Confidence intervals for ratio of two Poisson rates using the method of variance estimates recovery *

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Abstract Inference based on ratio of two independent Poisson rates is common in epidemiological studies. We study the performance of a variety of unconditional MOVER methods of combining separate confidence intervals for two single Poisson rates to form a confidence interval for their ratio. We consider confidence intervals derived from (i) the Fieller's theorem, (ii) the logarithmic transformation with the delta method and (iii) the substitution method. We evaluate the performance of 13 such types of confidence intervals by comparing their empirical coverage probabilities, empirical confidence widths, ratios of mesial non-coverage probability and total non-coverage probabilities. Our simulation results suggest that the MOVER Rao score confidence intervals based on the Fieller's theorem and the substitution method are preferable. We provide two applications to construct confidence intervals for the ratio of two poisson rates in a breast cancer study and in a study that examines coronary heart diseases incidences among post menopausal women treated with or without hormones.

Keywords Agresti-Coull Binomial method · Bayes interval · Fieller's theorem · Jeffreys interval · MOVER method · Rao score

1 Introduction

The Poisson probability model can be used to describe the occurrence of a wide variety of rare events (Haight 1967). It is frequently used when the events of interest occur randomly in time or space. In many biological, epidemiological, and medical studies, comparing Poisson rates (i.e. the number of occurrences per unit of time or space) from two independent samples is of great interest. For instance in a breast cancer study two groups of women were compared to determine whether those who had been examined using X-ray fluoroscopy during treatment for tuberculosis had a higher rate of breast cancer than those who had not been examined using X-ray fluoroscopy (Rothman & Greenland 1998; Graham et al. 2003). Forty-one cases of breast cancer in 28010 person-years at risk were reported in the treatment group with women receiving X-ray fluoroscopy and 15 cases of breast cases in 19017 person-years at risk in the control group with women not receiving X-ray fluoroscopy. In this trial, the goal was to determine whether the two Poisson rates were equivalent by comparing limits of a $100(1-\alpha)\%$ confidence confidence for the ratio of the two Poisson rates with the equivalence limits, say (δ_0, δ_1) with δ_0 and δ_1 being some clinical acceptable threshold (usually $\delta_0 = 1/\delta_1$). This means that if the $100(1-\alpha)\%$ confidence interval for the ratio of the two Poisson rates lies entirely inside the interval (δ_0, δ_1), one concludes that the two treatments are equivalent. Consequently, the construction of a confidence interval for the ratio of two Poisson rates plays an important role here.

A variety of approaches have been proposed for constructing a confidence interval for the ratio of two Poisson rates. There are three ways to construct a confidence interval for the ratio of two independent Poisson means (Sahai & Khurshid 1993) and there are further extensions of their method (Graham et al. 2003; Price & Bonett 2000). Tang and Ng (2004) studied the performance of three non-iterative confidence intervals for the ratio of two Poisson rates and noted that the aforementioned intervals were respectively identical to the square-root transformation interval, the interval based on converting the Wilson's interval for binomial parameter, and the log-linear model Wald's interval.

We use unconditional approaches to study confidence intervals for the ratio of two Poisson rates. For this purpose we construct separate confidence intervals for the two individual Poisson rates, then combine them into a single confidence interval for the ratio of the rates using the MOVER approach. An alternative method generally referred to as the square-and-add approach can also be a simple and effective method for finding a confidence interval for a difference between two independent proportions when separate confidence intervals for the two individual proportions are available (Donner & Zou 2002). The square-and-add approach preserves boundary-respecting properties, which makes it particularly suitable for comparing proportions. Justifications for the procedure were detailed in and summarized under the acronym MOVER (Method of variance estimates recovery) in a few papers (Zou & Donner 2008; Zou 2008). The MOVER and square-and-add methods combine confidence intervals based on separate samples and both methods are now known to be equivalent.

The aims of this paper are (i) to show that the MOVER method can be applied to find a confidence interval for the ratio of the two Poisson rates using separate confidence intervals constructed for each of the Poisson rates, (ii) to show that unequal sampling time frames can be directly accounted for in our analysis, and (iii) to use a simulation study to evaluate the performance of the MOVER method for finding a confidence interval for the ratio of the two Poisson rates when different methods of constructing confidence intervals for the separate confidence intervals are used. Specifically, we use a variety of performance measures to compare different methods and make recommendations how the MOVER can be best used to find a confidence interval for the ratio of the two Poisson rates.

Section 2 presents various MOVER approaches for constructing confidence intervals for the ratio of two Poisson rates and call them Fieller-type confidence intervals. We briefly review confidence intervals based on the delta method and confidence intervals based on the substitution method. For a single Poisson rate, we consider four types of confidence intervals constructed from the "Second Normal" method, the Rao score method, the Freeman and Tukey method and the Jeffrey's method. We also review non-MOVER types of confidence interval found from the mesially shrunk logit Wald method, the Wilson's Binomial method (WBM) and the Agresti-Coull's Binomial method (ACBM). We select these methods to study because they are reportedly the better-performing methods in the literature for finding accurate confidence interval(Brown et al. 2003; Swift 2009). In Section 3, we conduct a simulation study and use different performance measures to evaluate the performance of the MOVER method and other methods for finding a confidence interval for the ratio of two Poisson rates. In Section 4, we analyze data from a breast cancer study and a prospective study for examining the relationship between hormone use and coronary heart disease in post-menopausal women. Section 5 concludes with a discussion.

2 Confidence Intervals for the Ratio of two Poisson Rates

Suppose that two independent Poisson processes with parameters λ_1 and λ_2 are observed over times or space of size t_1 and t_2, respectively. Let X_1 and X_2 be the numbers of events in the two groups. That is, $X_i \sim Poisson(t_i\lambda_i)$ for $i = 1, 2$. Our main goal is to construct a confidence interval for $R = \lambda_2/\lambda_1$ using a variety of unconditional methods and determine which method or methods perform well. Such a ratio can be used to make inference on many types of problems, for example, on the number of automobile accident death on highways before and after a safety training program (Stapleton 1995) or the number of leukemia event rate per year in a pre and post nuclear accident period (Fleiss et al. 2003) and in the clinical applications described in Section 4.

It is instructive to first briefly review the MOVER method for finding a confidence interval for a risk difference. We then apply the method to find confidence interval for the ratio of the two Poisson rates. Both require separate confidence intervals for the two single rates and for this reason, we also briefly review various methods for finding a confidence interval for a single Poisson rate and different methods for estimating $R = \lambda_2/\lambda_1$ using a confidence interval. Justifications for the confidence limits can be found in the references provided.

2.1. MOVER confidence intervals (MOVER-D)

Suppose we wish to construct a $100(1-\alpha)\%$ two-sided confidence interval for $\theta_1 - \theta_2$ and its lower limit is L and its upper limit is U. Let $\hat{\theta}_1$ and $\hat{\theta}_2$ be the estimates for θ_1 and θ_2, and let $Var(\hat{\theta}_1)$ and $Var(\hat{\theta}_2)$ be their corresponding variances. By the Central Limit Theorem, if $\hat{\theta}_1$ and $\hat{\theta}_2$ are independent, the lower limit L and the upper limit U are given by

$$L = \hat{\theta}_1 - \hat{\theta}_2 - z_{\alpha/2}\sqrt{Var(\hat{\theta}_1) + Var(\hat{\theta}_2)}$$

and

$$U = \hat{\theta}_1 - \hat{\theta}_2 + z_{\alpha/2}\sqrt{Var(\hat{\theta}_1) + Var(\hat{\theta}_2)}.$$

