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M. S. T i k h o v (Nizhny Novgorod, NNGU). **Negative λ-binomial regression in dose-effect relationships.**

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Резюме: В сообщении используется случайная величина, имеющая отрицательное λ-биномиальное распределение. Мы строим ядерные оценки функции распределения в модели отрицательной λ-биномиальной регрессии с одномерными ковариатами. Исследуется асимптотическое поведение построенных оценок функции распределения и их квантилей.

Ключевые слова: Отрицательная λ-биномиальная регрессия, зависимость доза-эффект, непараметрические ядерные оценки.

The report discusses the problem of the dose-effect relationships according to binary responses. In doing so, we propose new variants that have not been consider before, yet which outperform existing methods.

In different fields such as pharmacology and toxicology, it is often interested in understanding the relationship between a binary response and a covariate. The formal description for the relationship is as follows. A dose of U is injected into the body, and either the presence of an effect or its absence is recorded. As a response (effect), the researcher has a binary value W, which will be an indicator of the event $(X < U)$, i. e. $W = I(X < U)$, where X is the threshold of sensitivity of the subject, the boundary from which the reaction begins. The random variable X is unobservable and it is necessary to construct an estimate of its distribution function $F(x) = P(X < x)$. We observe a two-dimensional random vector (U, W). If the random variables X and U are independent, then (see [1])

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

i. e. $F(x)$ is a regression and kernel regression estimates can be used to estimate the distribution function $F(x)$ (see [2]).

We consider the equispaced fixed design where u_i can be given uniformly or using quasi-random with low-discrepancy sequences. Articles [3], [4] describe the dose-effect relationship in a binomial regression model. Let W_{ij} denote the j-th response in m subjects at the covariate $u_i, i = 1, \dots, n,$ and the responses W_{ij} 's are mutually independent. Then $W_i = \sum_{j=1}^m W_{ij}$ has the binomial distribution $B(m, p_i)$ with parameter $(m, p_i = F(u_i)),$ and it is well known that the maximum likelihood estimate for p_i gives the ratio $w_i = W_i/m$ for each i. The data $\{(u_i, w_i), i = 1, 2, \dots, n\}$ immediately motivates us to construct an estimate of the distribution function. For these purposes the Nadaraya-Watson estimator is used, which well known as a basic kernel regression estimator and which is written in this situation as

$$F_n(x) = \frac{\sum\limits_{i=1}^n w_i K_h(x - u_i)}{\sum\limits_{i=1}^n K_h(x - u_i)},$$

where the kernel function $K_h(x) = h^{-1}K(x/h)$ is a finite with the support $[-1,1]$, bounded, symmetric distribution density, $h = h(n) = n^{-1/5}$ is the bandwith.

Under suitable regularity conditions (see [2]), it can be proved, that

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

where $\xrightarrow[n\to\infty]{d}$ indicates the convergence in distribution and $\parallel K \parallel^2 = \int_{-1}^{1} K^2(x)\,dx$. This statement highlight an important fact: we may guarantee the property of asymptotic normality for the normalized deviation $\sqrt{nh}(F_n(x) - \mathbf{E}(F_n(x)))$ in the binomial regression model. These theses consider the dose-effect relationships in *the negative* λ*-binomial regression model.*

Asymptotic performances. In the report presented here, a negative λ-binomial regression model is considered. For given r, p_i and λ, the negative λ-binomial distribution of the random variable Y_i considered for a given covariate u_i is defined as

$$p_\lambda(k) = \mathbf{P}(Y_i = k) = \frac{r\cdot(r+\lambda)\cdot\ldots\cdot(r+(k-1)\lambda)}{k!}\,(1-\lambda(1-p_i))^{\frac{r}{\lambda}}(1-p_i)^k,\ k = 0,1,\dots,$$

for which the mathematical expectation and variance are equal

$$\mathbf{E}(Y_i) = \frac{r(1-p_i)}{1-\lambda(1-p_i)}, \quad \mathbf{D}(Y_i) = \frac{r\lambda(1-p_i)^2}{(1-\lambda(1-p_i))^2} + \frac{r(1-p_i)}{1-\lambda(1-p_i)}.$$

