行政院國家科學委員會專題研究計畫　期中進度報告

序貫實驗之第二參數的區間估計(1/2)

計畫類別：個別型計畫
計畫編號：NSC94-2118-M-004-002-
執行期間：94 年 08 月 01 日至 95 年 07 月 31 日
執行單位：國立政治大學統計學系

計畫主持人：翁久幸

報告類型：精簡報告
報告附件：出席國際會議研究心得報告及發表論文
處理方式：本計畫可公開查詢

中　華　民　國 95 年 5 月 2 日

Report for NSC project 94-2118-M-004-002-, 2005/8/1 - 2006/7/31

CORRECTED CONFIDENCE INTERVALS FOR SECONDARY PARAMETERS FOLLOWING SEQUENTIAL TESTS

1 Introduction

Suppose that a sequential test is carried out to compare two treatments. Then, following the test, there is interest in making valid inferences about the different parameters. For example, the primary parameter will typically be some measure of the treatment difference and there may be several secondary parameters too. These could be the individual treatment effects or the effects of baseline covariates, such as age, gender, disease stage, and so on. However, the use of a sequential design leads to the usual maximum likelihood estimators being biased and associated confidence intervals having incorrect coverage probabilities. One approach to the estimation problem is to study the approximate bias and sampling distributions of the maximum likelihood estimators.

Until recently, much of the research on estimation following sequential tests focussed on primary parameters. For example, an approach based on approximately pivotal quantities was developed by Woodroofe (1992) in the context of a single stream of normally distributed observations. Here, interest lay in providing an approximate confidence interval for a mean. The work in the present paper extends this approach in several respects. We consider bivariate normal data, where interest lies in estimating the mean of the second component of the process when the first is being monitored sequentially. Further, we consider the case of an unknown covariance matrix for the process.

One of the first papers to address the problem of estimation of secondary parameters following a sequential test was Whitehead (1986). For large samples, he showed how the bias of the estimator of the secondary parameter is related to that of the primary parameter, and then showed how a bias-adjusted estimator of the secondary parameter could be constructed. Gorfine (2001) has shown how a theorem of Yakir (1997) may be used to define an unbiased estimator of the secondary parameter. Related work has been carried out by Liu and Hall (2001). More recently, Hall and Yakir (2003) develop tests and confidence procedures in a very general context.

Several authors have developed methods for the construction of confidence intervals based on approximately pivotal quantities. Whitehead, Todd and Hall (2000) show how approximate confidence intervals may be obtained for a bivariate normal process when the covariance matrix is known and then show how these may be applied to problems in which approximate bivariate normality can be assumed. Liu (2004) considers a similar problem and shows how the appropriate corrections may be obtained using moment expansions, though the method developed appears to be somewhat restricted. In the present paper, we consider both the known and the unknown covariance matrix cases.

The approximately pivotal quantities are constructed by considering the bivariate version of the signed root transformation, and then using a version of Stein's (1981) identity and very weak expansions to determine the correction terms. The results in the known covariance matrix case are obtained by applying those of Weng and Woodroofe (2000) for the two-parameter exponential family. In the unknown covariance matrix case, similar ideas to those used by Weng and Woodroofe (2006) in the context of stationary autoregressive processes are used to establish the asymptotic sampling distribution of the renormalised pivotal quantity. The resulting correction terms have a simple form and complement the results of Whitehead (1986).