Unfortunately, this procedure performs well only when sample sizes are sufficiently large or when the sampling distributions of $\hat{\theta}_i$ $(i = 1, 2)$ are close to normal distribution. Noticing the duality between the 2-sided hypothesis testing problem and the confidence interval construction problem, it is easy to see that L and U can be regarded as the minimum and maximum parameter values that satisfy

$$\frac{[(\hat{\theta}_1-\hat{\theta}_2)-L]^2}{Var(\hat{\theta}_1)+Var(\hat{\theta}_2)} = z^2_{\alpha/2} \qquad \text{and} \qquad \frac{[U-(\hat{\theta}_1-\hat{\theta}_2)]^2}{Var(\hat{\theta}_1)+Var(\hat{\theta}_2)} = z^2_{\alpha/2},$$

respectively. Let (l_1, u_1) and (l_2, u_2) be any two-sided $(1-\alpha)100$ percent confidence intervals for θ_1 and θ_2, respectively. Among the plausible values for θ_1 and θ_2 in each of the two intervals, the values closest to the minimum L and maximum U are respectively $l_1 - u_2$ and $u_1 - l_2$ in the spirit of the score-type confidence interval (Bartlett 1953). By the Central Limit Theorem, if we set $\theta_1 = l_1$ and $\theta_2 = u_2$, the variance estimates can now be recovered as $\hat{V}ar(\hat{\theta}_1) = (\hat{\theta}_1 - l_1)^2/z^2_{\alpha/2}$ and $\hat{V}ar(\hat{\theta}_2) = (u_2 - \hat{\theta}_2)^2/z^2_{\alpha/2}$ (Stapleton 1995). Accordingly, the lower limit is

$$L = \hat{\theta}_1 - \hat{\theta}_2 - \sqrt{(\hat{\theta}_1 - l_1)^2 + (u_2 - \hat{\theta}_2)^2} \tag{1}$$

and similarly, the upper limit is

$$U = \hat{\theta}_1 - \hat{\theta}_2 + \sqrt{(u_1 - \hat{\theta}_1)^2 + (\hat{\theta}_2 - l_2)^2}. \tag{2}$$

2.2. MOVER Fieller-type confidence interval (MOVER-R) To construct a confidence interval for $R = \lambda_2/\lambda_1$, first consider finding a confidence interval for $\lambda_2 - R\lambda_1$. Let L' and U' denote the lower and upper confidence limits for R respectively. For a given significance level α, these limits satisfy $Pr(L' \leq \lambda_2/\lambda_1 \leq U') = 1 - \alpha$, or equivalently,

$$\Pr(\lambda_2 - U'\lambda_1 \leq 0 \leq \lambda_2 - L'\lambda_1) = 1 - \alpha.$$

When values of L' and U' are fixed, we apply (1) to $\lambda_2 - L'\lambda_1$ and (2) to $\lambda_2 - U'\lambda_1$ with $\theta_1 = \lambda_2$ and $\theta_2 = \lambda_1$ and obtain

$$L' = \frac{\hat{\lambda}_2\hat{\lambda}_1 - \sqrt{(\hat{\lambda}_2\hat{\lambda}_1)^2 - l_1(2\hat{\lambda}_2 - l_1)[u_2(2\hat{\lambda}_1 - u_2)]}}{u_2(2\hat{\lambda}_1 - u_2)} \tag{3}$$

and

$$U' = \frac{\hat{\lambda}_2\hat{\lambda}_1 + \sqrt{(\hat{\lambda}_2\hat{\lambda}_1)^2 - u_1(2\hat{\lambda}_2 - u_1)[l_2(2\hat{\lambda}_1 - l_2)]}}{l_2(2\hat{\lambda}_1 - l_2)} \tag{4}$$

where $\hat{\lambda}_2 = X_2/t_2$, $\hat{\lambda}_1 = X_1/t_1$ and t_i is the sampling time frame for X_i, $i = 1, 2$. Other authors have arrived at the same set of equations as well (Li et al. 2010; Donner and Zou 2010; Zou and Donner 2010).

To obtain confidence interval for λ_2/λ_1 using (3) and (4), we require two separate confidence intervals, denoted by (l_1, u_1) and (l_2, u_2), for $\theta_1 = \lambda_2$ and $\theta_2 = \lambda_1$, respectively. We now list various formulae for the confidence limits (l_1, u_1) and (l_2, u_2) for the two individual Poisson rates when t_1, t_2 are the observed time frames for the two processes. They include

(1) the "Second Normal" interval (Byrne & Kabaila 2005):

$$l_i = \frac{X_i - \frac{1}{2} + z_{\alpha/2}\sqrt{X_i - \frac{1}{2}}}{t_i} \quad \text{and} \quad u_i = \frac{X_i + \frac{1}{2} + z_{\alpha/2}\sqrt{X_i + \frac{1}{2}}}{t_i}, \quad i = 1, 2.$$

(2) the Rao score interval (Altman et al. 2000):

$$l_i = \frac{X_i + \frac{1}{2}z_{\alpha/2}^2 - z_{\alpha/2}\sqrt{X_i + \frac{1}{4}z_{\alpha/2}^2}}{t_i} \quad \text{and} \quad u_i = \frac{X_i + \frac{1}{2}z_{\alpha/2}^2 + z_{\alpha/2}\sqrt{X_i + \frac{1}{4}z_{\alpha/2}^2}}{t_i}, \quad i = 1, 2.$$

(3) the Freeman and Tukey interval (Byrne & Kabaila 2005):

$$l_i = \frac{\frac{1}{4}[(\sqrt{X_i} + \sqrt{X_i+1} - z_{\alpha/2})^2 - 1]}{t_i} \quad \text{and} \quad u_i = \frac{\frac{1}{4}[(\sqrt{X_i} + \sqrt{X_i+1} + z_{\alpha/2})^2 - 1]}{t_i}, \quad i = 1, 2.$$

(4) The Jeffreys interval

A Bayesian confidence interval can be constructed from the Jeffrey's prior which is proportional to the square root of the determinant of the Fisher information matrix (Brown et al. 2003). The equal tailed Jeffrey's intervals for the Poisson rate is determined from the percentiles of the standard gamma distribution:

$$l_i = \Gamma_{\alpha/2, X_i+1/2, 1/t_i} \quad \text{and} \quad u_i = \Gamma_{1-\alpha/2, X_i+1/2, 1/t_i}, \quad i = 1, 2.$$

2.3. MOVER logarithmic transformation confidence interval (MOVER-DL)

A simple method to construct a confidence interval for the ratio λ_2/λ_1 is to first consider finding a confidence interval for $log(\lambda_2/\lambda_1)$ (i.e., $log\lambda_2 - log\lambda_1$). Let (L_{log}, U_{log}) be such an interval. From (1) and (2), we obtain a $100(1-\alpha)\%$ confidence interval for the log rate difference and so a $100(1-\alpha)\%$ confidence interval for λ_2/λ_1 is $[exp(L_{log}),\ exp(U_{log})]$. To obtain confidence interval for $log\lambda_2 - log\lambda_1$, we need two separate confidence intervals for $log\lambda_2$ and $log\lambda_1$. There are two common methods:

(A) *Delta method*

Let $\hat{\theta}$ be an estimator for a parameter θ of interest and let σ^2 be its variance. According to the delta method, we have $log(\hat{\theta}) \approx log(\theta) + (\hat{\theta} - \theta)/\theta$ and $Var[log(\hat{\theta})] \approx \sigma^2/\theta^2$ (Stamey & Hamilton 2006). It follows that a $100(1-\alpha)\%$ confidence interval for $log(\theta)$ is given by

$$[log(\hat{\theta}) - z_{\alpha/2}s/\hat{\theta}, log(\hat{\theta}) + z_{\alpha/2}s/\hat{\theta}],$$

where s^2 is an estimate of σ^2. For our two samples, we have $s_1^2 = \hat{\lambda}_1/t_1$, $\hat{\theta}_1 = \hat{\lambda}_1 = (X_1 + 0.5)/t_1$ (or $\hat{\theta}_1 = \hat{\lambda}_1 = X_1/t_1$), $s_2^2 = \hat{\lambda}_2/t_2$, $\hat{\theta}_2 = \hat{\lambda}_2 = (X_2 + 0.5)/t_2$ (or $\hat{\theta}_2 = \hat{\lambda}_2 = X_2/t_2$). It is not clear which of the two estimator for λ_i performs better as an interval estimator (Stamey & Hamilton 2006). Our simulation study also includes comparison of the two estimators: $\hat{\lambda}_i = (X_i + 0.5)/t_1$ or $\hat{\lambda}_i = (X_i)/t_i$, i=1,2.

