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Interval estimation of excess risk related effective doses in tobit models

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INTERVAL ESTIMATION OF EXCESS RISK RELATED EFFECTIVE DOSES IN TOBIT MODELS

by

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ABSTRACT

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In this thesis we consider interval estimation of excess risk related effective dose ($ERED$) in dose-response studies using tobit model. Let $P(x)$ be the probability of response at dose level x. Considering the background probability $P(0)$, excess risk at dose level $x > 0$ is $P(x) - P(0)$. Then $ERED_{100p}$ is the dose level at which $p = \frac{P(x)-P(0)}{1-P(0)}$. When $P(0) = 0$, $ERED$ is same as the regular ED.

Tobit regression model is used when the outcome variable in a dose-response study is left censored and continuous. We first describe the maximum likelihood estimation of $ERED$s in tobit model, and then we propose five interval estimation methods of $ERED$s, including the delta method, the Fieller method, the likelihood ratio method, the non-parametric bootstrap method and the parametric bootstrap method. For both non-parametric and parametric bootstrap methods, we consider three different

ways to construct the confidence interval, including the percentile method, bias-corrected model and bias-corrected accelerated method. Simulation studies show that when the normal assumption of the tobit model is met, i.e. the latent response is normally distributed, we recommend the delta method for $ERED_{50}$ and the likelihood ratio method and the parametric bootstrap percentile method for $ERED_{05}$. When the error distribution is non-normal but symmetric, we recommend the parametric bootstrap percentile method and the nonparametric bootstrap percentile method. When the error distribution is non-normal but asymmetric, we recommend the Fieller method, the likelihood ratio method and the parametric bootstrap bias-corrected method. When the error distribution is normal, the three nonparametric bootstrap methods are not recommended. When the error distribution is non-normal but symmetric, the parametric bootstrap bias-corrected method and the parametric bootstrap bias-corrected accelerated method are not recommended. When the error distribution is non-normal but asymmetric, the parametric bootstrap percentile method and the parametric bootstrap bias-corrected accelerated method are not recommended.

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Chapter 1

Introduction

Effective dose (ED) is usually determined by analyzing dose-response data. Let $P(x)$ denote the probability of response for dose level x. ED_{100p} satisfies $P(ED_{100p}) = p$. For example, in pharmacology, people usually focus on the association of dose levels and effectiveness. Effective dose ED_{100p} is the amount of drug that produces a therapeutic response in $100p$ percent of the subjects taking it. In toxicology, ED_{100p} is the amount of drug that have a toxic response in $100p$ percent of the subjects taking it. Two commonly used EDs are ED_{50} for $p = 0.5$ and ED_{05} for $p = 0.05$.

In some studies, some subjects can have response at zero dose level. Removing this background, we consider so-called excess risk (ER)(Simpson et al. 2004). For instance, in the aforementioned concept of pharmacology, it is defined as the difference between the proportion of subjects with a particular dose effect who were using drugs, $P(\text{Drug})$, and the proportion of subjects with the same effect who did not take drugs, $P(\text{no Drug})$, i.e.

$$ER = P(\text{Drug}) - P(\text{no Drug}). \tag{1.1}$$

Without loss of generality, we assume the background is at $x = 0$. Then the excess risk at dose level x is $P(x) - P(0)$, and the excess risk due to dose is given by

$$r(x) = \frac{P(x) - P(0)}{1 - P(0)}. \tag{1.2}$$

Excess risk related effective dose $ERED_{100p}$ is then defined by

$$r(ERED_{100p}) = p. \tag{1.3}$$

In general, ERED is different from the regular ED, but $EDER_{100p} = ED_{100p}$ if $P(0) = 0$.

Different models were proposed to fit dose-response data, such as logistic regression model, probit regression model and tobit regression model (Ashford and Smith 1964; Berkson 1944; Huang et al. 2002; Morgan 1992; Müller and Wang 1990; O'Brien et al. 2003; Ronald 2000). When the response is binary, such as dead or alive, logistic or probit regression model is often used.

In occasions where the response is a left censored continuous variable, tobit regression model (Tobin, 1958; Amemiya, 1984; O'Brien et al., 2003) is used. For example, O'Brien et al. (2003) conducted a study of ultrasound-induced lung hemorrhage in crossbred pigs to explore the biological mechanisms responsible for ultrasound-induced lung hemorrhage. Pigs were exposed to pulsed ultrasound focused on the lung. As described in O'Brien et al. (2003), in addition to observing the occurrence of lesions, defined as the existence of hemorrhage involving lung due to acoustic pressure, researchers also recorded the depth or surface area of the lesion in the lung, which results in a left censored continuous response. O'Brien then estimated ED using a tobit model.

In this thesis, we propose five different methods for interval estimation of $ERED$ under tobit regression model, the delta method, the Fieller method, the likelihood ratio method, the nonparametric bootstrap method and the parametric bootstrap method. Chapter 2 describes the maximum likelihood estimation of $EREDs$ under the tobit regression model. Chapter 3 describes five interval estimation methods. In Chapter 4, we compare the performance of these methods using simulation studies and suggest the delta method for $ERED_{50}$ and the likelihood ratio method and the parametric bootstrap percentile method for $ERED_{05}$ when the normal assumption holds. In Chapter 5, we give the conclusions and discuss some future work.

Chapter 2

Maximum likelihood estimation of ERED

Dose-response data with left censored response are usually fitted by tobit regression model . In a tobit regression model (Amemiya, 1984; O'Brien et al., 2003), the response variable y_i depends on a latent variable u_i, which is linearly related to the dose levels x_i. What we observed are response variables y_i and the dose levels x_i, but u_i are unobservable.

Define the indicator function $I(A) = 1$ if A is true, and 0 otherwise. Then the tobit regression model is defined as

$$\begin{aligned} u_i &= \beta_0 + \beta_1 x_i + \epsilon_i, \\ y_i &= u_i I(u_i > c). \end{aligned} \tag{2.1}$$

where $\boldsymbol{\beta} = (\beta_0, \beta_1)^T$ are unknown parameters, c is a known censoring threshold and ϵ_i's are independently and identically distributed (i.i.d.) normal errors with $E(\epsilon_i) = 0$ and $\text{Var}(\epsilon_i) = \sigma^2$. Without loss of generality, we assume that the threshold $c = 0$, then the tobit model is

$$\begin{aligned} y_i &= \max(0, u_i), \\ u_i &\sim N(\beta_0 + \beta_1 x_i, \sigma^2). \end{aligned} \tag{2.2}$$

From (2.2), we have

$$P(y_i > 0) = P(u_i > 0) = \Phi\left(\frac{\beta_0 + \beta_1 x_i}{\sigma}\right), \tag{2.3}$$

where $\Phi(\cdot)$ is the cumulative distribution function of the standard normal distribution. When $x_i = x$, the $100p$th percentile of y_i is

$$Q_{100p}(x_i) = \max(0, \beta_0 + \beta_1 x_i + \sigma\Phi^{-1}(p)). \tag{2.4}$$

Notice that the background probability is $P(0) = \Phi(\frac{\beta_0}{\sigma})$. Based on (1.2), excess risk $r(x) = p$ implies

$$q = P(x) = p + (1-p)P(0) = p + (1-p)\Phi\left(\frac{\beta_0}{\sigma}\right) \tag{2.5}$$

