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Simultaneous confidence bands for all contrasts of three or more simple linear regression models over an interval

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ABSTRACT

Simultaneous confidence intervals are used in Scheffé (1953) to assess any contrasts of several normal means. In this paper, the problem of assessing any contrasts of several simple linear regression models by using simultaneous confidence bands is considered. Using numerical integration, Spurrier (1999) constructed exact simultaneous confidence bands for all the contrasts of several regression lines over the whole range $(-\infty, \infty)$ of the explanatory variable when the design matrices of the regression lines are all equal. In this paper, a simulation-based method is proposed to construct simultaneous confidence bands for all the contrasts of the regression lines when the explanatory variable is restricted to an interval and the design matrices of the regression lines may be different. The critical value calculated by this method can be as close to the exact critical value as required if the number of replications in the simulation is chosen sufficiently large. The methodology is illustrated with a real problem in which sizes of the left atrium of infants in three diagnostic groups (severely impaired, mildly impaired and normal) are compared.

1. Introduction

There is a rich literature concerning multiple comparison of several normal means; see for example Miller (1981), Hochberg and Tamhane (1987), Hsu (1996), and Benjamini and Braun (2002). One of the most famous procedures is Scheffé (1953) which allows any contrasts of the normal means to be assessed by using simultaneous confidence intervals. This paper focuses on the problem of assessing any contrasts of several simple linear regression models, which generalises the problem of assessing any contrasts of several normal means. Spurrier (1999) was the first to study this problem by constructing simultaneous confidence bands for all contrasts of several simple linear regression models but under some restrictive assumptions. His work was followed by Spurrier (2002), Bhargava and Spurrier (2004), and Liu et al. (2004, 2007, 2009) among others who constructed simultaneous confidence bands for finite, such as pairwise and treatment-control, comparisons of several simple or multiple linear regression models.

Construction and application of confidence bands for one single linear regression model have been extensively studied by Working and Hotelling (1929), Gafarian (1964), Wynn and Bloomfield (1971), Bohrer and Francis (1972), Casella and Strawderman (1980), Uusipaikka (1983), Naiman (1986), Sun and Loader (1994), Sun et al. (1999), Efron (1997), Al-Saidy et al. (2002), Piegorsch et al. (2005), and Liu et al. (2005, 2008) and Liu and Hayter (2007), to name just a few.

Many large clinical studies compare two or more dose levels with a placebo control using several hundred or thousand patients. The primary and secondary study objectives (and thus the comparisons of interest) are often required to be

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specified in advance before study begins. Multiple test procedures tailored to these objectives are applied to guarantee a strict type I error rate control. In addition, post hoc analysis (also called data snooping) are often conducted to investigate the new treatment in a variety of different subgroups, which are often defined only after the primary data analysis. Examples of subgroups include age groups, disease severity at the beginning of study, races, gender, etc. or combinations of these. Given the confirmatory environment of later phase clinical trials, simultaneous confidence bands for all contrast of several linear regression models are therefore needed. These confidence bands are also useful when comparing the treatment effect of a new compound as a function of a covariate other than dose for several subgroups of patients; see the example in Section 4.

To be specific, suppose observations (x_{ij}, y_{ij}) are available from k $(k \geq 3)$ simple linear regression models

$$y_{ij} = \alpha_i + \beta_i x_{ij} + \epsilon_{ij}, \quad j = 1, \ldots, n_i,\ i = 1, \ldots, k,$$

where $\mathbf{b}_i = (\alpha_i, \beta_i)^T$ are the unknown regression coefficients of the ith regression line, and ϵ_{ij} are assumed to be independently and identically distributed $N(0, \sigma^2)$ random errors with $\sigma^2 > 0$ unknown. The design matrix for the ith regression line is given by $X_i = (\mathbf{1}, \mathbf{x}_i)$ where $\mathbf{1} = (1, \ldots, 1)^T$ and $\mathbf{x}_i = (x_{i1}, \ldots, x_{in_i})^T$. Let $\hat{\mathbf{b}}_i = (\hat{\alpha}_i, \hat{\beta}_i)^T$ denote the least squares estimator of $\mathbf{b}_i$, and $\hat{\sigma}^2$ denotes the usual pooled error mean square with distribution $\hat{\sigma}^2 \sim \sigma^2 \chi^2_\nu / \nu$, where $\nu = \sum_{i=1}^k (n_i - 2)$.