(B) *Substitution method*

The second method is the simple substitution method. As the name suggests, it substitutes a $100(1-\alpha)\%$ confidence interval for θ, say $[l_\theta, u_\theta]$ by a $100(1-\alpha)\%$ confidence interval for $log\ \theta$ by

$$[log(l_\theta), log(u_\theta)].$$

Accordingly, the four types of confidence intervals for $\theta_1 = \lambda_2$ and $\theta_2 = \lambda_1$ described in Section 2.2 can also be applied to obtain a confidence interval for the ratio of the two rates.

2.4. Three other confidence intervals for the ratio of two Poisson rates

There are at least three additional sets of confidence limits for the ratio of two Poisson rates (Tang & Ng 2004; Price & Bonett 2000).

(i) *Mesially shrunk logit Wald method*

Some authors (see Tang & Ng 2004; Price & Bonett 2000) proposed the statistic $ln[(X_2 + 0.5)/(X_1 + 0.5)]$ was used to derive the following Wald confidence interval for $\phi = t_1\lambda_2/(t_2\lambda_1)$:

$$\phi_L = \frac{t_1}{t_2}\left(\frac{X_2+0.5}{X_1+0.5}\right) exp\left[-z_{\alpha/2}\sqrt{\frac{1}{X_1+0.5} + \frac{1}{X_2+0.5}}\right] \text{ and } \phi_U = \frac{t_1}{t_2}\left(\frac{X_2+0.5}{X_1+0.5}\right) exp\left[z_{\alpha/2}\sqrt{\frac{1}{X_1+0.5} + \frac{1}{X_2+0.5}}\right].$$

This implies that the limits of the confidence interval for $R = \lambda_2/\lambda_1$ are

$$L = \left(\frac{X_2+0.5}{X_1+0.5}\right) exp\left[-z_{\alpha/2}\sqrt{\frac{1}{X_1+0.5} + \frac{1}{X_2+0.5}}\right] \quad \text{and} \quad U = \left(\frac{X_2+0.5}{X_1+0.5}\right) exp\left[z_{\alpha/2}\sqrt{\frac{1}{X_1+0.5} + \frac{1}{X_2+0.5}}\right].$$

(ii) *Wilson's Binomial method*

Given $X_2 + X_1 = y$, X_2 follows the binomial distribution $B(y, \pi)$ with $\pi = \lambda_2/(\lambda_1 + \lambda_2)$. If $[\pi_L, \pi_U]$ ia a confidence interval for π, the confidence interval limits for $R = \lambda_2/\lambda_1$ are $L = (1 - \pi_U)/(\pi_U)$ and $U = (1 - \pi_L)/(\pi_L)$. Setting $\hat{\pi} = X_2/y$, we have

$$\pi_L = \tfrac{y}{y+z_{\alpha/2}^2} \left\{ \hat{\pi} + \tfrac{z_{\alpha/2}^2}{2y} - z_{\alpha/2} \sqrt{\tfrac{1}{y}[\hat{\pi}(1-\hat{\pi}) + \tfrac{z_{\alpha/2}^2}{4y}]} \right\} \quad \text{and} \quad \pi_U = \tfrac{y}{y+z_{\alpha/2}^2} \left\{ \hat{\pi} + \tfrac{z_{\alpha/2}^2}{2y} + z_{\alpha/2} \sqrt{\tfrac{1}{y}[\hat{\pi}(1-\hat{\pi}) + \tfrac{z_{\alpha/2}^2}{4y}]} \right\}.$$

For different time frames, the confidence interval limits for $\phi = t_1\lambda_2/(t_2\lambda_1)$ are $\phi_L = (t_1 - t_1\pi_U))/(t_2\pi_U)$ and $\phi_U = (t_1 - t_1\pi_L)/(t_2\pi_L)$. The corresponding limits for R can then be easily deduced.

(iii) *Agresti-Coull Binomial method*

We let $X_2 + X_1 = y$ as before and let $\hat{\pi}_\alpha = (y + 2)/(y + 4)$. The confidence limits from the Agresti-Coull Binomial method are

$$\pi_L = \hat{\pi}_\alpha - z_{\alpha/2} \sqrt{\tfrac{\hat{\pi}_\alpha(1-\hat{\pi}_\alpha)}{y+4}} \quad \text{and} \quad \pi_U = \hat{\pi}_\alpha + z_{\alpha/2} \sqrt{\tfrac{\hat{\pi}_\alpha(1-\hat{\pi}_\alpha)}{y+4}}.$$

The point estimate of the success probability is not the sample proportion, but one that often refers to as a modified proportion estimate where we "add two successes and add two failures" to the sample proportion. The confidence interval for the ratio of the two Poisson rates is then given by (L, U) as in (i) and (ii) above.

3 A Simulation Study

In this section, we evaluated the performance of different types of confidence intervals constructed using the various methods in the previous section. For a given set of values for t_i and λ_i, $i = 1, 2$, let L and U denote respectively, the lower and upper limit of the constructed confidence interval. Confidence intervals for estimating the ratio R constructed from different methods were compared using the following performance measures: exact coverage probabilities (ECPs), expected widths (EWs), mesial non-coverage probabilities (MNCP) and distal non-coverage probabilities (DNCP). We expect good methods for constructing confidence intervals have their ECPs close to the pre-specified $1 - \alpha$ level. When the ECPs are well controlled, one then prefers confidence intervals with shorter widths: i.e., smaller EW values. When the EW are smaller, one would also prefer $MNCP/NCP$ to be between 0.4 and 0.6. These measures are discussed in Newcombe (1998) and Krishnamoorthy and Thomson (2004), and are defined as follows

$$ECP = \sum_{k_1=0}^{\infty} \sum_{k_2=0}^{\infty} \frac{e^{-t_1\lambda_1}(t_1\lambda_1)^{k_1}}{k_1!} \frac{e^{-t_2\lambda_2}(t_2\lambda_2)^{k_2}}{k_2!} I\{R \in [L, U]\},$$

$$EW = \sum_{k_1=0}^{\infty}\sum_{k_2=0}^{\infty} \frac{e^{-t_1\lambda_1}(t_1\lambda_1)^{k_1}}{k_1!}\frac{e^{-t_2\lambda_2}(t_2\lambda_2)^{k_2}}{k_2!}(U-L),$$

$$MNCP = \sum_{k_1=0}^{\infty}\sum_{k_2=0}^{\infty} \frac{e^{-t_1\lambda_1}(t_1\lambda_1)^{k_1}}{k_1!}\frac{e^{-t_2\lambda_2}(t_2\lambda_2)^{k_2}}{k_2!}I\{R\in A_1\}, \text{ and}$$

$$DNCP = \sum_{k_1=0}^{\infty}\sum_{k_2=0}^{\infty} \frac{e^{-t_1\lambda_1}(t_1\lambda_1)^{k_1}}{k_1!}\frac{e^{-t_2\lambda_2}(t_2\lambda_2)^{k_2}}{k_2!}I\{R\in A_2\},$$

where

$$A_1 = \begin{cases} (0,L), & \text{when} \quad R>1; \\ (0,L)\bigcup(U,+\infty), & \text{when} \quad R=1; \\ (U,+\infty), & \text{when} \quad R<1; \end{cases} \qquad A_2 = \begin{cases} (U,+\infty), & \text{when} \quad R>1; \\ \emptyset, & \text{when} \quad R=1; \\ (0,L), & \text{when} \quad R<1; \end{cases}$$

Clearly, computing the exact coverage probability and the expected widths directly from the theoretical distribution involve infinite series and approximations. Alternatively, following Tang and Ng (2004), Ng and Tang (2005), Ng et al. (2007) and Tang et al. (2009), one may choose to perform, as we did here, a Monte Carlo simulation study to evaluate the various methods for constructing the intervals. The simulation studies were conducted with different parameter settings. In the first simulation study, we considered scenarios with different sampling time frames as measured by $d = t_2/t_1 = 0.5, 1.0, 2.0$ and λ_1 and λ_2 were generated from the uniform distributions $(0.5, 5)$ and $(5, 10)$ and different type 1 error rates $\alpha = 0.01, 0.05, 0.10, 0.15, 0.20$. Without loss of generality we assumed throughout that $t_1 = 1$. For a fixed α and each of the 6 combinations of the three d values and the 2 values from uniform variates, we used MATLAB to generate 1000 λ_1 and 1000 λ_2 values and each time computed the corresponding value of $R = \lambda_2/\lambda_1$. This procedure was repeated $M = 10000$ times to independently generate a value $X_1^{(m)}$ from Poisson(λ_1) and a value $X_2^{(m)}$ from Poisson($d\lambda_2$) and construct an α-sized confidence interval with limits $L^{(m)}$ and $U^{(m)}$. For each of the $3\times5\times1000\times2 = 30000$ sets of three d values, five α levels, 1000 λ_1 values and 1000 λ_2 values, we computed estimates $\widehat{ECP}$, $\widehat{EW}$, $\widehat{MNCP}$, $\widehat{DNCP}$ for the above 4 measures based on $M = 10000$ sets of $X_1^{(m)}$and $X_2^{(m)}$ values. The corresponding confidence limits $L^{(m)}$ and $U^{(m)}$ for each of the 13 methods listed in Table 1 were then computed and compared. The reader may write to the first author and request the code used in our simulation study.

