_1, x_2, \Delta)\} = \sigma_K^2 \mathcal{V}^{(0,0,2)}(x_1, x_2, \Delta) h^2/2$, $\Sigma(\Delta)$ is the covariance matrix with the entry corresponding to $\text{cov}\{\widehat{\mathcal{V}}(x_1, x_2, \Delta), \widehat{\mathcal{V}}(x_3, x_4, \Delta)\}$ equal to $R_K\{\mathcal{M}(x_1, x_2, x_3, x_4, \Delta, \Delta, 0) + I(x_2 = x_4)\sigma_\epsilon^2 \mathcal{V}(x_1, x_3, 0) + I(x_1 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_2, x_4, 0) + (x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4\} + I(\Delta = 0)R_K\{\mathcal{M}(x_1, x_2, x_3, x_4, 0, 0, 0) + I(x_1 = x_4)\sigma_\epsilon^2 \mathcal{V}(x_2, x_3, 0) + I(x_2 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_1, x_4, 0) + I(x_1 = x_4, x_2 = x_3)\sigma_\epsilon^4\}$; $C(\Delta, \Delta')$ is the matrix with the entry corresponding to $\text{cov}\{\widehat{\mathcal{V}}(x_1, x_2, \Delta), \widehat{\mathcal{V}}(x_3, x_4, \Delta')\}$ equal to $I(\Delta' = -\Delta)\{\mathcal{M}(x_1, x_2, x_3, x_4, \Delta, -\Delta, -\Delta) + I(x_2 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_1, x_4, 0) + I(x_1 = x_4)\sigma_\epsilon^2 \mathcal{V}(x_2, x_3, 0) + I(x_1 = x_4, x_2 = x_3)\sigma_\epsilon^4\}$.

<u>THEOREM</u> 2 Under assumptions 1-7, for $\Delta \neq \pm\Delta'$, we have

$$(RLh)^{1/2} \left[\begin{array}{c} \widetilde{\mathcal{V}}(\Delta) - \mathcal{V}(\Delta) - \text{bias}\{\widetilde{\mathcal{V}}(\Delta)\} \\ \widetilde{\mathcal{V}}(\Delta') - \mathcal{V}(\Delta') - \text{bias}\{\widetilde{\mathcal{V}}(\Delta')\} \end{array} \right]$$

$$\Rightarrow \text{Normal} \left[0, \{\nu^2 f_1(0)\}^{-1} \left(\begin{array}{cc} \Omega(\Delta) & 0 \\ 0 & \Omega(\Delta') \end{array} \right) \right],$$

where $\text{bias}\{\widetilde{\mathcal{V}}(\Delta)\}$ is a vector with entries $\text{bias}\{\widetilde{\mathcal{V}}(x_1, x_2, \Delta)\} = \sigma_K^2 \mathcal{V}^{(0,0,2)}(x_1, x_2, \Delta) h^2/2$, $\Omega(\Delta)$ is the covariance matrix with the entry corresponding to $\text{cov}\{\widetilde{\mathcal{V}}(x_1, x_2, \Delta), \widetilde{\mathcal{V}}(x_3, x_4,$

$\Delta)\}$ equal to $(1/2)R_K\{\mathcal{M}(x_1, x_2, x_3, x_4, \Delta, \Delta, 0) + \mathcal{M}(x_1, x_2, x_3, x_4, \Delta, -\Delta, -\Delta) + I(x_2 = x_4)\sigma_\epsilon^2 \mathcal{V}(x_1, x_3, 0) + I(x_1 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_2, x_4, 0) + I(x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4 + I(x_2 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_1, x_4, 0) + I(x_1 = x_4)\sigma_\epsilon^2 \mathcal{V}(x_2, x_3, 0) + I(x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4\} + I(\Delta = 0)(1/2)R_K\{2\mathcal{M}(x_1, x_2, x_3, x_4, 0, 0, 0) + I(x_2 = x_4)\sigma_\epsilon^2 \mathcal{V}(x_1, x_3, 0) + I(x_1 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_2, x_4, 0) + I(x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4 + I(x_2 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_1, x_4, 0) + I(x_1 = x_4)\sigma_\epsilon^2 \mathcal{V}(x_2, x_3, 0) + I(x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4\}.$

$\underline{\text{COROLLARY}}$ **1** Suppose the covariance function has the separable structure in (3) with $\sum_{x_1} \sum_{x_2 \le x_1} G(x_1, x_2) \ne 0$, and $\widehat{\rho}(\Delta)$ is defined in (7). Then for $\Delta \ne 0$, we have

$$(RLh)^{1/2}[\widehat{\rho}(\Delta) - \rho(\Delta) - \text{bias}\{\widehat{\rho}(\Delta)\}] \Rightarrow \text{Normal}[0, \{\nu^2 f_1(0)\}^{-1} \sigma_\rho^2(\Delta)],$$

where $\text{bias}\{\widehat{\rho}(\Delta)\} = \{\rho^{(2)}(\Delta) - \rho(\Delta)\rho^{(2)}(0)\}\sigma_K^2 h^2/2$ is the asymptotic bias of $\widehat{\rho}(\Delta)$, $\sigma_\rho^2(\Delta) = \{\sum_{x_1} \sum_{x_2 \le x_1} G(x_1, x_2)\}^{-2}\{\mathbf{1}^T \Omega(\Delta)\mathbf{1} + \rho^2(\Delta)\mathbf{1}^T \Omega(0)\mathbf{1}\}.$

$\underline{\text{Remark:}}$ The measurement errors in (1) affect the covariance estimator mainly though the nugget effect (Cressie, 1993). In our covariance estimators (4) and (5), we eliminate the nugget effect by excluding the $k = i$ terms in the summation. As a result, the measurement errors do not introduce bias to our covariance estimators. However, they do affect the variation of the covariance estimators and hence the correlation estimator, as seen by the fact that σ_ϵ^2 is in the variance expressions for all our estimators.

4 Data Analysis

In this section we apply our methods to study the between-crypt dependence in the carcinogenesis experiment. Recall that the main subjects are rats, the units of interest are colonic crypts and the sub-units within a unit are cells, at which we observe the logarithms of p27 in a cell. The sub-unit locations that we work with in this illustration

are at $x = 0, 0.1, 0.2, \cdots, 1.0$. We discuss three key issues in our analysis, namely bandwidth selection, standard error estimation and positive semi-definite adjustment in the following three subsections.

4.1 Bandwidth Selection

4.1.1 Global Bandwidth

Diggle and Verbyla (1998) suggested a cross-validation procedure to choose the bandwidth for a kernel variogram estimator. We modify their procedure into the following two types of 'leave-one-subject-out' cross-validation criteria. The first is based on prediction error without assuming any specific covariance structure, and is given as

$$CV_1(h) = \sum_r \sum_{|\Delta_r(i,k)| < \Delta_0} \sum_{j=1}^{m} \sum_{l=1}^{m} [v_{r,ik}(x_j, x_l) - \tilde{\mathcal{V}}_{(-r)}\{x_j, x_l, \Delta_r(i,k)\}]^2, \qquad (11)$$

where $v_{r,ik}(x_j, x_l) = (Y_{rij} - \overline{Y}_{r \cdot j})(Y_{rkl} - \overline{Y}_{r \cdot l})$, $\tilde{\mathcal{V}}_{(-r)}(x_1, x_2, \Delta)$ is the kernel covariance estimator using bandwidth h, as defined in (5), with all information on the rth subject (rat) left out. Here we focus on the range $|\Delta_r(i,k)| < \Delta_0$, where Δ_0 is a pre-chosen cut-off point. The criterion $CV_1(h)$ thus evaluates the prediction error for different h within the range of $|\Delta_r(i,k)| < \Delta_0$.

Cross-validation criterion (11) assumes no specific covariance structure, while our second cross-validation criterion takes into account the separable structure in (3), and is given as

$$CV_2(h) = \sum_r \sum_{|\Delta_r(i,k)| < \Delta_0} \sum_{j=1}^{m} \sum_{l=1}^{m} [v_{r,ik}(x_j, x_l) - \widehat{G}_{(-r)}(x_j, x_l)\widehat{\rho}_{(-r)}\{\Delta_r(i,k)\}]^2 \qquad (12)$$

where $\widehat{G}_{(-r)}(x_1, x_2)$ and $\widehat{\rho}_{(-r)}(\Delta)$ are the estimators of G and ρ defined in (6) and (7), with the rth subject (rat) left out.

We evaluated both criteria to estimate the bandwidth h. We choose $\Delta_0 = 500$ microns. The first two columns of Table 1 gives the minimum points and minimum

values of the two cross-validation criterions.

By observing Table 1, we find the two criteria gave almost identical minimum values. Since the cross-validation scores are estimates of the prediction errors, the two cross-validation criteria represent prediction errors with or without the separable structure (3). The phenomenon, that $CV_1(\cdot)$ and $CV_2(\cdot)$ have almost the same minimum values, suggests that the separability assumption (3) fits the data well.

4.1.2   Two Bandwidths

The independent variables in the kernel estimator are $|\Delta_r(i,k)|$ for all pairs of crypts within one subject. As shown in Figure 1, the distribution of $|\Delta_r(i,k)|$ that are less than 1000 microns, even more than the target range of interest, is locally somewhat akin to a uniform distribution.

As a robustness check on the global bandwidth, we repeated our analysis, except we used one bandwidth for $|\Delta| \leq 200$ microns, and we used a second bandwidth for $|\Delta| > 200$, and then repeated the cross-validation calculations in (11) and (12). The minimum values of the two cross-validation criterions are reported in the $3^{\rm rd}$ column of Table 1.

Comparing the results in columns 2 and 3 in Table 1, we find the minimum values of the cross-validation functions did not change much, i.e. an extra smoothing parameter did not substantially reduce the prediction error for the domain $|\Delta| \leq 500$ microns. In other words, it appears sufficient to use a global bandwidth to estimate $\rho(\Delta)$ for $|\Delta| \leq 500$. For the following analysis, we use the bandwidth $h = 122$ microns, as suggested by CV_2, and the resulting estimate $\widehat{\rho}$ is shown as the solid curve in Figure 2.

4.2   Standard Error Estimation

Our primary goal in this section is to construct a standard error estimate for $\widehat{\rho}(\Delta)$.

13

The asymptotic variance of $\widehat{\rho}(\Delta)$ has a very complicated form, which involves the 4th moment function of the random field, $\mathcal{M}(x_1, x_2, x_3, x_4, u, v, w)$. With so many estimates of higher order moments involved, a plug-in method, while feasible, is not desirable. We instead use a bootstrap method to estimate the variance directly.

In our model assumptions, the number of subjects (rats) R is fixed, which means that bootstrapping solely on the subject level will not give a consistent estimator of the variance. Consequently, we decided to sub-sample within each subject. When the data are dependent, block bootstrap methods have been investigated and used, see Shao and Tu (1995). Politis and Sherman (2001) also justified using a block sub-sampling method to estimate the variance of a statistic when the data are from a marked point process. Our data can be viewed as a marked inhomogeneous Poisson process. However, because of the inhomogeneity, we need to modify their procedure: when we sub-sample a block from each subject and compute the statistic $\widehat{\rho}(\Delta)$ by combining these blocks, the variance of the statistic depends on the corresponding local intensity at the location where each block is sampled.

By letting $R = 1$ in Corollary 1, our theory implies that if the number of units goes to infinity, each subject will provide a consistent estimator of $\rho(\Delta)$. Now, suppose the Poisson process for each subject has a different local intensity, $\nu_r g_r^*(s)$, $r = 1, \cdots, R$. With a slight modification of our theoretical derivations, one can show that,

$$\{\sum_{r=1}^{R} \nu_r^2 f_{r,1}(0) Lh\}^{1/2} [\widehat{\rho}(\Delta) - \rho(\Delta) - \text{bias}\{\widehat{\rho}(\Delta)\}] \Rightarrow \text{Normal}\{0, \sigma_\rho^2(\Delta)\}$$

where $f_{r,1}(t) = \int g_r(t + u) g_r(u) du$, $r = 1, \cdots, R$, are the counterparts of $f_1(t)$ used in Theorem 1, 2 and Corollary 1.

Define $A(\Delta) = \sum_r \sum_i \sum_{k \neq i} K_h \{\Delta_r(i, k) - \Delta\}$, then by Lemma 2,

$$A(\Delta) / \{\sum_{r=1}^{R} \nu_r^2 f_{r,1}(0) L\} \to 1, \text{ in } L^2.$$

14

Note that $A(\Delta)$ here is defined slightly different from $a(\Delta)$ in Lemma 2.

This equation suggests a natural way to construct correction weights in a weighted block bootstrap procedure that accommodates the inhomogeneous local intensity. We now propose our weighted bootstrap procedure:

1. Re-sample R subjects (rats) with replacement.

2. Within each re-sampled subject, randomly sub-sample a block with length L^*.

3. Combine the R blocks as our re-sampled data, compute $\widehat{\rho}(\Delta)$ and $A(\Delta)$ using the re-sampled data, with the same bandwidth h as for the kernel estimator (7).

4. Repeat steps 1-3 B times, denoting the results from the bth iteration as $\widehat{\rho}_b^*(\Delta)$ and $A_b^*(\Delta)$.

