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NONPARAMETRIC ESTIMATION OF EFFECTIVE DOSES AT QUANTAL RESPONSE

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Abstract. For the quantal response model we propose a new direct method for nonparametric estimation of the effective dose level $ED_{100\lambda}$ $(0 < \lambda < 1)$. This method yields a simple and reliable monotone estimate of the effective dose level curve $\lambda \to ED_{100\lambda}$ and is appealing to users of conventional smoothing methods of kernel estimates. Moreover, it is computationally very efficient, because it does not require a numerical inversion of the estimate of the quantile dose response curve. We prove asymptotic normality of this new estimator and compare it with the DNP-estimator.

Keywords: binary response model, effective dose level, nonparametric estimate.

Mathematics Subject Classification: 62G05, 62G08, 62G20, 62P10.

1. Introduction

We consider the model of binary response which has a conventional title *dose-response relationship* [1] and which can be described as follows.

Let $\{(X_i, U_i), 1 \leqslant i \leqslant n\}$ be a potential repeated sample of an unknown distribution $F(x)\,Q(y)$, $F(x) = \mathbf{P}(X_i < x)$, $Q(y) = \mathbf{P}(U_i < y)$, $x, y \in \mathbf{R}$, instead of which one observes the sample $\mathcal{U}^{(n)} = \{(U_i, W_i),\ 1 \leqslant i \leqslant n\}$, where $W_i = \chi(X_i < U_i)$ are the indicator functions of the event $(X_i < U_i)$. Here U_i are regarded as injected doses, and W_i as an effect of the action of the dose U_i. Let $F(x) = \int_{-\infty}^{x} f(t)\,dt$ and $f(x) > 0$. We shall call this situation the *random* plan of an experiment.

Together with the random plan, we consider *fixed* plans of an experiment. Namely, the injected dose U is supposed to be non-random and we let $U_i = u_i$, $i = 0, 1, \ldots, n+1$, where $0 = u_0 < u_1 < \ldots < u_n < u_{n+1} = 1$.

On the main problem of the dose-response relationship is to estimate the *effective doses* $ED_{100\lambda} = F^{-1}(\lambda) = x_\lambda$, $0 < \lambda < 1$, by the sample $\mathcal{U}^{(n)}$. For fixed plans of an experiment, we shall consider several nonparametric estimator and we shall find their asymptotic (as $n \to \infty$) distributions.

The nonparametric approach to the estimating supposes the presence of kernel functions $K_r(x)$, $K_d(x)$, being in fact even compactly supported densities of distributions with the support on $[-1, 1]$, and bandwidth h_r, h_d, which are smoothing non-random parameters depending on the sampling size n and converging to zero as $n \to \infty$, but $nh_r \to \infty$, $nh_d \to \infty$ as $n \to \infty$. We also let $H_d(u) = \int_{-\infty}^{u} K_d(x)\,dx$.

To estimate the function $F(x)$, we shall make use of the following statistics,

$$F_{nh_r}(x) = \frac{1}{nh_r} \sum_{i=1}^{n} K_r\left(\frac{x - u_i}{h_r}\right) W_i.$$

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For fixed plans of an experiment in the dose-response relationship, in the present work we prove the asymptotic normality of the estimator

$$\hat{x}_{1,\lambda} = \frac{1}{nh_d} \sum_{i=1}^{n} \int_{-\infty}^{\lambda} K_d \left(\frac{F_{nh_r}(i/n) - u}{h_d} \right) du = $$

$$= \frac{1}{n} \sum_{i=1}^{n} H_d \left(\frac{\lambda - F_{nh_r}(i/n)}{h_d} \right) \tag{1}$$

for the effective dose x_λ that we call the DNP-*estimator*.

We shall also study the asymptotic behavior of the estimator

$$\hat{x}_{2,\lambda} = \frac{\sum\limits_{i=1}^{n} \frac{2i}{n} \int_{-\infty}^{\lambda} K_d \left(\frac{F_{nh_r}(i/n) - u}{h_d} \right) du}{\sum\limits_{i=1}^{n} \int_{-\infty}^{\lambda} K_d \left(\frac{u - F_{nh_r}(i/n)}{h_d} \right) du} =$$

$$= \frac{\sum\limits_{i=1}^{n} \frac{2i}{n} H_d \left(\frac{\lambda - F_{nh_r}(i/n)}{h_d} \right)}{\sum\limits_{i=1}^{n} H_d \left(\frac{\lambda - F_{nh_r}(i/n)}{h_d} \right)} \tag{2}$$

for x_λ that was suggested in work [2]. We show that the estimator $\hat{x}_{2,\lambda}$ has the same limiting distribution as the estimator $\hat{x}_{1,\lambda}$.

We also consider the asymptotic behavior of the estimator

$$\hat{x}_{3,\lambda} = \sqrt{\hat{S}_{2,\lambda} - b(h_r, h_d)},$$

where

$$\hat{S}_{2,\lambda} = \frac{1}{nh_d} \sum_{i=1}^{n} \frac{2i}{n} \int_{-\infty}^{\lambda} K_d \left(\frac{F_{nh_r}(i/n) - u}{h_d} \right) du = \frac{1}{n} \sum_{i=1}^{n} \frac{2i}{n} H_d \left(\frac{\lambda - F_{nh_r}(i/n)}{h_d} \right),$$

and $b(h_r, h_d)$ are some constants depending on h_r, h_d (see Theorem 4.1). We prove that the estimator $\hat{x}_{3,\lambda}$ is a consistent estimator for x_λ and its limiting dispersion is less than the limiting dispersion of the estimator $\hat{x}_{1,\lambda}, \hat{x}_{2,\lambda}$.

We observe that in work [3], there was considered the regression model

$$Y_i = m(X_i) + \sigma(X_i)\varepsilon_i, \quad i = 1, 2, \ldots, n, \tag{3}$$

where $\{X_i, Y_i\}_{i=1}^n$ is a two-dimensional sample of independent identically distributed random variables, at that, a random variable X_i has a density of distribution $f(x) > 0$ and its values are located in the segment $[0, 1]$, the random variables ε_i are also supposed to be independent and identically distributed with expectation 0 and to have the fourth moment (and $\{\varepsilon_i\}_{i=1}^n$ are independent of $\{X_i\}_{i=1}^n$), while the regression function $m(x)$ is supposed to be strictly monotonous. The estimator $m_I^{-1}(\lambda)$ of the form (1) for the function $m^{-1}(\lambda)$ was suggested. It was also shown that the estimator $m_I^{-1}(\lambda)$ is asymptotically normal. To prove the asymptotic normality of the estimator $m_I^{-1}(\lambda)$, in [3] the independence of the variables $\{\varepsilon_i\}_{i=1}^n$ was employed essentially. In the relationship *dose-response*, the variables W_i are binary quantities and therefore we can not employ representation (3). To prove the asymptotic normality, one needs to use another approach.

