DISSERTATION

APPLICATIONS OF GENERALIZED FIDUCIAL INFERENCE

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY LIDONG E ENTITLED APPLICATIONS OF GENERALIZED FIDUCIAL INFERENCE BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

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ABSTRACT OF DISSERTATION

APPLICATIONS OF GENERALIZED FIDUCIAL INFERENCE

Hannig (2008) generalized Fisher's fiducial argument and obtained a fiducial recipe for interval estimation that is applicable in virtually any situation. In this dissertation research, we apply this fiducial recipe and fiducial generalized pivotal quantity to make inference in four practical problems. The list of problems we consider is (a) confidence intervals for variance components in an unbalanced two-component normal mixed linear model (b) confidence intervals for median lethal dose (LD50) in bioassay experiments (c) confidence intervals for the concordance correlation coefficient (CCC) in method comparison (d) simultaneous confidence intervals for ratios of means of Lognormal distributions. For all the fiducial generalized confidence intervals (a)-(d), we conducted a simulation study to evaluate their performance and compare them with other competing confidence interval procedures from the literature. We also proved that the intervals (a) and (d) have asymptotically exact frequentist coverage.

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INTRODUCTION

1.1 Fiducial Inference History

The idea of fiducial probability and fiducial inference were introduced by R. A. Fisher (1930). In his 1930's paper entitled "Inverse Probability", Fisher discussed the importance of the maximum likelihood method and then produced a fiducial distribution for a parameter in roughly the following manner. Let T be a maximum likelihood estimate of a parameter θ. The distribution function for T given θ, $F(T|\theta)$, has a uniform distribution on the interval $[0, 1]$. Differentiating partially with respect to θ gives a function treated as a density function for the fiducial distribution of a parameter θ for a given statistics T. The idea behind fiducial inference is as follows: Suppose there is a population characterized by a density function $f(x; \theta)$, the form of f is known, but there is no prior information available about the true value of the parameter θ. Given a set of observations, one wants to assign probabilities to subsets of the set of admissible values of the parameter θ. The "classical" method of deriving such inference is by applying the Bayesian theory. The drawback of this method, is, however that it requires the specification of a prior distribution. Fisher regarded the specification of a prior distribution as being in conflict with the assumption that no prior information is available. In Fisher's 1935 paper entitled "The Fiducial Argument in Statistical Infereence", he solved the Behrens-Fisher problem by assuming that the fiducial distribution is an ordinary probability distribution of a random parameter. The same answer had been obtained by Jeffreys (1940) using a Bayesian argument with non-informative priors. Fisher argued that the logic behind Jeffreys' approach was unacceptable because of the use of an unjustified prior distribution on the parameters. He also criticized the use of subjective priors because of the subjective element that would inflict upon the posterior distribution. He thus conceived the fiducial inference as an alternative to Bayes approach, aiming to obtain a distribution for the unknown parameter without the use of priors.

The ingredients of the fiducial approach are, according to Fisher,

- a sufficient statistics for the parameter of interest,
- a pivot, function of both sufficient statistic and true value of the parameter, and
- the fiducial argument, which states that, from the distribution of the pivot, a distribution for the parameter can be derived based on the sampled sufficient statistic.

To better illustrate the fiducial approach, we provide a simple example as follows. Let $X_1, \ldots, X_n$ be iid with $X_i \sim (\mu, n)$ and $\bar{X} = \frac{1}{n}\sum_{i=1}^{n} X_i$. Then the pivotal random variable is $Z = \bar{X} - \mu \sim N(0,1)$. $\bar{X}$ is a sufficient statistic for the unknown parameter μ. Let $\bar{x}$ and z are observed values of $\bar{X}$ and Z respectively, then $\bar{x}$ and z are related by the algebraic relation $\bar{x} - \mu = z$. Suppose we observe that the value of $\bar{x}$ is 1. Then we measure the "likelihood" of values of μ by the corresponding value of $\bar{x}$. For example, we would say $\mu \leq -9$ is highly unlikely, since $z \geq 10$ is a highly unlikely event. The fiducial argument is to say the probability density function of μ is the same as the probability density function of $\bar{x} - Z$.

Unlike Fisher's many other original and important contributions to statistical methodology and theory, fiducial inference has never gained widespread acceptance. A number of authors criticized Fisher's fiducial approach and presented inconsistent results of his theory. See, for instance, Creasy (1954), Fieller (1954), Lindley (1958). Commenting on Fisher's work, Fraser (2006) summarized that the key aspects of fiducial inference that evoked criticism are : (a) that different pivots can lead to different distributions and thus different intervals; (b) that marginalization of a parameter distribution to a component parameter can give a distribution that depends on data in a way different from the obvious that would come from that data; (c) that constraints on the parameter can give a distribution without total probability being equal to 1; (d) that a fiducial distribution is typically not an inverse probability or default Bayesian posterior. He then stated :"Curiously one finds that the defalut Bayesian approach is subject to precisely the same criticisms (a), (b), (c) that have been attached to the fiducial approach. The fact (d) that a fiducial analysis is not in general a defult Bayesian analysis seems a rather criticism by Lindley.". On a positive note Fraser, in a series of articles (Fraser (1961), Fraser (1966)) and monograph (Fraser (1968)), attempted to resolve the problem of non-uniqueness by reformulating the fiducial probability for location and transformation models. He termed his approach *structural probability* to distinguish it with Fisher's formulation.

In 1989, Tusi and Werrahandi introduced the concept of generalized p values and generalized variables, which are useful for developing hypothesis tests in situations where exact tests are not available. In 1993, Weerahandi generalized the concept of a pivotal quantity for a scalar parameter by defining a Generalized Pivotal Quantity (GPQ). He then proposed a method for constructing a confidence intervals based on GPQs. He referred to such confidence intervals as Generalized Confidence Intervals (GCIs). In 2002, Iyer and Patterson developed a general recipe for the construction of generalized pivotal quantities and generalized confidence intervals based on Fraser's ideas of structural representations. They illustrated its application through a number of examples. During the past a few years, generalized confidence intervals have been used by many authors to solve many practical problems where exact nontrivial frequentist intervals are not available. See, for instance, Weerahandi 1995, Chang and Huang 2000, Hamada and Werrahandi 2000, McNally et al. 2001, Burdick and Park 2003, Kirshnamoorthy and Lu 2003, Kirshnamoorthy and Mathew 2003, Mathew and Kirshnamoorthy 2004, Weerahandi 2004, Arendacká 2005, Burdick et al. 2005, Daniels et al. 2005, Wang and Iyer 2006, Tian and Wu 2007, Zou and Donner 2008 and Daniels et al. 2008.

In 2006, Hannig et al. singled out a subclass of generalized pivotal quantities. They labeled the GPQs in this subclass as Fiducial Generalized Pivotal Quantities (FGPQs). A confidence interval derived from a FGPQ is referred to as a fiducial generalized confidence interval (FGCI). They explained the reason for chosing the term "FGPQ" is because GCIs based on FGPQs are in fact obtainable using the fiducial argument of Fisher (1935) within a suitably chosen framework, such as the structural inference of Fraser (1966, 1968). In fact, Hannig et al. (2006) not only established a clear connection between fiducial intervals and generalized confidence intervals, but also proved the asymptotic frequentist correctness of such intervals. In the next section, we describe the definition and applications of FGPQ.

It is interesting to note that most of the published works on fiducial inference concentrated on the inference for parameters of continuous distributions. Fisher was aware that it was difficult applying fiducial arguments to discrete distributions, even for distributions with a single parameter, because of the fact that the probability statements could not be preserved and only statements about inequalities were admissible. In 1950, Stevens derived a method of finding an unique fiducial distribution of a parameter of a discrete distribution by introducing a random variate. In his series of papers from 1966 through 1968 (Dempster (1966), Dempster (1968)), Dempster applied fiducial argument to the binomial and multinomial models and arrived at an upper and lower bounds on probability distributions, which was later picked up by Shafer (1976) and named "belief functions". In 2008, Hannig extended Fisher's fiducial argument and obtained a generalized fiducial recipe which is applicable in virtually any situation, both for continuous distribution and for discrete distribution. The resulting inference based on the generalized fiducial recipe is termed *generalized fiducial inference* to distinguish with the fiducial inference and emphasize connection with generalized inference as well as the fact that multiple generalized fiducial distributions can be defined for the same parameter. He argued that the non-uniqueness of fiducial inference is essentially caused by the Borel paradox, the fact that the conditional distribution conditioned on an event of probability 0 is not uniquely determined.

It is safe to say that the fiducial inference failed to secure a place in mainstream statistics. However many recent works, for example, Hannig et al. (2006), Hannig and Lee (2007), Hannig (2008), showed the fiduical argument leads to statistical procedures with both good small sample frequentist properties and good asymptotic properties. Hannig (2008) ends his paper with the statement "The surprisingly good small sample properties demonstrated by many statistical applications lead us to believe that if computer simulations have been available 60 years ago fiducial argument could have been part of statistical mainstream today." In Fisher Memorial Lecture of 1996, Efron (1998) discussed the desirability of something like fiducial inference in future statistics. In the section dealing with fiducial inference, he says "Maybe Fisher's biggest blunder will become a big hit in the 21st century!"

1.2 Generalized Fiducial Inference

In this work, our focus is on the application of generalized fiducial inference, especially the application of fiducial generalized pivotal quantity introduced by Hannig et al. (2006), generalized fiducial recipe and fiducial generalized distribution developed by Hannig (2008). Next, we give the definitions of FGPQ and fiducial generalized distribution, and illustrate their applications via some examples.

1.2.1 Fiducial Generalized Pivotal Quantity (FGPQ)

Let $\mathbb{S} \in \mathbb{R}^k$ denote an observable random vector whose distribution is indexed by a (possibly vector) parameter $\xi \in \mathbb{R}^p$. Suppose one is interested in making inferences about $\theta = \pi(\xi) \in \mathbb{R}^q$ $(q \geq 1)$. Let $\mathbb{S}^\star$ represent an independent copy of $\mathbb{S}$. Let $\mathbf{s}$ and $\mathbf{s}^\star$ denote realized values of $\mathbb{S}$ and $\mathbb{S}^\star$, respectively. Hannig et al. (2006) defines a fiducial generalized pivotal quantity for θ, denoted by $\mathcal{R}_\theta(\mathbb{S}, \mathbb{S}^\star, \xi)$, as a function of $(\mathbb{S}, \mathbb{S}^\star, \xi)$ with the following properties.

(FGPQ1) The conditional distribution of $\mathcal{R}_\theta(\mathbb{S}, \mathbb{S}^\star, \xi)$, conditional on $\mathbb{S} = \mathbf{s}$, is free of ξ.

(FGPQ2) For every allowable $\mathbf{s} \in \mathbb{R}^k$, $\mathcal{R}_\theta(\mathbf{s}, \mathbf{s}, \xi) = \theta$.

In the same paper, Hannig et al. (2006) also provided a few recipes for constructing FGPQs. One of these recipes is based on the structural method when an invertible pivotal quantity exists. This recipe can be described as follows. Suppose that there exist mappings $f_1, \ldots, f_k$, with $f_j : \mathbb{R}^k \times \mathbb{R}^k \to \mathbb{R}$, such that $\mathbf{f}= (f_1, \ldots, f_k)$ is an invertible pivotal quantity with inverse mapping $\mathbf{g}(\mathbf{s}, \cdot)$. Then

$$\begin{aligned}
\mathcal{R}_\theta &= \mathcal{R}_\theta(\mathbb{S}, \mathbb{S}^\star, \xi) \\
&= \pi(\mathrm{g}_1(\mathbb{S}, \mathbf{f}(\mathbb{S}^\star, \xi)), \ldots, \mathrm{g}_k(\mathbb{S}, \mathbf{f}(\mathbb{S}^\star, \xi))) \\
&= \pi(\mathrm{g}_1(\mathbb{S}, \mathbb{E}^\star), \ldots, \mathrm{g}_k(\mathbb{S}, \mathbb{E}^\star)),
\end{aligned}$$

is a FGPQ for $\theta = \pi(\xi)$, where $\mathbb{E}^\star = \mathbf{f}(\mathbb{S}^\star, \xi)$ is an independent copy of $\mathbb{E}$. When θ is a scalar parameter, an equal-tailed two-sided $(1-\alpha)100\%$ GCI for θ is given by $\mathcal{R}_{\theta,\alpha/2} \leq \theta \leq \mathcal{R}_{\theta,1-\alpha/2}$. Here $\mathcal{R}_{\theta,\gamma} = \mathcal{R}_{\theta,\gamma}(\mathbf{s})$ denotes the 100γth percentile of distribution of $\mathcal{R}_\theta$ conditional on $\mathbb{S} = \mathbf{s}$.

Here is an example given by Hannig (2008) to illustrate how to construct FGPQ. This example is also known as *Behrens-Fisher Problem.*

Example 1.1. Consider m iid observations $X_i, i = 1, \ldots, m$, from $\mathrm{N}(\mu_X, \sigma_X^2)$ and n iid observations $Y_j, j = 1, \ldots, n$, from $\mathrm{N}(\mu_Y, \sigma_Y^2)$, where μ_X, μ_Y, σ_X, and σ_Y are unknown parameters. The problem is to obtain confidence bounds for the difference $\theta = \mu_X - \mu_Y$. Let $\bar{X}$ and $\bar{Y}$ denote the sample means and let S_X^2 and S_Y^2 denote the sample variances for the two samples. Then we have $\bar{X} \sim \mathrm{N}(\mu_X, \sigma_X^2/m)$, $\bar{Y} \sim \mathrm{N}(\mu_Y, \sigma_Y^2/n)$, $(m-1)S_X^2/\sigma_X^2 \sim \chi^2(m-1)$, and $(n-1)S_Y^2/\sigma_Y^2 \sim \chi^2(n-1)$. The statistic $\mathbb{S} = (\bar{X}, \bar{Y}, S_X^2, S_Y^2)$ is complete and sufficient for $\xi = (\mu_X, \mu_Y, \sigma_X^2, \sigma_Y^2)$.

Note that $\mathbb{S}$ and ξ have an inverse pivotal relationship given by

$$f_1(\mathbb{S}) = \frac{\sqrt{m}(\bar{X} - \mu_X)}{\sigma_X} = E_1 \sim N(0,1) \qquad f_3(\mathbb{S}, \xi) = \frac{(m-1)S_X^2}{\sigma_X^2} = E_3 \sim \chi^2(m-1)$$
$$f_2(\mathbb{S}) = \frac{\sqrt{n}(\bar{Y} - \mu_Y)}{\sigma_Y} = E_2 \sim N(0,1) \qquad f_4(\mathbb{S}, \xi) = \frac{(n-1)S_Y^2}{\sigma_Y^2} = E_4 \sim \chi^2(n-1)$$

with inverse

$$\mathrm{g}_1(\mathbb{S}, \mathbb{E}) = \bar{X} - \frac{1}{\sqrt{m}} E_1 \sqrt{\frac{(m-1)S_X^2}{E_3}} \qquad \mathrm{g}_3(\mathbb{S}, \mathbb{E}) = \frac{(m-1)S_X^2}{E_3}$$
$$\mathrm{g}_2(\mathbb{S}, \mathbb{E}) = \bar{Y} - \frac{1}{\sqrt{n}} E_2 \sqrt{\frac{(n-1)S_Y^2}{E_4}} \qquad \mathrm{g}_4(\mathbb{S}, \mathbb{E}) = \frac{(n-1)S_Y^2}{E_4}$$

Now by the recipe a FGPQ for $\pi_X(\xi) = \mu_X$ is given by

$$\mathcal{R}_{\mu_X} = \mathcal{R}_{\mu_X}(\mathbb{S}, \mathbb{S}^\star, \xi) = \mathrm{g}_1(\mathbb{S}, \mathbf{f}(\mathbb{S}^\star, \xi)) = \bar{X} - (\bar{X}^\star - \mu_X)\sqrt{\frac{S_X^2}{{S_X^\star}^2}}$$

There is a similar expression for $\mathcal{R}_{\mu_Y}$. For $\theta = \pi_X(\xi) - \pi_Y(\xi)$ the recipe produces the following FGPQ

$$\mathcal{R}_\theta = \mathcal{R}_{\mu_X} - \mathcal{R}_{\mu_Y} = \bar{X} - \bar{Y} - \left((\bar{X}^\star - \mu_X)\sqrt{\frac{S_X^2}{{S_X^\star}^2}} - (\bar{Y}^\star - \mu_Y)\sqrt{\frac{S_Y^2}{{S_Y^\star}^2}} \right)$$

1.2.2 Fiducial Generalized Distribution

Let $\mathbb{X}$ be a random vector with a distribution indexed by a (possibly vector) parameter $\xi \in \Xi$. Hannig (2008) defines a generalized fiducial distribution for ξ as follows. Assume that $\mathbb{X}$ has a *structural representation* given by $\mathbb{X} = G(U, \xi)$, where U is a random variable or random vector whose distribution is fully known and free of unknown parameters, and G is a jointly measurable function of U and ξ. Let $T(\boldsymbol{x}, \boldsymbol{u})$ be a set-valued function defined by $T(\boldsymbol{x}, \boldsymbol{u}) = \{\xi : \boldsymbol{x} = G(\boldsymbol{u}, \xi)\}$. The set $\{\xi : \boldsymbol{x} = G(\boldsymbol{u}, \xi)\}$ may be empty, may consist of a single element, or, when the distribution of $\mathbb{X}$ is not continuous, may consist of more than one element (possibly uncountably many elements). The function $T(\mathbb{X}, U)$ may be viewed as an inverse of the function G. Here G defines $\boldsymbol{u}$ as an implicit function of ξ and $\boldsymbol{x}$ is regarded as fixed. Assume for any measurable set S, there is a random element $V(S)$ with support $\bar{S}$, where $\bar{S}$ is the closure of S. Following Hannig (2008) a generalized fiducial distribution of ξ is defined as a conditional distribution of

$$V(T(\boldsymbol{x}, U^*)) \quad \text{given} \quad \{T(\boldsymbol{x}, U^*) \neq \emptyset\}. \tag{1.1}$$

Here $\boldsymbol{x}$ is the observed value of $\mathbb{X}$ and U^* is an independent copy of U.

Next, we give two simple examples provided by Hannig (2008) to illustrate the definition of a generalized fiducial distribution.

Example 1.2. Suppose X_1 and X_2 are iid $N(\mu, 1)$. One is interested in the parameter μ. Let $U = (E_1, E_2)$ where E_i are iid $N(0, 1)$. Following Hannig (2008) we have

$$\mathbb{X} = (X_1, X_2) = G(\mu, U) = (\mu + E_1, \mu + E_2).$$

Let $\boldsymbol{x} = (x_1, x_2)$ and $\boldsymbol{u} = (e_1, e_2)$ be realizations of $\mathbb{X}$ and U respectively. Then the set-valued function T is given by

$$T(\boldsymbol{x}, \boldsymbol{u}) = \begin{cases} x_1 - e_1 & \text{if } x_1 - x_2 = e_1 - e_2, \\ \emptyset & \text{if } x_1 - x_2 \neq e_1 - e_2. \end{cases}$$

Notice that $T(\boldsymbol{x}, \boldsymbol{u})$ is either empty or it is a singleton. Therefore the quantity V is trivial and does not have to be considered here. By definiton, a generalized fiducial distribution of μ is the distribution of $x_1 - E_1^\star$ conditional on $E_1^\star - E_2^\star = x_1 - x_2$ where $U^\star = (E_1^\star, E_2^\star)$ is an independent copy of U. Hence a generalized fiducial distribution for μ is $N(\bar{x}, 1/2)$ where $\bar{x} = (x_1 + x_2)/2$.

Example 1.3. Let $\mathbb{X} = (X_1, \ldots, X_n)$ be a vector of iid Bernoulli random variables X_i with success probability p. Suppose $U = (U_1, \ldots, U_n)$ is a vector of iid uniform (0,1) random variables U_i. Let $\boldsymbol{x} = (x_1, \ldots, x_n)$ be a realization of $\mathbb{X}$ and $s = \sum_{i=1}^n x_i$ be the observed number of 1's. Then the mapping $T : [0,1]^n \to [0,1]$ is given by

$$T(\boldsymbol{x}, \boldsymbol{u}) = \begin{cases} [0, u_{1:n}] & \text{if } s = 0 \\ (u_{n:n}, 1] & \text{if } s = n \\ (u_{s:n}, u_{s+1:n}] & \text{if } s = 1, \ldots, n-1 \text{ and} \\ & \sum_{i=1}^n I(x_i = 1) I(u_i \le u_{s:n}) = s \\ \emptyset & \text{otherwise,} \end{cases}$$

where $U_{s:n}$ denotes the s^{th} order statistic among $U_1, \ldots, U_n$. By definition, a generalized fiducial distribution of p is given by the conditional distribution of $V(T(\boldsymbol{x}, \boldsymbol{U}^\star))$ conditional on the event $T(\boldsymbol{x}, \boldsymbol{U}^\star)$ is not empty where $V(T(\boldsymbol{x}, \boldsymbol{U}^\star))$ is any random variable whose support is contained in $T(\boldsymbol{x}, \boldsymbol{U}^\star)$. The exchangeability of $U_i^\star, i = 1, \ldots, n$, implies that the generalized fiducial distribution of p is the same as the distribution of $V([0, U_{1:n}^\star])$ when $s = 0$, $V([U_{s:n}^\star, U_{s+1:n}^\star])$ when $0 < s < n$, and $V([U_{n:n}^\star, 1])$ when $s = n$. Notice that if $T(\boldsymbol{x}, \boldsymbol{U}^\star)$ is non-empty, it is an entire interval. Therefore the choice V will have an effect on the result. Hannig (2008) suggested to use $V((a, b]) = a$ with probability 1/2 and $V((a, b]) = b$ with probability 1/2. In this case the FGPQ of p is $\mathcal{R}_p = BU_{s:n}^\star + (1 - B)U_{s+1:n}^\star$ where B is a Bernoulli(1/2) random variables. For detailed discussion of choices of V, readers are referred to Hannig (2008).

In this dissertation, we have applied the fiducial generalized pivotal quantity and generalized fiducial distribution to solve four practical issues. The dissertation is organized as follows. In chapter 2, we proposed interval estimation procedures for σ_α^2, σ_ε^2 and ρ in a two-component mixed effects linear model using the fiducial approach. In chapter 3, we applied the generalized fiducial recipe to propose a new method for constructing confidence intervals of LD_{50} for a logistic-response curve. In chapter 4, we developed the fiducial generalized confidence intervals for the concordance correlation coefficient and used it to conduct statistical tests. In chapter 5 we constructed simultaneous confidence intervals for all pairwise ratios of means of more than two Lognormal distributions based on a fiducial generalized pivotal quantity.

Chapter 2

FIDUCIAL GENERALIZED CONFIDENCE INTERVALS FOR VARIANCE COMPONENTS IN AN UNBALANCED TWO-COMPONENT NORMAL MIXED LINEAR MODEL

2.1 Introduction

Random effects and mixed effects linear models are useful in applications that require accounting for components of variability arising from multiple sources. For example, in animal breeding studies, mixed linear models with two variance components are often used. One variance component accounts for genetic variability and the other accounts for variability due to environmental factors. In industrial applications where one is interested in understanding process variability mixed models with multiple variance components are used to account for variability due to operators, due to batches of raw material, due to machine differences, due to measurement errors, and so on. In such situations it is of interest to estimate the components of variance and provide lower and upper confidence bounds for them.

Confidence intervals for variance components have been an important topic of research for over 70 years. Interestingly, the first published work on interval estimation for the between groups variance component in the standard one-way normal random model is by R. A. Fisher (1935) who gave a solution to this problem using his then new method of fiducial argument. Bross (1950) provided further computational details for the fiducial approach and informally compared it with approximate frequentist methods available at the time. Numerous subsequent articles have been written on this topic by many authors. See for instance, Green (1954), Huitson (1955), Graybill et al. (1956), Welch (1956), Healy (1961, 1963), Williams (1962), Broemeling (1969), Burdick and Sielken (1978), Venables and James (1978), Jeyaratnam and Graybill (1980), Graybill and Wang (1980), Seely (1980), Burdick and Graybill (1984), Harville and Fenech (1985), Wild (1981), among others. Most of these papers are concerned with developing exact or approximate confidence intervals for specified linear functions of variance components or their ratios. Some of the work was carried out in the context of inference on a heritability coefficient in animal breeding studies. Healy (1963), Venables and James (1978), and Wild (1981) consider fiducial approaches to the problem in the case of balanced data.

Our focus in this work is on unbalanced normal mixed linear models with two variance components. There are several good reasons for limiting ourselves to these models. Two-component mixed models are actually a fairly general class since there are no restrictions placed on the fixed-effects part of the model. Also, closed form expressions for minimal sufficient statistics are available for this situation. Such closed form expressions for minimal sufficient statistics are typically unavailable for general (unbalanced) mixed models with more than two variance components. Although, in principle, the fiducial approach can still be implemented in these cases, one loses the computational advantages that accompany closed form expressions for minimal sufficient statistics. These are perhaps some of the reasons explaining why most of the publications on this topic address only the special case of two-component mixed models.

While there are many papers addressing interval estimation problems for the two variance-component mixed linear model and its various special cases, a fiducial solution to the interval estimation problem in this context is not currently available. Here we develop such a fiducial solution and demonstrate via a simulation study that the resulting procedure has better overall frequentist performance than competing methods. We also establish the asymptotic exactness of the coverage probability of fiducial intervals for variance components of interest. Although we focus on confidence interval estimation, our results can be used to carry out hypothesis tests about the variance components. In the context of recovery of intra-block information, Portnoy (1973) has discussed tests of the null hypothesis that the variance component associated with blocks is zero and has proposed improved tests of parameters in such models. The procedures we develop in this work, automatically, make use of both inter- and intra-block information.

More specifically, let $\boldsymbol{Y}$ denote a $N \times 1$ vector of observable random variables. Suppose $\boldsymbol{Y}$ has a distribution described by the following mixed linear model with two variance components

$$\boldsymbol{Y} = \boldsymbol{X}\boldsymbol{\beta} + \boldsymbol{Z}\boldsymbol{u} + \boldsymbol{\varepsilon} \tag{2.1}$$

where $\boldsymbol{X}$ and $\boldsymbol{Z}$ are known incidence matrices of sizes $N \times p$ and $N \times a$, respectively, $\boldsymbol{\beta}$ is a $p \times 1$ vector of unknown parameters, $\boldsymbol{u} \sim N(\boldsymbol{0}, \sigma_\alpha^2 \boldsymbol{A})$ is a $a \times 1$ vector of random effects, $\boldsymbol{\varepsilon} \sim N(\boldsymbol{0}, \sigma_\varepsilon^2 \boldsymbol{I}_N)$ is the error vector of size $N \times 1$, and $\boldsymbol{u}$ and $\boldsymbol{\varepsilon}$ are independent. Without loss of generality we assume $\text{rank}(\boldsymbol{X}) = p$. Also $\boldsymbol{A}$ is a known matrix often referred to as a *relationship matrix* in animal breeding context since it describes the degree to which the elements $u_1, \ldots, u_a$ of the vector $\boldsymbol{u}$ covary. For example, if the elements u_1 and u_2 of $\boldsymbol{u}$ are the (additive) genetic effects corresponding to a parent and an offspring, respectively, then $Cov(u_1, u_2) = \sigma_\alpha^2/2$ (Falconer, 1989). Note that the standard unbalanced one-way random model given by

$$Y_{ij} = \mu + u_i + \varepsilon_{ij}, \qquad i = 1, \ldots, a; \quad j = 1, \ldots, n_i, \tag{2.2}$$

is a special case of model (1).

In this work, we focus on constructing confidence intervals for the variance components σ_α^2, σ_ε^2 and the heritability coefficient $\rho = \sigma_\alpha^2/(\sigma_\alpha^2 + \sigma_\varepsilon^2)$. In the special case of a one-way random effects model, σ_α^2 is the between-groups variance component and ρ is the intraclass correlation coefficient. Our proposed methods follow the fiducial generalized pivotal quantity (FGPQ) based interval procedures discussed in Hannig et al. (2006) and the generalizations of the fiducial method given in Hannig (2008).

The chapter is organized as follows. Section 2.2 provides a brief review of published confidence interval procedures for σ_α^2, σ_ε^2 and ρ. In Section 2.3 we outline the fiducial method for obtaining confidence intervals for general situations. We then apply this method to derive fiducial confidence intervals for σ_α^2, σ_ε^2 and ρ. Our procedure is applicable to the two component mixed model given in (2.1). We compare our proposed procedures for σ_α^2 with competing methods described in Section 2.2 using a simulation study. Details of the simulation study are described in Section 2.4 along with a discussion of the simulation results. In Section 2.5 we consider some data examples using previously published data and illustrate how our proposed procedures are applied.

2.2 Published Confidence Intervals for Two Component Mixed Models

In this section we list some of the published confidence intervals for σ_α^2, σ_ε^2, and $\rho = \sigma_\alpha^2/(\sigma_\alpha^2 + \sigma_\varepsilon^2)$ in a two-component mixed model. These will be compared to the proposed fiducial approach in the simulation study reported in Section 2.4. First we briefly review some well known results concerning minimal sufficient statistics for the mixed model in (2.1).

Let $\boldsymbol{H}$ be a $N \times (N-p)$ matrix such that $\boldsymbol{H}\boldsymbol{H}^T = \boldsymbol{I}_N - \boldsymbol{X}(\boldsymbol{X}^T\boldsymbol{X})^{-}\boldsymbol{X}^T$ and $\boldsymbol{H}^T\boldsymbol{H} = \boldsymbol{I}_{N-p}$. Using the fact that $\boldsymbol{Y} \sim N(\boldsymbol{X\beta}, \sigma_\varepsilon^2\boldsymbol{I}_N + \sigma_\alpha^2\boldsymbol{ZAZ}^T)$, it follows that

$$\boldsymbol{H}^T\boldsymbol{Y} \sim N(\boldsymbol{0}, \sigma_\varepsilon^2\boldsymbol{I}_{N-p} + \sigma_\alpha^2\boldsymbol{G}) \tag{2.3}$$

where $\boldsymbol{G} = \boldsymbol{H}^T\boldsymbol{ZAZ}^T\boldsymbol{H}$. Let $\lambda_1 >, \ldots, > \lambda_d \geq 0$ be the distinct eigenvalues of $\boldsymbol{G}$ having multiplicities $r_1, \ldots, r_d$, respectively. Let $\boldsymbol{P} = [\boldsymbol{P}_1, \ldots, \boldsymbol{P}_d]$ be a $(N-p) \times (N-p)$ orthogonal matrix such that $\boldsymbol{P}^T\boldsymbol{GP} = diag(\lambda_1\boldsymbol{1}_{r_1}^T, \ldots, \lambda_d\boldsymbol{1}_{r_d}^T)$, where $\boldsymbol{P}_i$ corresponding to λ_i is of size $(N-p) \times r_i$. Define

$$V_i = \boldsymbol{Y}^T\boldsymbol{H}\boldsymbol{P}_i\boldsymbol{P}_i^T\boldsymbol{H}^T\boldsymbol{Y}, \qquad i = 1, \ldots, d. \tag{2.4}$$

Olsen et al. (1976) showed that $(V_1, \ldots, V_d)$ is minimal sufficient for $(\sigma_\alpha^2, \sigma_\varepsilon^2)$ under (2.3). Furthermore,

$$U_i = \frac{V_i}{\lambda_i\sigma_\alpha^2 + \sigma_\varepsilon^2} \sim \chi_{r_i}^2, \qquad i = 1, \ldots, d, \tag{2.5}$$

and U_is' are mutually independent, where χ_v^2 represents a central chi-squared distribution with degrees of freedom v. Note that, when λ_d is zero, a *pure error* estimate of σ_ε^2 is given by V_d/r_d. An exact $100(1-\alpha)\%$ confidence interval for σ_ε^2 exists and is given by

$$\left[\frac{V_d}{\chi_{1-\alpha/2;r_d}^2}, \frac{V_d}{\chi_{\alpha/2;r_d}^2}\right], \tag{2.6}$$

where $\chi_{\alpha;v}^2$ represents the 100α-percentile of the chi-squared distribution with v degrees of freedom. We refer to the interval in (2.6) as EXACT (**EX**) confidence interval for σ_ε^2. When $\lambda_d > 0$ a pure error estimate of σ_ε^2 is not available. In particular, an exact confidence interval for σ_ε^2 is unavailable.

2.2.1 Confidence Intervals for σ_α^2 in an Unbalanced One-way Random Effects Model

Several methods are available in the literature for constructing approximate confidence intervals for σ_α^2 in the unbalanced one-way random effects model. Five different confidence interval procedures for σ_α^2 that have previously appeared in the literature are used in our simulation study as competitors to the fiducial approach. These methods are – (a) Burdick-Graybill (**BG**) confidence interval (Burdick and Graybill, 1992), (b) Thomas-Hultquist (**TH**) confidence interval (Thomas and Hultquist, 1978), (c) Burdick-Eickman (**BE**) confidence interval (Burdick and Eickman, 1986), (d) Hartung-Knapp (**HK**) confidence interval (Hartung and Knapp, 2000), and (e) Arendacká (**Ar**) confidence interval (Arendacká, 2005).

It is important to note that the first four interval procedures listed above apply only for the one-way random model. They do not apply to the general two-component mixed model in (2.1). For this case, the **Ar** method is applicable when a pure error estimate of σ_ε^2 is available. Next, we briefly review these five interval procedures.

Burdick-Graybill (BG) Confidence Interval

Before we introduce **BG** confidence interval, we give some notations used to define **BG** confidence interval. Let

$$\overline{Y}_{i\star} = \frac{\sum_{j=1}^{n_i} Y_{ij}}{N}, \quad \overline{Y}_{\star\star} = \frac{\sum_{i=1}^{a} n_i \overline{Y}_{i\star}}{N}, \quad N = \sum_{i=1}^{a} n_i, \quad n_0 = \frac{1}{a-1}\left(N - \frac{\sum_{i=1}^{a} n_i^2}{N}\right),$$

$$SS_1 = \sum_{i=1}^{a} n_i(\overline{Y}_{i\star} - \overline{Y}_{\star\star})^2, \quad SS_2 = \sum_{i=1}^{a}\sum_{j=1}^{n_i}(Y_{ij} - \overline{Y}_{i\star})^2, \quad \theta_1 = \sigma_\varepsilon^2 + n_0\sigma_\alpha^2, \quad \theta_2 = \sigma_\varepsilon^2,$$

$$S_1^2 = SS_1/(a-1), \text{ and } S_2^2 = SS_2/(N-a).$$

In an unbalanced design, SS_1/θ_1 has a chis-squared distribution if and only if $\sigma_\alpha^2 = 0$. If it is known that σ_α^2 is close to zero, then treating SS_1/θ_1 as a chi-squared random variable may be appropriate. Using this idea, Burdick and Graybill (1992) developed an approximate confidence interval for σ_α^2 based on the reasoning that SS_1/θ_1 has, approximately, a chi-squared distribution with $a-1$ degrees of freedom when σ_α^2 is close to zero. They obtained this approximate confidence interval by appropriately modifying the corresponding confidence interval in balanced case. The resulting approximate two-sided $(1-\alpha)100\%$ confidence interval is given by

$$\left[\max\left(\frac{S_1^2 - S_2^2 - \sqrt{V_L}}{n_0},\ 0\right),\ \max\left(\frac{S_1^2 - S_2^2 + \sqrt{V_U}}{n_0},\ 0\right)\right]$$

where

$$V_L = G_1^2 S_1^4 + H_2^2 S_2^4 + G_{12} S_1^2 S_2^2, \quad V_U = H_1^2 S_1^4 + G_2^2 S_2^4 + H_{12} S_1^2 S_2^2,$$

$$G_1 = 1 - \frac{1}{F_{1-\alpha/2;a-1,\infty}}, \quad G_2 = 1 - \frac{1}{F_{1-\alpha/2;N-a,\infty}},$$

$$H_1 = \frac{1}{F_{\alpha/2;a-1,\infty}} - 1, \quad H_2 = \frac{1}{F_{\alpha/2;N-a,\infty}} - 1,$$

$$G_{12} = \frac{\left(F_{1-\alpha/2;a-1,N-a} - 1\right)^2 - G_1^2 F_{1-\alpha/2;a-1,N-a}^2 - H_2^2}{F_{1-\alpha/2;a-1,N-a}},$$

$$H_{12} = \frac{\left(1 - F_{\alpha/2;a-1,N-a}\right)^2 - H_1^2 F_{\alpha/2;a-1,N-a}^2 - G_2^2}{F_{\alpha/2;a-1,N-a}},$$

and $F_{\alpha;v_1,v_2}$ represents the α-quantile of the F-distribution with v_1 and v_2 degrees of freedom. Since this procedure is based on the assumption that σ_α^2 is close to zero, it might result in very liberal intervals when σ_α^2 is far from zero (Burdick and Graybill, 1992).

Thomas-Hultquist (TH) Confidence Interval

Thomas and Hultquist (1978) derived an approximate pivotal quantity for θ_1 that can be used for constructing confidence intervals for σ_α^2 in the unbalanced one-way random effects model. This quantity is SS_3/θ_3 where

$$SS_3 = \sum_{i=1}^{a}\left(\overline{Y}_{i\star} - \frac{1}{a}\sum_{i=1}^{a}\overline{Y}_{i\star}\right)^2, \quad \theta_3 = \sigma_\alpha^2 + \frac{\sigma_\varepsilon^2}{\tilde{n}}, \quad \text{and } \tilde{n} = \frac{a}{\sum_{i=1}^{a}(1/n_i)}.$$

We define $S_3^2 = SS_3/(a-1)$. Note that SS_3 is the unweighted sum of squares of the treatment means and $\tilde{n}$ denotes the harmonic mean of n_i values. Thomas and Hultquist (1978) showed that the moment generating function of SS_3/θ_3 approaches that of a chi-squared random variable with $a-1$ degrees of freedom as all n_i approach a constant value or infinity, or if the ratio $\eta = \sigma_\alpha^2/\sigma_\varepsilon^2$ approaches infinity. Furthermore, SS_3 is independent of SS_2. Therefore, $(SS_3/\theta_3)/(SS_2/\theta_2)$ has an approximate $F_{a-1,N-a}$ distribution. Using these facts and modifying the Tukey-Williams confidence interval formula for σ_α^2 developed for the balanced case, Thomas and Hultquist (1978) proposed the following approximate two-sided $(1-\alpha)100\%$ confidence interval for σ_α^2

$$\left[\frac{\tilde{n}SS_3-(a-1)S_2^2F_{1-\alpha/2;a-1,N-a}}{\tilde{n}\chi^2_{1-\alpha/2;a-1}}, \frac{\tilde{n}SS_3-(a-1)S_2^2F_{\alpha/2;a-1,N-a}}{\tilde{n}\chi^2_{\alpha/2;a-1}}\right], \tag{2.7}$$

where $\chi^2_{\alpha;v}$ represents the α-quantile of the chi-squared distribution with v degrees of freedom. Results of their simulation study indicated that SS_3/θ_3 is not well approximated by a chi-squared random variable when $\eta < 0.25$ and the design is extremely unbalanced. In these cases, the confidence interval in (2.7) can be quite liberal.

Burdick-Eickman (BE) Confidence Interval

Williams (1962) constructed an interval for σ_α^2 in the balanced one-way random effects model by solving for the intersection of exact $(1-\alpha)100\%$ confidence intervals on $\sigma_\epsilon^2 + n\sigma_\alpha^2$ and the ratio η. Burdick and Eickman (1986) followed this strategy and combined approximate intervals for θ_3 and η. The approximate $(1-\alpha)100\%$ confidence interval for θ_3 they used is based on the Thomas-Hultquist (1978) approximation, and is given by

$$\left[\frac{SS_3}{\chi^2_{1-\alpha/2;a-1}}, \frac{SS_3}{\chi^2_{\alpha/2;a-1}}\right]. \tag{2.8}$$

The approximate $(1-\alpha)100\%$ confidence interval on η they used is the one developed by Burdick et al. (1986). This interval is $[L_{BM}, U_{BM}]$ where

$$\begin{aligned} L_{BM} &= \max\left(0,\ \frac{S_3^2}{S_2^2F_{1-\alpha/2;a-1,N-a}} - \frac{1}{\min(n_1,\ldots,n_a)}\right), \\ U_{BM} &= \max\left(0,\ \frac{S_3^2}{S_2^2F_{\alpha/2;a-1,N-a}} - \frac{1}{\max(n_1,\ldots,n_a)}\right). \end{aligned} \tag{2.9}$$

The interval in (2.9) has a confidence coefficient at least as great as $1-\alpha$. By finding the intersection region of (2.8) and (2.9), Burdick and Eickman arrived at an approximate two-sided $(1-\alpha)100\%$ confidence interval for σ_α^2. This interval is

$$\left[\left(\frac{\tilde{n}L_{BM}}{1+\tilde{n}L_{BM}}\right)\frac{SS_3}{\chi^2_{1-\alpha/2;a-1}}, \left(\frac{\tilde{n}U_{BM}}{1+\tilde{n}U_{BM}}\right)\frac{SS_3}{\chi^2_{\alpha/2;a-1}}\right]. \tag{2.10}$$

The confidence coefficient of the interval in (2.10) is at least $1-\alpha$.