2 The general method for two-parameter exponential families

Let $X_j = (X_{1j}, X_{2j})'$ for $j = 1, \ldots, n$ be independent random vectors distributed according to a two-parameter exponential family with probability density

$$p_\theta(x) \quad = \quad e^{\theta' x - b(\theta)},$$

where $\theta = (\theta_1, \theta_2)' \in \Omega$ and Ω is the natural parameter space, assumed to be open. Let $L_n(\theta)$ denote the log-likelihood function based on $x_1, \ldots, x_n$, and consider the bivariate version of the signed root transformation (*e.g.* Bickel and Ghosh, 1990) given by

$$Z_{n1} = Z_{n1}(\theta) = \sqrt{2\{L_n(\hat{\theta}_n) - L_n(\tilde{\theta}_n)\}}\text{sign}(\theta_1 - \hat{\theta}_{n1}) \qquad (1)$$

and

$$Z_{n2} = Z_{n2}(\theta) = \sqrt{2\{L_n(\tilde{\theta}_n) - L_n(\theta)\}}\text{sign}(\theta_2 - \tilde{\theta}_{n2}), \qquad (2)$$

where $\hat{\theta}_n = (\hat{\theta}_{n1}, \hat{\theta}_{n2})'$ is the maximum likelihood estimator and $\tilde{\theta}_n = (\theta_1, \tilde{\theta}_{n2})'$ is the restricted maximum likelihood estimator for fixed θ_1. Then we have $L_n(\theta) = L_n(\hat{\theta}_n) - ||Z_n||^2/2$, where $Z_n = (Z_{n1}, Z_{n2})'$.

Consider a Bayesian model in which θ has a prior density ξ with compact support in Ω. Let E_ξ denote expectation in the Bayesian model in which θ is replaced with a random vector Θ and let E_ξ^n denote conditional expectation given $\{X_j, j = 1, \ldots, n\}$. Then the posterior density of Θ given $X_1, ..., X_n$ is $\xi_n(\theta) \propto e^{L_n(\theta)}\xi(\theta)$, and the posterior density of Z_n is

$$\zeta_n(z) \propto J(\hat{\theta}_n, \theta)\xi_n(\theta) \propto J(\hat{\theta}_n, \theta)\xi(\theta)e^{-\frac{1}{2}||z||^2}, \qquad (3)$$

where z and θ are related by (1) and (2), and J is a Jacobian term. From (3),

$$\zeta_n(z) = f_n(z)\phi_2(z), \quad z \in \Re^2, \qquad (4)$$

where ϕ_2 denotes the standard bivariate normal density and

$$f_n(z) \propto J(\hat{\theta}_n, \theta)\xi(\theta).$$

Let $N = N_a$ be a family of stopping times, depending on a design parameter $a \geq 1$. Suppose that

$$\frac{a}{N_a} \to \rho^2(\theta)$$

in P_θ-probability for almost every $\theta \in \Omega$, where ρ is a continuous function on Ω. Suppose also that, for every compact set $K \subseteq \Omega$, there is an $\eta > 0$ such that

$$P_\theta(N_a \leq \eta a) = o(a^{-q}), \tag{5}$$

uniformly with respect to $\theta \in K$ as $a \to \infty$, for some $q \geq 1/2$. Lemma 3 below follows from Theorem 12 of Weng and Woodroofe (2000). Moreover, by their Lemma 5 and (5) above, we have $P_\theta(B_N^c) = o(1/a)$.

Lemma 2.1 *The random vector $Z_N = (Z_{N1}, Z_{N2})'$ is uniformly integrable with respect to P_ξ.*

In what follows, suppose that θ_1 is the primary parameter and that θ_2 is a nuisance parameter. Then, for inference about θ_1, it is appropriate to use Z_{N1}. Now, from Proposition 2,

$$E_\xi^N\{h(Z_{N1})\} = \Phi^1 h + \frac{1}{\sqrt{N}}(\Phi^1 Uh)E_\xi^N\{\Gamma_{1,1}^\xi(\hat{\theta}_N, \theta)\} + \frac{1}{N}E_\xi^N\{Vh(Z_{N1})\Gamma_{2,11}^\xi(\hat{\theta}_N, \theta)\}.$$