2. Main assumptions

Let $\{X_i,\ i = 1, \ldots, n\}$ be a sequence of independent identically distributed as X on the segment $[0,1]$ random variables with the distribution function $F(x)$, $P = \{u_0, u_1,\ \ldots,\ u_n, u_{n+1}\}$ be an ordered partition of the segment $[0,1]$, $u_0 = 0 < u_1 < \ldots < u_n < 1 = u_{n+1}$.

We formulate the assumptions for the parameters h_r and h_d.

Assumptions (H).

($\mathbf{H}_1$) $h_r = h_r(n)$, $h_d = h_d(n)$, and $h_r \underset{n\to\infty}{\longrightarrow} 0$, $h_d \underset{n\to\infty}{\longrightarrow} 0$, but $nh_r \to \infty$, $nh_d \to \infty$ as $n \to \infty$.

($\mathbf{H}_2$) $h_d/h_r \underset{n\to\infty}{\longrightarrow} 0$.

($\mathbf{H}_3$) $nh_r^5 = O(1)$ as $n \to \infty$.

($\mathbf{H}_4$) $nh_r h_d^{8/3} \underset{n\to\infty}{\longrightarrow} \infty$.

As an example, we consider $h_r = n^{-1/5}$, $h_d = n^{-1/4}$. It is obvious that these sequences satisfy Assumptions (**H**).

We let $\| K \|^2 = \int_{-1}^{1} K^2(x)\, dx$.

Assumptions for the kernel functions $K_r(x)$ and $K_d(x)$.

Assumptions (K).

($\mathbf{K}_1$) $K_{r(d)}(x) \geq 0$, and $K_{r(d)}(x) = 0, x \notin [-1,1]$.

($\mathbf{K}_2$) $\int\limits_{-1}^{1} K_r(x)\, dx = 1$, $\int\limits_{-1}^{1} K_d(x)\, dx = 1$.

($\mathbf{K}_3$) $K_{r(d)}(x) = K_{r(d)}(-x), x \in \mathbf{R}$.

($\mathbf{K}_4$) On the segment $[-1,1]$, there exist continuous bounded derivatives of the functions $K_r(x)$, $K_d(x)$.

($\mathbf{K}_5$) $\| K_j \|_\infty = \sup\limits_{x\in\mathbf{R}} |\, K_j(x)\, | = k_j < \infty$ for $j = r, d$.

Remark 2.1. *Under Assumptions (**K**), there exist the fourth moments for the distributions with the densities $K_r(x)$, $K_d(x)$ and*

$$\nu_r^2 = \int x^2 K_r(x)\, dx, \qquad \nu_d^2 = \int x^2 K_d(x)\, dx,$$

$$\mu_r^4 = \int x^4 K_r(x)\, dx, \qquad \mu_d^4 = \int x^4 K_d(x)\, dx.$$

Let us define the variation of the function K (cf. [4, p. 234]).

Let $K : [a,b] \to \mathbf{R}$. The *variation* of the function $K = K(u)$ on the segment $[a,b]$ is the following quantity, $\bigvee(K) = \bigvee_a^b(K) = \sup\limits_P \sum\limits_{k=0}^{m} |\, K(u_{k+1}) - K(u_k)\, |$, i.e., the supremum over all ordered partitions P of the segment $[a,b]$. Throughout the work we consider the variations of the functions on the segment $[0,1]$.

Remark 2.2. *The boundedness of the derivatives of the functions $K_r(x)$, $K_d(x)$ on the segment $[-1,1]$ (Assumption $\boldsymbol{K}_4$) imply that their derivatives are bounded (cf.* [4, p. 235]*), i.e.,* $\bigvee(K_{d(r)}) < \infty$.

Assumption (F).

($\mathbf{F}_1$) There exists the third continuous bounded derivative of the density of the distribution $f(x) = F'(x)$ and $f(x) \geq C_0 > 0$ for $0 \leqslant x \leqslant 1$, i.e., on the segment $[0, 1]$, the density $f(x)$ is separated from zero.

Assumption (P).

($\mathbf{P}_1$) As $n \to \infty$,

$$\max_{k=0,1,\ldots,n} \max\left\{\left|u_k - \frac{k}{n}\right|, \left|u_{k+1} - \frac{k}{n}\right|\right\} = O\left(\frac{1}{n}\right).$$

Assumption (**P**) yields $u_k = \dfrac{k}{n} + O\left(\dfrac{1}{n}\right)$, at that, the sequence $n\left(u_k - \dfrac{k}{n}\right)$ is bounded by a constant C uniformly in $0 \leqslant k \leqslant n$.

Throughout the work (Main) Assumptions (**H**), (**K**), (**F**), (**P**) are supposed to hold true.

3. Auxiliary results

In this section we provide auxiliary results needed to study the asymptotics for the aforementioned estimators $\hat{x}_{1,\lambda}$, $\hat{x}_{2,\lambda}$, $\hat{x}_{3,\lambda}$.

We give first the Koksma-Hlawka inequality (see [5, p. 18]) that allows one to estimate the rate of the convergence of integral sums to the corresponding integral.

Let $\mathcal{B}$ be the Lebesgue σ-algebra on $I = [0, 1]$ and ρ is the Lebesgue measure on $\mathcal{B}$. For $P = \{u_0, u_1, \ldots, u_n, u_{n+1}\}$ with $u_0 = 0 < u_1 < \ldots < u_n < 1 = u_{n+1}$ and $B \in \mathcal{B}$ we define

$$A(B; P) = \sum_{i=1}^{n} \chi_B(u_i), \quad D_n(\mathcal{B}; P) = \sup_{B\in\mathcal{B}} \left|\frac{A(B; P)}{n} - \rho(B)\right|,$$

where $\chi_B(x)$ is the indicator function for the set B. We let $D_n^*(P) = D_n(J_c^*, P)$, where J_c^* is a subset of I of the form $[0, u_i]$.

For each bounded function $\psi : \mathbf{R} \to \mathbf{R}$ we let $\| \psi \|_I = \sup_{x\in I} |\psi(x)|$.

Theorem 3.1 ([5], Koksma-Hlawka inequality)**.** *If a function $f(u)$ $(0 \leqslant u \leqslant 1)$ has a bounded variation $\bigvee(f)$ on $[0, 1]$, then for each $0 < u_1 < u_2 < \ldots < u_n < 1$ we have*

$$\left|\frac{1}{n}\sum_{i=1}^{n} f(u_i) - \int_0^1 f(u)\, du\right| \leqslant \bigvee(f) D_n^*(u_1, \ldots, u_n).$$

We give also two lemmata from [5].