Let $\boldsymbol{\theta} = (\beta_0, \beta_1, \sigma)^T$ and $\rho_p(\boldsymbol{\theta}) = ERED_{100p}$. When it is clear from context, we ignore its dependence on p and θ. Then we have

$$\rho = \frac{\sigma\Phi^{-1}(q) - \beta_0}{\beta_1}. \tag{2.6}$$

Let $d_i = I(y_i > 0)$. Since $P(y_i = 0) = 1 - \Phi\left(\frac{\beta_0+\beta_1 x_i}{\sigma}\right)$ and $P(y_i > 0) = \Phi\left(\frac{y_i-\beta_0-\beta_1 x_i}{\sigma}\right)$, the likelihood function can be written as

$$L = \prod_{i=1}^{n} \left\{ \left[\frac{1}{\sigma} \phi \left(\frac{y_i - \beta_0 - \beta_1 x_i}{\sigma} \right) \right]^{d_i} \times \left[1 - \Phi \left(\frac{\beta_0 + \beta_1 x_i}{\sigma} \right) \right]^{1-d_i} \right\}, \tag{2.7}$$

where $\phi(\cdot)$ is the density function of the standard normal distribution. And the log-likelihood function is

$$\log L = \sum_{i=1}^{n} \left\{ d_i \left[-\log\sigma + \log\phi \left(\frac{y_i - \beta_0 - \beta_1 x_i}{\sigma} \right) \right] + (1-d_i) \log \left[1 - \Phi \left(\frac{\beta_0 + \beta_1 x_i}{\sigma} \right) \right] \right\}. \tag{2.8}$$

The MLE of $\hat{\boldsymbol{\theta}} = (\hat{\beta}_0, \hat{\beta}_1, \hat{\sigma})^T$ is then given by maximizing (2.7). Then the MLE of $ERED_{100p}$ is

$$\hat{\rho} = \widehat{ERED}_{100p} = \frac{\hat{\sigma}\Phi^{-1}(\hat{q}) - \hat{\beta}_0}{\hat{\beta}_1}, \tag{2.9}$$

where $\hat{q} = p + (1-p)\Phi\left(\frac{\hat{\beta}_0}{\hat{\sigma}}\right)$. In the statistical programming language R, we can use the `survreg()` function in the *survival* package to fit a tobit regression model and obtain the MLE $\hat{\boldsymbol{\theta}}$.

Chapter 3

Interval estimation of ERED

Interval estimation is needed to reflect uncertainty in parameter estimation. Huang (2008) proposed interval estimation of ED in tobit model using the delta method, the Fieller method, the likelihood ratio method, parametric and non-parametric bootstrap method. In this chapter, we develop these approaches for interval estimation of ERED in tobit models.

3.1 The delta method

The delta method is based on the first-order Taylor expansion of the parameter estimates, by ignoring all the terms involving the quadratic term and higher power terms. Suppose that we have a sequence of random variables $\{X_n\}$ such that

$$\sqrt{n}(X_n - \theta) \xrightarrow{\mathrm{d}} N(0, \sigma^2) \quad \text{as} \quad n \to \infty,$$

where θ and σ^2 are some finite constants and $\xrightarrow{\text{d}}$ denotes *convergence in distribution.* If function g is differentiable and its derivative is not zero at θ, keeping the first-order Taylor series expansion of $g(X_n)$ around θ and ignoring all the higher order terms, we have

$$g(X_n) \approx g(\theta) + g'(\theta)(X_n - \theta).$$

Moving $g(\theta)$ to the left-hand side and multiplying both sides by $\sqrt{n}$, we have

$$\sqrt{n}[g(X_n) - g(\theta)] \approx g'(\theta)\sqrt{n}(X_n - \theta).$$

Since $\sqrt{n}(X_n - \theta) \xrightarrow{\text{d}} N(0, \sigma^2)$, we have

$$\sqrt{n}[g(X_n) - g(\theta)] \xrightarrow{\text{d}} N\left(0, \sigma^2[g'(\theta)]^2\right). \tag{3.1}$$

For the multivariate case with k parameters $\boldsymbol{\theta} = (\theta_1, \theta_2, \cdots, \theta_k)^T$, under similar assumptions and following the same technique for the one dimensional case, we assume

$$\sqrt{n}(\hat{\boldsymbol{\theta}} - \boldsymbol{\theta}) \xrightarrow{\text{d}} N(0, \Sigma(\boldsymbol{\theta})).$$

If g is a function of $\boldsymbol{\theta}$ with the first order partial derivatives $g'(\boldsymbol{\theta}) = \partial g/\partial\boldsymbol{\theta} = \left(\frac{\partial g}{\partial\theta_1}, \frac{\partial g}{\partial\theta_2}, \cdots, \frac{\partial g}{\partial\theta_k}\right)^T$, which is continuous and not all zero at $\boldsymbol{\theta}$, then by the Taylor expansion, we have

$$\sqrt{n}(g(\hat{\boldsymbol{\theta}}) - g(\boldsymbol{\theta})) \xrightarrow{\text{d}} N(0, [g'(\boldsymbol{\theta})]^T\Sigma(\boldsymbol{\theta})[g'(\boldsymbol{\theta})]). \tag{3.2}$$

According to (2.5), $ERED_{100p}$ is a function ρ of the model parameter $\boldsymbol{\theta}$, with $\boldsymbol{\theta} = (\beta_0, \beta_1, \sigma)^T$ in the tobit regression model. Therefore, the variance of $\widehat{ERED}_{100p}$ can be estimated using (3.2) as

$$\mathrm{Var}(\widehat{ERED}_{100p}) = [\rho'(\hat{\boldsymbol{\theta}})]^T \widehat{\Sigma(\boldsymbol{\theta})} \rho'(\hat{\boldsymbol{\theta}}) \tag{3.3}$$

Then an asymptotically $100(1-\alpha)\%$ confidence interval of $ERED_{100p}$ is given by

$$\widehat{ERED}_{100p} \pm z_{\alpha/2}\sqrt{\mathrm{Var}(\widehat{ERED}_{100p})}, \tag{3.4}$$

where z_α is the $(1-\alpha)$th quantile of the standard normal distribution. Since in R, the estimated covariance matrix $\hat{\Sigma}$ is based on $\eta = \log(\sigma)$ instead of σ, we re-parameterize the tobit regression model with η. From (2.8), we have

$$\widehat{ERED}_{100p} = \rho(\hat{\boldsymbol{\theta}}) = \frac{e^{\hat{\eta}}\Phi^{-1}(\hat{q}) - \hat{\beta}_0}{\hat{\beta}_1}, \tag{3.5}$$

where $\hat{q} = p + (1-p)\Phi\left(\frac{\hat{\beta}_0}{e^{\hat{\eta}}}\right)$ and $\rho'(\hat{\boldsymbol{\theta}}) = (\rho'_{\hat{\beta}_0}, \rho'_{\hat{\beta}_1}, \rho'_{\hat{\eta}})$ with

$$\begin{aligned}
\rho'_{\hat{\beta}_0} &= \frac{1}{\hat{\beta}_1}\left[\frac{(1-p)\phi(\frac{\hat{\beta}_0}{e^{\hat{\eta}}})}{\phi(\Phi^{-1}(\hat{q}))} - 1\right], \\
\rho'_{\hat{\beta}_1} &= -\frac{\rho(\hat{\boldsymbol{\theta}})}{\hat{\beta}_1}, \\
\rho'_{\hat{\eta}} &= \frac{1}{\hat{\beta}_1}\left[e^{\hat{\eta}}\Phi^{-1}(\hat{q}) - \frac{\hat{\beta}_0(1-p)\phi(\frac{\hat{\beta}_0}{e^{\hat{\eta}}})}{\phi(\Phi^{-1}(\hat{q}))}\right].
\end{aligned} \tag{3.6}$$

3.2 The Fieller method

The Fieller method was first introduced by Fieller (1954). It constructs confidence intervals by using ratios of a linear combination of random variables.

