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Confidence intervals for treatment effect from restricted maximum likelihood

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ABSTRACT

An explicit form of confidence intervals for the treatment effect in random effects meta-analysis model obtained from Harville–Jeske–Kenward–Roger approach is given. These restricted likelihood based intervals are compared to alternative procedures commonly used in collaborative studies when the number of participants is small and study-specific variances are heterogeneous. Monte Carlo simulation experiments show that the former intervals have quite conservative coverage probabilities and favor the latter intervals.

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1. Confidence estimation in meta-analysis problems

The subject of interest here is confidence intervals for the common mean when several different studies, methods, instruments or laboratories measure a given property of the same material or the difference between two treatments. The combination of such measurements to allow statistical analysis of several individual studies is a goal of meta-analysis. Although some debate concerning advantages of random effects models in meta-analysis continues (see Borenstein et al., 2009), the following heterogeneous model has become a common tool of choice.

Denote by n_i the number of observations made in the laboratory i, $i=1,\dots,p$. In interlaboratory studies applications which are of interest here, p is not large. As a matter of fact, the comparison of merely two methods ($p=2$) is a frequent problem in metrology. Rukhin (2009) discusses some practical examples arising in interlaboratory studies where this problem appears.

Partly for lack of better information, the observations are supposed to follow a Gaussian distribution as in the model below. Namely, the observed data x_{ik}, $k=1,\dots,n_i$, is assumed to have the form

$$x_{ik}=\mu+\ell_i+\epsilon_{ik},\quad i=1,\dots,p, \tag{1}$$

where μ is the treatment effect, common mean or the property value, ℓ_i represents the study (or method) effect, which is normal with mean 0 and unknown variance σ^2. The independent normal, zero mean random errors ϵ_{ik}, have unknown (different) variances τ_i^2. For a fixed i, $x_i=\sum_k x_{ik}/n_i$ is normally distributed with the mean μ and the variance $\sigma^2+\sigma_i^2$, where $\sigma_i^2=\tau_i^2/n_i$. If $\sigma^2+\sigma_i^2$ were known up to a factor, then the least squares estimator of μ could be used, $\tilde{\mu}=\sum_i \omega_i x_i$, with

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normalized weights

$$\omega_i = \frac{1}{\sigma^2+\sigma_i^2}\left[\sum_j \frac{1}{\sigma^2+\sigma_j^2}\right]^{-1}. \tag{2}$$

Then

$$\mathrm{Var}(\tilde{\mu}) = \Phi = \left[\sum_i \frac{1}{\sigma^2+\sigma_i^2}\right]^{-1}. \tag{3}$$

Following common practice, the same form of weighted statistic is used in which the weights themselves are estimated. In some problems of meta-analysis the sample sizes n_i are not available, but when they are, the classical unbiased statistic $s_i^2 = \sum_j (x_{ij}-x_i)^2/[n_i(n_i-1)]$ has the distribution $\sigma_i^2\chi^2(v_i)/v_i$, $v_i = n_i-1$, and is independent of x_i and s_j^2, $j \neq i$. This is the situation studied in this paper. Although σ^2 can be treated as a possibly negative variance component such that $\sigma^2+\sigma_i^2>0$, our σ^2 has the meaning of variance so that it must be non-negative.

To estimate σ's the restricted maximum likelihood estimator (REML) is commonly employed. It is well known that the plug-in version of (3), which replaces the unknown $\sigma^2,\sigma_1^2,\ldots,\sigma_p^2$ by REML statistics $\tilde{\sigma}^2,\tilde{\sigma}_1^2,\ldots,\tilde{\sigma}_p^2$ such that $E(\tilde{\sigma}^2+\tilde{\sigma}_i^2) \leq \sigma^2+\sigma_i^2$, underestimates the variance of the corresponding common mean estimator (Li et al., 1994). Our goal is to derive REML based confidence intervals for the treatment effect in model (1) which includes corrections to the traditional method by using Harville–Jeske–Kenward–Roger approach.

The organization of this paper is as follows. In Section 2 the method of Harville and Jeske (1992) and Kenward and Roger (1997) to obtain confidence intervals is reviewed. Explicit formulas for all REML related characteristics are found there. The confidence intervals are derived in Section 3 and are compared via a Monte Carlo study in Section 4. All mathematical derivations are collected in Appendix.