Lemma 3.1. *If $x_1, \ldots, x_n, y_1, \ldots, y_n \in [0, 1]$ satisfy the inequalities $|x_i - y_i| \leqslant \varepsilon$ for $1 \leqslant i \leqslant n$, then*

$$|D_n^*(x_1, \ldots, x_n) - D_n^*(y_1, \ldots, y_n)| \leqslant \varepsilon.$$

Remark 3.1. *Lemma 3.2 yields that $D_n^*(x_1, \ldots, x_n)$ is a continuous function of the variables $(x_1, \ldots, x_n)$.*

Lemma 3.2. *If $0 < u_1 < u_2 < \ldots < u_n < 1$, then*

$$D_n^*(u_1, \ldots, u_n) = \frac{1}{2n} + \max_{1\leqslant i\leqslant n} \left| u_i - \frac{2i - 1}{2n} \right|.$$

Remark 3.2. *If $u_i = \dfrac{i}{n}$, then $\dfrac{i}{n} - \dfrac{2i - 1}{2n} = \dfrac{1}{2n}$ and $D_n^*(u_1, \ldots, u_n) = \dfrac{1}{n}$.*

Theorem 3.2 ([6, p. 337], [7, p. 299]). *If $\varphi(n)\to\infty$ as $n\to\infty$ and*

$$\varphi(n)(T_n-\theta)\xrightarrow[n\to\infty]{d} N(0,\tau^2)$$

then

$$\varphi(n)(g(T_n)-g(\theta))\xrightarrow[n\to\infty]{d} N(0,\tau^2(g'(\theta))^2)$$

provided $g'(\theta)$ exists and is not zero.

In what follows we shall make use of the following auxiliary result.

We consider the function

$$\tilde f=\tilde f(u)=\frac{1}{h_d}K_d\left(\frac{F(u)-\lambda}{h_d}\right)$$

and let us estimate it variation on $[0,1]$.

Lemma 3.3. *If Main Assumptions hold true, then*

$$\bigvee(\tilde f\,)=\sup\sum_{j=1}^{l}|\,\tilde f(u_j)-\tilde f(u_{j-1})\,|=O\left(\frac{1}{h_d}\right),$$

where the supremum is taken over all ordered partitions $0<u_1<u_2<\ldots<u_l<1$ of the segment $[0,1]$.

Proof. Let $0<u_1<u_2<\ldots<u_l<1$ be an arbitrary ordered partition of the segment $[0,1]$. Then

$$\sum_{j=1}^{l}|\,\tilde f(u_j)-\tilde f(u_{j-1})\,|=\frac{1}{h_d}\sum_{j=1}^{l}\left|K_d\left(\frac{F(u_j)-\lambda}{h_d}\right)-K_d\left(\frac{F(u_{j-1})-\lambda}{h_d}\right)\right|=$$

$$=\frac{1}{h_d}\left\{\sum_{j=1}^{l_1}+\sum_{j=l_2+2}^{l}+\sum_{j=l_1+2}^{l_2}\right\}\left|K_d\left(\frac{F(u_j)-\lambda}{h_d}\right)-K_d\left(\frac{F(u_{j-1})-\lambda}{h_d}\right)\right|+$$

$$+\frac{1}{h_d}\left|K_d\left(\frac{F(u_{l_1+1})-\lambda}{h_d}\right)-K_d\left(\frac{F(u_{l_1})-\lambda}{h_d}\right)\right|+$$

$$+\frac{1}{h_d}\left|K_d\left(\frac{F(u_{l_2+1})-\lambda}{h_d}\right)-K_d\left(\frac{F(u_{l_2+2})-\lambda}{h_d}\right)\right|,$$

where l_1 and l_2 are so that

$$F(u_{l_1})\leqslant\lambda-h_d,\qquad F(u_{l_1+1})>\lambda-h_d,$$
$$F(u_{l_2+1})<\lambda+h_d,\qquad F(u_{l_2+2})\ge\lambda+h_d.$$

Since $K_d(x)=0$ for $|\,x\,|\ge 1$, the sum $\sum_{j=1}^{l_1}+\sum_{j=l_2+2}^{l}$ vanishes and

$$K_d\left(\frac{F(u_{l_1+1})-\lambda}{h_d}\right)=K_d(-1)+K_d'(\xi)\left(\frac{F(u_{l_1+1})-\lambda}{h_d}+1\right)\underset{n\to\infty}{\longrightarrow}0,$$

where $-1\leqslant\xi\leqslant\dfrac{F(u_{l_1+1})-\lambda}{h_d}$.

In the same way one can show that $K_d\left(\dfrac{F(u_{l_2})-\lambda}{h_d}\right)\underset{n\to\infty}{\longrightarrow}0$.

All the points $\dfrac{F(u_j)-\lambda}{h_d}$ in the remaining sum belongs to the segment $[-1,1]$ and hence

$$\frac{1}{h_d}\sum_{j=l_1+2}^{l_2}\left|K_d\left(\frac{F(u_j)-\lambda}{h_d}\right)-K_d\left(\frac{F(u_{j-1})-\lambda}{h_d}\right)\right|=$$

$$= \frac{1}{h_d} \sum_{j=l_1+2}^{l_2} |K_d'(\xi_j)| \; \frac{F(u_j) - F(u_{j-1})}{h_d} \leqslant \frac{M}{h_d^2}(F(u_{l_2}) - F(u_{l_1+2})) \leqslant$$

$$\leqslant \frac{2Mh_d}{h_d^2} = \frac{2M}{h_d},$$

where $\xi_j \in [-1,1]$, $|K_d'(\xi_j)| \leqslant M$ and M is independent of n. The proof is complete. □

4. Main results

4.1. Asymptotics for estimator $\hat{x}_{1,\lambda}$. We represent the statistics $\hat{x}_{1,\lambda}$ as

$$\hat{x}_{1,\lambda} = \frac{1}{nh_d} \sum_{i=1}^{n} \int_{-\infty}^{\lambda} K_d\left(\frac{F_{nh_r}(i/n) - u}{h_d}\right) du = x_{\lambda,n} + \Delta,$$

where

$$x_{\lambda,n} = \frac{1}{nh_d} \sum_{i=1}^{n} \int_{-\infty}^{\lambda} K_d\left(\frac{F(i/n) - u}{h_d}\right) du,$$

$$\Delta = \frac{1}{nh_d} \sum_{i=1}^{n} \int_{-\infty}^{\lambda} \left\{K_d\left(\frac{F_{nh_r}(i/n) - u}{h_d}\right) - K_d\left(\frac{F(i/n) - u}{h_d}\right)\right\} du =$$

$$= \frac{1}{n} \sum_{i=1}^{n} \left(H_d\left(\frac{F_{nh_r}(i/n) - u}{h_d}\right) - H_d\left(\frac{F(i/n) - u}{h_d}\right)\right).$$

The asymptotic behavior of $x_{\lambda,n}$ is described in the following lemma.