Table 1. Summary of abbreviations for various confidence interval estimators

Abbreviation	Confidence interval CI
$Dlog1:1$	MOVER logarithmic transformed CI based on delta method ($\hat{\theta}_i = (X_i + 0.5)/t_i$)
$Dlog2:2$	MOVER logarithmic transformed CI based on delta method ($\hat{\theta}_i = (X_i/t_i)$)
$SNIlog:3$	MOVER Second Normal CI based on substitution method
$RSIlog:4$	MOVER Rao score CI based on substitution method
$FTIlog:5$	MOVER Freeman and Tukey CI based on substitution method
$FJIlog:6$	MOVER Jeffreys CI based on substitution method
FSNI: 7	MOVER Second Normal CI based on Fieller's theorem
FRSI: 8	MOVER Rao score CI based on Fieller's theorem
FFTI: 9	MOVER Freeman and Tukey CI based on Fieller's theorem
FJI:10	MOVER Jeffreys CI based on Fieller's theorem
AWM:11	CI based on mesially shrunk logit Wald method
WBM:12	CI based on Wilson's Binomial method
ACBM:13	CI based on Agresti-Coull Binomial method

We evaluate the performance of each method using conventional performance measures for interval estimators, see for example (Tang et al. 2009). As before let R be the ratio of the two poisson rates, let M be the number of repetitions used in the simulation, let $I(.)$ be the indicator function and let $(L^{(m)}, U^{(m)})$ be the confidence interval obtained from the m-th simulated run.

(1) *Empirical Coverage Probability*

The empirical coverage probability is defined by

$$\widehat{ECP} = \sum_{m=1}^{M} \frac{e^{-t_1\lambda_1}(t_1\lambda_1)^{X_1^{(m)}}}{X_1^{(m)}!} \frac{e^{-t_2\lambda_2}(t_2\lambda_2)^{X_2^{(m)}}}{X_2^{(m)}!} I\{R \in [L^{(m)}, U^{(m)}]\}.$$

For WBM and $ACBM$, whenever $X_1 = X_2 = 0$, we defined $L = 0$ and $U = \infty$; $U = \infty$ whenever $X_1 = 0$ but $X_2 > 0$; and $L = 0$ whenever $X_2 = 0$ but $X_1 > 0$. For ACBM, we set L to be the L of WBM whenever $U > 1$; and U to be the U of WBM whenever $L \leq 0$.

(2) *Expected Interval Width*

An obvious measure of the usefulness of the interval estimator is its expected width. To preserve invariance properties, we measured the width of the confidence interval on an alternative transformed scale as follows (Newcombe 2012):

$$\widehat{EW} = \sum_{m=1}^{M} \frac{e^{-t_1\lambda_1}(t_1\lambda_1)^{X_1^{(m)}}}{X_1^{(m)}!} \frac{e^{-t_2\lambda_2}(t_2\lambda_2)^{X_2^{(m)}}}{X_2^{(m)}!} \left[\frac{U^{(m)}}{1+U^{(m)}} - \frac{L^{(m)}}{1+L^{(m)}}\right].$$

When $X_1 = 0$ and $X_2 = 0$, the resulting confidence intervals from ACBM and WBM produced either infinite upper confidence limits or were very wide. Accordingly, we abandoned confidence intervals constructed from these methods for conditional expected confidence width calculation.

(3) *Empirical Mesial Non-Coverage Probabilities (MNCPs) and Distal Non-Coverage Probabilities (DNCPs)* These are relatively new ways to judge whether the method used to construct a confidence interval performs adequately by examining the interval location in terms of its mesial and distal non-coverage probabilities. The terms mesial and distal are defined relative to the true value of R. For $R > 1$, when the interval is too far to the right to include R, this is sometimes referred to as non-coverage at the left or mesial end of the interval. Conversely, when the interval is too far to the left to include R, this is sometimes referred to as non-coverage at the right or distal end of the interval. However, if $R < 1$, when the interval is too far to the right to include R, this is sometimes referred as non-coverage at the left or distal end of the interval. Conversely, when the interval is too far to the left to include R, this is sometimes referred to d as non-coverage at the right or mesial end of the interval. Consequently, the definitions of MNCP and DNCP need to be interchanged here. When R = 1, left and right non-coverage should be balanced. By definition, only mesial non-coverage can occur. The mesial non-coverage probabilities (MNCP) and distal non-coverage probabilities (DNCP) can be estimated by

$$\widehat{MNCP} = \sum_{m=1}^{M} \frac{e^{-t_1\lambda_1}(t_1\lambda_1)^{X_1^{(m)}}}{X_1^{(m)}!} \frac{e^{-t_2\lambda_2}(t_2\lambda_2)^{X_2^{(m)}}}{X_2^{(m)}!} I\{R \in A_1^{(m)}\}, \text{ and}$$

$$\widehat{DNCP} = \sum_{m=1}^{M} \frac{e^{-t_1\lambda_1}(t_1\lambda_1)^{X_1^{(m)}}}{X_1^{(m)}!} \frac{e^{-t_2\lambda_2}(t_2\lambda_2)^{X_2^{(m)}}}{X_2^{(m)}!} I\{R \in A_2^{(m)}\},$$

where

$$A_1^{(m)} = \begin{cases} (0, L^{(m)}), & \text{when} \quad R > 1; \\ (0, L^{(m)}) \bigcup (U^{(m)}, +\infty), & \text{when} \quad R = 1; \\ (U^{(m)}, +\infty), & \text{when} \quad R < 1; \end{cases} \qquad A_2^{(m)} = \begin{cases} (U^{(m)}, +\infty), & \text{when} \quad R > 1; \\ \emptyset, & \text{when} \quad R = 1; \\ (0, L^{(m)}), & \text{when} \quad R < 1; \end{cases}$$

The ratio $\widehat{MNCP}/(\widehat{MNCP}+\widehat{DNCP}) = \widehat{MNCP}/\widehat{NCP}$ clearly lies between 0 and 1 and provides an effective location assessment separate from the overall coverage assessment. This ratio measure is considered generally as satisfactory if it is between 0.4 and 0.6. We call the interval too mesially located if it is below 0.4 and too distally located if it is above 0.6. Further details are in Newcombe (1998, 2012).

Figures 1 to 3 display our simulation results using box plots for the various measures. We recall that each box in the box plots contains the middle 50% of the data points in a data set with the median highlighted, the upper edge of the box represents the 75th percentile of the data set, and the lower edge represents the 25th percentile. The whiskers extend to the minimum and maximum values in the data set, with the maximum extension bounded to be 1.5 times of the inter-quartile range.

Each figure has several subfigures. Each subfigure displays the box plots of the measure of interest for all 13 methods and numbered as in Table 1. Different figures correspond to different settings for the parameters in the simulation study when some of the parameters are fixed and, each subfigure corresponds a selected varying parameter. We note that when R = 1, only mesial non-coverage can occur and so in the middle panel of the 3rd row of Figure 2, all MNCP/NCP values should be 1 (Newcombe, 1998, 2012) and this is what the subfigure suggests.