5. Obtain the estimator of the standard deviation as

$$\widehat{\text{sd}}\{\widehat{\rho}(\Delta)\} = [A^{-1}(\Delta)B^{-1}\sum_{b=1}^{B} A_b^*(\Delta)\{\widehat{\rho}_b^*(\Delta) - \widehat{\rho}_\cdot^*(\Delta)\}^2]^{1/2},$$

where $\widehat{\rho}_\cdot^*(\Delta) = B^{-1}\sum_{b=1}^{B}\widehat{\rho}_b^*(\Delta)$.

The block length L^* should increase slowly with L. Politis and Sherman (2001) proposed a block size selection procedure for dependent data on irregular spaced observation points which are from a homogenous point process. Their procedure is built on an asymptotic theory and needs a good pilot block size. The good performance of the procedure often requires a fairly large sample size. The implementation could be computationally intense.

One operational idea for a moderate sample size in our context is to choose L^* such that the correlation dies out outside the block but there are still a relatively large numbers of blocks. For this data set, we adopted a block size such that there are at

least a couple of non-overlapping blocks within each subject, and there are totally 24 non-overlapping blocks by pooling all subjects together. In our analysis, we took $L^* = 1$ cm (=10,000 microns). We also tried $L^* = 8$ mm and $L^* = 1.1$ cm, the results are very similar. We investigate the numerical performance of this simple procedure in both of the two simulation studies in Section 5, and it worked pretty well.

The two dotted curves in Figure 2 show $\widehat{\rho} \pm 2\times$ standard deviation. The plot implies that the correlation is practically zero when the crypt distance exceeds 500 microns.

4.3 Positive Semi-Definite Adjustment

By definition, $\rho(\Delta)$ is a stationary correlation function, therefore is positive semi-definite, i.e. $\int \int \rho(\Delta_1 - \Delta_2)\omega(\Delta_1)\omega(\Delta_2)d\Delta_1 d\Delta_2 \geq 0$ for all integrable functions $\omega(\cdot)$. By Bochner's theorem, the positive semi-definiteness is equivalent to nonnegativity of the Fourier transformation of ρ, i.e. $\rho^+(\theta) \geq 0$ for all θ, where $\rho^+(\theta) = \int_{-\infty}^{\infty} \rho(\Delta)\exp(i\theta\Delta)d\Delta = 2\int_0^\infty \rho(\Delta)\cos(\theta\Delta)d\Delta$.

To make $\widehat{\rho}$ a valid correlation function, we apply an adjustment procedure suggested by Hall and Patil (1994). First, we compute the Fourier transformation of $\widehat{\rho}(\cdot)$,

$$\widehat{\rho}^+(\theta) = 2\int_0^\infty \widehat{\rho}(\Delta)\cos(\theta\Delta)d\Delta.$$

In practice, we can not accurately estimate $\rho(\Delta)$ for a large Δ because of data constraints. So, what we should do is to multiply $\widehat{\rho}$ by a weight function $w(\Delta) \leq 1$, and let

$$\widehat{\rho}^+(\theta) = 2\int_0^\infty \widehat{\rho}(\Delta)w(\Delta)\cos(\theta\Delta)d\Delta.$$

Possible choices of $w(\cdot)$, suggested by Hall et al. (1994), are $w_1(\Delta) = I(|\Delta| \leq D)$ for some threshold value $D > 0$; and $w_2(\Delta) = 1$ if $|\Delta| < D_1$, $(D_2 - |\Delta|)/(D_2 - D_1)$ if $D_1 \leq |\Delta| \leq D_2$, 0 if $|\Delta| > D_2$.

16

The next step is to make $\widehat{\rho}^+$ nonnegative and then take an inverse Fourier transformation. So, the adjusted estimator is defined as

$$\widetilde{\rho}(\Delta) = (2\pi)^{-1} \int \max\{\widehat{\rho}^+(\theta), 0\} \cos(\theta\Delta) d\theta.$$

The adjusted estimate of correlation function for the colon carcinogenesis p27 data is given as the dashed curve in Figure 2.

5 Simulation Studies

We present three simulation studies to illustrate the numerical performance of the kernel correlation estimator under different settings.

5.1 Simulation 1

Our first simulation study is to mimic the colon carcinogenesis data, so that the result could be inferred to evaluate the performance of our estimators in the data analysis and to justify our choice of tuning parameters.

The simulated data arise from the model

$$Y_r^*(s_{ri}, x_j) = \Theta_r^*(s_{ri}, x_j) + \epsilon_{rij}^*,$$

where $\Theta_r^*(s, x)$ is the rth replicate of a zero-mean Gaussian random field $\Theta^*(s, x)$, $r = 1, \cdots, 12$. As in our data analysis, x takes values in $\{0.0, 0.1, \cdots, 0.9, 1.0\}$. We used the actual unit (crypt) locations from the data as the sample locations s_{ri} in the simulated data. In addition, $\Theta^*(s, x)$ has covariance structure (2) and (3), with

$$G^*(x_1, x_2) = (\sum_{r=1}^{12} N_r)^{-1} \sum_{r=1}^{12} \sum_{i=1}^{N_r} \{Y_{ri}(x_1) - \overline{Y}_{r\cdot}(x_1)\}\{Y_{ri}(x_2) - \overline{Y}_{r\cdot}(x_2)\}, \tag{13}$$

which is computed from the data, and $\rho^*(\Delta)$ chosen from the Matérn correlation family $\rho^*(\Delta; \phi, \kappa) = \{2^{\kappa-1}\Gamma(\kappa)\}^{-1}(\Delta/\phi)^\kappa K_\kappa(\Delta/\phi)$, where $K_\kappa(\cdot)$ is the modified Bessel function, see Stein (1999). In our simulation, we chose $\kappa = 1.5$ and $\phi = 120$ microns. In

addition, the ϵ^*_{rij} are independent identically distributed with Normal$(0, \sigma^2_{\epsilon*})$. For $\sigma^2_{\epsilon*}$, we use an estimate of σ^2_ϵ from the data: $\sigma^2_{\epsilon*} = \frac{1}{11} \sum_{j=1}^{11} \{G^*(x_j, x_j) - \widehat{G}(x_j, x_j)\}$, where $x_j = (j-1)/10$, $j = 1, \cdots, 11$, G^* and $\widehat{G}$ are defined in (13) and (6), respectively.

For each simulated data set, we computed $\widehat{\rho}(\Delta)$ and the standard deviation estimator $\widehat{SD}\{\widehat{\rho}(\Delta)\}$ that we proposed in Section 4.2, for bandwidth $h = 120$ and 200 microns. When doing the bootstrap, we used block size $L^* = 1$ cm, as we did in the p27 data analysis. We repeated the simulation 200 times.

Figure 3 shows the means, 5% and 95% pointwise percentiles of $\widehat{\rho}$ for the two bandwidths, and compares them to the truth ρ^*. Obviously, as expected from the theory, the larger bandwidth incurs the bigger bias. By the plots, it seems that when $h = 120$ the kernel estimator $\widehat{\rho}$ behaves quite well. We compare the true bias from the simulation study to the asymptotic bias computed with the true correlation function ρ^*, under bandwidth $h = 120$. We find the difference between the two are less than 0.04. This means the bias shown in Figure 3 is explainable by our asymptotic theory.

In Figure 4, we show the pointwise standard deviation of $\widehat{\rho}$ from the simulation and the mean of the bootstrap standard deviation estimates. The closeness of the two curves implies that our bootstrap procedure in Section 4.2 gives an approximately unbiased estimator of the true standard deviation, which also implies that our choice of block length, $L^* = 1$ cm, is reasonable. In our simulation, we also tried $L^* = 8$ mm and $L^* = 1.1$ cm: the results are very similar.

We applied the positive semi-definite adjustment procedure in Section 4.3 to the simulation, and the pointwise mean of $\widetilde{\rho}(\cdot)$ is also shown in Figure 3. We computed the integrated mean squared errors (IMSE) of $\widehat{\rho}$ and $\widetilde{\rho}$ up to $\Delta = 500$, and found that IMSE$(\widehat{\rho}) = 12.56$ whereas IMSE$(\widetilde{\rho}) = 8.50$. This result agrees with the theory in Hall and Patil (1994) that positive semi-definite adjustment can actually improve

18

the integrated mean squared error upon the raw kernel estimator. We found that most of the improvements come from the regions where $\rho(\cdot)$ is close to 0 or 1, the areas where the procedure corrects the shape of $\widehat{\rho}$ the most due to the enforcement of positive semi-definiteness.

5.2   Simulation 2

As suggested by the referees, we provide a second simulation study to evaluate the finite sample numerical performance of our correlation estimator when the locations or times are from an inhomogeneous Poisson process as assumed in Section 3. Also, we choose a correlation function which is similar in shape to that obtained from the p27 data example but is even less monotone; this clearly illustrate a situation that an 'off-the-shelf' parametric model fails to fit the data. The true correlation function is given as the solid curve in the middle panel in Figure 5, while the corresponding spectral density is given in the upper panel of the same Figure.

We kept the same simulation set-up as those in simulation 1 except that the spatial correlation $\rho(\Delta)$ was set to be the one given in Figure 5, that the locations are sampled from an inhomogeneous Poisson process as given in Section 3 with g to be a truncated normal density function on $[0, 1]$, and that we simulated only one subject on a prolonged domain $[0, L]$, with $L = 50,000$ and the expected number of units to be 500. We let bandwidth $h = 35$ and block size $L^* = 6,000$ for the weighted block bootstrap procedure.

We repeated the process described above for 200 times, and computed the proposed correlation estimator for each simulated data set. In the middle panel of Figure 5, the mean of our kernel correlation estimator is given by the dashed curve, while the dotted curve is the best approximation to the true correlation function from the Matérn family. As one can see, our nonparametric method can consistently estimate a non-monotone

19

correlation function.

In Figure 5 we also compare the mean of our bootstrap standard deviation estimator with the true pointwise standard deviation curve. We found that the proposed standard deviation estimator also works quite well given the finite sample size.

5.3 Simulation 3

Our third simulation study has the same setting as Simulation 2, except the correlation function is replaced by

$$\rho(\Delta) = \frac{1}{2} \frac{\cos(\Delta/60)}{1 + |\Delta|/100} + \frac{1}{2} \exp\left(-\frac{|\Delta|}{800}\right),$$

as suggested by one referee. This correlation is given by the solid curve in Figure 6. We use this simulation to illustrate the performance of the kernel correlation estimator and its adjusted version in the case that the true correlation function is not smooth at 0.

Because this function decays to 0 with a slower rate, we present the estimate up to $\Delta = 1000$. The dashed curve in Figure 6 gives the mean of $\widehat{\rho}$ over 200 simulations, and the two dotted curves give the pointwise 5% and 95% percentiles of $\widehat{\rho}$, and the dotdash curve gives the mean of $\widetilde{\rho}$. One can see that $\widehat{\rho}$ still behaves well even though the true function is not differentiable at 0. The adjustment procedure introduced some bias, but reduced the variation. We compared the IMSE of the two estimators over $[0, 50]$ and $[0, 500]$: the IMSE for $\widehat{\rho}$ over the two ranges are 0.40 and 6.59, while the corresponding IMSE for $\widetilde{\rho}$ are 0.19 and 4.53. The adjustment procedure improved the IMSE on both ranges, even in an area close to the origin.

This simulation study shows that our estimators work even when the differentiability assumption in Section 3 is mildly violated.

6 Discussion

We have proposed an estimator of stationary correlation functions for longitudinal or spatial data, where within-subject observations have a complex data structure. The application we presented has a functional data flavor, in that each unit (crypt) in a "time series" has sub-units (cells) the values from which can be viewed as a function. However, in this paper, we have focused on estimating the spatial correlation between the units.

We established an asymptotic normal limit distribution for the proposed estimator. The techniques used in our theoretical derivation were significantly different from those of standard kernel regression literature. In our theoretical framework, as long as we have an increasing number of observations within a subject, each subject yields a consistent estimate of the correlation function. Our method and theory are especially useful to the cases that the number of subjects is limited but we have a relatively large number of repeated measurements within each subject. Since having more subjects will just further reduce the variation of the estimator, our main theorems hold when R goes to infinity as well. In that case, we need to replace the condition that $Lh^5 = O(1)$ in assumption 7 in Section 3 with $RLh^5 = O(1)$. In fact, when the number of subjects $R \to \infty$, we can consistently estimate the within-subject covariance without a large number of units within each subject. For example, Yao et. al. (2005) proposed using smoothing methods to estimate within subject covariance for sparse longitudinal data.

In spatial statistics, many authors have considered the setup under the intrinsic stationary assumption (Besag, York and Mollie 1991, Besag and Higdon 1999). This is weaker than our second-order stationary assumption. In our case, each unit within a subject has further structure, so that we can define cross-variogram (Cressie 1993) instead of covariance function $\mathcal{V}(x_1, x_2, \Delta)$, and similar limiting distribution theorems

21

can be proved as in Theorem 1 and 2. However, when it comes to Spatio-Temporal modelling, many authors (Cressie and Huang 1999, Stein 2005) would still focus their attention to covariance estimation because it is a more natural way to introduce the separable structure (3). In our data analysis, we provided some practical ideas to justify the separable structure in our data, where we compare the cross-validation scores with or without the separable assumption.

We proposed a weighted Bootstrap method to estimate the standard deviation of the correlation estimator $\widehat{\rho}$, where the weights were constructed based on the outcome from Lemma 2 in the proofs. Our simulation studies show that the proposed correlation estimator and the weighted bootstrap standard deviation estimator work well numerically for finite sample sizes.