Lemma 4.1. *As $n \to \infty$,*

$$x_{\lambda,n} = x_\lambda + a_{2,d}h_d^2 + o(h_d^2),$$

where

$$x_\lambda = F^{-1}(\lambda), \quad a_{2,d} = \frac{1}{2}(F^{-1})''(\lambda)\nu_d^2 = -\frac{\nu_d^2 f'(x_\lambda)}{2f^3(x_\lambda)}.$$

Proof. Employing the Koksma-Hlawka inequality, Lemma 3.4, and Remark 3.2, we obtain

$$x_{\lambda,n} = \frac{1}{h_d} \int_0^1 \int_{-\infty}^{\lambda} K_d\left(\frac{F(x) - u}{h_d}\right) dudx + O\left(\frac{1}{nh_d}\right) =$$

$$= \int_0^1 dx \int_{\frac{F(x)-\lambda}{h_d}}^{1} K_d(z)\, dz + O\left(\frac{1}{nh_d}\right).$$

Since $\frac{F(x)-\lambda}{h_d} \leqslant -1$ as $x \leqslant F^{-1}(\lambda - h_d) \leqslant 1$, then

$$x_{\lambda,n} = \int_0^{F^{-1}(\lambda-h_d)} dx \int_{-1}^{1} K_d(z)\, dz + \int_{F^{-1}(\lambda-h_d)}^{1} dx \int_{\frac{F(x)-\lambda}{h_d}}^{1} K_d(z)\, dz + O\left(\frac{1}{nh_d}\right).$$

The first integral is equal to $F^{-1}(\lambda-h_d)$, while in the second we make the change $y=\frac{F(x)-\lambda}{h_d}$ and, bearing in mind that $\lambda<F(1)=1,\;\; F\in C^2,\; f(x)\geq C_0>0$, we obtain

$$x_{\lambda,n}=F^{-1}(\lambda-h_d)+h_d\int\limits_{-1}^{\frac{F(1)-\lambda}{h_d}}dy\int\limits_{y}^{1}K_d(z)(F^{-1})'(\lambda+h_dy)\,dz+O\left(\frac{1}{nh_d}\right)=$$

$$=F^{-1}(\lambda-h_d)+h_d\int\limits_{-1}^{1}dy\int\limits_{y}^{1}K_d(z)\{(F^{-1})'(\lambda)+(F^{-1})''(\lambda)yh_d+O(h_d^2)\}\,dz+O\left(\frac{1}{nh_d}\right).$$

Since

$$\int\limits_{-1}^{1}dy\int\limits_{y}^{1}K_d(z)\,dz=1,\qquad \int\limits_{-1}^{1}y\,dy\int\limits_{y}^{1}K_d(z)\,dz=\frac{1}{2}\nu_d^2-\frac{1}{2},$$

$$\sup_{t,x\in[0,1]}|(F^{-1})'(t)-(F^{-1})'(x)-(t-x)(F^{-1})''(x)|\leqslant\frac{1}{2}\sup_{x\in[0,1]}|(F^{-1})'''(x)|,$$

and

$$(F^{-1})'''(x)=\frac{3(f'(F^{-1}(x)))^2}{(f(F^{-1}(x)))^5}-\frac{f''(F^{-1}(x))}{(f(F^{-1}(x)))^4},$$

by the separation of the density from the zero and the boundedness of the derivatives for the density of distribution we obtain that

$$\sup_{t,x\in[0,1]}|(F^{-1})'(t)-(F^{-1})'(x)-(t-x)(F^{-1})''(x)|\leqslant C.$$

Thus,

$$x_{\lambda,n}=F^{-1}(\lambda-h_d)+$$

$$+h_d\left((F^{-1})'(\lambda)+(F^{-1})''(\lambda)h_d\int\limits_{-1}^{1}y\,dy\int\limits_{y}^{1}K_d(z)\,dz+O(h_d^2)\right)+O\left(\frac{1}{nh_d}\right)=$$

$$=F^{-1}(\lambda)+\frac{1}{2}h_d^2(F^{-1})''(\lambda)\nu_d^2+O\left(h_d^3+\frac{1}{nh_d}\right),$$

that completes the proof. □

Consider the variable Δ and represent it as

$$\Delta=\Delta_1+\frac{1}{2}\Delta_2+\frac{1}{6}\Delta_3.$$

Here

$$\Delta_1=-\frac{1}{nh_d}\sum_{i=1}^{n}K_d\left(\frac{\lambda-F(i/n)}{h_d}\right)(F_{nh_r}(i/n)-F(i/n)),$$

$$\Delta_2=\frac{1}{nh_d^2}\sum_{i=1}^{n}K_d'\left(\frac{\lambda-F(i/n)}{h_d}\right)(F_{nh_r}(i/n)-F(i/n))^2,$$

$$\Delta_3=-\frac{1}{nh_d^3}\sum_{i=1}^{n}K_d''\left(\frac{\lambda-\xi_i}{h_d}\right)(F_{nh_r}(i/n)-F(i/n))^3,$$

where $|\,\xi_i-F(i/n)\,|\;\leqslant|\,F(i/n)-F_{nh_r}(i/n)\,|$.

Lemma 4.2. *As* $n \to \infty$,

$$\sqrt{nh_r}(\Delta_1 - a_{2,r}h_d^2) \xrightarrow{d} N(0, g_2^2),$$

where

$$a_{2,r} = -\frac{\nu_r^2}{2} F''(F^{-1}(\lambda))(F^{-1})'(\lambda) = -\frac{\nu_r^2 f'(x_\lambda)}{2f(x_\lambda)},$$

$$g_2^2 = \lambda(1-\lambda)\| K_r \|^2 \left[(F^{-1})'(\lambda)\right]^2 = \frac{\lambda(1-\lambda)}{f^2(x_\lambda)}\| K_r \|^2.$$

Proof. We define the variables

$$\Delta_{1,1} = -\frac{1}{nh_d}\sum_{i=1}^n K_d\left(\frac{F(i/n)-\lambda}{h_d}\right)(F_{nh_r}(i/n) - \mathbf{E}(F_{nh_r}(i/n))),$$

$$\Delta_{1,2} = -\frac{1}{nh_d}\sum_{i=1}^n K_d\left(\frac{F(i/n)-\lambda}{h_d}\right)(\mathbf{E}(F_{nh_r}(i/n)) - F(i/n)).$$