Hartung-Knapp (HK) Confidence Interval

In the unbalanced one-way random effects model Wald (1940) showed that the quantity SS_4 defined by

$$SS_4 = \sum_{i=1}^{a} w_i \left(\overline{Y}_{i\star} - \frac{\sum_{i=1}^{a} w_i \overline{Y}_{i\star}}{\sum_{i=1}^{a} w_i} \right)^2,$$

where $w_i = n_i/(1+\eta n_i)$, is a pivotal quantity for $\eta = \sigma_\alpha^2/\sigma_\varepsilon^2$. Specifically, $SS_4/\sigma_\varepsilon^2$ follows chi-squared distribution with $a-1$ degrees of freedom. Furthermore, SS_4 and SS_2 are independent. Therefore, letting $S_4^2 = SS_4/(a-1)$, it follows that

$$R(\eta) = \frac{S_4^2}{S_2^2} \sim F_{a-1,N-a}$$

and an exact confidence interval for η may be obtained from an interval for $R(\eta)$. Wald (1940) showed that SS_4 is a strictly monotonic decreasing function in η, so the bounds of a $100(1-\alpha)\%$ confidence interval for η are given as the unique solutions to the equations

$$\begin{aligned} R(\eta) &= F_{1-\alpha/2;a-1,N-a}, \\ R(\eta) &= F_{\alpha/2;a-1,N-a}. \end{aligned} \tag{2.11}$$

Hartung and Knapp (2000) considered the solutions, η_L, η_U, to equations (2.11) and used these to construct an approximate two-sided $(1-\alpha)100\%$ confidence interval for σ_α^2. Their interval is given by

$$[S_2^2\eta_L', S_2^2\eta_U'],$$

where

$$\eta_L' = \begin{cases} \eta_L & \text{if } 0 \le \eta_L \le R(0) \\ 0 & \text{otherwise} \end{cases} \quad \text{and} \quad \eta_U' = \begin{cases} \eta_U & \text{if } 0 \le \eta_U \le R(0) \\ 0 & \text{otherwise} \end{cases}.$$

Arendacká (Ar) Confidence Interval

Arendacká (2005) considered the special case of $\lambda_d = 0$ and constructed a confidence interval for σ_α^2 using generalized test variables and generalized p-values. For a discussion of generalized p-values, see Weerahandi (1991). Arendacká showed that the quantity T defined by

$$T = \sum_{i=1}^{d-1} \left(U_i - \frac{v_i U_d}{v_d + \lambda_i \sigma_\alpha^2 U_d} \right), \tag{2.12}$$

is a generalized test variable, where $(v_1, \ldots, v_d)$ is a realization of $(V_1, \ldots, V_d)$. She further defined the function

$$\pi_T(v_1, \ldots, v_d, \sigma_\alpha^2) = \int_0^\infty \left(1 - F_W\left(\sum_{i=1}^{d-1} \frac{v_i u}{v_d + \lambda_i \sigma_\alpha^2 u}\right)\right) f_{U_d}(u) du,$$

where $W = \sum_{i=1}^{d-1} U_i$ and $f_{U_d}(u)$ is the p.d.f. of U_d. She showed that

$$L_{BA} \leq \sigma_\alpha^2 \leq U_{BA} \tag{2.13}$$

is a generalized confidence interval for σ_α^2, where L_{BA} and U_{BA} are obtained by solving the equations

$$\pi_T(v_1, \ldots, v_d, L_{BA}) = \alpha/2, \quad \text{and}$$
$$\pi_T(v_1, \ldots, v_d, U_{BA}) = 1 - \alpha/2.$$

In particular, $[L_{BA}, U_{BA}]$ has coverage probability approximately $(1-\alpha)$. It is worth noting that Arendacká's method is closely related to the generalized pivotal quantity for σ_α^2 derived in Iyer et al. (2004) in an unbalanced one-way random model with heterogeneous variances.

Arendacká (2005) also considered three other test variables based on the results in Zhou and Mathew (1994). Her simulation study showed that all the test variables perform equally well in terms of empirical coverages. But when comparing the average lengths of the intervals, the test variable T in (2.12) performed better overall than the other three test variables. Thus we use the interval in (2.13) for comparing with our proposed fiducial method.

2.2.2 Confidence Intervals for σ_ε^2 in a Two Variance Components Mixed Model

As mentioned earlier, an exact confidence interval for σ_ε^2 is available when $\lambda_d = 0$, i.e., a pure error estimate of σ_ε^2 is available. However, for the case $\lambda_d > 0$, to our knowledge, no confidence interval procedure has been proposed in the literature for σ_ε^2. Here we propose a fiducial interval estimate for σ_ε^2 that appears to have satisfactory coverage properties. The fiducial approach is discussed in Section 2.3.

2.2.3 Confidence Intervals for ρ in a Two Variance Components Mixed Model

In many applications the quantity $\rho = \sigma_\alpha^2/(\sigma_\alpha^2+\sigma_\varepsilon^2)$ is of interest. For example, in plant and animal breeding, ρ represents the proportion of the total variance that is explainable by additive genetic effects. It is often referred to as the heritability of the trait under study.

Many authors have considered the problem of constructing exact confidence intervals for ρ beginning with Wald (1940) and Wald (1947). Other contributors to this problem include Khuri (1981), Seely and El Bassiouni (1983), Verdooren (1988), Lee and Seely (1996), Fenech and Harville (1991), and Burch and Iyer (1997). The main tool used in these papers is the fact that independent quadratic forms V_i, $i = 1, \ldots, d$, given in (2.4) are available using which a pivotal quantity for ρ may be constructed in the form

$$R = \frac{\displaystyle\sum_{i\in I^c} \frac{V_i}{1+\rho(\lambda_i - 1)} \Bigg/ \sum_{i\in I^c} r_i}{\displaystyle\sum_{j\in I} \frac{V_j}{1+\rho(\lambda_j - 1)} \Bigg/ \sum_{j\in I} r_j}, \tag{2.14}$$

where I is any nonempty subset of $\{1, \ldots, d\}$. This pivotal quantity has a central F distribution. Burch and Iyer (1997) studied a subset of pivots of the above form that led to locally unbiased intervals for ρ and recommended the use of an optimal interval from this subclass. We refer to their recommended interval as **BI** confidence interval. Since nearly all of the exact intervals for ρ proposed in the literature belong to this class, for instance the Wald intervals, we compare our proposed fiducial interval for ρ with the **BI** intervals.

2.3 Fiducial Generalized Confidence Intervals for σ_α^2, σ_ε^2 and ρ

It is worth noting that generalized confidence intervals such as those proposed by Arendacká (2005) are closely related to fiducial intervals. This connection between generalized inference and fiducial inference is discussed in detail by Hannig et al. (2006). They also provide a recipe for constructing fiducial intervals when $\boldsymbol{X}$ has a continuous distribution. Hannig (2008) generalizes this to arbitrary distributions. They use the term *generalized fiducial inference* to emphasize the fact that the version of fiducial inference discussed in Hannig et al. (2006) and Hannig (2008) is a generalization of R. A. Fisher's fiducial argument.

In this section we describe fiducial interval (**FI**) procedures for σ_α^2, σ_ε^2 and ρ that are applicable under the general two-component mixed model in (2.1). The intervals we propose are obtained using the fiducial method described in Hannig et al. (2006) and Hannig (2008).

2.3.1 The Fiducial Approach

Following the Hannig's generalized fiducial recipe (Hannig (2008)) introduced in Chapter 1, we define a generalized fiducial distribution of parameter ξ of interest as a conditional distribution of

$$V(T(\boldsymbol{x}, U^*)) \quad \text{given} \quad \{T(\boldsymbol{x}, U^*) \neq \emptyset\}, \tag{2.15}$$

where the parameter ξ, random variable U^*, functions V and T, and observed value $\boldsymbol{x}$ have the same definitions as in (1.1). As introduced in Chapter 1, if the probability $P(T(\boldsymbol{x}, U^*) \neq \emptyset) = 0$, as it is in our case, the conditioning event will have to be interpreted using equations involving random variables. Therefore the fiducial distribution of $(\sigma_\alpha^2,\ \sigma_\varepsilon^2)$ is not unique. A different choice of the conditioning equations will result in a different fiducial distribution for $(\sigma_\alpha^2,\ \sigma_\varepsilon^2)$. This is related to the well known Borel's paradox described, for example, in Casella and Berger (2002), Section 4.9.3. We will present a particular way of interpreting (1.1) that seems very intuitively appealing and leads to fiducial distribution for $\sigma_\alpha^2, \sigma_\varepsilon^2$ with very good statistical properties.

We begin with the statistics $Q_i = V_i/r_i$, $i = 1, \ldots, d$, where V_i and r_i are defined in (2.4). Observe that they are minimal sufficient for $\{\sigma_\alpha^2, \sigma_\varepsilon^2\}$ under the model in (2.3). When $d = 2$, the relationship between $(\sigma_\alpha^2,\ \sigma_\varepsilon^2)$ and (Q_1, Q_2) is invertible. This makes fiducial inference for the case $d = 2$ quite straightforward and is not considered here. Hereafter we assume $d > 2$ which is the more general and challenging case. We rewrite the expressions in (2.5) as follows.

$$Q_1 = \frac{(\lambda_1\sigma_\alpha^2 + \sigma_\varepsilon^2)\,U_1}{r_1},\ Q_2 = \frac{(\lambda_2\sigma_\alpha^2 + \sigma_\varepsilon^2)\,U_2}{r_2}, \ldots,\ Q_d = \frac{(\lambda_d\sigma_\alpha^2 + \sigma_\varepsilon^2)\,U_d}{r_d}. \tag{2.16}$$

Note that (2.16) provide a structural representation for the observable random vector $\boldsymbol{Q} = (Q_1, \ldots, Q_d)$ in terms of the random vector $\boldsymbol{U} = (U_1, \ldots, U_d)$ whose distribution is completely known (the Us are independent, each U_i having the chi-squared distribution with r_i degrees of freedom). We denote realized values of Q_i and U_i by q_i and u_i, respectively, for $i = 1, \ldots, d$.

The main idea in interpreting (1.1) is to pick randomly two equations in (2.16) and solve for σ_α^2 and σ_ε^2. Then plug these solutions for σ_α^2 and σ_ε^2 into the remaining equations and use them for conditioning. More formally, the set-valued function $T(\boldsymbol{q}, \boldsymbol{U}^\star)$ in (1.1) is the set of all σ_α^2, σ_ε^2, with $\lambda_i\sigma_\alpha^2 + \sigma_\varepsilon^2 > 0$, $i = 1, \ldots, d$ for which the equations

$$q_i = \frac{(\lambda_i\sigma_\alpha^2 + \sigma_\varepsilon^2)\, U_i^\star}{r_i}, \quad i = 1, \ldots, d, \tag{2.17}$$

are satisfied. Here $\boldsymbol{U}^\star$ is an independent copy of $\boldsymbol{U}$. In particular, assuming that equations i, j in (2.17) were chosen and fixed, we solve them for σ_α^2 and σ_ε^2. This gives

$$\sigma_\alpha^2 = \frac{1}{(\lambda_i - \lambda_j)}\left(\frac{r_i q_i}{U_i^\star} - \frac{r_j q_j}{U_j^\star}\right), \quad \sigma_\varepsilon^2 = \frac{1}{(\lambda_i - \lambda_j)}\left(-\frac{\lambda_j r_i q_i}{U_i^\star} + \frac{\lambda_i r_j q_j}{U_j^\star}\right). \tag{2.18}$$

The system of equations in (2.17) then has a solution if and only if the values of σ_α^2 and σ_ε^2 in (2.18) also satisfy the remaining equations in (2.17). This requirement leads to the following set of constraints that must be satisfied by $\boldsymbol{U}^\star$:

$$q_k = \frac{U_k^\star}{r_k(\lambda_i - \lambda_j)}\left(\frac{r_i q_i(\lambda_k - \lambda_j)}{U_i^\star} - \frac{r_j q_j(\lambda_k - \lambda_i)}{U_j^\star}\right) \qquad \text{for } k \neq i, j. \tag{2.19}$$

Summarizing, the set $T(\boldsymbol{q}, \boldsymbol{U}^\star)$ is nonempty if and only if (2.19) holds, in which case the set $T(\boldsymbol{q}, \boldsymbol{U}^\star) = \left\{\left(\frac{1}{(\lambda_i - \lambda_j)}\left(\frac{r_i q_i}{U_i^\star} - \frac{r_j q_j}{U_j^\star}\right), \frac{1}{(\lambda_i - \lambda_j)}\left(-\frac{\lambda_j r_i q_i}{U_i^\star} + \frac{\lambda_i r_j q_j}{U_j^\star}\right)\right)\right\}$. This leads us to define the random variables $W_{1,i,j}$ $W_{2,i,j}$ $Z_{k,i,j}$ as follows.

$$W_{1,i,j} = \frac{1}{(\lambda_i - \lambda_j)}\left(\frac{r_i q_i}{U_i^\star} - \frac{r_j q_j}{U_j^\star}\right), \quad W_{2,i,j} = \frac{1}{(\lambda_i - \lambda_j)}\left(-\frac{\lambda_j r_i q_i}{U_i^\star} + \frac{\lambda_i r_j q_j}{U_j^\star}\right), \text{ and}$$
$$Z_{k,i,j} = \frac{U_k^\star}{r_k(\lambda_i - \lambda_j)}\left(\frac{r_i q_i(\lambda_k - \lambda_j)}{U_i^\star} - \frac{r_j q_j(\lambda_k - \lambda_i)}{U_j^\star}\right).$$

We can now interpret the conditional distribution in (1.1) as

$$W_{1,i,j}, W_{2,i,j} \mid Z_{k,i,j} = q_k, k \neq i, j. \tag{2.20}$$

This conditional distribution has a density that is proportional to the joint density of $W_{1,i,j}, W_{2,i,j}, Z_{k,i,j}, k \neq i, j$ computed at the point $w_1, w_2, \mathbf{q}$ respectively. Routine calculation shows that this density is given by

$$f_{i,j}(w_1, w_2, \mathbf{q}) = \frac{(\lambda_i - \lambda_j) q_i q_j}{2^{\sum_{k=1}^d \frac{r_k}{2}} (\lambda_i w_1 + w_2)(\lambda_j w_1 + w_2)}$$
$$\times \exp\left[-\frac{1}{2}\sum_{k=1}^d \frac{r_k q_k}{\lambda_k w_1 + w_2}\right] \prod_{k=1}^d \frac{r_k^{\frac{r_k}{2}} q_k^{\frac{r_k}{2}-1}}{\Gamma(\frac{r_k}{2})(\lambda_k w_1 + w_2)^{\frac{r_k}{2}}} I_{\{\lambda_k w_1 + w_2 > 0\}}.$$

Unfortunately, a careful inspection of $f_{i,j}(w_1, w_2, \mathbf{q})$ reveals that the conditional distribution (2.20) depends on the arbitrary choice of i, j.

To remedy this non-uniqueness we have considered the equation i, j to be selected at random. By taking this into account, the fiducial density of $(\sigma_\alpha^2, \sigma_\varepsilon^2)$ in (1.1) can therefore be computed as

$$f(w_1, w_2) = \lim_{\varepsilon \to 0^+} \frac{\binom{d}{2}^{-1} \sum_{i<j} \varepsilon^{-d} P(W_{1,i,j} \in (w_1, w_1 + \varepsilon), W_{2,i,j} \in (w_2, w_2 + \varepsilon), Z_{k,i,j} \in (q_k, q_k + \varepsilon), k \neq i, j)}{\binom{d}{2}^{-1} \sum_{i<j} \varepsilon^{-d+2} P(Z_{k,i,j} \in (q_k, q_k + \varepsilon), k \neq i, j)} \tag{2.21}$$

Notice that each term of the sum in the numerator of (2.21) converges to $f_{i,j}(w_1, w_2, \mathbf{q})$. The limit in (2.21) is then

$$f(w_1, w_2) = \frac{\sum_{i<j} f_{i,j}(w_1, w_2, \mathbf{q})}{\sum_{i<j} \iint f_{i,j}(w_1, w_2, \mathbf{q})\, dw_1\, dw_2}$$

which simplifies to a well-defined joint fiducial distribution of $(\sigma_\alpha^2, \sigma_\varepsilon^2)$, given as follows

$$f(w_1, w_2) = C \cdot g(w_1, w_2) \tag{2.22}$$

where

$$g(w_1, w_2) = \left(\sum_{i<j} \frac{(\lambda_i - \lambda_j) q_i q_j}{(\lambda_i w_1 + w_2)(\lambda_j w_1 + w_2)} \right) \left(\frac{\exp(-\frac{1}{2} \sum_{i=1}^{d} \frac{r_i q_i}{\lambda_i w_1 + w_2})}{\prod_{i=1}^{d} (\lambda_i w_1 + w_2)^{\frac{r_i}{2}}} \right) \prod_{i=1}^{d} I_{\{\lambda_i w_1 + w_2 > 0\}}.$$

and

$$C^{-1} = \int_{-\infty}^{0} \int_{-\lambda_1 w_1}^{\infty} g(w_1, w_2) dw_2 dw_1 + \int_{0}^{\infty} \int_{-\lambda_d w_1}^{\infty} g(w_1, w_2) dw_2 dw_1.$$

For future reference denote a random variable with density (2.22) by $(R_{\sigma_\alpha^2}, R_{\sigma_\varepsilon^2})$.

Hannig et al. (2006) outlined a method that can be used to prove that the fiducial distribution for $(\sigma_\alpha^2, \sigma_\varepsilon^2)$ given in (2.22) leads to asymptotically correct frequentist inference if d is fixed and $r_i \to \infty$. However, this is not sufficient for many applications, where we have a large number of different eigenvalues with multiplicities that are relatively small, such as the loin-eye data set discussed in Section 2.5. Consequently, Hannig have generalized his earlier theorem (Hannig et al. (2006)) by allowing the number of distinct eigenvalues d to take any value between 2 and n. However this requires the eigenvalues themselves to satisfy some natural conditions related to the Fisher's information in order to have asymptotically correct frequentist inference. The exact conditions are given in Theorem 2.1. The proof of this theorem can be found in E et al. (2008).

Theorem 2.1. *Denote $n = \sum_{i=1}^{d} r_i$ and assume that the limits*

$$\lim_{n\to\infty} \frac{1}{n} \sum_{i=1}^{d} \frac{\lambda_i^k r_i}{(\lambda_i \sigma_\alpha^2 + \sigma_\varepsilon^2)^2} = m_k \quad for \quad k = 0, 1, 2$$

are such that the matrix $\Sigma = \begin{pmatrix} m_0 & m_1 \\ m_1 & m_2 \end{pmatrix}$ is positive definite. Then the frequentist coverage probability of the $(1-\alpha)$ equal tailed fiducial interval based on the joint fiducial distribution of $(\sigma_\alpha^2, \sigma_\varepsilon^2)$ approaches the stated value as $n \to \infty$.

Remark 2.1. It is worth noting that the Fisher information matrix $\mathcal{F}$ for $(\sigma_\alpha^2, \sigma_\varepsilon^2)$ based on Q_i, $i = 1, \ldots, d$, is the 2 by 2 matrix whose (j, k) element is given by

$$\sum_{i=1}^{d} \frac{r_i \lambda_i^{j+k-2}}{2(\lambda_i \sigma_\alpha^2 + \sigma_\varepsilon^2)^2}$$

for $j, k = 1, 2$. Hence the conditions of the theorem is a statement of the requirement that $\frac{1}{n}\mathcal{F}$ converge to a positive definite matrix $\frac{1}{2}\Sigma$ as $n \to \infty$.

Moreover, it is shown in the proof of the Theorem 2.1 that the fiducial distribution just as Bayesian posteriors satisfies the Bernstein-von Mises theorem. Thus it is asymptotically efficient.

2.3.2 A Fiducial Generalized Confidence Interval for σ_α^2 and σ_ε^2

A fiducial distribution for σ_α^2 can be easily derived from the joint fiducial distribution of $(\sigma_\alpha^2, \sigma_\varepsilon^2)$ in (2.22) and is given by

$$f_{R_{\sigma_\alpha^2}}(w_1) = \begin{cases} C \int_{-\lambda_1 w_1}^{\infty} g(w_1, w_2)\, dw_2 & \text{if } w_1 < 0 \\ C \int_{-\lambda_d w_1}^{\infty} g(w_1, w_2)\, dw_2 & \text{otherwise.} \end{cases}$$

Let $\mathcal{R}_{\sigma_\alpha^2,\gamma}$ be the $100\gamma-$percentile of the fiducial distribution of σ_α^2. Then a two-sided $(1-\alpha)100\%$ fiducial confidence interval for σ_α^2 is given by

$$\left[\max(0, \mathcal{R}_{\sigma_\alpha^2,\alpha/2}), \max(0, \mathcal{R}_{\sigma_\alpha^2,1-\alpha/2})\right].$$

Similarly it follows that the fiducial distribution of σ_ε^2 is given by

$$f_{R_{\sigma_\varepsilon^2}}(w_2) = \begin{cases} C \int_{-w_2/\lambda_d}^{\infty} g(w_1, w_2)\, dw_1 & \text{if } w_2 < 0 \text{ and } \lambda_d > 0 \\ C \int_{-w_2/\lambda_1}^{\infty} g(w_1, w_2)\, dw_1 & \text{if } w_2 > 0 \\ 0 & \text{otherwise} \end{cases}$$

where C and $g(w_1, w_2)$ are the same as C and $g(w_1, w_2)$ in (2.22), respectively.

Let $\mathcal{R}_{\sigma_\varepsilon^2,\gamma}$ be the $100\gamma-$percentile of the fiducial distribution of σ_ε^2. Then a two-sided $(1-\alpha)100\%$ fiducial confidence interval for σ_ε^2 is given by

$$\left[\max(0, \mathcal{R}_{\sigma_\varepsilon^2,\alpha/2}), \max(0, \mathcal{R}_{\sigma_\varepsilon^2,1-\alpha/2})\right].$$

2.3.3 A Fiducial Generalized Confidence Interval for ρ

A fiducial distribution for ρ can be easily derived from the joint fiducial distribution of $(\sigma_\alpha^2,\ \sigma_\varepsilon^2)$ in (2.22). In fact, we obtain the fiducial density for ρ as the density of $R_\rho = R_{\sigma_\alpha^2}/(R_{\sigma_\alpha^2} + R_{\sigma_\varepsilon^2})$ given by

$$f_{R_\rho}(x) = \begin{cases} C\int_{-\infty}^{0} g(x,y)\,dy & \text{if } \dfrac{x}{1-x} < -\dfrac{1}{\lambda_d} \text{ and } \lambda_d > 0 \\ C\int_{0}^{\infty} g(x,y)\,dy & \text{if } \dfrac{x}{1-x} > -\dfrac{1}{\lambda_1} \\ 0 & \text{otherwise} \end{cases}$$

where

$$\begin{aligned} g(x,y) &= \left(\sum_{i<j} \frac{(\lambda_i-\lambda_j)q_iq_j}{((\lambda_i-1)xy+y)\,((\lambda_j-1)xy+y)}\right)\left(\frac{(1-x)^{(\sum_{i=1}^d r_i)/2}|y|}{\prod_{i=1}^d((\lambda_i-1)xy+y)^{\frac{r_i}{2}}}\right) \\ &\quad\times \exp\left(-\frac{1}{2}\sum_{i=1}^d \frac{(1-x)r_iq_i}{(\lambda_i-1)xy+y}\right)\prod_{i=1}^d I_{\{\frac{(\lambda_i-1)xy+y}{1-x}>0\}}, \qquad \text{and} \end{aligned}$$

$$C^{-1} = \begin{cases} \int_{-\infty}^{1/(1-\lambda_d)}\int_{-\infty}^{0} g(x,y)\,dy\,dx + \int_1^\infty\int_{-\infty}^0 g(x,y)\,dy\,dx + \int_{1/(1-\lambda_1)}^{1}\int_0^\infty g(x,y)\,dy\,dx, & \text{if } \lambda_d > 1 \\ \int_1^\infty\int_{-\infty}^0 g(x,y)\,dy\,dx + \int_{1/(1-\lambda_1)}^{1}\int_0^\infty g(x,y)\,dy\,dx, & \text{if } \lambda_d = 1 \\ \int_1^{1/(1-\lambda_d)}\int_{-\infty}^{0} g(x,y)\,dy\,dx + \int_{-\infty}^{1}\int_0^\infty g(x,y)\,dy\,dx + \int_{1/(1-\lambda_1)}^{\infty}\int_0^\infty g(x,y)\,dy\,dx, & \text{if } 0 < \lambda_1 < 1 \\ \int_1^{1/(1-\lambda_d)}\int_{-\infty}^{0} g(x,y)\,dy\,dx + \int_{-\infty}^{1}\int_0^\infty g(x,y)\,dy\,dx, & \text{if } \lambda_1 = 1 \\ \int_1^{1/(1-\lambda_d)}\int_{-\infty}^{0} g(x,y)\,dy\,dx + \int_{1/(1-\lambda_1)}^{1}\int_0^\infty g(x,y)\,dy\,dx, & \text{if } \lambda_1 > 1 \text{ and } 0 \le \lambda_d < 1. \end{cases}$$

Let $\mathcal{R}_{\rho,\gamma}$ be the 100γ-percentile of the fiducial distribution of ρ. Then a two-sided $(1-\alpha)100\%$ fiducial confidence interval for ρ is given by

$$\left[\max(0, \min(\mathcal{R}_{\rho,\alpha/2}, 1)), \max(0, \min(\mathcal{R}_{\rho,1-\alpha/2}, 1))\right].$$

The next two sections describe details of simulation studies we conducted to compare the proposed fiducial interval for σ_α^2, σ_ε^2 and ρ with previously proposed methods.

2.4 Simulation Study and Discussion of Results

We will use the abbreviations introduced in sections 2.2 and 2.3 when referring to various competing procedures in this and subsequent sections.

The coverage probability of a confidence interval on σ_α^2 depends on the design (e.g. number of within group measurements, $n_1, \ldots, n_a$) as well as the values of σ_α^2 and σ_ε^2. The degree of imbalance of the design, in the case of a one-way random effects model, has been quantified by Ahrens and Pincus (1981) using the measure Φ defined as $\Phi = \frac{a\tilde{n}}{N}$ with $N = \sum_{i=1}^{a} n_i$ and $\tilde{n} = \frac{a}{\sum_{i=1}^{a}(1/n_i)}$. Note that $0 < \Phi \leq 1$ and that Φ equals one if and only if n_i are all equal. The smaller the value of Φ is, the larger is the degree of imbalance. For our simulation study we selected seven different unbalanced patterns shown in Table 2.1. Patterns 1, 2 and 5 were also considered in Hartung and Knapp (2000). Pattern 4 was also considered in Arendacká (2005). We added the additional patterns 3, 6, and 7 to study the performance of confidence intervals in small sample situations. Without loss of generality, we assumed that $\mu = 0$. The values selected for $(\sigma_\alpha^2, \sigma_\varepsilon^2)$ are $(0.1, 10)$, $(0.5, 10)$, $(1, 10)$, $(0.5, 2)$, $(1, 1)$, $(2, 0.5)$, $(5, 0.2)$, and $(10, 0.1)$, where the settings $(0.1, 10)$, $(0.5, 2)$, $(1, 1)$, $(2, 0.5)$, $(5, 0.2)$ were used by Arendacká (2005). Three more settings were added to our study to better investigate the performance of confidence intervals under extremely large and small values of the ratio $\sigma_\alpha^2/\sigma_\varepsilon^2$.

For each setting of sample sizes n_i and values of $(\sigma_\alpha^2, \sigma_\varepsilon^2)$, 3000 independent data sets were generated and two-sided 95% confidence intervals for σ_α^2 were computed for each method. The methods compared were (a) **BG** interval, (b) **TH** interval, (c) **BE** interval, (d) **HK** interval, (e) **Ar** interval, and (f) **FI** interval. The criteria for judging the performance of the methods are (i) the empirical coverage probabilities and (ii) the average lengths of the confidence intervals. The simulation study was programmed in Fortran. Two IMSL (IMSL (1994)) subroutines – DQ2AGI and DTWODQ – were used to compute the needed one-dimensional integrals and the two-dimensional integrals respectively.

Table 2.1: Unbalanced Patterns Used in the Simulation Study.

Pattern	Φ	a	n_i
1	0.068	6	1 1 1 1 1 100
2	0.130	6	2 2 2 2 2 100
3	0.187	3	2 5 60
4	0.410	5	4 4 4 8 48
5	0.700	6	5 10 15 20 25 30
6	0.807	4	2 2 4 6
7	0.957	6	6 6 8 8 10 10

The results of simulation study are graphically summarized in Figures 2.1, 2.2, 2.3 and 2.4. The numerical results are listed in Appendix A. Figures 2.1 and 2.2 show the empirical coverage probabilities for settings with ratio $\eta = \sigma_\alpha^2/\sigma_\varepsilon^2 < 1$ and for settings with $\eta \geq 1$ respectively. Figures 2.3 and 2.4 show the differences of the average confidence interval lengths, relative to the Fiducial interval, for all competing procedures for settings with $\eta < 1$ and for settings with $\eta \geq 1$ respectively. These relative lengths are denoted by RL, which is defined as $(CL_M - CL_{FI})/CL_{FI}$, where CL_M denotes the average length of a competing interval and CL_{FI} denotes the average length of **FI** interval.

The results show that **BG** procedure is very liberal when the ratio η is large. The **TH** procedure is liberal for small values of η and very unbalanced designs. This finding agrees with the findings of Burdick and Eickman (1986). The **BE** procedure is conservative and its behavior for large η is similar to that of the **TH** procedure. The **HK** procedure becomes more conservative as the value of η becomes large. The **Ar** procedure appears to always maintain the stated confidence coefficient. The **FI** interval is conservative when the ratio η is less than 1, but maintains the stated confidence coefficient when η is greater than or equal to 1.

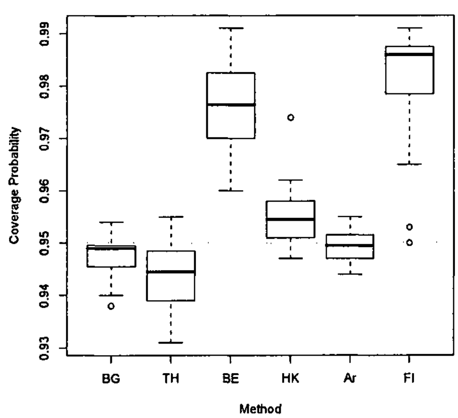

Figure 2.1: Empirical coverage probabilities for settings with $\eta < 1$.

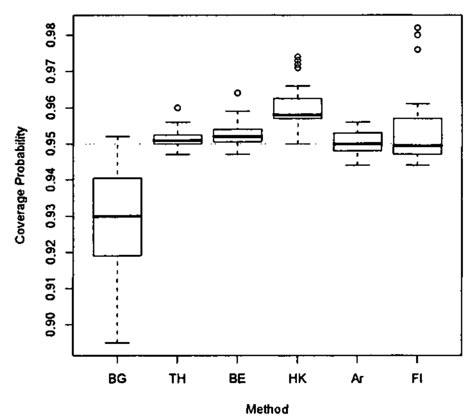

Figure 2.2: Empirical coverage probabilities for settings with $\eta \geq 1$.

Comparing average interval lengths, we observe that all the intervals behave very similarly except the **BG** interval and the **FI** interval. Although the **BG** interval has small

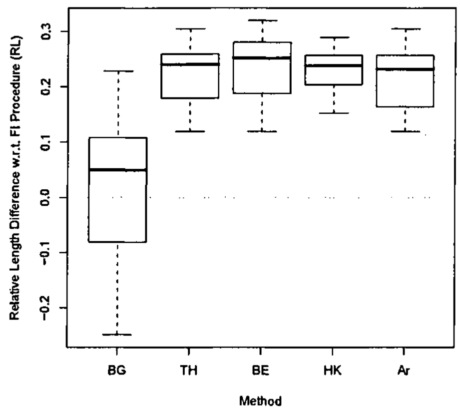

Figure 2.3: Relative differences of the average confidence interval lengths (RL) for settings with $\eta < 1$.

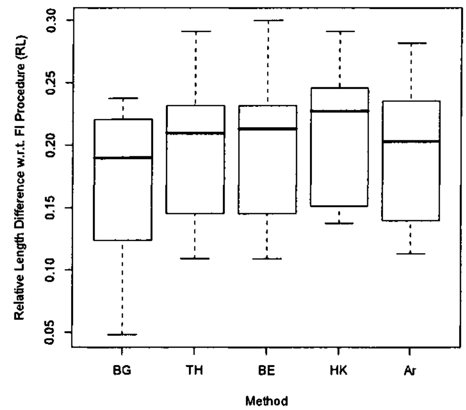

Figure 2.4: Relative differences of the average confidence interval lengths (RL) for settings with $\eta \geq 1$.

average lengths, it does not adequately maintain the stated coverage probabilities when η is large. Therefore the **BG** interval is not recommended. When compared with procedures other than the **BG** procedure, the **FI** interval always has the smallest average lengths and standard deviations, even when it is conservative. The average lengths of **FI** intervals are 10% to 25% smaller than the average lengths of other intervals, except **BG** interval. Based on these results, we recommend the **FI** intervals for σ_α^2 as the most suitable choice for practical applications.

2.5 Examples

As noted earlier, a fiducial interval for σ_α^2, σ_ε^2 and ρ is available in the general mixed model (2.1) with two variance components. In this section we give three examples, one of which involves incomplete block designs for slope-ratio assays and the other two arise from animal breeding studies. The first example is taken from Das and Kulkarni (1966). The second example uses a model that might be referred to as a *sire model.* Both examples have positive degrees of freedom for error and the eigenvalue λ_d is zero. The third example uses a model that may be referred to as a *full animal model.* All eigenvalues $\lambda_j, j = 1, \ldots, d$, are positive and hence there are no degrees of freedom available for error.

2.5.1 Incomplete Block Design for Slope-Ratio Assay

In a $(2k+1)-$point symmetrical slope-ratio assay, equal number of subjects are administered to each of k standard and test preparations and to blank dose. The responses are assumed to linearly depend on doses, usually on a logarithmic scale. This $(2k+1)-$point symmetrical slope-ratio assay requires blocks of size $2k+1$ for a randomized complete block design. Das and Kulkarni (1966) developed a modified BIB design with blocks of size $2k'+1(k'<k)$ for slope-ratio assays. Suppose s_i and t_i, $i=1,\ldots,k$, are the ith dose levels of standard preparation and test preparation respectively, where doses are equally spaced and sorted in ascending order. First a BIB design for k doses of the standard preparation in blocks of size k' is obtained and used as the basic design. The modified BIB design is then obtained by augmenting every block of the basic BIB design by a blank dose and k' doses of the test preparation, using the rule that dose t_i should be included in every block containing dose s_i. Das and Kulkarni (1966) claimed that the modified BIB design is more efficient than the randomized complete block design. Kulshreshtha (1969) later proved that the new design gives shorter confidence interval for relative potency based on Fieller's theorem than the random block design with equal replication of nonzero doses. The relative potency is defined as the ratio of the slope of the dose-response curve for the test preparation to that for the standard preparation. The model for slope-ratio assay considered by Das and Kulkarni (1966) and Kulshreshtha (1969) can be described by the equation

$$y_{ijm} = \mu + \beta_i x_{ij} + \gamma_m + \epsilon_{ijm}, \qquad i = s, t, \text{or } c; \quad j = 1, \ldots, k; \quad m = 1, \ldots, b, \tag{2.23}$$

where y_{sjm}, y_{tjm} and y_{cjm} denote the observation in mth block for jth dose of standard preparation, test preparation and blank dose respectively, x_{sj} and x_{tj} denote the jth dose of the standard and test preparation respectively, x_{cj} is equal to zero, γ_m represents the effect of mth block, ϵ_{ijm} are independent, identically distributed, random measurement errors with a $N(0,\sigma_\epsilon^2)$ distribution. The block effect γ_m is taken to be fixed in Das and Kulkarni (1966) and Kulshreshtha (1969). To illustrate the methods of this work we consider blocks as random and assume $\gamma_m \overset{iid}{\sim} N(0,\sigma_\alpha^2)$. Furthermore, γ_m are assumed to be independent of ϵ_{ijm}.

Das and Kulkarni (1966) gave several real data examples to illustrate the construction and analysis of the new designs. One example is a 9-point slope-ratio assay on riboflavin content of yeast with two replications of each dose. These data were first used by Bliss (1952). Das and Kulkarni (1966) deleted the observations on the highest dose of each preparation and used the remaining data to develop a modified BIB design for 7 doses in 3 blocks of size 5, with 2 replications of each preparation. The observations of titer per tube, arranged according to this design, are shown in Table 2.2. Here we calculate the fiducial distributions associated with σ_α^2, σ_ϵ^2, and ρ.

Table 2.2: Data and Modified BIB Design for Example of Slope-Ratio Assay.

Block	Blank	Standard			Test		
	c	s_1	s_2	s_3	t_1	t_2	t_3
1	0.72	2.15	4.35	-	2.35	4.40	-
2	0.78	-	4.05	6.10	-	4.70	6.10
3	0.76	2.30	-	5.60	2.45	-	5.10

There are three distinct eigenvalues of $\boldsymbol{G} = \boldsymbol{H}^T\boldsymbol{Z}\boldsymbol{A}\boldsymbol{Z}^T\boldsymbol{H}$, $\lambda_1 = 5$ with multiplicity $r_1 = 1$, $\lambda_2 = 4.545455$ with multiplicity $r_2 = 1$, and $\lambda_3 = 0$ with multiplicity $r_3 = 10$. The method of moments (MOM) estimates of σ_α^2 and σ_ε^2 are 0.0033 and 0.1045, respectively. The corresponding estimate of ρ is 0.0306. The REML estimates of σ_α^2 and σ_ε^2 are the same as the MOM estimates.

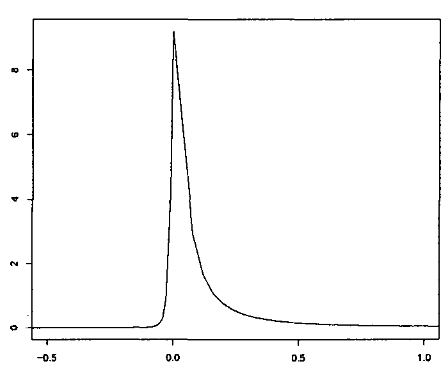

Figure 2.5: Fiducial density plot for σ_α^2 for the slope-ratio assay data.

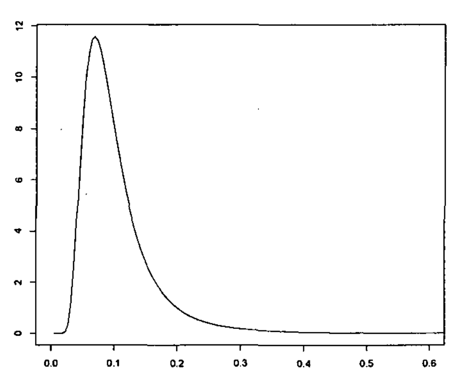

Figure 2.6: Fiducial density plot for σ_ε^2 for the slope-ratio assay data.

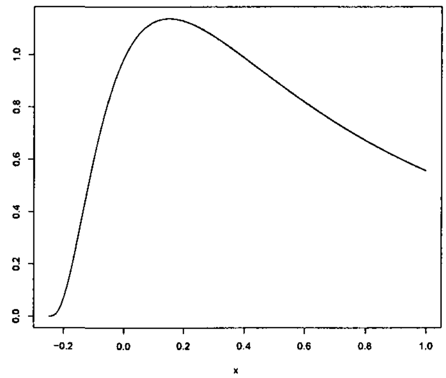

Figure 2.7: Fiducial density plot for ρ for the slope-ratio assay data.

Figures 2.5, 2.6, and 2.7 show plots of the fiducial densities of σ_α^2, σ_ε^2, and ρ, respectively. Note that the support of the fiducial density for σ_α^2, σ_ε^2 and ρ might be a proper superset of their natural boundaries. For instance, observe that the fiducial density for ρ for this data has the range of ρ equal to the interval $(1/(1-\lambda_1), 1), i.e., (-0.25, 1)$. When calculating fiducial confidence intervals, we replace negative confidence bounds with 0 and when a confidence bound for ρ happens to be bigger than 1 we replace it with 1. Table 2.3 shows the **Ar** and the **FI** confidence intervals for σ_α^2 with 90% and 95% nominal confidence coefficients.

Table 2.3: Nominally 90% and 95% Confidence Intervals on σ_α^2 for the Slope-Ratio Assay Data.

Method	90%	95%
Ar	(0, 0.898)	(0, 1.841)
FI	(0, 0.875)	(0, 1.781)

In this example, it might be of interest to test the existence of the block random effect, i.e. the hypothesis of $H_0 : \sigma_\alpha^2 = 0$ versus $H_a : \sigma_\alpha^2 > 0$. Portnoy (1973) proposed an efficient test of the above hypothesis, which used both intra-block (i.e., *between-subjects*) and inter-block (i.e., *within-subjects*) information. The test is based on three independent scaled chisquared statistics:

$$T \sim (\sigma_\varepsilon^2 + a\sigma_\alpha^2)\chi_{n_1}^2 \quad S_1 \sim (\sigma_\varepsilon^2 + b\sigma_\alpha^2)\chi_{n_2}^2 \quad S_2 \sim \sigma_\varepsilon^2\chi_m^2.$$

The null hypothesis is rejected if

$$\frac{(S_1+T)/(n_1+n_2)}{S_2/m} > F_{1-\alpha;(n_1+n_2),m} \tag{2.24}$$

where $F_{\gamma;v_1,v_2}$ represents the γ-quantile of F-distribution with v_1 and v_2 degrees of freedom. Portnoy's test statistic calculated from this slope-ratio assay data is equal to 2.7930, less than $F_{0.95;2,10} = 4.1028$. Thus one is unable to reject H_0. Note that the test given in (2.24) can not be inverted to provide a confidence interval of σ_α^2 since the test is applicable for testing the hypothesis $H_0 : \sigma_\alpha^2 = \sigma_0^2$ for the special case $\sigma_0^2 = 0$. On the other hand, the fiducial approach proposed here may be used to obtain a confidence interval for σ_α^2.

The hypothesis $\sigma_\alpha^2 = 0$ can also be tested using the fiducial confidence interval procedure. In particular, for this example, the 95% one-sided fiducial interval for σ_α is $(-0.0095, \infty)$ which contains zero. We again fail to reject H_0. Thus, in this example, the Portnoy (1973) test and the test based on a fiducial interval, both reach the same conclusion.

For sake of completeness, we show in Table 2.4 the **EX** and the **FI** confidence intervals for σ_ε^2 with 90% and 95% nominal confidence coefficients.

Table 2.4: Nominally 90% and 95% Confidence Intervals on σ_ε^2 for the Slope-Ratio Assay Data.

Method	90%	95%
EX	(0.045, 0.210)	(0.040, 0.254)
FI	(0.045, 0.211)	(0.040, 0.257)

For this example, there does not exist an unbiased **BI** confidence interval for ρ. In this case, we take $I = \{1,2\}$ in (2.14) which gives us the pivotal quantity having the closest "balance" between the numerator and the denominator degrees of freedom where $r_3 = 10$ and $\sum_{i=1}^{2} r_i = 2$. Table 2.5 shows the **FI** confidence interval and the **BI** confidence interval for ρ with 90% and 95% nominal confidence coefficients.

2.5.2 Sire Model

This data set was used in Harville and Fenech (1985) and Burch (1996). The data consist of the birth weight of male lambs which were obtained from five distinct population

Table 2.5: Nominally 90% and 95% Confidence Intervals on ρ for the Slope-Ratio Assay Data.

Method	90%	95%
BI	(0, 0.913)	(0, 0.956)
FI	(0, 0.916)	(0, 0.957)

lines (two control lines and three selection lines). Sixty-two observations were made on progeny of twenty-three rams and each lamb came from a different dam. The age of each dam was recorded as belonging to one of three categories: 1-2 years, 2-3 years, and over 3 years. The fixed effects in this case are population line and age of dam. The random effects are the ram's (additive) genetic effects (within lines) and error (which includes environmental effects).

The mixed linear model we consider is $Y_{ijkl} = \mu + \alpha_i + \beta_j + \gamma_{k(j)} + \varepsilon_{ijkl}$, $i = 1, ..., 3$, $j = 1, ..., 5$, $k = 1, ..., 23$, where Y_{ijkl} is the birthweight of the l^{th} lamb of the k^{th} ram in the j^{th} population line from a dam belonging to the i^{th} age category. Assume that the ram's genetic effects $\gamma_{k(j)}$ are distributed independently as $N(0, \sigma_\alpha^2)$ and the errors ε_{ijkl} are distributed as $N(0, \sigma_\varepsilon^2)$ independently of each other and of the ram's genetic effects. The quantity μ is the general mean, α_i are fixed effects due to the age group of the dam, and β_j are fixed effects due to the different population lines. The relationship matrix $\boldsymbol{A}$ is $\boldsymbol{I}_{56}$.