Acknowledgments

APPENDIX: PROOFS

The proofs are organized in the following way: in section A.1, we provide lemmas regarding asymptotic properties of the covariance estimators when there is only one

subject; in section A.2, we provide lemmas on the estimators with multiple subjects, and the proofs of Theorems 1, 2 and Corollary 1 are given in the end.

A.1 Estimation Within One Subject

We will first discuss a case that there is only one subject and the number of units goes to infinity. Let $N(\cdot)$ be the inhomogeneous Poisson process on $[0, L]$ with local intensity $\nu g^*(s)$. As in Karr (1986), denote $N_2(ds_1, ds_2) = N(ds_1)N(ds_2)I(s_1 \neq s_2)$. Let $\Theta(s, \cdot)$ denote the unit-level mean at unit location s, and $\Psi(\cdot)$ denote the subject-level mean. Define

$$
\begin{aligned}
a(\Delta) &= L^{-1}\sum_i \sum_{k \neq i} K_h(\Delta - \Delta_{ik}) = L^{-1}\int_0^L \int_0^L K_h\{\Delta - (s_1 - s_2)\}N_2(ds_1, ds_2); \\
b(x_1, x_2, \Delta) &= L^{-1}\sum_i \sum_{k \neq i} K_h(\Delta - \Delta_{ik})\{Y(S_i, x_1) - \Psi(x_1)\}\{Y(S_k, x_2) - \Psi(x_2)\} \\
&= L^{-1}\int_0^L \int_0^L K_h\{\Delta - (s_1 - s_2)\}\{Y(s_1, x_1) - \Psi(x_1)\} \\
&\qquad \times \{Y(s_2, x_2) - \Psi(x_2)\}N_2(ds_1, ds_2).
\end{aligned}
$$

LEMMA 1 Let that X_1 and X_2 be real valued random variables measurable with respect to $\mathcal{F}\{[0, t]\}$ and $\mathcal{F}\{[t + \tau, \infty)\}$ respectively, such that $|X_i| < C_i$, $i = 1, 2$. Then $|\text{cov}(X_1, X_2)| \leq 4C_1 C_2 \alpha(\tau)$. If X_1 and X_2 are complex random variables, this inequality holds with the constant 4 replaced by 16.

Proof: The proof is analogous to that of Theorem 17.2.1 in Ibragimov and Linnik (1971). Denote $T_1 = [0, t]$, $T_2 = [t + \tau, \infty)$, then we have

$$
|E(X_1 X_2) - E(X_1)E(X_2)| = |E[E\{X_1 X_2 | \mathcal{F}(T_1)\}] - E(X_1)E(X_2)|
$$

$$
= |E(X_1[E\{X_2 | \mathcal{F}(T_1)\} - E(X_2)])| \leq C_1 E|E\{X_2 | \mathcal{F}(T_1)\} - E(X_2)|
$$

$$
= C_1 E(u_1[E\{X_2 | \mathcal{F}(T_1)\} - E(X_2)])
$$

where $u_1 = \text{sign}[E\{X_2|\mathcal{F}(T_1)\} - E(X_2)]$. It is easy to see that u_1 is measurable with respect to $\mathcal{F}(T_1)$, therefore $|E(X_1X_2) - E(X_1)E(X_2)| \leq C_1|E(u_1X_2) - E(u_1)E(X_2)|$. By the same argument, we have $|E(u_1X_2) - E(u_1)E(X_2)| \leq C_2|E(u_1u_2) - E(u_1)E(u_2)|$, where $u_2 = \text{sign}[E\{u_1|\mathcal{F}(T_2)\} - E(u_1)]$. Now, we have $|E(X_1X_2) - E(X_1)E(X_2)| \leq C_1C_2|E(u_1u_2) - E(u_1)E(u_2)|$. Define the events $A_1 = \{u_1 = 1\} \in \mathcal{F}(T_1)$, $\overline{A}_1 = \{u_1 = -1\} \in \mathcal{F}(T_1)$, $A_2 = \{u_2 = 1\} \in \mathcal{F}(T_2)$ and $\overline{A}_2 = \{u_2 = -1\} \in \mathcal{F}(T_2)$. Then,

$$
\begin{aligned}
|E(u_1u_2) - E(u_1)E(u_2)| =\ & |P(A_1A_2) - P(A_1\overline{A}_2) - P(\overline{A}_1A_2) + P(\overline{A}_1\overline{A}_2) \\
& -P(A_1)P(A_2) + P(A_1)P(\overline{A}_2) + P(\overline{A}_1)P(A_2) - P(\overline{A}_1)P(\overline{A}_2)| \\
\leq\ & |P(A_1A_2) - P(A_1)P(A_2)| + |P(A_1\overline{A}_2) - P(A_1)P(\overline{A}_2)| \\
& +|P(\overline{A}_1A_2) - P(\overline{A}_1)P(A_2)| + |P(\overline{A}_1\overline{A}_2) - P(\overline{A}_1)P(\overline{A}_2)| \\
\leq\ & 4\alpha(\tau).
\end{aligned}
$$

Thus, the proof is completed for the real random variable case. If X_1 and X_2 are complex, we can apply the same arguments to the real and imaginary parts separately.

LEMMA 2 With the assumptions stated in Section 3, for any fixed Δ, we have $a(\Delta) \to \nu^2 f_1(0)$ in L^2 sense, as $L \to \infty$.

Proof: Recall that by definition of $f_1(\cdot)$, if X_1 and X_2 are independent and identically distributed with density $g(\cdot)$, then $f_1(u) = \int g(t+u)g(t)dt$ is the density of $X_1 - X_2$. Thus, for fixed Δ,

$$
\begin{aligned}
E\{a(\Delta)\} &= \nu^2 L^{-1} \int\int_{s_1 \neq s_2} K_h\{\Delta - (s_1 - s_2)\}g(s_1/L)g(s_2/L)ds_1ds_2 \\
&= \nu^2 L \int_0^1 \int_0^1 K_h\{\Delta - L(t_1 - t_2)\}g(t_1)g(t_2)dt_1dt_2 \\
&= \nu^2 L \int\int K_h(\Delta - Lu)g(t_2 + u)g(t_2)dudt_2 \\
&= \nu^2 L \int K_h(\Delta - Lu)f_1(u)du = \nu^2 \int K(v)f_1\{(\Delta - hv)/L\}dv \\
&= \nu^2 \int K(v)\{f_1(0) + O(L^{-1})\}dv = \nu^2 f_1(0) + O(L^{-1}).
\end{aligned}
$$

Next,

$$E\{a^2(\Delta)\} \quad = \quad L^{-2} \int_0^L \int_0^L \int_0^L \int_0^L K_h\{\Delta - (s_1 - s_2)\}K_h\{\Delta - (s_3 - s_4)\}$$

$$\times E\{N_2(ds_1, ds_2)N_2(ds_3, ds_4)\}.$$

Calculations as in Guan et al. (2004) show that

$$E\{N_2(ds_1, ds_2)N_2(ds_3, ds_4)\} = \nu^4 g^*(s_1)g^*(s_2)g^*(s_3)g^*(s_4)ds_1 ds_2 ds_3 ds_4$$

$$+\nu^3 g^*(s_1)g^*(s_2)g^*(s_4)\epsilon_{s_1}(ds_3)ds_1 ds_2 ds_4 + \nu^3 g^*(s_1)g^*(s_2)g^*(s_3)\epsilon_{s_1}(ds_4)ds_1 ds_2 ds_3$$

$$+\nu^3 g^*(s_1)g^*(s_2)g^*(s_4)\epsilon_{s_2}(ds_3)ds_1 ds_2 ds_4 + \nu^3 g^*(s_1)g^*(s_2)g^*(s_3)\epsilon_{s_2}(ds_4)ds_1 ds_2 ds_3$$

$$+\nu^2 g^*(s_1)g^*(s_2)\epsilon_{s_1}(ds_3)\epsilon_{s_2}(ds_4)ds_1 ds_2 + \nu^2 g^*(s_1)g^*(s_2)\epsilon_{s_1}(ds_4)\epsilon_{s_2}(ds_3)ds_1 ds_2,$$

where $\epsilon_x(\cdot)$ is a point measure defined in Karr (1986), such that $\epsilon_x(dy) = 1$ if $x \in dy$, 0 otherwise. Here dy is defined to be a small disc centered at y. There are 7 terms in the expression above, so the expression for $E\{a^2(\Delta)\}$ can be decomposed into 7 integrals: denote them as A_{11}-A_{17}. Similar to the calculations of $E\{a(\Delta)\}$, we have

$$A_{11} \quad = \quad \nu^4 L^{-2} \int\int_{s_1 \neq s_2} \int\int_{s_3 \neq s_4} K_h\{\Delta - (s_1 - s_2)\}K_h\{\Delta - (s_3 - s_4)\}$$

$$\times g(s_1/L)g(s_2/L)g(s_3/L)g(s_4/L)ds_1 ds_2 ds_3 ds_4$$

$$= \quad \nu^4 f_1^2(0) + o(1).$$

$$A_{12} \quad = \quad \nu^3 L^{-2} \int_{s_1 \neq s_2, s_4} K_h\{\Delta - (s_1 - s_2)\}K_h\{\Delta - (s_1 - s_4)\}$$

$$\times g(s_1/L)g(s_2/L)g(s_4/L)ds_1 ds_2 ds_4$$

$$= \quad \nu^3 L \int\int K_h(\Delta - Lu_1)K_h\{\Delta - L(u_1 - u_2)\}f_2(u_1, u_2)du_1 du_2$$

$$\text{(by definition of } f_2)$$

$$= \quad \nu^3 L^{-1} \int\int K(v_1)K(v_2)f_2\{(\Delta - hv_1)/L, (v_2 - v_1)h/L\}dv_1 dv_2$$

$$= \quad \nu^3 L^{-1} f_2(0, 0) + O(L^{-2}).$$

25

Similarly, $A_{13} - A_{15}$ are of order $O(L^{-1})$. Next,

$$
\begin{aligned}
A_{16} &= \nu^2 L^{-2} \int_{s_1 \neq s_2} K_h^2\{\Delta - (s_1 - s_2)\} g(s_1/L) g(s_2/L) ds_1 ds_2 \\
&= \nu^2 \int K_h^2(\Delta - Lu) f_1(u) du = \nu^2 L^{-1} h^{-1} \int K^2(v) f_1\{(\Delta - hv)/L\} dv \\
&= \nu^2 L^{-1} h^{-1} f_1(0) R_K + o(L h^{-1}).
\end{aligned}
$$

Similarly, we can show that A_{17} is of the same order as A_{16}. This means that A_{11} is the leading term in $E\{a^2(\Delta)\}$. Hence, $E\{a(\Delta) - \nu^2 f_1(0)\}^2 \to 0$, completing the proof.

<u>LEMMA</u> **3** For any fixed Δ, define $\beta(x_1, x_2, \Delta) = b(x_1, x_2, \Delta) - a(\Delta) \mathcal{V}(x_1, x_2, \Delta)$. Then

$$
E\{\beta(x_1, x_2, \Delta)\} = \nu^2 f_1(0)\{\mathcal{V}^{(0,0,2)}(x_1, x_2, \Delta) \sigma_K^2 h^2/2 + o(h^2)\},
$$

$$
\begin{aligned}
\mathrm{cov}\{\beta(x_1, x_2, \Delta), \beta(x_3, x_4, \Delta')\} &= \nu^2 L^{-1} h^{-1} R_K f_1(0)[I(\Delta = \Delta')\{\mathcal{M}(x_1, x_2, x_3, x_4, \Delta, \Delta, 0) \\
&\quad + I(x_2 = x_4)\sigma_\epsilon^2 \mathcal{V}(x_1, x_3, 0) + I(x_1 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_2, x_4, 0) + I(x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4\} \\
&\quad + I(\Delta = -\Delta')\{\mathcal{M}(x_1, x_2, x_3, x_4, \Delta, -\Delta, -\Delta) + I(x_2 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_1, x_4, 0) \\
&\quad + I(x_1 = x_4)\sigma_\epsilon^2 \mathcal{V}(x_2, x_3, 0) + I(x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4\}] + o(L^{-1} h^{-1}),
\end{aligned}
$$

where $\mathcal{V}^{(0,0,2)}(x_1, x_2, \Delta) = \partial^2 \mathcal{V}(x_1, x_2, \Delta)/\partial \Delta^2$.

