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# NEGATIVE BINOMIAL REGRESSION IN DOSE-EFFECT RELATIONSHIPS

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**Abstract.** This paper is devoted to problem on estimating the distribution function and its quantiles in the dose-effect relationships with nonparametric negative binomial regression. Most of the mathematical researches on dose-response relationships concerned models with binomial regression, in particular, models with binary data. Here we propose a kernel-based estimates for the distribution function, the kernels of which are weighted by a negative binomial random variable at each covariate. These covariates are quasirandom van der Corput and Halton low-discrepancy sequences. Our estimates are consistent, that is, they converge to their optimal values in probability as the number of observations $n$ grows to infinity. The proposed estimats are compared by their mean-square errors. We show that our estimates have a smaller asymptotic variance in comparison, in particular, with estimates of the Nadaraya-Watson type and other estimates. We present nonparametric estimates for the quantiles obtained by inverting a kernel estimate of the distribution function. We show that the asymptotic normality of these bias-adjusted estimates is preserved under some regularity conditions. We also provide a multidimensional generalization of the obtained results.

**Keywords:** negative binomial response model, effective dose level, nonparametric estimate.

**Mathematics Subject Classification:** 62G05, 62E20, 62P10

## 1. Introduction

The problem on estimating an unknown distribution is the most important problem in mathematical statistics for both complete and incomplete samples. In this paper we consider the problem of constructing efficient estimates of a distribution function $F(x)$ and a quantile function $F^{-1}(\lambda) = x_\lambda$, $0 < \lambda < 1$, in the dose-effect relationship for a model of *a negative binomial regression*, and we also study the asymptotic behavior of the proposed estimates. The aim of our paper is to provide usable practical estimates of dose-response curves. Such problems arise in biology [1], toxicology [2], in the evaluation of effective doses of drugs [3]. We note also that «dose-effect relationship» is a conventional name. The model we consider can be used, for example, to estimate the confidence time limits for the developmental stages of a child in pediatrics (see [1], [4]–[6]). This problem is most acute when estimating quantiles of either small or relatively high levels.

There are two main approaches to estimating $F(x)$ and its quantiles: a parametric approach using known distributions, in particular, the probit- and logit-models, and a nonparametric approach. The biological mechanisms of drug action and toxicity are often so complex that the shape of the $F(x)$ curve is mostly unknown and fitting a wrong model can lead to large and unpredictable deviations with unacceptable confidence boundaries. In this case, for the dose-response relationship, it becomes reasonable to use a non-parametric approach, which is as follows. There is a binary response model, which is conventionally called *dose-effect relationship* [3], [7]. Namely, let $\{(X_i, U_i), 1 \leqslant i \leqslant n\}$ be a potential sample with replacement of an unknown distribution

$$F(x)G(x), \qquad F(x) = \mathbf{P}(X_i < x), \qquad G(x) = \mathbf{P}(U_i < x),$$

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instead which we observe the sample

$$\mathcal{U}^{(n)} = \{(U_i, W_i),\ 1 \leqslant i \leqslant n\},$$

where $W_i = I(X_i < U_i)$ is the indicator of the event $(X_i < U_i)$. The problem is to estimate an unknown distribution function $F(x)$ by the sample $\mathcal{U}^{(n)}$. Here $U_i$ are treated as doses and $W_i$ as the effect of the dose $U_i$. Let

$$F(x) = \int_{-\infty}^{x} f(t)\,dt, \qquad G(x) = \int_{-\infty}^{x} g(t)\,dt, \qquad f(x) > 0, \qquad g(x) > 0.$$

We call such situation a *random* plan of experiment. Then the conditional expectation is equal to

$$\mathbf{E}(W|U = x) = \mathbf{P}(X < U|U = x) = \mathbf{P}(X < x|U = x) = \mathbf{P}(X < x) = F(x),$$

that is, the unknown distribution function $F(x)$ is a regression and to estimate $F(x)$ by the sample $\mathcal{U}^{(n)} = \{(U_i, W_i),\, 1 \leqslant i \leqslant n\}$ we can use kernel regression estimates.

Together with a random plan we shall consider *fixed* plans of experiment [8]. Namely, we suppose that the injected dose $U$ is not random and we let $U_i = u_i$, $i = 0, 1, \ldots, n+1$, where

$$0 = u_0 < u_1 < \ldots < u_n < u_{n+1} = 1.$$

In the paper we study the behavior of kernel estimates by the fixed plans.

For the dose-effect relationship with random plans of experiment and binary responses [3], [7], as an estimate for the distribution function $F(x)$, one usually takes the statistics

$$F_n(x) = \frac{S_{2n}(x)}{S_{1n}(x)}, \qquad S_{1n}(x) = \frac{1}{n}\sum_{i=1}^{n} K_h(x - U_i), \qquad S_{2n}(x) = \frac{1}{n}\sum_{i=1}^{n} W_i K_h(x - U_i),$$

if $S_{1n}(x) \neq 0$, where $K_h(x) = K(x/h)/h$, $K(x)$ is a finite symmetric density (kernel), $h = h(n) \to 0$, $nh \to \infty$ as $n \to \infty$. If $S_{1n}(x) = 0$, then $F_n(x)$ is supposed to be zero. For instance, as the kernel function $K(x)$ one often uses Epanechnikov kernel

$$K_1(x) = \frac{3}{4}(1 - x^2)I(|\,x\,| < 1),$$

as well as quartic kernel

$$K_2(x) = \frac{15}{16}(1 - x^2)^2 I(|\,x\,| < 1),$$

as $h(n)$ one chooses $n^{-1/5}$.

Under some regularity conditions, see [7], it turns out that as $n \to \infty$, the quantity $n^{2/5}(F_n(x) - \mathbf{E}(F_n(x)))$ is asymptotically normal $N(0, \sigma^2(x))$, where

$$\sigma^2(x) = F(x)(1 - F(x))\frac{\|\,K\,\|^2}{g(x)}, \qquad \|\,K\,\|^2 = \int_{-\infty}^{\infty} K^2(x)\,dx.$$

For fixed plans of experiments the dispersion of the estimate $F_n(x)$ equals

$$\sigma_1^2(x) = F(x)(1 - F(x))\|\,K\,\|^2.$$

The dose-effect relationship in the model with *binomial regression*, see, for instance, [9], [10], can be described as follows. Suppose that the response $W_{ij}$ is equal to 1 if it gives a needed reaction and $W_{ij} = 0$ if there no reaction, which is observed on each fixed covariate $u_i$.

Thus, $W_{ij}$ is the $j$th response of $m$ subjects when the covariate is equal to $u_i$, $i = 1, 2, \ldots, n$, and the responses $W_{ij}$ are mutually independent. The relation between them is determined by the probability that $W_{ij} = 1$ under condition $u_i$:

$$F(u_i) = \mathbf{P}(W_{ij} = 1) = \mathbf{P}(X_{ij} < u_i),$$

where $W_i = \sum_{j=1}^{m} W_{ij}$ has a binomial distribution $B(m, p_i)$ with the parameter $p_i = F(u_i)$, and it is well-known that the maximal likelihood for $p_i$ is given by the quotient $w_i = W_i/m$ for each $i$. The data $(u_i, w_i)$, $i = 1, 2, \dots, n$, allow us to construct an estimator for the distribution function of the form

$$F_n(x) = \frac{\sum_{j=1}^{n} w_i \eta_i(x)}{\sum_{j=1}^{n} \eta_i(x)}, \qquad \eta_i(x) = K_h(x - u_i).$$

For $m = 1$ we have a Bernoulli regression model. It was shown in [11] that for a fixed $x$ the difference $\sqrt{nh}(F_n(x) - \mathbf{E}(F_n(x)))$ is asymptotically normal $N(0, \sigma_1^2(x)/m)$ as $n \to \infty$. At the same time in each fiber we consider a sampling without replacing, in which the parameter $p_i = F(u_i)$ of the binomial distribution is not random. For a sampling without replacement we can suppose that the parameter of the binomial distribution is random, for instance, it has a Beta distribution $\mathbf{B}(\alpha, \beta)$. In this case we obtain a Beta-binomial distribution, then instead of the parameter $p_i$ we have the parameter $\alpha_i/(\alpha_i + \beta_i)$ and as its estimate we take $m_{1,i}/W_i$ as ML-estimate of «mean» probability and «mean» distribution function.