The number of distinct eigenvalues of $\boldsymbol{G} = \boldsymbol{H}^T \boldsymbol{Z} \boldsymbol{A} \boldsymbol{Z}^T \boldsymbol{H}$ is $d = 18$. The eigenvalues range in magnitude from $\lambda_1 = 5.087479$ to $\lambda_{18} = 0$. The eigenvalue $\lambda_{18} = 0$ with multiplicity $r_{18} = 37$, $\lambda_8 = 2.0$ with multiplicity $r_8 = 2$, and all remaining eigenvalues have a multiplicity of one. The method of moments (MOM) estimates of σ_α^2 and σ_ε^2 are 0.7676 and 2.7631, respectively. The corresponding estimate of ρ is 0.2174. We refer to this estimate as MOM estimate of ρ. The REML estimates of σ_α^2 and σ_ε^2 are 0.5171 and 2.9616, respectively. The corresponding estimate of ρ is 0.1486. We refer to this estimate as REML estimate of ρ.

Figures 2.8, 2.9, and 2.10 show plots of the fiducial densities of σ_α^2, σ_ε^2, and ρ, respectively. The supports of the fiducial densities for σ_α^2 and σ_ε^2 are $(-\infty, \infty)$ and $(0, \infty)$ respectively. The support of the fiducial density for ρ is $(1/(1-\lambda_1), 1), i.e., (-0.2446, 1)$.

Table 2.6 shows the **Ar** and the **FI** confidence intervals for σ_α^2 with 90% and 95% nominal confidence coefficients. Simulated empirical coverages associated with the nominally

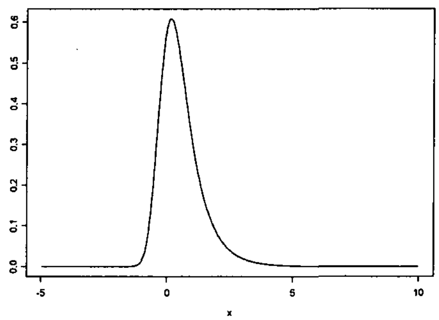

Figure 2.8: Fiducial density plot for σ_α^2 for the lamb birth-weight data.

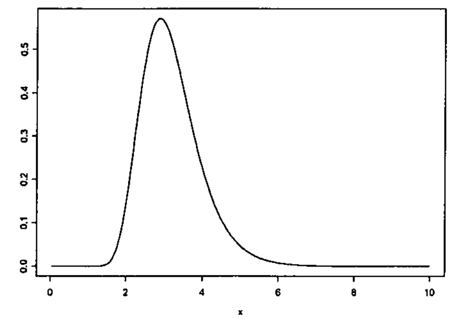

Figure 2.9: Fiducial density plot for σ_ε^2 for the lamb birth-weight data.

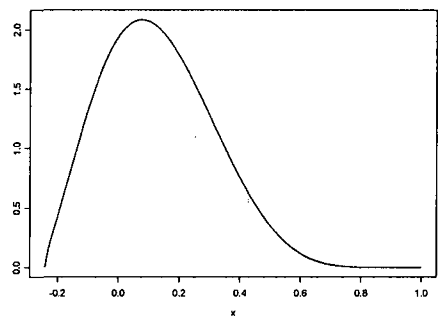

Figure 2.10: Fiducial density plot for ρ for the lamb birth-weight data.

90% and 95% confidence intervals for σ_α^2, along with their average lengths, using MOM and REML estimates of σ_α^2 and σ_ε^2 as their true values, respectively, are shown in Table 2.7.

Table 2.6: Nominally 90% and 95% Confidence Intervals on σ_α^2 for the Lamb Birth-weight Data.

Method	90%	95%
Ar	(0, 3.557)	(0, 4.346)
FI	(0, 2.150)	(0, 2.688)

The results show that the **FI** method gives shorter confidence intervals for this data set. Comparing the average lengths of the intervals, the **FI** confidence interval has smaller average lengths, despite being more conservative than the **Ar** confidence interval. In summary, the **FI** procedure performs better than the **Ar** method for this lamb birth-weight data set. Table 2.8 shows the **EX** and the **FI** confidence intervals for σ_ε^2 with 90% and

Table 2.7: Empirical Coverage Probabilities and Average Lengths (± Standard Deviation) of Nominally 90% and 95% Two-sided Confidence Intervals on σ_α^2 for the lamb birth-weight Data Using MOM Estimates and REML Estimates of σ_α^2 and σ_ε^2 as their True Values, respectively (based on 5000 simulations).

Method	90%		95%	
	MOM	REML	MOM	REML
Ar	0.899	0.898	0.948	0.946
	2.779±1.355	2.461±1.341	3.469±1.655	3.089±1.614
FI	0.903	0.907	0.953	0.959
	2.228±1.075	1.921±1.024	2.782±1.298	2.418±1.220

95% nominal confidence coefficients. Table 2.9 shows simulated empirical coverages associated with the nominally 90% and 95% confidence intervals for σ_ε^2, along with their average lengths, using MOM and REML estimates of σ_α^2 and σ_ε^2 as their true values, respectively. The results demonstrate that the **FI** interval has smaller average length, although it gives a slightly wider confidence interval for this data set.

Table 2.8: Nominally 90% and 95% Confidence Intervals on σ_ε^2 for the Lamb Birth-weight Data.

Method	90%	95%
EX	(1.959, 4.246)	(1.836, 4.625)
FI	(2.135, 4.633)	(1.996, 5.023)

Table 2.9: Empirical Coverage Probabilities and Average Lengths (± Standard Deviation) of Nominally 90% and 95% Two-sided Confidence Intervals on σ_ε^2 for the Lamb Birth-weight Data Using MOM Estimates and REML Estimates of σ_α^2 and σ_ε^2 as their True Values, respectively (based on 5000 simulations).

Method	90%		95%	
	MOM	REML	MOM	REML
EX	0.899	0.892	0.949	0.949
	2.300±0.541	2.450±0.573	2.802±0.654	2.978±0.688
FI	0.900	0.902	0.948	0.949
	2.237±0.472	2.349±0.488	2.713±0.571	2.847±0.590

There does not exist an unbiased **BI** confidence interval for ρ. In this case, we take $k = 17$ in the **BI** procedure which gives us the pivotal quantity having the closest "balance" between the numerator and the denominator degrees of freedom where $r_{18} = 37$ and

$\sum_{i=1}^{17} r_i = 18$. Table 2.10 shows the **FI** confidence interval and the **BI** confidence interval for ρ with 90% and 95% nominal confidence coefficients. Table 2.11 shows empirical coverages corresponding to these intervals along with their average lengths. These simulations are conducted with the MOM and REML estimates of σ_α^2, σ_ε^2 and ρ, respectively, as their true values. The results show that the **FI** method gives a shorter confidence interval for ρ in this data set. Comparing the average lengths of the intervals, the **FI** confidence interval has a smaller average length although it is more conservative than the **BI** confidence interval. In summary, the **FI** procedure performs better than the **BI** method for this lamb birth-weight data set.

Table 2.10: Nominally 90% and 95% Confidence Intervals on ρ for the Lamb Birth-weight Data.

Method	90%	95%
BI	(0, 0.592)	(0, 0.643)
FI	(0, 0.451)	(0, 0.512)

Table 2.11: Empirical Coverage Probabilities and Average Lengths ($\pm$ Standard Deviation) of the Nominally 90% and 95% Two-sided Confidence Intervals on ρ for the Lamb Birth-weight Data Using MOM Estimates and REML Estimates of σ_α^2, σ_ε^2 and ρ as their True Values, respectively (based on 5000 simulations).

Method	90%		95%	
	MOM	REML	MOM	REML
BI	0.900	0.900	0.951	0.951
	0.471±0.125	0.436±0.145	0.538±0.128	0.501±0.146
FI	0.909	0.919	0.962	0.965
	0.428±0.121	0.389±0.133	0.495±0.123	0.451±0.135

2.5.3 Full Animal Model

This data was used in Burch (1996) and Burch and Iyer (1997). Data were obtained on one hundred and seventy-one yearling bulls from a Red Angus seed stock in Montana. A trait of interest was the loin eye (i.e., ribeye) muscle area measured in square inches. Ultrasound techniques were used to obtain these measurements. The fixed effect was age of dam, which belongs to one of five categories: 2 years, 3 years, 4 years, 5-9 years, and

10 or more years. The random effects are animal's (additive) genetic effect and error. The mixed linear model being considered can be represented by

$$\boldsymbol{Y} = \boldsymbol{X\beta} + \boldsymbol{Zu} + \boldsymbol{\varepsilon},$$

where $\boldsymbol{Y}$ is a 171×1 vector of observable random variables, $\boldsymbol{X}$ is a 171×5 design matrix, $\boldsymbol{\beta}$ is a 5×1 vector of unknown parameters, $\boldsymbol{Z} = \boldsymbol{I}_{171}$, and $\boldsymbol{u}$ and $\boldsymbol{\varepsilon}$ are vectors of unobservable random variables of size 171×1. The relationship matrix $\mathbf{A}$ was determined using a recursive method given in Henderson (1976). This means $Var(\boldsymbol{u}) = \sigma_\alpha^2 \boldsymbol{A}$. The number of distinct eigenvalues of $\boldsymbol{G} = \boldsymbol{H}^T\boldsymbol{ZAZ}^T\boldsymbol{H}$ is $d = 165$. Eigenvalues range in magnitude from $\lambda_1 = 8.5692472$ to $\lambda_{165} = 0.5656916$. Except for $\lambda_{105} = 0.6718750$ having $r_{105} = 2$, all eigenvalues have a multiplicity of one. The REML estimates of σ_α^2 and σ_ε^2 are 0.2994 and 2.6539, respectively. The corresponding estimate of ρ is 0.1014. We refer to this estimate as REML estimate of ρ.

Figures 2.11, 2.12, and 2.13 show plots of the fiducial densities for σ_α^2, σ_ε^2, and ρ for the loin-eye data. The support of the fiducial density for σ_α^2 and for σ_ε^2 is $(-\infty, \infty)$. The support of the fiducial density for ρ is $\left\{\rho : \rho \in \left(\frac{1}{1-\lambda_1}, 1\right) \cup \left(1, \frac{1}{1-\lambda_d}\right)\right\}$, i.e., $\left\{\rho : \rho \in (-0.1321, 1) \cup (1, 2.3025)\right\}$. The **FI** confidence intervals for σ_α^2 with 90% and 95% nominal confidence coefficients are (0, 3.000) and (0, 3.750) respectively. The **FI** confidence intervals for σ_ε^2 with 90% and 95% nominal confidence coefficients are (0.625, 3.341) and (0.100, 3.513) respectively.

We estimated the coverage probabilities corresponding to the nominally 90% and 95% two-sided **FI** confidence intervals on σ_α^2 and σ_ε^2 using simulation with REML estimates of σ_α^2 and σ_ε^2 as their true values. The results are based on 2000 generated independent data sets. The simulation estimates of the empirical coverages for **FI** intervals on σ_α^2 are 0.935 and 0.975 corresponding to nominal confidence coefficients of 0.90 and 0.95 respectively. For the **FI** intervals on σ_ε^2 the coverage probability estimates are 0.923 and 0.959 corresponding to nominal confidence coefficients of 0.90 and 0.95 respectively.

The **BI** pivotal quantity that results in a locally unbiased confidence interval corresponds to $I = \{1, \ldots, 83\}$ in (2.14). In this case, $\sum_{i=1}^{83} r_i = \sum_{j=84}^{165} r_j = 83$. We will refer to this unbiased confidence interval as the **BI** confidence interval in the following discussion.

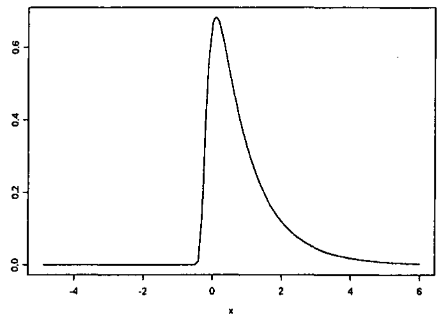

Figure 2.11: Fiducial density plot for σ_α^2 for the loin-eye data.

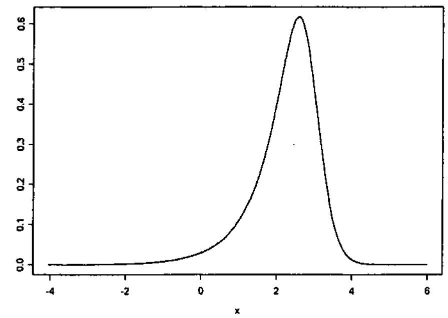

Figure 2.12: Fiducial density plot for σ_ε^2 for the loin-eye data.

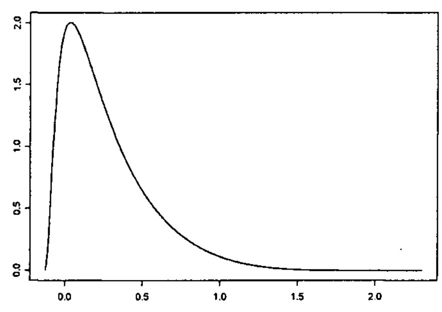

Figure 2.13: Fiducial density plot for ρ for the loin-eye data.

Table 2.12: Nominally 90% and 95% Confidence Intervals on ρ for the Loin-eye Data.

Method	90%	95%
BI	(0, 1.000)	(0, 1.000)
FI	(0, 0.824)	(0, 0.972)

Table 2.12 shows the **FI** confidence interval and the **BI** confidence interval for ρ with 90% and 95% nominal confidence coefficients. It is interesting to note that the **BI** confidence interval covers the entire parameter space. Inverting the pivotal quantity in (2.14) results in a confidence interval whose endpoints fall outside of the parameter space. Harville and Fenech (1985) attribute this to lack of sufficient information in the data about the parameter of interest in such cases. Table 2.13 shows the empirical coverages of these interval procedures for ρ using REML estimates of σ_α^2, σ_ε^2 and ρ as their true values, respectively. The results show that the **FI** method leads to a shorter confidence interval for ρ in this data set. Comparing the empirical coverages, the **FI** confidence interval is more conservative

Table 2.13: Empirical Coverage Probabilities of the Nominally 90% and 95% Two-sided Confidence Intervals on ρ for the Loin-eye Data Using REML Estimates of σ_{α}^2, σ_{ε}^2 and ρ as their True Values (based on 2000 simulations).

Method	90%	95%
BI	0.900	0.951
FI	0.939	0.977

than the **BI** confidence interval. In summary, the **FI** method performs better than the **BI** method for this data set.

Chapter 3

FIDUCIAL GENERALIZED CONFIDENCE INTERVALS FOR MEDIAN LETHAL DOSE (LD_{50})

3.1 Introduction

Median lethal dose (LD_{50}) is defined as the dose of a substance expected to kill 50% of subjects in a given population under a defined set of conditions. LD_{50} is frequently used as a measure of the acute toxicity of a compound in a species in quantal bioassay experiments. In these studies, a subject is administered a compound of interest at a certain single dose level, usually on a logarithmic scale, the death or survival is recorded. The probit and logit models have been used widely to estimate the LD_{50}. In this work, we only consider the logistic dose-response curve. Suppose the experiment involves k dose levels with logarithmic scale $x_1, x_2, \ldots, x_k$. n_i subjects are administered dose level x_i with s_i responses and response probability p_i, $i = 1, 2, \ldots, k$. Assume that the relationship between the dose level and response probability can be represented by the logistic-linear model, given by

$$\log(\frac{p_i}{1-p_i}) = \beta_0 + \beta_1 x_i = \beta_1(x_i - \mu), \tag{3.1}$$

where μ represents LD_{50}. Three standard methods are frequently used and recommended to obtain the confidence intervals for μ. They are delta method, Fieller method and likelihood ratio method. In this work, we propose a new method for constructing confidence intervals of LD_{50} based on a general fiducial recipe developed by Hannig (2008). A simulation study is done to compare the proposed procedure with these three standard procedures.

The chapter is organized as follows. In the next section, we briefly introduce three standard procedures for interval estimation of LD_{50}. In Section 3.3, we develop a fiducial generalized confidence interval on LD_{50}. In Section 3.4, we describe the simulation procedure. Finally, we compare our proposed procedure with competing methods described in Section 3.2 via a simulation study in Section 3.5.

3.2 Three Standard Confidence Intervals for LD_{50}

In this section, we briefly describe three widely used confidence intervals for LD_{50}, delta interval, Fieller interval and likelihood ratio interval. Let $\hat{\beta}_0$ and $\hat{\beta}_1$ denote the maximum likelihood estimators of β_0 and β_1 respectively. Let $\hat{\mu} = -\hat{\beta}_0/\hat{\beta}_1$ represent the maximum likelihood estimate of μ. Denote the estimated asymptotic variance matrix of $(\hat{\beta}_0, \hat{\beta}_1)$ by

$$V = \begin{pmatrix} v_{11} & v_{12} \\ v_{21} & v_{22} \end{pmatrix}$$

The delta method confidence procedure uses the fact that $\hat{\mu}$ is a function of $(\hat{\beta}_0, \hat{\beta}_1)$ and estimates the variance of $\hat{\mu}$ by delta method. A $100(1-\alpha)\%$ delta method confidence interval is given by

$$\hat{\mu} \pm \frac{z_{1-\alpha/2}}{\hat{\beta}_1^2}(v_{11} + 2\hat{\mu}v_{12} + \hat{\mu}^2 v_{22}) \tag{3.2}$$

where z_γ is the $\gamma-$quantile of standard normal distribution.

A $100(1-\alpha)\%$ Fieller confidence interval based on Fieller's theorem is given by the set of μ_0 satisfying

$$\frac{|\hat{\beta}_0 + \mu_0\hat{\beta}_1|}{\sqrt{v_{11} + 2\mu_0 v_{12} + \mu_0^2 v_{22}}} < z_{1-\alpha} \tag{3.3}$$

The likelihood ratio confidence interval is derived from the asymptotic likelihood ratio test of the null hypothesis $\mu = \mu_0$ against the alternative $\mu \neq \mu_0$. Let $D(\mu_0)$ and $D(\mu)$ denote the deviance under the null hypothesis and the deviance under the alternative hypothesis respectively. From the large sample theory, $L(\mu_0) = D(\mu_0) - D(\mu)$ asymptotically follows a chi-squared distribution with 1 degree of freedom under the null hypothesis. It follows that a $100(1-\alpha)\%$ likelihood ratio confidence interval of μ is given by the set of μ_0 satisfying $L(\mu_0) < z_{1-\alpha}^2$

It is worth to note that these three procedures are all based on the large sample theory. Delta method and Fieller method are also based on maximum likelihood estimators of β_0 and β_1. These estimators, however, do not always exist. If the dose-response curve is steep relative to the spread of doses, then fewer than two dose groups may have observed mortalities strictly intermediate between 0 and 100%. In such cases the maximum likelihood estimator of β_1 is not calculable. Delta method and Fieller method fail to provide a confidence interval. Furthermore when the standard wald test does not reject the hypothesis

$$H_0 : \beta_1 = 0 \qquad\qquad H_a : \beta_1 \neq 0, \tag{3.4}$$

the Fieller intervals are either the entire real line or unions of disjoint intervals. Likewise, if the hypothesis (3.4) could not be rejected by likelihood ratio test, the likelihood ratio confidence intervals are either the entire real line or unions of disjoint intervals. Sitter and Wu (1993) argue that making inference about μ makes no sense in such cases since the regression relationship is not significant at level α and suggest to either reassess the meaning of the LD_{50} or collect more data at other dose levels. Following Sitter and Wu (1993), these cases are excluded from the analysis in many studies, for example in Harris et al. (1999) and in Huang et al. (2002a). However when we are dealing with small experiments, we might not have enough information to reject $\beta_1 = 0$ although β_1 is not equal to zero. In recognition of these facts, we propose a fiducial solution which provides a finite confidence interval in any situation.

3.3 A Fiducial Generalized Confidence Interval for LD_{50}

In this section we develop a new procedure for constructing confidence intervals of μ based on the generalized fiducial distribution. First we describe the notation used in this chapter. Denote the generalized fiducial quantities of β_0, β_1 and $p_i, i = 1, \ldots, k$, by $\mathcal{R}_{\beta_0}$, $\mathcal{R}_{\beta_1}$ and $\mathcal{R}_{p_i}$ respectively. Suppose $\boldsymbol{U}_i = (U_{i1}, \ldots, U_{in_i})$, $i = 1, \ldots, k$, is a vector of i.i.d. uniform $(0, 1)$ random variables and $\boldsymbol{U}_i$ are mutually independent. Let $Y_{in_j}, i = 1, \ldots, k, j = 1, \ldots, n_i$ denote the j^{th} subject's response to the dose level x_i. Clearly Y_{in_j} follows a bernoulli distribution with success probability p_i. Let $S_i = \sum_{j=1}^{n_i} Y_{ij}$ and $\boldsymbol{Y}_i = (Y_{i1}, \ldots, Y_{in_i})$, $i = 1, \ldots, k$. Then we have $S_i \sim$Binomial(n_i, p_i).

Before we derive the fiducial generalized distribution of LD_{50}, we first consider the fiducial generalized distribution of $p_i, i = 1, \ldots, k$. This fiducial distribution has been derived by Hannig (2008) and is introduced in Section 1.2. For completeness, we rederive it here.

Define the mapping $T_i(\boldsymbol{y}_i, \boldsymbol{u}_i) : [0,1]^{n_i} \rightarrow [0,1], i = 1, \ldots, k$, as follows

$$T_i(\boldsymbol{y}_i, \boldsymbol{u}_i) = \begin{cases} [0, u_{i,1:n_i}] & \text{if } s_i = 0 \\ (u_{i,n_i:n_i}, 1] & \text{if } s_i = n_i \\ (u_{i,s_i:n_i}, u_{i,s_i+1:n_i}] & \text{if } s_i = 1, \ldots, n_i - 1 \text{ and} \\ & \sum_{j=1}^{n_i} I(y_{ij} = 1) I(u_{ij} \leq u_{i,s_i:n_i}) = s_i \\ \emptyset & \text{otherwise,} \end{cases}$$

where $\boldsymbol{y}_i$, s_i and $\boldsymbol{u}_i$ are realizations of $\boldsymbol{Y}_i$, S_i and $\boldsymbol{U}_i$ respectively, $i = 1, \ldots, k$. $U_{i,s_i:n_i}$ denotes the s_i^{th} order statistic among $U_{i1}, \ldots, U_{in_i}$. By definition, a generalized fiducial distribution of p_i is given by the conditional distribution of $V(T(\boldsymbol{y_i}, \boldsymbol{U}_i^\star))$ conditional on the event $T(\boldsymbol{y_i}, \boldsymbol{U}_i^\star)$ is not empty where $V(T(\boldsymbol{y_i}, \boldsymbol{U}_i^\star))$ is any random variable whose support is contained in $T(\boldsymbol{y_i}, \boldsymbol{U}_i^\star)$.

Next, we consider the fiducial distribution of $\boldsymbol{p} = (p_1, \ldots, p_k)$. Let $\boldsymbol{Y} = (\boldsymbol{Y_1}, \ldots, \boldsymbol{Y_k}), \boldsymbol{U}^\star = (\boldsymbol{U}_1^\star, \ldots, \boldsymbol{U}_k^\star)$ and $V(T(\boldsymbol{y}, \boldsymbol{U}^\star)) = (V(T_1(\boldsymbol{y}_1, \boldsymbol{U}_1^\star)), \ldots, V(T_k(\boldsymbol{y}_k, \boldsymbol{U}_k^\star)))$. Let's first assume all k groups are independent and there is no link, such as equation (3.1), among $p_1, \ldots, p_k$. Then it is easily seen that the generalized fiducial distribution of $\boldsymbol{p}$ is the conditional distribution of

$$V(T(\boldsymbol{y}, \boldsymbol{U}^\star)) | T(\boldsymbol{y}, \boldsymbol{U}^\star) \neq \emptyset. \tag{3.5}$$

However the equation (3.1) introduces an extra conditioning on $\boldsymbol{U}^\star$ and not all $\boldsymbol{U}^\star$ in (3.5) are allowed now. For example, suppose $k = 3$, then $\boldsymbol{U}^\star$ must satisfy not only $T(\boldsymbol{y}, \boldsymbol{U}^\star) \neq \emptyset$ but also the following equations

$$\frac{\operatorname{logit}(V(T_3(\boldsymbol{y_3}, \boldsymbol{U}_3^\star))) - \operatorname{logit}(V(T_1(\boldsymbol{y_1}, \boldsymbol{U}_1^\star)))}{x_3 - x_1} = \frac{\operatorname{logit}(V(T_3(\boldsymbol{y_3}, \boldsymbol{U}_3^\star))) - \operatorname{logit}(V(T_2(\boldsymbol{y_2}, \boldsymbol{U}_2^\star)))}{x_3 - x_2},$$

and

$$\frac{\operatorname{logit}(V(T_3(\boldsymbol{y_3}, \boldsymbol{U}_3^\star))) - \operatorname{logit}(V(T_1(\boldsymbol{y_1}, \boldsymbol{U}_1^\star)))}{x_3 - x_1} = \frac{\operatorname{logit}(V(T_2(\boldsymbol{y_2}, \boldsymbol{U}_2^\star))) - \operatorname{logit}(V(T_1(\boldsymbol{y_1}, \boldsymbol{U}_1^\star)))}{x_2 - x_1},$$

where $\operatorname{logit}(z) = \log(z/(1-z)), 0 < z < 1$. By extra conditioning on $\boldsymbol{U}^\star$, we are modifying the fiducial solution of a vector of binomial distribution parameters $\boldsymbol{p}$ given in (3.5). The extra condition is complicated and does not seem to be expressable in a simple close form. This makes it difficult to obtain the explicit analytical form of the generalized fiducial distribution of $\boldsymbol{p}$.

Based on the relationship between $\boldsymbol{p}$ and (β_0, β_1) in (3.1), the joint generalized fiducial distribution of (β_0, β_1) can be derived from the fiducial distribution of $\boldsymbol{p}$. For simplicity of notation, denote $U^\star_{i,0:n_i} = 0$ and $U^\star_{i,n_i+1:n_i} = 1$. Then by definition and the exchangeability of $\boldsymbol{U}^\star_i, i = 1, \ldots, k$, the generalized fiducial distribution of (β_0, β_1) is the same as the distribution of a random vector $V(Q(\boldsymbol{y}, \boldsymbol{U}^\star))$, where $Q(\boldsymbol{y}, \boldsymbol{U}^\star)$ is defined as follows

$$Q(\boldsymbol{y}, \boldsymbol{U}^\star) = \left\{ (\mathcal{R}_{\beta_0}, \mathcal{R}_{\beta_1}) \middle| \mathcal{R}_{\beta_0} + \mathcal{R}_{\beta_1} x_i \in \times_{i=1}^{k} \left(\log \frac{U^\star_{i,s_i:n_i}}{1 - U^\star_{i,s_i:n_i}}, \log \frac{U^\star_{i,s_i+1:n_i}}{1 - U^\star_{i,s_i+1:n_i}} \right),\ i = 1, \ldots, k \right\}.$$

By $\mu = -\beta_0/\beta_1$, the fiducial distribution of μ is the distribution of fiducial random variable $\mathcal{R}_\mu = -\mathcal{R}_{\beta_0}/\mathcal{R}_{\beta_1}$. Again due to the complicated conditioning, it is hard to obtain the explicit form of the fiducial distribution of μ. To solve this problem, we resort to MCMC method and sample the fiducial random variable $\mathcal{R}_\mu$. The detailed procedure is described in the next section.

3.4 Simulation Procedure

In this section we describe how to use Monte Carlo simulation to set up a confidence region for μ. The main simulation process is to generate a vector $\boldsymbol{u}^\star = (\boldsymbol{u}^\star_1, \ldots, \boldsymbol{u}^\star_k)$ in such a way that $Q(\boldsymbol{y}, \boldsymbol{u}^\star)$ is not empty. Then draw a sample from $Q(\boldsymbol{y}, \boldsymbol{u}^\star)$ to obtain a realization of $(\mathcal{R}_{\beta_0}, \mathcal{R}_{\beta_1})$, consequently a realization of $\mathcal{R}_\mu$. This process is repeated until the desired number of the realizations of $\mathcal{R}_\mu$ are obtained. The confidence interval of μ can be estimated based on these realizations. There are several ways to generate a $\boldsymbol{u}^\star$. Naively, one can generate $\boldsymbol{u}^\star_1$ through $\boldsymbol{u}^\star_k$ simultaneously and check if $Q(\boldsymbol{y}, \boldsymbol{u}^\star)$ is empty. If $Q(\boldsymbol{y}, \boldsymbol{u}^\star)$ is not empty, keep $\boldsymbol{u}^\star$. Otherwise, regenerate $\boldsymbol{u}^\star$. This procedure is easy to implement, but highly inefficient, especially when the number of doses, k, is large. To solve this problem, we use Gibbs Sampling approach and generate $\boldsymbol{u}^\star_1$ through $\boldsymbol{u}^\star_k$ sequentially instead. Each component of $\boldsymbol{u}^\star$ is updated conditional on the latest values of the other components of $\boldsymbol{u}^\star$. There are k components in $\boldsymbol{u}^\star$, thus k steps in iteration t. t is an integer. Note that generating $\boldsymbol{u}^\star_i$ is equivalent to generate $(u^\star_{i,s_i:n_i}, u^\star_{i,s_i+1:n_i})$. For simplicity of notation, denote $(u^\star_{i,s_i:n_i}, u^\star_{i,s_i+1:n_i})$ by $(w_{i1}, w_{i2}), i = 1, \ldots, k$. Let R_{β_0} and R_{β_1} be random variables with support $(-\infty, \infty)$. Let $R_\mu = -R_{\beta_0}/R_{\beta_1}$. Define

$$Q_i^{(t)}(\boldsymbol{y}, \boldsymbol{u}^\star) = \left\{ (R_{\beta_0}, R_{\beta_1}) \middle| \log \frac{w_{j1}^{(t)}}{1 - w_{j1}^{(t)}} < R_{\beta_0} + R_{\beta_1} x_i < \log \frac{w_{j2}^{(t)}}{1 - w_{j2}^{(t)}}, t \geq 0, j = 1, \ldots, i-1, \text{ and} \right.$$

$$\left. \log \frac{w_{j1}^{(t-1)}}{1 - w_{j1}^{(t-1)}} < R_{\beta_0} + R_{\beta_1} x_i < \log \frac{w_{j2}^{(t-1)}}{1 - w_{j2}^{(t-1)}}, t \geq 1, j = i+1, \ldots, k \right\},$$

$$m_{i1}^{(t)} = \min \left(\frac{\exp(R_{\beta_0} + R_{\beta_1} x_i)}{1 + \exp(R_{\beta_0} + R_{\beta_1} x_i)}, (R_{\beta_0}, R_{\beta_1}) \in Q_i^{(t)}(\boldsymbol{y}, \boldsymbol{u}^\star) \right), \text{ and}$$

$$m_{i2}^{(t)} = \max \left(\frac{\exp(R_{\beta_0} + R_{\beta_1} x_i)}{1 + \exp(R_{\beta_0} + R_{\beta_1} x_i)}, (R_{\beta_0}, R_{\beta_1}) \in Q_i^{(t)}(\boldsymbol{y}, \boldsymbol{u}^\star) \right),$$

The simulation proceeds as follows

For $t = 0$,

1. Generate $w_{i1}^{(t)}$ and $w_{i2}^{(t)}$, $i = 1, 2$, using the fact that $U^\star_{s_i:n_i}$ follows Beta$(s_i, n_i - s_i + 1)$ and the conditional distribution of $(1 - U^\star_{s_i+1:n_i})/(1 - U^\star_{s_i:n_i})$ given $U^\star_{s_i:n_i}$ is Beta$(n_i - s_i, 1)$. Note that if $s_i = 0$, by our definition $w_{i1}^{(t)} = 0$, only $w_{i2}^{(t)}$ is required to be generated. Likewise, if $s_i = n_i$, $w_{i2}^{(t)} = 1$ and only $w_{i1}^{(t)}$ is required to be generated.

2. From $i = 3$ through k,

   - if $s_i = 0$, draw $w_{i2}^{(t)}$ from truncated Beta$(1, n_i)$ with range $(m_{i1}^{(t)}, 1)$.
   - if $s_i = n_i$, draw $w_{i1}^{(t)}$ from truncated Beta$(n_i, 1)$ with range $(0, m_{i2}^{(t)})$.
   - if $0 < s_i < n_i$ and

     (a) $m_{i1}^{(t)} = 0$, draw $w_{i1}^{(t)}$ from truncated Beta$(s_i, n_i - s_i + 1)$ with range $(0, m_{i2}^{(t)})$, and draw a sample from Beta$(n_i - s_i, 1)$, denoted by $d_{i1}^{(t)}$. Then $w_{i2}^{(t)} = 1 - (1 - w_{i1}^{(t)}) * d_{i1}^{(t)}$.

     (b) $m_{i2}^{(t)} = 1$, draw $w_{i2}^{(t)}$ from truncated Beta$(s_i + 1, n_i - s_i)$ with range $(m_{i1}^{(t)}, 1)$, and draw a sample from Beta$(s_i, 1)$, denoted by $d_{i2}^{(t)}$. Then $w_{i1}^{(t)} = w_{i2}^{(t)} * d_{i2}^{(t)}$.

     (c) Otherwise, the ranges of $w_{i1}^{(t)}$ and $w_{i2}^{(t)}$ are shown in Figure 3.1. This is the most complicated but common case. The areas of A and B, denoted by $\tilde{p}_1$ and $\tilde{p}_2$, can be calculated as follows

$$\begin{aligned}
\tilde{p}_1 &= \int_{m_{i1}^{(t)}}^{m_{i2}^{(t)}} \int_x^1 \frac{n_i!}{(s_i-1)!(n_i-s_i-1)!} x^{s_i-1}(1-y)^{n_i-s_i-1} dy dx \\
&= B_{m_{i2}^{(t)};s_i,n_i-s_i+1} - B_{m_{i1}^{(t)};s_i,n_i-s_i+1}, \quad \text{and} \\
\tilde{p}_2 &= \int_{m_{i1}^{(t)}}^{1} \int_0^{m_{i1}^{(t)}} \frac{n_i!}{(s_i-1)!(n_i-s_i-1)!} x^{s_i-1}(1-y)^{n_i-s_i-1} dy dx \\
&= \frac{n_i!}{s_i!(n_i-s_i)!} m_{i1}^{(t)s_i}(1-m_{i1}^{(t)})^{n_i-s_i},
\end{aligned}$$

where $B_{\gamma;v_1,v_2}$ is the value of CDF of Beta(v_1,v_2), evaluated at γ. In this case, one has two choices with different probability to sample $w_{i1}^{(t)}$ and $w_{i2}^{(t)}$.

i) With probability $\tilde{p}_1/(\tilde{p}_1+\tilde{p}_2)$, draw $w_{i1}^{(t)}$ from truncated Beta(s_i, n_i-s_i+1) with range $(m_{i1}^{(t)}, m_{i2}^{(t)})$, and draw a sample from Beta$(n_i-s_i, 1)$, denoted by $d_{i1}^{(t)}$. Then $w_{i2}^{(t)} = 1-(1-w_{i1}^{(t)}) * d_{i2}^{(t)}$.

ii) With probability $\tilde{p}_2/(\tilde{p}_1+\tilde{p}_2)$, draw $w_{i2}^{(t)}$ from the distribution with the probability density function given by

$$\begin{aligned}
f_Y(y) &= \int_0^{m_{i1}^{(t)}} \frac{n_i!}{\tilde{p}_2(s_i-1)!(n_i-s_i-1)!} x^{s_i-1}(1-y)^{n_i-s_i-1} I_{(m_{i1}^{(t)},m_{i2}^{(t)})}(y) dx \\
&= \frac{n_i-s_i}{(1-m_{i2}^{(t)})^{n_i-s_i}}(1-y)^{n_i-s_i-1} I_{(m_{i2}^{(t)},1)}(y),
\end{aligned}$$

and draw $w_{i1}^{(t)}$ from the distribution with the probability density function given by

$$\begin{aligned}
f_{X|Y}(x,y) &= \frac{\frac{n_i!}{(s_i-1)!(n_i-s_i-1)!} x^{s_i-1}(1-y)^{n_i-s_i-1} I_{(0,m_{i1}^{(t)})}(x) I_{(m_{i1}^{(t)},1)}(y)}{\int_0^{m_{i1}^{(t)}} \frac{n_i!}{(s_i-1)!(n_i-s_i-1)!} x^{s_i-1}(1-y)^{n_i-s_i-1} I_{(m_{i1}^{(t)},1)}(y) dx} \\
&= \frac{s_i}{m_{i1}^{(t)s_i}} x^{s_i-1} I_{(0,m_{i1}^{(t)})}(x).
\end{aligned}$$

For $t=1,2,\ldots$, follow the procedures in Step 2 and draw $(w_{i1}^{(t)}, w_{i2}^{(t)}), i=1,\ldots,k$. Note that we obtain a set $Q_k^{(t)}(\boldsymbol{y},\boldsymbol{u}^\star)$ rather than a point after each iteration t. Thus, there are many choices to obtain a realization of $(R_{\beta_0}, R_{\beta_1})$, consequently a realization of R_μ. For example, one can take the centroid of $Q(\boldsymbol{y},\boldsymbol{u})$ as a realization. Based on our experience and simulation results, the best choice is to randomly select one of the vertices of $Q_k^{(t)}(\boldsymbol{y},\boldsymbol{U}^\star)$ as a realization of R_μ, denoted by $R_\mu^{(t)}$. By the construction process, the generated Markov chain $R_\mu^{(1)}, R_\mu^{(2)}, \ldots,$ converges to the fiducial generalized distribution of μ.

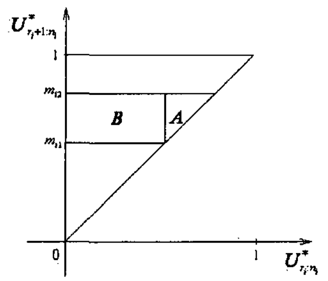

Figure 3.1: Illustration of case (c) in the simulation process.

Table 3.1: Experimental Configurations in the Simulation Study.

Design	Slope (β_1)	$\mathrm{LD}_{50}(\mu)$	$\log_{10}$dose (x_i)
1	2	3	1,2,3,4,5
2	1	4	1,2,3,4,5
3	2	5.1	2.056, 3.233, 4.411, 5.589, 6.767, 7.944
4	1	4.9	2.056, 3.233, 4.411, 5.589, 6.767, 7.944
5	1	2.0	0, 0.463, 3.045, 3.296, 3.584, 3.932, 4.394, 5.142
6	7	0.1	-0.3098, -0.2147,-0.1487, -0.0809, -0.0362, 0.0864, 0.1523, 0.2304, 0.2810

3.5 Simulation Study and Discussion of Results

To evaluate the performance of the proposed fiducial intervals, a simulation study was performed with six designs presented in Table 3.1. Designs 1 and 2 were also considered in Williams (1986), Sitter and Wu (1993), Huang et al. (2002a) and Huang (2005). Designs 3, 4 and 5 are based on the experimental configurations used by Huang et al. (2002a), Huang et al. (2002b) and Huang (2005). Design 6 was also considered in Sitter and Wu (1993), Harris et al. (1999) and Huang (2001). For each configuration listed in Table 3.1, every dose level has the same number of subjects n. $n = 6, 10$, and 20 were selected. Thus we had totally 18 sets. 1000 independent data sets were generated for each of 18 sets and two-sided 95% confidence intervals for μ were computed for each method. The methods compared were (a) delta method confidence interval, (b) Fieller confidence interval, (c) likelihood ratio confidence interval, and (d) fiducial confidence interval.

For fiducial intervals, we use Raftery and Lewis's method ((Raftery and Lewis, 1992) and (Gilks et al., 1995)) to determine the number of initial burn-in iterations discarded, M, and the number of iterations required after burn-in, N. Raftery and Lewis's method is one of popular methods for MCMC convergence diagnosis. It is intended to calculate the number of iterations necessary to estimate some quantile of interest within an acceptable of accuracy, at a specified probability level, from a single run of a Markov chain. We implement this method using the Raftery and Lewis's diagnostic function in CODA package (Plummer et al., 2006). The inputs are the quantile q to be estimated, the desired accuracy r, the required probability s of attaining the specified accuracy and a convergence tolerance ϵ. Here we are interested in two-sided 95% confidence intervals corresponding to $q = 0.025$ and 0.975. We select $r = 0.005$, $s = 0.95$ and $\epsilon = 0.001$. Brooks and Roberts (1999) examined the Raftery and Lewis's convergence diagnosis method and showed that this method might lead to an underestimate of the true burn-in length. To avoid this problem, we set $M = 1000$ if the value of M suggested by Raftery and Lewis's method is less than 1000. The largest value of M and N obtained for each combination of parameters (β_0, β_1, μ) and quantiles $(0.025, 0.975)$ are used as the burn-in length and number of iterations required after burn-in, respectively. The $M+N$ iterations are run and the diagnosis process is repeated to check if iterations are sufficient.

One concern with MCMC method is how to sample the output of a stationary Markov chain. A systemic subsample of the chain, using only every kth observation, is one of popular methods and it produces the approximately iid draws. Geyer (1992) and MacEachern and Berliner (1994) argued convincingly against the use of subsampling by proving that the estimator resulting from subsampling has larger variance and is poorer than the non-subsampled estimator. They suggest using the entire Markov chain, instead of subsampling. Based on their argument, we use the entire Markov chain in our study.

As mentioned in Section 3.1, the following three special cases were excluded from the analysis in most of literatures,

I The data set has either zero or one partial response.

II The standard wald test could not reject the hypothesis (3.4).

III The likelihood ratio test could not reject the hypothesis (3.4).

These cases rarely occur in large experiments, but occur frequently in experiments with small sample sizes or small number of doses. Table 3.2 lists the number of occurrences of three special cases in the simulation study. Since this paper focuses on the properties of intervals for small experiment designs, we include these three cases and set the coverages of delta method confidence intervals and Fieller intervals to be zero in the first case. The coverages of Fieller intervals and likihood ratio test intervals are set to be zero in Case II and Case III respectively since these two interval procedures fail to provide a confidence interval. Nonetheless, for consistency with other studies, we also report the results from the exclusion of three special cases. The simulation results are shown in Table 3.2 and graphically summarized in Figure 3.2 through 3.13. The numerical results are listed in Appendix B. Figure 3.2, 3.3, 3.4 and 3.5 show empirical coverage probabilities for designs with sample size $n = 6, 10, 20$ and all designs respectively, with inclusion of three special cases. Figure 3.6, 3.7, 3.8 and 3.9 show empirical coverage probabilities for designs with sample size $n = 6, 10, 20$ and all designs respectively, with exclusion of three special cases. Figures 3.10, 3.11, 3.12 and 3.13 show the averages of length ratios for designs with sample size $n = 6, 10, 20$ and all designs respectively, with exclusion of three special cases. The length ratio, denoted by LR, is defined as the interval length of competing procedures to the fiducial interval length.