Suppose that we have bivariate normal variables $\hat{\alpha}$ and $\hat{\beta}$ with mean vector (α, β) and variance covariance matrix V. Let V_{ij} be the (i, j)th element of the 2×2 matrix V. If $\theta = -\alpha/\beta$, that is $\alpha + \theta\beta = 0$. Considering the linear combination $\hat{\alpha} + \theta\hat{\beta}$, we have $\hat{\alpha} + \theta\hat{\beta} \xrightarrow{\mathrm{d}} N(0, \sigma^2)$, where $\sigma^2 = V_{11} + 2\theta V_{12} + \theta^2 V_{22}$. Then, a $100(1-\alpha)\%$ Fieller confidence interval for θ is given by the set of θ values that satisfy the inequality

$$\frac{(\hat{\alpha} + \hat{\beta}\theta)^2}{V_{11} + 2\theta V_{12} + \theta^2 V_{22}} < z^2_{\alpha/2}.$$

Now, we apply the Fieller method to construct confidence intervals of $ERED$s in the tobit regression.

From the asymptotic assumption of the MLE, the $100(1-\alpha)\%$ Fieller confidence interval for $ERED_{100p}$ is given by the set of values satisfying

$$\frac{\left(\hat{\beta}_1\rho - e^{\hat{\eta}}\Phi^{-1}(\hat{q}) + \hat{\beta}_0\right)^2}{\boldsymbol{a}^T \operatorname{Cov}(\hat{\boldsymbol{\theta}})\boldsymbol{a}} < z^2_{\alpha/2}, \tag{3.7}$$

and the limits of the confidence interval can be obtained by solving

$$(\hat{\beta}_1^{\,2} - v_{\beta_1} z^2_{\alpha/2})\rho^2 - 2(\hat{\rho}\hat{\beta}_1^{\,2} + v_{\beta_0\beta_1} z^2_{\alpha/2} - a_2 v_{\beta_1\eta} z^2_{\alpha/2})\rho + (\hat{\rho}\hat{\beta}_1)^2 - z^2_{\alpha/2}\boldsymbol{b}\Sigma_{(-2)}\boldsymbol{b}^T = 0, \tag{3.8}$$

where $\boldsymbol{a} = (a_1, \rho, a_2)^T$, $a_1 = 1 - \frac{e^{\hat{\eta}}(1-p)\phi\left(\frac{\hat{\beta}_0}{e^{\hat{\eta}}}\right)}{\phi(\Phi^{-1}(\hat{q}))}$, $a_2 = -e^{\hat{\eta}}\Phi^{-1}(\hat{q}) - \frac{\hat{\beta}_0(1-p)\phi\left(\frac{\hat{\beta}_0}{e^{\hat{\eta}}}\right)}{\phi(\Phi^{-1}(\hat{q}))}$, $\Sigma = Cov(\hat{\boldsymbol{\theta}}) = \begin{pmatrix} v_{\beta_0} & v_{\beta_0\beta_1} & v_{\beta_0\eta} \\ v_{\beta_0\beta_1} & v_{\beta_1} & v_{\beta_1\eta} \\ v_{\beta_0\eta} & v_{\beta_1\eta} & v_\eta \end{pmatrix}$, $\Sigma_{(-2)} = \begin{pmatrix} v_{\beta_0} & v_{\beta_0\eta} \\ v_{\beta_0\eta} & v_\eta \end{pmatrix}$, and $\boldsymbol{b} = (1, a_2)^T$.

Because the Fieller confidence interval is constructed by a quadratic equation, the confidence interval maybe finite, a union of two infinite intervals, the entire real line or non-exist. The Fieller method and the delta method are asymptotically equivalent. When the sample size is large, the two methods give similar results.

3.3 The likelihood ratio method

By inverting likelihood ratio (LR) tests, we can obtain LR confidence intervals for parameters (Shao, 2003). LR tests are defined as follows.

Assume that $L(\theta|X)$ is the likelihood function based on data X for unknown parameter θ in a parameter space Ω. Let Ω_0 and Ω_1 be two partitioned disjoint subsets of Ω. Suppose that we wish to test the hypotheses

$$H_0 : \theta \in \Omega_0 \qquad \text{versus} \qquad H_1 : \theta \in \Omega_1. \tag{3.9}$$

In order to compare these two hypotheses, we compute restricted maximum likelihood $L(\theta^\star|X) = \sup_{\theta\in\Omega_0} L(\theta|X)$ under the null hypothesis H_0 and unrestricted maximum likelihood $L(\hat{\theta}|X) = \sup_{\theta\in\Omega} L(\theta|X)$. Define the LR statistic $\lambda(X)$ as

$$\lambda(X) = \frac{L(\theta^\star|X)}{L(\hat{\theta}|X)}. \tag{3.10}$$

Then a LR test for hypotheses (3.9) is to reject the null hypothesis H_0 if $\lambda(X) < c$, where c is a constant.

Now assume that $\Omega = R^k$ and Ω_0 is determined by $H_0 : \boldsymbol{\theta} = g(\boldsymbol{\vartheta})$, where $\boldsymbol{\vartheta}$ is a $(k-r) \times 1$ vector of unknown parameters and g is a continuously differentiable function. Assume that there exists an MLE $\hat{\boldsymbol{\theta}}$ of $\boldsymbol{\theta}$ and an MLE $\hat{\boldsymbol{\vartheta}}$ of $\boldsymbol{\vartheta}$ under the null hypothesis H_0. Then the LR test statistic is

$$\lambda(X) = \frac{L(g(\hat{\boldsymbol{\vartheta}})|X)}{L(\hat{\boldsymbol{\theta}}|X)}.$$

Given some mild regularity conditions, under H_0, $-2\log\lambda(X) \xrightarrow{\mathrm{d}} \chi^2_r$, where χ^2_r is a random variable having the chi-square distribution with r degrees of freedom. Then the likelihood ratio test with rejection region $\lambda(X) < e^{-\chi^2_{r,\alpha/2}}$ has an asymptotic significance level α. So, if c is chosen to be $e^{-\chi^2_{r,\alpha/2}}$, an asymptotically $100(1-\alpha)\%$ confidence set of $\boldsymbol{\theta}$ is

$$C(X) = \{\boldsymbol{\theta} : -2(\log[L(g(\hat{\boldsymbol{\vartheta}})|X)] - \log[L(\hat{\boldsymbol{\theta}}|X)] \leq \chi^2_{r,\alpha}\}. \tag{3.11}$$

Now we show how to use the LR method to obtain confidence intervals for $ERED$s. Let $\rho = ERED_{100p}$. Considering null hypotheses

$$H_0 : \rho = \rho_0 \qquad \text{versus} \qquad H_1 : \rho \neq \rho_0. \tag{3.12}$$

First, re-parameterize the tobit model with parameter $\boldsymbol{\theta} = (\rho, \beta_1, \eta)^T$. Assume that the maximum log-likelihood function is $l(\hat{\boldsymbol{\theta}})$, where $\hat{\boldsymbol{\theta}}$ is the MLE of $\boldsymbol{\theta}$ and the profile log-likelihood is $l_p(\rho_0, \tilde{\beta}_1, \tilde{\eta})$, where $(\tilde{\beta}_1, \tilde{\eta})$ is restricted the MLE of (β_1, η) when setting

$\rho = \rho_0$. Then the LR test rejects the null hypothesis at significant level α when

$$-2[l_p(\rho_0, \tilde{\beta}_1, \tilde{\eta}) - l(\hat{\boldsymbol{\theta}})] > \chi^2_{1,\alpha}. \tag{3.13}$$

And the $100(1-\alpha_0)\%$ LR confidence interval for $ERED_{100p}$ is given by the set of ρ_0 that satisfies

$$l_p(\rho_0, \tilde{\beta}_1, \tilde{\eta}) - l(\hat{\boldsymbol{\theta}}) + \frac{1}{2}\chi^2_{1,\alpha} > 0. \tag{3.14}$$

3.4 The bootstrap methods

Bootstrap was first introduced by Efron (1979). It is a data-based resampling method to obtain statistical inferences, often for confidence intervals and standard errors. A thorough discussion on bootstrap can be found in Efron and Tibshirani (1993). The usage of bootstrap methods for our problem is essentially the same as in Huang (2008) except that our interest is to estimate ERED. But for completeness, we include the related part in Huang (2008) in the following.