Following Singer (2010), it is also helpful to investigate the effect of the Poisson rate on the performance of the various confidence intervals. Figure 4 displays results from a simulation study that briefly considers the case when $d = t_1 = t_2 = 1$, $\alpha = 0.05$ and $\lambda_1 = \lambda_2$. We generated $1000\lambda_1$ values from uniform $(0.5, 10)$ and used the same procedure as before to evaluate the performance of the confidence intervals. For all combinations of d, R and λ, we summarize the results in Table 2 in terms to mean coverage probability (MCP), minimum coverage probability (MinCP), mean expect width (MEW), mean $MNCP/NCP$. Figure 5 is a graphical representation of Table 2 when $\alpha = 0.2, 0.1, 0.05$ and 0.01.

We summarize our main findings from the simulation studies as follows.

- *(1) Effect of different sampling time frame ratios d:* Figure 1 shows the coverage probability, expected width and the ratio MNP/NCP for the 13 types of 95% confidence intervals for different sampling time frame ratios $d = 0.5, 1$ and 2. Confidence intervals constructed from FFTI: 9 are always liberal. The confidence intervals obtained from ACBM: 13 when $d = 2$ and from FTIlog: 5 when $d = 1$ are slightly liberal. The two methods RSIlog: 4 and FRSI: 8 outperform the others in the sense that the coverage probabilities on average are close to the nominal levels and expected widths are shorter than those constructed from other confidence intervals. For a pre-specified confidence level, the mean expected confidence width decreases as the sampling ratio d increases.

- *(2) Effect of different Poisson rates R:* Figure 2 summarizes results from the second simulation study with $\alpha = 0.05$ and $d = 1$ when $R = 0.5, 2/3, 1$ and $1.5, 2$. In the figure, $R < 1$ correspond to the case when $R = 0.5 and 2/3$, and $R > 1$ correspond to the case when $R = 1.5 and 2$. Except for the two mehtods FFTI: 9 and FTIlog: 5, we observe that all other methods seem robust to varying values of R. The expected widths of FJIlog: 6 and FJI: 10 are wider than those of the other confidence intervals. For the commonly used 95% confidence level and equal sampling time frames (d=1), the mean expected width decreases as the value of the ratio of the Poisson rates R increases.

- *(3) Effect of α:* As expected, from Figures 3, the medians of the expected widths increase with increasing nominal levels (or decreasing α values). When α values increase, SNIlog: 3, FTIlog: 5 and FSNI:7 tend to be slightly liberal.

- *(4) Effect of λ:* To better examine the effect of λ, the coverage probabilities and widths of the confidence intervals are plotted against the values of λ with $\alpha = 0.05$ and $d = 1$ in Figures 4. For $\lambda_i \in (0.5, 5)(i = 1, 2)$, FFTI: 9 and FTIlog: 5 are liberal and the expected widths of FJIlog: 6 and FJI: 10 are wider. For $\lambda_i \in (5, 10)(i = 1, 2)$, except AWM: 11, all other methods are robust. Further, the plots indicate that the expected widths of all the confidence intervals decrease when the common value of λ_1 and λ_2 increases.

- *(5) Effect of combination:* From Table 2, the $RSIlog$: 4 and $FRST$: 8 methods perform well in the sense that they (1) well control their expected coverage probabilities around the pre-assigned coverage level; (2) generally yield balanced mesial and distal non-coverage probabilities, and (3) have larger MinCP. These observations led us to recommend the hybrid Rao score confidence interval based on the Fieller's theorem and substitution method (i.e., $RSIlog$ and $FRSI$) for practical applications.

4 Examples

4.1. Breast cancer study

Our first application concerns a breast cancer study (Ng & Tang 2005). In the study, X_1 and X_2 were, respectively, the number of reported cancer cases in patients who were examined using X-ray fluoroscopy during treatment for tuberculosis and those who had not been examined using X-ray fluoroscopy. Here, $X_1 = 41$, $X_2 = 15$, $t_1 = 28010$, $t_2 = 19017$. The ratio between the incidence rates of receiving X-ray fluoroscopy and not receiving X-ray fluoroscopy is estimated to be 0.539. Table 3 reports the 95% confidence intervals for λ_2/λ_1 based on various methods. Since all resulting confidence intervals do not contain the value 1, our conclusion is that the incidence rate of breast cancer is greater for women who had been examined using X-ray fluoroscopy during treatment for tuberculosis that those who had not been examined using X-ray fluoroscopy. This result is the same as the one reported elsewhere (Ng et al. 2007), where their inference was based on the risk difference.

4.2. Coronary Heart Disease

Consider a prospective study examining the relationship of post-menopausal hormone use and coronary heart disease (CHD) (see Stampfer & Willett 1985). With postmenopausal hormone use in 54308.8 person years, there are 30 CHD cases; without postmenopausal hormone use in 51477.5 person-years, there are 60 CHD cases. In this study, we have $X_1 = 30$, $X_2 = 60$, $t_1 = 54308.8$, $t_2 = 51477.5$. The ratio between the incidence rate of CHD in post-menopausal hormone-use group and non-hormone-use group is estimated to be 2.11. Table 4 reports the 90% confidence intervals for λ_2/λ_1 based on various methods are reported. Since all resulting confidence intervals do not contain the value 1, our conclusion is that the incidence rates of CHD in the non-hormone-use group is higher than that in post-menopausal hormone-use group. This result agrees with the one reported elsewhere (Gu et al. 2008), where their inference was based on a hypothesis testing framework.

5 Conclusion

We proposed an unconditional MOVER method for constructing a confidence interval for the ratio of two Poisson rates by combining the two separate confidence intervals for the two individual Poisson rates. Specifically, we incorporated the MOVER method to construct confidence intervals for the ratio of two Poisson rates using the (i) Fieller's theorem; (ii) logarithmic transformation based on the delta method; and (iii) the substitution method. According to our simulation results, the MOVER Rao score confidence interval based on the Fieller's theorem and the substitution method outperform the rest in a number of ways. In particular, the method (1) adequately controls the expected coverage probabilities around the pre-assigned coverage level; (2) have shorter interval widths; (3) generally yields balanced mesial and distal non-coverage probabilities. Based on these empirical findings, we highly recommend the MOVER Rao score confidence intervals based on the Fieller's theorem and substitution method (i.e., $RSIlog$ and $FRSI$) for making inference on the ratio of two Poisson rates in practical applications.

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Figure 1: Box plots of coverage probability (top row), expected width (middle row) and the ratio $MNCP/NCP$ (bottom row) for the 13 CIs when $\alpha = 0.05$ and different sampling time frame ratios d.