Next, we will work with a random variable $Z_i = Y_i + \dfrac{r}{\lambda}$, $\mathbf{E}(Z_i) = \dfrac{r}{\lambda - \lambda^2(1-p_i)}$, and we will use the sample $\mathcal{Z} = \{(z_i, u_i), i = 1,2,\dots,n\}$ to construct an estimate of the distribution function $F(x)$ with known λ of the form:

$$\widehat{F}_n(x) = 1 - \frac{1}{\lambda} + \frac{1}{\lambda^2}\cdot\frac{r}{\sum\limits_{i=1}^{n} z_i\cdot K_h(x-u_i)}.$$

Remark 1. The limit

$$\lim_{\lambda\to 1} p_\lambda(k) = \frac{r(r+1)\ldots(r+k-1)}{k!}p_i^r(1-p_i)^k \quad k = 0,1,\dots,$$

is a probability function of a negative binomial random variable with parameters (r, p_i). Then as $\lambda \to 1$,

$$\lim \mathbf{E}(Y_i) = \frac{r(1-p_i)}{p_i}, \qquad \lim \mathbf{D}(Y_i) = \frac{r(1-p_i)}{p_i^2}.$$

Remark 2. The limit

$$\lim_{\lambda\to 0} p_\lambda(k) = \frac{(r(1-p_i))^k}{k!}\,e^{-r(1-p_i)}, \quad k = 0,1,\dots,$$

is a probability function of a Poisson random variable with parameters $r(1-p_i)$ and

$$\lim_{\lambda\to 0}\mathbf{E}(Y_i) = r(1-p_i), \qquad \lim_{\lambda\to 0}\mathbf{D}(Y_i) = r(1-p_i).$$

Theorem 1. *Let the regularity conditions* [5] *be satisfied, and also* $u_i = \dfrac{i}{n}$, $i = 1\ldots n$. *Then*

$$\sqrt{nh}(\widehat{F}_n(x) - \mathbf{E}(\widehat{F}_n(x))) \xrightarrow[n\to\infty]{d} N\left(0, \frac{(1-F(x))(1-\lambda(1-F(x)))^2}{r}\parallel K \parallel^2\right) = N(0, \sigma^2(x)).$$

Remark 3. Consider the variance values under the conditions of Theorem 1, when $\lambda \to 1$ and $\lambda \to 0$, having in mind

$$\text{a)} \lim_{\lambda \to 1} \sigma^2(x) = \frac{(1-F(x))F^2(x)}{r} \, ||K||^2; \quad \text{b)} \lim_{\lambda \to 0} \sigma^2(x) = \frac{1-F(x)}{r} \, ||K||^2.$$

Let's define now

$$\widehat{\xi}_{n,\alpha} = \inf\{x \in \mathbf{R} : \widehat{F}_n(x) \geqslant \alpha\}, \quad \xi_\alpha = F^{-1}(\alpha).$$

Theorem 2. *Let* $\widehat{\xi}_{n\alpha}$ *be the quantile estimate of order* $0 < \alpha < 1$, *the regularity conditions* [5] *are satisfied,* $u_i = \dfrac{i}{n}$, $i = 1 \dots n$, and $f(\xi_\alpha) > 0$. *Then*

$$\sqrt{nh}(\widehat{\xi}_{n\alpha} - \xi_\alpha - ah^2) \xrightarrow[n\to\infty]{d} N\left(0, \frac{(1-\lambda(1-\alpha))^2(1-\alpha)\ \|K\|^2}{rf^2(\xi_\alpha)}\right) = N(0, \sigma^2),$$

where $a = \dfrac{(1-\lambda(1-\alpha))f'(\xi_\alpha) - 2\lambda f^2(\xi_\alpha))}{2(1-\lambda(1-\alpha))\sigma} \, \nu_2(K)$, $\nu_2(K) = \int_{-1}^{1} x^2 \, K(x) \, dx$.

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Tikhov M. S. (Nizhny Novgorod, National Research Lobachevsky State University of Nizhny Novgorod). **Negative λ-binomial regression in dose-effect relationships.**

Abstract: In this report, used one discrete random variable, namely the negative l-binomial random variable. We construct kernel-based distribution function estimators in the nonparametric negative l-binomial regression problem with one-dimensional covariates. The report studies the asymptotic behavior of the constructed estimates of the distribution function and its quantiles.

Keywords: Negative λ-binomial regression, dose-effect relationships, nonparametric kernel estimator.