3.4.1 Bootstrap confidence intervals

Given bootstrap replications $\{\hat{\theta}^*_1, \hat{\theta}^*_2, \cdots, \hat{\theta}^*_B\}$ of an estimate $\hat{\theta}$ from B bootstrap samples, there are often three ways to construct bootstrap confidence intervals for a parameter θ, the percentile method, the bias-corrected (BC) method and bias-corrected accelerated method (BC_a).

The percentile method

Percentile method uses sample percentiles of bootstrap replicates to define the confidence limits. The $100(1-\alpha)\%$ confidence interval of θ is established by the $100\alpha/2$ and $100(1-\alpha)/2$ percentiles of the B bootstrap replicates $\hat{\theta}^*$,

$$[\hat{\theta}^{*(\alpha/2)}, \hat{\theta}^{*(1-\alpha/2)}]. \tag{3.15}$$

Although the percentile interval closely matches the exact confidence interval, in practice, they may not give dependably accurate coverage probabilities in all situations. Because of that, bias-corrected method BC and bias-corrected accelerated method BC_a are proposed as improved versions of the percentile method.

The bias-corrected method

In order to adjust the bias from the bootstrap distribution, the BC method was proposed. Let $\hat{\theta}$ be the estimate from the original data and define the factor $\hat{z}_0$, which is a measure of the discrepancy between the median of the B bootstrap estimates $\hat{\theta}^*$ and the original sample estimate $\hat{\theta}$, as

$$\hat{z}_0 = \Phi^{-1}(\#\{\hat{\theta}^* < \hat{\theta}\}/B). \tag{3.16}$$

Then the $100(1-\alpha)\%$ BC bootstrap confidence interval for θ is given by

$$\left[\hat{\theta}^{*(\alpha_1)}, \hat{\theta}^{*(\alpha_2)}\right], \tag{3.17}$$

where $\alpha_1 = \Phi(2\hat{z}_0 - z_{1-\alpha/2})$ and $\alpha_2 = \Phi(2\hat{z}_0 + z_{1-\alpha/2})$.

The bias-corrected accelerated method

The BC_a method as an improvement from the BC method. Define

$$\hat{a} = \frac{\sum_{i=1}^{n}(\hat{\theta}_{(.)} - \hat{\theta}_{(i)})}{6\left[\sum_{i=1}^{n}\left(\hat{\theta}_{(.)} - \hat{\theta}_{(i)}\right)^2\right]^{3/2}}, \tag{3.18}$$

where $\hat{\theta}_{(i)}$ is the ith jackknife estimate of θ and $\hat{\theta}_{(.)} = \sum_{i=1}^{n}\hat{\theta}_{(i)}/n$. Then the $100(1-\alpha)\%$ BC_a interval for θ is given by

$$\left[\hat{\theta}^{*(\alpha_3)}, \hat{\theta}^{*(\alpha_4)}\right], \tag{3.19}$$

where $\alpha_3 = \Phi\left\{\hat{z}_0 + \frac{\hat{z}_0 - z_{1-\alpha/2}}{1-\hat{a}(\hat{z}_0 - z_{1-\alpha/2})}\right\}$ and $\alpha_4 = \Phi\left\{\hat{z}_0 + \frac{\hat{z}_0 + z_{1-\alpha/2}}{1-\hat{a}(\hat{z}_0 + z_{1-\alpha/2})}\right\}$.

3.4.2 Nonparametric and parametric bootstrap methods

Bootstrap can be done either in a nonparametric way or a parametric way. Nonparametric bootstrap relies on the consideration of the discrete empirical distribution $\hat{F}$ generated by a random sample from an unknown distribution F. In empirical distribution $\hat{F}$, equal probability is assigned to each sample item. In the parametric bootstrap setting, we consider F to be a member of some prescribed parametric family and obtain $\hat{F}$ by estimating family parameters from the data.

The nonparametric bootstrap

The nonparametric bootstrap method is a simple pairwise resampling of (y_i, x_i). The procedure for the tobit regression model is listed as follows.

1. Randomly sample $i_1^*, i_2^*, \cdots, i_n^*$ with replacement from $\{1, 2, \cdots, n\}$.

2. For $j = 1, \cdots, n$, set $y_j^* = y_{i_j^*}, x_j^* = x_{i_j^*}$.

3. Fit the tobit regression model by using the sample $(y_1^*, x_1^*), \cdots, (y_n^*, x_n^*)$ and obtain the MLE of $ERED_{100p}$.

4. Repeat Steps 1-3 B times and establish a $100(1-\alpha)\%$ confidence interval for $ERED_{100p}$ by either the percentile method, the BC method or the BC_a method from B estimates of $ERED_{100p}$.

The parametric bootstrap

The parametric bootstrap is to resample the pseudo-residuals of the parametric model. This applies to the tobit regression model. We propose the procedure as follows.

1. Set $x_i^* = x_i$

2. For $y_i = 0$, generate the latent u_i based on the conditional distribution $U_i|U_i \leq 0$, which is a truncated normal distribution with mean $\hat{y}_i = \hat{\beta}_0 + \hat{\beta}_1 x_i$ and variance $\hat{\sigma}^2$ when the error term is assumed normal. Then obtain pseudo-residuals $\tilde{r}_i = u_i - \hat{y}_i$; and for $y_i > 0$, let $\tilde{r}_i = y_i - \hat{y}_i$.

3. Sample r_i^* from the pseudo residuals $(\tilde{r}_1, \tilde{r}_2, \cdots, \tilde{r}_n)$ with replacement.

4. Let $u_i^* = \hat{y}_i + r_i^*$ and $y_i^* = u_i^* I[u_i^* > 0]$.

5. Fit the tobit regression model using the bootstrap sample $(y_1^*, x_1^*), \cdots, (y_n^*, x_n^*)$ and obtain the MLE of $ERED_{100q}$.

6. Repeat Steps 1-5 B times and establish a $100(1-\alpha)\%$ confidence interval by using either the percentile method, the BC method or the BC_a method from B estimates of $ERED_{100p}$.

Chapter 4

Comparison of different interval estimation methods

In this Chapter, we further study the performance of the proposed estimation confidence intervals in Chapter 4 for $ERED_{50}$ and $ERED_{05}$ by simulation studies. We generated data from both normal and non-normal error distributions, with the normal error distribution corresponding to the case tobit regression is a correct model and the non-normal error distribution corresponding to the misspecified case. Hence, we can study both the efficiency and robustness of these interval estimation methods.

4.1 Simulation setup

In our simulation study, we consider simulated data set with differen sample sizes, from different error distributions and experiment designs. In Table 4.1, we summarize the data generating configurations, which is the same as in Huang (2008). For experiment designs, we consider random designs with dose levels from the uniform distribution on (1.5, 7) and fixed designs with five dose levels 2.5, 3.5, 4.5, 5.5 and 6.5

and also assume equal numbers of observations at each dose level. Then, we generated censored response from tobit regression model as follows,

$$\begin{aligned} u_i &= \beta_0 + \beta_1 x_i + \epsilon_i, \\ y_i &= u_i I(u_i > 0). \end{aligned}$$

True values of β_0 and β_1 and distribution of ϵ_i can be found in Table 4.1. We focus on five different error distributions F_ϵ.

(D1) standard normal distribution $N(0, 1)$.

(D2) the Cauchy distribution.