Then $\Delta_1 = \Delta_{1,1} + \Delta_{1,2}$, and $\Delta_{1,2}$ is non-random.
It follows from [8, p. 68] that

$$\sup_x |\,\mathbf{E}(F_{nh_r}(x) - F(x))\,| \leqslant \frac{1}{2}h_r^2\nu_r^2 \sup_x |\,f'(x)\,| \leqslant \frac{M_1 h_r^2 \nu_r^2}{2}.$$

Employing this fact, we obtain

$$\mathbf{E}(\Delta_1) = \mathbf{E}(\Delta_{1,2}) = -\frac{\nu_r^2 h_r^2}{2nh_d}\sum_{i=1}^n K_d\left(\frac{F(i/n)-\lambda}{h_d}\right)F''(i/n)(1+o(1)) =$$

$$= -\frac{\nu_r^2 h_r^2}{2h_d}\int_0^1 K_d\left(\frac{F(x)-\lambda}{h_d}\right)F''(x)\,dx(1+o(1)) + O\left(\frac{h_r^2}{nh_d}\right) =$$

$$= -\frac{\nu_r^2 h_r^2}{2}\int_{-1}^1 K_d(z)(F^{-1})'(\lambda + zh_d)F''(F^{-1}(\lambda + zh_d))\,dz\,(1+o(1)) + O\left(\frac{h_r^2}{nh_d}\right) =$$

$$= -\frac{\nu_r^2}{2}h_r^2(F^{-1})'(\lambda)F''(F^{-1}(\lambda)) + o(h_r^2).$$

Let us calculate the variance of Δ_1. We have

$$\mathbf{D}(\Delta_1) = \mathbf{D}(\Delta_{1,1}) =$$

$$= \frac{1}{n^4 h_d^2 h_r^2}\sum_{j=1}^n F(u_j)(1-F(u_j))\left\{\sum_{i=1}^n K_d\left(\frac{F(i/n)-\lambda}{h_d}\right)K_r\left(\frac{i/n - u_j}{h_r}\right)\right\}^2 =$$

$$= \frac{1}{n^2 h_d^2 h_r^2}\sum_{j=1}^n F(u_j)(1-F(u_j))\left\{\int_0^1 K_d\left(\frac{F(x)-\lambda}{h_d}\right)K_r\left(\frac{x-u_j}{h_r}\right)dx + O\left(\frac{1}{n}\right)\right\}^2.$$

We make the change $z = \dfrac{F(x)-\lambda}{h_d}$ and apply Koksma-Hlavka inequality. Then

$$\mathbf{D}(\Delta_1) = \frac{1}{nh_d^2 h_r^2}\int_0^1 F(y)(1-F(y))\times$$

$$\times \left\{ \int_0^1 K_d\left(\frac{F(x)-\lambda}{h_d}\right) K_r\left(\frac{x-y}{h_r}\right) dx + O\left(\frac{1}{n}\right) \right\}^2 dy + O\left(\frac{1}{n^2 h_r^2}\right).$$

Moreover, as $n \to \infty$

$$K_r\left(\frac{F^{-1}(\lambda + h_d z) - y}{h_r}\right) = K_r\left(\frac{F^{-1}(\lambda) - y}{h_r}\right) + o(1).$$

Taking into consideration the latter and making the change $t = \dfrac{F^{-1}(\lambda) - y}{h_r}$, we finally get

$$\mathbf{D}(\Delta_1) = \frac{\lambda(1-\lambda)\| K_r \|^2}{f^2(x_\lambda) n h_r} + o\left(\frac{1}{n h_r}\right).$$

Now, to prove the asymptotic normality of Δ_1, it is sufficient to prove the asymptotic normality of $\Delta_{1,1}$. In order to do it, we represent $\Delta_{1,1}$ as the sum $\Delta_{1,1} = \sum_{i=1}^n \xi_j$, where

$$\xi_j = -\frac{1}{n^2 h_d h_r} \left(\chi(X_j < u_j) - F(u_j)\right) \sum_{i=1}^n K_d\left(\frac{F(i/n)-\lambda}{h_d}\right) K_r\left(\frac{i/n - u_j}{h_r}\right).$$

Let $G(u) = F(u) - 4F^2(u) + 6F^3(u) - 3F^4(u)$. Then

$$\sum_{j=1}^n \mathbf{E}(\xi_j - \mathbf{E}(\xi_j))^4 = \sum_{j=1}^n \mathbf{E}(\xi_j)^4 = \frac{1}{n^8 h_d^4 h_r^4} \sum_{j=1}^n \mathbf{E}(\chi(X_j < u_j) - F(u_j))^4 \times$$

$$\times \left\{ \sum_{i=1}^n K_d\left(\frac{F(i/n)-\lambda}{h_d}\right) K_r\left(\frac{i/n - u_j}{h_r}\right) \right\}^4 =$$

$$= \frac{1}{n^8 h_d^4 h_r^4} \sum_{j=1}^n G(u_j) \left\{ \int_0^1 K_d\left(\frac{F(x)-\lambda}{h_d}\right) K_r\left(\frac{x-u_j}{h_r}\right) dx + O\left(\frac{1}{n}\right) \right\}^4 =$$

$$= \frac{1}{n^4 h_r^4} \sum_{j=1}^n G(u_j) \left\{ \int_0^1 K_d(y) K_r\left(\frac{x-u_j}{h_r}\right) x'_y \, dy + O\left(\frac{1}{n h_d}\right) \right\}^4 =$$

$$= \frac{1}{n^3 h_r^3} \int_{-1}^1 G(x - z h_r) \left\{ \int_{-1}^1 K_d(y) K_r(z) (F^{-1})'(\lambda + h_d y) \, dy \right\}^4 dz + O\left(\frac{1}{n^4 h_d^4}\right) = O\left(\frac{1}{n^3 h_d^3}\right).$$

Since

$$\frac{\sum_{j=1}^n \mathbf{E}(\xi_j - \mathbf{E}(\xi_j))^4}{\left(\mathbf{D}\left(\sum_{j=1}^n \xi_j\right)\right)^2} = \frac{\sum_{j=1}^n \mathbf{E}(\xi_j - \mathbf{E}(\xi_j))^4}{(\mathbf{D}(\Delta_1))^2} = O\left(\frac{1}{n h_r}\right) \xrightarrow[n\to\infty]{} 0,$$

the sequence $\sum_{j=1}^n \xi_j$ satisfies the assumptions of Lyapunov central limit theorem. This completes the proof. □