The results show that three competing confidence intervals are very liberal for designs with sample sizes when we include all three special cases in the analysis. This is due to the fact that three special cases, especially Case I, occur frequently in some experiments. For example, there are 260 Case I among 1000 datasets for design 6 with sample size $n = 6$. With increasing sample size, the occurrence of three special cases decrease and the empirical coverage probabilities are approaching to the nominal value. Among all the confidence interval procedures, fiducial confidence interval has the smallest variability in terms of coverage probability. It has the coverage probabilities close to nominal value even for designs with small sample sizes. When we exclude the three special cases from our analysis, the Fieller's confidence interval become conservative. Delta method confidence interval and likelihood ratio confidence interval are liberal sometimes, especially when the sample sizes

Table 3.2: The Number of Occurrence of Three Special Cases and the Means of Point Estimates of LD_{50} in the Simulation Study.

Design	Size	Method	$\tilde{\mu}$	N_1 N_2 N_3	Design	Size	Method	$\tilde{\mu}$	N_1 N_2 N_3
1	6	Fiducial Other	3.00 3.00	183 0 0	4	6	Fiducial Other	4.80 4.90	13 0 0
	10	Fiducial Other	3.00 3.00	57 0 0		10	Fiducial Other	4.88 4.89	1 0 0
	20	Fiducial Other	3.00 3.00	3 0 0		20	Fiducial Other	4.88 4.90	0 0 0
2	6	Fiducial Other	4.04 4.05	7 122 96	5	6	Fiducial Other	2.03 2.01	1 12 0
	10	Fiducial Other	4.01 4.03	1 14 12		10	Fiducial Other	2.00 1.99	0 0 0
	20	Fiducial Other	4.01 4.01	0 0 0		20	Fiducial Other	2.01 2.01	0 0 0
3	6	Fiducial Other	5.00 5.08	260 0 0	6	6	Fiducial Other	0.10 0.10	0 11 6
	10	Fiducial Other	5.12 5.10	85 0 0		10	Fiducial Other	0.10 0.10	0 0 0
	20	Fiducial Other	5.12 5.10	4 0 0		20	Fiducial Other	0.10 0.10	0 0 0

$\tilde{\mu}$: Mean of point estimates of LD_{50}.
N_1: The number of datasets having either zero or one partial response.
N_2: The number of datasets for which the standard Wald test could not reject the hypothesis (3.4) at the 0.05 level of significance.
N_3: The number of datasets for which the likelihood ratio test could not reject the hypothesis (3.4) at the 0.05 level of significance.

are small. Fiducial interval appears to maintain the stated confidence coefficient for most of situations.

Comparing average confidence interval lengths, we observe that delta method confidence intervals have the smallest average confidence interval lengths. Fieller confidence intervals have the largest average confidence interval lengths for most of situations. The performance of likelihood ratio confidence intervals and fiducial confidence intervals are similar. The difference of the average confidence interval lengths among four intervals decreases with increasing sample size.

The means of the point estimates of LD_{50}, denoted by $\tilde{\mu}$, are shown in Table 3.2. For three competing confidence intervals, $\tilde{\mu}$ is defined as the mean of MLEs of LD_{50} of datasets

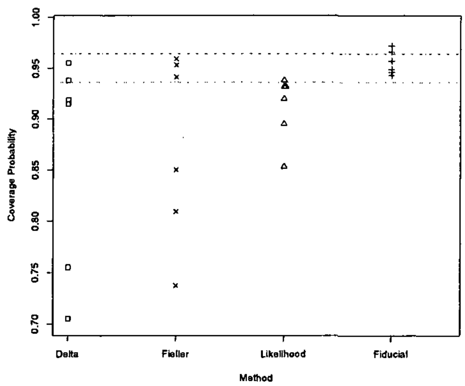

Figure 3.2: Empirical coverage probabilities for designs with sample size $n = 6$, with inclusion of three special cases.

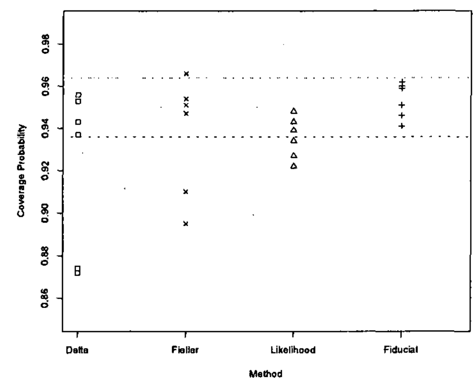

Figure 3.3: Empirical coverage probabilities for designs with sample size $n = 10$, with inclusion of three special cases.

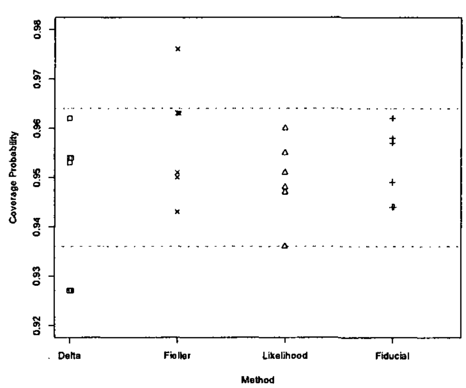

Figure 3.4: Empirical coverage probabilities for designs with sample size $n = 20$, with inclusion of three special cases.

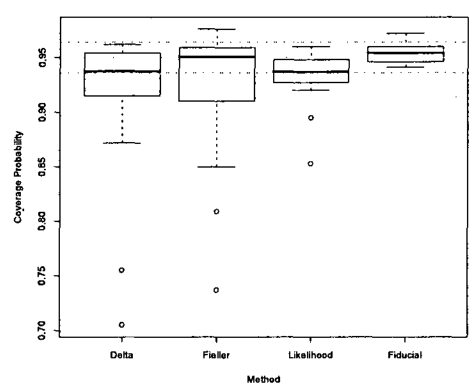

Figure 3.5: Empirical coverage probabilities for all designs, with inclusion of three special cases.

without three special cases. For fiducial intervals, we treat the median of the LD_{50} Markov chain as the point estimate of LD_{50} and define $\bar{\mu}$ as the mean of LD_{50} point estimates of all datasets. The results show that $\bar{\mu}$ of all confidence interval procedures are equal or very close to the true value.

Based on these results, fiducial interval has the best overall performance among all the intervals. we recommend the fiducial intervals for LD_{50} as the most suitable choice for practical applications.

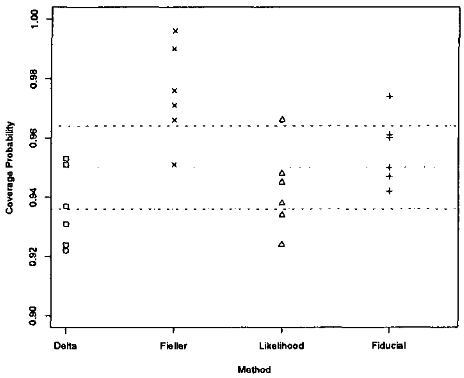

Figure 3.6: Empirical coverage probabilities for designs with sample size $n = 6$, with exclusion of three special cases.

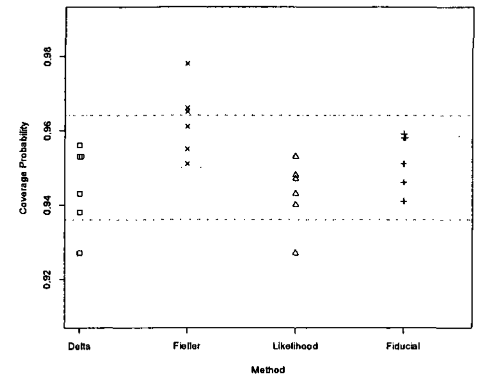

Figure 3.7: Empirical coverage probabilities for designs with sample size $n = 10$, with exclusion of three special cases.

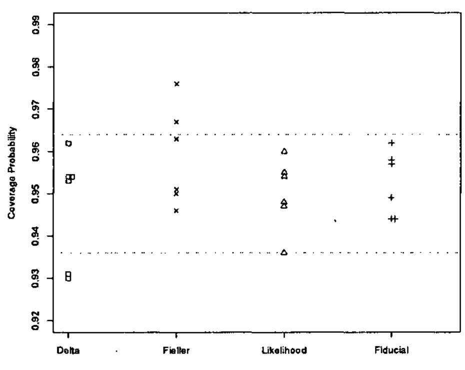

Figure 3.8: Empirical coverage probabilities for designs with sample size $n = 20$, with exclusion of three special cases.

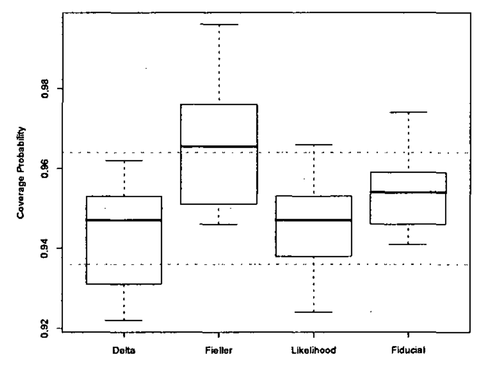

Figure 3.9: Empirical coverage probabilities for all designs, with exclusion of three special cases.

3.6 Example

This example is taken from Williams (1986). Williams (1986) used this example to illustrate different kinds of Fieller confidence intervals and likelihood ratio confidence intervals that can occur. Six sets are included in this example and presented in Table 3.3. Each set has five dose levels with equal sample size $n = 5$, and doses -2, -1, 0, 1 and 2 on logarithm scale. Sets 5 and 6 have zero and one partial response respectively. The delta method confidence interval and Fieller confidence interval for these two sets do not exist. For sets 2, 3 and 4, the standard wald test fails to reject the hypothesis (3.4) at the 0.05

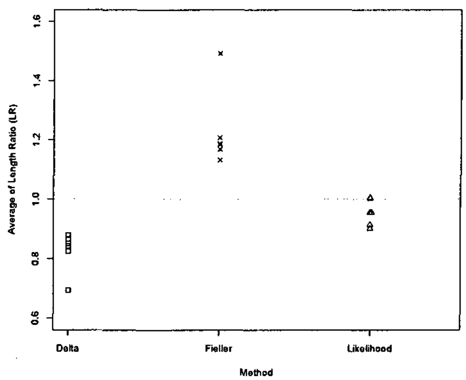

Figure 3.10: The averages of interval length ratios (LR) for designs with sample size $n = 6$, with exclusion of three special cases.

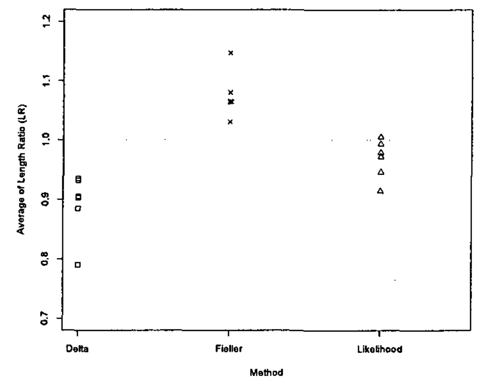

Figure 3.11: The averages of interval length ratios (LR) for designs with sample size $n = 10$, with exclusion of three special cases.

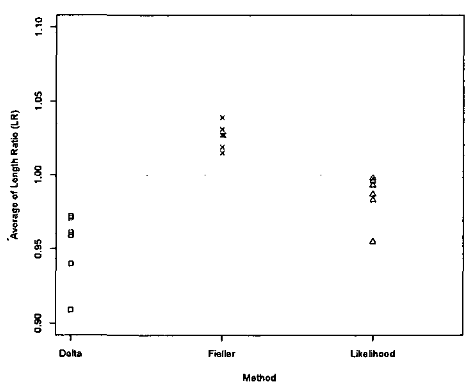

Figure 3.12: The averages of interval length ratios (LR) for designs with sample size $n = 20$, with exclusion of three special cases.

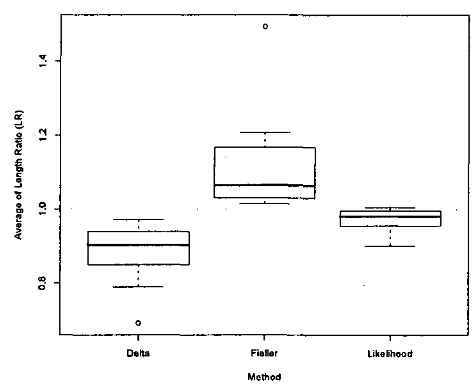

Figure 3.13: The averages of interval length ratios (LR) for all designs, with exclusion of three special cases.

level of significance. The Fieller confidence intervals for these three sets are either entire real line or or unions of disjoint intervals. For set 4, the likelihood ratio test fails to reject the hypothesis (3.4) at the 0.05 level of significance. The likelihood ratio confidence interval for set 4 is a union of two disjoint intervals. For comparison, the fiducial confidence intervals were also calculated and presented in Table 3.3. The same M and N selection strategy and parameter setting (r, s, ϵ, q) as in Section 3.4 were used. The results show that the confidence intervals obtained using fiducial procedure are always finite. fiducial procedure also provides a solution to the point estimate of LD_{50} for cases where maximum likelihood estimates of LD_{50} do not exist. For cases where maximum likelihood estimates of LD_{50} are

Table 3.3: The Point Estimates ($\hat{\mu}_1$) and Confidence Intervals of LD_{50} in Williams's Experimental Configurations.

Set	Observed number of death	$\hat{\mu}_1$	$\hat{\mu}_2$	Delta	Fieller	Likelihood	Fiducial
1	1, 3, 2, 4, 5	-0.61	-0.61	(-1.66, 0.44)	(-3.36, 0.75)	(-2.63, 0.49)	(-2.62, 0.61)
2	2, 2, 4, 3, 5	-1.02	-0.99	(-2.49, 0.45)	$(-\infty, 0.59)$U $(62.76, \infty)$	(-12.34, 0.33)	(-5.86, 1.00)
3	1, 3, 2, 4, 4	-0.46	-0.44	(-1.86, 0.95)	$(-\infty, \infty)$	(-11.59,1.65)	(-4.13, 2.17)
4	3, 2, 3, 4, 5	-1.45	-1.33	(-3.33, 0.44)	$(-\infty, 0.16)$U $(6.42,\infty)$	$(-\infty, 0.01)$U $(24.80, \infty)$	(-9.18, 4.07)
5	0, 0, 4, 5, 5	NA	-0.41	NA	NA	(-0.70, 0.11)	(-1.10, 0.27)
6	0, 0, 5, 5, 5	NA	-0.49	NA	NA	(-1.00, 0.00)	(-0.98, 0.02)

available, the fiducial estimates are very close to the maximum likelihood estimates, which is consistent with the simulation results in Section 3.4.

To study the convergence properties of Gibbs sampling for fiducial interval procedure, three chains with different randomly selected starting points were run for each set. Gelman and Rubin's statistic (Gelman and Rubin (1992)) and Geweke's statistic (Geweke (1992)) were calculated based on the the required N iterations after burn-in and used to diagnose the convergence of the MCMC output. The general rule of thumb is that the Gelman and Rubin's statistic should be below 1.2 for all parameters in order for the chain to be judged to have converged properly (Gelman et al. (1996)). Geweke's statistic is a standard Z-score. Therefore, Geweke's statistic inside of the range of, say 0.95 probability, of standard normal variates suggests good convergence. Table 3.4 summarizes the resulting Gelman and Rubin's statistics and Geweke's statistics. The results show that all Gelman and Rubin's statistics are less than 1.2 and only two among 64 Geweke's statistics are greater than 1.96, which suggests satisfactory convergence and complete mixture.

Table 3.4: Gelman and Rubin's Statistics and Geweke's Statistics for Parameters β_0, β_1 and μ in Williams's Experimental Configurations.

Design	Parameter	Gelman and Rubin's Statistic	Geweke's Statistic		
			Chain 1	Chain 2	Chain 3
1	β_0	1.00	-1.92	0.37	-0.59
	β_1	1.00	0.10	0.77	1.31
	μ	1.19	1.03	-2.67	-1.51
2	β_0	1.00	1.63	-0.72	-1.61
	β_1	1.01	0.55	1.77	-1.56
	μ	1.14	0.52	-0.14	-0.85
3	β_0	1.01	0.58	-1.77	-0.40
	β_1	1.00	-0.36	-1.51	0.59
	μ	1.18	-0.50	1.52	1.75
4	β_0	1.00	0.38	1.09	-1.42
	β_1	1.00	0.09	2.39	-1.05
	μ	1.12	-1.01	-0.87	-0.97
5	β_0	1.00	-1.02	0.81	0.02
	β_1	1.00	0.80	0.52	-0.25
	μ	1.00	1.41	-0.34	1.03
6	β_0	1.00	-0.81	-0.20	-1.03
	β_1	1.00	-1.03	-0.76	-1.44
	μ	1.00	-0.12	-0.34	0.66

Chapter 4

FIDUCIAL GENERALIZED CONFIDENCE INTERVALS FOR THE CONCORDANCE CORRELATION COEFFICIENT (CCC)

4.1 Introduction

Assessment of agreement between two methods of measurement is of considerable importance in many areas, for example, laboratory performance, instrument or assay validation, etc. In these studies, an equivalence test is usually conducted to evaluate the agreement between a new method and a traditional reference or gold standard before the new one is put into practice. For categorical responses, Cohen's Kappa statistic (Cohen (1960)) and weighted kappa statistic (Cohen (1968)) are basic methods to measure agreement. For continuous responses, concordance correlation coefficient (CCC) was widely used. CCC was introduced by Lin (1989). He considered the pairs of samples $(Y_{1i}, Y_{2i}), i = 1, 2, \ldots, n$, and assumed that they are independently selected from a bivariate population with means μ_1 and μ_2 and covariance matrix

$$\begin{pmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{12} & \sigma_2^2 \end{pmatrix}.$$

The concordance correlation coefficient is then defined as

$$\rho_c = 1 - \frac{E[(Y_{1i} - Y_{2i})^2]}{E_{indep}[(Y_{1i} - Y_{2i})^2]} = \frac{2\sigma_{12}}{\sigma_1^2 + \sigma_2^2 + (\mu_1 - \mu_2)^2} = \rho C_b, \tag{4.1}$$

where ρ is Pearson correlation coefficient,

$$C_b = 2(v + 1/v + u^2)^{-1},$$

$$v = \sigma_1/\sigma_2 = \text{scale shift}, \quad \text{and}$$

$$u = (\mu_1 - \mu_2)/\sqrt{\sigma_1\sigma_2} = \text{location shift relative to the scale.}$$

C_b measures how far the line fitted to the data deviates from the 45 °C line through the origin (measure of accuracy). ρ measures how far each observation deviates from the line fitted to the data (measure of precision). Denote the estimate of ρ_c by $\hat{\rho}_c$. $\hat{\rho}_c$ can be obtained by substituting the sample counterparts into the formula given in (4.1).

Lin (1992) later proposed a hypothesis test to test equivalence between two methods. The hypothesis test is given by

$$H_0 : \rho_c \leq \rho_c^\star \quad H_a : \rho_c > \rho_c^\star,$$

where $\rho_c^\star$ represents the least acceptable ρ_c. It's calculated using the ρ_c formula given in (4.1) by assuming we can accept $100x\%$ loss in precision (ρ can be dropped to $\sqrt{\rho^2 - x}$), $100u\%$ location shift per standard deviation, $100(1-v)\%$ scale shift. To illustrate, consider an equivalence specification where it is assumed that the test method could explain at least 98.5% ($\rho = 0.995$) of the standard method, the loss in precision is no more than $1\%(x = 0.01)$, the difference of the means is not more than 25% relative to the scale ($u = 0.25$), the standard deviations do not differ by more than 10% the standard deviation of the reference system ($v = 0.9$). This yield a least acceptable ρ_c of 0.95. The above hypothesis test can be carried out using the lower bound of ρ_c. If the lower bound is greater than $\rho_c^\star$, one would reject H_0 and infer the satisfactory agreement.

The concordance correlation coefficient was later generalized and adjusted to be applicable for different scenarios. Chinchilli et al. (1996) developed a weighted concordance correlation coefficient to quantify agreement between two methods for repeated measurement designs. King and Chinchilli (2001) considered alternative distance functions to the squared distance function in Lin's CCC and produced more robust versions of concordance correlation coefficient for continuous responses without replications. Barnhart et al. (2002) presented an overall concordance correlation coefficient (OCCC) for assessing agreement among multiple methods without replications. She (Barnhart et al. (2002)) later proposed the inter-method agreement index, inter-CCC, and the total agreement index, total-CCC, for agreement data with replications produced by multiple methods. Recently, King and Chinchilli (2007) proposed a repeated measures concordance correlation coefficient for data with repeated measures comparing two methods. Barnhart et al. (2007) proposed coefficient of individual agreement (CIA) to assess individual agreement between multiple methods based on the concept of individual bioequivalence.

Quiroz (2005) considered the two way ANOVA model without method and subject interaction in the repeated measurement design comparing two methods. He developed three sets of confidence bounds for concordance correlation coefficient to conduct equivalence tests. In Section 4.2, we consider the same measurement model and develop two fiducial generalized confidence intervals for CCC based on the Fiducial Generalized Pivotal Quantity (FGPQ) and the generalized fiducial distribution respectively. we compare our proposed procedures with the methods developed Quiroz (2005) via a simulation study in Section 3.5. In Section 4.3 we apply our fiducial procedure to the model with method and subject interaction. Simulation studies are carried out to evaluate the performance of the proposed confidence intervals.

4.2 Confidence Intervals for CCC under the Model without Method and Subject Interaction

4.2.1 Statistical Model and Concordance Correlation Coefficient

Quiroz (2005) considered a study where simultaneous continuous measurements from the same subject are obtained by using a test method and a reference method. The measurements are paired over time and the experiment is repeated multiple times. He assumed there is no interaction between the methods and the subjects. The measurement model is specified as

$$Y_{ijk} = \mu_i + S_j + \epsilon_{ijk}, i = 1, 2, j = 1, \dots, n, k = 1, \dots, m, \tag{4.2}$$

where Y_{ijk} represents the k^{th} measurement made on the subject j receiving the method i, μ_1 and μ_2 are the means of the test method and reference method respectively, S_j are individual effects and $S_j \overset{iid}{\sim} N(0, \sigma_s^2)$, ϵ_{ijk} are independent random measurement errors and $\epsilon_{ijk} \overset{iid}{\sim} N(0, \sigma_{\epsilon_i}^2)$, S_j and ϵ_{ijk} are jointly independent. The ANOVA table for this model is shown in Table 4.1 where the following notation is used

$$\overline{Y}_{ij\star} = \frac{\sum_{k=1}^{m} Y_{ijk}}{m}, \quad \overline{Y}_{i\star\star} = \frac{\sum_{j=1}^{n} \overline{Y}_{ij\star}}{n}, \quad \overline{Y}_{\star\star\star} = \frac{\sum_{i=1}^{2} \overline{Y}_{i\star\star}}{2}, \quad SS_B = 2m \sum_{j=1}^{n} (\overline{Y}_{\star j\star} - \overline{Y}_{\star\star\star})^2,$$

$$SS_{W_1} = \sum_{j=1}^{n} \sum_{k=1}^{m} (Y_{1jk} - \overline{Y}_{1j\star})^2, SS_{W_2} = \sum_{j=1}^{n} \sum_{k=1}^{m} (Y_{2jk} - \overline{Y}_{2j\star})^2, \text{ and } SS_M = \frac{nm}{2} (\overline{Y}_{1\star\star} - \overline{Y}_{2\star\star})^2.$$

Table 4.1: ANOVA for Model without Interaction between the Methods and the Subjects (Model (4.2)).

Source	DF	MS	EMS
Methods	$n_M = 1$	$S_M^2 = SS_M/n_M$	$\theta_M = (nm(\mu_1 - \mu_2)^2 + \sigma_{\varepsilon_1}^2 + \sigma_{\varepsilon_2}^2)/2$
Subjects	$n_B = n - 1$	$S_B^2 = SS_B/n_B$	$\theta_B = 2m\sigma_s^2 + (\sigma_{\varepsilon_1}^2 + \sigma_{\varepsilon_2}^2)/2$
Error (1)	$n_1 = n(m-1)$	$S_1^2 = SS_{W_1}/n_1$	$\theta_1 = \sigma_{\varepsilon_1}^2$
Error (2)	$n_2 = n(m-1)$	$S_2^2 = SS_{W_2}/n_2$	$\theta_2 = \sigma_{\varepsilon_2}^2$

It's easy to show that SS_{W_1}/θ_1,SS_{W_2}/θ_2 and SS_B/θ_B are central chi-squared random variables with degrees of freedom n_1, n_2 and n_B respectively. SS_M/θ_M is a noncentral chi-squared random variable with noncentrality parameter $\lambda = nm\theta_\mu/(\theta_1 + \theta_2)$, where $\theta_\mu = (\mu_1 - \mu_2)^2$. SS_{W_1}/θ_1, SS_{W_2}/θ_2, SS_B/θ_B and SS_M/θ_M are mutually independent.

Quiroz (2005) showed the concordance correlation coefficient under the model (4.2) can be expressed as

$$\rho_c = \frac{2\sigma_s^2}{2\sigma_s^2 + \sigma_{\varepsilon_1}^2 + \sigma_{\varepsilon_2}^2 + (\mu_1 - \mu_2)^2} = 2\rho(\phi + 1/\phi + \psi^2)^{-1}, \qquad (4.3)$$

where

$$\rho = \frac{Cov(Y_{1jk}, Y_{2jk})}{\sqrt{Var(Y_{1jk})Var(Y_{2jk})}} = \frac{\sigma_s^2}{\sqrt{(\sigma_s^2 + \sigma_{\varepsilon_1}^2)(\sigma_s^2 + \sigma_{\varepsilon_2}^2)}} = \text{Pearson correlation coefficient},$$

$$\phi = \sqrt{\frac{Var(Y_{1jk})}{Var(Y_{2jk})}} = \sqrt{\frac{\sigma_s^2 + \sigma_{\varepsilon_1}^2}{\sigma_s^2 + \sigma_{\varepsilon_2}^2}} = \text{scale shift, and}$$

$$\psi^2 = \frac{(\mu_1 - \mu_2)^2}{\sqrt{Var(Y_{1jk})Var(Y_{2jk})}} = \frac{(\mu_1 - \mu_2)^2}{\sqrt{(\sigma_s^2 + \sigma_{\varepsilon_1}^2)(\sigma_s^2 + \sigma_{\varepsilon_2}^2)}} = \text{location shift relative to the scale.}$$

4.2.2 Published Confidence Intervals for CCC

Quiroz (2005) developed three sets of lower confidence intervals for ρ_c based on the Z-transformation, a modification that adjusts formulas to take into account the random effects model and the generalized inference proposed by Weerahandi (1993) respectively. We denote these three confidence intervals as ZT confidence interval, MRM confidence interval and GCI confidence interval, respectively. Next, we briefly introduce these three intervals.

ZT Confidence Interval

For simplicity, we define the following statistics which are used in the construction of ZT confidence interval,

$$\hat{\theta}_1 = S_1^2, \hat{\theta}_2 = S_2^2, \hat{\theta}_B = S_B^2, \hat{\theta}_\mu = \frac{1}{nm}(2S_M^2 - (S_1^2 + S_2^2)), \text{ and } \hat{\theta}_S = \frac{1}{2m}(S_B^2 - (S_1^2 + S_2^2)/2).$$

Denote $\theta_S = \sigma_s^2$. One can show that $\hat{\theta}_1, \hat{\theta}_2, \hat{\theta}_B, \hat{\theta}_\mu$ and $\hat{\theta}_S$ are unbiased and consistent estimates of $\theta_1, \theta_2, \theta_B, (\mu_1 - \mu_2)^2$ and θ_S respectively.

Lin (1989) demonstrated that the inverse hyperbolic tangent transformation given by

$$\hat{W} = \frac{1}{2} \ln \frac{1 + \hat{\rho}_c}{1 - \hat{\rho}_c} \tag{4.4}$$

can improve the asymptotic convergence of estimates of CCC, denoted by $\hat{\rho}_c$. This transformation is also known as Z-transformation. $\hat{W}$ in (4.4) asymptotically follows a normal distribution with mean

$$\mu_{\hat{w}} = \frac{1}{2} \ln \frac{1 + \rho_c}{1 - \rho_c}, \tag{4.5}$$

and variance

$$\sigma_{\hat{w}}^2 = \frac{\sigma_{\hat{\rho}_c}^2}{(1 - \rho_c^2)^2}, \tag{4.6}$$

where $\sigma_{\hat{\rho}_c}^2$ is the variance of $\hat{\rho}_c$. Using Z-transformation method, Quiroz (2005) developed a $100(1 - \alpha)\%$ lower bound on CCC given as follows

$$L_{ZT} = \frac{\exp(2L) - 1}{\exp(2L) + 1}, \tag{4.7}$$

where $L = \hat{W} + z_\alpha \sqrt{\hat{\sigma}_{\hat{w}}^2}$, $\hat{\sigma}_{\hat{w}}^2$ is an estimate of $\sigma_{\hat{w}}^2$ in (4.6), and z_α is the α quantile of a standard normal distribution. $\hat{\rho}_c$ was calculated using $\hat{\theta}_1, \hat{\theta}_2, \hat{\theta}_\mu$ and $\hat{\theta}_S$, and is given by

$$\hat{\rho}_c = \frac{2\hat{\theta}_S}{2\hat{\theta}_S + \hat{\theta}_1 + \hat{\theta}_2 + \hat{\theta}_\mu}.$$

To compute $\hat{\sigma}_{\hat{w}}^2$, Quiroz first approximated $\sigma_{\hat{\rho}_c}^2$ in (4.6) using the delta method. Note that the formula of the approximation of $\sigma_{\hat{\rho}_c}^2$ provided by Quiroz is not right. The corrected version is given as follows

$$\begin{aligned} Var(\hat{\rho}_c) &= \frac{4(1 - \rho_c)^2 \rho_c^2 V_1 + \rho_c^4 V_2 - 4\rho_c^3 (1 - \rho_c) V_3}{4\theta_S^2} \\ &= \frac{4m^2(4(1 - \rho_c)^2 \rho_c^2 V_1 + \rho_c^4 V_2 - 4\rho_c^3 (1 - \rho_c) V_3)}{(2\theta_B - (\theta_1 + \theta_2))^2}, \end{aligned} \tag{4.8}$$

where

$$V_1 = \frac{1}{8m^2}\left(\frac{4\theta_B^2}{n-1} + \frac{\theta_1^2+\theta_2^2}{n(m-1)}\right)$$

$$V_2 = \frac{1}{m^2n^2}\left(2(\theta_1+\theta_2)^2 + 4nm(\theta_1+\theta_2)\theta_\mu + \frac{2(\theta_1^2+\theta_2^2)(nm+m-2)}{n^2m(m-1)}\right), \text{ and}$$

$$V_3 = -\frac{(nm-1)(\theta_1^2+\theta_2^2)}{2m^2n^2(m-1)}.$$

Quiroz estimated $Var(\hat{\rho}_c)$ by replacing $\rho_c, \theta_1, \theta_2, \theta_1^2, \theta_2^2$ and θ_B in (4.8) with consistent estimate $\hat{\rho}_c$, unbiased and consistent estimates $\hat{\theta}_1, \hat{\theta}_2, (n_1/(n_1+2))\hat{\theta}_1^2, (n_2/(n_2+2))\hat{\theta}_2^2$ and $(n_B/(n_B+2))\hat{\theta}_B^2$ respectively. Finally $\hat{\sigma}_{\hat{w}}^2$ was calculated as the estimate of $Var(\hat{\rho}_c)$ divided by $(1-\hat{\rho}_c^2)^2$. We refer the interval $[L_{ZT}, 1]$ as the ZT1 confidence interval.

Another way to estimate $Var(\hat{\rho}_c)$ is to replace $\rho_c, \theta_1, \theta_2, \theta_\mu$ and θ_B in (4.8) with the consistent estimates $\hat{\rho}_c, \hat{\theta}_1, \hat{\theta}_2, \hat{\theta}_\mu$ and $\hat{\theta}_B$ respectively. We refer to the resulting interval as the ZT2 confidence interval. We compare ZT1 and ZT2 confidence intervals with our proposed fiducial confidence intervals via a simulation study in Section 4.2.4.

MRM Confidence Interval

Dolezal et al. (1998) showed that the distribution of S_M^2 can be approximated by a scaled central chi-squared distribution. By using this approximation and the random model formulas developed by Graybill and Wang (1979), Quiroz (2005) developed a modified random model interval for ρ_c. A $100(1-\alpha)\%$ lower bound for ρ_c is given by

$$L_{MRM} = \frac{S_B^2 - (1/2)(S_1^2+S_2^2)F_{1-\alpha,n-1,n(m-1)}}{S_B^2 + 2F_{1-\alpha,n-1,n^\star}S_M^2/n + (1/2)(2m-1-2/n)(S_1^2+S_2^2)F_{1-\alpha,n-1,n(m-1)}} \tag{4.9}$$

where

$$n^\star = \left\lceil \frac{(1+2\hat{\lambda})^2}{1+4\hat{\lambda}} \right\rceil, \quad \hat{\lambda} = \frac{S_M^2}{S_1^2+S_2^2},$$

$\lceil . \rceil$ is the ceiling function, and F_{γ,v_1,v_2} represents the $\gamma-$quantile of F-distribution with v_1 and v_2 degrees of freedom. We refer to the interval $[L_{MRM}, 1]$ as the MRM confidence interval.

GCI Confidence Interval

Quiroz (2005) developed a generalized confidence interval of ρ_c based on the generalized inference method introduced by Weerahandi (1993). A generalized pivotal quantity (GPQ) for ρ_c was first set up and an approximate confidence interval for ρ_c was constructed by computing the required percentile of the GPQ using Monte Carlo simulation. We refer to this confidence interval as the GCI interval. In the construction of GPQ for $(\mu_1 - \mu_2)^2$, Quiroz first constructed a GPQ for $\mu_1 - \mu_2$ using the fact that $D = \overline{Y}_{1**} - \overline{Y}_{2**}$ has a normal distribution with mean $\mu_1 - \mu_2$ and variance $(\sigma^2_{\varepsilon_1} + \sigma^2_{\varepsilon_2})/nm$. This GPQ is given by

$$\mathcal{R}_\delta = d - Z_1\sqrt{\frac{n_1 s_1^2}{nmU_1} + \frac{n_2 s_2^2}{nmU_2}},$$

where d, s_1^2 and s_2^2 are realizations of D, S_1^2 and S_2^2 respectively, Z_1 is a standard normal random variable, U_1 and U_2 are chi-squared random variables with n_1 and n_2 degrees of freedom respectively, Z_1, U_1 and U_2 are jointly independent. By the delta method, the asymptotic distribution of D^2 is $N(\theta_\mu, 4\theta_\mu(\sigma^2_{\varepsilon_1} + \sigma^2_{\varepsilon_2})/nm)$. Based on this result, Quiroz constructed a GPQ for θ_μ which is given by

$$\mathcal{R}_{\theta_\mu} = d^2 - 2Z_2|\mathcal{R}_\delta|\sqrt{\frac{n_1 s_1^2}{nmU_3} + \frac{n_2 s_2^2}{nmU_4}} \tag{4.10}$$

where Z_2 is a random variable which follows a standard normal random distribution asymptotically, U_3 and U_4 are chi-squared random variables with n_1 and n_2 degrees of freedom respectively. In the Monte Carlo simulation process, Quiroz treated Z_2 as the standard normal random variable and generated the realizations of Z_1, Z_2, U_1, U_2, U_3 and U_4 independently. In fact, Z_1 and Z_2 are not independent, U_1 is the same as U_2, and U_3 is the same as U_4. Furthermore, by the construction process, the GPQ for ρ_c developed by Quiroz is not an exact GPQ since Z_2 is not a standard normal random variable. We expect this "approximate" GPQ might not have good properties as the exact GPQ. In the next section, we develop an exact GPQ for θ_{ρ_c} and construct a confidence interval based on it.

4.2.3 Fiducial Generalized Confidence Intervals for CCC

FGCI based on Fiducial Generalized Pivotal Quantity (FGPQ)

In this section we construct confidence intervals for ρ_c based on the Fiducial Generalized Pivotal Quantity (FGPQ) defined by Hannig et al. (2006). First, Observe that the statistic $\mathbb{S} = (SS_{W_1}, SS_{W_2}, SS_B, SS_M)$ and parameter $\xi = (\theta_1, \theta_2, \theta_B, \theta_\mu)$ have the following pivotal relationship under the model (4.2)

$$U_1 = \frac{SS_{W_1}}{\theta_1} \sim \chi^2_{n_1}, \quad U_2 = \frac{SS_{W_2}}{\theta_2} \sim \chi^2_{n_2}, \quad U_3 = \frac{SS_B}{\theta_B} \sim \chi^2_{n_B}, \text{ and } U_4 = \frac{2SS_M}{\theta_1+\theta_2} \sim \chi^2_{n_M,\lambda},$$

where $\lambda = nm\theta_\mu/(\theta_1+\theta_2)$, χ^2_v represents a central chi-squared distribution with degrees of freedom v, $\chi^2_{v_1,v_2}$ represents a noncentral chi-squared distribution with degrees of freedom v_1 and noncentrality parameter v_2, U_1, U_2, U_3 and U_4 are independent of each other. Applying the structural method for construction of FGPQ based on the invertible pivotal relationship given by Hannig et al. (2006), we obtain the following FGPQ for ρ_c

$$\mathcal{R}_{\rho_c} = \frac{2\mathcal{R}_{\theta_s}}{2\mathcal{R}_{\theta_s} + \mathcal{R}_{\theta_1} + \mathcal{R}_{\theta_2} + \mathcal{R}_{\theta_\mu}} \tag{4.11}$$

where

$$\mathcal{R}_{\theta_1} = \frac{SS_{W_1}}{SS^\star_{W_1}}\theta_1, \; \mathcal{R}_{\theta_2} = \frac{SS_{W_2}}{SS^\star_{W_2}}\theta_2, \; \mathcal{R}_{\theta_s} = \frac{1}{2m}\left(\frac{SS_B}{SS^\star_B}\theta_B - \frac{\mathcal{R}_{\theta_1}+\mathcal{R}_{\theta_2}}{2}\right),$$
$$\mathcal{R}_{\theta_\mu} = \frac{\mathcal{R}_{\theta_1}+\mathcal{R}_{\theta_2}}{nm} Q\left(F\left(\frac{2SS^\star_M}{\theta_1+\theta_2}; \frac{nm\theta_\mu}{\theta_1+\theta_2}\right); \frac{2SS_M}{\mathcal{R}_{\theta_1}+\mathcal{R}_{\theta_2}}\right),$$

$SS^\star_{W_1}$, $SS^\star_{W_2}$, $SS^\star_B$ and $SS^\star_M$ are independent copies of SS_{W_1}, SS_{W_2}, SS_B and SS_M respectively. $F(x,v)$ is the value of CDF of noncentral chi-squared distribution with 1 degree of freedom and noncentrality parameter v, evaluated at x. $Q(u,x)$ can be considered as the inverse function of $F(x,v)$ when $F(x,v)$ is viewed as a function of v, keeping x fixed. Given $F(x,v) = u \in (0,1)$, $Q(u,x)$ is defined as

$$Q(u,x) = \begin{cases} 0 & \text{if } u > F(x,0) \\ v & \text{otherwise.} \end{cases}$$

$Q(u,x)$ is guaranteed to exist by the monotonicity of $F(x,v)$ viewed as a function of v. Observe that $\mathcal{R}_{\theta_1}, \mathcal{R}_{\theta_2}, \mathcal{R}_{\theta_B}$ and $\mathcal{R}_{\theta_\mu}$ in (4.11) are FGPQs for $\theta_1, \theta_2, \theta_B$ and θ_μ, respectively. It follows that $\mathcal{R}_{\rho_c}$ is a FGPQ for ρ_c. Let $\mathcal{R}_{\rho_{c,\gamma}}$ denote the $\gamma-$quantile of the distribution of $\mathcal{R}_{\rho_c}$, then a $(1-\alpha)100\%$ lower bound for ρ_c is given by $[\mathcal{R}_{\rho_{c,\alpha}}, 1]$. We refer to this interval as the FGCI1 confidence interval.

FGCI based on Generalized Fiducial Distribution

In this section we describe another fiducial interval procedure for ρ_c. The fiducial intervals are obtained using the generalized fiducial distribution described in Hannig et al. (2006) and Hannig (2008). Before we derive the generalized fiducial distribution of ρ_c and construct a confidence interval for ρ_c, we first obtain the minimal sufficient statistics for $(\mu_1, \mu_2, \sigma^2_{\varepsilon_1}, \sigma^2_{\varepsilon_2}, \sigma^2_s)$ under the model (4.2).