<u>Proof:</u> Rewrite

$$
\begin{aligned}
\beta(x_1, x_2, \Delta) &= L^{-1} \int \int K_h\{\Delta - (s_1 - s_2)\} [\{Y(s_1, x_1) - \Psi(x_1)\} \\
&\quad \times \{Y(s_2, x_2) - \Psi(x_2)\} - \mathcal{V}(x_1, x_2, \Delta)] N_2(ds_1, ds_2),
\end{aligned}
$$

it follows that

$$
\begin{aligned}
E\{\beta(x_1, x_2, \Delta)\} &= \nu^2 L^{-1} \int \int_{s_1 \neq s_2} K_h\{\Delta - (s_1 - s_2)\} \\
&\quad \times \{\mathcal{V}(x_1, x_2, s_1 - s_2) - \mathcal{V}(x_1, x_2, \Delta)\} g(s_1/L) g(s_2/L) ds_1 ds_2 \\
&= \nu^2 L \int K_h(\Delta - Lu)\{\mathcal{V}(x_1, x_2, Lu) - \mathcal{V}(x_1, x_2, \Delta)\} f_1(u) du
\end{aligned}
$$

$$= \nu^2 \int K(v)\{-\mathcal{V}^{(0,0,1)}(x_1, x_2, \Delta)hv + \mathcal{V}^{(0,0,2)}(x_1, x_2, \Delta)h^2v^2/2 + o(h^2)\}$$

$$\times \{f_1(0) + O(L^{-1})\}dv$$

$$= \nu^2\{f_1(0)\mathcal{V}^{(0,0,2)}(x_1, x_2, \Delta)\sigma_K^2 h^2/2 + o(h^2)\}.$$

In addition,

$$\text{cov}\{\beta(x_1, x_2, \Delta), \beta(x_3, x_4, \Delta')\}$$

$$= L^{-2} \int \int \int \int K_h\{\Delta - (s_1 - s_2)\}K_h\{\Delta' - (s_3 - s_4)\}$$

$$[\mathcal{V}(x_1, x_2, \Delta)\mathcal{V}(x_3, x_4, \Delta') - \mathcal{V}(x_1, x_2, s_1 - s_2)\mathcal{V}(x_3, x_4, \Delta')$$

$$-\mathcal{V}(x_1, x_2, \Delta)\mathcal{V}(x_3, x_4, s_3 - s_4) + \mathcal{M}\{x_1, x_2, x_3, x_4, (s_1 - s_2), (s_3 - s_4), (s_2 - s_4)\}$$

$$+\mathcal{V}(x_1, x_2, s_1 - s_2)\mathcal{V}(x_3, x_4, s_3 - s_4)$$

$$+I(s_1 = s_3)I(s_2 \neq s_4)I(x_1 = x_3)\sigma_\epsilon^2\mathcal{V}\{x_2, x_4, (s_2 - s_4)\}$$

$$+I(s_1 = s_4)I(s_2 \neq s_3)I(x_1 = x_4)\sigma_\epsilon^2\mathcal{V}\{x_2, x_3, (s_2 - s_3)\}$$

$$+I(s_2 = s_3)I(s_1 \neq s_4)I(x_2 = x_3)\sigma_\epsilon^2\mathcal{V}\{x_1, x_4, (s_1 - s_4)\}$$

$$+I(s_2 = s_4)I(s_1 \neq s_3)I(x_2 = x_4)\sigma_\epsilon^2\mathcal{V}\{x_1, x_3, (s_1 - s_3)\}$$

$$+I(s_1 = s_3, s_2 = s_4)\{I(x_2 = x_4)\sigma_\epsilon^2\mathcal{V}(x_1, x_3, 0) + I(x_1 = x_3)\sigma_\epsilon^2\mathcal{V}(x_2, x_4, 0)$$

$$+I(x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4\}$$

$$+I(s_1 = s_4, s_2 = s_3)\{I(x_2 = x_3)\sigma_\epsilon^2\mathcal{V}(x_1, x_4, 0) + I(x_1 = x_4)\sigma_\epsilon^2\mathcal{V}(x_2, x_3, 0)$$

$$+I(x_1 = x_4, x_2 = x_3)\sigma_\epsilon^4\}]E\{N_2(ds_1, ds_2)N_2(ds_3, ds_4)\}$$

$$-\nu^4 L^{-2} \int \int \int \int K_h\{\Delta - (s_1 - s_2)\}K_h\{\Delta' - (s_3 - s_4)\}$$

$$\times \{\mathcal{V}(x_1, x_2, s_1 - s_2) - \mathcal{V}(x_1, x_2, \Delta)\}\{\mathcal{V}(x_3, x_4, s_3 - s_4) - \mathcal{V}(x_3, x_4, \Delta')\}$$

$$\times g(s_1/L)g(s_2/L)g(s_3/L)g(s_4/L)ds_1 ds_2 ds_3 ds_4.$$

As in Lemma 2, according to the expression for $E\{N_2(ds_1, ds_2)N_2(ds_3, ds_4)\}$, we can

summarize this covariance expression as the sum of 7 terms, denoted as A_{21}-A_{27}.

$$
\begin{aligned}
A_{21} &= \nu^4 L^{-2} \int_0^L \int_0^L \int_0^L \int_0^L K_h\{\Delta - (s_1 - s_2)\} K_h\{\Delta' - (s_3 - s_4)\} \\
&\quad \times \mathcal{M}\{x_1, x_2, x_1, x_2, (s_1 - s_2), (s_3 - s_4), (s_2 - s_4)\} \\
&\quad \times g(s_1/L) g(s_2/L) g(s_3/L) g(s_4/L) ds_1 ds_2 ds_3 ds_4 \\
&= \nu^4 L^2 \int_0^1 \int_0^1 \int_0^1 \int_0^1 K_h\{\Delta - L(t_1 - t_2)\} K_h\{\Delta' - L(t_3 - t_4)\} \\
&\quad \times \mathcal{M}\{x_1, x_2, x_1, x_2, L(t_1 - t_2), L(t_3 - t_4), L(t_2 - t_4)\} \\
&\quad \times g(t_1) g(t_2) g(t_3) g(t_4) dt_1 dt_2 dt_3 dt_4 \\
&= \nu^4 L^2 \int \int \int K_h(\Delta - Lu_1) K_h(\Delta' - Lu_2) \mathcal{M}(x_1, x_2, x_1, x_2, Lu_1, Lu_2, Lu_3) \\
&\quad f_3(u_1, u_2, u_3) du_1 du_2 du_3 \\
&= \nu^4 L^{-1} \int \int \int K(v_1) K(v_2) \mathcal{M}(x_1, x_2, x_1, x_2, \Delta - hv_1, \Delta' - hv_2, v_3) \\
&\quad f_3\{(\Delta - hv_1)/L, (\Delta' - hv_2)/L, v_3/L\} dv_1 dv_2 dv_3 \\
&\leq \nu^4 L^{-1} C \int \mathcal{M}(x_1, x_2, x_1, x_2, \Delta, \Delta', v) dv + o(L^{-1}),
\end{aligned}
$$

where C is the upper bound for the density function $f_3(u, v, w)$ on $[-1, 1]^3$. By assumption 1 in Section 3 that $g(\cdot)$ is bounded, one can easily derive that C is a finite constant.

$$
\begin{aligned}
A_{22} &= \nu^3 L^{-2} \int \int \int K_h\{\Delta - (s_1 - s_2)\} K_h\{\Delta' - (s_1 - s_4)\} \\
&\quad \times ([\mathcal{V}(x_1, x_2, \Delta) - \mathcal{V}\{x_1, x_2, (s_1 - s_2)\}][\mathcal{V}(x_3, x_4, \Delta') - \mathcal{V}\{x_3, x_4, (s_1 - s_4)\}] \\
&\quad + \mathcal{M}\{x_1, x_2, x_3, x_4, (s_1 - s_2), (s_1 - s_4), (s_2 - s_4)\} \\
&\quad + I(x_1 = x_3)\sigma_\epsilon^2 \mathcal{V}\{x_2, x_4, (s_2 - s_4)\}) g(s_1/L) g(s_2/L) g(s_4/L) ds_1 ds_2 ds_4 \\
&= \nu^3 L \int \int \int K_h\{\Delta - L(t_1 - t_2)\} K_h\{\Delta' - L(t_1 - t_4)\} \\
&\quad \times ([\mathcal{V}(x_1, x_2, \Delta) - \mathcal{V}\{x_1, x_2, L(t_1 - t_2)\}][\mathcal{V}(x_3, x_4, \Delta') - \mathcal{V}\{x_3, x_4, L(t_1 - t_4)\}] \\
&\quad + \mathcal{M}\{x_1, x_2, x_3, x_4, L(t_1 - t_2), L(t_1 - t_4), L(t_2 - t_4)\}
\end{aligned}
$$

$$+ I(x_1 = x_3)\sigma_\epsilon^2 \mathcal{V}\{x_2, x_4, L(t_2 - t_4)\}) g(t_1) g(t_2) g(t_4) dt_1 dt_2 dt_4$$

$$= \nu^3 L \int \int K_h(\Delta + L u_1) K_h(\Delta' + L u_2)$$

$$\times [\{\mathcal{V}(x_1, x_2, \Delta) - \mathcal{V}(x_1, x_2, -L u_1)\}\{\mathcal{V}(x_3, x_4, \Delta') - \mathcal{V}(x_3, x_4, -L u_2)\}$$

$$+ \mathcal{M}\{x_1, x_2, x_3, x_4, -L u_1, -L u_2, L(u_1 - u_2)\}$$

$$+ I(x_1 = x_3)\sigma_\epsilon^2 \mathcal{V}\{x_2, x_4, L(u_1 - u_2)\}] f_2(u_1, u_2) du_1 du_2$$

$$= \nu^3 L^{-1} \int \int K(v_1) K(v_2) [I(x_1 = x_3)\sigma_\epsilon^2 \mathcal{V}\{x_2, x_4, (v_1 - v_2)h + \Delta' - \Delta\}$$

$$+ \{\mathcal{V}(x_1, x_2, \Delta) - \mathcal{V}(x_1, x_2, \Delta - h v_1)\}\{\mathcal{V}(x_3, x_4, \Delta) - \mathcal{V}(x_3, x_4, \Delta' - h v_2)\}$$

$$+ \mathcal{M}\{x_1, x_2, x_3, x_4, \Delta - h v_1, \Delta' - h v_2, (v_1 - v_2)h + \Delta' - \Delta\}]$$

$$\times f_2\{(-\Delta + h v_1)/L, (-\Delta + v_1 h)/L\} dv_1 dv_2$$

$$= \nu^3 L^{-1} f_2(0, 0)\{\mathcal{M}(x_1, x_2, x_3, x_4, \Delta, \Delta', \Delta' - \Delta)$$

$$+ I(x_1 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_2, x_4, \Delta' - \Delta)\} + o(L^{-1}).$$

It is easy to see that A_{23}-A_{25} have the same order as A_{22}. Further, we have

$$A_{26} = \nu^2 L^{-2} \int \int K_h\{\Delta - (s_1 - s_2)\} K_h\{\Delta' - (s_1 - s_2)\}$$

$$\times (\mathcal{M}\{x_1, x_2, x_3, x_4, (s_1 - s_2), (s_1 - s_2), 0\}$$

$$+ [\mathcal{V}(x_1, x_2, \Delta) - \mathcal{V}\{x_1, x_2, (s_1 - s_2)\}][\mathcal{V}(x_3, x_4, \Delta') - \mathcal{V}\{x_3, x_4, (s_1 - s_2)\}]$$

$$+ \{I(x_2 = x_4)\sigma_\epsilon^2 \mathcal{V}(x_1, x_3, 0) + I(x_1 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_2, x_4, 0)$$

$$+ I(x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4\}) \times g(s_1/L) g(s_2/L) ds_1 ds_2$$

$$= I(\Delta = \Delta')\nu^2 \int \int K_h^2\{\Delta - L(t_1 - t_2)\}(\mathcal{M}\{x_1, x_2, x_3, x_4, L(t_1 - t_2), L(t_1 - t_2), 0\}$$

$$+ [\mathcal{V}(x_1, x_2, \Delta) - \mathcal{V}\{x_1, x_2, L(t_1 - t_2)\}][\mathcal{V}(x_3, x_4, \Delta) - \mathcal{V}\{x_3, x_4, L(t_1 - t_2)\}]$$

$$+ \{I(x_2 = x_4)\sigma_\epsilon^2 \mathcal{V}(x_1, x_3, 0) + I(x_1 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_2, x_4, 0)$$

$$+ I(x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4\}) \times g(t_1) g(t_2) dt_1 dt_2$$

$$= I(\Delta = \Delta')\nu^2 \int K_h^2(\Delta - L u)[\mathcal{M}(x_1, x_2, x_3, x_4, L u, L u, 0)$$

$$+\{\mathcal{V}(x_1, x_2, \Delta) - \mathcal{V}(x_1, x_2, Lu)\}\{\mathcal{V}(x_3, x_4, \Delta) - \mathcal{V}(x_3, x_4, Lu)\}$$

$$+\{I(x_2 = x_4)\sigma_\epsilon^2 \mathcal{V}(x_1, x_3, 0) + I(x_1 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_2, x_4, 0)$$

$$+I(x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4\}] \times f_1(u)du$$

$$= I(\Delta = \Delta')\nu^2 L^{-1}h^{-1}\int K^2(v)[\mathcal{M}(x_1, x_2, x_3, x_4, \Delta - hv, \Delta - hv, 0)$$

$$+\{\mathcal{V}(x_1, x_2, \Delta) - \mathcal{V}(x_1, x_2, \Delta - hv)\}\{\mathcal{V}(x_3, x_4, \Delta) - \mathcal{V}(x_3, x_4, \Delta - hv)\}$$

$$+\{I(x_2 = x_4)\sigma_\epsilon^2 \mathcal{V}(x_1, x_3, 0) + I(x_1 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_2, x_4, 0)$$

$$+I(x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4\}] \times f_1\{(\Delta - hv)/L\}dv$$

$$= I(\Delta = \Delta')\nu^2 L^{-1}h^{-1}R_K f_1(0)[\mathcal{M}(x_1, x_2, x_3, x_4, \Delta, \Delta, 0) + \{I(x_2 = x_4)\sigma_\epsilon^2$$

$$\times \mathcal{V}(x_1, x_3, 0) + I(x_1 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_2, x_4, 0) + I(x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4\} + o(1)].$$