In this note, announced in [12], we consider a negative binomial regression model (NBR-model). More precisely, for a given $m$ we consider a negative binomial distribution of the quantities $Z_i$ under a given covariate $u_i$:

$$\mathbf{P}(Z_i = k) = \frac{\Gamma(k+m)}{\Gamma(k+1)\Gamma(m)} p_i^m (1-p_i)^{k-m}, \quad k = m, m+1, \dots, \ \Gamma(k+1) = k!\,.$$

We choose a sample $\mathcal{Z} = \{(z_i, u_i), i = 1, 2, \dots, n\}$ for determining an estimate for $F(x)$ of the form

$$T_n(x) = \frac{\sum_{j=1}^{n} m\eta_i(x)}{\sum_{j=1}^{n} z_i \eta_i(x)}. \tag{1.1}$$

For so-called quasi-random *low-discrepancy sequences* $\{u_i\}, i = 1, 2, \dots, n$, where $u_i$ are not random, we prove the consistency and asymptotic normality of the constructed estimates as $n \to \infty$. We show that the limiting dispersion of the estimates under the normalization of $\sqrt{nh}$ is equal to

$$\sigma_2^2(x) = F^2(x)(1 - F(x)) \frac{\| K \|^2}{m},$$

which is less that the limiting dispersion

$$\sigma_1^2(x) = F(x)(1 - F(x)) \frac{\| K \|^2}{m}$$

of the estimates of the distribution function $F(x)$ of Nadaraya-Watson type in the binomial regression. On the base of statistics (1.1) we construct estimates for the quantiles and prove its asymptotic normality. On the base of unbiased estimate for the parameter $p$ as well as of the estimate of the maximal likelihood of the negative binomial distribution we propose an estimate for the unknown distribution function.

A negative binomial distribution naturally arises for small value of the parameters of the binomial distribution $p_i$ and large $m$, which can be approximated by the Poisson distribution. It is known that the mixture of the Poisson and Gamma distribution, see [13, Sect. 5.13], leads to the negative binomial distribution. One can also consider Pólya urn scheme and to show that the negative binomial distribution can be obtained by passing to the limit from the Pólya urn scheme, see [14, Sect. 10.9].

In applied problems, like our problem, apart of theoretical issues on treating specific situations, one has to take into consideration the choice of covariates $u_i$. They can be chosen deterministically with a uniform step, it is possible to build purely random constructions, it is possible, using the quasi-Monte Carlo method, to select them randomly from a given set. Under a good choice of the set, it is possible to obtain almost optimal results. Here we propose to consider almost uniform sequences of covariates.

## 2. Main conditions

Let $\{X_i,\ i=1,\dots,n\}$ be a sequence of independent identically distributed with $X$ on the segment $[0,1]$ random variables with the distribution function $F(x)$, and

$$P=\{u_0,u_1,\ \dots,\ u_n,u_{n+1}\},\qquad u_0=0<u_1<\dots<u_n<1=u_{n+1},$$

be a partition of the segment $[0,1]$. We shall assume the following conditions.

**Condition 1.** *As $n\to\infty$, the window width is $h=n^{-1/5}$.*

We shall refer this condition as Condition (**H**).

**Condition 2.** *$K(x)\geqslant 0$, and $K(x)=0$, $x\notin[-1,1]$.*

**Condition 3.** $\int\limits_{-1}^{1} K(x)\,dx=1.$

**Condition 4.** $K(x)=K(-x)$, $x\in\mathbb{R}$.

**Condition 5.** *There exist third continuous bounded derivatives of the function $K(x)$ on the segment $[-1,1]$.*

**Condition 6.** $\|K\|_\infty=\sup\limits_{-1\leqslant x\leqslant 1}|K(x)|=k_j<\infty$ .

We let

$$\|K\|^2=\int\limits_{-1}^{1}K^2(x)\,dx$$

and defined a *variation* of the function $f=f(x)$, $a\leqslant x\leqslant b$, see [15, Ch. VIII, Sect. 3].

Let $g:[a,b]\to\mathbb{R}$. A *variation* of the function $g=g(u)$ on the segment $[a,b]$ is the following quantity

$$\bigvee(g)=\bigvee_a^b(g)=\sup_P\sum_{k=0}^{m}|\,g(u_{k+1})-g(u_k)\,|,$$

that is, the supremum over all partitions $P$ of the segment $[a,b]$.

**Condition 7.** *A variation of the function $K(x)$ is bounded, that is, $\bigvee(K)<\infty$.*

We observe that if $K(x)$ is a smooth function, then $\bigvee_0^1(K)=\int\limits_0^1|\,K'(x)\,|\,dx$.

In what follows, Conditions (2-7) are referred to as Condition (**K**).

**Condition 8.** *There exists a third continuous bounded derivatives of the distribution density $f(x)=F'(x)$ and $f(x)>0$.*

This condition (8) will be referred to as Condition (**F**).

In the work we assume that Conditions (**H**), (**K**), (**F**) are satisfied; they will be called *regularity conditions*.

## 3. Auxiliary results

In this section we provide auxiliary results needed to studying the asymptotics of the introduced estimates.

We provide a Koksma-Hlawka inequality, see [16, Sect. 2.2], which allows one to estimate the rate of the convergence of the integral sums to the corresponding integral. Let $\mathcal{B}$ be the Lebesgue $\sigma$-measure on $I^s$, where $I=[0,1]$, and $\rho_s$ is the Lebesgue measure on $\mathcal{B}$, while $P$ is the set of the points $\mathbf{u}_1,\mathbf{u}_2,\dots,\mathbf{u}_N\in I^s$. We define a counter

$$A_n(B;P)=\sum_{i=1}^{n}I_B(u_i)$$

and a deviation

$$D_n(\mathcal{B}; P) = \sup_{B\in\mathcal{B}} \left| \frac{A_n(B;P)}{n} - \rho_s(B) \right|,$$

where $I_B(x)$ is the indicator of as set $B$. We let $D_n^*(P) = D_n(J_c^*; P)$, where $J_c^*$ is the family of the subintervals on $I^s$ of the form $\prod_{i=1}^{s}[0, u_i]$. Here $\rho_s\left(\prod_{i=1}^{s}[0,u_i]\right) = u_1 u_2 \dots u_s$. The quantity $D_n^*(P)$ is called a *discrepancy* of a sequence.

**Definition 3.1.** *We say that a sequence $P = \{u_1, u_2, \dots\}$ of random numbers is uniformly distributed if for each pair of real numbers $0 \leqslant a < b \leqslant 1$ we have:*

$$\lim_{n\to\infty} \frac{A_n([a,b), P)}{n} = b - a.$$

We shall deal with uniformly distributed sequences.

**Theorem 3.1** ([16, Sect. 2.2])**.** *(Koksma-Hlawka inequality). If a function $f(u)$ $(0 \leqslant u \leqslant 1)$ is continuous and has a bounded variation $\bigvee(f)$ on $[0, 1]$, then for each $u_1, u_2, \dots, u_n \in [0, 1]$ we have*

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

For a multi-dimensional unit cube $I^s = [0, 1)^s$, $\bar{I}^s = [0, 1]^s$ and the variation in the sense of Hardy and Krause the following result holds true [16, Sect. 2.2].