Lemma 4.3. *As $n \to \infty$,*

$$\Delta_2 + \Delta_3 = o\left(\frac{1}{\sqrt{n h_r}}\right).$$

Proof. First we consider Δ_2. We have

$$|\,\mathbf{E}(\Delta_2)\,| \leqslant \frac{1}{nh_d}\sum_{i=1}^{n}\left|\frac{1}{h_d}K_d'\left(\frac{\lambda - F(i/n)}{h_d}\right)\right|\mathbf{E}(F_{nh_r}(i/n) - F(i/n))^2 \leqslant$$

$$\leqslant \frac{C_1h_r^4}{nh_d}\sum_{i=1}^{n}\left|\frac{1}{h_d}K_d'\left(\frac{\lambda - F(i/n)}{h_d}\right)\right| =$$

$$= \frac{C_1h_r^4}{h_d}\int\limits_{-1}^{1}|\,K_d'(t)\,|\,dt + O\left(\frac{h_r^4}{nh_d^2}\right) =$$

$$= O\left(\frac{h_r^4}{h_d}\right) = o\left(\frac{1}{\sqrt{nh_r}}\right).$$

Then

$$-\mathbf{E}(\Delta_3) = \frac{1}{nh_d^3}\sum_{i=1}^{n}K_d''\left(\frac{\lambda - \xi_i}{h_d}\right)\mathbf{E}((F_{nh_r}(i/n) - F(i/n))^3).$$

Let $A(x) = \mathbf{E}((F_{nh_r}(x) - F(x))^3)$, then

$$A(x) = \mathbf{E}((F_{nh_r}(x) - \mathbf{E}(F_{nh_r}(x)) + \mathbf{E}(F_{nh_r}(x)) - F(x))^3) =$$

$$= \mathbf{E}((F_{nh_r}(x) - \mathbf{E}(F_{nh_r}(x)))^3) + (\mathbf{E}(F_{nh_r}(x)) - F(x)))^3 + 3\mathbf{D}(F_{nh_r})\cdot(\mathbf{E}(F_{nh_r}(x)) - F(x))) =$$

$$= \mathbf{E}((F_{nh_r}(x) - \mathbf{E}(F_{nh_r}(x)))^3) + O\left(h_r^6 + \frac{h_r}{n}\right),$$

and these estimates are uniform in x and thus

$$|\,\mathbf{E}(\Delta_3\,| \leqslant \frac{M_2}{h_d^3}\int_{-1}^{1}A(x)\,dx.$$

Consider now

$$\mathbf{E}((F_{nh_r}(x) - \mathbf{E}(F_{nh_r}(x)))^3) = \mathbf{E}((n^{-1}\sum_{j=1}^{n}\eta_j(x))^3),$$

where

$$\eta_j(x) = \frac{1}{h_r}(\chi(X_j < x) - F(x))K_r\left(\frac{x-u}{h_r}\right).$$

Then (cf. [9, p. 379])

$$\mathbf{E}((n^{-1}\sum_{j=1}^{n}\eta_j(x))^3) = n^{-2}\mathbf{E}(\eta_1^3(x)) = \frac{F(x) - 3F^2(x) + 2F^3(x)}{n^2h_r^3}K_r^3\left(\frac{x-u}{h_r}\right).$$

Employing the boundedness of $K_d''(t)$ and the fact that

$$\frac{1}{h_r}\int_{-1}^{1}K_r^3\left(\frac{x-u}{h_r}\right)\,dx \leqslant M_3 < \infty,$$

we obtain

$$|\,\mathbf{E}(\Delta_3)\,| = O\left(\frac{1}{n^2h_d^3h_r^2}\right) = o\left(\frac{1}{\sqrt{nh_r}}\right).$$

In the same one can show that $\mathbf{E}(\Delta_2^2)$, $\mathbf{E}(\Delta_3^2)$ converge to zero as $n \to \infty$. Hence, by Chebyshev inequality, we complete the proof. □

Lemmata 4.1-4.3 imply the following theorem.

Theorem 4.1. *As $n \to \infty$,*

$$\sqrt{nh_r}(\hat{x}_{1,\lambda} - x_\lambda - b_2(h_r, h_d)) \xrightarrow{d} N(0, g_2^2),$$

where

$$b_2(h_r, h_d) = a_{2,d}h_d^2 + a_{2,r}h_r^2, \quad a_{2,r} = -\frac{\nu_r^2 f'(x_\lambda)}{2f(x_\lambda)}, \quad a_{2,d} = -\frac{\nu_d^2 f'(x_\lambda)}{2f^3(x_\lambda)},$$

$$g_2^2 = \frac{\lambda(1-\lambda)\| K_r \|^2}{f^2(x_\lambda)}.$$

4.2. Asymptotics for estimators $\hat{x}_{2,\lambda}$ and $\hat{x}_{3,\lambda}$. To study the asymptotics for the estimators $\hat{x}_{2,\lambda}$, we represent it as

$$\hat{x}_{2,\lambda} = \frac{\hat{S}_{2,\lambda}}{\hat{x}_{1,\lambda}},$$

where

$$\hat{S}_{2,\lambda} = x_{2,\lambda} + 2\Lambda, \quad x_{2,\lambda} = \frac{2}{nh_d}\sum_{i=1}^{n}\frac{i}{n}\int_{-\infty}^{\lambda} K_d\left(\frac{F(i/n)-u}{h_d}\right)du,$$

$$\Lambda = \frac{1}{nh_d}\sum_{i=1}^{n}\frac{i}{n}\int_{-\infty}^{\lambda}\left\{K_d\left(\frac{F_{nh_r}(i/n)-u}{h_d}\right) - K_d\left(\frac{F(i/n)-u}{h_d}\right)\right\}du.$$

Lemma 4.4. *As $n \to \infty$,*

$$x_{2,\lambda} = x_\lambda^2 + h_d^2\nu_d^2 x_\lambda\left(-\frac{f'(x_\lambda)}{f^3(x_\lambda)} + \frac{1}{f^2(x_\lambda)}\right) + o(h_d^2).$$

Proof. Applying the Koksma-Hlawka inequality, we obtain

$$x_{2,\lambda} = \frac{2}{h_d}\int_0^1\int_{-\infty}^{\lambda} xK_d\left(\frac{F(x)-u}{h_d}\right)du dx + O\left(\frac{1}{nh_d}\right) =$$

$$= 2\int_0^1 x\,dx\int_{(F(x)-\lambda)/h_d}^{1} K_d(y)\,dy + O\left(\frac{1}{nh_d}\right) =$$

$$= 2\int_0^{F^{-1}(\lambda-h_d)} x\,dx\int_{-1}^{1} K_d(y)\,dy + 2\int_{F^{-1}(\lambda-h_d)}^{1} x\,dx\int_{(F(x)-\lambda)/h_d}^{1} K_d(y)\,dy + O\left(\frac{1}{nh_d}\right).$$