Proposition 4.1. *The minimal sufficient statistics for* $(\mu_1, \mu_2, \sigma^2_{\varepsilon_1}, \sigma^2_{\varepsilon_2}, \sigma^2_s)$ *under the model (4.2) are*

$$(\overline{Y}_{1\star\star}, \overline{Y}_{2\star\star}, SS_{W_1}, SS_{W_2}, SS_{B_1}, SS_{B_2}, SS_{12}).$$

where $\overline{Y}_{1\star\star}, \overline{Y}_{2\star\star}, SS_{W_1}$, *and* SS_{W_2} *have the same definition as in the ANOVA table in Table 4.1, and*

$$SSB_1 = \sum_{j=1}^{n} (\overline{Y}_{1j\star} - \overline{Y}_{1\star\star})^2, SSB_2 = \sum_{j=1}^{n} (\overline{Y}_{2j\star} - \overline{Y}_{2\star\star})^2, SS_{12} = \sum_{j=1}^{n} (\overline{Y}_{1j\star} - \overline{Y}_{1\star\star})(\overline{Y}_{2j\star} - \overline{Y}_{2\star\star}).$$

Proof. Let $\boldsymbol{Y}$ denotes a $2nm \times 1$ vector and $\boldsymbol{Y} = (Y_{111} \dots Y_{1nm}\ Y_{211} \dots Y_{2nm})'$. Then under the model (4.2), $\boldsymbol{Y}$ has a multivariate normal distribution whose probability density function is given by

$$f(\boldsymbol{Y}) = \frac{1}{(2\pi)^{nm}|\Sigma|^{\frac{1}{2}}} \exp\left(-\frac{1}{2}(\boldsymbol{Y} - \boldsymbol{\mu})'\Sigma^{-1}(\boldsymbol{Y} - \boldsymbol{\mu})\right) \tag{4.12}$$

where $\boldsymbol{\mu} = (\mu_1\ \mu_2)' \otimes \boldsymbol{I}_{nm}$ is the mean of $\boldsymbol{Y}$, and Σ is the covariance matrix of $\boldsymbol{Y}$. Σ can be expressed as follows

$$\Sigma = \sigma^2_s(\boldsymbol{U}_2 \otimes \boldsymbol{I}_n \otimes \boldsymbol{U}_m) + \mathrm{V}_E \otimes \boldsymbol{I}_n \otimes \boldsymbol{I}_m,$$

where $\otimes$ represents kronecker product, $\boldsymbol{I}_v$ represents a $v \times v$ identity matrix, $\boldsymbol{U}_v$ represents a $v \times v$ matrix whose elements are all equal to 1, and

$$\mathrm{V}_E = \begin{bmatrix} \sigma^2_{\varepsilon_1} & 0 \\ 0 & \sigma^2_{\varepsilon_2} \end{bmatrix}.$$

Next, we find the inverse of the covariance matrix Σ. We first rewrite Σ as follows

$$\Sigma = \sigma^2_s(\mathrm{V}_1 + \mathrm{V}_2 + \mathrm{V}_3 + \mathrm{V}_4) + \sigma^2_{\varepsilon_1}\mathrm{V}_5 + \sigma^2_{\varepsilon_2}\mathrm{V}_6,$$

where

$$\mathrm{V}_1 = \begin{bmatrix} 1 & 0 \\ 0 & 0 \end{bmatrix} \otimes \boldsymbol{I}_n \otimes \boldsymbol{U}_m, \quad \mathrm{V}_2 = \begin{bmatrix} 0 & 0 \\ 0 & 1 \end{bmatrix} \otimes \boldsymbol{I}_n \otimes \boldsymbol{U}_m, \quad \mathrm{V}_3 = \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix} \otimes \boldsymbol{I}_n \otimes \boldsymbol{U}_m$$
$$\mathrm{V}_4 = \begin{bmatrix} 0 & 0 \\ 1 & 0 \end{bmatrix} \otimes \boldsymbol{I}_n \otimes \boldsymbol{U}_m, \quad \mathrm{V}_5 = \begin{bmatrix} 1 & 0 \\ 0 & 0 \end{bmatrix} \otimes \boldsymbol{I}_n \otimes \boldsymbol{I}_m, \quad \mathrm{V}_6 = \begin{bmatrix} 0 & 0 \\ 0 & 1 \end{bmatrix} \otimes \boldsymbol{I}_n \otimes \boldsymbol{I}_m.$$

Assuming $\Sigma^{-1} = a\mathrm{V}_1 + b\mathrm{V}_2 + c\mathrm{V}_3 + d\mathrm{V}_4 + e\mathrm{V}_5 + f\mathrm{V}_6$, we have

$$\begin{aligned} \Sigma^{-1}\Sigma &= (\sigma_s^2(\mathrm{V}_1 + \mathrm{V}_2 + \mathrm{V}_3 + \mathrm{V}_4) + \sigma_{\varepsilon_1}^2 \mathrm{V}_5 + \sigma_{\varepsilon_2}^2 \mathrm{V}_6)(a\mathrm{V}_1 + b\mathrm{V}_2 + c\mathrm{V}_3 + d\mathrm{V}_4 + e\mathrm{V}_4 + f\mathrm{V}_4) \\ &= V_5 + V_6, \end{aligned} \tag{4.13}$$

where a, b, c, d, e and f are unknown constants. Solving the equation (4.13) for a, b, c, d, e and f, we get

$$\begin{aligned} a &= -\frac{\sigma_s^2 \sigma_{\varepsilon_2}^2}{\sigma_{\varepsilon_1}^2 (m\sigma_s^2 \sigma_{\varepsilon_1}^2 + m\sigma_s^2 \sigma_{\varepsilon_2}^2 + \sigma_{\varepsilon_1}^2 \sigma_{\varepsilon_2}^2)}, \\ b &= -\frac{\sigma_s^2 \sigma_{\varepsilon_1}^2}{\sigma_{\varepsilon_2}^2 (m\sigma_s^2 \sigma_{\varepsilon_1}^2 + m\sigma_s^2 \sigma_{\varepsilon_2}^2 + \sigma_{\varepsilon_1}^2 \sigma_{\varepsilon_2}^2)}, \\ c &= \frac{1}{\sigma_{\varepsilon_1}^2}, \\ d &= \frac{1}{\sigma_{\varepsilon_2}^2}, \text{ and} \\ e = f &= \frac{\sigma_s^2}{m\sigma_s^2 \sigma_{\varepsilon_1}^2 + m\sigma_s^2 \sigma_{\varepsilon_2}^2 + \sigma_{\varepsilon_1}^2 \sigma_{\varepsilon_2}^2}. \end{aligned}$$

After Plugging the above explicit form of Σ^{-1} into the pdf in (4.12), one can easily show that the minimal sufficient statistics of $(\mu_1, \mu_2, \sigma_{\varepsilon_1}^2, \sigma_{\varepsilon_2}^2, \sigma_s^2)$ under the model (4.2) are

$$(\overline{Y}_{1\star\star}, \overline{Y}_{2\star\star}, SS_{W_1}, SS_{W_2}, SS_{B_1}, SS_{B_2}, SS_{12}).$$

□

Next, we follow the generalized fiducial recipe developed by Hannig (2008) and derive the generalized fiducial distribution of ρ_c. We first define the following quantities

$$SS_{2|1} = SS_{B_2} - \frac{SS_{12}^2}{SS_{B_1}}, \ B = \frac{SS_{12}}{SS_{B_1}}, \ \theta_{2|1} = \theta_S + \frac{\theta_2}{m} - \frac{\theta_S^2}{\theta_S + \theta_1/m}, \text{ and } \beta = \frac{\theta_S}{\theta_S + \theta_1/m}.$$

Note that the quantities B and $SS_{2|1}$ are, respectively, the linear regression coefficient and the residual sum of squares from the regression of $\overline{Y}_{2j\star}$ on $\overline{Y}_{1j\star}$. It is easily seen that the statistics are associated with the following pivotal quantities with known distributions as indicated

$$\begin{array}{lll} U_1 = \dfrac{SS_{W_1}}{\theta_1} \sim \chi^2_{n-1} & U_2 = \dfrac{SS_{W_2}}{\theta_2} \sim \chi^2_{n-1} & U_3 = \dfrac{SS_{B_1}}{\theta_S + \theta_1/m} \sim \chi^2_{n-1} \\ U_4 = \dfrac{2SS_M}{\theta_1 + \theta_2} \sim \chi^2_{1,\lambda} & U_5 = \dfrac{SS_{2|1}}{\theta_{2|1}} \sim \chi^2_{n-2} & Z = \dfrac{B - \beta}{\sqrt{\theta_{2|1}/SS_{B_1}}} \sim N(0,1). \end{array} \tag{4.14}$$

where the random variables U_1, U_2, U_3, U_4, U_5 and Z are mutually independent.

We classify the equations in (4.14) into three groups, and rewrite the above pivotal relationship as follows

$$\mathbb{X}_1 = G_1(E_1, \xi_1) \tag{4.15}$$

$$\mathbb{X}_2 = G_2(E_2, \xi_2) \tag{4.16}$$

$$\mathbb{X}_3 = G_3(E_3, \xi_3) \tag{4.17}$$

where

$$\begin{array}{lll} \mathbb{X}_1 = (SS_{W_1}, SS_{W_2}, SS_{B_1}) & \xi_1 = (\theta_1, \theta_2, \theta_S) & E_1 = (U_1, U_2, U_3) \\ \mathbb{X}_2 = SS_M & \xi_2 = (\theta_\mu, \xi_1) & E_2 = U_4 \\ \mathbb{X}_3 = (SS_{2|1}, B) & \xi_3 = \xi_1 & E_3 = (U_5, Z). \end{array}$$

Let $\boldsymbol{x}_1 = (ss_{w_1}, ss_{w_2}, ss_{b_1}), \boldsymbol{x}_2 = ss_m$ and $\boldsymbol{x}_3 = (ss_{2|1}, b)$ be the realized values of $\mathbb{X}_1$, $\mathbb{X}_2$ and $\mathbb{X}_3$ respectively. Let $\boldsymbol{e}_1 = (u_1, u_2, u_3), \boldsymbol{e}_2 = u_4$ and $\boldsymbol{e}_3 = (u_5, z)$ be the realized values of E_1, E_2 and E_3 respectively. Define the set-valued functions $T_1(\boldsymbol{x}_1, \boldsymbol{e}_1)$ and $T_2(\boldsymbol{x}_2, \boldsymbol{e}_2)$ as follows

$$T_1(\boldsymbol{x}_1, \boldsymbol{e}_1) = \{\xi_1 : \boldsymbol{x}_1 = G_1(\boldsymbol{e}_1, \xi_1)\}, \tag{4.18}$$

$$T_2(\boldsymbol{x}_2, \boldsymbol{e}_2) = \{\theta_\mu : \boldsymbol{x}_2 = G_2(\boldsymbol{e}_2, (\theta_\mu, T_1(\boldsymbol{x}_1, \boldsymbol{e}_1)))\}. \tag{4.19}$$

The structural equations in (4.15),(4.16) and (4.17) are consistent if and only if the values of ξ_1 in (4.18) also satisfy the equations in (4.16) and (4.17). This requirement leads to the following set of constraints that must be satisfied by $\boldsymbol{x}$ and $\boldsymbol{e}$

$$T_2(\boldsymbol{x}_2, \boldsymbol{e}_2) \neq \emptyset, \text{ and} \tag{4.20}$$

$$\boldsymbol{x}_3 = G_3\left(\boldsymbol{e}_3, T_1(\boldsymbol{x}_1, \boldsymbol{e}_1)\right). \tag{4.21}$$

Equation (4.21) is equivalent to

$$ss_{2|1} = u_5\left(\frac{ss_{b_1}}{u_3} - \frac{ss_{w_1}}{mu_1} + \frac{ss_{w_2}}{mu_2} - \left(\frac{ss_{b_1}}{u_3} - \frac{ss_{w_1}}{mu_1}\right)^2\left(\frac{u_3}{ss_{b_1}}\right)\right),$$

$$b = 1 - \frac{1}{m}\frac{ss_{w_1}u_3}{ss_{b_1}u_1} + z\sqrt{\frac{1}{ss_{b_1}}\left(\frac{ss_{b_1}}{u_3} - \frac{ss_{w_1}}{mu_1} + \frac{ss_{w_2}}{mu_2} - \left(\frac{ss_{b_1}}{u_3} - \frac{ss_{w_1}}{mu_1}\right)^2\left(\frac{u_3}{ss_{b_1}}\right)\right)}. \tag{4.22}$$

Following Hannig et al. (2006), the generalized fiducial distribution of $\xi = (\theta_1, \theta_2, \theta_S, \theta_\mu)$ is the conditional distribution of

$$T_1(\boldsymbol{x}_1, E_1^\star), T_2(\boldsymbol{x}_2, E_2^\star))\,|\boldsymbol{x}_3 = G_3(E_3^\star, T_1(\boldsymbol{x}_1, E_1^\star)) \tag{4.23}$$

The distribution in (4.23) can be written as a product of two individual conditional distributions as follows

$$\begin{aligned} f\left(T_1(\boldsymbol{x}_1, E_1^\star), T_2(\boldsymbol{x}_2, E_2^\star)\,|\boldsymbol{x}_3 = G_3(E_3^\star, T_1(\boldsymbol{x}_1, E_1^\star))\right) = \\ f\left(T_1(\boldsymbol{x}_1, E_1^\star)|\boldsymbol{x}_3 = G_3(E_3^\star, T_1(\boldsymbol{x}_1, E_1^\star))\right) \times \\ f\left(T_2(\boldsymbol{x}_2, E_2^\star)\,|T_1(\boldsymbol{x}_1, E_1^\star) \neq \emptyset, \boldsymbol{x}_3 = G_3(E_3^\star, T_1(\boldsymbol{x}_1, E_1^\star))\right) \end{aligned}$$

Next, we derive the conditional distribution of $T_1(\boldsymbol{x}_1, E_1^\star)|\boldsymbol{x}_3 = G_3(E_3^\star, T_1(\boldsymbol{x}_1, E_1^\star))$. In view of equation (4.18) and equation (4.22), we define the random variables $W_1, \cdots, W_5$ as follows

$$W_1 = \frac{ss_{w_1}}{U_1^\star}, \qquad W_2 = \frac{ss_{w_2}}{U_2^\star}, \qquad W_3 = \frac{ss_{b_1}}{U_3^\star} - \frac{ss_{W_1}}{mU_1^\star},$$

$$W_4 = u_5\left(\frac{ss_{b_1}}{U_3^\star} - \frac{ss_{w_1}}{mU_1^\star} + \frac{ss_{w_2}}{mU_2^\star} - \left(\frac{ss_{b_1}}{U_3^\star} - \frac{ss_{w_1}}{mU_1^\star}\right)^2\left(\frac{U_3^\star}{ss_{b_1}}\right)\right), \text{ and}$$

$$W_5 = 1 - \frac{1}{m}\frac{ss_{w_1}U_3^\star}{ss_{b_1}U_1^\star} + z\sqrt{\frac{1}{ss_{b_1}}\left(\frac{ss_{b_1}}{U_3^\star} - \frac{ss_{w_1}}{mU_1^\star} + \frac{ss_{w_2}}{mU_2^\star} - \left(\frac{ss_{b_1}}{U_3^\star} - \frac{ss_{w_1}}{mU_1^\star}\right)^2\left(\frac{U_3^\star}{ss_{b_1}}\right)\right)}.$$

The conditional distribution of $T_1(\boldsymbol{x}_1, E_1^\star)|\boldsymbol{x}_3 = G_3(E_3^\star, T_1(\boldsymbol{x}_1, E_1^\star))$ is then the same as the conditional distribution of (W_1, W_2, W_3) given $W_4 = ss_{2|1}$ and $W_5 = b$. The routine calculation shows that the probability density function of this distribution is given by

$$f\left(W_1, W_2, W_3 \middle| W_4 = ss_{2|1}, W_5 = d\right) = \frac{(mW_1W_3 + mW_2W_3 + W_1W_2)^{\frac{1-n}{2}}}{(W_1 + mW_3)(W_1W_2)^{(1+\frac{n(m-1)}{2})}}$$
$$\times \exp\{-\frac{1}{2(mW_1W_3 + mW_2W_3 + W_1W_2)(W_1W_2)}(W_3(ss_{w_2}mW_1^2 + ss_{w_1}mW_2^2)$$
$$+W_1^2W_2(ss_{2|1}m + ss_{w_2} + ss_{b_1}mb^2) + W_1W_2^2(ss_{w_1} + ss_{b_1}m) + W_1W_2W_3(ss_{b_1}m^2$$
$$+ss_{w_2}m + ss_{b_1}b^2m^2 + ss_{2|1}m^2 + ss_{w_1}m - 2ss_{b_1}bm^2))\}I_{(0,\infty)}(W_1)I_{(0,\infty)}(W_2)I_{(0,\infty)}(W_3) \tag{4.24}$$

Notice that it's hard to obtain the explicit expression of probability density function of the conditional distribution $T_2\left(\boldsymbol{x}_2, E_2^\star\right)|T_1(\boldsymbol{x}_1, E_1^\star) \neq \emptyset, \boldsymbol{x}_3 = G_3\left(E_3^\star, T_1(\boldsymbol{x}_1, E_1^\star)\right)$ due to the implicity of the function $T_2\left(\boldsymbol{x}_2, E_2^\star\right)$ and the complicity of pdf of non-central chi-squared distribution. We resort to Monte Carlo simulation. The simulation procedure is as follows

1. Draw K samples of $(\theta_1, \theta_2, \theta_S)$, denoted by $(\tilde{\theta}_1^{(i)}, \tilde{\theta}_2^{(i)}, \tilde{\theta}_S^{(i)}), i = 1, \cdots, K$, from the distribution given in (4.24).

2. Generate K uniform variate, denoted by $\tilde{u}^{(i)}, i = 1, \cdots, K$, and use the bisection method to solve the following equations for θ_μ,

$$F\left(\frac{2ss_m}{\tilde{\theta}_1^{(i)} + \tilde{\theta}_2^{(i)}}, \frac{nm\theta_\mu}{\tilde{\theta}_1^{(i)} + \tilde{\theta}_2^{(i)}}\right) = \tilde{u}^{(i)}, i = 1, \cdots, K, \tag{4.25}$$

where $F(x, v)$ is the value of CDF of noncentral chi-squared distribution with 1 degree of freedom and noncentrality parameter v, evaluated at x. Denote the solution to the equation (4.25) by $\tilde{\theta}_\mu^{(i)}$. If $\tilde{u}^{(i)} > F(2ss_m/(\tilde{\theta}_1^{(i)} + \tilde{\theta}_2^{(i)}), 0)$, then set $\tilde{\theta}_\mu^{(i)}$ as 0 by definition.

After step 2, we obtain K samples of $(\theta_1, \theta_2, \theta_S, \theta_\mu)$ from the generalized fiducial distribution of $(\theta_1, \theta_2, \theta_S, \theta_\mu)$ given in (4.23). Plugging these samples into the ρ_c formula given in (4.3), we obtain K simulations of ρ_c. Let $\mathcal{R}'_{\rho_{c,\gamma}}$ denote the $\gamma-$quantile of the these K simulations, then a $(1-\alpha)100\%$ lower bound for ρ_c is given by $[\mathcal{R}'_{\rho_{c,\alpha}}, 1]$. We refer to this interval as the FGCI2 confidence interval.

4.2.4 Simulation Study and Discussion of Results

To evaluate the performance of the proposed fiducial intervals, a simulation study was performed using the design considered by Quiroz (2005). Four cases where $\mu_1 - \mu_2 = 0$ or 2, $\sigma^2_{\varepsilon_1} = 1$ or 1.25, and $\sigma^2_{\varepsilon_2} = 1$ were considered in the simulation study. For each case, the correlation coefficient $\rho = 0.99, 0.97, 0.95, 0.90, 0.80, 0.70$, and 0.50, were selected with sample size $n = 5, 15, 30$ and repeated measurements $m = 2$ and 5 per subject. Thus, we had 168 designs. To estimate the test size, some boundary scenarios were considered in our simulation study. We used the same cutoff value, 0.95, as in simulation study in Quiroz (2005) and selected $\sigma^2_{\varepsilon_1} = 0.1, 1, 5$ and 10, $\sigma^2_{\varepsilon_2} = 0.1$ and 2, $\rho = 0.99$ and 0.97. $\theta_\mu = (\mu_1 - \mu_2)^2$ was calculated using the formula (4.3) by setting $\rho_c = 0.95$. Simulations were conducted with combinations of $n = 5, 15, 30$, and $m = 2$ and 5. Combining 168 designs, we have totally 264 designs.

2000 independent data sets were generated for each of 264 designs and 95% lower confidence bounds were constructed for each method. For FGCI1 interval procedure, 10000 realizations of the random variable $\mathcal{R}_{\rho_c}$ given in (4.11) were generated to construct the confidence intervals for each data set. For FGCI2 interval procedure, the confidence intervals were calculated based on $K = 10000$ simulations of $(\tilde{\theta}_1, \tilde{\theta}_2, \tilde{\theta}_S, \tilde{\theta}_\mu)$, for each data set.

The methods compared were (a) ZT1 interval, (b) ZT2 interval, (c) MRM interval, (d) FGCI1 interval and (e) FGCI2 interval. The criteria for judging the performance of the methods are the empirical coverage probabilities and the average lengths of the confidence intervals. The normal approximation to the binomial distribution suggests that, when the true coverage probability is 0.95, then there is less than a 5% chance that the empirical coverage based on 2000 simulations will be less than 0.942. Thus, we consider the interval liberal if its coverage probability is less than 0.942. The simulation results are listed in Appendix C and summarized in Table 4.2 and Figures 4.1 through 4.8. The column 2 in Table 4.2 gives the percentage of empirical coverage probabilities (CP) less than 0.942. The column 3 lists the percentage of confidence intervals having lengths greater than the lengths of FDCI2 intervals. Figures 4.1 through 4.4 show the empirical coverage probabilities for different designs. Figures 4.5 through 4.8 show the relative differences of the average confidence interval length, denoted by RL. RL is defined as $(CL_M - CL_{FGCI2})/CL_{FGCI2}$, where CL_M denotes the average length of a competing interval and CL_{FGCI2} denotes the average length of FGCI2 interval.

Table 4.2: Comparison of Fiducial Intervals with Competing Intervals.

Method	$CP < 0.942$	$CL_M > CL_{FGCI2}$
ZT1	10.6%	81.4%
ZT2	10.9%	79.9%
MRM	0.0%	98.1%
FGCI1	0.4%	59.9%
FGCI2	0.0%	-

CP: Coverage Probability, CL_M: The average length of a competing interval, CL_{FGCI2}: The average length of FGCI2 interval.

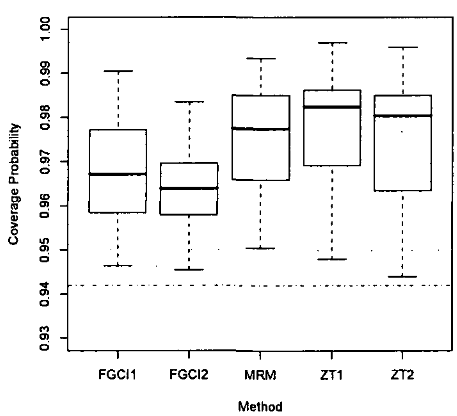

Figure 4.1: Empirical coverage probabilities for designs with sample size $n = 5$.

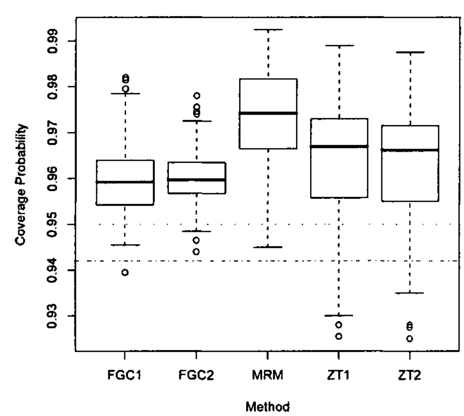

Figure 4.2: Empirical coverage probabilities for designs with sample size $n = 15$.

The results show that the ZT1 intervals and the ZT2 intervals are liberal sometimes. The MRM intervals are more conservative than other procedures for most of situations. The coverage probabilities of FGCI2 are the closest to the nominal value 0.95 for most of situations, especially when the sample size is small. Its behavior for designs with large sample size is similar to FGCI1.

Comparing the average interval lengths, we observe that FGCI2 has the smallest average confidence lengths among all other procedures most of times, especially when the

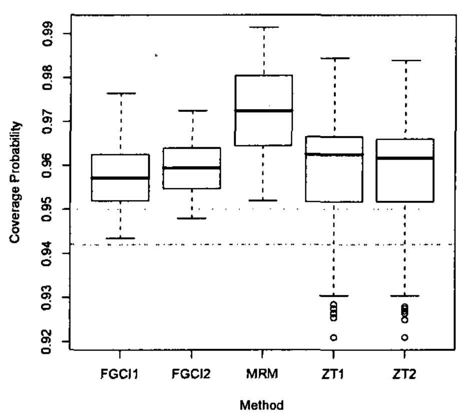

Figure 4.3: Empirical coverage probabilities for designs with sample size $n = 30$.

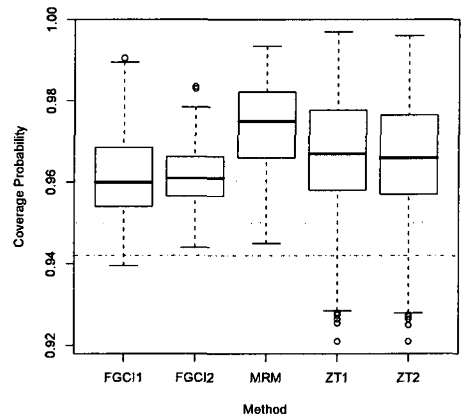

Figure 4.4: Empirical coverage probabilities for all designs.

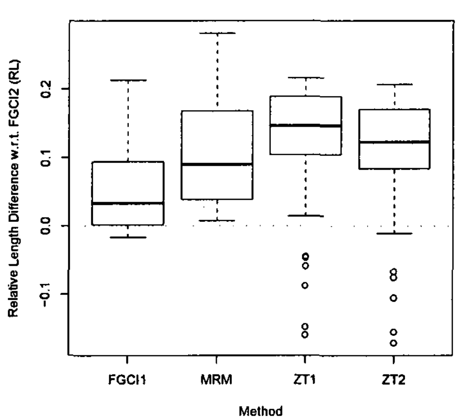

Figure 4.5: Relative differences of the average confidence interval lengths (RL) for designs with sample size $n = 5$.

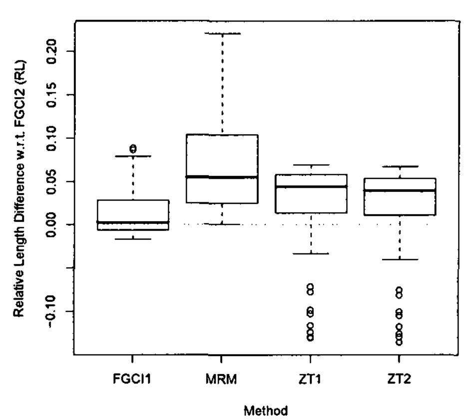

Figure 4.6: Relative differences of the average confidence interval lengths (RL) for designs with sample size $n = 15$.

sample size is small. MRM has the largest average lengths overall. The ZT2 procedure behaves slightly better than ZT1 procedure in terms of the confidence interval length.

Based on the above results, we recommend the FGCI2 intervals for ρ_c as the most suitable choice for practical application under the model (4.2).

4.3 Confidence Intervals for CCC under the Model with Method and Subject Interaction

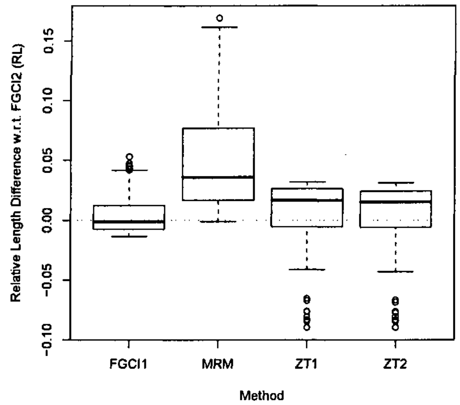

Figure 4.7: Relative differences of the average confidence interval lengths (RL) for designs with sample size $n = 30$.

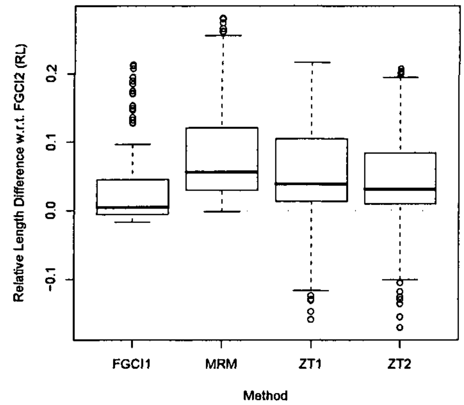

Figure 4.8: Relative differences of the average confidence interval lengths (RL) for all designs.

4.3.1 Statistical Model and Concordance Correlation Coefficient

In this section, we consider a general model with method and subject interaction, which is given below

$$Y_{ijk} = \mu_i + S_{ij} + \epsilon_{ijk}, i = 1, 2, j = 1, \ldots, n, k = 1, \ldots, m. \tag{4.26}$$

where Y_{ijk} is the k^{th} measurement made on the subject j receiving the method i, μ_1 and μ_2 are the means of test method and reference method respectively, S_{ij} is a random effect of subject j receiving method i, and ϵ_{ijk} are the within-subject measurement errors. The random variables ϵ_{ijk} are jointly independent and distributed normally with mean 0 and variance $\sigma^2_{\epsilon_i}, i = 1, 2$. The vector $S = [S_{1j}\ S_{2j}]'$ are mutually independent bivariate normal with zero means and a covariance matrix given by

$$V = \begin{pmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{12} & \sigma_2^2 \end{pmatrix}.$$

Finally, S_{ij} and ϵ_{ijk} are mutually independent. Note when $\sigma_1^2 = \sigma_2^2 = \sigma_{12} = \sigma_s^2$, the model (4.26) is reduced to the model (4.2). The ANOVA table for the model (4.26) is shown in Table 4.3. The collection of statistics SSM, SSB_1, SS_{W_1} and SS_{W_2} are mutually independent. Also, the collection of statistics SSM, SSB_2, SS_{W_1} and SS_{W_2} are mutually independent.

Table 4.3: ANOVA for Model with Interaction between the Methods and the Subjects (Model (4.26)).

Source	DF	MS	EMS
Methods	$n_M = 1$	$S_M^2 = SS_M/n_M$	$\theta_{M'} = 1/2(m(\sigma_1^2+\sigma_2^2-2\sigma_{12})/2$ $+nm(\mu_1-\mu_2)^2+\sigma_{\varepsilon_1}^2+\sigma_{\varepsilon_2}^2)$
Subject (1)	$n_{B_1} = n-1$	$S_{B_1}^2 = SS_{B_1}/n_{B_1}$	$\theta_{B_1} = \sigma_1^2+\sigma_{\varepsilon_1}^2/m$
Subject (2)	$n_{B_2} = n-1$	$S_{B_2}^2 = SS_{B_2}/n_{B_2}$	$\theta_{B_2} = \sigma_2^2+\sigma_{\varepsilon_2}^2/m$
Error (1)	$n_1 = n(m-1)$	$S_1^2 = SS_{W_1}/n_1$	$\theta_1 = \sigma_{\varepsilon_1}^2$
Error (2)	$n_2 = n(m-1)$	$S_2^2 = SS_{W_2}/n_2$	$\theta_2 = \sigma_{\varepsilon_2}^2$

For simplicity, the following parameter definitions are used in this Section,

$$\theta_1 = \sigma_{\varepsilon_1}^2 \qquad \theta_2 = \sigma_{\varepsilon_2}^2 \qquad \theta_{12} = \sigma_{12} \qquad \theta_{S_1} = \sigma_1^2 \qquad \theta_{S_2} = \sigma_2^2 \qquad \theta_\mu = (\mu_1-\mu_2)^2$$
$$\theta_B = \frac{1}{2}(m(\sigma_1^2+\sigma_2^2+2\sigma_{12})+\sigma_{\varepsilon_1}^2+\sigma_{\varepsilon_2}^2) \qquad \theta_{2|1} = \sigma_2^2+\frac{\sigma_{\varepsilon_2}^2}{m}-\frac{\sigma_{12}^2}{\sigma_1^2+\sigma_{\varepsilon_1}^2/m}$$
$$\theta_M = m(\theta_{S_1}+\theta_{S_2}-2\theta_{12})+\theta_1+\theta_2 \quad \beta = \frac{\sigma_{12}}{\sigma_1^2+\sigma_{\varepsilon_1}^2/m} \quad \lambda = \frac{nm(\mu_1-\mu_2)^2}{m(\sigma_1^2+\sigma_2^2-2\sigma_{12})+\sigma_{\varepsilon_1}^2+\sigma_{\varepsilon_2}^2}.$$

The statistics definitions in this section are the same as in Section 4.2 unless defined specifically.

By the definition of ρ_c, the concordance correlation coefficient under the model (4.26) can be expressed as follows

$$\begin{aligned}\rho_c &= 1-\frac{E[(Y_{1jk}-Y_{2jk})^2]}{E_{indep}[(Y_{1jk}-Y_{2jk})^2]} = \frac{2\sigma_{12}}{\sigma_1^2+\sigma_2^2+\sigma_{\varepsilon_1}^2+\sigma_{\varepsilon_2}^2+(\mu_1-\mu_2)^2} \\ &= 2\rho(\phi+1/\phi+\psi^2)^{-1}\end{aligned} \tag{4.27}$$

where

$$\rho = \frac{Cov(Y_{1jk},Y_{2jk})}{\sqrt{Var(Y_{1jk})Var(Y_{2jk})}} = \frac{\sigma_{12}}{\sqrt{(\sigma_1^2+\sigma_{\varepsilon_1}^2)(\sigma_2^2+\sigma_{\varepsilon_2}^2)}} = \text{Pearson correlation coefficient,}$$
$$\phi = \sqrt{\frac{Var(Y_{1jk})}{Var(Y_{2jk})}} = \sqrt{\frac{\sigma_1^2+\sigma_{\varepsilon_1}^2}{\sigma_2^2+\sigma_{\varepsilon_2}^2}} = \text{scale shift, and}$$
$$\psi^2 = \frac{(\mu_1-\mu_2)^2}{\sqrt{Var(Y_{1jk})Var(Y_{2jk})}} = \frac{(\mu_1-\mu_2)^2}{\sqrt{(\sigma_1^2+\sigma_{\varepsilon_1}^2)(\sigma_2^2+\sigma_{\varepsilon_2}^2)}} = \text{location shift relative to the scale.}$$

4.3.2 Published Confidence Interval for CCC

In this section, we follow the ZT interval construction procedure developed by Quiroz (2005) to construct a ZT interval for CCC under the model (4.26). The following statistics and parameters definitions are used in the construction of the ZT confidence intervals of ρ_c,

$$\hat\theta_1 = S_1^2 \qquad \hat\theta_2 = S_2^2 \qquad \hat\theta_{S_1} = S_{B_1}^2 - \frac{S_1^2}{m} \qquad \hat\theta_{S_2} = S_{B_2}^2 - \frac{S_2^2}{m}$$
$$\hat\theta_{12} = \frac{S_B^2}{m} - \frac{S_{B_1}^2 + S_{B_2}^2}{2} \qquad \hat\theta_\mu = \frac{2}{nm}(S_M^2 - m(S_{B_1}^2 + S_{B_2}^2) + S_B^2).$$

It's easy to show that $\hat\theta_1, \hat\theta_2, \hat\theta_{S_1}, \hat\theta_{S_2}, \hat\theta_{12}$ and $\hat\theta_\mu$ are unbiased and consistent estimators of $\theta_1, \theta_2, \theta_{S_1}, \theta_{S_2}, \theta_{12}$ and θ_μ, respectively. Using these estimators to estimate ρ_c, we get

$$\hat\rho_c = \frac{2\hat\theta_{12}}{\hat\theta_{S_1} + \hat\theta_{S_2} + \hat\theta_1 + \hat\theta_2 + \hat\theta_\mu} = \frac{2S_B^2/m - (S_{B_1}^2 + S_{B_2}^2)}{(2S_M^2 + 2S_B^2)/(nm) + (1 - \frac{2}{n})(S_{B_1}^2 + S_{B_2}^2) + (1 - \frac{1}{m})(S_1^2 + S_2^2)} \tag{4.28}$$

Let $\hat\theta = \hat\theta_{S_1} + \hat\theta_{S_2} + \hat\theta_1 + \hat\theta_2 + \hat\theta_\mu$. $\hat\rho_c$ in (4.28) can then be expressed as a ratio of $2\hat\theta_{12}$ to $\hat\theta$. By the delta method, the variance of this ratio is approximated as follows

$$Var(\hat\rho_c) = \frac{4\hat\theta_{12}^2}{\hat\theta^2}\left(\frac{Var(\hat\theta_{12})}{\hat\theta_{12}^2} - \frac{2Cov(\hat\theta, \hat\theta_{12})}{\hat\theta_{12}\hat\theta} + \frac{Var(\hat\theta)}{\hat\theta^2}\right). \tag{4.29}$$

It's easy to show that $Var(\hat\theta_{12}), Var(\hat\theta)$ and $Cov(\hat\theta, \hat\theta_{12})$ in (4.3.2) have the following expression

$$\begin{aligned}
Var(\hat\theta_{12}) &= \frac{1}{m^2}Var(S_B^2) + \frac{1}{4}\left(Var(S_{B_1}^2) + Var(S_{B_2}^2)\right) - \frac{1}{m}Cov(S_B^2, S_{B_1}^2) - \frac{1}{m}Cov(S_B^2, S_{B_2}^2) \\
&\quad + \frac{1}{2}Cov(S_{B_1}^2, S_{B_2}^2), \\
Var(\hat\theta) &= \frac{4}{m^2n^2}\left(Var(S_M^2) + Var(S_B^2)\right) + \left(1 - \frac{1}{m}\right)^2\left(Var(S_1^2) + Var(S_2^2)\right) + \left(1 - \frac{2}{n}\right)^2 \\
&\quad \times \left(Var(S_{B_1}^2) + Var(S_{B_2}^2) + 2Cov(S_{B_1}^2, S_{B_2}^2)\right) + \frac{4(n-2)}{n^2m}(Cov(S_B^2, S_{B_1}^2) \\
&\quad + Cov(S_B^2, S_{B_2}^2)), \\
Cov(\hat\theta, \hat\theta_{12}) &= \frac{2Var(S_B^2)}{nm^2} + \frac{n-3}{nm}\left(Cov(S_B^2, S_{B_1}^2) + Cov(S_B^2, S_{B_2}^2)\right) - \frac{n-2}{2n}(Var(S_{B_1}^2) \\
&\quad + Var(S_{B_2}^2) + 2Cov(S_{B_1}^2, S_{B_2}^2)).
\end{aligned} \tag{4.30}$$

The expression of the variance and covariance terms in (4.30) can be found in following upper triangular part of the covariance matrix Σ of the vector $[S_M^2\ S_B^2\ S_{B_1}^2\ S_{B_2}^2\ S_1^2\ S_2^2]'$

$$\Sigma = \begin{pmatrix} 2\theta_M(\theta_M + mn\theta_\mu) & 0 & 0 & 0 & 0 & 0 \\ & \frac{2\theta_B^2}{n-1} & \frac{m(\theta_{B_1}+\theta_{12})}{n-1} & \frac{m(\theta_{B_2}+\theta_{12})}{n-1} & 0 & 0 \\ & & \frac{2\theta_{B_1}^2}{n-1} & \frac{2\theta_{12}^2}{n-1} & 0 & 0 \\ & & & \frac{2\theta_{B_2}^2}{n-1} & 0 & 0 \\ & & & & \frac{2\theta_1^2}{n-1} & 0 \\ & & & & & \frac{2\theta_2^2}{n-1} \end{pmatrix}$$

The $Var(\hat{\rho}_c)$ is finally estimated by replacing $\theta_{B_1}, \theta_{B_2}, \theta_1, \theta_2, \theta_{12}$ and θ_μ with $\hat{\theta}_{B_1}, \hat{\theta}_{B_2}, \hat{\theta}_1, \hat{\theta}_2, \hat{\theta}_{12}$ and $\hat{\theta}_\mu$, respectively.

By plugging $\hat{\rho}_c$ in (4.3.2) and the estimate of the variance of $\hat{\rho}_c$ into the formula of Z-transformation lower bound given in (4.7) and setting $\alpha = 0.05$, we obtain a 95% lower confidence bound on ρ_c, denoted by L'_{ZT}. We refer to the interval $[L'_{ZT}, 1]$ as the ZT confidence interval.

4.3.3 A Fiducial Generalized Confidence Interval for CCC

In this section we construct a fiducial generalized confidence interval of ρ_c based on the Fiducial Generalized Pivotal Quantity.

Following the procedure of finding the minimal sufficient statistics given in Section 4.2.3, we obtain the following minimal sufficient statistics of $(\mu_1, \mu_2, \theta_1, \theta_2, \theta_{S_1}, \theta_{S_2}, \theta_{12})$ under the statistical model (4.26),

$$(\overline{Y}_{1**}, \overline{Y}_{2**}, SS_{W_1}, SS_{W_2}, SS_{B_1}, SS_{B_2}, SS_{12}).$$

Note these minimal sufficient statistics are the same as the ones under the model (4.2). However they are complete under the model (4.26). It is easily seen that the minimal sufficient statistics are associated with the following pivotal quantities with known distributions as indicated

$$U_1 = \frac{SS_{W_1}}{\theta_1} \sim \chi^2_{n-1} \qquad U_2 = \frac{SS_{W_2}}{\theta_2} \sim \chi^2_{n-1} \qquad U_3 = \frac{SS_{B_1}}{\theta_{B_1}} \sim \chi^2_{n-1}$$
$$U_4 = \frac{2SS_M}{\theta_M} \sim \chi^2_{1,\lambda} \qquad U_5 = \frac{SS_{2|1}}{\theta_{2|1}} \sim \chi^2_{n-2} \qquad Z = \frac{B-\beta}{\sqrt{\theta_{2|1}/SS_{B_1}}} \sim N(0,1)$$

where the random variables U_1, U_2, U_3, U_4, U_5 and Z are mutually independent. Based the above pivotal quantities, we apply the structural method for construction of FGPQ and obtain the following FGPQ for ρ_c

$$\mathcal{R}_{\rho_c} = \frac{2\mathcal{R}_{\theta_{12}}}{\mathcal{R}_{\theta_{S_1}} + \mathcal{R}_{\theta_{S_2}} + \mathcal{R}_{\theta_1} + \mathcal{R}_{\theta_2} + \mathcal{R}_{\theta_\mu}}, \tag{4.31}$$

where

$$\begin{aligned}
\mathcal{R}_{\theta_1} &= \frac{SS_{W_1}}{SS^\star_{W_1}}\theta_1, \quad \mathcal{R}_{\theta_2} = \frac{SS_{W_2}}{SS^\star_{W_2}}\theta_2, \quad \mathcal{R}_{\theta_{S_1}} = \frac{SS_{B_1}}{SS^\star_{B_1}}\theta_{B_1} - \frac{\mathcal{R}_{\theta_1}}{m},\\
\mathcal{R}_{\theta_{S_2}} &= \frac{SS_{2|1}}{SS^\star_{2|1}}\theta_{2|1} - \frac{\mathcal{R}_{\theta_1}}{m} + \frac{\mathcal{R}^2_{\theta_{12}}}{\mathcal{R}_{\theta_{S_1}} + \mathcal{R}_{\theta_1}/m},\\
\mathcal{R}_{\theta_{12}} &= \frac{SS_{B_1}}{SS^\star_{B_1}}\theta_{B_1}\left(B - \frac{B^\star - \beta}{\sqrt{(SS_{B_1}SS_{2|1})/(SS^\star_{B_1}SS^\star_{2|1})}}\right),\\
\mathcal{R}_{\theta_\mu} &= \frac{1}{nm}\left(m(\mathcal{R}_{\theta_{S_1}} + \mathcal{R}_{\theta_{S_2}} - 2\mathcal{R}_{\theta_{12}}) + \mathcal{R}_{\theta_1} + \mathcal{R}_{\theta_2}\right)Q(F(v_1; v_2); v_3),\\
v_1 &= \frac{2SS^\star_M}{m(\theta_{S_1} + \theta_{S_2} - 2\theta_{12}) + \theta_1 + \theta_2},\\
v_2 &= \frac{nm\theta_\mu}{m(\theta_{S_1} + \theta_{S_2} - 2\theta_{12}) + \theta_1 + \theta_2},\\
v_3 &= \frac{2SS_M}{m(\mathcal{R}_{\theta_{S_1}} + \mathcal{R}_{\theta_{S_2}} - 2\mathcal{R}_{\theta_{12}}) + \mathcal{R}_{\theta_1} + \mathcal{R}_{\theta_2}},
\end{aligned}$$

$SS^\star_{W_1}, SS^\star_{W_2}, SS^\star_{B_1}, SS^\star_{B_2}, SS^\star_{2|1}$ and $SS^\star_M$ are the independent copies of $SS_{W_1}, SS_{W_2}, SS_{B_1}, SS_{B_2}, SS_{2|1}$ and SS_M respectively, the functions $F(x, \lambda)$ and $Q(u, x)$ have the same definition as in Section 2.4.1. Observe that $\mathcal{R}_{\theta_1}, \mathcal{R}_{\theta_2}, \mathcal{R}_{\theta_{S_1}}, \mathcal{R}_{\theta_{S_2}}$ and $\mathcal{R}_{\theta_\mu}$ are the FGPQs for $\theta_1, \theta_2, \theta_{S_1}, \theta_{S_2}$ and θ_μ, respectively. It follows that $\mathcal{R}_{\rho_c}$ is the FGPQ for ρ_c. Let $\mathcal{R}_{\rho_c,\gamma}$ denote the $\gamma-$quantile of the distribution of $\mathcal{R}$, then a $(1-\alpha)100\%$ lower bound for ρ_c is given by $\mathcal{R}_{\rho_c}$. We refer to the interval $[\mathcal{R}_{\rho_c}, 1]$ as the FGCI confidence interval.