**Theorem 3.2.** [16, Sect. 2.2] *If a function $f(u)$ $(0 \leqslant u \leqslant 1)$ has a bounded variation $\bigvee(f)$ on $\bar{I}^s$ in the sense of Hardy and Krause, then for all $\boldsymbol{u}_1, \boldsymbol{u}_2, \dots, \boldsymbol{u}_n \in I^s$ we have*

$$\left| \frac{1}{n}\sum_{i=1}^{n} f(\boldsymbol{u}_i) - \int f(\boldsymbol{u})\,\boldsymbol{du} \right| \leqslant \bigvee(f) D_n^*(\boldsymbol{u}_1, \dots, \boldsymbol{u}_n).$$

It was shown in [16, Sect. 2.2] that $D_n^*(u_1, \dots, u_n)$ is a continuous function of variables $(u_1, \dots, u_n)$ and if $u_i = \frac{i}{n}$, then $D_n^*(u_1, \dots, u_n) = \frac{1}{n}$. In the same way one can show that for a continuous partition of a $s$-dimensional unit cube $I^s$ the discrepancy of finitely many points is $D_n^* \asymp \frac{1}{n}$, see [17]. For finite $n$ we can also calculate it using the algorithm given in [18].

**Remark 3.1.** *In the finite-dimensional case, if $u_0 = 0 < u_1 < u_2 < \ldots < u_n < u_{n+1} = 1$, then*

$$D_n^*(P) = \max_{0\leqslant k\leqslant n} \sup_{u_k<u\leqslant u_{k+1}} \left| \frac{A_n([0,u);P)}{n} - u \right| = \max_{0\leqslant k\leqslant n} \sup_{u_k<u\leqslant u_{k+1}} \left| \frac{k}{n} - u \right|$$
$$= \max_{0\leqslant k\leqslant n} \max\left( \left|\frac{k}{n} - x_k\right|, \left|\frac{k}{n} - x_{k+1}\right| \right),$$

*and this is the Kolmogorov statistics.*

Thus, if we treat $u_1 < u_2 < \ldots < u_n$ as a variation series of a sample and as a zero conjecture we choose the uniform distribution, then the discrepancy is the maximal deviation of the sampling distribution function from the uniform one. Large values indicates $D_n^*$ the concentration of the sequence $P$ in some domain.

This result is generalizaed on the multi-dimensional case [16, Sect. 2.2]. In this case the law of the reiterated logarithm holds, which was proved by Kiefer [20]:

$$\overline{\lim_{n\to\infty}} \frac{\sqrt{2\pi} D_n^*(P)}{\sqrt{2\ln\ln n}} = 1$$

almost everywhere.

To extend possible applications of the results given in Section 4, we consider *low-discrepancy sequences* [16, Ch. 3], which are *van der Corput and Halton sequences* [21].

Let

$$n = \sum_{j=0}^{\infty} a_j(n) b^j \tag{3.1}$$

be the representation of an integer number $n \geqslant 0$ by a natural base $b \geqslant 2$, where $a_j(n) \in Z_b = \{0, 1, \dots, b-1\}$ for each $j \geqslant 0$ and $a_j(n) = 0$ for all sufficiently large $j$.

**Definition 3.2.** *For $b \geqslant 2$, the radical inverse function $\phi_b$ be the base $b$ is defined as follows:*

$$\phi_b(n) = \sum_{j=0}^{\infty} a_j(n) b^{-j-1} \quad \textit{for each integer} \quad n \geqslant 0, \tag{3.2}$$

*where $a_j(n)$ come from representation (3.1) with the same $b$.*

**Definition 3.3.** *For each natural $b \geqslant 2$, the van der Corput sequence by the base $b$ is the sequence $\{u_0, u_1, \dots, u_n, \dots\}$ with $u_n = \phi_b(n)$ for each $n \geqslant 0$.*

Given a sequence $S = \{u_0, u_1, \dots\}$, we shall write $D_n(S) = D_n(u_0, u_1, \dots, u_{n+1})$ for the discrepancy of the first $n$ terms in $S$ and in the same way we write $D_n^*(S) = D_n^*(u_0, u_1, \dots, u_n)$.

It was shown in [16, Sect. 3.1] that if $S_b$ is a van der Corput sequence by the base $b$, then

$$D_N^*(S_b) \leqslant C_1 \frac{\ln N}{N} \quad \text{for all} \quad N \geqslant 2,$$

where a constant $C_1$ is independent of $b$.

**Definition 3.4.** *Let $s$ be an arbitrary dimension and $b_1, b_2, \dots, b_s \geqslant 2$, be mutually prime natural numbers. We define a Halton sequence by letting*

$$\boldsymbol{u}(n) = (\phi_{b_1}(n), \phi_{b_2}(n), \dots, \phi_{b_s}(n)) \in I^s \quad \textit{for each integer} \quad n \geqslant 0.$$

As $s = 1$, this definition is reduced to the definition of var der Corput sequence.

**Theorem 3.3** ([17, Ch. 5, Sect. 1])**.** *If $S$ is a Halton sequence, then there exist constants $C_2$ and $C_3$ depending only on $b_1, b_2, \dots, b_s$ such that for all $N \geqslant 1$,*

$$C_2 \frac{(\ln N)^{s-1}}{N} \leqslant D_N^*(S) \leqslant C_2 \frac{(\ln N)^s}{N}.$$

It was mentioned in [17, Ch. 5, Sect. 1] that for $s = 1$ the uniform grids are the best ones, while as $s$ increases, they approach to worst ones. It was shown how one should modify the grid to make it better. In the two-dimensional case a quadrature Fibonacci formula is also known [22]:

$$\frac{1}{b_n} \sum_{k=1}^{b_n} f\left(\frac{k}{b_n}, \left\{\frac{b_{n-1}}{b_n} k\right\}\right), \quad b_1 = b_2 = 1, \quad b_n = b_{n-1} + b_{n-2}, \quad n \geqslant 3,$$

where $\{a\}$ is the fractional part of the number $a$. Moreover, the following upper bound for the quadrature formulae was given in [23, Sect. 3.1.3]:

$$\sup_{f \in H_2^r} \left| \int\limits_{[0,1]^2} f(x_1, x_2)\, dx_1 dx_2 = \frac{1}{A} \sum_{k=1}^{A} f\left(\frac{k}{A}, \left\{\frac{b}{A} k\right\}\right) \right| \leqslant C \frac{1 + \ln A}{A^r},$$

where $r > 1$, $A$ and $b$, $1 < b < A$, are mutually prime integer numbers and the function $f(x_1, x_2)$ belongs to the class $H_2^r$ if in the unit cube $\bar{I}^s$ it possesses continuous derivatives of the form

$$\frac{\partial^k}{\partial x_1^{k_1} \dots \partial x_s^{k_s}} \quad (0 \leqslant k \leqslant rs,\ 0 \leqslant k_\nu \leqslant r).$$

We shall also make use a theorem on asymptotic behavior of the functions on such estimates.