(D3) a normal mixture distribution $2/3N(0, 1) + 1/3N(30, 1)$.

(D4) a normal mixture distribution $5/6N(0, 1) + 1/6N(30, 1)$.

(D5) the slash distribution. The slash distribution can be obtained by dividing a standard normal random variable by an independent uniform random variable $U(0, 1)$.

The last four distributions are non-normal with (D2) and (D5) being symmetric and (D3) and (D4) being asymmetric. When the error distribution is assumed the standard normal, based on the above setting, for random designs, about 30 percent of observations are censored; for fixed designs, this proportion is about 25 percent.

In each simulation study, we generated 500 Monte Carlo samples and for each interval estimation method, we calculate its coverage probability (CP) and median interval length (ML) corresponding to the 95% confidence intervals of $ERED_{50}$ and $ERED_{05}$. In total, nine interval estimation methods are considered, including the delta method (D), the Fieller method (F), the LR method (LR), parametric bootstraps percentile method (P-P), parametric bootstraps BC method (P-BC), parametric bootstraps BC_a method (P-BCa), nonparametric bootstraps percentile method (N-P), nonparametric bootstraps BC method (N-BC) and nonparametric bootstraps BC_a method

Table 4.1: Simulation configuration

Designs	n	F_ϵ	β_0	β_1	σ^2	x_i
Random	100, 50	Normal	-3	1	1	$U(1.5, 7)$
Fixed	100, 50	Normal	-3	1	1	$(2.5, 3.5, 4.5, 5.5, 6.5)$
Random	100, 50	Non-normal	-3	1	1	$U(1.5, 7)$
Fixed	100, 50	Non-normal	-3	1	1	$(2.5, 3.5, 4.5, 5.5, 6.5)$

(N-BCa). For bootstrap methods, the number of bootstrap replicates is $B = 200$. In Table 4.2-4.5, numbers in () in CP column are variance of coverage probability and numbers in () in ML column are median absolute deviation of median interval length times 1.4826.

4.2 Comparison of efficiency

First, we compare the efficiency of various interval estimation methods using data generated based on the normal error distribution. Column D1 in Tables 4.2-4.5 give the results for interval estimation of $ERED_{50}$ and $ERED_{05}$ in random designs and fixed designs. For $ERED_{50}$ in random designs, the delta method, the likelihood ratio method and the parametric bootstrap percentile method give coverage probability larger than 95%. Among these three methods, the delta method has the shortest median interval length. The Fieller method gives coverage probability 95.8% when $n = 100$, but only 94.6% when $n = 50$; the parametric bootstrap bias-corrected method gives coverage probability 95.2% when $n = 50$, but only 93.6% when $n = 100$. For $ERED_{50}$ in fixed designs, although all methods give coverage probability smaller than 95%, the delta method, the likelihood ratio method, the parametric bootstrap

percentile and the parametric bootstrap bias-corrected method give higher coverage probability, above 94% when $n = 100$ and above 92% when $n = 50$. The delta method still has the shortest median interval length. For $ERED_{05}$ in random designs, when $n = 100$, the delta method, the Fieller method and the likelihood ratio method give coverage probability larger than 95%. When $n = 50$, the delta method, the Fieller method, the likelihood ratio method, the parametric bootstrap percentile method, the parametric bootstrap bias-corrected method and the nonparametric bootstrap bias-corrected give coverage probability larger than 94%, where only the likelihood ratio method give coverage probability larger than 95%. The likelihood ratio method has the shortest median interval length when sample size is large and the parametric bootstrap bias-corrected method has the shortest median interval length when sample size is small. For $ERED_{05}$ in fixed designs, the delta method, the Fieller method, the likelihood ratio method and the parametric bootstrap bias-corrected method give coverage probability larger than 92.5% when $n = 100$; the likelihood ratio method, parametric bootstrap percentile method and the parametric bootstrap bias-corrected give coverage probability larger than 92.5% when $n = 50$.
Among all results, three nonparametric bootstrap methods give the lowest coverage probability most times, except when estimating $ERED_{05}$ at $n = 50$ in fixed designs. Controlling on sample size, for the same method, results from random designs are always give higher coverage probability than results from fixed designs. The biggest difference is 4.6% using parametric bootstrap percentile method at $n = 50$.

We recommend the delta method for $ERED_{50}$ and the likelihood ratio method, the parametric bootstrap percentile method and parametric bootstrap bias-corrected method for $ERED_{05}$. And the three nonparametric bootstrap methods are not recommended.

4.3 Comparison of robustness

In addition to comparing the efficiency, we further study the robustness to the normal error assumption by fitting the tobit regression model (2.1) to data generated from non-normal error distributions. When the error distribution is symmetric, such as the Cauchy distribution and the slash distribution, in random designs and fixed designs (column D2 and D5 in Tables 4.2-4.5), for $ERED_{50}$, we see that all methods have poor coverage probability, less than 85%. Comparing the results using same method under D2 and D5, when the coverage probability is close, median interval length is longer under D5. For $ERED_{05}$ under D2 in both designs, the parametric bootstrap percentile method and nonparametric bootstrap percentile method give the coverage probability larger than 89% when $n = 50$ and the parametric bootstrap percentile method gives coverage probability above 87% when $n = 100$. For $ERED_{05}$ under D5 in both designs, the likelihood ratio method and the nonparametric bootstrap percentile method give coverage probability larger than 95% when $n = 50$ and coverage probability larger than 84% when $n = 100$. Compare this two methods, when the coverage probability is close, nonparametric bootstrap percentile method always gives shorter median interval length. For all result of $ERED_{05}$ under D2 and D5, the parametric bootstrap bias-corrected method and the parametric bootstrap bias-corrected accelerated method give the coverage probability less than 60%. Also notice that, all methods give higher coverage probability when sample size is small.

When the true error distribution is not symmetric, like $2/3N(0,1) + 1/3N(30,1)$ or $5/6N(0,1) + 1/6N(30,1)$, in random designs and fixed designs (column D3 and D4 in Tables 4.2-4.5), for $ERED_{50}$, we see that all methods have poor coverage probability, especially, less than 21% under D3. For $ERED_{05}$ under D4 when $n =$

100, all methods have coverage probability less than 85%; when $n = 50$, the Fieller method and the likelihood ratio method give coverage probability larger than 88% and the likelihood ratio method has shorter median interval length. For $ERED_{05}$ under D3 in random designs, the Fieller method and the likelihood ratio method give coverage probability larger than 90%. Compare these two methods, the Fielller method has shorter median interval length when sample size is larger, while the likelihood ratio method has shorter median interval length when sample size is small. For $ERED_{05}$ under D3 in fixed designs, the delta method, the Fieller method, the likelihood ratio method, the parametric bootstrap bias-corrected method and the nonparametric bootstrap bias-corrected method give coverage probability larger than 90%. Among these methods, the parametric bootstrap bias-corrected method has the shortest median interval length. For $ERED_{05}$ under D3 in fixed designs, the nonparametric bootstrap percentile method and the nonparametric bias-corrected accelerated method also give coverage probability larger than 90% when sample size is small. For all results of $ERED_{05}$ under D3 and D4 in both designs, the parametric bootstrap percentile method and the parametric bootstrap bias-corrected accelerated method give the lower coverage probability.

Different from Section 4.2, the median length of the same method for $ERED_{50}$ is smaller than that for $ERED_{05}$ when the error distribution is not symmetric, however, the median length of the same method for $ERED_{50}$ is larger than that for $ERED_{05}$ when the error distribution is symmetric. For different sample sizes, it is also seen that for larger data sets, all interval estimation methods provide shorter intervals in all cases.