To determine the mean correction term for Z_{N1}, we take $h(z) = z$, in which case $\Phi^1 h = 0$, $\Phi^1 Uh = 1$ and $Vh(z) = 0$. Similarly, for the variance correction term, we take $h(z) = z^2$, in which case $\Phi^1 h = 1$, $\Phi Uh = 0$ and $Vh(z) = 1$. Denote by b_{ij} the partial derivatives $b_{ij}(\theta) = \partial^{i+j} b(\theta)/\partial\theta_1^i \partial\theta_2^j$, and similarly for ξ_{ij}. Let $i_1(\theta) = (b_{20} - b_{11}^2/b_{02})(\theta)$, $i_2(\theta) = b_{02}(\theta)$, $\Gamma_{1,1}^\xi(\theta, \theta) = \lim_{\omega \to \theta} \Gamma_{1,1}^\xi(\omega, \theta)$ and $\Gamma_{2,11}^\xi(\theta, \theta) = \lim_{\omega \to \theta} \Gamma_{2,11}^\xi(\omega, \theta)$, and let $\kappa(\theta)$ and $m(\theta)$ be such that

$$E_\xi\{\rho(\theta)\Gamma_{1,1}^\xi(\theta, \theta)\} = \int\int_\Omega \xi(\theta)\kappa(\theta) d\theta_1 d\theta_2 \tag{6}$$

and

$$E_\xi\{\rho^2(\theta)\Gamma_{2,11}^\xi(\theta, \theta) - 2\rho(\theta)\kappa(\theta)\Gamma_{1,1}^\xi(\theta, \theta) + \kappa^2(\theta)\} = \int\int_\Omega m(\theta)\xi(\theta) d\theta_1 d\theta_2. \tag{7}$$

Then some algebra yields

$$\kappa(\theta) = \frac{(-b_{02}, b_{11}) \cdot \nabla\rho}{b_{02} i_1^{1/2}}(\theta) + \rho(\theta)\left\{\frac{(b_{02}, -b_{11}) \cdot \nabla i_1}{6 b_{02} i_1^{3/2}}(\theta) + \frac{(b_{02}, -b_{11}) \cdot \nabla i_2}{2 b_{02}^2 i_1^{1/2}}(\theta)\right\}. \tag{8}$$

A similar, but more complicated expression, may also be obtained for $m(\theta)$.

Now, define

$$Z_N^{(0)} = \frac{Z_{N1} - \hat{\mu}_N^{(0)}}{\hat{\tau}_N^{(0)}}, \tag{9}$$

where

$$\hat{\mu}_N^{(0)} = \begin{cases} \hat{\kappa}_N/\sqrt{a} & \text{if } |\hat{\kappa}_N| \leq a^{1/6}\{\log(a)\}^{-1}, \\ a^{-1/3}\{\log(a)\}^{-1} & \text{if } \hat{\kappa}_N > a^{1/6}\{\log(a)\}^{-1}, \\ -a^{-1/3}\{\log(a)\}^{-1} & \text{if } \hat{\kappa}_N < -a^{1/6}\{\log(a)\}^{-1}, \end{cases} \tag{10}$$

and

$$\hat{\tau}_N^{(0)} = \begin{cases} \sqrt{1 + \hat{m}_N/a} & \text{if } |\hat{m}_N| \leq \sqrt{a}/\log(a), \\ 1 & \text{otherwise,} \end{cases} \tag{11}$$

with $\hat{\kappa}_N = \kappa(\hat{\theta}_N)$ and $\hat{m}_N = m(\hat{\theta}_N)$.

Theorem 2.1 *Let h be a bounded function. Suppose that $\rho(\theta)$ is almost differentiable with respect to θ_1 and θ_2. If (5) holds with $q = 1$ and $\xi \in \Xi_0$, then*

$$E_\xi\{h(Z_N^{(0)})\} = \Phi^1 h + o(1/a).$$

So, an asymptotic level $1 - \alpha$ confidence interval for θ_1 is

$$\mathcal{I}_N = \{\theta_1 : |Z_N^{(0)}| \leq z_{\alpha/2}\}, \tag{12}$$

where $z_{\alpha/2}$ is the $100(\alpha/2)$-th percentile of the standard normal distribution.