**Theorem 3.4.** [24, Th. 2.5.2] *(Delta method). 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 there exists a continuous non-zero derivative $g'(\theta)$ of the function $g(\theta)$.*

## 4. Main results

**4.1. NBR-estimates. Asymptotic behavior.** Let we be given a sample $\mathcal{Z}^{(n)} = \{(z_i, u_i), i = 1, 2, \dots, n\}$, where $z_i$ has a negative binomial regression $NB(m, F(u_i))$, and a sequence $u_i$, $i = 1, 2, \dots, n$, be a van der Corput one. We define a statistics

$$T_n(x) = \frac{\sum_{i=1}^{n} m\eta_i(x)}{\sum_{i=1}^{n} z_i\eta_i(x)}, \qquad \eta_i(x) = K_h(u_i - x).$$

Since $\frac{1}{n}\sum_{i=1}^{n} \eta_i(x) \to 1$ as $n \to \infty$, we consider an estimate

$$\hat{F}_n(x) = \frac{m}{\frac{1}{n}\sum_{i=1}^{n} z_i\eta_i(x)}. \tag{4.1}$$

We denote

$$S_1 = \frac{1}{n}\sum_{i=1}^{n} z_i\eta_i(x), \qquad \nu_j(K) = \int_{-1}^{1} t^j K(t)\,dt, j \in \mathbf{N}.$$

**Theorem 4.1.** *Let $\hat{F}_n(x)$ be an estimate for the distribution function $F(x)$ defined by formula (4.1) and $\{u_i, i = 1, 2, \dots, n\}$ be a van der Corput sequence and the regularity conditions be satisfied. Then*

$$\sqrt{nh}(F_n(x) - \boldsymbol{E}(F_n(x)) \xrightarrow[n\to\infty]{d} N\left(0, \frac{(1 - F(x))F^2(x)}{m}\| K \|^2\right).$$

*Proof.* It follows from [25, Lm. 3.4] that $\bigvee(K_h) = O(h^{-1})$ and this is why as $n \to \infty$ we have

$$\begin{aligned}
\mathbf{E}(S_1) = \mathbf{E}\left(\frac{1}{nh}\sum_{i=1}^{n} Z_i K\left(\frac{u_i - x}{h}\right)\right) &= \frac{1}{nh}\sum_{i=1}^{n} K\left(\frac{u_i - x}{h}\right)\mathbf{E}(Z_i) = \frac{1}{nh}\sum_{i=1}^{n} K\left(\frac{u_i - x}{h}\right)\frac{m}{F(u_i)} \\
&= m \cdot \frac{1}{h}\int_{-\infty}^{\infty} \frac{1}{F(u)} K\left(\frac{u - x}{h}\right) du + O\left(\frac{\ln n}{nh}\right) \\
&= m \int_{-x/h}^{(1-x)/h} \frac{K(t)}{F(x + ht)}\,dt + O\left(\frac{1}{n}\right) \\
&= m \int_{-\infty}^{\infty} \frac{K(t)}{F(x + ht)}\,dt + O\left(\frac{\ln n}{nh}\right) \\
&= m \int_{-\infty}^{\infty} \left(\frac{K(t)}{F(x)} + K(t)\left(\frac{1}{F(x + ht)} - \frac{1}{F(x)}\right)\right) dt + O\left(\frac{\ln n}{nh}\right) \\
&= \frac{m}{F(x)} + m\int_{-\infty}^{\infty} \frac{F(x) - F(x + ht)}{F(x)F(x + ht)} K(t)\,dt + O\left(\frac{\ln n}{nh}\right).
\end{aligned}$$

Now

$$\gamma_n = \int_{-\infty}^{\infty} \frac{F(x+ht)-F(x)}{F(x)F(x+ht)} K(t)\,dt$$
$$= \int_{-\infty}^{\infty} \frac{f(x)ht + (1/2)f'(x)h^2t^2 + (1/6)f''(x)h^3t^3 + (1/24)f'''(\zeta)h^4t^4}{F(x)F(x+ht)} K(t)\,dt,$$

where $\zeta$ is some «mean» point. Since

$$\left| h^4 \int_{-1}^{1} \frac{f'''(\zeta)}{F(x)F(x+ht)} h^4 t^4 K(t)\,dt \right| \leqslant h^4 \nu_4(K) \sup_{-1\leqslant t\leqslant 1} \frac{f'''(\zeta)}{F(x)F(x+ht)}$$
$$\leqslant \frac{2C_3 h^4}{F(x)(F(x)-\varepsilon)} \quad \text{for} \quad n \geqslant n_1,$$

then

$$\gamma_n = \frac{1}{F^2(x)} \int_{-\infty}^{\infty} \frac{f(x)ht + (1/2)f'(x)h^2t^2}{(1+(f(x)/F(x))ht) + O(h^2))} K(t)dt + O(h^4)$$
$$= \frac{1}{F^2(x)} \int_{-\infty}^{\infty} \left( f(x)ht + \frac{1}{2} f'(x)h^2t^2 - \frac{f^2(x)}{F(x)} h^2t^2 - \frac{1}{2}\frac{f'(x)f(x)}{F(x)} h^3t^3 \right) K(t)dt + O(h^3)$$
$$= \frac{1}{F^2(x)} \int_{-\infty}^{\infty} \left( f(x)ht + \frac{1}{2} f'(x)h^2t^2 - \frac{f^2(x)}{F(x)} h^2t^2 \right) K(t)dt + o(h^2)$$
$$= \left( \frac{1}{2}\frac{f'(x)}{F^2(x)} - \frac{f^2(x)}{F^3(x)} \right) h^2 \nu_2(K) + o(h^2),$$

therefore

$$\mathbf{E}(S_1) = \frac{m}{F(x)} - m \left( \frac{1}{2}\frac{f'(x)}{F^2(x)} - \frac{f^2(x)}{F^3(x)} \right) h^2 \nu_2(K) + o(h^2), \qquad \nu_2(K) = \int_{-\infty}^{\infty} t^2 K(t)\,dt.$$

We consider the dispersion of statistics $S_1$. We have

$$\mathbf{D}(S_1) = \mathbf{D}\left( \frac{1}{nh} \sum_{i=1}^{n} Z_i K\left(\frac{u_i - x}{h}\right) \right) = \frac{1}{n^2h^2} \sum_{i=1}^{n} K^2\left(\frac{u_i - x}{h}\right) \mathbf{D}(Z_i)$$
$$= \frac{1}{n^2h^2} \sum_{i=1}^{n} K^2\left(\frac{u_i - x}{h}\right) \frac{m(1-F(u_i))}{F^2(u_i)}$$
$$\sim \frac{m}{nh^2} \int_{-\infty}^{\infty} \frac{1-F(u)}{F^2(u)} K^2\left(\frac{u-x}{h}\right) du$$
$$= \frac{m}{nh} \int_{-\infty}^{\infty} \frac{1-F(x+ht)}{F^2(x+ht)} K^2(t)\,dt$$
$$\sim \frac{m(1-F(x))}{nh\,F^2(x)} \| K \|^2.$$

To prove the asymptotic normality of the $S_1$ statistics, we check the *Lyapunov condition*, for which we need the following inequality for $a > 1$:

$$|\, x + y \,|^a \leqslant 2^{a-1}(\,|\, x \,|^a + |\, y \,|^a), \tag{4.2}$$

which is implied by the convexity of the function $|\,x\,|^a$ as $a > 1$ and hence

$$\left|\frac{x+y}{2}\right|^a \leqslant \frac{|\,x\,|^a + |\,y\,|^a}{2}.$$

Let

$$\xi_j = \frac{1}{nh} Z_j K\left(\frac{u_i - x}{h}\right).$$

Then $S_1 = \sum\limits_{j=1}^{n} \xi_j$. Employing inequality (4.2) as $a = 4$, we find:

$$|\,\xi_j - \mathbf{E}(\xi_j)\,|^4 \leqslant 8(|\,\xi_j\,|^4 + |\,\mathbf{E}(\xi_j)\,|^4).$$

Calculating the expectation of both sides, we obtain:

$$\mathbf{E}((\xi_j - \mathbf{E}(\xi_j))^4) \leqslant 8(\mathbf{E}(\xi_j^4) + (\mathbf{E}(\xi_j))^4 \leqslant 16\mathbf{E}(\xi_j^4).$$