To sum up, when the error distribution is non-normal but symmetric, we suggest the parametric bootstrap percentile method when the error distribution has heavy tail like the cauchy distribution and the nonparametric bootstrap percentile method when the error distribution has extreme heavy tail like the slash distribution, but we do not recommend the parametric bootstrap bias-corrected method or the parametric bootstrap bias-corrected accelerated method. When the error distribution is non-normal but asymmetric, we suggest the parametric bootstrap bias-corrected method when there are more outliers like the normal mixture D3 and the Fieller method and the likelihood ratio method when there are less outliers like the normal mixture D4, but we do not recommend the parametric percentile method or the parametric bootstrap bias-corrected accelerated method.

4.4 Summary

Based on the above results, we conclude the followings:

1. When data are generated from the normal error distribution, which is satisfying the assumption of the tobit regression model, we recommend the delta method for $ERED_{50}$ and the likelihood ratio method and the parametric bootstrap percentile method for $ERED_{05}$.

2. When the error distribution is non-normal, not all of these methods perform well. When the error distribution is symmetric, we recommend the parametric bootstrap percentile method and nonparametric bootstrap percentile method. When the error distribution is asymmetric, we recommend the Fieller method, the likelihood ratio method and the parametric bootstrap bias-corrected method.

3. When the error distribution is normal, the three nonparametric bootstrap methods are not recommended. When the error distribution is non-normal but

symmetric, the parametric bootstrap bias-corrected method and the parametric bootstrap bias-corrected accelerated method are not recommended. When the error distribution is non-normal but asymmetric, parametric bootstrap percentile method and parametric bootstrap bias-corrected accelerated method are not recommended.

Table 4.2: 95% confidence intervals of $ERED_{50}$ in random designs

method	$(D1)$		$(D2)$		$(D3)$		$(D4)$		$(D5)$	
	CP	ML	CP	ML	CP	ML	CP	ML	CP	ML
n=100										
D	0.950	0.623	0.278	2.217	0.020	0.533	0.716	0.535	0.464	3.385
	(0.048)	(0.047)	(0.201)	(1.638)	(0.020)	(0.039)	(0.203)	(0.041)	(0.249)	(2.833)
F	0.958	0.633	0.094	2.817	0.012	0.539	0.676	0.541	0.080	5.239
	(0.040)	(0.050)	(0.085)	(2.505)	(0.012)	(0.040)	(0.210)	(0.042)	(0.074)	(5.488)
LR	0.968	0.663	0.216	3.531	0.020	3.370	0.714	3.365	0.300	5.540
	(0.031)	(0.100)	(0.169)	(3.207)	(0.020)	(0.062)	(0.204)	(0.088)	(0.210)	(5.740)
$P-P$	0.950	0.626	0.036	2.131	0.008	0.521	0.634	0.522	0.074	3.177
	(0.048)	(0.056)	(0.035)	(1.204)	(0.008)	(0.049)	(0.232)	(0.047)	(0.069)	(1.800)
$P-BC$	0.936	0.625	0.082	1.582	0.014	0.525	0.800	0.524	0.096	3.208
	(0.060)	(0.062)	(0.075)	(1.198)	(0.014)	(0.056)	(0.160)	(0.054)	(0.087)	(2.990)
$P-BCa$	0.936	0.627	0.096	1.521	0.016	0.526	0.802	0.527	0.108	2.990
	(0.060)	(0.064)	(0.097)	(1.102)	(0.016)	(0.057)	(0.0159)	(0.054)	(0.096)	(2.599)
$N-P$	0.936	0.613	0.242	2.674	0.014	0.519	0.698	0.520	0.344	4.224
	(0.060)	(0.066)	(0.183)	(2.105)	(0.014)	(0.056)	(0.211)	(0.053)	(0.226)	(3.914)
$N-BC$	0.930	0.612	0.150	2.819	0.014	0.519	0.732	0.520	0.164	5.127
	(0.065)	(0.068)	(0.128)	(2.422)	(0.014)	(0.056)	(0.196)	(0.058)	(0.137)	(5.362)
$N-BCa$	0.932	0.613	0.254	2.519	0.016	0.520	0.734	0.521	0.276	4.431
	(0.063)	(0.067)	(0.189)	(1.968)	(0.016)	(0.055)	(0.195)	(0.058)	(0.200)	(4.330)
n=50										
D	0.958	0.925	0.648	2.000	0.176	0.792	0.852	0.796	0.792	3.299
	(0.040)	(0.101)	(0.228)	(1.042)	(0.145)	(0.078)	(0.126)	(0.084)	(0.165)	(2.804)
F	0.946	0.954	0.398	2.822	0.122	0.811	0.776	0.816	0.358	7.572
	(0.051)	(0.111)	(0.240)	(2.131)	(0.107)	(0.083)	(0.174)	(0.091)	(0.230)	(6.574)
LR	0.956	1.036	0.488	4.048	0.168	0.969	0.832	0.917	0.594	8.485
	(0.042)	(0.228)	(0.250)	(3.960)	(0.140)	(0.403)	(0.140)	(0.299)	(0.241)	(10.502)
$P-P$	0.952	0.927	0.364	2.516	0.152	0.762	0.792	0.759	0.468	4.226
	(0.046)	(0.113)	(0.232)	(1.810)	(0.129)	(0.084)	(0.165)	(0.089)	(0.249)	(3.972)
$P-BC$	0.952	0.932	0.338	1.600	0.194	0.765	0.866	0.764	0.368	2.869
	(0.046)	(0.118)	(0.224)	(0.986)	(0.156)	(0.093)	(0.116)	(0.099)	(0.233)	(2.793)
$P-BCa$	0.946	0.926	0.374	1.578	0.204	0.765	0.868	0.769	0.394	2.652
	(0.051)	(0.123)	(0.224)	(0.949)	(0.162)	(0.093)	(0.115)	(0.104)	(0.230)	(2.516)
$N-P$	0.948	0.925	0.664	2.567	0.188	0.764	0.848	0.772	0.768	4.281
	(0.049)	(0.142)	(0.223)	(2.000)	(0.153)	(0.101)	(0.129)	(0.102)	(0.178)	(4.373)
$N-BC$	0.942	0.922	0.466	2.662	0.200	0.768	0.858	0.772	0.458	6.163
	(0.055)	(0.133)	(0.249)	(2.200)	(0.160)	(0.105)	(0.122)	(0.096)	(0.248)	(7.261)
$N-BCa$	0.930	0.920	0.534	2.434	0.208	0.772	0.860	0.772	0.532	4.587
	(0.065)	(0.138)	(0.249)	(1.854)	(0.165)	(0.104)	(0.120)	(0.099)	(0.249)	(4.918)