4.3.4 Simulation Study and Discussion of Results

A simulation study was carried out to evaluate the performance of the proposed fiducial intervals. Eight cases where $\mu_1 - \mu_2 = 0$ or 2, $\sigma^2_{\varepsilon_1} = 1$ or 1.25, $\sigma^2_{\varepsilon_2} = 1$, $\sigma^2_1 = 20$ or 25, $\sigma^2_2 = 20$ were considered in the simulation study. For each case, the correlation coefficient $\rho = 0.95, 0.9, 0.8$ and 0.7, were selected with sample size $n = 5, 15, 30$ and repeated measurements $m = 2$ and 5 per subject. Thus, we had 192 designs.

The simulation was done using 2000 independent data sets for each of a number of scenarios covering different parameter settings. For each simulated data set, the 95% lower confidence bounds were constructed for each method. For FGCI interval procedure, the confidence interval was estimated using 10000 realizations of the random variable $\mathcal{R}_{\rho_c}$ given in (4.31). The simulation results are listed in Appendix C and summarized in Table 4.4 and Figures 4.9 through 4.16. The column 2 in Table 4.4 gives the percentage of empirical coverage probabilities less than 0.942. The column 3 lists the percentage of the ZT confidence intervals having lengths greater than the lengths of FGCI intervals.

Table 4.4: Comparison of Fiducial Intervals with ZT Intervals

Method	$CP < 0.942$	$CL_{ZT} > CL_{FGCI}$
ZT	28.6%	10.42%
FGCI	0.0%	-

CP: Coverage Probability, CL_ZT: The average length of ZT interval, CL_{FGCI}: The average length of FGCI interval.

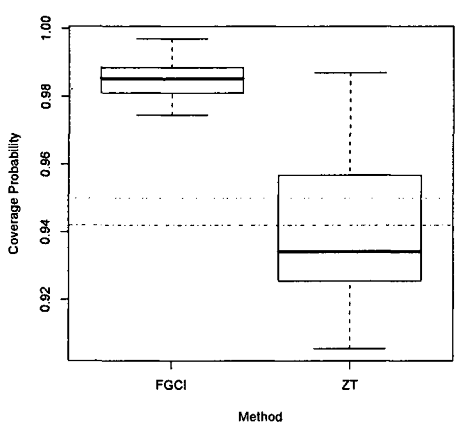

Figure 4.9: Empirical coverage probabilities for designs with sample size $n = 5$.

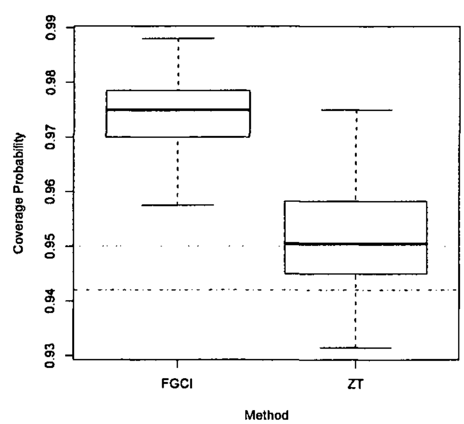

Figure 4.10: Empirical coverage probabilities for designs with sample size $n = 15$.

The simulation results show that ZT confidence intervals are liberal in many situations, especially when sample sizes are small. Overall, about 30% ZT confidence intervals have coverage probabilities less than 0.942. For designs with n=5, about 58% ZT confidence intervals are liberal. Nonetheless, no FGCI intervals are found to be liberal. Therefore

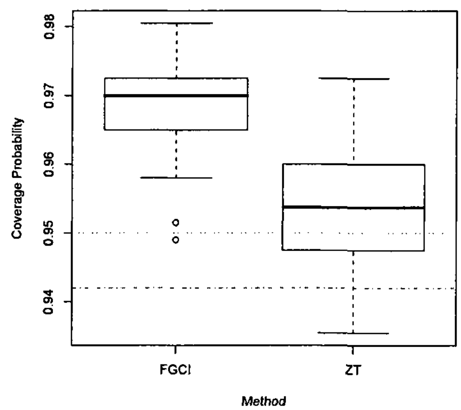

Figure 4.11: Empirical coverage probabilities for designs with sample size $n = 30$.

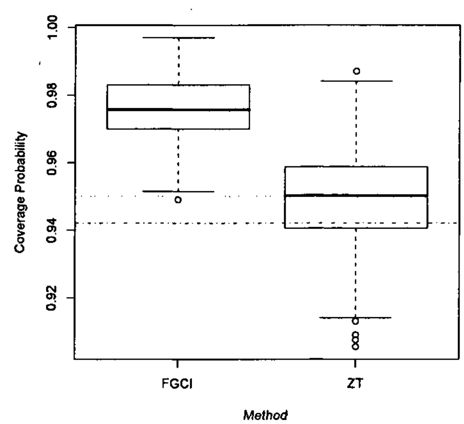

Figure 4.12: Empirical coverage probabilities for all designs.

although ZT intervals have shorter average confidence interval lengths than FGCI intervals in most of situations, FGCI intervals are more suitable for practical application, especially for small experiments.

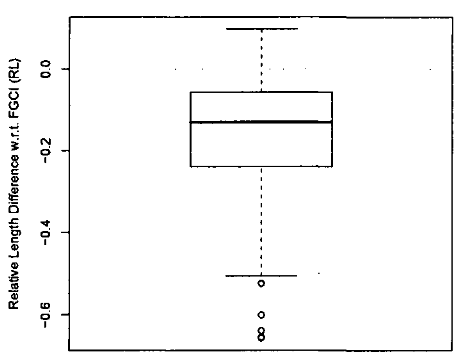

Figure 4.13: Relative differences of the average confidence interval lengths (RL) for designs with sample size $n = 5$.

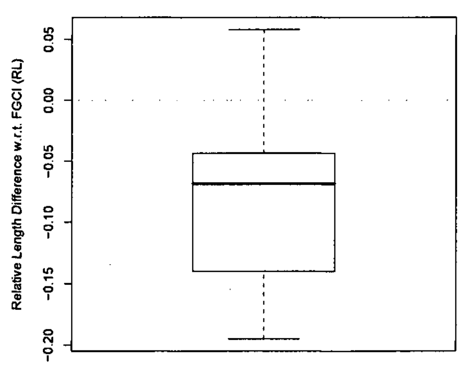

Figure 4.14: Relative differences of the average confidence interval lengths (RL) for designs with sample size $n = 15$.

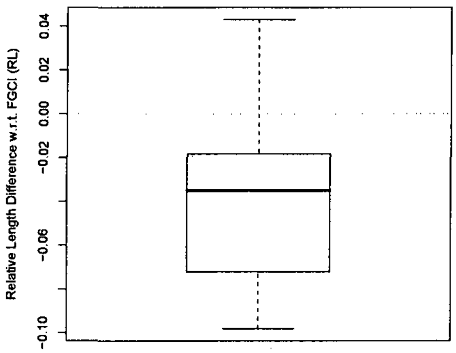

Figure 4.15: Relative differences of the average confidence interval lengths (RL) for designs with sample size $n = 30$.

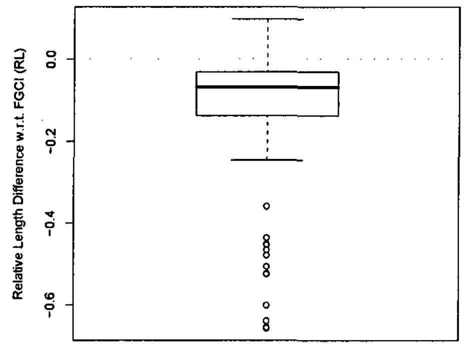

Figure 4.16: Relative differences of the average confidence interval lengths (RL) for all designs.

Chapter 5

SIMULTANEOUS FIDUCIAL GENERALIZED CONFIDENCE INTERVALS FOR RATIOS OF MEANS OF LOGNORMAL DISTRIBUTIONS

5.1 Introduction

Simultaneous confidence intervals for certain lognormal parameters are useful in pharmaceutical statistics. In bioequivalence studies comparing a test drug to a reference drug, it is of interest to compare the mean responses of the two drugs to ensure that they are (more or less) equally effective. With this in mind the U.S. Food and Drug Administration (FDA) requires the lab submitting an approval request to demonstrate that certain *equivalence criteria* are satisfied. One such criterion is called the average bioequivalence criterion which requires the ratio $\theta = \mu_T/\mu_R$ to be sufficently close to 1, where μ_T denotes the mean response to a test formulation of a drug and μ_R denotes the mean for the reference formulation of the drug. A confidence interval for the ratio $\theta = \mu_T/\mu_R$ is useful in this situation. A key response variable in such studies is called AUC which is the area under the curve relating the plasma drug concentration in a patient to the elapsed time after the drug is administered. As per the FDA guidelines, the analysis of AUC is to be carried out using the log scale. This is because the distribution of AUC is typically modeled well by a log-normal distribution. So the parameter of interest is the ratio of means of two log-normal distribution. This approach is termed bioequivalence and involves the calculation of the confidence interval for the ratio of the average of test and reference products.

The experimental design of choice in bioequivalence studies comparing two or more formulations of a drug is a crossover design with adequate washout periods to minimize carryover effects. However, a parallel design is more appropriate when the half lives of drugs being tested are very long and this is recognized in the U.S. Food and Drug Administration (2001). The two-group parallel design was considered by Kirshnamoorthy and Mathew

(2003) who derived FGCIs for the ratio of means of two Log-normal Distributions using the ideas of generalized p-values and generalized confidence intervals.

Some bioequivalence studies consider one or more reference drugs (for instance, the same drug in different forms – tablets, capsules, caplets, liquid, etc) and one or more test drugs. In such studies one is often interested in all pairs of ratios of means to help assess mutual bioequivalence of all formulations. More specifically, suppose $Y_{i1}, \ldots, Y_{in_i}$ is a random sample from $LN(\mu_i, \sigma_i^2)$, $i = 1, \ldots, k$, where $LN(\mu, \sigma^2)$ refers to a lognormal distribution with parameters μ, σ^2, i.e., $ln(Y_{ij}) \sim N(\mu_i, \sigma_i^2)$. We are interested in obtaining simultaneous confidence intervals for all pairwise ratios $\theta_{rs} = \theta_r/\theta_s$ $(1 \leq r < s \leq k)$ where θ_r is the mean of $LN(\mu_r, \sigma_r^2)$. In particular, $\log \theta_r = \mu_r + \sigma_r^2/2$. This is equivalent to the problem of obtaining simultaneous CIs for all pairwise differences of the form

$$\delta_{rs} = \log(\theta_r) - \log(\theta_s) = (\mu_r - \mu_s) + \frac{1}{2}(\sigma_r^2 - \sigma_s^2).$$

We propose a solution to this problem by applying the method introduced by Abdel-Karim (2005) for constructing simultaneous confidence intervals for for all pairwise differences of means of k normal distributions based on FGPQs. The performance of the proposed method is assessed using a statistical simulation study.

The chapter is organized as follows. In the next section we decribe the method used to construct simultaneous Fiducial Generalized Confidence Intervals for ratios of lognormal means. The performance of these intervals is assessed by statistical simulation which is described in Section 5.3. A proof of the asymptotic correctness of the proposed intervals is given in Section 5.4.

5.2 A Simultaneous Fiducial Generalized Confidence Interval for Ratios of Means of Lognormal Distributions

In this section we show how one may construct simultaneous confidence intervals for parameters of interest based on a vector FGPQ. First we describe the notation and terminology used in this chapter.

For $i = 1, \ldots, K$, suppose $Y_{ij} \overset{iid}{\sim} N(\mu_i, \sigma_i^2)$, for $j = 1, \ldots, n_i$. Then $\exp(Y_{ij})$, $j = 1, \ldots, n_i$ is an iid sample from a lognormal distribution with mean $\theta_i = \exp(\mu_i + \sigma_i^2/2)$.

The problem of constructing simultaneous confidence intervals for $\theta_{ij} = \theta_i/\theta_j$ for all $i \neq j$ is equivalent to the problem of constructing simultaneous confidence intervals for the parameters $\delta_{ij} = log(\theta_{ij}) = (\mu_i + \sigma_i^2/2) - (\mu_j + \sigma_j^2/2)$.

We first observe that a FGPQ for δ_{ij} is given by

$$\mathcal{R}_{\delta_{ij}}(\mathbb{S}, \mathbb{S}^\star, \xi) = \mathcal{R}_{\mu_i} - \mathcal{R}_{\mu_j} + \frac{1}{2}(\mathcal{R}_{\sigma_i^2} - \mathcal{R}_{\sigma_j^2})$$

where

$$\mathcal{R}_{\mu_p} = \bar{Y}_p - \frac{S_p}{S_p^\star}(\bar{Y}_p^\star - \mu_p)$$

and

$$\mathcal{R}_{\sigma_p^2} = \frac{S_p^2}{S_p^{\star 2}}\sigma_p^2$$

for $p = 1, \ldots, K$. Here $\bar{Y}_p$ denotes the mean and S_p^2 is the sample variance of Y_{pj} for $j = 1, \ldots, n_p$ and $\bar{Y}_p^\star$, $S_p^{\star 2}$ are independent copies of $\bar{Y}_p$, S_p^2.

Define

$$\mathcal{D}(\mathbb{S}, \mathbb{S}^\star, \xi) = \max_{i \neq j} \left| \frac{(\overline{Y}_i + (1/2)S_i^2) - (\overline{Y}_j + (1/2)S_j^2) - \mathcal{R}_{\delta_{ij}}(\mathbb{S}, \mathbb{S}^\star, \xi)}{\sqrt{V_{ij}}} \right| \tag{5.1}$$

where V_{ij} is a consistent estimator of the variance of $(\overline{Y}_i + (1/2)S_i^2) - (\overline{Y}_j + (1/2)S_j^2)$, i.e.,

$$V_{ij} = \frac{S_i^2}{n_i} + \frac{S_i^4}{2(n_i - 1)} + \frac{S_j^2}{n_j} + \frac{S_j^4}{2(n_j - 1)}. \tag{5.2}$$

Then $100(1-\alpha)\%$ two-sided simultaneous FGCIs for pairwise ratios $\theta_{ij}, i \neq j$ of means of more than two independent lognormal distributions are $[L_{ij}, U_{ij}]$ where

$$L_{ij} = \exp\left(\overline{Y}_i - \overline{Y}_j + (1/2)S_i^2 - (1/2)S_j^2 - d_{1-\alpha}\sqrt{V_{ij}}\right) \tag{5.3}$$

$$U_{ij} = \exp\left(\overline{Y}_i - \overline{Y}_j + (1/2)S_i^2 - (1/2)S_j^2 + d_{1-\alpha}\sqrt{V_{ij}}\right) \tag{5.4}$$

and d_γ denotes the 100γ-percentile of the conditional distribution of $\mathcal{D}(\mathbb{S}, \mathbb{S}^*, \xi)$ given $\mathbb{S} = \mathbf{s}$.

Remark 5.1. Let $\boldsymbol{\delta}$ denote a vector of parameters whose components are δ_{ij}, $1 \leq i < j \leq K$. It is instructive to note that the confidence region for $\boldsymbol{\delta}$ resulting from the proposed simultaneous intervals for δ_{ij} are one of the many possible ways in which to construct a generalized confidence region for $\boldsymbol{\delta}$. We begin with the vector FGPQ $\mathcal{R}_{\boldsymbol{\delta}}$ and obtain a confidence region for $\boldsymbol{\delta}$ that has a prespecified shape.

In the next section we examine the performance of these simultaneous intervals in small sample situations as well as large sample situations. Section 5.4 contains a theorem describing the asymptotic behavior of these intervals.

5.3 Simulation Study and Discussion of Results

Simultaneous FGCIs for all pairwise ratios of means of three independent lognormal distributions were considered in the simulation study. The simulations were done using 5000 independently generated datasets for each of a number of scenarios covering different parameter settings. For each simulated dataset the 95% simultaneous generalized confidence intervals were estimated using 10000 realizations of the random variable $\mathcal{D}(\mathbb{S}, \mathbb{S}^*, \xi)$ defined in (5.1). Without loss of generality, it was assumed that all μ_i's, $i = 1, 2, 3$, are equal to 0. The values used for sample sizes were 5, 25 and 125. Five levels of σ_1^2 were used – 0.01, 0.1, 1, 10 and 100. For each level of σ_1^2, σ_2^2 values were set at $2^l\sigma_1^2$, and σ_3^2 values were set at $2^m\sigma_1^2$, where l and m are integers and $0 \leq l \leq m \leq 3$. Thus, totally 995 settings were considered in this simulation study. The simulation results are listed in Appendix D and summarized in Table 5.1, Table 5.2 and Figures 5.1 through 5.4. Table 5.1 gives a classification of the various sample size combinations considered in the simulation study into small sample cases, medium sample cases and large sample cases. The last column of Table 5.1 gives the proportion of the simulation settings for which the empirical coverage probability is not significantly different from the target coverage rate of 0.95. Several scenarios with combinations of very large sample sizes and extreme variances were also included in the study to judge how soon the asymptotics take effect (see Section 5.4). The parameter settings for these large sample cases are given in in Table 5.2. The last column in Table 5.2 gives the empirical coverage probability for the particular simulation setting considered.

Table 5.1: Classification of Sample Sizes and Proportions of Empirical Coverage Probabilities within Limits of Simulation Error for Each Class (Three Populations)

Size	Combination	Proportion
small	(5 5 5) (5 5 25) (5 25 25) (5 5 125)	13.09%
medium	(25 25 25) (5 25 125) (5 125 125) (25 25 125) (25 125 125)	39.28%
large	(125 125 125)	62.86%

Figures 5.1 through 5.4 shows histograms of empirical coverage probabilities for small sample cases, medium sample cases, large sample cases, and all of the cases combined,

Table 5.2: Empirical Coverage Probabilities of 95% Fiducial Generalized Confidence Intervals for Designs with Very Large Sample Size and Extreme Variances (Three Populations).

n_1	n_2	n_3	σ_1	σ_2	σ_3	Empirical Coverage
125	125	125	0.01	0.01	0.01	0.9531
625	625	625	0.01	0.01	0.01	0.9490
1000	1000	1000	0.01	0.01	0.01	0.9491
2000	2000	2000	0.01	0.01	0.01	0.9498
125	125	125	100	800	1600	0.9509
625	625	625	100	800	1600	0.9488
1000	1000	1000	100	800	1600	0.9513
2000	2000	2000	100	800	1600	0.9484

respectively. It is seen that the empirical coverage rates are in the range from 0.94 to 1.0 and hence the proposed interval procedure is conservative. The results also show that most of the empirical coverages bigger than 0.98 occur with the combination of very small samples and large variances.

As the sample size increases, the empirical coverage approaches the claimed coverage and the proportion of empirical coverage within the binomial simulation error bounds increases. Table 5.2 shows that empirical coverages approach the claimed coverage as sample sizes increase even for very large variances. The convergence appears to be slower for scenarios with large variances than scenarios with small variances.

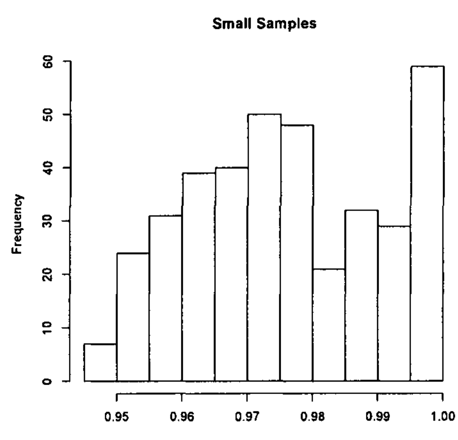

Figure 5.1: Empirical coverage probabilities for small sample cases.

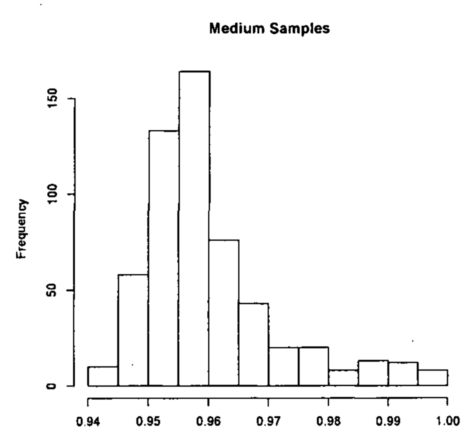

Figure 5.2: Empirical coverage probabilities for medium sample cases.

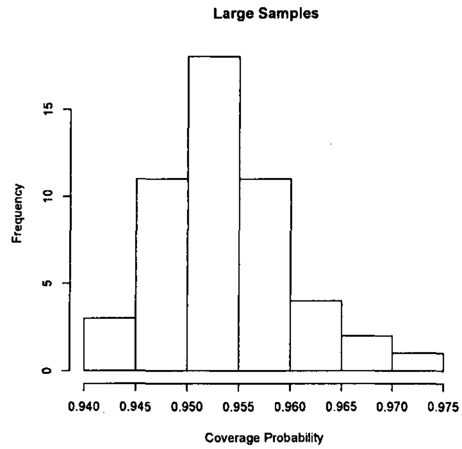

Figure 5.3: Empirical coverage probabilities for large sample cases.

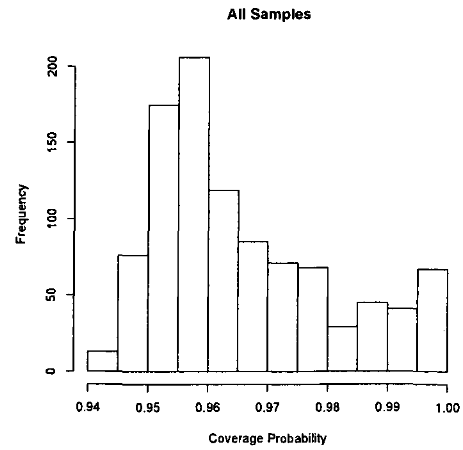

Figure 5.4: Empirical coverage probabilities for all cases.

5.4 Asymptotic Behavior of Simultaneous Fiducial Generalized Confidence Intervals for Ratios of Means of Lognormal Distributions

We continue to use the notation of the previous section. We now prove that the constructed simultaneous fiducial intervals have correct asymptotic coverage.

Theorem 5.1. *Let all $n_1, \ldots, n_K$ approach infinity in such a way that $r_j = \lim n_j/(n_1 + \cdots + n_K)$ exists and $0 < r_j < 1$. Then the $100(1-\alpha)\%$ two-sided simultaneous confidence intervals have asymptotically $100(1-\alpha)\%$ frequentist coverage, i.e.,*

$$P(L_{ij} \le \theta_{ij} \le U_{ij},\ \textit{for all } i,j) \to 1-\alpha.$$

Proof. Set $n = n_1 + \cdots + n_K$. Define a vector $\mathbf{m} = (\mu_1, \ldots, \mu_K, \sigma_1^2, \ldots, \sigma_K^2)$, and a diagonal matrix

$$D = \operatorname{diag}\left(\frac{\sigma_1}{\sqrt{r_1}}, \ldots, \frac{\sigma_K}{\sqrt{r_K}}, \frac{\sigma_1^2\sqrt{2}}{\sqrt{r_1}}, \ldots, \frac{\sigma_K^2\sqrt{2}}{\sqrt{r_K}}\right).$$

The central limit theorem implies that $\sqrt{n}(\mathbb{S}_n - \mathbf{m}) \xrightarrow{\mathcal{D}} D\mathbb{Z}$ where $\mathbb{Z} = (Z_1, \ldots, Z_{2K})$ are i.i.d. N(0,1) variables. By Skorokhod's theorem (see Billingsley (1995)) we can find a sequence $\bar{\mathbb{S}}_n$ independent of $\mathbb{S}^*$ such that $\bar{\mathbb{S}}_n$ has the same distribution as $\mathbb{S}$ and $\sqrt{n}(\bar{\mathbb{S}}_n - \mathbf{m}) \to D\mathbb{Z}$ almost surely. In what follows we can therefore assume without loss of generality that

$$\sqrt{n}(\mathbb{S}_n - \mathbf{m}) \to D\mathbb{Z} \text{ a.s.} \tag{5.5}$$

It follows from the Slutsky's theorem that as $n \to \infty$

$$\mathcal{D}(\mathbb{S}, \mathbb{S}^\star, \xi) \to \max_{i \neq j} \left| \frac{Z_i^\star \frac{\sigma_i}{\sqrt{r_i}} + Z_{i+K}^\star \frac{\sigma_i^2}{\sqrt{2r_i}} - Z_j^\star \frac{\sigma_j}{\sqrt{r_j}} - Z_{j+K}^\star \frac{\sigma_j^2}{\sqrt{2r_j}}}{\left(\frac{\sigma_i^2}{r_i} + \frac{\sigma_i^4}{2r_i} + \frac{\sigma_j^2}{r_j} + \frac{\sigma_j^4}{2r_j}\right)^{1/2}} \right| \text{ a.s.} \tag{5.6}$$

Here the a.s. comes from the a.s. convergence in (5.5).

Recall the definition of the percentile $d_\gamma(\mathbf{s})$ above. Since the limiting distribution in (5.6) is continuous, we have by the definition of convergence in distribution

$$d_\gamma(\mathbb{S}) \to q_\gamma, \tag{5.7}$$

where q_γ is the the 100γ-percentile of the limiting distribution in (5.6).

Finally, realize that (5.5) implies

$$\frac{\overline{Y}_i - \overline{Y}_j + (1/2)S_i^2 - (1/2)S_j^2 - \delta_{ij}}{\sqrt{V_{ij}}} \to \frac{Z_i \frac{\sigma_i}{\sqrt{r_i}} + Z_{i+K} \frac{\sigma_i^2}{\sqrt{2r_i}} - Z_j \frac{\sigma_j}{\sqrt{r_j}} - Z_{j+K} \frac{\sigma_j^2}{\sqrt{2r_j}}}{\left(\frac{\sigma_i^2}{r_i} + \frac{\sigma_i^4}{2r_i} + \frac{\sigma_j^2}{r_j} + \frac{\sigma_j^4}{2r_j}\right)^{1/2}} \text{ a.s.}$$

This, together with (5.7) and some algebra gives

$$\begin{aligned}
&P(L_{ij} \le \theta_{ij} \le U_{ij}, \text{ for all } i, j) \\
&= P\left(\max_{i \neq j} \left| \frac{\overline{Y}_i - \overline{Y}_j + (1/2)S_i^2 - (1/2)S_j^2 - \delta_{ij}}{\sqrt{V_{ij}}} \right| \le d_{1-\alpha}\right) \\
&\to P\left(\max_{i \neq j} \left| \frac{Z_i \frac{\sigma_i}{\sqrt{r_i}} + Z_{i+K} \frac{\sigma_i^2}{\sqrt{2r_i}} - Z_j \frac{\sigma_j}{\sqrt{r_j}} - Z_{j+K} \frac{\sigma_j^2}{\sqrt{2r_j}}}{\left(\frac{\sigma_i^2}{r_i} + \frac{\sigma_i^4}{2r_i} + \frac{\sigma_j^2}{r_j} + \frac{\sigma_j^4}{2r_j}\right)^{1/2}} \right| \le q_{1-\alpha}\right) \\
&= 1 - \alpha
\end{aligned}$$

as $n \to \infty$. $\square$

Chapter 6

CONCLUSIONS

In this dissertation, we have applied the fiducial generalized pivotal quantity and generalized fiducial recipe developed by Hannig (2006) and Hannig (2008) and solved four practical issues.

In Chapter 2, we have proposed interval estimation procedures for σ_α^2, σ_ε^2 and ρ in a two component mixed effects linear model using the fiducial approach. A simulation study was carried out to compare the proposed confidence interval for σ_α^2 with five other confidence intervals from the literature, the proposed confidence interval for σ_ε^2 with an exact confidence interval, and the proposed confidence interval for ρ with the method due to Burch and Iyer (1997). The results showed that the proposed fiducial intervals for σ_α^2 are satisfactory in terms of coverage probability. Although they are conservative for small values of the variance ratio $\eta = \sigma_\alpha^2/\sigma_\varepsilon^2$, they have the smallest average interval lengths among all confidence intervals. Three examples are given to illustrate the use of the proposed procedures. The results confirm that the fiducial intervals can be recommended for practical use over the methods previously discussed in the literature. We also proved that these fiducial intervals have asymptotically exact frequentist coverage probability.

Median lethal dose (LD_{50}) is a common measure of the acute toxicity of a compound in a species in quantal bioassay experiments. In this work, we applied the generalized fiducial recipe to propose a new method for constructing confidence intervals of LD_{50} for a logistic-response curve. The method uses the Gibbs sampling approach to empirically estimate the percentiles of the fiducial distribution for LD_{50}. The resulting intervals were compared with three other competing confidence interval procedures – Delta method, Fieller's method and Likelihood Ratio method. Our simulation results showed that fiducial intervals have satisfactory performance and are more stable than other confidence intervals in terms of coverage probability. The fiducial distributions also appear to give unbiased point estimates of LD_{50}. Williams's experimental configurations (Williams, 1986) were used to study the convergence properties of the Markov chains in Gibb's sampling.

Evaluation of the equivalence between two methods is often required in medicine and other areas to see if two methods sufficiently agree well. Lin (1989, 1992) proposed an index called concordance correlation coefficient (CCC) to quantify agreement between two methods of measurement. CCC has components of precision and accuracy and is widely used in method comparison studies due to its simplicity and good statistical properties. In chapter 4, we developed the Fiducial Generalized Confidence Intervals (FGCIs) for the concordance correlation coefficient and used it to conduct statistical tests. The statistical model for a repeated measurement design used by Quiroz (2005) and a generalization of this model were considered in this work. Simulation studies were conducted to compare the proposed method with the Z-transformation methods and modified random model methods. Our simulation results showed that the FGCIs based on the generalized fiducial distribution perform better than other procedures under the model without method and subject interaction. FGCI intervals based on the Fiducial Generalized Pivotal Quantities (FGPQ) have satisfactory performance in terms of coverage probability under the model with method and subject interaction.

In chapter 5 we constructed simultaneous confidence intervals for all pairwise ratios of means of more than two lognormal distributions based on a Fiducial Generalized Pivotal Quantity (FGPQ). We verified by means of a simulation study that these intervals perform satisfactorily in small samples. We also proved that the constructed confidence intervals have correct asymptotic coverage. The role of such intervals in bioequivalence studies was also discussed.

The asymptotic properties of the constructed fiducial generalized confidence intervals on LD_{50} and CCC need further investigation in the future work.

The fiducial approach was never accepted by mainstream statisticians. Our investigation in this thesis shows that the confidence intervals constructed using the generalized pivotal quantity and generalized fiducial recipe have satisfactory performance. Our investigations and those of Patterson (2006), Hannig et al. (2006) and Hannig (2008) suggest that it might be wise to reevaluate the role of fiducial inference in statistical inference.

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Appendix A

SIMULATION RESULTS FOR CONFIDENCE INTERVALS FOR σ_α^2 IN AN UNBALANCED ONE-WAY RANDOM EFFECTS MODEL

For a discussion of results see Section 2.4.

Table A.1: Empirical Coverage Probabilities of Nominally 95% Two-sided Confidence Intervals for σ_α^2

Design	Method	$(\sigma_\alpha^2, \sigma_\varepsilon^2)$							
		(0.1,10)	(0.5,10)	(1,10)	(0.5,2)	(1,1)	(2,0.5)	(5,0.2)	(10,0.1)
1	BG	0.949	0.947	0.949	0.945	0.926	0.907	0.896	0.895
	TH	0.937	0.936	0.941	0.945	0.947	0.950	0.951	0.950
	BE	0.985	0.984	0.981	0.979	0.959	0.952	0.951	0.950
	HK	0.950	0.949	0.951	0.954	0.956	0.958	0.960	0.958
	Ar	0.947	0.944	0.954	0.947	0.949	0.951	0.950	0.956
	FI	0.986	0.982	0.987	0.988	0.982	0.944	0.948	0.949
2	BG	0.949	0.947	0.946	0.938	0.917	0.905	0.898	0.898
	TH	0.937	0.938	0.943	0.948	0.948	0.950	0.952	0.950
	BE	0.986	0.982	0.978	0.971	0.954	0.951	0.952	0.950
	HK	0.951	0.951	0.954	0.957	0.957	0.958	0.960	0.957
	Ar	0.947	0.950	0.950	0.947	0.953	0.947	0.954	0.954
	FI	0.985	0.985	0.987	0.986	0.957	0.946	0.951	0.947
3	BG	0.948	0.952	0.949	0.940	0.937	0.934	0.931	0.928
	TH	0.931	0.940	0.941	0.943	0.951	0.953	0.950	0.948
	BE	0.991	0.983	0.976	0.966	0.955	0.953	0.950	0.948
	HK	0.949	0.949	0.954	0.959	0.950	0.958	0.954	0.950
	Ar	0.948	0.953	0.950	0.951	0.953	0.946	0.949	0.944
	FI	0.988	0.981	0.986	0.985	0.980	0.961	0.958	0.954
4	BG	0.952	0.949	0.940	0.938	0.926	0.921	0.922	0.922
	TH	0.938	0.943	0.945	0.947	0.952	0.951	0.956	0.954
	BE	0.991	0.981	0.971	0.962	0.954	0.951	0.956	0.954
	HK	0.950	0.960	0.958	0.958	0.958	0.958	0.958	0.957
	Ar	0.950	0.952	0.947	0.947	0.952	0.950	0.950	0.952
	FI	0.987	0.987	0.986	0.985	0.950	0.949	0.947	0.948
5	BG	0.951	0.949	0.943	0.941	0.936	0.932	0.929	0.935
	TH	0.931	0.945	0.948	0.953	0.949	0.950	0.952	0.952
	BE	0.990	0.982	0.975	0.965	0.951	0.950	0.952	0.952
	HK	0.955	0.953	0.958	0.958	0.957	0.959	0.960	0.958
	Ar	0.952	0.949	0.947	0.946	0.947	0.947	0.954	0.953
	FI	0.990	0.976	0.965	0.950	0.946	0.946	0.946	0.950
6	BG	0.947	0.949	0.948	0.949	0.948	0.943	0.944	0.938
	TH	0.944	0.949	0.951	0.955	0.960	0.953	0.953	0.947
	BE	0.977	0.976	0.971	0.969	0.964	0.953	0.953	0.947
	HK	0.947	0.958	0.961	0.974	0.971	0.972	0.974	0.973
	Ar	0.955	0.947	0.944	0.953	0.950	0.947	0.951	0.945
	FI	0.990	0.989	0.991	0.989	0.976	0.955	0.947	0.950
7	BG	0.950	0.951	0.950	0.954	0.948	0.952	0.948	0.948
	TH	0.947	0.953	0.954	0.955	0.952	0.954	0.951	0.950
	BE	0.975	0.969	0.965	0.960	0.952	0.954	0.951	0.950
	HK	0.954	0.955	0.961	0.962	0.963	0.963	0.966	0.962
	Ar	0.951	0.948	0.953	0.951	0.950	0.953	0.951	0.949
	FI	0.973	0.971	0.966	0.953	0.949	0.957	0.957	0.947

Table A.2: Average Lengths of Nominally 95% Two-sided Confidence Intervals for σ_α^2

Design	Method	$(\sigma_\alpha^2, \sigma_\varepsilon^2)$							
		(0.1,10)	(0.5,10)	(1,10)	(0.5,2)	(1,1)	(2,0.5)	(5,0.2)	(10,0.1)
1	BG	26.0	28.7	31.6	8.1	8.3	12.6	28.4	57.1
	TH	42.1	44.8	47.8	11.3	10.0	13.6	28.7	57.2
	BE	43.7	46.4	49.3	11.6	10.1	13.7	28.8	57.2
	HK	41.6	44.3	47.6	11.3	10.1	13.7	29.4	57.1
	Ar	41.5	44.0	47.4	11.2	9.9	13.6	29.1	56.3
	FI	31.0	32.9	34.5	8.6	7.9	11.0	25.2	48.5
2	BG	13.7	16.1	19.1	5.6	7.0	12.0	28.1	56.8
	TH	21.4	23.9	26.9	7.1	7.9	12.5	28.3	56.9
	BE	22.2	24.7	27.6	7.2	8.0	12.5	28.3	56.9
	HK	21.1	23.7	26.9	7.2	7.9	12.5	28.9	56.8
	Ar	21.2	23.5	26.6	7.1	7.8	12.4	28.8	56.0
	FI	16.0	20.1	20.5	5.5	5.6	10.6	24.8	49.0
3	BG	63.6	80.0	98.8	32.0	46.2	81.1	194.3	388.7
	TH	95.3	111.9	131.4	38.6	49.0	83.1	196.2	388.8
	BE	95.5	112.1	131.6	38.7	49.1	83.2	196.2	388.8
	HK	93.8	111.8	131.4	38.0	48.3	83.2	199.5	403.2
	Ar	93.5	111.9	130.1	37.9	47.8	82.2	196.5	398.8
	FI	73.5	87.1	99.5	29.1	35.8	62.4	149.6	296.4
4	BG	9.6	12.9	17.3	5.9	8.8	16.2	39.6	78.4
	TH	13.6	16.9	21.5	6.7	9.3	16.5	39.7	78.1
	BE	13.9	17.2	21.7	6.8	9.3	16.5	39.7	78.1
	HK	13.7	16.8	21.0	6.7	9.5	17.1	40.6	79.7
	Ar	13.8	17.1	21.2	6.6	9.1	16.7	39.9	77.9
	FI	10.2	12.8	15.5	5.0	7.2	12.7	32.0	62.9
5	BG	3.5	5.9	8.8	3.5	5.9	11.5	28.4	55.7
	TH	4.6	7.0	9.9	3.7	6.0	11.5	27.9	55.6
	BE	4.7	7.1	10.1	3.8	6.1	11.5	27.9	55.6
	HK	4.5	6.9	10.0	3.7	6.1	11.6	28.5	56.4
	Ar	4.6	6.9	10.1	3.7	6.0	11.5	28.3	57.2
	FI	3.2	5.1	7.4	2.7	4.7	8.8	21.7	43.7
6	BG	40.7	46.2	53.4	14.7	17.7	28.7	67.5	138.3
	TH	47.0	52.2	59.9	15.9	18.4	29.1	68.0	138.6
	BE	47.0	52.4	60.1	15.9	18.5	29.2	67.9	138.6
	HK	48.0	54.2	61.9	16.3	19.1	31.0	71.8	140.2
	Ar	45.3	50.6	58.6	16.4	18.1	29.2	68.9	135.5
	FI	39.1	43.4	47.9	12.9	14.5	23.0	54.8	106.3
7	BG	6.8	9.2	12.1	4.2	6.3	11.6	27.9	56.0
	TH	7.1	9.5	12.4	4.2	6.3	11.6	28.0	55.9
	BE	7.2	9.6	12.5	4.2	6.3	11.6	28.0	55.9
	HK	7.3	9.7	12.8	4.4	6.5	11.9	29.2	57.8
	Ar	7.1	9.4	12.3	4.2	6.4	11.5	28.4	57.0
	FI	6.1	8.2	10.8	3.7	5.5	10.2	24.9	49.8

Appendix B

SIMULATION RESULTS FOR CONFIDENCE INTERVALS FOR MEDIAN LETHAL DOSE (LD_{50})

For a discussion of results see Section 3.5.

Table B.1: Empirical Coverage Probabilities and Average Lengths of Nominally 95% Two-sided Confidence Intervals for LD_{50}

Design	Sample Size	Method	CP_1	CP_2	CL	Design	Sample Size	Method	CP_1	CP_2	CL
1	6	Delta	0.755	0.924	1.126	4	6	Delta	0.919	0.931	1.797
		Fieller	0.809	0.990	1.583			Fieller	0.953	0.966	2.351
		Likelihood	0.920	0.924	1.222			Likelihood	0.938	0.945	1.984
		Fiducial	0.957	0.960	1.337			Fiducial	0.949	0.950	2.077
	10	Delta	0.874	0.927	0.861		10	Delta	0.937	0.938	1.377
		Fieller	0.910	0.965	1.029			Fieller	0.954	0.955	1.572
		Likelihood	0.927	0.927	0.902			Likelihood	0.939	0.940	1.446
		Fiducial	0.959	0.958	0.953			Fiducial	0.941	0.941	1.477
	20	Delta	0.927	0.930	0.616		20	Delta	0.954	0.954	0.974
		Fieller	0.943	0.946	0.666			Fieller	0.963	0.963	1.034
		Likelihood	0.936	0.936	0.630			Likelihood	0.955	0.955	0.996
		Fiducial	0.944	0.944	0.641			Fiducial	0.957	0.957	1.003
2	6	Delta	0.938	0.937	4.028	5	6	Delta	0.915	0.922	1.878
		Fieller	0.850	0.976	8.679			Fieller	0.959	0.971	2.579
		Likelihood	0.853	0.948	5.842			Likelihood	0.932	0.934	2.041
		Fiducial	0.966	0.961	5.813			Fiducial	0.946	0.947	2.137
	10	Delta	0.953	0.953	2.008		10	Delta	0.943	0.943	1.425
		Fieller	0.947	0.961	2.916			Fieller	0.966	0.966	1.623
		Likelihood	0.934	0.947	2.555			Likelihood	0.948	0.948	1.481
		Fiducial	0.960	0.959	2.542			Fiducial	0.951	0.951	1.524
	20	Delta	0.962	0.962	1.101		20	Delta	0.953	0.953	0.989
		Fieller	0.951	0.951	1.244			Fieller	0.976	0.976	1.044
		Likelihood	0.947	0.947	1.206			Likelihood	0.960	0.960	1.004
		Fiducial	0.949	0.949	1.211			Fiducial	0.962	0.962	1.017
3	6	Delta	0.705	0.953	1.229	6	6	Delta	0.955	0.951	0.243
		Fieller	0.737	0.996	1.716			Fieller	0.941	0.951	0.343
		Likelihood	0.895	0.966	1.303			Likelihood	0.932	0.938	0.295
		Fiducial	0.972	0.974	1.446			Fiducial	0.943	0.942	0.294
	10	Delta	0.872	0.953	0.927		10	Delta	0.956	0.956	0.160
		Fieller	0.895	0.978	1.114			Fieller	0.951	0.951	0.182
		Likelihood	0.922	0.953	0.957			Likelihood	0.943	0.943	0.176
		Fiducial	0.962	0.958	1.047			Fiducial	0.946	0.946	0.177
	20	Delta	0.927	0.931	0.662		20	Delta	0.954	0.954	0.109
		Fieller	0.963	0.967	0.7174			Fieller	0.950	0.950	0.116
		Likelihood	0.951	0.954	0.672			Likelihood	0.948	0.948	0.114
		Fiducial	0.958	0.958	0.704			Fiducial	0.944	0.944	0.114

CP_1: The empirical coverage probabilities of confidence intervals, with inclusion of three special cases.