Similarly,

$$A_{27} = \nu^2 L^{-2}\int\int K_h\{\Delta - (s_1 - s_2)\}K_h\{\Delta' - (s_2 - s_1)\}$$

$$\times(\mathcal{M}\{x_1, x_2, x_3, x_4, (s_1 - s_2), (s_2 - s_1), (s_2 - s_1)\}$$

$$+[\mathcal{V}(x_1, x_2, \Delta) - \mathcal{V}\{x_1, x_2, (s_1 - s_2)\}][\mathcal{V}(x_3, x_4, \Delta') - \mathcal{V}\{x_3, x_4, (s_2 - s_1)\}]$$

$$+\{I(x_2 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_1, x_4, 0) + I(x_1 = x_4)\sigma_\epsilon^2 \mathcal{V}(x_2, x_3, 0)$$

$$+I(x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4\}) \times g(s_1/L)g(s_2/L)ds_1 ds_2$$

$$= I(\Delta = -\Delta')\nu^2\int\int K_h^2\{\Delta - L(t_1 - t_2)\}$$

$$\times(\mathcal{M}\{x_1, x_2, x_3, x_4, L(t_1 - t_2), L(t_2 - t_1), L(t_2 - t_1)\}$$

$$+[\mathcal{V}(x_1, x_2, \Delta) - \mathcal{V}\{x_1, x_2, L(t_1 - t_2)\}][\mathcal{V}(x_3, x_4, -\Delta) - \mathcal{V}\{x_3, x_4, L(t_2 - t_1)\}]$$

$$+\{I(x_2 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_1, x_4, 0) + I(x_1 = x_4)\sigma_\epsilon^2 \mathcal{V}(x_2, x_3, 0)$$

$$+I(x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4\}) \times g(t_1)g(t_2)dt_1 dt_2$$

$$= I(\Delta = -\Delta')\nu^2\int K_h^2(\Delta - Lu)[\mathcal{M}(x_1, x_2, x_3, x_4, Lu, -Lu, -Lu)$$

$$+\{\mathcal{V}(x_1, x_2, \Delta) - \mathcal{V}(x_1, x_2, Lu)\}\{\mathcal{V}(x_3, x_4, \Delta) - \mathcal{V}(x_3, x_4, Lu)\}$$

$$+\{I(x_2 = x_3)\sigma_\epsilon^2\mathcal{V}(x_1, x_4, 0) + I(x_1 = x_4)\sigma_\epsilon^2\mathcal{V}(x_2, x_3, 0)$$

$$+I(x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4\}] \times f_1(u)du$$

$$= I(\Delta = -\Delta')\nu^2 L^{-1}h^{-1}\int K^2(v)[\mathcal{M}(x_1, x_2, x_3, x_4, \Delta - hv, -\Delta + hv, -\Delta + hv)$$

$$+\{\mathcal{V}(x_1, x_2, \Delta) - \mathcal{V}(x_1, x_2, \Delta - hv)\}\{\mathcal{V}(x_3, x_4, \Delta) - \mathcal{V}(x_3, x_4, \Delta - hv)\}$$

$$+\{I(x_2 = x_3)\sigma_\epsilon^2\mathcal{V}(x_1, x_4, 0) + I(x_1 = x_4)\sigma_\epsilon^2\mathcal{V}(x_2, x_3, 0)$$

$$+I(x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4\}] \times f_1\{(\Delta - hv)/L\}dv$$

$$= I(\Delta = -\Delta')\nu^2 L^{-1}h^{-1}R_K f_1(0)[\mathcal{M}(x_1, x_2, x_3, x_4, \Delta, -\Delta, -\Delta) + \{I(x_2 = x_3)\sigma_\epsilon^2$$

$$\times \mathcal{V}(x_1, x_4, 0) + I(x_1 = x_4)\sigma_\epsilon^2\mathcal{V}(x_2, x_3, 0) + I(x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4\} + o(1)].$$

Both A_{26} and A_{27} are of order $O\{(Lh)^{-1}\}$, while the rest terms are of order $O(L^{-1})$. The proof is completed by summarizing the contribution of each term to $\text{cov}\{\beta(x_1, x_2, \Delta),$ $\beta(x_3, x_4, \Delta')\}$.

LEMMA 4 With $\beta(x_1, x_2, \Delta)$ defined as in Lemma 3, and with all assumptions in Section 3, we have

$$(Lh)^{1/2}[\beta(x_1, x_2, \Delta) - E\{\beta(x_1, x_2, \Delta)\}] \Rightarrow \text{Normal}\{0, \nu^2 f_1(0)\sigma^2(x_1, x_2, \Delta)\},$$

where $\sigma^2(x_1, x_2, \Delta) = R_K\{\mathcal{M}(x_1, x_2, x_1, x_2, \Delta, \Delta, 0) + \sigma_\epsilon^2\mathcal{V}(x_1, x_1, 0) + \sigma_\epsilon^2\mathcal{V}(x_2, x_2, 0) + \sigma_\epsilon^4\} + I(\Delta = 0)R_K[\{\mathcal{M}(x_1, x_2, x_1, x_2, 0, 0, 0) + I(x_1 = x_2)\{2\sigma_\epsilon^2\mathcal{V}(x_1, x_1, 0) + \sigma_\epsilon^4\}].$

Proof: The proof shares the similar structure to that of Theorem 2 in Guan et al. (2004). Define $a_1 = 0$, $b_1 = L^p - L^q$, $a_i = a_{i-1} + L^p$, $b_i = a_i + L^p - L^q$, $i = 2, \cdots, k_L$, for some $1/(1 + \delta) < q < p < 1$ (δ is defined in (10)). We thus have divided the interval $[0, L]$ into $k_L \approx L/L^p$ disjoint subintervals each having length $L^p - L^q$ and at least L^q apart. Define $I_i = [a_i, b_i]$, $I = \cup_{i=1}^{k_L}I_i$, $I'_i = [a_i/L, b_i/L]$, $I' = \cup_{i=1}^{k_L}I'_i$, and

$$\beta_i(x_1, x_2, \Delta) = L^{-1}\int\int_{I_i \times I_i} K_h\{\Delta - (s_1 - s_2)\}[\{Y(s_1, x_1) - \Psi(x_1)\}$$

$$\times \{Y(s_2, x_2) - \Psi(x_2)\} - \mathcal{V}(x_1, x_2, \Delta)]N_2(ds_1, ds_2),$$

$$\widetilde{\beta}(x_1, x_2, \Delta) = \sum_{i=1}^{k_L} \beta_i(x_1, x_2, \Delta).$$

Define independent random variables $\gamma_i(x_1, x_2, \Delta)$ on a different probability space, such that they have the same distributions as $\beta_i(x_1, x_2, \Delta)$, and define $\gamma(x_1, x_2, \Delta) = \sum_{i=1}^{k_L} \gamma_i(x_1, x_2, \Delta)$. Let $\phi(\xi)$ and $\psi(\xi)$ be the characteristic functions of $(Lh)^{1/2}[\widetilde{\beta}(x_1, x_2, \Delta) - E\{\widetilde{\beta}(x_1, x_2, \Delta)\}]$ and $(Lh)^{1/2}[\gamma(x_1, x_2, \Delta) - E\{\gamma(x_1, x_2, \Delta)\}]$, respectively.

We finish the proof in the following 3 steps:

(i) $(Lh)^{1/2}([\{\beta(x_1, x_2, \Delta) - E\{\beta(x_1, x_2, \Delta)\}\}] - \{\widetilde{\beta}(x_1, x_2, \Delta) - E\{\widetilde{\beta}(x_1, x_2, \Delta)\}\}]) \xrightarrow{p} 0;$

(ii) $\psi(\xi) - \phi(\xi) \to 0;$

(iii) $(Lh)^{1/2}[\gamma(x_1, x_2, \Delta) - E\{\gamma(x_1, x_2, \Delta)\}] \Rightarrow \text{Normal}\{0, \nu^2 f_1(0)\sigma^2(x_1, x_2, \Delta)\}.$

To show (i), notice that, with $|I_i| \to \infty$, calculations as in Lemma 3 show that

$$\sum_{i=1}^{k_L} \text{var}\{\beta_i(x_1, x_2, \Delta)\} = \sum_{i=1}^{k_L} \nu^2 L^{-1} h^{-1} R_K f_{i,1}(0)\{\sigma^2(x_1, x_2, \Delta) + o(1)\}, \quad (14)$$

where $f_{i,1}(u) = \int g_i(u+t)g_i(t)dt$ is the counterpart of $f_1(u)$, with $g_i(t) = g(t)I(t \in I_i')$. Since $g(\cdot)$ is bounded away from both 0 and ∞, $f_{i,1}(0) = \int_{I_i'} g^2(t) = O(|I_i'|) = O(L^{p-1})$, and $\text{var}\{\beta_i(x_1, x_2, \Delta)\} = O(L^{p-2}h^{-1})$.

Observe that $|I'| = \sum_{i=1}^{k_L} |I_i'| = k_L \times (L^p - L^q)/L \approx L/L^p \times (L^p - L^q)/L = 1 - L^{q-p} \to 1$, and

$$\sum_{i=1}^{k_L} f_{i,1}(0) = \sum_{i=1}^{k_L} \int_{I_i'} g(t)^2 dt = \int_{I'} g(t)^2 dt \to \int_0^1 g(t)^2 dt = f_1(0). \quad (15)$$

Therefore, $\sum_{i=1}^{k_L} \text{var}\{\beta_i(x_1, x_2, \Delta)\} = \text{var}\{\beta(x_1, x_2, \Delta)\} + o(L^{-1}h^{-1})$. Further but equivalent derivations show that $\sum_{i \neq j} \text{cov}\{\beta_i(x_1, x_2, \Delta), \beta_j(x_1, x_2, \Delta)\} = O(L^{-1})$. The calculations here are similar to those in Lemma 3, except that the $i \neq j$ condition excluded

terms like A_{22} through A_{27}. Now we have

$$
\begin{aligned}
\text{var}\{\widetilde{\beta}(x_1, x_2, \Delta)\} &= \sum_{i=1}^{k_L} \text{var}\{\beta_i(x_1, x_2, \Delta)\} + \sum_{i \neq j} \text{cov}\{\beta_i(x_1, x_2, \Delta), \beta_j(x_1, x_2, \Delta)\} \\
&= \text{var}\{\beta(x_1, x_2, \Delta)\} + o(L^{-1} h^{-1}).
\end{aligned}
$$

Similarly, one can show that

$$
\text{cov}\{\widetilde{\beta}(x_1, x_2, \Delta), \beta(x_1, x_2, \Delta)\} = \text{var}\{\beta(x_1, x_2, \Delta)\} + o(L^{-1} h^{-1}).
$$

Therefore, $(Lh)\text{var}[\{\beta(x_1, x_2, \Delta) - \{\widetilde{\beta}(x_1, x_2, \Delta)\}] \to 0$, and step (i) is established.

To show (ii), we follow similar arguments that prove Theorem 2 (S2) in Guan et al. (2004). Denote $U_i = \exp(Ix(Lh)^{1/2}[\beta_i(x_1, x_2, \Delta) - E\{\beta_i(x_1, x_2, \Delta)\}])$, where I is the unit imaginary number. Then by definitions, $\phi(x) = E(\prod_{i=1}^{k_L} U_i)$, $\psi(x) = \prod_{i=1}^{k_L} E(U_i)$.

Observing $|E(U_i)| \leq 1$ for all U_i, we have

$$
\begin{aligned}
|\phi(x) - \psi(x)| &\leq |E(\prod_{i=1}^{k_L} U_i) - E(\prod_{i=1}^{k_L-1} U_i)E(U_{k_L})| + |E(\prod_{i=1}^{k_L-1} U_i)E(U_{k_L}) - \prod_{i=1}^{k_L} E(U_i)| \\
&\leq |E(\prod_{i=1}^{k_L} U_i) - E(\prod_{i=1}^{k_L-1} U_i)E(U_{k_L})| + |E(\prod_{i=1}^{k_L-1} U_i) - \prod_{i=1}^{k_L-1} E(U_i)||E(U_{k_L})| \\
&\leq |E(\prod_{i=1}^{k_L} U_i) - E(\prod_{i=1}^{k_L-1} U_i)E(U_{k_L})| + |E(\prod_{i=1}^{k_L-1} U_i) - \prod_{i=1}^{k_L-1} E(U_i)|.
\end{aligned}
$$

By induction,

$$
|\phi(x) - \psi(x)| \leq \sum_{j=1}^{k_L-1} |E(\prod_{i=1}^{j+1} U_i) - E(\prod_{i=1}^{j} U_i)E(U_{j+1})| = \sum_{j=1}^{k_L-1} |\text{cov}(\prod_{i=1}^{j} U_i, U_{j+1})|.
$$

Observe that $\prod_{i=1}^{j} U_i$ and U_{j+1} are $\mathcal{F}([0, b_j])$ and $\mathcal{F}([a_{j+1}, b_{j+1}])$ measurable respectively, with $|\prod_{i=1}^{j} U_i| \leq 1$ and $|U_{j+1}| \leq 1$, and the index sets are at least L^q away. By Lemma 1,

$$
|\phi(x) - \psi(x)| \leq \sum_{j=1}^{k_L-1} 16\alpha(L^q) \leq 16L^{1-p} \times L^{-q\delta}.
$$

33

By our choice of p and q, it is easy to check $1-p-q\delta < 0$, and therefore $|\phi(x)-\psi(x)| \to 0$.