3 The bivariate normal model with known covariance matrix

Suppose that $X_j = (X_{1j}, X_{2j})'$ for $j = 1, \ldots, n$ are independent random vectors from a bivariate normal distribution with mean vector $\theta = (\theta_1, \theta_2)'$ and covariance matrix

$$\Sigma = \begin{pmatrix} \sigma_1^2 & \gamma\sigma_1\sigma_2 \\ \gamma\sigma_1\sigma_2 & \sigma_2^2 \end{pmatrix}.$$

Let $\psi = (\sigma_1^2, \sigma_2^2, \gamma)'$. As before, let $N = N_a$ be the stopping time depending on a. Then, since the likelihood function is not affected by the use of a stopping time (*e.g.* Berger and Wolpert, 1984), the density of X_N is

$$\begin{aligned} p(x;\theta,\psi) = \exp\Bigg[& -N\log(2\pi) - \frac{N}{2}\log\{\sigma_1^2\sigma_2^2(1-\gamma^2)\} \\ & -\frac{1}{2\sigma_1^2\sigma_2^2(1-\gamma^2)}\Bigg\{\sigma_2^2\sum_{j=1}^N (x_{1j}-\theta_1)^2 + \sigma_1^2\sum_{j=1}^N (x_{2j}-\theta_2)^2 \\ & -2\gamma\sigma_1\sigma_2\sum_{j=1}^N (x_{1j}-\theta_1)(x_{2j}-\theta_2)\Bigg\}\Bigg]. \end{aligned} \tag{13}$$

If we assume that θ is unknown and ψ is known, then this model is a two-parameter exponential family with density that satisfies

$$\log p(x;\theta) \quad = \quad c(x) + N\theta_1 t_1 + N\theta_2 t_2 - Nb(\theta),$$

where $t_1 = \bar{x}_1/\{\sigma_1^2(1-\gamma^2)\} - \gamma\bar{x}_2/\{\sigma_1\sigma_2(1-\gamma^2)\}$, $t_2 = \bar{x}_2/\{\sigma_2^2(1-\gamma^2)\} - \gamma\bar{x}_1/\{\sigma_1\sigma_2(1-\gamma^2)\}$ and $b(\theta) = \theta'\Sigma^{-1}\theta/2$. Since $b(\theta)$ is quadratic in θ, both $i_1(\theta)$ and $i_2(\theta)$ defined in Section 2.1 are constants; and therefore $\kappa(\theta)$ in (8) reduces to

$$\kappa(\theta) = \frac{(-b_{02}, b_{11}) \cdot \nabla\rho(\theta)}{b_{02} i_1^{1/2}} = -\sigma_1\rho_{10}, \tag{14}$$

where $\rho_{ij} = \partial^{i+j}\rho/\partial\theta_1^i\partial\theta_2^j$ and the second equality in (14) follows since the stopping time N is assumed to depend only on $X_{11}, \ldots, X_{1N}$. Simple calculations show that the maximum likelihood estimator of θ is $(\hat{\theta}_1, \hat{\theta}_2) = (\bar{X}_{N1}, \bar{X}_{N2})$ and that the restricted maximum likelihood estimator of θ_2 given θ_1 is $\tilde{\theta}_2 = \tilde{\theta}_2(\theta_1) = \hat{\theta}_2 - \gamma\sigma_2(\theta_1 - \hat{\theta}_1)/\sigma_1$. By (1) and (2), it is straightforward to obtain

$$(Z_{N1}, Z_{N2}) = (\sqrt{N}\sigma_1^{-1}(\theta_1 - \hat{\theta}_1), \sqrt{N}\sigma_2^{-1}(1-\gamma^2)^{-1/2}\{\theta_2 - \hat{\theta}_2 - \gamma\sigma_2(\theta_1 - \hat{\theta}_1)/\sigma_1\}).$$

Furthermore, since the stopping time depends only on the first population, it can be shown that $m(\theta)$ in (7) satisfies

$$m(\theta) = \kappa^2(\theta) = (\sigma_1\rho_{10})^2.$$

Then, substituting these Z_{N1}, κ and m into (9), (10), and (11), by Theorem 2.1, the approximate level $1-\alpha$ confidence interval for θ_1 is as in (12).