We consider $A_n = \sum\limits_{j=1}^{n} \mathbf{E}(\xi_j^4)$. We have:

$$A_n = \frac{1}{n^4h^4} \sum_{j=1}^{n} \mathbf{E}(Z_j^4) K^4\left(\frac{u_j - x}{h}\right).$$

We observe that a random variable $Z$ has a negative binomial distribution with the parameters $m$ and $p = 1 - q$, then its characteristic function is

$$\varphi(t) = \left(\frac{p \cdot \exp(it)}{1 - q \cdot \exp(it)}\right)^m,$$

the dispersion equals $\mathbf{D}(Z) = mq/p^2$, and the fourth initial moment reads as

$$\mathbf{E}(Z^4) = b_4 \frac{q^4}{p^4} + b_3 \frac{q^3}{p^3} + b_2 \frac{q^2}{p^2} + b_1 \frac{q}{p},$$

where

$$b_4 = m(m^3 + 6m^2 + 11m + 6), \quad b_3 = 6m(m^2 + 3m + 2), \quad b_2 = 7m(m+1), \quad b_1 = m.$$

In view of the above remarks we get that

$$A_n \sim \frac{1}{n^4h^4} \sum_{j=1}^{n} \left(b_4 \frac{(1 - F(u_j))^4}{F^4(u_j)} + b_3 \frac{(1 - F(u_j))^3}{F^3(u_j)} + b_2 \frac{(1 - F(u_j))^2}{F^2(u_j)} + b_1 \frac{1 - F(u_j)}{F(u_j)}\right) K^4\left(\frac{u_j - x}{h}\right)$$

$$\sim \frac{1}{n^3h^3}\left(b_4 \frac{(1 - F(x))^4}{F^4(x)} + b_3 \frac{(1 - F(x))^3}{F^3(x)} + b_2 \frac{(1 - F(x))^2}{F^2(x)} + b_1 \frac{1 - F(x)}{F(x)}\right) \int_{-\infty}^{\infty} K^4(t)\,dt = \frac{C_1}{n^3h^3},$$

where $C_1$ is an universal constant. Hence, for the Lyapunov quotient,

$$L_n = \frac{\sum_{j=1}^{n} \mathbf{E}((\xi_j - \mathbf{E}(\xi_j))^4)}{(\sum_{j=1}^{n} \mathbf{D}(\xi_j))^2} \leqslant \frac{C_1 n^2 h^2}{C_2 n^3 h^3} = \frac{C}{nh} \underset{n\to\infty}{\longrightarrow} 0,$$

that is, the assumption of the Lyapunov central limit theorem [26] is satisfied and

$$\frac{S_1 - \mathbf{E}(S_1)}{\sqrt{\mathbf{D}(S_1)}} \xrightarrow[n\to\infty]{d} N(0,1).$$

In other words,

$$\sqrt{nh}\left(S_1 - \frac{m}{F(x)}\right) \xrightarrow[n\to\infty]{d} N\left(m\left(\frac{f^2(x)}{F^3(x)} - \frac{1}{2}\frac{f'(x)}{F^2(x)}\right)\nu_2(K), \frac{m(1 - F(x))}{F^2(x)} \|\,K\,\|^2\right).$$

Now we consider an asymptotic behavior of the statistics $T = \dfrac{m}{S_1}$:

$$T = T_n(x) = \frac{\frac{1}{nh}\sum_{i=1}^n m\eta_i(x)}{\frac{1}{nh}\sum_{i=1}^n z_i\eta_i(x)} \sim \frac{m}{\frac{1}{nh}\sum_{i=1}^n z_i\eta_i(x)} = \frac{m}{S_{1n}(x)} = \frac{m}{S_1}.$$

Here the quantities $z_i$ has a negative binomial distribution with corresponding parameters. This is why, employing the delta method, we obtain:

$$g(x) = \frac{m}{x}, \quad g'(x) = -\frac{m}{x^2}, \quad g'\left(\frac{m}{F(x)}\right) = -\frac{F^2(x)}{m}, \quad \left(g'\left(\frac{m}{F(x)}\right)\right)^2 = \frac{F^4(x)}{m^2}.$$

The estimate $F_n(x) = \dfrac{m}{S_1}$ satisifies $F_n(n) \xrightarrow[n\to\infty]{p} F(x)$ and this is why

$$g(\theta_n) = g(\theta_0) + (\theta_n - \theta_0)g'(\theta_0) + O((\theta_n - \theta_0)^2) \Rightarrow g(\theta_n) - g(\theta_0) = (\theta_n - \theta_0)g'(\theta_0),$$

$$\sqrt{nh}(g(\theta_n) - g(\theta_0)) \sim \sqrt{nh}(\theta_n - \theta_0)g'(\theta_0) \sim N\left(a, (g'(\theta_0))^2 m\| K \|^2 \frac{1 - F(x)}{F^2(x)}\right).$$

But

$$(g'(\theta_0))^2 m\| K \|^2 \frac{1 - F(x)}{F^2(x)} = m\| K \|^2 \frac{1 - F(x)}{F^2(x)} \cdot \frac{F^4(x)}{m^2} = \frac{(1 - F(x))F^2(x)}{m}\| K \|^2,$$

and this implies

$$\sqrt{nh}(F_n(x) - \mathbf{E}(F_n(x))) \xrightarrow[n\to\infty]{d} N\left(0, \frac{(1 - F(x))F^2(x)}{m}\| K \|^2\right).$$

The proof is complete. □

**Remark 4.1.** *In the estimate $\hat{F}_n(x)$, instead of the statistics $S_1$, one can employ statistics* [27]

$$S_1^{PC}(x) = \sum_{i=1}^{n-1}(u_{i+1} - u_i)z_i\eta_i(x),$$

*which is also asymptotically normal with the same parameters as $S_1$.*

**Remark 4.2.** *Since the limiting dispersion of the estimate $\hat{F}_n(x)$ depends on an unknown distribution function $F(x)$, in order to estimate, one can use the statistics*

$$\hat{\sigma}^2(x) = \frac{m^2}{2n}\sum_{i=1}^{n-1}\frac{(z_{i+1} - z_i)^2}{S_1^4(x)}K_h(u_{i+1} - x)K_h(u_i - x),$$

*which is a consistent estimate of a function*

$$\frac{m(1 - F(x))}{F^2(x)}\| K \|^2.$$

**Remark 4.3.** *On the base of an unbiased estimate for the parameter $p$*

$$\hat{p} = \frac{m - 1}{m + z - 1}$$

*of the negative binomial distribution $NB(m,p)$* [28, Sect. 5.8.2] *we propose one more estimate for the distribution function $F(x)$ of form ($m \geqslant 2$)*

$$\hat{F}_n(x) = \frac{1}{nh}\sum_{i=1}^n \frac{m - 1}{m + z_i - 1}K\left(\frac{u_i - x}{h}\right).$$

The estimate $\hat{p}$ is an unbiased one and the Cramer-Rao lower bound for its dispersion reads as

$$\mathbf{D}(\hat{p}) \geqslant \frac{p^2 q}{m}.$$

We first find the second initial moment and then its dispersion. By the definition,

$$\mathbf{E}(\hat{p}^2) = \sum_{k=0}^{\infty} \frac{(m-1)^2}{(m+k-1)^2} \frac{\Gamma(m+k)}{k!\,\Gamma(m)} p^m q^k = p^m \sum_{k=0}^{\infty} \frac{m-1}{m+k-1} \frac{\Gamma(m+k-1)}{k!\,\Gamma(m-1)} q^k$$
$$= p^m {}_2F_1(m-1, m-1; m; q)$$
$$= (m-1)p^m \int_0^1 \frac{t^{m-1}}{(1-tq)^{m-1}\,dt},$$

where ${}_2F_1(a,b;c;x)$ is the Gauss hypergeometric function.