(iii) can be proved by applying Lyapounov's central limit theorem and by the fact that

$$(Lh)\sum_{i=1}^{k_L} \text{var}\{\gamma_i(x_1, x_2, \Delta)\} \to \nu^2 f_1(0)\sigma^2(x_1, x_2, \Delta),$$

which has been shown in (14) and (15).

It remains to check the Lyapounov's condition. By condition (9),

$$\sum_{i=1}^{k_L} \frac{E(|\gamma_i(x_1, x_2, \Delta) - E\{\gamma_i(x_1, x_2, \Delta)\}|^{2+\eta})}{[\text{var}\{\gamma(x_1, x_2, \Delta)\}]^{(2+\eta)/2}} = L^{1-p} \times \frac{O\{(L^{p-2}h^{-1})^{(2+\eta)/2}\}}{O\{(L^{-1}h^{-1})^{(2+\eta)/2}\}}$$

$$= O(L^{-(1-p)\eta/2}) \to 0.$$

The proof is thus complete.

<u>LEMMA</u> **5** Let $\vec{\beta}(\Delta)$ be the vector collecting all $\beta(x_1, x_2, \Delta)$ for distinct pairs of (x_1, x_2). Then, with all assumptions above, for $\Delta' \neq \Delta$,

$$(Lh)^{1/2} \left[\begin{array}{c} \vec{\beta}(\Delta) - E\{\vec{\beta}(\Delta)\} \\ \vec{\beta}(\Delta') - E\{\vec{\beta}(\Delta')\} \end{array} \right] \Rightarrow \text{Normal}\left\{0, \nu^2 f_1(0) \left(\begin{array}{cc} \Sigma(\Delta) & C(\Delta, \Delta') \\ C^T(\Delta, \Delta') & \Sigma(\Delta') \end{array} \right) \right\},$$

where $\Sigma(\Delta)$ is the covariance matrix with the entry corresponding to $\text{cov}\{\beta(x_1, x_2, \Delta), \beta(x_3, x_4, \Delta)\}$ equal to $R_K\{\mathcal{M}(x_1, x_2, x_3, x_4, \Delta, \Delta, 0) + I(x_2 = x_4)\sigma_\epsilon^2 \mathcal{V}(x_1, x_3, 0) + I(x_1 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_2, x_4, 0) + (x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4\} + I(\Delta = 0)R_K\{\mathcal{M}(x_1, x_2, x_3, x_4, 0, 0, 0) + I(x_1 = x_4)\sigma_\epsilon^2 \mathcal{V}(x_2, x_3, 0) + I(x_2 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_1, x_4, 0) + I(x_1 = x_4, x_2 = x_3)\sigma_\epsilon^4\}$; $C(\Delta, \Delta')$ is the matrix with the entry corresponding to $\text{cov}\{\beta(x_1, x_2, \Delta), \beta(x_3, x_4, \Delta')\}$ equal to $I(\Delta' = -\Delta)\{\mathcal{M}(x_1, x_2, x_3, x_4, \Delta, -\Delta, -\Delta) + I(x_2 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_1, x_4, 0) + I(x_1 = x_4)\sigma_\epsilon^2 \mathcal{V}(x_2, x_3, 0) + I(x_1 = x_4, x_2 = x_3)\sigma_\epsilon^4\}$.

<u>Proof</u>: Using similar proofs as for Lemma 3 and 4, we can show that any linear combination $\sum_{i=1}^{k} c_i\beta(x_{i1}, x_{i2}, \Delta) + \sum_{i=1}^{k'} c_i'\beta(x_{i1}, x_{i2}, \Delta')$ is asymptotically normal. By the Crámer-Wold device (Serfling 1980), the joint normality is established.

<u>Note</u>: If $\Delta' = -\Delta$, the limiting distribution on the right hand side is a degenerate multivariate normal distribution, because $\beta(x_1, x_1, \Delta) = \beta(x_1, x_1, -\Delta)$ for all x_1.

A.2 Estimation With Multiple Subjects

Now suppose we have R subjects, and R is a fixed number. Define

$$Y_{r,ik}(x_j, x_l) = \{Y_{rij} - \Psi_r(x_j)\}\{Y_{rkl} - \Psi_r(x_l)\},$$

$$a_r(\Delta) = L^{-1} \sum_i \sum_{k \neq i} K_h(\Delta - \Delta_{r,ik}),$$

$$b_r(x_j, x_l, \Delta) = L^{-1} \sum_i \sum_{k \neq i} Y_{r,ik}(x_j, x_l) K_h\{\Delta - \Delta_r(i, k)\},$$

$$\beta_r(x_j, x_l, \Delta) = b_r(x_j, x_l, \Delta) - a_r(\Delta)\mathcal{V}(x_j, x_l, \Delta),$$

$$c_r(x_j, \Delta) = L^{-1} \sum_i \sum_{k \neq i} \{Y_{rij} - \Psi_r(x_j)\} K_h\{\Delta - \Delta_r(i, k)\}.$$

Further, define $a(\Delta) = \sum_r a_r(\Delta)$, $b(x_j, x_l, \Delta) = \sum_r b_r(x_j, x_l, \Delta)$, $\beta(x_j, x_l, \Delta) = \sum_r \beta_r(x_j, x_l, \Delta)$, and $\widehat{\mathcal{V}}_0(x_1, x_2, \Delta) = b(x_1, x_2, \Delta)/a(\Delta)$. Let $\widehat{\mathcal{V}}_0(\Delta)$ and $\mathcal{V}(\Delta))$ be the vectors collecting all $\widehat{\mathcal{V}}_0(x_1, x_2, \Delta)$ and $\mathcal{V}(x_1, x_2, \Delta))$ for all distinct pairs of (x_1, x_2), respectively.

<u>LEMMA</u> **6** With the assumptions in Section 3, for $\Delta' \neq \Delta$,

$$(RLh)^{1/2} \left\{ \begin{array}{c} \widehat{\mathcal{V}}_0(\Delta) - \mathcal{V}(\Delta) - \sigma_K^2 \mathcal{V}^{(2)}(\Delta)h^2/2 \\ \widehat{\mathcal{V}}_0(\Delta') - \mathcal{V}(\Delta') - \sigma_K^2 \mathcal{V}^{(2)}(\Delta')h^2/2 \end{array} \right\}$$
$$\Rightarrow \text{Normal} \left[0, \{\nu^2 f_1(0)\}^{-1} \left(\begin{array}{cc} \Sigma(\Delta) & C(\Delta, \Delta') \\ C^T(\Delta, \Delta') & \Sigma(\Delta') \end{array} \right) \right],$$

where $\mathcal{V}^{(2)}(\Delta)$ is the vector collecting $\mathcal{V}^{(0,0,2)}(x_1, x_2, \Delta)$ for all distinct pairs of (x_1, x_2).

<u>Proof</u>: Notice that

$$\begin{aligned} \widehat{\mathcal{V}}_0(x_1, x_2, \Delta) - \mathcal{V}(x_1, x_2, \Delta) &= [\sum_{r=1}^R \{b_r(x_1, x_2, \Delta) - a_r(\Delta)\mathcal{V}(x_1, x_2, \Delta)\}]/\{\sum_{r=1}^R a_r(\Delta)\} \\ &= \beta(x_1, x_2, \Delta)/a(\Delta) \end{aligned}$$

Since subjects are independent, by Lemma 2, $a(\Delta)/\{\nu^2 R f_1(0)\} \xrightarrow{p} 1$. Also, by Lemma 5, $(R^{-1}Lh)^{1/2}\{\vec{\beta}(\Delta)^T, \vec{\beta}(\Delta')^T\}^T$ are asymptotically jointly normal with the covariance

matrix given in Lemma 5. Thus, by Slutsky's theorem (Serfling 1980),

$$(RLh)^{1/2} \begin{bmatrix} \beta(\Delta)/a(\Delta) - E\{\beta(\Delta)\}/a(\Delta) \\ \beta(\Delta')/a(\Delta') - E\{\beta(\Delta')\}/a(\Delta') \end{bmatrix}$$

$$\Rightarrow \text{Normal}\left[0, \{\nu^2 f_1(0)\}^{-1} \begin{pmatrix} \Sigma(\Delta) & C(\Delta, \Delta') \\ C^T(\Delta, \Delta') & \Sigma(\Delta') \end{pmatrix}\right].$$

Finally, by Lemma 3, $E\{\beta(x_1, x_2, \Delta)\} = R\nu^2 f_1(0)\{\mathcal{V}^{(0,0,2)}(x_1, x_2, \Delta)\sigma_K^2 h^2/2 + o(h^2)\}$,

so that we have $E\{\beta(x_1, x_2, \Delta)\}/a(\Delta) = \sigma_K^2 \mathcal{V}^{(0,0,2)}(x_1, x_2, \Delta)h^2/2 + o_p(h^2)$. The $o_p(h^2)$

term is eliminated by the assumption that $Lh^5 = O(1)$.

LEMMA 7 With all the assumptions above, we have that

$$\widehat{\mathcal{V}}(x_1, x_2, \Delta) = \widehat{\mathcal{V}}_0(x_1, x_2, \Delta) + O_p(L^{-1}h^{-1/2})$$

Proof: Notice that

$$\widehat{\mathcal{V}}(x_j, x_l, \Delta) = \widehat{\mathcal{V}}_0(x_j, x_l, \Delta) + \left[\sum_r \{\overline{Y}_{r\cdot j} - \Psi_r(x_j)\}c_r(x_l, \Delta) + \sum_r \{\overline{Y}_{r\cdot l} - \Psi_r(x_l)\}c_r(x_j, \Delta)\right.$$

$$\left. + \sum_r \{\overline{Y}_{r\cdot j} - \Psi_r(x_j)\}\{\overline{Y}_{r\cdot l} - \Psi_r(x_l)\}a_r(\Delta)\right] \times a^{-1}(\Delta), \quad (16)$$

$$c_r(x_1, \Delta) = L^{-1} \int\int \{Y(s_1, x_1) - \Psi_r(x_1)\}K_h\{\Delta - (s_1 - s_2)\}N_2(ds_1, ds_2).$$

Using the expression above, it is easy to see that $E\{c_r(x_1, \Delta)\} = 0$, and calculations as

in Lemma 3 show that

$$\text{var}\{c_r(x_1, \Delta)\} = L^{-2} \int\int\int\int K_h\{\Delta - (s_1 - s_2)\}K_h\{\Delta - (s_3 - s_4)\}[\mathcal{V}\{x_1, x_1, (s_1 - s_3)\}$$

$$+ I(s_1 = s_3)\sigma_\epsilon^2]E\{N_2(ds_1, ds_2)N_2(ds_3, ds_4)\}$$

$$= O(\nu^2 L^{-1}h^{-1}).$$

On the other hand, $\overline{Y}_{r\cdot j} - \Psi_r(x_j) = \frac{1}{N_r}\int\{Y_r(s, x_j) - \Psi_r(s, x_j)\}N(ds)$. It is easy to see

that $E\{\overline{Y}_{r\cdot j} - \Psi_r(x_j)\} = 0$, and that

$$\text{var}[N_r\{\overline{Y}_{r\cdot j} - \Psi_r(x_j)\}] = \int\int[\mathcal{V}\{x_j, x_j, (s_1 - s_2)\} + I(s_1 = s_2)\sigma_\epsilon^2]$$

36

$$\{\nu^2 g(s_1/L)g(s_2/L)ds_1 ds_2 + \nu g(s_1/L)\epsilon_{s_1}(ds_2)ds_1\}$$

$$= \nu^2 L^2 \int \mathcal{V}(x_j, x_j, Lu)f_1(u)du + \nu L \int \{\mathcal{V}(x_j, x_j, 0) + \sigma_\epsilon^2\}g(s_1)ds_1$$

$$= \nu^2 L f_1(0) \int \mathcal{V}(x_j, x_j, u)du + \nu L\{\mathcal{V}(x_j, x_j, 0) + \sigma_\epsilon^2\} + o(L).$$

By properties of Poisson processes, we have $N_r/(\nu L) \to 1$ a.s.. Therefore, we have $\overline{Y}_{r \cdot j} - \Psi_r(x_j) = O_p(L^{-1/2})$, $c_r(x_1, \Delta) = O_p(L^{-1/2}h^{-1/2})$. By Lemma 2, $a_r(\Delta) = O_p(1)$. Therefore, $\widehat{\mathcal{V}}(x_1, x_2, \Delta) - \widehat{\mathcal{V}}_0(x_1, x_2, \Delta) = O_p(L^{-1}h^{-1/2})$, completing the proof.

Proof of Theorem 1: This is a direct result from Lemma 6 and 7.

Proof of Theorem 2: For a fixed $\Delta \neq 0$, when $h \leq |\Delta|$, we have $\widetilde{\mathcal{V}}(x_1, x_2, \Delta) = \{\widehat{\mathcal{V}}(x_1, x_2, \Delta) + \widehat{\mathcal{V}}(x_1, x_2, -\Delta)\}/2$. This equation is true automatically for $\Delta = 0$. Therefore, asymptotic distribution of $\widetilde{\mathcal{V}}(\Delta)$ is the same as that of $\{\widehat{\mathcal{V}}(\Delta) + \widehat{\mathcal{V}}(-\Delta)\}/2$, for any fixed Δ.