For inference about the secondary parameter θ_2, it is not appropriate to use Z_{N2} as it depends on both θ_1 and θ_2. So, we consider the transformation

$$Z_{N1} = Z_{N1}(\theta) = \sqrt{2\{L_N(\hat{\theta}_{N1}, \hat{\theta}_{N2}) - L_N(\tilde{\theta}_{N1}, \theta_2)\}}\text{sign}(\theta_2 - \hat{\theta}_{N2}), \tag{15}$$

where $\tilde{\theta}_{N1} = \tilde{\theta}_{N1}(\theta_2)$ is the restricted maximum likelihood estimator of θ_1 given θ_2. Then $Z_{N1} = \sqrt{N}(\theta_2 - \hat{\theta}_2)/\sigma_2$. To obtain the mean correction term, we need to replace b_{ij} and ρ_{ij} in (14) with b_{ji} and ρ_{ji}. So,

$$E_\theta(Z_{N1}) \simeq \frac{1}{\sqrt{a}}\kappa(\theta) = \frac{1}{\sqrt{a}} \frac{(-b_{20}, b_{11}) \cdot \begin{pmatrix} \rho_{01} \\ \rho_{10} \end{pmatrix}}{b_{20}(b_{02} - \frac{b_{11}^2}{b_{20}})^{1/2}}(\theta) = -\frac{1}{\sqrt{a}}\sigma_1\gamma\rho_{10}. \tag{16}$$

Using a similar trick, we obtain

$$m(\theta) = \kappa^2(\theta) = (\sigma_1\gamma\rho_{10})^2. \tag{17}$$

With this Z_{N1} and its corresponding mean and variance corrections, we obtain a renormalised pivot $Z_N^{(0)}$ as in (9). Then, by Theorem 2.1, an asymptotic level $1-\alpha$ confidence interval for θ_2 is

$$\hat{\theta}_{N2} + \frac{\sigma_2}{\sqrt{N}}\hat{\mu}_N^{(0)} \pm \frac{\sigma_2}{\sqrt{N}}\hat{\tau}_N^{(0)} z_{\alpha/2}. \tag{18}$$

This interval is of the same form as the one obtained by Whitehead, Todd and Hall (2000). However, they use recursive numerical integration to calculate the correction terms instead of asymptotic approximations.

4 Extension to unknown covariance matrix case

In this section, we consider the following three cases:

C1. σ_1 and σ_2 are known, but γ is unknown;

C2. σ_1 and σ_2 are unknown, but γ is known;

C3. σ_1, σ_2 and γ are all unknown.

When the parameters are unknown, we estimate them by $\hat{\sigma}_i^2 = \sum_{j=1}^N (X_{ij} - \hat{\theta}_i)^2/(N-1)$ for $i = 1, 2$ and

$$\hat{\gamma} = \frac{\sum_{j=1}^N (X_{1j} - \hat{\theta}_1)(X_{2j} - \hat{\theta}_2)}{\sqrt{\sum_{j=1}^N (X_{1j} - \hat{\theta}_1)^2 \sum_{j=1}^N (X_{2j} - \hat{\theta}_2)^2}}.$$