In this case

$$\mathbf{D}(\hat{p}) = p^m\, {}_2F_1(m-1, m-1; m; q) - p^2.$$

If $m = 2$, then

$$\mathbf{D}(\hat{p}) = -p^2 \left(1 + \frac{\ln p}{q}\right) \geqslant \frac{p^2 q}{2}$$

and for small values of $q$ the left and the right hand sides are close. The limiting dispersion of the estimate $\hat{F}_n(x)$ is equal to

$$\sigma^2 = -F^2(x) \left(1 + \frac{\ln F(x)}{1 - F(x)}\right).$$

If $m = 3$, then

$$\sigma_3^2 = \mathbf{D}(\hat{p}) = p^2 \left(\frac{2p \ln p}{q^2} + \frac{1+p}{q}\right) \geqslant \sigma_0^2 = \frac{p^2 q}{3}$$

since

$${}_2F_1(2, 2; 3; x) = \frac{2\ln(1-x)}{x^2} + \frac{2}{x(1-x)}$$

and for small values of $q$ the left and right hand sides, that is, $\sigma_3^2$ and $\sigma_0^2$, are also close. We observe that

$$\mathbf{E}(\hat{p}^2) = \frac{(m-1)p^m}{q^{m-1}} \left[(-1)^{m-1} \ln p + \sum_{k=1}^{m-2} \frac{(-1)m-k}{k} \left(\frac{q}{p}\right)\right].$$

This relation was obtained first in work [29].

One can also construct a kernel estimate for the distribution function starting from the estimate of the maximal likelihood, which is equal to

$$\tilde{p} = \frac{m}{m+z}.$$

In this case

$$\mathbf{E}(\tilde{p}) = \sum_{k=0}^{\infty} \frac{m}{m+k} \cdot \frac{\Gamma(m+k)}{k!\,\Gamma(m)} p^m q^k = p^m {}_2F_1(m, m; m+1; q),$$

and, [30, Sect. 5.2.11, Eq. (15)],

$$\mathbf{E}(\tilde{p}^2) = \sum_{k=0}^{\infty} \frac{m^2}{(m+k)^2} \cdot \frac{\Gamma(m+k)}{k!\,\Gamma(m)} p^m q^k = m^2 p^m \int_0^{\infty} t e^{-mt} (1 - qe^{-t})^{-m}\,dt.$$

In particular, for $m = 1$ we have

$$\mathbf{E}(\tilde{p}) = -\frac{p \ln p}{q}, \qquad \mathbf{E}(\tilde{p}^2) = \frac{p}{q}\,\mathrm{dilog}(p).$$

As $m = 2$, we have:

$$\mathbf{E}(\tilde{p}) = \frac{2p}{q}(q + p\ln p), \quad \mathbf{E}(\tilde{p}^2) = -\frac{4p^2}{q^2}(\ln p + \operatorname{dilog}(p)), \quad \text{where} \quad \operatorname{dilog}(x) = \int\limits_1^x \frac{\ln t}{1-t}\,dt.$$

In view of this we see that the maximal likelihood estimate $\tilde{p}$ is not a consistent estimate for the parameter $p$ and this is why for $m = 2$, as a consistent estimate, we can propose the statistics

$$\hat{\theta} = \frac{m}{2(m+z)} \frac{1-\hat{p}}{1+\hat{p}(\ln\hat{p} - 1)},$$

but this estimate has a greater risk than estimate (4.1).

**4.2. Quantile estimation.** In this section we study asymptotic behavior of the quantiles estiomator in the dose-effect dependence by the fixed plans of experiments in the model of negative binomial regression.

We define an quantile estimator for $\xi_\lambda$ of order $0 < \lambda < 1$ as follows:

$$\hat{\xi}_{n\lambda} = \inf\{x \in \mathbf{R} : \ \hat{F}_n(x) \geqslant \lambda\}. \tag{4.3}$$

We let

$$a = \frac{(\lambda f'(\xi_\lambda) - 2f^2(\xi_\lambda))\nu_2(K)}{2\lambda\sigma}.$$

In the next theorem an asymptotic normality of the estimates $\hat{\xi}_{n\lambda}$ is shown.

**Theorem 4.2.** *Let $\hat{\xi}_{n\lambda}$ be the quantile estimator of order $0 < \lambda < 1$ defined by formula (4.3), $\{u_i, i = 1, 2, \dots, n\}$ be a van der Corput seuqence, the regularity conditions be satisfied and $f(\xi_\lambda) > 0$. Then*

$$\sqrt{nh}(\hat{\xi}_{n\lambda} - \xi_\lambda - ah^2) \underset{n\to\infty}{\overset{d}{\to}} N\left(0, \frac{\lambda^2(1-\lambda)\ \|K\|^2}{mf^2(\xi_\lambda)}\right).$$

*Proof.* Let

$$\sigma^2 = \frac{(1-\lambda)\lambda^2}{m}\| K \|^2, \qquad \delta = \delta(x) = \xi_\lambda + \frac{x\sigma}{\sqrt{nh}f(\xi_\lambda)}.$$

We have:

$$\begin{aligned}
\mathbf{P}\left(\frac{\sqrt{nh}f(\xi_\lambda))(\hat{\xi}_{n,\lambda} - \xi_\lambda)}{\sigma} \leqslant x\right) =& \mathbf{P}(\hat{\xi}_{n,\lambda} \leqslant \delta) = \mathbf{P}(F_n(\delta) \geqslant \lambda) = \mathbf{P}\left(\frac{m}{\frac{1}{n}\sum_{i=1}^n z_i\eta_i(\delta)} \geqslant \lambda\right) \\
=& \mathbf{P}\left(\frac{1}{n}\sum_{i=1}^n Z_iK_h(u_i - \delta) \leqslant \frac{m}{\lambda}\right) \\
=& \mathbf{P}\left(\frac{1}{n}\sum_{i=1}^n (Z_iK_h(u_i - \delta) - \theta_i) \leqslant \frac{1}{n}\sum_{i=1}^n \left(\frac{m}{\lambda} - \theta_i\right)\right) \\
=& \mathbf{P}\left(\frac{\sqrt{nh}\,\lambda^2}{m\sigma n}\sum_{i=1}^n (Z_iK_h(u_i - \delta) - \theta_i) \leqslant \frac{\sqrt{nh}\,\lambda^2}{m\sigma} \cdot \frac{1}{n}\sum_{i=1}^n \left(\frac{m}{\lambda} - \theta_i\right)\right),
\end{aligned}$$

where

$$\theta_i = \mathbf{E}\left(Z_iK_h(u_i - \delta)\right) = \frac{m}{F(u_i)}K_h(u_i - \delta).$$

We note that $h^2 = 1/\sqrt{nh}$ and the function $K_h(u - \delta)$ vanishes outside the segment

$$\mathcal{J}_\lambda = [\xi_\lambda - h + xh^2\sigma/f(\xi_\lambda), \xi_\lambda + h + xh^2\sigma/f(\xi_\lambda)].$$

Moreover, the function $1/F(u) > 0$ decays monotonically on $\mathcal{J}_\lambda$, $\{u_i, i = 1, 2, \dots, n\}$ is a van der Corput sequence and this is why $\bigvee_{\mathcal{J}_\lambda}(1/F(u)) < \infty$ and it follows from [16] that

$$\alpha_n = \frac{1}{n}\sum_{i=1}^n \theta_i = \frac{1}{n}\sum_{i=1}^n \frac{m}{F(u_i)}K_h(u_i - \delta) = \int\limits_{\mathcal{J}_\lambda} \frac{m}{F(u)}K_h(u - \delta)\,du + O\left(\frac{\ln n}{\sqrt{nh}}\right).$$