Table 4.3: 95% confidence intervals of $ERED_{50}$ in fixed designs

method	$(D1)$		$(D2)$		$(D3)$		$(D4)$		$(D5)$	
	CP	ML	CP	ML	CP	ML	CP	ML	CP	ML
n=100										
D	0.944	0.649	0.438	2.451	0.010	0.555	0.696	0.548	0.632	3.766
	(0.053)	(0.066)	(0.246)	(2.152)	(0.010)	(0.051)	(0.212)	(0.045)	(0.233)	(3.678)
F	0.936	0.661	0.142	3.717	0.006	0.562	0.642	0.555	0.130	7.796
	(0.060)	(0.070)	(0.122)	(4.003)	(0.006)	(0.053)	(0.230)	(0.046)	(0.113)	(8.341)
LR	0.944	0.676	0.310	4.340	0.008	0.672	0.676	0.669	0.408	8.300
	(0.053)	(0.133)	(0.214)	(4.762)	(0.008)	(0.323)	(0.219)	(0.269)	(0.242)	(10.138)
$P-P$	0.924	0.657	0.106	2.316	0.000	0.536	0.592	0.538	0.188	3.259
	(0.070)	(0.073)	(0.095)	(1.618)	(0.000)	(0.059)	(0.242)	(0.058)	(0.153)	(2.458)
$P-BC$	0.942	0.656	0.118	1.933	0.012	0.530	0.764	0.526	0.108	3.783
	(0.055)	(0.074)	(0.104)	(1.881)	(0.012)	(0.065)	(0.180)	(0.064)	(0.096)	(4.210)
$P-BCa$	0.942	0.653	0.128	1.794	0.016	0.530	0.766	0.528	0.132	3.448
	(0.055)	(0.072)	(0.112)	(1.651)	(0.016)	(0.064)	(0.179)	(0.061)	(0.115)	(3.769)
$N-P$	0.932	0.657	0.398	3.080	0.000	0.537	0.686	0.541	0.452	5.283
	(0.063)	(0.086)	(0.240)	(3.007)	(0.000)	(0.060)	(0.215)	(0.053)	(0.248)	(5.829)
$N-BC$	0.926	0.653	0.206	3.482	0.002	0.538	0.698	0.540	0.206	7.785
	(0.069)	(0.085)	(0.164)	(3.743)	(0.002)	(0.060)	(0.211)	(0.051)	(0.164)	(9.687)
$N-BCa$	0.928	0.655	0.336	3.072	0.004	0.537	0.700	0.541	0.288	5.993
	(0.067)	(0.083)	(0.223)	(3.048)	(0.004)	(0.059)	(0.210)	(0.053)	(0.205)	(7.026)
n=50										
D	0.946	0.920	0.740	2.229	0.116	0.777	0.816	0.766	0.848	3.274
	(0.051)	(0.131)	(0.192)	(1.404)	(0.103)	(0.098)	(0.150)	(0.096)	(0.129)	(2.863)
F	0.938	0.955	0.420	4.066	0.086	0.798	0.758	0.786	0.418	10.894
	(0.058)	(0.144)	(0.244)	(3.757)	(0.079)	(0.109)	(0.183)	(0.103)	(0.243)	(5.509)
LR	0.942	0.964	0.594	6.313	0.106	0.948	0.790	0.928	0.702	12.317
	(0.055)	(0.253)	(0.241)	(7.349)	(0.095)	(0.376)	(0.166)	(0.334)	(0.209)	(16.233)
$P-P$	0.906	0.931	0.452	3.105	0.082	0.755	0.722	0.750	0.492	4.973
	(0.085)	(0.135)	(0.248)	(2.696)	(0.075)	(0.099)	(0.201)	(0.105)	(0.250)	(4.987)
$P-BC$	0.926	0.932	0.386	2.041	0.140	0.741	0.840	0.736	0.344	5.497
	(0.069)	(0.133)	(0.237)	(1.717)	(0.120)	(0.103)	(0.134)	(0.103)	(0.226)	(6.733)
$P-BCa$	0.924	0.922	0.426	1.934	0.156	0.740	0.842	0.739	0.352	6.168
	(0.070)	(0.134)	(0.245)	(1.549)	(0.132)	(0.100)	(0.133)	(0.105)	(0.228)	(7.716)
$N-P$	0.922	0.925	0.774	3.180	0.114	0.764	0.778	0.762	0.792	6.063
	(0.072)	(0.151)	(0.175)	(2.904)	(0.101)	(0.093)	(0.173)	(0.100)	(0.165)	(7.012)
$N-BC$	0.908	0.925	0.502	3.655	0.120	0.759	0.782	0.751	0.414	7.827
	(0.084)	(0.150)	(0.250)	(3.736)	(0.106)	(0.091)	(0.170)	(0.090)	(0.243)	(9.801)
$N-BCa$	0.910	0.919	0.574	2.925	0.136	0.760	0.780	0.753	0.476	6.747
	(0.082)	(0.148)	(0.245)	(2.614)	(0.118)	(0.091)	(0.172)	(0.090)	(0.249)	(8.176)

Table 4.4: 95% confidence intervals of $ERED_{05}$ in random designs

method	$(D1)$		$(D2)$		$(D3)$		$(D4)$		$(D5)$	
	CP	ML	CP	ML	CP	ML	CP	ML	CP	ML
n=100										
D	0.950	0.920	0.500	0.491	0.850	0.784	0.698	0.778	0.758	0.486
	(0.048)	(0.063)	(0.250)	(0.223)	(0.128)	(0.074)	(0.211)	(0.078)	(0.183)	(0.232)
F	0.954	0.931	0.530	0.654	0.900	0.793	0.780	0.786	0.768	0.669
	(0.044)	(0.067)	(0.249)	(0.324)	(0.090)	(0.076)	(0.172)	(0.081)	(0.178)	(0.385)
LR	0.966	0.895	0.650	0.591	0.908	0.795	0.796	0.786	0.840	0.644
	(0.033)	(0.055)	(0.228)	(0.344)	(0.084)	(0.071)	(0.162)	(0.079)	(0.134)	(0.480)
$P-P$	0.936	0.876	0.884	1.050	0.772	0.664	0.548	0.665	0.778	0.913
	(0.060)	(0.085)	(0.103)	(0.399)	(0.176)	(0.078)	(0.248)	(0.070)	(0.173)	(0.410)
$P-BC$	0.936	0.872	0.182	0.146	0.826	0.655	0.626	0.658	0.294	0.194
	(0.060)	(0.091)	(0.149)	(0.192)	(0.144)	(0.081)	(0.234)	(0.077)	(0.208)	(0.227)
$P-BCa$	0.932	0.880	0.184	0.147	0.800	0.656	0.592	0.657	0.296	0.194
	(0.063)	(0.086)	(0.150)	(0.194)	(0.160)	(0.083)	(0.242)	(0.077)	(0.208)	(0.226)
$N-P$	0.926	0.876	0.716	0.658	0.786	0.671	0.590	0.675	0.886	0.666
	(0.069)	(0.105)	(0.203)	(0.298)	(0.168)	(0.079)	(0.242)	(0.076)	(0.101)	(0.394)
$N-BC$	0.926	0.865	0.614	0.627	0.828	0.675	0.638	0.675	0.794	0.623
	(0.069)	(0.102)	(0.237)	(0.331)	(0.142)	(0.081)	(0.231)	(0.084)	(0.164)	(0.388)
$N-BCa$	0.920	0.870	0.622	0.636	0.800	0.673	0.612	0.679	0.784	0.608
	(0.074)	(0.102)	(0.235)	(0.334)	(0.160)	(0.082)	(0.237)	(0.079)	(0.169)	(0.366)
n=50										
D	0.940	1.367	0.618	0.879	0.890	1.164	0.838	1.172	0.786	0.804
	(0.056)	(0.126)	(0.236)	(0.576)	(0.098)	(0.151)	(0.136)	(0.156)	(0.168)	(0.547)
F	0.940	1.394	0.624	1.511	0.922	1.192	0.880	1.198	0.804	1.773
	(0.056)	(0.141)	(0.235)	(0.652)	(0.072)	(0.159)	(0.106)	(0.165)	(0.158)	(0.494)
LR	0.962	1.284	0.844	1.135	0.928	1.179	0.894	1.189	0.952	1.367
	(0.037)	(0.106)	(0.132)	(0.627)	(0.067)	(0.125)	(0.095)	(0.128)	(0.046)	(1.218)
$P-P$	0.942	1.275	0.926	1.795	0.828	1.022	0.712	1.017	0.826	1.873
	(0.055)	(0.148)	(0.069)	(0.777)	(0.142)	(0.129)	(0.205)	(0.134)	(0.144)	(0.864)
$P-BC$	0.943	1.257	0.462	0.936	0.884	1.012	0.808	1.006	0.504	1.072
	(0.054)	(0.140)	(0.249)	(1.011)	(0.103)	(0.136)	(0.155)	(0.145)	(0.250)	(1.339)
$P-BCa$	0.934	1.270	0.470	0.978	0.848	1.011	0.770	1.006	0.520	1.133
	(0.062)	(0.151)	(0.249)	(1.076)	(0.129)	(0.136)	(0.177)	(0.140)	(0.250)	(1.413)
$N-P$	0.926	1.287	0.894	1.321	0.848	1.029	0.756	1.029	0.960	1.283
	(0.069)	(0.205)	(0.095)	(0.623)	(0.129)	(0.138)	(0.184)	(0.147)	(0.038)	(0.765)
$N-BC$	0.942	1.271	0.734	1.334	0.874	1.023	0.796	1.031	0.842	1.306
	(0.055)	(0.190)	(0.195)	(0.0875)	(0.110)	(0.144)	(0.162)	(0.153)	(0.133)	(1.004)
$N-BCa$	0.926	1.280	0.768	1.403	0.856	1.027	0.760	1.033	0.838	1.390
	(0.069)	(0.209)	(0.178)	(0.868)	(0.123)	(0.141)	(0.182)	(0.148)	(0.136)	(1.098)