As the main interest of this paper concerns inference about the secondary parameter θ_2, in the rest of the paper we let Z_{N1} be as in (15). So the corresponding $\kappa(\sigma_1, \gamma, \rho_{10})$ and $m(\sigma_1, \gamma, \rho_{10})$ are as in (16) and (17). For cases C1-C3, we consider $\hat{\kappa}_N^{(1)} = \kappa(\sigma_1, \hat{\gamma}, \hat{\rho}_{10})$, $\hat{\kappa}_N^{(2)} = \kappa(\hat{\sigma}_1, \gamma, \hat{\rho}_{10})$ and $\hat{\kappa}_N^{(3)} = \kappa(\hat{\sigma}_1, \hat{\gamma}, \hat{\rho}_{10})$, respectively; and correspondingly define $\hat{\mu}_N^{(k)}$ and $\hat{\tau}_N^{(k)}$ for $k = 1, 2, 3$ as in (10) and (11). Then, let

$$Z_N^{(1)} = \frac{Z_{N1} - \hat{\mu}_N^{(1)}}{\hat{\tau}_N^{(1)}} \tag{19}$$

and

$$Z_N^{(k)} = \frac{Z_{N1}(\hat{\sigma}_2) - \hat{\mu}_N^{(k)}}{\hat{\tau}_N^{(k)}} \tag{20}$$

for $k = 2, 3$, where $Z_{N1}(\hat{\sigma}_2) = \sqrt{N}(\theta_2 - \hat{\theta}_2)/\hat{\sigma}_2$. We will use $Z_N^{(k)}$ for $k = 1, 2, 3$ as pivotal quantities for cases C1, C2 and C3, respectively.

Define $\hat{\omega}_N = \hat{\sigma}_2^2/\sigma_2^2$. Then we can rewrite $Z_N^{(k)}$ for $k = 2, 3$ in (20) as

$$Z_N^{(k)} = \frac{(\frac{\sigma_2}{\hat{\sigma}_2})Z_{N1} - \hat{\mu}_N^{(k)}}{\hat{\tau}_N^{(k)}} = \frac{Z_{N1} - \hat{\mu}_N^{(k)}\hat{\omega}_N^{1/2}}{\hat{\omega}_N^{1/2}\hat{\tau}_N^{(k)}}. \tag{21}$$

In the rest of the paper, let Ξ denote the collection of all prior densities $\xi(\psi, \theta) = \xi_1(\psi)\xi_2(\theta)$ with compact support in $(0, \infty)^2 \times (-1, 1) \times \Omega$ for which ξ is twice differentiable almost everywhere under P_ξ and $\nabla^2\xi$ is bounded on its support.

Theorem 4.2 *Suppose that $\xi \in \Xi$ and that (5) holds with $q = 1$. Then, for $k = 2, 3$,*

$$\left| \int_{(0,\infty)^2 \times (-1,1)} \int_{\Omega} \left[E_{\psi,\theta}\{h(Z_N^{(k)})\} - \Phi^1 h - \frac{1}{a}(\Phi_4 h)\rho^2(\theta) \right] \xi(\psi,\theta) d\theta d\psi \right| = o(\frac{1}{a}) \tag{22}$$

for all bounded functions h.

The definition of Φ_4 and the proof are in Appendix A.4. Theorem 4.2 shows that $Z_N^{(k)}$ for $k = 2, 3$ are asymptotically distributed according to a t distribution with N degrees of freedom to order $o(1/a)$ in the very weak sense, since $\Phi^1 h + (\Phi_4 h)\rho^2(\theta)/a$ represents the first two terms in an Edgeworth-type expansion for the t distribution (*e.g.* Barndorff-Nielsen and Cox, 1989, Chap.2; Hall, 1992, Chap.2). Hence,

$$P_{\psi,\theta}\{|Z_N^{(k)}| \leq z\} = 2G_N(z) - 1 + o(1/a) \tag{23}$$

very weakly, where G_N denotes the t distribution with N degrees of freedom. So, an asymptotic level $1 - \alpha$ confidence interval for θ_2 is

$$\hat{\theta}_{N2} + \frac{\hat{\sigma}_2}{\sqrt{N}} \hat{\mu}_N^{(k)} \pm \frac{\hat{\sigma}_2}{\sqrt{N}} \hat{\tau}_N^{(k)} c_{N,\alpha/2},$$

where $c_{N,\alpha/2}$ is the $100(\alpha/2)$-th percentile of the t distribution with N degrees of freedom. Note that the form of the above interval is similar to one obtained by Keener (2005) using fixed θ expansions. However, his interval is only valid up to order $o(1/\sqrt{a})$ and only applicable to linear stopping boundaries.