Making the change

$$t = \frac{u-\delta}{h}$$

and taking into consideration that $0 \leqslant u \leqslant 1$, we conclude that

$$\alpha_n = \int\limits_0^1 \frac{m}{F(u)} K_h(u-\delta)\,du = \int\limits_{-\delta/h}^{(1-\delta)/h} \frac{m}{F(\xi_\lambda+\rho_1 h)}\,K(t)\,dt\,,$$

where

$$\rho_1 = t + \frac{x\sigma}{f(\xi_\lambda)} h$$

and for sufficiently large $n$, $n \geqslant n_1$,

$$\alpha_n = \int\limits_{-1}^{1} \frac{m}{F(\xi_\lambda+\rho_1 h)}\,K(t)\,dt\,.$$

Let $|\,x\,| \leqslant L$, where $L$ is large enough and $\omega_1 = \omega/\lambda$. Then

$$F(\xi_\lambda+\rho_1 h) = \lambda + f(\xi_\lambda)\rho_1 h + \frac{f'(\xi_\lambda)}{2}\rho_1^2 h^2 + \omega h^3 = \lambda(1 + a_1 h + b_1 h^2 + \omega_1 h^3),$$

where

$$a_1 = \frac{f(\xi_\lambda)}{\lambda} t, \qquad b_1 = \frac{2x\sigma + t^2 f'(\xi_\lambda)}{2\lambda}\,,$$

and it follows from the assumptions of the theorem that $|\,\omega_1\,|$ is bounded. Since

$$\left| \frac{1}{1 + a_1 h + b_1 h^2 + \omega_1 h^3} - 1 + a_1 h - (a_1^2 - b_1)h^2 \right|$$
$$= \left| \frac{((b_1 - a_1^2)\omega_1 h^2 + (a_1\omega_1 + b_1^2 - a_1^2 b_1)h + 2a_1 b_1 - \omega_1 - a_1^3}{1 + a_1 h + b_1 h^2 + \omega_1 h^3} \right| h^3 \leqslant C_2 h^3$$

and for $n \geqslant n_2$ and

$$\int\limits_{-1}^{1} tK(t)\,dt = 0,$$

we obtain that

$$\alpha_n = \frac{m}{\lambda} - \frac{m\sigma}{\lambda^2}\left(x + \frac{(\lambda f'(\xi_\lambda) - 2f^2(\xi_\lambda))\nu_2(K)}{2\lambda\sigma}\right) h^2 + o(h^2).$$

This implies that the sequence

$$\frac{\lambda^2}{m\sigma h^2}\cdot\left(\alpha_n - \frac{m}{\lambda}\right) + \left(x + \frac{(\lambda f'(\xi_\lambda) - 2f^2(\xi_\lambda))\nu_2(K)}{2\lambda\sigma}\right)$$

converges to zero uniformly in $|\,x\,| \leqslant L$ as $n \to \infty$, where $L > 0$ is chosen to be large enough.

Let

$$\Sigma_n(x) = \frac{1}{n}\sum_{i=1}^{n} \left(Z_i K_h(u_i - \delta) - \theta_i\right).$$

We are going to show that

$$\frac{\sqrt{nh}\lambda^2}{m\sigma}\cdot\Sigma_n(x) \xrightarrow[n\to\infty]{d} N(0,1).$$

In order to do this, we consider the dispersion of the quantity $\Sigma_n(x)$:

$$\mathbf{D}(\Sigma_n(x)) = \frac{1}{n^2}\sum_{i=1}^{n}\mathbf{D}\left(Z_i K_h(u_i-\delta)\right) = \frac{1}{n^2}\sum_{i=1}^{n} K_h^2(u_i-\delta)\mathbf{D}(Z_i)$$

$$
\begin{aligned}
&= \frac{1}{n^2h^2}\sum_{i=1}^{n} K^2\left(\frac{u_i-\delta}{h}\right)\frac{m(1-F(u_i)))}{F^2(u_i)} \\
&= \frac{1}{nh^2}\int_0^1 \frac{m(1-F(u))}{F^2(u)}K^2\left(\frac{u-\delta}{h}\right)du\,(1+o(1)) \\
&\sim \frac{m(1-\lambda)}{nh\lambda^2}\| K \|^2
\end{aligned}
$$

uniformly in $|\,x\,| \leqslant L$ in the latter relation. This yields:

$$\lim_{n\to\infty} \mathbf{D}\left(\frac{\lambda^2\sqrt{nh}}{m\sigma}\Sigma_n(x)\right) = 1\,.$$

The Lyapunov conditions can be checked as in the proof of Theorem 4.1. Thus, the assumptions of the Lyapunov central theorem are satisfied [26, Sect. 40] and this is why, for $|\,x\,| \leqslant L$,

$$\frac{\lambda^2\sqrt{nh}}{m\sigma}\Sigma_n(x) \xrightarrow[n\to\infty]{d} N(0,1).$$

It remains to show that for each $\varepsilon > 0$ we can choose $L > 0$ and $n \geqslant n_0$ so that

$$\beta_n = \mathbf{P}\left(\frac{\sqrt{nh}f(\xi_\lambda))|\,\hat{\xi}_{n,\lambda}-\xi_\lambda\,|}{\sigma} > L\right) < \varepsilon.$$

Since $\beta_n \leqslant \beta_{1n} + \beta_{2n}$, where

$$\beta_{1n} = \mathbf{P}\left(\frac{\sqrt{nh}f(\xi_\lambda))(\hat{\xi}_{n,\lambda}-\xi_\lambda)}{\sigma} > L\right), \quad \beta_{2n} = \mathbf{P}\left(\frac{\sqrt{nh}f(\xi_\lambda))(\hat{\xi}_{n,\lambda}-\xi_\lambda)}{\sigma} < -L\right),$$

we consider the first term. Arguing as above, we obtain:

$$
\begin{aligned}
\beta_{1n} = \mathbf{P}\Bigg(\frac{\sqrt{nh}\,\lambda^2}{m\sigma}\cdot\frac{1}{n}\sum_{i=1}^{n}(Z_iK_h(u_i-\delta(L))-\theta_i) >& \frac{\sqrt{nh}\,\lambda^2}{m\sigma}\cdot\frac{1}{n}\sum_{i=1}^{n}\left(\frac{m}{\lambda}-\theta_i\right)\Bigg) \\
=& \mathbf{P}\left(\frac{\lambda^2}{m\sigma h^2}\Sigma_n(L) > L+a\right) + o(1).
\end{aligned}
$$

We let $x = L + a$ and $\psi(x) = e^{tx}, t \geqslant 0$. Then

$$\mathbf{P}\left(\frac{\lambda^2}{m\sigma h^2}\Sigma_n(L) > x\right) \leqslant \mathbf{P}\left(\psi\left(\frac{\lambda^2}{m\sigma h^2}\Sigma_n(L)\right) > \psi(x)\right) \leqslant \frac{\mathbf{E}(\psi(\Sigma_n(L)))}{\psi(x)}.$$

This is why

$$\overline{\lim_{n\to\infty}}\ln\mathbf{P}\left(\frac{\lambda^2}{m\sigma h^2}\Sigma_n(L) > x\right) \leqslant -tx + \phi(t),$$

where

$$\phi(t) = \lim_{n\to\infty}\ln\mathbf{E}\left(\exp\left(\frac{t\lambda^2}{m\sigma h^2}\Sigma_n(L)\right)\right) = \frac{t^2}{2}.$$

Since the minimum of the function $-tx + \phi(t)$ is attained at $t = x$ and is equal $-x^2/2$, then the Gärtner-Ellis theorem [31] implies

$$\lim_{n\to\infty}\beta_{1n} \leqslant \exp(-(L+a)^2/2).$$

We choose $L$ so that for a given $\varepsilon > 0$ we have $\exp(-(L+a)^2/2) < \varepsilon/2$. In the same way we study the second term and this is why for a chosen $L$ we obtain $\lim\limits_{n\to\infty}\beta_n < \varepsilon$. This gives the statement of the theorem and completes the proof. □

**4.3. Multi-dimensional case.** In this section we study asymptotic behavior of the estimates for a two-dimensional distribution function in the dose-effect dependence by the fixed plans of experiments in the model of negative binomial regression; we restrict ourselves by the two-dimensional case only.