CP_2: The empirical coverage probabilities of confidence intervals, with exclusion of three special cases.

CL: The average lengths of confidence intervals, with exclusion of three special cases.

Appendix C

SIMULATION RESULTS FOR CONFIDENCE INTERVALS FOR CONCORDANCE CORRELATION COEFFICIENT

For a discussion of results see Section 4.2.4 and Section 4.3.4.

Table C.1: Empirical Coverage Probabilities and Average Lengths of Nominally 95% One-sided Confidence Intervals (Lower Bound) for CCC under the Model without Method and Subject Interaction (Model (4.2) in Section 4.2); $\mu_1 - \mu_2 = 0$, $\sigma^2_{\varepsilon_1} = 1$ and $\sigma^2_{\varepsilon_2} = 1$.

Parameter			Empirical Coverage					Average Confidence Interval Length				
ρ	n	m	ZT1	ZT2	MRM	FGCI1	FGCI2	ZT1	ZT2	MRM	FGCI1	FGCI2
0.99	5	2	0.917	0.952	0.992	0.978	0.988	0.049	0.059	0.094	0.069	0.086
		5	0.953	0.984	0.981	0.971	0.972	0.050	0.060	0.059	0.054	0.054
	15	2	0.915	0.925	0.988	0.973	0.974	0.021	0.022	0.032	0.025	0.027
		5	0.959	0.965	0.980	0.970	0.963	0.021	0.022	0.023	0.022	0.021
	30	2	0.928	0.932	0.986	0.970	0.969	0.017	0.017	0.022	0.018	0.019
		5	0.959	0.961	0.978	0.964	0.962	0.016	0.017	0.017	0.017	0.016
0.97	5	2	0.911	0.949	0.986	0.979	0.984	0.127	0.152	0.222	0.167	0.207
		5	0.954	0.981	0.973	0.968	0.966	0.122	0.146	0.141	0.129	0.130
	15	2	0.914	0.928	0.988	0.967	0.975	0.061	0.064	0.090	0.072	0.077
		5	0.962	0.970	0.979	0.969	0.965	0.061	0.063	0.067	0.062	0.062
	30	2	0.922	0.931	0.990	0.969	0.975	0.049	0.050	0.064	0.054	0.056
		5	0.956	0.963	0.979	0.965	0.963	0.048	0.049	0.052	0.049	0.049
0.95	5	2	0.923	0.955	0.992	0.983	0.991	0.199	0.235	0.325	0.249	0.306
		5	0.956	0.985	0.984	0.972	0.971	0.188	0.222	0.212	0.196	0.197
	15	2	0.932	0.943	0.990	0.976	0.982	0.103	0.106	0.147	0.117	0.127
		5	0.953	0.966	0.972	0.962	0.962	0.100	0.103	0.109	0.102	0.101
	30	2	0.920	0.927	0.988	0.970	0.974	0.082	0.083	0.105	0.089	0.093
		5	0.958	0.966	0.980	0.965	0.966	0.079	0.080	0.084	0.080	0.080
0.90	5	2	0.914	0.950	0.988	0.977	0.986	0.341	0.392	0.501	0.393	0.474
		5	0.955	0.981	0.978	0.972	0.969	0.319	0.370	0.347	0.323	0.326
	15	5	0.912	0.929	0.985	0.964	0.973	0.191	0.198	0.261	0.214	0.230
		5	0.956	0.964	0.974	0.959	0.959	0.187	0.194	0.202	0.190	0.189
	30	2	0.928	0.933	0.991	0.973	0.977	0.157	0.159	0.197	0.170	0.176
		5	0.963	0.966	0.977	0.967	0.964	0.154	0.156	0.163	0.157	0.156
0.80	5	2	0.927	0.956	0.992	0.976	0.988	0.540	0.603	0.713	0.575	0.676
		5	0.950	0.982	0.971	0.963	0.962	0.498	0.564	0.520	0.491	0.497
	15	2	0.926	0.940	0.988	0.972	0.974	0.356	0.367	0.450	0.381	0.409
		5	0.952	0.966	0.976	0.961	0.957	0.340	0.350	0.358	0.340	0.339
	30	2	0.923	0.928	0.990	0.967	0.969	0.299	0.302	0.360	0.315	0.328
		5	0.958	0.963	0.972	0.961	0.960	0.292	0.296	0.305	0.294	0.293
0.70	5	2	0.930	0.960	0.992	0.977	0.990	0.674	0.738	0.840	0.692	0.794
		5	0.959	0.985	0.979	0.971	0.972	0.641	0.708	0.653	0.620	0.629
	15	2	0.933	0.947	0.992	0.976	0.976	0.496	0.509	0.594	0.516	0.551
		5	0.958	0.971	0.977	0.964	0.959	0.476	0.488	0.491	0.471	0.471
	30	2	0.925	0.932	0.987	0.963	0.968	0.431	0.435	0.499	0.444	0.463
		5	0.961	0.965	0.976	0.963	0.960	0.414	0.418	0.427	0.414	0.413
0.50	5	2	0.929	0.963	0.994	0.968	0.990	0.851	0.896	1.003	0.834	0.921
		5	0.967	0.990	0.978	0.965	0.967	0.827	0.882	0.819	0.788	0.801
	15	2	0.935	0.947	0.988	0.968	0.978	0.732	0.747	0.811	0.726	0.772
		5	0.966	0.973	0.973	0.958	0.962	0.691	0.704	0.696	0.676	0.678
	30	2	0.931	0.940	0.989	0.964	0.973	0.668	0.674	0.728	0.669	0.693
		5	0.955	0.959	0.968	0.954	0.951	0.631	0.635	0.638	0.625	0.625

Table C.2: Empirical Coverage Probabilities and Average Lengths of Nominally 95% One-sided Confidence Intervals (Lower Bound) for CCC under the Model without Method and Subject Interaction (Model (4.2) in Section 4.2); $\mu_1 - \mu_2 = 2$, $\sigma^2_{\varepsilon_1} = 1$ and $\sigma^2_{\varepsilon_2} = 1$.

Parameter			Empirical Coverage					Average Confidence Interval Length				
ρ	n	m	ZT1	ZT2	MRM	FGCI1	FGCI2	ZT1	ZT2	MRM	FGCI1	FGCI2
0.99	5	2	0.955	0.979	0.985	0.969	0.976	0.131	0.155	0.163	0.136	0.150
		5	0.959	0.983	0.964	0.957	0.951	0.122	0.144	0.121	0.117	0.115
	15	2	0.948	0.962	0.978	0.955	0.958	0.063	0.065	0.070	0.064	0.064
		5	0.966	0.971	0.966	0.960	0.955	0.060	0.062	0.059	0.059	0.058
	30	2	0.949	0.951	0.968	0.952	0.949	0.049	0.050	0.053	0.050	0.050
		5	0.964	0.967	0.965	0.960	0.954	0.048	0.049	0.048	0.048	0.047
0.97	5	2	0.949	0.978	0.985	0.970	0.977	0.294	0.338	0.343	0.295	0.321
		5	0.962	0.987	0.964	0.960	0.957	0.283	0.328	0.276	0.268	0.266
	15	2	0.952	0.959	0.974	0.957	0.956	0.171	0.177	0.187	0.171	0.173
		5	0.962	0.970	0.961	0.957	0.954	0.162	0.167	0.160	0.158	0.156
	30	2	0.957	0.962	0.982	0.959	0.959	0.136	0.138	0.145	0.136	0.136
		5	0.964	0.967	0.964	0.962	0.956	0.134	0.136	0.134	0.133	0.131
0.95	5	2	0.959	0.981	0.983	0.968	0.977	0.407	0.460	0.459	0.399	0.434
		5	0.961	0.983	0.961	0.954	0.952	0.391	0.446	0.377	0.367	0.365
	15	2	0.955	0.963	0.979	0.959	0.958	0.259	0.267	0.279	0.257	0.260
		5	0.966	0.971	0.963	0.959	0.955	0.250	0.257	0.246	0.242	0.239
	30	2	0.956	0.962	0.981	0.962	0.960	0.213	0.215	0.225	0.213	0.213
		5	0.956	0.961	0.956	0.949	0.945	0.206	0.209	0.205	0.203	0.201
0.90	5	2	0.954	0.973	0.980	0.959	0.971	0.590	0.652	0.638	0.565	0.611
		5	0.963	0.987	0.961	0.956	0.954	0.567	0.631	0.541	0.529	0.527
	15	2	0.958	0.973	0.984	0.961	0.964	0.420	0.430	0.443	0.412	0.418
		5	0.966	0.973	0.961	0.957	0.952	0.410	0.421	0.401	0.396	0.393
	30	2	0.958	0.963	0.980	0.958	0.957	0.364	0.368	0.380	0.361	0.362
		5	0.958	0.961	0.955	0.952	0.944	0.356	0.360	0.353	0.350	0.347
0.80	5	2	0.964	0.981	0.985	0.965	0.978	0.781	0.837	0.816	0.737	0.788
		5	0.973	0.989	0.965	0.959	0.956	0.757	0.818	0.717	0.704	0.704
	15	2	0.959	0.969	0.981	0.957	0.960	0.629	0.641	0.648	0.611	0.621
		5	0.974	0.983	0.968	0.962	0.960	0.615	0.626	0.598	0.592	0.590
	30	2	0.967	0.971	0.981	0.963	0.964	0.570	0.574	0.585	0.561	0.564
		5	0.967	0.973	0.964	0.956	0.949	0.554	0.558	0.547	0.544	0.541
0.70	5	2	0.966	0.988	0.988	0.960	0.981	0.876	0.920	0.906	0.826	0.875
		5	0.979	0.992	0.963	0.954	0.952	0.852	0.903	0.807	0.794	0.797
	15	2	0.967	0.972	0.979	0.958	0.961	0.757	0.769	0.770	0.731	0.745
		5	0.974	0.983	0.964	0.959	0.955	0.736	0.747	0.716	0.710	0.708
	30	2	0.960	0.963	0.972	0.951	0.951	0.701	0.705	0.713	0.687	0.693
		5	0.968	0.972	0.958	0.952	0.947	0.684	0.687	0.674	0.670	0.668
0.50	5	2	0.977	0.994	0.989	0.951	0.982	0.962	0.982	1.000	0.916	0.956
		5	0.984	0.996	0.967	0.950	0.954	0.952	0.979	0.915	0.902	0.907
	15	2	0.978	0.986	0.986	0.958	0.971	0.906	0.915	0.911	0.876	0.893
		5	0.979	0.986	0.957	0.947	0.946	0.879	0.887	0.859	0.853	0.853
	30	2	0.968	0.971	0.979	0.951	0.957	0.862	0.866	0.869	0.846	0.854
		5	0.970	0.974	0.957	0.948	0.944	0.842	0.845	0.832	0.828	0.828

Table C.3: Empirical Coverage Probabilities and Average Lengths of Nominally 95% One-sided Confidence Intervals (Lower Bound) for CCC under the Model without Method and Subject Interaction (Model (4.2) in Section 4.2); $\mu_1 - \mu_2 = 0$, $\sigma^2_{\varepsilon_1} = 1.25$ and $\sigma^2_{\varepsilon_2} = 1$.

Parameter			Empirical Coverage					Average Confidence Interval Length				
ρ	n	m	ZT1	ZT2	MRM	FGCI1	FGCI2	ZT1	ZT2	MRM	FGCI1	FGCI2
0.99	5	2	0.924	0.951	0.989	0.984	0.985	0.049	0.060	0.095	0.069	0.087
		5	0.947	0.976	0.973	0.965	0.965	0.049	0.059	0.058	0.053	0.053
	15	2	0.928	0.941	0.990	0.975	0.980	0.021	0.022	0.031	0.024	0.027
		5	0.956	0.966	0.976	0.963	0.960	0.021	0.022	0.023	0.021	0.021
	30	2	0.922	0.927	0.990	0.970	0.972	0.017	0.017	0.022	0.018	0.019
		5	0.956	0.958	0.973	0.964	0.960	0.016	0.017	0.018	0.017	0.017
0.97	5	2	0.925	0.956	0.989	0.979	0.989	0.133	0.157	0.228	0.168	0.212
		5	0.951	0.979	0.978	0.967	0.966	0.126	0.150	0.145	0.133	0.134
	15	2	0.926	0.938	0.988	0.974	0.976	0.062	0.065	0.091	0.072	0.078
		5	0.951	0.959	0.971	0.963	0.956	0.061	0.063	0.068	0.063	0.062
	30	2	0.921	0.928	0.986	0.965	0.970	0.049	0.050	0.064	0.054	0.056
		5	0.952	0.959	0.971	0.963	0.958	0.048	0.049	0.051	0.049	0.048
0.95	5	2	0.919	0.955	0.988	0.978	0.985	0.199	0.234	0.324	0.248	0.304
		5	0.958	0.982	0.978	0.970	0.971	0.192	0.227	0.216	0.199	0.201
	15	2	0.935	0.949	0.990	0.976	0.980	0.100	0.104	0.143	0.115	0.124
		5	0.959	0.967	0.977	0.967	0.965	0.099	0.103	0.109	0.101	0.101
	30	2	0.914	0.921	0.988	0.969	0.967	0.080	0.081	0.103	0.087	0.091
		5	0.956	0.963	0.974	0.962	0.961	0.079	0.080	0.084	0.080	0.080
0.90	5	2	0.917	0.951	0.990	0.979	0.985	0.340	0.391	0.499	0.393	0.473
		5	0.950	0.976	0.973	0.967	0.965	0.310	0.359	0.337	0.314	0.317
	15	2	0.925	0.940	0.989	0.971	0.976	0.194	0.200	0.263	0.215	0.233
		5	0.955	0.967	0.975	0.965	0.960	0.189	0.195	0.204	0.191	0.190
	30	2	0.927	0.937	0.992	0.972	0.972	0.158	0.160	0.199	0.171	0.178
		5	0.951	0.958	0.976	0.962	0.957	0.154	0.156	0.163	0.156	0.155
0.80	5	2	0.916	0.950	0.990	0.978	0.989	0.539	0.602	0.712	0.577	0.675
		5	0.953	0.983	0.977	0.968	0.969	0.509	0.572	0.530	0.499	0.507
	15	2	0.924	0.937	0.988	0.972	0.975	0.358	0.369	0.453	0.384	0.412
		5	0.960	0.970	0.977	0.966	0.963	0.346	0.356	0.364	0.345	0.345
	30	2	0.919	0.926	0.989	0.967	0.972	0.299	0.302	0.359	0.314	0.328
		5	0.959	0.966	0.975	0.967	0.963	0.293	0.296	0.306	0.294	0.293
0.70	5	2	0.925	0.958	0.993	0.979	0.988	0.677	0.738	0.844	0.692	0.793
		5	0.962	0.987	0.979	0.970	0.972	0.645	0.713	0.656	0.622	0.633
	15	2	0.943	0.951	0.993	0.978	0.982	0.502	0.516	0.601	0.520	0.558
		5	0.952	0.960	0.969	0.957	0.953	0.471	0.483	0.487	0.466	0.467
	30	2	0.929	0.937	0.985	0.966	0.968	0.431	0.435	0.499	0.444	0.463
		5	0.962	0.966	0.978	0.963	0.963	0.417	0.420	0.429	0.416	0.415
0.50	5	2	0.928	0.960	0.986	0.970	0.981	0.847	0.892	1.002	0.833	0.917
		5	0.969	0.988	0.975	0.968	0.968	0.828	0.882	0.820	0.786	0.801
	15	2	0.938	0.953	0.991	0.969	0.979	0.741	0.756	0.819	0.732	0.780
		5	0.966	0.973	0.976	0.964	0.963	0.694	0.707	0.699	0.678	0.681
	30	2	0.941	0.948	0.987	0.967	0.975	0.666	0.672	0.725	0.666	0.691
		5	0.959	0.965	0.970	0.958	0.957	0.634	0.638	0.641	0.627	0.628

Table C.4: Empirical Coverage Probabilities and Average Lengths of Nominally 95% One-sided Confidence Intervals (Lower Bound) for CCC under the Model without Method and Subject Interaction (Model (4.2) in Section 4.2); $\mu_1 - \mu_2 = 2$, $\sigma^2_{\varepsilon_1} = 1.25$ and $\sigma^2_{\varepsilon_2} = 1$.

Parameter			Empirical Coverage					Average Confidence Interval Length				
ρ	n	m	ZT1	ZT2	MRM	FGCI1	FGCI2	ZT1	ZT2	MRM	FGCI1	FGCI2
0.99	5	2	0.951	0.969	0.982	0.966	0.973	0.123	0.145	0.155	0.128	0.142
		5	0.958	0.982	0.966	0.960	0.954	0.112	0.134	0.113	0.109	0.107
	15	2	0.954	0.960	0.983	0.963	0.963	0.058	0.060	0.066	0.059	0.060
		5	0.963	0.970	0.965	0.958	0.955	0.057	0.059	0.057	0.056	0.055
	30	2	0.955	0.959	0.979	0.960	0.959	0.046	0.046	0.050	0.046	0.046
		5	0.958	0.964	0.961	0.954	0.949	0.044	0.045	0.045	0.044	0.043
0.97	5	2	0.946	0.973	0.980	0.964	0.975	0.281	0.323	0.336	0.283	0.313
		5	0.964	0.983	0.966	0.960	0.959	0.268	0.312	0.264	0.255	0.253
	15	2	0.950	0.960	0.976	0.955	0.958	0.157	0.162	0.174	0.158	0.160
		5	0.961	0.972	0.962	0.957	0.954	0.152	0.157	0.151	0.149	0.147
	30	2	0.950	0.954	0.976	0.955	0.955	0.127	0.129	0.137	0.128	0.128
		5	0.956	0.962	0.959	0.953	0.945	0.124	0.126	0.124	0.123	0.122
0.95	5	2	0.956	0.982	0.988	0.970	0.981	0.395	0.448	0.453	0.390	0.427
		5	0.956	0.980	0.963	0.954	0.952	0.379	0.432	0.369	0.357	0.355
	15	2	0.957	0.965	0.975	0.961	0.962	0.244	0.252	0.267	0.244	0.247
		5	0.966	0.974	0.967	0.960	0.955	0.235	0.242	0.233	0.228	0.226
	30	2	0.949	0.953	0.972	0.954	0.953	0.199	0.201	0.212	0.199	0.200
		5	0.966	0.970	0.966	0.964	0.959	0.196	0.198	0.195	0.193	0.191
0.90	5	2	0.944	0.963	0.981	0.956	0.970	0.562	0.623	0.619	0.544	0.590
		5	0.965	0.987	0.966	0.953	0.951	0.549	0.612	0.527	0.512	0.512
	15	2	0.963	0.970	0.982	0.963	0.968	0.406	0.416	0.433	0.399	0.406
		5	0.971	0.978	0.969	0.963	0.959	0.394	0.404	0.387	0.381	0.378
	30	2	0.953	0.958	0.978	0.951	0.958	0.347	0.350	0.365	0.344	0.346
		5	0.964	0.970	0.963	0.955	0.953	0.338	0.342	0.336	0.333	0.330
0.80	5	2	0.954	0.981	0.984	0.960	0.976	0.766	0.823	0.807	0.722	0.779
		5	0.966	0.989	0.964	0.954	0.954	0.742	0.803	0.705	0.689	0.691
	15	2	0.961	0.972	0.983	0.956	0.965	0.610	0.622	0.634	0.592	0.605
		5	0.967	0.973	0.962	0.953	0.948	0.593	0.605	0.579	0.571	0.569
	30	2	0.963	0.967	0.982	0.962	0.960	0.551	0.555	0.568	0.542	0.547
		5	0.973	0.976	0.969	0.965	0.962	0.541	0.545	0.535	0.530	0.528
0.70	5	2	0.969	0.989	0.990	0.965	0.982	0.865	0.911	0.899	0.814	0.868
		5	0.970	0.991	0.960	0.955	0.953	0.845	0.897	0.803	0.787	0.792
	15	2	0.964	0.973	0.977	0.959	0.963	0.743	0.755	0.760	0.717	0.734
		5	0.974	0.980	0.965	0.959	0.957	0.722	0.733	0.704	0.696	0.695
	30	2	0.967	0.970	0.979	0.958	0.963	0.685	0.689	0.700	0.672	0.678
		5	0.969	0.972	0.960	0.956	0.951	0.670	0.673	0.661	0.656	0.654
0.50	5	2	0.965	0.986	0.982	0.947	0.970	0.955	0.977	0.997	0.908	0.953
		5	0.981	0.995	0.961	0.946	0.951	0.943	0.973	0.905	0.890	0.896
	15	2	0.972	0.978	0.982	0.955	0.965	0.897	0.906	0.905	0.865	0.886
		5	0.982	0.988	0.962	0.953	0.951	0.872	0.880	0.852	0.845	0.846
	30	2	0.969	0.973	0.981	0.949	0.960	0.851	0.854	0.859	0.833	0.842
		5	0.982	0.984	0.965	0.958	0.950	0.834	0.837	0.824	0.819	0.819

Table C.5: Empirical Coverage Probabilities and Average Lengths of Nominally 95% One-sided Confidence Intervals (Lower Bound) for CCC under the Model with Method and Subject Interaction (Model (4.26) in Section 4.3); $\sigma^2_{\varepsilon_2} = 1$.

Parameter				Empirical Coverage					Average Confidence Interval Length				
ρ	$\sigma^2_{\varepsilon_1}$	n	m	ZT1	ZT2	MRM	FGCI1	FGCI2	ZT1	ZT2	MRM	FGCI1	FGCI2
0.99	0.1	5	2	0.962	0.985	0.978	0.967	0.974	0.192	0.225	0.207	0.188	0.198
			5	0.964	0.988	0.962	0.959	0.954	0.187	0.220	0.178	0.177	0.174
		15	2	0.953	0.958	0.960	0.949	0.950	0.102	0.105	0.105	0.100	0.100
			5	0.967	0.974	0.956	0.956	0.950	0.100	0.103	0.097	0.096	0.095
		30	2	0.960	0.963	0.966	0.958	0.956	0.081	0.082	0.083	0.080	0.080
			5	0.963	0.967	0.957	0.959	0.950	0.080	0.081	0.078	0.078	0.077
0.99	1.0	5	2	0.945	0.972	0.964	0.948	0.954	0.187	0.219	0.202	0.179	0.193
			5	0.965	0.982	0.960	0.958	0.955	0.188	0.221	0.179	0.175	0.174
		15	2	0.962	0.969	0.967	0.962	0.961	0.102	0.106	0.106	0.100	0.101
			5	0.962	0.971	0.953	0.954	0.948	0.098	0.102	0.095	0.095	0.094
		30	2	0.959	0.964	0.966	0.958	0.955	0.081	0.082	0.083	0.081	0.080
			5	0.960	0.963	0.956	0.955	0.952	0.079	0.080	0.078	0.078	0.077
0.99	5.0	5	2	0.954	0.975	0.965	0.954	0.960	0.192	0.225	0.207	0.181	0.198
			5	0.967	0.984	0.962	0.960	0.959	0.192	0.226	0.182	0.179	0.178
		15	2	0.960	0.969	0.970	0.959	0.959	0.102	0.105	0.105	0.099	0.101
			5	0.965	0.974	0.953	0.954	0.950	0.099	0.103	0.096	0.099	0.095
		30	2	0.958	0.961	0.964	0.953	0.955	0.082	0.083	0.083	0.081	0.081
			5	0.965	0.969	0.959	0.961	0.954	0.080	0.081	0.079	0.079	0.078
0.99	10.0	5	2	0.955	0.979	0.968	0.953	0.962	0.194	0.226	0.209	0.183	0.200
			5	0.961	0.985	0.958	0.957	0.954	0.186	0.219	0.177	0.174	0.173
		15	2	0.963	0.970	0.969	0.962	0.959	0.102	0.105	0.105	0.099	0.101
			5	0.953	0.964	0.945	0.944	0.940	0.099	0.103	0.096	0.096	0.095
		30	2	0.950	0.956	0.959	0.954	0.946	0.081	0.082	0.083	0.080	0.080
			5	0.961	0.967	0.952	0.952	0.948	0.081	0.082	0.079	0.079	0.078
0.97	0.1	5	2	0.936	0.965	0.990	0.975	0.985	0.199	0.231	0.287	0.222	0.256
			5	0.955	0.982	0.976	0.962	0.959	0.192	0.225	0.205	0.190	0.188
		15	2	0.941	0.949	0.989	0.965	0.961	0.104	0.108	0.132	0.110	0.114
			5	0.959	0.964	0.969	0.957	0.954	0.100	0.103	0.104	0.099	0.098
		30	2	0.953	0.956	0.990	0.969	0.971	0.084	0.085	0.098	0.087	0.088
			5	0.956	0.962	0.968	0.954	0.954	0.079	0.080	0.082	0.079	0.078
0.97	1.0	5	2	0.928	0.953	0.982	0.967	0.975	0.201	0.234	0.288	0.212	0.261
			5	0.958	0.980	0.974	0.965	0.961	0.191	0.225	0.206	0.186	0.190
		15	2	0.933	0.946	0.986	0.963	0.966	0.105	0.109	0.133	0.109	0.118
			5	0.964	0.971	0.974	0.964	0.961	0.102	0.105	0.106	0.101	0.100
		30	2	0.933	0.939	0.982	0.959	0.960	0.084	0.085	0.099	0.086	0.090
			5	0.954	0.957	0.969	0.956	0.951	0.081	0.082	0.084	0.081	0.080
0.97	5.0	5	2	0.925	0.950	0.980	0.960	0.967	0.204	0.237	0.289	0.208	0.264
			5	0.949	0.971	0.966	0.953	0.954	0.184	0.217	0.198	0.179	0.183
		15	2	0.927	0.936	0.981	0.956	0.964	0.106	0.110	0.134	0.109	0.119
			5	0.961	0.969	0.974	0.961	0.958	0.100	0.104	0.105	0.099	0.099
		30	2	0.926	0.932	0.980	0.951	0.954	0.082	0.083	0.096	0.084	0.088
			5	0.958	0.963	0.969	0.960	0.958	0.080	0.081	0.083	0.080	0.080
0.97	10.0	5	2	0.910	0.945	0.978	0.962	0.969	0.203	0.235	0.288	0.207	0.263
			5	0.960	0.979	0.974	0.963	0.964	0.192	0.225	0.206	0.186	0.191
		15	2	0.923	0.935	0.979	0.961	0.961	0.107	0.110	0.134	0.110	0.120
			5	0.951	0.962	0.967	0.952	0.951	0.100	0.104	0.105	0.099	0.099
		30	2	0.930	0.937	0.975	0.951	0.957	0.083	0.084	0.097	0.084	0.089
			5	0.953	0.957	0.964	0.957	0.951	0.081	0.082	0.083	0.080	0.080

Table C.6: Empirical Coverage Probabilities and Average Lengths of Nominally 95% One-sided Confidence Intervals (Lower Bound) for CCC under the Model with Method and Subject Interaction (Model (4.26) in Section 4.3); $\sigma^2_{\varepsilon_2} = 2$.

Parameter				Empirical Coverage					Average Confidence Interval Length				
ρ	$\sigma^2_{\varepsilon_1}$	n	m	ZT1	ZT2	MRM	FGCI1	FGCI2	ZT1	ZT2	MRM	FGCI1	FGCI2
0.99	0.1	5	2	0.956	0.980	0.972	0.958	0.965	0.196	0.229	0.211	0.190	0.203
			5	0.967	0.990	0.965	0.962	0.960	0.187	0.220	0.178	0.176	0.174
		15	2	0.963	0.972	0.971	0.961	0.960	0.101	0.105	0.105	0.099	0.100
			5	0.966	0.973	0.960	0.956	0.954	0.101	0.104	0.098	0.098	0.096
		30	2	0.955	0.962	0.967	0.956	0.951	0.081	0.082	0.082	0.080	0.080
			5	0.961	0.965	0.954	0.957	0.950	0.080	0.081	0.079	0.079	0.078
0.99	1.0	5	2	0.959	0.981	0.974	0.963	0.966	0.199	0.232	0.214	0.195	0.204
			5	0.965	0.989	0.961	0.957	0.953	0.184	0.217	0.175	0.174	0.171
		15	2	0.960	0.967	0.967	0.958	0.959	0.102	0.106	0.106	0.100	0.100
			5	0.968	0.976	0.960	0.959	0.954	0.101	0.105	0.098	0.098	0.096
		30	2	0.960	0.961	0.964	0.959	0.954	0.082	0.083	0.084	0.081	0.081
			5	0.966	0.969	0.961	0.960	0.956	0.080	0.081	0.079	0.079	0.078
0.99	5.0	5	2	0.960	0.982	0.977	0.965	0.969	0.193	0.225	0.207	0.187	0.198
			5	0.964	0.985	0.956	0.954	0.950	0.188	0.221	0.178	0.176	0.174
		15	2	0.957	0.965	0.969	0.960	0.954	0.101	0.105	0.105	0.099	0.100
			5	0.964	0.972	0.960	0.958	0.954	0.100	0.103	0.096	0.096	0.095
		30	2	0.963	0.969	0.974	0.965	0.958	0.082	0.083	0.084	0.081	0.081
			5	0.972	0.975	0.969	0.967	0.964	0.081	0.082	0.079	0.079	0.078
0.99	10.0	5	2	0.958	0.982	0.975	0.963	0.967	0.202	0.235	0.215	0.193	0.206
			5	0.957	0.985	0.951	0.953	0.947	0.190	0.223	0.180	0.178	0.176
		15	2	0.958	0.964	0.966	0.953	0.953	0.103	0.107	0.106	0.101	0.101
			5	0.968	0.975	0.957	0.957	0.953	0.100	0.104	0.097	0.097	0.095
		30	2	0.964	0.968	0.969	0.962	0.958	0.081	0.082	0.083	0.080	0.080
			5	0.961	0.966	0.955	0.954	0.948	0.079	0.081	0.078	0.078	0.077
0.97	0.1	5	2	0.920	0.948	0.979	0.970	0.966	0.203	0.236	0.288	0.223	0.263
			5	0.954	0.977	0.971	0.962	0.960	0.185	0.218	0.199	0.184	0.184
		15	2	0.938	0.950	0.982	0.963	0.964	0.106	0.109	0.134	0.110	0.119
			5	0.954	0.964	0.967	0.958	0.954	0.101	0.104	0.105	0.100	0.100
		30	2	0.927	0.934	0.980	0.950	0.955	0.082	0.083	0.096	0.085	0.088
			5	0.960	0.962	0.967	0.961	0.958	0.081	0.082	0.084	0.081	0.080
0.97	1.0	5	2	0.933	0.961	0.992	0.974	0.984	0.204	0.237	0.293	0.227	0.262
			5	0.957	0.981	0.976	0.965	0.963	0.190	0.224	0.204	0.189	0.188
		15	2	0.934	0.944	0.982	0.964	0.962	0.102	0.106	0.129	0.108	0.112
			5	0.955	0.966	0.971	0.958	0.953	0.102	0.105	0.106	0.101	0.100
		30	2	0.941	0.948	0.986	0.962	0.961	0.082	0.083	0.096	0.085	0.086
			5	0.955	0.960	0.969	0.957	0.950	0.079	0.080	0.082	0.079	0.078
0.97	5.0	5	2	0.933	0.959	0.988	0.975	0.981	0.205	0.238	0.293	0.223	0.263
			5	0.962	0.984	0.983	0.969	0.965	0.196	0.230	0.209	0.192	0.193
		15	2	0.935	0.944	0.986	0.954	0.959	0.104	0.108	0.132	0.109	0.115
			5	0.958	0.965	0.971	0.959	0.955	0.099	0.103	0.104	0.098	0.098
		30	2	0.938	0.941	0.988	0.960	0.957	0.083	0.084	0.097	0.085	0.087
			5	0.961	0.963	0.971	0.959	0.956	0.080	0.081	0.083	0.080	0.079
0.97	10.0	5	2	0.913	0.944	0.977	0.958	0.969	0.204	0.237	0.293	0.218	0.264
			5	0.958	0.978	0.974	0.964	0.964	0.195	0.229	0.209	0.190	0.193
		15	2	0.932	0.942	0.981	0.952	0.960	0.104	0.107	0.131	0.108	0.115
			5	0.960	0.969	0.971	0.963	0.957	0.101	0.105	0.106	0.100	0.100
		30	2	0.945	0.947	0.982	0.963	0.962	0.082	0.083	0.096	0.084	0.087
			5	0.957	0.964	0.972	0.960	0.956	0.081	0.082	0.083	0.080	0.080

Table C.7: Empirical Coverage Probabilities and Average Lengths of Nominally 95% One-sided Confidence Intervals (Lower Bound) for CCC under the Model with Method and Subject Interaction (Model (4.26) in Section 4.3); $\mu_1 - \mu_2 = 0$ and $\sigma_2^2 = 20$.

Parameter					CP		CL		Parameter					CP		CL	
ρ	$\sigma_{\varepsilon_1}^2$	σ_1^2	n	m	ZT	FGCI	ZT	FGCI	ρ	$\sigma_{\varepsilon_1}^2$	σ_1^2	n	m	ZT	FGCI	ZT	FGCI
0.95	1.0	20.0	5	2	0.960	0.997	0.237	0.392	0.80	1.0	20.0	5	2	0.925	0.991	0.651	0.805
				5	0.977	0.990	0.223	0.277					5	0.918	0.984	0.643	0.786
			15	2	0.954	0.981	0.112	0.132				15	2	0.942	0.975	0.421	0.484
				5	0.973	0.978	0.105	0.108					5	0.948	0.978	0.412	0.469
			30	2	0.957	0.979	0.087	0.094				30	2	0.957	0.977	0.339	0.367
				5	0.965	0.969	0.082	0.083					5	0.946	0.970	0.331	0.355
0.95	1.0	25.0	5	2	0.945	0.992	0.245	0.405	0.80	1.0	25.0	5	2	0.908	0.983	0.664	0.801
				5	0.963	0.990	0.234	0.318					5	0.927	0.985	0.643	0.794
			15	2	0.950	0.982	0.119	0.140				15	2	0.947	0.977	0.422	0.4826
				5	0.964	0.979	0.110	0.118					5	0.948	0.981	0.416	0.472
			30	2	0.951	0.977	0.092	0.099				30	2	0.944	0.974	0.342	0.369
				5	0.963	0.971	0.088	0.090					5	0.949	0.971	0.337	0.361
0.95	1.25	20.0	5	2	0.957	0.996	0.238	0.381	0.80	1.25	20.0	5	2	0.928	0.991	0.651	0.805
				5	0.982	0.986	0.227	0.250					5	0.929	0.987	0.636	0.781
			15	2	0.959	0.988	0.111	0.129				15	2	0.951	0.980	0.422	0.484
				5	0.974	0.973	0.106	0.106					5	0.947	0.976	0.408	0.464
			30	2	0.954	0.972	0.085	0.091				30	2	0.950	0.974	0.342	0.369
				5	0.969	0.968	0.082	0.081					5	0.957	0.974	0.331	0.355
0.95	1.25	25.0	5	2	0.950	0.993	0.235	0.385	0.80	1.25	25.0	5	2	0.913	0.986	0.641	0.798
				5	0.967	0.986	0.224	0.279					5	0.926	0.985	0.643	0.785
			15	2	0.959	0.982	0.119	0.139				15	2	0.948	0.980	0.424	0.485
				5	0.970	0.978	0.109	0.114					5	0.932	0.964	0.408	0.463
			30	2	0.961	0.981	0.093	0.100				30	2	0.941	0.965	0.341	0.368
				5	0.968	0.975	0.088	0.089					5	0.946	0.972	0.337	0.361
0.90	1.0	20.0	5	2	0.948	0.991	0.407	0.620	0.70	1.0	20.0	5	2	0.916	0.978	0.835	0.883
				5	0.955	0.990	0.384	0.563					5	0.919	0.987	0.838	0.885
			15	2	0.945	0.984	0.224	0.267				15	2	0.941	0.975	0.587	0.647
				5	0.957	0.983	0.214	0.247					5	0.955	0.984	0.581	0.638
			30	2	0.942	0.974	0.172	0.189				30	2	0.937	0.965	0.486	0.517
				5	0.963	0.980	0.169	0.181					5	0.936	0.967	0.480	0.509
0.90	1.0	25.0	5	2	0.928	0.994	0.408	0.615	0.70	1.0	25.0	5	2	0.908	0.985	0.840	0.885
				5	0.940	0.986	0.393	0.571					5	0.917	0.983	0.830	0.878
			15	2	0.951	0.984	0.226	0.270				15	2	0.935	0.981	0.591	0.648
				5	0.950	0.975	0.219	0.252					5	0.940	0.974	0.580	0.636
			30	2	0.945	0.972	0.180	0.197				30	2	0.942	0.965	0.490	0.520
				5	0.952	0.976	0.174	0.187					5	0.943	0.970	0.482	0.510
0.90	1.25	20.0	5	2	0.934	0.992	0.393	0.599	0.70	1.25	20.0	5	2	0.906	0.985	0.837	0.877
				5	0.957	0.990	0.380	0.552					5	0.926	0.987	0.816	0.878
			15	2	0.953	0.982	0.221	0.264				15	2	0.941	0.976	0.589	0.647
				5	0.951	0.973	0.210	0.240					5	0.937	0.968	0.571	0.628
			30	2	0.946	0.971	0.173	0.189				30	2	0.947	0.973	0.487	0.518
				5	0.956	0.971	0.166	0.177					5	0.951	0.973	0.485	0.514
0.90	1.25	25.0	5	2	0.935	0.993	0.415	0.613	0.70	1.25	25.0	5	2	0.909	0.987	0.832	0.883
				5	0.955	0.989	0.409	0.587					5	0.920	0.987	0.835	0.882
			15	2	0.943	0.980	0.229	0.271				15	2	0.941	0.970	0.594	0.650
				5	0.945	0.978	0.215	0.246					5	0.946	0.973	0.580	0.636
			30	2	0.952	0.975	0.180	0.196				30	2	0.949	0.971	0.488	0.518
				5	0.955	0.972	0.175	0.186					5	0.952	0.975	0.485	0.513

Table C.8: Empirical Coverage Probabilities and Average Lengths of Nominally 95% One-sided Confidence Intervals (Lower Bound) for CCC under the Model with Method and Subject Interaction (Model (4.26) in Section 4.3); $\mu_1 - \mu_2 = 2$ and $\sigma_2^2 = 20$.

Parameter					CP		CL	
ρ	$\sigma_{\varepsilon_1}^2$	σ_1^2	n	m	ZT	FGCI	ZT	FGCI
0.95	1.0	20.0	5	2	0.973	0.983	0.455	0.499
				5	0.984	0.978	0.433	0.409
			15	2	0.966	0.967	0.259	0.258
				5	0.968	0.958	0.254	0.242
			30	2	0.973	0.972	0.212	0.210
				5	0.963	0.949	0.205	0.199
0.95	1.0	25.0	5	2	0.960	0.984	0.437	0.492
				5	0.976	0.975	0.444	0.441
			15	2	0.954	0.960	0.253	0.254
				5	0.966	0.958	0.246	0.237
			30	2	0.963	0.965	0.207	0.207
				5	0.969	0.964	0.200	0.196
0.95	1.25	20.0	5	2	0.970	0.986	0.452	0.489
				5	0.987	0.976	0.435	0.393
			15	2	0.973	0.972	0.260	0.258
				5	0.975	0.962	0.247	0.233
			30	2	0.969	0.969	0.210	0.208
				5	0.965	0.952	0.202	0.195
0.95	1.25	25.0	5	2	0.969	0.988	0.435	0.487
				5	0.980	0.977	0.426	0.410
			15	2	0.971	0.975	0.255	0.255
				5	0.973	0.962	0.245	0.234
			30	2	0.973	0.962	0.245	0.234
				5	0.966	0.961	0.200	0.195
0.90	1.0	20.0	5	2	0.942	0.989	0.557	0.664
				5	0.959	0.979	0.551	0.632
			15	2	0.962	0.9789	0.357	0.373
				5	0.960	0.974	0.344	0.352
			30	2	0.958	0.966	0.288	0.294
				5	0.964	0.967	0.280	0.282
0.90	1.0	25.0	5	2	0.941	0.985	0.562	0.670
				5	0.952	0.980	0.545	0.635
			15	2	0.957	0.973	0.348	0.366
				5	0.958	0.970	0.338	0.349
			30	2	0.960	0.969	0.282	0.288
				5	0.956	0.962	0.275	0.279
0.90	1.25	20.0	5	2	0.952	0.989	0.563	0.667
				5	0.962	0.980	0.545	0.621
			15	2	0.960	0.977	0.349	0.364
				5	0.957	0.966	0.343	0.349
			30	2	0.964	0.971	0.287	0.292
				5	0.959	0.962	0.280	0.282
0.90	1.25	25.0	5	2	0.944	0.987	0.554	0.666
				5	0.952	0.980	0.535	0.624
			15	2	0.955	0.970	0.347	0.365
				5	0.955	0.969	0.330	0.340
			30	2	0.949	0.962	0.280	0.285
				5	0.952	0.958	0.275	0.278

Parameter					CP		CL	
ρ	$\sigma_{\varepsilon_1}^2$	σ_1^2	n	m	ZT	FGCI	ZT	FGCI
0.80	1.0	20.0	5	2	0.935	0.987	0.745	0.826
				5	0.928	0.981	0.736	0.815
			15	2	0.949	0.976	0.511	0.546
				5	0.943	0.970	0.497	0.528
			30	2	0.957	0.973	0.425	0.440
				5	0.958	0.971	0.419	0.432
0.80	1.0	25.0	5	2	0.930	0.987	0.748	0.827
				5	0.926	0.984	0.714	0.808
			15	2	0.953	0.981	0.506	0.543
				5	0.954	0.979	0.497	0.529
			30	2	0.951	0.972	0.423	0.438
				5	0.957	0.975	0.423	0.436
0.80	1.25	20.0	5	2	0.937	0.983	0.740	0.826
				5	0.932	0.980	0.726	0.807
			15	2	0.950	0.976	0.504	0.538
				5	0.953	0.976	0.498	0.528
			30	2	0.954	0.968	0.424	0.439
				5	0.956	0.970	0.421	0.433
0.80	1.25	25.0	5	2	0.926	0.986	0.742	0.823
				5	0.931	0.979	0.709	0.802
			15	2	0.947	0.971	0.505	0.541
				5	0.946	0.969	0.493	0.526
			30	2	0.946	0.968	0.421	0.436
				5	0.956	0.971	0.416	0.429
0.70	1.0	20.0	5	2	0.925	0.981	0.886	0.897
				5	0.926	0.978	0.878	0.890
			15	2	0.945	0.974	0.645	0.682
				5	0.955	0.975	0.645	0.680
			30	2	0.947	0.967	0.552	0.571
				5	0.938	0.960	0.544	0.561
0.70	1.0	25.0	5	2	0.914	0.978	0.865	0.887
				5	0.919	0.985	0.868	0.890
			15	2	0.936	0.966	0.643	0.680
				5	0.941	0.975	0.633	0.670
			30	2	0.948	0.965	0.553	0.573
				5	0.952	0.966	0.552	0.570
0.70	1.25	20.0	5	2	0.923	0.983	0.873	0.893
				5	0.928	0.976	0.870	0.888
			15	2	0.948	0.976	0.644	0.681
				5	0.940	0.969	0.641	0.674
			30	2	0.948	0.961	0.548	0.567
				5	0.948	0.968	0.547	0.565
0.70	1.25	25.0	5	2	0.931	0.982	0.874	0.893
				5	0.931	0.985	0.866	0.891
			15	2	0.937	0.973	0.647	0.685
				5	0.948	0.971	0.642	0.678
			30	2	0.940	0.963	0.548	0.567
				5	0.955	0.970	0.544	0.562

Appendix D

SIMULATION RESULTS FOR SIMULTANEOUS FIDUCIAL GENERALIZED CONFIDENCE INTERVALS FOR RATIOS OF MEANS OF THREE LOGNORMAL DISTRIBUTIONS

For a discussion of results see Section 5.3.