For $\Delta_1 \neq \pm\Delta_2$, by Theorem 1, $\{\widehat{\mathcal{V}}(\Delta_1), \widehat{\mathcal{V}}(-\Delta_1)\}^T$ and $\{\widehat{\mathcal{V}}(\Delta_2), \widehat{\mathcal{V}}(-\Delta_2)\}^T$ are asymptotically independent, and the joint asymptotic normality of the four vectors can be established. Therefore $\widetilde{\mathcal{V}}(\Delta_1)$ and $\widetilde{\mathcal{V}}(\Delta_2)$ are jointly asymptotic normal and asymptotically independent. It suffices to show that $\Omega(\Delta)$ is the asymptotic covariance matrix of $\widetilde{\mathcal{V}}(\Delta)$.

For $\Delta \neq 0$, apply the delta method to the joint asymptotic distribution of $\widehat{\mathcal{V}}(\Delta)$ and $\widehat{\mathcal{V}}(-\Delta)$, the following gives the asymptotic covariance between $\widetilde{\mathcal{V}}(x_1, x_2, \Delta)$ and $\widetilde{\mathcal{V}}(x_3, x_4, \Delta)$:

$$(1/4)(RLh)^{-1}\{\nu^2 f_1(0)\}^{-1}R_K \times \{\mathcal{M}(x_1, x_2, x_3, x_4, \Delta, \Delta, 0) + \mathcal{M}(x_1, x_2, x_3, x_4, -\Delta, -\Delta, 0)$$

$$+2\mathcal{M}(x_1, x_2, x_3, x_4, \Delta, -\Delta, -\Delta) + 2I(x_2 = x_4)\sigma_\epsilon^2 \mathcal{V}(x_1, x_3, 0)$$

$$+2I(x_1 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_2, x_4, 0) + 2I(x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4$$

$$+2I(x_2 = x_3)\sigma_\epsilon^2 \mathcal{V}(x_1, x_4, 0) + 2I(x_1 = x_4)\sigma_\epsilon^2 \mathcal{V}(x_2, x_3, 0)$$

$$+2I(x_1 = x_3, x_2 = x_4)\sigma_\epsilon^4\}$$

Note that $\mathcal{M}(x_1, x_2, x_3, x_4, -\Delta, -\Delta, 0) = \mathcal{M}(x_1, x_2, x_3, x_4, \Delta, \Delta, 0)$ by the symmetry in the definition of $\mathcal{M}(x_1, x_2, x_3, x_4, u, v, w)$. Next, for $\Delta = 0$, we have $\widetilde{\mathcal{V}}(x_1, x_2, 0) = \widehat{\mathcal{V}}(x_1, x_2, 0)$, the asymptotic covariance between $\widetilde{\mathcal{V}}(x_1, x_2, 0)$ and $\widetilde{\mathcal{V}}(x_3, x_4, 0)$ is given in Theorem 1. The proof is completed.

Proof of Corollary 1: The result follows from Theorem 2 and the Delta-method. To see this, note that, with the separable structure in (3), we have $\mathcal{V}(x_1, x_2, \Delta) = G(x_1, x_2)\rho(\Delta)$ and $\mathcal{V}^{(0,0,2)}(x_1, x_2, \Delta) = G(x_1, x_2)\rho^{(2)}(\Delta)$. By the Delta-method, the asymptotic mean of $\widehat{\rho}(\Delta)$ is

$$
\frac{\sum_{x_1 \in \mathcal{X}} \sum_{x_2 \le x_1} \{\mathcal{V}(x_1, x_2, \Delta) + \sigma_K^2 \mathcal{V}^{(0,0,2)}(x_1, x_2, \Delta)h^2/2 + o_p(h^2)\}}{\sum_{x_1 \in \mathcal{X}} \sum_{x_2 \le x_1} \{G(x_1, x_2) + \sigma_K^2 G(x_1, x_2)\rho^{(2)}(0)h^2/2 + o_p(h^2)\}}
$$
$$
= \{\rho(\Delta) + \sigma_K^2 \rho^{(2)}(\Delta)h^2/2 + o_p(h^2)\}/\{1 + \sigma_K^2 \rho^{(2)}(0)h^2/2 + o_p(h^2)\}
$$
$$
= \{\rho(\Delta) + \sigma_K^2 \rho^{(2)}(\Delta)h^2/2 + o_p(h^2)\} * \{1 - \sigma_K^2 \rho^{(2)}(0)h^2/2 + o_p(h^2)\}
$$
$$
= \rho(\Delta) + \{\rho^{(2)}(\Delta) - \rho(\Delta)\rho^{(2)}(0)\}\sigma_K^2 h^2/2 + o_p(h^2).
$$

The asymptotic variance of $\widehat{\rho}(\Delta)$ also follows from the Delta-method.

References

Besag, J. and Higdon, D. (1999). Bayesian analysis of agricultural field experiments. *Journal of the Royal Statistical Society, Series B*, 61, 691-746.

Besag, J., York, J. and Mollie, A. (1991). Baysian image restoration, with two applications in spatial statistics (with Discussion). *Annals of the Institute of Statistical Mathematics*, 43, 1-59.

Cressie, N. A. C. (1993). *Statistics for Spatial Data*. New York: Wiley.

Cressie, N. A. C. and Huang, H. C. (1999). Classes of nonseparable, spatio-temporal stationary covariance functions. *Journal of the American Statistical Association*, 94, 448, 1330-1340.

Diggle, P. and Verbyla, A. P. (1998). Nonparametric estimation of covariance structure in longitudinal data. *Biometrics*, 54, 401-415.

Guan, Y., Sherman, M. and Calvin, J. A. (2004). A nonparametric test for spatial

isotropy using subsampling. *Journal of the American Statistical Association*, 99, 810-821.

Hall, P., Fisher, N. I., and Hoffmann, B. (1994). On the nonparametric estimation of covariance functions. *Annals of Statistics*, 22, 2115-2134.

Hall, P. and Patil, P. (1994). Properties of nonparametric estimators of autocovariance for stationary random fields. *Probability Theory and Related Fields*, 99, 399-424.

Ibragimov, I. A. and Linnik, Y. V. (1971). *Independent and Stationary Sequences of Random Variables*. Groningen: Wolters-Noordhoff.

Karr, A. F. (1986). Inference for stationary random fields given Poisson samples. *Advances in Applied Probability*, 18, 406-422.

Morris, J. S., Wang, N.,Lupton, J. R., Chapkin, R. S., Turner, N. D., Hong, M. Y. and Carroll, R. J. (2001). Parametric and nonparametric methods for understanding the relationship between carcinogen-induced DNA adduct levels in distal and proximal regions of the colon. *Journal of the American Statistical Association*, 96, 455, 816-826.

Politis, D. N. and Sherman, M. (2001). Moment estimation for statistics from marked point processes. *Journal of the Royal Statistical Society, Series B*, 63, 261-275.

Ramsay, J. O. and Silverman, B. W. (1997). *Functional Data Analysis*. New York: Springer-Verlag.

Serfling, R. J. (1980). *Approximation Theorems of Mathematical Statistics*. New York: Wiley.

Shao, J. and Tu, D. (1995). *The Jackknife and Bootstrap*. New York: Springer-Verlag.

Stein, M. L. (1999). *Interpolation of Spatial Data: Some Theory for Kriging*. New York: Springer-Verlag.

Stein, M. L. (2005). Space-time covariance functions. *Journal of the American Statistical Association*, 100, 469, 310-321.

Yao, F., Müller H. G. and Wang, J. (2005). Functional data analysis for sparse longitudinal data. *Journal of the American Statistical Association*, 100, 470, 577-590.

	optimal h	min CV score	min score, 2 par
CV_1	124.2334	6.5073	6.4867
CV_2	122.7202	6.4955	6.4788