We denote

$$F_{ij} = \frac{\partial^2}{\partial x_i \partial x_j} F(x_1, x_2), \qquad F_i = \frac{\partial}{\partial x_i} F(x_1, x_2), \qquad \nabla_F^T = (F_1, F_2),$$

$$\mathcal{H}_F = \begin{pmatrix} F_{11} & F_{12} \\ F_{12} & F_{22} \end{pmatrix}, \qquad \mathbf{H} = \begin{pmatrix} h_1 & 0 \\ 0 & h_2 \end{pmatrix}, \qquad \mathbf{J}^T = (1,1), \qquad \mathbf{h} = \mathbf{HJ} = \begin{pmatrix} h_1 \\ h_2 \end{pmatrix}.$$

Let $\mathcal{K}(\boldsymbol{x}) = \mathcal{K}(x_1, x_2)$ be a symmetric compactly supported square integrable distribution density such that

$$\int \boldsymbol{x}\boldsymbol{x}^T \mathcal{K}(\boldsymbol{x})\, d\boldsymbol{x} = \nu_2(\mathcal{K})\mathbf{I}_s,$$

where $\nu_2(\mathcal{K})$ is a real number and $\mathbf{I}_2$ is the unit matrix of the second order,

$$\mathcal{K}_{\mathbf{H}}(\boldsymbol{x}) = |\,\mathbf{H}\,|^{-1}\mathcal{K}(\mathbf{H}^{-1}\boldsymbol{x}), \quad N = n_1 n_2,$$

$$\mathbf{S}_1 = \mathbf{S}_1(\boldsymbol{x}) = \frac{1}{|\,\mathbf{H}\,|N} \sum_{i=1}^{n_1}\sum_{j=1}^{n_2} Z_{ij}\mathcal{K}_{\mathbf{H}}(\boldsymbol{U}_{ij} - \boldsymbol{x}), \quad \hat{F}_N(\boldsymbol{x}) = \frac{m}{\mathbf{S}_1}. \tag{4.4}$$

**Theorem 4.3.** *Let $\hat{F}_N(\boldsymbol{x})$ be the estimate for the distribution function $F(\boldsymbol{x})$ defined by formula (4.4), $\{\boldsymbol{u}_{ij}, i = 1, 2, \ldots, n_1; j = 1, 2, \ldots, n_2;\}$ be a Halton sequence and the regularity conditions are satisfied. Then as $N \to \infty$,*

$$(i) \quad \boldsymbol{E}(\boldsymbol{S}_1(\boldsymbol{x})) = \frac{m}{F(\boldsymbol{x})} + \frac{m}{2F^3(\boldsymbol{x})}(2\nabla_F^T \boldsymbol{h}\boldsymbol{h}^T \nabla_F - \nu_2(\mathcal{K})\boldsymbol{h}\mathcal{H}_F\boldsymbol{h}^T)(1 + o(1));$$

$$(ii) \quad \boldsymbol{D}(\boldsymbol{S}_1(\boldsymbol{x})) = \frac{m(1 - F(\boldsymbol{x}))}{N\,|\,\boldsymbol{H}|F^2(\boldsymbol{x})} \|\,\mathcal{K}\,\|^2 (1 + o(1));$$

$$(iii) \quad \sqrt{N\,|\,\boldsymbol{H}|}(\hat{F}_N(\boldsymbol{x}) - \boldsymbol{E}(F_n(N)) \xrightarrow[n\to\infty]{d} N\left(0, \frac{(1 - F(\boldsymbol{x}))F^2(\boldsymbol{x})}{m} \|\,\mathcal{K}\,\|^2\right).$$

*Proof.* The proof follows the lines of the one-dimensional case and this is why we only mention the differences. We expand the function $F(\mathbf{x} + \mathbf{Ht})$, where $\mathbf{t}^T = (t_1, t_2)$, into the Taylor series:

$$F(\mathbf{x} + \mathbf{Ht}) = F(x_1 + t_1h_1, x_2 + t_2h_2) = F(x_1, x_2) + \left[t_1h_1\frac{\partial}{\partial x_1} + t_1h_1\frac{\partial}{\partial x_2}\right] F(x_1, x_2)$$
$$+ \frac{1}{2}\left[t_1h_1\frac{\partial}{\partial x_1} + t_1h_1\frac{\partial}{\partial x_2}\right]^2 F(x_1, x_2) + o(|\,\mathbf{H}\,|)\,.$$

Then

$$\frac{1}{1 + a_1h_1 + a_2h_2 + \frac{1}{2}(b_{11}h_1^2 + 2b_{12}h_1h_2 + b_{22}h_2^2)} = 1 - a_1h_1 - a_2h_2 + \frac{1}{2}\Big((2a_1^2 - b_{11})h_1^2$$
$$+ (4a_1a_2 - b_{12})h_1h_2 + (2a_2^2 - b_{22})h_2^2\Big) + \ldots$$
$$= \frac{1}{F(x_1, x_2)} - \frac{\left[t_1h_1\frac{\partial}{\partial x_1} + t_1h_1\frac{\partial}{\partial x_2}\right] F^2(x_1, x_2)}{F(x_1, x_2)}$$
$$+ \frac{\left(\left[t_1h_1\frac{\partial}{\partial x_1} + t_1h_1\frac{\partial}{\partial x_2}\right] F(x_1, x_2)\right)^2}{F^3(x_1, x_2)}$$
$$- \frac{1}{2}\frac{\left[t_1h_1\frac{\partial}{\partial x_1} + t_1h_1\frac{\partial}{\partial x_2}\right]^2 F(x_1, x_2)}{F^2(x_1, x_2)} + \ldots$$

This yields:

$$\mathbf{E}(S_1) = \frac{m}{F(x_1,x_2)} + m\left(\frac{\left(\left[t_1h_1\frac{\partial}{\partial x_1} + t_1h_1\frac{\partial}{\partial x_2}\right]F(x_1,x_2)\right)^2}{F^3(x_1,x_2)} - \frac{\nu_2(\mathcal{K})}{2}\frac{\left[t_1h_1\frac{\partial}{\partial x_1} + t_1h_1\frac{\partial}{\partial x_2}\right]^2 F(x_1,x_2)}{F^2(x_1,x_2)}\right)$$
$$= \frac{m}{F(\boldsymbol{x})} + \frac{m}{2F^3(\boldsymbol{x})}\left(2\nabla_F^T\mathbf{h}\mathbf{h}^T\nabla_F - \nu_2(\mathcal{K})F(\boldsymbol{x})\mathbf{h}^T\mathcal{H}_F\mathbf{h}\right)(1+o(1)).$$

In the same way,

$$\mathbf{D}(S_1) \sim \frac{m(1-F(\boldsymbol{x}))}{n|\,\mathbf{H}\,|F^2(\boldsymbol{x})}\|\,\mathcal{K}\,\|^2.$$

The Lyapunov conditions are confirmed as in the one-dimensional case and this gives Statement (iii) of the theorem. The proof is complete. □

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