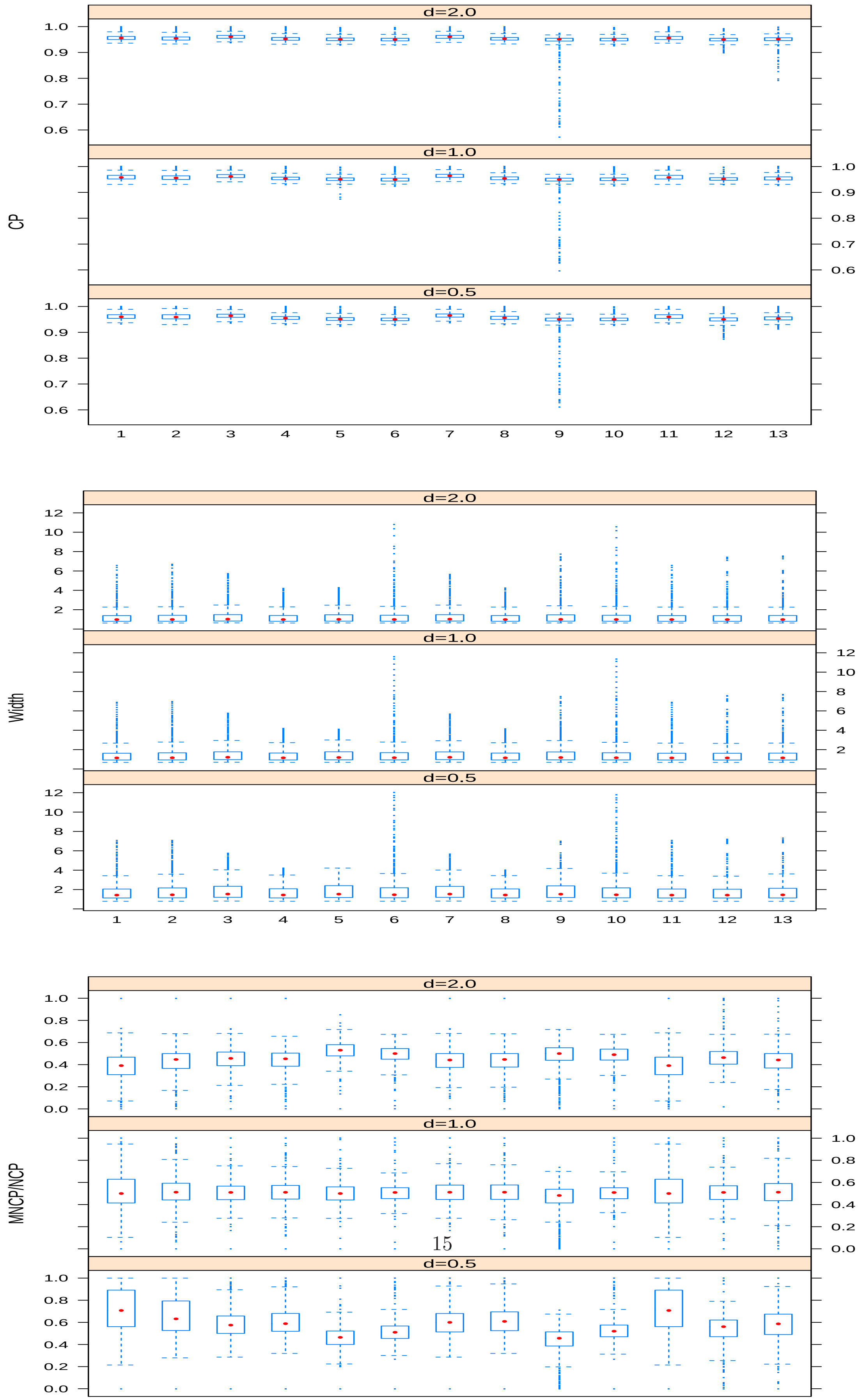

Figure 2: Box plots of coverage probability (top row), expected width of confidence interval (middle row) and the ratio $MNCP/NCP$ (bottom row) for the 13 CIs when $\alpha = 0.05$, $d = 1.0$ and different values of the Poisson rates Ratio R.

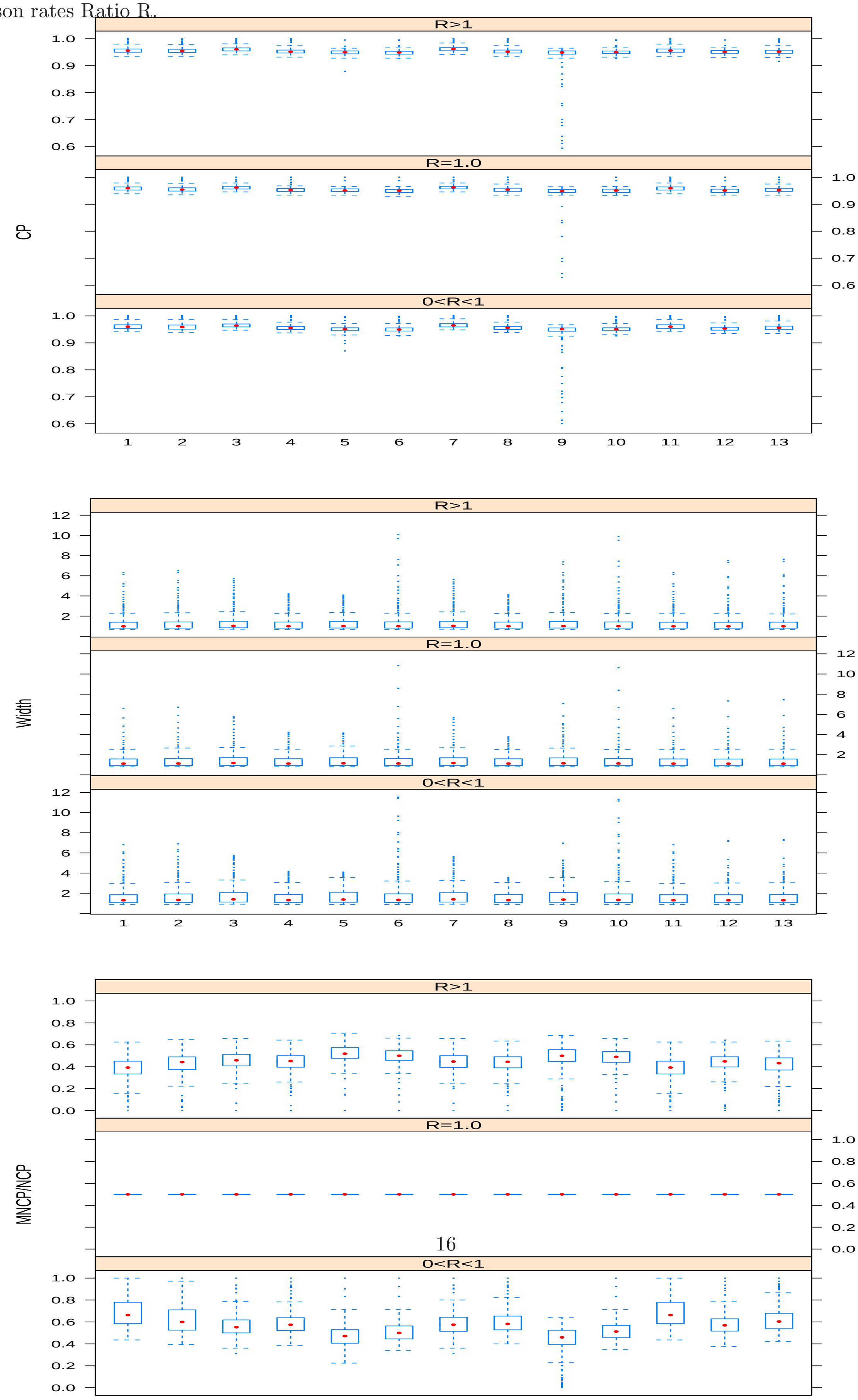

Figure 3: Box plots of coverage probability (top row), expected width of confidence interval (middle row) and the ratio $MNCP/NCP$ (bottom row) for the 13 CIs for different α levels.