The proof of Theorem 4.2 reveals that the correction term $(\Phi_4 h)\rho^2(\theta)/a$ in (22) arises from the use of $\hat{\omega}_N$. Since σ_2 is known for $Z_N^{(1)}$ in (19), this correction term vanishes in the asymptotic expansion for $Z_N^{(1)}$ and an immediate corollary to Theorem 4.2 is the following result.

Corollary 4.1 *Suppose that $\xi \in \Xi$ and that (5) holds with $q = 1$. Then*

$$\left| \int_{(0,\infty)^2 \times (-1,1)} \int_{\Omega} [E_{\psi,\theta}\{h(Z_N^{(1)})\} - \Phi^1 h] \xi(\psi,\theta) d\theta d\psi \right| = o(\frac{1}{a})$$

for all bounded functions h.

Therefore, $Z_N^{(1)}$ is asymptotically standard normal to order $o(1/a)$ in the very weak sense, and consequently

$$P_{\psi,\theta}\{|Z_N^{(1)}| \leq z\} = 2\Phi^1(z) - 1 + o(1/a)$$

very weakly. From this, one can set confidence intervals for θ_2 as in (18), but with $\hat{\mu}_N^{(0)}$ and $\hat{\tau}_N^{(0)}$ replaced by $\hat{\mu}_N^{(1)}$ and $\hat{\tau}_N^{(1)}$.

5 A practical example

In this section, we illustrate the proposed confidence interval method using the data obtained by Bellissant *et al.* (1997). This study was concerned with the treatment of infants of up to eight years of age suffering from gastroesophageal reflux. The infants were randomised between metoclopramide and placebo, which they received for a two-week period. The pH level in the oesophagus was measured continuously using a flexible electrode secured above the lower oesophageal sphincter. The primary response variable was the percentage reduction in acidity, measured by the proportion of time that pH < 4, over the two weeks of treatment.

The above variable was taken to be normally distributed and the triangular test (Whitehead, 1997, Chap.4) was used to monitor the study. Inspections were made after groups of about four patients and the trial was stopped after the seventh interim analysis, with the conclusion that metoclopramide is not an improvement over placebo. Although Bellissant *et al.* (1997) mention various normally distributed secondary response variables of interest, only standard analyses of them are carried out. For example, uncorrected confidence intervals are given for secondary parameters of interest. Thus, it is interesting to apply the corrected confidence intervals presented in Section 3 in this case.

In order to illustrate the confidence interval method, we assume that there is a single secondary response variable, the proportion of time that pH < 4 on day 14, and that the patients arrive in pairs, with one patient in each pair being assigned to metoclopramide and the other to placebo. The trial data give the estimates $\hat{\theta}_1 = 0.3$, $\hat{\theta}_2 = 0.07$, $\hat{\sigma}_1 = 0.5$ and $\hat{\sigma}_2 = 0.1$. To simulate the trial, we treated these values as the true values for the parameters. Further, since the sample covariance matrix was not available, we simulated the trial when $\gamma = 0.4$ and $\gamma = 0.8$, as for the two sequential tests in Section 4. As in the original trial of Bellissant *et al.* (1997), we use a one-sided triangular test to test $H_0 : \theta_1 = 0$ against $H_1 : \theta_1 > 0$ and choose the design parameters so that it has significance level 5% and 95% power for $\theta_1 = 0.5$.