The first integral can be immediately calculated, while in the other we make the change $t = \dfrac{F(x)-\lambda}{h_d}$. It yields

$$x_{2,\lambda} = (F^{-1}(\lambda-h_d))^2 +$$

$$+2h_d\int_{-1}^{(F(1)-\lambda)/h_d}(F^{-1})'(\lambda+th_d)F^{-1}(\lambda+th_d)\,dt\int_t^1 K_d(y)\,dy + O\left(\frac{1}{nh_d}\right) =$$

$$= \left\{F^{-1}(\lambda) - (F^{-1})'(\lambda)h_d + (F^{-1})''(\lambda)\frac{h_d^2}{2} + o(h_d^2)\right\}^2 +$$

$$+2h_d(F^{-1})'(\lambda)F^{-1}(\lambda)\int_{-1}^{1}dt\int_t^1 K_d(y)\,dy +$$

$$+2h_d^2 \int_{-1}^{1} t\,dt \int_{t}^{1} K_d(y)\,dy \left\{(F^{-1})''(\lambda)F^{-1}(\lambda) + \left[(F^{-1})'(\lambda)\right]^2\right\} + o(h_d^2).$$

Since

$$\int_{-1}^{1} dt \int_{t}^{1} K_d(y)\,dy = 1, \quad 2\int_{-1}^{1} dt \int_{t}^{1} K_d(y)t\,dy = \nu_d^2 - 1,$$

then

$$x_{2,\lambda} = \left\{(F^{-1}(\lambda))^2 + ((F^{-1})'(\lambda))^2 h_d^2 - 2F^{-1}(\lambda)(F^{-1})'(\lambda)h_d + \right.$$
$$\left. + F^{-1}(\lambda)(F^{-1})''(\lambda)h_d^2\right\} + 2(F^{-1})'(\lambda)F^{-1}(\lambda)h_d +$$
$$+ h_d^2(\nu_d^2 - 1)F^{-1}(\lambda)\left\{(F^{-1})''(\lambda) + ((F^{-1})'(\lambda))^2\right\} + o(h_d^2).$$

It completes the proof. □

We represent the variable Λ as the sum $\Lambda = \Lambda_1 + \frac{1}{2}\Lambda_2 + \frac{1}{6}\Lambda_3$, where

$$\Lambda_1 = -\frac{1}{nh_d}\sum_{i=1}^{n} K_d\left(\frac{\lambda - F(i/n)}{h_d}\right)\frac{i}{n}(F_{nh_r}(i/n) - F(i/n)),$$

$$\Lambda_2 = \frac{1}{nh_d^2}\sum_{i=1}^{n} K_d'\left(\frac{F(i/n) - u}{h_d}\right)\frac{i}{n}(F_{nh_r}(i/n) - F(i/n))^2,$$

$$\Lambda_3 = -\frac{1}{nh_d^3}\sum_{i=1}^{n} K_d''\left(\frac{\xi_i - u}{h_d}\right)\frac{i}{n}(F_{nh_r}(i/n) - F(i/n))^3,$$

$$|\,\xi_i - F(i/n)\,| \leqslant |\,F(i/n) - F_{nh_r}(i/n)\,|.$$

Lemma 4.5. *As $n \to \infty$,*

$$\sqrt{nh_r}(\Lambda_1 - a_{1,r}h_r^2) \xrightarrow{d} N(0, g_1^2),$$

where

$$a_{1,r} = -\frac{\nu_r^2 x_\lambda f'(x_\lambda)}{f^4(x_\lambda)}, \quad g_1^2 = \frac{4\lambda(1-\lambda)x_\lambda^2}{f^2(x_\lambda)}\|\,K_r\,\|^2.$$

Proof. Let

$$\Lambda_{1,1} = -\frac{1}{nh_d}\sum_{i=1}^{n} K_d\left(\frac{F(i/n) - \lambda}{h_d}\right)\frac{i}{n}(F_{nh_r}(i/n) - \mathbf{E}(F_{nh_r}(i/n))),$$

$$\Lambda_{1,2} = -\frac{1}{nh_d}\sum_{i=1}^{n} K_d\left(\frac{F(i/n) - \lambda}{h_d}\right)\frac{i}{n}(\mathbf{E}(F_{nh_r}(i/n)) - F(i/n)).$$

Then $\Lambda_1 = \Lambda_{1,1} + \Lambda_{1,2}$.

Taking into consideration that $\mathbf{E}(F_{nh_r}(x) - F(x)) = \dfrac{\nu_r^2 h_r^2}{2} f'(x) + o(h_r^2)$, we obtain

$$\mathbf{E}(\Lambda_1) = \mathbf{E}(\Lambda_{1,2}) = -\frac{\nu_r^2 h_r^2}{2nh_d}\sum_{i=1}^{n} K_d\left(\frac{F(i/n) - \lambda}{h_d}\right)\frac{i}{n}F''(i/n)(1 + o(1)) =$$

$$= -\frac{\nu_r^2 h_r^2}{2h_d}\int_{0}^{1} K_d\left(\frac{F(x) - \lambda}{h_d}\right) xF''(x)\,dx(1 + o(1)) + O\left(\frac{h_r^2}{nh_d}\right) =$$

$$= -\frac{\nu_r^2 h_r^2}{2}\int_{-1}^{1} K_d(z)F^{-1}(\lambda + zh_d)(F^{-1})'(\lambda + zh_d)F''(F^{-1}(\lambda + zh_d))\,dz(1 + o(1)) + O\left(\frac{h_r^2}{nh_d}\right) =$$

$$= -\frac{\nu_r^2 h_r^2}{2} F^{-1}(\lambda)(F^{-1})'(\lambda)F''(F^{-1}(\lambda)) + o(h_d^2).$$

Let us calculate the variance of the variable Λ_1. We have

$$\mathbf{D}(\Lambda_1) = \mathbf{D}(\Lambda_{1,1}) =$$

$$= \frac{1}{n^4 h_d^2 h_r^2} \sum_{j=1}^{n} F(u_j)(1-F(u_j)) \left\{ \sum_{i=1}^{n} K_d\left(\frac{F(i/n)-\lambda}{h_d}\right) K_r\left(\frac{i/n-u_j}{h_r}\right) \frac{i}{n} \right\}^2 =$$

$$= \frac{1}{n^2 h_d^2 h_r^2} \sum_{j=1}^{n} F(u_j)(1-F(u_j)) \left\{ \int_0^1 K_d\left(\frac{F(x)-\lambda}{h_d}\right) K_r\left(\frac{x-u_j}{h_r}\right) x\,dx + O\left(\frac{1}{n}\right) \right\}^2.$$

Making the change $z = \dfrac{F(x)-\lambda}{h_d}$ and applying again Koksma-Hlawka inequality, we obtain

$$\mathbf{D}(\Lambda_1) = \frac{1}{n h_d^2 h_r^2} \int_0^1 F(u)(1-F(u))\,du \times$$

$$\times \left\{ \int_0^1 K_d(z) K_r\left(\frac{F^{-1}(\lambda+zh_d)-u}{h_r}\right) F^{-1}(\lambda+zh_d)(F^{-1})'(\lambda+zh_d)\,dx + O\left(\frac{1}{n}\right) \right\}^2 + O\left(\frac{1}{n^2 h_r^2}\right).$$