Table D.1: Empirical Coverage Probabilities of Nominally 95% Two-sided Simultaneous Fiducial Generalized Confidence Intervals for Ratios of Means of Three Lognormal Distributions.

$\sigma_1^2 = 0.01$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP
0.01	0.01	5	5	5	0.979
0.01	0.01	5	5	25	0.970
0.01	0.01	5	5	125	0.958
0.01	0.01	5	25	125	0.952
0.01	0.01	5	25	25	0.956
0.01	0.01	5	125	125	0.959
0.01	0.01	25	25	25	0.954
0.01	0.01	25	25	125	0.950
0.01	0.01	25	125	125	0.952
0.01	0.01	125	125	125	0.953
0.01	0.02	5	5	5	0.980
0.01	0.02	5	5	25	0.972
0.01	0.02	5	5	125	0.962
0.01	0.02	5	25	25	0.961
0.01	0.02	5	25	125	0.954
0.01	0.02	5	125	125	0.951
0.01	0.02	25	25	25	0.956
0.01	0.02	25	25	125	0.953
0.01	0.02	25	25	5	0.957
0.01	0.02	25	125	125	0.953
0.01	0.02	25	125	5	0.950
0.01	0.02	25	5	5	0.962
0.01	0.02	125	125	125	0.950
0.01	0.02	125	125	25	0.950
0.01	0.02	125	125	5	0.952
0.01	0.02	125	25	25	0.954
0.01	0.02	125	25	5	0.952
0.01	0.02	125	5	5	0.954
0.01	0.04	5	5	5	0.980
0.01	0.04	5	5	25	0.971
0.01	0.04	5	5	125	0.960
0.01	0.04	5	25	25	0.963
0.01	0.04	5	25	125	0.959
0.01	0.04	5	125	125	0.958
0.01	0.04	25	25	25	0.953
0.01	0.04	25	25	125	0.957
0.01	0.04	25	25	5	0.949
0.01	0.04	25	125	125	0.953
0.01	0.04	25	125	5	0.954
0.01	0.04	25	5	5	0.963
0.01	0.04	125	125	125	0.953
0.01	0.04	125	125	25	0.949
0.01	0.04	125	125	5	0.949
0.01	0.04	125	25	25	0.947
0.01	0.04	125	25	5	0.953
0.01	0.04	125	5	5	0.956

$\sigma_1^2 = 0.1$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP
0.1	0.1	5	5	5	0.986
0.1	0.1	5	5	25	0.974
0.1	0.1	5	5	125	0.970
0.1	0.1	5	25	125	0.961
0.1	0.1	5	25	25	0.967
0.1	0.1	5	125	125	0.951
0.1	0.1	25	25	25	0.956
0.1	0.1	25	25	125	0.954
0.1	0.1	25	125	125	0.953
0.1	0.1	125	125	125	0.956
0.1	0.2	5	5	5	0.985
0.1	0.2	5	5	25	0.978
0.1	0.2	5	5	125	0.968
0.1	0.2	5	25	25	0.964
0.1	0.2	5	25	125	0.959
0.1	0.2	5	125	125	0.948
0.1	0.2	25	25	25	0.958
0.1	0.2	25	25	125	0.956
0.1	0.2	25	25	5	0.957
0.1	0.2	25	125	125	0.954
0.1	0.2	25	125	5	0.963
0.1	0.2	25	5	5	0.976
0.1	0.2	125	125	125	0.952
0.1	0.2	125	125	25	0.952
0.1	0.2	125	125	5	0.956
0.1	0.2	125	25	25	0.955
0.1	0.2	125	25	5	0.962
0.1	0.2	125	5	5	0.967
0.1	0.4	5	5	5	0.991
0.1	0.4	5	5	25	0.986
0.1	0.4	5	5	125	0.976
0.1	0.4	5	25	25	0.972
0.1	0.4	5	25	125	0.966
0.1	0.4	5	125	125	0.955
0.1	0.4	25	25	25	0.959
0.1	0.4	25	25	125	0.957
0.1	0.4	25	25	5	0.964
0.1	0.4	25	125	125	0.958
0.1	0.4	25	125	5	0.952
0.1	0.4	25	5	5	0.975
0.1	0.4	125	125	125	0.944
0.1	0.4	125	125	25	0.950
0.1	0.4	125	125	5	0.953
0.1	0.4	125	25	25	0.957
0.1	0.4	125	25	5	0.960
0.1	0.4	125	5	5	0.971

$\sigma_1^2 = 1$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP
1	1	5	5	5	0.999
1	1	5	5	25	0.993
1	1	5	5	125	0.978
1	1	5	25	125	0.960
1	1	5	25	25	0.974
1	1	5	125	125	0.959
1	1	25	25	25	0.974
1	1	25	25	125	0.965
1	1	25	125	125	0.962
1	1	125	125	125	0.955
1	2	5	5	5	0.998
1	2	5	5	25	0.996
1	2	5	5	125	0.985
1	2	5	25	25	0.979
1	2	5	25	125	0.970
1	2	5	125	125	0.963
1	2	25	25	25	0.980
1	2	25	25	125	0.976
1	2	25	25	5	0.967
1	2	25	125	125	0.957
1	2	25	125	5	0.960
1	2	25	5	5	0.987
1	2	125	125	125	0.959
1	2	125	125	25	0.955
1	2	125	125	5	0.955
1	2	125	25	25	0.970
1	2	125	25	5	0.963
1	2	125	5	5	0.981
1	4	5	5	5	0.997
1	4	5	5	25	0.997
1	4	5	5	125	0.994
1	4	5	25	25	0.982
1	4	5	25	125	0.974
1	4	5	125	125	0.961
1	4	25	25	25	0.971
1	4	25	25	125	0.975
1	4	25	25	5	0.957
1	4	25	125	125	0.961
1	4	25	125	5	0.957
1	4	25	5	5	0.982
1	4	125	125	125	0.956
1	4	125	125	25	0.954
1	4	125	125	5	0.958
1	4	125	25	25	0.956
1	4	125	25	5	0.958
1	4	125	5	5	0.974

continued on next page

Table D.1: Empirical Coverage Probabilities of Nominally 95% Two-sided Simultaneous Fiducial Generalized Confidence Intervals for Ratios of Means of Three Lognormal Distributions.

$\sigma_1^2 = 0.01$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP
0.01	0.08	5	5	5	0.972
0.01	0.08	5	5	25	0.976
0.01	0.08	5	5	125	0.972
0.01	0.08	5	25	25	0.956
0.01	0.08	5	25	125	0.962
0.01	0.08	5	125	125	0.945
0.01	0.08	25	25	25	0.960
0.01	0.08	25	25	125	0.955
0.01	0.08	25	25	5	0.960
0.01	0.08	25	125	125	0.957
0.01	0.08	25	125	5	0.956
0.01	0.08	25	5	5	0.963
0.01	0.08	125	125	125	0.953
0.01	0.08	125	125	25	0.949
0.01	0.08	125	125	5	0.954
0.01	0.08	125	25	25	0.954
0.01	0.08	125	25	5	0.950
0.01	0.08	125	5	5	0.962
0.02	0.02	5	5	5	0.977
0.02	0.02	5	5	25	0.971
0.02	0.02	5	5	125	0.961
0.02	0.02	5	25	25	0.962
0.02	0.02	5	25	125	0.957
0.02	0.02	5	125	125	0.957
0.02	0.02	25	25	25	0.955
0.02	0.02	25	25	125	0.952
0.02	0.02	25	25	5	0.954
0.02	0.02	25	125	125	0.954
0.02	0.02	25	125	5	0.958
0.02	0.02	25	5	5	0.967
0.02	0.02	125	125	125	0.952
0.02	0.02	125	125	25	0.947
0.02	0.02	125	125	5	0.951
0.02	0.02	125	25	25	0.949
0.02	0.02	125	25	5	0.952
0.02	0.02	125	5	5	0.957
0.02	0.04	5	5	5	0.975
0.02	0.04	5	5	25	0.974
0.02	0.04	5	5	125	0.963
0.02	0.04	5	25	5	0.969
0.02	0.04	5	25	25	0.955
0.02	0.04	5	25	125	0.951
0.02	0.04	5	125	5	0.955
0.02	0.04	5	125	25	0.953
0.02	0.04	5	125	125	0.957
0.02	0.04	25	25	25	0.957

$\sigma_1^2 = 0.1$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP
0.1	0.8	5	5	5	0.985
0.1	0.8	5	5	25	0.987
0.1	0.8	5	5	125	0.982
0.1	0.8	5	25	25	0.966
0.1	0.8	5	25	125	0.961
0.1	0.8	5	125	125	0.959
0.1	0.8	25	25	25	0.964
0.1	0.8	25	25	125	0.956
0.1	0.8	25	25	5	0.963
0.1	0.8	25	125	125	0.960
0.1	0.8	25	125	5	0.960
0.1	0.8	25	5	5	0.971
0.1	0.8	125	125	125	0.943
0.1	0.8	125	125	25	0.950
0.1	0.8	125	125	5	0.953
0.1	0.8	125	25	25	0.962
0.1	0.8	125	25	5	0.963
0.1	0.8	125	5	5	0.973
0.2	0.2	5	5	5	0.988
0.2	0.2	5	5	25	0.981
0.2	0.2	5	5	125	0.965
0.2	0.2	5	25	25	0.968
0.2	0.2	5	25	125	0.966
0.2	0.2	5	125	125	0.960
0.2	0.2	25	25	25	0.957
0.2	0.2	25	25	125	0.961
0.2	0.2	25	25	5	0.966
0.2	0.2	25	125	125	0.957
0.2	0.2	25	125	5	0.959
0.2	0.2	25	5	5	0.975
0.2	0.2	125	125	125	0.954
0.2	0.2	125	125	25	0.954
0.2	0.2	125	125	5	0.955
0.2	0.2	125	25	25	0.963
0.2	0.2	125	25	5	0.954
0.2	0.2	125	5	5	0.964
0.2	0.4	5	5	5	0.988
0.2	0.4	5	5	25	0.983
0.2	0.4	5	5	125	0.974
0.2	0.4	5	25	5	0.979
0.2	0.4	5	25	25	0.974
0.2	0.4	5	25	125	0.966
0.2	0.4	5	125	5	0.967
0.2	0.4	5	125	25	0.965
0.2	0.4	5	125	125	0.957
0.2	0.4	25	25	25	0.959

$\sigma_1^2 = 1$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP
1	8	5	5	5	0.984
1	8	5	5	25	0.998
1	8	5	5	125	0.997
1	8	5	25	25	0.974
1	8	5	25	125	0.974
1	8	5	125	125	0.960
1	8	25	25	25	0.958
1	8	25	25	125	0.966
1	8	25	25	5	0.958
1	8	25	125	125	0.964
1	8	25	125	5	0.959
1	8	25	5	5	0.971
1	8	125	125	125	0.953
1	8	125	125	25	0.954
1	8	125	125	5	0.960
1	8	125	25	25	0.954
1	8	125	25	5	0.954
1	8	125	5	5	0.968
2	2	5	5	5	0.999
2	2	5	5	25	0.995
2	2	5	5	125	0.979
2	2	5	25	25	0.991
2	2	5	25	125	0.970
2	2	5	125	125	0.965
2	2	25	25	25	0.974
2	2	25	25	125	0.969
2	2	25	25	5	0.967
2	2	25	125	125	0.961
2	2	25	125	5	0.966
2	2	25	5	5	0.991
2	2	125	125	125	0.960
2	2	125	125	25	0.955
2	2	125	125	5	0.958
2	2	125	25	25	0.963
2	2	125	25	5	0.960
2	2	125	5	5	0.978
2	4	5	5	5	0.997
2	4	5	5	25	0.996
2	4	5	5	125	0.993
2	4	5	25	5	0.986
2	4	5	25	25	0.993
2	4	5	25	125	0.987
2	4	5	125	5	0.979
2	4	5	125	25	0.977
2	4	5	125	125	0.968
2	4	25	25	25	0.962

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Table D.1: Empirical Coverage Probabilities of Nominally 95% Two-sided Simultaneous Fiducial Generalized Confidence Intervals for Ratios of Means of Three Lognormal Distributions.

$\sigma_1^2 = 0.01$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP
0.02	0.04	25	25	125	0.950
0.02	0.04	25	25	5	0.959
0.02	0.04	25	125	25	0.954
0.02	0.04	25	125	125	0.956
0.02	0.04	25	125	5	0.957
0.02	0.04	25	5	25	0.964
0.02	0.04	25	5	125	0.959
0.02	0.04	25	5	5	0.962
0.02	0.04	125	125	125	0.953
0.02	0.04	125	125	25	0.946
0.02	0.04	125	125	5	0.955
0.02	0.04	125	25	125	0.948
0.02	0.04	125	25	25	0.947
0.02	0.04	125	25	5	0.946
0.02	0.04	125	5	125	0.950
0.02	0.04	125	5	25	0.958
0.02	0.04	125	5	5	0.954
0.02	0.08	5	5	5	0.972
0.02	0.08	5	5	25	0.977
0.02	0.08	5	5	125	0.967
0.02	0.08	5	25	5	0.967
0.02	0.08	5	25	25	0.968
0.02	0.08	5	25	125	0.96
0.02	0.08	5	125	5	0.960
0.02	0.08	5	125	25	0.958
0.02	0.08	5	125	125	0.954
0.02	0.08	25	25	25	0.955
0.02	0.08	25	25	125	0.954
0.02	0.08	25	25	5	0.953
0.02	0.08	25	125	25	0.953
0.02	0.08	25	125	125	0.958
0.02	0.08	25	125	5	0.953
0.02	0.08	25	5	25	0.954
0.02	0.08	25	5	125	0.958
0.02	0.08	25	5	5	0.961
0.02	0.08	125	125	125	0.946
0.02	0.08	125	125	25	0.946
0.02	0.08	125	125	5	0.948
0.02	0.08	125	25	125	0.949
0.02	0.08	125	25	25	0.948
0.02	0.08	125	25	5	0.951
0.02	0.08	125	5	125	0.957
0.02	0.08	125	5	25	0.949
0.02	0.08	125	5	5	0.956
0.04	0.04	5	5	5	0.976
0.04	0.04	5	5	25	0.972

$\sigma_1^2 = 0.1$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP
0.2	0.4	25	25	125	0.957
0.2	0.4	25	25	5	0.959
0.2	0.4	25	125	25	0.958
0.2	0.4	25	125	125	0.957
0.2	0.4	25	125	5	0.961
0.2	0.4	25	5	25	0.963
0.2	0.4	25	5	125	0.960
0.2	0.4	25	5	5	0.977
0.2	0.4	125	125	125	0.952
0.2	0.4	125	125	25	0.956
0.2	0.4	125	125	5	0.957
0.2	0.4	125	25	125	0.956
0.2	0.4	125	25	25	0.957
0.2	0.4	125	25	5	0.9622
0.2	0.4	125	5	125	0.958
0.2	0.4	125	5	25	0.963
0.2	0.4	125	5	5	0.974
0.2	0.8	5	5	5	0.985
0.2	0.8	5	5	25	0.984
0.2	0.8	5	5	125	0.979
0.2	0.8	5	25	5	0.977
0.2	0.8	5	25	25	0.976
0.2	0.8	5	25	125	0.969
0.2	0.8	5	125	5	0.973
0.2	0.8	5	125	25	0.963
0.2	0.8	5	125	125	0.957
0.2	0.8	25	25	25	0.959
0.2	0.8	25	25	125	0.959
0.2	0.8	25	25	5	0.960
0.2	0.8	25	125	25	0.961
0.2	0.8	25	125	125	0.957
0.2	0.8	25	125	5	0.957
0.2	0.8	25	5	25	0.965
0.2	0.8	25	5	125	0.966
0.2	0.8	25	5	5	0.975
0.2	0.8	125	125	125	0.952
0.2	0.8	125	125	25	0.962
0.2	0.8	125	125	5	0.957
0.2	0.8	125	25	125	0.954
0.2	0.8	125	25	25	0.956
0.2	0.8	125	25	5	0.958
0.2	0.8	125	5	125	0.963
0.2	0.8	125	5	25	0.965
0.2	0.8	125	5	5	0.974
0.4	0.4	5	5	5	0.988
0.4	0.4	5	5	25	0.978

$\sigma_1^2 = 1$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP
2	4	25	25	125	0.979
2	4	25	25	5	0.960
2	4	25	125	25	0.956
2	4	25	125	125	0.966
2	4	25	125	5	0.958
2	4	25	5	25	0.973
2	4	25	5	125	0.969
2	4	25	5	5	0.985
2	4	125	125	125	0.957
2	4	125	125	25	0.962
2	4	125	125	5	0.953
2	4	125	25	125	0.958
2	4	125	25	25	0.961
2	4	125	25	5	0.957
2	4	125	5	125	0.958
2	4	125	5	25	0.960
2	4	125	5	5	0.975
2	8	5	5	5	0.990
2	8	5	5	25	0.997
2	8	5	5	125	0.995
2	8	5	25	5	0.975
2	8	5	25	25	0.988
2	8	5	25	125	0.985
2	8	5	125	5	0.974
2	8	5	125	25	0.972
2	8	5	125	125	0.971
2	8	25	25	25	0.968
2	8	25	25	125	0.966
2	8	25	25	5	0.952
2	8	25	125	25	0.964
2	8	25	125	125	0.965
2	8	25	125	5	0.956
2	8	25	5	25	0.967
2	8	25	5	125	0.967
2	8	25	5	5	0.979
2	8	125	125	125	0.950
2	8	125	125	25	0.961
2	8	125	125	5	0.952
2	8	125	25	125	0.959
2	8	125	25	25	0.957
2	8	125	25	5	0.948
2	8	125	5	125	0.969
2	8	125	5	25	0.965
2	8	125	5	5	0.969
4	4	5	5	5	0.996
4	4	5	5	25	0.990

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Table D.1: Empirical Coverage Probabilities of Nominally 95% Two-sided Simultaneous Fiducial Generalized Confidence Intervals for Ratios of Means of Three Lognormal Distributions.

$\sigma_1^2 = 0.01$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP
0.04	0.04	5	5	125	0.961
0.04	0.04	5	25	25	0.965
0.04	0.04	5	25	125	0.961
0.04	0.04	5	125	125	0.956
0.04	0.04	25	25	25	0.958
0.04	0.04	25	25	125	0.955
0.04	0.04	25	25	5	0.954
0.04	0.04	25	125	125	0.953
0.04	0.04	25	125	5	0.955
0.04	0.04	25	5	5	0.957
0.04	0.04	125	125	125	0.949
0.04	0.04	125	125	25	0.952
0.04	0.04	125	125	5	0.949
0.04	0.04	125	25	25	0.957
0.04	0.04	125	25	5	0.953
0.04	0.04	125	5	5	0.956
0.04	0.08	5	5	5	0.974
0.04	0.08	5	5	25	0.971
0.04	0.08	5	5	125	0.972
0.04	0.08	5	25	5	0.972
0.04	0.08	5	25	25	0.962
0.04	0.08	5	25	125	0.964
0.04	0.08	5	125	5	0.962
0.04	0.08	5	125	25	0.960
0.04	0.08	5	125	125	0.956
0.04	0.08	25	25	25	0.953
0.04	0.08	25	25	125	0.960
0.04	0.08	25	25	5	0.962
0.04	0.08	25	125	25	0.952
0.04	0.08	25	125	125	0.950
0.04	0.08	25	125	5	0.955
0.04	0.08	25	5	25	0.960
0.04	0.08	25	5	125	0.957
0.04	0.08	25	5	5	0.959
0.04	0.08	125	125	125	0.944
0.04	0.08	125	125	25	0.957
0.04	0.08	125	125	5	0.954
0.04	0.08	125	25	125	0.952
0.04	0.08	125	25	25	0.955
0.04	0.08	125	25	5	0.955
0.04	0.08	125	5	125	0.954
0.04	0.08	125	5	25	0.953
0.04	0.08	125	5	5	0.959
0.08	0.08	5	5	5	0.976
0.08	0.08	5	5	25	0.969
0.08	0.08	5	5	125	0.965

$\sigma_1^2 = 0.1$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP
0.4	0.4	5	5	125	0.973
0.4	0.4	5	25	25	0.977
0.4	0.4	5	25	125	0.966
0.4	0.4	5	125	125	0.965
0.4	0.4	25	25	25	0.961
0.4	0.4	25	25	125	0.953
0.4	0.4	25	25	5	0.964
0.4	0.4	25	125	125	0.951
0.4	0.4	25	125	5	0.964
0.4	0.4	25	5	5	0.976
0.4	0.4	125	125	125	0.946
0.4	0.4	125	125	25	0.953
0.4	0.4	125	125	5	0.960
0.4	0.4	125	25	25	0.959
0.4	0.4	125	25	5	0.960
0.4	0.4	125	5	5	0.969
0.4	0.8	5	5	5	0.989
0.4	0.8	5	5	25	0.983
0.4	0.8	5	5	125	0.974
0.4	0.8	5	25	5	0.978
0.4	0.8	5	25	25	0.981
0.4	0.8	5	25	125	0.974
0.4	0.8	5	125	5	0.972
0.4	0.8	5	125	25	0.967
0.4	0.8	5	125	125	0.961
0.4	0.8	25	25	25	0.956
0.4	0.8	25	25	125	0.957
0.4	0.8	25	25	5	0.967
0.4	0.8	25	125	25	0.958
0.4	0.8	25	125	125	0.954
0.4	0.8	25	125	5	0.957
0.4	0.8	25	5	25	0.967
0.4	0.8	25	5	125	0.958
0.4	0.8	25	5	5	0.977
0.4	0.8	125	125	125	0.951
0.4	0.8	125	125	25	0.955
0.4	0.8	125	125	5	0.958
0.4	0.8	125	25	125	0.955
0.4	0.8	125	25	25	0.960
0.4	0.8	125	25	5	0.966
0.4	0.8	125	5	125	0.957
0.4	0.8	125	5	25	0.956
0.4	0.8	125	5	5	0.968
0.8	0.8	5	5	5	0.989
0.8	0.8	5	5	25	0.974
0.8	0.8	5	5	125	0.972

$\sigma_1^2 = 1$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP
4	4	5	5	125	0.985
4	4	5	25	25	0.997
4	4	5	25	125	0.982
4	4	5	125	125	0.976
4	4	25	25	25	0.965
4	4	25	25	125	0.970
4	4	25	25	5	0.955
4	4	25	125	125	0.969
4	4	25	125	5	0.956
4	4	25	5	5	0.978
4	4	125	125	125	0.959
4	4	125	125	25	0.959
4	4	125	125	5	0.956
4	4	125	25	25	0.960
4	4	125	25	5	0.961
4	4	125	5	5	0.976
4	8	5	5	5	0.992
4	8	5	5	25	0.988
4	8	5	5	125	0.991
4	8	5	25	5	0.980
4	8	5	25	25	0.993
4	8	5	25	125	0.993
4	8	5	125	5	0.979
4	8	5	125	25	0.982
4	8	5	125	125	0.980
4	8	25	25	25	0.961
4	8	25	25	125	0.969
4	8	25	25	5	0.955
4	8	25	125	25	0.958
4	8	25	125	125	0.968
4	8	25	125	5	0.953
4	8	25	5	25	0.959
4	8	25	5	125	0.959
4	8	25	5	5	0.972
4	8	125	125	125	0.951
4	8	125	125	25	0.952
4	8	125	125	5	0.956
4	8	125	25	125	0.958
4	8	125	25	25	0.958
4	8	125	25	5	0.955
4	8	125	5	125	0.961
4	8	125	5	25	0.955
4	8	125	5	5	0.971
8	8	5	5	5	0.989
8	8	5	5	25	0.974
8	8	5	5	125	0.974

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Table D.1: Empirical Coverage Probabilities of Nominally 95% Two-sided Simultaneous Fiducial Generalized Confidence Intervals for Ratios of Means of Three Lognormal Distributions.

$\sigma_1^2 = 0.01$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP
0.08	0.08	5	25	25	0.970
0.08	0.08	5	25	125	0.959
0.08	0.08	5	125	125	0.955
0.08	0.08	25	25	25	0.959
0.08	0.08	25	25	125	0.953
0.08	0.08	25	25	5	0.954
0.08	0.08	25	125	125	0.950
0.08	0.08	25	125	5	0.957
0.08	0.08	25	5	5	0.968
0.08	0.08	125	125	125	0.947
0.08	0.08	125	125	25	0.953
0.08	0.08	125	125	5	0.955
0.08	0.08	125	25	25	0.955
0.08	0.08	125	25	5	0.950
0.08	0.08	125	5	5	0.966

$\sigma_1^2 = 0.1$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP
0.8	0.8	5	25	25	0.978
0.8	0.8	5	25	125	0.971
0.8	0.8	5	125	125	0.968
0.8	0.8	25	25	25	0.963
0.8	0.8	25	25	125	0.960
0.8	0.8	25	25	5	0.964
0.8	0.8	25	125	125	0.956
0.8	0.8	25	125	5	0.958
0.8	0.8	25	5	5	0.975
0.8	0.8	125	125	125	0.946
0.8	0.8	125	125	25	0.961
0.8	0.8	125	125	5	0.961
0.8	0.8	125	25	25	0.959
0.8	0.8	125	25	5	0.961
0.8	0.8	125	5	5	0.976

$\sigma_1^2 = 1$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP
8	8	5	25	25	0.990
8	8	5	25	125	0.989
8	8	5	125	125	0.990
8	8	25	25	25	0.958
8	8	25	25	125	0.948
8	8	25	25	5	0.954
8	8	25	125	125	0.963
8	8	25	125	5	0.954
8	8	25	5	5	0.970
8	8	125	125	125	0.960
8	8	125	125	25	0.956
8	8	125	125	5	0.958
8	8	125	25	25	0.960
8	8	125	25	5	0.958
8	8	125	5	5	0.966

$\sigma_1^2 = 10$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP
10	10	5	5	5	1.000
10	10	5	5	25	0.999
10	10	5	5	125	0.984
10	10	5	25	25	0.984
10	10	5	25	125	0.954
10	10	5	125	125	0.951
10	10	25	25	25	0.999
10	10	25	25	125	0.966
10	10	25	125	125	0.964
10	10	125	125	125	0.965
10	20	5	5	5	0.999
10	20	5	5	25	1.000
10	20	5	5	125	0.999
10	20	5	25	25	0.989
10	20	5	25	125	0.977
10	20	5	125	125	0.952
10	20	25	25	25	0.987
10	20	25	25	125	0.989
10	20	25	25	5	0.965
10	20	25	125	125	0.960
10	20	25	125	5	0.952
10	20	25	5	5	0.996
10	20	125	125	125	0.963
10	20	125	125	25	0.956
10	20	125	125	5	0.950
10	20	125	25	25	0.963
10	20	125	25	5	0.955
10	20	125	5	5	0.978

$\sigma_1^2 = 100$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP
100	100	5	5	5	1.000
100	100	5	5	25	1.000
100	100	5	5	125	0.987
100	100	5	25	25	0.995
100	100	5	25	125	0.951
100	100	5	125	125	0.956
100	100	25	25	25	1.000
100	100	25	25	125	0.968
100	100	25	125	125	0.960
100	100	125	125	125	0.971
100	200	5	5	5	1.000
100	200	5	5	25	1.000
100	200	5	5	125	1.000
100	200	5	25	25	0.994
100	200	5	25	125	0.974
100	200	5	125	125	0.957
100	200	25	25	25	0.992
100	200	25	25	125	0.990
100	200	25	25	5	0.965
100	200	25	125	125	0.961
100	200	25	125	5	0.956
100	200	25	5	5	0.995
100	200	125	125	125	0.966
100	200	125	125	25	0.957
100	200	125	125	5	0.940
100	200	125	25	25	0.960
100	200	125	25	5	0.956
100	200	125	5	5	0.972

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Table D.1: Empirical Coverage Probabilities of Nominally 95% Two-sided Simultaneous Fiducial Generalized Confidence Intervals for Ratios of Means of Three Lognormal Distributions.

$\sigma_1^2 = 10$						$\sigma_1^2 = 100$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP	σ_2^2	σ_3^2	n_1	n_2	n_3	CP
10	40	5	5	5	0.997	100	400	5	5	5	0.995
10	40	5	5	25	1.000	100	400	5	5	25	1.000
10	40	5	5	125	1.000	100	400	5	5	125	1.000
10	40	5	25	25	0.985	100	400	5	25	25	0.987
10	40	5	25	125	0.978	100	400	5	25	125	0.981
10	40	5	125	125	0.954	100	400	5	125	125	0.956
10	40	25	25	25	0.971	100	400	25	25	25	0.973
10	40	25	25	125	0.990	100	400	25	25	125	0.993
10	40	25	25	5	0.958	100	400	25	25	5	0.956
10	40	25	125	125	0.962	100	400	25	125	125	0.965
10	40	25	125	5	0.949	100	400	25	125	5	0.946
10	40	25	5	5	0.975	100	400	25	5	5	0.976
10	40	125	125	125	0.950	100	400	125	125	125	0.960
10	40	125	125	25	0.955	100	400	125	125	25	0.951
10	40	125	125	5	0.944	100	400	125	125	5	0.948
10	40	125	25	25	0.955	100	400	125	25	25	0.957
10	40	125	25	5	0.956	100	400	125	25	5	0.952
10	40	125	5	5	0.969	100	400	125	5	5	0.971
10	80	5	5	5	0.982	100	800	5	5	5	0.987
10	80	5	5	25	0.999	100	800	5	5	25	1.000
10	80	5	5	125	1.000	100	800	5	5	125	1.000
10	80	5	25	25	0.982	100	800	5	25	25	0.991
10	80	5	25	125	0.982	100	800	5	25	125	0.982
10	80	5	125	125	0.949	100	800	5	125	125	0.953
10	80	25	25	25	0.968	100	800	25	25	25	0.970
10	80	25	25	125	0.986	100	800	25	25	125	0.983
10	80	25	25	5	0.954	100	800	25	25	5	0.953
10	80	25	125	125	0.958	100	800	25	125	125	0.954
10	80	25	125	5	0.954	100	800	25	125	5	0.950
10	80	25	5	5	0.971	100	800	25	5	5	0.976
10	80	125	125	125	0.954	100	800	125	125	125	0.961
10	80	125	125	25	0.962	100	800	125	125	25	0.950
10	80	125	125	5	0.945	100	800	125	125	5	0.949
10	80	125	25	25	0.955	100	800	125	25	25	0.962
10	80	125	25	5	0.947	100	800	125	25	5	0.949
10	80	125	5	5	0.965	100	800	125	5	5	0.972
20	20	5	5	5	1.000	200	200	5	5	5	1.000
20	20	5	5	25	0.999	200	200	5	5	25	0.999
20	20	5	5	125	0.988	200	200	5	5	125	0.992
20	20	5	25	25	1.000	200	200	5	25	25	1.000
20	20	5	25	125	0.977	200	200	5	25	125	0.974
20	20	5	125	125	0.962	200	200	5	125	125	0.962
20	20	25	25	25	0.983	200	200	25	25	25	0.986
20	20	25	25	125	0.974	200	200	25	25	125	0.975
20	20	25	25	5	0.960	200	200	25	25	5	0.961
20	20	25	125	125	0.979	200	200	25	125	125	0.979

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Table D.1: Empirical Coverage Probabilities of Nominally 95% Two-sided Simultaneous Fiducial Generalized Confidence Intervals for Ratios of Means of Three Lognormal Distributions.

$\sigma_1^2 = 10$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP
20	20	25	125	5	0.962
20	20	25	5	5	0.993
20	20	125	125	125	0.962
20	20	125	125	25	0.955
20	20	125	125	5	0.962
20	20	125	25	25	0.961
20	20	125	25	5	0.955
20	20	125	5	5	0.968
20	40	5	5	5	0.998
20	40	5	5	25	0.999
20	40	5	5	125	0.999
20	40	5	25	5	0.990
20	40	5	25	25	1.000
20	40	5	25	125	0.995
20	40	5	125	5	0.977
20	40	5	125	25	0.977
20	40	5	125	125	0.965
20	40	25	25	25	0.969
20	40	25	25	125	0.980
20	40	25	25	5	0.949
20	40	25	125	25	0.968
20	40	25	125	125	0.971
20	40	25	125	5	0.955
20	40	25	5	25	0.962
20	40	25	5	125	0.962
20	40	25	5	5	0.982
20	40	125	125	125	0.953
20	40	125	125	25	0.955
20	40	125	125	5	0.949
20	40	125	25	125	0.957
20	40	125	25	25	0.955
20	40	125	25	5	0.946
20	40	125	5	125	0.952
20	40	125	5	25	0.948
20	40	125	5	5	0.965
20	80	5	5	5	0.993
20	80	5	5	25	1.000
20	80	5	5	125	0.999
20	80	5	25	5	0.975
20	80	5	25	25	0.994
20	80	5	25	125	1.000
20	80	5	125	5	0.977
20	80	5	125	25	0.975
20	80	5	125	125	0.963
20	80	25	25	25	0.966
20	80	25	25	125	0.976

$\sigma_1^2 = 100$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP
200	200	25	125	5	0.953
200	200	25	5	5	0.992
200	200	125	125	125	0.958
200	200	125	125	25	0.955
200	200	125	125	5	0.952
200	200	125	25	25	0.959
200	200	125	25	5	0.952
200	200	125	5	5	0.967
200	400	5	5	5	0.997
200	400	5	5	25	0.999
200	400	5	5	125	1.000
200	400	5	25	5	0.990
200	400	5	25	25	1.000
200	400	5	25	125	0.998
200	400	5	125	5	0.977
200	400	5	125	25	0.978
200	400	5	125	125	0.964
200	400	25	25	25	0.969
200	400	25	25	125	0.979
200	400	25	25	5	0.952
200	400	25	125	25	0.966
200	400	25	125	125	0.975
200	400	25	125	5	0.952
200	400	25	5	25	0.956
200	400	25	5	125	0.953
200	400	25	5	5	0.976
200	400	125	125	125	0.960
200	400	125	125	25	0.952
200	400	125	125	5	0.951
200	400	125	25	125	0.957
200	400	125	25	25	0.951
200	400	125	25	5	0.956
200	400	125	5	125	0.957
200	400	125	5	25	0.952
200	400	125	5	5	0.956
200	800	5	5	5	0.986
200	800	5	5	25	0.999
200	800	5	5	125	0.999
200	800	5	25	5	0.970
200	800	5	25	25	0.995
200	800	5	25	125	1.000
200	800	5	125	5	0.973
200	800	5	125	25	0.975
200	800	5	125	125	0.963
200	800	25	25	25	0.964
200	800	25	25	125	0.978

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Table D.1: Empirical Coverage Probabilities of Nominally 95% Two-sided Simultaneous Fiducial Generalized Confidence Intervals for Ratios of Means of Three Lognormal Distributions.

$\sigma_1^2 = 10$						$\sigma_1^2 = 100$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP	σ_2^2	σ_3^2	n_1	n_2	n_3	CP
20	80	25	25	5	0.952	200	800	25	25	5	0.952
20	80	25	125	25	0.958	200	800	25	125	25	0.958
20	80	25	125	125	0.974	200	800	25	125	125	0.970
20	80	25	125	5	0.950	200	800	25	125	5	0.944
20	80	25	5	25	0.961	200	800	25	5	25	0.963
20	80	25	5	125	0.953	200	800	25	5	125	0.952
20	80	25	5	5	0.969	200	800	25	5	5	0.968
20	80	125	125	125	0.954	200	800	125	125	125	0.957
20	80	125	125	25	0.953	200	800	125	125	25	0.951
20	80	125	125	5	0.951	200	800	125	125	5	0.949
20	80	125	25	125	0.955	200	800	125	25	125	0.956
20	80	125	25	25	0.950	200	800	125	25	25	0.955
20	80	125	25	5	0.947	200	800	125	25	5	0.953
20	80	125	5	125	0.957	200	800	125	5	125	0.946
20	80	125	5	25	0.947	200	800	125	5	25	0.950
20	80	125	5	5	0.959	200	800	125	5	5	0.958
40	40	5	5	5	0.997	400	400	5	5	5	0.997
40	40	5	5	25	0.988	400	400	5	5	25	0.993
40	40	5	5	125	0.985	400	400	5	5	125	0.988
40	40	5	25	25	0.998	400	400	5	25	25	0.999
40	40	5	25	125	0.995	400	400	5	25	125	0.995
40	40	5	125	125	0.987	400	400	5	125	125	0.986
40	40	25	25	25	0.958	400	400	25	25	25	0.954
40	40	25	25	125	0.957	400	400	25	25	125	0.965
40	40	25	25	5	0.952	400	400	25	25	5	0.954
40	40	25	125	125	0.980	400	400	25	125	125	0.981
40	40	25	125	5	0.951	400	400	25	125	5	0.955
40	40	25	5	5	0.962	400	400	25	5	5	0.966
40	40	125	125	125	0.951	400	400	125	125	125	0.947
40	40	125	125	25	0.956	400	400	125	125	25	0.952
40	40	125	125	5	0.956	400	400	125	125	5	0.948
40	40	125	25	25	0.951	400	400	125	25	25	0.945
40	40	125	25	5	0.949	400	400	125	25	5	0.951
40	40	125	5	5	0.954	400	400	125	5	5	0.953
40	80	5	5	5	0.989	400	800	5	5	5	0.988
40	80	5	5	25	0.993	400	800	5	5	25	0.991
40	80	5	5	125	0.992	400	800	5	5	125	0.992
40	80	5	25	5	0.971	400	800	5	25	5	0.976
40	80	5	25	25	0.994	400	800	5	25	25	0.993
40	80	5	25	125	0.999	400	800	5	25	125	0.998
40	80	5	125	5	0.975	400	800	5	125	5	0.971
40	80	5	125	25	0.990	400	800	5	125	25	0.991
40	80	5	125	125	0.989	400	800	5	125	125	0.992
40	80	25	25	25	0.951	400	800	25	25	25	0.949
40	80	25	25	125	0.964	400	800	25	25	125	0.960
40	80	25	25	5	0.949	400	800	25	25	5	0.949

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Table D.1: Empirical Coverage Probabilities of Nominally 95% Two-sided Simultaneous Fiducial Generalized Confidence Intervals for Ratios of Means of Three Lognormal Distributions.

$\sigma_1^2 = 10$						$\sigma_1^2 = 100$					
σ_2^2	σ_3^2	n_1	n_2	n_3	CP	σ_2^2	σ_3^2	n_1	n_2	n_3	CP
40	80	25	125	25	0.964	400	800	25	125	25	0.958
40	80	25	125	125	0.967	400	800	25	125	125	0.968
40	80	25	125	5	0.947	400	800	25	125	5	0.953
40	80	25	5	25	0.956	400	800	25	5	25	0.948
40	80	25	5	125	0.944	400	800	25	5	125	0.951
40	80	25	5	5	0.962	400	800	25	5	5	0.960
40	80	125	125	125	0.954	400	800	125	125	125	0.949
40	80	125	125	25	0.952	400	800	125	125	25	0.956
40	80	125	125	5	0.947	400	800	125	125	5	0.955
40	80	125	25	125	0.945	400	800	125	25	125	0.950
40	80	125	25	25	0.949	400	800	125	25	25	0.952
40	80	125	25	5	0.945	400	800	125	25	5	0.947
40	80	125	5	125	0.951	400	800	125	5	125	0.957
40	80	125	5	25	0.956	400	800	125	5	25	0.956
40	80	125	5	5	0.953	400	800	125	5	5	0.954
80	80	5	5	5	0.980	800	800	5	5	5	0.981
80	80	5	5	25	0.975	800	800	5	5	25	0.973
80	80	5	5	125	0.973	800	800	5	5	125	0.978
80	80	5	25	25	0.990	800	800	5	25	25	0.990
80	80	5	25	125	0.994	800	800	5	25	125	0.993
80	80	5	125	125	0.995	800	800	5	125	125	0.995
80	80	25	25	25	0.949	800	800	25	25	25	0.948
80	80	25	25	125	0.949	800	800	25	25	125	0.952
80	80	25	25	5	0.951	800	800	25	25	5	0.952
80	80	25	125	125	0.963	800	800	25	125	125	0.961
80	80	25	125	5	0.948	800	800	25	125	5	0.952
80	80	25	5	5	0.956	800	800	25	5	5	0.955
80	80	125	125	125	0.950	800	800	125	125	125	0.950
80	80	125	125	25	0.948	800	800	125	125	25	0.948
80	80	125	125	5	0.958	800	800	125	125	5	0.944
80	80	125	25	25	0.948	800	800	125	25	25	0.955
80	80	125	25	5	0.942	800	800	125	25	5	0.950
80	80	125	5	5	0.950	800	800	125	5	5	0.950