2. Restricted maximum likelihood method: variance approximations and information matrix

In a general context of mixed effects linear models, Harville and Jeske (1992, Section 4.2) suggested an estimator of the variance of a sample counterpart of the least squares statistic, which in our case is the weighted average

$$\tilde{x} = \sum_i x_i\tilde{\omega}_i = \tilde{\Phi}\sum_i \frac{x_i}{\tilde{\sigma}^2+\tilde{\sigma}_i^2}$$

with $\tilde{\omega}_i = (\tilde{\sigma}^2+\tilde{\sigma}_i^2)^{-1}/\sum_j(\tilde{\sigma}^2+\tilde{\sigma}_j^2)^{-1} = (\tilde{\sigma}^2+\tilde{\sigma}_i^2)^{-1}\tilde{\Phi}$. They proposed the use of the REML variances estimators and gave two following approximations based on Taylor's formula or the propagation-of-error method. The first one deals with the mean squared difference between $\tilde{x}$ and $\tilde{\mu}$

$$E(\tilde{x}-\tilde{\mu})^2 \approx \mathrm{tr}(\mathcal{V}\Lambda). \tag{4}$$

Here $\mathcal{V}$ is the mean squared error matrix of the random vector $(\tilde{\sigma}^2,\tilde{\sigma}_1^2,\ldots,\tilde{\sigma}_p^2)$, and Λ is the covariance matrix of the gradient $(\tilde{\mu}'_0,\tilde{\mu}'_1,\ldots,\tilde{\mu}'_p)^T$, $\partial\sigma_0^2 = \partial\sigma^2$. The exact form of the elements of these two matrices is given later in this section. This approximation was originally introduced by Kackar and Harville (1984).

The second approximation corrects for the bias of the plug-in estimator $\tilde{\Phi}$ of Φ

$$E\tilde{\Phi} \approx \Phi + \tfrac{1}{2}\,\mathrm{tr}(\mathcal{V}H) = \Phi - \mathrm{tr}(\mathcal{V}\Lambda). \tag{5}$$

Here H is the Hessian of Φ, which is a negative semidefinite matrix, evaluated at $\sigma^2,\sigma_1^2,\ldots,\sigma_p^2$. In the model (1), $\Lambda = -H/2$. The formula (5) requires (approximate) unbiasedness of $(\tilde{\sigma}^2,\tilde{\sigma}_1^2,\ldots,\tilde{\sigma}_p^2)$, so that the linear term in $(\tilde{\sigma}^2-\sigma^2,\tilde{\sigma}_1^2-\sigma_1^2,\ldots,\tilde{\sigma}_p^2-\sigma_p^2)$ can be neglected. Since $\tilde{x}$ is an unbiased estimator of μ, such that $\tilde{x}-\tilde{\mu}$ is uncorrelated with $\tilde{\mu}$, one has $\mathrm{Var}(\tilde{x}) = E(\tilde{x}-\tilde{\mu})^2+\Phi$. This identity suggests the formula

$$\widehat{\mathrm{Var}}(\tilde{x}) = \tilde{\Phi} + 2\,\mathrm{tr}(\tilde{\mathcal{V}}\tilde{\Lambda}), \tag{6}$$

where $\tilde{\mathcal{V}}$ is the estimated mean squared error matrix of $(\tilde{\sigma}^2,\tilde{\sigma}_1^2,\ldots,\tilde{\sigma}_p^2)$, and $\tilde{\Lambda}$ has a similar meaning.

The variance estimator (6) was also recommended by Kenward and Roger (1997) who gave a formalization of these approximations in more general mixed effects linear models when the inverse of the restricted likelihood information matrix $\mathcal{J}$ is used in lieu of $\mathcal{V}$. Via a Monte Carlo study they demonstrated good performance of the resulting variance estimators and test statistics in several settings more general than (1). These approximations are implemented in the SAS/STAT@ procedure "MIXED" (SAS 9.1.3 Help and Documentation, Cary, NC: SAS Institute Inc., 2000–2004).

Because the matrices $\mathcal{V}$ and $\Lambda \neq 0$ are positive semidefinite, $\mathrm{tr}(\mathcal{V}\Lambda) > 0$, and Eq. (4) confirms negative bias of the estimator $\tilde{\Phi}$. However in our model all non-negative estimators of σ^2 are biased although $(\tilde{\sigma}_1^2,\ldots,\tilde{\sigma}_p^2)$ can be assumed to be an (approximately) unbiased estimator of $(\sigma_1^2,\ldots,\sigma_p^2)$. To adjust for the former fact, the formula

$$E\tilde{\Phi} \approx \Phi + \Upsilon\Phi^2\sum_i \frac{1}{(\sigma^2+\sigma_i^2)^2} - \mathrm{tr}(\mathcal{V}\Lambda), \quad \Upsilon = E(\tilde{\sigma}^2-\sigma^2)$$