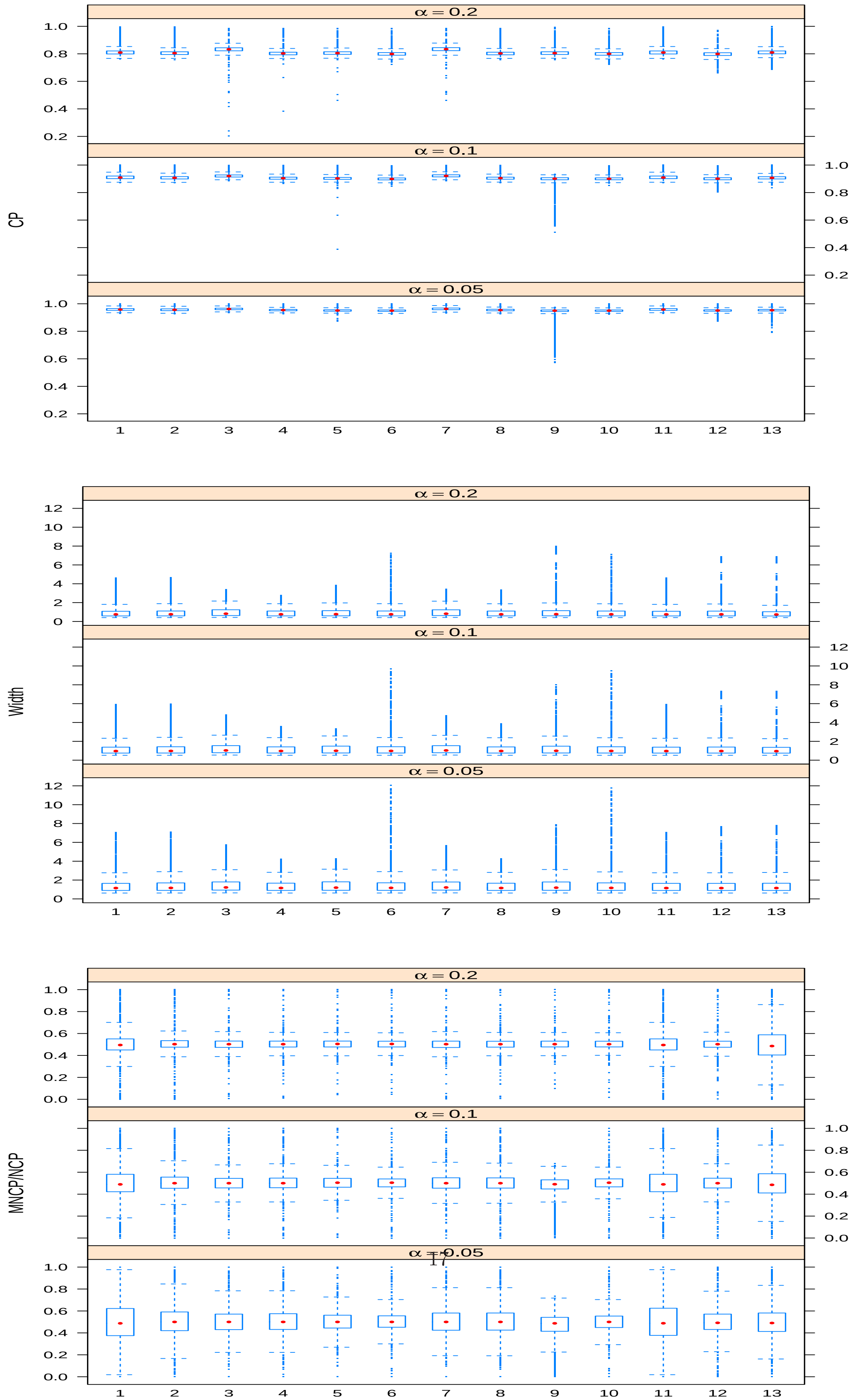

Figure 4: Plots of coverage probability (CP) and expected width (EW) of the 13 confidence intervals when $\alpha = 0.05$, $d = 1.0$ and $\lambda_1 = \lambda_2$ has values between 0.5 and 10:

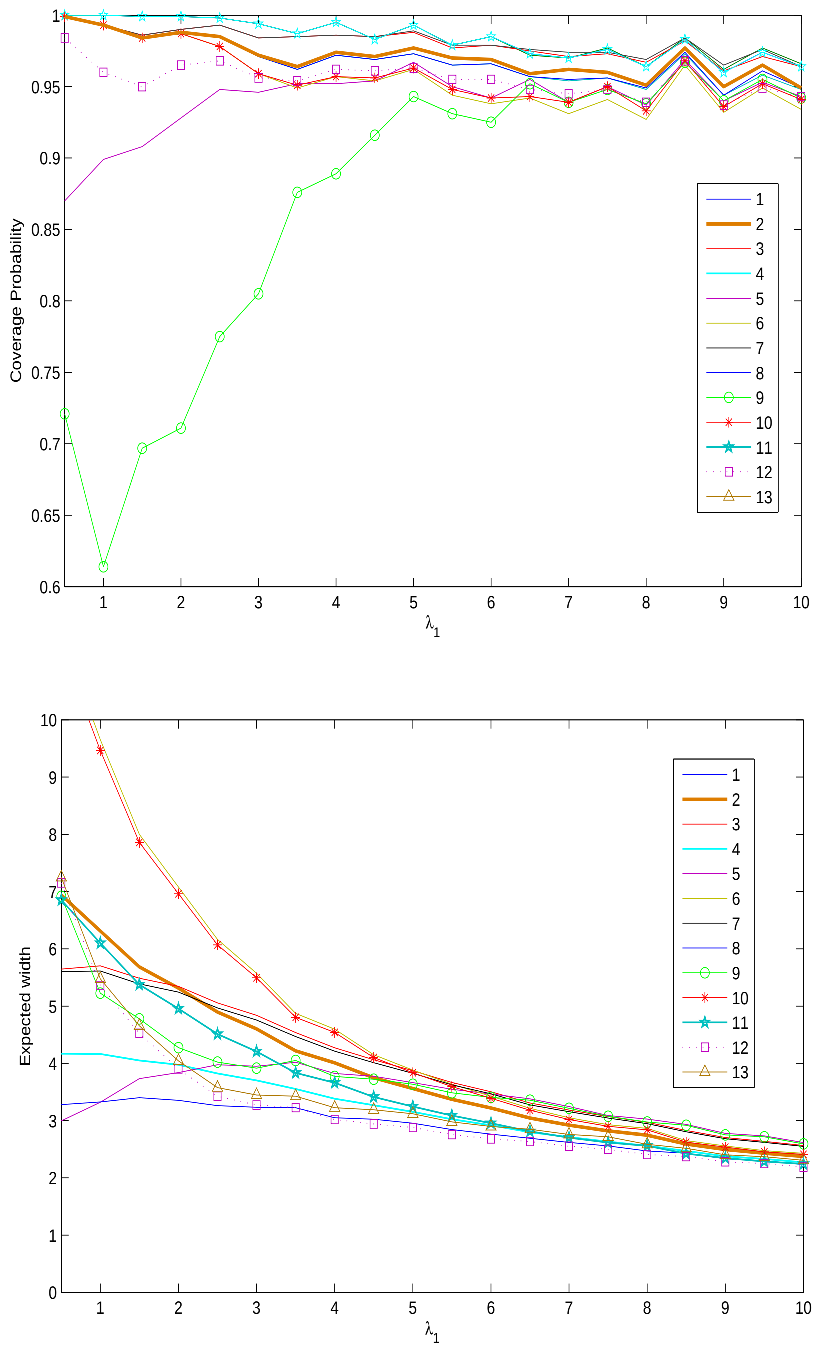

Table 2: Mean coverage probability(MCP), minimal coverage probability (MinCP), mean expected width (MEW) and mean ratio MNCP/NCP of the 13 types of confidence intervals for various parameter configurations when $\lambda_1 = \lambda_2$ is repeatedly sampled from a uniform distribution on $(0.5, 10)$ 1000 times.