Let m_a denote the group size, possibly depending on $a > 0$. Then the stopping time for the above triangular test is essentially of the form

$$N = \inf\{n \geq 1 : m_a | n, \quad S_{n1}/\hat{\sigma}_1 \geq a + bn - 0.583 \quad \text{or} \quad S_{n1}/\hat{\sigma}_1 \leq -a + 3bn + 0.583\},$$

where $m_a|n$ means that m_a divides n and S_{n1} denotes the sum of the first n differences in response between metoclopramide and placebo. Values are chosen for the parameters $a > 0$ and $b > 0$ in order to satisfy the error probability requirements, and the number 0.583 is a correction for overshoot of the stopping boundaries due to the discreteness of the inspection process (*e.g.* Whitehead, 1997, Chap.4). Upon termination of the test, H_0 is rejected if $S_{N1}/\hat{\sigma}_1 \geq a + bN - 0.583$ and accepted if $S_{N1}/\hat{\sigma}_1 \leq -a + 3bN + 0.583$. Now, the above stopping time may be rewritten as

$$N = \inf\{n \geq 1 : m_a | n \quad \text{and} \quad nq(\hat{\theta}_{n1}/\hat{\sigma}_1) \geq a - 0.583\}, \tag{24}$$

where $q(y) = \max(y-b, 3b-y)$. Note that (24) is a special case of more general stopping times studied by, for example, Morgan (2003). So we have $a/N \to \rho^2$, where $\rho = \max(\sqrt{\theta_1/\sigma_1 - b}, \sqrt{3b - \theta_1/\sigma_1})$, provided that $m_a = o(a)$. As in Bellissant *et al.* (1997), we take $a = 5.495$ and $b = 0.2726$. These values may be obtained using PEST 4 (Brunier and Whitehead, 2000). Since the data are being monitored after groups of four patients, we have $m_a = 2$.

In table below, we report the probabilities of rejecting H_0, that is, the power, the expected numbers of pairs of patients, and the coverage probabilities using Z_{N1} and $Z_N^{(3)}$, all of the results being based on 10,000 replications. Although the simulated sequential test satisfies the power requirement for $\theta_1 = 0.5$, it is a little conservative. This is because the above stopping time is not exactly the same as the original. Now, we know from Section 4 that the confidence intervals based on Z_{N1} have coverage probabilities below the nominal values and that those based on $Z_N^{(3)}$ have roughly the correct coverage probabilities. The results in table show that the use of $Z_N^{(3)}$ leads to coverage probabilities which are usually quite close to the nominal values, especially given the small sample sizes. Note that, since our theory has been developed for the case where $\rho = \rho(\theta_1)$, when calculating the correction terms, σ_1 has been replaced with its estimate except in terms involving $\hat{\rho}$, when its true value is used.

Table 5. Triangular test with unknown σ_1, σ_2 and γ; replicates=10,000.
($\pm$ means 1.96 standard deviations)

			Z_{N1}		$Z_N^{(3)} : t_N$		$Z_N^{(3)} : t_{a/\hat{\rho}^2}$	
$(\theta_1, \theta_2, \gamma)$	Power	$E_{\psi,\theta}(N)$	90%	95%	90%	95%	90%	95%
(0.00, 0.07, 0.40)	0.021	7.43	0.807	0.864	0.848	0.921	0.892	0.935
(0.00, 0.07, 0.80)	0.021	7.43	0.815	0.867	0.857	0.919	0.896	0.936
(0.30, 0.07, 0.40)	0.574	10.49	0.826	0.885	0.866	0.927	0.894	0.949
(0.30, 0.07, 0.80)	0.574	10.49	0.780	0.849	0.860	0.921	0.892	0.956
(0.50, 0.07, 0.40)	0.956	8.17	0.818	0.877	0.860	0.926	0.893	0.942
(0.50, 0.07, 0.80)	0.956	8.17	0.812	0.867	0.859	0.923	0.896	0.945
$\pm$			0.006	0.004	0.006	0.004	0.006	0.004

Returning to the actual trial, a standard analysis gives an uncorrected confidence interval for θ_2 of (0.018, 0.122), whereas the corrected confidence interval is (0.008, 0.124) when $\gamma = 0.4$ and (0.002, 0.122) when $\gamma = 0.8$. So the approach is useful in practice, especially if the correlation coefficient is large.

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