Let $\mathcal{C}$ be the set of vectors $\mathbf{c} = (c_1, \ldots, c_k)^T$ such that $\sum_{i=1}^k c_i = 0$, and let $\mathbf{x} = (1, x)^T$. The focus of this paper is the construction of $1 - \alpha$ level simultaneous confidence bands for all the contrasts among the k regression lines over a given finite or infinite interval (l, u) of the covariate x. Specifically, we consider confidence bands of the form

$$\sum_{i=1}^k c_i \mathbf{x}^T \mathbf{b}_i \in \sum_{i=1}^k c_i \mathbf{x}^T \hat{\mathbf{b}}_i \pm r\hat{\sigma} \sqrt{\sum_{i=1}^k c_i^2 \mathbf{x}^T (X_i^T X_i)^{-1} \mathbf{x}} \quad \text{for all } x \in (l, u) \text{ and all } \mathbf{c} \in \mathcal{C}, \tag{1}$$

where $-\infty \leq l < u \leq +\infty$ are given numbers, and r is a suitably chosen critical constant so that the simultaneous coverage probability of all the confidence bands in (1) is equal to the pre-specified level $1-\alpha$. The value of r depends on α, k, ν, (l, u), and $X_1, \ldots, X_k$.

Spurrier (1999) provides elegant distributional results which allow r to be computed exactly by using numerical integration but only for the special case of $(l, u) = (-\infty, +\infty)$ and $X_1 = \cdots = X_k$. In many applications, the requirement of equal design matrices across groups is too restrictive, however. Furthermore, confidence bands on a finite interval (l, u) are more useful since a regression model is often a reasonable approximation only over a limited range of x, and restricting x to (l, u) results in narrower confidence bands which allow sharper statistical inference. In this paper a simulation-based method is given to approximate r so long as the design matrices are non-singular. The proposed method can achieve any desired accuracy in the approximation of r with a sufficiently large number of replications in the simulation process. In this general setting, it is unlikely that useful distributional results can be established for exact computation of r.

This paper is organized as follows. In Section 2 the simulation method and the required computational implementation are described. In Section 3 numerical results are provided to validate the accuracy of the simulation method. Application of the method to a real problem considered in Hewett and Lababidi (1982) is given Section 4. Finally, the Appendix contains some proofs.

2. Simulation method

The confidence level of the simultaneous confidence bands in (1) is given by

$$\begin{aligned}
&\mathrm{P}\left\{\sum_{i=1}^k c_i \mathbf{x}^T \mathbf{b}_i \in \sum_{i=1}^k c_i \mathbf{x}^T \hat{\mathbf{b}}_i \pm r\hat{\sigma} \sqrt{\sum_{i=1}^k c_i^2 \mathbf{x}^T (X_i^T X_i)^{-1} \mathbf{x}} \text{ for all } x \in (l, u) \text{ and all } \mathbf{c} \in \mathcal{C}\right\} \\
&= \mathrm{P}\left\{\sup_{\mathbf{c}\in\mathcal{C},\ x\in(l,u)} \left|\sum_{i=1}^k c_i \mathbf{x}^T (\hat{\mathbf{b}}_i - \mathbf{b}_i)\right| \Big/ \sqrt{\sum_{i=1}^k c_i^2 \mathbf{x}^T (X_i^T X_i)^{-1} \mathbf{x}} \leq r\hat{\sigma}\right\} \\
&= \mathrm{P}\left\{\sup_{\mathbf{c}\in\mathcal{C},\ x\in(l,u)} \left|\sum_{i=1}^k c_i \mathbf{x}^T (\hat{\mathbf{b}}_i - \mathbf{b}_i)\right| \Big/ \sqrt{\mathrm{Var}\left(\sum_{i=1}^k c_i \mathbf{x}^T (\hat{\mathbf{b}}_i - \mathbf{b}_i)\right)} \leq r\hat{\sigma}/\sigma\right\} \\
&= \mathrm{P}\{W \leq r\}
\end{aligned}$$

where

$$W = \frac{T}{\hat{\sigma}/\sigma} \quad \text{and} \quad T = \sup_{\mathbf{c}\in\mathcal{C},\ x\in(l,u)} \frac{\left|\sum_{i=1}^k c_i \mathbf{x}^T (\hat{\mathbf{b}}_i - \mathbf{b}_i)\right|}{\sqrt{\mathrm{Var}\left(\sum_{i=1}^k c_i \mathbf{x}^T (\hat{\mathbf{b}}_i - \mathbf{b}_i)\right)}}. \tag{2}$$