$1-\alpha$	method	MCP	MinCP	MEW	mean $MNCP/NCP$
0.80	Dlog1: 1	0.815	0.769	1.012	0.483
	Dlog2: 2	0.810	0.765	1.051	0.489
	SNIlog: 3	0.831	0.449	1.113	0.495
	RSIlog: 4	0.804	0.643	0.988	0.493
	FTIlog: 5	0.806	0.666	1.079	0.496
	FJIlog: 6	0.800	0.734	1.113	0.496
	FSNI: 7	0.833	0.564	1.114	0.496
	FRSI: 8	0.805	0.760	0.983	0.494
	FFTI: 9	0.807	0.765	1.161	0.499
	FJI: 10	0.801	0.738	1.107	0.495
	AWM: 11	0.772	0.663	1.012	0.496
	WBM: 12	0.781	0.651	1.049	0.496
	ACBM: 13	0.784	0.664	0.997	0.495
0.85	Dlog1: 1	0.865	0.825	1.137	0.480
	Dlog2: 2	0.861	0.823	1.181	0.485
	SNIlog: 3	0.878	0.714	1.257	0.497
	RSIlog: 4	0.855	0.821	1.107	0.492
	FTIlog: 5	0.852	0.654	1.129	0.496
	FJIlog: 6	0.850	0.808	1.256	0.497
	FSNI: 7	0.879	0.713	1.250	0.494
	FRSI: 8	0.856	0.821	1.097	0.491
	FFTI: 9	0.840	0.511	1.359	0.561
	FJI: 10	0.851	0.814	1.248	0.495
	AWM: 11	0.836	0.683	1.137	0.496
	WBM: 12	0.825	0.680	1.162	0.498
	ACBM: 13	0.826	0.692	1.113	0.495
0.90	Dlog1: 1	0.914	0.879	1.299	0.478
	Dlog2: 2	0.912	0.875	1.349	0.482
	SNIlog: 3	0.922	0.891	1.429	0.496
	RSIlog: 4	0.906	0.874	1.260	0.489
	FTIlog: 5	0.903	0.714	1.300	0.496
	FJIlog: 6	0.899	0.856	1.444	0.497
	FSNI: 7	0.923	0.892	1.421	0.493
	FRSI: 8	0.906	0.874	1.244	0.488
	FFTI: 9	0.887	0.565	1.423	0.587
	FJI: 10	0.900	0.866	1.435	0.495
	AWM: 11	0.889	0.804	1.299	0.497
	WBM: 12	0.891	0.802	1.305	0.497
	ACBM: 13	0.884	0.814	1.273	0.495
0.95	Dlog1: 1	0.960	0.935	1.548	0.472
	Dlog2: 2	0.959	0.933	1.608	0.478
	SNIlog: 3	0.963	0.939	1.674	0.493
	RSIlog: 4	0.954	0.931	1.490	0.487
	FTIlog: 5	0.951	0.902	1.592	0.506
	FJIlog: 6	0.950	0.928	1.742	0.499
	FSNI: 7	0.964	0.941	1.664	0.490
	FRSI: 8	0.955	0.931	1.464	0.518
	FFTI: 9	0.934	0.607	1.664	0.652
	FJI: 10	0.950	0.929	1.729	0.498
	AWM: 11	0.943	0.629	1.548	0.495
	WBM: 12	0.933	0.629	1.518	0.497
	ACBM: 13	0.931	0.628	1.557	0.500
0.99	Dlog1: 1	0.993	0.982	2.035	0.463
	Dlog2: 2	0.993	0.982	2.113	0.462
	SNIlog: 3	0.993	0.983	2.123	0.479
	RSIlog: 4	0.991	0.980	1.922	0.472
	FTIlog: 5	0.990	0.975	2.079	0.514
	FJIlog: 6	0.989	0.976	2.359	0.498
	FSNI: 7	0.993	0.984	2.109	0.476
	FRSI: 8	0.992	0.980	1.881	0.471
	FFTI: 9	0.951	0.397	2.141	0.504
	FJI: 10	0.990	0.978	2.337	0.491
	AWM: 11	0.965	0.888	2.035	0.492
	WBM: 12	0.973	0.906	1.915	0.492
	ACBM: 13	0.978	0.559	2.115	0.629

Figure 5: Graphical Comparison of the Performance of the 13 Methods for Constructing Confidence Intervals using the 4 Measures in Table 2 (Triangle: MEW; Plus: minCP; Cross: MCP and Square: MNCP/NCP). The red horizontal line is the targeted Confidence Coefficient level: 80%(top left), 90%(top right), 95%(bottom left) and 99%(bottom right).

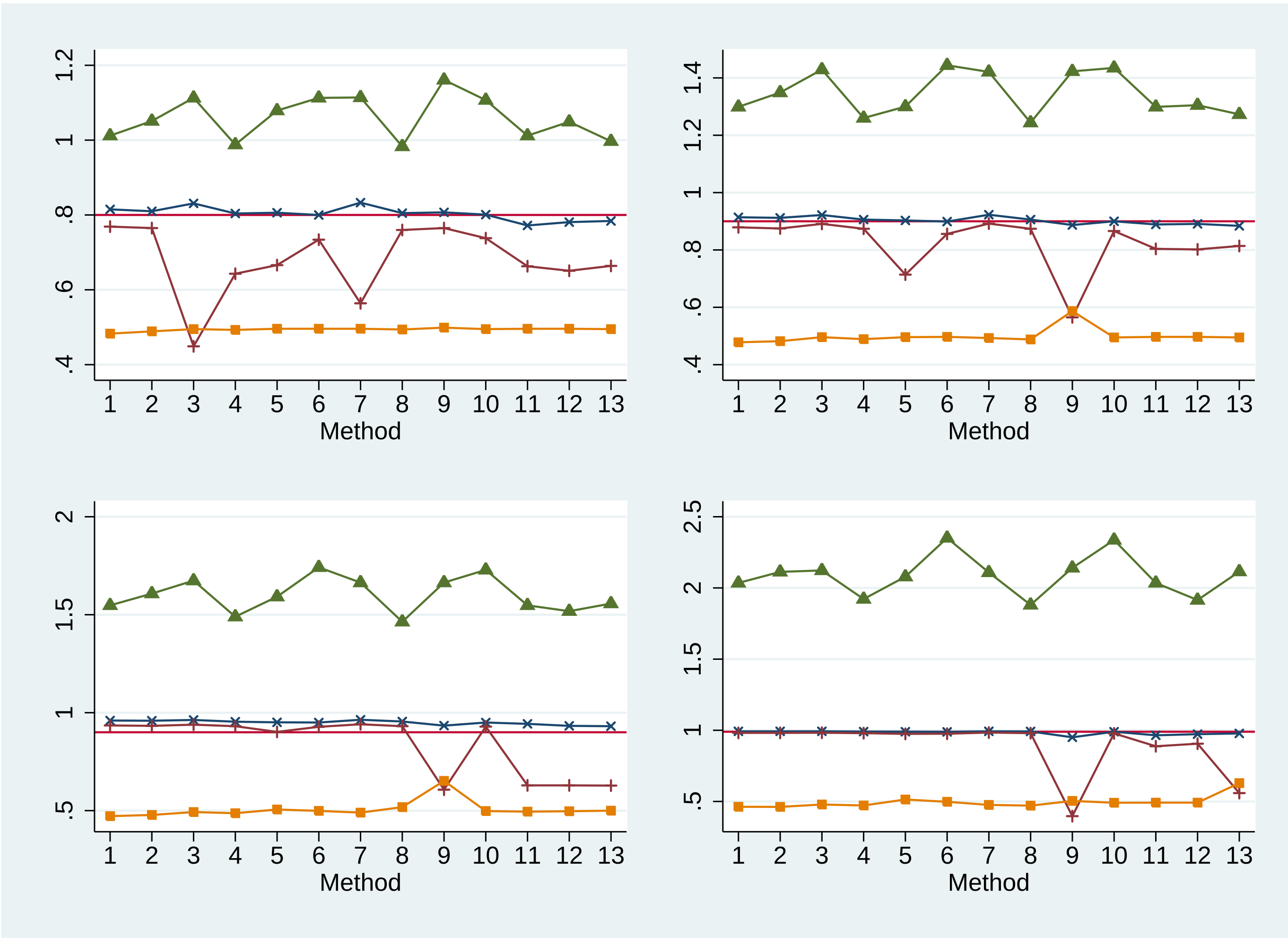

Table 3 Various 95% CIs for λ_2/λ_1 based on the Breast Cancer Data Set.

Method	Lower limit	Upper limit
Dlog1	0.3070	0.9859
Dlog2	0.2983	0.9735
SNIlog	0.2873	0.9882
RSIlog	0.2993	0.9682
FTIlog	0.2834	0.9538
FJIlog	0.2913	0.9548
FSNI	0.2889	0.9916
FRSI	0.3007	0.9714
FFTI	0.2850	0.9559
FJI	0.2928	0.9573
AWM	0.3070	0.9859
WBM	0.3008	0.9655
ACBM	0.3002	0.9711

Table 4 Various 90% CIs for λ_2/λ_1 based on the Coronary Heart Disease Study.

Method	Lower limit	Upper limit
Dlog1	1.4523	3.0154
Dlog2	1.4607	3.0480
SNIlog	1.4422	3.1071
RSIlog	1.4625	3.0470
FTIlog	1.4675	3.0849
FJIlog	1.4678	3.0660
FSNI	1.4408	3.1017
FRSI	1.4611	3.0424
FFTI	1.4666	3.0793
FJI	1.4667	3.0608
AWM	1.4523	3.0154
WBM	1.4636	3.0418
ACBM	1.4520	3.0022