Employing that, as $n \to \infty$,

$$K_r\left(\frac{F^{-1}(\lambda+h_d z)-y}{h_r}\right) = K_r\left(\frac{F^{-1}(\lambda)-y}{h_r}\right) + o(1),$$

and making the change $\dfrac{F^{-1}(\lambda)-u}{h_r}$, we finally get

$$\mathbf{D}(\Lambda_1) = \frac{1}{nh_r}\lambda(1-\lambda)(F^{-1}(\lambda)(F^{-1})'(\lambda))^2 \| K_r \|^2 + o\left(\frac{1}{nh_r}\right) = \frac{\lambda(1-\lambda)x_\lambda^2 \| K_r \|^2}{nh_r f^2(x_\lambda)} + o\left(\frac{1}{nh_r}\right).$$

Taking into the fact 2 in the definition of the statistics $\hat{S}_{2,\lambda}$, we complete the proof. □

Lemma 4.6. *As $n \to \infty$,*

$$\Lambda_2 + \Lambda_3 = o\left(\frac{1}{\sqrt{nh_r}}\right).$$

Proof. Bearing in mind that $0 \leqslant i/n \leqslant 1$ and reproducing the proof of Lemma 4.3, we obtain the statement of the lemma. □

Lemma 4.7. *As $n \to \infty$,*

$$\sqrt{nh_r}(\hat{S}_{2,\lambda} - x_\lambda^2 - a_1(h_r, h_d)h_d^2) \xrightarrow{d} N(0, g_1^2),$$

where

$$g_1^2 = \frac{\lambda(1-\lambda)x_\lambda^2}{f^2(x_\lambda)} \| K_r \|^2,$$

$$a_{1,d} = \nu_d^2 \left(-\frac{x_\lambda f'(x_\lambda)}{f^3(x_\lambda)} + \frac{1}{f^2(x_\lambda)} \right).$$

The proof of this lemma follows the same lines as that of Lemma 4.4 and we omit it.

We represent the estimator $\hat{x}_{2,\lambda}$ as the fraction $\frac{\beta}{\alpha}$, where

$$\beta = x_{2,\lambda} + \Lambda_1, \quad \alpha = \frac{1}{nh_d} \sum_{i=1}^{n} \int_{-\infty}^{\lambda} K_d \left(\frac{F_{nh_r}(i/n) - u}{h_d} \right) du.$$

We let

$$\mu_1 = x_\lambda^2 \quad \mu_2 = x_\lambda.$$

The representation

$$\hat{x}_{2,\lambda} - \frac{\mu_1}{\mu_2} = \frac{\beta - \mu_1}{\mu_2} - \frac{\mu_1}{\mu_2^2}(\alpha - \mu_2) +$$
$$+ O_p((\beta - \mu_1)(\alpha - \mu_2)) + O_p((\alpha - \mu_2))$$

(see[10, p. 327]) and the fact that, as $n \to \infty$,

$$\tilde{g}^2 = \frac{g_1^2}{\mu_2^2} + \frac{g_2^2 \mu_1^2}{\mu_2^4} - 2\mathbf{cov}\left(\frac{\beta}{\mu_2}, \frac{\alpha\mu_1}{\mu_2^2} \right) \sim g^2 = \frac{\lambda(1-\lambda)}{f^2(x_\lambda)} \| K_r \|^2$$

imply the following theorem.

Theorem 4.2. *As $n \to \infty$,*

$$\sqrt{nh_r}(\hat{x}_{2,\lambda} - x_\lambda - b(h_r, h_d)) \xrightarrow{d} N(0, g^2),$$

where

$$b_1(h_r, h_d) = a_{1,d} h_d^2 + a_{1,r} h_r^2,$$

$$a_{1,r} = -\frac{\nu_r^2 x_\lambda f'(x_\lambda)}{f^4(x_\lambda)}, \quad a_{1,d} = \nu_d^2 \left(-\frac{x_\lambda f'(x_\lambda)}{f^3(x_\lambda)} + \frac{1}{f^2(x_\lambda)} \right).$$

In Lemma 4.7 and Theorem 4.2 there appear the quantities $a_{1,r}$ and $a_{1,d}$ involving the derivatives of the inverse function $F^{-1}(\lambda)$, namely, $(F^{-1})'(\lambda)$, $(F^{-1})''(\lambda)$, which are known. As their estimators, we suggest the following statistics,

$$\hat{c}_1 = \frac{1}{nh_d} \sum_{i=1}^{n} K_d \left(\frac{F_{nh_r}(i/n) - \lambda}{h_d} \right) \quad \text{and} \quad \hat{c}_2 = -\frac{1}{nh_d^2} \sum_{i=1}^{n} K_d' \left(\frac{F_{nh_r}(i/n) - \lambda}{h_d} \right).$$

Arguing as above, one can show that as $n \to \infty$, they converge in probability to $(F^{-1})'(\lambda)$ and $(F^{-1})''(\lambda)$, respectively. Then a consistent estimator for $\hat{b}_1(h_r, h_d)$ is $\nu_r^2 h_r^2 \hat{c}_1 \hat{c}_2 + \nu_d^2 h_d^2 (\hat{c}_2 + \hat{c}_1^2)$.

Theorem 4.2 implies that the dispersion of the limiting distribution of the estimator $\hat{x}_{2,\lambda}$ is the same as for the estimator $\hat{x}_{1,\lambda}$ and this is why we consider the estimator

$$\hat{x}_{3,\lambda} = \sqrt{\hat{S}_{2,\lambda} - \hat{b}_1(h_r, h_d)}.$$

Employing Theorem 3.1, it is easy to obtain the following result.

Theorem 4.3. *As $n \to \infty$,*

$$\sqrt{nh_r}(\hat{x}_{3,\lambda} - x_\lambda) \xrightarrow[n \to \infty]{d} N(0, g_3^2),$$

where

$$g_3^2 = \frac{\lambda(1-\lambda)x_\lambda}{f^2(x_\lambda)} \| K_r \|^2.$$

Since $0 < x_\lambda < 1$, by Theorem 4.3 we conclude that the limiting dispersion of the estimator $\hat{x}_{3,\lambda}$ is less than that of the estimators $\hat{x}_{1,\lambda}$ and $\hat{x}_{2,\lambda}$.

The constructed estimator $\hat{x}_{3,\lambda}$ was employed to find effective doses for the examples borrowed from book [1] as well as for the Finney's example, see [11, p. 98].

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