Table 1: Outcomes of two cross-validation procedures on the carcinogenesis p27 data. The data used in the validation are those with Δ values less than $\Delta_0 = 500$ microns. The first column gives the optimal global bandwidth, the second column gives the value of the cross-validation function at the optimal global bandwidth; the third column gives the minimum value of cross-validation functions using two different smoothing parameters.
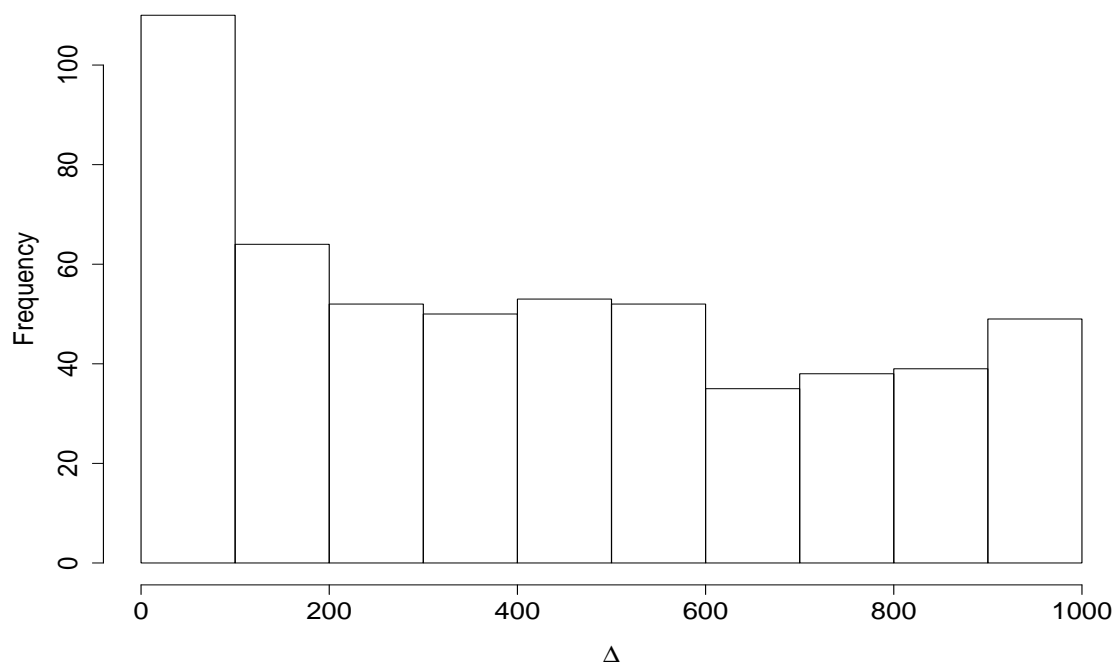
Figure 1: Histogram of $|\Delta_r(i,k)|$ in the carcinogenesis p27 data. $|\Delta|$ less than 1000 microns are considered.
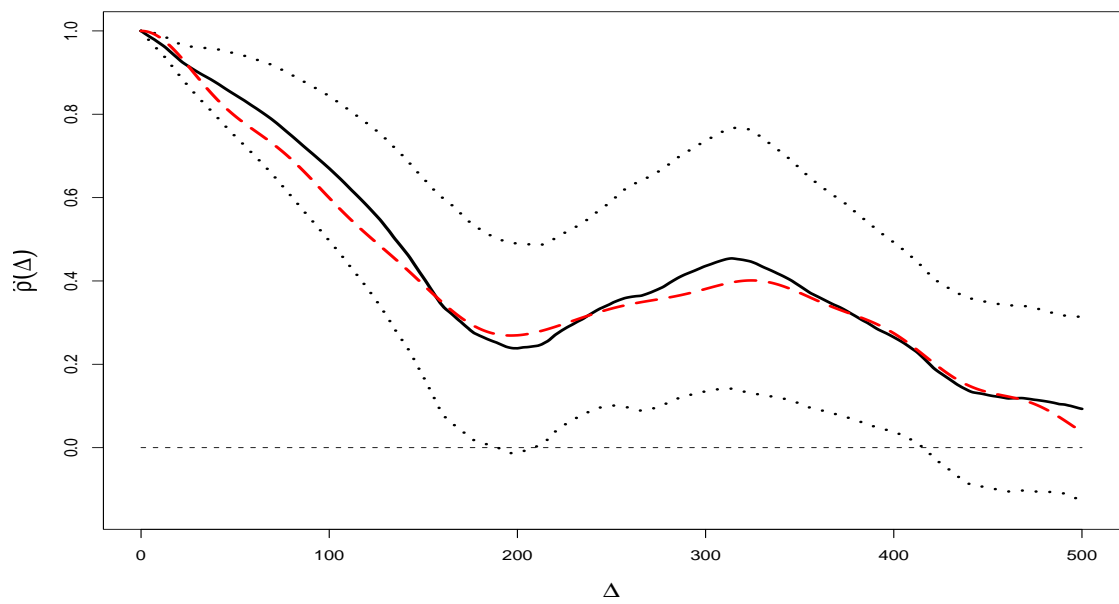
Figure 2: Estimated correlation function for the carcinogenesis p27 data. The solid curve is $\widehat{\rho}(\Delta)$, the dotted curves are $\widehat{\rho}(\Delta) \pm 2 \times \widehat{SD}\{\widehat{\rho}(\Delta)\}$, and dashed curve is the positive semi-definite adjusted estimate, $\widetilde{\rho}(\Delta)$.
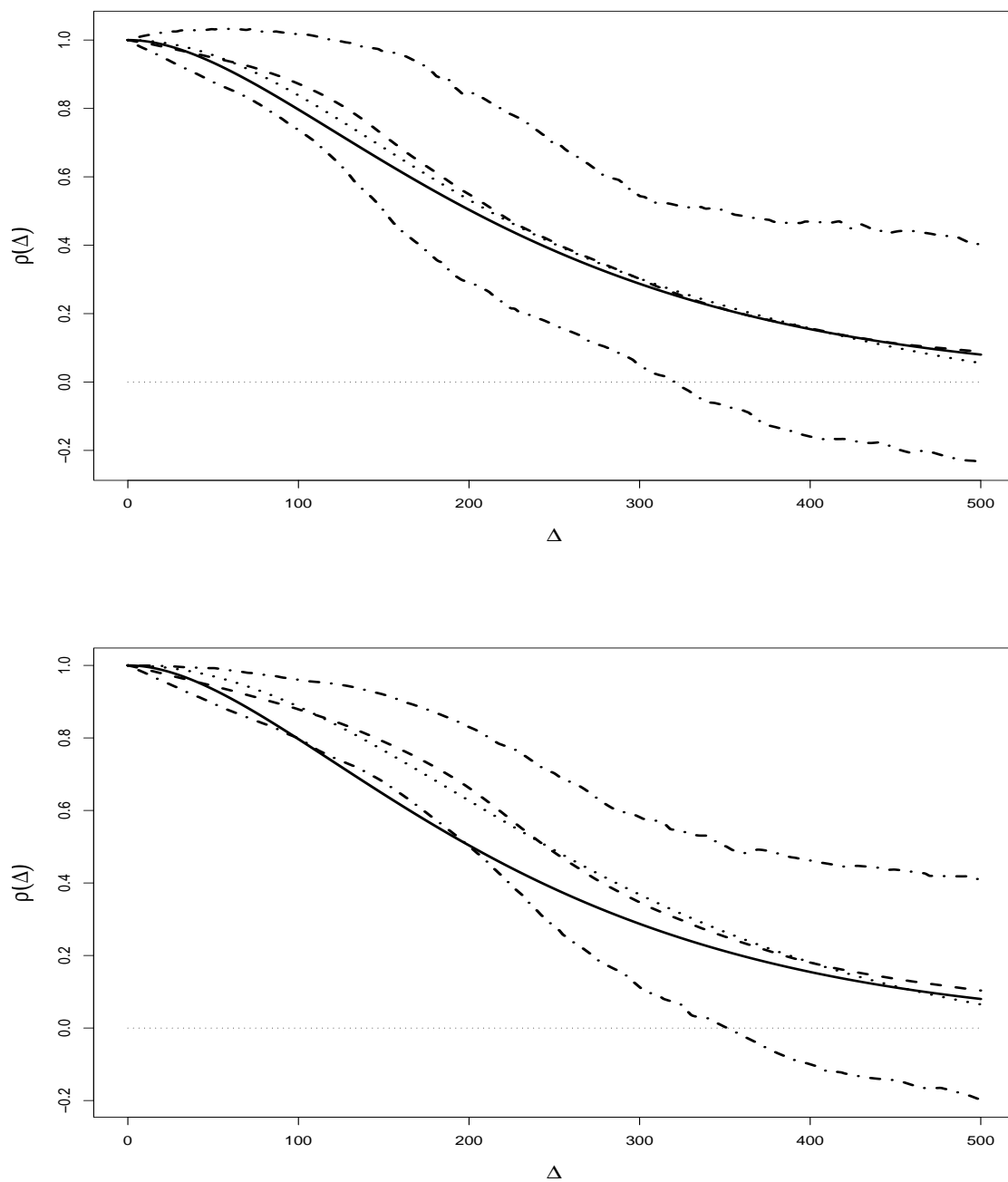
Figure 3: Plots of the correlation estimators in Simulation 1. Upper panel: $h = 120$; lower panel: $h = 200$. In each plot, the solid curve is the true correlation function $\rho(\cdot)$, the dashed curve is the mean of $\widehat{\rho}(\cdot)$, the dotted curve is the mean of $\widetilde{\rho}(\cdot)$, and the dot-dash curves are the 5% and 95% pointwise percentiles of $\widehat{\rho}$, respectively. $h = 200$ over-smoothes the curve, hence incurs larger bias.
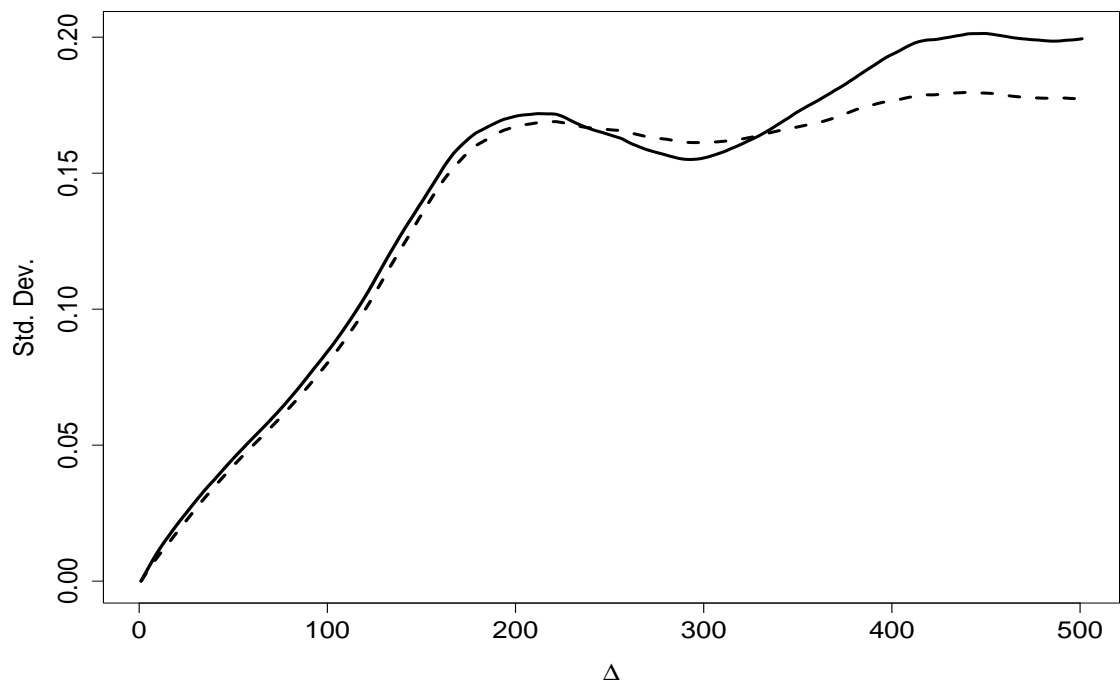
Figure 4: Standard deviation of $\widehat{\rho}$ in Simulation 1. The solid curve is the pointwise standard deviation of $\widehat{\rho}$ from the simulation in Section 5.1, and the dashed curve is the mean of the 200 bootstrap standard deviation estimates. The bandwidth $h = 120$ was used.
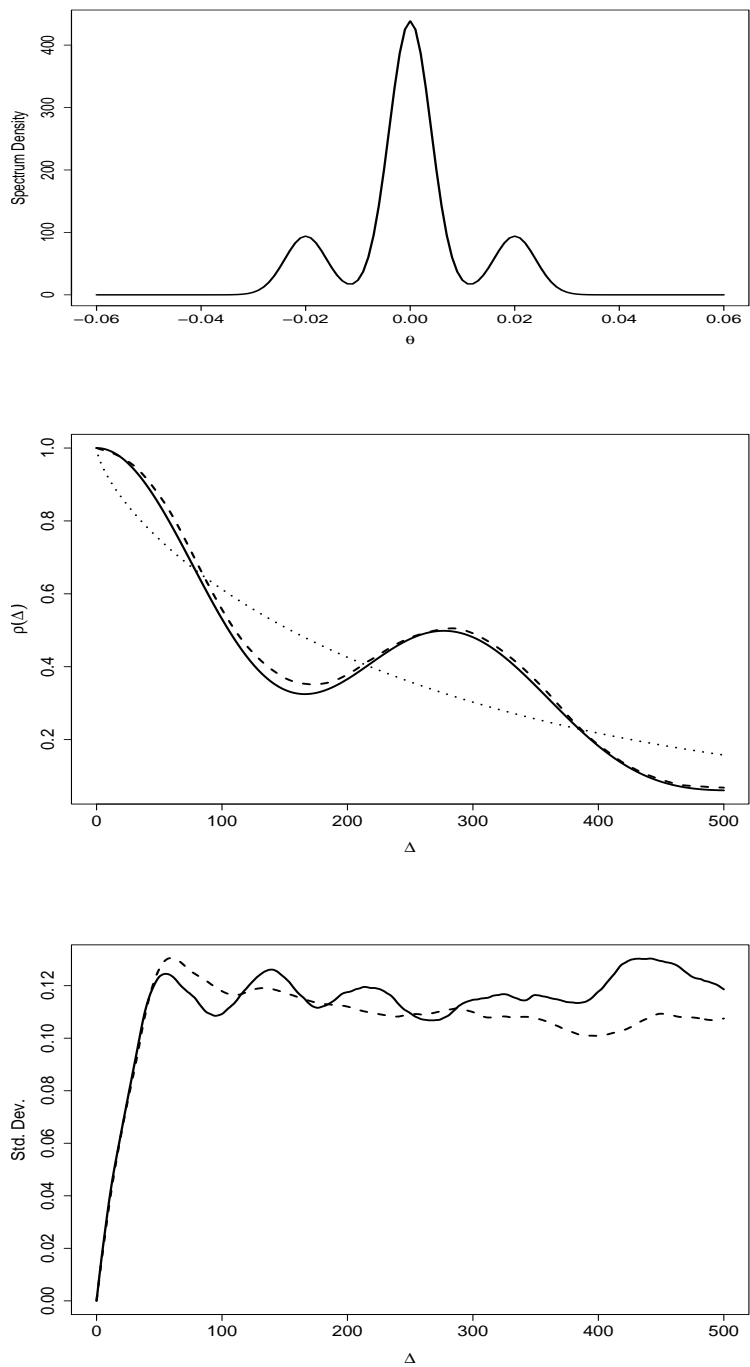
Figure 5: Simulation2. Upper panel: the spectral density of the correlation used in the simulation; middle panel: the solid curve is the true correlation function, the dashed curve is the mean of the kernel correlation estimator and the dotted curve is the best Matérn approximation to the true correlation; lower panel: the solid curve is the true pointwise standard deviation for the kernel correlation estimator, the dashed curve is the mean for the bootstrap standard deviation estimator.
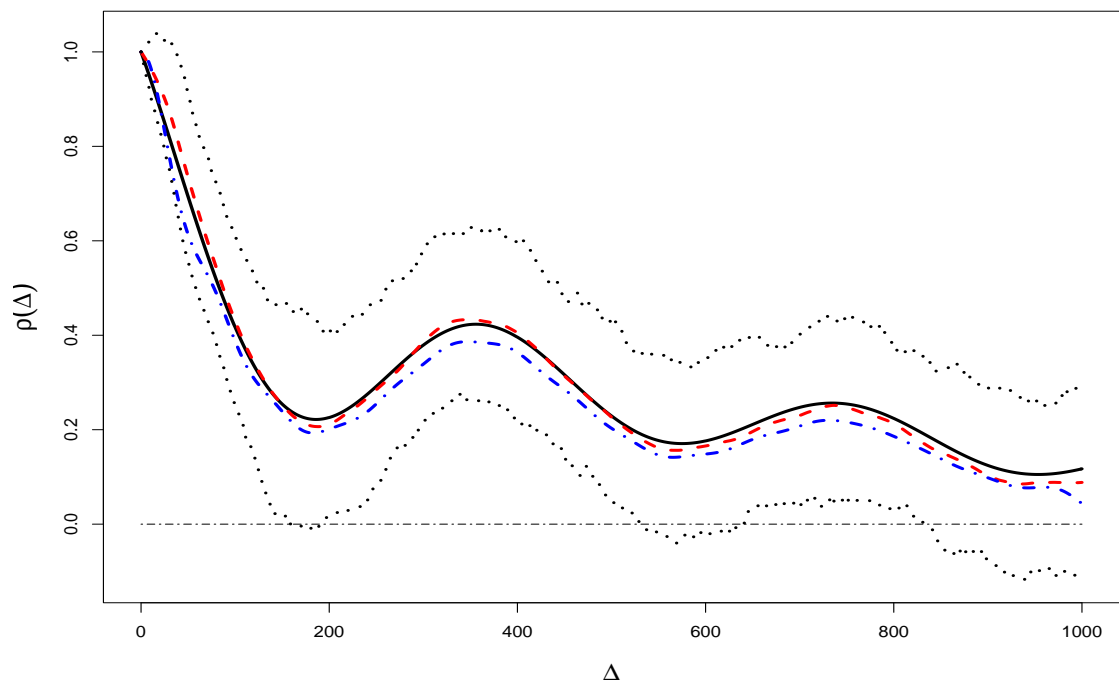
Figure 6: Simulation3. The solid curve is the true correlation function, the dashed curve is the mean of our kernel estimator $\widehat{\rho}$, the two dotted curves are the 5% and 95% percentiles of $\widehat{\rho}$, and the dotdash curve is the mean of the adjusted estimator $\widetilde{\rho}$.