Table 4.5: 95% confidence intervals of $ERED_{05}$ in fixed designs

method	$(D1)$		$(D2)$		$(D3)$		$(D4)$		$(D5)$	
	CP	ML	CP	ML	CP	ML	CP	ML	CP	ML
n=100										
D	0.930	1.026	0.478	0.551	0.912	0.870	0.796	0.859	0.716	0.536
	(0.065)	(0.072)	(0.250)	(0.290)	(0.080)	(0.098)	(0.162)	(0.088)	(0.203)	(0.324)
F	0.928	1.046	0.522	0.813	0.936	0.883	0.828	0.870	0.744	0.831
	(0.067)	(0.078)	(0.250)	(0.347)	(0.060)	(0.102)	(0.142)	(0.090)	(0.190)	(0.414)
LR	0.950	0.991	0.686	0.769	0.950	0.879	0.848	0.870	0.866	0.859
	(0.048)	(0.058)	(0.215)	(0.578)	(0.048)	(0.091)	(0.129)	(0.083)	(0.116)	(0.774)
$P-P$	0.918	0.962	0.874	1.111	0.898	0.767	0.776	0.760	0.798	1.121
	(0.075)	(0.090)	(0.110)	(0.443)	(0.092)	(0.096)	(0.174)	(0.102)	(0.161)	(0.517)
$P-BC$	0.926	0.964	0.210	0.191	0.908	0.768	0.724	0.754	0.302	0.236
	(0.069)	(0.083)	(0.166)	(0.252)	(0.084)	(0.104)	(0.200)	(0.099)	(0.211)	(0.299)
$P-BCa$	0.914	0.962	0.212	0.188	0.888	0.769	0.696	0.757	0.304	0.223
	(0.079)	(0.084)	(0.167)	(0.250)	(0.099)	(0.101)	(0.212)	(0.103)	(0.212)	(0.297)
$N-P$	0.916	0.961	0.712	0.772	0.898	0.769	0.746	0.772	0.932	0.794
	(0.077)	(0.109)	(0.205)	(0.414)	(0.092)	(0.091)	(0.189)	(0.087)	(0.063)	(0.486)
$N-BC$	0.924	0.959	0.544	0.762	0.906	0.771	0.786	0.770	0.760	0.197
	(0.070)	(0.108)	(0.248)	(0.512)	(0.085)	(0.094)	(0.168)	(0.089)	(0.182)	(0.701)
$N-BCa$	0.924	0.959	0.558	0.793	0.898	0.773	0.764	0.768	0.742	0.826
	(0.070)	(0.111)	(0.247)	(0.563)	(0.092)	(0.094)	(0.180)	(0.086)	(0.191)	(0.744)
n=50										
D	0.900	1.413	0.598	0.898	0.910	1.206	0.836	1.191	0.804	0.864
	(0.090)	(0.153)	(0.240)	(0.659)	(0.082)	(0.196)	(0.137)	(0.180)	(0.158)	(0.559)
F	0.902	1.468	0.632	1.796	0.942	1.241	0.890	1.223	0.812	2.435
	(0.088)	(0.174)	(0.233)	(0.911)	(0.055)	(0.212)	(0.098)	(0.194)	(0.153)	(0.911)
LR	0.936	1.329	0.866	1.264	0.942	1.227	0.890	1.207	0.982	1.432
	(0.060)	(0.102)	(0.116)	(0.873)	(0.055)	(0.133)	(0.098)	(0.140)	(0.018)	(1.374)
$P-P$	0.928	1.299	0.930	1.793	0.894	1.070	0.806	1.064	0.890	1.780
	(0.067)	(0.149)	(0.065)	(0.667)	(0.095)	(0.168)	(0.156)	(0.162)	(0.098)	(0.798)
$P-BC$	0.930	1.300	0.498	1.152	0.900	1.067	0.810	1.061	0.596	1.558
	(0.065)	(0.142)	(0.250)	(1.135)	(0.090)	(0.165)	(0.154)	(0.159)	(0.241)	(1.992)
$P-BCa$	0.922	1.302	0.508	1.194	0.884	1.065	0.792	1.063	0.600	1.594
	(0.072)	(0.139)	(0.250)	(1.125)	(0.103)	(0.163)	(0.165)	(0.159)	(0.240)	(2.040)
$N-P$	0.922	1.286	0.922	1.299	0.904	1.073	0.792	1.063	0.984	1.420
	(0.072)	(0.178)	(0.072)	(0.601)	(0.087)	(0.149)	(0.165)	(0.148)	(0.016)	(0.866)
$N-BC$	0.922	1.274	0.736	1.355	0.928	1.083	0.832	1.063	0.836	1.547
	(0.072)	(0.177)	(0.194)	(0.736)	(0.067)	(0.152)	(0.140)	(0.151)	(0.137)	(1.229)
$N-BCa$	0.916	1.282	0.744	1.413	0.916	1.074	0.806	1.062	0.846	1.576
	(0.077)	(0.182)	(0.190)	(0.740)	(0.077)	(0.145)	(0.156)	(0.151)	(0.130)	(1.311)

Chapter 5

Conclusions and future work

In this thesis, we propose five interval estimation methods of $ERED$s in tobit models and compare their efficiency and robustness by simulations. Simulation studies show that, when data are generated from the normal error distribution, which is satisfying the assumption of the tobit regression model, we recommend the delta method for $ERED_{50}$ and the likelihood ratio method and the parametric bootstrap percentile method for $ERED_{05}$. When the error distribution is non-normal but symmetric, we recommend the parametric bootstrap percentile method and the nonparametric bootstrap percentile method. When the error distribution is non-normal but asymmetric, we recommend the Fieller method, the likelihood ratio method and the parametric bootstrap bias-corrected method. When the error distribution is normal, the three nonparametric bootstrap methods are not recommended. When the error distribution is non-normal but symmetric, the parametric bootstrap bias-corrected method and the parametric bootstrap bias-corrected accelerated method are not recommended. When the error distribution is non-normal but asymmetric, the parametric bootstrap percentile method and the parametric bootstrap bias-corrected accelerated method are not recommended.

In our simulation studies, we found three interesting phenomena on interval estimation for $ERED$s. All methods give higher coverage probability when sample size is relative small. When the normal assumption holds, controlling on sample size, for the same method, results from random designs are always give higher coverage probability than results from fixed designs. The median length of the same method for $ERED_{50}$ is smaller than that for $ERED_{05}$ when the error distribution is non-normal but asymmetric, however, the median length of the same method for $ERED_{50}$ is larger than that for $ERED_{05}$ when the error distribution is non-normal but symmetric. These issues deserve further consideration.

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